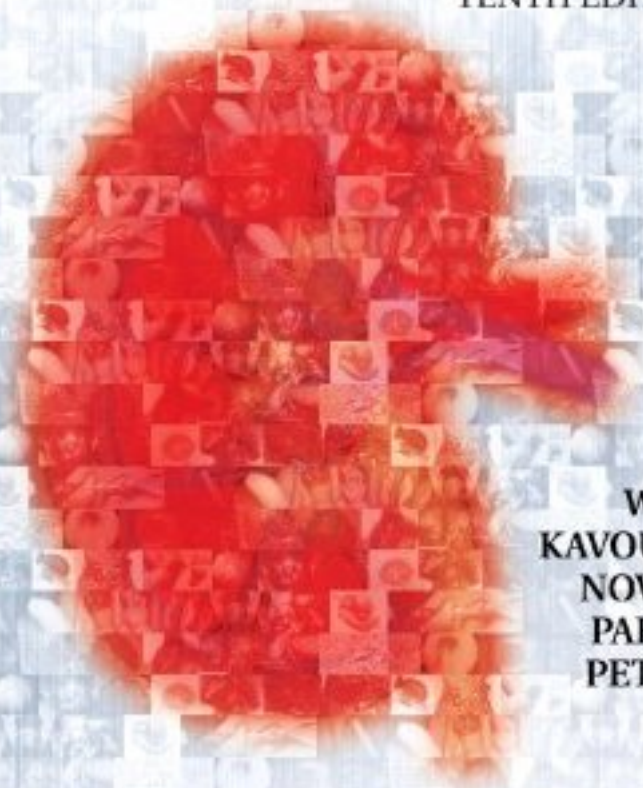
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TENTH EDITION



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Urology

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Editors

Louis R. Kavoussi, MD, MBA
Chairman and Waldbaum-Gardner Distinguished Professor
Smith Institute for Urology
Hofstra North Shore–LIJ School of Medicine
New York, New York

Andrew C. Novick, MD
Chairman, Glickman Urological Institute
Cleveland Clinic Foundation;
Professor of Surgery
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Cleveland, Ohio

Alan W. Partin, MD, PhD
Professor and Director of Urology
Johns Hopkins School of Medicine
Baltimore, Maryland

Craig A. Peters, MD, FACS, FAAP
Chief, Division of Surgical Innovation, Technology, and Translation
Principal Investigator, Sheikh Zayed Institute for Pediatric Surgical Innovation
Children's National Medical Center;
Professor of Urology and Pediatrics
The George Washington University
Washington, DC

CAMPBELL-WALSH

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Volume 1

EDITOR-IN-CHIEF

Alan J. Wein, MD, PhD (Hon), FACS
Founders Professor of Urology
Perelman School of Medicine
University of Pennsylvania;
Chief of Urology
Penn Medicine/University of Pennsylvania Health System
Perelman Center for Advanced Medicine
Philadelphia, Pennsylvania

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1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

CAMPBELL-WALSH UROLOGY, TENTH EDITION ISBN: 978-1-1460-6911-9
INTERNATIONAL EDITION ISBN: 978-0-8089-2439-5
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Library of Congress Cataloging-in-Publication Data

Campbell-Walsh Urology. – 10th ed. / editor-in-chief, Alan J. Wein ; editors, Louis R. Kavoussi … [et al.].
p. ; cm.
Urology
Includes bibliographical references and index.
ISBN 978-1-4160-6911-9 (set : hardcover : alk. paper) – ISBN 978-0-8089-2439-5 (international ed., hardcover : alk. paper) 1. Urology. I. Wein, Alan J. II. Kavoussi, Louis R. III. Campbell, Meredith F. (Meredith Fairfax), 1894-1968. IV. Title: Urology.
[DNLM: 1. Female Urogenital Diseases. 2. Male Urogenital Diseases. 3. Urology–methods. WJ 100]
RC871.C33 2012
616.6–dc22

2011015024

Acquisitions Editor: Stefanie Jewell-Thomas
Senior Developmental Editor: Jennifer Shreiner
Publishing Services Manager: Patricia Tannian
Senior Project Manager: Kristine Feeherty
Design Direction: Lou Forgione

Printed in the United States of America

Last digit is the print number: 9 8 7 6 5 4 3 2 1

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Dedication

This edition of *Campbell-Walsh Urology* is dedicated to the memory and contributions of Andrew Carl Novick. Andy was world class in every way—as a scholar, a surgeon, an innovator, and a friend. Andy assumed the chairmanship of Urology at the Cleveland Clinic in 1985 at the age of 37 and died at the too young age of 60 from complications of lymphoma. His lifetime dream of a urologic and kidney institute at the Cleveland Clinic was realized approximately 1 month before his death, with Andy as its first director. He joined the *Campbell*'s editorial staff as an associate for the 8th edition, was one of the five editors of the 9th edition, and was an equal contributor in organizing and selecting the authors for this 10th edition. Andy always strove for excellence and recognized and acknowledged quality. We hope he would have been proud of this edition.

Contributors

Robert Abouassaly, MD, MSc

Assistant Professor, Department of Urology
Case Western Reserve University School of Medicine;
Urologic Oncologist
Urologic Institute
University Hospitals Case Medical Center
Cleveland, Ohio

Paul Abrams, MD

Professor, Department of Urology
Bristol Urologic Institute
Southmead Hospital
Bristol, United Kingdom

Mark C. Adams, MD, FAAP

Professor, Department of Urology and Pediatrics
Vanderbilt University Medical Center;
Division of Pediatric Urology
Monroe Carell Jr. Children's Hospital at Vanderbilt
Nashville, Tennessee

Ashok Agarwal, PhD

Professor of Surgery
Department of Urology
Case Western Reserve University;
Director of Andrology
Director, Center for Reproductive Medicine
Department of Urology
Cleveland Clinic
Cleveland, Ohio

Mohamad E. Allaf, MD

Associate Professor, Departments of Urology, Oncology, and Biomedical Engineering
Johns Hopkins Medical Institutions;
Director of Minimally Invasive and Robotic Surgery
Johns Hopkins Hospital
Baltimore, Maryland

James Kyle Anderson, MD

Assistant Professor, Department of Urologic Surgery
University of Minnesota;
Staff Urologist, Department of Urologic Surgery
VA Medical Center
Minneapolis, Minnesota

Karl-Erik Andersson, MD, PhD

Professor, Department of Urology
Wake Forest University School of Medicine;
Professor, Institute for Regenerative Medicine
Wake Forest University Baptist Medical Center
Winston Salem, North Carolina

Kenneth W. Angermeier, MD

Associate Professor
Center for Genitourinary Reconstruction
Glickman Urological and Kidney Institute
Cleveland Clinic
Cleveland, Ohio

Emmanuel S. Antonarakis, MD

Assistant Professor of Oncology
Department of Medical Oncology
Johns Hopkins University;
Attending Physician, Department of Medical Oncology
Sidney Kimmel Comprehensive Cancer Center at John Hopkins
Baltimore, Maryland

Dean G. Assimos, MD

Professor of Surgical Sciences
Department of Urology
Wake Forest University School of Medicine;
Attending Physician, Department of Urology
Wake Forest University Baptist Medical Center
Winston-Salem, North Carolina

Anthony Atala, MD

W. Boyce Professor and Chair
Department of Urology
Wake Forest University School of Medicine;
Director, Wake Forest Institute for Regenerative Medicine
Winston Salem, North Carolina

Darius J. Bägli, MDCM, FRCSC, FAAP, FACS

Professor, Department of Surgery
Division of Urology and Institute of Medical Science
University of Toronto;
Senior Attending Urologist
Associate Surgeon-in-Chief
The Hospital for Sick Children;
Director of Urology Research
Senior Associate Scientist
Division of Developmental and Stem Cell Biology
The Hospital for Sick Children Research Institute
Toronto, Ontario, Canada

John Maynard Barry, MD

Professor Emeritus of Surgery
Divisions of Urology and Abdominal Organ Transplantation
The Oregon Health and Science University;
Staff Surgeon
University Hospital and Doenbecher Children's Hospital;
Consultant, Surgery
Veterans Affairs Medical Center
Portland, Oregon

Julia Spencer Barthold, MD

Professor of Urology and Pediatrics
Jefferson Medical College at Thomas Jefferson University
Philadelphia, Pennsylvania;
Associate Chief and Head of Urology Research Laboratory
Department of Surgery/Urology
Nemours/Alfred I. DuPont Hospital for Children;
Head, Urology Laboratory
Nemours Biomedical Research
Wilmington, Delaware

Stuart B. Bauer, MD

Professor of Surgery (Urology)
Harvard Medical School;
Senior Associate in Urology
Children's Hospital Boston
Boston, Massachusetts

Clair J. Beard, MD

Director, Testicular Cancer Center
Department of Radiation Oncology
Dana-Farber Cancer Institute and Brigham and Women's Hospital
Boston, Massachusetts

Arie S. Belldegrun, MD

Roy and Carol Doumani Chair in Urologic Oncology
Professor and Chief, Urologic Oncology
Director, Institute of Urologic Oncology
David Geffen School of Medicine at UCLA;
Department of Urology
Ronald Reagan UCLA Medical Center
Los Angeles, California

Mitchell C. Benson, MD

Herbert & Florence Irving and George F. Cahill Professor and Chair
Department of Urology
Columbia University College of Physicians and Surgeons;
Urologist-in-Chief, Department of Urology
New York-Presbyterian Hospital, Columbia University Medical Center
New York, New York

Brian M. Benway, MD

Assistant Professor, Department of Surgery
Division of Urologic Surgery
Washington University School of Medicine
St. Louis, Missouri

Ryan Kent Berglund, MD

Assistant Professor of Surgery
Glickman Urologic and Kidney Institute
Cleveland Clinic Lerner College of Medicine at Case Western Reserve University
Cleveland Clinic
Cleveland, Ohio

David M. Berman, MD, PhD

Associate Professor, Departments of Pathology, Oncology, and Urology
Johns Hopkins University School of Medicine;
Attending Pathologist
Johns Hopkins Hospital
Baltimore, Maryland

Sam B. Bhayani, MD

Associate Professor, Department of Surgery
Co-Director of Robotic Surgery
Division of Urologic Surgery
Washington University School of Medicine
St. Louis, Missouri

Jay Todd Bishoff, MD, FACS

Clinical Professor of Surgery
Department of Urology
University of Utah School of Medicine;
Director, Intermountain Urological Institute
Intermountain Healthcare;
Director, Department of Urology
LDS Hospital
Salt Lake City, Utah;
Director, Department of Urology
Intermountain Medical Center
Murray, Utah

Michael L. Blute, Sr., MD

Professor, Department of Surgery
Mary C. DeFeudis Chair, Cancer Care and Research
University of Massachusetts Memorial Medical School;
Director, Cancer Center of Excellence
Interim Chief, Department of Urology
UMass Memorial Medical Center
Worcester, Massachusetts

Joseph G. Borer, MD

Assistant Professor, Department of Surgery
Harvard Medical School;
Assistant in Urology
Department of Urology
Children's Hospital Boston
Boston, Massachusetts

George J. Bosl, MD

Professor, Department of Medicine
Weill Cornell Medical College;
Chair, Department of Medicine
Memorial Sloan-Kettering Cancer Center
New York, New York

Charles B. Brendler, MD

Clinical Professor, Department of Surgery
Division of Urology
University of Chicago Medical Center
Chicago, Illinois;
Vice Chairman, Research and Development
Department of Surgery
North Shore University Health System
Evanston, Illinois

Gregory A. Broderick, MD

Professor, Department of Urology
Mayo Clinic College of Medicine;
Consultant, Department of Urology
Mayo Clinic
Jacksonville, Florida

James D. Brooks, MD

Associate Professor, Department of Urology
Stanford University School of Medicine
Stanford, California

Arthur L. Burnett, MD, MBA, FACS

Patrick C. Walsh Professor of Urology
Department of Urology
Johns Hopkins Medical Institutions
Baltimore, Maryland

Jeffrey A. Cadeddu, MD

Professor, Departments of Urology and Radiology
University of Texas Southwestern Medical Center
Dallas, Texas

Anthony A. Caldamone, MD, MMS, FAAP, FACS

Professor of Surgery (Urology) and Pediatrics
Division of Urology
Warren Alpert Medical School of Brown University
Rhode Island Hospital;
Head of Pediatric Urology
Hasbro Children's Hospital
Providence, Rhode Island

Steven C. Campbell, MD, PhD

Professor of Surgery
Department of Urology
Cleveland Clinic Lerner of College of Medicine at Case Western Reserve University;
Professor of Surgery
Director, Urology Residency Program
Vice Chairman, Urology
Center for Urologic Oncology
Cleveland Clinic
Cleveland, Ohio

Douglas A. Canning, MD

Professor, Department of Urology
University of Pennsylvania School of Medicine;
Director, Division of Pediatric Urology
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Michael A. Carducci, MD

AEGON Professor in Prostate Cancer Research
Departments of Oncology and Urology
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Baltimore, Maryland

Michael C. Carr, MD, PhD

Associate Professor, Department of Urology
University of Pennyslvania School of Medicine;
Attending Surgeon, Division of Pediatric Urology
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Peter R. Carroll, MD, MPH

Professor and Chair, Department of Urology
University of California, San Francisco
UCSF Medical Center
San Francisco, California

Herbert Ballentine Carter, MD

Professor, Departments of Urology and Oncology
Johns Hopkins School of Medicine
Baltimore, Maryland

Anthony J. Casale, MD

Professor and Chairman, Department of Urology
University of Louisville;
Chief of Urology
Kosair Children's Hospital;
Chief of Urology and Surgery (Urology)
University of Louisville Hospital
Louisville, Kentucky

Pasquale Casale, MD

Assistant Professor, Department of Urology
University of Pennsylvania School of Medicine;
Attending Surgeon, Division of Pediatric Urology
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

William J. Catalona, MD

Professor, Department of Urology
Northwestern University Feinberg School of Medicine;
Director, Clinical Prostate Cancer Program
Robert H. Lurie Comprehensive Cancer Center
Northwestern Memorial Hospital
Chicago, Illinois

R. Duane Cespedes, MD

Associate Professor, Department of Urology
Johns Hopkins School of Medicine;
Co-Director, Women's Center for Pelvic Health
James Buchanan Brady Urological Institute
Johns Hopkins Medical Institutions
Baltimore, Maryland

Michael B. Chancellor, MD

Clinical Professor, Department of Urology
Oakland University William Beaumont School of Medicine;
Director, Neurourology Program
William Beaumont Hospital
Royal Oak, Michigan

Christopher R. Chapple, MD, FRCS (Urol), FEBU

Honorary Professor, Faculty of Health and Wellbeing
Sheffield Hallam University;
Honorary Senior Lecturer of Urology
University of Sheffield;
Consultant Urological Surgeon
Department of Urology
Sheffield Teaching Hospitals NHS Foundation Trust
Sheffield, United Kingdom;
Adjunct Secretary General for Education
European Association of Urology
Arnhem, The Netherlands

Christopher J. Chermansky, MD

Assistant Professor, Department of Urology
Louisiana State University Health Sciences Center
New Orleans School of Medicine
New Orleans, Louisiana

Robert L. Chevalier, MD

Harrison Professor of Pediatrics
Department of Pediatrics
University of Virginia;
Pediatric Nephrologist
University of Virginia Health System
Charlottesville, Virginia

George K. Chow, MD

Assistant Professor, Department of Urology
Consultant in Urology
Mayo Clinic
Rochester, Minnesota

Jeanne S. Chow, MD

Assistant Professor, Department of Radiology
Harvard Medical School;
Pediatric Radiologist
Children's Hospital Boston
Boston, Massachusetts

Benjamin I. Chung, MD

Assistant Professor, Department of Urology
Stanford University School of Medicine;
Director, Laparoscopic and Minimally Invasive Urologic Surgery
Department of Urology
Stanford Hospital and Clinics
Stanford, California

Ralph V. Clayman, MD

Dean, University of California, Irvine School of Medicine
Professor, Department of Urology
University of California, Irvine;
Professor, Department of Urology
UC Irvine Medical Center
Orange, California
Professor, Department of Urology
Long Beach Veterans Administration Hospital
Long Beach, California

Michael Joseph Conlin, MD, FACS

Associate Professor of Urology
Department of Surgery
Oregon Health & Science University
Portland, Oregon

Raymond A. Costabile, MD

Senior Associate Dean for Clinical Strategy
Professor, Department of Urology
University of Virginia
Charlottesville, Virginia

Paul L. Crispen, MD

Assistant Professor, Department of Surgery
Division of Urology
University of Kentucky
Lexington, Kentucky

Juanita M. Crook, MD, FRCPC

Professor, Department of Radiation Oncology
University of British Columbia;
Active Medical Staff
Department of Radiation Oncology
Kelowna General Hospital;
Radiation Oncologist
British Columbia Cancer Agency
Kelowna, British Columbia, Canada

Douglas M. Dahl, MD

Assistant Professor of Surgery (Urology)
Harvard Medical School;
Associate Urologist
Massachusetts General Hospital
Boston, Massachusetts

Anthony V. D'Amico, MD, PhD

Professor and Chief, Genitourinary Radiation Oncology
Brigham and Women's Hospital and Dana-Farber Cancer Institute
Boston, Massachusetts

John W. Davis, MD

Assistant Professor, Department of Urology
University of Texas MD Anderson Cancer Center
Houston, Texas

G. Joel DeCastro, MD, MPH

Assistant Professor, Department of Urology
Columbia University College of Physicians and Surgeons
New York, New York

John D. Denstedt, MD, FRCSC, FACS

Richard Ivey Professor and Chair, Department of Surgery
Schulich School of Medicine & Dentistry
The University of Western Ontario
Richard Ivey Professor and Chair, Division of Urology
Department of Surgery
London Health Sciences Centre and St. Joseph's Health Care London
London, Ontario, Canada

Theodore L. DeWeese, MD

Professor and Chair, Department of Radiation Oncology and Molecular Radiation Sciences
Johns Hopkins University School of Medicine;
Radiation Oncologist-in-Chief
Johns Hopkins Hospital and Health System
Baltimore, Maryland

David Andrew Diamond, MD

Associate Professor of Surgery (Urology)
Harvard Medical School;
Senior Associate in Urology
Department of Urology
Children's Hospital Boston
Boston, Massachusetts

Roger R. Dmochowski, MD, FACS

Professor of Urologic Surgery
Vanderbilt University School of Medicine;
Director, Vanderbilt Continence Center
Director, Vanderbilt Female Reconstructive Fellowship
Executive Physician, Safety
Vanderbilt University Hospital
Nashville, Tennessee

Leo R. Doumanian, MD

Assistant Professor, Department of Urology
Temple University School of Medicine
Philadelphia, Pennsylvania

Marcus Drake, DM, MA, FRCS (Urol)

Senior Lecturer in Urology
School of Clinical Sciences
University of Bristol;
Consultant Surgeon
Urology Department
Southmead Hospital
Bristol, United Kingdom

Branden Duffey, DO

Endourology Fellow
Department of Urology
University of Minnesota and University of Minnesota Medical Center
Minneapolis, Minnesota

Daniel D. Dugi III, MD

Assistant Professor, Department of Urology
Oregon Health & Science University
Portland, Oregon

James A. Eastham, MD

Chief, Urology Service
Department of Surgery
Memorial Sloan-Kettering Cancer Center
New York, New York

Louis Eichel, MD

Clinical Assistant Professor, Department of Urology
University of Rochester Medical Center;
Director, Minimally Invasive Surgery
Center For Urology
Rochester, New York

Mario A. Eisenberger, MD

R. Dale Hughes Professor of Oncology and Urology
Johns Hopkins University and The Johns Hopkins Hospital
Baltimore, Maryland

Jonathan I. Epstein, MD

Reinhard Professor of Urological Pathology
Departments of Pathology, Urology, and Oncology
Johns Hopkins Medical Institutions;
Director, Surgical Pathology
Department of Pathology
Johns Hopkins Hospital
Baltimore, Maryland

Carlos R. Estrada, Jr., MD

Assistant Professor, Department of Surgery
Harvard Medical School;
Assistant in Urology
Department of Urology
Children's Hospital Boston
Boston, Massachusetts

Robert L. Fairchild, PhD

Professor, Department of Molecular Medicine
Cleveland Clinic;
Professor, Department of Pathology
Case Western Reserve University School of Medicine
Cleveland, Ohio

Amr Fergany, MD, PhD

Staff Sections of Oncology, Minimally Invasive Surgery, and Robotics
Glickman Urological and Kidney Institute
Cleveland Clinic
Cleveland, Ohio

Michael N. Ferrandino, MD

Assistant Professor, Department of Surgery
Division of Urology
Duke University and Duke University Medical Center
Durham, North Carolina

Lynne R. Ferrari, MD

Associate Professor, Department of Anethesia
Harvard Medical School;
Medical Director, Preoperative Services and Operating Rooms
Chief, Division of Perioperative Anesthesia
Department of Anethesiology, Perioperative, and Pain Management
Children's Hospital Boston
Boston, Massachusetts

James H. Finke, PhD

Professor of Molecular Medicine
Department of Pathology
Case Western Reserve University School of Medicine;
Professor of Immunology
Joint-Appointment, Glickman Urological Institute and Taussig Cancer Institute
Cleveland Clinic
Cleveland, Ohio

John M. Fitzpatrick, MCh, FRCSI, FC Urol (SA), FRCSGlas, FRCS

Professor and Chairman, Department of Surgery
University College Dublin;
Professor of Surgery and Consultant Urologist
Department of Urology
Mater Misericordiae University Hospital
Dublin, Ireland

Robert C. Flanigan, MD

Albert J. Jr. and Claire R. Speh Professor and Chair
Department of Urology
Loyola University Medical Center and Stritch School of Medicine;
Professor, Department of Urology
Loyola University Health System
Maywood, Illinois

Stuart M. Flechner, MD, FACS

Professor, Department of Surgery
Cleveland Clinic Lerner College of Medicine at Case Western Reserve University;
Director of Clinical Research
Section of Renal Transplantation
Glickman Urological and Kidney Institute
Cleveland Clinic
Cleveland, Ohio

Tara Lee Frenkl, MD, MPH

Clinical Associate, Department of Surgery
Division of Urology
University of Pennyslvania Medical Center
Philadelphia, Pennsylvania

Dominic C. Frimberger, MD

Associate Professor, Department of Urology
University of Oklahoma Health Sciences Center;
Department of Urology
Children's Hospital and Presbyterian Hospital
Oklahoma City, Oklahoma

Pat F. Fulgham, MD, DABU, FACS

Clinical Professor, Department of Urology
University of Texas Southwestern Medical School;
Surgical Director, Oncology Services
Texas Health Presbyterian Dallas
Dallas, Texas

John P. Gearhart, MD

Professor and Director
Division of Pediatric Urology
Johns Hopkins University School of Medicine
Baltimore, Maryland

Glenn S. Gerber, MD

Associate Professor of Surgery/Urology
University of Chicago Pritzker School of Medicine;
Director, Endourology
University of Chicago Medical Center
Chicago, Illinois

Jason L. Gerboc, DO

Staff Urologist
Department of Urology
Wilford Hall Medical Center
Lackland Air Force Base, Texas

Robert H. Getzenberg, PhD

The Donald S. Coffey Professor of Urology, Pharmacology, and Molecular Sciences
Department of Urology
Johns Hopkins University School of Medicine;
Director, James Buchanan Brady Urological Institute
Johns Hopkins Hospital
Baltimore, Maryland

Islam A. Ghoneim, MD, PhD

Staff, Urology Department
Cairo University
Cairo, Egypt;
Fellow, Department of Urology
Glickman Urologic and Kidney Institute
Cleveland Clinic
Cleveland, Ohio

Inderbir S. Gill, MD, MCh

Professor and Chairman, Department of Urology
Keck School of Medicine
University of Southern California
Director, USC Institute of Urology
Los Angeles, California

Timothy D. Gilligan, MD, MS

Director, Late Effects Clinic
Program Director, Hematology/Oncology Fellowship
Department of Solid Tumor Oncology
Taussig Cancer Institute;
Deputy Editor, Cleveland Clinic Journal of Medicine
Cleveland Clinic
Cleveland, Ohio

David A. Goldfarb, MD

Professor of Surgery
Department of Urology
Cleveland Clinic Lerner College of Medicine at Case Western Reserve University;
Surgical Director, Renal Transplantaton
Department of Urology
Glickman Urological and Kidney Institute
Cleveland Clinic
Cleveland, Ohio

Marc Goldstein, MD, DSc (Hon)

Matthew P. Hardy Distinguished Professor, Urology and Reproductive Medicine
Weill Cornell Medical College;
Surgeon-in Chief, Male Reproductive Medicine and Surgery
Attending Urologist, Department of Urology
New York-Presbyterian Hospital, Weill Cornell Medical Center;
Senior Scientist, Center for Biomedical Reseach
The Population Council
New York, New York

Leonard G. Gomella, MD, FACS

Chairman, Department of Urology
The Bernard W. Godwin Jr. Professor of Prostate Cancer
Jefferson Medical College at Thomas Jefferson University;
Associate Director, Kimmel Cancer Center;
Director, Kimmel Cancer Center Network;
Chairman, Department of Urology
Thomas Jefferson University Hospital
Philadelphia, Pennsylvania

Mark L. Gonzalgo, MD, PhD

Associate Professor, Department of Urology
Stanford University School of Medicine
Stanford, California

Ethan J. Halpern, MD, MSCE

Professor, Departments of Radiology and Urology
Jefferson Medical College at Thomas Jefferson University
Philadelphia, Pennsylvania

Misop Han, MD, MS

Associate Professor, Department of Urology
Johns Hopkins University School of Medicine;
Staff Surgeon, Department of Urology
Johns Hopkins Medical Institutions
Baltimore, Maryland

Philip M. Hanno, MD, MPH

Professor of Urology
Department of Surgery
University of Pennsylvania School of Medicine;
Attending Urologist, Department of Surgery
Hospital of the University of Pennsylvania and the Veterans Administration Medical Center
Philadelphia, Pennsylvania

Harry W. Herr, MD

Professor, Department of Urology
Weill Cornell Medical College;
Attending Surgeon, Department of Urology
Memorial Sloan-Kettering Cancer Center
New York, New York

Sender Herschorn, MDCM, FRCSC

Professor and Chairman, Division of Urology
Martin Barkin Chair, Urological Research
University of Toronto;
Attending Urologist, Division of Urology
Sunnybrook Health Sciences Centre
Toronto, Ontario, Canada

Thomas H.S. Hsu, MD

Director of Laparoscopic, Robotic, and Minimally Invasive Urologic Surgery
Northern California Kaiser Permanente Medical Center
Santa Clara, California

Mark Hurwitz, MD

Department of Radiation Oncology
Harvard Medical School;
Director, Regional Program Development
Department of Radiation Oncology
Dana-Farber/Brigham and Women's Cancer Center
Boston, Massachusetts

Douglas A. Husmann, MD

Professor and Chair, Department of Urology
Mayo Clinic
Rochester, Minnesota

Thomas W. Jarrett, MD

Professor and Chairman, Department of Urology
George Washington University School of Medicine
Washington, DC

J. Stephen Jones, MD, MBA

Professor of Surgery
Department of Urology
Cleveland Clinic Lerner College of Medicine at Case Western Reserve University;
Chairman, Department of Regional Urology
Glickman Urological and Kidney Institute
Cleveland Clinic
Cleveland, Ohio

Gerald H. Jordan, MD, FACS, FAAP (Hon), FRCS (Hon)

Professor, Department of Urology
Eastern Virginia Medical School;
Urology of Virginia
Norfolk, Virginia

David B. Joseph, MD, FACS, FAAP

Professor, Department of Surgery
Chief, Pediatric Urology
University of Alabama at Birmingham;
Beverly P. Head Endowed Chair in Pediatric Urology
Children's Hospital
Birmingham, Alabama

Martin Kaefer, MD, FAAP, FACS

Professor, Department of Urology
Division of Pediatric Urology
Indiana University School of Medicine
Indianapolis, Indiana

Jihad H. Kaouk, MD

Professor, Department of Surgery
Cleveland Clinic Learner College of Medicine;
Director, Laparoscopic and Robotic Surgery
Department of Urology
Cleveland Clinic
Cleveland, Ohio

Irving D. Kaplan, MD

Assistant Professor, Department of Radiation Oncology
Harvard Medical School;
Staff Radiation Therapist
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Louis R. Kavoussi, MD, MBA

Chairman and Waldbaum-Gardner Distinguished Professor
Smith Institute for Urology
Hofstra North Shore–LIJ School of Medicine
New York, New York

Parviz K. Kavoussi, MD

Andrology Fellow
Department of Urology
University of Virginia
Charlottesville, Virginia;
Andrologist/Urologist
Austin Fertility & Reproductive Medicine
Austin, Texas

Patrick A. Kenney, MD

Clinical Associate, Department of Urology
Tufts University School of Medicine
Boston, Massachusetts;
Chief Resident, Institute of Urology
Lahey Clinic
Burlington, Massachusetts

Antoine E. Khoury, MD, FRCSC, FAAP

Professor, Department of Urology
Chief, Pediatric Urology
University of California, Irvine;
Medical Director, Pediatric Urology
Children's Hospital of Orange County;
Chief, Pediatric Urology
UCI Medical Center
Orange, California

Roger Sinclair Kirby, MD, MA, FRCS

Professor, Department of Urology
University of London;
The Prostate Centre
London, United Kingdom

Eric A. Klein, MD

Professor, Department of Surgery
Cleveland Clinic Lerner College of Medicine at Case Western Reserve University;
Chairman, Glickman Urological and Kidney Institute
Cleveland Clinic
Cleveland, Ohio

Kathleen C. Kobashi, MD

Associate Clinical Professor, Department of Urology
University of Washington School of Medicine;
Head, Section of Urology and Renal Transplantation
Department of Surgery
Virginia Mason Medical Center
Seattle, Washington

Michael O. Koch, MD

Chairman and John P. Donohue Professor
Department of Urology
Indiana University School of Medicine
Indianapolis, Indiana

John N. Krieger, MD

Professor, Department of Urology
University of Washington School of Medicine;
Chief, Department of Urology
VA Puget Sound Health Care System;
Attending Surgeon, Department of Urology
University of Washington Medical Center and Harborview Medical Center
Seattle, Washington

Bradley P. Kropp, MD, FAAP

Professor and Vice Chairman, Department of Urology
Chief, Pediatric Urology
University of Oklahoma Health Science Center
Oklahoma City, Oklahoma

Alexander Kutikov, MD

Assistant Professor of Urologic Oncology
Department of Surgical Oncology
Fox Chase Cancer Center
Philadelphia, Pennsylvania

Sarah M. Lambert, MD

Assistant Professor, Department of Surgery
The University of Pennsylvania;
Staff Urologist, Department of Surgery
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Raymond S. Lance, MD

The Paul F. Schellhammer Professor of Cancer Research
Associate Professor, Departments of Urology and Microbiology and Cancer Biology
Eastern Virginia Medical School;
Sentara Norfolk General Hospital
Sentara Medical Group—Urology of Virginia
Norfolk, Virginia

Brian R. Lane, MD, PhD

Clinical Associate Professor, Department of Surgery
Michigan State University;
Attending Physician, Department of Urology
Spectrum Health Hospital System
Grand Rapids, Michigan

William A. Larchian, MD

Associate Professor, Department of Surgery
Case Western Reserve University School of Medicine;
Center for Urologic Oncology
Urological Institute
University Hospitals Case Medical Center
Cleveland, Ohio

Richard S. Lee, MD

Assistant Professor of Surgery (Urology)
Harvard Medical School;
Assistant in Urology
Children's Hospital Boston
Boston, Massachusetts

Herbert Lepor, MD

Professor and Martin Spatz Chairman, Department of Urology
Professor of Pharmacology
New York University School of Medicine;
Director, Urology
NYU Langone Medical Center
New York, New York

Seth P. Lerner, MD, FACS

Professor, Department of Urology
Baylor College of Medicine;
Medical Staff, Department of Urology
The Methodist, St. Luke's Episcopal Hospital and Ben Taub General Hospital
Houston, Texas

John A. Libertino, MD

Professor, Department of Urology
Tufts University School of Medicine
Boston, Massachusetts;
Chair, Institute of Urology
Director, Sophia Gordon Cancer Center
Lahey Clinic Medical Center
Burlington, Massachusetts

W. Marston Linehan, MD

Chief, Urologic Oncology Branch
National Cancer Institute;
Physician-in-Chief, Urologic Surgery
Clinical Research Center
National Institutes of Health
Bethesda, Maryland

James E. Lingeman, MD

Volunteer Clinical Professor, Department of Urology
Indiana University School of Medicine
Indianapolis, Indiana

Richard Edward Link, MD, PhD

Associate Professor, Department of Urology
Director, Division of Minimally Invasive Surgery
Scott Department of Urology
Baylor College of Medicine
Houston, Texas

Mark S. Litwin, MD, MPH

Professor of Urology and Health Services
UCLA School of Medicine and Public Health
University of California, Los Angeles
Los Angeles, California

Stacy Loeb, MD

Resident, Department of Urology
James Buchanan Brady Urological Institute
Johns Hopkins Medical Institutions
Baltimore, Maryland

Yair Lotan, MD

Associate Professor, Department of Urology
University of Texas Southwestern Medical Center
Dallas, Texas

Tom F. Lue, MD, ScD (Hon), FACS

Professor and Vice Chairman
Department of Urology
University of California, San Francisco
San Francisco, California

Dawn Lee MacLellan, MD, FRCSC

Assistant Professor, Departments of Urology, Surgery, and Pathology
Izaak Walton Killam Health Centre
Dalhousie University
Halifax, Nova Scotia, Canada

Stanley Bruce Malkowicz, MD

Co-Director, Urologic Oncology
Department of Urology
University of Pennsylvania
Philadelphia, Pennsylvania

Vitaly Margulis, MD

Assistant Professor, Department of Urology
The University of Texas Southwestern Medical Center
Dallas, Texas

Ranjiv I. Mathews, MD

Associate Professor, Pediatric Urology
James Buchanan Brady Urological Institute
Johns Hopkins Medical Institutions
Baltimore, Maryland

Surena F. Matin, MD

Associate Professor, Department of Urology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Brian R. Matlaga, MD, MPH

Associate Professor, Department of Urology
Johns Hopkins University School of Medicine;
Director, Stone Disease
James Buchanan Brady Urological Institute
Baltimore, Maryland

Steven D. Mawhorter, MD, DTM&H

Associate Professor, Department of Medicine
Cleveland Clinic Lerner College of Medicine at Case Western Reserve University;
Staff Physician, Infectious Disease
Cleveland Clinic
Cleveland, Ohio

Kurt A. McCammon, MD, FACS

Assistant Professor and Chairman, Department of Urology
Eastern Virginia Medical School;
Chief, Department of Urology
Sentara Norfolk General Hospital;
Urology of Virginia
Norfolk, Virginia

W. Scott McDougal, MD, MA (Hon)

Professor of Urology
Harvard Medical School;
Chief, Urology
Massachusetts General Hospital
Boston, Massachusetts

James M. McKiernan, MD

John and Irene Given Associate Professor of Urology
Department of Urology
Columbia University College of Physicians and Surgeons;
Associate Attending Urologist
New York-Presbyterian Hospital, Columbia University Medical Center
New York, New York

Alan W. McMahon, MD

Associate Professor, Department of Medicine
University of Alberta
Edmonton, Alberta, Canada

Thomas Anthony McNicholas, MBBS, FRCS, FEBU

Visiting Professor, Faculty of Health and Human Services
University of Hertfordshire;
Consultant Urological Surgeon
Department of Urology
Lister Hospital
Hertfordshire, United Kingdom;
Honorary Senior Lecturer
Institute of Urology
University College London
London, United Kingdom

Alan Keith Meeker, PhD, MA

Assistant Professor, Departments of Pathology, Urology, and Oncology
Johns Hopkins University School of Medicine
Baltimore, Maryland

Cathy Mendelsohn, PhD

Associate Professor, Departments of Urology, Pathology, and Genetics and Development
Columbia University College of Physicians and Surgeons
New York, New York

Carlos E. Méndez-Probst, MD

Fellow in Endourology
Department of Surgey
Schulisch School of Medicine and Dentistry
The University of Western Ontario and St. Joseph's Health Care London
London, Ontario, Canada

Maxwell V. Meng, MD

Associate Professor, Department of Urology
University of California, San Francisco
San Francisco, California

David C. Miller, MD, MPH

Assistant Professor, Department of Urology
University of Michigan Medical School
Ann Arbor, Michigan

Ian Milsom, MD, PhD

Professor, Department of Obstetrics and Gynecology
Institute of Clinical Sciences
Sahlgrenska Academy at Gothenburg University;
Consultant Gynecologist
Sahlgrenska University Hospital
Gothenburg, Sweden

Manoj Monga, MD, FACS

Professor, Department of Surgery
The Cleveland Clinic Lerner College of Medicine at Case Western Reserve University;
Director, Steven Streem Center for Endourology & Stone Disease
Glickman Urological Institute
Cleveland Clinic
Cleveland, Ohio

Drogo K. Montague, MD

Professor, Department of Surgery
Cleveland Clinic Lerner College of Medicine at Case Western Reserve University;
Director, Center for Genitourinary Reconstruction
Glickman Urological and Kidney Institute
Cleveland Clinic
Cleveland, Ohio

Courtenay Kathryn Moore, MD

Assistant Professor, Department of Surgery
Cleveland Clinic Lerner College of Medicine at Case Western Reserve University;
Staff Physcian
Glickman Urological and Kidney Institute
Cleveland Clinic
Cleveland, Ohio

Alvaro Morales, MD, FACS, FRCS

Professor, Department of Urology
Director, Centre for Applied Urological Research
Queen's University;
Attending, Department of Urology
Kingston General Hospital and the Hotel Dieu Hospital
Kingston, Ontario, Canada

Allen F. Morey, MD, FACS

Professor and Paul C. Peters MD Chair of Urology
Department of Urology
University of Texas Southwestern Medical Center;
Chief, Urology Service
Parkland Health and Hospital System
Dallas, Texas

Michael J. Morris, MD

Assistant Professor, Department of Medicine
Weill Cornell Medical College;
Assistant Member, Genitourinary Oncology Service
Department of Medicine
Memorial Sloan-Kettering Cancer Center
New York, New York

John P. Mulhall, MD, MSc (Anat)

Professor, Department of Urology
Weill Cornell Medical College;
Director, Sexual and Reproductive Medicine
Department of Urology Service
Memorial Sloan-Kettering Cancer Center
New York, New York

Stephen Y. Nakada, MD

David T. Uehling Professor and Chairman
Department of Urology
University of Wisconsin, Madison;
Professor and Chairman, Department of Urology
University of Wisconsin Hospital and Clinics
Madison, Wisconsin

Joel B. Nelson, MD

Frederic N. Schwentker Professor and Chairman
Department of Urology
University of Pittsburgh School of Medicine;
Chairman, Department of Surgery
UPMC Shadyside Hospital
Pittsburgh, Pennsylvania

J. Curtis Nickel, MD, FRCSC

Professor, Department of Urology
Queen's University;
Staff Urologist
Kingston General Hospital;
Canada Institute of Health Research Tier One
Canada Research Chair in Urologic Pain and Inflammation
Kingston, Ontario, Canada

Victor W. Nitti, MD

Professor and Vice Chairman, Department of Urology
New York University School of Medicine;
Attending Physician, Department of Urology
NYU Langone Medical Center
New York, New York

[†]Andrew C. Novick, MD

Chairman, Glickman Urological Institute
Cleveland Clinic Foundation;
Professor of Surgery
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Cleveland, Ohio

Michael C. Ost, MD

Associate Professor, Department of Urology
University of Pittsburgh School of Medicine;
Associate Professor, Department of Urology
Children's Hospital of Pittsburgh
Magee-Women's Hospital
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

[†]Deceased.

Priya Padmanabhan, MD, MPH

Assistant Professor, Department of Urology
The University of Kansas Medical Center
Kansas City, Kansas

Jeffrey S. Palmer, MD, FACS, FAAP

Associate Professor of Surgery
Cleveland Clinic Lerner College of Medicine at Case Western Reserve University
Cleveland, Ohio

Lane S. Palmer, MD, FAAP, FACS

Clinical Professor, Department of Urology
Albert Einstein College of Medicine
Bronx, New York;
Chief, Department of Pediatric Urology
Cohen Children's Medical Center of New York
North Shore–Long Island Jewish Health System
New Hyde Park, New York

John M. Park, MD

Cheng-Yang Chang Professor of Pediatric Urology
Department of Urology
University of Michigan Medical School;
The University of Michigan Health System
Ann Arbor, Michigan

Alan W. Partin, MD, PhD

Professor and Director of Urology
Johns Hopkins School of Medicine
Baltimore, Maryland

Christopher K. Payne, MD

Associate Professor, Department of Urology (and Gynecology, by courtesy)
Stanford University School of Medicine;
Director, Female Urology & Neurourology
Stanford University Medical Center
Stanford, California

Margaret S. Pearle, MD, PhD

Professor, Departments of Urology and Internal Medicine
University of Texas Southwestern Medical Center
Dallas, Texas

Craig A. Peters, MD, FACS, FAAP

Chief, Division of Surgical Innovation, Technology, and Translation
Principal Investigator, Sheikh Zayed Institute for Pediatric Surgical Innovation
Children's National Medical Center;
Professor of Urology and Pediatrics
The George Washington University
Washington, DC

Andrew C. Peterson, MD, FACS

Associate Professor of Urology
Department of Surgery
Duke University
Durham, North Carolina

Curtis A. Pettaway, MD

Professor, Departments of Urology and Cancer Biology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Paul K. Pietrow, MD

Director, Minimally Invasive Surgery
Hudson Valley Urology, PC
Poughkeepsie, New York

Louis Leon Pisters, MD

Professor, Department of Urology
Surgical Staff, Department of Urology
University of Texas MD Anderson Cancer Center
Houston, Texas

Elizabeth A. Platz, ScD, MPH

Professor, Department of Epidemiology
Johns Hopkins University Bloomberg School of Public Health
Baltimore, Maryland

Emilio D. Poggio, MD

Associate Professor of Medicine, Nephrology, and Hypertension
Cleveland Clinic Lerner College of Medicine at Case Western Reserve University;
Director, Renal Function Laboratory
Glickman Urological and Kidney Institute
Cleveland Clinic
Cleveland, Ohio

John C. Pope IV, MD

Associate Professor, Departments of Urology, Surgery, and Pediatrics
Vanderbilt University Medical Center;
Associate Professor, Pediatric Urology
Monroe Carell Jr. Children's Hospital at Vanderbilt
Nashville, Tennessee

Jeannette M. Potts, MD

Director, Pelvic Pain Center and Alternative Urological Therapies
Urological Institute
Case Western Reserve University;
University Hospitals of Cleveland
Cleveland, Ohio

Glenn M. Preminger, MD

Professor of Urologic Surgery
Director, Duke Comprehensive Kidney Stone Center
Duke University Medical Center
Durham, North Carolina

John C. Rabets, MD

Department of Urology
Glickman Urological and Kidney Institute
Cleveland Clinic
Cleveland, Ohio

Raymond Robert Rackley, MD

Professor, Department of Surgery
Cleveland Clinic Lerner College of Medicine at Case Western Reserve University;
Staff, Center for Pelvic Health and Recontructive Surgery
Glickman Urological and Kidney Institute;
Director, Urothelial Biology Laboratory
Department of Cancer Biology
Lerner Research Institute
Cleveland Clinic
Cleveland, Ohio

Hassan Razvi, MD, FRCSC

Professor and Chairman, Division of Urology
Department of Surgery
Schulich School of Medicine and Dentistry
University of Western Ontario;
Chief, Division of Urology
St. Joseph's Hospital and London Health Sciences Centre
London, Ontario, Canada

Neil M. Resnick, MD

Thomas Detre Endowed Professor of Medicine
Department of Medicine
University of Pittsburgh School of Medicine;
Chief, Division of Geriatric Medicine and Gerontology
Department of Medicine;
Associate Director, Institute on Aging
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

Lee Richstone, MD

Assistant Professor, Department of Urology
Hofstra–North Shore LIJ School of Medicine;
Director, Laparoscopic and Robotic Surgery
The Smith Institute for Urology
The North Shore University Hospital (NSUH)
New Hyde Park, New York;
Assistant Professor, Department of Urology
The Albert Einstein College of Medicine
New York, New York

Richard C. Rink, MD, FACS, FAAP

Robert A. Gameh Professor of Pediatric Urologic Research
Department of Pediatric Urology
Indiana University School of Medicine;
Chief, Pediatric Urology
Riley Hospital for Children
Indianapolis, Indiana

Michael L. Ritchey, MD, FAAP, FACS

Professor, Department of Urology
Mayo Clinic College of Medicine
Scottsdale, Arizona;
Chief, Department of Surgery
Phoenix Children's Hospital
Phoenix, Arizona

Ronald Rodriguez, MD, PhD

Associate Professor, Department of Urology
Johns Hopkins University School of Medicine
Baltimore, Maryland

Claus G. Roehrborn, MD

Professor and Chairman, Department of Urology
University of Texas Southwestern Medical School;
Attending Urologist
University Hospital UT Southwestern Medical Center
Parkland Health and Hospital System
VA Medical Center
Dallas, Texas

Eric S. Rovner, MD

Professor, Department of Urology
Medical University of South Carolina;
Attending Staff, Department of Urology
Medical University Hospital
Charleston, South Carolina

Edmund Sabanegh, Jr., MD

Chairman, Department of Urology
Cleveland Clinic
Cleveland, Ohio

Arthur I. Sagalowsky, MD

Professor and Dr. Paul Peters Chair in Urology in Memory of Rumsey and Louis Strickland
Department of Urology
Chief, Urology Oncology
University of Texas Southwestern Medical Center;
Department of Urology
Zale Lipshy University Medical Center
St. Paul University Medical Center
Dallas, Texas

Richard A. Santucci, MD

Clinical Professor, Department of Urology
Michigan State College of Osteopathic Medicine;
Specialist-in-Chief, Department of Urology
The Detroit Medical Center
Detroit, Michigan

Peter T. Scardino, MD, FACS

Attending Urologist
New York-Presbyterian Hospital, Weill Cornell Medical Center;
The David H. Koch Chair, Department of Surgery
Memorial Sloan-Kettering Cancer Center
New York, New York

Harriette Miles Scarpero, MD

Associated Urologists
St. Thomas Hospital
Nashville, Tennessee

Anthony J. Schaeffer, MD

Chairman and Herman L. Kretschmer Professor
Department of Urology
Northwestern University Feinberg School of Medicine;
Chairman, Department of Urology
Northwestern Memorial Hospital
Chicago, Illinois

Edward M. Schaeffer, MD, PhD

Associate Professor, Department of Urology
John Hopkins University;
James Buchanan Brady Urological Institute
John Hopkins Medical Institutions
Baltimore, Maryland

Howard I. Scher, MD

Professor, Department of Medicine
Weill Cornell Medical College;
Chief, Genitourinary Oncology Service
Department of Medicine
Memorial Sloan-Kettering Cancer Center
New York, New York

Douglas S. Scherr, MD

The Ronald Stanton Clinical Scholar in Urology
Associate Professor, Department of Urology
Weill Cornell Medical College;
Associate Professor of Urology, Department of Urology
New York-Presbyterian Hospital
New York, New York

Richard N. Schlussel, MD

Assistant Professor, Department of Urology
Columbia University College of Physicians and Surgeons;
Associate Director, Pediatric Urology
Morgan Stanley Children's Hospital of New York-Presbyterian
New York, New York

Francis X. Schneck, MD

Associate Professor, Department of Urology
University of Pittsburgh Medical Center;
Clinical Director, Department of Pediatric Urology
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

Michael J. Schwartz, MD

Assistant Professor, Department of Urology
Hofstra North Shore–LIJ School of Medicine
Hempstead, New York;
Attending Physician
Arthur Smith Institute for Urology;
North Shore University Hospital
New Hyde Park, New York;
Long Island Jewish Hospital
Manhasset, New York

Robert C. Shamberger, MD

Robert E. Gross Professor, Department of Surgery
Harvard Medical School;
Chief, Department of Surgery
Children's Hospital Boston
Boston, Massachusetts

Ellen Shapiro, MD

Professor, Department of Urology
New York University School of Medicine;
Director, Pediatric Urology
NYU Langone Medical Center
New York, New York

David S. Sharp, MD

Assistant Professor, Department of Urology
Ohio State University Medical Center;
Attending Physician, Department of Urology
James Cancer Hospital and Solove Research Institute
Columbus, Ohio

Joel Sheinfeld, MD

Professor, Department of Urology
Weill Cornell Medical College;
Deputy Chief, Department of Urology
Memorial Sloan-Kettering Cancer Center
New York, New York

Linda Marie Dairiki Shortliffe, MD

Stanley McCormick Memorial Professor and Chair of Urology
Department of Urology
Stanford University School of Medicine;
Chief, Department of Urology
Stanford University Medical Center;
Chief, Pediatric Urology
Lucile Salter Packard Children's Hospital
Stanford, California

Daniel A. Shoskes, MD, MSc, FRCSC

Professor, Department of Urology
Cleveland Clinic Lerner College of Medicine at Case Western Reserve University;
Director, Novick Center for Clinical and Translational Research
Glickman Urological and Kidney Institute
Cleveland Clinic
Cleveland, Ohio

Jennifer D.Y. Sihoe, MD

Honorary Clinical Assistant Professor
Department of Surgery
The Chinese University of Hong Kong;
Associate Consultant
Divisions of Pediatric Surgery and Pediatric Urology
Prince of Wales Hospital
Hong Kong

Iqbal Singh, MCh (Urology), DNB (Genitourinary Surgery), MS, DNB

Professor of Urology
Department of Surgery
University of Delhi College of Medical Sciences;
Senior Consultant Urologist
Department of Surgery
UCMS and Guru Teg Bahadur Hospital
Delhi, India;
Formerly Clinical Instructor (Fellow)
Department of Urology
Wake Forest University School of Medicine and WFUMC and Baptist Medical Center
Winston-Salem, North Carolina

Donald G. Skinner, MD

Professor and Chair *(Retired)*
Department of Urology
Keck School of Medicine
University of Southern California;
USC Norris Comprehensive Cancer Center
Los Angeles, California

Eila C. Skinner, MD

Professor of Clinical Urology
Department of Urology
Keck School of Medicine
University of Southern California;
Attending Physician, Department of Urology
USC University Hospital and Norris Comprehensive Cancer Center
LAC + USC Medical Center
Los Angeles, California

Joseph A. Smith, Jr., MD

Professor and Chairman, Department of Urologic Surgery
Vanderbilt University Medical Center
Nashville, Tennessee

Warren T. Snodgrass, MD

Professor, Department of Urology
University of Texas Southwestern Medical Center;
Chief, Pediatric Urology
Children's Medical Center Dallas
Dallas, Texas

Graham Sommer, MD

Professor of Radiology
Division of Diagnostic Radiology
Stanford University School of Medicine
Stanford, California

Ramaprasad Srinivasan, MD, PhD

Senior Staff Clinician, Department of Urologic Oncology
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Joph Steckel, MD, FACS

Department of Urology
North Shore - LIJ Health System
New Hyde Park, New York;
Vice Chairman, Department of Urology
North Shore University Hospital
Manhasset, New York

[†]John P. Stein, MD

Associate Professor, Department of Urology
Keck School of Medicine
University of Southern California;
USC Norris Comprehensive Cancer Center
Los Angeles, California

Andrew J. Stephenson, MD, FACS, FRCSC

Associate Professor, Department of Urology
Cleveland Clinic Lerner College of Medicine at Case Western Reserve University;
Director, Center for Urologic Oncology
Glickman Urological and Kidney Institute
Cleveland Clinic
Cleveland, Ohio

Cora N. Sternberg, MD, FACP

Chief, Department of Medical Oncology
San Camillo Forlanini Hospital
Rome, Italy

Jack W. Strandhoy, PhD

Professor, Deparment of Physiology and Pharmacology
Wake Forest University School of Medicine
Winston-Salem, North Carolina

Li-Ming Su, MD

David A. Cofrin Professor of Urology
Associate Chairman of Clinical Affairs
Department of Urology
University of Florida College of Medicine
Gainesville, Florida

[†]Deceased.

Stasa D. Tadic, MD, MS

Assistant Professor, Department of Medicine
Division of Geriatric Medicine and Gerontology
University of Pittsburgh School of Medicine;
Attending Physician, Department of Medicine
Division of Geriatric Medicine and Gerontology
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

Ian M. Thompson, Jr., MD

Director, Cancer Therapy and Research Center
Professor, Department of Urology
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Joanna Maya Togami, MD

Clinical Assistant Professor, Department of Urology
Louisiana State University School of Medicine;
Senior Staff Urologist, Department of Urology
Ochsner Medical Center
New Orleans, Louisiana

Edouard J. Trabulsi, MD, FACS

Associate Professor, Department of Surgery
Jefferson Medical College at Thomas Jefferson University;
Associate Professor, Department of Urology
Co-Director, Jefferson Prostate Diagnostic Center
Kimmel Cancer Center
Thomas Jefferson University Hospital
Philadelphia, Pennsylvania

Howard Trachtman, MD

Professor, Department of Pediatrics
Albert Einstein College of Medicine
Bronx, New York;
Chief, Division of Nephrology
Department of Pediatrics
Cohen Children's Medical Center of New York
New Hyde Park, New York;
Investigator
Feinstein Institute for Medical Research
Manhasset, New York

Paul J. Turek, MD, FACS, FRSM

Director, The Turek Clinic;
Attending Physician, Department of Urology
California Pacific Medical Center;
Founder, Clinic by the Bay Volunteer Medical Clinic
San Francisco, California

Robert G. Uzzo, MD

G. Willing Pepper Chair, Department of Surgery
Professor of Urologic Oncology
Department of Surgical Oncology
Fox Chase Cancer Center
Philadelphia, Pennsylvania

Sandip P. Vasavada, MD

Associate Professor of Surgery (Urology)
Cleveland Clinic Lerner College of Medicine at Case Western Reserve University;
Center for Female Pelvic Medicine and Genitourinary Reconstructive Surgery
Glickman Urological and Kidney Institute
Cleveland Clinic
Cleveland, Ohio

Robert W. Veltri, PhD

Associate Professor, Departments of Urology and Oncology
Johns Hopkins School of Medicine;
James Buchanan Brady Urological Institute
Johns Hopkins Medical Institutions
Baltimore, Maryland

Manish A. Vira, MD

Assitant Professor, Department of Urology
Hofstra University School of Medicine
New York, New York

Patrick C. Walsh, MD

University Distinguished Service Professor of Urology
Department of Urology
Johns Hopkins University School of Medicine;
James Buchanan Brady Urological Institute
John Hopkins Medical Institutions;
Department of Urology
Johns Hopkins Hospital
Baltimore, Maryland

Thomas J. Walsh, MD, MS

Assistant Professor, Department of Urology
University of Washington School of Medicine
Seattle, Washington

Alan J. Wein, MD, PhD (Hon), FACS

Founders Professor of Urology
Perelman School of Medicine
University of Pennsylvania;
Chief of Urology
Penn Medicine/University of Pennsylvania Health System
Perelman Center for Advanced Medicine
Philadelphia, Pennsylvania

Robert M. Weiss, MD

Donald Gutherie Professor, Department of Surgery
Division of Urology
Yale University School of Medicine;
Chief, Division of Urology
Department of Surgery
Yale-New Haven Hospital
New Haven, Connecticut

Hunter Wessells, MD, FACS

Professor and Nelson Chair, Department of Urology
University of Washington School of Medicine
Seattle, Washington

Wesley M. White, MD

Director, Laparoscopic and Robotic Urologic Surgery
Department of Urology
The University of Tennessee Medical Center, Knoxville
Knoxville, Tennessee

Jack Christian Winters, MD

Chairman, Department of Urology
H. Eustis Reilly Professor of Urology and Gynecology
Louisiana State University School of Medicine;
Fellowship Director, Female Pelvic Medicine and Reconstructive Surgery
Department of Urology and Gynecology
Louisiana State University Health Sciences Center
New Orleans, Louisiana

J. Stuart Wolf, Jr., MD, FACS

The David A. Bloom Professor of Urology
Director, Division of Endourology
Department of Urology
University of Michigan Health System
Ann Arbor, Michigan

Christopher G. Wood, MD

Professor and Deputy Chairman
Department of Urology
The University of Texas MD Anderson Cancer Center
Houston, Texas

David P. Wood, Jr., MD

The George F. and Sandra G. Valassis Professor of Urology
University of Michigan Medical School;
Chief, Urologic Oncology
Department of Urology
University of Michigan Hospital
Ann Arbor, Michigan

John R. Woodard, MD

Clinical Professor of Urology *(Retired)*
Director, Pediatric Urology *(Retired)*
Emory University School of Medicine;
Chief of Urology *(Retired)*
Henrietta Egleston Hospital for Children
Atlanta, Georgia

Chad Wotkowicz, MD

Senior Staff, Department of Urology
Lahey Clinic
Burlington, Massachusetts

Subbarao V. Yalla, MD

Professor of Surgery (Urology)
Harvard Medical School;
Urologist, Surgical Service
Brigham and Women's Hospital
VA Boston Healthcare System
Boston, Massachusetts;
Urologist, Surgical Service
Togus VA Medical Center
Augusta, Maine

C.K. Yeung, MD

Honorary Clinical Professor in Paediatric Surgery & Paediatric Urology
Chinese University of Hong Kong;
Chief of Paediatric Surgery & Paediatric Urology
Union Hospital
Hong Kong

Naoki Yoshimura, MD, PhD

Professor, Department of Urology
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Richard N. Yu, MD, PhD

Instructor in Surgery (Urology)
Harvard Medical School;
Department of Urology
Children's Hospital Boston
Boston, Massachusetts

Preface

The editors are proud and pleased to present the tenth edition of the acknowledged standard textbook of urology, now titled *Campbell-Walsh Urology*. The field of urology continues to evolve, constantly adding new material on basic physiology and pharmacology, epidemiology and pathophysiology, medical and surgical management, and ever-increasing sophistication in the methodology of the evaluation and conclusions drawn from retrospective and prospective outcome studies. This applies to virtually every area included under the urology umbrella, but with the proviso that little of the "classic" knowledge or techniques is ever totally discarded, as opposed to being modified or augmented. With this in mind, our goal was to put together, in a logical order, a series of comprehensive mini-texts on every major subject in the field while keeping within a four-volume framework. We have added 14 new chapters, 5 of which are the result of combining the subject matter of 2 separate existing chapters in the ninth edition, and added 70 new "best and brightest" authors, resulting in extensive revisions of many chapters, all as an attempt to provide the most contemporary information possible in an organized sequential format.

We have continued with the use of extensive boldface and Key Points boxes for special emphasis points. All tables and most figures and diagrams are in color. The text is fully accessible online for owners and contains an extensive video library. The book includes an Expert Consult website, which will provide semi-annual updates/reviews for each area of interest and allow you to access and perform rapid searches on the entire content of the book, with references linked to PubMed abstracts.

Volume 1 covers surgical anatomy; the essentials of clinical decision making, including a chapter on outcomes research; the basics of perioperative care, instrumentation, endoscopy, laparoscopy, and robotics; infection, inflammation, and pelvic pain; the fundamentals of molecular, cellular, and cancer biology and regenerative medicine; male reproductive function and dysfunction; sexual function and dysfunction in men and women; and benign and malignant diseases of the male genitalia, including cancers of the testis, penis, and urethra.

Volume 2 begins with renal physiology and pathophysiology, including renal hypertension and nephropathy secondary to various causes, including ischemia and obstruction. Upper urinary tract trauma constitutes a separate chapter, followed by a section on renal failure and transplantation. Urolithiasis—its pathophysiology, medical endourologic management, and surgical management—follows. The section on upper urinary tract neoplasms includes benign and malignant renal parenchymal tumors with management by observation, open and laparoscopic/robotic surgery, and ablative therapy, and urothelial tumors, including management by endoscopic, laparoscopic/robotic, and open surgery. A new chapter on retroperitoneal tumors is included. The volume ends with a consideration of adrenal physiology and pathophysiology, including benign and malignant disorders, and surgical considerations.

Volume 3 begins with a 21-chapter mini-text on lower urinary tract physiology, pharmacology, function, and dysfunction, including renal, pelvic, and ureteral transport. All aspects of evaluation, conservative and surgical therapy of urinary incontinence, pelvic floor prolapse, and other abnormalities of lower tract filling/storage and emptying are considered. There are separate stand-alone chapters on urodynamics and video-urodynamics, neuromuscular dysfunction, overactive bladder, nocturia (new chapter), electrical stimulation, drug therapy, prolapse repair, all types of sling tape and sphincter surgery for urinary incontinence, fistulae, diverticula, and special considerations in the elderly. Evaluation and management of bladder tumors, including laparoscopic and robotic applications, are the subject of 5 chapters, followed by 3 on the various types of urinary diversion procedures. Sections on genital and lower urinary tract trauma and lower urinary tract calculi follow, and the volume concludes with 21 chapters covering prostatic development and physiology, and benign and malignant diseases of the prostate. All management modalities for obstructive benign prostatic hyperplasia and for prostatic cancer are presented in detail in updated and totally new chapters.

Volume 4 remains a 28-chapter, 800-page updated textbook of pediatric urology with new chapters on renal functional development and its abnormalities, perioperative management, the extrophy–epispadias complex, pediatric stone disease, and renal transplantation.

The companion study guide for the tenth edition has been extensively redone and improved, including format, questions, answers, and explanations, under the leadership of W. Scott McDougal, MD, MA (Hon), a former head of the American Urological Association Examination Committee.

All of us remain proud and grateful to be a part of the continuing tradition of excellence of this textbook, and we wish to express our gratitude to the superb job done by all authors and to the outstanding staff at Elsevier who facilitated the organization and efforts necessary to bring this tenth edition to publication. In particular, Rebecca Gaertner, Senior Acquisitions Editor; Kristina Oberle, Senior Developmental Editor; Stefanie Jewell-Thomas, Acquisitions Editor; Kristine Feeherty, Senior Project Manager; and Jennifer Shreiner, Senior Developmental Editor.

Alan J. Wein, MD, PhD (Hon), FACS
On behalf of the editors

chapter 1

Surgical Anatomy of the Retroperitoneum, Adrenals, Kidneys, and Ureters

James Kyle Anderson, MD ● Jeffrey A. Cadeddu, MD

Retroperitoneum
Adrenal Glands
Kidneys
Ureters

There is no greater aid to surgical expertise than an intimate knowledge of anatomy. For the urologist, the areas of greatest importance are the retroperitoneum and pelvis. In this chapter, retroperitoneal structures important to the practice of urologic surgery are described in detail and clinical correlations are provided where helpful.

RETROPERITONEUM

The retroperitoneum is bounded posteriorly by the abdominal wall, which consists of the lumbodorsal fascia and the enclosed sacrospinalis and quadratus lumborum muscles (Fig. 1–1). Laterally, the retroperitoneum is contiguous with the preperitoneal fat and is bounded laterally by the transversus abdominis musculature of the lateral abdominal wall. The peritoneum is the anterior limit, whereas cranially the diaphragm (Fig. 1–2) limits the retroperitoneum. Caudally the retroperitoneum is contiguous with the extraperitoneal pelvic structures.

Posterior Abdominal Wall

Posterior Musculature and Lumbodorsal Fascia

See Figures 1–3 to 1–6 and Table 1–1. The lumbodorsal fascia surrounds the sacrospinalis and quadratus lumborum, which together comprise the posterior abdominal wall. The lumbodorsal fascia originates from the spinous processes of the lumbar vertebrae and extends anteriorly and cranially. As it progresses upward, it separates into three layers: posterior, middle, and anterior.

The posterior layer provides the posterior covering for the sacrospinalis muscle and is the origin of the latissimus dorsi muscle. The middle layer forms the fascial layer separating the anterior aspect of the sacrospinalis muscle from the posterior aspect of the quadratus lumborum. The anterior layer of the lumbodorsal fascia provides the anterior covering to the quadratus lumborum muscle and forms the posterior margin of the retroperitoneum. As one moves laterally away from the sacrospinalis and quadratus lumborum muscles, the lumbodorsal fascial layers fuse together and then connect with the transversus abdominis muscle.

The quadratus lumborum and sacrospinalis muscles (see Figs. 1–6 and 1–7) **form the muscular portion of the posterior abdominal wall, filling the space among the 12th rib, spine, and iliac crest.** The quadratus lumborum serves a number of functions. It supports the 12th rib, thus improving diaphragmatic contraction and inspiration, as well as aiding intercostal muscle function during forced expiration. Finally, it controls lateral bending of the trunk. The sacrospinalis also controls movement of the trunk by promoting extension of the spine. These muscular and fascial relationships become important clinically when performing a **dorsal lumbotomy incision.** As seen in Figure 1–7, this is a vertical incision lateral to the border of the sacrospinalis and quadratus lumborum. This approach

Key Points: Retroperitoneum

- The three layers of the lumbodorsal fascia cover the musculature of the posterior abdominal wall.
- The lower ribs are in intimate contact with the kidneys and adrenal glands. Injury to the lower ribs suggests injury to retroperitoneal structures.
- The renal artery lies posterior to the renal vein, but this relationship is reversed when the aorta and inferior vena cava divide into the common iliac vessels. Here, the common iliac arteries are anterior to the common iliac veins.
- As lymphatic drainage moves within the retroperitoneum from caudal to cranial there is also a predominantly right-to-left flow.
- The nervous system is divided into the autonomic and somatic systems.
- The autonomic system is further divided into sympathetic and parasympathetic innervation. The sympathetics originate from the thoracic and lumbar vertebrae. From the sympathetic chain ganglia preganglionic fibers proceed to autonomic plexuses. From these plexuses postganglionic sympathetic fibers proceed to their targets. The parasympathetics originate from the cranial and sacral vertebrae and again synapse in peripheral plexuses before proceeding to their targets.
- The somatic system provides innervation to the retroperitoneum and lower extremities via the lumbosacral plexus.

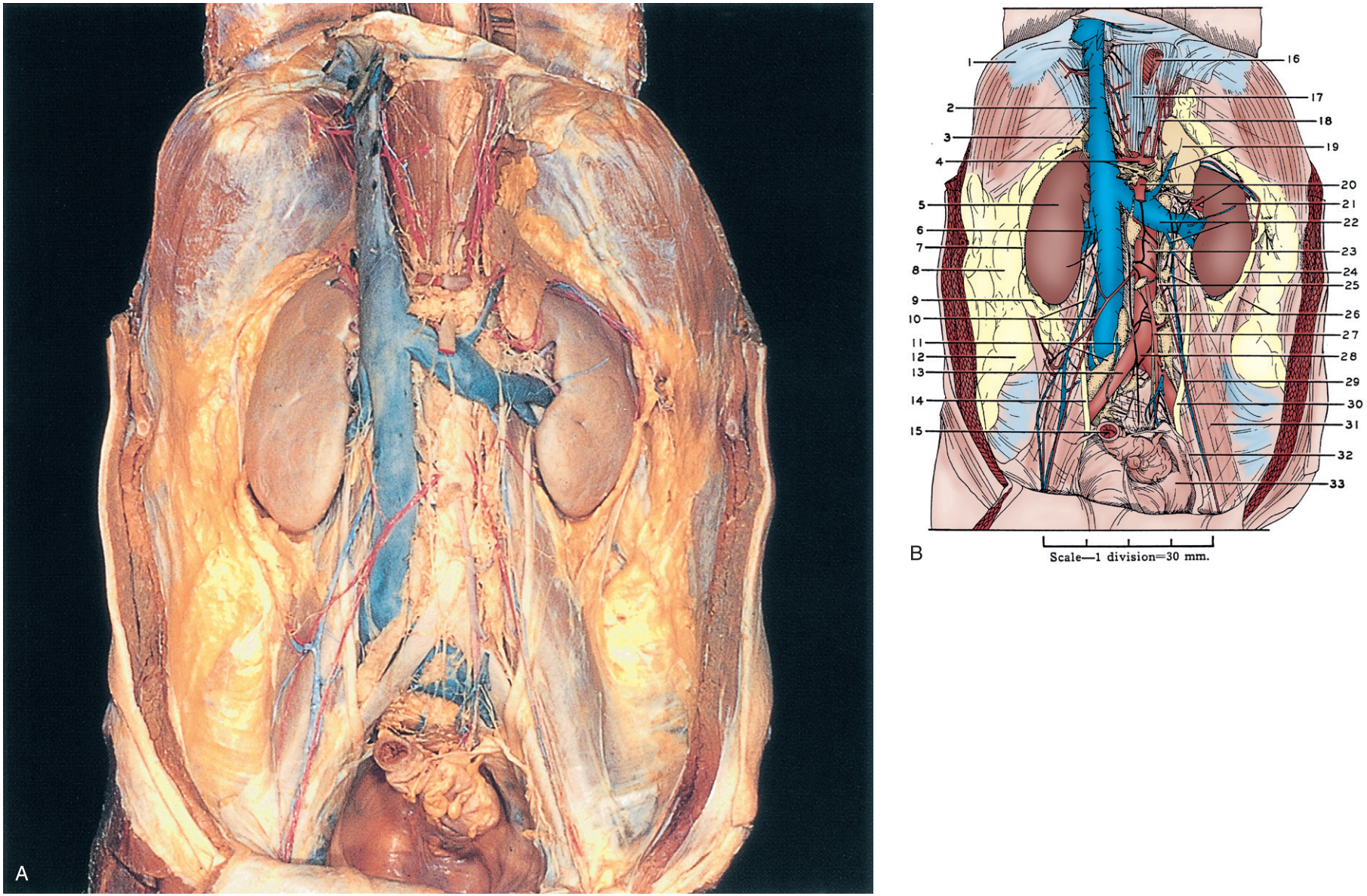
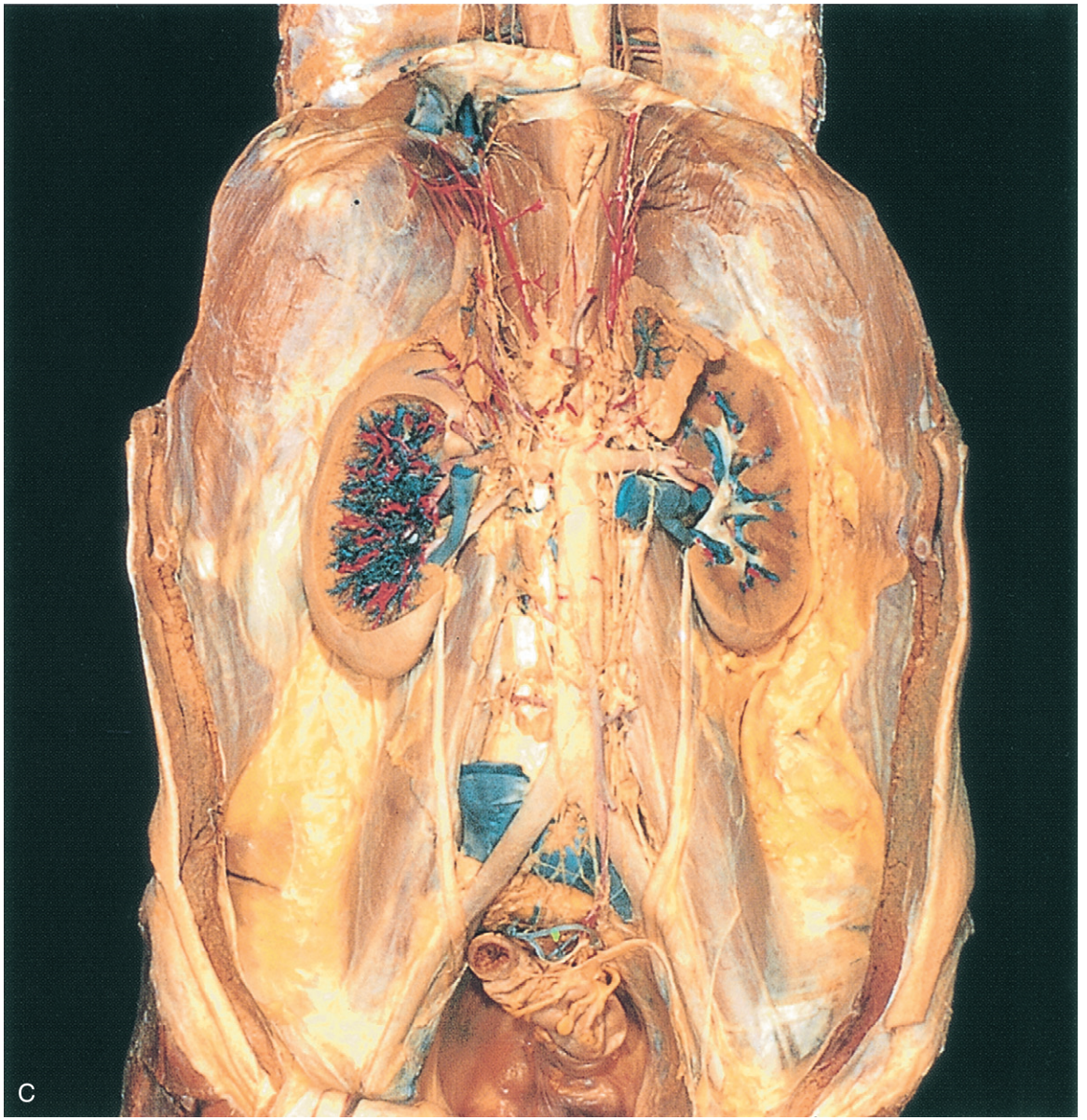


Figure 1–1. **A,** The retroperitoneum dissected. The anterior perirenal (Gerota) fascia has been removed. **B,** 1, Diaphragm. 2, Inferior vena cava. 3, Right adrenal gland. 4, *Upper pointer,* celiac artery; *lower pointer,* celiac autonomic nervous plexus. 5, Right kidney. 6, Right renal vein. 7, Gerota fascia. 8, Pararenal retroperitoneal fat. 9, Perinephric fat. 10, *Upper pointer,* right gonadal vein; *lower pointer,* right gonadal artery. 11, Lumbar lymph nodes. 12, Retroperitoneal fat. 13, Right common iliac artery. 14, Right ureter. 15, Sigmoid colon (cut). 16, Esophagus (cut). 17, Right crus of diaphragm. 18, Left inferior phrenic artery. 19, *Upper pointer,* left adrenal gland; *lower pointer,* left adrenal vein. 20, *Upper pointer,* superior mesenteric artery; *lower pointer,* left renal artery. 21, Left kidney. 22, *Upper pointer,* left renal vein; *lower pointer,* left gonadal vein. 23, Aorta. 24, Perinephric fat. 25, Aortic autonomic nervous plexus. 26, *Upper pointer,* Gerota fascia; *lower pointer,* inferior mesenteric ganglion. 27, Inferior mesenteric artery. 28, Aortic bifurcation into common iliac arteries. 29, Left gonadal artery and vein. 30, Left ureter. 31, Psoas major muscle covered by psoas sheath. 32, Cut edge of peritoneum. 33, Pelvic cavity.



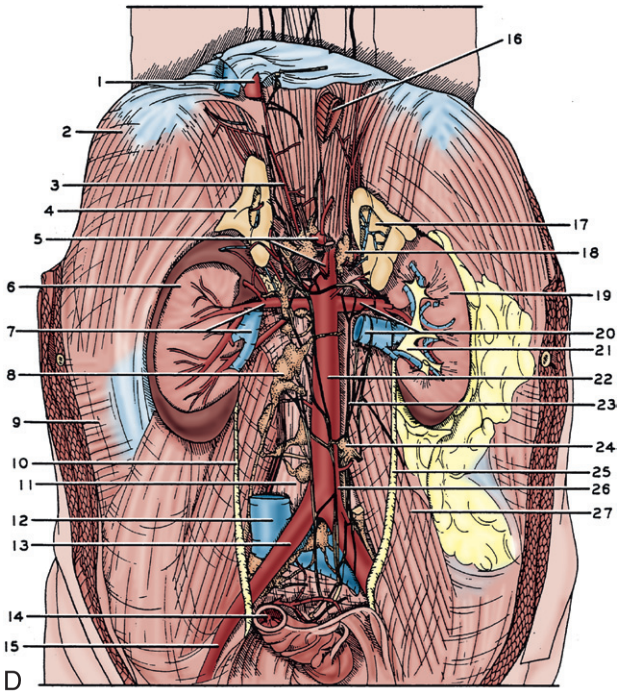


Figure 1–1, cont'd. **C,** The retroperitoneum dissected. The kidneys and adrenal glands have been sectioned, and the inferior vena cava has been excised over most of its intra-abdominal course. **D,** 1, Inferior vena cava (cut). 2, Diaphragm. 3, Right inferior phrenic artery. 4, Right adrenal gland. 5, *Upper pointer,* celiac artery; *lower pointer,* superior mesenteric artery. 6, Right kidney. 7, *Upper pointer,* right renal artery; *lower pointer,* right renal vein (cut). 8, Lumbar lymph node. 9, Transversus abdominis muscle covered with transversalis fascia. 10, Right ureter. 11, Anterior spinous ligament. 12, Inferior vena cava (cut). 13, Right common iliac artery. 14, Sigmoid colon (cut). 15, Right external iliac artery. 16, Esophagus (cut). 17, Left adrenal gland. 18, Celiac ganglion. 19, Left kidney. 20, *Upper pointer,* left renal artery; *lower pointer,* left renal vein (cut). 21, Left renal pelvis. 22, Aorta. 23, Aortic autonomic nervous plexus. 24, Inferior mesenteric ganglion. 25, Left ureter. 26, Inferior mesenteric artery. 27, Psoas major muscle covered by psoas sheath. (**A** to **D,** Reproduced from the Bassett anatomic collection, with permission granted by Dr. Robert A. Chase.)

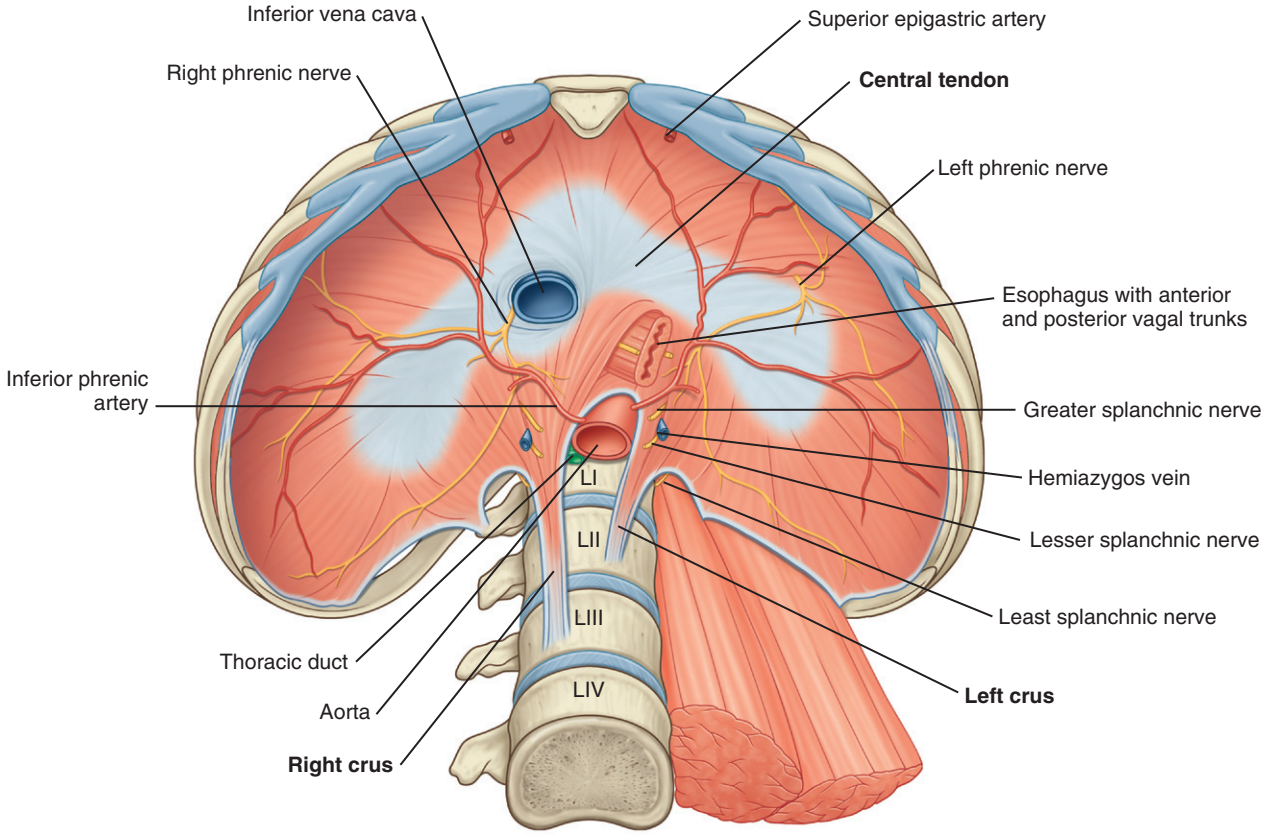


Figure 1–2. The diaphragm: abdominal surface. (From Drake RL, Vogl W, Mitchell AWM. Gray's anatomy for students. Philadelphia: Elsevier; 2005. p. 317.)

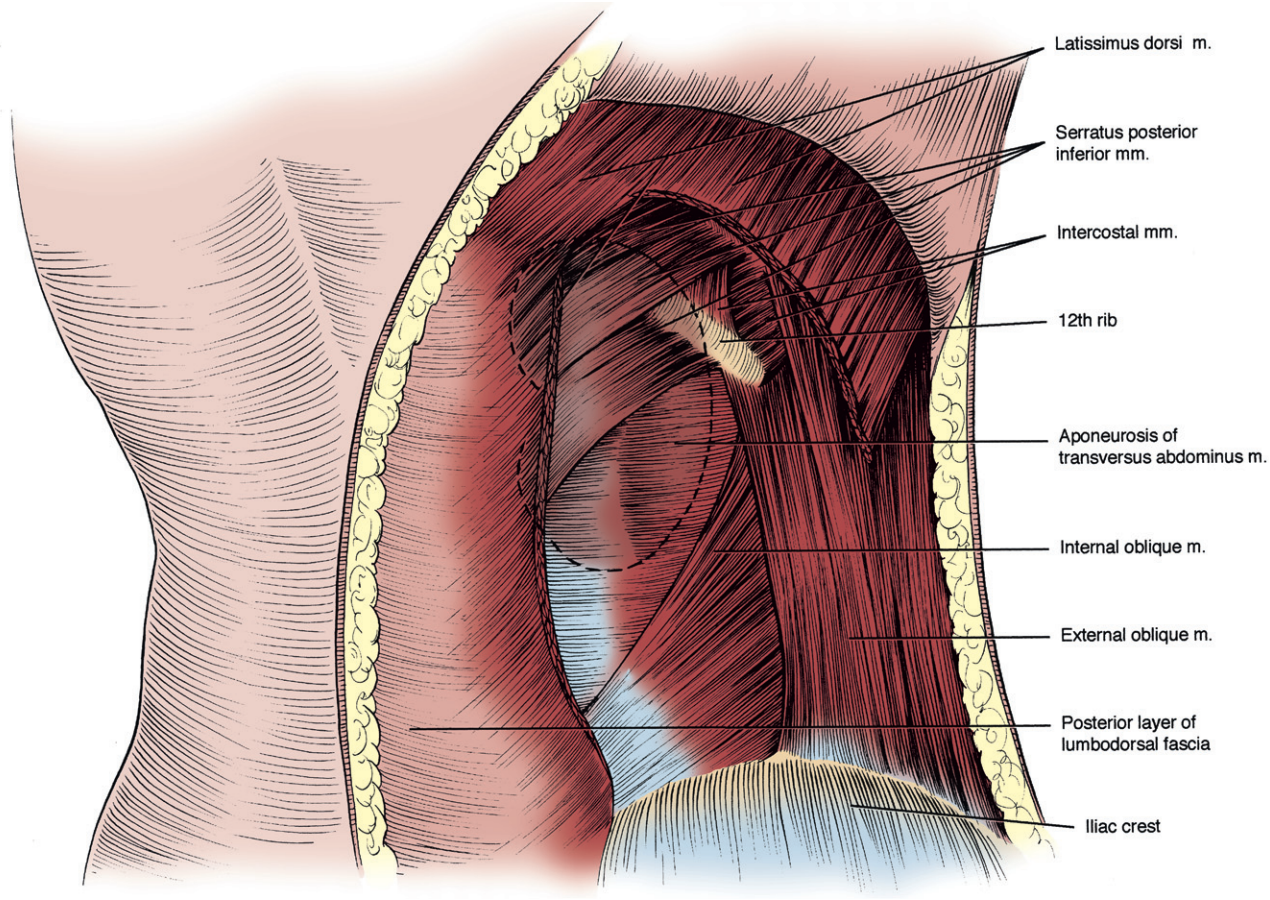


Figure 1–3. Posterior abdominal wall musculature, superficial dissection. A section of the latissimus dorsi muscle has been removed. The location of the right kidney within the retroperitoneum is shown by *dashed outline*.

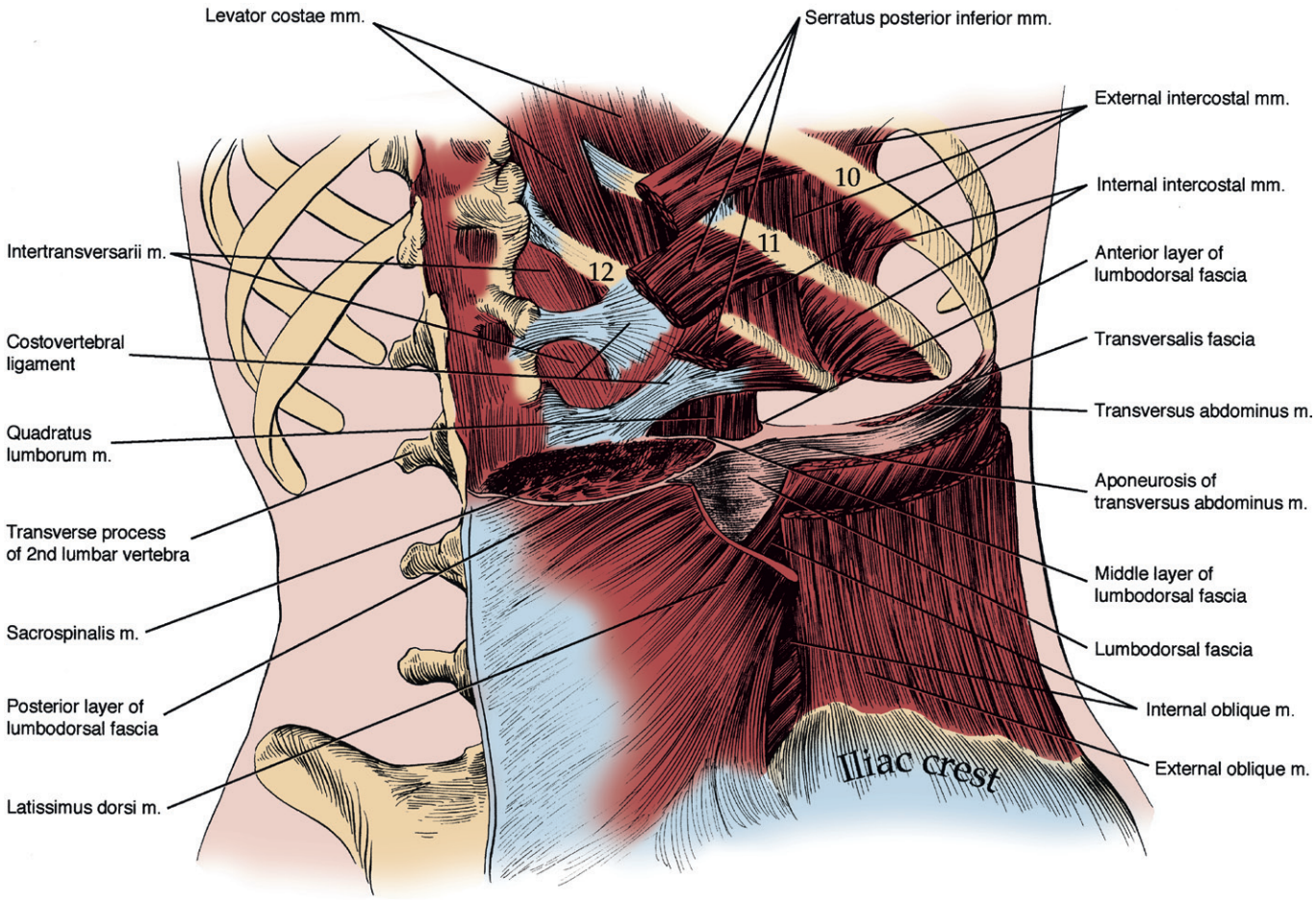


Figure 1–4. Posterior abdominal wall musculature, intermediate dissection. The sacrospinalis muscle and three anterolateral flank muscle layers are seen in cut section, and the three layers of the lumbodorsal fascia posteriorly can be appreciated.

allows entrance to the retroperitoneum without violation of the musculature.

Lateral Flank Musculature

See Figure 1–8 and Table 1–1. Three muscular layers comprise the lateral flank musculature. From superficial to internal, these are the external oblique, internal oblique, and transversus abdominis muscles. The most superficial structure is the external oblique muscle. This muscle arises from the lower ribs and moves from lateral to medial as it progresses caudally. Final attachment is to the iliac crest caudally and the rectus sheath anteriorly. The posterior border remains free as it terminates before reaching the lumbodorsal fascia. Next is the internal oblique muscle. Again, this muscle arises from the lower rib cage, but the orientation of the fibers is from medial to lateral as they move caudally. Final attachment is to the iliac crest and lumbodorsal fascia. The final structures are the transversus abdominis muscle and transversalis fascia. The transversus abdominis muscle arises from the lumbodorsal fascia with fibers running directly transversely until it attaches anteriorly and medially onto the rectus sheath. Immediately deep to the transversus abdominis muscle is the transversalis fascia and then the retroperitoneal space. The function of the lateral flank musculature is to compress and stabilize the abdomen and trunk. This provides controlled movement and protection for the abdominal organs.

Psoas and Iliacus Muscles

The psoas major muscle originates on the 12th thoracic through the 5th lumbar vertebrae (see Fig. 1–6). A smaller psoas minor is identifiable in about one half of the population and resides medial to the psoas major. The psoas muscle(s) is covered by the psoas fascia. In close proximity to the psoas muscle is the iliacus muscle, which attaches to the inner aspect of the iliac pelvic wing. As the iliacus progresses caudally it joins with the psoas muscle to form the iliopsoas muscle. This combined muscle then joins to the lesser trochanter of the femur and controls flexion of the hip.

Lower Rib Cage

See Figure 1–9. In addition to the protection provided by the muscular layers of the posterior and lateral abdominal wall, **the 10th, 11th, and 12th ribs safeguard the upper retroperitoneal space and are intimately related to the adrenal glands and kidneys. Given the close proximity, injury to these ribs can be associated with significant retroperitoneal injury.** While providing protection, the lower ribs and the accompanying pleura and lung limit surgical exposure to the upper retroperitoneum. The limits of the pleura are the 8th rib anteriorly, the 10th rib in the midaxillary line, and the 12th rib posteriorly. Given this location of the pleura, flank incisions at or above the 11th or 12th ribs risk pleural violation.

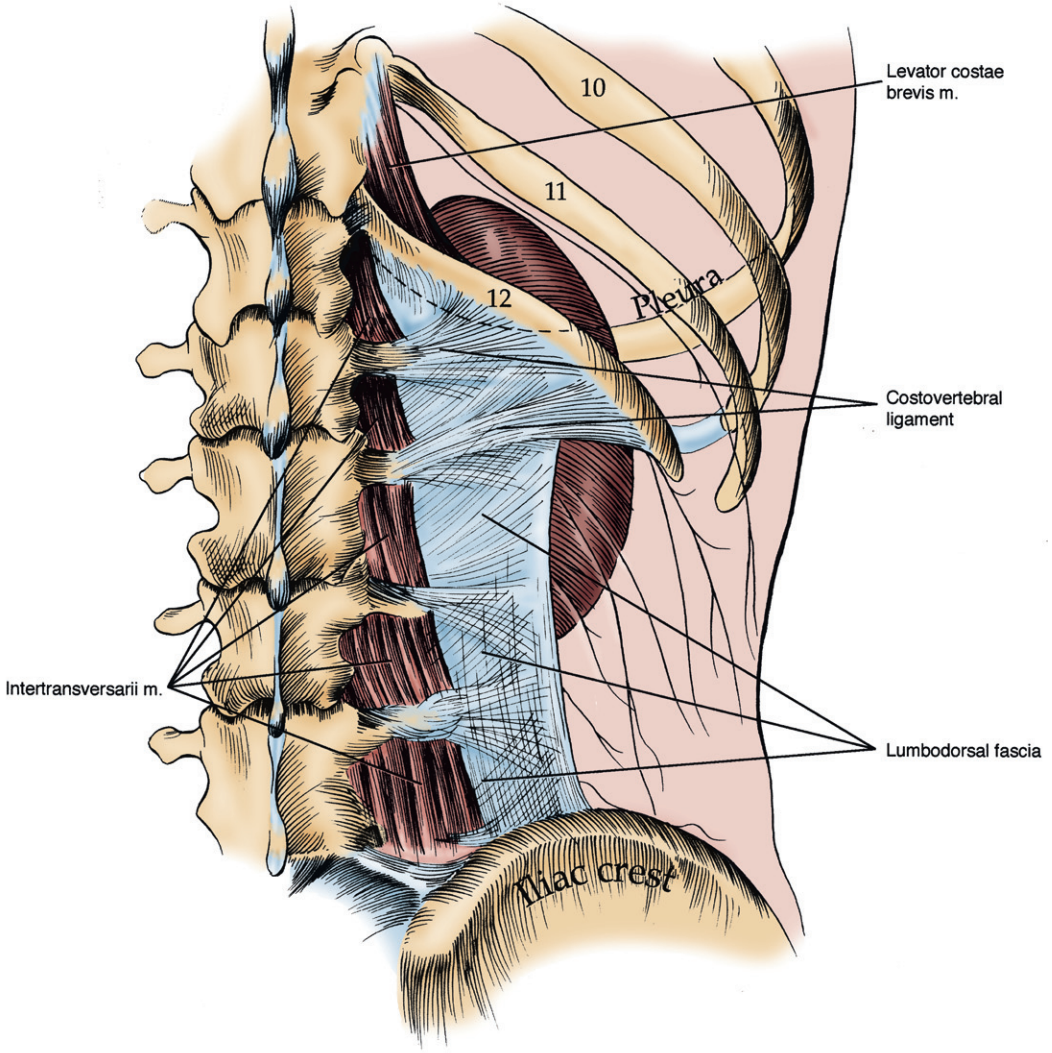


Figure 1–5. Posterior abdominal wall musculature, deep dissection. The lumbodorsal fascia and costovertebral ligament are visualized, arising from the transverse processes of the lumbar vertebrae. The relation of the kidney and pleura is also shown.

Great Vessels

The abdominal aorta and inferior vena cava are the great vessels of the abdomen, providing vascular supply to the abdominal organs and lower extremities (Figs. 1–10 and 1–11).

Abdominal Aorta

The aorta enters the abdomen via the aortic hiatus found between the diaphragmatic crura in the posterior diaphragm at the level of the 12th thoracic vertebrae (see Fig. 1–2). It continues caudally to the 4th lumbar vertebrae, where it bifurcates into the common iliac arteries. During its course through the abdomen the aorta gives off a number of large branches (Table 1–2). **The paired inferior phrenic arteries are first.** They supply the inferior diaphragm and the superior portion of the adrenal gland (see Fig. 1–2). **Next is the celiac trunk, which is the origin for the common hepatic, left gastric, and splenic arteries that supply the liver, stomach, and spleen, respectively. The paired adrenal arteries follow with an artery going to each adrenal gland. The superior mesenteric artery leaves the aorta on the anterior side and supplies the entire small intestine and majority of the large intestine.** Also of note, this artery communicates with the celiac trunk vasculature via the pancreaticoduodenal artery. Overlying the 2nd lumbar vertebrae, the paired renal arteries are the next branching point of the aorta. To the urologist, renal artery anatomy is obviously of great importance and is discussed in detail in the kidney section.

Moving distally on the aorta, the paired gonadal arteries are encountered. In the male this artery is also called the *testicular artery* and in the female it is the *ovarian artery.* The initial course in both the male and female is similar, with the artery moving caudally and laterally from the aorta, with **the right gonadal artery crossing anterior to the inferior vena cava. In men, the gonadal artery then crosses over the ureter and exits the retroperitoneum at the internal inguinal ring. In women the course is different: Instead of exiting the pelvis, the artery crosses medially back over the external iliac vessels and enters the pelvis.** It then proceeds via the suspensory ligament to the ovary. The destination of the gonadal artery (the testis in the male and the ovary in the female) has significant collateral sources of arterial blood, from the deferential and cremasteric arteries in the male and the uterine artery in the female. Thus the gonadal artery can generally be ligated during retroperitoneal surgery without detrimental effect.

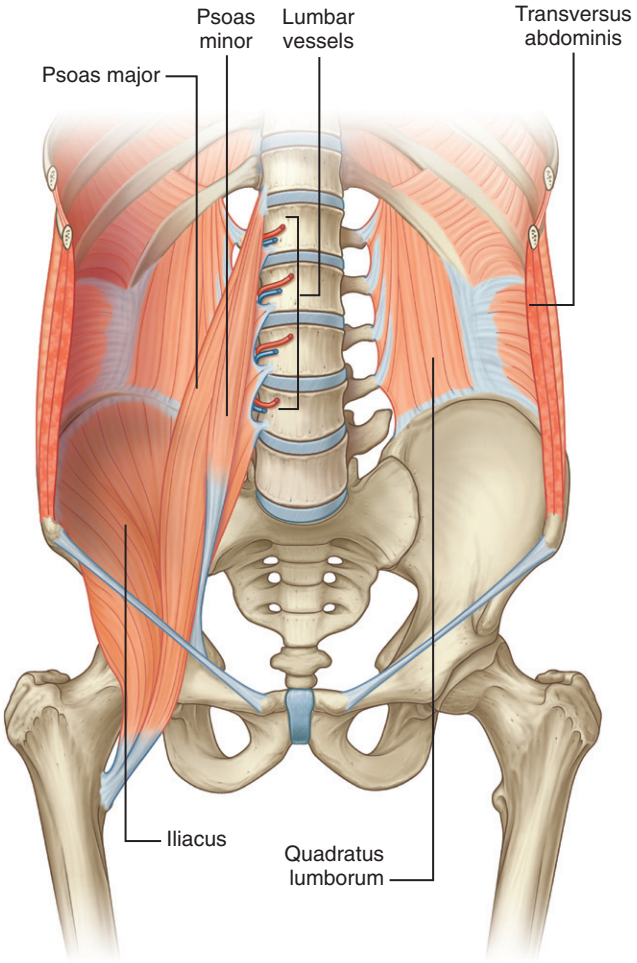


Figure 1–6. Muscles of the posterior abdominal wall. (From Drake RL, Vogl W, Mitchell AWM. Gray's anatomy for students. Philadelphia: Elsevier; 2005. p. 316.)

Table 1–1.

Musculature of the Posterior and Lateral Abdominal Wall

MUSCLE	ORIGIN	INSERTION	FUNCTION
Sacrospinalis	Sacrum and lumbar vertebrae	Lower ribs and thoracic vertebrae	Extension of the spine
Quadratus lumborum	5th lumbar vertebra	1st through 4th lumbar vertebrae, 12th rib	Depress and stabilize 12th rib, lateral bending of the trunk
External oblique	Lower eight ribs	Lateral lip of iliac crest, aponeurosis ending in midline raphe	Compress abdominal contents, flexion of the trunk
Internal oblique	Lumbodorsal fascia, iliac crest	Lower 4 ribs, aponeurosis ending in linea alba	Compress abdominal contents, flexion of the trunk
Transversus abdominis	Lumbodorsal fascia, medial lip of iliac crest	Aponeurosis ending in linea alba	Compress abdominal contents
Psoas	12th thoracic through 5th lumbar vertebrae	Lesser trochanter of femur	Flexion of the hip
Iliacus	Inner aspect of iliac pelvic wing	Lesser trochanter of femur	Flexion of the hip

Adapted from Drake RL, Vogl W, Mitchell AWM. Gray's anatomy for students. Philadelphia: Elsevier; 2005. p. 250, 316.

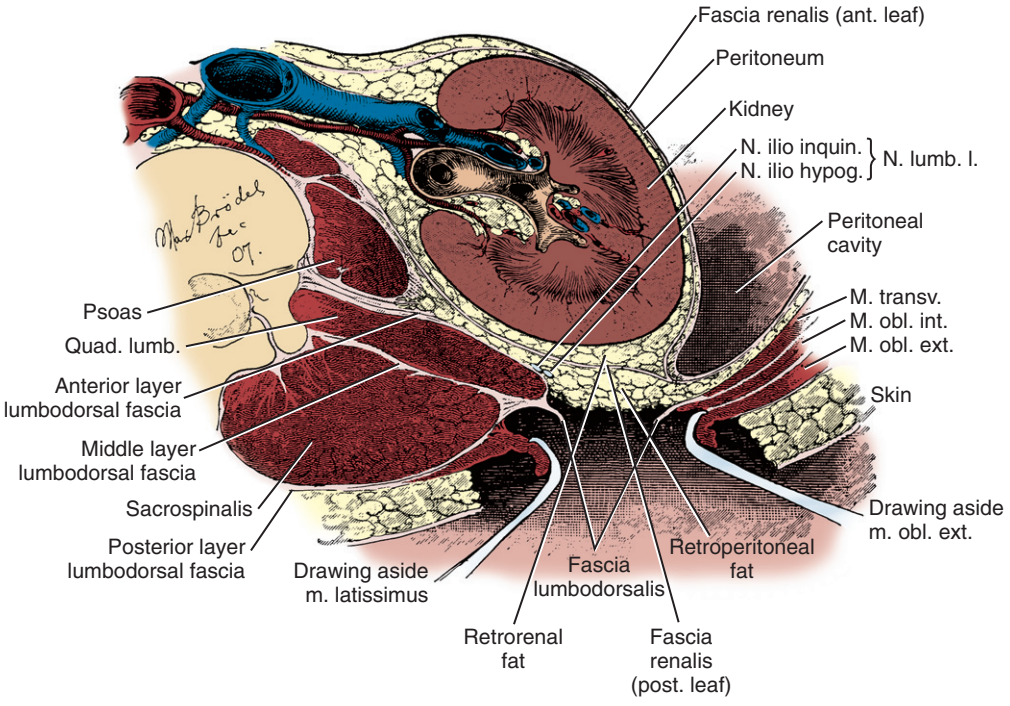


Figure 1–7. Transverse section through the kidney and posterior abdominal wall showing the lumbodorsal fascia incised. Note that through such a lumbodorsal incision, the kidney can be reached without incising muscle. (After Kelly and Burnam, from McVay C. Anson & McVay surgical anatomy. 6th ed. Philadelphia: WB Saunders; 1984.)

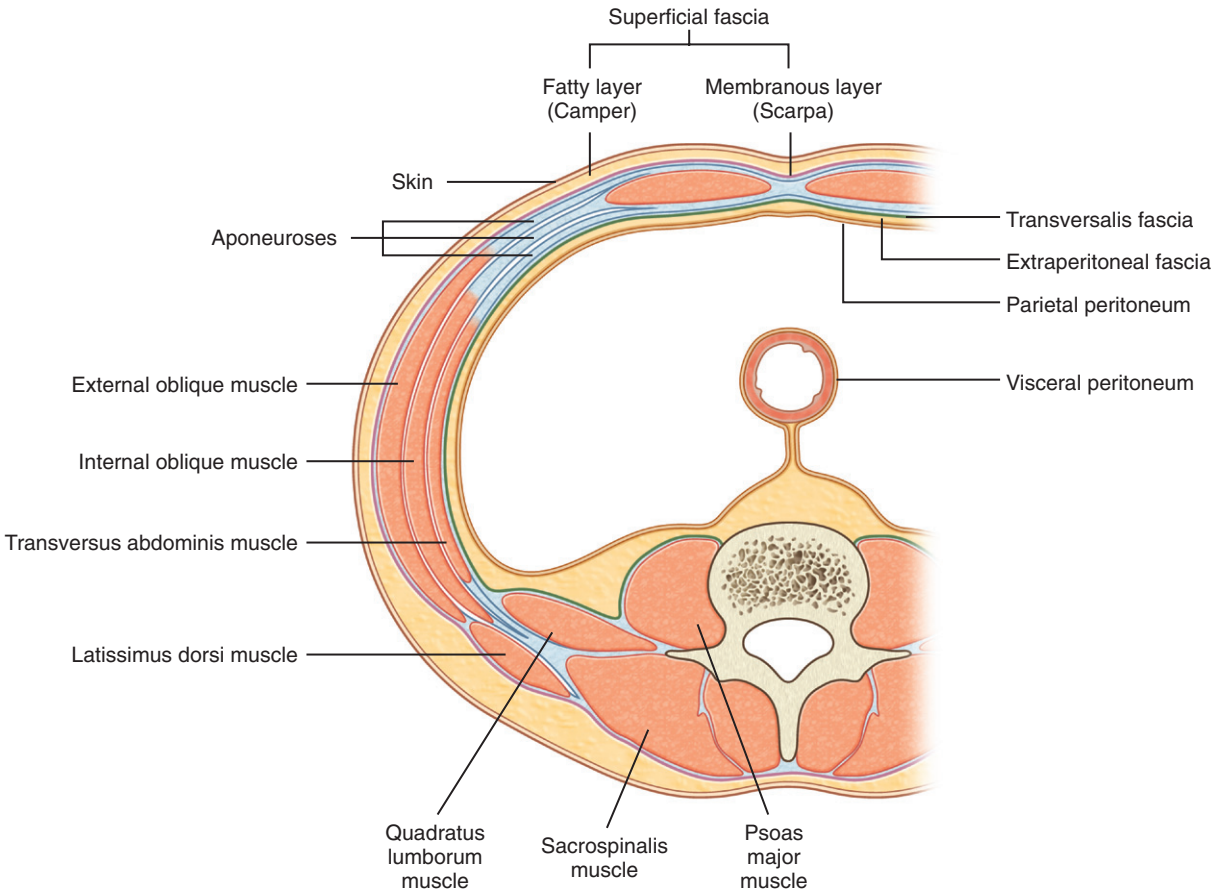


Figure 1–8. Transverse section showing layers of the lateral flank musculature. (From Drake RL, Vogl W, Mitchell AWM. Gray's anatomy for students. Philadelphia: Elsevier; 2005. p. 252.)

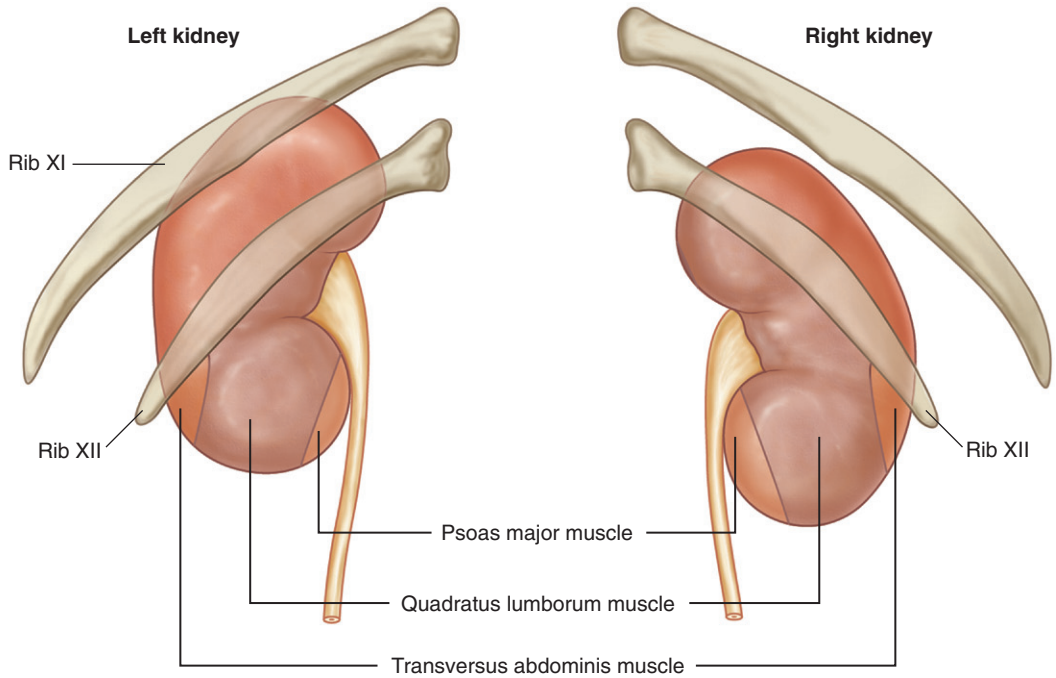


Figure 1–9. Structures related to the posterior surface of the kidney. (From Drake RL, Vogl W, Mitchell AWM. Gray's anatomy for students. Philadelphia: Elsevier; 2005. p. 322.)

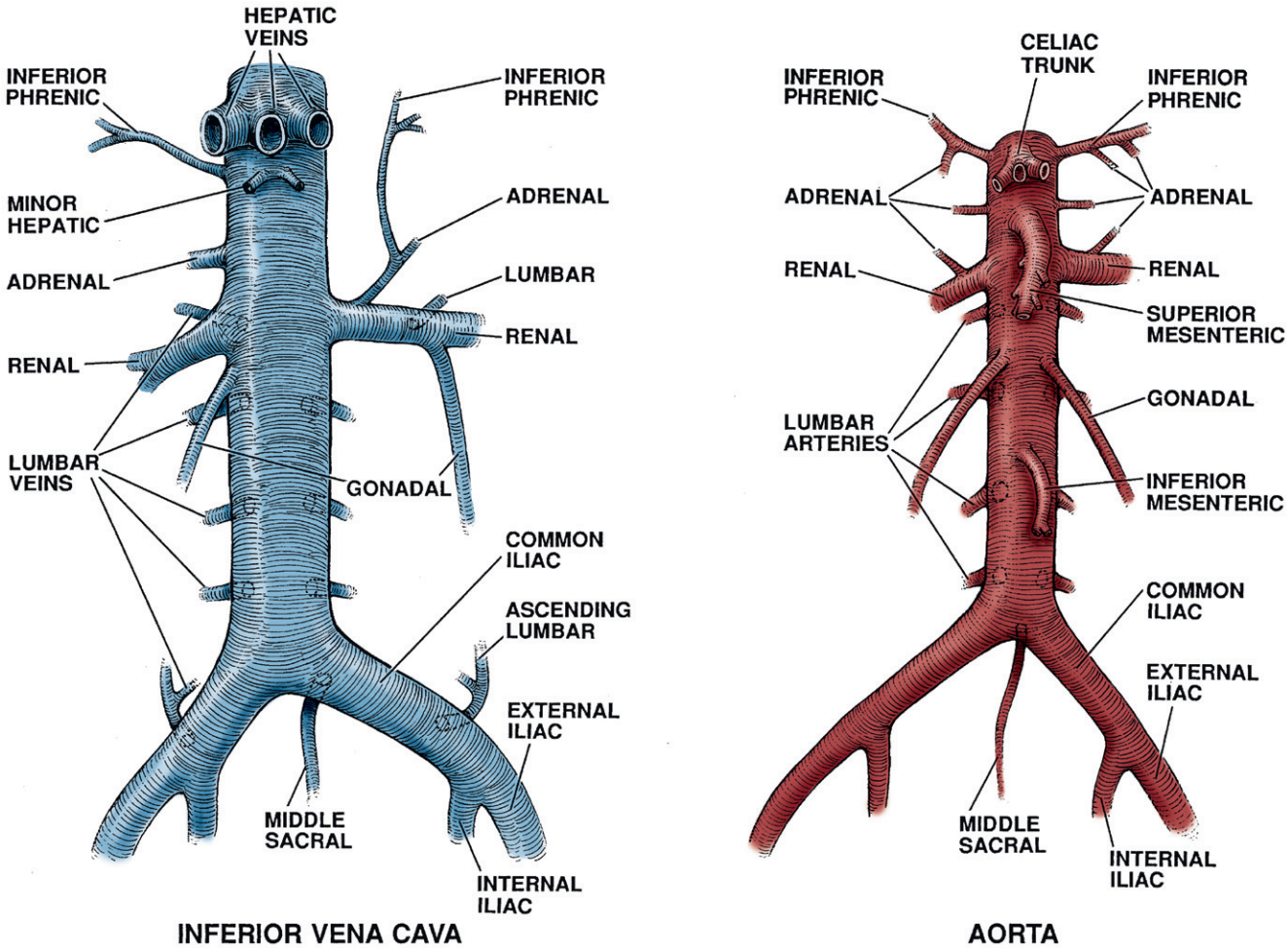


Figure 1–10. Inferior vena cava and abdominal aorta and their branches.

After the gonadal arteries, **the inferior mesenteric artery is found on the anterior side of the aorta before its bifurcation into the common iliac vessels.** This vessel provides vascular supply to the left third of the transverse colon, descending colon, sigmoid colon, and rectum. In patients without significant vascular disease, this artery can be sacrificed without ill effect because there is collateral circulation to these bowel segments from the superior mesenteric, middle hemorrhoidal, and inferior hemorrhoidal arteries.

In addition to the listed arteries that exit the aorta from its anterior or lateral aspect, there are a number of small branches from the posterior side of the aorta. **Lumbar arterial branches are found at regular intervals along the length of the aorta, with generally four pairs located within the retroperitoneum.** These branches supply the posterior body wall and spine. Again these arteries can generally be ligated without detrimental effects, although spinal ischemia and paralysis has occurred after ligation at multiple levels. **The final posterior branch from the aorta is the middle sacral artery,** which exits the aorta immediately before the branching of the common iliac arteries and then sends branches to the rectum and anterior sacrum. The common iliac arteries then proceed into the pelvis, thus completing the arterial course through the retroperitoneum.

Inferior Vena Cava

The inferior vena cava (IVC) arises from the confluence of the common iliac veins at the level of the fifth lumbar vertebra (see Fig. 1–10). **Because the common iliac veins lie medial and posterior to the iliac arteries, the confluence of the iliac veins is posterior and to the right of the aortic bifurcation.** As the IVC progresses cranially through the abdomen, tributaries include the gonadal, renal, adrenal, and hepatic veins. In addition, the middle sacral vein enters the inferior vena cava posteriorly and the lumbar veins enter throughout the length of the abdominal vena cava.

The first tributary encountered along the IVC is the **middle sacral vein,** which enters at the junction of the common iliac veins. Also entering along the posterior aspect of the IVC throughout its course are **lumbar veins.** These veins course anterior to the spinal transverse processes and generally parallel the lumber arteries. In addition to providing vascular drainage, the lumbar veins connect the IVC to the azygous venous system on the right side and hemiazygos venous system on the left side of the thorax. This provides alternate routes of venous drainage within the retroperitoneum (Fig. 1–12).

The next tributaries to the IVC are the gonadal veins, whose course is analogous to the gonadal arteries until approaching the

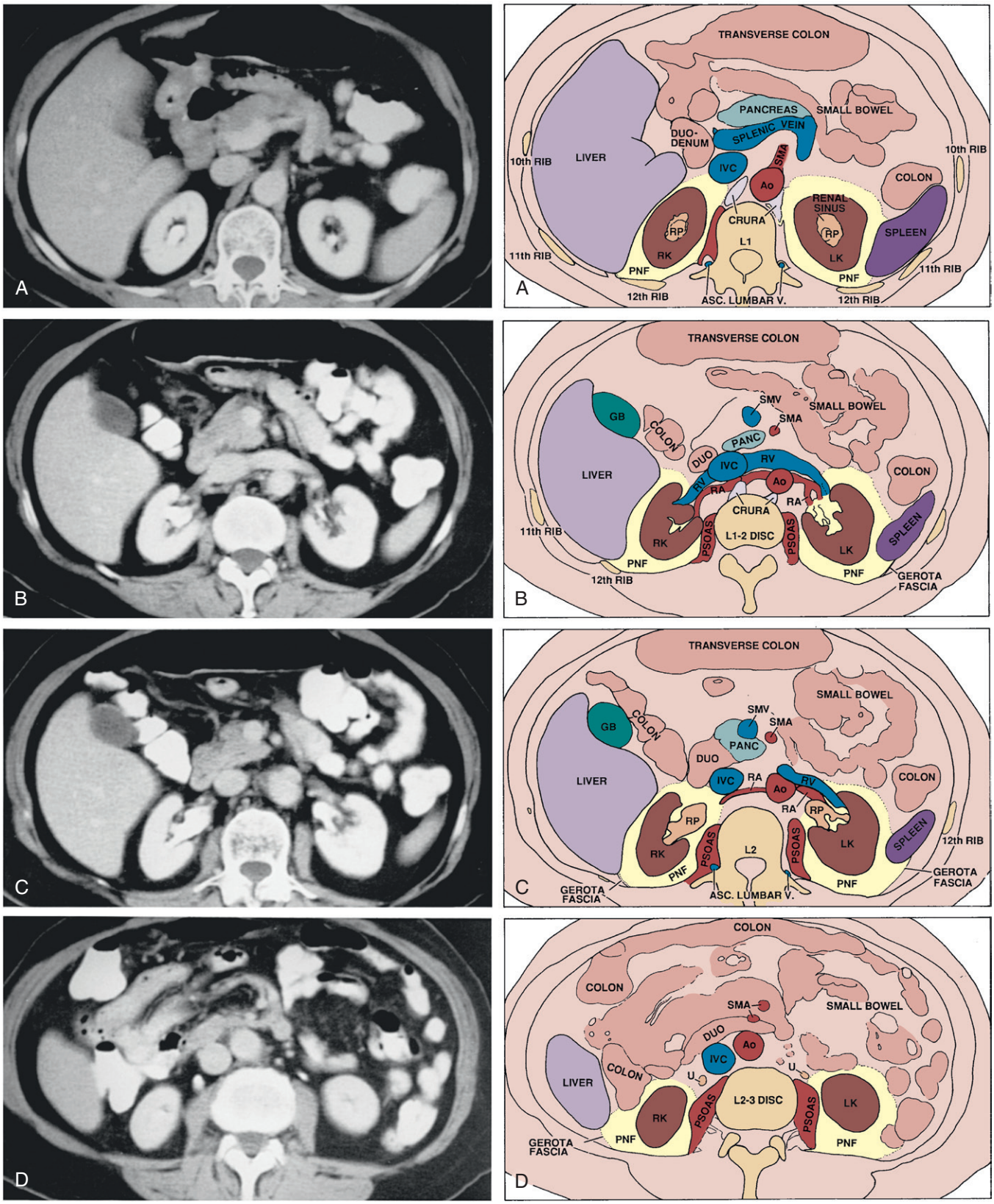


Figure 1–11. Cross-sectional anatomy of the upper abdomen at the level of the kidneys demonstrated with transverse sections obtained by computed tomography. Sections are arranged from most cephalic to caudal. **A,** Section through the upper poles of the kidneys, superior to the renal vascular pedicles. **B,** Section through the level of the renal arteries and veins. **C,** Slightly more inferior section showing the renal pelves and relation of the duodenum to the right renal hilum. **D,** Section through the lower poles of the kidneys showing the upper ureters. Ao, aorta; DUO, duodenum; GB, gallbladder; IVC, inferior vena cava; LK, left kidney; PANC, pancreas; PNF, perinephric fat; RA, renal artery; RK, right kidney; RP, renal pelvis; RV, renal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein; U, ureter.

Table 1–2.
Branches of the Abdominal Aorta

ARTERY	BRANCH	ORIGIN	PARTS SUPPLIED
Celiac trunk	Anterior	Immediately inferior to aortic hiatus of diaphragm	Abdominal foregut
Superior mesenteric artery	Anterior	Immediately inferior to celiac trunk	Abdominal midgut
Inferior mesenteric artery	Anterior	Inferior to renal arteries	Abdominal hindgut
Middle adrenal arteries	Lateral	Immediately superior to renal arteries	Adrenal glands
Renal arteries	Lateral	Immediately inferior to superior mesenteric artery	Kidneys
Testicular or ovarian arteries	Paired anterior	Inferior to renal arteries	Testes in male and ovaries in female
Inferior phrenic arteries	Paired	Immediately inferior to aortic hiatus	Diaphragm
Lumbar arteries	Posterior	Usually 4 pairs	Posterior abdominal wall and spinal cord
Median sacral arteries	Posterior	Just superior to aortic bifurcation, pass inferiorly across lumbar vertebrae, sacrum, and coccyx	
Common iliac arteries	Terminal	Bifurcation usually occurs at the level of L4 vertebra	

From Drake RL, Vogl W, Mitchell AWM. Gray's anatomy for students. Philadelphia: Elsevier; 2005. p. 331.

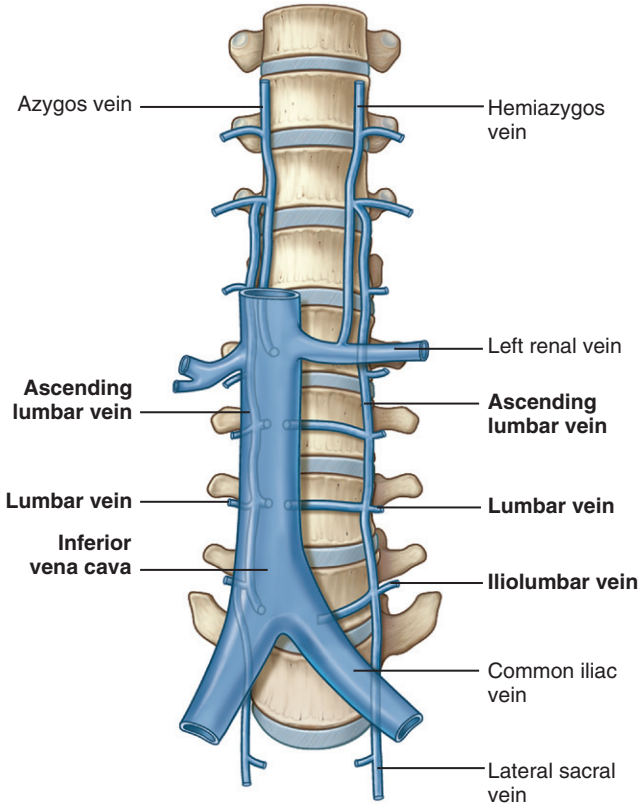


Figure 1–12. Lumbar, azygos, and hemiazygos veins. (From Drake RL, Vogl W, Mitchell AWM. Gray's anatomy for students. Philadelphia: Elsevier; 2005. p. 332.)

IVC. During the cranial portion of their course these veins are more lateral and closer to the ipsilateral ureter. Of surgical importance is their terminal drainage because **the right gonadal vein drains directly into the IVC and the left empties into the inferior aspect of the left renal vein** (see Fig. 1–10).

After the gonadal veins, the renal veins are encountered. **The renal veins are generally directly anterior to the accompanying renal artery, but it is not unusual for them to be separated by 1 to 2 cm in the craniocaudal direction.** The right renal vein typically is short and without branches, but in a small minority of patients the right gonadal vein can enter the right renal vein as opposed to the IVC. In a second anatomic variation, a lumbar vein will enter on the posterior aspect of the right renal vein as opposed to entering the IVC directly. The left renal vein is significantly longer than the right and receives additional branches before entering the IVC. Typically after exiting the renal hilum, the left renal vein receives a lumbar vein posteriorly, the left gonadal vein inferiorly, and the adrenal vein superiorly. Next, the left renal vein crosses anterior to the aorta and under the caudal edge of the superior mesenteric artery before draining into the IVC. Rarely the left renal vein crosses the aorta to the IVC in a retroaortic or circumaortic path.

Proceeding cranially, **the posterior aspect of the IVC receives the right adrenal vein.** This short vein is located posteriorly on the IVC, making it challenging to expose during right adrenal or renal surgery. As noted already, the left adrenal vein drains into the left renal vein as opposed to the IVC. **The inferior phrenic vein on the right side enters along the posterior or posterior lateral aspect of the IVC, with the left inferior phrenic vein typically entering the left renal vein.** The final tributaries to the IVC before it leaves the retroperitoneum are the short hepatic veins draining the liver. Inferiorly these veins are small, but superiorly three large hepatic trunks are encountered.

Lymphatics

Lymphatic drainage of the lower extremities, external genitalia, testes, kidneys, and intestines is located in the retroperitoneum (Fig. 1–13). Knowledge of these lymphatic channels is useful not only for urologic oncology (e.g., testis cancer) but also for prevention of complications such as lymphocele. Drainage of the lower extremities, perineum, and external genitalia progresses through the retroperitoneum via common iliac lymph vessels and then forms ascending vertical lumbar lymphatic chains. **There is flow not only cranially but also laterally, predominantly from the right to the left.** Gastrointestinal lymphatic drainage also follows the vascular supply, with the majority of the lymphatics paralleling the inferior mesenteric, superior mesenteric, and celiac arteries. Eventually these lymphatics join posterior to the aorta at the level of the first or second lumbar vertebrae to form the **thoracic duct.** This coalescence is classically marked by a

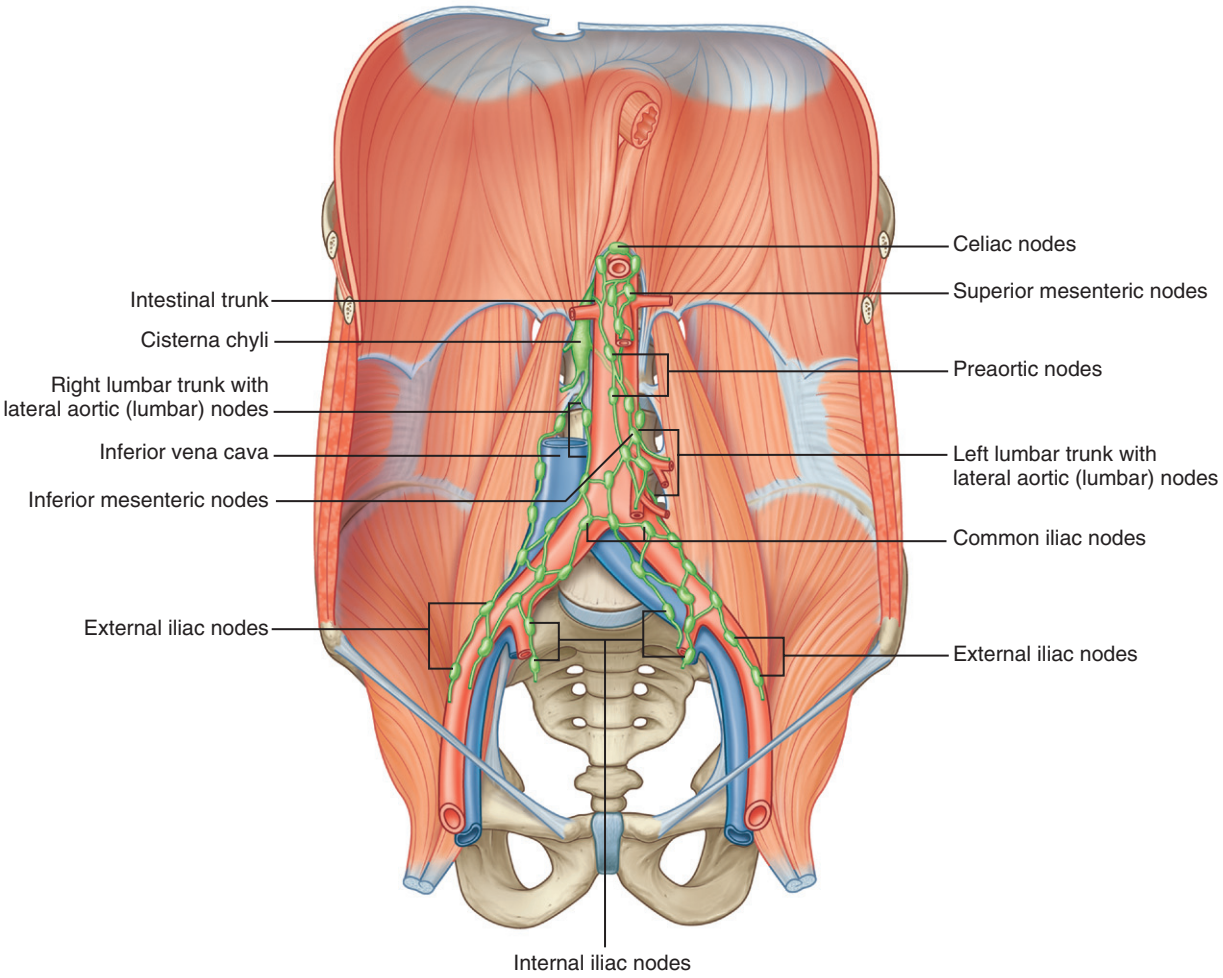


Figure 1–13. Retroperitoneal lymphatics. (From Drake RL, Vogl W, Mitchell AWM. Gray's anatomy for students. Philadelphia: Elsevier; 2005. p. 335.)

local dilation called **the cisterna chyli,** which tends to lie within the thorax just to the right of the aorta in a retrocrural position.

For the urologist, the lumbar lymphatics are important as the primary lymphatic drainage from two urologic organs: the kidneys and testes. Given the kidney's retroperitoneal location, the lumbar path of its lymphatic drainage is not surprising and is discussed in more depth later in this chapter. Embryologically, the testes develop within the retroperitoneum and maintain both blood flow (testicular arteries) and lymphatic drainage through this area even after they descend into the scrotum. To better describe the lymphatic drainage within the retroperitoneum, a practical system has been developed. This system defines three major nodal areas: right paracaval, interaortocaval, and left para-aortic. The right paracaval nodal region extends from the midline of the IVC to the right ureter. The interaortocaval region extends from the midline of the IVC to the midline of the aorta, and the left para-aortic region extends from the midline of the aorta to the left ureter.

Study of lymphatic metastases from testicular tumors have shown that testicular lymphatic drainage is consistent and follows the general scheme of vertical drainage with lateral flow from right to left. Lymphatic metastases from the right testis drain primarily into the interaortocaval nodes with significant drainage to the right paracaval nodes. In addition there is a small amount of drainage to the left para-aortic nodes. On the other hand, the left testis drains primarily to the left para-aortic nodes with significant drainage to the interaortocaval nodes. There is essentially no drainage to the right paracaval nodes from left-sided tumors.

Nervous System Structures

The nervous structures within the retroperitoneum are part of the peripheral nervous system and can be divided into two categories: autonomic and somatic nerves. **The autonomic nerves provide afferent and efferent innervation to organs, blood vessels, glands, and smooth muscles. They are further characterized by the presence of peripheral synapses. Thus there are at least two peripheral nerves between the central nervous system and the viscera. The somatic nerves supply afferent and efferent innervation to the skin, skeletal muscles, and joints.** Although these two nerve types leave the spinal column within shared spinal nerves, their course and functions quickly diverge.

Autonomic System

The autonomic system is further divided into sympathetic and parasympathetic fibers. The origin of these two nerve types is quite different, with **the sympathetic preganglionic fibers originating from the thoracic and lumbar portions of the spinal column and the parasympathetic preganglionic fibers beginning in the cranial and sacral spinal column**

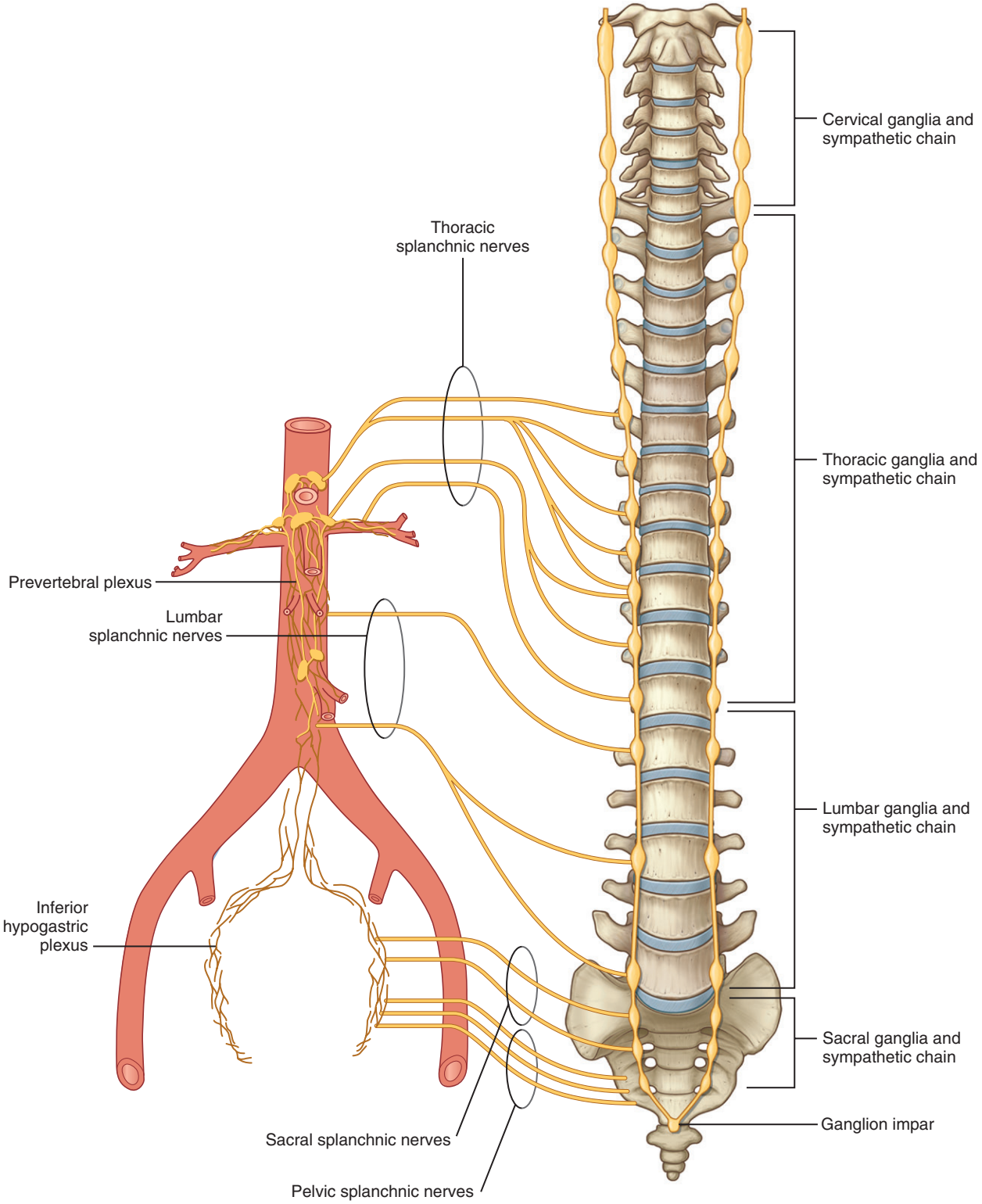


Figure 1–14. Sympathetic chain and splanchnic nerves. (From Drake RL, Vogl W, Mitchell AWM. Gray's anatomy for students. Philadelphia: Elsevier; 2005. p. 309.)

segments. Preganglionic sympathetic fibers enter the retroperitoneum through both the paired sympathetic chains and input from the lumbar spinal nerves (Fig. 1–14). **The lumbar portion of this sympathetic chain then sends preganglionic fibers to autonomic plexuses associated with the major branches of the abdominal aorta. Within these aortic plexuses the preganglionic fibers synapse and postganglionic fibers are then distributed to the various abdominal viscera and organs. Parasympathetic input from the vagus nerve also supplies these ganglia.**

In more detail, the thoracic and lumbar portions of the sympathetic chain originate from preganglionic sympathetic fibers arising from the first thoracic through the third lumbar spinal

nerves (see Fig. 1–14). **This chain then courses vertically along the anterolateral aspect of the spine just medial to the psoas muscle.** Within the retroperitoneum, lumbar arteries and veins are closely associated with the lumbar sympathetic chain, in some instances even splitting the fibers as they cross the chain perpendicularly. **From this sympathetic chain preganglionic fibers follow one of three courses. First, preganglionic fibers are sent to the various autonomic plexuses (splanchnic nerves). Once in the plexus, the preganglionic fibers synapse within a ganglion to postganglionic fibers, which in turn proceed to the abdominal viscera. Second, preganglionic fibers can synapse within the sympathetic chain ganglia and send postganglionic fibers to the body wall and lower extremities. Finally, preganglionic sympathetic fibers can proceed directly to the adrenal gland without synapsing. Within the adrenal medulla, these preganglionic fibers control release of catecholamines.**

The major autonomic nerve plexuses are associated with the primary branches of the aorta. These plexuses include the celiac, superior hypogastric, and inferior hypogastric plexuses (Fig. 1–15). These plexuses receive sympathetic input from the sympathetic chains via the greater, lesser, and least thoracic splanchnic nerves originating from the 5th through 12th thoracic spinal nerves. They also receive input from the lumbar portion of the sympathetic chain via the lumbar splanchnic nerves, as well as parasympathetic input via the vagus nerve.

The largest is the celiac plexus and is located on either side of the celiac arterial trunk as a paired structure. It is through this plexus that much or all of the autonomic input to the kidney, adrenal, renal pelvis, and ureter passes. In addition, some of the sympathetic innervation to the testes passes through this ganglion before continuing in parallel with the testicular artery to the testis. A separate aorticorenal ganglion usually exists as an inferior extension of the celiac ganglion, forming part of the renal autonomic plexus. The latter plexus surrounds the renal artery and its branches and is contiguous with the celiac plexus. At the lower extent of the abdominal aorta, **much of the autonomic input to the pelvic urinary organs and genital tract travels through the superior hypogastric plexus.** This plexus lies on the aorta anterior to its bifurcation and extends inferiorly on the anterior surface of the fifth lumbar vertebra. This plexus is contiguous bilaterally with inferior hypogastric plexuses, which extend into the pelvis. **Disruption of the sympathetic nerve fibers that travel through these plexuses during retroperitoneal dissection can cause loss of seminal vesicle emission and/or failure of bladder neck closure, resulting in retrograde ejaculation.**

Somatic

The somatic sensory and motor innervation to the abdomen and lower extremities arises in the retroperitoneum and is called the lumbosacral plexus. The lumbosacral plexus is formed from branches of all lumbar and sacral spinal nerves, with some contribution from the 12th thoracic spinal nerve as well (Fig. 1–16). Superiorly, nerves of this plexus form within the body of the psoas muscle and pierce this muscle, with more inferior branches passing medial to the psoas as the pelvis is entered (Fig. 1–17). The origins and functions of these lumbosacral somatic nerves are summarized in Table 1–3.

The subcostal nerve is the anterior extension of the 12th thoracic nerve and extends laterally beneath the 12th rib. As one proceeds inferiorly, the **iliohypogastric nerve** and the **ilioinguinal nerve** originate together as an extension from the first lumbar spinal nerve. These three nerves cross the anterior or inner surface of the quadratus lumborum muscle before piercing the transversus abdominis muscle and continuing their course between

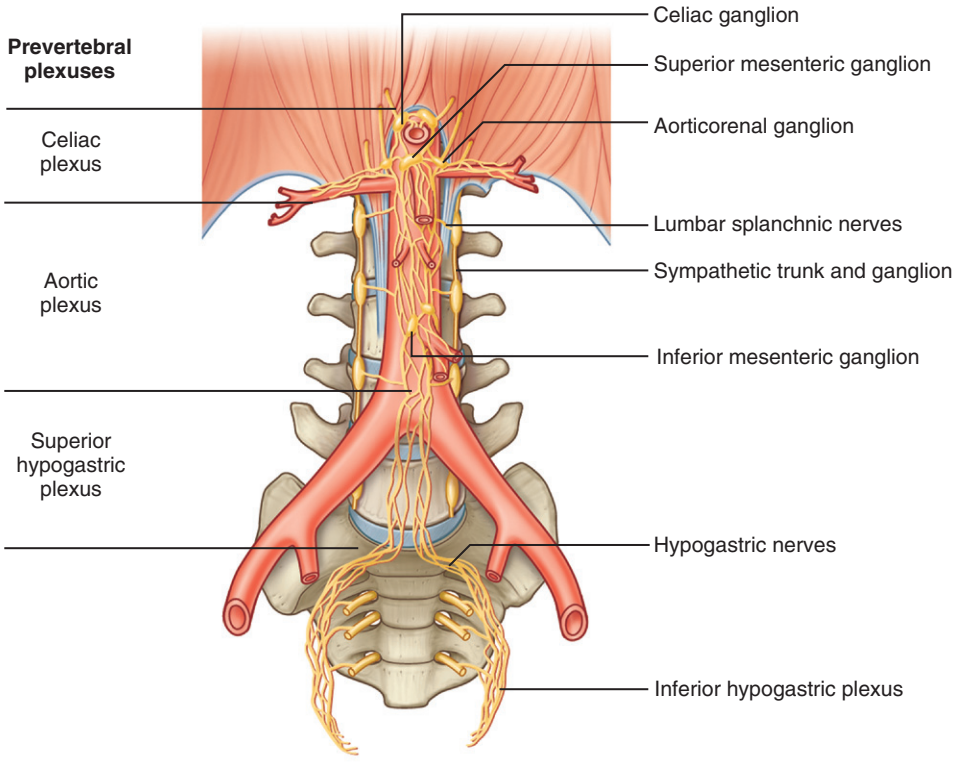


Figure 1–15. Autonomic plexuses associated with branches of the aorta. (From Drake RL, Vogl W, Mitchell AWM. Gray's anatomy for students. Philadelphia: Elsevier; 2005. p. 337.)

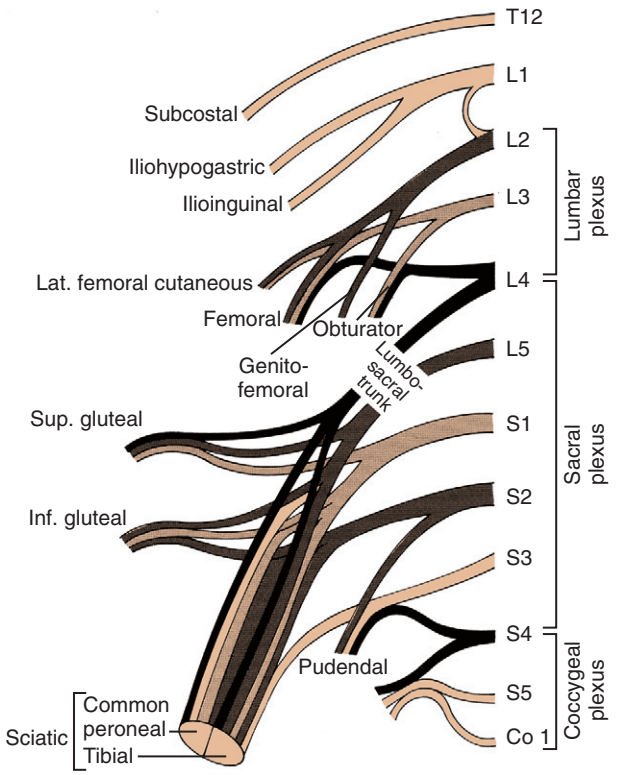


Figure 1–16. Diagrammatic representation of the lumbosacral nervous plexus.

this and the internal oblique muscle. Together they provide multiple motor branches to the muscles of the abdominal wall, as well as sensory innervation to the skin of the lower abdomen and genitalia. The **lateral femoral cutaneous nerve** and the **genitofemoral nerve** arise from the 1st through 3rd lumbar nerves and are primarily sensory nerves to the skin of the upper thigh and genitalia; however, the genital branch of the genitofemoral nerve also supplies the cremaster and dartos muscles in the scrotum. The genitofemoral nerve lies directly atop and parallels the psoas muscle throughout most of its retroperitoneal course and is easily identified in this position.

The **femoral nerve** is a larger structure arising from the second through fourth lumbar spinal nerves and is largely hidden by the body of the psoas muscle before exiting the abdomen just lateral to the femoral artery. This important nervous structure supplies the psoas and iliacus muscles, as well as the large muscle groups of the anterior thigh. It also provides sensory innervation of the anteromedial portions of the lower extremity. Intraoperatively, it may be compressed by retractor blades placed inferolaterally against the inguinal ligament in lower abdominal incisions, producing a significant motor palsy that prevents active extension of the knee.

The final lumbosacral plexus nerves include the **obturator and sciatic nerves.** The obturator nerve, an important pelvic landmark, arises behind the psoas muscle in the retroperitoneum from the third and fourth lumbar spinal nerves. It then courses inferiorly, where its major function is to supply the adductor muscles of the thigh. The **sciatic nerve** receives input from the

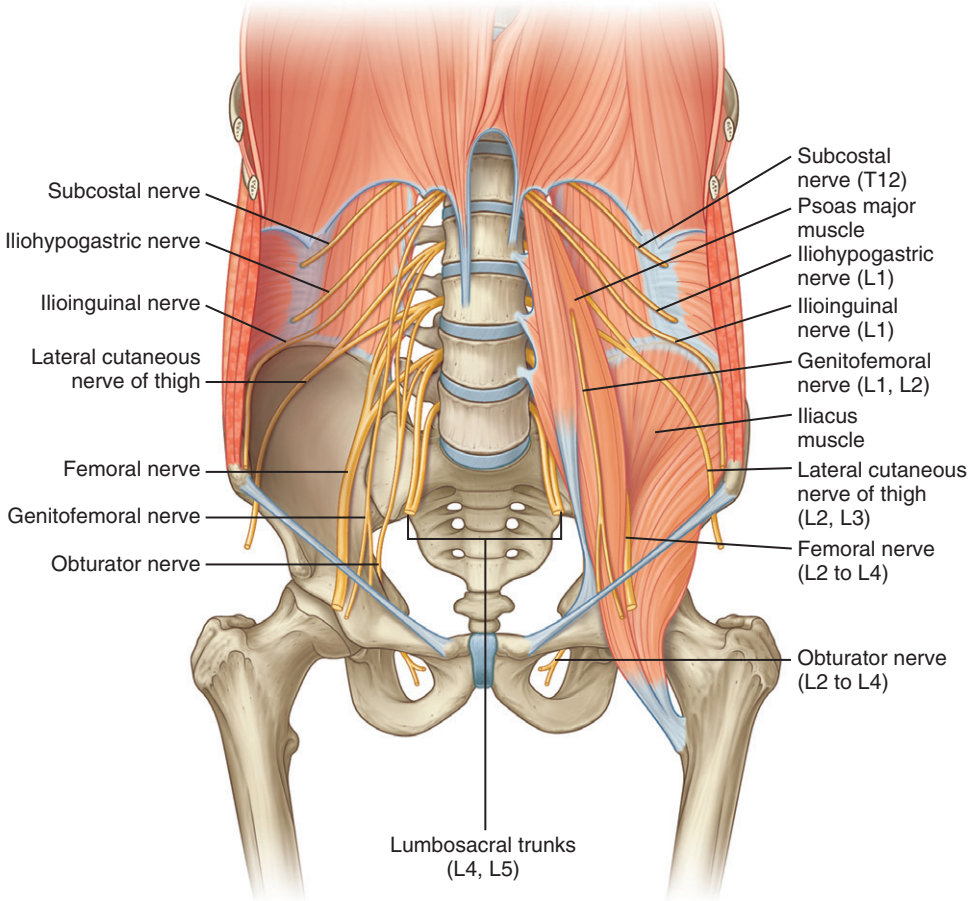


Figure 1–17. Lumbar plexus in the posterior abdominal region. (From Drake RL, Vogl W, Mitchell AWM. Gray's anatomy for students. Philadelphia: Elsevier; 2005. p. 341.)

Table 1–3.
Branches of the Lumbosacral Plexus

BRANCH	ORIGIN	SPINAL SEGMENTS	FUNCTION: MOTOR	FUNCTION: SENSORY
Iliohypogastric	Anterior ramus L1	L1	Internal oblique and transversus abdominis	Posterolateral gluteal skin and skin in pubic region
Ilioinguinal	Anterior ramus L1	L1	Internal oblique and transversus abdominis	Skin in the upper medial thigh, and either the skin over the root of the penis and anterior scrotum or the mons pubis and labium majus
Genitofemoral	Anterior rami L1 and L2	L1, L2	Genital branch—male cremasteric muscle	Genital branch—skin of anterior scrotum or skin of mons pubis and labium majus; femoral branch—skin of upper anterior thigh
Lateral cutaneous nerve of thigh	Anterior rami L2 and L3	L2, L3		Skin on anterior and lateral thigh to the knee
Obturator	Anterior rami L2 to L4	L2 to L4	Obturator externus, pectineus, and muscles in medial compartment of thigh	Skin on medial aspect of the thigh
Femoral	Anterior rami L2 to L4	L2 to L4	Iliacus, pectineus, and muscles in anterior compartment of thigh	Skin on anterior thigh and medial surface of leg

From Drake RL, Vogl W, Mitchell AWM. Gray's anatomy for students. Philadelphia: Elsevier; 2005. p. 340.

fourth lumbar through third sacral spinal nerves, taking final form in the deep posterior pelvis as the body's single largest nerve, supplying the bulk of both sensory and motor innervation to the lower extremity.

Duodenum, Pancreas, Colon

See Figure 1–18 on the Expert Consult website. The duodenum is divided into four anatomic components. The first (ascending) portion is short (5 cm) and intimately related to the gallbladder. **The second (descending portion) is of most importance to the urologist because it lies immediately anterior to the right renal hilum and pelvis.** This portion of the duodenum is frequently mobilized (referred to as a *Kocher maneuver*) to expose the right kidney, right renal pelvis, and additional upper abdominal structures. The second portion of the duodenum also receives the common bile duct and surrounds the head of the pancreas. The third (horizontal) and fourth (ascending) portions of the duodenum cross from right to left over the IVC and aorta before transitioning into the jejunum.

As noted earlier, the head of the pancreas is on the medial border of the descending duodenum. **The body and tail of the pancreas continue across the IVC and aorta to the left side of the abdomen, where the pancreas is closely related to the left adrenal gland and the upper pole of the left kidney.** The splenic artery and vein travel laterally along the posterior aspect of the pancreas, with the artery just superior to the vein. In this position these vascular structures are also closely related to the upper pole of the left kidney.

The final retroperitoneal gastrointestinal structure is the colon, with the ascending and descending portions being retroperitoneal. **Both the ascending colon at the hepatic flexure and descending colon at the splenic flexure overlie the ipsilateral kidney.** In addition, the hepatocolic ligament and splenocolic ligament tether the liver and spleen to the respective portions of the colon. Given the close anatomic relationship to the kidneys, mobilization of the colon and its mesentery is important for transperitoneal exposure of the kidneys and ureters.

ADRENAL GLANDS

See Figure 1–19 on the Expert Consult website.

Anatomic Relationships

The adult adrenal glands are 3 to 5 cm in greatest transverse dimension and weigh approximately 5 g. Grossly, they are yellow-orange and noticeably more orange than the surrounding adipose tissue. The position of this bilateral gland varies from right to left, but both glands are enclosed within the perirenal (Gerota) fascia and are separated from the upper pole of the kidneys by a layer of connective tissue.

The right gland is more superiorly located in the retroperitoneum and is pyramidal. It is almost directly cranial to the upper pole of the right kidney. Surrounding structures include the liver anterolaterally, the duodenum anteromedially, and the inferior vena cava medially. It is also important to note that there is often a retrocaval extension of one wing. The left gland is more

Key Points: Adrenal Glands

- Embryologically the adrenals are distinct from the kidney. Developmental abnormalities of one do not affect the other.
- The adrenal is divided into the medulla and the cortex.
- The adrenal medulla receives preganglionic sympathetic input that stimulates the release of catecholamines from medullary chromaffin cells.
- The adrenal cortex is composed of three distinct areas: the zona glomerulosa, zona fasciculata, and zona reticularis.
- Arterial supply to the adrenal comes from branches of the inferior phrenic artery, aorta, and renal artery.
- Venous drainage of the adrenal varies by side, with the right adrenal vein directly entering the IVC and the left adrenal vein draining into the left renal vein.

crescenteric and medial to the upper pole of the left kidney. The upper and anterior aspects are related to the stomach, tail of the pancreas, and splenic vessels.

Composition

Embryologically, the adrenal is distinct from the kidney. Thus in cases of renal ectopia, the adrenal gland is not affected. **Histologically, the adrenal is divided into two components: the centrally located medulla and the peripherally located cortex** (Fig. 1–20 on the Expert Consult website). **The medulla itself is composed of chromaffin cells derived from neural crest origin. These chromaffin cells are innervated directly by presynaptic sympathetic fibers traveling to the adrenal gland from the sympathetic chains. The secretion of neuroactive catecholamines by the adrenal medulla is thus under sympathetic control.**

The adrenal cortex is of mesodermal origin and makes up approximately 90% of the adrenal mass. It is composed of three layers, from external to internal: zona glomerulosa, zona fasciculata, and zona reticularis. Each layer has a different function, with the glomerulosa producing mineralocorticoids (e.g., aldosterone), the fasciculata producing glucocorticoids (e.g., cortisol), and the reticularis synthesizing sex steroids (androgens).

Adrenal Vessels

The arterial supply to the adrenal gland originates from three sources (Fig. 1–21). **Superiorly, branches from the inferior phrenic artery feed the adrenal, whereas middle branches originate directly from the aorta. Finally, branches from the ipsilateral renal artery supply the adrenal gland.** The venous drainage varies by side, although both adrenal glands are drained by a single large vein that exits anteromedially. On the left side this vein joins with the inferior phrenic vein and enters the cranial aspect of the left renal vein. On the right side, the adrenal vein enters the IVC directly on its posterolateral aspect. The lymphatic drainage of the adrenals follows the course of these veins and empties into para-aortic lymph nodes.

KIDNEYS

Gross and Microscopic Anatomy

The kidneys serve a number of important functions required to maintain normal human physiologic function. They are the primary organs for maintaining fluid and electrolyte balance, and they play a large role in maintaining acid-base balance. They produce renin, which plays a vital role in controlling blood pressure, and erythropoietin, which affects red blood cell production. They affect calcium metabolism, in particular calcium absorption, by converting a precursor of vitamin D to the most active form, 1,25-dihydroxyvitamin D.

Grossly, the kidneys are bilaterally paired reddish brown organs (see Figs. 1–1 and 1–22). Typically each kidney weighs 150 g in the male and 135 g in the female. The kidneys generally measure 10 to 12 cm vertically, 5 to 7 cm transversely, and 3 cm in the anteroposterior dimension. Because of compression by the liver, the right kidney tends to be somewhat shorter and wider. In children, the kidneys are relatively larger and possess more prominent fetal lobations. These lobations are present at birth and generally disappear by the first year of life, although occasionally they persist into adulthood. An additional common feature of the gross renal anatomy is a focal renal parenchymal bulge along the kidney's lateral contour, known as a *dromedary hump*. This is a normal variation without pathologic significance. It is more common on

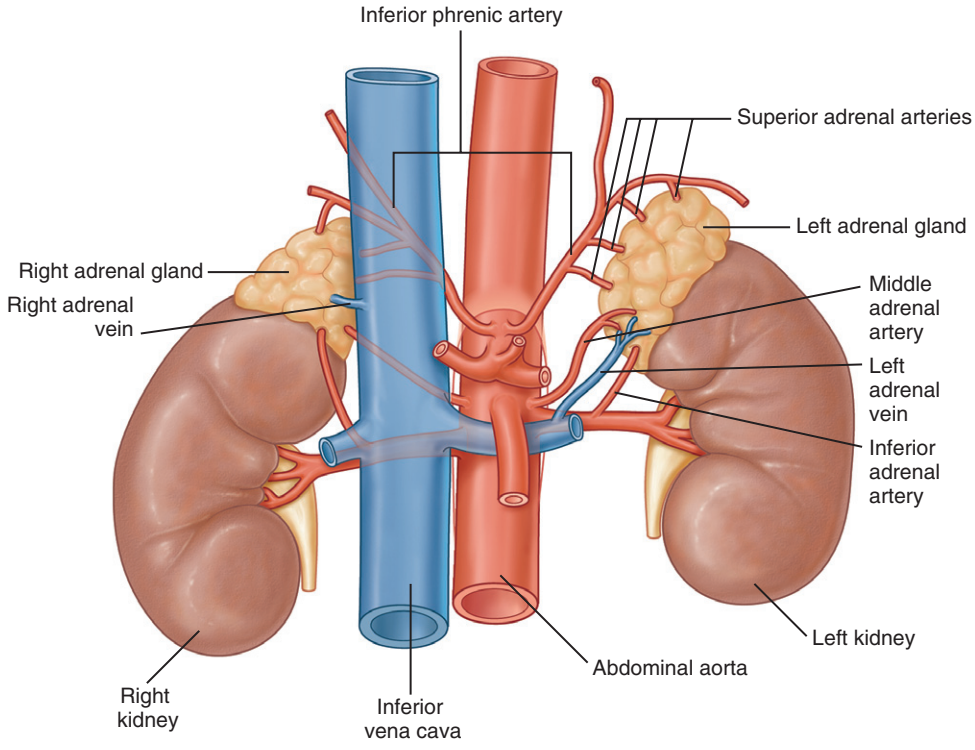


Figure 1–21. Arterial supply to the adrenal glands. (From Drake RL, Vogl W, Mitchell AWM. Gray's anatomy for students. Philadelphia: Elsevier; 2005. p. 329.)

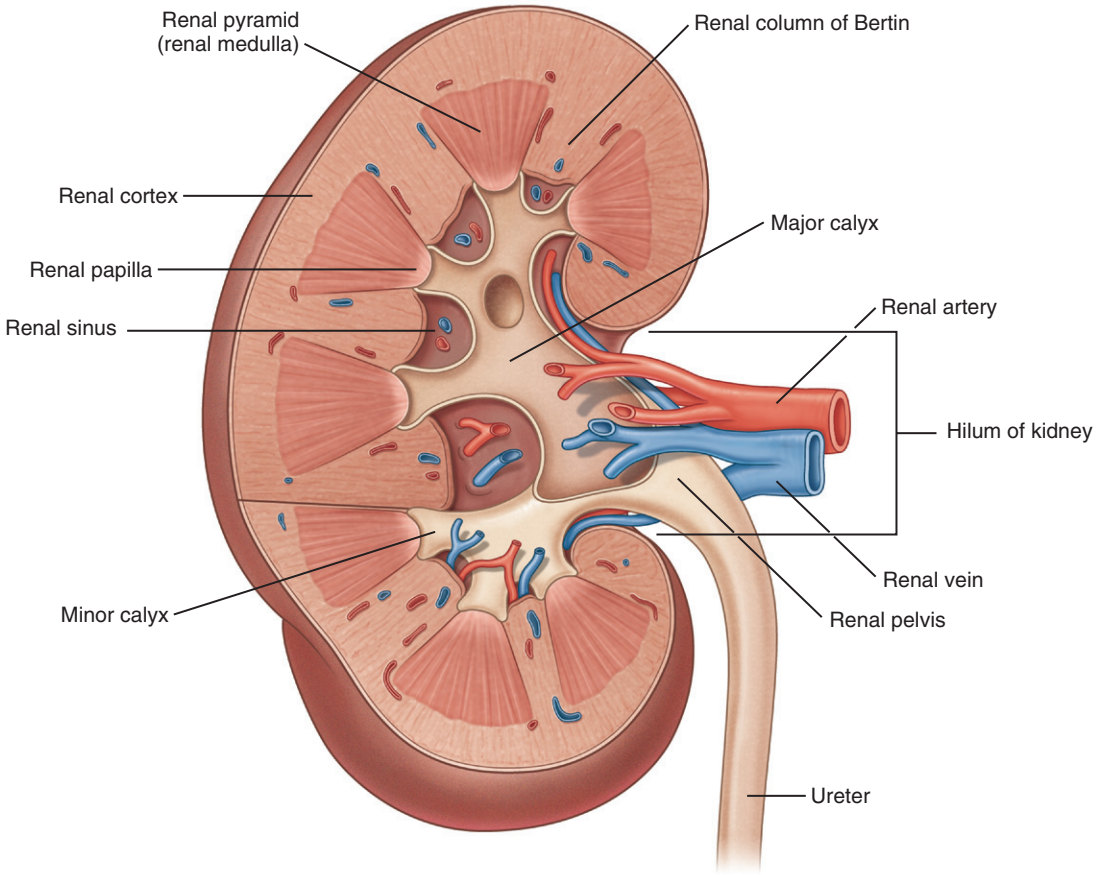


Figure 1–22. Internal structure of the kidney. (From Drake RL, Vogl W, Mitchell AWM. Gray's anatomy for students. Philadelphia: Elsevier; 2005. p. 323.)

the left than the right and is believed to be caused by downward pressure from the spleen or liver.

As one proceeds centrally from the peripherally located reddish brown parenchyma of the kidney, the renal sinus is encountered. Here the vascular structures and collecting system coalesce before exiting the kidney medially. These structures are surrounded by yellow sinus fat, which provides an easily recognized landmark during renal procedures such as partial nephrectomy. At its medial border, the renal sinus narrows to form the renal hilum. It is through the hilum that the renal artery, renal vein, and renal pelvis exit the kidney and proceed to their respective destinations.

Both grossly and microscopically there are two distinct components within the renal parenchyma: the medulla and the cortex. **Unlike the adrenal gland, the renal medulla is not a contiguous layer. Instead, the medulla is composed of multiple, distinct, conically shaped areas noticeably darker in color than the cortex** (see Fig. 1–22). **These same structures are also frequently called renal pyramids, making the terms *renal medulla* and *renal pyramid* synonymous. The apex of the pyramid is the renal papilla, and each papilla is cupped by an individual minor calyx.**

The renal cortex is lighter in color than the medulla and not only covers the renal pyramids peripherally but also extends between the pyramids themselves. The extensions of cortex between the renal pyramids are given a special name: the **columns of Bertin.** These columns are significant surgically because it is through these columns that renal vessels traverse from the renal sinus to the peripheral cortex, decreasing in diameter as the columns move peripherally. It is because of this anatomy that percutaneous access to the collecting system is made through a renal pyramid into a calyx, thus avoiding the columns of Bertin and the larger vessels present within them.

Many of these gross anatomic structures can be seen on modern imaging modalities such as computed tomography (see Fig. 1–11), as well as ultrasound and magnetic resonance imaging (Fig. 1–23).

Relations and Investing Fascia

Anatomic Relationships

The position of the kidney within the retroperitoneum varies greatly by side, degree of inspiration, body position, and presence of anatomic anomalies (Fig. 1–24 on the Expert Consult website). The right kidney sits 1 to 2 cm lower than the left in most individuals owing to displacement by the liver. Generally, the right kidney resides in the space between the top of the first lumbar vertebra to the bottom of the third lumbar vertebra. The left kidney occupies a more superior space from the body of the 12th thoracic vertebral body to the 3rd lumbar vertebra.

Of surgical importance are the structures surrounding the kidney (see Figs. 1–9 and 1–25). Both kidneys have similar muscular surroundings. Posteriorly, the diaphragm covers the upper third of each kidney, with the 12th rib crossing at the lower extent of the diaphragm. Also important to note for percutaneous renal procedures and flank incisions is that the pleura extends to the

Key Points: Kidneys

- The kidney is divided into cortex and medulla. The medullary areas are pyramidal, more centrally located, and separated by sections of cortex. These segments of cortex are called the *columns of Bertin*.
- Orientation of the kidney is greatly affected by the structures around it. Thus the upper poles are situated more medially and posteriorly than the lower poles. Also, the medial aspect of the kidney is more anterior than the lateral aspect.
- Gerota fascia envelops the kidney on all aspects except inferiorly, where it is not closed but instead remains an open potential space.
- From anterior to posterior, the renal hilar structures are the renal vein, renal artery, and collecting system.
- The renal artery splits into segmental branches. Typically, the first branch is the posterior segmental artery, which passes posterior to the collecting system. There are generally three to four anterior segmental branches that pass anteriorly to supply the anterior kidney.
- The progression of arterial supply to the kidney is as follows: renal artery → segmental artery → interlobar artery → arcuate artery → interlobular artery → afferent artery.
- The venous system anastomoses freely throughout the kidney. The arterial supply does not. Thus occlusion of a segmental artery leads to parenchymal infarction, but occlusion of a segmental vein is not problematic because there are many alternate drainage routes.
- Anatomic variations in the renal vasculature are common, occurring in 25% to 40% of kidneys.
- Each renal pyramid terminates centrally in a papilla. Each papilla is cupped by a minor calyx. A group of minor calyces join to form a major calyx. The major calyces combine to form the renal pelvis. There is great variation in the number of calyces, calyceal size, and renal pelvis size. The only way to determine pathologic from normal is by evidence of dysfunction.

level of the 12th rib posteriorly. Medially the lower two thirds of the kidney lie against the psoas muscle, and laterally the quadratus lumborum and aponeurosis of the transversus abdominis muscle are encountered. The effect of the muscular relations on the kidneys is severalfold (Fig. 1–26). First, the lower pole of the kidney lies laterally and anteriorly relative to the upper pole. Second, the medial aspect of each kidney is rotated anteriorly at an angle of approximately 30 degrees. An understanding of this renal orientation is again of particular interest for percutaneous renal procedures in which kidney orientation influences access site selection.

Anteriorly, the right kidney is bordered by a number of structures (see Fig. 1–25). Cranially, the upper pole lies against the liver and is separated from the liver by the peritoneum except for the liver's posterior bare spot. The hepatorenal ligament further attaches the right kidney to the liver because this extension of parietal peritoneum bridges the upper pole of the right kidney to the posterior liver. Also at the upper pole, the right adrenal gland is encountered. On the medial aspect, the descending duodenum is intimately related to the medial aspect of the kidney and hilar structures. Finally, on the anterior aspect of the lower pole lies the hepatic flexure of the colon.

The left kidney is bordered superiorly by the tail of the pancreas with the splenic vessels adjacent to the hilum and upper pole of the left kidney. Also cranial to the upper pole is the left adrenal gland and further superolaterally, the spleen. The splenorenal ligament attaches the left kidney to the spleen. This attachment can lead to splenic capsular tears if excessive downward pressure is applied to the left kidney. Superior to the pancreatic tail, the posterior gastric wall can overlie the kidney. Caudally, the kidney is covered by the splenic flexure of the colon.

Gerota Fascia

Interposed between the kidney and its surrounding structures is the perirenal or Gerota fascia (Figs. 1–27 through 1–29). This fascial layer encompasses the perirenal fat and kidney and encloses the kidney on three sides: superiorly, medially, and laterally. Superiorly and laterally Gerota fascia is closed, but medially it extends across the midline to fuse with the contralateral side. Inferiorly, Gerota fascia is not closed and remains an open potential space. Gerota fascia serves as an anatomic barrier to the spread of malignancy and a means of containing perinephric fluid collections. Thus perinephric fluid collections can track inferiorly into the pelvis without violating Gerota fascia.

Renal Vasculature

The renal pedicle classically consists of a single artery and a single vein that enter the kidney via the renal hilum (see Fig. 1–22). These structures branch from the aorta and inferior vena cava just below the superior mesenteric artery at the level of the second lumbar vertebra. **The vein is anterior to the artery. The renal pelvis and ureter are located farther posterior to these vascular structures.**

Renal Artery

Specifically, the right renal artery leaves the aorta and progresses with a caudal slope under the IVC toward the right kidney. The left renal artery courses almost directly laterally to the left kidney. Given the rotational axis of the kidney (see Fig. 1–26), both renal arteries move posteriorly as they enter the kidney. Also, both arteries have branches to the respective adrenal gland, renal pelvis, and ureter.

Upon approaching the kidney, the renal artery splits into four or more branches, with five being the most common. These are the renal segmental arteries (Fig. 1–30). Each segmental artery supplies a distinct portion of the kidney with no collateral circulation between them (Fig. 1–31). Thus occlusion or injury to a segmental branch will cause segmental renal infarction. Generally, the first and most constant branch is the posterior segmental branch, which separates from the renal artery before it enters the renal hilum. Typically there are four anterior branches, which from superior to inferior are apical, upper, middle, and lower. The relationship of these segmental arteries is important because the posterior segmental branch passes posterior to the renal pelvis while the others pass anterior to the renal pelvis. Ureteropelvic junction obstruction caused by a crossing vessel can occur when the posterior segmental branch passes anterior to the ureter causing occlusion. This division between the posterior and anterior segmental arteries has an additional surgical importance in that between these circulations is an avascular plane (see Figs. 1–26 and 1–31). This longitudinal plane lies just posterior to the lateral aspect of the kidney. Incision within this plane results in significantly less blood loss than outside this plane. However, there is significant variation in the location of this plane, requiring

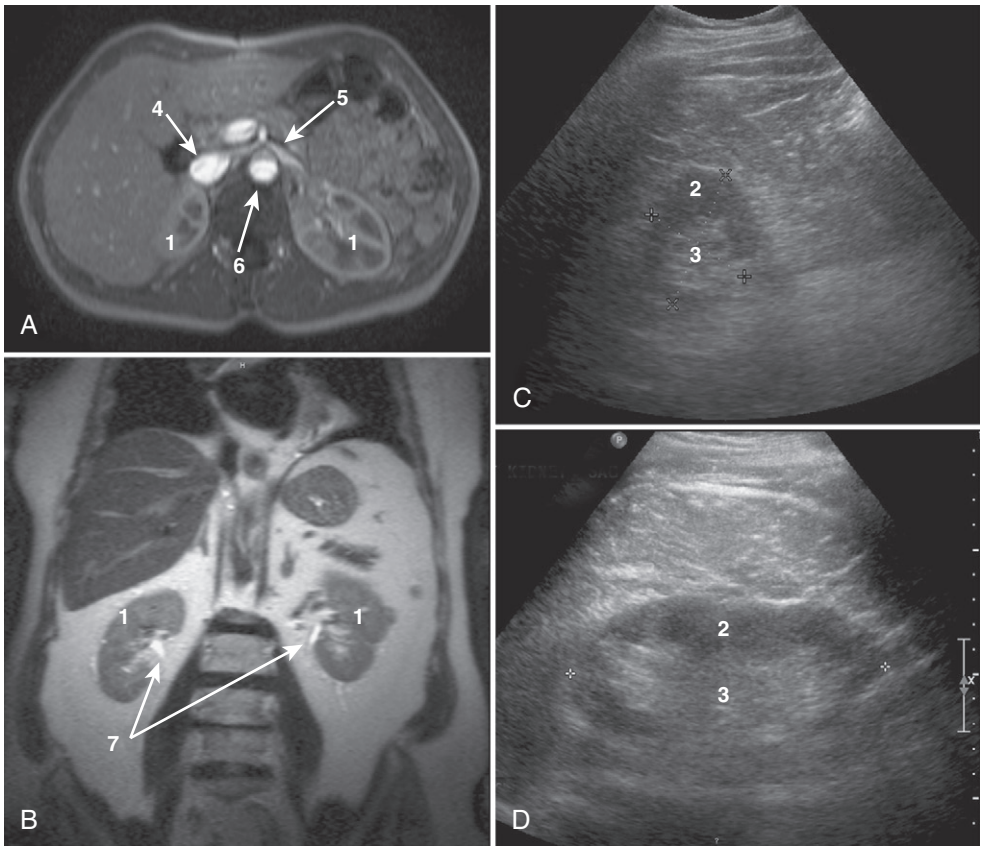


Figure 1–23. Cross-sectional imaging of the normal kidney. **A,** T1-weighted gadolinium-enhanced axial magnetic resonance imaging (MRI) of kidneys including the inferior vena cava, aorta, left renal vein, and superior mesenteric artery. **B,** Coronal T2 MRI of the kidneys. **C,** Transverse ultrasound imaging of the kidney. **D,** Sagittal ultrasound imaging of the kidney. 1, Kidney. 2, Renal cortex. 3, Renal medulla. 4, Inferior vena cava. 5, Left renal vein. 6, Aorta. 7, Renal collecting system.

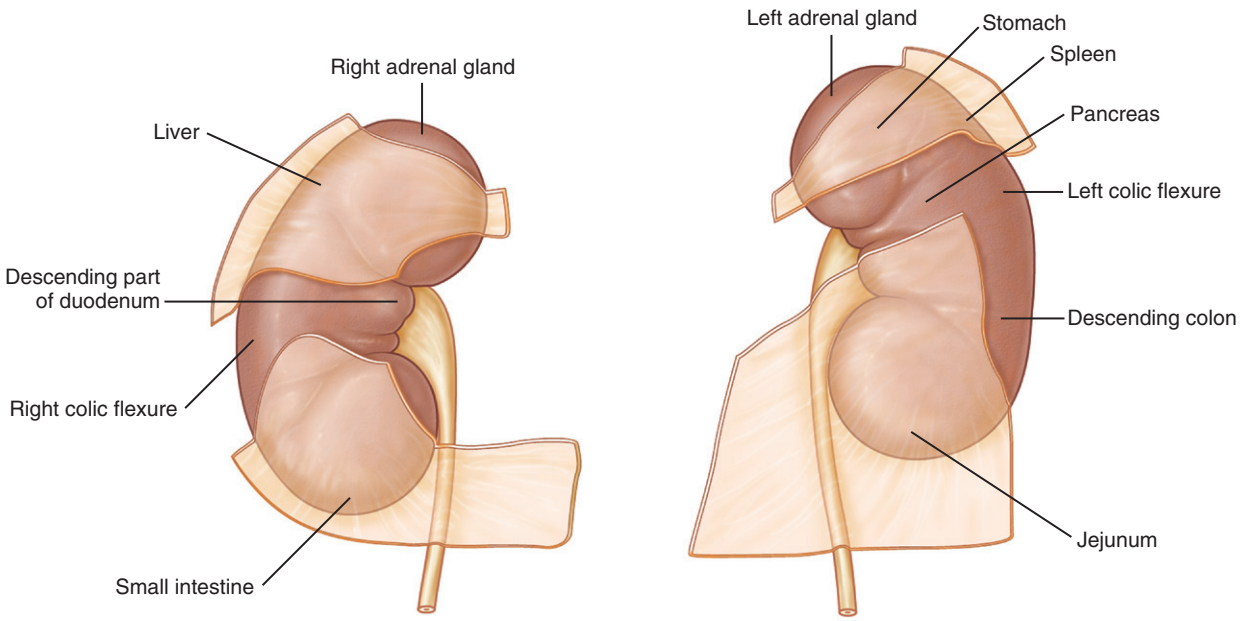


Figure 1–25. Structures related to the anterior surfaces of each kidney. (From Drake RL, Vogl W, Mitchell AWM. Gray's anatomy for students. Philadelphia: Elsevier; 2005. p. 321.)

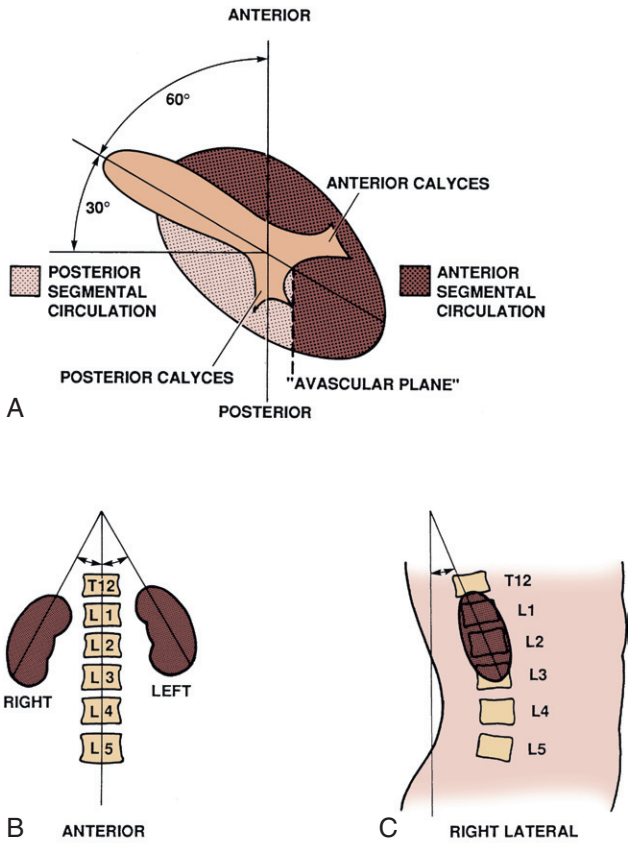


Figure 1–26. Normal rotational axes of the kidney. **A,** Transverse view showing approximate 30-degree anterior rotation of the left kidney from the coronal plane, relative positions of the anterior and posterior rows of calyces, and location of the relatively avascular plane separating the anterior and posterior renal circulation. **B,** Coronal section demonstrating slight inward tilt of the upper poles of the kidneys. **C,** Sagittal view showing anterior displacement of the lower pole of the right kidney.

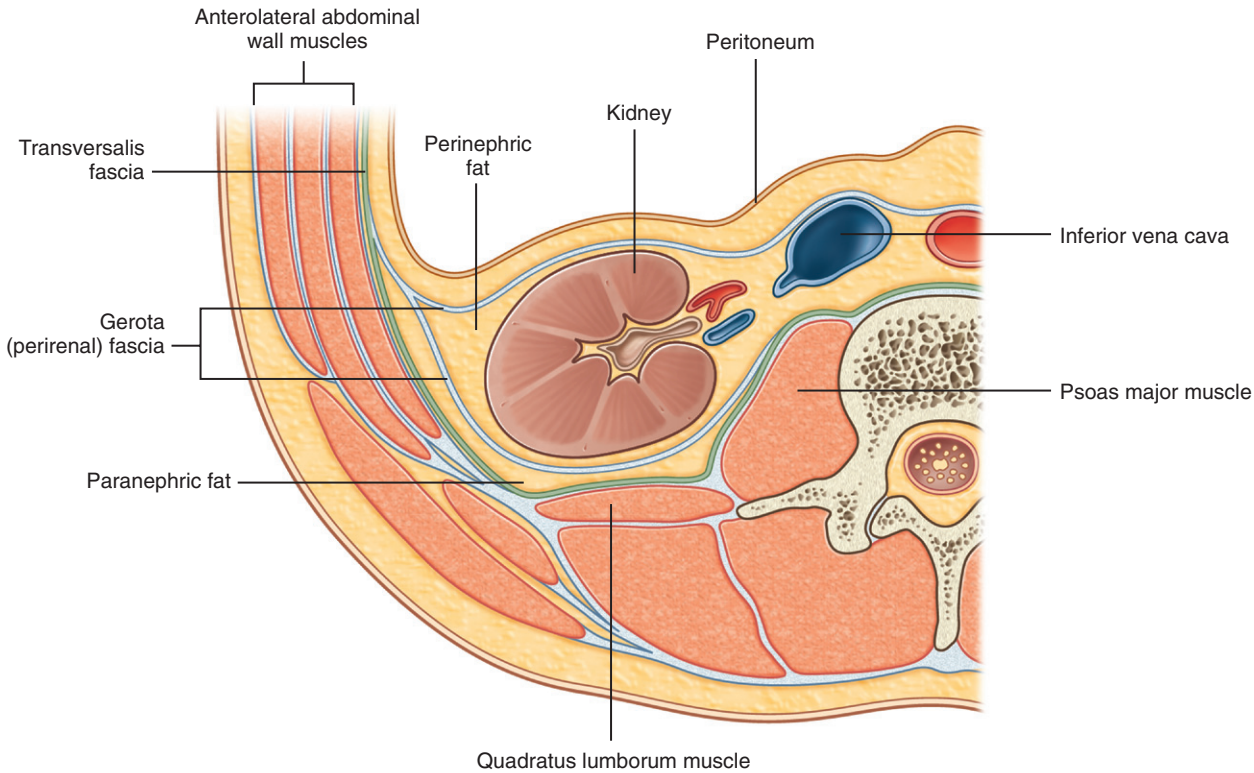


Figure 1–27. Organization of the fat and fascia surrounding the kidney. (From Drake RL, Vogl W, Mitchell AWM. Gray's anatomy for students. Philadelphia: Elsevier; 2005. p. 322.)

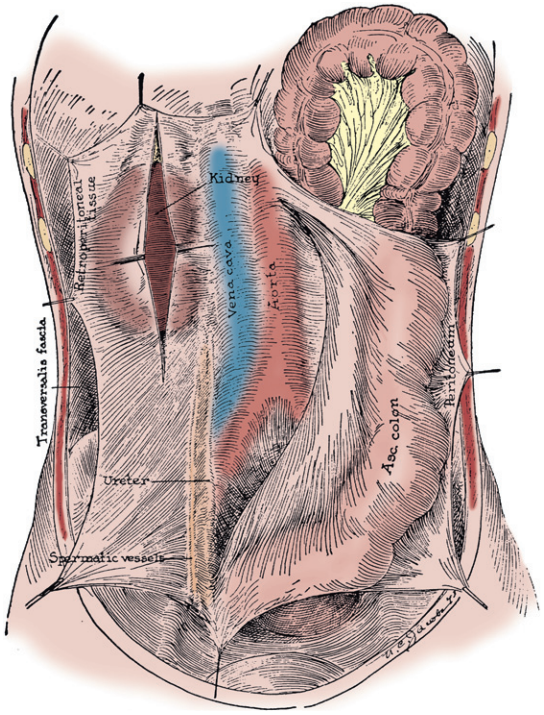


Figure 1–28. Anterior view of Gerota fascia on the right side, split over the right kidney (which it contains), and showing inferior extension enveloping the ureter and gonadal vessels. The ascending colon and overlying peritoneum have been reflected medially. (From Tobin CE. The renal fascia and its relation to the transversalis fascia. Anat Rec 1944;89:295–311.)

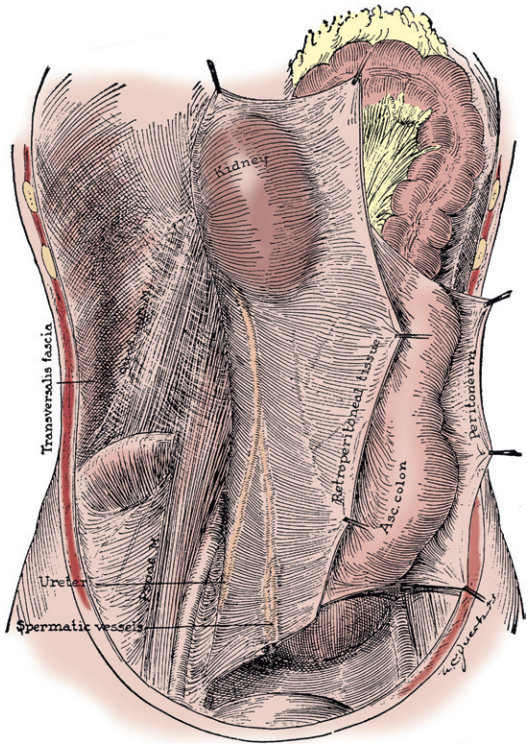


Figure 1–29. Posterior view of Gerota fascia on the right side, rotated medially with the contained kidney, ureter, and gonadal vessels, exposing the muscular posterior body wall covered by the transversalis fascia. (From Tobin CE. The renal fascia and its relation to the transversalis fascia. Anat Rec 1944;89:295–311.)

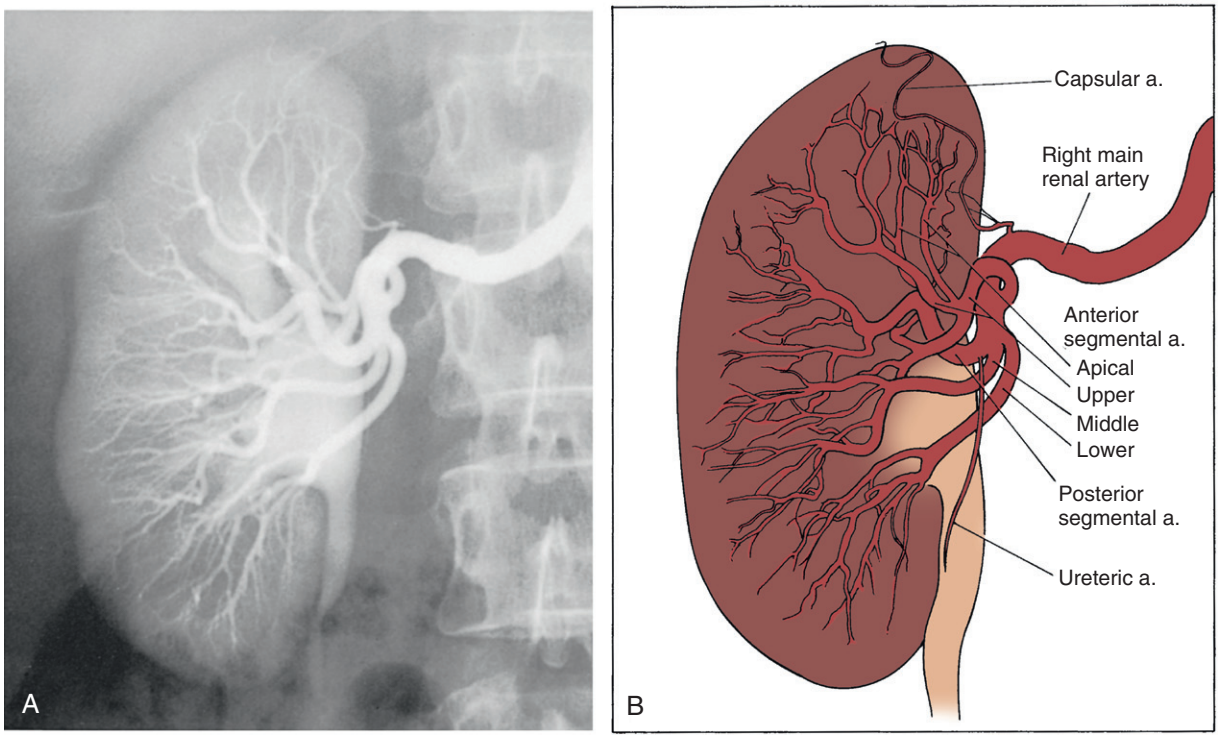


Figure 1–30. **A** and **B,** Segmental branches of the right renal artery demonstrated by renal angiogram.

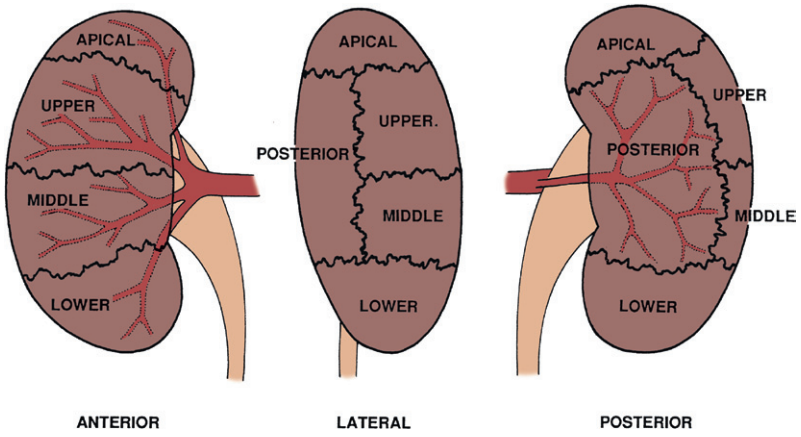


Figure 1–31. Typical segmental circulation of the right kidney, shown diagrammatically. Note that the posterior segmental artery is usually the first branch of the main renal artery and it extends behind the renal pelvis.

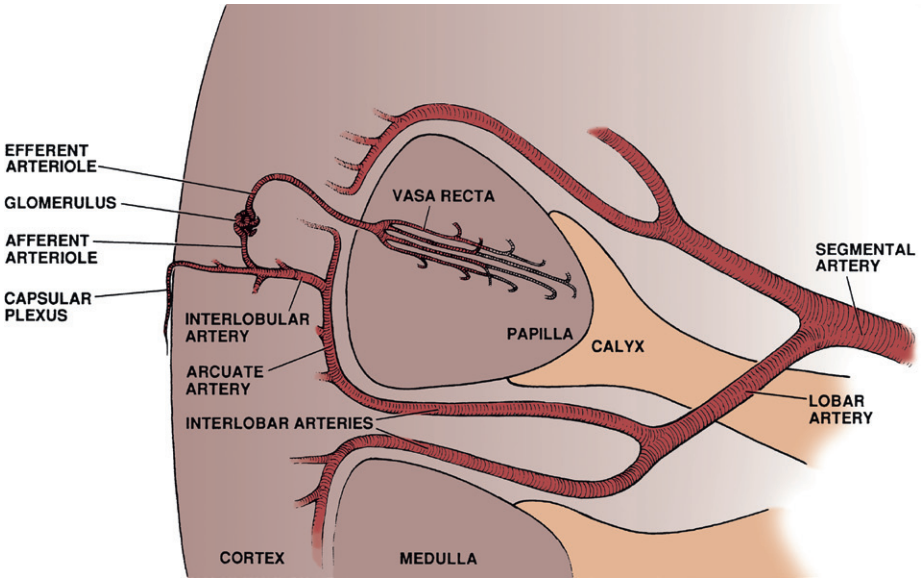


Figure 1–32. Intrarenal arterial anatomy.

delineation before incision. This can be done with either preoperative angiography or intraoperative segmental arterial injection of a dye such as methylene blue.

Once in the renal sinus, the segmental arteries branch into **lobar arteries,** which further subdivide in the renal parenchyma to form **interlobar** arteries (Fig. 1–32). These interlobar arteries progress peripherally within the cortical columns of Bertin, thus avoiding the renal pyramids but maintaining a close association with the minor calyceal infundibula. At the base (peripheral edge) of the renal pyramids, the interlobar arteries branch into **arcuate arteries.** Instead of moving peripherally, the arcuate arteries parallel the edge of the corticomedullary junction. **Interlobular arteries** branch off the arcuate arteries and move radially, where they eventually divide to form the **afferent arteries** to the glomeruli.

The 2 million glomeruli within each kidney represent the core of the renal filtration process. Each glomerulus is fed by an afferent arteriole. As blood flows through the glomerular capillaries, the urinary filtrate leaves the arterial system and is collected in the glomerular (Bowman) capsule. Blood flow leaves the glomerular capillary via the efferent arteriole and continues to one of two locations: secondary capillary networks around the urinary tubules in the cortex or descending into the renal medulla as the vasa recta.

Renal Veins

The renal venous drainage correlates closely with the arterial supply. **The interlobular veins drain the postglomerular capillaries. These veins also communicate freely via a subcapsular venous plexus of stellate veins with veins in the perinephric fat. After the interlobular veins, the venous drainage progresses through the arcuate, interlobar, lobar, and segmental branches, with the course of each of these branches paralleling the respective artery.** After the segmental branches, the venous drainage coalesces into three to five venous trunks that eventually combine to form the renal vein. **Unlike the arterial supply, the venous drainage communicates freely through venous collars around the infundibula, providing for extensive collateral circulation in the venous drainage of the kidney** (Fig. 1–33). **Surgically, this is important because unlike the arterial supply, occlusion of a segmental venous branch has little effect on venous outflow.**

The renal vein is located directly anterior to the renal artery, although this position can vary up to 1 to 2 cm cranially or caudally relative to the artery. The right renal vein is generally 2 to 4 cm in length and enters the right lateral to posterolateral edge of the IVC. The left renal vein is typically 6

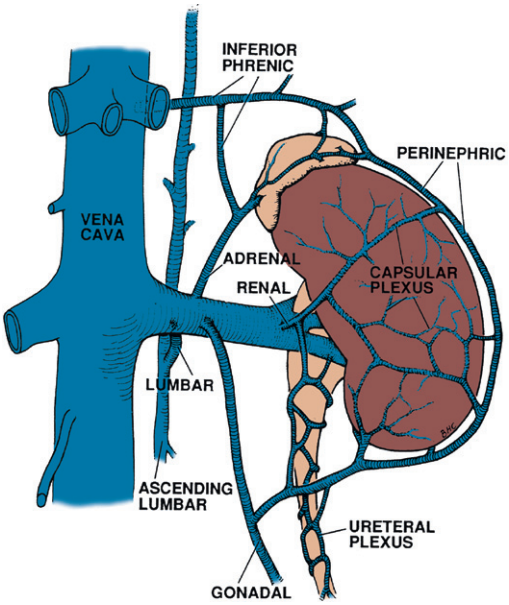


Figure 1–33. Venous drainage of the left kidney showing potentially extensive venous collateral circulation.

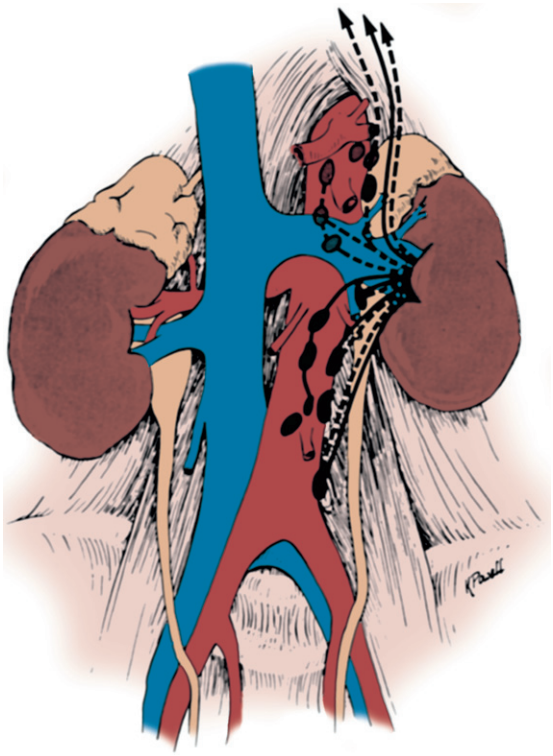


Figure 1–35. Regional lymphatic drainage of the left kidney. *Dark nodes,* anterior; *light nodes,* posterior. *Solid lines,* anterior lymphatic channels; *dashed lines,* posterior lymphatic channels. *Arrows* lead to the thoracic duct.

to 10 cm in length and enters the left lateral aspect of the IVC after passing posterior to the superior mesenteric artery and anterior to the aorta (Fig. 1–34 on the Expert Consult website). Compared with the right renal vein, the left renal vein enters the IVC at a slightly more cranial level and a more anterolateral location. **Additionally, the left renal vein receives the left adrenal vein superiorly, lumbar vein posteriorly, and left gonadal vein inferiorly** (see Fig. 1–33). The right renal vein typically does not receive any branches.

Common Anatomic Variants

Anatomic variations in the renal vasculature are common, occurring in 25% to 40% of kidneys. The most common variation is supernumerary renal arteries, with up to five arteries reported. This occurs more often on the left. These additional arteries can enter through the hilum or directly into the parenchyma. **Lower pole arteries on the right tend to cross anterior to the IVC, whereas lower pole arteries on either side can cross anterior to the collecting system, causing a ureteropelvic junction obstruction.** When the kidney is ectopic, supernumerary arteries are even more common and their origin even more varied, with the celiac trunk, superior mesenteric artery, or iliac arteries all possible sources of ectopic renal arteries. Supernumerary veins occur as well, but this is a less common entity. The most common example is duplicate renal veins draining the right kidney via the right renal hilum. Polar veins are quite rare. Finally, the left renal vein may course behind the aorta or divide and send one limb anterior and one limb posterior to the aorta, resulting in a collar-type circumaortic formation.

Renal Lymphatics

The renal lymphatics largely follow blood vessels through the columns of Bertin and then form several large lymphatic trunks within the renal sinus. As these lymphatics exit the hilum, branches from the renal capsule, perinephric tissues, renal pelvis, and upper ureter drain into these lymphatics. They then empty into lymph nodes associated with the renal vein near the renal hilum. From here, the lymphatic drainage between the two kidneys varies (Figs. 1–35 and 1–36). **On the left, primary lymphatic drainage is into the left lateral para-aortic lymph nodes including nodes anterior and posterior to the aorta between the inferior mesenteric artery and the diaphragm. Occasionally, there will be additional drainage from the left kidney into the retrocrural nodes or directly into the thoracic duct above the diaphragm. On the right, drainage is into the right interaortocaval and right paracaval lymph nodes** including nodes located anterior and posterior to the vena cava, from the common iliac vessels to the diaphragm. Occasionally, there will be additional drainage from the right kidney into the retrocrural nodes or the left lateral para-aortic lymph nodes.

Renal Collecting System

Microscopic Anatomy from Glomerulus to Collecting System

Microscopically, the renal collecting system originates in the renal cortex at the glomerulus as filtrate enters into Bowman capsule (Fig. 1–37 on the Expert Consult website). Together the glomerular capillary network and Bowman capsule form the renal corpuscle (malpighian corpuscle) (Fig. 1–38). The glomerular capillary network is covered by specialized epithelial cells called **podocytes** that, along with the capillary epithelium, form a selective barrier across which the urinary filtrate must pass. The filtrate is initially collected in Bowman capsule and then moves to the proximal convoluted tubule. The **proximal tubule** is composed of a thick cuboidal epithelium covered by dense

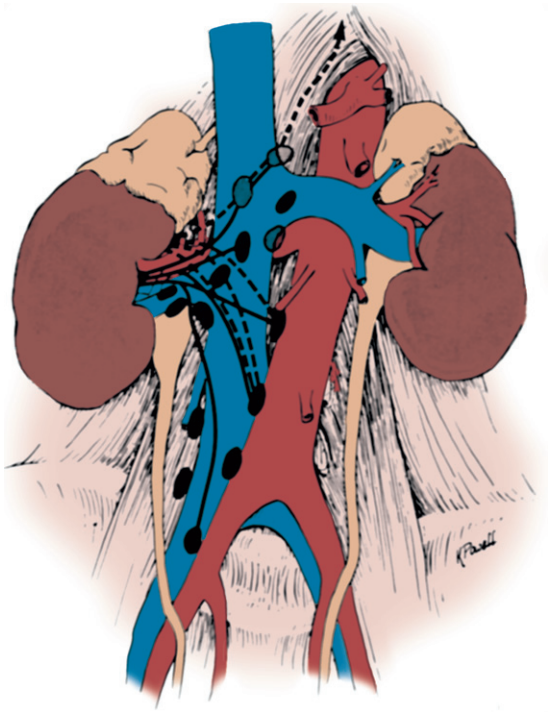


Figure 1–36. Regional lymphatic drainage of the right kidney. *Dark nodes,* anterior; *light nodes,* posterior. *Solid lines,* anterior lymphatic channels; *dashed lines,* posterior lymphatic channels. *Arrow* leads to the thoracic duct.

microvilli. These microvilli greatly increase the surface area of the proximal tubule, allowing a large portion of the urinary filtrate to be reabsorbed in this section of the nephron.

The proximal tubule continues deeper into the cortical tissue where it becomes the **loop of Henle.** The loop of Henle extends variable distances into the renal medulla. Within the renal medulla, the loop of Henle reverses course and moves back toward the periphery of the kidney. As it ascends out of the medulla the loop thickens and becomes the **distal convoluted tubule.** This tubule eventually returns to a position adjacent to the originating glomerulus and proximal convoluted tubule. Here the distal convoluted tubule turns once again for the interior of the kidney and becomes a collecting tubule. Collecting tubules from multiple nephrons combine into a collecting duct that extends inward through the renal medulla and eventually empties into the apex of the medullary pyramid, the renal papilla.

Renal Papillae, Calyces, and Pelvis

The renal papillae are the tip of a medullary pyramid and constitute the first gross structure of the renal collecting system. Typically, there are 7 to 9 papillae per kidney, but this number is variable, ranging from 4 to 18. The papillae are aligned in two longitudinal rows situated approximately 90 degrees from one another. There is an anterior row that owing to the orientation of the kidney faces in a lateral direction and a posterior row that extends directly posterior (see Figs. 1–26 and 1–39). **Each of these papillae is cupped by a minor calyx** (see Fig. 1–22). At the upper and lower poles, compound calyces are often encountered. These compound calyces are the result of renal pyramid fusion and because of their anatomy are more likely to allow reflux into the renal parenchyma (Fig. 1–40). Clinically, this can result in more severe scarring of the parenchyma overlying compound calyces.

After cupping an individual papilla, each minor calyx narrows to an infundibulum. Just as there is frequent variation in the number of calyces, the diameter and length of the infundibula vary greatly. **Infundibuli combine to form two or three major calyceal branches. These are frequently termed the *upper, middle,* and *lower pole calyces,* and these calyces in turn combine to form the renal pelvis. The renal pelvis itself can vary greatly in size, ranging from a small intrarenal pelvis to a large predominantly extrarenal pelvis.** Eventually the pelvis narrows to form the ureteropelvic junction, marking the beginning of the ureter.

On close examination, it is clear that there is significant variation in the anatomy of the renal collecting system (Figs. 1–41 through 1–43). Number of calyces, diameter of the infundibuli, and size of the renal pelvis all vary significantly among normal individuals. Even in the same individual, the renal collecting systems may be similar but are rarely identical. **Because of this variation, it can be difficult to distinguish pathologic from normal on the basis of anatomy alone. Instead, it is demonstrated dysfunction that is necessary to make the diagnosis of a pathologic anatomic formation within the renal collecting system.**

Renal Innervation

Sympathetic preganglionic nerves originate from the eighth thoracic through first lumbar spinal segments and then travel to the celiac and aorticorenal ganglia. From here, postganglionic fibers travel to the kidney via the autonomic plexus surrounding the renal artery. Parasympathetic fibers originate from the vagus nerve and travel with the sympathetic fibers to the autonomic plexus along the renal artery. The primary function of the renal autonomic innervation is vasomotor, with the sympathetics inducing vasoconstriction and the parasympathetics causing vasodilation. Despite this innervation, it is important to realize that the kidney functions well even without this neurologic control, as evidenced by the successful function of transplanted kidneys.

URETERS

The ureters are bilateral tubular structures responsible for transporting urine from the renal pelvis to the bladder (see Fig. 1–1). They are generally 22 to 30 cm in length with a wall composed of multiple layers (Fig. 1–44). The inner layer is transitional epithelium. Next is the lamina propria. This is a connective tissue layer that along with the epithelium makes up the mucosal lining. Overlying the lamina propria is a layer of smooth muscle that is contiguous with muscle covering the renal calyces and pelvis,

Key Point: Ureters

- The course of the ureter begins posterior to the renal artery and continues along the anterior edge of the psoas muscle. The gonadal vessels cross anterior to the ureter in this region. The ureter next passes over the iliac vessels, generally marking the bifurcation of common iliac into internal and external iliacs.

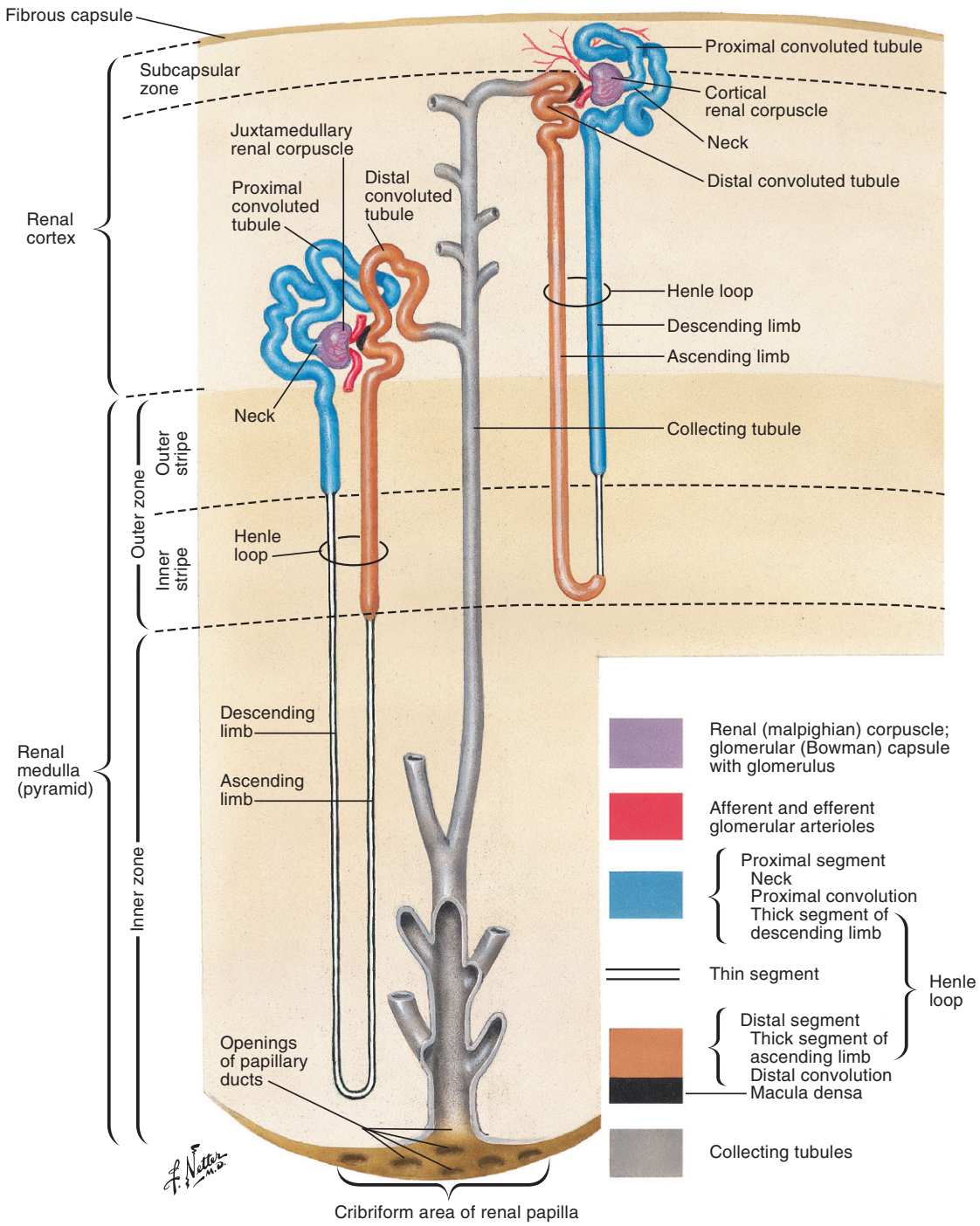


Figure 1–38. Renal nephron and collecting tubule. (From Netter FH. Atlas of human anatomy. 4th ed. Philadelphia: Elsevier; 2006. p. 336.)

although in the ureter this layer is divided into an inner longitudinal and an outer circular layer. Together, these muscular layers provide the peristaltic wave that actively transports urine from the renal collecting system through the ureter to the bladder. The outermost layer is the adventitia. This thin layer surrounds the ureter and encompasses the blood vessels and lymphatics that travel along the ureter.

Anatomic Relationships

Key to many urologic procedures is an understanding of ureteral anatomic relationships. The ureter begins at the ureteropelvic junction, which lies posterior to the renal artery and vein. It then progresses inferiorly along the anterior edge of the psoas muscle. Anteriorly, the right ureter is related to the ascending colon, cecum, colonic mesentery, and appendix. The left ureter is closely related to the descending and sigmoid colon and their accompanying mesenteries. Approximately a third of the way to the bladder the ureter is crossed anteriorly by the gonadal vessels. As it enters the pelvis the ureter crosses anterior to the iliac vessels. **This crossover point is usually at the bifurcation of the common iliac into the internal and external iliac arteries, thus making this a useful landmark for pelvic procedures.**

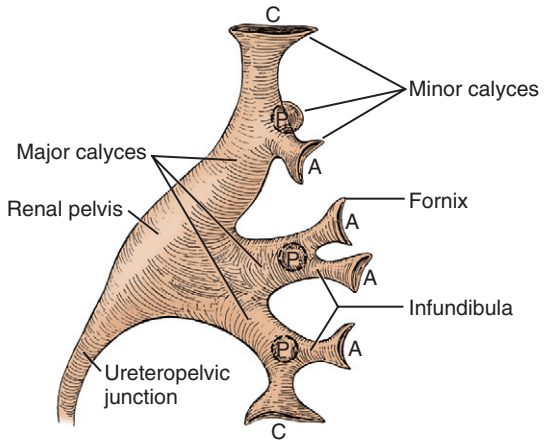


Figure 1–39. The renal collecting system (left kidney) showing major divisions into minor calyces, major calyces, and renal pelvis. A, anterior minor calyces; C, compound calyces at the renal poles; P, posterior minor calyces.

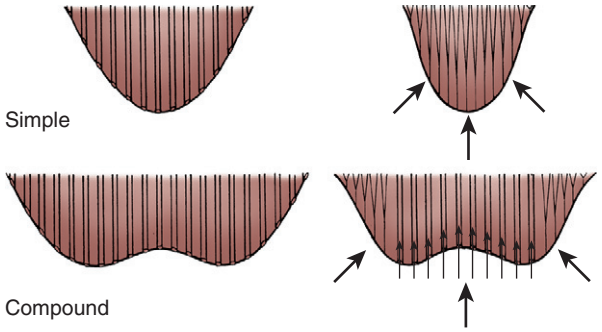


Figure 1–40. Diagram demonstrating structural and functional distinctions between simple and compound renal papillae. Back pressure causes closure of the collecting ducts in a simple papilla, effectively preventing reflux of urine into the renal parenchyma. The structure of the compound papilla allows intrarenal reflux of urine with sufficient back pressure.

Given the proximity of the ureters to several bowel segments, malignant and inflammatory processes of the terminal ileum, appendix, right or left colon, and sigmoid colon may involve the ureter. Effects can range from microhematuria to fistula or total obstruction. Within the female pelvis, the ureters are crossed anteriorly by the uterine arteries and are closely related to the uterine cervix. This location places the ureters at risk during hysterectomy. Pathologic processes of the fallopian tube and ovary may also encroach on the ureter at the pelvic brim.

Normal Variations in Ureteral Caliber

The normal ureter is not of uniform caliber, with three distinct narrowings classically described: the

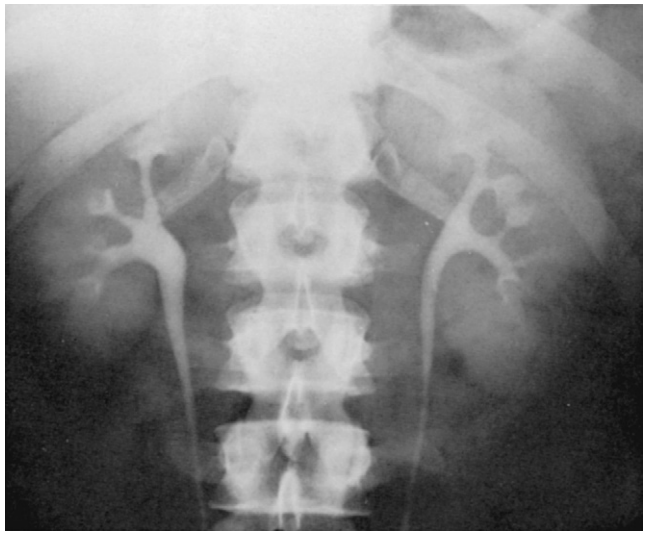


Figure 1–41. Normal bilateral renal collecting systems, demonstrated by excretory urography.

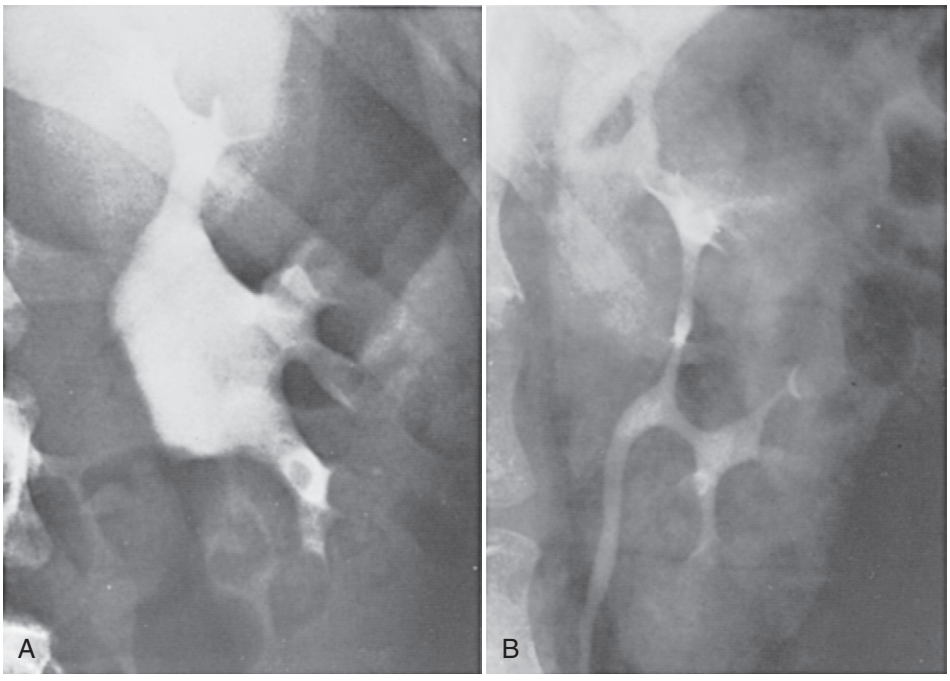


Figure 1–42. Significant variation between two normal renal pelves, demonstrated by excretory urography. **A,** Large, extrarenal pelvis. **B,** Narrow, completely intrarenal pelvis, barely larger in caliber than the ureter.

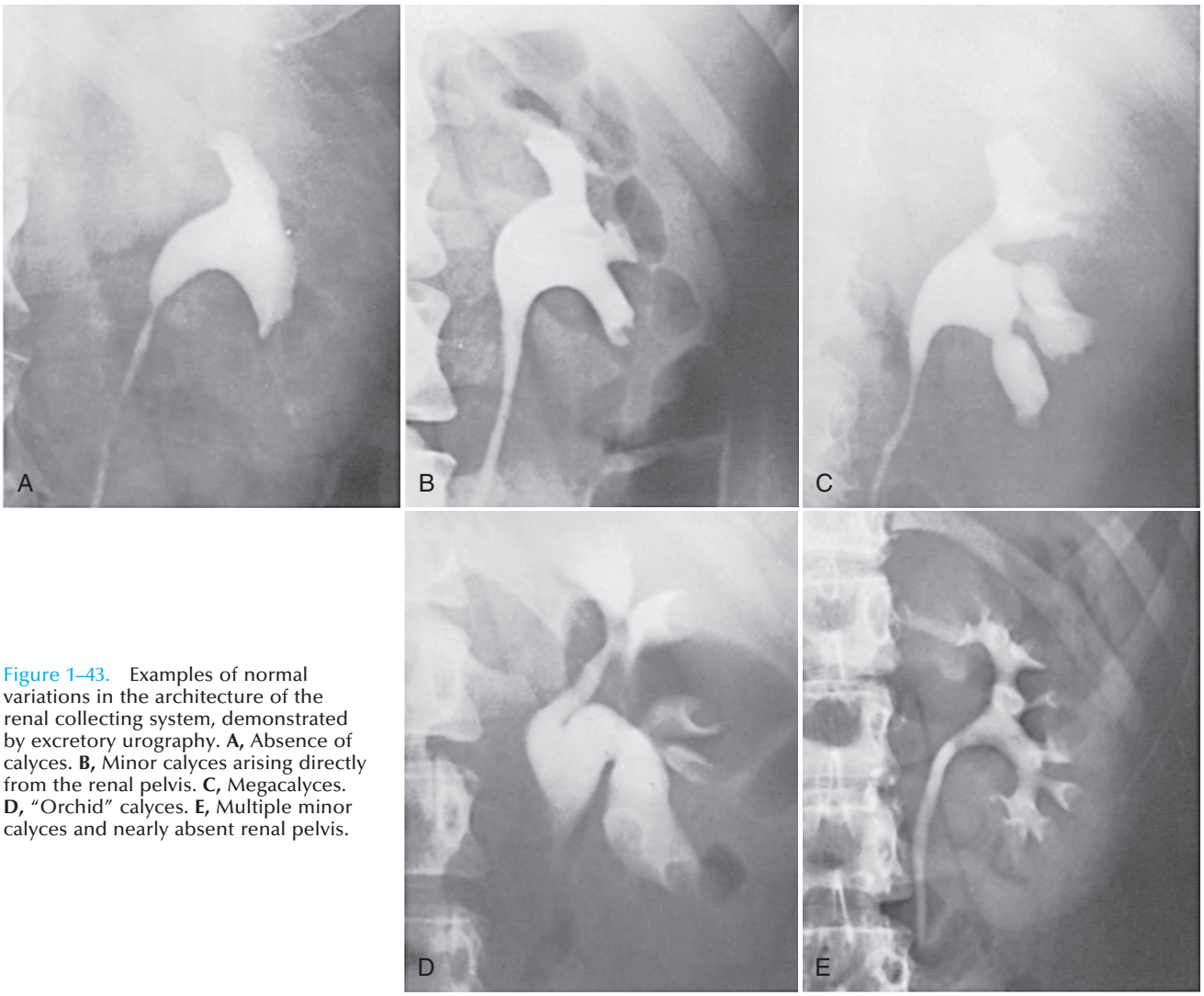


Figure 1–43. Examples of normal variations in the architecture of the renal collecting system, demonstrated by excretory urography. **A,** Absence of calyces. **B,** Minor calyces arising directly from the renal pelvis. **C,** Megacalyces. **D,** "Orchid" calyces. **E,** Multiple minor calyces and nearly absent renal pelvis.

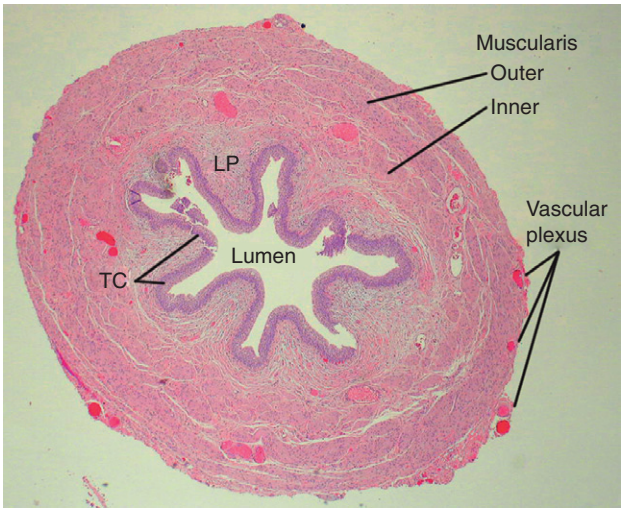


Figure 1–44. Transverse microscopic section through the ureter. Inner longitudinal layer is distinguished from outer circular and oblique muscle fibers. The rich vascular supply of the ureter is also demonstrated. LP, lamina propria; TC, transitional epithelium. (Courtesy of Dr. Hossein Saboorian.)

ureteropelvic junction, crossing of the iliac vessels, and the ureterovesical junction (Fig. 1–45). At the ureteropelvic junction, the renal pelvis tapers into the proximal ureter. In many cases, this perceived narrowing may be more apparent than real, with no evidence of obstruction evident on radiographic or endoscopic investigation. The second region of narrowing occurs as the ureter crosses the iliac vessels. This is due to a combination of extrinsic compression of the ureter by the iliac vessels and the necessary anterior angulation of the ureter as it crosses the iliac vessels to enter into the pelvis. There is also no intrinsic change in the ureteral caliber at this location. The third site of narrowing observed in the normal ureter is the ureterovesical junction. There is a true physical restriction of the ureter as it makes the intramural passage through the bladder wall to the ureteral orifice. These three sites of ureteral narrowing are clinically significant because they are common locations for urinary calculi to lodge during passage. In addition, the angulation of the ureter, first anteriorly as it passes over the iliac vessels, then posteromedially as it enters the pelvis and courses behind the bladder, may restrict successful passage of rigid endoscopes. Appreciation of this normal angulation and the three-dimensional course of the ureter is critical for safe and successful ureteral endoscopy.

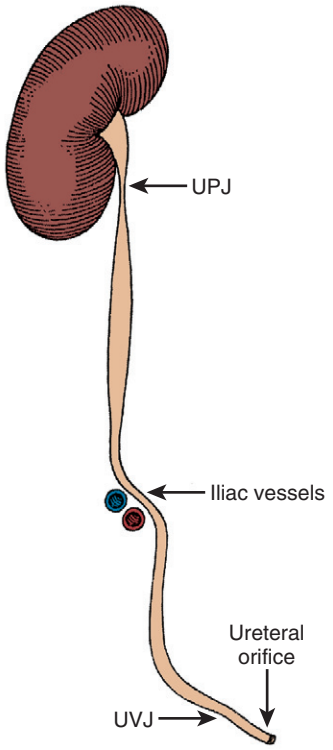


Figure 1–45. The ureter demonstrating sites of normal functional or anatomic narrowing at the ureteropelvic junction (UPJ), the iliac vessels, and the ureterovesical junction (UVJ). Note also the anterior displacement and angulation of the ureter, which occurs over the iliac vessels, as shown here diagrammatically.

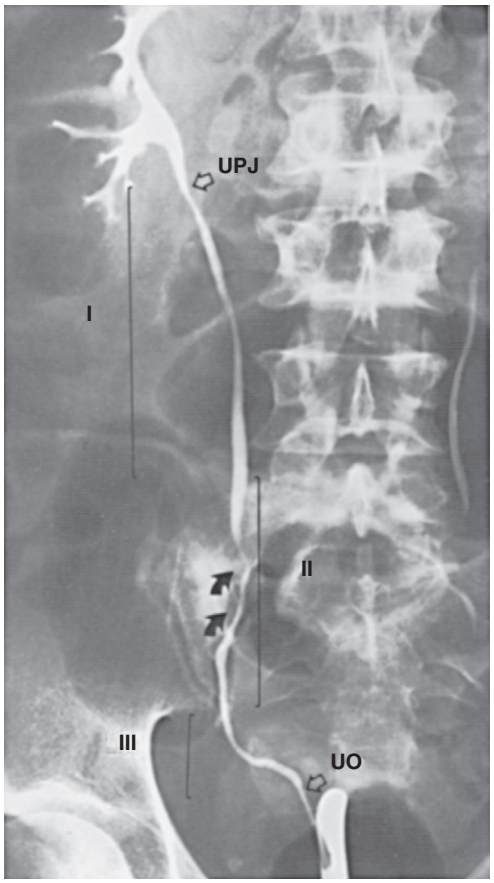


Figure 1–46. The right ureter, illustrated by retrograde injection of contrast material. UO, ureteral orifice in the bladder; UPJ, ureteropelvic junction; I, upper ureter, extending to the upper border of the sacrum; II, middle ureter, extending to the lower border of the sacrum; III, distal or lower ureter, traversing the pelvis to end in the bladder. *Arrows* indicate the course of the common iliac artery and vein.

Ureteral Segmentation and Nomenclature

The ureter is often arbitrarily divided into segments to assist ureteral description. The simplest system divides the ureter into the abdominal ureter extending from renal pelvis to the iliac vessels and the pelvic ureter extending from the iliac vessels to the bladder. **Alternatively, the ureter can be divided into upper, middle, and lower segments** (Fig. 1–46). **The upper ureter extends from the renal pelvis to the upper border of the sacrum. The middle ureter comprises the segment from the upper to the lower border of the sacrum. The lower (distal or pelvic) ureter extends from the lower border of the sacrum to the bladder.**

Ureteral Blood Supply and Lymphatic Drainage

The ureter receives its blood supply from multiple arterial branches along its course (Fig. 1–47). **Of greatest importance to the surgeon is that arterial branches to the abdominal ureter approach from a medial direction, whereas arterial branches to the pelvic ureter approach from a lateral direction.** For the upper ureter these branches originate from the renal artery, gonadal artery, abdominal aorta, and common iliac artery. After entering the pelvis, additional small arterial branches to the distal ureter may arise from the internal iliac artery or its branches, especially the vesical and uterine arteries, but also from the middle rectal and vaginal arteries. **After reaching the ureter, the arterial vessels course longitudinally within**

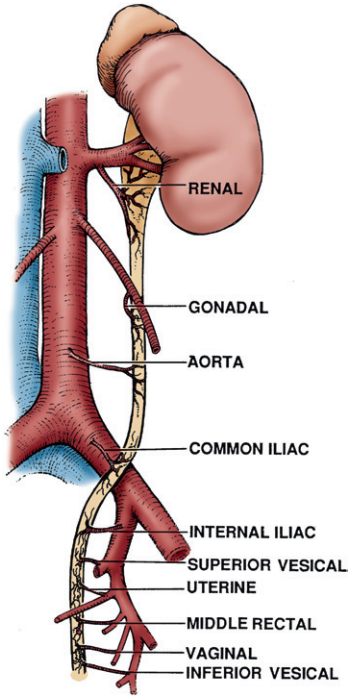


Figure 1–47. Sources of arterial blood supply to the ureter.

the periureteral adventitia in an extensive anastomosing plexus. It is this longitudinal vascularity that allows the ureter to be safely mobilized from the surrounding retroperitoneal tissues without compromising the vascular supply, provided that the periureteral adventitia is not stripped. The venous and lymphatic drainage of the ureter parallels the arterial supply. Thus ureteral lymphatic drainage varies by ureteral level. In the pelvis, ureteral lymphatics drain to internal, external, and common iliac nodes. In the abdomen the left para-aortic lymph nodes are the primary drainage site for the left ureter, whereas the abdominal portion of the right ureter is drained primarily to right paracaval and interaortocaval lymph nodes. The lymphatic drainage of the upper ureter and renal pelvis tends to join the renal lymphatics and is identical to that of the ipsilateral kidney.

Ureteral Innervation

The exact role of the ureteral autonomic input is unclear. Normal ureteral peristalsis does not require outside autonomic input but, rather, originates and is propagated from intrinsic smooth muscle pacemaker sites located in the minor calyces of the renal collecting system. The autonomic nervous system may exert some modulating effect on this process, but the exact role is unclear. The ureter receives preganglionic sympathetic input from the 10th thoracic through 2nd lumbar spinal segments. Postganglionic fibers arise from several ganglia in the aorticorenal, superior, and inferior hypogastric autonomic plexuses. Parasympathetic input is received from the 2nd through 4th sacral spinal segments.

Pain Perception and Somatic Referral

Renal pain fibers are stimulated by tension (distention) in the renal capsule, renal collecting system, or ureter. Direct mucosal irritation in the upper urinary tract may also stimulate nociceptors. Signals travel with the sympathetic nerves and result in a visceral-type pain referred to the sympathetic distribution of the kidney and ureter (eighth thoracic through second lumbar). Pain and reflex muscle spasm are typically produced over the distributions of the subcostal, iliohypogastric, ilioinguinal, and/or genitofemoral nerves, resulting in flank, groin, or scrotal (or labial) pain and hyperalgesia, depending on the location of the noxious visceral stimulus (Fig. 1–48).

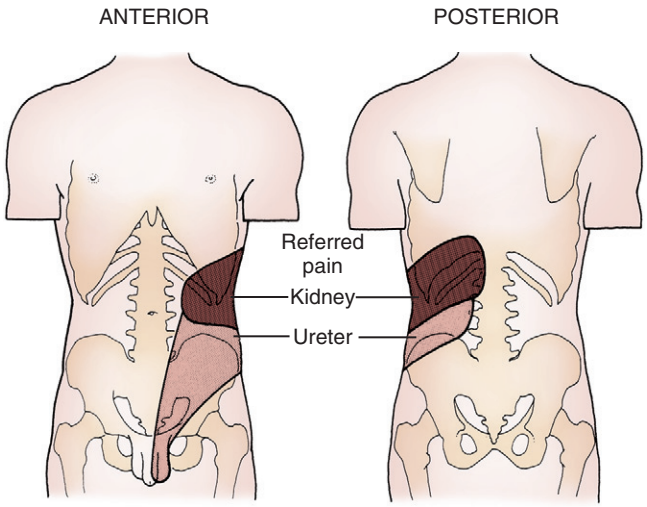


Figure 1–48. Patterns of referred somatic pain from the upper urinary tract.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

SUGGESTED READINGS

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The complete reference list is available online at www.expertconsult.com.

chapter 2

Anatomy of the Lower Urinary Tract and Male Genitalia

Benjamin I. Chung, MD ● Graham Sommer, MD ● James D. Brooks, MD

Bony Pelvis
Anterior Abdominal Wall
Soft Tissues of the Pelvis
Pelvic Circulation
Pelvic Innervation
Pelvic Viscera
Perineum

This chapter provides a general anatomic framework to guide the pelvic surgeon. The bony, ligamentous, and muscular framework of the pelvis is presented first. Next, the pelvic vessels and nerves and the genital, urinary, and gastrointestinal viscera are discussed. Finally, the perineum and external genitalia are reviewed.

BONY PELVIS

The pelvic bones are the sacrum (the termination of the axial skeleton) and the two innominate bones. The latter are formed by the fusion of the iliac, ischial, and pubic ossification centers at the acetabulum (Fig. 2–1). The ischium and pubis also meet below, in the center of the inferior ramus, to form the obturator foramen. The weight of the upper body is transmitted from the axial skeleton to the innominate bones and lower extremities through the strong sacroiliac (SI) joints. As a whole, the pelvis is divided into a bowl-shaped false pelvis, formed by the iliac fossae and largely in contact with intraperitoneal contents, and the circular true pelvis wherein the urogenital organs lie. At the pelvic inlet, the true and false pelves are separated by the arcuate line, which extends from the sacral promontory to the pectineal line of the pubis. The lumbar lordosis that accompanies erect posture tilts the axis of the pelvic inlet so that it parallels the ground; the pelvic inlet faces anteriorly, and the inferior ischiopubic rami lie horizontal (Fig. 2–2). When approaching the pelvis through a low midline incision, the surgeon gazes directly into the true pelvis.

The anterior and posterior iliac spines, the iliac crests, the pubic tubercles, and the ischial tuberosities are palpable landmarks that orient the pelvic surgeon (see Fig. 2–1). Cooper (pectineal) ligament overlies the pectineal line and offers a sure hold for sutures in hernia repairs and urethral suspension procedures (Fig. 2–3). The ischial spine is palpable transvaginally and attaches to the pelvic diaphragm and the sacrospinous ligament. The sacrospinous ligament separates the greater and lesser sciatic foramina. Together with the sacrotuberous ligament, it stabilizes the SI joint by preventing downward rotation of the sacral promontory. The SI joint, synovial in type, gains additional strength from anterior and posterior ligaments. In pelvic trauma, fractures virtually never involve this joint but occur adjacent to it. The pubes, the thinnest of the pelvic bones, are nearly always fractured, and their fragments may injure the adjacent bladder, urethra, and vagina. Resection or congenital nonunion of the pubes (e.g., bladder exstrophy) does not affect ambulation because of the strength of the SI joint (Waterhouse et al, 1973; Golimbu et al, 1990).

ANTERIOR ABDOMINAL WALL

Skin and Subcutaneous Fasciae

To minimize scarring, incisions of the anterior abdominal wall and flank should follow Langer lines of cleavage. These lines parallel dermal collagen fibers and are oriented along lines of stress. They correspond to the segmental thoracic and lumbar nerves. The skin is backed by Camper fascia, a loose layer of fatty tissue that varies in thickness with the nutritional status of the patient. The superficial circumflex iliac, external pudendal, and superficial inferior epigastric vessels branch from the femoral vessels to run in this layer (Figs. 2–4 and 2–5). The superficial inferior epigastric vessels are encountered during inguinal incisions and can cause troublesome bleeding during placement of pelvic laparoscopic ports.

Scarpa fascia forms a distinct layer deep to Camper fascia, although it may be difficult to discern in older patients. Superiorly and laterally, it blends with Camper fascia. Inferiorly, it fuses with the deep fascia of the thigh 1 cm below the inguinal ligament along a line from the anterior superior iliac spine to the pubic tubercle. Medially, it is continuous with Colles fascia of the perineum (see Fig. 2–4). Colles fascia attaches to the posterior edge of the urogenital diaphragm and the inferior ischiopubic rami. It is continuous with the dartos fascia of the penis and scrotum. These fasciae can limit both the spread of infection in necrotizing fasciitis of the scrotum (Fournier gangrene) and the extent of urinary extravasation in an anterior urethral injury. For instance, blood and urine can accumulate in the scrotum and penis deep to the dartos fascia after an anterior urethral injury. In the perineum, their spread is limited by the fusions of Colles fascia

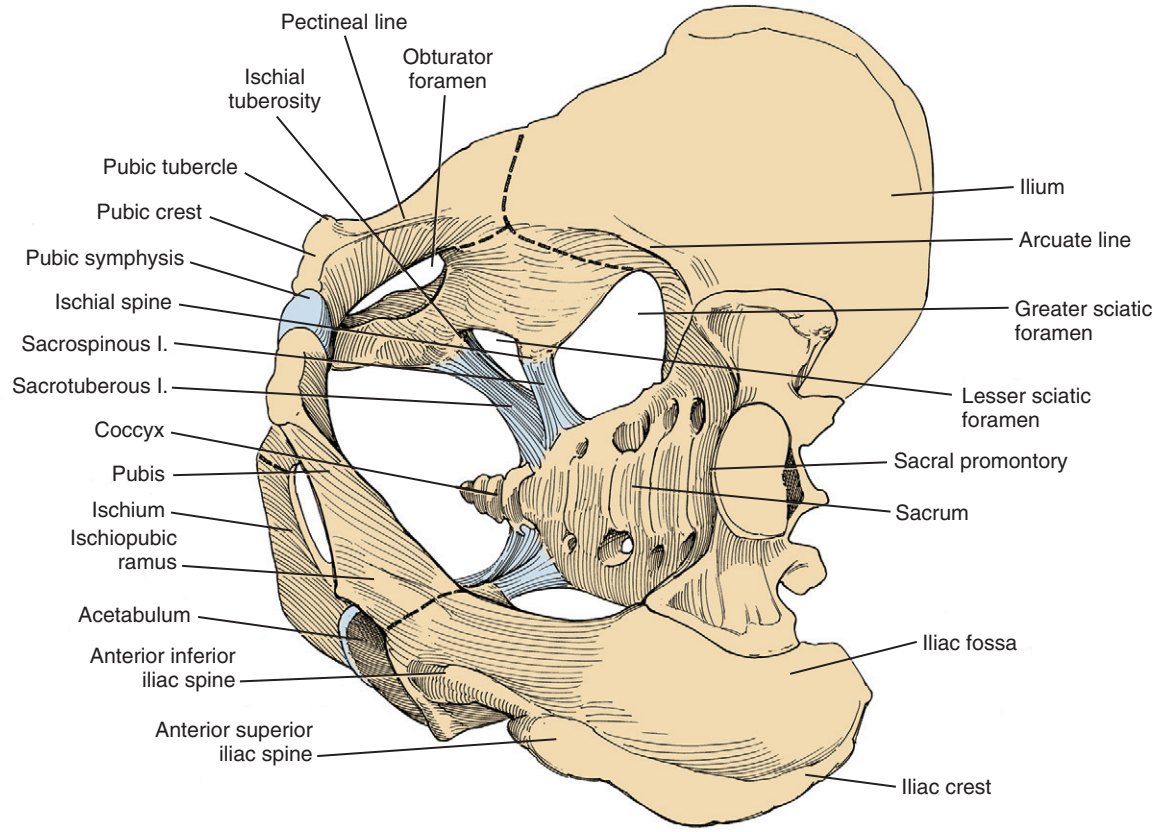


Figure 2–1. The bones and ligaments of the pelvis. (From Hinman F Jr. Atlas of urosurgical anatomy. Philadelphia: WB Saunders; 1993. p. 196.)

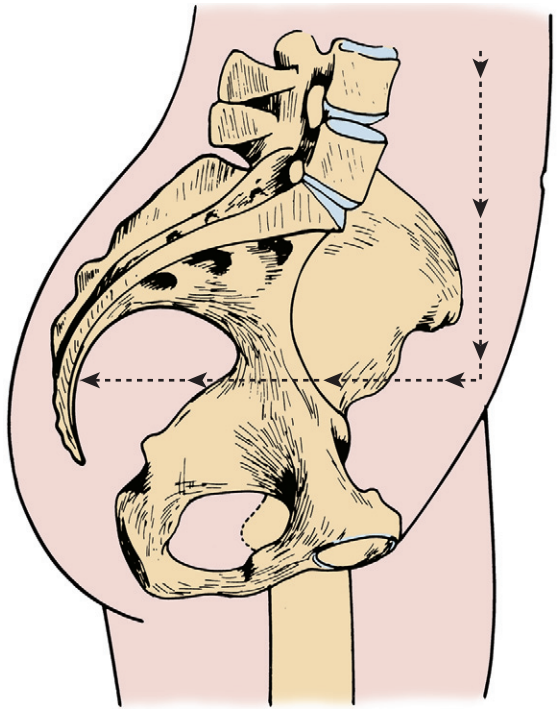


Figure 2–2. Pelvis in standing position. The axis of the pelvic cavity is horizontal because of lumbar lordosis. (From Zacharin RF. Pelvic floor anatomy and the surgery of pulsion enterocele. New York: Springer-Verlag; 1985. p. 15.)

to the ischiopubic rami laterally and to the posterior edge of the perineal membrane; the resulting hematoma is therefore butterfly shaped. Because of these fasciae, bleeding, infection, or urinary extravasation will not extend down the leg or into the buttock but can freely travel up the anterior abdominal wall deep to Scarpa fascia to the clavicles and around the flank to the back.

Abdominal Musculature

The abdominal musculature lies immediately below Scarpa fascia. The origins of the external oblique, internal oblique, and transversus abdominis muscles and the orientation of their fibers are presented in Chapter 1. **These muscles terminate on the anterior abdominal wall as broad, tough aponeurotic sheets that fuse in the midline (linea alba) and form the rectus sheath** (see Fig. 2–5). The linea alba is avascular and is a convenient point of access to the peritoneal and pelvic cavities. In its upper portion, the anterior rectus sheath is formed by the aponeurosis of the external oblique muscle and a portion of the internal oblique muscle (Fig. 2–6). The posterior sheath is derived from the remaining internal oblique aponeurosis and the transversus abdominis aponeurosis. Two thirds of the distance from the pubis to the umbilicus, the arcuate line is formed, as all aponeurotic layers abruptly pass anterior to the rectus abdominis, leaving this muscle clothed only by transversalis fascia and peritoneum posteriorly.

The rectus abdominis arises from the pubis medial to the pubic tubercle and inserts on the xyphoid process

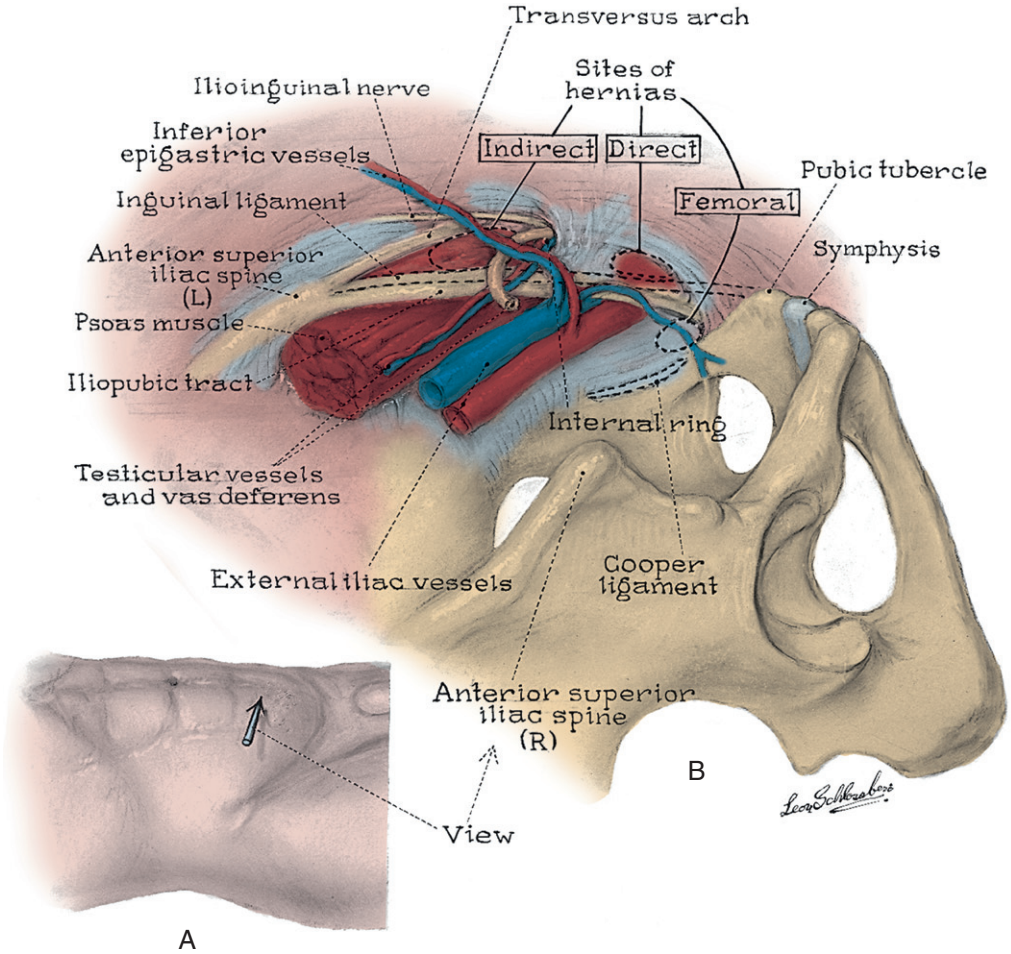


Figure 2–3. Topography (**A**) and posterior wall (**B**) of the left inguinal canal, viewed from the preperitoneal space. The location of three types of inguinal hernia is demonstrated. (From Schlegel PN, Walsh PC. Simultaneous preperitoneal hernia repair during radical pelvic surgery. J Urol 1987;137:1181.)

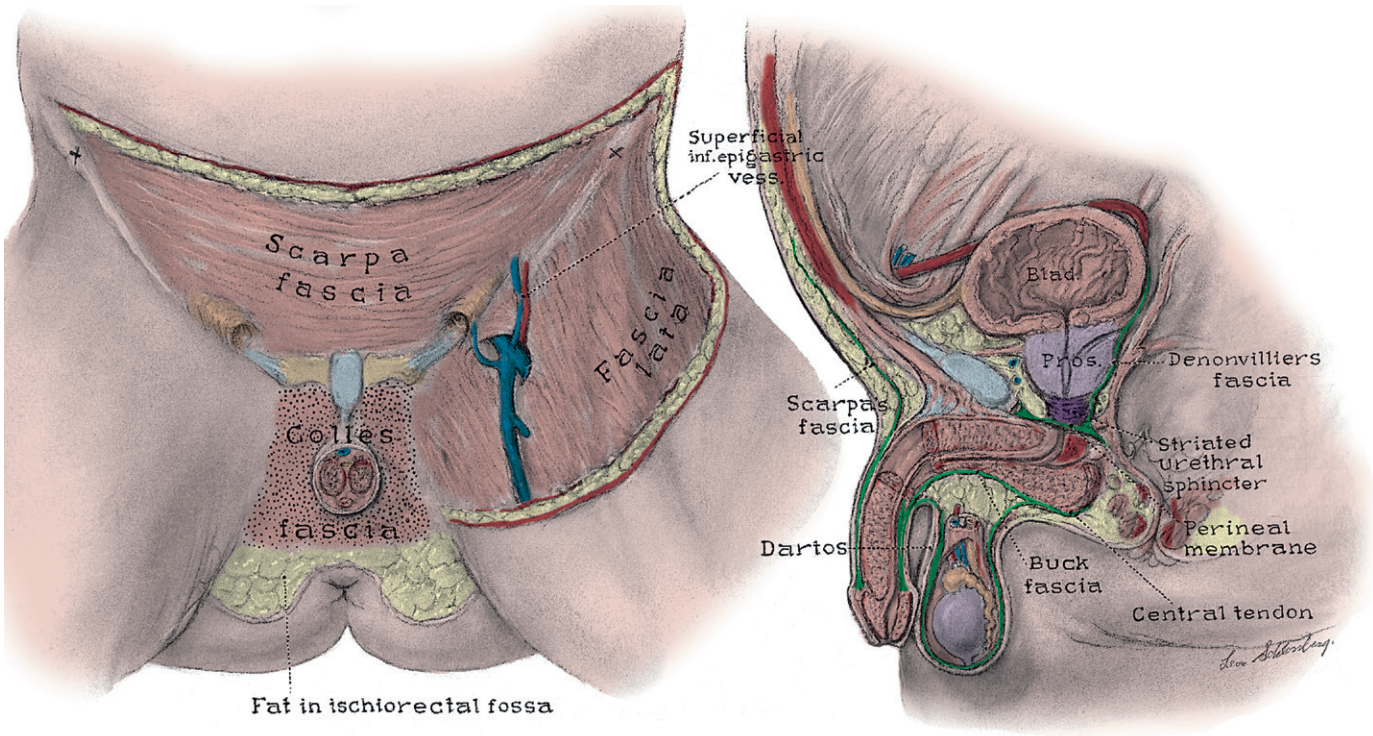


Figure 2–4. *Left,* Anterior view of the deep fasciae of the abdomen, perineum, and thigh. Note the superficial inferior epigastric artery passing superiorly in Camper fascia. *Right,* Midline sagittal view of the pelvic fasciae and their attachments.

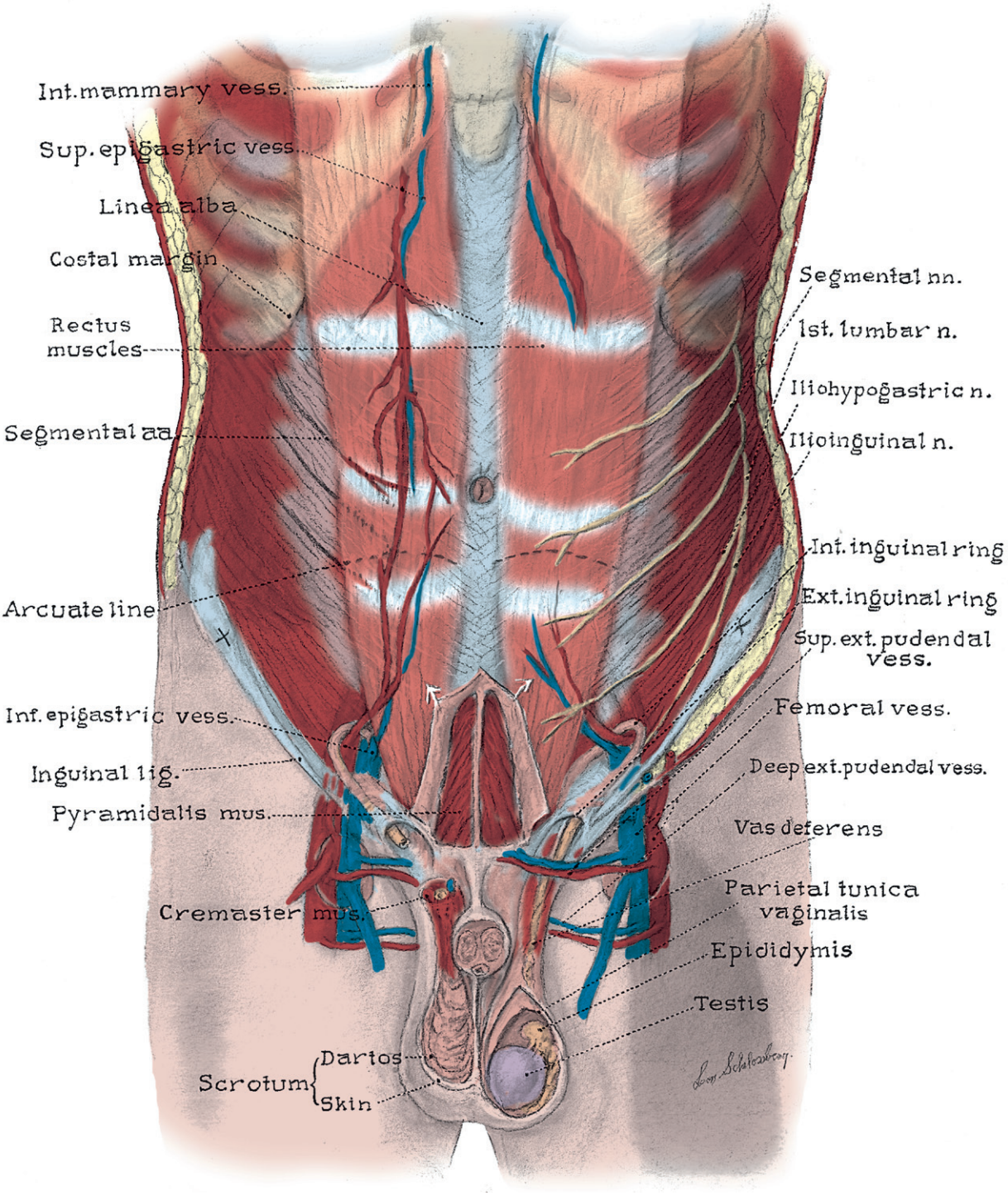


Figure 2–5. Muscles, vessels, and nerves of the anterior abdominal wall.

and adjacent costal cartilages. The muscle is crossed by three or four tendinous intersections that are firmly attached to the anterior rectus sheath; thus the muscle can be divided transversely without significant retraction. It is supplied by the last six thoracic segmental nerves that enter it laterally. Paramedian incisions lateral to the rectus divide these nerves, cause atrophy of the rectus, and predispose to ventral hernia. Anterior to the rectus and within its sheath, the triangle-shaped pyramidalis muscle arises from the pubic crest and inserts into the linea alba (see Fig. 2–5). It is supplied by the subcostal nerve (T12).

Inguinal Canal

The inguinal canal transmits the spermatic cord in the male, the round ligament in the female, and the ilioinguinal nerve in both sexes (Fig. 2–7; see also Fig. 2–5). Its anterior wall and floor are formed by the external oblique muscle, which folds over at its inferior edge as the inguinal ligament. Above the pubic tubercle, the fibers of the external oblique aponeurosis split to form the lateral edges (crura) of the external inguinal ring. Transverse (intercrural) fibers bridge the crura to

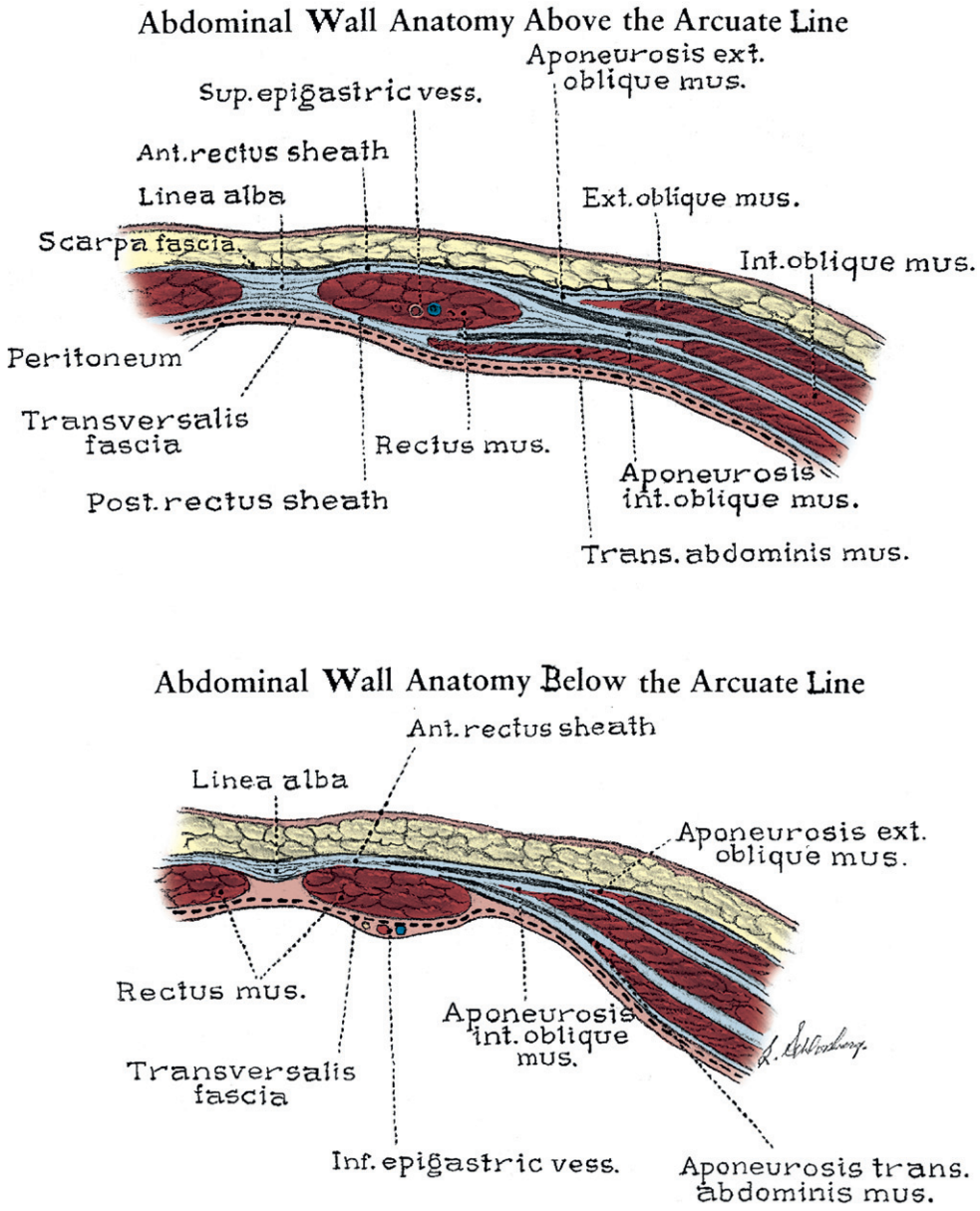


Figure 2–6. Cross section of the rectus sheath. *Top,* Above the arcuate line, the aponeurosis of the external oblique muscle forms the anterior sheath, and the transversus aponeurosis forms the posterior sheath. The internal oblique muscle splits to contribute to both the anterior and the posterior sheaths. *Bottom,* Below the arcuate line, all aponeuroses pass anterior to the rectus.

form the superior edge of the external ring. By dividing the intracrural fibers, the external oblique can be separated along its fibers to gain access to the cord. The posterior wall of the canal is formed by the transversalis fascia, which lines the inner surface of the abdominal wall. The cord structures pierce this fascia lateral to the inferior epigastric vessels at the internal inguinal ring (see Fig. 2–3). The internal inguinal ring lies midway between the anterior superior iliac spine and the pubic tubercle, above the inguinal ligament, and 4 cm lateral to the external ring. Fibers of the internal oblique and transversus abdominis arise from the iliopsoas fascia and inguinal ligament lateral to the internal ring and arch over the canal to form its roof. They fuse as the conjoint tendon, pass posterior to the cord, and insert into the rectus sheath and pubis. The conjoint tendon reinforces the posterior wall of the inguinal canal at the external ring. With contraction of the internal oblique and transversus muscles, the roof of the canal closes against the floor, preventing herniation of intra-abdominal contents into the canal. Hernias into the canal may occur medial (direct) or lateral (indirect) to the inferior epigastric vessels (see Figs. 2–3 and 2–7).

Internal Surface of the Anterior Abdominal Wall

Approached laparoscopically, **three elevations of the peritoneum, referred to as the *median, medial,* and *lateral umbilical folds,*** are visible on the anterior abdominal wall below the umbilicus (Fig. 2–8). The median fold overlies the median umbilical ligament (urachus), a fibrous remnant of the cloaca that attaches the bladder to the anterior abdominal wall. The obliterated umbilical artery in the medial umbilical fold serves as an

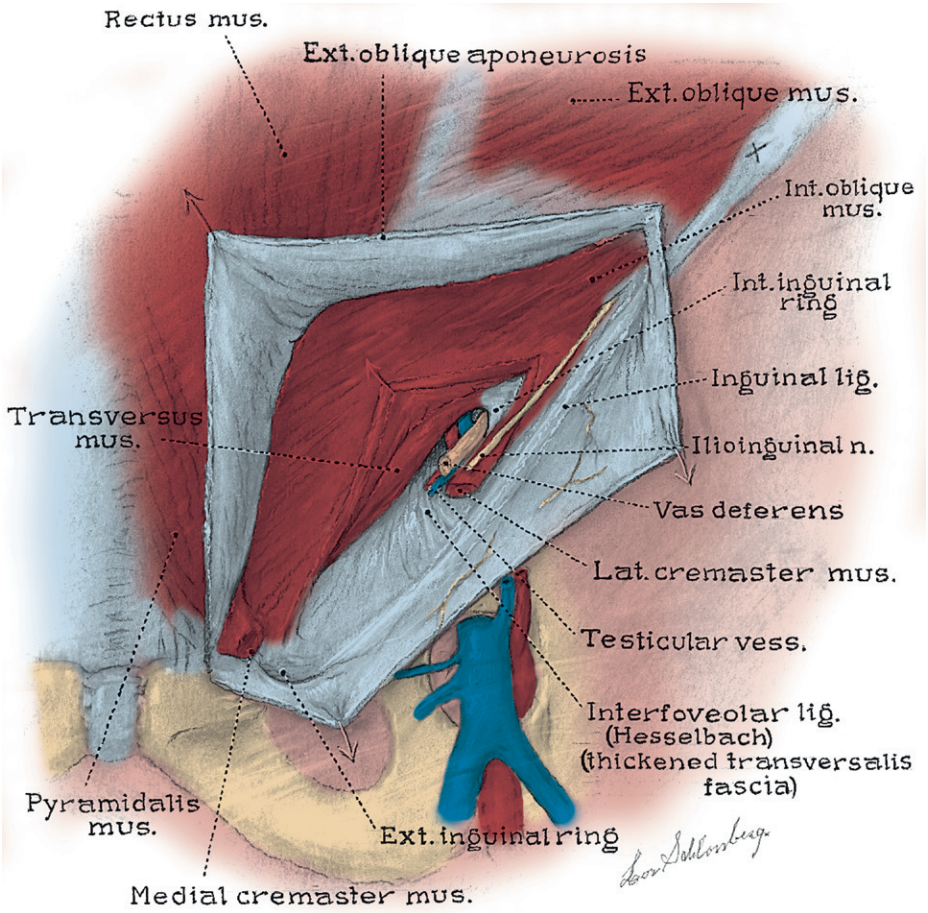


Figure 2–7. Deep structures of the left inguinal canal, viewed from the front.

important landmark for the surgeon. It may be traced to its origin from the internal iliac artery to locate the ureter, which lies on its medial side. During transperitoneal laparoscopic pelvic lymph node dissection, the obturator packet is accessed by incising the peritoneum lateral to the obliterated umbilical artery. In addition, during the performance of transperitoneal laparoscopic or robotic radical prostatectomy, the medial umbilical folds are used as landmarks to guide the dissection of the bladder to expose the space of Retzius. The lateral umbilical fold contains the inferior epigastric vessels as they ascend to supply the rectus abdominis.

SOFT TISSUES OF THE PELVIS

Pelvic Musculature

Muscles and fascia line the true pelvis and form its floor. The obturator internus arises from the inner surface of the obturator foramen and the obturator membrane and passes through the lesser sciatic foramen to insert on the femur (see Fig. 2–8). The fascia on the pelvic surface of this muscle is thickened into a tough line extending from the lower half of the pubis to the ischial spine. This tendinous arc of the levator ani serves as the origin of the muscles of the pelvic diaphragm: pubococcygeus and iliococcygeus (Fig. 2–9). These muscles are not truly separable, and they form a diaphragm that closes the pelvic outlet. Anteriorly, a narrow U-shaped hiatus remains, through which the urethra and rectum exit in the male, and the urethra, vagina, and rectum exit in the female (Fig. 2–10). The muscle bordering this hiatus has been referred to as *pubovisceral* because it provides a sling for (pubourethralis, puborectalis), inserts directly into (pubovaginalis, puboanalis, levator prostatae), or inserts into a structure intimately associated with the pelvic viscera (Lawson, 1974). The pubovisceral group provides strong fixation and support for the pelvic viscera. The coccygeus muscle extends from the sacrospinous ligament to the lateral border of the sacrum and coccyx to complete the pelvic diaphragm. Muscles of the pelvic diaphragm contain type I (slow-twitch) fibers, which provide tonic support to pelvic structures, and type II (fast-twitch) fibers, for sudden increases in intra-abdominal pressure (Gosling et al, 1981).The piriformis muscle arises from the lateral aspect of the sacrum and passes through and fills the greater sciatic foramen to form the posterolateral wall of the pelvis.

It is important to recognize that the pelvic diaphragm is not flat or bowl shaped, as it is frequently depicted. At the urogenital and anal hiatus, the muscles lie in a near-vertical configuration and are thickened inferiorly (see Fig. 2–10) (Brooks et al, 1998; Myers et al, 1998). Behind the anus, they flatten to form a nearly horizontal diaphragm, referred to as the *levator plate*. In the female, the levator plate provides critical support to the pelvic viscera, as discussed later.

Pelvic Fasciae

The pelvic fasciae are not merely collagenous; they are also rich in elastic tissue and smooth muscle. This suggests that they are active in the support, and possibly the function, of the pelvic viscera. The pelvic fasciae are continuous with the retroperitoneal fasciae and have been categorized somewhat

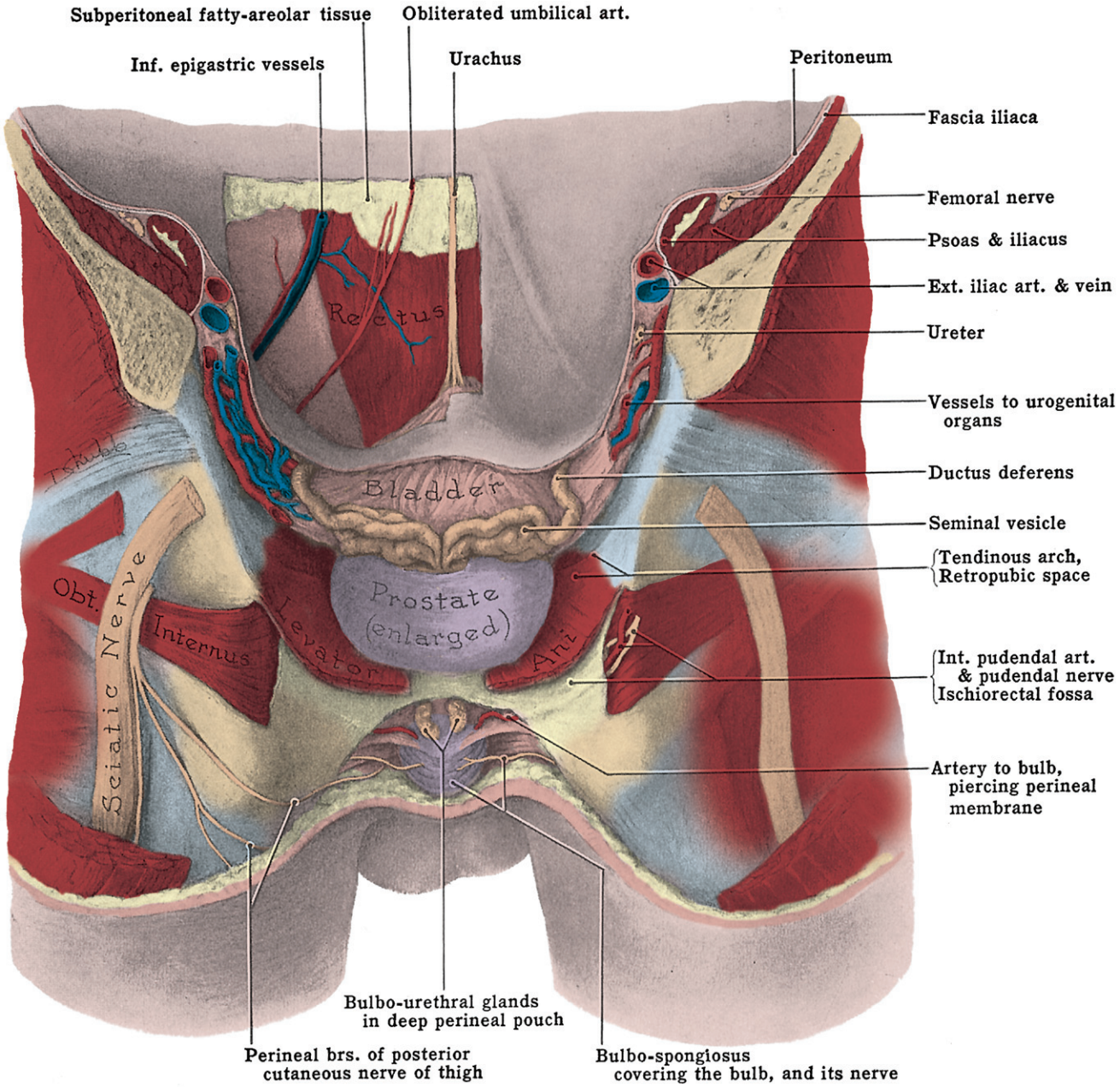


Figure 2–8. Male pelvis and anterior abdominal wall viewed from behind. The sacrum and ilia have been removed. (From Anderson JE. Grant's atlas of anatomy. 7th ed. Baltimore: Williams & Wilkins; 1978. Fig. 3–41.)

arbitrarily into outer, intermediate, and inner strata. The outer stratum, or endopelvic fascia, lines the inner surface of the pelvic muscles and is continuous with the transversalis layer of the abdomen. It is fixed to the arcuate line of the pelvis, Cooper ligament, the sacrospinous ligament, the ischial spine, and tendinous arc of the levator ani. The intermediate stratum embeds the pelvic viscera in a fatty, compressible layer that accommodates their filling and emptying. Its tissues are easily swept aside to reveal the retropubic, paravesical, rectogenital, and retrorectal potential spaces. All pelvic vessels and some pelvic nerves travel in this stratum and are subject to injury when these potential spaces are developed at surgery. The intermediate stratum coalesces around vessels and nerves supplying the pelvic organs to form named ligaments (e.g., cardinal, uterosacral, lateral, and posterior vesical) that suspend and tether these organs in the pelvis. This fascia also thickens around the pelvic urogenital organs to form their visceral fascia. These are not true ligaments but rather a meshwork of connective tissue and smooth muscle investing the visceral neurovascular pedicles (DeCaro et al, 1998). The inner stratum lies just beneath the peritoneum and is associated with the entire gastrointestinal tract. In the pelvis, it covers the rectum and dome of the bladder and forms the rectogenital septum (Denonvilliers fascia). This septum is the developmental remains of the rectogenital pouch of peritoneum that extended between the rectum and internal genitalia to the pelvic floor.

The pelvic fasciae have been given a confusing array of appellations by anatomists and surgeons interested in female pelvic organ prolapse. To add to the confusion, the strength of pelvic fasciae can differ significantly between individuals and races and these differences may predispose some individuals to pelvic

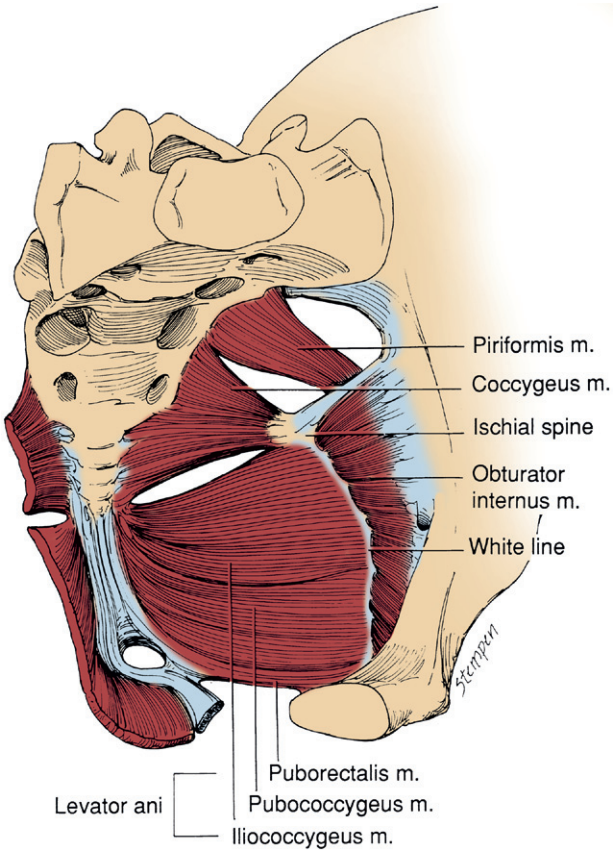


Figure 2–9. Muscles of the true pelvis (three-quarter view).

prolapse (Zacharin, 1985). **The pelvic fasciae have three important components: (1) Anteriorly, the puboprostatic ligaments** attach to the lower fifth of the pubis, lateral to the symphysis and to the junction of the prostate and external sphincter. They are called the pubourethral ligaments in the female and insert on the proximal third of the urethra (Fig. 2–11 on the Expert Consult website). (2) Laterally, the arcus tendineus fascia pelvis extends from the puboprostatic (pubourethral) ligament to the ischial spine (see Fig. 2–11). This fascia forms at the junction of the endopelvic and visceral fasciae. It should not be confused with the arcus tendineus levator ani, which lies above its anterior portion (Fig. 2–12). In the male, the arcus tendineus fascia pelvis is found at the base of a sulcus between the pelvic side wall and the prostate and bladder. In the female, it corresponds to the lateral attachment of the anterior bladder wall to the pelvic side wall. Paravaginal suspension procedures for stress urinary incontinence entail lateral reapproximation of the vaginal wall to this tendinous arc (Richardson et al, 1981). The lateral branches of the dorsal venous complex are directly beneath the arcus tendineus fascia pelvis; thus the endopelvic fascia should be opened lateral to this landmark. In the female, the fascia extending medially from this arch carries a variety of names (pubovesical, periurethral, urethropelvic ligament) and provides important support to the urethra and anterior vaginal wall. Damage to this fascia and its attachments has been implicated in urethrocele, cystocele, and stress urinary incontinence. (3) Posterior to the ischial spine, the fascia fans out to either side of the rectum and attaches to the pelvic side wall as the lateral and posterior vesical ligaments. In the female, these are the strong cardinal and uterosacral ligaments. They are not true ligaments; rather, they are condensations of intermediate stratum around visceral neurovascular pedicles. The peritoneum over these ligaments forms discrete folds (rectovesical in the male and rectouterine in the female) that can be appreciated at cystectomy (Fig. 2–13). Taken as a whole, the pelvic fasciae form a Y-shaped scaffolding for the pelvic viscera (see Fig. 2–12).

Fasciae of the Perineum and the Perineal Body

The weakest point in the pelvic floor, the urogenital hiatus, is bridged by the urogenital diaphragm, a structure unique to humans (see Fig. 2–10). The fibrous perineal membrane lies at the center of, and defines, the urogenital diaphragm (see Figs. 2–4, 2–10, and 2–14). It is triangular and spans the inferior ischiopubic rami from the pubis to the ischial tuberosities. Posteriorly, it ends abruptly; the superficial and deep transverse perinei run along its free edge (Fig. 2–15). The external genitalia attach to its inferior surface; superiorly, it supports the urethral sphincter (discussed later). The perineal body represents the point of fusion between the free posterior edge of the urogenital diaphragm and the posterior apex of the urogenital hiatus. This pyramid-shaped structure forms the hub of pelvic support. Virtually every pelvic muscle (superficial and deep transverse perinei, bulbocavernosus, levator ani, rectourethralis, external anal sphincter, striated urethral sphincter) and fascia (perineal membrane, Denonvilliers, Colles, and endopelvic) insert into the perineal body. At its core are abundant elastin and richly innervated smooth muscle, which suggests that it may have a dynamic role in support. Damage to the perineal body during perineal prostatectomy risks postoperative urinary incontinence.

PELVIC CIRCULATION

Arterial Supply

Major arteries of the pelvis are summarized in Table 2–1. At the bifurcation of the aorta, the **middle sacral artery** arises posteriorly and travels on the pelvic surface of the sacrum to supply branches to the sacral foramina and the rectum. The common iliac arteries arise at the level of the fourth lumbar vertebra, run anterior and lateral to their accompanying veins, and bifurcate into the external and internal iliac arteries at the SI joint (Fig. 2–16). The external iliac artery follows the medial border of the iliopsoas muscle along the arcuate line and leaves the pelvis beneath the inguinal ligament as the femoral artery (Fig. 2–17). Its inferior epigastric artery is given off proximal to the inguinal ligament and ascends medial to the internal inguinal ring to supply the rectus muscle and overlying skin. Because the rectus is richly collateralized from above and laterally, the inferior epigastric arteries may be ligated with impunity. A rectus myocutaneous flap based on this artery has been used to correct major pelvic and perineal tissue defects. Near its origin, the inferior epigastric artery sends a deep circumflex iliac branch laterally and a pubic branch medially. Both vessels travel on the iliopubic tract and may be injured during inguinal hernia repair. Its cremasteric branch joins the spermatic cord at the internal inguinal ring and forms a distal anastomosis with the testicular artery (Fig. 2–18). In 25% of people, an accessory obturator artery arises from the inferior epigastric artery and runs medial to the femoral vein to reach the obturator canal. This vessel must be avoided during obturator lymph node dissection.

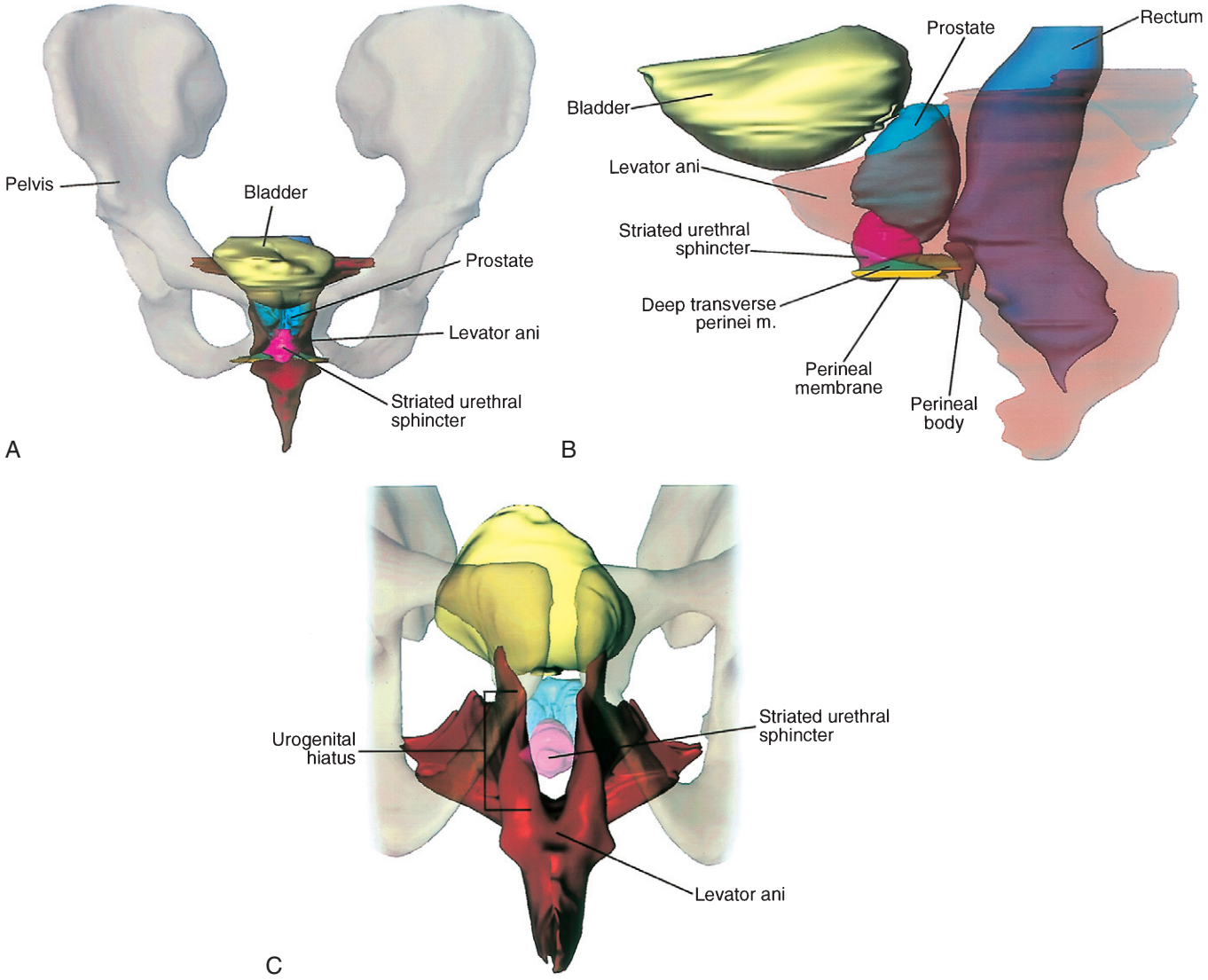


Figure 2–10. Location and contour of the levator ani and pelvic viscera. **A,** Anterior view demonstrating the near-vertical orientation of the lateral walls of the levator ani and the horizontal wings at its posterior superior aspect. **B,** Lateral view in which the levator ani has been made transparent. The perineal membrane bridges the urogenital hiatus, and the urethral sphincter fills much of the hiatus. **C,** View of the levator ani from below showing the urogenital hiatus and the thickened inferior border of the levator ani. The perineal body and related structures are not shown. (From Brooks JD, Chao W-M, Kerr J. Male pelvic anatomy reconstructed from the visible human data set. J Urol 1998;159:868–72.)

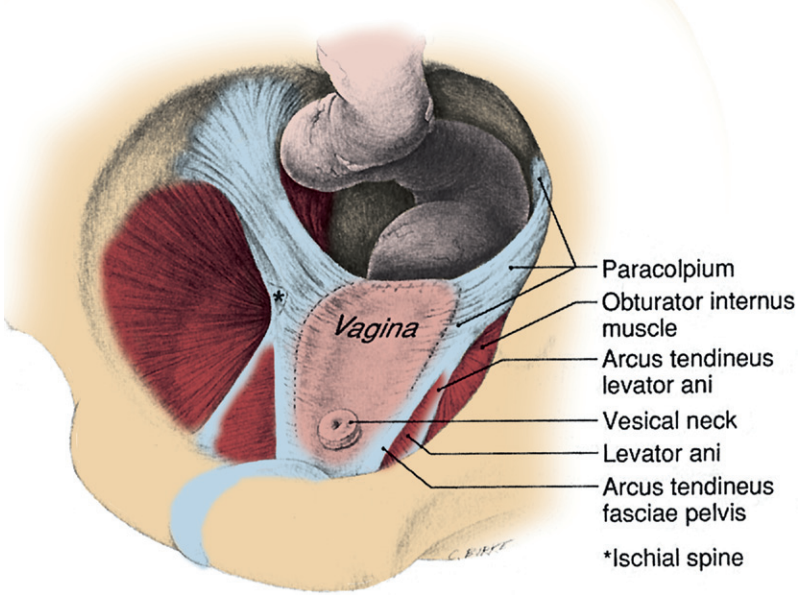


Figure 2–12. Vagina and supportive structures after removal of the bladder and uterus. The arcus tendineus fascia pelvis and the cardinal and uterosacral ligaments (paracolpium) form a continuous structure that supports the pelvic viscera. (From DeLancey JOL. Structural support of the urethra as it relates to stress urinary continence: the hammock hypothesis. Am J Obstet Gynecol 1994;170:1719.)

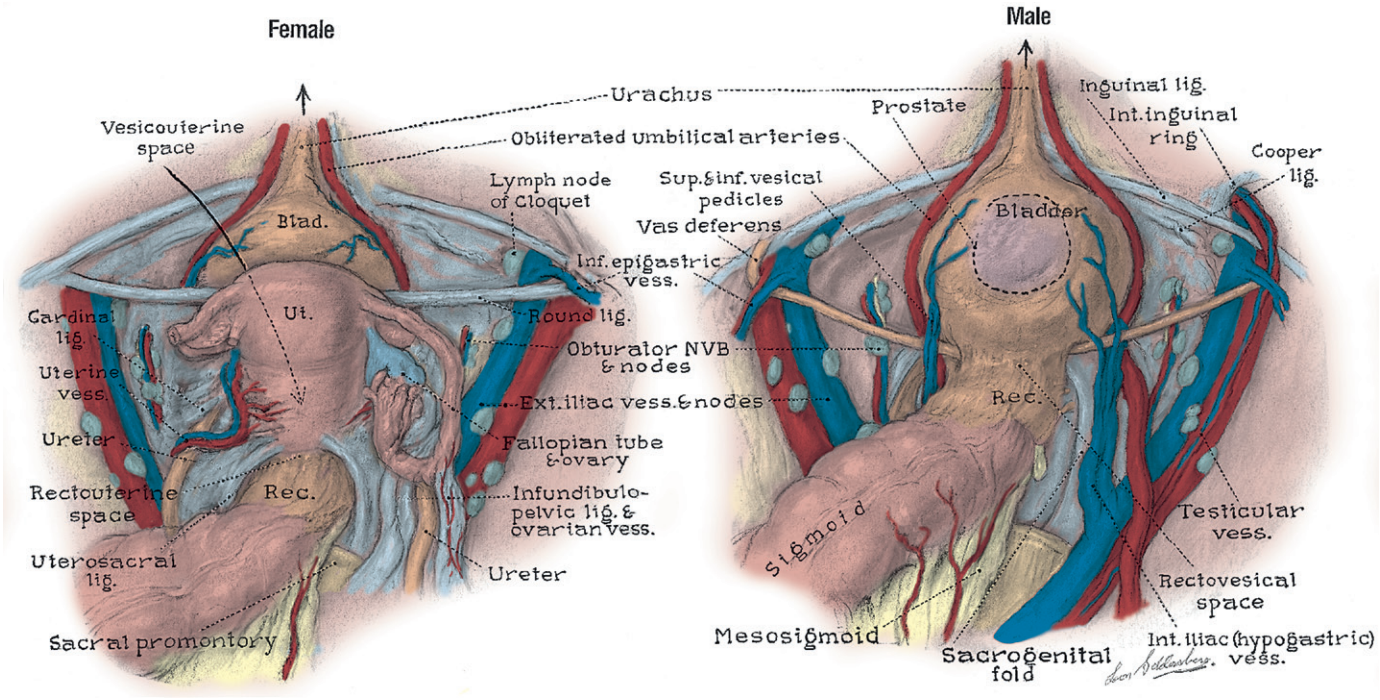


Figure 2–13. Peritoneal surfaces of the female and male pelves. In the female, the ureter passes medial to the ovarian vessels, then deep to the uterine artery within the substance of the cardinal ligament. The sacrogenital and sacrouterine folds represent the posterior portions of pelvic fascial support.

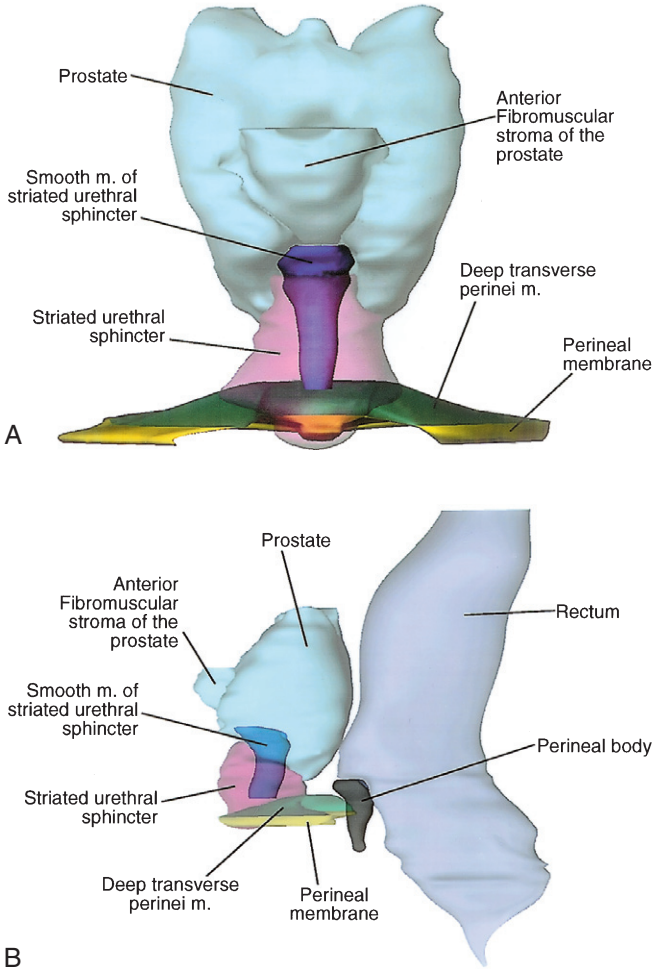


Figure 2–14. Structure of the male striated urethral sphincter. **A,** Anterior projection shows the cone shape of the sphincter and the smooth muscle of the sphincter. **B,** Viewed laterally, the anterior wall of the sphincter is nearly twice the length of the posterior wall, although both are of comparable thickness. (From Brooks JD, Chao W-M, Kerr J. Male pelvic anatomy reconstructed from the visible human data set. J Urol 1998;159:871.)

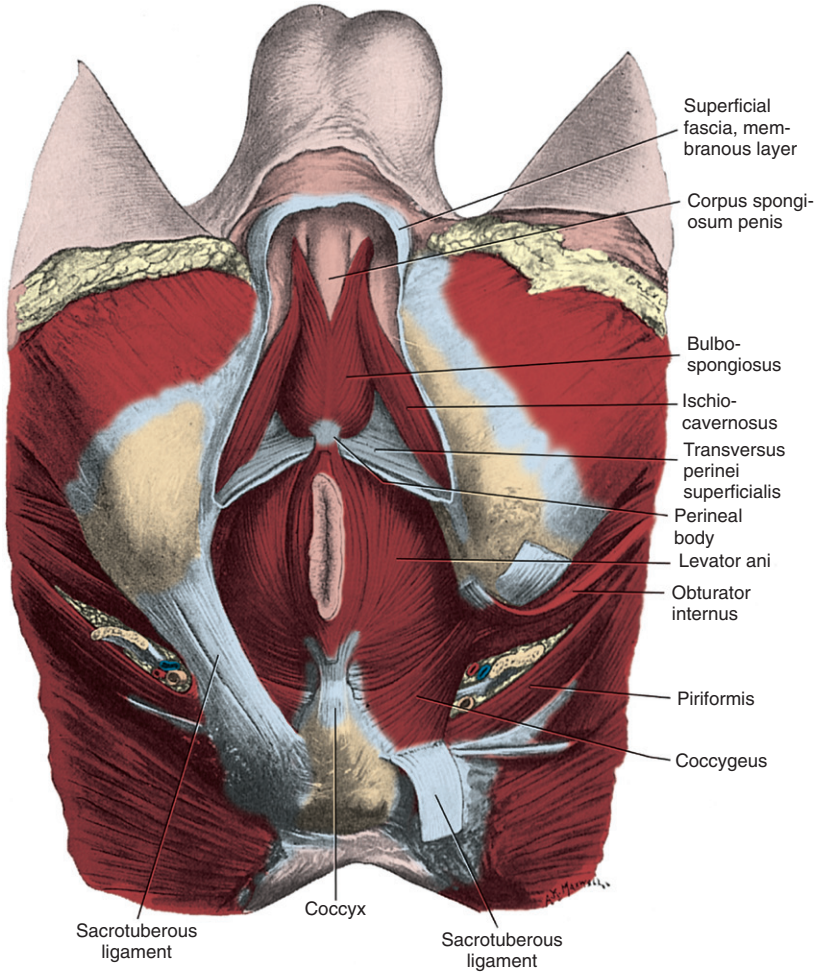


Figure 2–15. Muscles of the male perineum. The transversus perinei and ischiocavernosi frame the urogenital diaphragm. (From Williams PL, Warwick R. Gray's anatomy. 35th British ed. Philadelphia: WB Saunders; 1973. p. 530.)

Table 2–1.

Arteries of the Pelvis

ARTERY NAME	ORIGIN	SUPPLIES
Middle sacral	Aorta	Sacral nerves and sacrum
External Iliac Branches		
Inferior epigastric	External iliac	Rectus abdominis muscle and overlying skin and fascia
Deep circumflex iliac	Inferior epigastric	Inguinal ligament and surrounding structures laterally
Pubic	Inferior epigastric	Inguinal ligament and surrounding structures medially
Cremasteric	Inferior epigastric	Vas deferens and testis
Internal Iliac Branches		
Superior gluteal	Posterior trunk	Gluteus muscles and overlying skin
Ascending lumbar	Posterior trunk	Psoas and quadratus lumborum muscles and adjacent structures
Lateral sacral	Posterior trunk	Sacral nerves and sacrum
Superior vesical	Anterior trunk	Bladder, ureter, vas deferens, and seminal vesicle
Middle rectal	Anterior trunk	Rectum, ureter, and bladder
Inferior vesical	Anterior trunk	Bladder, seminal vesicle, prostate, ureter, and the neurovascular bundle
Uterine	Anterior trunk	Uterus, bladder, and ureter
Internal pudendal	Anterior trunk	Rectum, perineum, and external genitalia
Obturator	Anterior trunk	Adductor muscles of the leg and overlying skin
Inferior gluteal	Anterior trunk	Gluteus muscles and overlying skin

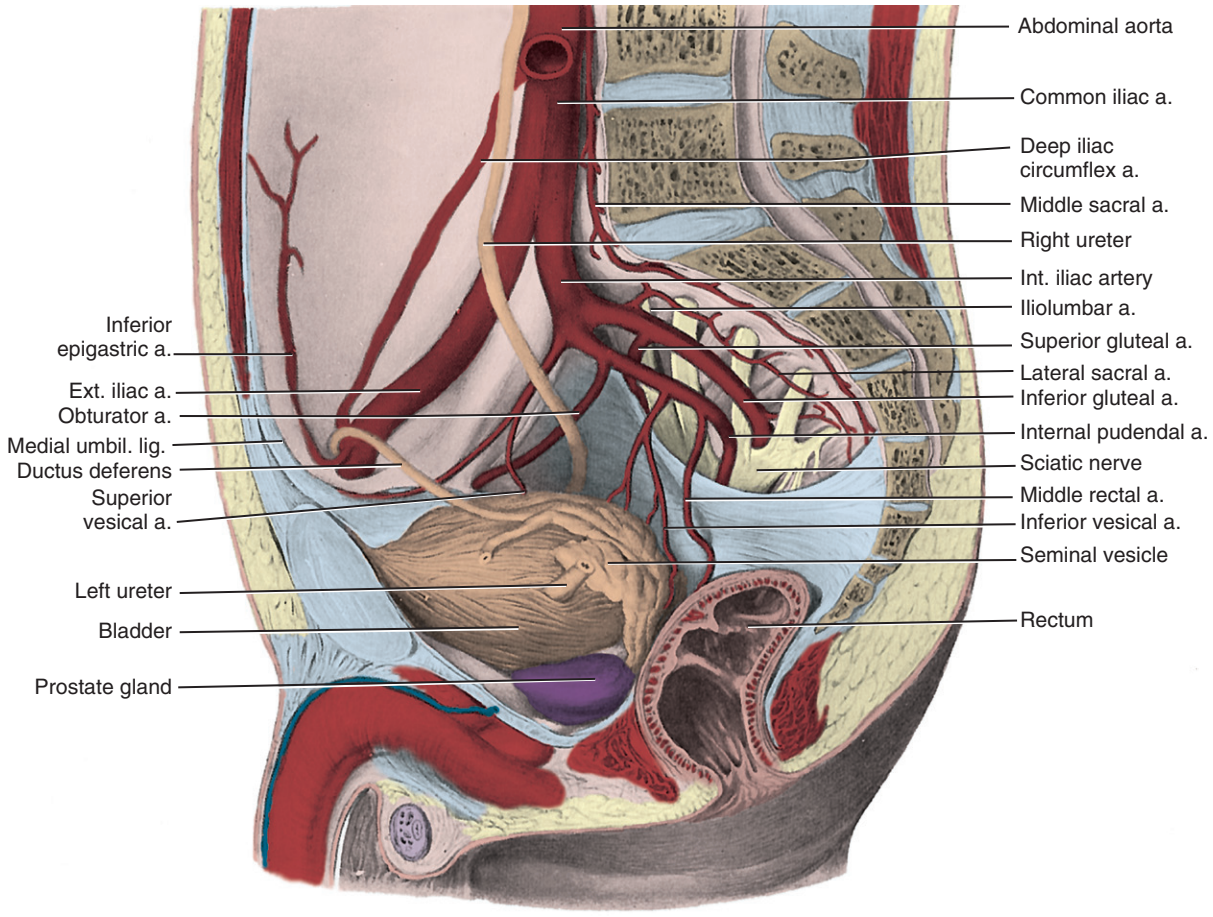


Figure 2–16. Right internal and external iliac arteries. The ureter and vas deferens pass medial to the vessels. (From Clemente CD. Gray's anatomy. 30th American ed. Philadelphia: Lea & Febiger; 1985. p. 750.)

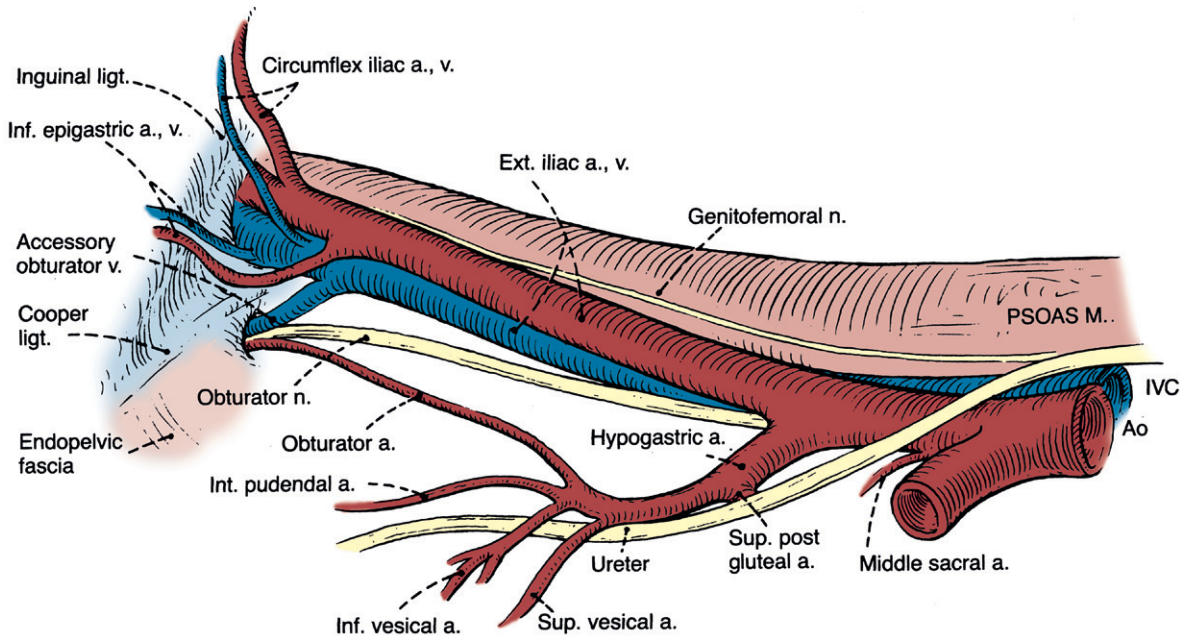


Figure 2–17. Right obturator fossa, showing the iliac vessels and obturator nerve. (From Skinner DG. Pelvic lymphadenectomy. In: Glenn JF, editor. Urological surgery. 2nd ed. New York: Harper & Row; 1975. p. 591.)

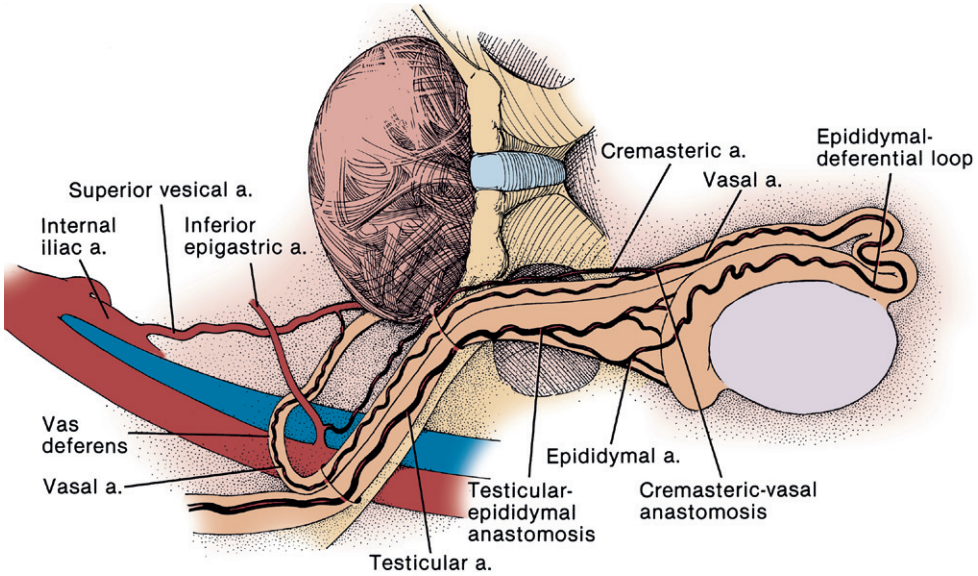


Figure 2–18. Collateral arterial circulation to the testis. (From Hinman F Jr. Atlas of urosurgical anatomy. Philadelphia: WB Saunders; 1993. p. 497.)

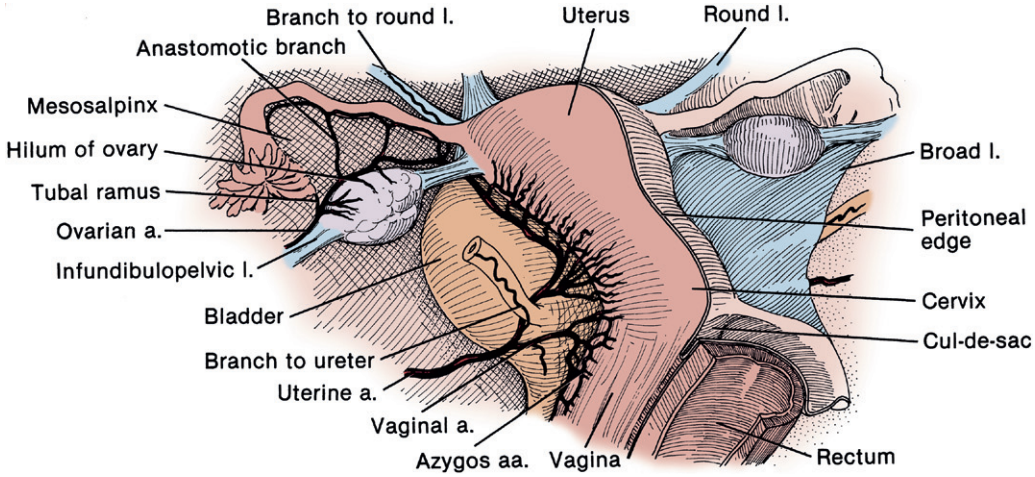


Figure 2–19. Female internal genitalia, from behind. The ureter passes beneath the uterine artery. (From Hinman F Jr. Atlas of urosurgical anatomy. Philadelphia: WB Saunders; 1993. p. 402.)

The internal iliac (hypogastric) artery descends in front of the SI joint and divides into an anterior and a posterior trunk (see Fig. 2–16). The posterior trunk gives rise to three parietal branches: (1) the superior gluteal, which exits the greater sciatic foramen; (2) the ascending lumbar, which supplies the posterior abdominal wall; and (3) the lateral sacral, which passes medially to join the middle sacral branches at the sciatic foramina.

The anterior trunk gives off seven parietal and visceral branches: (1) The superior vesical artery arises from the proximal portion of the obliterated umbilical artery and gives off a vesiculodeferential branch to the seminal vesicles and vas deferens. The artery of the vas deferens travels the length of the vas to meet the cremasteric and testicular arteries distally (see Fig. 2–18). Because of these anastomoses, the testicular artery may be sacrificed without compromising the viability of the testis. (2) The middle rectal artery gives small branches to the seminal vesicles and prostate and anastomoses with the inferior and superior rectal arteries in the rectal wall. (3) The inferior vesical branches supply the lower ureter, the bladder base, the prostate, and the seminal vesicles. In the female, they supply the ureter, the bladder base, and the vagina. (4) The uterine artery passes above and in front of the ureter ("water flows under the bridge") to ascend the lateral wall of the uterus and meet the ovarian artery in the lateral portion of the fallopian tube (see Figs. 2–13 and 2–19). The ureter is vulnerable during division of the uterine pedicles. (5) The internal pudendal artery leaves the pelvic cavity through the greater sciatic foramen, passes around the sacrospinous ligament, and enters the lesser sciatic foramen to gain access to the perineum. Its perineal course is discussed later. (6) The obturator artery, variable in origin, travels through the obturator fossa medial and inferior to the obturator nerve and passes through its canal to supply the adductors of the thigh (see Fig. 2–17). (7) The inferior gluteal artery travels through the greater sciatic foramen to supply the buttock and thigh.

The internal iliac artery can be ligated to control severe pelvic hemorrhage. Ligation decreases the pulse pressure, allowing hemostasis to occur more readily. Internal iliac blood flow does not stop but reverses its direction because of critical anastomoses (lumbar segmentals to iliolumbar; median sacral to lateral sacral; and superior rectal and middle rectal). Bilateral ligation almost invariably produces vasculogenic impotence.

Venous Supply

The dorsal vein of the penis passes between the inferior pubic arch and the striated urinary sphincter to reach the pelvis, where it trifurcates into a central superficial branch and two lateral plexuses (Reiner and Walsh, 1979) (Fig. 2–20). To minimize blood loss at radical retropubic prostatectomy, the dorsal vein complex is best divided distally, before its ramification. Part of this complex runs within the anterior and lateral wall of the striated sphincter; thus care must be taken not to injure the sphincter when securing hemostasis. The superficial branch pierces the visceral endopelvic fascia between the puboprostatic ligaments and drains the retropubic fat, anterior bladder, and anterior prostate (see Fig. 2–20).

The lateral plexuses sweep down the sides of the prostate, receiving drainage from it and the rectum, and communicate with the vesical plexuses on the lower part of the bladder. Three to five inferior vesical veins emerge from the vesical plexus laterally and drain into the internal iliac vein. In the female, the dorsal vein of the clitoris bifurcates to empty into the laterally placed vaginal plexuses. These connect with the vesical, uterine, ovarian, and rectal plexuses and drain into the internal iliac veins.

The internal iliac vein is joined by tributaries corresponding to the branches of the internal iliac artery and ascends medial and posterior to the artery. This vein is relatively thin walled and at risk for injury during dissection of the artery or the nearby pelvic ureter. The external iliac vein travels medial and inferior to its artery and joins the internal iliac vein behind the internal iliac artery. In half the patients, one or **more accessory obturator veins drain into the underside of the external iliac vein and can be easily torn during lymphadenectomy** (see Fig. 2–17).

Pelvic Lymphatics

The pelvic lymph nodes can be difficult to appreciate on gross examination because they are embedded in the fatty and fibrous tissue of the intermediate stratum. Three major lymph node groups are associated with the pelvic vessels (Fig. 2–21). A substantial portion of pelvic visceral lymphatic drainage passes through the **internal iliac nodes and their tributaries: the presacral, obturator, and internal pudendal nodes.** The external iliac nodes lie lateral, anterior, and medial to the vessels and drain the anterior abdominal wall, urachus, bladder, and, in part, internal genitalia. The external genitalia and perineum drain into the superficial and deep inguinal nodes (see later discussion). The inguinal nodes communicate directly with the internal and external iliac chains. The common iliac nodes receive efferent vessels from the external and internal iliac nodes and the pelvic ureter and drain into the lateral aortic nodes.

PELVIC INNERVATION

Lumbosacral Plexus

The lumbosacral plexus and its rami are well illustrated in Chapter 1; only the pelvic courses of its nerves are reviewed here (see Figs. 2–7 and 2–12 and Table 2–2). The **iliohypogastric nerve** (L1) travels between, and supplies, the internal oblique and the transversus muscles and pierces the internal and external oblique muscles 3 cm above the external inguinal ring to supply sensation over the lower anterior abdomen and pubis (see Fig. 2–5). The ilioinguinal nerve (L1) passes through the internal oblique muscle

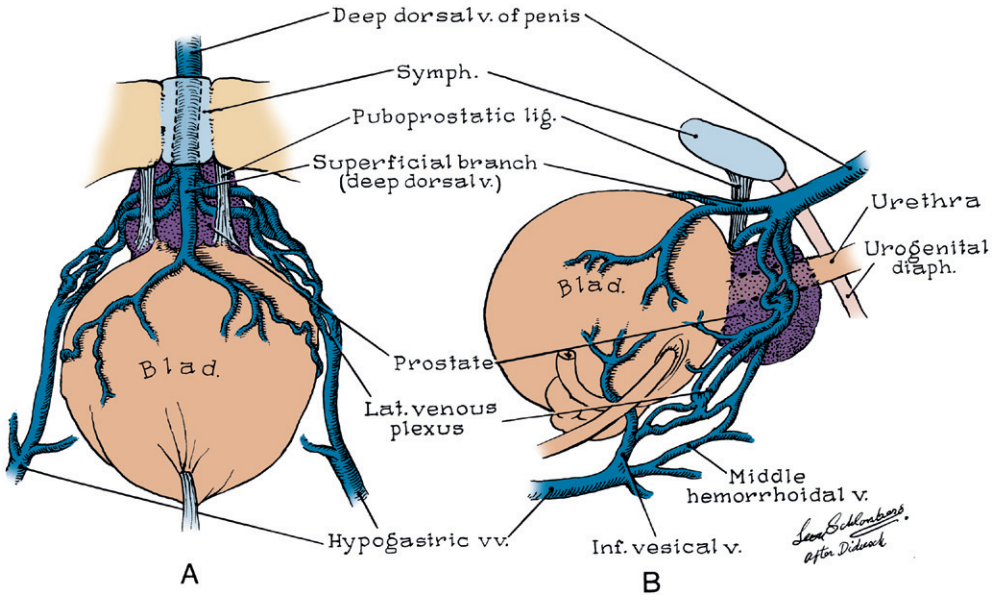


Figure 2–20. Pelvic venous plexus. **A,** Trifurcation of the dorsal vein of the penis, viewed from the retropubic space. The relationship of the venous branches to the puboprostatic ligaments is shown. **B,** Lateral view of the pelvic venous plexus after removal of the lateral pelvic fascia. Normally these structures are difficult to see because they are embedded in pelvic fascia. (From Reiner WG, Walsh PC. An anatomical approach to the surgical management of the dorsal vein and Santorini's plexus during radical retropubic surgery. J Urol 1979;121:200.)

to enter the inguinal canal laterally. It travels anterior to the cord and exits the external ring to provide sensation to the mons pubis and anterior scrotum or labia majora (see Figs. 2–5 and 2–7). The genitofemoral nerve (L1, L2) pierces the psoas muscle to reach its anterior surface in the retroperitoneum and then travels to the pelvis and splits into genital and femoral branches. The latter supplies sensation over the anterior thigh below the inguinal ligament. The genital branch follows the cord through the inguinal canal, supplies the cremaster muscle, and supplies sensation to the anterior scrotum.

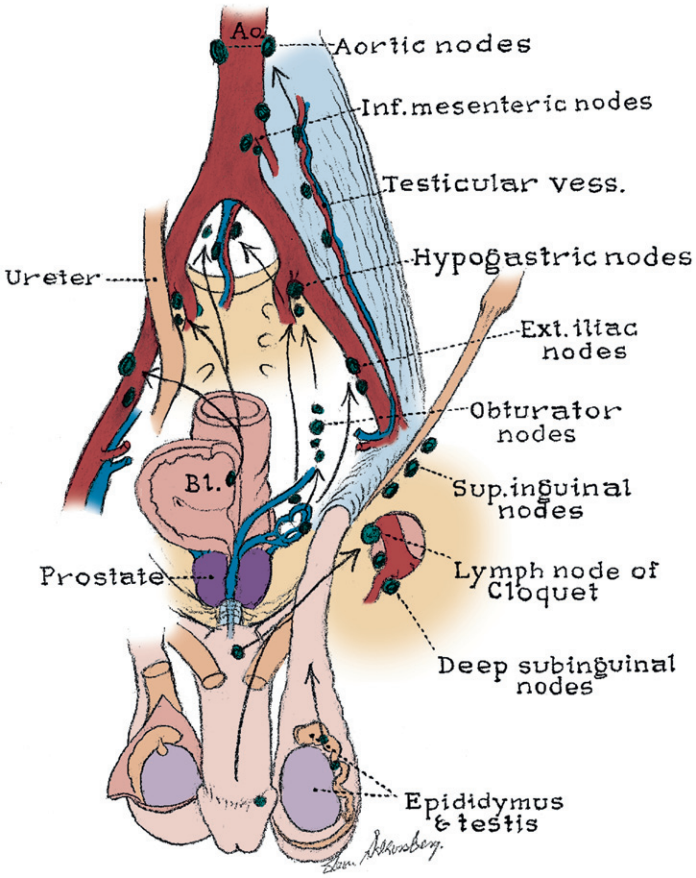


Figure 2–21. Lymphatic drainage of the male pelvis, perineum, and external genitalia.

For most of its pelvic course, the femoral nerve (L2, L3, L4) travels within the substance of the psoas muscle and then exits its lateral side to pass under the inguinal ligament (Fig. 2–22). It supplies sensation to the anterior thigh and motor innervation to the extensors of the knee. **During a psoas hitch, sutures should be placed in the direction of the nerve (and the psoas muscle fibers) to avoid nerve damage or entrapment. Retractor blades must not rest on the psoas muscle because they can produce a femoral nerve palsy,** a potentially dangerous setback after pelvic surgery. The lateral femoral cutaneous nerve (L2, L3) may be seen lateral to the psoas in the iliacus fascia.

The **obturator nerve** (L2, L3, L4) emerges in the true pelvis from beneath the psoas muscle, lateral to the internal iliac vessels, and passes through the obturator fossa to the obturator canal. In the fossa, it is lateral and superior to the obturator vessels and surrounded by the obturator and internal iliac lymph nodes. Damage to this nerve during pelvic lymphadenectomy weakens the adductors of the thigh.

The lumbosacral trunk (L4, L5) passes into the true pelvis behind the psoas and unites with the ventral rami

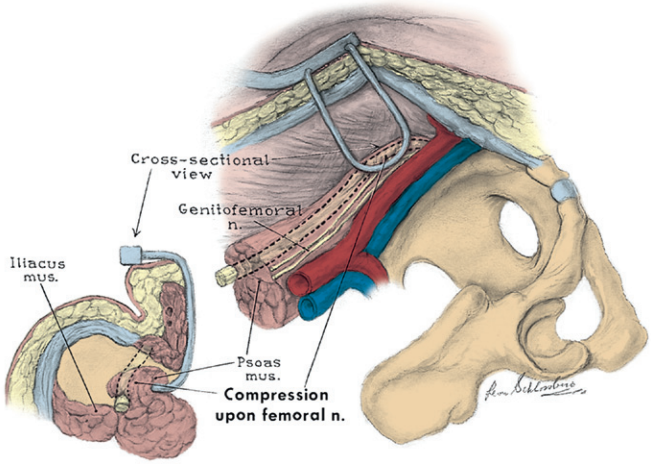


Figure 2–22. Femoral nerve as it relates to the psoas muscle. Retractor blades may compress this nerve to produce a femoral nerve palsy. (From Burnett AL, Brendler CB. Female neuropathy following major pelvic surgery: etiology and prevention. J Urol 1994;151:163.)

Table 2–2.

Somatic Nerves of the Lower Abdomen and Pelvis

NERVE NAME	ORIGIN	SUPPLIES
Iliohypogastric	L1	Motor supply to internal oblique, transversus muscles, sensation over lower anterior abdominal wall
Ilioinguinal	L1	Sensation over anterior pubis (mons) and anterior scrotum or labia
Genitofemoral	L1, L2	Genital branch: motor supply to cremaster muscle sensation to anterior scrotum Femoral branch: sensation to anterior thigh
Femoral	L2, L3, L4	Motor supply to extensors of the knee sensory to anterior thigh
Obturator	L2, L3, L4	Motor supply to adductors of the thigh, sensation to medial thigh
Lumbosacral trunk	L4, L5	Joins the sacral nerves to form the lumbosacral plexus that supplies motor and sensory innervation to the lower extremities
Posterior femoral cutaneous	S2, S3	Sensation to perineum, posterior scrotum, and posterior thigh
Pudendal	S2, S3, S4	Motor to levator ani, muscles of the urogenital diaphragm, anal and striated urethral sphincter, sensation to the perineum, scrotum, penis
Pelvic somatic efferents	S2, S3, S4	Motor supply to levator ani and striated urethral sphincter
Nervi erigentes	S2, S3, S4	Parasympathetic fibers from the sacral cord supply the pelvic viscera

of the sacral segmental nerves to form the sacral plexus. This plexus lies on the pelvic surface of the piriformis deep to the endopelvic fascia and posterior to the internal iliac vessels (see Fig. 2–16). It leaves the pelvis through the greater sciatic foramen immediately posterior to the sacrospinous ligament (where it may be injured during sacrospinous culposuspension) and supplies motor and sensory innervation to the posterior thigh and lower leg. An exaggerated lithotomy position may stretch this nerve or place pressure on its peroneal branch at the fibular head to produce foot drop. Pelvic and perineal branches of the sacral plexus include (1) the posterior femoral cutaneous nerve (S2, S3), which, after passing through the greater sciatic foramen, gives an anterior sensory branch to the perineum and posterior scrotum (see Fig. 2–8); (2) the pudendal nerve (S2, S3, S4), which follows the internal pudendal artery to the perineum (to be discussed); (3) the nervi erigentes (S2, S3, S4) to the autonomic plexus; and (4) pelvic somatic efferent nerves from the ventral rami of S2, S3, and S4 (Fig. 2–23). The latter nerves travel on the pelvic surface of the levator ani in close association with the rectum and prostate and are separated from the pelvic autonomic plexus by the endopelvic fascia. They supply the levator ani and extend anteriorly to the striated urethral sphincter (Lawson, 1974; Zvara et al, 1994).

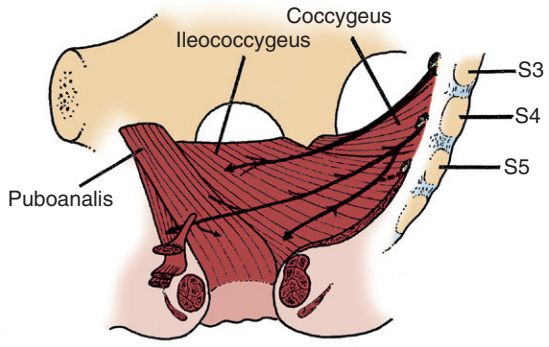


Figure 2–23. Pelvic floor somatic efferent nerves extending anteriorly on the pelvic surface of the levator ani to supply this muscle and the striated urethral sphincter. (From Lawson JO. Pelvic anatomy. I. Pelvic floor muscles. Ann R Coll Surg Engl 1974;54:250.)

Pelvic Autonomic Plexus

The presynaptic sympathetic cell bodies that project to the pelvic autonomic plexus reside in the lateral column of gray matter in the last three thoracic and first two lumbar segments of the spinal cord. They reach the pelvic plexus by two pathways: (1) The superior hypogastric plexus is formed by sympathetic fibers from the celiac plexus and the first four lumbar splanchnic nerves (Fig. 2–24). Anterior to the bifurcation of the aorta, it divides into two hypogastric nerves that enter the pelvis medial to the internal iliac vessels, anterior to the sacrum, and deep to the endopelvic fascia. (2) The pelvic continuations of the sympathetic trunks pass deep to the common iliac vessels and medial to the sacral foramina and fuse in front of the coccyx at the ganglion impar (see Fig. 2–24). Each chain comprises four to five ganglia that send branches anterolaterally to participate in the formation of the pelvic plexus.

Presynaptic parasympathetic innervation arises from the intermediolateral cell column of the sacral cord. Fibers emerge from the second, third, and fourth sacral spinal nerves as the pelvic splanchnic nerves (nervi erigentes) to join the hypogastric nerves and branches from the sacral sympathetic ganglia to form the inferior hypogastric (pelvic) plexus (see Fig. 2–24). Some pelvic parasympathetic efferent fibers travel up the hypogastric nerves to the inferior mesenteric plexus, where they provide parasympathetic innervation to the descending and sigmoid colon.

The pelvic plexus is rectangular, approximately 4 to 5 cm long, and its midpoint is at the tips of the seminal vesicles (Schlegel and Walsh, 1987). It is oriented in the sagittal plane on either side of the rectum and pierced by the numerous vessels going to and from the rectum, bladder, seminal vesicles, and prostate (Fig. 2–25). **Division of these vessels (the so-called lateral pedicles of the bladder and prostate) risks injury to the pelvic plexus with attendant postoperative impotence** (Walsh and Donker, 1982; Walsh et al, 1983). The right and left components of the pelvic plexus communicate behind the rectum and anterior and posterior to the vesical neck. Branches of the pelvic plexus follow pelvic blood vessels to reach the pelvic viscera, although nerves to the ureter may join it directly as it passes nearby. Visceral afferent and efferent nerves travel on the vas deferens to reach the testis and epididymis (see later discussion).

The most caudal portion of the pelvic plexus gives rise to the innervation of the prostate and the important cavernosal nerves (Walsh and Donker, 1982). After passing the tips of the seminal vesicles, these nerves lie within leaves of the lateral endopelvic fascia near its juncture with, but outside, Denonvilliers fascia (Lepor et al, 1985). They travel at the posterolateral border of the prostate on the surface of the rectum and are lateral to the prostatic capsular arteries and veins (see Fig. 2–25). Because the nerves are composed of multiple fibers not visible on gross inspection, these vessels serve as a surgical landmark for the course of these nerves (the neurovascular bundle of Walsh). During radical prostatectomy, the nerves are most vulnerable at the apex of the prostate, where they closely approach the prostatic capsule at the 5- and 7-o'clock positions. On reaching the membranous urethra, the nerves divide into superficial branches, which travel on the lateral surface of the striated urethral sphincter at 3- and 9-o'clock positions, and deep fibers, which penetrate the substance of this muscle and send twigs to the bulbourethral glands. As the nerves reach the hilum of the penis, they join to form one to three discrete bundles, related to the urethra at 1- and 11-o'clock positions, superficial to the cavernous veins and dorsomedial to the cavernous arteries (Fig. 2–26) (Lue et al, 1984; Breza et al, 1989). With the arteries, they pierce the corpora cavernosa to supply the erectile tissue (see later discussion). Small fibers also join the dorsal nerves of the penis as they course distally. In the female, the nerves to vestibular bodies and corpora cavernosa of the clitoris travel between the anterior vaginal wall and the bladder in association with the lateral venous plexuses.

PELVIC VISCERA

Rectum

The rectum begins with the disappearance of the sigmoid mesentery opposite the third sacral vertebra. **Peritoneum continues anteriorly over the upper two thirds of the rectum as the rectovesical pouch in males and as the rectouterine pouch (of Douglas) in females** (Fig. 2–27; see also Fig. 2–11). Incision of the anterior wall of this peritoneal pouch exposes the seminal vesicles behind the bladder. Inferior to this pouch, the

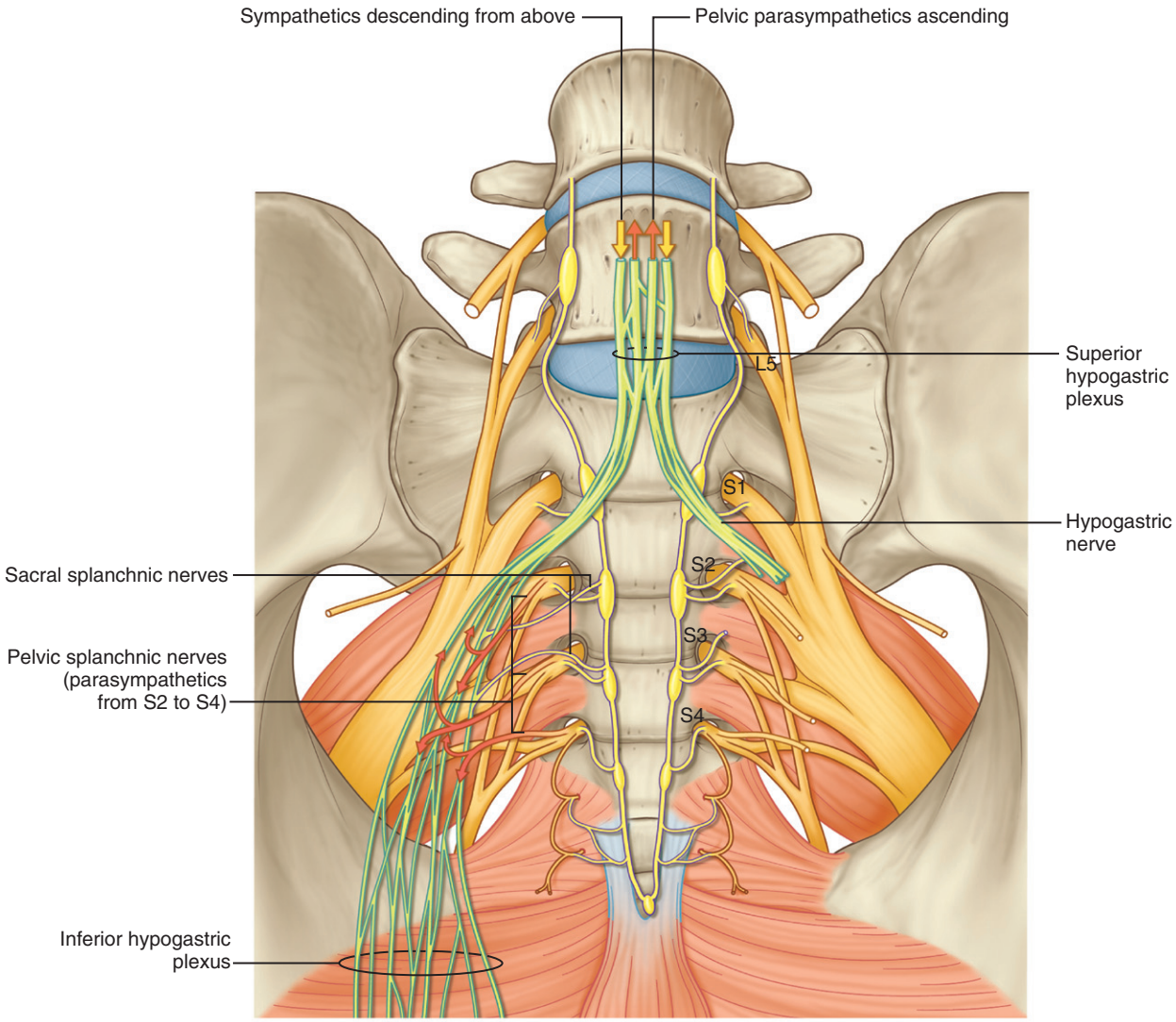


Figure 2–24. Sympathetic and parasympathetic contributions to the pelvic autonomic nervous plexus.

anterior rectum is related to its fascial continuation (the rectogenital or Denonvilliers fascia) down to the level of the striated urethral sphincter (see Figs. 2–4, 2–27, and 2–28). The rectum describes a gentle curve on the sacrum, coccyx, and levator plate (see Fig. 2–24) and receives innervation from the laterally placed pelvic autonomic plexus and blood supply from the superior (from inferior mesenteric), middle (from internal iliac), and inferior (from internal pudendal) rectal arteries.

The rectal wall is composed of an inner layer of circular smooth muscle and a virtually continuous sheet of outer longitudinal smooth muscle derived from the tenia of the colon. In its lowest part, the rectum dilates to form the rectal ampulla. At the most inferior portion of the ampulla, anterior fibers of the longitudinal muscle leave the rectum to join Denonvilliers fascia and the posterior striated urethral sphincter in the apex of the perineal body (Brooks et al, 2002). During perineal prostatectomy, these fibers, **the rectourethralis muscle, are 2 to 10 mm thick and must be divided to gain access to the prostate** (Fig. 2–29). The apices of the prostate and rectal ampulla are in close proximity, and rectal injuries during radical prostatectomy commonly occur at this location. As the rectourethralis is given off, the rectum makes a right-angle turn posteroinferiorly to exit the pelvis at the anal canal (see Fig. 2–10). The anatomy of the anal canal is considered with the perineum.

Pelvic Ureter

The ureter is divided into abdominal and pelvic portions by the common iliac artery. The structure of the ureter and its abdominal course are reviewed in Chapter 1. Intraoperatively, the ureter is identified by its peristaltic waves and is readily found anterior to the bifurcation of the common iliac artery. At ureteroscopy, pulsations of this artery can be seen in the posterior ureteral wall. **The ovarian vessels (infundibulopelvic ligament) cross the iliac vessels anterior and lateral to the ureter, and dissection of the ovarian vessels at the pelvic brim is a common cause of ureteral injury** (see Fig. 2–13) (Daly and Higgins, 1988). Pyeloureterography discloses a narrowing of the ureter at the iliac vessels, and ureteral calculi frequently become lodged at this location. Because the ureter and iliac vessels rest on

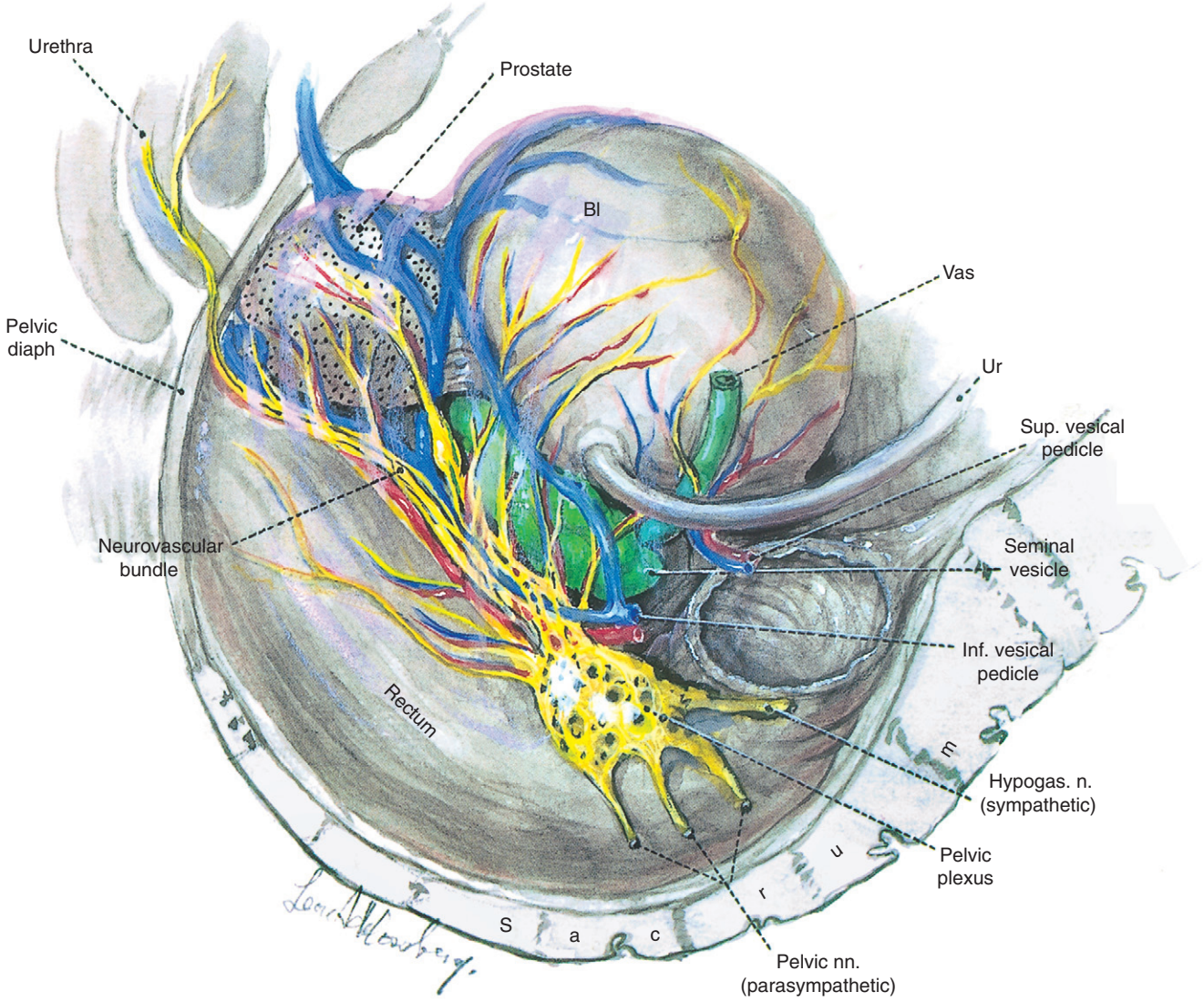


Figure 2–25. Lateral view showing the left pelvic autonomic nervous plexus and its relation to the pelvic viscera. (From Schlegel PN, Walsh PC. Neuroanatomical approach to radical cystoprostatectomy with preservation of sexual function. J Urol 1987;138:1403.)

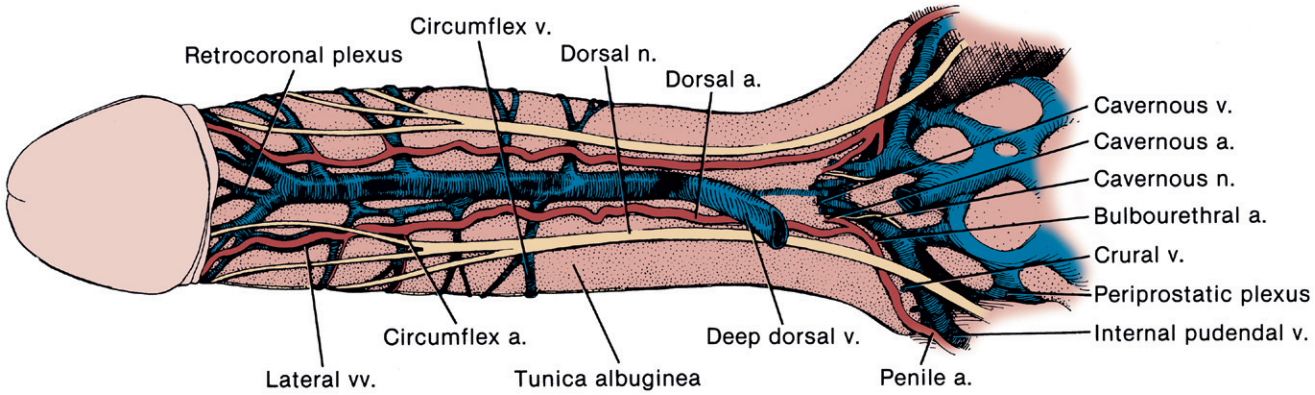


Figure 2–26. Dorsal penile arteries, veins, and nerves. (From Hinman F Jr. Atlas of urosurgical anatomy. Philadelphia: WB Saunders: 1993. p. 445.)

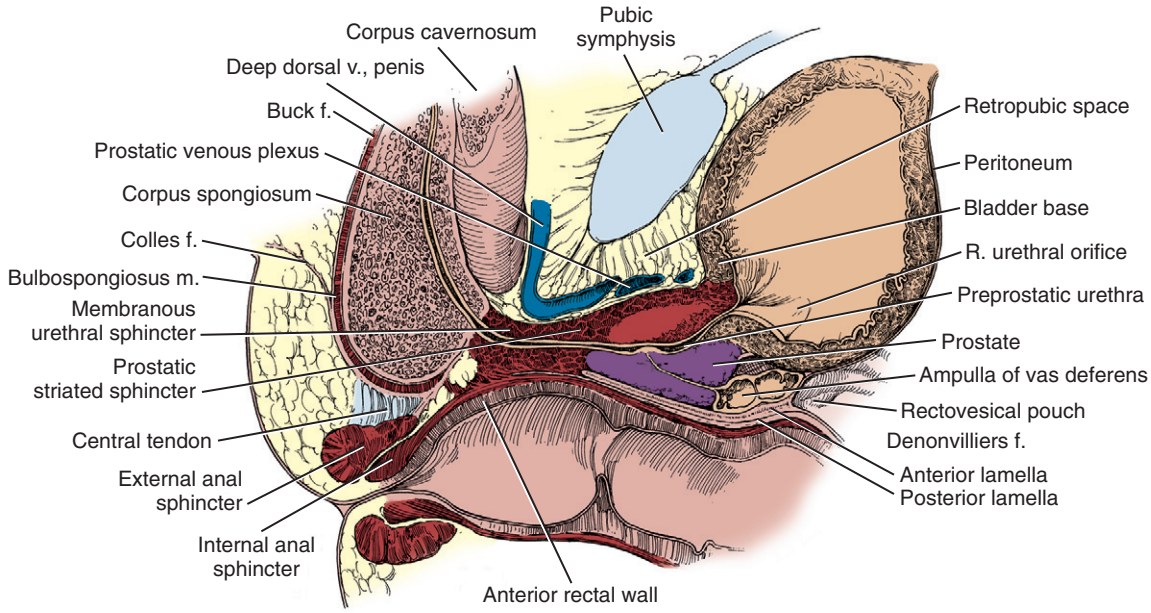


Figure 2–27. Sagittal section through the prostatic and membranous urethra, demonstrating the midline relations of the pelvic structures. (From Hinman F Jr. Atlas of urosurgical anatomy. Philadelphia: WB Saunders; 1993. p. 356.)

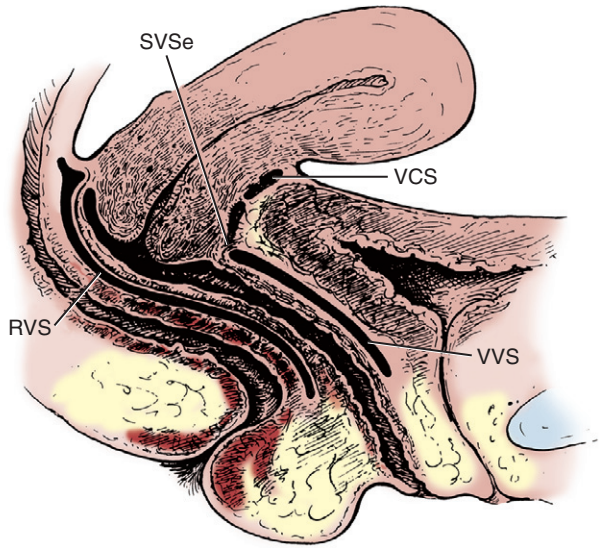


Figure 2–28. Median sagittal section of the female pelvis, showing the potential spaces between the pelvic organs. The posterior two thirds of the vagina lies nearly horizontal and rests with the uterine cervix on the rectum, which is in turn supported by the posterior portion of levator ani (the levator plate, not shown). RVS, rectovaginal space, the anterior wall is formed by the rectovaginal (Denonvilliers) fascia; SVSe, supravaginal septum, the fusion between the bladder and cervix; VCS, vesicocervical space; VVS, vesicovaginal space. (From Nichols DH, Randall CL. Vaginal surgery. 3rd ed. Baltimore: Williams & Wilkins; 1989. p. 34.)

the arcuate line, the ureter is subject to compression and obstruction by the gravid uterus and by masses within the true pelvis.

The ureters come within 5 cm of each other as they cross the iliac vessels. On entering the pelvis, they diverge widely along the pelvic side walls toward the ischial spines. The ureter travels on the anterior surface of the internal iliac vessels and is related laterally to the branches of the anterior trunk. Near the ischial spine, the ureter turns anteriorly and medially to reach the bladder. **In men,** the anteromedial surface of the ureter is covered by peritoneum, and the ureter is embedded in retroperitoneal connective tissue, which varies in thickness (see Fig. 2–13). As the ureter courses medially, it is crossed anteriorly by the vas deferens and runs with the inferior vesical arteries, veins, and nerves in the lateral vesical ligaments. Viewed from the peritoneal side, the ureter is just lateral and deep to the rectogenital fold. In women, the ureter first runs posterior to the ovary and then turns medially to run deep to the base of the broad ligament before entering a loose connective tissue tunnel through the substance of the cardinal ligament (see Fig. 2–13). As in the male, the ureter can be found slightly lateral and deep to the rectouterine folds of peritoneum. It is crossed anteriorly by the uterine artery and can be injured during hysterectomy. As it passes in front of the vagina, it crosses 1.5 cm anterior and lateral to the uterine cervix. The ureter can be injured at this level during hysterectomy, resulting in a ureterovaginal fistula. The ureter courses 1 to 4 cm on the anterior vaginal wall to reach the bladder. Occasionally, a stone lodged in the distal ureter can be palpated through the anterior vaginal wall. The intramural ureter is discussed with the bladder.

The pelvic ureter receives abundant blood supply from the common iliac artery and most branches of the internal iliac artery. The inferior vesical and uterine arteries usually supply the ureter with its largest pelvic branches. **Blood supply to the pelvic ureter enters laterally; thus the pelvic peritoneum should be incised only medial to the ureter.** Intramural vessels of the ureter run within the adventitia and generally follow one of two patterns. In approximately 75% of specimens, longitudinal vessels run the length of the ureter and are formed by anastomoses of segmental ureteral vessels. In the remaining ureters, the vessels form a fine interconnecting mesh (plexiform) with less collateral flow (Shafik, 1972). Therefore primary repair of injuries to the pelvic ureter fare poorly and are more prone to stricture formation (Hinman, 1993). Lymphatic drainage of the pelvic ureter is to the external, internal, and common iliac nodes. Pathologic enlargement of the common and internal iliac nodes can encroach on and obstruct the ureter.

The pelvic ureter has rich adrenergic and cholinergic autonomic innervation derived from the pelvic plexus. The functional

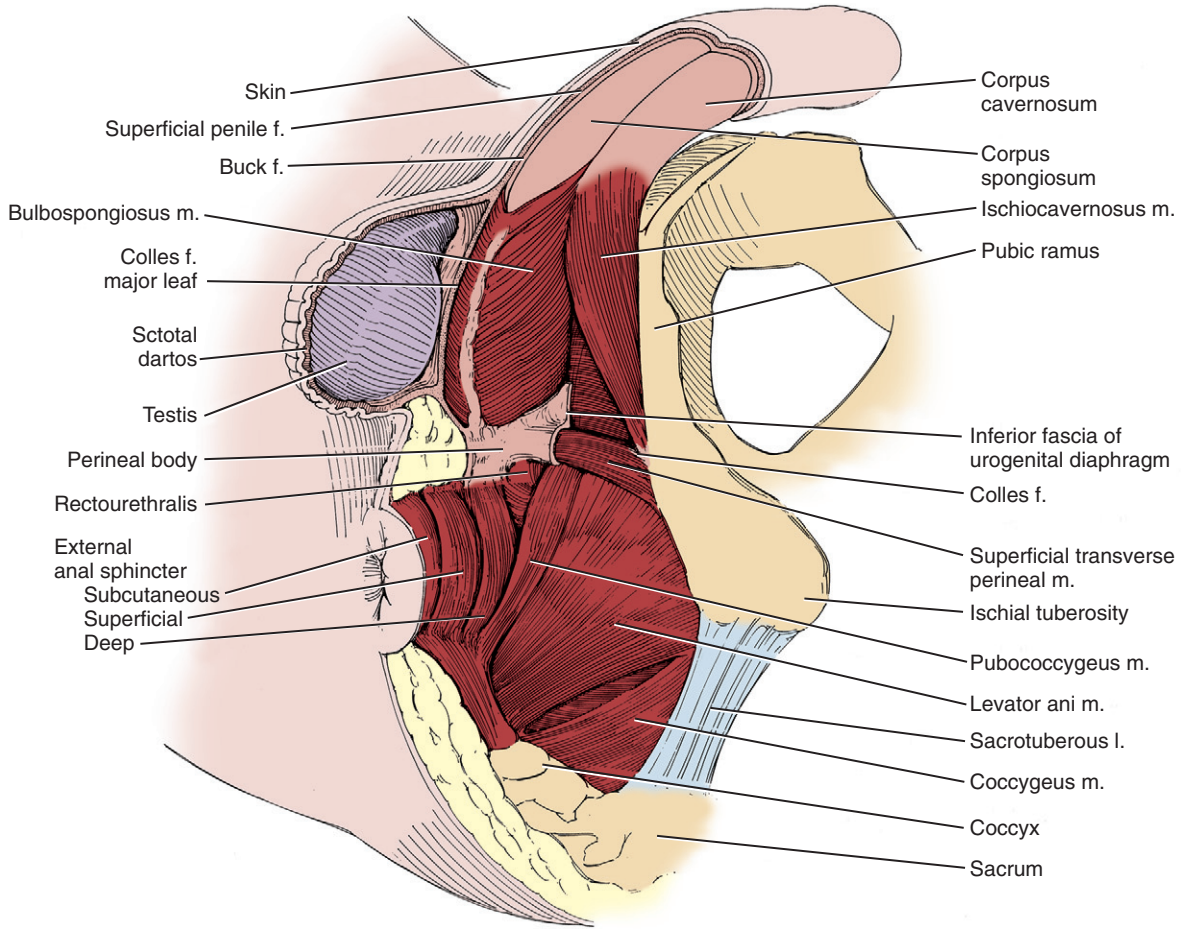


Figure 2–29. Muscles and superficial fasciae of the male perineum. (From Hinman F Jr. Atlas of urosurgical anatomy. Philadelphia: WB Saunders; 1993. p. 219.)

significance of this innervation is unclear, inasmuch as the ureter continues to contract peristaltically after denervation. Afferent neural fibers travel through the pelvic plexus and account for the visceral quality of referred pain from ureteral irritation or acute obstruction.

Bladder

Relationships

When filled, the bladder has a capacity of approximately 500 mL and assumes an ovoid shape. The empty bladder is tetrahedral and is described as having a superior surface with an apex at the urachus, two inferolateral surfaces, and a posteroinferior surface or base with the bladder neck at the lowest point (see Fig. 2–27).

The urachus anchors the bladder to the anterior abdominal wall (see Fig. 2–8). There is a relative paucity of bladder wall muscle at the point of attachment of the urachus, predisposing to diverticula formation. The urachus is composed of longitudinal smooth muscle bundles derived from the bladder wall. Near the umbilicus, it becomes more fibrous and usually fuses with one of the obliterated umbilical arteries. Urachal vessels run longitudinally, and the ends of the urachus must be ligated when it is divided. An epithelium-lined lumen usually persists throughout life and uncommonly gives rise to aggressive urachal adenocarcinomas (Begg, 1930). In rare instances, luminal continuity with the bladder serves as a bacterial reservoir or results in an umbilical urinary fistula.

The superior surface of the bladder is covered by peritoneum. Anteriorly, the peritoneum sweeps gently onto the anterior abdominal wall (see Fig. 2–13). With distention, the bladder rises out of the true pelvis and separates the peritoneum from the anterior abdominal wall. It is therefore possible to perform a suprapubic cystostomy without risking entry into the peritoneal cavity. Posteriorly, the peritoneum passes to the level of the seminal vesicles and meets the peritoneum on the anterior rectum to form the rectovesical space.

Anteroinferiorly and laterally, **the bladder is cushioned from the pelvic side wall by retropubic and perivesical fat and loose connective tissue. This potential space (of Retzius) may be entered anteriorly by dividing the transversalis fascia and provides access to the pelvic viscera as far posteriorly as the iliac vessels and ureters** (see Fig. 2–11). The bladder base is related to the seminal vesicles, ampullae of the vas deferentia, and terminal ureter. The bladder neck, located at the internal urethral meatus, rests 3 to 4 cm behind the midpoint of the symphysis pubis. It is firmly fixed by the pelvic fasciae (see earlier discussion) and by its continuity with the prostate; its position changes little with varying conditions of the bladder and rectum.

In the female, the peritoneum on the superior surface of the bladder is reflected over the uterus to form the vesicouterine pouch and then continues posteriorly over

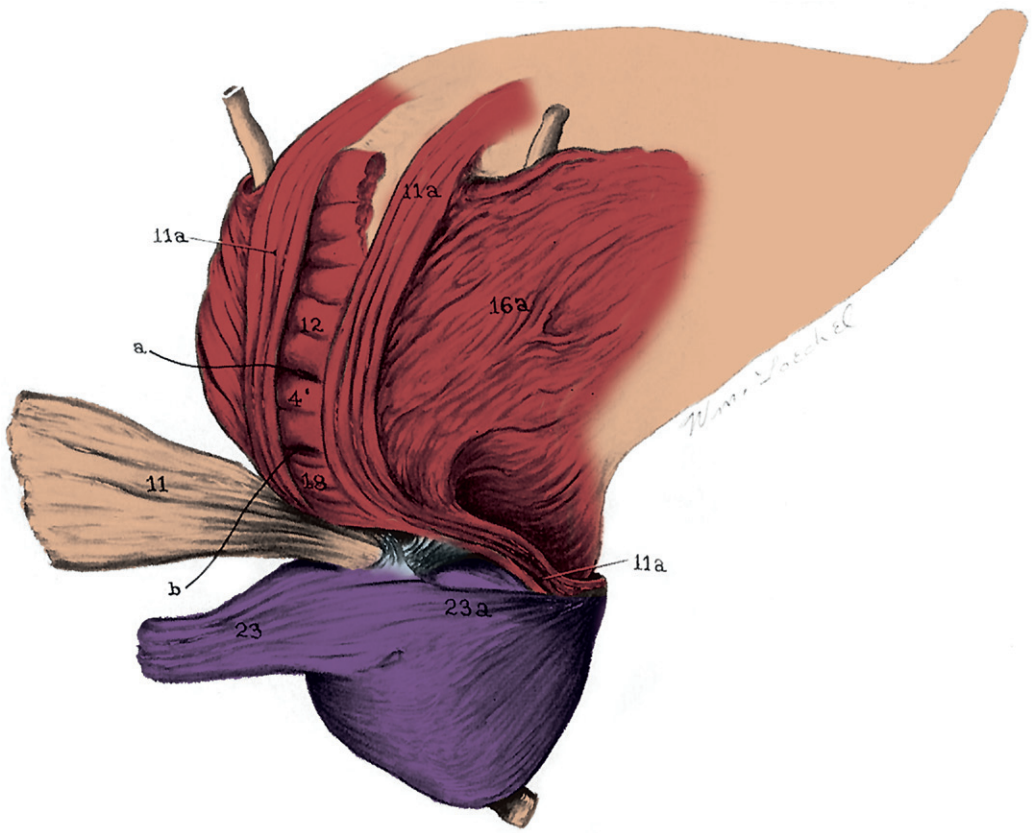


Figure 2–30. Dissection of the male bladder. 11, Posterior outer longitudinal detrusor, which forms the backing of the ureters (folded back); 11a, posterolateral portion of the outer longitudinal muscle forming a loop around the anterior bladder neck; 4′, 12, and 18, middle circular layer backing the trigone; 23 and 23a, lateral pedicle of the prostate. (From Uhlenhuth E. Problems in the anatomy of the pelvis. Philadelphia: JB Lippincott; 1953. p. 187.)

the uterus as the rectouterine pouch (see Fig. 2–13). The vagina and uterus intervene between the bladder and the rectum so that the base of the bladder and urethra rest on the anterior vaginal wall. Because the anterior vaginal wall is firmly attached laterally to the levator ani, contraction of the pelvic diaphragm (e.g., during increases in intra-abdominal pressure) elevates the bladder neck and draws it anteriorly. In many women with stress incontinence, the bladder neck drops below the pubic symphysis. In infants, the true pelvis is shallow and the bladder neck is level with the upper border of the symphysis. The bladder is a true intra-abdominal organ that can project above the umbilicus when full. By puberty, the bladder has migrated to the confines of the deepened true pelvis.

Structure

The internal surface of the bladder is lined with transitional epithelium, which appears smooth when the bladder is full but contracts into numerous folds when the bladder empties. This urothelium is usually six cells thick and rests on a thin basement membrane. Deep to this, the lamina propria forms a relatively thick layer of fibroelastic connective tissue that allows considerable distention. This layer is traversed by numerous blood vessels and contains smooth muscle fibers collected into a poorly defined muscularis mucosa. Beneath this layer lies the smooth muscle of the bladder wall. The relatively large muscle fibers form branching, interlacing bundles loosely arranged into inner longitudinal, middle circular, and outer longitudinal layers (Fig. 2–30). However, in the upper aspect of the bladder, these layers are clearly not separable, and any one fiber can travel between each of the layers, change orientation, and branch into longitudinal and circular fibers. This meshwork of detrusor muscle is ideally suited for emptying the spherical bladder.

Near the bladder neck, the detrusor muscle is clearly separable into the three layers described earlier. Here, the smooth muscle is morphologically and pharmacologically distinct from the remainder of the bladder because the large-diameter muscle fascicles are replaced by much finer fibers. The structure of the bladder neck appears to differ between men and women. In men, radially oriented inner longitudinal fibers pass through the internal meatus to become continuous with the inner longitudinal layer of smooth muscle in the urethra.

The middle layer forms a circular preprostatic sphincter that is responsible for continence at the level of the bladder neck (Fig. 2–31 on the Expert Consult website). The bladder wall posterior to the internal urethral meatus and the anterior fibromuscular stroma of the prostate form a continuous ringlike structure at the bladder neck (Brooks et al, 1998). The fact that perfect continence can be maintained in men in whom the striated urethral sphincter is destroyed attests to the efficacy of this sphincter (Waterhouse et al, 1973). This muscle is richly innervated by adrenergic fibers, which, when stimulated, produce closure of the bladder neck (Uhlenhuth, 1953). Damage to the sympathetic nerves to the bladder, as a result of diabetes mellitus or retroperitoneal lymph node dissection for testis cancer, can cause retrograde ejaculation.

The outer longitudinal fibers are thickest posteriorly at the bladder base. In the midline, they insert into the apex of the trigone and intermix with the smooth muscle of the prostate to provide a strong trigonal backing. Laterally, the fibers from this posterior sheet pass anteriorly and fuse to form a loop around the bladder neck (see Fig. 2–30). This loop is thought to participate in continence at the bladder neck. On the lateral and anterior surfaces of the bladder, the longitudinal fibers are not as well

developed. Some anterior fibers course forward to join the puboprostatic ligaments in men and the pubourethral ligaments in women. These fibers contribute smooth muscle to these supports and are speculated to contribute to bladder neck opening during micturition (DeLancey, 1989).

At the female bladder neck, the inner longitudinal fibers converge radially to pass downward as the inner longitudinal layer of the urethra, as described earlier. The middle circular layer does not appear to be as robust as that of the male, and several authors have denied its existence altogether (Gosling, 1979, 1985; Williams et al, 1989). Although several other investigators have noted an anterior loop of external longitudinal muscle (Fig. 2–32), the authors just cited deny the existence of this structure as well. They maintain instead that the external fibers pass obliquely and longitudinally down the urethra to participate in forming the inner longitudinal layer of smooth muscle. Regardless, the female bladder neck differs strikingly from the male in possessing little adrenergic innervation. In addition, its sphincteric function is limited; in 50% of continent women, urine enters the proximal urethra during a cough (Versi et al, 1986).

Ureterovesical Junction and the Trigone

As the ureter approaches the bladder, its spirally oriented mural smooth muscle fibers become longitudinal. Two to 3 cm from the bladder, a fibromuscular sheath (of Waldeyer) extends longitudinally over the ureter and follows it to the trigone (Tanagho, 1992). The ureter pierces the bladder wall obliquely, travels 1.5 to 2 cm, and terminates at the ureteral orifice (Fig. 2–33). As it passes through a hiatus in the detrusor (intramural ureter), it is compressed and narrows considerably. This is a common site in which ureteral stones become impacted. The intravesical portion of the ureter lies immediately beneath the bladder urothelium and therefore is quite pliant; it is backed by a strong plate of detrusor muscle. With bladder filling, this arrangement is thought to result in passive occlusion of the ureter, like a flap valve. Indeed, reflux does not occur in fresh cadavers when the bladder is filled (Thomson et al, 1994). Vesicoureteral reflux is thought to result from insufficient submucosal ureteral length and poor detrusor backing. Chronic increases in intravesical pressure resulting from bladder outlet obstruction can cause herniation of the bladder mucosa through the weakest point of the hiatus above the ureter and produce a "Hutch diverticulum" and reflux (Hutch et al, 1961).

The triangle of smooth urothelium between the two ureteral orifices and the internal urethral meatus is referred to as the *trigone of the bladder* (see Fig. 2–33). The fine longitudinal smooth muscle fibers from each ureter fan out over the base of the bladder to form a triangular sheet of muscle

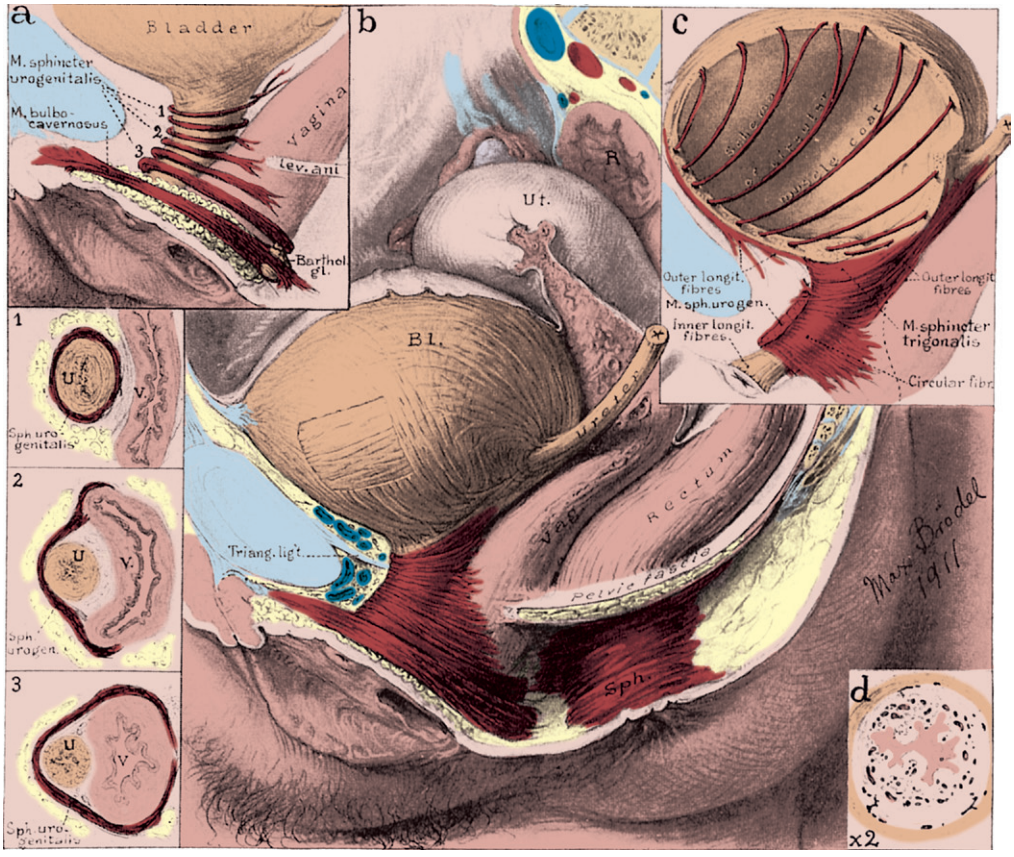


Figure 2–32. Female bladder and striated urethral sphincter. a, Diagram of striated urethral sphincter showing disposition of the muscle fibers. 1, The proximal third of the sphincter encircles the urethra entirely. 2, The middle bundles surround the urethra in front and pass off the lateral sides to blend with the vaginal wall (compressor urethrae). 3, The distal portion surrounds the urethra and vagina together and has been called the *urethrovaginal sphincter.* The bulbocavernosus also acts as a sphincter around the vaginal vestibule. b, Urethral sphincter in its entirety. The relationship of the pelvic viscera is shown. Interlacing detrusor fibers are also demonstrated. c, Posterolateral outer longitudinal detrusor muscle, looping anterior to the bladder neck. Inner longitudinal smooth muscle fibers run the length of the urethra, deep to the striated sphincter. d, Cross section of the urethra, showing thick, highly vascularized lamina propria and folded mucosa, which act as a urethral seal. Longitudinal smooth muscle surrounds the lamina propria. (Original art in the Max Brödel Archives, Department of Art as Applied to Medicine, The Johns Hopkins University School of Medicine.)

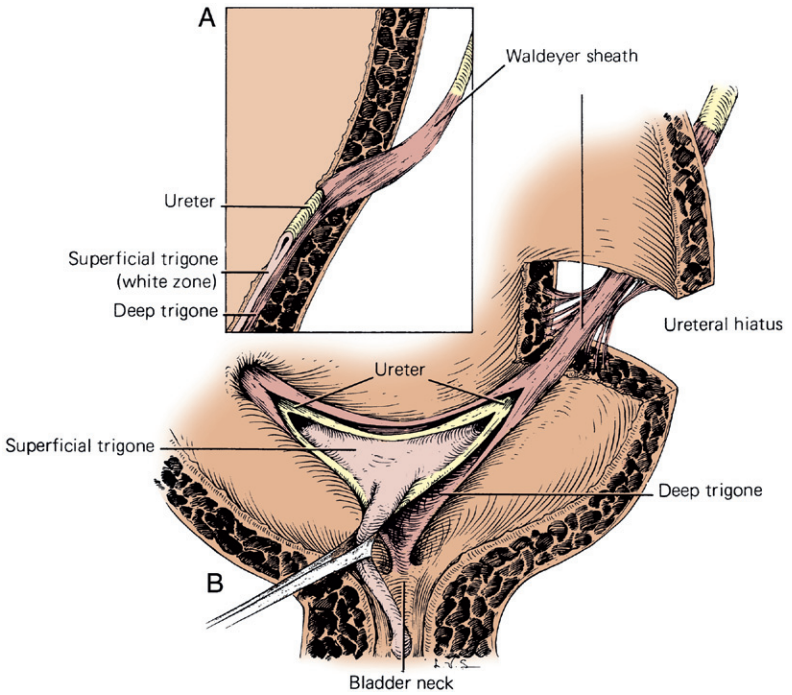


Figure 2–33. Normal ureterovesical junction and trigone. **A,** Section of the bladder wall perpendicular to the ureteral hiatus shows the oblique passage of the ureter through the detrusor and also shows the submucosal ureter with its detrusor backing. Waldeyer sheath surrounds the prevesical ureter and extends inward to become the deep trigone. **B,** Waldeyer sheath continues in the bladder as the deep trigone, which is fixed at the bladder neck. Smooth muscle of the ureter forms the superficial trigone and is anchored at the verumontanum. (From Tanagho EA, Pugh RCB. The anatomy and function of the ureterovesical junction. Br J Urol 1963;35:151.)

that extends from the two ureteral orifices to the internal urethral meatus. The edges of this muscular sheet can be thickened between the ureteral orifices (the interureteric crest or Mercier bar) and between the ureters and the internal urethral meatus (Bell muscle).

The muscle of trigone forms three distinct layers: (1) a superficial layer, derived from the longitudinal muscle of the ureter, which extends down the urethra to insert at the verumontanum; (2) a deep layer, which continues from Waldeyer sheath and inserts at the bladder neck; and (3) a detrusor layer, formed by the outer longitudinal and middle circular smooth muscle layers of the bladder wall. Through its continuity with the ureter, the superficial trigonal muscle anchors the ureter to the bladder. During ureteral reimplantation, this muscle is tented up and divided in order to gain access to the space between Waldeyer sheath and the ureter. In this space, only loose fibrous and muscular connections are found. This anatomic arrangement helps prevent reflux during bladder filling by fixing and applying tension to the ureteral orifice. As the bladder fills, its lateral wall telescopes outward on the ureter, thereby increasing intravesical ureteral length (Hutch et al, 1961).

The urothelium overlying the muscular trigone is usually only three cells thick and adheres strongly to the underlying muscle by a dense lamina propria. During filling and emptying of the bladder, this mucosal surface remains smooth.

Bladder Circulation

In addition to the vesical branches, the bladder may be supplied by any adjacent artery arising from the internal iliac artery. For convenience, surgeons refer to the vesical blood supply as the *lateral* and *posterior* pedicles, which, when the bladder is approached from the rectovesical space, are lateral and posteromedial to the ureters, respectively. These pedicles are the lateral and posterior vesical ligaments in the male and part of cardinal and uterosacral ligaments in the female (see Fig. 2–13). The veins of the bladder coalesce into the vesicle plexus and drain into the internal iliac vein. Lymphatics from the lamina propria and muscularis drain to channels on the bladder surface, which run with the superficial vessels within the thin visceral fascia. Small paravesical lymph nodes can be found along the superficial channels. The bulk of the lymphatic drainage passes to the external iliac lymph nodes (see Fig. 2–21). Some anterior and lateral drainage may go through the obturator and internal iliac nodes, whereas portions of the bladder base and trigone may drain into the internal and common iliac groups.

Bladder Innervation

Autonomic efferent fibers from the anterior portion of the pelvic plexus (the vesical plexus) pass up the lateral and posterior ligaments to innervate the bladder. The bladder wall is richly supplied with parasympathetic cholinergic nerve endings and has abundant postganglionic cell bodies. Sparse sympathetic innervation of the bladder has been proposed to mediate detrusor relaxation but probably lacks functional significance. A separate nonadrenergic, noncholinergic (NANC) component of the autonomic nervous system participates in activating the detrusor, although the neurotransmitter has not been identified (Burnett, 1995). As mentioned, the male bladder neck receives abundant sympathetic innervation and expresses α_1-adrenergic receptors. The female bladder neck has little adrenergic innervation. Nitric oxide synthase–containing neurons have been identified in the detrusor, particularly at the bladder neck, where they assist relaxation during micturition. The trigonal muscle is innervated by adrenergic and nitric oxide synthase–containing neurons. Like the bladder neck, it relaxes during micturition. Afferent innervation from the bladder travels with both sympathetic (via the hypogastric nerves) and parasympathetic nerves to reach cell bodies in the dorsal root ganglia located at thoracolumbar and sacral levels. As a consequence, presacral neurectomy (division of the hypogastric nerves) is ineffective in relieving bladder pain.

Prostate

Relationships

The normal prostate weighs 18 g; measures 3 cm in length, 4 cm in width, and 2 cm in depth; and is traversed by the prostatic urethra (see Fig. 2–27). Although ovoid, **the prostate is referred to as having anterior, posterior, and lateral surfaces, with a narrowed apex inferiorly and a broad base superiorly** that is contiguous with the base of the bladder. It is enclosed by a capsule composed of collagen, elastin, and abundant smooth muscle. Posteriorly and laterally, this capsule has an average thickness of 0.5 mm, although it may be partially transgressed by normal glands. Microscopic bands of smooth muscle extend from the posterior surface of the capsule to fuse with Denonvilliers fascia. Loose areolar tissue defines a thin plane between Denonvilliers fascia and the rectum. On the anterior and anterolateral surfaces of the prostate, the capsule blends with the visceral continuation of endopelvic fascia. Toward the apex, the puboprostatic ligaments extend anteriorly to fix the prostate to the pubic bone. The superficial branch of the dorsal vein lies outside this fascia in the retropubic fat and pierces it to drain into the dorsal vein complex.

Laterally, the prostate is cradled by the pubococcygeal portion of levator ani and is directly related to its overlying endopelvic fascia (see Figs. 2–8 and 2–10). Below the juncture of the parietal and visceral endopelvic fascia (arcus tendineus fascia pelvis), the pelvic fascia and prostate capsule separate and the space between them is filled by fatty areolar tissue and the lateral divisions of the dorsal vein complex. During a radical retropubic prostatectomy, the endopelvic fascia should be divided lateral to the arcus tendineus fascia pelvis to avoid injury to the venous complex. In the process, the endopelvic fascia overlying the levator ani is actually peeled off the muscle and displaced medially with the prostate. Although this is truly a parietal endopelvic fascia, it is commonly referred to as the "lateral prostatic fascia" (Myers, 1994). As mentioned earlier, the cavernosal nerves run posterolateral to the prostate in the substance of the parietal pelvic fascia (lateral prostatic fascia). Thus to preserve these nerves, this fascia must be incised lateral to the prostate and anterior to the neurovascular bundle (Walsh et al, 1983). Therefore an understanding of the fascial layers that overlie the prostate is crucial in the performance of an accurate nerve-sparing radical prostatectomy (Fig 2–34).

Recently, with the adoption of robotic and laparoscopic radical prostatectomy techniques, there has been a renewed interest in the description of these fascial layers with respect to the neurovascular bundle because these layers may be better visualized with the magnification afforded by these techniques (Tewari et al, 2006). Better definition of the "lateral prostatic fascia" at the level of the prostatic pedicles has become necessary in preserving the cavernosal nerves because the dissection is often performed antegrade in these techniques. Anatomic studies have revealed nerve bundles that course along the prostate laterally and anteriorly to the nerves, commonly referred to as the *neurovascular bundle* (Eichelberg et al, 2007; Raychaudhuri and Cahill, 2008). Whether these nerves contribute to erectile function remains controversial.

The apex of the prostate is continuous with the striated urethral sphincter (see Fig. 2–14). Histologically normal prostatic glands can be found to extend into the striated muscle with no intervening fibromuscular stroma or "capsule." At the base of the prostate, outer longitudinal fibers of the detrusor fuse and blend with the fibromuscular tissue of the capsule. As mentioned, the middle circular and inner longitudinal muscles extend down the prostatic urethra as a preprostatic sphincter. As with the apex, no true capsule separates the prostate from the bladder. In surgically resected prostate carcinomas, this peculiar anatomic arrangement can make interpretation of these margins difficult and has led some pathologists to propose that the prostate does not possess a true capsule (Epstein, 1989).

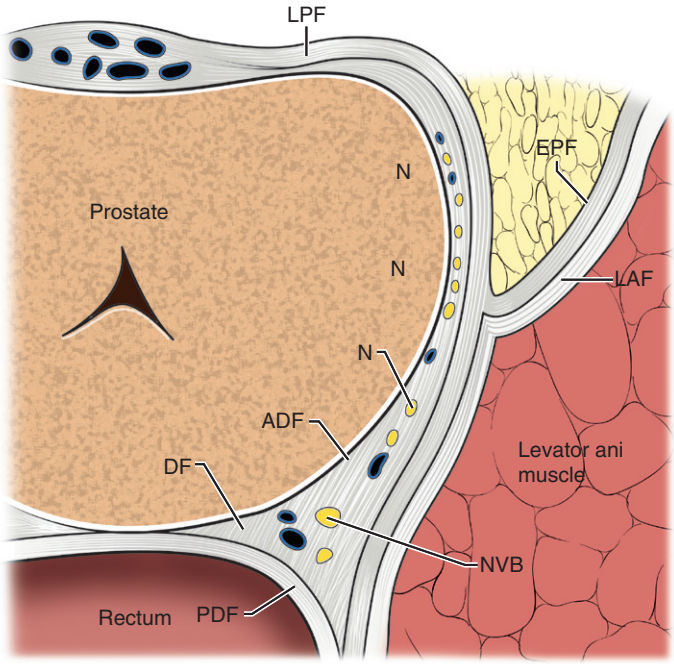


Figure 2–34. Cross section of prostate with prostatic fascial layers outlined including the lateral prostatic fascia (LPF), endopelvic fascia (EPF), levator ani fascia (LAF), Denonvilliers fascia (DF), anterior lamina of Denonvilliers fascia (ADF), posterior lamina of Denonvilliers fascia, neurovascular bundle (NVB), and lateral nerves (N). (From Walz J, Graefen M, Huland H. Basic principles of anatomy for optimal surgical treatment of prostate cancer. World J Urol 2007;25:31–8.)

Structure

The prostate is composed of approximately 70% glandular elements and 30% fibromuscular stroma. The stroma is continuous with capsule and is composed of collagen and abundant smooth muscle. It encircles and invests the glands of the prostate and contracts during ejaculation to express prostatic secretions into the urethra.

The urethra runs the length of the prostate and is usually closest to its anterior surface. It is lined by transitional epithelium, which may extend into the prostatic ducts. The urothelium is surrounded by an inner longitudinal and an outer circular layer of smooth muscle. A urethral crest projects inward from the posterior midline, runs the length of the prostatic urethra, and disappears at the striated sphincter (Fig. 2–35). To either side of this crest, a groove is formed (prostatic sinuses) into which all glandular elements drain (McNeal, 1972). At its midpoint, the urethra turns approximately 35 degrees anteriorly, but this angulation can vary from 0 to 90 degrees (see Figs. 2–27, 2–31, 2–36, and 2–37). This angle divides the prostatic urethra into proximal (preprostatic) and distal (prostatic) segments that are

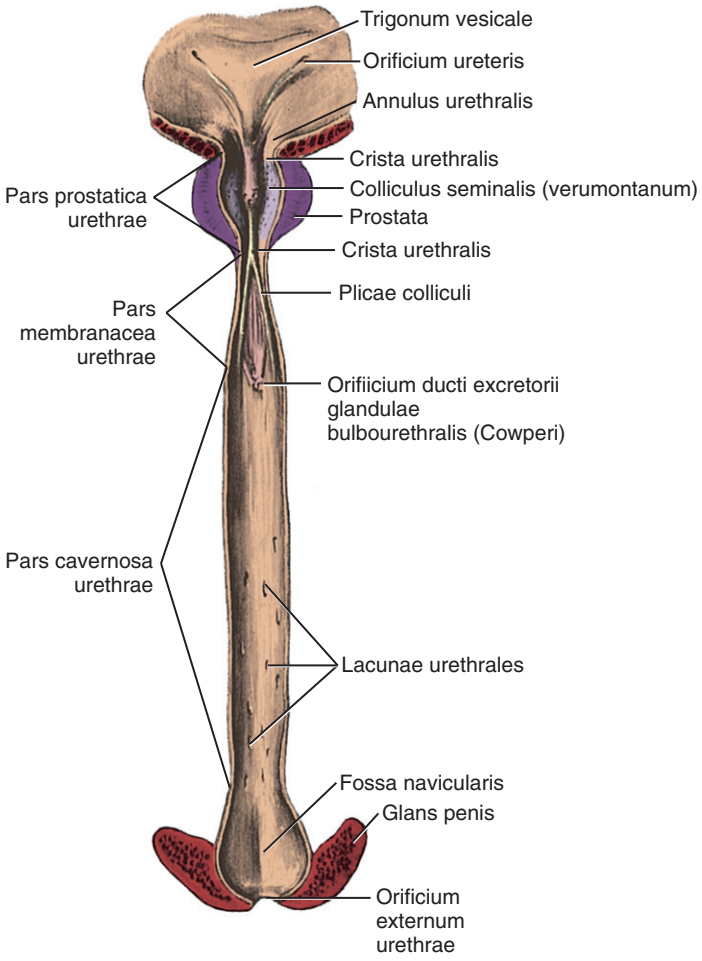


Figure 2–35. Posterior wall of the male urethra. (From Anson BJ, McVay CB. Surgical anatomy. 6th ed. Philadelphia: WB Saunders; 1984. p. 833.)

functionally and anatomically discrete (McNeal, 1972, 1988). In the proximal segment, the circular smooth muscle is thickened to form the involuntary internal urethral (preprostatic) sphincter described earlier. Small periurethral glands, lacking periglandular smooth muscle, extend between the fibers of the longitudinal smooth muscle to be enclosed by the preprostatic sphincter. Although these glands constitute less than 1% of the secretory elements of the prostate, they can contribute significantly to prostatic volume in older men as one of the sites of origin of benign prostatic hypertrophy.

Beyond to the urethral angle, all major glandular elements of the prostate open into the prostatic urethra. The urethral crest widens and protrudes from the posterior wall as the verumontanum (see Figs. 2–35, 2–37, and 2–38). The small slitlike orifice of the prostatic utricle is found at the apex of the verumontanum and may be visualized cystoscopically. The utricle is a 6-mm müllerian remnant in the form of a small sac that projects upward and backward into the substance of the prostate. In males with ambiguous genitalia, it may form a large diverticulum that protrudes from the posterior side of the prostate. To either side of the utricular orifice, the two small openings of the ejaculatory ducts may be found. The ejaculatory ducts form at the juncture of the vas deferens and seminal vesicles and enter the prostate base, where it fuses with the bladder. They course nearly 2 cm through the prostate in line with the distal prostatic urethra and are surrounded by circular smooth muscle (see Fig. 2–36; see also Figs. 2–27 and 2–31).

In general, **the glands of the prostate are tubuloalveolar with relatively simple branching and are lined with simple cuboidal or columnar epithelium. Scattered neuroendocrine cells, of unknown function, are found between the secretory cells. Beneath the epithelial cells, flattened basal cells line each acinus.** Each acinus is surrounded by a thin layer of stromal smooth muscle and connective tissue.

The glandular elements of the prostate have been divided into discrete zones, distinguished by the location of their ducts in the urethra, by their differing pathologic lesions, and, in some cases, by their embryologic origin (see Fig. 2–36). These zones can be demonstrated clearly with transrectal ultrasonography (Fig 2–39). **At the angle dividing the preprostatic and prostatic urethra, the ducts of the transition zone arise and pass beneath the preprostatic sphincter to travel on its lateral and posterior sides.** Normally, the transition zone accounts for 5% to 10% of the glandular tissue of the prostate. A discrete fibromuscular band of tissue separates the transition zone from the remaining glandular compartments and may be visualized at transrectal ultrasonography of the prostate. The transition zone commonly gives rise to benign prostatic hypertrophy, which expands to compress the fibromuscular band into a surgical capsule seen at enucleation of an adenoma. It is estimated that 20% of adenocarcinomas of the prostate originate in this zone.

The ducts of the central zone arise circumferentially around the openings of the ejaculatory ducts. This zone constitutes 25% of the glandular tissue of the prostate and expands in a cone shape around the ejaculatory ducts to the base of the bladder. The glands are structurally and immunohistochemically distinct from the remaining prostatic glands (which branch directly from the urogenital sinus), which has led to the suggestion that they are of wolffian origin (McNeal, 1988). In keeping with this suggestion, only 1% to 5% of adenocarcinomas arise in the central zone, although it may be infiltrated by cancers from adjacent zones.

The peripheral zone makes up the bulk of the prostatic glandular tissue (70%) and covers the posterior and lateral aspects of the gland. Its ducts drain into the prostatic sinus along the entire length of the (postsphincteric) prostatic urethra. Seventy percent of prostatic cancers arise in this zone, and it is the zone most commonly affected by chronic prostatitis.

Up to one third of the prostatic mass may be attributed to the nonglandular **anterior fibromuscular stroma.** This region normally extends from the bladder neck to the striated sphincter, although considerable portions of it may be replaced by glandular tissue in adenomatous enlargement of the prostate. It is directly continuous with the prostatic capsule, anterior visceral fascia, and anterior portion of the preprostatic sphincter and is composed of elastin, collagen, and smooth and striated muscle. It is rarely invaded by carcinoma.

Clinically, the prostate is often spoken of as having two lateral lobes, separated by a central sulcus that is palpable on rectal examination, and a middle lobe, which may project into the bladder in older men. These lobes do not correspond to histologically defined structures in the normal prostate but are usually related to pathologic enlargement of the transition zone laterally and the periurethral glands centrally.

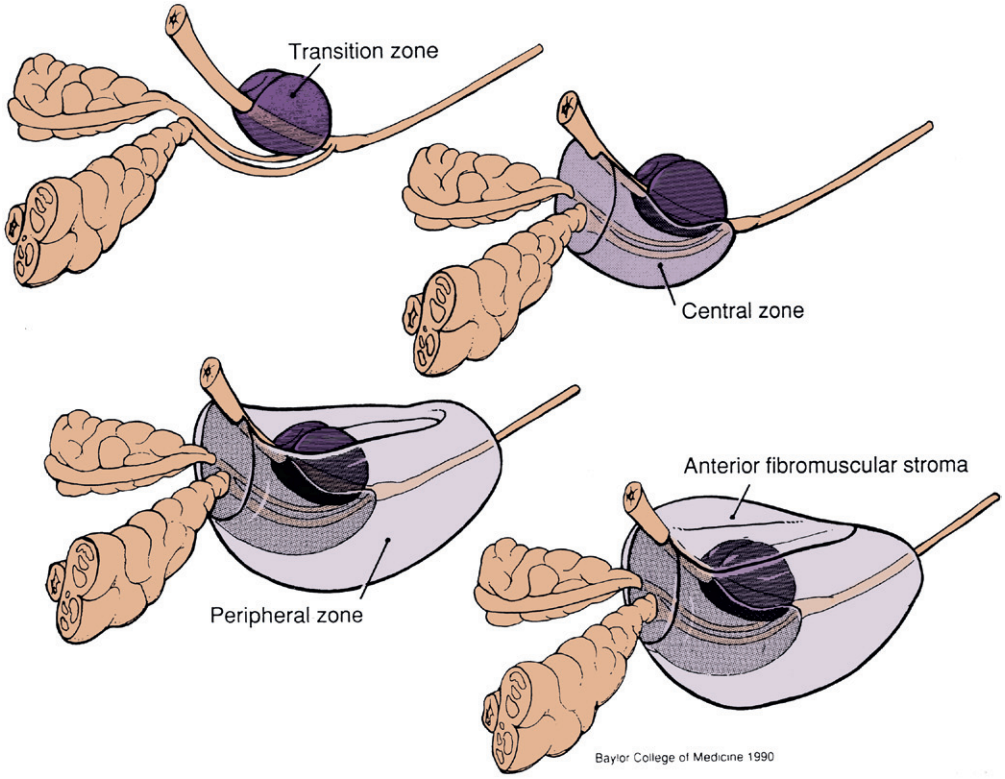


Figure 2–36. Zonal anatomy of the prostate as described by J.E. McNeal (Normal histology of the prostate. Am J Surg Pathol 1988;12:619–33). The transition zone surrounds the urethra proximal to the ejaculatory ducts. The central zone surrounds the ejaculatory ducts and projects under the bladder base. The peripheral zone constitutes the bulk of the apical, posterior, and lateral aspects of the prostate. The anterior fibromuscular stroma extends from the bladder neck to the striated urethral sphincter. (© 1990, Baylor College of Medicine.)

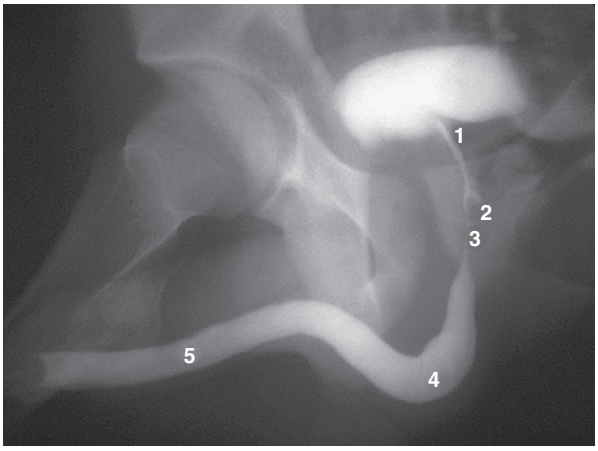


Figure 2–37. Retrograde urethrogram of the male urethra demonstrating urethral anatomy. 1, prostatic urethra; 2, verumontanum, into which enter the ejaculatory ducts; 3, membranous urethra, note physiologic narrowing of urethral luminal diameter due to external striated sphincter; 4, bulbar urethra; 5, pendulous urethra.

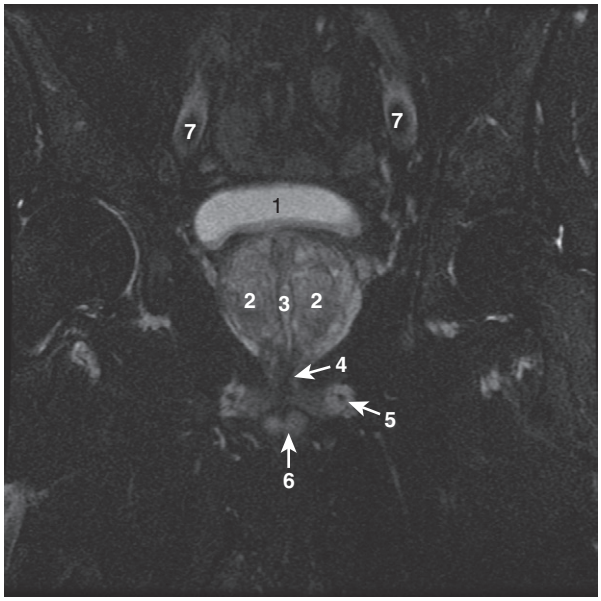


Figure 2–38. Axial T2-weighted magnetic resonance image of the male pelvis through the prostate gland and adjacent structures. 1, urinary bladder; 2, lateral lobes of prostate; 3, verumontanum; 4, striated urethral sphincter; 5, inferior pubic ramus; 6, corpus spongiosum in cross section; 7, external iliac artery.

Vascular Supply

Most commonly, **the arterial supply to the prostate arises from the inferior vesical artery.** As it approaches the gland, the artery (often several) divides into two main branches (Fig. 2–40). The urethral arteries penetrate the prostatovesical junction posterolaterally and travel inward, perpendicular to the urethra. They approach the bladder neck in the 1- to 5-o'clock and 7- to 11-o'clock positions, with the largest branches located posteriorly. They then turn caudally, parallel to the urethra, to supply it, the periurethral glands, and the transition zone. Thus in benign prostatic hypertrophy, these arteries provide the principal blood supply of the adenoma (Flocks, 1937). When these glands are resected or

enucleated, the most significant bleeding is commonly encountered at the bladder neck, particularly at the 4- and 8-o'clock positions.

The capsular artery is the second main branch of the prostatic artery. This artery gives off a few small branches that pass anteriorly to ramify on the prostatic capsule. The bulk of this artery runs posterolateral to the prostate with the cavernous nerves (neurovascular bundles) and ends at the pelvic diaphragm. The capsular branches pierce the prostate at right angles and follow the reticular bands of stroma to supply the glandular tissues. Venous drainage of the prostate is abundant through the periprostatic plexus (see Fig. 2–20).

Lymphatic drainage is primarily to the obturator and internal iliac nodes (see Fig. 2–21). A small portion of drainage may initially pass through the presacral group or, less commonly, the external iliac nodes.

Nerve Supply

Sympathetic and parasympathetic innervation from the pelvic plexus travels to the prostate through the cavernous nerves. Nerves follow branches of the capsular artery to ramify in the glandular and stromal elements. Parasympathetic nerves end at the acini and promote secretion; sympathetic fibers cause contraction of the smooth muscle of the capsule and stroma.

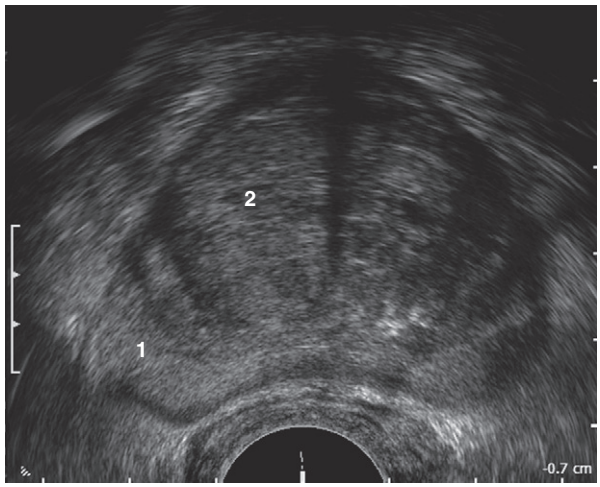


Figure 2–39. Transrectal ultrasound of the prostate demonstrating the 1, peripheral zone and 2, transition zone.

α_1-Adrenergic blockade diminishes prostate stromal and preprostatic sphincter tone and improves urinary flow rates in men affected with benign prostatic hypertrophy; this emphasizes that this disease affects both the stroma and the epithelium. Peptidergic and nitric oxide synthase–containing neurons also have been found in the prostate and may affect smooth muscle relaxation (Burnett, 1995). Afferent neurons from the prostate travel through the pelvic plexuses to pelvic and thoracolumbar spinal centers. A prostatic block may be achieved by instilling local anesthetic into the pelvic plexuses.

Membranous Urethra

In its course from the apex of the prostate to the perineal membrane, **the membranous urethra spans on average 2 to 2.5 cm** (range 1.2 to 5 cm) (Myers, 1991) (see Fig 2–37). It is surrounded by the striated (external) urethral sphincter, which is often incorrectly depicted as a flat sheet of muscle sandwiched between two layers of fascia. The striated sphincter is actually signet ring shaped, broad at its base, and narrowing as it passes through the urogenital hiatus of the levator ani to meet the apex of the prostate (see Fig. 2–14; see also Figs. 2–10, 2–27, and 2–38). In utero, this muscle forms a vertically oriented tube that extends from the perineal membrane to the bladder neck (Oelrich, 1980). As the prostate grows, posterior and lateral portions of this muscle atrophy, although transverse fibers persist on the entire anterior prostate through adulthood. At the apex of the prostate, circular fibers surround the urethra and thin posteriorly to insert into a fibrous raphe. Distally, the fibers do not meet posteriorly; rather, they acquire an Ω shape as they fan out laterally over the perineal membrane. Throughout its length, the posterior portion of the striated sphincter inserts into the perineal body. When the sphincter contracts, the walls of the urethra are pulled posteriorly toward the perineal body (Strasser et al, 1998). In contrast to the levator ani, the sphincter consists only of fine, type I (slow-twitch) fibers, rich in acid-stable myosin ATPase, which appear designed for tonic contraction. The myofibrils are surrounded by abundant connective tissue that blends with adjacent supporting structures.

The striated sphincter is related anteriorly to the dorsal vein complex (which may invade its anterior portion with age) and laterally to the levator ani. **Connective tissue from deep within the lateral and anterior walls inserts into the puboprostatic ligaments posteriorly and into the suspensory ligament of the penis anteriorly to form a sling of fibrous tissue that suspends the urethra from the pubis**

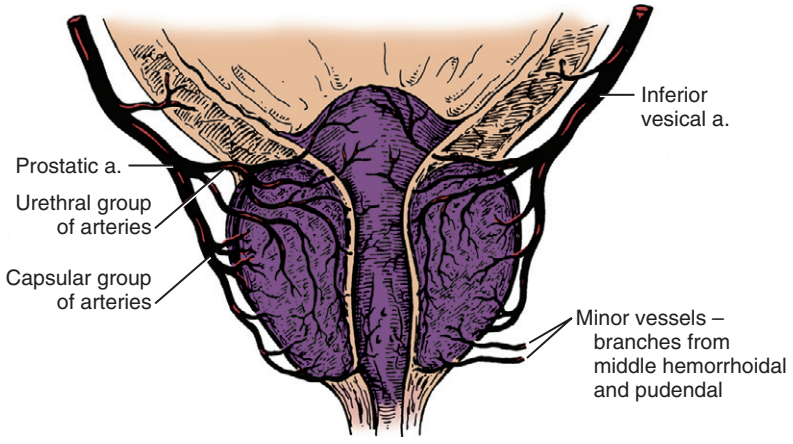


Figure 2–40. Arterial supply of the prostate. (Adapted from Flocks RH. The arterial distribution within the prostate gland: its role in transurethral prostatic resection. J Urol 1937;37:527.)

(Steiner, 1994). A similar suspensory mechanism is found in the female urethra (see later discussion and Fig. 2–41). Two bulbourethral glands lie superior to the perineal membrane and are invested in the broad base of sphincter muscle. During sexual excitement, these glands secrete clear mucus into the bulbous urethra.

The striated sphincter corresponds to the location of peak urethral closing pressure and is responsible for continence after prostatectomy. Components involved in generating this closing pressure are (1) the pseudostratified columnar epithelium, which contracts into radial folds as it meets to occlude the lumen; (2) the submucosa, which is rich with blood vessels and soft connective tissue and contributes to urethral sealing (Raz et al, 1972); (3) the longitudinal and circular urethral smooth muscle (intrinsic component of the external sphincter); (4) the striated sphincter; and (5) the pubourethral component of the levator ani.

Gross dissection and retrograde axonal tracing techniques have confirmed that the striated sphincter is supplied by the pudendal nerve (Tanagho et al, 1982). However, urologists have long been puzzled as to why pudendal nerve sectioning does not ablate sphincter activity. Lawson (1974) and Zvara and colleagues (1994) identified **a second source of somatic innervation to the sphincter: a branch of the sacral plexus that runs on the pelvic surface of the levator ani** (see Fig. 2–23). Injury to this nerve at radical prostatectomy may contribute to postoperative urinary incontinence (Hollabaugh et al, 1997). Autonomic innervation to the intrinsic smooth muscle of the membranous urethra is likely given by the cavernous nerves as they pass nearby, although dividing these nerves does not appear to affect urinary continence significantly (Steiner et al, 1991). Afferent fibers from the striated sphincter have not been defined but are sure to have interesting and important functional roles because this muscle lacks proprioceptive muscle spindles (Gosling et al, 1981).

Vas Deferens and Seminal Vesicle

As it arises from the tail of the epididymis, the vas (ductus) deferens is somewhat tortuous for 2 to 3 cm (Fig. 2–42). It runs posterior to the vessels of the cord and through the inguinal canal and emerges in the pelvis lateral to the inferior epigastric vessels (see Fig. 2–3). At the internal ring, it diverges from the testicular vessels and passes medial to all structures of the pelvic side wall to reach the base of the prostate posteriorly (see Figs. 2–3, 2–13, and 2–16). The terminal vas is dilated and tortuous (ampulla) and is capable of storing spermatozoa. The vas has a thick wall of outer longitudinal and inner circular smooth muscle and is lined by pseudostratified columnar epithelium with nonmotile stereocilia.

The seminal vesicle is a lateral outpouching of the vas, approximately 5 cm long, with a capacity of 3 to 4 mL (see Figs. 2–8, 2–36, and 2–43). Despite its name, it does not store sperm but contributes the largest portion of fluid to the ejaculate. The seminal vesicle comprises a single coiled tube with several outpouchings that is lined by columnar epithelium with goblet cells. The tube is encased in a thin layer of smooth muscle and is held in its coiled configuration by a loose adventitia.

The seminal vesicle and ampulla of the vas lie posterior to the bladder. The ureter enters the bladder medial to the tip of the seminal vesicle. As the seminal vesicle and vas join to form the ejaculatory duct, their smooth muscle coats fuse with the prostatic capsule at its base. **Denonvilliers fascia or, occasionally, the rectovesical pouch of peritoneum separates these structures from the rectum** (see Fig. 2–27). Unless involved by a pathologic process, these structures are not palpable on rectal examination.

The blood supply for the seminal vesicles and vasa comes from the vesiculodeferential artery, a branch of the superior vesical artery. This artery supplies the vas throughout its length and then passes onto the anterior surface of the seminal vesicle near its tip. During radical prostatectomy the artery is invariably found between the vas and seminal vesicle and must be isolated and controlled. Additional arterial supply may come from the inferior vesical artery. The pelvic vas and seminal vesicle drain into the pelvic venous plexus. Lymphatic drainage passes to the external and internal iliac nodes (see Fig. 2–21). Innervation

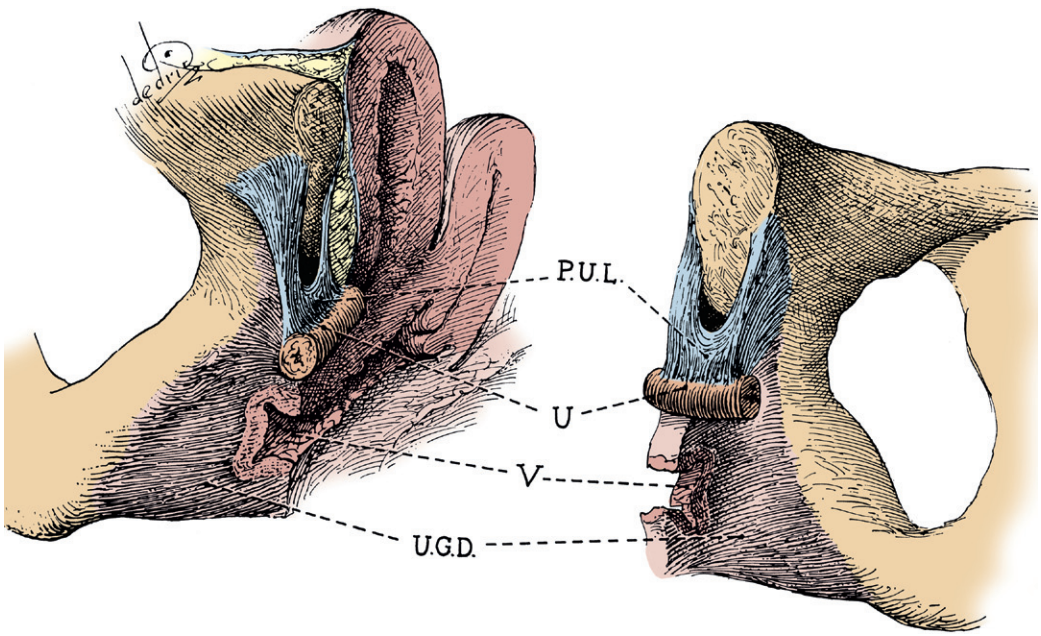


Figure 2–41. Urethral suspensory mechanism. The pubourethral ligament (P.U.L.) is composed of an anterior portion (suspensory ligament of the clitoris), a posterior portion (pubourethral ligament of endopelvic fascia), and an intermediate portion that bridges the other two. (From Milley PS, Nichols DH. The relationship between the pubo-urethral ligaments and the urogenital diaphragm in the human female. Anat Rec 1971;170:283.)

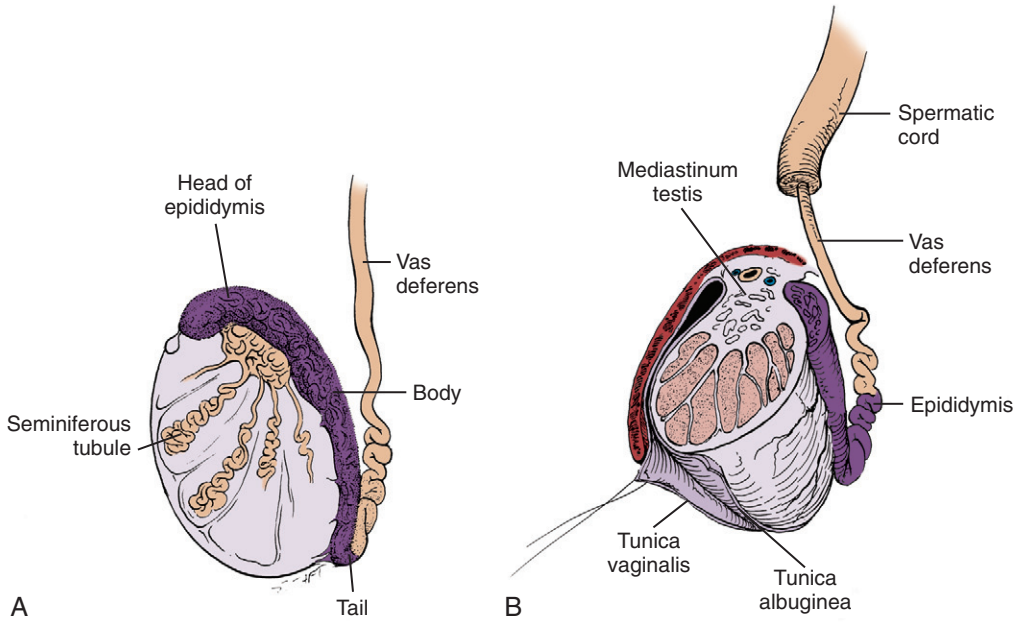


Figure 2–42. Testis and epididymis. **A,** One to three seminiferous tubules fill each compartment and drain into the rete testis in the mediastinum. Twelve to 20 efferent ductules become convoluted in the head of the epididymis and drain into a single coiled duct of the epididymis. The vas is convoluted in its first portion. **B,** Cross section of the testis, showing the mediastinum and septations continuous with the tunica albuginea. The parietal and visceral tunica vaginalis are confluent where the vessels and nerves enter the posterior aspect of the testis.

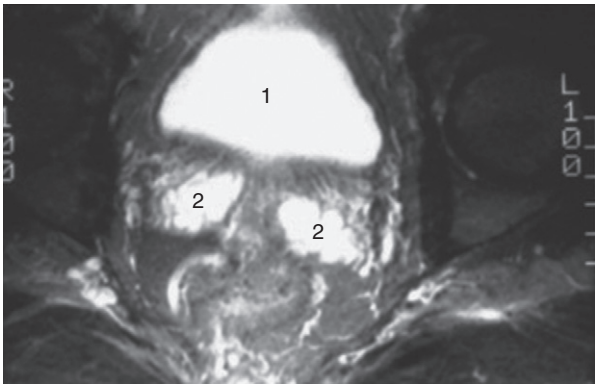


Figure 2–43. Axial T2-weighted magnetic resonance image of the male pelvis illustrating the 1, bladder and 2, seminal vesicles.

arises from the pelvic plexus, with major excitatory efferents contributed by the (sympathetic) hypogastric nerves (Kolbeck and Steers, 1993).

Female Pelvic Viscera

The uterus measures 8 × 6 × 4 cm in a normal woman and is composed largely of dense smooth muscle (see Figs. 2–19 and 2–44). It has a narrowed neck, the cervix, which opens through the anterior vaginal wall and a broad corpus that is capped by the rounded fundus. As discussed earlier, it lies in front of the rectum and over the dome of bladder; its impression can be observed cystoscopically (see Figs. 2–28 and 2–32). The fallopian tubes extend laterally from the junction of the corpus and fundus and are draped by leaves of peritoneum called the *broad ligaments* (see Figs. 2–13 and 2–19). As they extend to the pelvic side walls, the fallopian tubes angle up and backward to open posteromedially.



Figure 2–44. Key anatomic relationships in the female pelvis illustrated on sagittal midline T2-weighted magnetic resonance image. 1, urinary bladder; 2, pubic symphysis; 3, urethra; 4, vagina—note that the vagina is retroflexed posteriorly over the levator plate. The levator plate provides critical female pelvic support; 5, cervix; 6, uterus.

The tubes are divided into four segments—uterine, isthmus, ampulla, and infundibulum—and are crowned by the fimbriae. The ovary rests posterior to the elbow of the tube and is supported by its own peritoneal fold, the mesovarium. The ureter may be found directly posterior to the ovary, covered by pelvic peritoneum. The infundibulopelvic ligament, mentioned earlier,

suspends the ovary and lateral fallopian tube from the pelvic side wall and transmits the ovarian vessels to both structures. The round ligament of the ovary passes medially through the broad ligament to fix the ovary to the lateral wall of the uterus. Beneath its point of attachment, the round ligament of the uterus passes laterally, in the leaves of the broad ligament, to exit through to the inguinal canal and attach to the labial fat pad (see Figs. 2–13 and 2–19).

The uterine artery crosses in front of the ureter and runs in the broad and cardinal ligaments to supply the proximal vagina, uterus, and medial two thirds of the fallopian tube (see Fig. 2–19). It is joined by a rich plexus of uterine veins that freely connect with the ovarian veins. Nerves from the pelvic plexus travel to the female pelvic viscera through the cardinal and uterosacral ligaments in the company of the vessels; therefore hysterectomy can cause a flaccid neurogenic bladder.

The vagina extends inward from the vestibule at a 45-degree angle and then turns horizontal over the levator plate (see Figs. 2–28 and 2–44). It is lined by rugated nonkeratinized squamous epithelium backed by a thick, well-vascularized lamina propria. It is surrounded by a smooth muscle coat of inner circular and stronger external longitudinal layers. In cross section, the vagina is H shaped (see Fig. 2–41) as a result of firm attachments of its anterior wall to the levator ani at the arcus tendineus fascia pelvis, and of its posterior wall to the rectovaginal septum. The anterior vaginal wall is pierced by the cervix proximally. The shallow fossae around the cervix are referred to as the *anterior, lateral,* and posterior fornices. Because the apex of the vagina is covered with the peritoneum of the rectouterine pouch, the peritoneal cavity may be accessed through the posterior fornix (see Fig. 2–28).

Immediately in front of the cervix, the base of the bladder rests on the vaginal wall. Smooth muscle fibers tether the posterior bladder wall and base to the uterine cervix and vagina (see Figs. 2–28 and 2–44). Division of these fibers yields posterior access to the vesicovaginal space. This space extends distally to the proximal third of the urethra (where the urethra and vagina fuse) and is limited to each side by the lateral ligaments of the bladder. It may be accessed transvaginally through incision of the anterior vaginal wall in front of the cervix. Incision of the anterior vaginal wall to either side of the urethra leads into the retropubic space (see Fig. 2–12). The tough leaves of the visceral endopelvic fascia are felt medially and should be included in all transvaginal urethral suspension procedures (Mostwin, 1991).

The vagina is separated from the rectum by the rectovaginal septum (see Fig. 2–28), and rectoceles result from a loss of integrity of this septum. Deep to this septum lies a second potential space, the rectovaginal space. The bowel may herniate into this space to form an enterocele. On its lateral surfaces, the vagina is related to the levator ani. Near the vestibule, fibers of the levator ani blend and fuse with the vaginal muscularis. The vaginal vessels and nerves lie on the anterolateral surface of the vagina deep to the arcus tendineus fascia pelvis.

Female Urethra

On average, the female urethra traverses 4 cm from the bladder neck to the vaginal vestibule (see Fig. 2–44). **Its lining changes gradually from transitional to nonkeratinized stratified squamous epithelium. Many small mucous glands open into the urethra** and can give rise to urethral diverticula. Distally, these glands group together on either side of the urethra (Skene glands) and empty through two small ducts to either side of the external urethral meatus. A thick, richly vascular submucosa supports the urethral epithelium and glands (see Fig. 2–32). Together, the mucosa and submucosa form a cushion that contributes significantly to urethral closure pressure (Raz et al, 1972). These layers are estrogen dependent; at menopause they may atrophy, resulting in stress incontinence. A relatively thick layer of inner longitudinal smooth muscle continues from the bladder to the external meatus to insert into periurethral fatty and fibrous tissue. In contrast to the male proximal urethra, no circular smooth muscle sphincter can be identified. A rather thin layer of circular smooth muscle envelops the longitudinal fibers throughout the length of the urethra. It is thought that the longitudinal smooth muscle of the urethra contracts coordinately with the detrusor during micturition to shorten and widen the urethra (Gosling, 1979).

The striated urethral sphincter invests the distal two thirds of the female urethra (Oelrich, 1983). It is composed exclusively of delicate type I (slow-twitch) fibers surrounded by abundant collagen. Proximally, it forms a complete ring around the urethra that corresponds to the zone of highest urethral closure pressure (see Fig. 2–32). Farther down the urethra, the fibers do not meet posteriorly but continue off the lateral sides of the urethra onto the anterior and lateral wall of the vagina. Contraction of these fibers (the compressor urethrae) closes the urethra against the fixed anterior vaginal wall. Near the vestibule, the fibers completely surround the urethra and vagina to form a urethrovaginal sphincter. Contraction of this muscle group, along with bulbospongiosus, tightens the urogenital hiatus.

The suspensory ligament of the clitoris (anterior urethral ligament) and the pubourethral ligaments (posterior urethral ligaments) form a sling that suspends the urethra beneath the pubis (see Figs. 2–12 and 2–41) (Zacharin, 1963). The striated urethral sphincter receives dual somatic innervation, like that in the male, from the pudendal and pelvic somatic nerves (Borirakchanyavat et al, 1997). Little sympathetic innervation is found in the female urethra. Parasympathetic cholinergic fibers are found throughout the smooth muscle. Somatic and autonomic nerves to the urethra travel on the lateral walls of the vagina near the urethra. During transvaginal incontinence surgery, the anterior vaginal wall should be incised laterally to avoid these nerves and prevent type III urinary incontinence (Ball et al, 1997).

Female Pelvic Support

The pelvic muscles and fasciae cooperate to prevent prolapse of the urogenital organs through the hiatus. **Three functional supportive elements are recognized: (1) the pubovisceral and perineal muscles, which form a sphincter around the urogenital hiatus** (see Fig. 2–32); **(2) the levator plate,** which acts as a horizontal shelf beneath the bladder, uterine cervix, posterior vagina, and rectum (see Fig. 2–28); and **(3) the cardinal and uterosacral ligaments,** which anchor the pelvic viscera over the levator plate (Zacharin, 1985; Mostwin, 1991; DeLancey, 1993). The pelvic muscles contract tonically to counteract gravitational forces. In response to stress, the levator ani contracts, closing the urogenital hiatus and increasing the anteroposterior length of the levator plate. Increased intra-abdominal pressure forces the pelvic viscera downward against a fixed levator plate, closing the vagina like a flap valve.

Pelvic and perineal muscles play the greatest role in pelvic support. Damage to the perineal body during parturition destroys the urogenital sphincter, enlarges the urogenital hiatus,

and erodes the levator plate. Aging and birth trauma partially denervate and weaken the levator ani (Snooks et al, 1985). With loss of muscular support, intra-abdominal forces impinge directly on the pelvic fasciae; over time, these either tear or stretch. Procedures to correct pelvic prolapse or urinary incontinence that rely solely on these fasciae may be successful initially but do not fare well over time (Trockman et al, 1995). Repair of a single pelvic defect—a cystocele for instance—may unmask another (enterocele, rectocele); therefore successful repair of pelvic prolapse must address all components of anatomic support (Zacharin, 1985; DeLancey, 1993).

PERINEUM

The perineum lies among the pubis, thighs, and buttocks and is limited superiorly by the levator ani. Viewed from below, the symphysis pubis, ischial tuberosities, and coccyx outline the diamond shape of the perineum; the inferior ischiopubic rami and sacrotuberous ligaments form its bony and ligamentous walls (Fig. 2–45; see also Figs. 2–29 and 2–46). A line drawn through the ischial tuberosities divides the perineum into an anal and a urogenital triangle.

Anal Triangle

At the apex of the prostate, the rectum turns approximately 90 degrees posteriorly and inferiorly to become the anus (see Figs. 2–10 and 2–14). It traverses 4 cm to reach the skin near the center of the anal triangle. The subcutaneous fat that surrounds the anus is continuous with that of the urogenital triangle, buttocks, and medial thigh. Laterally, the fat fills the ischiorectal fossa, a space bounded by the levator ani medially, and obturator internus, and the sacrotuberous ligament laterally (see Fig. 2–15). Anteriorly, this space extends into a recess above the urogenital diaphragm; posteriorly, it is continuous with the intermediate stratum of the pelvis through the sciatic foramina. Through this continuity, infections may travel between the perineum and the pelvic cavity.

The anal sphincter is divided into internal and external components. **The internal sphincter represents a thickening of the inner circular smooth muscle layer of the rectum.** The outer longitudinal smooth muscle thins beyond the rectourethralis and blends with the external sphincter, although a few fibers insert in the skin around the anus (corrugator cutis ani) to give it a puckered appearance. **The external sphincter surrounds the internal sphincter and is divided into subcutaneous, superficial, and deep portions.** The subcutaneous part attaches to the perineal body by collagenous and muscular fibers that are thickest superficially and referred to as the *central tendon of the perineum*. The superficial sphincter attaches to the perineal body and coccyx. At the posterior inflection of the rectum, the deep sphincter blends with the puborectalis sling of levator ani. At this level, a firm band may be felt on rectal examination and corresponds to the internal and external sphincter. Division of this muscular band results in fecal incontinence. The prostate may be accessed anterior to the sphincter, by dividing the central tendon and sphincteric attachments to the perineum (Young procedure) or by following the anterior rectal wall beneath the external anal sphincter (Belt procedure).

Male Urogenital Triangle

The entire urogenital triangle is bridged by the urogenital diaphragm. The scrotum hangs from the anterior aspect of the urogenital triangle; in the posterior aspect, skin and subcutaneous fat overlie Colles fascia. The perineal membrane and the posterior and lateral attachments of Colles fascia limit a potential space known as the *superficial pouch* (see Figs. 2–4, 2–15, and 2–29). In this space, the three erectile bodies of the penis have their bony and fascial attachments (the root of the penis). The paired corpora cavernosa attach to the inferior ischiopubic rami and perineal membrane and are surrounded by the ischiocavernosus muscles. The corpus spongiosum dilates as the bulb of the penis and is fixed to the center of the perineal membrane. It is encompassed by the bulbospongiosus muscles (see Fig. 2–46) that arise from the perineal body and from a central tendinous raphe and pass around

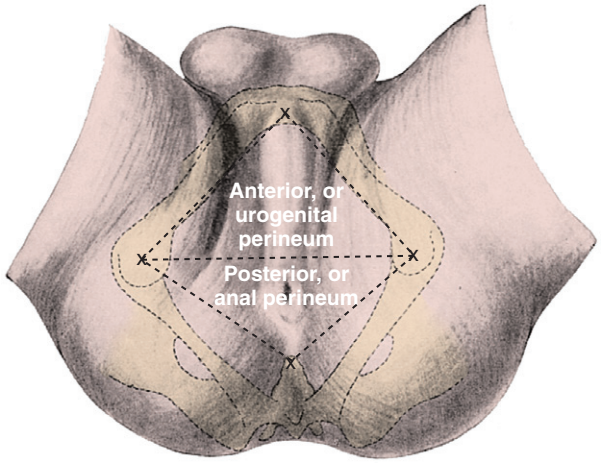


Figure 2–45. Male perineum. (From Anson BJ, McVay CB. Surgical anatomy. 6th ed. Philadelphia: WB Saunders; 1984. p. 893.)

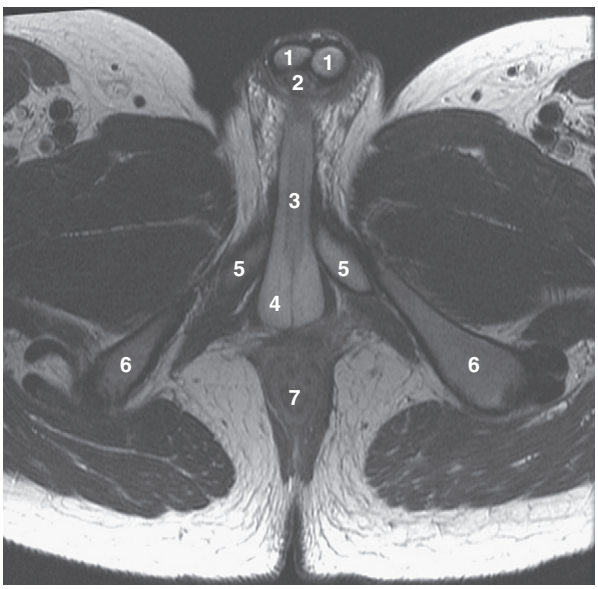


Figure 2–46. Axial T1-weighted magnetic resonance image of male pelvis. 1, corpora cavernosa in cross section; 2, corpus spongiosum in cross section; 3, corpus spongiosum in perineum; 4, bulbospongiosus muscle, which assists urine or seminal fluid expulsion from bulbar urethra; 5, crura of corpora cavernosa—note divergence of crura as they insert on pubic bone; 6, ischial tuberosities; 7, rectum.

the bulb to attach to the perineal membrane and dorsum of the penis. Contraction of the ischiocavernosus and bulbospongiosus muscles compresses the erectile bodies and potentiates penile erection. The transversus perinei muscles (superficial and deep) run along the posterior edge of the perineal membrane and are thought to stabilize the perineal body. Deep to the perineal membrane rests the striated urethral sphincter (discussed earlier).

Blood supply to the anal and urogenital triangles is derived largely from the internal pudendal vessels (Fig. 2–47). After entering the perineum through the lesser sciatic foramen, the artery runs in a fascial sheath on the medial aspect of obturator internus, the pudendal canal (of Alcock). Early in its course, it gives off three or four inferior rectal branches to the anus. Its perineal branch pierces Colles fascia to supply the muscles of the superficial pouch and continues anteriorly to supply the back of the scrotum. The internal pudendal terminates as the common penile artery (to be discussed).

The internal pudendal veins communicate freely with the dorsal vein complex by piercing the levator ani. These communicating vessels enter the pelvic venous plexus on the lateral surface of the prostate and are a common, often unexpected, source of bleeding during apical dissection of the prostate. The inferior rectal veins anastomose with the middle and superior rectal veins and produce an important connection between the portal and systemic circulation. Obstruction of the portal or systemic venous system may cause shunting of collateral venous drainage through the portal system, manifested by hemorrhoids.

The pudendal nerve follows the vessels in their course through the perineum (see Fig. 2–47). Its first branch, the dorsal nerve of the penis, travels ventral to the main pudendal trunk in Alcock canal. Several inferior rectal branches supply the external sphincter muscle and provide sensation to perianal skin. The perineal branches follow the perineal artery into the superficial pouch to supply the ischiocavernosus, bulbospongiosus, and transversus perinei muscles. A few of these branches continue anteriorly to supply sensation to the posterior scrotum. Additional perineal branches pass deep to the perineal membrane to supply the levator ani and striated urethral sphincter.

Penis

As discussed, the root of the penis is fixed to the perineum within the superficial pouch. **The corpora cavernosa join beneath the pubis (penile hilum) to form the major portion of the body of the penis.** They are separated by a septum that becomes pectiniform distally, so their vascular spaces freely communicate. They are enclosed by the tough tunica albuginea, which is predominantly collagenous (Fig. 2–48). Its outer longitudinal and inner circular fibers form an undulating meshwork when the penis is flaccid and appear tightly stretched with erection (Goldstein et al, 1982). Smooth muscle bundles traverse the erectile bodies to form the endothelium-lined cavernous sinuses. These sinuses give the erectile tissue a spongy appearance on gross examination.

Distal to the bulb, the corpus spongiosum tapers and runs on the underside (ventrum) of the corpora cavernosa (see Fig. 2–46) and then expands to cap them as the glans penis. The corona separates the base of the glans from the shaft of the penis. The

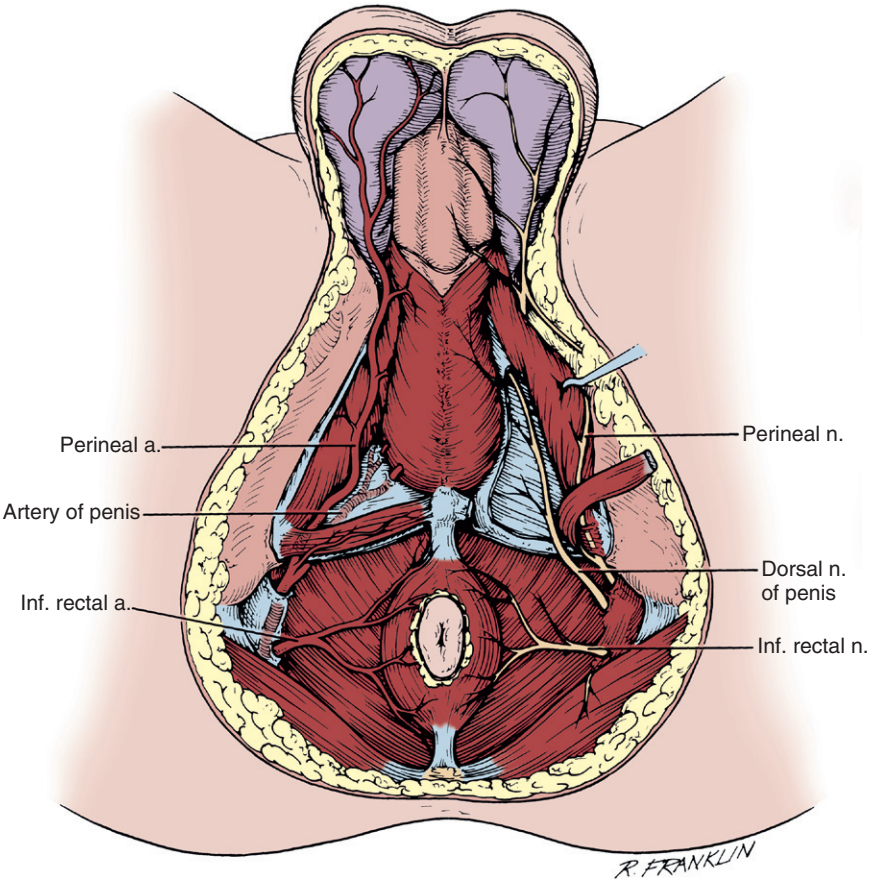


Figure 2–47. Male perineum, illustrating the internal pudendal artery and its branches on the left and the pudendal nerve and its branches on the right.

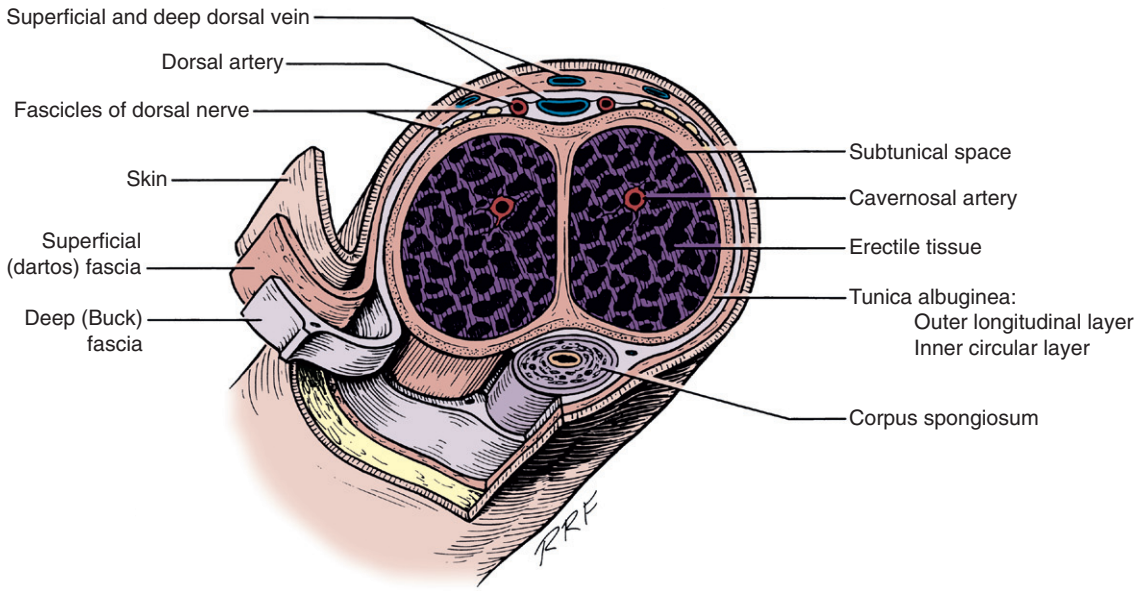


Figure 2–48. Cross section of the penis, demonstrating the relationship between the corporal bodies, penile fascia, vessels, and nerves. (From Devine Jr CJ, Angermeier KW. Anatomy of the penis and mate perineum. AUA Update Series 1994;13:10–23.)

spongiosum is traversed throughout its length by the anterior urethra, which begins at the perineal membrane (see Figs. 2–35 and 2–37). The anterior urethra is dilated in its bulbar and glanular segments (fossa navicularis) and narrowest at the external meatus. Proximally, it is lined by stratified and pseudostratified columnar epithelium, distally by stratified squamous epithelium. The mucus-secreting glands (of Littre) may be seen as small outpouchings of the mucosa.

Buck fascia surrounds both cavernosal bodies dorsally and splits to surround the spongiosum ventrally (see Fig. 2–48). Elastic and collagenous fibers from the rectus sheath blend with and surround Buck fascia as the fundiform ligament of the penis. Deeper fibers from the pubis form the suspensory ligament of the penis. In the perineum, Buck fascia fuses with the tunica albuginea deep to the muscles of the erectile bodies (Uhlenhuth et al, 1949). Distally, it fuses with the base of the glans at the corona. Bleeding from a tear in the corporal bodies (e.g., penile fracture) is usually contained within Buck fascia, and ecchymosis is limited to the penile shaft.

The skin of the penile shaft is highly elastic and without appendages (hair or glandular elements), except for the smegma-producing glands at the base of the corona. It is devoid of fat and quite mobile because of the loose attachment of its dartos backing to Buck fascia. Distally, it folds over the glans as the foreskin and attaches firmly below the corona. Its blood supply is independent of the erectile bodies and is derived from the external pudendal branches of the femoral vessels (see Fig. 2–5). These vessels enter the base of the penis to run longitudinally in the dartos fascia as a richly anastomotic network. Thus penile skin may be mobilized on a vascular pedicle as the ideal tissue for urethral reconstruction. The skin of the glans is immobile as a result of its direct attachment to the underlying, thin tunica albuginea.

The common penile artery continues in Alcock canal, above the perineal membrane, and terminates in three branches to supply the erectile bodies (Fig. 2–49). The bulbourethral artery penetrates the perineal membrane to enter the spongiosum from above at its posterolateral border. This large, short artery can be difficult to isolate and control during urethrectomy. It supplies the urethra, spongiosum, and glans. The cavernosal artery pierces the corporal body in the penile hilum to near the center of its erectile tissue. It gives off straight and helicine arteries that ramify to supply the cavernous sinuses. The dorsal artery of the penis passes between the crus penis and the pubis to reach the dorsal surface of the corporal bodies. It runs between the dorsal vein and the dorsal penile nerve and with them attaches to the underside of Buck fascia (see Fig. 2–26). As it courses to the glans, it gives off cavernous branches and circumferential branches to the spongiosum and urethra. The rich blood supply to the spongiosum allows safe division of the urethra during stricture repair (Devine and Angermeier, 1994).

The surgeon contemplating penile revascularization must be aware **that the penile arteries are highly variable in their branching, courses, and anastomoses** (Bare et al, 1994). It is not uncommon for a single cavernosal artery to supply both corporal bodies or to be absent altogether. Alternatively, an accessory pudendal artery may supplement or completely replace branches of the common penile artery. This artery usually arises from the obturator or inferior vesical arteries and runs anterolateral to or within the prostate to reach the penis in the company of the dorsal vein. This artery has been identified in 7 of 10 cadaveric specimens (Breza et al, 1989) and noted at 4% of radical prostatectomies (Polascik and Walsh, 1995); its resection at prostatectomy may adversely affect postoperative potency (Droupy et al, 1999).

At the base of the glans, several venous channels coalesce to form the dorsal vein of the penis, which runs in a groove between the corporal bodies and drains into the preprostatic plexus (see Fig. 2–26). The circumflex veins originate in the spongiosum and pass around the cavernosa to meet the deep dorsal vein perpendicularly. They are present only in the distal two thirds of the penile shaft and number 3 to 10. Intermediary venules form from the cavernous sinuses to drain into a subtunical capillary plexus. These plexuses give rise to emissary veins, which commonly follow an oblique path between the layers of the tunica and drain into the circumflex veins

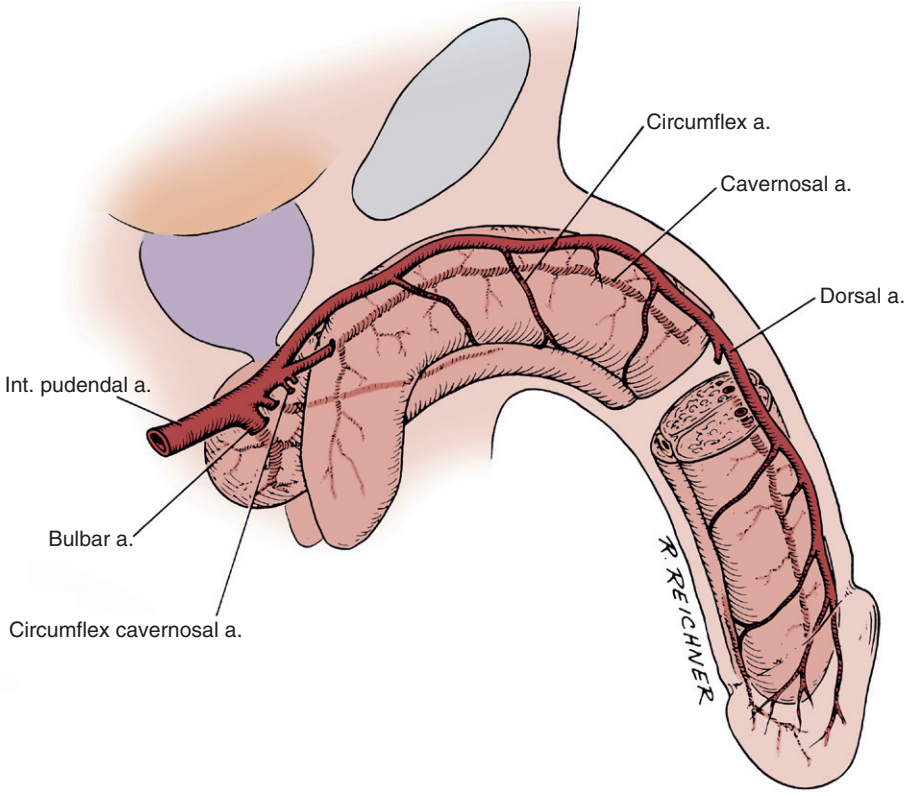


Figure 2–49. Arterial supply of the penis.

dorsolaterally. Emissary veins in the proximal third of the penis join on the dorsomedial surface of the cavernous bodies to form two to five cavernous veins. At the hilum of the penis, these vessels pass between the crura and the bulb, receiving branches from each, and join the internal pudendal veins. Valves are found in the emissary, cavernosal, and deep dorsal veins and may thwart attempts to revascularize the penis by arteriovenous anastomosis (Sohn, 1994).

The dorsal nerves provide sensory innervation to the penis. These nerves follow the course of the dorsal arteries and richly supply the glans (see Fig. 2–26). Small branches from the perineal nerve supply the ventrum of the penis near the urethra as far as the glans distally (Uchio et al, 1999). These nerves must be anesthetized when performing a penile block to numb the ventrum of the penis. The route of the cavernous nerves has been described. After piercing the corporal bodies, they ramify in the erectile tissue to supply sympathetic and parasympathetic innervation from the pelvic plexus. Tonic sympathetic tone inhibits erection. Parasympathetic nerves release acetylcholine, nitric oxide, and vasoactive intestinal polypeptide, which cause the cavernosal smooth muscle and arterial relaxation necessary for erection (Burnett, 1995). It is thought that during erection, the subtunical venules are occluded by being compressed against the nondistensible tunica albuginea. Insufficient venous occlusion, particularly in vessels draining into the deep dorsal and cavernosal veins, is thought to cause vasculogenic impotence.

Scrotum

The scrotal skin is pigmented, hair bearing, devoid of fat, and rich in sebaceous and sweat glands. It varies from loose and shiny to highly folded with transverse rugae, depending on the tone of the dartos smooth muscle. A midline raphe runs from the urethral meatus to the anus and represents the line of fusion of the genital tubercles. Deep to this raphe, the scrotum is separated into two compartments by a septum.

The dartos layer of smooth muscle is continuous with Colles, Scarpa, and the dartos fascia of the penis (see Figs. 2–4 and 2–29). The testes are suspended by their cords in the scrotal compartments. As the testes descend, they acquire coverings from the layers of the abdominal wall, known as the ***spermatic fascia,*** that form part of the scrotal wall (Fig. 2–50). The external spermatic fascia derives from the external oblique fascia and remains firmly attached to the borders of the external ring. The cremasteric muscle and fascia arise from the internal oblique muscle and attach laterally to the inguinal ligament and iliopsoas fascia and medially to the pubic tubercle. The internal spermatic fascia is a continuation of the transversalis fascia. The parietal and visceral tunica vaginalis surround the testis with a mesothelium-lined pouch and are derived from the peritoneum. They are continuous at the posterolateral border of the testis at its mesentery, where it is fixed to the scrotal wall. The testis is also fixed at its lower pole by the gubernaculum. Occasionally, the mesentery and gubernaculum may be deficient, leaving the testis unfixed (bell-clapper deformity) and predisposing to torsion of the cord.

The anterior wall of the scrotum is supplied by the external pudendal vessels and the ilioinguinal and genitofemoral nerves (see Fig. 2–5). The anterior vessels and nerves typically run parallel to the rugae and do not cross the raphe; thus transverse or midline raphe scrotal incisions are most hemostatic. The back of the scrotum is supplied by the posterior scrotal branches of the perineal vessels and nerves (see Fig. 2–47). In addition, the posterior femoral cutaneous nerve (S3) gives a perineal branch to supply the scrotum and perineum (see Fig. 2–8). In accordance with their origin, the spermatic fasciae have a blood

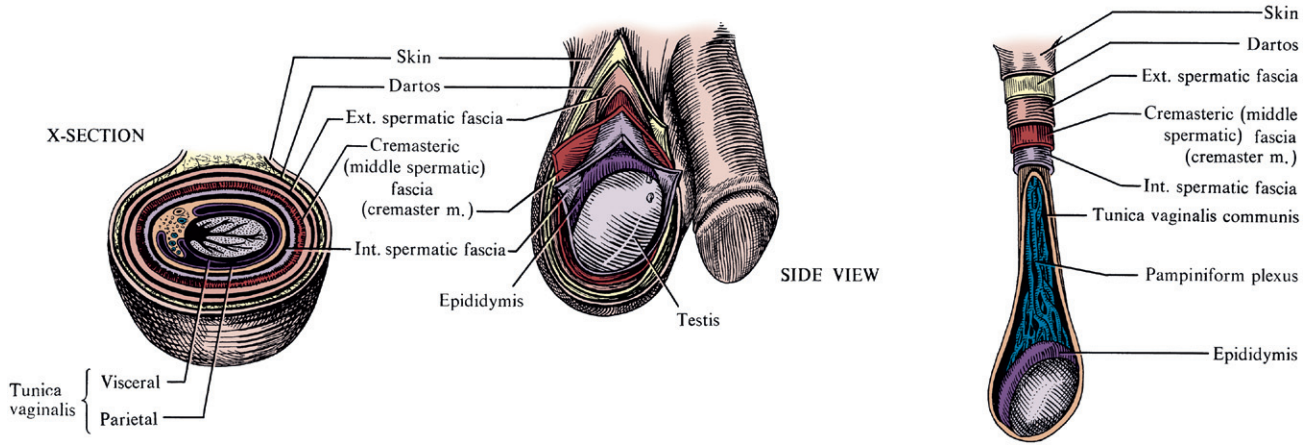


Figure 2–50. Scrotum and its layers. (From Pansky B. Review of gross anatomy. 6th ed. New York: McGraw-Hill; 1987. p. 483.)

supply (cremasteric, vasal, testicular) separate from that of the scrotal wall. Fournier gangrene usually does not involve these structures, and they may be spared during débridement.

Perineal Lymphatics

The penis, scrotum, and perineum drain into the inguinal lymph nodes. These nodes may be divided into superficial and deep groups, which are separated by the deep fascia of the thigh (fascia lata). In relation to the external pudendal, superficial inferior epigastric, and superficial circumflex iliac vessels, the superficial nodes lie at the saphenofemoral junction. At the saphenous opening (fossa ovalis) in the fascia lata, the greater saphenous vein joins the femoral vein and the superficial nodes communicate with the deep group. Most of the deep inguinal nodes lie medial to the femoral vein and send their efferents through the femoral ring (beneath the inguinal ligament) to the external iliac and obturator nodes. Just outside the femoral ring, a large node (Cloquet or Rosenmuller node) is consistently present.

The scrotal lymphatics do not cross the median raphe and drain into the ipsilateral superficial inguinal lymph nodes. Lymphatics from the shaft of the penis converge on the dorsum and then ramify to both sides of the groin. Those of the glans pass deep to Buck fascia dorsally and drain to superficial and deep groups in both sides of the groin. Direct lymphatic channels from the glans to the pelvic nodes, which bypass the inguinal nodes, have been proposed by anatomists; however, clinical studies have not confirmed their existence. Other studies have suggested that all penile lymphatic drainage passes through "sentinel nodes," which lie medial to the superficial inferior epigastric veins. Clinical studies have also called this speculation into question (Catalona, 1988). The perineal skin and fasciae drain into superficial inguinal nodes; the structures of the superficial pouch likely drain into the superficial and deep inguinal node groups.

Testes

The testes are 4 to 5 cm long, 3 cm wide, and 2.5 cm deep and have a volume of 30 mL. They are enclosed in a tough capsule comprising (1) the visceral tunica vaginalis; (2) tunica albuginea, with collagenous and smooth muscle elements; and (3) the tunica vasculosa. The epididymis attaches to the posterolateral aspect of the testis. Beneath it, the tunica albuginea projects inward to form

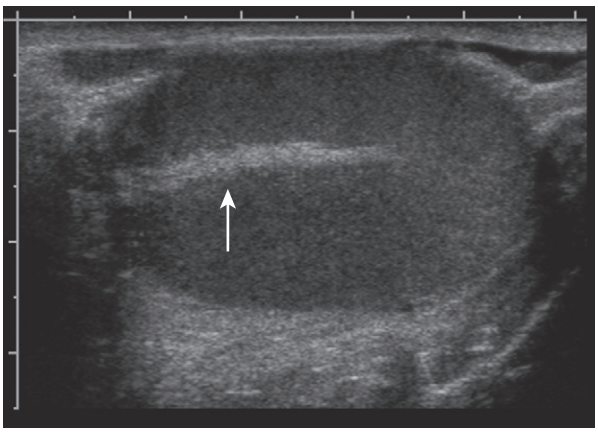


Figure 2–51. Testis ultrasound demonstrating rete testis *(arrow)*.

the mediastinum testis, the point at which vessels and ducts traverse the testicular capsule (see Fig. 2–42). Septa radiate from the mediastinum to attach to the inner surface of the tunica albuginea to form 200 to 300 cone-shaped lobules, each of which contains one or more convoluted seminiferous tubules. Each tubule is U shaped and has a stretched length of nearly 1 meter. Interstitial (Leydig) cells lie in the loose tissue surrounding the tubules and are responsible for testosterone production. Toward the apices of the lobules, the seminiferous tubules become straight (tubuli recti) and enter the mediastinum testis to form an anastomosing network of tubules lined by flattened epithelium. This network, known as the *rete testis* (Fig. 2–51), forms 12 to 20 efferent ductules and passes into the largest portion of the epididymis, the caput. Here, the efferent ductules enlarge, become more convoluted, and form conical lobules. The duct from each lobule drains into a single epididymal duct, which winds approximately 6 m within the fibrous sheath of the epididymis to form its body and tail. As the duct approaches the tail, it thickens and straightens to become the vas deferens.

The spermatic cord is composed of the vas deferens, testicular vessels, and spermatic fasciae. As discussed in Chapter 1, the testicular arteries arise from the aorta and travel in the intermediate stratum of the retroperitoneum to reach the internal inguinal ring. **Lateral to the internal inguinal ring, the attachments of**

the intermediate stratum form the lateral spermatic fascia. These attachments can be taken down at orchidopexy to gain cord length. At the internal ring, the vessels are joined by the genital branch of the genitofemoral nerve, ilioinguinal nerve, cremasteric artery, and vas deferens and its artery.

In its course to the testis, the testicular artery branches into an internal artery and an inferior testicular artery and into a capital artery to the head of the epididymis (see Fig. 2–18). The level of this branching varies and has been noted to occur within the inguinal canal in 31% to 88% of cases (Beck et al, 1992; Jarow et al, 1992). When performing an inguinal varicocelectomy, the surgeon must remember that there may be two or three arterial branches at this level (Hopps et al, 2003). A rich arterial anastomosis occurs at the head of the epididymis, between the testicular and the capital arteries, and at the tail between the testicular, epididymal, cremasteric, and vasal arteries (see Fig. 2–18). The testicular arteries enter the mediastinum and ramify in the tunica vasculosa, principally in the anterior, medial, and lateral portions of the lower pole and the anterior segment of the upper pole (Fig. 2–52 on the Expert Consult website and Fig. 2–53). Thus placement of a traction suture through the lower pole tunica albuginea risks damaging these important superficial vessels and devascularizing the testis (Jarow, 1991). Testicular biopsy should be carried out in the medial or lateral surface of the upper pole, where the risk of vascular injury is minimal.

The testicular veins form several highly anastomotic channels that surround the testicular artery as the pampiniform plexus. This arrangement allows countercurrent heat exchange, which cools the blood in the testicular artery. At the level of the inguinal canal, the veins join to form two or three channels and then a single vein that drains into the inferior vena cava on the right and the renal vein on the left. The testicular veins may anastomose with the external pudendal, cremasteric, and vasal veins (Fig. 2–54). These connections can allow varicoceles to recur after ablative procedures. Testicular lymphatic vessels drain to the para-aortic and interaortocaval nodes as detailed in Chapter 1.

Visceral innervation to the testis and epididymis travels by two routes. A portion arises in the renal and aortic plexuses and travels with the gonadal vessels. Additional gonadal afferent and efferent nerves course from the pelvic plexus in association with the vas deferens (Rauchenwald et al, 1995). Intractable orchialgia may respond to anesthesia of the pelvic plexus (Zorn et al, 1994). Intriguingly, some afferent and efferent nerves cross over to the contralateral pelvic plexus (Taguchi et al, 1999). This neural cross-communication might explain how pathologic processes in one testis (e.g., tumor or varicocele) may affect the function of the contralateral testis. The genital branch of the genitofemoral nerve supplies sensation to the parietal and visceral tunica vaginalis and the overlying scrotum.

Female Urogenital Triangle

The vestibule of the vagina runs vertically throughout the length of the urogenital triangle. The labia majora form its lateral sides and fuse anteriorly as the hood of the clitoris. The subcutaneous fat pad of the mons pubis continues posteriorly in the labia majora to frame the vestibule. The labial fat pads receive blood supply from the external pudendal vessels and may be raised on these vessels as a rotational flap for repair of vesicovaginal or urethrovaginal fistulas (Fig. 2–55). The urethra enters the vestibule between the clitoris and the vagina.

The structure of the superficial pouch is similar to that of the male (Fig. 2–56). The crura of the clitoris attach to the inferior ischiopubic rami, surrounded by the ischiocavernosus muscles, and converge to form the body of the clitoris. The vestibular bulbs lie to either side of the vaginal vestibule, covered by the bulbospongiosus muscles. As homologues of the penile bulb, they are composed of erectile tissue and meet anteriorly to form the glans of the clitoris. The vestibular glands are deep to the vestibular bulbs but, unlike the bulbourethral glands in the male, are superficial to the perineal membrane. Their ducts travel 2 cm to open in the vaginal vestibule on the posteromedial sides of the labia minora. The perineal membrane, pierced in its center by the vagina, is less well developed than that of the male. The innervation, blood supply, and lymphatic drainage of the external genitalia and superficial pouch are similar to those described in the male.

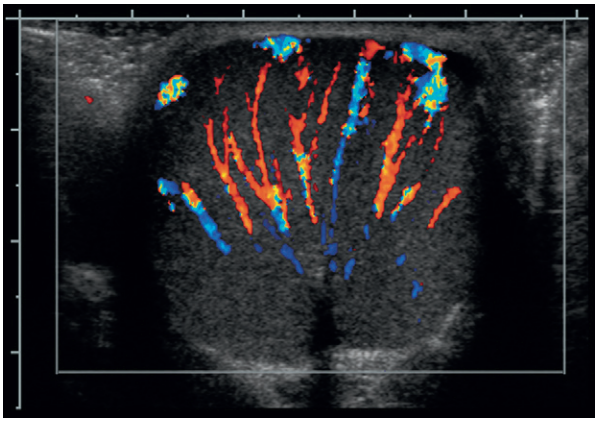


Figure 2–53. Doppler ultrasound of testis demonstrating spokelike radiation of testicular vessels originating from the mediastinum testis.

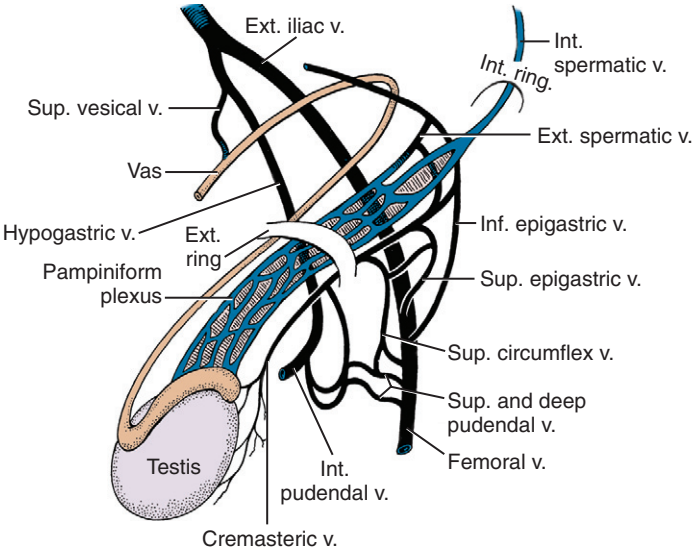


Figure 2–54. Venous drainage of the testis and epididymis. Note connections between the pampiniform plexus and the saphenous, internal iliac, and external iliac veins.

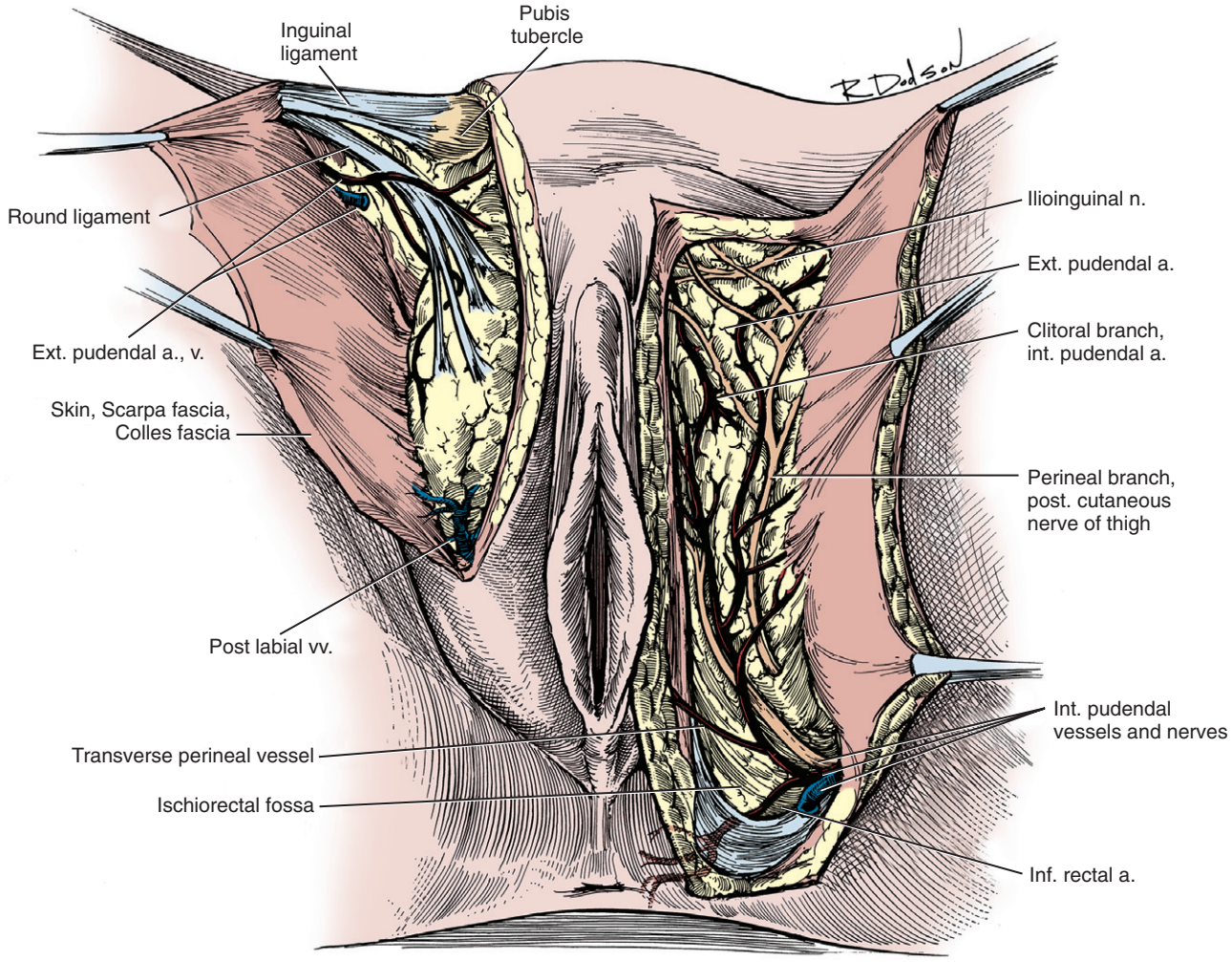


Figure 2–55. Arteries and nerves of the female perineum. (From Doherty MG. Clinical anatomy of the pelvis. In: Copeland LJ, editor. Textbook of gynecology. Philadelphia: WB Saunders; 1993. p. 51.)

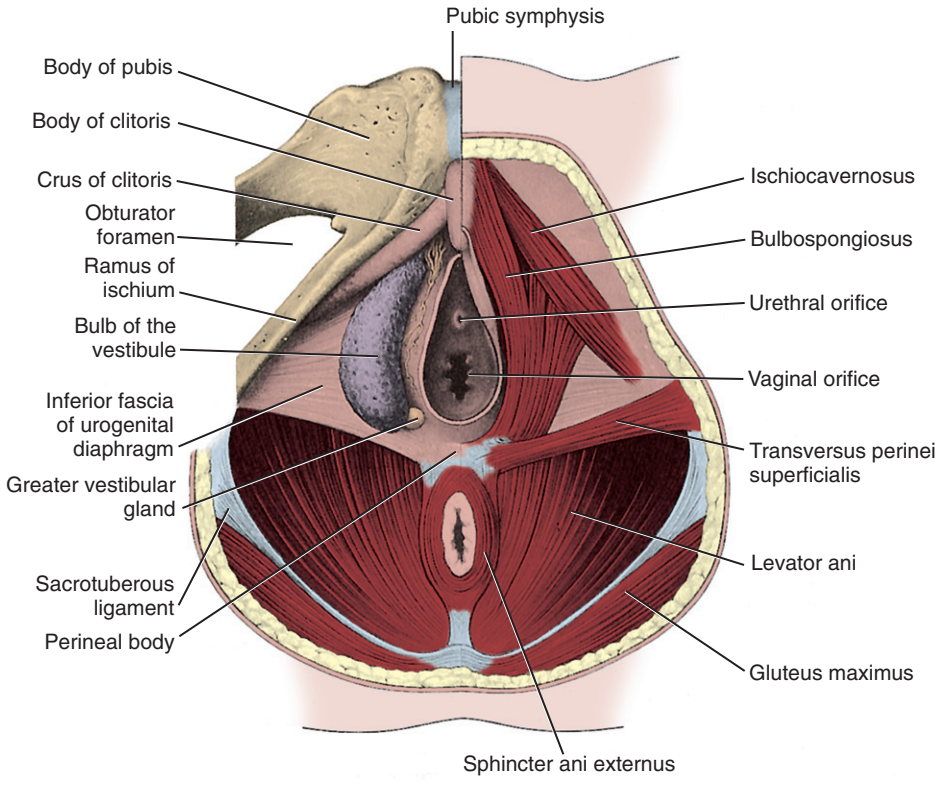


Figure 2–56. Female superficial perineal pouch. On the left side, the muscles have been removed to show the vestibular bulb and Bartholin gland. (From Williams PL, Warwick R. Gray's anatomy. 35th British ed. Philadelphia: WB Saunders; 1973. p. 1364.)

Key Points

- The pelvic cavity is divided into the false pelvis superiorly, and the true pelvis, inferiorly, wherein lie all of the pelvic organs.
- The bony prominences and ligaments of the pelvis and lower abdomen will orient the surgeon during physical examination and in the operating room.
- The pelvic floor is closed off by the levator ani and urogenital diaphragm and the muscles and fasciae of the pelvic floor provide critical support for the pelvic organs.
- The rectum, bladder, prostate, seminal vesicles, uterus, vagina, penis, and clitoris receive blood supply from the anterior trunk of the internal iliac artery and innervation from the pelvic autonomic plexus.
- The urethra, vagina, and anus exit through the perineum in association with the external genitalia.
- Detailed knowledge of the relationships of the pelvic organs to each other and the bones and muscles of the pelvis, as well as the locations of the blood supply and innervation of all pelvic and perineal structures, is critical for safely performing all pelvic operations.

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The complete reference list is available online at www.expertconsult.com.

chapter 3

Evaluation of the Urologic Patient: History, Physical Examination, and Urinalysis

Glenn S. Gerber, MD ● Charles B. Brendler, MD

History
Physical Examination
Urinalysis
Summary

Urologists have a unique position in medicine because their patients encompass all age groups including prenatal, pediatric, adolescent, adult, and geriatric. Because there is no medical subspecialist with similar interests, **the urologist has the ability to make the initial evaluation and diagnosis and to provide medical and surgical therapy for all diseases of the genitourinary (GU) system.** Historically, the diagnostic armamentarium included urinalysis, endoscopy, and intravenous pyelography. Recent advances in ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and endourology have expanded our diagnostic capabilities. Despite these advances, however, the basic approach to the patient is still dependent on taking a complete history, executing a thorough physical examination, and performing a urinalysis. These basics dictate and guide the subsequent diagnostic evaluation.

HISTORY

Overview

The medical history is the cornerstone of the evaluation of the urologic patient, and a well-taken history will frequently elucidate the probable diagnosis. However, many pitfalls can inhibit the urologist from obtaining an accurate history. The patient may be unable to describe or communicate symptoms because of anxiety, language barrier, or educational background. Therefore the urologist must be a detective and lead the patient through detailed and appropriate questioning to obtain accurate information. There are practical considerations in the art of history taking that can help to alleviate some of these difficulties. In the initial meeting, an attempt should be made to help the patient feel comfortable. During this time, the physician should project a calm, caring, and competent image that can help foster two-way communication. Impaired hearing, mental capacity, and facility with English can be assessed promptly. These difficulties are frequently overcome by having a family member present during the interview or, alternatively, by having an interpreter present.

Patients need to have sufficient time to express their problems and the reasons for seeking urologic care; the physician, however, should focus the discussion to make it as productive and informative as possible. Direct questioning can then proceed logically. The physician needs to listen carefully without distractions to obtain and interpret the clinical information provided by the patient. **A complete history can be divided into the chief complaint and history of the present illness, the patient's past medical history, and a family history.** Each segment can provide significant positive and negative findings that will contribute to the overall evaluation and treatment of the patient.

Chief Complaint and Present Illness

Most urologic patients identify their symptoms as arising from the urinary tract and frequently present to the urologist for the initial evaluation. For this reason, the urologist frequently has the opportunity to act as both the primary physician and the specialist. The chief complaint must be clearly defined because it provides the initial information and clues to begin formulating the differential diagnosis. Most importantly, **the chief complaint is a constant reminder to the urologist as to why the patient initially sought care.** This issue must be addressed even if subsequent evaluation reveals a more serious or significant condition that requires more urgent attention. In our personal experience, a young woman presented with a chief complaint of recurrent urinary tract infections (UTIs). In the course of her evaluation, she was found to have a right adrenal mass. We subsequently focused on this problem and performed a right adrenalectomy for a benign cortical adenoma. We forgot about the woman's original symptoms until she presented for her subsequent postoperative examination. She reminded us of her original symptoms at that time, and subsequent evaluation revealed that she had a nylon suture that had eroded into the anterior wall of her bladder from a previous abdominal vesicourethropexy performed 2 years earlier for stress urinary incontinence. Her UTIs resolved after surgical removal of the suture.

In obtaining the history of the present illness, **the duration, severity, chronicity, periodicity, and degree of disability are important considerations.** The patient's symptoms need to be clarified for details and quantified for severity. Listed next are a variety of typical initial complaints. Specific questions that focus the differential diagnosis are provided.

Pain

Pain arising from the GU tract may be quite severe and is usually associated with either urinary tract obstruction or inflammation. Urinary calculi cause severe pain when they obstruct the upper urinary tract. Conversely, large, nonobstructing stones may be totally asymptomatic. Thus a 2-mm-diameter stone lodged at the ureterovesical junction may cause excruciating pain, whereas a large staghorn calculus in the renal pelvis or a bladder stone may be totally asymptomatic. Urinary retention from prostatic obstruction is also quite painful, but the diagnosis is usually obvious to the patient.

Inflammation of the GU tract is most severe when it involves the parenchyma of a GU organ. This is due to edema and distention of the capsule surrounding the organ. Thus pyelonephritis, prostatitis, and epididymitis are typically quite painful. Inflammation of the mucosa of a hollow viscus such as the bladder or urethra usually produces discomfort, but the pain is not nearly as severe.

Tumors in the GU tract usually do not cause pain unless they produce obstruction or extend beyond the primary organ to involve adjacent nerves. Thus pain associated with GU malignancies is usually a late manifestation and a sign of advanced disease.

Renal Pain. Pain of renal origin is usually located in the ipsilateral costovertebral angle just lateral to the sacrospinalis muscle and beneath the 12th rib. **Pain is usually caused by acute distention of the renal capsule, generally from inflammation or obstruction.** The pain may radiate across the flank anteriorly toward the upper abdomen and umbilicus and may be referred to the testis or labium. A corollary to this observation is that renal or retroperitoneal disease should be considered in the differential diagnosis of any man who complains of testicular discomfort but has a normal scrotal examination. Pain due to inflammation is usually steady, whereas pain due to obstruction fluctuates in intensity. Thus the pain produced by ureteral obstruction is typically colicky in nature and intensifies with ureteral peristalsis, at which time the pressure in the renal pelvis rises as the ureter contracts in an attempt to force urine past the point of obstruction.

Pain of renal origin may be associated with gastrointestinal symptoms because of reflex stimulation of the celiac ganglion and because of the proximity of adjacent organs (liver, pancreas, duodenum, gallbladder, and colon). Thus renal pain may be confused with pain of intraperitoneal origin; it can usually be distinguished, however, by a careful history and physical examination. Pain that is due to a perforated duodenal ulcer or pancreatitis may radiate into the back, but the site of greatest pain and tenderness is in the epigastrium. Pain of intraperitoneal origin is seldom colicky, as with obstructive renal pain. Furthermore, pain of intraperitoneal origin frequently radiates into the shoulder because of irritation of the diaphragm and phrenic nerve; this does not occur with renal pain. Typically, patients with intraperitoneal pathology prefer to lie motionless to minimize pain, whereas patients with renal pain usually are more comfortable moving around and holding the flank.

Renal pain may also be confused with pain resulting from irritation of the costal nerves, most commonly T10-T12. Such pain has a similar distribution from the costovertebral angle across the flank toward the umbilicus. However, the pain is not colicky in nature. Furthermore, the intensity of radicular pain may be altered by changing position; this is not the case with renal pain.

Ureteral Pain. **Ureteral pain is usually acute and secondary to obstruction.** The pain results from acute distention of the ureter and by hyperperistalsis and spasm of the smooth muscle of the ureter as it attempts to relieve the obstruction, usually produced by a stone or blood clot. The site of ureteral obstruction can often be determined by the location of the referred pain. With obstruction of the midureter, pain on the right side is referred to the right lower quadrant of the abdomen (McBurney point) and thus may simulate appendicitis; pain on the left side is referred over the left lower quadrant and resembles diverticulitis. Also, the pain may be referred to the scrotum in the male or the labium in the female. Lower ureteral obstruction frequently produces symptoms of vesical irritability including frequency, urgency, and suprapubic discomfort that may radiate along the urethra in men to the tip of the penis. Often, by taking a careful history, the astute clinician can predict the location of the obstruction. Ureteral pathology that arises slowly or produces only mild obstruction rarely causes pain. Therefore ureteral tumors and stones that cause minimal obstruction are seldom painful.

Vesical Pain. Vesical pain is usually produced either by overdistention of the bladder as a result of acute urinary retention or by inflammation. **Constant suprapubic pain that is unrelated to urinary retention is seldom of urologic origin.** Furthermore, patients with slowly progressive urinary obstruction and bladder distention (e.g., diabetics with a flaccid neurogenic bladder) frequently have no pain at all despite residual urine volumes over 1L.

Inflammatory conditions of the bladder usually produce intermittent suprapubic discomfort. Thus the pain in conditions such as bacterial cystitis or interstitial cystitis is usually most severe when the bladder is full and is relieved at least partially by voiding. Patients with cystitis sometimes experience sharp, stabbing suprapubic pain at the end of micturition, and this is termed *strangury*. Furthermore, patients with cystitis frequently experience pain referred to the distal urethra that is associated with irritative voiding symptoms such as urinary frequency and dysuria.

Prostatic Pain. **Prostatic pain is usually secondary to inflammation with secondary edema and distention of the prostatic capsule.** Pain of prostatic origin is poorly localized, and the patient may complain of lower abdominal, inguinal, perineal, lumbosacral, penile, and/or rectal pain. Prostatic pain is frequently associated with irritative urinary symptoms such as frequency and dysuria, and, in severe cases, marked prostatic edema may produce acute urinary retention.

Penile Pain. **Pain in the flaccid penis is usually secondary to inflammation in the bladder or urethra, with referred pain that is experienced maximally at the urethral meatus.** Alternatively, penile pain may be produced by *paraphimosis,* a condition in which the uncircumcised penile foreskin is trapped behind the glans penis, resulting in venous obstruction and painful engorgement of the glans penis (see later). Pain in the erect penis is usually due to Peyronie disease or priapism (see later).

Testicular Pain. Scrotal pain may be either primary or referred. **Primary pain arises from within the scrotum and is usually secondary to acute epididymitis or torsion of the testis or testicular appendices.** Because of the edema and pain associated with both acute epididymitis and testicular torsion, it is frequently difficult to distinguish these two conditions. Alternatively, scrotal pain may result from inflammation of the scrotal wall itself. This may result from a simple infected hair follicle or sebaceous cyst, but it may also be secondary to Fournier gangrene,

a severe, necrotizing infection arising in the scrotum that can rapidly progress and be fatal unless promptly recognized and treated.

Chronic scrotal pain is usually related to noninflammatory conditions such as a hydrocele or a varicocele, and the pain is generally characterized as a dull, heavy sensation that does not radiate. Because the testes arise embryologically in close proximity to the kidneys, pain arising in the kidneys or retroperitoneum may be referred to the testes. Similarly, the dull pain associated with an inguinal hernia may be referred to the scrotum.

Hematuria

Hematuria is the presence of blood in the urine; **greater than three red blood cells per high-power microscopic field (HPF) is significant.** Patients with gross hematuria are usually frightened by the sudden onset of blood in the urine and frequently present to the emergency department for evaluation, fearing that they may be bleeding excessively. Hematuria of any degree should never be ignored and, in adults, should be regarded as a symptom of urologic malignancy until proved otherwise. In evaluating hematuria, several questions should always be asked, and the answers will enable the urologist to target the subsequent diagnostic evaluation efficiently:

Is the hematuria gross or microscopic?
At what time during urination does the hematuria occur (beginning or end of stream or during entire stream)?
Is the hematuria associated with pain?
Is the patient passing clots?
If the patient is passing clots, do the clots have a specific shape?

Gross versus Microscopic Hematuria. The significance of gross versus microscopic hematuria is simply that **the chances of identifying significant pathology increase with the degree of hematuria.** Thus patients with gross hematuria usually have identifiable underlying pathology, whereas it is quite common for patients with minimal degrees of microscopic hematuria to have a negative urologic evaluation.

Timing of Hematuria. The timing of hematuria during urination frequently indicates the site of origin. **Initial hematuria usually arises from the urethra;** it occurs least commonly and is usually secondary to inflammation. Total hematuria is most common and indicates that the bleeding is most likely coming from the bladder or upper urinary tracts. Terminal hematuria occurs at the end of micturition and is usually secondary to inflammation in the area of the bladder neck or prostatic urethra. It occurs at the end of micturition as the bladder neck contracts, squeezing out the last amount of urine.

Association with Pain. Hematuria, although frightening, is usually not painful unless it is associated with inflammation or obstruction. Thus patients with cystitis and secondary hematuria may experience painful urinary irritative symptoms, but the pain is usually not worsened with passage of clots. More commonly, **pain in association with hematuria usually results from upper urinary tract hematuria with obstruction of the ureters with clots.** Passage of these clots may be associated with severe, colicky flank pain similar to that produced by a ureteral calculus, and this helps identify the source of the hematuria.

Presence of Clots. The presence of clots usually indicates a more significant degree of hematuria, and, accordingly, the probability of identifying significant urologic pathology increases.

Shape of Clots. Usually, if the patient is passing clots, they are amorphous and of bladder or prostatic urethral origin. However, **the presence of vermiform (wormlike) clots, particularly if associated with flank pain, identifies the hematuria as coming from the upper urinary tract** with formation of vermiform clots within the ureter.

It cannot be emphasized strongly enough that **hematuria, particularly in the adult, should be regarded as a symptom of malignancy until proved otherwise and demands immediate urologic examination.** In a patient who presents with gross hematuria, cystoscopy should be performed as soon as possible, because frequently the source of bleeding can be readily identified. Cystoscopy will determine whether the hematuria is coming from the urethra, bladder, or upper urinary tract. In patients with gross hematuria secondary to an upper tract source, it is easy to see the jet of red urine pulsing from the involved ureteral orifice.

Although inflammatory conditions may result in hematuria, all patients with hematuria, except perhaps young women with acute bacterial hemorrhagic cystitis, should undergo urologic evaluation. Older women and men who present with hematuria and irritative voiding symptoms may have cystitis secondary to infection arising in a necrotic bladder tumor or, more commonly, flat carcinoma in situ of the bladder. **The most common cause of gross hematuria in a patient older than age 50 years is bladder cancer.**

Lower Urinary Tract Symptoms

Irritative Symptoms. *Frequency* is one of the most common urologic symptoms. The normal adult voids five or six times per day, with a volume of approximately 300 mL with each void. **Urinary frequency is due to either increased urinary output (polyuria) or decreased bladder capacity.** If voiding is noted to occur in large amounts frequently, the patient has polyuria and should be evaluated for diabetes mellitus, diabetes insipidus, or excessive fluid ingestion. Causes of decreased bladder capacity include bladder outlet obstruction with decreased compliance, increased residual urine, and/or decreased functional capacity due to irritation, neurogenic bladder with increased sensitivity and decreased compliance, pressure from extrinsic sources, or anxiety. By separating irritative from obstructive symptoms, the astute clinician should be able to arrive at a proper differential diagnosis.

Nocturia is nocturnal frequency. Normally, adults arise no more than twice at night to void. As with frequency, nocturia may be secondary to increased urine output or decreased bladder capacity. **Frequency during the day without nocturia is usually of psychogenic origin and related to anxiety. Nocturia without frequency may occur in the patient with congestive heart failure and peripheral edema in whom the intravascular volume and urine output increase when the patient is supine. Renal concentrating ability decreases with age; therefore urine production in the geriatric patient is increased at night, when renal blood flow is increased as a result of recumbency.** In general, nocturia may be attributed to nocturnal polyuria (nocturnal urine overproduction) and/or diminished nocturnal bladder capacity (Weiss and Blaivas, 2000). Nocturia may also occur in people who drink large amounts of liquid in the evening, particularly caffeinated and alcoholic beverages, which have strong diuretic effects. In the absence of these factors, nocturia signifies a problem with bladder function secondary to urinary outlet obstruction and/or decreased bladder compliance.

Dysuria is painful urination that is usually caused by inflammation. **This pain is usually not felt over the bladder but is commonly referred to the urethral meatus.** Pain occurring

at the start of urination may indicate urethral pathology, whereas pain occurring at the end of micturition (strangury) is usually of bladder origin. Dysuria is frequently accompanied by frequency and urgency.

Obstructive Symptoms. *Decreased force of urination* is usually secondary to bladder outlet obstruction and commonly results from benign prostatic hyperplasia (BPH) or a urethral stricture. In fact, except for severe degrees of obstruction, **most patients are unaware of a change in the force and caliber of their urinary stream.** These changes usually occur gradually and go generally unrecognized by most patients. The other obstructive symptoms noted later are more commonly recognized and are usually secondary to bladder outlet obstruction in men due to either BPH or a urethral stricture.

Urinary hesitancy refers to a delay in the start of micturition. Normally, urination begins within a second after relaxing the urinary sphincter, but it may be delayed in men with bladder outlet obstruction.

Intermittency refers to involuntary start-stopping of the urinary stream. It most commonly results from prostatic obstruction with intermittent occlusion of the urinary stream by the lateral prostatic lobes.

Postvoid dribbling refers to the terminal release of drops of urine at the end of micturition. **This is secondary to a small amount of residual urine in either the bulbar or the prostatic urethra that is normally "milked back" into the bladder at the end of micturition** (Stephenson and Farrar, 1977). In men with bladder outlet obstruction, this urine escapes into the bulbar urethra and leaks out at the end of micturition. Men will frequently attempt to avoid wetting their clothing by shaking the penis at the end of micturition. In fact, this is ineffective, and the problem is more readily solved by manual compression of the bulbar urethra in the perineum and blotting the urethral meatus with a tissue. Postvoid dribbling is often an early symptom of urethral obstruction related to BPH, but, in itself, seldom necessitates any further treatment.

Straining refers to the use of abdominal musculature to urinate. Normally, it is unnecessary for a man to perform a Valsalva maneuver except at the end of urination. Increased straining during micturition is a symptom of bladder outlet obstruction.

It is important for the urologist to distinguish irritative from obstructive lower urinary tract symptoms. This most frequently occurs in evaluating men with BPH. Although BPH is primarily obstructive, it produces changes in bladder compliance that result in increased irritative symptoms. In fact, men with BPH more commonly present with irritative than obstructive symptoms, and the most common presenting symptom is nocturia. **The urologist must be careful not to attribute irritative symptoms to BPH unless there is documented evidence of obstruction.** In general, lower urinary tract symptoms are nonspecific and may occur secondary to a wide variety of neurologic conditions, as well as to prostatic enlargement (Lepor and Machi, 1993). In this regard, two important examples are mentioned. Patients with high-grade flat carcinoma in situ of the bladder may present with urinary irritative symptoms. The urologist should be particularly aware of the diagnosis of carcinoma in situ in men who present with irritative symptoms, a history of cigarette smoking, and microscopic hematuria. In our personal experience, we cared for a 54-year-old man who presented with this history and was treated for BPH for 2 years before the diagnosis of bladder cancer was established. Once the correct diagnosis was made, the patient had developed muscle-invasive disease and required a cystectomy for cure.

The second important example is irritative symptoms resulting from neurologic disease such as cerebrovascular accidents, diabetes mellitus, and Parkinson disease. Most neurologic diseases encountered by the urologist are upper motor neuron in etiology and result in a loss of cortical inhibition of voiding with resultant decreased bladder compliance and irritative voiding symptoms. The urologist must be extremely careful to rule out underlying neurologic disease before performing surgery to relieve bladder outlet obstruction. Such surgery not only may fail to relieve the patient's irritative symptoms but also may result in permanent urinary incontinence.

Since its introduction in 1992, **the American Urological Association (AUA) symptom index has been widely used and validated as an important means of assessing men with lower urinary tract symptoms** (Barry et al, 1992). The original AUA symptom score is based on the answers to seven questions concerning frequency, nocturia, weak urinary stream, hesitancy, intermittency, incomplete bladder emptying, and urgency. The International Prostate Symptom Score (I-PSS) includes these seven questions, as well as a global quality-of-life question (Table 3–1). The total symptom score ranges from 0 to 35 with scores of 0 to 7, 8 to 19, and 20 to 35 indicating mild, moderate, and severe lower urinary tract symptoms, respectively. The I-PSS is a helpful tool both in the clinical management of men with lower urinary tract symptoms and in research studies regarding the medical and surgical treatment of men with voiding dysfunction.

The use of symptom indices has limitations, and it is important for the physician to discuss the patient's responses with him. It has been demonstrated that a grade 6 reading level is necessary to understand the I-PSS, and some patients with neurologic disorders and dementia may also have difficulty completing the symptom score (MacDiarmid et al, 1998). In addition, the symptom score and obstructive and irritative voiding symptoms are nonspecific, and the symptoms may be caused by a variety of conditions other than BPH. Similar symptom scores have been demonstrated to be present in age-matched men and women between 55 and 79 years of age (Lepor and Machi, 1993). **Despite these limitations, the I-PSS is a simple adjunct in assessing men with lower urinary tract symptoms and may be used in the initial evaluation of men with lower urinary tract symptoms, as well as in the assessment of treatment response.**

Incontinence. *Urinary incontinence* is the involuntary loss of urine. A careful history of the incontinent patient will often determine the etiology. Urinary incontinence can be subdivided into four categories.

Continuous Incontinence. **Continuous incontinence is most commonly due to a urinary tract fistula that bypasses the urethral sphincter.** The most common type of fistula that results in urinary incontinence is a vesicovaginal fistula usually secondary to gynecologic surgery, radiation, or obstetric trauma. Less commonly, ureterovaginal fistulas may occur from similar causes.

A second major cause of continuous incontinence is an ectopic ureter that enters either the urethra or the female genital tract. An ectopic ureter usually drains a small, dysplastic upper pole segment of kidney, and the amount of urinary leakage may be quite small. Such patients may void most of their urine normally but have a continuous amount of small urinary leakage that may be misdiagnosed for many years as a chronic vaginal discharge. In our experience, we cared for a 30-year-old woman—who had been misdiagnosed with enuresis in childhood and as having a chronic vaginal discharge in adult

Table 3–1.

International Prostate Symptom Score

SYMPTOM	NOT AT ALL	<1 TIME IN 5	LESS THAN HALF THE TIME	ABOUT HALF THE TIME	MORE THAN HALF THE TIME	ALMOST ALWAYS	YOUR SCORE
1. Incomplete emptying							
Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
2. Frequency							
Over the past month, how often have you had to urinate again <2 hours after you finished urinating?	0	1	2	3	4	5	
3. Intermittency							
Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency							
Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak stream							
Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining							
Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	NONE	1 TIME	2 TIMES	3 TIMES	4 TIMES	≥5 TIMES	
7. Nocturia							
Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5	
Total I-PSS Score							

QUALITY OF LIFE DUE TO URINARY SYMPTOMS	DELIGHTED	PLEASED	MOSTLY SATISFIED	MIXED—ABOUT EQUALLY SATISFIED AND DISSATISFIED	MOSTLY DISSATISFIED	UNHAPPY	TERRIBLE
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

From Cockett ATK, Aso Y, Denis L, et al. The Second International Consultation on Benign Prostatic Hyperplasia (BPH). In: Cockett ATK, Aso Y, Chatelain C, et al, editors. The Second International Consultation on Benign Prostatic Hyperplasia (BPH). Paris: Scientific Communication International; 1994. p. 553.

life—whose urinary leakage was totally corrected by surgical removal of the dysplastic, upper pole segment of her right kidney. Ectopic ureters never produce urinary incontinence in males because they always enter the bladder neck or prostatic urethra proximal to the external urethral sphincter.

Stress Incontinence. Stress incontinence refers to the sudden leakage of urine with coughing, sneezing, exercise, or other activities that increase intra-abdominal pressure. During these activities, intra-abdominal pressure rises transiently above urethral resistance, resulting in a sudden, usually small amount of urinary leakage. Stress incontinence is most common in women after childbearing or menopause and is related to a loss of anterior vaginal support and weakening of pelvic tissues. Stress incontinence is also observed in men after prostatic surgery, most commonly radical prostatectomy, in which there may be injury to the external urethral sphincter. **Stress urinary incontinence is difficult to manage pharmacologically, and patients with significant stress incontinence are usually best treated surgically.**

Urgency Incontinence. Urgency incontinence is the precipitous loss of urine preceded by a strong urge to void. This symptom is commonly observed in patients with cystitis, neurogenic bladder, and advanced bladder outlet obstruction with secondary loss of bladder compliance. It is important to distinguish urgency

incontinence from stress incontinence for two reasons. First, **urgency incontinence may result from a secondary underlying pathologic process, which should be identified;** treatment of this primary problem such as infection or bladder outlet obstruction may result in resolution of urgency incontinence. Second, patients with urgency incontinence are usually not amenable to surgical correction but, rather, are more appropriately treated with pharmacologic agents that increase bladder compliance and/or increase urethral resistance.

Overflow Urinary Incontinence. Overflow urinary incontinence, often called *paradoxical incontinence,* is secondary to advanced urinary retention and high residual urine volumes. In these patients, the bladder is chronically distended and never empties completely. Urine may dribble out in small amounts as the bladder overflows. This is particularly likely to occur at night when the patient is less likely to inhibit urinary leakage. **Overflow incontinence has been termed *paradoxical incontinence* because it can often be cured by relief of bladder outlet obstruction.** It is, however, often difficult to make the diagnosis of overflow incontinence by history and physical examination alone, particularly in the obese patient, in whom percussion of the distended bladder may be difficult. Overflow incontinence usually develops over a considerable length of time, and patients may be totally unaware of incomplete bladder emptying. Thus any patient with significant incontinence should undergo measurement of postvoid residual urine.

Enuresis. *Enuresis* refers to urinary incontinence that occurs during sleep. It occurs normally in children up to 3 years of age **but persists in about 15% of children at age 5 and about 1% of children at age 15** (Forsythe and Redmond, 1974). Enuresis must be distinguished from continuous incontinence, which occurs in the day and night and which, in a young girl, usually indicates the presence of an ectopic ureter. All children older than age 6 years with enuresis should undergo a urologic evaluation, although the vast majority will be found to have no significant urologic abnormality.

Sexual Dysfunction

Male sexual dysfunction is frequently used synonymously with *impotence* or erectile dysfunction, although impotence refers specifically to the inability to achieve and maintain an erection adequate for intercourse. Patients presenting with "impotence" should be questioned carefully to rule out other male sexual disorders including loss of libido, absence of emission, absence of orgasm, and, most commonly, premature ejaculation. Obviously, it is important to identify the precise problem before proceeding with further evaluation and treatment.

Loss of Libido. Because androgens have a major influence on sexual desire, a decrease in libido may indicate androgen deficiency arising from either pituitary or testicular dysfunction. This can be evaluated directly by **measurement of serum testosterone that, if abnormal, should be further evaluated by measurement of serum gonadotropins and prolactin.** Because the amount of testosterone required to maintain libido is usually less than that required for full stimulation of the prostate and seminal vesicles, patients with hypogonadism may also note decreased or absent ejaculation. Conversely, if semen volume is normal, it is unlikely that endocrine factors are responsible for loss of libido. A decrease in libido may also result from depression and a variety of medical illnesses that affect general health and well-being.

Impotence. *Impotence* refers specifically to the inability to achieve and maintain an erection sufficient for intercourse. **A careful history will often determine whether the problem is primarily psychogenic or organic.** In men with psychogenic impotence, the condition frequently develops rather quickly secondary to a precipitating event such as marital stress or change or loss of a sexual partner. In men with organic impotence, the condition usually develops more insidiously and frequently can be linked to advancing age or other underlying risk factors.

In evaluating men with impotence, it is important to determine whether the problem exists in all situations. Many men who report impotence may not be able to have intercourse with one partner but will with another. Similarly, it is important to determine whether men are able to achieve normal erections with alternative forms of sexual stimulation (e.g., masturbation, erotic videos). Finally, the patient should be asked whether he ever notes nocturnal or early morning erections. In general, **patients who are able to achieve adequate erections in some situations but not others have primarily psychogenic rather than organic impotence.**

Failure to Ejaculate. **An ejaculation may result from several causes: (1) androgen deficiency, (2) sympathetic denervation, (3) pharmacologic agents, and (4) bladder neck and prostatic surgery.** Androgen deficiency results in decreased secretions from the prostate and seminal vesicles causing a reduction or loss of seminal volume. Sympathectomy or extensive retroperitoneal surgery, most notably retroperitoneal lymphadenectomy for testicular cancer, may interfere with autonomic innervation of the prostate and seminal vesicles, resulting in absence of smooth muscle contraction and absence of seminal emission at time of orgasm. Pharmacologic agents, particularly α-adrenergic antagonists, may interfere with bladder neck closure at time of orgasm and result in retrograde ejaculation. Similarly, previous bladder neck or prostatic urethral surgery, most commonly transurethral resection of the prostate, may interfere with bladder neck closure, resulting in retrograde ejaculation. Finally, retrograde ejaculation may develop spontaneously in diabetic men.

Patients who complain of absence of ejaculation should be questioned regarding loss of libido or other symptoms of androgen deficiency, present medications, diabetes, and previous surgery. A careful history will usually determine the cause of this problem.

Absence of Orgasm. **Anorgasmia is usually psychogenic or caused by certain medications used to treat psychiatric diseases.** Sometimes, however, anorgasmia may be due to decreased penile sensation owing to impaired pudendal nerve function. Most commonly, this occurs in diabetics with peripheral neuropathy. Men who experience anorgasmia in association with decreased penile sensation should undergo vibratory testing of the penis and further neurologic evaluation as indicated.

Premature Ejaculation. Men who complain of premature ejaculation should be questioned carefully because this is obviously a subjective symptom. It is common for men to ejaculate within 2 minutes after initiation of intercourse, and many men who complain of premature ejaculation in actuality have normal sexual function with abnormal sexual expectations. However, there are men with true premature ejaculation who reach orgasm within less than 1 minute after initiation of intercourse. **This problem is almost always psychogenic** and best treated by a clinical psychologist or psychiatrist who specializes in treatment of this problem and other psychologic aspects of male sexual dysfunction. With counseling and appropriate modifications in sexual technique, this problem can usually be overcome. Alternatively, treatment with serotonin reuptake inhibitors such as sertraline

and fluoxetine has been demonstrated to be helpful in men with premature ejaculation (Murat Basar et al, 1999).

Hematospermia

Hematospermia refers to the presence of blood in the seminal fluid. **It almost always results from nonspecific inflammation of the prostate and/or seminal vesicles and resolves spontaneously, usually within several weeks.** It frequently occurs after a prolonged period of sexual abstinence, and we have observed it several times in men whose wives are in the final weeks of pregnancy. Patients with hematospermia that persists beyond several weeks should undergo further urologic evaluation, because, rarely, an underlying etiology will be identified. A genital and rectal examination should be done to exclude the presence of tuberculosis, a prostate-specific antigen (PSA) and a rectal examination done to exclude prostatic carcinoma, and a urinary cytology done to exclude the possibility of transitional cell carcinoma of the prostate. It should be emphasized, however, that hematospermia almost always resolves spontaneously and rarely is associated with any significant urologic pathology.

Pneumaturia

Pneumaturia is the passage of gas in the urine. In patients who have not recently had urinary tract instrumentation or a urethral catheter placed, this is almost always **due to a fistula between the intestine and the bladder. Common causes include diverticulitis, carcinoma of the sigmoid colon, and regional enteritis (Crohn disease).** In rare instances, patients with diabetes mellitus may have gas-forming infections, with carbon dioxide formation from the fermentation of high concentrations of sugar in the urine.

Urethral Discharge

Urethral discharge is the most common symptom of venereal infection. A purulent discharge that is thick, profuse, and yellow to gray is typical of gonococcal urethritis; the discharge in patients with nonspecific urethritis is usually scant and watery. A bloody discharge is suggestive of carcinoma of the urethra.

Fever and Chills

Fever and chills may occur with infection anywhere in the GU tract but are most commonly observed in patients with pyelonephritis, prostatitis, or epididymitis. **When associated with urinary obstruction, fever and chills may portend septicemia and necessitate emergency treatment to relieve obstruction.**

Medical History

The past medical history is extremely important because it frequently provides clues to the patient's current diagnosis. The past medical history should be obtained in an orderly and sequential manner.

Previous Medical Illnesses with Urologic Sequelae

There are obviously many diseases that may affect the GU system, and it is important to listen and record the patient's previous medical illnesses. **Patients with diabetes mellitus frequently develop autonomic dysfunction that may result in impaired urinary and sexual function.** A previous history of tuberculosis may be important in a patient presenting with impaired renal function, ureteral obstruction, or chronic, unexplained UTIs. Patients with hypertension have an increased risk of sexual dysfunction because they are more likely to have peripheral vascular disease and because many of the medications that are used to treat hypertension frequently cause impotence. Patients with neurologic diseases such as multiple sclerosis are also more likely to develop urinary and sexual dysfunction. In fact, 5% of patients with previously undiagnosed multiple sclerosis present with urinary symptoms as the first manifestation of the disease (Blaivas and Kaplan, 1988). As mentioned earlier, in men with bladder outlet obstruction, it is important to be aware of preexisting neurologic conditions. Surgical treatment of bladder outlet obstruction in the presence of detrusor hyperreflexia may result in increased urinary incontinence postoperatively. Finally, patients with sickle cell anemia are prone to a number of urologic conditions including papillary necrosis and erectile dysfunction secondary to recurrent priapism. There are obviously many other diseases with urologic sequelae, and it is important for the urologist to take a careful history in this regard.

Family History

It is similarly important to obtain a detailed family history because many diseases are genetic and/or familial. Examples of genetic diseases include adult polycystic kidney disease, tuberous sclerosis, von Hippel-Lindau disease, renal tubular acidosis, and cystinuria; these are but a few common and well-recognized examples.

In addition to these diseases of known genetic predisposition, there are other conditions in which the precise pattern of inheritance has not been elucidated but that clearly have a familial tendency. It is well known that individuals with a family history of urolithiasis are at increased risk for stone formation. More recently, it has been recognized that **8% to 10% of men with prostate cancer have a familial form of the disease that tends to develop about a decade earlier than the more common type of prostate cancer** (Bratt, 2000). Other familial conditions are mentioned elsewhere in the text, but suffice it to state again that obtaining a careful history of previous illnesses and a family history of urologic disease can be extremely valuable in establishing the correct diagnosis.

Medications

It is similarly important to obtain an accurate and complete list of present medications because many drugs interfere with urinary and sexual function. For example, **most of the antihypertensive medications interfere with erectile function, and changing antihypertensive medications can sometimes improve sexual function.** Similarly, many of the psychotropic agents interfere with emission and orgasm. In our own recent experience, we cared for a man who presented with anorgasmia. He had been to several physicians without improvement in this problem. When we obtained his past medical history, he mentioned that he had been taking a psychotropic agent for transient depression for several years, and his anorgasmia resolved when this no-longer-needed medication was discontinued. The list of medications affecting urinary and sexual function is exhaustive, but, once again, each medication should be recorded and its side effects investigated to be sure that the patient's problem is not drug related. A listing of common medications that may cause urologic side effects is presented in Table 3–2.

Previous Surgical Procedures

It is important to be aware of previous operations, particularly in a patient in whom surgery is intended. Obviously, previous operations may make subsequent ones more difficult. If the previous

Table 3–2.
Drugs Associated with Urologic Side Effects

UROLOGIC SIDE EFFECTS	CLASS OF DRUGS	SPECIFIC EXAMPLES
Decreased libido	Antihypertensives	Hydrochlorothiazide
		Propranolol
Erectile dysfunction	Psychotropic drugs	Benzodiazepines
Ejaculatory dysfunction	α-Adrenergic antagonists	Prazosin
		Tamsulosin
		α-Methyldopa
	Psychotropic drugs	Phenothiazines
		Antidepressants
Priapism	Antipsychotics	Phenothiazines
	Antidepressants	Trazodone
	Antihypertensives	Hydralazine
		Prazosin
Decreased spermatogenesis	Chemotherapeutic agents	Alkylating agents
	Drugs with abuse potential	Marijuana
		Alcohol
		Nicotine
	Drugs affecting endocrine function	Antiandrogens
		Prostaglandins
Incontinence or impaired voiding	Direct smooth muscle stimulants	Histamine
		Vasopressin
	Others	Furosemide
		Valproic acid
	Smooth muscle relaxants	Diazepam
	Striated muscle relaxants	Baclofen
Urinary retention or obstructive voiding symptoms	Anticholinergic agents or musculotropic relaxants	Oxybutynin
		Diazepam
		Flavoxate
	Calcium channel blockers	Nifedipine
	Antiparkinsonian drugs	Carbidopa
		Levodopa
	α-Adrenergic agonists	Pseudoephedrine
		Phenylephrine
	Antihistamines	Loratadine
		Diphenhydramine
Acute renal failure	Antimicrobials	Aminoglycosides
		Penicillins
		Cephalosporins
		Amphotericin
	Chemotherapeutic drugs	Cisplatin
	Others	Nonsteroidal anti-inflammatory drugs
		Phenytoin
Gynecomastia	Antihypertensives	Verapamil
	Cardiac drugs	Digoxin
	Gastrointestinal drugs	Cimetidine
		Metoclopramide
	Psychotropic drugs	Phenothiazines
	Tricyclic antidepressants	Amitriptyline
		Imipramine

surgery was in a similar anatomic region, it is worthwhile to try to obtain the previous operative report. In our own experience, this small additional effort has been rewarded on numerous occasions by providing a clear explanation of the patient's previous surgery that greatly simplified the subsequent operation. In general, **it is worthwhile obtaining as much information as possible *before* any intended surgery** because most surprises that occur in the operating room are unhappy ones.

Smoking and Alcohol Use

Cigarette smoking and consumption of alcohol are clearly linked to a number of urologic conditions. **Cigarette smoking is associated with an increased risk of urothelial carcinoma, most notably bladder cancer, and it is also associated with increased peripheral vascular disease and erectile dysfunction. Chronic alcoholism may result in autonomic and peripheral neuropathy with resultant impaired urinary and sexual function. Chronic alcoholism may also impair hepatic metabolism of estrogens, resulting in decreased serum testosterone, testicular atrophy, and decreased libido.**

In addition to the direct urologic effects of cigarette smoking and alcohol consumption, patients who are actively smoking or drinking at the time of surgery are at increased risk for perioperative complications. Smokers are at increased risk for both pulmonary and cardiac complications. If possible, they should **discontinue smoking at least 8 weeks before surgery to optimize their pulmonary function** (Warner et al, 1989). If they are unable to do this, they should at least quit smoking for 48 hours before surgery, because this will result in a significant improvement in cardiovascular function. Similarly, chronic alcoholics are at increased risk for hepatic toxicity and subsequent coagulation problems postoperatively. Furthermore, alcoholics who continue drinking up to the time of surgery may experience acute alcohol withdrawal during the postoperative period that can be life threatening. Prophylactic administration of lorazepam (Ativan) greatly reduces the potential risk of this significant complication.

Allergies

Finally, medicinal allergies should be questioned because, obviously, these medications should be avoided in future treatment of the patient. **All medicinal allergies should be marked boldly on the front of the patient's chart** to avoid potential complications from inadvertent exposure to the same medications.

In summary, a careful and thorough medical history including the chief complaint and history of present illness, past medical history, and family history should be obtained in every patient. Unfortunately, time constraints often make it difficult for the physician to spend the necessary time to obtain a full history. A reasonable substitute is to have a trained nurse or other health professional see the patient first. By using a standard history form, much of the information discussed previously can be obtained in a preliminary interview. It then remains for the urologist to only fill in the blanks, have the patient elaborate on potentially relevant aspects of the past medical history, and then perform a complete physical examination.

PHYSICAL EXAMINATION

A complete and thorough physical examination is an essential component of the evaluation of patients who present with urologic disease. Although it is tempting to become dependent on results of laboratory and radiologic tests, **the physical examination often simplifies the process and allows the urologist to select the most appropriate diagnostic studies.** Along with the history, the physical examination remains a key

Key Points

- The urologist can undertake the initial evaluation and establish a diagnosis for almost all patients with diseases of the GU system.
- A complete history and appropriate physical examination is critical in the assessment of urologic patients.
- A complete urinalysis including chemical and microscopic analyses should be performed because this may provide important information critical to the diagnosis and treatment of urologic patients.

component of the diagnostic evaluation and should be performed conscientiously.

General Observations

The visual inspection of the patient provides a general overview. The skin should be inspected for evidence of jaundice or pallor. The nutritional status of the patient should be noted. **Cachexia is a frequent sign of malignancy, and obesity may be a sign of underlying endocrinologic abnormalities.** In this instance, one should search for the presence of truncal obesity, a "buffalo hump," and abdominal skin striae, which are stigmata of hyperadrenocorticism. In contrast, debility and hyperpigmentation may be signs of hypoadrenocorticism. Gynecomastia may be a sign of endocrinologic disease and a possible indicator of alcoholism or previous hormonal therapy for prostate cancer. Edema of the genitalia and lower extremities may be associated with cardiac decompensation, renal failure, nephrotic syndrome, or pelvic and/or retroperitoneal lymphatic obstruction. Supraclavicular lymphadenopathy may be seen with any GU neoplasm, most commonly prostate and testis cancer; inguinal lymphadenopathy may occur secondary to carcinoma of the penis or urethra.

Kidneys

The kidneys are fist-sized organs located high in the retroperitoneum bilaterally. In the adult, the kidneys are normally difficult to palpate because of their position under the diaphragm and ribs with abundant musculature both anteriorly and posteriorly. Because of the position of the liver, the right kidney is somewhat lower than the left. **In children and thin women, it may be possible to palpate the lower pole of the right kidney with deep inspiration.** However, it is usually not possible to palpate either kidney in men, and the left kidney is almost always impalpable unless it is abnormally enlarged.

The best way to palpate the kidneys is with the patient in the supine position. **The kidney is lifted from behind with one hand in the costovertebral angle** (Fig. 3–1). On deep inspiration, the examiner's hand is advanced firmly into the anterior abdomen just below the costal margin. At the point of maximal inspiration, the kidney may be felt as it moves downward with the diaphragm. With each inspiration, the examiner's hand may be advanced deeper into the abdomen. Once again, it is more difficult to palpate kidneys in men because the kidneys tend to move downward less with inspiration and because they are surrounded with thicker muscular layers. In children, it is easier to palpate the kidneys because of decreased body thickness. In neonates, the kidneys can be felt quite easily by palpating the flank between the thumb anteriorly and the fingers over the costovertebral angle posteriorly.

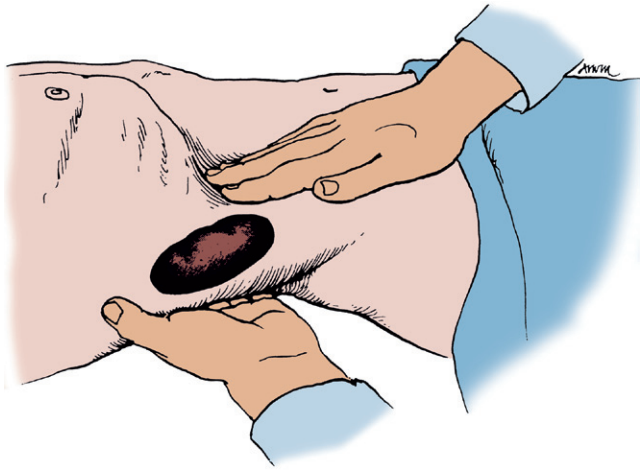


Figure 3–1. Bimanual examination of the kidney. (From Judge RD, Zuidema GD, Fitzgerald FT, editors. Clinical diagnosis. 5th ed. Boston: Little, Brown; 1989. p. 370.)

Transillumination of the kidneys may be helpful in children younger than 1 year of age with a palpable flank mass. Such masses are frequently of renal origin. A flashlight or fiberoptic light source is positioned posteriorly against the costovertebral angle. Fluid-filled masses such as cysts or hydronephrosis produce a dull reddish glow in the anterior abdomen. Solid masses such as tumors do not transilluminate. Other diagnostic maneuvers that may be helpful in examining the kidneys are percussion and auscultation. Although renal inflammation may cause pain that is poorly localized, percussion of the costovertebral angle posteriorly more often localizes the pain and tenderness more accurately. Percussion should be done gently because in a patient with significant renal inflammation, this may be quite painful. Auscultation of the upper abdomen during deep inspiration may occasionally reveal a systolic bruit associated with renal artery stenosis or an aneurysm. A bruit may also be detected in association with a large renal arteriovenous fistula.

Every patient with flank pain should also be examined for possible nerve root irritation. The ribs should be palpated carefully to rule out a bone spur or other skeletal abnormality and to determine the point of maximal tenderness. Unlike renal pain, radiculitis usually causes hyperesthesia of the overlying skin innervated by the irritated peripheral nerve. This hypersensitivity can be elicited with a pin or by pinching the skin and fat overlying the involved area. Finally, the pain experienced during the pre-eruptive phase of herpes zoster involving any of the segments between T11 and L2 may also simulate pain of renal origin.

Bladder

A normal bladder in the adult cannot be palpated or percussed until there is at least 150 mL of urine in it. At a volume of about 500 mL, the distended bladder becomes visible in thin patients as a lower midline abdominal mass.

Percussion is better than palpation for diagnosing a distended bladder. The examiner begins by percussing immediately above the symphysis pubis and continuing cephalad until there is a change in pitch from dull to resonant. Alternatively, it may be possible in thin patients and in children to palpate the

bladder by lifting the lumbar spine with one hand and pressing the other hand into the midline of the lower abdomen.

A careful bimanual examination, best done with the patient under anesthesia, is invaluable in assessing the regional extent of a bladder tumor or other pelvic mass. The bladder is palpated between the abdomen and the vagina in the female (Fig. 3–2) or the rectum in the male (Fig. 3–3). In addition to defining areas of induration, the bimanual examination allows the examiner to assess the mobility of the bladder; such information cannot be obtained by radiologic techniques such as CT and MRI, which convey static images.

Penis

If the patient has not been circumcised, the foreskin should be retracted to examine for tumor or balanoposthitis (inflammation of the prepuce and glans penis). **Most penile cancers occur in uncircumcised men and arise on the prepuce or glans penis.** Therefore in a patient with a bloody penile discharge in whom the foreskin cannot be withdrawn, a dorsal slit or circumcision must be performed to adequately evaluate the glans penis and urethra.

The position of the urethral meatus should be noted. It may be located proximal to the tip of the glans on the ventral surface (hypospadias) or, much less commonly, on the dorsal surface (epispadias). The penile skin should be examined for the presence of superficial vesicles compatible with herpes simplex and for ulcers that may indicate either venereal infection or tumor. The presence of venereal warts (condylomata acuminata), which appear as irregular, papillary, velvety lesions on the male genitalia, should also be noted.

The urethral meatus should be separated between the thumb and the forefinger to inspect for neoplastic or inflammatory lesions within the fossa navicularis. The dorsal shaft of the penis should be palpated for the presence of fibrotic plaques or ridges typical of Peyronie disease. Tenderness along the ventral aspect of the penis is suggestive of periurethritis, often secondary to a urethral stricture.

Scrotum and Contents

The scrotum is a loose sac containing the testes and spermatic cord structures. The scrotal wall is made up of skin and an underlying thin muscular layer. The testes are normally oval, firm, and smooth; in adults, they measure about 6 cm in length and 4 cm in width. They are suspended in the scrotum, with the right testis normally anterior to the left. The epididymis lies posterior to the testis and is palpable as a distinct ridge of tissue. The vas deferens can be palpated above each testis and feels like a piece of heavy twine.

The scrotum should be examined for dermatologic abnormalities. **Because the scrotum, unlike the penis, contains both hair and sweat glands, it is a frequent site of local infection and sebaceous cysts.** Hair follicles can become infected and may present as small pustules on the surface of the scrotum. These usually resolve spontaneously, but they can give rise to more significant infection, particularly in patients with reduced immunity and diabetes. Patients often become concerned about these lesions, mistaking them for testicular tumors.

The testes should be palpated gently between the fingertips of both hands. The testes normally have a firm, rubbery consistency with a smooth surface. Abnormally small testes suggest

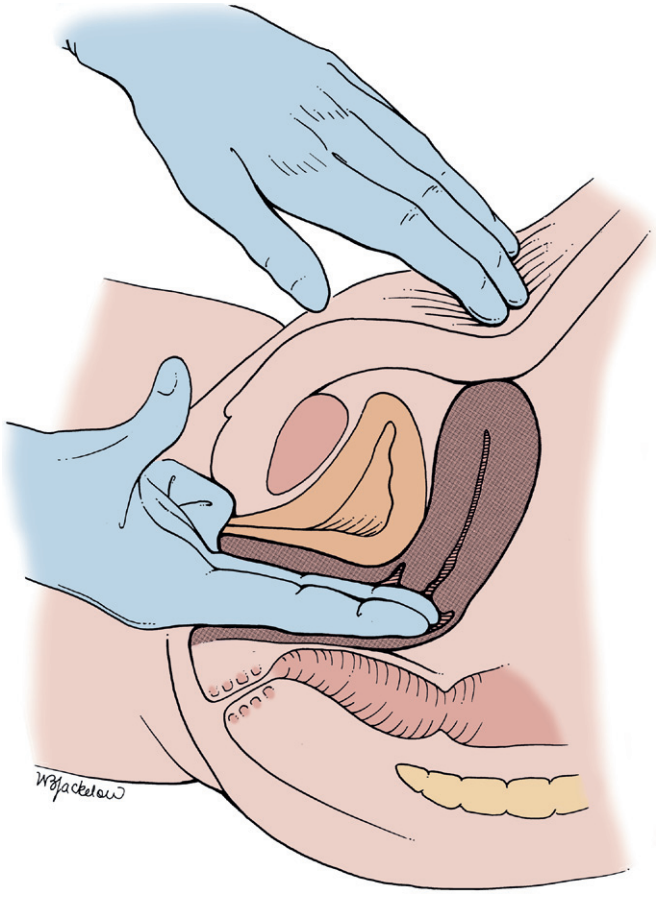


Figure 3–2. Bimanual examination of the bladder in the female. (From Swartz MH. Textbook of physical diagnosis. Philadelphia: WB Saunders; 1989. p. 405.)

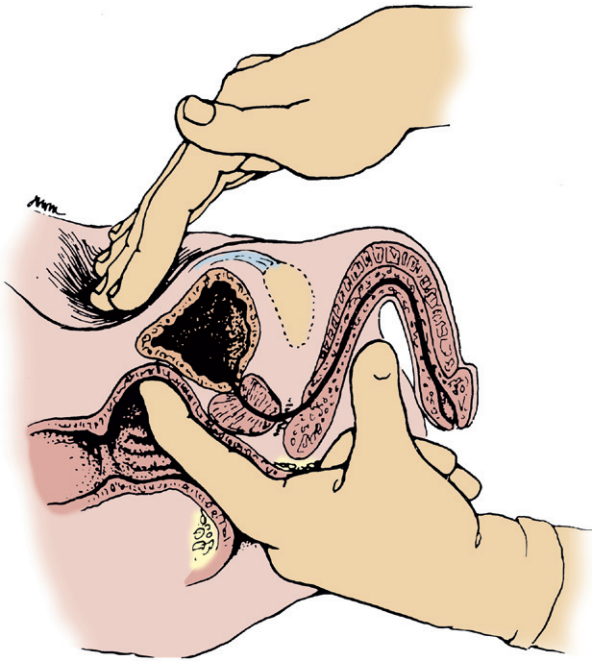


Figure 3–3. Bimanual examination of the bladder in the male. (From Judge RD, Zuidema GD, Fitzgerald FT, editors. Clinical diagnosis. 5th ed. Boston: Little, Brown; 1989. p. 376.)

hypogonadism or an endocrinopathy such as Klinefelter disease. **A firm or hard area within the testis should be considered a malignant tumor until proved otherwise.** The epididymis should be palpable as a ridge posterior to each testis. Masses in the epididymis (spermatocele, cyst, and epididymitis) are almost always benign.

To examine for a hernia, the physician's index finger should be inserted gently into the scrotum and invaginated into the external inguinal ring (Fig. 3–4). The scrotum should be invaginated in front of the testis, and care should be taken not to elevate the testis itself, which is quite painful. Once the external ring has been located, the physician should place the fingertips of his or her other hand over the internal inguinal ring and ask the patient to bear down (Valsalva maneuver). A hernia will be felt as a distinct bulge that descends against the tip of the index finger in the external inguinal ring as the patient bears down. Although it may be possible to distinguish a direct inguinal hernia arising through the floor of the inguinal canal from an indirect inguinal hernia prolapsing through the internal inguinal ring, this is seldom possible and of little clinical significance because the surgical approach is essentially identical for both conditions.

The spermatic cord is also examined with the patient in the standing position. A varicocele is a dilated, tortuous spermatic vein that becomes more obvious as the patient performs a Valsalva maneuver. The epididymis can again be palpated as a ridge of tissue running longitudinally, posterior to each testis. The testis should be palpated again between the fingers of both hands, once again taking care not to exert any pressure on the testis itself so as to avoid pain.

Transillumination is helpful in determining whether scrotal masses are solid (tumor) or cystic (hydrocele, spermatocele). A small flashlight or fiberoptic light cord is placed behind the mass. A cystic mass transilluminates easily, whereas light is not transmitted through a solid tumor.

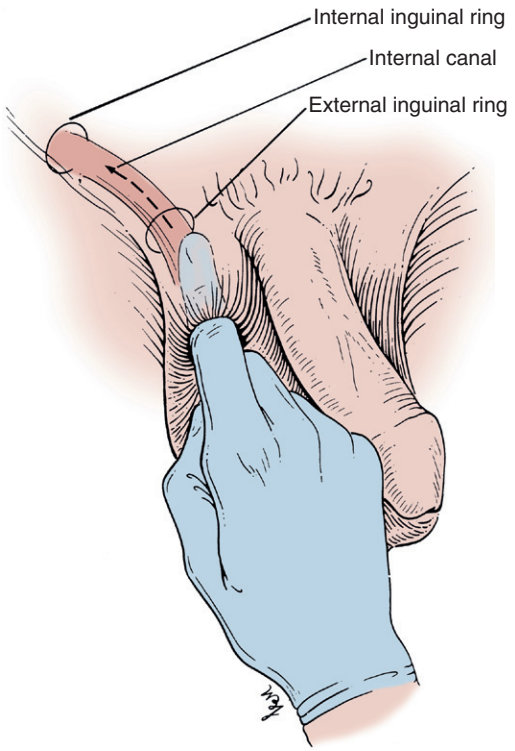


Figure 3–4. Examination of the inguinal canal. (From Swartz MH. Textbook of physical diagnosis. Philadelphia: WB Saunders; 1989. p. 376.)

Rectal and Prostate Examination in the Male

Digital rectal examination (DRE) should be performed in every male after age 40 years and in men of any age who present for urologic evaluation. Prostate cancer is the second most common cause of male cancer deaths after age 55 years and the most common cause of cancer deaths in men older than 70 years. Many prostate cancers can be detected in an early curable stage by DRE, and about 25% of colorectal cancers can be detected by DRE in combination with a stool guaiac test.

DRE should be performed at the end of the physical examination. It is done best with the patient standing and bent over the examining table or with the patient in the knee-chest position. In the standing position, the patient should stand with his thighs close to the examining table. The feet should be about 18 inches apart, with the knees flexed slightly. The patient should bend at the waist 90 degrees until his chest is resting on his forearms. The physician should give the patient adequate time to get in the proper position and relax as much as possible. A few reassuring words before the examination are helpful. The physician should place a glove on the examining hand and should lubricate the index finger thoroughly.

Before performing the DRE, the physician should place the palm of his other hand against the patient's lower abdomen. This provides subtle reassurance to the patient by allowing the physician to make gentle contact with the patient before touching the anus. It also allows the physician to steady the patient and provide gentle counterpressure if the patient tries to move away as the DRE is being performed. The DRE itself begins by separating the buttocks and inspecting the anus for pathology, usually hemorrhoids, but, occasionally, an anal carcinoma or melanoma may be detected. The gloved, lubricated index finger is then inserted gently into the anus. Only one phalanx should be inserted initially to give the anus time to relax and to easily accommodate the finger. Estimation of anal sphincter tone is of great importance; a flaccid or spastic anal sphincter suggests similar changes in the urinary sphincter and may be a clue to the diagnosis of neurogenic disease. If the physician waits only a few seconds, the anal sphincter will normally relax to the degree that the finger can be advanced to the knuckle without causing pain. The index finger then sweeps over the prostate; the entire posterior surface of the gland can usually be examined if the patient is in the proper position. **Normally, the prostate is about the size of a chestnut and has a consistency similar to that of the contracted thenar eminence of the thumb (with the thumb opposed to the little finger).**

The index finger is extended as far as possible into the rectum, and the entire circumference is examined to detect an early rectal carcinoma. The index finger is then withdrawn gently, and the stool on the glove is transferred to a guaiac-impregnated (Hemoccult) card for determination of occult blood. Although there may be a significant incidence of false-positive and false-negative results associated with fecal occult blood testing, particularly without dietary and drug restrictions, **the guaiac test is simple and inexpensive and may lead to the detection of significant gastrointestinal abnormalities** (Bond, 1999). Adequate tissues, soap, and towels should be available for the patient to cleanse himself after the examination. The physician should then

leave the room and allow the patient adequate time to wash and dress before concluding the consultation.

Pelvic Examination in the Female

Male urologists should always perform the female pelvic examination with a female nurse or other health care professional present. The patient should be allowed to undress in privacy and be fully draped for the procedure before the physician enters the room. The examination itself should be performed in standard lithotomy position with the patient's legs abducted. Initially, the external genitalia and introitus should be examined, with particular attention paid to atrophic changes, erosions, ulcers, discharge, or warts, all of which may cause dysuria and pelvic discomfort. The urethral meatus should be inspected for caruncles, mucosal hyperplasia, cysts, and mucosal prolapse. The patient is then asked to perform a Valsalva maneuver and is carefully examined for a cystocele (prolapse of the bladder) or rectocele (prolapse of the rectum). The patient is then asked to cough, which may precipitate stress urinary incontinence. Palpation of the urethra is done to detect induration, which may be a sign of chronic inflammation or malignancy. Palpation may also disclose a urethral diverticulum, and palpation of a diverticulum may cause a purulent discharge from the urethra. Bimanual examination of the bladder, uterus, and adnexa should then be performed with two fingers in the vagina and the other hand on the lower abdomen (see Fig. 3–3). Any abnormality of the pelvic organs should be evaluated further with a pelvic ultrasound or CT scan.

Neurologic Examination

There are various clinical situations in which the neurologic examination may be helpful in evaluating urologic patients. In some cases, the level of neurologic abnormalities can be localized by the pattern of sensory deficit noted during physical examination using a dermatome map (Fig. 3–5). Sensory deficits in the penis, labia, scrotum, vagina, and perianal area generally indicate damage or injury to sacral roots or nerves. In addition to sensory examination, testing of reflexes in the genital area may also be performed. The most important of these is the bulbocavernosus reflex (BCR), which is a reflex contraction of the striated muscle of the pelvic floor that occurs in response to various stimuli in the perineum or genitalia. This reflex is most commonly tested by placing a finger in the rectum and then squeezing the glans penis or clitoris. If a Foley catheter is in place, the BCR can also be elicited by gently pulling on the catheter. If the BCR is intact, tightening of the anal sphincter should be felt and/or observed. The BCR tests the integrity of the spinal cord mediated reflex arc involving S2-S4 and may be absent in the presence of sacral cord or peripheral nerve abnormalities.

The cremasteric reflex can be elicited by lightly stroking the superior and medial thigh in a downward direction. The normal response in males is contraction of the cremasteric muscle that results in immediate elevation of the ipsilateral scrotum and testis. There is limited clinical utility for testing superficial reflexes such as the cremasteric when investigating neurologic dysfunction. However, there may be a role for testing this reflex when assessing patients with suspected testicular torsion or epididymitis. Finally, an overly active cremasteric reflex in children can lead to the mistaken diagnosis of an undescended testis in some cases.

URINALYSIS

The urinalysis is a fundamental test that should be performed in all urologic patients. Although, in many instances a simple dipstick urinalysis will provide the necessary information, **a complete urinalysis includes both chemical and microscopic analyses.**

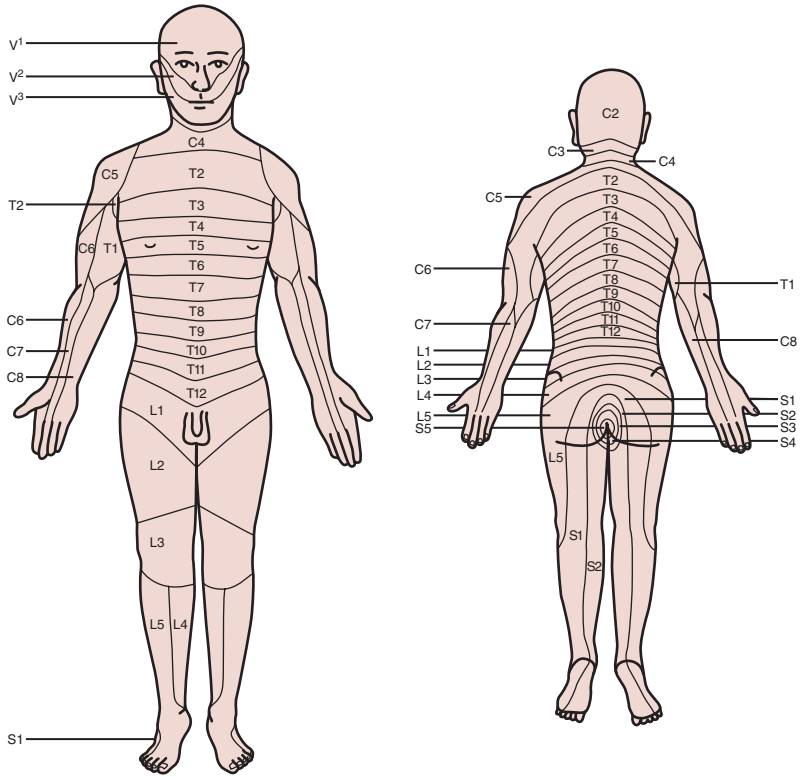


Figure 3–5. Sensory dermatome maps used to help localize the level of neurologic deficit.

Collection of Urinary Specimens

Males

In the male patient, a midstream urine sample is obtained. The uncircumcised male should retract the foreskin, cleanse the glans penis with antiseptic solution, and continue to retract the foreskin during voiding. The male patient begins urinating into the toilet and then places a wide-mouth sterile container under his penis to collect a midstream sample. This avoids contamination of the urine specimen with skin and urethral organisms.

In men with chronic UTIs, four aliquots of urine are obtained. **These aliquots have been designated Voided Bladder 1, Voided Bladder 2, Expressed Prostatic Secretions, and Voided Bladder 3 (VB1, VB2, EPS, and VB3).** The VB1 is the initial 5 to 10 mL of urine voided, whereas the VB2 is the midstream urine. The EPS is the secretions obtained after gentle prostatic massage, and the VB3 specimen is the initial 2 to 3 mL of urine obtained after prostatic massage. The value of these cultures for localization of UTIs is that the VB1 sample represents urethral flora; the VB2, bladder flora; and the EPS and VB3 samples, prostatic flora. The VB3 sample is particularly helpful when there is little or no prostatic fluid obtained by massage. To better obtain prostatic secretions, patients should be instructed to attempt to void during prostatic massage and to avoid tightening the anal sphincter and pelvic floor muscles. The four-part urine sample is particularly useful in evaluating men with suspected bacterial prostatitis (Meares and Stamey, 1968).

Females

In the female, it is more difficult to obtain a clean-catch midstream specimen. The female patient should cleanse the vulva, separate the labia, and collect a midstream specimen as described for the male patient. If infection is suspected, however, the midstream specimen is unreliable and should never be sent for culture and sensitivity. **To evaluate for a possible infection in a female, a catheterized urine sample should always be obtained.**

Neonates and Infants

The usual way to obtain a urine sample in a neonate or infant is to place a sterile plastic bag with an adhesive collar over the infant's genitalia. Obviously, however, these devices may not be able to distinguish contamination from true UTI. Whenever possible, **all urine samples should be examined within 1 hour of collection and plated for culture and sensitivity if indicated.** If urine is allowed to stand at room temperature for longer periods of time, bacterial overgrowth may occur, the pH may change, and red and white blood cell casts may disintegrate. If it is not possible to examine the urine promptly, it should be refrigerated at 5° C.

Physical Examination of Urine

The physical examination of the urine includes an evaluation of color, turbidity, specific gravity and osmolality, and pH.

Color

The normal pale yellow color of urine is due to the presence of the pigment urochrome. **Urine color varies most commonly because of concentration, but many foods, medications, metabolic products, and infection may produce abnormal urine color.** This is important because many patients will seek consultation primarily because of a change in their urine color. Thus it is important for the urologist to be aware of the common causes of abnormal urine color, and these are listed in Table 3–3.

Table 3–3.

Common Causes of Abnormal Urine Color

Colorless	Very dilute urine
	Overhydration
Cloudy/milky	Phosphaturia
	Pyuria
	Chyluria
Red	Hematuria
	Hemoglobinuria/myoglobinuria
	Anthocyanin in beets and blackberries
	Chronic lead and mercury poisoning
	Phenolphthalein (in bowel evacuants)
	Phenothiazines (e.g., Compazine)
	Rifampin
Orange	Dehydration
	Phenazopyridine (Pyridium)
	Sulfasalazine (Azulfidine)
Yellow	Normal
	Phenacetin
	Riboflavin
Green-blue	Biliverdin
	Indicanuria (tryptophan indole metabolites)
	Amitriptyline (Elavil)
	Indigo carmine
	Methylene blue
	Phenols (e.g., IV cimetidine [Tagamet], IV promethazine [Phenergan])
	Resorcinol
	Triamterene (Dyrenium)
Brown	Urobilinogen
	Porphyria
	Aloe, fava beans, and rhubarb
	Chloroquine and primaquine
	Furazolidone (Furoxone)
	Metronidazole (Flagyl)
	Nitrofurantoin (Furadantin)
Brown-black	Alcaptonuria (homogentisic acid)
	Hemorrhage
	Melanin
	Tyrosinosis (hydroxyphenylpyruvic acid)
	Cascara, senna (laxatives)
	Methocarbamol (Robaxin)
	Methyldopa (Aldomet)
	Sorbitol

From Hanno PM, Wein AJ. A clinical manual of urology. Norwalk (CT): Appleton-Century-Crofts; 1987. p. 67.

Turbidity

Freshly voided urine is clear. **Cloudy urine is most commonly due to phosphaturia,** a benign process in which excess phosphate crystals precipitate in an alkaline urine. Phosphaturia is intermittent and usually occurs after meals or ingestion of a large quantity of milk. Patients are otherwise asymptomatic. The diagnosis of phosphaturia can be accomplished either by acidifying the urine with acetic acid, which will result in immediate clearing, or by performing a microscopic analysis, which will reveal large amounts of amorphous phosphate crystals.

Pyuria, usually associated with a UTI, is another common cause of cloudy urine. The large numbers of white blood cells cause the urine to become turbid. **Pyuria is readily distinguished from**

phosphaturia either by smelling the urine (infected urine has a characteristic pungent odor) or by microscopic examination, which readily distinguishes amorphous phosphate crystals from leukocytes.

Rare causes of cloudy urine include chyluria (in which there is an abnormal communication between the lymphatic system and the urinary tract resulting in lymph fluid being mixed with urine), lipiduria, hyperoxaluria, and hyperuricosuria.

Specific Gravity and Osmolality

Specific gravity of urine is easily determined from a urinary dipstick and usually varies from 1.001 to 1.035. Specific gravity usually reflects the patient's state of hydration but may also be affected by abnormal renal function, the amount of material dissolved in the urine, and a variety of other causes mentioned later. A specific gravity less than 1.008 is regarded as dilute, and a specific gravity greater than 1.020 is considered concentrated. A fixed specific gravity of 1.010 is a sign of renal insufficiency, either acute or chronic.

In general, specific gravity reflects the state of hydration but also affords some idea of renal concentrating ability. Conditions that decrease specific gravity include (1) increased fluid intake, (2) diuretics, (3) decreased renal concentrating ability, and (4) diabetes insipidus. Conditions that increase specific gravity include (1) decreased fluid intake; (2) dehydration owing to fever, sweating, vomiting, and diarrhea; (3) diabetes mellitus (glucosuria); and (4) inappropriate secretion of antidiuretic hormone. Specific gravity will also be increased above 1.035 after intravenous injection of iodinated contrast and in patients taking dextran.

Osmolality is a measure of the amount of material dissolved in the urine and usually varies between 50 and 1200 mOsm/L. Urine osmolality most commonly varies with hydration, and the same factors that affect specific gravity will also affect osmolality. Urine osmolality is a better indicator of renal function, but it cannot be measured from a dipstick and must be determined using standard laboratory techniques.

pH

Urinary pH is measured with a dipstick test strip that incorporates two colorimetric indicators, methyl red and bromothymol blue, which yield clearly distinguishable colors over the pH range from 5 to 9. Urinary pH may vary from 4.5 to 8; the average pH varies between 5.5 and 6.5. A urinary pH between 4.5 and 5.5 is considered acidic, whereas a pH between 6.5 and 8 is considered alkaline.

In general, the urinary pH reflects the pH in the serum. In patients with metabolic or respiratory acidosis, the urine is usually acidic; conversely, in patients with metabolic or respiratory alkalosis, the urine is alkaline. Renal tubular acidosis (RTA) presents an exception to this rule. In patients with both type I and II RTA, the serum is acidemic, but the urine is alkalotic because of continued loss of bicarbonate in the urine. In severe metabolic acidosis in type II RTA, the urine may become acidic, but in type I RTA, the urine is always alkaline, even with severe metabolic acidosis (Morris and Ives, 1991). Urinary pH determination is used to establish the diagnosis of RTA; inability to acidify the urine below a pH of 5.5 after administration of an acid load is diagnostic of RTA.

Urine pH determinations are also useful in the diagnosis and treatment of UTIs and urinary calculus disease. **In patients with a presumed UTI, an alkaline urine with a pH greater than 7.5 suggests infection with a urea-splitting organism, most commonly *Proteus*.** Urease-producing bacteria convert ammonia to ammonium ions, markedly elevating the urinary pH and causing precipitation of calcium magnesium ammonium phosphate crystals. The massive amount of crystallization may result in staghorn calculi.

Urinary pH is usually acidic in patients with uric acid and cystine lithiasis. Alkalinization of the urine is an important feature of therapy in both of these conditions, and frequent monitoring of urinary pH is necessary to ascertain adequacy of therapy.

Chemical Examination of Urine

Urine Dipsticks

Urine dipsticks provide a quick and inexpensive method for detecting abnormal substances within the urine. Dipsticks are short, plastic strips with small marker pads that are impregnated with different chemical reagents that react with abnormal substances in the urine to produce a colorimetric change. **The abnormal substances commonly tested for with a dipstick include (1) blood, (2) protein, (3) glucose, (4) ketones, (5) urobilinogen and bilirubin, and (6) white blood cells.**

Substances listed in Table 3–3 that produce an abnormal urine color may interfere with appropriate color development on the dipstick. In our experience, this most commonly occurs in patients taking phenazopyridine (Pyridium) for a UTI. Phenazopyridine turns the urine bright orange and makes dipstick evaluation of the urine unreliable.

Appropriate technique must be used to obtain an accurate dipstick determination. The reagent areas on the dipstick must be completely immersed in a fresh uncentrifuged urine specimen and then must be withdrawn immediately to prevent dissolution of the reagents into the urine. As the dipstick is removed from the urine specimen container, the edge of the dipstick is drawn along the rim of the container to remove excess urine. The dipstick should be held horizontally until the appropriate time for reading and then compared with the color chart. **Excess urine on the dipstick or holding the dipstick in a vertical position will allow mixing of chemicals from adjacent reagent pads on the dipstick, resulting in a faulty diagnosis.** False-negative results for glucose and bilirubin may be seen in the presence of elevated ascorbic acid concentrations in the urine. However, increased levels of ascorbic acid in the urine do not interfere with dipstick testing for hematuria. Highly buffered alkaline urine may cause falsely low readings for specific gravity and may lead to false-negative results for urinary protein. Other common causes of false results with dipstick testing are outdated test strips and exposure of the sticks, leading to damage to the reagents. In general, when the sticks are damaged, there will be color changes on the pads before their immersion in urine. If such color changes are noted, results with the dipstick may be inaccurate.

Hematuria

Normal urine should contain fewer than three red blood cells per HPF. A positive dipstick for blood in the urine indicates either hematuria, hemoglobinuria, or myoglobinuria. **The chemical detection of blood in the urine is based on the peroxidase-like activity of hemoglobin.** When in contact with an organic peroxidase substrate, hemoglobin catalyzes the reaction and causes subsequent oxidation of a chromogen indicator, which

changes color according to the degree and amount of oxidation. The degree of color change is directly related to the amount of hemoglobin present in the urine specimen. Dipsticks frequently demonstrate both colored dots and field color change. If present, free hemoglobin and myoglobin in the urine are absorbed into the reagent pad and catalyze the reaction within the test paper, thereby producing a field change effect in color. Intact erythrocytes in the urine undergo hemolysis when they come in contact with the reagent test pad, and the localized free hemoglobin on the pad produces a corresponding dot of color change. Obviously, the greater the number of intact erythrocytes in the urine specimen, the greater the number of dots that will appear on the test paper, and a coalescence of the dots occurs when there are more than 250 erythrocytes/mL.

Hematuria can be distinguished from hemoglobinuria and myoglobinuria by microscopic examination of the centrifuged urine; the presence of a large number of erythrocytes establishes the diagnosis of hematuria. If erythrocytes are absent, examination of the serum will distinguish hemoglobinuria and myoglobinuria. A sample of blood is obtained and centrifuged. In hemoglobinuria, the supernatant will be pink. This is because free hemoglobin in the serum binds to haptoglobin, which is water insoluble and has a high molecular weight. This complex remains in the serum, causing a pink color. Free hemoglobin will appear in the urine only when all of the haptoglobin-binding sites have been saturated. In myoglobinuria, the myoglobin released from muscle is of low molecular weight and water soluble. It does not bind to haptoglobin and is therefore excreted immediately into the urine. Therefore in myoglobinuria the serum remains clear.

The sensitivity of urinary dipsticks in identifying hematuria, defined as greater than three erythrocytes/HPF of centrifuged sediment examined microscopically, is higher than 90%. Conversely, the specificity of the dipstick for hematuria compared with microscopy is somewhat lower, reflecting a higher false-positive rate with the dipstick (Shaw et al, 1985).

False-positive dipstick readings are most often due to contamination of the urine specimen with menstrual blood. Dehydration with resultant urine of high specific gravity can also yield false-positive results owing to the increased concentration of erythrocytes and hemoglobin. The normal individual excretes about 1000 erythrocytes/mL of urine, with the upper limits of normal varying from 5000 to 8000 erythrocytes/mL (Kincaid-Smith, 1982). Therefore examining urine of high specific gravity such as the first morning voided specimen increases the likelihood of a false-positive result. In addition to dehydration, another cause of false-positive results is exercise, which can increase the number of erythrocytes in the urine.

The efficacy of hematuria screening using the dipstick to identify patients with significant urologic disease is somewhat controversial. Studies in children and young adults have shown a low rate of significant disease (Woolhandler et al, 1989). In older adults, one study from the Mayo Clinic of 2000 patients with asymptomatic hematuria showed that only 0.5% had a urologic malignancy and only 1.8% developed other serious urologic diseases within 3 years after identification of the hematuria (Mohr et al, 1986). Conversely, investigators at the University of Wisconsin found that 26% of adults who had at least one positive dipstick reading for hematuria were subsequently found to have significant urologic pathology (Messing et al, 1987). Obviously, the age of the population, the completeness of the subsequent urologic evaluation, and the definition of significant disease all influence the disease rate in the group of patients with asymptomatic hematuria identified by dipstick screening. It is important to remember that, before proceeding to more complicated studies, the dipstick result should be confirmed with a microscopic examination of the centrifuged urinary sediment.

Differential Diagnosis and Evaluation of Hematuria. Hematuria may reflect either significant nephrologic or urologic disease. **Hematuria of nephrologic origin is frequently associated with casts in the urine and almost always associated with significant proteinuria. Even significant hematuria of urologic origin will not elevate the protein concentration in the urine into the 100 to 300 mg/dL or 2+ to 3+ range on dipstick,** and proteinuria of this magnitude almost always indicates glomerular or tubulointerstitial renal disease.

Morphologic evaluation of erythrocytes in the centrifuged urinary sediment also helps localize their site of origin. **Erythrocytes arising from glomerular disease are typically dysmorphic and show a wide range of morphologic alterations. Conversely, erythrocytes arising from tubulointerstitial renal disease and of urologic origin have a uniformly round shape;** these erythrocytes may or may not retain their hemoglobin ("ghost cells"), but the individual cell shape is consistently round. In individuals without significant pathology with minimal amounts of hematuria, the erythrocytes are characteristically dysmorphic but the number of cells observed is far fewer than that observed in patients with nephrologic disease. Erythrocyte morphology is more easily determined using phase contrast microscopy, but with practice this can be accomplished using a conventional light microscope (Schramek et al, 1989).

Glomerular Hematuria. Glomerular hematuria is suggested by the presence of dysmorphic erythrocytes, red blood cell casts, and proteinuria. Of those patients with glomerulonephritis proven by renal biopsy, however, about 20% will have hematuria alone without red blood cell casts or proteinuria (Fassett et al, 1982).

The glomerular disorders associated with hematuria are listed in Table 3–4. Further evaluation of patients with glomerular hematuria should begin with a thorough history. Hematuria in children and young adults, usually males, associated with low-grade fever and an erythematous rash suggests a diagnosis of immunoglobulin A (IgA) nephropathy (Berger disease). A family history of renal

Table 3–4.

Glomerular Disorders in Patients with Glomerular Hematuria

DISORDER	PATIENTS
IgA nephropathy (Berger disease)	30
Mesangioproliferative GN	14
Focal segmental proliferative GN	13
Familial nephritis (e.g., Alport syndrome)	11
Membranous GN	7
Mesangiocapillary GN	6
Focal segmental sclerosis	4
Unclassifiable	4
Systemic lupus erythematosus	3
Postinfectious GN	2
Subacute bacterial endocarditis	2
Others	4
TOTAL	100

GN, glomerulonephritis; IgA, immunoglobulin A.

Adapted from Fassett RG, Horgan BA, Mathew TH. Detection of glomerular bleeding by phase-contrast microscopy. Lancet 1982;1:1432.

disease and deafness suggests familial nephritis or Alport syndrome. Hemoptysis and abnormal bleeding associated with microcytic anemia are characteristic of Goodpasture syndrome, and the presence of a rash and arthritis suggest systemic lupus erythematosus. Finally, poststreptococcal glomerulonephritis should be suspected in a child with a recent streptococcal upper respiratory tract or skin infection.

Further laboratory evaluation should include measurement of serum creatinine, creatinine clearance, and, when proteinuria in the urine is 2+ or greater, a 24-hour urine protein determination. Although these tests will quantitate the specific degree of renal dysfunction, further tests are usually required to establish the specific diagnosis and particularly to determine whether the disease is due to an immune or a nonimmune etiology. **Frequently, a renal biopsy is necessary to establish the precise diagnosis, and biopsies are particularly important if the result will influence subsequent treatment of the patient.** Renal biopsies are extremely informative when examined by an experienced pathologist using light, immunofluorescent, and electron microscopy.

An algorithm for the evaluation of glomerular hematuria is provided in Figure 3–6.

IgA Nephropathy (Berger Disease). IgA nephropathy, or Berger disease, is the most common cause of glomerular hematuria, accounting for about 30% of cases (Fassett et al, 1982). Therefore it is described in greater detail in this section. IgA nephropathy occurs most commonly in children and young adults, with a male predominance (Berger and Hinglais, 1968). Patients typically present with hematuria after an upper respiratory tract infection or exercise. Hematuria may be associated with a low-grade fever or rash, but most patients have no associated systemic symptoms. Gross hematuria occurs intermittently, but microscopic hematuria is a constant finding in some patients. The disease is chronic, but the prognosis in most patients is excellent. Renal function remains normal in the majority, but about 25% will subsequently develop renal insufficiency. An older age at onset, initial abnormal renal function, consistent proteinuria, and hypertension are indicators of a poor prognosis (D'Amico, 1988).

The pathologic findings in Berger disease are limited to either focal glomeruli or lobular segments of a glomerulus. The changes are proliferative and usually confined to mesangial cells (Berger and Hinglais, 1968). Renal biopsy reveals deposits of IgA, IgG, and β_{1c}-globulin, although IgA and IgG mesangial deposits are found in other forms of glomerulonephritis as well. The role of IgA in the disease remains uncertain, although the deposits may trigger an inflammatory reaction within the glomerulus (van den Wall Bake et al, 1989). Because gross hematuria frequently follows an upper respiratory tract infection, a viral etiology has been suspected but not established. The frequent association between hematuria and exercise in this condition remains unexplained.

The clinical presentation of IgA glomerulonephritis is alarming and similar to certain systemic diseases including Schönlein-Henoch purpura, systemic lupus erythematosus, bacterial endocarditis, and Goodpasture syndrome. Therefore a careful clinical and laboratory evaluation is indicated to establish the correct diagnosis. The presence of red blood cell casts establishes the glomerular origin of the hematuria. In the absence of casts, a urologic evaluation is indicated to exclude the urinary tract as a source of bleeding and to confirm that the hematuria is arising from both kidneys. The diagnosis of IgA nephropathy is confirmed by renal biopsy demonstrating the classic deposits of immunoglobulins in mesangial cells, as described previously. Once the diagnosis has been established, repeat evaluations for hematuria are generally not indicated. Although there is no effective treatment for this condition, renal function remains stable in most patients and there are no other known long-term complications.

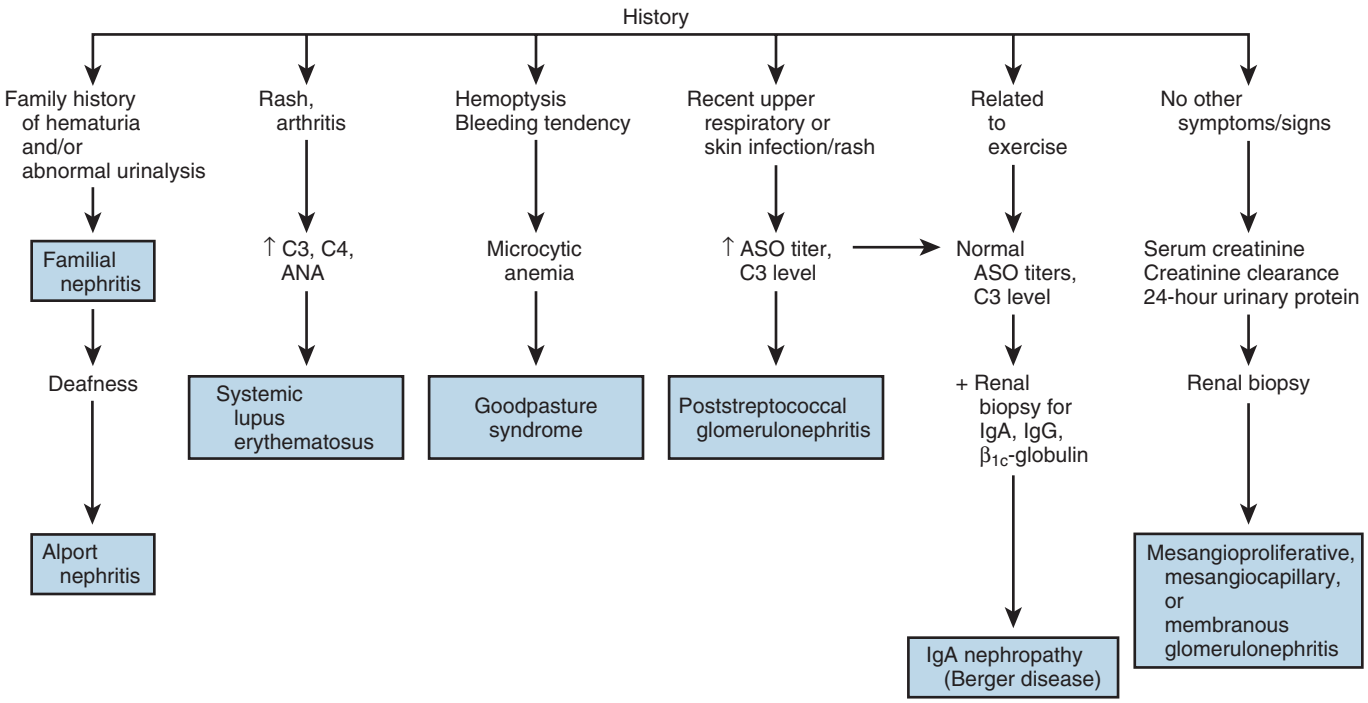


Figure 3–6. Evaluation of glomerular hematuria (dysmorphic erythrocytes, erythrocyte casts, and proteinuria). ANA, antinuclear antibody; ASO, antistreptolysin O; Ig, immunoglobulin.

Nonglomerular Hematuria

Medical. Except for renal tumors, nonglomerular hematuria of renal origin is secondary to either tubulointerstitial, renovascular, or systemic disorders. **The urinalysis in nonglomerular hematuria is distinguished from that of glomerular hematuria by the presence of circular erythrocytes and the absence of erythrocyte casts.** Like glomerular hematuria, nonglomerular hematuria of renal origin is frequently associated with significant proteinuria, which distinguishes these nephrologic diseases from urologic diseases in which the degree of proteinuria is usually minimal, even with heavy bleeding.

As with glomerular hematuria, a careful history frequently helps establish the diagnosis. A family history of hematuria or bleeding tendency suggests the diagnosis of a blood dyscrasia, which should be investigated further. A family history of urolithiasis associated with intermittent hematuria may indicate stone disease, which should be investigated with serum and urine measurements of calcium and uric acid. A family history of renal cystic disease should prompt further radiologic evaluation for medullary sponge kidney and adult polycystic kidney disease. **Papillary necrosis as a cause of hematuria should be considered in diabetics, African Americans (secondary to sickle cell disease or trait), and suspected analgesic abusers.**

Medications may induce hematuria, particularly anticoagulants. **Anticoagulation at normal therapeutic levels, however, does not predispose patients to hematuria.** In one study, the prevalence of hematuria was 3.2% in anticoagulated patients versus 4.8% in a control group. Urologic disease was identified in 81% of patients with more than one episode of microscopic hematuria, and the cause of hematuria did not vary between groups (Culclasure et al, 1994). Thus anticoagulant therapy per se does not appear to increase the risk of hematuria unless the patient is excessively anticoagulated.

Exercise-induced hematuria is being observed with increasing frequency. It typically occurs in long-distance runners (>10 km), is usually noted at the conclusion of the run, and rapidly disappears with rest. The hematuria may be of renal or bladder origin. An increased number of dysmorphic erythrocytes have been noted in some patients, suggesting a glomerular origin. Exercise-induced hematuria may be the first sign of underlying glomerular disease such as IgA nephropathy. Conversely, cystoscopy in patients with exercise-induced hematuria frequently reveals punctate hemorrhagic lesions in the bladder, suggesting that the hematuria is of bladder origin.

Vascular disease may also result in nonglomerular hematuria. Renal artery embolism and thrombosis, arteriovenous fistulas, and renal vein thrombosis may all result in hematuria. Physical examination may reveal severe hypertension, a flank or abdominal bruit, or atrial fibrillation. In such patients, further evaluation for renal vascular disease should be undertaken.

An algorithm for the evaluation of nonglomerular hematuria is provided in Figure 3–7.

Surgical. Nonglomerular hematuria or essential hematuria includes primarily urologic rather than nephrologic diseases. Common causes of essential hematuria include urologic tumors, stones, and UTIs.

The urinalysis in both nonglomerular medical and surgical hematuria is similar in that both are characterized by circular erythrocytes and the absence of erythrocyte casts. Essential hematuria is suggested, however, by the absence of significant proteinuria usually found in nonglomerular hematuria of renal parenchymal origin. It should be remembered, however, that proteinuria is not always present in glomerular or nonglomerular renal disease.

The American Urological Association (AUA) Best Practice Policy Panel on Microscopic Hematuria has formulated practice recommendations for the detection and evaluation of asymptomatic microscopic hematuria (Grossfeld et al, 2001a, 2001b). The panel concluded that, due to the lack of specificity of urinary dipstick examination, as well as the risk and expense of evaluation, patients with a positive dipstick test should only undergo complete evaluation for hematuria if this is confirmed by the finding of 3 or more RBC/HPF on subsequent microscopic evaluation. The mainstays of evaluation, according to the panel, are voided urinary cytology, cystoscopy, and urinary tract imaging using ultrasonography, CT, and/or intravenous urography (IVU). The use of these tests in an individual patient should be based in most cases on the relative risk of significant urinary tract pathology.

An algorithm for the evaluation of essential hematuria is provided in Figure 3–8.

Proteinuria

Although healthy adults excrete 80 to 150 mg of protein in the urine daily, the qualitative detection of proteinuria in the urinalysis should raise the suspicion of underlying renal disease. **Proteinuria may be the first indication of renovascular, glomerular, or tubulointerstitial renal disease, or it may represent the overflow of abnormal proteins into the urine in conditions such as multiple myeloma.** Proteinuria can also occur secondary to nonrenal disorders and in response to various physiologic conditions such as strenuous exercise.

The protein concentration in the urine obviously depends on the state of hydration, but it seldom exceeds 20 mg/dL. In patients with dilute urine, however, significant proteinuria may be present at concentrations less than 20 mg/dL. **Normally, urine protein is about 30% albumin, 30% serum globulins, and 40% tissue proteins, of which the major component is Tamm-Horsfall protein.** This profile may be altered by conditions that affect glomerular filtration, tubular reabsorption, or excretion of urine protein, and determination of the urine protein profile by such techniques as protein electrophoresis may help determine the etiology of proteinuria.

Pathophysiology. **Most causes of proteinuria can be categorized into one of three categories: glomerular, tubular, or overflow. Glomerular proteinuria is the most common type of proteinuria and results from increased glomerular capillary permeability to protein, especially albumin.** Glomerular proteinuria occurs in any of the primary glomerular diseases such as IgA nephropathy or in glomerulopathy associated with systemic illness such as diabetes mellitus. Glomerular disease should be suspected when the 24-hour urine protein excretion exceeds 1 g and is almost certain to exist when the total protein excretion exceeds 3 g.

Tubular proteinuria results from failure to reabsorb normally filtered proteins of low molecular weight such as immunoglobulins. In tubular proteinuria, the 24-hour urine protein loss seldom exceeds 2 to 3 g and the excreted proteins are of low molecular weight rather than albumin. Disorders that lead to tubular proteinuria are commonly associated with other defects of proximal tubular function such as glucosuria, aminoaciduria, phosphaturia, and uricosuria (Fanconi syndrome).

Overflow proteinuria occurs in the absence of any underlying renal disease and is due to an increased plasma concentration of abnormal immunoglobulins

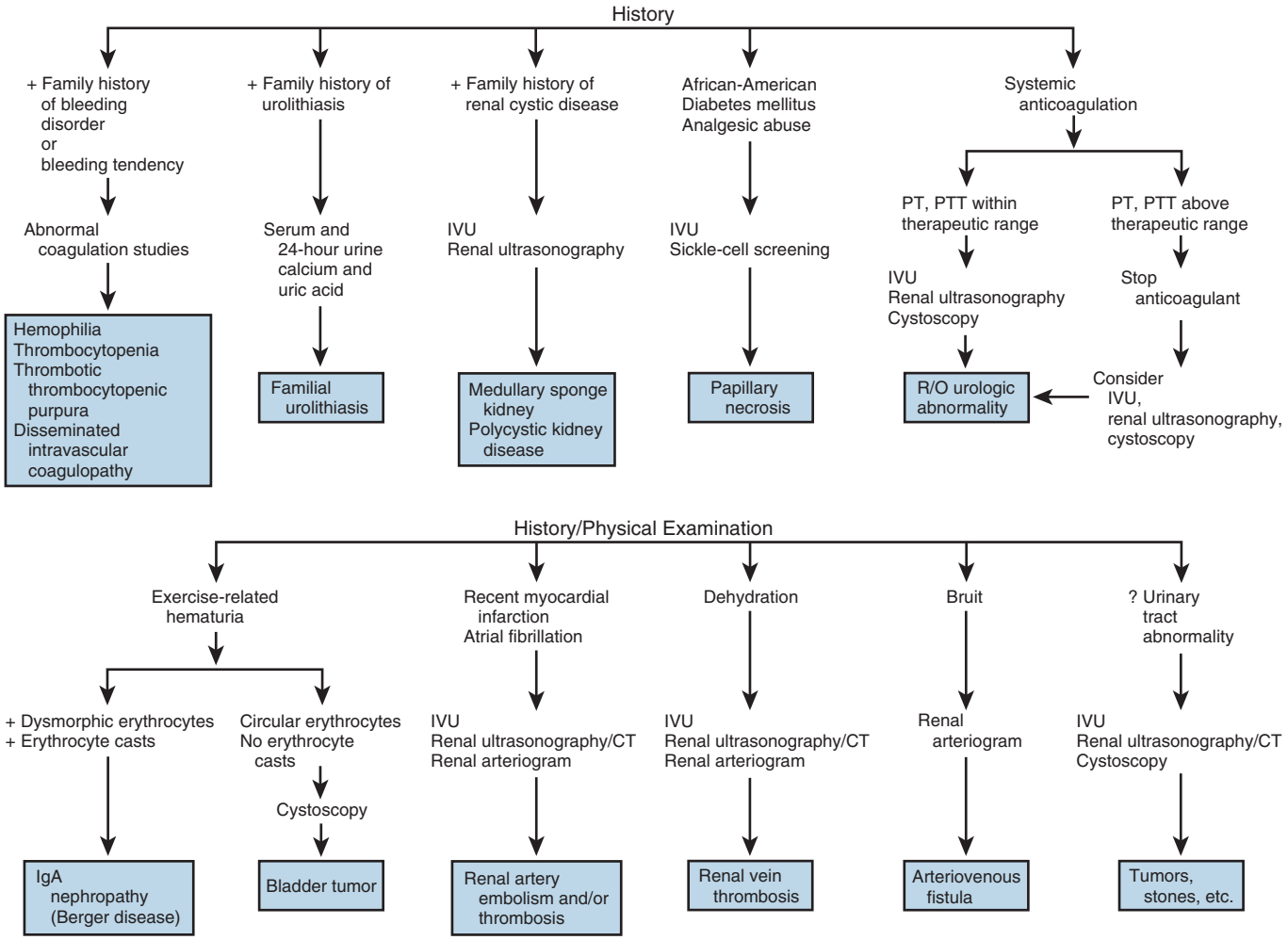


Figure 3–7. Evaluation of nonglomerular renal hematuria (circular erythrocytes, no erythrocyte casts, and proteinuria). CT, computed tomography; IgA, immunoglobulin A; IVU, intravenous urography; PT, prothrombin time; PTT, partial thromboplastin time; R/O, rule out.

and other low-molecular-weight proteins. The increased serum levels of abnormal proteins result in excess glomerular filtration that exceeds tubular reabsorptive capacity. The most common cause of overflow proteinuria is multiple myeloma, in which large amounts of immunoglobulin light chains are produced and appear in the urine (Bence Jones protein).

Detection. Qualitative detection of abnormal proteinuria is most easily accomplished with a dipstick impregnated with tetrabromophenol blue dye. The color of the dye changes in response to a pH shift related to the protein content of the urine, mainly albumin, leading to the development of a blue color. Because the background of the dipstick is yellow, various shades of green will develop, and the darker the green, the greater the concentration of protein in the urine. The minimal detectable protein concentration by this method is 20 to 30 mg/dL. **False-negative results can occur in alkaline urine, dilute urine, or when the primary protein present is not albumin.** Nephrotic range proteinuria in excess of 1 g/24 hr, however, is seldom missed on qualitative screening. Precipitation of urinary proteins with strong acids such as 3% sulfosalicylic acid will detect proteinuria at concentrations as low as 15 mg/dL and is more sensitive at detecting other proteins and albumin. Patients whose urine is negative on dipstick but strongly positive with sulfosalicylic acid should be suspected of having multiple myeloma, and the urine should be tested further for Bence Jones protein.

If qualitative testing reveals proteinuria, this should be quantitated with a 24-hour urinary collection. Further qualitative assessment of abnormal urinary proteins can be accomplished by either protein electrophoresis or immunoassay for specific proteins. **Protein electrophoresis is particularly helpful in distinguishing glomerular from tubular proteinuria. In glomerular proteinuria, albumin makes up about 70% of the total protein excreted, whereas in tubular proteinuria, the major proteins excreted are immunoglobulins with albumin making up only 10% to 20%. Immunoassay is the method of choice for detecting specific proteins such as Bence Jones protein in multiple myeloma.**

Evaluation. Proteinuria should first be classified by its timing into transient, intermittent, or persistent. Transient proteinuria occurs commonly, especially in the pediatric population, and usually resolves spontaneously within a few days (Wagner et al, 1968). It may result from fever, exercise, or emotional stress. In older patients, transient proteinuria may be due to congestive heart failure. If a nonrenal cause is identified and a subsequent urinalysis is negative, no further evaluation is necessary. Obviously, if proteinuria persists, it should be evaluated further.

Proteinuria may also occur intermittently, and this is frequently related to postural change (Robinson, 1985). Proteinuria that occurs only in the upright position is a frequent

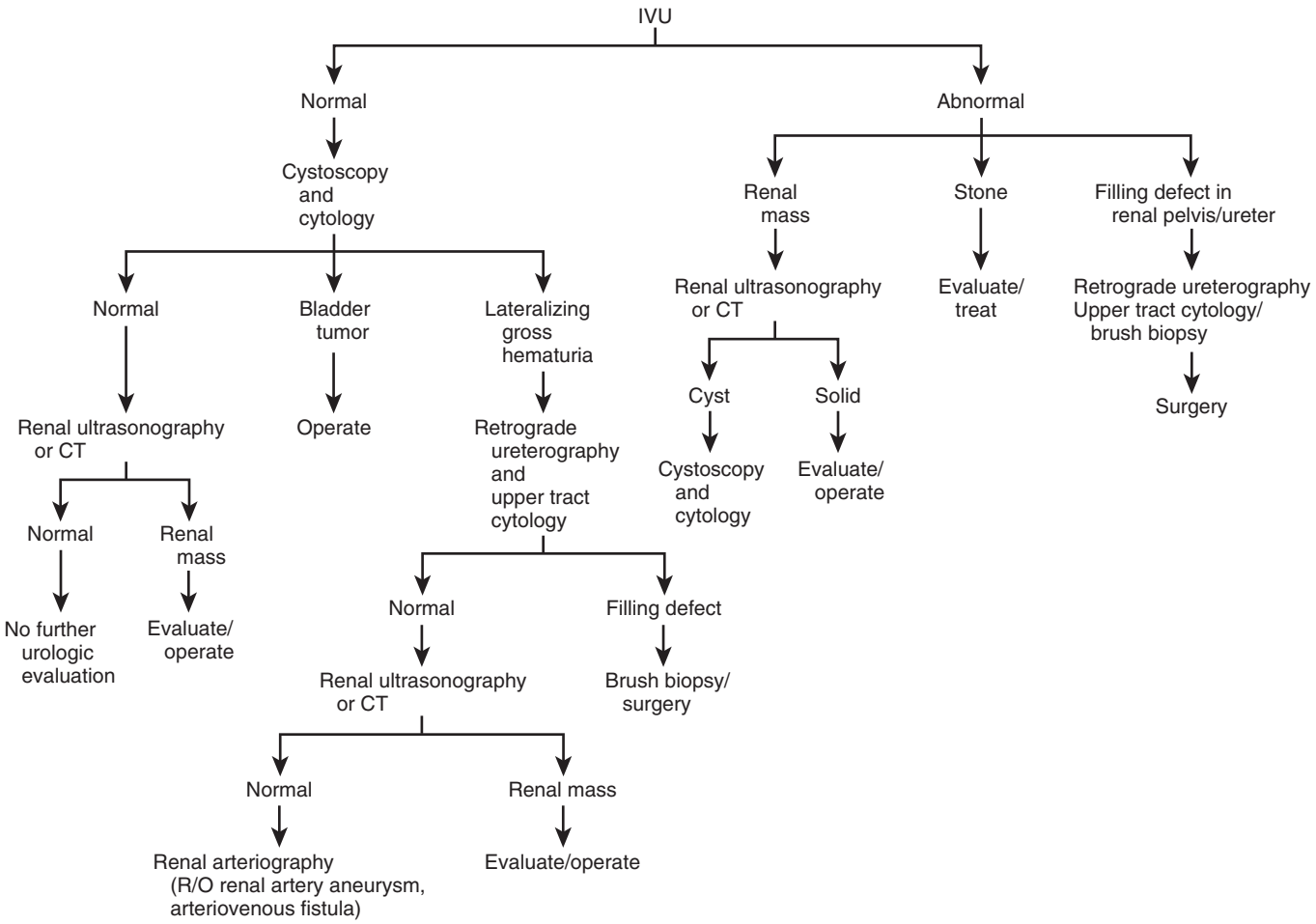


Figure 3–8. Evaluation of essential hematuria (circular erythrocytes, no erythrocyte casts, no significant proteinuria). CT, computed tomography; IVU, intravenous urography; R/O, rule out.

cause of mild, intermittent proteinuria in young males. Total daily protein excretion seldom exceeds 1 g, and urinary protein excretion returns to normal when the patient is recumbent. Orthostatic proteinuria is thought to be secondary to increased pressure on the renal vein while standing. It resolves spontaneously in about 50% of patients and is not associated with any morbidity. Therefore if renal function is normal in patients with orthostatic proteinuria, no further evaluation is indicated.

Persistent proteinuria requires further evaluation, and most cases have a glomerular etiology. A quantitative measurement of urinary protein should be obtained through a 24-hour urine collection, and a qualitative evaluation should be obtained to determine the major proteins excreted. The findings of greater than 2 g of protein excreted per 24 hours, of which the major components are high-molecular-weight proteins such as albumin, establish the diagnosis of glomerular proteinuria. Glomerular proteinuria is the most common cause of abnormal proteinuria, especially in patients presenting with persistent proteinuria. If glomerular proteinuria is associated with hematuria characterized by dysmorphic erythrocytes and erythrocyte casts, the patient should be evaluated as outlined previously for glomerular hematuria (see Fig. 3–6). Patients with glomerular proteinuria who have no or little associated hematuria should be evaluated for other conditions, of which the most common is diabetes mellitus. Other possibilities include amyloidosis and arteriolar nephrosclerosis.

In patients in whom total protein excretion is 300 to 2000 mg/day, of which the major components are low-molecular-weight globulins, further qualitative evaluation with immunoelectrophoresis is indicated. This will determine whether the excess proteins are normal or abnormal. Identification of normal proteins establishes a diagnosis of tubular proteinuria, and further evaluation for a specific cause of tubular dysfunction is indicated.

If qualitative evaluation reveals abnormal proteins in the urine, this establishes a diagnosis of overflow proteinuria. Further evaluation should be directed to identify the specific protein abnormality. The finding of large quantities of light-chain immunoglobulins or Bence Jones protein establishes a diagnosis of multiple myeloma. Similarly, the finding of large amounts of hemoglobin or myoglobin establishes the diagnosis of hemoglobinuria or myoglobinuria.

An algorithm for the evaluation of proteinuria is provided in Figure 3–9.

Glucose and Ketones

Urine testing for glucose and ketones is useful in screening patients for diabetes mellitus. Normally, almost all the glucose filtered by the glomeruli is reabsorbed in the proximal tubules. Although small amounts of glucose may normally be excreted in the urine, these amounts are not clinically significant and are below the level of detectability with the dipstick. If, however, the amount of

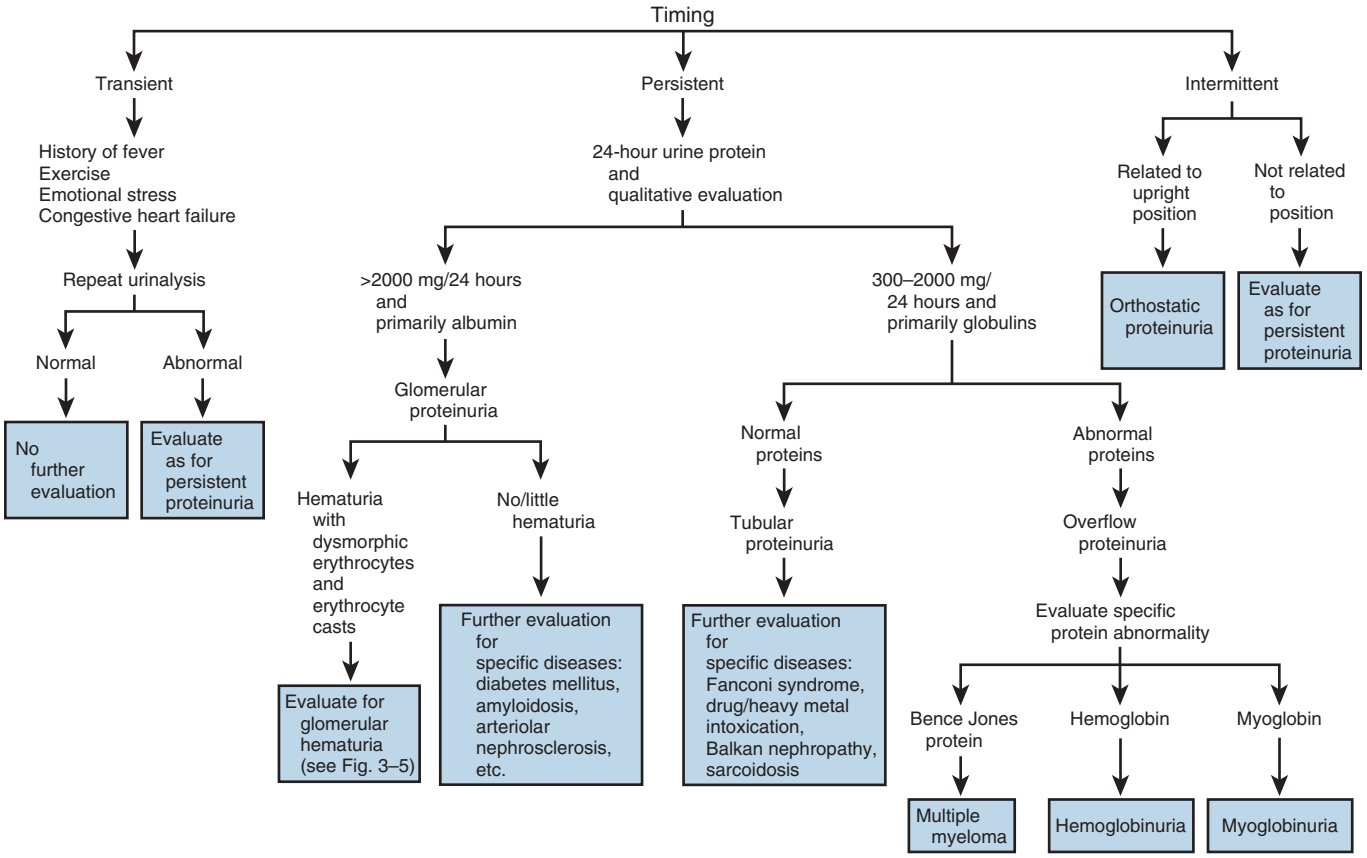


Figure 3–9. Evaluation of proteinuria.

glucose filtered exceeds the capacity of tubular reabsorption, glucose will be excreted in the urine and detected on the dipstick. **This so-called renal threshold corresponds to serum glucose of about 180 mg/dL; above this level, glucose will be detected in the urine.**

Glucose detection with the urinary dipstick is based on a double sequential enzymatic reaction yielding a colorimetric change. In the first reaction, glucose in the urine reacts with glucose oxidase on the dipstick to form gluconic acid and hydrogen peroxide. In the second reaction, hydrogen peroxide reacts with peroxidase, causing oxidation of the chromogen on the dipstick, producing a color change. **This double-oxidative reaction is specific for glucose, and there is no cross-reactivity with other sugars.** The dipstick test becomes less sensitive as the urine increases in specific gravity and temperature.

Ketones are not normally found in the urine but will appear when the carbohydrate supplies in the body are depleted and body fat breakdown occurs. This happens most commonly in diabetic ketoacidosis but may also occur during pregnancy and after periods of starvation or rapid weight reduction. **Ketones excreted include acetoacetic acid, acetone, and β-hydroxybutyric acid. With abnormal fat breakdown, ketones will appear in the urine before the serum.**

Dipstick testing for ketones involves a colorimetric reaction: sodium nitroprusside on the dipstick reacts with acetoacetic acid to produce a purple color. **Dipstick testing will identify acetoacetic acid at concentrations of 5 to 10 mg/dL but will not detect acetone or β-hydroxybutyric acid.** Obviously, a dipstick that tests positively for glucose should also be tested for ketones, and diabetes mellitus is suggested. False-positive results, however, can occur in acidic urine of high specific gravity, in abnormally colored urine, and in urine containing levodopa metabolites, 2-mercaptoethane sulfonate sodium, and other sulfhydryl-containing compounds (Csako, 1987).

Bilirubin and Urobilinogen

Normal urine contains no bilirubin and only small amounts of urobilinogen. There are two types of bilirubin, direct (conjugated) and indirect. Direct bilirubin is made in the hepatocyte, where bilirubin is conjugated with glucuronic acid. **Conjugated bilirubin has a low molecular weight, is water soluble, and normally passes from the liver into the small intestine through the bile ducts, where it is converted to urobilinogen. Therefore conjugated bilirubin does not appear in the urine except in pathologic conditions in which there is intrinsic hepatic disease or obstruction of the bile ducts.**

Indirect bilirubin is of high molecular weight and bound in the serum to albumin. It is water insoluble and therefore does not appear in the urine even in pathologic conditions.

Urobilinogen is the end product of conjugated bilirubin metabolism. Conjugated bilirubin passes through the bile ducts, where it is metabolized by normal intestinal bacteria to urobilinogen. Normally, about 50% of the urobilinogen is excreted in the stool and 50% reabsorbed into the enterohepatic circulation. A small amount of absorbed urobilinogen, about 1 to 4 mg/day, will escape hepatic uptake and be excreted in the urine. Hemolysis and hepatocellular diseases that lead to increased bile pigments can result in increased urinary urobilinogen. Conversely,

obstruction of the bile duct or antibiotic usage that alters intestinal flora, thereby interfering with the conversion of conjugated bilirubin to urobilinogen, will decrease urobilinogen levels in the urine. In these conditions, obviously, serum levels of conjugated bilirubin rise.

There are different dipstick reagents and methods to test for both bilirubin and urobilinogen, but the basic physiologic principle involves the binding of bilirubin or urobilinogen to a diazonium salt to produce a colorimetric reaction. False-negative results can occur in the presence of ascorbic acid, which decreases the sensitivity for detection of bilirubin. False-positive results can occur in the presence of phenazopyridine because it colors the urine orange and, similar to the colorimetric reaction for bilirubin, turns red in an acid medium.

Leukocyte Esterase and Nitrite Tests

Leukocyte esterase activity indicates the presence of white blood cells in the urine. The presence of nitrites in the urine is strongly suggestive of bacteriuria. Thus both of these tests have been used to screen patients for UTIs. Although these tests may have application in nonurologic medical practice, the most accurate method to diagnose infection is by microscopic examination of the urinary sediment to identify pyuria and subsequent urine culture. All urologists should be capable of performing and interpreting the microscopic examination of the urinary sediment. Therefore leukocyte esterase and nitrite testing are less important in a urologic practice. For purposes of completion, however, both techniques are described briefly herein.

Leukocyte esterase and nitrite testing are performed using the Chemstrip LN dipstick. Leukocyte esterase is produced by neutrophils and catalyzes the hydrolysis of an indoxyl carbonic acid ester to indoxyl (Gillenwater, 1981). The indoxyl formed oxidizes a diazonium salt chromogen on the dipstick to produce a color change. It is recommended that leukocyte esterase testing be done 5 minutes after the dipstick is immersed in the urine to allow adequate incubation (Shaw et al, 1985). The sensitivity of this test subsequently decreases with time because of lysis of the leukocytes. Leukocyte esterase testing may also be negative in the presence of infection because not all patients with bacteriuria will have significant pyuria. Therefore if one uses leukocyte esterase testing to screen patients for UTI, it should always be done in conjunction with nitrite testing for bacteriuria (Pels et al, 1989).

Other causes of false-negative results with leukocyte esterase testing include increased urinary specific gravity, glycosuria, presence of urobilinogen, medications that alter urine color, and ingestion of large amounts of ascorbic acid. **The major cause of false-positive leukocyte esterase tests is specimen contamination.**

Nitrites are not normally found in the urine, but many species of gram-negative bacteria can convert nitrates to nitrites. Nitrites can readily be detected in the urine because they react with the reagents on the dipstick and undergo diazotization to form a red azo dye. The specificity of the nitrite dipstick for detecting bacteriuria is higher than 90% (Pels et al, 1989). The sensitivity of the test, however, is considerably less, varying from 35% to 85%. The nitrite test is less accurate in urine specimens containing fewer than 10^5 organisms/mL (Kellog et al, 1987). As with leukocyte esterase testing, the major cause of false-positive nitrite testing is contamination.

It remains controversial whether dipstick testing for leukocyte esterase and nitrites can replace microscopy in screening for significant UTIs. This issue is less important to urologists, who usually have access to a microscope and who should be trained and encouraged to examine the urinary sediment. **A protocol combining the visual appearance of the urine with leukocyte esterase and nitrite testing has been proposed** (Fig. 3–10). It reportedly detects 95% of infected urine specimens and decreases the need for microscopy by as much as 30% (Flanagan et al, 1989). Other studies, however, have shown that dipstick testing is not an adequate replacement for microscopy (Propp et al, 1989). In summary, it has not been demonstrated conclusively that dipstick testing for UTI can replace microscopic examination of the urinary sediment. In our personal experience, we always examine the urinary sediment whenever we suspect a UTI and subsequently culture the urine when pyuria is identified.

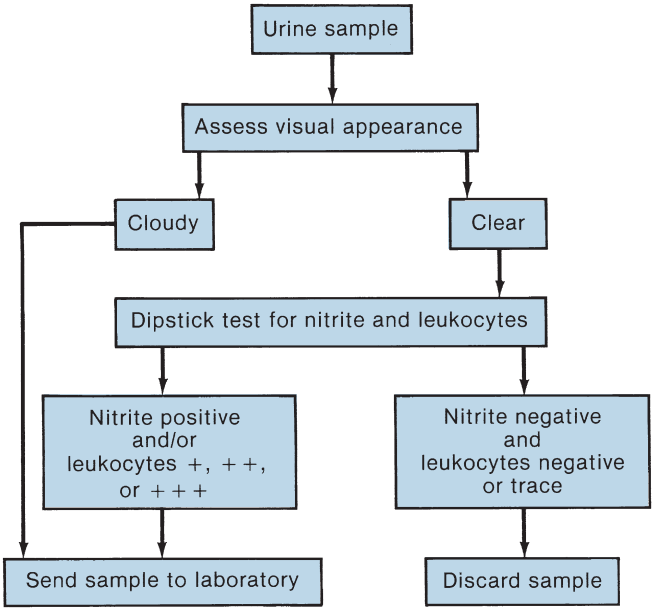


Figure 3–10. Protocol for determining the need for urine sediment microscopy in an asymptomatic population. (From Flanagan PG, Rooney PG, Davies EA, Stout RW. Evaluation of four screening tests for bacteriuria in elderly people. Lancet 1989;1:1117. © by The Lancet Ltd., 1989.)

Urinary Sediment

Obtaining and Preparing the Specimen

A clean-catch midstream urine specimen should be obtained. As described earlier, uncircumcised men should retract the prepuce and cleanse the glans penis before voiding. It is more difficult to obtain a reliable clean-catch specimen in females because of contamination with introital leukocytes and bacteria. If there is any suspicion of a UTI in a female, a catheterized urine sample should be obtained for culture and sensitivity.

If possible, **the first morning urine specimen is the specimen of choice and should be examined within 1 hour.** A standard procedure for preparation of the urine for microscopic examination has been described (Cushner and Copley, 1989). Ten to 15 milliliters of urine should be centrifuged for 5 minutes at 3000 rpm. The supernatant is then poured off, and the sediment is resuspended in the centrifuge tube by gently tapping the bottom of the tube. Although the remaining small amount of fluid can be poured onto a microscope slide, this usually results in excess fluid

on the slide. It is better to use a small pipette to withdraw the residual fluid from the centrifuge tube and to place it directly on the microscope slide. This usually results in an ideal volume of between 0.01 and 0.02 mL of fluid deposited on the slide. The slide is then covered with a coverslip. The edge of the coverslip should be placed on the slide first to allow the drop of fluid to ascend onto the coverslip by capillary action. The coverslip is then gently placed over the drop of fluid, and this technique allows for most of the air between the drop of fluid and the coverslip to be expelled. If one simply drops the coverslip over the urine, the urine will disperse over the slide and there will be a considerable number of air bubbles that may distort the subsequent microscopic examination.

Microscopy Technique

Microscopic analysis of the urinary sediment should be performed with both low-power (×100 magnification) and high-power (×400 magnification) lenses. The use of an oil immersion lens for higher magnification is seldom, if ever, necessary. Under low power, the entire area under the coverslip should be scanned. **Particular attention should be given to the edges of the coverslip, where casts and other elements tend to be concentrated.** Low-power magnification is sufficient to identify erythrocytes, leukocytes, casts, cystine crystals, oval fat macrophages, and parasites such as *Trichomonas vaginalis* and *Schistosoma hematobium*.

High-power magnification is necessary to distinguish circular from dysmorphic erythrocytes, to identify other types of crystals, and, particularly, to identify bacteria and yeast. In summary, **the urinary sediment should be examined microscopically for (1) cells, (2) casts, (3) crystals, (4) bacteria, (5) yeast, and (6) parasites.**

Cells

Erythrocyte morphology may be determined under high-power magnification. Although phase contrast microscopy has been used for this purpose, circular (nonglomerular) erythrocytes can generally be distinguished from dysmorphic (glomerular) erythrocytes under routine brightfield high-power magnification (Figs. 3–11 to 3–15). **This is assisted by adjusting the microscope condenser to its lowest aperture, thus reducing the intensity of background light. This allows one to see fine detail not evident otherwise and also creates the effect of phase microscopy because cell membranes and other sedimentary components stand out against the darkened background.**

Circular erythrocytes generally have an even distribution of hemoglobin with either a round or crenated contour, whereas dysmorphic erythrocytes are irregularly shaped with minimal hemoglobin and irregular distribution of cytoplasm. Automated techniques for performing microscopic analysis to distinguish the two types of erythrocytes have been investigated but have not yet been accepted into general urologic practice and are probably unnecessary. In one study using a standard Coulter counter, microscopic analysis was found to be 97% accurate in differentiating between the two types of erythrocytes (Sayer et al, 1990). **Erythrocytes may be confused with yeast or fat droplets** (Fig. 3–16). Erythrocytes can be distinguished, however, because yeast will show budding and oil droplets are highly refractile.

Leukocytes can generally be identified under low power and definitively diagnosed under high-power magnification (Figs. 3–17 and 3–18; see also Fig. 3–16). It is normal to find 1 or 2 leukocytes/

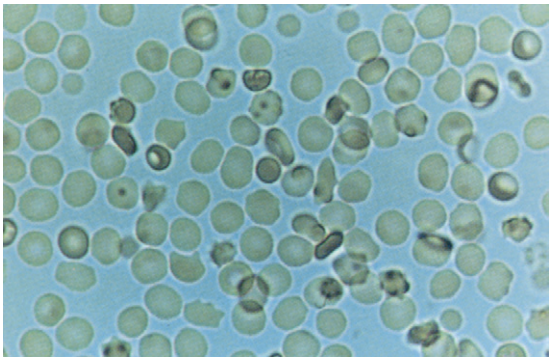


Figure 3–11. Red blood cells, both smoothly rounded and mildly crenated, typical of epithelial erythrocytes.

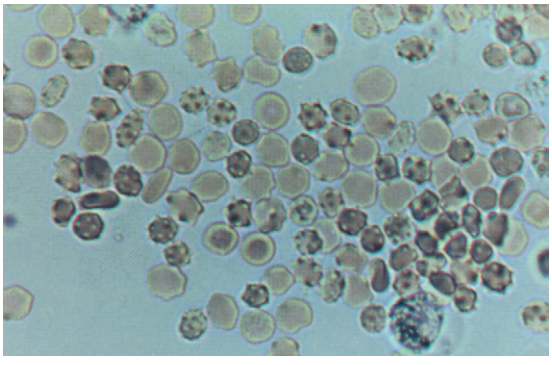


Figure 3–12. Red blood cells from a patient with a bladder tumor.

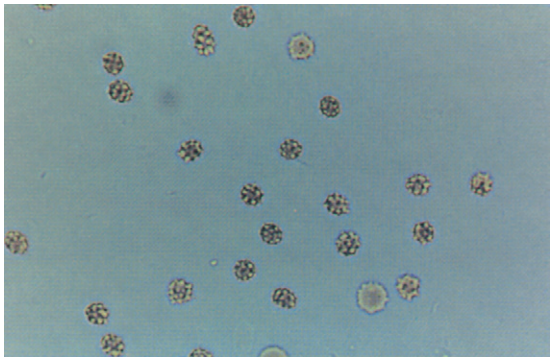


Figure 3–13. Red blood cells from a patient with interstitial cystitis. Cells were collected at cystoscopy.

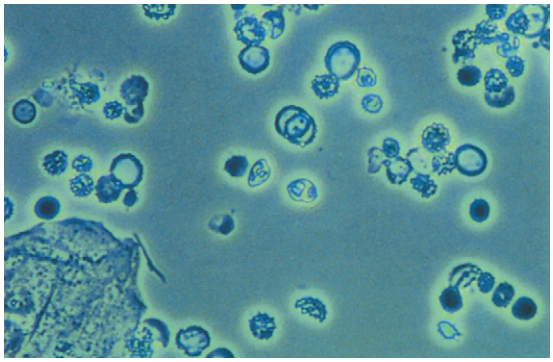


Figure 3–14. Red blood cells from a patient with Berger disease. Note variations in membranes characteristic of dysmorphic red blood cells.

HPF in men and up to 5/HPF in women in whom the urine sample may be contaminated with vaginal secretions. A greater number of leukocytes generally indicates infection or inflammation in the urinary tract. It may be possible to distinguish **old leukocytes, which have a characteristic small and wrinkled appearance** and which are commonly found in the vaginal secretions of normal women, from fresh leukocytes, which are generally indicative of urinary tract pathology. Fresh leukocytes are generally larger and rounder, and, when the specific gravity is less than 1.019, the granules in the cytoplasm demonstrate glitter-like movement, so-called glitter cells.

Epithelial cells are commonly observed in the urinary sediment. Squamous cells are frequently detected in female urine specimens and are derived from the lower portion of the urethra, the trigone of postpubertal females, and the vagina. **Squamous epithelial cells are large, have a central small nucleus about the size of an erythrocyte, and have an irregular cytoplasm with fine granularity.**

Transitional epithelial cells may arise from the remainder of the urinary tract (Fig. 3–19). Transitional cells are smaller than squamous cells, have a larger nucleus, and demonstrate prominent cytoplasmic granules near the nucleus. Malignant transitional cells have altered nuclear size and morphology and can be identified with either routine Papanicolaou staining or automated flow cytometry.

Renal tubular cells are the least commonly observed epithelial cells in the urine but are most significant because their presence in the urine is always indicative of renal pathology. Renal tubular cells may be difficult to distinguish from leukocytes, but they are slightly larger.

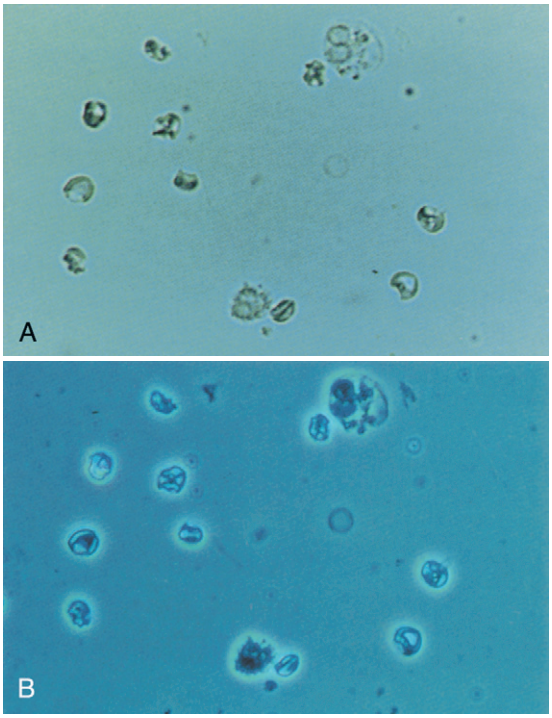


Figure 3–15. Dysmorphic red blood cells from a patient with Wegener granulomatosis. **A,** Brightfield illumination. **B,** Phase illumination. Note irregular deposits of dense cytoplasmic material around the cell membrane.

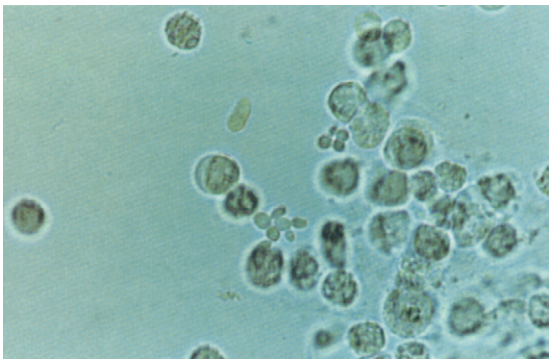


Figure 3–16. *Candida albicans*. Budding forms surrounded by leukocytes.

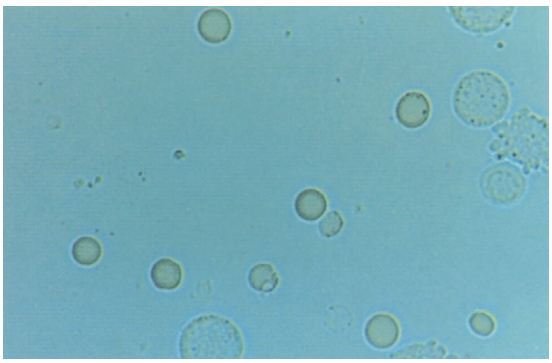


Figure 3–18. Fresh "glitter cells" with erythrocytes in background.

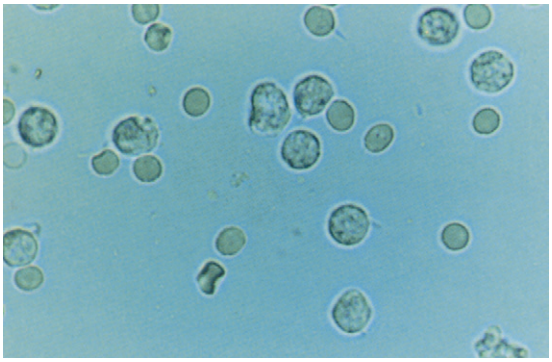


Figure 3–17. Old leukocytes. Staghorn calculi with *Proteus* infection.

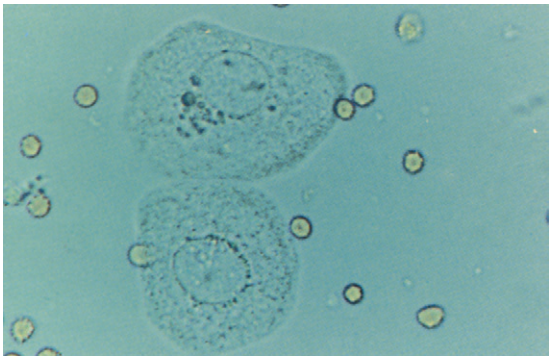


Figure 3–19. Transitional epithelial cells from bladder lavage.

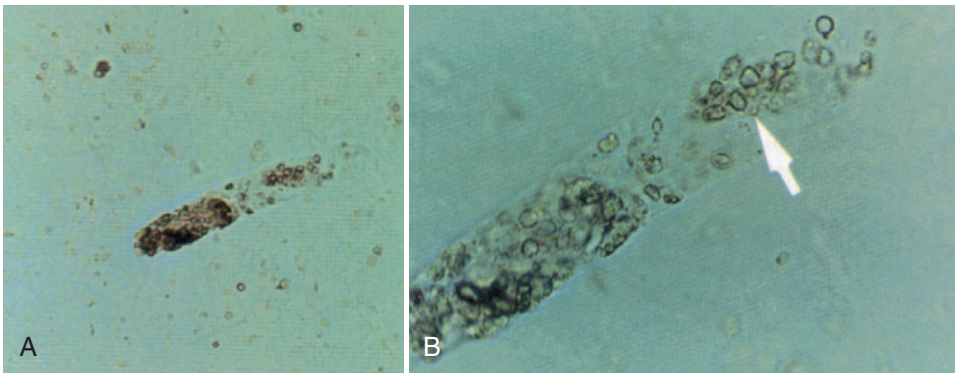


Figure 3–20. Red blood cell cast. **A,** Low-power view demonstrates distinct border of hyaline matrix. **B,** High-power view demonstrates the sharply defined red blood cell membranes *(arrow)*. Berger disease.

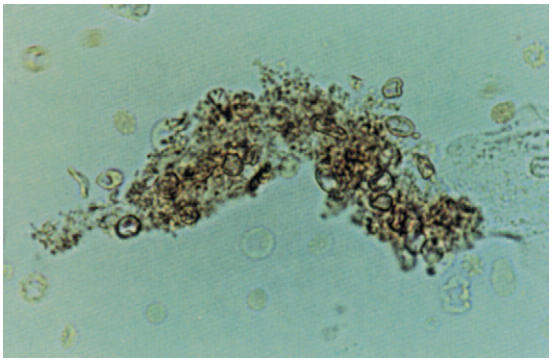


Figure 3–21. Red blood cell cast.

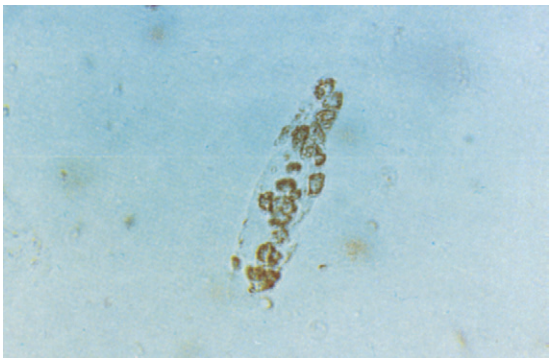


Figure 3–22. Cellular cast. Cells entrapped in a hyaline matrix.

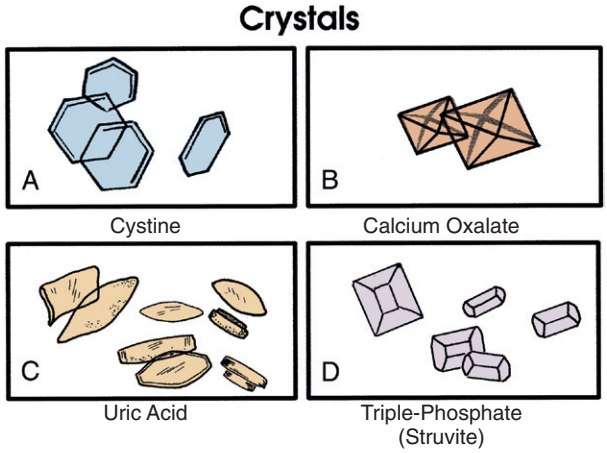


Figure 3–23. Urinary crystals. **A,** Cystine. **B,** Calcium oxalate. **C,** Uric acid. **D,** Triple phosphate (struvite).

Casts

A cast is a protein coagulum that is formed in the renal tubule and traps any tubular luminal contents within the matrix. **Tamm-Horsfall mucoprotein is the basic matrix of all renal casts; it originates from tubular epithelial cells and is always present in the urine.** When the casts contain only mucoproteins, they are called hyaline casts and may not have any pathologic significance. Hyaline casts may be seen in the urine after exercise or heat exposure but may also be observed in pyelonephritis or chronic renal disease.

Red blood cell casts contain entrapped erythrocytes and are diagnostic of glomerular bleeding, most likely secondary to glomerulonephritis (Figs. 3–20 and 3–21). White blood cell casts are observed in acute glomerulonephritis, acute pyelonephritis, and acute tubulointerstitial nephritis. Casts with other cellular elements, usually sloughed renal tubular epithelial cells, are indicative of nonspecific renal damage (Fig. 3–22). Granular and waxy casts result from further degeneration of cellular elements. Fatty casts are seen in nephrotic syndrome, lipiduria, and hypothyroidism.

Crystals

Identification of crystals in the urine is particularly important in patients with stone disease because it may help determine the etiology (Fig. 3–23). Although other types of crystals may be seen in normal patients, **the identification of cystine crystals establishes the diagnosis of cystinuria.** Crystals precipitated in acidic urine include calcium oxalate, uric acid, and cystine. Crystals precipitated in an alkaline urine include calcium phosphate and triple-phosphate (struvite) crystals. Cholesterol crystals are rarely seen in the urine and are not related to urinary pH. They occur in lipiduria and remain in droplet form.

Bacteria

Normal urine should not contain bacteria; and in a fresh uncontaminated specimen, the finding of bacteria is indicative of a UTI. Because each HPF views between 1/20,000 and 1/50,000 mL, each bacterium seen per HPF signifies a bacterial count of more than

30,000/mL. Therefore, **5 bacteria/HPF reflects colony counts of about 100,000/mL.** This is the standard concentration used to establish the diagnosis of a UTI in a clean-catch specimen. This level should apply only to women, however, in whom a clean-catch specimen is frequently contaminated. The finding of any bacteria in a properly collected midstream specimen from a male should be further evaluated with a urine culture.

Under high power, it is possible to distinguish various bacteria. Gram-negative rods have a characteristic bacillary shape (Fig. 3–24), whereas streptococci can be identified by their characteristic beaded chains (Figs. 3–25 and 3–26) and staphylococci can be identified when the organisms are found in clumps (Fig. 3–27).

Yeast

The most common yeast cells found in urine are *Candida albicans*. The biconcave oval shape of yeast can be confused with erythrocytes and calcium oxalate crystals, but **yeasts can be distinguished by their characteristic budding and hyphae** (see Fig. 3–16). Yeasts are most commonly seen in the urine of patients with diabetes mellitus or as contaminants in women with vaginal candidiasis.

Parasites

***Trichomonas vaginalis* is a frequent cause of vaginitis in women and occasionally of urethritis in men.** Trichomonads can be readily identified in a clean-catch specimen under low power (Fig. 3–28). Trichomonads are large cells with rapidly moving flagella that quickly propel the organism across the microscopic field.

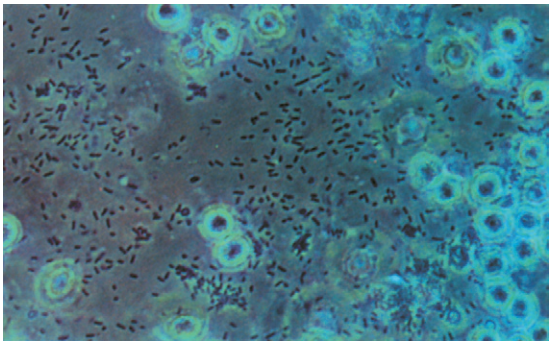


Figure 3–24. Gram-negative bacilli. Phase microscopy of *Escherichia coli.*

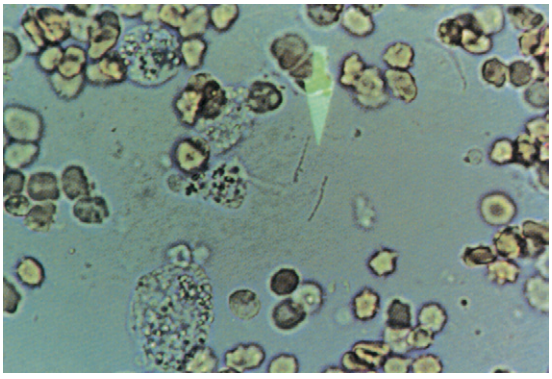


Figure 3–25. Streptococcal urinary tract infection with typical chain formation *(arrow).*

***Schistosoma hematobium* is a urinary tract pathogen that is not found in the United States but is extremely common in countries of the Middle East and North Africa. Examination of the urine shows the characteristic parasitic ova with a terminal spike.**

Expressed Prostatic Secretions

Although not strictly a component of the urinary sediment, the expressed prostatic secretions should be examined in any man suspected of having prostatitis. Normal prostatic fluid should contain few, if any, leukocytes, and the presence of a larger number or clumps of leukocytes is indicative of prostatitis. **Oval fat macrophages are found in postinfection prostatic fluid** (Figs. 3–29 and 3–30). Normal prostatic fluid contains numerous secretory granules that resemble but can be distinguished from leukocytes under high power because they do not have nuclei.

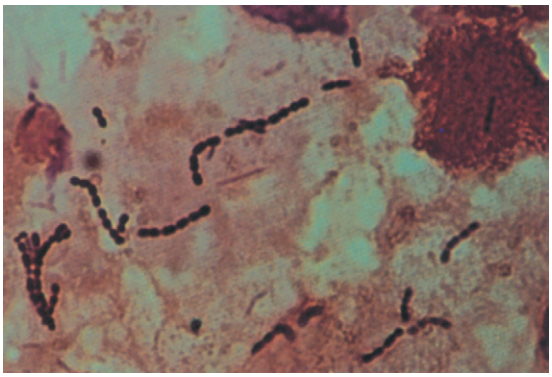


Figure 3–26. Streptococcal urinary tract infection (Gram stain).

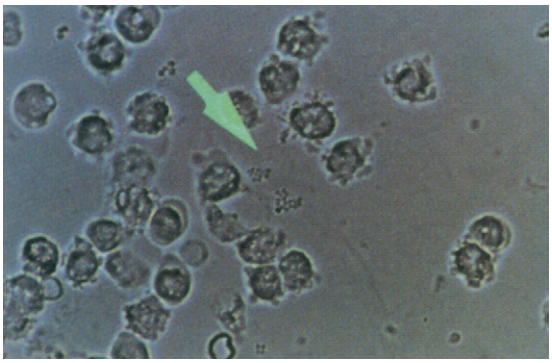


Figure 3–27. *Staphylococcus aureus* in typical clumps *(arrow).*

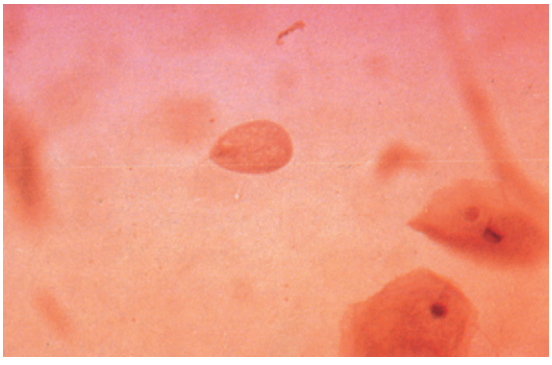


Figure 3–28. Trichomonad with ovoid shape and motile flagella.

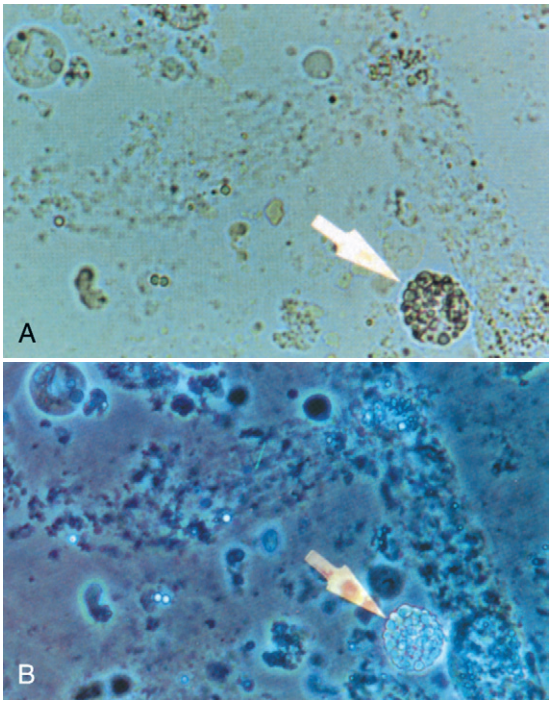


Figure 3–29. Oval fat macrophage. **A,** High-power view showing doubly refractile fat particles *(arrow)*. **B,** Phase microscopy of the same specimen *(arrow)*.

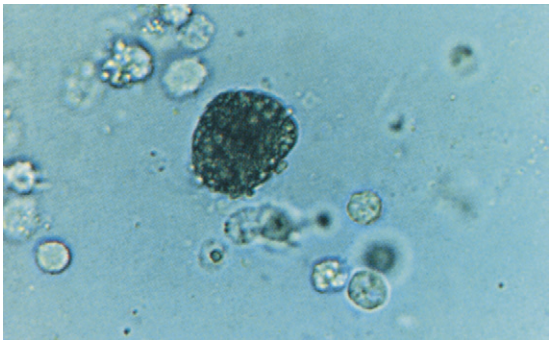


Figure 3–30. Oval fat microphage, high-power view. Note the fine secretory granules in the prostatic fluid.

SUMMARY

This chapter has detailed the basic evaluation of the urologic patient, which should include a careful history, physical examination, and urinalysis. These three basic components form the cornerstone of the urologic evaluation and should precede any subsequent diagnostic procedures. After completion of the history, physical examination, and urinalysis, the urologist should be able to establish at least a differential, if not specific, diagnosis that will allow the subsequent diagnostic evaluation and treatment to be carried out in a direct and efficient manner.

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chapter 4

Urinary Tract Imaging: Basic Principles

Pat F. Fulgham, MD, DABU, FACS ● Jay Todd Bishoff, MD, FACS

Conventional Radiography
Radiation Management in Uroradiology
Contrast Media
Intravenous Urography
Plain Abdominal Radiography
Retrograde Pyelography
Loopography
Retrograde Urethrography
Static Cystography
Voiding Cystourethrogram
Ultrasonography
Nuclear Scintigraphy
Computed Tomography
Magnetic Resonance Imaging

Imaging plays an indispensable role in the diagnosis and management of urologic diseases. Because many urologic conditions are unable to be assessed by physical examination, conventional radiography has long been critical to the diagnosis of conditions of the kidneys, ureters, and bladder. Ultrasonography revolutionized the diagnosis of prostatic disease. The urologist's familiarity with ultrasonography led to its widespread use for many conditions in the office and the operating room. The development of axial imaging and the use of intravenous contrast agents have provided detailed anatomic, functional, and physiologic information about urologic conditions. In this chapter we discuss the indications for imaging in urology with an emphasis on the underlying physical principles of the imaging modalities. The strengths and limitations of each modality, as well as the techniques necessary to maximize image quality and minimize the risks and harms to urologic patients, are discussed.

CONVENTIONAL RADIOGRAPHY

Conventional radiography, though eclipsed by axial imaging for certain indications, remains useful in a variety of urologic conditions. Conventional radiography includes abdominal plain radiography, intravenous excretory urography, retrograde pyelography, loopography, retrograde urethrography, and cystography. Urologists increasingly perform and interpret conventional radiography examinations including fluoroscopic examinations in the office and operating room environments.

Physics

It is imperative that urologists understand the physics of conventional radiography and fluoroscopy, as well as the implications of radiation exposure to the patient and the operator. The underlying physical principles of conventional radiography involve emitting a stream of photons from an x-ray source. These photons travel through the air and strike tissue, imparting energy to that tissue. Some of the photons emerge from the patient with varying amounts of energy attenuation and strike an image recorder such as a film cassette or the input phosphor of an image-intensifier tube, thus producing an image (Fig. 4–1).

RADIATION MANAGEMENT IN URORADIOLOGY

When diagnostic radiation passes through tissue, it creates ion pairs. The resultant charge per unit mass of air is referred to as the **radiation exposure.** The current unit of radiation exposure is coulombs(C)/kg. **Absorbed dose** is the energy absorbed from the radiation exposure and is measured in units called gray (Gy). The older unit of absorbed dose was called the rad (1 rad = 100 Gy).

Because different types of radiation have different types of interaction with tissue, a conversion factor is applied to better express the amount of energy absorbed by a given tissue. The application of this conversion factor to the **absorbed dose** yields the **equivalent dose** measured in sieverts (Sv). For diagnostic radiographs the conversion factor is 1, so the absorbed dose is the same as the equivalent dose. When discussing the amount of radiation energy absorbed by patients during therapeutic radiation, the dose is given in gray. When discussing exposure to patients or medical personnel due to diagnostic ionizing radiation procedures, the dose is given in sieverts.

The distribution of energy absorption in the human body will be different on the basis of the body part being imaged and various other factors. The most important risk of radiation exposure from diagnostic imaging is the development of cancer. The **effective dose** is a quantity used to denote the radiation risk (expressed in **sieverts**) to a population of patients from an imaging study.

See Table 4–1 for a description of the relationship between these measures of radiation exposure.

The average person living in the United States is exposed to 1 to 3 mSv of radiation per year from ambient sources such as radon and cosmic rays. The recommended occupational exposure limit to medical personnel is 50 mSv per year (NCRP, 1993). Exposure to the eyes and gonads has a more significant biologic impact than exposure to the extremities, so recommended exposure limits vary according to the body part. However, there is no safe dose of radiation. An effective radiation dose of as little as 10 mSv may result in the development of a malignancy in 1 of 1000 individuals exposed (NRCNA, 2006).

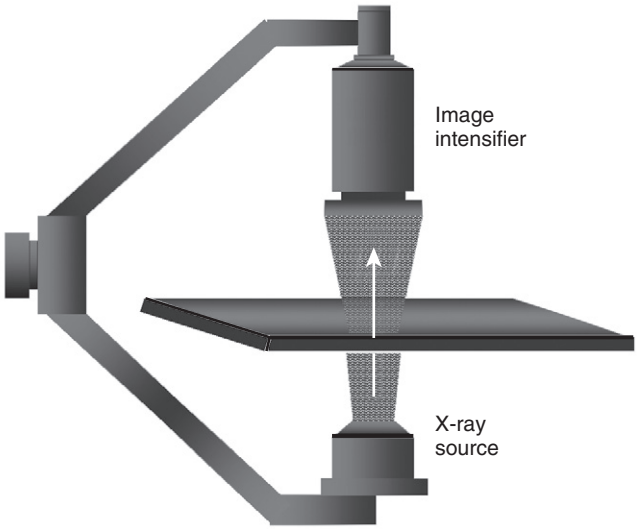


Figure 4–1. Equipment setup for fluoroscopy. The x-ray source located beneath the table reduces the radiation exposure to the proceduralist. Locating the image intensifier as close to the patient as feasible reduces scatter radiation. Equipment setup will vary on the basis of the application.

Relative Radiation Levels

The assessment of biologic risk from radiation exposure is complex. By estimating the range of effective doses for various imaging modalities, they can be assigned a **relative radiation level (RRL)** (Table 4–2).

The effective dose from a three-phase computed tomography (CT) scan of the abdomen and pelvis without and with contrast may be as high as 25 to 40 mSv. An often overlooked source of significant radiation exposure is fluoroscopy. Fluoroscopy for 1 minute results in a radiation dose to the skin equivalent to 10 times that of a single radiograph of the same anatomic area (Geise and Morin, 2000).

Radiation Protection

The cumulative dose of radiation to patients increases relatively rapidly with repeated axial imaging studies or procedures guided by fluoroscopy. Certain patient populations such as those with recurrent renal calculus disease or those with a urologic malignancy may be at risk because of repeated exposures to ionizing radiation. Attempts should be made to limit axial imaging studies to the anatomic area of interest and to substitute imaging studies not requiring ionizing radiation when feasible. The cumulative dose of radiation to medical personnel (including physicians) may increase relatively rapidly in circumstances where fluoroscopy is used.

Reduction in radiation exposure to medical personnel is achieved by three major mechanisms: (1) limiting the time of

Table 4–1.

Units of Radiation Exposure and Clinical Relevance of the Measures

RADIATION QUANTITY	TRADITIONAL UNIT	SI UNIT	CONVERSION	CLINICAL RELEVANCE
Exposure	Roentgen (R)	Coulomb (C)/kg	1 C/kg = 3876 R	Charge per unit mass
Absorbed dose	Rad	Gray (Gy)	1 Gy = 100 rad	Energy absorbed by tissue
Equivalent dose	Rem	Sievert (Sv)	1 Sv = 100 rem	Absorbed energy based on tissue type
Effective dose	Rem	Sievert (Sv)		Biologic risk associated with absorbed energy

Adapted from Geise RA, Morin RL. Radiation management in uroradiology. In: Pollack HM, McClennan BL, editors. Clinical urography. 2nd ed. Philadelphia: WB Saunders; 2000. p. 13.

Table 4–2.

Relative Radiation Level Designations along with Common Example Examinations for Each Classification

RELATIVE RADIATION LEVEL*	ADULT EFFECTIVE DOSE ESTIMATE RANGE	PEDIATRIC EFFECTIVE DOSE ESTIMATE RANGE	EXAMPLE EXAMINATIONS
O	0	0 mSv	Ultrasound, MRI
☢	<0.1 mSv	<0.03 mSv	Chest radiographs, hand radiographs
☢☢	0.1-1 mSv	0.03-0.3 mSv	Pelvis radiographs, mammography
☢☢☢	1-10 mSv	0.3-3 mSv	Abdomen CT, nuclear medicine bone scan
☢☢☢☢	10-30 mSv	3-10 mSv	Abdomen CT without and with contrast, whole body PET
☢☢☢☢☢	30-100 mSv	10-30 mSv	Transjugular intrahepatic portosystemic shunt placement, aortic aneurysm stent graft treatment

*The RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (e.g., the region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as NS (not specified).
From American College of Radiology. ACR appropriateness criteria: radiation dose assessment introduction. ⟨http://www.acr.org/SecondaryMainMenuCategories/quality_safety/app_criteria/RRLInformation.aspx⟩; [accessed 19.01.11].

exposure; (2) maximizing distance from the radiation source; and (3) shielding. Radiation dose during fluoroscopy is directly proportional to the **time of exposure** and to the **number of exposures.** The exposure time during fluoroscopy should be minimized by using short bursts of fluoroscopy and using the "last image hold" feature of the fluoroscopy unit. Radiation beams diverge with distance and therefore radiation exposure diminishes as the square of the distance from the radiation source. Maintaining the maximum practical distance from an active radiation source significantly decreases exposure to medical personnel. Positioning the image intensifier as close to the patient as feasible substantially reduces scatter radiation. Standard aprons and thyroid shields provide significant shielding for medical personnel and should be worn by all personnel involved in the use of fluoroscopy.

Key Points: Conventional Radiography/Radiation Management in Uroradiology

- The effective radiation dose describes the potential for adverse health effects from ionizing radiation.
- The effective dose is a quantity used to denote the radiation risk (expressed in sieverts) to a population of patients from an imaging study. See Table 4–1 for a description of the relationship between these measures of radiation exposure.
- There is no safe dose of radiation.
- Filling of the bladder may stimulate bladder spasms at low volumes, and some patients are unable to hold adequate volumes for investigation. Bladder filling in patients with spinal cord injuries higher than T6 may precipitate autonomic dysreflexia.
- Relative radiation levels (RRL) categorize diagnostic imaging studies by their estimated effective dose of radiation.
- Radiation protection for medical personnel includes (1) limiting time of exposure, (2) maximizing distance from radiation source, and (3) shielding.

CONTRAST MEDIA

The urologist ordering a radiographic evaluation on a patient must consider the risks and benefits associated with a contrast-enhanced imaging study, as well as alternative imaging modalities that could provide the same information without the need for contrast exposure.

Many different types of contrast media have been used to enhance medical imaging and thus improve diagnostic and therapeutic decisions made by urologists. These agents are used on a daily basis throughout the world with great safety and efficacy. However, like all other pharmaceuticals, there are inherent risks associated with the use of contrast media. Adverse side effects and adverse drug reactions (ADRs) can be a direct result from the use of contrast media and vary from minor disturbances to severe, life-threatening situations. Imaging centers must be prepared with trained personnel, readily available medications, equipment, and an ongoing system to educate clinic personnel on the recognition and treatment of ADRs associated with contrast media.

Intravascular Iodinated Contrast Media

Iodine is the most common element in general use as an intravascular radiologic contrast medium (IRCM). With an atomic weight of 127, iodine has radiopacity, whereas other elements included in IRCM have no radiopacity and act only as carriers of the iodine elements, increasing solubility and reducing toxicity. Four basic types of iodinated IRCM are available for clinical use: ionic monomer, nonionic monomer, ionic dimer, and nonionic dimer. They can be further characterized as being iso-, hyper-, or low-osmolar compared with physiologic osmolality of 300 mOsm/kg H_2O (Table 4–3).

All are derived from a 2,4,6 tri-iodinated benzene ring compound with three atoms of iodine in the case of monomers and six atoms of iodine in the case of dimers. The chemical composition of these agents make them highly hydrophilic, low in lipid solubility, and of low binding affinity for protein receptors or membranes. Because they do not enter red blood cells or tissue cells and are rapidly excreted, they are designed for use in imaging and are not therapeutic. Approximately 90% will be eliminated by the kidneys within 12 hours of administration.

Table 4–3.

Properties of Commonly Used Radiocontrast Media

TYPE	GENERIC NAME	IODINE, mg/mL	OSMOLALITY, mOsm/KG	VISCOSITY, CPS AT 37° C
Iso osmolar				
Nonionic dimmer	Iotrolan	300	320	8.1
Nonionic dimmer	Iodixanol	320	290	11.4
Low osmolar				
Ionic dimmer	Meglumine ioxaglate	320	580	7.5
Ionic dimmer	Sodium oxalate	320	580	7.5
Nonionic monomer	Iopamidol	300	616	4.7
Nonionic monomer	Iohexol	300	640	6.3
Nonionic monomer	Ioversol	300	645	5.5
Nonionic monomer	Iopromide	300	610	4.6
High osmolar				
Ionic monomer	Sodium iothalamate	325	1843	2.75
Ionic monomer	Meglumine diatrizoate	306	1530	5.0

From Pannu N, Wiebe N, Tonelli M, et al. Prophylaxis strategies for contrast-induced nephropathy. JAMA 2006;295(23):2765–79.

Relative to the body's iron stores, large quantities of iodine are required for imaging enhancement. The total body iodine content, found mainly in the thyroid gland, is 0.01 g and the average daily turnover of iodine is only 0.0001 g. For renal CT imaging a common dose of IRCM will expose the patient to between 25 and 50 g of iodine, which is approximately 400,000 times the daily turnover rate in the human body, but this dose will rarely cause any toxicity or lasting effects (Morris, 1993).

Adverse Reactions to Intravascular Iodinated Contrast Media

Adverse drug reactions (ADR) associated with intravenous contrast media can be divided into two broad categories: idiosyncratic anaphylactoid (IA) and nonidiosyncratic (NI) reactions. IA reactions are most concerning because they are potentially fatal and can occur without any predictable or predisposing factors. Approximately 85% of IA reactions occur during or immediately after injection of IRCM and are more common in patients with a prior ADR to contrast media, asthmatics, diabetics, patients with impaired renal function or diminished cardiac function, and those who are taking β-adrenergic blockers.

The exact mechanism of IA reactions is not known but is thought to be a combination of systemic effects. IA reactions have not been shown to result from a true IgE antibody immunologic reaction to the contrast media (Dawson, 1999). At least four mechanisms may play a role in IA reactions: (1) release of vasoactive substances including histamine; (2) activation of physiologic cascades including complement, kinin, coagulation, and fibrinolytic systems; (3) inhibition of enzymes including cholinesterase, which may cause prolonged vagal stimulation; and (4) the patient's own anxiety and fear of the actual procedure. **IA reactions are not dose dependent. Severe reactions have been reported after only 1 mL injected at the beginning of the procedure and have also occurred after completion of a full dose despite no reaction to the initial test dose** (Nelson et al, 1988; Thomsen et al, 1999; ACR, 2008).

Nonidiosyncratic (NI) reactions are dose dependent and consequently related to the osmolality, concentration, volume, and injection rate of the IRCM. Because the concentration of absorbed or free iodine is low, only patients with an underlying iodine deficiency are at risk for increased intake of iodine during contrast imaging. Patients with endemic goiter may develop thyrotoxicosis after injection of IRCM agents.

The hyperosmolar contrast media (HOCM) have an osmolality that is five times greater than physiologic osmolality of body cells (300 mOsm/kg water). The hyperosmolar agents are associated with erythrocyte damage, endothelial damage, vasodilation, hypervolemia, interruption of the blood-brain barrier, and cardiac depression. Chemotoxic reactions to IRCM include cardiac, vascular, neurologic, and renal toxicity. The low osmotic contrast media (LOCM) have an osmolality the same as or slightly higher than physiologic osmolality and are associated with fewer ADRs and toxic events (Morcos, 1999).

Contrast Complications

All contrast ADRs are more common with HOCM (12%) compared with LOCM (3%) (Katayama et al, 1990; Heinrich et al, 2005). **Previous adverse reaction to IRCM and a history of asthma are two of the most concerning predisposing conditions predicating an ADR with use of contrast media. Additional factors that may predict an ADR include history of known allergy to iodine, severe cardiac disease, renal insufficiency, dehydration, sickle cell anemia, anxiety, apprehension, hyperthyroidism, and presence of adrenal pheochromocytoma.**

Minor Reactions

It is common to have nausea, flushing, pruritus, urticaria, headache, and even emesis after injection of IRCM. These reactions are usually mild and do not require additional treatment. Arm pain can also result from venous spasm or infiltration of the media outside the vein. An H_1 receptor blocker like diphenhydramine (Benadryl) PO/IM/IV 1 to 2 mg/kg, up to 50 mg may be helpful in this patient population.

Intermediate Reactions

Worsening or more severe minor reactions including hypotension or bronchospasm occur in 0.5% to 2% of patients. These are usually transient and do not need treatment. If necessary, 4 to 10 mg of chlorphenamine administered orally, IV, or IM; 5 mg of diazepam for anxiety; 100 to 500 mg of hydrocortisone IM or IV; or two to three puffs of beta-agonist inhalators for bronchospasm (bronchiolar dilators such as metaproterenol [Alupent], terbutaline [Brethaire], or albuterol [Proventil or Ventolin]) are administered; repeat as needed.

Severe Reactions

Life-threatening reactions occur in approximately 1/1000 uses for high-osmolar agents and are far less for low-osmolar contrast media, with both types of agents resulting in mortality rates of 1/170,000 uses (Spring et al, 1997). Severe reactions include seizure, laryngeal spasm, bronchospasm, pulmonary edema, cardiac arrhythmia, respiratory collapse, or cardiac arrest (Katayama et al, 1990). Ready access to a crash cart and trained personnel are necessary components of any imaging center. If needed, cardiopulmonary resuscitation is started immediately. Many different medications have been used for the treatment of an acute severe life-threatening reaction to IRCM. **However, rapid administration of epinephrine is the treatment of choice for severe contrast reactions. Current guidelines recommend immediate delivery of 0.01 mg/kg of body weight to a maximum of 0.5 mg of 1:1000 concentration of epinephrine, injected IM in the lateral thigh as first-line treatment.** Subcutaneous injection is much less effective. Intravenous injection can be given with more dilute concentration and must be given slowly (ACR, 2008; Lightfoot et al, 2009).

Large-volume extravasation can be seen with power injections not monitored with electrical skin impedance devices that detect extravasation and arrest the injection process. When large-volume extravasation of IRCM occurs, the result can be cellulitis, edema, and compartment syndrome leading to tissue necrosis. The most severe consequences may not be manifest immediately. Consequently, admission to the hospital for observation or frequent follow-up in the clinic may be necessary in some cases of large-volume extravasation.

Premedication Strategies

No known premedication strategy will eliminate the risk of a severe adverse reaction to IRCM. The regimens suggested in the literature include the use of

Table 4–4.

Premedication Strategies to Reduce Severity of Reactions to Contrast Media

Prednisone	50 mg by mouth at 13 hr, 7 hr, and 1 hr before contrast media injection **Plus** diphenhydramine (Benadryl)—50 mg IV, IM, or by mouth 1 hr before contrast medium injection
Methylprednisolone (Medrol)	32 mg by mouth 12 hr and 2 hr before contrast media injection **Plus** diphenhydramine (Benadryl)—50 mg IV, IM, or by mouth 1 hr before contrast medium injection

From American College of Radiology Manual on Contrast Media, version 6, pp. 9-10, <http://www.acr.org/SecondaryMainMenuCategories/quality_safety/contrast_manual.aspx> [accessed 01.10.10].

corticosteroids, antihistamines, H_1 and H_2 antagonists, and ephedrine. Patients at high risk should be premedicated with corticosteroids and possibly antihistamines 12 to 24 hours before and after use of IRCM. LOCM can be used in these patients. Several premedication regimens have been proposed to reduce the frequency and/or severity of reactions to contrast media. Two frequently used regimens are outlined in Table 4–4.

It has been demonstrated that the use of nonionic contrast media combined with a premedication strategy including corticosteroids results in a reduction in reaction rates compared with other protocols for patients who have experienced a prior contrast media–induced reaction. However, no controlled studies are available to determine whether pretreatment alters the incidence of serious reactions. Oral administration of steroids seems preferable to intravascular administration, and prednisone and methylprednisolone are equally effective. If the patient is unable to take oral medication, 200 mg of hydrocortisone IV may be substituted for oral prednisone. **One consistent finding is that the steroids should be given at least 6 hours before the injection of contrast media regardless of the route of steroid administration. It is clear that administration for 3 hours or less before contrast does not decrease adverse reactions** (Lasser, 1988).

Supplemental administration of an H_1 antihistamine (e.g., diphenhydramine), orally or IV, may reduce the frequency of urticaria, angioedema, and respiratory symptoms. In emergency situations, intravenous corticosteroid (e.g., 200 mg hydrocortisone) every 4 hours plus an H_1 antihistamine (e.g., 50 mg diphenhydramine) 1 hour before the procedure has been used. In patients who have a prior documented contrast reaction, the use of a different contrast agent has been advocated and may be protective. Switching to a different agent should be in combination with a premedication regimen.

Specific Clinical Considerations

Metformin. **Patients with type II diabetes mellitus on metformin oral biguanide hyperglycemic therapy may have an accumulation of the drug after administering IRCM, resulting in biguanide lactic acidosis presenting with vomiting, diarrhea, and somnolence. This condition is fatal in approximately 50% of cases** (Wiholm, 1993). **Biguanide lactic acidosis is rare in patients with normal renal function. Consequently, in patients with normal renal function and no known comorbidities there is no need to discontinue metformin before IRCM use, nor is there a need to check creatinine following the imaging study. However, in patients with renal insufficiency, metformin should be discontinued the day of the study and withheld for 48 hours. Postprocedure creatinine should be measured at 48 hours and metformin started once kidney function is normal** (Bailey and Turner, 1996). **It is not necessary to discontinue metformin before gadolinium-enhanced magnetic resonance studies when the amount of gadolinium administered is in the usual dose range of 0.1 to 0.3 mmol per kg of body weight.**

Contrast-Induced Nephropathy. Contrast-induced nephropathy (CIN) is defined as a rise in serum creatinine 25% above baseline, or more than 0.5 mg/dL within 3 days following exposure to contrast media, in the absence of an alternative cause. The precise cause of CIN continues to elude investigators but is believed to be a combination of tubular injury and renal ischemia (Katholi et al, 1998). High doses of IRCM can impair renal function in some patients for 3 to 5 days. CIN in patients with normal kidney function is rare (Pannu et al, 2006; Kelly et al, 2008). CIN is the third most common cause of acute kidney failure in the hospitalized patients (Nash et al, 2002). **The most common patient-related risk factors are chronic kidney disease (creatinine clearance <60 mL/min), diabetes mellitus, dehydration, congestive heart failure, age, hypertension, low hematocrit, and ventricular ejection fraction less than 40%. The patients at highest risk for developing CIN are those with both diabetes *and* preexisting renal insufficiency. The most common non–patient-related causes are high-osmolar contrast agents, ionic contrast, increased contrast viscosity, and large-contrast volume infusion** (Pannu et al, 2006).

Despite significant discussion on the part of radiologists and urologists, the literature does not support an absolute serum creatinine level that prohibits the use of contrast media. Prevention of CIN has been the subject of many research studies, and the results have been summarized by several different meta-analyses. In these meta-analyses the baseline serum creatinine of study participants ranged from 0.9 to 2.5 mg/dL. **In one survey the policies regarding the cutoff value for serum creatinine varied widely among radiology practices. Thirty-five percent of respondents used 1.5 mg/dL, 27% used 1.7 mg/dL, and 31% used 2.0 mg/dL (mean, 1.78 mg/dL) as a cutoff value in patients with no risk factors other than elevated creatinine; threshold values were slightly lower in diabetics (mean 1.68 mg/dL). Patients in end-stage renal disease who have no remaining natural renal function are no longer at risk for CIN and may receive LOCM or IOCM** (Elicker et al, 2006).

The summary of the meta-analysis for the prevention of CIN after contrast media use supports using hydration, bicarbonate, iso- or low-osmolar contrast media, and N-acetylcysteine. In one review article, N-acetylcysteine was determined to be more protective than hydration alone. Furosemide was found to increase the risk of developing CIN (Pannu et al, 2006; Kelly et al, 2008).

N-acetylcysteine is inexpensive, readily available, administered orally, and associated with few drug interactions or side effects. Its mechanism of protection against CIN is not understood but may serve as a scavenger of oxygen-free radicals and/or augment the vasodilatory effects of nitric oxide in the kidney (Safirstein et al, 2000). Doses used in the different studies ranged from 600 to

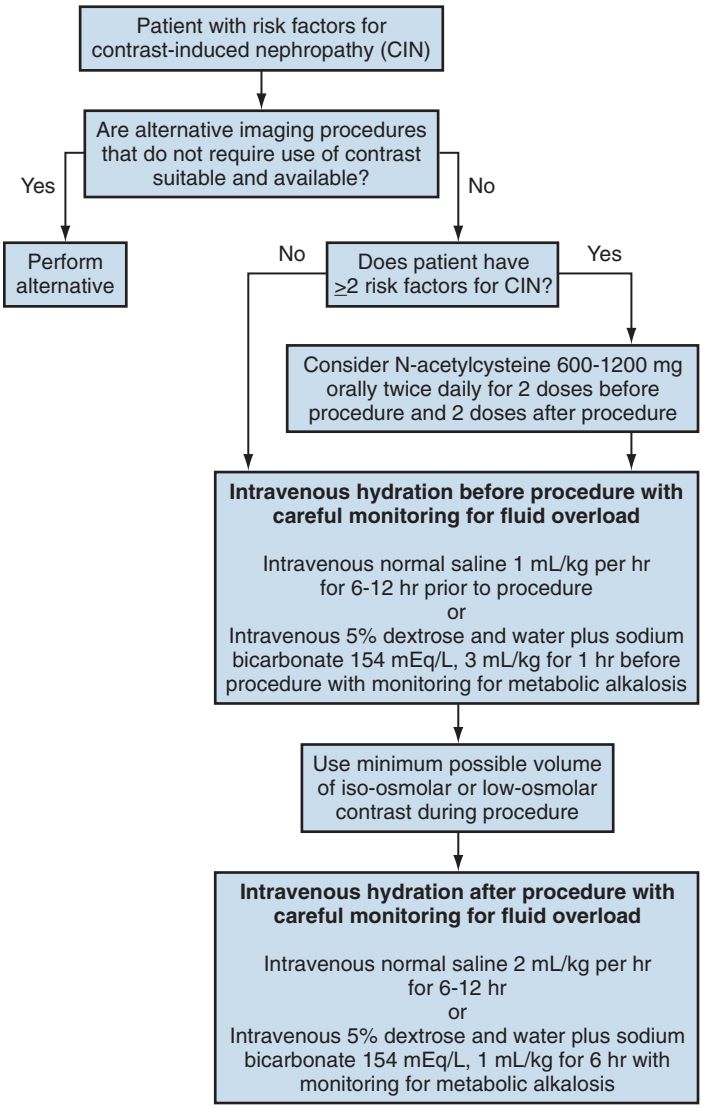


Figure 4–2. Preventive strategies for patient with risk factors for contrast-induced nephropathy (CIN).

1200 mg orally twice a day for 2 doses before the contrast-enhanced study and 2 doses after the procedure (Fig. 4–2).

Magnetic Resonance Imaging Contrast Agents

Because magnetic resonance imaging (MRI) offers previously unseen detailed soft tissue imaging compared with CT, it was initially believed that MRI would not require contrast enhancement. However, by 2005, almost 50% of MRI studies were being performed with contrast media. Extracellular MRI contrast agents contain paramagnetic metal ions. Copper, manganese, and gadolinium were the potential paramagnetic ions for use with MRI. Gadolinium, however, is the most powerful having seven unpaired electrons, but its toxicity required encapsulation by a chelate. Paramagnetic agents like gadolinium are positive enhancers reducing the T1 and T2 relaxation times and increasing tissue signal intensity on T1-weighted images, while having little effect on T2-weighted images.

Although gadolinium chelates can be differentiated on the basis of stability, viscosity, and osmolality, they cannot be differentiated on the basis of efficacy. Acute adverse reactions are encountered less frequently with gadolinium than after administration of iodinated contrast media. The frequency of all acute adverse events after an injection of 0.1 or 0.2 mmol/kg of gadolinium chelate ranges from 0.07% to 2.4%. The vast majority of these reactions are mild including coldness at the injection site, nausea, emesis, headache, warmth or pain at the injection site, paresthesias, dizziness, and itching. Reactions resembling an "allergic" response occur frequently, from 0.004% to 0.7%. Systemic reactions consisting of rash, hives, or urticaria are the most frequent of this group, and rarely bronchospasm. The severe, life-threatening anaphylactoid or nonallergic anaphylactic reactions are exceedingly rare (0.0001% to 0.001%). In a meta-analysis of 687,000 gadolinium doses for MRI, there were only five severe reactions. In another survey based on 20 million administered doses there were 55 cases (0.0003%) of severe reactions. Fatal reactions to gadolinium chelate agents have been reported, but they are extremely rare events (Murphy et al, 1999).

Extracellular MRI agents are known to interfere with some serum chemistry assays. For example, serum calcium tests will often be measured as a false reading of hypocalcemia for 24 hours after MRI with gadolinium enhancement, even though serum calcium is actually in the normal range. Other tests including iron, magnesium, iron binding capacity, and zinc may also have spurious results. Biochemical assessment is more reliable when performed 24 hours after exposure to gadolinium contrast media.

Nephrogenic Systemic Fibrosis

Gadolinium-based contrast media (GBCM) are considered to have no nephrotoxicity at approved dosages for MRI. Magnetic resonance with gadolinium has been used instead of contrast-enhanced CT in those at risk for developing worsening renal failure if exposed to iodinated contrast media. However, nephrogenic systemic fibrosis (NSF) has recently been reported in patients with advanced renal insufficiency (glomerular filtration rate [GFR] <30 mL/min). **Nephrogenic systemic fibrosis (NSF) is a fibrosing disease of the skin, subcutaneous tissues, lungs, esophagus, heart, and skeletal muscles. Initial symptoms typically include skin thickening and/or pruritus. Symptoms and signs may develop and progress rapidly, with some affected patients developing contractures and joint immobility within days of exposure. Death may result in some patients, presumably as a result of visceral organ involvement.**

In 1997 NSF was described in dialysis patients who had not been exposed to GBCM. The condition was previously known as nephrogenic fibrosing dermopathy. In 2006 and again in 2007 independent reports surfaced defining a strong association with gadolinium-based contrast media (Grobner, 2006; Marckmann et al, 2006). **Onset of NSF varies between 2 days and 3 months. Early manifestations include subacute swelling of distal extremities, followed by severe skin induration and later even organ involvement.** In a 2007 survey performed by the American College of Radiology, 156 cases of NSF were reported by 27 responding institutions; 140 of these 156 patients were known to have received GBCM. In 78 patients, the specific GBCM was known. Forty-five of them received gadodiamide, 17 gadopentetate dimeglumine, 13 gadoversetamide, and 3 gadobenate dimeglumine. NSF following gadoteridol administration has also been reported. Many of the cases in which agents other than

gadodiamide and gadopentetate dimeglumine were used are confounded by the fact that affected patients were injected with other agents as well (ACR, 2008). Patients with chronic kidney disease (CKD) have a 1% to 7% chance of developing NSF after MRI imaging with gadolinium agents (Todd et al, 2007).

Patients with GFR less than 30 mL/min/1.73m^2 (not on chronic dialysis) are the most difficult patient population in terms of choosing an imaging modality. They are at risk for CIN if exposed to iodinated contrast media for CT imaging and are also at significant risk of developing NSF if exposed to GBCM during MRI. Recent data suggest that the risk of NSF may be greatest in patients with a GFR of less than 15 mL/min/1.73m^2 and much less in patients with GFRs that are higher. Patients with severe chronic kidney disease have a 1% to 7% chance of developing NSF after GBCM MRI (Kanal et al, 2008). In the chronic kidney disease patient population, it is recommended that contrast media be avoided if possible. If MRI contrast media is absolutely essential, use of the lowest possible doses (needed to obtain a diagnostic study) of selected GBCM is recommended. In this setting, the patient should be informed of the risks of GBCM administration and must give their consent to proceed. There is no proof that any GBCM is completely safe in this patient group; however, some have suggested avoiding gadodiamide and considering use of macrocyclic agents (Kanal et al, 2008). Patients with CKD but GRF greater than 30 mL/min/1.73m^2 are considered to be at extremely low or no risk for developing NSF if a dose of GBCM of 0.1 mmol/kg or less is used. Patients with GFR greater than 60 mL/min/1.73 m^2 do not appear to be at increased risk of developing NSF, and the current consensus is that all GBCM can be administered safely to these patients. In their publications, the American College of Radiology stresses that the current information on NSF and its relationship to GBCM administration is preliminary and further research is necessary to better understand this potentially devastating complication.

Key Points: Contrast Media

- Type II diabetics with renal insufficiency on oral metformin biguanide hyperglycemic therapy are at risk for developing biguanide lactic acidosis after exposure to intravascular radiologic contrast media and should stop metformin the day before the procedure and restart 48 hours after if they have a normal or baseline serum creatinine.
- Patients at risk for adverse reaction to contrast include those with previous adverse reactions, a history of asthma, severe cardiac disease, renal insufficiency, dehydration, sickle cell anemia, anxiety, apprehension, hyperthyroidism, and presence of adrenal pheochromocytoma.
- The treatment of choice for a severe adverse drug reaction is 0.01 mg/kg of epinephrine (1:1000 concentration) IM in the lateral thigh.
- Patients at greatest risk for contrast-induced nephropathy are those with diabetes mellitus and dehydration.
- Steroids given to prevent adverse contrast agents should be given at least 6 hours before injection.

INTRAVENOUS UROGRAPHY

Once the mainstay of urologic imaging, the intravenous excretory urographic (IVU) study has essentially been replaced by CT and MRI. With the ability of new scanners to perform axial, sagittal, and coronal reconstruction of the upper tract urinary system, essentially all of the data and information obtained by traditional IVU can be realized with CT imaging. In addition, some parenchymal defects, cysts, and tumors can be better delineated with CT than IVU.

Technique

Bowel prep may help to visualize the entire ureters and upper collecting systems. Patients with chronic constipation may benefit most from complete bowel prep with clear liquids for 12 to 24 hours and an enema 2 hours before the procedure. Most patients will need only clear liquids for 12 hours and an enema 1 hour before the procedure.

Before injection of contrast, a scout radiograph or KUB (kidneys, ureters, bladder) film is taken demonstrating the top of the kidneys and the entire pelvis to the pubic symphysis. This allows determination of adequate bowel prep, confirms correct positioning, and exposes kidney stones or bladder stones.

Contrast is injected as a bolus of 50 to 100 mL of contrast. The nephrogenic phase is captured with a radiograph immediately after injection. In the past, tomograms were used to look for parenchymal defects but now CT or MRI is preferred. A film is taken at 5 minutes and then additional films at 5-minute intervals until the question that prompted the IVU is answered. Abdominal compression may be used to better visualize the ureters. Occasionally oblique films will be used to better define the course of the ureter in the bony pelvis and to precisely differentiate ureteral stones from pelvic calcifications.

Upright films may be helpful in certain situations. In the rare case of suspected symptomatic renal ptosis, IVU can be particularly helpful (Fig. 4–3). Supine films are compared with upright films to measure the degree of ptosis. Such a comparison cannot be made with MRI or CT. In the case of calyceal stones or milk of calcium stones, layering of the contrast can be helpful to evaluate the anatomy of the calyx harboring the stones.

Postvoid films are obtained to evaluate the presence of outlet obstruction, prostate enlargement, and bladder filling defects including stones and urothelial cancers.

Indications

1. Demonstrate the renal collecting systems and ureters
2. Investigate the level of ureteral obstruction in renal units displaying delayed function
3. Demonstrate intraoperative opacification of collecting system during extracorporeal shock wave lithotripsy or percutaneous access to the collecting system
4. Demonstrate renal function during emergent evaluation of unstable patients
5. Demonstrate renal and ureteral anatomy in special circumstances (e.g., ptosis, after transureteroureterostomy, after urinary diversion)

PLAIN ABDOMINAL RADIOGRAPHY

The plain abdominal radiograph is a conventional radiography study, which, in urology, is intended to display the kidneys, ureters and bladder. The plain abdominal radiograph may be employed (1) as a primary study or (2) as a scout film in anticipation of contrast media. Plain films are widely used in the management of renal calculus disease. Plain radiography is also useful in evaluation of the trauma patient because it can be performed as a

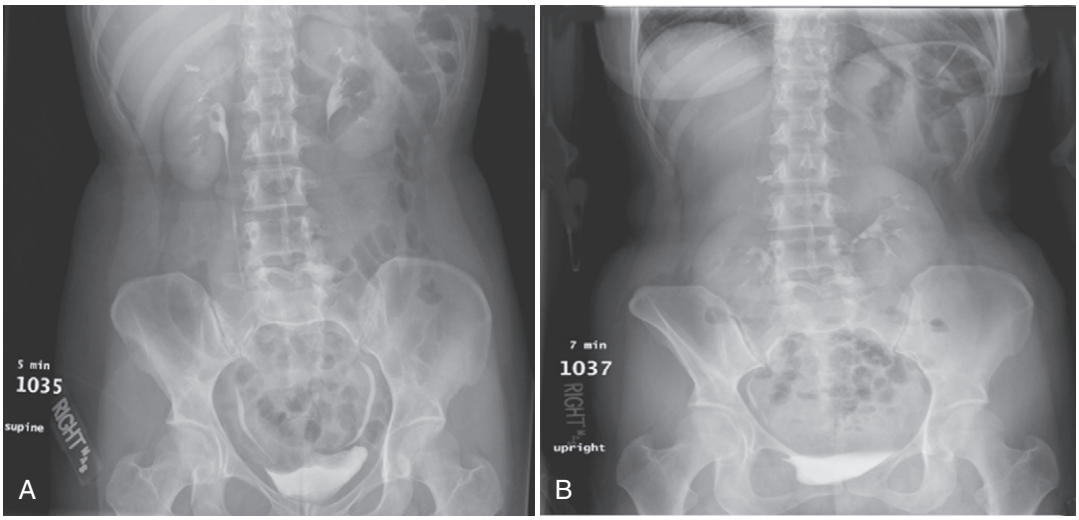


Figure 4–3. Intravenous excretory urogram (IVU) in a 40-year-old female with the complaint of a mobile mass in the right lower quadrant with standing associated with bilateral flank and back pain that resolved in the supine position. **A,** Supine IVU shows kidneys in the normal position, with normal ureters and proximal collecting systems. **B,** Standing film shows significant displacement of both kidneys with the right kidney moving onto the pelvis as described by the patient.

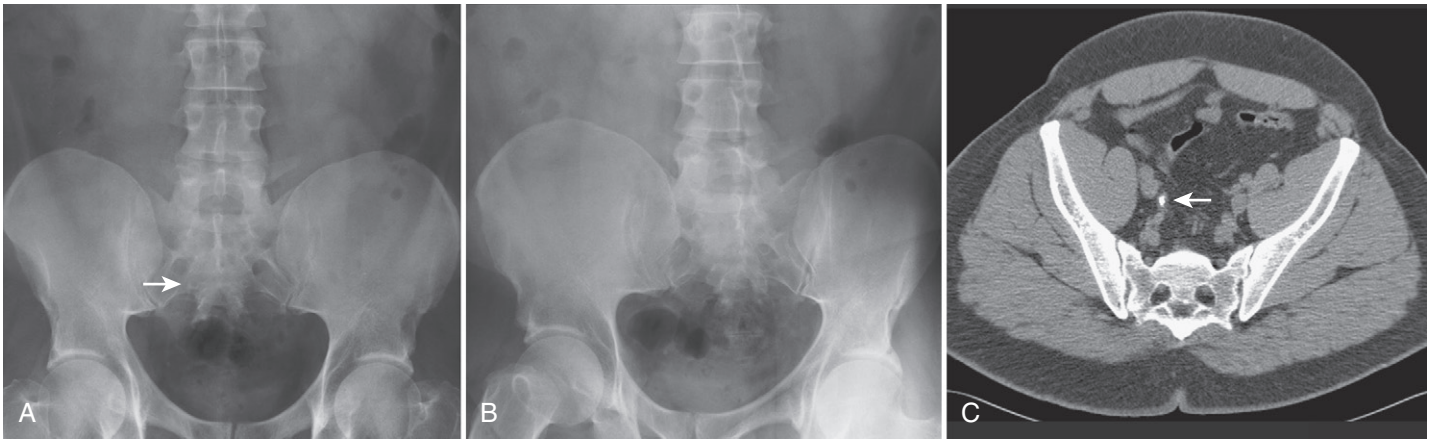


Figure 4–4. **A,** Right ureteral calculus *(arrow)* overlying the sacrum is difficult to visualize on the plain film. **B,** The right posterior oblique study fails to confirm the location of the ureteral calculus. **C,** Computed tomography confirms this 6-mm calculus in the right ureter at the level of the third sacral segment.

portable study in the trauma unit. Secondary findings on plain radiography such as rib fractures, fractures of the transverse processes of the vertebral bodies, and pelvic fractures may indicate serious associated urologic injuries.

Technique

An abdominal plain radiograph is obtained with the patient in the supine position, using an anterior to posterior exposure. The study typically includes that portion of the anatomy from the level of the diaphragm to the inferior pubic symphysis. It may occasionally be necessary to make two exposures to cover the desired anatomic field. Depending on the indication for the study, oblique films are obtained to clarify the position of structures in relation to the urinary tract. If small bowel obstruction or free peritoneal air is suspected, upright films will be obtained.

Indications

1. To be a preliminary film in anticipation of contrast administration
2. To assess the presence of residual contrast from a previous imaging procedure
3. To assess renal calculus disease before and after treatment
4. To assess the position of drains and stents
5. To be an adjunct to the investigation of blunt or penetrating trauma to the urinary tract

Limitations

Although plain film radiography is often used in the evaluation of renal colic, it is unreliable in the demonstration of calculus disease for various reasons: (1) overlying stool and bowel gas may obscure small calculi; (2) stones may be obscured by other structures such as bones or ribs (Fig. 4–4); (3) calcifications in pelvic veins or vascular structures may be confused with ureteral calculi; and (4) stones that are poorly calcified or composed of uric acid may be radiolucent. Nevertheless, plain film radiography is valuable in assessing the suitability of a patient for extracorporeal shock wave lithotripsy because the ability to identify the stone on fluoroscopy is critical to targeting. Furthermore, a KUB film is cost-effective for monitoring residual stone burden after treatment

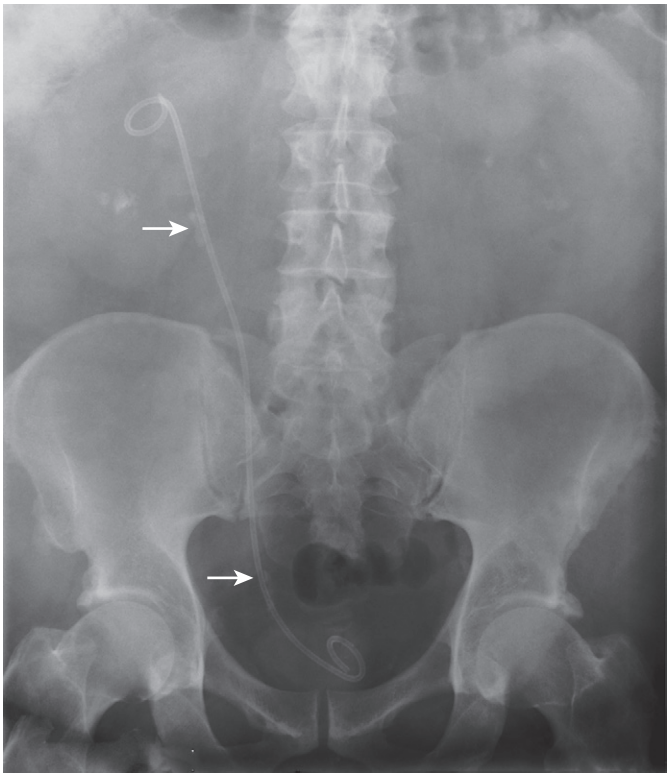


Figure 4–5. Kidney ureter bladder film demonstrating residual stone fragments *(arrows)* adjacent to a right ureteral stent 1 week following right extracorporeal shock wave lithotripsy.

(Fig. 4–5). For complex pathology of the urinary tract, plain abdominal radiography has been supplanted by axial imaging. Plain radiography has a limited role in evaluating soft tissue abnormalities of the urinary tract.

RETROGRADE PYELOGRAPHY

Retrograde pyelograms are performed to opacify the ureters and intrarenal collecting system by the retrograde injection of contrast media. Any contrast media that can be used for excretory urography is also acceptable for retrograde pyelography. Attempts should be made to sterilize the urine before retrograde pyelography because there is a risk of introducing bacteria into the upper urinary tracts or into the bloodstream. Although many studies are able to document the presence or absence of dilation of the ureter, retrograde pyelography has the unique ability to document the normalcy of the ureter distal to the level of obstruction and to better define the extent of the ureteral abnormality.

Technique

Retrograde pyelography is usually performed with the patient in the dorsal lithotomy position. An abdominal plain radiograph (scout film) is obtained to ensure that the patient is in the appropriate position to evaluate the entire ureter and intrarenal collecting system. Cystoscopy is performed and the ureteral orifice is identified.

Contrast may be injected through either a nonobstructing catheter or an obstructing catheter. Nonobstructing catheters include whistle tip, spiral tip, or open-ended catheters. Use of nonobstructing catheters allows passage of the catheter into the ureter and up to the collecting system, over a guidewire if necessary. Contrast can then be introduced directly into the upper collecting system, and the ureters can be visualized by injection of contrast as the catheter is withdrawn.

The other commonly employed method is the use of an obstructing ureteral catheter such as a bulb-tip, cone-tip, or wedge-tip catheter. These catheters are inserted into the ureteral orifice and then pulled back against the orifice to effectively obstruct the ureter. Contrast is then injected to opacify the ureter and intrarenal collecting system. Depending on the indication for the study, it is useful to dilute the contrast material to 50% or less with sterile fluid. This prevents subtle filling defects in the collecting system or ureter from being obscured. Contrast is injected slowly, usually requiring from 5 to 8 mL to completely opacify the ureter and intrarenal collecting system in adults (Fig. 4–6). More or less contrast may be required depending on the size of the patient and the capaciousness of the collecting system. Limited use of fluoroscopy while injecting will help prevent overdistension of the collecting system and reduce the risk of extravasation of contrast. Care should be taken to evacuate air bubbles from the syringe and catheter before injection. Such air bubble artifacts could be mistaken for stones or tumors.

Historically, when a retrograde pyelogram consisted of a series of radiographs taken at intervals, it was important to document various stages of filling and emptying of the ureter and collecting systems. Because of peristalsis the entire ureter will often not be seen on any given static exposure or view. With current equipment including tables that incorporate fluoroscopy, it is possible to evaluate the ureter during peristalsis in real time, thus reducing the need for static image documentation. Documentary still images or "spot films" may be saved for future comparison. Urologists interpret retrograde pyelograms in real time as they are performed.

Indications

1. Evaluation of congenital ureteral obstruction
2. Evaluation of acquired ureteral obstruction
3. Elucidation of filling defects and deformities of the ureters or intrarenal collecting systems
4. Opacification or distention of collecting system to assist percutaneous access
5. In conjunction with ureteroscopy or stent placement
6. Evaluation of hematuria
7. Surveillance of transitional cell carcinoma
8. In the evaluation of traumatic or iatrogenic injury to the ureter or collecting system

Limitations

Retrograde pyelography may be difficult in cases where the bladder is involved with diffuse inflammation or neoplastic changes, especially when bleeding is present. Identification of the ureteral orifices may be assisted by the intravenous injection of indigotindisulfonate sodium or methylene blue in such cases. Changes associated with bladder outlet obstruction may result in angulation of the intramural ureters. This may make cannulation with an obstructing catheter quite difficult. Attempts to cannulate the ureteral orifice may result in trauma to the ureteral orifice and extravasation of contrast material into the bladder wall. The potential for damage to the intramural ureter must be weighed against the potential information to be obtained by the retrograde pyelogram.

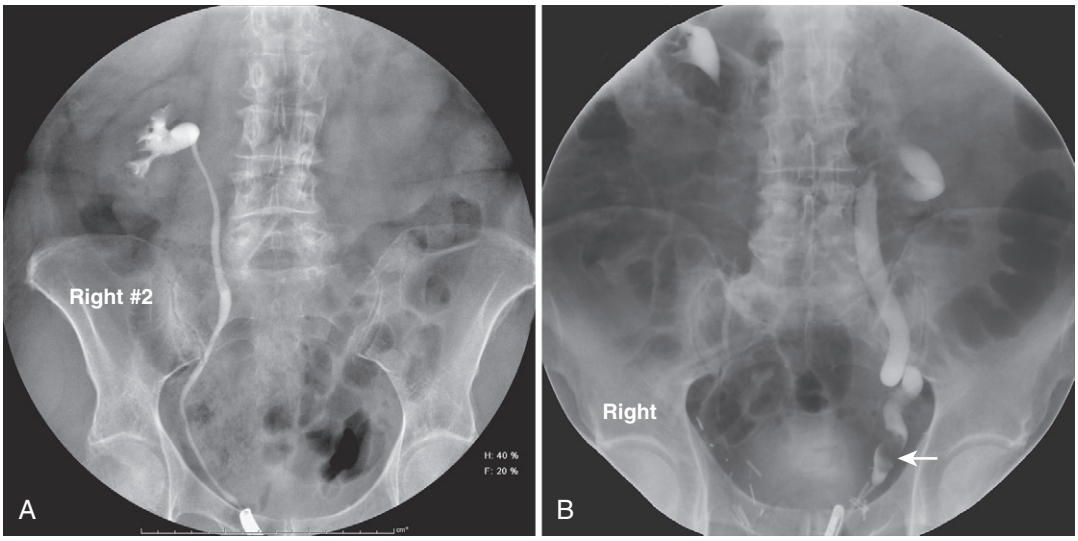


Figure 4–6. **A,** Right retrograde pyelogram performed using an 8-Fr cone-tipped ureteral catheter and dilute contrast material. The ureter and intrarenal collecting system are normal. **B,** Left retrograde pyelogram using an 8-Fr cone-tipped ureteral catheter. A filling defect in the left distal ureter *(arrow)* is a low-grade transitional cell carcinoma. The ureter demonstrates dilation, elongation, and tortuosity, the hallmarks of chronic obstruction.

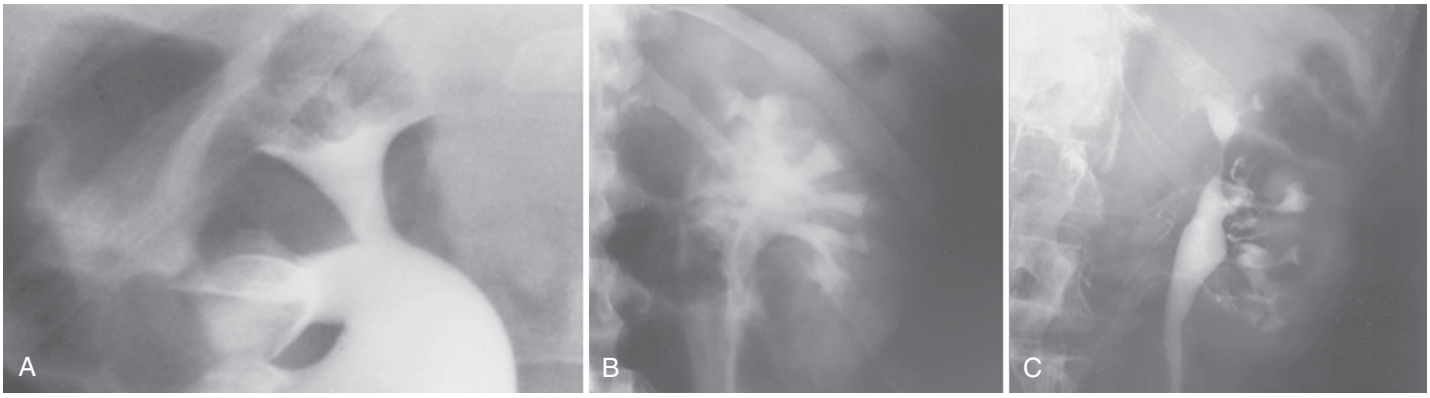


Figure 4–7. Patterns of backflow during retrograde pyelography. **A,** Pyelotubular backflow. **B,** Pyelosinus backflow. **C,** Pyelolymphatic backflow.

Complications

Backflow occurs during retrograde pyelography when contrast is injected under pressure and escapes the collecting system. Contrast may escape the collecting system by one of four routes: **Pyelotubular** backflow occurs when contrast fills the distal collecting ducts producing opacification of the medullary pyramids (Fig. 4–7A). **Pyelosinus** backflow occurs when a tear in the calyces at the fornix allows contrast to leak into the renal sinus (Fig. 4–7B). **Pyelolymphatic** backflow is characterized by opacification of the renal lymphatic channels (Fig. 4–7C). **Pyelovenous** backflow is seen when contrast enters the venous system, resulting in visualization of the renal vein.

Although backflow does not usually cause measurable clinical harm, the potential implications of backflow include (1) introduction of bacteria from infected urine into the vascular system and (2) the absorption of contrast media, which could result in adverse reactions in susceptible patients. It has been demonstrated that the risk of significant urinary tract infection is only about 10% and the risk of sepsis is low when antibiotic prophylaxis therapy is administered before endoscopic procedures (including retrograde pyelography) (Christiano et al, 2000). Although contrast reactions are rare with retrograde pyelography, they have been reported (Johenning, 1980; Weese et al, 1993). In patients with documented severe contrast allergy, prophylactic pretreatment may be appropriate. In those patients considered at risk, care should be taken to inject under low pressures to minimize the probability of backflow and absorption of the contrast into the vasculature system.

LOOPOGRAPHY

Loopography is a diagnostic procedure performed in patients who have undergone urinary diversion. Historically the term "loopogram" has been associated with ileal conduit diversion but may be used in reference to any bowel segment serving as a urinary conduit. When imaging patients with a continent diversion involving a reservoir or neobladder, "pouch-o-gram" would be more accurately descriptive. Because an ileal conduit urinary diversion usually has freely refluxing ureterointestinal anastomoses, the ureters and upper collecting systems may be visualized. In other forms of diversion, the ureterointestinal anastomoses may be purposely nonrefluxing. In such circumstances, when opacification of the upper urinary tract is desirable, antegrade ureteral imaging such as IVU, CT, or MRI urography or antegrade nephrostography may be required. When the patient has compromised

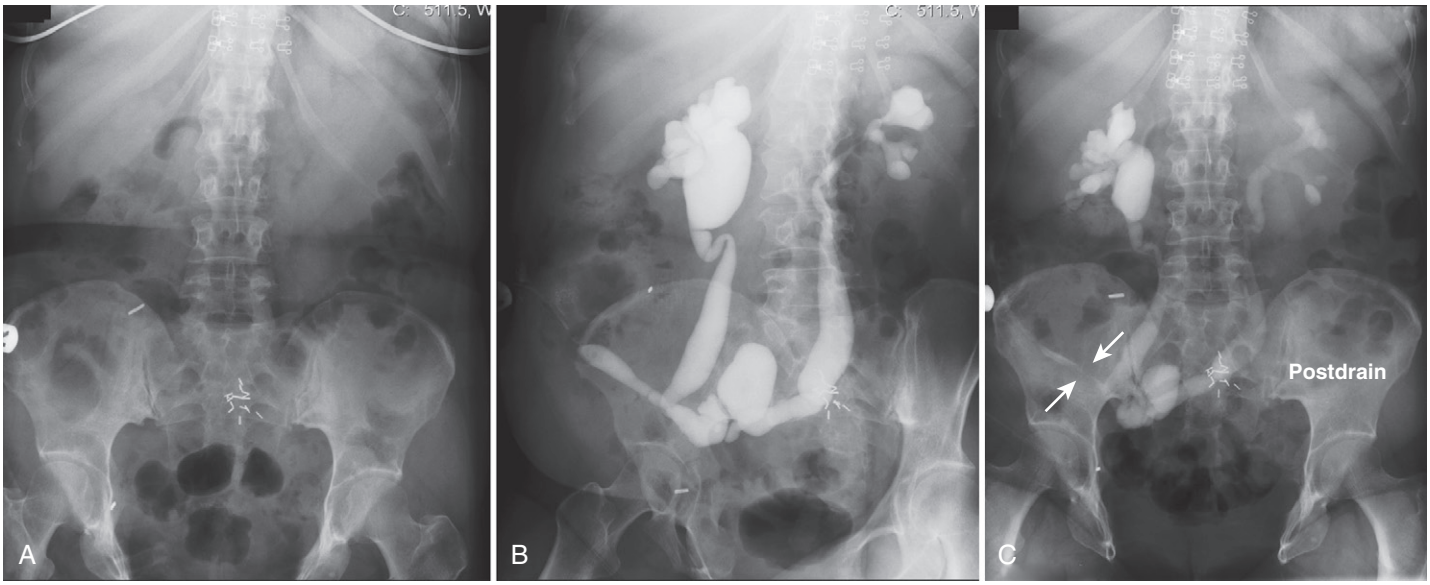


Figure 4–8. Loopography in a patient with epispadias/exstrophy and ileal conduit urinary diversion. The plain film (**A**) shows wide diastasis of the pubic symphysis. After contrast administration via a catheter placed in the ileal conduit, free reflux of both ureterointestinal anastomoses is demonstrated (**B**). A postdrain radiograph (**C**) demonstrates persistent dilation of the proximal loop indicating mechanical obstruction of the conduit *(arrows)*.

renal function or is allergic to iodinated contrast material, loopography can be performed with a low risk of systemic absorption (Hudsen et al, 1981).

Technique

The patient is positioned supine. An abdominal plain radiograph is obtained before the introduction of contrast material (Fig. 4–8A). A commonly employed technique is to insert a small-gauge catheter into the ostomy of the loop, advancing it just proximal to the abdominal wall fascia. The balloon on such a catheter can then be inflated to 5 to 10 mL with sterile water. By gently introducing contrast through the catheter, the loop can be distended, usually producing bilateral reflux into the upper tracts. Oblique films should be obtained in order to evaluate the entire length of the loop (Fig. 4–8B). Because of the angle at which many loops are constructed, a traditional anteroposterior (AP) view will often show a foreshortened loop and could miss a substantial pathology. A drain film should be obtained (Fig. 4–8C). This may demonstrate whether there is obstruction of the conduit.

Indications

1. Evaluation of infection, hematuria, renal insufficiency, or pain after urinary diversion
2. Surveillance of upper urinary tract for obstruction
3. Surveillance of upper urinary tract for urothelial neoplasia
4. Evaluation of the integrity of the intestinal segment or reservoir

RETROGRADE URETHROGRAPHY

A retrograde urethrogram is a study meant to evaluate the anterior and posterior urethra. Retrograde urethrography may be particularly beneficial in demonstrating the total length of a urethral stricture, which cannot be negotiated by cystoscopy. Retrograde urethrography also demonstrates the anatomy of the urethra distal to a stricture, which may not be assessable by voiding cystourethrography. Retrograde urethrography may be performed in the office or in the operating room before performing visual internal urethrotomy or formal urethroplasty.

Technique

A plain film radiograph is obtained before injection of contrast. The patient is usually positioned slightly obliquely to allow evaluation of the full length of urethra. The penis is placed on slight tension. A small catheter may be inserted into the fossa navicularis with the balloon inflated to 2 mL with sterile water. Contrast is then introduced via catheter-tipped syringe. Alternatively, a penile clamp (e.g., Brodney clamp) may be used to occlude the urethra around the catheter (Fig. 4–9).

Indications

1. Evaluation of ureteral stricture disease
2. Assessment for foreign bodies
3. Evaluation of penile or urethral penetrating trauma
4. Evaluation of traumatic gross hematuria

STATIC CYSTOGRAPHY

Static cystography is employed primarily to evaluate the structural integrity of the bladder. The shape and contour of the bladder may give information about neurogenic dysfunction or bladder outlet obstruction. Filling defects such as tumors and stones may be appreciated.

Technique

The patient is positioned supine. A plain radiograph is performed to evaluate for stones and residual contrast and to confirm position and technique. The bladder is filled with 200 to 400 mL of contrast depending on bladder size and patient comfort. Adequate filling is important to demonstrate intravesical pathology or bladder rupture. Oblique films should be obtained because

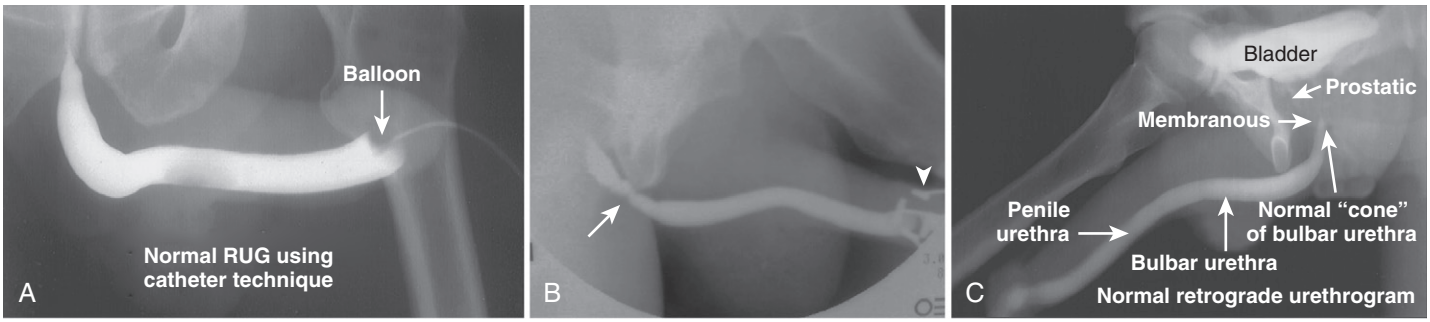


Figure 4–9. Normal retrograde urethrogram demonstrating (**A**) the balloon technique for retrograde urethrography; (**B**) Brodney clamp *(arrowhead)* technique; note the bulbar urethral stricture *(arrow)*. **C**, Normal structures of the male urethra as seen on retrograde urethrogram.

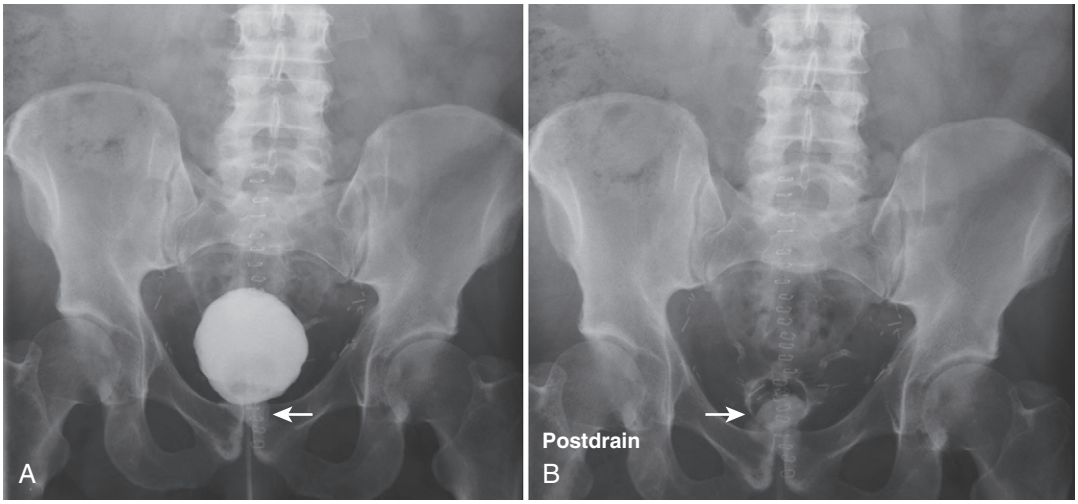


Figure 4–10. The patient has undergone radical retropubic prostatectomy. **A,** During bladder filling, contrast is seen adjacent to the vesicoureteral anastomoses *(arrow)*. **B,** The postdrain film clearly demonstrates a collection of extravasated contrast *(arrow)*.

posterior diverticula or fistulae may be obscured by the full bladder. A postdrainage film completes the study (Fig. 4–10).

Indications

1. Evaluation of intravesical pathology
2. Evaluation of bladder diverticula
3. Evaluation of inguinal hernia involving the bladder
4. Evaluation of colovesical or vesico-vaginal fistulae
5. Evaluation of bladder or anastomotic integrity after surgical procedure
6. Evaluation of blunt or penetrating trauma to the bladder

Limitations

Abdominal and pelvic CT is so commonly used in the evaluation of blunt or penetrating trauma to the abdomen that CT cystography is often performed in conjunction with the trauma evaluation. However, studies have shown that conventional static cystography is as sensitive as CT cystography in detecting bladder rupture (Quagliano et al, 2006; Broghammer and Wessells, 2008).

VOIDING CYSTOURETHROGRAM

A voiding cystourethrogram (VCUG) is performed to evaluate the anatomy and physiology of the bladder and urethra. The study provides valuable information regarding the posterior urethra in pediatric patients. VCUG has long been used to demonstrate vesicoureteral reflux.

Technique

The study may be performed with the patient supine or in a semiupright position using a table capable of bringing the patient into the full upright position. A preliminary pelvic plain radiograph is obtained. In children a 5- to 8-Fr feeding tube is used to fill the bladder to the appropriate volume. Patient comfort should be taken into account when determining the appropriate volume. In the adult population a standard catheter may be placed and the bladder filled to 200 to 400 mL. The catheter is removed and a film is obtained. During voiding, AP and oblique films are obtained. The bladder neck and urethra may be evaluated by fluoroscopy during voiding. Bilateral oblique views may demonstrate low-grade reflux, which cannot be appreciated on the AP film. In addition, oblique films will demonstrate bladder or urethral diverticula, which are not always visible in the straight AP projection. Postvoiding films should be performed (Fig. 4–11).

Indications

1. Evaluation of structural and functional bladder outlet obstruction
2. Evaluation of reflux
3. Evaluation of the urethra in males and females

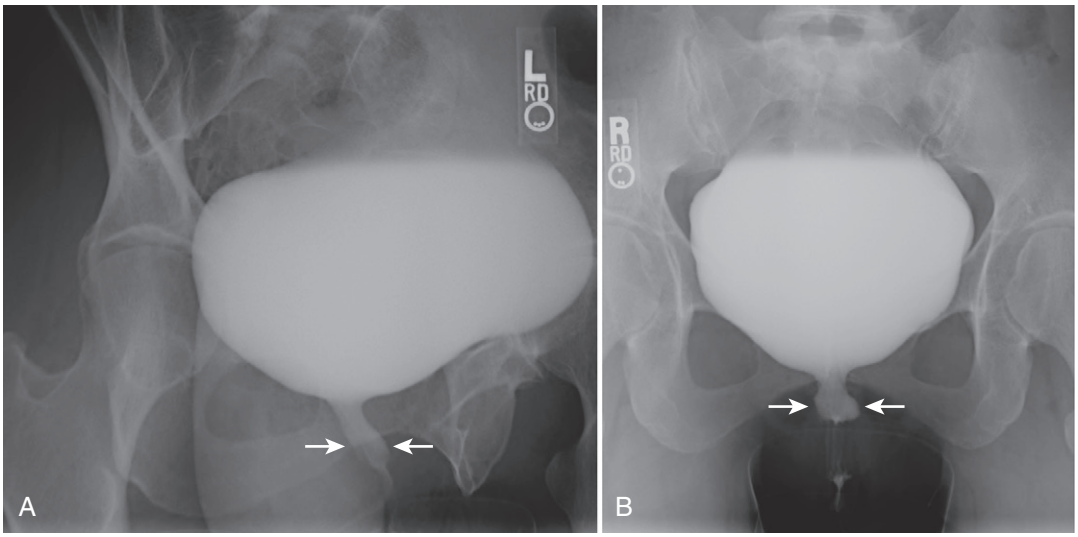


Figure 4–11. A voiding cystourethrography performed for the evaluation of recurrent urinary tract infection in this female patient. **A,** An oblique film during voiding demonstrates thickening of the midureteral profile *(arrows)*. **B,** After interruption of voiding, a ureteral diverticulum is clearly visible extending posteriorly and to the left of the midline *(arrows)*.

Limitations

This study requires bladder filling using a catheter. This may be traumatic in children and difficult in some patients with anatomic abnormalities of the urethra or bladder neck. Filling of the bladder may stimulate bladder spasms at low volumes, and some patients are unable to hold adequate volumes for investigation. **Bladder filling in patients with spinal cord injuries higher than T6 may precipitate autonomic dysreflexia** (Barbaric, 1976; Fleischman and Shah, 1977; Linsenmeyer et al, 1996).

ULTRASONOGRAPHY

The use of ultrasonography is fundamental to the practice of urology. Ultrasonography is a versatile and relatively inexpensive imaging modality that has the unique feature of being the only imaging modality to provide real-time evaluation of urologic organs and structures without the need for ionizing radiation. In order for urologists to best use this technology on behalf of their patients, they must have a mature understanding of the underlying physical principles of ultrasound. They must also understand how the manipulation of ultrasound equipment can affect the quality of ultrasound images. The technical skills required to perform and interpret urologic ultrasonography represent a combination of practical scanning ability and knowledge of the underlying disease process in organs being imaged. In order to communicate the findings appropriately, urologists should understand the nomenclature of ultrasonography and have a specific plan for documentation of each type of study. Understanding how ultrasonography interacts with human tissues will allow urologists to use this modality effectively, appropriately, and safely.

Principles

All ultrasound imaging is the result of the interaction of sound waves with tissues and structures within the human body. Ultrasound waves are produced by applying short bursts of alternating electrical current to a series of crystals housed in the transducer. Alternating expansion and contraction of the crystals via the piezoelectric effect creates a mechanical wave that is transmitted

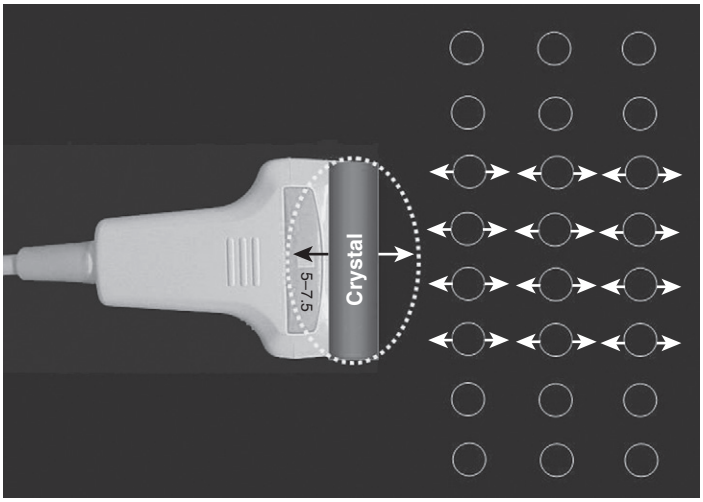


Figure 4–12. The alternating expansion and contraction of the crystal produces longitudinal mechanical waves. In this simplified schematic drawing, the individual molecules (depicted as *circles*) are displaced in the direction of the propagated wave.

through a coupling medium to the skin and then into the body. The waves that are produced are longitudinal waves. In a longitudinal wave the particle motion is in the same direction as the propagation of the wave (Fig. 4–12). This motion produces areas of rarefaction and compression of tissue in the direction of travel of the ultrasound wave (Fig. 4–13). A portion of the wave is reflected toward the transducer. The transducer then serves as a receiver and "listens" for the returning sound wave reconverting the mechanical to electrical energy. The transducer must be in direct, secure contact with the subject to transmit and receive the reflected sound waves.

The appearance of the image produced by ultrasonography is the result of the interaction of mechanical ultrasound waves with biologic tissues and materials. Because ultrasound waves are transmitted and received at frequent intervals, the images can be rapidly reconstructed and refreshed, providing a real-time image. The frequency of the sound waves used for urologic ultrasound imaging is in the range of 3.5 MHz to 12 MHz.

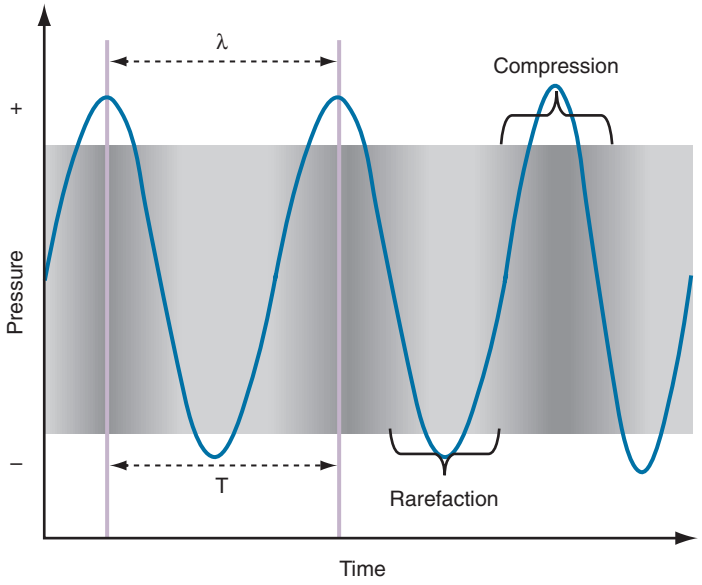


Figure 4–13. Areas of compression alternating with areas of rarefaction are depicted as a sine wave. The wavelength (λ) is the length from peak compression to peak compression in this drawing. This graphic depiction is critical to the understanding of the behavior of sound waves in the human body and of how ultrasound images are generated. (Adapted from Merritt CRB. Physics of ultrasound. In: Rumack CM, Wilson SR, Charboneau JW, editors: Diagnostic ultrasound. 3rd ed. St Louis: Elsevier; 2005. p. 4.)

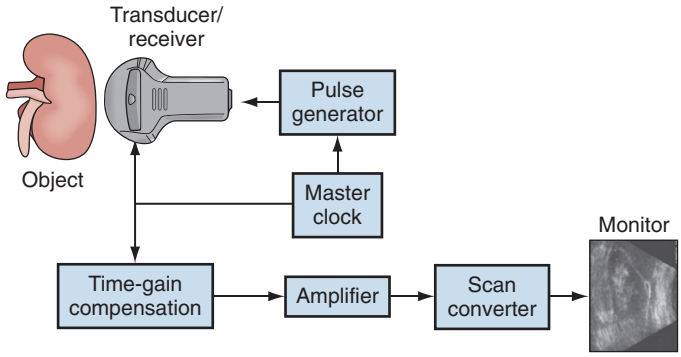


Figure 4–14. In this simplified schematic diagram of ultrasound imaging, the ultrasound wave is produced by virtue of a pulse generator controlled by a master clock. The reflected waves received by the transducer are analyzed for amplitude and transit time within the body. The scan converter produces the familiar picture seen on the monitor. The actual image is a series of vertical lines that are continuously refreshed to produce the familiar real-time, gray-scale image.

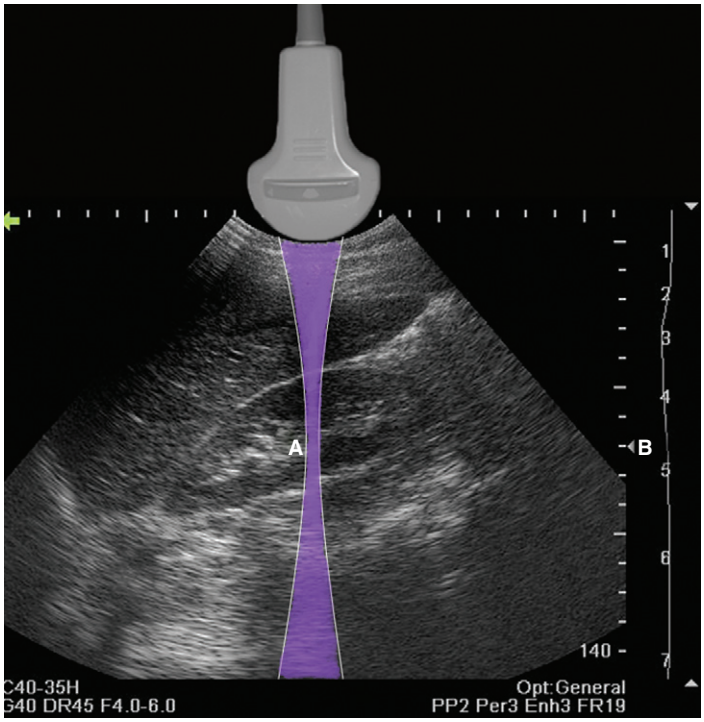


Figure 4–15. The shape of the ultrasound beam is simulated in this drawing (purple). The focal zone (**A**) is located to produce the best lateral resolution of the medial renal cortex. The location of the focal zone is designated by the caret (**B**). The location of the focal zone can be adjusted by the operator.

Mechanical waves are represented graphically as a sine wave alternating between a positive and negative direction from the baseline. Ultrasound waves are described using the standard nomenclature for sine waves. A wavelength (λ) is described as the distance between one peak of the wave and the next peak. The complete path traveled by the wave from one peak to the next is called a *cycle*. One cycle per second is known as *1 hertz* (Hz). The "period" is the time it takes for one complete cycle of the wave.

The "amplitude" of a wave is the maximal excursion in the positive or negative direction from the baseline. Amplitude corresponds to the mechanical energy associated with the sound wave and is a key property in assigning pixel brightness to a gray-scale ultrasound image. The greater the amplitude is, the brighter the corresponding pixel.

Ultrasound Image Generation

The image produced by an ultrasound machine begins with the transducer. In ultrasound imaging, the transducer has a dual function as a sender and receiver. Sound waves are created in short pulses and transmitted into the body and are then at least partially reflected. Reflected mechanical sound waves are received by the transducer and converted back into electrical energy. The transducer acts as a receiver more than 99% of the time. The electrical energy is converted by the ultrasound instrument to an image displayed on a monitor (Fig. 4–14).

Resolution

The resolution of an ultrasound image refers to the ability to discriminate two objects in close proximity to one another. **Axial resolution** refers to the ability to identify as separate two objects in the direction of the traveling sound wave. Axial resolution is directly dependent on the frequency of sound waves. The higher the sound wave's frequency is, the better the axial resolution. **Lateral resolution** refers to the ability to identify separately objects that are equidistant from the transducer. Lateral resolution is a function of the focused width of the ultrasound beam and is a characteristic of the transducer. The location of the narrowest beam width can be adjusted by the user. The more focused the beam is, the better the lateral resolution at that location. Thus image quality can be enhanced by locating the narrowest beam width (focus or focal zone) at the depth of the object or tissue of interest (Fig. 4–15).

The velocity with which a sound wave travels through tissue is a product of its frequency and wavelength (Fig. 4–16). The **average velocity of sound in human tissues is 1540 meters per**

second. Because the average velocity of sound in tissue is a constant, changes in frequency will result in changes in wavelength.

The optimal ultrasound image requires tradeoffs between resolution and depth of penetration. High-frequency transducers of 6 to 10 MHz may be used to image structures near the surface of the body (e.g., testis, pediatric kidney) with excellent resolution. However, deeper structures (e.g., right kidney, bladder) require lower frequencies of 3.5 to 5 MHz to penetrate. Such images will have poorer axial resolution.

Mechanisms of Attenuation

As sound waves transit tissues, energy is lost or attenuated. Mechanisms of attenuation include **reflection, scattering, interference, and absorption**. Reflection is the key physical phenomenon that allows for information to return to the transducer as mechanical energy. Reflection occurs when ultrasound waves strike an object, a surface, or a boundary (called an **interface**) between unlike tissues. The shape and size of the object and the angle at which the advancing wave strikes the object are critical determinants of the amount of energy reflected. The amount of energy reflected from an interface is also influenced by the **impedance** of the two tissues at the interface. Impedance is a property that is influenced by tissue stiffness and density. It is the difference in impedance that allows an appreciation of interfaces between different types of tissue (Table 4–5).

The impedance difference between perinephric fat and the kidney allows a sharp visual distinction at the interface. If the impedance difference between tissues is small (such as that between liver and kidney), the interface between the tissues will be more difficult to see (Fig. 4–17A). If impedance differences are large, there will be significant reflection of the sound wave producing an acoustical shadow distal to the interface (Fig. 4–17B).

Scattering occurs when sound waves strike a small or irregular object. The resulting spherical wave overlaps those of surrounding scattering objects (Fig. 4–18).

When interacting sound waves are in phase or out of phase, their amplitude will be enhanced or diminished. This **pattern of interference** is partially responsible for the echo architecture or texture of organs. One pattern of interference, commonly called **"speckling"** (Fig. 4–19), is seen in organs with fine, internal histology such as the testis.

Absorption occurs when the mechanical energy of the ultrasound waves is converted to heat. Absorption is directly proportional to frequency. Therefore the higher the frequency of the incident wave, the greater will be the absorption of energy and the more tissue heating that will result. It follows that higher-frequency waves are more rapidly attenuated and therefore have a limited depth of penetration (Fig. 4–20).

$$v = f \times \lambda$$
$$\textit{velocity} = \textit{frequency} \times \textit{wavelength}$$

Figure 4–16. The relationship between velocity, frequency, and wavelength of sound waves in tissue. Wavelength and frequency vary in an inverse relationship.

Artifacts

The interaction of ultrasound waves with tissues may produce images that do not reflect the true underlying anatomy. These misrepresentations are called "artifacts." Artifacts may be

Table 4–5.

Density and Impedance of Tissues Encountered During Urologic Ultrasound

	DENSITY	IMPEDANCE
Air and other gases	1.2	0.0004
Fat tissue	952	1.38
Water and other clear liquids	1000	1.48
Kidney (average of soft tissue)	1060	1.63
Liver	1060	1.64
Muscle	1080	1.70
Bone and other calcified objects	1912	7.8

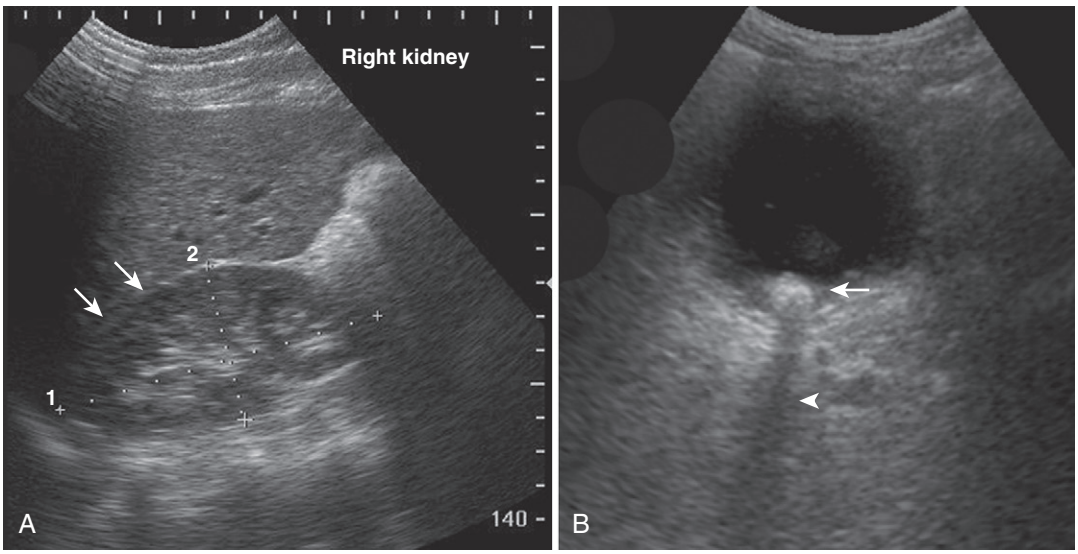


Figure 4–17. **A,** In this sagittal view of the right kidney, the paucity of perinephric fat and the small impedance difference make it difficult to distinguish the interface between the kidney and the liver *(arrows)*. **B,** The large impedance difference at the interface between urine and this bladder stone *(arrow)* results in significant reflection and attenuation of the sound wave. An acoustic shadow is seen distal to the stone *(arrowhead)*.

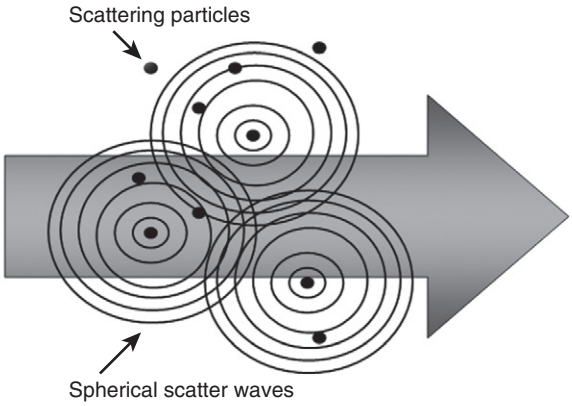


Figure 4–18. Scattering is a phenomenon that occurs when sound waves strike small objects. The resulting pattern of energy dispersal often results in interference.

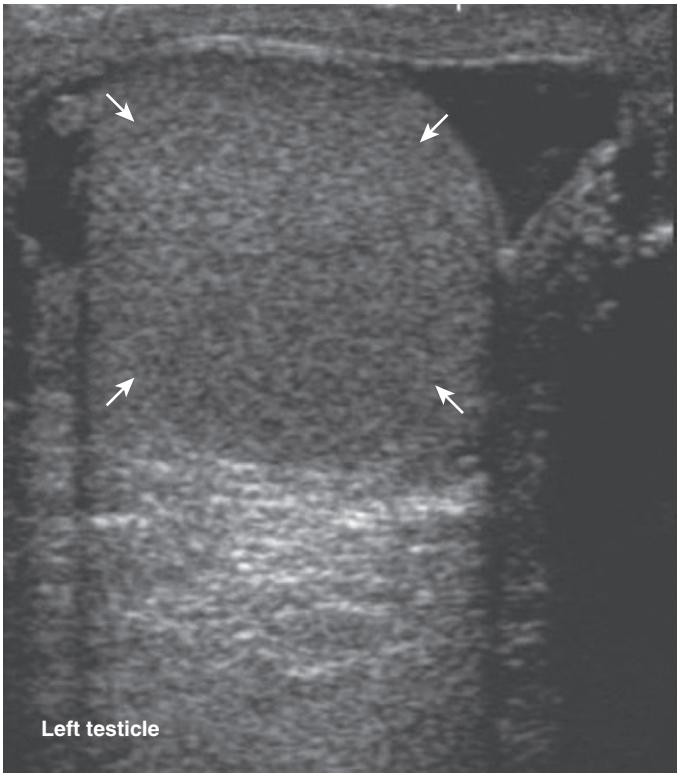


Figure 4–19. Fine internal echogenicity called "speckle" is caused by scattering of sound waves and the resultant pattern of interference. Note the resulting finely granular, homogenous echogenicity *(arrows)* of the testicular parenchyma.

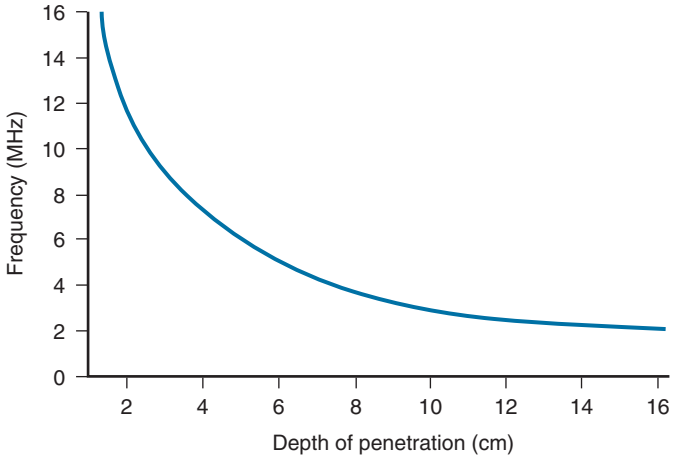


Figure 4–20. The relationship between frequency and tissue penetration. High-frequency sound waves are rapidly attenuated and are unable to penetrate deeply. Conversely, low-frequency waves are less attenuated and able to penetrate deeply to internal structures.

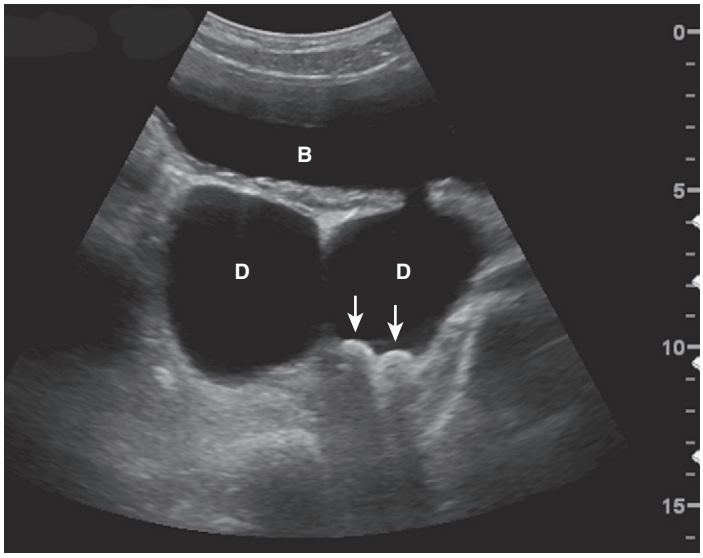


Figure 4–21. In this transverse view of the urinary bladder (B), there are two large bladder diverticula (D). Two stones *(arrows)* strongly reflect and attenuate the incident sound wave, producing an acoustical shadow. Note that the stones appear crescentic even though they are ovoid in shape.

misleading but, if recognized, may also assist diagnosis. **Acoustical shadowing** occurs when there is significant attenuation of sound waves at a tissue interface. Echo information posterior to the interface may be obscured or lost. An anechoic or hypoechoic "shadow" is produced. Under these conditions, three-dimensional objects such as stones may appear as crescentic objects, making it difficult to obtain accurate measurements (Fig. 4–21). Important pathology posterior to such an interface may be missed. This problem may often be overcome by changing the angle of insonation, changing the frequency of the transducer, or changing the focal zone of the transducer.

Increased through transmission is observed when sound waves are less attenuated while passing through a given structure or tissue than by the surrounding tissues. For example, when imaging a simple cyst of the kidney, sound waves passing through the cyst are less attenuated than those passing through the surrounding renal cortex and renal sinus. When the waves transiting the cyst strike the back wall of the cyst and posterior renal tissue, the waves are more energetic on arrival to these tissues. The reflected sound waves are also more energetic and less attenuated as they return to the transducer. The result is that tissue posterior to the cyst appears hyperechoic compared with the surrounding renal tissue, even though the tissues are histologically identical (Fig. 4–22). The effect of this artifact can be mitigated by changing the angle of insonation or adjusting the time-gain compensation (TGC) settings.

An **edging artifact** occurs when sound waves strike a curved surface or interface at an incident angle, resulting in refraction of the wave along the plane of the interface (Fig. 4–23).

An incident wave at this angle (the critical angle) will not be directly reflected to the transducer, resulting in a hypoechoic "shadow." This artifact is commonly seen in testicular ultrasonography and transrectal ultrasonography (Fig. 4–24). It can be overcome by changing the angle of insonation.

A **reverberation artifact** results when there are large differences in impedance between two adjacent tissues or surfaces with a strong reflection of the incident wave. The ultrasound wave bounces back and forth (reverberates) between the transducer interface and the reflective interface. With the second transit of the sound wave, the ultrasound equipment interprets a second object that is twice as far away as the first. There is ongoing attenuation of the sound wave with each successive reverberation, resulting in a slightly less intense image displayed on the screen. Therefore echoes are produced, spaced at equal intervals from the transducer but progressively less intense (Fig. 4–25).

The reverberation artifact can also be seen in cases where the incident sound wave strikes a series of smaller reflective objects (such as the gas-fluid mixture in the small bowel), which results in multiple reflected sound waves of various angles and intensity (Fig. 4–26). The resultant echo pattern is a collection of hyperechoic artifactual reflections distal to the structure with progressive attenuation of the sound wave.

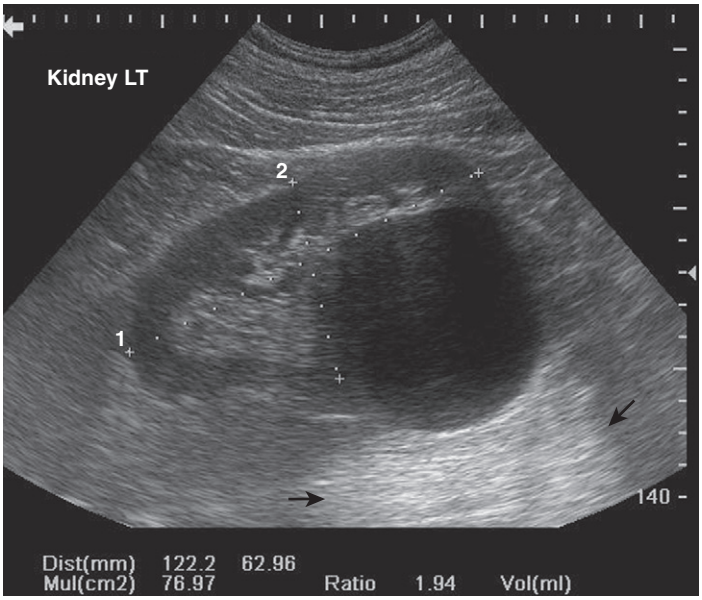


Figure 4–22. Increased thru-transmission (also called *distal enhancement*) is demonstrated in this longitudinal view of the left kidney. The tissue distal to the cyst appears hyperechoic (indicated by *arrows*) compared with adjacent tissue.

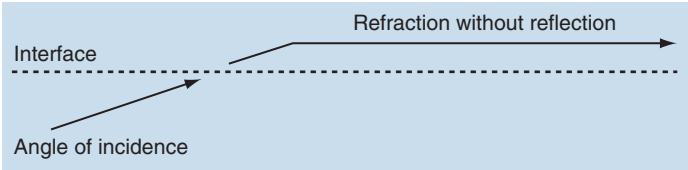


Figure 4–23. When sound waves strike a surface or interface at a "critical angle," the wave is refracted without significant reflection.

Modes of Ultrasound

Gray-Scale Ultrasound

Gray-scale B-mode ultrasonography is the most commonly employed mode of ultrasound. This pulsed-wave technique produces real-time two-dimensional images consisting of shades of gray. The generation of this image involves assigning a pixel brightness to the amplitude of the returning sound waves received by the transducer. The position of the pixel is determined by the duration of the round trip of the sound wave. Individual lines of data are displayed sequentially on the monitor to produce a continuous or real-time image. Evaluation of gray-scale imaging requires the ability to recognize normal patterns of echogenicity from anatomic structures. Variations from these expected patterns of echogenicity indicate disorders of anatomy or physiology.

Doppler Ultrasound

The Doppler ultrasound mode depends on the physical principle of frequency shift when sound waves strike a moving object. The basic principle of Doppler ultrasound is that sound waves of a certain frequency will be shifted or changed on the basis of the direction and velocity of the moving object, as well as the angle of insonation. This phenomenon allows for the characterization of motion, most commonly the motion of blood through vessels, but it may also be useful for detecting the flow of urine.

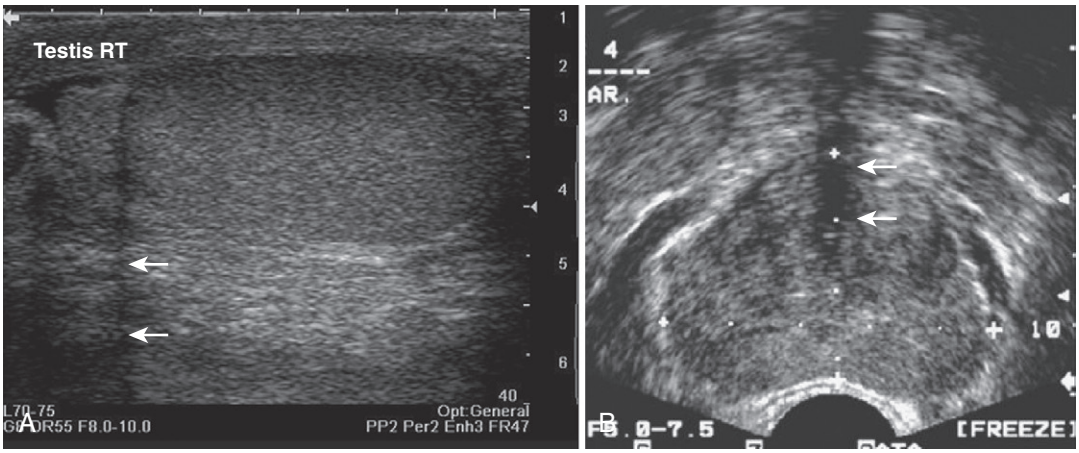


Figure 4–24. **A,** The curved surface of the tunica albuginea of the upper pole of testis creates a critical angle edging artifact *(arrows)*. **B,** The rounded surfaces of the lateral lobes of the prostate as they meet in the prostatic urethra create an edging artifact *(arrows)* in this transverse image of the prostate.

Color Doppler ultrasonography allows for evaluation of the velocity and direction of motion. A color map may be applied to direction with the most common assignation of the color blue to motion away from the transducer and red for motion toward the transducer. The velocity of motion is designated by the intensity of the color; thus the brighter the color is, the more rapid the motion. Color Doppler may be used to evaluate the presence of absence of blood flow in the kidney, testes, penis, and prostate. It also may be useful in the detection of ureteral "jets" of urine emerging from the ureteral orifices.

Color Flow with Spectral Display is a mode that allows the interrogation of particular areas within an ultrasound image for flow and displays the flow as a continuous wave form. This mode is commonly used to evaluate the pattern and velocity of blood flow in the intrarenal or penile vasculature. The waveform provides information about peripheral vascular resistance in the tissues. The most commonly used index of these velocities is the resistive index. The **resistive index** is a ratio of peak systolic velocity minus the end-diastolic velocity over the peak systolic velocity. This index is helpful in characterizing a number of clinical conditions including renal artery stenosis, ureteral obstruction, and penile arterial insufficiency.

Power Doppler ultrasonography is a mode that assigns the amplitude of frequency change to a color map. This does not permit evaluation of velocity or direction of flow but is less affected by back-scattered waves and therefore a more sensitive mode for detecting blood flow. Power Doppler is less angle dependent than color Doppler and is three to five times as sensitive as color Doppler ultrasound for detecting flow.

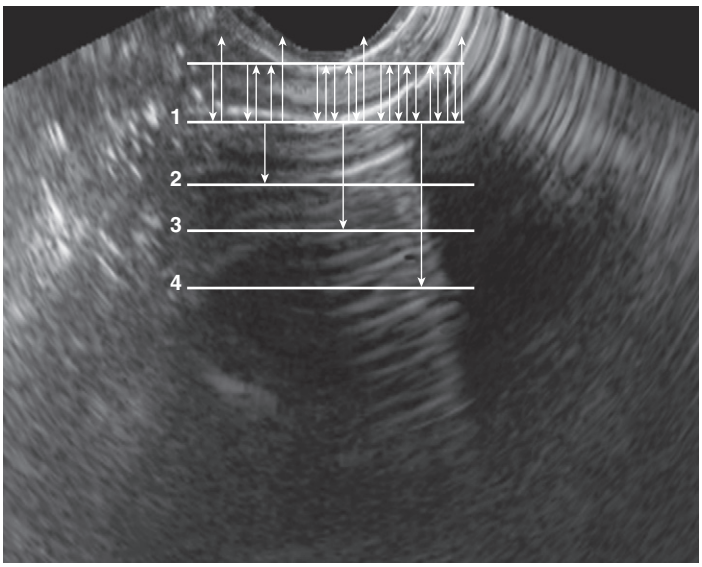


Figure 4–25. Reverberation artifact: The strongly reflective interface is projected with decreasing amplitude as the incident sound wave makes multiple round trips.

Harmonic Scanning

Harmonic scanning makes use of aberrations related to the nonlinear propagation of sound waves within tissue. These asymmetrically propagated waves generate fewer harmonics, but those that are generated have greater amplitudes. Because these harmonics are not subject to scattering associated with the incident wave, there is less noise associated with the signal. By concentrating on the harmonic frequencies produced within the body and reflected to the transducer, it is possible to produce an image with less artifact and greater resolution (Fig. 4–27).

Spatial Compounding

Spatial compounding is a scanning mode whereby the direction of insonation is electronically altered and a composite image is generated. This technique reduces the amount of artifact and noise, producing a scan of better clarity.

Three-Dimensional Scanning

Three-dimensional (3-D) scanning has been used extensively in obstetrics and gynecology but so far has limited application in urology. 3-D scanning produces a composite of images (data set), which can then be manipulated to generate additional views of the anatomy in question (Fig. 4–28). 3-D rendering may be important in procedural planning and precise volumetric assessments

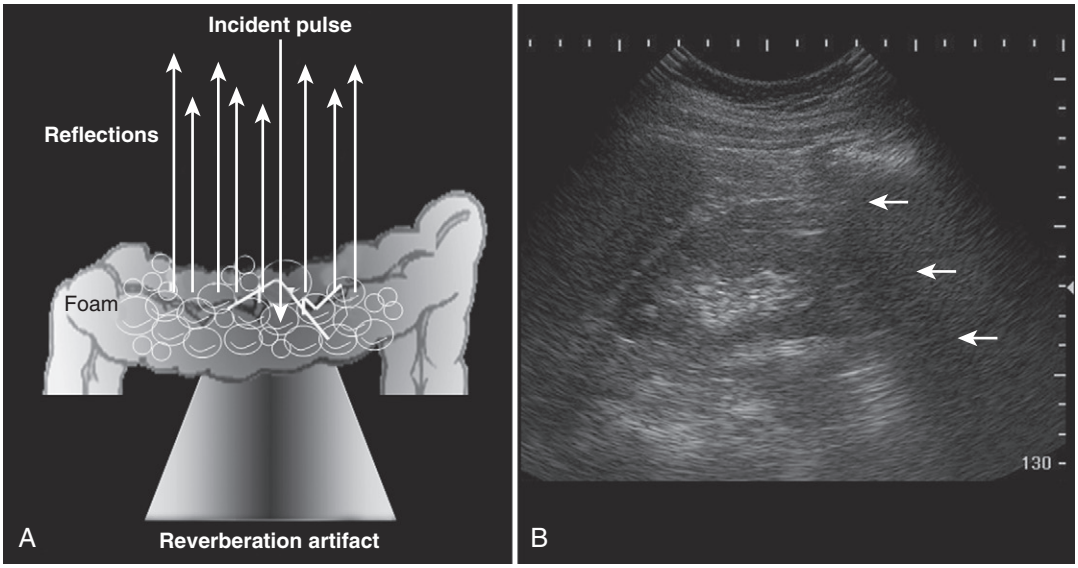


Figure 4–26. When ultrasound strikes a structure such as bowel, which contains gas bubbles (**A**), the resultant reverberation artifact has a characteristic appearance sometimes called a "comet tail." **B,** A comet tail artifact produced by bowel gas *(arrows)* obscures the lower pole of the kidney.

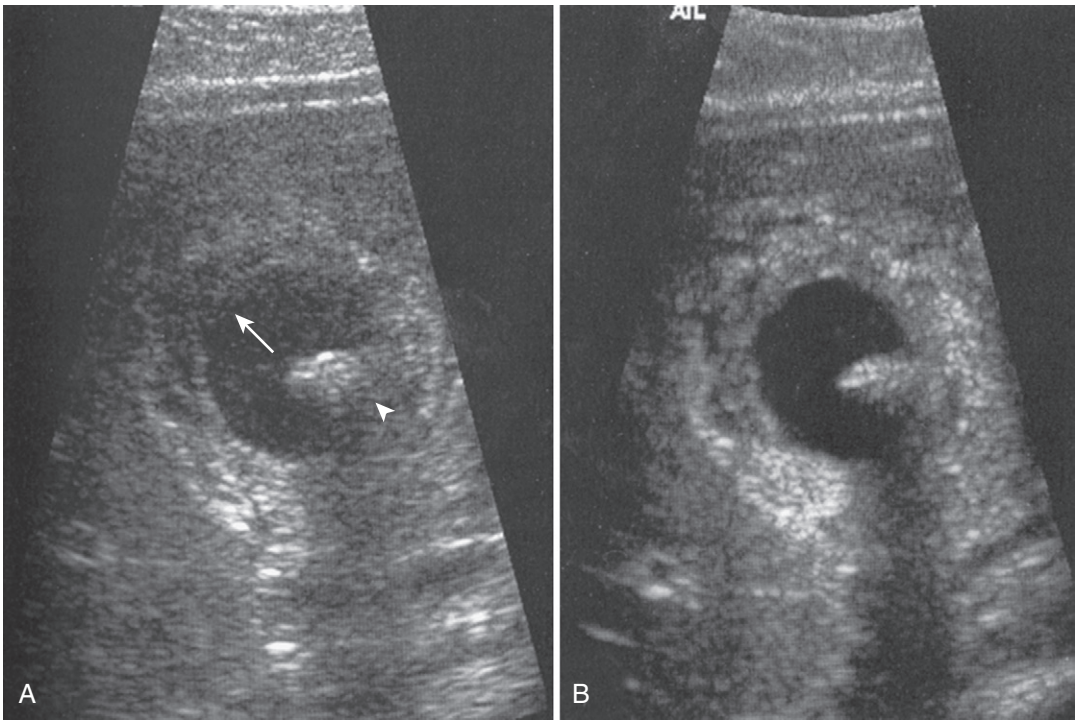


Figure 4–27. **A,** Standard gray-scale image of a cyst containing a mural nodule *(arrowhead)*. Note the artifactual echogenicity within the cyst *(arrow)*. **B,** The same structure on harmonic scanning is more clearly seen. There is less artifact within and distal to the cyst. (From Rumack CM, Wilson, SR, Charboneau JW, Johnson J, editors. Diagnostic ultrasound. 3rd ed. St Louis: Elsevier; 2005. Fig. 1–17, p. 17.)

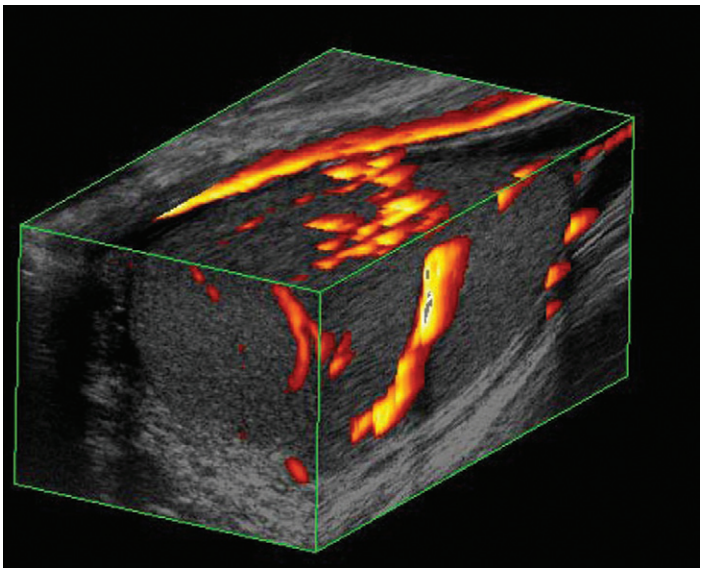


Figure 4–28. A three-dimensional image of the testis demonstrating intratesticular blood flow on power Doppler. The image can be virtually rotated and manipulated to produce unique anatomic perspectives. (Used with permission by BK Medical.)

(Ghani et al, 2008a, 2008b). 3-D scanning may allow the recognition of some tissue patterns that would otherwise be inapparent on two-dimensional scanning (Mitterberger et al, 2007b; Onik and Barzell, 2008).

Contrast Agents in Ultrasound

Intravenous compounds that contain microbubbles have been used for enhancing the echogenicity of blood and tissue.

Description of ultrasound images

The liver is used as a benchmark for echogenicity:

- Hypoechoic = darker and black
- Hyperechoic = brighter and white
- Isoechoic = similar to reference point of liver
- Anechoic = black, without echoes

Figure 4–29. The nomenclature for describing the appearance of ultrasound images.

Microbubbles are distributed in the vascular system and create strong echoes with harmonics when struck by sound waves. The bubbles themselves are rapidly degraded by their interaction with the sound waves. Contrast agents may be useful in prostatic ultrasonography by enhancing the ability to recognize areas of increased vasculature. The use of intravenous ultrasound contrast agents is considered investigational but has shown promise in a number of urologic scanning situations (Mitterberger et al, 2007a; Wink et al, 2008).

Documentation

When urologists perform and interpret ultrasound studies, it is important that appropriate nomenclature be used to describe the objects imaged (Fig. 4–29). By convention, the liver is used as a benchmark for echogenicity. If a structure is hypoechoic, it means it is darker than the surrounding tissues. If it is hyperechoic, it means it is brighter than the surrounding tissues. Isoechoic means it is similar to the surrounding tissues. Structures that do not generate echoes are called *anechoic*. A simple cyst is an example of a structure with an anechoic interior. In general, a high water content causes tissue to appear hypoechoic. In general, a high fat content causes tissue to appear hyperechoic.

By convention, structures imaged by ultrasonography should be oriented so that the superior aspect of the structure is to the left as the image is viewed and the inferior aspect of the structure to the right. With paired structures it is critically important to document right or left. It is useful to use equipment-generated icons to illustrate patient position and the orientation of insonation (Fig. 4–30).

The appropriate number of images to be captured for documentation is the number necessary to document a systematic and complete examination and to document relevant pathology.

Patient Safety

Diagnostic ultrasonography transmits energy into the patient that has the potential to produce biologic effects. The two main categories of biologic effects are **mechanical effects** and **thermal effects.**

The mechanical effects of ultrasonography are torque and streaming. The mechanical effects of an acoustic field may produce a phenomenon called *cavitation.* **Cavitation** occurs when small gas-filled bubbles form and then collapse. These collapsing bubbles liberate a large amount of energy, which may cause damage to tissue in certain circumstances. Mechanical effects are most likely to be observed around gas-containing structures such as lung and bowel. The thermal effects of ultrasonography are primarily the result of tissue heating resulting from the absorption of energy. The amount of tissue heating is influenced by several factors including beam focusing, transducer frequency, exposure time, scanning mode, and tissue density.

To assist the sonographer in monitoring the bioeffects of ultrasound, the ultrasonography community has adopted the **output display standard (ODS).** Two values are typically displayed: the **mechanical index (MI)** and the **thermal index (TI).** These indices are calculated **estimates** of the potential for bioeffects of ultrasonography based on the mode of ultrasonography being used, frequency, power output, and time of insonation. The MI indicates the probability that cavitation will occur. For tissues not containing stabilized gas bodies (lung and intestine), the risk of cavitation is low as long as the MI is less than or equal to 0.7. For structures adjacent to lung or intestine, scanning time should be limited if the MI exceeds 0.4. The TI indicates the probability that tissue temperature within the sonographic field will be increased by 1° C. The precise consequences of tissue heating are not completely understood, but even tissue temperature elevations of up to 6° C are not likely to be dangerous unless exposure time exceeds 60 seconds. The MI and TI are typically displayed on the monitor during ultrasound examinations, and all practitioners should be familiar with the location. **It is important to note that these indices are not safety limits.**

In general, ultrasonography performed by urologists has a low risk for patient harm as long as standard protocols are followed (Fowlkes, 2008). Although tissue heating may occur, there are no confirmed biologic effects of tissue heating in nonfetal scanning except when they are sustained for extended periods. Users should be aware that for soft tissues not known to contain gas bodies, there is no basis in present knowledge to suggest an adverse nonthermal bioeffect from current diagnostic instruments not exceeding the U.S. Food and Drug Administration output limits (Fowlkes, 2008). Nevertheless, all urologists should endeavor to follow the principles of **ALARA,** which stands for **"As Low As Reasonably Achievable."** The ALARA principle is intended to limit the total energy imparted to the patient during an examination. This can be accomplished by (1) keeping power outputs low, (2) using appropriate scanning modes, (3) limiting examination times, (4) adjusting focus and frequency, and (5) using the cine function during documentation.

In summary, ultrasound scanning offers an excellent, cost-effective modality for diagnosing and treating urologic conditions. **The most important factor in ultrasound safety is the informed operator.** Urologists should endeavor to perform limited examinations using consistent technique for specific indications. Patient safety and equipment maintenance should be emphasized in all the environments where ultrasound technology is used.

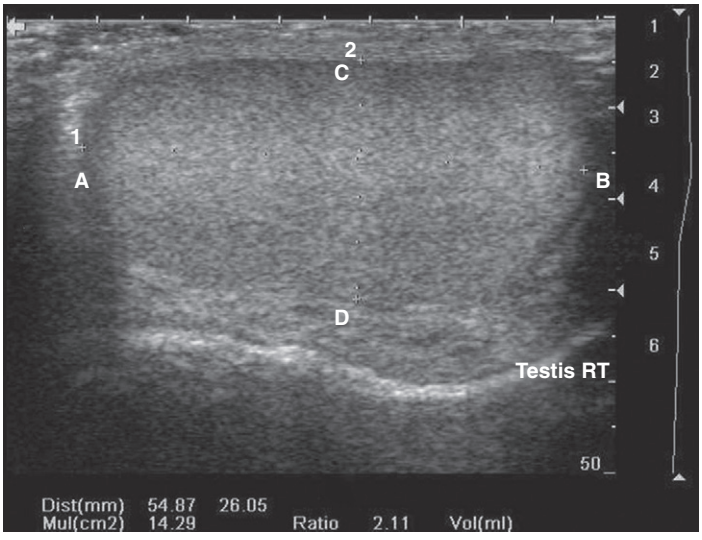


Figure 4–30. In this sagittal image of the right testis, the superior pole of the testis (A) is to the left, the inferior pole of the testis (B) is to the right. The anterior aspect of the testis (C) is at the top of the image and the posterior aspect (D) at the bottom. Without the label, there would be no way to distinguish the right from the left testis.

Clinical Urologic Ultrasound

The use of ultrasonography in urology has expanded dramatically because of its profound utility in the clinic and operating room. Long the mainstay of the diagnosis of prostatic disease, ultrasonography is increasingly being used by urologists in the clinical environment for initial diagnosis, interventional management, and longitudinal follow-up of urologic diseases.

Renal Ultrasound

Introduction. Urologists, by virtue of their intimate knowledge of surgical anatomy of the kidneys and retroperitoneum, are uniquely qualified to perform and interpret selected ultrasound examinations of the abdomen. These skills are relevant in both the office and the operating room environment. Urologists generally perform abdominal ultrasonography for a specific clinical indication and less often for general screening of the abdominal contents. Therefore in most clinical situations, a limited retroperitoneal examination is used in urologic practice.

Technique. The transducer normally used for renal ultrasonography is a curved array transducer of 3.5 to 5.0 MHz. Transducers of a higher frequency may be used for pediatric patients. For intraoperative and laparoscopic renal ultrasonography, a linear array transducer of 6 to 10 MHz is typically employed.

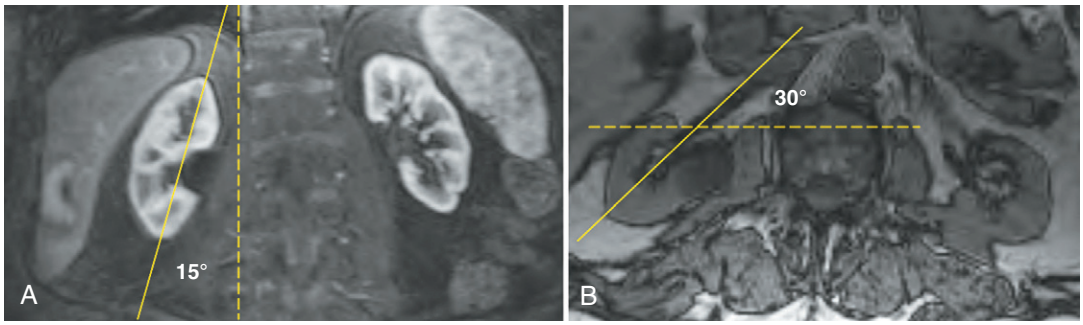


Figure 4–31. The lower pole of the kidney is displaced 15 degrees laterally compared with the upper pole (**A**). The kidney is rotated 30 degrees posterior to the true coronal plane (**B**). The lower pole of the kidney is slightly anterior compared with the upper pole.

Scanning of the right kidney is performed with the patient supine. The kidney is located by beginning in the midclavicular line in the right upper quadrant. In the sagittal plane the transducer is moved laterally until the midsagittal plane of the kidney is imaged. Once the kidney has been imaged anteriorly and posteriorly in the sagittal plane, the probe is rotated 90 degrees counterclockwise. The midtransverse plane will demonstrate the renal hilum containing the renal vein. The kidney is scanned from upper pole to lower pole.

The technique and documentation for left renal ultrasonography is identical to that of the right side. However, the left kidney is slightly more cephalad than the right kidney. Bowel gas is more problematic on the left because of the position of the splenic flexure of the colon. Visualization of the left kidney often requires the patient to be turned into a lateral position. Ultrasound imaging of the left kidney lacks the liver as an acoustic window, and it is sometimes more difficult to image the left kidney in a true sagittal plane.

Indications

1. Assessment of renal and perirenal masses
2. Assessment of the dilated upper urinary tract
3. Assessment of flank pain during pregnancy
4. Evaluation of hematuria in patients who are not candidates for intravenous pyelography (IVP), CT, or MRI because of renal insufficiency, contrast allergy, or physical impediment
5. Assessment of the effects of voiding on the upper urinary tract
6. Evaluation for and monitoring of urolithiasis
7. Intraoperative renal parenchyma and vascular imaging for ablation of renal masses
8. Percutaneous access to the renal collecting system
9. Guidance for transcutaneous renal biopsies, cyst aspiration, or ablation of renal masses
10. Postoperative evaluation of patients after renal and ureteral surgery
11. Postoperative evaluation of renal transplant patients

Normal Findings. It is helpful during scanning of the kidney to understand its anatomic position within the retroperitoneum. This assists identifying the midsagittal plane, which serves as a reference point for a complete examination (Fig. 4–31).

The adult right kidney in the sagittal view demonstrates a cortex that is usually hypoechoic with respect to the liver. The central band of echoes in the kidney is a hyperechoic area that contains the renal hilar adipose tissue, blood vessels, and collecting system. Acoustic shadowing from ribs overlying the inferior pole can be eliminated by moving the probe to a more lateral position or into the intercostal space. By having the patient take a deep breath, the kidney can be moved inferiorly to assist complete imaging (Fig. 4–32).

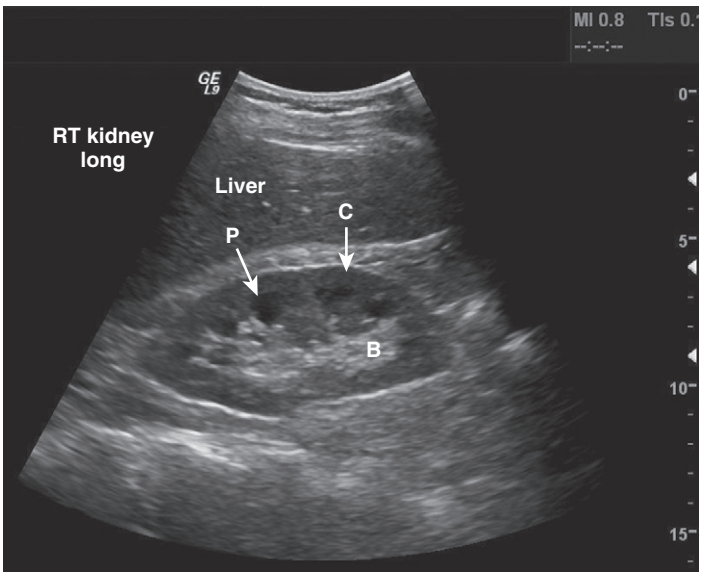


Figure 4–32. Midsagittal plane of the kidney. Note the relative hypoechogenicity of the renal pyramids (P) compared with the cortex (C). The central band of echoes (B) is hyperechoic compared with the cortex. The midsagittal plane will have the greatest length measurement pole to pole. A perfectly sagittal plane will result in a horizontal long axis of the kidney.

The echogenicity of the kidney varies with age. The renal cortex of an infant is relatively hyperechoic compared with that of an adult. In addition, there is a smaller and less apparent central band of echoes in the infant. In the adult, the echogenicity of the renal cortex is usually hypoechoic with respect to the liver (Emamian et al, 1993a). In patients with chronic medical renal diseases the renal cortex is often thinned and isoechoic or hyperechoic with respect to the liver (O'Neill, 2001).

Renal size changes over the lifetime of an individual. Nomograms for pediatric renal size should be consulted. These are based on age, height, and weight of the patient. The average adult kidney measures 10 to 12 cm in length and 4 to 5 cm in width. Measurements of renal volume may be appropriate in cases of severe renal impairment. Renal measurements should be obtained in the midsagittal plane and midtransverse plane. Measurements taken in other than the midsagittal plane and midtransverse may be spuriously low. The thickness of the parenchyma is the average distance between the renal capsule and the central band of echoes. The precise location for making this measurement is somewhat

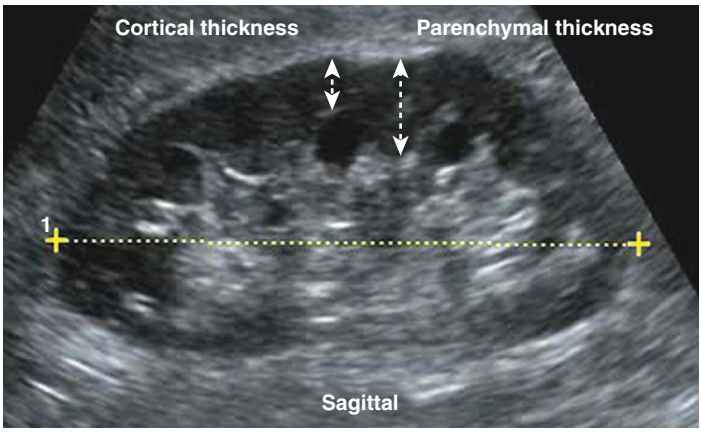


Figure 4–33. The distinction between renal cortical thickness and renal parenchymal thickness is that the renal parenchyma is measured from the central band of echoes to the renal capsule. The renal cortex is measured from the outer margin of the medullary pyramid to the renal capsule.

subjective. The midlateral renal parenchyma in the sagittal view is a common choice for obtaining this measurement (Fig. 4–33). Although there is no universal standard, the renal cortical thickness should be greater than 7 mm (Roger et al, 1994), and the renal parenchymal thickness should be greater than 15 mm in adults (Emamian et al, 1993b).

Doppler ultrasound may be helpful in evaluating the renal artery and renal vein and assessing the vascular resistance in the kidney. Doppler modes may also be useful in evaluating neovascularity associated with renal tumors and in correctly characterizing hypoechoic structures in the renal pelvis such as a parapelvic cyst, the renal vein, or the dilated collecting system.

Limitations. Some patients are not favorable candidates for renal ultrasonography. Obesity, intestinal gas, and physical deformity may be impediments to complete renal evaluation. Renal ultrasonography has poor sensitivity for renal masses less than 2 cm (Warshauer et al, 1988). There is a lack of specificity for renal tumor type except for angiomyolipoma. Angiomyolipoma has characteristics that are distinctive on ultrasonography (highly echoic), but some small renal cell carcinomas have been shown to be indistinguishable from angiomyolipoma by ultrasound criteria (Yamashita et al, 1992; Forman et al, 1993).

Transabdominal Pelvic Ultrasound

Introduction. Transabdominal pelvic ultrasonography is a tremendously versatile tool for the urologist. It is a noninvasive method for evaluating the lower urinary tract and prostate in men and the bladder in women. A curved array transducer of 3.5 to 5 MHz is most commonly employed to perform transabdominal ultrasonography. In pediatric patients a higher-frequency transducer may be used. In cases where only a residual urine or bladder volume is to be determined, an automated bladder scanner is often employed.

Technique. Bladder ultrasonography is most commonly performed with the patient supine and the sonographer on the patient's right side. The scan should be performed in a warm room, and the patient draped to provide for comfort and privacy. If necessary, a roll may be placed beneath the patient's hips. Scanning technique depends on the circumstances and the reason for the examination but in general should be performed with a moderately filled bladder. The bladder should be scanned in a sagittal and transverse manner angling the probe into the pelvis so that the bladder can be visualized beneath the pubic bone. Although the prostate cannot be imaged with the same resolution achieved during transrectal scanning, the size and morphology of the prostate can be demonstrated. Although transabdominal scanning is the most common means of evaluating the bladder, the bladder may also be assessed via a transvaginal and transrectal approach. These approaches are useful in patients who are obese or who are not suitable candidates for transabdominal scanning.

Indications

1. Measurement of bladder volume or postvoid residual urine
2. Assessment of prostate size and morphology
3. Demonstration of secondary signs of bladder outlet obstruction
4. Evaluate bladder wall configuration and thickness
5. Evaluation of hematuria of lower urinary tract origin
6. The detection of ureteroceles
7. Assessment for ureteral obstruction
8. Detection of perivesical fluid collections
9. Evaluation of clot retention
10. Confirmation of catheter position
11. Removal of retained catheter
12. Guidance of suprapubic tube placement
13. To establish bladder volume before flow rate determination

Normal Findings. Transabdominal pelvic ultrasonography should include evaluation of the lumen of the bladder, as well as bladder wall configuration and thickness. The presence of specific lesions such as stones or tumors should be documented. The structures immediately surrounding the bladder may also be evaluated including the distal ureters, the prostate in men, and the uterus and ovaries in women (Fig. 4–34). The emergence of urine from the ureteral orifices (ureteral jets) can be demonstrated. The clinical value of demonstrating ureteral jets has been questioned. Up to 10 minutes of continuous observation may be required to verify the absence of a ureteral jet (Fig. 4–35) (Delair and Kurzrock, 2006).

Bladder volume can be calculated manually by obtaining measurements in the midtransverse and midsagittal planes (Fig. 4–36). Numerous studies have shown that for bladder volumes between 100 and 500 mL, such calculated volumes are within 10% to 20% of the actual bladder volume (Roehrborn et al, 1986).

Measuring bladder wall thickness may assist the clinician in understanding the degree of bladder outlet obstruction (Fig. 4–37). Bladder wall thickness varies depending on the volume of urine in the bladder and on which part of the bladder wall is measured. It has been shown that measuring bladder wall thickness may predict bladder outlet obstruction with greater accuracy than free uroflowmetry, postvoid residual urine, and prostate volume (Oelke et al, 2007).

Transabdominal prostatic ultrasonography requires angling the probe beneath the pubic bone. In the transverse plane the transducer is fanned inferiorly until the largest transverse diameter of the prostate is identified. Measurements of the transverse width and height are obtained (Fig. 4–38A). The transducer is then rotated 90 degrees clockwise to produce a true sagittal image of the prostate. The transducer is fanned until the midline is identified. This is recognized by a v-shaped indention at the bladder neck (Fig. 4–38B). Depending on the degree of prostatic hypertrophy and the presence or absence of a middle lobe, this "v" may be more or less apparent and more or less anterior or posterior in its position. A sagittal measurement is made from the bladder neck to the apex of the prostate. The apex of the prostate may be identified by using the hypoechoic urethra as a guide.

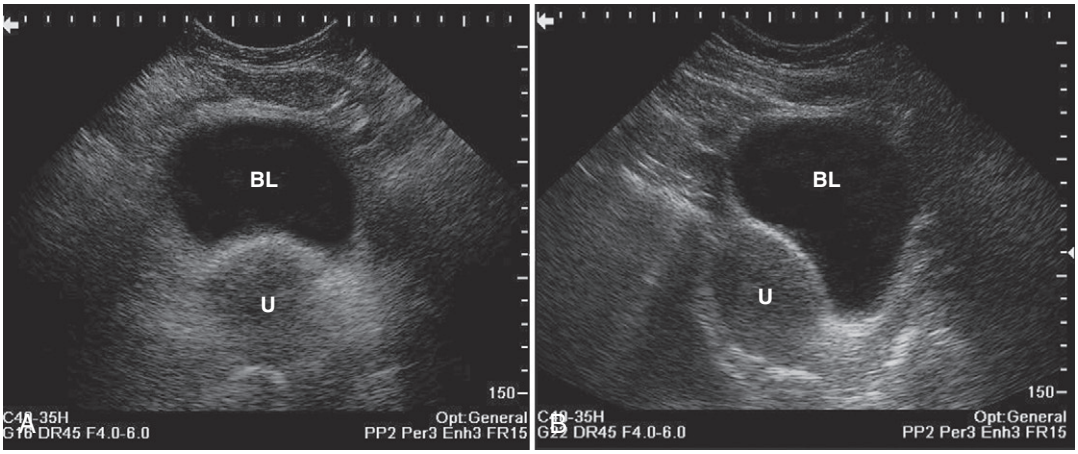


Figure 4–34. **A,** Transverse view of the bladder in this female patient demonstrates the uterus (U). **B,** Sagittal view of the bladder shows the uterus posterior to the bladder.

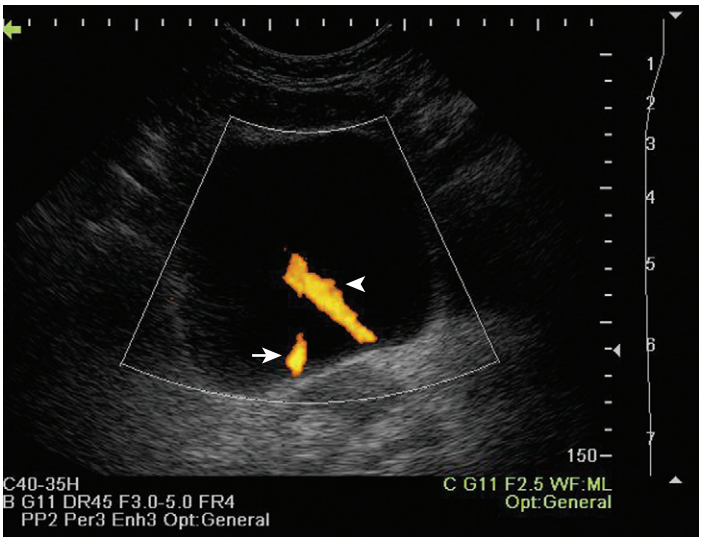


Figure 4–35. In this transverse view of the bladder, urine "jets" emerging from the left *(arrow)* and right *(arrowhead)* ureteral orifices are demonstrated by power Doppler.

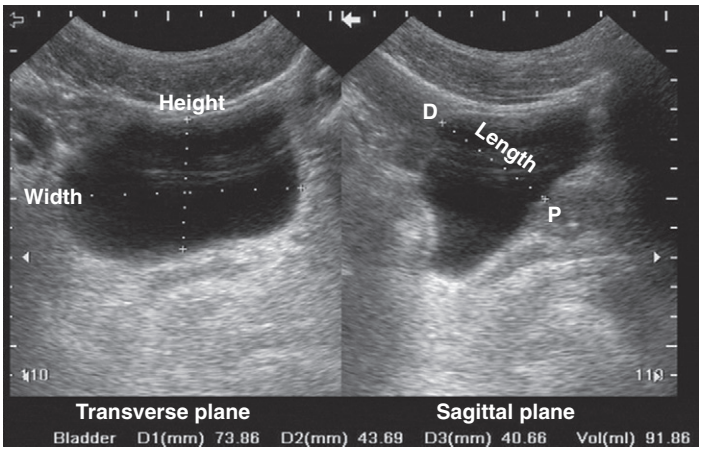


Figure 4–36. Measurement of bladder volume using this formula: bladder volume = width (transverse plane) × height (transverse plane) × length (midsagittal plane) × 0.625. In the sagittal plane, the dome (D) of the bladder is to the left and the prostate (P) to the right.

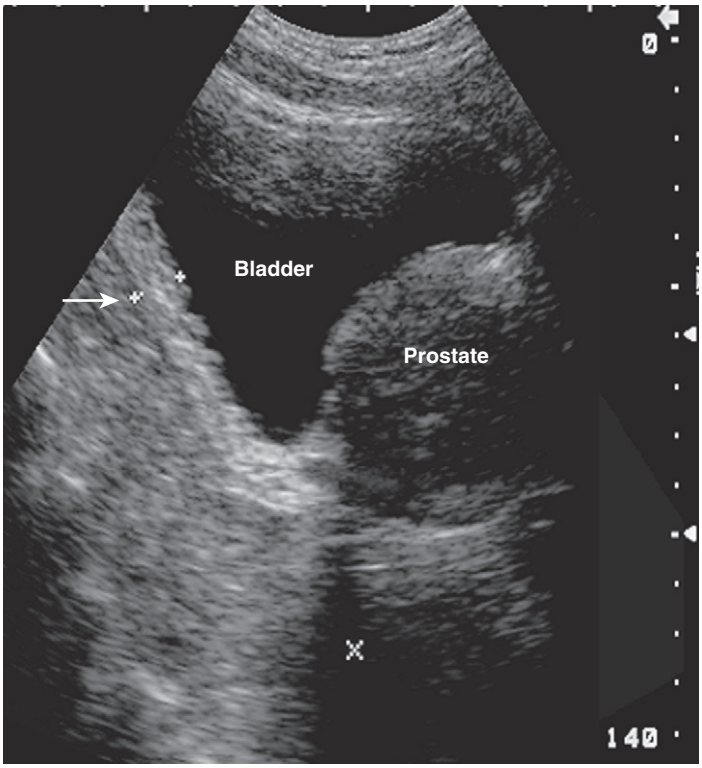


Figure 4–37. Bladder wall thickness may provide information about bladder outlet obstruction. In this sagittal view, bladder wall thickness is measured posteriorly *(arrow)* near the midline. Note the trabeculation of the relatively hyperechoic bladder wall.

The degree of protrusion of the prostate into the bladder may have some predictive value for bladder outlet obstruction. It has been shown that intravesical prostatic protrusion correlates relatively well with formal urodynamic evaluation of bladder outlet obstruction (Chia et al, 2003; Keqin et al, 2007). The measurement is obtained by drawing a line corresponding to the bladder base on sagittal scan and measuring the perpendicular distance from bladder base to greatest protrusion of the prostate into the bladder (Fig. 4–39).

Transabdominal ultrasonography of the prostate is useful in characterizing prostatic urethral length, the size and configuration

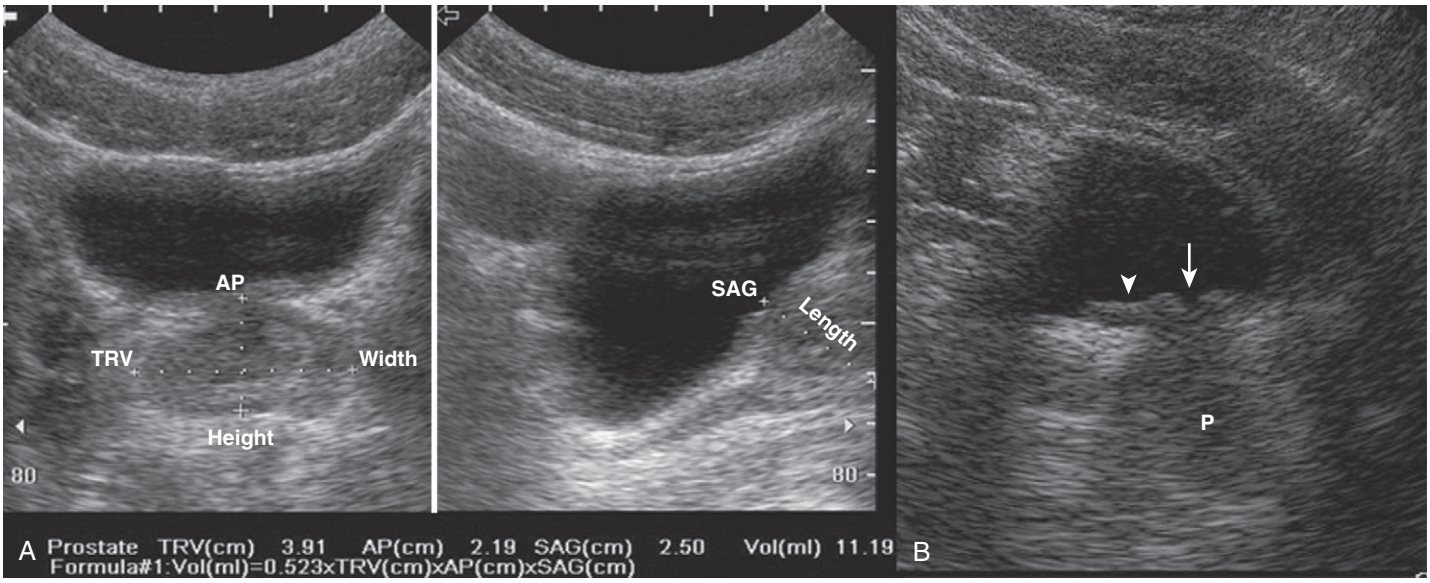


Figure 4–38. **A,** Transabdominal ultrasound is extremely useful for measuring prostatic volume and evaluating prostatic morphology. The volume of the prostate can be calculated using this formula: prostate volume (mL) = width (cm) × height (cm) × length (cm) × 0.523. **B,** In this midsagittal view of the prostate, the bladder neck is identified as a V-shaped indentation *(arrow)*. Note the characteristically hyperechoic trigone *(arrowhead)*.

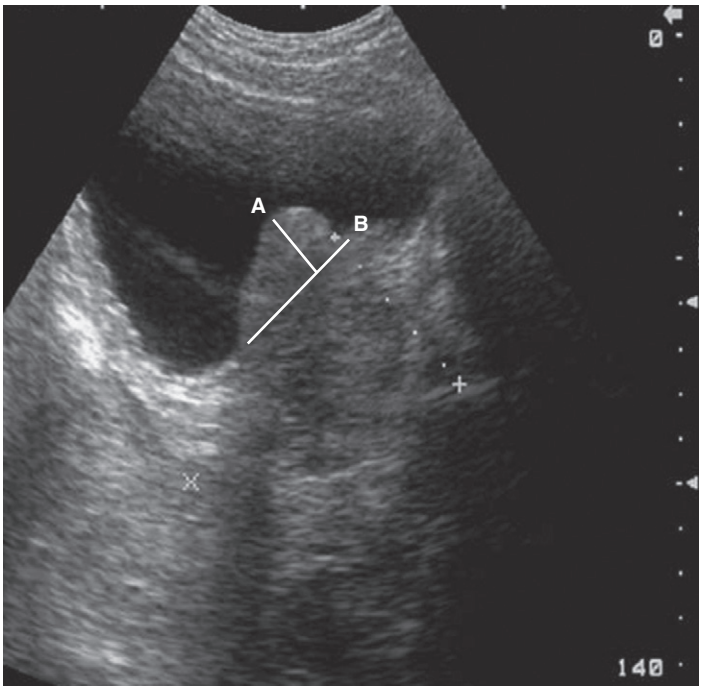


Figure 4–39. In this sagittal view of the prostate, the middle lobe extends into the bladder (A). The bladder base is defined by the line (B). The length of line (A) is the intravesical prostatic protrusion (IPP).

of the middle lobe of the prostate, and some secondary information about the physiology of bladder outlet obstruction. This information is valuable in treatment planning for bladder outlet obstruction.

Limitations. Transabdominal pelvic ultrasonography yields limited information in patients with an empty bladder. The ability to identify distal ureteral obstruction, bladder stones, and bladder tumors requires a full bladder. Although prostatic morphology and volume can be assessed with an empty bladder, it is much easier when the bladder is full. Pelvic structures may be difficult to evaluate in patients with a protuberant abdomen or panniculus. **Automated measurement of bladder volume or residual urine, though using ultrasonography, is not an imaging study.** Lack of imaging confirmation can lead to inaccurate residual urine determinations in patients with obesity, clot retention, ascites, bladder diverticulum, or perivesical fluid collection (e.g., urinoma, lymphocele).

Ultrasonography of the Scrotum

Introduction. No aspect of urologic care is better suited to the use of ultrasonography than evaluation of the scrotum. Urologists have a surgical understanding of the anatomy and extensive experience with the diagnosis and treatment of disorders that affect the scrotum. Because the scrotum and its contents are superficial, high-frequency transducers may be employed to yield excellent and detailed anatomic and physiologic information. Imaging information can be correlated with findings on direct physical examination.

Technique. Sound technique is critical to performing adequate ultrasonography of the scrotum. In general, the examination should be carried out in a quiet room that is adequately warm for patient comfort. The patient should be supine with the scrotum supported on a towel or on the anterior thighs. The patient should be draped in such a way as to hold the penis out of the way and to ensure patient privacy. Copious amounts of conducting gel should be used to provide a good interface between the transducer and the scrotal skin because air trapping by scrotal hair will result in unwanted artifacts. Complete but gentle contact between skin and transducer is essential because excessive pressure results in movement of testis or compression of the testis. Compression may change echogenicity and obscure fine anatomic detail. In addition, compression may significantly alter volume measurements.

Scrotal ultrasonography is performed with a high-frequency linear array transducer, generally in the range of 6 to 12 MHz. Transducers may be 4 to 7.5 cm in width. Some sonographers prefer the maneuverability of a 4-cm transducer, whereas others

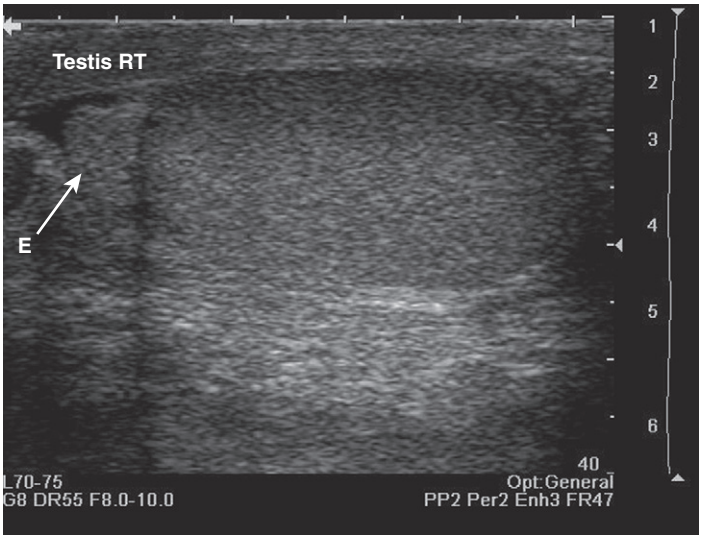


Figure 4–40. In this longitudinal view the head of the epididymis (E) is seen to the left, and the lower pole of the testis is to the right. Normal testicular sonographic anatomy is characterized by a homogeneous finely granular appearance of the testis.

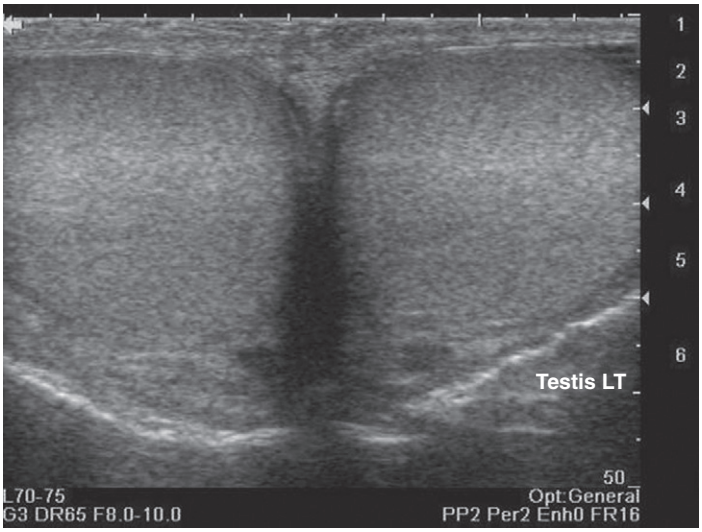


Figure 4–41. Simultaneous bilateral views are important to rule out a diffuse infiltrative process such as lymphoma. A diffuse and homogenous change in echogenicity in one testis could otherwise be unappreciated. In this example, the testes are symmetric and normal.

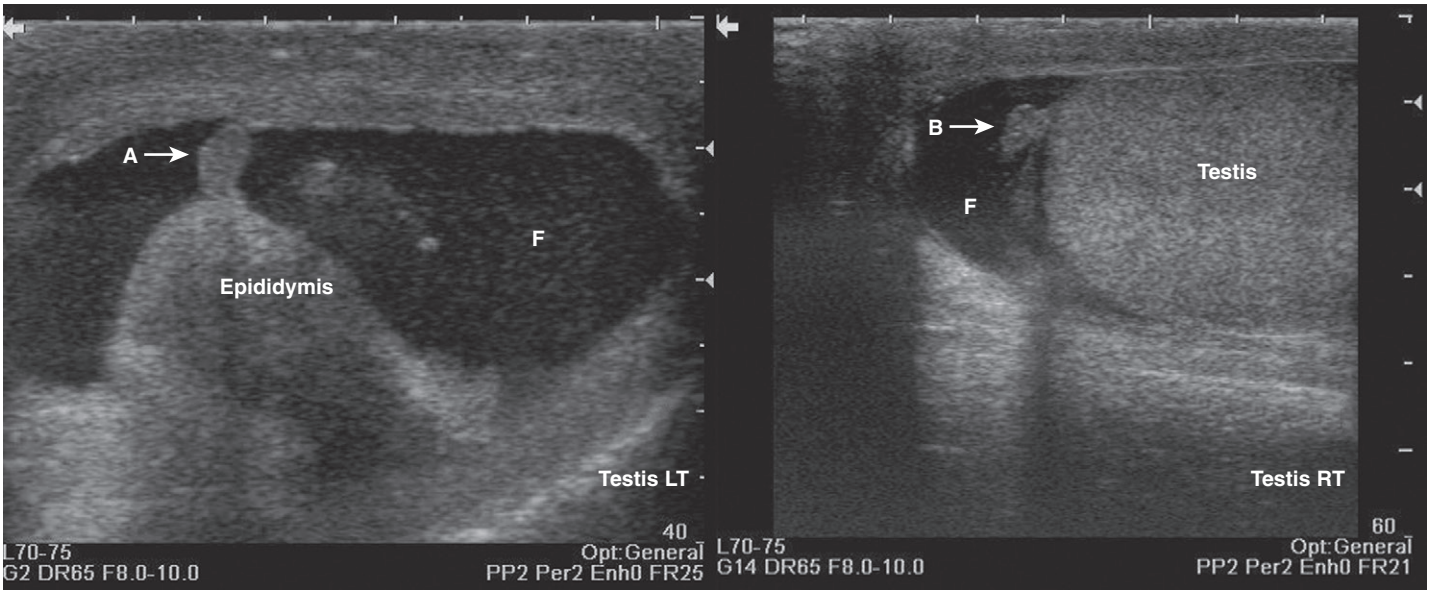


Figure 4–42. The presence of paratesticular fluid (F) permits the identification of the appendix epididymis (A) and the appendix testis (B).

prefer the longer 7.5-cm transducer for its ability to simultaneously image the entire testis in the sagittal plane. Imaging should be done in a systematic fashion and should include sagittal and transverse views of the testis. The sagittal view should proceed from the midline medially and then laterally and from the midtransverse section of the testis to the upper pole and the lower pole of the testis. In addition to the testis, the epididymis and entire scrotal contents should be imaged.

Indications

1. Assessment of scrotal and testicular mass
2. Assessment of scrotal and testicular pain
3. Evaluation of scrotal trauma
4. Evaluation of infertility
5. Follow-up of scrotal surgery
6. Evaluation of the empty or abnormal scrotum

Normal Findings. It is important to document the size and, if appropriate, the volume of the testes. The echo architecture of the testis should be described (Fig. 4–40). It is important to compare the testes for echogenicity because some infiltrative processes may result in diffuse changes in a testis that would only be noticed when that testis is compared with its contralateral mate (Fig. 4–41). For example, lymphomatous or leukemic involvement of the testis may result in a diffusely hypoechoic and homogeneous appearance, which may be unilateral (Mazzu et al, 1995).

If paratesticular fluid is present, the epididymis and the testicular and epididymal appendages are more easily identified (Fig. 4–42).

Normal testicular blood flow may be demonstrated with color or power Doppler (Barth and Shortliffe, 1997) (Fig. 4–43). Intratesticular blood flow is low velocity with the average peak systolic

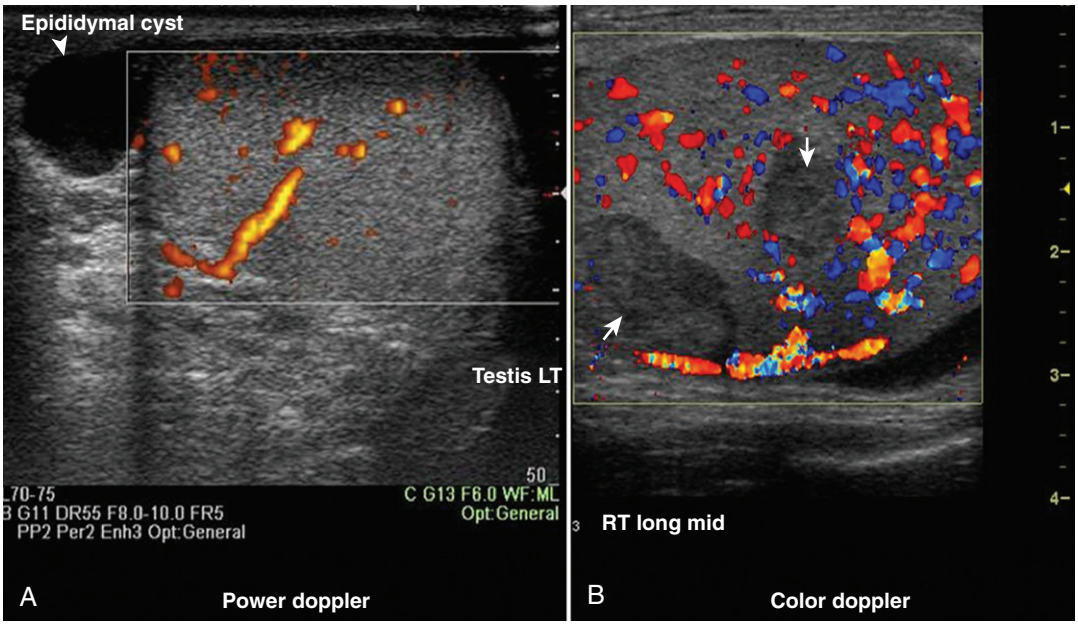


Figure 4–43. **A,** Normal intratesticular blood flow by power Doppler; note the epididymal cyst *(arrowhead)*. **B,** Increased blood flow in an irregular pattern demonstrated by color Doppler was associated with necrotizing vasculitis; note the relatively hypoechoic areas of decreased vascularity *(arrows)*.

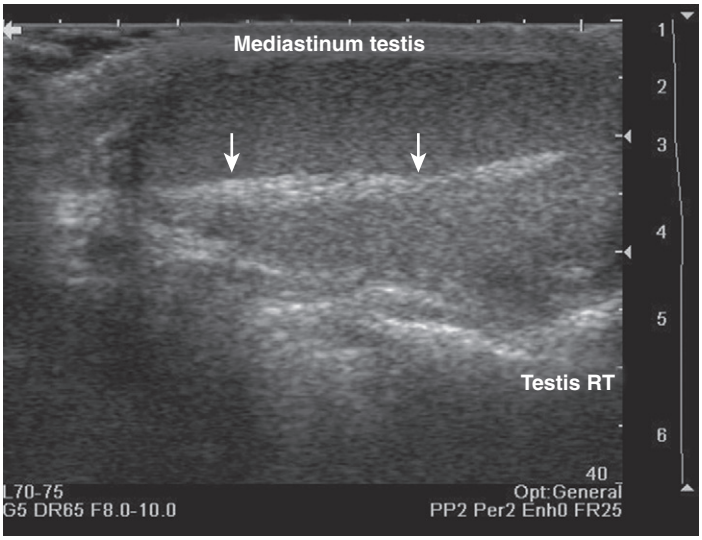


Figure 4–44. The sagittal image of this testis demonstrates a common anatomic finding, the hyperechoic mediastinum testis *(arrows)*. The mediastinum testis is a normal structure resulting from the coalescence of the fibrous septa of the testis.

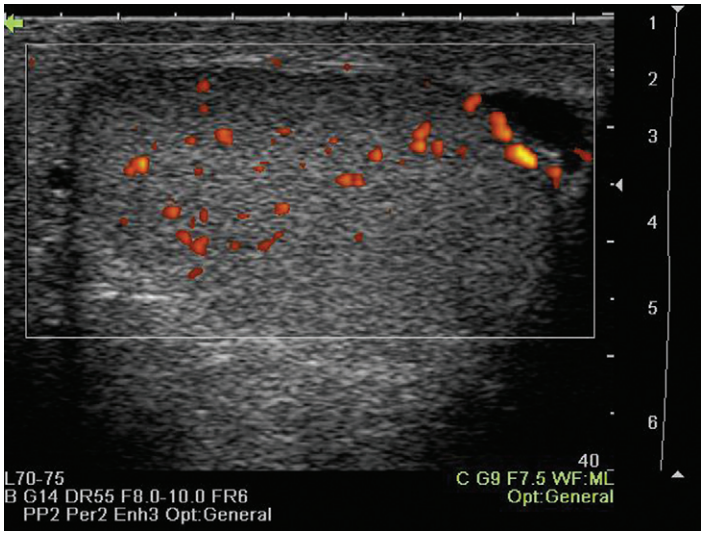


Figure 4–45. Demonstration of intratesticular blood flow by power Doppler in this normal testis.

velocity (PSV) of less than 10 cm/sec (Middleton et al, 1989). Intratesticular blood flow is primarily supplied by the testicular artery, which ultimately divides to supply the individual testicular septa. The fibrous septa coalesce to form the mediastinum testis, which is a hyperechoic linear structure seen in the sagittal plane (Fig. 4–44).

Limitations. Caution should be used when interpreting Doppler flow studies in the evaluation of suspected testicular torsion. The hallmark of testicular torsion is the absence of **intratesticular** blood flow (Fig. 4–45). Paratesticular flow in epididymal collaterals may appear within hours of torsion. Comparison with the contralateral testis should be performed to ensure that the technical attributes of the study are adequate to demonstrate intratesticular blood flow.

Ultrasonography of the Penis and Male Urethra

Introduction. Ultrasonography of the penis and male urethra provides exquisite anatomic detail and may be used in many cases in lieu of studies requiring ionizing radiation.

Technique. Penile and urethral ultrasonography is performed with a 6- to 12-MHz linear array transducer. The technique for penile and urethral ultrasonography includes imaging the phallus in the longitudinal and transverse plane. The examination should be performed in a systematic fashion beginning at the base of the

penis and proceeding distally to the glans. It is possible to get an image of the proximal urethra and corporal bodies by scanning through the scrotum or the perineum.

It may be helpful when evaluating the penile urethra, especially for stricture disease, to inject gel into the urethra in a retrograde fashion. This distends the urethra and allows better identification of urethral anatomy and the anatomy of the corpus spongiosum.

Indications

1. Evaluation of erectile dysfunction
2. Documentation of fibrosis of the corpora cavernosa
3. Localization of foreign body
4. Evaluation of urethral stricture
5. Evaluation of urethral diverticulum
6. Assessment of penile trauma or pain

Normal Findings. Transverse scanning of the phallus reveals the two corpora cavernosa dorsally and the urethra ventrally. The sagittal view of the phallus demonstrates the corpora cavernosa with a hyperechoic, double linear structure representing the cavernosal artery (Fig 4–46). The corpus spongiosum is isoechoic to slightly hypoechoic and contains the coapted urethra. The urethra is collapsed except during voiding.

Limitations. The evaluation of erectile dysfunction requires qualitative and quantitative measurements of blood flow in the penile arteries. Such evaluation requires blood flow measurements before and after the intracavernosal injection of vasoactive substances.

Transrectal Ultrasonography of the Prostate

Transrectal ultrasonography of the prostate (TRUS) is the sonographic imaging procedure most commonly performed by urologists. The technique, indications, normal findings, and complications are discussed in Chapter 97.

NUCLEAR SCINTIGRAPHY

Radionuclide imaging is the procedure of choice to evaluate renal obstruction and function. It is sensitive to changes that induce focal or global changes in kidney function. Because neither gadolinium nor iodinated intravenous contrast agents are used, scintigraphy does not damage the kidney, has no lingering toxicity, results in minimal absorbed radiation, and is free from allergic reactions. Compared with other diagnostic imaging studies such as retrograde pyelogram, renal scintigraphy is noninvasive, has minimal risk, minimal discomfort, and allows determination of the function of the kidney.

Key Points: Ultrasonography

- An ultrasound wave is a mechanical wave creating alternating areas of compression and rarefaction in tissue.
- Axial resolution improves with increasing frequency of the ultrasound wave.
- Depth of ultrasound penetration decreases with increasing frequency.
- Optimal ultrasound imaging requires trade-offs between resolution and depth of penetration.
- Artifacts may be helpful in the diagnosis of certain conditions.
- The appropriate number of images to be captured for documentation is the number necessary to document a systematic and complete examination and to document relevant pathology.
- The mechanical index and the thermal index are not safety limits.
- The ALARA principle is intended to limit the total energy imparted to the patient during an examination.
- The most important factor in ultrasound safety is the informed operator.
- Angiomyolipoma has a characteristic hyperechoic appearance, but some renal cell carcinomas are also hyperechoic.
- Automated measurement of bladder volume or residual urine, though using ultrasonography, is not an imaging study.
- The hallmark of testicular torsion is the absence of intratesticular blood flow.

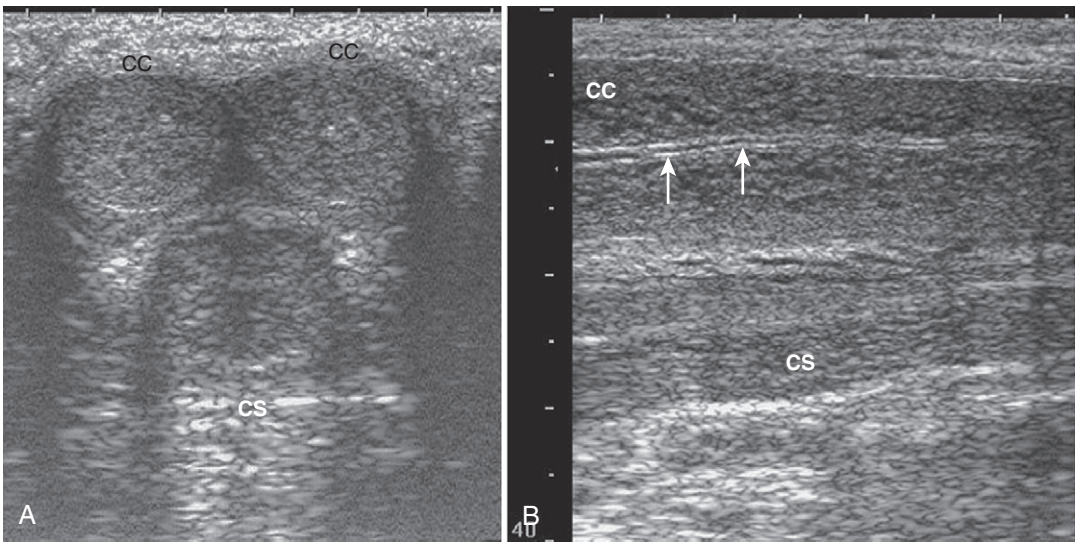


Figure 4–46. **A,** In the transverse plane scanning from the dorsal surface of the midshaft of the penis the corpora cavernosa (CC) are paired structures seen dorsally while the corpus spongiosum (CS) is seen ventrally in the midline. **B,** In the parasagittal plane the corporus cavernosum (CC) is dorsal with the relatively hypoechoic corpus spongiosum (CS) seen ventrally. Within the corporus cavernosum the cavernosal artery is identified as a bright hyperechoic structure *(arrows)*.

Once the agent is injected IV, gamma scintillation cameras measure radiation emitted from the radioisotope and digital workstations gather, process, and display the information. There is an extensive list of radiopharmaceuticals used for renal scintigraphy. This section is limited to those agents most commonly used in urologic practice.

Technetium 99m-diethylene triamine pentaacetic acid (^{99m}Tc-DTPA) is primarily a glomerular filtration agent (Peters, 1998; Gates, 2004). It is most useful for evaluation of obstruction and renal function. Because it is excreted through the kidney and dependent on glomerular filtration rate (GFR), it is less useful in patients with renal failure because impaired GRF may limit adequate evaluation of the collecting system and ureters. It is readily available and relatively inexpensive (Klopper et al, 1972).

Technetium 99m-dimercaptosuccinic acid (^{99m}Tc-DMSA) is cleared by both filtration and secretion.

^{99m}Tc-DMSA localizes to the renal cortex with little accumulation in the renal papilla and medulla (Lin et al, 1974). Therefore it is most useful for identifying cortical defects and ectopic or abhorrent kidneys. With these properties, ^{99m}Tc-DMSA can distinguish a benign functioning abnormality in the kidney from a space-occupying malignant lesion, which would not have normal renal function. No valuable information on the ureter or collecting system can be obtained with ^{99m}Tc-DMSA, but it remains a standard for renal cortical imaging.

Technetium 99m-mercaptoacetyl triglycine (^{99m}Tc-MAG3) is an excellent agent for imaging due to its photon emission, 6-hour half-life, and ease of preparation. It is cleared mainly by tubular secretion (Fritzberg et al, 1986). **A small amount, approximately 10%, of MAG3 is excreted by extrarenal means and most of this is hepatobiliary excretion** (Eshima et al, 1990; Itoh, 2001). Because it is extensively bound to protein in plasma, it is limited in its ability to measure GFR but is an excellent choice for patients with renal insufficiency and urinary obstruction. The tracer is well suited for evaluation of renal function and diuretic scintigraphy. Also, it is an excellent tracer to evaluate renal plasma flow.

Diuretic Scintigraphy

Nuclear medicine imaging plays a crucial role unmet by CT, MRI, or ultrasonography in the diagnosis of upper tract obstruction and its unique characteristics provide noninvasive information regarding dynamic renal function. The diuretic renal scan using ^{99m}Tc-MAG3 is able to provide differential renal function and clearance time comparing right and left kidneys, which is pivotal in patient management. The initial phase is the flow phase in which 2-second images are gathered for 2 minutes and then 1-second images for 60 seconds. The flow phase shows renal uptake, background clearance, and abnormal vascular lesions, which may indicate arteriovenous malformations, tumors, or active bleeding. In the second phase the renal phase, time-to-peak uptake is typically between 2 and 4 minutes. The renal phase is the most sensitive indicator of renal dysfunction. One-minute images are taken for 30 minutes. In the final phase, the excretory phase, 1-minute images are taken for 30 minutes. **A diuretic (usually furosemide 0.5 mg/kg) is administered when maximum collecting system activity is visualized. The $T_{1/2}$ is the time it takes for collecting system activity to decrease by 50% from that at the time of diuretic administration. This is highly technician dependent because the diuretic must be given when the collecting system is displaying maximum activity. Transit time through the collecting system in less than 10 minutes is consistent with a normal, nonobstructed collecting system. $T_{1/2}$ of 10 to 20 minutes shows mild to moderate delay and may be a mechanical obstruction. The patient's perception of pain after diuretic administration can be helpful for the treating urologist to consider when planning surgery in the patient with middle to moderate obstruction. A $T_{1/2}$ of greater than 20 minutes is consistent with a high-grade obstruction. Level of obstruction can usually be determined, as can abnormalities such as ureteral duplication** (Ell and Gambhir, 2004). A normal renal scan is shown in Figure 4–47.

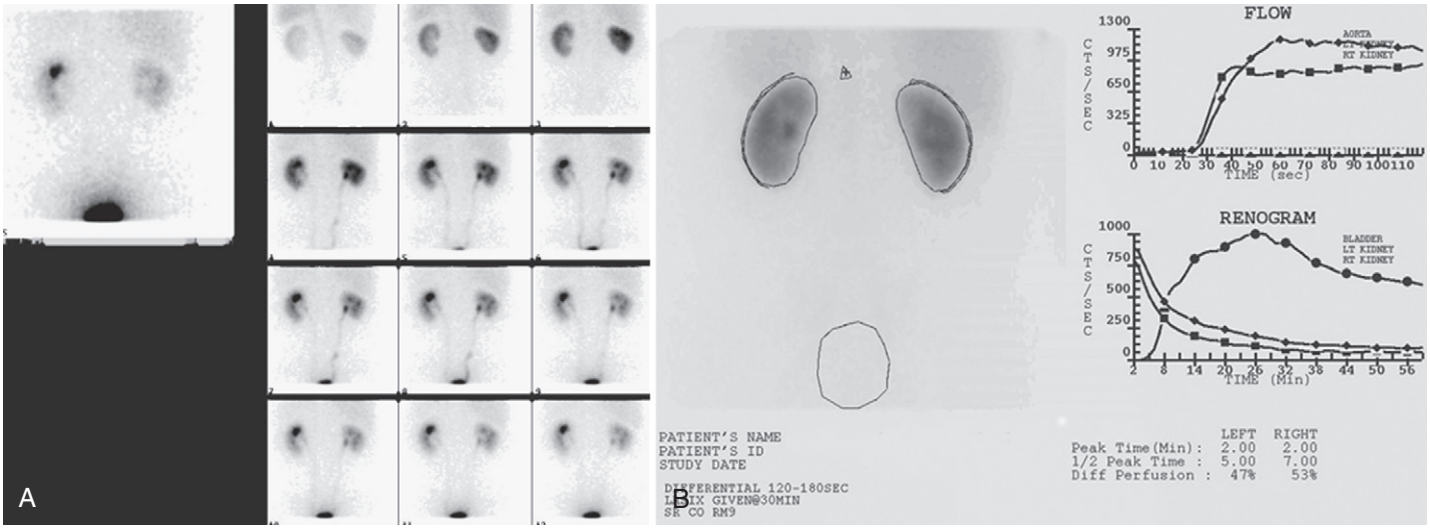


Figure 4–47. **A,** Technetium 99m mercaptoacetyl triglycine (^{99m}Tc-MAG3) perfusion images demonstrate normal, prompt, symmetric blood flow to both kidneys. **B,** Perfusion time-activity curves demonstrating essentially symmetric flow to both kidneys. Note the rising curve typical of ^{99m}Tc-MAG3 flow studies. Dynamic function images demonstrate good uptake of tracer by both kidneys and prompt visualization of the collecting systems. This renogram demonstrates prompt peaking of activity in both kidneys. The downslope represents prompt drainage of activity from the kidneys. Printout of quantitative data shows the differential renal function to be 47% on the left, 53% on the right. The normal half-life for drainage is less than 20 minutes when ^{99m}Tc-MAG3 is used. The $T_{1/2}$ is 5 minutes on the left and 7 minutes on the right, consistent with both kidneys being unobstructed.

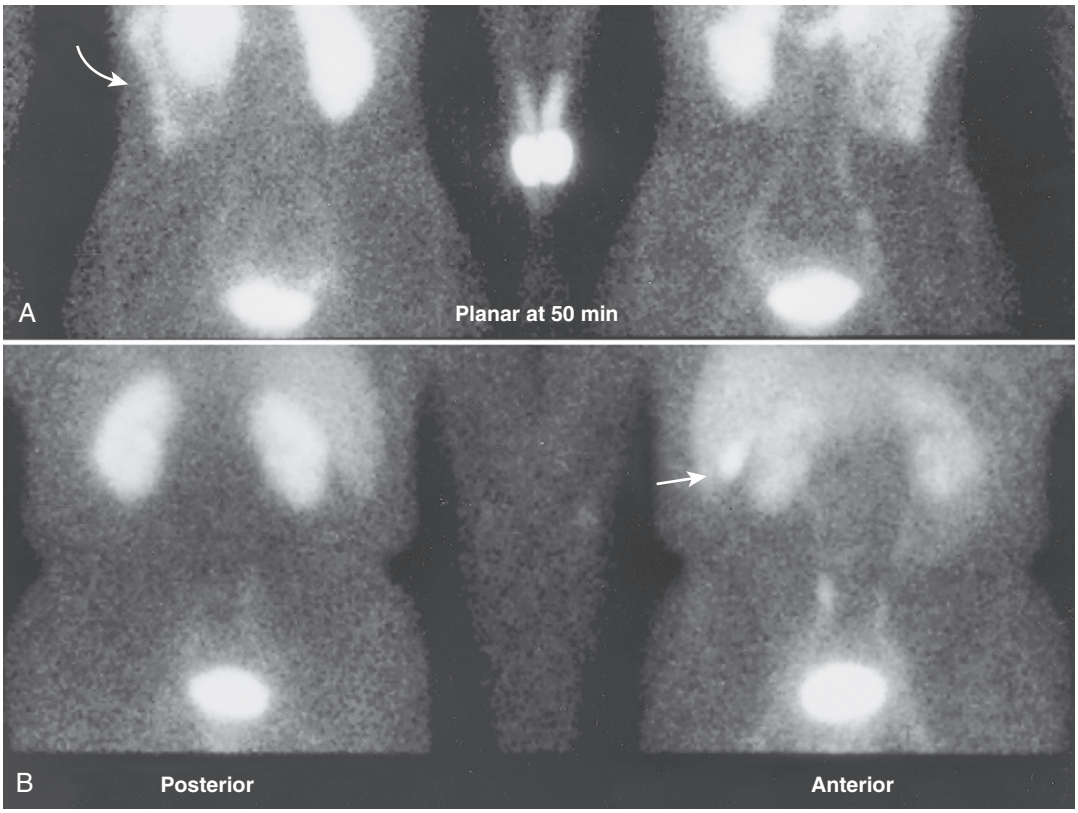


Figure 4–48. Delayed static images in the posterior and anterior projections demonstrate intestinal activity (*arrow* in **A**) and gallbladder activity (*arrow* in **B**), reflecting a normal mode of excretion of technetium 99m mercaptoacetyl triglycine (^{99m}Tc-MAG3). Gallbladder activity, in particular, can cause false-positive interpretation when it overlies activity in the renal collecting system or is inappropriately included in the area of interrogation. Liver activity is variable and tends to be more pronounced in children and patients with renal insufficiency.

Hepatobiliary excretion can cause false-positive readings if the area of intestinal activity or gallbladder activity is included in the area of interrogations during the study (Fig. 4–48).

The diuretic renal scan is another imaging study where communication with the interpreting physician is vital for correct performance of the test, as well as appropriate interpretation. For example, there are times when patients with unilateral or bilateral ureteral stents are sent for diuretic scintigraphy to determine differential renal function. If a bladder catheter is not placed and open to drainage during the diuretic renal scan, the radiopharmaceutical excreted from the healthy kidney may wash up into or back flow via the ureteral stent into the stented kidney, giving the false-positive appearance to have more function that is physiologically present. This false-positive test may lead to inappropriately reconstructing a kidney that in reality has little or insufficient function.

Nuclear Medicine in Urologic Oncology

Whole Body Bone Scan

Conventional radionuclide imaging in urologic malignancy has long been the standard for detecting bone metastasis. The whole body bone scan or skeletal scintigraphy is the most sensitive method for detecting bone metastasis (Narayan et al, 1988). A "positive" bone scan is not specific for cancer and may require plain film radiography, CT, or MRI to confirm, as well as correlation with prior history of bone fractures, trauma, surgery, or arthritis. In patients with diffuse metastatic bone involvement, the bone scan can be mistaken for normal because there is uniformly increased uptake in the boney structures (Kim et al, 1991).

Positron Emission Tomography

The most recent advance in nuclear scintigraphy is in the detection of primary and metastatic cancer using positron emission tomography (PET). Molecular imaging with PET may help individualize the surgical and medical care of urologic oncology patients. PET is certainly having an impact in general oncology and is being actively investigated for use in urologic malignancies. The exact role in the practice of urology has yet to be determined but will certainly have a great role in the future as more tracers specific to urologic cancers are discovered. Using the combination of nuclear imaging and ever-increasing knowledge about cancer cell biology, radiotracers have been developed to be incorporated into dividing cells or cellular mechanisms involved in the increased metabolic activity of malignancies, which can then be detected using PET imaging. Combining PET with high-resolution CT (PET/CT) has the ability to increase our detection of recurrent or metastatic urologic cancers. Many different isotopes are being investigated for the detection of metastatic disease. One example is 18F fluorodeoxyglucose (FDG), which was first introduced in 1976. This isotope takes advantage of increased glycolysis and decreased dephosphorylation in some malignant cells. The 18F fluorodeoxyglucose is transported into cancer cells, where it is preferentially retained relative to normal tissue. This allows detection of some primary and metastatic cancers using PET/CT imaging.

There are some data on the use of PET/CT in testis cancer, where PET/CT was found to have a higher

diagnostic accuracy than CT for staging and restaging in the assessment of a CT-visualized residual mass following chemotherapy for seminoma and nonseminomatous germ cell tumors (Albers et al, 1999; Hain et al, 2000). There may be a role for detection of recurrent nonteratoma disease and the assessment of residual masses after chemotherapy. In a series of seminoma patients who were evaluated postchemotherapy for residual retroperitoneal masses, PET was accurate in 14/14 patients with tumors greater than 3 cm and in 22/23 patients with lesions less than 3 cm. Overall the sensitivity and specificity was 89% and 100%, respectively (De Santis et al, 2004). The accuracy of PET seems to be compromised if performed within 2 weeks of completion of chemotherapy, likely due to decreased metabolism and increased macrophage activity (Eary, 1999). It is recommended that PET/CT be delayed for 4 to 12 weeks following completion of chemotherapy (Shvarts et al, 2002).

PET/ CT may have a promising role in clear cell renal cell carcinoma. An antibody (cG250) recognizing carbonic anhydrase IX has been developed. Carbonic anhydrase IX is a protein related to the unrestrained growth of clear cell renal cancers. A positron-emitting radionuclide (iodine 124) has been attached to the cG250 antibody and injected into renal cell cancer patients. The radionuclide antibody complex attaches to the carbonic anhydrase IX protein from clear cell renal cancer cells and can be detected on PET/CT imaging. Using this scheme in 26 patients with renal tumors, before surgery, there was 94% sensitivity and 100% specificity in renal cell carcinoma (Larson and Schröder, 2008).

At least seven tracers are being investigated for detection of metastatic prostate cancer. Each tracer is directed at a different part of cell function such as glycolysis, amino acid transport, choline kinase activity, fatty acid synthesis, androgen receptor, and bone mineralization. FDG as a PET tracer was investigated in 91 patients with PSA recurrence after radical prostatectomy. FDG-PET was able to detect local or systemic recurrence in only 34% of patients (Schröder et al, 2005).

Few studies have addressed the use of PET in bladder cancer. FDG is renal excreted and not useful in bladder cancer. Only 78% of bladder cancer could be visualized using 11C-methioninie tracer, and PET did not improve local staging of the disease. 11 C-choline was also found to be a poor predictor of primary or metastatic urothelial carcinoma (Ahlstrom et al, 1996; de Jong et al, 2002).

PET/CT in urologic oncology is in its infancy. With a seemingly countless number of potential targets for tracers, it will be many years into the future before it defines its role and use in urology. PET has the capability of demonstrating in vivo gene expression. As a result, the ultimate utility may transcend diagnostic imaging and allow determination of the efficacy of targeted gene therapy.

PET is still in the early stages of investigation for urologic tumors. It is more sensitive for detection of seminoma and nonseminoma after chemotherapy compared with CT imaging.

COMPUTED TOMOGRAPHY

The 1979 Nobel Prize in Medicine and Physiology was awarded to Allan M. Cormack and Sir Godfrey N. Hounsfield for the development of computer-assisted tomography. Although basic principals remain the same, significant advances over the past 30 years have resulted in the development of multidetector CT devices, improving soft tissue detail and allowing the possibility of rapid 3-D reconstruction of the entire genitourinary system.

Key Points: Nuclear Scintigraphy

- During diuretic renal scan, the diuretic must be given when maximum activity is seen in the kidney.
- An elimination $T_{1/2}$ less than 10 minutes is an unobstructed system and a $T_{1/2}$ greater than 20 minutes is consistent with high-grade obstruction.
- If ureteral stents are in place, patients undergoing diuretic renal scan should have an unclamped bladder catheter in place during the study.
- Technetium 99m-mercaptoacetyl triglyceride (MAG3) is the agent of choice for diuretic renal scan to determine differential renal function and obstruction.

CT has become one of the most integral parts of urologic practice, and the CT urogram (CTU) has replaced IVU as the imaging modality of choice in modern urology for the workup of hematuria, urologic malignancies, detection of kidney stones, and preoperative planning. As in the case of conventional radiographic imaging, the basis for CT imaging is the attenuation of x-ray photons as they pass through the patient. Tomography is an imaging method that produces 3-D images of internal structures by recording the passage of x-rays as they pass through different body tissues. In the case of CT, a computer reconstructs cross-sectional images of the body on the basis of measurements of x-ray transmission through thin slices of the body tissue (Brant, 1999). A collimated x-ray beam is generated on one side of the patient, and the amount of transmitted radiation is measured by a detector placed on the opposite side of the x-ray beam. These measurements are then repeated systematically, while a series of exposures from different projections is made as the x-ray beam rotates around the patient. The result is production of a 3-D image of internal structures in the human body by recording the passage of different energy waves through various internal structures. Data collected by the detectors is as reconstructed by computerized algorithms to result in a viewable tomographic display.

Several different imaging variables are adjusted to allow adequate, detailed image resolution, while minimizing the time on the scanner and limiting exposure to radiation. The variable application of pitch, beam collimation, detector size, and tube voltage are used by the radiologist and imaging technologist for ideal image requisition. A detailed description of each of these variables is beyond the scope of this chapter. (See "Suggested Readings" later.)

Perhaps the greatest recent advancement in CT is the use of helical image acquisition techniques with multichannel detectors or multidetectors (MDCT). In a helical CT the patient moves through a continuously rotating gantry. The helical raw images are processed using interpolation algorithms in order to visualize the internal structures as sagittal, coronal, or axial reconstructed images. The "single-slice spiral CT," introduced in 1988, had a single row of detectors and required multiple passes to visualize a small area of interrogation. The scanners in use today have more than 64 rows of detectors, which allow the patient's entire body to be imaged during a single breath hold, with few or no motion artifacts (Wang and Vannier, 1994; Mahesh, 2002) (Fig. 4–49).

MDCT offers the advantages of faster scanning, fewer motion artifacts, thinner imaging sections, more precise diagnostic accuracy, increased concentration of contrast material, shorter scanning time, and significant increase in anatomic coverage with a

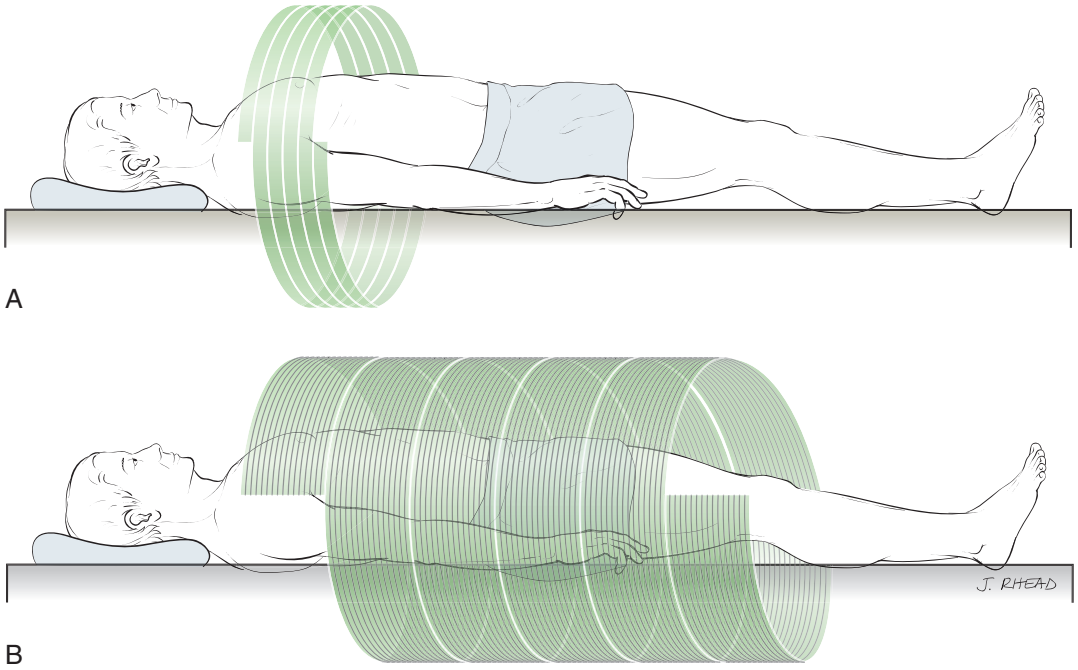


Figure 4–49. **A,** A computed tomography scanner with a single-row detector requires five circular passes around the patient to image a small area of the patient's body. **B,** With a 16-slice, multirow detector the chest, abdomen, and pelvis can be imaged with five circular passes, easily obtained during a single breath hold. The thin slices offered by the 16-slice detector offer much greater detail of internal structures.

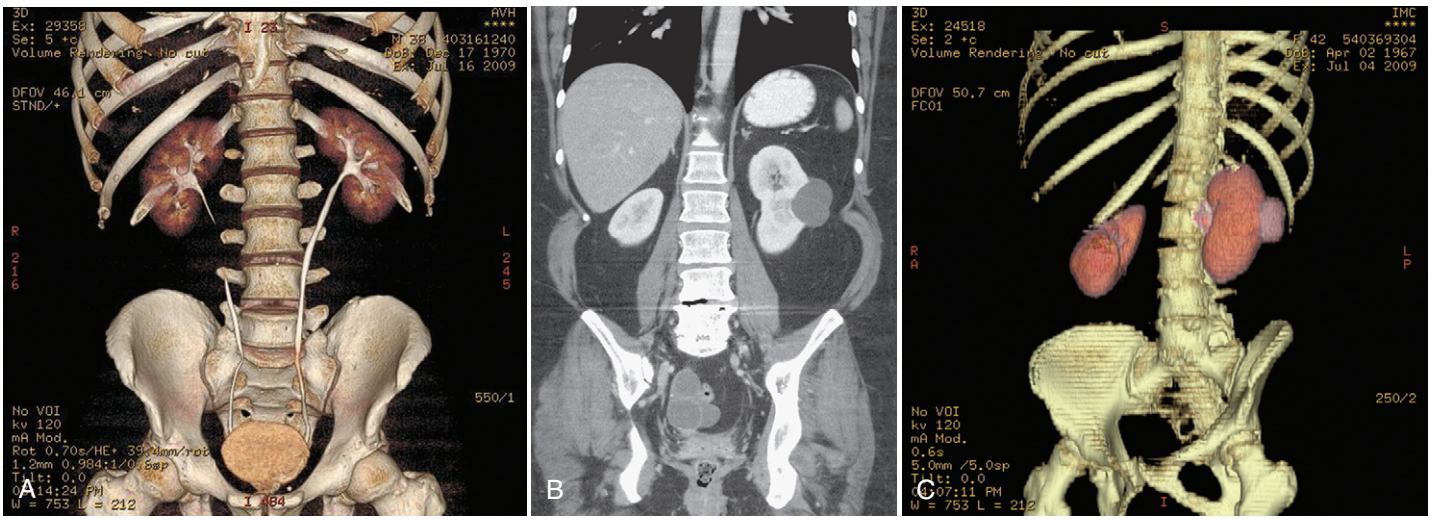


Figure 4–50. **A,** Three-dimensional (3-D) colored reconstruction of the kidneys ureter and bladder from computed tomography urogram. **B,** Coronal reconstruction in a patient with a clear cell renal cell carcinoma in a complex renal cystic mass and enhancing mural nodule. **C,** 3-D Reconstruction of the same patient with slight posterior rotation.

single scan. For example, a 16-slice MDCT can scan the chest, abdomen, and pelvis in 20 seconds.

Readily available software is capable of 3-D processing of CT images to recreate the urinary system. These 3-D images offer improved preoperative planning, appreciation of proximity to adjacent organs, the ability to define vasculature, and improved communication with patients, who can now easily see their particular pathology and better appreciate the challenges faced by their surgeon (Fig. 4–50).

Real-time CT fluoroscopy is now available as an option on new CT imaging equipment. CT fluoroscopy gives a 3-D CT image that is much more detailed and offers greater soft tissue contrast and resolution than conventional CT. The most common use in urology is for biopsy of the kidney. CT fluoroscopy helps to overcome movement of the kidney during respiratory variation. It has also been used for fluid aspiration, drain placement, catheter placement, percutaneous cryoablation, and radiofrequency ablation of renal tumors. **One significant disadvantage of CT fluoroscopy is increased radiation exposure to the patient and radiologist or surgeon performing the procedure** (Daly et al, 1999; Keat, 2001; Gupta et al, 2006).

The CTU is an excretory urography in which MDCT is used for imaging of the urinary tract. It is indicated in the workup of hematuria, kidney stones, renal masses, renal colic, and urothelial tumors. The CT scan examination starts with the physician's request for imaging.

Radiologists around the world appreciate, from the urologist, a brief description of the question to be answered by the CT scan. Equipped with a better understanding of why the CT was ordered, the radiologist and the CT technician can adjust different CT variables and choose the appropriate contrast media needed to deliver a valuable report back to the ordering urologist.

Urologists often request a CT evaluation of the abdomen and pelvis. An abdominal CT starts at the diaphragm and ends at the iliac crest. If the pelvis is to be imaged, a separate request is usually required. The pelvic CT begins at the iliac crest and terminates at the pubis symphysis. Intravenous contrast may be required for better delineation of soft tissue. Oral contrast is not commonly used in urology but may be helpful in certain cases to differentiate bowel from lymph nodes, scar, or tumor (Fig. 4–51)

Hounsfield Units

A single CT image generated by the scanner is divided into many tiny blocks of different shades of black and white called pixels. The actual grayscale of each pixel on a CT depends on the amount of radiation absorbed at that point, which is termed an *attenuation value*. **Attenuation values are expressed in Hounsfield units (HU). The HU scale or attenuation value is based on a reference scale where air is assigned a value of –1000 HU and dense bone is assigned the value of +1000 HU. Water is assigned 0 HU.**

Urolithiasis

Patients presenting to the emergency department with abdominal pain or renal colic are frequently evaluated with CT imaging. The use of nonenhanced CT imaging to identify urolithiasis was first reported in 1995 (Smith et al, 1995) and has now become the standard diagnostic tool to evaluate renal colic. It offers the advantages over IVU of avoiding contrast and has the ability to diagnose other abdominal abnormalities that can also cause abdominal pain. MDCT can readily diagnose radiolucent stones that may not have been seen on IVU, as well as small stones even in the distal ureter (Federle et al, 1981). **With the exception of some indinavir stones, all renal and ureteral stones can be detected on helical CT scan** (Schwartz et al, 1999). In the workup of urolithiasis, the unenhanced CT has a sensitivity ranging between 96% and 100% and specificity ranging between 92% and 100% (Memarsadeghi et al, 2005). **Stones in the distal ureter can be difficult to differentiate between pelvic calcifications. In these cases the urologist needs to look for other signs of obstruction that indicate the presence of a stone including ureteral dilation, inflammatory changes in the perinephric fat, hydronephrosis, and a soft tissue rim surrounding the calcification within the ureter. The soft tissue rim around a stone represents irritation and edema in the ureteral wall** (Heneghan et al, 1997; Dalrymple et al, 2000) (Fig. 4–52).

Stone patients are frequently subjected to radiation exposure as part of diagnosis, treatment, and follow-up. Increasing awareness of the potential long-term adverse effects of radiation exposure has encouraged urologists and radiologists to discover means to decrease the amount of radiation exposure. The low-dose unenhanced helical CT scan is gaining increasing popularity for initial diagnosis of renal colic suspected to be due to urolithiasis and for follow-up in stone patients. Using low-dose CT protocols, the specificity and sensitivity of unenhanced low-dose helical CT scan are approximately 96% and 97%, respectively. Low-dose techniques offer a 99% positive at 90%-negative predictive value for urolithiasis. The end result is a 50% to 75% decrease in the patient's total radiation exposure for each CT obtained (Liu et al, 2000; Hamm et al, 2002; Kalra et al, 2005).

Cystic and Solid Renal Masses

The frequent CT imaging in emergency department patients has resulted in an increase in the detection of incidental renal masses. Using CT imaging the mass can be characterized as a simple or complex cyst or a solid mass. On the basis of the HU attenuation scale we would expect simple cysts to have HU near zero (Fig. 4–53).

When the unenhanced CT images of a renal mass are compared with the enhanced images obtained in the cortical medullary or nephrogenic phase, an increase in HU (measured in the area of the renal mass) by 15 to 20 HU confirms the presence of a solid enhancing mass, which is usually renal cancer. The presence of fat, which should enhance less than 10 HU, is diagnostic for angiomyolipoma. A hyperdense cyst shows no change in density between the postcontrast and delayed-phase images (Fig. 4–54).

Complex cystic masses are usually characterized on the basis of the Bosniak classification system. The most important criteria used to differentiate a lesion that should be considered for surgery versus a nonsurgical lesion is the presence or absence of tissue vascularity or enhancement. Bosniak category I, II, and IIF lesions do not enhance to any measurable degree. Category I lesions are simple cysts and considered to be benign. Category II lesions are more complicated and may have calcifications, high attenuation fluid, and several thin septae. Category III lesions are more complex, have small areas of calcification, and may also have irregular walls or septate where there is measurable enhancement. Cystic lesions discovered on CT scan that are difficult to categorize as either II or III are now currently categorized as IIF. **Category IV lesions are cystic masses that meet all the criteria of category III but also have enhancing soft tissue components adjacent or independent of the wall or septum of the cyst. Bosniak III and IV lesions have an increased likelihood of being malignant and require close follow-up or surgical extirpation** (Bosniak, 1997; Isreal and Bosniak, 2005).

Hematuria

The CTU is one of the most common studies ordered for the workup of gross or microscopic hematuria. With MDCT it is possible to perform a comprehensive evaluation of the patient with one single examination (Chai et al, 2001). The study images the abdomen and pelvis and typically includes four different phases. The first scan is an unenhanced CT to distinguish between different masses that can be present in the kidney and uncover kidney stones that would later be obscured by the excretion of contrast into the renal collecting system. At 30 to 70 seconds after contrast injection, the corticomedullary phase is captured with another pass through the MDCT, helping to define vasculature and perfusion. The nephrogenic phase occurs between 90 to 180 seconds after injection of contrast and, when compared with the nonenhanced images, allows sensitive detection and characterization of renal masses. The final phase is the excretory phase, imaged approximately 3 to 5 minutes after injection of contrast. The excretory phase allows complete filling of the collecting system

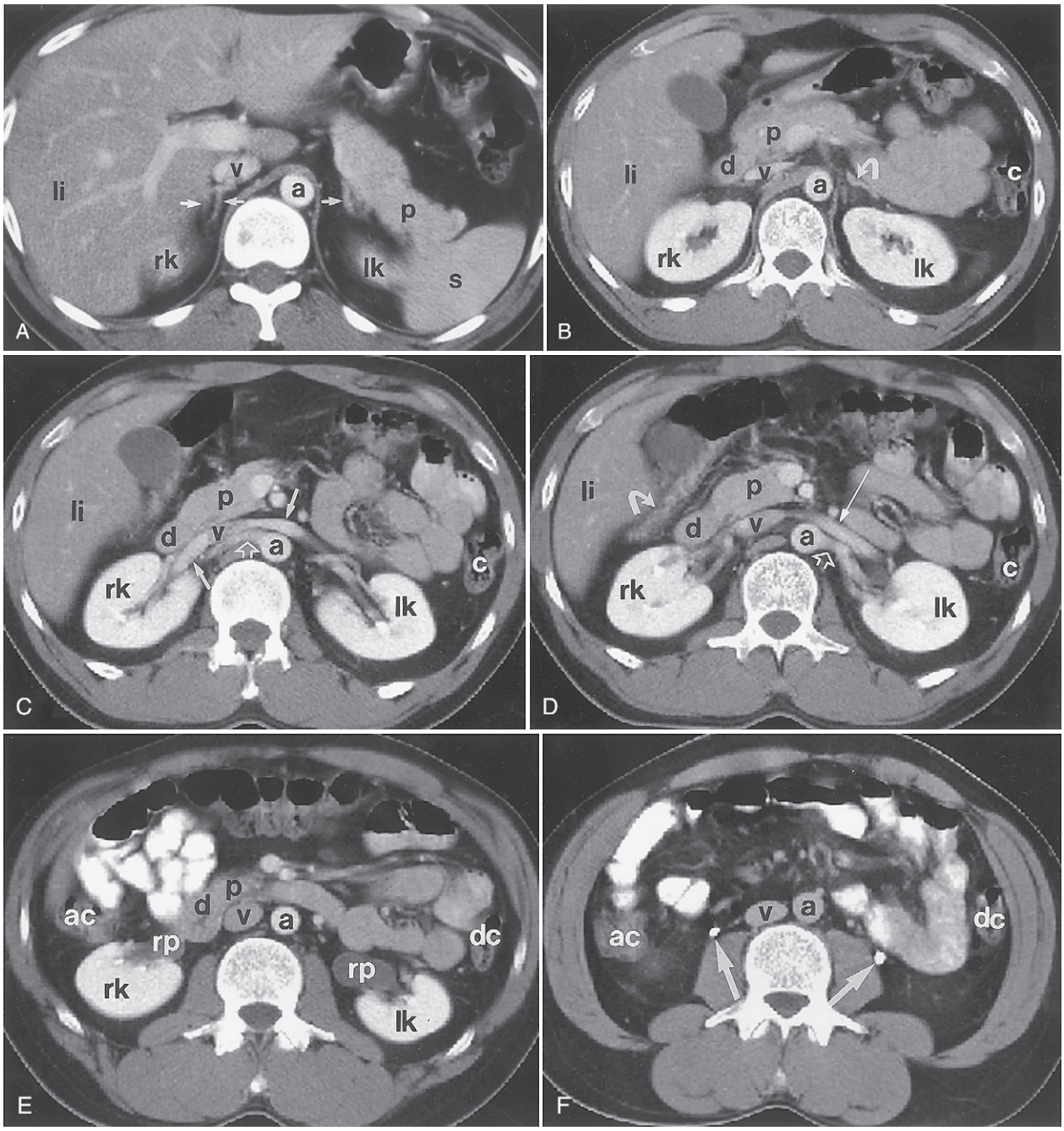


Figure 4–51. Computed tomography (CT) of the abdomen and pelvis demonstrating normal genitourinary anatomy. **A,** The adrenal glands are indicated with *arrows*. The upper pole of the right and left kidneys is indicated with rk and lk, respectively. a, aorta; li, liver; p, pancreas; s, spleen; v, inferior vena cava. **B,** Scan through the upper pole of the kidneys. The left adrenal gland is indicated with an *arrow*. a, aorta; c, colon; d, duodenum; li, liver; lk, left kidney; p, pancreas; rk, right kidney; v, inferior vena cava. **C,** Scan through the hilum of the kidneys. The main renal veins are indicated with *solid arrows,* and the right main renal artery is indicated with an *open arrow*. a, aorta; c, colon; d, duodenum; li, liver; lk, left kidney; p, pancreas; rk, right kidney; v, inferior vena cava. **D,** Scan through the hilum of the kidneys slightly caudal to **C**. The left main renal vein is indicated with a *solid straight arrow,* and the left main renal artery is indicated with an *open arrow*. The hepatic flexure of the colon is indicated with a *curved arrow*. a, aorta; c, colon; d, duodenum; li, liver; lk, left kidney; p, pancreas; rk, right kidney; v, inferior vena cava. **E,** Scan through the mid to lower polar region of the kidneys. a, aorta; ac, ascending colon; d, duodenum; dc, descending colon; lk, left kidney; p, pancreas; rk, right kidney; rp, renal pelvis; v, inferior vena cava. **F,** CT scan obtained below the kidneys reveals filling of the upper ureters *(arrows)*. The wall of the normal ureter is usually paper thin or not visible on CT. a, aorta; ac, ascending colon; dc, descending colon; v, inferior vena cava.

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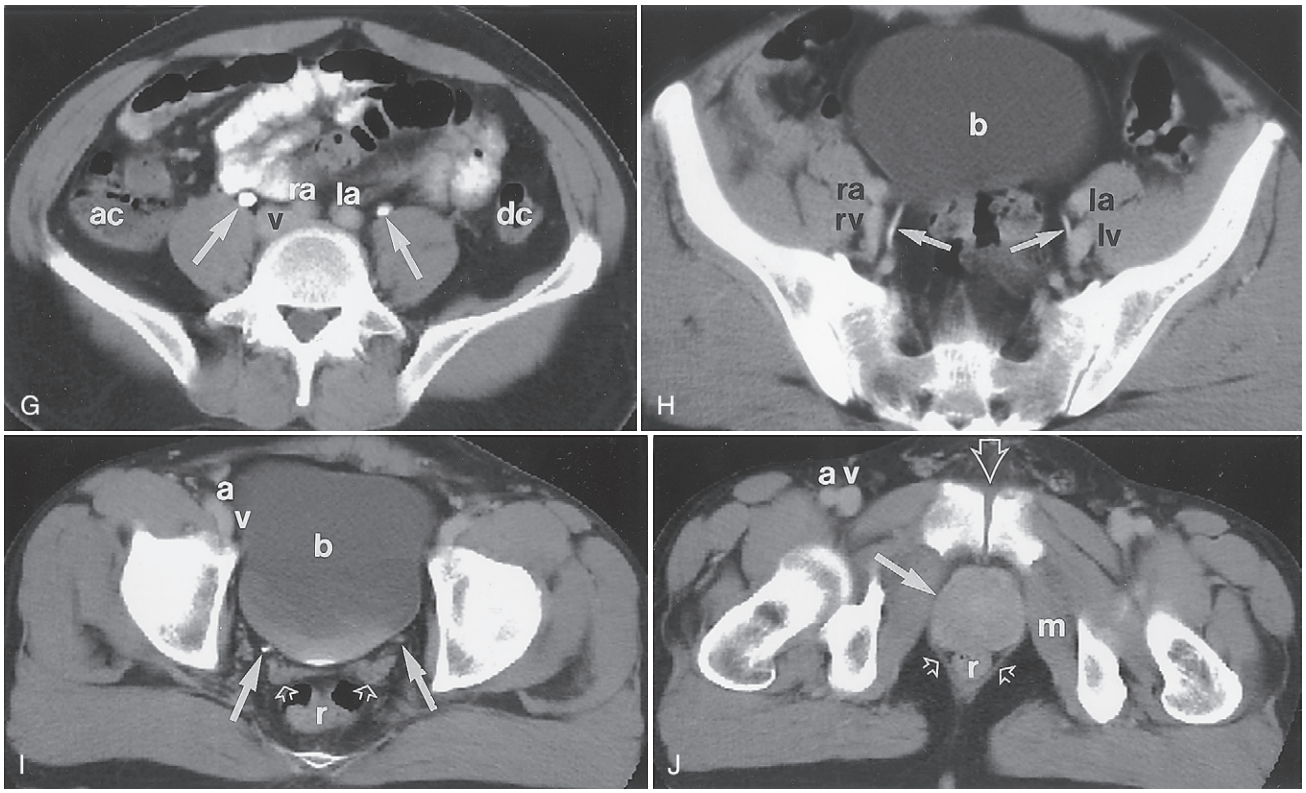


Figure 4–51, cont'd. **G,** Contrast filling of the midureters *(arrows)* on a scan obtained at the level of the iliac crest and below the aortic bifurcation. ac, ascending colon; dc, descending colon; la, left common iliac artery; ra, right common iliac artery; v, inferior vena cava. **H,** The distal ureters *(arrows)* course medial to the iliac vessels on a scan obtained below the promontory of the sacrum. b, urinary bladder; la, left external iliac artery; lv, left external iliac vein; ra, right external iliac artery; rv, right external iliac vein. **I,** Scan through the roof of the acetabulum reveals distal ureters *(solid arrows)* near the ureterovesical junction. The bladder (b) is filled with urine and partially opacified with contrast material. The normal seminal vesicle *(open arrows)* usually has a paired bow-tie structure with slightly lobulated contour. a, right external iliac artery; r, rectum; v, right external iliac vein. **J,** Scan at the level of the pubic symphysis *(open arrow)* reveals the prostate gland *(solid arrow)*. a, right external iliac artery; m, obturator internus muscle; r, rectum; v, right external iliac vein.

and usually allows visualization of the ureter (Joudi et al, 2006) (see Fig. 4–54).

CTU has been shown to be sensitive in detecting upper tract urothelial cancers. In one series of 57 patients with hematuria, 38 were found to have urothelial carcinoma. CT urography detected 37/38 urothelial cancers for a sensitivity of 97%, compared with retrograde pyelogram, which detected 31/38 lesions and had a sensitivity of 82%. Approximately 90% of malignant upper tract lesions can be detected with CT urography (McCarthy and Cowan, 2002; Lang et al, 2003; Caoili et al, 2005). CT urography is not as sensitive as cystoscopy for the detection of urothelial tumors in the bladder. Only large bladder tumors are visualized with CT imaging studies as filling defect in the lumen of the bladder. Carcinoma in situ cannot be visualized on CT scanning and therefore cystoscopy is still an important part of a comprehensive hematuria workup.

Key Points: CT Imaging

- The CT urogram is an excellent imaging choice to evaluate the kidney, upper tract collecting system, and ureter.
- The CT urogram is highly sensitive and specific for upper tract urothelial carcinoma.
- A renal mass in the kidney seen on CT urogram that enhances more than 15 to 20 HU is most likely a renal cancer.
- With the exception of indinavir stones, all types of urolithiasis are visible on unenhanced CT of the abdomen and pelvis.

MAGNETIC RESONANCE IMAGING

CT imaging remains the mainstay of urologic cross-sectional body imaging; however, MRI is increasingly being applied to the genitourinary system. With constant improvements in technology, MRI is gradually narrowing the overall resolution quality gap between it and CT. A significant advantage of MRI is the excellent contrast resolution of soft tissue, without the need for contrast in many situations. Currently MRI is used when patients cannot be given iodinated contrast and when tissue findings in the urinary system cannot be resolved using CT or ultrasonography.

To obtain magnetic resonance images, the patient is placed on a gantry that passes through the bore of the magnet. When exposed to a magnet field of sufficient strength, the free water protons in the patient orient themselves along the magnetic field's z-axis. This is the head-to-toe axis, straight through the bore of the magnet. A radiofrequency (RF) antenna or "coil" is placed over the body part to be imaged. It is the coil that transmits the RF pulses through the patient. When the RF pulse stops, protons

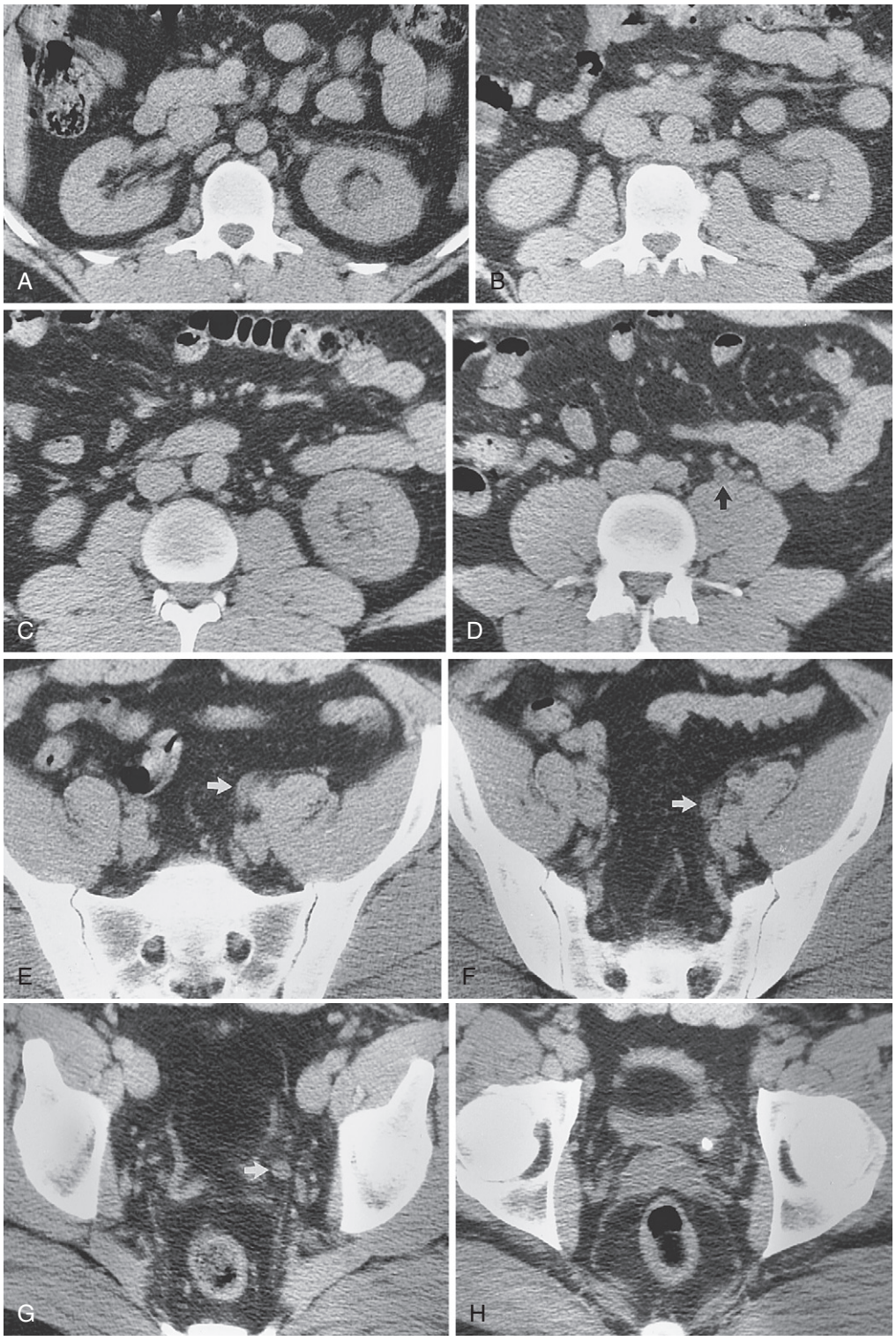


Figure 4–52. Computed tomography of the abdomen and pelvis in a patient with an obstructing ureteral stone at the level of the ureterovesical junction (UVJ). **A,** Level of the left upper pole. Mild renal enlargement, caliectasis, and perinephric stranding are apparent. **B,** Level of the left renal hilum. Left pyelectasis with a dependent stone, mild peripelvic and perinephric stranding, and a retroaortic left renal vein are shown. **C,** Level of the left lower pole. Left caliectasis, proximal ureterectasis, and mild periureteral stranding are present. **D,** Level of the aortic bifurcation. The dilated left ureter *(arrow)* has lower attenuation than do nearby vessels. **E,** Level of the upper portion of the sacrum. A dilated left ureter *(arrow)* crosses anteromedial to the common iliac artery. **F,** Level of the midsacrum. A dilated left ureter *(arrow)* is accompanied by periureteral stranding. **G,** Level of the top of the acetabulum showing a dilated pelvic portion of the left ureter *(arrow)*. **H,** Level of the UVJ. The impacted stone with a "cuff" or "tissue rim" sign that represents the edematous wall of the ureter. (Reprinted from Talner LB, O'Reilly PH, Wasserman NF. Specific causes of obstruction. In: Pollack HM, McClennan BL, Dyer R, Kenney PJ, editors. Clinical urography. 2nd ed. Philadelphia: WB Saunders; 2000.)

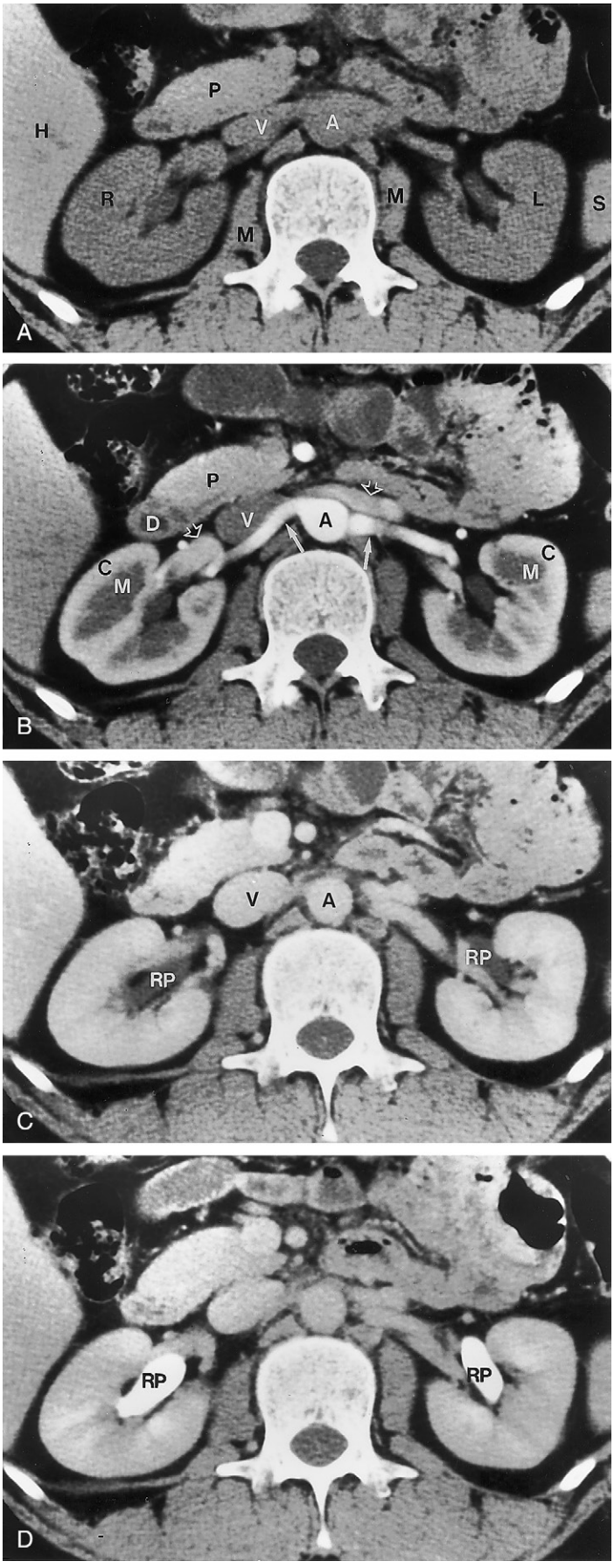


Figure 4–53. Renal computed tomography (CT) demonstrating normal nephrogenic progression. **A,** Unenhanced CT scan obtained at the level of the renal hilum shows right (R) and left (L) kidneys of CT attenuation values slightly less than those of the liver (H) and pancreas (P). A, abdominal aorta; M, psoas muscle; S, spleen; V, inferior vena cava. **B,** Enhanced CT scan obtained during a cortical nephrographic phase, generally 25 to 80 seconds after contrast medium injection, reveals increased enhancement of the renal cortex (C) relative to the medulla (M). The main renal artery is indicated with *solid arrows* bilaterally. Main renal veins *(open arrows)* are less opacified with respect to the aorta (A) and arteries. D, duodenum; P, pancreas; V, inferior vena cava. **C,** CT scan obtained during the homogeneous nephrographic phase, generally between 85 and 120 seconds after contrast medium administration, reveals a homogeneous, uniform, increased attenuation of the renal parenchyma. The wall of the normal renal pelvis (RP) is paper thin or not visible on the CT scan. A, abdominal aorta; V, inferior vena cava. **D,** CT scan obtained during the excretory phase shows contrast medium in the renal pelvis (RP) bilaterally; this starts to appear approximately 3 minutes after contrast medium administration.



Figure 4–54. Small renal cell carcinoma in the infrahilar lip of the right kidney is not easily seen on unenhanced image (**A**). On corticomedullary phase image (**B**), the lesion is subtly visible as a hyperenhancing focus within the renal medulla. On nephrographic (**C**) and pyelographic phase (**D**) images, the full extent of the lesion *(arrow)* within the medulla and cortex is depicted. (Reprinted from Brink JA, Siegel CL. Computed tomography of the upper urinary tract. In: Pollack HM, McClennan BL, Dyer R, Kenney PJ, editors. Clinical urography. 2nd ed. Philadelphia: WB Saunders; 2000.)

release their energy, which is detected and processed to obtain the magnetic resonance image. A magnetic resonance sequence exploits the body's different tissue characteristics and the particular manner that each type of tissue absorbs and then releases this energy.

Weighting of the image depends on how the energy is imparted through the physics of the pulse sequence and whether the energy is released quickly or slowly. Images are described as being T1 or T2 weighted. The T1-weighted images are generated by the time to return to equilibrium in the z-axis. The T2-weighted images are generated by the time required to return to equilibrium in the xy-axis. **On T1-weighted magnetic resonance images, fluid has a low signal and appears dark. T2-weighted magnetic resonance images have a high signal and appear bright. In the kidney this translates into the cortex having a higher signal or being brighter than the medulla, which gives off a lower signal and is darker** (Fig. 4–55).

Intravenous gadolinium contrast enhancement can be used in renal imaging to augment the relaxation of protons on T1-weighted images, making the kidney brighter and increasing the chance of detecting and characterizing a renal mass. Urine in the bladder has low-signal intensity or appears dark on T1-weighted images and demonstrates high-signal intensity or is bright on T2-weighted images (Bassignani, 2006) (Fig. 4–56) (Table 4–6).

Indications

MRI is indicated in the evaluation of solid renal masses, cystic renal masses, staging of renal malignancy, evaluation of venous structures, determination of vena cava involvement by renal cell carcinoma, and characterization of adrenal pathology. MRI is an imaging modality preferred over CT scanning in patients with a history of contrast allergy, compromised renal function, or suspected renal vein or vena cava involvement of renal cell carcinoma.

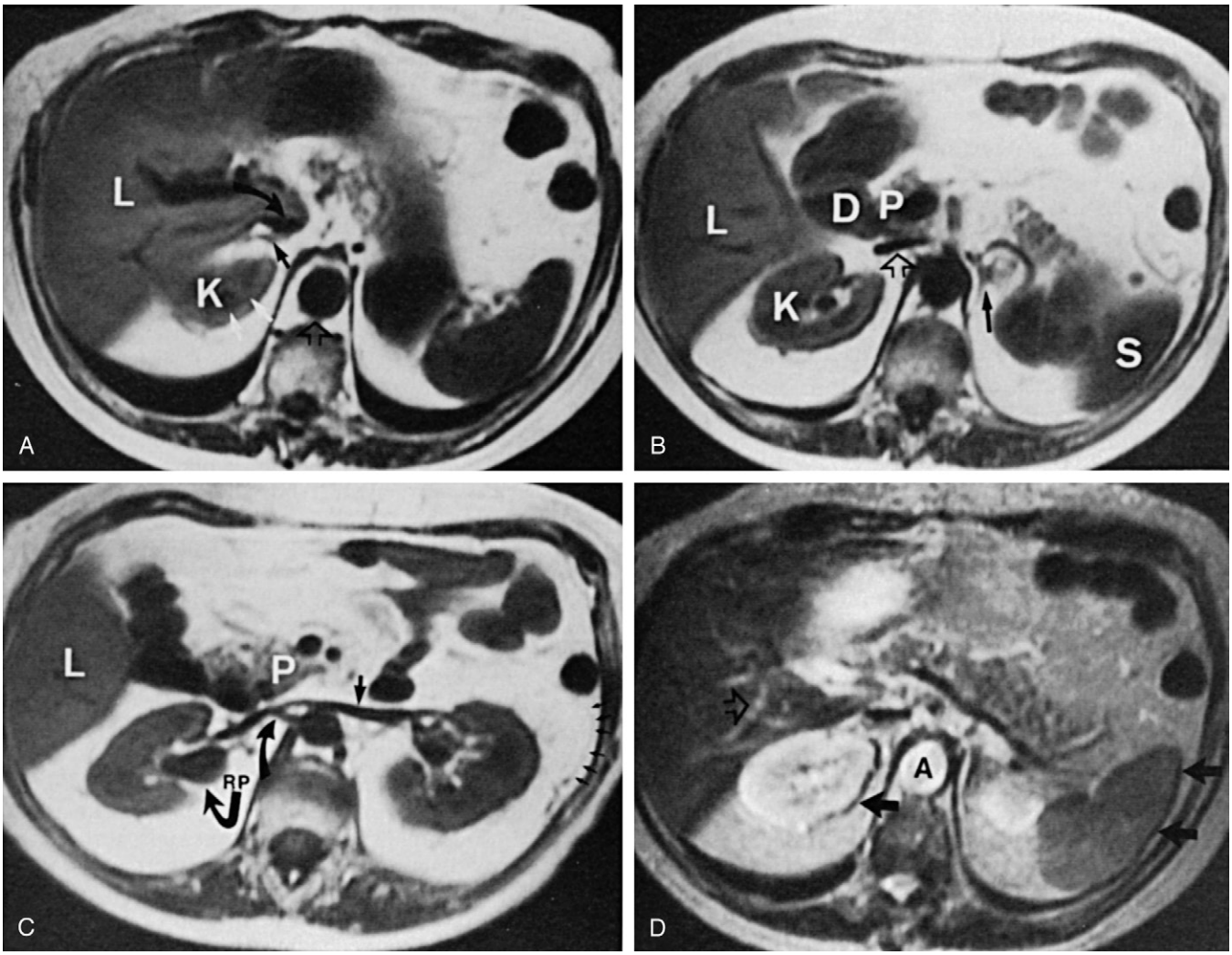


Figure 4–55. Magnetic resonance imaging (MRI) of the upper abdomen and kidneys. Axial MRI (T1-weighted) was taken through the level of the upper pole of the left kidney (K). The renal medulla is of lower signal intensity *(white arrows)* than the cortex, and it appears darker. The right adrenal gland *(arrow)* is identified with an inverted-V configuration, immediately posterior to the inferior vena cava *(curved arrow)*. The inferior vena cava and the aorta *(open short arrow)* demonstrate the flow void phenomenon and appear low in signal intensity. **B,** T1-weighted, short TR/TE (TR = 400 msec, TE = 20 msec) scan performed 1.5 cm below that shown in **A**. The left adrenal gland is now identified *(black arrow)*. The liver (L), kidney (K), spleen (S), duodenum (D), pancreas (P), and inferior vena cava *(open arrow)* are also noted. **C,** T1-weighted, short TR/TE (TR = 400 msec, TE = 20 msec) scan through the renal hilum is shown. The left renal vein is identified *(short arrow)* as it traverses anterior to the aorta and enters the inferior vena cava. The right renal artery *(upper curved arrow)* is identified posterior to the inferior vena cava. The somewhat diluted extrarenal pelvis (RP) is identified as a structure of low-signal intensity arising in the hilum. A minimal amount of renal sinus fat is identified as a high-signal region surrounding the renal pelvis. Gerota fascia is visualized faintly *(short arrows)* on the left. Also identified are the liver (L) and the pancreas (P). **D,** T2-weighted image in the midabdomen. The kidney is of higher signal intensity than the liver or spleen. Chemical shift artifact is demonstrated *(arrows)*. The aorta (A) and intrahepatic vessels *(open arrow)* are of high signal intensity owing to the gradient moment nulling techniques that have been employed to minimize motion artifacts in this patient. (Reprinted from Kressel HY, Chen Q, Prasad P, Hatabu H. Magnetic resonance imaging. In: Pollack HM, McClennan BL, Dyer R, Kenney PJ, editors. Clinical urography. 2nd ed. Philadelphia: WB Saunders; 2000.)

Some patients are not suited for imaging using MRI or have implants that make MRI dangerous. Patients who should not undergo MRI are those who have difficulty with breath holding, severe claustrophobia, pacemakers, sterile magnetic implants, retained magnetic foreign bodies, cochlear implants, neurovascular aneurysm clips, or cardiac defibrillators. MRI is also a poor choice to evaluate the presence of urolithiasis because stones do not have signal characteristics that allow them to be detected.

MRI for urologic abnormalities usually requires 30 minutes inside the bore of the magnet. Patients are required to hold their breath for 20 to 30 seconds during the imaging sequence. Patients who are not cooperative or have difficulty holding their breath will compromise the quality and value of the magnetic resonance study.

Renal Magnetic Resonance Imaging

MRI is superior to CT imaging in the workup for renal cell carcinoma when surgical planning related to invasion into the renal vein or inferior vena cava is required. MRI can detect venous invasion with the sensitivity of 100% compared with 79% for CT imaging (Kallman et al, 1992). MRI is equivalent to CT scanning detecting renal tumors of 1 cm or greater and also in detecting

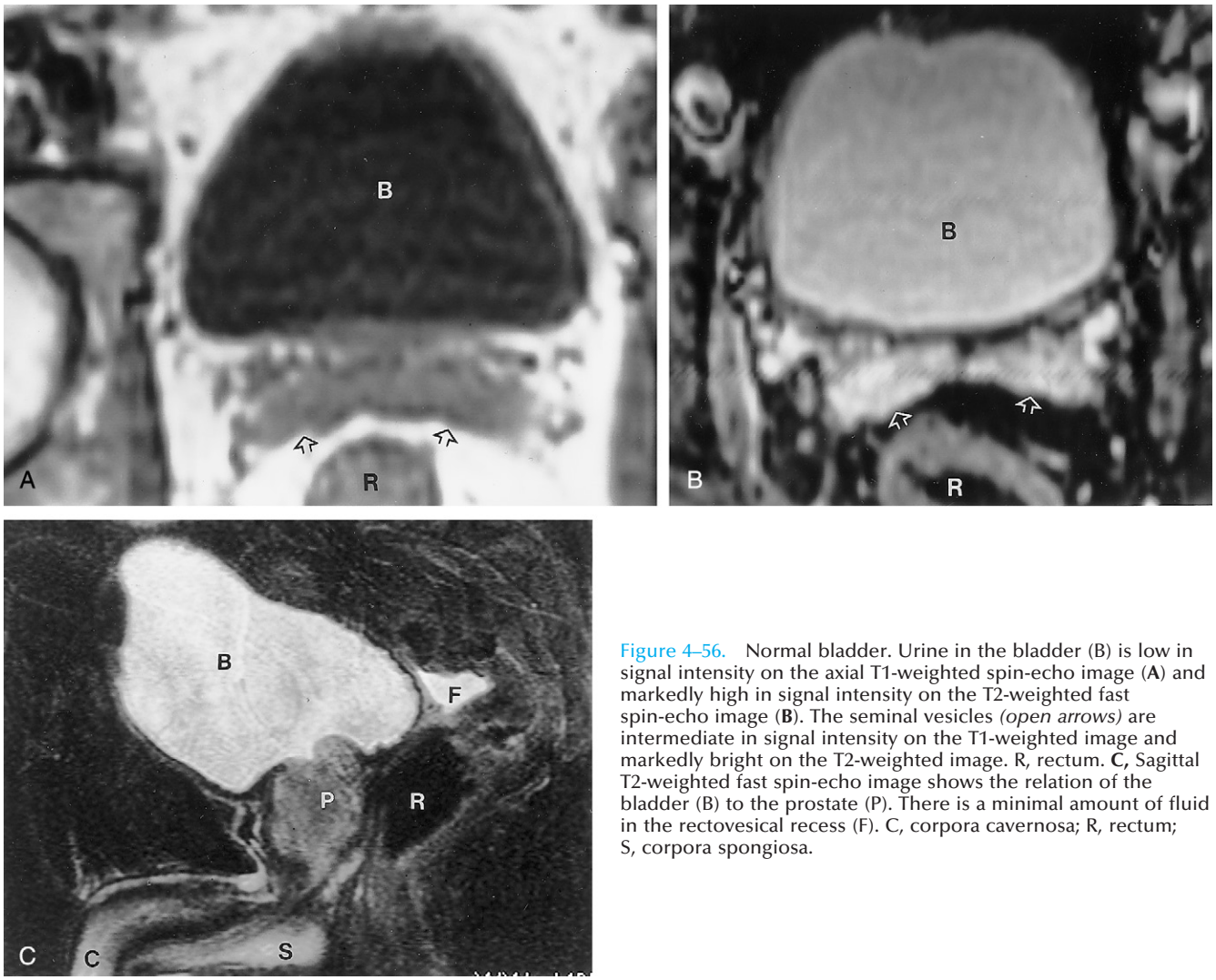


Figure 4–56. Normal bladder. Urine in the bladder (B) is low in signal intensity on the axial T1-weighted spin-echo image (**A**) and markedly high in signal intensity on the T2-weighted fast spin-echo image (**B**). The seminal vesicles *(open arrows)* are intermediate in signal intensity on the T1-weighted image and markedly bright on the T2-weighted image. R, rectum. **C,** Sagittal T2-weighted fast spin-echo image shows the relation of the bladder (B) to the prostate (P). There is a minimal amount of fluid in the rectovesical recess (F). C, corpora cavernosa; R, rectum; S, corpora spongiosa.

Table 4–6.

Characteristics of Magnetic Resonance T1- and T2-Weighted Images

	T1-WEIGHTED	T2-WEIGHTED
Body fluid: bladder, gallbladder, cerebrospinal fluid	Low signal or dark	High signal or bright
Fat	High signal or bright	High signal or bright
Kidney	Cortex high signal or bright Medulla low signal or dark	High signal or bright

lymphadenopathy associated with renal cell cancer (Pretorius et al, 2000).

The most important characteristic of a solid neoplasm is the presence of enhancement. Magnetic resonance enhancement is evaluated by comparing nonenhanced T1-weighted images to gadolinium-enhanced T1-weighted images. Any detectable lesion is assessed for measurable increase in signal intensity after gadolinium contrast administration. If the lesion is brighter on the postcontrast image and increases in signal intensity by more than 15%, it is declared enhancing and is consistent with renal cancer. Benign lesions including angiomyolipomas will also enhance with gadolinium contrast. However, on T1-weighted images high-signal fat content will be detected. Neither MRI nor CT imaging can differentiate an oncocytoma from renal cell carcinoma (Pretorius et al, 2000).

Simple cysts have similar characteristics on ultrasound, CT, and MRI. Complex cysts can also be differentiated or characterized on MRI. Hemorrhage within the cyst results in a high signal on T1-weighted images because of the paramagnetic effects of blood breakdown products (Roubidoux, 1994). Proteinaceous contents within a cyst can also yield high signal on T1-weighted images, and on T2-weighted images old hemorrhage results in a black ring along the cyst wall. **For benign, complex cysts there should be no enhancement of any component of the cyst** (Israel et al, 2004). **Because MRI is insensitive to calcifications, any calcifications present on the lining of a complex cyst are not seen on MRI. When evaluating independent risk factors for renal cell carcinoma, enhancement of the cyst wall was more sensitive and specific for the presence of**

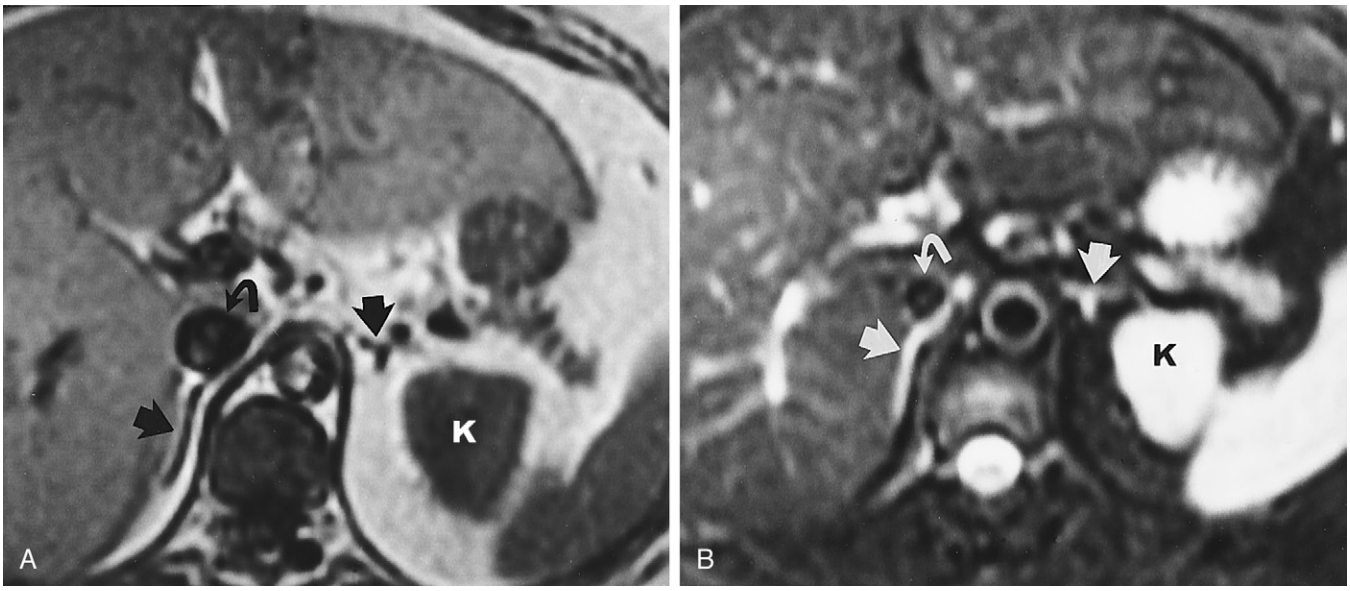


Figure 4–57. Magnetic resonance imaging of normal adrenals. **A,** Axial T1-weighted image (two-dimensional flash, TR = 130 msec, TE = 4 msec) shows the normal adrenals *(straight arrows)*. Note the vena cava *(curved arrow)* and the left kidney (K). **B,** Axial T2-weighted image (TR = 2000 msec/TE = 100 msec) with fat suppression of the same patient. The adrenals appear relatively hyperintense. (Reprinted from Mitty H, Parsons RB. Adrenal embryology, anatomy, and imaging techniques. In: Pollack HM, McClennan BL, Dyer R, Kenney PJ, editors. Clinical urography. 2nd ed. Philadelphia: WB Saunders; 2000.)

renal cell carcinoma than were calcifications on the cyst wall. On CT scan, calcifications can cause artifact that can inhibit the ability to detect enhancement of small nodules within the wall of a complex cyst. MRI has the advantage of not being influenced by calcifications embedded within the wall of a complex cyst. Therefore MRI is more likely to detect enhancement of a renal cell carcinoma in the wall of the complex cyst compared with CT imaging when mural calcifications are present (Israel and Bosniak, 2003).

Key Points: MRI

- When a renal mass is seen on MRI, the most important characteristic indicating the presence of a malignancy is enhancement of the mass.
- Nephrogenic systemic fibrosis is seen in patients with severe renal insufficiency who are exposed to gadolinium contrast media.
- Pheochromocytoma, metastatic lesion to the adrenal gland, and primary adrenal cortical carcinoma are all bright on T2-weighted images.

Adrenal Magnetic Resonance Imaging

MRI has proven to be of great value in the evaluation of the adrenal gland. MRI can easily separate adrenal adenomas from adrenal metastasis without using intravenous contrast. The high lipid content in adenomas makes them more readily differentiated from malignant processes that do not have high lipid content (Dunnick and Korobkin, 2002). The pheochromocytoma is also characterized by MRI without the need for contrast enhancement, avoiding a potential hypertensive crisis that has been associated with iodine contrast media in these patients. **Pheochromocytoma, adrenal cortical carcinoma, and metastatic lesions to the adrenal gland are usually of high signal intensity or bright on T2-weighted images** (Korobkin et al, 1996). **The benign adrenal myolipoma is easily demonstrated on T1-weighted images because fat within these lesions has a high signal or is bright compared with surrounding tissue** (Fig. 4–57).

Using MRI artifact referred to as *chemical shift,* MRI can define benign lipid-containing adenomas. The term chemical shift describes an artifact that occurs when approximately the same amount of lipid and water are in the same volume being imaged. The two different signals of these components cancel one another out when the chemical shift is maximized. The lipid-sensitive sequence is performed in two separate sequences of one scan. In one sequence known as "in phase," chemical shift artifact is at a minimum and the signals of lipid and water are additive. In the second sequence or "opposed phase," chemical shift artifact is at a maximum and the signals of lipid and water cancel one another, resulting in the adrenal mass being darker on the opposed phase images compared with the in-phase images. Loss of signal on chemical shift MRI is 95% sensitive and 100% specific for adrenal adenoma (Hood et al, 1999; Israel et al, 2004; Elsayes et al, 2005).

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chapter

5

Outcomes Research

Mark S. Litwin, MD, MPH

Access to Care

Costs of Care

Quality of Care

Health-Related Quality of Life

Future Implications

The discipline of health services research, often loosely referred to as *outcomes research,* focuses on the study of access to care, costs of care, and quality of care.

ACCESS TO CARE

Access to care includes the "actual use of personal health services and everything that facilitates or impedes their use. **It is the link between health services systems and the populations they serve"** (Andersen and Davidson, 2001). Andersen presented a behavioral model for considering health care access in which three categories of factors determine how and whether individuals use medical services. These include predisposing factors (e.g., health beliefs, attitudes); enabling factors (e.g., health insurance, geographic proximity); and need factors (e.g., the presence of symptoms or diseases) (Aday and Andersen, 1981; Andersen, 1995). Barriers to health care access often result from financial determinants such as the lack of health insurance or adequate income, logistic challenges in coordinating child care, public transportation, and work schedules; clinic waiting times; and difficulties with the geographic proximity of clinics and hospitals (Griffiths et al, 2004).

Adequate access requires more than a guarantee of payment for services; even with generous benefits, individuals must navigate nonfinancial barriers. Among these are minority status (Mandelblatt et al, 1999; Eisenberg and Power, 2000; Institute of Medicine, 2003; Lurie and Dubowitz, 2007); gender (Saigal et al, 2008); environmental factors (Davidson et al, 2004); health behaviors (Call et al, 2006); acculturation, language, and citizenship (De Alba et al, 2005; Echeverria and Carrasquillo, 2006; Flores, 2006); provider proximity (Schroen et al, 2005); available safety-net services (Call et al, 2006); and the absence of a usual source of care (Sox et al, 1998; Petterson et al, 2009).

Barriers to access may also result from more subtle factors such as fear of the health care system, ethnic disparities, cultural norms, embarrassment, perceived health status (Fitzpatrick et al, 1998), lack of self-efficacy, knowledge (Deibert et al, 2007), or special social circumstances. Even in health care systems that are considered to provide "equal access," such as the U.S. Veterans Affairs hospitals, different patient groups use outpatient and inpatient care at markedly different rates, leading to variations in outcomes. Differences in access to care have been cited as a fundamental reason for disparities in health status among various populations (Kelley et al, 2005a, 2005b).

In this context, differential access to care has been proposed as an important determinant of racial/ethnic disparities in prostate cancer screening, treatment, morbidity, and mortality (Mandelblatt et al, 1999; Hoffman et al, 2001; Underwood et al, 2004; Talcott et al, 2007). This is supported by empiric data demonstrating that African-American men with prostate cancer are more likely than whites to be uninsured; to receive their usual medical care in a public clinic or emergency department; and to see different clinicians on subsequent prostate cancer–related visits (Talcott et al, 2007). Likewise, discrepancies in accessibility and continuity of medical care may explain the lower use and awareness of prostate specific antigen (PSA) testing among Hispanic men in the United States (Spencer et al, 2006; McFall, 2007); it remains unknown whether access or continuity issues mediate the greater dissatisfaction with prostate cancer treatment decisions among Hispanic men (Hoffman et al, 2003).

Access to health care reflects not only the potential for entry into the health care system, but also the actual consumption of services. In one public-assistance program for low-income, uninsured men with prostate cancer, special attention to overcoming the financial and nonfinancial barriers has eliminated racial/ethnic disparities in health services utilization (Miller et al, 2008a). Nonetheless, because men from historically disadvantaged groups often do not access adequate and timely care, they continue to suffer a disproportionate burden (Miller et al, 2009b).

COSTS OF CARE

The cost of medical care may be measured in many ways. Although it is difficult to put a price tag on the toll of human suffering, physicians today are asked to reduce costs, improve quality, and provide services for greater numbers of patients in an increasingly austere environment. This often requires rationing of resources, though it is seldom explicitly labeled as such. In the present era of sweeping change in health care financing and health services delivery, increasing emphasis has been placed on efficiency in the allocation of scarce medical resources. The field of medical economics is well beyond its nascence, and broad public interest has emerged in studying the costs of medical and surgical therapies. As we spend more administrative dollars on cost containment, scrutiny is reaching all potential areas for conservation including oncology, a province once considered sacred and off limits to cost-cutting efforts.

Urologists have long been attentive to issues of cost in managing health care. In his autobiography, Hugh Hampton Young, the father of American urology, described a patient on whom he agreed to perform a prostatectomy in the 1920s for a fixed fee of $500 with a promise of only 3 weeks in the hospital. Because the patient suffered complications and remained hospitalized for much longer than planned, Young had to spend his entire professional fee plus an additional $350 to pay off the hospital bill (Young, 1940).

Health policy decisions today are based not only on biomedical research but also on sound evaluations of health care costs. The introduction of oral erectogenics, beginning in the late 1990s, provides a perfect illustration of the tension between therapeutic advances and economic forces. The scientific discoveries that led to the advent of sildenafil and similar agents (Rajfer et al, 1992) were rewarded with a Nobel Prize, yet insurers initially fervently resisted paying for them (Lee, 1999). This led to potent controversy, generated numerous studies, and even raised constitutional law questions (Keith, 2000; Smith and Roberts, 2000; Connolly, 2001). As a surgical subspecialty with large numbers of Medicare patients, many of whom suffer waning turgor, urology is a discipline in which cost-saving maneuvers may have tremendous financial impact.

Terms and Methods of Analysis

In its purest form, **research on health care costs involves counting the amount of money that is expended on facilities, equipment, supplies, and personnel during the provision of medical care.** But many costs are hidden. A more extensive approach would also include the opportunity cost of the time patients spend receiving care. For example, when estimating the cost of an interval cystoscopy after resection of a bladder tumor, a thorough assessment would include not only the cost of overhead, supplies, lidocaine jelly, urine cytology, and professional fees but also the cost to the patient in lost wages—or to his or her employer in lost productivity—during the time away from work for the procedure, travel, or any complications. This component is not insignificant. Employee absence from work has been estimated to cost U.S. businesses tens of millions of dollars annually (Walsh et al, 1989; Luz and Green, 1997; Stewart et al, 2003).

Because true costs are difficult to quantify at the individual, institutional, or population level, researchers instead often report data on charges. ***Charges* represent the amount that is billed for a service, whereas *costs* reflect what the provider expended to supply that service.** Most of the available administrative databases in health care are based on either financial discharge abstracts from hospitals or claims data from large payers, insurance companies, or government agencies such as the Center for Medicare and Medicaid Services. These data sets primarily include information on charges and payments, but not costs. The major advantage of using charge data is that they are much easier to obtain. The primary disadvantage is that they may not accurately reflect the true underlying costs of individual medical services. For example, a hospital that is losing money on intravenous pyelograms may make up the deficit by increasing its charges for urine cytologies. This practice may help balance the annual budget, but it corrupts the quality of the charge data. An economic analysis using charges for bladder cancer follow-up in this hospital will err by incorporating the inflated amounts charged for interval urine cytologies. Some analysts attempt to circumvent this problem by calculating a ratio of costs to charges for entire facilities, individual medical services, or diagnosis-based categories of care. Although imperfect, charges are frequently used to estimate the amount of money spent on health care.

To avoid the inherent problems in calculating costs and charges, some researchers instead measure *resource utilization* in terms of duration, frequency, and intensity of services (Munoz et al, 1988b). One of the most commonly reported units of comparative analysis is length of stay (LOS). After 1983, when the prospective payment system was instituted to reimburse hospitals a predetermined amount of money on the basis of the diagnosis-related group (DRG) into which each Medicare inpatient is classified (Munoz et al, 1988a; Kahn et al, 1990; Munoz et al, 1990a, 1990b, 1990c), attention to LOS as an outcome variable in cost analyses greatly increased. In the United States, inpatient LOSs are now believed to have reached their floor, and effort has shifted from this measure.

Costs of care may be measured as intensity or numbers of services provided. For example, rather than calculating the costs or charges for a 3-day hospitalization for radical nephrectomy, analysis may be based on the total number of complete blood counts, chest radiographs, bags of intravenous fluid, doses of antibiotic, and doses of narcotic and antibiotic ordered on any given day of the hospital stay or during the entire stay. By examining duration or frequency of medical services when studying costs, researchers can avoid the biases involved in using financial data.

Cost-effectiveness analysis is another popular technique used to evaluate new or established medical therapies. A cost-effectiveness analysis is performed by developing a probability model of the possible medical outcomes of different interventions (or a nonintervention such as watchful waiting for benign prostatic hyperplasia) (Saigal et al, 2007), identifying the expenses associated with each outcome, and comparing the results, typically reported as cost per year of life saved (Shepard and Thompson, 1979; Henriksson and Edhag, 1987; Chandhoke and DeAntoni, 1998; Manca et al, 2003). **Years of life saved, or *life-years (LYs),* are calculated for a population, not for individuals.** Ten LYs might represent 2 patients, each of whom survives for 5 additional years, or 120 patients, each of whom survives for 1 additional month (Smith et al, 1993). LYs are usually adjusted to account for different health states that may result from various treatments. These are called *quality-adjusted life-years (QALYs)*. For example, when comparing two treatments for localized prostate cancer, if both options are determined to cost $10,000 per year of life saved, then the two may seem equivalent. However, if one treatment yields years that are compromised by bothersome sexual dysfunction, while the other yields years that are free of such problems, then the difference in quality of the years saved must be factored into the equation. Analyses that rely on QALYs are facilitated by the estimation of patient utilities, or preferences, for various health states (Nease and Owens, 1994; Albertsen et al, 1998; Saigal et al, 2001; Saigal et al, 2002). If patients appraise an impotent year as being worth less than a potent year, then quality adjustments may make the first treatment more expensive per QALY saved. *Cost-benefit analysis* differs by including not only the costs but also the equivalent monetary value of any benefits garnered during the extra years of life. Often, this refers to wages earned or income accrued during that time. In more sophisticated analyses, future income and expenses related to a particular health state are discounted to present value by incorporating projected interest and inflation rates over time.

Cost studies may be undertaken as descriptive analyses that chronicle the economic burden of one disease in a group of patients, such as the cost of care for interstitial cystitis in a managed care plan (Clemens et al, 2008). They may examine the

financial impact on the general population such as national annual expenditures for urolithiasis (Lotan, 2009). They may also track cumulative costs over time, such as for different prostate cancer treatments (Wilson et al, 2007). Alternatively, they may present economic models comparing different approaches to managing an illness such as whether it is more costly to correct cryptorchidism in infants or older boys (Hsieh et al, 2009), or to manage small renal tumors with laparoscopic or percutaneous cryoablation (Badwan et al, 2008).

Patterns of Care

Much of the current research into the cost of treating patients is predicated on the observation that patterns of care differ substantially for certain conditions. Physician demographics and patient age have been found to affect practice patterns (Bennett et al, 1991; O'Leary et al, 2000; Bird et al, 2003; Joudi et al, 2003; Fallon et al, 2005). The availability of evidence does not always predict the diffusion of new technologies (Michel, 2006), especially in urology. For example, robotic prostatectomy has seen nearly ubiquitous adoption, largely driven by overwhelming commercial and market forces, despite the absence of evidence showing superiority (Hu et al, 2006, 2009). Conversely, some advances with strong evidence-based advantages such as partial or laparoscopic nephrectomy for small renal masses or neobladder reconstruction following cystectomy, have diffused much more slowly (Gore et al, 2006; Miller et al, 2008b).

Despite the relative scarcity of cost analyses in urology, significant variations in length of stay and charges have been reported for many nonurologic medical and surgical hospitalizations (Fisher et al, 2003a, 2003b; Weinstein et al, 2004; Wennberg, 2004). Cost savings can be achieved by identifying variations in urologists' practice habits and targeting them for reduction in intensity and duration (Sage et al, 1988; Kramolowsky et al, 1995a, 1995b). These changes in urologic practice have been shown to result in equivalent medical outcomes (Cleary et al, 1991), despite the finding that patients historically have tended to dislike shorter postoperative hospital stays (Litwin et al, 1997; Durieux et al, 2004). Overall, studies have been mixed. Some have described the successful use of cost-control mechanisms in urology (Cuckow, 1992a, 1992b), whereas others have failed to show sustained results (Forrest et al, 1981).

Analysis of both medical and surgical DRGs indicates that consistent patterns of resource utilization are identifiable during the course of hospitalizations, suggesting that elements of utilization may be managed more effectively to yield cost savings (Carter and Melnick, 1990). This is particularly true in treatments for genitourinary conditions such as hematuria, incontinence, or prostatitis (Taylor et al, 2008), many of which may be standardized. Urology is a fertile area for economic analysis because so little is known about the cost-effectiveness of screening and treatment interventions for even the most common genitourinary conditions (Perlman et al, 1996; Grossfeld and Carroll, 1998; Benoit et al, 2001; Mor et al, 2001; Shaw, 2004).

The advent of managed care has greatly assisted the study of practice patterns and medical outcomes. **Most researchers agree that health maintenance organizations (HMOs) improve access to medical services and cost efficiency of care without compromising quality** (Holtgrewe, 1998a, 1998b; Haffer and Bowen, 2004; Roetzheim et al, 2008). However, contrary evidence suggests that cancer patients may wait longer for treatment in HMOs than in fee-for-service plans (Greenwald, 1987). Among men newly diagnosed with prostate cancer, those cared for in HMOs are almost 1.5 times more likely to receive radiation than surgery for clinically localized tumors. This appears consistent with the general HMO emphasis on outpatient care. In this study, HMO patients had a lower overall mortality rate than did non-HMO patients. Interestingly, low-income men treated in HMOs enjoyed survival times that were significantly greater than for middle- or high-income men in HMOs or fee-for-service plans (Greenwald and Henke, 1992).

The National Institute of Diabetes and Digestive and Kidney Diseases funds the Urologic Diseases in America project (www.udaonline.net), which seeks to define the burden of urologic disease on the American public by quantifying trends in resource utilization, practice patterns, costs, outcomes, and epidemiology across the spectrum of urologic conditions (Litwin et al, 2005; Miller et al, 2009a). Documenting these trends has broad implications for quality of health care, access to care, and the equitable allocation of scarce resources, both in terms of medical services and research budgets. Among the most financially burdensome urologic conditions are urolithiasis (Lotan, 2009), urinary tract infection (Griebling, 2005a, 2005b), urinary incontinence (Anger et al, 2006), and benign prostatic hyperplasia (Nickel, 2006a, 2006b). Urologic diseases exert a substantial impact on resource utilization within the U.S. Veterans Affairs health system (Anger et al, 2008).

Case Mix

When studying patterns of care or medical costs, it is critical to adjust for case mix. ***Case mix* refers to the severity of illness and degree of comorbidity in a group of patients** (Iezzoni, 1996, 1997). These patient characteristics may influence treatment outcomes. For example, because they typically have a greater burden of comorbidity, older patients are more likely to experience complications after surgery. This comorbidity must be accounted for in evaluations of clinical outcomes (Glance et al, 2008). If this fact is not considered when comparing surgical complication rates across hospitals, evaluators may erroneously conclude that a hospital with an older patient population is providing poorer-quality care. To use outcomes to measure quality of care, we need to adjust for these other factors including baseline patient characteristics and intervening treatments. This adjustment (referred to as case-mix adjustment or risk adjustment) can be extremely complex, and the selection of factors must be carried out carefully so that outcomes can be interpreted accurately. For a variety of reasons, sicker patients cost more, and it is important to control for this difference in comparative analyses. When examining the factors that lead to higher hospital charges for more ill patients, two forces must be considered: duration and intensity of care. **Duration is usually quantified as inpatient LOS, whereas intensity of care may be assessed as numbers of services or charges per day.** Patients with greater comorbidity may remain hospitalized longer even if they do not receive more intense care during their stays. Duration and not intensity appears to be the primary force driving up hospital charges for sicker urology patients (Litwin et al, 1993).

Typically, comorbidity is quantified by extracting diagnoses from claims data (Klabunde et al, 2002); however, some comorbidity measures rely on patient self-report. Various comorbidity measures (Kaplan and Feinstein, 1974; Charlson et al, 1987; Greenfield et al, 1993, 1995; Crabtree et al, 2000; Di Gangi et al, 2003) have been used by researchers to adjust for case mix and predict mortality from competing causes in clinical studies. Although all perform

reasonably well in the research setting, most are based on diagnoses from retrospective chart review and difficult to apply clinically (Albertsen et al, 1996).

The impact of case mix on urologic disease outcomes has been studied most broadly in men treated for prostate cancer. The presence and severity of cardiovascular disease negatively affect outcomes in men treated with radiation or surgery (van de Poll-Franse et al, 2008a, 2008b). Higher body mass index is associated with poorer outcomes after robotic prostatectomy. In obese men, surgical times are more than an hour longer, blood loss is higher, and positive margin rates are higher (Herman et al, 2007). Obese men undergoing open radical prostatectomy have more aggressive tumors, more positive margins, and higher rates of biochemical progression than nonobese men (Freedland et al, 2008), although their long-term survival is unaffected (Siddiqui et al, 2006). Comorbidity is more important than age in predicting perioperative mortality rates after radical prostatectomy (Alibhai et al, 2005, 2006; Daskivich et al, 2010a).

The available general comorbidity indices do not appear to be equally effective at adjusting for case mix in men with prostate cancer (Alibhai et al, 2008). The optimal comorbidity index for prostate cancer should be disease specific and use empirically derived weights for component conditions (Klabunde et al, 2007). The Total Illness Burden Index for Prostate Cancer (TIBI-CaP) is a patient-reported measure of comorbidity, which identifies patients at high risk for non–prostate cancer mortality. It is a robust predictor of both mortality and future quality of life. Men in the highest risk category are 13 times more likely to die of causes other than prostate cancer over a 3.5-year period than the men who had the lowest scores (Litwin et al, 2007; Daskivich et al, 2010b).

Comorbidities such as obesity also affect the incidence and severity of benign urologic conditions (e.g., urinary incontinence, chronic prostatitis/chronic pelvic pain syndrome, benign prostatic hyperplasia/lower urinary tract symptoms, erectile dysfunction) (Pontari et al, 2005; Bhojani et al, 2008a, 2008b; Subak et al, 2009). The interrelationships between erectile dysfunction, obesity, cardiovascular disease, and metabolic syndrome are complex (Bener et al, 2008; Yassin et al, 2008).

Cost Savings in Urology

Physicians have been largely successful at attenuating the increases in hospital costs by eliminating unnecessary hospital days, but maximal savings may have been reaped from this strategy (Bodenheimer, 2005). Nevertheless, continued tailoring of the intensity and duration of service to patient burden of illness may still be shown to reduce costs. Urology has played a central role in the ongoing struggle to balance the competing priorities of minimizing costs and maximizing quality in health care (Loughlin, 2003). One recent government strategy adopted in pursuit of this goal is Medicare's pay-for-performance initiative, in which providers are differentially reimbursed on the basis of their adherence to various condition-specific quality indicators (Corrigan and Ryan, 2004), many of which also result in cost savings.

QUALITY OF CARE

Quality of care research evaluates "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge" (Lohr 1990; Lohr et al, 1992; Institute of Medicine, 2001). Several initiatives are under way to collect and disseminate performance information about medical care. For example, the National Committee on Quality Assurance (www.ncqa.org) provides information to health care purchasers about the comparative performance of health plans in the United States. The Joint Commission (www.jointcommission.org) applies outcomes-based quality measures to accredit hospitals. Hundreds of performance indicators have been collected in its National Library of Healthcare Indicators. The Foundation for Accountability (www.facct.org), a consumer organization, "creates tools that help people understand and use quality information, develops consumer-focused quality measures, supports efforts to gather and provide quality information, and encourages health policy to empower and inform consumers."

The conceptual framework for the measurement of quality of care in medicine was established 45 years ago by Donabedian (Donabedian, 1966). In this model, quality of care measures are categorized into three domains—structure, process, and outcome. Structure of care includes the equipment, resources, and provider experience necessary to provide care. Examples include volume of cases and board certification of providers. Process of care refers to technical and interpersonal elements of care that transpire between doctor and patient such as the extent of the history and physical examination, documentation of the workup, and ordering of diagnostic and laboratory tests. Process measures are often considered to be the best measure of quality (Brook et al, 1996; Brook et al, 2000). Outcomes of care include survival rates, complications, and patient-reported outcomes (PROs) such as health-related quality of life. As underscored in his exposition on quality of care, Blumenthal argues that the most important new development in our current understanding of medical outcomes was the recognition that it is patients who define which outcomes are most important and whether or not they have been achieved (Blumenthal, 1996a, 1996b; Blumenthal and Epstein, 1996). Hence we have seen the advent of patient-reported outcomes as primary end points in clinical trials and the primary focus of much attention in evidence-based medicine. In 2006 the U.S. Food and Drug Administration formally issued guidance for the development of PROs to be used in its assessment of new drugs and devices (www.fda.gov) (Sloan et al, 2007).

Leading the national effort in the United States to establish an infrastructure for improving quality of care, the federal Agency for Healthcare Quality and Research (AHRQ) has published a series of quality indicators (www.qualityindicators.ahrq.gov). On the basis of extensive reviews of available evidence, AHRQ developed four categories of quality indicators (prevention, patient safety, inpatient, and pediatric), which are now being used to modulate hospital and physician reimbursement. In this model, quality of care is assumed to be directly related to adherence to these published quality indicators.

One substrate for the study of quality of care in urology is prostate cancer; it is prevalent, costly, and associated with great clinical uncertainty (Miller et al, 2005). RAND Corporation researchers proposed a detailed infrastructure for measuring structure, process, and outcomes of care in men with prostate cancer (Litwin et al, 2000; Spencer et al, 2003). This underpinned a national assessment of quality of care by applying specific quality indicators developed from the RAND work. Wide geographic variations exist in compliance with the RAND quality indicators; teaching/research hospitals and Comprehensive Cancer Centers have the highest compliance; racial differences are not observed for any indicator (Spencer et al, 2008). Early data suggest that radiation oncologists provide care that appears more compliant than that of urologists with the RAND quality indicators (Miller et al, 2007).

Structure of Care

Structure encompasses the human, technical, and financial resources needed to provide medical care. Organizations such as the Joint Commission and the American College of Surgeons measures have generally relied on structural measures in their accreditation procedures. Important structural attributes for quality of care may include clinician characteristics (e.g., percentage of physicians who have board certification, average years of experience, distribution of specialties); organizational characteristics (e.g., staffing patterns, reimbursement method); patient characteristics (e.g., insurance type, illness profile); and community characteristics (e.g., *per capita* hospital beds, transportation system, environmental risks). Structural measures specific to prostate cancer quality could include the presence of a multidisciplinary cancer center or psychologic support services.

Although certain structural characteristics may be necessary to provide good care, they are usually insufficient to ensure quality of care. Therefore the best structural measures are those that can be shown to have a positive influence on the process of care and on patient outcomes, although this relationship has not been confirmed (Brook et al, 1990). One structural measure that is positively associated with outcomes is the volume or number of cases treated by a particular physician or institution (Joshi and Miller, 2004; Joudi and Konety, 2004; Katz et al, 2004; Lee et al, 2004; Nuttall et al, 2004; Dibra et al, 2005; Killeen et al, 2005; Lyman et al, 2005; Vitale et al, 2005; Anger et al, 2007; Jeldres et al, 2008).

Evidence links surgical volume with outcomes across multiple disease conditions; however, the explanation and significance of this finding remains unclear. First noted in 1979 (Luft et al, 1979), the volume-outcomes relationship has been extensively explored for various surgical and medical conditions. An Institute of Medicine analysis of 27 diagnoses and procedures revealed that in general volume is associated with morbidity and mortality outcomes, but the magnitude of the relationship varies widely (Halm et al, 2002). Surgical volume has gained traction in health policy decisions as a marker of surgical quality (Cooperberg et al, 2009).

Patients who undergo urologic cancer surgery for prostate, bladder, kidney, or testis tumor are less likely to experience complications and mortality if their surgery is performed by a high-volume surgeon in a high-volume hospital (Joudi and Konety, 2004; Taub et al, 2004; Hollenbeck et al, 2007; Hollenbeck et al, 2007; Gilbert et al, 2008; Siu et al, 2008; Mayer et al, 2009). This observation also holds in men undergoing transurethral prostatectomy (Riley and Lubitz, 1986).

Patients treated at facilities or by surgeons who performed fewer radical prostatectomies experience more surgical complications than those treated by higher-volume providers (Lu-Yao et al, 1996; Ellison et al, 2000; Begg et al, 2002; Hu et al, 2003). Patients undergoing external beam radiation fare better when the radiation oncologist has a caseload of at least 10 per year or 200 cumulatively (Jeldres et al, 2008). It is not clear which characteristics of providers (surgeons or hospitals) performing many surgeries contribute to better outcomes; however, high volume appears to be an important predictor of good-quality care. As predicted with great prescience 3 decades ago by Harvard's then-surgeon-in-chief, Dr. Francis D. Moore (Moore, 1980), regionalization of care for complex surgical procedures addresses disparities in quality. This has occurred for malignant and benign conditions in urology (Hollenbeck et al, 2005; Hollenbeck et al, 2006; Morris et al, 2006).

Process of Care

Process of care is the set of activities that goes on between patients and practitioners and is often divided into interpersonal process and technical process. *Interpersonal process* refers to how the clinician relates to the patient and includes issues such as whether the clinician supplies sufficient information in a clear enough manner for the patient to make an informed treatment choice. Patient survey data are generally used to assess quality of interpersonal process.

***Technical process* refers to whether medically appropriate decisions are made when diagnosing and treating the patient and whether care is provided in an effective and skillful manner.** One way to evaluate the appropriateness of medical treatment is to determine if the care provided is consistent with current medical knowledge and adheres to the professional standard. This assessment can be done by developing *quality indicators* that describe a process of care that should occur for a particular type of patient in a specific clinical circumstance. In order to be valid, these quality indicators should be based on the evidence in the medical literature and on current professional standards of care. Determining the latter often requires an expert panel in order to achieve consensus. The performance of physicians and health plans is then assessed by calculating rates of adherence to the indicators for a sample of patients.

Using quality indicators to evaluate appropriateness of care is relatively straightforward. However, assessing the effectiveness or skill of technical process of care is much more difficult. Indeed, direct observation may be necessary to assess quality of technical process of care. Alternatively, we may have to rely on measuring outcomes to evaluate whether care was provided in a skillful manner. For example, measurement of surgical blood loss or number of specimens with positive margins, both surgical outcomes, may be indicators of the quality of surgical technical process. Conversely, operative time may represent the surgeon's manual dexterity or the technical complexity of a case. Hence celerity is not generally considered an accurate indicator of operative quality.

Process measures form the basis for most extant quality assurance efforts including the National Center for Quality Assurance's Health Plan Employer Data and Information Set (HEDIS) and underlie most of the new "pay-for-performance (P4P)" incentives being pursued for reimbursement incentive systems (Epstein et al, 2004). However, quality assessment efforts should also incorporate structure and outcome measures. Birkmeyer and colleagues have suggested a framework in which quality metrics are driven by the risk a procedure poses to a patient and the average hospital caseload for the procedure (Birkmeyer et al, 2004). For high-risk, low-volume procedures such as nephrectomy with caval thrombectomy, structural measures are most appropriate because samples are too small to assess processes and outcomes. For high-risk, high-volume procedures such as radical prostatectomy, efforts may be more focused on processes and outcomes. The National Surgical Quality Improvement Program (NSQIP) developed by the U.S. Department of Veterans Affairs (VA) (Khuri et al, 1998) and under evaluation for non-VA hospitals (Fink et al, 2002) provides a framework for high-risk, high-volume procedures.

Outcomes of Care

Outcomes include changes in patients' current and future health status including health-related quality of life and satisfaction. Cancer researchers generally use survival

or progression-free survival as the main outcome measure in clinical studies. Sometimes proxy measures (also called *surrogate end points* or *intermediate outcomes*) that do not measure the outcome directly but are thought to be correlated with it are used. When a proxy measure is used as a quality indicator, there must be evidence that the proxy measure is truly a substitute for the outcome of interest. For example, rapid PSA velocity after treatment for localized prostate cancer appears to be associated with cause-specific mortality (Patel et al, 1997; D'Amico et al, 2005), so PSA doubling time may be a reasonable proxy outcome. Although the ultimate outcome may be mortality, many conditions in urology such as prostate cancer take an indolent course, making mortality impractical (and often irrelevant). In such conditions, more proximal outcomes such as length of stay, complications, and the need for salvage therapy provide a useful proxy (Hu et al, 2008). For proxy measures to be useful as quality measures, intervention should affect both the measure and the underlying disease (Schatzkin et al, 1996).

The most important patient-reported outcome is health-related quality of life, a multidimensional construct that includes somatic symptoms, functional ability, emotional well-being, social functioning, body image, as well as overall well-being (Guyatt et al, 1986; Cella and Bonomi, 1995; Guyatt et al, 1997). Quality of life assessment, typically by patient survey, provides a comprehensive evaluation of how the illness and its treatment affect patients.

Another patient-reported outcome commonly measured is patient satisfaction (Strasser et al, 1993), which refers to patients' perceptions of the quality of care they received. Patient satisfaction is also usually assessed by patient survey. One limitation of satisfaction ratings is that patients are not generally able to evaluate the technical quality of their care. In fact, studies have found no consistent relationship between patient satisfaction and technical quality of care (Cleary and McNeil, 1988; Hayward et al, 1993). That is, a physician who interacts with patients in a warm and open way may provide care that is technically poor (Aharony and Strasser, 1993). In addition, patients' satisfaction ratings may vary with their expectations. Nonetheless, when used in conjunction with other measures, data about patient satisfaction can provide useful information about overall quality of care.

Challenges to Using Outcomes to Evaluate Quality of Care

Adverse outcomes may be uncommon events, so large samples of patients may be necessary when using outcome measures to detect differences in quality among health systems or hospitals. For example, to detect a 2% point difference in the rate of postoperative wound infections between two hospitals (e.g., 5% for 1 and 7% for the other), each hospital would need to have at least 1900 patients who had the surgery.

In addition, a single outcome may be affected by many different factors, making it difficult to establish accountability. When comparing differences in surgical outcomes across hospitals, one does not know if the differences in outcomes are related to the skill of the surgeon, the competence of the surgical team, the postoperative care, the case mix, or some unmeasured factor. And the more time that elapses between the intervention and the outcome, the more difficult this problem becomes. For example, comparing 10-year outcomes in women treated for incontinence at different facilities, what is more important, the quality of the initial treatment or the quality of care for recurrent symptoms?

Outcomes can also be measured for more than one purpose. Although we are interested in developing outcome measures for evaluating the quality of care received by patients with urologic diseases, outcomes are also used clinically to track a patient's progress and, in clinical trials, to measure the efficacy or effectiveness of a new drug or intervention (Williams et al, 2004). The same measures can sometimes be used for both purposes, but certain measures are better suited for one purpose or the other. For example, 5-year survival rates are a standard measure used in many studies of new cancer treatments. However, when measuring quality of care for purposes of accountability or quality improvement, we generally need a shorter time horizon than 5 years. If we compared the 5-year survival of patients with bladder cancer at two institutions, we might indeed find that one institution had higher survival rates, suggesting that it had better quality of care. However, during those 5 years, changes in staff, revamped procedures, or new technology may have improved or weakened the quality of care at the hospitals, thereby making the comparison of only historical relevance.

Other Quality Measurement Approaches

In addition to the Donabedian model, other approaches to measuring quality of care rely on implicit review or assessment without explicit criteria. This typically involves having an acknowledged expert carry out a formal evaluation of the episode of care by reviewing the medical chart without the establishment of specific criteria for quality. The evaluator makes an implicit judgment of whether or not the care rendered was of high quality. This approach is *de facto* qualitative and may not yield results that are as valid and reproducible.

HEALTH-RELATED QUALITY OF LIFE

Health-related quality of life (HRQOL) is one of several variables commonly studied in the field of medical outcomes research. HRQOL encompasses a wide range of human experience including the daily necessities of life such as food and shelter, intrapersonal and interpersonal responses to illness, and activities associated with professional fulfillment and personal happiness (Patrick and Erickson, 1993). Contemporary interpretations of HRQOL are based on the World Health Organization's longstanding definition of health as a "state of complete physical, mental, and social well-being and not merely the absence of disease" (WHO, 1948). Because illness may affect both quantity and quality of life, all constituents of well-being must be addressed when treating patients with urologic diseases. Perhaps most importantly, HRQOL involves patients' own perceptions of their health and ability to function in life. Indeed, patient perceptions of physical function have prognostic value in predicting survival (Fossa, 1994). In light of evidence that survival and clinical outcomes may be similar across treatments for many conditions, quality of life considerations may be the critical factor in medical decision making for some instances.

Key Point: World Health Organization Definition of Health

- Health is not merely the absence of disease but a state of complete physical, mental, and social well-being.

Although quantity of life is relatively easy to assess in terms of survival, the measurement of quality of life presents more challenges, primarily because it is less familiar to most clinicians (Litwin, 1994; Meyer and Clayton, 2009). To quantify these qualitative phenomena, the principles of psychometric test theory are applied. This discipline provides the theoretic underpinnings for the science of survey research (Tulsky, 1990; Aaronson, 1991; Deyo et al, 1991; McSweeny and Creer, 1995; Testa and Simonson, 1996; Guyatt et al, 1997). Data are collected with HRQOL surveys, called instruments. Instruments typically contain questions, or items, that are organized into scales. Each scale measures a different aspect, or domain, of HRQOL. For example, items on a particular instrument may address a patient's ability to have an erection and his satisfaction with ejaculation, both of which might be included in a sexual domain.

Some scales comprise dozens of items, whereas others may include only one or two items. Each item contains a stem (which may be a question or a statement) and a response set. Most response sets are one of the following types: (1) Likert scale, in which the respondent selects from a list of degrees of agreement or disagreement with the stem; (2) Likert-type scale, in which the respondent chooses from a list of text responses; (3) visual analog scale, in which the respondent marks a point on a line that is anchored on both ends by descriptors; and (4) numeric rating scale, in which the respondent chooses a number, usually between 0 and 10. Other response sets and approaches have been developed for children, people of low literacy, and various other populations (Nelson et al, 1990; Adler et al, 2000; Finlay and Lyons, 2001).

It is axiomatic that HRQOL assessments capture patients' own perceptions of their health and ability to function in life. Instruments are best when they are self-administered by the patient, but if interviewer assistance is required, it must be from a neutral third party in a standardized fashion. Some studies have demonstrated that physicians typically underestimate the symptom burden experienced by prostate cancer patients, perhaps because their queries are not sensitive enough or because patients tend to understate their problems when speaking directly with the primary caregiver (Slevin et al, 1988; Fossa et al, 1990; Litwin et al, 1998b; Sonn et al, 2009). Other studies, however, suggest that physicians tend to overestimate the impact of the disease and its treatment on patients' psychosocial functioning and sense of well-being (Fossa et al, 1996; Lampic et al, 1996; Sneeuw et al, 1997) Conversely, spouses may overstate some domains and understate others when compared with patient assessments (Sprangers and Aaronson, 1992). Kornblith et al (1994) presented results from a large sample of patients and spouses, both of whom were administered several validated HRQOL measures. Spouses reported greater psychologic distress but fewer sexual problems than did patients themselves. In a study of perspectives on HRQOL during antihypertensive therapy, Testa (1993) demonstrated that physicians were less sensitive to the impact of side effects, reporting less than 15% of the symptoms reported by patients. Spousal reports were more sensitive than patient self-assessments, particularly in the area of sexual functioning.

HRQOL Instruments

HRQOL instruments may be general or disease specific. General HRQOL domains address the components of overall well-being, whereas disease-specific domains focus on the impact of particular organic dysfunctions that may affect HRQOL. General HRQOL instruments typically address general health perceptions, sense of overall well-being, and function in the physical, emotional, and social domains. Disease-specific HRQOL instruments focus on special and/or more directly relevant domains such as anxiety about cancer recurrence, dizziness from antihypertensive medications, or suicidal thoughts during depression therapy (Patrick and Deyo, 1989). **Disease-specific and general HRQOL domains often impact each other, leading to important interactions that must be considered in the interpretation of HRQOL data** (Fossa et al, 1997). Further research is necessary in urology to explore how much of the variation in overall HRQOL is explained by variation in the disease-specific domains.

In some conditions such as chronic renal failure, cirrhosis with ascites, and stroke, general HRQOL may be so profoundly impacted that disease-specific HRQOL assessment is unnecessary. In many indolent conditions, however, the treatments may alter bodily functions that are not fully appreciated by assessing only the broader domains of general HRQOL. Conversely, in patients with advanced cancer, HRQOL may be affected predominantly by pain, fatigue, and other constitutional symptoms that are well captured by general HRQOL instruments.

Numerous HRQOL instruments have been validated for use in urologic and other conditions. Many psychologists, sociologists, and statisticians devote their entire professional careers to the activity of developing and validating these instruments. Most medical research collaboratives devote substantial efforts to the development and standardization of HRQOL instruments (Moinpour et al, 1990; Sprangers et al, 1998). One medical journal, *Quality of Life Research,* is dedicated exclusively to presenting this research. Hence an abundance of literature exists on general HRQOL, and a significant body of work has been published on HRQOL in patients with various conditions (McDowell and Ewell, 1987; Patrick and Erickson, 1993). In urology, HRQOL research has been broad, but much has focused on individuals with prostate cancer, urinary incontinence, benign prostatic hyperplasia, end-stage renal disease, and bladder cancer (Edgell et al, 1996; Blaivas, 1998; Eton and Lepore, 2002; Botteman et al, 2003; Penson et al, 2003; Matza et al, 2004). A comprehensive resource for validated HRQOL instruments is available at www.proqolid.org. The National Cancer Institute has been particularly active in establishing interest in outcomes measurement for patients with malignant disease (www.outcomes.cancer.gov). Table 5–1 presents many of the validated health-related quality of life instruments available for the assessment of patients with urologic conditions. For each instrument, the table includes the number of items, recall time, and Flesh-Kinkaid reading grade level (Flesch, 1948; Kincaid et al, 1975).

General HRQOL Instruments

General quality of life instruments have been extensively studied and validated in many types of patients, sick and well. Examples include the RAND Medical Outcomes Study 36-Item Health Survey, also known as the SF-36 (Ware and Sherbourne, 1992; Ware et al, 1994; Gandek et al, 1998b), the Quality of Well-Being scale (Kaplan et al, 1976; Kaplan and Bush, 1982; Kaplan and Anderson, 1988; Anderson et al, 1989; Kaplan et al, 1997; Kaplan et al, 1998), the Sickness Impact Profile (Bergner et al, 1976; Bergner et al, 1981), and the Nottingham Health Profile (Martini and McDowell, 1976; McDowell et al, 1978; Hunt et al, 1985). Each assesses various components of HRQOL including physical and emotional functioning, social functioning, and symptoms. Each has been thoroughly validated and tested for reliability, validity, and responsiveness.

Table 5–1.

Characteristics of Health-Related Quality of Life (HRQOL) Instruments in Urologic Diseases

INSTRUMENT NAME	ITEMS	TIME RECALL, WEEKS	READING GRADE LEVEL OF ITEMS, MEDIAN (RANGE)	REFERENCE
General HRQOL				
MOS 36-Item Health Survey (SF-36)	36	4	5.9 (2.2-12.0)	(Ware and Sherbourne, 1992)
MOS 12-Item Health Survey (SF-12)	12	4	5.2 (2.2-12.0)	(Ware et al, 1996)
Quality of Well-Being Scale (QWB)	24	1	6.3 (0.9-12.0)	(Kaplan et al, 1976)
Sickness Impact Profile (SIP)	136	1 and 7	7.4 (0.5-12.0)	(Bergner et al, 1981)
Nottingham Health Profile (NHP)	38	At present	4.5 (2.1-12.0)	(Hunt et al, 1985)
Profile of Mood States (POMS)	65	1	7.2 (0.6-12.0)	(Norcross et al, 1984)
Mental Health Inventory (MHI)	38	4	5.8 (0.6-12.0)	(Berwick et al, 1991)
McGill-Melzack Pain Questionnaire	20	At present	N/A	(Melzack, 1975)
General HRQOL in Cancer				
Functional Assessment of Cancer Therapy–General (FACT-G)	28	1	3.4 (1.1-12.0)	(Cella et al, 1993)
Cancer Rehabilitation Evaluation System Short Form (CARES-SF)	59	4	8.2 (1.0-12.0)	(Schag et al, 1991)
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ-C30)	30	1	2.6 (1.8-12.0)	(Aaronson et al, 1993)
Rotterdam Symptom Checklist	27	1	4.6 (0.7-12.0)	(de Haes et al, 1990)
Prostate Cancer Treatment Outcome Questionnaire (PCTO-Q)	41	1	6.2 (2.1-12.0)	(Shrader-Bogen et al, 1997)
Prostate Cancer				
University of California, Los Angeles Prostate Cancer Index (UCLA-PCI)	20	4	5.2 (1.2-12.0)	(Litwin et al, 1998a)
UCLA-PCI Short Form (UCLA-PCI-SF)	15	4	4.9 (1.2-12.0)	(Litwin and McGuigan, 1999)
Expanded Prostate Cancer Index-50 (EPIC-50)	50	4	5.8 (2.5-11.9)	(Wei et al, 2000)
Functional Assessment of Cancer Therapy–Prostate (FACT-P)	47	1	2.8 (0.5-12.0)	(Esper et al, 1997)
Prostate Cancer Specific Quality of Life Instrument (PROS-QOLI)	10	1 and 7	6.4 (2.8-10.4)	(Stockler et al, 1998)
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Module (EORTC-QLQ-PR25)	25	1	6.7 (0.5-12.0)	(Borghede and Sullivan, 1996)
Total Illness Burden Index–Prostate Cancer (TIBI-CaP)	25	26	7.6 (2.4-11.3)	(Litwin et al, 2007)
The Prostate Cancer Radiation Late Toxicity Questionnaire (PCRT)	29	4	9.2 (3.6-12.0)	(Rodrigues et al, 2007)
Quality of Life Module-Prostate 14 (QOLM-P14)	14	1	3.2 (0.6-9.0)	(Osoba et al, 1999)
Memorial Anxiety Index–Prostate Cancer (MAX-PC)	18	1	6.2 (3.7-12.0)	(Roth et al, 2003)
Clark & Talcott	20	1	5.8 (2.4-10.4)	(Clark and Talcott, 2001)
Clark et al	35	4	5.2 (1.0-10.7)	(Clark et al, 2003)
Dale et al	35	1	7.1 (2.8-11.8)	(Dale et al, 1999)
Borghede et al	19	1	6.7 (2.3-12.0)	(Borghede et al, 1997)
Giesler et al	52	4	8.8 (3.6-12.0)	(Giesler et al, 2000)
Bladder Cancer				
Functional Assessment of Cancer Therapy–Bladder (FACT-BL)	40	1	3.6 (0.7-12.0)	(Mansson et al, 2002)
Functional Assessment of Cancer Therapy Vanderbilt Cystectomy Index (FACT-VCI)	19	1	3.7 (0.6-10.2)	(Cookson et al, 2003)
European Organization for Research and Treatment for Cancer Quality of Life Questionnaire Bladder Module (EORTC-QLQ-BLS24)	24	1	5.5 (0.5-12.0)	(Pavone-Macaluso et al, 1997)
Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms				
American Urological Association Symptom Index (AUASI) (a.k.a. IPSS)	7	4	9.3 (2.2-12.0)	(Barry et al, 1992b)
Benign Prostatic Hyperplasia Health-Related Quality of Life Survey (BPH-HRQOL)	49	4	7.3 (1.8-12.0)	(Lukacs et al, 1997)

Continued

Table 5–1.

Characteristics of Health-Related Quality of Life (HRQOL) Instruments in Urologic Diseases—cont'd

INSTRUMENT NAME	ITEMS	TIME RECALL, WEEKS	READING GRADE LEVEL OF ITEMS, MEDIAN (RANGE)	REFERENCE
Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms—cont'd				
Benign Prostatic Hyperplasia Impact Index (BPHii)	4	4	9.8 (5.9-11.8)	(Barry et al, 1995a)
Danish Prostatic Symptom Score-1 (DAN-PSS-1)	15	4	8.1 (2.2-12.0)	(Meyhoff et al, 1993)
International Continence Society–Male Questionnaire (ICSmale)	34	4	5.4 (1.2-12.0)	(Donovan et al, 2000)
International Continence Society–Quality of Life questionnaire (ICSQoL)	8	4	6.9 (3.6-9.0)	(Donovan et al, 1997)
Nocturia Quality of Life Questionnaire (NQOL)	13	2	5.3 (2.3-9.3)	(Mock et al, 2008)
Overactive Bladder symptom and health-related quality of life questionnaire (OAB-q)	33	4	4.7 (0.6-12.0)	(Coyne et al, 2005)
Urgency questionnaire (UQ)	19	1	4.2 (1.0-12.0)	(Coyne et al, 2004)
Primary Overactive Bladder Symptom Questionnaire (POSQ)	5	2	6.2 (2.4-12.0)	(Matza et al, 2005)
Patient Perception of Bladder Condition (PPBC)	1	At present	8.8 (8.1-9.4)	(Matza et al, 2005)
Prostatitis				
National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI)	9	1	7.7 (3.8-11.7)	(Litwin et al, 1999)
Giessen Prostatitis Symptom Score (GPSS)	12	Not spec	8.8 (1.2-12.0)	(Brahler et al, 1997)
Nickel and Sorensen	20	1	8.7 (5.0-12.0)	(Nickel and Sorensen, 1996)
Neal and Moon	4	Not spec	12.0 (12.0-12.0)	(Neal and Moon, 1994)
Erectile Dysfunction				
International Index of Erectile Function (IIEF)	15	4	7.7 (4.7-12.0)	(Rosen et al, 1997)
Self-Esteem and Relationship Questionnaire (SEAR)	14	4	4.8 (2.1-12.0)	(Cappelleri et al, 2004)
Male Sexual Health Questionnaire (MSHQ)	25	4	9.0 (5.2-12.0)	(Rosen et al, 2004)
Brief Sexual Function Inventory (BSFI)	11	4	6.9 (5.0-12.0)	(Mykletun et al, 2006)
Erectile Dysfunction Inventory of Treatment Satisfaction Questionnaire (EDITS)	11	4	6.7 (4.4-12.0)	(Althof et al, 1999)
Erection Distress Scale (EDS)	5	Not spec	6.7 (3.6-9.0)	(Seftel et al, 2007)
Urinary Incontinence				
Incontinence Impact Questionnaire (IIQ)	30	Not spec	7.0 (2.3-12.0)	(Shumaker et al, 1994)
Incontinence Impact Questionnaire Short Form (IIQ-7)	7	Not spec	12.0 (4.4-12.0)	(Uebersax et al, 1995)
Urological Distress Inventory (UDI)	19	Not spec	5.8 (0.8-12.0)	(Shumaker et al, 1994)
Urogenital Distress Inventory Short Form (UDI-6)	6	Not spec	8.4 (4.8-12.0)	(Uebersax et al, 1995)
International Consultation on Incontinence Questionnaire–Female Lower Urinary Tract Symptoms (ICIQ-FLUTS)	12	4	1.0 (0.5-9.3)	(Brookes et al, 2004)
International Consultation on Incontinence Questionnaire (ICIQ)	4	4	4.6 (0.7-8.7)	(Avery et al, 2004)
Symptoms of Incontinence Questionnaire (a.k.a., PRAFAB-Q)	20	Not spec	6.7 (2.2-11.9)	(Hendriks et al, 2008)
Urinary Incontinence Quality of Life Questionnaire (I-QOL)	22	Not spec	8.9 (4.3-12.0)	(Wagner et al, 1996)
Stress-Related Leak, Emptying Ability, Anatomy, Protection, Inhibition, Quality of Life, Mobility and Mental Status (SEAPI-QMM)	15	Not spec	9.4 (3.6-12.0)	(Raz and Erickson, 1992)
King's Health Questionnaire (KHQ)	21	At present	4.5 (0.7-12.0)	(Kelleher et al, 1997)
Bristol Female Lower Urinary Tract symptoms questionnaire (BFLUTS)	33	Not spec	7.1 (2.2-12.0)	(Jackson et al, 1996)
Bristol Female Lower Urinary Tract symptoms questionnaire short form (BFLUTS-SF)	19	Not spec	6.3 (3.2-12.0)	(Brookes et al, 2004)
Urge-Incontinence Impact Questionnaire (U-IIQ)	32	4	4.1 (0.5-12.0)	(Lubeck et al, 1999)
Urge-Urinary Distress Inventory (U-UDI)	10	4	4.9 (1.8-12.0)	(Lubeck et al, 1999)
Symptom Severity Index (SSI)	13	1 and 52	3.6 (2.2-6.2)	(Black et al, 1996)
Symptom Impact Index (SII)	3	Not spec	7.3 (4.9-10.8)	(Black et al, 1996)
Stress and Urge Incontinence and Quality of Life Questionnaire	9	1 and 26	5.8 (0.8-12.0)	(Kulseng-Hanssen and Borstad, 2003)

Table 5–1.
Characteristics of Health-Related Quality of Life (HRQOL) Instruments in Urologic Diseases—cont'd

INSTRUMENT NAME	ITEMS	TIME RECALL, WEEKS	READING GRADE LEVEL OF ITEMS, MEDIAN (RANGE)	REFERENCE
Urinary Incontinence Severity Score (UISS)	10	Not spec	9.2 (2.8-12.0)	(Stach-Lempinen et al, 2004)
CONTILIFE	28	2 and 4	5.6 (0.8-12.0)	(Amarenco et al, 2003)
Female Incontinence Severity Index (ISI)	2	Not spec	5.8 (0.8-10.7)	(Sandvik et al, 1993)
Interstitial Cystitis				
O'Leary Sant Interstitial Cystitis Symptom Index and Problem Index (OSICSI-PI)	23	4	7.1 (2.3-11.0)	(O'Leary et al, 1997)
Pelvic Pain and Urgency/Frequency Questionnaire (PUF)	8	Not spec	4.9 (0.5-12.0)	(Parsons et al, 2002)
Female Genitourinary Pain Index (FGUPI)	9	1	7.7 (3.8-11.7)	(Parsons et al, 2002)
Kidney Cancer				
Functional Assessment of Cancer Therapy–Kidney Symptom Index (FKSI-15)	15	1	1.3 (0.3-8.2)	(Cella et al, 2006)
Renal Transplant				
End-Stage Renal Disease Symptom Checklist–Transplantation Module (ESRD-SCL)	43	4	6.2 (1.8-12.0)	(Franke et al, 1999)
Kidney Disease and Quality of Life Questionnaire (KDQOL-36)	36	4	4.9 (0.8-12.0)	(Hays et al, 1998)
Urinary Tract Infection				
Activity Impairment Assessment (AIA)	5	1 and 7	9.7 (3.6-12.0)	(Wild et al, 2005)
Sexuality				
Index of Premature Ejaculation (IPE)	10	4	9.1 (1.3-12.0)	(Althof et al, 2006)
Sexual Quality of Life (Male) Instrument (SQOL-M)	11	Not spec	8.6 (2.6-12.0)	(Abraham et al, 2008)
Profile of Female Sexual Function (PFSF)	38	Not spec	4.3 (0.5-12.0)	(Derogatis et al, 2004)
Brief Profile of Female Sexual Function (B-PFSF)	7	Not spec	3.9 (0.9-9.2)	(Rust et al, 2007)
Male Sexual Quotient Questionnaire (MSQ)	10	6	7.0 (14-12.0)	(Abdo, 2007)

The RAND Medical Outcomes Study 36-Item Health Survey (a.k.a., SF-36) is one of the most commonly used instruments and is regarded by some as a "gold standard" measure of general HRQOL. It is a 36-item, self-administered instrument that takes less than 10 minutes to complete and quantifies HRQOL in multi-item scales that address eight different health concepts—physical function, role limitation due to physical problems, bodily pain, general health perceptions, social function, emotional well-being, role limitation due to emotional problems, and energy/fatigue. The SF-36 may also be scored in two summary domains—physical and mental. Recently, a shorter 12-item version, the SF-12, has been developed for use in studies requiring greater efficiency. It provides a somewhat narrower view of overall health status and is usually scored only in the two summary domains (Ware et al, 1995; Ware et al, 1996; Gandek et al, 1998a). A useful resource for clinicians and researchers interested in the SF-36, SF-12, and related measures may be found at www.sf-36.org.

The Quality of Well-Being scale (QWB) summarizes three aspects of health status—mobility, physical activity, and social activity—in terms of QALY, quantifying HRQOL as a single number that may range from death to complete well-being. The original QWB contains only 18 items, but it requires a trained interviewer. A newer self-administered version of the QWB is now available and has been shown to produce scores that are equivalent to the interviewer-administered version and stable over time (Kaplan et al, 1997). The Sickness Impact Profile (SIP) measures health status by assessing the impact of sickness on changing daily activities and behavior. It is self-administered but contains 136 items and can take 30 minutes or longer to complete. The Nottingham Health Profile (NHP) covers six types of experience that may be affected by illness: pain, physical mobility, sleep, emotional reactions, energy, and social isolation by using a series of weighted yes or no items. It contains 38 self-administered items and can be completed fairly quickly.

Mental health is often measured with the Profile of Mood States (POMS) (Jacobson et al, 1978; Norcross et al, 1984; Cella et al, 1987; Albrecht and Ewing, 1989), a 65-item self-administered instrument that measures dimensions of affect or mood in six domains including anxiety, depression, anger, vigor, fatigue, and confusion. A validated short form is also available (Baker et al, 2002). Another commonly used measure of depression is the Center for Epidemiologic Studies Depression index (CES-D) (Weissman et al, 1977). Comprising items from previously developed scales, the CES-D includes 20 statements of depressive symptoms, which the respondent rates with a frequency ranging from rarely/none of the time to most/all of the time. A score of 16 or higher indicates a high likelihood of depression.

Another approach to quantifying general HRQOL is to blend a self-assessment of physical, emotional, and social functioning and well-being with a self-report of preferences, or utilities, for those health states. Developed by the Euroqol Group, a measurement collaborative, the EQ-5D is such an instrument (EuroqolGroup, 1990; Brooks, 1996; Johnson and Coons, 1998; Johnson et al, 1998; Sullivan et al, 2005). It is a short, generic measure of

well-being in five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of which is colored with a self-rating of no problems, mild/moderate problems, or severe problems. Responses are then weighted to yield a summary index, which ranges from worst to best possible health. Used extensively throughout the world, it was developed to incorporate patient preferences with the health states assessed by several existing generic instruments.

Benign Disease-Targeted HRQOL Instruments

The best-known outcomes instrument in urology is no doubt the American Urological Association Symptom Index (AUASI) (Barry et al, 1992a, 1992b; Barry et al, 1995a). Its simplicity belies its elegance and utility. Developed and published in the early 1990s, the AUASI revolutionized the longitudinal assessment of men with prostatic obstruction. For generations, urologists assessed men with prostatic enlargement by recording an inventory of obstructive and irritative voiding symptoms in qualitative categories such as 3+ hesitancy and nocturia ×2. Previous symptom indices (Barry et al, 1992a) never quite reached a tipping point, but with the imprimatur of the American Urological Association, the AUASI was rapidly and widely adopted as a quantitative measure of voiding symptoms (Gee et al, 1995). It includes seven items, each self-rated on a scale of 0 to 5, yielding a summary score that ranges from 0 to 35. Symptom scores are considered mild (0-7), moderate (8-19), or severe (20-35). A 3-point difference is considered clinically meaningful (Barry et al, 1995a). With the addition of a separate quality of life item that is not included in the summary score, the worldwide urology community embraced the AUASI as the International Prostate Symptom Score (IPSS).

The other areas in benign urology that have garnered the most interest in outcomes assessment are renal transplantation (Butt et al, 2008) and female urinary incontinence. The majority of HRQOL assessments in renal transplant patients rely on general measures such as the SF-36, the SIP, or the RAND Kidney Disease Quality of Life Index (Hays et al, 1994). Studies of quality of life have shown that women with stress or urge incontinence are more likely to experience social isolation, emotional disturbances, and sleep disturbances (Ekelund et al, 1993; Grimby et al, 1993). Younger women and those with primarily urge incontinence are most profoundly affected (Wyman et al, 1987; Hunskaar and Vinsnes, 1991).

Numerous validated instruments are available for the academic and clinical study of women with urinary incontinence. Table 5-2 lists several questionnaires that were highly recommended by the Third International Consultation on Incontinence (Donovan et al, 2005). The Urinary Incontinence–Specific Quality of Life Instrument (I-QOL) (Patrick et al, 1999b) contains 22 statements, such as "I worry about not being able to get to the toilet on time." The respondent endorses each on a 5-point scale that ranges from not at all to extremely. Item responses are converted to a 100-point scale with higher scores representing better outcomes.

The 30-item Incontinence Impact Questionnaire (IIQ) and 19-item Urogenital Distress Inventory (UDI) (Shumaker et al, 1994) are often used together in their validated short forms that contain seven and six items, respectively (Uebersax et al, 1995). They address both the dysfunction and the distress associated with urinary incontinence with items such as "Has urine leakage/prolapse affected household chores?" and "How much are you bothered by frequent urination?" The response set for each statement is a 4-point scale that ranges from not at all to greatly.

In the 15-item quality of life index from the Stress-Related Leak, Emptying Ability, Anatomy, Protection, Inhibition, Quality of Life, Mobility and Mental Status (SEAPI-QMM) instrument, each symptom is graded 0 to 3 to yield a score range of 0 to 45 with higher scores indicating worse outcomes (Stothers, 2004). Results are stratified into several domains including social interactions, personal strain, interference with sexual activity, and global impact.

Table 5–2.

Selected Validated Instruments for Urinary Incontinence Recommended by the Third International Consultation on Incontinence

Symptoms	
Women	Urogenital Distress Inventory (UDI)
	Urogenital Distress Inventory Short Form (UDI-6)
	Incontinence Severity Index
	Bristol Female Lower Urinary Tract Symptoms (BFLUTS)
Men	International Continence Society male (ISCmale)
	Danish Prostate Symptom Score (DAN-PSS)
Quality of Life Impact	
Men and women	Incontinence–Quality of Life (I-QOL)
	SEAPI-QMM
Women	King's Health Questionnaire
	Incontinence Impact Questionnaire (IIQ)
	Incontinence Impact Questionnaire Short Form (IIQ-7)
	Urinary Incontinence Severity Score (UISS)
	CONTILIFE
Symptoms and Quality of Life Impact	
Men and women	International Consultation on Incontinence Questionnaire (ICIQ)
Women	Bristol Female LUTS–Short Form (BFLUTS-SF)
	Stress and Urge Incontinence and Quality of Life Questionnaire (SUIQQ)
Men	ICS male Short Form (ICSmaleSF)

Adapted from Donovan J, Bosch R, et al. Symptom and quality of life assessment. Third International Consultation on Incontinence. In: Abrams P, Cardozo L, Wein A, editors. United Kingdom: Health Publications; 2005. p. 519–84. Table 5–3.

The term *overactive bladder* is commonly used to denote urinary frequency with or without urge incontinence. It was coined by the pharmaceutic industry during the development and promotion of new oral medications to treat these symptoms. A variety of instruments is available to assess patients with symptoms of overactive bladder. As in many urologic conditions, this condition is driven by patient experience and hence measures of outcome must be standardized within or across studies (Coyne et al, 2002; Brubaker et al, 2006; Coyne et al, 2006).

Several reviews of available instruments summarize their psychometric properties and performance in various populations and stress the importance of standardization in measurement (Lose et al, 2001; Symonds, 2003; Haywood et al, 2008).

Cancer-Specific HRQOL Instruments

Because of the well-documented impact of malignancies and their treatment on HRQOL, cancer-specific domains have also been investigated extensively. Numerous instruments have been developed and tested that measure the special impact of cancer (regardless of primary site) on patients' routine activities. Examples include the European Organization for the Research and

Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (Aaronson et al, 1993), the Functional Assessment of Cancer Therapy (FACT) (Cella et al, 1993), and the Cancer Rehabilitation Evaluation System (CARES) and its short form (CARES-SF) (Schag and Heinrich, 1990; Schag et al, 1991; Schag et al, 1994). Each has been validated and tested in patients with various types of cancer. Readers are directed to the Quality of Life Instruments Database (www.qolid.org) for guidance when selecting an instrument for quality of life measurement in studies of prostate or other cancers.

The EORTC QLQ-C30 was designed to measure cancer-specific HRQOL in patients with a variety of malignancies. Its 30 items address domains that are common to all cancer patients. The questionnaire includes five functional scales (physical, role, emotional, cognitive, and social functioning); a global health scale; three symptom scales (fatigue, nausea/vomiting, and pain); and six single items concerning dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties due to disease. The EORTC QLQ-C30 has performed well in populations with urologic malignancies (Curran et al, 1997). Disease-specific modules for cancers of the prostate (Aaronson and van Andel, 2001), breast (Sprangers et al, 1996), lung (Bergman et al, 1994), head and neck (Bjordal et al, 1994), and other sites have been developed according to methodologically rigorous techniques. Additional disease-specific modules are available.

The FACT is usually applied as a two-part instrument that includes a general item set pertaining to all cancer patients (FACT-G) and one of several item sets containing special questions for patients with specific tumors. Each item is a statement that a patient may agree or disagree with across a 5-point range. The FACT-G domains include well-being in five main areas: physical, social/family, relationship with doctor, emotional, and functional. The FACT-G includes 28 items and is easily self-administered. Disease-specific modules are available for numerous patient tumor groups including prostate (Esper et al, 1997), bladder (Mansson et al, 2002), colorectal (Ward et al, 1999), breast (Brady et al, 1997), ovary (Basen-Engquist et al, 2001), and other cancers. Modules are also available for issues specific to bone marrow transplantation (McQuellon et al, 1997), anemia, and fatigue (Cella, 1997; Yellen et al, 1997).

The CARES Short Form (CARES-SF) is a 59-item, self-administered instrument that measures cancer-related quality of life with five multi-item scales: physical, psychosocial, medical interaction, marital interaction, and sexual function. A large and valuable database of patients with many different tumors including urologic tumors has been collected by the instrument's authors (Schag et al, 1994). These data are helpful when comparing the experience of prostate cancer patients with that of patients with other types of cancer.

Selecting a Quality of Life Instrument

Investigators or clinicians considering measuring HRQOL in a clinical study or in clinical practice should choose an instrument (or instruments) depending on the particular population being studied and the clinical questions being asked. Using previously validated instruments, to the extent they are applicable and appropriate, obviates the need for an arduous process of instrument development and validation. A general and a disease-specific module in combination are suitable for most studies. However, if a particular domain (e.g., pain) is the focus of the study, specific, expanded questionnaires should be sought focusing on the area of interest. Respondent burden needs to be considered, particularly for longitudinal studies where subjects will complete the same instruments multiple times. Pretesting instruments that will be used in clinical studies is advisable.

Psychometric Validation of New HRQOL Instruments

The development and validation of new instruments and scales is a long and arduous process. It is not undertaken lightly. Simply drawing up a list of questions that seem appropriate is fraught with potential traps and pitfalls. For this reason, it is always preferable to use established, validated HRQOL instruments (Guyatt et al, 1992).

When scales and instruments are developed, they are first pilot tested to ensure that the target population can understand and complete them with ease. Pilot testing is usually preceded by focus groups to refine the wording of items and to ensure comprehensive coverage of concepts and domains deemed important by respondents. Pilot testing of an instrument should also include formal cognitive testing. This process is typically led by behavioral scientists who specialize in developing and assessing the wording and ordering of questionnaire items to ensure that they can be easily understood by respondents, and that the answers that respondents provide are what investigators hope to learn from their study. Cognitive testing is usually performed on a small number of respondents, usually 5-10 volunteers, who are asked to "think aloud" during the process of questionnaire completion. Following cognitive testing, a larger pilot test is then performed on a somewhat larger sample, using the exact same planned enrollment procedures and materials that are intended for the full study. Pilot testing can reveal problems that might otherwise go unrecognized by researchers. For example, many terms that are commonly used by medical professionals are poorly understood by patients. This may result in missing data if patients leave questions blank. In fact, because the average adult reads at the fifth- to eighth-grade level, items should be drafted at no higher than an eighth-grade reading level (Paasche-Orlow et al, 2003). Furthermore, because many patients with urologic malignancy are older and may have poor eyesight, pilot testing often identifies easily corrected visual barriers such as type size and page layout. In addition, self-administered instruments with complicated skip patterns (e.g., "If you answered yes to item 16b, continue with item 16c; if you answered no to item 16b, skip to item 19a") may be too confusing for even the most competent patients to follow. This, too, can result in missing data and introduce difficulties in the analysis. Pilot testing is a necessary and valuable part of instrument development. It serves as a reality check on those developing the scales.

Scales and instruments are also evaluated for three fundamental statistical properties—reliability, validity, and responsiveness (Stewart et al, 1992; Lohr et al, 1996; Litwin, 2002).

Reliability

Reliability (Table 5–3) **refers to how free the scale is of measurement error;** that is, what proportion of a patient's test score is true and what proportion is due to chance variation. Two of the most commonly used metrics are test-retest and internal consistency reliability.

Test-retest reliability is the most commonly used indicator of survey instrument reliability. It is measured by having the same respondents complete a survey at two different points in time to

Table 5–3.
Reliability Assessments for Health-Related Quality of Life Instruments

TYPE OF RELIABILITY	CHARACTERISTICS	COMMENTS
Test-retest	Measures the stability of responses over time, typically in the same group of respondents	Requires administration of survey to a sample at 2 different and appropriate points in time. Time points that are too far apart may produce diminished reliability estimates that reflect actual change over time in the variable of interest.
Intraobserver	Measures the stability of responses over time, in the same individual respondent	Requires completion of a survey by an individual at 2 different and appropriate points in time. Time points that are too far apart may produce diminished reliability estimates that reflect actual change over time in the variable of interest.
Alternate-form	Uses differently worded stems or response sets to obtain the same information about a specific topic	Requires 2 items in which the wording is different but aimed at the same specific variable and at the same vocabulary level
Internal consistency	Measures how well several items in a scale vary together in a sample	Usually requires a computer and statistician to carry out calculations
Interobserver	Measures how well 2 or more different respondents rate the same phenomenon	May be used to demonstrate reliability of a survey or may itself be the variable of interest in a study

see how stable their responses are. It is a measure of how reproducible a set of results is. Correlation coefficients are then calculated to compare the two sets of responses. These correlation coefficients are collectively referred to as the survey instrument's test-retest reliability. In general, the correlation coefficients are considered good if they are at least 0.70. This implies that the survey responses are reasonably consistent from one point in time to another. When measuring test-retest reliability, one must be careful not to select items or scales that measure variables likely to change over short periods of time. Variables that are likely to change over a given period of time will produce low test-retest reliability in measurement instruments. This does not mean that the survey instrument is performing poorly but simply that the attribute itself has changed. One can certainly measure characteristics that tend to change over time. In fact, this is often the purpose of HRQOL research. But test-retest reliability must be documented over shorter periods to decrease the degree of measurement error attributable to the survey itself.

When measuring test-retest reliability, one must also consider that individuals may become familiar with the items and answer partly on the basis of their memory of what they answered the last time. Called the *practice effect,* this presents a challenging problem to address in measures of test-retest reliability over short periods of time. As a result of the practice effect, test-retest reliability figures can be falsely inflated.

Alternate-form reliability provides one way to escape the problem of the practice effect. It involves using differently worded items to measure the same attribute. Questions and responses are reworded or their order is changed to produce two items that are similar but not identical. One must be careful to create items that address the same exact aspect of behavior with the same vocabulary level and the same level of difficulty. Items must differ only in their wording. Items or scales are administered to the same population at different time points, and correlation coefficients are again calculated. If these are high, the survey instrument or item is said to have good alternate-form reliability. One common way to test alternate-form reliability is to change the order of the response set. Changing the order of the response set is most effective when the two time points are close together. This approach forces the respondent to read the items and response sets carefully, thereby decreasing the practice effect. Another way to test alternate-form reliability is to change the wording of the response sets without changing the meaning (Fig. 5–1). Another common method to test alternate-form reliability is to change the actual wording of the items themselves. Again, one must be careful to design items that are truly equivalent to each other. Items that are worded with different degrees of reading difficulty do not measure the same attribute.

Item 1: Circle one number in each response set

During the last week, how often did you usually empty your bladder?	
1 to 2 times per day	1
3 to 4 times per day	2
5 to 8 times per day	3
12 times per day	4
More than 12 times per day	5
During the last week, how often did you usually empty your bladder?	
Every 12 to 24 hours	1
Every 6 to 8 hours	2
Every 3 to 5 hours	3
Every 2 hours	4
More than every 2 hours	5

Item 2: Circle one number in each response set

During the last 4 weeks, how much did you leak urine?	
Never	1
A little bit	2
A moderate amount	3
A lot	4
Constantly	5
During the last 4 weeks, how much did you leak urine?	
I used no pads in my underwear	1
I used 1 pad per day	2
I used 2 to 3 pads per day	3
I used 4 to 6 pads per day	4
I used 7 or more pads per day	5

Figure 5–1. Alternate-form reliability. Equivalent but differently worded response sets to two items on urinary function are presented. The response sets for each item are differently worded but functionally equivalent. This makes them good candidates for use in a test of alternate-form reliability.

They are more likely to measure the reading comprehension or cognitive function of the respondent.

Sometimes data are not collected from a group of subjects but are recorded by a single observer. In this case, test-retest reliability is assessed by having that individual make two separate measurements. Both data sets from the same observer are then compared with each other. The correlation between two data sets from the same individual is commonly known as *intraobserver reliability.* It measures the stability of responses from the same respondent and is a form of test-retest reliability.

Interobserver (inter-rater) reliability provides a measure of how well two or more evaluators agree in their assessment of a variable. It is usually reported as a correlation coefficient between different data collectors. When survey instruments are self-administered respondent and designed to measure the respondent's own behaviors or attitudes, interobserver reliability is not used. However, whenever there is a subjective component in the measurement of an external variable, it is important to calculate this statistic. Sometimes interobserver reliability is used as a psychometric property of a survey instrument, whereas other times it is itself the variable of interest. Interobserver reliability is often used when the measurement process is less quantitative than the variable being measured.

***Internal consistency reliability* is a measure of the similarity of an individual's responses across several items, indicating the homogeneity of a scale** (Tulsky, 1990). It is applied not to single items but to groups of items that are thought to measure different aspects of the same concept. Internal consistency is an indicator of how well the different items measure the same issue. This is important because a group of items that purports to measure one variable should indeed be clearly focused on that variable. Although single items may be quicker and less expensive to administer, the data set is richer and more reliable if several different items are used to gain information about a particular behavior or topic. The statistic most often used to quantify this unidimensionality or internal consistency of a scale is called Cronbach coefficient alpha (Cronbach, 1951). Internal consistency can be reported for any scale with more than one item, whereas test-retest reliability requires the scale to be administered to some patients twice within a short interval, preferably less than 1 month.

Validity

Validity (Table 5–4) **refers to how well the item, scale, or instrument measures the attribute it is intended to measure.** An item designed to measure pain should measure pain and not some related variable like anxiety. A scale meant to measure emotional quality of life should not measure depression, which is a related but different variable. When an instrument has validity, it is said to measure the truth. Validity provides evidence to support drawing inferences about quality of life from the scale scores. Validity has three general forms: content, criterion, and construct.

Content validity, sometimes casually referred to as face validity, involves a subjective assessment of the scope and completeness of a scale and is usually measured in the early stages of an instrument's development from experts and patient focus groups. The assessment of content validity typically involves an organized review of an instrument's contents to ensure that it includes everything it should and does not include anything it should not. Patients should be involved in this assessment. Clinicians may be unaware of the subtle nuances experienced by patients who live day to day with a given condition. Families also may provide helpful insights into dimensions that might otherwise be overlooked by experts. This said, it remains important for clinicians to review the items for relevance to and focus on the variables of interest. Content validity is not quantified with statistics. Rather, it is presented as an overall opinion of a group of trained judges. Nevertheless, it provides a good foundation on which to build a methodologically rigorous assessment of a survey instrument's validity.

Criterion validity is a more quantitative approach to assessing the performance of scales and instruments. It requires the correlation of scales scores with results from other established tests (concurrent validity) or with future measurable outcomes (predictive validity). For example, concurrent validity of a new sexual function scale might be correlated with objective performance on infusion cavernosometry. Likewise, the predictive validity of a new quality of life scale for physical function might be correlated with the number of subsequent physician visits or hospitalizations.

Concurrent validity requires that the survey instrument in question be judged against some other method that is acknowledged as a gold standard for assessing the same variable. It may be a published psychometric index, a scientific measurement of some factor, or another generally accepted test. The fundamental requirement is that it be regarded as a good way to measure the same concept. The statistic is calculated as a correlation coefficient with that test. A high correlation suggests good concurrent validity. Alternatively, a test may be selected for comparison that is expected to measure an attribute or behavior that is opposite to the dimension of interest. In this case, a low correlation indicates good concurrent validity. The reason one would not simply use the established gold standard as a measure of choice is that it may be too cumbersome, expensive, or invasive to apply.

Table 5–4.

Validity Assessments for Health-Related Quality of Life Instruments

TYPE OF VALIDITY	CHARACTERISTICS	COMMENTS
Content	Formal expert review of how good an item or series of items appear	Usually assessed by individuals with expertise in some aspect of the subject under study
Criterion: Concurrent	Measures how well the item or scale correlates with gold-standard measures of the same variable	Requires the identification of an established generally accepted gold standard
Criterion: Predictive	Measures how well the item or scale predicts expected future observations	Used to predict outcomes or events of significance that the item or scale might subsequently be used to predict
Construct	A theoretic measure of how meaningful a survey instrument is, usually after years of experience by numerous investigators	Not easily quantifiable

Predictive validity is the ability of a survey instrument to forecast future events, behaviors, attitudes, or outcomes. It may be used during the course of a study to predict response to a stimulus, success of an intervention, or time to a medical end point. Over a brief interval, predictive validity is similar to concurrent validity in that it involves correlating the results of one test with the results of another test administered around the same time. If the time frame is longer and the second test occurs much later, then the assessment is of predictive validity. Like concurrent validity, predictive validity is calculated as a correlation coefficient between the initial test and the secondary outcome.

Construct validity is the most valuable yet most difficult way of assessing a survey instrument. Often determined only after years of experience with an instrument, it is a measure of how meaningful the scale or survey instrument is when in practical use. It is typically not calculated as a statistic, but as a gestalt of how well a survey instrument performs in a multitude of settings and populations over a number of years. Construct validity implies that the instrument of interest yields results that are similar to (convergent validity) or different from (divergent validity) several other methods for obtaining the same information about a given trait or concept.

Responsiveness

Responsiveness of an HRQOL instrument refers to how sensitive the scales are to change over time (Deyo et al, 1991; Stockler et al, 1998). That is, a survey may be reliable and valid when used at a single point in time, but in some circumstances it must also be able to detect meaningful improvements or decrements in quality of life during longitudinal studies. The instrument must "react" in a time frame that is relevant for patients over time. Because HRQOL may change over time, longitudinal measurement of these outcomes is important (Olschewski and Schumacher, 1990; Zwinderman, 1990). Different domains may become more or less prominent over time as the course of disease and recovery evolves. Although their perception of cure waxes and wanes with time since treatment or the latest PSA level, patients may feel more or less impacted by their HRQOL impairments.

In order to make useful inferences regarding absolute scores or change scores over time, it is important to determine what meaning different numeric values have (Samsa et al, 1999). For example, the minimally important difference of the AUASI (Barry et al, 1992b) has been measured at 3 points (Barry et al, 1995b). When no such thresholds have been established, one can roughly approximate the smallest difference that is important to the patient as one third to one half of a standard deviation (Norman et al, 2003; Sloan and Dueck, 2004). A more quantitative approach involves calculating an effect size, or Guyatt statistic, typically expressed as the ratio of the raw change in score among those who change to the standard deviation of the change among those who did not change (Guyatt et al, 1987; Guyatt et al, 2002).

Over time, patients' perceptions of quality of life impairments may change. This phenomenon, known as *response shift,* must be considered when evaluating longitudinal patterns in HRQOL outcomes (Breetvelt and Van Dam, 1991; Sprangers, 1996).

Responsiveness and minimally important difference may be ascertained by correlation with a self-administered global response assessment (GRA) item that measures improvement or worsening over time on a Likert-type scale such as markedly, moderately, or minimally worse; unchanged; or minimally, moderately, or markedly better.

Comparison Groups

Prospective, longitudinal data collection beginning at baseline before treatment is always best because this approach may reveal time-dependent evolution of HRQOL domains (Talcott et al, 1998). Patients may then serve as their own controls. Assessing HRQOL at baseline before treatment allows for the inclusion of baseline age- or comorbidity-related changes that should not be attributed to treatment. This approach facilitates the stratification of discriminants from determinants of HRQOL.

However, investigators often use methodologies in which HRQOL is assessed cross-sectionally, rather than longitudinally. In cross-sectional surveys, patients cannot serve as their own temporal controls because recall of pretreatment HRQOL is notoriously inaccurate (Aseltine et al, 1995; Herrmann, 1995). Hence studies must rely on appropriate comparison groups. Selecting the best comparison group is an important step in conducting a meaningful analysis of HRQOL outcomes. If normal is defined as the absence of any dysfunction, then treatment groups may be held to too high a standard. For example, in order to interpret the HRQOL effects of prostate cancer treatment meaningfully, a valid context is provided by assessing HRQOL in older men without prostate cancer (Litwin, 1999) or in prostate cancer patients on watchful waiting. Hence in comparisons of the effect of treatment efficacy on HRQOL, longitudinal studies starting pretreatment provide the most compelling results. In cross-sectional studies, a suitable comparison group is critical.

Cultural Issues and Translations

When designing new HRQOL instruments or applying established ones in populations of different ethnicity or nationality, one must make sure that the items translate well into both the language and culture of the target audience. Although the items may have been linguistically translated into a new language, they may not measure the same dimension in that culture (Herdman et al, 1997). This is particularly relevant when studying social attitudes and health behaviors (e.g., as related to pain, sexual function, or urinary incontinence). Different cultures have different concepts of health, well-being, illness, and disease. A well-developed concept in one culture may not even exist in another. Failing to be attentive to multicultural issues may result in significant bias when collecting data. For example, when classifying ethnicities, survey researchers often categorize all Asians together. For some projects this may be acceptable; however, many attitudes and behaviors vary markedly among Chinese, Japanese, Filipino, Korean, Indian, and other cultures within Asia. By collapsing them all into one group, researchers may overlook differences that are important to the conclusions.

When translating an HRQOL instrument into a new language, one must also consider issues of linguistics. Specific methodologies have been developed for cross-validating HRQOL instruments in other languages (Vela Navarrete et al, 1994; Boyle, 1997). One begins by having two to three bilingual individuals perform independent "forward translations" into the new language. Next, these translators reconcile any differences in word choice in the new language. Next, two to three different bilingual individuals perform independent "back translations," in which the reconciled translation is converted back into the primary language. Then, translators independently review the forward, reconciled, and back translated versions in order to iron out any language

differences in the translation and agree on a final wording in the new language. Finally, after pilot testing the instrument with bilingual subjects, a larger-scale validation must be conducted in order to establish reliability and validity in the new language. This process has been accomplished for a variety of instruments used in the assessment of patients with urologic diseases (Sagnier et al, 1994; Arocho et al, 1995; Sagnier et al, 1996; Boyle, 1997; Krongrad et al, 1997; Badia et al, 1998; Gandek et al, 1998a, 1998b; Patrick et al, 1999a; Collins et al, 2001; Hochreiter et al, 2001; Kakehi et al, 2002; Duarte et al, 2005).

During a recent linguistic translation of an instrument to measure symptoms in men with chronic prostatitis, researchers collected data from many Spanish-speaking patients including subjects from Argentina, Mexico, Spain, and the United States. The translation had high overall reliability; however, respondents expressed difficulty in distinguishing the response categories "a menudo" ("often") from "normalmente" ("usually") in one of the items. Hence the researchers revised "a menudo" to "muchas veces" ("much of the time") and "normalmente" to "casi siempre" ("almost always") to improve the distinctiveness of response categories.

In addition to varying cultural perspectives on disease and health, international differences in health systems may also have a substantial impact on the way patients view their quality of life. For example, in countries where patients are required to pay all or most of the treatment costs, spending a lot of money for marginally better survival rates may have a larger effect on quality of life than the disease or treatments. Furthermore, in cultures where the patient's relatives are compelled to absorb the costs of care, the quality of life of the entire family unit should also be considered.

Caveats on the Collection of HRQOL Data

Although there are some single instruments that are multidimensional, many quality of life researchers have endorsed a "battery approach," in which the various components of HRQOL are measured with different scales to assure that each domain receives adequate attention. Longer instruments can provide greater precision, but they also increase the chance that patients will tire of the exercise and not provide reliable or valid answers. This is particularly true in the multicenter clinical trial setting. Hence shorter instruments are generally preferable when obtaining HRQOL measurements under such circumstances. In general, it is easier and more efficient to use established instruments that have already undergone psychometric validation. HRQOL data collected using published instruments allow the researcher to compare the study results to data from other samples or diverse populations with various chronic diseases. Nevertheless, sometimes it is necessary to develop new questionnaire items to ensure that a particular concept is adequately evaluated. Under such circumstances new scales can be tested for reliability and validity during the course of data collection.

Once an instrument is thoroughly pilot tested and found to be reliable and valid, it must be administered in a manner that minimizes bias. Quality of life data cannot and should not be collected from patients directly by the treating health care provider. Patients often provide socially desirable responses under such circumstances (Tannock, 1990). This introduces measurement error. No matter how objective the treating clinician may claim to be, it is impossible for him or her to collect objective and unbiased outcomes data through direct questioning. Variations in phrasing, inflection, eye contact, rapport, mood, and other factors are difficult or impossible to eliminate. Data must be gathered by disinterested third parties using established psychometric scales and instruments.

FUTURE IMPLICATIONS

HRQOL research questions begin with the need for basic descriptive analysis of quality of life in patients treated for urologic diseases. Depiction of the fundamental elements in quality of life for these individuals requires study of their health perceptions and how their daily activities are affected by both their general health and their cancer. Physical and emotional well-being form the cornerstone of this approach, but research must also extend to other issues that can affect a patient's quality of life and satisfaction such as eating and sleeping habits, anxiety and fatigue, depression, rapport with the physician, presence of a spouse or partner, and social interactions. Characterization of all domains must address not only the actual functions but also the relative importance of these issues to patients.

Beyond simple descriptive analysis, HRQOL outcomes must be compared between patients undergoing different modes of therapy. General and disease-specific HRQOL must be measured to facilitate comparison with patients treated for diabetes, heart disease, arthritis, and other common chronic conditions. Quality of life outcomes may be correlated with medical variables such as comorbidity or sociodemographic variables such as age, race, education, income, insurance status, geographic region, and access to health care. In this context, HRQOL may be linked with many factors other than the traditional medical ones.

All clinical trials and observational cohort studies in patients with benign or malignant urologic disease should include an HRQOL component. Two cohort studies have been particularly fruitful in prostate cancer. First, the Cancer of the Prostate Strategic Urologic Research Endeavor (CAPSURE) is a longitudinal disease registry of more than 10,000 men with prostate cancer (Lubeck et al, 1996; Lubeck et al, 1997; Cooperberg et al, 2004), which has provided valuable insights into evolving practice patterns, technology diffusion, outcomes, and severity of disease from data collected in community settings across the United States. Second, the Prostate Cancer Outcomes and Satisfaction with Treatment: Quality Assessment (PROST-QA) is a consortium of nine academic centers that has tracked more than 1800 patients and spouses for several years with a specific focus on quality of life outcomes after surgery or radiation (Sanda et al, 2008).

Resources are scarce in any clinical trial, but clinical trials provide the best setting for prospective outcomes measurement and contribute to the thoughtful interpretation of more clinical endpoints (Steineck et al, 2002). Nonetheless, HRQOL data collections are labor-intensive; hence, when planning clinical trial budgets investigators must be aware that they are expensive to include. The more instruments that are selected, the richer the potential database, however it is important to remain parsimonious in instrument selection, choosing only the relevant domains of HRQOL.

The ultimate goal of quality of life research is to improve medical care and assist in medical decision-making (Table 5–5). Individual patients who incorporate quality of life considerations into their decision equations tend to feel better about their treatment choices, are more satisfied overall with their care, and

Table 5–5.

Quality of Life Objectives in Research and Practice

To assess overall treatment efficacy including subjective morbidity
To help determine whether the goals of treatment have been met
To educate patients and clinicians about the full spectrum of treatment outcomes
To facilitate medical decision making
To provide the defining issue if treatments are otherwise equivalent

experience less regret (Cassileth et al, 1989). Hence patient education provides a potent impetus for studying and reporting quality of life. With accurate measurement of quality of life outcomes, we can better assess whether the specific and overall goals of therapy have been met. This allows individuals and societies to balance the competing health care priorities of optimizing survival, quality of life, and resource utilization. Furthermore, the evaluation of patient-perceived HRQOL permits assessment of low-grade subjective morbidity that, although not typically life-threatening, may present considerable distress for the patient. These outcomes are often overlooked during the busy daily routine of patient care.

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chapter 6

Core Principles of Perioperative Care

Manish A. Vira, MD ● Joph Steckel, MD, FACS

Preoperative Evaluation
Presurgical Testing
Surgical Risk Evaluation
Optimization of Comorbid Illness
Special Populations
Preparation for Surgery
Anesthetic Considerations
Blood Products
Patient Environment
Abdominal Incisions and Wound Closure

PREOPERATIVE EVALUATION

The perioperative management of patients undergoing urologic surgery continues to evolve. Over the past 2 decades, the economics of health care has added increasing pressure for more outpatient surgery and decreased hospital stays. Furthermore, the acuity of surgical patients is increasing in that patients are older with more significant comorbidities. It has become standard for patients undergoing even the most sophisticated and complex urologic procedures in the hospital to be admitted on the same day of the surgery. **Therefore the urologic surgeon is responsible for assuring that the patient has been thoroughly evaluated by the other physicians in the health care team and presents to the operating room in the most optimized medical condition.** The preoperative use of appropriate medical specialist consults will result in improved patient safety and obviate the need for unnecessary cancelled surgeries due to the inadequacy of medical optimization.

PRESURGICAL TESTING

The goal of presurgical testing is to identify undiagnosed comorbidity or significant exacerbation of existing comorbid illnesses that may affect the operative outcome (Townsend et al, 2008). Although the preoperative evaluation should be individualized on the basis of age, history, and physical examination, each hospital or surgery center generally has specific guidelines for the necessary presurgical tests. Interestingly, routine testing has never been shown to be cost effective. In fact, it is less predictive of perioperative morbidity than the American Society of Anesthesiologists (ASA) status or the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for surgical risk. Generally, presurgical testing includes complete blood count (CBC), basic metabolic panel (BMP), prothrombin time/partial prothrombin time/international normalized ratio (PT/PTT/INR; controversial), electrocardiogram (ECG), and chest radiograph. The routine use of a PT/PTT in a patient not using warfarin or in a patient who gives no prior history of increased bleeding with other surgical procedures is controversial. **Often overlooked but extremely important is the requirement for a urine pregnancy test on the morning of surgery in any woman of childbearing age unless the ovaries or uterus have been previously surgically removed** (Halaszynski et al, 2004). The value of a preoperative ECG in identification of underlying acute cardiac disease and predicting perioperative cardiac morbidity is also controversial. Some studies show that ECG abnormalities have no significant predictive value (Goldman et al, 1978), whereas others have shown that an abnormal ECG was the best diagnostic predictor of an adverse cardiac event (Carliner et al, 1985). Nonetheless, current recommendations generally suggest that a preoperative ECG be done in patients older than 40 years of age or those with a history of any cardiac disease. Similarly, the routine preoperative use of a chest radiograph, in the absence of preexisting cardiopulmonary disease, is not indicated. Overall, even an ASA Task Force on preanesthesia evaluation could not make firm recommendations other than "preoperative tests may be ordered, required, or performed on a selective basis for purposes of guiding or optimizing perioperative management" (Practice advisory, 2002).

SURGICAL RISK EVALUATION

American Society of Anesthesiologists Classification and Risk Stratification

Approximately 27 million patients undergo surgery each year in the United States and 8 million or 30% have significant coronary artery disease or other cardiac comorbidities. Appropriately, the cardiovascular system is targeted during the preoperative assessment of patients. The ASA classification was first developed in 1961 and has been revised to categorize risk into six stratifications.

- ASA Class I—Normal healthy patient
- ASA Class II—Patient with mild systemic disease

Table 6–1.

Goldman's Cardiac Risk Index

PATIENT RISK FACTORS	POINTS
Third heart sound or jugular venous distention	11
Recent myocardial infarction	10
Nonsinus rhythm or premature atrial contraction on electrocardiogram	7
>5 premature ventricular contractions	7
Age >70 yr	5
Emergency operations	4
Poor general medical condition	3
Intrathoracic, intraperitoneal, or aortic surgery	3
Important valvular aortic stenosis	3
For noncardiac surgery, the risk of cardiac complications are:	
• *0-5 points = 1% risk*	
• *6-12 points = 7% risk*	
• *13-35 points = 14% risk*	
• *>26 points = 78% risk*	

Adapted from Akhtar S, Silverman DG. Assessment and management of patients with ischemic heart disease. Crit Care Med 2004;32:S126–36.

Table 6–2.

Modified Cardiac Risk Index

PATIENT RISK FACTORS	POINTS
Ischemic heart disease	1
Congestive heart failure	1
Cerebral vascular disease	1
High-risk surgery	1
Preoperative insulin treatment for diabetes	1
Preoperative creatinine of ≥2 mg/dL	1
Each increment in point increases risk of perioperative cardiovascular morbidity	

Adapted from Akhtar S, Silverman DG. Assessment and management of patients with ischemic heart disease. Crit Care Med 2004;32:S126–36.

- ASA Class III—Patient with severe systemic disease that limits activity but is not incapacitating
- ASA Class IV—Patients who have incapacitating disease that is a constant threat to life
- ASA Class V—Moribund patient not expected to survive 24 hours with or without an operation
- ASA Class VI—A declared brain-dead patient whose organs are being removed for donor purposes
- ASA Class E—Emergent nature of surgery (added through I through V classes)

The goal of the classification system is to assess the overall physical status of the patient before surgery (not to assess surgical risk), and although quite subjective, it remains as a significant independent predictor of mortality (Davenport et al, 2006). Other tools to assess the preoperative risks were developed by multivariate statistical analysis of patient-related factors correlated with surgical outcomes. One such scoring system, Goldman's criteria (Table 6–1), assigns points to easily reproducible characteristics. The points are then added to compute the perioperative risk of cardiac-related complication. Another system, the Cardiac Risk Index, simplified this concept employing only six predictors to estimate cardiac complication risk in noncardiac surgical patients (Table 6–2) (Akhtar and Silverman, 2004).

Cardiac Evaluation

The preoperative cardiac evaluation, which consists of an initial history and physical examination and ECG, attempts to identify potential serious cardiac disorders such as coronary artery disease, heart failure, symptomatic arrhythmias, the presence of a pacemaker or implantable defibrillator, or a history of orthostatic hypotension (Eagle et al, 1996). Furthermore, it is essential to define the severity and stability of existing cardiac disease before surgery. Cardiac-specific risk is also altered by the patient's functional capacity, age, and other comorbid conditions such as diabetes, peripheral vascular disease, renal dysfunction, and chronic obstructive pulmonary disease. The American College of Cardiology and American Heart Association recently collaborated to develop guidelines regarding perioperative cardiac evaluation before surgery (Fleisher et al, 2007a). The guidelines generally use three categories of clinical risk predictors: clinical markers, functional capacity, and type of surgical procedure (Eagle et al, 2002).

Clinical Markers

The major clinical predictors of increased perioperative cardiovascular risk are a documented acute myocardial infarction less than 7 days previously, a recent myocardial infarction (defined as >7 days but <1 month before surgery), unstable angina, evidence of any ischemic burden by clinical symptoms or noninvasive testing, decompensated heart failure, significant arrhythmias, and severe valvular disease. Intermediate predictors include mild angina, previous myocardial infarction by history or pathologic Q waves, compensated heart failure, diabetes, or renal insufficiency (creatinine >2 mg/dL). Minor predictors of risk are advanced age, abnormal electrocardiogram, rhythms other than sinus (i.e., atrial fibrillation), history of stroke, or uncontrolled systemic hypertension. The historical dictum of the timing of elective surgery after a myocardial infarction into a 3-month and 6-month interval is now currently avoided (Tarhan et al, 1972). **The ACC cardiovascular database committee stratifies risk on the basis of the severity of the myocardial infarction and the likelihood of reinfarction based on a recent exercise stress test.** However, in the absence of adequate clinical trials on which to base firm recommendations, it is reasonable to wait 4 to 6 weeks after myocardial infarction to perform elective surgery.

Functional Capacity

Functional capacity, or one's ability to meet aerobic demands for a specific activity, is quantified as metabolic equivalents or METs. For example, a 4-MET demand is comparable with a patient's ability to climb two flights of stairs. This simple measurement continues to be an easy and inexpensive method to determine a patient's cardiopulmonary functional capacity (Biccard, 2005). **The Duke Activity Status Index** (Table 6–3) **allows the physician to easily determine a patient's functional capacity** (Hlatky et al, 1989). **Generally, a capacity of 4 METs indicates no further need for invasive cardiac evaluation.**

Surgery-Specific Cardiac Risk

Two important factors determine the surgery-specific cardiac risk: the type of surgery and the degree of hemodynamic stress. Surgery-specific risk is stratified into high-, intermediate-, and low-risk procedures. High-risk procedures include both major emergent surgery, particularly in the elderly, and surgery associated with

Table 6–3.

Duke Activity Status Index*

ACTIVITY	YES	NO
Can you take care of yourself (eating, dressing, bathing, or using the toilet)?	2.75	0
Can you walk indoors such as around your house?	1.75	0
Can you walk a block or two on level ground?	2.75	0
Can you climb a flight of stairs or walk up a hill?	5.50	0
Can you run a short distance?	8.00	0
Can you do light work around the house like dusting or washing dishes?	2.70	0
Can you do moderate work around the house like vacuuming, sweeping floors, or carrying in groceries?	3.50	0
Can you do heavy work around the house like scrubbing floors or lifting and moving heavy furniture?	8.00	0
Can you do yardwork like raking leaves weeding or pushing a power mower?	4.50	0
Can you have sexual relations?	5.25	0
Can you participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football?	6.00	0
Can you participate in strenuous sports like swimming, singles tennis, football, basketball, or skiing?	7.50	0

Duke activity status index (DASI) = SUM (values for all 12 questions).
Estimated Peak Oxygen Uptake (VO_{2peak}) in mL/min = (0.43 × [DASI]) + 9.6.
VO_{2peak} mL/kg/min × 0.286 (mL/kg/min)$^{-1}$ = METS.
*The most widely recognized measure of cardiorespiratory fitness is maximal oxygen consumption (VO_{2peak}) measured in mL/kg/min. The Index score correlates directly with VO_{2peak} and therefore is an indirect measure of maximal METS.
Adapted from Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). Am J Cardiol 1989;64:651–4.

increased operative time resulting in large fluid shifts or blood loss. Intermediate risk procedures include intraperitoneal surgery, laparoscopic procedures, and robotic-assisted laparoscopic surgeries. Low-risk procedures include endoscopic procedures or superficial surgeries (i.e., not involving entrance into a body cavity) (Eagle et al, 2002).

Pulmonary

Preoperative pulmonary evaluation is important in all urologic procedures but critical in those surgeries involving the thoracic or abdominal cavities. These later procedures, which include intra-abdominal, laparoscopic, or robotic surgeries, can decrease pulmonary function and predispose to pulmonary complications. Accordingly, it is wise to consider pulmonary functional assessment in patients who have significant underlying medical disease, significant smoking history, or overt pulmonary symptoms. Pulmonary function tests that include a forced expiratory volume in 1 second (FEV_1), forced vital capacity, and the diffusing capacity of carbon monoxide are quite easily obtainable and provide a preoperative baseline. **Patients with an FEV_1 of less than 0.8 L/sec or 30% of predicted are at high risk for complications** (Arozullah et al, 2003). Specific pulmonary risk factors include chronic obstructive pulmonary disease, smoking, preoperative sputum production, pneumonia, dyspnea, and obstructive sleep apnea**. It has been shown that smokers have a four-fold increased risk for postoperative pulmonary morbidity and as high as a 10-fold higher mortality rate** (Fowkes et al, 1982). In general, it is interesting to note that patients with restrictive pulmonary disease fare better than those with obstructive pulmonary disease because the former group maintains an adequate maximal expiratory flow rate, which allows for a more effective cough with less sputum production (Pearce and Jones, 1984). In addition to the specific pulmonary risk factors, general factors contribute to increased pulmonary complications such as increased age, lower serum albumin levels, obesity, impaired sensorium, previous stroke, immobility, acute renal failure, and chronic steroid use.

Specific preoperative interventions can decrease pulmonary complications. Smoking must be discontinued at least 8 weeks before surgery to achieve a risk reduction. Patients who discontinue smoking less than 8 weeks before surgery may actually have a higher risk of complication because the acute absence of the noxious effect of cigarette smoke decreases postoperative coughing and pulmonary toilet. **However, patients who have stopped smoking at least 8 weeks preoperatively will significantly lower their complication rate, and patients who have ceased smoking for more than 6 months have a pulmonary morbidity comparable with nonsmokers** (Warner et al, 1989). The use of preoperative bronchodilators in COPD patients can dramatically reduce postoperative pulmonary complications. Aggressive treatment of preexisting pulmonary infections with antibiotics, as well as the pretreatment of asthmatic patients with steroids, is essential in optimizing pulmonary performance. Likewise, the use of epidural and regional anesthetics, vigorous pulmonary toilet, rehabilitation, and continued bronchodilation therapy are all beneficial (Arozullah et al, 2003).

Hepatobiliary

Because the survival of patients with advanced liver disease has improved over the past decade, surgery is being performed more frequently in these patients. Furthermore, patients with mild to moderate hepatic disease are often asymptomatic. These patients need to be identified and evaluated before surgery. Patients are usually aware of a prior diagnosis of hepatitis, and they should be questioned regarding the timing of diagnosis and the precipitating factors. This history is particularly important in a situation when a member of the health care team is inadvertently stuck with a needle or scalpel during the surgical procedure. A review of systems should include questions regarding pruritus, excessive bleeding, abnormal abdominal distention, and weight gain. On physical examination, jaundice and scleral icterus may be evident with serum bilirubin levels higher than 3 mg/dL. Skin changes such as caput medusae, palmar erythema, spider angiomas, and clubbing all indicate hepatic dysfunction. Severe manifestations include abdominal distention, encephalopathy, asterixis, or cachexia. Again, identification of underlying hepatic illness is important in the preoperative risk assessment of the patient. Although the estimation of perioperative mortality is limited by the lack of high-quality clinical studies, the use of the Child classification and Model for End-Stage Liver Disease (MELD) score offers a reasonable estimation.

The Child classification assesses perioperative morbidity and mortality in patients with cirrhosis and is based on the patient's serum markers (bilirubin, albumin, prothrombin time) and severity of clinical manifestations (i.e., encephalopathy and ascites). **Mortality risk for patients undergoing surgery stratified by Child class is as follows: Child Class A—10%, Child Class B—30%, and Child Class C—76% to 82%.** The Child classification also correlates with the frequency of complications such as liver failure, encephalopathy, bleeding, infection, renal failure, hypoxia, and intractable ascites. Independent risk factors

other than the Child class that can increase the mortality rate in patients with liver disease include emergency surgery and chronic obstructive pulmonary disease (O'Leary et al, 2009; Pearce and Jones, 1984).

The MELD score is perhaps a more accurate assessment of perioperative mortality in patients with hepatic dysfunction. The score is derived from a linear regression model based on serum bilirubin, creatinine levels, and the international normalized ratio (INR). It is more accurate than the Child classification in that it is objective, gives weights to each variable, and does not rely on arbitrary cut-off values (Teh et al, 2007). **Clinicians can use a website (http://mayoclinic.org/meld/mayomodel9.html) to calculate the 7-day, 30-day, 90-day, 1-year, and 5-year surgical mortality risk on the basis of the patient's age, ASA class, INR, serum bilirubin, and creatinine levels.** Taken together, the Child classification and the MELD score complement each other and provide an accurate assessment of the risk of surgery in cirrhotic patients (O'Leary and Friedman, 2007; O'Leary et al, 2009).

OPTIMIZATION OF COMORBID ILLNESS

Just as adequate preoperative evaluation is important, optimization of comorbid illness is critical in reducing perioperative morbidity and mortality. With regards to cardiac disease, many studies have evaluated the prophylactic use of nitrates, calcium-channel blockers, and β-blockers for patients who are at risk for perioperative myocardial ischemia. Only β-blockade has shown to improve outcomes (Pearse et al, 2004). In a landmark study, Mangano and colleagues reported in the *New England Journal of Medicine* that there was an improvement in outcomes with the prophylactic use of atenolol in patients undergoing vascular surgery (Mangano et al, 1996). Similarly, a retrospective, cooperative group study of more than half a million patients showed that perioperative beta blockade is associated with a reduced risk of death among high-risk patients undergoing major noncardiac surgery (Lindenauer et al, 2005). In addition to β-blockade, the concept of goal-directed therapy, employing the judicious use of fluids, inotropes, and oxygen therapy to achieve therapeutic goals, may further reduce perioperative risk (Pearse et al, 2004). This concept was validated by Shoemaker, who reported an impressive reduction in mortality from 28% to 4% ($P < .02$) when goal-directed therapy was used (Shoemaker et al, 1988).

As with cardiac comorbidity, the preoperative management of the diabetic patients is quite important. Perioperative hyperglycemia can lead to impaired wound healing and a higher incidence of infection (Golden et al, 1999). Hypoglycemia in an anesthetized or sedated diabetic patient may be unrecognized and carries its own significant risks. **Noninsulin diabetics may need to discontinue long-acting hypoglycemics because of this risk of intraoperative hypoglycemia. Shorter-acting agents or sliding scale insulin regimens are generally preferable.** It is recommended that blood glucose levels be controlled between 80 and 250 mg/dL. Frequent fingerstick glucose checks and the use of a sliding scale short-acting insulin regimen are used in the postoperative period. Once the patient is eating, the usual insulin regimen can be resumed. Patients who monitor their diabetes with the use of insulin pumps should continue their basal insulin infusions on the day of surgery. The pump is then used to correct the glucose level as it is measured. It is important to know the sensitivity factor that corrects the glucose so that the patient's sugars can be managed in the operating room (Townsend et al, 2008).

Patients with either hyperthyroidism or hypothyroidism should be evaluated by an endocrinologist and surgery should be deferred until a euthyroid state is achieved. **The greatest risk in the hypothyroid patient is thyrotoxicosis or thyroid storm, which can present with fevers, tachycardia, confusion, and cardiovascular collapse.** Atrial fibrillation may also be present in 20% of hyperthyroid patients (Klein and Ojamaa, 2001). With regards to hyperthyroidism, careful attention should be given to the airway because the trachea can be compressed or deviated by a large goiter. Generally, antithyroid medications such as propylthiouracil or methimazole, as well as β-blockers, are continued on the day of surgery. In the event of thyroid storm, iodine and steroids may be necessary (Schiff and Welsh, 2003). Hypothyroidism is generally associated with an increased sensitivity to medications such as anesthetic agents and narcotics. Severe hypothyroidism can be associated with myocardial dysfunction, coagulopathy, electrolyte imbalance, and a decreased gastrointestinal motility. Symptoms include lethargy, cold intolerance, hoarseness, constipation, dry skin, and apathy. The decrease in metabolic rate produces periorbital edema, thinning of the eyebrows, brittle hair, dry skin, hyperthermia, bradycardia, and a prolonged relaxation of the deep tendon reflexes (Murkin, 1982). Once the diagnosis is confirmed by a low thyroxine level and an elevated thyroid stimulating hormone level, thyroid replacement with levothyroxine can be initiated (Schiff and Welsh, 2003).

The evaluation of the patient either taking corticosteroids or suspected of having an abnormal response of the hypothalamic-pituitary-adrenal axis (HPA) is also important. There is a wide variability in the HPA suppression in patients on exogenous steroids. Nonetheless, it seems clear that oral steroids equivalent to less than 5 mg of prednisone for any duration of time does not cause clinically significant suppression of the HPA axis. **By contrast, any patient taking more than 20 mg of prednisone or its equivalent per day for more than 3 weeks or who is clinically Cushingoid has probable HPA axis suppression** (LaRochelle et al, 1993). HPA suppression can even occur in patients using potent topical steroids at doses of 2 g per day, as well as in patients using inhaled corticosteroids at doses of 0.8 mg per day. Although the duration of a functional HPA axis suppression after glucocorticoids have been stopped is debatable, perioperative supplemental steroids are recommended for patients who had HPA axis suppressive doses within 1 year of surgery. A low-dose ACTH stimulation test can be used to assess the HPA axis and the need for stress steroids. For patients who take 5 mg of prednisone or the equivalent each day, no supplemental steroids are necessary and the usual daily glucocorticoid dose may be given in the perioperative period. **For those in whom the HPA axis is presumed to be suppressed or is documented to be suppressed, then 50 to 100 mg of intravenous hydrocortisone is given before the induction of anesthesia and 25 to 50 mg of hydrocortisone is given every 8 hours thereafter for 24 to 48 hours until the usual steroid dose can be resumed.** Minor procedures under local anesthesia do not require stress-dose steroids (Schiff and Welsh, 2003).

SPECIAL POPULATIONS

Elderly

In the next 20 years, the percentage of patients older than 85 years of age may reach 5% or 15 million people. This represents a rapidly

growing segment of our aging population (Monson et al, 2003). Accordingly, octogenarians and nonagenarians are undergoing an increasing number of surgeries annually. Because of the elderly patients' special physiologic, pharmacologic, and psychologic needs, a unique set of health care challenges are encountered. It is still unclear whether advanced age independently predicts surgical risk or whether it is coexisting medical conditions that adversely affect surgical outcomes. However, in a large study published by Turrentine, it was shown that increased age independently predicted morbidity and mortality (Turrentine et al, 2006). This confirmed the study by Vemuri, who also found increased age as an independent risk factor for morbidity and mortality in patients undergoing aneurysm surgery (Vemuri et al, 2004). The studies suggest that perhaps the elderly patient cannot meet the increased functional demand required during perioperative and postoperative period. Hypertension and dyspnea were the most frequently seen comorbid risk factors in patients older than 80 years, and preoperative transfusion history, emergency operation, and weight loss best predicted postoperative morbidity. Each 30-minute increment of operative time increased the odds of mortality by 17% in octogenarians (Turrentine et al, 2006). A unique and important factor in the perioperative care of the elderly is in the identification and prevention of delirium. Often overlooked as "sundowning," delirium can be the first clinical sign of metabolic and infectious complications (Townsend et al, 2008).

Morbid Obesity

With the rising incidence of obesity, as well as the vast experience gathered from bariatric surgery, the care of the morbidly obese patient has been extensively studied. One must carefully weigh the risk of any surgical procedure with the natural history of the disease when deciding the optimal time of the surgery in the morbidly obese. **It is estimated that patients with a body mass index (BMI) of greater than or equal to 45 kg/m^2 may lose anywhere from 8 to 13 years of life** (Fontaine et al, 2003). The careful selection of the morbidly obese patient for elective surgery is of paramount importance. Cardiac symptoms such as exertional dyspnea and lower extremity edema are nonspecific in the morbidly obese patients, and many of these patients have poor functional capacity. The physical examination often underestimates cardiac dysfunction in the severely obese patient. Severely obese patients with greater than three coronary heart disease risk factors may require noninvasive cardiac evaluation (Poirier et al, 2009). Obesity is associated with a vast array of comorbidities. Morbidly obese patients often have atherosclerotic cardiovascular disease, heart failure, systemic hypertension, pulmonary hypertension related to sleep apnea and obesity, hypoventilation, cardiac arrhythmias, deep vein thrombosis, history of pulmonary embolism, and poor exercise capacity. There are also numerous pulmonary abnormalities that result in a ventilation perfusion mismatch and alveolar hypoventilation. Obesity is a risk factor for postoperative wound infections, and, when appropriate, laparoscopic surgery should be considered.

Pregnancy

Urologic surgery in the pregnant woman is generally related to the management of renal colic and urinary tract stones. In the asymptomatic woman, the stones can be discovered during the sonographic evaluation of the fetus or during the evaluation of the pregnant woman who is experiencing renal colic. **The fetus is at the highest risk from radiation exposure from the preimplantation period to approximately 15 weeks' gestation.** Because the radiation dose that is associated with congenital malformations is 10 cGy, the evaluation of renal colic in a pregnant patient is performed usually with sonography (radiation dose with abdominal CT: 1 cGy, intravenous pyelogram: 0.3 cGy). The indications for operative intervention in the pregnant patient are discussed elsewhere in this book. Anesthetic risks during pregnancy concern both the mother and the fetus. During the first trimester, the fetus may be directly exposed to the teratogenic effects of certain anesthetic agents. Later in pregnancy, anesthesia places the mother at risk for preterm labor and the fetus at risk for hypoxemia secondary to changes in uterine blood flow and maternal acid base balance. These risks seem to be greatest during the first and third trimesters. **For semielective procedures, an attempt should be made to delay surgery until after the first trimester.** However, one must consider the continued exposure of the underlying condition in relation to the operative risks to both the mother and the fetus. **The second trimester is the safest time to perform surgery because organ system differentiation has occurred and there is almost no risk for anesthetic-induced malformation or spontaneous abortion.** When contemplating surgery on the pregnant female, consultation with the obstetrician, perinatologist, and anesthesiologist is essential. These specialists will help determine the optimum technique to monitor the status of the fetus in the pregnant mother. Fetal heart rate monitors and tocometer monitoring for uterine activity are used before and after the procedure. Postoperative pain is best managed with narcotic analgesics because they have not been shown to cause birth defects in humans when used in normal dosages. Nonsteroidal antiinflammatory medication should be avoided because of the risk for premature closure of the ductus arteriosus. Chronic use of narcotics during pregnancy may cause fetal dependency, and it is recommended that the pregnant postsurgical patient be weaned off narcotic use as soon as possible (Mikami et al, 2008).

Nutritional Status

Malnutrition compromises host defenses and increases the risk of perioperative morbidity and mortality. Adequate nutritional status is essential for proper wound healing, management of infections, return of gastrointestinal activity, and maintenance of vital organ function (McDougal, 1983). The preoperative evaluation of the patient's nutritional status consists of the assessment of any recent weight loss and the measurement of the lymphocyte count and serum albumin. A 20-pound weight loss in the preceding 3 months before surgery is considered to be a reflection of severe malnutrition. The lymphocyte count and serum albumin level reflect visceral protein status with lower levels indicating malnutrition (Reinhardt et al, 1980). There are two methods for nutritional support. Total parenteral nutrition (TPN) is used for patients who are severely malnourished and who have a nonfunctioning gastrointestinal tract. Several studies have shown that 7 to 10 days of preoperative parenteral nutrition improves postoperative outcome in undernourished patients (Von Meyenfeldt et al, 1992). On the contrary, its use in well-nourished or mildly undernourished patients is either of no benefit or even with increased risk of sepsis (Perioperative total parenteral nutrition in surgical patients, 1991). On the other hand, enteral nutrition has a fewer complications than TPN and can provide a more balanced physiologic diet. Elemental nutrition is accomplished via a feeding tube, a gastrostomy, or feeding jejunostomy. Enteral nutrition maintains the gut-associated lymphoid tissue, enhances mucosal blood flow, and

maintains the mucosal barrier. There are hundreds of enteral products on the market, and most have a caloric density of 1 to 2 kcal/mL. These formulas are also lactose free and provide the recommended daily allowances of vitamins and minerals in less than 2 L per day. The patients on enteral feeds must be monitored for improvement in nutritional status, gastrointestinal intolerance, and fluid and electrolyte imbalance. **Preoperative enteral feedings can decrease postoperative complication rates by 10% to 15% when used for 5 to 20 days before surgery** (Guidelines, 2002). **The guidelines recommend postoperative parenteral nutrition in patients who are unable to meet their caloric requirements within 7 to 10 days.** Just as in the perioperative state, enteral feedings are preferred over parenteral nutrition when feasible. Moreover, the routine use of postoperative TPN has not proven useful in well-nourished patients or in those with adequate oral intake within 1 week after surgery (Byers and Hameed, 2008). Complications can occur with either enteral nutrition or parenteral nutrition. Dislodgement of nasoenteral tubes and percutaneous enteral catheters can result in pulmonary and peritoneal complications. Adynamic ileus may also occur because of decreased splanchnic perfusion, sympathetic tone, or opiate use. With regards to TPN, establishing central access is associated with a significant risk of complications. These include pneumothorax/hemothorax secondary to poor line placement and chylothorax secondary to thoracic duct injury. Line sepsis is the most common complication of indwelling central catheters and necessitates catheter removal. Venous thrombosis with associated thrombophlebitis and extremity edema has been reported. Catheter thrombosis has also been reported and can be treated with thrombolytic agents (Guidelines, 2002).

PREPARATION FOR SURGERY

Antibiotic Prophylaxis

In 1999 the Centers for Disease Control (CDC) issued its third report on the prevention of surgical site infections (SSIs) highlighting the importance of standardization of prophylaxis treatment to prevent this universal surgical complication (Mangram et al, 1999). **The report indicated that SSIs account for approximately 40% of nosocomial infections in surgical patients and potentially prolong hospital stay by 7 to 10 days.** A study of national SSIs from the 2005 Healthcare Cost and Utilization Project National Inpatient Sample (HCUP NIS) calculated an increase in hospital stay of 9.7 days and in per-patient cost of $20,892 (de Lissovoy et al, 2009). This translated nationally into an additional 1 million inpatient hospital days and additional health care cost of $1.6 billion. Bowater and colleagues recently published a systematic review of meta-analyses (level 1 evidence) and concluded that there was substantial evidence that antibiotic prophylaxis was an effective prevention for SSI over a wide variety of surgical procedures (Bowater et al, 2009). **Given both the ethical responsibility of the surgeon to decrease surgical morbidity and the recent policy shift by the Centers of Medicare and Medicaid Services to withhold reimbursement for hospital admissions secondary to specific SSI, it is mandatory for urologists to understand the principles behind and practice SSI prevention.**

Along with antibiotic prophylaxis, proper hand washing/scrubbing and sterile preparation of the operative field have always been central to the prevention of SSI. For procedures involving the gastrointestinal tract, mechanical and oral antibiotic bowel preparation had been standard practice until more recent literature calling into question its usefulness (discussed later). Preoperative hair removal has not been associated with a decrease in SSI, but if performed, use of mechanical clippers or depilatory creams as opposed to razors are associated with a decrease risk of SSI (Wolf et al, 2008).

The risk of SSI and therefore the recommendation for antibiotic prophylaxis is composed of three risk factors: the patient's susceptibility to and the ability to respond to localized and systemic infection, procedural risk of infection, and the potential morbidity of infection. Patient-related factors, listed in Table 6–4, increase risk by decreasing natural defenses, increasing the local bacterial concentration, and/or altering the spectrum of bacterial flora. Secondly, surgical procedure–specific factors can affect the route of entry, site of infection, and pathogen involved. This idea was first described in the landmark study from the National Research Council and later formalized by the CDC; specifically, surgical wounds are now classified by degree of contamination (i.e., the inoculum of potential pathogen) (Table 6–5; Hart et al, 1968). To predict the risk of SSI, several scoring systems have been developed incorporating patient-related factors with wound classification. Finally, the risk to the patient from SSI is an important

Table 6–4.

Patient Factors That Increase the Risk of Infection

Advanced age
Anatomic anomalies
Poor nutritional status
Smoking
Chronic corticosteroid use
Immunodeficiency
Chronic indwelling hardware
Infected endogenous/exogenous material
Distant coexistent infection
Prolonged hospitalization

Data from Cruse PJ. Surgical wound infection. In: Wonsiewicz MJ, editor. Infectious disease. Philadelphia: WB Saunders; 1992. p. 758–764; and Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1999;20:250–78; quiz 279–80.

Table 6–5.

Surgical Wound Classification

Clean	• Uninfected wound without inflammation or entry into the genital, urinary, or alimentary tract • Primary wound closure closed drainage
Clean contaminated	• Uninfected wound with controlled entry into the genital, urinary, or alimentary tract • Primary wound closure closed drainage
Contaminated	• Uninfected wound with major break in sterile technique (gross spillage from gastrointestinal tract or nonpurulent inflammation) • Open fresh accidental wounds
Dirty infected	• Wound with preexisting clinical infection or perforated viscera • Old traumatic wounds with devitalized tissue

Data from Garner JS. CDC guideline for prevention of surgical wound infections, 1985. Supersedes guideline for prevention of surgical wound infections published in 1982. (Originally published in 1995.) Revised. Infect Control 1986;7(3):193–200; and Simmons BP. Guideline for prevention of surgical wound infections. Infect Control 1982;2:185–96.

consideration in determining the need for prophylaxis. For example, routine cystoscopy in the evaluation of microhematuria in an otherwise young, healthy patient may not warrant prophylaxis; however, the same procedure in an elderly, insulin-dependent diabetic (immunocompromised) does warrant prophylaxis given the high likelihood that a postprocedural urinary tract infection would result in a significant deterioration in the patient's overall health. Understanding the three factors together then allows the urologist to make a rational decision as to the risk/benefit of antibiotic prophylaxis.

Once the decision for antibiotic prophylaxis is made, the keys to successful prevention are proper timing and administration of the antibiotic and the proper choice of antibiotic for the particular procedure. Since the pivotal study by Classen and colleagues, particular emphasis has been placed on the timing of prophylaxis to be given within 2 hours of incision (Classen et al, 1992). This emphasis is exemplified by the Joint Commission's Surgical Care Improvement Project (SCIP) guideline for administration of antibiotic prophylaxis 60 minutes before incision in a broader effort to decrease surgical complications by 25% by 2010. A recent multi-institutional trial involving more than 4400 patients at 29 institutions reported results of their analysis on the optimal timing of antibiotic prophylaxis (Steinberg et al, 2009). **Their results suggested an improvement in prevention of SSI when antibiotics were administered within 30 minutes of incision as compared with 31 to 60 minutes (adjusted odds ratio [OR] 1.48, *P* = .06).** More importantly, this larger study confirmed the significantly increased risk of SSI when antibiotics were administered at the time of or following incision with adjusted OR of 2.20, $P = .02$. The duration of antibiotic prophylaxis is more controversial; however, most recommendations advocate no more than 24 hours in a patient without an established infection. Routine antibiotic use beyond 24 hours increases the risk of *Clostridium difficile* colitis, increases the development of antibiotic resistance, and increases costs. Along with timing and duration, proper administration of antibiotics implies proper dosing. Antibiotic dose is dependent on the patient's body weight, renal function/hepatic function, and duration of procedure (requiring re-dosing if >4 hours). The second key to successful prevention is the proper choice of antibiotic for the procedure in question. As mentioned earlier, surgery-specific factors affect the type of pathogen, route of entry, and likelihood of systemic infection. For example, the choice of antibiotic is different before a transurethral resection of the prostate (need coverage for common urinary tract pathogens) as compared with a cystectomy with planned sigmoid colon urinary diversion (need coverage for anaerobic bacteria). Another important consideration is the rate of antibiotic resistance in the community. **Although there is level 1 evidence for the use of fluoroquinolones as prophylaxis for urologic endoscopic procedures, the emerging *Escherichia coli* resistance in the community is changing practice patterns in many practices and high-resistance hospitals.** One resource that is particularly useful is the hospital antibiogram. These reports are published monthly at most major hospitals and quantify the susceptibility/resistance of common organisms to a wide variety of antibiotics. A summary of the recent American Urological Association (AUA) best practice statement on antibiotic prophylaxis is shown in Table 6–6.

Bowel Preparation

Since antibiotics were first shown to reduce infectious complications in gastrointestinal surgery, mechanical and antibiotic bowel preparation has been a mainstay of urologic surgery employing intestinal segments. The rationale for bowel preparation before intestinal surgery is to decrease intraluminal feces and decrease bacterial colony counts in order to decrease the rate of anastomotic leak, intra-abdominal abscesses, and wound infections. The bacterial flora in the bowel consists of aerobic organisms, the most common of which are *Escherichia coli* and *Enterococcus faecalis,* and anaerobic organisms, the most common of which are *Bacteroides* species and *Clostridium* species. **The bacterial concentration ranges from 10 to 10^5 organisms per gram of fecal content in the jejunum, 10^5 to 10^7 in the distal ileum, 10^6 to 10^8 in the ascending colon, and 10^{10} to 10^{12} in the descending colon.** The preparation itself consists of two components: antibiotic preparation and mechanical preparation. Because there are only a few small series in the urologic literature, the rationale for each must be inferred from the general surgery literature, specifically, from colorectal surgery literature.

Although preoperative parenteral antibiotic prophylaxis before intestinal surgery is well established and widely used, oral antibiotic preparation is still somewhat controversial. Several oral antibiotic regimens are used today. The most commonly used regimen, oral neomycin and erythromycin, first became established with the landmark study by Drs. Nichols and Condon in 1977 (Clarke et al, 1977). In a double-blind, placebo-controlled study, 167 patients undergoing elective colonic surgery were randomized to receive mechanical bowel preparation with or without oral neomycin and erythromycin. The overall septic complications were 43% in the mechanical-only prep and 9% in the antibiotic plus mechanical prep group, $P = .001$. With the widespread use of preoperative parenteral antibiotics, the benefit of oral preparation has been debated. Several older studies reported decreased infectious complications; however, these studies were small and there have been no randomized controlled trials to document the benefit. **The disadvantage of oral antibiotic preparation is primarily related to increased incidence of pseudomembranous colitis secondary to *C. difficile* infection.** In a retrospective analysis of 304 patients, Wren and colleagues reported a significantly decreased incidence of *C. difficile* colitis in patients who did not receive oral antibiotics before elective colorectal surgery (2.6% vs. 7.2%, $P = .03$) (Wren et al, 2005). Despite the lack of evidence in the literature, a recent survey of colorectal surgeons revealed that up to 87% of surgeons continue to administer oral antibiotic bowel preparation before elective surgery (Zmora et al, 2003).

Mechanical bowel preparation predates the use of antibiotics in intestinal surgery and was thought to decrease the rate of anastomotic complications. Before the development of nonabsorbable liquids, patients underwent several days of oral laxatives, bowel irrigations via nasogastric tubes, and repeat enemas. These regimens were associated with significant patient discomfort and clinical morbidity due to electrolyte imbalances. The development of polyethylene glycol solution (GoLytely) and sodium phosphate solution (Fleet's Phospho-soda) reduced much of the electrolyte disturbances and allowed for mechanical bowel preparation to be done in the outpatient setting. **Both regimens are suitable for most patients; however, polyethylene glycol is preferred in the elderly and in patients with renal insufficiency, congestive heart failure, existing electrolyte disturbances, and cirrhosis because it is completely nonabsorbable.**

The benefit of mechanical bowel preparation has been assumed for decades as evidenced by 99% positive response by colorectal surgeons when asked if mechanical preparation is routinely used

Table 6–6.

AUA Best Practice Statement on Recommended Antimicrobial Prophylaxis for Urologic Procedures

PROCEDURE	ORGANISMS*	PROPHYLAXIS INDICTATED?	ANTIMICROBIALS OF CHOICE	ALTERNATIVE ANTIMICROBIALS	DURATION
Lower Tract Instrumentation					
Removal of external urinary catheter	GU tract	If risk factors	• Fluoroquinolone • TMP-SMX	• Aminoglycoside ± ampicillin • 1st/2nd gen. cephalosporin • Amoxicillin/clavulanate	≤24 hr
Cystography, urodynamic study, or simple cystoscopy	GU tract	If risk factors	• Fluoroquinolone • TMP-SMX	• Aminoglycoside ± ampicillin • 1st/2nd gen. cephalosporin • Amoxicillin/clavulanate	≤24 hr
Cystoscopy with manipulation	GU tract	All	• Fluoroquinolone • TMP-SMX	• Aminoglycoside ± ampicillin • 1st/2nd gen. cephalosporin • Amoxicillin/clavulanate	≤24 hr
Prostate brachytherapy or cryotherapy	Skin	Uncertain	• 1st gen. cephalosporin	• Clindamycin	≤24 hr
Transrectal prostate needle biopsy	Intestine	All	• Fluoroquinolone • 2nd/3rd gen. cephalosporin	• Aminoglycoside + metronidazole or clindamycin	≤24 hr
Upper Tract Instrumentation					
Shock-wave lithotripsy	GU tract	All	• Fluoroquinolone • TMP-SMX	• Aminoglycoside ± ampicillin • 1st/2nd gen. cephalosporin • Amoxicillin/clavulanate	≤24 hr
Percutaneous renal surgery	GU tract Skin	All	• 1st/2nd gen. cephalosporin • Aminoglycoside + metronidazole or clindamycin	• Ampicillin/sulbactam • Fluoroquinolone	≤24 hr
Ureteroscopy	GU tract	All	• Fluoroquinolone • TMP-SMX	• Aminoglycoside ± ampicillin • 1st/2nd gen. cephalosporin • Amoxicillin/clavulanate	≤24 hr
Open or Laparoscopic Surgery					
Vaginal surgery (including urethral sling procedures)	GU tract Skin Group B *Streptococcus*	All	• 1st/2nd gen. cephalosporin • Aminoglycoside + metronidazole or clindamycin	• Ampicillin/sulbactam • Fluoroquinolone	≤24 hr
Open/lap without entering GU tract	Skin	If risk factors	• 1st gen. cephalosporin	• Clindamycin	Single dose
Surgery involving entry into GU tract	GU tract Skin	All	• 1st/2nd gen. cephalosporin • Aminoglycoside + metronidazole or clindamycin	• Ampicillin/sulbactam • Fluoroquinolone	≤24 hr
Intestinal surgery	GU tract Skin Intestinal flora	All	• 2nd/3rd gen. cephalosporin • Aminoglycoside + metronidazole or clindamycin	• Ampicillin/sulbactam • Ticarcillin/clavulanate • Piperacillin/tazobactam • Fluoroquinolone	≤24 hr
Implanted prosthesis	GU tract Skin	All	• Aminoglycoside + 1st/2nd gen. cephalosporin or vancomycin	• Ampicillin/sulbactam • Ticarcillin/clavulanate • Piperacillin/tazobactam	≤24 hr

AUA, American Urological Association.

*Common pathogens include GU tract: *Escherichia coli, Proteus* sp., *Klebsiella* sp., *Enterococcus;* Skin: *Staphylococcus aureus,* coagulase-negative *Staphylococcus* sp., Group A *Streptococcus* sp.; and Intestine: *E. coli, Klebsiella* sp., *Enterobacter, Serratia* sp., *Proteus* sp., *Enterococcus,* and anaerobes.

Adapted from Wolf JS Jr, Bennett CJ, Dmochowski RR, et al. Best practice policy statement on urologic surgery antimicrobial prophylaxis. J Urol 2008;179:1379–90.

Table 6–7.

Mechanical and Pharmacologic Venous Thromboembolism Prophylaxis

PROPHYLAXIS	DOSE	ADVANTAGES	DISADVANTAGES
Pneumatic compression stockings	N/A	• Can be used in patients with high bleeding risk • Easily standardized for all patients • Studied in multiple patient groups	• No standards for size, pressure • Individual models not specifically studied • Less effective than pharmacologic prophylaxis in high-risk groups
Low-molecular-weight heparin	40 mg SQ once daily	• Once-daily dosing • Less risk of heparin-induced thrombocytopenia • No blood monitoring necessary	• Not reversible • Cost • Relative contraindication in patients with renal insufficiency
Low-dose unfractionated heparin	5000 U SQ every 8 hr	• Reversible • Can be used safely in patients with renal insufficiency • Relatively inexpensive	• Needs redosing every 8-12 hr • Heparin-induced thrombocytopenia

(Zmora et al, 2003). However, recent randomized controlled trials (RCT) have called into doubt the true benefit. Slim and colleagues recently published a meta-analysis of RCTs including a total of 4859 patients (Slim et al, 2009). The analysis included 14 trials including 2 recently completed large trials from the Netherlands and Sweden (Contant et al, 2007; Jung et al, 2007). **Overall, the analysis revealed that mechanical bowel preparation provided no benefit for anastomotic leak (OR 1.12, 95%; CI 0.82 to 1.53; *P* = .46), abdominal/pelvic abscess (OR 0.90, CI 0.47 to 1.72; *P* = .75), or mortality (OR 0.91, CI 0.57 to 1.45; *P* = .70).** In fact, when considering overall SSI, mechanical bowel preparation was associated with a significantly increased risk (OR 1.40, CI 1.05 to 1.87; *P* = .02). These results were reiterated in a recent Cochrane review, which found no significant differences in anastomotic leak rate, wound infection, need for reoperation, and mortality rates (Guenaga et al, 2009). The authors concluded that there was no evidence that mechanical bowel preparation improves patient outcome following elective colorectal surgery. Although similar studies have not been done in patients undergoing elective urologic surgery, urologists can infer from the colorectal literature and should re-evaluate the common practice of mechanical bowel preparation before urologic intestinal surgery. Two specific exceptions are transrectal ultrasound-guided prostate needle biopsy (PNBx) and laparoscopic urologic surgery. Given the portal of entry and subsequent risk of bacteremia, most urologists advocated for mechanical rectal cleansing with an enema before transrectal PNBx. With regards to laparoscopy, minimally invasive surgeons have long believed that preoperative bowel preparation improves operative exposure due to bowel decompression and decreases the incidence of postoperative ileus. However, to date there have been no trials to support this assertion.

Venous Thromboembolic Prophylaxis

Venous thromboembolic (VTE) complications are a major cause of potentially preventable morbidity and mortality among surgical patients in the United States. A recent study from the Center for Quality Improvement and Patient Safety and the Agency for Healthcare Research and Quality found postoperative VTE as the second most common cause of excess length of stay, charges, and mortality among surgical patients discharged from acute care hospitals (Zhan and Miller, 2003). Urology patients in particular have an increased incidence estimated to be 10% to 40% in patients without any prophylaxis (Geerts et al, 2008). Although these estimates are based on historical studies before the routine use of mechanical prophylaxis and the recognition of the benefits of early ambulation, the increased risk continues in more recent studies with reported incidence of 1% to 5%. Urologic patients followed prospectively in the European RISTOS study developed VTE in 1.9% undergoing open surgery despite a high rate of prophylaxis (Scarpa et al, 2007). Overall, VTE represents the most important cause of nonsurgical mortality among urology patients (Forrest et al, 2009).

Although the use of perioperative mechanical prophylaxis (pneumatic compression stockings) is fairly universal, pharmacologic prophylaxis is only administered after weighing the risk of VTE versus risk of perioperative bleeding complications (Table 6–7). Leonardi and colleagues reviewed and analyzed 33 randomized controlled trials to assess the incidence of bleeding complications in general surgery patients receiving pharmacologic prophylaxis (Leonardi et al, 2006). **Although there was a significantly higher rate of minor complications (injection site bruising and wound hematoma), there was no significant difference in major complications (i.e., GI tract [0.2%] or retroperitoneal bleeding [<0.1%]).** Although these results are generally applicable to urology patients, certain urologic procedures have a specifically higher rate of bleeding complications such as transurethral resection of the prostate and partial nephrectomy. Regarding an individual's risk of VTE, both surgery-related risk factors and patient-related risk factors must be considered. Surgical factors specific to urologic surgery to be weighed include general versus neuraxial anesthesia, supine versus dorsal lithotomy position, abdominal versus pelvic surgery with/without lymphadenectomy, and open versus laparoscopic approach. Patient-related risk factors are listed in Table 6–8 with increasing age, malignancy, history of cancer therapy, and others being fairly common among urology patients. In fact, both the RISTOS study and a recent report on minimally invasive radical prostatectomy confirmed several of these factors as increased risk of VTE in urologic patients (Scarpa et al, 2007; Secin et al, 2008). In 2008 the American College of Chest Physicians (ACCP) issued guidelines on the prevention of VTE with a strong recommendation that hospitals develop a formal, active strategy to address VTE prevention. **Although prior recommendations from the ACCP advocated individualized risk assessment models to guide therapy, the current recommendations advocate implementation of group-specific thromboprophylaxis routinely for all patients who belong to each of the major surgical groups (i.e., urologic surgery)** (Geerts et al, 2008). The AUA recently published a best practice statement on

Table 6–8.

Patient-Related Factors Increasing Risk for Venous Thromboembolism (VTE)

Surgery
Trauma (major trauma or lower-extremity injury)
Immobility, lower-extremity paresis
Cancer (active or occult)
Cancer therapy (hormonal, chemotherapy, angiogenesis inhibitors, radiotherapy)
Venous compression (tumor, hematoma, arterial abnormality)
Previous VTE
Increasing age
Pregnancy and the postpartum period
Estrogen-containing oral contraceptives or hormone replacement therapy
Selective estrogen receptor modulators
Erythropoiesis-stimulating agents
Acute medical illness
Inflammatory bowel disease
Nephrotic syndrome
Myeloproliferative disorders
Paroxysmal nocturnal hemoglobinuria
Obesity
Central venous catheterization
Inherited or acquired thrombophilia

Adapted from Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. 8th ed. Chest 2008;133:381S–453S.

Table 6–9.

Patient Risk Assessment Model (A) and American Urological Association Best Practice Recommendations (B)

A

Patient Risk Stratification	
Low risk	• Minor surgery in patients <40 yr with no additional risk factors
Moderate risk	• Minor surgery in patients with additional risk factors • Surgery in patients aged 40-60 yr with no additional risk factors
High risk	• Surgery in patients >60 yr • Surgery in patients aged 40-60 yr with additional risk factors (see Table 6–8)
Highest risk	• Surgery in patients with multiple risk factors (e.g., age >40 yr, cancer, prior venous thromboembolism)

B

Level of Risk	**Recommendations**
Low risk	• No prophylaxis other than early ambulation
Moderate risk	• Heparin 5000 units every 12 hr subcutaneous starting after surgery or • Enoxaparin 40 mg (for Cr Cl < 30 mL/min, use 30 mg) subcutaneous daily or • Pneumatic compression device if risk of bleeding is high
High risk	• Heparin 5000 units every 12 hr subcutaneous starting after surgery or • Enoxaparin 40 mg (for Cr Cl < 30 mL/min, use 30 mg) subcutaneous daily or • Pneumatic compression device if risk of bleeding is high
Highest risk	• Enoxaparin 40 mg (for Cr Cl < 30 mL/min, use 30 mg) subcutaneous daily and adjuvant pneumatic compression device, or • Heparin 5000 units every 8 hr subcutaneous starting after surgery and adjuvant pneumatic compression device

Adapted from Forrest JB, Clemens JQ, Finamore P, et al. AUA Best Practice Statement for the prevention of deep vein thrombosis in patients undergoing urologic surgery. J Urol 2009;181:1170–7.

the use of VTE prophylaxis in urologic patients (Forrest et al, 2009). Their recommendations combine an individualized risk assessment model with each type of urologic surgery. For example, a high-risk patient (multiple patient risk factors) and low-risk surgery may require pharmacologic prophylaxis just as a low-risk patient undergoing high-risk surgery. The recommendations are summarized in Table 6–9.

Antithrombotic Therapy

With most urologic patients suffering from medical comorbidities, urologists frequently encounter patients on chronic vitamin K antagonists (e.g., warfarin) or anti-platelet therapy for the management of atrial fibrillation, mechanical heart valves, or coronary artery disease. The perioperative management of interruption of this antithrombotic therapy can be a challenging problem. Unlike VTE pharmacologic prophylaxis, warfarin and antiplatelet therapy have been shown to be associated with significant bleeding complications after surgery. Therefore urologists must carefully consider the risk of interruption of chronic anticoagulation to determine the best course of perioperative management of these medications.

Chronic anticoagulation with warfarin is most frequently encountered in patients with atrial fibrillation, mechanical heart valves, or prior VTE. **The pharmacologic half-life of warfarin is 36 to 42 hours, and therefore most guidelines recommend cessation of therapy 5 days before surgery to ensure an INR less than 1.5.** The larger issue is whether patients require bridge with short-term anticoagulation between the time of subtherapeutic INR and surgery. The decision is based on risk of thrombotic event. Regarding atrial fibrillation, clinical scoring systems such as congestive heart failure-hypertension-age-diabetes-stroke ($CHADS_2$) stratify patients into risk groups that predict risk of stroke off anticoagulation. Patients with mechanical heart valves can also be stratified into risk groups according to the location (mitral versus aortic) and type of valve used. Similarly, patients with a prior history of VTE are stratified according to duration since last VTE and the patient's risk of recurrent VTE (Table 6–10). **In general, the ACCP, which released its guidelines in 2008, recommends that patients in the moderate- and high-risk groups undergo bridging anticoagulation with therapeutic dose subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin** (Douketis et al, 2008).

An increasing number of patients are receiving chronic antiplatelet therapy in the prevention of cardiovascular events and, more importantly, in the prevention of coronary stent thrombosis. Although the former indication poses little controversy for the urologist, the latter indication presents a significant and complex clinical question in which the urologist must weigh the risk of bleeding with the potentially devastating risk of perioperative stent thrombosis. Aspirin and clopidogrel are the two most commonly used antiplatelet drugs and are frequently used together.

Table 6–10.

Risk Stratification for Arterial/Venous Thromboembolism Events during Perioperative Period in Patients on Chronic Anticoagulant Therapy

	Indications for Anticoagulant Therapy		
	MECHANICAL HEART VALVE	ATRIAL FIBRILLATION	RECENT VENOUS THROMBOEMBOLISM (VTE)
Low	• Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	• $CHADS_2$ score of 0-2 (and no prior stroke or transient ischemic attack)	• Single VTE occurred >12 mo ago and no other risk factors
Moderate*	• Bileaflet aortic valve prosthesis and 1 of the following: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age >75 yr	• $CHADS_2$ score of 3-4	• VTE within the past 3-12 mo • Nonsevere thrombophilic conditions (e.g., heterozygous factor V Leiden mutation, heterozygous factor II mutation) • Recurrent VTE • Active cancer (treated within 6 mo or palliative)
High*	• Any mitral valve prosthesis • Recent (within 6 mo) stroke or transient ischemic attack	• $CHADS_2$ score of 5 or 6 • Recent (within 3 mo) stroke or transient ischemic attack • Rheumatic valvular heart disease	• Recent (within 3 mo) VTE • Severe thrombophilia (e.g., deficiency of protein C, protein S or antithrombin, antiphospholipid antibodies, multiple abnormalities)

*Patients at moderate or high risk are recommended to undergo bridging anticoagulation with therapeutic-dose subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin.

Adapted from Douketis JD, Berger PB, Dunn AS, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. 8th ed. Chest 2008;133:299S–339S.

Both are irreversible inhibitors of platelet function and therefore need to be stopped 7 to 10 days before surgery in order to minimize bleeding risk. **Current recommendations require dual antiplatelet therapy for 6 weeks after bare metal coronary stents and 12 months for drug-eluting stents. Premature interruption of antiplatelet therapy has been associated with a 25% to 50% risk of significant myocardial infarction with resultant increased perioperative mortality** (O'Riordan et al, 2009). In most cases, urologists should defer elective surgery until after antiplatelet therapy can be safely interrupted. Even then, because acute stent thrombosis has been described with drug-eluting stents after 12 months, urologists should strongly consider at least single-agent antiplatelet therapy in these patients. Given the current lack of clinically useful alternatives to antiplatelet therapy, in cases in which surgery cannot be delayed (i.e., malignancy), the ACCP strongly recommends continuing aspirin and clopidogrel during the perioperative period (Douketis et al, 2008). Obviously, communication between the urologist and the cardiologist throughout the perioperative period is essential to minimize complications.

ANESTHETIC CONSIDERATIONS

The basic tenet of anesthesia is to deliver hypnosis, amnesia, and analgesia while maintaining satisfactory operating conditions. An understanding of the basic pharmacologic principles, anesthetic equipment and monitoring, and patient analgesia is important to any surgeon including the urologist for successful operative outcomes and avoidance of surgical complications. Although urologists are performing increasingly more procedures in the office, the bulk of urologic surgery occurs in the operating room under monitored anesthesia care (MAC), regional anesthesia, or general anesthesia. Current practice in operative anesthesia employs a combination of inhalational agents and intravenous medications along with analgesics (for pain control) and benzodiazepines (for anxiolysis and amnesia). Of course, improved presurgical evaluation, pharmacologic drugs, and perioperative monitoring have dramatically decreased the risks of anesthesia. A recent study of New York hospital-based and free-standing ambulatory surgical centers reported the risk of all-cause mortality of 1 in 49,012 and immediate rate of admission to an inpatient facility of 0.6% (Fleisher et al, 2007b).

Selection of Mode of Anesthesia

An important role of the urologist in the anesthetic evaluation is to determine what mode of anesthesia is best for the particular patient and surgical procedure. The choice depends on patient-related factors including comorbidities, airway, and patient preference and procedural factors including complexity, duration, anatomic location, and expected fluid/blood loss. A basic understanding of each method of anesthesia and the pharmacologic principles will aid the urologist in making recommendations to the anesthesiologist.

Monitored Anesthesia Care

Although monitored anesthesia care (MAC) is defined as conscious sedation under the care of an anesthesiologist in a monitored situation, MAC encompasses a wide range of levels of anesthesia from minimal sedation to brief intervals of unconscious general anesthesia. Most commonly, anesthesiologists combine intravenous opioid analgesics and benzodiazepines to maintain a sufficient level of patient comfort and anxiolysis. MAC is widely used in urology in the ambulatory setting and is suitable for short-duration endoscopic procedures, transrectal ultrasound-based procedures, and, when combined with a local anesthetic, superficial procedures of the external genitalia. Conscious sedation can be administered in the office setting but only with proper monitoring of the patient during and after the procedure. **The Joint Commission has strict guidelines to ensure that the patients receive the same level of monitoring as if under the care of an anesthesiologist including a requirement for a trained monitoring assistant, immediate access to airway and resuscitation equipment, and specific preprocedure/postprocedure evaluations.**

Regional Anesthesia

Regional anesthesia incorporates different levels of anesthesia directed to the surgical site including local anesthesia, spinal anesthesia, and epidural anesthesia. The use of local anesthetics is typically combined with MAC for superficial procedures in an isolated anatomic location. The keys to proper local anesthetic administration are avoidance of intravascular injection and knowledge of pharmacology. The two most commonly used drugs are lidocaine and bupivacaine with the primary difference being the onset and duration of action.

Spinal and epidural anesthesia involves injection of anesthetic (most commonly lidocaine or bupivacaine) into the subarachnoid space or epidural space with direct effect on the spinal cord resulting in sensory, motor, and sympathetic blockade. In urologic procedures, epidural anesthesia is most useful for postoperative pain management for major abdominal procedures, thereby avoiding the adverse effects of high doses of intravenous opioids (i.e., respiratory depression, gastrointestinal dysfunction). Spinal anesthesia is suitable for most urologic endoscopic procedures and lower abdominal surgical procedures and is limited only by the duration of anesthesia required. Spinal anesthesia avoids the cardiopulmonary effects and complications of general anesthesia. Several factors affect the spinal level and efficacy of administration. Generally, larger volume and increased doses result in longer duration and increased cephalad migration. The addition of low-dose opioids and/or vasoconstrictors prolongs the duration of analgesia while reducing the dose of anesthetic. The anesthetic-related adverse effect is hypotension as a result of sympathetic blockade and occurs in 10% to 40% of patients (Di Cianni et al, 2008). **The primary technique-related complication is postdural puncture headache (results from cerebrospinal fluid leak) with an incidence of less than 2% with currently used 29-gauge pencil-tipped needles** (Turnbull and Shepherd, 2003). **Overall, spinal anesthesia has become safe with the incidence of serious neurologic deficits being 0.05%.**

General Anesthesia

Inhalational General Anesthesia

Inhalational drug development has emphasized inhalational agents that facilitate rapid induction and emergence and are nontoxic. **Two of the most important characteristics of inhalational anesthetics are the blood/gas (B/G) solubility coefficient and the minimum alveolar concentration (MAC). The B/G refers to the serum uptake of the inhaled agent, and the MAC is a measure of the potency of a volatile anesthetic (i.e., the serum level required to prevent movement in response to a skin incision in 50% of patients).** The various inhalational agents differ not only in the B/G and MAC but also in the cardiopulmonary effects. Obviously, a basic understanding of these properties is important for the urologic surgeon, especially during instances of surgical complication.

Nitrous oxide (NO) is one of the most commonly used agents due to its propensity of rapid induction and emergence; however, due to its low potency, it is often combined with other agents. Because of NO's high B/G and tendency to increase the volume and pressure of closed spaces, its use is contraindicated in certain clinical situations such as small bowel obstruction and pneumothorax. During laparoscopic abdominal procedures, surgeons often prefer to avoid the use of NO due to resultant bowel distention and subsequent interference in the operative field. Although this effect is debated in the surgical literature, El-Galley and colleagues reported significantly increased bowel distention and surgical interference with NO use in patients undergoing laparoscopic donor nephrectomy (El-Galley et al, 2007).

Once introduced in the 1950s, halothane rapidly became one of the most commonly used anesthetic agents due to its high potency. **However, halothane has several important risks that have since limited its use. It has significant cardiac effects and can precipitate failure in patients with left ventricular dysfunction. Furthermore, it sensitizes the myocardium to the effects of catecholamines (relevant for local anesthetics injected into the surgical site).** Finally, there is a 1 in 35,000 incidence of fulminant hepatitis, which can be lethal due to overaccumulation of toxic metabolites. More recent advancements in inhalational agents have focused on reduction in toxicity while maintaining the potency and rapidity of halothane. Three of the most commonly used current agents are isoflurane, sevoflurane, and desflurane. Isoflurane, less expensive than the other agents due to availability of generic equivalents, is widely used due to its low cardiac depression, less myocardial sensitization to catecholamines, and minimal metabolism. The primary unique toxicity is variable response tachycardia, which can lead to significantly increased myocardial oxygen consumption. Unlike isoflurane which has a putrid odor, sevoflurane is often used for inhalation induction (odorless) due to its rapid induction and emergence, decreased incidence of postoperative nausea (important in outpatient surgery), and minimal cardiac toxicity. It is the generally preferred agent for difficult airways requiring mask induction and in patients with severe bronchospastic disease. Desflurane, like isoflurane, has a pungent odor and is not used for inhalational induction. Its primary advantage over isoflurane is a more rapid recovery in patients requiring anesthesia over 3 hours.

Intravenous General Anesthesia

Intravenous anesthesia consists of a combination of induction agent, opioid, and neuromuscular relaxant. Anesthesiologists often prefer intravenous induction with a combination of inhalational and intravenous agents for maintenance of anesthesia. Intravenous induction offers several advantages in that it is rapid, minimizes patient discomfort, and is preferred by children and most adults. Thiopental, the oldest and least expensive agent, is a suitable choice for uncomplicated patients but is limited in more complex cases due to its significant vasodilation, cardiac depression, and risk of bronchospasm, especially in patients with reactive airway disease. Ketamine is a preferred choice for procedures that are brief and superficial because of its profound amnesia and somatic analgesia. It is associated with increased arteriolar and bronchomotor tone and is advantageous during induction for hypovolemic and asthmatic patients. **Propofol is among the most commonly used anesthetic agents, especially in outpatient surgery. It has a rapid onset, produces excellent bronchodilation in patients with reactive airway disease, and perhaps most importantly, is associated with smooth, nausea-free emergence from anesthesia.** Its primary adverse effect is significant blood pressure reduction. Midazolam, never used as a single agent, produces profound amnesia and anxiolysis while having rapid onset/short duration and producing minimal cardiac side effects.

Although these agents induce unconsciousness and amnesia, opioids have become an integral component to all forms of anesthesia. Opioids result in significant analgesia without an increase in cardiac side effects. Several studies have documented the decreased requirements of other agents when used in combination with opioids, thus reducing the overall cardiopulmonary side effects of anesthesia (Fukuda, 2009). Opioids themselves are differentiated in their potency, onset of action, duration of action, and metabolism/excretion. **Fentanyl (synthetic opioid) is probably the most widely used because of its potency (100 to 150 times that of morphine), rapid onset, and short duration of action.** Newer synthetics are geared to shorter duration and more rapid metabolism.

For major operative cases, complete neuromuscular relaxation is required for sufficient exposure and successful outcome. Although full relaxation can be achieved with intravenous and inhalational agents, the dose required is extremely high. The use of intravenous neuromuscular blockers allows for neuromuscular relaxation and minimization of inhalational/intravenous drugs. **There are two types of neuromuscular blockers: depolarizing drugs, which depolarize the plasma membrane of skeletal muscle fibers making the fibers resistant to further stimulation by acetylcholine, and nondepolarizing drugs, which block the binding of acetylcholine to cholinergic receptors on the presynaptic and postsynaptic membrane.** Succinylcholine, the only depolarizing drug on the market, is chosen for its rapid onset (used in rapid induction sequences), relatively short duration (around 5 minutes), and rapid metabolism. Its use is limited due to the risk of malignant hyperthermia (when used in combination with volatile inhalational agent), hyperkalemia, and bradycardia in children. In cases where succinylcholine is contraindicated, nondepolarizing agents are used. Several nondepolarizing drugs are available and differ in routes of metabolism and adverse effects. Furthermore, multiple medications including desflurane can alter the metabolism of these drugs and potentiate their actions. The most important consideration in the use of neuromuscular blockers is the assessment of adequate return of neuromuscular function following withdrawal of the drug. The most common complication of neuromuscular-blocking drugs is inadequate reversal resulting in respiratory failure and reintubation. Numerous reports in the literature correlate residual neuromuscular blockade with increased postoperative pulmonary complications in the postanesthetic care unit (PACU) and in the postoperative period. **The concept of train of four fade ratio (TOF) was developed to devise an objective measure of adequate neuromuscular function. This concept refers to the magnitude of the fourth of four twitches in response to maximal stimuli to the ulnar nerve delivered at 0.5-sec intervals. Historically, a TOF of 0.7 (meaning that the fourth twitch was 70% the magnitude of the first twitch) correlated with adequate return of neuromuscular function; however, more recent standards have raised the threshold to 0.9 as an indicator of complete return of neuromuscular function** (Kopman et al, 1997). Currently, anesthesiologists use several clinical assessments including head lift, tongue depressor test, and hand grip to estimate a TOF of 0.9. A recent study revealed that using clinical assessments alone, 16% and 45% of patients 2 hours after single intubating dose of neuromuscular blocker had TOF of less than 0.7 and less than 0.9, respectively, in the PACU (Debaene et al, 2003). As such, current recommendations are that quantitative TOF measurement (acceleromyography) be combined with clinical assessments before extubation in the operating room (Viby-Mogensen, 2009).

BLOOD PRODUCTS

Given the vascular nature of urologic organs, the urologist often confronts the issue of indication and necessity of transfusion in the perioperative period. Therefore it is important that the urologist understand the indications, implications, and risks associated with blood product transfusion. Before the AIDS epidemic, blood transfusion was liberally administered often for any patient with hematocrit less than 30%. However, fear and concern about the infectious risk led to the convening of a National Institutes of Health (NIH) panel to develop consensus recommendations for the indication of blood product transfusion (NIH Consensus Statement, 1988). The principles in these guidelines largely hold true today as reflected by the ASA practice guidelines issued in 2006 (Practice guidelines, 2006). **To summarize, the guidelines indicate that transfusion is rarely indicated with hematocrit greater than 30% and often indicated for hematocrit less than 21%. For levels between 21% and 30%, clinical factors such as risk of complications from inadequate oxygenation should guide the need for transfusion balancing the risks and benefits.** In general, patients with relatively minor comorbidities can tolerate hematocrit of greater than 21% before transfusion is indicated. Patients with moderate to severe comorbidity (i.e., significant pulmonary compromise, coronary artery disease, or vascular insufficiency, or with signs/symptoms of hypovolemic, hemorrhagic shock) warrant transfusion to achieve hematocrit greater than 30%. Ultimately, until technology is derived to directly measure inadequate oxygen-carrying capacity, the urologist should individualize the decision to transfuse for each patient and clinical situation.

A major advance in blood banking and product transfusion has been the development of component therapy allowing for administration for specific fractions of whole blood. Packed red blood cells (PRBCs) are equivalent to whole blood minus the plasma component. Whereas the hematocrit in whole blood is 40%, it is 70% in PRBC units. These units are reconstituted and administered with crystalloid. Given the lack of the remaining components, in instances of massive PRBC transfusions and associated bleeding, platelets and occasionally fresh frozen plasma should be given to avoid dilutional coagulopathy. Platelet transfusion is rarely indicated empirically except in patients with significant thrombocytopenia (<50,000/mm^3) and planned surgical procedure or with moderate thrombocytopenia (50,000-100,000/mm^3) and either high-risk procedure or evidence of platelet dysfunction. Similarly, empiric transfusion with fresh frozen plasma (FFP) for massive transfusion is not indicated. With the development of component therapy, the use of FFP increased dramatically, leading to consensus statements from the NIH and the ASA to guide practitioners (Consensus conference, 1985; Practice guidelines, 2006). **The current indications for FFP transfusion are immediate reverse of warfarin-induced coagulopathy, replacement in patients with specific clotting factor deficiencies, and evidence of bleeding and INR greater than 1.5. According the ASA guidelines, in patients with massive transfusion and no INR readily available, FFP should be given after replacement of 1 blood volume.**

There are well-documented risks of transfusion, and these risks should always be discussed with the patient before administration. Hemolytic transfusion reactions occur due to incompatibility between donor and recipient (either ABO or non-ABO incompatibility). According to the U.S. Food and Drug Administration (FDA) Annual Summary, from 2005-2007 transfusion reactions accounted for 22% of transfusion-related fatality in the United States (FDA Annual Summary for Fiscal Year 2007, 2007). Transfusion reactions occur relatively frequently and, if identified early, can be treated with rare catastrophic events. The early signs/symptoms include fever, chills, chest pain, hypotension, and bleeding diathesis occurring during or immediately after transfusion. Reactions may also occur in a delayed fashion, which is characterized by significant intravascular hemolysis secondary to recipient antibodies. The treatment of transfusion reaction is centered on fluid resuscitation, cessation of the transfusion, and alkalinization of the urine to prevent renal failure. **The most common cause of transfusion-related fatality is transfusion-related acute lung injury (TRALI). This entity accounted for 55% of transfusion mortality from 2005-2007. The injury is characterized by noncardiogenic pulmonary edema injury and manifests itself 1 to 2 hours after transfusion.** Although no specific treatment other than supportive measures are indicated, most patients recover without significant sequelae. Finally, one of the most feared complications (at least in the public eye) is the transmission of bacterial/viral infection. Although the risk of hepatitis virus and human immunodeficiency virus (HIV) transmission were unacceptably high in the 1970s and 1980s, the initiation of more stringent screening procedures for high-risk populations and the development of nucleic acid amplification technology (PCR and transcription-mediated amplification) have resulted in dramatically reduced risk and incidence of viral transmission. **Currently, the risk of HIV and hepatitis C transmission is approximately 1 in 2 million cases, whereas the risk of hepatitis B is 1 in 200,000.** The highest risk of infectivity occurs with platelet transfusion in which bacterial contamination develops at a rate of 1 in 5000 units (Eder et al, 2007).

PATIENT ENVIRONMENT

Patient Temperature

Although hypothermia can be therapeutic in certain situations of trauma and brain injury, for elective surgical procedures, hypothermia is associated with significantly increased morbidity to the patient. **There are two primary reasons for hypothermia to develop in the operating room. Anesthetic agents induce peripheral vasodilation redistributing heat from the core (trunk, head) with resultant drop in immediate core temperature after induction. Throughout the rest of the procedure, radiation and conductive heat loss account for most of the heat loss during a surgical procedure.** Normothermia is defined as core temperature between 36° C and 38° C, and even hypothermia of 1° C to 2° C results in adverse effect. **Rajagopalan and colleagues performed a meta-analysis of randomized controlled trials and reported that mild hypothermia (decrease of 1°C) resulted in a 16% increase in estimated blood loss and 22% increase in transfusion requirements** (Rajagopalan et al, 2008). The increased bleeding risk is thought to result from a hypothermia-associated decrease in clotting cascade enzymatic function and platelet aggregation. Even more significant is the increase in the risk of surgical site infections (SSI) associated with mild hypothermia (34° C to 36° C). Hypothermia increases the risk of SSI by impairing immune mechanisms and vasoconstriction, resulting in regional tissue hypoxia. In a landmark study, Kurz and colleagues with The Study of Wound Infection and Temperature Group tested the hypothesis that hypothermia increases the rate of wound infection and hospital stay in 200 patients undergoing elective colorectal surgery (Kurz et al, 1996). **Hypothermia was associated with a three times increased risk of wound infection and a 2.6-day increase in hospitalization.** More recent studies have generally confirmed these findings in other series of surgical patients (Mauermann and Nemergut, 2006). In its overall goal of reducing SSI, the SCIP has also included perioperative normothermia as one of its guidelines. Strategies to improvement maintenance of normothermia including regular use of warming blankets, warmed intravenous fluids, warmed irrigation fluids (especially during TURP and other prolonged endoscopic procedures), warmed/humidified CO_2 gas during laparoscopy, and increase in ambient operating room temperature. Although there have been few studies in the urologic literature, the findings can be generalized to all surgical patients.

Skin Preparation

Sterile skin preparation is fundamental in the prevention of SSI for any procedure. Currently, the most commonly used skin antiseptics are alcohol, povidone-iodine, or chlorhexidine based. Whichever antiseptic is chosen, the solution should be applied in concentric circles from the center of the surgical site and be allowed to dry before incision. **A recent review from the Cochrane database did not find sufficient evidence to recommend one skin preparation over another** (Edwards et al, 2004). Furthermore, although the CDC clearly recommends preoperative showering/bathing to reduce SSI, there is no evidence that bathing with an antiseptic solution reduces the rate of infection (Webster and Osborne, 2007). Regarding hair removal, the CDC recommends that if hair removal is performed, it should be performed immediately before the surgical procedure and performed with clippers (rather than shaving) (Mangram et al, 1999).

Patient Safety

In 1991 Brennan and colleagues published their seminal work describing adverse events, defined as injuries caused by medical management in hospitalized patients, revealing that 48% of the events accompanied a surgical operation (Brennan et al, 1991; Leape et al, 1991). This important study inspired the publication of "To Err Is Human, Building a Safer Health System," a comprehensive study by the Institute of Medicine on medical errors. Regarding surgical patients, the most frequent venue of preventable injuries is the operating room. **Although the surgeon is the "captain of the ship" and ultimately responsible, it takes cognizance and attention to detail from each member of the operating room team to prevent iatrogenic injuries to the patient.** Three causes of immediately preventable injuries are retractor-associated injuries, thermal injuries, and patient position–related injuries. There are several reports in the literature documenting increased rate of neuropathy (especially femoral nerve) following laparotomy with self-retaining retractors versus without self-retaining retractors (Irvin et al, 2004). Careful attention to be certain that the lateral blades do not directly compress the psoas muscle and only cradle the rectus abdominal muscles will ensure avoidance of femoral neuropathy.

Furthermore, periodic reinspection of the retractor blades is also warranted. Many devices used in urologic surgery employ thermal energy for desired effect and therefore can result in thermal injury to the patient. These include Bovie cautery, argon beam coagulator, bipolar devices, and laser. In both endoscopic and laparoscopic surgery, high-wattage light sources are used to illuminate the operative field. While illuminated, the ends of the light cords can result in burns when in direct contact with the patient (even through draping). These light sources should be turned off at all times when not in use. Special mention is deserved for the morbidly obese patient. The operating room should be equipped with a hydraulic table, extra-long instruments, additional padding, wide venous compression devices, and side extensions to ensure a safe operating room environment for the patient.

Patient Positioning

Although often given only a cursory evaluation, proper patient positioning in the operating room can prevent potentially devastating complications. Ultimately, proper positioning is the shared responsibility of each member of the operating room team. Much of the knowledge and guidelines for avoidance of position-related injury are drawn from the anesthesia literature. In fact, in response to a 1999 study of the ASA Closed Claims Database, which found neuropathy as second-leading cause of liability, the ASA published a practice advisory for the prevention of perioperative peripheral neuropathies (Practice advisory, 2000). The recommendations are listed in Table 6–11. **Although the exact mechanisms of peripheral neuropathy are not always known, the etiology of position-related neuropathy is generally secondary to excessive stretch, prolonged compression, or ischemia.** Given the variety of different patient positions used in urologic surgery, it is critical for the urologist to be an active participant in the positioning of the patient and to understand the potential patient compromise that accompanies each position.

The supine position, used in abdominal, pelvic, and penile procedures, is generally considered the safest patient position. However, several specific issues should be considered. **Excessive upper extremity abduction (>90 degrees) can lead to tension on the brachial plexus, leading to upper extremity neuropathy.** The arm board should be padded to avoid excessive pressure on the ulnar groove and spiral groove of the humerus (radial nerve injury). In cases in which the arms are tucked at the patient's side, care must be taken to avoid excessive pressure on hand and forearm. Moreover, peripheral intravenous catheter infiltration must be identified quickly because forearm compartment syndrome may develop.

One of the most frequent positions used in urology is the lithotomy position. Improper positioning can lead to transient and occasionally prolonged lower extremity neuropathy. In a retrospective evaluation of more than 190,000 cases from 1957 to 1991 involving the lithotomy position, persistent neuropathy was found in 0.03%; however, the same group in a prospective study of 991 patients reported an incidence of 1.5% (15 patients) with resolution of symptoms by 6 months in all but one patient (Warner et al, 1994, 2000). **The basic principle of position involves manipulation of both lower extremities simultaneously with flexion of the hips at 80 to 100 degrees with 30- to 45-degree abduction.** The legs should be padded to avoid excessive compression against the stirrup. Particular caution should be given to the patient's hands to avoid entrapment within the moving parts of the stirrups.

For most open and laparoscopic upper urothelial tract and renal procedures, the patient is placed in some degree of lateral decubitus position. Proper padding of the patient is important with appropriate anterior and posterior support to maintain the decubitus position. The most frequent focus of compromise involves

Table 6–11.

American Society of Anesthesiologists Task Force Recommendations on the Prevention of Perioperative Peripheral Neuropathies

Preoperative assessment	When judged appropriate, it is helpful to ascertain that patients can comfortably tolerate the anticipated operative position
Upper extremity positioning	Arm abduction should be limited to 90 degrees in supine patients; patients who are positioned prone may comfortably tolerate arm abduction greater than 90 degrees
	Arms should be positioned to decrease pressure on the postcondylar groove of the humerus (ulnar groove). When arms are tucked at the side, a neutral forearm position is recommended. When arms are abducted on armboards, either supination or a neutral forearm position is acceptable
	Prolonged pressure on the radial nerve in the spiral groove of the humerus should be avoided
	Extension of the elbow beyond a comfortable range may stretch the median nerve
Lower extremity positioning	Lithotomy positions that stretch the hamstring muscle group beyond a comfortable range may stretch the sciatic nerve
	Prolonged pressure on the peroneal nerve at the fibular head should be avoided
	Neither extension nor flexion of the hip increases the risk of femoral neuropathy
Protective padding	Padded armboards may decrease the risk of upper extremity neuropathy
	The use of chest rolls in laterally positioned patients may decrease the risk of upper extremity neuropathies
	Padding at the elbow and at the fibular head may decrease the risk of upper and lower extremity neuropathies, respectively
Equipment	Properly functioning automated blood pressure cuffs on the upper arms do not affect the risk of upper-extremity neuropathies
	Shoulder braces in steep head-down positions may increase the risk of brachial plexus neuropathies
Postoperative assessment	A simple postoperative assessment of extremity nerve function may lead to early recognition of peripheral neuropathies
Documentation	
	Charting specific positioning actions during the care of patients may result in improvements of care by (1) helping practitioners focus attention on relevant aspects of patient positioning and (2) providing information that continuous improvement processes can use to effect refinements in patient care

Adapted from Practice advisory for the prevention of perioperative peripheral neuropathies: a report by the American Society of Anesthesiologists Task Force on Prevention of Perioperative Peripheral Neuropathies. Anesthesiology 2000;92:1168–82.

positioning of the arms and potential for brachial plexus injury. The ipsilateral arm should be placed on an elevated arm rest or gel pad avoiding abduction more than 90 degrees and excessive stretch on the shoulder. The contralateral arm should be placed on an arm board with ulnar padding. Furthermore, in patients in full flank position, an axillary roll should be placed just caudal to the axilla (not in the axilla) to avoid compression of the contralateral brachial plexus. Finally, after the patient is positioned and before sterile draping, the operating table should be fully rotated to ensure that the patient is adequately secured in all positions.

Two patient positions used in specific urologic cases deserve attention: the prone position for percutaneous nephroscopy and the full Trendelenburg position for robotic-assisted laparoscopic procedures in the pelvis. In the prone position, special care should be taken to pad the torso, elbows, hips, and legs. The anesthesiologist should ensure that the endotracheal tube and all vascular access are properly secured. Coordination of the entire team is required during transfer from the supine position on the stretcher to the prone position on the operating room table. A stretcher should always be available immediately in case of airway compromise and the need for rapid transfer to the supine position. Regarding the full Trendelenburg position for minimally invasive pelvic procedures, the primary issues involve the physiologic changes in respiratory function, cardiovascular function, and increases in central venous and intracranial pressures. **Patient positioning should focus on properly securing and padding the patient to the operating table to prevent cephalad sliding. Although fixed shoulder braces will undoubtedly prevent patient movement, these braces should be avoided due to the risk of brachial plexus compression and resultant neuropathy.**

ABDOMINAL INCISIONS AND WOUND CLOSURE

Abdominal Incisions

Urologic surgery can encompass a large area of the trunk, and therefore the urologist should be familiar with all type of incisions of the abdomen. The most commonly used incision in surgery including urology is the midline abdominal incision. This incision can provide access to the entire peritoneum and retroperitoneum. For procedures focused on particular areas of the abdomen, alternative incisions provide more focused exposure with certain benefits. A Pfannenstiel incision (transverse lower abdominal incision) can be used for virtually all pelvic procedures and results in improved cosmesis and possibly decreased pain. For access to the lower third of the ureter, a Gibson incision (i.e., an oblique incision in the lower quadrant) can be used. Using a Gibson incision, entry into the retroperitoneum is gained by splitting the external and internal oblique muscles in the direction of its fibers. Access to the upper abdomen and retroperitoneum for renal and adrenal surgery can be gained using various kinds of incisions. An extraperitoneal approach is best performed via a flank incision over the 11th or 12th rib, with or without partial rib removal. An extraperitoneal approach avoids the complications of transperitoneal surgery such as bowel injury, postoperative ileus, and adhesion formation. Transperitoneal access can be obtained via an anterior subcostal incision (two finger breadths below the costal margin). This incision provides better access to the midline vascular structures by allowing for complete medial mobilization of the posterior peritoneum. For large or locally advanced (vena cava thrombus) tumors, a thoracoabdominal or chevron incision generally provides the best exposure. A thoracoabdominal approach is preferred for large upper retroperitoneal tumors or tumors with extension into the thoracic cavity (supradiaphragmatic vena cava tumor thrombus). On the other hand, a chevron incision is preferred for access to both the right and left abdomen (e.g., bilateral renal tumors). In summary, proper choice of incision is often critical to successful surgical outcome, especially for complex operative cases.

Wound Healing

Knowledge of the basic principles of wound healing is important in order to properly assess incision closure and its associated complications. All cutaneous wounds progress stepwise through a series of events toward complete wound repair, understanding that in a particular wound, different phases of events may occur simultaneously. **The series of steps can be divided broadly into three stages: reactive phase, proliferative phase, and maturational phase.** The reactive phase occurs immediately with the two primary responses of hemostasis and inflammation. Disruption of vascular membranes results in platelet activation and aggregation, which in turn initiate the inflammatory response. During this stage of wound healing, inflammatory cells including polymorphonuclear cells, macrophages, and lymphocytes migrate into the wound and become activated, leading to cytokine activation and secretion of various growth factors. The second stage, proliferative, results in the formation of granulation tissue. The stage is characterized by proliferation of endothelial cells and fibroblasts leading angiogenesis and epithelialization, which eventually results in growth of immature blood vessels and deposition of extracellular matrix and early collagen scaffolding. Finally, the maturation stage occurs with further deposition of collagen and wound contraction. **The maturational phase begins approximately 1 week after injury and progresses rapidly over 6 weeks with increasing wound strength over the next 12 months. The scar regains approximately 3% strength after 1 week, 20% after 3 weeks, and 80% after 3 months** (Witte and Barbul, 1997).

Wound Closure

Along with choice of incision, proper closure is necessary to avoid certain surgical complications including wound infection and fascial dehiscence. In general there are three types of wound closure: primary, secondary, and tertiary (or delayed primary closure). In the vast majority of elective cases, the urologist should attempt a permanent closure following the operation (primary closure). Secondary closure is reserved for heavily contaminated wounds for which the fascia is closed primarily, but the skin/subcutaneous tissues are allowed to heal re-epithelialization and contraction. Tertiary closures are reserved for patients with abdominal compartment syndrome or in patients requiring re-explorations in which temporary closure is initially performed with intention of future permanent closure. Unless the case is heavily contaminated, incision closure involves reapproximation of the fascia (in one or multiple layers) and the skin. Choice of suture type by the surgeon depends on preferences of braided versus nonbraided, monofilament versus multifilament, and absorbable versus nonabsorbable. A full description of different suture types and their properties is listed in Table 6–12 (Hochberg et al, 2009). Although the method of fascial closure has been studied extensively, a definitive, superior method is not

Table 6–12.

Properties of Suture Materials

SUTURE	ORIGIN	TISSUE ABSORPTION	PHYSICAL CONFIGURATION	TENSILE STRENGTH	COMMENTS
Vicryl	Synthetic	Absorbable	Braided	65% 2 wk 40% 4 wk	Slower loss of function and higher knot-breaking strength compared with polyglycolic acid (Dexon)
Dexon	Synthetic	Absorbable	Braided	63% 2 wk 17% 3 wk	Lubricant coating decreases coefficient of friction
Monocryl	Synthetic	Absorbable	Monofilament	30%-40% 2 wk (dyed) 25% 2 wk (undyed)	Excellent tensile strength allows use of smaller sutures for skin closure
PDS	Synthetic	Delayed absorbable	Monofilament	74% 2 wk 50% 4 wk 25% 6 wk	No absorption until after 90 days; low reactivity, tends to maintain strength in presence of infection; newer barbed version is knotless
Maxon	Synthetic	Delayed absorbable	Monofilament	81% 2 wk 59% 4 wk 30% 6 wk	
Chromic gut	Natural	Absorbable	Monofilament	0% 3 wk	Can also be found as plain gut (untreated) for faster absorption
Nylon	Synthetic	Nonabsorbable	Monofilament	50% 1-2 yr	Very low tissue reactivity
Prolene	Synthetic	Nonabsorbable	Monofilament	No significant loss over time	High plasticity, extremely smooth surface (requires extra knot throws)
Silk	Natural	Nonabsorbable	Braided	Degraded over time	Braided for easier handling; can be prone to infection
Mersilene	Synthetic	Nonabsorbable	Braided or monofilament	No significant loss over time	Braided should not be used in infection

universally agreed on. van't Reit and colleagues performed the most recent meta-analysis of available randomized controlled trials (van 't Riet et al, 2002). **In all, 6566 patients from 15 studies were included with the primary outcome measure being incidence of incisional hernia. Their analysis indicated that between slowly absorbable or nonabsorbable sutures, there was no difference in risk of incisional hernia in continuous versus interrupted fascial closures although nonabsorbable closure was associated with increased wound pain and sinus formation. For rapidly absorbable suture types, continuous fascial closure was significantly associated with increased rate of incisional hernias.** Due to the limited number of patients, a definitive conclusion could not be made for interrupted rapidly absorbable suture closure versus continuous slowly nonabsorbable suture closure. The authors, however, concluded that mass closure with slowly absorbable suture in a continuous fashion is the optimal method. To address the limitation found in the recent meta-analysis, Seiler and colleagues completed a randomized control trial of 625 patients (Seiler et al, 2009). Patients were randomized to one of three arms: interrupted closure with rapidly absorbable suture or continuous closure with one of two different slowly absorbable sutures. They found no significant difference in incisional hernia (15.9% vs. 8.4% vs. 12.2%, $P = .09$), fascial dehiscence, wound infection, or serious adverse events. In conclusion, although incisions may be closed either with interrupted, rapidly absorbable suture closure or with continuous slowly absorbable suture closure, careful attention should be given to the technique given the relatively high incidence of incisional hernia.

Perhaps the most frequently encountered complication of abdominal wounds is the surgical site infection. Because of different reporting methods and descriptions in the literature, the National Health Care Safety Network of the CDC published definitions of surgical site infections with clearly defined, objective criteria (Kirby and Mazuski, 2009). The infections are classified as follows:

- Superficial incisional infection: involves only skin and subcutaneous tissue occurring within 30 days of surgery
- Deep incisional infection: involves deep soft tissues (muscle or fascial planes) within 30 days of surgery (or within 1 year if implant is in place)
- Organ/space infection: involves any part of the body that is opened or manipulated by the operative procedure and has purulent drainage from a drain placed in the wound or evidence of infection by radiographic imaging

Specific risk factors predisposing for surgical site infections were previously listed in Table 6–4. The mainstay of treatment centers on adequate drainage of the infected area. **Superficial infections and some deep incisional infections can generally be managed with opening of the skin incision and packing of the wound. Care should be taken to open the incision widely to ensure complete drainage of underlying purulent fluid. The use of oral/intravenous antibiotics is not necessary unless it is associated with significant skin cellulitis (erythema extending >2 cm from incision edge or systemic signs of toxicity, e.g., fever, sepsis)** (Barie and Eachempati, 2005). Once opened, the wound should be allowed to heal by secondary intention. Many deeper incisional infections are too extensive for bedside incision and require operative debridement under anesthesia. It is critical for careful examination of any infected wound for signs of necrotizing infection most commonly secondary to *Clostridia perfringens*. Signs include drainage of grayish, dishwater-colored fluid, frank necrosis of the fascial layer, and wound crepitus. A necrotizing infection requires immediate return to the operating room for wide debridement and washout. In contrast to incisional infections, deeper organ/space infections may present without superficial signs at the level of the incision. Rather, patients often show systemic signs of infection, pain, and or sepsis leading to cross-sectional imaging revealing the putative source. Again, the principle of adequate drainage applies, and management involves

percutaneous or operative drainage of the abscess fluid. A controversial issue in the prevention of organ/space infections is the routine placement of drainage systems at the time of the initial operative procedure. A wide variety of surgical drains is available. Drains are broadly categorized as open/nonsuction, closed/nonsuction, and closed/suction drains. Open/nonsuction drains are employed when accurate quantification of drainage amount is not necessary. These drains are associated with less patient discomfort and are the easiest to remove. Closed drains are chosen if quantification of drainage amounts or characterization of drainage fluid is necessary. The use of suction in closed drain systems is generally preferred if immediate recognition of small amounts of drainage is important (e.g., a drain around an ureterointestinal anastomosis). Although drains continue to be widely used in various urologic procedures, several prospective studies in the general surgical literature have failed to show significant benefit; therefore most experts caution against their routine use (unless strong indication exists) (Barie, 2002).

Perhaps the most dreaded complication of surgical incisions is acute wound failure (or fascial dehiscence). Overall, the incidence of fascial dehiscence is 1% to 2% and usually occurs 1 week after surgery, although it may occur up to 30 days postoperatively. Risk factors for dehiscence include patient-related factors (advanced age, malnutrition, corticosteroid use, obesity, and prior history of radiotherapy); surgical site infection; and technical errors at the time of wound closure. The most common technical errors associated with wound failure are placing the suture too close to the fascial edge, knot slippage, and excessive suture tension. **Multiple studies have investigated the type of closure and there is no difference in dehiscence risk between interrupted and continuous closures as long as rapidly absorbable sutures are not used with the latter.** Historically, in high-risk patients retention sutures were strongly advocated and widely used as a preventive measure for wound dehiscence. Literature evidence, however, was primarily retrospective and subsequent prospective trials have failed to show evidence of benefit (Carlson, 1997). One recent trial by Rink and colleagues randomized 95 high-risk patients to retention sutures versus standard closure reporting that although no difference in wound failure rates was seen, retention sutures were associated with significantly increased rate of patient morbidity, primarily pain (Rink et al, 2000). As such, recent surgical trends suggest a movement away from the use of retention sutures and, alternatively, toward the increased use of grafts and synthetic mesh in wounds thought to be at increased risk of fascial dehiscence. **When acute wound failure does occur, it is usually immediately preceded by a sudden gush of serosanguineous fluid from the wound. Some small fascial disruptions can be managed conservatively with wound packing and close observation, but the majority of disruptions, particularly in the setting of bowel evisceration, mandate urgent return to the operating room. At the bedside, sterile, saline-moistened towel should be placed over the eviscerated components while the patient is being prepared for the operating room.** At the time of reoperation, the fascial edges are inspected for the etiology of the disruption. In cases of technical errors or fascial tearing in which the fascial edges are healthy and can be brought together without tension, a primary closure is appropriate. In all other cases, the fascial edges are debrided and the wound is closed with absorbable mesh or biologic prosthetic grafts. A full discussion of the different materials is beyond the scope of this chapter, but needless to say, strong consideration should be given for an intraoperative general surgical consult.

Key Points

- Proper preoperative evaluation of the patient will prevent unanticipated cancellations and decrease the risk of postoperative complications.
- The indications for preoperative cardiac testing depend on three factors including the functional capacity of the patient, cardiac risk factors, and surgical specific risk factors.
- Surgical site infections are one of the leading causes of perioperative complications and increased hospital stay. Antibiotic prophylaxis is indicated in virtually all surgical procedures.
- Venous thromboembolism is a common complication of urologic procedures, and the AUA recommends either mechanical or pharmacologic prophylaxis (or both for highest risk) for all urologic procedures.
- Proper understanding of the pharmacologic principles of anesthesia will allow the urologist to actively participate in the decision process of choosing which mode of anesthesia will be appropriate for a particular patient and procedure.
- Current guidelines advocate blood product transfusion for hematocrit less than 21% in most patients unless there are specific cardiopulmonary risk factors.
- Perioperative hypothermia of even 1° C to 2° C is associated with increased estimated blood loss and increased risk of surgical site infection.
- Proper choice of surgical incision results in optimal surgical exposure and therefore improved outcomes.
- Current literature suggests that closure with continuous, slowly absorbing suture results in the lowest risk of incisional-related complication.

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chapter 7

Fundamentals of Instrumentation and Urinary Tract Drainage

Carlos E. Méndez-Probst, MD ● Hassan Razvi, MD, FRCSC ● John D. Denstedt, MD, FRCSC, FACS

Lower Urinary Tract

Upper Urinary Tract Ureteral Stents

Endoscopy of the lower urinary tract and the establishment of urinary tract drainage are basic skills required by all urologists and uniquely define the specialty of urology. A basic understanding of the indications, instrumentation used, and the techniques involved in urethral catheterization, ureteral stent placement, and nephrostomy insertion are essential and are covered in this chapter.

LOWER URINARY TRACT

For Urethral Catheterization

Historical Background

Instruments to drain the urinary bladder are among the most ancient medical devices in the historical record. One of the earliest descriptions of a urinary catheter can be found in the Hippocratic text *On Diseases* (400 BC), in which bladder drainage was considered a basic skill in the armamentarium of Greek physicians (Moog et al, 2005a). The practice of bladder catheterization to permit urine drainage seems to have been widespread throughout the ancient world, with records of its application also found in India, Egypt, and the Byzantine and Roman empires. In Avicenna's *Canon of Medicine,* mention is also made of urethral catheterization as a means to deliver intravesical therapy (Madineh, 2009). Surviving examples of early catheters include hollow tubes made of bronze, paper, animal hide, cloth soaked in wax, and lead (Moog et al, 2005b). In the 16th century, Ambroise Pare used catheters made of silver, brass, and copper. In the early 18th century, natural rubber was first used and the coudé tip was introduced by Mercier not long after. The self-retaining balloon catheter was introduced in the 20th century by Foley (Ellis, 2006), leading the way to permit development of catheters of synthetic materials with specialized coatings and drug-eluting properties.

Indications

The most common indications for the use of a bladder catheter can be broadly divided into two main categories: to obtain drainage or to allow the instillation of diagnostic or therapeutic agents.

The relief of acute or chronic urinary retention due to either bladder outlet obstruction or neurogenic bladder dysfunction is probably the most common indication for urethral catheterization (UC). Following in frequency is its use to monitor urinary output.

Urinary diversion by a catheter is used to allow healing after lower urinary tract surgery/trauma and to evacuate the bladder when the urine contains particulate matter, especially in combination with simultaneous irrigation (post transurethral resection, clot/purulent material evacuation). Other indications include the collection of microbiologic clean urine (uncooperative patients because of age or mental status or comorbidities that prevent voluntary voiding) and to measure postvoid residual urine volume samples for diagnostic purposes.

Urethral catheterization is also used to provide access to the bladder for urinary tract imaging studies such as cystography, which requires the instillation of radiographic contrast material.

UC with a pressure monitoring catheter is used during urodynamic testing for physiologic assessment of voiding function. It is also used to allow instillation of pharmacologic agents for local therapy of some bladder pathologies such as chemo/immunotherapy for transitional cell carcinoma (mitomycin, bacillus of Calmette Guerin), interstitial cystitis (dimethyl sulfoxide), and intractable hematuria (e.g., alum, formalin instillation).

Catheter Selection

The size and type of urinary catheter used depends on the indication for catheter insertion, age of the patient, and type of fluid expected to be drained. Currently there is a wide variety of catheter types. Catheters can be classified on the basis of material, coating, number of channels (Fig. 7–1), and tip form (Fig. 7–2). Each of these characteristics is reviewed.

Catheter size is measured in the Charrière or French scale, whereby one Fr or Ch is equal to 0.33 mm. This measurement indicates the total circumference of the catheter and not the lumen size. As a general rule, catheter size should be the smallest size that can accomplish the desired drainage (i.e., 12 to 14 Fr for clear urine and 20 to 24 for thick pus or blood-filled urine). In children, choosing a catheter of appropriate size is essential to avoid unnecessary urethral trauma (Table 7–1). The use of feeding tubes as urethral catheters should be discouraged because their stiffness and length can be a source of complications (ischemic ulcers, urethral strictures, and knotting in the bladder) (Smith, 2003; Robson et al, 2006).

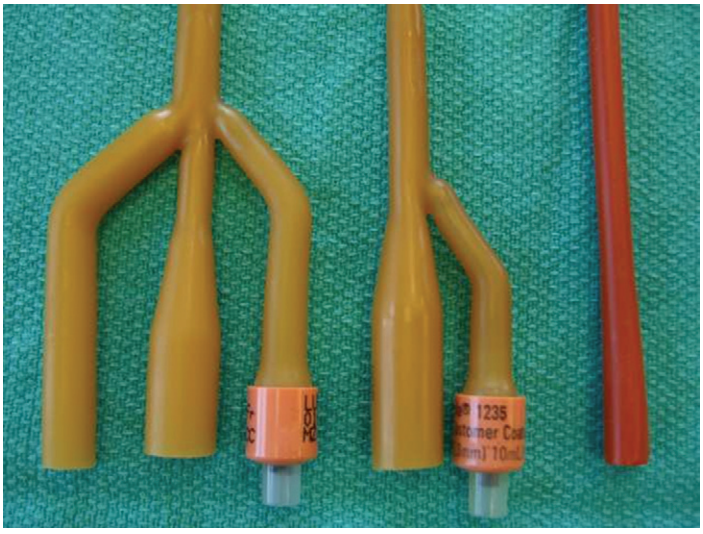


Figure 7–1. Three-way, two-way, and single-lumen catheters.

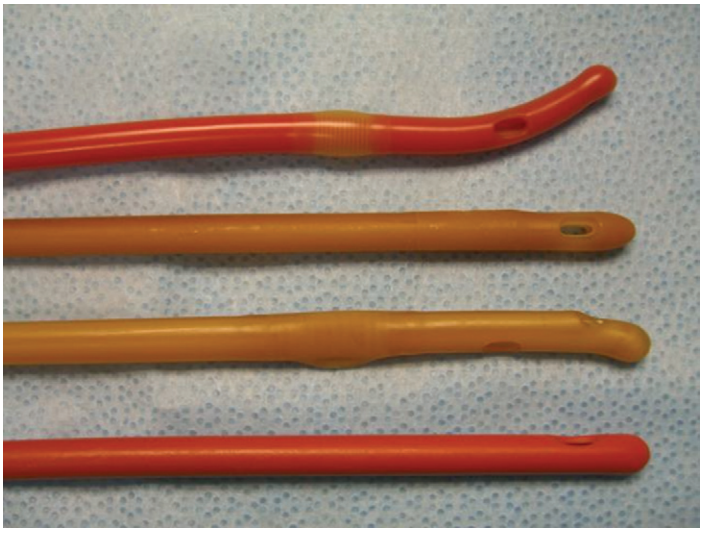


Figure 7–2. From top to bottom: coudé tip, two-way Foley, three-way Foley, and Nelaton.

Material

Modern urinary catheters are most frequently made of latex, rubber, silicone, and polyvinylchloride (PVC). Rubber and latex catheters are often chosen for short-term drainage. Silicone catheters are indicated when there is rubber/latex sensitivity or allergy and are particularly suited for patients requiring a longer period of indwelling time. Silicone is relatively inert, causing less tissue reaction, and is associated with less bacterial adherence than other catheter materials (Roberts et al, 1990). Evidence suggests that the use of silicone catheters is associated with a lower incidence of urinary tract infections compared with those made of latex (Crnich et al, 2007).

Coating

Various coatings on urethral catheters have been applied in an attempt to reduce urethral trauma and infection risks. The use of hydrophilic coatings has been evaluated among patients on chronic self-intermittent catheterization, with some studies suggesting less discomfort, a decrease in symptomatic urinary tract infection (UTI) rates, and urethral strictures (Wyndaele J, 2002; Vapnek et al, 2003; De Ridder et al, 2005; Bjerklund et al, 2007). Thus far, the evidence is contradictory for the use of antiseptic-coated catheters to prevent the incidence of UTIs, with most of the studies to date having been restricted to small pilot studies (Johnson et al, 2006).

The application of a viable bacterial coating onto catheter surfaces as a method of reducing catheter-associated urinary tract infection (CAUTI) by bacterial interference is a novel approach that has shown promise in a small pilot study involving the use of *Escherichia coli*–coated catheters. The rationale is based on natural competition by nonpathogenic bacteria overpowering any pathogenic bacteria that may enter the urinary tract (Trautner et al, 2007). Further study is necessary to confirm if this will be an effective strategy.

Table 7–1.

Catheter Size Based on Age

AGE IN YR	CATHETER SIZE (FR)
<5	5-8
5-10	8-10
10-14	10
>14	10-14

Number of Channels

The most basic catheters are constructed with a single lumen to permit urinary drainage or irrigation/instillation. Additional lumens are added to permit addition of a retention balloon (two-way catheter) and for simultaneous drainage and irrigation (three-way catheter). The ability to allow bidirectional flow with a three-way catheter is particularly useful when there is need to drain thick fluid such as pus or blood from the bladder because it allows thinning of the solute, preventing reaccumulation by rapid exchange of clean fluid in a washing effect. The insertion of a three-way catheter for continuous bladder irrigation is most often performed after transurethral resection procedures of the bladder or prostate, which additionally can be combined with a large-volume retention balloon (30 to 50 mL), which under slight traction can often achieve complete hemostasis of the resected prostatic fossa. It should be borne in mind, however, that the addition of a multichannel catheter is accomplished by decreasing the overall internal diameter or lumen of the main drainage channel; a 24-Fr three-way catheter has a smaller internal drainage diameter than a 24-Fr two-way, which has a narrower lumen than a 24-Fr one-way catheter.

Tip Shape

Most catheters are designed with a blunt straight tip that is blind ending. Catheters with curved tips or with an end hole have specific utility in certain clinical scenarios (e.g., a coudé tip for patients with a high bladder neck or prominent median prostate lobe, a Councill catheter when catheterization over a guidewire is required). The various catheters and their typical applications are presented in (Table 7–2).

Technique of Catheter Insertion

Once the need for urethral catheterization has been established, the procedure should be described to the patient and potential complications discussed. A focused clinical history including allergies, urologic pathology, previous urologic surgeries, and catheterization attempts may increase suspicion of the potential for difficulties with catheterization.

Table 7–2.

Features of Ureteral Catheters

FORM OF TIP	SIDE HOLE	RETAINING MECHANISM	NAME	USES (ADVANTAGES)
Straight	Single or multiple	None	Robinson Nelaton Jaques	One-time drainage, instillation or irrigation in children, females, and most males
		Balloon	Foley	Continuous drainage or irrigation in children, females, and most males
		Balloon/retention plug	Madduri	Used for urethrography, allows proximal and distal occlusion and contrast instillation in the intermediate section
		2 or 4 wings	Malecot	Continuous drainage or irrigation in children, females, and most males (less prone to retaining mechanism failure and increased lumen diameter because no channel is necessary for device activation)
		Umbrella	Pezzer	Continuous drainage or irrigation in children, females, and most males (less prone to retaining mechanism failure and increased lumen diameter because no channel is necessary for device activation)
Curved		Balloon	Coudé	Continuous drainage or irrigation (ease of insertion males with enlarged prostate midlobe or high bladder neck)
End hole			Councill	Continuous drainage or irrigation in children, females, and most males (end hole permits insertion or exchange over a previously placed guidewire)
			Whistle tip	Has a large diameter end hole occupying half of its beveled tip, for increased drainage/instillation capacity

The patient should be in the supine position at a comfortable height for the physician performing catheterization. In female patients a "frog-leg" position is most suitable, and the use of stirrups can be considered, especially in the obese.

Catheterization should be carried out in a sterile fashion with antiseptic preparation and draping of the patient's meatal and genital area.

When catheterization for more than just immediate urinary drainage is required, the catheter's retention balloon should be tested and every catheter should be generously coated with sterile lubricant before insertion.

Anesthetic

The use of topical anesthetic gels before urethral catheterization is widely practiced; however; the evidence to support their use is conflicting. The agent used, temperature of the drug on administration, and indwell times before instrumentation are variable across the studies (McFarlane et al, 2001; Ho et al, 2003; Chung et al, 2007; Garbutt et al, 2008). There is some evidence that cooling to 4° C diminished the discomfort of lignocaine gel instillation, probably due to a cryo-analgesic effect (Thompson et al, 1999; Goel and Aron, 2003). Studies employing 2% lidocaine gel left indwelling at least 15 minutes have been reported to be associated with less pain (Siderias et al, 2004). If topical anesthesia is to be used, evidence suggests it requires a minimum of 10 minutes of exposure (depending on the agent), sufficient volume of the agent (20 to 30 mL), and slow instillation time (>3 to 10 seconds) (Schede and Thüroff, 2006; Tzortzis et al, 2009) to have the most effect.

The systemic absorption of topical urethral lidocaine through intact mucosa is minimal, resulting in low measurable concentrations at doses of up to 550 mg (Ouellette et al, 1985). Rare toxicity has been reported, however, after traumatic procedures that disrupt the mucosal barrier, leading to high and rapid peak concentrations. Seizures, confusion, and disorientation, which usually precede cardiovascular toxicity (Sundaram, 1987; Priya et al, 2005), have been described.

The main benefit of intraurethral anesthetic gel during bladder catheterization may be the additional lubrication providing less traumatic catheter passage and reduced patient discomfort on that basis.

The steps involved in urethral catheter placement obviously vary between males and females. Therefore the techniques for each are described separately. The techniques described pertain to the use of the standard Foley catheter, which is the most commonly used catheter for straightforward bladder drainage.

Male Patients

Anatomic Considerations

The male urethra follows a sigmoid curse, with a proximal curve at the junction of the membranous and bulbar urethra and another at the junction of the bulbar and penile urethra. The adult male urethra is approximately 18 to 20 cm in length, and its diameter is variable, from a mere slit to 6 mm during the passage of urine (Urinary system, 1995).

After sterile skin preparation and draping, grasp the shaft of the penis with the nondominant hand (which is now regarded as contaminated) and hold the penis at a 90-degree angle or perpendicular to the patient. This maneuver eliminates the distal or pendulous urethral curvature. Insert the lubricated tip of the catheter into the urethral meatus and gently but firmly continue to advance the catheter for 7 to 10 cm, while simultaneously bringing the shaft of the penis to the horizontal plane or parallel to the patient. Continue to advance the catheter, while expecting to feel a slight increase in resistance as the membranous urethra (external striated sphincter) is traversed.

Once the entire length of the catheter has been introduced (up to the juncture of the connector or to the two-way bifurcation), wait for spontaneous urine passage, confirming proper placement of the catheter. If spontaneous drainage of urine is not seen, gently press on the patient's suprapubic area. If despite this maneuver no drainage occurs, slowly instill 20 mL of saline using a

catheter-tipped syringe into the drainage port of the catheter and then slowly aspirate the fluid instilled. This maneuver should clear any obstruction of the catheter side hole by lubricant or other material. If the catheter is in the bladder, fluid should be aspirated without resistance. If the catheter is still within the urethra, the negative pressure produced during aspiration will cause collapse of the urethral wall and will not permit the return of the instilled fluid.

Only when the position of the catheter has been verified should the retaining balloon be inflated, with the amount of fluid indicated on the catheter. Most catheters do safely permit twice the indicated amount of fluid without risk of balloon rupture. Sterile water is the preferred solution for balloon inflation. Air is compressible and might leak, and electrolyte or glucose-based solutions can precipitate and occlude the tubing and valve mechanism.

The catheter should be attached to a sterile closed bag system as soon as urine is draining. The drainage bag should be placed below the level of the bladder to encourage one-way gravity flow with the tubing as straight as possible and avoiding kinks that might impair drainage. It has been shown that even the retention of 50 mL of urine in catheterized patients has been associated with an increase in UTIs in up to one third of the patients (Garcia et al, 2007).

The temporal exception to this is in patients with acute urinary retention with significant bladder distension in which rapid bladder drainage might precipitate decompression-induced hematuria or "ex vacuo hematuria." In these patients the catheter should be intermittently clamped and released to permit gradual bladder decompression over 30 to 60 minutes.

If the patient is uncircumcised, at this point return the foreskin to its normal reduced position to avoid paraphimosis.

Secure the catheter to the patient, allowing for a normal range of motion and without tension, using adhesive tape or a commercial securing device.

Female Patients

Anatomic Considerations

The female urethra is approximately 3.5 to 4 cm long. The meatus is usually in an anterior location and the bladder neck in a posterior location in the horizontal plane, giving the urethra a slight posterior inclination.

After antiseptic preparation and sterile draping, use the nondominant hand to spread the patient's labia (now considered contaminated) to reveal the urethral meatus. After lubrication, insert the tip of the catheter and gently advance using a slightly downward direction, until about half the length of the catheter has been inserted. Check for urine return and activate the anchoring mechanism if used.

Difficulties during female catheterization may be encountered for several reasons including the inability to locate the urethral meatus due to obesity and age-related changes and less frequently to strictures (postsurgery, radiotherapy, neoplastic causes).

In the obese patient, the use of one or more assistants to provide labial retraction or the use of stirrups can be helpful. In the case of postmenopausal vaginal atrophy or other conditions resulting in the urethral meatus receding into the introitus, we suggest the following alternatives. Holding the index and middle fingers of the nondominant hand together, slowly slide posterior along the introitus until the urethral meatus is palpated and then proceed to slide the fingers just distal to the inferior margin of the meatus. Using the dominant hand, pass the catheter along the groove made by the fingers (this serves a dual purpose—it creates a posterior border with the fingertips and provides a guide for the catheter). As the catheter tip crosses the meatus, it can be felt with the fingertips, thus ensuring proper placement. A second maneuver is to use a vaginal speculum to aid in the retraction and fixation of the introitus. Finally use a coudé tip catheter angled upward and gently slide the tip along the anterior vaginal wall in the midline, until it enters the meatus, and then advance into the bladder.

Special Considerations in Children

Whenever possible the procedure should be explained in clear and age-appropriate language to the child.

Catheterization in children is most commonly performed for drainage, performance of voiding cystourethrogram, or obtaining urine for culture. When attempting to obtain a urine sample for cultures, the use of a portable bladder ultrasound is recommended to ensure that an adequate amount of urine is present in the bladder, thus minimizing the risk of unproductive catheterization (Robson et al, 2006).

In female children the correct identification of the urethral meatus is essential to avoid unnecessary catheter contact with the sensitive introitus, leading to discomfort and possibly loss of cooperation by the child. The meatus is just above the superior margin of the introitus and frequently hidden by the superior portion of the hymen. Gentle downward pressure on the upper aspect of the hymen with a cotton ball may allow visualization of the meatus. Failing this maneuver, the catheter tip should be inserted just above the hymen in the midline.

In uncircumcised boys, retract the foreskin only until the meatus is visible. In infants and children younger than 3 years of age, when the normal foreskin adhesions have not yet involuted, simply align the preputial opening with the meatus to assist catheter insertion.

Difficult Catheterization

Difficulty inserting a catheter into the bladder is most commonly due to prostatic growth, urethral stricture(s), bladder neck contracture, or false passage from previous urethral instrumentation. Rarely it is the result of phimosis or urethral calculi. Although these difficulties occur mostly in men, the techniques described herein may be applied to place a catheter regardless of gender (Fig. 7–3).

If there is no clinical history of previous sexually transmitted infections (STIs), catheterization, trauma, urethral surgery, or radiotherapy in an adult male over 40 years of age, the most likely cause is prostatic enlargement. Using adequate urethral lubrication and a 16- or 18-Fr coudé tip silicone catheter is often successful in this scenario. If multiple previously unsuccessful attempts have been made and urethral trauma is suspected due to the appearance of a bloody urethral discharge, a false passage or a stricture is likely. A single atraumatic attempt can be made using a 12-Fr silicon/straight or coudé tip catheter. If this maneuver is unsuccessful, then depending on the availability of equipment and the level of experience of the clinician, several other options can be considered. The authors' preference is to use a flexible cystoscope, allowing a direct visual approach that can be both diagnostic and therapeutic and minimizes the risk of further urethral injury. Under direct vision, the area where the false passage was created or the site of stricture formation is identified and an

attempt is made to identify the true urethral lumen. Once identified, a 0.035 in Teflon-coated guidewire (e.g., Bentson type) is passed along the urethral lumen and into the bladder. Depending on the circumstances, urethral dilation may be required as in the situation of a tight urethral stricture or bladder neck contracture. Dilation can be accomplished over the guidewire using Amplatz dilators or purpose-built commercially available urethral dilators (Fig. 7–4A-C). Once the urethral lumen is deemed of adequate diameter to permit placement of the catheter size required, a Councill catheter, which can be advanced over the guidewire into the bladder, is selected.

If flexible instruments are unavailable and a urethral stricture is suspected, then a blind technique. although less desirable, can be used. This technique involves using filiforms and followers (Fig. 7–5).

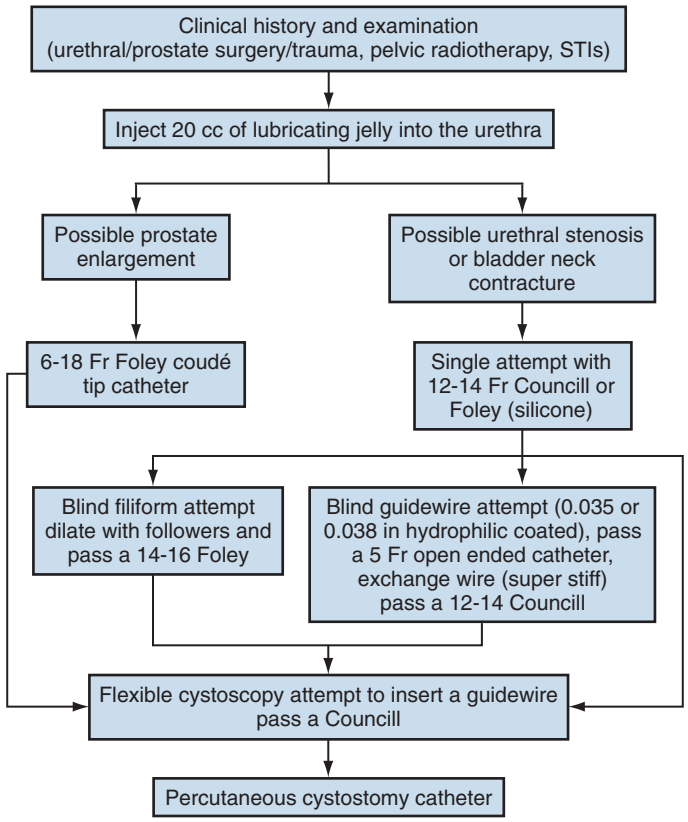


Figure 7–3. Management of the difficult-to-catheterize patient.

The first step is to pass a small female filiform catheter. In many cases the initial filiform will frequently end up entrapped in the stricture membrane or in the false passage, rather than following the true lumen. Insertion of additional filiforms will then fill the false passage or stricture membrane until one is successfully directed into the true lumen. Once a filiform is successfully passed, male sections (followers) of increasing size are attached to the filiform to permit sequential dilation of the urethra. Once dilation to at least 14 to 16 Fr has been achieved, a 12- to 14-Fr catheter is then passed.

Alternatively, one can blindly pass a Councill catheter to the point of resistance and then attempt to advance a hydrophilic-coated guidewire. If guidewire advancement seems to go easily, a 5-Fr open-ended or angled ureteral catheter can be advanced over the wire to permit urine drainage and confirm bladder positioning. Once bladder positioning of the guidewire is assured, urethral dilation can be performed over the guidewire followed by Councill catheter placement.

Both blind techniques require a level of experience, especially a tactile sense of what is acceptable resistance during guidewire and filiform insertion. It is worth restating our belief that whenever possible the use of flexible cystoscopy and a direct visual approach are preferable. The use of fluoroscopy is another alternative, but the lack of immediate availability in most settings may logistically limit utility.

If none of these techniques are successful, a suprapubic catheter should then be inserted.

Complications of Urethral Catheterization

UTIs account for 40% of all nosocomial infections. The major risk factor is the use of urethral catheters, which are responsible for up to (80%) of UTIs in the hospital setting (Ha and Cho, 2006). Risk factors for CAUTIs include patients requiring more than 6 days of catheterization, female gender, active nonurinary infection sites, preexisting medical conditions, malnutrition, renal insufficiency, catheter insertion other than in the operating room, and having drainage tubing or a bag elevated above the level of the bladder (Maki and Tambyah, 2001).

Avoidance of unnecessary catheterization, atraumatic technique at insertion, and the use of a closed collection circuit have been shown to decrease the incidence of CAUTI. The use of aseptic technique, although universally practiced and recommended by expert opinion, is not evidence based (Pratt et al, 2007).

The use of antiseptic gels or irrigations of the bladder or collection bag, catheter clamping, or antireflux valves have not been shown to prevent CAUTIs (Phipps et al, 2006; Jahn et al, 2007; Tenke et al, 2008). Multiple trials to date have failed to show that

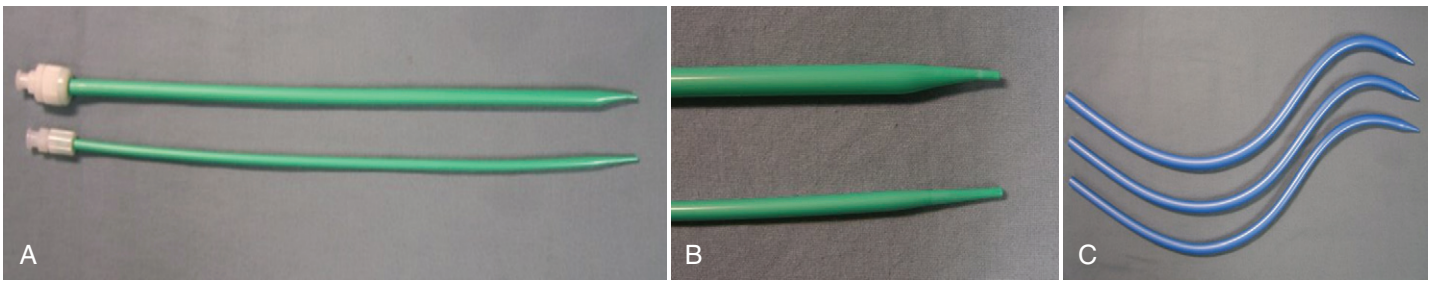


Figure 7–4. **A,** Urethral dilators (12 and 18 Fr); **B,** dilator tip, showing gradual increase of diameter; **C,** Male urethral dilators.

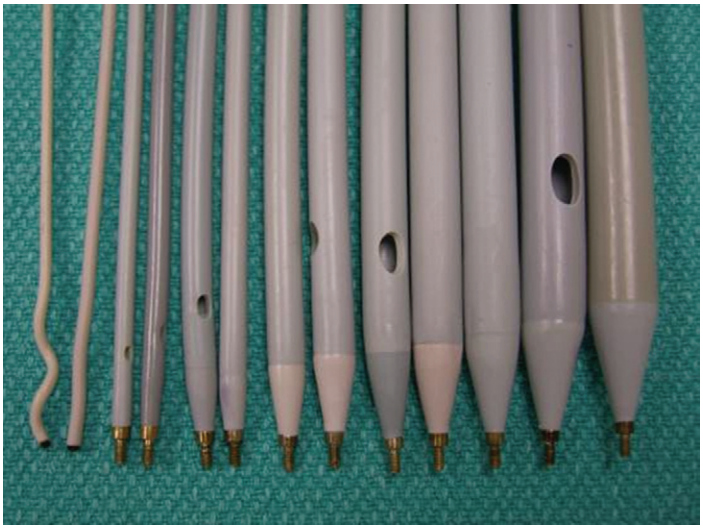


Figure 7–5. Filiform dilators (left pair) and followers, from 2 Fr to 30 Fr.

hydrogel-coated catheters have a role in reducing the incidence of infections. The application of antibiotic coatings onto catheter surfaces and the concept of drug elution have shown some promise in preclinical investigations such as the application of nitrofurazone and minocycline/rifampin coatings, which have shown effectiveness in limited trials by reducing the incidence of asymptomatic bacteriuria (Lee et al, 2004; Stensballe et al, 2007). Evidence of the benefit of employing silver alloy coating to catheter surfaces has been conflicting (Davenport and Keeley, 2005; Srinivasan et al, 2006; Schumm et al, 2008). A recent Cochrane review reported a decrease in the rates of asymptomatic bacteriuria; however, whether this equates to a decrease in symptomatic infections is not clear (Jahn et al, 2007). The routine use of catheter coatings is currently not supported by the available literature.

A unique complication of urethral catheterization is the inability to remove the catheter from the bladder. This problem has been reported in the pediatric population when using feeding tubes that can become knotted or entangled. A more frequent occurrence, however, is the inability to remove a straight Foley catheter, either due to encrustation, entrapment by sutures, or inability to disengage/deflate the retaining balloon. The latter problem may be due to a faulty valve, inflation channel blockage, or rarely crystallization within the balloon.

If the catheter has been indwelling for a long period of time, encrustation should be considered and imaging studies (plain film or ultrasound) will be confirmatory. In many instances the encrustation is easily dislodged with gentle traction on the catheter. For more significant encrustations, one can consider using a semirigid ureteroscope and the holmium:YAG laser to remove the stone fragments. If the catheter is quite rigidly fixed and in the setting of recent bladder or prostate surgery, semirigid ureteroscopy along the catheter and using the holmium:YAG to release the suture have also been described (Bagley et al, 1998; Nagarajan et al, 2005). Because the suture materials used in bladder and prostate surgery are often absorbable, waiting for suture dissolution is another option.

An inability to deflate a Foley balloon can be managed using a stepwise approach. One should first attempt to place another 1 to 2 mL of fluid in the balloon to ensure normal balloon contour, which may be important with the large-volume balloons. Failing this maneuver, the next step is to cut the inflation port. If the valve is the source of the problem, balloon deflation should then occur.

If the balloon remains inflated, the problem is along the catheter's inflation lumen or in the balloon itself. Although overinflation of the balloon has been described in an attempt to rupture the balloon, we do not recommend it because this maneuver may be painful to the patient and may cause bladder injury and fragmentation and retention of the balloon fragments (Gülmez et al, 1996). Similarly, the use of chemical instillations such as ether or toluene to induce balloon rupture should be discouraged because these agents can cause chemical cystitis (Patterson et al, 2006).

Our preferred approach is to insert a surgical steel wire (24 or 28 gauge; often included as an obturator for small-caliber ureteral catheters) or the stiff end of a 0.035-inch hydrophilic-coated guidewire through the valve inflation lumen. This usually bypasses the site of obstruction or creates a small perforation of the balloon.

Should none of these maneuvers be successful, the use of ultrasound-guided needle puncture can be conducted with a long spinal needle (22 gauge) using either a transrectal, transvaginal, or suprapubic surface probe (Daneshmand et al, 2002). In most instances, retained catheters can be removed without the need for open surgery.

Other complications of urethral catheterization include hematuria, urethral and meatal strictures, urethral perforation, and allergic reactions including anaphylaxis (Thomas et al, 2009; Wyndaele, 2002). Especially at risk are patients with long-term indwelling catheters, in whom other complications may also include malignant neoplasms (2.3% to 10%), stone formation (46% to 53%), bladder neck and urethral erosions (Igawa et al, 2008).

Suprapubic Catheterization

Indications

Suprapubic catheter (SC) insertion is most often selected for those patients in whom urethral access is not possible such as complete urethral stenosis, bladder neck contracture, and traumatic urethral disruption. Also, some patients who do not meet these criteria may be candidates for selective SC (Abrams et al, 2008), especially in the context of the need for a chronic indwelling catheter (i.e., neurogenic bladder, poor patient or cooperation/support for clean intermittent catheterization) because some evidence suggests that an SC may be associated with less discomfort than a urethral catheter (McPhail et al, 2006). The evidence that SC reduces the risk for symptomatic bacteriuria is relatively weak (Niël-Weise and van den Broek, 2005). Relative indications for SC placement also include patients who decline urethral catheterization for sexual or self-image purposes.

Indications for short-term SC as a method of postoperative urinary diversion to allow bladder or urethral healing include following surgical procedures (e.g., open prostatic adenectomy, intestinal bladder substitution) or in the pediatric patients following reflux surgery, and during trans urethral prostate resection to theoretically prevent fluid absorption in high risk surgical patients (Sanchez Zalabardo et al, 2003).

Technique (Percutaneous)

The distended bladder should be palpated or percussed to delineate its borders. Failure to palpate the bladder is a relative contraindication to blind percutaneous access techniques and should prompt the clinician to either wait until the bladder is more distended and palpable or use ultrasound imaging guidance for catheter placement (Aguilera et al, 2004). Because of the wide

availability of portable ultrasound, ease of use, and added safety over the blind technique, we strongly advocate for its preferential use in percutaneous cystostomy placement to reduce possible complications.

The patient's infraumbilical abdomen should be prepped and draped in a sterile field. Local anesthesia should be infiltrated into the skin and subcutaneous tissues. A 5- to 10-mm incision is then made 3 to 4 cm above the symphysis pubis in the midline of the abdomen.

Access can then be obtained using a trocar technique, in which a sharp stylet or trocar is used to penetrate the layers of the abdominal wall and bladder. Once entry into the bladder is confirmed by urine flashback or aspiration, the stylet is withdrawn while the catheter is advanced (coaxial system) or the catheter can be fed through the lumen (peel away sheath system). The anchoring mechanism is then activated, the catheter is sutured to the patient's skin, and a sterile dressing is applied to the site.

An alternative approach employs the Seldinger technique. An 18-gauge hollow needle is advanced under continuous aspiration with a syringe until urine flashback appears, confirming the bladder has been entered. The needle is then advanced 1 cm more, the syringe is detached from the needle, and a floppy-tip guidewire (0.035 or 0.038 in Bentson) is advanced and coiled in the bladder. The needle is withdrawn, a small incision is made on the anterior abdominal fascia, and the tract is coaxially dilated either in one step with a balloon-dilating catheter or with sequential graduated dilators (Fig. 7–6). A 16- to 18-Fr Councill catheter can then be advanced over the guidewire and into the bladder.

Contraindications to the use of a blind percutaneous approach are uncorrected coagulopathy, previous lower abdominal surgery, or pelvic radiation (Lawrentschuk et al, 2003). In these situations, an open technique with exposure of the anterior surface of the bladder should be used. The use of a retrograde simultaneous cystoscopy to manually displace the bladder dome and serve as a visual and palpatory reference in both the closed and open technique has been described in an effort to diminish the chance of bowel injury (Alagiri and Seidmon, 1998; Lawrentschuk et al, 2003; Sawant et al, 2009).

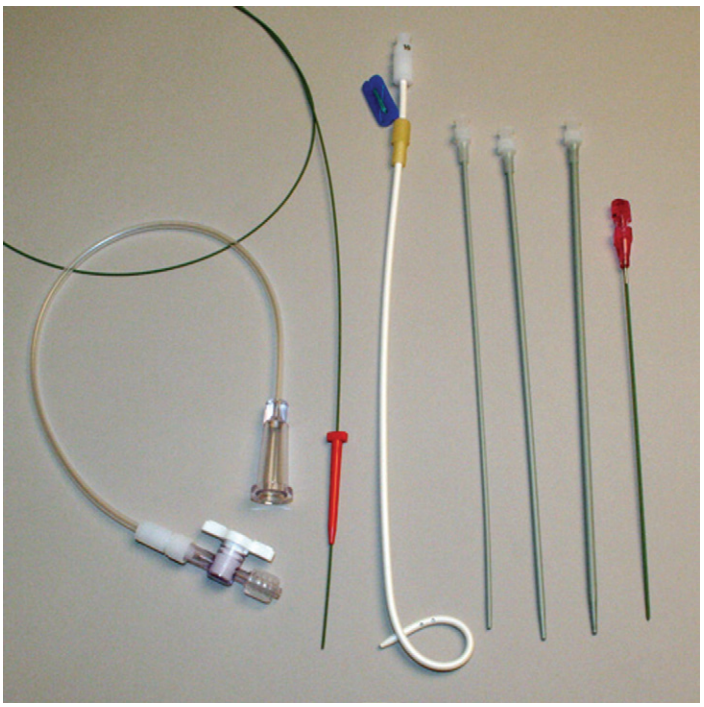


Figure 7–6. Percutaneous suprapubic catheter kit (left to right, guidewire, drainage bag connection tubing, Cope loop catheter, Amplaz dilators, and cystostomy needle). (Courtesy of Cook Urological, Spencer, IN.)

Technique (Open)

The open technique entails prepping and draping the anterior abdomen of the patient. An incision is made approximately 2 to 3 cm above superior margin of the symphysis pubis in the midline. Both blunt and sharp dissections are then used to expose the anterior layer of rectus fascia, which is then incised. The Retzius space is developed with blunt dissection, taking care not to enter the peritoneal cavity until the anterior wall of the bladder is identified. Two 1-0 silk stay sutures are used to stabilize the bladder wall, and electrocautery is used to make a 1-cm incision in all layers of the bladder in between the sutures. Urine is drained, and a suprapubic catheter is placed through the abdominal wall by a stab incision, inserted into the bladder, and secured with a purse string or uninterrupted running suture (2-0 absorbable suture). The anchoring device is deployed at this point to avoid entrapment or puncture by the suture, and the anterior rectus fascia, sub-cutaneous tissue, and skin are closed per personal preferences.

Complications

Potential complications associated with suprapubic catheters include those related to initial insertion (hematuria, perivesical fluid collections, surrounding organ injury). With long-term use other adverse events can include catheter blockage/encrustation, dislodgement, skin site infections, symptomatic UTI, urothelial neoplasms, and stone formation (Shiøtz et al, 1989; Sheriff et al, 1998; Berman et al, 2003; Lawrentschuk et al, 2003; Kumar and Pati, 2005; Ahluwalia et al, 2006; Feifer and Corcos, 2008; Sugimura et al, 2008).

UPPER URINARY TRACT URETERAL STENTS

Rudimentary versions of a ureteral stent were first conceived and used in the late 19th and early 20th centuries on the basis of Albarran's pioneering work to aid in open surgery of the ureter. Zimskind in 1967 was the first to describe endoscopic stent placement to relieve ureteral obstruction. This early era was plagued with frequent stent migration and device expulsion. A novel design developed by Gibbons in the 1970s initially addressed this issue, but it was not until the revolutionary development of the Double J and pigtail stents independently by Finney and Hepperlen and colleagues (1978) that the use of ureteral stents became widespread (Watterson et al, 2002, Chew and Denstedt, 2004).

Ureteral stents have become a fundamental tool in today's urologic armamentarium and are employed for a number of indications including obstruction relief as a prophylaxis against obstruction or ureteral injury and as use as a ureteral splint.

Indications for Ureteral Stents Placement

Stents are often inserted to relieve either extrinsic (tumor, retroperitoneal fibrosis) or intrinsic ureteral obstruction (stones, tumors, strictures) as a temporary measure while definitive treatment is

instituted or as permanent measure when no corrective treatment is possible. In the context of bilateral obstruction, solitary kidney (anatomic or functional), refractory renal colic or obstruction associated with infection (fever, leukocytosis, pyuria) stent placement to secure drainage is often an emergent absolute indication.

Current percutaneous lithotripsy techniques do not require routine stenting. Exceptions to this practice include extensive perforation of the collecting system, significant stone burden remains with the need for subsequent shock wave lithotripsy (SWL), ureteral obstruction due to edema, concurrent ureteropelvic obstruction, stone fragment migration into the ureter, supracostal access, and persistent urinary fistula after nephrostomy tube removal.

The use of routine stenting before SWL is not associated with either a decrease of steinstrasse formation or increase in stone-free rates. However, stenting is clearly associated with increased morbidity. Kirkali and colleagues (1993) reported on 351 patients with renal stones less than 30 mm. The stone-free rate was not significantly different between groups (stented 31% vs. unstented 30%). Half of the patients in the stented group reported bladder discomfort and symptoms that were relieved on removal of the stent. In another report, stented subjects experienced significantly higher incidence and duration of urinary symptoms (urgency, hematuria, bladder discomfort, and frequency) compared with nonstented subjects (Preminger et al, 1989). Indications for pre-SWL stenting are stone burden greater than 2 cm (Libby et al, 1988; Sulaiman et al, 1999; Preminger et al, 2005), when bilateral SWL is to be undertaken (at least one renal unit), and when treating a solitary kidney.

In 2007 a cosponsored American Urological Association/European Association of Urology guideline panel recommended that routine ureteral stent insertion is not necessary after SWL for ureteral calculi because available evidence shows it does not improve patient outcomes (Preminger et al, 2007). Current evidence has also shown that routine stenting after uncomplicated ureteroscopy is unnecessary because unstented patients do not experience an increased risk of complications and have fewer postoperative symptoms (Hosking et al 1999; Rane et al, 2000; Denstedt et al, 2001). Stenting in association with ureteroscopy is recommended in patients with an impacted ureteral calculi, incomplete fragmentation, after formal ureteral dilation, and if there are procedural complications such as ureteral perforation.

Urinary calculi during pregnancy, although uncommon, presents a unique therapeutic challenge. Drainage, if indicated, can be achieved with an internal stent or a percutaneous nephrostomy tube; however, the indwelling time should be limited and exchange is recommended at a 6-week interval due to the increased risk of rapid encrustation triggered by gestational hyperuricosuria and hypercalciuria (Riddell and Denstedt, 2000).

Another indication for stenting (Double J or 5 open-ended ureteral catheter exteriorized and taped to the urethral catheter) is to serve as a surgical landmark for ureteral identification in order to avoid iatrogenic ureteral injury in abdominal or pelvic surgery. Light-emitting ureteral stents have been developed to serve as an additional optical aid, which may be especially helpful in the context of video-assisted surgery (i.e., laparoscopy), in which the tactile sense is diminished.

The use of a stent for ureteral splinting brings us back to the earliest uses of stents. In this setting the stent accomplishes two tasks—one is as a splint or scaffold to promote organized tissue healing and the other equally important role is to allow unhindered urinary flow across the healing segment of the ureter. The main areas where stents are used are following ureteral trauma such as perforation or transection and following ureteral repair (i.e., primary reanastomosis, urinary-intestinal anastomosis, ureterotomy, ureteral reimplantation). One particular indication is kidney transplants because stenting reduces the risk of major urologic complications (obstruction, urinary fistulas) (Wilson et al, 2005) without increasing the risk of infections (Eschwege et al, 1996).

Stents can be used to prevent the occurrence of urinary fistulas (i.e., after percutaneous nephrostolithotomy [PCNL], ureteral anastomosis) or treat them by creating a path of preferential flow away from the defect. Their use is indicated in cases of upper urinary tract fistulas (renal or ureteral) or retroperitoneal urinomas after blunt or open trauma (Haas et al, 1998).

Technique of Ureteral Stent Insertion

The insertion of a ureteral stent can be accomplished via one of several approaches (either open or endoscopic and by antegrade or retrograde techniques). The retrograde approach is most commonly used, often as an adjunct to ureteroscopy or SWL. Although retrograde insertion can be performed with either the aid of flexible or rigid cystoscopy, the need for fluoroscopy and a guidewire are common to both techniques. The safest way to place an internal ureteral stent is by advancing the stent over a guidewire. This can be accomplished by passing a stent that is open at both ends through the working channel of a rigid cystoscope through which a guidewire has been passed and advanced up the ureter to the renal pelvis. The stent is advanced with a pusher while visually observing the ureteral orifice through the cystoscope. Advancement of the stent up the ureter should be monitored fluoroscopically. When the pusher becomes visible at the level of the bladder neck, the wire is extracted, allowing the stent to curl in the bladder.

An alternative technique that relies more on fluoroscopic visualization for stent placement and less on cystoscopic visualization is often advantageous when dealing with more challenging stent placements such as impacted ureteral stones or malignant obstruction (Figs. 7–7 through 7–16).

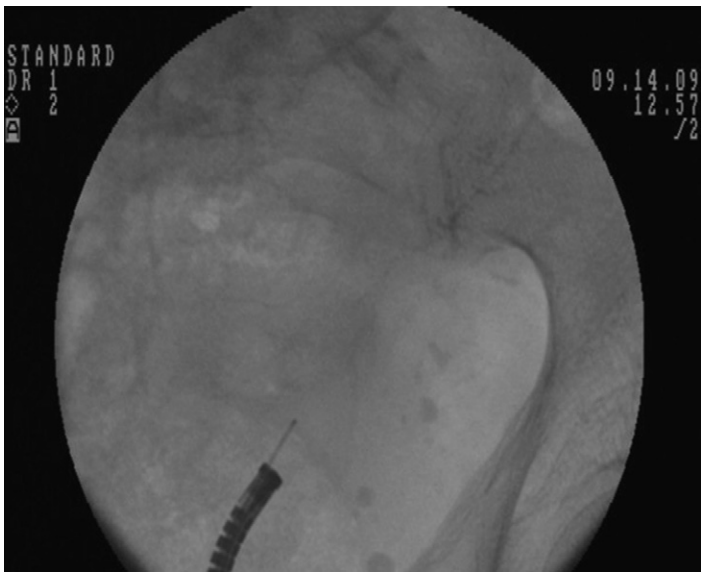


Figure 7–7. Flexible cystoscopy is used to locate and, under fluoroscopic guidance, pass a floppy tip guidewire through the ureteral meatus.

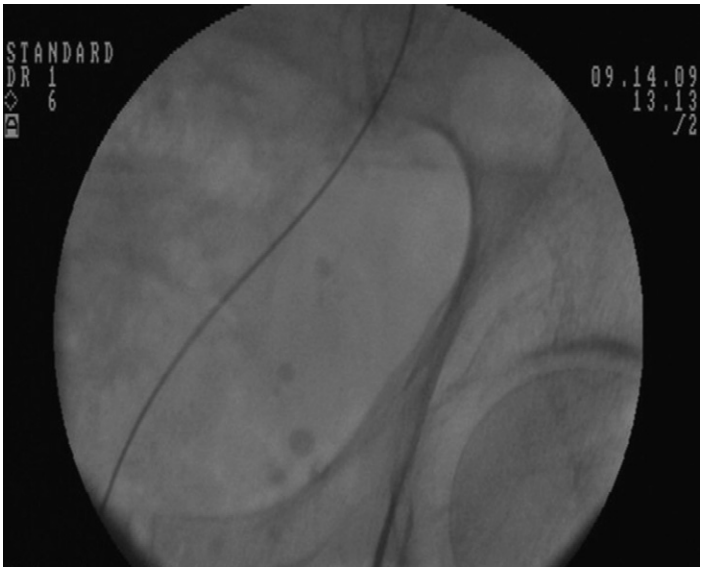


Figure 7–8. Guidewire is advanced in a retrograde fashion.



Figure 7–10. 8/10 coaxial dilator is passed into the ureter.

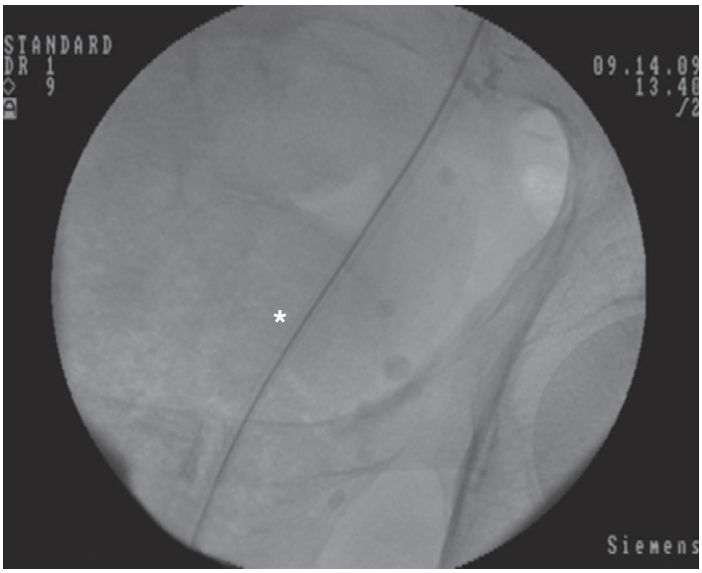


Figure 7–9. The 8 portion has been removed. *Asterisk* shows the faint outline of the 10 portion along the guidewire.

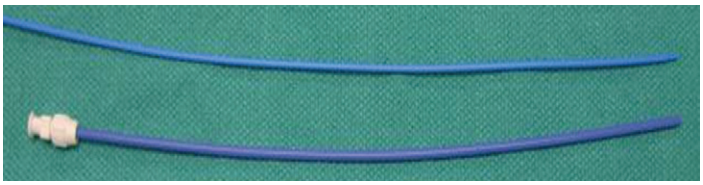


Figure 7–11. A disassembled 8/10 coaxial dilator (bottom is 10 Fr, top is 8 Fr).

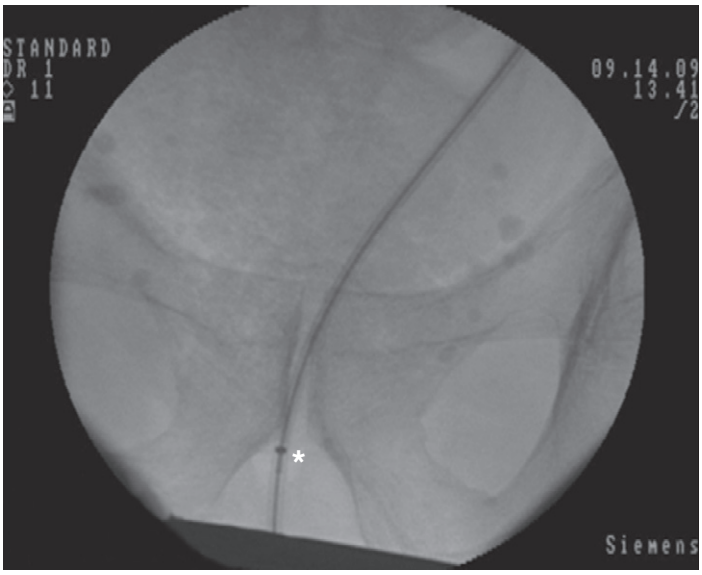


Figure 7–12. The stent is inserted into the ureter. *Asterisk* shows the tip of the stent.

After obtaining bladder access with either a flexible or rigid cystoscope, a floppy-tip guidewire is advanced into the ureteral meatus and coiled in the renal pelvis using fluoroscopy, the cystoscope is then removed and an 8- to 10-Fr coaxial dilator is advanced under fluoroscopy until the 10-Fr sheath is at the urethral meatus. The 8-Fr internal dilator is removed, leaving a conduit (10-Fr outer sheath) through which to advance the stent.

The ureteral stent is then advanced over the guidewire through the 10-Fr sheath by using a pusher with a small fluoroscopically visible metal band at its tip. The metal tip pusher is advanced under fluoroscopic control to the upper border of the pubic symphysis in male patients and lower border in female patients, while stabilizing the position of the lower end of the stent. The 10-Fr sheath and subsequently the guidewire are removed, allowing the stent to curl in the bladder.

Stent Technology

In the more than 30 years that have elapsed since the introduction of the first self-retaining ureteral stents, there have been ongoing efforts to design a stent with better patient tolerability and biocompatibility. In the following sections we address some of the



Figure 7–13. A metal tip pusher is used to advance the stent to the desired position. *Asterisk* shows the pushers radiopaque marker.

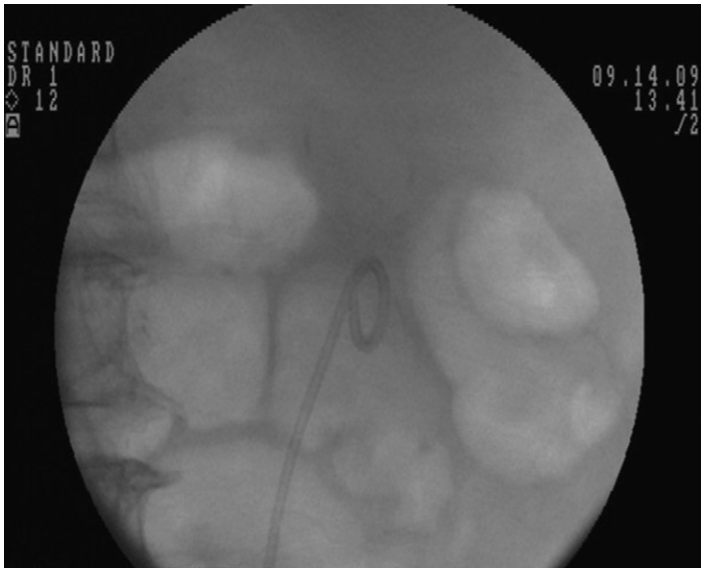


Figure 7–14. The distal third of the guidewire is removed to form the kidney coil.



Figure 7–15. While maintaining the tip of the pusher fixed just distally to the inferior border of the pubic symphysis, the 10 portion of the dilator is removed. *Asterisk* shows the tip of the 10 portion.

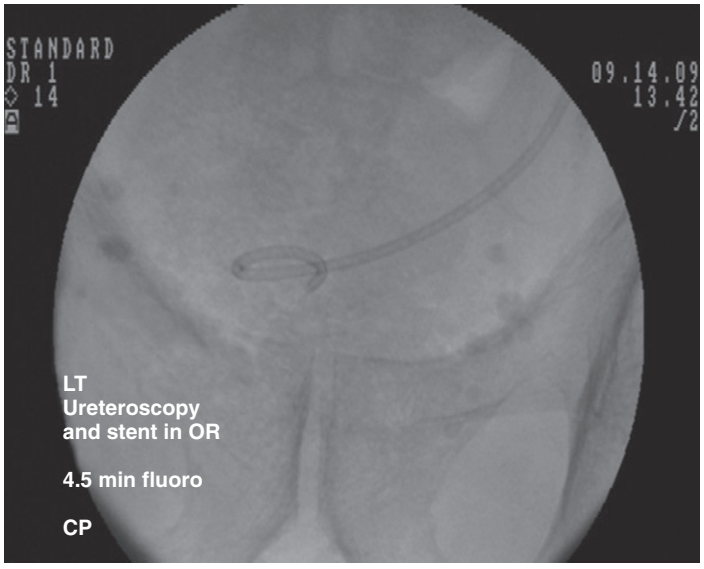


Figure 7–16. While maintaining the pusher's position, the guidewire is removed to form the bladder coil. Then the pusher is removed.

characteristics of current stents, as well as future trends in stent technology.

The physical characteristics of a stent are dictated by the material employed and design used in its construction. Early stents were manufactured out of glass, tantalum, or vitalum tubes (Wignall and Denstedt, 2008). Polyethylene (PE) was the first plastic polymer used in stents; however, it proved to be fracture prone and has since fallen out of favor. Silicon is the most biocompatible material tested to date; however, due to its less than optimal handling characteristics (high friction coefficient and extreme flexibility) and low radial force, which makes it prone to occlusion (Chew and Denstedt, 2004), it is not widely used. Polyurethane shares characteristics common to both silicon and PE, making a good overall stent material. Various proprietary polymers are now available including C-flex, Silitek, Tecoflex, and Percuflex. These materials have been developed in an effort to increase biocompatibility and handling.

A further evolution in stent materials has been the design of biodegradable stents, which in theory could eliminate the need for cystoscopic stent removal. The main challenge of this technology has been the inability to reliably control the degradation rate. The first attempts used pH-triggered degradation of stent polymers (Shlick and Planz, 1997, 1998). In vitro studies demonstrated an ability to cause stent dissolution, but in vivo studies are lacking. Dissolution of a poly-L-lactic-co-glycolide (PLGA) stent has also been demonstrated in a porcine model for short-term drainage after endopyelotomy (Olweny et al, 2002). Although dissolution was achieved, tissue inflammation was a prominent finding.

A poly-L-D-lactide copolymer stent tested in a canine model demonstrated 50% stent dissolution at 12 weeks, 100% dissolution, and no difference in histologic changes when compared with a nondegradable stent at 24 weeks (Lumiaho et al, 2000). Uriprene, a copolyester compound, has been tested in the porcine model showing complete degradation by 10 weeks without a difference in the inflammatory response when compared with conventional stents and without any retained fragments in the subepithelial tissues (Hadaschik et al, 2008). Only one trial to date involving human subjects has been reported using a proprietary polymer material stent (Lingeman et al, 2003). In 88 patients stented post-ureteroscopy, the stent was effective in providing ureteral drainage in 78.2% of patients with a 7.9% stent-related complication rate, mostly due to proximal/distal migration or fragment retention. Eighty-four percent of the patients were stent free at 30 days and 96.6% at 90 days. Although early in development, tissue-engineering techniques have been used to create stents made from chondrocytes over an absorbable scaffold (Amiel et al, 2001) and may overcome the limitations identified with prior dissolving stents.

The development of metallic mesh stents to combat stent occlusion by radial compression in the setting of chronic extrinsic ureteral obstruction is a relatively recent innovation. These devices can be self-expandable, balloon expandable, mesh, or continuous wire stents with or without thermo-expandable shape memory. Indications to date have primarily been for patients with malignant ureteral obstruction, in whom a conventional stent would not reliably relieve obstruction. The literature to date describing the experience with metallic stents is limited to small series, given the narrow indications for their use (Kulkarni and Bellamy, 2001). Complications reported include failure to relieve obstruction, erosion, encrustation, and migration (Pauer and Lugmayr, 1996; Diaz-Lucas et al, 1997; Arya et al, 2001; Agrawal et al, 2009; Liatsikos et al, 2010). The most recently released metallic stent is the titanium Resonance stent (Cook). Borin and colleagues (2006) reported follow-up of 14 months, with an overall 30% failure rate mostly due to epithelial ingrowth and 24% macroscopic encrustation rate. Garg and colleagues (2009) reported their experience with the use of the Resonance stent in benign conditions (ureteral and ureteroenteric strictures), finding an 89% rate of distal migration in their population. Nagele and colleagues (2008) reported that after a mean 8.6-month follow-up, 57% of the stents had to be removed (urinary symptoms, drainage failure, hematuria, infection, or encrustation).

Stent Design Modifications

Most ureteral stents on the market today are based on a common design consisting of a central lumen, multiple side holes, and a mechanism to limit stent movement (Fig. 7–17). The most commonly used stent is the double pigtail configuration in some variation such as the Double J stent, the dual durometer (softer distal curl and rigid proximal curl), or those with tail shape changes (e.g., Percuflex Tail Plus has a 3-Fr lumen-less soft tail, Polaris Loop has two thinner tail loops) (Dunn et al, 2000; Liatsikos et al, 2002).

Various design changes to the original standard double-coiled internal ureteral stent have appeared.

One such design modification aimed at improving stone clearance after lithotripsy is in the form of a self-expanding stent (OPEN Pass J) with multiple baskets in the stent body to increase ureteral lumen diameter (up to 6.5 mm) and trap stone fragments until stent removal (L'Esperance et al, 2007).

In an effort to improve urinary drainage in the setting of extrinsic ureteral compression, a double-lumen stent (SP-1 and SP-2 ACMI) demonstrated a lower flow versus two side-by-side 7-Fr stents but greater flow when compared with a single 7-Fr stent when tested in an ex-vivo model (Hafron et al, 2006). The Open-8 and Open-I are stents designed to provide drainage using a similar principle, on an I beam or open-sided omega configuration.

Other designs intended to improve drainage are the grooved stents (Towers Peripheral Ureteral Stent by Cook and Lithostent by ACMI), polyurethane metal-reinforced spiral stents (by Braun) designed to resist extrinsic compression and severe angulation (Tschada et al, 1994), and an externally ridged stent (Spirastent by Urosurge) theoretically aimed at increasing extra luminal flow and stone passage (Stoller et al, 2000).

Task-specific stents such as a stent incorporating a magnetic tip for noncystoscopic retrieval (Magnetip by ACMI) and variable-diameter tapered stents for splinting after endopyelotomy have also been developed.

Another exciting area in stent development involves application of coatings onto stents in an effort to reduce friction,

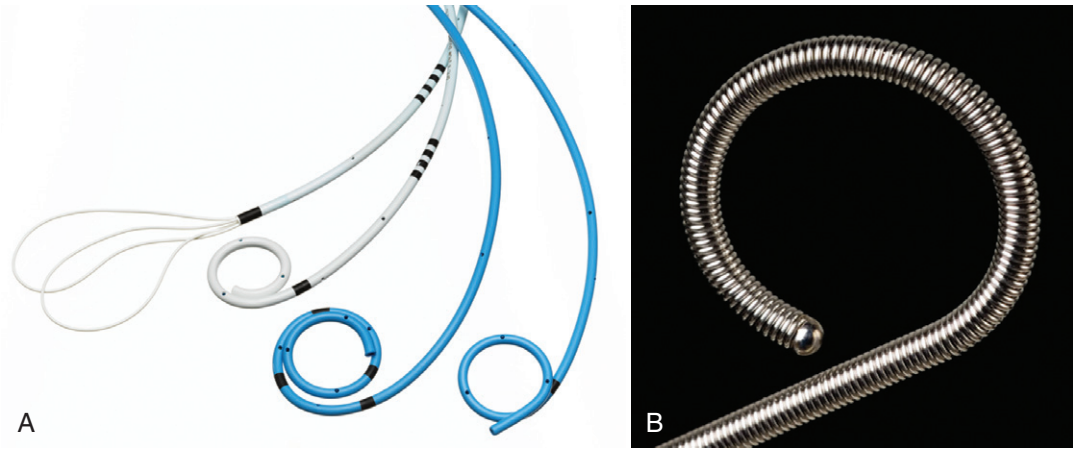


Figure 7–17. **A,** Types of ureteral stents. **B,** Metallic ureteral stent. (**A,** Courtesy of Boston Scientific Corporation, Natick, MA. **B,** Courtesy of Cook Urological, Spencer, IN.)

encrustation, bacterial biofilm formation, or patient discomfort. Various coatings have been successfully applied, albeit with varying degrees of clinical effectiveness.

A hydrogel coating made of a hydrophilic polymer film attached to the stent surface allows water absorption, increasing the elasticity and decreasing friction in an attempt to ease insertion and enhance patient comfort.

Bacterial oxalate decarboxylase, monomethoxy poly(ethyleneglycol)-3,4-dihydroxyphenylalanine (mPEG-$DOPA_3$), and diamond-like carbon coatings have all shown promising results in small trials to reduce encrustation or bacterial adherence both in vitro and in vivo (Watterson et al, 2003; Laube et al, 2007; Ko et al, 2008). Data on the use of heparin-coated stents have been conflicting. A recent in-vitro trial showed no difference in either bacterial adherence or biofilm formation (Lange et al, 2009), but small, uncontrolled clinical series (in total >20 patients) demonstrated a significant reduction in both encrustation and biofilm (Riedl et al, 2002; Tenke et al, 2004; Cauda et al, 2008). Additional clinical trials are necessary to fully validate these results. Stickler and colleagues (2002) have developed a phosphoryl-choline (PC)-coated stent in an attempt to mimic cell membrane lipids and to increase biocompatibility. In a 12-week trial involving 44 patients, the PC coating decreased encrustation by 14%, biofilm formation by 40%, and bacterial colonization by 17%.

Although the initial foray into stent coating development has failed to entirely eliminate the problems of stent discomfort and infections, the results have been encouraging enough to stimulate ongoing research in this area. Within the next decade it is likely we will see a number of products for clinical use using drug elution technology.

Stent Complications

Although ureteral stents play an essential role in various endourologic and open surgical procedures, the potential complications related to their use should not be underestimated. In one series, 32% of patients had their ureteral stents removed sooner than planned due to complications attributable to the stent (Ringel et al, 2000).

Stent Symptoms

From a patient perspective, stent morbidity can be significant. Lower urinary tract symptoms such as frequency, urgency, dysuria, and pain (flank or suprapubic) occur almost universally (Haleblian et al, 2008). More than 80% of patients experience stent-related pain affecting daily activities, 32% report sexual dysfunction, and 58% report reduced work capacity (Joshi et al, 2003).

The pathophysiology of these symptoms has not been completely elucidated, but it is most commonly believed that adverse stent symptoms are induced by bladder mucosal irritation due to contact by the distal curl of the stent, smooth muscle spasm, and reflux of urine resulting in flank pain.

The anatomic position of the stent curl has been shown to increase symptoms if it is located in a calyx or if it crosses the midline of the bladder (El Nahas et al, 2006). Rane and colleagues (2001) showed that an incomplete distal curl also increased discomfort. Stent composition does not seem to impact the incidence of symptoms with the currently available stent materials (Pryor et al, 1991).

Multiple pharmacologic approaches have been applied to stent symptoms such as oral anticholinergics, phenazopyridine, and standard analgesic medications (Norris et al, 2008). Intravesical instillation of ketorolac or oxybutynin decreased pain after stent insertion for up to 60 minutes when compared with placebo or to lidocaine (Beiko et al, 2004). The use of α_1-adrenoreceptor blockers (tamsulosin and alfuzosin) has demonstrated beneficial effects reducing stent symptoms and pain (Deliveliotis et al, 2006; Damiano et al, 2008).

Urinary Tract Infection

As with any implanted foreign body, stents are a potential target for bacterial colonization and a source of urinary infection. The duration of stent insertion is a significant risk factor with 6.8% of patients becoming infected and 20.5% developing stent colonization at 30 days versus 28.6% developing a UTI and 64.9% stent colonization after 90 days. Predisposing factors include chronic renal failure, diabetes, and female gender (Kehinde et al, 2002).

Migration

Stent migration is reported in 2% to 8% of patients and is usually related to a stent that was incorrectly sized for the patient's height (Breau and Norman, 2001). Jeon and colleagues (2007) have advocated for the determination of ureteral length measurement using a guidewire rather than patient height to more accurately allow stent length selection. Treatment for distal migration is reinsertion, and in the case of proximal migration the use of a ureteral dilation balloon (Chin and Denstedt, 1992) or ureteroscopy can be used to retrieve the stent.

Forgotten Stent

This is a source of considerable impact on patient well-being and a threat to renal function. Every effort should be made to counsel patients on the importance of returning for follow-up and stent removal. The establishment of a stent registry has also been described as a method of tracking patients in order to avoid the forgotten or neglected stent (Lynch et al, 2007).

Encrustation

Minor degrees of encrustation, particularly on the bladder curl, are not uncommon in many stented patients. More extensive encrustation often related to the forgotten/retained stent can be one of the most challenging tasks for the urologist requiring various endourologic interventions and on occasion open surgery. If left untreated, extreme degrees of encrustation may lead to compromise of the renal unit and even patient mortality (Walther et al, 1985; Singh et al, 2005).

The duration of indwelling time seems to affect the rate of stent encrustation with polyurethane stents (9.2% before 6 weeks, 47.5% in 6 to 12 weeks, and 76.3% after 12 weeks) (El-Faqih et al, 1991). An interesting observation, however, is that not all stents become encrusted, even after long indwell times. In a series of patients who had an indwelling stent for more than 1 year (mean 36 months), Park and colleagues (2004) found this occurred in only 33% of the stents. Reported risk factors are urinary tract infections (especially when involving urease-producing microorganisms) and pregnancy (Vanderbrink et al, 2008). Most manufacturers recommend that indwelling times should be limited to 4 months. Those at heightened risk of accelerated encrustation such as the pregnant patient should have their stents removed within 6 to 8 weeks (Aravantinos et al, 2006).

The discovery of the encrusted stent is often unsuspected until the withdrawal attempt is made and may be faced by the urologist in an office setting where fluoroscopy is not available. In this situation attempts to remove the stent are associated with resistance or even inability to pull the stent without causing severe pain to the patient. At this point no further traction should be attempted to avoid stent fragmentation, ureteral trauma, or even avulsion. Radiologic imaging, ideally with computed tomography (CT), must be arranged to assess the stone burden and proximal coil orientation. It has been our experience that often a kidney, ureter, bladder radiograph underestimates the degree of encrustation.

If no obvious encrustation is seen on CT, stent retrieval can be reattempted under fluoroscopic guidance. The distal end of the stent should be grasped and if possible exteriorized in an attempt to pass a guidewire through the stent lumen. This maneuver may allow straightening of the proximal coil, permitting stent removal.

If gross encrustation is present, additional treatment will be required. Depending on the sites of encrustation and the degree, single or multimodal approaches may be necessary. SWL has been successful for small-volume renal coil calcifications. PCNL for the larger proximal stone burdens is sometimes required. Cystolithotapaxy and ureteroscopy are used for mostly distally located encrustations. The holmium:YAG laser has been particularly useful in these settings. Renal function studies should be ordered in cases of severe gross encrustation. When renal function has been severely compromised, nephrectomy may be most appropriate.

Endourologic treatment either singly or in multiple stages ultimately succeeds in removing up to 85% to 97% of the stents (Bultitude et al, 2003; Gonzalez Ramirez et al, 2009).

Although chemolysis (Suby solution or hemiacidrin) has been reported as an alternative to invasive treatment of encrusted stents, Vanderbrink and colleagues (2008) suggest it should be reserved as a last resort measure due to its irritating effects on the urinary tract and potential electrolytic imbalances if systemic absorption occurs.

Nephrostomy Tube Drainage

The use of a percutaneously inserted nephrostomy tube for the direct drainage of a kidney was first described in 1955 by Goodwin and colleagues. The procedure remained relatively uncommon until 1976, when Fernström and Johansson purposely established a percutaneous tract for the removal of kidney calculi. With the popularity of PCNL, percutaneous nephrostomy access became a common technique in the endourologist's armamentarium.

Clinical situations occur when a ureteral stent may not provide adequate urinary drainage of the upper urinary tract. Nephrostomy tube (NT) insertion may be a more effective option. As a method of urinary tract drainage, it has been shown in several studies that NTs provide better urine flow in comparison with internal stents. Stented subjects experience both low- and high-pressure vesico-ureteral reflux (Ramsay et al, 1985; Fine et al, 1989; Hübner et al, 1992, 1993) and may not drain at all, especially in the setting of extrinsic ureteral compression (Docimo and Dewolf, 1989). Stents can induce deleterious physiologic and histologic effects on the ureter not observed with NTs. Ryan and colleagues (1994) showed elevated intrapelvic pressures and reduced or absent and ureteral peristalsis, increasing the time it took an artificial stone to traverse the length of the ureter from 3.4 days to 16 days in stented versus unstented ureters, respectively. Microscopic analysis showed collagen deposition and muscular hypertrophy in ureters that were stented.

Nephrostomy Tube Design

Nephrostomy tubes must accomplish the same tasks as standard urethral catheters, mainly to provide unimpaired kidney drainage while being able to remain within the renal cavities resisting accidental dislodging; however, there is also the need to place the catheter blindly through a surgically created tract, so guidance capability is necessary. Councill catheters are commonly used as NTs because they have the previously mentioned qualities. Other catheters used for NT drainage are modified Foley (by cutting an end hole) and Pezzer and Malecot catheters. The latter two have the advantage of having a larger lumen due to their lack of retention balloon tubing.

Re-entry catheters are designed to permit nephrostomy drainage while ensuring access to the ureter should this be necessary (Paul et al, 2003) (Fig. 7–18).

Both the Smith and Hulbert percutaneous endopyelotomy stents (Cook Medical) have a variable diameter starting at 10 to 22 Fr and gradually tapering to 8.2 to 4.7 Fr, distally ending with a pigtail curl. This configuration allows for splinting of the upper urinary tract after endopyelotomy or ureterotomy, while allowing percutaneous drainage/access.

Circle or U-loop NT designs are available to provide continuous irrigation or drug instillation into the kidney while ensuring drainage.

Indications

Short Term

One of the most common indications for acute nephrostomy tube insertion is to establish urinary tract drainage following a failed attempt at retrograde stent insertion. An inability to insert a retrograde stent may be due to several reasons including an impacted ureteral stone or malignant obstruction. In patients with high-grade bilateral ureteric obstruction or obstruction of a solitary renal unit leading to obstructive nephropathy and metabolic derangements, the ability to place the nephrostomy tube in a

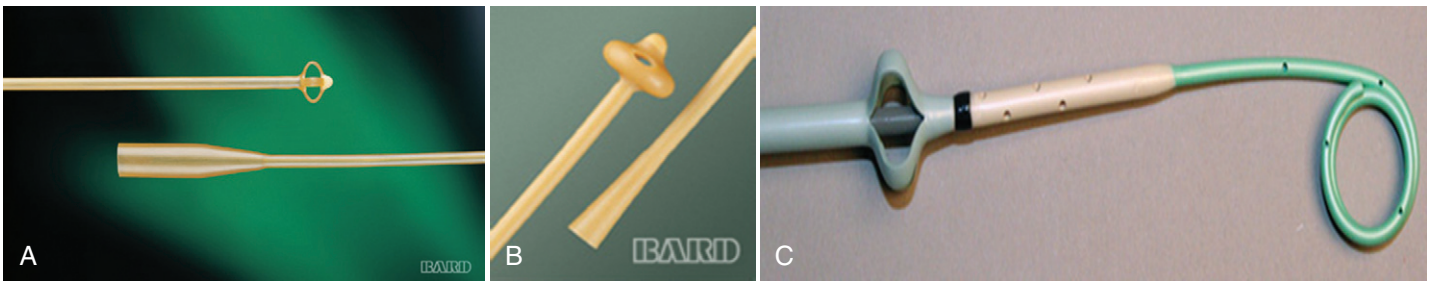


Figure 7–18. Types of nephrostomy catheters. **A** to **C**, Malecot, Pezzer, and Hulbert re-entry catheter.

radiology procedure room under local anesthesia may be the safest and most expeditious way to achieve upper tract drainage. Similarly, the patient presenting with urinary tract sepsis and hemodynamic instability may be a more appropriate candidate for urgent NT insertion rather than an attempt at ureteral stent placement in some circumstances and depending on the local logistics.

An NT is often placed as an adjunct to another procedure such as PCNL to aid hemostasis, drain purulent material or blood clots, and provide future renal access if necessary. Administration of therapeutic drugs (chemolysis, chemotherapy, or immunotherapy) in the context of renal calculi or upper urinary tract malignancy, respectively, is another well described use for an NT.

An NT can also serve a diagnostic role in the performance of the Whittaker test or contrast instillation to clarify complex anatomy (nephrostography).

The insertion of a nephrostomy tube at the completion of PCNL was long considered an essential step of the procedure until recently. Various authors have demonstrated NTs can be safely avoided in select patients (Karami et al, 2007; Shah et al, 2009).

Long Term

It is in the setting of palliative care and extrinsic obstruction where chronic NT tubes might have a significant role. Ku and colleagues (2004) compared NT versus ureteral stent in the setting of advanced extrinsic ureteral obstruction and found stents were exchanged more often than NTs and diversion failure was also more frequent with stents (11% vs. 1.3%). There was no difference in the rate of acute pyelonephritis; however, patient's self-perception and quality of life were better with the use of chronic NTs.

Complications

NT-related complications can occur at the time of obtaining initial renal access, and additionally those that occur as a result of the nephrostomy tube itself. It is estimated that the overall complication rate associated with NTs is approximately 8.8% to 10%.

Complications related to the access procedure include hematuria; clot colic; and pulmonary injuries (pneumothorax, empyema, hydrothorax or hemothorax), which may be as high as 8% to 12% with upper calyceal approaches and sepsis (1.3% to 2.2%). Rarer complications include injuries to nearby organs (liver, spleen, and bowel) and arteriovenous fistulas. The need for blood transfusion related to the NT insertion alone is reported to be as high as 3.2% in some series (Lewis and Patel, 2004; Wah et al, 2004; Hausegger and Portugaller, 2006).

Biofilm Formation on Urinary Tract Biomaterials

Despite a wide array of novel materials available for the manufacture of urinary catheters, no biomaterial used to date is able to withstand the effects of the urinary environment (Wollin et al, 1998). Biofilms and their related complications are a significant cause of morbidity in the urologic patient requiring a urinary drainage device and remain the most common cause of stent failure (Chew et al, 2006).

A biofilm is the microorganism's attempt to control its immediate environment by limiting exposure to harmful factors (waste products, antimicrobial agent, the host's immune response) while enhancing the exposure to trophic factors. The organisms residing in the biofilm can also undergo other adaptative changes such as metabolic dormancy, which may lead to increased antibiotic resistance (Fujiwara et al, 1998; Donlan, 2003). The structure of a biofilm is complex, usually consisting of three layers: the innermost or linking film that is attached to the surface of the tissue or biomaterial, a base film that contains the attached microorganisms, and the outermost layer called the surface film that can be used as a point of access/egress for planktonic organisms (Beiko et al, 2004).

Biofilm structure and the bacterium residing within it behave more like a tissue of a higher organism (Costerton et al, 1995). It has been shown that bacteria within the biofilm can "communicate" with one another and initiate cell dispersal and detachment (Davies et al, 1998). The size of the biofilm can range from a few isolated monolayers to 400 cells deep, effectively covering the complete luminal area of a catheter and reaching a population of up to 5×10^9 colony-forming units (Ganderton et al, 1992).

The initial step in biofilm genesis is the deposition of a layer of urine constituents (proteins, electrolytes, and organic molecules) called a conditioning film. This step usually occurs within minutes after the device has been implanted (Tieszer et al, 1998; Wollin et al, 1998) and modifies the surface of the biomaterial by providing or blocking possible receptor sites for uropathogens. The next step in biofilm formation is microbial adhesion to the surface of the biomaterial, a process influenced by multiple physical properties such as electrostatic and hydrophobic interactions, ionic forces, osmolality and urinary pH (Gristina, 1987; Pratt-Terpstra et al, 1989; Uyen et al, 1989; Printzen, 1996; Reid et al, 1996, 1999). Following this event, the organism undergoes cell division, forming microcolonies that develop inside a matrix of bacterial exopolysaccharide and glycocalix. Once this point is reached, biofilm eradication is usually not possible with anything less than the removal of the involved biomaterial.

Biofilm formation in some cases is a preliminary step to biomaterial encrustation. Urease-producing bacteria cause an increase in urinary pH and, once attached to the biofilm, lead to the precipitation of magnesium and calcium, forming struvite encrustations across the surface (Sofer and Denstedt, 2000).

Thus the development of a biofilm-resistant stent has to achieve success over several factors: a large number of bacterial species able to cause stent-related infections, deposition of host urinary conditioning films that coat and negate the effects of a desirable surface or coating or both, and the microorganism's ability to destroy and exclude host protection factors and antibiotics and to remain metabolically dormant (Denstedt and Cadieux, 2009).

Without question, the future of urinary catheter development requires a better understanding of biofilm formation and ways to avoid their occurrence. This knowledge along with improvements in biomaterials and in drug elution technology will pave the way for the next evolution in urologic device development.

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chapter
8

Principles of Endoscopy

Branden Duffey, DO ● Manoj Monga, MD, FACS

Equipment
Cystourethroscopy
Upper Urinary Tract Endoscopy
Patient Preparation

The purpose of this chapter is to introduce the basic principles of endoscopy as they relate to retrograde instrumentation and visualization of both the lower and the upper urinary tract. In addition to discussing strategies for both routine and difficult retrograde access, emphasis is placed on patient positioning and preparation, basic equipment, and ancillary instrumentation required for both cystourethroscopy and ureteropyeloscopy. In-depth discussion of treatment strategies for specific pathologic processes is beyond the scope of this chapter and the reader is directed to specific chapters throughout this text.

EQUIPMENT

Retrograde visualization of the urinary tract is a routine part of the urologist's practice and may be performed in a variety of settings. Straightforward procedures (i.e., cystoscopy with minimal intervention) may be performed in the office setting and requires only an endoscope, light source, and irrigating fluid. The urologist views the procedure through the optical eyepiece at the proximal end of the instrument. Either xenon or halogen external light sources deliver cool light to the endoscope through a fiberoptic cable. Typical irrigation fluids include sterile water, glycine, or normal saline. If electrocautery use is anticipated, a solution free of electrolytes should be used. Video-endoscopic units, comprising a light source, camera for the endoscope, image processor and recorder, and monitor, are usually arranged on a mobile tower and commonly found in both the office and operating room settings (Fig. 8–1). Images are transmitted to the image processor by a camera attached to the eyepiece and displayed on a viewing monitor. In the case of digital endoscopes there is no eyepiece and the image is sent directly to the image processor. In both cases, still images and live sequences can be transferred to a recording device for incorporation into the medical record, postprocedure review, and patient education. Video-endoscopic units are advantageous in that they (1) avoid surgeon contact with bodily fluids; (2) may facilitate more ergonomic surgeon positioning during the procedure; (3) enhance the teaching of endourologic skills; and (4) may decrease discomfort in male patients during cystoscopy performed using local anesthesia (Patel et al, 2007). Light source modifications, specifically narrow band imaging and porphyrin-based fluorescence, have been developed in efforts to improve the detection of urothelial carcinoma during endoscopy. Narrow band imaging technology filters white light into two separate bands (415 nm and 540 nm) that are absorbed by hemoglobin, which aids in the detection of hypervascular urothelial neoplasia (Herr and Donat, 2008). In fluorescence-based endoscopy, a solution of 5-aminolevulinic acid or hexaminolevulinate is instilled in the bladder and then inspected with blue light (wavelength 380 to 450 nm). These substances aid in tumor detection because they are converted to porphyrins that preferentially accumulate in neoplastic cells and fluoresce red when illuminated with blue light (Kriegmair et al, 1996). Urology-specific endoscopy suites are found in the operating room and generally have full video capabilities in addition to fluoroscopy provided by either a mobile C-arm or endoscopy table. Fluoroscopy is used to perform retrograde pyelography and ureteral stenting and to localize endoscopes and instruments during the procedure. It is imperative that operating room personnel minimize radiation exposure by wearing leaded aprons, thyroid shields, and eyewear.

CYSTOURETHROSCOPY

Indications

Cystourethroscopy is used to directly visualize the anterior urethra, posterior urethra, and the bladder. One of the most common indications for cystourethroscopy is the evaluation of microscopic and gross hematuria. Other indications for cystourethroscopy include evaluation of voiding symptoms, surveillance of urothelial carcinoma, foreign body removal, and assisting in difficult placement of a catheter. Although its primary use is in the diagnosis and treatment of lower urinary tract disorders, it is also used to access the upper urinary tract for both diagnostic and therapeutic interventions.

Specific to the lower urinary tract, cystourethroscopy is an adjunctive procedure that permits macroscopic visualization that may be correlated with signs and symptoms of lower urinary tract pathologic processes. Additionally, fluid and tissue specimens may be obtained for cytologic and histologic evaluation.

The upper urinary tract may be accessed using cystoscopic techniques. Diagnostic evaluation of the upper urinary tract is accomplished by selective intubation of the ureteral orifices and retrograde instillation of contrast material. Ureteral catheters and brushes can be passed into the upper urinary tract to obtain specimens for cytologic and histologic evaluation. In cases of upper tract obstruction, ureteral stents are often placed with cystoscopic assistance. Fluoroscopy is utilized in many, if not all, of these retrograde interventions.



Figure 8–1. Video-endoscopic unit consisting of a portable cart, monitor, light source, image processor, video-recording device, and printer.

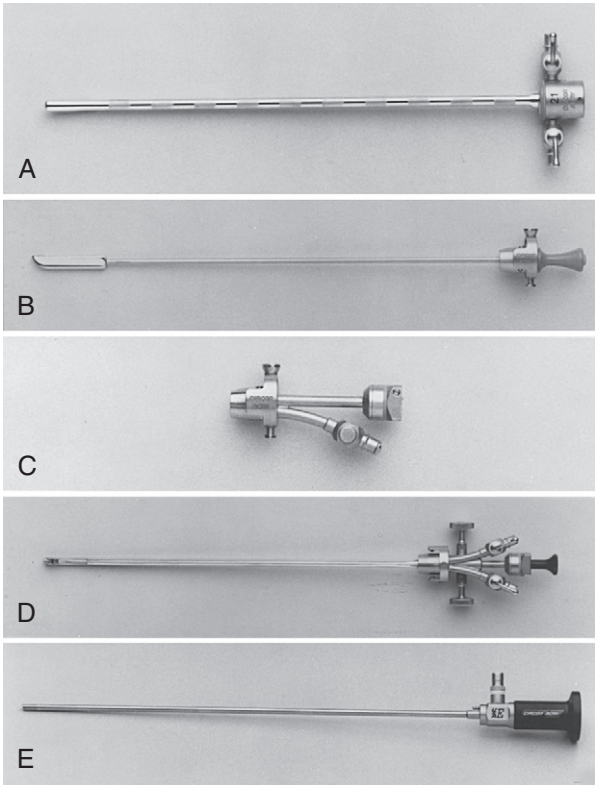


Figure 8–2. Rigid cystoscope consists of metal sheath to which a water source is attached (**A**); obturator (**B**); bridge (**C**); deflector system (Alberran lever) (**D**); and lens to which a light source is attached (**E**). (**A** to **E,** Courtesy of Circon Corp., Santa Barbara, CA.)

Equipment

Cystourethroscopy may be accomplished using either a rigid or flexible endoscope. Both of these instruments allow for thorough endoscopy and access to the upper urinary tract but have specific advantages that may direct their use depending on the clinical situation. Rigid endoscopes are of benefit in that (1) the rod-lens optical system allows for improved image quality compared with the fiberoptic system utilized in flexible endoscopes; (2) a larger working channel allows passage of a wider variety of instruments; (3) the larger lumen allows for improved irrigant flow and thus visualization; (4) they are easier to manipulate and orient during endoscopy; and (5) they are easier to stabilize with one hand, which allows the surgeon's second hand to manipulate accessory instruments through the working channel. Advantages of the flexible cystourethroscope include (1) improved patient comfort; (2) increased options for patient positioning; (3) ease in passage over an elevated bladder neck or median lobe; and (4) the ability to deflect the endoscope tip in any direction, permitting full inspection of the bladder.

Endoscope sizes are expressed using the French (Fr) scale and refer to the outer circumference in millimeters. Pediatric endoscopes are generally 8 to 12 Fr whereas adult scopes range from 16 to 25 Fr. The size of the endoscope selected will depend on the specific procedure performed, the need for additional working instruments, and the degree of irrigant flow that will be required, but in general the smallest diameter endoscope that will accomplish the goals of the procedure is selected to minimize genitourinary tract trauma.

Rigid cystourethroscopes require assembly before use and are composed of a sheath, obturator, bridge, and optical telescopic lens (Fig. 8–2). Markings on the sheath indicate the endoscope size as well as the maximum size of a single instrument or two instruments (as in the case of a bridge with two working channels) the endoscope will accept (Fig. 8–3). Irrigant is instilled through tubing that is attached to the sheath. Obturators are inserted into the working sheath to provide a smooth blunt surface during endoscope passage. Typically, an obturator will be employed for insertion of the rigid cystoscope in females whereas direct visualization will be utilized for cystoscope insertion in males. The

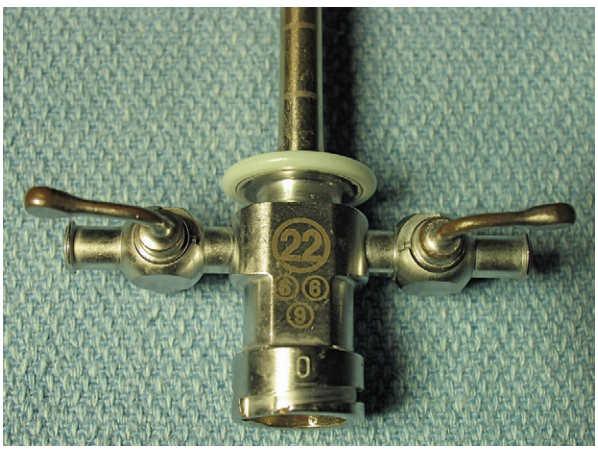


Figure 8–3. Markings on a rigid cystoscope sheath. The largest number indicates the outer diameter (22 Fr). The smaller numbers below indicate the size of the two largest simultaneous instruments (6 Fr) or single largest instrument (9 Fr) that may be passed through the sheath.

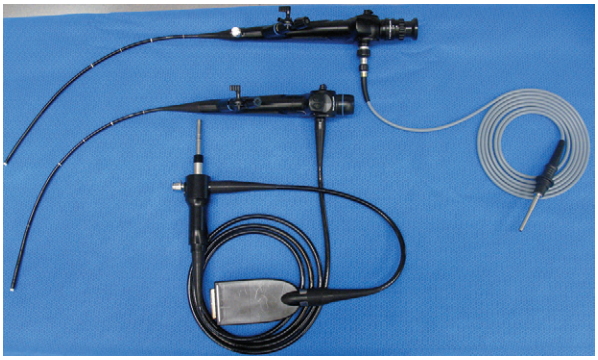


Figure 8–4. Flexible cystoscopes with an attached light source and flexible tips. Imaging systems in flexible cystoscopes are either fiberoptic *(top)* or digital *(bottom)*.

bridge is attached to the sheath and may have one or two working channels, facilitating the passage of instruments into the endoscope. The Albarran bridge enables the urologist to deflect catheters and wires placed through the working channel by manipulating a lever attached to the bridge. The telescopic lens is attached to the sheath by means of the bridge. The light source cable is connected to the telescope.

Telescopes used in rigid cystoscopy utilize a rod-lens system. The telescope's metal shaft contains a series of cylindrical lenses with air interfaces that transmit both light to the object to be viewed and the image to the eyepiece. Telescopes are available with different angled tips to enhance viewing of specific structures. Urethroscopy is best accomplished with a 0-degree or 12-degree lens providing a straight-ahead view. In the bladder, a 30-degree lens is commonly used and provides excellent visualization of the trigone, dome, and posterior and lateral walls. Telescopes with a 70-degree lens provide better visualization of the anterior wall, dome, and inferior lateral walls. Telescopes with a 120-degree lens are utilized for inspection of the bladder neck.

Flexible cystourethroscopes are available in fiberoptic and digital models (Fig. 8–4). Traditional flexible endoscopes contain fiberoptic bundles within a flexible shaft that illuminate the viewing area and transmit images to the eyepiece. The tip of the endoscope may be deflected up to 210 degrees by a lever near the eye piece. The endoscope shaft has a channel that is shared for irrigation and the passage of working instruments. Recent advances in solid-state camera chips have facilitated the development of digital cystourethroscopes. In these models an imaging chip is placed at the distal end of the endoscope that converts light into an electrical charge that is eventually displayed on a viewing screen. Digital systems are advantageous because they have higher optical resolution, contrast, and color differentiation; in many centers digital systems have replaced fragile fiberoptic systems, which are prone to breakage (Quayle et al, 2005; Borin et al, 2006). However, the durability of digital scopes has yet to be established.

Patient Preparation

Before performing cystourethroscopy it is important to ensure the patient does not have a urinary tract infection, because mechanical manipulation and bladder distention can exacerbate the infection. Informed consent should be obtained after explaining the procedure, its purpose, and the associated risks and benefits. **Antimicrobial prophylaxis is not recommended before simple cystourethroscopy unless patient risk factors are present** (Table 8–1) (Wolf et al, 2008). **When risk factors are present or additional manipulation (e.g., bladder biopsy, ureteral catheterization) is anticipated, prophylactic antibiotics should be administered before the procedure with an expected treatment duration of 24 hours or less.** Antimicrobial agents of choice in these situations are the fluoroquinolones and trimethoprim-sulfamethoxazole. The patient is placed in the dorsal lithotomy position for rigid cystourethroscopy or the supine position for flexible cystourethroscopy (with a slight frog-leg position for females) and prepped and draped sterilely.

Table 8–1.

Patient Risk Factors Precluding Simple Cystoscopy Without Antimicrobial Prophylaxis

Advanced age
Anatomic anomalies of the urinary tract
Poor nutritional status
Smoking
Chronic corticosteroid use
Immunodeficiency
Externalized catheters
Colonized endogenous/exogenous material
Distant coexistent infection
Prolonged hospitalization

Preoperative intraurethral injection of a water-soluble lubricant-anesthetic is often used in an attempt to provide greater patient comfort and enable the surgeon to access the upper urinary tract and perform bladder and urethral biopsies as well as bladder fulguration. In male patients a urethral clamp may be used to retain the urethral anesthetic, allowing for prolonged direct contact with the urethral mucosal surfaces before instrumentation. Goldfischer and colleagues (1997) found that 30 mL of intraurethral lidocaine gel left to dwell for 20 minutes before rigid cystoscopy significantly reduced procedure-related pain in men but not women. Most randomized prospective placebo-controlled studies of flexible cystoscopy conclude that lubricant-anesthetic instillation does not decrease patient discomfort (Patel et al, 2008b).

Several strategies have been evaluated to improve patient comfort and tolerance during cystourethroscopy. Positioning the video monitor so the patient and surgeon can simultaneously view the procedure may be beneficial in male patients but not females (Patel et al, 2007, 2008a). A real-time explanation of the procedure may decrease patient anxiety and discomfort. Specifically, male patients are reassured and counseled that discomfort will be encountered in the membranous and prostatic urethra; they are informed that the length of this segment is 2 to 5 cm, and they are encouraged to relax their pelvic muscles during this portion of the examination to facilitate scope passage (Taghizadeh et al, 2006).

Technique

Before cystourethroscopy the urethral meatus should be inspected. If it is not large enough to permit passage of the endoscope, sequential dilation may be performed using well-lubricated metal sounds. Once the urethral meatus is large enough to permit passage of the endoscope, the sheath should be generously lubricated and a survey of lower urinary tract anatomy is performed.

In males the glans is grasped and the penis held on stretch at 90-degree angle to the abdominal wall during visualization of the



Figure 8–5. When performing flexible cystoscopy the distal penis is grasped between the surgeons third and fourth fingers. This allows the penis to be placed on continuous gentle stretch while the thumb and index finger guide the cystoscope into the urethral meatus.

fossa navicularis, penile urethra, and bulbar urethra. For flexible cystoscopy, the glans is held on stretch between the third and fourth digits, allowing the thumb and forefinger to remain free to guide the endoscope through the urethra (Fig. 8–5). The cystourethroscope tip is inserted and the irrigant turned on, distending the urethra to allow for clear visualization. Periurethral glands of Littre are noted as they enter the urethra dorsally. Strictures may be encountered that require dilation (see Chapter 7) or visual internal urethrotomy (see Chapter 36). The membranous urethra is identified by its striated mucosa and may visibly contract. As the membranous urethra is traversed, the cystourethroscope must be directed anteriorly to navigate the transition from the proximal bulbar urethra to the membranous urethra and into the prostatic urethra. As the distal prostatic urethra is entered, the verumontanum is identified posteriorly. Prostate length, the lateral lobes, and the median lobe are evaluated as the cystourethroscope continues its passage to the bladder. Additional anterior angulation may be necessary to elevate the endoscope over the bladder neck and pass into the bladder.

In females the urethral meatus is visually inspected and then cystoscopy is performed by inserting the cystourethroscope and directing it cephalad and anterior. For rigid cystoscopy, it is our preference in most cases to bluntly cannulate the female urethra with an obturator in the sheath and perform urethroscopy while withdrawing the cystourethroscope.

Once the bladder is entered it should be systematically surveyed and the observations recorded. A 30-degree telescope is generally used for initial inspection. The trigone and interureteric ridge are identified just inside the bladder neck. The ureteral orifices, located at the lateral most aspects of the interureteric ridge, should be evaluated for location, number, and the efflux of urine. The floor and posterior wall of the bladder are evaluated next. Systematic inspection of the dome, anterior wall, and lateral walls is performed by rotation of the cystoscope to redirect the 30-degree lens, or with the assistance of a 70-degree telescope, using the air bubble at the dome as a landmark. The anterior wall just beyond the bladder neck is best evaluated using the 70-degree telescope in the partially filled bladder and applying manual suprapubic pressure to bring it into view. After thorough inspection of the bladder and urethra, the bladder is drained and the instrument removed.

Special Considerations

Suprapubic Tubes

Patients with urinary drainage from a suprapubic catheter deserve special mention based on the additional clinical scenarios and technical aspects associated with evaluation of the lower urinary tract. Indications for cystourethroscopy are the same as described earlier but also include regular inspection for bladder stones and surveillance for bladder tumors in patients with suprapubic catheters longer than 5 to 10 years (Kaufman et al, 1977; DeVivo et al, 1985; Hess et al, 2003; Subramonian et al, 2004). Endoscopy may be performed per urethra (when patent) or through the suprapubic tract. Navigation and visualization of the suprapubic tract is usually straightforward in patients with normal body habitus and a mature urinary tract. Conversely, immature urinary tracts or those traversing a large mobile pannus may be difficult to follow. When these situations occur, it is helpful to place a wire through the suprapubic tract into the urinary bladder to guide the endoscope during inspection. The wire can be backloaded into the working channel to further guide the endoscope. Rigid cystoscopes may fit into large mature urinary tracts and are advantageous when ancillary procedures are indicated, but they may be difficult to maneuver in long urinary tracts and orientation in the bladder can be challenging. Flexible cystoscopes offer improved maneuverability and may fit into smaller urinary tracts. For prolonged endoscopic procedures, continuous irrigation can be facilitated by endoscopy through the urinary tract with simultaneous drainage of irrigation through the urethra or vice versa. Identification of the ureteral orifices may be challenging owing to edema related to the indwelling catheter or to the angle of vision through the tract. This may be overcome by the use of a flexible cystoscope to visualize the efflux of urine after administration of intravenous indigo carmine or methylene blue.

Continent Urinary Diversions

Continent urinary diversion is a common urinary reconstructive technique used after cystectomy. Diversions can be broadly categorized as cutaneous continent diversions or orthotopic diversions. In cutaneous continent urinary diversions, detubularized bowel is arranged to create a urinary reservoir with a catheterizable limb anastomosed to the umbilicus or another site on the abdominal wall that provides access for drainage. In orthotopic diversions the urinary reservoir is anastomosed to the urethra, allowing for volitional voiding. Detailed understanding of the diversion construction is crucial before any endoscopic intervention. Key elements include the type and location of the ureteroenteric anastomosis, the presence or absence of an afferent limb, and the continence mechanism employed. Many neobladders have an afferent limb extending from the reservoir to which the ureters are anastomosed. In orthotopic neobladders the continence mechanism is the external urinary sphincter. Typical continence mechanisms in cutaneous catheterizable diversions include the tunneled appendix (Mitrofanoff), the tapered/imbricated terminal ileum and ileocecal valve, and the intussuscepted nipple valve (see Chapter 86). The Mitrofanoff and tapered/imbricated ileal continence mechanisms are fragile, and aggressive manipulation can lead to stomal stenosis and/or loss of urinary continence.

In these cases, simple visualization and reservoir filling through the catheterizable channel may be performed with small caliber flexible endoscopes (e.g., a flexible ureteroscope), but if ancillary procedures are indicated, percutaneous access should be used (Patel and Bellman, 1995). Similarly, percutaneous access

Key Points: Cystourethroscopy

- Endoscope sizes are expressed using the French (Fr) scale and refer to the outer circumference in millimeters.
- In general the smallest diameter endoscope that will accomplish the goals of the procedure is selected to minimize genitourinary tract trauma.
- Antimicrobial prophylaxis is not recommended before simple cystourethroscopy unless patient risk factors are present.
- A prophylactic antimicrobial agent should be administered before cystoscopy with anticipated additional manipulation (e.g., biopsy, fulguration, ureteral catheterization) and simple cystoscopy in patients with risk factors.

for interventions other than simple diagnostic procedures in orthotopic neobladders may avoid the risk of bladder neck contracture or sphincteric damage. In both types of diversions, orientation and visualization can be impaired by mucus and debris, bowel peristalsis, mucosal folding, and tortuous afferent limbs. Steps to overcome these difficulties include thorough irrigation and use of fluoroscopy with intravesical administration of a contrast agent to identify the os of the afferent limb and guide endoscope advancement. When present, afferent limbs are best visualized with flexible endoscopes because they are best suited to navigate limb folding, kinking, and tortuosity.

UPPER URINARY TRACT ENDOSCOPY

Indications

Ureteroscopy is a standard urologic technique that provides direct visualization of the upper urinary tract, facilitating both diagnostic and therapeutic interventions. Ureteroscopy is most commonly used for the treatment of nephrolithiasis (see Chapter 48). Other common indications include evaluation of lateralizing hematuria, abnormal urinary cytology, and abnormal upper tract imaging studies. Surveillance and treatment of upper tract urothelial carcinoma may be performed using ureteroscopic techniques (see Chapter 53). Ureteroscopy may also be utilized in cases of ureteral stricture and ureteropelvic junction obstruction (see Chapter 41).

Equipment

Ureteroscopes

Ureteroscopes are available as flexible or semirigid instruments. Semirigid ureteroscopes have a shaft that is able to accommodate a small amount of bend and typically have a tapered distal tip (6.0 to 7.5 Fr) that gradually widens toward the eyepiece (8.0 to 9.5 Fr). The metal shaft contains fiberoptic bundles for light and image transmission as well as an irrigation channel and one or more working channels (2.4 to 4.0 Fr) for the passage of instruments. A digital semirigid ureteroscope based on a charge-coupled device (CCD) video-chip technology has been released by Olympus (Center Valley, PA). The clinical benefit of digital semirigid ureteroscopy has yet to be determined because the potential improvement in visualization is accompanied by an increase in the distal tip diameter that may impair ureteral intubation. Compared with their flexible counterparts, semirigid ureteroscopes offer larger irrigation channels, improved irrigant flow and visualization, and generally a larger field of view. **Semirigid ureteroscopy is typically used for diagnosis and treatment of pathologic processes below the iliac vessels.** In female patients the semirigid endoscope can frequently be passed safely into the proximal ureter, but this is less common in males. In males, a longer urethral length, a relatively immobile prostatic urethra, and more developed psoas muscles make semirigid ureteroscope navigation past the iliac vessels difficult. Caution should be exercised when performing semirigid ureteroscopy in the proximal ureter because the shaft can accommodate some flexion but may bend or even fracture as the shaft fatigues.

Flexible ureteroscopes contain imaging systems and working channels within a flexible shaft that allows for complete visualization of the entire upper urinary tract including the lower pole of the kidney. Flexible ureteroscopy is typically used for the diagnosis and treatment of pathologic processes above the level of the iliac vessels. Flexible ureteroscopy in the more distal portions of the ureter may be challenging owing to the inherent flexible nature of the instrument (lack of rigidity) and difficulty stabilizing the distal portion of the instrument.

Table 8–2 lists some of the currently available flexible ureteroscopes. The distal tip of these endoscopes ranges from 5.3 to 8.7 Fr and gradually tapers toward the proximal shaft. Active deflection of the distal tip typically ranges from 130 to 250 degrees in one direction and 160 to 275 degrees in the other, with newer flexible ureteroscopes having exaggerated primary deflection that allows

Table 8–2.

Characteristics of Available Flexible Ureteroscopes

	GYRUS-ACMI DUR 8	GYRUS-ACMI DUR 8 ELITE	GYRUS-ACMI DUR D	OLYMPUS URF-V	OLYMPUS URF-5	WOLF 7325.071	KARL STORZ FLEX-X^2
Tip size (Fr)	6.8	6.8	8.7	8.5	5.3	6	7.5
Shaft size (Fr)	10.1	10.1	9.3	9.6	8.4	8.8	8.5
Working channel (Fr)	3.6	3.6	3.6	3.6	3.6	3.6	3.6
Working length (cm)	65	64	65	67	70	68	67
Field of view (degrees)	80	80	80	90	90	85	88
Active tip deflection (degrees)	170/180	170/180 primary 130 active secondary	250/250 Digital optical system	180/275 Digital optical system	180/275	270/270	270/270

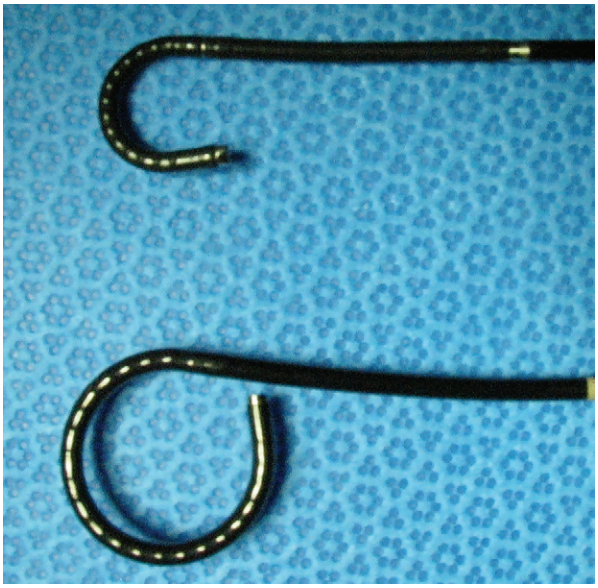


Figure 8–6. Flexible ureteroscopes with standard primary deflection *(above)* and exaggerated primary deflection *(below)*.

for improved visualization of the lower pole and increased ease of manipulation (Fig. 8–6) (Monga et al, 2007). Secondary active deflection, available in the DUR-8 Elite (Gyrus-ACMI, Southborough, MA) and the Stryker Flexvision (Stryker Endoscopy, San Jose, CA), refers to a segment of active deflection several centimeters proximal to the area of primary deflection that, when activated by a second hand-piece lever, provides an additional 130 degrees of visualization and facilitates entry into the lower pole calyx. Passage of working instruments (e.g., lasers, baskets) tends to increase the stiffness of the ureteroscope shaft, reduce maximal deflection, and decrease irrigation flow through the shared 3.6-Fr channel (Abdelshehid et al, 2005; Bach et al, 2008; Paffen et al, 2008). Imaging systems in flexible ureteroscopes are either traditional fiberoptic systems or digital, based on CCD or complementary metal–oxide–semiconductor (CMOS) technology. Preliminary clinical experience suggests that digital ureteroscopes offer improved optical resolution compared with their fiberoptic counterparts (Traxer et al, 2007). Technologic advancements in flexible ureteroscopes have enabled reductions in shaft diameter, improved visualization, and provided a greater range of deflection, but they remain fragile instruments with significant purchase and repair costs (Chiu et al, 2004; Sung et al, 2005; Monga et al, 2006).

Ancillary Equipment

Wires. Guidewires used during retrograde instrumentation serve to provide access to a particular area of the urinary tract and serve as a guide to pass catheters, stents, and sheaths (Clayman et al, 2004; Liguori et al, 2008). Guidewire properties vary with respect to length, diameter, composition, tip design, surface coating, and shaft rigidity. Guidewire diameters and lengths range from 0.018 to 0.038 inch and 145 to 280 cm, respectively. The ideal guidewire should have a flexible lubricous tip allowing for easy atraumatic passage through a tortuous, obstructed ureter while providing sufficient rigidity of the shaft for the passage of catheters and instruments. The physical properties and design of the various wires lend to their use in different situations.

Basic guidewire composition consists of an inner core that determines shaft rigidity and an outer covering responsible for low resistance passage through the ureter. The outer surface, designed to reduce friction during passage, is typically coated with either a polytetrafluoroethylene (PTFE)-jacketed tightly coiled stainless steel spring or a hydrophilic polymer. The distal tip is a 3- to 15-cm section designed to be flexible and soft, minimizing tissue trauma during passage. Distal tips may be straight or angled and may be coated with a hydrophilic polymer. The PTFE-coated floppy tipped Bentson-type wire is a typical general purpose guidewire. Hydrophilic polymer coated wires are excellent for maneuvering in a tortuous ureter and around impacted ureteral calculi but often lack sufficient rigidity for the passage of catheters or stents and may migrate out of the ureter during manipulation. Extra-stiff wires with a stainless steel core add increased shaft rigidity (resistance to kinking) and are commonly utilized for passage of ureteral access sheaths, catheters, and coaxial or balloon ureteral dilators. Hybrid wires, such as the Sensor (Boston Scientific, Natick, MA), combine a hydrophilic tip for ease of passage with a PTFE-coated nickel-titanium (nitinol) shaft for increased stiffness to facilitate coaxial placement of stents or sheaths.

Flexible ureteroscope passage may be facilitated by backloading it over a wire and passing it into the ureter under visual or fluoroscopic guidance. Passage over an extra-stiff wire can lead to working channel damage and costly repairs (Vanlangendonck and Landman, 2004). Dual floppy-tip wires have a softer proximal tip and may reduce working channel damage.

Ureteral Dilators. Ureteral dilation is utilized in the treatment of strictures and to facilitate ureteroscopy. **Ureteral dilation is most commonly required at the ureterovesical junction, the narrowest portion of the ureter, to permit ureteroscope passage.** Dilation may be needed more proximally in cases of benign, malignant, or iatrogenic strictures. Coaxial dilation may be accomplished by passing successively larger tapered polyethylene catheters; however, this may be associated with significant shearing forces and ureteral injury (Ford et al, 1984; Gaylis et al, 2000). **Balloon dilators** exert radial force on a specific ureteral segment through 4- to 7-Fr catheters passed over a wire with inflatable balloons ranging from 4 to 10 cm in length, have a 4- to 10-mm outer diameter, and can exert pressures up to 20 atm (Hendlin et al, 2005). In-vitro testing can predict which balloons will function the best if presented with tight radial constriction (Hendlin et al, 2005). Typically, a retrograde pyelogram is first performed to delineate the area of narrowing. With the use of fluoroscopy the radiopaque markers at the proximal and distal ends of the balloon are placed across the area needing treatment. Then, an assistant fills the balloon with a contrast agent using a pressurizing system while the surgeon stabilizes it to prevent inadvertent migration.

Older, larger-diameter ureteroscopes routinely required ureteral dilation for successful passage into the upper tract. **Technologic advancements in the field of endoscopy have facilitated the miniaturization of endoscopes and eliminated the need for ureteral dilation in routine cases** (Rodrigues et al, 1990; Stoller et al, 1992; Harmon et al, 1997). **Ureteral dilation is not necessary in every ureteroscopic intervention and should be performed only when ureteroscope passage is impaired.**

Irrigation Systems. Irrigation during ureteroscopy is essential to maintain a clear visual field by displacing stone fragments, blood, and cellular debris and by distending the luminal structure under inspection. Irrigation systems either are gravity dependent (passive) or are driven by a hand or foot pump (active). Passive system irrigation systems provide the least amount of impulse, which may prevent stone migration, but are limited in the ability to provide enough force necessary for specific intraoperative conditions

(Hendlin et al, 2008). Gravity irrigation alone may not provide sufficient flow to clear the visual field while instruments are in the working channel (Abdel Razzak and Bagley, 1994; Chiu et al, 2003). Active hand irrigation can generate renal pressures of 100 mm Hg or more (Auge et al, 2004a). Although active irrigation systems allow for finer control of the amount and force of irrigation used, they generate higher pressures, which can lead to stone migration, bleeding from hydrodistention, and pyelolymphatic or pyelovenous fluid absorption. **Care should be taken to use only as much irrigation needed to provide a clear visual field.** Ureteral access sheaths may be used to decrease renal pressures during ureteroscopy (Auge et al, 2004a). Irrigants used are typically physiologic solutions (i.e., normal saline). However, with a ureteral access sheath in place, fluid absorption is low (estimated to be 1 mL/min of ureteroscopy) and may permit the use of alternative irrigants (i.e., water) that improve light transmission and visibility (Cybulski et al, 2004a). Studies utilizing water for ureteroscopy have focused on short (<1 hour), uncomplicated procedures. Pharmacologic adjuvants have recently been evaluated as a way to further decrease intraluminal pressure through ureteropelvic relaxation during ureteroscopy. In-vitro and in-vivo studies have shown that catecholamines, calcium channel blockers, and a potassium channel opener (PKF 217–744b) relax ureteral smooth musculature (Selmy et al, 1994; Weiss et al, 2002; Holst et al, 2005; Jung et al, 2008). Future research is required to determine if the addition of a muscle relaxant drug to the irrigation fluid is a practical idea to facilitate a safer endoscopic procedure.

Ureteral Access Sheaths. The ureteral access sheath was initially developed in the 1970s to facilitate insertion of flexible ureteroscopes (Takayasu and Aso, 1974). These sheaths are placed over a wire, consist of an outer sheath and a tapered dilating obturator, are frequently coated with hydrophilic polymers for easier insertion, and range in outer diameter and length from 9 to 18 Fr and 20 to 55 cm, respectively (Fig. 8–7).

Ureteral access sheaths have been shown to significantly reduce renal pressures during ureteroscopy, functioning as an open conduit into to the kidney, allowing fluid to enter through the endoscope and exit through the sheath around the scope (Landman et al, 2002; Rehman et al, 2003; Auge et al, 2004a). **Shorter operative times and reduced costs have been demonstrated when ureteral access sheaths are utilized during ureteroscopy.** Use of these sheaths during ureteroscopy provides direct visualization of ureteroscope insertion and simple reentry and facilitates ureteroscopic basketing and retrieval of calculi that would otherwise require lithotripsy into smaller fragments able to pass spontaneously (Kourambas et al, 2001; Monga et al, 2001). Ureteral access sheaths decrease endoscope damage and prolong the period between servicing by reducing both axial forces on the ureteroscope and working channel trauma from repetitive backloading over a wire (Pietrow et al, 2002). Kourambas and associates (2001) noted decreased postoperative symptoms when a ureteral access sheath was used for ureteral dilation when compared with balloon dilation.



Figure 8–7. The distal *(top)* and proximal *(bottom)* portions of a typical ureteral access sheath. The distal portion of the internal obturator *(blue)* is tapered, gradually widening to meet the hydrophilic sheath. The access sheath is placed over a super-stiff guidewire and the internal obturator is removed before ureteroscope insertion. The proximal end of the obturator accepts a Luer-Lok syringe, facilitating retrograde pyelography.

Although these sheaths are associated with cost savings and shorter operative times there is only a single series addressing stone-free rates after ureteroscopy with adjunctive ureteral access sheath placement: in their retrospective review in 2005 of 256 ureteroscopic procedures for the removal of renal calculi, L'Esperance and colleagues reported the overall stone-free rate in the ureteral access sheath group was significantly higher than in the non–ureteral access sheath group (79% and 67%, respectively). All studies evaluating the impact of a ureteral access sheath on outcomes and cost are retrospective—no level 1 evidence exists to support or refute their use.

Concerns regarding ureteral stricture formation from ureteral access sheath–induced ischemia and necrosis have largely been disregarded, because the incidence of stricture after ureteroscopy with a ureteral access sheath has been demonstrated to be the same as that with ureteroscopy alone (1.4%) (Delvecchio et al, 2003; Vanlangendonck and Landman, 2004). Rapoport and colleagues (2007) evaluated return trips to the emergency department after ureteroscopy and observed that use of a ureteral access sheath increased the likelihood of return to the emergency department if no stent was placed. They advocate ureteral stent placement in cases in which a ureteral access sheath has been used.

Indications for use of these sheaths has been extended as an adjunct to percutaneous nephrolithotomy. The ureteral access sheath simplifies ureteroscope passage into the upper tract with the patient in the prone position. The ureteroscope is advanced into the calyx of interest and facilitates percutaneous access by providing a landmark for needle puncture and may be used to snare wires to establish through-and-through access. Landman and associates (2002) found that placement of a ureteral access sheath during percutaneous nephrolithotomy significantly reduces intrarenal pressures and increases irrigant flow. Initial clinical experience treating large upper tract calculi using a combined percutaneous and retrograde approach with a ureteral access sheath in place has been favorable. A large renal stone burden may be successfully managed through a single percutaneous access with limited blood loss and no effect on stone-free rates (Landman et al, 2003; Marguet et al, 2005).

The 12/14-Fr ureteral access sheath is our most commonly utilized sheath and can be placed in most unstented patients. At this size, flow and intrarenal pressures are improved compared with the 10/12-Fr sheath and are equivalent to the larger 14/16 Fr sheath (Rehman et al, 2003). If the 12/14-Fr sheath cannot be passed, the 10/12-Fr sheath is used. It is the preference at our institution to use a 35-cm sheath in female patients and a 45-cm sheath in male patients.

Two problems associated with the use of ureteral access sheaths include buckling in the bladder during insertion and kinking after removal of the inner dilator. In-vitro studies can be used to predict which ureteral access sheath will function best with regard to buckling or kinking (Monga et al, 2004b; Pedro et al, 2007a). The Flexor sheath (Cook Medical, Bloomington, IN) is least likely to buckle at forces commonly used for sheath placement, an observation validated in a randomized prospective clinical trial (Monga et al, 2004a; Pedro et al, 2007b).

Intracorporeal Lithotriptors. Several intracorporeal lithotriptors are reviewed in detail in Chapter 48. In this section

the intracorporeal lithotriptors most commonly utilized during ureteroscopy area reviewed. **Ballistic lithotripsy utilizes pneumatic or electrokinetic energy sources to forcefully drive a projectile or ballistic body against a probe tip, creating a "jackhammer" effect** (Leidi et al, 1997; Keeley et al, 1999; Aghamir et al, 2003). Advantages of ballistic lithotripsy include reusable components and thus lower costs, ability to fragment all types of calculi including calcium monohydrate and cystine, and a high safety margin because little heat is generated at the probe tip. Disadvantages include the inability to simultaneously remove fragments while breaking up stones, lack of effective probes for use during flexible ureteroscopy, and stone retropulsion (Michel et al, 2002; Auge et al, 2004b). The lack of effective flexible probes prohibits flexible ureteroscopy, limiting its use to semirigid ureteroscopes. Proximal migration may place stone fragments in inaccessible locations requiring either flexible ureteroscopy or extracorporeal shockwave lithotripsy. Delvecchio and associates (2000) described a ballistic lithotripter combined with a suction device that facilitated fragment removal while preventing proximal migration and yielded a 3-month stone-free rate of 95%.

Electrohydraulic lithotripsy (EHL) probes utilize electrical energy to overcome the resistance between two insulated electrodes to produce a spark (Vorreuther and Engelmann, 1995). **The spark leads to formation of cavitation bubbles that may collapse symmetrically or asymmetrically resulting in a secondary shockwave or high-speed microjets, respectively. Both secondary shockwaves and microjets are involved in stone fragmentation** (Willscher et al, 1988; Denstedt and Clayman, 1990). Advantages of EHL include low cost and probe flexibility. A recent evaluation of flexible ureteroscopes showed that the 1.9-Fr EHL probe caused a similar decrement in maximal tip deflection compared with the 200-µm laser fiber, allowing for lithotripsy throughout the entire upper urinary tract (Abdelshehid et al, 2005). The main disadvantage of EHL is its propensity to damage the ureteral mucosa and associated ureteral perforation. The diameter of the cavitation bubble varies with the energy applied but can be 1.5 cm or greater and deliver substantial energy to surrounding tissues. Reported ureteral perforation rates may be as high as 40%, with the risk of perforation higher in the treatment of stones that are harder (higher energy requirements) or impacted (mucosal edema and impaired visualization) (Raney, 1978). Retropulsion of stones with EHL is more pronounced than with the holmium:yttrium-aluminum-garnet (YAG) laser and may decrease stone-free rates (Yang and Hong, 1996; Teichman et al, 1997).

The holmium:YAG laser is recognized to be the gold standard for ureteroscopic intracorporeal lithotripsy. The holmium laser crystalline matrix is a YAG crystal doped with chromium, thulium, and holmium (Teichmann et al, 2007). The pulsed solid-state laser operates in the near-infrared portion of the electromagnetic spectrum at 2100 nm. **At this wavelength the laser energy is strongly absorbed by water molecules and propagates no farther than 0.5 to 1.0 mm, providing a substantial safety margin during intracorporeal lithotripsy.** At 2100 nm the laser energy is effectively delivered through flexible silica quartz fibers ranging from 200 to 1000 µm. Generally, 200- to 400-µm fibers are used during ureteroscopy. **Holmium laser lithotripsy occurs primarily through a photothermal mechanism resulting in calculus vaporization** (Dushinski and Lingeman, 1998; Wollin and Denstedt, 1998).

Advantages of the holmium:YAG laser are many and include:

- All stone types can be fragmented (Wollin and Denstedt, 1998).
- Lithotripsy produces smaller stone fragments compared with other lithotriptor systems, reducing the need to basket fragments (Teichman et al, 1998).
- The production of weak shock waves causes less calculus retropulsion compared with other lithotriptors (Teichman et al, 1998; Vassar et al, 1999).
- Stone-free rates or 90% or more have been reported in several case series (Grasso, 1996; Yip et al, 1998; Sofer et al, 2002).
- There is a wide margin of safety with less adjacent tissue trauma (Grasso and Chalik, 1998; Wollin and Denstedt, 1998).

The primary disadvantage of the holmium:YAG laser is the high initial purchase price of the generator and laser fibers. However, this disadvantage may be offset by the wide variety of other upper tract conditions that may be addressed using this laser, including ureteral strictures, ureteropelvic junction obstruction, urothelial carcinoma, and symptomatic calyceal diverticula. **Limiting pulse energy to 1.0 J or less and varying the pulse frequency as needed can facilitate efficient lithotripsy by yielding smaller stone fragments, reducing stone retropulsion, and minimizing laser fiber damage** (Spore et al, 1999; Lee et al, 2003).

Stone Migration Devices. The risk of proximal migration is influenced by the type of intracorporeal lithotriptor used, irrigant fluid pressure, stone volume, site and degree of calculus obstruction, and degree of proximal ureteral dilation (Delvecchio et al, 2000; Lee et al, 2003; Ahmed et al, 2009). Proximal migration may result in lower stone-free rates and increased need for additional procedures (Teichman et al, 1997). Several devices have been developed to minimize calculus retropulsion and proximal migration during lithotripsy (Fig. 8–8). The **Stone Cone** (Boston Scientific, Natick, MA) is composed of a nitinol-wrapped stainless steel wire arranged in concentric coils and placed proximal to calculi before lithotripsy (Dretler, 2001). The Stone Cone has been shown to reduce the incidence of residual stone fragments larger than 3 mm and the need for auxiliary procedures (Desai et al, 2002). The **NTrap** (Cook Medical, Bloomington, IN) consists of a mesh netting composed of tightly woven nitinol fibers that is deployed through a 3-Fr catheter and placed proximal to calculi functioning as a backstop (Holley et al, 2005). In-vitro studies have shown that the Stone Cone and NTrap eliminated retropulsion and equally improved fragmentation efficiency during holmium laser lithotripsy (Lee et al, 2008). The **Accordion** (PercSys, Palo Alto, CA)

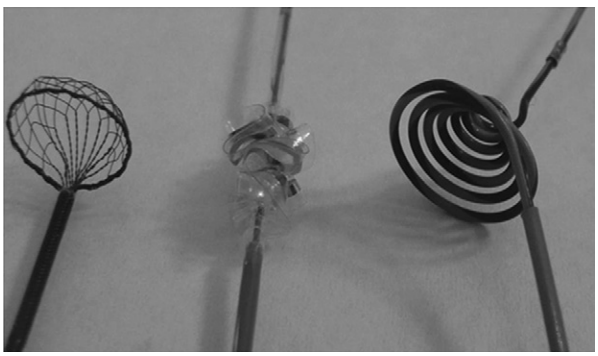


Figure 8–8. Stone migration devices designed to prevent calculus retropulsion during lithotripsy. *From left to right:* NTrap (Cook Medical, Bloomington, IN), Accordion (PercSys, Palo Alto, CA), and Stone Cone (Boston Scientific, Natick, MA).

consists of a two-part nylon and stainless steel guidewire with a short length of polyurethane film attached to the wire sections that forms a bottle-brush–like obstruction within the ureteral lumen preventing stone retropulsion (Chew, 2007). An in-vitro study showed that the anti-retropulsion section of the Accordion was significantly more resistant to laser damage compared with other stone migration devices (Vejdani et al, 2009). Viscous lubricant and lidocaine jelly have been injected proximal to calculi to improve lithotripsy, proximal migration rates, and stone-free rates (Ali et al, 2004; Mohseni et al, 2006; Zehri et al, 2008). **UroJel** (Fossa Medical, Boston, MA) is a thermosensitive polymer that is solid at body temperature and liquid at cooler temperatures (Mirabile et al, 2008). It is deployed proximal to a stone through a ureteral catheter and temporarily occludes the ureter preventing proximal migration. After lithotripsy, polymer dissolution occurs by irrigating it with cool saline. A recent in-vitro study showed that UroJel effectively occludes the ureter during ureteroscopic lithotripsy without damaging the urothelium (Mirabile et al, 2008).

Baskets. Ureteroscopic baskets are most commonly utilized to retrieve ureteral and renal calculi but are also of use in ureteral tumor biopsy. Baskets are composed of flat, round, or triangular wires of either nitinol or stainless steel and are configured into tipped (helical or spherical) or tipless designs. Basket size ranges from 1.3 to 3.2 Fr. They are deployed under direct vision through the ureteroscope and are activated with a handheld device that controls basket opening and, in some cases, rotation and deflection. Basket size, configuration, material, opening characteristics, and safety profiles may direct the surgeon to use a specific basket depending on the clinical situation.

Nitinol-based wires are advantageous in that they are flexible, are kink resistant, and permit a tipless basket design (Fig. 8–9). The tipless design is less traumatic during use in the ureter and kidney compared with tipped baskets, especially when retrieving or repositioning calyceal stones (Honey, 1998; el-Gabry and Bagley, 1999; Kourambas et al, 2000). The flexibility of nitinol baskets is superior to that of their stainless steel counterparts, allowing for consistent retrieval from lower pole calyces (Honey, 1998). Smaller baskets (≤1.5 Fr) improve irrigant flow and may permit passage of a laser alongside it in the ureteroscope working channel, which is a distinct advantage when multiple exchanges between the basket and the intracorporeal lithotripter are anticipated or when calculi are entrapped in the basket (Canales et al, 2006). Some basket models have rotation or deflection capabilities that may improve stone capture and retrieval and assist in the lithotripsy of entrapped calculi (Canales et al, 2006; Zeltser and Bagley, 2007). Flat wire design baskets are useful in the biopsy and retrieval of papillary ureteral lesions. Stainless steel baskets offer improved radial dilation forces, which may be beneficial when significant ureteral edema or stone impaction is present (Hendlin et al, 2004). Drawbacks of stainless steel baskets include an increased tendency for ureteral perforation and decreased flexibility, which limits their use in flexible ureteroscopes. **Complications of ureteroscopic basketing range widely in severity and include ureteral avulsion, intussusception, abrasion, perforation, postoperative stricture formation, and basket breakage or entrapment** (de la Rosette et al, 2006). **The following principles are key in preventing basketing-related complications: (1) avoidance of forceful basket manipulation, (2) limiting retrieval to calculi or fragments that are small enough to be easily extracted with minimal trauma, (3) direct visualization of the basket and its contents at all times, and (4) avoiding contact of the laser with the basket unless the laser is employed intentionally to release an entrapped stone.**

PATIENT PREPARATION

A variety of techniques and approaches may be used to access, visualize, and treat pathologic processes of the upper urinary tract. The methods presented here reflect our techniques and preferences, but the basic endoscopic principles apply to all surgeons performing ureteroscopy.

Before performing ureteroscopy, informed consent must be obtained, specifically addressing the purpose of the procedure, the associated risks and benefits, the potential complications, and the possibility of inserting an indwelling ureteral stent. Anesthetic choices include local anesthesia with or without intravenous sedation, regional anesthesia (either spinal or epidural), and general anesthesia (Cybulski et al, 2004b; Park et al, 2004; Reisiger et al, 2007). General anesthesia is most commonly used at our institution, especially during lithotripsy when inadvertent patient movement could result in ureteral trauma. Most ureteroscopic procedures can be

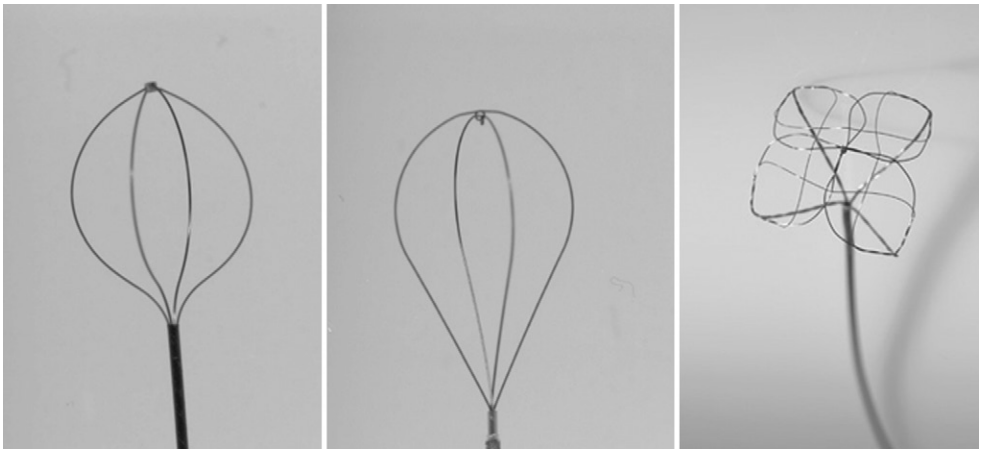


Figure 8–9. Nitinol baskets utilized in ureteroscopy. *From left to right:* 1.5-Fr Halo (Sacred Heart Medical, Minnetonka, MN) used for routine ureteral and pelvicalyceal stone retrieval; 2.2-Fr N-Circle (Cook Medical, Bloomington, IN) basket frequently utilized for retrieving adherent intrarenal calculi; and 2.4-Fr N-Compass (Cook Medical, Bloomington, IN) with a multiwire parachute-like basket well suited for capturing small stone fragments.

Key Points: Upper Urinary Tract Endoscopy

- Semirigid ureteroscopy is typically utilized for diagnosis and treatment of pathologic processes below the iliac vessels. Flexible ureteroscopy is typically used above the iliac vessels.
- Ureteral dilation is not necessary in every ureteroscopic intervention and should be performed only when ureteroscope passage is impaired.
- Utilizing the minimum amount of irrigation necessary to provide a clear view during ureteroscopy minimizes stone migration, bleeding from hydrodistention, and pyelolymphatic or pyelovenous backflow.
- Ureteral access sheaths reduce operative time and costs, simplify ureteroscope reentry, facilitate calculus retrieval, and reduce ureteroscope damage.
- The holmium:YAG laser is the gold standard for ureteroscopic intracorporeal lithotripsy.
- Holmium laser lithotripsy occurs primarily through a photothermal mechanism resulting in calculus vaporization.
- Limiting pulse energy to 1.0 J or less and varying pulse frequency as needed can facilitate efficient lithotripsy by yielding smaller stone fragments, reducing stone retropulsion, and minimizing laser fiber damage.

performed as an outpatient procedure. All patients undergoing elective ureteroscopy should have a negative urine culture or have completed a course of culture-directed antimicrobial therapy before instrumentation.

Antimicrobial Prophylaxis

Urinary tract infection occurs in 4% to 25% of patients undergoing ureteroscopy (Rao et al, 1991; Puppo et al, 1999; Grabe, 2001, 2004). Knopf and associates (2003) noted a significant reduction in postoperative bacteriuria in patients who received a single dose of levofloxacin before ureteroscopy versus those who received no preoperative antibiotics (13% vs. 2%). Christiano and colleagues (2000) demonstrated that a single preoperative dose of ciprofloxacin is as effective and costs less than a single dose of intravenous cefazolin. **In 2007 the American Urological Association released a best practice statement on urologic surgery antimicrobial prophylaxis, recommending that all patients undergoing ureteroscopy receive antimicrobial prophylaxis** (Wolf et al, 2008). The antimicrobial agents of choice are the fluoroquinolones and trimethoprim-sulfamethoxazole, and the duration of therapy should be less than 24 hours.

Patient Positioning

Ureteroscopy may be performed with the patient in the supine, prone, and flank positions. When performed in the prone position, ureteroscopy is commonly utilized as an adjunct for establishment of percutaneous access and percutaneous nephrolithotomy (Kidd and Conlin, 2003; Marguet et al, 2005). In most cases it is our preference to position the patient in the dorsal lithotomy position. Many surgeons prefer to have the ipsilateral leg somewhat straighter and lower than the contralateral leg because this may increase the surgeon's working space to operate rigid instruments in line with the ureter and may facilitate ureteral access and navigation over the psoas muscle. **When operating in the kidney or proximal ureter, slight Trendelenburg positioning may aid calculi displacement into an upper pole calyx, a location that is typically easier to access than the lower pole. When operating in the middle and distal ureter, reverse Trendelenburg positioning may reduce lithotripsy- and irrigation-induced calculus retropulsion.**

Cystoscopy

Cystoscopy is performed before ureteroscopy to insert a 0.035 to 0.038-inch hybrid wire with a hydrophilic tip and stiff shaft (i.e., Sensor, Boston Scientific, Natick, MA) into the ureter and up to the renal pelvis until it is coiled. Either rigid or flexible cystoscopy may be used for initial wire placement. **If the ureteral orifice is difficult to identify, the following steps may be taken:** (1) identify the contralateral ureteral orifice and follow the ureteric ridge across the trigone to the expected location on the side of interest; (2) empty the bladder if it is full, which may compress the orifice and displace it laterally; (3) fill the bladder if it is empty, because mucosal folds in the bladder can preclude identification of the orifice; (4) exchange the telescopic lens for a 30 or 70-degree lens (if using a rigid cystoscope); (5) switch from rigid to flexible cystoscope or vice versa; and (6) intravenously administer colored dye (i.e., indigo carmine) and identify the ureteral orifice of interest when a blue jet of urine is observed.

Safety Guidewire

Before upper tract manipulation, a guidewire should be placed under cystoscopic and fluoroscopic guidance. **This wire functions as a safety wire that preserves access to the kidney and allows for placement of an indwelling ureteral stent in cases that are complicated by ureteral perforation or excessive bleeding that impairs adequate visualization and requires termination of the procedure. Standard practice is to have a safety wire in place throughout the procedure. Some authors have recently reported ureteroscopy without a guidewire** (Johnson et al, 2006; Eandi et al, 2008). **However, typically a guidewire does not interfere with successful completion of an endoscopic procedure and often not only serves as a safety precaution but also straightens a tortuous ureter and facilitates advancement of the ureteroscope.**

Typically one will be able to cannulate the ureteral orifice with the floppy end of the wire. Occasionally it may be necessary to utilize a 5-Fr open-ended ureteral catheter over the guidewire to help stabilize it at the ureteral orifice. Patients who have undergone reconstructive procedures such as ureteroneocystostomy, urinary diversion, and renal transplant may require a combination of angled wires and catheters to achieve an appropriate wire tip angle to cannulate the ureteral orifice (Del Pizzo et al, 1998; Nelson et al, 2003; Wallis et al, 2003). Resistance to the passage of the guidewire may be appreciated by tactile or visual feedback as noted on fluoroscopy or by detecting buckling of the wire in the bladder under direct vision through the cystoscope. If this occurs, a 5-Fr open-ended catheter is gently advanced over the guidewire under fluoroscopic guidance to the point of obstruction; then the guidewire is removed and a retrograde pyelogram is performed to delineate the anatomy.

Ureteral calculi or neoplasia, ureteral tortuosity, and ureteropelvic junction obstruction may impede guidewire placement. **If the wire cannot pass any of these obstructions, the wire is**

left just distal to the obstruction and the following steps may be attempted: (1) insert a 5-Fr ureteral catheter over the wire to increase the stiffness of the wire and provide backing to pass the wire beyond the obstruction; (2) exchange the wire for one with a hydrophilic tip and reattempt passage; and (3) exchange the 5-Fr ureteral catheter for an angled ureteral catheter or vascular catheter in combination with the straight or angled hydrophilic tipped guidewire and reattempt passage. If these maneuvers are unsuccessful, percutaneous access and an antegrade approach may be necessary. Alternatively, ureteroscopy can be performed to the level of obstruction in an attempt to identify the ureteral lumen at the site of obstruction and a guidewire can then be advanced under direct vision through the ureteroscope.

An appropriately placed guidewire should traverse the entire ureter and coil in the intrarenal collection system. If there is any question regarding where the guidewire has been passed, a retrograde pyelogram should be performed by exchanging the wire for a 5-Fr ureteral catheter and instilling radiopaque contrast to outline the collection system. Ureteral perforation may occur during wire manipulation and is evidenced by extravasation of contrast material on the retrograde pyelogram. In cases of severe hydroureteronephrosis with ureteral tortuosity, the proximal ureter may be quite capacious and permit guidewire coiling within the proximal ureter, making it difficult to determine the proximal location of the wire. In these cases, retrograde pyelography should be used to confirm appropriate wire positioning within the renal pelvis.

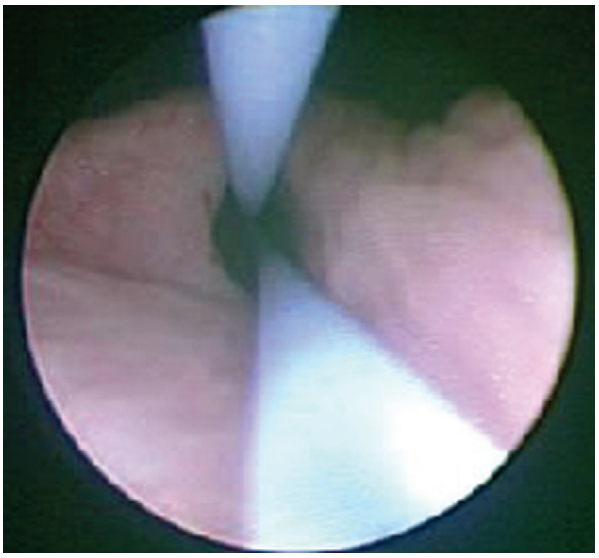


Figure 8–10. Passing a semirigid ureteroscope between two "railroad" wires during difficult ureteral access. The ureteroscope is maneuvered underneath the safety wire *(top),* tenting up the orifice. A second wire *(bottom)* is passed through the working channel and up the ureter with fluoroscopic guidance. The ureteroscope is then gently advanced between the wires until ureteral access is achieved.

Ureteroscope Insertion

Once the safety wire is in place the bladder is completely drained and the cystoscope is removed. The next step depends on whether semirigid or flexible ureteroscopy is planned. Semirigid ureteroscopy is performed when the pathologic process of interest is known or expected to reside in the distal or middle ureter. In addition to clearing the distal ureter of a pathologic process, semirigid ureteroscopy also dilates the ureteral orifice and permits the passage of a second "working" wire under direct vision, expediting subsequent flexible ureteroscopy or placement of a ureteral access sheath. When semirigid ureteroscopy is elected, the ureteroscope is gently advanced under direct vision with care to avoid creating false passages in the urethra. The ureteroscope is passed into the bladder and guided into the ureter alongside the safety wire. Typically, attempts to lift the guidewire with the tip of the ureteroscope positioned under the guidewire may facilitate entry into the orifice. **If the ureteroscope does not pass easily, the following steps may be performed:** (1) rotate the beak of the ureteroscope while engaging the ureteral orifice and providing adequate irrigation; (2) pass a super-stiff wire into the ureter through the working channel, rotate the ureteroscope so that the tip lies between the two wires, and guide the ureteroscope into the ureter between the two "railroading" wires (Fig. 8–10); (3) dilate the ureteral orifice with a 6/10-Fr coaxial dilator over a guidewire; (4) dilate the ureteral orifice with a 4-mm radially expanding balloon dilator; or (5) if the preceding measures fail, place an indwelling ureteral stent and allow for passive dilation for 2 weeks. Once the semirigid ureteroscope has been passed to the point where further inspection is limited by ureteral course, diameter, or length, a second wire is placed under direct vision and the ureteroscope is removed. Alternatively, if semirigid ureteroscopy is not utilized to inspect the distal ureter, a second wire may be placed through either an 8/10-Fr coaxial dilator or a 6/10-Fr dual lumen catheter over the safety wire.

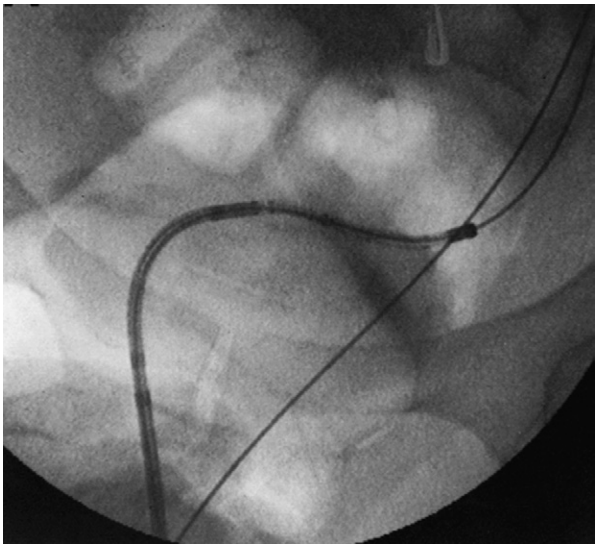


Figure 8–11. Difficulty passing a flexible ureteroscope frequently manifests as buckling in the bladder.

The flexible ureteroscope may be advanced into the ureter by backloading it over a double floppy tip super-stiff working wire and guiding it into the ureter under fluoroscopic guidance. This technique is used when less than three passes of the ureteroscope are planned (i.e., diagnostic ureteroscopy, ureteral biopsy, and small urinary stone burden). The ureteroscope should be kept as straight as possible during insertion by adequate tensioning of the working wire by the assistant while the surgeon advances the endoscope. Difficulty traversing the ureteral orifice with the flexible ureteroscope frequently manifests as buckling within the bladder (Fig. 8–11). Passage is facilitated by similar maneuvers as previously described for semirigid ureteroscopes, in particular rotating the ureteroscope to realign the working channel with the

Key Points: Patient Preparation

- The American Urological Association best practice statement on urologic surgery antimicrobial prophylaxis recommends that all patients undergoing ureteroscopy receive antimicrobial prophylaxis.
- Safety wires should be placed at the onset of ureteroscopy, facilitate indwelling ureteral stent placement should the procedure be terminated for ureteral perforation or bleeding, straighten a tortuous ureter, and ease ureteroscope advancement.
- When ureteral obstruction preventing passage of a wire is encountered the following tactics can be employed: increasing wire rigidity with a 5-Fr ureteral catheter, exchanging wires for one with a straight or angled hydrophilic tip, and exchanging the 5-Fr ureteral catheter for an angled ureteral or vascular catheter.
- When difficulty is encountered during ureteroscope passage the following maneuvers may be performed: (1) ureteroscope rotation; (2) passing the ureteroscope between two "railroad" wires; (3) ureteral dilation with either balloon or coaxial dilators; and (4) placement of stent to allow passive dilation for 2 weeks.

ureteral orifice. Alternatively, placement of a ureteral access sheath over a super-stiff working wire facilitates ureteroscope passage through the ureteral orifice and obviates the need for backloading.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter
9

Fundamentals of Laparoscopic and Robotic Urologic Surgery

Louis Eichel, MD ● Ralph V. Clayman, MD

Preoperative Patient Management
In the Operating Room
Strategic Placement of Operative Team and Equipment
Performing the Procedure
Postoperative Patient Management
Physiologic Considerations in the Adult
Troubleshooting in Laparoscopic Surgery
Limitations and Advantages of Transperitoneal versus Extraperitoneal Approach to the Flank and Pelvis
Training and Practicing Laparoscopic and Robotic Surgery
Conclusion

More than 100 years ago the "father of modern medicine," Sir William Osler, challenged surgeons to perpetually refine their craft, stating, "Diseases that harm require treatments that harm less." In pursuit of this noble goal the urologists of the 20th century brought us great achievements in our field, but it has been over the past 25 years, in particular, that the specialty of minimally invasive urology has become predominant. The earliest techniques that laid the foundation for modern laparoscopic and robotic urologic procedures were developed at academic institutions throughout the world and have continuously been validated and improved. Subsequently, an increasing number of multi-institutional studies have emerged comparing laparoscopic and robotic procedures to their open surgical counterparts and showing equivalent efficacy, acceptable efficiency, as well as the distinct advantages of decreased postoperative pain, better cosmesis, faster recovery, a shorter hospital stay, and, in many cases, less cost. Indeed, it has become increasingly clear that the objectives of many open urologic surgeries, be it of the adrenal gland, kidney, ureter, bladder, prostate, or lymph nodes, can now be achieved with minimally invasive surgery with less patient injury and suffering. Therefore, whereas open surgery has had a steadily diminishing role in the treatment of urologic diseases, laparoscopic and robotic surgery have moved into the mainstream of urologic surgery and knowledge of the required principles and techniques is essential for the practicing urologist. This chapter is intended to provide a basic fund of knowledge on which the aspiring minimally invasive urologist can build.

PREOPERATIVE PATIENT MANAGEMENT

Patient Selection and Contraindications

Careful patient selection and identification of possible relative and absolute contraindications are vital to a successful outcome of laparoscopic and robotic procedures. To this end, a meticulous past history, focusing on prior surgeries, and physical examination, detailing the location and extent of all abdominal scars, are the initial steps in patient evaluation for possible minimally invasive surgery.

Age- and health-based laboratory studies, an electrocardiogram, and a chest radiograph should be obtained according to the same criteria established for any other significant surgical procedure that is undertaken with general anesthesia.

In patients presenting with severe chronic obstructive pulmonary disease (COPD), further studies (i.e., arterial blood gases and pulmonary function tests) are required. In patients with severe COPD, helium as an alternative insufflant should be considered and available at the time of the procedure. Cardiac arrhythmias should be evaluated and treated preoperatively because hypercarbia and the resulting acidosis may have adverse effects on the myocardium, thereby exacerbating any preexisting myocardial instability.

Contraindications to laparoscopic surgery include uncorrectable coagulopathy, intestinal obstruction unless intention to treat, significant abdominal wall infection, massive hemoperitoneum or hemoretroperitoneum, generalized peritonitis, and suspected malignant ascites. Select circumstances in which laparoscopy is being contemplated necessitate careful risk-benefit analysis and detailed and specific informed consent with the patient. The following conditions may portend potential difficulties with a laparoscopic approach.

Morbid Obesity. Laparoscopic procedures in morbidly obese patients are technically challenging. Difficulties may include inadequate length of instruments, decreased range of motion of trocars and instruments, need for higher pneumoperitoneum pressures to elevate the abdominal wall, and poor anatomic orientation owing to excessive amounts of adipose tissue. Traditionally, these difficulties translated into a higher rate of associated complications; in a multi-institutional review of laparoscopy in

125 morbidly obese individuals, one or more intraoperative or postoperative complications occurred in 30% (Mendoza et al, 1996). In comparison to open surgery, however, it has been found that the laparoscopic approach to renal and adrenal procedures actually has a lower complication rate than the open approach. In a comparison of major laparoscopic renal and adrenal procedures (N = 21) versus similar open procedures (N = 21) in obese patients (body mass index [BMI] ≥ 30), although operative time was longer in the former group (210 minutes vs. 185 minutes; $P = .16$), the laparoscopic group had significantly superior outcomes regarding blood loss (100 mL vs. 350 mL; $P = .001$), resumption of oral intake and ambulation (<1 day vs. 5 days; $P = .001$), narcotic analgesic requirements (12 mg vs. 279 mg; $P = .001$), median hospital stay (<1 day vs. 5 days; $P = .001$), and convalescence (3 weeks vs. 9 weeks; $P = .001$). The overall complication rate in the laparoscopic group was 29% (19% major, 10% minor) versus 67% in the open group (33% major, 33% minor) ($P = .16$) (Fazeli-Matin et al, 1999). These findings have been further confirmed at several other centers (Fugita et al, 2004; Kapoor et al, 2004) even for complicated procedures such as partial nephrectomy (Colombo et al, 2007; Romero et al, 2008) and nephroureterectomy (Brown et al, 2008).

With regard to laparoscopic and robotic radical prostatectomy in obese men, it has been found that although the operation can be performed without compromising pathologic outcomes, obese patients have a greater risk of perioperative complications (26% vs. 5%) (Ahlering et al, 2005). Obese patients had a higher rate of deep vein thrombosis and pulmonary embolism (10%). Additionally, obese patients were less likely to achieve continence and more likely to have higher urinary bother scores at 3-, 6-, and 9-month follow-up.

Extensive Prior Abdominal or Pelvic Surgery. When extensive intra-abdominal or pelvic adhesions are suspected, careful consideration must be given to the possible site of Veress needle insertion as well as to obtaining open access with a Hasson-style cannula. The surgeon needs to understand the five potential points of Veress needle access to the abdomen (umbilicus and at the Palmer point—midclavicular line subcostal on either side, and just off the iliac crest—two fingerbreadths up and two fingerbreadths medial) as well as have knowledge regarding open (e.g., Hasson type) access. Alternatively, in these patients a retroperitoneal approach may be preferable to a transperitoneal approach or the procedure can be initiated retroperitoneally and the peritoneum then entered (Cadeddu et al, 1999).

A patient history of prior retroperitoneal surgery increases the difficulty of reentering the retroperitoneal space and therefore should be approached with caution. Subsequent attempts at extraperitoneoscopy or retroperitoneoscopy should only be ventured by individuals with considerable experience and comfort with this approach. In the authors' experience, prior percutaneous renal procedures do not necessarily constitute a contraindication to subsequent retroperitoneoscopy, provided that entry is away from the area of the prior nephrostomy tube placement.

Pelvic Fibrosis. Pelvic fibrosis owing to previous peritonitis, pelvic surgery, or extensive endometriosis may constitute a severe technical challenge to the laparoscopic surgeon when surgery of the lower urinary tract is indicated. Similar problems may be encountered when trying to perform pelvic lymph node dissection in patients who have a hip prosthesis; leakage of the polymethylmethacrylate cement can create a dense inflammatory reaction and fibrosis in the adjacent pelvis (Cooper et al, 1997).

Organomegaly. Known or preoperatively diagnosed organomegaly necessitates a cautious approach when obtaining the pneumoperitoneum. The site of Veress needle insertion must be chosen at a safe distance from any enlarged organs. Alternatively, open access with the Hasson cannula may be considered. Open access should be considered in cases of marked hepatomegaly or splenomegaly.

Ascites: Benign Etiology. Patients with severe ascites are under increased risk of injury to the bowel owing to closer proximity of bowel loops to the anterior peritoneum. In addition, a watertight wound closure is required and a firm wound dressing should be applied to prevent prolonged postoperative leakage.

Pregnancy. Initial access to the abdomen must be obtained at a safe distance from the fundus of the gravid uterus. As such, trocar placement is usually performed more cephalad on the abdominal wall, depending on the fundus of the uterus. The left or right upper quadrant in the subcostal midclavicular line (i.e., at Palmer point) is often the preferred site of access. Prolonged intra-abdominal pressures of 15 mm Hg or greater may result in hypotension, owing to significantly reduced venous return because the vena cava is already mechanically compromised by the enlarged uterus. Prolonged CO_2 pneumoperitoneum, which may result in maternal hypercarbia and acidosis with subsequent adverse effects on the fetus, should be avoided. Accordingly, a working pneumoperitoneum of 10 mm Hg is recommended in the pregnant patient. The second trimester is a preferred time for necessary surgery given the completion of fetal organogenesis and less chance of inducing labor.

As pregnancy progresses beyond the 20th week the technical possibility of performing laparoscopic procedures decreases significantly, correlating with the increasing size of the gravid uterus. Both laparoscopic nephrectomy and adrenalectomy have been successfully accomplished in the pregnant female (Nezhat et al, 1997; O'Connor, et al, 2004; Sainsbury et al, 2004).

Hernia. A diaphragmatic hernia may result in leakage of a significant amount of CO_2 into the mediastinum, which, although rarely noted, may eventually result in clinical problems such as respiratory compromise or cardiac tamponade (e.g., pneumopericardium) (Knos et al, 1991).

Any evidence of uncorrected or surgically corrected umbilical hernia or abdominal wall hernia should rule out these sites for obtaining a pneumoperitoneum.

Iliac or Aortic Aneurysm. Significant aneurysms warrant evaluation by the vascular surgeon. If the aneurysm does not require immediate surgical correction, insertion of the Veress needle should be performed in the left upper quadrant to stay well away from the area of the aneurysm. Of course, open access with the Hasson technique can be employed. Insertion of accessory trocars must be done under strict endoscopic control to avoid the area of the aneurysm.

Informed Consent

Although laparoscopic/robotic surgery is generally associated with decreased pain and morbidity, it should be remembered that there is considerable potential for serious complications, similar to that associated with standard open incisional surgery. It is essential for the patient to understand the inherent risk with all minimally invasive procedures such that the procedure may need to be converted to open surgery owing to hemorrhage, bowel injury, failure to progress, or other complications at any point during the intraoperative or postoperative course. Alternatively, in select cases, with less emergent complications, conversion to a completely open approach may be avoided by first switching to a hand-assisted approach and only going to an open approach if the

hand-assisted approach fails to provide the necessary control of the situation.

All alternative forms of surgical or nonsurgical treatment (if applicable), with their known advantages and disadvantages, must be discussed. The patient needs to be aware of both complications unique to laparoscopy and robotic surgery (e.g., fatal gas embolism, problems owing to hypercarbia, postoperative crepitus, pneumothorax, electrosurgical bowel injury, or robotic mechanical failure), and procedure-specific complications (e.g., damage of obturator nerve in pelvic lymphadenectomy).

Time spent obtaining informed consent is well invested. It is both the patient's right and the physician's responsibility. A good beginning augurs a good end.

Bowel Preparation

For extraperitoneoscopy and retroperitoneoscopy, no bowel preparation is necessary, but it may help with postoperative constipation. For transperitoneal laparoscopic/robotic procedures *not* involving the use of bowel segments for urinary tract reconstruction, a light mechanical bowel preparation can be given in an effort to decompress the bowel. A traditional example of such a prep would consist of a clear liquid diet and a Dulcolax suppository or half a bottle of magnesium citrate the day before the procedure. More recently, emphasis has been placed on "fast tracking" patients in an effort to streamline care and decrease length of hospital stay. Breda and associates (2007) found that a modified bowel prep and avoidance of narcotic analgesics postoperatively (with routine administration of ketorolac) was instrumental in achieving a hospital stay of 1.1 days for patients undergoing laparoscopic donor nephrectomy. The bowel prep consists of clear liquids for 2 days before surgery, two bottles of magnesium citrate the day before surgery, an enema the night before surgery, and nothing to eat after midnight (Breda et al, 2007).

The need for a full mechanical (e.g., GoLYTELY, 2 to 4 L, or 3 ounces of Fleet Phospho-Soda followed by a clear liquid diet and Fleet enema) and antibiotic (e.g., neomycin, 1 g by mouth, and metronidazole, 500 mg by mouth; three doses of each the day before surgery, plus 1 g of intravenous cefotetan on call to the operating room) bowel preparation is subject to question and becomes an issue only if one anticipates encountering dense intraabdominal adhesions or if the surgery involves entering the bowel (e.g., enteric augmentation of the bladder or enteric conduit formation).

Preparation of Blood Products

Serum type and screen are sufficient for diagnostic laparoscopy or procedures associated with a low chance of major hemorrhage. More extensive laparoscopic/robotic procedures (e.g., nephrectomy, partial nephrectomy, adrenalectomy), especially early in one's experience, should be managed like any other major open surgical procedure, with packed red blood cells available before surgery. This is most important during one's initial major laparoscopic/robotic cases; with experience, a "type and hold" suffices because the need for transfusion among patients undergoing major procedures, such as radical nephrectomy or radical nephroureterectomy, is quite low (3% to 12%), with an estimated average blood loss in the range of 106 to 255 mL (Ono 1999; Dunn et al, 2000; Jeschke et al, 2000; Shalhav et al, 2000). Similarly, the transfusion rate with laparoscopic/robotic radical prostatectomy is low (2.5% at experienced centers) such that a "type and hold" is sufficient (Guillonneau and Vallancien 2000; Ahlering et al, 2004).

Optional Preoperative Endourologic and Radiologic Procedures

Preoperative computed tomography (CT), spiral angiographic CT with 3D reconstruction, and magnetic resonance imaging (MRI) are helpful in depicting the anatomic relationship of the operative site to adjacent organs and/or blood vessels. Of course, the necessary studies required as part of a routine metastatic workup for cancer are mandatory. For partial nephrectomy or in the patient with ureteropelvic junction obstruction, preoperative spiral CT angiography with 3D reconstruction can be helpful. These studies may help to clearly define the renal vasculature and in the case of a renal mass can clearly delineate the optimal plane and depth of dissection. For the latter situation, coronal and sagittal views may be requested. When nephrectomy is performed for large malignant renal tumors (i.e., >10 cm), preoperative embolization of the renal artery may be considered immediately before the laparoscopic surgery; this procedure allows the surgeon to secure and divide the renal vein earlier in the transperitoneal procedure (i.e., before taking the renal artery) and may help to decompress collateral veins. In other disease states, preoperative placement of a ureteral catheter or a percutaneous drainage catheter can be quite helpful because intraoperative filling (e.g., with indigo carmine–stained saline) and drainage of the surgical site can aid in its identification and subsequent treatment (e.g., pyeloplasty, lymphocele or intrarenal cyst, calyceal diverticulum). Conversely, removal of an indwelling stent before a ureteral reconstructive procedure is recommended by some to enable the surgeon to work with a noninflamed ureter, thus facilitating the creation of a noninflamed anastomosis and subsequent healing.

A variety of catheters, both opaque and light bearing, can be placed in the ureter to facilitate ureteral identification and dissection in nephrectomy, pyeloplasty, nephroureterectomy, ureterolysis, ureterolithotomy, and retroperitoneal lymph node dissection. The need for preplacement of a ureteral stent is dependent on the pathologic process and the surgeon's prior laparoscopic/robotic experience.

IN THE OPERATING ROOM

Setup of the Operating Room

The operating room has to provide enough space to accommodate all necessary personnel and the equipment required by both the surgeon and the anesthesiologist. Positioning of equipment, surgeon, assistants, nurses, anesthesiologist, and other support staff should be clearly defined and established for each laparoscopic or robotic case. All equipment must be fully functional and in operating condition before any laparoscopic procedure is started (Table 9–1). A separate tray with open laparotomy instruments must be ready for immediate use in the event of complications or problems necessitating emergent open incisional surgery.

Patient Positioning and Draping

Positioning of the patient depends primarily on the procedure to be performed. In the supine position the arms can be tucked snugly at the sides or rest on specially designed sleds. In the

Table 9–1.

Instrumentation Checklist for Making a Skin Incision for Obtaining the Pneumoperitoneum

1. Irrigation-aspiration unit is working.
2. Electrosurgical unit is working.
3. CO_2 tank is full, with extra CO_2 tank in the room.
4. Camera is white balanced, and light source is working.
5. Insufflation is checked for flow and response to kinking of the tubing.
6. Veress needle is checked for flow and proper tip retraction.

Trendelenburg or lateral position, tape and security belts applied across the chest and thighs provide safe and stable positioning of the patient; shoulder braces should not be used because of a risk of brachial plexus injury. In the lateral position, all bony prominences in contact with the table must be carefully padded; likewise, the point of contact between any of the positioning straps and the hip or shoulder should be padded. In the lateral position, the bottom leg is flexed approximately 45 degrees while the upper leg is kept straight; pillows are placed between the legs as a cushion and also to elevate the upper leg so that it lies level with the flank, thereby obviating any undue stretch on the sciatic nerve. Pads should be placed between the table and the knee and ankle of the lower leg because these are high pressure areas. In the lateral decubitus position an axillary roll should be used. Application of an active warming system may prevent hypothermia, should a lengthy laparoscopic procedure be anticipated.

A host of new advances in padding and table mounted accessories are now available but none has been conclusively demonstrated to significantly reduce pressure on the patient's flank in the lateral position. Researchers at the University of California, Irvine, showed that women have significantly lower interface pressures than men (Deane et al, 2008). A BMI greater than or equal to 25, use of a kidney rest, and full table flexion as opposed to half-table flexion were all associated with increases in interface pressures; of these, use of the kidney rest was believed to be the most detrimental and its use beyond 20 to 30 minutes was disparaged. Therefore, male patients with a BMI of 25 or higher undergoing laparoscopic surgery in the lateral position with the kidney rest elevated and the table completely flexed are at highest risk of developing rhabdomyolysis from flank pressure. In this study the unaugmented operating table mattress was superior to egg crate or gel padding as an augmenting surface material; of note, egg crate padding was equal or superior to the more expensive gel padding.

Table-mounted accessories for all major commercial operating room tables now exist that aid in safely and effectively positioning patients in the lateral decubitus position and in the prone position. Specifically, for lateral decubitus positioning the buttock and upper back can be supported by padded reinforced stabilizer bars that mount on the side rails of the table. The entire bed and especially the kidney rest can also be padded and the upper arm can be supported on a table-mounted adjustable armboard. Special head supports for the lateral decubitus position are also available. For laparoscopic or robotic procedures on the pelvis, the patient can be placed in Trendelenburg position with the legs on split-leg positioners. Shoulder supports or braces should never be used in this position owing to the risk of brachial nerve injury. Allen stirrups have fallen out of favor because of the risk of calf neuropraxia. Split-leg positioners are available as built-in table features (Fig. 9–1A on the Expert Consult website) or as optional add-on features that can be used with any table (see Fig. 9–1B on the Expert Consult website).

The full extent of the abdominal wall should be prepared and draped from nipples to pubis. In some procedures, it is advantageous to extend the preparation to the knees and to drape the external genitalia into the surgical field. For example, gently pulling on the testis may help identify the intrapelvic location of the vas deferens and spermatic vessels, transvaginal palpation facilitates identification of the cervical cuff and posterior bladder junction, and free access to the urethral meatus enables the performance of auxiliary procedures such as flexible cystoscopy or manipulation of ureteral catheters during nephroureterectomy or for stent placement during pyeloplasty.

Before laparoscopic or retroperitoneoscopic procedures, placement of a nasogastric/orogastric tube and a Foley catheter should be performed to decompress the stomach and bladder, respectively, thereby decreasing the chance of injury of abdominal contents during surgery. Pneumatic compression stockings are applied for antiembolic prophylaxis. The administration of 5000 units of subcutaneous heparin preoperatively is also an option in higher-risk patients, such as the morbidly obese.

STRATEGIC PLACEMENT OF OPERATIVE TEAM AND EQUIPMENT

Standard Laparoscopic Carts. Traditionally, the mandatory hardware for laparoscopic procedures (monitor, light source, insufflator) is located on carts or "towers" that can be rolled around the operating room and be adapted to various types of surgical procedures and approaches (Fig. 9–2A on the Expert Consult website). If only one monitor is used (as in intrapelvic procedures), it is typically placed at the foot of the table or between the legs if the patient is in stirrups or on split-leg positioners. If two monitors are used, they are positioned on both sides of the table to allow an unobstructed view for all key operative team staff.

The main laparoscopic cart should contain the insufflator, placed at the surgeon's eye level to allow continuous monitoring of the CO_2 pressure. The light source, camera controls, and any recording device are usually also on the cart. Placement of a *sterile* plastic sheet over the front of this cart enables the surgical team to directly control the intensity of the light as well as the pneumoperitoneum pressure with these controls on the equipment.

Integrated Endoscopy Systems. More recently, most major manufacturers of endoscopy equipment offer "integrated" systems that consist of flat panel displays and equipment towers that are mounted on adjustable ceiling booms (see Fig. 9–2B on the Expert Consult website). Thus, the display monitors can be suspended over the patient and placed directly in front of the surgeon at any height or angle. This feature may reduce eye and body strain. Furthermore, the tower containing the light source, camera system, and insufflator can be placed in any area around the patient depending on the operation at hand. The more sophisticated systems are frequently controlled by a touch screen display used by the surgeon or a nurse, or by voice command, or by using the controls on the camera head instead of manually adjusting instruments at the tower level. In addition to the laparoscopic equipment, other aspects of the operating room environment can be controlled from the touch screen or by voice, such as the room lighting, input from digital radiology systems, and recording devices. Although they are not a necessity, these types of systems offer unique advantages with regard to operating room efficiency

and may further improve the ergonomics for the operating surgeon and staff.

Robotic Systems. Currently, the only robotic surgical system in widespread use for laparoscopic surgery is the da Vinci Robotic System (Intuitive Surgical, Sunnyvale, CA). In its current state this system can be used in almost any modern operating room. The three major components of the system are the robotic tower to which the instruments attach and are mechanically manipulated within the patient, a surgeon's console that is the workstation at which the surgeon sits to manipulate the robotic instruments, and finally the ancillary vision cart that supports a flat screen monitor, an insufflator, light source, and components of the camera system (Fig. 9–3 on the Expert Consult website). Additional monitors (either standard or boom-mounted flat screen) can be linked with the robotic system and used for the assistant and support staff image viewing.

Placement of the Operative Team for Laparoscopic Procedures

Transperitoneal Procedures in the Upper Abdomen. For laparoscopic procedures such as nephrectomy the patient is positioned in a modified lateral decubitus position for transperitoneal laparoscopic renal surgery procedures. This is at approximately a 30-degree angle to the table and allows for more effective lateral retraction of the kidney and exposure of the renal vessels during the hilar dissection. The kidney rest may be elevated at the outset and the table slightly flexed if necessary to provide adequate exposure for port placement; **after port placement, the kidney rest should be completely lowered.** The surgeon and assistant usually stand opposite the area of surgical interest (i.e., for a left nephrectomy the surgeon and assistant stand on the patient's right side). The instrument table and the scrub nurse are best located on the opposite side of the patient such that instruments can be handed to the surgeon over the table (Fig. 9–4). Incoming lines from insufflators, suction/irrigation, and electrosurgical devices enter from the contralateral side of the table. Optional technology (e.g., harmonic scalpel, argon beam coagulator) must be arranged in an orderly fashion using either preexisting or improvised pockets of the surgical drape. Again, these lines ideally should enter the field from the contralateral side of the table or from the ipsilateral head of the table. Additional technology (e.g., laparoscopic ultrasound probe) may be moved to the operating table depending on the surgeon's needs as well as on the availability of space.

To provide more comfortable positioning of the surgeon's arms, a 6 × 4-foot, 6-inch lift can be used, because most operating tables designed before widespread use of laparoscopy cannot be lowered sufficiently to allow the surgeon to hold the laparoscopic instruments with his or her elbows held comfortably at the side rather than extended laterally. This is most important during suturing. Several newer tables recently on the market, however, can be set at very low elevations (e.g., 60 cm) for the Maquet Alphamaxx (Getinge USA, Rochester, NY) so that platforms are not necessary.

Retroperitoneal Upper Abdominal Procedures. For retroperitoneal procedures the patient is placed in the true, 90-degree lateral decubitus position with the body at a right angle to the table. All of the proper steps for padding in this position should be followed (see earlier). **The table is angled at the hip to accentuate and increase the distance between the 12th rib and the iliac crest. Maximizing this distance is paramount with regard to port placement.** If necessary, the kidney rest can be raised; however, the surgeon must keep in mind that this causes increased pressure on the tableside hip and may increase the risk of pressure necrosis if left elevated for prolonged periods of time.

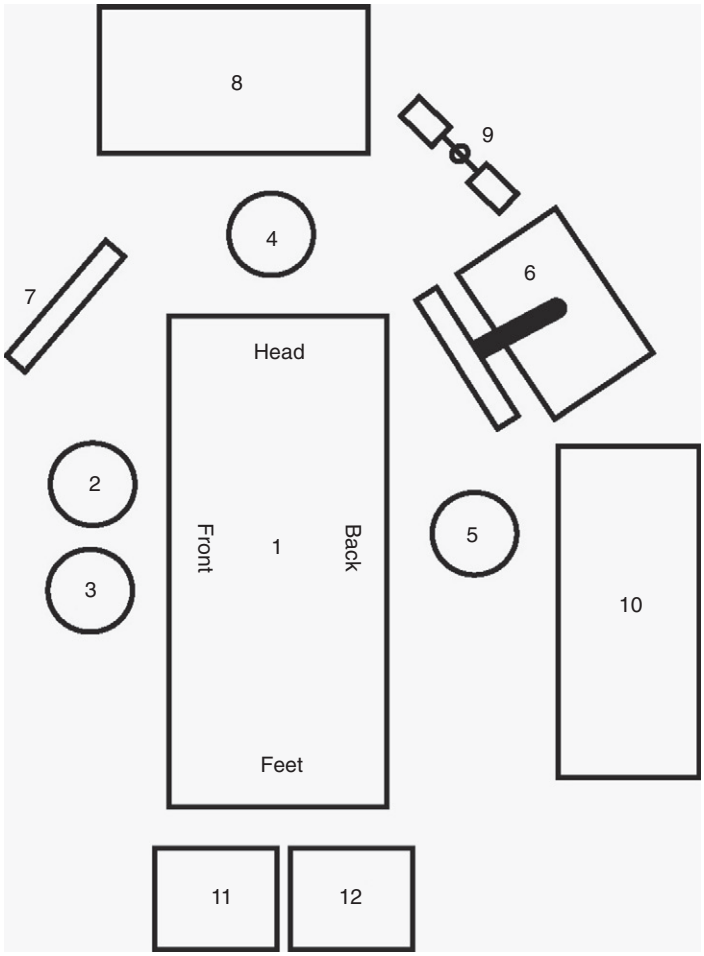


Figure 9–4. Placement of the operative team for transperitoneal procedures in the upper abdomen: 1, operating table; 2, surgeon; 3, assistant; 4, anesthesiologist; 5, scrub assistant; 6, laparoscopic cart/tower; 7, auxiliary video monitor; 8, anesthesia equipment; 9, suction/irrigation unit; 10, scrub assistant's instrument table; 11, electrocautery unit #1; and 12, electrocautery unit #2.

Most experts recommend lowering the kidney rest except when it is needed for key portions of a case. The operative field should include the space between the costal margin and the iliac crest and from the umbilicus to the spine. Both the primary surgeon and the camera assistant stand facing the patient's back (Fig. 9–5). The scrub nurse/technician stands facing the patient's front, and instruments are handed across the patient accordingly.

Transperitoneal and Extraperitoneal Pelvic Procedures

The patient is positioned in the supine position with the legs on split-leg positioners or elevated in stirrups that have knee and leg supports to avoid perineal nerve injury. The table is angled (flexed) slightly at the hip to accentuate the pelvis. The patient's arms are tucked at the sides; plastic sleds can be used to support the arms. Adequate padding should be applied to the arms and legs. A slightly snug chest strap should be placed directly across the patient's chest. The table is placed in the 30-degree Trendelenburg position. Genitalia are draped into the operative field, which extends from the mid chest to thighs and from midaxillary line to midaxillary line. The surgeon stands on the side of the table where he or she is comfortable, and the assistant stands on the side of the table opposite the surgeon (Fig. 9–6).

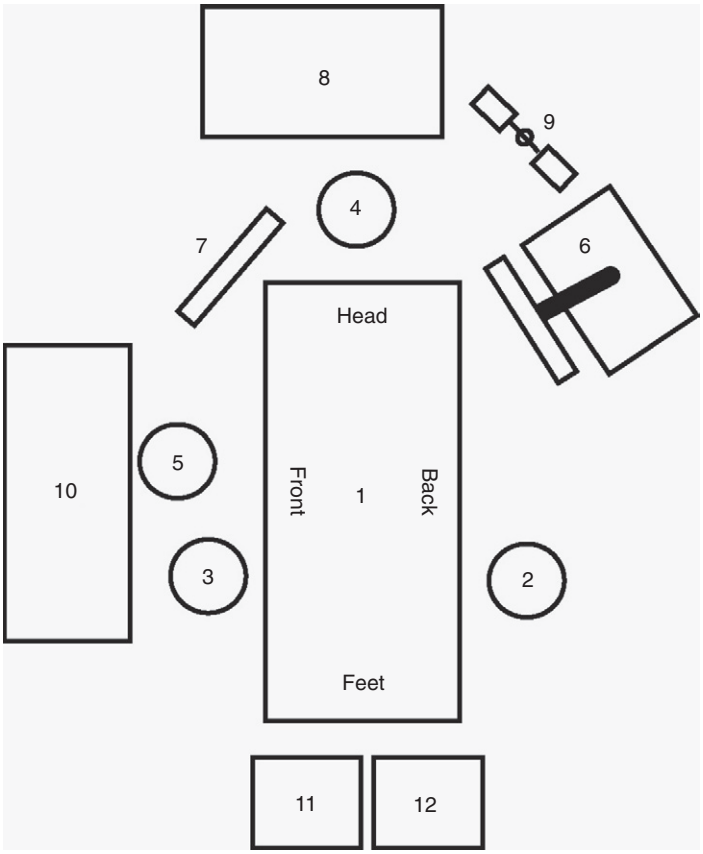


Figure 9–5. Placement of the operative team for retroperitoneal procedures in the upper abdomen: 1, operating table; 2, surgeon; 3, assistant; 4, anesthesiologist; 5, scrub assistant; 6, laparoscopic cart/tower; 7, auxiliary video monitor; 8, anesthesia equipment; 9, suction/irrigation unit; 10, scrub assistant's instrument table; 11, electrocautery unit #1; and 12, electrocautery unit #2.

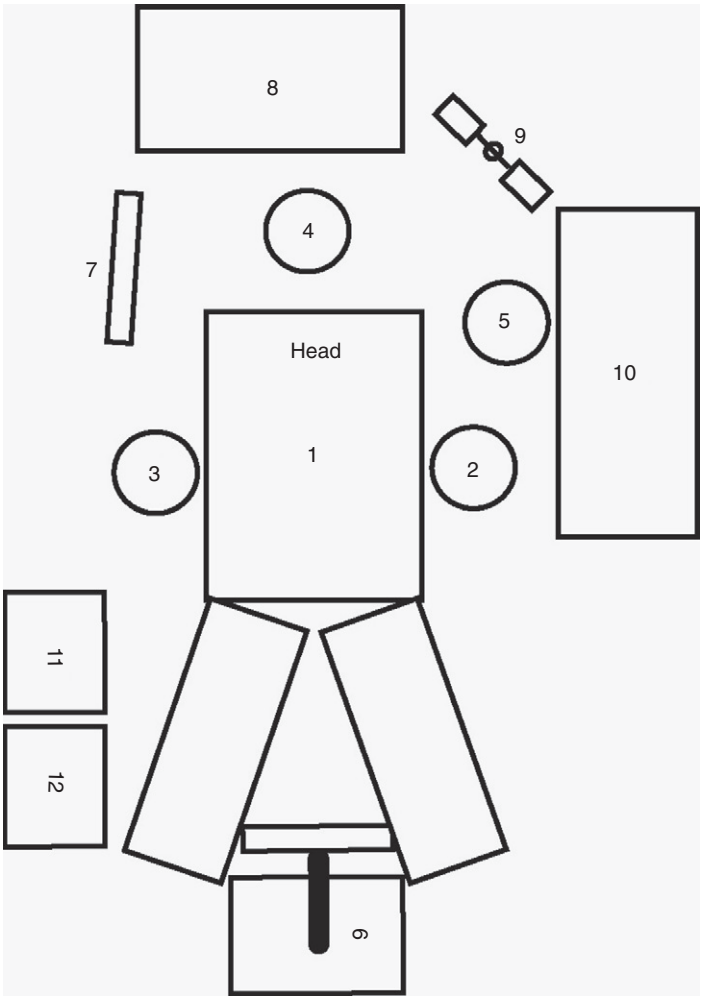


Figure 9–6. Placement of the operative team for pelvic surgery: 1, operating table; 2, surgeon; 3, assistant; 4, anesthesiologist; 5, scrub assistant; 6, laparoscopic cart/tower; 7, auxiliary video monitor; 8, anesthesia equipment; 9, suction/irrigation unit; 10, scrub assistant's instrument table; 11, electrocautery unit #1; and 12, electrocautery unit #2.

Robotic Surgery. For robotic procedures involving the kidney and adrenal gland the patient is positioned exactly as described for transperitoneal upper abdominal surgery as described earlier. The surgeon and assistant stand on the side opposite the pathologic process. The robotic tower is positioned on the ipsilateral side of the pathology such that the robotic arms stretch over the patient and can then be docked to the preplaced ports. In general it is best to angle the robot slightly such that the lens is pointing directly toward the site of interest (Fig. 9–7 on the Expert Consult website). Following this the surgeon ungowns and takes his or her place at the surgeon's console while the assistant remains on the side of the table opposite the robotic tower.

For robotic procedures on the pelvis the patient is positioned exactly as described earlier for laparoscopic pelvic procedures. After port placement the robotic tower is placed between the patient's legs and the assistant can remain on either side of the table depending on surgeon preference. The scrub nurse/technician can be positioned on the same side as the assistant to facilitate passing instruments because passing instruments across the robotic arms can be cumbersome.

PERFORMING THE PROCEDURE

Before the Initial Incision

A checklist ensuring that all essential equipment is present and operational should be completed just before initiating the pneumoperitoneum (see Table 9–1). For laparoscopic surgery this list should include (1) light cable on the table, connected to the light source and operational; (2) laparoscope connected to the light cable and to the camera, with an image that has been white balanced and focused using a white gauze sponge; (3) operational irrigator/aspirator; (4) insufflator tubing connected to the insufflator, which is turned on to allow the surgeon to see that there is proper flow of CO_2 through the tubing; kinking of the tubing should result in an immediate increase in the pressure recorded by the insufflator, with concomitant cessation of CO_2 flow; (5) an extra tank of CO_2 in the room; and (6) a Veress needle, checked to ensure that its tip retracts properly and that, when it is connected to the insufflator tubing, the pressure recorded with 2 L/min CO_2 flow through the needle is less than 2 mm Hg.

Additional items to check when utilizing the da Vinci Robotic System would include ensuring that all plugs for the console, vision cart, and surgical cart are plugged into different circuits and that all cables connecting these carts are connected properly. The system should be turned on and the self test and homing routine should be complete. The 3D camera and endoscopes should be calibrated, the image black/white balanced, and target alignment should be performed according to the manufacturer's instructions. The surgical cart should be draped and ready.

Achieving Transperitoneal Access

Pneumoperitoneum

The insufflant system (i.e., insufflator, tubing, and chosen gas) is essential for establishing a pneumoperitoneum. This is brought into use after either closed (i.e., Veress needle) or open (i.e., Hasson cannula or hand-assist device) access to the peritoneal cavity is established. If hand-assisted or single-port access laparoscopy is to be performed, the pneumoperitoneum can be established directly after placement of the port.

Most commonly, CO_2 is used as the insufflant because it does not support combustion and is very soluble in blood (LD_{50} for CO_2 is 1750 mL) (air = 357 mL) (Bordelon and Hunter, 1994). However, in patients with chronic respiratory disease, CO_2 may accumulate in the bloodstream to dangerous levels. Accordingly, in these patients, helium may be used for insufflation once the initial pneumoperitoneum has been established with CO_2 (Leighton et al, 1993). The drawback of helium is that it is much less soluble in blood than CO_2; however, its use precludes problems of hypercarbia. For this reason, even in patients with chronic respiratory disease, the procedure is initiated with CO_2 and then the change is made during the case to helium if necessary. Other gases that were once used as insufflants (room air, oxygen, nitrous oxide) are no longer routinely used because of their potential side effects (e.g., air embolus, intra-abdominal explosion, potential to support combustion). "Noble gases" such as xenon or argon are inert and nonflammable but are not routinely used for insufflation because of their high cost and poor solubility in blood.

Closed Technique: Veress Needle

Sites for Needle Passage. Disposable (70- or 120-mm, 14-gauge, and 2-mm outer diameter) as well as nondisposable (metal) Veress needles can be used. Proper needle function is ensured before the procedure. The blunt tip of the needle is tested to make sure it retracts easily; also, the needle is connected to the CO_2 line to ensure that there is no resistance to gas inflow (i.e., at 2-L/min flow, pressure remains at ≤2 mm). Lastly, saline is flushed through the needle with the tip manually occluded to make sure there is no leakage at the juncture between the shaft and the hub of the needle.

With the patient in the supine position, the head of the bed is lowered 10 to 20 degrees; insertion of the Veress needle is commonly accomplished at the superior border of the umbilicus (Fig. 9–8). There are certain advantages to choosing the umbilical area as the site for initial trocar placement: the abdominal wall is thinnest, and postoperative cosmesis is excellent. However, this point of entry is fraught with the potential for injury to a major vessel, in particular the left common iliac vessels, aorta, or vena cava.

Another important factor with regard to passing the Veress needle is body habitus; in obese patients, the umbilicus tends to migrate inferiorly. In nonobese patients the umbilicus lies in its commonly described position, directly above the bifurcation of the aorta and vena cava. Thus, for umbilical access in nonobese patients the Veress needle should be passed through the abdominal wall angled toward the pelvis to avoid injury to the bowel and great vessels that lie directly beneath. In more obese patients, because the umbilicus lies more caudad, less angulation is needed and the Veress needle should be passed perpendicular to the umbilical incision (Loffer and Pent, 1976). In addition, it has also been found that pneumoperitoneum pressure and volume as well as the ease of trocar or needle insertion is not significantly affected by body habitus. In a combined human and porcine study, McDougall and associates (1994) prospectively performed pressure-volume analysis on 41 individuals undergoing transperitoneal laparoscopic procedures and found that 94% of the maximal intraperitoneal volume is achieved with an insufflation pressure of 15 mm Hg. Additional pressure (up to 30 mm Hg) did not significantly increase volume. Furthermore, in the porcine component of the study, elevation of the pneumoperitoneum pressure above 15 mm Hg did not significantly ease bladed trocar insertion. **Therefore the pneumoperitoneum pressure need never be raised above 15 mm Hg unless it is done so in the setting of a vascular venous injury to control bleeding** (a discussion of this technique is outlined later).

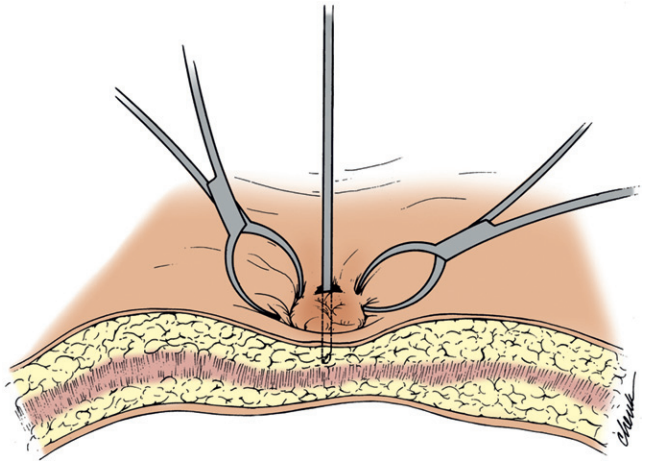


Figure 9–8. Insertion of Veress needle at umbilicus. The towel clips stabilize the abdominal wall as the needle is advanced. (From Clayman RV, McDougall EM, editors. Laparoscopic urology. St. Louis: Quality Medical Publishing; 1993.)

If the patient is in a lateral decubitus position, then the Veress needle is passed 2 fingerbreadths medial and 2 fingerbreadths superior to the anterior superior iliac spine. Just before insertion of the Veress needle a 12-mm incision is made in the previously described area, in anticipation of placing a 10- to 12-mm trocar. The subcutaneous tissues are spread with a Kelly clamp, and the anterior fascia is secured with an Allis clamp. The abdominal wall is stabilized, but not lifted, with the Allis clamp. The Veress needle is grasped at midshaft and is passed perpendicularly through the 12-mm incision using a gentle, steady pressure; two points of resistance are traversed: the abdominal wall fascia and the peritoneum. With this approach, the only organ at risk is the bowel; neither a vascular organ nor a major vessel can be injured using this insertion site.

Other potential insertion sites when the patient is either supine or in a lateral decubitus position are at the Palmer point (i.e., subcostal in the midclavicular line on the right side) and at the corresponding site on the left side. In this instance, stabilization or even a slight upward tension on the Allis clamps is essential; the needle if inserted too deeply will potentially hit the liver on either side or, rarely, the spleen, so care must be exercised. Chung and coworkers (2003) applied this method of laparoscopic access and trocar placement in 622 consecutive cases. Prior abdominal surgery had been performed in 192 patients (31%), and the BMI was 30 or greater in 98 patients. Blind Veress needle placement was successful in 579 (93%), and outcome was not associated with laterality, type of surgery, or prior surgery. In 34 cases (5%), a minor laceration to the liver was managed conservatively without sequelae; and in 21 cases (3%) the omentum or falciform ligament

was traversed without significant injury. No major complications, such as vascular or hollow-organ perforation, were caused by either the Veress needle or trocar. Neither the spleen nor bowel was ever injured. No patient developed an incisional hernia at the upper quadrant trocar site (Chung et al, 2003).

Aspiration/Irrigation/Aspiration. With the use of a 10-mL syringe containing 5 mL of saline, the Veress needle is aspirated to check for blood or bowel contents. If this test result is negative, then the saline is injected into the abdominal cavity; this should occur without any resistance. Next, the plunger of the syringe is again withdrawn; no fluid should return into the barrel of the syringe. An additional injection of 2 to 3 mL of saline will help to expel any omentum that may have been sucked into the needle tip with the original aspiration technique. Lastly, the syringe is detached from the Veress needle and any fluid left in the hub of the needle should fall swiftly into the peritoneal cavity (i.e., the "drop" test).

Advancement Test. If the needle has truly just entered the peritoneal cavity, then the surgeon ought to be able to advance the needle 1 cm deeper without the tip meeting any resistance. Resistance at this stage usually means the needle is still in the preperitoneal space and needs to be advanced through the remaining peritoneum.

Once proper needle placement is verified, insufflation is started at 2 L/min with the abdominal pressure set at 10 mm Hg. If free flow of CO_2 is noted (i.e., intra-abdominal pressure remains <10 mm Hg), then after 0.5 L has entered the abdomen the flow can be increased to maximal capacity of 9 L/min (however, no more than 2 L/min flow can be achieved through a 14-gauge needle) and the abdominal pressure set at 15 mm Hg. As soon as the preset limit of 15 mm Hg of intra-abdominal pressure is reached, free flow stops.

In a previously operated abdomen, Veress needle insertion should be performed in an unscarred quadrant of the abdomen. Alternatively, if there is no scar-free area, then an open technique (see later) should be used.

Open Access Techniques. The pneumoperitoneum can be more easily, and in one's early experience, more safely established using an open technique; however, its use involves making a larger incision and increases the chances of port-site gas leakage during the procedure. **The open technique is recommended specifically when extensive adhesions are anticipated. Studies in general surgery have shown the open technique to be as efficient as the closed approach and slightly more or equally as safe** (Bonjer et al, 1997).

In the unscarred abdomen, a 2-cm semicircular incision is made at the lower edge or slightly below the umbilicus. The fascia and peritoneum are opened individually with a transverse incision, sufficient to accommodate the surgeon's index finger. After visual and digital confirmation of entry into the peritoneal cavity, two 0 silk traction sutures are placed on either edge of the fascia. Next, the Hasson cannula is advanced through the incision with the blunt tip protruding (Fig. 9–9A). The funnel-shaped adapter of the Hasson cannula is advanced until it rests firmly in the incision, and it is then tightened onto the cannula with the attached screw; fixation to the abdominal wall is provided with the fascial sutures that are wrapped around the struts on the funnel-shaped adapter of the Hasson cannula, thereby anchoring it in place. After removal of the obturator, free flow of CO_2 into the peritoneal cavity is achieved by attaching the CO_2 tubing to the cannula. The insufflator can be set at maximum inflow, thereby creating the pneumoperitoneum quickly.

A far simpler type of open cannula is a balloon retention device (e.g., Blunt Tip Trocar With Balloon Tip, US Surgical, Norwalk, CT)

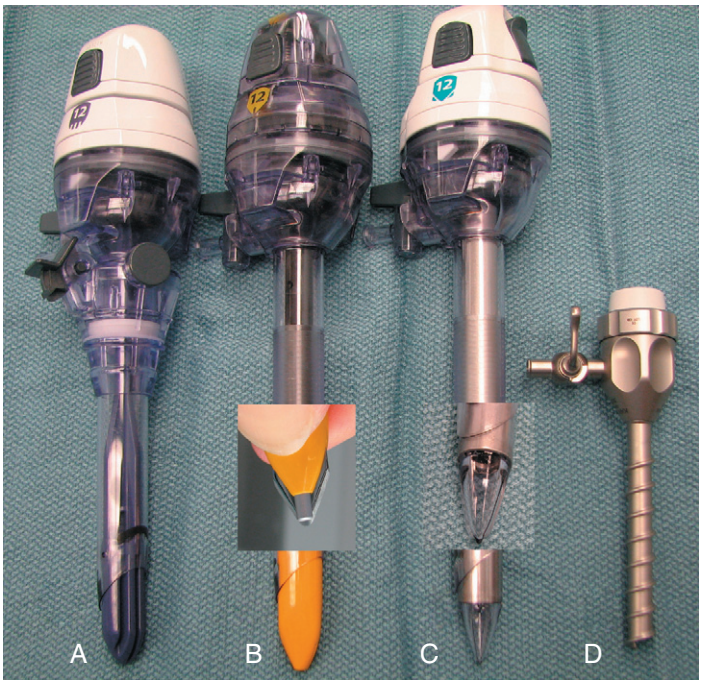


Figure 9–9. Various trocar designs showing (**A**) Hasson type, (**B**) bladed, (**C**) fascial dilating, and (**D**) screw-like designs. Enlarged images of the bladed and dilating tips are provided.

(Fig. 9–10 on the Expert Consult website). Once the cannula is positioned in the abdominal cavity, the balloon is inflated; the cannula is pulled upward until the balloon is snug on the underside of the abdominal wall. Next, the soft foam collar on the outside surface of the cannula is slid downward until it is snug on the skin and locked in place. This process creates an excellent seal, precluding gas leakage as well as subcutaneous emphysema.

Closed Technique

Blind Trocar Insertion. Generally this technique is not considered basic and should be used by the experienced laparoscopist in patients who are very unlikely to have intra-abdominal adhesions. Indeed, although reports of its use have been very favorable in the gynecologic literature, the authors are unaware of any reports in the urologic literature; similarly, none of the authors has employed this method.

This method is performed by means of a subumbilical 12-mm transverse incision; the rectus sheath on either side of the incision is grasped with a towel clip, and a surgeon on either side lifts the abdominal wall upward. It is claimed that this creates a distance of 6 to 8 cm between the underside of the abdominal wall and the underlying viscera. A 5-mm incision is made in the elevated rectus sheath, and a 10- to 12-mm disposable shielded or optical view trocar is passed vertically. In a prospective randomized study, comprising 578 patients, the direct insertion technique was found to be associated with fewer complications (4.2%) than a standard Veress insertion (complications of 14.6%); also of note, entry failure occurred in only 0.7% of the direct trocar insertion patients versus 4.6% of the Veress needle group (Gunenc et al, 2005). However, this complication rate for the Veress needle is distinctly higher than cited in other major series or meta-analyses in which Veress needle–associated vascular or bowel injuries were noted in 0.8% and 0.8% of patients (Bonjer et al, 1997).

EndoTip Entry. For this technique the abdominal wall is not tented using towel clips. It is left flat. A 5-mm incision is made in the skin at an appropriate site for a 5-mm port. The EndoTip trocar

(Storz, Germany) is a 5-mm trocar with a "corkscrew"-type self advancing and self-retaining entry system and a blunt tip (see Fig. 9–9D). The trocar can be advanced through the abdominal wall while a 5-mm, 0-degree lens is positioned inside the trocar 1 cm from the advancing tip. Once the abdominal wall muscle is engaged, the EndoTip can be lifted up slightly while continuing to rotate it through the tissues; this maneuver lifts the peritoneum, and one can watch as the blunt tip works its way through the peritoneum and into the abdominal cavity. Again, this technique should be used only in patients in whom intra-abdominal adhesions are unlikely.

Hand Port Access. If the hand port is going to be placed in the midline, then the midline should be marked before placing the patient in the 45-degree (modified) flank position. The pneumoperitoneum can be obtained before or after making the hand port incision, but if one wishes to ensure the minimum size of the skin incision then the incision should be made after obtaining the pneumoperitoneum because this places the skin more on stretch. However, if the surgeon has little experience with achieving a pneumoperitoneum, the safest maneuver is to place the hand port into a 7-cm open incision and then create the pneumoperitoneum through the hand port.

If one elects to obtain a pneumoperitoneum first, then the surgeon should carefully plan out the hand port entry site as well as the additional instrument and camera port sites. Every hand port device has a "footprint" that can be drawn on the abdominal wall; that footprint varies depending on the diameter of the external appliance. **Care should be taken to plan out the additional trocar sites carefully to avoid interference between the hand port and the instrument ports;** this is most easily done once the pneumoperitoneum has been established. After the footprint is traced, the hand port incision site is marked; the length of the incision should correspond to the surgeon's glove size (i.e., 7 glove size = 7-cm incision). The skin is incised, and the fascia is divided. The peritoneum is entered, and the insufflation is temporarily stopped. The hand port device is then placed according to the manufacturer's instructions. Additional 5-mm or 10- to 12-mm ports can be placed rapidly under manual control with the surgeon's intra-abdominal hand being used to guide the additional trocars through the abdominal wall. Alternatively, a trocar can be placed through the hand port and the abdomen can be re-insufflated. A laparoscope can then be placed through the port and the rest of the trocars can be placed under direct vision.

Laparoendoscopic Single-Site Surgery (LESS) and Natural Orifice Transluminal Endoscopic Surgery (NOTES). Recent advances in abdominal access technology combined with the development of curved and articulating laparoscopic instrumentation have made it possible to perform selected procedures through a single incision (typically 2.5 cm transumbilical); using three access ports through this incision, the laparoscope and two working instruments can be introduced.

Much the same as for hand port access the incision can be made before or after obtaining a pneumoperitoneum depending on surgeon preference. Typically, the incision is made periumbilically for cosmetic purposes. If large/intact specimen extraction is required for the procedure at hand (as in donor nephrectomy), the incision should be made just large enough to remove the specimen. If specimen removal is not necessary or the specimen is small, then the incision can be minimized to as little as 2.5 cm. Once the incision is made, several ports side by side or a single tri-port access device can be placed and a pneumoperitoneum is re-established at high flow. Thus far, LESS has been used for a variety of upper abdominal procedures including adrenalectomy (Hirano et al, 2005; Castellucci et al, 2008); renal biopsy (Kaouk et al, 2008b); renal cyst decortication; renal tumor cryoablation (Goel and Kaouk, 2008); pyeloplasty (Kaouk et al, 2008a); ileal ureter interposition; psoas hitch ureteroneocystostomy; simple, radical, and donor nephrectomy (Gill et al, 2008; Ponsky et al, 2008b; Raman et al, 2008); and partial nephrectomy (Kaouk et al, 2008b). Additionally, pelvic procedures have been performed including varicocelectomy (Kaouk and Palmer 2008), sacroculpopexy (Kaouk et al, 2008b), radical prostatectomy, and radical cystectomy with extended lymphadenectomy (Kaouk et al, 2008b).

The theoretical advantages of LESS over standard multi-incision laparoscopy are improved cosmesis, decreased pain, and faster recovery time. At the present time, however, there are insufficient data regarding LESS available to either support or refute these potential benefits (Raman et al, 2008). Research in this area is ongoing, and until well established methods and results are available surgeons are urged to approach LESS in a responsible and graduated fashion. Proper training through a combination of educational courses, hands-on laboratory training, case observation, and proctoring should be undertaken by surgeons who wish to start a successful program in LESS. One method of transitioning from standard laparoscopy to LESS for selected procedures is to gradually decrease the number of ports one uses until the procedure can be performed through a single incision. **Conversely, when one is having difficulty performing a procedure using LESS, the surgeon should not hesitate to place one or more extra trocars at separate incision sites to improve triangulation and thereby ensure safety and a quality result.**

Although the transgastric removal of an appendix in 2004 and the transvaginal removal of the gallbladder in 2007 have stimulated much interest in the realm of general surgery, natural orifice transluminal endoscopic surgery (NOTES) has remained an investigational laboratory procedure in urology. Using a transgastric and transvaginal approach, Ponsky and colleagues (2008b) have removed a porcine kidney whereas Lima and colleagues (2007) have used a transgastric and transvesical approach to excise, but not remove, the porcine kidney. These latest developments are built on the original work by Gettman and associates in 2002 in which transvaginal nephrectomies were accomplished in the pig. However, to date, there have been no NOTES procedures in clinical urology (Lima et al, 2006; Isariyawongse et al, 2008).

Instrumentation for Developing the Retroperitoneal Space

Balloon Dilation

Gradual distention of a balloon dilator in the retroperitoneal space atraumatically displaces the mobile fat and moves the peritoneum forward relative to the immobile body musculature. This device thus creates a working space equivalent to the size of the balloon.

Commercially Available Balloons. A commercially available trocar-mounted preperitoneal balloon dissector (PDB) (Covidien Ltd., Mansfield, MA) is commonly employed. The transparent, high-tensile strength silicone balloon is inflated with a sphygmomanometer bulb insufflator using room air (Fig. 9–11). The balloon has a maximum capacity of 800 mL (40 pumps of the inflating bulb). A primary advantage is that the balloon is affixed to the end of a stiff, hollow, transparent plastic shaft. The shaft allows precisely directed placement of the balloon dilator (see later).

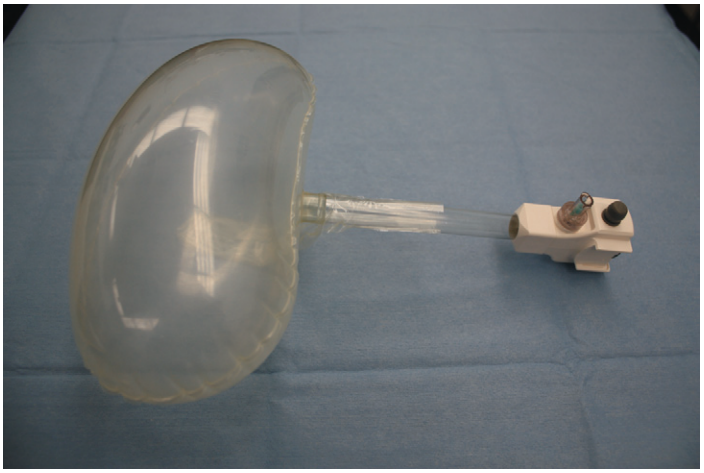


Figure 9–11. Example of a commercially available balloon dilator for creating space in the retroperitoneum: preperitoneal balloon dissector. (Courtesy of Covidien Ltd., Mansfield, MA.)

Furthermore, because the laparoscope can actually be inserted into the shaft of the balloon dilator during the inflation process it provides the capability for endoscopic confirmation of the proper positioning of the transparent balloon and of the adequacy of the controlled radial dilation of the extraperitoneal area. Balloon dilators are commercially available in two different shapes: a round balloon for dilation of the pelvic extraperitoneal space and a horizontally oriented, oblong-shaped balloon for dilation of the retroperitoneal space.

Self-Styled Dilators. Gaur's original (1992) version of the balloon dilator was a size 7 surgeon's glove mounted on a No. 8 red rubber catheter. The external end of the catheter was connected to a sphygmomanometer bulb insufflator, and the balloon was insufflated to 110 mm Hg. After this initial description, several other self-styled dilators were described: the middle finger of a size 7 to 8 glove, two fingers of a size 7 to 8 glove tied over each other for additional strength, a sterile condom, and the cot of an O'Connor-style drape mounted on a 16- or 18-Fr red rubber or whistle-tip catheter (Webb et al, 1993; Chiu et al, 1995). For the balloons made from the middle finger of a surgeon's glove, the finger is affixed to the rubber catheter with two 0 silk sutures. These self-styled dilators were filled with saline rather than air. The device may be backloaded into a well-lubricated (i.e., K-Y jelly) 30-Fr Amplatz sheath to facilitate introduction through a laparoscopic port. Although it is economically advantageous, drawbacks of the self-styled balloon include the lack of a stiff shaft to manually direct the balloon into a specific location for precise dilation as well as the inability to endoscopically monitor the dilation process from within the balloon.

An ex-vivo laboratory study demonstrated that increasing volumes of saline induced gradual pressure increments within the middle finger of a surgeon's glove. At a volume of 1000 mL, the average pressure was 15 mm Hg. Pressures remained 15 mm Hg at 1500 mL and increased to 17 mm Hg at 2000 mL (McDougall et al, 1994). In practice there is no need to exceed the 1000-mL limit. Also, latex balloons have less tensile strength than silicone balloons, making them more likely to rupture. Regardless, with either balloon setup, on the few occasions that either type of balloon has ruptured there has been no obvious complication. However, the latex balloon has a tendency to rupture into multiple pieces whereas the Silastic balloon usually leaves only one large fragment, making retrieval an easier task.

Complications associated with balloon dilation stem from improper balloon placement or balloon rupture. Intramuscular dilation may result in hernia formation, or inadvertent peritoneal disruptions may occur (Gaur, 1992; Adams et al, 1996).

Manual Dilation. Creation of a working space within the retroperitoneum may be achieved exclusively with a combination of digital and laparoscopic instrument dissection (Kerbl et al, 1993). After access to the extraperitoneal area is gained, to-and-fro movements of the laparoscope are performed to create a working space (McKernan, 1995). This technique has been employed to perform various simple and advanced procedures in the retroperitoneum (Rassweiler et al, 1998a; Abbou et al, 1999). Although it is effective, potential disadvantages of this technique include frequent cleaning of the laparoscope and the lack of clear landmarks initially due to the smaller, undeveloped working space.

Technique for Balloon Placement: Open (Hasson) Technique. This is the most commonly employed technique because it affords the greatest precision during development of the retroperitoneal space (Gill, 1998). Initial access is obtained through a 2.0- to 2.5-cm transverse incision in the midaxillary line, just below the tip of 12th rib. The wound is opened with a pair of S-retractors. Under direct vision, the posterior layer of the lumbodorsal fascia is incised and muscle fibers are split or divided. The retroperitoneal space is entered, **under direct vision,** by making a small incision in the anterior thoracolumbar fascia with an electrocautery blade or, less commonly, by bluntly piercing the fascia digitally or with a hemostat. Care should be taken that this fascial opening is snug around the index finger and no larger, so that intraoperative air leak is minimized. Index finger palpation of the belly of the psoas muscle posteriorly and the Gerota fascia–covered inferior pole of the kidney anteriorly confirms proper entry into the retroperitoneal space (Fig. 9–12A). The index finger is employed to digitally create a space in this precise location for placement of the balloon dilator; two inflations of the balloon are then done—one directed cephalad and the second directed caudad to fully dilate the retroperitoneal space (see Fig. 9–12B). Thus, balloon dilation is performed anterior to the psoas muscle and fascia and outside and posterior to the Gerota fascia. In cases involving definitive ureteric mobilization (e.g., retroperitoneoscopic donor nephrectomy, nephroureterectomy, ureterolithotomy, pyeloplasty), an additional balloon dilation may be performed more caudad to the primary site of dilation (Gill et al, 1995). Similarly, during a retroperitoneoscopic adrenalectomy, it is helpful after the initial balloon dilation to move the balloon up higher in the retroperitoneum and perform a second even more cephalic balloon dilation along the undersurface of the diaphragm (Sung and Gill, 2000).

Instrumentation for Developing the Extraperitoneal Space

Open (Hasson) Technique

A 1.5- to 2-cm curvilinear incision is made along the inferior umbilical crease. The anterior rectus sheath is incised vertically for 1.5 cm, and the rectus muscle is separated in the midline to expose the posterior rectus sheath. With the surgeon's index finger positioned posterior to the rectus muscle and anterior to the posterior rectus sheath, gentle tunneling motions are made in a caudal direction until the area of the symphysis pubis is reached. At this

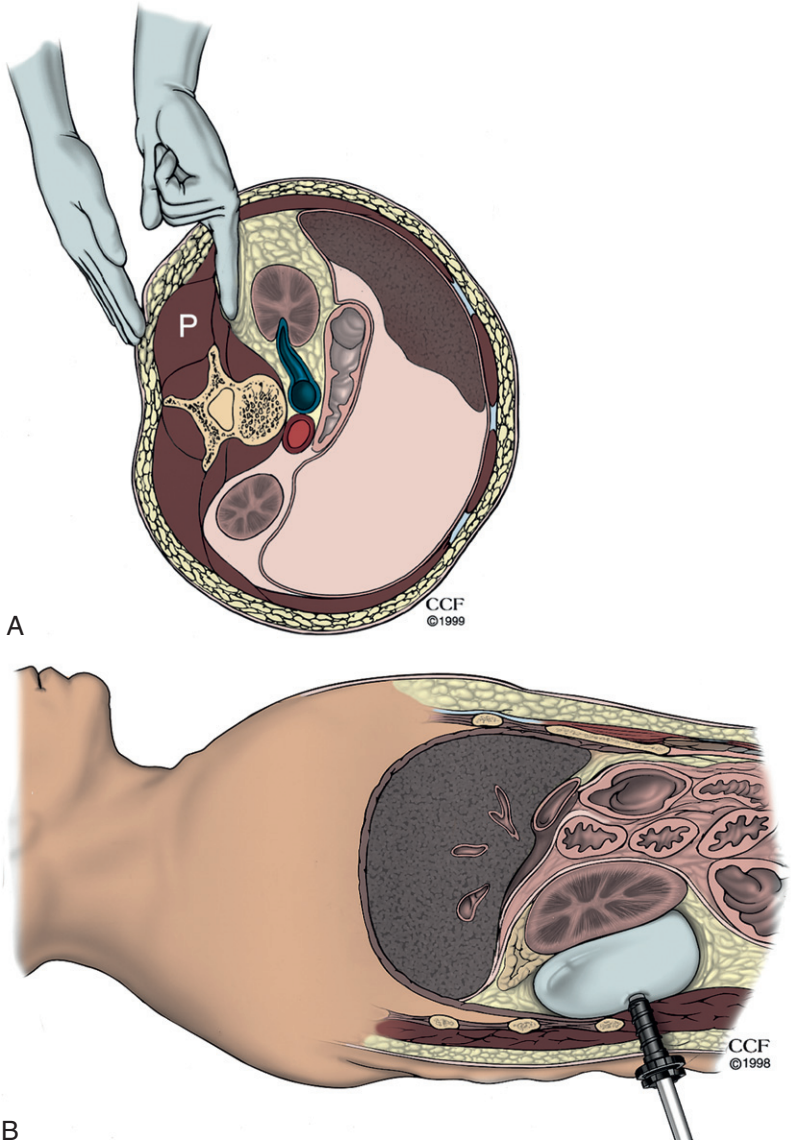


Figure 9–12. **A**, Access into the right retroperitoneum. Through the primary port incision at the tip of the lowest (12th) rib, open access is gained into the retroperitoneum after piercing the thoracolumbar fascia. Finger dissection is performed anterior to the psoas muscle and fascia to create a space for insertion of the balloon dilator. Confirmation that the finger dissection is indeed being performed in the proper plane is obtained by palpating the psoas and erector spinae muscles between the retroperitoneally located index finger and the fingertips of the opposite hand positioned on the patient's back. The fat-covered lower pole of the kidney can be palpated in a cephalad direction by turning the finger clockwise in the retroperitoneum on the right side. **B**, Balloon dilation in the posterior pararenal space facilitates the creation of a working space for retroperitoneal laparoscopic nephrectomy *(coronal view)*. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1998-2011. All Rights Reserved.)

distal location, the fascia transversalis is punctured with the fingertip and gentle side-to-side digital dissection is performed in the prevesical space, posterior to the pubic bone. Into this predeveloped space, a balloon dilator (see earlier) is inserted and distended to create an adequate working space. Balloon dilation effectively displaces the prevesical fat and reflects the peritoneum cephalad. The balloon is initially inflated in the midline and then re-inflated on either side to further expand the working area (Meraney and Gill, 2001).

Caveat: The classic Hasson cannula requires the placement of two 0 silk sutures into the fascia that are then affixed to the cone-shaped portion of the cannula to effect a seal between the cannula and the fascia. This arrangement invariably results in a significant leakage of gas because the seal is rarely airtight. Indeed, in earlier studies of retroperitoneoscopy, excessive subcutaneous emphysema and higher carbon dioxide levels were the norm owing to use of the standard Hasson cannula (Wolf et al, 1995; Ng et al, 1999); this situation was rectified with the introduction of the open access blunt port, which has a balloon to secure it against the underside of the abdominal wall and a soft foam cuff to secure it to the outer abdominal wall, thereby effecting an airtight seal (Ng et al, 1999).

Access Technology: Trocars, Hand-Ports, and Single-Port Access

Trocars. Trocars enable the laparoscopist to introduce working instruments into the gas-filled abdomen or retroperitoneum. They also maintain or reestablish a pneumoperitoneum by conveying the insufflant and may serve as pathways for delivering small amounts of dissected tissue from the surgical area. Typically a trocar consists of an outer hollow sheath (also called a cannula or port) and an inner bladed obturator, which is removed as soon as the outer sheath has entered the peritoneal cavity.

A variety of nondisposable and disposable trocars are available. Standard models range from 3 to 20 mm in diameter and 5 to 20 cm in length. One-way valves within the trocar allow the surgeon to exchange instruments through the port without the escape of significant amounts of gas. Some older trocar models have trapdoor or flap valves. In such trocars it is necessary to depress the valve lever to open the valve widely during retrieval of tissue or needles. More recently, multi-seal type valves have become available for 10- and 12-mm trocars that accommodate the passage of 5 mm and larger instruments without any air leak occurring; if large amounts of tissue are to be withdrawn, removal

of the outer seal or of the entire valve is necessary for this procedure. The outer seal/valve can then be replaced before reinserting instruments.

Initially, only sharp tipped/bladed trocars were available. On these trocars the sharp obturator incised the various layers of tissue as it entered the peritoneal cavity. To protect the underlying viscera from the sharp tip of these trocars, a plastic safety shield was later incorporated into the disposable trocars that would spring forward to shield the blade once the trocar entered the gas-filled abdomen (see Fig. 9–9B). **However, bladed trocars should be only of historical interest because they have been superseded by safer noncutting dilating trocars, which no longer require a safety shield.** These trocars enter the abdomen by spreading the abdominal wall musculature, rather than cutting it (see Fig. 9–9C). As such there is less chance of injuring an abdominal wall vessel and the resulting entry site is less prone to subsequent herniation; indeed, the risk of either of these complications is fivefold less than with blunt versus sharp trocars (Hashizume and Sugimachi, 1997; Thomas et al, 2003).

As with the older sharp trocars there are both disposable and nondisposable blunt trocar units. The Step Needle/Sleeve (Covidien Ltd., Mansfield, MA) is a disposable system that uses a needle port with an outer diameter of 2.1 mm (6.5 Fr) that incorporates a Veress needle introducer. After correct and successful puncture of the abdomen and establishment of the pneumoperitoneum, the Veress needle introducer is removed and the needlescopic port serves either as a camera-bearing sheath of a 1.9-mm needlescope or as a working port for needlescopic scissors or graspers used to perform needlescopic surgery. Alternatively, the needle can carry the initial port into the abdomen; this is an expandable port that in its collapsed state is 2.1 mm at the distal tip and 3.8 mm along the body of the trocar. This trocar can then be expanded by passage of a blunt-tipped obturator to expand the collapsed sheath to 5 mm, 10 mm, or 12 mm, depending on the surgeon's needs. The port has an adjustable seal that allows introduction of laparoscopic instruments within a range of 4.4 to 12 mm in diameter. Thus, the tissues of the abdominal wall are stretched rather than incised, thereby precluding the need for placement of fascial sutures at the end of the procedure.

Other blunt-tipped trocars are produced by all of the major trocar manufacturers. These devices have a variety of tips that enable their placement by spreading the tissues; some also have a clear plastic tip such that the surgeon can pass an endoscope into the trocar to endoscopically monitor its passage through the abdominal wall and its entry into the gas-filled abdomen. One of the blunt-tipped disposable trocars incorporates a curved cutting blade that is trigger activated by the surgeon as the clear port is passed under endoscopic control (i.e., Visiport Plus RPF Single Use Optical Trocar with Versiport Plus RPF Converterless Trocar Sleeve, US Surgical, Norwalk, CT). This hybrid of a blunt and sharp trocar is used sparingly owing to the cutting blade, which can still injure vessels or viscera; also the port site created by passage of this trocar requires a sutured closure of the fascia.

The only reusable blunt-tip port, the EndoTip system (Karl Storz, Culver City, CA), is a screwlike device that has no sharp points or cutting edges (see Fig. 9–9D). It comes in 5-, 10-, and 12-mm designs; however, the 10- and 12-mm trocars require use of a cumbersome reducer system because they are not of a multiseal design (see earlier). It is introduced through the skin incision, by rotating the cannula in a clockwise manner until the gas-filled abdomen is entered; alternatively, an appropriately sized 0-degree lens laparoscope can be used to monitor the penetration of the various tissue layers. Indeed, this combination can be used in the situation when use of the Veress needle to obtain a pneumoperitoneum has failed; in this case, once the EndoTip engages the abdominal wall musculature the device is held upward while continuing to rotate it—in this manner the peritoneum is lifted upward and safely entered. Unlike the action of trocars with a sharp tip, the tissue is not cut but is only displaced and bluntly dilated, thereby preserving the closing mechanism of the overlying muscle and fascia. Because of its innovative design, this device reduces injury to the intra-abdominal organs, stays securely in place, and seals the point of entry against any inadvertent loss of gas.

On removal of any of the blunt-tip ports, the fascia does not need to be sutured, except when it is placed in a non-midline area. However, some surgeons do not place a suture even with midline placement provided that postoperative palpation of the entry site reveals a small defect (Siqueira et al, 2004).

All primary and some secondary trocars have sidearm insufflation line input valves and a small distal hole near the tip to prevent formation of a vacuum, which may suck viscera into the cannula when the cannula is removed. Some less expensive, smaller trocars do not have sidearm stopcocks and can be used only as secondary trocars.

Reducers allow downsizing of working channels in 10-mm or larger trocars to accommodate smaller, 5-mm working instruments without any leakage of CO_2; however, the development of multiseal technology has resulted in valves that can accommodate 5- to 12-mm instruments without the need for a reducer. This development saves significant time during a long procedure.

Retention of the cannula at the port site is essential to decrease air leak and subcutaneous emphysema and facilitate the timely completion of a procedure. In the past it was necessary to affix a suture to the insufflation sideport and the skin to secure the trocar. At present, myriad retention mechanisms prevent dislocation of cannulas: threaded sleeves, adjustable threaded sleeves, expandable arms, and inflatable balloons. In this regard the older plastic devices used to affix a metal trocar to the abdominal wall should never be used; this combination can result in inadvertent capacitive coupling electrosurgical injury to the bowel or other viscera owing to the insulating effect of the plastic device.

Hand-Assist Devices. The first generation of hand port devices consisted of the Handport, Intromit, and Pneumosleeve. As with most first-generation laparoscopic devices, they were adequate with regard to functionality but each had its drawbacks (Stifelman and Nieder, 2002). These products have now been replaced by a second generation of improved devices: The Gelport (Applied Medical, Rancho Santa Margarita, CA), the Omniport (Advanced Surgical Concepts, Wicklow, Ireland), and the LapDisc (Ethicon Endosurgery, Cincinnati, OH).

The Gelport (Fig. 9–13A on the Expert Consult website) consists of a gel-like disc that easily admits the surgeon's hand and then molds around the wrist and arm. The latest Gelport design has a 12-cm footprint. To set up the two-piece Gelport system the surgeon inserts the lubricated wound protector through a 7- to 8-cm incision and adjusts it to create a tight seal across the abdominal wall. A gel disc is then snapped on top of the wound protector and held in place with a small lever. The Gelport offers the advantages of never losing a pneumoperitoneum on hand exchange because it immediately seals after hand removal and it does not require adjustment to maintain a seal. Additional instruments can be passed alongside the surgeon's hand, through the gel material, also without loss of the pneumoperitoneum.

The Lapdisc (see Fig. 9–13B on the Expert Consult website) is a one-piece unit that has an inner diaphragm that is used to anchor it across the abdominal wall and an outer appliance that dials down a thin plastic sheet, like a camera iris, around the surgeon's wrist. Although this device has a low profile and small footprint (12 cm) it does result in loss of the pneumoperitoneum every time the hand is removed and reinserted and instruments cannot be passed parallel to the surgeon's hand.

The Omniport (see Fig. 9–13C on the Expert Consult website) is a balloon-like device that anchors itself as one piece across the abdominal wall. The inflated device also creates a seal between itself and the surgeon's wrist. The device has a smaller footprint (12 cm); however, it must be uninflated and reinflated each time a hand is exchanged, which results in loss of the pneumoperitoneum. Furthermore, no additional devices can be passed parallel to the surgeon's hand through the device.

In a recent study, 130 urologists participating in a series of hand-assist courses evaluated the different devices for a variety of features. The overall scores in this study were 8.6, 7.4, and 7.3 on a scale of 10 (10 being best) for the Gelport, LapDisc, and OmniPort, respectively (Patel and Stifelman, 2004). Advantages of the Gelport included sturdiness, ease of hand exchange, maintenance of the pneumoperitoneum, as well as the ability to pass both a hand and a laparoscopic instrument simultaneously. Of note, the price to the surgeon of using a hand-assist device is not inconsequential. For the surgeon, pain and numbness of the hand/wrist/forearm and, to a lesser extent, overall fatigue are much greater when using a hand-assist device versus standard laparoscopy (Monga et al, 2004; Gofrit et al, 2008).

Access Devices and Techniques for LESS. There are two basic methods used to achieve intra-abdominal access for LESS. One technique is to make a 2.5-cm incision, typically periumbilical or transumbilical (although an alternate site may be necessary), through which a skin flap can be raised off of the abdominal wall fascia. Then, through this single incision several (two to four) standard 5-mm laparoscopic ports can be placed in close proximity to one another. A laparoscope and working instruments can then be placed through these ports. **The size of the skin incision should correspond to the surgical task at hand. If the procedure does not require removal of a large intact specimen, then the incision should be minimized to as little as 2.5 cm. If the procedure requires large intact specimen removal (as in donor nephrectomy), then the incision should be large enough to extract the specimen.**

Another technique is to use a commercially available single site surgery device. These devices currently require a single incision that is typically placed periumbilically or transumbilically unless the procedure dictates an alternate site. Currently there are three devices that are available for commercial use. The TriPort (Advanced Surgical Concepts, Bray, Ireland) is a two-piece system consisting of an inner diaphragm that works like a wound protector and an outer piece containing the ports (Fig. 9–14A). The wound protector component is adjustable and cinches down the outer attachment, creating a tight seal on the abdominal wall. The TriPort, which requires a 12- to 25-mm incision, has room for a 5-mm laparoscope and two 5-mm working instruments plus a separate insufflation valve. The same manufacturer also makes a four-port model called the QuadPort that contains two 12-mm and two 5-mm instrument insertion sites; it requires a 2.5- to 6.5-cm incision. The Uni-X (Pnavel Systems, Cleveland, OH) is a similar device that is anchored to the abdominal wall by preplaced facial sutures. It has three 5-mm insertion sites and can be placed through a 1.5-cm incision (Kaouk et al, 2008b).

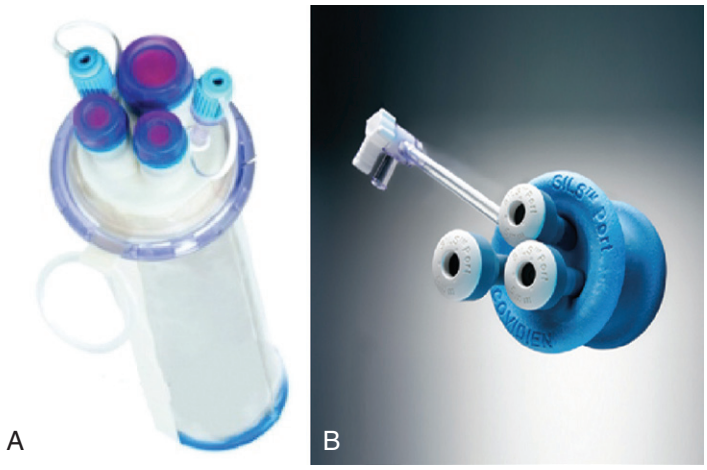


Figure 9–14. Commercially available ports for LESS surgery. **A,** Triport. **B,** SILS port.

The SILS port (Covidien Ltd., Mansfield, MA) can be placed into a 2-cm incision and can house three 5-mm ports or two 5-mm ports and a 5- to 10-mm port (see Fig. 9–14B).

These devices have been used successfully to perform single-site nephrectomy, adrenalectomy, pyeloplasty, renal cyst decortications, and renal cryoablation (Castellucci et al, 2008; Gill et al, 2008; Goel and Kaouk, 2008; Kaouk et al, 2008b; Ponsky et al, 2008b; Rane and Rao, 2008).

Placement of Initial Trocar. For pelvic procedures, the patient is usually positioned with the head slightly down and the intra-abdominal CO_2 pressure is kept at 15 mm Hg. After establishment of a Veress needle pneumoperitoneum (i.e., closed technique), the edges of the wound and subcutaneous tissue are spread with a blunt forceps. Next, the trocar is held in the dominant hand with the middle finger extending along the shaft and the trocar is inserted using a twisting downward motion. If the surgical site is in the mid to upper abdomen, then the trocar is passed perpendicular to the umbilical incision; however, for pelvic procedures, the trocar is directed 70 degrees caudad. Proof of entering the gas-filled intraperitoneal cavity is the sound of CO_2 escaping from the open sidearm. After the sidearm is closed, the obturator is removed and the CO_2 insufflation line is connected to the side port of the trocar. If using a clear blunt port, a 0-degree laparoscopic lens is placed so the entire entry of the trocar is endoscopically monitored.

For procedures such as nephrectomy or nephroureterectomy the patient is placed in the modified flank (i.e., lateral decubitus) position and the pneumoperitoneum pressure is increased to 20 mm Hg. The initial incision is usually either 2 fingerbreadths medial and 2 fingerbreadths superior to the anterior-superior iliac spine or subcostal in the midclavicular line (e.g., at the Palmer point on the right). The trocar is passed perpendicular to the skin incision in the manner described for the transumbilical approach.

When an **open technique** is performed to obtain the pneumoperitoneum, the Hasson-style cannula used to obtain access to the abdomen also serves as the initial trocar.

Transperitoneal Approach: Abdominal Inspection. The sterile laparoscope is white balanced. If the laparoscope is a standard optical lens then it can be pre-warmed using a thermos with warm water. Although it is a minor extra expense, a dedicated fluid warmer to

warm the shaft of the standard endoscope is a very useful adjunct. However, **newer endoscopes that have electronics embedded in the tip of the shaft should not be submerged in water.** A standard defogging agent may also be applied to the tip of the endoscope.

The **entire abdomen** is inspected systematically. Initially, abdominal inspection is performed to rule out any injury to the underlying viscera that may have occurred during access or placement of the initial trocar. The laparoscope is then introduced through a second port to "look back" at the initial port placement site. Then, if the patient is supine, the following pelvic anatomic landmarks are visualized: bladder, urachus, medial umbilical ligaments, and internal inguinal rings, followed by the appendix and the lower parts of the colon; in the male the vasa deferentia can sometimes be seen, whereas in the female the round ligaments, uterus, and ovaries are viewed. Next, turning toward the upper abdomen, the liver, gallbladder, spleen, stomach, omentum, and small bowel are visualized. However, abdominal inspection is usually limited to the superior ipsilateral half of the abdomen if the patient has undergone insufflation and port placement in the lateral decubitus position.

Hand-Assist Placement. The hand-assist device can be placed either as an initial "port" or as a secondary port depending on the surgeon's preference. The former approach is easier because the procedure then begins with making a standard midline (for right or left renal surgery) or right lower quadrant (i.e., for right renal surgery) 6.5- to 7.5-cm incision at the planned hand-assist site. The peritoneal cavity is entered in the standard open surgical fashion, following which the hand-assist device is placed. Next, a blunt cannula is passed through the hand-assist device and a pneumoperitoneum is established. Alternatively, a Veress or Hasson pneumoperitoneum may be initially established and the hand-assist device can then be placed under endoscopic monitoring. Before initiating a hand-assist procedure, the surgeon is advised to wrap the arm/glove seam on the hand that is to be used through the handport either with a 1010 drape or an Ioban (3M, St. Paul, MN) "sticky drape" to waterproof his or her arm; if a 1010 drape is used, the surgeon will need to place a second glove on the hand-port hand to prevent its dislodgment during the procedure.

Additional blunt ports can be rapidly and safely placed using the surgeon's one hand to place the port while the intra-abdominal hand is used to palpate the tip of the trocar and hence guide its entry into the abdomen. **Lastly, the use of a brown glove on the intra-abdominal hand is recommended because they do not reflect the light from the laparoscope and thus reduce glare** (Wolf, 2005).

Secondary Trocar Placement

Transperitoneal Standard. Number, size, and exact location of secondary trocars depend largely on the intended laparoscopic procedure. Their configuration should be planned so that neither the tips nor handles of the cannulas cross or come into close contact with one another (a problem termed *crossing swords* and *rollover*, respectively) such that adequate working space is provided for all instruments to be used during a particular procedure and allowing for effective triangulation at the surgical site by the endoscope and two working ports. In general, it is reasonable to place the ports in a four-point diamond pattern such that the site of the operation is encircled within the diamond. **This is particularly important when considering reconstructive renal procedures, because the angle between the horizontal plane and the needle drivers should be less than 55 degrees whereas the angle between the surgeon's suturing instruments should be in the 25- to 45-degree range** (Rassweiler and Frede, 2002).

Secondary trocars are placed under direct optical control. The 30-degree lens is ideal for this portion of the procedure because turning the lens 180 degrees away from the surgical site provides the surgeon with a panoramic view of the anterior abdominal wall. The operative lights are dimmed, and the tip of the laparoscope is moved upward toward the intended site of port placement, thereby, in the thin patient, transilluminating any superficial blood vessels that need to be avoided while passing the trocar. Using a No. 12 hook or No. 15 small blade, a skin incision is made just wide enough to accept the selected cannula. When placing secondary ports, it is of great importance to direct them toward the intended surgical field to provide tension-free maneuverability of the laparoscopic instruments. This is especially important in obese patients because the errant port will provide resistance to the surgeon throughout the rest of the procedure. Similar to placement of the initial port, all secondary ports are advanced through the abdominal wall using a slow, twisting motion and constant pressure. If necessary, the abdominal wall can be elevated by towel clips placed at the edges of the skin incision made for port entry, to facilitate safe advancement of trocars into the peritoneal cavity. Each secondary port is passed into the peritoneal cavity under meticulous endoscopic monitoring. After placement of the second port, a 5- or 10-mm laparoscope is advanced through this port to inspect the entry site of the first trocar into the peritoneal cavity to rule out any inadvertent injury to the bowel, underlying viscera, or an abdominal wall vessel. To prevent dislocation, ports that do not possess self-retaining mechanisms may be anchored to the skin using No. 2 nonabsorbable sutures. In this regard it is very important for the surgeon to never use a plastic retention sleeve with a metal cannula; this combination creates a situation in which stray electrosurgical current may injure the bowel or other structures adjacent to the cannula since the plastic sleeve insulates the abdominal wall, resulting in increased current density along the metal intra-abdominal portion of the cannula.

Transperitoneal: Hand-Assist. When the hand-assist device is in place, then secondary trocars can be placed with digital guidance. After inspection of the abdomen rules out any potentially interfering adhesions, the surgeon's index finger is placed on the underside of the abdominal wall at the planned site of trocar placement. A skin incision is made over the surgeon's index finger and the nonbladed trocar is passed with the other hand and guided by the surgeon's finger into the abdominal cavity. This is a very rapid and safe way to place all of the secondary nonbladed trocars.

Retroperitoneoscopy Approach. After controlled balloon dilation of the retroperitoneum, the balloon dilator is replaced with a 10-mm Bluntport (US Surgical, Norwalk, CT). A feature unique to this port is the presence of an internal doughnut-shaped retention balloon and an external adjustable foam cuff, a combination that effectively creates an airtight seal at the location of the primary port site (see Fig. 9–10 on the Expert Consult website). **Use of this device minimizes CO_2 leakage around the 1.5-cm primary port incision, thus reducing the incidence of subcutaneous emphysema and hypercarbia.** In our experience this is far superior to the reusable Hasson cannula; with this device efforts directed at minimizing gas leak, such as placing a deep mattress stay suture or placing petroleum jelly gauze around the cannula, were rarely effective.

For retroperitoneoscopy, several port arrangements are possible: a three-port (I distribution) approach can be employed (Gill, 1998;

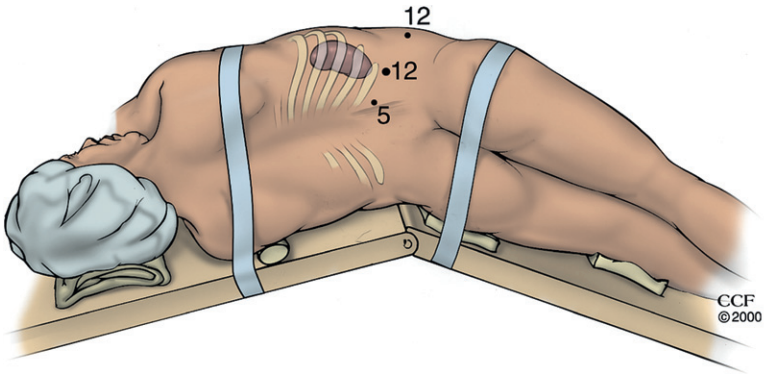


Figure 9–15. For retroperitoneal laparoscopy the patient is positioned in the standard full-flank position. The kidney rest is elevated, and the operating table is flexed to maximize the space between the iliac crest and the lowest rib. A three-port approach is employed. The primary 12-mm port is placed inferior to the tip of the 12th rib. An anterior 12-mm port is placed near the anterior axillary line 3 cm cephalad to the iliac crest. A posterior 5-mm port is placed at the junction of the lateral border of the paraspinal muscles and the 12th rib. (*Note:* After port placement, the kidney rest is lowered.) (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1998-2011. All Rights Reserved.)

Hsu et al, 1999), the authors prefer a four-port approach (T distribution), whereas Abbou and colleagues (1999) described a five-port approach (W distribution). A 30-degree or flexible laparoscope is used, and all secondary nonbladed ports are introduced under laparoscopic or digital control. The posterior secondary port is placed at the lateral border of the paraspinal muscles along the inferior border of the lowermost (12th) rib, and an anterior port is placed at the anterior axillary line, subcostal; thus the three ports are all in a line, hence an I-shaped configuration (Fig. 9–15). A fourth port may be placed, in the middle axillary line, 2 to 3 fingerbreadths above the anterior-superior iliac spine near the Petit triangle thereby creating a T configuration. Placement of this anterior port any closer to the iliac crest limits the amount of cranial angulation of the cannula. A fifth port can be placed just lateral to the anterior axillary line and on the same level as the fourth port, creating a W configuration. Depending on the anticipated technical difficulty of the procedure, patient obesity, and tumor size, for the I configuration, two 12-mm secondary ports or one 5-mm port and one 12-mm secondary port are used. In either situation, a 12-mm port is routinely placed for the surgeon's dominant hand to allow interchangeable use of various large-caliber instruments, including a 10-mm Endo Clip applier, a 12-mm Endo GIA stapler, a 10-mm right-angle dissector, and a 10-mm reusable expandable retractor. The two secondary ports should be inserted as far apart as possible to minimize the possibility of instrument tips clashing within the retroperitoneum. The additional two ports can be 5, 10, or 12 mm depending on the surgeon's preference. Contrary to common conception, the occurrence of an inadvertent peritoneotomy during retroperitoneoscopy does not usually interfere with the subsequent steps of the procedure and conversion to a transperitoneal laparoscopic technique is not mandatory (Gill et al, 2000).

Extraperitoneal Access to the Pelvis. After balloon dilation the Bluntport is inserted at the infraumbilical incision. The retention balloon is inflated, and the foam cuff is cinched down onto the abdomen. **For robotic procedures a standard 12-mm trocar is placed in the extraperitoneal space and hence care should be taken not to create an incision larger than 12 mm** (Esposito et al, 2008). The extraperitoneal space is insufflated with CO_2 at a pressure of 12 to 15 mm Hg, and secondary ports are introduced under visual control. Depending on the procedure to be performed, three to four secondary ports are inserted in a triangle-, diamond-, fan-, or W-shaped configuration. Pneumoextraperitoneum is reduced to 10 to 12 mm Hg for the remainder of the procedure. Unlike with retroperitoneoscopy, the occurrence of a peritoneotomy during extraperitoneoscopy may interfere with the performance of subsequent extraperitoneal dissection and conversion to a transperitoneal technique may be required (Meraney and Gill, 2001).

Robotic Considerations. If a robotic procedure is planned, then the camera port is a 12-mm trocar site and the two (or three if the fourth arm is employed) auxiliary ports are 8 mm. All the ports need to be placed 8 to 10 cm apart to reduce the possibility of the robotic arms clashing with each other. In addition, if the patient is in a flank position, then the lowest port placement should not be inferior to the umbilicus or else the arm may be blocked from a full range of motion by the patient's upside leg. An assistant's port is placed on a line either caudal or inferior to the robotic arms; placement of the assistant's port in between the arms of the robot makes it quite awkward for the assistant to work and limits the range of motion of the assistant's instrument owing to clashing with the arms of the robot.

Laparoscopic Instrumentation

Instruments for Visualization

To create a laparoscopic image, four components are required: the laparoscope, light source, camera, and monitor. To record the image, video recorders, digital video disc, and video printers are available. Laparoscopes that are most commonly used have 0- or 30-degree lenses (range, 0 to 45 degrees) and are available in sizes from 2.7 to 10 mm (most commonly, 5 or 10 mm); however, newer deflectable laparoscopes now exist in which the tip of the endoscope can deflect in four directions up to 90 degrees (Olympus, Melville, NY). Another novel endoscope design is the EndoCAMeleon (Karl Storz, Tuttlingen, Germany). This scope maintains the familiar feel of a standard rigid laparoscope but has a variable-view swing prism that enables the surgeon to change viewing angles from 0 to 30, 45, 90, or 120 degrees. An advantage of the EndoCAMeleon is that it has a standard eyepiece, allowing it to be used with most camera systems.

With standard laparoscopes, image transmission employs an objective lens, a rod-lens system with or without an eyepiece, and a fiberoptic cable. From the eyepiece, the optical image is magnified and transferred to the camera and onto the monitor. Light is transmitted from the light source through the fiberoptic cable onto the light post of the laparoscope (Fig. 9–16A on the Expert Consult website). Some newer laparoscopes have a mini charge-coupled device (CCD) camera mounted at the tip (EndoEYE, Olympus, Melville, NY), which improves image quality and avoids the need for an external light chord that can sometimes impede the movement of other instruments (see Fig. 9–16B on the Expert Consult website). Historically the advantage of the larger

laparoscopes is that they could provide a wider view, better optical resolution, and a brighter image. However, today, many of the 5-mm laparoscopes provide an image that rivals traditional 10-mm scopes. These 5-mm laparoscopes, especially those designed with a low profile handle and a deflectable tip, are particularly of use for LESS procedures.

A special variant is the offset "working laparoscope," which includes a working channel for passage of basic laparoscopic instrumentation; use of this type of laparoscope enables the surgeon to work in a direct line with the image and may allow a reduction in the number of trocars needed to accomplish a particular procedure. However, the working channel occupies space that would otherwise be used for the optical system; thus the resulting image is usually of lesser quality compared with that of laparoscopes without this feature.

The **camera system** consists of a camera and a video monitor. All currently made cameras can be gas or liquid sterilized, thereby facilitating their use and limiting possible intraoperative contamination. For standard laparoscopes the camera is attached directly to the end of the laparoscope and transfers the view of the surgical field through a cable to the camera box unit. After reconstruction of the optical information the image is displayed on one or two video monitors.

A wide variety of cameras are currently available: single-chip, single-chip/digitized, three-chip, three-chip/digitized, interchangeable fixed-focus lenses, zoom lenses, beam splitter, and direct coupler. Three-chip cameras are superior to single-chip cameras in that they provide a higher-quality image with superior color resolution. Again, some endoscopes have the added advantage of having the chip directly at the tip of the laparoscope such that the images are directly processed without interruption thus greatly improving image quality (EndoEYE, Olympus, Melville, NY). This allows the entire system to be built into the handle such that the endoscope connects directly to the camera box; as such, a better image is obtained and the handle has a very low profile (see Fig. 9–16B on the Expert Consult website). **To obtain a "true" upright image of the surgical field on the monitor, the camera's orientation mark must be placed at the 12-o'clock position. With 0-degree laparoscopes the camera is locked to the eyepiece in the "true" position. In contrast, with the 30-degree laparoscope the camera is loosely attached to the eyepiece of the laparoscope so the laparoscope can be rotated. Accordingly, the assistant must hold the camera in the "true" upright position with one hand while rotating the laparoscope through a 360-degree arc to peer over and around vascular and other intra-abdominal structures; the 30-degree lens thus provides the surgeon with a more complete view of the surgical field than does a 0-degree lens. A more recent advancement in laparoscope technology is the four-way deflectable endoscope (EndoEYE Deflectable Tip Video Laparoscope, Olympus, Melville, NY), which offers many potential angles from which to view a structure but requires an adept assistant.**

Three-Dimensional (3D) Laparoscopic Systems. 3D laparoscopic systems offer the surgeon the distinct advantage of depth perception. Optimal 3D laparoscopy is performed with a two-lens system that duplicates the two-eye perception of 3D. In this way binocular vision is maintained. The most commonly used 3D vision system currently in use is the InSite Vision System (Intuitive Surgical, Sunnyvale, CA), which provides vision for the da Vinci Robotic System. The laparoscope and high definition camera are heavy (4 lb for the standard scope and camera head and 5.5 lb for the high-definition scope and camera head) but are controlled by a robotic arm that is under direct control of the surgeon from the ergonomic console. The surgeon maintains a steady, magnified 3D view of the surgical field. Zero- and 30-degree lenses are currently available.

Handheld 3D laparoscopic systems are also available but currently require the surgeon to wear headgear with miniature video screens to display the 3D image (EndoSite 3Di Digital Vision System, Viking Systems Inc., La Jolla, CA). With these systems it is often useful to employ the use of a mechanical or robotic camera manipulator because the slight movements associated with handheld camera manipulation can be distracting when displayed in 3D.

The most vexing problem with any laparoscope is fogging of the lens. To prevent fogging of the laparoscope after insertion into the warm intraperitoneal cavity it is advisable to initially warm the laparoscope in a container holding warm saline before it is passed into the abdomen. The most efficient way to warm the laparoscope is to use a dedicated solution warming basin that is long enough to accommodate the laparoscope; alternatively a warming thermos can be used (Applied Medical, Rancho Santa Margarita, CA). In addition, wiping the tip with a commercial defogging fluid or with povidone-iodine solution is also recommended. Should moisture buildup occur between the eyepiece and the camera both components must be disconnected and carefully cleansed with a dry gauze pad; this is not a problem with the digital endoscopes because the only connection is from the endoscope directly into the display box. **Again, digital endoscopes that house electronic components at the tip of the instrument should NOT be submerged in water.**

Video monitors are available in various sizes ranging from 15 to 26 inches and come in the form of standard cathode ray tube (CRT) monitors or newer flat panel displays. With standard CRT monitors, a larger monitor does not produce a better picture; indeed, given the same number of lines on both monitors, a higher-resolution image is obtained with a smaller screen. To obtain a better image, more lines of resolution are needed. High-resolution monitors have 1125 lines of resolution but must be matched with a camera system of similar capability. Flat panel video monitors are becoming more popular; one advantage is that these screens are usually mounted on a ceiling boom that allows the surgeon to obtain a clear view of both the monitor and the surgical field with the patient in any position. In addition, the flat screen can be lowered and angled close to the surgical site, thereby placing the surgeon's line of sight and the actual operating field in a truer alignment. Flat panel displays are available in standard and high-definition resolution.

Light sources use high-intensity halogen, mercury, or xenon vapor bulbs with an output of 250 to 300 watts. In addition to manual control of brightness, some units have automatic adjustment capabilities to prevent too much illumination, which may result in a "washed-out" image. Any breakage of fibers in the fiberoptic cable, which may occur during sterilization and/or improper handling, results in decreased light transfer from the light source to the laparoscope. Newer light cables are transparent, allowing the surgeon to actually see when light-bearing cables have been damaged. In the event of bulb failure, an extra bulb (or light source) should always be available.

Videocassette recorders, digital video recorders, and video printers serve for documentation of laparoscopic procedures. Videocassette recorders are very reliable for taping procedures but are very cumbersome when it comes to storing, viewing, and editing for replay. Newer systems that use digital tapes,

compact discs, or digital video discs are much more compact and easier to use when it comes to replaying and editing for video production. With regard to still images, the newer digital recorders have the advantage of storing thousands of images and maintain the ability to print paper copies of the desired images.

Instrumentation for Grasping and Blunt Dissection

Most graspers and dissectors are used in their 5-mm size but are available in a range from 3 to 12 mm, in predominantly reusable forms. Grasping instruments have either single-action (only one jaw moves during opening) or double-action (both jaws move) tip design.

Wide variations exist with regard to configuration of tip, surface characteristics of jaws, handle design, and possible electrosurgical properties. Tip designs include blunt-coarse, pointed (dolphin), straight (duck bill), curved (Maryland), and angled. The surface of the jaws may be atraumatic or traumatic. Serrated or smooth surfaces allow gentle tissue manipulation in atraumatic graspers (e.g., bowel forceps with a 3-cm long grasping jaw). Traumatic graspers have toothed or clawed surfaces on their jaws to allow them to grasp and hold tissues firmly. In addition, each of these instruments may be equipped with tip-rotation and/or articulating features. Both reusable and disposable instruments are available.

Depending on the design of the handle, grasping instruments may be locking or nonlocking. Most nonlocking forceps have a scissor-type handle. Different designs allow for locking capabilities; in particular, bar-type and spring-loaded locking handles are convenient when prolonged grasping of tissue is required. Some newer dissectors in addition to grip and rotation actually offer additional degrees of freedom by means of an articulating joint activated through wrist movements of the surgeon (RealHand, Novare Surgical, Cupertino, CA; Autonomy Lapro-Angle, Cambridge Endoscopic Devices Inc., Framingham, MA) (Fig. 9–17). **These instruments are most helpful if one is to perform a LESS procedure because the angulation of the shaft then provides the triangulation necessary for approaching the surgical field.** In addition, the shafts of these instruments may be of variable length (i.e., 34, 45, or 75 cm), again allowing for less clashing of handles during a LESS procedure.

In addition to standard dissecting instruments, both the laparoscopic suction apparatus as well as the "heel" of the hook electrode can be used for effective and rapid blunt dissection. Along these same lines, the development of laparoscopic "peanuts" or Kittners (i.e., 5- and 10-mm gauze-tipped disposable dissectors) has been most helpful. These disposable blunt dissectors typically come with the usual absorbent material on the tip, in which case the device needs to be continually switched out for a fresh Kittner owing to absorption of fluid or blood during the procedure. A newer nonporous material has now been affixed to the 10-mm Kittners, allowing one device to suffice through an entire case (Vascular Technologies Inc., Nashua, NH). These dissectors can be twirled or moved side to side or up and down in an area of adipose tissue to rapidly tease away the fat surrounding vital structures such as the renal hilum or the adrenal gland. In addition, the device can be used to raise an entire "line" of tissue (e.g., pararenal fat), allowing for its rapid and safe division because neither the shaft nor tip of the Kittner will conduct electrosurgical current.

Water Jet Dissection. Water jet dissectors such as the Helix Hydro-Jet (ERBE, Tubingen, Germany) use an extremely thin, high-pressure laminar liquid jet to develop a cleavage plane in tissues. Pressures of 250 to 350 psi are sufficient for dissecting soft tissue while leaving vascular structures and nerves intact (Shekarriz et al, 2004). The device is activated using a foot pedal and the water jet is administered from a 5-mm wand. This device may have particular application in parenchymal transection as in partial nephrectomy or in nerve-sparing procedures such as during retroperitoneal lymph node dissection (Basting et al, 2000; Shekarriz et al, 2004). However, owing to fluid accumulation in the abdomen, changes in tissue turgor (i.e., fluid laden) and, in particular, splash back from the fluid stream that can foul the laparoscope lens, these devices have not come into widespread usage.

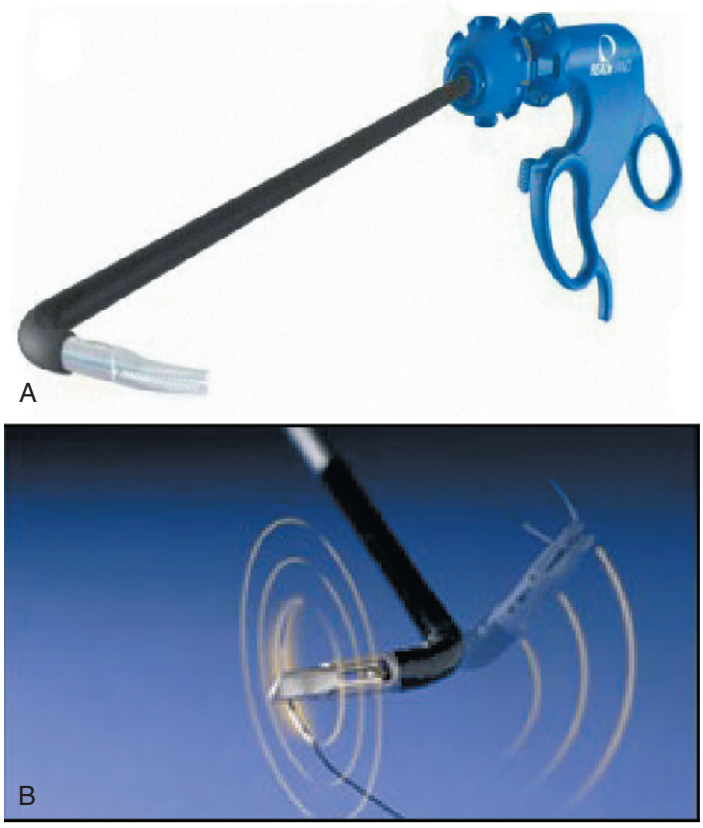


Figure 9–17. Examples of deflecting graspers. **A**, RealHand (Novare Surgical, Cupertino, CA). **B**, Autonomy Lapro-Angle (Cambridge Endoscopic Devices Inc., Framingham, MA).

Instrumentation for Incising and Hemostasis

Laparoscopic scissors, scalpels, electrocautery, and lasers (CO_2, neodymium:yttrium-aluminum-garnet [Nd:YAG], or potassium titanyl phosphate [KTP]) are used to incise or cut tissue during laparoscopic surgery.

Laparoscopic scissors are available in disposable and nondisposable forms. The blades of laparoscopic scissors are shorter than their open surgical counterparts. The configuration of the tip may be useful for selected situations: serrated tips for cutting fascia, hooked tips for cutting sutures, microscissors for spatulating the ureter during a pyeloplasty, and curved tips for dissection. Incision of the tissue is achieved using either an electrosurgical ("hot") or a mechanical ("cold") approach. The scissors may come with either permanent blades or with replaceable tips; the latter ensures "sharp" scissors for each procedure. In addition, the shaft of the scissors may rotate and, in some disposable scissors, even articulate up to 90 degrees. The latter feature is particularly helpful when spatulating the ureter during a pyeloplasty.

A **laparoscopic scalpel** is also available. It is of particular use for incision of the ureter during laparoscopic ureterolithotomy.

For **electrosurgical incision** of tissue, a selection of different electrodes is available: needle electrodes (Corson type) produce fine cuts that are useful in making peritoneal incisions, spatula electrodes are used in blunt dissection and cutting, and hook electrodes (J and L configurations) are of particular value during dissection of vessels because tissue can be pulled away from delicate structures before the cutting current is activated. **The thinner the metal tip of the probe, the higher the density of the electrical current, and the greater the cutting power.**

As with all insulated instruments, certain precautions must be followed during monopolar electrosurgery to avoid local or distant transmitted thermal injury. Consequently, the electrosurgical probe should not be activated unless the metal part is in complete view. The insulation of the electrosurgical instrument should be carefully checked for any damage. The probe should not be activated unless it is in direct contact with the tissue to be incised. Also, use of the monopolar electrosurgical instrument through a metal rather than a plastic cannula decreases the chances of inadvertent electrosurgical injury owing to capacitive coupling. In this regard, one should never use a metal trocar in conjunction with an outer plastic retaining ring because stray current can no longer be harmlessly dissipated through the metal cannula directly to the surrounding peritrocar abdominal wall and hence, any juxtaposed visceral structure may be damaged in an area remote to the laparoscopist's vision. The same precautions apply with monopolar equipped grasping forceps, which might be used during a procedure to obtain hemostasis.

To avoid the potential dangers of stray current from use of monopolar electrosurgical equipment, the surgeon can use monopolar current in conjunction with active electrode monitoring (Encision Inc., Boulder, CO). This instrumentation is constructed such that there is ongoing feedback during activation of the electrosurgical current; as such, any break in the insulation of the shaft results in immediate deactivation of the instrument.

Floating Ball Electrode (Monopolar Device). The Endo FB3.0 floating ball electrode (Salient Surgical Technologies, Dover, NH) is a saline cooled radiofrequency surface coagulator/sealer. Skimming a FB3.0 floating ball over a tissue surface in small circles seals the tissue, stopping the flow of blood and other fluids by effectively shrinking the natural collagen in the tissue. The wet energy from the FB3.0 cools tissue and keeps temperatures less than 100° C, preventing tissue charring and eschar formation. This device has been proven to be quite useful for coagulating the parenchymal bed after partial nephrectomy before application of a hemostatic agent and/or bolster (Stern et al, 2004; Urena et al, 2004).

Bipolar Electrosurgical Devices. The laparoscopic surgeon can also use bipolar electrosurgical devices that require less energy for performance than their monopolar counterparts. There is also a decreased likelihood of injury to surrounding tissue because the electrical current is passing only from one jaw to the other, thereby precluding the potential problems of capacitive coupling commonplace with monopolar electrosurgical current. With bipolar current, the extent of coagulative damage is less than with monopolar electrosurgery: 1 to 6 mm versus 5 to 7 mm with monopolar current (Landman et al, 2003).

The LigaSure vessel-sealing system (Valleylab, Boulder, CO) consists of a 5- or 10-mm grasper/dissector connected to a bipolar radiofrequency generator. When the vascular structure is grasped by the instrument the tissue is evaluated by a feedback-response system that subsequently delivers the optimal energy required to seal the vessel effectively. Because of the high-current and low-voltage output, the vascular structure enclosed by the jaws of the instrument degrades quickly and a protein-based seal is presumably created; this mechanism of electrical current delivery to the tissues results in less charring and less collateral thermal damage (1 to 3 mm) (Landman et al, 2003). Indeed, use of this instrument during partial nephrectomy does not compromise the ability of the pathologist to read the surgical margin (Phillips et al, 2008).

An audible signal alerts the surgeon that the sealing of the vessel is complete; the instrument has a trigger activated blade that the surgeon can then use to cut the sealed tissue. Vessels up to and including 7 mm appear to be effectively occluded with this device (Carbonell et al, 2003; Landman et al, 2003). Recent porcine studies have confirmed that the LigaSure effectively seals veins, arteries up to 9 mm in diameter, and ureters of a similar size to above normal physiologic pressures, but only with one LigaSure application to the structure as opposed to multiple applications. Indeed, multiple applications may weaken the seal (Truong et al, 2008).

Another simultaneous vessel sealing and cutting device is the EnSeal PTC. This is a 5-mm instrument that can also act as a grasper/dissector. The electrode design employs a temperature sensitive polymer that helps to limit current spread to surrounding tissues. The device has an I-beam–shaped blade that draws the jaws of the instrument together with increasing force as the blade is advanced through the tissue. Hence, the surgeon can control the rate of cutting by how quickly the instrument handle is squeezed. The device can be used to seal vessels up to 7 mm but is reported to require a longer vessel sealing time than the LigaSure V (Ethicon Endosurgery, Cincinnati, OH) (Lamberton et al, 2008).

Laser Instrumentation. **Lasers** (CO_2, KTP, Nd:YAG, holmium) are most frequently used through the working channel of an operating laparoscope. The CO_2 laser provides excellent cutting and vaporization of surface lesions; it requires a rigid hand piece and probe. In contrast, the 400- and 600-μm KTP fibers are flexible and allow for noncontact cutting and fulguration. Nd:YAG laser fibers are also flexible and allow noncontact fulguration and contact cutting. Holmium laser fibers are also flexible and are used in a contact mode for cutting. Fibers with sculpted tips provide more precise cutting. Laser-specific goggles must be worn during all laser-related procedures by every individual in the operating room, including the patient. Lasers are not used in urologic laparoscopy; likewise, in general surgery they have largely been supplanted by electrosurgical instruments. Only in gynecology is the CO_2 laser used extensively, generally in the treatment of endometriosis.

Ultrasound Instrumentation. Ultrasonic technology is another option for cutting and hemostasis in endoscopic surgery. It provides an especially attractive alternative to monopolar electrosurgery when one is working around particularly delicate tissues or operating on patients with an implanted pacemaker/cardioverter defibrillator (Gossot et al, 1999; Strate et al, 1999). In ultrasonic surgery, electrical energy is transformed into mechanical energy by the use of a piezoelectric crystal system. Mechanical vibrations produced by this system in the tip of the instrument are capable of causing the following effects on tissue: cavitation, coaptation/coagulation, and cutting (Strate et al, 1999).

In the ultrasonically activated harmonic scalpel/shears, electrical energy is produced by a power-supply generator and transformed into mechanical vibration at the tip of the instrument through a piezoelectric crystal interface (Suzuki et al, 1995; Takeda et al, 1997; Gossot et al, 1999). Mechanical vibration with a tip excursion of 80 to 200 μm (at a frequency of 55.5 kHz) is subsequently transferred to the tip of the instrument. Multifunctionality (grasping, cutting, dissecting, and coagulation) is provided with the shears. In addition to the absent risk of local thermal

damage and tissue charring because of a working temperature of less than 80° C, the depth of penetration is limited to the targeted tissue within a diameter of 1 mm (Landman et al, 2003). Reduced tissue charring may result in a reduced rate of postoperative adhesions (Amaral and Chrotstek, 1997). As with bipolar energy, use of ultrasonic energy during partial nephrectomy does not compromise the ability of the pathologist to read the surgical margin (Phillips et al, 2008). In addition, the harmonic scalpel eliminates other problems associated with monopolar electrosurgery, specifically, problems of remote site tissue damage owing to capacitive coupling, insulation defects in the instrumentation, and direct coupling. Potential disadvantages of the harmonic technology include slower vessel sealing (Lamberton et al, 2008) and the fact that the metal portion of the shears becomes quite hot during activation (often over 200° C compared with the bipolar energy–based devices which stay below 100° C) and must not come into direct contact with any bowel surrounding the area of dissection. In fact, the harmonic shears take roughly twice as long to cool to a "safe" temperature after firing (often up to 45 seconds) (Kim et al, 2008).

Other Instrumentation. The **argon beam coagulator** provides a noncontact form of electrocoagulation. Electrical current originating from a monopolar electrosurgical generator is conducted to the tissue through an ionized argon gas stream. The gas stream blows away blood from the tissue, resulting in better exposure of the bleeding site and, hence, more effective delivery of the electrosurgical current. Argon is a colorless, odorless, inert gas that clears the body within one respiratory cycle (Quinlan et al, 1992). Holding the handpiece at an oblique 60-degree angle within 1 cm of the surface of the target tissue provides optimal coagulation effects. During argon beam coagulation, the sidearm on one of the laparoscopic ports must be opened to prevent buildup of excessive intra-abdominal pressures. Because argon beam coagulation has its major advantage when hemostasis must be achieved over a diffusely bleeding surface, its most practical indication in laparoscopic urologic surgery is during partial nephrectomy, during wedge excision of a small renal tumor, or for control of small liver or spleen lacerations.

Surgical Pharmaceuticals. Recently, a vast array of topical hemostatic agents, sealants, and glues have entered the surgical realm. These agents, depending on their individual properties, can be used for a variety of surgical tasks and have become a valuable addition to the surgeon's tray.

Fibrin-Based Glue. Fibrin glue has been used to promote hemostasis in parenchymal beds, in particular after partial nephrectomy or to seal a liver laceration. The two components of the fibrin glue, fibrinogen and thrombin, are delivered through separate channels and then combine at the tip of the delivery system during application to the tissue. Fibrin glue has an adhesive quality once dry where it essentially hardens into a rubbery coagulum. Tisseel VH Fibrin Sealant (Baxter, Glendale, CA) has the maximum concentration of human fibrinogen available (75 to 115 mg/mL). It can be delivered by means of a laparoscopic applicator in liquid form or in an aerosolized form. One disadvantage of Tisseel is that it requires a preparation time of 20 minutes before it can be applied by the surgeon. If the application at hand requires immediate application (bleeding) then fibrin glue is not a viable option unless it has been prepared in anticipation of possible hemorrhage. Once prepared, Tisseel VH has a shelf life of 36 hours.

Another fibrin-based sealant that can be delivered in a similar manner is Evicel (Johnson & Johnson, New Brunswick, NJ). This agent, which contains 40 to 60 mg/mL human fibrinogen, comes frozen and thus requires no reconstitution. It can be thawed in the hand in 5 minutes and available in another minute. Once thawed, Evicel has a shelf life of 1 month under refrigeration (Tredree et al, 2006). Another advantage is that it contains no bovine serum components (e.g., aprotinin) and hence can be used in individuals with allergies to bovine-derived products. This product can also be applied laparoscopically with an available applicator.

Although all types of fibrin glue use pooled human fibrinogen, the preparations are treated to inactivate viruses. As of 2006 there were no reported cases of viral transmission to a recipient (Tredree et al, 2006).

Non–Fibrin-Based Surgical Hemostats. In contrast to the fibrin-based glues, other hemostatic agents such as thrombin-soaked oxidized cellulose particles (FloSeal, Baxter, Glendale, CA; Surgifoam, Johnson & Johnson, Princeton, NJ) have no adhesive capability at all but are excellent hemostatic agents in the presence of active bleeding from parenchymal surfaces such as a partial nephrectomy bed, a liver/spleen laceration, or an oozing adrenal bed. This agent is also prepared by the scrub assistant and takes 2 minutes to prepare. It is applied through a tube applicator with a syringe. It is most effective when pressure is applied after its delivery; this can be done either with an instrument (e.g., 10-mm gauze-tipped dissector) or with a bolster.

Avitene Microfibrillar Collagen Hemostat (Davol, Cranston, RI) is an active collagen hemostat that accelerates clot formation by enhancing platelet aggregation and the release of fibrin. Similar to FloSeal, it has no tissue sealing capability but is useful for counteracting parenchymal bleeding. EndoAvitene is available in a preloaded endoscopic delivery system designed for use in endoscopic procedures. Developed to easily pass through standard trocars and cannulas, it is available in both 5- and 10-mm diameters.

Chemical-Based Sealants. BioGlue (CryoLife, Inc., Kennesaw, GA) is a two-component adhesive composed of purified bovine serum albumin and glutaraldehyde. The solutions are mixed during application from a controlled delivery system. The glutaraldehyde then crosslinks the BSA molecules to each other and then to the tissue protein at the site of use. Once applied, the agent polymerizes within 20 to 30 seconds and reaches its full bonding strength within 2 minutes. The delivery system comes ready for immediate use. BioGlue is a sealant and must be applied to a dry field and allowed to dry. Thus it cannot be used to counteract active bleeding but can be used to seal a raw, nonbleeding surface.

CoSeal (Baxter, Glendale, CA) is a completely synthetic product composed of two distinct polyethylene glycol polymers that chemically bond together to seal tissue surfaces, suture lines, and synthetic grafts. It does not require thawing, heating, or light activation and hence can be ready in 1 minute. It must be applied to a dry (non-bloody) surface because it does not interact with the clotting cascade and hence is not useful in the setting of active hemorrhage.

Now that the benefits of such substances have come into the spotlight in surgery it is important for the surgeon to be familiar with the properties of these various agents and thereby able to choose one that is most appropriate for the job at hand. A comparison of popular hemostatic agents is presented in Table 9–2.

Instrumentation for Suturing and Tissue Anastomosis

Suturing and knot tying are among the most difficult tasks in laparoscopic surgery. A significant amount of practice is needed to achieve a sufficient level of proficiency. **Laparoscopic needle**

Table 9–2.

Some Commonly Used Topical Tissue Sealants and Hemostatic Agents

AGENT	MANUFACTURER (TIME TO SET UP)	ACTIVE INGREDIENTS	KEY USES/ PROPERTIES
Tisseel	Baxter, Glendale, CA (20 min)	Fibrinogen CaCl Aprotinin Thrombin	Topical hemostasis Tissue glue
CrossSeal	Johnson & Johnson, New Brunswick, NJ (Immediate)	Fibrinogen CaCl Aprotinin Thrombin	Topical hemostasis Tissue glue
FloSeal	Baxter, Glendale, CA (2 min)	Crosslinked gelatin granules Thrombin	Topical hemostasis
EndoAvetine	Davol, Cranston, RI (Immediate)	Avetine Microfibrillar collagen powder	Topical hemostasis
BioGlue	CryoLife Inc., Kennesaw, GA (Immediate)	Bovine serum albumin and glutaraldehyde	Tissue sealant
CoSeal	Baxter, Glendale, CA (Immediate)	Two polyethylene glycol polymers	Tissue sealant



Figure 9–18. Different handle designs for commonly used laparoscopic needle drivers.

holders have one fixed jaw and one jaw that opens by squeezing the spring-loaded handle of the instrument (Fig. 9–18). They all have a locking mechanism to secure the needle in their jaws; this is done with a ratchet, spring-loaded, or Castroviejo-type mechanism. Some needle holders also possess a feature that allows the jaws to rotate around the main axis relative to the handle. The handles may be straight or provide a pistol-type grip. In addition to standard rigid needle drivers some companies have recently developed articulating needle drivers that aid in obtaining more optimal suturing angles with the needle. The actuation of the articulation mechanism is controlled by the surgeon's wrist motion (see Fig. 9–17) (Laparo-Angle, CambridgeEndo, Hopkinton, MA; RealHand, Novare Surgical, Cupertino, CA).

The Endo Stitch (Covidien Ltd., Mansfield, MA) device is an innovative, disposable, 10-mm instrument that facilitates laparoscopic suture placement and knot tying (Adams et al, 1995). The suture is secured to the center of a straight needle with two pointed ends, thereby allowing tissue penetration in either direction. The needle is shuttled back and forth between the jaws of the instrument after each passage through the tissue, applying a long-known principle used in sewing machines. In this way, passing the needle through the tissue and regrasping the needle after it has traversed the tissue become simple tasks because they are done by a one-handed squeeze of the handle and a flip of the needle-securing lever, respectively. Use of this sewing apparatus has had a major impact on decreasing operative times, especially in laparoscopic pyeloplasty (Chen et al, 1998). However, one drawback of suturing in this manner is that the site of needle passage is invariably larger than the needle itself (i.e., because the suture is passed alongside the needle each time); hence if used to close a cavotomy there is oozing along the needle tract that requires placement of either fibrin glue or thrombin-soaked oxidized cellulose. With experience with standard laparoscopic needle holders and especially with the advent of robotic-assisted procedures, use of the Endo Stitch has become less common.

Lapra-Ty clips (Ethicon Endo-Surgery, Somerville, NJ) are a very useful adjunct to suturing and knot tying. These 3.5-mm clips are made of absorbable polydioxanone and are designed to provide secure anchoring of sutures for up to 14 days in low-tension to mid-tension environments (Ames et al, 2005). According to the manufacturer, these suture anchors can be secured to the end of a single strand of polyglactin 910 (Vicryl) suture as fine as 4-0. Experimental models from two different laboratories have shown that these clips are least likely to fall off of polyglactin 910 sutures from size 1-0 to 3-0 (Ames et al, 2005; Weld et al, 2008). In the laboratory environment Lapra-Ty clips have been shown to be slip resistant with 2-0 Monocryl and PDS suture as well. In multiple test trials for each suture type, a percentage of monofilament sutures size 3-0 and smaller as well as 4-0 suture of any type did have slippage of the clip. Hence, it seems logical to avoid Lapra-Ty use with 4-0 suture and to avoid excessive tension when using these clips with 3-0 monofilament suture. **The clip acts as a knot, thereby precluding time-consuming intracorporeal laparoscopic knot tying** (Fig. 9–19). When they are used to secure a single suture, it is helpful if the suture has a pre-tied loop on its end; the needle is passed through the tissues to be secured and is then passed through the pre-tied loop. Next, the suture is pulled taut, thereby tightening its hold on the encircled tissue; the Lapra-Ty clip is then affixed to the suture material just as it exits the loop. For a running suture, the Lapra-Ty clip can be used both to anchor the end of the suture and to secure the suture on completion of the run. It has also been found to be useful for anchoring bolsters during renorrhaphy for laparoscopic partial nephrectomy (Orvieto et al, 2004).

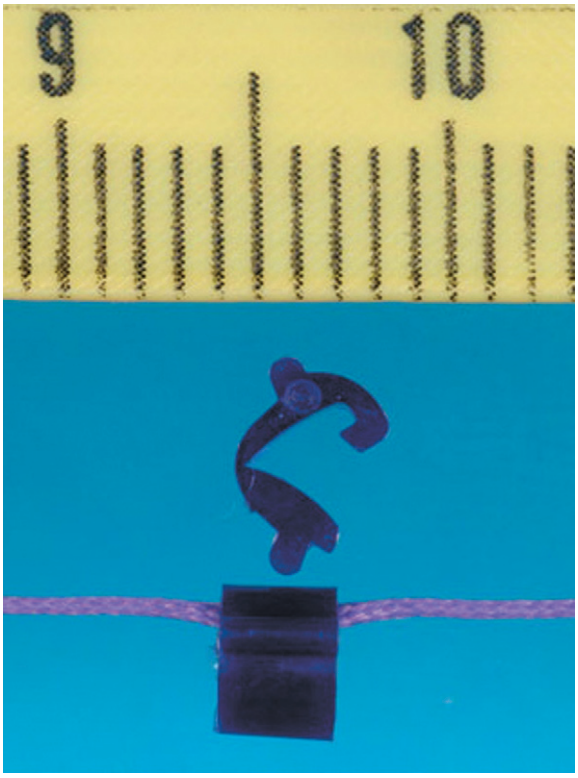


Figure 9–19. Example of a Lapra-Ty Clip (Ethicon Endo-Surgery, Somerville, NJ) affixed to a suture.



Figure 9–20. Example of a laparoscopic stapling device.

Instrumentation for Stapling and Clipping

Stapling Devices. Various stapling devices are available for tissue occlusion and division (Fig. 9–20). The Endo GIA Universal 12-mm stapler/linear cutting device (Covidien Ltd., Mansfield, MA) requires a 12-mm port and delivers two triple-staggered rows of staples and simultaneously cuts in between the rows. The universal stapler can be loaded with a variety of 30-, 45-, or 60-mm loads and fired any number of times. Similarly, the ETS-Flex 45 stapler (Ethicon, Somerville, NJ) also requires a 12-mm port and delivers two triple rows of staples while cutting between rows 3 and 4. This stapler has a maximum fire limit of 8 staple loads. Articulating/roticulating staplers are available from both companies, which enable the surgeon to properly align the instrument with the tissue to be occluded and divided. **Each staple load cartridge is color coded depending on the size of the staples: 2.0-mm staples (gray) or 2.5-mm staples (white) are preferred for vascular (renal vein or renal artery) stapling, whereas 3.8-mm (blue) and 4.8-mm (green) staples are used in thicker tissues (ureter, bowel, bladder).** In addition, for laparoscopic live donor nephrectomy, a single Endo-TA (linear noncutting) stapler can be used to secure the patient's side of the renal vein, thereby providing a longer donor renal vein, because there is no need to trim staples from the vessels before anastomosis in the recipient (Meng et al, 2003). Linear noncutting staplers deliver either three or four staple rows, 30 or 60 mm long. These staplers can also be used to close an enterotomy after a side-to-side bowel anastomosis. **When using laparoscopic staplers, special attention must be paid to the markers on the cartridge to ensure that all the targeted tissue is properly situated proximal to the markers before the cartridge is fired. The stapler should not be fired across any previously placed clips because this is thought to possibly cause stapler malfunction.** Indeed, in a 9-year review of stapler use (1992–2001), Brown and Woo (2004) noted U.S. Food and Drug Administration–recorded reports of 112 mortalities and 2180 injuries attributed to use of the stapler; overall, malfunctions were reported 22,804 times.

Clipping Devices. Disposable and nondisposable clip appliers are available from different manufacturers. Generally they contain occlusive clips ranging in size from 6 to 11 mm; they require either 5-, 10-, or 12-mm laparoscopic ports. Disposable clip appliers possess a rotating shaft and multifire, self-reloading features, whereas nondisposable instruments have to be reloaded for each clip to be deployed at the site of surgery and often do not have a rotating shaft. A right-angle clip applier that fits through a 10-mm trocar and deploys an 8-mm titanium clip is also available (US Surgical, Norwalk, CT).

Electrocoagulation must be avoided in the vicinity of clips placed for occlusion of vessels to prevent conductive tissue necrosis and subsequent clip dislocation. To ensure reliable function, the closed ends of the occlusive clips must be seen extending slightly beyond the targeted vessel and should be placed perpendicular to the longitudinal axis of the vessel.

In addition to the metal "crush" type clips, polymer clips that completely encircle and lock down around a vessel are available (Hem-o-Lok polymer ligation clip system Weck Closure Systems, Research Triangle Park, NC). They are available in four sizes (M, ML, L, and XL). Up to 10 mm of tissue can be ligated through a 5-mm trocar, and up to 16 mm of tissue can be ligated through a 10-mm trocar. Of note, because of results from a survey put forth by the American Society of Transplant Surgeons, in which use of these clips was associated with hemorrhage from the renal artery stump, the company producing the clips put fourth a statement contraindicating their use for securing the renal artery during laparoscopic live donor nephrectomies (Friedman et al, 2006). Subsequently, a multi-institutional study of 1695 patients from nine different institutions undergoing laparoscopic donor nephrectomy with ligation of the renal artery with Hem-o-Lok clips concluded that the clips were safe to use because in their review there were no adverse bleeding events (Ponsky et al, 2008a). **The authors did acknowledge, however, that proper technique of application must be strictly adhered to, including application of at least two clips on the stump of the artery and that a 2-mm cuff of artery should be left distal to the clips** (Table 9–3). Removal of a Hem-o-Lok clip is possible using the removal instrument provided by the company should a structure be clipped in error.

Instrumentation for Specimen Entrapment

Various organ entrapment and retrieval systems are available. Depending on the size of the tissue and on whether in-situ morcellation or intact organ retrieval is planned, the laparoscopic surgeon is able to choose among different-sized sacks, materials, and

Table 9–3.

Basic Principles of Hem-o-Lok Clip Placement

Complete circumferential dissection of the vessel
Visualization of the curved tip of the clip around and beyond the vessel, often with curved end of the clip placed between artery and vein
Confirmation of the tactile snap when the clip engages
No cross clipping
Not squeezing clip handles too hard (compared with the application of metal clips)
Careful removal of the applier after application given; the tips are sharp and can cause a laceration of nearby vessels (e.g., renal vein)
During transaction of vessels only a partial division is performed initially to confirm hemostasis before complete transaction.
Minimum of two clips placed on the patient side of the renal hilar vessel

From Ponsky L, Cherullo E, Moinzadeh A, et al. The Hem-o-Lok clip is safe for laparoscopic nephrectomy: a multi-institutional review. Urology 2008;71(4): 593–6.

designs. Studies have been conducted to test organ retrieval bags for permeability to tumor cells and bacteria before and after morcellation, as well as for stability during morcellation and resistance to tearing forces (Urban et al, 1993; Rassweiler et al, 1998b). The originally designed (1990) LapSac (Cook Urological, Spencer, IN), which is made of nylon with a polyurethane inner coating and a polypropylene drawstring, is the least susceptible entrapment sack to tearing (Eichel et al, 2004) or leakage of cells. However, deployment of the LapSac and subsequent organ entrapment remain challenging endeavors. To aid in the opening of the LapSac, the neck of the sack can be modified at the time of surgery by the surgeon; using a nitinol guidewire a double wrap (every other hole) of the guidewire is placed around the neck of the sack, such that both ends of the guidewire exit the sack similar to the drawstring (Sundaram et al, 2002). The outward expansion of the nitinol guidewire serves to "open" the neck of the sack. The drawstring is then cut and removed. The sack is loaded onto a nondisposable two tine LapSac introducer (i.e., Cook Urological, Spencer, IN). For a right kidney, the sack is rolled from top to bottom in a clockwise manner, whereas for a left kidney it is rolled from top to bottom in a counterclockwise manner; the handles of the two tine introducer and the ends of the nitinol guidewire should all be on the same side. This ensures that as the sack is unwound in the abdomen, the bottom of the sack remains caudal to the neck of the sack thereby facilitating its complete expansion in the abdomen. If this is not done, then the bottom of the sack lies cephalad to the body of the sack and the surgeon needs to expend additional energy and time to move the bottom of the sack caudal. As a rule, it is easiest to deploy the LapSac through the umbilical or supraumbilical 12-mm port site with the laparoscope placed in the subcostal midclavicular 12-mm port; if an 8 × 10-inch sack is being used (i.e., the largest available sack) the cannula is removed and the LapSac is passed under endoscopic guidance through the 12-mm incision site. Once the sack is completely in the abdomen it is then unwound and the introducer is removed; the 12-mm port is replaced. Atraumatic grasping forceps are then used to unfurl the sack. The sack is further expanded by passing the laparoscope into it and moving the endoscope in an ever-widening circle as it is being withdrawn; the nitinol guidewire at the neck of the sack further aids the opening of the sack. The specimen is moved cephalad until it lies on the surface of the liver or spleen before the entrapment sack is inserted. The three tabs of the mouth of the sack can be secured with locking grasping forceps, thereby opening the sack as though it were a tent. The base of the sack is then moved to a position beneath the edge of the liver or spleen; the specimen can then be moved into the sack. Up to a 2-kg specimen can be secured within the LapSac.

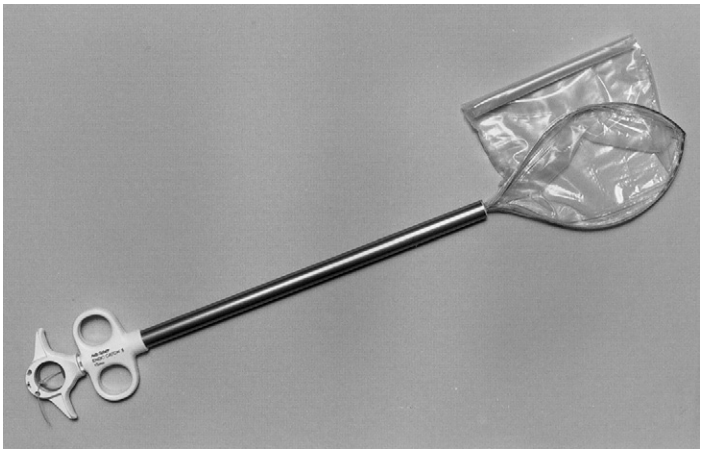


Figure 9–21. Organ retrieval bag.

Other entrapment sacks offer marked advantages when the only goal is organ entrapment and intact removal, rather than morcellation. These sacks have spring wires that, when activated by the surgeon, deploy the bag after its introduction into the abdomen; this facilitates tissue entrapment because the broad wire supports stabilize the opened sack, thereby allowing the surgeon to literally scoop the specimen into the sack (Fig. 9–21). The entrapped specimen can easily be withdrawn through a hand-assist site or by enlarging a laparoscopic port site, usually to 5 to 7 cm for most specimens.

Instrumentation for Morcellation

Various techniques of tissue morcellation have been used in laparoscopic surgery. The simplest method for fragmentation of tissue within the entrapment sack is use of the index finger or ring forceps. The first mechanical morcellation devices worked by punching out pieces of tissue (i.e., serrated-edge macromorcellators) (Semm, 1991). They were designed for removing relatively small amounts of tissue. The advent of laparoscopic nephrectomy resulted in the development of a foot-activated, aspirating, electrical morcellator for tissue fragmentation and evacuation (Cook Urological, Spencer, IN) (Clayman et al, 1992). However, this instrument is no longer available, having been removed from the market in 2001. Traditionally, ring forceps or a large Kelly clamp have been used. Recently, however, it has been shown that ring forceps are the preferred instrument for manual morcellation because they are less likely to puncture the entrapment sack (Eichel et al, 2004). A larger type of ring forceps that has proved helpful in this regard is the Sopher forceps that are commonly used in obstetrics and gynecology; the sturdy jaws of the Sopher forceps are 14 × 45 mm versus only 12 × 22 for the usual ring forceps. If morcellation is performed intracorporeally, the entrapment sack should be a LapSac; however, a variation recently reported by Landman and colleagues for morcellation uses one of the plastic entrapment sacks. In this method, the morcellation is performed above the abdominal wall, by extending the extraction site incision to 3 cm in length. **All tissue is fragmented and removed under direct vision above the abdominal surface; at no time is the morcellating**

instrument out of the direct vision of the surgeon. With this approach, specimens could be morcellated rapidly, with the entire entrapment and morcellation process taking only 13 minutes for clinical specimens as large as 700 g; also fragment size increased from 1.5 to 4.5 g, which might afford better tissue assessment with regard to capsular, vascular, or renal sinus fat invasion (Landman et al, 2003).

When morcellating a renal malignancy, the neck of the sack is triply draped to preclude any contamination: a towel drape, sticky drape (Ioban, 3M, St. Paul, MN) **and nephrostomy drape are commonly used. At the end of the morcellation procedure, the morcellating surgeon and assistants re-gown and re-glove. The extraction site can be bathed in povidone-iodine in an effort to further reduce the chance of any wound seeding.** Indeed, there has been only one noted wound seeding with morcellation in a LapSac (Fentie et al, 2000); however, with intact specimen extraction without entrapment there has also been a wound seed reported (Iwamura et al, 2004). Indeed, in a multi-institutional study, comprising 2064 radical nephrectomies among which 826 were removed by entrapment and morcellation, there was no instance of a wound seeding with tumor (Micali et al, 2004).

Instrumentation for Aspiration and Irrigation

Available as disposable and nondisposable devices, a combination of aspiration and irrigation abilities in one instrument is most practical. The aspirator, which is connected to a suction system, consists of a 5- or 10-mm metal tube, with suction controlled by either a one-way stopcock or a spring-controlled trumpet valve. The irrigation channel is also operated by either a one-way stopcock or a trumpet valve. The irrigation fluid is pressurized to allow for effective delivery of the irrigant and flushing of any bleeding site for accurate hemostasis. Usually, saline or lactated Ringer solution is used as the irrigation fluid. Heparin (5000 units/L) may be added to prevent blood clots from forming, should there be any intraoperative bleeding.

Instrumentation for Retraction

Retractors greatly facilitate laparoscopic surgery. They help expose the area of surgical interest by holding away tissue and organs (e.g., fat, liver, bowel). Sometimes they also facilitate vascular dissection by putting tissue and/or organs closely associated with the vascular structures on stretch. Many varieties of retractors with different features are available. The simplest retractor is a metal bar with an atraumatic tip or a curved saddle shape; the latter is helpful for retracting a vessel during lymph node dissection. Similarly, the disposable laparoscopic "peanut," in either its 5- or 10-mm rendition, is very helpful because it can both dissect and atraumatically retract tissue.

However, the most useful retractors are the expanding types: fan retractors with three or four atraumatic finger-like extensions, fan retractors with V-hinge joints, balloon retractors, and kite-style instruments (e.g., PEER retractors) (Jarit, Hawthorne, NY) (Brooks, 1993). The 5-mm kite style retractor provides a 2 × 3-cm retracting area, whereas the 10-mm instrument doubles the area of direct retraction to 4 × 3 cm (Fig. 9–22 on the Expert Consult website); this type of retractor is very helpful for firm retraction, such as on the kidney to put the renal hilum on stretch.

Another type of retractor is malleable and thus can be shaped to the needs of the surgeon. The Diamond-Flex angled 80-mm triangular retractor (Snowden Pencer, Tucker, GA) can be adapted to many different angles, curves, and shapes, and the surgeon can lock in its particular configuration. This feature is of particular value when retraction of a delicate organ such as the liver is required. This instrument forms a broad retracting surface 8 cm in length.

Retraction of tube-like structures (e.g., vessels, ureter) can also be achieved by placing a suture, a vessel loop, or an umbilical tape around the tissue and applying traction either with a grasper inside the abdomen or by pulling the ends of the retraction loop out of the abdomen through a small stab incision using a Carter-Thomason device (Carter, 1994) or by encircling the structure with a suture affixed to a Keith needle, which can be passed across the abdominal wall, around the structure to be retracted and then back out the abdominal wall (see later under Exiting the Abdomen). The retraction loop can then be secured under slight tension on the surface of the abdomen with a small hemostat. Care should be taken during the use of this technique because excessive tension may injure the structure being retracted.

Also, for blunt retraction, the surgeon's hand, placed into a hand-assist device, is most helpful. In this regard, two key aspects for retraction are of note. First is the concept that the hand should be deployed such that the palm faces the laparoscope as much as possible. In this manner, tissue is brought by the hand toward the laparoscope. It is helpful to use a brown glove that will not reflect the light as much as the standard glove. A second helpful maneuver is the C configuration, as described by Strup, to dissect the renal hilum (Strup et al, 2005). In this maneuver the forearm is passed through the hand-assist device parallel to the aorta/cava while the palm faces laterally. The wrist is flexed to 45 to 90 degrees to allow the fingers to lift the kidney while the thumb pushes inferomedial to retract the tissues overlying the renal hilum. Accordingly, excellent traction and countertraction are achieved, which may speed a safe hilar dissection (Wolf, 2005).

Mechanical Assistants. External mechanical devices such as the EndoHolder (Codman, Raynham, MA) or the LaproStat (Civco, Kalona, IA) can be used to keep grasping forceps or locking retractors in position, thereby taking the place of a tableside assistant. This device is usually mounted on the side of the table opposite the surgeon; the malleable free arm of it is then affixed to the shaft of a grasping forceps or laparoscopic retractor. When the surgeon has employed the retractor to its given purpose, the malleable arm of the external mechanical device is locked in place, thereby providing reliable, continued traction. The advantage of the EndoHolder is that it has no disposables associated with it; however, it is constructed with a gooseneck configuration that requires the scrub nurse to unscrew it and reaffix it each time the retractor needs to be moved. In contrast, the LaproStat, once locked, can still be moved without having to unlock it; however, this device requires use of a new sterile plastic disposable drape for each case (cost: $10.00 US).

Robotic Instrumentation. For the da Vinci Robotic System (Intuitive Surgical, Sunnyvale, CA) the camera lens fits through a variety of standard 12-mm disposable trocars. The 8- and 5-mm instruments fit through proprietary reusable 8- and 5-mm trocars that couple directly with the robotic arms. These reusable metal trocars have disposable valves that must be changed with each new case. Similarly, a wide variety of articulating instruments are available. The proprietary Endowrist technology offers articulation at the tip of the instruments with 7 degrees of freedom, mimicking the wrist movements of the surgeon at the robotic console (Fig. 9–23). A full line of 8-mm scissors, dissectors, bipolar dissectors, electrocautery cutting devices, needle drivers, clip appliers, retractors, as well as an ultrasonic scalpel are available. The 5-mm line of instruments is slightly more limited but still offers a relatively complete line of instruments. It should be noted, however, that the 5-mm



Figure 9–23. Examples of 8-mm interchangeable instruments for the da Vinci Robotic System.

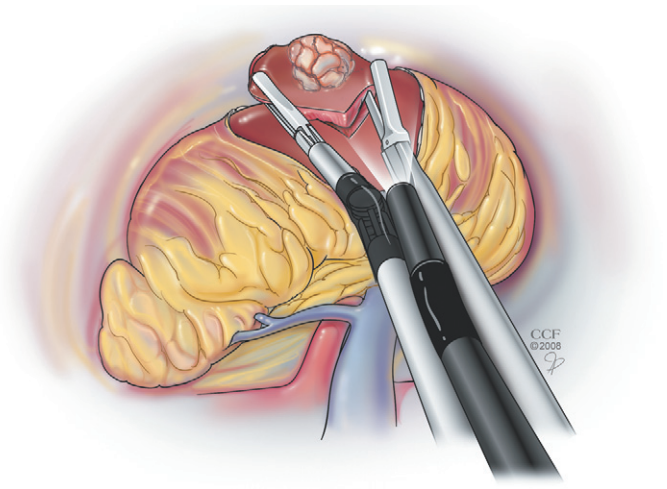


Figure 9–24. Deflecting laparoscopic instrumentation can be used to maintain triangulation during LESS. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1998-2011. All Rights Reserved.)

robotic laparoscope offers a two-dimensional (2D) not 3D image. All robotic instruments for the da Vinci Surgical System (except the laparoscopes) have a 10-case limit before they must be replaced. The number of "lives" left on each instrument should be recorded with each case. **An additional safety feature on all robotic grasping devices is a small Allen bolt that can manually open the jaws of the instrument in the case of a robotic arm malfunction or loss of power in which the grasper is locked on to tissue or a needle at the time of failure.** Of note, robot failure is quite rare; in the series from the University of Chicago, a robot failure was recorded in less than 1% of cases; half of these problems (e.g., failure to power up, optical malfunction) were discovered before the patient entered the operating room. In addition, in the few instances in which there was a system malfunction (e.g., loss of 3D vision, robotic arm failure) during the case (0.4%) the procedure could still be completed without converting to an open option (Zorn et al, 2007).

Instrumentation for LESS

A detailed description of abdominal access and access devices for LESS such as the TriPort and Uni-X has previously been presented in this chapter. By definition, in LESS, all of the instrumentation for the case including a camera/lens for visualization as well as working instruments to perform the procedure must be placed though a single incision. This creates ergonomic challenges with regard to instrument collisions inside and outside the abdominal cavity. Furthermore, the typical trocar arrangement for laparoscopy that affords one the ability to "triangulate" is largely lost with LESS. Much of the emphasis on instrumentation for LESS therefore centers on minimizing instrument collisions outside the abdominal cavity and re-creating the "triangulation" necessary to approach the surgical site safely (Fig. 9–24).

With regard to endoscope choice, one issue encountered is that the light cord often attaches to the telescope at a 90-degree angle and can thus hinder the movement of the lens or other instruments (see Fig. 9–16A on the Expert Consult website). To avoid this problem one can use an endoscope that has the light cord attached end-on from the back directly into the endoscope (Karl Storz, Tuttlingen, Germany) or a one-piece endoscope that already has an end-on integrated light cord (Olympus, Orangeburg, NY) (see Fig. 9–16B on the Expert Consult website). Alternatively an extra-long laparoscopic lens can be used to keep the light cord away from the shorter standard working laparoscopic instruments. Similarly, using laparoscopic instruments of different lengths can help keep the handles from clashing with one another.

With regard to overcoming the parallel nature of the instrument paths and reestablishing a triangular arrangement of instrumentation, several technologic advances have been developed so far. At the very least an angled lens (30- or 45-degree fixed angle) should be used. Preferably, a laparoscope with a deflecting tip (Olympus EndoEYE) or adjustable angle tip (Karl Storz Endo-CAMeleon) should be used because these telescope designs offer the greatest adjustability for optimal viewing.

Additionally, the use of articulating instrumentation is essential to avoid instrument collision outside the abdomen and to achieve proper triangulation for tissue retraction, exposure, and dissection. Disposable articulating instruments are available from Real Hand (Novare Surgical Systems, Cupertino, CA) and from Autonomy Laparo-angle (Cambridge Endo, Framingham, MA) (see Fig. 9–17). In the near future, curved laparoscopic instrumentation (not yet commercially available) will likely be quite helpful and may provide a nondisposable alternative to the current articulating instruments, which are all one-time-use items.

Finally, the use of the robot for LESS procedures has been introduced in the laboratory, originally by Box and colleagues (2008) to perform a transumbilical and transvaginal nephrectomy. Subsequently using the robot arms on both the transumbilical navel port system and on a transvaginal port, Haber and associates (2008) successfully performed a series of pyeloplasties, partial nephrectomies, and total nephrectomies. To be sure, the ability of the robotic arms to articulate is a major plus and one can envision that LESS will follow the path of standard laparoscopy into the robotic age.

Instrumentation for Natural Orifice Transluminal Endoscopic Surgery (NOTES)

The concept of NOTES is not truly new; indeed, the first NOTES procedure would have been Philipp Bozzini's cystoscopy in 1804. What is new is the use of flexible endoscopic technology to perform procedures heretofore unthinkable with a transgastric (e.g., appendectomy in 2004 by Rao and Reddy) or transvaginal approach (e.g., appendectomy in 2004 and cholecystectomy in 2007 independently by Bressler and then Marescaux). Over time these increasingly complex endoscopes have developed from purely diagnostic instruments for visualization of intraluminal surfaces to highly functional endoscopes capable of carrying therapeutic tools that can be used to treat visualized problems. Recently,



Figure 9–25. **B,** Special suture anchors for enterotomy closure (g-Cath, USGI Medical, San Juan Capistrano, CA).

further advances in this type of technology have led to the development of endoscopes specifically for transluminal surgery. The potential advantages of transluminal endoscopic surgery are better cosmesis, less pain, elimination of the risk for wound infection, hernias, and a reduction in adhesions (Swanstrom et al, 2008a, 2008b).

There are several prototype endoscopes currently under evaluation for NOTES. Generally these endoscopes offer larger working channels than standard endoscopes and allow larger instrumentation. Some endoscopes such as the Transport (USGI Medical, San Juan Capistrano, CA) are designed with a guideable locking overtube through which other instruments can be placed; within the 20-mm overtube there are four ports (7 mm, 6 mm, 4 mm, and 4 mm) to accommodate the endoscope and up to three additional instruments. One of the working channels houses a standard 6-mm endoscope for vision, and the other working channels are for instrumentation (Fig. 9–25A on the Expert Consult website). Some endoscopes offer triangulating instrumentation. Major hurdles still exist in terms of developing better and more effective instrumentation and especially devices for suturing and enterotomy closure. The Transport, for instance, can be used to perform enterotomy closure using special suture anchors (g-Cath, USGI Medical, San Juan Capistrano, CA) (see Fig. 9–25B).

Thus far, in urologic practice, NOTES is still in an experimental phase, albeit the seminal paper on this topic being Gettman and associates' porcine transvaginal nephrectomies in 2002. Case reports of NOTES transgastric and transvaginal nephrectomy (Isariyawongse et al, 2008), transgastric and transvesical (Lima et al, 2007) and transvaginal and transumbilical (actually NOTES assisted) nephrectomy with the Transport system (Box et al, 2008) in swine have been reported; however, NOTES has not been applied clinically as of the end of 2008.

Exiting the Abdomen

Port Removal

Port removal and fascial closure are key elements of the procedure that, if not performed in a step-by-step, organized fashion, can result in major, possibly fatal, complications. Herniation, possible bowel incarceration, and postoperative hemorrhage are the results of a poorly performed or haphazard, overly rapid exiting of the abdomen.

Before port removal is initiated, the operative site and the intra-abdominal entry sites of each cannula must be carefully inspected with the intra-abdominal pressure lowered to 5 mm Hg. After achieving perfect hemostasis, the surgical site is irrigated with the option of leaving behind 500 to 1000 mL of irrigation fluid, which contains cefazolin, 1 g/L, and heparin, 5000 U/L. Whether this maneuver truly results in a lower incidence of postoperative adhesions or in less infection is undetermined. To avoid any possible acute herniation of intra-abdominal contents into the previous port sites, removal of all laparoscopic ports must be undertaken strictly under laparoscopic visual control.

In the rare case in which bladed trocars are used, after inspection at 5 mm Hg, the first 10- or 12-mm port is removed and the fascia at the entry site is secured with 0-0 Vicryl. This is most efficiently accomplished using a commercially available dual-channeled cone and a suture-passing device such as a Carter-Thomason suture passer (see later) (Inlet Medical, Eden Prairie, MN). This suture is not tied at the time of placement, but instead a 10-mm plastic introducer rod is passed back into the abdominal cavity through the port site incision. The 10-mm cannula is then slid over the 10-mm plastic introducer and the plastic introducer is removed. In this manner, the ports can continue to be used for the passage of the 10-mm laparoscope and the passage of a grasping forceps to facilitate the closure of each 10-mm port site. Accordingly, all fascial sutures are placed under direct endoscopic control as the 10-mm laparoscope is moved from port to port to visualize the placement of each suture. After all fascial sutures have been placed, each 5-mm port is removed under endoscopic control at 5 mm Hg pressure; 5-mm ports are not closed in the adult but are closed in the pediatric patient (there is also a 5-mm cone to aid closure of the 5-mm port with a needle-nosed suture passer). Then each of the non–endoscope-bearing 10-mm ports can be removed under endoscopic control and the fascial suture can be tied and the closure inspected endoscopically. The final 10-mm port is removed with the endoscope in place to assess for any bleeding along the tract; however, the hemostasis of this port site should have been ensured at the time of placement of the fascial closure suture. In this manner, each port is visually assessed for any bleeding at 5 mm Hg, thereby precluding the possibility of removing a port and missing an injured vessel. After removal of all ports, the CO_2 is allowed to pass out passively through the 5-mm port sites.

Presently, with the shift away from bladed to nonbladed trocars, the need for port closure for even 12 mm ports has come into question. Reports by Shalhav have shown that 12-mm ports regardless of site (i.e., midline vs. transmuscular) do not require fascial closure (Siqueira et al, 2004). **In the literature, the switch from bladed to blunt trocars has resulted in a marked decrease in abdominal wall bleeding (from 0.83% to only 0.16%) and in port site hernia formation (1.83% to 0.19%)** (Hashizume and Sugimachi, 1997; Thomas et al, 2003).

With regard to the hand-assist device, it should be removed before removal of the other port sites. The hand-assist device wound is closed as one would close a typical abdominal wound; however, **recent data support an interrupted closure with nonabsorbable suture** (Troxel and Das, 2005) **because complications from the hand-port site (11%, see later) exceed what would be expected with a standard laparoscopic approach by almost fourfold overall.** Indeed, wound infection, hernia or dehiscence at the hand-port site has been noted in 6.8%, 3.5%, and 0.5% of patients, respectively, in the series from the University of Michigan (Montgomery et al, 2005). After closure, the pneumoperitoneum is reestablished and the other port sites are closed as previously described. Proceeding in this

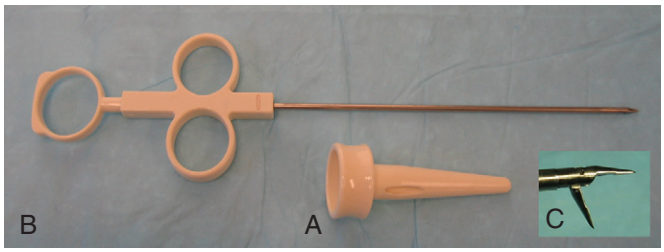


Figure 9–26. Carter-Thomason device. Cone (**A**); needle-point, single-action grasper (**B**); and tip of grasper in open condition (**C**).

fashion precludes the chance of injuring the bowel or omentum beneath the hand-port site and ensures an airtight closure.

Instrumentation for Port Site Closure

Several possibilities for closure of port sites exist. The **simplest method** is retracting the skin with Senn retractors, grasping the fascia with Kocher clamps, and suturing it with absorbable 0-0 suture. However, in any patient with a BMI greater than 30, securely accessing the fascia is very difficult to accomplish.

Fortunately, several devices for complete en bloc closure of fascia, muscle, and peritoneum under direct vision have been developed (Carter 1994; Monk et al, 1994; Garzotto et al, 1995; Elashry et al, 1996). These work well in patients of all sizes.

The **Carter-Thomason needlepoint suture passer** (Inlet Medical, Eden Prairie, MN) consists of a 5-, 10-, or 12-mm cone that has two integrated, hollow, angled, cylindrical passages located 180 degrees opposite each other (Fig. 9–26). With the sharp-needlepoint, single-action grasper, the 0-0 Vicryl suture is inserted through one of the cylinders in the metal or plastic cone, thereby traversing muscle, fascia, and peritoneal layers in an ever-widening angle; the end of the suture is grasped with a 5-mm grasper through one of the other ports. The needlepoint grasper is reintroduced through the other cylinder of the cone, and the intra-peritoneal end of the suture is grasped by the needlepoint grasper and pulled out of the abdomen. The cone is slid off both ends of the suture. Subsequently, closure of the fascia, muscle layer, and peritoneum is accomplished by tying the suture. **The Carter-Thomason needlepoint device not only is helpful for wound closure but also can be used as a fifth port during nephrectomy to help hold the sack open or to encircle the ureter with a vessel loop through a small stab incision.**

The **disposable Endo Close** suture carrier (Covidien Ltd., Mansfield, MA) is a device with a spring-loaded suture carrier at its tip. Loaded with a suture, the device traverses fascia, muscle, and peritoneum alongside the port. After reinsertion on the opposite side of port entry, it is reloaded with the suture, aided by a 5-mm grasper, and is pulled out again under optical control so that the suture can then be tied.

A far simpler, less expensive, homemade solution is available to all surgeons for closing ports in a large patient. This **angiocatheter technique** applies the previously described principles. A 14-gauge, sheathed needle is passed alongside the port through the abdominal layers. After removal of the needle, a 0-0 Vicryl suture is inserted through the angiocatheter sheath until it is deep inside the peritoneal cavity. After the sheath is removed, the same maneuver is repeated on the opposite side, but this time a 30-inch 0-0 Prolene suture folded in half is passed into the peritoneal cavity through the sheath to act as a retrieving loop. A 5-mm grasper passed through another port is then passed through the loop of 0-0 Prolene suture and used to grasp the end of the 0-0 Vicryl suture. The 0-0 Vicryl suture is pulled through the Prolene loop and released. By pulling the Prolene loop upward through the angiocatheter sheath, the entrapped 0-0 Vicryl suture is then retrieved from the abdomen. After the angiocatheter sheath is removed, the two ends of the suture can be tied or the cannula replaced until all of the designated port sites have been properly sutured (see later).

Removal of 5-mm Ports. All 5-mm sheaths are removed under optical control at 5 mm Hg. In adults, the fascia of the 5-mm port entry sites is not sewn closed; however, in children, these port sites require closure with a single absorbable suture.

Closure of the Skin

The skin of all 10-mm port sites is closed with subcuticular 4-0 absorbable suture. Adhesive strips are applied to all port sites to close (for incisions <10 mm) or to further approximate (for incisions ≥10 mm) the skin. As an alternative, the skin can be closed using octylcyanoacrylate glue. This has been found to speed closure time and provide an equivalent cosmetic result compared with suturing (Sebesta and Bishoff, 2004).

POSTOPERATIVE PATIENT MANAGEMENT

Limited laparoscopic procedures (e.g., laparoscopic varicocelectomy, diagnostic laparoscopy) may allow discharge of patients the same day on an outpatient basis. More extensive procedures may require several days of hospitalization.

After a routine major laparoscopic or robotic procedure emphasis can be placed on "fast tracking" the patient. Fast tracking actually starts preoperatively (as mentioned earlier in this chapter) during which time the patient is premedicated with an antiemetic agent, a non-narcotic pain reliever such as ketorolac (if not a renal failure patient), and an antacid. All incision cites are infiltrated with 1% lidocaine before making the incision to minimize postoperative pain. To avoid postoperative ileus and constipation, patients without renal insufficiency can be administered ketorolac every 6 hours for a total of four doses to avoid narcotic analgesic use. Routine use of a nonsedating antiemetic agent for the first 24 hours is also advisable.

The patient is usually given clear liquids on returning to the outpatient area or the hospital floor. A regular diet is provided either the evening of surgery or the morning thereafter.

Ambulation depends on the type of procedure performed as well as the overall health status and morbidity of the patient before surgery. The healthy patient after a laparoscopic/robotic procedure is encouraged to ambulate as soon as possible after the procedure. Pneumatic compression stockings for prophylaxis against deep venous thrombosis are left on until the patient is fully ambulatory. The use of subcutaneous heparin injection for deep venous thrombosis prophylaxis should be used at the discretion of the surgeon (a full discussion of this topic is provided later in this chapter).

For procedures not involving the bladder, the Foley catheter is removed either while the patient is still in the operating room (pneumoperitoneum <2 hours) or the following morning (pneumoperitoneum >2 hours). Indwelling Foley time will vary after procedures involving the bladder. A good rule of thumb is to leave the catheter for 7 days after a procedure in which the bladder was opened. For procedures involving the bladder in a previously

irradiated field it may be necessary to allow additional time for healing. Nasogastric tubes are removed in the operating room immediately on completion of the procedure for most procedures but may be left in longer if bowel is used for urinary diversion or augmentation depending on surgeon preference.

Antibiotics are usually discontinued after 24 hours unless the risk of infection is high as in the case of nephrectomy for xanthogranulomatous pyelonephritis. Laboratory values are obtained in a standardized manner (hemoglobin, hematocrit, sodium, bicarbonate, chloride, potassium, creatinine) postoperatively and the next morning as needed. In general, for a healthy patient undergoing an uneventful laparoscopic procedure, no laboratory studies are needed. However, after a major procedure or for high-risk patients, postoperative and 24-hour laboratory studies are warranted. This is especially important in the patient with pulmonary disease because the greatest risk of hypercarbia may occur 2 to 3 hours after the procedure. After an uncomplicated laparoscopic procedure, a postoperative chest radiograph is no longer recommended (Simon et al, 2005).

Parenteral analgesia (e.g., morphine, ketorolac) is given on the day of surgery and is usually replaced by oral pain medication on the first postoperative day. By using the previously stated or similar methods to "fast track" patients after laparoscopic nephrectomy there has been a significant reduction in nausea, improved pain control, and shortened hospital stay (Recart et al, 2005).

PHYSIOLOGIC CONSIDERATIONS IN THE ADULT

The rapidly expanding number of newly developed laparoscopic and robotic procedures in operative urology has resulted in an increasing need for urologists, as well as anesthesiologists, to familiarize themselves with both the physiology and the potential complications related to the pneumoperitoneum and patient positioning.

Choice of Insufflant

Carbon Dioxide

CO_2 is the insufflant most commonly used for laparoscopic surgery. Owing to its properties (colorless, noncombustible, and inexpensive), it is favored by most laparoscopists. Prolonged postoperative distention of the abdomen does not occur because CO_2 is quickly absorbed (Wolf and Stoller, 1994). It is highly soluble in water and easily diffuses in body tissues. Because of its high diffusion coefficient relative to oxygen and other respiratory gases, it readily moves out of the peritoneal cavity, owing to a high diffusion gradient caused by the difference in concentration of CO_2 between the intraperitoneal space and the surrounding components (e.g., blood). However, the characteristic of rapid absorption, which lessens the chance of a CO_2 gas embolus, may also lead to potential problems (e.g., hypercapnia, hypercarbia, associated cardiac arrhythmias). In particular, patients with COPD may not be able to compensate for the absorbed CO_2 by increased ventilation; this may result in dangerously elevated levels of CO_2 in these patients, thereby necessitating the direct testing of arterial blood gases during laparoscopy in the pulmonary compromised patient population. Carbon dioxide also stimulates the sympathetic nervous system, which results in an increase in heart rate, cardiac contractility, and vascular resistance. Lastly, CO_2 is also stored in various body compartments (e.g., viscera, bones, muscles). After prolonged laparoscopic procedures it may take hours before the patient has eliminated the extra CO_2 that has accumulated in these storage areas; again, this is more often the case and a problem in patients with pulmonary compromise (Lewis et al, 1972; Puri and Singh, 1992; Tolksdorf et al, 1992; Wolf and Stoller, 1994). Therefore, as previously noted, all patients, and in particular those with pulmonary disease, must be closely monitored after a lengthy laparoscopic procedure for possible signs or symptoms of hypercarbia; indeed, their greatest chance of compromise due to hypercarbia may occur after extubation in the postanesthesia recovery room.

Alternative Gases

Nitrous oxide is less irritating to the peritoneum and causes fewer acid-base changes and cardiovascular adverse effects (e.g., arrhythmias) compared with CO_2 (Scott and Julian, 1972; El-Minawi et al, 1981; Minoli et al, 1982; Sharp et al, 1982). However, some studies have shown that nitrous oxide insufflation reduces cardiac output and increases mean arterial pressure, heart rate, and central venous pressure (Marshall et al, 1972; Shulman and Aronson, 1984). Because nitrous oxide supports combustion it can be used only during laparoscopic procedures that do not involve the use of electrosurgical instruments.

Helium is an inert and noncombustible insufflant. Initial studies performed in various animal models showed favorable effects on arterial partial pressure of CO_2 and pH with no evidence of hypercarbia (Fitzgerald et al, 1992; Leighton et al, 1993; Rademaker et al, 1995). These results were corroborated by clinical studies (Bongard et al, 1991; Fitzgerald et al, 1992; Leighton et al, 1993; Neuberger et al, 1994; Rademaker et al, 1995; Jacobi et al, 1997). **As such, helium is particularly useful for the patient with pulmonary disease in whom hypercarbia would be poorly tolerated.** In a recent study from Johns Hopkins University, 10 patients at high risk for hypercarbia underwent laparoscopic renal surgery with helium insufflation. These patients were successfully managed, with only one patient developing an end-tidal CO_2 over 45 mm Hg (Makarov et al, 2007). **Likewise, if hypercarbia develops during a laparoscopic procedure with CO_2, rather than aborting the procedure or converting to an open approach the surgeon can change the insufflant to helium and usually salvage the case** (Brackman et al, 2003). There is also evidence that the use of helium may cause a decrease in tumor cell growth and inflammatory reactions within the peritoneal cavity (Jacobi et al, 1997, 1999; Dahn et al, 2005). It has also been demonstrated that helium insufflation can be used for laparoscopic procedures (e.g., cholecystectomy, appendectomy, hernia repair) performed under local and regional anesthesia in high-risk patients, not only because of its favorable metabolic features but also because of its lack of peritoneal irritation and its association with decreased postoperative pain (Crabtree and Fishman, 1999). However, laparoscopists have to bear in mind that helium may be associated with a higher risk of gas embolism because of its lower blood solubility. When helium is going to be used, it is advised to initially obtain the pneumoperitoneum with CO_2 and then change to helium, thereby lowering the chances of a helium gas embolus. Also, helium is significantly more expensive than CO_2 ($45 vs. $11 per tank). Lastly, when using helium a separate "yoke" (i.e., line from the gas tank to the insufflator) is needed; accordingly, one needs to make sure that a "helium yoke" is available in the operating room or make arrangements to have one provided when performing

laparoscopy on patients with severe pulmonary compromise. In practice, the use of helium may be quite difficult; however, argon may also be used in circumstances when hypercarbia occurs. Indeed, the gas from the argon beam coagulator can be used to maintain the pneumoperitoneum. With argon being an inert gas, like helium, the same precautions, however, apply (Badger et al, 2008).

Other insufflants **(e.g., room air, oxygen)** have been used to establish a pneumoperitoneum in the past. However, possible serious side effects (e.g., air embolus, intra-abdominal explosion, combustion with oxygen and room air) have terminated their clinical use. Other options for insufflants include some of the other noble gases (e.g., xenon and krypton), which are inert and nonflammable; however, their widespread clinical use has not been adopted.

Choice of Pneumoperitoneum Pressure

Overall, the most commonly selected pressure for performing laparoscopy is 15 mm Hg. However, McDougall and colleagues (1994) showed a marked reduction in oliguria when working at 10 mm Hg. In contrast, Kavoussi preferred a pressure of 20 mm Hg, noting increased insufflant filling volume of 22% and possibly less venous bleeding during the procedure (Adams, et al, 1999). In contrast, McDougall and colleagues (1994) noted that, despite the increased volume, there was only a very small increase in abdominal girth at higher pressures. Indeed, recent studies support a pressure of 12 mm Hg, as this results in no perturbations in cardiac parameters (i.e., no change in stroke volume) versus a pressure of 15 mm Hg (Mertens zur Borg et al, 2004). Working at lower pneumoperitoneum pressures has also been found to reduce postoperative pain (Sarli et al, 2000).

Various cardiovascular, renal, and respiratory effects seen during different intra-abdominal pressures in the supine state are summarized in Table 9–4. It is of note that these physiologic parameters may be further altered (i.e., overridden or reversed) owing to the health of the individual patient and to changes in the patient's position.

Table 9–4.

Pressure Effects: 5, 10, 20, and 40 mm Hg

EFFECTS	5 mm Hg	10 mm Hg	20 mm Hg	40 mm Hg
Cardiovascular				
Heart rate	↑	↑	↑	↓
Mean arterial pressure	↑	↑	↑	↑
Systemic vascular resistance	↑	↑	↑	↑
Venous return	→/↓	↓↑	↓↑	↓
Cardiac output	→/↓	→/↑	→/↓	↓
Renal				
Glomerular filtration rate	→	↓	↓↓	↓↓
Urine output	→	↓	↓↓	↓↓
Respiratory				
End-tidal CO_2	→	→/↑	→/↑	↑
Pco_2	→	↑	↑	↑
Arterial pH	→	→/↓	↓	↓

CO_2, carbon dioxide; PCO_2, partial pressure of carbon dioxide.

Cardiovascular Effects of the Pneumoperitoneum

Venous Flow

Animal studies have shown that the effects of the pneumoperitoneum on venous return depend on atrial pressures, which, in turn, are a reflection of the hydration state of the subject (Ivankovich et al, 1975; Diamant et al, 1978; Kashtan et al, 1981). If atrial pressures are low (normal or hypovolemic state), then, during a pneumoperitoneum of up to 20 mm Hg, venous return is reduced owing to increased compression of the vena cava from the pneumoperitoneum. If atrial pressures are high (hypervolemic state), the vena cava resists elevated intra-abdominal pressure and venous return is actually enhanced. However, these principles apply only to an intra-abdominal pressure of up to 20 mm Hg. By further increasing pneumoperitoneum pressures, especially to 40 mm Hg and above, capacitance vessels are collapsed, vascular resistance increases, blood flow decreases markedly, and venous return is significantly reduced. Lower extremity venous return is also reduced by elevated intra-abdominal pressures. Reduced venous blood flow in the lower extremities could facilitate deep vein thrombosis; however, this remains a rare clinical complication of laparoscopy (Jorgensen et al, 1993).

These pathophysiologic insights, gained through animal experiments, have been corroborated by clinical studies (Kelman et al, 1972; Motew et al, 1973; Lee, 1975; Jorgensen et al, 1993).

As a result of these trials, intra-abdominal pressures during laparoscopy should not be allowed to exceed 20 mm Hg over extended periods (Arthur, 1970; Seed et al, 1970; Lee, 1975), and a working pressure of 10 to 12 mm Hg is recommended.

Cardiac Arrhythmias

Tachycardia and ventricular extrasystoles may be seen as results of hypercapnia (Scott and Julian, 1972). Peritoneal irritation may lead to vagal stimulation and subsequently to bradyarrhythmias (Doyle and Mark, 1989). Also, dysrhythmias can serve as clinical warning signs for the occurrence of pneumothorax, hypoxia, and gas embolism (Wolf and Stoller, 1994).

Unreliability of Central Venous Pressure Readings

As previously noted, intravenous pressures may actually rise with low intra-abdominal pressures. In addition, increasing intra-abdominal pressures may artificially elevate central venous pressure readings owing to an increase in intrathoracic pressure. Therefore, it is important for the anesthetist *not* to rely on central venous pressure readings for any clinical decision making. If information regarding vascular volume and central venous pressure is needed, a Swan-Ganz catheter should be placed.

Respiratory Effects of the Pneumoperitoneum

Pressure-Mediated Effects

Owing to increased intra-abdominal pressure, diaphragmatic motion is limited. Pulmonary dead space remains unchanged, but functional reserve capacity decreases (Wolf and Stoller, 1994). The average peak airway pressure needed to keep up a constant tidal volume increases parallel to the increasing intra-abdominal pressure (Alexander et al, 1969; Motew et al, 1973; Wolf and Stoller, 1994).

Although usually not of great clinical importance in a healthy patient population, it is advisable to use positive end-expiratory pressure techniques when patients with lung disease undergo general anesthesia for a laparoscopic procedure (Ekman et al, 1988; Wolf and Stoller, 1994; Hazebroek et al, 2002).

Non–Pressure-Related Respiratory Effects

The head-down position has an adverse effect on respiration. It elevates the diaphragm and decreases vital capacity. It can also lead to a dislocation of the endotracheal tube that, in turn, may cause right main bronchus intubation. Although of little clinical significance in healthy patients, the head-down position may cause pulmonary edema in patients with increased left-sided heart pressures (Prentice and Martin, 1987). Also, during lengthy procedures performed in the head-down position it is useful to limit fluid administration if possible because it will minimize facial swelling postoperatively.

Renal and Other Visceral Effects of the Pneumoperitoneum

Oliguria

Increased intra-abdominal pressure was found to be associated with a significant decrease in urinary output. A number of investigators, with the oldest study dating back to 1923, have observed oliguria and anuria associated with an ongoing increase in intra-abdominal pressure (Thorington and Schmidt, 1923; Harmann et al, 1982; Richards et al, 1983). Decreased renal vein blood flow and direct renal parenchymal compression, rather than marked hormonal changes or ureteral compression, have been shown to be the likely reasons for the oliguric state (Chiu et al, 1994; McDougall et al, 1996). Of interest, renal cortical blood flow decreased with increasing intra-abdominal pressures, whereas renal medullary blood flow increased up to pressures of 20 mm Hg; above this level, medullary blood flow also decreased (Chiu et al, 1994). In a porcine study, neither application of dopamine nor insertion of ureteral catheters was able to improve oliguria owing to elevated intra-abdominal pressure (McDougall et al, 1996). These changes occurred regardless of intraperitoneal or extraperitoneal insufflation. Of note, oliguria was not a problem if a gasless, abdominal wall lift method was used to establish the working space in the abdomen. The decreased renal blood flow seen during pneumoperitoneum may be associated with changes in endothelin-1 (ET) and/or nitric oxide (NO). One recent study in a rat model showed that the effects of pneumoperitoneum can be accentuated using ET or NO blockers or avoided by using ET or NO potentiators (Abassi et al, 2008). There is also experimental evidence showing increased apoptosis in the renal cortex and medulla of rats that have undergone pneumoperitoneum compared with controls. The level of apoptosis appears to be pressure dependent, again supporting the use of lower insufflation pressures, as recommended (i.e., ≤12 mm Hg) (Khoury et al, 2008).

These experimental findings in animals have been corroborated in the clinical setting (Iwase et al, 1992; Chang et al, 1994; McDougall et al, 1996); however, at least one recent clinical study did show that low-dose dopamine (2 μg/kg/min) can prevent the dip in urine output associated with pneumoperitoneum (Perez et al, 2002). Whether antidiuretic hormone and plasma arginine vasopressin, both of which have been measured at increased levels by some investigators, play a major role in oliguria during clinical laparoscopic procedures remains unclear (Melville et al, 1985; Solis Herruzo et al, 1989). **In general, if one desires to avoid an oliguric state during a laparoscopic procedure, a pressure of 10 mm Hg or less is recommended. In addition, clinically the use of furosemide (Lasix) (mg dose = 20 times the patient's creatinine), mannitol (12.5 to 25 g), and dopamine at 2 μg/kg/min can help to overcome oliguria. With this regimen and judicious fluid administration, the patient can usually be maintained with a urine output in excess of 100 mL/hr. The key is to use these pharmaceutical modalities in lieu of excessive hydration and fluid boluses** (Perez et al, 2002), **which may lead to significant fluid overload and edema.**

Effects on Mesenteric Blood Flow and Intestinal Motility

Decreased blood flow during laparoscopic procedures was found not only in the kidney but also in mesenteric vessels and other organs (e.g., liver, pancreas, stomach, spleen, small and large intestines) (Caldwell and Ricotta, 1987; Ishizaki et al, 1993; Hashikura et al, 1994). This may rarely lead to mesenteric thrombosis with catastrophic results. This complication may take days to develop (Schorr, 1998).

Open, incisional abdominal surgery usually results in some postoperative impairment of gastric and intestinal emptying owing to intestinal paralysis (physiologic ileus) (Kemen et al, 1991). Interestingly, clinical observation and studies undertaken during laparoscopic and open surgical cholecystectomy have shown that laparoscopic surgery causes less significant disturbances of the gastrointestinal motility pattern, therefore resulting in no or less postoperative physiologic ileus than occurs with open surgery (Sezeur et al, 1993; Halevy et al, 1994). The exact mechanisms responsible for this difference have yet to be defined; however, it is postulated that perhaps it is related to the hypercarbia (Aneman et al, 2000). Additionally, intestinal perfusion does not change significantly during prolonged pneumoperitoneum at a pressure of 15 mm Hg with CO_2 or helium (Goitein et al. 2005); however, at least in the rat model, there does seem to be an increase in bacterial translocation that is proportional to the pneumoperitoneum pressure (Sukhotnik et al, 2006).

Also, despite the increased intra-abdominal pressures associated with laparoscopy, there has been no increased incidence of gastroesophageal reflux and regurgitation in patients undergoing laparoscopic procedures (Schippers et al, 1992).

Acid-Base Metabolic Effects of Pneumoperitoneum

Animal and human studies have demonstrated that prolonged laparoscopic procedures may result in hypercarbia and respiratory acidosis (Motew et al, 1973). Because there is no increase in ventilatory dead space during laparoscopy, the resulting respiratory acidosis has been attributed to transperitoneal absorption of CO_2 during establishment and maintenance of the pneumoperitoneum (Motew et al, 1973; Leighton et al, 1993). Although the resulting mild respiratory acidosis does not adversely affect otherwise normal patients and can be corrected by increasing the minute ventilation, increased absorption of CO_2 can become dangerous in patients with COPD owing to their impaired ability to release pulmonary CO_2. **To ensure proper monitoring of acid-base status, intermittent arterial blood gas sampling should be performed in patients with COPD and**

during any laparoscopic procedure that requires more than 1 hour of CO_2 insufflation; also in the patients with COPD, arterial blood gas sampling should continue in the postanesthesia recovery area because after extubation these patients may be at risk of significant hypercarbia owing to subsequent mobilization of procedurally absorbed CO_2.

Pneumoinsufflation with CO_2 results in variable amounts of gas absorption, thereby raising the partial pressure of CO_2 in the blood. Carbon dioxide is absorbed from the peritoneal membrane during transperitoneal laparoscopy and from preperitoneal adipose and connective tissue during retroperitoneoscopy and extraperitoneoscopy (Collins, 1981). Others have also implicated the disrupted microvascular and lymphatic channels for CO_2 absorption during preperitoneal laparoscopy (Glascock et al, 1996). The potential for developing hypercarbia exists during both transperitoneal and preperitoneal laparoscopy. Conceivably, this assumes greater importance in patients with preexisting airway and cardiovascular compromise. Although transperitoneal and retroperitoneoscopic approaches are routinely employed safely at numerous centers worldwide, vigilant perioperative anesthetic management is essential to prevent the development of potential complications related to CO_2 buildup.

End-tidal CO_2 and O_2 saturation are monitored intraoperatively using a capnometer. Furthermore, arterial blood gases are obtained during prolonged laparoscopic procedures and in patients with increased risk of developing hypercarbia (owing to airway disease, renal failure, congestive heart failure, or advanced age). A rise in end-tidal CO_2 should prompt the anesthesiologist to adjust the respiratory rate and tidal volume to enhance CO_2 elimination. Simultaneously, the surgeon should decrease the insufflation pressure of CO_2 or, if necessary, desufflate the abdomen completely until the hypercarbia has been resolved. Several studies have demonstrated that CO_2 absorption during either laparoscopic approach (transperitoneal or retroperitoneal) increases significantly during the initial 30 to 60 minutes of the procedure and reaches a steady-state plateau thereafter (Wolf et al, 1995; Ng et al, 1999). Which one of the two approaches is associated with greater CO_2 absorption remains a debated issue. Although some studies have demonstrated greater absorption during transperitoneal laparoscopy (Giebler et al, 1997), others have demonstrated greater absorption during retroperitoneal laparoscopy using a standard Hasson cannula (Wolf et al, 1995). However, in another study, no significant clinical difference was seen (Ng et al, 1999), provided a blunt port type Hasson cannula was used that tightly sealed the site of entry in between the balloon and soft cuff carried on the shaft of the cannula.

Hemodynamic Effects Related to Patient Position and Type of Approach

Several animal and human studies have examined hemodynamic changes owing to different surgical positions (Kelman et al, 1972; Joris et al, 1993; Williams and Murr, 1993). In the supine position, cardiac output remains unchanged or decreases when intra-abdominal pressures are less than 15 mm Hg, whereas mean arterial pressure (MAP) and systemic vascular resistance increase (Pearle, 1996). If pneumoperitoneum pressures are increased beyond 20 mm Hg, cardiac output is reduced because of decreasing venous return and hence MAP decreases.

Changes in patient position have a marked impact on hemodynamic parameters. Specifically, in the head-up position, heart rate increases, MAP decreases, systemic vascular resistance increases, and cardiac output decreases; in contrast, in the head-down position, heart rate drops, MAP rises, systemic vascular resistance falls, and cardiac output increases (Pearle, 1996). These results have also been shown to hold true in steep Trendelenburg position used for laparoscopic and robotic radical prostatectomy (Falabella et al, 2007). The head-down position seems to be favorable for the laparoscopy patient owing to higher cardiac output caused by increased venous return. However, this beneficial effect is completely negated if pneumoperitoneum pressure is increased to 30 to 40 mm Hg; at pressures this high, the concomitant decrease in venous return results in a decrease in cardiac output.

There is some evidence that the extraperitoneal approach may be beneficial in this regard compared with transperitoneal laparoscopy. Giebler and coworkers (1997) demonstrated that transperitoneal laparoscopy was associated with more pronounced changes in cardiac output ($P = .001$), pulmonary artery pressure ($P = .007$), central venous pressure ($P = .001$), iliac venous pressure ($P = .001$), and inferior vena caval pressure gradient ($P = .00001$) as compared with retroperitoneal laparoscopy. With regard to pelvic laparoscopy, Meininger and associates (2004) compared the effects of prolonged intraperitoneal and extraperitoneal CO_2 insufflation on hemodynamics and gas exchange. With both insufflation methods, arterial CO_2 pressure increased rapidly, reaching higher levels with extraperitoneal insufflation. Therefore patients managed with extraperitoneal insufflation required a significantly higher minute ventilation. Heart rate and central venous pressure increased in both groups, whereas mean arterial blood pressure and pH decreased.

Hormonal and Metabolic Effects during Laparoscopic Surgery

As in other surgical procedures, several hormones (e.g., β-endorphin, cortisol, prolactin, epinephrine, norepinephrine, dopamine) have been noted to increase during laparoscopic surgery as a response to tissue manipulation, intraoperative trauma, and postoperative pain (Cooper et al, 1982; Lehtinen et al, 1987; Lefebvre et al, 1992). The clinical significance of increased serum arginine vasopressin levels seen in open surgery and in response to intraperitoneal insufflation during laparoscopy remains unexplained (Cochrane et al, 1981; Melville et al, 1985; Solis Herruzo et al, 1989).

Several adverse metabolic changes observed during open cholecystectomy are less pronounced with laparoscopic cholecystectomy: (1) reduced postoperative plasma glucose elevation, (2) less decrease in insulin sensitivity, and (3) reduced hepatic stress response (Thorell et al, 1993; Jakeways et al, 1994; Glerup et al, 1995).

One important feature of the catabolic response is a complex intra-organ shift of nitrogen; this reaction has been best characterized in the liver (Glerup et al, 1995). The conversion of amino acids to urea by the liver is much higher after open incisional cholecystectomy than it is after laparoscopic cholecystectomy; hence, the catabolic reaction of the body is decreased with a laparoscopic versus an open, incisional approach (Fischer, 1995). Indeed, in the laparoscopic patient, the reduced postoperative hepatic catabolic stress associated with reduced tissue loss of amino-nitrogen may, in some way, be responsible for the more rapid convalescence that is the hallmark of laparoscopy in general. Lastly, catabolic responses, in the form of released cytokines and opioids, owing to augmented neurohumoral stimuli resulting

from incisional tissue trauma may also be lessened with a laparoscopic approach (Fischer, 1995).

Immunologic Effects of Laparoscopic Surgery

A number of animal and clinical studies measuring a wide spectrum of inflammatory response mediators (e.g., C-reactive protein, interleukin-6) and other markers of cellular immune functions (pan–T cells [CD3], helper T cells [CD4], suppressor cells [CD8], and natural killer cells [CD16]; delayed-type hypersensitivity skin tests; serial phytohemagglutinin-induced T cell proliferation) have suggested that laparoscopic procedures generally result in less immunosuppression than do their open surgical counterparts (Kloosterman et al, 1994; Trokel et al, 1994; Cristaldi et al, 1997; Karayiannakis et al, 1997; Nguyen et al, 1999; Bolla and Tuzzato, 2003). This may also play a role in hastening convalescence after laparoscopic procedures. Some data have also suggested that the CO_2 pneumoperitoneum in and of itself, as opposed to exposure of tissues to room air, results in a more favorable immunologic state (Watson et al, 1995). Also, experimental evidence shows that less tumor cell growth occurs after laparoscopic procedures than after open procedures (Bouvy et al, 1997). Although these data are intriguing, further well-designed, prospectively randomized clinical studies are needed to compare immunologic responses after laparoscopic versus open surgical procedures for urologic cancer. Whether decrease in inflammatory response mediators and improved postlaparoscopic immune status will translate into a better long-term prognosis for patients with urologic cancers remains to be determined. Indeed, in a recent study by Landman and colleagues (2004) in patients undergoing open or transperitoneal laparoscopic radical/total nephrectomy for renal cancer there was no discernible difference in immunologic parameters; part of the explanation for this observation could well be secondary to the immunosuppressive effects of the tumor itself.

TROUBLESHOOTING IN LAPAROSCOPIC SURGERY

Historically, in large series, the overall incidence of laparoscopic complications in urology has been in the range of 4%. Mortality has been distinctly unusual, with a rate of 0.03% to 0.08% (Mintz 1977; Winfield et al, 1991; Chapron et al, 1998; Fahlenkamp et al, 1999; Harkki-Siren et al, 1999). However, because of the increasing complexity of laparoscopic urologic procedures (e.g., nephrectomy, prostatectomy) and the continued decrease in simpler laparoscopic procedures (e.g., varicocelectomy, bladder neck suspension, pelvic lymph node dissection), laparoscopic complications in urology appear to be on the rise. In one update from Johns Hopkins University regarding transperitoneal laparoscopic retroperitoneal procedures (e.g., renal surgery, retroperitoneal lymph node dissection), Parsons and colleagues (2004) report a 0.2% mortality rate and a 12% overall complication rate. Of concern, the most often cited injury was vascular, occurring in 2.8% of patients followed by bowel injury in 1.1% of patients (Table 9–5). The authors attribute this increased incidence to the larger number of surgeons now doing laparoscopy and moving through the learning curve, the addition of several new procedures that are substantially more challenging than past procedures (e.g., partial nephrectomy, retroperitoneal lymph node dissection), and the aging and higher risk of our population in general (Parsons et al, 2004). Of interest, the complications for pelvic laparoscopy although higher than for retroperitoneal laparoscopy are of a more minor nature. Indeed, Vallancien and colleagues (2002) noted a 22.6% overall complication rate among 1311 procedures, of which 84% were pelvic; however, there were no deaths and the most often injured organ was bowel at 1.2%; vascular injuries were cited in only 0.5% of their procedures (see Table 9–5). Another recent meta-analysis of radical prostatectomy techniques compared open, laparoscopic, and robotic complications. The overall complication rates for the different approaches were 10.3%, 15.6%, and 6.6%, respectively (Berryhill et al, 2008). Another recent series of 1500 robotic radical prostatectomy cases reported a postoperative complication rate of 4.3%. Intraoperatively, the complication rate was only 0.13% (two rectal injuries) (Patel et al, 2008). Possible reasons for the difference in the complication rates between laparoscopic and robotic prostatectomy might be that the robotic platform expedites the learning curve for the procedure, provides a more comfortable working environment for the surgeon, and allows the surgeon to work in an intuitive 3D environment with 6 degrees of freedom instrumentation.

Table 9–5.

Major Complications of Transperitoneal Abdominal Surgery

TOTAL PROCEDURES	894* (100% ABDOMINAL)	1311† (84% PELVIC)
Overall complications	13.2%	22.6%
Intraoperative/ postoperative	5.7%/7.5%	3.6%/19%
Deaths	0.2%	0%
Vascular injury	2.8%	0.5%
Bowel injury	1.1%	1.2%
Adjacent organ injury	1.1%	0.8%
Conversion rate	1.7%	1.7%

*Data from Parsons JK, Varkarakis I, Rha KH, et al. Complications of abdominal urologic laparoscopy: longitudinal five-year analysis. Urology 2004;63:27–32.

†Data from Vallancien G, Cathelineau X, Baumert H, et al. Complications of transperitoneal laparoscopic surgery in urology: review of 1,311 procedures at a single center. J Urol 2002;168:23–6.

Minimizing the Incidence of Complications during the Laparoscopic Learning Curve

Early in one's experience with laparoscopic and robotic surgery it is wise to apply this minimally invasive approach to low-risk surgical candidates of normal body habitus. In addition, it is advisable and recommended by many laparoscopic organizations, as well as by hospital credentialing boards, that the neophyte minimally invasive surgeon seek training in three arenas: (1) in-depth instructional courses, including didactic, "live-case" transmissions and "hands-on" laboratory sessions; (2) preceptor training in which the surgeon-in-training views more than five or more procedures being done by an already skillful laparoscopic surgeon; and (3) a mentoring experience, during which a trained laparoscopic surgeon oversees the initial procedures performed by the surgeon-in-training (Society of American Gastrointestinal and Endoscopic Surgeons, 2003). Further training can be obtained through self-teaching using videotapes and a pelvic trainer. The latter is extremely helpful for developing one's sense of laparoscopic

proprioception and for becoming facile with laparoscopic suturing and knot tying. Data have clearly shown benefits for individuals who have taken the time to practice their laparoscopic skills using a pelvic trainer in all areas of laparoscopy (cutting, clipping, and suturing) compared with individuals who had no such training (Derossis et al, 1998). Similarly, participation in a 1-week mini-residency has been found to increase the likelihood that participants would perform more complex laparoscopic procedures (81% of participants) (Corica et al, 2006). The use of virtual reality simulators is under evaluation but further validation testing is required before these complex and often expensive trainers can be recommended strongly. A detailed discussion of laparoscopic and robotic practice and training is presented later in this chapter.

General Procedural Complications

Aside from training in the basic psychomotor skills, neophyte minimally invasive surgeons must be educated with regard to prevention, recognition, and appropriate treatment of complications. Accordingly the following section covers the myriad complications that can occur with any laparoscopic/robotic procedure. Recognition, resolution, and prevention of these various problems are discussed.

Malfunction of Equipment

A successful outcome of any laparoscopic procedure depends not only on the psychomotor technical skills of the surgeon but also on a proper working knowledge of all the equipment involved in performing these procedures. To ensure undisturbed functioning of all technology, the surgeon must be supported by well-trained staff who are capable not only of quickly recognizing any equipment malfunction but also of providing an immediate, adequate response to correct problems. In this regard, the Society of American Gastrointestinal Endoscopic Surgeons has issued a troubleshooting guide for video and electronic failure. Newer laparoscopy systems have become more simplified in some ways offering automatic settings, touch screen control, and voice command; however, these new systems can be more taxing as well because they offer a host of optional settings and capabilities. For integrated operating room systems offered by most major equipment manufacturers the surgeon and operating room staff need to receive in-depth training on the system's operation, capabilities, and limitations. In this way, equipment failure will be minimized. Additionally, the contact information for the equipment vendor's trouble shooting experts should be readily available.

With regard to the da Vinci Robotic System, equipment malfunction is rare. In a review of 11 institutions with a total of 8240 cases reviewed, the overall incidence of malfunction was 0.4%. Of the 34 cases with malfunction, 24 cases were canceled before the procedure, 2 cases were converted to laparoscopic, and 8 were converted to open surgery (Lavery et al, 2008).

Complications Related to Obtaining the Pneumoperitoneum

Complications Associated with Closed Access (Veress Needle Placement)

Preperitoneal Placement. Preperitoneal placement of the Veress needle may preclude successful trocar placement. If not recognized early, 1 to 2 L of CO_2 may be instilled; indeed, once this much CO_2 has been insufflated into the preperitoneal space, many signs indicative of correct intraperitoneal insufflation may be present (e.g., distention, tympanic sound on percussion) thereby misleading the surgeon until the first trocar is placed. **The first sign of preperitoneal insufflation is that there may be a steep rise in pressure with only 500 mL of CO_2; plus, if more CO_2 is instilled, unequal distention of the abdomen occurs.** If this early sign is missed, then the laparoscope reveals only fat after trocar placement; the intraperitoneal viscera are not seen.

The next step is to evacuate the CO_2 through the sidearm of the trocar and proceed with an open insertion technique. The initial incision can be widened, and the peritoneal surface can be grasped with a pair of Allis clamps and incised. A Hasson cannula is then secured in place, as previously described, and the peritoneal cavity is insufflated.

Several steps can be taken to avoid this complication. First, if the Veress needle is preperitoneal on initial insufflation, pressures are usually higher than the maximal initial allowable pressure of 10 mm. Second, if the Veress needle is preperitoneal, it cannot be easily advanced 1 cm deeper without resistance. If one has truly entered the peritoneal cavity properly, the Veress needle should be able to be moved 0.5 to 1 cm deeper without meeting any resistance (the "advancement test").

Vascular Injuries. During initial placement of the Veress needle at the umbilicus, minor or major intra-abdominal blood vessels may be punctured by the 14-gauge needle. The first sign of intravascular entry is blood appearing in the hub of the needle. Aspiration results in additional blood filling the syringe. As long as the needle has not been manipulated, it can usually be withdrawn without excessive bleeding. An alternative site for Veress needle placement or open cannula insertion should be used at this point.

To prevent this problem it is important when using an umbilical approach to direct the Veress needle toward the hollow of the pelvis. Passing the Veress needle through a 12-mm incision, bluntly spreading the subcutaneous fat, and grasping and stabilizing the anterior fascia with a pair of Allis clamps may help prevent this problem when using an umbilical access. These maneuvers become especially important in children, who have less space between intra-abdominal structures and the abdominal wall. **Lastly, for a case in which this problem occurs, it is important that the path of the initial Veress needle passage be traced on proper entry into the abdomen. The prior site of the Veress needle passage is carefully inspected at a pressure of 5 mm Hg; any site of bleeding can be expeditiously treated by the application of a surgical hemostatic agent such as thrombin-impregnated gelatin matrix or fibrin glue. Gentle pressure can be applied to the bleeding vessel.** Likewise, any hemodynamic instability associated with loss of "working space" within the abdomen during the procedure should alert the surgeon to the possibility of an expanding "unseen" retroperitoneal hematoma, a distinctly unusual occurrence.

Prevention of vascular complications can be further achieved in one of two manners. First, using a nonumbilical site for Veress needle passage (i.e., just superior and medial to the iliac crest or subcostal in the midclavicular line) places no major vessels in danger. Second, the use of only blunt trocars decreases the chance of injury of the epigastric vessels by fivefold (reduced incidence from 0.83% to 0.16%) (Hashizume and Sugimachi, 1997; Thomas et al, 2003).

Visceral Injuries. During Veress needle placement, intra-abdominal organs may be punctured. The initial signs of this complication consist of aspiration of blood, urine, or bowel contents through the Veress needle or, in the case of a solid organ, high pressures on initial insufflation.

Management consists of simply removing the Veress needle. The Veress needle may then be reintroduced at a different site, or an open cannula placement can be used through a separate incision site. On entry into the abdomen, any bleeding site on the liver or spleen can be treated with an argon beam coagulator or the application of a surgical hemostatic agent (e.g., thrombin containing gelatin matrix or fibrin glue) (see earlier).

Bowel or bladder entry of the Veress needle needs no further treatment other than needle withdrawal. These problems can be prevented by placing a nasogastric tube and a transurethral indwelling bladder catheter to decompress the stomach and bladder, respectively, before Veress needle passage. Stabilization of the abdominal wall fascia with towel clips or Allis clamps at the time of Veress needle puncture may help in stabilizing the fascia. One should not lift up on the fascia because this will only increase the space between the fascia and the peritoneum while not changing the intra-abdominal space. Likewise, insufflation should never be initiated unless *all* of the signs for proper peritoneal entry (negative aspiration, easy irrigation of saline, negative aspiration of saline, positive drop test, and normal advancement test) have been confirmed.

Complications Related to Insufflation and Pneumoperitoneum

Bowel Insufflation. If entry into the bowel is not recognized at the time of irrigation and aspiration through the Veress needle, then the surgeon may well insufflate the small or large bowel. The first sign of this problem is asymmetrical abdominal distention. Associated signs may be passage of flatus and insufflation of only a small amount of CO_2 (<2 L) before high pressures are reached.

If this complication is suspected, then the insufflation line should be disconnected; the outflow of gas will immediately confirm bowel entry. The needle can be withdrawn, and open access cannula placement should be done at a different abdominal site. Prevention of this problem is ensured if one properly performs the aspiration/irrigation/aspiration tests recommended for safe Veress needle placement and if one avoids sites of prior surgery. Similarly, initial open cannula insertion may decrease the chances of this complication.

Gas Embolism. Carbon dioxide gas has favorable solubility in blood, as opposed to air, helium, or nitrous oxide ($LD_{50} = 1750$ mL); however, use of CO_2 may still result in a gas embolus. The most common cause of CO_2 embolism is puncture of a blood vessel or organ with the Veress needle, followed by insufflation; this can occur only when the surgeon has ignored the previously described tests for proper entry into the peritoneal cavity. The first sign of intravascular insufflation is acute cardiovascular collapse. Other signs include dysrhythmias, tachycardia, cyanosis, and pulmonary edema. The diagnosis is usually made by the anesthesiologist based on an abrupt increase of end-tidal CO_2 accompanied by a sudden decline in oxygen saturation and then a marked decrease in end-tidal CO_2 (Loris, 1994). Sometimes, a "millwheel" precordial murmur can be auscultated (Keith et al, 1974). In addition, the anesthesiologist may notice foaming of a drawn blood sample owing to the presence of insufflated CO_2.

The treatment is immediate cessation of insufflation and prompt desufflation of the peritoneal cavity. The patient, if at all possible, is turned into a left lateral decubitus, head-down position (i.e., right side up) in hopes of minimizing right ventricular outflow problems and forcing the air embolus to rise into the apex of the right ventricle. The patient is hyperventilated with 100% oxygen. Advancement of a central venous line into the right side of the heart with subsequent attempts to aspirate gas may rarely be helpful. The use of hyperbaric oxygen and cardiopulmonary bypass have also been reported (McGrath et al, 1989; Diakun, 1991; Abdel-Meguid and Gomella, 1996).

This devastating complication can be precluded by meticulous attention to Veress needle and initial trocar placement and performance of each of the recommended tests for intraperitoneal entry. Insufflation should never be initiated if the surgeon has even the slightest doubt about correct positioning of the Veress needle; instead, the surgeon should withdraw the Veress needle and pass it at an alternate site or immediately proceed with open cannula access.

Barotrauma. Prolonged elevated pressures (>15 mm Hg) may result in barotrauma (McGrath et al, 1989; Diakun, 1991; Abdel-Meguid and Gomella, 1996). Prolonged high pressures may be caused by insufficient and infrequent monitoring of CO_2 pressure, malfunction of the insufflator, or additional pressures produced by auxiliary devices (e.g., argon beam coagulator, CO_2-cooled laser). Furthermore, barotrauma may be caused by ventilation techniques using positive end-expiratory pressure resulting in rupture of a pulmonary bleb or bulla.

The initial sign of barotrauma may be hypotension owing to decreased cardiac output secondary to an acute drop in venous return caused by compression of the vena cava. Also, a pneumothorax or pneumomediastinum may develop because of high ventilation pressures. Increased intra-abdominal pressures may exacerbate a hiatal hernia as well.

The anesthesiologist usually alerts the surgeon to the problem of excessive intra-abdominal pressure; it usually presents as an increase in ventilation pressures. The surgeon should desufflate the abdomen and, once the hemodynamic changes have been reversed, reinitiate the pneumoperitoneum at 10 mm Hg. Any malfunctioning insufflator should be replaced. Also, if one is using an argon beam coagulator or a CO_2-cooled laser device, the sidearm on one port should be left open to allow high-pressure excess gas to readily escape while the device is being activated.

These problems are avoided by the alert, meticulous surgeon. The insufflator should always be checked before initiating the procedure; at maximum inflow settings, gas should flow freely at less than 2 mm Hg pressure down the opened, unconnected insufflation line, and when the line is purposely kinked by the surgeon, the insufflator-recorded pressure should rise rapidly to its preset limit (usually 15 mm Hg), the inflow of CO_2 should cease, and the high pressure alarm should sound. Again, troubleshooting the insufflator should be part of the routine prelaparoscopy check in every case.

Subcutaneous Emphysema. This problem develops owing to improper placement of the Veress needle or, more commonly, to leakage of CO_2 around ports. The latter situation occurs when port site incisions are too large, when the procedure is particularly lengthy, or when high intra-abdominal pressures are used. The pathognomonic sign is crepitus over the abdomen and thorax; in male patients, a pneumoscrotum may also develop.

If the problem is due to improper placement of the Veress needle, then withdrawal of the Veress needle and open insertion are recommended. If the problem develops intraoperatively, the surgeon should check for gas leakage around a port site. If this is found, the surgeon can either place a purse-string suture around the port or, preferably, change the trocar to a larger size or switch to the balloon-based Hasson type cannula, which creates a tight seal between the intra-abdominal balloon and its outer soft foam cuff. Also, the surgeon should consider reducing the insufflation pressure.

This complication is eminently avoidable if the surgeon adheres to all the diagnostic tests for proper Veress needle placement and if the port site incisions are carefully tapered to the size of the port to be placed. In this regard, it is important to place each port so that it is pointing toward the surgical field, to avoid the continued forceful redirection of the port during the procedure that results in widening of the tissue tract around the port and subsequent escape of CO_2 into the surrounding subcutaneous tissues. In addition, the cannulas must be secured so they do not pull back into the abdominal wall tissues; to this end, the surgeon can use a screw-type cannula or may elect to simply use a suture to fix the sidearm of the port to the skin, thereby precluding its retraction beyond a certain point. If the former solution is chosen, the surgeon must be careful to never use a plastic retaining collar with a metal trocar; this situation greatly increases the chance of inadvertent monopolar electrosurgical injury owing to stray current along the exposed shaft of the now partially insulated metal trocar. Also, the insufflator must be tested before each procedure, as part of a preincisional routine checklist, to make sure it is functioning properly, so that when high pneumoperitoneum pressures develop, the inflow of CO_2 automatically ceases.

Several studies have demonstrated that the incidence of subcutaneous emphysema is somewhat higher during retroperitoneal laparoscopy than during transperitoneal laparoscopy, albeit without any clinically significant sequelae (Wolf et al, 1995; Zhao et al, 2008). However, the risk of surgical emphysema and other CO_2-related sequelae during retroperitoneoscopic and extraperitoneoscopic surgery can be effectively minimized by adopting a variety of practical measures (Gill, 1998; Ng et al, 1999). Specifically working at a lower pressure is helpful (i.e., 12 mm Hg). In one study, in the initial 20 cases with an insufflation pressure of 15 mm Hg, subcutaneous emphysema was noted in three patients (15%); however, in the subsequent 180 cases the insufflation pressure was maintained below 12 mm Hg and subcutaneous emphysema was noted in only two patients (1.1%) (Rassweiler et al, 1998a). Also, use of the balloon-based Hasson cannula to seal the initial entry site is important. Invariably, the problem resolves itself during the initial 2 to 3 postoperative days.

Pneumomediastinum, Pneumothorax, and Pneumopericardium. Gas leaking along major blood vessels through congenital defects or secondary enlargement of openings in the diaphragm may lead to pneumomediastinum, pneumopericardium, or pneumothorax (Kalhan et al, 1990; Pascual et al, 1990; See et al, 1993; Abreu et al, 2004; Zhao et al, 2008). Although a pneumomediastinum is usually not associated with specific clinical symptoms, a pneumopericardium may result in impaired cardiac function. The incidence of the latter complication is estimated to be 0.8% (Abreu et al, 2004). The diagnosis is rarely made during the procedure unless cardiac impairment occurs. Usually, the diagnosis is made on a chest radiograph taken in the recovery room. However, if there is sudden cardiac decompensation during a procedure, the same maneuvers are undertaken as described for treatment of a suspected gas embolism—interruption of the procedure and desufflation of the abdomen. If there is a strong suspicion of pericardial tamponade, pericardiocentesis is indicated.

A pneumothorax may be associated with pneumomediastinum, barotrauma, or with direct puncture of the pleural space with a trocar (Doctor and Hussain, 1973; Kalhan et al, 1990; Pascual et al, 1990). The incidence of this complication in a recent series was 1.6% to 4.0% (Abreu et al, 2004; Zhao et al, 2008). Like subcutaneous emphysema, the incidence of pneumothorax is more common in retroperitoneal procedures (Zhao et al, 2008). The earliest signs of this problem may be the development of subcutaneous emphysema, especially in the neck and chest area. More ominous signs, such as hypotension and decreased breath sounds with an increase in ventilatory pressure, are indicative of a *tension* pneumothorax. Although a chest radiograph will confirm the diagnosis, the development of pulmonary collapse with loss of breath sounds on one side mandates immediate decompression of the chest by passage of a 16-gauge needle into the second or third intercostal space in the midclavicular line followed by tube thoracostomy if a tension pneumothorax is suspected (See et al, 1993).

Of note, the occurrence of pulmonary complications appears to be greater with a retroperitoneal approach. Indeed, in one large series, 90% of these complications were associated with retroperitoneoscopy, whereas only 10% of these problems occurred in patients undergoing transperitoneal laparoscopy (Abreu et al, 2004).

Prevention of these problems is similar to the means to avoid subcutaneous emphysema: keep the intra-abdominal pressure at 15 mm Hg or less, make sure all port site incisions are tight around the laparoscopic cannulas, and make sure all cannulas are well seated in the peritoneal cavity. In addition, all trocars must remain below the 12th rib. While dissecting in the upper quadrants of the abdomen, especially during laparoscopic ablative renal surgery, the surgeon should be aware of the anatomic relationships of the kidneys, adrenal glands, and great vessels to the diaphragm to avoid direct injury.

Complications during Open Access (Hasson Technique). Potential problems associated with open access are similar to, albeit less frequent than, problems associated with a closed Veress needle pneumoperitoneum. The biggest major risk in this regard is injury to underlying viscera while traversing the peritoneum. In a densely scarred abdomen, the bowel may be adherent to the underside of the abdominal wall and hence may still be injured. If a bowel injury is recognized early, it can often be repaired through the same incision that was made for insertion of the Hasson cannula. Although vascular injury with this approach is distinctly rare, the surgeon must realize that even with open access this devastating complication can occur (Hanney et al, 1999).

The only minor risk in using the open access technique is failure of the surgeon to obtain secure transfascial retaining sutures on either side of the cannula. If this is not done, the bulb of the Hasson cannula will not be seated tightly into the incision, thereby resulting in significant leakage of gas and subsequent subcutaneous emphysema. One way to prevent this problem is to also place a purse-string suture in the fascia to better secure it to the hub struts of the Hasson cannula. In addition, some Hasson type cannulas have built-in retention systems. The Bluntport (US Surgical, Norwalk, CT) has a retention balloon that can be inflated in the peritoneal cavity and then drawn up tightly against the peritoneal side of the abdominal wall; an outer foam sealing ring can then be advanced down the extra-abdominal shaft of the cannula, thereby sandwiching the abdominal wall between the inflated balloon and the foam seal, effectively precluding any leakage of gas during the case. This is especially effective when doing retroperitoneoscopic procedures. Another self-sealing trocar, the Anchorport (SurgiQuest, Orange, CT) has an elastic self-sealing trocar shaft that automatically forms to the patient's body wall when the inner cannula is removed, creating a tight seal.

Complications Related to Initial "Blind" Placement of the First Trocar after Obtaining a Veress Needle Pneumoperitoneum. With the advent of nonbladed trocars (several of which also have clear tips for direct visualization of individual abdominal wall layers during port placement), the likelihood of catastrophic injuries to vital

structures has been markedly reduced (Thomas et al, 2003). Accordingly, the authors no longer consider the use of bladed trocars to be clinically appropriate and these trocars have been removed from our operating rooms.

Injury to Gastrointestinal Organs. Perforation of the small or large intestine during passage of the primary port is the most common cause of trocar-induced injury of gastrointestinal organs. Other organs (e.g., stomach) are affected much less frequently. Given the lateral positioning of the spleen and liver, injury of these organs with the passage of the primary trocar is distinctly unusual. The first sign that one has entered the bowel depends on whether the injury is through one wall or both walls ("through-and-through" injury) of the bowel. In the former instance, as soon as the laparoscope is introduced the surgeon sees the mucosal folds of the interior of the bowel. However, with a through-and-through injury the diagnosis is not made until the first secondary trocar is passed; **at that time the surgeon should routinely pass the laparoscope through the secondary port to inspect the puncture site of the initial port.** The trocar will be seen passing completely through both walls of the bowel. If the surgeon fails to perform this maneuver routinely this injury will not be noted until the end of the case when the trocars are being removed, thereby resulting in a broader injury and a prolonged time of intraperitoneal contamination. A missed bowel injury of this nature leads to peritonitis, when diagnosed intraoperatively, and possible death, when discovered only in the postoperative period.

In the case of a one-wall injury of the bowel, the surgeon can elect to leave the trocar in place and pass a second trocar in another location using an open access technique. On inspection of the abdomen the site of injury to the bowel will be immediately apparent because the initial trocar will still be residing in the bowel. At this time, the surgeon may elect to open and repair the bowel or, if skilled in laparoscopy, may place two more ports and proceed to close the bowel using laparoscopic suturing or stapling techniques. An intraoperative consultation with a general surgeon should be obtained regardless of whether the urologist performs the repair; from a medicolegal and quality of care standpoint, involvement of the general surgeon at the time of the acute event facilitates subsequent care should further complications arise while ensuring the best possible repair of the injury at the time of the acute event.

When the injury to the bowel is a through-and-through injury, the safest path is to open and proceed with repair; alternatively, if particularly skilled, one may consider laparoscopic repair. In either case, the abdomen should be irrigated with 4 to 5 L of saline containing an antibiotic solution and the patient must be placed on broad-spectrum, triple-drug antibiotic coverage.

In an effort to preclude bowel injury, a mechanical and antibiotic bowel preparation is recommended in patients with a history of extensive prior abdominal surgery. For those patients with a low risk of bowel injury, a simple mechanical preparation to "empty" the bowels should suffice. Commonly this is accomplished with magnesium citrate the day before the procedure; in addition, the patient can be placed on a clear liquid diet for 1 to 2 days preoperatively.

Perforation of the stomach is distinctly rare; however, to best preclude this problem patients should refrain from oral intake for 12 hours before surgery. To decompress the stomach, a nasogastric or orogastric tube should be placed before puncture of the abdomen with the Veress needle. The management of this complication is the same as for injury to the bowel with primary closure and general surgery consultation. In all of these cases a nasogastric tube is left indwelling until the output to gravity is minimal.

Injury to Intra-Abdominal Vessels. Major vascular injury is a rare but serious complication, occurring in 0.11% to 2% of cases (Hanney et al, 1995; Geers and Holden, 1996; Usal et al, 1998; Lin and Grow, 1999; Vallancien et al. 2002; Parsons et al, 2004) (Fig. 9–27). It is far more common in procedures related to the retroperitoneum, as opposed to pelvic laparoscopy. The aorta and common iliac arteries are most frequently involved. The inferior vena cava is less affected because of its lateral location in relation to the aorta; likewise, the common iliac vein is rarely involved given its posterior position in relation to the common iliac artery. Rarely, in a patient with adhesions or prior surgery, intestinal mesenteric vessels servicing a "fixed" loop of bowel may be injured. In addition, the epigastric vessels are at risk for injury during trocar placement.

The first sign of a major vascular complication is the onset of sudden hypotension and associated tachycardia. If the trocar has not been moved, then, as the obturator is withdrawn, the diagnosis is made immediately based on whether there is a pulsatile (arterial) or nonpulsatile (venous) profuse return of blood from the trocar sheath. If the trocar has been displaced from the injured vessel, then, depending on the vessel injured, the surgeon will see blood rapidly accumulating in the abdominal cavity, a mesenteric hematoma, blood dripping from the trocar entry site, or, rarely, blood that preferentially accumulates retroperitoneally, in which case, the space within the peritoneal cavity will appear to be markedly reduced and actively decreasing because of the expanding retroperitoneal hematoma.

The response to injury to a major arterial structure must be rapid. A vascular or trauma surgeon should be called to the room. If blood is coming through the trocar, then the trocar should be closed and left in place. An emergency laparotomy is performed, and the trocar is followed to its point of entry into the vessel. Controlling sutures can be placed on either side of the trocar or a Satinsky clamp can be placed to isolate the area of injury, so that, as the trocar is withdrawn, the wound can be rapidly controlled. Alternatively, the procedure can be converted to a hand-assisted approach and the surgeon can then use the intra-abdominal hand to control the bleeding vessel.

If the injury is discovered at the time of passage of the laparoscope (i.e., the trocar is no longer residing in the vessel), then the sheath and laparoscope can be swung up to the underside of the abdominal wall and an immediate cutdown can be done on top of the laparoscope and sheath, thereby providing for a rapid and safe laparotomy. The site of injury must be rapidly located and controlled. Again, the aid of a vascular or trauma surgeon in this case is quite helpful.

The best way to handle this complication is to avoid it completely. In this regard, knowledge of the exact location and possible anatomic variations of major intra-abdominal blood vessels is mandatory. The CT scan should be reviewed before passage of any trocars to look for vena caval or other abnormalities of the great vessels. Because of limited intraperitoneal space, special care must be given to trocar placement in children and very thin adults. Strict adherence to laparoscopic guidelines, such as ensuring that all the safety signs of passage of a Veress needle are present before proceeding with trocar passage, obtaining an adequate pneumoperitoneum before trocar passage (intra-abdominal pressure may be raised to 25 mm Hg temporarily for placement of the primary trocar), passing the initial trocar under direct endoscopic control (i.e.,

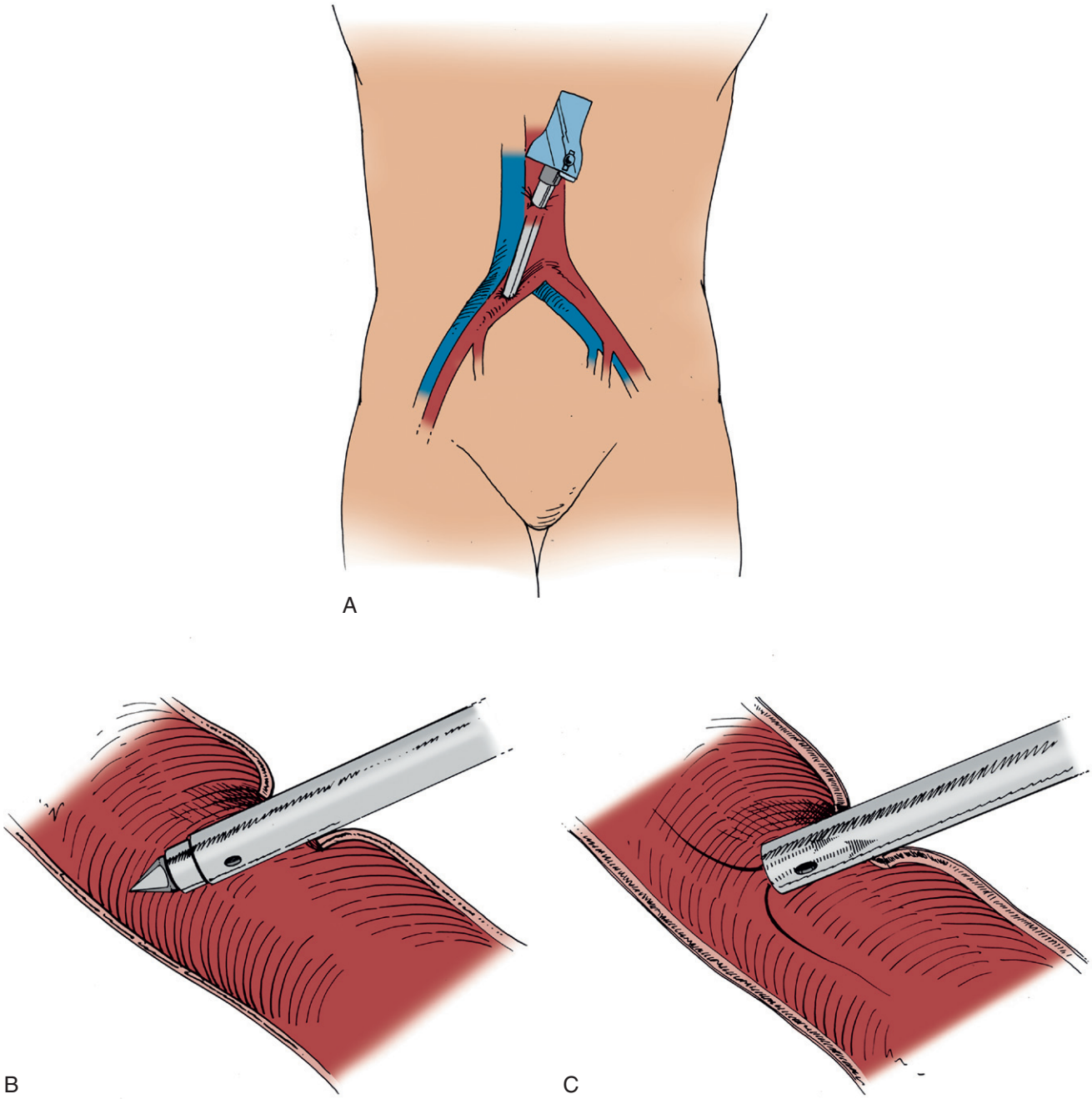


Figure 9–27. **A** and **B,** The right common iliac artery has been punctured by a trocar. **C,** As soon as the obturator is removed, blood fills the cannula. (From Clayman RV, McDougall EM, editors. Laparoscopic urology. St. Louis: Quality Medical Publishing; 1993.)

clear plastic port), and avoiding initial trocar passage through an abdominal scar, are important in helping to prevent this problem. Similarly, avoidance of the epigastric vessels is ensured if trocars are either placed in the midline or at least 6 cm lateral to the midline.

With regard to hemorrhage, when the situation is recognized but controlled, which occurs more commonly with venal caval than arterial injuries, the surgeon has the ability to "prepare" for subsequent conversion. In that regard, a second suction unit should be obtained, the vascular or trauma surgeon should be in attendance, and the anesthesiologist has time to make sure the patient is well hydrated and that blood is in the room for transfusion. In addition, before conversion, the use of a 4 × 8-inch laparoscopic pad, which can be introduced through a 12-mm port may be helpful (personal communication: I. Gill); however, if the bleeding is profuse then the surgeon should have available ample amounts of large gauze rolls (e.g., Kerlix) for packing the area as soon as the abdomen is opened.

Furthermore, it is helpful to consider having a "hemorrhage" tray available in the operating room at all times (Table 9–6). **This laparoscopic tray should contain a Satinsky clamp, a 10-mm suction tip for large clot evacuation, an Endo Stitch device with 4-0 Vicryl suture, a Lapra-Ty clip applier and a rack of Lapra-Ty clips (6 clips**

Table 9–6.

Contents of Hemorrhage Tray for Laparoscopic Surgery

Laparoscopic Satinsky clamp
Ten-millimeter suction/irrigation tip
Endo Stitch device with 4-0 absorbable suture
Lapra-Ty clip applier and a packet of Lapra-Ty clips
Six-inch length of 4-0 vascular suture on an SH needle with a Lapra-Ty clip preplaced on the end
Two laparoscopic needle drivers
Topical hemostatic agent of choice

per rack), two laparoscopic needle holders, and 4-0 vascular suture. With this tray available, some injuries to major venous structures (e.g., inferior vena cava) can be successfully resolved laparoscopically.

Injury to the Urinary Tract. Urinary tract injuries during laparoscopy are most commonly associated with trocar passage. The incidence of this problem varies widely as reported in the gynecologic literature: 0.02% to 8.3% range (Ostrzenski and Ostrzenska, 1998; Lin and Grow, 1999; Soong et al, 2007). Usually, these injuries occur to the bladder at the time of initial trocar placement. Chances of this problem occurring have been greatly reduced by the introduction of blunt trocars.

Trocar injuries of the urinary tract have reportedly affected only the bladder. The initial sign of this problem is pneumaturia or macroscopic hematuria. The diagnosis is confirmed by retrograde intravesical instillation of indigo carmine diluted with saline; this allows the surgeon to rapidly identify the cystotomy site. The injury can be repaired laparoscopically, either with laparoscopic suturing techniques or by use of the laparoscopic tissue stapler; extensive defects may require open surgical repair (Ostrzenski and Ostrzenska, 1998). These injuries should always be closed and not left to heal "on their own" with prolonged Foley catheter drainage.

Prevention of this problem is simple. Preoperative placement of a urethral catheter to drain the bladder is recommended for all major laparoscopic urologic cases. Not only does it largely preclude bladder injury, but it also provides the necessary means for monitoring urine output during major laparoscopic urologic procedures.

Complications Related to Placement of Secondary Trocars

Bleeding at the Cannula Site. Blood dripping from the port entry site and onto the underlying abdominal viscera is the first sign of an injured abdominal wall vessel. The exact site of hemorrhage is determined by cantilevering the trocar into each of the four quadrants and noting which positioning of the trocar tamponades the bleeding.

Definitive therapy for this problem can be undertaken in one of three ways. The simplest method, albeit the most costly, is the insertion of curved electrosurgical scissors or forceps through another port; this instrument can be articulated up into the port site to electrocoagulate the bleeding site.

The least expensive method is to suture the area of hemorrhage. This can be accomplished by inserting a straight Keith needle with a 0-0 absorbable suture from the outside of the abdomen at one side of the affected quadrant and then grasping the needle with laparoscopic forceps and pushing it back out of the abdomen at the opposite side of the affected quadrant until it can be recovered on the surface of the abdomen (Fig. 9–28 on the Expert Consult website). This broad suture is then tied over a gauze 4 × 4-inch bolster on the abdominal surface; the port can be used throughout the procedure. Alternatively, various port closure devices, in particular the Carter-Thomason device, may be used to similarly pass a suture to control the bleeding (Ortega, 1996); at the end of the procedure, a device of this nature should be used to definitively close the port site and occlude the injured vessel.

This problem can often be avoided by routinely transilluminating the abdominal wall, especially in the thin patient, before trocar placement so large surface vessels can be avoided. In addition, the routine spreading of the subcutaneous tissues of the proposed port site with a blunt clamp (e.g., Kelly clamp) may be helpful. Also, the use of only blunt trocars reduces the chance of vascular wall injury nearly 10-fold. Finally, careful laparoscopic inspection of the peritoneal surface before each secondary port site placement is helpful to identify the area of the inferior epigastric vessels as well as any overlying peritoneal vessels, which can then be avoided; in this regard, port sites should be placed either in the midline or at least 6 cm lateral to the midline (Hashizume and Sugimachi, 1997).

Trocar Position-Related Problems. Three potential problems may occur when the secondary trocars are not properly positioned: "crossing swords," "striking handles," and "rollover." The problem of "crossing swords" is due to the trocars being placed too close to one another; as a result, the intra-abdominal portions of two trocars cross each other so that the two cannot easily be used to deliver instruments to the same surgical site (Fig. 9–29). Similarly, the problem of "striking handles" is also due to trocars being placed too close to one another; as a result, the upper portions of the trocars strike one another on the abdominal surface, again precluding delivery of instruments to a specific surgical site. "Rollover" is a variant of the crossing swords problem, but it occurs between the laparoscope and an instrument. Instead of running parallel to the surgical site, the primary cannula holding the laparoscope and one of the instrument-holding secondary ports are pointed toward each other; as the instrument is advanced toward the surgical site, it strikes and is deflected by the larger laparoscope, thereby rolling over the laparoscope and hence suddenly moving out of the field of view. Because of the large size of most laparoscopes and the much smaller size of the working instruments, it is commonly the surgeon who is most sensitive to this problem.

By definition, these problems are more likely to occur during laparoendoscopic single-site surgery. Because the ports are purposely placed in close proximity to one another the surgeon must use advanced techniques or special equipment such as articulating instrumentation or using instruments with different shaft lengths or a low-profile 5-mm laparoscope to overcome these pitfalls. Similarly, when using the da Vinci Robotic System the ports should be placed at least 8 to 10 cm away from one another to avoid robotic arm collision. This can sometimes be challenging on thin patients with limited abdominal wall space.

Usually these problems are a minor annoyance, and the surgeon and assistant need to experience the problem only once to adjust for it. Specifically, to avoid the problem of "striking handles," the sheaths can be withdrawn a bit from the abdomen, thereby increasing the space between the handles of the instruments. The problems of "crossing swords" and "rollover" can be remedied by moving the handles of the crossing trocars closer to one another, thereby moving the tips of the trocars farther apart. When this is done to correct a "rollover" the surgical site may be displaced into one corner of the monitor; however, the desired delivery of the instrument to the surgical site can then be accomplished. A

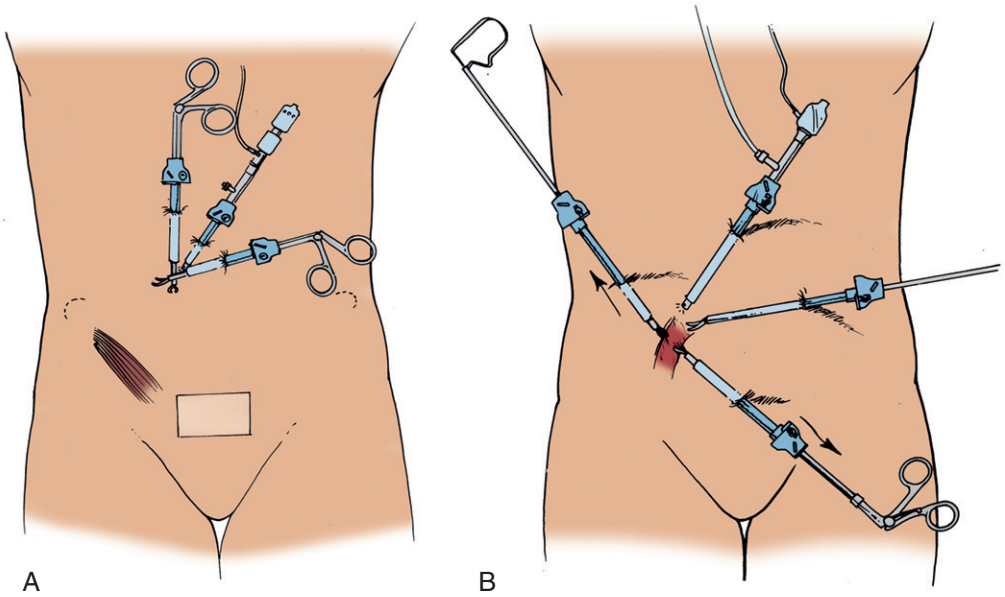


Figure 9–29. **A,** The cannulas have been placed too close to each other; hence, the intra-abdominal portions of the cannulas are also too close to each other, thereby impairing use of instruments passed through the ports. **B,** Correct spacing of the trocars eliminates this problem. (From Clayman RV, McDougall EM, editors. Laparoscopic urology. St. Louis: Quality Medical Publishing; 1993.)

30-degree laparoscopic lens can usually allow the laparoscope to be placed parallel to the instrument it is rolling over and then rotated to maintain the operative site image and eliminate the rollover. Alternatively, the handle of the instrument causing the rollover can be moved toward the extra-abdominal end of the laparoscope, thereby "separating" them intra-abdominally.

The best way to handle these situations is to properly place and direct each trocar at the beginning of the case. For some procedures, such as pyeloplasty, this may be accomplished by placing all the trocars on the same line (i.e., midline) so they are all working parallel to each other, whereas for procedures such as nephrectomy the goal is to place the trocars so that they surround the surgical site, forming a diamond pattern within which the kidney lies. Regardless, each trocar needs to be inserted such that it "points" to the pathology; this precludes the problem of having to redirect the trocar throughout the case, adding to surgeon fatigue and unnecessary trauma to the peritoneum and abdominal wall musculature. Also, the surgeon should avoid advancing sheaths too far into the abdomen. This can be accomplished by selecting the proper length of trocar for each patient. **Lastly, if trocar interactions become particularly vexing during a procedure, the surgeon should not hesitate to place an additional 5-mm secondary trocar in a more conducive site to eliminate the problem.**

Complications Related to General Anesthesia Unique to Laparoscopy

Cardiac Arrhythmias and Cardiac Arrest. Cardiac arrhythmias are frequently seen during anesthesia in laparoscopic procedures. The most common arrhythmia is sinus tachycardia; bradyarrhythmias (e.g., atrioventricular dissociation, nodal rhythm, sinus bradycardia) may develop independently or in combination with tachycardia during the same procedure (Myles, 1991). Conditions leading to development of arrhythmias are CO_2 insufflation, hypercapnia, increased vagal tone owing to traction on pelvic or peritoneal structures, Trendelenburg position, anesthetic drugs (especially halothane in combination with spontaneous ventilation), preoperative patient anxiety, endobronchial intubation, and gas embolism (Harris et al, 1984; Myles, 1991). In rare cases, asystolic cardiac arrest and cardiovascular collapse may develop (Shifren et al, 1992).

The role of the anesthesiologist throughout the laparoscopic procedure is of paramount importance. Continuous monitoring of cardiovascular (electrocardiogram, arterial blood pressure), and pulmonary (capnometry, in-line oxygen, airway pressures and tidal volume, frequent arterial blood gas analyses) parameters is essential. Invasive cardiac monitoring should be instituted in patients with heart disease (using a Swan-Ganz catheter) or in high-risk (i.e., American Society of Anesthesiologists type 3 or 4) patients when prolonged and complicated laparoscopic procedures are expected, especially because a central venous pressure line cannot be relied on for accurate readings during laparoscopy.

Because hypercarbia is one of the most common underlying causes of cardiac arrhythmias it is essential to monitor and control this problem. Overall, hypercapnia can be corrected rapidly by adjustment of ventilatory rate and tidal volume, use of positive end-expiratory pressure as needed, and reduction of intra-abdominal pressure to 10 mm Hg. The surgeon can also desufflate the abdomen for 5 to 10 minutes to allow the anesthesiologist to "catch up" and correct the hypercarbia; pneumoperitoneum can then be reinitiated at a lower pressure (5 to 10 mm Hg).

In rare cases, if the hypercarbia cannot be controlled by these maneuvers, helium should be substituted for CO_2 as the insufflant; however, this is a rare event and one that can usually be predicted before the procedure. For patients with preoperatively known severe pulmonary compromise, it is prudent to have a tank of helium and the proper helium yoke available in the operating room so the insufflant can be easily switched. Alternatively, argon gas can be used in the acute situation because it is readily available in many operating rooms owing to the argon beam coagulator (Badger et al, 2008).

In the event of cardiac arrest, the surgeon should immediately desufflate the abdomen and provide cardiac massage (compressions) while the anesthesiologist administers 100% oxygen and appropriate drug therapy. If a CO_2 embolus is suspected, additional

maneuvers, such as immediately turning the patient to a left lateral decubitus, head-down position and possibly attempting to aspirate the embolus, may be performed.

Preventive measures include avoidance of excessive intra-abdominal pressures (>25 mm Hg) over a prolonged period of time and avoidance of certain anesthetic agents or situations (e.g., halothane and spontaneous ventilation). Premedication with atropine may prevent excessive vagal stimulation (Wolf and Monk, 1996).

Changes in Blood Pressure. Hypertension may be caused by inadequate general anesthesia, elevated intra-abdominal pressures, or hypercarbia. Hypotension may be the result of hypoxia, pneumothorax, pneumomediastinum, gas embolus, or hemorrhage (Abdel-Meguid and Gomella, 1996).

Intermittent or continuous noninvasive blood pressure measurements or invasive monitoring of intra-arterial (e.g., radial artery) pressure is part of all laparoscopic procedures. In the event of a marked change in blood pressure, one of the aforementioned conditions must be ruled out. **The initial response of the surgeon, provided that there is neither active bleeding nor evidence of retroperitoneal hemorrhage, should be to desufflate the abdomen.** In addition to desufflation, therapy specific to an underlying laparoscopic cause may include CO_2 elimination by increased ventilation, attempts to increase oxygen saturation, treatment of an underlying pneumothorax, pneumomediastinum, or gas embolus, and pharmacologic (vasodilators or vasoconstrictors) therapy.

Aspiration of Gastric Contents. Aspiration of gastric contents may occur more frequently in patients with a hiatal hernia, significant obesity, diabetes with a history of gastroparesis, or any form of gastric outlet obstruction (Hanley, 1992). The combination of elevated intra-abdominal pressures from the pneumoperitoneum, morbid obesity, and use of the Trendelenburg position increases the likelihood of this complication (Abdel-Meguid and Gomella, 1996).

The diagnosis is easily made because the problem usually occurs during intubation, with associated coughing. The response to suspected aspiration depends on the intubation status of the patient. If the patient is not intubated, the head should be turned sideways and all gastric secretions should be vigorously suctioned (Hagberg and Boin, 1999). If the endotracheal tube is already in place, it should be left in situ and aggressive suctioning should be initiated. If aspiration of gastric contents occurs postoperatively, reintubation with mechanical ventilation and positive end-expiratory pressure may be indicated (Hagberg and Boin, 1999). Neither corticosteroid nor broad-coverage antibiotic administration is indicated (Tasch, 1999).

To prevent this problem in high-risk patients, oral or intravenous administration of 10 mg of metoclopramide is recommended. This medication may decrease the incidence of aspiration by increasing the tone of the lower esophageal sphincter. In addition, in patients with known gastroesophageal reflux, H_2 blockers reduce gastric acidity and attendant morbidity if aspiration of gastric contents should occur (Hanley, 1992; Abdel-Meguid and Gomella, 1996). Also, in patients with known gastroesophageal reflux or other predisposing factors for gastric aspiration, a cuffed endotracheal tube should always be placed. Lastly, among these high-risk patients, administration of atropine should be avoided because it decreases the tone of the lower esophageal sphincter (Duffey, 1979).

Hypothermia. The patient's body core temperature may drop during prolonged laparoscopic procedures, especially if there is leakage of insufflant around the port sites. The CO_2 that is used is typically neither warm nor humidified. The resulting decrease in temperature may be 0.3° C for each 50 L of CO_2 insufflated (Ott, 1991a). The ambient operating room temperature may exacerbate this effect.

The clinical effects of hypothermia are well described. Core body temperatures around the 35° C level may result in (1) increased bleeding tendency owing to impaired platelet function, reduced activity of coagulation factors in the coagulation cascade, and enhanced fibrinolysis; (2) increased adrenergic response with vasoconstriction and increased arterial blood pressure; (3) prolonged recovery time due to increased blood gas solubility; (4) twofold to threefold increase in the incidence of early postoperative myocardial ischemia in high-risk patients; and (5) impaired wound healing and increased susceptibility to wound infections (Rosenberg and Frank, 1999).

In general there are no specific anesthetic symptoms that can be appreciated intraoperatively except for cardiac arrhythmias. In particular, atrial fibrillation may occur in extreme cases of hypothermia (body core temperature around 30° C). In such a case, if the patient arrests, cardiac resuscitative efforts should be **prolonged** because the patient must be warmed for resuscitative efforts to have their proper impact. The problem is combated by use of warm intravenous fluid and application of active warming systems.

In almost all cases, hypothermia can be avoided. Adjuncts to support the patient's body temperature include intravenous fluid warming, active warming by forced-air systems, circulating warm-water mattresses, and radiant heaters (Rosenberg and Frank, 1999). In addition, warming and humidifying CO_2 to physiologic levels, especially when a prolonged laparoscopic procedure is anticipated, is helpful (Ott, 1991b). However, warming the insufflant alone, should be avoided, because this causes a drying of the intraperitoneal tissues and has been associated with increased postoperative patient discomfort (Slim et al, 1999).

Complications Related to the Surgical Procedure

Bowel Injury: Electrosurgical Etiology. Electrosurgically induced thermal injury may occur because of one of four mechanisms: inappropriate direct activation, coupling to another instrument, capacitive coupling, and insulation failure. Active electrode trauma by unintended activation causes direct bowel or other organ injury; it may occur when the instrument is left unobserved within the peritoneal cavity or when electrode activation is carried out by someone other than the primary surgeon. Furthermore, active electrode trauma may be seen when coagulation extends beyond the intended site and reaches other adjacent structures (e.g., bowel, blood vessels, nerves, ureter); this is more commonly seen when high electrocoagulation settings (i.e., >30 watts) are used instead of blended or pure cutting current. Direct coupling may occur when the active electrosurgical instrument touches another instrument that is in direct contact with other tissue (e.g., bowel). If this happens outside the field of view provided by the laparoscope, it may remain unnoticed by the surgical team. Injury owing to capacitive coupling occurs when the surrounding charge, which is intrinsic to all activated monopolar electrodes, is not allowed to conduct back to and disperse through the abdominal wall (Zucker et al, 1995; Munro, 1997). This condition may develop when a metal cannula is anchored to the skin with a nonconductive plastic grip, which, as previously noted, should never be done (Fig. 9–30). As a result, the electrical field, which builds up around the activated electrosurgical instrument and is conducted to the metal trocar through which it has been placed, cannot then be conducted to the abdominal wall because the plastic retainer acts

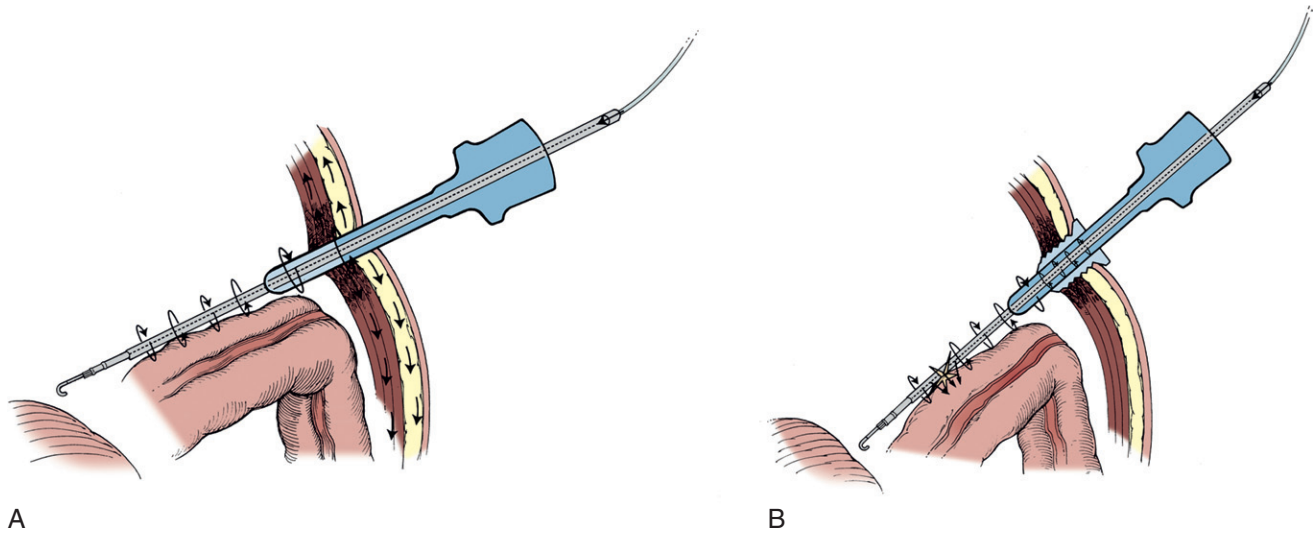


Figure 9–30. Capacitive coupling. **A,** Charge surrounding the activated monopolar electrode is conducted back to the all-metal cannula and dispersed by the abdominal wall. **B,** The electrosurgical instrument is being used through a metal cannula that has been anchored to the skin with a nonconductive plastic grip; accordingly, the electrical field cannot be conducted to the abdominal wall because the plastic retainer acts as an insulator; a stronger electrical charge is thus conducted to any other tissue in contact with the cannula.

as an insulator. This may lead to a high power density along the portion of the metal cannula that is inside the abdomen; the electrical charge built up on the cannula can then travel to other tissues in contact with the cannula. Similarly, capacitive coupling may constitute a risk when electrosurgical probes are used through operating laparoscopes, which are, in turn, inserted through plastic sheaths. The metal shaft of the laparoscope then becomes a repository for electrical current and may discharge this energy to any tissue in contact with the laparoscope. In general, the side-arm operating laparoscope is rarely used during urologic procedures. The risk of this complication is also increased when older generators with high-voltage output and/or electrodes with thicker diameters are used, especially in coagulation rather than cutting mode (Munro, 1997). Lastly, insulation breakdown may allow current to escape along the shaft of the instrument, thereby harming tissues that are otherwise outside the field of view of the laparoscope. Insulation breakdown along the shaft of the instrument may be a result of repeated use, resterilization, or mechanical damage to the instrument during repeated insertion through a trocar. In this situation, the small break in insulation results in an area of very high power density that then discharges to the nearest soft tissue.

Intraoperatively, thermal injuries of the bowel may present as whitish spots on the serosal lining. In severe cases, the muscularis mucosae or the intestinal lumen may be seen. However, in many patients, the event of thermal injury of the bowel is not realized at the time of the procedure. **Postoperatively, the patient with unrecognized bowel trauma may not develop fever, nausea, or signs of peritonitis for many days; indeed, the full extent of the bowel necrosis may take up to 18 days to fully develop** (Abdel-Meguid and Gomella, 1996). **Therefore, the problem often does not become manifest until the patient has actually been discharged from the hospital.**

Accordingly, bowel injury must be ruled out for any patient who develops a fever beyond postoperative day 1 or who complains of increasing abdominal discomfort. Abdominal radiographs are notoriously inaccurate because the CO_2 from the laparoscopy may remain as "free air" for upwards of 9 days after the procedure; however, an ileus pattern is usually present. The more sensitive test is an abdominal CT scan with oral contrast accompanied by delayed films, usually 6 or more hours after the initial oral contrast load. Laboratory values may be remarkable for leukocytosis with an associated left shift (i.e., increased percentage of neutrophils); in some patients, the latter occurs in the face of a normal or even low leukocyte count, making the "left shift" a more reliable sign than the absolute white cell count.

Minor postoperative thermal injuries of the bowel, discovered late in the postoperative period (i.e., >5 to 7 days postoperatively) may be managed conservatively, aided by administration of antibiotics and an elemental diet. Indeed, a closed fistula may develop that will heal with this approach. However, if the patient does not respond rapidly or develops worsening peritonitis, open surgical exploration is mandatory. Thermal injury caused by monopolar cautery often results in tissue damage that extends beyond the visible area of necrosis. With this in mind, the surgeon should perform a bowel resection with a safety margin of 6 cm on either side before completing an end-to-end anastomosis (Abdel-Meguid and Gomella, 1996).

Thermal injury caused by bipolar electrosurgery is more confined to the visible area of damage. These injuries only occur due to direct firing of the instrument on the bowel. If the injury is small, it can be managed by simple excision of the defect and closure of the bowel wall. Bipolar injuries that involve more than half of the circumference of the bowel should be treated by excision of the affected segment of the bowel followed by end-to-end anastomosis (Abdel-Meguid and Gomella, 1996).

The goal of every laparoscopic surgeon is to never experience a thermal complication. To this end there are several actions the surgeon can take to lessen the risks. First, electrosurgical instruments must be carefully inspected before use for any "breaks" in the insulation; if these are found, the instrument must be sent out to be recoated. Next, electrosurgical instruments should never be left untended within the abdomen; when not in use they must be removed from the abdomen. Also, control of electrode activation should be performed *only* by the primary surgeon. The foot pedal

should be placed so that only the surgeon can depress it. To facilitate surgeon-only activation of the instrument, some newer laparoscopic instruments such as the 5-mm LigaSure (ValleyLab, Boulder, CO) are designed with ergonomic thumb-operated mechanisms that only the operative surgeon can activate. Also, isolation of the area to be cauterized from the surrounding tissues (vessels, nerves, ureter), as well as use of bipolar electrocautery, reduces the risk of thermal injury to other tissues. In addition, the electrosurgical device should never be activated unless the entire extent of the metal portion of the instrument is in view; this includes not only the active tip of the instrument but also any exposed, uncoated metal joints that may lie just behind the tip of the instrument. In this manner both inadvertent direct injury to adjacent tissue and direct coupling to another instrument can be avoided. Problems of capacitive coupling can be precluded by not creating a situation in which a mixture of conducting and nonconducting elements are used by the surgeon (e.g., metal trocars combined with plastic retainers, electrosurgical devices through uncoated operating laparoscopes passed through plastic trocars). In addition, use of modern generators and small-diameter electrodes significantly decreases the risk of capacitive coupling (Munro, 1997), as does greater use of blended or pure cutting current. The high voltages needed for pure coagulation current pose the greatest threat for electrosurgical injury, especially through the mechanism of capacitive coupling and insulation failure. Lastly, an active electrode monitoring system (Encision, Boulder, CO) is extremely helpful; with this system, any sudden break in the insulation of the electrosurgical instrument (e.g., with scissors or hook electrode) results in immediate shutdown of the electrosurgical current, thereby precluding an electrosurgical injury.

Bowel Injury: Mechanical. Inadvertent mechanical damage can be caused by a wide variety of sharp and blunt instruments (e.g., laparoscopic graspers, scissors, retractors). This type of injury is more visible to the surgeon and is usually discovered intraoperatively or at the end of the procedure when the surgical site is irrigated. Direct visual identification during the procedure allows the surgeon to repair the injury laparoscopically, even though the patient has not had a formal bowel preparation. Given its localized nature, bowel resection is rarely necessary. The abdomen should be irrigated copiously at the end of the procedure with 4 to 5 L of an antibiotic-containing solution.

If the situation is missed during the procedure, then postoperatively symptoms develop much earlier than with an electrosurgical injury. Fever, nausea, ileus, and peritonitis develop in the very early postoperative period. Diagnosis is confirmed by an abdominal CT scan with oral contrast material. This type of injury should be managed with immediate return to the operating room to correct the problem by local excision or resection of bowel with subsequent end-to-end anastomosis and copious irrigation of the abdomen (see later).

Delicate handling of tissue with laparoscopic instruments by the main surgeon and the assistants is essential to avoiding this complication. Likewise, it is important that introduction of laparoscopic instruments into the peritoneal cavity be done under strict visual control. Instruments should never be left untended; if they are not in use, they should be withdrawn from the abdominal cavity. Attentiveness, economy of motion, and deftness of touch are essential characteristics of both the successful open and laparoscopic surgeon.

Vascular Injury. Fortunately, direct vascular injury during laparoscopic dissection is a rare event. The use of only blunt trocars, the small nature of the instrumentation, the limitations on surgical speed, and the magnification of the surgical field by the laparoscope all combine to decrease this potential problem.

During right renal dissection, in particular, the chance of a vena cava or renal vein injury is heightened. When this occurs the surgeon can undertake several steps to resolve the bleeding. **First, the pneumoperitoneum pressure can be raised to 25 mm Hg, thereby slowing or stopping any venous bleeding.** With the use of the irrigator/aspirator, the blood can be cleared and the bleeding site identified; if necessary a second insufflator can be brought into the room and connected to maintain pneumoperitoneum pressure even during use of suction at the site of injury. Next, through one of the 12-mm ports, a gauze sponge or a 4 × 18-inch laparotomy pad can be introduced into the abdomen and handled with a grasping forceps, thereby allowing the surgeon to identify and tamponade the area of bleeding. If the injury is small, then it may respond to simple tamponade; alternatively, a hemostatic patch and/or fibrin glue or thrombin-impregnated granules (e.g., Floseal) may be applied. If the injury is larger, then the surgeon must decide whether to obtain a vascular consult and proceed to convert to an open procedure or to attempt securing the injury with a laparoscopic Satinsky clamp and proceed with intracorporeal suturing, either freehand or with an Endo Stitch and 4 inches of a 4-0 Vicryl suture with a Lapra-Ty clip secured at its end. Care should be taken to use a laparoscopic grasper to introduce the Lapra-Ty clip into the abdomen first, followed by the Endo Stitch device; the shaft of the Endo Stitch cannot be passed alongside the Lapra-Ty clip because the two together are too broad to pass side by side through a 12-mm cannula. With the Endo Stitch device a running suture is done, with the initial Lapra-Ty clip serving as the distal "knot"; after the defect is closed, the suture is again secured with a Lapra-Ty clip. *One caveat is important:* specifically, owing to the larger holes in the tissue caused by the Endo Stitch needle and suture passing side by side the sewn tissue may ooze slightly after the repair; this can be nicely controlled by the application of thrombin-impregnated granules (e.g., Floseal). Throughout this period, it is essential for the anesthesiologist to administer sufficient fluids or blood replacement to preclude a hypovolemic state because the hypovolemic patient has a higher risk of possible air embolism at these higher intra-abdominal pressures (O'Sullivan et al, 1997).

If the surgeon is able to gain temporary control of the vessel with a grasper then it is often helpful to place an extra 5-mm port that can be used by the assistant for suction/irrigation or to optimize the plane of approach to the injury, thereby facilitating laparoscopic suturing. Either way the additional port allows the surgeon to repair the bleeding site using two hands and with excellent visualization of the surgical field.

Alternatively, the surgeon can convert from standard laparoscopy to a hand-assisted approach. The hand in this case is valuable because it can rapidly tamponade the bleeding site. In this regard it is recommended, if at all possible, to pinch the sidewalls of the vein (e.g., inferior vena cava) closed rather than just putting direct pressure on the top of the injury; the latter approach has a tendency to result in a gradual enlargement of the hole in the vein. Also, by pinching the hole closed, a Satinsky clamp can be more easily passed beneath the surgeon's fingers to provide reliable control of the injury in preparation for a sutured repair.

Minor arterial injuries usually respond to tamponade. Larger aortic or renal artery injuries are much more difficult to resolve laparoscopically. Although the latter, if it occurs during a planned nephrectomy, can be handled by expeditiously taking the renal artery with a vascular stapler, the former almost invariably leads to immediate conversion and open repair. In this case, the area of

injury should be tamponaded with a laparoscopic forceps. A vascular surgeon can be called into the room and the surgeon can proceed to rapidly make a midline incision by swinging one of the midline ports up to the underside of the abdominal wall and cutting down on the shaft of the port. The tamponading laparoscopic forceps directs the surgeon immediately to the site of injury, which can then be properly repaired.

As mentioned previously in this chapter, because most bleeding episodes are unexpected, it is wise to have in the room a hemorrhage tray equipped with all instruments necessary to control bleeding. In most cases, a successful outcome is heavily dependent on a rapid and effective response on the part of the surgeon, which is only possible if the equipment is immediately available and the operating room team is knowledgeable and efficient. A hemorrhage tray that can quickly be opened in case of a vascular injury containing all needed instruments is highly recommended (see Table 9–6). The authors recommend that this tray be wrapped in a red cloth or other highly visible unique wrapping so it is always readily identifiable in the operating room.

Injury to the Urinary Tract

Bladder Injury. Electrocautery dissection, blunt and sharp dissection (with laparoscopic scissors), and laser dissection have been identified as intraoperative causes of bladder injury (Ostrzenski and Ostrzenska, 1998). Concomitant bladder or pelvic anomalies or pathologic conditions (acute or chronic inflammation, prior pelvic or bladder surgery, endometriosis, malignant infiltration, bladder diverticula, amyloidosis, or previous radiation) are predisposing factors that increase the chances of this complication (Ostrzenski and Ostrzenska, 1998).

When a bladder injury has occurred, the intraoperative signs may be subtle. One of the first signs is the presence of blood or gas in the Foley catheter bag. Also, the surgeon may notice clear fluid welling up in the pelvis, although this sign is often obscured if irrigation has been used during the procedure.

Postoperatively, if the bladder injury was missed, the patient may develop oliguria and urinary ascites; this may be accompanied by hyponatremia and, rarely, hyperkalemia with mild elevation of the serum creatinine concentration owing to the peritoneal absorption of urine. Patients who have been discharged from the hospital because of the minor nature of their laparoscopic procedure may contact their physician complaining of lower abdominal discomfort, abdominal swelling, fever, and, in the case of a gynecologic procedure, vaginal discharge.

The intraoperative suspicion of a bladder injury may first arise due to the recognition of an air-expanded urine collection bag; this presumptive diagnosis can be confirmed by the injection of saline mixed with indigo carmine through the Foley catheter. Postoperatively, the diagnosis can be made by radiologic examinations (pelvic ultrasonography, pelvic CT, and/or voiding cystourethrography). Similarly, an endoscopic examination with the injection of 5 mL of indigo carmine intravenously is helpful if a vesical fistula is suspected; the surgeon can then look for blue-tinged vaginal or rectal discharge (Chapron et al, 1995; Ostrzenski and Ostrzenska 1998).

The intraoperative diagnosis of a bladder injury can be followed by laparoscopic repair: suturing with absorbable suture, closing the defect with a laparoscopic stapler, or, if the injury is quite small, using preformed suture loops to encircle and secure the cystotomy (Poffenberger, 1996; Ostrzenski and Ostrzenska, 1998). More extensive defects may require open incisional repair.

When bladder injury is diagnosed postoperatively, the key factor is whether the drainage is extraperitoneal or intraperitoneal, which is largely dependent on the preceding laparoscopic access. Extraperitoneal extravasation without any complicating additional problems may be treated by simple placement of a transurethral indwelling Foley catheter. Intraperitoneal drainage is an indication for subsequent laparoscopic or open repair.

Prevention of bladder injury requires preoperative placement of a Foley catheter. Strict adherence to basic laparoscopic principles remains the hallmark of an uncomplicated laparoscopic procedure; in this regard, avoidance of excessive coagulation near the bladder and dissection with exact knowledge of bladder anatomy (urachus, medial umbilical, and vesicocervical ligaments) are key.

Ureteral Injury. Ureteral injury is usually a result of thermal damage caused by dissection using monopolar electrocautery in the immediate vicinity of the ureter. Its incidence in laparoscopic hysterectomy is 1%; it may also occur during laparoscopic endometriosis ablation and tubal ligation and has been reported during pelvic lymphadenectomy and laparoscopic radical prostatectomy (Baumann et al, 1988; Grainger et al, 1990; Poffenberger, 1996; Liu et al, 1997; Ostrzenski and Ostrzenska, 1998; Guillonneau et al, 2002).

The intraoperative diagnosis is made by the astute laparoscopist when urine is seen to be welling up in the wound. However, if irrigation has been used during the procedure this sign is invariably obscured. As opposed to a bladder injury, macroscopic hematuria or pneumaturia is distinctly unusual with this injury.

Typically, ureteral injuries remain unnoticed throughout the laparoscopic procedure. Within 2 to 3 days after surgery, patients may present with abdominal and/or flank pain, fever, signs of peritonitis, and leukocytosis (Grainger et al, 1990; Liu and McFadden, 2000).

Most of these diagnoses are made during the postoperative period when an intravenous pyelogram or abdominal/pelvic CT is ordered owing to the patient's complaint of flank pain, abdominal swelling, and/or the physical signs of urinary ascites. Depending on the function of the contralateral kidney and the amount of urine leakage, serum chemistries may reveal hyponatremia and, rarely, hyperkalemia with a mild elevation in the serum creatinine concentration.

If identified intraoperatively, the injury can be repaired laparoscopically. If the injury is due to mechanical trauma, simple closure of the defect can be accomplished with laparoscopic suturing techniques followed by stent placement. If the injury is due to monopolar electrosurgical current, then a formal resection of the affected area and an end-to-end spatulated ureteroureterostomy and stent placement are indicated; ureteral reimplantation is indicated if the level of injury is at the ureterovesical junction. This can be done laparoscopically but may require conversion to an open procedure. An indwelling ureteral stent is placed.

If the problem is detected in the postoperative period, the first step is to place an indwelling ureteral stent and a bladder drainage catheter. If a stent cannot be placed, then a laparoscopic or open surgical intervention is indicated to repair the area of injury; alternatively one can consider a percutaneous nephrostomy and an antegrade attempt at stent placement before seeking a laparoscopic/open solution. Once a cystogram reveals reflux without extravasation, the bladder drainage catheter can be removed. The stent is left in place for 6 to 8 weeks. Careful follow-up is necessary to rule out the development of a ureteral stricture that may require endourologic or formal surgical repair.

Prevention of this injury again harkens back to the importance of the surgeon's knowledge of laparoscopic anatomy and the course of the ureter with regard to its topographic relation to other

anatomic structures (medial umbilical ligament, round ligament or vas deferens, and common iliac artery). During dissection, the use of monopolar electrosurgical coagulation current should be used with great discretion around the ureter. In particular, a "cutting" rather than "coagulation" mode should be used whenever possible; when employing "coagulation" current the wattage should not exceed 30 watts. In addition, fine-tipped electrosurgical instruments should be employed and the duration of discharge should be brief (i.e., multiple short bursts of current rather than a continuous multisecond discharge).

Pancreatic Injury. Injury to the pancreas during left-sided laparoscopic adrenalectomy or radical nephrectomy is most commonly associated with mechanical retraction. The tail of the pancreas overlies the adrenal and may be injured during dissection of the medial aspect of the adrenal and the securing of the splenorenal ligament. The incidence of this complication is 2.1% for radical left nephrectomy and 8.6% for left adrenalectomy (Varkarakis et al, 2004). Of note, the diagnosis is rarely made intraoperatively; indeed, 75% of pancreatic injuries are diagnosed during the postoperative period.

Among the few in whom this diagnosis is made intraoperatively, general surgery consultation can be obtained and the injury possibly repaired by freeing up the tail of the pancreas and excising the injured portion with an Endo GIA stapler. However, more commonly the patient presents postoperatively with abdominal discomfort. Evaluation reveals elevated serum lipase and amylase levels, as well as leukocytosis. CT reveals a fluid collection that can often be drained percutaneously. A nasogastric tube is placed and oral intake is stopped. When drainage drops below 50 mL/24 hr, the drain can be removed, followed by removal of the nasogastric tube and initiation of a low fat diet. Of note, the average hospital stay among patients with this complication was 18 days.

Prevention of this complication requires the surgeon to widely dissect the line of Toldt and the splenophrenic attachments. The latter are freed to the level of the diaphragm. The colon is broadly reflected from the Gerota fascia, and the splenocolic and splenorenal ligaments are divided. With these maneuvers the spleen and colon rotate medially carrying with them the tail of the pancreas, well away from the medial surface of the adrenal gland.

Splenic Injury. The advent of laparoscopic surgery has been associated with a significant decrease in incidental splenectomy, with a fall from 4.3% to only 1.5%. These injuries are invariably discovered intraoperatively and can effectively be treated with argon beam coagulation or with one of the newer hemostatic agents such as fibrin glue or thrombin-impregnated granules. **Avoidance of this complication is best achieved by wide mobilization of the spleen during left radical/total nephrectomy.** To this end the splenophrenic attachments as well as the splenocolic and splenorenal ligaments need to be divided. Retraction in the area of the spleen should never be on the spleen itself but beneath the area of the splenocolic ligament such that the retractor is placed on these thicker tissues (Cooper et al, 1996; Simon et al, 2004).

Also, the laparoscopic surgeon must ever be vigilant of the splenic vein. This often tortuous vein may run parallel and within millimeters of the superomedial surface of the adrenal gland and the upper pole of the left kidney.

Nerve Injury. There is no problem more vexing to physician and patient alike than a postoperative nerve injury; a technically and surgically successful procedure is marred by an acute complication in a totally unrelated area. This problem is invariably due to patient positioning in combination with the duration of the procedure. The exact incidence of this problem is not known, but in a recent survey of neuromuscular injuries associated with laparoscopic urologic surgery completed by 18 urologists from 15 institutions in the United States it was found that of a total of 1651 procedures there were 46 neuromuscular injuries in 45 patients (2.7%). This included abdominal wall neuralgia (14), extremity sensory deficit (12), extremity motor deficit (8), clinical rhabdomyolysis (6), shoulder contusion (4), and back spasm (2) (Wolf et al, 2000). If the patient is inadequately positioned and/or padded, nerve damage may result owing to abnormal nerve stretching or compression. Among position-related nerve injuries, the brachial plexus appears to be most at risk. Injury may be inflicted in several ways: (1) abduction of the arm beyond 90 degrees, (2) extreme outward rotation of the head of the humerus, and (3) compression damage when shoulder braces are used in the Trendelenburg position, which pushes the clavicle into the retroclavicular space. Other nerves that can be affected by positioning include the femoral nerve, owing to extreme lateral rotation and abduction of the hip joint, and the sciatic nerve, owing to stretching along the superior leg when the patient is in the lateral decubitus position (Hershlag et al, 1990; Abdel-Meguid and Gomella, 1996). In addition, nerves may be injured during the surgery itself because of either direct mechanical injury or monopolar electrosurgical current. In this regard, the nerves most susceptible to damage in urologic laparoscopy are the obturator nerve during pelvic lymphadenectomy and the genitofemoral nerve during radical nephrectomy/nephroureterectomy. The diagnosis is invariably made postoperatively. On awakening from anesthesia, the patient complains of weakness or inability to contract the affected musculature, paresthesias, and/or anesthesia of the innervated skin areas.

Mechanical or electrosurgical injury to a nerve during laparoscopy may be recognized intraoperatively. A common example is transection of the obturator nerve during pelvic lymphadenectomy. A neurosurgical consultation can be obtained, and the nerve can be repaired with 6-0 suture using an open or laparoscopic approach.

In contrast, nerve palsy owing to positioning is recognized only postoperatively, often in the postanesthesia recovery room or on the first postoperative day when the patient tries to ambulate. From both a medical and a legal standpoint, a neurology consultation should be obtained as soon as the patient calls the surgeon's attention to a possible nerve injury. Neurologic examination with possible nerve conduction studies to document acute damage is important. Physical therapy may facilitate recovery. However, recovery in these cases, if it does not occur within the first few postoperative days, is often slow, requiring months.

Prevention is paramount. Table-mounted accessories for all major commercial operating room tables now exist that aid in safely and effectively positioning patients in the lateral decubitus position and in the prone position. The kidney rest, if used, should be lowered after the pneumoperitoneum or retroperitoneum is obtained and trocars placed. Special head supports are also available. If the arms are to be at the patient's side, they should be pronated to protect the brachial plexus. If the patient is to be in a lateral decubitus position, all bony prominences should be padded with additional gel pads (i.e., hip, knee, and ankle on the downside leg); a pillow is always placed between the legs. Padding should also be placed beneath Velcro straps and tape which may be used on the upside hip and shoulder. Shoulder braces should not be used owing to risk of brachial plexus injury. Instead, a well-padded wide strap directly across the upper chest is an excellent way to secure the patient when in the extreme Trendelenburg position, which is often required during laparoscopic radical

prostatectomy. Extreme abduction of the hip is also to be avoided. Padding must be checked each time the table position is changed. Lastly, as with all areas of laparoscopy, judicious use of monopolar coagulation current and knowledge of anatomy are key to avoiding direct nerve injury during the procedure.

Complications Related to Exiting the Abdomen

Bowel Entrapment. During removal of laparoscopic ports and release of the pneumoperitoneum, omentum, or bowel may be entrapped at one of the port sites. If missed during the process of cannula removal, then in the early postoperative period, usually on the second or third postoperative day, the patient develops an ileus and point tenderness at the port site incision.

The treatment is laparoscopic. The pneumoperitoneum is reestablished through one of the unaffected port sites, and three ports are replaced: one for the camera and two for grasping forceps. The entrapped bowel is visualized, and an atraumatic bowel clamp is placed on the bowel on either side of the area of herniation. Once this is done, the skin sutures of the affected port site are carefully cut and the wound is opened; the surgeon uses a fingertip to manually reduce the bowel into the abdominal cavity. The bowel can then be carefully inspected; if it appears viable, which is usually the case, it can be left in place and the port site closed. Rarely is formal bowel resection and anastomosis required.

This particular problem is the result of a technical error. Indeed, most laparoscopic ports have a hole drilled into the side of the port within a few millimeters of the end of the port's shaft. This hole equalizes the pressure in the port and the abdomen as the port is pulled out of the abdomen, thereby precluding any bowel being withdrawn with the port. Furthermore, if each port site is endoscopically inspected at the time of cannula removal, bowel or omentum that may have entered the port site can be readily identified and positioned back into the abdominal cavity. When the last endoscope-bearing port is removed, the assistant should pull up on the closure sutures or on a fascial clamp, and the surgeon should back the cannula out of the wound and up onto the shaft of the endoscope so that the endoscope is the last thing to leave the abdomen. This maneuver, again, visually assures the surgeon that no bowel or omentum has entered the track of the final trocar.

Bleeding at the Sheath Site. This problem has been previously discussed under the heading of trocar placement. However, there are times when this problem does not become apparent until the end of the procedure owing to tamponade from the trocar itself. Again, it is essential to inspect each trocar site at 5 mm Hg to rule out this problem. Its resolution and avoidance are as previously described.

Early Postoperative Complications

Acute Hydrocele. When significant amounts of irrigation fluid are used during a laparoscopic case in a male, it is not unusual for this fluid to accumulate in the scrotum if the patient has a patent processus vaginalis or a small hernia. The problem is usually not recognized until late in the first postoperative day when the patient is ambulating. The scrotum enlarges noticeably, and there may be dull, aching scrotal discomfort.

Direct visual inspection and transillumination suffice to make the diagnosis. If a possible underlying testicular pathologic process is a concern, scrotal ultrasonography can be done.

Treatment of acute hydrocele is simply observation and scrotal support. Reabsorption of fluid occurs within a week. Preventative effort with regard to this problem involves aspiration of irrigation fluid at the end of the procedure.

Scrotal and Abdominal Ecchymosis. This is another problem that may not become apparent until the second postoperative day. It is usually a result of delayed subcutaneous bleeding from one of the port sites. There are no specific symptoms, but the purplish discoloration of a large area of skin surrounding a port site is very disconcerting to the patient and family. Indeed, with pelvic ports, the discoloration in the male patient may involve the scrotum, too. There is no specific treatment other than observation and reassurance. The purplish discoloration of the skin eventually turns yellow and then disappears. The patient should be informed of these expected changes in color to preclude further alarm. The best method of prevention is to observe each port entry site after port removal to check for evidence of bleeding.

Pain. Pain may be localized or diffuse. If postoperative pain is limited to a port site, it may be secondary to herniation (immediate or late) or to infection (late). Localized pain combined with a subcutaneous bulge may indicate a rectus sheath hematoma, bleeding and hematoma formation at a port site, or a port site hernia. Pain at a port site without swelling may be due to a particularly broad fascial suture or palpation of the knot of a port site fascial suture in a thin patient. Early in the postoperative course, port site discomfort is to be expected; however, if it appears to be increasing on subsequent postoperative days, then herniation should be suspected.

Immediate, severe, diffuse abdominal pain may be related to the release of noxious material during the procedure (e.g., cyst fluid in patients with autosomal-dominant polycystic kidney disease) or to a bowel injury. Immediate postoperative scapular discomfort may be a result of the CO_2 pneumoperitoneum itself causing some irritation of the diaphragm; rarely, this discomfort may be sufficiently severe to mimic the symptoms of a pulmonary embolus. Of note is that this pain is invariably along the area of the right posterior shoulder region. Delayed diffuse abdominal discomfort and development of peritoneal signs or simply ongoing abdominal discomfort accompanied by low-grade fever may be due to an unsuspected bowel injury; usually, this is the result of a monopolar electrosurgical injury and may present as late as 18 days after the procedure. Of note, these patients may not have a leukocytosis; however, the differential usually shows a left shift.

The cause of localized pain can usually be discerned by the astute surgeon. A fascial knot or hematoma causing localized port site pain can be readily palpated; similarly, a port site hematoma is discernible by the firm mass it produces. When none of these signs is present in a patient complaining of localized pain over a port site, a hernia should be suspected; CT readily reveals the diagnosis.

For diffuse pain, an associated low-grade fever and mild leukocytosis/leukopenia with a left shift are hallmarks of bowel injury. This is best diagnosed by CT with oral contrast material and repeat CT 6 to 8 hours later. If chest pain is present, an electrocardiogram plus cardiac enzymes as well as spiral CT of the chest with intravenous administration of a contrast agent or ventilation-perfusion scan of the lungs plus arterial blood gas tests should be performed to rule out myocardial infarction and pulmonary embolism, respectively.

The treatment of localized pain is directed by the diagnosis. Thus, for localized pain owing to a hematoma or a fascial suture, time, reassurance, and a heating pad are all that is necessary. For a port site hernia, laparoscopic reduction, as previously described, is the next step. The treatment of diffuse pain is guided by the CT results. For suspected bowel injury, if it is early in the postoperative course (i.e., if the patient is still in the hospital), reexploration

and surgical correction are indicated. If the bowel injury is detected late and CT shows that it is already confined, then it can be managed as a closed fistula with observation and an elemental or parenteral diet; it often takes months for the problem to completely resolve when managed nonsurgically.

Prevention of most of these causes of postoperative pain requires a meticulous, careful inspection of the entire abdomen before ending the procedure. Various methods have been tried, with variable success, to decrease discomfort owing to the pneumoperitoneum; these have included placement of a drain to help expel all the CO_2, flushing of the abdomen with nitrous oxide at the end of the procedure to expel the CO_2 and replace it with a less irritating gas, maintaining the pneumoperitoneum pressure as low as possible (i.e., 10 to 12 mm Hg), and selective bathing of the surgical site with a solution of local anesthetic (e.g., 30 mL of ¼% bupivacaine).

Incisional Hernia. In adults, the occurrence of an incisional hernia is usually confined to port sites larger than 10 mm. However, in the pediatric population, this complication can occur even with 5-mm ports. The patient usually complains of localized discomfort accompanied by nausea and signs of ileus. Rarely, diffuse abdominal pain and/or signs of a complete bowel obstruction may be present. On examination there is tenderness and, at times, swelling overlying the affected port site. A plain film of the abdomen may show an ileus pattern; however, the definitive study is abdominal CT, which can actually reveal the bowel protruding above the fascial level.

Laparoscopic repair with dissection of the hernia and subsequent intra-abdominal closure can be accomplished. The method for performing this procedure has already been described. In complicated cases in which a strangulated hernia is suspected or confirmed laparoscopically, open surgical repair is indicated.

This problem is most easily avoided by performing a meticulous fascial suture closure of all "bladed" trocar entry sites equal to or larger than 10 mm in all adults. This should always be done under direct endoscopic monitoring. In children, it is advisable to perform fascial closure of any "bladed" port site 5 mm or larger. The fascial layer is usually closed with an absorbable 0-0 suture as previously described. For patients in whom only nonbladed trocars have been used, fascial closure is indicated only of the midline ports or any port site that has been unduly stretched (e.g., passage of a LapSac entrapment sack). Indeed, some authors recommend no closure even of midline nonbladed trocar sites. Although there has been one report of a hernia developing after use of a nonbladed trocar, this is distinctly rare (Lowry et al, 2003). Indeed, the incidence of postoperative hernia formation has been noted to fall from 1.8% with bladed trocars to only 0.19% for nonbladed larger trocars (Boike et al, 1995; Hashizume and Sugimachi, 1997; Thomas et al, 2003). Of note, with midline hand-assist approaches, a higher incidence of hernia formation has been identified than would otherwise be expected: 4.0% to 7.3%. As such, some authors have recommended closure of this midline incision with interrupted nonabsorbable suture rather than a running, absorbable closure (Troxel and Das, 2005).

Deep Venous Thrombosis and Pulmonary Embolism. Although it seems reasonable to expect decreased venous return and, hence, increased stasis with concomitant higher risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing laparoscopy, this is remarkably **not** the case. Indeed, there is no evidence that this complication occurs more often during laparoscopic procedures versus open incisional surgery (Abdel-Meguid and Gomella, 1996; Secin et al, 2008).

Signs of DVT include localized calf tenderness with associated swelling. However, most patients with postoperative DVT have a subclinical course. Indeed, unfortunately, the most common clinical scenario is detection of a DVT only after a patient has developed a PE. Signs of PE include acute shortness of breath, decreased oxygen saturation, and pleuritic chest pain. Additionally, an electrocardiogram might show a right-sided heart strain pattern. The diagnosis of a DVT is made clinically and confirmed using Doppler ultrasonography of the lower extremities. PE is diagnosed most expeditiously by contrast-enhanced chest CT.

Treatment is immediate anticoagulation, initially with heparin and then with warfarin. In patients with a pulmonary embolus who are not candidates for anticoagulation, a vena caval filter can be placed under radiographic control.

Thus far there have been no randomized controlled trials addressing the issue of DVT prophylaxis in patients undergoing laparoscopic and robotic surgery. **The American Urological Association has released a "Best Practice Policy Statement" for the prevention of DVT in patients undergoing urologic surgery. Noting the lack of data available directly pertaining to laparoscopic and robotic surgery, the panel recommended the use of pneumatic compression stockings placed before the procedure for all patients. Additionally, they acknowledged that certain high-risk groups may require the use of low-dose unfractionated heparin or low molecular weight heparin before, during, or after surgery.**

Pneumatic compression stockings should be placed preoperatively and continued for 48 to 72 hours postoperatively. Additionally, in morbidly obese patients or in individuals at high risk for thrombosis, the addition of unfractionated perioperative heparin (5000 units 2 hours preoperatively and then every 12 hours postoperatively) has also been recommended (Clagett et al, 1995; Capan and Miller, 1999). However, **with specific respect to upper retroperitoneal (renal/adrenal/ureter) laparoscopic procedures, at least one recent study by** Montgomery and Wolf (2005) **indicated that sequential pneumatic compressive stockings provide equivalent DVT prophylaxis compared with subcutaneous fractionated heparin and that the use of subcutaneous heparin may increase the incidence of hemorrhagic complications.** Three-hundred and forty-four patients (172 in each group) nonrandomly received heparin or sequential pneumatic compressive stockings as DVT prophylaxis beginning on the day of surgery. In both groups the rate of thrombotic complication was 1.2%. The rate of hemorrhagic complication was 9.3% in the heparinized group, of which 7.0% were considered major. The hemorrhagic complication rate was only 3.5% in the sequential pneumatic compressive stockings group, with 2.9% considered major (P = .045). **Thus, after urologic laparoscopy of the upper retroperitoneum, subcutaneous heparin may be associated with increased hemorrhagic complications, without a reduction in thrombotic complications, compared with sequential pneumatic compressive stockings;** however, it must be stressed that this was a nonrandomized study obtained from a prospective database augmented by retrospective chart review. Another retrospective multi-institutional review of DVT and PE comprised 5951 patients undergoing laparoscopic or robotic radical prostatectomy; 31 (0.5%) developed symptomatic thrombotic complications (22 DVT, 4 PE, and 5 with both). Two patients died of PE (Secin et al, 2008). These results are similar to the rates of thromboembolic complication

with open radical retropubic prostatectomy (Lepor and Kaci, 2003).

Wound Infections. Superficial wound infections may occur at any of the port entry sites. This problem usually presents as local tenderness, redness, and swelling; rarely, it is accompanied by a low-grade fever. Incision and drainage of the port site are both diagnostic and therapeutic; antibiotic therapy is routinely administered.

Prevention of this complication is similar to that done in open surgery and includes attention to antiseptic preparation and sterile draping of the abdominal wall, irrigation of each port site at the end of the procedure, and meticulous closure of the wound. Overall, this is a rare complication with standard laparoscopy. However, with the hand-assist approach a higher incidence of wound infections has been noted. In one report the postoperative wound infection rate at the hand-assist site was 9% (Nelson and Wolf, 2002).

Rhabdomyolysis. Rhabdomyolysis is a devastating complication after laparoscopic surgery. The exact incidence of this problem is not known, but in one survey of neuromuscular injuries associated with laparoscopic urologic surgery completed by 18 urologists from 15 institutions in the United States it was found that of a total of 1651 procedures there were 6 cases (0.4%) of clinical rhabdomyolysis (Wolf et al, 2000). In a more recent study, it was estimated that the occurrence of this problem among patients undergoing retroperitoneal laparoscopic procedures (e.g., renal, ureteral, adrenal) was higher, 1% (Reisiger et al, 2005). Rhabdomyolysis is invariably associated with male patients undergoing longer laparoscopic renal procedures, especially if the kidney rest has been employed for the entire case. Although extra padding applied to pressure areas can be useful in avoiding nerve compression and rhabdomyolysis, gel pads and foam "egg crate" padding have not been conclusively demonstrated to significantly reduce pressure on the patient's flank in the lateral position (Deane et al, 2008). Women have significantly lower interface pressures than men. A BMI of 25 or greater, use of a kidney rest, and full-table flexion as opposed to half-table flexion were all associated with increases in interface pressures; of these, use of the kidney rest was believed to be the most detrimental and its use beyond 20 to 30 minutes was disparaged. Therefore, male patients with a BMI of 25 or greater undergoing laparoscopic surgery in the lateral position with the kidney rest elevated and the table completely flexed are at highest risk of developing rhabdomyolysis due to flank pressure. In this study the unaugmented operating table mattress was superior to egg crate or gel padding as an augmenting surface material; of note, egg crate padding was equal or superior to the more expensive gel padding.

Rhabdomyolysis presents immediately in the postanesthesia recovery room with the patient complaining of severe pain in the downside hip area. Brown urine may also be noted. The serum creatine kinase value invariably exceeds 5000 units/dL. The treatment is hydration and alkalinization; these maneuvers are undertaken to try to prevent subsequent renal failure. Acute renal failure and the need for transient dialysis occurs in a minority of patients. The more difficult and ominous problem is that of long-term disability caused by muscle necrosis. Extended physical therapy is often required.

Prevention of this problem is essential. This can, to some extent, be done by avoiding use of the kidney rest or employing it for only the earliest part of the case (i.e., less than an hour) and avoiding prolonged periods of hypotension during the procedure (Cadeddu et al, 2001; Kuang et al, 2002; Parsons et al, 2004; Reisiger et al, 2005). Lastly, with increasing skill and experience, few procedures should proceed beyond 5 hours.

Late Postoperative Complications

Complications beyond the 3-week postoperative period are rare. These include primarily lymphatic complications and incisional hernia. The latter has been addressed in the prior discussion because it can also appear as an early postoperative complication.

Lymphocele Formation. Lymphocele formation is most commonly associated with pelvic procedures, such as pelvic lymph node dissection (1.3% incidence) (Kavoussi et al, 1993) or with renal transplantation. The lymphocele may take weeks to develop and may occur despite a transperitoneal approach. Presentation may be by a mass effect, but the astute clinician should realize that it may also present due to local compression causing lower extremity edema, and in rare cases, venous thrombosis and pulmonary embolism. The lymphocele is diagnosed readily by CT. **Treatment is immediate percutaneous drainage. Sclerosant therapy can be used to treat the lymphocele; however, if unsuccessful or if the lymphocele is not amenable to percutaneous drainage, then a transperitoneal laparoscopic marsupialization procedure is usually successful.** At the time of the procedure, a tag of omentum can be placed into the opening made in the lymphocele to try to prevent closure of the opening and recurrence.

Prevention of lymphocele formation requires marked attention to clipping suspected lymphatic structures. Monopolar electrocoagulation does not work well to seal lymphatics. Bipolar or harmonic devices have been shown to effectively seal lymphatic channels; the bipolar devices created seals that were 5- to 10-fold stronger than the harmonic device (Box et al, 2009).

Chylous Ascites. After left-sided retroperitoneal surgery (i.e., left radical nephrectomy, donor nephrectomy, left-sided retroperitoneal lymph node dissection), the patient may return complaining of a distended abdomen. Although this complaint is common in the initial few days after a laparoscopic procedure, owing to the pneumoperitoneum, irrigation fluid, and/or ileus, it is distinctly rare late in the patient's course. There is no associated fever, pain, or bowel dysfunction, and routine laboratory studies are within normal limits. If the suspicion is high for chylous ascites, one may simply prescribe a low fat, medium-chain triglyceride diet and choose to observe the patient. Usually the condition is self-limited and resolves without any intervention.

If the presentation is not straightforward, then abdominal CT will reveal the underlying problem and diagnose the presence of ascites. If tapped, the fluid, which is commonly turbid, should be sent for culture, complete blood cell count, and determination of triglyceride, cholesterol, and electrolyte levels. The chylous ascitic fluid may well have elevations in the level of lymphocytes, cholesterol, and triglycerides, the latter two being particularly more likely if following a fatty meal.

Treatment is usually dietary, as previously noted. One may also consider giving somatostatin (Leibovitch et al, 2002). In the rare situation in which the fluid does not resolve with these conservative measures or if the patient is symptomatic, the fluid can be tapped once or twice. If it continues to accumulate, then an open or laparoscopic exploration is undertaken; before the procedure, the patient should be given a "fatty" meal or an intravenous load of hyperalimental lipids, which should create a whitish discoloration of the lymphatic fluid and make the point of lymphatic

leakage more visible. Once identified, the leaking lymphatic channel is dissected and secured with either suture or clips (Molina et al, 2003).

Prevention of this type of problem is extremely difficult because the lymphatics are not readily visible during the procedure. In addition, with the recent advent of avoiding clips around the renal hilum, the problem may become more prevalent. To date, instances of post-laparoscopic chylous ascites have been cited only sparingly in the literature (Leibovitch et al, 2002; Molina et al, 2003). However, the authors believe that because the condition is usually self-limited and responds well to dietary measures, it is likely underreported.

LIMITATIONS AND ADVANTAGES OF TRANSPERITONEAL VERSUS EXTRAPERITONEAL APPROACH TO THE FLANK AND PELVIS

Laparoscopy versus Retroperitoneoscopy

Limitations. Retroperitoneoscopy is associated with unique anatomic orientation and a relatively restricted initial working area compared with transperitoneal laparoscopy. This results in a steeper learning curve with the former technique. Moreover, the fact that a comparatively limited space is available necessitates precise accuracy regarding the strategic placement of ports. The degree of technical difficulty increases in the presence of large-sized specimens. Additionally, retroperitoneoscopic entrapment of these larger specimens may be difficult. The latter problem can be overcome by laparoscopically creating an intentional peritoneotomy at the end of the procedure to allow entrapment of the specimen within the larger peritoneal cavity. Laparoscopic reconstruction and intracorporeal suturing are technically demanding procedures; in the retroperitoneal space, reconstruction can be more challenging compared with transperitoneal laparoscopy due to suboptimal instrument angulation and a smaller working space. One potential way to overcome some of these limitations is to use a robotic approach to the retroperitoneum. Kaouk and coworkers (2008c) reported the Cleveland Clinic experience using a robotic retroperitoneal approach to perform dismembered pyeloplasty in 10 patients. They noted that the enhanced dexterity of the robotic platform did facilitate reconstructive suturing in a smaller working space. Although a retroperitoneal approach might not be advantageous for every surgery there are certain instances in which this approach might be more appropriate (as in the case of multiple prior transabdominal surgeries).

If a patient has a history of prior open retroperitoneal surgery, subsequent attempts at retroperitoneoscopy should be approached with extreme caution. However, as mentioned earlier in this chapter, prior percutaneous renal procedures do not necessarily constitute a contraindication to subsequent retroperitoneoscopy. Lastly, of interest is an increase in pulmonary complications after retroperitoneoscopy versus transperitoneal laparoscopy (see later).

Advantages. With retroperitoneoscopy, morbidity that is usually associated with the transperitoneal approach is commonly avoided (Kavoussi et al, 1993). The risks of inadvertent bowel injury and postoperative ileus are minimized, although not eliminated. This results in a slightly more rapid postoperative recovery. During retroperitoneoscopy and extraperitoneoscopy the bowel can be effectively and safely retracted within its peritoneal cover. Although out of sight, the bowel should never be out of mind, because bowel injuries can still occur. Transperitoneal laparoscopy may be associated with an increased incidence of postoperative shoulder-tip pain, a feature rarely associated with retroperitoneoscopy. In addition, extraperitoneoscopy and retroperitoneoscopy are associated with a significantly lower incidence of postoperative trocar site hernias.

A significant benefit of this technique is rapid and direct access to the renal hilum, with the renal artery being the first hilar structure encountered and controlled. Furthermore, if a partial nephrectomy is planned, it may be more effective to approach a posterior tumor from the retroperitoneal approach whereas anterior tumors are often more easily approached from the transperitoneal approach.

Transperitoneal versus Extraperitoneal Pelvic Surgery

The transperitoneal approach to the pelvis offers easy access to all areas of the pelvic cavity after which the space of Retzius, iliac/obturator fossa, or the rectovesical space is entered directly through the peritoneum. The working space is maximized because the peritoneum does not limit camera or instrument motion once it is incised. The potential limitations associated with this approach, however, are that it is possible to cause mechanical or thermal injury to the bowel and it may be necessary to utilize more extreme Trendelenburg positioning or additional retraction of the bowel to prevent it from impinging on the operative field. The possibility of prolonged ileus has also been suggested; however, in a large prospective study comparing 165 transperitoneal versus 165 extraperitoneal laparoscopic radical prostatectomy patients, Ruiz and colleagues (2004) did not find significant differences between the two groups in terms of hospital stay or medical and surgical complications. Operative time was half an hour shorter in the extraperitoneal group (220.0 vs. 248.5 minutes, $P < .0001$); however, there was also a trend toward higher positive margins in patients with pT2 (organ confined) cancers in the extraperitoneal group (17.0% vs. 13.0%; $P = .42$). In two other studies comparing the two approaches, patients undergoing radical prostatectomy were matched with regard to important preoperative attributes and the authors found no significant differences between the extraperitoneal and transperitoneal approaches regarding all important parameters except that the operative time for the extraperitoneal approach is generally a little shorter (30 minutes) (Erdogru et al, 2004; Madi et al, 2007). Interestingly, in one study comparing the two approaches with 50 patients in each arm, in addition to there being no difference between the groups with regard to intraoperative and postoperative parameters, free intraperitoneal air was found on all extraperitoneal patients on the kidney-ureter-bladder radiograph taken on postoperative day 1 (Bivalacqua et al, 2008). Thus this finding should not necessarily be interpreted as an ominous sign of bowel injury unless the patient has other signs and symptoms present (i.e., fever, pain, nausea, elevated white blood cell count). One undeniable advantage in favor of the extraperitoneal approach is that it avoids the necessity of lysis of adhesions in patients who have had prior abdominal surgery. In contrast, for patients who have had prior laparoscopic inguinal hernia repair, a transperitoneal approach is more advantageous.

In summary, for most cases there does not seem to be a clear advantage to using a transperitoneal versus extraperitoneal

approach for laparoscopic pelvic surgery. In selected cases described earlier there may be advantages of one approach over the other. The usual determinant for the laparoscopic approach is that of surgeon preference.

TRAINING AND PRACTICING LAPAROSCOPIC AND ROBOTIC SURGERY

Surgeons learning how to perform laparoscopic procedures face several hurdles, including an altered 2D view of a 3D space, counterintuitive control of instruments, different ergonomic constraints, and an altered perspective of surgical anatomy (Piechaud and Pansadoro, 2006). Robotic surgical systems such as the da Vinci Robotic System overcome several of these issues by providing 3D vision and intuitive instrument motion but they, too, have hurdles, such as complete lack of tactile feedback and a learning curve regarding the syncopation of the surgeon's console. Additionally, much like life in general, the only thing constant about laparoscopic and robotic surgery is change. It is therefore necessary for minimally invasive surgeons, no matter how experienced, to master new skills and familiarize themselves with new technologies as they develop. With an ever-increasing emphasis on patient safety and operating room efficiency it is widely accepted that new surgical skills and techniques should be developed and honed outside the operating room and then transferred into the operating room once proficiency has been developed.

Equipment for Practicing Laparoscopic and Robotic Surgery

A wide variety of practice models exist for both laparoscopic and robotic surgery ranging from inanimate laparoscopic training boxes to live animal and human cadaveric models. There has also been heightened interest in the development of computer-driven virtual reality trainers that can be used to practice standard techniques and whole procedures. As a general premise, nonliving models should be used unless it is absolutely essential to have a live model.

Standard Laparoscopic Training Boxes. The items necessary for a basic laparoscopic training box are a box with an opaque top that is suitable for placement of laparoscopic ports and a vision system consisting of a video monitor, a source of light, and a camera or camera/lens combination. Several commercially available training boxes are available that contain all of the necessary components (Fig. 9–31 on the Expert Consult website). Alternatively, one can construct a training box from relatively inexpensive materials such as a cardboard box and a web camera with a computer screen or video camera. Although it adds a hint of reality, trocars are not mandatory. In general the instruments and camera should be configured in a triangular fashion such that the camera lies between the right- and left-hand instruments. For optimal ergonomic positioning the angle formed between the right- and left-hand instruments should be between 25 and 45 degrees. Additionally, the angle between the instruments and the horizontal plane should be less than 55 degrees (Frede et al, 1999). Some more formal training boxes will have built-in camera holders such that one person can practice alone without the assistance of a "camera driver." When possible, however, a camera driver can adjust the lens/camera in, out, up, and down to match the motions of the surgeon. This is most helpful during more delicate maneuvers such as suturing in which panning the view from wide to closeup is essential. This gives the assistant the opportunity to practice "driving camera," which is also an essential skill for laparoscopy.

Instruments. Necessary instruments might include laparoscopic graspers, scissors, and dissectors, essentially any instrument necessary to meet the requirements of the training drill. Practice for basic suturing requires a pair of laparoscopic needle drivers and some suture. A 3-0 suture on an SH needle is best for general practice. Other suture and needle types can be used for practicing more specialized procedures.

Inanimate Training Models. Training models for basic tasks such as touching areas of the box at different depths and heights within space, passing objects between instruments and through and around obstacles, and other helpful maneuvers such as cutting and tissue manipulation can be constructed from common materials such as paper, sponges, rubber gloves, rubber tubing, and other commonly found, abundant materials (Fig. 9–32 on the Expert Consult website). Alternatively, a wide variety of commercially available models exist that are more realistic looking and may mimic actual operative scenarios more closely (Fig. 9–33 on the Expert Consult website). Whether simple or complex, training models can be placed within standard training boxes and act as the basis for general skills acquisition and progression.

Nonliving Animal Tissue Models. The advantage of using real but nonliving animal tissue to create training models is that it creates a more realistic environment providing true to life tissue handling. Generally the tissues used are inexpensive and can be purchased at a butcher shop or market. The disadvantage is that it requires more intense cleanup after practice. Generally the field inside the training box is set up to mimic a specific surgical scenario and develop specific skills. For instance, the stomach and esophagus of a chicken can be divided and then sewn back together laparoscopically to practice the fashioning of a vesicourethral anastomosis or pyeloplasty (Laguna et al, 2006; Ramachandran et al, 2008).

Live Animal Models. The obvious advantage of live animal models is the opportunity to train under more realistic conditions, including more accurate anatomic relationships of tissue and the necessity for hemostasis that does not exist with inanimate models. The disadvantages of using live animal models is that it requires extensive resources such as a veterinary facility, personnel for care of and providing anesthesia for the animals, and, eventually, euthanasia of the animals. For these reasons, practicing surgical skills on live animals is not appropriate for daily practice. Instead, these opportunities are usually reserved for formal training courses or when the need for a realistic environment warrants the necessary resources. In general the species of animal used for practice must have a sufficient peritoneal compartment to provide an adequate working space. For fine procedures, animals as small as rabbits can be used. Swine are the most common animals used for laparoscopic and robotic training because they are readily available, they have the appropriate size peritoneal compartment, and their anatomy mimics relatively well that of humans. It must be noted, however, that the amount of bleeding that comes from a pig kidney (in partial nephrectomy, for example) is not realistic compared with that of a human. Additionally, the porcine bladder is almost completely intraperitoneal.

Cadaveric Models. One of the first experiences most medical students have in training is anatomy, and this entails cadaveric dissection. The reason is simple. Short of operating on real patients there is no better or more realistic way to learn human anatomy. This holds true for surgical practice as well: however, owing to the

major resources necessary to have an anatomic gift program and the significantly high cost for a cadaver compared with alternative models, it is often not practical to use cadavers. If, however, facilities and funding are available and there is a need for practicing a procedure in the most realistic environment, there is no substitute for cadaveric models.

Virtual Reality Trainers. Virtual reality (VR) trainers are computer-based simulators that offer the opportunity to practice laparoscopic and robotic skills through specific tasks as well as whole procedures. Typically, trainees view the computer-generated operative field or training drill on a computer monitor and perform tasks using laparoscopic manipulators. The instruments are depicted on the viewer and correspond with the trainee's movements. A major advantage of VR trainers is that they can collect information regarding trainee performance and track progress over time in terms of precision, economy of motion, and other parameters of interest. Because the trainers are computer based it is possible to develop training programs and curricula including didactics, videos, and live practice sessions. The trainee can progress through the curriculum based on performance. VR trainers have been shown to improve the skills of trainees helping to prepare them for better performance during live surgery (Seymour et al, 2002; Lucas et al, 2008). Several commercially produced VR trainers for laparoscopy are available but are quite costly owing to the advanced technology and software development necessary. An experimental VR trainer for robotic surgery is also under development (Albani and Lee, 2007).

Formal Training Programs. Surgical competence is defined by technical and nontechnical skills (Hoznek et al, 2006). Traditionally these skills have been passed down from teacher to apprentice in the process of caring for and operating on real patients during residency training. The technical skills were taught during real operative procedures and the nontechnical skills such as surgical judgment, problem anticipation and avoidance, economy of motion, and so on were gained by experience of the trainee with supervision from a more senior instructor. In this way, traditional residency programs have been more "learning" programs than "teaching" programs. With ever-increasing emphasis being placed on patient safety, operating room efficiency, and cost containment there has been a great interest in evaluating the efficacy of formal training programs in laparoscopic and robotic surgery. Such programs offer the opportunity to receive formal instruction in a safe, stress-free environment with the intention of honing both technical and nontechnical skills.

With this concept in mind one method of concentrated instruction and skills acquisition is the "mini-residency" or "mini-fellowship." In this training model surgeons spend a period of several days (typically 5 days) receiving concentrated instruction on a given set of surgical skills or procedures including didactic sessions, clinical case observation, and laboratory training using both inanimate and animate models. Typically, the attendees also gain access to expert proctors during their initial learning curve for the new procedure. Mini-residency training has been shown to be effective in helping postgraduate urologists incorporate new laparoscopic and robotic procedures into their clinical practices. In one study of laparoscopic renal surgery mini-fellowship trainees at the University of California, Irvine, 73% of attendees were performing laparoscopic renal surgery 3 years later (Kolla et al, 2010). This was also found with robotic surgical training: of 47 urologists who took a 5-day training course for robotic radical prostatectomy, 90% were performing the procedure in their own practice at 3-year follow-up (Gamboa et al, 2009).

Key Points

- Careful patient selection and identification of possible relative and absolute contraindications are vital to a successful outcome of laparoscopic and robotic procedures. To this end, a meticulous past history, focusing on prior surgeries, and physical examination, detailing the location and extent of all abdominal scars, are the initial steps in patient evaluation for possible minimally invasive surgery.
- Now that the benefits of surgical pharmaceuticals have come into the spotlight, it is important for the surgeon to be familiar with the properties of these various agents and thereby able to choose one that is most appropriate for the job at hand.
- After a routine major laparoscopic or robotic procedure emphasis can be placed on "fast tracking" the patient. Fast tracking actually starts preoperatively during which time the patient is pre-medicated with an antiemetic agent, a nonnarcotic pain reliever such as ketorolac (if not a renal failure patient), and an antacid. All incision sites are infiltrated with 1% lidocaine before making the incision to minimize postoperative pain. To avoid postoperative ileus and constipation, patients without renal insufficiency can be administered ketorolac every 6 hours for a total of four doses to avoid narcotic analgesic use. Routine use of a nonsedating antiemetic agent for the first 24 hours is also advisable.
- Intra-abdominal pressures during laparoscopy should not be allowed to exceed 20 mm Hg over extended periods, and a working pressure of 10 to 12 mm Hg is recommended.
- Early in one's experience with laparoscopic and robotic surgery it is wise to apply the minimally invasive approach to low-risk surgical candidates of normal body habitus. In addition, it is advisable and recommended by many laparoscopic organizations, as well as by hospital credentialing boards, that the neophyte minimally invasive surgeon seek training in three arenas: (1) in-depth instructional courses, including didactic, "live-case" transmissions and "hands-on" laboratory sessions; (2) preceptor training in which the surgeon-in-training views more than five or more procedures being done by an already skillful laparoscopic surgeon; and (3) a mentoring experience, during which a trained laparoscopic surgeon oversees the initial procedures performed by the surgeon-in-training.

CONCLUSION

Yesterday's humor is today's reality. Cartoons in the 1990s often depicted several surgeons standing around an operating table with a patient in whom numerous laparoscopic ports had been placed. The caption was "Can anyone open?" While this concern has been a rallying cry for the maximally invasive surgeon, the less invasive surgeon sees this as a manifestation of the progress that has occurred in the past 15 years. Laparoscopic procedures unthinkable in early 1990 are now routine. The indications for performing these procedures through a single site are expanding. The use of a robotic surgical platform to perform complex reconstructive procedures is improving the precision and often the outcomes of these operations and makes it possible for a greater number of urologists to perform high-quality laparoscopic procedures. As

robotics and flexible endoscopically guided technologies advance in the future we may see adoption of NOTES and our patients may undergo operations that leave no visible scar. The benefit will be more proficient laparoscopic and robotic surgeons who can handle any procedure and any complication without the massive incisions of yore. It is hoped that in the near future a similar cartoon may show a group of urologists in an image-guidance suite or in an office gathered around a patient with the caption: "Can anyone do laparoscopy?" Such should be the next step of our surgical and pharmacologic paths of discovery. At that point Osler's 20th century admonition, "Diseases that harm require treatments that harm less," will be truly fulfilled. We are as yet still on the bridge to the future.

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The complete reference list is available online at www.expertconsult.com.

chapter 10

Infections of the Urinary Tract

Anthony J. Schaeffer, MD ● Edward M. Schaeffer, MD, PhD

Definitions
Incidence and Epidemiology
Pathogenesis
Clinical Manifestations
Imaging Techniques
Principles of Antimicrobial Therapy
Antimicrobial Prophylaxis for Common Urologic Procedures
Bladder Infections
Kidney Infections
Bacteremia, Sepsis, and Septic Shock
Bacteriuria in Pregnancy
Bacteriuria in the Elderly
Catheter-Associated Bacteriuria
Management of UTI in Patients with Spinal Cord Injury
Other Infections

Urinary tract infections (UTIs) are common, affect men and women of all ages, and vary dramatically in their presentation and sequelae. They are a common cause of morbidity and can lead to significant mortality. Although the urinary tract is normally free of bacterial growth, bacteria that generally ascend from the rectal reservoir may cause UTIs. When bacterial virulence increases or host defense mechanisms decrease, bacterial inoculation, colonization, and infection of the urinary tract occur. Careful diagnosis and treatment result in successful resolution of infections in most instances. A better understanding of the pathogenesis of UTIs and the role of host and bacterial factors has improved the ability to identify patients at risk and prevent or minimize sequelae. Clinical manifestations can vary from asymptomatic bacterial colonization of the bladder to irritative symptoms such as frequency and urgency associated with bacterial infection; upper tract infections associated with fever, chills, and flank pain; and bacteremia associated with severe morbidity, including sepsis and death. New antimicrobial agents that achieve high urinary and tissue levels, that can be administered orally, and that are not nephrotoxic have significantly reduced the need for hospitalization for severe infection. Shorter-course therapy and prophylactic antimicrobial agents have reduced the morbidity and cost associated with recurrent cystitis in women. Although the vast majority of patients respond promptly and are cured by therapy, early identification and treatment of patients with complicated infections that place them at significant risk remains a clinical challenge to urologists.

DEFINITIONS

UTI is an inflammatory response of the urothelium to bacterial invasion that is usually associated with bacteriuria and pyuria.

***Bacteriuria* is the presence of bacteria in the urine, which is normally free of bacteria.** It has been assumed to be a valid indicator of either bacterial colonization or infection of the urinary tract. Although this is usually true, studies in animals (Hultgren et al, 1985; Mulvey et al, 1998) and humans (Elliott et al, 1985) have indicated that bacteria may be in the urothelium in the absence of bacteriuria. Alternatively, bacteriuria may represent bacterial contamination of an abacteriuric specimen during collection.

The possibility of contamination increases as the reliability of the collection technique decreases from suprapubic aspiration to catheterization to voided specimens. The term *significant bacteriuria* has a clinical connotation and is used to describe the number of bacteria in a suprapubically aspirated, catheterized, or voided specimen that exceeds the number usually caused by bacterial contamination of the skin, the urethra, or the prepuce or introitus, respectively. Hence it represents a UTI.

Bacteriuria can be *symptomatic* or *asymptomatic*. When it is detected by population studies (screening surveys), *screening bacteriuria* is a more precise and descriptive term than *asymptomatic bacteriuria,* especially because the latter term is clinically useful for describing the presence or absence of symptoms in an individual patient.

***Pyuria,* the presence of white blood cells (WBCs) in the urine, is generally indicative of infection and an inflammatory response of the urothelium to the bacterium.** Bacteriuria without pyuria is generally indicative of bacterial colonization without infection of the urinary tract. Pyuria without bacteriuria warrants evaluation for tuberculosis, stones, or cancer.

Infections are often defined clinically by their presumed site of origin.

Cystitis describes a clinical syndrome of dysuria, frequency, urgency, and occasionally suprapubic pain. These symptoms, although generally indicative of bacterial cystitis, may also be associated with infection of the urethra or vagina or noninfectious conditions such as interstitial cystitis, bladder carcinoma, or



Figure 10–1. Excretory urogram demonstrates focal, coarse scarring in the right kidney of an 18-year-old girl with a history of many recurrent fevers between 2 months and 2 years of age. A cystogram when the patient was 2 years old established an atrophic left kidney with marked reflux up to the left kidney and slight reflux up to the right kidney. Excretory urography at the age of 6 years established severe atrophy of the left kidney. She had no infections between the ages of 6 and 15 years. Several reinfections occurred at the age of 15 years, and they ceased with prophylactic therapy. Her blood pressure has remained normal, and her serum creatinine level was 0.9 mg/dL at the age of 18 years. At 21 years of age she stopped antimicrobial prophylaxis for 18 months without infections or introital colonization with Enterobacteriaceae. Note that all calyces are blunted and that one extends to the capsule *(arrowhead)* because of atrophy of the overlying cortex.

calculi. Conversely, patients may be asymptomatic and have infection of the bladder and possibly the upper urinary tract.

***Acute pyelonephritis* is a clinical syndrome of chills, fever, and flank pain that is accompanied by bacteriuria and pyuria, a combination that is reasonably specific for an acute bacterial infection of the kidney.** The term should not be used if flank pain is absent. It may have no morphologic or functional components detectable by routine clinical modalities. There may be serious difficulties in diagnosing spinal cord–injured and elderly patients who may be unable to localize the site of their discomfort.

Chronic pyelonephritis describes a shrunken, scarred kidney, diagnosed by morphologic, radiologic, or functional evidence of renal disease that may be postinfectious but is frequently not associated with UTI. Bacterial infection of the kidney may cause a *focal, coarse scar* in the renal cortex overlying a calyx, almost always accompanied by some calyceal distortion (Fig. 10–1), which can be detected radiographically or by gross examination of the kidney. Less commonly, renal scarring from infection can result in atrophic pyelonephritis or generalized thinning of the renal cortex, with a small kidney appearing radiographically similar to one with postobstructive atrophy (Fig. 10–2).

Table 10–1.

Factors That Suggest Complicated UTI

Functional or anatomic abnormality of urinary tract
Male gender
Pregnancy
Elderly patient
Diabetes
Immunosuppression
Childhood UTI
Recent antimicrobial agent use
Indwelling urinary catheter
Urinary tract instrumentation
Hospital-acquired infection
Symptoms for more than 7 days at presentation

Reprinted from Schaeffer AJ. Urinary tract infections. In: Gillenwater JY et al, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 212.

UTIs may also be described in terms of the anatomic or functional status of the urinary tract and the health of the host.

***Uncomplicated* describes an infection in a healthy patient with a structurally and functionally normal urinary tract.** The majority of these patients are women with isolated or recurrent bacterial cystitis or acute pyelonephritis, and the infecting pathogens are usually susceptible to and eradicated by a short course of inexpensive oral antimicrobial therapy.

***A complicated* infection is associated with factors that increase the chance of acquiring bacteria and decrease the efficacy of therapy** (Table 10–1). **The urinary tract is structurally or functionally abnormal, the host is compromised, and/or the bacteria have increased virulence or antimicrobial resistance. The majority of these patients are men.**

Renal diseases that reduce the concentrating ability of the kidney or neurologic conditions that alter bladder-emptying capabilities are commonly encountered functional abnormalities.

Examples of anatomic abnormalities include obstruction associated with calculi or enlargement of the prostate or congenital or acquired sites of residual urine, such as calyceal or bladder diverticula. A complicated infection is frequently caused by bacteria that have exposure to many antimicrobial agents.

Chronic is a poor term that should be avoided in the context of UTIs, except for chronic pyelonephritis or bacterial prostatitis, because the duration of the infection is not defined.

UTIs may also be defined by their relationship to other UTIs:

A ***first*** or ***isolated*** infection is one that occurs in an individual who has never had a UTI or has one remote from a previous UTI.

An ***unresolved*** infection is one that has not responded to antimicrobial therapy.

A ***recurrent*** infection is one that occurs after documented, successful resolution of an antecedent infection.

The term *reinfection* describes a new event associated with reintroduction of bacteria into the urinary tract from outside.

***Bacterial persistence* refers to a recurrent UTI caused by the same bacteria reemerging from a focus within the urinary tract, such as an infectious stone or the prostate.** *Relapse* is frequently used interchangeably. These definitions require careful clinical and bacteriologic assessment and are important because they influence the type and extent of the patient's evaluation and treatment.

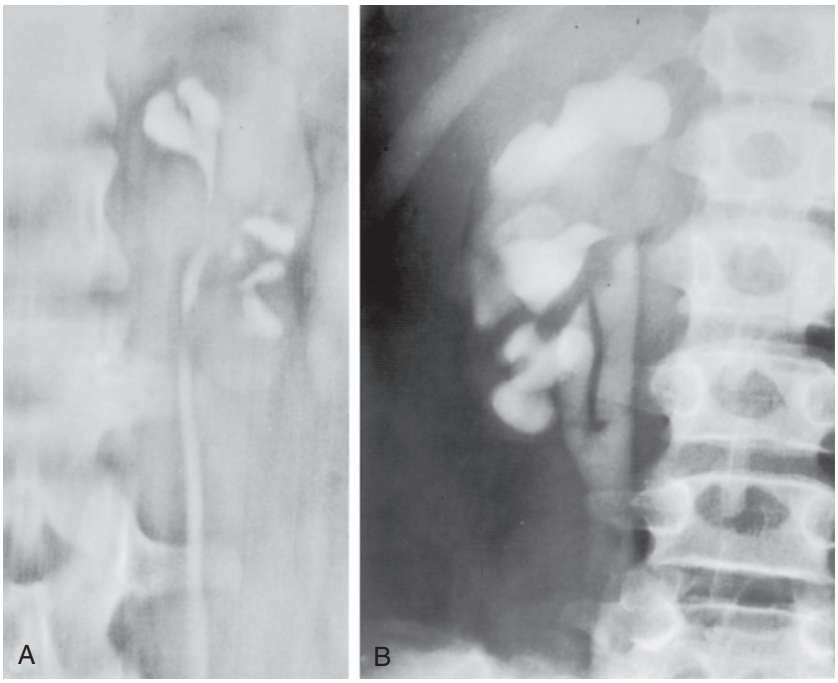


Figure 10–2. **A,** Excretory urogram of the contralateral left kidney from the same patient as in Figure 10–1. The severe pyelonephritic atrophy, undoubtedly caused by febrile urinary infections during early infancy with reflux into different segments of the kidney, produced irregular cortical scarring. Note how all the calyces extend to the capsule with irregular, intervening areas of cortex. **B,** Pyelonephritic atrophy, suggestive of postobstructive atrophy, in a 20-year-old woman with spina bifida, neurogenic bladder, and many episodes of fever and bacteriuria in early childhood. Observe the uniform, regular atrophy of the renal cortex that suggests reflux of bacteria simultaneously into virtually all nephrons. This type of pyelonephritic atrophy is uncommon compared with that shown in **A** and is characteristic of obstruction with superimposed infection.

***Antimicrobial prophylaxis* is the prevention of reinfections of the urinary tract by the administration of antimicrobial drugs.** If the term is used correctly in reference to the urinary tract it can be assumed that bacteria have been eliminated before prophylaxis is begun. **Surgical antimicrobial prophylaxis entails administration of an antimicrobial agent before and for a *limited* time after a procedure to prevent local or systemic postprocedural infections.**

***Antimicrobial suppression* is the prevention of growth of a focus of bacterial persistence that cannot be eradicated.** A low, nightly dosage of an antimicrobial agent usually results in the urine showing no growth, as in the case of a small infectious stone or in bacterial prostatitis caused by *Escherichia coli*. *Suppressive* is also a useful term when recurrent acute symptoms are prevented in a poor-risk patient, such as one with a large staghorn calculus in whom the antimicrobial agent reduces but does not eliminate the bacteria in the urine.

Domiciliary* or *outpatient UTIs occur in patients who are not hospitalized or institutionalized at the time they become infected. **The infections are generally caused by common bowel bacteria** (e.g., Enterobacteriaceae or *Enterococcus faecalis*), which are susceptible to most antimicrobial agents.

***Nosocomial* or *health care–associated UTIs* occur in patients who are hospitalized or institutionalized,** and these are typically caused by *Pseudomonas* and other more antimicrobial-resistant strains.

Key Points: Definitions

- Infection of the urinary tract occurs when bacterial virulence increases and/or host defense mechanisms decrease.
- The majority of patients respond promptly to short courses of antimicrobial therapy.
- Early identification and treatment of complicated UTIs is essential to prevent major sequelae or death.

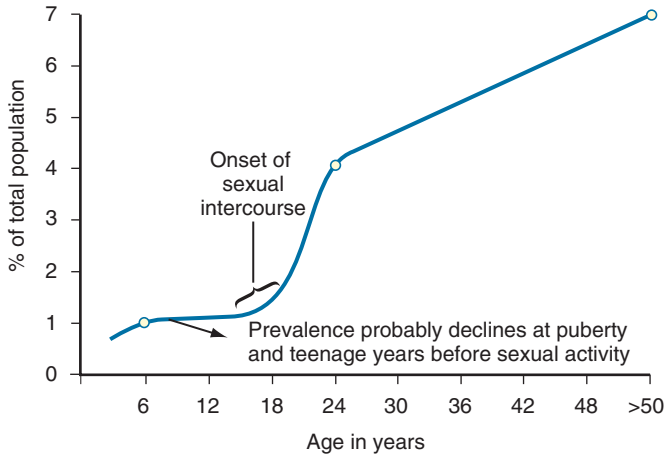


Figure 10–3. Prevalence of bacteriuria in females as a function of age. (From Stamey TA. The prevention of recurrent urinary infections. New York: Science and Medicine; 1973.)

INCIDENCE AND EPIDEMIOLOGY

UTIs are considered to be the most common bacterial infection. They account for more than 7 million visits to physicians' offices and necessitate or complicate over 1 million office visits and 1 million emergency department visits, resulting in 100,000 hospitalizations annually (Patton et al, 1991, Hooton and Stamm, 1997; Foxman et al, 2000). **They account for 1.2% of all office visits by women and 0.6% of all office visits by men** (Schappert, 1997).

The overall prevalence of bacteriuria in women has been estimated at 3.5%, with prevalence generally increasing with age in a linear trend (Evans et al, 1978). Surveys screening for bacteriuria have shown that about 1% of schoolgirls (aged 5 to 14 years) (Kunin et al, 1962) have bacteriuria and that this figure increases to about 4% by young adulthood and then by an additional 1% to 2% per decade of age (Fig. 10–3). **Nearly 30% of women will**

have had a symptomatic UTI requiring antimicrobial therapy by age 24, and almost half of all women will experience a UTI during their lifetime. The prevalence of bacteriuria in young women is 30 times more than in men. However, **with increasing age, the ratio of women to men with bacteriuria progressively decreases. At least 20% of women and 10% of men older than 65 years have bacteriuria** (Boscia and Kaye, 1987; Juthani-Mehta, 2007).

The incidence of bacteriuria also increases with institutionalization or hospitalization and concurrent disease (Sourander, 1966). In a study of women and men older than 68 years, Boscia and Kaye (1987) found that 24% of functionally impaired nursing home residents had bacteriuria compared with 12% of healthy domiciliary subjects (Boscia et al, 1986). UTIs account for approximately 38% of the 2 million nosocomial infections each year (Sedor and Mulholland, 1999; Lo et al, 2008). More than 80% of nosocomial UTIs are secondary to an indwelling urethral catheter (Sedor and Mulholland, 1999). The incidence of UTIs is also increased during pregnancy and in patients with spinal cord injuries, diabetes, multiple sclerosis, and human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS).

The financial impact of community-acquired UTIs is nearly $1.6 billion in the United States alone (Foxman, 2002); the annual cost of nosocomial UTIs has been estimated to range from between $515 million and $548 million (Jarvis, 1996).

Little is known about the natural history of untreated bacteriuria in women because most women are treated when they are diagnosed, but a few studies in which treatment with antimicrobial agents is compared with placebo have been done. These show that 57% to 80% of bacteriuric women who are untreated or treated with placebo clear their infections spontaneously (Mabeck, 1972; Guttmann, 1973). Mabeck (1972) found that 8 of 53 bacteriuric women placed on placebo needed treatment with an antimicrobial agent because of symptoms, but 32 of the remaining 45 women cleared without treatment within a month, and 43 of the 45 had spontaneously cleared of bacteriuria within 5 months; only 2 women remained persistently bacteriuric.

Once a patient has an infection, he or she is likely to develop subsequent infections. Many adults had UTIs as children, underscoring the importance of genotypic factors in UTIs (Gillenwater et al, 1979). Of 45 women with untreated UTIs whose infection cleared, 20 (46%) had recurrences within a year (Mabeck, 1972).

When women with recurrent bacteriuria were observed after treatment, about one sixth (37 of 219) had a very high recurrence rate (2.6 infections per year) whereas the remaining women had a recurrence rate of only 0.32 per year (Mabeck, 1972). Similar separation was seen in a prospective study in which only 28.6% of 60 women who experienced their first symptomatic UTI had recurrent infections over the first 18 months of observation, as opposed to recurrences in 82.5% of 106 women who had had previous UTIs (Harrison et al, 1974). **Other investigators also have found that the probability of recurrent UTIs increases with the number of previous infections and decreases in inverse proportion to the elapsed time between the first and the second infections** (Mabeck, 1972). Of these recurrent infections, 71% to 73% are caused by reinfection with different organisms, rather than recurrence with the same organism (Mabeck, 1972; Guttmann, 1973).

Women with frequent reinfections have a rate of 0.13 to 0.25 UTIs per month (1.6 to 3.1 infections per year) when the infections are treated with antimicrobial agents (Mabeck, 1972; Guttmann, 1973; Kraft and Stamey, 1977; Vosti, 2002).

In a prospective long-term study of 235 women with more than 1000 confirmed infections studied over a period ranging from 1 to nearly 20 years, about half of the patients had clusters of infections, which ranged in frequency from 2 to 12 infections per cluster. Infections were followed by remission-free intervals that averaged approximately 1 year. **Most reinfections occurred after 2 weeks** (Harrison et al, 1974) and within 5 months (Mabeck, 1972), and most occurred early in this interval (Kraft and Stamey, 1977; Vosti, 2002) (Fig. 10–4). Rates of reinfection were independent of bladder dysfunction, radiologic changes of chronic pyelonephritis, and vesicoureteral reflux (Guttmann, 1973). The reinfections did not occur evenly over time. In the Stanford series (Kraft and Stamey, 1977), 23 women with frequent recurrent infections were studied with monthly urine cultures when asymptomatic and with immediate cultures when symptomatic for cystitis, for a mean of 3 years. Thirty-four percent of infections were followed by infection-free intervals of at least 6 months (average, 12.8 months), and 22 of the 23 women had such intervals. However, even these long intervals were followed by further infections (Kraft and Stamey, 1977), thus underscoring the importance of genotypic factors in the pathogenesis of UTIs in women (Schaeffer et al, 1981).

When the Stanford data (Kraft and Stamey, 1977) on recurrent UTIs in highly susceptible females are analyzed by examining sets of infections separated by remissions of at least 6 months, 69% of the sets contain only one infection. After this first set, the remaining sets show a 33% remission rate in infections, which means a patient who has two or more infections within 6 months has only a 33% probability of remaining free of infection for the next 6 months. Therefore, **if antimicrobial prophylaxis is started after the second or any succeeding infection within a set, about two thirds of the women will benefit.**

Whether a patient receives no treatment at all or short-term, long-term, or prophylactic antimicrobial treatment the risk of recurrent bacteriuria remains the same; prophylactic antimicrobial therapy reduces reinfections but does not alter the underlying predisposition to recurring infection. Asscher and associates (1973) found that reinfections occurred in 17 patients (34%) treated with a 7-day course of nitrofurantoin and in 13 patients (29%) receiving

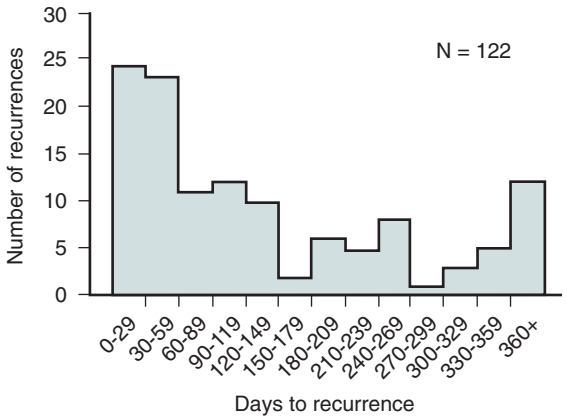


Figure 10–4. Days between recurrent UTIs grouped by 30-day intervals. (From Kraft JK, Stamey TA. The natural history of symptomatic recurrent bacteriuria in women. Medicine 1977;56:55.)

placebo during a 3- to 5-year follow-up. Mabeck (1972) found that 46% (20 of 43) of untreated patients had recurrent infections by 12 months compared with about 40% of treated patients who had recurrences. Both studies suggest that it makes little difference whether a UTI is cured with an antimicrobial agent or is allowed to clear spontaneously—the susceptibility to recurrent UTI remains the same. Moreover, patients with frequent UTI who take prophylactic antimicrobial agents for extended periods (≥6 months) may decrease their infections during the time of prophylaxis but the rate of infection returns to the pretreatment rate after prophylaxis is stopped (Vosti, 1975; Stamm et al, 1980a). Even long interruptions in the pattern of recurrence, therefore, do not appear to alter the patient's basic susceptibility to infections.

The sequelae of complicated UTIs are substantial. It is well established in the presence of obstruction, infection stones, diabetes mellitus, and other risk factors that UTIs in adults can lead to progressive renal damage (Freedman, 1975). **The long-term effects of uncomplicated recurrent UTIs are not completely known, but, so far, no association between recurrent infections and renal scarring, hypertension, or progressive renal azotemia has been established** (Asscher et al, 1973; Freedman, 1975). Indeed, one investigator was unable to find a single case of unequivocal nonobstructive chronic pyelonephritis in 22 patients in whom chronic pyelonephritis was the cause of end-stage renal failure (Schechter et al, 1971). Similar data were reported by Huland and Busch (1982).

In pregnant women the prevalence and rate of recurrent infection are the same but their bacteriuria progresses to acute clinical pyelonephritis more frequently than in nonpregnant women. This variation in the natural history of recurrent infections in females is discussed in a later section on UTIs in pregnancy.

Key Points: Incidence and Epidemiology

- UTIs are the most common bacterial infection.
- They cause significant morbidity but do not cause renal damage unless comorbidities are present.
- Antimicrobial therapy reduces morbidity and the time to recurrent bacteriuria, but the risk of recurrence remains the same.

PATHOGENESIS

UTIs are a result of interactions between the uropathogen and the host. Successful infection of the urinary tract is determined in part by the virulence factors of the bacteria, the inoculum size, and the inadequacy of host defense mechanisms. These factors also play a role in determining the ultimate level of colonization and damage to the urinary tract. Whereas increased bacterial virulence appears to be necessary to overcome strong host resistance, bacteria with minimal virulence factors are able to infect patients who are significantly compromised.

Routes of Infection

Ascending Route

Most bacteria enter the urinary tract from the bowel reservoir via ascent through the urethra into the bladder. Adherence of pathogens to the introital and urothelial mucosa plays a significant role in ascending infections. This route is further enhanced in individuals with significant soilage of the perineum with feces, women who use spermicidal agents (Hooton et al, 1996; Foxman, 2002; Handley et al, 2002), and patients with intermittent or indwelling catheters.

Although cystitis is often restricted to the bladder, approximately 50% of infections can extend into the upper urinary tract (Busch and Huland, 1984). The weight of clinical and experimental evidence strongly suggests that **most episodes of pyelonephritis are caused by retrograde ascent of bacteria from the bladder through the ureter to the renal pelvis and parenchyma. Although reflux of urine is probably not required for ascending infections, edema associated with cystitis may cause sufficient changes in the ureterovesical junction to permit reflux.** Once the bacteria are introduced into the ureter, they may ascend to the kidney unaided. However, this ascent would be greatly increased by any process that interferes with the normal ureteral peristaltic function. Gram-negative bacteria and their endotoxins, as well as pregnancy and ureteral obstruction, have a significant antiperistaltic effect.

Bacteria that reach the renal pelvis can enter the renal parenchyma by means of the collecting ducts at the papillary tips and then ascend upward within the collecting tubules. This process is hastened and exacerbated by increased intrapelvic pressure from ureteral obstruction or vesicoureteral reflux, particularly when it is associated with intrarenal reflux.

Hematogenous Route

Infection of the kidney by the hematogenous route is uncommon in normal individuals. However, the kidney is occasionally secondarily infected in patients with *Staphylococcus aureus* bacteremia originating from oral sites or with *Candida fungemia*. Experimental data indicate that infection is enhanced when the kidney is obstructed (Smellie et al, 1975).

Lymphatic Route

Direct extension of bacteria from the adjacent organs via lymphatics may occur in unusual circumstances, such as a severe bowel infection or retroperitoneal abscesses. There is little evidence that lymphatic routes play a significant role in the vast majority of UTIs.

Urinary Pathogens

Most UTIs are caused by facultative anaerobes usually originating from the bowel flora. Uropathogens such as *Staphylococcus epidermidis* and *Candida albicans* originate from the flora of the vagina or perineal skin.

***E. coli* is by far the most common cause of UTIs, accounting for 85% of community-acquired and 50% of hospital-acquired infections.** Other gram-negative Enterobacteriaceae, including *Proteus* and *Klebsiella,* and gram-positive *E. faecalis* and *Staphylococcus saprophyticus* are responsible for the remainder of most community-acquired infections. Nosocomial infections are caused by *E. coli, Klebsiella, Enterobacter, Citrobacter, Serratia, Pseudomonas aeruginosa, Providencia, E. faecalis,* and *S. epidermidis* (Kennedy et al, 1965). Less common organisms such as *Gardnerella vaginalis, Mycoplasma* species, and *Ureaplasma urealyticum* may infect patients with intermittent or indwelling catheters (Josephson et al, 1988; Fairley and Birch, 1989).

The prevalence of infecting organisms is influenced by the patient's age. For example, *S. saprophyticus* is now recognized as causing approximately 10% of symptomatic lower UTIs in young, sexually active females (Latham et al, 1983) whereas it rarely causes infection in males and elderly individuals. A seasonal variation with a late summer to fall peak has been reported (Hovelius and Mardh, 1984).

Fastidious Organisms

Anaerobes in the Urinary Tract

Although symptomatic anaerobic infections of the urinary tract are documented, they are uncommon. However, the distal urethra, perineum, and vagina are normally colonized by anaerobes. Whereas 1% to 10% of voided urine specimens are positive for anaerobic organisms (Finegold, 1977), anaerobic organisms found in suprapubic aspirates are much more unusual (Gorbach and Bartlett, 1974). Clinically symptomatic UTIs in which only anaerobic organisms are cultured are rare, but these organisms must be suspected when a patient with bladder irritative symptoms has cocci or gram-negative rods seen on microscopic examination of the centrifuged urine (catheterized, suprapubic aspirated, or voided midstream urine) and routine quantitative aerobic cultures fail to grow organisms (Ribot et al, 1981).

Anaerobic organisms are frequently found in suppurative infections of the genitourinary tract. In one study of suppurative genitourinary infections in males, 88% of scrotal, prostatic, and perinephric abscesses included anaerobes among the infecting organisms (Bartlett and Gorbach, 1981). The organisms found are usually *Bacteroides* species, including *B. fragilis*, *Fusobacterium* species, anaerobic cocci, and *Clostridium perfringens* (Finegold, 1977). The growth of clostridia may be associated with cystitis emphysematosa (Bromberg et al, 1982).

Mycobacterium tuberculosis and Other Nontuberculous Mycobacteria

Mycobacterium tuberculosis and other nontuberculous mycobacteria may be found when cultures for acid-fast bacteria are requested; they do not grow under routine aerobic conditions and may be found during evaluation for sterile pyuria. It has been emphasized that the mere presence of mycobacteria may not indicate tissue invasion. Therefore factors such as symptoms, endoscopic or radiologic evidence of infection, abnormal urine sediment, the absence of other pathogens, repeated demonstration of the organism, and the presence of granulomas should be considered before therapy is instituted (Brooker and Aufderheide, 1980; Thomas et al, 1980). (*M. tuberculosis* is discussed in Chapter 16.)

Chlamydia

Chlamydiae are not routinely grown in aerobic culture but have been implicated in genitourinary infections. (Their role in the urinary tract is discussed in Chapter 13.)

Bacterial Virulence Factors

Virulence characteristics play a role in determining both if an organism will invade the urinary tract and the subsequent level of infection within the urinary tract. It is generally believed that uropathogenic strains resident in the bowel flora, such as uropathogenic *E. coli* (UPEC), can infect the urinary tract not only by chance but also by the expression of virulence factors that enable them to adhere to and colonize the perineum and urethra and migrate to the urinary tract where they establish an inflammatory response in the urothelium (Schaeffer et al, 1981; Yamamoto et al, 1997; Schlager et al, 2002; Moreno et al, 2008). The same virulence factors can be found on bacterial strains that cause recurrent UTI in patients (Foxman et al, 1995). Some of these virulence determinants are located on one of approximately 20 UPEC-specific pathogenicity-associated islands ranging from 30 to 170 kb (Hacker, 1999; Oelschlaeger et al, 2002). These pathogenicity islands collectively increase the size of the pathogen genome by about 20% over a commensal strain. A recent genomic analysis of a UPEC strain revealed the presence of genes for putative chaperone-usher systems as well as autotransporter proteins that may function as adhesins, toxins, proteases, invasins, serum resistance factors, or motility mediators (Henderson and Nataro, 2001). One UPEC-specific autotransporter, Sat, seems toxic to urinary tract cells in vitro (Guyer et al, 2000) and can cause cytoplasmic vacuolation and severe histologic damage in mouse kidneys (Guyer et al, 2002). Another toxin, hemolysin HlyA, forms pores in a variety of host cell membranes (Uhlen et al, 2000). In addition to proteases and toxins, UPEC produces several iron acquisition systems, including aerobactin (Johnson et al, 1988; Johnson, 2003) and the more recently described IroN system (Russo et al, 1999; Sorsa et al, 2003). Lastly, most UPEC strains produce an acid polysaccharide capsule that protects the bacteria from phagocytosis by human polymorphonuclear leukocytes and inhibits activation of complement (Johnson, 2003).

Early Events in UPEC Pathogenesis

Bacterial Adherence

Bacterial adherence to vaginal and urothelial epithelial cells is an essential step in the initiation of UTIs. This interaction is influenced by the adhesive characteristics of the bacteria, the receptive characteristics of the epithelial surface, and the fluid bathing both surfaces. Bacterial adherence is a specific interaction that plays a role in determining the organism, the host, and the site of infection. Portions of this section on bacterial adherence have been published (Schaeffer et al, 1981).

Bacterial Adhesins. UPEC expresses a number of adhesins that allow it to attach to urinary tract tissues (Mulvey, 2002). These adhesins are classified as either fimbrial or afimbrial, depending on whether the adhesin is displayed as part of a rigid fimbria or pilus (Fig. 10–5). Bacteria may produce a number of

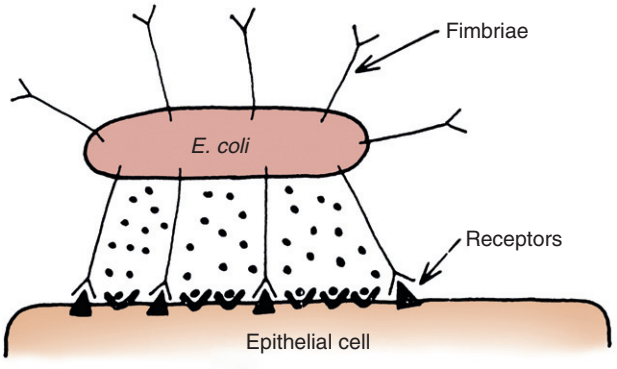


Figure 10–5. Bacterial adherence. Adhesins on pili (fimbriae) mediate attachment to specific epithelial cell receptors.

antigenically and functionally different pili on the same cell; others produce a single type; in some, no pili are seen (Klemm, 1985). A typical piliated cell may contain 100 to 400 pili. The pilus is usually 5 to 10 nm in diameter, is up to 2 μm long, and appears to be composed primarily of subunits known as pilin (Klemm, 1985). Pili are defined functionally by their ability to mediate hemagglutination of specific types of erythrocytes. The most well-described pili are types 1, P, and S.

Type 1 (Mannose Sensitive) Pili. Type 1 pili are commonly expressed on both nonpathogenic and pathogenic *E. coli*. Type 1 pili consist of a helical rod composed of repeating FimA subunits joined to a 3-nm wide distal tip structure containing the adhesin FimH (Jones et al, 1995). These pili mediate hemagglutination of guinea pig erythrocytes (Duguid et al, 1979). The reaction is inhibited by the addition of mannose; thus type 1 pili are termed *mannose-sensitive hemagglutination* (MSHA) (Svenson et al, 1984; Reid and Sobel, 1987).

The role of type 1 pili as a virulence factor in UTIs has been established. This evidence has been obtained (1) from the analysis of bacteria isolated from the urine of patients with UTIs, which were found to express mannose-sensitive (MS) adhesins (Ljungh and Wadstrom, 1983); (2) from studies with animal models (Fader and Davis, 1982; Hagberg et al, 1983a, 1983b; Iwahi et al, 1983; Hultgren et al, 1985) in which inoculation of type 1 piliated organisms into the bladder resulted in significantly more colonization of the urinary tract than inoculation of nonpiliated organisms; and (3) from the observation that anti-type 1 pili antibodies and competitive inhibitors such as methyl-α-D-mannopyranoside protected mice from contracting UTIs (Aronson et al, 1979; Hultgren et al, 1985). **Recent studies have demonstrated that interactions between FimH and receptors expressed on the luminal surface of the bladder epithelium are critical for the ability of many UPEC strains to colonize the bladder and cause disease** (Connell et al, 1996; Langermann et al, 1997; Thankavel et al, 1997; Mulvey et al, 1998).

P (Mannose Resistant) Pili. **P pili confer tropism to the kidney, the designation "P" standing for pyelonephritis** (Mulvey, 2002). P pili, which are found in most pyelonephritogenic strains of UPEC, mediate hemagglutination of human erythrocytes that is not altered by mannose and is thus termed *mannose-resistant hemagglutination* (MRHA) (Kallenius et al, 1979). The adhesin PapG, at the tip of the pilus, recognizes the α-D-galactopyranosyl-(1-4)-β-D-galactopyranoside moiety present in the globoseries of glycolipids (Kallenius et al, 1980; Leffler and Svanborg-Eden, 1980), which are found on P-blood group antigens and on uroepithelium (Svenson et al, 1983).

The MRHA adhesins of UPEC that do not show the digalactoside-binding specificity have been provisionally named X adhesins (Vaisanen et al, 1981). In some strains of UPEC, hemagglutination is mediated by nonpiliated adhesins or hemagglutinins (Duguid et al, 1979).

Svanborg-Eden and coworkers (1978) were the first to report a correlation between bacterial adherence and severity of UTIs. They showed that UPEC strains from girls with acute pyelonephritis had high adhesive ability whereas strains causing asymptomatic bacteriuria or from the feces of healthy girls had low bacterial adherence. Between 70% and 80% of the pyelonephritic strains, but only 10% of the bowel isolates, had adhesive capacity. Furthermore, P pili were present in 91% of urinary strains causing pyelonephritis, 19% of strains causing cystitis, and 14% of strains causing asymptomatic bacteriuria but only 7% of bowel isolates from healthy children, highlighting the correlation between bacterial adherence and UTIs (Kallenius et al, 1981).

Whereas MRHA and P pili are strongly associated with pyelonephritis, these virulence factors are not associated with renal scarring and reflux due to bacterial infection (Vaisanen et al, 1981). Studies suggest minimal correlation between P-piliated *E. coli* strains and recurrent pyelonephritis with gross reflux in girls (Lomberg et al, 1983). Thus it would appear that P pili in acute pyelonephritis are important mainly in nonrefluxing or minimally refluxing children.

Other Adhesins. S pili, which bind to sialic acid residues via the SfaS adhesin, have been associated with both bladder and kidney infection (Mulvey, 2002). F1C pili bind to glycosphingolipids in renal epithelial cells and induce an interleukin-8 inflammatory response (Backhed et al, 2002).

UPEC also expresses a group of afimbrial adhesins (AFA), which have been clustered with the Dr adhesin family for their recognition of decay-accelerating factor and for their similar genetic structure. Decay-accelerating factor is found on numerous different epithelial sites, and Dr adhesins are known to bind to many locations throughout the urinary tract (Anderson et al, 2004b).

Phase Variation of Bacterial Pili in Vivo

Early evidence for the role of type 1 and P pili in adherence in UTIs in humans was contradictory. Pili were visible by electron microscopy on *E. coli* in the urine of 31 of 37 patients (Ljungh and Wadstrom, 1983). Conversely, no MS adhesins were found in 22 of 24 urine isolates from patients with indwelling catheters (Ofek et al, 1981), and 19 of 20 samples from patients with acute UTIs were devoid of pili and nonadherent until subcultured in broth (Harber et al, 1982). Assessment of pili production by clinical *E. coli* isolates demonstrates that environmental growth conditions can produce rapid changes in pilus expression (Duguid et al, 1966; Goransson and Uhlin, 1984; Hultgren et al, 1986), wherein cells switch back and forth between piliated and nonpiliated phases (Eisenstein, 1981). For example, some bacteria grown in a broth medium express pili whereas the same strain grown on the same medium in a solid state will cease production of pili. **This process, called phase variation, can also occur in vivo and has obvious biologic and clinical implications.** For example, the presence of type 1 pili may be advantageous to the bacteria for adhering to and colonizing the bladder mucosa but disadvantageous because the pili enhance phagocytosis and killing by neutrophils (Silverblatt et al, 1979).

An animal model of ascending UTIs and studies of bacterial isolates from different sites in patients with UTI provide evidence that phase variation can occur during *E. coli* UTI in vivo. Type 1 piliated *E. coli* organisms that were capable of phase variation were introduced into the mouse bladder in the piliated phase, and the bacteria recovered from the bladder and urine 24 or more hours after inoculation were tested for piliation. All of the animals had bladder colonization, and 78% of the bacteria recovered showed type 1 piliation. The bacteriologic state of the urine often differed from that of the bladder. The urine was sterile in 59% of the animals with bladder colonization, and the organisms recovered from the urine were often nonpiliated.

When bladder and kidney cultures were examined 1, 3, and 5 days after intravesical inoculation of piliated bacteria, organisms recovered from the bladder remained piliated, whereas organisms recovered from the kidney showed significantly less piliation (Schaeffer et al, 1987) (Fig. 10–6).

Studies in humans using indirect immunofluorescence of fresh urine bacteria have confirmed in-vivo expression and phase

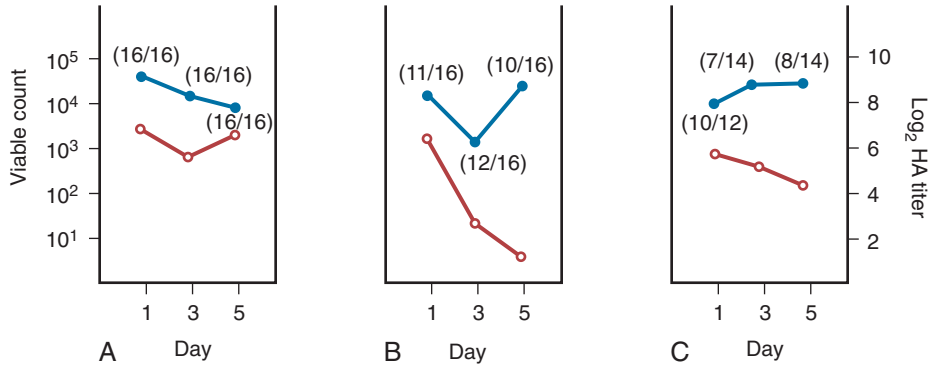


Figure 10–6. Time study after intravesical inoculation with *E. coli* strain I-I49 that compared the mean viable bacteria count *(solid circles)* and hemagglutination (HA) titer *(open circles)* for bladders (**A**), kidneys (**B**), and urine specimens (**C**) from the same animals. Each point is the mean of all the animals tested. The numbers in parentheses show the proportion of animals inoculated that gave positive cultures. The HA titers were tested after 18 hours of growth on agar. The HA titer of bacteria recovered from the kidney decreased significantly by day 5 ($P < .001$). (**A** to **C,** From Schaeffer AJ, Schwan WR, Hultgren SJ, Duncan JL. Relationship of type 1 pilus expression in *Escherichia coli* to ascending urinary tract infections in mice. Infect Immun 1987;55:373–80.)

variation of pili. Analysis of the urine of adults with lower UTI detected type 1 pili in 31 of 41 specimens and P pili in 6 of 18 specimens (Kisielius et al, 1989). The piliation status of the bacterial population in the urine was heterogeneous, varying from predominantly piliated to a mixture of piliated and nonpiliated cells (Fig. 10–7). Strains isolated from different sites in the urogenital tract showed variation in the state of piliation. These results demonstrate that type 1 and P pili are expressed and subject to phase variation in vivo during acute UTIs.

This process of phase variation has obvious biologic and clinical implications. For example, the presence of type 1 pili may be advantageous to the bacteria for initially adhering to and colonizing the bladder mucosa. Subsequently, type 1 pili may be unnecessary for strains in suspension in urine and in fact detrimental because they enhance apoptosis, phagocytosis, and killing by neutrophils (Silverblatt et al, 1979; Mulvey et al, 1998). In the kidney, P pili may then take over as the primary mediator of bacterial attachment by means of their binding to the glycolipid receptors (Stapleton et al, 1995).

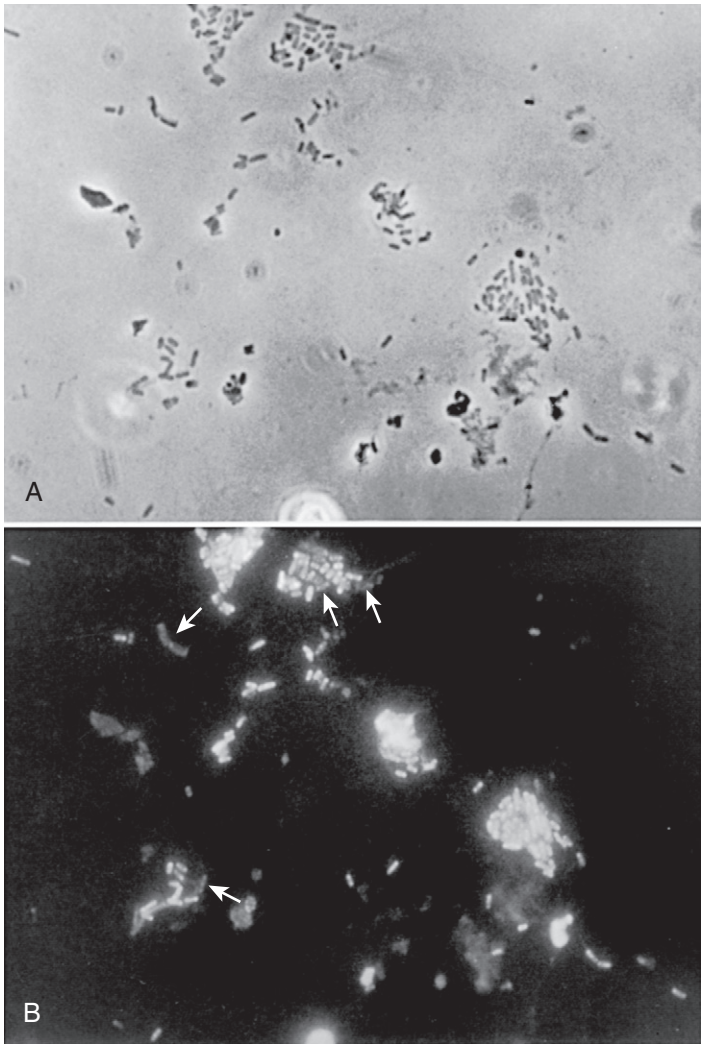


Figure 10–7. Phase-contrast micrograph (**A**) and immunofluorescence micrograph (**B**) of a sample stained with antiserum to type 1 pili of strain I-49 and with FITC-conjugated second antibody against nonadherent *E. coli* in the urine of a patient with acute UTI show a mixture of piliated and nonpiliated (*arrows* in **B**) cells. (**A** and **B,** From Kisielius PV, Schwan WR, Amundsen SK, et al. In vivo expression and variation of *Escherichia coli* type 1 and P pili in the urine of adults with acute urinary tract infections. Infect Immun 1989;57:1656.)

Epithelial Cell Receptivity

Vaginal Cells

The significance of epithelial cell receptivity in the pathogenesis of ascending UTI has been studied initially by examining adherence of *E. coli* to vaginal epithelial cells and uroepithelial cells collected from voided urine specimens. Fowler and Stamey (1977) established that certain indigenous microorganisms (e.g., lactobacilli, *S. epidermidis*) avidly attached themselves to washed epithelial cells in large numbers. When vaginal epithelial cells were collected from patients susceptible to reinfection and compared with such cells obtained from controls resistant to UTI, the *E. coli* strains that cause cystitis adhered much more avidly to the epithelial cells from the susceptible women. **These studies established increased adherence of pathogenic bacteria to vaginal epithelial cells as the first demonstrable biologic difference that could be shown in women susceptible to UTI.**

Subsequently, Schaeffer and colleagues (1981) **confirmed these vaginal differences in women, but in addition they observed that the increased bacterial adherence was also characteristic of buccal epithelial cells.** As can be seen in

Figure 10–8, there is a striking similarity in the ability of both cell types to bind to the same *E. coli* strain. In addition, there was a significant relationship between vaginal cell and buccal cell receptivity. Seventy-seven different *E. coli* strains were tested for their ability to bind to vaginal and buccal epithelial cells. A direct nonlinear relationship between buccal and vaginal adherence in controls and patients was confirmed for urinary, vaginal, and anal isolates. Thus high vaginal cell receptivity was associated with high buccal cell receptivity.

These observations emphasize that the increase in receptor sites for UPEC on epithelial cells from women with recurrent UTIs is not limited to the vagina and thus suggest that a genotypic trait for epithelial cell receptivity may be a major susceptibility factor in UTIs. This concept was extended by examining the human leukocyte antigens (HLAs), which are the major histocompatibility complex in humans and have been associated statistically with many diseases (Schaeffer et al, 1983). The A3 antigen was identified in 12 (34%) of the patients, which is significantly higher than the 8% frequency observed in healthy controls. Thus HLA-A3 may be associated with increased risk of recurrent UTIs.

Variation in Receptivity. A small variation in both vaginal cell and buccal cell receptivity may be observed from day to day in healthy controls. Adherence ranges from 1 to 17 bacteria per cell and appears to be both cyclic and repetitive. When adherence was correlated with the days of a woman's menstrual cycle, higher values were noted in the early phase, diminishing shortly after the time of expected ovulation (day 14). The number of bacteria per epithelial cell often correlated with the value obtained on the same day of the menstrual cycle 1 or 2 months previously. Premenopausal women are particularly susceptible to attachment of uropathogenic *E. coli* and nonpathogenic lactobacilli at certain times during the menstrual cycle and to *E. coli* during the early stages of pregnancy. **The importance of such hormones as estrogens in the pathogenesis of UTI is therefore a matter of great interest, especially because the clinical urologist may see women who have recurrent cystitis at regular intervals, possibly in response to these hormonal changes.**

Reid and Sobel (1987) found that uropathogens attached in larger numbers to uroepithelial cells from women older than 65 years of age than to cells from premenopausal women 18 to 40 years of age. Raz and Stamm (1993) noted that susceptibility to recurrent UTI was increased by the lowered estrogen levels found in the postmenopausal women and that estrogen replacement decreased uropathogenic bacterial colonization and the incidence of UTI.

Blood group antigens and carbohydrate structures bound to membrane lipids or proteins also constitute an important part of the uroepithelial cell membrane. The presence or absence of blood group determinants on the surface of uroepithelial cells may influence an individual's susceptibility to a UTI. Sheinfeld and associates (1989) determined the blood group phenotypes in women with recurrent UTI and compared them with those of age-matched women controls. Women with Lewis Le(a–b–) and Le(a+b–) phenotypes had a significantly higher incidence of recurrent UTIs than women with Le(a–b+) phenotypes. There was no significant difference in the distribution of ABO or P blood group phenotypes. The Lewis antigen controls fucosylation. The protective effect in women with the Le(a–b+) phenotype may be due to fucosylated structures at the vaginal cell surface or in the overlying mucus, which decreases availability of putative receptors for *E. coli* (Navas et al, 1993). The nonsecretor status has also been associated with female acute uncomplicated pyelonephritis, especially in premenopausal women (Ishitoya et al, 2002). Stapleton and coworkers (1995) have shown that unique *E. coli*-binding glycerides are found in vaginal epithelial cells from nonsecretors but not from

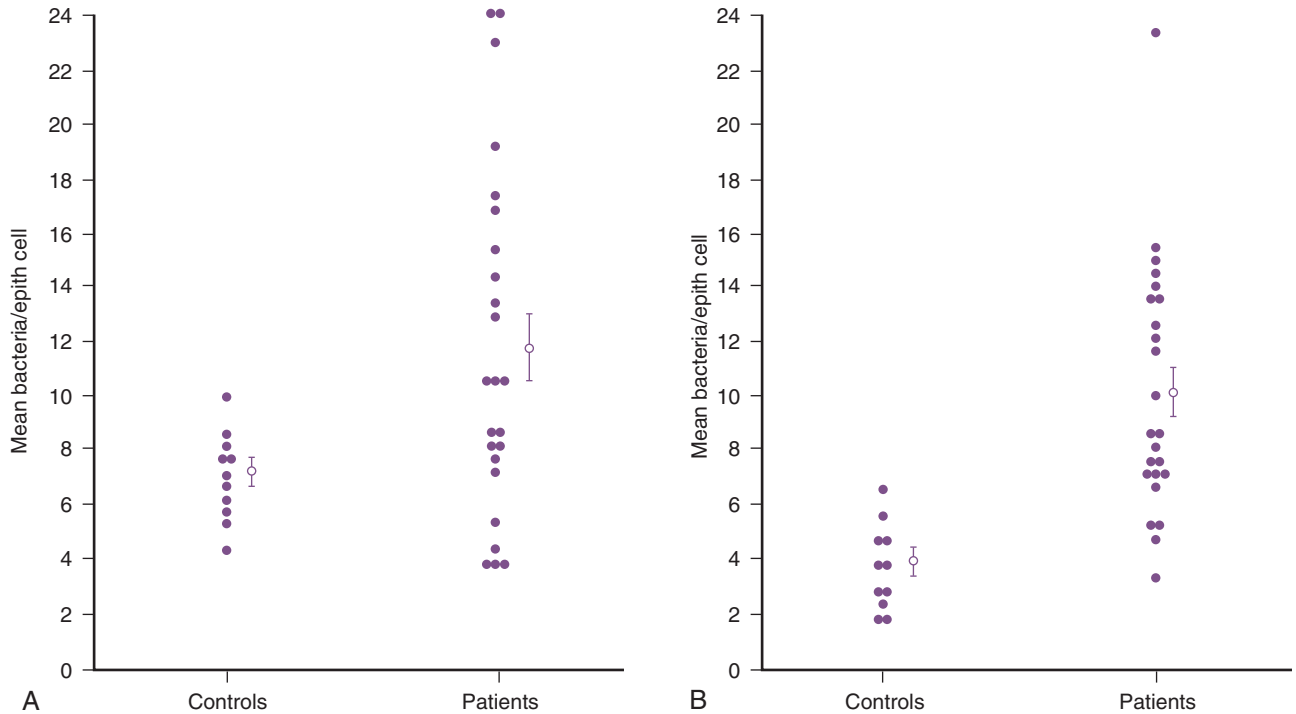


Figure 10–8. In-vitro adherence of *E. coli* to vaginal (**A**) and buccal (**B**) cells from healthy controls and patients with recurrent UTIs. Values represent an average of 14 (**A**) and 11 (**B**) determinations in each individual. The *open circles* and *bars* represent the means + standard error of the mean. (**A** and **B,** From Schaeffer AJ, Jones JM, Dunn JK. Association of in vitro *Escherichia coli* adherence to vaginal and buccal epithelial cells with susceptibility of women to recurrent urinary tract infections. N Engl J Med 1981;304:1062–6.)

secretors. **These studies individually and collectively support the concept that there is an increased epithelial receptivity for *E. coli* on the introital, urethral, and buccal mucosa that is characteristic of women susceptible to recurrent UTIs and may be a genotypic trait.**

The possibility that vaginal mucus might influence bacterial receptivity was investigated by Schaeffer and colleagues (1994). Type 1 piliated *E. coli* bound to all of the vaginal fluid specimens (Venegas et al, 1995). The binding capacity of vaginal fluid from women colonized with *E. coli* in vivo was greater than that from noncolonized women (Schaeffer, 1999). The importance of vaginal fluid in bacteria/epithelial cell interactions was investigated in an in-vitro model that measured the effect of vaginal fluid on the binding of bacteria to an epithelial cell line (Gaffney et al, 1995). Vaginal fluid from colonized women enhanced binding of bacteria to epithelial cells. Conversely, vaginal fluid from noncolonized women inhibited adherence. Thus the vaginal fluid appears to influence adherence to cells and, presumably, vaginal mucosal colonization. Subsequent studies demonstrated that secretory IgA is the primary glycoprotein responsible for vaginal fluid receptivity (Rajan et al, 1999).

Bladder Cells

FimH binds mannosylated residues on the uroplakin molecules covering bladder superficial epithelial cells. The luminal surface of the bladder is lined by umbrella cells. The apical surfaces of umbrella cells appear as a quasi-crystalline array of hexagonal complexes composed of four integral membrane proteins known as uroplakins (Sun, 1996). In-vitro binding assays have shown that two of the uroplakins, UPIa and UPIb, can specifically bind UPEC expressing type 1 pili (Wu et al, 1996). High-resolution freeze-fracture electron microscopy has shown that the tips of these pili, including the adhesins, are buried in the central cavity of the uroplakin hexameric rings (Mulvey et al, 2000) (Fig. 10–9A). **Thus fimH-mediated binding to the bladder epithelium is the initial step in the intricate cascade of events leading to UTIs.**

UPEC Persistence in the Bladder. Soon after attachment to the epithelium, UPEC is quickly internalized into the bladder superficial cells (Martinez and Hultgren, 2002; Anderson et al, 2004b) (Fig. 10–9B). FimH is essential for UPEC invasion; isogenic fimH-mutants do not invade, and invasion of wild-type bacteria can be inhibited by the addition of mannose. In addition, polystyrene latex beads coated with fimH are quickly internalized in a process identical to bacteria expressing type 1 pili. This process is the result of localized actin rearrangement and engulfment of the bound bacterium by zippering of the membrane around the microorganism (Martinez and Hultgren, 2002). Invasion into the superficial epithelium of the bladder allows UPEC to establish a new niche in an effort to protect itself from the host innate immune response (Anderson et al, 2004b).

Once intracellular, the UPEC organisms rapidly grow and divide within the cell cytosol, forming small clusters of bacteria termed *early intracellular bacterial communities* (IBCs) (Anderson et al, 2004b; Justice et al, 2004). As they grow, the bacteria maintain their typical rod shape of approximately 3 μm and form a loosely organized cluster, with microorganisms randomly oriented in the cell cytoplasm. Between 6 to 8 hours after inoculation, early IBCs

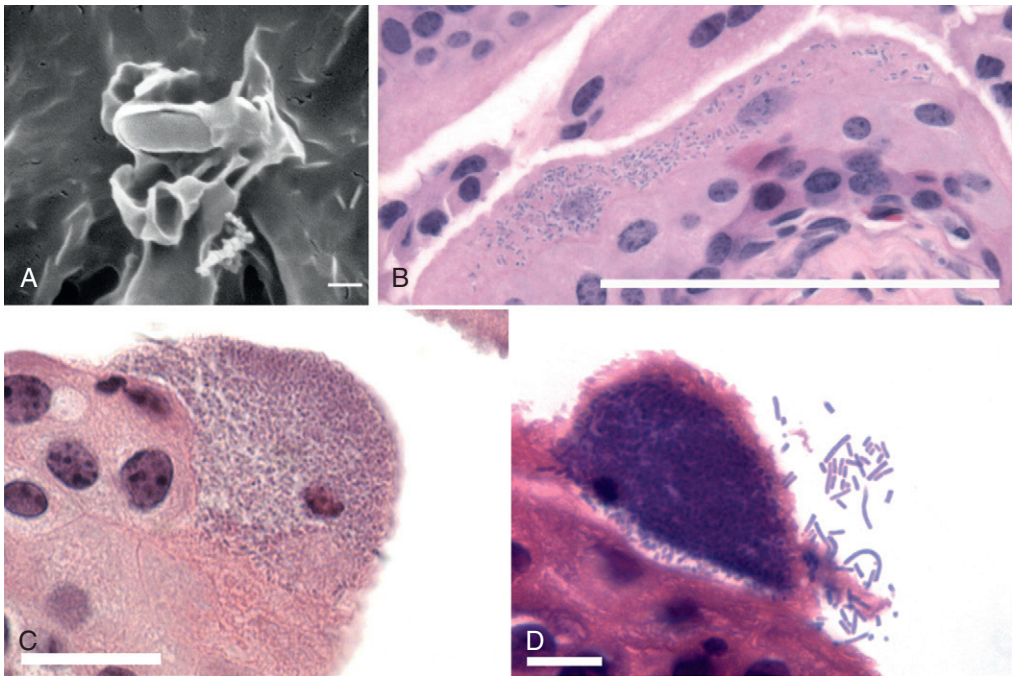


Figure 10–9. UPEC binds, invades, and multiplies inside the superficial cells of the bladder epithelium. **A,** Scanning electron microscopy shows a single UPEC bound to the surface of a bladder cell. Type 1 pilus-mediated contact between bacterium and host cell initiates signaling cascades in the bladder cell, leading to localized actin rearrangements and membrane protrusions around the bacterium. Scale bar, 0.5 μm. **B,** Once inside the bladder superficial cells, UPEC rapidly multiplies to form disordered bacterial clusters in the host cell cytoplasm, called an early intracellular bacterial community (IBC). Bacteria are visible as dark-staining rods inside the cell in this hematoxylin and eosin (H&E)-stained thin bladder section. Scale bar, 100 μm. **C,** H&E-stained thin bladder section reveals a middle IBC, wherein the constituent bacteria have organized themselves into a biofilm-like state within the bladder cell. Scale bar, 20 μm. **D,** A late IBC, visible by H&E staining, is typified by detachment of peripheral bacteria and fluxing of these organisms into the bladder lumen. Scale bar, 10 μm. (From Anderson GG, Martin SM, Hultgren SJ. Host subversion by formation of intracellular bacterial communities in the urinary tract. Microbes Infect 2004;6:1094–1101.)

show a drop in bacterial growth rate resulting in doubling times greater than 60 minutes, a significant shortening of the bacterial morphology to an average of 0.7 µm, and a phenotypic switch into a biofilm-like community (Justice et al, 2004) (see Fig 10–9C).

Biofilms shield bacteria from environmental challenges such as antimicrobial agents and the host immune response (Donlan and Costerton, 2002). **Characteristics of the biofilm that increase protection include the slower growth rate of the bacteria with associated physiologic changes, expression of factors that inhibit antimicrobial activity, and the inability of the antimicrobial agent to penetrate the biofilm matrix** (Anderson et al, 2004b). The biofilm also protects the bacteria from neutrophils because they are unable to effectively penetrate the IBC and engulf the bacteria. In animal models, bacteria on the edge of IBCs eventually detach, differentiate to typical rod morphology, become motile, and then escape the host cell into the bladder lumen in a process called fluxing (Mulvey et al, 2001) (see Fig. 10–9D). These bacteria may become highly filamentous, reaching up to 70 µm or greater in length. This process occurs by approximately 24 hours after inoculation (Justice et al, 2004). It is possible that the filaments may help the bacteria evade the immunologic response.

The escaped bacteria readhere and reinvade superficial cells to lead to second IBC formation. In subsequent rounds, further IBC formation occurs. After a few days, the invasive bacteria become more quiescent. In animal models, the bacteria can persist in this dormant reservoir state for some time before reemerging to cause recurrent UTIs (Anderson et al, 2004a).

Natural Defenses of the Urinary Tract

Periurethral and Urethral Region

The normal flora of the vaginal introitus, the periurethral area, and the urethra usually contain microorganisms such as lactobacilli, coagulase-negative staphylococci, corynebacteria, and streptococci that form a barrier against uropathogenic colonization (Fair et al, 1970; Pfau and Sacks, 1977; Marrie et al, 1978). Changes in the vaginal environment related to estrogen, cervical IgA (Stamey et al, 1978), and low vaginal pH (Stamey and Timothy, 1975) may alter the ability of these bacteria to colonize. More commonly, however, acute changes in colonization have been associated with use of antimicrobial agents and spermicidal agents that alter the normal flora and increase the receptivity of the epithelium for uropathogens.

Little is known about the factors that predispose patients to urethral colonization with uropathogens. The proximity of the urethral meatus to the vulvar and perianal areas suggests that contamination occurs frequently. The nature of urethral defense mechanisms other than flow of urine is largely unknown. Bacterial multiplication in the normal urethra may be inhibited by the indigenous flora (Chan et al, 1984). Although colonization of the periurethral and urethral regions is prerequisite to most infections, the ability of the organisms to overcome the normal defense mechanisms of the urine and the bladder is clearly pivotal.

Urine

In general, fastidious organisms that normally colonize the urethra will not multiply in urine and rarely cause UTIs (Cattell et al, 1974). In contrast, urine will usually support the growth of nonfastidious bacteria (Asscher et al, 1968). Urine from normal individuals may be inhibitory, especially when the inoculum is small (Kaye, 1968). The most inhibitory factors are the osmolality, urea concentration, organic acid concentration, and pH. Bacterial growth is inhibited by either very dilute urine or a high osmolality when associated with a low pH. Much of the antimicrobial activity of urine is related to a high urea and organic acid content (Solomon et al, 1983). From a clinical perspective, however, these conditions do not appear to significantly distinguish between patients who are susceptible or resistant to infection.

Uromodulin (Tamm-Horsfall protein), a kidney-derived mannosylated protein that is present in an extraordinarily high concentration in the urine (greater than 100 mg/mL), may play a defensive role by saturating all the mannose-binding sites of the type 1 pili, thus potentially blocking bacterial binding to the uroplakin receptors of the urothelium (Duncan, 1988; Kumar and Muchmore, 1990).

Bladder

Bacteria presumably make their way into the bladder fairly often. Whether small inocula of bacteria persist, multiply, and infect the host depends in part on the ability of the bladder to empty (Cox and Hinman, 1961). Additional factors responsible for defense involve both innate and adaptive immunity and exfoliation of epithelial cells.

Immune Response

Pathogen Recognition. The host recognition of the pathogen is mediated by a series of pathogen-associated molecular pattern receptors (PAMPs), such as Toll-like receptors (TLRs) (Anderson et al, 2004b), which provide the link between recognition of invading organisms and development of the innate immune response. TLRs recognize molecular patterns that are conserved among many species of pathogens, such as lipopolysaccharide (LPS) and peptidoglycan (PG), and activate signaling pathways that initiate immune and inflammatory responses to kill pathogens. Superficial bladder epithelial cells express TLR4 on their membranes, which along with CD14 recognize LPS from the bacteria and activate the innate immune response (Anderson et al, 2004a). The newly identified TLR11, which recognizes UPEC and protects the kidneys from ascending infection, is also expressed on uroepithelial cells as well as renal cells (Zhang et al, 2004).

The innate system response to an infection in the bladder or kidneys is primarily local inflammation.

The innate immune response occurs more rapidly than the adaptive response and involves a variety of cell types, including polymorphonuclear leukocytes, neutrophils, macrophages, eosinophils, natural killer cells, mast cells, and dendritic cells. In addition, increased transcription of inducible nitric oxide synthase by polymorphonuclear leukocytes results in high levels of nitric oxide and related breakdown products that also have toxic effects on the bacteria (Poljakovic et al, 2001; Poljakovic and Persson, 2003). The innate response aids in establishing adaptive immunity due to interactions of macrophages, dendritic cells, and natural killer cells with T and B lymphocytes. Adaptive immunity involves the specific recognition of pathogens by T and B lymphocytes and production of high-affinity antibodies, a process that occurs 7 to 10 days after infection.

The urinary tract is part of the secretory immune system. In pyelonephritis, IgG and SIgA appear in the urine and may become evident before antibodies are detected in the serum. These antibodies are synthesized locally within the kidney and may enhance bacterial opsonization and ingestion by local phagocytic cells. These antibodies may have further protective function. Svanborg-Eden and Svennerholm (1978) showed that IgG and SIgA derived

from the urine of patients with acute pyelonephritis reduced in-vitro adherence of the same strain of *E. coli* to uroepithelial cells. Similarly, immunization with *E. coli* P pili resulted in immunoglobulin production in experimental animals that prevented ascending pyelonephritis by reducing the adhesive capacity of the invading autologous uropathogenic *E. coli* (Roberts and Phillips, 1979; O'Hanley, 1983).

The possibility that immunologic factors may be modified to reduce susceptibility to infection has been explored primarily through immunization in animal and human systems. For example, in a monkey model, vaccination with P fimbria has been shown to reduce adherence of P-fimbriated *E. coli* to uroepithelial cells and prevent acute pyelonephritis (Roberts and Phillips, 1979). Similarly, vaccination of mice with FimH adhesin prevents cystitis in mice (Langermann et al, 1997). Vaccination of women may reduce colonization of the vaginal introitus and subsequent ascending bacteria (Uehling et al, 1994).

Induced Exfoliation. Mulvey and colleagues (1998) **demonstrated that exfoliation and excretion of infected and damaged superficial cells is mediated by type 1 piliated bacteria that induce programmed cell death.** By utilizing an in-vivo mouse model, it has been demonstrated that mice exhibiting a strong exfoliation response to UPEC infiltration are unlikely to form IBCs (Anderson et al, 2004b). However, mice with a much milder exfoliation response tend to form biofilms, which become sequestered in the bladder and presumably could lead to recurrent UTIs. **It has also been shown that many uropathogenic bacteria can suppress NFκB, increase apoptosis, and decrease the inflammatory responses** (Klumpp et al, 2001), **a process that could lead to subsequent bacterial invasion into deeper tissues. Thus in some instances apoptosis may be a bacterial offense maneuver rather than a host defense.**

Alterations in Host Defense Mechanisms

Obstruction

Obstruction to urine flow at all anatomic levels is a key factor in increasing host susceptibility to UTI. Obstruction inhibits the normal flow of urine, and the resulting stasis compromises bladder and renal defense mechanisms. **Stasis also contributes to the growth of bacteria in the urine and their ability to adhere to the urothelial cells.** In the animal model of experimental hematogenous pyelonephritis the kidney is relatively resistant to infection unless a ureter is ligated. Under these circumstances only the obstructed kidney becomes infected (Beeson and Guze, 1956). Clinical observations support the role of obstruction in pathogenesis of UTI and in increasing severity of infection. **Mild episodes of cystitis or pyelonephritis can become life threatening when obstruction to urine flow becomes present.** Although obstruction clearly increases the severity of infection, it need not be a predisposing factor. For example, men with large residual urine may remain uninfected for years. However, if they are catheterized, even small inocula may lead to severe infections that are difficult to eradicate.

Vesicoureteral Reflux

Hodson and Edwards (1960) first described the association of vesicoureteral reflux, UTI, and renal clubbing and scarring. **Children with gross reflux and UTIs usually develop progressive renal damage manifested by renal scarring, proteinuria, and renal failure. Those with a lesser degree of reflux usually improve or completely recover spontaneously or after treatment of the UTI. In adults, the presence of reflux does not appear to decrease renal function unless there is stasis and concurrent UTIs.**

Underlying Disease

There is a high incidence of renal scarring in patients with underlying conditions that cause chronic interstitial nephritis, virtually all of which produce primary renal papillary damage. These conditions include diabetes mellitus, sickle cell disorders, adult nephrocalcinosis, hyperphosphatemia, hypokalemia, analgesic abuse, sulfonamide nephropathy, gout, heavy-metal poisoning, and aging (Freedman, 1979).

Diabetes Mellitus

An increased incidence of clinical asymptomatic and symptomatic UTIs appears to occur in women with diabetes mellitus, but there is no substantial increase among diabetic men (Vejlsgaard, 1973; Ooi et al, 1974; Forland et al, 1977; Meiland et al, 2002). Diabetes also results in three times more hospitalizations for acute pyelonephritis among women (10.86/10,000) than for men (3.32/10,000) (Nicolle et al, 1996). Autopsy studies have shown the incidence of pyelonephritis to be fourfold to fivefold higher in diabetic than in nondiabetic individuals (Robbins and Tucker, 1944). However, such studies may be misleading because it is difficult to distinguish renal parenchymal changes resulting from pyelonephritis from the interstitial inflammatory changes of diabetic nephropathy.

Although most UTIs in diabetic patients are asymptomatic, diabetes appears to predispose the patient to more severe infections. There is no evidence that increased frequency of infection is due to glycosuria (Geerlings et al, 2000). One study using antibody-coated bacteria techniques to localize the site of infection showed the upper urinary tract to be involved in nearly 80% of diabetic patients with UTIs (Forland et al, 1977). This evidence of increasing immunologic response in diabetic patients who acquire bacteriuria suggests renal parenchymal involvement and a potential increase in morbidity.

Infections are frequently caused by atypical organisms such as yeast and result in upper tract infections and significant sequelae such as emphysematous pyelonephritis, papillary necrosis, perinephric abscess, or metastatic infection (Wheat, 1980; Stapleton, 2002).

Renal Papillary Necrosis

The role of infection in the development and progression of renal papillary necrosis (RPN) is controversial. **Multiple predisposing conditions have been associated with the development of RPN, particularly diabetes, analgesic abuse, sickle cell hemoglobinopathy, and obstruction** (Table 10–2).

Clinically, RPN is a spectrum of disease. Patients may have an acute fulminating illness with rapid progression or may have a chronic disease that is incidentally discovered. Some patients may chronically pass necrotic tissue in their urine (Hernandez et al, 1975), and some may never pass papillae (Lindvall, 1978). Retained necrotic papillae may calcify, especially in association with infection. Furthermore, this necrotic tissue may form the nidus for chronic infection. Opportunistic fungal infections have been reported (Madge and Lombardias, 1973; Juhasz et al, 1980; Vordermark et al, 1980; Tomashefski and Abramowsky, 1981). Renal ultrasonography may be useful to diagnose RPN (Buonocore et al, 1980; Hoffman et al, 1982).

Table 10–2.

Conditions Associated with Renal Papillary Necrosis

Diabetes mellitus
Pyelonephritis
Urinary tract obstruction
Analgesic abuse
Sickle cell hemoglobinopathies
Renal transplant rejection
Cirrhosis of the liver
Dehydration, hypoxia, and jaundice of infants
Miscellaneous: renal vein thrombosis, cryoglobulinemia, renal candidiasis, contrast media injection, amyloidosis, calyceal arteritis, necrotizing angiitis, rapidly progressive glomerulonephritis, hypotensive shock, acute pancreatitis

From Eknoyan G, Qunibi WY, Grissom RT, et al. Renal papillary necrosis: an update. Medicine 1982;61:55.

The early diagnosis of RPN is important to improve prognosis and reduce morbidity. In addition to chronic infection, patients with analgesic abuse–associated papillary necrosis may have an increased incidence of urothelial tumors; routine urinary cytologic examinations may be helpful to diagnose these tumors early (Jackson et al, 1978). In patients who have analgesic abuse–induced RPN, the disease stabilizes if the analgesic intake is stopped (Gower, 1976). Furthermore, adequate antimicrobial therapy to control infection and early recognition and treatment of ureteral obstruction caused by sloughed necrotic tissue can minimize a decline in renal function. A patient who suffers from an acute ureteral obstruction due to a sloughed papilla and who has a concomitant UTI has a urologic emergency. In this case, immediate removal of the obstructing papilla by stone basket (Jameson and Heal, 1973) or acute drainage of the kidney by ureteral catheter or percutaneous nephrostomy is necessary.

Other conditions that may increase the susceptibility of the kidney to infection include hypertension and vascular obstruction (Freedman, 1979). Association of renal infection with several other renal diseases, including glomerulonephritis, atherosclerosis, and tubular necrosis, which are not associated with papillary necrosis, does not lead to pyelonephritis and scarring.

Human Immunodeficiency Virus

UTIs are fivefold more prevalent in HIV-positive individuals than in control subjects (Schonwald et al, 1999). Furthermore, the pathologic flora are more reminiscent of complicated UTIs. It also appears that HIV-positive patients with UTIs have a tendency for recurrence and require longer treatment.

Pregnancy

The prevalence of bacteriuria in pregnant women varies from 4% to 7%, and the incidence of acute clinical pyelonephritis ranges from 25% to 35% in untreated bacteriuric women (Stamey, 1980). This is probably the result of dilation of the ureters and pelvis of the kidney secondary to pregnancy-related hormonal alterations. In addition, urine obtained from pregnant women exhibits a more suitable pH for growth of *E. coli* in all stages of gestation (Asscher et al, 1973). **It is not surprising that untreated bacteriuria in the first trimester is accompanied by a substantial increase in the incidence of acute pyelonephritis, because half of these women have upper tract bacteriuria** (Fairley et al, 1966). Untreated bacteriuria involving these dilated upper tracts would be expected to produce a significant number of abnormalities that should be radiologically apparent. Kincaid-Smith and Bullen (1965) performed a culture on 4000 women at their first antenatal visit. Of 240 bacteriuric women, 148 returned for excretory urography 6 weeks after delivery. Approximately 40% of these patients had radiologic abnormalities consistent with pyelonephritis or analgesic nephritis. Brumfitt and colleagues (1967) showed that the incidence of radiologic abnormalities in bacteriuria of pregnancy was proportional to the difficulty in clearing the infection. Patients who responded promptly to a single course of therapy had a 23% incidence of radiologic abnormalities, but those who remained bacteriuric despite repeated therapeutic efforts had a 65% incidence of radiologic changes. Thus prolonged bacteriuria and pyelonephritis of pregnancy appear to be associated with significant radiologic abnormalities. However, there is little evidence to suggest that bacteriuria of pregnancy or acute pyelonephritis of pregnancy causes these renal radiologic abnormalities.

Spinal Cord Injury with High-Pressure Bladders

Of all patients with bacteriuria, no group compares in severity and morbidity with those who have spinal cord injury. Nearly all these patients require catheterization early after their injuries because of bladder overactivity or flaccidity, and significant numbers develop ureterectasis, hydronephrosis, reflux, and renal calculi. Bacteriologic and urodynamic advances in the management of these patients have vastly reduced their morbidity and mortality. Special problems associated with spinal cord injury are presented in a later section.

Key Points: Pathogenesis

- Most UTIs are caused by bacteria, usually originating from the bowel flora.
- Bacterial virulence factors, including adhesin, play a role in determining which bacteria invade and the extent of infection.
- Increased epithelial cell receptivity predisposes patients to recurrent UTIs and is a genotypic trait.
- Obstruction to urine flow is a key factor in increasing host susceptibility to UTIs.

CLINICAL MANIFESTATIONS

Symptoms and Signs

Cystitis is usually associated with dysuria, frequency, and/or urgency. Suprapubic pain and hematuria are less common. Lower tract symptoms are commonly present and usually predate the appearance of upper tract symptoms by several days. Pyelonephritis is classically associated with fever, chills, and flank pain. Nausea and vomiting may be present. Renal or perirenal abscess may cause indolent fever and flank mass and tenderness. In the elderly the symptoms may be much more subtle (e.g., epigastric or abdominal discomfort) or the patient may be asymptomatic (Romano and Kaye, 1981). Patients with indwelling catheters often have asymptomatic bacteriuria, but fever associated with bacteremia may occur rapidly and become life threatening.

Diagnosis

Presumptive diagnosis of UTI is made by direct or indirect analysis of the urine and is confirmed by urine culture. The urine and the urinary tract are normally free of bacteria and inflammation. False-negative urinalysis and culture can occur in the presence of UTI, particularly early in an infection when the numbers of bacteria and WBCs are low or diluted by increased fluid intake and subsequent diuresis. Occasionally, the urine may be free of bacteria and WBCs despite bacterial colonization and inflammation of the uroepithelium (Elliott et al, 1985; Hultgren et al, 1985). False-positive urinalysis and culture are caused by contamination of the urine specimen with bacteria and WBCs during collection. This is most likely to occur in voided specimens but can also occur during urethral catheterization. Suprapubic aspiration of bladder urine is least likely to cause contamination of the specimen; therefore it provides the most accurate assessment of the status of bladder urine.

Urine Collection

Voided and Catheterized Specimens. **Diagnostic accuracy can be improved by reducing bacterial contamination when the urine is collected.** In circumcised men, voided specimens require no preparation. For men who are not circumcised, the foreskin should be retracted and the glans penis washed with soap and then rinsed with water before specimen collection. The first 10 mL of urine (representative of the urethra) and a midstream specimen (representative of the bladder) should be obtained. Prostatic fluid is obtained by performing digital prostatic massage and collecting the expressed prostatic fluid on a glass slide. In addition, collection of the first 10 mL of voided urine after massage will reflect the prostatic fluid added to the urethral specimen. **Catheterization of a male patient for urine culture is not indicated unless the patient cannot urinate.**

In women, contamination of a midstream urine specimen with introital bacteria and WBCs is common, particularly when the woman has difficulty spreading and maintaining separation of the labia. Therefore the female should be instructed to spread the labia, wash and cleanse the periurethral area with a moist gauze, and then collect a midstream urine specimen. Cleansing with antiseptics is not recommended because they may contaminate the voided specimen and provide a false-negative urine culture. **The voided specimen is contaminated if it shows evidence of vaginal epithelial cells and lactobacilli on urinalysis, and a catheterized specimen should be collected.**

Catheterization and collection of a midcathterized specimen is more accurate than a voided specimen but carries a risk of iatrogenic infection. **Although a single dose of an oral antimicrobial agent, such as trimethoprim-sulfamethoxazole (TMP-SMX) may be effective for prophylaxis, because antimicrobial usage encourages development of bacterial resistance, prophylaxis should be limited to high-risk patients. Men should be catheterized for a urine culture if they cannot urinate.**

Suprapubic Aspiration. Suprapubic aspiration is highly accurate, but because it carries some morbidity there is limited clinical usefulness except for a patient who cannot urinate on command, such as patients with spinal cord injuries. It is highly useful in newborns (Newman et al, 1967) and in patients with paraplegia. A single aspirated specimen reveals the bacteriologic status of the bladder urine without introducing urethral bacteria, which can start a new infection.

Before a suprapubic aspiration is performed, the patient should force fluids until the bladder is full. The site of the needle puncture is in the midline, between the symphysis pubis and the umbilicus and directly over the palpable bladder. The full bladder in the male is usually palpable because of its greater muscle tone; unfortunately, the full bladder in the female is frequently not palpable. In such patients, the physician performing the aspiration must rely on the observation that suprapubic pressure directly over the bladder produces an unmistakable desire to urinate. After determining the approximate site for needle puncture, the local area is shaved and the skin is cleansed with an alcohol sponge; a cutaneous wheal is raised with a 25-gauge needle and any local anesthetic. A 3.5-inch spinal, 22-gauge needle is introduced through the anesthetized skin. The progress of the needle is arrested just below the skin within the anesthetized area, and with a quick plunging action, similar to that of any intramuscular injection, the needle is advanced into the bladder. Most patients experience more discomfort from the initial anesthetization of the skin than they feel during the second stage when the needle is advanced into the bladder. After the needle has been introduced, a 20-mL syringe is used to aspirate 5 mL of urine for culture and 15 mL of urine for centrifugation and urinalysis. The obturator is reintroduced into the needle, and both needle and obturator are withdrawn. A small dressing is placed over the needle site in the skin. If urine is not obtained with complete introduction of the needle, the patient's bladder is not full and is usually deep within the retropubic area. When no urine is obtained on the first attempt, it is probably wise to wait until the bladder is full.

Urinalysis

For patients with urinary symptoms, microscopic urinalysis for bacteriuria, pyuria, and hematuria should be performed. Urinalysis provides rapid identification of bacteria and WBCs and presumptive diagnosis of UTI. Usually, the sediment from a 5- to 10-mL specimen obtained by centrifugation for 5 minutes at 2000 rpm is analyzed. Microscopic bacteriuria is found in more than 90% of infections with counts of 10^5 colony-forming units (cfu) per milliliter of urine or greater and is a highly specific finding (Stamm, 1982; Jenkins et al, 1986). However, bacteria are usually not detectable microscopically with lower colony count infections (10^2 to 10^4/mL). **This important error (i.e., a false-negative result) occurs because of the limitation imposed by the microscope on the volume of urine that can be observed.** If the volume of urine that can easily rest beneath a standard 22-mm cover glass is carefully measured (0.01 mL) and the number of high dry fields (×570 magnification) present beneath the cover glass is estimated, it is disturbing to find that one high dry field represents a volume of approximately 1/30,000 mL. There are excellent studies showing that the bacterial count must be approximately 30,000/mL before bacteria can be found in the sediment, stained or unstained, spun or unspun (Sanford et al, 1956; Kunin, 1961). For these reasons, a negative urinalysis for bacteria never excludes the presence of bacteria in numbers of 30,000/mL and less.

The second error of urinalysis (i.e., a false-positive result) is the reverse of the first error: bacteria are seen in the microscopic sediment but the urine culture shows no growth. The voided urine from a female patient can contain many thousands of lactobacilli and corynebacteria. These bacteria are readily seen under the microscope; and although they are gram-positive, they often appear gram-negative (gram-variable) if stained. Strict anaerobes, usually gram-negative bacilli, also make

up a significant mass of the normal vaginal flora (Marrie et al, 1978).

In practice, these problems can be minimized by using other information provided by urinalysis that can help the clinician to decide whether a patient has a UTI (Stamm et al, 1982b). **The validation of the midstream urine specimen can be questioned if numerous squamous epithelial cells (indicative of preputial, vaginal, or urethral contaminants) are present.**

Pyuria and hematuria are good indicators of an inflammatory response. Although the number of WBCs per high-power field in a centrifuged urine sample is useful, it is important to remember that other factors can influence the number of cells seen. These include the state of hydration; the intensity of tissue reaction; the method of urine collection; the volume, speed, and time of centrifugation; and the volume in which the sediment is resuspended.

The presence of bacteruria has a sensitivity of 40% to 70% and a specificity of 85% to 95%, depending on the number of bacteria observed (Fihn, 2003).

Significant pyuria can be determined simply and reliably with a microscope by accurately examining the centrifuged sediment or by using a hemocytometer to count the number of WBCs in the unspun urine. One to 2 WBCs per high-power field (HPF) in sediment from a centrifuged specimen represents about 10 WBCs/mm^3 in an unspun specimen. More than 2 WBCs per HPF in a centrifuged specimen or 10 WBCs/mm^3 of urine correlates well with the presence of bacteriuria and is rarely seen in nonbacteriuric patients (Stamm et al, 1981). **In clinical studies, determination of pyuria in voided urine specimens has a reported sensitivity of 80% to 95% and a specificity of 50% to 76% for UTI (depending on the definition of infection, the patient population, and the method used to evaluate for pyuria)** (Stamm, 1982; Schultz et al, 1984; Wong et al, 1984; Wigton et al, 1985).

The absence of pyuria should cause the diagnosis of UTI to be questioned until urine culture data are available. Conversely, many diseases of the urinary tract produce significant pyuria in the absence of bacteriuria. Whereas tuberculosis is the well-recognized example of abacterial pyuria, staghorn calculi and stones of smaller size can produce intense pyuria with clumps of WBCs in the absence of UTI. Almost any injury to the urinary tract, from chlamydial urethritis to glomerulonephritis and interstitial cystitis, can elicit large numbers of fresh polymorphonuclear leukocytes (glitter cells). Depending on the stage of hydration, the intensity of the tissue reaction producing the cells, and the method of urine collection, any number of WBCs can be seen in the microscopic sediment in the presence of an uninfected urinary tract.

Microscopic hematuria is found in 40% to 60% of cases of cystitis and is uncommon in other dysuric syndromes (Stamm et al, 1980b; Wigton et al, 1985).

Rapid Screen Methods. Biochemical and enzymatic tests have been devised to detect bacteriuria and pyuria (Pezzlo, 1988). The Griess test detects the presence of nitrite in urine that is formed when bacteria reduce the nitrate normally present in urine. Tests for detecting pyuria by determining leukocyte esterase activity have also been developed (Chernow et al, 1984). In a study comparing traditional urine culture with these indirect tests, the combination of nitrite and leukocyte esterase tests (either test positive) had a sensitivity of 71% and a specificity of 83% when compared with 10^3 cfu/mL or greater of urine cultures (Pfaller and Koontz, 1985). However, several investigators (Pels et al, 1989; Hurlbut and Littenberg, 1991) noted substantial variability in the sensitivity and specificity results, which could be markedly influenced by the types of patients and infections chosen to evaluate the tests. This concept of spectrum bias was illustrated by a study that reported differences in the sensitivity of reagent strip testing, ranging from 56% to 92%, by changing only the groups of patients included in the analysis. Although false-positive results are relatively uncommon, the borderline sensitivity of these tests, especially among patients with less characteristic symptoms of UTIs, does not allow these inexpensive tests to replace careful microscopic urinalysis in symptomatic patients (Semeniuk and Church, 1999). **Their main role is in screening asymptomatic patients** (Pezzlo, 1988).

Urine Culture

Two techniques for urine culture are available. Direct surface plating of a known amount of urine on split-agar disposable plates is the traditional quantitative culture technique used by most microbiology laboratories. One half of the plate is blood agar, which grows both gram-positive and gram-negative bacteria, and the other is desoxycholate or eosin-methylene blue (EMB), which grows gram-negative bacteria (some of them, such as *E. coli*, in a very characteristic manner). Simple curved-tip eye droppers are sufficient to deliver about 0.1 mL of urine onto each half of the plate. After overnight incubation, the number of colonies is estimated, often identified (after some experience), and multiplied by 10 to report the number of cfu per milliliter of urine. The technique has been presented elsewhere in detail (Stamey, 1980).

A simpler but somewhat less accurate technique is the use of dip slides (Fig. 10–10). These inexpensive plastic slides are attached to screw-top caps; they have soy agar (a general nutrient agar to grow all bacteria) on one side and EMB or MacConkey agar for gram-negative bacteria on the opposite side. A slide is dipped into urine, the excess is allowed to drain off, and the slide is replaced in its plastic bottle and incubated. The volume of urine that attaches to the slide is between 1/100 mL and 1/200 mL. Hence, the colony count is 100 to 200 times the number of colonies that become visible with incubation. In actual practice, the growth is compared with a visual standard and reported as such. The species

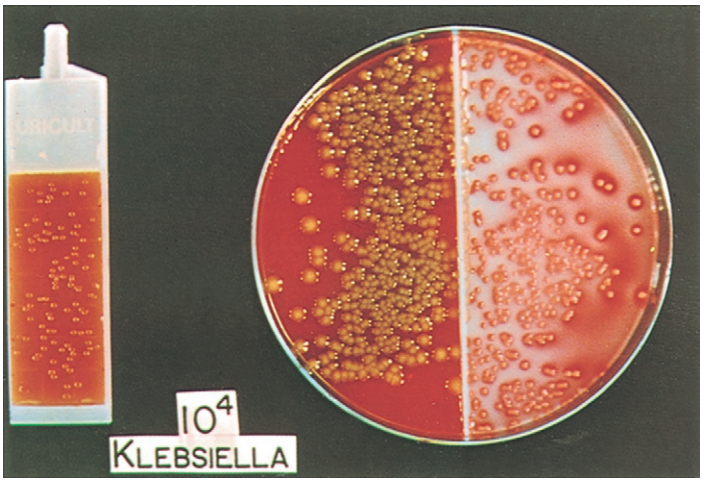


Figure 10–10. The dip slide on the left is compared with a split-agar surface plate on the right. The urine contained 10,000 colonies of *Klebsiella* per milliliter (about 200 times the number of colonies on the dip slide and 10 times the number on either side of the split-agar plate).

of bacteria is more difficult to recognize when this technique is used, but the technique is completely adequate.

The urine must be refrigerated immediately on collection and should be cultured within 24 hours of refrigeration. One advantage to the dip slide is the ease with which the urine can be immediately cultured without the necessity of refrigeration. Patients can culture their own urine at home, keep the slide at room temperature, and bring it to the office within 48 hours.

Although most bacteria allowed to incubate for several hours in bladder urine reach cfu counts of 10^5/mL, this statistical number is fraught with two limitations. The first is that 20% to 40% of women with symptomatic UTIs present with bacteria counts of 10^2 to 10^4 cfu/mL of urine (Stamey et al, 1965; Mabeck, 1969; Kunz et al, 1975; Kraft and Stamey, 1977), probably because of the slow doubling time of bacteria in urine (every 30 to 45 minutes) combined with frequent bladder emptying (every 15 to 30 minutes) from irritation. **Thus, in dysuric patients, an appropriate threshold value for defining significant bacteriuria is 10^2 cfu/mL of a known pathogen** (Stamm and Hooton, 1993). Fortunately, most of these patients have symptoms of UTI and pyuria on urinalysis.

The second limitation of the 10^5 cutoff is overdiagnosis. Women susceptible to infection often carry large numbers of pathogenic bacteria on the perineum that contaminate otherwise sterile bladder urine. Uncircumcised men may harbor uropathogenic bacteria on their foreskins. In the original studies by Kass (1960), a single culture of 10^5 cfu/mL or more had a 20% chance of representing contamination. There is no statistical way to avoid these two major limitations on the interpretation of the midstream voided culture in women and in uncircumcised men without careful preparation.

Localization

Kidney

Fever and Flank Pain. Fever and flank pain are thought to indicate pyelonephritis, but few studies have tested the hypothesis. Aggressive localization studies in children and adults (Huland and Busch, 1982; Busch and Huland, 1984), as well as in patients with end-stage renal disease (Huland et al, 1983), have shown substantial incidences of fever and even flank pain in bacteriuric patients in whom infection was localized to the bladder (see later section on Acute Pyelonephritis).

Ureteral Catheterization. **Ureteral catheterization allows not only separation of bacterial persistence into upper and lower urinary tracts but also separation of the infection between one kidney and the other, and even localization of infection to ectopic ureters or to nonrefluxing ureteral stumps (by using saline solution irrigation)** (Stamey, 1980).

Stamey began in 1959 to localize the site of bacteriuria by ureteral catheterization studies; the technique was published in 1963 (Stamey and Pfau, 1963) and the results in 1965 (Stamey et al, 1965). The technique is simple but exacting; the urologist should consult a more detailed description (Stamey, 1980) before actually performing this localization technique. The validity depends on controlling the number of bacteria from the bladder that contaminate the ureteral catheters as they pass through the bladder into the ureteral orifices. The bladder must be thoroughly irrigated before both ureteral catheters are passed into a small volume of residual irrigating fluid. A sample is obtained through both ureteral catheters simultaneously, and then each catheter is passed into the ureter or renal pelvis. Four serial cultures are obtained from each kidney. It is mandatory that the patient be started on the appropriate antimicrobial agent before leaving the cystoscopy room. In addition to quantitative bacterial counts on each specimen, determination of either specific gravity or urine creatinine levels on the renal samples can be very helpful in interpreting a change in diuresis in relation to bacterial counts. Examples of infections localized to the bladder, to one kidney, and to both kidneys have been published (Stamey, 1980). Clinical examples of results from each site are shown in Table 10–3.

When this technique was applied to large numbers of bacteriuric patients, 45% were found to have bladder infection only; 27%, unilateral renal bacteriuria; and 28%, bilateral renal bacteriuria (Table 10–4) (Stamey et al, 1965). These figures have been confirmed by at least five investigators in three countries (the United States, England, and Australia) and can be taken as a good approximation for any general bacteriuric adult population. **Although renal stones and other kidney abnormalities in the presence of bacteriuria can increase the proportion of renal infections, the urologist should never assume the kidney is involved if an important decision is to be made.**

Tissue and Stone Cultures. It is clinically useful to culture stones removed from the urinary tract to document that bacteria reside within their interstices. Tissue cultures are primarily useful for research information.

Table 10–3.

Clinical Examples of Ureteral Catheterization Studies in Localizing the Site of Bacteriuria

SOURCE OF RENAL INFECTION	BLADDER INFECTION (BACTERIA/mL)	LEFT RENAL INFECTION (BACTERIA/mL)	RIGHT RENAL INFECTION (BACTERIA/mL)	BILATERAL (BACTERIA/mL)
CB	$>10^5$	5000	$>10^5$	4000
WB	900	300	1000	20
LK_1	20	2000	20	400
LK_2	0	2200	0	350
LK_3	0	2500	0	500
LK_4	0	2200	0	400
RK_1	10	0	10,000	260
RK_2	0	0	10,000	220
RK_3	0	0	8000	300
RK_4	0	0	12,000	250

CB, catheterized patient, cystoscopic specimen; LK_1, LK_2, etc., serial cultures of urine from the left kidney; RK_1, RK_2, etc., serial cultures of urine from the right kidney; WB, controlled, "wash bladder" specimen collected after copious irrigation of the bladder.

Table 10–4.

Localization of UTIs in 95 Females and 26 Males with Bacteriuria

NO. PATIENTS	BLADDER ONLY	UNILATERAL RENAL BACTERIURIA	BILATERAL RENAL BACTERIURIA
95 females	38 (40%)	27 (28%)	30 (32%)
26 males	16 (62%)	6 (26%)	4 (15%)
121 combined	54 (45%)	33 (27%)	34 (28%)

From Stamey TA, Govan DE, Palmer JM. The localization and treatment of urinary tract infections: the role of bactericidal urine levels as opposed to serum level. Medicine 1965;44:1.

Using sterile technique at the operating table, the surgeon places the stone or fragment of tissue into a sterile culture tube containing 5 mL of saline solution; the culture is packed in ice and sent to the bacteriologic laboratory, where, after agitation of the stone or tissue in the 5 mL of saline solution, 0.1 mL is surface-streaked on both blood agar and EMB agar. The saline solution is then poured off the specimen; and, with sterile forceps, the stone or tissue is transferred to a second 5 mL of sterile saline solution. After agitation to ensure a reasonable washing action, the saline solution is again decanted and the specimen is transferred to a third 5 mL of saline solution and finally to a fourth 5 mL of saline solution. This last saline solution wash is cultured quantitatively in the same manner as the first. The remainder of this fourth 5 mL of saline solution is poured with the stone into a sterile mortar and pestle dish.

After the stone is crushed (or the tissue is ground in a tissue blender) in the fourth saline solution wash, 0.1 mL is again cultured on both blood agar and EMB agar. The difference in colony counts between the first and the fourth saline solution washes represents the washing effect of the saline solution transfers on the surface bacteria of the stone or tissue. The difference between the fourth saline wash before and after crushing (or grinding, for tissue) represents the difference between surface bacteria and bacteria within the specimen.

Prostate and Urethral Localization Studies. The technique for localizing infections to the urethra or prostate is covered in detail in Chapter 11.

Key Points: Clinical Manifestations

- The urine and the urinary tract are normally sterile.
- Bacteriuria and WBCs provide a presumptive diagnosis of UTI.
- In diagnosing patients, 10^2 cfu/mL confirms a symptomatic UTI.

IMAGING TECHNIQUES

Imaging studies are not required in most cases of UTI because clinical and laboratory findings alone are sufficient for correct diagnosis and adequate management of most patients. However, infection in most men or a compromised host, febrile infections, signs or symptoms of urinary tract obstruction, failure to respond to appropriate therapy, and a pattern of recurrent infections suggesting bacterial persistence within the urinary tract warrant imaging for identification of underlying abnormalities that require modification of medical management or percutaneous or surgical intervention.

Table 10–5.

Indications for Radiologic Investigation in Acute Clinical Pyelonephritis

Potential ureteral obstruction (e.g., due to stone, ureteral stricture, tumor)
History of calculi, especially infection (struvite) stones
Papillary necrosis (e.g., patients with sickle cell anemia, severe diabetes mellitus, analgesic abuse)
History of genitourinary surgery that predisposes to obstruction, such as ureteral reimplantation or ureteral diversion
Poor response to appropriate antimicrobial agents after 5 to 6 days of treatment
Diabetes mellitus
Polycystic kidneys in patients in dialysis or with severe renal insufficiency
Neuropathic bladder
Unusual infecting organisms, such as tuberculosis, fungus, or urea-splitting organisms (e.g., *Proteus*)

Indications

Radiologic studies are unnecessary for evaluation of most women with genitourinary infections. Several reports of women patients with recurrent UTIs show that excretory urograms are unnecessary for routine evaluation if women who have special risk factors are excluded (Fair et al, 1979; Engel et al, 1980; Fowler and Pulaski, 1981; Fairchild et al, 1982). In none of these studies was information that was useful in the management of these patients obtained from excretory urograms. Furthermore, excluding excretory urograms in the routine evaluation of such patients represents a substantial financial saving.

However, in high-risk patients, including women with febrile infections and most men, radiologic studies may determine acute infectious processes that require further intervention or may find the cause of complicated infections.

First, radiologic procedures are needed in patients with risk factors that may require intervention in addition to antimicrobial treatment (Table 10–5).

A UTI associated with possible urinary tract obstruction must be evaluated. These are patients with calculi, especially infection (struvite) stones; ureteral tumors; ureteral strictures; congenital obstructions; or previous genitourinary surgery, such as ureteral reimplantation or urinary diversion procedures that may have caused obstruction. Patients with diabetes mellitus can develop special complications from UTIs; they may acquire emphysematous pyelonephritis or papillary necrosis. Impacted necrotic papillae may cause acute ureteral obstruction. Patients with polycystic kidney disease who are on dialysis are particularly prone to developing perinephric abscesses.

Urologic imaging is indicated in patients whose symptoms of acute clinical pyelonephritis persist after 5 to 6 days of appropriate antimicrobial therapy; they often have perinephric or renal abscesses. In addition, patients with unusual organisms, including urea-splitting organisms (e.g., *Proteus* species), should be examined for abnormalities within the urinary tract, such as obstructing stones, strictures, or fungus balls.

Table 10–6.

Correctable Urologic Abnormalities That Cause Bacterial Persistence

Infection stones
Chronic bacterial prostatitis
Unilateral infected atrophic kidneys
Ureteral duplication and ectopic ureters
Foreign bodies
Urethral diverticula and infected periurethral glands
Unilateral medullary sponge kidneys
Nonrefluxing, normal-appearing, infected ureteral stumps after nephrectomy
Infected urachal cysts
Infected communicating cysts of the renal calyces
Papillary necrosis
Perivesical abscess with fistula to bladder

The second reason for radiologic evaluation is to diagnose a focus of bacterial persistence. **In patients whose bacteriuria fails to resolve after appropriate antimicrobial therapy or who have rapid recurrence of infection, abnormalities that cause bacterial persistence should be sought.** Although these patients are uncommon, it is important to identify them because they may have correctable urologic abnormalities that represent the only surgically curable causes of recurrent UTIs. Acquired or congenital urologic abnormalities that can cause unresolved or recurrent UTIs are listed in Table 10–6.

Ultrasonography

The renal ultrasound study is an important renal imaging technique because it is noninvasive, easy to perform, and rapid and offers no radiation or contrast agent risk to the patient. It is particularly useful in identifying calculi and hydronephrosis, pyonephrosis, and perirenal abscesses. A single radiograph for calculi should accompany ultrasonography. Ultrasonography is also useful for diagnosing postvoid residual urine. A disadvantage is that the study is dependent on the interpretative and performance skills of the examiner. Furthermore, the study may be technically poor in patients who are obese or who have dressings, drainage tubes, or open wounds overlying the area of interest.

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

The radiologic modalities that offer the best anatomic detail are CT and MRI. They are more sensitive than excretory urography or ultrasonography in the diagnosis of acute focal bacterial nephritis, renal and perirenal abscesses, and radiolucent calculi (Kuhn and Berger, 1981; Mauro et al, 1982; Wadsworth et al, 1982; Soulen et al, 1989; Soler et al, 1997). When used to localize renal and perirenal abscesses, CT improves the approach to surgical drainage and permits percutaneous approaches. MRI has not superseded CT in the evaluation of renal inflammation, but it has provided some advantages in delineating extrarenal extension of inflammation.

Voiding Cystourethrography

The voiding cystourethrogram is an important examination in assessing vesicoureteral reflux. It may be used to evaluate patients with neuropathic bladders and the rare female patient who has a urethral diverticulum causing her persistent infections.

Radionuclide Studies

Hippuran I-131 and technetium-99m (^{99m}Tc) glucoheptonate scans are used to detect focal parenchymal damage, renal function impairment, and decreased renal perfusion in acute renal infections (McAfee, 1979). Although gallium-67 scanning has been reported to be useful in the diagnosis of pyelonephritis and renal abscess, it is uncommonly required and may be positive in noninfectious entities. Indium-111–labeled WBC studies have limited efficacy in establishing the presence of an inflammatory focus, particularly when the patient's clinical presentation does not suggest an infectious process.

Key Points: Imaging Techniques

- Imaging studies are not required in most women with UTIs.
- Men and compromised patients or those who do not respond to therapy require imaging to identify abnormalities.
- CT and MRI provide the best anatomic data on the site, cause, and extent of infection.

PRINCIPLES OF ANTIMICROBIAL THERAPY

Therapy for UTIs must ultimately eliminate bacterial growth in the urinary tract. This can occur within hours if the proper antimicrobial agent is used (Stamey, 1980). **Efficacy of the antimicrobial therapy is critically dependent on the antimicrobial levels in the urine and the duration that this level remains above the minimal inhibitory concentration of the infecting organism** (Hooton and Stamm, 1991). **Hence, resolution of infection is closely associated with the susceptibility of the bacteria to the concentration of the antimicrobial agent achieved in the urine** (McCabe and Jackson, 1965; Stamey et al, 1965, 1974). The concentration of useful antimicrobial agents in the serum and urine of healthy adults is shown in Table 10–7, which demonstrates that the urinary levels are often several hundred times greater than the serum levels. Inhibitory concentrations in urine are achieved after oral administration of all commonly used antimicrobial agents, except for the macrolides (erythromycin). The question of serum levels versus urinary levels is a practical one because the policy of testing antimicrobial susceptibility agents at concentrations obtainable only in the serum discourages the physician from using drugs that are effective at the urinary level; for example, oral penicillin G for *E. coli* and *Proteus mirabilis* and tetracycline for *P. aeruginosa*.

The concentration of the antimicrobial agent achieved in blood is not important in treatment of uncomplicated UTIs. However, blood levels are critical in patients with bacteremia and febrile urinary infections consistent with parenchymal involvement of the kidney and prostate.

In patients with renal insufficiency, dosage modifications are necessary for agents that are cleared primarily by the kidneys and cannot be cleared by another mechanism. In renal failure, the kidneys may not be able to concentrate

Table 10–7.

Serum and Urinary Antimicrobial Levels in Adults*

ANTIMICROBIAL AGENT	DOSE (mg)	PEAK SERUM LEVEL (mg/L)	PERCENTAGE BOUND TO PROTEIN	HALF-LIFE SERUM PEAK (hr)	MEAN (ACTIVE) URINE LEVELS* (g/mL)	DOSE EXCRETED IN URINE (%)	DOSE ACTIVE IN URINE (IF DIFFERENT) (%)
Ampicillin	250 PO qid	3 at 2 hr	15	1	350	42	–
Carbenicillin	764 PO qid	11-17 at 1.5 hr	60	1.2	1000	40	–
Cephalexin	250 PO qid	9 at 2 hr	12	0.9	800	98	–
Ciprofloxacin	500 PO bid	2.3 at 1.2 hr	35	3.9	200	30	–
Colistin	75 IM bid	1.8 at 4 hr	10	2	34	75	50
Gentamicin	1 mg/kg IM tid (200 mg/day)	4 at 1 hr	Negligible	2	125	80	–
Kanamycin	500 IM bid	18 at 1 hr	Negligible	2	750	94	–
Levofloxacin	500 mg PO qd	6.0 mg/L	30-50	6	N/A	95	95
Nalidixic acid	1000 PO qid	34 at 2-23 hr	85	1.5	75	79	5
Nitrofurantoin	100 PO qid	<2		0.3	150	42	–
Norfloxacin	400 PO bid	1.5 at 1.5 hr	15	3.3	170	27	–
Penicillin G	500 PO qid	1 at 1 hr	60	0.5	300	20	–
Sulfamethizole	250 PO qid		98	10	700	95	85
Tetracycline hydrochloride	250 PO qid	2-3 at 4 hr	31	6	500	60	–
TMP-SMX	160/800 PO bid	1.7/32 at 2 hr	45/66	10/9	150/400	55/50	–/37
Trimethoprim	100 PO bid	1.0 at 2-4 hr	45	10	92	55	–

TMP-SMX, trimethoprim-sulfamethoxazole.
*These average urinary concentrations are based on the amount of biologically active drug excreted by normal kidneys at a urine flow rate of 1200 mL/24 hr.
Modified from Stamey TA. The pathogenesis and treatment of urinary infections. Baltimore: Williams & Wilkins; 1980. p. 59.

an antimicrobial agent in the urine; hence, difficulty in eradicating bacteria may occur. Urinary tract obstruction may also reduce concentration of antimicrobial agents within the urine.

A decision regarding the antimicrobial selection and the duration of therapy must consider the spectrum of activity of the drug against the known pathogen or the most probable pathogens based on the presumed source of acquisition of infection, whether the infection is judged to be uncomplicated or complicated, potential adverse effects, and cost. An often underemphasized but important characteristic is the drug's impact on the bowel and vaginal flora and the hospital bacterial environment. Bacterial susceptibility will vary dramatically in patients exposed to antimicrobial agents and in individuals in inpatient and outpatient settings. It is imperative that each clinician keep abreast of changes that affect antimicrobial use and susceptibility patterns.

Bacterial Resistance

In the past several years, the frequency and spectrum of antimicrobial-resistant UTIs have increased in both the hospital and community. The increasing frequency of drug resistance has been attributed to combinations of microbial characteristics, bacterial selection pressure due to antimicrobial use, and societal and technologic changes that enhance the transmission of drug resistance (Cohen, 1992).

Bacterial resistance may occur because of inherited chromosomal-mediated resistance or by acquired chromosomal- or extrachromosomal (plasmid)-mediated resistance due to exposure of an organism to antimicrobial agents.

Inherited chromosomal resistance exists in a bacterial species because of the absence of the proper mechanism on which the antimicrobial agent can act. For example, *Proteus* and *Pseudomonas* species are always resistant to nitrofurantoin.

Acquired chromosomal resistance occurs during therapy for UTIs. Before antimicrobial therapy, relatively resistant bacteria called mutators may be present in the urine at very low concentrations. Frequencies in mutations for high-level antimicrobial resistance are 1000-fold higher in mutators than in normal strains, indicating the increased adaptability of these strains (Miller et al, 2004). The remainder of the bacteria, which are susceptible to the administered antimicrobial agent, will be eradicated by therapy, but within 24 to 48 hours a repeat urine culture will show high bacterial counts of the resistant mutant. In essence, the antimicrobial therapy has selected out the resistant mutant. This phenomenon is most likely to occur when the antimicrobial level in the urine is close to or below the minimal inhibitory concentration of the drug. **Selection of resistant clones in the course of therapy for a previously sensitive bacteriuric population occurs between 5% and 10% of the time, clearly not an insignificant factor and one that must be considered in resolving bacteriuria.** Underdosing and noncompliance, as well as diuresis induced by increased fluid intake, can contribute to this process. Therefore the clinician should select an antimicrobial agent with a urinary concentration that exceeds the minimal inhibitory concentration by the widest margin possible, avoid underdosing, and emphasize patient compliance.

Extrachromosomal-mediated resistance may be acquired and transferable via plasmids, which contain the genetic material for the resistance. **This so-called R-factor resistance occurs in the bowel flora and is much more common than selection of preexisting mutants in the urinary tract. All antimicrobial classes are capable of causing plasmid-mediated resistance. However, for the fluoroquinolones resistance is rarely transmitted by plasmids and nitrofurantoin plasmid-mediated resistance has not been reported.** Therefore patients previously exposed to β-lactams, aminoglycosides, sulfonamides, TMP, and tetracycline will often have R-factor resistance to both the antimicrobial agent to which

the bacteria were exposed and also to other antimicrobial agents. In addition, the plasmids carrying the resistant genetic material are transferable both within species and across genera. Thus, for example, a patient receiving tetracycline may harbor several bowel strains that are resistant to tetracycline, ampicillin, sulfonamides, and TMP. **Because the bowel flora is the major reservoir for bacteria that ultimately colonize the urinary tract, infections that occur after antimicrobial therapy and that can cause plasmid-mediated resistance are commonly caused by organisms with multidrug resistance. However, resistant *E. coli* in the bowel flora that infect the urinary tract almost always show susceptibility to nitrofurantoin or to the quinolones.**

Antimicrobial resistance is also influenced by the duration and amount of antimicrobial agent used. For example, documented increased use of fluoroquinolones in the hospital setting has been directly associated with increased resistance of bacteria (particularly *Pseudomonas*) to the fluoroquinolones. Resistance tends to increase the longer the agent is used. Conversely, reduction in duration of therapy and in the amount of the drug used may lead to reemergence of more susceptible strains.

Most studies reporting antimicrobial resistance have been based on surveys of laboratory isolates, generally without correlation with clinical or epidemiologic factors (e.g., the presence and nature of symptoms, age, sex, and whether the infection was complicated). Gupta and colleagues (1999) determined the prevalence of and trends in antimicrobial resistance among uropathogens isolated from a large, well-defined population of women with acute uncomplicated cystitis. Over a 5-year period, the prevalence of resistance to TMP/SMX, ampicillin, and cephalothin increased significantly, whereas resistance to nitrofurantoin and ciprofloxacin remained uncommon. **However, fluoroquinolone resistance of *E. coli* has increased from less than 1% to 10% in hospitalized patients** (Karlowsky et al, 2003). In a transplant unit, where fluoroquinolones are commonly administered prophylactically, *E.* coli resistance can be 80%. **Previous use of fluoroquinolones and the presence of underlying urologic diseases were the strongest determinants for UTIs caused by resistant strains** (Ena et al, 1995). Fluoroquinolone resistance is an increasing problem in some European countries. A multiple-resistant phenotype involving fluoroquinolone resistance is now present in most countries in Europe, and this phenotype is selected for not only by the use of quinolones but also by the use of ampicillin, sulfamethoxazole, and TMP/SMX (Kahlmeter and Menday, 2003). This is a concern because fluoroquinolones, which are associated with chromosomal-mediated but not plasmid-mediated resistance, are the current drug of choice for patients who have been exposed to agents causing plasmid-mediated resistance.

The clinical significance of these in-vitro trends in resistance has been addressed in studies that correlated in-vitro resistance to TMP/SMX with clinical outcome in uncomplicated cystitis and pyelonephritis (Gupta and Stamm, 2002). Clinical failures occurred in 40% to 50% of women if the bacteria were resistant and the bacteriologic failure approached 60%. (For further information on the role of TMP-SMX in prophylaxis, see Bladder Infections, later in this chapter.)

Antimicrobial Formulary

The mechanism of action, reliable coverage, and common adverse reactions, precautions, and contraindications for antimicrobial agents used in the treatment of UTIs are indicated in Tables 10–8, 10–9, and 10–10, respectively.

Table 10–8.

Mechanism of Action of Common Antimicrobials Used in the Treatment of UTIs

DRUG OR DRUG CLASS	MECHANISM OF ACTION	MECHANISMS OF DRUG RESISTANCE
β-Lactams (penicillins, cephalosporins, aztreonam)	Inhibition of bacterial cell wall synthesis	Production of β-lactamase Alteration in binding site of penicillin-binding protein Changes in cell wall porin size (decreased penetration)
Aminoglycosides	Inhibition of ribosomal protein synthesis	Downregulation of drug uptake into bacteria Bacterial production of aminoglycoside-modifying enzymes
Quinolones	Inhibition of bacterial DNA gyrase	Mutation in DNA gyrase-binding site Changes in cell wall porin size (decreased penetration) Active efflux
Nitrofurantoin	Inhibition of several bacterial enzyme systems	Not fully elucidated—develops slowly With prolonged exposure
Trimethoprim-sulfamethoxazole	Antagonism of bacterial folate metabolism	Draws folate from environment (enterococci)
Vancomycin	Inhibition of bacterial cell wall synthesis (at β-lactams)	Enzymatic alteration of peptidoglycan different point than target

Trimethoprim/Sulfamethoxazole

The combination of TMP-SMX has been the most widely used antimicrobial agent for the treatment of acute UTIs. TMP alone is as effective as the combination for most uncomplicated infections and may be associated with fewer side effects (Johnson and Stamm, 1989); however, the addition of SMX contributes to efficacy in the treatment of upper tract infection via a synergistic bactericidal effect and may diminish the emergence of resistance (Burman, 1986) and does attain therapeutic levels in most tissues. **TMP alone or in combination with SMX is effective against most common uropathogens, with the notable exception of *Enterococcus* and *Pseudomonas* species. TMP and TMP-SMX are inexpensive and have minimal adverse effects on the bowel flora. Disadvantages are relatively common adverse effects, consisting primarily of rashes and gastrointestinal complaints** (Cockerill and Edson, 1991). TMP-SMX should be avoided during pregnancy.

Nitrofurantoin

Nitrofurantoin is effective against common uropathogens, but it is not effective against *Pseudomonas* and

Table 10–9.

Reliable Coverage of Antimicrobials Used in the Treatment of UTIs of Commonly Encountered Pathogens*

ANTIMICROBIAL AGENT OR CLASS	GRAM-POSITIVE PATHOGENS	GRAM-NEGATIVE PATHOGENS
Amoxicillin or ampicillin	*Streptococcus* Enterococci	*Escherichia coli* *Proteus mirabilis*
Amoxicillin with clavulanate	*Streptococcus* Enterococci	*E. coli* *P. mirabilis* *Klebsiella* species
Ampicillin with sulbactam	*Staphylococcus* (not MRSA) Enterococci	*P. mirabilis* *Haemophilus influenzae, Klebsiella* species
Antistaphylococcal penicillins	*Streptococcus* *Staphylococcus* (not MRSA)	None
Antipseudomonal penicillins	*Streptococcus* Enterococci	Most, including *Pseudomonas aeruginosa*
First-generation cephalosporins	*Streptococcus* *Staphylococcus* (not MRSA)	*E. coli* *P. mirabilis* *Klebsiella* species
Second-generation cephalosporins (cefamandole, cefuroxime, cefaclor)	*Streptococcus* *Staphylococcus* (not MRSA)	*E. coli, P. mirabilis* *H. influenzae, Klebsiella* species
Second-generation cephalosporins (cefoxitin, cefotetan)	*Streptococcus*	*E. coli, Proteus* species (including indole-positive) *H. influenzae, Klebsiella* species
Third-generation cephalosporins (ceftriaxone)	*Streptococcus* *Staphylococcus* (not MRSA)	Most, excluding *P. aeruginosa*
Third-generation cephalosporins (ceftazidime)	*Streptococcus*	Most, including *P. aeruginosa*
Aztreonam	None	Most, including *P. aeruginosa*
Aminoglycosides	*Staphylococcus* (urine)	Most, including *P. aeruginosa*
Fluoroquinolones	*Streptococcus**	Most, including *P. aeruginosa*
Nitrofurantoin	*Staphylococcus* (not MRSA) Enterococci	Many Enterobacteriaceae (not *Providencia, Serratia, Acinetobacter*) *Klebsiella* species
Trimethoprim-sulfamethoxazole	*Streptococcus* *Staphylococcus*	Most Enterobacteriaceae (not *P. aeruginosa*)
Vancomycin	All, including MRSA	None

*Depends on the antimicrobial agent.
MRSA, methicillin-resistant *Staphylococcus aureus*.

***Proteus* species** (Iravani, 1991). **It is rapidly excreted from the urine but does not attain therapeutic levels in most body tissues, including the gastrointestinal tract. Therefore it is not useful for upper tract and complicated infections** (Wilhelm and Edson, 1987). **It has minimal effects on the resident bowel and vaginal flora and has been used effectively in prophylactic regimens for more than 40 years.** Acquired bacterial resistance to this drug is exceedingly low. Nitrofurantoin should be used only during the first two trimesters of pregnancy.

Cephalosporins

All three generations of cephalosporins have been used for the treatment of acute UTIs (Wilhelm and Edson, 1987). In general, as a group, activity is high against Enterobacteriaceae and poor against enterococci. First-generation cephalosporins have greater activity against gram-positive organisms as well as common uropathogens such as *E. coli* and *Klebsiella pneumoniae,* whereas second-generation cephalosporins have activity against anaerobes. Third-generation cephalosporins are more reliably active against community-acquired and nosocomial gram-negative organisms than other β-lactam antimicrobials. **Selective pressure engendered by these broad-spectrum agents should limit their use to complicated infections and situations in which parenteral therapy is required and resistance to standard antimicrobial agents is likely. They are also safe for use during pregnancy.**

Aminopenicillins

Ampicillin and amoxicillin have been used often in the past for the treatment of UTIs, but the emergence of resistance in 40% to 60% of common urinary isolates has lessened the usefulness of these drugs (Hooton and Stamm, 1991). The effects of these agents on the normal bowel and vaginal flora can predispose patients to reinfection with resistant strains and often lead to candidal vaginitis (Iravani, 1991). The addition of the β-lactamase inhibitor clavulanate to amoxicillin greatly improves activity against β-lactamase–producing bacteria resistant to amoxicillin alone. However, its high cost and frequent gastrointestinal side effects limit its usefulness. The extended-spectrum penicillin derivatives (e.g., piperacillin, mezlocillin, azlocillin) retain ampicillin's activity against enterococci and offer activity against many ampicillin-resistant gram-negative bacilli. **This makes them attractive agents for use in patients with nosocomially acquired UTIs and as the initial parenteral treatment of acute uncomplicated pyelonephritis acquired outside of the hospital, although less expensive agents are equally effective.**

Aminoglycosides

When combined with TMP-SMX or ampicillin, aminoglycosides are the first drugs of choice for febrile UTIs. Their nephrotoxicity and ototoxicity are well recognized; hence, careful monitoring of patients for renal

Table 10–10.

Common Adverse Reactions, Precautions, and Contraindications for Antimicrobial Agents Used in Treatment of UTI

DRUG OR DRUG CLASS	COMMON ADVERSE REACTIONS	PRECAUTIONS AND CONTRAINDICATIONS
Amoxicillin or ampicillin	Hypersensitivity (immediate or delayed) Diarrhea (esp. with ampicillin), GI upset AAPMC Maculopapular rash (not hypersensitivity) Decreased platelet aggregation	Increased risk of rash with concomitant viral disease, allopurinol therapy
Amoxicillin with clavulanic acid	Increased diarrhea, GI upset with amoxicillin/clavulanic acid	
Ampicillin with sulbactam	Same as amoxicillin with ampicillin	
Antistaphylococcal penicillins	Same as with amoxicillin/ampicillin GI upset (with oral agents) Acute interstitial nephritis (esp. with methicillin)	
Antipseudomonal penicillins	Same as with amoxicillin/ampicillin Hypernatremia (these drugs are given as sodium salt; esp. carbenicillin, ticarcillin) Local injection site reactions	Use with caution in patients very sensitive to sodium loading.
Cephalosporins	Hypersensitivity (less than with penicillins) GI upset (with oral agents) Local injection site reactions AAPMC Positive Coombs test Decreased platelet aggregation (esp. with cefotetan, cefamandole, cefoperazone)	Should not be used in patients with immediate hypersensitivity to penicillins; may use with caution in patients with delayed hypersensitivity reactions.
Aztreonam	Hypersensitivity (less than with penicillins)	Less than 1% incidence of cross reactivity in penicillin-or-cephalosporin-allergic patients; may be used with caution in these patients
Aminoglycosides	Ototoxicity: vestibular and auditory components Nephrotoxicity: nonoliguric azotemia Neuromuscular blockade with high levels	Avoid in pregnant patients. Avoid if possible in patients with severely impaired renal function, diabetes, or hepatic failure. Use with caution in myasthenia gravis patients (owing to potential for neuromuscular blockade). Use with caution with other potentially ototoxic and nephrotoxic drugs.
Fluoroquinolones	Mild GI effects; dizziness, lightheadedness; photosensitivity CNS effects, including dizziness, tremors, confusion, mood disorder, hallucinations Tendon rupture	Avoid in children or pregnant patients due to arthropathic effects. Concomitant antacid or iron or zinc or sucralfate use dramatically decreases oral absorption; use another antimicrobial agent or discontinue sucralfate use while on quinolones. Space administration of quinolones from antacids or iron or zinc products by at least 2 hr to ensure adequate absorption. Ensure adequate patient hydration. These agents can significantly increase theophylline plasma levels (ciprofloxacin and enoxacin seem to have a greater effect than norfloxacin or ofloxacin); avoid quinolones or monitor theophylline levels closely. These agents can lower seizure threshold; avoid in patients with epilepsy and in patients with other risk factors (medications or illness) that may lower the seizure threshold. Monitor glucose levels in patients on antidiabetic agents because hypoglycemia and hyperglycemia have been reported in patients treated concurrently with fluoroquinolones and antidiabetic agents. These agents can enhance warfarin effects; closely monitor coagulation tests.
Nitrofurantoin	GI upset Peripheral polyneuropathy (esp. in patients with impaired renal function, anemia, diabetes, electrolyte imbalance, vitamin B deficiency, and debilitated) Hemolysis in patients with G6PD deficiency Pulmonary hypersensitivity reactions can range from acute to chronic and include cough, dyspnea, fever, and interstitial changes	Do not use in patients with low creatinine clearance (<50 mL/min) because adequate urine concentrations will not be achieved. Monitor long-term patients closely. Avoid concomitant probenecid use, which blocks renal excretion of nitrofurantoin. Avoid concomitant magnesium or quinolones, which are antagonistic to nitrofurantoin.

Table 10–10.

Common Adverse Reactions, Precautions, and Contraindications for Antimicrobial Agents Used in Treatment of UTI—cont'd

DRUG OR DRUG CLASS	COMMON ADVERSE REACTIONS	PRECAUTIONS AND CONTRAINDICATIONS
Trimethoprim-sulfamethoxazole	Hypersensitivity, rash GI upset Photosensitivity Hematologic toxicity (AIDS patients)	Higher incidence of all adverse reactions occurs in AIDS patients and the elderly. Avoid in pregnant patients. Avoid in patients receiving warfarin; concomitant use can significantly elevate prothrombin time.
Vancomycin	"Red-man's syndrome": flushing, fever, chills, rash, hypotension (histaminic effect) Nephrotoxicity and/or ototoxicity when combined with other nephrotoxic and/or ototoxic drugs Local injection site reactions	Use with caution with other potentially ototoxic and nephrotoxic drugs.

AAPMC, antimicrobial-associated pseudomembranous colitis; CNS, central nervous system; GI, gastrointestinal; G6PD, glucose-6-phosphate dehydrogenase.
From McEvoy GK, editor. American Hospital Formulary Service Drug Information. Bethesda (MD): American Society of Health-System Pharmacists; 1995.

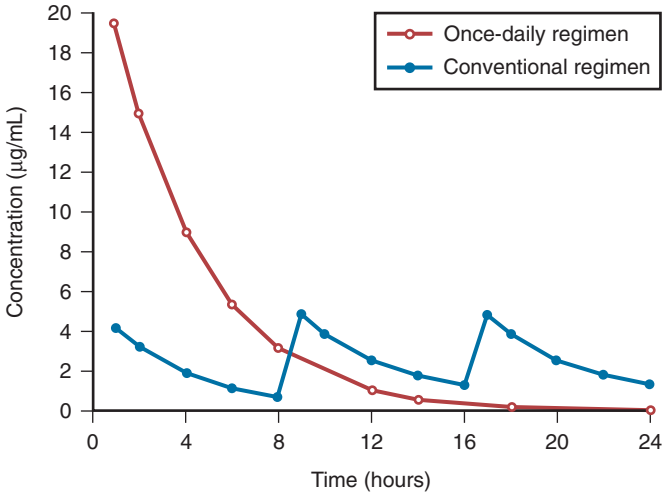


Figure 10–11. Simulated concentration-versus-time profile of once-daily (7 mg/kg/24 hr) and conventional (1.5 mg/kg/8 hr) regimens for patients with normal renal function. (From Nicolau DP, Freeman CD, Belliveau PP, et al. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother 1995;39:650–5.)

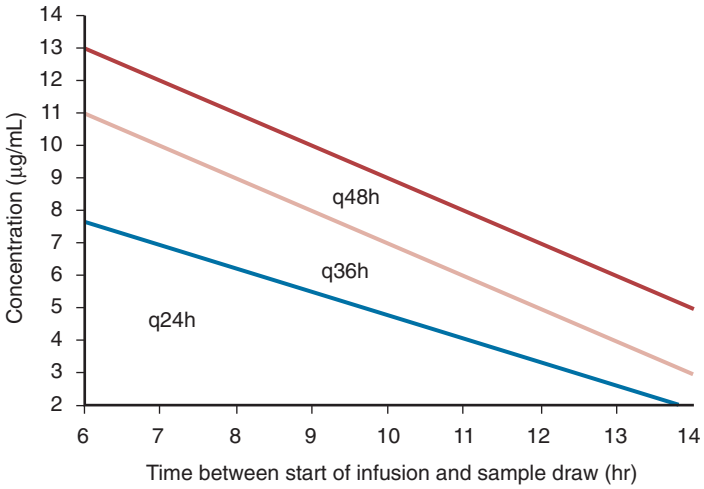


Figure 10–12. Once-daily aminoglycoside nomogram for gentamicin and tobramycin at 7 mg/kg. (From Nicolau DP, Freeman CD, Belliveau PP, et al. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother 1995;39:650–5.)

and auditory impairment associated with infection is indicated. Once-daily aminoglycoside regimens have been instituted to maximize bacterial killing by optimizing the peak concentration-to-minimal inhibitory concentration ratio and reduce potential for toxicity (Fig. 10–11) (Nicolau et al, 1995). Administering an aminoglycoside as a single daily dose can take advantage not only of its concentration-dependent killing ability but also of two other important characteristics: time-dependent toxicity and a more prolonged post-antimicrobial effect (Gilbert, 1991; Zhanel et al, 1991). The regimen consists of a fixed 7-mg/kg dose of gentamicin or 5 to 7 mg/kg of tobramycin. Subsequent interval adjustments are made by using a single concentration in serum and a nomogram designed for monitoring of once-daily therapy (Fig. 10–12). Antimicrobial doses are given at the interval determined by the drug concentration of a sample obtained after the start of the initial infusion. For example, if the serum concentration was 7 mg/mL 10 hours after the start of the infusion, subsequent 7 mg/kg doses would be given every 36 hours. This regimen is clinically effective, reduces the incidence of nephrotoxicity, and provides a cost-effective method for administering aminoglycosides by reducing ancillary service times and serum aminoglycoside determinations.

Aztreonam

Aztreonam has a similar spectrum of activity as the aminoglycosides, and as with all β-lactams, it is not nephrotoxic. However, its spectrum of activity is less broad than the third-generation cephalosporins. **It should be used primarily in patients who have penicillin allergies.**

Fluoroquinolones

Fluoroquinolones share a common predecessor in nalidixic acid and inhibit DNA gyrase, a bacterial enzyme integral to replication. The fluoroquinolones have a broad spectrum of activity that makes them ideal for the empirical treatment of UTIs. **They are highly effective against Enterobacteriaceae as well as *P. aeruginosa*. Activity is also high against *S. aureus* and *S. saprophyticus*, but, in general, antistreptococcal coverage is marginal.** Most anaerobic bacteria are resistant to these

drugs; therefore the normal vaginal and bowel flora are not altered (Wright et al, 1993). **Bacterial resistance initially appeared to be uncommon, but it is being reported at an increasing rate because of indiscriminate use of these agents** (Wright et al, 1993; Vromen et al, 1999).

These drugs are not nephrotoxic, but renal insufficiency prolongs the serum half-life, requiring adjusted dosing in patients with creatinine clearances of less than 30 mL/min. Adverse reactions are uncommon; gastrointestinal disturbances are more common. Hypersensitivity, skin reactions, mild central and peripheral nervous system reactions, and even acute renal failure have been reported (Hootkins et al, 1989). Achilles tendon disorders, including rupture, have been estimated to occur in 20 cases per 100,000 and therefore fluoroquinolone use should be discontinued at the first sign of tendon pain (Greene, 2002). The mechanism of tendon rupture is unclear, but ciprofloxacin stimulates matrix-degrading protease activity from fibroblasts and exerts an inhibitory effect on fibroblast metabolism and synthesis of matrix ground substance, factors that may contribute to tendinopathy (Williams et al, 2000). Administration of the fluoroquinolones to immature animals has caused damage to the developing cartilage; therefore they are currently contraindicated in children, adolescents, and pregnant or nursing women (Christ et al, 1988). There are important drug interactions associated with the fluoroquinolones. Antacids containing magnesium or aluminum interfere with absorption of fluoroquinolones (Davies and Maesen, 1989). Certain fluoroquinolones (enoxacin and ciprofloxacin) elevate plasma levels of theophylline and prolong its half-life (Wright et al, 1993). For most uncomplicated UTIs, the fluoroquinolones have been only slightly more effective than TMP-SMX. However, as resistance to TMP-SMX increases, the fluoroquinolones have distinct advantages in empirical treatment of patients recently exposed to antimicrobial agents and in the outpatient treatment of complicated UTIs (Dalkin and Schaeffer, 1988; Gupta et al, 1999). They may be considered as first-line agents in areas where a significant level of resistance (greater than 20%) exists (in common bacteria) to agents such as ampicillin and TMP-SMX.

Choice of Antimicrobial Agents

Many antimicrobial agents have been shown to be effective in the treatment of UTIs. **Factors important in aiding selection of empirical therapy include whether the infection is complicated or uncomplicated; the spectrum of activity of the drug against the probable pathogen; a history of hypersensitivity; potential side effects, including renal and hepatic toxicity; and cost.** In addition, favorable or unfavorable effects of the antimicrobial agent on the vaginal and bowel flora are important in women with recurrent UTIs. The bacterial susceptibility and cost of the drug vary dramatically among inpatient and outpatient settings throughout the country. It is imperative, therefore, that each clinician keep abreast of changes in bacterial susceptibility and cost and use current information when choosing antimicrobial agents.

Duration of Therapy

The duration of therapy needed to cure a UTI appears to be related to a number of variables, including the extent and duration of tissue invasion, the bacterial concentration in urine, the achievable urine concentration of the antimicrobial agent, and risk factors (see later) that impair the host and natural defense mechanisms.

Key Points: Principles of Antimicrobial Therapy

- Effective antimicrobial therapy must eliminate bacterial growth in the urinary tract.
- Antimicrobial resistance is increasing because of excessive utilization.
- Antimicrobial selection should be influenced by efficacy, safety, cost, and compliance.

ANTIMICROBIAL PROPHYLAXIS FOR COMMON UROLOGIC PROCEDURES

Principles

Surgical antimicrobial prophylaxis entails treatment with an antimicrobial agent before and for a *limited* time after a procedure to prevent local or systemic postprocedural infections. For most procedures, prophylaxis should be initiated between 30 minutes and 120 minutes before the procedure (Bratzler and Houck, 2004). **Efficacious levels should be maintained for the duration of the procedure and, in special circumstances, a limited time (24 hours, at most) after the procedure** (Bratzler and Houck, 2004). Although prospective studies addressing prophylaxis for urologic procedures exist, most focus on only a narrow spectrum of procedures. However, application of the principles of these studies with additional consideration of both the patient and the type of procedure provides a framework for determining when and what type of antimicrobial prophylaxis may be indicated. An additional, nontraditional type of prophylaxis in urology entails periprocedural treatment of the urinary tract with an antimicrobial agent to prevent local or systemic sequelae from the manipulation of colonized hardware such as a stent or urethral catheter.

A wide array of patients undergo invasive procedures in urology. The ability of a host to respond to bacteriuria or bacteremia and the sequelae of a possible infection are two important considerations when assessing the need for antimicrobial prophylaxis. Factors that affect the host's ability to respond to infection include advanced age, anatomic anomalies, poor nutritional status, smoking, chronic corticosteroid use, other concurrent medication use, and immunodeficiencies such as untreated HIV infection (Table 10–11). Additionally, chronic indwelling hardware, infected endogenous material such as stones, distant infectious sites, and prolonged hospitalizations also increase the risk of infectious complications by increasing the local bacterial concentration and/or altering the spectrum of bacterial flora. The potential seeding of artificial heart valves or prosthetic joints increases the sequelae of a systemic infection in hosts who otherwise may not be at an increased risk of infection. Thus a thorough history and examination of the patient is crucial in directing antimicrobial prophylaxis before a urologic procedure.

The type of procedure will also help direct the timing, duration, and spectrum of antimicrobial prophylaxis needed (see Table 10–12 for a summary of antimicrobial prophylaxis

Table 10–11.

Host Factors That Increase the Risk of Infection

Advanced age
Anatomic anomalies
Poor nutritional status
Smoking
Chronic corticosteroid use
Immunodeficiency
Chronic indwelling hardware
Infected endogenous/exogenous material
Distant coexistent infection
Prolonged hospitalization

Data from Cruse PJ. Surgical wound infection. In: Wonsiewicz MJ, editor. Infectious disease. Philadelphia: WB Saunders; 1992. p. 758–64; and Mangram AJ et al. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1999;20:250–78; quiz 279–80.

recommendations). Consideration should be given to the extent of the local tissue injury incurred and the anticipated type of flora at the site.

Antimicrobial prophylaxis is not without morbidity because allergic complications, although rare, may result in minor reactions such as rash or gastric disturbances or significant sequelae such as early withdrawal of therapy, allergic nephritis, or anaphylaxis.

Urethral Catheterization and Removal

The indications for the routine use of prophylactic antimicrobial agents before urethral catheterization vary and depend on the health, sex, and specific living circumstances of the individual patient as well as on the indication for catheterization (Schaeffer, 2006). **The risk of infection after one-time urethral catheterization is 1% to 2% in healthy domiciliary women; however, this risk rises significantly in hospitalized patients** (Turck et al, 1962; Thiel and Spuhler, 1965). Thus for patients with risk factors for infection (see Table 10–11), antimicrobial prophylaxis with an oral agent such as TMP-SMX or a fluoroquinolone should decrease the risk of postprocedural infection (see Table 10–12).

Prolonged use of an indwelling urethral catheter is common in hospitalized patients and is associated with an increased risk of bacterial colonization, with a 3% to 10% incidence of bacteriuria per catheter day in one study and 100% incidence of bacteriuria with long-term catheterization (>30 days) (Kass, 1956; Nickel et al, 1985; Liedl, 2001). Prophylactic administration of antimicrobial agents during catheterization is not generally recommended because bacterial resistance can develop rapidly and complicate subsequent antimicrobial treatment (Clarke et al, 2005). This is supported by the Cochrane Database of Systematic Reviews that concluded that antimicrobials given postprocedurally until removal or for the first three postoperative days did not reduce rates of bacteriuria or infection (Niël-weise and Van der Broek, 2005).

The natural history of bacteriuria after catheter removal has not been comprehensively studied. Harding and associates (1991) reported that in asymptomatic bacteriuric women who had been catheterized for 4 to 6 days, 25% developed a UTI within 14 days of catheter removal. In this study, 1-day treatment with TMP-SMX was as effective as a 10-day course at resolving infections. Similar studies on the natural history of postcatheterization bacteriuria have not been performed in male patients. Note that antimicrobial treatment before removal of an indwelling catheter in a patient suspected of having bacteriuria is not considered prophylaxis but rather is treatment for a presumptive UTI and duration of treatment generally should follow previously outlined guidelines for uncomplicated or complicated UTIs.

Data from Polastri and colleagues (1990) suggest that antimicrobial prophylaxis for chronic indwelling catheter changes is not indicated. In their study of 46 catheter changes, bacteremia occurred 4% of the time and when noted was associated with very low concentrations of bacteria in the cultures. Systemic sequelae were not noted.

Urodynamics

Urodynamics, like cystoscopy, is a minimally traumatic procedure with limited urothelial injury that poses a small risk of local infection in hosts with normal anatomy and immune response. Several recent studies support this notion. In a series of women with urinary incontinence randomized to receive 1 day of nitrofurantoin or placebo, Cundiff and coworkers (1999) noted no difference in postprocedural UTI (5% vs. 7%) 1 week after evaluation. Similarly, Peschers and associates (2001) reported infections 1 week after multichannel urodynamics in 5% and 6% in nondiabetic women treated with placebo or cotrimoxazole. Conversely, Kartal and colleagues (2006) demonstrated a reduction in UTIs from 14% to 1% with administration of a single dose of ciprofloxacin in a blinded 192 patient trial. Most series examining the use of antimicrobial prophylaxis exclude patients with altered anatomy such as large prostates or comorbidities, including neurogenic bladder, spinal cord injury, or diabetes, all factors that increase the risk of infection. This is illustrated in work performed by Payne and colleagues in which frequencies of bacteriuria after urodynamics were much higher in men (36%) compared with the women studied (15%) (Payne et al, 1988). **In sum, antimicrobial prophylaxis should be considered for patients with a more complex clinical history or anatomy such as men with large postvoid residual amounts or spinal cord–injured patients.**

Transrectal Ultrasound-Guided Prostate Biopsy

The use of prophylactic antimicrobials for transrectal ultrasound-guided prostate biopsy reduces postprocedural fever and UTI in most studies. The class and duration of antimicrobial treatment are more varied and controversial. One major population-based screening program reported fever (>38.5° C [101.3° F]) in 3.5% of cases utilizing 1 day of TMP-SMX for most cases and ciprofloxacin for patients with comorbid conditions. This series did not report the frequency of UTIs. Alternatively, Sieber and associates (1997) reported a 0.1% rate of UTI in a large community-based practice in men given 4 days of ciprofloxacin. More recent studies suggest a single-dose/day of fluoroquinolones is as effective as 3 days of treatment (Sabbagh et al, 2004). Together these data suggest that a minimum of 1 day of an antimicrobial agent is indicated for transrectal ultrasound-guided prostate biopsies and that in otherwise healthy men confounding factors including cost of drugs can help direct the class and duration of therapy (Griffith et al, 2002).

Table 10–12.

Guide for Antimicrobial Prophylaxis for Uncomplicated Urologic Procedures

PROCEDURE	ORGANISMS	PROPHYLAXIS INDICATED	ANTIMICROBIAL(S) OF CHOICE	ALTERNATIVE ANTIMICROBIAL(S)	DURATION OF THERAPY*
Lower Tract Instrumentation					
Removal of external urinary catheter	GU tract†	If risk factors§	Fluoroquinolone TMP-SMX¶	Aminoglycoside ± ampicillin 1st/2nd gen. cephalosporin¶	≤24 hr¶
Cystography, urodynamic study, or simple cystourethroscopy	GU tract	If risk factors§	Fluoroquinolone TMP-SMX	Amoxicillin/clavulanate Aminoglycoside ± ampicillin 1st/2nd gen. cephalosporin	≤24 hr
Cystourethroscopy with manipulation‖	GU tract	All	Fluoroquinolone TMP-SMX	Amoxicillin/clavulanate	≤24 hr
Prostate brachytherapy or cryotherapy	Skin	Uncertain	1st gen. cephalosporin	Aminoglycoside ± ampicillin 1st/2nd gen. cephalosporin Amoxicillin/clavulanate Clindamycin**	≤24 hr
Transrectal prostate biopsy	Intestine††	All	Fluoroquinolone	Aminoglycoside ± metronidazole or clindamycin**	≤24 hr
Upper Tract Instrumentation					
Shock-wave lithotripsy	GU tract	All	Fluoroquinolone TMP-SMX	Aminoglycoside ± ampicillin 1st/2nd gen. cephalosporin	≤24 hr
Percutaneous renal surgery	GU tract and skin‡‡	All	1st/2nd gen. cephalosporin Aminoglycoside + metronidazole or clindamycin	Amoxicillin/clavulanate Ampicillin/sulbactam Fluoroquinolone	≤24 hr
Ureteroscopy	GU tract	All	Fluoroquinolone TMP-SMX	Aminoglycoside ± ampicillin 1st/2nd gen. cephalosporin Amoxicillin/clavulanate	≤24 hr
Open or Laparoscopic Surgery					
Vaginal surgery	GU tract, skin, and group B *Streptococcus*	All	1st/2nd gen. cephalosporin Aminoglycoside + metronidazole or clindamycin	Ampicillin/sulbactam	≤24 hr
Without entering urinary tract	Skin	If risk factors	1st gen. cephalosporin	Fluoroquinolone	Single dose
Involving entry into urinary tract	GU tract and skin	All	1st/2nd gen. cephalosporin Aminoglycoside + metronidazole or clindamycin	Clindamycin	≤24 hr
Involving intestine§§	GU tract, skin, and intestine	All	2nd/3rd gen. cephalosporin Aminoglycoside + metronidazole or clindamycin	Ampicillin/sulbactam Fluoroquinolone	≤24 hr
Involving implanted prosthesis	GU tract and skin	All	Aminoglycoside + 1st/2nd gen. cephalosporin or vancomycin	Ampicillin/sulbactam Ticarcillin/clavulanate Piperacillin/tazobactam Fluoroquinolone Ampicillin/sulbactam Ticarcillin/clavulanate Piperacillin/tazobactam	≤24 hr

Order of agents in each column is not indicative of preference. The absence of an agent does not preclude its appropriate use depending on specific situations.
*Additional antimicrobial therapy may be recommended at the time of removal of an externalized urinary catheter.
†GU tract: Common urinary tract organisms are *E. coli, Proteus* species, *Klebsiella* species, *Enterococcus.*
§If urine culture shows no growth before the procedure, antimicrobial prophylaxis is not necessary.
¶Or full course of culture-directed antimicrobial agents for documented infection (which is treatment, not prophylaxis).
‖Includes transurethral resection of bladder tumor and prostate, and any biopsy, resection, fulguration, foreign body removal, urethral dilation or urethrotomy, or ureteral instrumentation including catheterization or stent placement/removal.
**Clindamycin or an aminoglycoside + metronidazole or clindamycin is an alternative to penicillins and cephalosporins in patients with penicillin allergy, even when not specifically listed.
††Intestine: common intestinal organisms are *E. coli, Klebsiella* species, *Enterobacter, Serratia* species, *Proteus* species, *Enterococcus,* and anaerobes.
‡‡Skin: common skin organisms are *S. aureus,* coagulase negative *Staphylococcus* species, group A *Streptococcus* species.
§§For surgery involving the colon, bowel preparation with oral neomycin plus either erythromycin base or metronidazole can be added to or substituted for systemic agents.
gen, generation; GU, genitourinary; TMP-SMX, trimethoprim-sulfamethoxazole.
Drug doses: ampicillin, 25 mg/kg/dose; gentamicin, 1.5 mg/kg/dose; cefazolin, 25 mg/kg/dose.
Adapted from Wolf JS, Bennett CJ, Dmochowski RR, et al. Best practice statement on urologic surgery antimicrobial prophylaxis. J Urol 2008;179:1379–90.

Shockwave Lithotripsy

The incidence of UTIs after shockwave lithotripsy is reported to range from 0% to 28% without antimicrobial prophylaxis. A recent meta-analysis of contemporary randomized controlled trials examined the utility and cost-effectiveness of antimicrobial prophylaxis for shockwave lithotripsy and demonstrated, in individuals with sterile preprocedure urine cultures, a reduction in the rate of UTIs after shockwave lithotripsy from 5.7% to 2.1% (Pearle and Roehrborn, 1997). This analysis also demonstrated cost-effectiveness of prophylaxis when consideration was given for the treatment of the rare but more morbid complications of urosepsis and pyelonephritis. A history of a recent UTI or of infectious stones should warrant a full treatment course of antimicrobial agents before shockwave lithotripsy.

Endoscopic Procedures: Lower Urinary Tract

Cystoscopy

Cystoscopy is a minimally traumatic procedure with limited urothelial injury performed on a diverse spectrum of patients including young healthy women and older men. Several prospective trials (Manson, 1988; Clark and Higgs, 1990; Burke et al, 2002) of patients with preprocedure sterile urine report culture-proven rates of UTI between 2.2% and 7.8% after cystoscopy without antimicrobial prophylaxis. In Clark's report the risk of infection was higher in patients with a previous history of UTI. In a similarly designed study, Rane and colleagues (2001) report a significantly higher postprocedure culture-proven infection rate of 21% without antimicrobial prophylaxis. More recently, Johnson and colleagues (2007) reported a randomized controlled trial of over 2000 patients that demonstrated reductions in bacteriuria with administration of single-dose trimethoprim or ciprofloxacin. In all the studies, single doses of antimicrobial agents reduced infections to between 1% and 5%. In none of these studies were significant systemic infections reported after the cystoscopic procedures.

Together these studies illustrate two key concepts: (1) despite appropriate periprocedural preparation, a small inoculum of bacteria is likely introduced into the bladder during cystoscopy and (2) the significance of the bacteriuria is dependent on host factors, including the ability to mount an appropriate immune response to bacterial inoculation and the ability to clear the bacterial inoculation. For example, in a man with urinary retention, a small inoculum of bacteria could persist and divide in the retained fraction of urine and result in a symptomatic infection. In a host with a reduced ability to respond to infection this bacteriuria could become significant. In contrast, a middle-aged woman undergoing cystoscopy for microscopic hematuria is more likely to efficiently empty her bladder and clear the inoculum but may be exposed to an increased inoculum of bacteria if inappropriately prepared for the examination. **Thus we recommend prophylaxis when aberrant host factors could increase the probability or significance of an infection** (see Table 10–12). A single dose of a fluoroquinolone is commonly used but other agents such as trimethoprim have also been utilized.

Transurethral Resection of the Prostate and Bladder

Therapeutic transurethral lower urinary tract procedures increase the risk of localized infections compared with simple diagnostic cystoscopy. Although not delineated in any prospective studies, several risk factors likely increase infectious complications, including trauma to the mucosa, increased duration and/or degree of difficulty of the procedure, pressurized irrigants, and manipulation or resection of infected material. The most well-studied lower urinary tract procedure is transurethral resection of the prostate. In a meta-analysis of 32 studies (Berry and Barratt, 2002), a risk reduction was noted in bacteriuria from 26% to 9% on postoperative urine cultures obtained 2 to 5 days after the procedure for patients treated with prophylactic antimicrobial agents. Similarly, septicemia (defined as rigors, persistently elevated temperature [>38.5° C], and an elevated C-reactive protein level) decreased from 4.4% to 0.9% with antimicrobial prophylaxis. The most effective antimicrobial classes included fluoroquinolones, aminoglycosides, cephalosporins, and TMP/SMX (Bactrim, cotrimoxazole). Single doses of antimicrobial agents did lower the relative risk of bacteriuria but not as significantly as antimicrobial agents administered for short courses (2 to 5 days) while the urethral catheter remained in place. Although continuation of antimicrobial therapy while the catheter is in place is not truly prophylaxis, continuation of the initial prophylactic antimicrobial agent for an anticipated short period of time (with catheter in place) does not increase the risk of developing antimicrobial-resistant organisms. No recent trials have investigated prophylaxis for transurethral resection of bladder tumors; however, evidence from transurethral resection of the prostate procedures would suggest that prophylaxis would reduce bacteriuria in these procedures.

Patients who are known preoperatively to have UTIs should have the infections eradicated before the procedure is started; hence, in these patients, preoperative antimicrobial agents are therapeutic and not prophylactic. Failure to eradicate bacteriuria results in bacteremia in 50% of patients (Morris et al, 1976).

Diagnostic and therapeutic upper tract studies are performed with pressurized irrigants and may induce urothelial injury. Prophylaxis with antimicrobial agents that cover uropathogens is indicated.

Endoscopic Procedures: Upper Urinary Tract

Ureteroscopy

Diagnostic and therapeutic upper tract endoscopic procedures have an increased risk of localized infections compared with simple diagnostic cystoscopy due to several factors, including increased trauma to the mucosa, increased duration and/or degree of difficulty of most ureteroscopic procedures, increased pressure of irrigants, and (when applicable) manipulation or resection of infected material. The use of antimicrobial prophylaxis is supported by a randomized trial by Knopf and colleagues (2003) in which prophylactic fluoroquinolone administration significantly reduced postprocedure UTIs in a healthy population of individuals with ureteral stones and uninfected preoperative urine. If an infection or infectious material is suspected, culture and a full treatment course of an appropriate antimicrobial is recommended before the procedure.

Percutaneous Procedures

Percutaneous renal surgery is commonly performed for large renal stones, ureteropelvic junction obstruction, and transitional cell carcinoma surveillance. Pyrexia and bacteremia occur frequently and likely stem from a combination of renal parenchymal injury, pressurized irrigation, and, in some cases, manipulation of

infectious stones. Several studies demonstrated a relationship between the risk of postoperative infectious complications (including bacteriuria and sepsis) and the duration of the procedure and amount of irrigant used (Dogan et al, 2002). If preoperative urine cultures are positive, treatment of the infection should occur before surgery. Conversely, if preoperative cultures are negative, antimicrobial prophylaxis covering common urinary pathogens should be instituted (Wolf et al, 2008) (see Table 10–12).

Open and Laparoscopic Surgery

Open surgical procedures can be classified as clean, clean contaminated, contaminated, and dirty (Table 10–13). **Antimicrobial prophylaxis is indicated for clean contaminated and contaminated wounds, whereas antimicrobial treatment with an appropriate agent should be instituted for dirty-infected wounds.** To date, no large studies have evaluated the risk of surgical site infections for different laparoscopic urologic procedures. However, data in the general surgery literature suggest that the laparoscopic approach lowers the risk of surgical site infections (Kluytmans, 1997). Clean surgeries in urology include radical nephrectomy if the urinary tract is not entered. All urologic procedures in which the urinary tract is opened electively are considered clean contaminated procedures, whereas entry into an infected urinary tract is considered a contaminated procedure and carries a higher rate of surgical site infection (Cruse, 1992). Antimicrobial agents should be active against the most likely infecting organism and should be administered within 1 hour of the procedure and discontinued 24 hours after because several studies have failed to demonstrate beneficial effects of long courses of prophylaxis (Conte et al, 1972; Goldmann et al, 1977). In the United States, first-generation cephalosporins are commonly used for prophylaxis of clean contaminated procedures because they have low incidences of allergic reactions, long half-lives, and low cost. For patients with a β-lactam allergy, the 2004 National Surgical Infection Prevention Project (NSIPP) guidelines recommend either vancomycin or clindamycin. Prophylaxis for urinary reconstruction with intestine requires increased anaerobic coverage, and thus use of second-generation cephalosporins is recommended (Bratzler and Houck, 2004). When use of the colon or appendix is anticipated for urologic reconstruction, the 2004 NSIPP recommendations include orally administered antimicrobial bowel preparation (neomycin plus erythromycin or neomycin plus metronidazole) 18 to 24 hours before surgery and parenteral cefotetan or cefoxitin 30 to 60 minutes before incision (Bratzler and Houck, 2004). Recommendations for patients with a β-lactam allergy include clindamycin plus gentamicin, aztreonam, or ciprofloxacin. Dirty wounds in urology include all abscesses and traumatic perforation of the genitourinary tract. Treatment of a dirty wound should begin with broad coverage of anticipated organisms and intraoperative wound cultures. Subsequent therapy and treatment duration depends on the sensitivities of the cultured organism.

Table 10–13.

Surgical Wound Classification

Clean	Uninfected wound without inflammation or entry into the genital, urinary, or alimentary tract Primary wound closure ± closed drainage
Clean contaminated	Uninfected wound with controlled entry into the genital, urinary, or alimentary tract Primary wound closure ± closed drainage
Contaminated	Uninfected wound with major break in sterile technique (gross spillage from gastrointestinal tract or nonpurulent inflammation) Open fresh accidental wounds
Dirty infected	Wound with preexisting clinical infection or perforated viscera Old traumatic wounds with devitalized tissue

Adapted from Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1999;20:250–78; quiz 279–80.

Special Considerations

Patients with Risk of Endocarditis

The risk of endocarditis after urologic procedures is low; however, the urinary tract is the second most common site of entry of organisms that cause endocarditis (Dajani et al, 1997). **Nonetheless, the 2007 American Heart Association's updated guidelines no longer recommend antimicrobial prophylaxis solely to prevent infectious endocarditis.** This recommendation is based on an overall assessment that antimicrobial prophylaxis during genitourinary procedures is not an effective strategy for the prevention of infectious endocarditis and is outweighed by the risk of antimicrobial-related adverse events.

Patients with Indwelling Orthopedic Hardware

Bacterial seeding of implanted orthopedic hardware is a rare but morbid event. A joint commission of the American Urological Association, the American Academy of Orthopaedic Surgeons, and infectious disease specialists convened in 2003 and released an advisory statement on antimicrobial prophylaxis for urologic patients with total joint replacement (American Urological Association and American Academy of Orthopaedic Surgeons, 2003) (Table 10–14). **In general, antimicrobial prophylaxis for urologic patients with total joint replacements, pins, plates, or screws is not indicated. Prophylaxis is advised for individuals at higher risk of seeding a prosthetic joint, including those with recently inserted implants**

Table 10–14.

Antimicrobial Regimens for Patients with Indwelling Orthopedic Hardware

PATIENT TYPE	ANTIMICROBIAL RECOMMENDATION
Total joint inserted >2 years ago, pins, plates, screws + no host risk factors	Not recommended empirically
Total joint inserted <2 years ago or aberrant host factor(s)	Oral quinolone or ampicillin, 2 g IV + gentamicin, 1.5 mg/kg IV, 30-60 min before procedure Substitute vancomycin, 1 g IV, over 1-2 hr before procedure if ampicillin allergy

From American Urological Association, American Academy of Orthopaedic Surgeons. Antibiotic prophylaxis for urological patients with total joint replacements. J Urol 2003;169:1796–7.

(within 2 years) and/or host risk factors as delineated earlier. Prophylaxis on the basis of potential seeding of a prosthetic joint should be instituted for procedures including stone manipulation, transmural incision of the urinary tract, upper tract endoscopic procedures, procedures involving bowel segments, and transrectal prostate biopsy. Additionally, patients with recent prosthetic joints or compromised host factors and urinary diversions, indwelling stents or catheters, a recent history of urinary retention, or UTIs should receive antimicrobial prophylaxis before urinary tract procedures. The AUA Advisory Statement recommends for these patients either an oral quinolone or ampicillin, 2 g IV (vancomycin, 1 g IV over 1 to 2 hours for ampicillin-allergic patients), and gentamicin, 1.5 mg/kg IV, 30 to 60 minutes before the procedure.

Key Points: Antimicrobial Prophylaxis for Common Urologic Procedures

- Antimicrobial prophylaxis entails treatment with an antimicrobial agent before and for a limited time after a procedure to prevent local or systemic postprocedural infections.
- The type of procedure and competency of the host defenses determine the need for antimicrobial prophylaxis.
- Special considerations for antimicrobial prophylaxis include patients with indwelling orthopedic hardware.

Table 10–15.

Risk Factors for UTIs

Reduced Urine Flow
Outflow obstruction, prostatic hyperplasia, prostatic carcinoma, urethral stricture, foreign body (calculus)
Neurogenic bladder
Inadequate fluid uptake (dehydration)
Promote Colonization
Sexual activity—increased inoculation
Spermicide—increased binding
Estrogen depletion—increased binding
Antimicrobial agents—decreased indigenous flora
Facilitate Ascent
Catheterization
Urinary incontinence
Fecal incontinence
Residual urine with ischemia of bladder wall

BLADDER INFECTIONS

Uncomplicated Cystitis

Most cases of uncomplicated cystitis occur in women. Each year, approximately 10% of women report having had a UTI and more than 50% of all women have at least one such infection in their lifetime (Foxman et al, 2000). Uncomplicated cystitis occasionally occurs in prepubertal girls, but it increases greatly in incidence in late adolescence and during the second and fourth decades of life. Twenty-five to 30 percent of women 20 to 40 years of age have a history of UTIs (Kunin, 1987). **Although it is much less common, young men may also experience acute cystitis without underlying structural or functional abnormalities of the urinary tract** (Krieger et al, 1993). Risk factors (Table 10–15) include sexual intercourse and use of spermicides (Hooton et al, 1996; Foxman, 2002; Handley et al, 2002). Sexual transmission of uropathogens has been suggested by demonstrating identical *E. coli* in the bowel and urinary flora of sex partners (Johnson and Stamm, 1989).

Clinical Presentation

The presenting symptoms of cystitis are variable but usually include dysuria, frequency, and/or urgency (Fig. 10–13). **Suprapubic pain, hematuria, or foul-smelling urine may develop. The probability of cystitis in a woman with these symptoms alone or in combination is 50% to 90%, respectively** (Bent et al, 2002). When a woman who previously has had cystitis has symptoms suggesting a recurrence, the probability that an infection is present is about 90% (Gupta et al, 2001). Because acute cystitis, by definition, is a superficial infection of bladder mucosa, fever, chills, and other signs of dissemination are not present. Some patients may experience suprapubic tenderness, but most have no diagnostic physical findings. In women, physical examination should include the possibility of vaginitis, herpes, and urethral pathology, such as a diverticulum.

A remarkably narrow spectrum of etiologic agents with highly predictable profiles of antimicrobial susceptibility cause infections in young women with acute uncomplicated cystitis. ***E. coli* is the causative organism in 75% to 90% of cases of acute cystitis in young women** (Latham et al, 1983; Ronald, 2002). ***S. saprophyticus*, a commensal organism of the skin, is the second most common cause of acute cystitis in young women, accounting for 10% to 20% of these infections** (Jordan et al, 1980). **Other organisms less commonly involved include *Klebsiella* and *Proteus* species and *Enterococcus*. In men, *E. coli* and other Enterobacteriaceae are the most commonly identified organisms.**

Laboratory Diagnosis

The presumptive laboratory diagnosis of acute cystitis is based on microscopic urinalysis, which indicates microscopic pyuria, bacteriuria, and hematuria. Indirect dipstick tests for bacteria (nitrite) or pyuria (leukocyte esterase) may also be informative and more convenient but are less sensitive than microscopic examination of the urine. Dipsticks are most accurate when the presence of either nitrite or leukocyte esterase is considered a positive result. **Urine culture remains the definitive test; and in symptomatic patients the presence of 10^2 cfu/mL or more of urine usually indicates infection** (Stamm et al, 1982b).

However, routine urine cultures are often not necessary. It is generally more cost-effective to manage many patients who have symptoms and urinalysis findings characteristic of uncomplicated cystitis without an initial urine culture because treatment decisions are usually made and therapy is often completed before culture results are known (Komaroff, 1986). This position was supported by a cost-effectiveness study (Carlson and Mulley, 1985) in which it was estimated that the routine use of pretherapeutic urine cultures for lower UTI increases costs by 40% but decreases the overall duration of symptoms by only 10%.

Thus in women with recent onset of symptoms and signs suggesting acute cystitis and in whom factors associated with upper tract or complicated infection are absent, a urinalysis that is positive for pyuria, bacteriuria, or hematuria, or a combination, should provide

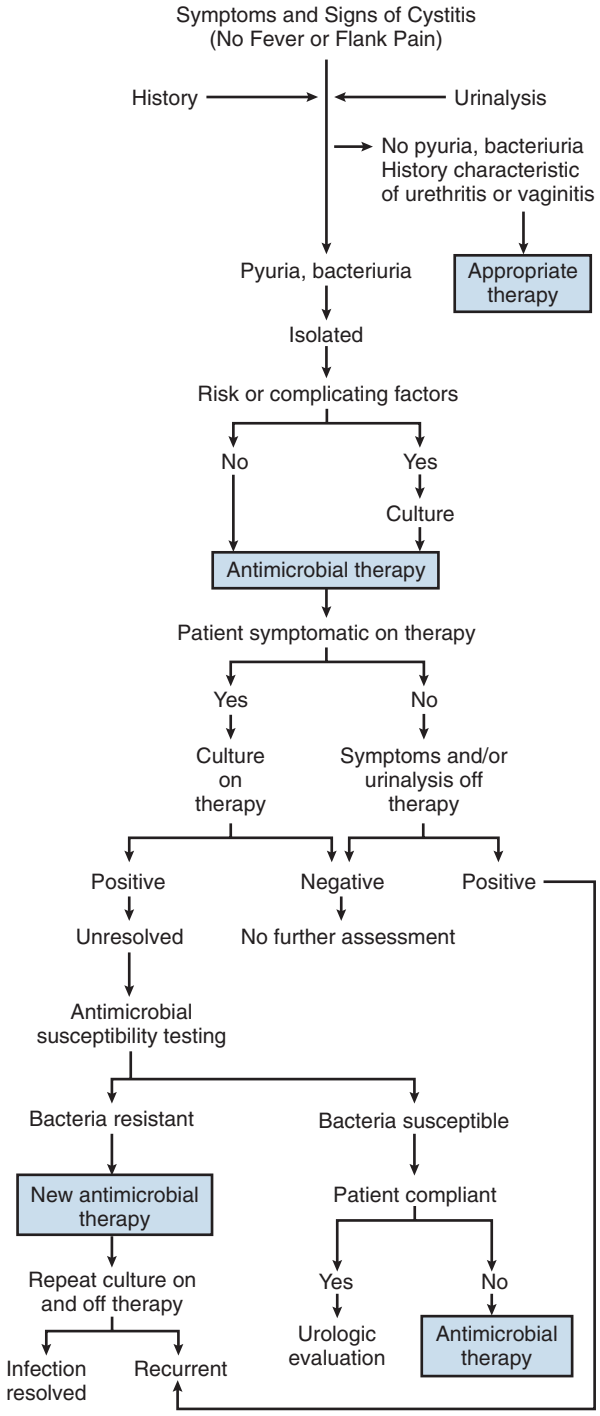


Figure 10–13. Management of acute cystitis.

sufficient documentation of UTI and a urine culture may be omitted (McIsaac et al, 2002). **A urine culture should be obtained for patients in whom symptoms and urine examination findings leave the diagnosis of cystitis in doubt. Pretherapeutic cultures and susceptibility tests are also essential in the management of patients with recent antimicrobial therapy or UTI.** In these situations, various pathogens may be present and antimicrobial therapy is less predictable and must be tailored to the individual organism (Stamm, 1986).

Differential Diagnosis

Cystitis must be differentiated from other inflammatory infectious conditions in which dysuria may be the most prominent symptom, including vaginitis, urethral infections caused by sexually transmitted pathogens, and miscellaneous noninflammatory causes of urethral discomfort (Komaroff, 1984). Characteristic features of the history, physical examination, and voided urine or other specimens allow patients with dysuria to be assigned to one of these diagnostic categories. Vaginitis is characterized by irritative voiding associated with vaginal irritation and is subacute in onset. A history of vaginal discharge or odor and multiple or new sexual partners is common. Frequency, urgency, hematuria, and suprapubic pain are not present. Physical examination reveals a vaginal discharge, and examination of vaginal fluid demonstrates inflammatory cells. Differential diagnosis includes herpes simplex virus infection, gonorrhea, infection with *Chlamydia,* trichomoniasis, yeast infection, and bacterial vaginosis. Urethritis causes dysuria that is usually subacute in onset and is associated with a history of discharge and new or multiple sexual partners. Frequency and urgency of urination may be present but are less pronounced than in patients with cystitis, and fever and chills are absent. Urethral discharge with inflammatory cells or initial pyuria in the male is characteristic. The common causes of urethritis include Neisseria gonorrhoeae, *Chlamydia,* herpes simplex virus, and trichomoniasis. Appropriate cultures and immunologic tests are indicated. Urethral injury associated with sexual intercourse, chemical irritants, or allergy may also cause dysuria. A history of trauma or exposure to irritants and a lack of discharge or pyuria are characteristic.

Management

Antimicrobial Selection. Oral antimicrobial agents for treatment of acute uncomplicated cystitis are listed in Table 10–16. **TMP and TMP-SMX are effective and inexpensive agents for empirical therapy,** resulting in bacteriologic cure (i.e., eradication of the pathogen from the urine) within 7 days after the start of treatment in approximately 94% of women (Warren et al, 1999). **They are recommended in areas where the prevalence of resistance to these drugs among *E. coli* strains causing cystitis is less than 20%** (Warren et al, 1999). The probability of resistant strains can be predicted in part from the history of recent antimicrobial usage. Women who have taken TMP-SMX recently are approximately 16 times as likely to be infected with an isolate resistant to this agent compared with women who have not taken the antimicrobial agent recently. In addition, those who have taken any other antimicrobial agent are more than twice as likely to be infected with a resistant isolate (Brown et al, 2002). With a 30% rate of resistance to TMP-SMX, the bacteriologic eradication rate is predicted to be 80% and the clinical cure rate is predicted to be 85% (Gupta et al, 2001). When used alone, TMP is as efficacious as TMP-SMX and is associated with fewer side effects, presumably because of the absence of the sulfa component (Harbord and Gruneberg, 1981). It can be prescribed to patients who are allergic to sulfa. However, TMP can cause hypersensitivity and rashes that may be erroneously attributed to sulfa (Alonso et al, 1992).

Nitrofurantoin has maintained an excellent level of activity over 4 decades and is well tolerated, but it is more expensive than TMP-SMX and it is considerably less active against aerobic gram-negative rods other than *E. coli*. Furthermore, it is usually prescribed for 7 days and may cause

Table 10–16.

Treatment Regimens for Acute Cystitis

CIRCUMSTANCES	ROUTE	DRUG	DOSAGE (mg)	FREQUENCY PER DOSE	DURATION (DAYS)	COST PER DAY*
Women						
Healthy	Oral	Ciprofloxacin	500 mg	bid	3	$0.50
		Levofloxacin	500 mg	qd		$5.07
		TMP-SMX	1 double-strength tablet (160-800 mg)	bid		$0.26
		Trimethoprim	100 mg	bid		$1.32
		Nitrofurantoin macrocrystals	100 mg	bid		$3.24
		Norfloxacin	400 mg	bid		
Symptoms for >7 days, recent UTI, age >65 yr, diabetes, diaphragm use		TMP-SMX or Fluoroquinolone	As above	As above	7	As above
Pregnancy	Oral	Amoxicillin	250 mg	tid	7	$0.68
		Cephalexin	500 mg	qid		$1.76
		Nitrofurantoin macrocrystals	As above	As above		As above
		TMP-SMX*	As above	As above		As above
Men						
Healthy and age <50 yr	Oral	TMP-SMX	As above	As above	7	As above
		Fluoroquinolone	As above	As above		As above

*Use of TMP-SMX during the first trimester of pregnancy is cautioned because there is early potential for teratogenicity and late potential for kernicterus after delivery.
From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY et al, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 211–72.

gastrointestinal upset. It is not associated with plasmid-mediated resistance, however, so it is an excellent choice for patients with recent exposure to most other antimicrobial agents. The high in-vitro resistance to ampicillin and sulfonamide and the high cost of amoxicillin/clavulanate and the cephalosporins limit their usefulness.

The fluoroquinolones offer excellent activity and are well tolerated. Resistance to the fluoroquinolones remains below 5% in most places (Fihn et al, 1988); however, it is increasing in certain areas. Twice-daily and once-daily extended-release fluoroquinolones are equally effective (Henry et al, 2002). Their use for uncomplicated cystitis should be limited to patients with allergy to TMP-SMX, to patients with previous exposure to antimicrobial agents causing bacterial resistance, and to areas where the prevalence of resistance to TMP or TMP-SMX is 20% or greater (Warren et al, 1999; Hooton et al, 2004).

The effects of an antimicrobial agent on the vaginal flora are also important in recurrence of bacteriuria (Fihn et al, 1988). The concentrations of TMP and the fluoroquinolones that have been studied in vaginal secretions are high, eradicating *E. coli* but minimally altering normal anaerobic and microaerophilic vaginal flora (Hooton and Stamm, 1991). Single-dose regimens using these drugs are less effective than multiple-day regimens in this regard (Fihn et al, 1988), which probably explains why there are more early recurrent infections after single-dose therapy with these drugs. Nitrofurantoin and β-lactam drugs are generally not effective in eliminating *E. coli* from the vagina.

Duration of Therapy. **Three-day therapy is the preferred regimen for uncomplicated cystitis in women** (Norrby, 1990; Warren et al, 1999). In an excellent review of more than 300 separate clinical trials of single-dose, 3-day, or 7-day treatment with TMP, TMP-SMX, fluoroquinolones, and β-lactam antimicrobial therapies, it was concluded that, irrespective of the antimicrobial used, 3-day therapy is more effective than single-dose therapy. Three-day therapy with TMP-SMX, TMP, amoxicillin, or cloxacillin has been associated with cure rates similar to longer courses of therapy and an incidence of adverse effects about as low as that seen with single-dose therapy and lower than seen with longer courses of therapy (Charlton et al, 1976; Kunin, 1985; McCue, 1986; Warren et al, 1999). Because 7-day therapy often causes more adverse effects, it is recommended only for women with symptoms of 1 week or more, men, and individuals with possible complicating factors. Other options include nitrofurantoin, perhaps as 7-day therapy, and fosfomycin single-dose therapy; each of these requires further study. β-Lactams as a group are less effective in treatment of cystitis than TMP, TMP-SMX, and the fluoroquinolones.

Seven-day therapy is the preferred regimen in uncomplicated cystitis in men.

Cost of Therapy. **The cost of treating a UTI involves not only the initial evaluation and cost of the drug but also what occurs subsequently. The most important prediction of high cost-effectiveness is high efficacy against the most common urinary pathogen, *E. coli*.** The lower the effectiveness against this bacterium, the greater the number of revisits, cases of progression to pyelonephritis, and follow-up costs. Antimicrobial cost is a poor prediction of cost-effectiveness, as illustrated by the finding that the most expensive and least expensive drugs, the fluoroquinolones and TMP-SMX, are approximately equally cost-effective (Rosenberg, 1999). Both of these drugs are more cost-effective than nitrofurantoin and amoxicillin.

Follow-Up

Approximately 90% of women are asymptomatic within 72 hours after initiating antimicrobial therapy (Fihn et al, 1988). **Follow-up visit or culture is not required in young women who are asymptomatic after therapy. A follow-up visit, urinalysis, and urine culture are recommended in older women or those with potential risk factors and in men. Urologic evaluation is unnecessary in women and is usually unnecessary in young men who respond to therapy** (Lipsky, 1989; Abarbanel et al, 2003). **However, UTIs in most men should be considered**

complicated until proven otherwise. Andrews and associates (2002) showed that approximately 50% of men with UTIs have a significant abnormality. Furthermore, if a patient does not respond to therapy, appropriate microbiologic urologic evaluations should be undertaken for the causes of unresolved and complicated UTIs.

Asymptomatic Bacteriuria

Asymptomatic bacteriuria is a microbiologic diagnosis based on the isolation of a specified quantitative count of bacteria in a properly collected specimen of urine from a patient who is without symptoms or signs referable to UTI. In healthy individuals, the absence of symptoms is clear cut, but in, for example, catheterized or neurologically comprised patients it may be difficult to discern whether the UTI is truly asymptomatic. Kass (1962) originally proposed that for asymptomatic women two consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts of 10^5 cfu/mL is consistent with asymptomatic bacteriuria. In men, a single clean-catch voided specimen with similar counts is adequate. A single catheterized urine specimen with a solitary isolate with a quantitative count of 10^2 cfu/mL identifies bacteriuria in women or men (Nicolle et al, 2005). The prevalence of pyuria with asymptomatic bacteriuria ranges from approximately 30% in young women (Hooton et al, 2000) to 100% in catheterized patients. In addition, many coexisting factors, such as stones, can incite inflammation in these patients and therefore the presence or absence of pyuria is not sufficient to diagnose bacteriuria nor does it differentiate symptomatic from asymptomatic patients or provide indication for antimicrobial treatment (Nicolle et al, 2005).

The prevalence of asymptomatic bacteriuria varies widely and depends on the age, sex, and the presence of other genitourinary abnormalities (Table 10–17). *E. coli* is the most common isolate among patients with bacteriuria, and it contains fewer virulence characteristics than isolates from patients with symptomatic infections (Svanborg and Godaly, 1997). Other Enterobacteriaceae (e.g., *P. mirabilis*) and gram-positive uropathogens, including group B streptococci and coagulase-negative staphylococci, become more prevalent in concert with increased underlying abnormalities. For patients who are institutionalized and/or with indwelling urologic devices, *P. aeruginosa*, *Proteus,* and other highly resistant organisms are more prevalent.

Management of asymptomatic bacteriuria is determined by the population and their risk for adverse outcome, which can be prevented with antimicrobial treatment of asymptomatic bacteriuria (Nicolle et al, 2005) (Table 10–18). **These recommendations are based on the observation that in adult populations asymptomatic bacteriuria has not been shown to be harmful.** Furthermore, although persons with bacteriuria are at increased risk of symptomatic urinary tractions, treatment of asymptomatic bacteriuria does not decrease the frequency of symptomatic infections or improve other outcomes. **Thus, in populations other than those for whom treatment has been documented to be beneficial (e.g., pregnant women and patients undergoing urologic interventions), screening for or treatment of asymptomatic bacteriuria is not appropriate and should be discouraged** (Nicolle et al, 2005).

Table 10–17.

Prevalence of Asymptomatic Bacteriuria in Selected Populations

POPULATION	PREVALENCE (%)	REFERENCE
Healthy, premenopausal women	1.0-5.0	Nicolle, 2003
Pregnant women	1.9-9.5	Nicolle, 2003
Postmenopausal women aged 50-70 years	2.8-8.6	Nicolle, 2003
Diabetic patients		
Women	9.0-27	Zhanel, 1991
Men	0.7-11	Zhanel, 1991
Elderly persons in the community		
Women	10.8-16	Nicolle, 2003
Men	3.6-19	Nicolle, 2003
Elderly persons in a long-term care facility		
Women	25-50	Nicolle, 1997
Men	14-50	Nicolle, 1997
Patients with spinal cord injuries		
Intermittent catheter use	23-89	Bakke and Digranes, 1991
Sphincterotomy and condom catheter in place	57	Waites, 1993
Patients undergoing hemodialysis	28	Chaudhry, 1993
Patients with indwelling catheter use		
Short-term	9-23	Stamm, 1991
Long-term	100	Warren, 1982

From Nicolle LE, Bradley S, Colgan R, et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis 2005;40:643–54.

Table 10–18.

Screening for and Treatment of Asymptomatic Bacteriuria

Premenopausal nonpregnant women	Not recommended
Pregnant women	Recommended
Diabetic women	Not recommended
Older persons residing in the community	Not recommended
Elderly institutionalized subjects	Not recommended
Subjects with spinal cord injuries	Not recommended
Patients with indwelling urethral catheters	Not recommended
Note: Antimicrobial treatment of asymptomatic women with catheter-associated bacteriuria that persists 48 hours after catheter removal may be considered.	
Urologic interventions	Recommended
Immunocompromised patients and transplant patients	Not recommended

From Nicolle LE, Bradley S, Colgan R, et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis 2005;40:643–54.

Complicated Cystitis

Complicated UTIs are those that occur in a patient with a compromised urinary tract or that are caused by a very resistant pathogen (Table 10–19). **These complicating factors may be readily apparent from the severity of the presenting illness or the past medical history. However, they may not be obvious at first and may only become evident from subsequent failure of the patient to respond to appropriate therapy** (see discussion on unresolved or recurrent UTIs, later).

Table 10–19.

Complicating Host Factors

Functional/structural abnormalities of urinary tract
Recent urinary tract instrumentation
Recent antimicrobial agent use
Diabetes mellitus
Immunosuppression
Pregnancy
Hospital-acquired infection

Table 10–20.

Treatment of Complicated UTIs

COMMON PATHOGENS	MITIGATING CIRCUMSTANCES	RECOMMENDED EMPIRICAL TREATMENT
E. coli, Proteus species, *Klebsiella* species, *Pseudomonas* species,	Mild-to-moderate illness, no nausea or vomiting—outpatient therapy	Oral* norfloxacin, ciprofloxacin, or ofloxacin for 10-14 days
Serratia species, enterococci, staphylococci	Severe illness or possible urosepsis—hospitalization required	Parenteral† ampicillin and gentamicin, ciprofloxacin, levofloxacin, ceftriaxone, aztreonam, ticarcillin-clavulanate or imipenem-cilastin until fever gone; then oral* trimethoprim-sulfamethoxazole, norfloxacin, ciprofloxacin, or levofloxacin for 14-21 days

*Oral regimens for pyelonephritis and complicated UTI: trimethoprim-sulfamethoxazole, 160 to 800 mg q12h; norfloxacin, 400 mg q12h; ciprofloxacin, 500 mg q12h; levofloxacin, 500 mg/day.

†Parenteral regimens: ciprofloxacin, 400 mg q12h; levofloxacin, 500 mg/day; gentamicin, 1 mg/kg q8h; ceftriaxone, 1 to 2 g/day; ampicillin, 1 g q6h; imipenem-cilastin, 250 to 500 mg q6-8h; ticarcillin-clavulanate, 3.1 g q6h; and aztreonam, 1 g q8-12h.

Modified from Stamm WE, Hooton TM. Management of urinary tract infections in adults. N Engl J Med 1993;329:1328–34. Copyright 1993, Massachusetts Medical Society. All rights reserved.

The clinical spectrum ranges from mild cystitis to life-threatening kidney infections and urosepsis (kidney infections and urosepsis are discussed subsequently). These infections can be caused by a broad range of bacteria with resistance to multiple antimicrobial agents. Therefore urine cultures are mandatory to identify the bacteria and its antimicrobial susceptibility.

Because of the wide range of host conditions and pathogens and a lack of adequate controlled trials, guidelines for empirical therapy are limited. For patients with mild to moderate illness who can be treated as an outpatient with oral therapy, the fluoroquinolones provide a broad spectrum of activity with excellent urine and tissue levels and safety. If the susceptibility pattern of the pathogen is known, TMP-SMX may be effective (Table 10–20).

For patients requiring hospitalization, intravenous antimicrobial agents should be administered based on the susceptibility patterns of the known uropathogens at that institution.

Because therapy will be compromised without addressing the complicating factor(s), every effort should be made to correct any underlying urinary tract abnormalities and treat host factors that exacerbate the infection.

Therapy is usually continued for 10 to 14 days and switched from parenteral to oral therapy when the patient is afebrile and clinically stable. Repeat urine cultures should be performed if the patient fails to respond to therapy.

Table 10–21.

Causes of Unresolved Bacteriuria, in Descending Order of Importance

Bacterial resistance to the drug selected for treatment
Development of resistance from initially susceptible bacteria
Bacteriuria caused by two different bacterial species with mutually exclusive susceptibilities
Rapid reinfection with a new, resistant species during initial therapy for the original susceptible organism
Azotemia
Papillary necrosis from analgesic abuse
Giant staghorn calculi in which the "critical mass" of susceptible bacteria is too great for antimicrobial inhibition
Self-inflicted infections or deception in taking antimicrobial drugs (a variant of Munchausen syndrome)

Unresolved UTIs

Clinical Presentation

Unresolved infection indicates that initial therapy has been inadequate in eliminating symptoms and/or bacterial growth in the urinary tract. If the symptoms of UTI do not resolve by the end of treatment or if symptoms recur shortly after therapy, urinalysis and urine culture with susceptibility testing should be obtained. If the patient's symptoms are significant, empirical therapy with a fluoroquinolone is appropriate pending results of the culture and susceptibility testing.

The causes of unresolved bacteriuria during antimicrobial therapy are shown in Table 10–21. **Most commonly, the bacteria are resistant to the antimicrobial agent selected to treat the infection.** Typically, the patient has received the antimicrobial therapy in the recent past and developed bowel colonization with resistant bacteria. β-Lactams, tetracycline, and sulfonamides are notorious for causing plasmid-mediated R factors that simultaneously carry resistance to multiple antimicrobial agents. **The second most common cause is development of resistance in a previously susceptible population of bacteria during the course of treatment of UTIs. This problem occurs in approximately 5% of the patients receiving antimicrobial therapy. It is easy to recognize clinically because the culture on therapy shows that the previous susceptible population has been replaced by resistant bacteria of the same species.** It can be shown that resistant organisms were actually present before contact with the initial antimicrobial agent, but they were present in such low numbers that it was impossible to detect by in-vitro susceptibility studies before therapy. When the antimicrobial concentration in the urine is insufficient to kill all the bacteria present, the more resistant forms will emerge. This characteristically is seen in patients who are underdosed or who are poorly compliant and hence have inadequate dose regimens. **The third cause is the**

presence of an unsuspected, second pathogen that was present initially and is resistant to the antimicrobial therapy chosen. Treatment of the dominant organism unmasks the presence of the second strain. **The fourth cause is rapid reintroduction of a new resistant species while the patient is undergoing initial therapy.** Rapid reinfection that mimics unresolved bacteriuria should alert the clinician to the possibility of an enterovesical fistula.

If the culture obtained on therapy shows that the initial species is still present and susceptible to the antimicrobial chosen to treat the infection, the unresolved infection must be caused by either inability to deliver an adequate concentration of antimicrobial agents into the urinary tract or an excessive number of bacteria that "override" the antimicrobial activity. In patients with azotemia, a determination of urinary antimicrobial concentrations usually shows that the level of the drug is below the minimal inhibitory concentration of the infecting organism.

In patients with papillary necrosis, severe defects in the medullary concentrating ability dilute the antimicrobial agent. A large mass of bacteria within the urinary tract is most commonly associated with a giant staghorn calculus. Even though adequate urinary levels of bactericidal drugs are present, the concentration is inadequate to sterilize the urine. This occurs because even susceptible bacteria cannot be inhibited once they reach a certain critical density, particularly if attached to a foreign body.

The last cause of unresolved bacteriuria occurs in those patients who have variants of Munchausen syndrome. These patients secretly inoculate their bladders with uropathogens or omit their oral antimicrobial agents while steadfastly asserting that they never miss a dose. The patient with Munchausen syndrome presents with an inconsistent clinical history and invariably a normal urinary tract on urologic imaging. Careful bacteriologic observations usually indicate the implausibility of the clinical picture.

Laboratory Diagnosis

Urinalysis and urine culture are mandatory to determine the cause of unresolved bacteriuria. The first four causes that are associated with resistant bacteria require no further evaluation. However, if reculture shows that the bacteria is sensitive to the antimicrobial agent the patient is taking, renal function and radiologic evaluation should be performed to identify renal or urinary tract abnormalities.

Management

Initial empirical antimicrobial selection should be based on the assumption that the bacteria are resistant. Therefore an antimicrobial agent different from the original agent should be selected. Fluoroquinolones offer excellent coverage in most cases and should be given for 7 days. When the bacterial susceptibilities are available, adjustments can be made if necessary. Urine cultures should be performed during and 7 days after therapy to ensure microbiologic efficacy.

Recurrent UTIs

Recurrent UTIs are caused by either reemergence of bacteria from a site within the urinary tract (bacterial persistence) or new infections from bacteria outside the urinary tract (reinfection). Clinical identification of these two types of recurrence is based on the pattern of recurrent infections (Fig. 10–14). **Bacterial persistence must be caused by the same organism in each instance, and infections that occur at close intervals are characteristic. Conversely, reinfections usually occur at varying and sometimes long intervals and often are caused by different species. The distinction between bacterial persistence and reinfection is important in management because patients with bacterial persistence can usually be cured of the recurrent infections by identification and surgical removal or correction of the focus of infection. Conversely, women with reinfection usually do not have an alterable urologic abnormality and require long-term medical management. Reinfections in men are uncommon and may be associated with an underlying abnormality, such as urethral stricture; therefore, at a minimum, endoscopic evaluation is indicated.**

Bacterial Persistence

Once the bacteriuria has resolved (i.e., the urine shows no growth for several days after the antimicrobial agent has been stopped), recurrence with the same organism can arise from a site *within* the urinary tract that was excluded from the high urine concentrations of the

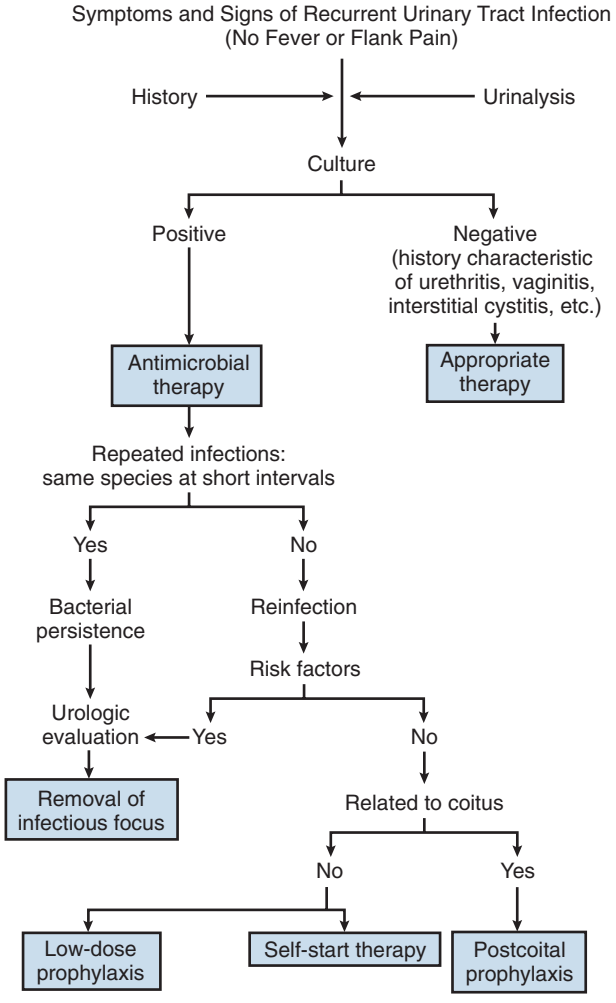


Figure 10–14. Management of recurrent UTI.

antimicrobial agent. The 12 correctable urologic abnormalities that cause bacteria to persist within the urinary tract between episodes of recurrent bacteriuria are listed in Table 10–6. The relationship of these abnormalities to bacterial persistence, as well as the documentation that surgical excision removes the infection as a source of recurrent bacteriuria, is presented elsewhere in detail (Stamey, 1980). Once the urologist recognizes that the cause of the patient's recurrent bacteriuria is bacterial persistence, Table 10–6 should serve as a checklist for known, correctable causes. Some of the causes are subtle, and many require cystoscopic localization of the infection with ureteral catheters to accurately define the focus of bacterial persistence.

Although patients with bacterial persistence are relatively uncommon, their identification is important because they represent the only surgically curable cause of recurrent UTIs. A systematic radiologic and endoscopic evaluation of the urinary tract is mandatory. CT and cystoscopy provide the initial screening. Retrograde urography may be required in selected patients to delineate abnormalities, such as diverticulum or nonrefluxing ureteral stump.

Urea-Splitting Bacteria That Cause Struvite Renal Stones. The infection that ultimately leads to an infection stone commonly begins inconspicuously as inadequately treated cystitis. Most patients with *P. mirabilis* cystitis do not form struvite stones. But struvite stones form in those patients who have a protracted infection with *P. mirabilis*, an infection that is often asymptomatic or minimally symptomatic. *P. mirabilis* causes intense alkalinization of the urine with precipitation of calcium, magnesium, ammonium, and phosphate salts and the subsequent formation of branched struvite renal stones. Bacteriuria in most of these patients with struvite stones recurs almost immediately on stopping antimicrobial therapy, usually within 5 to 7 days. The bacteriologic consequences are substantial because the bacteria persist inside these struvite stones even when the urine shows no growth. Indeed, struvite infection stones, together with the occasional oxalate or apatite stone that becomes secondarily colonized, constitute the major cause of bacterial persistence in women in the absence of azotemia.

Underlying urinary tract abnormalities are not a prerequisite for this type of infection. However, patients with indwelling catheters, urinary diversions, or other urinary tract abnormalities are particularly susceptible to these infections. Urea-splitting organisms, such as *P. mirabilis,* cause infection stones that are relatively radiolucent. If such a stone is suspected, plain film tomograms or CT scans without contrast medium enhancement should be obtained (Greenberg et al, 1982). Medical management with continued suppressive antimicrobial therapy and acidification temporarily relieves symptoms and retards deterioration of renal function in some patients. Complete removal of the calculus is generally required for bacteriologic cure and to prevent renal damage due to obstruction (Silverman and Stamey, 1983). Percutaneous nephrolithotomy and extracorporeal shockwave lithotripsy are now the preferred treatment for most renal and upper ureteral calculi.

When extracorporeal shockwave lithotripsy is used to fragment infection stones, the patient should be maintained on appropriate antimicrobial therapy until the fragments pass. Occasionally, long-term antimicrobial therapy can result in eradication of bacteriuria even if some fragments persist after lithotripsy, presumably because the shockwaves have rendered the entrapped bacteria more susceptible to antimicrobial therapy (Michaels et al, 1988). **If percutaneous or open surgery is used, all the residual particles of struvite stones must be removed at surgery to prevent recurrent bacteriuria from bacterial persistence in the calculus.** Rocha and Santos (1969) have shown that soaking these stones in iodine and alcohol for 6 hours will not kill the bacteria within the interior of the stone. **The importance of recognizing this fact is twofold: (1) The bacteria cannot be killed by antimicrobial therapy, even though the urine may show no growth for months or even years** (Shortliffe et al, 1984), **and (2) any fragments left behind at the time of surgical removal leave residual bacteria within the interstices of the stone; these bacteria ensure recurrence of the staghorn calculus with its attendant morbidity.**

If fragments remain after surgery, a small, multiholed polyethylene catheter should be left for postoperative irrigation with Renacidin or Suby G solution (Silverman and Stamey, 1983). Follow-up radiographs are essential to ensure that all the stone fragments are removed, and cultures must demonstrate that the urease-splitting bacteria are eradicated.

Most of the other congenital or acquired abnormalities listed in Table 10–6 require surgical removal for eradication of the source of bacterial persistence. Chronic bacterial prostatitis is treated initially with long-term antimicrobial therapy and, in select cases, by radical transurethral resection (Mears, 1978).

In patients in whom the focus of infection cannot be eradicated, long-term, low-dose antimicrobial suppression is necessary to prevent symptoms of infection. The antimicrobial drugs used for low-dose prophylaxis will also be effective for bacterial suppression if the persistent strain is susceptible. These include nitrofurantoin, TMP-SMX, cephalexin, and the fluoroquinolones.

Reinfections

Patients with recurrent infections caused by different species or occurring at long intervals almost invariably have reinfections. These reinfections most often occur in women and girls and are associated with ascending colonization from the bowel flora. Reinfections in men are often associated with a urinary tract abnormality. The possibility of a vesicoenteric or vesicovaginal fistula should be considered when the patient has any history of pneumaturia, fecaluria, diverticulitis, obstipation, previous pelvic surgery, or radiation therapy. **Evaluation of the patient with presumed reinfections must be individualized.**

Failure to recognize and correct abnormalities that reduce formation, transmission, and elimination of urine by the urinary tract increases the incidence of reinfection in susceptible patients and reduces the effectiveness of antimicrobial therapy. Abnormalities should be corrected and urinary tract function restored by medical, pharmacologic, or surgical management. A thorough urologic evaluation is essential in all men and in women with evidence of upper tract infections (fevers, chills, flank pain, hemorrhagic cystitis, or other risk factors, such as history of unexplained hematuria, obstructive symptoms, neurogenic bladder dysfunction, renal calculi, fistula, analgesic abuse, or severe disease such as diabetes mellitus). In women, diaphragm-spermicide use has been associated with an increased risk of UTI and vaginal colonization with *E. coli* (Hooton et al, 1991b). Spermicides containing the active ingredient nonoxynol-9 may provide a selective advantage in colonizing the vagina, perhaps by a reduction in vaginal lactobacilli and through enhancement of adherence of *E. coli* to epithelial cells (Gupta et al, 2000; Hooton et al, 1991a). Thus spermicides should be discontinued in women with recurrent UTI and other forms of contraception should be used.

Postmenopausal women have frequent reinfections (Hooton and Stamm, 1991; Raz and Stamm, 1993). These infections are sometimes attributable to residual urine after voiding, which is often associated with bladder or uterine prolapse. In addition, the lack of estrogen causes marked changes in the vaginal microflora, including a loss of lactobacilli and increased colonization by *E. coli* (Raz and Stamm, 1993). Estrogen replacement frequently restores the normal vaginal environment, allows recolonization with lactobacilli, and thus eliminates bacterial uropathogenic colonization. A reduced incidence of UTIs has been documented with this approach (Raz and Stamm, 1993).

Urinary tract imaging will demonstrate the anatomy of the urinary tract and provide reasonable assessment of its functional status. In healthy women, upper tract abnormalities associated with reinfections are very rare; therefore routine urologic imaging is not indicated. Cystoscopy should be performed in men or women who have frequent reinfections and symptoms suggestive of obstruction, bladder dysfunction, and fistula. If the patient has residual urine that is judged to be significant (e.g., 100 mL) and due to a narrowing of the urethra, a single dilation of the urethra to improve bladder emptying would appear appropriate. There is little evidence, however, that repeated urethral dilation is indicated in the routine management of most women.

Antimicrobial management in women who have had two or more symptomatic UTIs over a 6-month period or three or more episodes within a 12-month period involves one of three regimens: low-dose continuous prophylaxis, self-start intermittent therapy, or postintercourse prophylaxis.

Low-Dose Continuous Prophylaxis

Biologic Basis of Successful Prophylaxis: Antimicrobial Effect on Bowel and Vaginal Bacterial Flora. The success of prophylaxis depends, in large part, on the effect an antimicrobial agent has on the introital and bowel reservoirs of pathogenic bacteria. Antimicrobial agents that eliminate pathogenic bacteria from these sites and/or do not cause bacterial resistance at the sites can be effective for antimicrobial prophylaxis of UTIs (Table 10–22).

Winberg and his colleagues were among the first to emphasize that oral antimicrobial therapy causes resistant strains in the bowel flora and subsequent resistant UTIs (Lincoln et al, 1970; Winberg et al, 1973). The increase in resistant strains of *E. coli*, as well as the proliferation of other Enterobacteriaceae species, *Candida albicans*, enterococci, and other pathogenic bacteria in the bowel and vaginal flora that accompanies even short-term, full-dose oral administration of tetracyclines, ampicillin, sulfonamides, amoxicillin, and cephalexin is well documented (Sharp, 1954; Daikos et al, 1968; Hinton, 1970; Lincoln et al, 1970; Datta et al, 1971; Gruneberg et al, 1973; Winberg et al, 1973; Toivanen et al, 1976; Ronald et al, 1977; Preiksaitis et al, 1981). These ecologic changes may interfere with antimicrobial prophylaxis in the urinary tract and must be considered in the choice of prophylactic agents.

Effective Drugs. The oral antimicrobial agents with minimal adverse effects on the bowel and vaginal flora are TMP-SMX or TMP alone, nitrofurantoin, cephalexin (in minimal dosage), and the fluoroquinolones.

TMP-SMX eradicates gram-negative aerobic flora from the bowel and vaginal fluid. Vaginal fluid measurements of TMP and SMX in patients showed that TMP infused across the noninflamed vaginal wall and produced concentrations that exceeded serum levels (Stamey and Condy, 1975); SMX was undetectable in vaginal fluid. These observations on diffusion and concentration of TMP and vaginal fluid and on the effects of TMP-SMX in clearing Enterobacteriaceae from the rectal and vaginal flora clearly indicate why TMP-SMX is such a powerful prophylactic agent for the prevention of reinfections in the female. These important biologic effects occur in addition to the bactericidal levels of TMP-SMX that are present in the urine during nightly prophylaxis.

Kasanen and his colleagues (1978) in Finland studied the bowel flora in volunteers and patients who took 100 mg of TMP per day for periods of 3 weeks to 36 months; 4 of 20 patients treated for long periods developed coliforms resistant to TMP (>8 μg/mL). Svensson and his associates (1982) gave 100 mg of TMP once daily for 6 months to 26 patients with recurrent UTIs. The infection recurrence rate before prophylaxis was 26 per 100 months compared with 3.3 recurrences per 100 months during prophylaxis (P = .001). The postprophylactic infection rate returned to 23 recurrences per 100 months. It is important to note that all *E. coli* UTIs after prophylaxis were sensitive to TMP, the number of rectal Enterobacteriaceae was markedly reduced during prophylaxis, and, although a 10% incidence of TMP-resistant organisms from rectal swabs was observed less than 1 month into prophylaxis there was no significant further accumulation of resistant bacteria.

These studies on TMP alone suggest that it should be as effective as TMP-SMX for prophylactic prevention of recurrent UTIs. Stamm and coworkers (1980a) noted only one resistant strain of *E. coli* in 316 rectal, urethral, and vaginal isolates from 15 patients receiving 100 mg of TMP and 15 others receiving 40 mg of TMP with 200 mg of SMX nightly for 6 months; their unbelievably low recovery of TMP-resistant *E. coli* was due to their method of sampling, which did not include streaking cultures from these colonization sites directly onto media containing TMP.

These studies on TMP-SMX and TMP prophylactic therapy usually have been limited to 6 months to test continuing susceptibility in patients with reinfections. Two studies (Pearson et al, 1979; Harding et al, 1982), however, continued TMP-SMX prophylaxis from 2 to 5 years without showing any increase in "breakthrough" infections or any increase in TMP-resistant recurrent infections. Indeed, in the 15 patients treated for 2 years with one-half tablet of TMP-SMX thrice weekly (Harding et al, 1982), 100 of 116 cultures from the periurethral area (91%) and 60 of 97 cultures from the anal canal (68%) showed no aerobic gram-negative bacilli at these colonization sites.

Nitrofurantoin, which does not alter the bowel flora, is present for brief periods at high concentrations in the urine and leads to repeated elimination of bacteria from the urine, presumably interfering with bacterial initiation of infection. Because of either its complete absorption in the upper intestinal tract or its degradation and inactivation in the intestinal tract, it produces minimal effects on bowel flora (Stamey et al, 1977). Unlike the situation in prophylaxis with TMP-SMX that eliminates colonization, in prophylaxis with nitrofurantoin colonization of the vaginal introitus with Enterobacteriaceae continues throughout therapy. The bacteria colonizing the vagina nearly always remain susceptible because of the lack of bacterial resistance in the bowel flora. Patients on long-term therapy should be monitored for adverse reactions (e.g., pulmonary fibrosis). **The risk of an adverse reaction increases with age, with the greatest number occurring in patients older than 50 years. If a patient develops a chronic cough, the drug should be discontinued and a chest radiograph obtained.**

Fairley and his associates (1974) first reported on the prophylactic efficacy of 500 mg of cephalexin per day in preventing recurrent infections during a 6-month period of observation. Of

Table 10–22.

Low-Dose Prophylaxis for Recurrent UTIs in Women

INVESTIGATORS	REGIMEN	INFECTIONS PER PATIENT-YEAR
Bailey et al (1971)	Nitrofurantoin, 50 or 100 mg daily	0.09
	Nitrofurantoin, 50 mg daily	0.19
	Placebo	2.1
Harding and Ronald (1974)	Sulfamethoxazole, 500 mg daily	2.5
	TMP-SMX, 40 and 200 mg daily	0.1
	Methenamine mandelate, 2 g daily, plus ascorbic acid, 2 g	1.6
Kasanen et al (1974)	Nitrofurantoin, 50 mg daily	0.32
	Methenamine hippurate, 1 g daily	0.39
	Trimethoprim, 100 mg daily	0.13
	TMP-SMX, 80 and 400mg daily	0.19
Gower (1975)	Cephalexin, 125 mg daily	0.10
Stamey et al (1977)	TMP-SMX, 40 and 200 mg daily	0.00
	Nitrofurantoin macrocrystals, 100 mg daily	0.74
Harding et al (1979)	TMP-SMX, 40 and 200 mg daily three times weekly	0.1
Stamm et al (1980)	TMP-SMX, 40 and 200 mg daily	0.15
	Trimethoprim, 100 mg daily	0.00
	Nitrofurantoin macrocrystals, 100 mg daily	0.14
	Placebo	2.8
Brumfitt et al (1981)	Nitrofurantoin, 50 mg twice daily	0.19
	Methenamine hippurate, 1 g twice daily	0.57
Harding et al (1982)	TMP-SMX, 40 and 200 mg three times weekly	0.14
Brumfitt et al (1983)	Trimethoprim, 100 mg daily	1.53
	Methenamine hippurate, 1 g daily	1.38
	Povidone-iodine wash, twice daily	1.79
Wong et al (1985)	TMP-SMX, 40 and 200 mg daily	0.2
	Self-administered cotrimoxazole, 4 × 80 and 400 mg	2.2
Martinez et al (1985)	Cephalexin, 250 mg daily	0.18
Brumfitt et al (1985)	Trimethoprim, 100 mg daily	1.00
	Nitrofurantoin macrocrystals, 100 mg daily	0.16
Nicolle et al (1989)	Nitrofurantoin, 200 mg daily	0.00
	Norfloxacin, 200 mg daily	0.00
Raz and Boger (1991)	Norfloxacin, 200 mg daily	0.04

TMP-SMX, trimethoprim-sulfamethoxazole.
From Nicolle LE, Ronald AR. Recurrent urinary tract infection in adult women: diagnosis and treatment. Infect Dis Clin North Am 1987;1:793–806.

the 22 patients, 17 remained free of infection, an impressive record because several patients had papillary necrosis, chronic pyelonephritis, and even renal calculi. Gower (1975) treated 25 women with 125 mg of cephalexin nightly for 6 to 12 months and found only 1 infection, whereas 13 of 25 women receiving a placebo had infection.

Martinez and coworkers (1985) studied the effect on the vaginal and rectal flora of 250 mg of cephalexin nightly for 6 months in 23 patients with reinfections of the urinary tract. Throughout prophylaxis, 22 of the 23 patients maintained a sterile urine; a single patient developed two enterococcal UTIs, both of which responded to nitrofurantoin. No change was detected in the rectal or vaginal carriage of Enterobacteriaceae. More importantly, not a single resistant strain of *E. coli* was detected in 154 cultures obtained at monthly intervals during cephalexin therapy. These results are in contrast to those of Preiksaitis and colleagues (1981), who found rectal Enterobacteriaceae resistance in 38% of patients when cephalexin was administered at a dose of 500 mg four times daily for 14 days. **Cephalexin at 250 mg or less nightly is an excellent prophylactic agent because bowel flora resistance does not develop at this low dosage.**

With short-course fluoroquinolone therapy (Hooton et al, 1989), eradication of Enterobacteriaceae from the bowel and vaginal (Nord, 1988; Tartaglione et al, 1988) flora has been documented, observations that have been exploited in the use of these agents for prophylaxis. More recently, Nicolle and coworkers (1989) documented the prophylactic efficacy of norfloxacin for the prevention of recurrent UTIs in women. Of 11 women who completed 1 year of prophylaxis (with 200 mg orally), all remained free of infection. By comparison, the majority of individuals receiving placebos developed UTIs. The drug was well tolerated. In addition to preventing symptomatic UTIs, norfloxacin virtually eradicated periurethral and bowel colonization with aerobic gram-negative organisms. A larger study by Raz and Boger (1991) confirmed these results.

Because the fluoroquinolones are expensive and can be used only in nonpregnant women, we favor their use only when antimicrobial resistance or patient intolerance to TMP-SMX, TMP, nitrofurantoin, or cephalexin occurs. Further studies are required to determine the minimal effective regimen and efficacy of the fluoroquinolones for prophylaxis of recurrent UTIs in women.

Efficacy of Prophylaxis. Low-dose continuous prophylaxis is indicated when the urine culture shows no growth (usually when a patient has completed antimicrobial therapy). Nightly therapy is then begun with one of the following drugs: (1) nitrofurantoin, 50 to 100 mg half-strength (HS) (Stamey et al, 1977); (2) TMP-SMX, 40 to 200 mg (Stamm et al, 1982a); (3) TMP, 50 mg (Stamm et al, 1982a); or (4) cephalexin (Keflex), 250 mg (Martinez et al, 1985). **Prophylactic therapy has been repeatedly**

documented as being effective in the management of women with recurrent UTIs, with recurrences decreased by 95% when compared with placebo or with the patients' prior experiences as controls. These reported results of prophylaxis, together with agents and doses, have been summarized by Nicolle and Ronald (1987) (see Table 10–22). These studies consistently show a remarkable reduction in the reinfection rate from 2.0 to 3.0 per patient-year to 0.1 to 0.4 per patient-year with the use of prophylaxis. Urinary antiseptics, such as methenamine mandelate or hippurate, have resulted in some decrease in recurrences, but they are not as effective as antimicrobial agents.

Every-other-night therapy is also effective and is probably practiced by most patients. **When breakthrough infections occur, they are not necessarily accompanied by symptoms; therefore we advocate monitoring for infections every 1 to 3 months, even in asymptomatic patients. Breakthrough infections usually respond to full-dose therapy with the drug used for prophylaxis. However, cultures and susceptibility tests may indicate that another drug is indicated. After the infection is cured, prophylaxis may be reinstituted. Low-dose prophylaxis is usually discontinued after about 6 months, and the patient is monitored for reinfection.** Approximately 30% of women will have spontaneous remissions that last up to 6 months (Kraft and Stamey, 1977). Unfortunately, many of the remissions are followed by reinfections, and low-dose prophylaxis must be reinstituted. At this point, many patients prefer an alternative form of management.

Self-Start Intermittent Therapy. **With self-start intermittent therapy, the patient is given a dip slide device to culture the urine and is instructed to perform a urine culture when symptoms of UTI occur** (Schaeffer and Stuppy, 1999; Blom et al, 2002). The patient is also provided a 3-day course of empirical, full-dose antimicrobial therapy to be started immediately after performing the culture. It is important that the antimicrobial agent selected for self-start therapy have a broad spectrum of activity and achieve high urinary levels to minimize development of resistant mutants. In addition, there should be minimal or no side effects on the bowel flora. Fluoroquinolones are ideal for self-start therapy because they have a spectrum of activity broader than any of the other oral agents and are superior to many parenteral antimicrobials, including aminoglycosides. Nitrofurantoin and TMP-SMX are acceptable alternatives, although they are somewhat less effective. Antimicrobial agents such as tetracycline, ampicillin, SMX, and cephalexin in full doses should be avoided because they can give rise to resistant bacteria (Wong et al, 1985).

The culture is brought to the office as soon as possible. If the culture is positive and the patient is asymptomatic, a culture is performed 7 to 10 days after therapy to determine efficacy. In most cases, the therapy is limited to two inexpensive dip slide cultures and a short course of antimicrobial therapy. If the patient has symptoms that do not respond to initial antimicrobial therapy, a repeat culture and susceptibility testing of the initial culture specimen are performed and therapy adjusted accordingly. If symptoms of infection are not associated with positive cultures, urologic evaluation should be performed to rule out other causes of irritative bladder symptoms, including carcinoma in situ, interstitial cystitis, and neurogenic bladder dysfunction. The authors' experience with this technique has been very favorable, and is particularly attractive to patients who have less frequent infections and are willing to play an active role in their diagnosis and management.

Postintercourse Prophylaxis. Antimicrobial management through postintercourse prophylaxis is based on research establishing that sexual intercourse can be an important risk factor for acute cystitis in women (Nicolle et al, 1982). Diaphragm users have a significantly greater risk of UTI than do women who use other contraceptive methods (Fihn et al, 1985). Postintercourse therapy with antimicrobial agents, such as nitrofurantoin, cephalexin, TMP-SMX, or a fluoroquinolone taken as a single dose, will effectively reduce the incidence of reinfection (Pfau et al, 1983; Melekos et al, 1997).

Other Strategies. Cranberry juice contains proanthocyanidins that block adherence of pathogens to uroepithelial cells in vitro (Foo et al, 2000). Randomized trials in low-risk patients show that 200 to 750 mL daily of cranberry or lingonberry juice or cranberry-concentrate tablets reduce the risk of symptomatic, recurrent infection by 12% to 20% (Avorn et al, 1994; Kontiokari et al, 2001; Stothers, 2002; McMurdo et al, 2009). However, the actual cranberry content of juices and tablets varies substantially; therefore their efficacy is not predictable (Consumer Reports, 2001; Klein, 2002). Furthermore, other trials of cranberry products show no benefit and there is no evidence that they are effective for treatment of UTIs (Jepson et al, 2001; Raz et al, 2004).

Other factors, such as hygiene, frequency and timing of voiding, wiping patterns, use of hot tubs, and type of undergarments, have not been shown to predispose women to recurrent infection and there is no rationale for giving women specific instructions regarding them.

Key Points: Bladder Infections

- Uncomplicated cystitis should be treated for 3 days.
- Asymptomatic bacteriuria should be treated only in pregnant women and prior to urologic intervention.
- Recurrent UTIs due to bacterial persistence require urologic management; reinfections can be managed medically.

KIDNEY INFECTIONS

Renal Infection (Bacterial Nephritis)

Although renal infection is less prevalent than bladder infection it often is a more difficult problem for the patient and his or her physician because of its often varied and morbid presentation and course, the difficulty in establishing a firm microbiologic and pathologic diagnosis, and its potential for significantly impairing renal function. **Although the classic symptoms of acute onset of fever, chills, and flank pain are usually indicative of renal infection, some patients with these symptoms do not have renal infection. Conversely, significant renal infection may be associated with an insidious onset of nonspecific local or systemic symptoms or it may be entirely asymptomatic.** Therefore a high clinical index of suspicion and appropriate radiologic and laboratory studies are required to establish the diagnosis of renal infection.

Unfortunately, **the relationship between laboratory findings and the presence of renal infection often is poor. Bacteriuria and pyuria, the hallmarks of UTI, are not predictive of renal infection. Conversely, patients with significant renal infection may have sterile urine if the ureter draining the kidney is obstructed or the infection is outside the collecting system.**

The pathologic and radiologic criteria for diagnosing renal infection may also be misleading. Interstitial renal inflammation, once thought to be caused predominantly by bacterial infection, is now recognized as a nonspecific histopathologic change associated with a variety of immunologic, congenital, or chemical lesions that usually develop in the absence of bacterial infection. Infectious granulomatous diseases of the kidney often have either radiologic or pathologic characteristics that mimic renal cystic disease, neoplasia, or other renal inflammatory disease.

The effect of renal infection on renal function is varied. Acute or chronic pyelonephritis may transiently or permanently alter renal function, but nonobstructive pyelonephritis is no longer recognized as a major cause of renal failure (Baldassarre and Kaye, 1991; Fraser et al, 1995). However, pyelonephritis, when associated with urinary tract obstruction or granulomatous renal infection, may lead rapidly to significant inflammatory complications, renal failure, or even death.

Pathology

The opportunity for pathologic confirmation of acute bacterial nephritis is rare. The kidney may be edematous. Focal acute suppurative bacterial nephritis caused by hematogenous dissemination of bacteria to the renal cortex is characterized by multiple focal areas of suppuration on the surface of the kidney (Fig. 10–15). Histologic examination of the renal cortex shows focal suppurative destruction of glomeruli and tubules. Adjacent cortical structures and the medulla are not involved in the inflammatory reaction. Acute ascending pyelonephritis is characterized by linear bands of inflammation extending from the medulla to the renal capsule (Fig. 10–16). Histologic examination usually reveals a focal wedge-shaped area of acute interstitial inflammation with the apex of the wedge in the renal medulla. Polymorphonuclear leukocytes or a predominantly lymphocytic and plasma cell response are seen. Bacteria also may be present.

The changes that appear to be most specific for chronic pyelonephritis are evident on careful gross examination of the kidney and consist of a cortical scar associated with retraction of the corresponding renal papilla (Hodson, 1965a, 1965b; Heptinstall, 1974; Freedman, 1979). The kidney shows evidence of patchy involvement with numerous chronic inflammatory foci mainly confined to the cortex but also involving the medulla (Fig. 10–17).

The scars may be separated by intervening zones of normal parenchyma, causing a grossly irregular renal outline. The microscopic appearance, as with most chronic interstitial disease, includes the presence of lymphocytes and plasma cells. Although glomeruli within scars may be surrounded by a cuff of fibrosis or be partially or completely hyalinized, glomeruli outside these severely scarred zones are relatively normal. Vascular involvement is variable, but in patients with hypertension, nephrosclerosis may be found. Papillary abnormalities include deformity, sclerosis, and sometimes necrosis. Studies in animals have clearly indicated the critical role of the papilla in the initiation of pyelonephritis (Freedman and Beeson, 1958). However, these changes are not necessarily specific for bacterial infection and may occur in the absence of infection as a result of other disorders such as analgesic abuse, diabetes, and sickle cell disease.

Acute Pyelonephritis

Although pyelonephritis is defined as inflammation of the kidney and renal pelvis, the diagnosis is clinical. True infection of the "upper urinary tract" can be proved by catheterization tests (ureteral catheterization or bladder washout) as described in this chapter, but these are impractical and unnecessary in most patients with acute pyelonephritis. None of the noninvasive tests that have been developed to determine infection in the kidney or bladder is totally reliable.

Clinical Presentation. **The clinical spectrum ranges from gram-negative sepsis to cystitis with mild flank pain** (Stamm and Hooton, 1993). **The classic presentation is an abrupt onset of chills, fever (100° F or greater), and unilateral or bilateral flank or costovertebral angle pain and/or tenderness. These so-called upper tract signs are often accompanied by dysuria, increased urinary frequency, and urgency.**

Although some authors regard loin pain and fever in combination with significant bacteriuria as diagnostic of acute pyelonephritis, it is clear from localization studies using ureteral catheterization (Stamey and Pfau, 1963) or the bladder washout technique (Fairley et al, 1967) that **clinical symptoms correlate poorly with the site of infection** (Stamey et al, 1965; Eykyn et al, 1972; Fairley, 1972; Smeets and Gower, 1973).

In a large study of 201 women and 12 men with recurrent UTIs, Busch and Huland (1984) **showed that fever and flank pain are no more diagnostic of pyelonephritis than**

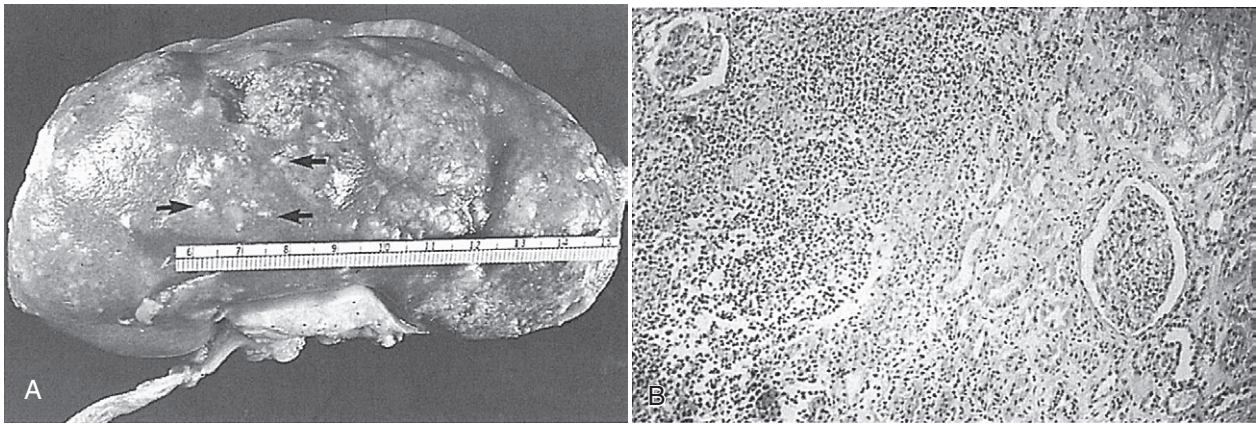


Figure 10–15. Acute focal suppurative bacterial nephritis. **A,** Surface of kidney. *Arrows* indicate focal areas of suppuration. **B,** Renal cortex showing focal suppuration destruction of glomeruli and tubules. (From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY, et al, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 211–72.)

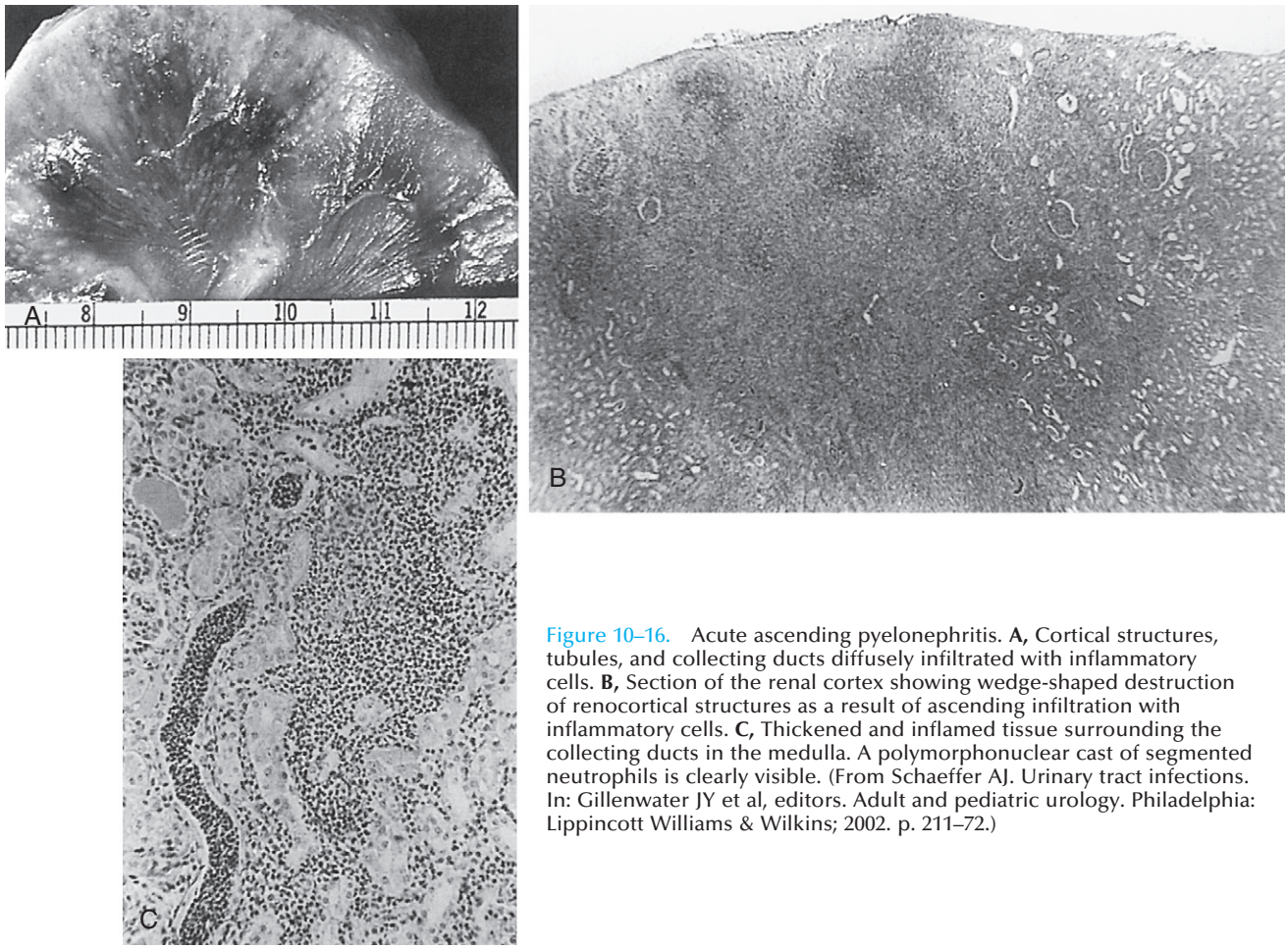


Figure 10–16. Acute ascending pyelonephritis. **A,** Cortical structures, tubules, and collecting ducts diffusely infiltrated with inflammatory cells. **B,** Section of the renal cortex showing wedge-shaped destruction of renocortical structures as a result of ascending infiltration with inflammatory cells. **C,** Thickened and inflamed tissue surrounding the collecting ducts in the medulla. A polymorphonuclear cast of segmented neutrophils is clearly visible. (From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY et al, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 211–72.)

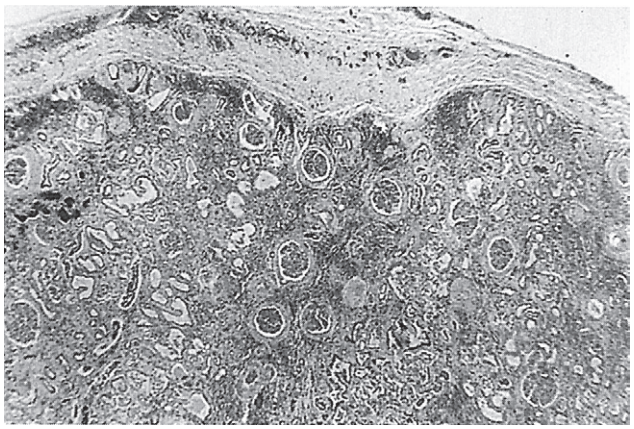


Figure 10–17. Chronic pyelonephritis. The renal cortex shows thickened fibrous capsule and focal retracted scar on surface of kidney. Focal destruction of tubules in center of picture is accompanied by periglomerular fibrosis and scarring. (From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY et al, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 211–72.)

they are of cystitis. Of patients with flank pain and/or fever, over 50% had lower tract bacteriuria. Conversely, patients with bladder symptoms or no symptoms frequently had upper tract bacteriuria. Approximately 75% of patients give a history of previous lower UTIs.

On physical examination there often is tenderness to deep palpation in the costovertebral angle. Variations of this clinical presentation have been recognized. Acute pyelonephritis may also simulate gastrointestinal tract abnormalities with abdominal pain, nausea, vomiting, and diarrhea. Asymptomatic progression of acute pyelonephritis to chronic pyelonephritis, particularly in compromised hosts, may occur in the absence of overt symptoms. Acute renal failure may be present in the rare case (Richet and Mayaud, 1978; Olsson et al, 1980).

Laboratory Diagnosis. The patient may have leukocytosis with predominance of neutrophils. **Urinalysis usually reveals numerous WBCs, often in clumps, and bacterial rods or chains of cocci.** Leukocytes exhibiting brownian motion in the cytoplasm (glitter cells) may be present if the urine is hypotonic, but they are not in themselves diagnostic of pyelonephritis. **The presence of large amounts of granular or leukocyte casts in the urinary sediment is suggestive of acute pyelonephritis.** A specific type of urinary cast characterized by the presence of bacteria in its matrix has been demonstrated in the urine of patients who have had acute pyelonephritis (Fig. 10–18) (Lindner et al, 1980). Bacteria in the casts were not easily distinguished by simple brightfield microscopy without special staining of the sediment. Staining of the sediment with a basic dye such as dilute toluidine blue or KOVA stain (I.C.L. Scientific, Fountain Valley, CA) demonstrated the bacteria in casts without difficulty. Blood tests may show leukocytosis with a predominance of neutrophils, increased erythrocyte sedimentation rate, elevated C-reactive protein levels, and elevated creatinine levels if renal

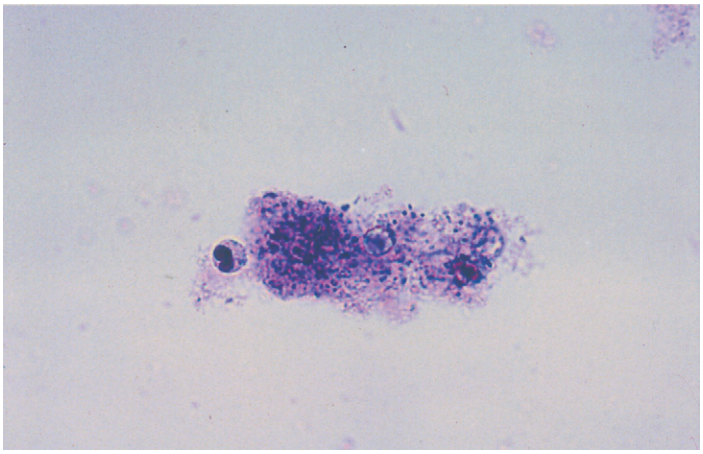


Figure 10–18. Brightfield micrograph of a mixed bacterial leukocyte cast from patient with acute pyelonephritis. Only the bacteria and the nucleus of a leukocyte stain strongly. Many bacteria are clearly demonstrated by through-focusing (toluidine blue O, ×640). (From Lindner LE, Jones RN, Haber MH. A specific urinary cast in acute pyelonephritis. Am J Clin Pathol 1980;73:809–11.)

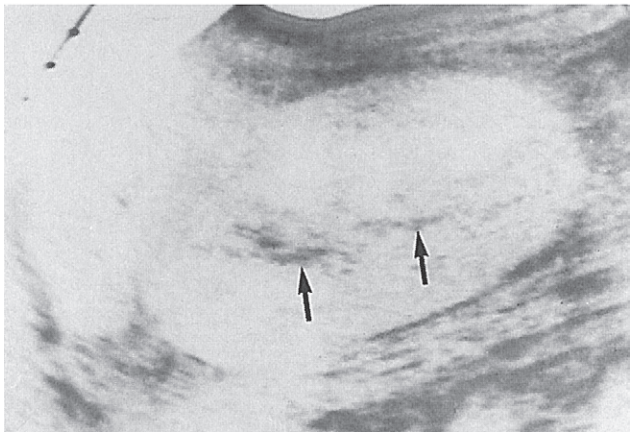


Figure 10–19. Acute pyelonephritis. Ultrasound image of the right kidney demonstrates renal enlargement, hypoechoic parenchyma, and compressed central collecting complex *(arrows)*. (From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY et al, editors. Adult and pediatric urology. Philadelphia: Lippincott William & Wilkins; 2002. p. 211–72.)

failure is present. In addition, creatinine clearance may be decreased. Blood cultures may be positive.

Bacteriology. **Urine cultures are positive, but about 20% of patients have urine cultures with fewer than 10^5 cfu/mL and, therefore, negative results on Gram staining of the urine** (Rubin et al, 1992).

***E. coli*, which constitutes a unique subgroup that possesses special virulence factors, accounts for 80% of cases.** If vesicoureteral reflux is absent, a patient bearing the P blood group phenotype may have special susceptibility to recurrent pyelonephritis caused by *E. coli* that have P pili and bind to the P blood group antigen receptors (Lomberg et al, 1983). Bacterial K antigens and endotoxins also may contribute to pathogenicity (Kaijser et al, 1977). Many cases of community-acquired pyelonephritis are caused by a limited number of multiple-antimicrobial–resistant clonal groups (Manges et al, 2004).

More resistant species, such as *Proteus, Klebsiella, Pseudomonas, Serratia, Enterobacter,* or *Citrobacter* should be suspected in patients who have recurrent UTIs, are hospitalized, or have indwelling catheters, as well as in those who required recent urinary tract instrumentation. Except for *E. faecalis, S. epidermidis,* and *S. aureus,* gram-positive bacteria rarely cause pyelonephritis.

Blood cultures are positive in about 25% of cases of uncomplicated pyelonephritis in women, and the majority replicate the urine culture and do not influence decisions regarding therapy. Therefore blood cultures should not be routinely obtained for the evaluation of uncomplicated pyelonephritis in women. **However, they should be performed in men and women with systemic toxicity or in those requiring hospitalization or with risk factors such as pregnancy** (Velasco et al, 2003).

Renal Ultrasonography and Computed Tomography. These studies are commonly used to evaluate patients initially for complicated UTIs or factors or to reevaluate patients who do not respond after 72 hours of therapy (see later). Ultrasonography (Fig. 10–19) and CT show renal enlargement, hypoechoic or attenuated parenchyma, and a compressed collecting system. They also may delineate focal bacterial nephritis and obstruction. When parenchymal destruction becomes pronounced, a more disorganized parenchyma and abscess formation associated with complicated renal and perirenal infections may be identified (Soulen et al, 1989).

Differential Diagnosis. **Acute appendicitis, diverticulitis, and pancreatitis can cause a similar degree of pain, but the location of the pain often is different.** Results of the urine examination are usually normal. Herpes zoster can cause superficial pain in the region of the kidney but is not associated with symptoms of UTI; the diagnosis will be apparent when shingles appear.

Management

Initial Management. Infection in patients with acute pyelonephritis can be subdivided into (1) uncomplicated infection that does not warrant hospitalization, (2) uncomplicated infection in patients with normal urinary tracts who are ill enough to warrant hospitalization for parenteral therapy, and (3) complicated infection associated with hospitalization, catheterization, urologic surgery, or urinary tract abnormalities (Fig. 10–20).

It is critical to determine whether the patient has an uncomplicated or complicated UTI because significant abnormalities have been found in 16% of patients with acute pyelonephritis (Shen and Brown, 2004). In patients with presumed uncomplicated pyelonephritis that will be managed as outpatients, initial radiologic evaluation can usually be deferred. **However, if there is any reason to suspect a problem or if the patient will not have reasonable access to imaging if there should be no change in condition, we prefer renal ultrasound evaluation to rule out stones or obstruction.** In patients with known or suspected complicated pyelonephritis, CT provides excellent assessment of the status of the urinary tract and the severity and extent of the infection.

For patients who will be managed as outpatients, single-drug oral therapy with a fluoroquinolone is more effective than TMP-SMX for patients with domiciliary infections (Talan et al, 2000). Many physicians administer a single parenteral dose of an antimicrobial agent (ceftriaxone, gentamicin, or a fluoroquinolone) before initiating oral therapy (Israel et al, 1991; Pinson et al, 1994). If a gram-positive organism is suspected, amoxicillin or amoxicillin/clavulanic acid is recommended (Warren et al, 1999).

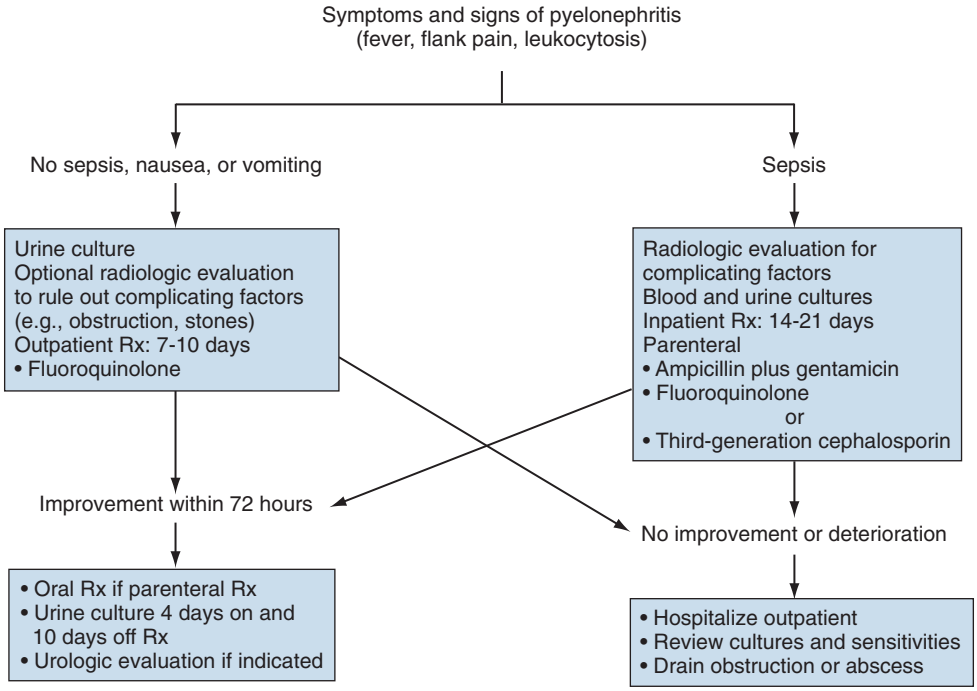


Figure 10–20. Management of acute pyelonephritis.

Table 10–23.

Treatment Regimens for Acute Complicated and Uncomplicated Pyelonephritis in Women

CIRCUMSTANCES	ROUTE	DRUG	DOSAGE	FREQUENCY PER DOSE	DURATION (DAYS)
Outpatient—moderately ill, no nausea or vomiting	Oral	TMP-SMX	160-800 mg	bid	10-14
		Ciprofloxacin	500 mg	bid	
		Levofloxacin	500 mg	qd	
		Norfloxacin	400 mg	bid	
Inpatient—severely ill, possible sepsis	Parenteral	TMP-SMX	160-800 mg	bid	14
		Ampicillin and gentamicin	1 g	qid	
			1.5 mg/kg	tid	
		Ciprofloxacin	400 mg	bid	
		Levofloxacin	500 mg	qd	
		Ceftriaxone	1 to 2g	qd	Take until afebrile, then take oral
		TMP-SMX or fluoroquinolone			
Pregnant	Parenteral	Ceftriaxone	1-2 g	qd	14
		Ampicillin and gentamicin	1 g	qid	
			1 mg/kg	tid	
		Aztreonam	1 g	tid-qid	Take until afebrile, then take oral
	Oral	Cephalexin	500 mg	bid	

TMP-SMX, trimethoprim-sulfamethoxazole.

Modified from Stamm WE, Hooton TM. Management of urinary tract infections in adults. N Engl J Med 1993;329:1328–34. Copyright 1993, Massachusetts Medical Society. All rights reserved.

If a patient has an uncomplicated infection but is sufficiently ill to require hospitalization (high fever, high WBC count, vomiting, dehydration, evidence of sepsis), has complicated pyelonephritis, or fails to improve during the initial outpatient treatment period, a parenteral fluoroquinolone, an aminoglycoside with or without ampicillin, or an extended-spectrum cephalosporin with or without an aminoglycoside is recommended (Warren et al, 1999) (Table 10–23). If gram-positive cocci are causative, ampicillin/sulbactam with or without an aminoglycoside is recommended.

Hospitalization, initially with complete bed rest, intravenous fluids, and antipyretics, is required.

An obstructed kidney has difficulty concentrating and excreting antimicrobial agents. Any substantial obstruction must be relieved expediently by the safest and simplest means.

A Gram stain of the urine sediment is helpful to guide the selection of the initial empirical antimicrobial therapy. In all cases, antimicrobial therapy should be active against potential uropathogens and achieve antimicrobial levels in renal tissue as well as urine.

Subsequent Management. Even though the urine usually becomes sterile within a few hours of starting antimicrobial therapy,

patients with acute uncomplicated pyelonephritis may continue to have fever, chills, and flank pain for several more days after initiation of successful antimicrobial therapy (Behr et al, 1996). They should be observed.

Ambulatory patients should be treated with a fluoroquinolone for 7 days (Talan et al, 2000). Fluoroquinolone therapy is associated with greater bacteriologic and clinical cure rates than 14-day TMP-SMX therapy (Talan et al, 2000). Alterations in antimicrobial therapy may be made depending on the patient's clinical response and the results of the culture and susceptibility tests. Susceptibility tests should also be used to replace potentially toxic drugs, such as aminoglycosides, with less toxic drugs, such as the fluoroquinolones, aztreonam, and cephalosporins.

Patients with complicated pyelonephritis and positive blood cultures should be treated with parenteral therapy until clinically stable. If blood cultures are negative, 2- to 3-day parenteral therapy is sufficient. Following parenteral therapy, an appropriate oral antimicrobial drug (fluoroquinolone, TMP, TMP-SMX, or amoxicillin or amoxicillin/clavulanic acid for gram-positive organisms) should be continued in full dosage for an additional 10 to 14 days.

Unfavorable Response to Therapy. When the response to therapy is slow or the urine continues to show infection, an immediate reevaluation is mandatory. Urine and blood cultures must be repeated and appropriate alterations in antimicrobial therapy made on the basis of susceptibility testing. CT is indicated to attempt to identify unsuspected obstructive uropathy, urolithiasis, or underlying anatomic abnormalities that may have predisposed the patient to infection, prevented a rapid therapeutic response, or caused complications of the infectious process, such as renal or perinephric abscess. **In patients with fever lasting longer than 72 hours, CT is most helpful for ruling out obstruction and identifying renal and perirenal infections** (Soulen et al, 1989). Radionuclide imaging may be useful to demonstrate functional changes associated with acute pyelonephritis (decrease in renal blood flow, delay in peak function, and delay in excretion of the radionuclide) (Fischman and Roberts, 1982) and cortical defects associated with vesicoureteral reflux.

Follow-Up. **Repeat urine cultures should be performed on the fifth to the seventh day of therapy and 10 to 14 days after discontinuing antimicrobial therapy to ensure that the urinary tract remains free of infections. Between 10% and 30% of individuals with acute pyelonephritis relapse after a 14-day course of therapy. Patients who experience relapse usually are cured by a second 14-day course of therapy, but occasionally a 6-week course is necessary** (Tolkoff-Rubin et al, 1984; Johnson and Stamm, 1987).

Depending on the clinical presentation and response and initial urologic evaluation, some patients may require additional evaluation (e.g., voiding cystourethrogram, cystoscopy, bacterial localization studies) and correction of an underlying abnormality of the urinary tract. Raz and colleagues (2003) evaluated the long-term impact of acute pyelonephritis in women. Scanning with ^{99m}Tc-dimercaptosuccinic acid (^{99m}Tc-DMSA) 10 to 20 years after acute pyelonephritis revealed scars in approximately 50% of the patients but changes in renal function were minimal and not associated with renal scarring.

Acute Focal or Multifocal Bacterial Nephritis

Acute focal or multifocal bacterial nephritis is an uncommon, severe form of acute renal infection in which a heavy leukocyte infiltrate is confined to a single renal lobe (focal) or multiple lobes (multifocal).

Clinical Presentation. **The clinical presentation of patients with acute bacterial nephritis is similar to that of patients with acute pyelonephritis but usually is more severe. About half of the patients are diabetic, and sepsis is common.** Generally, leukocytosis and UTI resulting from gram-negative organisms are found; more than 50% of the patients are bacteremic (Wicks and Thornbury, 1979).

Radiologic Findings. The diagnosis must be made by radiologic examination. The mass has slightly less nephrographic density than the surrounding normal renal parenchyma.

Ultrasonography and CT establish the diagnosis. On ultrasonography the lesion is typically poorly marginated and relatively sonolucent with occasional low-amplitude echoes that disrupt the cortical medullary junction (Corriere and Sandler, 1982) (Fig. 10–21A). **Enhancement with a contrast agent is necessary with CT studies because the lesion is difficult to visualize on the unenhanced study** (see Fig. 10–21B). **Wedge-shaped areas of decreased enhancement are seen.** No definite wall is evident, and frank liquefaction is absent. Conversely, abscesses tend to have liquid centers, are usually round, and are present both before and after contrast medium enhancement. More chronic abscesses may also show a ring-shaped area of increased enhancement surrounding the lesion (Corriere and Sandler, 1982). Gallium scanning reveals uptake that is in the region of and larger than the previously demonstrated mass (Rosenfield et al, 1979). In patients with multifocal disease the findings are similar but multiple lobes are involved.

Management. Acute bacterial nephritis probably represents a relatively early phase of frank abscess formation. In a series of cases reported by Lee and coworkers (1980) a patient with acute focal bacterial nephritis progressed to abscess formation. **Treatment includes hydration and intravenous antimicrobial agents for at least 7 days, followed by 7 days of oral antimicrobial therapy.** Patients with bacterial nephritis typically respond to medical therapy, and follow-up studies will show resolution of the wedge-shaped zones of diminished attenuation. **Failure to respond to antimicrobial therapy is an indication for appropriate studies to rule out obstructive uropathy, renal or perirenal abscess, renal carcinoma, or acute renal vein thrombosis.** Long-term follow-up studies performed in a few patients with multifocal disease have demonstrated a decrease in renal size and focal calyceal deformities suggestive of papillary necrosis (Davidson and Talner, 1978).

Emphysematous Pyelonephritis

Emphysematous pyelonephritis is a urologic emergency characterized by an acute necrotizing parenchymal and perirenal infection caused by gas-forming uropathogens. The pathogenesis is poorly understood. **Because the condition usually occurs in diabetic patients, it has been postulated that the high tissue glucose levels provide the substrate for microorganisms such as *E. coli*, which are able to produce carbon dioxide by the fermentation of sugar** (Schainuck et al, 1968). Although glucose fermentation may be a factor, the explanation does not account for the rarity of emphysematous pyelonephritis despite the high frequency of gram-negative UTI in diabetic patients, nor does it explain the rare occurrence of the condition in nondiabetic patients.

In addition to diabetes, many patients have urinary tract obstruction associated with urinary calculi or papillary necrosis and significant renal functional

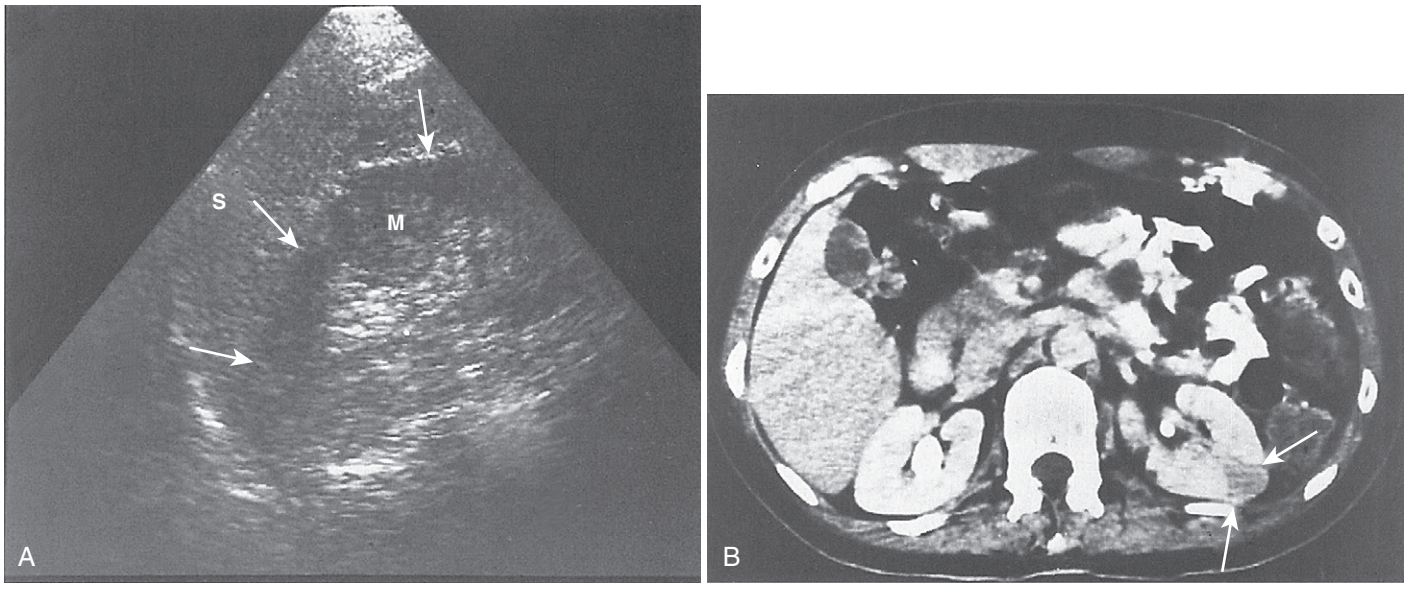


Figure 10–21. Acute focal bacterial nephritis. **A,** Ultrasound image: longitudinal view of the left kidney demonstrates spleen (S) and left kidney *(arrows)*. Note irregular midpole mass (M) of slightly higher echo texture than surrounding normal renal parenchyma. **B,** Contrast medium–enhanced CT scan demonstrates a wedge-shaped area of low density *(arrows)* in the middle portion of the left kidney. The findings resolved after antimicrobial therapy. (From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY et al, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 211–72.)

impairment. The overall mortality rate has been reported to be between 43% (Freiha et al, 1979) and 19% (Huang and Tseng, 2000).

Clinical Presentation. **All of the documented cases of emphysematous pyelonephritis have occurred in adults** (Hawes, 1983). Juvenile diabetic patients do not appear to be at risk. Women are affected more often than men.

The usual clinical presentation is severe, acute pyelonephritis, although in some instances a chronic infection precedes the acute attack. **Almost all patients display the classic triad of fever, vomiting, and flank pain** (Schainuck et al, 1968). Pneumaturia is absent unless the infection involves the collecting system. Results of urine cultures are invariably positive. *E. coli* is most commonly identified. *Klebsiella* and *Proteus* are less common.

Radiologic Findings. **The diagnosis is established radiographically. Tissue gas that is distributed in the parenchyma may appear on abdominal radiographs as mottled gas shadows over the involved kidney** (Fig. 10–22). This finding is often mistaken for bowel gas. A crescentic collection of gas over the upper pole of the kidney is more distinctive. As the infection progresses, gas extends to the perinephric space and retroperitoneum. This distribution of gas should not be confused with cases of emphysematous pyelitis in which air is in the collecting system of the kidney. Emphysematous pyelitis is secondary to a gas-forming bacterial UTI, often occurs in nondiabetic patients, is less serious, and usually responds to antimicrobial therapy.

Ultrasonography usually demonstrates strong focal echoes suggesting the presence of intraparenchymal gas (Brenbridge et al, 1979; Conrad et al, 1979). **CT is the imaging procedure of choice in defining the extent of the emphysematous process and guiding management** (Figs. 10–23 and 10–24). **An absence of fluid in CT images or the presence of streaky or mottled gas with or without bubbly and loculated gas appears to be associated with rapid destruction of renal parenchyma and a 50% to 60% mortality rate** (Wan et al, 1996; Best et al, 1999). The presence of renal or perirenal fluid, the presence of bubbly or loculated gas or gas in the collecting system, and the absence of streaky or mottled gas patterns is associated with a less than 20% mortality rate. Obstruction is demonstrated in approximately 25% of the cases. A nuclear renal scan should be performed to assess the degree of renal function impairment in the involved kidney and the status of the contralateral kidney.

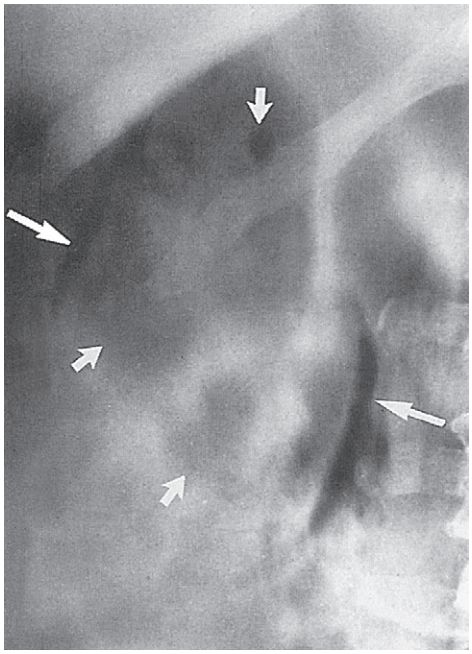


Figure 10–22. Emphysematous pyelonephritis; plain film. Extensive perinephric *(long arrows)* and intraparenchymal *(short arrows)* gas secondary to acute bacterial pyelonephritis. (From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY et al, editors. Adult and pediatric urology. Philadelphia: Lippincott William & Wilkins; 2002. p. 211–72.)

Management. **Emphysematous pyelonephritis is a surgical emergency. Most patients are septic, and fluid**

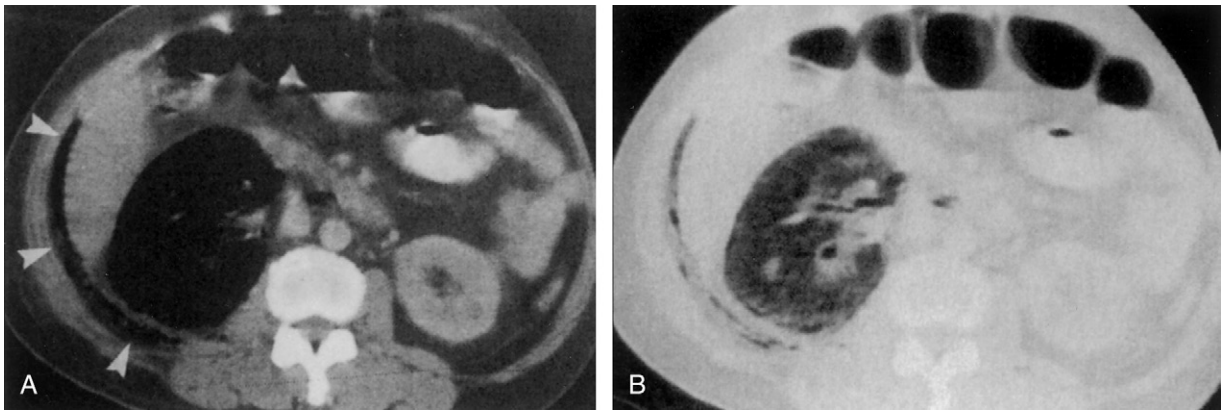


Figure 10–23. Type I emphysematous pyelonephritis with complete renal destruction in a 49-year-old woman. **A,** CT scan of the right kidney shows complete destruction with gas *(arrowheads)* extending beyond the renal fascia. **B,** CT scan with a modified lung window display shows the characteristic streaky gas in the completely destroyed kidney. The patient died on arrival in the emergency department. (**A** and **B,** From Wan YL, Lee TY, Bullard MJ, Tsai CC. Acute gas-producing bacterial renal infection: correlation between imaging findings and clinical outcome. Radiology 1996;198:433–8.)

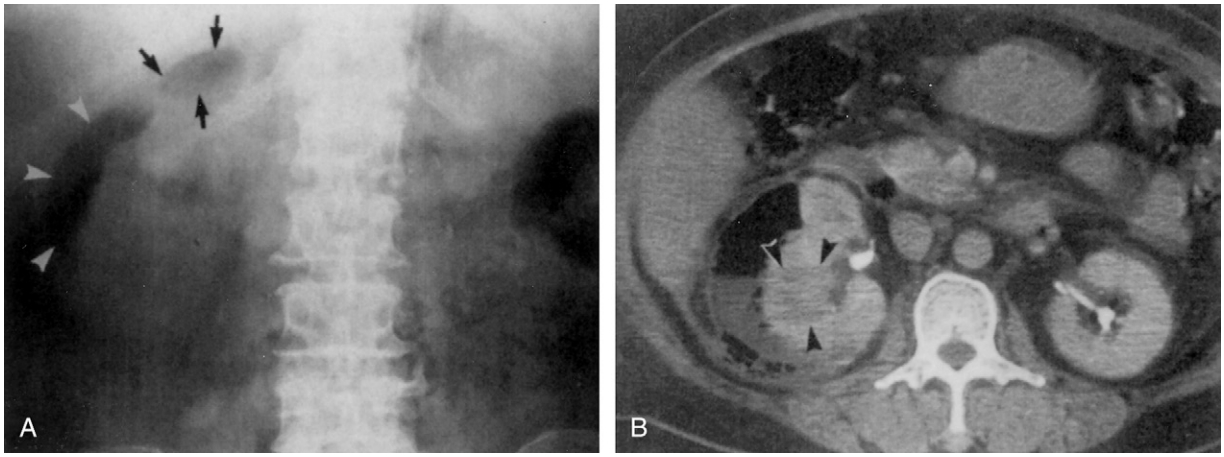


Figure 10–24. Type II emphysematous pyelonephritis in a 57-year-old woman. **A,** Radiograph shows crescent-shaped *(arrowheads)* and loculated *(arrows)* gas in the right renal area. **B,** CT scan obtained after administration of contrast material shows a low-attenuation area *(arrowheads)* in the right kidney due to acute pyelonephritis as well as a subcapsular abscess with fluid and bubbly and loculated gas. The patient survived after percutaneous drainage was performed. (**A** and **B,** From Wan YL, Lee TY, Bullard MJ, Tsai CC. Acute gas-producing bacterial renal infection: correlation between imaging findings and clinical outcome. Radiology 1996;198:433–8.)

resuscitation and broad-spectrum antimicrobial therapy are essential. If the kidney is functioning, medical therapy can be considered (Wan et al, 1996; Best et al, 1999). Nephrectomy is recommended for patients who do not improve after a few days of therapy (Malek and Elder, 1978). If the affected kidney is nonfunctioning and not obstructed, nephrectomy should be performed because medical treatment alone is usually lethal. If a kidney is obstructed, catheter drainage must be instituted. If the patient's condition improves, nephrectomy may be deferred pending a complete urologic evaluation. Although there are isolated case reports of retention of renal function after medical therapy combined with relief of obstruction, most patients require nephrectomy (Hudson et al, 1986).

Renal Abscess

Renal abscess or carbuncle is a collection of purulent material confined to the renal parenchyma. Before the antimicrobial era, 80% of renal abscesses were attributed to hematogenous seeding by staphylococci (Campbell, 1930). Although experimental and clinical data document the facility for abscess formation in normal kidneys after hematogenous inoculation with staphylococci, widespread use of antimicrobial agents since about 1950 appears to have diminished the propensity for gram-positive abscess formation (DeNavasquez, 1950; Cotran, 1969).

Since about 1970, gram-negative organisms have been implicated in the majority of adults with renal abscesses. Hematogenous renal seeding by gram-negative organisms may occur, but this is not likely to be the primary pathway for gram-negative abscess formation. Clinically there is no evidence that gram-negative septicemia antedates most lesions. Furthermore, gram-negative hematogenous pyelonephritis is virtually impossible to produce in animals unless the kidney is traumatized or completely obstructed (Cotran, 1969; Timmons and Perlmutter, 1976). The partially obstructed kidney rejects blood borne gram-negative inocula as well as a normal kidney. Thus ascending infection associated with tubular obstruction from prior infections or calculi appears to be the primary pathway for the establishment of gram-negative abscesses. Two-thirds of gram-negative abscesses in adults are associated with renal calculi or damaged kidneys (Salvatierra et al, 1967). Although the association of pyelonephritis with vesicoureteral reflux is well established, the association of renal abscess with vesicoureteral reflux has been infrequently

noted (Segura and Kelalis, 1973). More recent observations, however, indicate that reflux is frequently associated with renal abscesses and persists long after sterilization of the urinary tract (Timmons and Perlmutter, 1976).

Clinical Presentation. **The patient may present with fever, chills, abdominal or flank pain, and occasionally with weight loss and malaise.** Symptoms of cystitis may occur. Occasionally these symptoms may be vague and delay diagnosis until surgical exploration or, in more severe cases, autopsy (Anderson and McAninch, 1980). **A thorough history may reveal a gram-positive source of infection 1 to 8 weeks before the onset of urinary tract symptoms. The infection may have occurred in any area of the body.** Multiple skin carbuncles and intravenous drug abuse introduce gram-positive organisms into the bloodstream. Other common sites are the mouth, lungs, and bladder (Lyons et al, 1972). Complicated UTIs associated with stasis, calculi, pregnancy, neurogenic bladder, and diabetes mellitus also appear to predispose the patient to abscess formation (Anderson and McAninch, 1980).

Laboratory Diagnosis. **The patient typically has marked leukocytosis.** The blood cultures are usually positive. Pyuria and bacteriuria may not be evident unless the abscess communicates with the collecting system. **Because gram-positive organisms are most commonly blood borne, urine cultures in these cases typically show no growth or a microorganism different from that isolated from the abscess.** When the abscess contains gram-negative organisms, the urine culture usually demonstrates the same organism isolated from the abscess.

Ultrasonography and CT distinguish abscess from other inflammatory renal diseases. **Ultrasonography is the quickest and least expensive method to demonstrate a renal abscess. An echo-free or low-echodensity space-occupying lesion with increased transmission is found on the ultrasound image** (Fig. 10–25). The margins of an abscess are indistinguishable in the acute phase, but the structure contains a few echoes and the surrounding renal parenchyma is edematous (Fiegler, 1983). Subsequently, the appearance tends to be that of a well-defined mass. The internal appearance, however, may vary from a virtually solid lucent mass to one with large numbers of low-level internal echoes (Schneider et al, 1976). The number of echoes depends on the amount of cellular debris within the abscess. The presence of air results in a strong echo with a shadow. Differentiation between an abscess and a tumor is impossible in many cases. Arteriography is used infrequently to demonstrate abscesses. The center of the mass tends to be hypervascular or avascular, with increased vascularity at the cortical margins and lack of vascular displacement and neovascularity.

CT appears to be the diagnostic procedure of choice for renal abscesses, because it provides excellent delineation of the tissue. On CT, abscesses are characteristically well defined both before and after contrast agent enhancement. The findings depend in part on the age and severity of the abscess (Baumgarten and Baumgartner, 1997). Initially, CT shows renal enlargement and focal, rounded areas of decreased attenuation (Fig. 10–26). After several days of the onset of the infection, a thick fibrotic wall begins to form around the abscess. An echo-free or slightly echogenic mass due to the presence of necrotic debris is seen. CT of a chronic abscess shows obliteration of adjacent tissue planes, thickening of the Gerota fascia, a round or oval parenchymal mass of low attenuation, and a surrounding inflammatory wall of slightly higher attenuation that forms a ring when the scan is enhanced with contrast material (Fig. 10–27). The ring sign is caused by the increased vascularity of the abscess wall (Callen, 1979; Gerzof and Gale, 1982).

Radionuclide imaging with gallium or indium is sometimes useful in evaluating patients with renal abscesses (see earlier sections in this chapter and Chapter 4).

Management. **Although the classic treatment for an abscess has been percutaneous or open incision and drainage there is good evidence that the intravenous use of antimicrobial agents and careful observation of a small abscess less than 3 cm in diameter, if begun early enough in the course of the process, may obviate surgical procedures** (Hoverman et al, 1980; Levin et al, 1984; Shu et al,

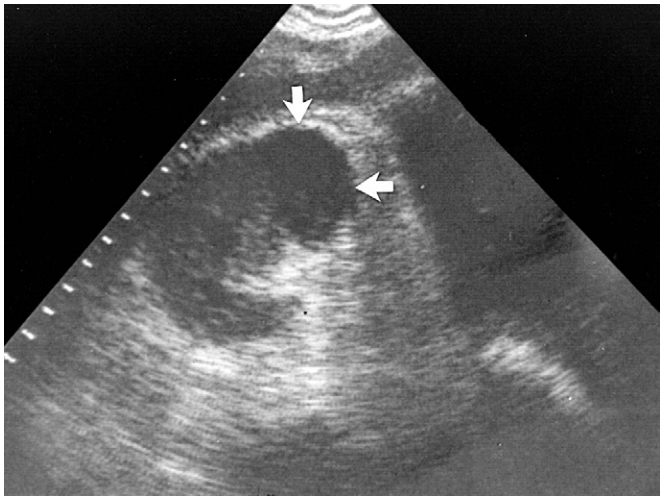


Figure 10–25. Acute renal abscess. Transverse ultrasound image of the right kidney demonstrates a poorly marginated rounded focal hypoechoic mass *(arrows)* in the anterior portion of the kidney.

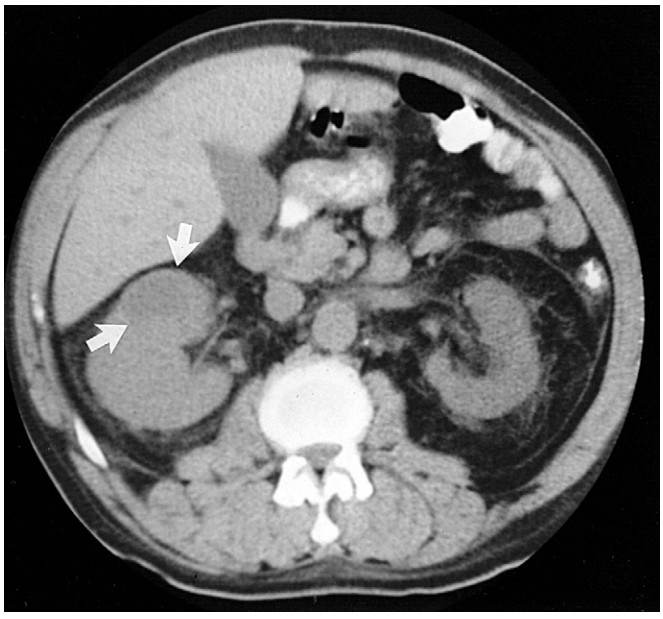


Figure 10–26. Acute renal abscess. Nonenhanced CT scan through the mid pole of the right kidney demonstrates right renal enlargement and an area of decreased attenuation *(arrows)*. After antimicrobial therapy, a follow-up scan showed complete regression of these findings.

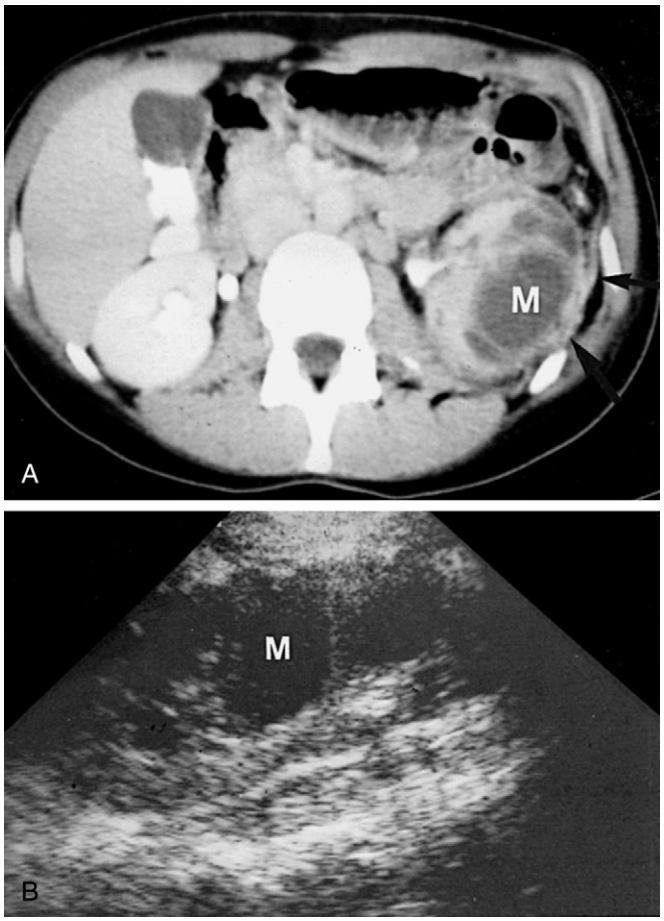


Figure 10–27. Chronic renal abscess. **A,** Enhanced CT scan shows an irregular septated low-density mass (M) extensively involving the left kidney. Note thickening of perinephric fascia *(arrowheads)* and extensive compression of the renal collecting system. Findings are typical of renal abscess. **B,** Ultrasound longitudinal image demonstrates a septated hypoechoic mass (M) occupying much of the renal parenchymal volume.

2004). **CT- or ultrasound-guided needle aspiration may be necessary to differentiate an abscess from a hypervascular tumor.** Aspirated material should be cultured and appropriate antimicrobial therapy instituted on the basis of the findings.

The selection of empirical antimicrobial therapy is dependent on the presumed source of the infection and the resistance patterns within the hospital. When hematogenous dissemination is suspected, the pathogenic organism most frequently is penicillin-resistant *Staphylococcus,* and the antimicrobial of choice therefore is a penicillinase-resistant penicillin (Schiff et al, 1977). If a history of penicillin hypersensitivity is present, the recommended drug is vancomycin. Cortical abscesses that occur in the abnormal urinary tract are associated with more typical gram-negative pathogens and should be treated empirically with intravenous third-generation cephalosporins, antipseudomonal penicillins, or aminoglycosides until specific therapy can be instituted. Patients should have serial examinations with ultrasonography or CT until the abscess resolves. A clinical course contrary to this should lead to the suspicion of misdiagnosis or an uncontrolled infection with the development of perinephric abscess or infection with an organism resistant to the antimicrobial agents used in therapy.

Abscesses 3 to 5 cm in diameter and smaller abscesses in immunocompromised hosts or those that do not respond to antimicrobial therapy should be drained percutaneously (Fernandez et al, 1985; Fowler and Perkins, 1994; Siegel et al, 1996). Surgical drainage, however, currently remains the procedure of choice for most renal abscesses greater than 5 cm in diameter.



Figure 10–28. Pyonephrosis: gross specimen. The kidney shows marked thinning of the renal cortex and medulla, suppurative destruction of the parenchyma *(arrows),* and distention of the pelvis and calyces. Previous incision released a large quantity of purulent material. The ureter showed obstruction distal to the point of section.

Infected Hydronephrosis and Pyonephrosis

***Infected hydronephrosis* is bacterial infection in a hydronephrotic kidney. The term *pyonephrosis* refers to infected hydronephrosis associated with suppurative destruction of the parenchyma of the kidney, in which there is total or nearly total loss of renal function** (Fig. 10–28). Where infected hydronephrosis ends and pyonephrosis begins is difficult to determine clinically. Rapid diagnosis and treatment of pyonephrosis are essential to avoid permanent loss of renal function and to prevent sepsis.

Clinical Presentation. **The patient is usually very ill, with high fever, chills, flank pain, and tenderness.** Occasionally, however, a patient may have only an elevated temperature and a complaint of vague gastrointestinal discomfort. A previous history of urinary tract calculi, infection, or surgery is common. **Bacteriuria may not be present if the ureter is completely obstructed.**

Radiologic Findings. The ultrasonographic diagnosis of infected hydronephrosis depends on demonstration of internal echoes within the dependent portion of a dilated pyelocalyceal system. CT is nonspecific but may show thickening of the renal pelvis, stranding of the perirenal fat, and a striated nephrogram. Ultrasonography demonstrates hydronephrosis and fluid debris levels within the dilated collecting system (Corriere and Sandler, 1982) (Fig. 10–29A). The diagnosis of pyonephrosis is suggested if focal areas of decreased echogenicity are seen within the hydronephrotic parenchyma.

Management. **Once the diagnosis of pyonephrosis is made, treatment is initiated with appropriate antimicrobial drugs and drainage of the infected pelvis.** A ureteral catheter can be passed to drain the kidney, but if the obstruction prevents this, a percutaneous nephrostomy tube

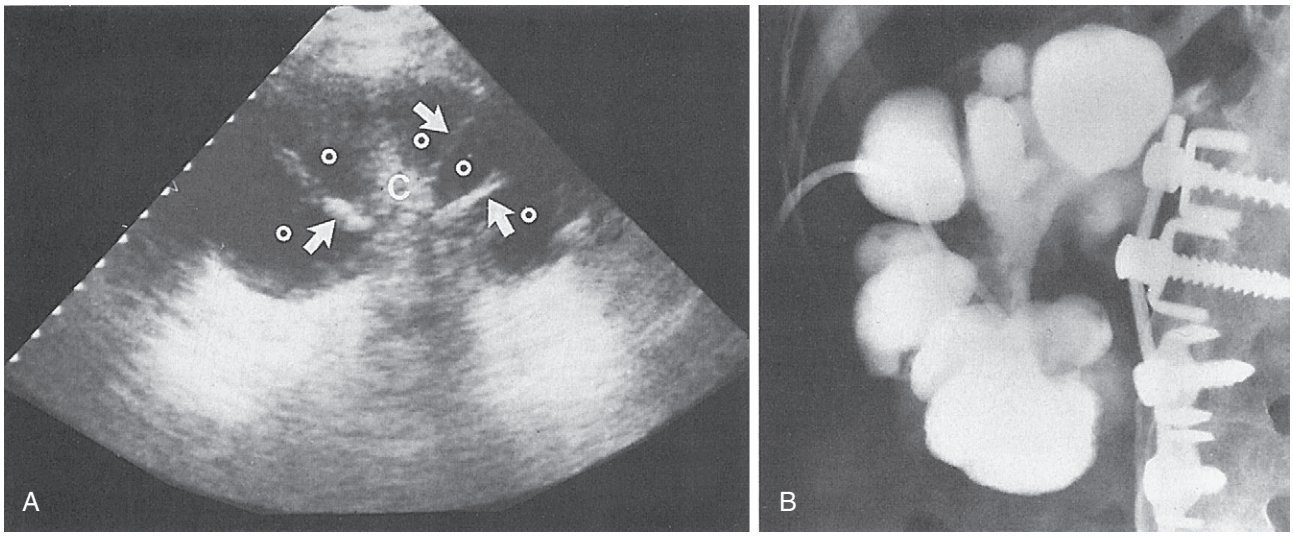


Figure 10–29. Pyonephrosis. **A,** Longitudinal ultrasound image of the right kidney demonstrates echogenic central collecting complex (C) with radiating echogenic septa *(arrows)* and thinned hypoechoic parenchyma. Multiple dilated calyces (o) with diffuse low-level echoes are seen. **B,** Antegrade pyelogram performed through a percutaneous nephrostomy catheter correlates well with the ultrasound image. Dilated pus-filled calyces are demonstrated. The renal pelvis is obliterated by chronic scarring and stone disease. The kidney did not regain function. (From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY et al, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 211–72.)

should be placed (Camunez et al, 1989) (see Fig. 10–29B). When the patient becomes hemodynamically stable, other procedures are usually needed to identify and treat the source of the obstruction.

Perinephric Abscess

Perinephric abscess usually results from rupture of an acute cortical abscess into the perinephric space or from hematogenous seeding from sites of infection. Patients with pyonephrosis, particularly when a calculus is present in the kidney, are susceptible to perinephric abscess formation. Diabetes mellitus is present in approximately one third of patients with perinephric abscess (Thorley et al, 1974; Edelstein and McCabe, 1988). In about one third of the cases, perinephric abscess is caused by hematogenous spread, usually from sites of skin infection. A perirenal hematoma can become secondarily infected by the hematogenous route or by direct extension of a primary renal infection. When a perinephric infection ruptures through the Gerota fascia into the pararenal space, the abscess becomes paranephric. Paranephric abscesses may also result from infectious disorders of the bowel, pancreas, or pleural cavity. Conversely, perinephric or psoas abscess may be the result of bowel perforation, Crohn disease, or spread of osteomyelitis from the thoracolumbar spine. *E. coli, Proteus,* and *S. aureus* account for most infections.

Clinical Presentation. The onset of symptoms is typically insidious. Symptoms are present for more than 5 days in most patients with perinephric abscess compared with only about 10% of patients with pyelonephritis. The clinical presentation may be similar to that of pyelonephritis; however, more than one third of patients may be afebrile. An abdominal or flank mass can be felt in about half of the cases. Psoas abscess should be suspected if the patient has a limp and flexion and external rotation of the ipsilateral hip. Laboratory features include leukocytosis, elevated levels of serum creatinine, and pyuria in more than 75% of cases. Edelstein and McCabe (1988) showed that results of urine cultures predicted perinephric abscess isolates in only 37% of cases; a blood culture, particularly with multiple organisms, was often indicative of perinephric abscess but identified all organisms in only 42% of cases. **Therefore therapy based on the results of urine and blood cultures often may be inadequate. Pyelonephritis usually responds within 4 to 5 days of appropriate antimicrobial therapy; perinephric abscess does not. Thus perinephric abscess should be suspected in a patient with UTI and abdominal or flank mass or persistent fever after 4 days of antimicrobial therapy.**

CT is particularly valuable for demonstrating the primary abscess. In some cases, the abscess is confined to the perinephric space; however, extension to the flank or psoas muscle may occur (Fig. 10–30). CT is able to show with exquisite anatomic detail the route of spread of infection into the surrounding tissues (Fig. 10–31). This information may be helpful in planning the approach for surgical drainage. Ultrasonography demonstrates a diverse appearance ranging from a nearly anechoic mass displacing the kidney to an echogenic collection that tends to blend with normally echogenic fat within the Gerota fascia (Corriere and Sandler, 1982). Occasionally a retroperitoneal or subdiaphragmatic infection may spread to the paranephric fat that is outside this fascia. The clinical symptoms of insidious onset of fever, flank mass, and tenderness are indistinguishable from those associated with perinephric abscess. UTI, however, is absent. Ultrasonography and CT can usually delineate the abscess outside the Gerota fascia.

Management. Although antimicrobial agents are useful to control sepsis and to prevent spread of infection, the primary treatment for perinephric abscess is drainage; reports of successful treatment by antimicrobial agents alone are unusual (Herlitz et al, 1981). A detailed analysis of 52 perinephric abscess patients by Thorley and colleagues (1974) supports this tenet. In this study, half the patients were admitted to medical services and the other half to surgical services; 65% of those admitted to medical services died, whereas 23% of those admitted to surgical services died. These mortality rates reflect differences in the population of patients. Those admitted to the

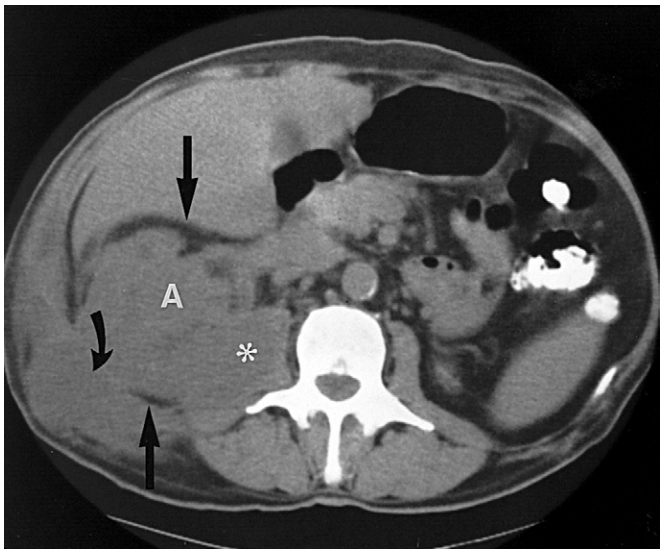


Figure 10–30. Nonenhanced CT scan through the lower pole of the right kidney (previous left nephrectomy) shows extensive perinephric abscess. Extensive abscess (A) distorts and enlarges the renal contour, infiltrates perinephric fat *(straight arrows),* and also extends into the psoas muscle *(asterisk)* and the soft tissues of the flank *(curved arrow)*. Also note that normal renal collecting system fat has been obliterated by the process.

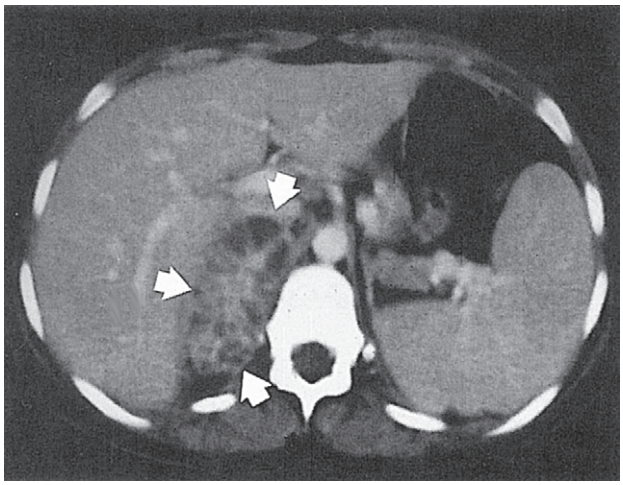


Figure 10–31. Perinephric abscess involving the right adrenal gland. CT scan shows large right pararenal mass *(arrows)* with multiple low-density areas within. At surgery, a large pararenal abscess with extensive involvement of the right adrenal was found. (From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY et al, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 211–72.)

medical services were usually sicker and had higher temperatures, more underlying diseases, and vaguer symptoms. More importantly, none of those admitted to medical wards had an admission diagnosis of perinephric abscess, whereas 73% of those admitted to surgical wards did. Although 71% of all the patients had eventual surgical treatment of their perinephric abscesses, the diagnostic delay of those patients admitted to medical services postponed definitive treatment and consequently caused higher mortality.

Although surgical drainage, or nephrectomy if the kidney is nonfunctioning or severely infected, is the classic treatment for perinephric abscesses, renal ultrasonography and CT make percutaneous aspiration and drainage of small perirenal collections possible (Haaga and Weinstein, 1980; Elyaderani et al, 1981; Edelstein and McCabe, 1988). Haaga and Weinstein (1980), however, consider percutaneous drainage to be contraindicated in large abscess cavities filled with thick, purulent fluid.

Gram stain identifies the pathogenesis and guides antimicrobial therapy. An aminoglycoside together with an antistaphylococcal agent, such as methicillin or oxacillin, should be started immediately. If the patient has a penicillin hypersensitivity, cephalothin or vancomycin may be used.

Once the perinephric abscess has been drained, the underlying problem must be dealt with. Some conditions such as renal cortical abscess or enteric communication require prompt attention. Nephrectomy for pyonephrosis may be performed concurrent with drainage of the perinephric abscess if the patient's condition is good. In other instances it is best to drain the perinephric abscess first and correct the underlying problem or perform a nephrectomy when the patient's condition has improved.

Perinephric Abscess versus Acute Pyelonephritis. It has already been emphasized that the greatest obstacle to the treatment of perinephric abscess is the delay in diagnosis. **In the series of** Thorley and colleagues (1974) **a common misdiagnosis was acute pyelonephritis. In their review they found that two factors differentiated perinephric abscess and acute pyelonephritis: (1) most patients with uncomplicated pyelonephritis were symptomatic for less than 5 days before hospitalization, whereas most with perinephric abscesses were symptomatic for longer than 5 days; and (2) no patient with acute pyelonephritis remained febrile for longer than 4 days once appropriate antimicrobial agents were started. All patients with perinephric abscesses had a fever for at least 5 days, with a median of 7 days. Similar results were noted by** Fowler and Perkins (1994).

Patients with polycystic renal disease who undergo hemodialysis may be particularly susceptible to the progression from acute UTIs to perinephric abscess. Of 445 patients undergoing chronic hemodialysis at the Regional Kidney Disease Program in Minneapolis, 5.4% had polycystic kidney disease and 33.3% of these patients developed symptomatic UTIs (Sweet and Keane, 1979). Eight (62.5%) developed perinephric abscesses, and 3 of these patients died. According to the investigators, all UTIs, even those that progressed to perinephric abscesses, were promptly treated with appropriate antimicrobial agents, and all patients in this group became afebrile and asymptomatic when the agents were stopped. Yet later, after various times, symptoms attributable to perinephric abscess developed in 8 of the patients. The mechanism of this process is not clear, but the limited bioavailability of some antimicrobial agents in cysts is variable and could contribute to the progression of renal infection.

Chronic Pyelonephritis

In patients without underlying renal or urinary tract disease, chronic pyelonephritis secondary to UTI is a rare disease and an even more rare cause of chronic renal failure. In patients with underlying functional or structural urinary tract abnormalities, however, chronic renal infection can cause significant renal impairment. Thus it is essential that appropriate studies be used to diagnose, localize, and treat chronic renal infection.

The prevalence of chronic pyelonephritis has also been assessed in patients undergoing dialysis for end-stage renal disease. Despite

a 2% to 5% prevalence of bacteriuria in women, pyelonephritis uncomplicated by obstruction or urinary tract malformation does not cause end-stage renal disease. Schechter and colleagues (1971) analyzed the cause for renal failure in 170 patients referred to them for dialysis. Chronic pyelonephritis was the primary cause of end-stage renal disease in 22 (13%) but was usually associated with an underlying structural defect. Unequivocal nonobstructive chronic pyelonephritis was not found. The authors also observed that symptomatic infections tended to occur before the onset of azotemia in most patients with chronic pyelonephritis. Similarly, Huland and Busch (1982) evaluated 161 patients with end-stage renal disease and found that 42 had chronic pyelonephritis. However, in addition to a history of UTIs, these 42 patients had complicating defects, such as vesicoureteral reflux, analgesic abuse, nephrolithiasis, or obstruction. Nonobstructive uncomplicated UTI alone was never found to be the cause of renal insufficiency. Thus, using end-stage renal disease seen at autopsy or at the dialysis clinic as an indicator, the prevalence of uncomplicated chronic bacterial pyelonephritis is rare.

In addition, the role of bacterial infection in development of chronic renal disease can be assessed in patients with renal interstitial and tubular damage similar to that which has classically been called chronic pyelonephritis. The frequency with which various potential causes of interstitial damage are operative in patients with interstitial nephritis was assessed by Murray and Goldberg (1975). These investigators not only concluded that UTI is rarely the sole cause of chronic renal disease in the adult but also observed that 89% of their azotemic patients had a readily identifiable primary cause of their interstitial nephritis. Thus, when patients with a clinical diagnosis of chronic interstitial nephritis are selected as the starting point, it is easy to associate many factors with this disease but UTI does not seem to be one of them.

Clinical Presentation. **There are no symptoms of chronic pyelonephritis until it produces renal insufficiency, and then the symptoms are similar to those of any other form of chronic renal failure.** If a patient's chronic pyelonephritis is thought to be an end result of many episodes of acute pyelonephritis, a history of intermittent symptoms of fever, flank pain, and dysuria may be elicited. Similarly, urinary findings and the presence of renal infection correlate poorly. Bacteriuria and pyuria, the hallmarks of UTI, are not predictive of renal infection. Conversely, patients with significant renal infection may have sterile urine if the ureter draining the kidney is obstructed or the infection is outside the collecting system.

The pathologic and radiologic criteria for diagnosing renal infection may also be misleading. Asscher (1980) has tabulated eight long-term follow-up studies from the literature on kidneys of adults with UTIs. The data from these reports on 901 patients show that bacteriuria present in otherwise healthy adults for long periods may be associated with nonexistent or extremely minimal evidence of kidney damage. Conversely, patients who have chronic pyelonephritis may have negative urine cultures.

Radiologic Findings. **The diagnosis of chronic pyelonephritis can be made with the greatest confidence on the basis of pyelographic findings. The essential features are asymmetry and irregularity of the kidney outlines, blunting and dilation of one or more calyces, and cortical scars at the corresponding site** (Fig. 10–32). In the absence of stones, obstruction, and tuberculosis, and with the single exception of analgesic nephritis with papillary necrosis (which can be readily excluded by history), chronic pyelonephritis is virtually the only disease that produces a localized scar over a deformed calyx (Stamey, 1980). In advanced pyelonephritis, calyceal distortion and irregularity together with cortical scars complete the picture. Hodson (1965a) pointed out that renal infarction, an extremely rare condition, may closely resemble pyelonephritic scars but that the renal pyramid remains with renal infarction in contradistinction to pyelonephritis.

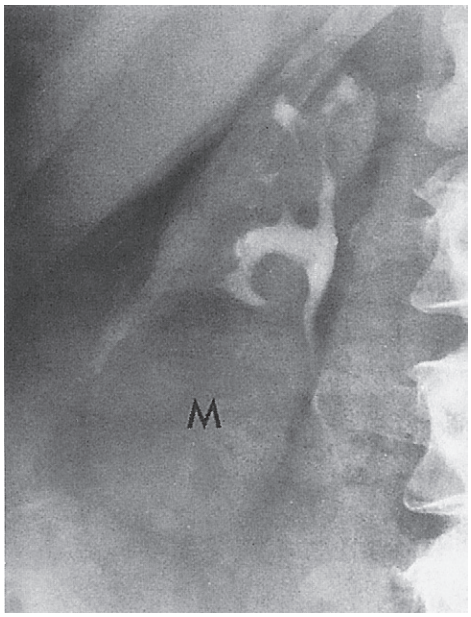


Figure 10–32. Chronic pyelonephritis. Ten-minute excretory urogram demonstrates irregular renal outline with upper pole parenchymal atrophy. Note significant loss of renal cortical thickness over blunted and dilated calyces. Lower pole mass (M) is a simple cyst. (From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY et al, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 211–72.)

Pathology. **In chronic pyelonephritis, the gross kidney is often diffusely contracted, scarred, and pitted.** The scars are Y-shaped, flat, broad-based depressions with red-brown granular bases. The scarring is often polar with underlying calyceal blunting. The parenchyma is thin, and the corticomedullary demarcation is lost. **Histologic changes are patchy.** There is usually an interstitial infiltrate of lymphocytes, plasma cells, and occasional polymorphonuclear cells. Portions of the parenchyma may be replaced by fibrosis, and, although glomeruli may be preserved, periglomerular fibrosis is often seen. In some affected areas, glomeruli may be completely fibrosed and tubules atrophied. Leukocyte and hyaline casts are sometimes present in the tubules; the latter may cause resemblance to the thyroid colloid, hence the description *renal thyroidization* (Braude, 1973). In general, the changes are nonspecific; they also may be seen in toxic exposures, postobstructive atrophy, hematologic disorders, postirradiation nephritis, ischemic renal disease, and nephrosclerosis.

Management. **Management of radiographic evidence of pyelonephritis should be directed at treating infection, if present; preventing future infections; and monitoring and preserving renal function.** The treatment of existing infection must be based on careful antimicrobial susceptibility tests and selection of drugs that can achieve bactericidal concentrations in the urine and yet are not nephrotoxic. Achievement of acceptable bactericidal levels of a drug in the urine of a patient with chronic pyelonephritis may be difficult because the diminished concentrating ability of pyelonephritis may impair excretion

and concentration of the antimicrobial agent. The duration of antimicrobial therapy is often prolonged to maximize the chance of cure. With patients in whom renal damage develops or progresses in the presence of UTI, the working hypothesis should be that there is an underlying renal, usually papillary, lesion or underlying urologic condition, such as obstruction or calculus, that has increased susceptibility to renal damage. Appropriate nephrologic and urologic evaluation should be undertaken to identify and, if possible, correct these abnormalities.

Bacterial "Relapse" from a Normal Kidney

The concept that bacteria persist in the renal parenchyma between bacteriuric episodes and cause "relapsing" UTIs was based on a study by Turck and colleagues (1968) that suggested that bacterial persistence could be recognized by simply identifying two consecutive recurrent infections with the same organism. Unfortunately this study did not indicate whether the urine was cultured during therapy to ensure that the original infection had actually been eradicated. It is possible that some of these so-called relapses were in fact unresolved initial infections and that ureteral edema associated with catheterization may have impeded clearance of the initial infecting strain.

Subsequent studies summarized by Stamey (1980) **and** Forland and associates (1977) **have shown that in a normal urinary tract recurrent infections are not caused by relapse from bacterial persistence in the kidney.** With ureteral catheterization techniques, Cattell (1973) localized the site of bacteriuria in 42 patients who had follow-up for 6 months after therapy. He analyzed the response to antimicrobial therapy of 2 weeks' duration. Of the 26 patients who were cured of their initial infection, 16 had recurrence with the same organism, 8 had upper tract infections, and 8 had bladder bacteriuria.

Most of the changes of chronic pyelonephritis seem to occur in infancy, probably because the growing kidney is most susceptible to scarring. In a review that examined the long-term effect of UTIs in adults it was concluded that renal damage is rare in nonobstructive UTIs (Stamey, 1980) but that it does occur (Bailey et al, 1969; Davies et al, 1972; Davidson and Talner, 1973; Feldberg, 1982).

The association between hypertension and the pyelonephritic kidney has been addressed by Pfau and Rosenmann (1978), who concluded that the association of chronic pyelonephritis and hypertension is usually coincidental. Their conclusion agrees with that of a study by Parker and Kunin (1973) that examined 74 women who had been admitted to the hospital 10 to 20 years previously for pyelonephritis. Only 14.5% of these women had hypertension, a rate similar to that found in a random female population of the same age.

Infectious Granulomatous Nephritis

Xanthogranulomatous Pyelonephritis

Xanthogranulomatous pyelonephritis is a rare, severe, chronic renal infection typically resulting in diffuse renal destruction. Most cases are unilateral and result in a nonfunctioning, enlarged kidney associated with obstructive uropathy secondary to nephrolithiasis. Xanthogranulomatous pyelonephritis is characterized by accumulation of lipid-laden foamy macrophages. It begins within the pelvis and calyces and subsequently extends into and destroys renal parenchymal and adjacent tissues. It has been known to imitate virtually every other inflammatory disease of the kidney, as well as renal cell carcinoma, on radiographic examination (Malek and Elder, 1978; Tolia et al, 1980). In addition, the microscopic appearance of xanthogranulomatous pyelonephritis has been confused with clear cell adenocarcinoma of the kidney on frozen section and has led to radical nephrectomy (Anhalt et al, 1971; Malek and Elder, 1978; Flynn et al, 1979; Lorentzen and Nielsen, 1980; Tolia et al, 1980). The entity is uncommon and is found in only about 0.6% (Malek et al, 1972) to 1.4% (Ghosh, 1955) of patients with renal inflammation who are evaluated pathologically.

Pathogenesis. **The primary factors involved in the pathogenesis of xanthogranulomatous pyelonephritis are nephrolithiasis, obstruction, and infection** (Gregg et al, 1999). Nephrolithiasis has been noted in as many as 83% of the patients in various series; approximately half of the renal stones have been of the staghorn type (Parsons et al, 1983; Chuang et al, 1992; Nataluk et al, 1995). It has been proposed clinically and demonstrated experimentally that primary obstruction followed by infection with *E. coli* can lead to tissue destruction and collections of lipid material by macrophages (Povysil and Konickova, 1972). These macrophages (xanthoma cells) are distributed in sheets around parenchymal abscesses and calyces and are intermixed with lymphocytes, giant cells, and plasma cells. The bacteria appear to be of low virulence because spontaneous bacteremia has rarely been described. Other possible interrelated factors include venous occlusion and hemorrhage, abnormal lipid metabolism, lymphatic blockage, failure of antimicrobial therapy in UTI, altered immunologic competence, and renal ischemia (Friedenberg and Spjut, 1963; Mering et al, 1973; Goodman et al, 1979; McDonald, 1981; Tolia et al, 1981). The concept that xanthogranulomatous pyelonephritis is related to incomplete bacterial degradation and altered host response has received mixed support (Nielsen and Lorentzen, 1981; Khalyl-Mawad et al, 1982). Thus it appears that there is probably no single factor that is instrumental in the pathogenesis of this disease. Rather, there is an inadequate host acute inflammatory response within an obstructed, ischemic, or necrotic kidney.

Pathology. **The kidney is usually massively enlarged and has a normal contour.** Xanthogranulomatous pyelonephritis may be diffuse, as in approximately 80% of the patients, or segmental. In the diffuse form of the disease the entire kidney is involved, whereas in segmental xanthogranulomatous pyelonephritis only the parenchyma surrounding one or more calyces or one pole of a duplicated collecting system is involved. On sectioning, the kidney usually demonstrates nephrolithiasis and peripelvic fibrosis. The calyces are dilated and filled with purulent material, but fibrosis surrounding the pelvis usually prevents dilation. The papillae are often destroyed by papillary necrosis (Goodman et al, 1979). In advanced stages of the disease, multiple parenchymal abscesses are filled with viscous pus and lined by yellowish tissue (Fig. 10–33A). The cortex is often thin and replaced by xanthogranulomatous tissue. The capsule is often thickened, and extension of the inflammatory process into the perinephric or paranephric space is common (Goodman et al, 1979; McDonald, 1981; Gregg et al, 1999).

On microscopic examination the yellowish nodules that line the calyces and surround the parenchymal abscesses contain dark sheets of lipid-laden macrophages (foamy histiocytes with small, dark nuclei and clear cytoplasm) intermixed with lymphocytes, giant cells, and plasma cells (see Fig. 10–33B). Xanthogranulomatous cells are not specific to xanthogranulomatous pyelonephritis but may be present anywhere inflammation or obstruction

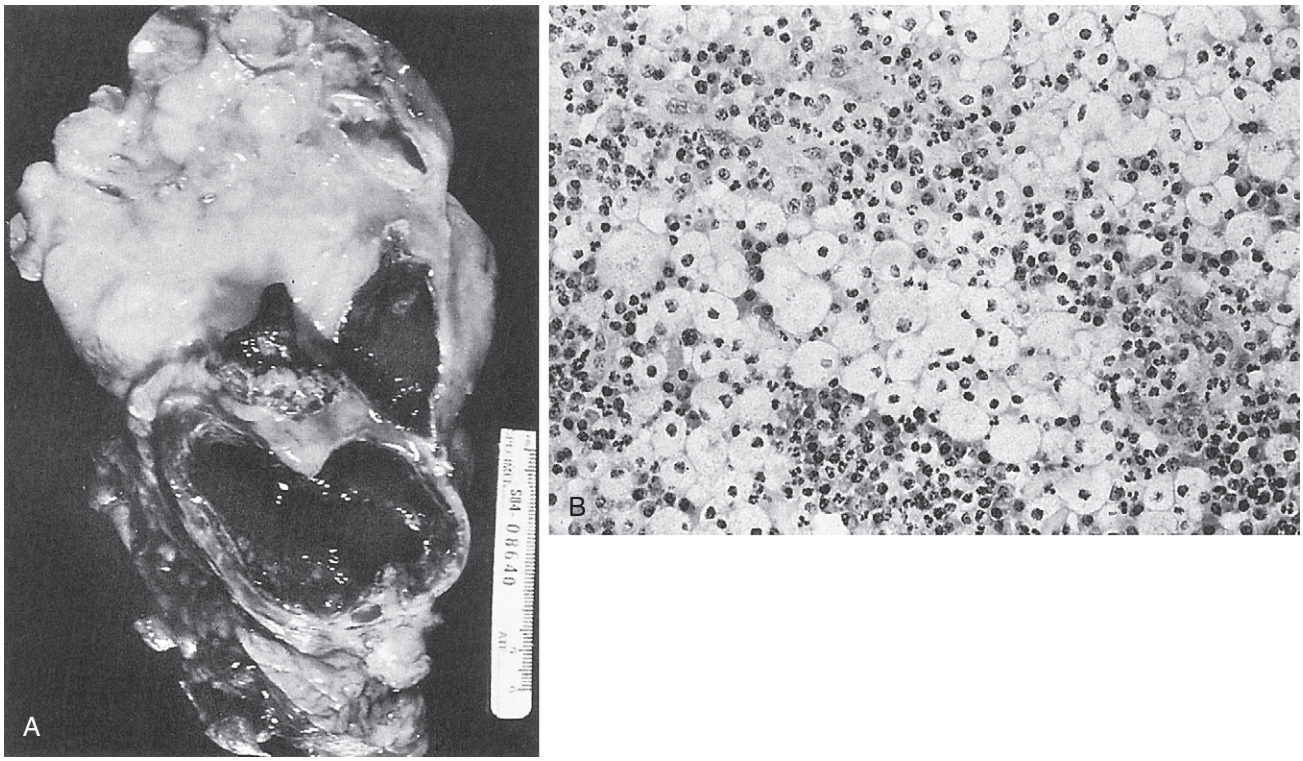


Figure 10–33. Xanthogranulomatous pyelonephritis. **A,** Gross specimen. Kidney is massively enlarged, measuring 23 × 12 cm; the normal architecture is replaced by a shaggy yellow upper pole mass corresponding to xanthogranulomatous inflammation and numerous distorted and dilated calyces. **B,** Microscopically, the shaggy yellow tissue is composed primarily of lipid-laden histiocytes mixed with other inflammatory cells. (From Schaeffer AJ. Urinary tract infections. In: Gillenwater JY et al, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 211–72.)

coexists. The origin of the fatty substance is disputed. Cholesterol esters that make up a part of the lipid might be derived from lysis of erythrocytes after hemorrhage (Saeed and Fine, 1963).

Clinical Presentation. **Xanthogranulomatous pyelonephritis should be suspected in patients with UTIs and a unilateral enlarged nonfunctioning or poorly functioning kidney with a stone or a mass lesion indistinguishable from malignant tumor. Most patients present with flank pain (69%), fever and chills (69%), and persistent bacteriuria (46%)** (Malek and Elder, 1978). **Additional vague symptoms, such as malaise, may be present. On physical examination, 62% of the patients had a flank mass and 35% had previous calculi** (Malek and Elder, 1978). Less commonly, hypertension, hematuria, or hepatomegaly is the presenting complaint. The medical history is often positive for UTIs and urologic instrumentation (Malek and Elder, 1978; Flynn et al, 1979; Goodman et al, 1979; Grainger et al, 1982; Yazaki et al, 1982; Petronic et al, 1989; Eastham et al, 1994; Nataluk et al, 1995). Diabetics also appear to be at greater risk of developing the disease (Eastham et al, 1994). Although it may occur at any age, the peak incidence of xanthogranulomatous pyelonephritis is in the fifth to the seventh decade. Women are more commonly affected than men. There is no predilection for either kidney.

Bacteriology and Laboratory Diagnosis. **Although review of the literature shows *Proteus* to be the most common organism involved with xanthogranulomatous pyelonephritis** (Anhalt et al, 1971; Tolia et al, 1981), ***E. coli* is also common.** The prevalence of *Proteus* organisms may reflect their association with stone formation and subsequent chronic obstruction and irritation. Malek and Elder (1978), in their analysis of 26 cases, found that renal tissue cultures grew bacteria in 22 of 23 cases. Anaerobes also have been cultured (Malek and Elder, 1978).

Approximately 10% of patients have mixed cultures. About one third of patients have no growth in their urine, probably because many patients have recently taken or are taking antimicrobial agents when cultures are obtained. The infecting organism may be revealed only by tissue cultures obtained during surgery. Urinalysis usually shows pus and protein. In addition, blood tests often reveal anemia and may show hepatic dysfunction in up to 50% of the patients (Malek and Elder, 1978).

Xanthogranulomatous pyelonephritis is almost always unilateral; therefore azotemia or frank renal failure is uncommon (Goodman et al, 1979; Gregg et al, 1999).

CT is probably the most useful radiologic technique in evaluating patients with xanthogranulomatous pyelonephritis (Fig. 10–34). **Fifty to 80 percent of patients show the classic triad of unilateral renal enlargement with little or no function and a large calculus in the renal pelvis** (Elder, 1984). **CT usually demonstrates a large, reniform mass with the renal pelvis tightly surrounding a central calcification but without pelvic dilatation** (Solomon et al, 1983; Goldman et al, 1984; Hartman, 1985). Renal parenchyma is replaced by multiple water-density masses representing dilated calyces and abscess cavities filled with varied amounts of pus and debris. On enhanced scans the walls of these cavities demonstrate a prominent blush owing to the abundant vascularity within the granulation tissue. The cavities themselves, however, fail to enhance, whereas tumors and other inflammatory lesions usually do. The CT scan is particularly helpful in demonstrating the extent of renal involvement and may indicate whether

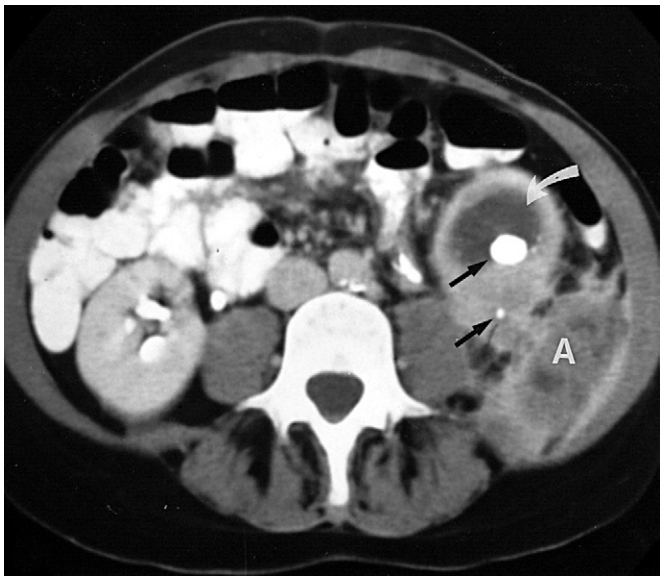


Figure 10–34. Xanthogranulomatous pyelonephritis. Enhanced CT scan shows collecting system and parenchymal calculi *(straight arrows)* with lower pole pyonephrosis *(curved arrow)* and an irregular, predominantly low-density perinephric abscess (A) extending into the soft tissues of the flank.

adjacent organs or the abdominal wall are involved by xanthogranulomatous pyelonephritis (Eastham et al, 1994; Kaplan et al, 1997).

Ultrasonography usually demonstrates global enlargement of the kidney (Merenich and Popky, 1991). The normal renal architecture is replaced by multiple hypoechoic fluid-filled masses that correspond to debris-filled, dilated calyces or foci of parenchymal destruction (Fagerholm, 1983; Hartman et al, 1984). With focal involvement, a solid mass involving a segment of the kidney is demonstrated with an associated calculus in the collecting system or ureter. Renal cell carcinoma and other solid renal lesions must be considered in the differential diagnosis (Elder, 1984).

Radionuclide renal scanning using ^{99m}Tc-DMSA is used to confirm and quantify the differential lack of function in the involved kidney (Gregg et al, 1999). MRI has not yet superseded CT in the evaluation of renal inflammation but it provides some advantages in delineating extrarenal extension of inflammation (Soler et al, 1997). Lesions of xanthogranulomatous pyelonephritis may appear as cystic foci of intermediate signal intensity on T1-weighted images and of hyperintensity on T2-weighted images. Arteriography shows hypervascular areas, but there may be some hypovascular areas (Malek and Elder, 1978; Van Kirk et al, 1980; Tolia et al, 1981). Therefore radiologic studies, although distinctive, often cannot be used to differentiate between xanthogranulomatous pyelonephritis and renal cell carcinoma.

Differential Diagnosis. Diagnosis of segmental xanthogranulomatous pyelonephritis without calculi may be difficult. Xanthogranulomatous pyelonephritis in association with massive pelvic dilation cannot be distinguished from pyonephrosis. When xanthogranulomatous pyelonephritis occurs within a small contracted kidney, the radiographic findings are nonspecific and nondiagnostic. Renal parenchymal malacoplakia may show renal enlargement and multiple inflammatory masses replacing the normal renal parenchyma, but calculi are usually not present. Renal lymphoma may be associated with multiple hypoechoic masses surrounding the contracted, nondilated pelvis, but lymphoma is usually clinically obvious, and renal involvement is usually bilateral and not associated with calculi (Hartman, 1985).

Management. The primary obstacle to the correct treatment of xanthogranulomatous pyelonephritis is incorrect diagnosis. Today, with CT technology, the diagnosis of xanthogranulomatous pyelonephritis is made preoperatively nearly 90% of the time (Eastham et al, 1994; Nataluk et al, 1995). Antimicrobial therapy may be necessary to stabilize the patient preoperatively, and, occasionally, long-term antimicrobial therapy will eradicate the infection and restore renal function (Mollier et al, 1995). Because the renal abnormality may be diagnosed preoperatively as a renal tumor and/or is diffuse, nephrectomy is usually performed. If localized xanthogranulomatous pyelonephritis is diagnosed preoperatively or at exploration, it is amenable to partial nephrectomy (Malek and Elder, 1978; Tolia et al, 1980; Osca et al, 1997).

The lipid-laden macrophages associated with xanthogranulomatous pyelonephritis, however, closely resemble clear cell adenocarcinoma and may be difficult to distinguish solely on the basis of frozen section. Furthermore, xanthogranulomatous pyelonephritis has been associated with renal cell carcinoma, papillary transitional cell carcinoma of the pelvis or bladder, and infiltrating squamous cell carcinoma of the pelvis (Schoborg et al, 1980; Pitts et al, 1981; Tolia et al, 1981); thus if malignant renal tumor cannot be excluded, nephrectomy should be performed. When diffuse and extensive disease into the retroperitoneum exists, removal of the kidney and perinephric fat may be needed. Under these circumstances the surgery may be difficult and may involve dissection of granulomatous tissue from the diaphragm, great vessels, and bowel (Malek and Elder, 1978; Flynn et al, 1979). It is important to remove the entire inflammatory mass because in nearly three fourths of patients xanthogranulomatous tissue is infected. If incision and drainage alone are performed rather than nephrectomy the patient may continue to suffer from protracted debilitating illness and may develop a renal cutaneous fistula; an even more difficult nephrectomy will then be necessary. In one early case-matched series of laparoscopic nephrectomies performed for xanthogranulomatous pyelonephritis it was concluded that the benefits of laparoscopic surgery do not extend to the treatment of this disease (Bercowsky et al, 1999); however, a larger review of a modern xanthogranulomatous pyelonephritis experience suggests that laparoscopic nephrectomy is a reasonable treatment approach.

Malacoplakia

Malacoplakia, from the Greek word meaning "soft plaque," is an unusual inflammatory disease that was originally described to affect the bladder but has been found to affect the genitourinary and gastrointestinal tracts, skin, lungs, bones, and mesenteric lymph nodes. It is an inflammatory lesion described originally by Michaelis and Gutmann (1902). It was characterized by von Hansemann (1903) as soft, yellow-brown plaques with granulomatous lesions in which the histiocytes contain distinct basophilic lysosomal inclusion bodies or Michaelis-Gutmann bodies. Although its exact pathogenesis is unknown, malacoplakia probably results from abnormal macrophage function in response to a bacterial infection, which is most often due to *E. coli*.

Pathogenesis. The pathogenesis is unknown, but several theories are popular. In 93 patients who had cultures of urine, diseased tissue, or blood, 89.4% had coliform infections (Stanton and Maxted, 1981). Moreover, 40% of the patients in this review had

an immunodeficiency syndrome, autoimmune disease, carcinoma, or another systemic disorder. This association of coliform infections and compromised health status in patients with malacoplakia is well recognized.

It is hypothesized that bacteria or bacterial fragments form the nidus for the calcium phosphate crystals that laminate the Michaelis-Gutmann bodies. Most investigations into the pathogenesis of this disease support theories that a defect in intraphagosomal bacterial digestion accounts for the unusual immunologic response that causes malacoplakia.

Pathology. **The diagnosis is made by biopsy. The lesion is characterized by large histiocytes, known as *von Hansemann cells,* and small basophilic, extracytoplasmic, or intracytoplasmic calculospherules called Michaelis-Gutmann bodies, which are pathognomonic** (Fig. 10–35). Electron microscopy has revealed intact coliform bacteria and bacterial fragments within phagolysosomes of the foamy-appearing malacoplakic histiocytes (Lewin et al, 1976; Stanton and Maxted, 1981). In their review of the subject, Stanton and Maxted (1981) and Esparza and associates (1989) emphasized that, although pathognomonic for the disease, Michaelis-Gutmann bodies may be absent in early malacoplakia and are not necessary for the diagnosis.

It has been shown that macrophages in malacoplakia involving the kidney and bladder contain large amounts of immunoreactive α_1-antitrypsin (Callea et al, 1982). The amount of α_1-antitrypsin remains unchanged during the morphogenetic stages of the pathologic process. Macrophages from other pathologic processes, closely resembling malacoplakia but without Michaelis-Gutmann bodies, do not contain α_1-antitrypsin except for a few macrophages in tuberculosis and xanthogranulomatous pyelonephritis. **Therefore immunohistochemical staining for α_1-antitrypsin may be a useful test for an early and accurate differential diagnosis of malacoplakia.**

Clinical Presentation. **Most patients are older than 50 years.** The ratio of females to males with malacoplakia within the urinary tract is 4:1, but this disparity does not occur in other body tissues (Stanton and Maxted, 1981). The patients often are debilitated, are immunosuppressed, and have other chronic diseases. The symptoms of bladder malacoplakia are bladder irritability and hematuria. Cystoscopy reveals mucosal plaques or nodules. As these lesions progress they may become fungating, firm, sessile masses that cause filling defects of the bladder, ureter, or pelvis on excretory urograms. The distal ureter may become strictured or stenotic and cause subsequent renal obstruction or nonfunction (Sexton et al, 1982). A typical patient with renal parenchymal disease may have one or more radiographic masses and chronic

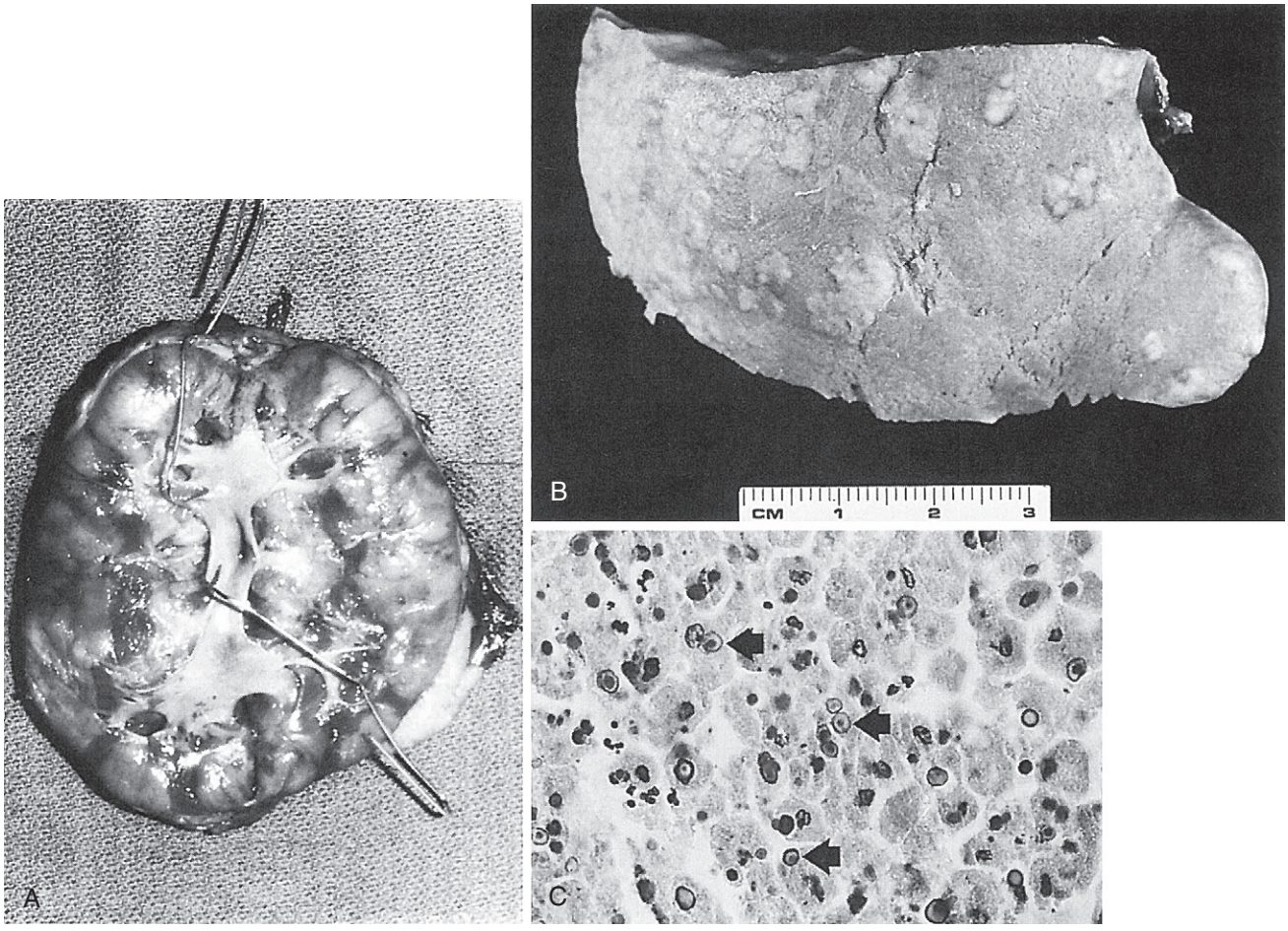


Figure 10–35. Renal parenchymal malacoplakia. **A,** Cut surface demonstrates extensive cortical and upper medullary replacement by multifocal, confluent, tumor-like masses. **B,** Cortical surface exhibits multiple, firm, plaquelike lesions. **C,** Hallmark of malacoplakia is demonstration of the Michaelis-Gutmann body *(arrows),* which represents incompletely destroyed bacteria surrounded by lipoprotein membrane (hematoxylin-eosin stain). (From Hartman DS. Radiologic pathologic correlation of the infectious granulomatous diseases of the kidney: I and II. Monogr Urol 1985;6:3.)

E. coli infections. Renal parenchymal malacoplakia may be complicated by renal vein thrombosis and inferior vena cava thrombosis (McClure, 1983). When malacoplakia involves the testis, epididymo-orchitis is present. Malacoplakia of the prostate is rare, but, when it occurs, it may be confused with carcinoma clinically (Shimizu et al, 1981). Mortality can exceed 50%, and the morbidity can be substantial (Stanton and Maxted, 1981).

Radiologic Findings. **Multifocal malacoplakia on excretory urography typically presents as enlarged kidneys with multiple filling defects.** Renal calcification, lithiasis, and hydronephrosis are absent. The multifocal nature is best appreciated by using ultrasonography, CT, or arteriography. Ultrasound examination may demonstrate renal enlargement and distortion of the central echo complex. The masses are often confluent, resulting in an overall increase in the echogenicity of the renal parenchyma (Hartman et al, 1980). On CT the foci of malacoplakia are less dense than the surrounding enhanced parenchyma (Hartman, 1985). Arteriography typically reveals a hypovascular mass without peripheral neovascularity (Cavins and Goldstein, 1977; Trillo et al, 1977).

Unifocal malacoplakia on excretory urography appears as a noncalcified mass that is indistinguishable from other inflammatory or neoplastic lesions. Ultrasonography and CT may demonstrate a solid or cystic structure, depending on the degree of internal necrosis. Angiography may demonstrate neovascularity (Trillo et al, 1977). Extension beyond the kidney, which can occur with either multifocal or uniform malacoplakia, is best demonstrated by CT.

Differential Diagnosis. The differential diagnosis includes renal cystic disease, neoplasia, and renal inflammatory disease (Hartman, 1985). Malacoplakia should be considered when one or more renal masses are observed, particularly in female patients with recurrent UTIs with *E. coli,* altered immune response syndromes, or cystoscopic evidence of malacoplakia or filling defects in the collecting system (Charboneau, 1980). Malacoplakia should also be suspected when these radiographic findings occur in a renal transplant patient who has persistent UTI despite appropriate antimicrobial therapy. Cystic disease generally can be excluded by careful ultrasound and CT evaluations. Renal involvement with metastatic disease or lymphomas usually occurs late in the course of the disease, which is well established. Multifocal renal cell carcinoma is most often seen in the context of von Hippel-Lindau disease with its other clinical manifestations. Patients with xanthogranulomatous pyelonephritis usually have signs and symptoms of UTI. As with malacoplakia, the involved kidney is enlarged but renal calculi and obstruction are common. Multiple renal abscesses are often associated with hematogenous dissemination resulting from cardiac disease.

Management. **Management of malacoplakia should be directed at control of the UTIs, which should stabilize the disease process.** This subject is well reviewed by Stanton and Maxted (1981). Although multiple long-term antimicrobial agents, including many antituberculosis agents, have been used, the sulfonamides, rifampin, doxycycline, and TMP are thought to be especially useful because of their intracellular bactericidal activity (Maderazo et al, 1979). Fluoroquinolones are taken up by macrophages directly and have also proven effective in the management of malacoplakia (Vallorosi et al, 1999). Other investigators have used ascorbic acid and cholinergic agents such as bethanechol in conjunction with antimicrobial therapy and have reported good results (Abdou et al, 1977; Zornow et al, 1979; Stanton et al, 1983). Both agents are thought to increase intracellular cyclic guanosine monophosphate levels, which have been postulated as the biologic defect causing macrophage dysfunction. Surgical intervention, however, may be necessary if the disease progresses in spite of antimicrobial treatment. Nephrectomy is usually performed for the treatment of symptomatic unilateral renal lesions.

The long-term prognosis appears to be related to the extent of the disease. When parenchymal renal malacoplakia is bilateral or occurs in the transplanted kidney, death usually occurs within 6 months (Bowers and Cathey, 1971; Deridder et al, 1977). Patients with unilateral disease usually have a long-term survival after nephrectomy.

Renal Echinococcosis

Echinococcosis is a parasitic infection caused by the larval stage of the tapeworm *Echinococcus granulosus*. The disease is prevalent in dogs, sheep, cattle, and humans in South Africa, Australia, New Zealand, Mediterranean countries (especially Greece), and some parts of the former Soviet Union. In the United States the disease is rare, but it is found in immigrants from Eastern Europe or other foreign endemic areas or as an indigenous infection among American Indians in the Southwest and in Eskimos (Plorde, 1977).

Pathogenesis and Pathology. **Echinococcosis is produced by the larval form of the tapeworm, which in its adult form resides in the intestine of the dog, the definitive host.** The adult worm is 3 to 9 mm long. The ova in the feces of the dog contaminate grass and farmlands and are ingested by sheep, pigs, or humans, the intermediate hosts. Larvae hatch, penetrate venules in the wall of the duodenum, and are carried by the bloodstream to the liver. Those larvae that escape the liver are next filtered by the lungs. Approximately 3% of the organisms that escape entrapment in the liver and lungs may then enter the systemic circulation and infect the kidneys. The larvae undergo vesiculation, and the resultant hydatid cyst gradually develops at a rate of about 1 cm/yr. Thus the cyst may take 5 to 10 years to reach pathologic size.

Echinococcosis cysts of the kidney are usually single and located in the cortex (Nabizadeh et al, 1983). The wall of the hydatid cyst has three zones: a peripheral zone of fibroblasts derived from tissues of the host becomes the adventitia and may calcify; an intermediate laminated layer becomes hyalinized; and a single inner layer is composed of nucleated epithelium and is called the *germinal layer.* The germinal layer gives rise to brood capsules that increase in number, become vacuolated, and remain attached to the germinal membrane by a pedicle. New larvae (scoleces) develop in large numbers from the germinal layer within the brood capsule (Fig. 10–36). The hydatid cyst is also filled with fluid. When brood capsules detach, they enlarge and move freely in the fluid and are then called daughter cysts. Hydatid sand is composed of free larvae and daughter cysts.

Clinical Presentation. **The symptoms of echinococcosis are those of a slowly growing tumor. Most patients are asymptomatic or have a flank mass, dull pain, or hematuria** (Gilsanz et al, 1980; Nabizadeh et al, 1983). Because the cyst is focal, it rarely affects renal function. Rarely, the cyst ruptures into the collecting system, and the patient may experience severe colic and passage of debris resembling grape skins in the urine (hydatiduria). The cyst may also rupture into an adjacent viscus or the peritoneal cavity. The fluid is extremely antigenic (Hartman, 1985).

Laboratory Diagnosis. **If cyst rupture occurs, the definitive diagnosis can be established by identifying daughter cysts in the urine or by identifying the laminated wall of the cyst** (Sparks et al, 1976). Fewer than half of the patients

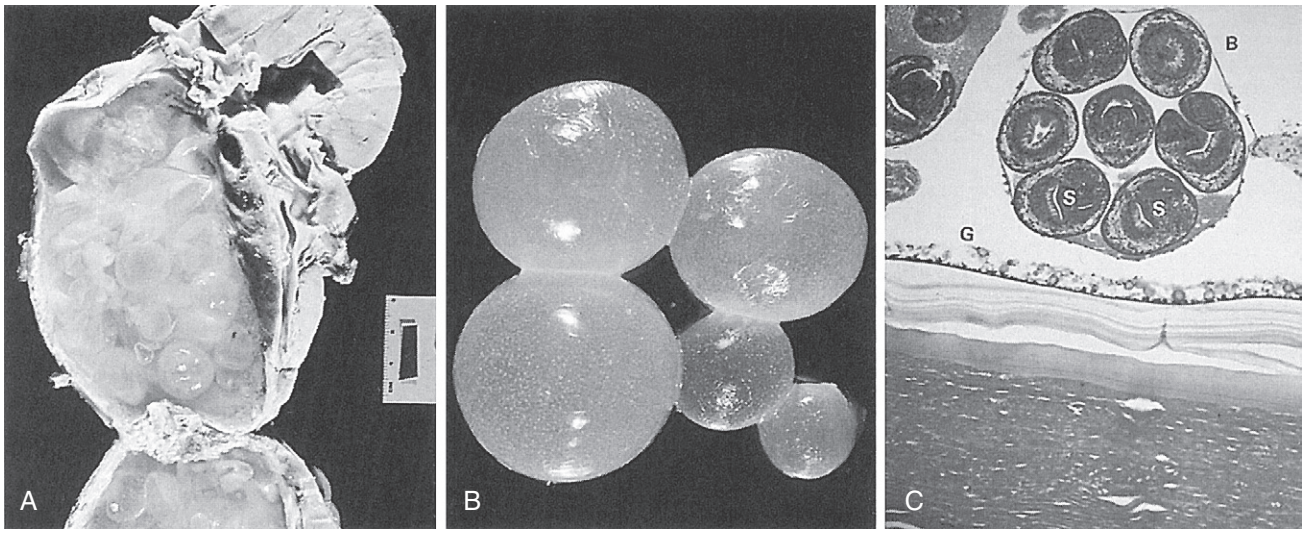


Figure 10–36. Echinococcosis. **A,** Gross specimen. A cystic mass measuring 7 × 11 cm in the lower pole. Smaller daughter cysts are identified within the larger cystic mass. **B,** Gross specimen. Daughter cysts represent brood capsules that have detached and move freely. **C,** Photomicrograph. Brood capsules (B) arising from the germinal layer (G) contain viable and degenerating scoleces (S). (From Hartman DS. Radiologic pathologic correlation of the infectious granulomatous diseases of the kidney: III and IV. Monogr Urol 1985;6:26.)

have eosinophilia. The most reliable diagnostic test uses partially purified hydatid arc 5 antigens in a double-diffusion test (Coltorti and Varela-Diaz, 1978). Complement fixation, HA, and the Casoni intradermal skin tests are less reliable but, when combined, are positive in about 90% of patients (Sparks et al, 1976).

Radiologic Findings. **Excretory urography typically shows a thick-walled cystic mass, occasionally calcified** (Buckley et al, 1985). If the cyst ruptures into the collecting system, daughter cysts may be outlined in the pelvis as an irregular mass or as multiple solitary lesions (Gilsanz et al, 1980). Occasionally, direct filling of the cyst with contrast medium occurs.

Ultrasonography and CT are useful in characterizing the mass. Ultrasonography usually demonstrates a multicystic or multiloculated mass. A sudden change in position may demonstrate bright falling echoes corresponding to hydatid sand, which can be observed during real-time evaluation of hydatid cysts (Saint Martin and Chiesa, 1984).

On CT several patterns of renal echinococcosis may be recognized. The most specific is a cystic mass with discrete, round daughter cysts and a well-defined enhancing membrane (Martorana et al, 1981). The less-specific pattern is that of a thick-walled multiloculated cystic mass (Gilsanz et al, 1980). The presence of daughter cysts within the mother cyst differentiates the lesion from a simple renal cyst and from renal abscesses, infected cysts, and necrotic neoplasm.

Both CT and ultrasonography are useful in evaluating the liver. Angiography is seldom required. **Diagnostic aspiration should not be performed because of the danger of rupture and spillage of the highly antigenic cyst contents and risk of fatal anaphylaxis.** Nevertheless, Baijal and coworkers (1995) described a percutaneous management of renal hydatidosis as a minimally invasive diagnostic and therapeutic option.

Management. **The prognosis of echinococcosis is good but depends on the site and size of the cysts.** Medical treatment with benzimidazole compounds such as mebendazole or albendazole has shown limited success with significant side effects (Nabizadeh et al, 1983).

Surgery remains the mainstay of treatment of renal echinococcosis (Poulios, 1991). The cyst should be removed without rupture to reduce the chance of seeding and recurrence. If the cyst wall is calcified, the larvae are probably dead and the risk of seeding is low, although a daughter cyst may be viable. If the cyst ruptures or cannot be removed and marsupialization is required, then the contents of the cyst initially should be aspirated and filled with a scolicidal agent such as 30% sodium chloride, 0.5% silver nitrate, 2% formalin, or 1% iodine for approximately 5 minutes to kill the germinal portion (Sparks et al, 1976; Nabizadeh et al, 1983; Shetty et al, 1992).

Key Points: Kidney Infections

- Acute pyelonephritis classically presents as the abrupt onset of chills, fever, and flank or costovertebral angle tenderness but can present as symptoms as mild as cystitis or as severe as sepsis.
- Emphysematous pyelonephritis is a life-threatening infection diagnosed radiographically by the presence of gas in the parenchyma or collecting system and managed surgically.
- Renal abscesses are well delineated by CT and are classically managed with intravenous antimicrobial agents and drainage.
- Pyonephrosis is a bacterial infection in a hydronephrotic kidney. Prompt diagnosis is critical; treatment entails intravenous antimicrobial agents and drainage of the obstructed renal unit.
- Xanthogranulomatous pyelonephritis is a chronic renal infection that is often found in poorly functioning renal units obstructed secondary to nephrolithiasis. Xanthogranulomatous pyelonephritis can be mistaken for renal tumors.
- Malacoplakia is an unusual inflammatory disease thought to result from abnormal macrophage function. Michaelis-Gutmann bodies are lysosomal inclusion bodies that characterize this disease microscopically.

BACTEREMIA, SEPSIS, AND SEPTIC SHOCK

Sepsis is a clinical syndrome characterized by extremes of body temperature, heart rate, respiratory rate, and WBC count that occur in response to an infection. A typical host response to infection involves localized containment and elimination of bacteria and repair of damaged tissue. This process is facilitated by macrophages and dendritic cells and orchestrated by CD4+ T helper cells via the release of both proinflammatory and anti-inflammatory molecules (cytokines, chemokines, interferons). Sepsis occurs when a local infectious process becomes an uncontrolled systemic blood-borne inflammatory response resulting in damage to tissues or organs remote from the initial site of infection or injury.

Definitions

Bacteremia: the presence of viable bacteria in the blood.

Systemic inflammatory response syndrome (SIRS): a clinical syndrome characterized by the 2001 International Sepsis Definitions Conference (Levy et al, 2003) as extremes of body temperature, heart rate, ventilation, and immune response. A detailed list of diagnostic criteria is presented in Table 10–24. **SIRS can occur in response to multiple insults including systemic infection, trauma, thermal injury, or a sterile inflammation.**

Sepsis: SIRS and infection either documented or strongly suspected.

Septic shock: an extreme form of sepsis complicated by organ dysfunction and persistent circulatory failure despite fluid and pharmacologic resuscitation.

Table 10–24.

Characteristics of Sepsis

General
Fever (core temperature >38.3° C)
Hypothermia (core temperature <36° C)
Heart rate >90 min, 1 or 2 SD above the normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (20 mL/kg/24 hr)
Hyperglycemia (plasma glucose >120 mg/dL or 7.7 mol/L) in the absence of diabetes
Inflammatory
Leukocytosis (WBC count >12,000/μL)
Leukopenia (WBC count <4000/μL)
Normal WBC count with >10% immature forms
Organ Dysfunction
Arterial hypoxemia (PaO_2/FIO_2 >300)
Acute oliguria (urine output 0.5 mL/kg in 1 hr for at least 2 hr)
Creatinine increase of 0.5 mg/dL
Coagulation abnormalities (INR 1.5 or aPTT >60 sec)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count <100,000/μL)
Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)
Tissue Perfusion
Hyperlactatemia (>1 mmol/L)
Decreased capillary refill or mottling

INR, international normalized ratio; aPTT, activated partial thromboplastin time.
From Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003;31:1250–6.

Pathophysiology

Initial studies of pathophysiologic features of septic shock concentrated on the interactions of lipopolysaccharides (LPS) from the gram-negative bacterial cell wall with various innate immune system pathways. More recent investigations now focus on understanding the activation and regulation of both the innate and acquired immune systems and the array of cytokines that are released during localized and systemic inflammatory responses.

Bacterial Cell Wall Components in Septic Shock

The exotoxins produced by some bacteria (e.g., exotoxin A produced by *P. aeruginosa*) can initiate septic shock. **However, the bacteria themselves, and in particular their cell wall components, are primarily responsible for the development of septic shock. These components activate numerous innate immunologic pathways, including macrophages, neutrophils, and dendritic cells and the complement system. The prime initiator of gram-negative bacterial septic shock is endotoxin, an LPS component of the bacterial outer membrane.** Endotoxin can directly activate the coagulation, complement, and fibrinolytic systems, leading to the release of small molecules that cause vasodilation and increased endothelial permeability (Tapper and Herwald, 2000).

Cytokine Network

Monocytic cells appear to have a pivotal role in mediation of the biologic effects of SIRS and septic shock. Monocytes can remove and detoxify LPS and be beneficial to the host. However, LPS-stimulated monocytes produce cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-1. The intravascular activation of inflammatory systems involved in septic shock is mainly the consequence of an overproduction of these and other cytokines. Production of these cytokines is modulated by CD4+ T helper cells. Type 1 CD4+ T helper cells release proinflammatory cytokines including TNF-α, interferon-γ, and IL-2. These cytokines are also produced by macrophages, endothelial cells, and other cells stimulated by microbial products. The systemic release of large amounts of the cytokine TNF is associated with death from septic shock in humans (Waage et al, 1987; Calandra et al, 1988; Girardin et al, 1988). However, despite the fact that TNF is classically regarded as a central mediator of pathophysiologic changes associated with sepsis, the role of attenuation of this and other proinflammatory cytokines remains unclear. For example, in one animal model of peritonitis, survival was worsened by the administration of antibodies blocking TNF (Eskandari et al, 1992). Also, patients suffering from rheumatoid arthritis treated with TNF-α agents remain susceptible to the development of septic shock. Lastly, a meta-analysis of clinical trials utilizing anti-inflammatory agents in sepsis suggested these agents were generally harmful in all but a small subset of patients (Hotchkiss and Karl, 2003). More recently, anti-inflammatory cytokines, including IL-4 and IL-10, released by type II CD4+ T helper cells, have also been noted to be elevated in sepsis, further illustrating the complex regulation of the both proinflammatory and anti-inflammatory cytokines in a septic patient. In summary, both proinflammatory and anti-inflammatory cytokines are elements

of early sepsis; however, the role of cytokine modulation in the treatment of sepsis remains unclear.

Clinical Presentation and Diagnosis

Early signs of the systemic inflammatory response syndrome include temperature extremes (>38° C [100.4° F] or <36° C [96.8° F]), tachycardia (heart rate >90 beats per minute), tachypnea, and altered mental status. The classic bedside findings differentiating septic shock from other types of shock include a warm patient, brisk capillary refill, and a bounding pulse reflecting pyrexia, peripheral vasodilation, and decreased systemic vascular resistance. Other diagnostic criteria include evidence of organ dysfunction such as hypotension, oliguria, or ileus and laboratory abnormalities including leukocytosis or leukopenia, hyperbilirubinemia, hyperlactatemia, hyperglycemia, coagulation abnormalities, and elevated C-reactive protein and procalcitonin (see Table 10–24 for complete list of Consensus Conference criteria). The classic clinical presentation of fever and chills followed by hypotension is manifest only in about 30% of patients with gram-negative bacteremia (McClure, 1983). Even before temperature extremes and the onset of chills, bacteremic patients often begin to hyperventilate. Thus the earliest metabolic change in septicemia is a resultant respiratory alkalosis. In critically ill patients, the sudden onset of hyperventilation should lead to blood drawing for culture and careful evaluation of the patient. Changes in mental status can also be important clinical clues. Although the most common pattern is lethargy or obtundation, an occasional patient may become excited, agitated, or combative. Cutaneous manifestations such as the bull's-eye lesion associated with *P. aeruginosa* may be identified.

Metastatic infections secondary to genitourinary tract bacteremia have been described (Siroky et al, 1976). In this review of 137 patients who developed metastatic infections from bacteremia with a genitourinary source, 79% had undergone prior urologic instrumentation, 59% developed skeletal infections, mainly of the spine; and 29% developed endocarditis, most commonly caused by *E. faecalis*.

Bacteriology

In classic studies of sepsis syndrome and septic shock, gram-negative bacteria were predominant organisms isolated in 30% to 80% of cases and gram-positive bacteria in 5% to 24% (Ispahani et al, 1987; Calandra et al, 1988; Bone, 1991). Although *E. coli* is the most common organism causing gram-negative bacteremia, many nosocomial catheter-associated infections are caused by highly resistant gram-negative organisms: *P. aeruginosa*, *Proteus*, *Providencia*, and *Serratia*. *Acinetobacter* and *Enterobacter* are also emerging as important nosocomial pathogens. In a large series, *E. coli* caused about one third of the cases; the *Klebsiella-Enterobacter-Serratia* family, approximately 20%; and *Pseudomonas*, *Proteus, Providencia,* and anaerobic species, approximately 10% each (Kreger et al, 1980). Anaerobic organisms may cause bacteremia when the source is a postsurgical intra-abdominal abscess or transrectal prostatic biopsy. More recent studies suggest the incidence of sepsis caused by both gram-positive bacterial and fungal organisms is increasing (Martin et al, 2003) and reinforce the need for initial broad-spectrum antimicrobial coverage.

Management

The principles of management of sepsis include resuscitation, supportive care, monitoring, administration of broad-spectrum antimicrobial agents, and drainage or elimination of infection (Dellinger et al, 2004; Sessler et al, 2004). Although the identification and early intervention of sepsis by the urologist is important, the use of expert consultants is also recommended because management of sepsis and the critically ill patient is complex and always evolving.

Principles of resuscitation include support of the airway and breathing and optimization of perfusion. Intubation and mechanical ventilation may be required in patients who are obtunded and are unable to protect their airway. Supplemental oxygen may be instituted, but supranormal oxygen delivery is no longer considered a goal of therapy (Dellinger et al, 2004). Tissue perfusion should first be optimized with fluid resuscitation to restore mean circulating filling pressures. If additional blood pressure support is needed, vasoactive agents including phenylephrine, norepinephrine, and dopamine can be instituted; however, low-dose dopamine administration for renal protection is no longer recommended by critical care experts. Other principles of resuscitation and supportive care include optimization of oxygen delivery, the use of stress-dose corticosteroid therapy, correction of coagulopathies if clinically significant, maintenance of blood glucose levels below 150 mg/dL, and implementation of hemofiltration as needed.

Identification of the presumptive source of infection and cultures from corresponding fluids and blood should be obtained before the initiation of antimicrobial therapy. Multiple blood cultures for aerobic and anaerobic organisms should be obtained. In addition, all potential sources of bacteremia must be cultured (i.e., urine, sputum, and wounds). Careful attempts to identify the source of infection should be made, because the choice of appropriate antimicrobial coverage depends on the organisms that are thought most likely to cause the infection. The severity of the underlying disease and the possibility of synergistic interactions are also important considerations. If the urinary tract is the most likely portal of entry, a broad-spectrum antimicrobial agent either alone or in combination with an aminoglycoside should be administered. **Three clinical factors have been predictive of the subsequent isolation of a resistant pathogen: (1) the use of an antimicrobial drug in the last month, (2) advanced age, and (3) male sex** (Leibovici et al, 1992). If the infection is hospital acquired, or if the patient has had multiple infections or is immunocompromised or severely ill, an aminoglycoside and anti-*Pseudomonas* β-lactam or a third-generation cephalosporin should be used. When identification and drug susceptibilities of the offending organism are known, antimicrobial therapy should be changed to use the lowest cost, least toxic antimicrobial with the narrowest antimicrobial coverage. Antimicrobial treatment should be continued until the patient has been afebrile for 3 to 4 days and is clinically stable. Local infections that may have provided the focus for the bacteremia should be treated individually as appropriate.

Early studies suggested that recombinant human activated protein C (drotrecogin alfa), an inhibitor of multiple inflammatory and coagulation pathway components, could be used to lower mortality in sepsis (Bernard et al, 2001). However, meta-analysis of two large randomized trials raised doubt about the clinical usefulness of activated protein C in reducing mortality in sepsis (Wiedermann and Kaneider, 2005).

Key Points: Bacteremia, Sepsis, and Septic Shock

- Sepsis is a clinical syndrome characterized by extremes of body temperature, heart rate, respiratory rate, and WBC count that occurs in response to an infection.
- The principles of management of sepsis include resuscitation, supportive care, monitoring, administration of broad-spectrum antimicrobial agents, and drainage or elimination of infection.

BACTERIURIA IN PREGNANCY

Asymptomatic bacteriuria is one of the most common infectious complications of pregnancy. The prevalence of bacteriuria does not change initially with the occurrence of pregnancy and ranges from 2% to 7% (Hooton et al, 2000). The risk of acquiring bacteriuria during pregnancy increases with the progression of pregnancy (Norden and Kass, 1968; Campbell-Brown et al, 1987; Stenqvist et al, 1989), lower socioeconomic class, multiparity, and sickle cell traits (Patterson and Andriole, 1987; Stenqvist et al, 1989).

The site of bacteriuria in pregnant female patients probably also reflects the situation before conception. In two studies that localized the origin of the bacteriuria, one using the Stamey ureteral catheterization technique and the other the Fairley bladder washout, upper tract infections were found in 44% and 24.5% of pregnant female patients, respectively (Fairley et al, 1966; Heineman and Lee, 1973). In nonpregnant females with recurrent bacteriuria, Stamey (1980) has reported about a 50% probability that the origin is in the upper tract. With other techniques, which may reflect the severity of tissue infection rather than the location of infection, the results are similar; approximately 50% of women with screening bacteriuria of pregnancy are fluorescent antibody-positive (Fa^+) and thus have evidence of upper tract infection (Harris et al, 1976). Fairley and his group (1973) found that the site of infection is unrelated to the likelihood that pyelonephritis will develop during pregnancy.

Spontaneous resolution of bacteriuria in pregnant women is unlikely unless treated. Nonpregnant patients often clear their asymptomatic bacteriuria (Hooton et al, 2000), **but pregnant women become symptomatic more frequently and tend to remain bacteriuric** (Elder et al, 1971).

Pyelonephritis develops in 1% to 4% of all pregnant women (Sweet, 1977) **and in 20% to 40% of pregnant women with untreated bacteriuria** (Pedler and Bint, 1987; Wright et al, 1993). **Of the women who develop pyelonephritis during pregnancy, 60% to 75% acquire it during the third trimester** (Cunningham et al, 1973), **when hydronephrosis and stasis in the urinary tract are most pronounced. From 10% to 20% of pregnant women who get pyelonephritis develop it again before or just after the delivery** (Cunningham et al, 1973; Gilstrap et al, 1981). Moreover, a third of pregnant women who develop pyelonephritis have a documented prior history of pyelonephritis (Gilstrap et al, 1981). Treatment of screening bacteriuria of pregnancy decreases the incidence of acute pyelonephritis during pregnancy from a range of 13.5% to 65% to a range of 0% to 5.3% (Sweet, 1977).

In Sweet's excellent review (1977) of bacteriuria and pyelonephritis during pregnancy, he suggests that patients with a renal source of bacteriuria are more likely to have persistent postpartum bacteriuria than those with cystitis alone. In addition, those women with persistent bacteriuria may have an increased incidence of impaired creatinine clearance and urinary concentrating ability and an increased incidence of radiographic changes compatible with chronic pyelonephritis. His review of 12 studies revealed that follow-up excretory urograms in pregnant women with bacteriuria showed an 8% to 33% incidence of radiologic changes compatible with chronic pyelonephritis; the incidence of all urinary tract abnormalities in this group was 18% to 80%.

Zinner and Kass (1971) estimated that approximately 10% of bacteriuric pregnant females have pyelographic evidence of pyelonephritis, and, in their study, these abnormalities were most common in women who had bacteriuria 10 to 14 years after pregnancy. The highest incidence of radiographic changes of pyelonephritis was found in women who had their infections localized to the upper urinary tract (Fairley et al, 1966). In this study, abbreviated excretory urograms were performed within a few days of localization of the infection by ureteral catheterization. Six women (30%) with upper UTIs revealed radiographic renal abnormalities compatible with chronic pyelonephritis on the side to which the infection was localized, and two (10%) had nonexcretion of one kidney with infection in the contralateral one. No patient with an infection localized to the bladder showed radiographic evidence of pyelonephritis.

In their evaluation of renal function, Zinner and Kass (1971) found that women who had had bacteriuria during pregnancy and had it again 10 to 14 years later on follow-up showed significantly lower mean maximal urine osmolalities than those who were not bacteriuric on follow-up. Others have found evidence of decreased creatinine clearance and concentrating ability in bacteriuric women post partum (Sweet, 1977). It is unlikely, however, that uncomplicated bacteriuria in pregnant women produces changes in kidney appearance or function different from those found in nonpregnant bacteriuric women. After observing 40 bacteriuric women during pregnancy, Kincaid-Smith (1978) stated that there was no difference in renal size or function between 6 months and 4 years after delivery. Pregnancy, therefore, may provide the opportunity for bacteriuria to be discovered, but this bacteriuria probably reflects only a susceptibility to UTI that was present at conception. **The increased likelihood that bacteriuria may progress to acute pyelonephritis during pregnancy alters the morbidity of bacteriuria for this group.** Treatment of asymptomatic bacteriuria found early in pregnancy has been shown to decrease the prevalence of subsequent acute pyelonephritis from 28% to less than 3% (Sweet, 1977).

Pathogenesis

The anatomic and physiologic changes induced by the gravid state significantly alter the natural history of bacteriuria (Patterson and Andriole, 1987). **These changes may cause pregnant women to be more susceptible to pyelonephritis and may require alteration of therapy.** These changes have been well summarized in several reviews (Davidson and Talner, 1978; Waltzer, 1981).

Anatomic and Physiologic Changes during Pregnancy

Increase in Renal Size

Renal length increases approximately 1 cm during normal pregnancy. It is thought that this does not represent true hypertrophy

but is the result of increased renal vascular and interstitial volume. No histologic changes have been identified in renal biopsy specimens (Waltzer, 1981).

Smooth Muscle Atony of the Collecting System and Bladder

The collecting system, especially the ureters, undergoes decreased peristalsis during pregnancy, and most women in their third trimester show significant ureteral dilatation (Davison and Lindheimer, 1978; Kincaid-Smith, 1978; Waltzer, 1981) (Fig. 10–37). This hydroureter has been attributed both to the muscle-relaxing effects of increased progesterone during pregnancy and to mechanical obstruction of the ureters by the enlarging uterus at the pelvic brim. Progesterone-induced smooth muscle relaxation also may cause an increased bladder capacity (Waltzer, 1981). Later in pregnancy, the dilation may be the result of the obstructive effect of the enlarging uterus (Poole and Thorsen, 1999).

Bladder Changes

The enlarging uterus displaces the bladder superiorly and anteriorly. The bladder becomes hyperemic and may appear congested endoscopically (Waltzer, 1981). Estrogen stimulation probably causes bladder hypertrophy as well as squamous changes of the urethra (Waltzer, 1981).

Augmented Renal Function

The transient increases in glomerular filtration rate and renal plasma flow during pregnancy have been well summarized by several authors and are probably secondary to the increase in cardiac output (Zacur and Mitch, 1977; Davison and Lindheimer, 1978; Kincaid-Smith, 1978; Waltzer, 1981). Glomerular filtration increases by 30% to 50%, and urinary protein excretion increases. **The significance of these physiologic changes is apparent when the normal serum creatinine and urea nitrogen values for pregnant women are surveyed** (Table 10–25). **Values considered normal in nonpregnant women may represent renal insufficiency during pregnancy.**

Davison and Lindheimer (1978) recommend that pregnant patients with serum creatinine levels greater than 0.8 mg/dL or urea nitrogen levels greater than 13 mg/dL undergo further evaluation of renal function. Similarly, **urinary protein in pregnancy is not considered abnormal until greater than 300 mg of protein in 24 hours is excreted.**

These significant physiologic changes in pregnancy, which may develop as early as the first trimester, lead to urinary stasis and

Table 10–25.

Average Values for Serum Creatinine and Urea Nitrogen

	NONPREGNANT FEMALES (mg/dL)	PREGNANT FEMALES (mg/dL)
Serum creatinine	0.7	0.5
Urea nitrogen	13.0	9.0

Data from Davison JM, Lindheimer MD. Renal disease in pregnant women. Clin Obstet Gynecol 1978;21:411.

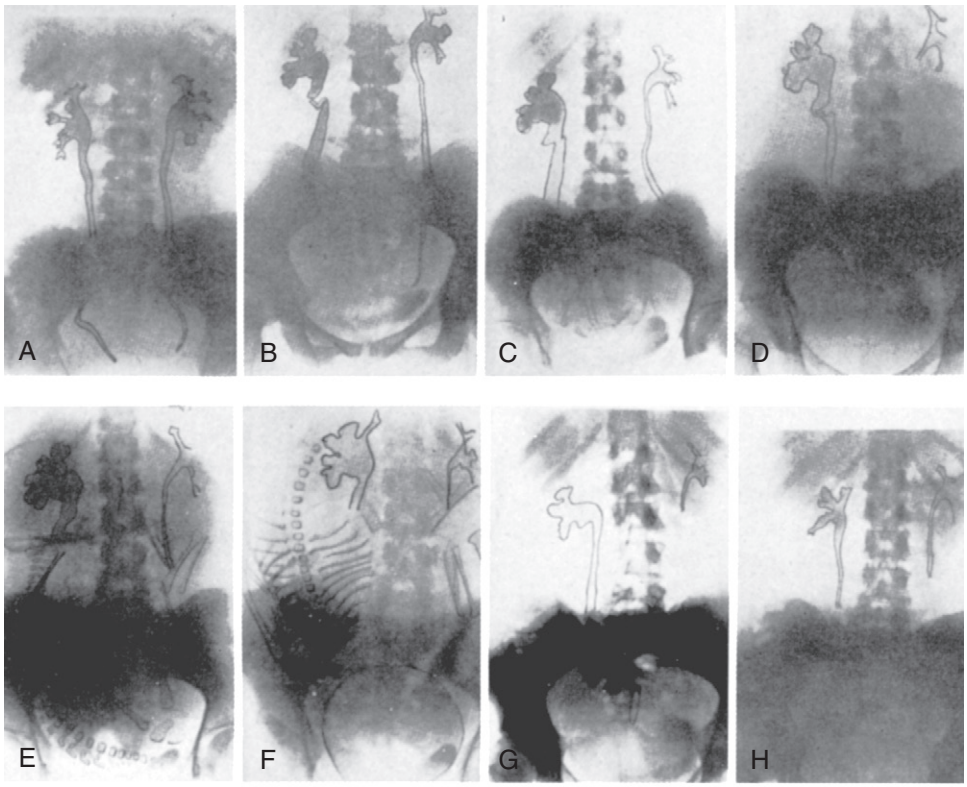


Figure 10–37. Progressive hydroureter and hydronephrosis observed on IVGs during a normal pregnancy. **A,** 15 weeks; **B,** 18 weeks; **C,** 22 weeks; **D,** 26 weeks; **E,** 34 weeks; **F,** 39 weeks; **G,** 1 week post partum; **H,** 6 weeks post partum. Bilateral hydroureter and hydronephrosis are shown as early as 15 weeks (**A**). **B** to **H,** Successive urograms are from one patient during a normal pregnancy. Dilation occurs mainly on the right side, and both urinary tracts are normal by 6 weeks after delivery. (**A** to **H,** From Hundley JM, Walton HJ, Hibbits JT, et al. Physiologic changes occurring in the urinary tract during pregnancy. Am J Obstet Gynecol 1935;30:625–49.)

mild hydroureteronephrosis, and contribute to development of pyelonephritis.

Recent studies of *E. coli* adhesins and their respective specific tissue receptors have established an adhesin-based mechanism of pyelonephritis-induced preterm births and low birth weights in mice (Kaul et al, 1999). There is a higher incidence of *E. coli*-bearing Dr adhesins during the third trimester of pregnancy in women with gestational pyelonephritis (Nowicki et al, 1994) and an upregulation of Dr adhesin in the kidney, endometrium, and placenta during the third trimester of pregnancy (Martens et al, 1993). When infected intravesically with *E. coli*-bearing Dr adhesin, nearly 90% of mice that were hyporesponsive to bacterial lipopolysaccharide and had a deficient immune response delivered preterm, compared with 10% of mice infected with *E. coli* without Dr adhesin. Also, there was a significant reduction in fetal birth weight in the Dr adhesin-infected group. Bacterial tissue culture showed systemic spread of the *E. coli*-bearing Dr adhesins to the placentae and fetuses.

Complications Associated with Bacteriuria during Pregnancy

Prematurity and Prenatal Mortality

In the preantimicrobial era, pregnant women with symptomatic UTIs and bacterial pyelonephritis were reported to have a high incidence of prematurity, low birth weight, and death (Gilstrap et al, 1981). The relationship between asymptomatic bacteriuria and prematurity is less clear. Gilstrap and colleagues (1981) found no difference in pregnancy among patients treated for asymptomatic bacteriuria as compared with nonbacteriuric controls. **However, because women with asymptomatic bacteriuria are at higher risk for developing a symptomatic UTI that results in adverse fetal sequelae, complications associated with bacteriuria during pregnancy, and pyelonephritis and its possible sequelae, such as sepsis in the mother, all women with asymptomatic bacteriuria should be treated** (Smaill, 2001).

Maternal Anemia

Although several studies suggest that bacteriuria untreated during pregnancy is associated with maternal anemia, not all studies support this. Some difficulties in interpreting the results of these surveys have been caused by inadequate documentation of bacteriuria. In one survey in which urine cultures were obtained by suprapubic aspiration, the data suggest that pregnant patients requiring three or more treatments for bacteriuria have lower levels of serum hemoglobin and folate than controls (McFadyen et al, 1973). In another study from England, investigators showed a statistically significant difference in the incidence of anemia between 410 bacteriuric pregnant women and 409 control pregnant women (Williams et al, 1973). In this survey, 14.6% of bacteriuric women and 10% of control women were anemic at the first prenatal visit. This separation increased during the third trimester (32 weeks), when 25% of women treated with placebo alone had anemia but only 16.8% of those women treated with antimicrobial agents had anemia. Furthermore, in the 31 untreated (placebo-treated) bacteriuric women who subsequently developed pyelonephritis, the incidence of anemia was 45.2%. These investigators concluded that "untreated bacteriuria increases the likelihood of developing anemia during pregnancy and that this risk is enhanced by the development of acute pyelonephritis, even if it is treated promptly."

Laboratory Diagnosis

Significant false-negative rates occur if screening is conducted by urinalysis or reagent strip testing (Preston et al, 1999; McNair et al, 2000). **Therefore an initial screening culture should be performed in all pregnant women during the first trimester** (Stenqvist et al, 1989). If the culture shows no growth, repeat cultures are generally unnecessary because patients who have no growth in their urine early in their pregnancy are unlikely to develop bacteriuria later (Norden and Kass, 1968; McFadyen et al, 1973). Pregnant women with a history of recurrent UTI or vesicoureteral reflux may benefit from antimicrobial prophylaxis (Bukowski et al, 1998).

Management

Selection of an antimicrobial agent to treat the bacteriuria must be made, however, with special considerations given to maternal and fetal toxicity. The physiologic changes of pregnancy may decrease tissue and serum drug concentrations. Maternal expanded fluid volume, the distribution of the drug in the fetus, increased renal blood flow, and increased glomerular filtration decrease the serum drug concentration. If the culture is positive, special consideration must be given to the selection of antimicrobial agents chosen to treat infection to prevent fetal toxicity. The pathogens are similar to those seen in nonpregnant women (MacDonald et al, 1983). Table 10–26 lists the antimicrobial agents and dosing for use in pregnancy. The aminopenicillins and cephalosporins are considered safe and generally effective throughout pregnancy. In patients with penicillin allergy, nitrofurantoin is a reasonable alternative. It may be used safely during the first two trimesters in patients without glucose-6-phosphate dehydrogenase deficiency. Given the low efficacy of short-course β-lactam therapy in nonpregnant women, it is prudent to describe a full 3- to 7-day course of therapy in pregnant women. Follow-up cultures should be obtained to document absence of infection. If the culture is positive, the cause of bacteriuria must be determined to be lack of resolution, bacterial persistence, or reinfection. If the infection is unresolved, proper selection and administration of another drug probably will solve the problem. If the problem is bacterial persistence or rapid reinfection, antimicrobial suppression of infection or prophylaxis (Pfau and Sacks, 1992) throughout the remainder of the pregnancy should be considered.

Pregnant women with acute pyelonephritis should be hospitalized and treated initially with parenteral antimicrobial agents. More than 95% of these patients respond within 24 hours using ampicillin and an aminoglycoside (Cunningham et al, 1973) or cephalosporins (Sanchez-Ramos et al, 1995). Appropriate oral agents should then be given for at least 14 days (Faro et al, 1984). After the treatment course is completed, low-dose prophylaxis with nitrofurantoin, amoxicillin, or cephalexin has been shown to be effective in preventing reinfection (Van Dorsten et al, 1987; Sandberg and Brorson, 1991). The efficacy of postcoital prophylaxis with either cephalexin (250 mg) or nitrofurantoin (50 mg) has been reported (Pfau and Sacks, 1992).

Drugs that are relatively contraindicated during pregnancy include the fluoroquinolones, TMP, chloramphenicol, erythromycin, tetracycline, sulfonamides, and sometimes nitrofurantoin (Nicolle, 1987). Fluoroquinolones are contraindicated because of their effects on immature cartilage. TMP may have teratogenic effects and should be avoided, especially in the first trimester. The "gray baby" syndrome is a toxic effect of chloramphenicol on neonates resulting from the inability of the infant to metabolize

Table 10–26.

Oral Antimicrobial Agents Used in Pregnancy

DRUG	DOSAGE	COMMENTS
Agents Considered Safe		
Penicillins		
Ampicillin	500 mg qid	Extensively used
Amoxicillin	250 mg tid	Safe and effective
Penicillin V	500 mg qid	Used less frequently but achieves excellent urinary levels
Cephalosporins		
Cephalexin	500 mg qid	Extensively used
Cefaclor	500 mg qid	Somewhat more effective against gram-negative organisms
Nitrofurantoin	100 mg qid	May be used during the first two trimesters; may result in hemolytic anemia in patients with G6PD deficiency
Sulfasoxazole	1 g, followed by 500 mg qid	May cause kernicterus in the newborn; also may cause hemolytic anemia when G6PD deficiency is present; especially avoid in last few weeks of gestation
Agents That Should Be Avoided		
Fluoroquinolones		Possible damage to immature cartilage
Chloramphenicol		Associated with "gray baby" syndrome
Trimethoprim		May cause megaloblastic anemia because of anti–folic acid action
Erythromycin		Associated with maternal cholestatic jaundice
Tetracyclines		May cause acute liver decompensation in the mother and inhibition of new bone growth in the fetus

G6PD, glucose-6-phosphate dehydrogenase.

Adapted from Schaeffer AJ. Urinary tract infections. In: Gillenwater JY, Grayhack JT, Howards SS, Mitchell ME, editors. Adult and pediatric urology. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 211–72.

or excrete the drug. Erythromycin may cause cholestatic jaundice in the mother. Tetracycline may cause fetal malformations and maternal liver decompensation. Sulfonamides may cause kernicterus and neonatal hyperbilirubinemia and should be avoided in the third trimester. As mentioned earlier, nitrofurantoin can cause hemolytic anemia in both mother and child when glucose-6-phosphate dehydrogenase deficiency is present (Nicolle, 1987).

Pregnancy in Women with Renal Insufficiency

With current management of recurrent UTIs, infections alone are no contraindication to pregnancy. In patients who have renal insufficiency with or without UTIs, Davison and Lindheimer (1978) emphasize that renal function should be carefully evaluated by both serum creatinine levels and creatinine clearance before a woman is counseled about conceiving or continuing a pregnancy. Although little is known about the outcome of pregnancies with differing degrees of renal insufficiency, it is known that normal pregnancy is rare if the preconception serum creatinine level exceeds 3 mg/dL (about 30 mL/min clearance).

Table 10–27.

Bacteriuria in Two Population Surveys

AGE (yr)	MEN (%)	WOMEN (%)
65-70	2-3	20-21
>80	21-22	23-50

Data from Brocklehurst JC, Dillane JB, Griffiths L, et al. Prevalence and symptomatology of urinary infection in an aged population. Gerontol Clin 1968;10:242–53; and Sourander LB. Urinary tract infections in the aged: an epidemiological study. Ann Med Intern Fenn 1966;55(Suppl. 45):7–55.

The degree of renal function impairment is the major determinant for pregnancy outcome. The fetal survivors of pregnant women with mild or moderate renal disease (serum creatinine <1.4 mg/dL and from 1.4 mg/dL to 2.4 to 2.8 mg/dL, respectively) is only slightly diminished, and irreversible deterioration of maternal renal function is uncommon. However, the perinatal mortality is approximately four times higher with severe disease. The rate of perinatal morbidity due to low birth weight or prematurity doubles from mild to moderate renal disease, and again from moderate to severe disease (Vidaeff et al, 2008).

Key Points: Bacteriuria in Pregnancy

- Screening for bacteriuria with a culture should be performed in all pregnant women during the first trimester.
- The prevalence of bacteriuria does not change with the occurrence of pregnancy; however, unlike in nonpregnant women, spontaneous resolution of bacteriuria in pregnant women is unlikely.
- All pregnant women with bacteriuria should be treated.
- Bacteriuria more commonly progresses to acute pyelonephritis during pregnancy.
- Pyelonephritis develops in 1% to 4% of all pregnant women (Sweet, 1977) and in 20% to 40% of pregnant women with untreated bacteriuria.
- Pregnant women with acute pyelonephritis should be hospitalized and treated initially with parenteral antimicrobial agents.

BACTERIURIA IN THE ELDERLY

UTIs in the elderly are a common and expanding health problem (Kaye, 1980). In 2003 there were almost 34 million Americans older than 65 years (U.S. Census Bureau, 2003). As the life expectancy increases, the diagnosis, treatment, morbidity, and mortality of UTIs in the elderly will assume increasing importance.

Epidemiology

At least 20% of women and 10% of men older than 65 years have bacteriuria (Boscia and Kaye, 1987). In contrast to young adults, in whom bacteriuria is 30 times more prevalent in women than in men, the ratio in women to men with bacteriuria progressively decreases to 2:1. Most elderly patients with bacteriuria are asymptomatic; estimates among women living in nursing homes range from 17% to 55%, as compared with 15% to 31% for their male cohorts (Nicolle, 1994). The prevalence of bacteriuria in the elderly increases with age (Table 10–27) (Sourander, 1966; Brocklehurst et al, 1968) and concurrent disease (Fig. 10–38) and may exceed 50% in selective groups (Boscia and Kaye, 1987;

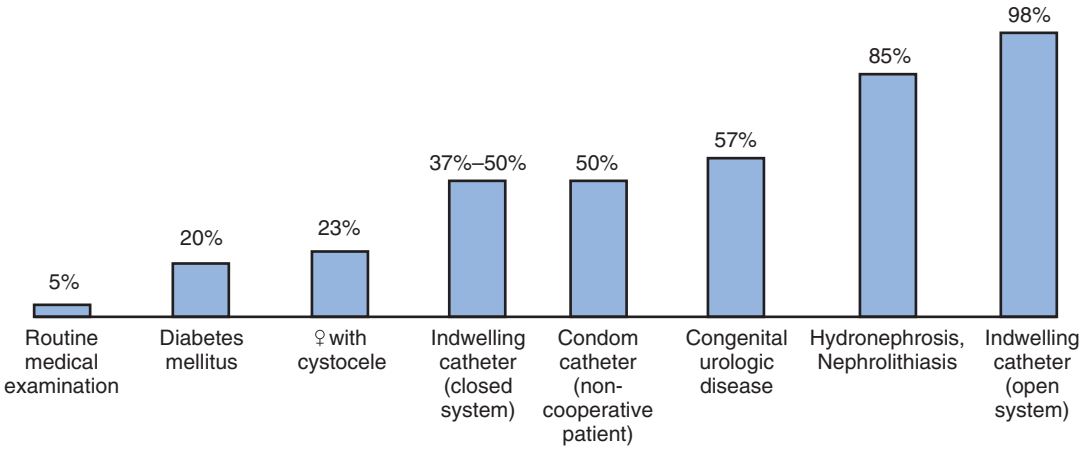


Figure 10–38. Frequency of significant bacteriuria related to underlying disease. (Adapted from Jackson GG, Arana-Sialer JA, Andersen BR. Profiles of pyelonephritis. Arch Intern Med 1962;110:663–75.)

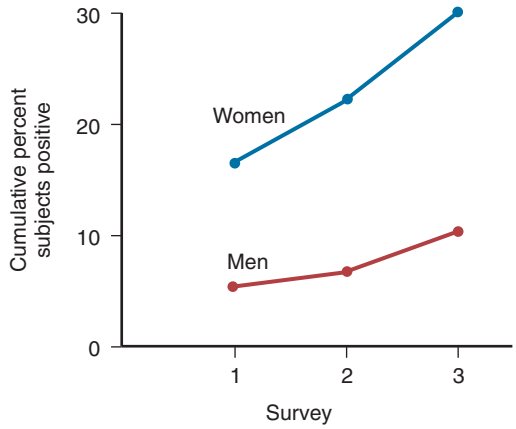


Figure 10–39. Cumulative percentage of subjects (age = 65 years) with at least one positive urine culture survey result over three surveys performed at 6-month intervals. (From Boscia JA, Kobasa WD, Knight RA, et al. Epidemiology of bacteriuria in an elderly ambulatory population. Am J Med 1986;80:208.)

Schaeffer, 1991). Risk factors can be compounded. In a study of 373 women and 150 men older than 68 years, 24% of functionally impaired nursing home residents had bacteriuria compared with 12% of healthy domiciliary subjects (Boscia et al, 1986). Longitudinal studies have clarified the dynamic aspect of bacteriuria in the elderly with frequent, spontaneous alteration between positive and negative urine cultures (Monane et al, 1995) (Fig. 10–39). There is only a small pool of elderly patients with persistent bacteriuria (Kaye, 1980). The incidence of asymptomatic bacteriuria is much more common than is apparent from a single survey, implying that most elderly will eventually have episodes of bacteriuria (Boscia et al, 1986).

Pathogenesis

The pathophysiology of increased susceptibility is multifactorial and poorly understood. **Age-related changes include decline in cell-mediated immunity, neurogenic bladder dysfunction, increased perineal soiling as a result of fecal and urinary incontinence, increased incidence of urethral catheter placement, and, in women, changes in the vaginal environment associated with estrogen depletion** (Schaeffer, 1991; Raz and Stamm, 1993). Increased receptivity of uroepithelial cells (Reid et al, 1984) and a decrease in prostatic and vaginal antimicrobial factors associated with changes in pH and levels of zinc and hormones have been observed (Boscia et al, 1986). Bacteriologic characteristics of infection in the elderly differ from those in younger patients (Baldassarre and Kaye, 1991). *E. coli* remains the most common uropathogen, causing 75% of these infections. There is a significant increase in the incidence of *Proteus, Klebsiella, Enterobacter, Serratia,* and *Pseudomonas* species, as well as enterococci. Bacteriuria due to gram-positive bacteria is much more common in elderly men than in elderly women (Jackson et al, 1962). *S. saprophyticus* is not seen in this population. Polymicrobial bacteriuria is more common among the elderly (Nicolle et al, 1987). The shift in the pattern of uropathogens, the high frequency of polymicrobial infections, and antimicrobial resistance in UTIs in the elderly are due in large part to the high frequency of institutionalization and hospitalization, catheterization, and antimicrobial usage in this population (Fig. 10–40).

Laboratory Diagnosis

Diagnosis of bacteriuria and UTIs in the elderly can be difficult. **Urinary tract symptoms are often absent, and concomitant disease can mask or mimic UTI. Even severe upper tract infections may not be associated with fever or leukocytosis** (Baldassarre and Kaye, 1991). Therefore a high index of suspicion is warranted, and diagnosis should rely on the results of a carefully obtained urinalysis and culture. The presence of greater than 10^5 cfu/mL of urine remains the standard for diagnosis in these patients. However, counts of 10^2 or more bacteria are clinically significant in catheterized specimens (Kunin, 1987; Nicolle et al, 2005).

Pyuria alone is not a good predictor nor an indication for antimicrobial treatment of bacteriuria in this population (Ouslander et al, 1996; Nicolle et al, 2005). Boscia and associates (1989) reported that more than 60% of women with pyuria of 10 WBCs/mm^3 or greater (noted in midstream specimens) did not have a concurrent bacteriuria. However, the absence of pyuria was a good predictor of the absence of bacteriuria.

Because urinary tract abnormalities can often predispose and complicate bacteriuria in the elderly, a thorough urologic evaluation is warranted. Renal dysfunction, calculi, hydronephrosis, urinary retention, neurogenic bladder dysfunction, and other abnormalities should be identified by serum creatinine measurement, excretory urography, CT, ultrasonography, urodynamics,

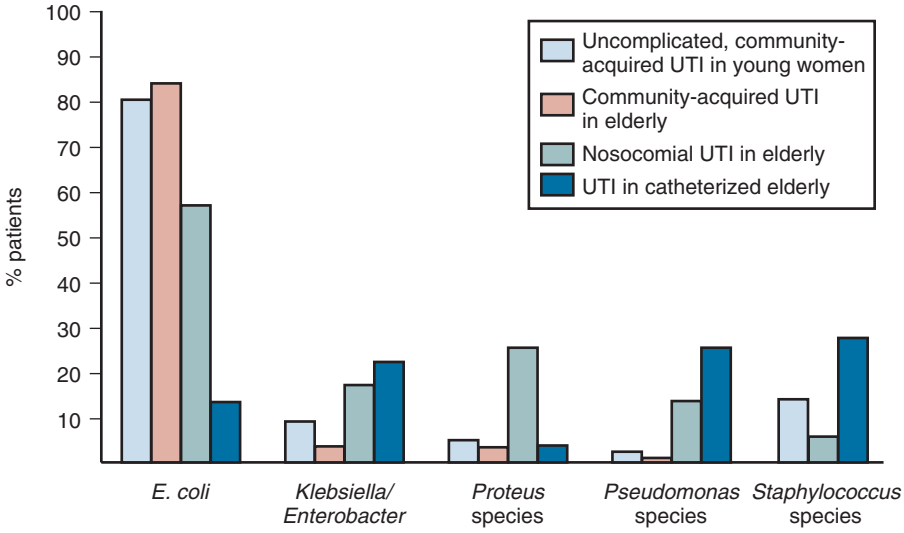


Figure 10–40. Microbiology of urinary tract infections. (Data compiled from Stark RP, Maki DG. Bacteriuria in the catheterized patient: what quantitative level of bacteriuria is relevant? N Engl J Med 1984;311:560–4; Kunin CM. Detection, prevention, and management of urinary tract infections. 4th ed. Philadelphia: Lea & Febiger; 1987. p. xiii; Nicolle LE, Bjornson J, Harding GKM. Bacteriuria in elderly institutionalized men. N Engl J Med 1983;309:1420–5; Krieger JN, Kaiser DL, Wenzel RP. Urinary tract etiology of bloodstream infections in hospitalized patients. J Infect Dis 1983;148:57–62.)

and/or cystoscopy. The timing and sequence of these tests should be dictated by the clinical setting.

Significance of Screening Bacteriuria

Screening for asymptomatic bacteriuria in elderly residents in the community or long-term care facilities is not recommended (Nicolle et al, 1983; Nordenstam et al, 1986; Boscia et al, 1987; Abutryn et al, 1994). **There is no documented relationship between asymptomatic bacteriuria and uncomplicated UTIs and worsening renal function in this population.** The treatment of asymptomatic bacteriuria to improve incontinence has not been justified (Baldassarre and Kaye, 1991; Ouslander et al, 1995). Although studies have demonstrated decreased survival in bacteriuric patients compared with nonbacteriuric control subjects, it is unclear whether increased mortality rates and bacteriuria are causally related (Baldassarre and Kaye, 1991; Abutryn et al, 1994).

Studies that have found a significantly increased mortality among persons with bacteriuria have looked at populations that were heterogeneous in terms of age and underlying disease (Dontas et al, 1981; Latham et al, 1985). An age difference of only 2 years increases mortality by 20% (Dontas et al, 1968). Therefore, in the studies mentioned previously (Dontas et al, 1968) and others (Abutryn et al, 1994), it is not clear how much of the observed association between bacteriuria and mortality was due to differences in age between the bacteriuric and the abacteriuric groups. In a study of bacteriuria and mortality in a homogeneous 70-year-old population, the association between bacteriuria and mortality was weaker and linked to fatal diseases not attributable to bacteriuria (Dontas et al, 1968). Nicolle and associates (1987) randomized institutionalized women with bacteriuria to treatment or observation and followed these patients for more than 1 year. Treatment did not result in improved survival and was associated with a number of adverse effects.

Bacteriuria that leads to UTIs in elderly subjects in the presence of underlying structural urinary tract abnormalities (e.g., obstruction with hydronephrosis) or systemic conditions (e.g., severe diabetes mellitus) are clinically significant, can lead to renal failure, and require prompt therapy. In addition, UTIs caused by urea-splitting bacteria, such as *Proteus* or *Klebsiella* species that cause formation of infection stones, may also lead to severe renal damage.

Sepsis and its sequelae (sepsis syndrome and septic shock) are increasingly common in the elderly. This is in part due to the aggressive use of catheters (Kunin et al, 1992) and other invasive equipment, implantation of prosthetic devices, and the administration of chemotherapy to cancer patients or corticosteroids in other immunosuppressed patients with organ transplants or inflammatory diseases. In addition, modern medical care has given longer life spans to the elderly and patients with metabolic, neoplastic, or immunodeficiency disorders, who remain at increased risk for infection.

Management

Prospective randomized comparative trials of antimicrobial or no therapy in elderly male and female nursing home residents with asymptomatic bacteriuria consistently document no benefit of antimicrobial therapy. There was no decrease in symptomatic episodes and no improvement in survival. In fact, treatment with antimicrobial therapy increases the occurrence of adverse drug effects and reinfection with resistant organisms and increases the cost of treatment. **Therefore asymptomatic bacteriuria in elderly residents of long-term care facilities should not be treated with antimicrobial agents.**

If patients present with lower tract symptoms, 7 days of therapy is recommended. For individuals presenting with fever or more severe systemic infection 10 to 14 days of therapy is recommended. The goal in this population is to eliminate symptoms but not sterilize the urine (McMurdo and Gillespie, 2000).

The 10% to 15% decrease in susceptibility of uropathogens to β-lactams, TMP-SMX, and fluoroquinolones in isolates from nursing home residents is disturbing and most likely due to a pattern of empirical prescribing in the nursing homes. In contrast, the susceptibility of isolates from patients with acute uncomplicated UTI in an outpatient setting has not changed appreciably in 10 years. The difference in susceptibility between the isolates from the outpatient and nursing home settings can be attributed to the presence of additional risk factors for antimicrobial resistance in the latter group. These risk factors include frequent antimicrobial

usage, overcrowding, underlying pathology, and the presence of catheters and other invasive devices. Antimicrobial use needs to be guided by current surveillance studies of targeted uropathogenic bacteria and implemented (Vromen et al, 1999).

The elderly population is more susceptible than young patients to the toxic and adverse effects of antimicrobial agents (Grieco, 1980; Carty et al, 1981; Boscia et al, 1986) because the metabolism and excretion of antimicrobial agents may be impaired and the resulting increased serum levels can further damage renal function. Interactions with other medications can occur (Stahlmann and Lode, 2003). The safety margin between therapeutic and toxic doses is significantly narrowed. Therefore antimicrobial agents must be used judiciously, and dosing and drug levels should be carefully monitored.

The fluoroquinolones are effective in this population, and the side effects are not more apparent than in a younger population. However, fluoroquinolones can cause QT interval prolongation; therefore they should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia or hypomagnesemia, and patients receiving some antiarrhythmic agents (Stahlmann and Lode, 2003).

Chondrotoxicity of fluoroquinolones has led to restricted use in pediatric patients, but there is no indication that similar effects could occur in joint cartilage of adults. Tendinitis and tendon ruptures have occurred in rare cases. Chronic renal diseases, concomitant use of corticosteroids, and age older than 60 years have been recognized as risk factors for fluoroquinolone-induced tendon disorders (Stahlmann and Lode, 2003).

Key Points: Bacteriuria in the Elderly

- Bacteriuria is very common in both elderly women and men.
- Screening for bacteriuria is not recommended in elderly patients because there is no relationship between asymptomatic bacteriuria and uncomplicated UTIs or deteriorating renal function; asymptomatic bacteriuria should not be treated.
- Infections of the urinary tract may present as subtle signs, and a high index of suspicion is often required for diagnosis.
- Treatment of symptomatic UTI requires modifications for physiologic and pathophysiologic conditions of the elderly.

CATHETER-ASSOCIATED BACTERIURIA

Catheter-associated bacteriuria is the most common hospital-acquired infection, accounting for up to 40% of such infections and more than 1 million per year (Haley et al, 1985; Stamm, 1991). **The development of bacteriuria in the presence of an indwelling catheter is inevitable and occurs at an incidence of approximately 10% per day of catheterization. Sterile and clean intermittent catheterization has been associated with rates of bacteriuria ranging from 1% to 3% per catheterization** (Warren, 1997). The most important risk factors associated with increased likelihood of developing catheter-associated bacteriuria are duration of catheterization, female gender, absence of systemic antimicrobial agents, and catheter-care violations (Stamm, 1991). Most catheter-associated UTIs are asymptomatic. In patients with short-term catheter placement, only 10% to 30% of bacteriuric episodes produce typical symptoms of acute infection (Haley et al, 1981; Hartstein et al, 1981). Similarly, although patients with long-term catheters are bacteriuric, the incidence of febrile episodes occurs at a rate of only 1 per 100 days of catheterization (Warren, 1991). The extra direct cost associated with catheter-associated UTIs is about $600 per year per patient. The nosocomial costs for *E. coli* infections with relatively susceptible strains are considerably lower than for those caused by resistant gram-negative bacteria, which often require expensive parenteral antimicrobial therapy (Tambyah et al, 2002). Recently, the Center for Medicare Services (CMS) announced that they will no longer reimburse hospitals for the extra costs resulting from catheter-associated UTIs.

Pathogenesis

Bacteria enter the urinary tract of a catheterized patient by several routes. Bacteria can be introduced at the time of initial catheter placement by either mechanical inoculation of urethral bacteria or contamination from poor technique. Subsequently the bacteria most commonly gain access via a periurethral or intraluminal route (Stamm, 1991). In women, periurethral entry is the most prevalent. Daifuku and Stamm (1984) found that among 18 women who developed catheter-associated bacteriuria, 12 had antecedent urethral colonization with the infecting strain. Bacteria may also enter the drainage bag and follow the intraluminal route to the bladder. This route is particularly common in patients who are clustered among other patients with indwelling catheters (Maizels and Schaeffer, 1980; Tambyah et al, 1999).

The urinary catheter system provides a unique environment that allows for two distinct populations of bacteria: those that grow within the urine and another population that grows on the catheter surface. A biofilm represents a microbial environment of bacteria embedded in an extracellular matrix of bacterial products and host proteins that often lead to catheter encrustation (Stamm, 1991; Bonadio et al, 2001). Certain bacteria, particularly of the *Pseudomonas* and *Proteus* species, are adept at biofilm growth, which may explain their higher incidence in this clinical setting (Mobley and Warren, 1987). The uropathogens isolated from the catheterized urinary tract often differ from those found in noncatheterized ambulatory patients. *E. coli* is still the most common organism isolated, but *Pseudomonas, Proteus,* and *Enterococcus* species are very prevalent (Warren, 1991). In patients with long-term catheterization of more than 30 days, the bacteriuria is usually polymicrobial and the presence of four or five pathogens is not uncommon (Warren et al, 1982). Although certain species may persist for long periods, the bacterial populations in these patients tend to be dynamic.

Clinical Presentation

Most patients are asymptomatic. Suprapubic discomfort and development of fever, chills, or flank pain may indicate a symptomatic UTI.

Laboratory Diagnosis

Significant bacteriuria in patients with catheters is present when greater than 100 cfu/mL is present because even this low level progresses to greater than 10^5 cfu/mL in almost all patients (Maizels and Schaeffer, 1980; Stark and Maki, 1984). Pyuria is not a discriminate indicator of infection in this population.

Management

Careful aseptic insertion of the catheter and maintenance of a closed dependent drainage system are essential to minimize development of bacteriuria. The catheter-meatal junction should be cleaned daily with water, but antimicrobial agents should be avoided because they lead to colonization with resistant pathogens, such as *Pseudomonas*.

Incorporation of silver oxide (Schaeffer et al, 1988) or silver alloy (Saint et al, 1998) into the catheter and hydrogen peroxide into the drainage bag has been reported to decrease the incidence of bacteriuria in some studies (Schaeffer et al, 1988) but not in other populations (Stamm, 1991). The major benefit of silver alloy is in decreasing the likelihood of bacteriuria in hospitalized adults catheterized for the short-term (Saint et al, 2000; Newton et al, 2002; Brosnahan et al, 2004). If an asymptomatic catheterized patient has had an indwelling catheter for 3 or more days, and will have the catheter removed, a dipstick test can be used to rule out bacteriuria (Tissot et al, 2001). **Concurrent administration of systemic antimicrobial agents transiently decreases the incidence of bacteriuria associated with short-term catheterization, but after 3 to 4 days the incidence of bacteriuria is similar to the rate in catheterized patients not taking systemic antimicrobials agents, and the prevalence of resistant bacteria and side effects is substantial.** The concept of instilling nonvirulent bacteria into the bladder to completely block colonization and infection by pathogens has been tested in patients with spinal cord injuries (Hull et al, 2000). Patients successfully colonized with the nonvirulent strain had reduced symptomatic UTI and a subjective improvement in quality of life.

Patients with indwelling catheters should be treated only if they become symptomatic (e.g., febrile). Urine cultures should be performed before initiating antimicrobial therapy. The antimicrobial agent should be discontinued within 48 hours of resolution of the infection. If the catheter has been indwelling for several weeks, encrustation may shelter bacteria from the antimicrobial agent; therefore the catheter should be changed.

When a catheter is to be removed and there is a high probability of bacteriuria or the dipstick test is positive, a culture should be obtained 24 hours before removal (Tissot et al, 2001). **If the probability is low or the dipstick is negative, a culture may not be necessary. The patient should be started on empirical antimicrobial therapy such as TMP-SMX or a fluoroquinolone just before decatheterization and maintained on therapy for 2 days. A post-therapy culture should be obtained 7 to 10 days later to confirm the eradication of the bacteriuria.**

Key Points: Catheter-Associated Bacteriuria

- Careful aseptic insertion of the catheter and maintenance of a closed dependent drainage system are essential to minimize development of bacteriuria.
- The development of catheter-associated bacteriuria is inevitable.
- If bacteriuria is suspected in a catheterized patient, a culture should be obtained and antimicrobial therapy initiated before decatheterization.
- Only symptomatic catheter-associated UTIs require treatment.
- Antimicrobial therapy should be continued for 2 to 3 days and a post-therapy culture obtained 7 to 10 days later.

MANAGEMENT OF UTI IN PATIENTS WITH SPINAL CORD INJURY

Patients with spinal cord injury have unique concerns that affect the risk, diagnosis, and management of UTIs, which are all considered complicated.

Epidemiology

UTIs are among the most common urologic complications of spinal cord injury. It has been estimated that approximately 33% of spinal cord-injured patients have bacteriuria at any time (Stover et al, 1989) and that eventually almost all of spinal cord-injured patients will become bacteriuric and many will suffer significant morbidity and mortality. One prospective study of patients on intermittent catheterization or condom catheterization reported an incidence of significant bacteriuria of 18 episodes per person per year and an annual incidence of febrile UTIs of 1.8 per person per year (Waites et al, 1993). In addition, UTI is the most common cause of fever in the spinal cord–injured patient (Beraldo et al, 1993). **The 1992 National Institute on Disability and Rehabilitation Research Consensus Conference (1993) examined the problems associated with UTIs in spinal cord–injured patients. Among the risk factors identified were impaired voiding, overdistention of the bladder, elevated intravesical pressure, increased risk of urinary obstruction, vesicoureteral reflux, instrumentation, and increased incidence of stones. Other factors that have been implicated are decreased fluid intake, poor hygiene, perineal colonization, decubiti and other evidence of local tissue trauma, and reduced host defense associated with chronic illness** (Gilmore et al, 1992; Waites et al, 1993).

Pathogenesis

The method of bladder management has profound impact on UTI. The National Institute on Disability and Rehabilitation Research Consensus Conference (1993) noted that indwelling catheters were most likely to lead to UTI and that the vast majority of patients with an indwelling catheter for 30 days are bacteriuric. Suprapubic catheters and indwelling urethral catheters eventually have an equivalent infection rate (Kunin et al, 1987; Tambyah and Maki, 2000; Biering-Sorensen, 2002). However, the onset of bacteriuria may be delayed using a suprapubic catheter compared with a urethral catheter. During a 2-year period, 170 patients with spinal cord injury were evaluated regarding type of urinary drainage and infection (Warren et al, 1982). In patients using indwelling urethral catheters, all urine cultures were positive. The corresponding values for the suprapubic catheter group were 44%. Condom drainage systems are also associated with an incidence of bacteriuria from 63% (Dukes, 1928) to almost 100% (Pyrah et al, 1955).

Since its introduction by Lapides and colleagues (1972), clean (but not sterile) intermittent catheterization (CIC) has earned general recognition in the management of spinal cord injury patients (National Institute on Disability and Rehabilitation Research, 1993). **Although never rigorously compared with indwelling urethral catheterization, CIC has been shown**

to decrease lower tract complications by maintaining low intravesical pressure and reducing the incidence of stones (Stover et al, 1989). CIC also appears to reduce complications associated with an indwelling catheter, such as UTI, fever, bacteremia, and local infections such as epididymitis and prostatitis. Weld and Dmochowski (2000) followed 316 patients with spinal cord injury with different bladder management for a mean of 18.3 years and recorded all complications. The CIC group had statistically significantly lower complication rates compared with the urethral catheterization group and no significantly higher complication rates relative to all other management methods for each type of complication studied. Thus it is generally agreed that CIC places patients with spinal cord injury at the lowest risk for significant long-term urinary tract complications (Stamm, 1975).

There is conflicting evidence over the value of sterile versus nonsterile or "no touch" methods of CIC. Some studies have reported a lower incidence of infection in patients treated with sterile techniques (Foley, 1929), whereas others have not (Pyrah et al, 1955; Nyren et al, 1981). Bennett and coworkers (1997) reported on a sterile method of CIC that uses an introducer tip to bypass the distal 1.5 cm of the urethra and showed a significant decrease in UTI with the use of the urethral introducer tip. Different types of catheters have been used for CIC. The low-friction catheters might be less traumatic for the urethra (Casewell and Phillips, 1977; Garibaldi et al, 1980), but their impact on bacteriuria and UTI has to be studied.

Clinical Presentation

The majority of patients with spinal cord injury with bacteriuria are asymptomatic. Because of a loss of sensation, patients usually do not experience frequency, urgency, or dysuria. More often they complain of flank, back, or abdominal discomfort, leakage between catheterizations, increased spasticity, malaise, lethargy, and/or cloudy, malodorous urine. UTI is the most common cause of fever in spinal cord–injured patients (Beraldo et al, 1993).

Bacteriology and Laboratory Diagnosis

Urinalysis will show bacteriuria and pyuria. Pyuria is not diagnostic of infections, because it may occur from the irritative effects of the catheter. The National Institute on Disability and Rehabilitation Research Consensus Statement (1993) recommended the following criteria for the diagnosis of significant bacteriuria in spinal cord–injured patients. Any detectable bacteria from indwelling or suprapubic catheter aspirates was considered significant because the vast majority of patients with an indwelling catheter and low-level bacteriuria showed an increase to greater than 10^5 cfu/mL within a short period of time (Cardenas and Hooton, 1995). For patients on CIC, greater than or equal to 10^2 cfu/mL was considered significant. For catheter-free males, a clean voided specimen showing greater than or equal to 10^4 cfu/mL was considered significant.

Bacteriuria in patients with spinal cord injury differs from that in patients with intact spinal cords in its etiology, complexity, and antimicrobial susceptibility and is influenced by the type and duration of catheterization. *E. coli* is isolated in approximately 20% of patients. Enterococci, *P. mirabilis*, and *Pseudomonas* are more common among spinal cord–injured patients than patients with intact spinal cords. Other common organisms are *Klebsiella* species, *Serratia* species, *Staphylococcus*, and *Candida* species. Most bacteriuria in short-term catheterization is of a single organism, whereas patients catheterized for longer than a month will usually demonstrate a polymicrobial flora caused by a wide range of gram-negative and gram-positive bacterial species (Edwards et al, 1983). Such specimens commonly have two to four bacterial species, each at concentrations of 10^5 cfu/mL or more (Monson and Kunin, 1974; Nickel et al, 1987). Some may have up to six to eight species at that concentration (Monson and Kunin, 1974). This phenomenon is due to an incidence of new episodes of bacteriuria approximately every 2 weeks and the ability of these strains to persist for weeks and months in the catheterized urinary tract (Edwards et al, 1983; Gabriel et al, 1996). Two of the most persistent species are *E. coli* and *Providencia stuartii*. *P. stuartii* is rarely found outside the long-term catheterized urinary tract and may use the catheter itself as a niche (Lindberg et al, 1975; Hockstra, 1999).

Management

Because of the diverse flora and high probability of bacterial resistance, a urine culture must be obtained before initiating empirical therapy. For afebrile patients, an oral fluoroquinolone is the agent of choice (Cardenas and Hooton, 1995). β-Lactams, TMP-SMX, and nitrofurantoin are not recommended because of the high prevalence of bacterial resistance to these drugs. An indwelling catheter should be changed to ensure maximal drainage and eliminate bacterial foci in catheter encrustations. **Spinal cord–injured patients with fever or chills are usually admitted and treated with a parenteral aminoglycoside and a penicillin or a third-generation cephalosporin** (Cardenas and Hooton, 1995). In this patient population, consultation with a physician with expertise in antimicrobial management may be necessary, especially in a patient with recurrent infections.

If clinical improvement does not occur within 24 to 48 hours, reculture and adjustment of antimicrobial therapy based on the initial culture and susceptibility should be performed. Imaging studies should be obtained to rule out obstruction, stones, and abscess. The duration of therapy is not established, but 4 to 5 days is recommended for the mildly symptomatic patient and 10 to 14 days for sicker patients (Cardenas and Hooton, 1995). Post-therapy cultures are usually not necessary because asymptomatic recolonization is common and not clinically significant. However, if a urea-splitting bacterium is identified, a follow-up culture should be obtained to ensure its eradication. Spinal cord–injured patients with recurrent symptomatic UTIs should undergo urinary tract imaging and urodynamic testing and a review of their bladder management program with particular attention to catheter drainage, intermittent catheterization techniques, and frequency of intermittent catheterization or voiding schedule (Cardenas and Hooton, 1995).

Antimicrobial prophylaxis is not supported for most patients who have neurogenic bladder caused by spinal cord injury (Morton et al, 2002). Antimicrobial prophylaxis did not significantly decrease symptomatic UTIs and resulted in an approximately twofold increase in antimicrobial-resistant bacteria.

Recurrent UTIs may be associated with high storage pressures, and intervention to decrease storage pressure may decrease the incidence of symptomatic UTI. Evidence from studies in spinal cord–injured patients suggests that bladder catheterization for longer than 10 years is associated with an increased risk of carcinoma of the bladder. West and colleagues (1999) examined two databases with more than 33,000 spinal

cord–injured patients and identified 130 patients with bladder cancer (0.4%) during a 5-year period. Several risk factors for bladder cancer have been proposed. Vereczky and associates (cited in Weyrauch and Bassett, 1951) tested different risk factors based on the outcome of 153 spinal cord-injured patients in which 7 were diagnosed with bladder cancer. Of a total of 31 possible predictors, only duration of catheterization was significant. **Chronic infection and inflammation of the bladder mucosa could be the carcinogenic stimulus in these patients** (Pyrah et al, 1955). **Nitrosamines produced in infected urine have also been implicated** (Najenson et al, 1969).

For further discussion of spinal cord injury and urinary infection, see Chapter 65.

Key Points: Management of UTI in Patients with Spinal Cord Injury

- UTI in patients with spinal cord injury commonly presents as fever; flank, back, or abdominal discomfort; leakage between catheterizations; increased spasticity; malaise; lethargy; and/or cloudy, malodorous urine.
- The majority of spinal cord–injured patients with bacteriuria are asymptomatic.
- Only symptomatic patients require therapy.
- Urine culture before the initiation of empirical therapy is essential because spinal cord–injured patients often culture diverse flora with a high probability of bacterial resistance.
- Clean intermittent catheterization places patients with spinal cord injury at the lowest risk for significant long-term urinary tract complications.
- Chronic infection can be carcinogenic.

OTHER INFECTIONS

Fournier Gangrene

Fournier gangrene is a potentially life-threatening form of necrotizing fasciitis involving the male genitalia. It is also known as idiopathic gangrene of the scrotum, streptococcal scrotal gangrene, perineal phlegmon, and spontaneous fulminant gangrene of the scrotum (Fournier, 1883, 1884). As originally reported by Baurienne in 1764, and by Fournier in 1883, it was characterized by an abrupt onset of a rapidly fulminating genital gangrene of idiopathic origin in previously healthy young patients that resulted in gangrenous destruction of the genitalia. The disease now differs from these descriptions in that it involves a broader age range, including older patients (Bejanga, 1979; Wolach et al, 1989), follows a more indolent course, and has a less abrupt onset; and, in approximately 95% of the cases, a source can now be identified (Macrea, 1945; Burpee and Edwards, 1972; Kearney and Carling, 1983; Jamieson et al, 1984; Spirnak et al, 1984).

Infection most commonly arises from the skin, urethra, or rectal regions. An association between urethral obstruction associated with strictures and extravasation and instrumentation has been well documented. **Predisposing factors include diabetes mellitus, local trauma, paraphimosis, periurethral extravasation or urine, perirectal or perianal infections, and surgery such as circumcision or herniorrhaphy. In cases originating in the genitalia the infecting bacteria probably pass through the Buck fascia of the penis and spread along the dartos fascia of the scrotum and penis, the Colles fascia of the perineum, and the Scarpa fascia of the anterior abdominal wall.** In view of the typical foul odor associated with this condition, a major role for anaerobic bacteria is likely. **Wound cultures generally yield multiple organisms, implicating anaerobic-aerobic synergy** (Meleney, 1933; Miller, 1983; Cohen, 1986). Mixed cultures containing facultative organisms (*E. coli*, *Klebsiella,* enterococci) along with anaerobes (*Bacteroides, Fusobacterium, Clostridium,* microaerophilic streptococci) have been obtained from the lesions.

Clinical Presentation

Patients frequently have a history of recent perineal trauma, instrumentation, urethral stricture associated with sexually transmitted disease, or urethral cutaneous fistula. Pain, rectal bleeding, and a history of anal fissures suggest a rectal source of infection. Dermal sources are suggested by history of acute and chronic infections of the scrotum and spreading recurrent hidradenitis suppurativa or balanitis.

The infection commonly starts as cellulitis adjacent to the portal of entry. Early on, the involved area is swollen, erythematous, and tender as the infection begins to involve the deep fascia. Pain is prominent, and fever and systemic toxicity are marked (Paty and Smith, 1992). The swelling and crepitus of the scrotum quickly increase, and dark purple areas develop and progress to extensive gangrene. If the abdominal wall becomes involved in an obese patient with diabetes, the process can spread very rapidly. Specific genitourinary symptoms associated with the condition include dysuria, urethral discharge, and obstructed voiding. Alterations in mental status, tachypnea, tachycardia, and temperature greater than 38.3° C (101° F) or less than 35.6° C (96° F) suggest gram-negative sepsis.

Laboratory Diagnosis and Radiologic Findings

Anemia occurs secondary to a decreased functioning erythrocyte mass caused by thrombosis and ecchymosis coupled with decreased production secondary to sepsis (Miller, 1983). Elevated serum creatinine levels, hyponatremia, and hypocalcemia are common. Hypocalcemia is believed to be secondary to bacterial lipases that destroy triglycerides and release free fatty acids that chelate calcium in its ionized form.

Because crepitus is often an early finding, a plain film of the abdomen may be helpful in identifying air. Scrotal ultrasonography is also useful in this regard. Biopsy of the base of an ulcer is characterized by superficially intact epidermis, dermal necrosis, and vascular thrombosis and polymorphonuclear leukocyte invasion with subcutaneous tissue necrosis. Stamenkovic and Lew (1984) noted that the use of frozen sections within 21 hours after the onset of symptoms could confirm a diagnosis earlier and lead to early institution of appropriate treatment.

Management

Prompt diagnosis is critical because of the rapidity with which the process can progress. The clinical differentiation of necrotizing fasciitis from cellulitis may be difficult because the initial signs including pain, edema, and erythema are not distinctive. However, the presence of marked systemic toxicity out of proportion to the local finding should alert the clinician. Intravenous hydration and antimicrobial therapy are indicated in preparation for surgical debridement. Antimicrobial regimens include combinations of ampicillin plus sulbactam or a parenteral third-generation cephalosporin such as ceftriaxone, gentamicin, and clindamycin. If there is no response to clindamycin, chloramphenicol may be used.

Immediate debridement is essential. In the patient in whom diagnosis is clearly suspected on clinical grounds (deep pain with patchy areas of surface hypoesthesia or crepitation, or bullae and skin necrosis), direct operative intervention is indicated. **Extensive incision should be made through the skin and subcutaneous tissues, going beyond the areas of involvement until normal fascia is found. Necrotic fat and fascia should be excised, and the wound should be left open. A second procedure 24 to 48 hours later is indicated if there is any question about the adequacy of initial debridement.** Orchiectomy is almost never required, because the testes have their own blood supply independent of the compromised fascial and cutaneous circulation to the scrotum. Suprapubic diversion should be performed in cases in which urethral trauma or extravasation is suspected. Colostomy should be performed if there is colonic or rectal perforation. Hyperbaric oxygen therapy has shown some promise in shortening hospital stays, increasing wound healing, and decreasing the gangrenous spread when used in conjunction with debridement and antimicrobial agents (Paty and Smith, 1992). Once wound healing is complete, reconstruction, for example, using myocutaneous flaps, improves cosmetic results.

Outcome

The mortality rate averages approximately 20% (Cohen, 1986; Baskin et al, 1990; Clayton et al, 1990) but ranges from 7% to 75%. Higher mortality rates are found in diabetics, alcoholics, and those with colorectal sources of infection who often have a less typical presentation, greater delay in diagnosis, and more widespread extension. Regardless of the presentation, **Fournier gangrene is a true urologic emergency that demands early recognition, aggressive treatment with antimicrobial agents, and surgical debridement to reduce morbidity and mortality.**

Periurethral Abscess

Periurethral abscess is a life-threatening infection of the male urethra and periurethral tissues. Initially, the area of involvement can be small and localized by Buck fascia. However, when Buck fascia is penetrated there can be extensive necrosis of the subcutaneous tissue and fascia. Fasciitis can spread as far as the buttocks posteriorly and the clavicle superiorly. Rapid diagnosis and treatment are essential to reduce the morbidity and high mortality historically associated with this disease.

Pathogenesis

Periurethral abscess is frequently a sequela of gonorrhea, urethral stricture disease, or urethral catheterization. Frequent instrumentation is also associated with periurethral abscess formation. The source of the infecting organism is the urine. Gram-negative rods, enterococci, and anaerobes are most frequently identified. The presence of multiple organisms is common. Anaerobes, normal residents of the male urethra, are also frequently found in wound cultures.

Clinical Presentation

Presenting signs and symptoms include scrotal swelling in 94% of patients, fever (70%), acute urinary retention (19%), spontaneously drained abscess (11%), and dysuria or urethral discharge (5% to 8%). The average interval between initial symptoms and presentation is 21 days. Urinalysis of the first glass specimen reveals pyuria and bacteriuria.

Management

Treatment consists of immediate suprapubic urinary drainage and wide debridement. Antimicrobial therapy with an aminoglycoside and a cephalosporin is usually adequate for empirical coverage. More selective antimicrobial therapy can be instituted when the antimicrobial susceptibility of the organisms is available. Perineal urethrostomy or chronic suprapubic diversion occasionally has been helpful to prevent recurrences, and it should be considered in patients with diffuse stricture disease. The presence of a malignancy is unusual, but biopsy is important.

Key Points: Other Infections

- Fournier gangrene is necrotizing fasciitis arising from the perineal skin, scrotum, urethra, or rectum.
- Emergent surgical debridement and broad-spectrum antimicrobial agents are the essentials of treatment of Fournier gangrene.
- Periurethral abscess can occur secondarily to urethral stricture or catheterization; treatment entails surgical debridement, suprapubic urinary drainage, and antimicrobial agents.

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chapter 11

Prostatitis and Related Conditions, Orchitis, and Epididymitis

J. Curtis Nickel, MD, FRCSC

Prostatitis and Related Conditions

Orchitis

Epididymitis

PROSTATITIS AND RELATED CONDITIONS

Historical Aspects

Modern descriptions of the clinical presentation, pathology, and microscopic evaluation of prostate-specific specimens of prostatitis patients were firmly established by Young, Gereghty, and Stevens (1906) by the turn of the 20th century. Bacterial and cytologic localization studies of the lower urinary tract were described shortly thereafter (Hitchens and Brown, 1913) and standardized by 1930 (Von Lackum, 1927, 1928; Nickel, 1930, 1999a). **The primary form of therapy for prostatitis during most of the 20th century was repetitive prostate massage** (Farman, 1930; O'Conor, 1936; Henline, 1943; Campbell, 1957). With the introduction of sulfanilamide in the 1930s, antimicrobial therapy became the main therapeutic approach (Ritter and Lippow, 1938). However, even in the 1950s and 1960s, the significance of inflammatory cells and bacteria in the expressed prostatic secretion (EPS) was questioned (O'Shaughnessy et al, 1956; Bowers and Thomas, 1958; Bourne and Frishette, 1967), and it was even recognized that, in many cases, antibiotics were performing little better than placebo in the treatment of prostatitis (Gonder, 1963).

The next era of prostatitis management began in the 1960s with Meares and Stamey's (1968) description of the four-glass lower urinary tract segmented localization study. Prostatic massage as the mainstay of prostatitis therapy was abandoned, and antimicrobial therapy was rationalized for the very small percentage of patients with bacteria localized to prostate-specific specimens. Unfortunately the vast majority of patients who were diagnosed with a nonbacterial cause continued to suffer the indignities of dismal urologic management (Nickel, 1998a). The establishment of new definitions and a classification system, better understanding of the etiopathogenesis, completion of randomized placebo-controlled trials with validated outcome indices, and the evolving insight that patients with prostatitis have variable clinical phenotypes has radically changed the way this condition is managed.

Epidemiology

Prostatitis is the most common urologic diagnosis in men younger than age 50 years and the third most common urologic diagnosis in men older than age 50 years after benign prostatic hyperplasia (BPH) and prostate cancer (McNaughton Collins et al, 1998). There were almost 2 million U.S. physician visits annually from 1990 to 1994 with prostatitis listed as the diagnosis (McNaughton Collins et al, 1998), Approximately 5% of visits to U.S. urologists were reported to be for inflammatory diseases of the prostate (Schappert, 1994). In the mid 1990s urologists in Wisconsin in the United States saw an average of 173 patients with prostatitis per year (Moon, 1997) whereas Canadian urologists reported an average of 264 patients with prostatitis per year, with 38% of whom newly diagnosed (Nickel et al, 1998a). Based on both a physician survey study in Dane County, Wisconsin (Moon, 1997), and a survey of younger men from a Wisconsin National Guard unit (Moon et al, 1997), it was estimated that 5% of men (aged 20 to 50 years) have a history of prostatitis. In the Netherlands, de la Rosette and colleagues (1992a) noted that 4% of respondents reported a history of prostatitis, whereas researchers in Finland reported a 14% overall lifetime prevalence in that country (Mehik et al, 2000). McNaughton Collins and colleagues (2002) noted that 16% of health care professionals in the United States report either a previous or current diagnosis of prostatitis. Roberts and associates (1998) reviewed the medical records of 2113 men from July 1992 through February 1996 (a median of 50 months' follow-up) in the Olmsted County community-based cohort in Minnesota and found the overall prevalence of a physician's diagnosis of prostatitis was 9%.

Many of these epidemiologic studies are limited by physicians' or patients' long-term recollection and the unreliability of a physician's coding or diagnosis of prostatitis. **Population-based studies employing the validated National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI)** (Litwin et al, 1999) **to determine the prevalence of prostatitis-like symptoms in the general population of men showed widely variant results** (**12.2% in Nigeria** [Ejike and Ezeanyika, 2008], **8.0% in Malaysia** [Cheah et al,

2003], **6.6% in Canada** [Nickel et al, 2001b], **2.7% in Singapore** [Tan et al, 2002], **and approximately 2.2% in older men in Olmsted County** [Roberts et al, 2002]). Employing NIH-CPSI definitions of prostatitis-like symptoms in a managed care population, Clemens and colleagues (2006) estimated that between 5.9% and 11.2% have prostatitis-like symptoms depending on the specific definition. Whereas retrospective billing data studies have indicated that up to 8% of U.S. male patients seen in urologic outpatient practice have a diagnosis of prostatitis (McNaughton Collins et al, 1998), prospective practice audit studies have shown that as many as 12% of men presenting to Italian urologists are diagnosed with prostatitis (Rizzo et al, 2003), whereas only 2.8% of men had a clinical diagnosis of prostatitis in a similar study carried out in Canada (Nickel et al, 2005c). Symptoms of prostatitis wax and wane, with approximately one third to one half of patients experiencing relief of symptoms over a 1-year period (Nickel et al, 2002b; Turner et al, 2004b, Propert et al, 2006b).

It has traditionally been believed that prostatitis is a disease of younger men (e.g., aged 35 to 50 years). Epidemiologic studies described in this section confirm that prostatitis affects men of all ages, unlike BPH and prostate cancer, which are predominantly diseases of older men. Compared with men aged 66 years and older, a diagnosis of prostatitis is 1.6-, 2.6-, and 2.1-fold greater in men aged 18 to 35, 36 to 50, and 51 to 65 years, respectively, in the Olmsted County study (Roberts et al, 1998). The age-specific prevalence of a physician-assigned diagnosis of prostatitis was highest in patients between the ages of 20 and 49 years and increased again in those older than 70 years. The cumulative probability of having a diagnosis of prostatitis (acute or chronic) by 85 years of age was 26%. In the Canadian prevalence study (Nickel et al, 2001b) there was no significant difference in the prevalence of prostatitis-like symptoms in men younger than 50 years (11.5% reported at least mild symptoms over the previous week) compared with men older than 50 years (8.5% reported at least mild symptoms over the previous week). As many as 20% of men diagnosed with BPH also report prostatitis-like symptoms (Nickel 2005a). Interestingly, although prostatitis symptoms appear to be as prevalent in older versus younger males they are reported to be less distressing with age (Hedelin and Jonsson, 2007).

Chronic prostatitis is associated with substantial costs and significant predicted resource consumption (Calhoun et al, 2004; Turner et al, 2004a; Duloy et al, 2007). Overall spending in the United States for the diagnosis and management of prostatitis, exclusive of pharmaceutical spending, totaled 84 million dollars in 2000 and appears to be increasing (Pontari et al, 2007). This economic factor needs increased attention when evaluating the incidence and treatment of this prevalent condition.

Histopathology

For the pathologist, prostatitis is defined as an increased number of inflammatory cells within the prostatic parenchyma (Cotran et al, 1999). **Prostatic inflammation may or may not be noted in patients with a diagnosis of prostatitis** (True et al, 1999), **BPH** (Nickel et al, 1999c), **or prostate cancer** (Zhang et al, 2000) **and is noted in autopsy series in as many as 44% of prostate tissue samples from men without any definitive prostate disease** (McNeal, 1968).

A consistent description of fairly distinct, although often coexisting, patterns of chronic inflammation can be found in the prostate gland of patients with or without prostate disease. **The most common pattern of inflammation is a lymphocytic infiltrate in the stroma immediately adjacent to the prostatic acini** (Kohnen and Drach, 1979; Nickel et al, 1999b). The intensity of the inflammatory process varies considerably from only scattered lymphocytes to dense lymphoid nodules. Stromal lymphocytic infiltrates frequently coexist with periglandular inflammation. Sheets, clusters, and occasional nodules of lymphocytes and scattered plasma cells are seen within the fibromuscular stroma with no apparent relationship to the ducts and acini. Infiltrates of inflammatory cells restricted to the glandular epithelium and lumen are found in association with prostatitis and BPH but can be found in asymptomatic patients. The intraepithelial inflammatory cells may be neutrophils, lymphocytes, or macrophages, or all of these, whereas neutrophils and macrophages are typically found in the lumen. Figure 11–1 illustrates the various inflammatory patterns seen in a prostate specimen of a patient with chronic prostatitis.

Corpora amylacea, which may develop from the deposition of prostatic secretions around a sloughed epithelial cell or other irritant, are not usually associated with inflammation unless they become large enough to distend or obstruct the prostatic gland (Attah, 1975). Prostatic calculi may contribute to prostatic inflammation by obstructing central prostate ducts and thus preventing drainage or providing a nidus in which bacteria can survive host defenses and antibiotics (Meares, 1974; Roberts et al, 1997).

Granulomatous prostatitis presents a nonspecific and variable histologic pattern typified by heavy lobular, mixed, inflammatory infiltrates that include abundant histiocytes, lymphocytes, and plasma cells. Small, discrete granulomas may be present, or the pattern may be typified by well-defined granulomas. Granulomatous prostatic inflammation is a common consequence of

Key Points: Epidemiology

- Two percent to 12% of men older than age 20 years currently experience prostatitis-like symptoms.
- Nine percent to 16% of men have had a diagnosis of prostatitis.
- Prostatitis represents 3% to 12% of male outpatient visits to urologists.

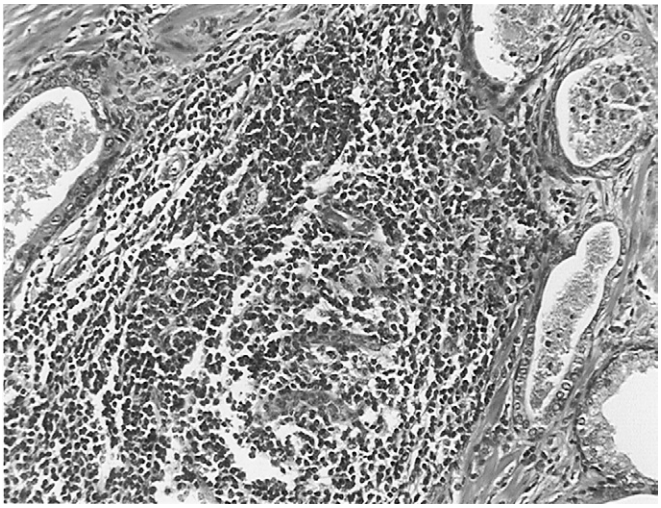


Figure 11–1. Histologic preparation of a prostate specimen demonstrating areas of glandular, periglandular, and stromal inflammation (×400). (Courtesy of Dr. Alexander Boag.)

surgery (Eyre et al, 1986) or therapy with bacillus Calmette-Guérin (BCG) (Lafontaine et al, 1997) and a rare event in patients with systemic tuberculosis (Saw et al, 1993).

A consensus group of urologists and pathologists have developed a classification system to describe histologic inflammatory patterns in the prostate (Nickel et al, 2001d), but it is only useful for comparative research purposes.

Etiology

Microbiologic

Gram-Negative Uropathogens. **Acute bacterial prostatitis is a generalized infection of the prostate gland and is associated with both lower urinary tract infection (UTI) and generalized sepsis. Chronic bacterial prostatitis is associated with recurrent lower UTIs (i.e., cystitis) secondary to areas of focal uropathogenic bacteria residing in the prostate gland. The most common cause of bacterial prostatitis is the Enterobacteriaceae family of gram-negative bacteria, which originate in the gastrointestinal flora.** The most common organisms are strains of *Escherichia coli,* which are identified in 65% to 80% of infections (Stamey, 1980; Lopez-Plaza and Bostwick, 1990; Weidner et al, 1991b; Schneider et al, 2003). *Pseudomonas aeruginosa, Serratia* species, *Klebsiella* species, and *Enterobacter aerogenes* are identified in a further 10% to 15% (Meares, 1987; Weidner et al, 1991b). **However, in acute bacterial prostatitis, the organisms that result from previous manipulation of the lower urinary tract show different patterns of virulence and resistance (e.g., to ciprofloxacin and cephalosporins) compared with the organisms associated with spontaneous acute prostatitis** (Millan-Rodriquez et al, 2006; Ha et al, 2008).

Urovirulence factors play a significant role in the pathogenesis of bacterial prostatitis (Ruiz et al, 2002; Johnson et al, 2005). For instance, bacterial P-fimbria (or pili) bind to the urothelial receptors, and this subsequently facilitates ascent into the urinary tract as well as establishing deep infections in the prostate gland itself (Dilworth et al, 1990; Neal et al, 1990; Andreu et al, 1997). Colonization of the lower urinary tract by *E. coli* is also facilitated by the presence of the type 1 fimbria, also known as mannose-sensitive fimbria. The receptor is a common moiety of the uroepithelial uromucoid; this association has been shown to be important in the development of cystitis in humans, and its presence in prostatitis has also been documented (Correll et al, 1996). Phase variation of type 1 pili during the establishment of acute bacterial prostatitis may occur in the setting of prostatitis (Schaeffer, 1991). Multiple virulence factors appear to be necessary to produce prostatitis (Mitsumori et al, 1999; Ruiz et al, 2002). Bacteria reside deep in the ducts of the prostate gland and when threatened, with host defense and antimicrobial therapy, tend to form aggregates (also called biofilms), which appears to be a protective mechanism allowing bacteria to persist in the prostate gland even when the cystitis is treated with antibiotics (Nickel and Costerton, 1993; Nickel et al, 1994). Hemolysin appears to be a virulence factor associated with *E. coli* acute prostatitis, but hemolysin may also be associated with increased ability of certain strains of *E. coli* to persist in the prostate as biofilms in patients with chronic bacterial prostatitis (Soto et al, 2007).

Gram-Positive Bacteria. Enterococci are believed to account for 5% to 10% of documented prostate infections (Drach, 1974a; Meares, 1987; Bergman, 1994). The role of other gram-positive organisms, which are also commensal organisms in the anterior urethra, is controversial (Jimenez-Cruz et al, 1984; Fowler and Mariano, 1984b, Krieger et al, 2002). An etiologic role for gram-positive organisms such as *Staphylococcus saprophyticus,* hemolytic streptococci, *Staphylococcus aureus,* and other coagulase-negative staphylococci has been suggested by a number of authors (Drach, 1974a, 1986; Bergman, 1994). Nickel and Costerton (1992) have shown coagulase-negative *Staphylococcus* to be present in the EPS as well as transperineal prostate biopsy tissue of men with chronic prostatitis (microscopy and culture). Although this and other studies (Carson et al, 1982; Pfau, 1983; Bergman et al, 1989; Wedren, 1989) suggested that coagulase-negative staphylococci are involved in the pathogenesis of chronic prostatitis, these studies did not conclusively demonstrate that these bacteria were actually causing the inflammation and symptom-complex rather than simply colonizing the prostate (Krieger et al, 2002). However, eradication of gram-positive bacteria in the prostate of men experiencing recent onset of prostatitis symptoms resulted in similar clinical results compared with men with gram-negative uropathogens localizing to the prostate (Magri et al, 2007a; Nickel and Xiang, 2008). In both cases, eradication of the bacteria localized to the prostate was strongly correlated with a good clinical outcome. However, the inconsistent localization of gram-positive bacteria in prostate-specific specimens from patients with chronic prostatitis suggests that this relationship may not be as strong as suggested (e.g., Krieger et al, 2005).

Anaerobic Bacteria. In studies in which the prostate-specific specimens were cultured anaerobically, anaerobic bacteria could be identified in a small number of patients (Nielsen and Justesen, 1974; Mardh and Colleen, 1975; Szoke et al, 1998). This has not been a consistent finding, and the role of anaerobic bacteria is essentially unknown.

***Corynebacterium* Infection.** *Corynebacterium* species have usually been acknowledged as prostate nonpathogens but have been suggested as potential etiologic agents in this disease (Riegel et al, 1995; Domingue, 1998). Domingue and colleagues (1997) suggested that these difficult-to-culture coryneforms could be missed by routine culturing of EPS. Direct Gram staining of the EPS showed gram-variable pleomorphic coccobacillary rods that do not usually grow on routine media. The presence of these pleomorphic swollen rods was also shown by fluorescent acridine orange staining. Tanner and associates (1999), using polymerase chain reaction (PCR) techniques, were able to identify a bacterial signal (phylogenetically gram-positive organisms with predominance of *Corynebacterium* species) in 65% of 17 patients with chronic prostatitis. Approximately half of these patients tended to respond to antimicrobial therapy, whereas patients in whom molecular signals for these bacteria could not be identified did not.

Chlamydial Infection. **The evidence supporting the role of *Chlamydia trachomatis* as an etiologic agent in chronic prostatic inflammation is both confusing and conflicting.** Mardh and Colleen (1972) found that one third of men with chronic prostatitis had antibodies to *C. trachomatis* compared with 3% of controls. Shortliffe and coworkers (1992) found that 20% of patients with nonbacterial prostatitis had antichlamydial antibody titers in the prostatic fluid. Koroku and associates (1995) detected *C. trachomatis*–specific immunoglobulin A (IgA) in 29% of men with chronic nonbacterial prostatitis. Bruce and colleagues (1981) found that 56% of patients with "subacute or chronic prostatitis" were infected with *C. trachomatis* (after examining early morning urine, prostatic fluid, or semen specimens). In a follow-up study, Bruce and Reid (1989) found that 6 of 55 men with abacterial prostatitis, including 31 believed to have chlamydial prostatitis, met strict criteria for positive diagnosis for

chlamydial prostatitis based on identification of the organisms by culturing or immunofluorescence. Kuroda and colleagues (1989) identified *C. trachomatis* in the urethras of 20% of men with prostatitis. Other investigators have come to similar conclusions (Nilsson et al, 1981; Weidner et al, 1983). *Chlamydia* has also been isolated in prostate tissue specimens. Poletti and coworkers (1985) isolated *C. trachomatis* from prostate samples obtained by transrectal aspiration biopsy of men with "nonacute abacterial prostatitis." Abdelatif and colleagues (1991) identified intracellular *Chlamydia* employing "in-situ hybridization techniques" in transurethral prostate chips from 30% of men with histologic evidence of "chronic abacterial prostatitis." Shurbaji and associates (1998) identified *C. trachomatis* in paraffin-embedded secretions in 31% of men with histologic evidence of prostatitis compared with none in patients with BPH without inflammation.

Although Mardh and Colleen (1972) suggested that *C. trachomatis* may be implicated in as many as one third of men with chronic prostatitis, their follow-up studies employing culturing and serologic tests could not confirm *C. trachomatis* as an etiologic agent in idiopathic prostatitis (Mardh and Colleen, 1975; Mardh et al, 1978). Shortliffe and Wehner (1986) came to a similar conclusion when her group evaluated antichlamydial antibody titers in prostatic fluid. Twelve percent of controls (compared with 20% of patients with nonbacterial prostatitis) had detectable antibodies. Berger and coworkers (1989) could not culture *C. trachomatis* from the urethras in men with chronic prostatitis nor did they find a serologic or local immune response to *C. trachomatis* in such patients. Doble and associates (1989b) were not able to culture or detect by immunofluorescence *Chlamydia* in transperineal biopsy specimens of abnormal areas of the prostate in men with chronic abacterial prostatitis. Krieger and colleagues (1996b) were only able to find *Chlamydia* in 1% of prostate tissue biopsy specimens in men with chronic prostatitis. A further localization and culture series by Krieger and associates (2000) also failed to culture *Chlamydia* from either urethral or prostate specimens. Further elucidation of the role of chlamydial etiology of prostate infection is required to make any definitive statement on the association between isolation of this organism and its prostatic origin and effect (Weidner et al, 2002).

***Ureaplasma* Infection.** *Ureaplasma urealyticum* is a common organism isolated from the urethra of both asymptomatic men and men with nonspecific urethritis. Weidner and colleagues (1980) found high *U. urealyticum* concentrations in prostate-specific specimens in patients with signs and symptoms of abacterial prostatitis. Isaacs (1993) cultured *U. urealyticum* from prostate secretion in 8% of patients with chronic nonbacterial prostatitis. Fish and Danziger (1993) found significant *U. urealyticum* concentrations in 13% of patients with prostatitis. Treatment with specific antimicrobial therapy cleared the organisms in all cases. Ohkawa and associates (1993a) isolated *U. urealyticum* cells from the prostates of 18 of 143 patients with chronic prostatitis. Antibiotics eradicated the organism in all, improved the symptoms in 10, and cleared the leukocytes in the EPS in 4 (Ohkawa et al, 1993b).

Other investigators (Mardh and Colleen, 1975), employing similar techniques, were unable to implicate *U. urealyticum* in patients with nonbacterial prostatitis. The problems encountered in all these studies include the absence of controls and the fact that it was difficult to account for possible urethral contamination in collecting specific prostate specimens.

Other Microorganisms. *Candida* (Golz and Mendling, 1991; Indudhara et al, 1992) and other mycotic infections such as aspergillosis and coccidioidomycosis (Schwarz, 1982; Chen and Schijj, 1985; Campbell et al, 1992; Truett and Crum, 2004) have been implicated in prostatic inflammation. However, in most cases it was usually an isolated finding in immunosuppressed patients or those with systemic fungal infection. Viruses (Doble et al, 1991; Benson and Smith, 1992) have also been implicated in prostatic inflammation, but no systematic evaluation of the role of these agents in prostatitis has been undertaken. *Trichomonas* has been described in the prostate glands of patients complaining of prostatitis-like symptoms (Kuberski, 1980; Gardner et al, 1996; Skerk et al, 2002a).

Nonculturable Microorganisms. There are significant limitations to the culture techniques employed to attempt to identify etiologic microorganisms associated with prostatitis (Lowentritt et al, 1995; Domingue et al, 1997; Domingue, 1998). Bacteria may exist in aggregated biofilms adherent to the prostatic ductal walls or within the obstructed ducts in the prostate (Nickel and MacLean, 1998). Nickel and Costerton (1993) observed that 60% of patients with previously diagnosed chronic bacterial prostatitis who progressed to sterile EPS cultures but continued to have symptoms despite antimicrobial therapy had positive cultures in prostate biopsy specimens showing an organism similar to the initial organism. As discussed earlier, such organisms appear to persist in small aggregates or biofilms in the ducts and acini of the prostate gland.

Berger and associates (1997) cultured urine specimens and transperineal prostate biopsy specimens specifically for commensal and fastidious organisms. These investigators demonstrated that, in prostate biopsy cultures, men with evidence of inflammation in EPS are more likely to have bacteria isolated, positive cultures for anaerobic bacteria, higher total bacterial counts, and more bacterial species isolated than men without EPS inflammation. Krieger and colleagues (1996b), Riley and coworkers (1998), and Tanner and associates (1999) used a combination of clinical, culture, and molecular biologic methods (i.e., PCR) and found a strong correlation between inflammation and EPS and the detection of bacteria-specific 16S rRNA (gram-negative and gram-positive organisms) in the prostate tissue. But other researchers did not show any association between culture and PCR findings in men with nonbacterial prostatitis compared with men with prostatitis symptoms (Keay et al, 1999; Lee et al, 2003; Leskinen et al, 2003b). Nanobacteria are intriguing organisms that are difficult to isolate and culture but may be implicated in some chronic urologic conditions, including chronic prostatitis (Wood and Shoskes, 2006). A number of investigators (Shoskes et al, 2005; Short et al, 2008) have demonstrated the possibility that nanobacteria associated with and without prostatic calculi may be implicated in some cases of chronic prostatitis.

It has been estimated that less than 10% of all environmental bacteria have been identified (Domingue, 1998), so it is possible that fastidious and nonculturable microorganisms might be present in the prostate gland and that such organisms might be involved in the inflammatory process and subsequent development of symptoms.

Altered Prostatic Host Defense

Risk factors that allow bacterial colonization or infection of the prostate with potentially pathogenic bacteria include intraprostatic ductal reflux (Kirby et al, 1982); **phimosis** (VanHowe, 1998); **specific blood groups** (Lomberg et al, 1986); **unprotected penetrative anal rectal intercourse; UTI; acute epididymitis** (Berger et al, 1987); **indwelling urethral catheters and condom catheter drainage** (Meares, 1998); **and transurethral surgery, especially in men who**

have untreated, infected urine (Meares, 1989). Secretory dysfunction of the prostate characterized by an alteration in the composition of prostatic secretions can be diagnostic of patients with prostatitis: there is a decrease in the levels of fructose; citric acid; acid phosphatase; the cations zinc, magnesium, and calcium; and the zinc-containing prostatic antibacterial factor; but pH, the ratio of isoenzymes lactate dehydrogenase-5 to lactate dehydrogenase-1, levels of inflammatory proteins such as ceruloplasmin, and complement C3 are increased (Meares, 1989). These defined alterations in the prostate secretory function have also been blamed for adversely affecting the normal antibacterial nature of prostatic secretions. A decrease in prostatic antibacterial factor may reduce the intrinsic antibacterial activity of the prostatic fluid (Fair et al, 1976), whereas the alkaline pH may hamper diffusion of certain basic antimicrobial drugs into the prostatic tissue and fluid (Fair and Cordonnier, 1978). However, caution is warranted because it is not known whether these compositional changes are a cause or a consequence of inflammation.

Dysfunctional Voiding

Anatomic or neurophysiologic obstruction resulting in high-pressure dysfunctional flow patterns has been implicated in the pathogenesis of the prostatitis syndrome. Blacklock (1974, 1991) demonstrated that bladder neck, prostatic, and urethral anatomic abnormalities predisposed some men to developing prostatitis. Urodynamic studies confirm that many patients, particularly those with prostatodynia, have decreased maximal urinary flow rates and obstructive-appearing flow patterns (Barbalias et al, 1983; Ghobish, 2002). On videourodynamic studies, many patients with prostatitis syndromes show incomplete funneling of the bladder neck as well as vesicourethral dyssynergic patterns (Kaplan et al, 1994, 1997; Hruz et al, 2003). Investigators (Dellabella et al, 2006) have described ultrasound alterations of the preprostatic sphincter in men with chronic prostatitis. In a study of 48 treatment refractory chronic prostatitis patients with no associated infection, Hruz and associates (2003) determined that 29 (60%) had bladder neck hypertrophy diagnosed by endoscopic and urodynamic criteria. This dyssynergic voiding may lead to an autonomic overstimulation of the perineal-pelvic neural system with subsequent development of a chronic neuropathic pain state. Alternatively, this high-pressure, dysfunctional voiding may result in intraprostatic ductal reflux in susceptible individuals (see the next section).

Intraprostatic Ductal Reflux

Reflux of urine and possibly bacteria into the prostatic ducts has been postulated as one of the most important etiologic mechanisms involved in the pathogenesis of chronic bacterial and nonbacterial prostatic inflammation. Anatomically, the ductal drainage of the peripheral zone is more susceptible than other prostatic zones to intraprostatic ductal reflux (Blacklock, 1974, 1991). Kirby and associates (1982) instilled a carbon particle solution into the bladders of men diagnosed with nonbacterial prostatitis. Carbon particles were found in the EPS macrophages and prostatic acini and ductal system after surgery in men with nonbacterial prostatitis. Persson and Ronquist (1996) noted high levels of urate and creatinine in EPS, which they postulated was caused by urine reflux into the prostatic ducts. Terai and coworkers (2000) provided molecular epidemiologic evidence for ascending infection in acute bacterial prostatitis.

Prostatic calculi are composed of substances found only in urine, not in prostatic secretions (Sutor and Wooley, 1974; Ramiraz et al, 1980), **further evidence that urinary intraprostatic reflux occurs and likely contributes to the formation of prostatic calculi. If pathogenic bacteria reflux into the prostate gland, they may exist in protected aggregates within prostatic calculi themselves.** High culture counts of pathogens encrusted in prostatic calculi have been demonstrated by Eykyn and colleagues (1974). This type of bacterial colonization in protective bacterial aggregates or biofilms associated with prostatic calculi may lead to recalcitrant chronic prostatitis and subsequent recurrent UTIs despite what seems to be adequate antibiotic therapy. Ludwig and coworkers (1994), employing transrectal ultrasonography, showed that men with chronic inflammatory prostatitis had a significantly increased frequency of prostatic calculi compared with men without prostate inflammation (prostatodynia). It appears that prostatic calcification is common in patients with nonbacterial chronic prostatitis and is associated with greater inflammation, bacterial colonization, pelvic floor spasm, and symptom duration (Shoskes et al, 2007). The inflammation resulting from chemical, bacterial, or immunologic stimulation has been shown to possibly cause an increase in intraprostatic pressures, measurable with transperineally inserted pressure transducers (Mehik et al, 2002).

Immunologic Alterations

The local prostatic immune system is activated by infection in bacterial prostatitis. In acute bacterial prostatitis, serum and prostatic fluid antigen-specific (i.e., bacterial antigen) IgG and IgA can be detected immediately after the onset of infection, and after successful antibiotic therapy they decline to normal levels over the next 6 to 12 months (Fowler and Mariano, 1984a; Meares, 1977, 1998; Kumon, 1992). **Prostate-specific antigen (PSA) levels can be markedly elevated during an acute episode of bacterial prostatitis** (Dalton, 1989; Moon et al, 1992; Neal et al, 1992) **and slowly resolve to normal levels over the course of 6 weeks, provided there is no recrudescence of the infection.** In chronic bacterial prostatitis, no serum immunoglobulin elevation is detected, whereas prostatic fluid IgA and IgG levels are both increased (Shortliffe and Wehner, 1986; Kumon, 1992). After successful antibiotic therapy, IgG levels return to normal after several months but the IgA (particularly secretory IgA) levels remain elevated for almost 2 years (Shortliffe et al, 1981a, 1981b; Fowler and Mariano, 1984a). Antibody-coated bacteria detected in urine, EPS, and semen is another prominent feature of chronic bacterial prostatitis (Riedasch et al, 1984, 1991).

Noninfectious inflammation (nonbacterial prostatitis) might also be secondary to immunologically mediated inflammation due to some unknown antigen or perhaps even related to an autoimmune process. IgA and IgM antibody levels (not microorganism-specific) are elevated (Shortliffe and Wehner, 1986; Shortliffe et al, 1989, 1992), and similar antibodies as well as fibrinogen and complement C3 (Vinje et al, 1983; Doble et al, 1990) have been identified in prostatic biopsy specimens from patients with chronic prostatitis. Both animal model studies (Donadio et al, 1998; Ceri et al, 1999; Lang et al, 2000) and human studies (Alexander et al, 1997; Batstone et al, 2002; Maake et al, 2003; Motrich et al, 2007) have suggested that prostatitis may be an autoimmune process. A number of candidates have been suggested for the self-antigen, including PSA (Ponniah et al, 2000). Other specific immunologic and neuroendocrine alterations such as cytokine production (Alexander et al, 1998; Jang et al, 2003) and nerve growth factor (Miller et al, 2002) have a subsequent role to play in the process of inflammation. Specifically, interleukin-10 has been implicated in the etiology and

clinical manifestations in chronic prostatitis (Miller et al, 2002; Shoskes et al, 2002) but other cytokines such as interleukin (IL)-1β and tumor necrosis factor-α have also been implicated (Nadler et al, 2000). IL-8 is the most common cytokine localized to the semen in men with chronic prostatitis (Khadra et al, 2006; Penna et al, 2007). There may be a genetic phenotype that promotes specific immunologic parameters that predispose to immunologically induced prostatic inflammation (Riley et al, 2002; Shoskes et al, 2002). These immunophenotypic patterns have even been observed in noninflammatory category IIIB chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) (Barghorn et al, 2001). Whatever the initiating event, the immunologic cascade appears to have an important role in the development of prostatitis in those patients who develop prostatic inflammation (Moon, 1998; Kumon, 1999).

Chemically Induced Inflammation

Investigators have demonstrated that urine and its metabolites (e.g., urate) are present in the prostatic secretion of patients with chronic prostatitis (Persson and Ronquist, 1996). These investigators have hypothesized that the prostatic inflammation and subsequent symptoms may be simply due to a chemically induced inflammation secondary to the noxious substances in the urine that have refluxed into the prostatic duct.

Pelvic Floor Muscle Abnormalities

Some investigators (Zermann et al, 1999) **propose that the sensory or motor disturbances or both consistent with neural dysregulation of the lower urinary tract may be a consequence of acquired abnormalities in the central nervous system.** Certainly, extraprostatic tenderness is identified in many patients with chronic prostatitis (Berger et al, 2007; Shoskes et al, 2008). Zermann and Schmidt (1999) describe 103 patients with chronic pelvic pain whom they evaluated at a specialized neurourologic unit. They showed that a majority of the men had insufficient conscious control of their somatically innervated striated pelvic floor muscles. The patients showed various levels of identity with their pelvic floor muscles, but none was able to demonstrate the full range of pelvic floor contraction and relaxation repetitively and effortlessly. This was true whether or not there was evidence of inflammation. They conclude that their findings reflect a functional disassociation between the central nervous system and the peripheral target, the pelvic floor muscles.

Other clinicians (Anderson, 1999; Potts, 2003) believe that the source of the pain is specifically at the pelvic musculature attachment area at the sacrum, coccyx, ischial tuberosity, pubic rami, and endopelvic fascia. These areas are immediately adjacent to the prostate and bladder and can be recognized by the demonstration of a hyperirritable spot or myofascial trigger point that is painful on compression. It is hypothesized that the formation of myofascial trigger points in this area results from mechanical abnormalities in the hip and lower extremities, chronic holding patterns such as those that occur during toilet training, sexual abuse, repetitive minor trauma and constipation, sports that create chronic pelvic stimulation, trauma or unusual sexual activity, recurrent infections, and surgery (Anderson, 1999). More recently, it has been hypothesized that the pain experienced in some men with CPPS may be explained by pudendal nerve entrapment, which causes subsequent neuropathic pain (Antolak et al, 2002). Unfortunately, all these studies examining pelvic floor muscle abnormalities did not compare findings to a control group (a criticism that can apply to many of the studies cited in this etiology section).

Neuroendocrine Mechanisms

The pain associated with the chronic prostatitis syndromes is similar in many respects to neuropathic pain. **Objective autonomic nervous system changes can be observed in men with a chronic prostatitis, suggesting that altered autonomic nervous system responses may be responsible for the pain associated with this chronic pelvic pain syndrome** (Yilmaz et al, 2007). Pain that may have originated in the prostate or pelvic floor muscles, through mechanisms of cross-sensitization, may have spread to adjacent organs and/or structures. We are only recently beginning to understand the complexity of overlapping neuropathways and possible mechanisms underlying pelvic organ crosstalk (Malykhina, 2007).

It has been shown that **men with chronic prostatitis showed evidence of dysfunctional hypothalamic-pituitary-adrenal axis function** reflected in augmented awakening cortisol responses (Anderson et al, 2008). Another study evaluating the adrenocortical hormone abnormalities in men with chronic prostatitis suggested that some men with this condition may even meet the diagnostic criteria for nonclassic congenital hyperplasia (Dimitrakov et al, 2008).

Psychological Factors

Psychological factors have always been considered to play an important role in the development or exacerbation of the chronic prostatitis syndromes. Some researchers who have investigated the psychopathology in these patients concluded that this syndrome should be viewed as a psychosomatic disorder (Mendlewich et al, 1971; Mellan et al, 1973; Keltikangas-Jarvinen et al, 1982). De la Rosette and associates (1993b) compared a group of 50 patients with chronic prostatitis with a group of 50 patients seen for vasectomy and showed that, although there were significant statistical differences between the groups (with patients with chronic prostatitis scoring consistently higher personality disorder scores), these differences in scores were quite small compared with those between patients with prostatitis and psychiatric patients. Berghuis and coworkers (1996) compared 51 prostatitis patients with a group of 34 men without any chronic pain condition and concluded that depression and psychological disturbances are common among prostatitis patients. Egan and Krieger (1994) compared prostatitis patients with those seeking treatment for chronic low back pain. Major depression was more common in prostatitis patients, but back pain caused more somatically focused depression and anxiety. Ku and coworkers (2002) suggested that depression and weak masculine identity may be associated with an early stage of chronic prostatitis. A large case-control study confirmed that depression and panic disorders are significantly more common in men with chronic pelvic pain conditions than in control subjects (Clemens et al, 2008). These more recent studies demonstrate that psychological factors are involved in the disease, but it seems unjustified to label this group of patients as neurotic or as having a psychopathologic condition. However, recent analyses of the large prostatitis cohorts showed that psychological variables, such as depression, maladaptive coping techniques (e.g., pain catastrophizing and pain contingent resting), poor social support, and stress are important in chronic prostatitis outcomes (Tripp et al, 2004, 2005, 2006; Ulrich et al, 2005; Nickel et al, 2008b). Factors such as catastrophizing are particularly important because they have been found to be stronger predictors of patient pain reports than depression (Tripp et al, 2006), indicating that negative cognitive appraisals of pain experience may be a primary target for psychosocial interventions. This

may be especially important given the strong association that pain catastrophizing has shown with elevations in depression, disability, and lower quality of life manifest in patients with chronic prostatitis (Tripp et al, 2005, 2006; Nickel et al, 2008b).

Association with Interstitial Cystitis (Painful Bladder Syndrome)

Interstitial cystitis, now referred to many as painful bladder syndrome or bladder pain syndrome, is an ill-defined CPPS occurring primarily in females, and a number of investigators have hypothesized that chronic nonbacterial prostatitis may have a similar cause (Pontari, 2006; Forrest et al, 2007). Unfortunately the cause of interstitial cystitis remains unknown, but the pathogenic mechanisms are theorized to be very similar to those that cause chronic prostatitis in men (Sant and Nickel, 1999; Eisenberg et al, 2003; Parsons 2003). Some researchers have proposed that in some patients diagnosed with prostatitis, a bladder-orientated interstitial cystitis mechanism actually accounts for the symptoms and that the prostate is only indirectly involved (Sant and Kominski, 1997). Certainly, the pain and voiding symptoms of interstitial cystitis and chronic prostatitis overlap to some extent (Miller et al, 1995; Novicki et al, 1998; Sant and Nickel, 1999; Forrest and Schmidt, 2004), and men with prostatitis diagnoses have findings on cystoscopic (Berger et al, 1998), urodynamic (Siroky et al, 1981), and potassium sensitivity testing (Parsons et al, 2002, 2005) very similar to those of patients with interstitial cystitis. However, Yilmaz and associates (2004) did not confirm positive potassium sensitivity testing in prostatitis patients and Keay and colleagues (2004) have shown that men diagnosed with chronic prostatitis (pain only) have normal antiproliferative factor activity whereas men diagnosed with interstitial cystitis (pain and irritative voiding symptoms) have detectable levels of urine antiproliferative factor.

An Interrelated, Pluricausal, Multifactorial Etiology

It is likely that the nonbacterial prostatitis syndromes have a multifactorial etiology, either a spectrum of etiologic mechanisms or, more likely, a progression or cascade of events after some initiating factor. In an important review on mechanisms involved in the pathogenesis of chronic prostatitis, Pontari and Ruggieri (2004) concluded that, "the symptoms of chronic prostatitis/chronic pelvic pain syndrome appear to result from an interplay between psychological factors and dysfunction in the immune, neurological and endocrine systems." Figure 11–2 describes a hypothetical scenario that could potentially involve most of the proposed and interrelated causes described in this section.

Key Points: Etiology

- Gram-negative Enterobacteriaceae and enterococci are responsible for most cases of bacterial prostatitis.
- Nonbacterial prostatitis syndromes are caused by an interrelated cascade of inflammatory, immunologic, neuroendocrine, and neuropathic mechanisms that begins with an initiator in a genetically or anatomically susceptible man.

Definition and Classification

Traditional Classification

The traditional classification system is based on the landmark paper by Meares and Stamey (1968) describing the differential diagnosis of the prostatitis syndromes. This classic paper described in great details the serial cultures (and treatment) in four patients with chronic prostatitis and introduced the so-called Meares-Stamey four-glass test. This localization test, which segmentally assesses inflammation and cultures of the male lower urinary tract, is described later in this chapter (see Lower Urinary Tract Evaluation). **Based on 10 years of clinical experience with this test, a classification system describing four categories of prostatitis was described by** Drach and colleagues in 1978**. Differentiation of the four categories depended on an analysis of prostatic fluid, which included microscopy (examination for white blood cells [WBCs], inflammatory cell clumps, mucus debris, oval fat bodies, and macrophages) and culturing (identifying traditional uropathogens).**

Acute bacterial prostatitis was diagnosed when prostatic fluid was clinically purulent, systemic signs of infectious disease were present, and bacteria were cultured from prostatic fluid. **Chronic bacterial prostatitis** was diagnosed when pathogenic bacteria were recovered in significant numbers from a purulent prostatic fluid in the absence of a concomitant UTI or significant systemic signs. **Nonbacterial prostatitis** was diagnosed when significant numbers of bacteria could not be cultured from prostatic fluid but the fluid consistently revealed microscopic

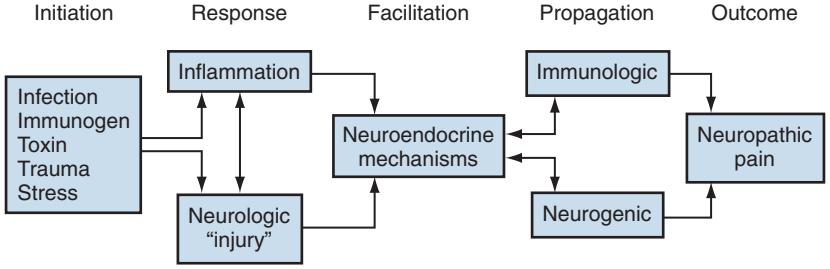


Figure 11–2. It is very likely that the etiology and pathogenesis of chronic prostatitis/chronic pelvic pain syndrome (category III CPPS) involves a pluricausal, multifactorial mechanism. An initiating stimulus such as infection, reflux of some "toxic" or "immunogenic" urine substance, perineal/pelvic "trauma," and/or psychological stress starts a cascade of events in an anatomically or genetically susceptible man, resulting in a local response of either inflammation or neurogenic injury (or both). Further immunologic or neuropathic (possibly interrelated) mechanisms mediated by neuroendocrine pathways propagate or sustain the chronicity of the initial (or ongoing) event. The final outcome is the clinical manifestation of chronic perineal/pelvic pain–associated symptoms associated with local and central neuropathic mechanisms.

Table 11–1.
Classification System for the Prostatitis Syndromes

TRADITIONAL	NATIONAL INSTITUTES OF HEALTH	DESCRIPTION
Acute bacterial prostatitis	Category I	Acute infection of the prostate gland
Chronic bacterial prostatitis	Category II	Chronic infection of the prostate gland
N/A	Category III chronic pelvic pain syndrome (CPPS)	Chronic genitourinary pain in the absence of uropathogenic bacteria localized to the prostate gland employing standard methodology
Nonbacterial prostatitis	Category IIIA (inflammatory CPPS)	Significant number of white blood cells in expressed prostatic secretions, post–prostatic massage urine sediment (VB3) or semen
Prostatodynia	Category IIIB (noninflammatory CPPS)	Insignificant number of white blood cells in expressed prostatic secretions, post–prostatic massage urine sediment (VB3) or semen
N/A	Asymptomatic inflammatory prostatitis (AIP)	White blood cells (and/or bacteria) in expressed prostatic secretions, post–prostatic massage urine sediment (VB3), semen or histologic specimens of prostate gland

purulence. **Prostatodynia** was diagnosed in the remaining patients who had persistent pain and voiding complaints as in the previous two categories but who had no significant bacteria or purulence in the prostatic fluid. This clinical differentiation of the prostatitis syndromes is now referred to as the "traditional" classification system (Table 11–1).

The significant limitations of this classification system included the abandonment by most physicians of the rigorous Meares-Stamey four-glass test (Moon, 1997; Nickel et al, 1998a; McNaughton Collins et al, 1999, 2000a), the realization that only the very rare patient would be subsequently diagnosed with chronic bacterial prostatitis, the perception that patients responded to specific therapy (e.g., antibiotics) independent of this classification system, and the dawning realization that, in many cases, patients presenting with prostatitis syndromes were not easily classified into one of these categories (e.g., patients in whom specific cultures were negative because of previous antibiotic therapy or those thought to have a cause other than the prostate gland) (Nickel, 1998a).

National Institutes of Health Classification

The limitations of the traditional diagnostic algorithm and traditional classification system led to the development of the National Institutes of Health (NIH) classification system (see Table 11–1) (Krieger et al, 1999). The new definition recognized that pain is the main symptom in "abacterial chronic prostatitis" (with variable voiding and sexual dysfunction), and it was the optimal criterion to differentiate chronic prostatitis patients from control patients or patients experiencing other genitourinary problems (e.g., BPH). **This classification differed from the traditional system in two main areas: the descriptions of category III CP/CPPS and category IV asymptomatic inflammatory prostatitis.**

Category I is identical to the acute bacterial prostatitis category of the traditional classification system. **Category II** is identical to the traditional chronic bacterial prostatitis classification, except that it now usually refers to patients with recurrent lower urinary tract infections (with a prostate nidus of infection) (Schaeffer, 2006). **Category III** is defined as the "presence of genitourinary pain in the absence of uropathogenic bacteria detected by standard microbiologic methodology." This syndrome is further categorized into **category IIIA,** or inflammatory CP/CPPS (based on the presence of excessive leukocytes in EPSs or post–prostatic massage urine or semen), and **category IIIB,** or noninflammatory CP/CPPS (no significant leukocytes in similar specimens). Category IV, or asymptomatic inflammatory prostatitis, addressed one of the major problems and omissions of the traditional classification system. Patients are classified as having **category IV** prostatitis by the presence of significant leukocytes (or bacteria or both) in prostate-specific specimens (EPS, semen, and tissue biopsies) in the absence of typical chronic pelvic pain.

The NIH International Prostatitis Collaborative Network met in Washington in 1998 and confirmed the value of this classification system, not only in clinical research studies but also in clinical practice (Nickel et al, 1999c).

Key Point: Classification

- The NIH classification of the prostatitis syndromes has now become recognized as the best system for research and clinical practice.

Clinical Presentation

Category I: Acute Bacterial Prostatitis

Acute bacterial prostatitis, category I, is a rare but important lower urinary tract infectious disease. It is characterized by an acute onset of pain combined with irritative and obstructive voiding symptoms in a patient with manifestations of a systemic febrile illness. The patient typically complains of urinary frequency, urgency, and dysuria. Obstructive voiding complaints including hesitancy, poor interrupted stream, strangury, and even acute urinary retention are common. The patient complains of perineal and suprapubic pain and may have associated pain or discomfort of the external genitalia. In addition, there are usually significant systemic symptoms including fever, chills, malaise, nausea and vomiting, and even frank septicemia with hypotension. The combination and severity of symptoms in category I, acute bacterial prostatitis, vary from patient to patient. Approximately 5% of patients with acute bacterial prostatitis may progress to chronic bacterial prostatitis (Cho et al, 2005).

Category II: Chronic Bacterial Prostatitis

The most important clue in the diagnosis of category II, chronic bacterial prostatitis, is a history of documented recurrent UTIs. From 25% to 43% of patients diagnosed with chronic bacterial

prostatitis employing a four-glass test had a history of recurrent UTIs (Weidner and Ludwig, 1994; Wright et al, 1994). Patients may be relatively asymptomatic between acute episodes, or they may present with a long history of a CPPS, which is described extensively in the next section. The prevalence of bacterial prostatitis ranges from 5% to 15% of prostatitis cases (Schaeffer et al, 1981; Krieger and Egan, 1991; Weidner and Ludwig, 1994). In one of the largest and most comprehensive clinical series, Weidner and associates (1991b) found significant bacteriuria (with uropathogenic organisms) in 4.4% of patients with symptoms of chronic prostatitis.

Category III: CP/CPPS

The presenting symptoms of inflammatory category IIIA CP/CPPS (similar to the previous category of chronic nonbacterial prostatitis) are indistinguishable from those of patients with noninflammatory category IIIB disease (previously referred to as prostatodynia). The symptoms experienced by patients with CP/CPPS have been studied extensively by Krieger and colleagues (1996a). They evaluated 50 patients with CP/CPPS seen in a prostatitis clinic (compared with 75 control patients). Alexander and Trissel (1996) surveyed a cohort of 163 prostatitis patients on the Internet. These symptoms were best defined in the development of prostatitis symptom scores by Neal and Moon (1994), Krieger and colleagues (1996a), Nickel and Sorensen (1996b), and Brahler and coworkers (1997). **The predominant symptom in all these studies was pain, which was most commonly localized to the perineum, suprapubic area, and penis but can also occur in the testes, groin, or low back. Pain during or after ejaculation is one of the most prominent, important, and bothersome features in many patients** (Shoskes et al, 2004). Irritative and obstructive voiding symptoms including urgency, frequency, hesitancy, and poor interrupted flow are associated with this syndrome in many patients. Erectile dysfunction and sexual disturbances have been reported in patients with CPPS (Mehik et al, 2001; Liang et al, 2004; Zaslau et al, 2005; Muller and Mulhall, 2006; Marzalek et al, 2007; Smith et al, 2007a, 2007b; Lee et al, 2008a) but are not pathognomonic features of this syndrome. The best description of the CP/CPPS patient was provided by the NIH Chronic Prostatitis Cohort Study (Schaeffer et al, 2002). A detailed description of 488 men with CP/CPPS noted that the most frequently reported pain/discomfort was in the perineum, followed by pain/discomfort in the suprapubic area. Over half of the men had pain/discomfort during or after sexual climax (ejaculatory pain may be the most discriminatory symptom).

By definition, the syndrome becomes chronic after 3 months' duration. The symptoms tend to wax and wane over time; approximately one third of patients improve over 1 year (usually patients with shorter duration and fewer symptoms) (Nickel et al, 2002; Turner et al, 2004; Propert et al, 2006). An age-matched case-control study of risk factors in men with CP/CPPS (Pontari et al, 2005) showed that compared with asymptomatic controls, men with CP/CPPS reported a significantly greater life time prevalence of nonspecific urethritis (12% vs. 4%), cardiovascular disease (11% vs. 2%), neurologic disease (41% vs. 14%), psychiatric conditions (29% vs. 11%), and blood or infectious disease (41% vs. 20%).

The impact of this condition on health status is significant. The quality of life of many patients diagnosed with CP/CPPS is greatly diminished. Wenninger and associates (1996), employing a generic health status measure, the Sickness Impact Profile, showed that the mean scores were within the range of scores reported in the literature for patients with a history of myocardial infarction, angina, or Crohn disease. McNaughton Collins and coworkers (2001b) employed similar quality of life assessment instruments in the NIH Chronic Prostatitis Cohort Study of almost 300 patients and confirmed this finding. These investigators noted that the mental health component was affected more than the physical component of the quality of life assessment. CP/CPPS patients' quality of life was lower than those observed in the most severe subgroups of men with congestive heart failure and diabetes mellitus. This significant impact on quality of life has also been reported in a cohort of CP/CPPS men evaluated in a primary care setting (Turner et al, 2002). Patients with a diagnosis of CP/CPPS may present with depression (Tripp et al, 2005, 2006), stress (Ulrich et al, 2005), or a history of abuse (sexual, physical, or emotional) (Hu et al, 2007). Depression, maladaptive coping techniques (e.g., catastrophizing and pain contingent resting) and poor social support are associated with a poorer quality of life (Nickel et al, 2008b).

Category IV: Asymptomatic Inflammatory Prostatitis

Category IV, asymptomatic inflammatory prostatitis, by definition, does not cause symptoms. The patients present with BPH, an elevated PSA level, prostate cancer, or infertility. Subsequent microscopy of EPS or semen and/or histologic examination of BPH chips, prostate cancer specimens, or prostate biopsy specimens disclose evidence of prostatic inflammation.

Symptom Assessment

In a syndrome such as CP/CPPS, in which the objective parameters of the disease are unknown, controversial, or not validated, evaluation outcomes become of critical importance. In a syndrome defined primarily by its symptom-complex, analysis of specific prostatitis-like symptoms, the quality of life, the patient's functional status, and the patient's satisfaction with medical care will result in not only better evaluation of the prostatitis patient but also improved therapeutic follow-up. Scientifically validated symptom indices not only improve the care of patients but also optimize clinical decision making in terms of comparing clinical trial outcomes. Since the early 1990s, several different symptom indices have been described in clinical research (Neal and Moon, 1994; Krieger et al, 1996a; Nickel and Sorensen, 1996b; Brahler et al, 1997; Chiang et al, 1997) and have been sporadically employed in clinical practice (McNaughton Collins and O'Leary, 1999). Although each of these symptom indices was successful at the time it was developed for the specific purpose or study, none was believed to be ideal for use in general research or clinical practice because they were not validated according to the rigorous standards that now must be met for an accepted urologic disease-specific index (O'Leary et al, 1992).

The NIH Chronic Prostatitis Collaborative Research Network (CPCRN) developed a reproducible and valid instrument to measure the symptoms and quality of life of patients with chronic prostatitis for use in research protocols as well as clinical practice (Litwin et al, 1999). The steps followed in the development of the NIH-CPSI included a systematic literature review, focus groups, cognitive testing, an expert panel review, a validation test, and psychometric analyses. **The final index consists of nine questions that address the three most important domains of the chronic prostatitis experience. Pain (which is the primary symptom of CP/CPPS) was captured in four questions that focused on its location, severity, and**

frequency. Urinary function, the second most important component of patients' symptoms, was captured in two questions, one concerning irritative, and the other obstructive, function. The quality of life or impact was captured in three additional questions that asked about the effect of symptoms on daily activities. The NIH-CPSI (Fig. 11–3) **has now been accepted by the international prostatitis research community as an accepted outcome measure** (Nickel et al, 1999c) **and has shown validity and responsiveness in primary care samples** (Turner et al, 2003) **and clinical trials** (Propert et al, 2006). It has been translated and validated in many languages other than English (Collins et al, 2001; Kunishima et al, 2002; Leskinen et al, 2003a; Schneider et al, 2004; Karakiewicz et al, 2005). The symptom index has also proved its usefulness in the evaluation and follow-up of patients in general clinical urologic practice (Nickel, 1999b, 2001c).

NIH-Chronic Prostatitis Symptom Index (NIH-CPSI)

Pain or Discomfort

1. In the last week, have you experienced any pain or discomfort in the following areas?

	Yes	No
a. Area between rectum and testicles (perineum)	❑ 1	❑ 0
b. Testicles	❑ 1	❑ 0
c. Tip of the penis (not related to urination)	❑ 1	❑ 0
d. Below your waist, in your pubic or bladder area	❑ 1	❑ 0

2. In the last week, have you experienced:

	Yes	No
a. Pain or burning during urination?	❑ 1	❑ 0
b. Pain or discomfort during or after sexual climax (ejaculation)?	❑ 1	❑ 0

3. How often have you had pain or discomfort in any of these areas over the last week?

❑ 0 Never
❑ 1 Rarely
❑ 2 Sometimes
❑ 3 Often
❑ 4 Usually
❑ 5 Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?

❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
0	1	2	3	4	5	6	7	8	9	10
NO PAIN									PAIN AS BAD AS YOU CAN IMAGINE	

Urination

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?

❑ 0 Not at all
❑ 1 Less than 1 time in 5
❑ 2 Less than half the time
❑ 3 About half the time
❑ 4 More than half the time
❑ 5 Almost always

6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?

❑ 0 Not at all
❑ 1 Less than 1 time in 5
❑ 2 Less than half the time
❑ 3 About half the time
❑ 4 More than half the time
❑ 5 Almost always

Impact of Symptoms

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

❑ 0 None
❑ 1 Only a little
❑ 2 Some
❑ 3 A lot

8. How much did you think about your symptoms, over the last week?

❑ 0 None
❑ 1 Only a little
❑ 2 Some
❑ 3 A lot

Quality of Life

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

❑ 0 Delighted
❑ 1 Pleased
❑ 2 Mostly satisfied
❑ 3 Mixed (about equally satisfied and dissatisfied)
❑ 4 Mostly dissatisfied
❑ 5 Unhappy
❑ 6 Terrible

Scoring the NIH-Chronic Prostatitis Symptom Index Domains

Pain: Total of items 1a, 1b, 1c, 1d, 2a, 2b, 3, and 4 = ____

***Urinary Symptoms*:** Total of items 5 and 6 = ____

Quality of Life Impact: Total of items 7, 8, and 9 = ____

Figure 11–3. The National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) captures the three most important domains of the prostatitis experience: pain (location, frequency, and severity), voiding (irritative and obstructive symptoms), and quality of life (including impact). This index is useful in research studies and clinical practice. (Reprinted with permission from Litwin MS, McNaughton Collins M, Fowler FJ, et al. The NIH Chronic Prostatitis Symptom Index [NIH-CPSI]: development and validation of a new outcome measure. J Urol 1999;162:369–375.)

Key Point: Symptom Assessment

- The validated NIH-CPSI is a useful research and clinical tool for evaluating CP/CPPS patients.

Lower Urinary Tract Evaluation

Physical Examination

Physical examination is an important part of the evaluation of a patient with prostatitis, but it is usually not helpful in making a definitive diagnosis or further classifying the disorder. It assists in ruling out other perineal, anal, neurologic, pelvic, or prostate abnormalities and is an integral part of the lower urinary tract evaluation by providing prostate-specific specimens.

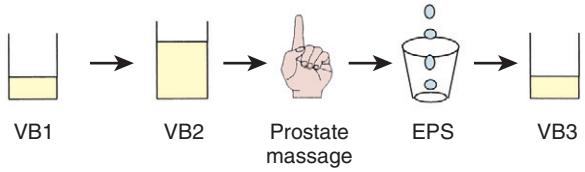
In category I, acute bacterial prostatitis, the patient may be systemically toxic, that is, flushed, febrile, tachycardic, tachypneic, and even hypotensive. The patient usually has suprapubic discomfort and perhaps has clinically detectable acute urinary retention. Perineal pain and anal sphincter spasm may complicate the digital rectal examination. The prostate itself is usually described as hot, boggy, and exquisitely tender. The expression of prostatic fluid is believed to be totally unnecessary and perhaps even harmful.

The physical examination of a patient with category II, chronic bacterial prostatitis and category III CPPS is usually unremarkable (except for pain). Careful examination and palpation of external genitalia, groin, perineum, coccyx, external anal sphincter (tone), and internal pelvic floor and side walls may pinpoint prominent areas of pain or discomfort. **The digital rectal examination should be performed after the patient has produced pre-prostatic massage urine specimens (see later). The prostate may be normal in size and consistency, and it has also been described as enlarged and boggy (loosely defined by the author as softer than normal). The degree of elicited pain during prostatic palpation is variable and is unhelpful in differentiating a prostatitis syndrome.** The prostate should be carefully checked for prostatic nodules before a vigorous prostatic massage is performed to produce prostate-specific specimens (EPS and post–prostatic massage urine sample).

Lower Urinary Tract Cytologic Examination and Culture Techniques

In patients presenting with category I, acute bacterial prostatitis, a urine culture is the only laboratory evaluation of the lower urinary tract required. It has been suggested that the vigorous prostatic massage necessary to produce EPS can exacerbate the clinical situation, although such fears have never been substantiated in the literature. A midstream urine specimen will show significant leukocytosis and bacteriuria microscopically, and culturing usually discloses typical uropathogens. Blood cultures may show the same organism.

In 1968, Meares and Stamey described the classic four-glass urine collection technique to distinguish urethral, bladder, and prostate infections in men with chronic prostatitis, and for 3 decades this has remained the "gold standard" for the evaluation of this lower urinary tract syndrome. The voided bladder-1 (VB1) specimen includes the first 10 mL of urine and represents the urethral specimen. The voided bladder-2 (VB2) specimen is similar to a midstream urine collection and represents the bladder urine. EPS should be collected directly into a sterile container during prostatic massage. The voided bladder-3 (VB3) specimen, the first 10 mL of urine voided after prostatic massage, includes any EPS trapped in the prostatic urethra. The three urine specimens are centrifuged for 5 minutes and the sediment examined under high power for leukocytes (including aggregates of leukocytes), macrophages, oval fat bodies, erythrocytes, bacteria, and fungal hyphae. A wet mount of a drop of EPS can be examined under a coverslip in a similar manner. Some researchers (Muller et al, 2001; Krieger et al, 2003) point out that quantitative determination of the EPS WBC concentration by a counting chamber method is superior to the standard wet mount method but probably only indicated in research studies. In fact, the NIH Chronic Prostatitis Cohort Study (Schaeffer et al, 2002; Nickel et al, 2003a) suggested that leukocyte determination did not appear to add significant clinical information to the assessment of a patient with CP/CPPS. All four specimens are sent to the laboratory for quantitative culturing. Figure 11–4 illustrates the technique and interpretation of the four-glass test.



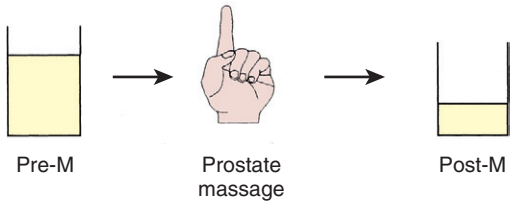
4-Glass Test (Meares-Stamey Test)

Classification	Specimen	VB1	VB2	EPS	VB3
CAT II	WBC	–	+/–*	+	+
	Culture	–	+/–*	+	+
CAT IIIA	WBC	–	–	+	+
	Culture	–	–	–	–
CAT IIIB	WBC	–	–	–	–
	Culture	–	–	–	–

Figure 11–4. Technique and interpretation of the Meares-Stamey four-glass lower urinary tract localization test for CP/CPPS.

Category II, chronic bacterial prostatitis, is diagnosed if there is a 10-fold increase in bacteria in the EPS or VB3 specimen compared with the VB1 and VB2 specimens. In a patient who has acute cystitis this localization is impossible, and in this case the patient can be treated with a short course (1 to 3 days) of therapy with an antibiotic such as nitrofurantoin, which penetrates the prostate poorly but eradicates the bladder bacteriuria. Subsequent localization of bacteria in the post–prostatic massage urine or EPS is then diagnostic of category II prostatitis. Category IIIA CP/CPPS is diagnosed when no uropathogenic bacteria are cultured, but excessive leukocytosis (usually defined as more than 5 to 10 WBCs/high-power field [hpf]) is noted in the prostate-specific specimens (EPS or VB3 or both). Category IIIB CP/CPPS is diagnosed when no uropathogenic bacteria are cultured and there is no significant leukocytosis noted on microscopic examination of EPS or the sediment of VB3.

Although the four-glass test remains the gold standard diagnostic evaluation of prostatitis patients, numerous surveys (Moon, 1997; Nickel et al, 1998a; McNaughton Collins et al, 1999, 2000a) have confirmed that clinicians have more or less abandoned this time-consuming and expensive rigorous evaluation. **The pre-massage and post-massage test (or two-glass test), originally suggested by** Weidner and Ebner (1985) **and popularized**



2-Glass Test (PPMT)

Classification	Specimen	Pre-M	Post-M
CAT II	WBC	+/–*	+
	Culture	+/–*	+
CAT IIIA	WBC	–	+
	Culture	–	–
CAT IIIB	WBC	–	–
	Culture	–	–

Figure 11–5. Technique and interpretation of the pre- and post-massage two-glass lower urinary tract localization test for CP/CPPS.

by Nickel (1995, 1996, 1997a), **is a simple, cost-effective screen to categorize patients with chronic prostatitis.** The patient provides a midstream pre-massage urine specimen and a urine specimen (initial 10 mL) after prostatic massage. Microscopy (sediment) and culturing of these two screening urine specimens allows categorization of the majority of patients presenting with a chronic prostatitis syndrome. Figure 11–5 illustrates the technique and interpretation of the two-glass pre-massage and post-massage test.

In a retrospective personal series and a review of series in the literature, Nickel (1997a) noted that this test had 91% sensitivity and specificity compared with the gold standard Meares-Stamey test. Its limitations were thought to be due to the exclusion of the urethral and EPS specimen. However, in patients without clinical urethritis, Krieger and associates (2000) demonstrated that urethral swabs are more efficient in picking up urethral inflammation than the VB1 specimen. But in this series of 235 patients only 3% had more than 1 WBC/hpf. Therefore the urethral specimens rarely detected significant urethral inflammation, and in this series rarely did cultured organisms change the direction of clinical therapy in patients with prostatitis (without clinical urethritis). In the same study (Krieger et al, 2000) comparing EPS with post–prostatic massage urine, the investigators demonstrated that EPS examination detected 76%, whereas post-massage urine examination detected 82% of the patients who had inflammation on one or both tests. Ludwig and associates (2000), in a series of 328 patients in whom both EPS and a VB3 specimen were obtained, demonstrated that VB3 is almost as accurate as EPS (92% sensitivity; 99% specificity) in detecting prostate-specific inflammation. Seiler and associates (2003) came to the same conclusion in their study of 143 chronic prostatitis patients. Nickel and colleagues from the NIH CPCRN (2006) examined a cohort of 353 CP/CPPS men with complete four-glass data and noted that the two-glass test predicted a positive four-glass result with clinically acceptable accuracy (over 95% of men would have had the same diagnosis if the four-glass test was performed). This test, however, is only a screening test, and in patients in whom it is important to localize bacteria to the prostate versus the urethra (e.g., patients with recurrent UTIs, suspicion of urethral abnormality), a follow-up VB1 specimen or urethral swab may be very helpful. If typical urethral organisms are localized to the prostate when the pre-massage and post-massage test is used and the clinician is inclined to consider them pathogenic and subsequently treat the patients, urethral and EPS specimens to definitively localize the specific bacteria to the prostate are appropriate. As a general rule, it is always best to examine the EPS (if obtainable) microscopically.

Key Point: Lower Urinary Tract Culture Technique

- The two-glass pre- and post-massage test is a simple, useful screen for inflammation and infection of the lower urinary tract in patients presenting with chronic prostatitis.

Microbiologic Considerations. Both the traditional and the NIH classification systems depend on culturing for standard uropathogens. The Enterobacteriaceae (e.g., *E. coli, Serratia, Klebsiella, Proteus, Pseudomonas*) represent the most common uropathogens, followed by gram-positive enterococci. However, as discussed earlier in the section on etiology, other gram-positive organisms that typically colonize the urethra (*Staphylococcus epidermidis, Staphylococcus saprophyticus, Streptococcus* species, *Corynebacterium,* and *Bacteroides*) can be localized to the prostate specimens, including semen (>10-fold colony-forming unit count in prostate-specific specimens compared with pre–prostatic massage specimens), and their association with the prostatic inflammation symptom-complex remains unclear. At this time, these patients are still considered as having category III CP/CPPS, but as more research results become available this may change as our understanding of bacterial pathogenicity in the prostate gland evolves (Nickel and Moon, 2005; Nickel and Xiang, 2008).

Cytologic Considerations. The differentiation of the two subtypes of category III CP/CPPS depend on cytologic examination of the urine or EPS or both. The urine specimens are centrifuged for 5 minutes, and the sediment is resuspended under a coverslip and examined at high power (×300 to ×400) while the wet mount of a drop of EPS is examined under a coverslip at the same power. WBCs have traditionally been reported as numbers of leukocytes per high-power field (Fig. 11–6). **There is no validated cutoff point for the level of WBCs per high-power field that is required to differentiate an inflammatory from a noninflammatory CP/CPPS. Although the suggested limits have ranged from as low as 2** (Anderson and Weller, 1979) **to as high as 20** (Blacklock and Beavis, 1978) **the consensus appears to favor 5 to 10 WBCs/hpf in EPS as the upper level of normal** (Meares and Stamey, 1968; Pfau et al, 1978; Schaeffer et al, 1981). But inflammatory cells in the EPS fluctuate over time (Anderson and Weller, 1979; Schaeffer et al, 1981) and with the frequency of ejaculation (Jameson, 1967; Yavascaoglu et al, 1999). A disadvantage of looking at a drop of prostatic fluid or urine sediment is that the cells may clump or aggregate, which renders quantifying them virtually impossible. Also, an unstained specimen does not allow differentiation of the type of WBC present (e.g., polymorphonuclear leukocytes, lymphocytes, monocytes, macrophages). If accuracy is required (i.e., research), then the WBCs can be counted in a glass hemacytometer (so they may be quantified as cells per square millimeter) and subsequently stained to differentiate the inflammatory cell subtype (Anderson and Weller, 1979).

The clinical relevance of adding cytologic examination of semen specimens (which is difficult without special staining techniques) is unknown. Certainly, semen examination increases the percentage of patients identified as inflammatory category IIIA CP/CPPS (Krieger et al, 2000).

Nickel and colleagues (2003a) compared the number of WBCs in the EPS in patients with CP/CPPS to EPS specimens from normal

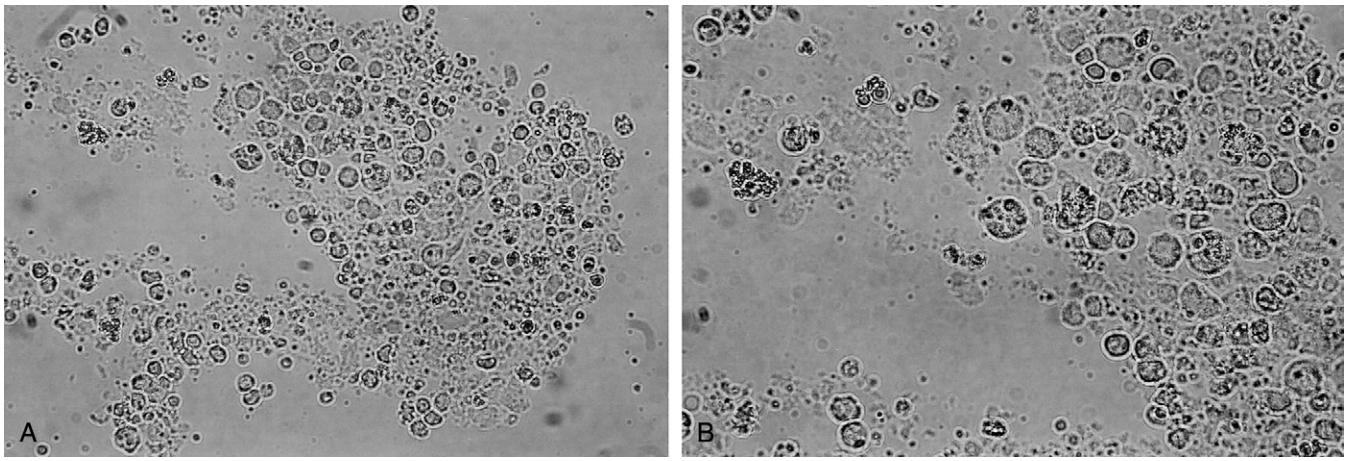


Figure 11–6. **A** and **B,** Unstained photomicrographs showing individual white blood cells, clumps of white blood cells, and lipid-laden macrophages in the expressed prostatic secretion (EPS) of a patient with category IIIA CPPS (**A,** ×250; **B,** ×400).

asymptomatic control men and noted that while there was a statistically significant difference in WBC counts in the CP/CPPS men the clinical significance was not apparent (e.g., 50% of CPPS men had >5 WBCs/hpf compared with 40% of control men). The relevance of examining urine and EPS for white cells in routine clinical practice has been challenged (Nickel et al, 2003a). In fact, **we have not been able to confirm the association between histologically proven prostate inflammation and prostatitis symptoms** (Nickel et al, 2007), **further confusing the issue of whether we really need to determine prostate-specific specimen inflammation,** which is really just a surrogate for prostate inflammation. However, some investigators (Nickel, 2002d) have recommended that urine cytology (for malignant cells) become a standard diagnostic test for men presenting with prostatitis-like symptoms, particularly if the symptom-complex includes irritative voiding symptoms, dysuria, and/or suprapubic/bladder pain.

Urodynamics

Pain is the dominant symptom in patients presenting with CP/CPPS, but a wide constellation of irritative and obstructive voiding symptoms are associated with this syndrome. Proposed causes to account for the persistent irritative and obstructive voiding symptoms include detrusor vesical neck or external sphincter dyssynergia, proximal or distal urethral obstruction, and fibrosis or hypertrophy of the vesical neck (Blacklock, 1974, 1986; Bates et al, 1975; Orland et al, 1985; Theodorou et al, 1999). These abnormalities can often be clarified and diagnosed by urodynamics, particularly video-urodynamics. Others have suggested that men with defined primary voiding dysfunction have been misdiagnosed with chronic prostatitis (Webster et al, 1980; Siroky et al, 1981; Murnaghan and Millard, 1984). Siroky and associates (1981) noted that urodynamics revealed that 50% of 47 men with recurrent voiding symptoms, perigenital pain, or both previously diagnosed as chronic prostatitis had bladder acontractility during a study with nonrelaxing perineal floor (striated muscle spasm) and that another 36% had detrusor overactivity with appropriate striated sphincter relaxation. Barbalias (1990) and Barbalias and colleagues (1983) noted decreased peak and mean urinary flow rates, a significantly elevated maximal urethral closing pressure, and incomplete funneling of the bladder neck accompanied by urethral narrowing at the level of the external urinary sphincter during voiding with urodynamic evaluation of men diagnosed with chronic prostatitis. Hellstrom and colleagues (1987) also noted elevated urethral pressures, "hyperreflexia" of the external urethral sphincter, and intraprostatic reflux in three patients with unremitting symptoms of chronic nonbacterial prostatitis.

Kaplan and associates (1994, 1996, 1997) postulated that chronic lower urinary tract symptoms in young men are often misdiagnosed as chronic nonbacterial prostatitis when in fact they indicate a cohort of men with undiagnosed chronic voiding dysfunction. This conclusion is based on the video-urodynamic studies of 137 consecutive men 50 years of age or younger diagnosed with chronic prostatitis (Kaplan et al, 1996). These researchers demonstrated a variety of urodynamic abnormalities, including 54% of patients with primary vesical neck obstruction, 24% with functional obstruction localized to the membranous urethra (pseudodyssynergia), 17% with impaired bladder contractility, and 5% with an acontractile bladder. They noted detrusor overactivity in 49% of the men. Simple documentation of uroflowmetry and residual urine bladder scan abnormalities may suggest proceeding to more sophisticated urodynamics (Ghobish, 2000). Other groups dispute the benefits of urodynamics and have noted very few urodynamic abnormalities in patients presenting with classic chronic prostatitis symptoms (Mayo et al, 1998).

Endoscopy

Clinical experience (rather than controlled clinical studies) suggests that lower urinary tract endoscopy (i.e., cystoscopy) is not indicated in the majority of men presenting with CP/CPPS. However, cystoscopy is indicated in patients in whom the history (e.g., hematuria), lower urinary tract evaluation (e.g., VB1 urinalysis), or ancillary studies (e.g., urodynamics) indicate the possibility of a diagnosis other than CP/CPPS. In these patients, occasionally lower urinary tract malignancy, stones, urethral strictures, bladder neck abnormalities, and so forth that can be surgically corrected are discovered. Cystoscopy can probably be justified in men refractory to standard therapy.

Transrectal Ultrasonography

Transrectal ultrasonography has become one of the best radiologic methods to evaluate prostate disease and has become an especially helpful clinical tool for the assessment of prostate volume and ultrasound guidance of biopsy needles. **The diagnostic value of ultrasonography in differentiating benign from malignant prostate disease is controversial, and the**

further differentiation of the various benign conditions of the prostate is even more so. Di Trapani and colleagues (1988) described inhomogeneous echo structures, constant dilatation of periprostatic venous plexus, elongated seminal vesicles, and thickening of the inner septa in patients with prostatitis. Doble and Carter (1989) described seven ultrasound signs associated with the presence of symptoms of chronic prostatitis compared with controls, and although the sensitivity increased with higher leukocyte counts the signs were not sufficiently specific to differentiate clinical groups.

Peeling and Griffiths (1984) describe the heterogeneity of the echo pattern and prostatic calculi as ultrasound features related to prostatitis. Ludwig and coworkers (1994) described the ultrasound features such as prostatic calcifications and seminal vesicle abnormalities that appear to be indicative of signs of inflammation but not proof of the presence of chronic prostatitis. Harada and associates (1980) concluded that the presence of stones is not related to a specific prostate disease process. De la Rosette and colleagues (1992b) performed ultrasonography in 22 patients with nonbacterial prostatitis and compared the results with those of a control group of 22 patients without lower urinary tract symptoms. This study indicated that there were no significant differences in ultrasound patterns of patients with nonbacterial prostatitis and the control group. Others have employed color Doppler ultrasonography (Veneziano et al, 1995) and automated computer analysis (de la Rosette et al, 1995) in an attempt to improve the value of transrectal ultrasonography in the evaluation of prostatitis patients; however, the results are not conclusive enough to indicate that this is a clinically useful tool.

Transrectal ultrasonography can be valuable in diagnosing medial prostatic cysts in patients with prostatitis-like symptoms (Dik et al, 1996), **diagnosing and draining prostatic abscesses** (Granados et al, 1992), **or diagnosing and draining obstructed seminal vesicles** (Littrup et al, 1988). It is not required in all cases of acute bacterial prostatitis but rather only in those patients who are failing appropriate antimicrobial therapy (Horcajada et al, 2003).

Prostate Biopsy

Occasionally, because of an elevated PSA level or abnormal digital rectal examination, prostate biopsy is indicated (Kawakami et al, 2004). Some clinicians will consider starting patients with elevated screening PSA levels and a history of prostatitis or symptoms of CPPS on antibiotics, but this practice is really only rational in patients with acute or chronic bacterial prostatitis (Nickel, 2002c), conditions that invariably lead to elevated PSA levels. The diagnosis of CP/CPPS should be used only as a reason against a prostate biopsy if the clinician is looking for an excuse not to biopsy (Nickel, 2002c). A comprehensive review on PSA and prostatitis is available (Kawakami et al, 2004).

Out of desperation, urologists sometimes resort to prostate biopsy in an attempt either to demonstrate histologic evidence of prostatic inflammation or to culture an organism that cannot be cultured employing the standard approach. The importance and interpretation of prostate biopsies in prostatitis performed for reasons other than prostate cancer screening is unclear. Doble and associates (1990) demonstrated immune complexes in the prostate of patients with prostatitis but found culture of the prostatic tissue unhelpful (Doble et al, 1989a). Nickel and Costerton (1993) were able to confirm the presence of potentially uropathogenic bacteria in patients with a documented history of chronic bacterial prostatitis in whom EPS cultures became sterile after antibiotic therapy. Berger and associates (1997) also confirmed the presence of potential uropathogenic bacteria in prostate biopsy specimens (which correlated to some extent with prostatic inflammation in EPS) in patients in whom the same bacteria did not grow standard prostatic specimens (e.g., EPS). Krieger and colleagues (1996b) demonstrated the possible presence of microorganisms in the prostate gland of a majority of men with chronic prostatitis syndrome using the molecular biologic technique of polymerase chain reaction. **At this time, histologic, culture, and molecular biologic evaluations of prostate biopsy specimens in patients with CP/CPPS remain research tools only.**

Seminal Vesiculitis

Occasionally, seminal vesiculitis can occur as a consequence of local bacterial infection in acute and chronic bacterial prostatitis (Zeitlin, 1999) and patients can present with seminal vesicle abscesses (Stearns, 1963; Kennelly and Oesterling, 1989). Seminal vesicle abscesses were traditionally diagnosed clinically by a positive ejaculate culture and seminal vesiculography (Dunnick et al, 1982; Baert et al, 1986) but is now imaged with computed tomography (Patel and Wilbur, 1987), transrectal ultrasonography (Littrup et al, 1988), magnetic resonance imaging (Sue et al, 1989) or recently with technetium-99m ciprofloxacin radioisotope scan (Choe et al, 2003).

Other Possible Markers

Wishnow and associates (1982) found that control patients (10 patients) and men with chronic abacterial prostatitis (4 patients) had no antibodies to gram-negative bacterial antigens, in contrast to men with bacterial prostatitis (6 patients). They hypothesized that immunologic analysis may provide a better diagnostic tool than culturing and microscopy. Shortliffe and coworkers (1981a, 1981b, 1986, 1989, 1992) found that the total IgA and IgG levels in the prostatic fluid in men with chronic abacterial prostatitis were higher than those of controls. They also discovered that prostatic fluid from control or abacterial prostatitis patients did not contain specific antibodies to gram-negative urinary pathogens (in contrast to men with bacterial prostatitis). Nickel and colleagues (2001a) used a similar antibody screening procedure in evaluation of 102 men with CP/CPPS who were subsequently treated with quinolone antibiotics. However, "antibody-positive" patients did not have a better response to antibiotic therapy than "antibody-negative" patients after 12 weeks of therapy. Li and associates (2001) demonstrated increased endotoxin concentrations in EPS and VB3 of men with bacterial prostatitis and inflammatory category IIIA CPPS and suggested that endotoxin levels might be used to identify these categories of patients with chronic prostatitis.

Alexander and colleagues (1998) discovered that men with chronic abacterial prostatitis had higher mean levels of the proinflammatory cytokines IL-1α and TNF-α in seminal plasma compared with controls. Ruggieri and coworkers (2000) noted that levels of both IL-1α and IL-8 were significantly higher in semen in category IIIA patients (leukocytes) than in category IIIB patients, but there was no statistically significant difference in levels of TNF-α, IL-1α, or IL-6. This group found no correlation between cytokine levels and the number of leukocytes in EPS. The increased IL-8 levels in the semen of patients with prostatitis symptoms has recently been confirmed by Khadra and coworkers (2006) and Penna and associates (2007), suggesting that this could be a surrogate marker for CP/CPPS. Nadler and colleagues (2000) found that mean levels of IL-1α in EPS were higher in men with inflammatory chronic abacterial prostatitis and noninflammatory

chronic bacterial prostatitis compared with controls. Hochreiter and associates (2000a) did find a direct significant correlation between the number of leukocytes in EPS and IL-1α levels in EPS. **One of the most intriguing possible biomarkers includes monocyte chemoattractant protein-1 and macrophage inflammatory protein-1α detected in EPS. Both of these chemokines are elevated in category IIIA and IIIB CP/CPPS, whereas macrophage inflammatory protein-1α may be a further marker for clinical pain in these patients** (Desireddi et al, 2008). The sensitivity, specificity, and, more importantly, the clinical applicability of all these immunologic tests is really unknown and none of them is yet indicated in clinical practice.

Marmar and associates (1980) hypothesized that zinc levels in EPS would be a useful marker for prostatitis and found that, indeed, zinc levels in men with chronic abacterial prostatitis and bacterial prostatitis were significantly lower than zinc levels in control patients and men with prostatodynia. However, Zaichick and colleagues (1996) found no differences in zinc levels between patients with chronic abacterial prostatitis, BPH, and controls. At this time the measurement of zinc levels in prostatic or semen specimens is clinically unhelpful.

Tanner and associates (1999) detected positive signals (rRNA-based molecular technique with prostatic fluid) in 65% of patients with chronic prostatitis. Seven of 11 patients with bacterial signals but none of 6 patients without bacterial signals was improved on antibiotic therapy. The same group (Shoskes and Shahed, 2000) subsequently confirmed this finding with a larger cohort of patients. These results are intriguing, and controlled studies evaluating the potential clinical significance of differentiating patients based on molecular biologic techniques are required.

An Approach to Diagnosis and Classification

A diagnostic algorithm that provides a practical approach to the workup of the majority of men presenting with CP/CPPS is shown in Figure 11–7. Table 11–2 shows the tests recommended by the NIH Third International Prostatitis Collaborative Network (Nickel, 2003).

Key Points: Lower Urinary Tract Evaluation

- Mandatory evaluation includes history-taking, physical examination, urinalysis, and urine culture.
- Recommended evaluation includes lower urinary tract localization test (culture), NIH-CPSI, flow rate, residual urine determination, and urine cytology.

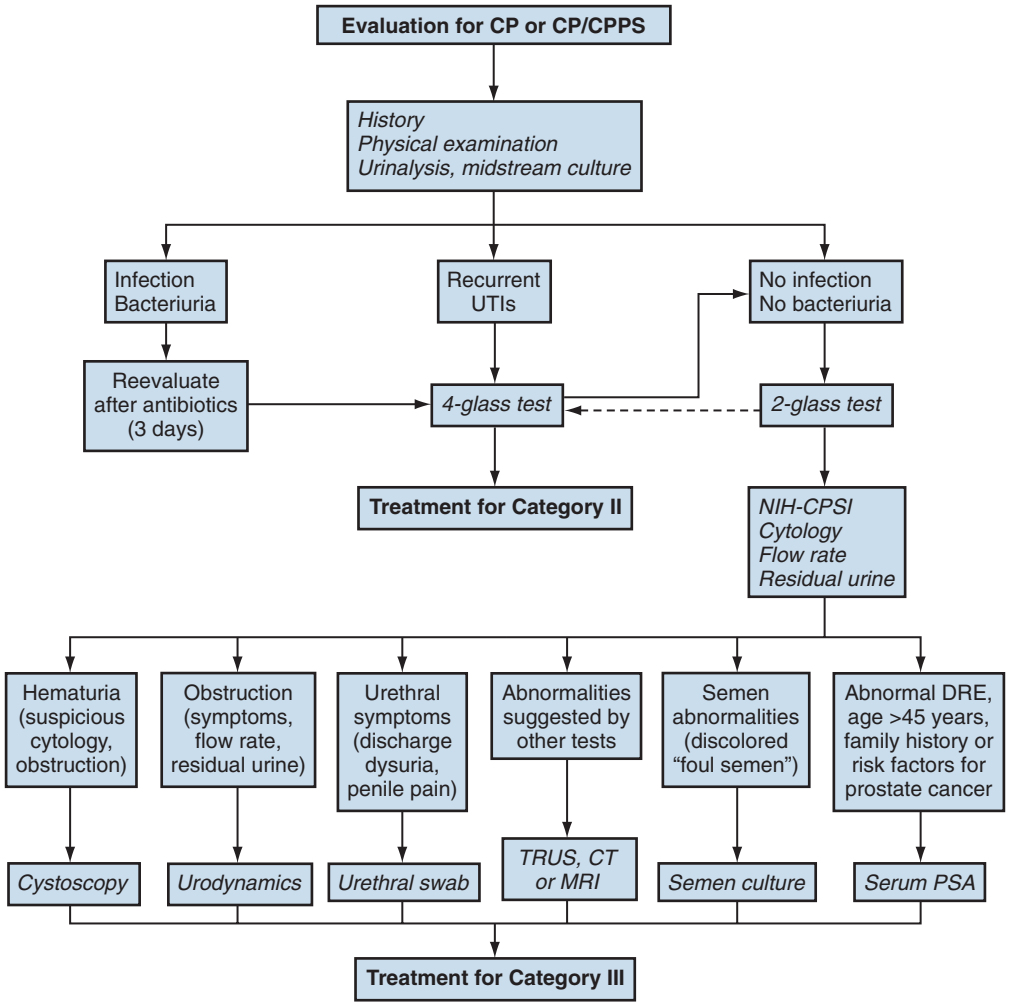


Figure 11–7. A suggested diagnostic algorithm for the evaluation of patients presenting with CP/CPPS. UTIs, urinary tract infections; TRUS, transrectal ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; DRE, digital rectal examination; PSA, prostate-specific antigen.

Table 11–2.

Suggested Evaluation of a Man with Chronic Pelvic Pain Syndrome*

Mandatory
History
Physical examination, including digital rectal examination
Urinalysis and urine culture
Recommended
Lower urinary tract localization test
Symptom inventory or index (NIH-CPSI)
Flow rate
Residual urine determination
Urine cytology
Optional
Semen analysis and culture
Urethral swab for culture
Pressure-flow studies
Video-urodynamics (including flow-electromyography)
Cystoscopy
Transrectal ultrasonography
Pelvic imaging (ultrasonography, CT, MRI)
Prostate-specific antigen

*See text for explanation, rationale, and description of each test.

Treatment

In this section the rationale for each of the various treatments advocated for the prostatitis syndromes is presented followed by a review of the clinical trial data that support (or not) the use of those specific therapeutic modalities in clinical practice. Recent rigorous prospective studies in chronic bacterial prostatitis and randomized placebo-controlled trials employing standardized definitions and validated outcomes in CP/CPPS have allowed us to develop a best-evidence-based treatment strategies in a therapeutic field that used to be based on poor clinical data, dogma, and anecdotal experience (McNaughton Collins et al, 2000b, 2001a; Nickel, 2002a, 2002b, 2004; Schaeffer, 2006; Nickel, 2008b).

Antimicrobial Agents

Rationale. It is generally accepted that acute and chronic bacterial prostatitis are etiologically secondary to bacterial infection of the prostate gland. Many urologists further believe that, although bacteria are cultured in only 5% to 10% of cases of prostatitis, bacteria may be the cause of prostatitis in a significant percentage of patients presenting with this syndrome. **Antimicrobial therapy is the most commonly prescribed treatment for the chronic prostatitis syndromes** (Moon, 1997; Nickel et al, 1998a; McNaughton Collins et al, 2000b, 2001a), independent of culture status.

Pharmacology and Pharmacokinetics. Most antimicrobial pharmacokinetic studies were performed in animal models (dogs and rats) (Madsen et al, 1978; Nickel, 1997b). Stamey (1980) and Stamey and associates (1970) found that acid antibiotic drugs can be detected in prostatic secretions only in very low concentrations, even when plasma concentrations of the drug are very high. Alkaline antibiotic drugs are found in concentrations greater than the simultaneous plasma levels. In dogs, this was explained by the presence of a pH gradient across the prostate epithelium. This phenomenon of ion trapping, and the fact that drug penetration was believed to be a passive transport mechanism based on diffusion and concentration, suggested that drug penetration is dependent on the lipid solubility, degree of ionization, degree of protein binding, and size and shape of the antimicrobial molecule. In dogs, the pH of plasma was found to be 7.4, whereas that of prostatic secretion is 6.4. Therefore, in this model, weak acids (low pKa) concentrate on the plasma side whereas antibiotics with a higher pKa (weak bases) concentrate in the prostatic secretion.

Because infection may alter the local prostatic environment, thus changing the pharmacokinetic parameters, animal models were developed that introduced infection into the process (Baumueller and Madsen, 1977; Madsen et al, 1994; Nickel et al, 1995). All these animal studies (with and without infection) showed that trimethoprim concentrates in prostatic secretion and prostatic interstitial fluid (exceeding plasma levels), whereas sulfamethoxazole and ampicillin do not. The fluoroquinolones, which are neither pure acids nor bases but have characteristics of both, being zwitterionic drugs (e.g., those that have two pKa values) (Gasser et al, 1986), should allow drug concentration in the prostate at various pH ranges. In the dog model, ciprofloxacin and norfloxacin did not concentrate in prostatic secretion as predicted, and this may be accounted for by their lipid solubility and protein-binding characteristics. Carbenicillin, which for years was the only antibiotic approved by the U.S. Food and Drug Administration for the treatment of bacterial prostatitis, could not be detected in prostatic secretion at all. Aminoglycosides did not concentrate in prostatic secretion and for unknown reasons may not follow the rules of nonionic diffusion of drugs across biologic membranes.

It is difficult to extrapolate the animal pharmacokinetic studies to humans (Sharer and Fair, 1982). Fair and Cordonnier (1978) found that the prostatic secretion of normal men is slightly alkaline (pH ~ 7.3) but also that the pH of prostatic secretion in men with prostatic infection is markedly increased (pH ~ 8.3). This has been confirmed in other studies (Anderson and Fair, 1976; Blacklock and Beavis, 1978; Pfau et al, 1978), and because the pH gradation is crucial to ion trapping we should not apply the results from animal studies directly to humans. Unfortunately, drug diffusion studies are difficult to perform in humans and most studies determine antibiotic concentrations in transurethrally resected BPH adenomas. These studies are further complicated because the high drug concentrations in urine can substantially alter the results. Employing a method to reduce urine contamination, Naber and Madsen (1999) demonstrated that for most fluoroquinolones the ratio of concentrations in prostatic fluid to concentrations in plasma is less than 1 (norfloxacin ratio 0.12, ciprofloxacin ratio 0.18 to 0.26, lomefloxacin ratio 0.48). Concentrations in seminal fluid usually exceed corresponding plasma concentrations of ciprofloxacin and ofloxacin, with ciprofloxacin demonstrating the highest ratio of seminal fluid to plasma (Naber, 1999). The numerous studies evaluating fluoroquinolone concentrations in prostatic tissue demonstrated that the fluoroquinolone concentration in the adenoma tissue is usually higher than that in plasma.

Clinical Trial Data. Unless the patient has a significant anatomic abnormality of the lower urinary tract or develops a prostate abscess, antimicrobial therapy is universally successful in eradicating the bacteria and curing the patient presenting with acute bacterial prostatitis (Nickel and Moon, 2005). **In the acutely inflamed prostate gland the pharmacokinetic considerations described in the previous section probably do not play a significant role in antibiotic penetration,** and it is believed that most antibiotics achieve reasonable intraprostatic concentrations in the acute phase of the disease. Although prospective clinical trial data are unavailable, **most experts suggest therapy initially with parenteral antibiotics (depending on the seriousness of the infection) followed by oral**

antibiotics with wide-spectrum antimicrobial activity (Becopoulos et al, 1990). The most common drugs suggested for initial therapy (Neal, 1999; Ludwig, 2008; Benway and Moon, 2008) are a combination of penicillin (i.e., ampicillin) and an aminoglycoside (i.e., gentamicin), second- or third-generation cephalosporins, or one of the fluoroquinolones. **Once the acute infection has settled down, therapy should be continued with one of the oral antimicrobial agents appropriate for the treatment of chronic bacterial prostatitis (e.g., trimethoprim or fluoroquinolones). The duration of optimal therapy is unknown; between 2 and 4 weeks has been suggested** (Nickel, 1998b; Bjerklund-Johansen et al, 1998; Wagenlehner et al, 2007; Ludwig, 2008).

In the 1970s to 1990s the most commonly used antimicrobial agent in the treatment of chronic prostatitis was trimethoprim-sulfamethoxazole (co-trimoxazole) (Moon, 1997; Nickel et al, 1998a) **and, to a lesser extent, trimethoprim alone.** In patients with chronic bacterial prostatitis, eradication of pathogens (the only objective measurement in most chronic prostatitis studies) with trimethoprim-sulfamethoxazole or trimethoprim alone ranged from a low of 0% (Smith et al, 1979) to a high of 67% (Paulson and White, 1978), with most studies demonstrating an efficacy rate of between 30% and 50% (Meares, 1973, 1975, 1978; Drach, 1974b; McGuire and Lytton, 1976). It appears that longer-duration therapy (90 days) provides the best clinical results. **Trimethoprim-sulfamethoxazole is less effective both in bacterial eradication and cost-effectiveness when compared with the newer fluoroquinolones** (Kurzer and Kaplan, 2002).

Except for the well-studied fluoroquinolones, most antibiotics (including minocycline, cephalexin, and carbenicillin) do not demonstrate significant clinical efficacy in clinical studies in which patients were observed for sufficient time (Paulson and White, 1978; Oliveri et al, 1979; Mobley, 1981). One notable exception has been the macrolides, erythromycin (Mobley, 1974), azithromycin (Skerk et al, 2003), and clarithromycin (Skerk et al, 2002b), particularly when *C. trachomatis* is implicated.

The fluoroquinolones have demonstrated improved therapeutic results, especially in prostatitis caused by *E. coli* and other members of the Enterobacteriaceae but not necessarily in prostatitis due to *P. aeruginosa* or enterococci. Naber (1999) analyzed the many studies available in the literature evaluating fluoroquinolones in the treatment of chronic prostatitis and found eight comparable studies in which the diagnosis was obtained by localization studies and in which the patients were observed for a sufficient time after completion of therapy (Weidner et al, 1987; Pust et al, 1989; Schaeffer and Darras, 1990; Heidler, 1990; Weidner et al, 1991a; Pfau, 1991; Ramirez et al, 1994; Koff, 1996); in these studies the researchers evaluated norfloxacin, ciprofloxacin, ofloxacin, and lomefloxacin. In 2005 Naber (reported at the Sixth International Consultation on New Developments in Prostate Cancer and Prostate Disease, Paris, June, 2005) added three more recent studies that met these strict criteria (Naber et al, 2000, 2002; Bundrick et al, 2003). These studies are outlined in Table 11–3. A subsequent study has suggested that levofloxacin may also be effective in treating chronic bacterial prostatitis (Naber et al, 2008). For chronic prostatitis caused by *E. coli,* treatment duration of 1 month for the fluoroquinolones seems to be superior to the usual 3-month treatment with trimethoprim-sulfamethoxazole. It has been suggested that antibiotics should be continued only for 4 to 6 weeks if pretreatment cultures are positive and/or the patient has reported positive effects from treatment (Wagenlehner et al, 2007). Some clinicians have observed that as many as 20% of patients who fail an initial treatment period could be rescued with a second cycle of treatment with another antibiotic (Magri et al, 2007). In microbiologically diagnosed chronic bacterial prostatitis, eradication of bacteria is associated with both short-term and long-term clinical success (Nickel and Xiang, 2008). This appears to be true in men with recent onset of prostatitis associated with bacterial localization

Table 11–3.

Clinical Trials of Fluoroquinolone Treatment of Chronic Bacterial Prostatitis*

ANTIBIOTIC	DOSE	DURATION OF THERAPY (days)	NO. OF PATIENTS	BACTERIOLOGIC CURE (%)	FOLLOW-UP (mo)	REFERENCE
Norfloxacin	400 mg bid	28	14	64	6	Schaeffer and Darras, 1990
Norfloxacin	400 mg bid	174	42	60	8	Petrikkos et al, 1991
Ciprofloxacin	500 mg bid	14	15	60	12	Weidner et al, 1987
Ciprofloxacin	500 mg bid	28	16	63	21-36	Weidner et al, 1991
Ciprofloxacin	500 mg bid	60-150	7	86	12	Pfau, 1991
Ciprofloxacin	250 mg bid	21-42	34	62	6	Heidler, 1990
Ciprofloxacin	500 mg bid	28	34	76	6	Naber et al, 2001
Ciprofloxacin/Lomefloxacin	500 mg bid	28	78	72	6	Naber et al, 2002
	400 mg qd	28	75	63	6	
Ofloxacin	200 mg bid	14	21	67	12	Pust et al, 1989
Ofloxacin/Lomefloxacin	300 mg bid	42	30	57	6	Ramirez et al, 1994
	400 mg qd	42				
Ofloxacin/Lomefloxacin	200 mg bid	42	33	60	6	Koff, 1996
	400 mg qd	42		67	6	
Ciprofloxacin/Levofloxacin	500 mg bid	28	125	56 (clinical†)	6	Bundrick et al, 2003
	500 mg qd	28	136	53 (clinical†)	6	
Levofloxacin	500 mg qd	28	117	91	6	Naber et al, 2008

*Naber (1999) reviewed the world literature in respect to clinical trials of fluoroquinolone treatment of chronic bacterial prostatitis and noted only eight studies in which the diagnosis of prostatitis was obtained by localization studies and in which the patients were observed for at least 6 months. Naber has subsequently expanded his list of suitable available trials in 2005 (reported at the 6th International Consultation on New Developments in Prostate Cancer and Prostate Disease, Paris, June, 2005).

†Clinical success at 6 months: bacterial eradication post therapy was 75% for levofloxacin and 77% for ciprofloxacin.

with the traditional uropathogens (gram-negative uropathogens and enterococci species) as well as nontraditional bacteria (gram-positive such as coagulase-negative staphylococcal and streptococcal species) (Magri et al, 2007; Nickel and Xiang, 2008). A number of investigators (Baert and Leonard, 1988; Jimenez-Cruz et al, 1988; Yamamoto et al, 1996; Guercini et al, 2005b) have advocated direct injection of antibiotics into the prostate gland, but this method has never been rigorously evaluated or become popular among urologists.

Many studies evaluating physicians' practice patterns in prostatitis syndromes (de la Rosette et al, 1992a; Moon, 1997; Nickel et al, 1998a; McNaughton Collins et al, 1998, 2000a) have confirmed that most patients diagnosed with chronic prostatitis, irrespective of culture results, are treated with antimicrobial therapy. Older studies have generally indicated that approximately 40% of patients with nonbacterial chronic prostatitis have some symptomatic improvement with antimicrobial therapy (Berger et al, 1989; Weidner, 1992; de la Rosette et al, 1993a; Ohkawa et al, 1993b; Bergman, 1994; Bjerklund-Johansen et al, 1998; Tanner et al, 1999; Nickel et al, 2001a). Antibiotic therapy may benefit CP/CPPS patients by three different mechanisms: a strong placebo effect, the eradication or suppression of noncultured microorganisms (Nickel et al, 2001a), or the independent anti-inflammatory effect of some antibiotics (Yoshimura et al, 1996; Galley et al, 1997). It has been suggested by a European consensus group evaluating the role of antibiotics in the treatment of chronic prostatitis (Bjerklund-Johansen et al, 1998) that antibiotics should be considered empirical treatment for category IIIA CP/CPPS but the benefits should be appraised after a minimum of 2 to 4 weeks of therapy. The antibiotics could be continued for 4 to 6 weeks if the patient has reported positive effects from treatment (Wagenlehner et al, 2007). These recommendations remain controversial, particularly because new data appear to provide conflicting interpretations. Two multicenter randomized placebo controlled studies have assessed the efficacy of 6 weeks of levofloxacin (Nickel et al, 2003b) and ciprofloxacin (Alexander et al, 2004) in men with CP/CPPS. In these trials the participants had chronic symptoms for a long duration (many years) and had been heavily treated (including treatment with antibiotics). In the study by Nickel and associates (2003b), 80 patients were randomized to levofloxacin or placebo whereas in the NIH-sponsored study reported by Alexander and colleagues (2004) 196 men with CP/CPPS were randomized in a 2×2 factorial design to ciprofloxacin, tamsulosin, the combination of ciprofloxacin and tamsulosin, or placebo. In both of these prospective-designed controlled multicenter trials, no significant difference was reported between the fluoroquinolone and placebo in terms of symptom amelioration. **Antibiotics should not be prescribed for previously treated men with CP/CPPS of long duration.** However, two recent prospective trials comparing the effect of 4 to 6 weeks of antibiotics (Magri et al, 2007; Nickel and Xiang, 2008) in men with localization of both traditional uropathogens and organisms not usually believed to be uropathogenic (and therefore classified as category III CP/CPPS) showed similar eradication and clinical success rates (75% to 80%). Furthermore, in the study by Nickel and Xiang (2008), the eradication of those organisms, whether or not they were considered to be uropathogens, correlated with both short- and long-term clinical success. Because the majority of patients in Nickel and Xiang's study (2008) had a short history of prostatitis and were antibiotic naive for that episode, it was concluded **that antibiotic treatment may be considered for antibiotic-naive patients with recent diagnosis of prostatitis, regardless of culture status.**

α-Adrenergic Blocker Therapy

Rationale. Patients with CP/CPPS have significant lower urinary tract symptoms, which appear to be related to poor relaxation of the bladder neck during voiding (Barbalias et al, 1983; Murnaghan and Millard, 1984; Blacklock, 1986; Hellstrom et al, 1987; Barbalias, 1990; Kaplan et al, 1997). The subsequent turbulent "dysfunctional" voiding may predispose the patient to reflux of urine into the prostatic ducts, causing intraprostatic inflammation and subsequently pain (Kirby et al, 1982). **The bladder neck and prostate are rich in a receptors, and it is hypothesized that α-adrenergic blockade may improve outflow obstruction, improving urinary flow and perhaps diminishing intraprostatic ductal reflux.**

Clinical Trial Data. A number of older clinical trials suggested that the α-adrenergic blockers diphenoxybenzamine (Dunzendorfer et al, 1981), phenoxybenzamine (Osborn et al, 1981), alfuzosin (de la Rosette et al, 1992c; Barbalias et al, 1998), terazosin (Neal and Moon, 1994; Barbalias et al, 1998; Lacquaniti et al, 1999; Gül et al, 2001), doxazosin (Evliyaoglu and Burgut, 2002) and tamsulosin (Lacquaniti et al, 1999) resulted in significant symptomatic improvement of prostatitis-related symptoms; however, these trials were small, most were uncontrolled, and outcome measures were not validated. The study by Barbalias and associates (1998) further seemed to indicate that the combination of antibiotics and α-adrenergic blockers improved the clinical result in patients with chronic bacterial prostatitis.

Four randomized placebo controlled trials with clearly defined CP/CPPS patients (NIH classification) and employing the NIH-CPSI as the outcome parameter appear to have confirmed the efficacy of α-adrenergic blockers but only in men who have recent onset disease not those heavily pretreated and who are on therapy for longer than 6 weeks. Cheah and colleagues (2003) randomized 86 patients with chronic prostatitis to either terazosin or placebo for 14 weeks. Patients on terazosin had a 50% reduction in mean symptom score compared with 37% in the placebo-treated group. Terazosin resulted in modest but significant improvement in all domains of the NIH-CPSI. Mehik and colleagues (2003) followed 19 patients randomized to 6 months of alfuzosin treatment and 20 patients on 6 months of placebo therapy and both groups were followed for a further 6 months after discontinuing the active or placebo medication. Patients in the alfuzosin group had a significant amelioration of symptoms compared with the placebo therapy group that was evident at 4 months and became even more clinically significant by 6 months. At 6 months 65% of alfuzosin patients were rated as responders compared with 24% of placebo group. The beneficial effect appeared to wear off over the next 6 months after the alfuzosin was discontinued. Nickel and colleagues (2004b) randomized 57 men with CP/CPPS to tamsulosin, 0.4 mg, or placebo after a 2-week placebo run-in and observed the two groups for 6 weeks. Patients treated with tamsulosin had a statistically significant (but only modest clinically significant) treatment effect compared with patients taking a placebo. A significant treatment effect was not observed in patients who had mild symptoms, but patients with severe symptoms (75th percentile) had a statistically and clinically significant response compared with placebo. It appears that the response to α-adrenergic blockers is durable, for at least up to 24 to 38 weeks (Mehik et al, 2003; Cheah et al, 2004). Another study (Tugcu et al, 2007) included 90 treatment-naive patients with CP/CPPS randomized to receive doxazosin, 4 mg/day, alone or a triple therapy (doxazosin, 4 mg/day plus an anti-inflammatory agent—ibuprofen,

400 mg/day, and a myorelaxant-thiocolchicoside, 12 mg/day) or placebo. Over 6 months, the total NIH-CPSI score significantly improved in the doxazosin group (from 23.1 to 10.5 points) and triple-therapy groups (from 21.9 to 9.2) while it remained stable in the placebo group (from 22.9 to 21.9).

In contrast, the results from the NIH CPCRN randomized controlled trial (Alexander et al, 2004) **comparing 6 weeks of ciprofloxacin, tamsulosin, and the combination of ciprofloxacin and tamsulosin to placebo in very chronic and heavily pretreated patients failed to show any improvement in patients treated with tamsulosin (± ciprofloxacin) compared with patients treated with placebo.** A number of meta-analyses and comprehensive reviews of these data recommended that α-adrenergic blockers provided significant symptom amelioration only after more than 6 weeks of therapy in less heavily treated patients with recent onset of moderate to severe symptoms (Mishra et al, 2007; Yang et al, 2006; Nickel, 2008a). **To test this hypothesis, an NIH multicenter, randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy of 12 weeks of alfuzosin or placebo to reduce symptoms in 272 randomized men with CP/CPPS diagnosed within 2 years previously and who had not been previously treated with an α-adrenergic blocker** (Nickel et al, 2008a). The rate of the primary outcome (reduction of at least 4 points in NIH-CPSI total score from baseline) was 49% in both treatment groups. The response rates at 12 weeks measured with a global response assessment were also similar, 34% and 35%, for the placebo and alfuzosin groups, respectively ($P = .90$). These important findings did not support the use of α-adrenergic blockers in recently diagnosed α-adrenergic blocker–naive men with CP/CPPS.

Anti-Inflammatory Agents and Immune Modulators

Rationale. Prostatic inflammation is associated with category IIIA CP/CPPS, and elevated cytokine levels are noted in the semen (Alexander et al, 1998; Ruggieri et al, 2000) and EPS (Nadler et al, 2000; Hochreiter et al, 2000b) of patients with inflammatory CPPS. **Nonsteroidal anti-inflammatory drugs, corticosteroids, and immunosuppressive drugs theoretically should improve the inflammatory parameters within the prostate and possibly result in a reduction of symptoms** (Pontari, 2002).

Clinical Trial Data. Canale and associates (1993a) found that nimesulide (a nonsteroidal anti-inflammatory drug) quickly reduced inflammatory-type symptoms such as dysuria, strangury, and painful ejaculation. A second study by Canale's group (1993b) found that, by the rectal route, ketoprofen was inferior to nimesulide (both drugs were used as suppositories). Prednisolone has been suggested as a potent anti-inflammatory for chronic prostatitis (Bates and Talbot, 2000) and a randomized study presented by Dimitrakov and associates (2004) indicates that high-dose methylprednisolone (followed by rapid tapering of dose) may have more efficacy than placebo, even after 12 months, but the side effect profile makes this type of therapy less attractive. A small randomized trial evaluating oral corticosteroids did not show superiority of the active therapy over placebo (Bates et al, 2007).

The new class of cyclooxygenase-2 inhibitors has proved successful for long-term treatment of other chronic inflammatory conditions such as rheumatoid arthritis and chronic osteoarthritis, and many urologists employed these medications for prostatitis patients with some anecdotal successes reported. The results of a North American randomized control trial comparing the cyclooxygenase-2 inhibitor rofecoxib to placebo indicated that many men with CPPS benefited (in terms of pain and quality of life) from rofecoxib therapy compared with placebo. In this study in which 161 patients were randomized to rofecoxib 25 mg, rofecoxib 50 mg, or placebo, only patients on the high dose showed any clinical improvement compared with the placebo. Very few patients, however, had complete resolution of their symptoms (Nickel et al, 2003c). Another study from China (Zeng et al, 2004) assessing the effectiveness of two doses of the cyclooxygenase-2 inhibitor celecoxib also demonstrated a dose-dependent response (200 mg twice a day for 6 weeks was more effective than 200 mg once a day). At this time, high-dose, long-duration therapy with cyclooxygenase-2 inhibitors is not recommended.

Because the clinical and pathologic characteristics are similar to those of interstitial cystitis, Wedren (1987) compared the efficacy of pentosan polysulfate, a glycosaminoglycan drug that has been used in the treatment of interstitial cystitis, with placebo. In this small study the treated group was noted to have a statistically significant improvement in symptoms but the major symptom that improved was nonspecific myalgias and arthralgias. An uncontrolled pilot study evaluating oral pentosan polysulfate in 32 men with CPPS demonstrated amelioration of symptoms and improvement in the quality of life in over 40% after treatment for 6 months (Nickel et al, 2000). The results of a multicenter, randomized, placebo-controlled trial that randomized 100 men to pentosan polysulfate, 900 mg/day (three times the usual dose), or placebo indicated this medication provided modest benefit for some men with CPPS (Nickel et al, 2005b).

Thalidomide, a cytokine modulating drug, was assessed in 30 men with chronic abacterial prostatitis and abnormal semen cytokine levels (IL-2, IL-6, IL-8, IL-10, and TNF-α) in a randomized placebo-controlled trial (Guercini et al, 2005). Despite a significant reduction in cytokine levels in semen, no difference in symptom relief was noted. A similar lack of efficacy was noted in a small placebo-controlled trial evaluating the leukotriene antagonist zafirlukast (Goldmeier et al, 2005).

The potential of various anti-inflammatory agents, immune modulators, and cytokine inhibitors makes these classes of drugs potentially useful as adjunctive therapy for the chronic prostatitis syndromes, but clinical trials suggest that they are not a useful monotherapy.

Muscle Relaxants

Rationale. Many investigators believe that CPPS is the ultimate reflection of a smooth and skeletal neuromuscular dysregulatory phenomenon in the perineum or pelvic floor (Osborn et al, 1981; Egan and Krieger, 1997; Anderson, 1999; Zermann and Schmidt, 1999). **The use of α-blockers to relax smooth muscle** (see earlier discussion of α-adrenergic blockers) **and skeletal muscle relaxants combined with adjuvant medical and physical therapies has been advocated and promoted** (Anderson, 1999; Zerman and Schmidt, 1999).

Clinical Trial Data. In one of the few studies to compare muscle relaxants to placebo, Osborn and associates (1981) conducted a prospective double-blind study comparing phenoxybenzamine, baclofen (a striated muscle relaxant), and placebo in 27 patients with prostatodynia (category IIIB). Patients were treated with each agent for 1 month in a crossover trial. Symptomatic improvement was seen in 37% of the patients treated with baclofen compared with 8% treated with placebo. Simmons and Thin (1985) compared diazepam with an antibiotic in patients with chronic abacterial prostatitis and found no difference in symptom improvement

between the diazepam group (8 of 11 men improved) and the antibiotic group (7 of 12 men improved). Unfortunately **these studies were hindered by a lack of controlled and defined entry criteria and no quantified measurement of patients' responses and therefore the role of muscle relaxants has yet to be determined.**

Hormone Therapy

Rationale. Prostate growth and function are influenced by the local hormonal milieu, especially by androgens. **Theoretically, antiandrogens (including 5α-reductase inhibitors) could result in regression of prostatic glandular tissue (inflammation is believed to begin at the level of the ductal epithelium), improved voiding parameters (especially in older patients with BPH and prostatitis), and reduced intraprostatic ductal reflux** (Nickel, 1999c).

Clinical Trial Data. Holm and Meyhoff (1996) were the first to note that the 5α-reductase inhibitor finasteride had potential in alleviating symptoms by observing the effect of finasteride therapy in 4 patients with chronic prostatitis or prostatodynia. Leskinen and colleagues (1999) randomized 41 patients with chronic idiopathic prostatitis (i.e., nonbacterial prostatitis and prostatodynia) to treatment with placebo (25%, or 10 patients) or finasteride (75%, or 31 patients) for 1 year. Compared with placebo, finasteride reduced prostatitis and BPH symptom scores; however, there was no statistically significant difference in pain between the two groups. The baseline characteristics of the two groups were not comparable, and the enrolled patients consisted of an unknown mixed population with inflammatory and non-inflammatory prostatitis syndromes. A randomized open label comparative trial in CP/CPPS men showed significantly more improvement in men treated for a year with finasteride compared with saw palmetto, an herbal therapy (Kaplan et al, 2004). A randomized controlled trial compared the reduction of NIH-CPSI in 64 men with CP/CPPS randomized to finasteride or placebo (Nickel et al, 2004c). Six months of finasteride resulted in a numerical but not statistically significant reduction in symptoms compared with the symptom reduction noted in the placebo group. **Finasteride cannot be recommended as a monotherapy except perhaps in men with associated BPH.**

Testosterone and dihydrotestosterone are not the only hormones with a possible effect on prostate inflammation; estrogens may also play a role. A number of small, poorly controlled studies (Cavallini, 2001; Saita et al, 2001) suggested that mepartricin (a drug that lowers estrogen levels in the prostate) may be useful in the treatment of CP/CPPS. A small prospectively designed trial randomized 26 men with CP/CPPS to 60 days therapy with mepartricin or placebo (De Rose et al, 2004). The study showed a statistical and perhaps clinically significant benefit (60% vs. 20% improvement, respectively) that should stimulate further research in the role of hormonal manipulation (in this case estrogens) in the treatment of CP/CPPS.

Phytotherapeutic Agents

Rationale. A number of plant extracts have been shown in many in-vitro experiments to have 5α-reductase activity, α-adrenergic blockade activity, effects on bladder contractility, and anti-inflammatory properties (Lowe and Fagelman, 1999; Shoskes, 2002).

Clinical Trial Data. Three specific phytotherapeutic agents have been tested in clinical trials, Cernilton, a pollen extract (Buck et al, 1989; Rugendorff et al, 1993), Quercetin, a natural bioflavonoid (Shoskes et al, 1999) and *Serenoa repens* (saw palmetto berry) extract (Kaplan et al, 2004; Reissigl et al, 2004). Rugendorff and coworkers (1993) noted that over half of 72 patients with chronic prostatitis without other lower urinary tract abnormalities had favorable improvements in pain and irritative voiding symptoms when treated with Cernilton, but no control group was included in this study. A randomized study of pollen extract (Cernilton) in 122 men with category IIIA showed that men on the active treatment had statistically significant improvements in the pain and quality-of-life components of the CPSI (Wagenlehner et al, 2009). A controlled, randomized study of a similar preparation, Prostat/Poltit (grass pollen extract, including rye pollen), in 60 patients showed greater improvement in patients on active therapy compared with placebo but no validated outcome index incorporated into the study design (Elist, 2006). Shoskes and associates (1999) randomized 15 patients to the bioflavonoid Quercetin and 13 patients to placebo for 1 month. Sixty-seven percent of the patients in the treatment group were considered responders compared with only 20% of the patients in the placebo arm. Kaplan and associates (2004) did not note any appreciable long-term improvement in any CP/CPPS parameters when compared with 12 months of finasteride in a randomized open-label comparative study. However, Reissigl and colleagues (2004) reported that there was a moderate/marked improvement in over 60% of 72 CP/CPPS patients after 12 months of therapy with *Serenoa repens* extract compared with less than 25% in the 70 men in the placebo-treated group. However, further follow-up did not support the durability of this therapy (Reissigl et al, 2005). **Phytotherapy for CP/CPPS may look promising but further multicenter randomized controlled trials with well-characterized, standardized, and stable herbal components should be considered to assess their role in therapy.**

Neuromodulator Therapy

Rationale. One proposed mechanism is that CP/CPPS, particularly in chronic cases of long standing, represents a neurogenic pain syndrome and that the subsequent pain is actually a neuropathic pain (Pontari and Ruggieri, 2004). Patients with CP/CPPS have a history of neurologic disease that is almost five times more likely among cases than control subjects (Pontari et al, 2005), and men with CP/CPPS have been found to have abnormalities of both the afferent and efferent autonomic nervous systems (Yang et al, 2003; Yilmaz et al, 2007). This type of neuropathic pain related to central nervous system sensitization responds to gabapentinoids in other chronic pain conditions (Rosenstock et al, 2004; Crofford et al, 2005).

Clinical Trial Data. A recent NIH CPCRN randomized placebo-controlled trial evaluated effect of the gabapentinoid pregabalin on symptoms of men with long-standing, treatment-refractory CP/CPPS (Pontari et al, 2010). Among the 103 men assigned to pregabalin, 47% reported at least a 6-point decrease in total NIH-CPSI score at 6 weeks (primary end point) compared with 35.8% of 106 men assigned to placebo (P = .072). The NIH-CPSI total score decreased by a mean of 6.6 and 4.2 points (of 43) in the pregabalin and placebo groups respectively (P = .008), whereas significantly more men in the pregabalin arm reported they were markedly or moderately improved compared with placebo (31% and 19%, respectively; P = .023). Although 6 weeks of pregabalin therapy was not superior to placebo for treating symptoms of CP/CPPS based on the primary end point, the impressive differences in secondary end points suggest that pregabalin may prove effective in some men with long-standing CP/CPPS.

Allopurinol

Rationale. Persson and Ronquist (1996) theorized that the intraprostatic ductal reflux of urine increases the concentration of metabolites containing purine and pyrimidine bases in the prostatic ducts, causing inflammation.

Clinical Trial Data. Persson and associates (1996) compared allopurinol therapy with placebo in a double-blind controlled study in 54 men. The allopurinol groups had lower levels of serum urate, urine urate, and EPS urate and xanthine. With variations in accepted statistical methodology, the investigators were able to show a difference in the mean patient-reported discomfort score between the study and the control groups at certain times in this trial with 330 days of follow-up. However, a re-examination of the data employing more standardized statistical analyses did not convince other groups that changes in the urine and prostatic secretion of purine and pyrimidine bases resulted in significant amelioration of symptoms in this particular trial (Nickel et al, 1996a). A follow-up randomized clinical trial further showed no advantage of allopurinol compared with placebo (Ziaee et al, 2006).

Prostatic Massage

Prostatic massage has been the principal therapy for prostatitis since the turn of the 20th century (O'Conor, 1936; Campbell, 1957). With the introduction of the scientific approach advocated by Meares and Stamey in 1968, prostatic massage became important only as a diagnostic tool, but as a therapy it was abandoned by urologists. Currently it is regaining some popularity, primarily because of the failure of standard medical therapy in patients with refractory symptoms of chronic prostatitis. Its benefits are believed to arise from draining theoretically occluded prostatic ducts and improving circulation and antibiotic penetration (Hennenfent and Feliciano, 1998). Independent but uncontrolled studies (Nickel et al, 1999a; Shoskes and Zeitlin, 1999) describe clinical benefits in one third to two thirds of patients treated with repetitive prostatic massage (two to three times per week) for 4 to 6 weeks along with antibiotic therapy. However, another trial indicated that prostatic massage does not significantly improve the response of men with CP/CPPS treated with antibiotics (Ateya et al, 2006). It appears that some patients may improve with prostatic massage, but a panel of North American "prostatitis experts" (Nickel et al, 1999) could not come to a consensus on the potential overall benefit or even the mechanism of achieving that benefit if it does occur. **A subsequent systematic review of the literature concluded that evidence for a role of repetitive prostatic massage as an adjunct in the management of chronic prostatitis is at most "soft" but could be considered as part of multimodal therapy in selected patients** (Mishra et al, 2008). Frequent ejaculation may achieve the same function as prostatic massage (Yavascaoglu et al, 1999).

Perineal or Pelvic Floor Massage and Myofascial Trigger Point Release

Most clinicians recognize that men with prostatitis syndromes, especially the noninflammatory category or prostatodynia, have specific anatomic areas that cause discomfort. Anderson (1999) believes that prolonged or chronic tension, distention, or distortion in the muscle bands (e.g., in the perineum) leads to a painful trigger point that is responsible for the pain. Predisposing factors leading to the formation of myofascial trigger points in the perineum or pelvis may include mechanical abnormalities in the hip and lower extremities, chronic urinary holding patterns (dysfunctional toilet training), sexual abuse, repetitive minor trauma, constipation, trauma, unusual sexual activity, recurrent infections or surgery, and perhaps stress and anxiety. Treatment of these trigger points includes heat therapy, physiotherapy massage, ischemic compression, stretching, anesthetic injections, acupuncture, electroneural modulation, and mind-body interactions such as progressive relaxation exercises, yoga, and hypnosis (Potts, 2003). Anderson and associates (2005) report that employing these techniques with a team consisting of a urologist, physiotherapist, and psychologist results in more than half of patients having or demonstrating a clinically detectable improvement. A case study analysis indicates that this may be an effective therapeutic approach in some patients (Anderson et al, 2005) and may result in improvement not just in pain but also in sexual function (Anderson et al, 2006). A recently reported NIH pilot study of men and women with chronic pelvic pain treated with either relaxation massage or specific pelvic massage therapy demonstrated improvement in women but could not corroborate these findings in men (Peters K, presented at AUA annual meeting, May 19, 2008).

Pudendal Nerve Entrapment Therapy

It has been hypothesized that the symptoms of CPPS could be caused by entrapment of the pudendal nerve, perhaps between the sacrotuberous and sacrospinous ligaments, in the canal of Alcock or by the falciform process of the sacrotuberous ligament (Robert et al, 1998). Pudendal nerve blocks (Thoumas et al, 1999; McDonald and Spigos, 2000; Peng and Tumber, 2008) and neurolysis surgery (Robert et al, 1993; Mauillon et al, 1999) have been suggested for treatment. The role of the pudendal nerve in chronic perineal pain deserves more scientific scrutiny.

Biofeedback

It is possible that the voiding and pain symptoms associated with CP/CPPS may be secondary to some form of pseudodyssynergia during voiding or repetitive perineal muscle spasm; biofeedback has the potential to improve this process. Kaplan and associates (1997), Nadler (2002), Ye and colleagues (2003), and Cornel and coworkers (2005) have demonstrated in small uncontrolled studies that biofeedback does ameliorate specific prostatitis-like symptoms in some men. Controlled clinical trials will be necessary to evaluate this mode of therapy.

Acupuncture

Acupuncture is an accepted traditional Chinese therapy for chronic pain, including prostatitis (Ge et al, 1988; Katai, 1992; Ikeuchi and Iguchi, 1994). Chen and Nickel (2003) determined in a pilot study of 12 treatment-refractory men that acupuncture was safe and provided effective and durable symptom improvement. A subsequent study comparing 10 weeks of acupuncture versus sham acupuncture treatment indicated that the active acupuncture proved to be almost twice as likely as sham treatment to improve CP/CPPS symptoms (Lee et al, 2008).

Psychological Support

Data from the NIH Prostatitis Cohort (Tripp et al, 2005, 2006; Nickel et al, 2008b) support a biopsychosocial model that associates the chronic pain and poor quality of life of CP/CPPS with depression and suggests that physicians may be able to advise patients to avoid certain pain coping strategies that can be associated with greater depression. Nickel and colleagues (2008) have developed an evidence-based cognitive behavioral treatment

program for men with CP/CPPS. This program specifically targets empirically supported biopsychosocial variables (e.g., pain catastrophizing, depressive thinking, social support) and encourages patients to critically evaluate their patterns of thinking and to entertain novel thinking and behavioral responses to their troublesome symptoms, with an end objective to improve overall quality of life.

Studies also show that the maladaptive pain coping technique of employing "pain contingent resting" (using rest rather than more active behaviors to control pain) is reported by CP/CPPS patients in response to their pain (Tripp et al, 2006; Nickel et al, 2008b). It was suggested by Tripp and coworkers (2006) that such sedentary behaviors in the presence of pain may be associated with elevated disability in men with CP/CPPS. A double-blind randomized study showed that men participating in aerobic exercise were significantly better than those who were randomized to stretching and motion exercise, suggesting that increased physical activity is a valid option in men with CP/CPPS (Giubilei et al, 2007). The results of a study examining perceived helpfulness of medical and self-management strategies suggested that clinicians may find it useful to support patients' use of safe, inexpensive, self-management approaches, such as warm baths, increased water intake, exercise, and avoidance of prolonged sitting (Turner et al, 2006).

Minimally Invasive Therapies

Balloon Dilatation. Lapatin and coworkers (1990) employed balloon dilatation in an uncontrolled trial of seven patients with nonbacterial prostatitis and prostatodynia and showed improvement in voiding symptoms during a 1- to 5-month follow-up. Pain and discomfort were not assessed. This treatment effect has never been substantiated, and balloon dilatation has not been routinely employed in clinical practice. Suzuki and coworkers (1995) combined the potential beneficial effects of balloon dilatation with prostatic hyperthermia in five men with CP/CPPS and demonstrated significant improvement in symptoms in one patient and partial improvement in three. Nickel and associates (1998b) were not able to duplicate this beneficial effect in a small pilot trial evaluating the "hot balloon" (heating by radiofrequency energy rather than laser energy).

Transurethral Needle Ablation. Chiang and associates (1997) employed transurethral needle ablation (TUNA) of the prostate in 7 patients with chronic nonbacterial prostatitis, assessed the patients before and after therapy (6 months of follow-up) employing a modification of the Symptom Severity Index (Nickel and Sorensen, 1996b), and reported favorable results in 4. A follow-up study by Chiang and Chiang (2004) showed significant improvement in symptoms in the majority of 32 patients treated with TUNA. But Leskinen and colleagues (2002) investigated the effectiveness and durability of TUNA in 25 patients randomized to TUNA and 8 patients randomized to sham treatment and they reported that the efficacy of TUNA in CP/CPPS is comparable to sham treatment and so could not recommend TUNA as therapy for CP/CPPS.

Other Minimally Invasive Surgeries. Serel and colleagues (1997) reported significantly meaningful beneficial effects in 30 patients with chronic abacterial prostatitis and prostatodynia employing the neodymium:yttrium-aluminum-garnet laser. Ruedi and associates (2003) suggested that high-frequency electrostimulation may be harnessed to treat chronic prostatitis. A number of other minimally invasive treatments have been examined in small pilot studies. These include pelvic and sacral electromagnetic therapy (Leippold et al, 2005; Rowe et al, 2005), extracorporeal shockwave therapy (Zimmerman et al, 2008), and injection of botulinum toxin directly into the prostate (Chuang and Chancellor, 2006).

Sham control trials will be required before minimally invasive surgery can be recommended as a treatment for CP/CPPS.

Microwave Hyperthermia and Thermotherapy. It is believed that the heat applied to the prostate gland by the microwave process could shorten the natural resolution of the inflammatory process, perhaps by accelerating the process of fibrosis or scar formation in the area of chronic inflammation. In addition, heat therapy, particularly with the higher temperatures achieved with transurethral microwave thermotherapy, could alter the afferent nerve fibers that convey the objective symptom of pain from the inflamed prostate gland (intraprostatic sympathectomy) (Perachino et al, 1993). It may even be possible that the microwave energy kills nonculturable or cryptic bacteria within the prostate gland (Sahin et al, 1998).

Although many uncontrolled trials employing heat therapy have shown benefit (Nickel, 1999d; Zeitlin, 2002), only three published studies have used sham controls. Vassily and associates (1999) noted symptom improvement in 75% of men in a transrectal microwave hyperthermia-treated group compared with 52% of men in the sham-treated group. Shaw and colleagues (1993) documented treatment success (defined as a greater than 50% improvement in symptoms) in 55% of the men in a transrectal microwave hyperthermia group (15 patients) compared with 10% of patients treated with sham therapy (13 patients) at 3 months. Nickel and Sorensen (1996b) examined the safety and efficacy of transurethral microwave thermotherapy in 20 men randomized to therapy or sham. At 3 months' follow-up, the transurethral microwave thermotherapy–treated patients had significantly improved symptom scores compared with sham-treated patients (7 of 10 men treated with transurethral microwave thermotherapy had a favorable result compared with 1 of 10 men treated with a sham therapy). A recently reported study in men with CP/CPPS treated with cooled transurethral microwave thermotherapy using the NIH-CPSI as an outcome (Kastner et al, 2004) again suggested that thermotherapy remains a promising treatment for intractable chronic prostatitis, particularly when it is associated with concomitant BPH. Although this prospective study showed a significant reduction in NIH-CPSI score compared with baseline in 35 men followed for 12 months, it was not a randomized sham controlled trial. **Heat therapy appears to be a promising therapeutic approach but, until larger-scale studies are performed, should be restricted to patients with refractory or end-stage symptoms.**

Surgery

In acute bacterial prostatitis (category I), urinary obstruction is a very common symptom. Traditionally, it has been suggested that the insertion of a suprapubic cystotomy tube is the optimal therapy because an indwelling Foley catheter may further obstruct urethral ducts, resulting in the potential to develop prostate abscesses (Dajani and O'Flynn, 1968; Pai and Baht, 1972; Weinberger et al, 1988). **In most patients, however, an in-and-out catheterization to relieve the initial obstruction or short-term (12 hours) indwelling catheterization with a small-caliber Foley catheter is appropriate. A developing prostate abscess, best detected with transrectal ultrasonography or computed tomography** (Rovik and Doehlin, 1989), **in patients who fail to respond quickly to antibiotics is optimally drained by the transurethral incision route** (Pai and Baht, 1972). **However, transperineal incision**

and drainage (Granados et al, 1992) **must be considered when the abscess has penetrated beyond the prostatic capsule or penetrated through the levator ani muscle. More recently it has been suggested that percutaneous drainage of the abscess is the most effective and less morbid procedure** (Varkarakis et al, 2004).

Surgery does not have an important role in the treatment of most chronic prostatitis syndromes unless a specific indication is discovered during the evaluation of the patient (Kirby, 1999). These indications are usually noted during specific and ancillary investigations such as cystoscopy, transrectal ultrasonography, urodynamics, or computed tomography/magnetic resonance imaging. Certainly, patients with urethral strictures benefit from surgical correction. Kaplan and associates (1994) have suggested that men with chronic nonbacterial prostatitis-like symptoms and urodynamic evidence of vesical neck obstruction benefit from endoscopic incision of the bladder neck.

Seminal vesicle abscesses can be managed with antibiotic therapy, transrectal aspiration, and, if necessary, an operation to remove the seminal vesicles. Traditionally seminal vesiculectomy was performed as a difficult open procedure, but recently laparoscopic excision of the seminal vesicles was reported to be the least morbid procedure (Nadler and Rubenstein, 2001).

Radical transurethral resection of the prostate (Barnes et al, 1982; Sant et al, 1984) has been advocated in patients who have either relapsing or refractory chronic bacterial prostatitis (category II) secondary to bacterial persistence within the prostate gland. Although prostatic calculi are not pathognomonic of prostatitis (Harada et al, 1980), it has been clearly shown that bacteria can persist in protective biofilms or aggregates within the interstices or on the surface of the calculus material (Meares, 1974; Nickel et al, 1994). Theoretically, removal of all the infected material, including potentially infected calculi, can be achieved (with appropriate intraoperative radiographs or ultrasound studies), but except for small anecdotal case series (Barnes et al, 1982; Sant et al, 1984) there is no substantial proof in the literature as to the efficacy of major prostate surgery in category II chronic prostatitis. Radical transurethral resection of the prostate has not been advocated for category III CP/CPPS, but open radical prostatectomy has been shown anecdotally to benefit a few patients with symptoms of nonbacterial prostatitis or prostatodynia or both (Davis and Weigel, 1990; Frazier et al, 1992). **No definitive clinical series or long-term follow-up has ever been presented, and this type of surgery should not be encouraged or recommended at this time.**

Treatment Summary

Acute bacterial prostatitis is relatively simple to treat; eradicate the bacteria with appropriate antibiotic therapy. The objective for chronic bacterial prostatitis is similar—eradication of bacteria, but long-term symptom amelioration sometimes eludes us. Our standard therapies for CP/CPPS, when used as monotherapy, offer only modest improvement in symptoms (Nickel et al, 2004a; Nickel, 2008b). Multimodal therapy employing multiple concurrent treatment strategies may offer the best results at this time (Shoskes et al, 2003; Shoskes and Katz, 2005). However, a number of well-controlled prospective studies did not demonstrate increased efficacy by combining α-adrenergic blockers and antibiotics (Alexander et al, 2004) or α-adrenergic blockers and anti-inflammatory agents (Batstone et al, 2005). The explanation for this difficulty in treating chronic prostatitis may be that the patients become peripherally and centrally sensitized and that treatment targeted to the initiators of the process may not work as well when the condition becomes chronic (Yang et al, 2003; Pontari and Ruggieri, 2004; Pontari, 2007). Table 11–4 is a list of the various standard medical therapies that are currently recommended. Further investigations should focus not only on the mechanisms inducing the symptoms, including the pain, but also on the mechanisms maintaining the pain.

To evaluate and compare the many clinical trials assessing the various therapies advocated for CP/CPPS it is important to clearly define and classify the patient population (NIH classification system), determine results by employing a standardized outcome index (NIH-CPSI), prospectively compare a treated group to a similar group randomized to placebo, and fulfill the requirements of peer review for publication in a reputable journal (Nickel et al, 1999c; Propert et al, 2002). **In the past several years the results of a significant number of such trials have been published** (Nickel, 2004, 2008a; Schaeffer, 2006), **allowing the reader to assess and compare the efficacy of antibiotics, α-adrenergic blockers, anti-inflammatory agents, phytotherapies, and hormonal agents in CP/CPPS** (Table 11–5). A suggested treatment algorithm based on these assessments is presented in Figure 11–8.

Key Points: Therapy

- The following medical therapies have been evaluated in standardized randomized placebo controlled trials in CPPS: antibiotics, α-adrenergic blockers, anti-inflammatory agents, hormonal therapies, phytotherapies, and pregabalin.
- The following medical therapies have shown benefits in placebo- or sham-controlled studies in CPPS: marked benefit—none; moderate benefit in some selected trials—α-adrenergic blockers and pregabalin; and modest benefit—anti-inflammatory agents and phytotherapies.

Phenotypic Approach to Pelvic Pain (PAPP): UPOINT Management of CP/CPPS

Many clinicians dedicated to practicing an evidence-based approach to managing patients with CP/CPPS have become frustrated. Many of the traditional and new promising therapies that appear to work in real-life clinical practice fail to show significant efficacy when subjected to large randomized placebo-controlled trials (Schaeffer, 2006; Nickel, 2008b). Only recently have we become aware that patients with urologic chronic pelvic pain syndromes, such as CP/CPPS, are not a homogeneous group of patients with identical etiologic mechanisms, genitourinary pain, voiding symptoms, and/or psychosexual problems but rather a heterogeneous group of individual patients with widely differing clinical phenotypes. This realization has led the NIH to fund the Multidisciplinary Approach to Pelvic Pain (MAPP) study group to explore basic science (particularly biomarker and etiologic studies) and epidemiology to better understand the differences in this very heterogeneous group of patients. It is hoped that "phenotyping" patients may explain our very inconsistent therapeutic results and that the concept eventually may be applicable to direct better management strategies.

Table 11–4.

Suggested Medical Therapy for CP/CPPS

DRUG CLASS	SPECIFIC THERAPY	DOSE	DURATION OF THERAPY (wk)	EVIDENCE
Antibiotics	TMP-SMX	160/800 mg bid	12	See Table 11–3 for summary of clinical trial data.
	Norfloxacin	400 mg bid	4-12	
	Ciprofloxacin	500 mg bid	4-12	
	Ofloxacin	300 mg bid	4-12	
	Lomefloxacin	400 mg qd	4-12	
	Levofloxacin	500 mg qd	4-12	
α-Adrenergic blockers	Terazosin	5 mg qd	>14	Cheah et al, 2003
	Alfuzosin	10 mg qd	>12	Mehik et al, 2003 Nickel et al, 2008a
	Tamsulosin	0.4 mg qd	>6	Nickel et al, 2004b Alexander et al, 2004
Phytotherapy	Pollen extract	1 tab tid	24	Buck et al, 1989 Rugendorff et al, 1993
	Quercetin	500 mg bid	4	Shoskes et al, 1999
	Saw palmetto	150 mg qd	24	Reissigl et al, 2004
Anti-inflammatory agents	Nimesulide	100 mg bid	2-4	Canale et al, 1993a
	Rofecoxib	25-50 mg qd	>6	Nickel et al, 2003
	Other NSAIDs Indomethacin Diclofenac Ibuprofen	Various	2-4	Evans, 1999
	Pentosan polysulfate	100 mg tid	24	Wedren, 1987 Nickel et al, 1999 Nickel et al, 2005
Hormonal agents	Finasteride	5 mg qd	24	Leskinen et al, 1999 Nickel et al, 2004
	Mepartricin	40 mg qd	8	De Rose et al, 2004
Gabapentinoids	Pregabalin	50-100 mg tid	6	Pontari et al, 2010

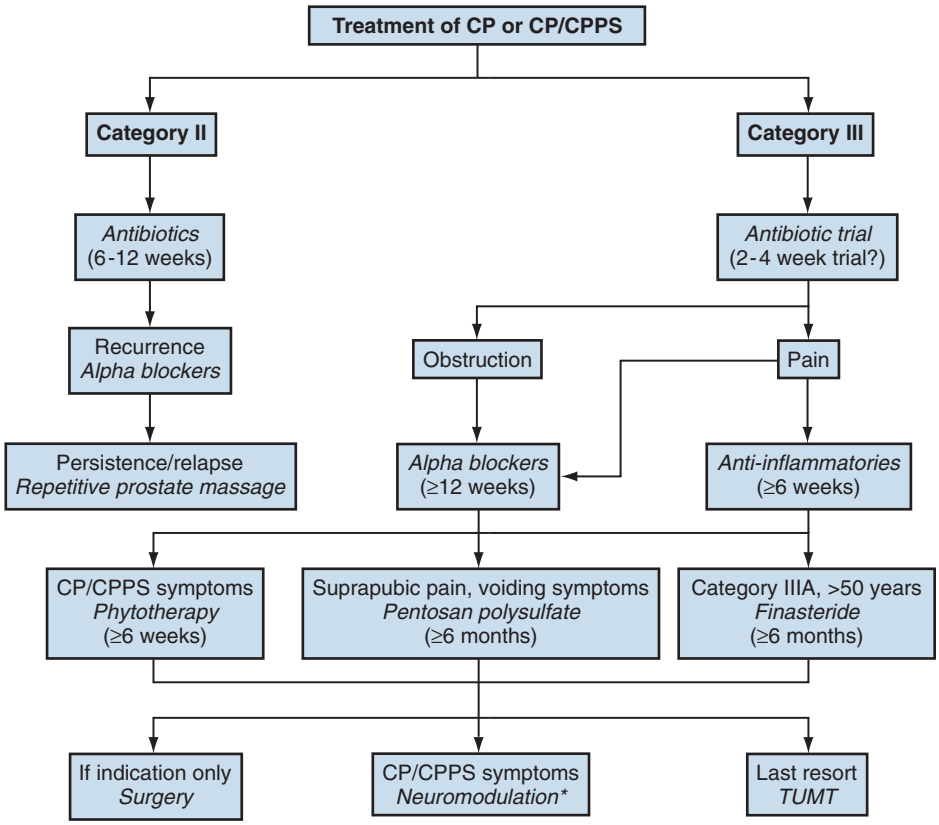
TMP-SMX, trimethoprim-sulfamethoxazole.

Table 11–5.

Clinical Trials Evaluating Therapy for CP/CPPS That Met the Evidence-Based Criteria Established by Nickel (see text)

			Patients (n)		Responders (%)		Change in NIH-CPSI		TREATMENT
ACTIVE AGENT	REFERENCE	DURATION	ACTIVE	PLACEBO	ACTIVE	PLACEBO	ACTIVE	PLACEBO	EFFECT
Levofloxacin	Nickel et al, 2003	6 wk	35	45	42	37	–5.4	–2.9	2.5
Terazosin	Cheah et al, 2003	14 wk	43	43	NK	NK	–14.3*	–10.2	4.1
Alfuzosin	Mehik et al, 2003	24 wk	17	20	65*	24	–9.9*	–3.8	6.1
Tamsulosin	Nickel et al, 2004a	6 wk	27	30	52	33	–9.1*	–5.5	3.6
Ciprofloxacin	Alexander et al, 2004	6 wk	49	49	22	22	–6.2	–3.4	2.8
Tamsulosin			49		24		–4.4		1.0
Tamsulosin + Ciprofloxacin			49		10		–4.1		0.7
Alfuzosin	Nickel et al, 2008b	12 wk	138	134	49.3† 34.8‡	49.3† 33.6‡	–7.1	–6.5	0.6
Rofecoxcib 25 mg	Nickel et al, 2003	6 wk	53	59	46	40	–4.9	–4.2	0.7
Rofecoxib 50 mg	Nickel et al, 2003	6 wk	49	59	63*	40	–6.2	–4.2	2.0
Pentosan polysulfate	Nickel et al, 2005	16 wk	51	49	37	18	–5.9	–3.2	2.7
Finasteride	Nickel et al, 2004	24 wk	33	31	33	16	–3.0	–0.8	2.2
Mepartricin	de Rose et al, 2004	8 wk	13	13	NK	NK	–15.0	–5.0	10.0
Quercetin	Shoskes et al, 1999	4 wk	15	13	67*	20	–7.9*	–1.4	6.5
Pregabalin	Pontari et al, 2010	6 wk	103	106	47.2† (31*)‡	35.8† (19)‡	–6.6*	–4.2	2.4

*Significant difference between active and placebo ($P < .05$).
†Primary end point (CPSI responders—see text).
‡Global Response Assessment responders.
NK, not known.



*Amitriptyline, gabapentin, biofeedback, massage therapy, acupuncture, neurostimulation.

Figure 11–8. A suggested therapeutic algorithm for the treatment of patients presenting with CP/CPPS. TUMT, transurethral microwave thermotherapy.

There are a number of reasons why the majority of randomized placebo-controlled trials reported in the literature and this chapter have been "negative," making it difficult to develop evidence-based management guidelines. The first reason is because treatments based on a single etiologic mechanism are doomed to fail when tested in the whole CP/CPPS population. As discussed earlier under Etiology, most of the mechanisms examined are based on sound scientific theory and all are associated with at least some confirmatory clinical data. We must accept that there is no one all encompassing etiologic mechanism responsible for all cases of CP/CPPS. In addition, we cannot be sure that the patients we routinely manage in clinical practice are the same patients who have been enrolled in clinical trials. In fact, the most rigorously designed NIH-sponsored randomized controlled trials (Alexander et al, 2004; Nickel et al, 2008a; Pontari et al, 2010) did not enroll over 90% of the CP/CPPS patients who were screened. Finally, were the negative trials reported in the literature and this chapter really negative? A reappraisal of the study results would suggest otherwise. Table 11–6 outlines such a reappraisal of results in "negative" studies in CPPS. Antibiotics tended to work better in less chronic heavily pretreated patients (marginally significant improvement in levofloxacin trial) (Nickel et al, 2003b) compared with ciprofloxacin trial (Alexander et al, 2004), further substantiated by the 75% improvement seen using ciprofloxacin or levofloxacin treatment in patients with very early (4 to 8 weeks of symptoms associated with that particular episode) presentation (Nickel and Xiang, 2008). Whereas large NIH-sponsored multicenter studies failed to confirm the benefits of α-adrenergic blockers in both chronic heavily pretreated (Alexander et al, 2004) and recently diagnosed α-adrenergic blocker–naive (Nickel et al, 2008a) CP/CPPS patients, at least four other randomized controlled trials (Cheah et al, 2003; Mehik et al, 2003; Nickel et al, 2004b; Tugcu et al, 2007) with less rigorous selection criteria did show significant efficacy with α-adrenergic blockers. Although trials examining anti-inflammatory agents (Nickel et al, 2004c), pentosan polysulfate (Nickel et al, 2005b), finasteride (Nickel et al, 2004c), and pregabalin (Pontari et al, 2010) were considered negative trials based on the primary end point analysis, these trials showed efficacy for many of the validated outcomes (including responder analyses employing the validated subjective global or global response assessment scale) of statistical (Nickel et al, 2003c; Nickel et al, 2005b; Pontari et al, 2010) or marginal significance (Nickel et al, 2004c) (see Table 11–6 for details). So what do all these seemingly negative trials mean to physicians treating CP/CPPS? It is very likely that we will never discover a single overall cure for all patients diagnosed with this condition. This reevaluation of trial results, however, strongly suggests that some patients do, in fact, respond to these various therapies. We must be able to identify patients who may respond to specific therapies.

A clinically practical phenotyping classification system for patients diagnosed with urologic chronic pelvic pain syndromes (CP/CPPS and Interstitial Cystitis) has been proposed (Shoskes et al, 2009a, 2009b). **UPOINT is a 6-point clinical classification system that categorizes the phenotype of patients with UCPPS into one or more of six clinically identifiable domains: *U*rinary, *P*sychosocial, *O*rgan-Specific, *I*nfection, *N*eurologic/Systemic, and *T*enderness (muscle)** (Fig. 11–9). It has been suggested that UPOINT will be a new clinical tool for urologists to use to direct individually based therapy. UPOINT has been evaluated and validated in female interstitial cystitis (Nickel et al, 2009) and male CP/CPPS (Shoskes et al, 2009). For both of these urologic chronic pelvic pain conditions

Table 11–6.

"Negative" Randomized Placebo-Controlled Treatment Trials in CP/CPPS*

INTERVENTION	REFERENCE	PRIMARY OUTCOME (*P* NONSIGNIFICANT)	ALTERNATIVE INTERPRETATION
Ciprofloxacin	Alexander et al, 2004	Mean NIH-CPSI score	2 × 2 factorial design has limitations Cohort was heavily pretreated and long duration Other studies show benefit†
Levofloxacin	Nickel et al, 2001	Mean NIH-CPSI score	Less heavily pretreated cohort Significant benefit at 3 wk Marginally significant benefit at 6 wk (*P* = .06) Other studies show benefit†
Rofecoxib	Nickel et al, 2004c	Pain severity (0-10 scale)	Significant benefit at 50-mg dose for secondary outcome (SGA)
Tamsulosin	Alexander et al, 2004	Mean NIH-CPSI score	2 × 2 factorial design has limitations Cohort was heavily pretreated and long duration Other trials show benefit‡
Alfuzosin	Nickel et al, 2008a	4-point decrease in NIH-CPSI	α-Adrenergic blocker nave, recently diagnosed Other trials show benefit‡
Finasteride	Nickel et al, 2004c	SGA	Marginally significant benefit (*P* = .06) for primary and secondary outcome
Pentosan polysulfate	Nickel et al, 2005b	SGA numeric score	Significant benefit for secondary outcome (percentage of SGA responders)
Pregabalin	Pontari et al, 2010	6-point decrease in NIH-CPSI	Significant benefit seen for all important secondary outcomes (GRA, total and subscore NIH-CPSI, pain questionnaire)

*An alternative interpretation that suggests there may be subgroups of patients who benefit from the tested intervention.
†Other studies showed benefit with earlier intervention (see text for details).
‡Four other trials with less rigorous enrollment criteria showed benefit (see text for details).
NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; SGA, Subjective Global Assessment; GRA, Global Response Assessment. (SGA and GRA are essentially the same index.)

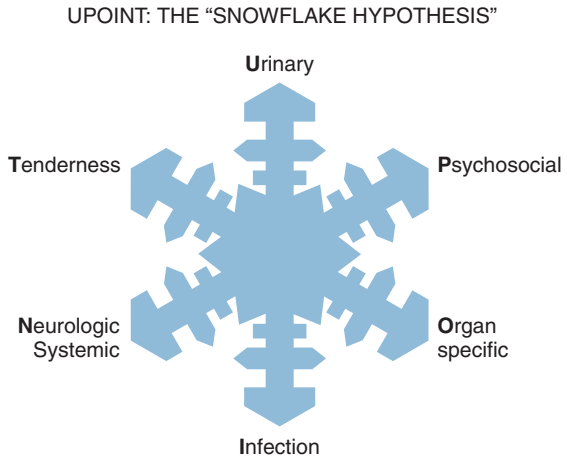


Figure 11–9. The UPOINT phenotypic classification system has six clinically defined domains (*U*rinary, *P*sychosocial, *O*rgan Specific, *I*nfection, *N*eurologic/Systemic, and *T*enderness). Because each individual patient presents with a unique phenotype, the six-point UPOINT system has been called the "snowflake hypothesis."

each domain has been clinically defined using standard clinical assessment, linked to specific mechanisms of symptom production or propagation, and associated with specific therapy (criteria for inclusion in the specific CP/CPPS domains are listed in Table 11–7).

In one study researchers determined the phenotype of a cohort of men with documented CP/CPPS using the UPOINT system and assessed the frequency of individual domains and their effect on symptom severity (Shoskes et al, 2009). The percentage of patients positive for each domain was 52%, 34%, 61%, 16%, 37%, and 53% for the urinary, psychosocial, organ-specific, infection, neurologic/systemic, and tenderness domains, respectively. Only 22% were positive for only one domain, and a significant stepwise increase was found in the total CPSI score as the number of positive domains increased (in other words, symptom severity was associated with the number of identified domains). As symptom duration increased, so did the number of positive domains (suggesting a phenotype progression). The domains with the most significant effect on symptoms included the urinary, psychosocial, organ-specific, and neurologic/systemic domains. For pain, the psychosocial, neurologic/systemic, and tenderness domains had significantly greater scores, whereas only the psychosocial and neurologic/systemic domains influenced the patients' quality of life. This suggests that domains active outside the pelvis may have the most profound effect on symptoms and quality of life. It is postulated that identifying and managing these phenotypic domains may result in more effective amelioration of CP/CPPS symptoms and greater improvement in quality of life. Based on best available evidence to date, suggested treatment regimens based on this new clinical phenotyping strategy are presented in Table 11–7. The author and his colleagues are currently developing and testing a specific questionnaire that will provide urologists with a clinical instrument to identify the six major phenotypes but also the subclassifications that will likely be relevant within each specific domain. A better understanding of etiology, mechanisms of disease, and disease progression and the discovery of specific biomarkers that will allow better phenotype identification will further improve management of CP/CPPS.

Table 11–7.

Phenotypic Approach to Pelvic Pain (PAPP): UPOINT Classification and Directed Therapy for CP/CPPS

UPOINT DOMAIN	CLINICAL CRITERIA	POSSIBLE THERAPY*
Urinary	Bothersome urgency, frequency, and/or nocturia Increased postvoid residual urine Dysuria	Diet modification α-Adrenergic blockers Pyridium Anticholinergic agents
Psychosocial	Depression Maladaptive coping Social dysfunction Stress Anxiety	Cognitive behavioral therapy Counseling Antidepressants Antianxiolytics
Organ specific	Specific prostate tenderness Leukocytosis in prostate specimens Hematospermia Extensive prostate calcification Lower urinary tract obstruction	Quercetin α-Adrenergic blockers Prostate massage Surgery
Infection	Exclude patients with clinical category I or II prostatitis† Gram-negative bacilli or enterococci in prostate-specific specimens History of previous resolution with antibiotics	Antibiotics
Neurologic/Systemic	Pain beyond abdomen and pelvis Associated medical conditions such as irritable bowel syndrome, fibromyalgia, etc.	Gabapentinoids Amitriptyline Neuromodulation
Tenderness (of skeletal muscles)	Palpable tenderness, painful spasm or trigger points in pelvis or abdomen	Physiotherapy Muscle relaxants Exercises

*Therapies listed are not necessarily evidence based but suggested on best-available evidence, interpretation of clinical trial data, and clinical experience. Therapies should be targeted against specific symptom or clinical assessment within a particular phenotype. Some treatments will be effective only in a subcategory of a specific phenotype and not effective in others.

†This category does not include category II chronic bacterial prostatitis patients, defined as men with recurrent urinary tract infections (usually same organism) with identical organism identified in prostate-specific specimens between episodes of infection (see text). These patients have the requirements for inclusion in the category III CP/CPPS: genitourinary and/or pelvic pain with no history of recurrent urinary tract infections.

Key Points: Phenotypic Management of CP/CPPS

- UPOINT classification of CP/CPPS patients allows better descriptions of individual phenotypes.
- Specific multimodal therapy directed at individual UPOINT phenotypes may result in better management outcomes.

ORCHITIS

Definition and Classification

By definition, orchitis is inflammation of the testis, but the term has been used to describe testicular pain localized to the testis without objective evidence of inflammation. Acute orchitis represents sudden occurrence of pain and swelling of the testis associated with acute inflammation of that testis. **Chronic orchitis** involves inflammation and pain in the testis, usually without swelling, persisting for more than 6 weeks. A classification (Nickel and Beiko, 2001) based on etiology is presented in Table 11–8.

Table 11–8.

Classification of Orchitis

Acute bacterial orchitis
Secondary to urinary tract infection
Secondary to sexually transmitted disease
Nonbacterial infectious orchitis
Viral
Fungal
Parasitic
Rickettsial
Noninfectious orchitis
Idiopathic
Traumatic
Autoimmune
Chronic orchitis
Chronic orchialgia

Pathogenesis and Etiology

Isolated orchitis is a relatively rare condition and is usually viral in origin. It spreads to the testis by a hematogenous route. Most cases of orchitis, particularly bacterial, occur secondary to local spread of an ipsilateral epididymitis and are referred to as *epididymo-orchitis*. UTIs are usually the underlying source in boys and elderly men. In young sexually active men, sexually transmitted diseases are often responsible (Berger, 1998). Truly noninfectious orchitis is often idiopathic or related to trauma, although autoimmune disease has rarely been implicated (Pannek and Haupt, 1997). It may be impossible to clinically distinguish chronic orchitis from chronic orchialgia.

Bacterial orchitis is usually associated with epididymitis and is therefore often caused by urinary pathogens, including *E. coli* and *Pseudomonas*. Less commonly, *Staphylococcus* species or

Streptococcus species are responsible. The most common sexually transmitted microorganisms responsible are *Neisseria gonorrhoeae, C. trachomatis,* and *Treponema pallidum*. Xanthogranulomatous orchitis, usually associated with *Proteus* and *E. coli*, is an extremely rare inflammatory destructive lesion of the testes that is treated with orchiectomy (Kang et al, 2007; Al-Said et al, 2007).

Mycobacterial infections, tuberculosis (Chen et al, 2004; Park et al, 2008), and bacillus Calmette-Guérin therapy (Hill et al, 2008) can also cause orchitis. The most common cause of **viral orchitis** is mumps (Jalal et al, 2004; Masarani et al, 2006; Emerson et al, 2007), but infectious mononucleosis has also been implicated (Weiner, 1997). **Fungal infections** occasionally involve the testis, with candidiasis, aspergillosis, histoplasmosis, coccidiomycosis, blastomycosis, and actinomycosis all having been reported as causes of orchitis (Wise, 1998). **Parasitic infections** rarely cause orchitis in the Western Hemisphere, but filariasis (Hazen Smith and von Lichtenberg, 1998) and trypanosomiasis (Ehrhardt et al, 2006) have been described in some endemic areas of Africa, Asia, and South America.

Diagnosis

In patients presenting with **acute infectious orchitis,** history discloses a recent onset of testicular pain, often associated with abdominal discomfort, nausea, and vomiting. These symptoms may be preceded by symptoms of parotitis in boys or young men, by UTIs in boys or elderly men, or alternatively by symptoms of a sexually transmitted disease in sexually active men. Although the process is usually unilateral, it is sometimes bilateral, especially if viral. Physical examination may reveal a toxic and febrile patient. The skin of the involved hemiscrotum is erythematous and edematous, and the testis is quite tender to palpation or can be associated with a transilluminating hydrocele. The patient should be clinically assessed for prostatitis and urethritis. For acute noninfectious orchitis the clinical picture resembles the just-presented description except that these patients lack the toxic appearance and fever.

For **chronic orchitis and orchialgia** there may have been a history of previous episodes of testicular pain, usually secondary to acute bacterial orchitis, trauma, or other causes. The patient has chronic testicular (and possibly epididymal) pain to a degree that could seriously affect his day-to-day functioning and quality of life. Patients with this diagnosis usually become very frustrated with this problem. On examination the patient does not appear toxic and does not have a fever. The scrotum is not usually erythematous, but the testis may be somewhat indurated and is almost always tender to palpation.

Laboratory tests employed to assist in the diagnosis include urinalysis, urine microscopy, and urine culture. For a patient in whom a sexually transmitted disease is suspected, a urethral swab should also be taken for culture. If the diagnosis is not evident from the history, physical examination, and these simple tests, scrotal ultrasonography should be performed (to rule out malignancy in patients with chronic orchitis/orchialgia). The most important differential diagnosis in young men and boys is testicular torsion. Testicular torsion is often difficult to differentiate from an acute inflammatory condition. Scrotal ultrasound evaluations (with use of Doppler imaging to determine testicular blood flow) are especially helpful in differential diagnosis (Mernagh et al, 2004; Gunther et al, 2006), but occasionally the diagnosis will be missed (particularly with intermittent or partial torsion) and the clinician should err in favor of the surgically correctable diagnosis of torsion.

Treatment

General principles of therapy include bed rest, scrotal support, hydration, antipyretics, anti-inflammatory agents, and analgesics. **Antibiotic therapy** (specific for UTI, prostatitis, or sexually transmitted diseases) should be employed for infectious orchitis and is ideally based on culture and sensitivity testing but may be based on microscopic or Gram stain results. There are no specific antiviral agents available to treat orchitis caused by mumps, and the previously mentioned supportive measures are important. If early testing is negative or results are unavailable, empirical treatment should be initiated, directed at the most likely pathogens based on the available clinical information: a fluoroquinolone would be the best agent in this scenario. Most patients can be readily managed on an outpatient basis. Surgical intervention is rarely indicated, unless testicular torsion (or rarely xanthogranulomatous orchitis) is suspected (as discussed previously). Spermatic cord blocks with injection of a local anesthetic may sometimes be needed to relieve the patient of severe pain. Abscess formation is rare, but if it does occur then percutaneous or open drainage is necessary.

Treatment of chronic orchitis/orchialgia is supportive. Anti-inflammatory agents, analgesics, support, heat therapies, and nerve blocks all have a role in ameliorating symptoms. It is generally believed that the condition is self-limited but could take years (and sometimes decades) to resolve. **Orchidectomy is indicated only in cases in which pain control is refractory to all other measures (and even this might not be successful in alleviating the chronic pain)** (Nariculam et al, 2007).

EPIDIDYMITIS

Definitions and Classification

Epididymitis by definition is inflammation of the epididymis. Acute epididymitis represents sudden occurrence of pain and swelling of the epididymis associated with acute inflammation of the epididymis (Nickel et al, 2002). **Chronic epididymitis** refers to inflammation and pain in the epididymis, usually without swelling (but with induration in long-standing cases), persisting for over 6 weeks (Nickel et al, 2002). Inflammation is not always clinically evident in many cases of localized epididymal pain. Approximately 1 man in 100 attending a North American urology clinic has a diagnosis of epididymitis (Nickel et al, 2005c). In the late 1990s the average cost per episode of epididymitis managed in the United States was 368 dollars (Gift and Ownes, 2006), a cost considerably less than that reported for men with a diagnosis of chronic prostatitis. A classification for epididymitis is presented in Table 11–9 (Nickel et al, 2002).

Pathogenesis and Etiology

Acute epididymitis usually results from the spread of infection from the bladder, urethra, or prostate via the ejaculatory ducts and vas deferens into the epididymis. The process starts in the tail of the epididymis and then spreads through the body of the structure to the head of the epididymis. In infants and boys, epididymitis is often related to a UTI and/or an underlying genitourinary congenital anomaly (Merlini et al, 1998) or even to the presence of a foreskin (Bennett et al, 1998). In elderly men, BPH and associated stasis, UTI, and catheterization is the most common cause of epididymitis. Bacterial prostatitis

Table 11–9.

Classification of Epididymitis

Acute bacterial epididymitis
Secondary to urinary tract infection
Secondary to sexually transmitted disease
Nonbacterial infectious epididymitis
Viral
Fungal
Parasitic
Noninfectious epididymitis
Idiopathic
Traumatic
Autoimmune
Amiodarone-induced
Associated with a known syndrome (e.g., Behçet disease)
Chronic epididymitis
Chronic epididymalgia

and/or seminal vesiculitis are associated with epididymal infection in postpubertal males of all ages (Furuya et al, 2004). In sexually active men younger than 35 years of age, epididymitis is commonly the result of a sexually transmitted infection (Berger, 1998). In most cases of acute epididymitis, the testis is also involved in the process and thus the condition is referred to as epididymo-orchitis.

Chronic epididymitis may result from inadequately treated acute epididymitis, recurrent epididymitis, or some other cause including associations with other disease processes such as Behçet disease (Cho et al, 2003; Arromdee and Tanakitivirul, 2006; Pektas et al, 2008) or treatment with amiodarone (Nikolaou et al, 2007). The etiology of chronic epididymalgia is usually unclear. Certainly one of the best known and studied is the chronic epididymitis/epididymalgia that occurs in some men after a vasectomy. About 1 in 100 men describe severe pain 6 months after a vasectomy that noticeably affects their quality of life (up to 15% of men report some discomfort 6 months after the procedure) (Leslie et al, 2007).

The most common causative microorganisms in the pediatric and elderly age groups are the coliform organisms that cause bacteriuria (Berger et al, 1979). In men younger than the age of 35 who are sexually active with women, the most common offending organisms causing epididymitis are the usual bacteria that cause urethritis, namely *N. gonorrhoeae*, and *C. trachomatis*. In homosexual men practicing anal intercourse, *E. coli* and *Haemophilus influenzae* are most commonly responsible. Both tuberculosis (Lui et al, 2005; Tsili et al, 2008) and mycobacteria, such as bacillus Calmette-Guérin (Harada et al, 2006), can be associated with epididymitis. As with orchitis, viral, fungal, mycoplasmal, and parasitic microorganisms have all been implicated in epididymitis (Berger, 1998; Wise, 1998; Hazen Smith and von Lichtenberg, 1998; Scagni et al, 2008). Rarely, epididymitis as a complication of brucellosis has been described (Akinci et al, 2006; Queipo-Ortuno et al, 2006; Colmenero et al, 2007).

Diagnosis

Both acute infectious and acute noninfectious epididymitis present in much the same way as do acute infectious and acute noninfectious orchitis, respectively. Physical examination localizes the tenderness to the epididymis. However, in many cases the testis is also involved in the inflammatory process and subsequent pain and this is referred to as epididymo-orchitis. The spermatic cord is usually tender and swollen. Early on in the process, only the tail of the epididymis is tender, but the inflammation quickly spreads to the rest of the epididymis and if it continues to the testis then the swollen epididymis becomes indistinguishable from the testis.

There may be no clinical or etiologic differentiation between chronic epididymitis and epididymalgia. The patient usually presents with a long-standing history of pain (waxing and waning or constant) localized to the epididymis, and like chronic orchitis/orchialgia these symptoms may have a significant impact on the patient's quality of life (Nickel et al, 2002).

Laboratory tests should include Gram staining of a urethral smear and a midstream urine specimen. Gram-negative bacilli can usually be identified in patients with underlying cystitis. If the urethral smear reveals the presence of intracellular gram-negative diplococci, a diagnosis of infection with *N. gonorrhoeae* is established. If only WBCs are seen on the urethral smear, a diagnosis of *C. trachomatis* will be established two thirds of the time. A urethral swab and midstream urine specimen should be sent for culture and sensitivity testing. When an infant or young boy is diagnosed with epididymitis he should be further evaluated with abdominopelvic ultrasonography, voiding cystourethrography, and possibly cystoscopy (Shortliffe, 1998; Al-Taheini et al, 2008). If the diagnosis is uncertain, duplex Doppler scrotal ultrasonography to look for increased blood flow to the affected epididymis may be performed (also to rule out torsion as described under orchitis) (Mernagh et al, 2004). Ultrasonography can sometimes be helpful to rule out other epididymal and scrotal pathology (Lee et al, 2008).

Treatment

Management of acute infectious epididymitis depends on the likely cause and organism (Tracy et al, 2008). **The Centers for Disease Control and Prevention's 2006 guidelines for the treatment of infectious epididymitis includes ceftriaxone or doxycycline for men younger than age 35 years and levofloxacin or ofloxacin for men older than age 35 years** (Centers for Disease Control and Prevention et al, 2006).

For chronic epididymitis, a 4- to 6-week trial of antibiotics that would potentially be effective against possible bacterial pathogens and particularly *C. trachomatis* may be appropriate (Nickel, 2005). Anti-inflammatory agents, analgesics, scrotal support, and nerve blocks have all been recommended as empirical treatment (Nickel, 2005). It is generally believed that chronic epididymitis is a self-limited condition that will eventually "burn out," but this could take years (or even decades). **Surgical removal of the epididymis**

Key Points: Orchitis and Epididymitis

- Orchitis usually occurs with epididymitis (except for viral causation).
- Etiology of epididymitis and orchitis is usually related to the age of the patient.
- Acute presentation is usually related to infection or ischemia.
- In the young patient the most important differential diagnosis is torsion of the testis.
- Treatment of chronic epididymitis or epididymo-orchitis is difficult.

(epididymectomy) should be considered only when all conservative measures have been exhausted and the patient accepts that the operation will have at best a 50% chance of curing his pain (Padmore et al, 1996; Tracy et al, 2008). However, better surgical results (up to 70%) have been reported for epididymectomy for postvasectomy pain (Siu et al, 2007).

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chapter 12

Bladder Pain Syndrome (Interstitial Cystitis) and Related Disorders

Philip M. Hanno, MD, MPH

Definition
Historical Perspective
Epidemiology
Etiology
Pathology
Diagnosis
Classification
Treatment
Principles of Management

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a **condition diagnosed on a clinical basis** and requiring a high index of suspicion on the part of the clinician. Simply put, **it should be considered in the differential diagnosis of the patient presenting with chronic pelvic pain that is often exacerbated by bladder filling and associated with urinary frequency.** One can argue that it is a symptom-complex because it has a differential diagnosis that should be explored in a timely fashion before or at the time of initiation of empirical therapy (Blaivas, 2007). Once other conditions have been ruled out it can be considered a syndrome that generally responds to one of a variety of therapeutic approaches in the majority of cases. The perception that the original term *interstitial cystitis* was not at all descriptive of the clinical syndrome or even the pathologic findings in many cases has led to the current effort to reconsider the name of the disorder and even the way it is positioned in the medical spectrum (Hanno, 2008). What was originally considered a bladder disease is now considered a chronic pain syndrome (Janicki, 2003) that may begin as a pathologic process in the bladder in most but not all patients and eventually can develop into a disease that in a small subset of those affected even cystectomy may not benefit (Baskin and Tanagho, 1992). Its relationship to type III chronic pelvic pain syndrome (CPPS)/nonbacterial prostatitis is unclear (Chai, 2002; Hakenberg and Wirth, 2002). Its association with other chronic pain syndromes has taken on more importance recently as a promising clue to unlock the challenging etiologic and therapeutic puzzle of this condition.

BPS/IC encompasses a major portion of the "painful bladder" disease complex. "Painful bladder disorders" comprise a large group of patients with bladder and/or urethral and/or pelvic pain, irritative voiding symptoms (urgency, frequency, nocturia, dysuria), and sterile urine cultures. Painful bladder conditions with well-established causes include radiation cystitis, cystitis caused by microorganisms that are not detected by routine culture methodologies, and systemic disorders that affect the bladder. In addition, many gynecologic disorders can mimic BPS/IC (Kohli et al, 1997; Howard, 2003a, 2003b). BPS/IC has no easily discernible etiology.

The symptoms are allodynic, an exaggeration of normal sensations. There are no pathognomonic findings on pathologic examination, and even the finding of petechial hemorrhages on the bladder mucosa during cystoscopy after bladder hydrodistention under anesthesia is no longer considered the sine qua non of BPS/IC that it had been until a decade ago (Erickson, 1995; Waxman et al, 1998; Erickson et al, 2005). **BPS/IC is truly a diagnosis of exclusion.** It may have multiple causes and represent a final common reaction of the bladder to different types of insult.

DEFINITION

"It resembles a constellation of stars; its components are real enough but the pattern is in the eye of the beholder" (Makela and Heliovaara, 1991). This evocative description of fibromyalgia could equally apply to BPS/IC. Indeed, it has been argued, not necessarily convincingly, that each medical specialty has at least one somatic syndrome (irritable bowel syndrome, chronic pelvic pain, fibromyalgia, tension headache, noncardiac chest pain, hyperventilation syndrome) that might be better conceptualized as a part of a general functional somatic syndrome than with the symptom-based classification that we have now that may be more a reflection of professional specialization and access to care (Wessely and White, 2004).

BPS/IC is a clinical diagnosis based primarily on chronic symptoms of pain perceived by the patient to emanate from the bladder and/or pelvis associated with urinary urgency/frequency in the absence of other identified causes for the symptoms. It has been defined and redefined over the past century, and as the problem of definition

Table 12–1.

Definitions of Bladder Pain Syndrome/Painful Bladder Syndrome/Interstitial Cystitis Syndrome over the Past Century

YEAR	DEFINITION	SOURCE
1887	Skene: An inflammation that has destroyed the mucous membrane partly or wholly and extended to the muscular parietes	Skene, 1887
1915	Hunner: A peculiar form of bladder ulceration whose diagnosis depends ultimately on its resistance to all ordinary forms of treatment in patients with frequency and bladder symptoms (spasms)	Hunner, 1915
1951	Bourque: Patients who suffer chronically from their bladder; and we mean the ones who are distressed, not only periodically but constantly, having to urinate at all hours of the day and of the night suffering pains every time they void.	Bourque, 1951
1978	Messing and Stamey: Nonspecific and highly subjective symptoms of around-the-clock frequency, urgency, and pain somewhat relieved by voiding when associated with glomerulations upon bladder distention under anesthesia.	Messing and Stamey, 1978
1990	Revised NIDDK criteria: Pain associated with the bladder or urinary urgency, and glomerulations or Hunner ulcer on cystoscopy under anesthesia, in patients with 9 months or more of symptoms—at least 8 voids per day, 1 void per night, and cystometric bladder capacity less than 350 mL	Wein et al, 1990
1997	NIDDK Interstitial Cystitis Database entry criteria: Unexplained urgency or frequency (7 or more voids per day) *or* pelvic pain of at least 6 months' duration in the absence of other definable causes.	Simon et al, 1997
2008	European Society for the Study of Interstitial Cystitis: Chronic (>6 months) pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or frequency. Confusable diseases as the cause of the symptoms must be excluded.	Van de Merwe et al, 2008
2009	Japanese Urological Association: A disease of the urinary bladder diagnosed by three conditions: (1) lower urinary tract symptoms such as urinary frequency, bladder hypersensitivity and/or bladder pain; (2) bladder pathology proven endoscopically by Hunner ulcer and/or mucosal bleeding after overdistention; and (3) exclusion of confusable diseases such as infection, malignancy, or calculi of the urinary tract.	Homma et al, 2009
2009	Society for Urodynamics and Female Urology informal international dialogue consensus meeting: An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks' duration, in the absence of infection or other identifiable causes.	Hanno and Dmochowski, 2009

Data from Hanno PM, Lin AT, Nordling J, et al. Bladder pain syndrome. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence. Paris: Health Publication Ltd.; 2009. p. 1459–518.

has become more prominent lately so have the number of definitions and attempts to crystallize just what the diagnosis means (Table 12–1). **The International Continence Society (ICS) prefers the term *painful bladder syndrome* (PBS), defined as "the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology"** (Abrams et al, 2002). **The ICS reserves the diagnosis of IC to patients with "typical cystoscopic and histological features," without further specifying these. This definition may miss 36% of patients, primarily because it confines the pain to a suprapubic location and mandates a relationship of pain to bladder filling** (Warren et al, 2006).

In the absence of clear criteria for IC, this chapter will refer to BPS/IC and IC interchangeably, because all but recent literature terms the syndrome IC. The definition of the European Society for the Study of Interstitial Cystitis (ESSIC) is a clinically useful one, and changes made since its original iteration have likely made it more sensitive and inclusive (Mouracade et al, 2008). Minor modifications made at a meeting under the auspices of the Society for Urodynamics and Female Urology (SUFU) may be preferred by some clinicians. Perhaps more than for most diseases, how we arrived at this point is instructive and critical to an overall understanding of BPS/IC. The paradigm change that has resulted in morphing what was originally considered a bladder disease (aptly named interstitial cystitis) to a chronic pain syndrome (bladder pain syndrome) also merits discussion.

HISTORICAL PERSPECTIVE

Recent historical reviews confirm that IC was recognized as a pathologic entity during the 19th century (Christmas, 1997; Parsons and Parsons, 2004). Joseph Parrish, a Philadelphia surgeon, described three cases of severe lower urinary tract symptoms in the absence of a bladder stone in an 1836 text (Parrish, 1836) and termed the disorder *tic doloureux of the bladder.* Teichman and associates (2000) argue that this may represent the first description of IC. Fifty years later Skene (1887) used the term *interstitial cystitis* to describe an inflammation that has "destroyed the mucous membrane partly or wholly and extended to the muscular parietes."

Early in the 20th century, at a New England Section meeting of the American Urological Association, Guy Hunner (1915, 1918) reported on eight women with a history of suprapubic pain, frequency, nocturia, and urgency lasting an average of 17 years. He drew attention to the disease, and the red, bleeding areas he described on the bladder wall came to have the pseudonym of Hunner ulcer. As Anthony Walsh (1978) observed, this has proven to be unfortunate. In the early part of the 20th century the very best cystoscopes available gave a poorly defined and ill-lit view of the fundus of the bladder. It is not surprising that when Hunner saw red and bleeding areas high on the bladder wall he thought they were ulcers. For the next 60 years urologists would look for ulcers and fail to make the diagnosis in their absence. The disease was thought to be focal rather than a pancystitis.

Hand (1949) authored the first comprehensive review about the disease, reporting 223 cases. In looking back, his paper was truly

a seminal one, years ahead of its time. Many of his epidemiologic findings have held up to this day. His description of the clinical findings bears repeating. "I have frequently observed that what appeared to be a normal mucosa before and during the first bladder distention showed typical interstitial cystitis on subsequent distention." He notes, "small, discrete, submucosal hemorrhages, showing variations in form … dot-like bleeding points … little or no restriction to bladder capacity." He portrays three grades of disease, with grade 3 matching the small-capacity, scarred bladder described by Hunner. Sixty-nine percent of patients had grade 1 disease, and only 13% had grade 3 disease.

Walsh (1978) later coined the term *glomerulations* to describe the petechial hemorrhages that Hand had described. But it was not until Messing and Stamey (1978) discussed the "early diagnosis" of IC that attention turned from looking for an ulcer to make the diagnosis to the concepts that (1) symptoms and glomerulations at the time of bladder distention under anesthesia were the disease hallmarks and (2) the diagnosis was primarily one of exclusion.

Bourque's *Aunt Minnie (she is hard to define, but you know her when you see her)* description of IC is over 50 years old and is worth recalling: "We have all met, at one time or another, patients who suffer chronically from their bladder; and we mean the ones who are distressed, not only periodically but constantly, having to urinate often, at all moments of the day and of the night, and suffering pains every time they void. We all know how these miserable patients are unhappy, and how those distressing bladder symptoms get finally to influence their general state of health physically at first, and mentally after a while" (Bourque, 1951).

Although memorable and right on the mark, this description and others like it were not suitable for defining this disease in a manner that would help physicians make the diagnosis and design research studies to learn more about the problem. Physician interest and government participation in research were sparked through the efforts of a group of frustrated patients led by Dr. Vicki Ratner, an orthopedic surgery resident in New York City, who founded the first patient advocacy group, the Interstitial Cystitis Association, in the living room of her small New York City apartment in 1984 (Ratner et al, 1992; Ratner and Slade, 1997). The first step was to develop a working definition of the disease. The modern history of PBS/IC is best viewed through the development of the modern definition.

Evolution of Definition

There are data to suggest that true urinary frequency in women can be defined as regularly having to void at intervals of less than 3 hours and 25% of women older than age 40 years have nocturia at least once (Glenning, 1985; Fitzgerald and Brubaker, 2003). Whereas bladder capacity tends to fall in women by the eighth and ninth decades of life, bladder volume at first desire to void tends to rise as women age (Collas and Malone-Lee, 1996). Based on a 90th percentile cut-off to determine the ranges of normality, the highest "normal" frequency ranges in the 4th decade range from 6 for men to 9 for women (Burgio et al, 1991). Large variation in the degree of bother with varying rates of frequency (Fitzgerald et al, 2002) makes a symptomatic diagnosis of PBS/IC based on an absolute number of voids subject to question, and frequency per volume of intake or even the concept of "perception of frequency" as a problem may be more accurate than an absolute number.

In an effort to define IC so that patients in different geographic areas, under the care of different physicians, could be compared, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) held a workshop in 1987 at which consensus criteria were established for the diagnosis of IC (Gillenwater and Wein, 1988). These criteria were not meant to define the disease but rather to ensure that groups of patients included in basic and clinical research studies would be relatively comparable. After pilot studies testing the criteria were performed, the criteria were revised at another NIDDK workshop a year later (Wein et al, 1990). These criteria are presented in Table 12–2.

Although meant initially to serve only as a research tool, the NIDDK "research definition" became a de facto definition of this disease, diagnosed by exclusion and colorfully termed a "hole in the air" by Hald (cited in George, 1986). Certain of the exclusion criteria serve mainly to make one wary of a diagnosis of IC but should by no means be used for categorical exclusion of such a diagnosis. However, because of the ambiguity involved, these patients should probably be eliminated from research studies or categorized separately. In particular, exclusion criteria 4, 5, 6, 8, 9, 11, 12, 17, and 18 are only relative. What percentage of patients with idiopathic sensory urgency has IC is unclear (Frazer et al,

Table 12–2.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Diagnostic Criteria for Interstitial Cystitis

To be diagnosed with interstitial cystitis, patients must have either glomerulations on cystoscopic examination or a classic Hunner ulcer, and they must have either pain associated with the bladder or urinary urgency. An examination for glomerulations should be undertaken after distention of the bladder under anesthesia to 80 to 100 cm H_2O for 1 to 2 minutes. The bladder may be distended up to two times before evaluation. The glomerulations must be diffuse—present in at least three quadrants of the bladder—and there must be at least 10 glomerulations per quadrant. The glomerulations must not be along the path of the cystoscope (to eliminate artifact from contact instrumentation). The presence of any one of the following excludes a diagnosis of interstitial cystitis:

- Bladder capacity of greater than 350 mL on awake cystometry using either a gas or liquid filling medium
- Absence of an intense urge to void with the bladder filled to 100 mL of gas or 150 mL of liquid filling medium
- The demonstration of phasic involuntary bladder contractions on cystometry using the fill rate just described
- Duration of symptoms less than 9 months
- Absence of nocturia
- Symptoms relieved by antimicrobial agents, urinary antiseptic agents, anticholinergic agents, or antispasmodic agents
- A frequency of urination while awake of less than 8 times per day
- A diagnosis of bacterial cystitis or prostatitis within a 3-month period
- Bladder or ureteral calculi
- Active genital herpes
- Uterine, cervical, vaginal, or urethral cancer
- Urethral diverticulum
- Cyclophosphamide or any type of chemical cystitis
- Tuberculous cystitis
- Radiation cystitis
- Benign or malignant bladder tumors
- Vaginitis
- Age younger than 18 years

From Wein AJ, Hanno PM, Gillenwater JY. Interstitial cystitis: an introduction to the problem. In: Hanno PM, Staskin DR, Krane RJ, Wein AJ, editors. Interstitial cystitis. London: Springer-Verlag; 1990. p. 13–5.

1990). **The specificity of the finding of bladder glomerulations has come into question** (Erickson, 1995; Waxman et al, 1998; Tomaszewski et al, 2001). Similarly, **the sensitivity of glomerulations is also unknown, but clearly patients with IC symptoms can demonstrate an absence of glomerulations under anesthesia** (Awad et al, 1992; Al Hadithi et al, 2002). **Bladder ulceration is extremely rare** and exists in less than 5% of patients in my experience and in the experience of others (Sant, 1991). A California series found 20% of patients to have ulceration (Koziol, 1994). Specific pathologic findings represent a glaring omission from the criteria, because **there is a lack of consensus as to which pathologic findings, if any, are required for, or even suggestive of, a tissue diagnosis** (Hanno et al, 1990, 2005a; Tomaszewski et al, 1999, 2001).

The unexpected use of the NIDDK research criteria by the medical community as a definition of IC led to concerns that many patients suffering from this syndrome might be misdiagnosed. The multicenter Interstitial Cystitis Database (ICDB) study through NIDDK accumulated data on 424 patients with IC, enrolling patients from May 1993 through December 1995. Entry criteria were much more symptom driven than those promulgated for research studies (Simon et al, 1997) and are noted in Table 12–3. In an analysis of the defining criteria (Hanno et al, 1999a, 1999b), it appeared the NIDDK research criteria fulfilled their mission. Fully 90% of expert clinicians agreed that patients diagnosed with IC by those criteria in the ICDB indeed had the disorder. However, 60% of patients deemed to have IC by these experienced clinicians would not have met NIDDK research criteria. **Thus, IC remains a clinical syndrome defined by some combination of chronic symptoms of urgency, frequency, and/or pain in the absence of other reasonable causation. Whereas IC symptom and problem indices have been developed and validated** (O'Leary et al, 1997; Goin et al, 1998), **these are not intended to diagnose or define IC but rather to measure the severity of symptomatology and monitor disease progression or regression** (Moldwin and Kushner, 2004).

Table 12–3.

Interstitial Cystitis Database (ICDB) Study Eligibility Criteria

1. Providing informed consent to participate in the study
2. Willing to undergo a cystoscopy under general or regional anesthesia when indicated during the course of the study
3. At least 18 years of age
4. Having symptoms of urinary urgency, frequency, or pain for more than 6 months
5. Urinating at least 7 times per day or having some urgency or pain (measured on linear analog scales)
6. No history of current genitourinary tuberculosis
7. No history of urethral cancer
8. No history of bladder malignancy, high-grade dysplasia, or carcinoma in situ
9. Males: no history of prostate cancer
10. Females: no occurrence of ovarian, vaginal, or cervical cancer in the previous 3 years
11. Females: no current vaginitis or clue cell, trichomonal, or yeast infections
12. No bacterial cystitis in the previous 3 months
13. No active herpes in the previous 3 months
14. No antimicrobials for urinary tract infections in previous 3 months
15. Never having been treated with cyclophosphamide
16. No radiation cystitis
17. No neurogenic bladder dysfunction (e.g., due to a spinal cord injury, stroke, Parkinson disease, multiple sclerosis, spina bifida, or diabetic cystopathy)
18. No bladder outlet obstruction (determined by urodynamic investigation)
19. Males: no bacterial prostatitis for previous 6 months
20. Absence of bladder, ureteral, or urethral calculi for previous 3 months
21. No urethritis for previous 3 months
22. Not having had a urethral dilation, cystometrogram, bladder cystoscopy under full anesthesia, or a bladder biopsy in previous 3 months
23. Never having had an augmentation cystoplasty, cystectomy, cystolysis, or neuroectomy
24. Not having a urethral stricture of less than 12 Fr

From Simon LJ, Landis JR, Erickson DR, Nyberg LM. The Interstitial Cystitis Data Base Study: concepts and preliminary baseline descriptive statistics. Urology 1997;49:64–75.

Nomenclature and Taxonomy

Recent international consultations have essentially agreed that the nomenclature of "interstitial cystitis" should be revised and I will use the terminology of the International Consultation on Incontinence of *bladder pain syndrome* but keep the term *interstitial cystitis* to facilitate recognition and understanding. This change implies that it is the symptoms that drive treatment, and **the question as to whether *interstitial cystitis* should refer to a distinct subgroup of the bladder pain syndrome is, as yet, unclear.**

The literature over the past 170 years has seen numerous changes in description and nomenclature of the disease. The syndrome has variously been referred to as tic douloureux of the bladder, IC, cystitis parenchymatosa, Hunner ulcer, panmural ulcerative cystitis, urethral syndrome, and painful bladder syndrome (Skene, 1887; Hunner, 1918; Powell and Powell, 1949; Bourque, 1951; Christmas, 1997; Teichman et al, 2000; Dell and Parsons, 2004). The term *interstitial cystitis,* which Skene is credited with coining and Hunner brought in to common usage, is a misnomer; in many cases not only is there no interstitial inflammation, but also, histopathologically, there may be no inflammation at all (Lynes et al, 1990a; Denson et al, 2000; Tomaszewski et al, 2001; Rosamilia et al, 2003). By literally focusing exclusively on the urinary bladder, the term *interstitial cystitis* furthermore does not do justice to the condition from both the physician's and the patient's perspective. The textual exclusiveness ignores the high comorbidity with various pelvic, extrapelvic, and nonurologic symptoms and associated disorders (Clauw et al, 1997) that frequently precede or develop after the onset of the bladder condition (Wu et al, 2006).

With the formal definition of the term *painful bladder syndrome* by the ICS in 2002, the terminology discussion became an intense international focal point (Abrams et al, 2002):

- In Kyoto at the International Consultation on Interstitial Cystitis Japan in March 2003, it was agreed that the term *interstitial cystitis* should be expanded to *interstitial cystitis/chronic pelvic pain syndrome* when pelvic pain is at least of 3 months' duration and associated with no obvious treatable condition/pathology (Ueda et al, 2003).
- The European Society for the Study of Interstitial Cystitis (ESSIC) held its first meeting in Copenhagen soon after the Kyoto meeting. Nomenclature was discussed, but no decision was reached because the participants concentrated on how to evaluate patients for diagnosis (Nordling et al, 2004).

- At the 2003 meeting of the NIDDK titled, "Research Insights into Interstitial Cystitis," it was concluded that "interstitial cystitis" will ultimately be replaced as a sole name for this syndrome. It will be a gradual process over several years. At the meeting it was referred to as "interstitial cystitis/painful bladder syndrome" in keeping with International Continence Society nomenclature (Hanno et al, 2005b).
- At the 2004 inaugural meeting of the Multinational Interstitial Cystitis Association in Rome it was concluded that the syndrome should be referred to as "painful bladder syndrome/interstitial cystitis" or "PBS/IC" to indicate an intellectual and taxonomical hierarchy within the acronym (Hanno et al, 2005b).
- The International Consultation on Incontinence in 2004, sponsored by both the ICS and the Société Internationale d'Urologie in association with the World Health Organization, included the syndrome as a part of its consultation. The chapter in the report was titled, "Painful Bladder Syndrome (including Interstitial Cystitis)," suggesting that the IC formed an identifiable subset within the broader syndrome. Because such a distinction is difficult to define, within the body of the chapter, coauthored by nine committee members and five consultants from four continents, it was referred to as PBS/IC (one inclusive entity) (Hanno et al, 2005a). **IC may be a subgroup that encompasses those patients with typical histologic and cystoscopic features** (Peeker and Fall, 2002), **but what these features are is still controversial and somewhat vague.**
- In June 2006, Abrams and colleagues published an editorial focusing on the nomenclature problem (Abrams et al, 2006). They noted that "It is an advantage if the medical term has clear diagnostic features that translate to a known pathophysiologic process so that effective treatment may be given. Unfortunately, the latter is not the case for many of the pain syndromes suffered by patients seen at most pain, gynecological, and urological clinics. For the most part these 'diagnoses' describe syndromes that do not have recognized standard definitions, yet imply knowledge of a pathophysiologic cause for the symptoms. Unfortunately the terminology used to describe the condition may promote erroneous thinking about treatment on the part of physicians, surgeons and patients. These organ based diagnoses are mysterious, misleading and unhelpful, and can lead to therapies that are misguided or even dangerous." The editorial went on to note that a single pathologic descriptive term (*interstitial cystitis*) for a spectrum of symptom combinations ill serves patients. The umbrella term *painful bladder syndrome* was proposed, with a goal to define and investigate subsets of patients who could be clearly identified within the spectrum of PBS. It would fall within the rubric of chronic pelvic pain syndrome. Sufferers would be identified according to the primary organ that appears to be affected on clinical grounds. Pain not associated with an individual organ would be described in terms of the symptoms.

One can see in this the beginnings of a new paradigm that might be expected to change the emphasis of both clinical and basic science research and that removes the automatic presumption that the end organ in the name of the disease should necessarily be the sole or primary target of such research.

At the major biannual IC research conference in the fall of 2006, held by the NIDDK (Frontiers in Painful Bladder Syndrome/Interstitial Cystitis), the ESSIC group was given a block of time with which to present their thoughts and conclusions. Because (1) the term PBS did not fit into the taxonomy of other pelvic pain syndromes such as urethral or vulvar pain syndromes, (2) as defined by the International Continence Society missed over a third of afflicted patients, and (3) is a term open to different interpretations, the ESSIC suggested that *painful bladder syndrome* be redesignated as bladder pain syndrome (BPS), followed by a type designation. BPS is indicated by two symbols, the first of which corresponds to cystoscopy with hydrodistention findings (1, 2, or 3 indicating increasing grade of severity) and the second to biopsy findings (A, B, and C indicating increasing grade of pathologic severity) (Table 12–4). Although neither cystoscopy with hydrodistention nor bladder biopsy was prescribed as an essential part of the evaluation, by categorizing patients as to whether either procedure was done and, if so, the results, it is possible to follow patients with similar findings and study each identified cohort to compare natural history, prognosis, and response to therapy (van de Merwe et al, 2008).

As Baranowski and associates (2008) conceived it, **BPS is defined as a pain syndrome with a collection of symptoms, the most important of which is pain perceived to be in the bladder. IC is distinguished as an end-organ, visceral-neural pain syndrome, whereas BPS can be considered a pain syndrome that involves the end-organ (bladder) and neurovisceral (myopathic) mechanisms. In IC, one expects an end-organ primary pathologic process. This is not necessarily the case in the broader BPS.**

A didactically very demonstrative way to conceptualize the dawning shift in conception of the condition is with the drawing of a target (Fig. 12–1). There may be many causes of chronic pelvic pain. When an etiology cannot be determined, it is characterized as pelvic pain syndrome. To the extent that it can be distinguished

Table 12–4.

European Society for the Study of Interstitial Cystitis Classification System

		Cystoscopy with Hydrodistention		
BIOPSY	NOT DONE	NORMAL	GLOMERULATIONS*	HUNNER LESION†
Not done	XX	1X	2X	3X
Normal	XA	1A	2A	2A
Inconclusive	XB	1B	2B	3B
Positive‡	XC	1C	2C	3C

*Cystoscopy granulations grade II to III.
†With or without glomerulations.
‡Histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or tissue granulation and/or interfascicular fibrosis.
From van de Merwe JP, Nordling J, Bouchelouche P, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol 2008;53:60.

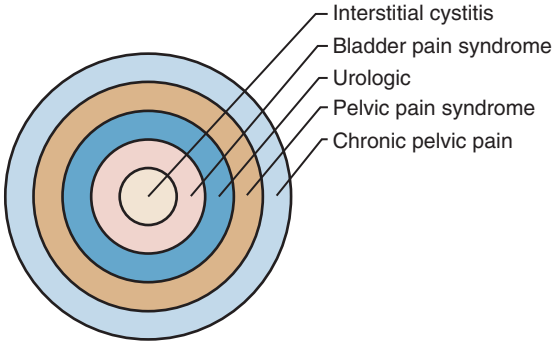


Figure 12–1. Conceptualization of pelvic pain syndrome classification. (From Hanno P. Interstitial cystitis/painful bladder syndrome/bladder pain syndrome: the evolution of a new paradigm. In: Proceedings of the International Consultation on Interstitial Cystitis. Japan: Comfortable Urology Network; 2008. p. 2–9.)

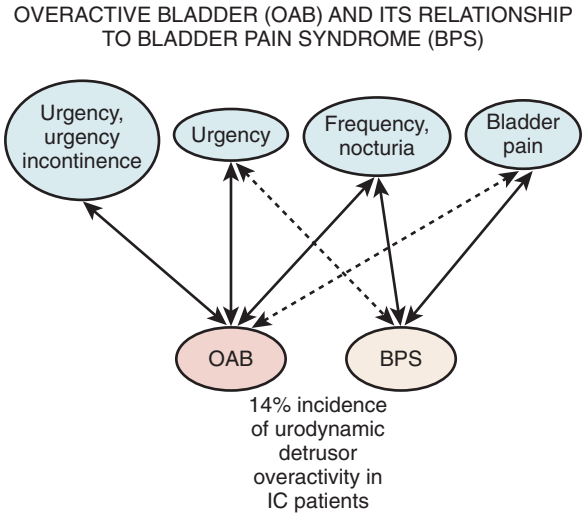


Figure 12–2. Overactive bladder (OAB) and its relationship to bladder pain syndrome (BPS). IC, interstitial cystitis. (From Abrams PH, Hanno PM, Wein AJ. Overactive bladder and painful bladder syndrome: there need not be confusion. Neurourol Urodyn 2005;24:149–50.)

as urologic, gynecologic, dermatologic, and the like, it is further categorized by organ system. A urologic pain syndrome can sometimes be further differentiated on the site of perceived pain. Bladder, prostate, testicular, and epididymal pain syndromes follow. Finally, types of BPS can be further defined as IC or simply categorized by ESSIC criteria. Patient groups have expressed their concerns with regard to any nomenclature change that potentially drops the term *interstitial cystitis* because the U.S. Social Security Administration and private insurances recognize IC but not the term BPS and benefits potentially could be adversely affected. Whether the term *interstitial cystitis,* as difficult as it is to define and as potentially misleading as it is with regard to etiology and end-organ involvement, should be maintained is a subject of ongoing controversy (Hanno and Dmochowski, 2009).

Key Points: Definition

- The *painful bladder disease complex* includes a large group of patients with bladder and/or urethral and/or pelvic pain, irritative voiding symptoms, and sterile urine cultures, many with specific identifiable causes.
- *Bladder pain syndrome* comprises a part of this complex and is a clinical diagnosis based primarily on chronic symptoms of pain perceived by the patient to emanate from the bladder and/or pelvis associated with urinary urgency/frequency *in the absence* of other identified etiology for the symptoms.
- The question as to whether the older term *interstitial cystitis* should refer to a distinct subgroup of the bladder pain syndrome is, as yet, unclear.

Urgency is a common complaint of this group of patients. **The ICS definition of urgency** (Abrams et al, 2002), "the complaint of a sudden compelling desire to pass urine, which is difficult to defer," **could be interpreted as compatible with either detrusor overactivity or BPS/IC depending on the weight one attaches to the word *sudden*.** There are those who see hypersensitivity or sensory urgency as bridging both overactive bladder and BPS/IC (Haylen et al, 2007; Yamaguchi et al, 2007), and the issue has been nicely addressed by Homma (2008). **Pain and pressure are more involved in the frequency of BPS/IC, and fear of incontinence seems the reason for the urgency of overactive bladder** (Abrams et al, 2005). Thus, urgency is not required to define BPS/IC, because it would tend to obfuscate the borders of overactive bladder and PBS/IC and is unnecessary for definition purposes. Figure 12–2 (Abrams et al, 2005) is a graphic depiction of one view of the relationship between these two, sometimes confused, conditions. The 14% incidence of urodynamic detrusor overactivity in the PBS/IC patients (Nigro et al, 1997) is probably close to what one might expect in the general population if studied urodynamically (Salavatore et al, 2003).

Still, there remains some ambiguity, and further research is necessary with regard to urgency. Studies are hampered by the fact that patients tend to use words to describe lower urinary tract symptoms but attribute meanings to the words different from physicians and researchers (Digesu et al, 2008). An analysis of urgency by the University of Maryland group reported that 65% of patients with BPS experienced an urge to urinate to relieve pain, with 46% agreeing that they had an urge to relieve pain and not to prevent incontinence. Still, 21% reported that urgency was for fear of impending incontinence and that this sensation was not present before the onset of BPS symptoms (Diggs et al, 2007). In some patients the term connotes an intensification of the normal urge to void, and in others it is a different sensation (Blaivas et al, 2009).

New efforts to phenotype the chronic urologic pain syndromes (BPS and chronic nonbacterial prostatitis/CPPS in men) are being explored (Nyberg et al, 2009; Shoskes et al, 2009a, 2009b). The hope is that looking at psychological, physical, and organ-specific parameters of afflicted patients, and specifically focusing on

Key Points: Urgency

- *Urgency* has been defined as the complaint of a sudden compelling desire to pass urine, which is difficult to defer.
- The cause the patient attributes to what precipitates the sensation is not a part of the definition and has resulted is some ambiguity. Fear of incontinence is more consistent with overactive bladder, whereas pressure, pain, or discomfort suggests bladder pain syndrome.

associated disorders, will aid in proper selection of therapeutic agents that may have selective specificity for different symptom constellations and also may improve productivity and results of research on etiology, prognosis, and new therapeutic agents.

EPIDEMIOLOGY

Prevalence

Epidemiology studies of PBS/IC are hampered by many problems (Bernardini et al, 1999). The lack of an accepted definition, the absence of a validated diagnostic marker, and questions regarding etiology and pathophysiology make much of the literature difficult to interpret. This is most apparent when one looks at the variation in **prevalence reports** in the United States and around the world (Table 12–5). These **range from 1.2 per 100,000 population and 4.5 per 100,000 females in Japan** (Ito et al, 2000), **to a questionnaire-based study that suggests a figure in American women of 20,000 per 100,000** (Parsons and Tatsis, 2004)!

It has been estimated that the prevalence of chronic pain due to benign causes in the population is at least 10% (Verhaak et al, 1998). Numerous case series have, until recently, formed the basis of epidemiologic information regarding PBS/IC. Farkas and associates (1977) discussed IC in adolescent girls. Hanash and Pool (1969) reviewed their experience with IC in men. Geist and Antolak (1970) reviewed and added to reports of disease occurring in childhood. **A childhood presentation is extremely rare and must be differentiated from the much more common and benign-behaving *extraordinary urinary frequency syndrome of childhood,*** a self-limited condition of unknown etiology (Koff and Byard, 1988; Robson and Leung, 1993). Nevertheless there is a small cohort of children with chronic symptoms of bladder pain, urinary frequency, and sensory urgency in the absence of infection who have been evaluated with urodynamics, cystoscopy, and bladder distention and have findings consistent with the diagnosis of PBS/IC. In Close and colleagues' review of 20 such children (1996) the median age at **onset was younger than 5 years and the vast majority of patients had long-term remissions with bladder distention.**

A study conducted at the Scripps Research Institute (Koziol et al, 1993) included 374 patients at Scripps as well as some members of the Interstitial Cystitis Association, the large patient support organization. A more recent, but similar study in England (Tincello and Walker, 2005) concurred with the Scripps findings of urgency, frequency, and pain in the vast majority of these patients, devastating effects on quality of life, and often unsuccessful attempts at therapy with a variety of treatments. Although such reviews provide some information, they would seem to be necessarily biased by virtue of their design.

Several population-based studies have been reported in the literature (Fig. 12–3), and these studies tend to support the reviews of selected patients or from individual clinics and the comprehensive follow-up case-control study by Koziol (1994). The first population-based study (Oravisto, 1975) included "almost all the patients with interstitial cystitis in the city of Helsinki." This superb, brief report from Finland surveyed all diagnosed cases in a population approaching 1 million. The prevalence of the disease in women was 18.1 per 100,000. The joint prevalence in both sexes was 10.6 cases per 100,000. The annual incidence of new female cases was 1.2 per 100,000. Severe cases accounted for about 10% of the total. Ten percent of cases were in men. The disease onset was generally subacute rather than insidious, and full development of the classic symptom-complex occurred over a relatively short time. IC does not progress continuously but usually reaches its final stage rapidly (within 5 years) in the Koziol study (1993) and then continues without significant change in symptomatology. Subsequent major deterioration was found by Oravisto to be unusual. The duration of symptoms before diagnosis was 3 to 5 years in the Finnish study. Analogous figures in a classic American paper a quarter of a century earlier were 7 to 12 years (Hand, 1949).

Another early population study, this one in the United States, first demonstrated the potential extent of what had been considered a very rare disease (Held et al, 1990). The following population groups were surveyed: (1) random survey of 127 board-certified urologists, (2) 64 IC patients selected by the surveyed urologists and divided between the last patient with IC seen and the last patient with IC diagnosed, (3) 904 female patients belonging to the Interstitial Cystitis Association, and (4) random phone survey of 119 persons from the U.S. population. This 1987 study reached the following conclusions:

1. There were 43,500 to 90,000 diagnosed cases of IC in the United States (twice the Finnish prevalence).
2. There was up to a fivefold increase in IC prevalence if all patients with painful bladder and sterile urine had been given the diagnosis, yielding up to half million possible cases in the United States.

Table 12–5.

Prevalence of BPS/IC per 100,000 Women

STUDY	PREVALENCE
Oravisto, 1975 (Finland)	18
Jones, 1989 (USA)	500
Held et al, 1990 (USA)	30
Bade et al, 1995 (Netherlands)	12
Curhan et al, 1999 (USA)	60
Ito et al, 2000 (Japan)	4.5
Roberts et al, 2003 (USA)	1.6
Leppilahti et al, 2005 (Finland)	300
Clemens, 2007b (USA)	197
Temml et al, 2007 (Austria)	306
Song et al, 2009 (China)	100
Berry et al, 2009 (USA)	2600

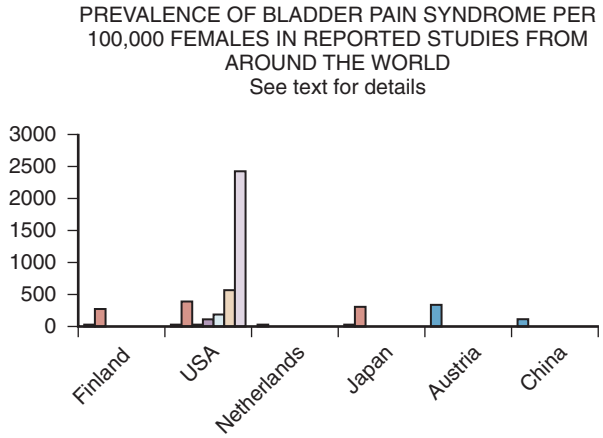


Figure 12–3. Prevalence of bladder pain syndrome per 100,000 females in reported studies from around the world. See text for details.

3. Median age at onset was 40 years.
4. Late deterioration in symptoms was unusual.
5. The temporary spontaneous remission rate was 50%, with mean duration of 8 months.
6. There was a 10 times higher incidence of childhood bladder problems in IC patients versus controls.
7. There was twice the incidence of a history of urinary tract infection versus controls.
8. Of IC patients 14% were Jewish (15% in the Koziol [1994] sample) versus 3% Jewish in a general population sample.
9. The study patients had a lower quality of life than dialysis patients.
10. Costs including lost economic production in 1987 totaled $427 million.

Other population studies followed. Jones and Nyberg (1997) obtained their data from self-report of a previous diagnosis of IC in the 1989 National Household Interview Survey. The survey estimated that 0.5% of the population, or more than 1 million people in the United States, reported having a diagnosis of IC. There was no verification of this self-report by medical records. Bade and colleagues (1995) did a physician questionnaire-based survey in the Netherlands yielding an overall prevalence of 8 to 16/100,000 females, with diagnosis heavily dependent on pathology and presence of mast cells. This prevalence in females compares to 4.5/100,000 in Japan (Ito et al, 2000).

The Nurses Health Study I and II (Curhan et al, 1999) showed a prevalence of IC between 52 and 67/100,000 in the United States, which was twice the prevalence in the study by Held and associates (1990) and threefold greater than the study by Bade and colleagues (1995) in The Netherlands. It improved on previous studies by using a large sample derived from a general population and careful ascertainment of the diagnosis. If the 6.4% confirmation rate of their study were applied to the Jones and colleagues' National Health Interview Survey data, the prevalence estimates of the two studies would be nearly identical.

Leppilahti and coworkers (2002, 2005) used the O'Leary-Sant IC symptom and problem index (never validated for making a diagnosis per se) to select women with IC symptoms from the Finnish population register. Of 1331 respondents, 32 had moderate or severe symptoms involving a suspicion of BPS/IC (symptom score 7 or higher). Of 21 who consented to clinical evaluation, 7 had probable or possible BPS/IC. Corrected estimates yielded a prevalence of 300/100,000 women. Similar studies without clinical confirmation suggested prevalence in Austrian women of 306/100,000 (Temml et al, 2007) and in Japanese women of 265/100,000 (Inoue et al, 2009). Using the Bristol Female Lower Urinary Tract Symptoms questionnaire, a 100/100,000 prevalence of BPS symptoms was reported in Fuzhou Chinese women (Song et al, 2009).

Roberts and coworkers (2003), using a physician diagnosis as the arbiter of IC, found annual incidence in Olmsted County, Minnesota, of 1.6 per 100,000 in women and 0.6 per 100,000 in men, a figure remarkably similar to that of Oravisto in Helsinki. The cumulative prevalence by age older than 80 years in the Minnesota study was 114 per 100,000, a figure comparable to that in the Nurses Health Study if one takes into account the younger age group in the Curhan data. Clemens and colleagues (2007b) calculated a prevalence of diagnosed disease in a managed care population of 197 per 100,000 women and 41 per 100,000 men, but when the diagnosis was tested by eliminating those who had not been evaluated with endoscopy or in whom exclusionary conditions existed, the numbers dropped considerably. The Boston Area Community Health Survey estimated a prevalence of painful bladder syndrome symptoms of 1% to 2% of the population depending on the definition used.

Looking at office visits to practices with an interest in urologic problems, 2.8% of patients in Canadian urologist offices had BPS/IC (Nickel et al, 2005) and probable BPS/IC was found in 0.57% in a primary care office in Michigan (Rosenberg and Hazzard, 2005).

An estimation of the prevalence at this time, recognizing that a consistent definition of the condition has not been used in epidemiologic studies, appears to be about 300/100,000 females and a male prevalence of 10% to 20% of the female estimate. A National Institutes of Health (NIH)-sponsored 5-year Rand Corporation epidemiology study is due to be completed in 2010 and may yield the most reliable data yet (Bogart et al, 2007). **Preliminary results reported at the annual American Urological Association meeting revealed that 2.5% to 2.7% of the population of U.S. women meet a high specificity symptom definition suggesting BPS/IC.** With the use of an epidemiologic definition with higher sensitivity, the prevalence was 6.5%. This translates to a prevalence in women older than 18 years of age in the United States who have symptoms by self-report compatible with BPS/IC of 3.4 to 7.9 million, significantly higher than most previous prevalence estimates (Berry et al, 2009).

Whether the considerable variability in prevalence in studies within the United States and around the world is related to methodology or true differences in incidence is an important question yet to be answered. It is clear that the prevalence of BPS/IC symptoms is much greater than the prevalence of a physician diagnosis of the disease (Clemens et al, 2007a). Familial occurrence of PBS/IC has been reported (Dimitrakov, 2001). **A hereditary aspect to incidence has been suggested** by Warren and associates (2001, 2004) in a pioneering study who found that adult female first-degree relatives of patients with IC may have a prevalence of IC 17 times that found in the general population. This, together with previously reported evidence showing a greater concordance of IC among monozygotic than dizygotic twins suggests, but does not prove, a genetic susceptibility to IC that could partially explain the discord in prevalence rates in different populations.

Key Point: Prevalence

- Prevalence studies show wide variation, but more modern studies tend to show higher values (see Table 12–5).

Characteristics and Natural History

Most studies show a female-to-male preponderance of 5:1 or greater (Clemens et al, 2005; Hanno et al, 2005a). In the absence of a validated marker it is often difficult to distinguish PBS/IC from CPPS (nonbacterial prostatitis, prostatodynia) that affects males (Forrest and Schmidt, 2004), and the percentage of men with PBS/IC may actually be higher (Miller et al, 1995, 1997; Novicki et al, 1998). **Men tend to be diagnosed at an older age and have a higher percentage of Hunner ulcer in the case series reported** (Novicki et al, 1998; Roberts et al, 2003). Costs of the disorder are not insignificant and can range from 4 to 7 thousand dollars a year not including lost wages, costs preceding diagnosis, alternative therapies, and costs attributable to misdiagnosis (Clemens et al, 2008c, 2009).

The Interstitial Cystitis Database Cohort (ICDB) of patients has been carefully studied, and the findings seem to bear out those of other epidemiologic surveys (Propert et al, 2000). Patterns of change in symptoms with time suggest regression to the mean and an intervention effect associated with the increased follow-up and care of cohort participants. **Although all symptoms fluctuated there was no evidence of significant long-term change in overall disease severity. The data suggest that PBS/IC is a chronic disease, and no current treatments have a significant impact on symptoms over time in the majority of patients. Quality of life studies suggest that PBS/IC patients are six times more likely than individuals in the general population to cut down on work time owing to health problems but only half as likely to do so as patients with arthritis** (Shea-O'Malley and Sant, 1999). There is an associated high incidence of comorbidity, including depression, chronic pain, and anxiety and overall mental health issues (Michael et al, 2000; Rothrock et al, 2002; Hanno et al, 2005a). **There seems to be no effect on pregnancy outcomes** (Onwude and Selo-Ojeme, 2003).

Female patients with BPS/IC seem to report significant dyspareunia and other manifestations of sexual dysfunction. **All domains of female sexual function including sexually related distress, desire, and orgasm frequency can be affected** (Ottem et al, 2007; Peters et al, 2007b). Sexual function is an important predictor of physical quality of life and was the only strong predictor of mental quality of life in one recent study of patients with severe BPS/IC (Nickel et al, 2007).

The Boston Area Community Health Survey (BACH) (Link et al, 2008) **showed an overall prevalence of symptoms suggestive of BPS of 2% with twice as many women as men affected.** It was most common among middle-aged respondents with an earlier peak in women. It also was most common among minorities and those of lower socioeconomic status, and socioeconomic status seemed to overcome any effect due to race or ethnicity. **Emotional, sexual, and physical abuse was shown to be a risk factor in BACH** (Link and Lutfey, 2007), and this has been borne out in other studies. A Michigan study compared a control group of 464 women with 215 BPS/IC patients and found 22% of the control group having experienced abuse versus 37% of the patient group (Peters and Kalinowski, 2007). Those with a history of sexual abuse may present with more pain and fewer voiding symptoms (Seth and Teichman, 2008). How reliable these data are is not clear, and it would be wrong to jump to any conclusions about abuse in an individual patient. However, practitioners need to have sensitivity for the possibility of an abusive relationship history in all pain patients and in BPS patients in particular. When patients are found to have multiple diagnoses, the rate of previous abuse also increases, and these patients may need referral for further counseling at a traumatic stress center (Fenton et al, 2008).

Key Points: Natural History

- The female to male preponderance is 5:1.
- Symptoms tend to fluctuate, with the majority of patients showing no long-term deterioration.
- There is no deleterious effect on pregnancy outcomes.
- Men are diagnosed at an older age and have a higher prevalence of a Hunner lesion.

Associated Disorders

Knowledge of associated diseases is relevant for the clues it engenders with regard to etiology and possible treatment of this enigmatic pain syndrome. It is well known that patients with chronic pain syndromes including chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder share key symptoms and can often develop overlapping conditions, including chronic pelvic pain (Aaron and Buchwald 2001; Aaron et al, 2001). In a case-control study Erickson found that **patients with IC had higher scores than controls for pelvic discomfort, backache, dizziness, chest pain, aches in joints, abdominal cramps, nausea, palpitations, and headache** (Erickson et al, 2001). Buffington theorizes that a common stress response pattern of increased sympathetic nervous system function in the absence of comparable activation of the hypothalamic-pituitary-adrenal axis may account for some of these related symptoms (Buffington, 2004). It has been suggested that panic disorder, a diagnosis associated with some BPS/IC patients (Clemens et al, 2008a), may sometimes be a part of a familial syndrome that includes IC, thyroid disorders, and other disorders of possible autonomic or neuromuscular control (Weissman et al, 2004). **Depression** has been associated with BPS/IC in both men and women (Hall et al, 2008; Clemens et al, 2008a), but whether this is an association or effect of the disorder is uncertain (Fitzgerald et al, 2007).

Newly diagnosed patients are most concerned with the possibility that BPS/IC could be a forerunner of bladder carcinoma. **No reports have ever documented a relationship to suggest that IC is a premalignant lesion.** Utz and Zincke (1973) discovered bladder cancer in 12 of 53 men treated for IC at the Mayo Clinic. Three of 224 women were eventually diagnosed with bladder cancer. Four years later additional cases were reported (Lamm and Gittes, 1977). Tissot and coworkers (2004) reported 1% of 600 patients previously diagnosed as having IC were found to have transitional cell carcinoma as the cause of symptoms. Somewhat ominously, 2 of these patients had no hematuria. In all patients, irritative symptoms resolved after treatment of the malignancy. From this experience has come the dictum that all patients with presumed IC should undergo cystoscopy, urine cytology, and bladder biopsy of any suspicious lesion to be sure that a bladder carcinoma is not masquerading as BPS/IC. It would seem that **in the absence of microhematuria, and with a negative cytology, the risk of missing a cancer is negligible but not zero. There is no evidence that BPS/IC itself is associated with a higher risk of bladder cancer or transitions to cancer over time** (Murphy et al, 1982).

A large-scale survey of 6783 individuals diagnosed by their physicians as having IC studied the incidence of associated disease in this population (Alagiri et al, 1997). Data from the 2405 responders was validated by comparison with 277 nonresponders (Fig. 12–4). **Allergies** were the most common association, with over 40% affected. Allergy was also the primary association in Hand's study (Hand, 1949). Thirty percent of patients had a diagnosis of **irritable bowel syndrome,** a finding confirming that of Koziol (1994). Altered visceral sensation has been implicated in irritable bowel syndrome in that these patients experience intestinal pain at intestinal gas volumes that are lower than those that cause pain in healthy persons (Lynn and Friedman, 1993), strikingly similar to the pain on bladder distention in IC.

Fibromyalgia, another disorder frequently considered functional because no specific structural or biochemical cause has been found, is also overrepresented in the BPS/IC population. This is a

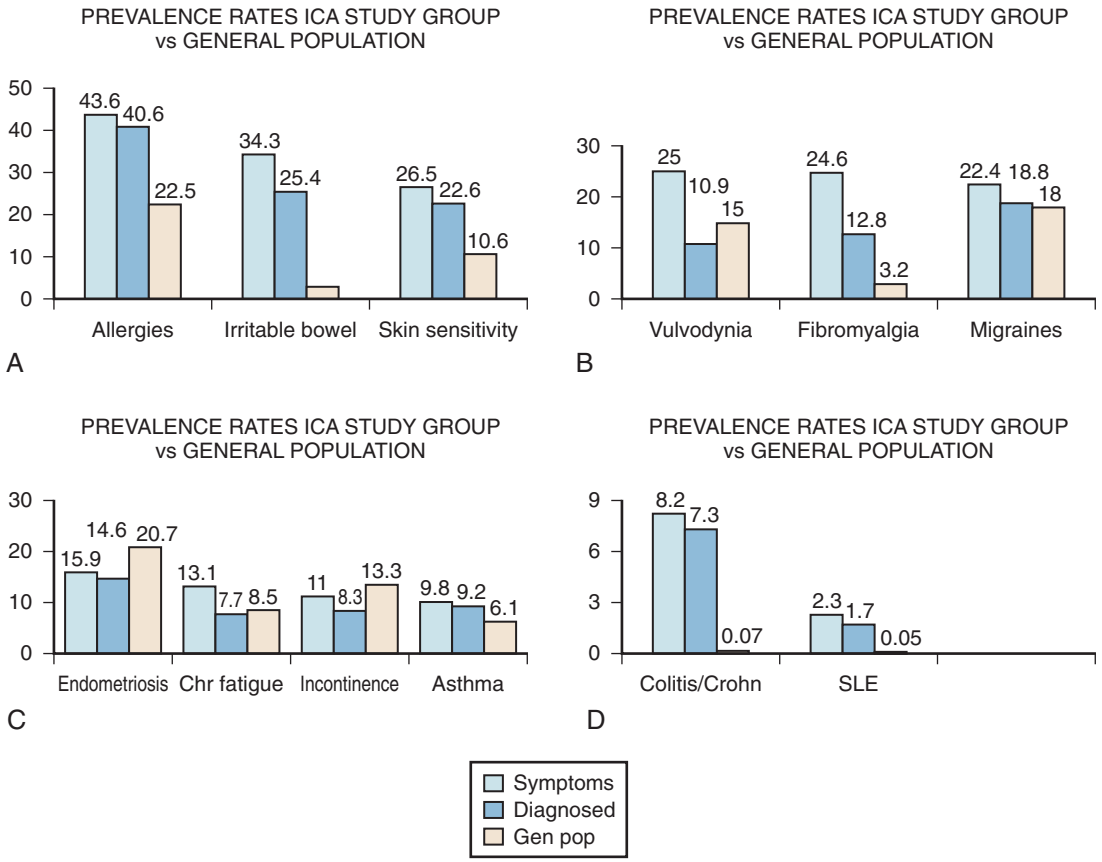


Figure 12–4. Comparison of disease prevalence rates between the Interstitial Cystitis Association (ICA) study group patients who report symptoms of a disorder, those who have been diagnosed with a disorder, and the general population. SLE, systemic lupus erythematosus. (From Alagiri M, Chottiner S, Ratner V, et al. Interstitial cystitis: unexplained associates with other chronic pain syndromes. Urology 1997;49[Suppl 5A]:52–7.)

painful, nonarticular condition predominantly involving muscles; it is the most common cause of chronic, widespread musculoskeletal pain. It is typically associated with persistent fatigue, nonrefreshing sleep, and generalized stiffness. As in BPS/IC, women are affected at least 10 times more often than men (Consensus document on fibromyalgia, 1993). The association is intriguing because both conditions have nearly identical demographic features, modulating factors, associated symptoms, and response to tricyclic antidepressants (Clauw et al, 1997).

Diagnosed **vulvodynia, migraine headaches, endometriosis, chronic fatigue syndrome, incontinence, and asthma had similar prevalence as in the general population.** Several publications have noted an association between BPS/IC and systemic lupus erythematosus (SLE) (Fister, 1938; Boye et al, 1979; De la Serna and Alarçon-Segovia, 1981; Weisman et al, 1981; Meulders et al, 1992). The question has always been as to whether the bladder symptoms represent an association of these two disease processes or rather are a manifestation of lupus involvement of the bladder (Yukawa et al, 2008) or even a myelopathy with involvement of the sacral cord in a small group of these patients (Sakakibara et al, 2003). The beneficial response of the cystitis of systemic lupus erythematosus to corticosteroids (Meulders et al, 1992) tends to support the latter view. No association with discoid lupus has been demonstrated (Jokinen et al, 1972b). Although the actual numbers are small, the Alagiri study demonstrated a 30 to 50 times greater incidence of systemic lupus erythematosus in the IC group compared with the general population. Overall, the incidence of collagen vascular disease in the IC population is low. Parsons (1990) found only 2 of 225 consecutive IC patients to have a history of an autoimmune disorder.

Inflammatory bowel disease was found in over 7% of the IC population Alagiri studied, a figure 100 times higher than in the general population. Although unexplained at this time, abnormal leukocyte activity has been implicated in both conditions (Bhone et al, 1962; Kontras et al, 1971).

The University of Maryland group sought antecedent nonbladder syndromes in 313 patients with incident BPS/IC and compared them to 313 matched controls (Warren et al, 2009). They found 11 antecedent syndromes were more often diagnosed in those with BPS/IC, and most syndromes appeared in clusters. The **most prominent cluster (45%) comprised fibromyalgia—chronic widespread pain, chronic fatigue syndrome, sicca syndrome, and/or irritable bowel syndrome.** Most of the other syndromes and identified clusters were associated with it. They found probable chronic fatigue syndrome in 20% of BPS/IC patients, probable fibromyalgia in 22%, and probable irritable bowel in 27% of the BPS patients. Far fewer had physician reported diagnoses of these syndromes, and odds ratios (OR) for BPS/IC versus controls were 2.5 to 2.9. Study of a managed care database in Portland Oregon revealed that patients coded for gastritis (OR = 12.2), child abuse (OR = 9.3), fibromyalgia (OR = 3.0), anxiety disorder (OR = 2.8), headache (OR = 2.5), and depression (OR = 2.0) were commonly diagnosed with BPS/IC (Clemens et al, 2008b).

A mysterious disorder that has been associated with IC is focal vulvitis. Vulvar vestibulitis syndrome is a

constellation of symptoms and findings involving and limited to the vulvar vestibule consisting of (1) severe pain on vestibular touch to attempted vaginal entry, (2) tenderness to pressure localized within the vulvar vestibule, and (3) physical findings confined to vulvar erythema of various degrees (Marinoff and Turner, 1991). McCormack (1990) reported on 36 patients with focal vulvitis, 11 of whom also had IC. Fitzpatrick and coworkers (1993) has added three more cases. The concordance of these noninfectious inflammatory syndromes involving the tissues derived from the embryonic urogenital sinus and the similarity of the demographics argue for a common etiology.

An association has been reported between IC and **Sjögren syndrome,** an autoimmune exocrinopathy with a female preponderance manifested by dry eyes, dry mouth, and arthritis but that can also include fever, dryness, and gastrointestinal and lung problems. Van de Merwe and colleagues (1993) investigated 10 IC patients for the presence of Sjögren syndrome. Two patients had both the keratoconjunctivitis sicca and focal lymphocytic sialoadenitis allowing a primary diagnosis of Sjögren syndrome. Only 2 patients had neither finding. These researchers later (2003) reported an incidence of 28% of Sjögren syndrome in patients with IC. The incidence of symptoms of PBS/IC in patients with Sjögren syndrome has been estimated to be up to 5% (Leppilahti et al, 2003).

A negative correlation with diabetes has been noted (Parsons, 1990; Koziol, 1994; Warren et al, 2009).

Further epidemiologic studies are warranted because the epidemiology of this disorder may ultimately yield as many clues to etiology and treatment as other avenues of research. The heterogeneity of causes and symptoms of CPPS suggests that proper clinical phenotyping could foster the development of better treatments for individual phenotypes and more successful treatments for all afflicted patients (Baranowski et al, 2008; Shoskes et al, 2009b).

Key Points: Associated Disorders

- Look for symptoms of the following disorders, which may be associated with some cases of BPS: depression, Sjögren syndrome, irritable bowel syndrome, allergies, fibromyalgia, chronic fatigue syndrome, inflammatory bowel disease, and focal vulvitis.
- No reports have ever documents a relationship to suggest that BPS is a premalignant condition.

ETIOLOGY

It is likely that PBS/IC has a multifactorial etiology that may act predominantly through one or more pathways resulting in the typical symptom-complex (Holm-Bentzen et al, 1990; Mulholland and Byrne, 1994; Erickson 1999; Levander, 2003; Keay et al, 2004b) (Fig. 12–5). There are numerous theories regarding its pathogenesis, but confirmatory evidence gleaned from clinical practice has proven sparse. Among numerous **proposals** that shall be further explored in this section are **"leaky epithelium," mast cell activation,** and **neurogenic inflammation,** or **some combination** of these and other **factors leading to a self-perpetuating process resulting in chronic bladder pain and voiding dysfunction** (Elbadawi, 1997). Irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, and various other chronic pain disorders may precede or follow the development of BPS/IC in some patients, but development of associated syndromes is not inevitable by any means, and their relationship to etiology is currently unknown (Warren et al, 2009; Nickel et al, 2010).

Animal Models

The problem with animal models is how accurately they mirror the human situation. A section on animal models appears in the electronic edition along with Figure 12–6 (see the Expert Consult website).

Infection

Often, a diagnosis of BPS/IC is made only after a patient has been seen by a number of physicians and treated with antibiotics for presumed urinary tract infection without resolution of symptoms (Held et al, 1990). The symptom-complex looks to the patient and physician like an infectious process (Porru et al, 2004). The epidemiology of urinary tract infection and its predominance in women mirror the BPS/IC data (Warren, 1994). The acute to subacute onset in many patients has fascinated clinicians who often associate an insidious onset with a chronic condition such as PBS/IC.

Reverse logic led some to suspect that antibiotics may be instrumental in causing IC (Holm-Bentzen et al, 1990). Most patients have been treated with antibiotics once or several times before the diagnosis is made. Numerous antibiotics, primarily in the penicillin family, can induce a cystitis (Bracis et al, 1977; Moller, 1978; Chudwin et al, 1979; Cook et al, 1979; Marx and Alpert, 1984), but no evidence has ever been documented that these antibiotics or the supposedly "surface active" nitrofurantoins or tetracyclines have any involvement in pathogenesis of IC (Ruggieri et al, 1987; Levin et al, 1988).

To determine whether there is an infectious cause of BPS certain procedures are necessary (Warren, 1994). Not just urine but bladder epithelium as well must be cultured for appropriate microorganisms, including bacteria, viruses, and fungi. Because some organisms might be culturable yet fastidious, special culture techniques should be used. Because some organisms in urine or tissue might be viable but nonculturable, specific nonculture techniques for discovery and identification should be employed. Most important, the same procedures must be carried out in a control population.

Attempts to show an infectious etiology go back to the dawn of the disease, but **the case has never been a strong one** (Duncan and Schaeffer, 1997). Hunner (1915) originally proposed that IC resulted from chronic bacterial infection of the bladder wall secondary to hematogenous dissemination. Harn and associates (1973) proposed a relationship between IC and streptococcal and post-streptococcal inflammation. They produced a progressive chronic inflammation in rabbit bladders by injecting small numbers of *Streptococcus pyogenes* in the bladder wall. The discovery that *Helicobacter pylori* is related to the pathogenesis of chronic atrophic gastritis and peptic ulcer disease and that antibiotic treatment can heal ulceration (Parsonnet et al, 1991; National Institutes of Health, Consensus Development Panel, 1994; Sung et al, 1995) has continued to focus attention of researchers in IC on the possibility that an infectious etiology is not only reasonable but will ultimately be found. Studies of *H. pylori* itself have failed to demonstrate an association with IC (English et al, 1998; Agarwal and Dixon 2003; Atug et al, 2004; Haq et al, 2004). Wilkins and colleagues (1989) found bacteria in catheterized urine specimens and/or bladder biopsy specimens in 12 of 20 patients with IC.

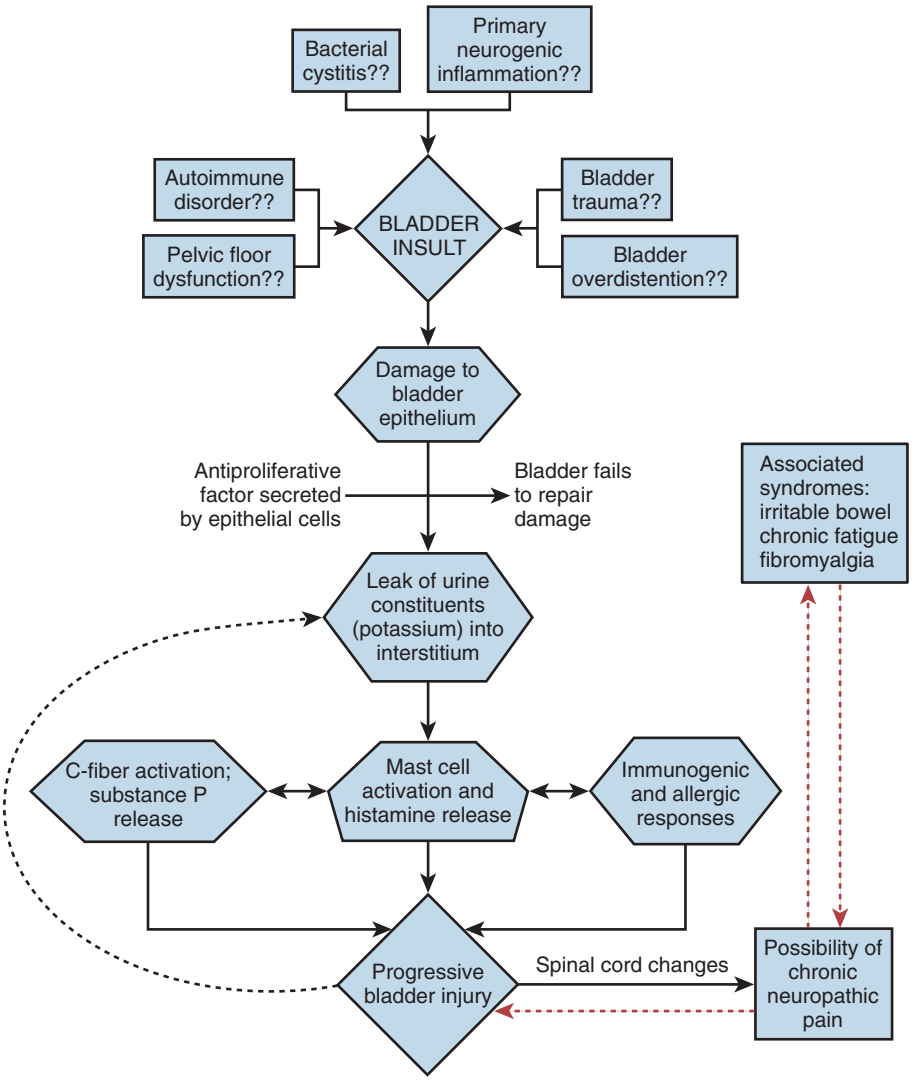


Figure 12–5. Hypothesis of etiologic cascade of bladder pain syndrome. (From Hanno P, Lin AT, Nordling J, et al. Bladder pain syndrome. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence. Paris: Health Publication Ltd.; 2009. p. 1459–518.)

However, 8 of the isolates were fastidious bacteria, *Gardnerella vaginalis,* and *Lactobacillus* species and no controls were included in the study. Polyomaviruses have been reported to cause a BPS/IC-like syndrome that responds to cidofovir treatment (Eisen et al, 2009). These viruses are excreted intermittently in the urine of healthy, asymptomatic adults, making diagnosis of a true infection problematic.

Negative studies far outnumber the positive ones. Hanash and Pool (1970) performed viral, bacterial, and fungal studies on 30 IC patients and failed to substantiate an infectious cause. Hedelin and coworkers (1983) found only 3 of 19 IC patients to have urine cultures positive for *Ureaplasma urealyticum* and indirect hemagglutination antibodies to *Mycoplasma hominis* to be no greater than in controls. Potts and colleagues (2000) cultured *U. urealyticum* in 22 of 48 patients with "chronic urinary symptoms" and had great success in these patients (none of whom had established IC) with short courses of commonly prescribed antibiotics. Given the history of empirical use of antibiotics in the vast majority of IC patients, it is doubtful if this group represents even a small percentage of the IC diagnosed population. Nevertheless it illustrates that BPS/IC is a diagnosis of exclusion and that the urine culture is critical whereas an empirical short course of antibiotics is certainly reasonable if the patient has not already been treated for presumed infection. Empirical use of doxycycline has been successful in this situation (Burkhard et al, 2004).

The development of highly sensitive, rapid, and specific molecular methods of identifying infectious agents by the direct detection of DNA or RNA sequences unique to a particular organism (Naber, 1994) resulted in a flurry of activity into the search for a responsible virus or microorganism. Hampson and associates (1993) could find no evidence of mycobacterial involvement in 8 cases of BPS/IC using DNA probes. Haarala and colleagues (1996) confirmed an absence of bacterial DNA in the bladder of 11 BPS/IC patients with no documented history of urinary tract infection. Hukkanen and associates (1996) reported an absence of adenovirus and BK virus genomes in urinary bladder biopsy specimens of IC patients. Domingue and coworkers' (1995) provocative finding of the presence of bacterial 16S rRNA genes in bladder biopsy specimens from 29% of IC patients but not from control bladders, and his discovery of 0.22-μm filterable forms in culture of biopsy tissue from 14 of 14 IC patients and none of 15 controls has never been confirmed or repeated.

A preliminary study found a statistically significant increase in urine polymerase chain reaction studies to *Chlamydia pneumoniae* major outer membrane protein gene in patients with BPS/IC as compared with controls (Franke et al, 1999). Other studies have shown that similar percentages of both IC and control patient populations have nonculturable bacteria in their bladder on the basis of polymerase chain reaction studies of bladder biopsy specimens (Heritz et al, 1997; Keay et al, 1998a). The spirochete *Borrelia*

burgdorferi has been found in the bladder biopsy specimens and urine of patients with Lyme disease and can cause frequency, urgency, and nocturia. DNA studies have failed to show a role for *Borrelia* in IC (Haarala et al, 2000).

The role of infection in the pathogenesis of BPS/IC remains a mystery. **At this time there are little data to support the role of an infectious etiology** but investigators keep returning to an infectious theory. New insights into the mechanisms by which bacteria adhere, grow, and persist in association with host tissue and form intracellular pods capable of subverting host defense mechanisms and allowing replication within epithelial cells lay the foundation for a possible role of infection in initiating the BPS/IC pathologic cascade (Kau et al, 2005). The University of Maryland group proposes a model of BPS in which bladder epithelial damage such as that caused by bacterial cystitis may be the first step leading to a low-level inflammatory response we call BPS/IC (Keay and Warren, 1998). Domingue writes that "It is logical to suggest that even if organisms are not causative agents, their presence may lead to immune and host-cell responses that could initiate or exacerbate an inflammatory state" (Domingue and Ghoniem, 1997).

If infection does play a role it would be predicted that appropriate treatments to minimize microbial presence in the tissue would significantly improve the morbidity associated with BPS/IC. Durier's incredible series (1992) purporting to cure 27 of 27 IC patients with the use of up to five sequential antibiotics covering the anaerobic spectrum has never been duplicated. Warren and associates' (2000) prospective, double-blind, placebo-controlled, randomized trial of 50 patients may well prove the end of long-term empirical antibiotic treatment in established BPS/IC. Either a placebo or antibiotics (sequential doxycycline, erythromycin, metronidazole, clindamycin, amoxicillin, and ciprofloxacin for 3 weeks each) were administered for 18 weeks. Most patients guessed the arm to which they were assigned. Of the 25 patients in the active arm, 80% had new nonurinary symptoms perceived as side effects. There was minimal improvement in some patients associated with the active arm of the study, but the conclusion that intensive antibiotics do not represent a major advance in therapy for IC seems well justified.

Although the concept that a urinary tract infection may trigger BPS in some patients is appealing (Elgavish et al, 1995; Elbadawi, 1997), **it is unlikely that active infection is involved in the ongoing pathologic process or that antibiotics have a role to play in treatment.**

Autoimmunity/Inflammation

Immune/neuroimmune mechanisms may have an important role in the pathogenesis of BPS/IC. Excessive release of sensory nerve neurotransmitters and mast cell inflammatory mediators is thought by some to be responsible for the development and propagation of symptoms (Luo, 2005). Inflammation results in altered nerve growth factor content of the bladder and in morphologic changes in sensory and motor neurons innervating the bladder. Such neuroplasticity may be a possible explanation for the association of bladder inflammation with long-term symptoms and pain after inflammation subsides (Dupont et al, 2001). Up to one third of BPS/IC patients may have an acute urinary tract infection that immediately precedes the onset of chronic symptoms (Warren et al, 2008). However, abnormal differentiation in the urothelium with a loss of barrier function markers and altered differentiation markers may be independent and occur independently of inflammation (Hauser et al, 2008).

The role of inflammation may stem from inflammation originating in organs other than the bladder. Pain syndromes such as irritable bowel syndrome and BPS, which are associated with visceral hyperalgesia, are often comorbid with endometriosis and chronic pelvic pain. One of the possible explanations for this phenomenon is viscerovisceral cross-sensitization, in which increased nociceptive input from an inflamed pelvic organ sensitizes neurons that receive convergent input to the same dorsal root ganglion (DRG) from an unaffected visceral organ. Visceral sensory integration in the dorsal root ganglia has been demonstrated in a rodent model and may underlie the observed comorbidity of female pelvic pain syndromes (Li et al, 2008).

For many years the possibility that BPS may represent some type of autoimmune disorder has been considered. Narrowly defined, autoimmune diseases are clinical syndromes caused by the activation of T cells or B cells, or both, in the absence of an ongoing infection or other discernible cause (Davidson and Diamond, 2001). To establish a disease as autoimmune, three types of evidence can be considered: (1) direct evidence from transfer of pathogenic antibody or pathogenic T cells; (2) indirect evidence based on reproduction of the autoimmune disease in experimental animals; and (3) circumstantial evidence from clinical clues (Rose and Bona, 1993). Circumstantial evidence would include (1) association with other autoimmune diseases in the same individual or same family; (2) lymphocytic infiltration of target organ; (3) statistical association with a particular major histocompatibility complex haplotype; and (4) favorable response to immunosuppression.

Circumstantial evidence by itself cannot define an autoimmune disease, and **at this point the case for autoimmunity in BPS/IC is far from clear.** Three different possibilities exist: (1) BPS is caused by a direct autoimmune attack on the bladder, (2) some of the autoimmune symptoms and pathology of BPS arise indirectly as a result of tissue destruction and inflammation from other causes, and (3) autoimmune phenomena in BPS patients are coincident and unrelated to the disease (Ochs, 1997).

Silk (1970) found bladder antibodies in 9 of 20 IC patients and none in 35 pathologic or normal control patients. Gordon and associates (1973) found antibladder antibodies present in biopsy specimens from 6 of 8 IC patients and in 3 of 5 control patients. No control patient demonstrated antibodies in the muscle, whereas 3 of 5 IC patients with muscle in the biopsy did so. Jokinen and colleagues (1972a) looked at sera from 33 IC patients and found 28 with an antinuclear antibody titer of 1:10 or greater, but no bladder-specific antibodies were detected with immunofluorescence. There was poor correlation between antinuclear antibody titers and symptom severity. These researchers noted in a later study (Jokinen et al, 1973) that elevated antibody titers against cell nuclei and crude kidney homogenate decreased within 12 months after cystectomy in 3 IC patients. All of this provided hints that BPS/IC could fall into the autoimmune group of diseases.

Oravisto (1980) summarized the world literature on this idea in 1980, concluding that the chronic course of disease, the absence of infection, the pathologic findings, the occurrence of antinuclear antibodies, and the reported responses to corticosteroids at that time provided strong circumstantial evidence of autoimmunity. He discounted the paucity of activated lymphocytes that speak against an autoimmune process. Studies on autoantibodies in BPS/IC have shown that these mainly consist of antinuclear antibodies (Jokinen et al, 1972a) similar to the autoantibody profiles in some systemic diseases such as Sjögren syndrome, which is well known to be of autoimmune origin (Tan, 1989; Leppilahti et al, 2003). Mattila (1982) presented evidence of

immune deposits in the bladder vascular walls in 33 of 47 BPS/IC patients. Studying sera from 41 patients with IC, he concluded that the classical pathway activation of the complement system was involved, supporting the possibility that a chronic local immunologic process was indeed occurring (Mattila et al, 1983). The autoantibodies tested were found to be directed against cytoskeletal intermediate filaments. Because the autoantibodies have to gain access to intracellular structures to cause in-vivo deposits, primary tissue injury of unknown etiology has to be postulated (Mattila and Linder, 1984).

Anderson and colleagues (1989) studied 26 patients with BPS/IC and compared them to a control group of similar age and sex with other urologic complaints. They performed a standard autoimmune profile and looked for specific antibodies to normal human bladder in the serum. Sixty-five percent of IC patients and 36% of controls demonstrated non–organ-specific antibodies; 40% of IC patients had antinuclear antibodies; 75% of IC patients and 40% of controls had antibladder antibodies present in the serum. There was no increase in immunoglobulin deposition in the bladder epithelium in IC patients versus controls. Although IC patients demonstrated a nonspecific increase in antibody formation, this was not significantly different from a similar group of other urologic patients. The lack of specificity indicates the immunologic findings are likely secondary to inflammation rather than a primary etiology.

In a study looking for active immune cellular deposition in BPS/IC patients, no statistically significant difference between controls and nonulcerative IC patients was identified (Harrington et al, 1990). In contrast, the ulcerative BPS group had focal sheets of plasma cells, aggregates of T cells, B-cell nodules, a decreased or normal helper-to-suppressor cell ratio, and suppressor cytotoxic cells in germinal centers. Flow cytometry analysis of peripheral blood lymphocyte subsets showed increased numbers of secretory-Ig–positive B cells and activated lymphocytes in the nonulcerative group and increased numbers of secretory-Ig–positive cells and activated lymphocytes in the ulcerative group. These results may suggest a partial role for an immune mechanism in IC. Erickson and coworkers (1997a) have also noted a major difference in inflammatory cell types as well as clinical features in BPS/IC patients with severe inflammation, suggesting two different patient groups with two different underlying pathophysiologies.

Hanno and colleagues (1990) found CD4 cell predominance in all layers of the bladder in BPS/IC patients. Christmas (1994) reported increased numbers of CD4+ and CD8+ T cells in bladder biopsy specimens from patients with IC and bacterial cystitis as compared with controls. These T cells were present in the urothelium and submucosa but not in the detrusor. Control bladder tissue demonstrated only CD8 cells in the urothelium and both CD4+ and CD8+ cells in the submucosa. The number of plasma cells was significantly greater in IC patients than in normal controls and controls with bacterial cystitis.

MacDermott and colleagues (1991b) found a normal distribution of peripheral blood lymphocytes in IC patients, a finding not supportive of an autoimmune mechanism in the disease. The lamina propria showed a predominance of CD4 (helper T cells) lymphocytes over CD8 cells in both IC and other cystitis patients. The same pattern was seen in the epithelium of patients with bacterial or mechanical cystitis, but patients with IC had a predominance of CD8 lymphocytes in the urothelium, which was identical to that found in control subjects. The findings suggest that the urothelium is not involved in the inflammatory reaction, as is the lamina propria, making the urothelium an unlikely source for the initiating factor.

Miller and coworkers (1992) investigated the function of peripheral blood lymphocytes from nonulcerative IC patients, testing the proliferative response and cytokine production of T cells to nonspecific mitogenic stimulation and the proliferative response of T cells to urine components. Proliferation and cytokine production after mitogen stimulation were the same for controls and BPS/IC patients. Moreover, no immunologic response to IC urine by autologous peripheral blood lymphocytes in in-vitro assays was observed. Their findings cast doubt on theories suggesting that IC is an autoimmune disease.

Numerous inflammatory mediators have been studied with regard to their relation to BPS (Elgebaly et al, 1992; Felsen et al, 1994; Lotz et al, 1994; Steinert et al, 1994; Zuraw et al, 1994). Patients with BPS/IC exhibit varying degrees of inflammation that can separate them into clusters (Tomaszewski et al, 2001; Green et al, 2004). Bladder inflammation in IC is categorized by elevated urinary interleukin-6 (Erickson et al, 1997a) and activation of the kallikrein-kinin system (Rosamilia et al, 1999b). The absence of urinary interleukin-1β in IC argues against an immunologic or autoimmune etiology of the disorder (Martins et al, 1994). Neurogenic inflammation may play a role in the etiology, because long-term exposure of afferent nerve terminals to inflammatory mediators can alter ion channels and result in bladder hyperalgesia (Buffington and Wolfe, 1998; Yoshimura and de Groat, 1999). Substance P itself does not seem to be the single initiator of inflammation in the bladder, and its blockade does not protect the bladder in animal models from inflammatory responses (Luber-Narod et al, 1997). Urinary nitric oxide synthase (NOS) activity is known to be elevated in patients with urinary infection and thought to play a role in the bladder's response to infection and in the inflammatory process that follows infection. The finding that urinary NOS activity is decreased in BPS/IC patients has puzzled researchers but could explain the reduction in functional bladder capacity associated with the disorder (Smith et al, 1996; Foster et al, 1997).

Urothelial cell activation in IC may result in aberrant immune responses and immune activation within the bladder wall (Liebert et al, 1993) that could relate to pathogenesis of the disease but might not reflect initiating etiology (Ochs et al, 1994). It has been proposed that inflammatory and/or immune responses in IC could be exacerbated by persistent activation of the nuclear factor-kappa B (NF-κB) (Abdel-Mageed and Ghoniem, 1998; Abdel-Mageed, 2003). Angiogenic factors such as platelet-derived endothelial cell growth factor/thymidine phosphorylase and transforming growth factor-β may be involved in the inflammatory process to induce painful symptoms in patients with IC or bladder carcinoma (Ueda et al, 2002).

The exact role of autoimmunity in IC remains controversial (Ochs, 1997). Suplatast tosylate, a new immunoregulator,

Key Points: Autoimmunity and Inflammation

- Neuroplasticity may be a possible explanation for the association of bladder inflammation with long-term symptoms and pain after inflammation subsides.
- Abnormal differentiation in the urothelium with a loss of barrier markers and altered differentiation markers may be independent and occur independently of inflammation.
- Visceral sensory integration may result in inflammation originating in organs other than the bladder causing symptoms identified with BPS.

has shown efficacy in a small, uncontrolled IC study in which improvements in symptoms and bladder capacity were correlated with changes in autoimmune parameters (Ueda et al, 2000). **Although the immune system remains a target for therapy, no clear indication of a primary role for autoimmunity as the cause of IC has been observed** (Liebert, 1997).

Mast Cell Involvement

Although mast cells are thought of primarily in the context of allergic disorders, and certain acute inflammatory responses, these cells have also been implicated in biologic responses as diverse as angiogenesis and wound healing, bone remodeling, peptic ulcer disease, atherosclerosis, and reactions to neoplasms (Galli, 1993). Mast cells remain one of the most enigmatic cells in the body. They secrete significant amounts of numerous proinflammatory mediators that contribute to a number of chronic inflammatory conditions, including stress-induced intestinal ulceration, rheumatoid arthritis, scleroderma, and Crohn disease. They have been described even among the lowest order of animals, having been discovered in the frog mesentery over 100 years ago. Their raison d'etre may be for initiating and coordinating the host's inflammatory and immune responses against microbial pathogens (Abraham and Malaviya, 1997). Recently they have been implicated in a range of neuroinflammatory diseases, especially those worsened by stress (Theoharides, 2004; Theoharides and Cochrane, 2004). These include multiple sclerosis, migraines, inflammatory arthritis, atopic dermatitis, coronary inflammation, irritable bowel syndrome, and BPS/IC. They may be activated through their Fc receptors by immunoglobulins other than IgE, as well as by anaphylatoxins, neuropeptides, and cytokines to secrete mediators selectively without overt degranulation.

Mast cells have frequently been reported to be associated with IC, both as a pathogenetic mechanism and as a pathognomonic marker (Simmons, 1961; Bhone et al, 1962; Smith and Dehner, 1972; Larsen et al, 1982; Hofmeister et al, 1997). The association of bladder mastocytosis, IC, and irritable bowel syndrome (Pang et al, 1996) and chronic urticaria (Sant et al, 1997) is intriguing. Evidence of their importance is mounting, suggesting that **they may serve as the final common pathway through which the symptomatic condition is expressed. Mast cells produce, among other compounds, histamine. Histamine release in tissue causes pain, hyperemia, and fibrosis, all notable features of IC.**

Simmons (1961) was the first to suggest mast cells as a cause of IC. Contribution of mast cells to the cellular infiltrate in IC (Fig. 12–7) has been shown to vary from about 20% in nonulcer IC patients to 65% in patients with ulceration (Sant et al, 1988; Enerback et al, 1989). Mast cells participate in allergic reactions (hypersensitivity type I) during which IgE antibody is synthesized in response to specific antigens. IgE binds to mast cell receptors, and antigen binds to the IgE, leading to degranulation (Lagunoff et al, 1983). Other triggers of mast cell secretion include acetylcholine, anaphylatoxins, cationic peptides such as substance P, chemicals, contrast agents, cytokines, opioids, antihistamines, exercise, hormones, viruses, and bacterial toxins (Sant and Theoharides, 1994). Mast cells promote infiltration of neutrophils, T and B lymphocytes, monocytes, and eosinophils. T lymphocytes secrete substances capable of activating mast cells, thus perpetuating the cycle of inflammation (Kaplan et al, 1985).

Since the presence of mast cells within the bladder wall was first recognized (Simmons and Bunce, 1958), numerous investigators have tried to determine whether there is an increase in the number of mast cells in the bladder of patients with IC or differences in their location or functional state (Larsen et al, 1982; Kastrup et al, 1983; Fall et al, 1987; Feltis et al, 1987; Lynes et al, 1987; Christmas and Rode, 1991). An increase in urothelial mast cells appears to be part of the generalized inflammatory cell reaction regardless of etiology, and not a specific feature of IC, whereas the presence of increased numbers of mast cells in the detrusor is more specific for IC. However, one study did report detrusor mastocytosis in 64% of IC patients and 80% of a control group with other urologic disease, with no statistically significant difference between the mean number of detrusor mast cells in the two groups (Hanno et al, 1990).

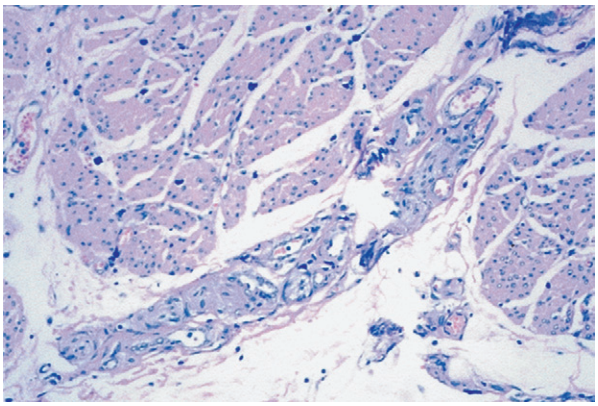


Figure 12–7. Giemsa stain shows detrusor mastocytosis and nerve hypertrophy in bladder pain syndrome (original magnification ×400). (Courtesy of John Tomaszewski, Hospital of the University of Pennsylvania, Department of Pathology.)

Aldenborg and associates (1986) reported that mast cells are found predominantly in the detrusor muscle in patients with classic IC, but there is also a secondary population of mast cells in the lamina propria and the bladder epithelium, with staining characteristics distinct from those in the detrusor. None of these epithelial mast cells was found in controls. These findings were interpreted to indicate a transepithelial migration of mast cells in patients with IC. This second population of mast cells does not appear to be involved in the nonulcer type of IC (Aldenborg et al, 1989). This mucosal population of mast cells can also differ from the mast cells found in deeper tissues in physiologic responses and release of secretory products (Sant, 1991). The "mucosal mast cells" are susceptible to aldehyde fixation and require special fixation and staining techniques for proper demonstration. Detrusor mast cells are not susceptible to fixation techniques. Recent studies have shown that although all human mast cells contain the proteinase tryptase there is a population of mast cells that also contain the proteinase chymase. The mast cell expansion in IC involves both types (Yamada et al, 2000). Mast cell activation is far more pronounced in the ulcerative form, which in addition displays prominent inflammation, in contrast to nonulcer IC in which it is sparse. Thus the basic pathologic processes may differ (Peeker et al, 2000b). Because activated mast cells lose their histologically identifiable granules once degranulation occurs, estimates of mast cell density using standard histologic techniques may underestimate mast cell numbers (Sant and Theoharides, 1994).

Electron microscopy has confirmed that mast cells in IC are more likely to be degranulated or activated than those found in other conditions (Larsen et al, 1982; Theoharides and Sant, 1991; Theoharides et al, 1995). In at least a subpopulation of IC patients

this may be explained by increased stimulation of mast cells by stem cell factor (Pang et al, 1998). A chronic exposure of detrusor muscle to histamine in IC patients is suggested by the finding that there is an impairment of the direct contractile response to histamine in detrusor muscle affected by IC in comparison to control detrusor, suggesting a receptor desensitization (Palea et al, 1993). The clinical relationship between an increased number of mast cells and symptoms of IC has not been definitively established. Some studies have found no correlation (Holm-Bentzen et al, 1987b; Lynes et al, 1987; Dondore et al, 1996). Although mast cell infiltration in intestinal segments used for augmentation has been associated with pain and failure of the procedure (Kisman et al, 1991), others have shown that mast cell infiltration in intestine used in the urinary tract is the norm and not pathologic (MacDermott et al, 1990).

Many of the substances that have been shown to induce mast cell secretion are released from neurons that innervate the organ containing the mast cells (Christmas et al, 1990). The capsaicin-sensitive sensory neurons that innervate the bladder are thought to have a dual "sensory-efferent" function, in which an axon reflex-induced release of neuropeptides results in local inflammation (Foreman, 1987; Barbanti et al, 1993). Hand (1949) reported an increase in the submucosal nerve density in IC, a phenomenon confirmed by Christmas and associates (1990), who showed an increase in nerve fiber proliferation in IC but not in patients with bacterial or lupus cystitis. Increased innervation by nerves releasing substances affecting mast cells could lead to increased mast cell secretion. Among these substances is acetylcholine. Mast cells can be stimulated by cholinergic agonists to secrete serotonin (Theoharides and Sant, 1991). Substance P–containing fibers have been found to be increased in bladders from IC patients and are found adjacent to mast cells (Pang et al, 1995b). In mice, mast cells modulate the inflammatory response of the bladder to substance P and to *Escherichia coli* lipopolysaccharide (Bjorling et al, 1999).

An increase in adrenergic but not cholinergic nerves in IC patients as compared with controls has been reported (Hohenfellner et al, 1992). These researchers also found increased numbers of neurons staining for vasoactive intestinal polypeptide and neuropeptide Y (NPY), both of which are associated with sympathetic nerves. Studies in rats have revealed that psychological stress can activate bladder mast cells through the action of sensory neuropeptides (Spanos et al, 1997; Alexacos et al, 1999). Diurnal cortical variations have been associated with symptom levels in PBS/IC (Lutgendorf et al, 2002), and the mast cell may represent a pathway for stress to be reflected in bladder symptomatology.

Mast cells can alter their environment by regulating tissue gene expression (Saban et al, 2001). The finding of increased synthesis of urinary leukotriene E4 in patients with IC and detrusor mastocytosis when compared with healthy controls suggests that cysteinyl containing leukotrienes are involved in the inflammatory reaction observed in the urinary bladder of patients with IC and may be produced from tissue mast cells in the bladder wall or macrophages (Bouchelouche et al, 2001a).

Could mast cell products be useful in diagnosing BPS/IC? They are not specific for BPS/IC and are increased in bladder carcinoma (Serel et al, 2004). Elevated histamine levels have been found in bladder biopsy specimens of IC patients (Kastrup et al, 1983; Lynes et al, 1987; Enerback et al, 1989) as well as from bladder washings (Lundeberg et al, 1993). Holm-Bentzen and colleagues (1987c) reported a significantly elevated urinary excretion of 1,4-methylimidazole acetic acid, the major metabolite of histamine. Others have found no differences between IC and controls in random spot tests of urinary histamine (Yun et al, 1992). Levels were elevated after hydrodistention in IC patients but not in control subjects, which is a possible consequence of hydrodistention and resultant mast cell degranulation. El Mansoury and coworkers (1994) found increased methylhistamine, a histamine metabolite, in spot and 24-hour urine samples from IC patients as compared with controls. Although such an increase could still be interpreted as indicating a systemic rather than a bladder syndrome, subsequent findings of elevated mast cell tryptase in the urine of IC patients could come only from the bladder (Boucher et al, 1995). Erickson and colleagues (2004) reported that urine methylhistamine is not useful as an objective marker of response to bladder distention or as a predictor of response to distention or as a substitute for bladder biopsy to determine mast cell counts.

The realization that mast cells are associated with the syndrome of BPS by no means diminishes the other multiple theories of causation. The poor clinical results with antihistamine therapy would argue against their being a primary factor. Their very presence could be related to injury from any of the proposed theories of etiology, and degranulation could likewise reflect a final common pathway resulting in pain and frequency from multiple causes. Rickard and Lagunoff (1995) proposed, based on results with mast cell granules and epithelial cells in tissue culture, that mast cells could contribute to failure of epithelialization of the bladder surface after injury by two potential mechanisms: (1) inhibition of epithelial cell replication and (2) interference with epithelial cell spreading, thus resulting in the "leaky epithelium" found in some patients. Mast cells may actually be the mediator through which female hormones play a role, accounting for the 10:1 female-to-male preponderance of the disease (Vliagoftis et al, 1992; Pang et al, 1995a; Patra et al, 1995; Bjorling and Wang, 2001). Estradiol augments the secretion of mast cell histamine in response to substance P. It has been proposed that the symptoms of BPS/IC may depend on an imbalance of the relative number of estrogen receptors to progesterone receptors on bladder mast cells (Letourneau et al, 1996).

To summarize, much important IC research has centered on the mast cell. These cells are strategically localized in the urinary bladder close to blood vessels, lymphatics, nerves, and detrusor smooth muscle (Saban et al, 1997). **Studies to date strongly suggest that BPS is a syndrome with neural, immune, and endocrine components in which activated mast cells play a central, although not primary, pathogenetic role in many patients** (Elbadawi and Light, 1996; Filippou et al, 1999). Studies in a mast cell–deficient mouse model demonstrate that mast cells promote cystitis pain and bladder pathophysiology through the separable actions of histamine and tumor necrosis factor, respectively, suggesting that pain is independent of pathology and inflammation and that histamine receptors may represent direct therapeutic targets for pain in BPS/IC (Rudick et al, 2008).

Key Points: Mast Cells and Histamine

- Mast cells may be a pathognomonic marker for BPS and also represent a pathogenetic mechanism of the syndrome. They could serve as a final common pathway through which the symptomatic condition is expressed.
- Histamine, produced by mast cells, may cause pain, hyperemia, and fibrosis, all notable features of BPS.

Bladder Glycosaminoglycan Layer and Epithelial Permeability

Until the early 1970s most investigators thought that the major barrier to free flow of urinary constituents was at the level of the epithelial cells. Tight junctions between urothelial cells, specialized "umbrella cells" lining the surface, and direct bactericidal activity of the vesical mucosa were thought capable of defense of the internal milieu from bacteria, molecules, and ions in the urine (Ratliff et al, 1994). Staehelin and colleagues (1972) proposed that lipid and other hydrophobically bonded materials were important in any barrier to permeability in the luminal membrane because permeants leaked through the interplaque regions if the particles alone limited transport. It has been shown that inflammation of the underlying muscle and lamina propria can disrupt the bladder permeability barrier by damaging tight junctions and apical membranes and causing sloughing of epithelial cells. Leakage of urinary constituents through the damaged epithelium may then exacerbate the inflammation in the underlying tissues (Lavelle et al, 1998, 2000).

It was Parsons and Hurst (1990) who hypothesized and popularized **the concept that IC in a subset of patients is the result of some defect in the epithelial permeability barrier of the bladder surface GAGs.** The major classes of GAGs include hyaluronic acid, heparin sulfate, heparin, chondroitin 4-sulfate and chondroitin 6-sulfate, dermatan sulfate, and keratan sulfate. These carbohydrate chains, coupled to protein cores, produce a diverse class macromolecules, the proteoglycans (Trelstad, 1985). GAGs exist as a continuous layer on the bladder urothelium (Dixon et al, 1986; Cornish et al, 1990). Except heparin, all the other types of GAGs have been found on the bladder surface (Ruoslahti, 1988). The GAG layer functions as a permeability and antiadherence barrier. When impaired, its functions can be duplicated by exogenous GAG (Hanno et al, 1978). In the absence of this protective layer in the urinary bladder its susceptibility to infection would increase, and the production of nitric oxide in the urothelial cells, and of substance P in the intraepithelial afferent C-fiber terminals, increases. Consequently, the permeability of both the urothelium and the blood vessels in the mucous membrane increases and the blood flow slows owing to vasodilatation (Hohlbrugger, 1999).

Parsons and Hurst (1990) reported a lower excretion of urinary uronic acid and GAGs in IC patients than in normal volunteers and hypothesized that a leaky transitional epithelium might be absorbing these substances to its surface. The data are interesting in that one might expect urinary GAG to increase with injury to the bladder and decrease with resolution (Uehling et al, 1988). The San Diego group (Lilly and Parsons, 1990; Parsons et al, 1990) went on to show experimentally that one can damage the GAG layer with protamine sulfate with resultant back-diffusion of urea through the bladder lumen, and that this urea loss can be prevented with a bladder instillation of exogenous GAG (heparin). By placing a solution of concentrated urea into the bladder of IC patients and measuring absorption versus controls, Parsons and associates (1991) found support for his theory in patients with IC. The rationale of the epithelial permeability school is nicely summarized in four publications (Parsons 1993, 1994; Hurst et al, 1997; Hohlbrugger and Riedl, 2000) and provides a comprehensive, if somewhat imperfect, theory of the disorder.

Support for an epithelial abnormality from a different perspective has come from Bushman and coworkers (1994), who found aneuploid DNA profiles on barbotage specimens from IC patients that may signal an underlying abnormality of the epithelial cell population in some patients with IC. Wilson and colleagues (1995) identified a loss of type IV collagen in the urothelial basement membrane in 5 of 11 IC patients. Hurst's group (1996) studied bladder biopsy specimens of IC patients and control subjects and concluded that there is a deficit of bladder luminal and basal proteoglycans associated with the disorder. The basal abnormality may reflect an altered urothelial differentiation program. In a later study, IC bladder biopsy specimens showed abnormalities in 24 of 27 patients when examined by immunohistochemical assessment of E-cadherin, ZO-1, uroplakin, and chondroitin sulfate (Slobodov et al, 2004). Erickson and coworkers (1996) measured a glycoprotein (epitectin) in the urine of IC patients and found a decrease compared with a control population, although a significant overlap was detected. Buffington and Woodworth (1997) gave 6 IC patients and 6 control subjects oral fluorescein dye. IC patients had higher levels of fluorescein in their plasma and lower urinary excretion of the dye, suggesting altered membrane permeability and increased fluorescein reabsorption in the bladder wall of IC patients. Erickson and colleagues (1998) compared urinary levels of hyaluronic acid in IC patients and control subjects, reporting higher urinary hyaluronic acid in the patient group, which possibly was accounted for by leakage of this GAG across the epithelium.

In feline IC, the only naturally occurring animal model of the disorder, the urothelium has been shown to have decreased transepithelial resistance and increased water and urea permeability compared with controls in response to hydrodistention (Lavelle et al, 2000). This indicates that barrier function is compromised, which could lead to the sensitization of sensory nerves by irritants from urine crossing into the muscle layer. Bladder strip studies have shown that bladders of cats with feline IC have significantly more spontaneous Ca^{2+} transients in the mucosal layer than control bladders. Coupled with increased sensitivity of muscarinic receptors in the mucosal layer, these bladders may manifest enhanced smooth muscle spontaneous contractions. This finding could play a contribution in the symptoms of BPS/IC (Ikeda et al, 2009). In fact, human cell culture studies comparing BPS/IC and normal bladder urothelial cells have shown greater sensitivity of IC bladder urothelial cells to carbachol, suggesting that BPS/IC pathobiology may also include alterations in muscarinic signaling (Gupta et al, 2009).

Further data for an abnormal surface mucin came from Moskowitz and colleagues (1994) who studied biopsy specimens from 23 IC patients with regard to the presence of a glycoprotein component of the surface mucin referred to as GP1 and compared the results to those in 11 normal controls. Qualitative GP1 changes in a majority of IC patients were identified. GP1 reactivity was noted in all controls but was absent in 35% of IC patients and diminished in 61%. This study may provide evidence of an abnormal bladder urothelium, but the effects of bladder distention in the IC group is unknown and may have contributed to the results. There were no pathologic controls used, and no attempt was made to correlate GP1 reactivity with IC symptoms (Messing, 1994). Castration in female rabbits is associated with bladder mucosal changes resulting in increased mucosal permeability (Parekh et al, 2004). Birder and colleagues have shown that feline IC results in increased baseline production of nitric oxide due to inducible nitric oxide synthase (iNOS) (Birder et al, 2005). These changes in transmitter release may have a role in altering mucosal barrier properties.

Vascular endothelial growth factor (VEGF) plays a key role in bladder inflammation and is closely associated with the vascular

alterations observed in patients with BPS/IC. VEGF and coreceptors (neuropilins [NRPs]) are strongly expressed in human bladder urothelium. NRP2 and VEGF-R1 are significantly downregulated in IC when compared with control subjects (Saban et al, 2008). GAG modification of NRPs plays a critical role in modulating VEGF/NRP signaling (Shintani et al, 2006), suggesting another possible mechanism in which a GAG deficiency could act by interfering with the functionality of this signaling system.

Some have cited the "potassium sensitivity test" as providing strong evidence for a population with mucosal leak (Parsons et al, 1994b). Parsons and colleagues placed water or 0.4 M potassium chloride (KCl) intravesically into normal volunteers and IC patients. Water did not provoke pain in either group, but KCl provoked the symptom in 4.5% of normal subjects and 70% of IC patients. Symptomatic responses were reduced in patients on heparinoid therapy. Similar findings occur in patients with radiation cystitis (100%) (Parsons et al, 1994c), urinary infection (100%) (Parsons et al, 1998), detrusor instability (25%) (Parsons et al, 1998), "urethral syndrome" (55%) (Parsons et al, 2001b), and more than 80% of women with endometriosis, vulvodynia, and pelvic pain (Parsons et al, 2001a, 2002b). Up to 33% of unselected Turkish women may test positive (Sahinkanat et al, 2008). Eighty-four percent of men with prostatitis also have a positive test (Parsons and Albo, 2002). **The poor specificity of the potassium test** suggests that it does not provide unequivocal evidence of a permeability dysfunction. **Because it is known that the normal bladder epithelium can never be absolutely tight, and there is always some leak, however small** (Hohlbrugger, 1997), **it is conceivable that the findings of pain with KCl are related to a hypersensitivity of the sensory nerves in this condition, rather than to pathologic epithelial permeability, at least in some patients.** In fact, KCl administered intravesically to cats with feline IC seems to *inhibit* afferent firing of peripheral Aδ fibers. Heightened sensitivity of afferent nerve fibers can explain KCl results without necessarily evoking increased permeability (Lutgendorf and Kreder, 2005; Roppolo et al, 2005). Intravesical administration of KCl has since been proposed as a diagnostic test for IC (Parsons et al, 1998) (see later).

How central abnormal epithelial permeability is to IC is, however, by no means clear. Tamm-Horsfall protein (THP), a high-molecular-weight glycoprotein synthesized exclusively by the ascending loop of Henle and the distal tubule of the kidney, has been studied as a potential marker of urothelial permeability. Fowler and associates (1988) provided graphic data that the urothelium might be leaky in IC. With immunohistochemical techniques this group assayed the bladder biopsy specimens of 14 IC patients and 10 normal control subjects for intraurothelial THP to assess indirectly the in-vivo permeability of the urothelium. Eight pathologic controls were also assessed. Ten of 14 IC patients versus 1 of 18 controls demonstrated intraurothelial THP. Serum THP autoantibody is higher in BPS/IC patients versus controls (Neal et al, 1991). It is known that excretion rates of THP vary widely, even in repeat samples taken from the same individual (Reinhart et al, 1990). Subsequent studies in IC have failed to show differences in the presence of intraurothelial THP in the IC population versus controls, nor in antibody reactivity to THP (Stone et al, 1992; Stein et al, 1993). Parsons and associates (2007) reported that the THP protein is qualitatively different in patients with IC than in controls, even if the urinary concentration of the protein is the same. Bade and coworkers (1996) failed to find THP in the bladder tissue from 10 IC patients. Others have suggested that when THP is seen in bladder tissue it is an incidental finding of no clinical significance. The finding of intraurothelial THP has not been shown to be a harbinger of IC or any other bladder disorder (Truong et al, 1994).

Finally, we must look at a body of literature that has failed to find GAG abnormality or hyperpermeability. Ultrastructural, biochemical, and functional studies of bladder GAGs have not supported this theory (Collan et al, 1976; Dixon et al, 1986; Johansson and Fall, 1990; Ruggieri et al, 1991). Nickel's group (Nickel et al, 1993) reported sophisticated electron micrography using a specific antimucus, antisera stabilization technique to study the ultrastructural morphologic appearance of the GAG layer. No significant difference in the morphologic appearance of the mucus or GAG layer was noted in IC versus control subjects. Urinary chondroitin sulfates, heparan sulfate, and total sulfated GAGs normalized to creatinine are not altered in IC (Erickson et al, 1997b). Although an increased ratio of total GAGs to sulfated GAGs in IC may indicate an altered GAG layer, whether it reflects a cause or is a result of the primary pathologic process(s) is unknown (Wei et al, 2000). That leaves one to postulate an as yet unknown functional abnormality, rather than GAG deficiency, to account for any increase in permeability.

Chelsky and coworkers (1994) measured bladder permeability in IC using direct measurement by transvesical absorption of technetium-99m–labeled diethylenetriaminepentaacetic acid (^{99mTc}-DTPA). Whereas some IC patients had a more permeable bladder than others, the same was true for normal volunteers. Increased permeability in the IC group could not be demonstrated. However, three IC patients had marked absorption of ^{99m}Tc-DTPA and may represent a subpopulation of patients with increased epithelial permeability. Intravesical instillation of 10% and 20% ethanol in rabbits was reported to be a reliable quantitative measure of bladder hyperpermeability by the San Diego group (Monga et al, 2001) and subsequently failed to demonstrate bladder permeability in humans with IC (Gordon et al, 2003).

Overall, it does seem that there is a population of BPS/IC patients with increased epithelial permeability but the issue is far from closed. Increased mucosal permeability is nonspecific and a consequence of bladder inflammation and also occurs with cyclophosphamide-induced bladder injury, bacterial infection, and cystitis after intravesical challenge with antigen after sensitization (Engelmann et al, 1982; Kim et al, 1992). **It may also be a consequence of aging itself** (Jacob et al, 1978). **Whether this represents a primary cause of IC or merely reflects the result of an as yet unidentified source of inflammation is unclear.** Treatments that tend to damage the GAG layer, including transurethral resection and laser of ulcerated areas, bladder distention, and the administration of silver nitrate,

Key Points: Epithelial Permeability

- There is a population of BPS patients with increased epithelial permeability.
- Increased mucosal permeability is nonspecific and a consequence of bladder inflammation. It also occurs with cyclophosphamide-induced bladder injury, bacterial infection, and cystitis after intravesical challenge with antigen after sensitization.
- Whether this represents a primary cause of BPS or merely reflects the result of an as yet unidentified source of inflammation is unclear.

oxychlorosene (Clorpactin), or the organic solvent dimethyl sulfoxide (DMSO) have all been used with varying results to treat IC.

One does not need increased permeability of the mucosa as a foundation of the many potential causes or contributing factors to BPS/IC. Enhanced adenosine triphosphate (ATP) release from the urothelium of patients with BPS/IC has been described (Kumar et al, 2007). This nonneuronal ATP may act as a sensory neurotransmitter. Increased purinergic activity may thus lead to a condition in which the bladder is oversensitive to distention.

Increased permeability and epithelial dysfunction must be only a part of the story.

Inhibition of Uroepithelial Cell Proliferation: Antiproliferative Factor

The finding that cells from the bladder lining of normal controls grow significantly more rapidly in culture than cells from BPS/IC patients led Keay and associates (1996) at the University of Maryland to the discovery of an **antiproliferative factor (APF) produced by the urothelium of IC patients.** Normal bladder cells were cultured in the presence of urine from patients with IC, asymptomatic controls, bacterial cystitis, and vulvovaginitis. Only urine from IC patients inhibited bladder cell proliferation (Keay et al, 1998b). **The presence of APF was found to be a sensitive and specific biomarker for IC** (Keay et al, 2001) (Table 12–6). It was found in bladder urine but not in renal pelvic urine of IC patients, indicating **production by the bladder urothelial cells** (Keay et al, 1999). Subsequent studies indicated **that APF is associated with decreased production of heparin-binding epidermal growth factor–like growth factor** (HB-EGF) (Keay et al, 2000, 2003b). **APF activity was related to increased production of epidermal growth factor (EGF), insulin-like growth factor-1, and insulin-like growth factor binding protein-3** by the bladder cells from IC patients but not by the cells from healthy bladders. Studies of IC patients and asymptomatic controls showed **urine levels of APF, HB-EGF, and EGF to reliably separate out IC from controls** (Keay et al, 2001; Erickson et al, 2002).

Table 12–6.

Prevalence of Urine Antiproliferative Factor Activity in Interstitial Cystitis Patients and Control Groups

GROUPS	NO. OF PATIENTS POSITIVE/TOTAL	% POSITIVE
Patients		
Interstitial cystitis	206/219	94
Controls		
Asymptomatic	10/113	9
Overactive bladder	2/32	6
Bacterial cystitis	7/58	12
Microscopic hematuria	2/19	10
Stress incontinence	1/10	10
Neurogenic bladder	0/11	0
Benign prostatic hyperplasia	1/14	7
Nonbacterial prostatitis	1/16	6
Vulvovaginitis	0/12	0
Miscellaneous	1/16	6

From Keay SK, Zhang CO, Shoenfelt J, et al. Sensitivity and specificity of antiproliferative factor, heparin-binding epidermal growth factor–like growth factor, and epidermal growth factor as urine markers for interstitial cystitis. Urology 2001;57:9.

APF levels in the urine were found to discriminate between men with IC versus those with CPPS or nonbacterial prostatitis (Keay et al, 2004a). APF activity dropped significantly in IC patients within 2 hours after hydrodistention (Chai et al, 2000b) and after 5 days of sacral neuromodulation (Chai et al, 2000a). Cell culture studies showed that APF actually caused decrease in HB-EGF and increase in EGF, mirroring the differences in urine levels of these growth factors between IC patients and controls and suggesting that APF is the primary abnormality (Keay et al, 2003b).

Whereas APF may prove to be a useful marker for BPS/IC, it may also unlock the etiology of the syndrome. It has been hypothesized by Keay and colleagues (2003a) **that BPS/IC may result from an inhibition of bladder epithelial cell proliferation caused by the APF, which is mediated by its regulation of growth factor production from bladder cells. Conceivably, any of a variety of injuries to the bladder (infection, trauma, and overdistention) in a susceptible individual may result in BPS/IC if APF is present and suppresses production of HB-EGF** (Keay and Warren, 1998). Theoretically, if production of APF could be "turned off" by genetic techniques, or its effects were nullified by exogenous HB-EGF, the clinical syndrome might be prevented. HB-EGF functionally antagonizes APF activity via a mitogen-activated protein kinase pathway activation (Kim et al, 2009a).

APF has been purified (Fig. 12–8) and proved to be **a frizzled 8 protein that belongs to a newly discovered family of proteins that seem to be important in the development of nerve tissues, skin, and the lining of organs** (Keay et al, 2004b). The frizzled family of receptors is critically involved in embryogenesis, and there is substantial evidence that members of this family also regulate tissue homeostasis in many different organs in the adult (Schulte and Bryja, 2007).

It appears that the cell cycle regulatory protein TP53 is an important mediator of APF-induced effects on bladder epithelial cells (Kim et al, 2007). APF treatment suppresses cell proliferation by cell cycle arrest of human bladder urothelial cells. Evidence shows that TP53 levels increase significantly after APF stimulation; TP53 downregulation enhances the suppressive effect of APF on cell growth; and overexpression of TP53 induces cell cycle arrest in the absence of APF. It is possible that targeting of TP53 could be a means of abrogating the pathologic effects of urinary APF and lead to new options for clinical therapy.

Studies are ongoing to confirm the research by Keay and colleagues and expand on its significance in diagnosis and development of a rational treatment approach (Rashid et al, 2004). The development of animal models with specific signaling abnormalities found in BPS/IC epithelial, endothelial, smooth muscle, neuronal, or immune cells to determine whether these animals develop a disease similar to the human disorder would be an extremely useful and potentially very productive pathway to learning more about potential therapeutic pathways (Keay, 2008).

Key Points: Antiproliferative Factor

- The frizzled 8 protein termed *antiproliferative factor* (APF) has been proposed as a marker to identify cases of BPS/IC.
- It is secreted by bladder epithelial cells of BPS patients and inhibits bladder epithelial cell proliferation through mediation of growth factor production. As such it could be a proximal cause of the syndrome in many patients.

MEWGYLLEVT SLLAALALLQ RSSGAAAASA KELACQEITV PLCKGIGYNY TYMPNQFHD
TQDEAGLEVH QFWPLVEIQC SPDLKFFLCS MYTPICLEDY KKPLPPCRSV CERAKAGCAP
LMRQYGFAWP DRMRCDRLPE QGNPDTLCMD YNRTDLTTAA PSPPRRLPPP PPGEQPPSGS
GHGRPPGARP PHRGGGRGGG GGDAAAPPAR GGGGGGKARP PGGGAAPCEP
GCQCRAPMVS VSSERHPLYN RVKTGQIANC ALPCHNPFFS QDERAFTVFW IGLWSVLCFV
STFATVSTFL IDMERFKYPE RPIIFLSACY LFVSVGYLVR LVAGHEKVAC SGGAPGAGGA
GGAGGAAAGA GAAGAGGP GGRGEYEELG AVEQHVRYET TGPALCTVVF LLVYFFGMAS
SIWWVILSLT WFLAAGMKWG NEAIAGYSQY FHLAAWLVPS VKSIAVLALS SVDGDPVAGI
CYVGNQSLDN LRGFVLAPLV IYLFIGTMFL LAGFVSLFRI RSVIKQQDGP TKTHKLEKLM
IRLGLFTVLY TVPAAVVVAC LFYEQHNRPR WEATHNCPCL RDLQPDQARR PDYAVFMLKY
FMCLVVGITS GVWVVWSGKTL ESWRSLCTRC CWASKGAAVG GGAGATAAGG
GGGPGGGGGG GPGGGGGPGG GGGSLYSDVS TGLTWRSGTA SSVSYPKQMP LSQV

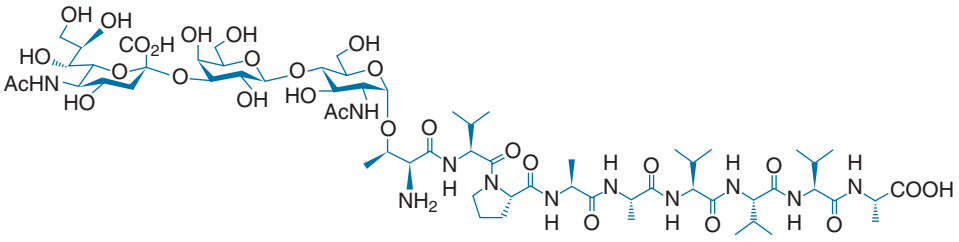


Figure 12–8. Composition and structure of antiproliferative factor. (From Keay SK, Szekely Z, Conrads TP, et al: An antiproliferative factor from interstitial cystitis patients is a frizzled 8 protein-related sialoglycopeptide. Proc Natl Acad Sci U S A 2004;101:11803–8.)

Neurobiology

Neuropeptides present in primary afferents and the dorsal horn of the spinal cord have an important role in the mediation of nociceptive input under normal conditions. Under pathologic conditions, such as chronic inflammation or after peripheral nerve injury, the production of peptides and peptide receptors is dramatically altered, leading to a number of functional consequences (Wiesenfeld-Hallin and Xu, 2001). Inflammatory painful stimuli, especially if repeated, can chronically alter innervation, central pain-processing mechanisms, and tissue responses (Steers and Tuttle, 1997). It has been known for some time that the sensory nervous system can generate some of the manifestations of inflammation (Foreman, 1987; Dimitriadou et al, 1991, 1992). Activation of capsaicin-sensitive afferent neurons locally and centrally may be involved in stress-related pathologic changes in the rat bladder (Ercan et al, 2001). **Activation of sensory nerves, specifically pain fibers, is known to trigger neurogenic inflammation through release of neuropeptides such as substance P, neurokinin A, and calcitonin gene–related protein, and subsequent increase in vascular permeability, with leukocyte adhesion and tissue edema. The neuropeptide mediators have been shown to also cause degranulation of mast cells with release of additional potent mediators of inflammation and to lead to injury and increased permeability of epithelial surfaces** (Elbadawi and Light, 1996). An increase in nerve fibers within the suburothelium and detrusor muscle in ulcerative IC has been noted (Lundeberg et al, 1993). A correlation was found between the number of nerve fibers and numbers of mast cells as well as between the number of nerve fibers and the amount of histamine. **Consolidating the leaky urothelium theory and mast cell activation, neurogenic inflammation is an attractive proposal for etiology and can readily accommodate infectious, immunologic, and autoimmunologic mechanisms as factors** (Elbadawi and Light, 1996).

Harrison and colleagues (1990) proposed that small-diameter sensory nerves in the bladder wall may have a role in the transmission of the sensation of pain and in the triggering of inflammatory reactions rather than forming the afferent limb of the micturition reflex. Abelli and associates (1991) demonstrated in the rat urethra that mechanical irritation alone can cause neuropeptide release from peripheral capsaicin-sensitive primary afferent neurons, resulting in neurogenic inflammation. Extracellular ATP can act through the purinergic receptor subtype $P2X_3$ to transmit a pain signal to the central nervous system. These subunits expressed by cultured IC bladder urothelial cells are upregulated during in-vitro stretch and may phenotypically mimic sensory neurons (Sun and Chai, 2004).

Several pieces of additional information support a theory of neurogenic inflammation. Levels of nerve growth factor are elevated in bladder biopsy specimens of IC patients (Lowe et al, 1997). Studies in rats using pseudorabies virus clearly show that bladder inflammation can be induced from a somatic structure through a neural mechanism and that central nervous system dysfunction can bring about a peripheral inflammation (Doggweiler et al, 1998; Jasmin et al, 1998). Pelvic nerve stimulation in the rat increases urothelial permeability that is antagonized by capsaicin, indicating both an efferent effect of afferent nerves and afferent-mediated neuroepithelial interaction (Lavelle et al, 1999).

Numerous studies indicate increased sympathetic activity in IC. Hohenfellner and colleagues (1992) suggested that IC is associated with increased sympathetic outflow into the bladder and altered metabolism of vasoactive intestinal polypeptide and neuropeptide Y. Neuropeptide Y (NPY) inhibits bladder afferents and therefore may be involved in autonomic disturbances affecting the bladder. Elevation of urinary catecholamines in IC patients and plasma catecholamines in cats with feline IC has been observed (Stein et al, 1999; Buffington and Pacak, 2001a), as has an increased density and number of nerve fibers immunoreactive for tyrosine hydroxylase in IC patients (Peeker et al, 2000a). Whether these changes reflect a cause of IC or are merely the result of long-standing intense pain and a severely pathologic voiding pattern is unknown.

Galloway and associates (1991) proposed that the changes in IC may be explained by an increase in sympathetic discharge,

analogous to that seen in reflex sympathetic dystrophy (RSD) of limbs. The pathology in RSD is the development of abnormal synaptic activity between sensory afferent and sympathetic efferent neurons. Nerve cells in the spinal cord become hypersensitive to sensory input, and this sustains abnormal sympathetic outflow and corresponding vasomotor dysregulation. The excess sympathetic outflow leads to constriction of blood vessels and tissue ischemia, setting up further sensory changes and perpetuating the cycle. In RSD there is usually a trigger event leading to these changes. With the acute phase of RSD, regional signs of inflammation are evident in the affected extremity. One school of thought believes an inflammatory response to an injury initiates RSD. Increased capillary permeability is a direct result (Goris and Jan, 1998). Perhaps a urinary infection could trigger such a pathologic cycle in some IC patients?

Herbst and colleagues (1937) produced bladder lesions in a dog resembling the ulceration of IC by ligating the blood vessels to the posterior bladder wall and infecting the area with *Streptococcus viridans*. Studies using laser Doppler flowmetry have shown that when the bladder is distended under anesthesia the blood flow increases in control patients to a statistically significant degree as compared with IC patients (Irwin and Galloway, 1993; Pontari et al, 1999). Another study has purported to show that topical heparin therapy can normalize urothelial permeability and vesical blood flow in IC (Hohlbrugger et al, 1998). Decreased microvascular density has been described in the suburothelium but not in the deeper mucosa in bladder biopsy specimens of women with IC (Rosamilia et al, 1999a). Hyperbaric oxygen has been suggested to have a limited effectiveness for the treatment of BPS/IC (van Ophoven et al, 2004b, 2006; Tanaka et al, 2007) as well as radiation-induced cystitis (Weiss and Neville, 1989).

If lumbar sympathetic blocks can decrease the pain of IC, a role of the sympathetic nervous system in IC pathogenesis is a reasonable supposition (Irwin et al, 1993; Doi et al, 2001). An increase in sympathetic activity has been shown in cats with feline IC (Buffington and Pacak, 2001b; Buffington et al, 2002). Similar findings have been reported in a small study of IC patients (Dimitrakov et al, 2001), and sympathetic activity may be an underlying common denominator in many disorders associated with PBS/IC (Buffington, 2004).

Nevertheless, **no studies performed to date can confirm any case of IC is related to the syndrome of reflex sympathetic dystrophy** (Ratliff et al, 1994). No single test can be used to exclude sympathetically maintained pain, and there are no clear symptoms that predict sympathetically mediated pain (Baron, 2000). In the animal model, bladder ischemia is associated with detrusor overactivity or impaired detrusor contraction, not sensory urgency (Azadzoi et al, 1999). Those patients with RSD who have voiding symptoms rarely have a picture that would be confused with IC (Chancellor et al, 1996).

Before leaving the neurogenic theory of etiology it is important to note that the nervous system itself almost surely contributes to the chronic nature of this pain syndrome, regardless of initiating cause (Vrinten et al, 2001). Repetitious stimulation of a peripheral nerve, at sufficient intensity to activate C fibers, results in a progressive buildup of the magnitude of the electrical response recorded in the second-order dorsal horn neurons. This "windup" phenomenon is central to the concept of chronic pain. Biochemically it is dependent on activation of *N*-methyl-D aspartate (NMDA) receptors in the spinal cord (Bennett, 1999). With persistent NMDA receptor activation, spinal cord cells undergo trophic changes and the pain resulting from subsequent stimulation becomes exaggerated and prolonged. This "pain memory" in the spinal cord may be what causes IC patients to become refractory to different therapies (Brookoff, 1997). NMDA-receptor–driven formation of new connections in the spinal cord may account for the expansion of the pain field.

Table 12–7.

Non-Nociceptive Pain: Characteristic Clinical Features

1. The description of the pain seems inappropriate in comparison with the degree of tissue pathology, or no tissue pathology may be discernible.
2. Noxious stimuli result in a pain experience that is greater and more unpleasant than would normally be expected (hyperalgesia).
3. Normally non-noxious stimuli may result in pain (allodynia).
4. The extent of the pain boundary is greater than would be expected on the basis of the site of the original tissue pathology.

From Bennett RM. Emerging concepts in the neurobiology of chronic pain: evidence of abnormal sensory processing in fibromyalgia. Mayo Clin Proc 1999;74:385–98.

Upregulation of the CNS and augmented sensory processing has been referred to as non-nociceptive pain (NNP) (Bennett, 1999). The four characteristic features of NNP would seem to apply very well to the clinical syndrome of IC (Table 12–7). Chronic neuropathic pain may continue after the resolution of tissue damage and persist on the basis of a maladaptive mechanism (Urban et al, 2002).

Burnstock's observation (1999) that ATP has a role in mechanosensory transduction by the epithelial lining of hollow viscus organs such as bladder has been followed up by Sun and colleagues (2001). Stretched epithelial cells lining hollow organs release ATP, which acts on purinergic nociceptive receptors on subepithelial sensory nerve terminals. ATP levels were significantly elevated in the urine of PBS/IC patients, and the stretch-activated release of ATP was augmented in IC urothelium.

Neurogenic inflammation may be the cause of some cases of BPS or may be the result of other initiating etiologic events. It is not incompatible with the central role of the mast cell or with the leaky epithelium theory. It conceivably could result in the appearance of autoimmune phenomena or result from an episode of infection. The central nervous system may also be implicated in dysregulation of the pelvic floor, resulting in chronic pelvic pain and contributing to IC (Zermann et al, 1999) and perhaps in the rare cases of IC that chronologically seem to relate to trauma or pelvic surgery (Zermann et al, 1998). It is an etiologic theory that provides fertile ground for new treatment possibilities.

Key Points: Neurogenic Inflammation

- Numerous studies indicate increased sympathetic activity in BPS/IC. Activation of sensory pain fibers is known to trigger neurogenic inflammation through release of neuropeptides such as substance P, neurokinin A, and calcitonin gene–related protein.
- Neurogenic inflammation may be the cause of some cases of BPS/IC. Chronic neuropathic pain may continue after the resolution of tissue damage and persist on the basis of a maladaptive mechanism.

Pelvic Organ Cross-Sensitization

Clinical observations of viscerovisceral referred pain in patients with gastrointestinal and genitourinary disorders suggest an overlap of neurohumoral mechanisms underlying both bowel and urinary bladder dysfunctions. Close proximity of visceral organs within the abdominal cavity complicates identification of the exact source of chronic pelvic pain, where it originates, and how it relocates with time. Cross-sensitization among pelvic structures may contribute to chronic pelvic pain of unknown etiology and involves convergent neural pathways of noxious stimulus transmission from two or more organs. **Inflammation, nerve injury, ischemia, peripheral hyperalgesia, metabolic disorders, and other pathologic conditions can dramatically alter the function of directly affected pelvic structures as well as organs located next to a damaged domain** (Malykhina, 2007). It has been demonstrated in a rat model that acute colitis can sensitize lumbosacral spinal neurons receiving input from the urinary bladder (Qin et al, 2008). Acute colitis and acute cystitis in the rat model can each cross-sensitize the bladder and colon, respectively (Pezzone et al, 2005).

It is thought that chronic widespread pain in chronic fatigue syndrome and fibromyalgia (disorders associated with BPS/IC in many patients) can be a consequence of central sensitization. Central sensitization is an increased central neuronal responsiveness and causes hyperalgesia, allodynia, and referred pain and hyperalgesia across multiple spinal segments, leading to chronic widespread pain. Triggers include windup or temporal summation, dysregulated descending inhibitory pathways, and upregulated facilitatory modulation. Windup or temporal summation is the result of repetitive noxious stimuli, leading to an increase in electrical discharges in the dorsal horn. Inhibitory modulation can be impaired by abnormalities in the central nervous system, and the facilitatory pain pathways can be stimulated by certain behavioral and cognitive factors (Meeus and Nijs, 2007).

It is possible that a combination of central sensitization and pelvic cross talk may account for the association of BPS/IC with bowel symptoms in some patients and the use of dietary alterations for managing the severity of BPS symptoms. Relatively minor gut stimuli, which otherwise cause no symptoms, could exacerbate established, bladder-driven pelvic pain, because even slight increases of inputs from a second site like the gut might lead to a sum of inputs that is considerably elevated above a threshold necessary to induce pain (Rudick et al, 2007; Klumpp and Rudick, 2008). Central pain amplification might also account for the increased startle responses described in female BPS/IC patients in the context of a threat of abdominal pain (Twiss et al, 2009).

Key Points: Sensitization of Neural Pathways

- Cross-sensitization among pelvic structures may contribute to chronic pelvic pain syndromes.
- Neural pathways from two or more organs, one or both of which are carrying noxious stimuli transmissions, may converge. Theoretically this could lead to alteration of the function of not only the directly affected pelvic structures but also organs located nearby.

Nitric Oxide Metabolism

Regulation of urinary NOS activity has been proposed to be of importance for immunologic responses in BPS. The oral administration of L-arginine, the substrate for nitric oxide production (Moncada and Higgs, 1993) has been shown to increase nitric oxide–related enzymes and metabolites in the urine of patients with BPS (Smith et al, 1996). It has been reported that differences in nitric oxide evaporation between ulcerative and nonulcerative BPS allows for subtyping of cases meeting the NIDDK criteria. This could potentially replace cystoscopy as a tool for identifying ulcerative BPS/IC (Logadottir et al, 2004). Increased levels of endogenously formed nitric oxide correspond to increased iNOS in mRNA expression and protein levels in BPS patients. iNOS has been found to be localized to the urothelium and has also been found in macrophages in the bladder mucosa. Whether high levels of endogenously formed nitric oxide are a part of the pathogenesis in BPS/IC and whether it has a protective or damaging role remain to be elucidated (Koskela et al, 2008).

Urine Abnormalities

Current theories of pathogenesis generally involve access of a component of urine to the interstices of the bladder wall, resulting in an inflammatory response induced by toxic, allergic, or immunologic means. The substance in the urine may be a naturally occurring one—a substance that acts as an initiator only in particularly susceptible individuals—or may act like a true toxin, gaining access to the urine by a variety of mechanisms or metabolic pathways (Wein and Broderick, 1994). Clemmensen and colleagues (1988) noted that 8 of 11 IC patients had positive skin reactions to patch tests with their own urine. Immediate reactions were not observed, and the histology suggested a toxic rather than an allergic reaction. Lynes and associates (1990b) were unable to find a urinary myotropic substance unique to IC patients. The San Diego group found IC urine to result in higher cell death of cultured transitional cells than normal urine, suggesting a toxic compound in the urine of some IC patients (Parsons and Stein, 1990). They identified heat-labile, cationic components of low molecular weight that bind to heparin and that when separated from the bulk of urinary wastes are cytotoxic to urothelial cells as well as underlying smooth muscle cells (Parsons et al, 2000). They reported a 12% increase in 72-kD stress protein in cells treated with urine from IC patients compared with controls (Ito et al, 1998).

Others have not been able to demonstrate in-vitro cytotoxicity (Beier-Holgersen et al, 1994) or immunohistochemical changes in the nociceptive centers in the spinal cord or bladder wall when IC urine was compared with control urine (Baykara et al, 2003). Efforts to induce an IC-like picture in the rabbit bladder from exposure to urine of IC patients have failed to demonstrate conclusive changes (Perzin et al, 1991; Ruggieri et al, 1993; Kohn et al, 1998). Increased levels of soluble mediators associated with activation of sensory neurons and/or mast cells have been found in the urine of both IC and bladder cancer patients (Okragly et al, 1999).

Circumstantial evidence for the toxicity of IC urine is suggested by the failure of substitution cystoplasty and continent diversions in some of these patients because of the development of pain or contraction of the bowel segment over time (Nielsen et al, 1990; Baskin and Tanagho, 1992; Trinka et al, 1993; Lotenfoe et al, 1995) and the histologic findings similar to IC found to occur in

bowel used to augment the small-capacity IC bladder (Singh and Thomas, 1996; McGuire et al, 1973). Intestinal mucosa in contact with urine undergoes progressive changes as long as 3 years after surgery, and the significance of the histologic IC-like changes has been questioned (MacDermott et al, 1990; Davidsson et al, 1996).

The Role of Genetics in BPS

Warren and colleagues (2001) report findings from a small cohort of twins that demonstrated a greater concordance of BPS among monozygotic than among dizygotic twins. This finding suggested that there could be a genetic susceptibility to BPS. A later study by the same research group (Warren et al, 2004) suggested that adult female first-degree relatives of patients with BPS may have a prevalence of IC 17 times that found in the general population. This coupled with the previously reported twin data suggests, but does not prove, a genetic component adds to the susceptibility for BPS.

The report by Weissman and associates (2004) of the increased frequency of BPS in patients and their first-degree relatives with panic disorder and other seemingly disparate disorders has suggested that there is a familial syndrome consisting of BPS and other disorders of possible autonomic or neuromuscular dysfunction. More recent studies by the same group (Talati et al, 2008) from a case-control study suggested that this syndrome might include other anxiety disorders as well and that families with and without this collection of symptoms were genetically distinguishable on chromosome 13.

Gene expression profiles in cultured IC cells have been investigated and compared with controls (Erickson et al, 2008a). Few differences were appreciated, indicating that rather than being genetically based the abnormal urothelium in BPS/IC may be due to post-translational changes and/or to the bladder environment. It has been suggested that epigenetic reprogramming mechanisms in the bladder may provide an explanation for uroepithelial, mast cell, and nerve cell abnormalities in BPS/IC, as well as propagation of this altered state in the absence of the signal that may have triggered it (Elgavish, 2009). Viewing medically unexplained symptoms from the perspective of underlying developmental influences involving epigenetic modulation of gene expression that affect function of a variety of organs based on familial predispositions rather than from the traditional viewpoint of isolated organ-originating diseases may open up new areas of investigation for this class of "functional" disorders (Buffington, 2009).

Other Potential Causes

Various other etiologic theories have been proposed (Ratliff et al, 1994), but none has received much scientific support. Voiding almost hourly, always having to be aware of how far the nearest restroom facilities are, and suffering constant pain would be expected to lead to psychological stress. However, could there be individual differences in the propensity to develop IC that result from a dysregulation of anxiety and mood (Nesse, 1999; Bodden-Heidrich, 2004)? **There are no data currently to suggest that stress *initiates* the chronic syndrome of BPS/IC, although it certainly can increase symptom severity** (Lutgendorf et al, 2000). Cats restricted to indoor living are five times more likely to have urinary problems as cats allowed outdoors (Buffington, 2002). Female patients with PBS/IC have been shown to have increased heart rate at baseline and throughout a laboratory mental stress challenge but did not demonstrate greater autonomic reactivity to stress (Lutgendorf et al, 2004). Until stress can be shown to produce PBS/IC de novo in humans, it is just as reasonable to speculate that the stress is a result of the syndrome as a primary cause of it.

Speculation that abnormalities in or obstruction of lymphatics or vascular structures is causative has never been borne out. The fact that some of these patients have had a hysterectomy probably relates more to the attempt of the physician to treat chronic pelvic pain than a postsurgical change causing the IC syndrome (Chung, 2004).

The knowledge that there is at least a 5:1 female-to-male preponderance immediately makes the role of the hormonal milieu potentially important (Bjorling and Wang, 2001). Paradoxically, it is known that estrogens can control hematuria in hemorrhagic cystitis, perhaps by decreasing the fragility of the mucosal microvasculature of the bladder (Liu et al, 1990). Estradiol augments while the estrogen receptor blocker tamoxifen inhibits mast cell secretion (Vliagoftis et al, 1992). Bladder mast cells express high-affinity estrogen receptors, and there is a higher number of such cells present in patients with IC compared with controls. Although this may help explain why IC is so common in women, the hormonal role can only account for the propensity of IC to occur in females and not be the ultimate etiology.

Pelvic floor dysfunction has been associated with PBS/IC for many years (Schmidt and Vapnek, 1991), and uncontrolled trials suggest that treatment of this disorder can be effective in ameliorating symptoms (Lilius et al, 1973; Doggweiler-Wiygul et al, 2001, 2002; Holzberg et al, 2001; Weiss, 2001; Oyama et al, 2004). Speculation that abnormalities of the pelvic floor muscular function may contribute to the cause of some cases of CPPS in men are well accepted (Segura et al, 1979; Schmidt and Vapnek, 1991; Zermann et al, 1999) and a similar case might be made for patients with PBS/IC, although scientific support for a direct etiologic relationship is lacking.

One can understand the complexity of BPS/IC by looking at the myriad theories of etiology and the associated disorders that have been described. Complex functional disorders with patterns of comorbidity, where there is overlap of what had once been regarded as independent syndromes, appear to fall outside the biomedical framework. It has been said that they "fully escape the profession's divided and divisive grip. By their mere existence, they challenge the medical community's view of the body, their understanding of what it is to be human and question whether present approaches to obtaining knowledge are adequate for helping people who suffer" (Kirkengen and Ulvestad, 2007).

Key Points: Etiology

- Both stress and pelvic floor dysfunction can contribute to BPS symptom severity and may be targets for treatment. Whether they can be contributing initiators of the syndrome complex is unclear at this time. The 5:1 female preponderance suggests hormonal involvement in etiology.

PATHOLOGY

Please see the Expert Consult website for more discussion of this topic.

Key Points: Pathology

- The role of histopathology is primarily to exclude other possible diagnoses that might be responsible for the symptoms.
- There is no histology pathognomonic of BPS, and one cannot make the diagnosis on pathology alone in the absence of the cardinal symptoms.
- Completely normal-appearing bladder biopsy specimens in symptomatic patients are not uncommon.

DIAGNOSIS

BPS/IC can be considered a functional pain disorder (Mayer and Bushnell, 2009) and one of the chronic visceral pain syndromes, affecting the urogenital and rectal area, many of which are well described but poorly understood (Wesselmann et al, 1997; Wesselmann, 2001). These include vulvodynia, orchialgia, penile pain, perineal pain, and rectal pain. In men, many of the entities have now been included in the rubric of CPPS and can be difficult to distinguish from BPS/IC (Hakenberg and Wirth, 2002; Forrest and Schmidt, 2004). The diagnosis of BPS/IC is by its very nature based on the definition. In the past this was by default the symptom criteria enumerated by the NIDDK (Hanno et al, 1999a; Hanno et al, 1999b) (see Table 12–2). **It has now morphed largely into a diagnosis of chronic pain, pressure, or discomfort associated with the bladder, usually accompanied by urinary frequency in the absence of any identifiable cause** (Hanno et al, 2005a, 2005b). Diagnostic approaches vary widely, and **general agreement on a diagnostic algorithm remains a future goal** (Chai, 2002; Nordling, 2004; Nordling et al, 2004). A current algorithm is illustrated in Figure 12–9. The disorder can be very difficult to diagnose until symptoms become well established, unless one has a high level of suspicion (Porru et al, 2004). **Frequency and pelvic pain of long duration perceived to be related to the bladder unrelated to other known causes establishes a working diagnosis.** It is often difficult for patients to distinguish between sensations of pain, pressure, discomfort, and urgency. **Ask a patient why he or she voids hourly, and it is usually because of discomfort rather than convenience.** Heavy reliance on other aspects of the NIDDK research criteria will result in underdiagnosing more than half of the cases (Hanno et al, 1999b). **IC symptom scales** (O'Leary et al, 1997; Goin et al, 1998; Moldwin and Kushner, 2004), **such as the American Urological Association's symptom score for BPH, are designed to evaluate the severity of symptomatology and monitor disease progression or regression with or without treatment. They have not been validated as diagnostic criteria.**

One must rule out infection and less common conditions including but not limited to carcinoma (Utz and Zincke, 1974; Tissot et al, 2004), eosinophilic cystitis (Hellstrom et al, 1979; Sidh et al, 1980; Littleton et al, 1982; Aubert et al, 1983; Abramov et al, 2004), **malakoplakia, schistosomiasis, scleroderma** (Batra and Hanno, 1997), **and detrusor endometriosis** (Sircus et al, 1988; Price et al, 1996). In men younger than the age of 50, video-urodynamics are useful to rule out voiding dysfunction resulting from vesical neck obstruction, "pseudo" dyssynergia, or impaired contractility (Kaplan et al, 1996). Musculoskeletal dysfunction may also play a role in causation or increasing symptom severity and should be looked for in the diagnostic phase of evaluation (Prendergast and Weiss, 2003). Reports of successful treatment of IC symptoms by laparoscopic adhesiolysis (Chen et al, 1997) or urethral diverticulum excision (Daneshgari et al, 1999) give credence to the fact that IC is a diagnosis of exclusion. Many drugs including cyclophosphamide, aspirin, nonsteroidal anti-inflammatory agents, and allopurinol have caused a nonbacterial cystitis that resolves with drug withdrawal (Bramble and Morley 1997; Gheyi et al, 1999).

Various gynecologic problems can mimic the pain of IC (Kohli et al,1997). The pelvic congestion syndrome, a condition of the reproductive years and equally prevalent among parous and nulliparous women, is manifest by shifting location of pain, deep dyspareunia and postcoital pain, and exacerbation of pain after prolonged standing (Stones, 2003). Similar symptoms can be seen in BPS/IC. Other gynecologic disorders can include pelvic

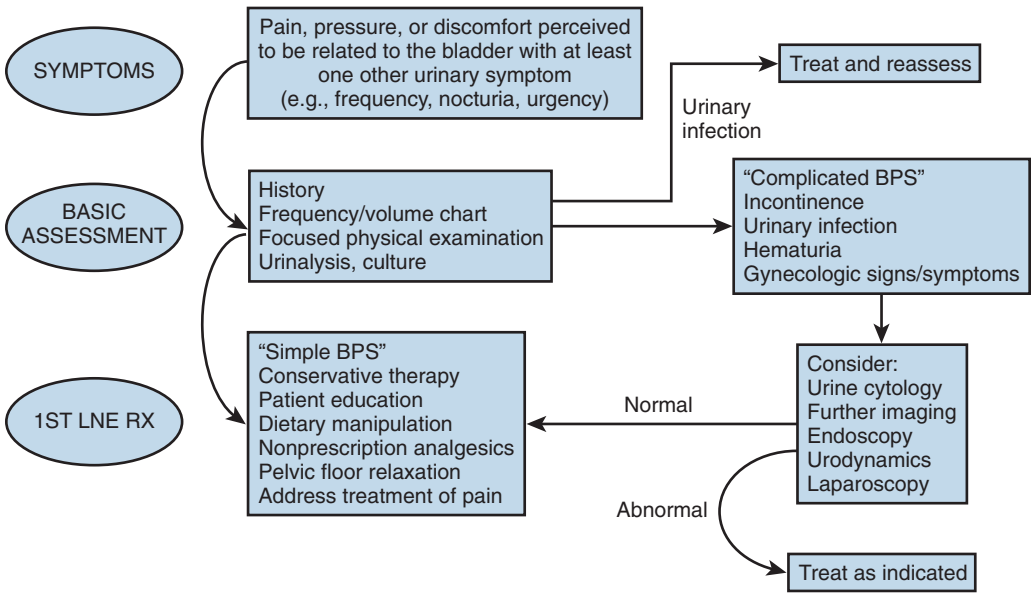


Figure 12–9. Diagnostic algorithm for bladder pain syndrome (BPS).

tumors, vaginal atrophy, vulvodynia, vestibulitis, pelvic relaxation, pelvic adhesive disease, levator ani myalgia, and undiagnosed chronic pelvic pain (Myers and Aguilar, 2002). Pelvic surgery is more common in women with a diagnosis of BPS/IC than in a control population as studied by Ingber and associates (2008). In this series the diagnosis of BPS/IC occurred 1 to 5 years after hysterectomy in most patients, suggesting that pelvic surgery may be performed for pain related to undiagnosed BPS.

Endometriosis can be a cause of pelvic pain (Evans et al, 2007), an idea largely based on findings of two randomized, placebo-controlled studies of laser laparoscopy (Sutton et al, 1995, 1997; Abbott et al, 2004). Nevertheless, it is disconcerting that any claim linking endometriosis with pain fails to account for the common experience that identical lesions can be found in symptomatic and asymptomatic women (Vercellini, 1997). Between 2% and 43% of asymptomatic women are found to have endometriosis (Moen and Stokstad, 2002). Furthermore, there does not appear to be any risk for patients with asymptomatic mild endometriosis to develop symptoms even after more than 10 years (Moen and Stokstad, 2002). Although 70% to 90% of women with chronic pelvic pain have endometriosis, this does not definitively establish causation (Gambone et al, 2002). For these reasons, laparoscopy, which is not considered essential before initiating hormonal treatment of endometriosis (Ling, 1999; Howard, 2003b), should not be considered a part of any routine evaluation of BPS/IC unless an experienced practitioner believes it is likely to benefit the patient.

A presumptive diagnosis can be made merely by ruling out known causes of frequency and pain/urgency in a patient with compatible chronic symptoms (Table 12–8). Often this will involve a complete history, physical examination, appropriate cultures, and local cystoscopy. **In the absence of microhematuria the value of cytology is questionable** (Duldulao et al, 1997) **but something we still consider important, especially if bladder carcinoma in-situ is a serious possibility, as in patients older than 40 and those with a smoking history.** The report of a large series of BPS/IC patients indicating that 1% actually had transitional cell carcinoma and that four of the six cancer patients did not have microhematuria, provides evidence for the justification of local cystoscopic examination (Tissot et al, 2004).

It must be recognized that one may sacrifice a certain level of confidence in the diagnosis without the supporting evidence that can be furnished by additional studies. In a long-term illness such as IC, many patients and physicians ultimately want to base a diagnosis and treatment plan on the most complete data set possible (Rovner and Wein, 1999). **A more thorough evaluation for IC would also include a urodynamic evaluation and cystoscopy under anesthesia with hydrodistention of the bladder** (Hanno et al, 1990; Hanno, 1994b). **Bladder biopsy is indicated only if necessary to rule out other disorders that might be suggested by the cystoscopic appearance. Cystoscopy under anesthesia with bladder distention has been important in the identification of a Hunner lesion.** Experimental data suggest that measurement of increased nitric oxide levels in the bladder can also accurately identify those with ulcerative disease (Logadottir et al, 2004). The diagnosis is generally subject to more rigorous testing in Europe (Fall et al, 2008) than in North America, where symptoms in the absence of other obvious causes seems to be the gold standard (Nordling 2004; Nordling et al, 2004; Hanno et al, 2005a). Japanese guidelines are described in Table 12–9.

Although sensations reported during cystometric bladder filling are subjective, they have a normal pattern and may be helpful in

Table 12–8.

International Consultation on Incontinence 2009: Diagnosis of Bladder Pain Syndrome

History

A general thorough medical history should emphasize:

1. Previous pelvic surgery
2. Previous urinary tract infection
3. Bladder history and urologic diseases
4. Location of pelvic pain and relationship to bladder filling/emptying
5. Characteristics, onset, correlation of pain with other events
6. Previous pelvic irradiation
7. Autoimmune diseases
8. Associated syndromes (irritable bowel, fibromyalgia, chronic fatigue)

Physical Examination

The physical examination should emphasize:

1. Standing: kyphosis, scars, hernia
2. Supine: abduction/adduction of hips, hyperesthetic areas
3. Females: Vaginal examination with pain mapping of vulvar region, vaginal palpation for tenderness of the bladder, urethra, levator and adductor muscles of the pelvic floor
4. Males: digital rectal examination with pain mapping of the scrotal-anal region and palpation of tenderness of the bladder, prostate, levator and adductor muscles of the pelvic floor and scrotal contents

Laboratory Testing

1. Urinalysis
2. Urine culture
3. Urine cytology in risk groups

Symptom Evaluation

1. Voiding diary
2. O'Leary-Sant Symptom and Problem Score
3. Visual analog scale for pain in the last 24 hours

Urodynamics (optional)

Cystoscopy with or without hydrodistention under anesthesia (optional)

Bladder biopsy (optional)

From Hanno P, Lin AT, Nordling J, et al. Bladder pain syndrome. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence. Paris: Health Publication Ltd.; 2009. p. 1459–518.

Table 12–9.

Recommended Tests for Diagnosis of Interstitial Cystitis

MANDATORY	RECOMMENDED	OPTIONAL
Clinical history	Urine culture	Ultrasonography
Physical examination	Urine cytology	Urodynamic study
Urinalysis	Symptom scores	Radiographic examination
	Quality of life scores	Potassium test
	Frequency-volume chart	Biopsy
	Residual urine measurement	
	Prostate specific antigen	
	Cystoscopy	
	Hydrodistention	

From Homma Y, Ueda T, Ito T, et al. Japanese guideline for diagnosis and treatment of interstitial cystitis. Int J Urol 2009; 16:4–16. ©Japanese Urological Association.

distinguishing a bladder pathologic process (Wyndaele, 1998). Many dispute the need for urodynamic study (Cameron and Gajewski, 2009), but Siroky (1994) and Kim and colleagues (2009b) argue that not only can it help to assess bladder compliance and sensation and reproduce the patient's symptoms during bladder filling but also it can help to rule out detrusor overactivity. Women with pain on filling can be indistinguishable from those with detrusor overactivity in their perception of bladder fullness (Creighton et al, 1991). **One should be wary of diagnosing IC in patients with discrete, involuntary bladder contractions whose symptoms respond to antimuscarinic therapy. The two problems coexist in 15% to 19% of patients** (Gajewski and Awad, 1997; Kirkemo et al, 1997), **but the pathophysiology is possibly very different.** Patients who respond to anticholinergic medication tend not to respond to standard therapy for IC (Perez-Marrero et al, 1987). If involuntary contractions are noted and the patient's symptoms of frequency and pain continue despite treatment for overactive bladder, one is on firmer ground in considering a diagnosis of IC. Complex cases may benefit from full video-urodynamic studies (Carlson et al, 2001).

Cystometry in conscious IC patients generally demonstrates normal function, the exception being decreased bladder capacity and hypersensitivity. Pain on bladder filling that reproduces the patient's symptoms is very suggestive of IC. **Bladder compliance in patients with IC is normal, because hypersensitivity would prevent the bladder from filling to the point of noncompliance** (Siroky, 1994; Rovner and Wein, 1999). The possible addition of including a second cystometrogram after instillation of intravesical lidocaine to help to determine if pain is bladder related is a provocative one worth further study (Teichman et al, 1997). It is not uncommon to find evidence of outlet obstruction in BPS/IC, presumably related to associated pelvic floor dysfunction (Cameron and Gajewski, 2009).

Long before it was considered a diagnostic tool, cystoscopy with hydrodistention of the bladder was used as a therapeutic modality for IC (Bumpus, 1930). **When done under anesthesia this procedure allows for sufficient distention of the bladder to afford visualization of either glomerulations or Hunner ulcers** (Figs. 12–10 and 12–11). **After filling to 80 cm H_2O for 1 to 2 minutes, the bladder is drained and refilled. The terminal portion of the effluent is often tinged with blood. Reinspection will reveal the pinpoint petechial hemorrhages that develop throughout the bladder after distention and are not usually seen after examination without anesthesia** (Nigro and Wein, 1997).

Glomerulations are not specific for IC (Erickson, 1995; Waxman et al, 1998), and only when seen in conjunction with the clinical criteria of pain and frequency can the finding of glomerulations be viewed as potentially significant. **Glomerulations can be seen after radiation therapy, in patients with carcinoma, after exposure to toxic chemicals or chemotherapeutic agents, and often in patients on dialysis or after urinary diversion when the bladder has not filled for prolonged periods.** They have been reported in the majority of men with **prostate pain syndromes,** begging the question as to whether CPPS in men is closely linked with IC (Berger et al, 1998). They are observed in 20% of men undergoing transurethral prostatectomy for lower urinary tract symptoms (Furuya et al, 2007). We have speculated that they may simply reflect the response of the bladder to distention after a prolonged period of chronic underfilling because of sensory urgency rather than result from a primary pathologic process. Although the presence of a Hunner ulcer has been associated with pain and urinary urgency, neither the findings of bloody irrigating fluid nor

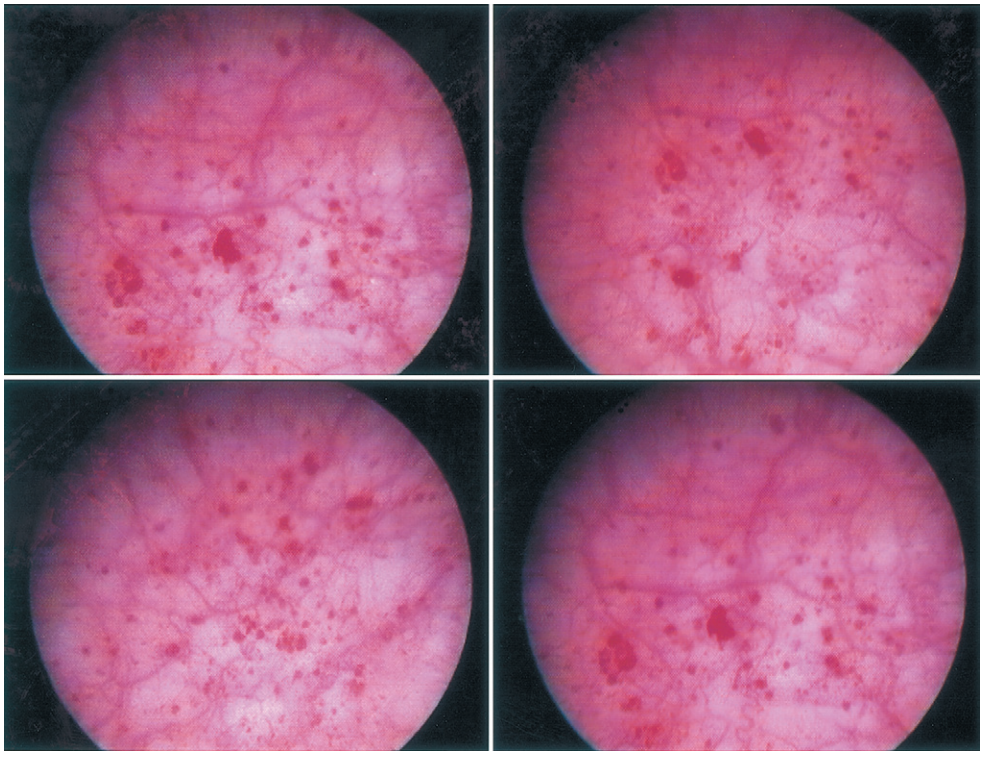


Figure 12–10. Typical appearance of glomerulations after bladder distention in a patient with nonulcerative bladder pain syndrome.

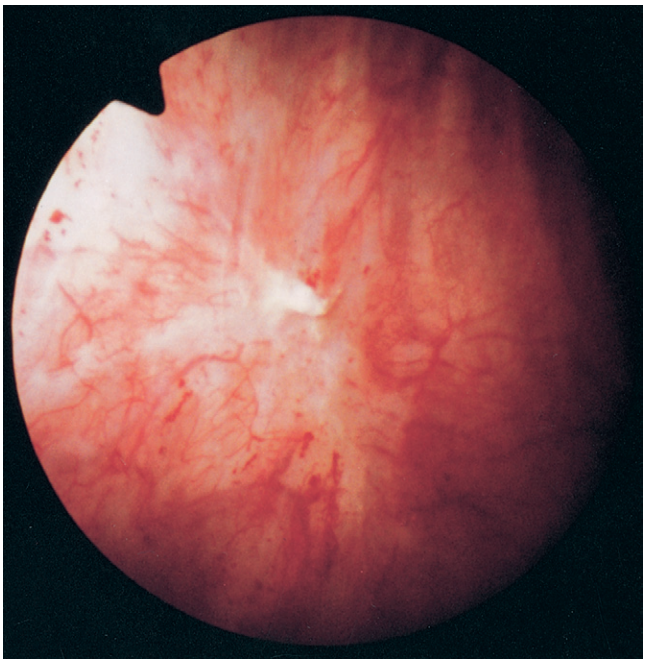


Figure 12–11. Typical appearance of a Hunner lesion in a patient with bladder pain syndrome before bladder distention.

glomerulations are strongly associated with any particular symptom in patients in the IC database (Messing et al, 1997).

Further confusion arises when the patient demonstrates the symptoms of IC but the cystoscopic findings under anesthesia are completely normal. This occurred in 8.7% of patients undergoing cystoscopy with hydrodistention of the bladder entered into the IC database (Messing et al, 1997). Awad and colleagues recognized this entity soon after the NIDDK research criteria had been described. They reported on a series of patients in whom the symptomatology, urodynamic evaluation, histology, and response to therapy were identical to that of IC and in whom findings on cystoscopy with hydrodistention of the bladder were normal. It was termed *idiopathic reduced bladder storage* (Awad et al, 1992). Clinical, urodynamic, and cystoscopic data strongly suggest that the presence of glomerulations is not selecting out a meaningful difference in patients with symptoms of BPS/IC (Al Hadithi et al, 2002). **The presence of glomerulations on cystoscopy under anesthesia meeting the NIDDK criteria may identify a group of patients with worse daytime frequency and nocturia and lower bladder capacity under anesthesia but does not have any relationship to biopsy findings, bladder pain, or urgency** (Erickson et al, 2005).

The Search for a Marker

What is the value of a "diagnostic test" in what is essentially a clinical syndrome defined by a symptom-complex? If a patient has chronic pain associated with the bladder usually accompanied by urinary frequency with no discernible cause, BPS/IC is diagnosed. In essence, once well-characterized pathologic entities are ruled out, the patient makes the diagnosis by relating symptoms; much like a patient with impotence makes that diagnosis. Testing for impotence may give clues as to etiology but impotence cannot be ruled out in a patient who cannot function sexually by doing a test!

This is not to say that establishment of a valid diagnostic marker would not be a major advance in our understanding of IC. Just as with phenotyping, it will be important largely to the extent that it can predict prognosis in a given group of patients, predict response to therapy in a given group of patients, and/or distinguish between BPS/IC and another possible cause of the symptom-complex that has been diagnosed. Ultimately, marker identification may enable us to stratify patients with the symptom-complex in such a way that treatments will be specific to the specific etiology (disease) the patient has. As various causes are identifiable, the diagnosis of BPS may itself become a rarity, much as what has happened to "acute urethral syndrome" (Stamm et al, 1980).

In just such an effort, numerous investigators have looked at the mast cell as a possible diagnostic marker for IC. The current standard involves detrusor muscle biopsy specimens examined with tryptase staining of 3-µm thick sections, with every seventh section used for quantification (Larsen et al, 2008). The finding of 27 mast cells/mm^3 is considered indicative of mastocytosis. The results in the past have been very contradictory; and at this time, in terms of the use of mast cell criteria in diagnosis, the issue remains moot (Kastrup et al, 1983; Feltis et al, 1987; Holm-Bentzen et al, 1987c; Lynes et al, 1987; Hanno et al, 1990; Christmas and Rode, 1991; Moore et al, 1992; Dundore et al, 1996; Hofmeister et al, 1997). Methylhistamine, a histamine metabolite found in the urine and thought to reflect mast cell activation was not associated with symptom scores, response to bladder distention, cystoscopic findings, or bladder biopsy features, including mast cell determination by tryptase staining (Erickson et al, 2004).

Attempts have been made to look at other markers (Erickson, 2001), including eosinophil cationic protein (Lose et al, 1987), GAG excretion (Hurst et al, 1993), and urinary histamine and methylhistamine (El Mansoury et al, 1994). Proposals for measuring smooth muscle isoactin expression (Rivas et al,1997) and urinary levels of neurotrophin-3, nerve growth factor, glial cell line–derived neurotrophic factor, and tryptase (Okragly et al, 1999) have been suggested. Low levels of GP51, a urinary glycoprotein with a molecular weight of 5 kD have been documented in IC patients compared with normal controls and patients with other urinary tract diseases (Byrne et al, 1999). Cell cultures (Elgavish et al, 1997) have been proposed as a screening technique.

The measurement of elevated nitric oxide levels in air instilled and incubated in the bladder has been proposed for office screening (Lundberg et al, 1996; Ehren et al, 1999). Increased levels of endogenously formed nitric oxide in patients with IC correspond to increased iNOS mRNA expression and protein levels in these patients. Furthermore, iNOS was found to be localized to the urothelium but it was also found in macrophages in the bladder mucosa (Koskela et al, 2008). The simple technique allows for discrimination of ulcer from nonulcer disease (Logadottir et al, 2004) and may provide an objective measure of treatment response (Hosseini et al, 2004).

The urine APF identified by Keay and colleagues (see earlier) may prove to be an accurate marker of BPS/IC if it can be confirmed by other centers and become a biochemical rather than biologic assay. **It appears to have the highest sensitivity and specificity of the variety of possible markers tested** and fits nicely into an etiologic schema (Keay et al, 2001; Erickson et al, 2002). It has also been shown to differentiate men with PBS/IC symptoms from controls and differentiate men with bladder-associated pain and irritative voiding symptoms from those with pelvic/perineal pain alone and other nonspecific findings compatible with the CPPS in men (CPPS III), previously referred to as "nonbacterial prostatitis" (Keay et al, 2004a). This question as to whether CPPS and BPS/IC are two different disorders will

doubtless be the subject of future research and is an integral question that the NIDDK is hoping to answer with current research (see www.mappnetwork.org).

Much work in markers is ongoing. Uroplakin III-delta 4 is a potential marker for identifying nonulcerative IC (Zeng et al, 2007). Most recently, the feasibility of diagnosing IC in humans and domestic cats from the spectra of dried serum films (DSFs) using infrared microspectroscopy has been reported (Rubio-Diaz et al, 2009).

Potassium Chloride Test

Parsons has championed an intravesical KCl challenge, comparing the sensory nerve provocative ability of sodium versus potassium using a 0.4-M KCl solution. Pain and provocation of symptoms constitutes a positive test. **Whether the results indicate abnormal epithelial permeability in the subgroup of positive patients or hypersensitivity of the sensory nerves is unclear.** Normal bladder epithelium can never be absolutely tight, and there is always some leak, however small (Hohlbrugger, 1997). The concentration of potassium used is 400 mEq/L, far exceeding the physiologic urinary concentrations of 20 to 80 mEq/L depending on dietary intake (Vander, 1995). Healthy controls can distinguish KCl from sodium chloride, although they do not experience severe pain (Roberto et al, 1997). **The hope is that this test may stratify patients into those who will respond to certain treatments (perhaps those designed to fortify the GAG layer), but to date this information is lacking** (Teichman and Nielsen-Omeis, 1999).

Used as a diagnostic test for IC, the KCl test is not valid (Chambers et al, 1999). The gold standard in defining BPS/IC for research purposes has been the NIDDK criteria. These criteria are recognized to constitute a set of patients that virtually all researchers can agree have PBS/IC, although they are far too restrictive to be used in clinical practice (Hanno et al, 1999b). Thus, this group of patients should virtually all be positive if the KCl test is to have the sensitivity needed to aid in diagnosis. **Up to 25% of patients meeting the NIDDK criteria will have a negative KCl test** (Parsons et al, 1998). **In the group it should perform the best in it is lacking in sensitivity.**

When we look at the specificity side of the equation, in the universe of unselected persons, recent studies reported a 36% false-positive rate in asymptomatic men (Yilmaz et al, 2004) and a 33% positive rate in a fixed population of Turkish textile workers (Sahinkanat et al, 2008). In the patient population with confounding conditions for which we would want help in sorting out BPS/IC from other disorders, 25% of patients with overactive bladder test positive and virtually all patients with irritative symptoms from radiation cystitis and urinary tract infection test positive (Parsons et al, 1994b, 1998). The results with CP/CPPS in men are variable, but 50% to 84% of men have been reported to test positive (Parsons and Albo, 2002; Yilmaz et al, 2004; Parsons et al, 2005). In women with pelvic pain the results are similar (Parsons et al, 2002b); and based on these findings, Parsons and colleagues (2002a) have expressed the view that BPS/IC may affect over 20% of the female population of the United States. Another way to interpret the findings would be that the KCl test is very nonspecific, missing a significant number of BPS/IC patients and overdiagnosing much of the population.

Prospective and retrospective studies looking at the KCl test for diagnosis in patients presenting with symptoms of BPS/IC have found no benefit of the test in comparison with standard techniques of diagnosis (Chambers et al, 1999; Gregoire et al, 2002; Kuo, 2003), **nor is it useful in monitoring results of treatment** (Sairanen et al, 2007). The development of a painless modification of the KCl test (Daha et al, 2003) using cystometric capacity and a 0.2-M solution may improve acceptability among patients, but further research is needed to determine what place, if any, this test will have in the diagnostic or treatment algorithm.

Confusable Diseases (Differential Diagnosis)

The diagnosis of BPS can be made on the basis of exclusion of confusable diseases and confirmed by the recognition of the presence of the specific combination of symptoms and signs of BPS. If the main urinary symptoms are not explained by a single diagnosis, the presence of a second diagnosis is possible. One must remember that BPS may occur together with confusable diseases such as chronic or remitting urinary infections or endometriosis. Table 12–10 summarizes confusable diseases related to BPS and their mode of exclusion based on aforementioned diagnostic proposals and procedures as outlined by the ESSIC group (van de Merwe et al, 2008).

Key Points: Diagnosis

- Bladder pain syndrome remains a diagnosis of exclusion in patients who meet the symptomatic criteria for diagnosis after confusable disorders have been ruled out.
- Cystoscopy with bladder distention under anesthesia aids in the diagnosis of a Hunner lesion but is not considered a prerequisite for beginning treatment.
- Cystoscopy and upper tract imaging are mandatory in patients with hematuria who have not been previously evaluated for this finding.
- Urodynamics are optional and generally reserved for complex cases.

CLASSIFICATION

IC was originally described as bladder disease with severe inflammation of the bladder wall described by Hunner (1915) as an ulcer. The lesion is, however, not an ulcer but a vulnus (weakness, vulnerability) that can ulcerate on distention, and the name of the bladder lesion has consequently been changed to *Hunner lesion* (van de Merwe et al, 2008). The finding of a Hunner lesion could therefore originally be regarded as a diagnostic criterion for IC. Messing and Stamey introduced glomerulations as another typical finding for IC, and this was included in the NIDDK criteria (Wein et al, 1990). Fall and associates (1987) proposed that patients with Hunner lesion (classic IC) and patients with glomerulations (nonulcerative type) represented two different subtypes with different clinical pictures, different outcomes, and different responses to treatment (Peeker and Fall, 2002), meaning that patients fulfilling the NIDDK criteria represent at least two different patient populations. Moreover, up to 60% of patients clinically believed to have BPS by experienced clinicians do not fulfill the NIDDK criteria (Hanno et al, 1999b) and whether these patients are comparable to the patients fulfilling the NIDDK criteria is unknown. Finally, Japanese urologists consider that "interstitial cystitis" should be

Table 12–10.

Confusable Diseases for Bladder Pain Syndrome

CONFUSABLE DISEASE	EXCLUDED OR DIAGNOSED BY
Carcinoma and carcinoma in situ	Cystoscopy and biopsy
Infection with:	
Common intestinal bacteria	Routine bacterial culture
Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma hominis, Mycoplasma genitalium, Corynebacterium urealyticum, Candida species, *Mycobacterium tuberculosis*	Special cultures
	Dipstick; if "sterile" pyuria culture for *M. tuberculosis*
Herpes simplex and human papillomavirus	Physical examination
Radiation	Medical history
Chemotherapy, including immunotherapy with cyclophosphamide	Medical history
Anti-inflammatory therapy with tiaprofenic acid	Medical history
Bladder neck obstruction and neurogenic outlet obstruction	Uroflowmetry and ultrasonography
Bladder stone	Imaging or cystoscopy
Lower ureteral stone	Medical history and/or hematuria; upper urinary tract imaging (CT or IVP)
Urethral diverticulum	Medical history and physical examination
Urogenital prolapse	Medical history and physical examination
Endometriosis	Medical history and physical examination
Vaginal candidiasis	Medical history and physical examination
Cervical, uterine, and ovarian cancer	Physical examination
Incomplete bladder emptying (retention)	Postvoid residual urine volume measured by ultrasound evaluation
Overactive bladder	Medical history and urodynamics
Prostate cancer	Physical examination and PSA test
Benign prostatic obstruction	Uroflowmetry and pressure-flow studies
Chronic bacterial prostatitis	Medical history, physical examination, culture
Chronic nonbacterial prostatitis	Medical history, physical examination, culture
Pudendal nerve entrapment	Medical history, physical examination; nerve block may prove diagnosis
Pelvic floor muscle–related pain	Medical history, physical examination

CT, computed tomography; IVP, intravenous pyelogram; PSA, prostate-specific antigen.

From van de Merwe JP, Nordling J, Bouchelouche P, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol 2008;53:60–7.

preserved as a disease name reserved for patients with urinary symptoms and cystoscopic findings of glomerulations or Hunner lesion as outlined in the NIDDK criteria (Homma, 2008).

In an attempt to unite these different philosophies into a coherent schema, the **ESSIC proposed a classification of BPS based on findings during cystoscopy with hydrodistention and morphologic findings in bladder biopsy specimens** (van de Merwe et al, 2008) (see Table 12–4). The classification includes groups not having had cystoscopy with hydrodistention (group X) as well as groups not having had morphologic investigation of bladder biopsy specimens (group XX). By using this classification future research will be able to identify if findings of glomerulations and/or Hunner lesion as well as morphologic changes in bladder biopsy specimens do have significant importance for disease prognosis and/or treatment outcome.

TREATMENT

Conservative Therapies

Once the diagnosis has been made one must decide whether to institute therapy or employ a policy of conservative "*watchful waiting*." **If the patient has not had an empirical course of *antibiotics* for his or her symptoms by the time the PBS/IC diagnosis is made, such a trial is reasonable.** Doxycycline has been reported efficacious in a Swiss study (Burkhard et al, 2004). Further attempts to alleviate symptoms with antibiotics are unlikely to be worthwhile and are not recommended in the absence of positive cultures. **Stress reduction, exercise, warm tub baths, and efforts by the patient to maintain a normal lifestyle all contribute to overall quality of life** (Whitmore, 1994). In a controlled study of 45 PBS/IC patients and 31 healthy controls, higher levels of stress were related to greater pain and urgency in patients with IC but not in the control group (Rothrock et al, 2001). Maladaptive strategies for coping with stress may impact adversely on symptoms (Rothrock et al, 2003). **Biofeedback, soft tissue massage, and other physical therapies may aid in muscle relaxation of the pelvic floor** (Mendelowitz and Moldwin, 1997; Meadows, 1999; Holzberg et al, 2001; Lukban et al, 2001; Markwell, 2001). This is a reasonable intervention given the association of pelvic floor dysfunction and BPS/IC (Peters et al, 2007a), and an NIDDK trial is now in its final phases and should provide further information on efficacy of physical therapy. A preliminary NIDDK trial demonstrated the feasibility of such a study and strongly suggested the efficacy of physical therapy when compared with global therapeutic massage (National Institutes of Health, 2008a, 2008b; FitzGerald et al, 2009).

Mendelowitz and Moldwin (1997) had a 69% success rate in 16 patients treated with electromyographic biofeedback, but treatment response did not correlate to changes in muscle identification and the placebo effect may have been considerable. Acupuncture has been used for PBS/IC and many other chronic pain syndromes. There is limited evidence that it is more effective

than nontreatment for chronic pain, and inconclusive evidence that acupuncture is more effective than placebo, sham acupuncture, or standard care (Ezzo et al, 2000). In general, results with acupuncture for PBS/IC have been disappointing (Geirsson et al, 1993).

Diet

Elaborate dietary restrictions are unsupported by any literature, but many patients do find their symptoms are adversely affected by specific foods and would do well to avoid them (Koziol et al, 1993; Koziol, 1994). **Often this includes caffeine, alcohol, artificial sweeteners, hot pepper, and beverages that might acidify the urine such as cranberry juice** (Shorter et al, 2007). **Anecdotal association of IC with many foods has spawned the recommendation of various "IC diets" with little in the way of objective, scientific basis** (Table 12–11). The only placebo-controlled dietary study, although small, failed to demonstrate a relationship between diet and symptoms (Fisher et al, 1993). Bade and colleagues found that IC patients tend to have a healthier diet than the general population but could discern no rationale for dietary or fluid intake change other than decreasing caffeine intake (Bade et al, 1997b). Nguan and coworkers (2005) performed a prospective, double-blind, crossover study consisting of crossover instillations of urine at physiologic pH (5.0) and neutral buffered pH (7.5). There was no statistically significant difference in subjective pain scores, suggesting that adjusting urine pH with diet or dietary supplements may have little influence on symptomatology. Orange and grapefruit juices, rich in potassium and citrate, tend to increase urinary pH (Wabner and Pak, 1993) but are avoided by many IC patients based on "IC diet" recommendations. Urinary alkalinization may be worth trying, but supporting studies are lacking. Some patients have had benefit with calcium glycerophosphate, an over-the-counter food acid–reducing agent (Hill et al, 2008), but supporting controlled trials are lacking.

A large NIH study in which patients with newly diagnosed BPS/IC were treated with a focus on four targeted areas: (1) how to control or manage their symptoms, (2) controlling fluid intake, (3) changing diet which may improve symptoms, and (4) bladder training/urge suppression. A behavioral approach to stress and pain management was also used to help patients learn skills to reduce stress in their lives. Forty-five percent of 135 patients randomized to this approach without additional medication were

Table 12–11.

Interstitial Cystitis Association Recommendations of Foods to Avoid

Milk/Dairy Products	**Beverages**
Aged cheeses	Alcoholic beverages including beer and wine
Sour cream	Carbonated drinks
Yogurt	Coffee
Chocolate	Tea
Vegetables	Fruit juices
Fava beans	Seasonings
Lima beans	Mayonnaise
Onions	Ketchup
Tofu	Mustard
Soybeans	Salsa
Tomatoes	Spicy foods (Chinese, Mexican, Indian, Thai)
Fruits	Soy sauce
Apples	Miso
Apricots	Salad dressing
Avocados	Vinegar
Bananas	**Preservatives and Additives**
Cantaloupes	Benzyl alcohol
Citrus fruits	Citric acid
Cranberries	Monosodium glutamate
Grapes	Artificial sweeteners
Nectarines	Preservatives
Peaches	Artificial ingredients
Pineapples	Food coloring
Plums	**Miscellaneous**
Pomegranates	Tobacco
Rhubarb	Caffeine
Strawberries	Diet pills
Juices from above fruits	Junk foods
Carbohydrates and Grains	Recreational drugs
Rye bread	Allergy medications with ephedrine or pseudoephedrine
Sourdough bread	Certain vitamins
Meats and Fish	
Aged, canned, cured processed, smoked meats and fish	
Nuts	

Modified from Interstitial Cystitis Association. IC/PBS food list. <www.ichelp.org/Document.Doc?id=7>; 2009 [accessed 15.05.11].

moderately or markedly improved at the 12-week end point (Foster et al, 2010).

Unfortunately, education and self-help are often not sufficient, and most patients will require one or more of a variety of therapies.

Oral Therapies

Some oral medications that have been used for treatment of BPS are listed in Table 12–12 and discussed in the following sections.

Amitriptyline

Amitriptyline, a tricyclic antidepressant, has become a staple of oral treatment for BPS/IC. The tricyclic antidepressants possess varying degrees of at **least three major pharmacologic actions:** (1) they have central and peripheral anticholinergic actions at some but not all sites, (2) they block the active transport system in the presynaptic nerve ending that is responsible for the reuptake of the released amine neurotransmitters serotonin and norepinephrine, and (3) they are sedatives, an action that occurs presumably on a central basis but perhaps is related to their antihistaminic properties. Amitriptyline, in fact, is one of the most potent tricyclic antidepressants in terms of blocking H_1-histaminergic receptors (Baldessarini, 1985). There is also evidence that they desensitize α_2-adrenergic receptors on central noradrenergic neurons. Paradoxically they also have been shown to block α-adrenergic receptors and serotonin receptors. Theoretically tricyclic agents have actions that might tend to stimulate predominantly β-adrenergic receptors in bladder body smooth musculature, an action that would further facilitate urine storage by decreasing the excitability of smooth muscle in that area (Barrett and Wein, 1987).

Hanno and Wein (1987) first reported a therapeutic response in IC after noting a "serendipitous" response to amitriptyline in one of their patients concurrently being treated for depression. The following year a similar report appeared relating a response to desipramine hydrochloride (Renshaw, 1988). Reasoning that a drug used successfully at relatively low dosages for many types of chronic pain syndromes, which would also have anticholinergic properties, β-adrenergic bladder effects, sedative characteristics, and strong H_1-antihistaminic activity would seem to be ideal for IC, Hanno and associates (1989) performed the first clinical trial with promising results. A subsequent follow-up study (Hanno, 1994a) reported that in 28 of 43 patients who could tolerate therapy for at least a 3-week trial at a dosage of 25 mg at bedtime gradually increasing to 75 mg at bedtime over 2 weeks, 18 had total remission of symptoms with a mean follow-up of 14.4 months, 5 dropped out because of side effects, and 5 derived no clinical benefit. Benefits were apparent within 4 weeks. All patients had failed hydrodistention and intravesical DMSO therapy. **Sedation was the main side effect.** Kirkemo and colleagues (1990) treated 30 patients and had a 90% subjective improvement rate at 8 weeks. Both studies noted that patients with bladder capacities over 450 to 600 mL under anesthesia seemed to have the best results. Another uncontrolled study of 11 patients with urinary frequency and pelvic pain (Pranikoff and Constantino, 1998) related success in 9 of the patients, with 5 reporting complete resolution of symptoms and 4 significant relief. Two patients could not tolerate the medication. In a 4-month intent-to-treat placebo-controlled double-blind trial of 50 patients, 63% on amitriptyline at doses of 25 to 75 mg (dose as tolerated) at bedtime reported good or excellent satisfaction versus 4% on placebo (van Ophoven et al, 2004a). At 19-month follow-up there was little tachyphylaxis

Table 12–12.

Some Oral Medications That Have Been Used for Treatment of BPS: Oxford System Recommendations

DRUG	LEVEL OF EVIDENCE	GRADE OF RECOMMENDATION	REFERENCES
Amitriptyline	2	B	Pranikoff and Constantino, 1998; van Ophoven et al, 2004a; van Ophoven and Hertle, 2005; Foster et al, 2010
Analgesics	4	C	
Antibiotic regimens	4	D	Wilkins et al, 1989; Durier, 1992; Warren et al, 2000
Azathioprine	4	D	Oravisto and Alfthan, 1976
Benzydamine	3	D	Walsh, 1976, 1977
Chloroquine derivatives	4	D	Oravisto and Alfthan, 1976
Cimetidine	3	C	Seshadri et al, 1994; Dasgupta et al, 2001; Lewi, 2001
Cyclosporine	3	C	Forsell, et al, 1996; Sairanen et al, 2004
Doxycycline	4	D	Burkhard et al, 2004
Duloxetine	4	–C (ineffective)	van Ophoven and Hertle, 2007
Gapapentin	4	C	Sasaki et al, 2001
Hydroxyzine	1	D	Theoharides, 1993; Sant et al, 2003
L-Arginine	1	–A (ineffective)	Korting et al, 1999; Cartledge et al, 2000
Methotrexate	4	D	Moran et al, 1999
Misoprostol	4	D	Kelly et al, 1998
Montellukast	4	D	Bouchelouche et al, 2001c
Nalmefene	1	–A (ineffective)	Stone, 1994
Nifedipine	4	D	Fleischmann et al, 1991
Quercetin	4	D	Katske et al, 2001
Sodium pentosan polysulfate	1	D (conflicting randomized controlled trial results)	Holm-Bentzen et al, 1987a; Parsons and Mulholland 1987; Mulholland et al, 1990; Parsons et al, 1993; Sant et al, 2003
Suplatast tosilate	3	D	Ueda et al, 2000; Nagaoka et al, 2003
Vitamin E	4	D	Van Duzen and Mustain, 1951

From Hanno P, Lin AT, Nordling J, et al. Bladder pain syndrome. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence. Paris: Health Publication Ltd.; 2009. p. 1459–518.

and good response rates were observed in the entire spectrum of BPS/IC symptoms (van Ophoven and Hertle, 2005).

The large, double-blind, randomized controlled trial by the NIDDK comparing education and behavioral modification with and without oral amitriptyline showed a 55% response to the study arm that included both medication and conservative therapy compared with a 45% response to education and behavioral therapy alone (Foster et al, 2010). The difference was not statistically significant. However, **if only patients who could tolerate 25 mg or more of medication or placebo are included the success compared with conservative therapy alone was 73% compared with 53% at 12 weeks.** Frequently, O'Leary-Sant symptom and problem scores also showed significant improvement. **Thus, on an intent-to-treat basis there was not significant benefit from amitriptyline, but in the 62% of patients who could tolerate the relatively low doses of drug the benefits appear substantial. Patients should be cautioned about fatigue, constipation, dry mouth, increased appetite, and dizziness.** Slowly titrating the dose on a weekly basis, beginning at 10 mg at bedtime and increasing by 10 mg weekly to a maximum tolerated dose of 50 mg at bedtime seems to minimize side effects.

Amitriptyline has proven analgesic efficacy with a **median preferred dose of 50 mg in a range of 25 to 150 mg/day.** This range is lower than traditional doses for depression of 150 to 300 mg. The speed of onset of effect is much faster (1 to 7 days) than reported in depression, and the analgesic effect is distinct from any effect on mood (McQuay and Moore, 1997). Tricyclic antidepressants are contraindicated in patients with long QT syndrome or significant conduction system disease (bifascicular or trifascicular block) after recent myocardial infarction (within 6 months), unstable angina, congestive heart failure, frequent premature ventricular contractions, or a history of sustained ventricular arrhythmias. They should be used with caution in patients with orthostatic hypotension (Low and Dotson, 1998). Doses greater than 100 mg are associated with increased relative risk of sudden cardiac death (Ray et al, 2004).

Other Antidepressants

Other tricyclic antidepressants that have been used for BPS. One trial employed the combination of doxepin and piroxicam, a cyclooxygenase-2 inhibitor. Twenty-six of 32 patients (81%) experienced remission of symptoms (Wammack et al, 2002). Another study reported satisfactory outcome with desipramine (Renshaw, 1988). The safety and efficacy of duloxetine, a serotonin and norepinephrine reuptake inhibitor, for BPS/IC was assessed in an observational study with 48 women (van Ophoven and Hertle, 2007). Patients were prospectively treated for 2 months following an uptitration protocol to the target dose of 40 mg duloxetine twice daily. Five patients were identified as responders, and 17 patients dropped out due to side effects, including nausea in all 17 patients. No severe adverse events were reported. In the 5 responders, the 40-mg twice-daily dose was required to see efficacy. Overall, duloxetine did not result in clinically meaningful improvement of symptoms.

Antihistamines

The use of antihistamines goes back to the late 1950s and stems from work by Simmons (1961), who postulated that the local release of histamine may be responsible for, or accompany, the development of, IC. He reported on 6 patients treated with pyribenzamine. The results were far from dramatic, with only half of the patients showing some response. The therapy is notable for this disease in that it was very logically conceived. It has been Theoharides who has spearheaded mast cell research in this field and been a major modern proponent of antihistamine therapy (Theoharides, 1994). He has used the unique piperazine H_1-receptor antagonist hydroxyzine, a first-generation antihistamine (Simons 2004), which can block neuronal activation of mast cells (Minogiannis et al, 1998). In 40 patients treated with 25 mg at bedtime increasing over 2 weeks (if sedation was not a problem) to 50 mg at night and 25 mg in the morning, virtually every symptom evaluated improved by 30%. Only 3 patients had absolutely no response. As with many IC drug reports, these responses were evaluated subjectively and without being blinded or placebo controlled. A subsequent study suggested improved efficacy in patients with documented allergies and/or evidence of bladder mast cell activation (Theoharides and Sant 1997a, 1997b). **No significant response to hydroxyzine was found in an NIDDK placebo-controlled trial** (Sant et al, 2003).

Why an H_2 antagonist would be effective is unclear, but uncontrolled studies show improvement of symptoms in two thirds of patients taking cimetidine in divided doses totaling 600 mg (Seshadri et al, 1994; Lewi, 1996). It proved effective in a double-blind, placebo-controlled trial (Thilagarajah et al, 2001), but histologic studies show the bladder mucosa to be unchanged before and after treatment and the mechanism of any efficacy remains unexplained (Dasgupta et al, 2001). Cimetidine is a common treatment in the United Kingdom, where over a third of patients reported having used it (Tincello and Walker, 2005).

Pentosan Polysulfate

Parson's suggestion that a defect in the epithelial permeability barrier, the GAG layer, contributes to the pathogenesis of IC has led to an attempt to correct such a defect with the synthetic sulfated polysaccharide sodium pentosan polysulfate (PPS), a heparin analogue available in an oral formulation, 3% to 6% of which is excreted into the urine (Barrington and Stephenson, 1997). It is sold under the trade name Elmiron. **Studies have been contradictory.**

Fritjofsson and coworkers (1987) treated 87 patients in an open multicenter trial in Sweden and Finland. Bladder volume with and without anesthesia was unchanged. Relief of pain was complete in 35% and partial in 23% of patients. Daytime frequency decreased from 16.5 to 13, and nocturia decreased from 4.5 to 3.5. Mean voided volumes increased by almost a tablespoon in the nonulcer group. Holm-Bentzen and associates (1987a) studied 115 patients in a double-blind, placebo-controlled trial. Symptoms, urodynamic parameters, cystoscopic appearance, and mast cell counts were unchanged after 4 months. Bladder capacity under anesthesia increased significantly in the group with mastocytosis, but this had no bearing on symptoms or awake capacity.

Parsons and colleagues (1983) had a more encouraging initial experience, and subsequently the results of two placebo-controlled multicenter trials in the United States were published (Mulholland et al, 1990; Parsons et al, 1993). In the initial study, overall improvement of greater than 25% was reported by 28% of the PPS-treated group versus 13% in the placebo group. In the later study the respective figures were 32% on drug versus 16% on placebo. Average voided volume on PPS increased by 20 mL. No other objective improvements were documented. An NIDDK 2 × 2 factorial study to evaluate PPS and hydroxyzine looked at each drug used alone and in combination and compared results with a placebo group (Sant et al, 2003). Patients were treated for 6 months. No statistically significant response to either medication

was documented. No significant trend was seen in the PPS treatment groups (34%) compared with non-PPS groups (18%). Of the 29 patients on PPS alone, 28% had global response (the primary end point) of moderately or markedly improved versus 13% on placebo, a number remarkably similar to the results in the 3-month pivotal trials, although not reaching statistical significance in the 6-month study. A subsequent industry-sponsored trial showed no dose-related efficacy response in the range of 300 to 900 mg/day, but adverse events *were* dose related (Nickel et al, 2001). Another 6-month trial that compared PPS with cyclosporine yielded a 19% response rate for PPS compared with 75% global response to cyclosporine (Sairanen et al, 2005a).

Long-term experience with PPS is consistent with efficacy in a subset of patients that may drop below 30% of those initially treated (Jepsen et al, 1998). **Tachyphylaxis seems to be uncommon in responders. Adverse events with PPS occurred in less than 4% of patients at the dose of 100 mg three times daily** (Hanno, 1997) **and include reversible alopecia, diarrhea, nausea, and rash. Rare bleeding problems have been reported** (Rice et al, 1998). It promotes cellular proliferation in vitro in the MCF-7 breast cancer cell line, and caution has been suggested in prescribing it in groups at high-risk for breast cancer and premenopausal females (Zaslau et al, 2004). **A 3- to 6-month treatment trial is generally required to see symptom improvement.** In a small trial, PPS has shown efficacy when administered intravesically (Bade et al, 1997a). It may be of value in the management of radiation cystitis (Parsons, 1986; Hampson and Woodhouse, 1994) and cyclophosphamide cystitis (Toren and Norman, 2005), but its value in the treatment of BPS/IC seems marginal.

Immunosuppressant Drugs

Cyclosporine. Cyclosporine, a widely used immunosuppressive drug in organ transplantation, was the subject of a novel BPS trial (Forsell et al, 1996). Eleven patients received cyclosporine for 3 to 6 months at an initial dose of 2.5 to 5 mg/kg/day and a maintenance dose of 1.5 to 3 mg/kg/day. Micturition frequency decreased, and mean and maximum voided volumes increased significantly. Bladder pain decreased or disappeared in 10 patients. After cessation of treatment, symptoms recurred in the majority of patients.

In a longer-term follow-up study, 20 of 23 refractory IC patients on cyclosporine therapy followed for a mean of 60.8 months became free of bladder pain. Bladder capacity more than doubled. Eleven patients subsequently stopped therapy; and in 9 the symptoms recurred within months but responded to reinitiating cyclosporine (Sairanen et al, 2004). Sairanen and colleagues (2005b) further found that cyclosporine was far superior to sodium PPS in all clinical outcome parameters measured at 6 months. Patients who responded to cyclosporine had a significant reduction of urinary levels of EGF (Sairanen et al, 2008).

Suplatast Tosylate. Suplatast tosylate is an immunoregulator that selectively suppresses IgE production and eosinophilia via suppression of helper T cells that produce interleukin-4 and interleukin-5. It is used in Japan to treat allergic disorders, including asthma, atopic dermatitis, and rhinitis. Ueda and colleagues (2000) reported a small study in 14 women with IC. Treatment for 1 year resulted in a significantly increased bladder capacity and decreased urinary urgency, frequency, and lower abdominal pain in 10 women. Concomitant changes occurred in blood and urine markers, suggesting an immune system response. Larger, multicenter, randomized controlled trials in the United States and Japan have not led to the governmental approval of the BPS/IC indication or the introduction of the drug into the United States.

Azathioprine and Chloroquine Derivatives. In a single report in 1976, Oravisto and Alfthan (1976) used azathioprine or chloroquine derivatives for BPS patients not responding to other treatments. About 50% patients responded.

Mycophenolate Mofetil. In an aborted multicenter randomized placebo-controlled NIDDK trial, mycophenolate mofetil (Cellcept 1 to 2 g/day in divided doses) failed to show efficacy in the treatment of symptoms of refractory BPS/IC (National Institutes of Health, 2007). The trial, which included 59 patients randomized 2:1 to the active arm, was halted when the U.S Food and Drug Administration issued a new black box warning for the drug (*miscarriage and congenital malformations have been associated with its use*), and **an interim analysis showed no benefit.**

Miscellaneous Agents

L-Arginine. Foster and colleagues (1997) were the original proponents of L-arginine in the therapy of IC. Eight patients with IC were given 500 mg of L-arginine three times daily. After 1 month, urinary NOS activity increased eightfold and 7 of the 8 patients noticed improvement in symptoms. An open-label study of 11 patients showed improvement in all 10 of the patients who remained on L-arginine for 6 months (Smith et al, 1997).

An open-label study of 9 women in Sweden failed to find any change in symptom scores or in nitric oxide production in the bladder (Ehren et al, 1998). A placebo-controlled randomized trial of 53 BPS/IC patients could find no difference on an intent-to-treat analysis between drug and placebo-treated patients (Korting et al, 1999). A smaller randomized placebo-controlled crossover trial of 16 BPS patients found no clinically significant improvement with L-arginine and concluded that it could not be recommended for IC treatment (Cartledge et al, 2000).

The body of evidence does not support the use of L-arginine for the relief of symptoms of IC.

Quercitin. Quercetin, a bioflavonoid available in many over-the-counter products, may have the anti-inflammatory effects of other members of this class of compounds found in fruits, vegetables, and some spices. Katske and coworkers (2001) administered 500 mg twice daily to 22 BPS patients for 4 weeks. All but 1 patient had some improvement in the O'Leary-Sant symptom and problem scores as well as in a global assessment score. Further studies are necessary to determine efficacy.

Antibiotics. Warren and associates (2000) randomized 50 patients to receive 18 weeks of placebo or antibiotics including rifampin plus a sequence of doxycycline, erythromycin, metronidazole, clindamycin, amoxicillin, and ciprofloxacin for 3 weeks each. Intent-to-treat analysis demonstrated that 12 of 25 patients in the antibiotic and 6 of 25 patients in the placebo group reported overall improvement while 10 and 5, respectively, noticed improvement in pain and urgency. The study was complicated by the fact that 16 of the patients in the antibiotic group underwent new BPS therapy during the study as did 13 of the placebo patients. There was no statistical significance reached. What was statistically significant were adverse events in 80% of participants who received antibiotic compared with 40% in the placebo group. Nausea and/or vomiting and diarrhea were the predominant side effects. Most patients on antibiotics correctly guessed what treatment arm they were in, and those who guessed correctly were significantly more likely to note improvement after the study. No duration in improvement after completion of the trial of antibiotics was reported.

Burkhard and colleagues (2004) recorded a 71% success in 103 women presenting with a history of urinary urgency and frequency and chronic urethral and/or pelvic pain often associated

with dyspareunia and/or a history of recurrent urinary tract infection. This was a large, inclusive group and one that is probably broader than the BPS we are focusing on. Nevertheless, they recommended empirical doxycycline in this group. The overwhelming majority of BPS patients have been treated with empirical antibiotics before diagnosis.

At this time there is no evidence to suggest that antibiotics have a place in the therapy for BPS in the absence of a culture-documented infection (Maskell, 1995). **Nevertheless, it would not be unreasonable to treat patients with *one* empirical course of antibiotic if they have never been on an antibiotic for their urinary symptoms.**

Methotrexate. Low-dose oral methotrexate significantly improved bladder pain in 4 of 9 women with BPS but did not change urinary frequency, maximum voided volume, or mean voided volume (Moran et al, 1999). No placebo-controlled randomized trial has been done with this agent.

Montelukast. Mast cell triggering releases two types of proinflammatory mediators, including granule stored preformed types such as heparin and histamine and newly synthesized prostaglandins and leukotriene B_4 and C_4. Classic antagonists, such as montelukast, zafirlukast, and pranlukast, block cysteinyl leukotriene-1 receptors. In a pilot study (Bouchelouche et al, 2001b), 10 women with IC and detrusor mastocytosis received 10 mg of montelukast daily for 3 months. Frequency, nocturia, and pain improved dramatically in 8 of the patients. Further study would seem to be warranted, especially in patients with detrusor mastocytosis, which is defined as more than 28/mm^2.

Nifedipine. The calcium channel antagonist nifedipine inhibits smooth muscle contraction and cell-mediated immunity. In a pilot study (Fleischmann, 1994), 30 mg of an extended-release preparation was administered to 10 female patients and titrated to 60 mg daily in 4 of the patients who did not get symptom relief. Within 4 months 5 patients showed at least a 50% decrease in symptom scores and 3 of the 5 were asymptomatic. No further studies have been reported.

Misoprostol. The oral prostaglandin analogue misoprostol was studied in 25 patients at a dose of 600 µg/day (Kelly et al, 1998). At 3 months 14 patients were significantly improved, and at 6 months 12 patients still had a response. A cytoprotective action in the urinary bladder was postulated.

Analgesics

The long-term, appropriate use of pain medications forms an integral part of the treatment of a chronic pain condition such as IC. Most patients can be helped markedly with medical pain management using pain medications commonly used for chronic neuropathic pain syndromes, including antidepressants, anticonvulsants, and opioids (Wesselmann et al, 1997). Many nonopioid analgesics including acetaminophen and the nonsteroidal anti-inflammatory drugs (NSAIDs) and even antispasmodic agents (Rummans, 1994) have a place in therapy along with agents designed to specifically treat the disorder itself.

Studies on the use of analgesics for BPS are sparse, and the majority of data is inferred from non-BPS types of pain and expert opinion. Health care professionals should ask about pain, and the patient's self-report should be the primary source of assessment. Clinicians should assess pain with easily administered rating scales and should document the efficacy of pain relief at regular intervals after starting or changing treatment.

Unlike opioids, with increasing doses acetaminophen, aspirin, and the other NSAIDs all reach a ceiling for their maximum analgesic effect (Drugs for pain, 1998). Gabapentin, introduced in 1994 as an anticonvulsant, has found efficacy in neuropathic pain disorders including diabetic neuropathy (Backonja et al, 1998) and postherpetic neuralgia (Rowbotham et al, 1998). It demonstrates synergism with morphine in neuropathic pain (Gilron et al, 2005). It may give some benefit in chronic pelvic pain syndromes and BPS/IC (Sasaki et al, 2001). Pregabalin is also reported to be effective for neuropathic pain and the pain of fibromyalgia (Freynhagen et al, 2005; Arnold et al, 2008).

With the results of major surgery anything but certain, the use of long-term opioid therapy in the patient who has failed more conservative therapies also may be considered (Table 12–13). Opiates are seldom the first choice of analgesics in chronic pain states, but they should not be withheld if less powerful analgesics have failed (Portenoy et al, 1997; Bennett, 1999). This is a difficult decision that requires much thought and discussion between patient and urologist, and involvement of a pain specialist is indicated. A single practitioner has to take responsibility for pain treatment and write all prescriptions for pain medications (Brookoff, 1997). Opioids are effective for most forms of moderate and severe pain and have no ceiling effect other than that imposed by adverse effects. The common side effects include sedation, nausea, mild confusion, and pruritus. These are generally transient and

Table 12–13.

General Guidelines for the Use of Opioids in Chronic/Nonacute Urogenital Pain

1. All other reasonable treatments must have been tried and failed.
2. The decision to instigate long-term opioid therapy should be made by an appropriately trained specialist in consultation with another physician (preferably the patient's family doctor).
3. When there is a history or suspicion of drug abuse a psychiatrist or psychologist with an interest in pain management and drug addiction should be involved.
4. The dose required needs to be calculated by careful titration.
5. The patient should be made aware (and possibly give written consent):
   a. That opioids are strong drugs and associated with addiction and dependency
   b. The opioids will normally only be prescribed from one source
   c. The drugs will be prescribed for fixed periods of time and a new prescription will not be available until the end of that period
   d. The patient will be subjected to spot urine and possibly blood checks to ensure that the drug is being taken as prescribed and that non-prescribed drugs are not being taken
   e. Inappropriate aggressive behavior associated with demanding the drug will not be accepted
   f. Hospital specialist review will normally occur at least once a year
   g. The patient may be requested to attend a psychiatric/psychology review
   h. Failure to comply with the above may result in the patient being referred to a drug dependency agency and the use of therapeutic analgesic opioids being stopped.
6. Morphine is the first-line drug, unless there are contraindications to morphine or special indications for another drug. The drug should be prescribed in a slow release/modified release form. Short-acting preparations are undesirable and should be avoided when possible. Parenteral dosing is undesirable and should be avoided when possible.

Modified from Fall M, Baranowski A, Elneil S et al. Guidelines on chronic pelvic pain. In: European Association of Urology; 2008. p. 1–99. www.uroweb.org/professional-resources/guidelines/.

easily managed. Respiratory depression is extremely rare if they are used as prescribed. Constipation is common, and a mild laxative is generally necessary. The major impediment to the proper use of these drugs when they are prescribed for long-term nonmalignant pain is the fear of addiction. Studies suggest the risk is low (Gourlay, 1994). The long-acting narcotic formulations that result in steady levels of drug over many hours are preferable.

Chronic pain patients often receive inadequate doses of short-acting pain medications, which put them on cycles of short-term relief, anxiety, and pain. It leads to doctor shopping and to drug-seeking behavior confused by physicians with drug addiction. Although physical dependence to opioids will be unavoidable, physical addiction, a chronic disorder characterized by the compulsive use of a substance resulting in physical, psychological, or social harm to the user and the continued use despite that harm, is rare. Chronic opioid therapy can be considered in carefully selected patients. It is best administered in a pain clinic setting, requiring frequent reassessment by both patient and physician (Portenoy and Foley, 1986).

Table 12–14.

Intravesical Therapy for BPS: Assessments According to Oxford System

INTRAVESICAL AGENT	LEVEL OF EVIDENCE	GRADE OF RECOMMENDATION
DMSO	2	B
Heparin	3	C
Hyaluronic acid	1	D
Chondroitin sulfate	4	D
Pentosan polysulfate	4	D
Capsaicin/resiniferatoxin	1	–A (ineffective)
Bacillus Calmette-Guérin (BCG)	1	–A (ineffective
Oxybutynin	4	D
Lidocaine	2	C
Botulinum toxin	4	D

From Hanno P, Lin AT, Nordling J, et al. Bladder pain syndrome. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence. Paris: Health Publication Ltd.; 2009. p. 1459–518.

Key Points: Oral Therapies

- Few of the oral therapies commonly used for the treatment of BPS have unequivocal evidence of efficacy in large, multicenter, randomized controlled clinical trials.
- There is little evidence that any change the natural history of the disease, although many seem effective in individual patients.

Intravesical and Intradetrusor Therapies

Assessments according to the Oxford System for intravesical therapy for BPS are shown in Table 12–14.

Silver Nitrate

Although the evidence base for treating BPS/IC using intravesical preparations is limited and the potential for meta-analysis reduced by variation in the outcome measures used (Dawson and Jamison, 2007), intravesical lavage with one of a variety of preparations has remained a mainstay of treatment in the therapeutic armamentarium of BPS. Perhaps the oldest of the intravesical therapies is silver nitrate. The use of silver nitrate has been attributed to Mercier (cited in Pool and Rives, 1944), who reported in 1855 that excellent results with bladder instillations had been obtained in patients suffering from symptoms compatible with IC. Dodson (1926) advocated the use of solutions of silver nitrate in increasing strengths as the treatment of choice for this condition. Pool and Rives (1944) reported on 74 patients with IC treated with intravesical silver nitrate. The treatment was carried out as follows:

A urethral catheter is inserted and the contents of the bladder are evacuated. The bladder is then irrigated with a saturated solution of boric acid. Then 30 to 60 mL of a 1:5000 solution of silver nitrate is instilled into the bladder and permitted to remain there for 3 or 4 minutes if it does not cause intolerable irritation. At the end of this period the solution is permitted to run out through the catheter, which is then withdrawn. The patient usually experiences some dysuria and vesical irritability for 2 or 3 hours. Treatments are repeated every other day. At subsequent treatments the concentration of silver nitrate in the solution is increased to 1:2500, 1:1000, 1:750, 1:500, 1:400, 1:200, and finally 1:100. If at any time the reaction is too severe, the concentration is increased more slowly (Pool and Rives, 1944).

Although the initial treatments are performed with the patient under general anesthesia, later treatments are given on an outpatient basis. Ureteral reflux would be a contraindication, and it goes without saying that bladder biopsy would be contraindicated just before instillation for fear of extravasation. Twenty-three years later, Pool (1967) wrote that he still considered this treatment regimen the most efficacious form of treatment. He reported excellent results in 70% of patients with a mean response of 7.6 months. Burford and Burford (1958) reported a 14% cure rate and 79% improved figure. DeJuana and Everett (1977) had a 50% response rate in 102 patients.

Although **silver nitrate is rarely used in the current treatment of BPS,** an animal study showing that intravesical administration of nanocrystalline silver (1%) decreased urine histamine, bladder TNF-α, and mast cell activation in an experimental inflammation model without any toxic effect may restimulate interest in silver compounds (Boucher et al, 2008).

Clorpactin

O'Connor (1955) reported the use of intravesical Clorpactin WCS 90. Clorpactin is a generic term for closely related, highly reactive chemical compositions having a modified derivative of hypochlorous acid in a buffered base. Its activity depends on the liberation of hypochlorous acid and its resulting oxidizing effects, wetting and penetrating properties, and detergency. Wishard treated 20 patients with 0.2% Clorpactin gently lavaged in the bladder for 3 to 5 minutes without anesthesia, of whom 14 reported subjective improvement (Wishard et al, 1957). Murnaghan and coworkers (1970) noted improvement in 14 of 17 patients, although 10 required further treatment during the average 2-year follow-up. Most commonly the treatments are given as described by Messing and Stamey (1978), using 0.4% solution administered at 10 cm H_2O under anesthesia. Multiple instillations can be given, with a 1-month pause after the first 2 instillations to await a therapeutic response. The success rate of these researchers was 72%, with average 6-month duration of response. La Rock and Sant (1995) noted a 50% to 55% meaningful improvement rate occurring within 4 to 6 weeks of treatment. A case of ureteral fibrosis complicating the treatment prompted the recommendation that vesicoureteral reflux be considered a contraindication to the procedure

(Messing and Freiha, 1979). Our method of Clorpactin delivery is as follows:

Reflux is excluded with a cystogram. Under anesthesia the bladder is distended for 2 minutes at 60 to 80 cm H_2O and emptied. The perineum is shielded with a moistened towel. A solution of 0.4% freshly prepared Clorpactin (4 g in 1000 mL of sterile water) is instilled by gravity drainage (the Foley catheter held 10 cm above the level of the bladder) in 150- to 200-mL aliquots for a dwell time of 2 to 3 minutes and drained by gravity. This continues until the entire 1000-mL solution has been used. The bladder and introitus are then irrigated with normal saline, and the catheter is removed.

Dimethyl Sulfoxide

A mainstay of the treatment of BPS is the intravesical instillation of 50% DMSO (Sant, 1987). DMSO is a product of the wood pulp industry and a derivative of lignin. It has exceptional solvent properties and is freely miscible with water, lipids, and organic agents. Pharmacologic properties include membrane penetration, enhanced drug absorption, anti-inflammatory, analgesic, collagen dissolution, muscle relaxant, and mast cell histamine release. In-vitro effects on bladder function belie its positive effects in vivo (Freedman et al, 1989), where histamine release has not been demonstrated after treatment (Stout et al, 1995). It has been suggested that DMSO actually desensitizes nociceptive pathways in the lower urinary tract (Birder et al, 1997). Tests for DMSO for treatment of human illness began in the 1960s in the areas of musculoskeletal inflammation and the cutaneous manifestations of scleroderma.

Stewart and colleagues (1968) are credited for popularizing intravesical DMSO for BPS/IC. In the mid 1960s they applied it to the skin over the suprapubic area in a group of patients whose condition was refractory to conventional forms of therapy. Results were poor, but intravesical delivery of 50 mL of a 50% solution instilled for 15 minutes by catheter and repeated at intervals of 2 to 4 weeks showed positive effects in 6 of 8 patients lasting 2 to 12 months. The lack of side effects, other than a garlic-like odor on the breath, and of the need for inpatient administration were significant breakthroughs over previous treatments. Further reports by this group confirmed safety and efficacy (Stewart et al, 1971, 1972; Stewart and Shirley, 1976; Shirley et al, 1978) with symptom-free intervals of 1 to 3 months in 73% of patients. Ek and associates (1978) reported a 70% success rate but found most patients ultimately required re-treatment or further therapy with other modalities. Prospective series of Fowler (1981) and Barker and associates (1987) revealed symptomatic success rates of greater than 80%, although relapse was not uncommon. Fowler noted only minimal improvements in functional bladder capacity and attributed the beneficial effects of DMSO to a direct effect on the sensory nerves of the bladder. Perez-Marrero and associates (1988) compared DMSO with saline and showed a 93% objective improvement and 53% subjective improvement compared with 35% and 18%, respectively, for saline. Patients with bladder instability do not respond (Emerson and Feltis, 1986).

With its ease of administration (Biggers, 1986), **low morbidity, and reasonable symptomatic results, DMSO certainly merits its place as a useful treatment for BPS/IC.** In-vivo studies on rat bladder strips exposed to various concentrations of DMSO for 7 minutes showed absence of electrical field stimulation contraction at a 40% concentration and diminished compliance at 30% concentration (Melchior et al, 2003). Concentrations of 25% or less had negligible effects in this model. How it relates to use of DMSO in humans is unknown. A rare case of eosinophilic cystitis has been reported after DMSO instillation (Abramov et al, 2004).

Glycosaminoglycans

Exogenous GAGs have been shown to be effective in providing an epithelial permeability barrier in bladders in which the epithelium has been injured with protamine (Nickel et al, 1998). **Heparin,** which can mimic the activity of the bladder's own mucopolysaccharide lining (Hanno et al, 1978), has anti-inflammatory effects as well as actions that inhibit fibroblast proliferation, angiogenesis, and smooth muscle cell proliferation. Because of its numerous effects the possibility that heparin could be used for therapeutic reasons other than the control of coagulation has been the subject of much inquiry and speculation (Lane and Adams, 1993). Weaver and associates (1963) first reported intravesical heparin for IC treatment. Given intravesically there is virtually no systemic absorption, even in an inflamed bladder (Caulfield et al, 1995). Although uncontrolled studies suggested some beneficial effect for subcutaneous administration (Lose et al, 1983, 1985), the obvious risks of anticoagulation and osteoporosis have prevented this form of administration from undergoing further trials and general usage. Ten thousand units can be administered intravesically in sterile water either alone or with DMSO at varying intervals, with good results being reported (Perez-Marrero et al, 1993; Parsons et al, 1994a). Kuo (2001) reported 50% or more improvement in the International Prostate Symptom Score in 29 of 40 women with IC treated with 25,000 units intravesically twice weekly for 3 months.

Parsons (2000) has used daily intravesical doses of 40,000 units of heparin in 20-mL sterile water administered by the patient daily and held for 30 to 60 minutes. "Reasonable improvement of symptoms" can be expected between 6 months and 2 years after starting therapy. Adding alkalinized lidocaine to the heparin instillation provides better pain relief (Parsons, 2005). These encouraging outcomes must be kept in perspective, given that they are unproven by any placebo-controlled trial. The addition of 8 mL of 2% lidocaine and 4 mL of 8.4% sodium bicarbonate may improve results (Welk and Teichman, 2008). In fact, a combination of 200 mg of lidocaine with 8.4% sodium bicarbonate (10 mL total solution) *without* heparin showed a 30% response rate 3 days after completion of daily intravesical administration for 5 days and was statistically superior to a placebo cocktail (Nickel et al, 2009b).

Another GAG analogue, **pentosan polysulfate (PPS),** administered intravesically at 300 mg twice weekly in 50 mL of normal saline, showed some modest benefit in a small trial (Bade et al, 1997a). A 41-patient trial comparing oral PPS with oral and intravesical administration showed that the 24% reduction in O'Leary-Sant scores with oral therapy alone rose to a 46% reduction in the group that also received intravesical PPS (Davis et al, 2008).

The nonsulfated GAG, **hyaluronic acid,** has also been used intravesically. Trials using 40 mg dissolved in 40 mL of normal saline weekly for 4 to 6 weeks and then monthly treatments thereafter have had response rates varying from 71% (Morales et al, 1996) to 30% (Porru et al, 1997). In the summer of 2003, Bioniche Life Science (Interstitial Cystitis Association, 2003), and in the spring of 2004 Seikagaku Corporation, reported double-blind, placebo-controlled, multicenter clinical studies of their hyaluronic acid preparations (40 mg or 200 mg/mL, respectively), and neither showed significant efficacy of sodium hyaluronate compared with placebo. These negative studies have not been published in peer-reviewed literature. Neither preparation has been approved for use for BPS/IC in the United States. An Austrian open-label study showed 13 of 27 patients with BPS and a positive potassium test

responded to intravesical hyaluronic acid, 40 mg, given weekly for 10 weeks, although initial nonresponders at 5 weeks also were treated with intravesical PPS 200 mg thrice weekly for the remaining 5 weeks (Daha et al, 2008). The best results for hyaluronic acid come from Riedl and colleagues (2008), who studied 126 patients with a positive modified potassium test who could hold the solution for 2 hours, using 40 mg weekly for a minimum 10 weeks. Eight-four percent had significant improvement. Treatment-resistant cases have been managed with a combination of sequential bladder distention under anesthesia accompanied by a hyaluronic acid instillation every 1 to 3 months depending on response, with a 74% success rate in 23 patients (Ahmad et al, 2008). **Although used in Europe and Canada, the efficacy of hyaluronic acid for BPS/IC remains unproven in controlled and blinded trials** (Iavazzo et al, 2007).

Hurst (2003) has shown by immunohistochemistry a deficit of chondroitin sulfate from the luminal bladder surface in IC patients. Small uncontrolled studies using intravesical **chondroitin sulfate** have shown success rates of 33% (Steinhoff et al, 2002) to 50% (Sorensen, 2003). A multicenter, open-label study using 2% solution of sodium chondroitin sulfate weekly for 6 weeks and then monthly for 4 months had a 60% response rate with no safety issues (Nickel et al, 2009a). A large open-label experience using the device for all forms of "chronic cystitis" concluded that it was effective in improving urgency, voided volumes, and nocturia and well-tolerated when administered weekly for a maximum of eight instillations (Nordling and van Ophoven, 2008). The GAGs can be combined for instillation (Cervigni et al, 2008).

Other Intravesical Therapies

Doxorubicin (Khanna and Loose, 1990) and the mast cell stabilizer **cromolyn sodium** (Edwards et al, 1986; Kennelly and Konnak, 1995) have been tried in pilot trials with the promising results we come to expect in such studies. Follow-up studies are lacking, and these drugs have not become a part of the intravesical pharmacopeia.

The use of intravesical **bacillus Calmette-Guérin (BCG)** for IC was first reported by Zeidman and colleagues (1994). A subsequent randomized, prospective, double-blind, placebo controlled trial of 30 patients treated weekly for 6 weeks and followed for a mean of 8 months noted a 60% response rate compared with a 27% placebo response (Peters et al, 1997). Surprisingly, BCG was tolerated as well as placebo. Even more surprisingly, 8 of 9 BCG responders continued to have an excellent response in all parameters measured at 27 months of follow-up (Peters et al, 1998). It is unclear how BCG achieved this result, but immunologic and/or anti-inflammatory mechanisms have been postulated (Peters et al, 1999). A double-blind crossover Swedish study comparing DMSO to BCG failed to substantiate the efficacy of BCG (Peeker et al, 2000c).

A large multicenter randomized controlled trial by NIDDK comparing BCG with placebo found a 12% response rate for placebo compared with a 21% response for BCG. Placebo responders in the trial had the same durability of response (up to 68 weeks) as the BCG responders (Propert et al, 2008). In a follow-up open-label phase of the trial the response rate was 18% in both the group originally randomized to BCG and the group initially randomized to placebo, indicating a second course of therapy does not improve response rate (Propert et al, 2007). The small response rate in the randomized controlled trial failed to reach statistical significance at the $P = .05$ level, and this large study of 265 patients suggests that **BCG has no place in the treatment of moderate to severe BPS/IC** (Mayer et al, 2005). Although the BCG safety profile was considered acceptable in the NIDDK trial, adverse events were not uncommon and rare hypersensitivity reactions to intravesical BCG can occur (Parker et al, 2004). Although small, uncontrolled trials showing efficacy of BCG have been reported (Aghamir et al, 2007; El-Bahnasy et al, 2009), the NIDDK trial dampened enthusiasm for this treatment modality.

Efforts to bring new therapies directly to the bladder continue to be the focus of investigators. Oxybutynin has shown efficacy in preliminary studies when administered intravesically at doses of 10 mg dissolved in saline (Bade et al, 2000; Barbalias et al, 2000). Electromotive drug administration, the active transport of ionized drugs by the application of an electric current, using lidocaine and dexamethasone, has shown a 25% success rate up to 6 months after instillation (Rosamilia et al, 1997). A similar trial using repeated instillations noted success rates of 60% with a mean duration of 6.6 months (Riedl et al, 1997). **Capsaicin,** the main pungent ingredient in hot peppers of the genus *Capsicum,* is a specific neurotoxin that desensitizes C fiber afferent neurons. **Resiniferatoxin (RTX),** an ultrapotent analogue of capsaicin appears to have similar effects with less of the acute pain and irritation associated with capsaicin application. Both compounds have been tested intravesically for the relief of bladder instability and hyperreflexia (Chancellor and de Groat, 1999). Clinical trials for the use of these compounds in bladder pain and urgency/frequency could show this to be a new and viable treatment modality in the future, but **current data on efficacy in BPS are lacking** (Cruz et al, 1997; Lazzeri et al, 1996, 2000). A phase 2 safety and proof of concept multicenter, placebo-controlled trial conducted by ICOS Corporation (Bothell, WA, USA) found no significant efficacy of a single intravesical administration RTX compared with placebo, although no safety issues were identified (Payne et al, 2005). Studies using other concentrations and multiple administrations may be worthwhile (Peng and Kuo, 2007).

Key Points: Intravesical Therapies

- The potential for high efficacy combined with safety and low side effect profile that is gained by applying a treatment directly to the bladder lining has made research into new methods of intravesical therapy a high priority of researchers and pharmaceutical companies.
- Patients in whom pain and other symptoms are not related directly to a pathologic process of the bladder would not be expected to respond well to this type of organ-directed therapy.

Intradetrusor Therapies

The therapeutic value of **botulinum toxin type A (Botox)** stems partially from its ability to temporarily inhibit acetylcholine release and cause flaccid paralysis in a dose-related manner. It can correct focal dystonia when injected into a muscle. In recent years there has been increasing evidence that Botox might also have analgesic properties (Rajkumar and Conn, 2004). Initially this was thought to be due to relief of muscle spasm. However, botulinum has been shown to reduce peripheral sensitization by inhibiting the release of several neuronal signaling markers, including glutamate and substance P, and reducing c-*FOS* gene expression. It may affect the sensory feedback loop to the central nervous system by decreased input from the muscle tissue, possibly by inhibiting acetylcholine release from gamma motor neurons innervating intrafusal fibers of the muscle spindle (Rosales et al, 1996). It

inhibits the release of sensory neurotransmitters from isolated bladder preparations in rat bladder models of both acute injury and chronic inflammation (Lucioni et al, 2008). Botox has been used effectively for years in different conditions with muscular hypercontractions. Intravesical Botox administration blocks the acetic acid–induced calcitonin gene–related peptide release from afferent nerve terminals in the bladder mucosal layer in rats (Chuang et al, 2004). In an animal model of bladder permeability barrier disruption, intravesical Botox minimized bladder irritability and restored afferent neural responses to baseline levels (Vemulakonda et al, 2005). These results support clinical trials of Botox for the treatment of BPS/IC and other types of visceral pain (Chancellor and Yoshimura, 2004).

A multi-institutional case series using Botox or Dysport intravesical injections in 13 patients with refractory BPS/IC reported improvement in 9 patients. Improvements in symptoms lasted a mean of 3.72 months (mean, 1 to 8 months). No systemic complications were observed, although 2 patients had a diminished flow with some need to strain to void (Smith et al, 2004). Rackley and colleagues (2005) at the Cleveland Clinic reported no change in objective or subjective outcome measures in a series of 10 BPS/IC patients in whom the trigone was spared in the injection technique. A 1-year follow-up in 15 patients treated with 200 units Botox in 20 mL of normal saline showed that the success rate fell from 86.6% at 3 months to 26.6% at 5 months and was 0 at 12 months (Giannantoni et al, 2008). Bladder biopsy specimens 2 weeks after Botox intradetrusor injection show nerve growth factor production levels fall to those of controls in patients who respond (Liu et al, 2009). It is hypothesized that treatment-refractory patients may have developed antibodies after initial botulinum injection (Schulte-Baukloh, 2008). **At this time Botox can be recommended for BPS/IC use only in the context of carefully controlled clinical trials** (Cruz and Dinis, 2007; Del Popolo, 2008; Apostolidis et al, 2009).

Submucosal injection of 10 mL of 40 mg/mL triamcinolone acetonide injected in 0.5-mL aliquots was used for the treatment of Hunner lesions in 30 patients (Cox et al, 2009). Seventy percent of patients were very much improved, and duration of improvement was estimated to be 7 to 12 months.

Neuromodulation

Because it is a chronic pain syndrome it is reasonable to consider therapeutic options that directly interface with the nervous system in the treatment of PBS/IC. This approach is further supported by the association of pelvic floor dysfunction with pelvic pain syndromes (Zermann et al, 1999).

Pain diversion by **transcutaneous electrical nerve stimulation (TENS)** is routine in a variety of painful conditions (Fall, 1987). Fall and colleagues (1980) were the first to use electrical stimulation in IC, reporting on 14 women treated successfully with long-term intravaginal or TENS. Subsequently McGuire and coworkers (1983) noted improvement in 5 of 6 patients treated with electrical stimulation.

The primary intention in applying peripheral electrical nerve stimulation in IC is to relieve pain by stimulating myelinated afferents in order to activate segmental inhibitory circuits. As a secondary effect, urinary frequency may also be reduced. In the most complete review of the subject to date (Fall and Lindstrom, 1994) 33 patients with ulcerative IC and 27 patients with nonulcerative IC were treated by means of suprapubic TENS. Electrodes were positioned 10 to 15 cm apart immediately above the pubic symphysis. High- or low-frequency (2-50 Hz) TENS was employed. If there was no effect with high frequency after 1 month, low frequency was used. Thirty to 120 minutes of TENS was prescribed daily. Pain improved more than frequency. Good results or remission were described in 26% of nonulcer patients and in a surprising 54% of patients with ulcerative disease. The authors caution that the experience is based on open studies, relatively few patients, and the knowledge of a significant placebo effect with peripheral pain stimulation.

Acupuncture has been used to treat frequency, urgency, and dysuria (Chang, 1988). Twenty-two of 26 patients treated at the Sp. 6 point had clinically symptomatic improvement. A study looking at both acupuncture and TENS in IC showed limited effects of both modalities (Geirsson et al, 1993). **Lumbar epidural blockade** is the subject of a positive recent case report (Pelaez et al, 2004) but in an earlier series resulted in only short-term (mean 15 days) pain relief in IC (Irwin et al, 1993). **Posterior tibial nerve stimulation** was successful in 60% of 37 patients with symptoms of bladder overactivity in an uncontrolled Dutch study (van Balken et al, 2001). An Australian double-blind placebo controlled study of transdermal posterior tibial nerve laser therapy showed no benefit in 56 patients when comparing active to placebo arms, but the placebo effect was remarkably strong, indicating the importance of such trials when evaluating invasive therapies (O'Reilly et al, 2004). A Chinese study of posterior tibial nerve stimulation twice weekly for 5 weeks in BPS/IC patients failed to show improvement in pain scores, and none of 18 patients thought the treatment had a significant effect (Zhao et al, 2008).

Direct sacral nerve stimulation has been explored in the treatment of IC and urgency/frequency and is referred to as **neuromodulation,** a technique whose urologic potential was developed through the basic and clinical research of Tanagho and Schmidt (Schmidt, 1993; Fandel and Tanagho, 2005). They and others have observed that patients who do best with this treatment modality are those who have identifiable pain *and* dysfunction in the pelvic muscles (Everaert et al, 2001; Siegel et al, 2001; Aboseif et al, 2002). Those patients reporting pelvic pain in the absence of demonstrable pelvic floor dysfunction and levator tenderness did poorly (Schmidt, 2001). As initially practiced, trial stimulation was performed with a percutaneous temporary electrode for a 3- to 4-day temporary stimulation period to access efficacy. The S_3 nerve is most frequently used. A wire electrode is inserted into the foramen and connected to an external pulse generator (Medtronic Inc., Minneapolis, MN, USA). If the trial is successful, the patient would be considered for implantation of a permanent neural prosthesis. More recently, a staged procedure has supplanted the traditional percutaneous approach, because the response to stimulation can be better assessed with more accurate lead placement and stability than through the more hit-or-miss percutaneous lead placement (Peters et al, 2003). Peters' test to implant rate increased from 52% to 94%. Other reports have noted a test to implant rate in the percutaneous technique from 76% in 33 PBS/IC patients (Whitmore et al, 2003) to 40% in 211 patients with refractory urge incontinence, urgency-frequency syndrome, and urinary retention (Scheepens et al, 2002b).

Neuromodulation has been shown to be effective in treating refractory urinary urge incontinence (Schmidt et al, 1999; Spinelli et al, 2001). Studies on therapeutic potential in BPS/IC followed (van Kerrebroeck, 1999). The University of Maryland group described decrease in antiproliferative activity and normalization of HB-EGF levels in patients with successful test stimulation (Chai et al, 2000a). Peters and coworkers (2003) reported success in two thirds of BPS/IC patients with sacral nerve stimulation; Global Response Assessment as determined by the patient correlated with

objective findings (Peters et al, 2008). In another study (Comiter, 2003) success was noted in 17 of 25 patients with test stimulation and they went on to permanent implantation of the Interstim device (Medtronics, St. Paul, MN). Thirteen of 15 who underwent staged implantation were permanently implanted versus 4 of 10 undergoing percutaneous test stimulation. With a mean follow-up of 14 months, in 16 of 17 patients the treatment was judged successful, giving an intent-to-treat success rate of 64%. Although sacral neuromodulation can decrease narcotic requirements significantly in refractory BPS/IC, the majority of patients taking chronic narcotics for pain will likely continue to use them for pain relief even after implantation (Peters and Konstandt, 2004). One center reported a long-term improvement rate of 45% for the urgency/frequency indication (Elhilali et al, 2005).

Unilateral stimulation should be performed before bilateral sacral stimulation is considered (Oerlemans and van Kerrebroeck, 2008). A bilateral test stimulation could be indicated when a unilateral test fails (Steinberg et al, 2007). The only prospective randomized crossover trial to compare the unilateral with bilateral sacral nerve stimulation found no significant differences comparing the results (Scheepens et al, 2002a). The presence of pain is a predictor of adverse events (White et al, 2009); and although sacral neuromodulation is effective in 56% of patients with urgency/frequency, when pain is the major complaint then caution is indicated. Surgical revision rates are 7% to 18% (van Kerrebroeck et al, 2007). When used for BPS symptoms, frequent reprogramming is often required (Maxwell et al, 2008).

Key Points: Neuromodulation

- The association of pelvic floor dysfunction with pelvic pain syndromes makes neuromodulation a rational therapeutic alternative.
- Patients with pelvic pain in the absence of demonstrable pelvic floor dysfunction and levator tenderness may not respond as well as those with urgency/frequency associated with pelvic floor dysfunction. Controlled trials of sacral nerve stimulation for bladder pain syndrome are needed.

Surgical Therapy

Hydrodistention

Hydrodistention of the bladder under anesthesia, while technically a surgical treatment, is often the first therapeutic modality employed, often as a part of the diagnostic evaluation. Because there have been no standard methods of distention (Turner and Stewart, 2005), results vary markedly. Frontz (1922) first suggested hydraulic overdistention of the bladder for IC, and Bumpus (1930) reported the first series 8 years later. Simple bladder filling at cystoscopy will give relief to some patients (Hald et al, 1986); others have reported an office-based procedure with intravesical lidocaine anesthesia using electromotive drug administration (Rose et al, 2005), whereas Dunn and associates (1977) reported on 25 patients whose bladders were distended under anesthesia to the level of the systolic blood pressure for up to 3 hours. Sixteen of the patients were symptom free with a mean follow-up of 14 months; 2 patients suffered bladder rupture. The bladder in IC patients can be very thin, and the possibility of perforation or rupture must always be kept in mind and discussed with the patient (Badenoch, 1971; Hamer et al, 1992). Prolonged distention probably has little or no benefit over a short-term distention measured in minutes (Taub and Stein, 1994; McCahy and Styles, 1995). Using epidural anesthesia and a balloon distention technique to the mean arterial pressure for 3 hours continuously, Glemain and colleagues (2002) reported good but transient efficacy in patients with a bladder capacity of greater than 150 mL on predistention cystometry. In their prospective series of 30 patients, 18 had maintained a therapeutic response at 6 months and 13 at 1 year of follow-up. Moderate hematuria was almost universal, worsening of symptoms occurred in 5% of patients, and low back and hypogastric pain were common sequelae. There was one bladder rupture, one episode of sepsis, and one episode of prolonged retention.

Our method is to perform an initial cystoscopic examination (which is generally unremarkable), obtain urine for cytology, and distend the bladder for 1 to 2 minutes at a pressure of 80 cm H_2O. The bladder is emptied and then refilled to look for glomerulations or ulceration. A therapeutic hydraulic distention follows for another 8 minutes. Biopsy, if indicated, is performed after the second distention. Therapeutic responses in patients with a bladder capacity under anesthesia of less than 600 mL showed 26% with an excellent and 29% with a fair result compared with 12% excellent and 43% with a fair result in patients with larger bladder capacities (Hanno and Wein, 1991). Most favorable responses were extremely brief, however, with the exceptional patient noting improvement for 6 months and thus being a candidate for repeat therapeutic distention.

Acute hydrodistention does not seem to result in any long-term bladder dysfunction (Kang et al, 1992; Lasanen et al, 1992). Any efficacy is probably related to damage to mucosal afferent nerve endings (Dunn et al, 1977). It has no benefits in patients with detrusor hyperreflexia or instability (Taub and Stein, 1994; McCahy and Styles, 1995). Over half of men with prostate pain and without bacteriuria may have glomerulations. Symptoms in this group have been reported to improve with hydrodistention (Berger et al, 1998). While many patients with IC have sensory urgency at awake capacities of less than 100 mL, hydrodistention under anesthesia seems to allow for "staging" of the disease, giving the clinician some idea of the capacity he or she has to work with conservative therapies. A capacity under anesthesia of under 200 mL would not bode well for the likelihood of success of medical therapy. Fortunately these cases are relatively rare.

Surgical Considerations

Please see the Expert Consult website for more discussion on this topic.

Assessing Treatment Results

The diversity of BPS/IC therapies underscores the lack of understanding about the treatment of this syndrome (Rovner et al, 2000). It has been not only a difficult condition to diagnose but also a difficult condition for which to assess therapeutic impact. **There is a 50% incidence of temporary remission unrelated to therapy, with a mean duration of 8 months** (Held et al, 1990). A somewhat surprising finding from the Interstitial Cystitis Database was that although there was initial improvement in symptoms partially due to regression to the mean (Sech et al, 1998) and the intervention effect there was no evidence of a long-term change in average symptom severity over the 4-year course of follow-up (Propert et al, 2000). In a chronic, devastating condition with primarily subjective symptomatology, no known cause, and no cure, patients are desperate and often seem to respond to any new therapy (Fig. 12–12). They are often victims of unorthodox health care providers with untested forms of therapy, some medical, some homeopathic, and some even surgical.

Key Points: Surgical Therapy

- Major surgery for bladder pain syndrome is a reasonable alternative for patients with severe symptoms who have failed standard attempts at treatment and when the disease course suggests that spontaneous remission of symptoms is unlikely.
- Patients with a small bladder capacity under anesthesia are less likely to respond to conservative attempts at therapy.
- Patients with a Hunner lesion may have the best results with major surgery.
- If one conceptualizes bladder pain syndrome as two disorders, one of pain and the other of frequency, it becomes easier for the patient and physician to rationalize the decision.
- Conduit urinary diversion can be relied on to resolve the frequency symptoms, and if the patient would consider this alone to make for a successful procedure there is reason to seriously consider this option.
- Diversion, and even cystectomy with diversion, cannot guarantee a pain-free result, and it is critical for the patient to factor this into the decision about this often irrevocable step.

The Placebo Conundrum

When possible, the results of randomized controlled studies should be used for decision making. Placebo, double-blind studies are optimal in this disorder for which there is no generally effective standard therapy.

Placebo effects influence patient outcomes after any treatment which the clinician and patients believe is effective, including surgery. Placebo effects plus disease natural history and regression to the mean can result in high rates of good outcomes, which may be misattributed to specific treatment effects (Gillespie et al, 1991; Gillespie, 1994; Turner et al, 1994; Propert et al, 2000). Unfortunately, **too few BPS treatments have been subjected to a placebo-controlled trial.** This is not to say that what seems effective is not, but rather that a high index of skepticism is healthy, even in treatments tested in controlled trials (Schulz et al, 1995).

Although in many diseases an argument can be made against using a true placebo control as opposed to an orthodox treatment of approved or accepted value (Rothman and Michels, 1994), a good case for true placebo comparison can readily be made for BPS. The vagaries of the natural history, the general lack of progression of symptom severity over time, and the fact that it is not life threatening mean that there is little to lose and much to gain by subjecting new treatments to the vigorous scrutiny of placebo control. Many patients who volunteer for such trials have already run the gamut of accepted (although generally unproved) therapies. It has long been recognized in protocols that use subjective criteria for assessment that "improvement" may be expected in up to 35% of placebo-treated patients (Benson and Epstein, 1976). Because the spontaneous remission rate (although temporary) for BPS is 11% (Oravisto and Alfthan, 1976) to 50% (Held et al, 1990), combined with the placebo improvement it can be difficult to prove efficacy.

Even in placebo-controlled trials it is reasonable to surmise that some degree of unblinding may occur as a result of somatic or psychological side effects of the active arm, impairing the validity of the trial results and giving the active arm a slight edge over

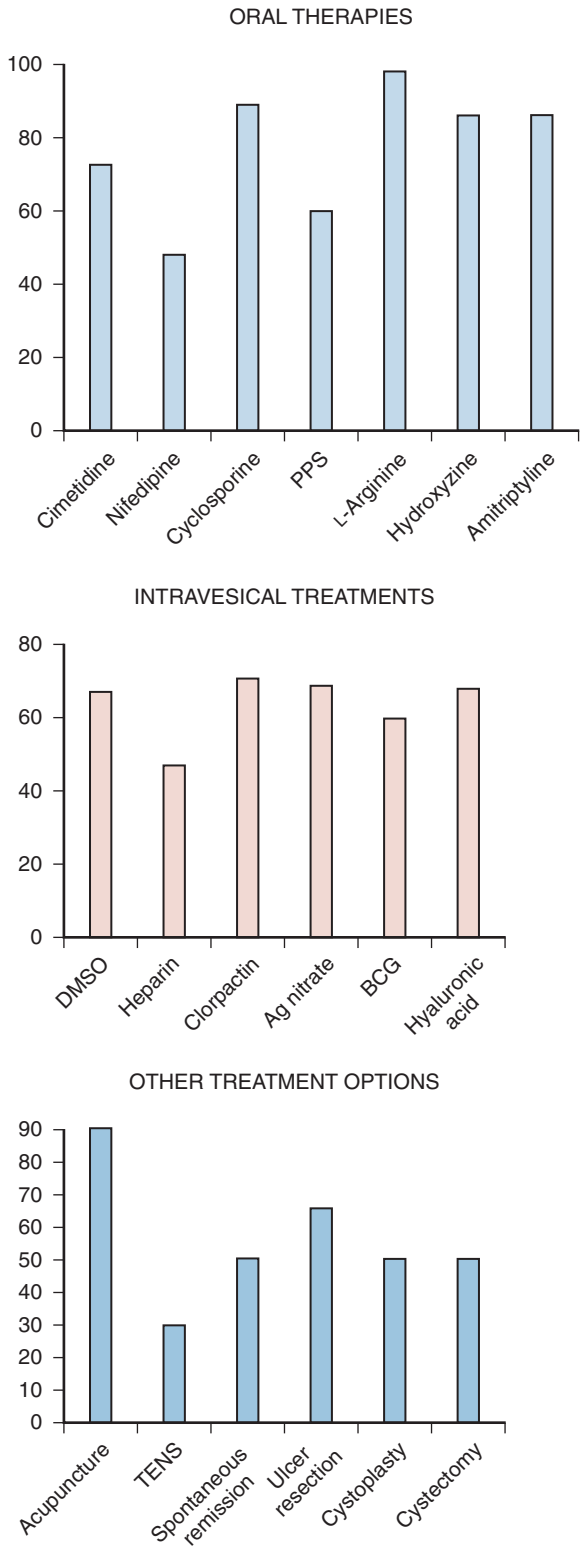


Figure 12–12. Selected reported treatment outcomes in uncontrolled studies in the bladder pain syndrome/interstitial cystitis literature: percentage of patients initially improved. Ag nitrate, silver nitrate; BCG, bacillus Calmette-Guérin; DMSO, dimethyl sulfoxide; PPS, sodium pentosan polysulfate; TENS, transcutaneous electrical nerve stimulation.

placebo (DuBeau et al, 2005; Rees et al, 2005). Failure to recognize unblinding can easily bias results of a study and has not been routinely measured in clinical trials (Desbiens, 2002). When occurring late in a study after one would expect onset of a therapeutic effect, unblinding could be the result of side effect profile or drug efficacy. Early in the trial it reflects poor placebo or study design. The degree of blinding needs to be ascertained throughout the trial. This is of specific concern in BPS and any disorder where primary outcomes may be subject to patient-specific psychological and physiologic factors.

The ethics and necessity of placebo-controlled trials have been questioned, especially in situations in which an effective treatment exists and also when delay in treatment has been shown to result in disease progression (Streiner, 1999; Anderson, 2006; Polman et al, 2008). However, there are methodologic concerns with equivalence and noninferiority active agent comparison trials (Streiner, 2007). These include an inability to determine if the treatments are equally good or equally bad, and the possibility that successive noninferiority trials can lead to a gradual decrease in treatment efficacy. Although the use of placebo-controlled trials raises ethical concerns when proven effective treatment exists for the condition under investigation, they are ethically justified, provided that stringent criteria for protecting research subjects are satisfied (Miller et al, 2004).

The value of placebo-controlled trials is aptly illustrated by the recent decisions by pharmaceutical manufacturers not to pursue FDA approval in the United States for seemingly promising intravesical therapies for BPS/IC (Morales et al, 1996; Chancellor and de Groat, 1999) after placebo-controlled trials failed to establish efficacy. These include low concentration hyaluronic acid (Bioniche, Canada), high concentration hyaluronic acid (SKK, Tokyo), and resiniferatoxin (ICOS, Bothell, WA, USA). Nalmefene, an initially promising oral therapy in the 1990s (Stone, 1994), also failed phase 3 trials (IVAX, Miami). Placebo trials are impractical in surgery and it can be difficult to evaluate surgical reports. The many older medications currently used off label might not meet success if tested in the stringent manner in which new molecular entities are tested. The expense of testing therapies currently used off label often requires dependence on the largesse of government agencies such as the NIH (Propert et al, 2002; Sant et al, 2003; Mayer et al, 2005).

Finally, when considering objective changes, the concept of statistical versus clinical significance is paramount. Investigators should, but rarely do, point out differences between statistical improvement and what they consider to be clinically significant improvement (Wein and Broderick, 1994). As Gertrude Stein reportedly stated, "A difference, to be a difference, must make a difference." An increase in bladder capacity of 30 mL may be statistically significant but clinically irrelevant. Number needed to treat and number needed to harm data (McQuay, 2003) may be particularly important in BPS/IC and typically have not been included in efficacy analysis.

Clinical Symptom Scales

There are three published BPS/IC symptom questionnaires: the University of Wisconsin IC Scale, the O'Leary-Sant IC Symptom Index and IC Problem Index, and the Pelvic Pain and Urgency/Frequency (PUF) Scale.

The University of Wisconsin IC Scale includes 7 PBS/IC symptom items (Table 12–15). **It has not been validated for identification or diagnosis of BPS/IC. It captures severity of symptom expression** (Keller et al, 1994; Goin et al, 1998). BPS/IC patients do not appear to indiscriminately report higher scores than controls for different somatic and general complaints (Porru et al, 2005). Unlike the other two instruments it addresses some quality-of-life issues, and this is an advantage when such issues are subject of investigation. Its most attractive aspects are its clinically apparent face validity and its ease of implementation.

The O'Leary-Sant indices (Table 12–16) are a **validated** questionnaire that was originally developed by focus groups, subjected to test-retest reliability analysis, and validated by administration to IC patients and asymptomatic controls (O'Leary et al, 1997; Lubeck et al, 2001). The questionnaire centers on 3 questions related to urgency/frequency and 1 on bladder-associated pain. It does not address generalized pelvic pain or symptomatology associated with sexual activity. This is not because these questions were not considered in the formulation of the questionnaire. Of 73 questions in the preliminary instrument covering domains of urinary symptoms, pain, sexual function, menstrual variability, and general health, only the 4 questions now in the instrument were needed to reliably and validly describe the illness experience of those with IC and distinguish these patients from those without the disorder (O'Leary and Sant, 1997).

Another instrument is the **PUF questionnaire** (Parsons et al, 2002a) (Table 12–17). It was specifically designed to include questions that directly reflect a wide variety of the symptoms experienced by patients who are affected by this disorder. One third of the questions address pelvic pain, including pain anywhere in the pelvis: the vagina, labia, lower abdomen, urethra, perineum, testes, penis, or scrotum. A large study utilizing the PUF questionnaire has concluded that up to 23% of American females have BPS/IC (Parsons et al, 2002a). This makes one wary as to the utility

Table 12–15.

University of Wisconsin Symptom Instrument

SYMPTOM	SCORE 1-6 (0 = NOT AT ALL) (6 = A LOT)
1. Bladder discomfort	
2. Bladder pain	
3. Other pelvic discomfort	
4. Headache	
5. Backache	
6. Dizziness	
7. Feelings of suffocation	
8. Chest pain	
9. Ringing in ears	
10. Getting up at night to go to the bathroom	
11. Aches in joints	
12. Swollen ankles	
13. Nasal congestion	
14. Flu	
15. Abdominal cramps	
16. Numbness or tingling in fingers or toes	
17. Nausea	
18. Going to the bathroom frequently during the day	
19. Blind spots or blurred vision	
20. Heart pounding	
21. Difficulty sleeping because of bladder symptoms	
22. Sore throat	
23. Urgency to urinate	
24. Coughing	
25. Burning sensation in bladder	

From Sirinian E, Azevedo K, Payne CK. Correlation between 2 interstitial cystitis symptom instruments. J Urol 2005;173:835–40.

Table 12–16.

O'Leary-Sant Indices

INTERSTITIAL CYSTITIS SYMPTOM INDEX	INTERSTITIAL CYSTITIS PROBLEM INDEX
During the past month …	*During the past month how much has each of the following been a problem for you:*
Q1. … how often have you felt the strong need to urinate with little or no warning? 0. ____ Not at all 1. ____ Less than 1 time in 5 2. ____ Less than half the time 3. ____ About half the time 4. ____ More than half the time 5. ____ Almost always	*Q1. Frequent urination during the day* 0. ____ No problem 1. ____ Very small problem 2. ____ Small problem 3. ____ Medium problem 4. ____ Big problem
Q2. … how often have you had to urinate less than 2 hours after you finished urinating? 0. ____ Not at all 1. ____ Less than 1 time in 5 2. ____ Less than half the time 3. ____ About half the time 4. ____ More than half the time 5. ____ Almost always	*Q2. Getting up at night to urinate?* 0. ____ No problem 1. ____ Very small problem 2. ____ Small problem 3. ____ Medium problem 4. ____ Big problem
Q3. … how often did you most typically get up at night to urinate? 0. ____ None 1. ____ Once 2. ____ 2 times 3. ____ 3 times 4. ____ 4 times 5. ____ 5 times	*Q3. Need to urinate with little warning?* 0. ____ No problem 1. ____ Very small problem 2. ____ Small problem 3. ____ Medium problem 4. ____ Big problem
Q4. … have you experienced pain or burning in your bladder? 0. ____ Not at all 2. ____ A few times 3. ____ Fairly often 4. ____ Usually 5. ____ Almost always	*Q4. Burning, pain, discomfort, or pressure in your bladder?* 0. ____ No problem 1. ____ Very small problem 2. ____ Small problem 3. ____ Medium problem 4. ____ Big problem
Add the numerical values of the checked entries. **Total score:** _____	**Add the numerical values of the checked entries.** **Total score:** _____

From O'Leary MP, Sant GR, Fowler FJ, et al. The interstitial cystitis symptom index and problem index. Urology 1997;49:58–63.

Table 12–17.

Pelvic Pain and Urgency/Frequency Patient Symptom Scale (PUF)

PATIENT SYMPTOM SCALE
Patient's Name: _____ Today's Date: _____
Please circle the answer that best describes how you feel for each question.

	0	1	2	3	4	SYMPTOM SCORE	BOTHER SCORE
1. How many times do you go to the bathroom during the day?	3-6	7-10	11-14	15-19	20+		
2. a. How many times do you go to the bathroom at night?	0	1	2	3	4+		
b. If you get up at night to go to the bathroom, does it bother you?	Never bothers	Occasionally	Usually	Always			
3. Are you currently sexually active? YES ____ NO ____							
4. a. If you are sexually active, do you now or have you ever had pain or symptoms during or after sexual activity?	Never	Occasionally	Usually	Always			
b. If you have pain, does it make you avoid sexual activity?	Never	Occasionally	Usually	Always			
5. Do you have pain associated with your bladder or in your pelvis (vagina, labia, lower abdomen, urethra, perineum, penis, tests or scrotum)?	Never	Occasionally	Usually	Always			
6. a. If you have pain, is it usually		Mild	Moderate	Severe			
b. Does your pain bother you?	Never	Occasionally	Usually	Always			
7. Do you still have urgency after you go to the bathroom?	Never	Occasionally	Usually	Always			
8. a. If you have urgency, is it usually		Mild	Moderate	Severe			
b. Does your urgency bother you?	Never	Occasionally	Usually	Always			

Total Score (Symptom Score + Bother Score) Symptom Score (1, 2a, 4a, 5, 6a, 7, 8a) Bother Score (2b, 4b, 6b, 8b)
Total score ranges are from 1 to 35.

From Parsons CL, Dell J, Stanford EL, et al: Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynecologic cases identified using a new symptom questionnaire and intravesical potassium sensitivity. Urology 2000;60:573–8.

and face-validity of the PUF (Ito et al, 2003). A total score of 10 to 14 equals a 74% likelihood of a positive potassium test (PST); 15 to 19 equals 76%; and 20+ equals 91%. To the extent that the PST is suspect, the reliability of PUF data comes into question. Question No. 4 of the PUF is problematic. Patients who are sexually active can gain up to 6 more points than those who are not, and patients who over time begin sexual activity because they are feeling better can actually accumulate a falsely elevated PUF score owing to this anomaly.

None of the questionnaires has been shown to be of value in diagnosis (Moldwin and Kushner, 2004), **although they may suggest who should be screened further for the syndrome** (Kushner and Moldwin, 2006). **The O'Leary-Sant and University of Wisconsin instruments correlate strongly in a large population of patients with BPS/IC** (Sirinian and Payne, 2001). **Both the O'Leary-Sant and University of Wisconsin questionnaires are responsive to change over time and thus good for following the natural history of the disorder and the results of treatment.**

Treatment outcome studies have also used the **Global Response Assessment** (GRA); a balanced patient self-report on overall response to therapy developed for NIDDK-sponsored multicenter therapeutic trials (Sant et al, 2003) (Table 12–18). A one-category change in GRA correlates with a 1.2-point change in the O'Leary-Sant indices and a 3.1-point change in the University of Wisconsin instrument (Propert et al, 2006).

PRINCIPLES OF MANAGEMENT

The information currently available in the literature does not lend itself to easily formulating a diagnostic or treatment guideline that would be universally accepted (Hanno and Dmochowski, 2009). Different groups of "experts" would undoubtedly create different "best practices." The compromise approach constructed by an experienced cross section of urologists and gynecologists from around the world at the International Consultation on Incontinence 2008 meeting in Paris seems reasonable and allows for significant latitude in individual practice and to account for patient preference (Hanno et al, 2009). It is outlined in Figures 12–13 and 12–14 and in Table 12–19.

Table 12–18.

Global Response Assessment (GRA)

–3: Markedly Worse
–2: Moderately Worse
–1: Slightly Worse
0: No Change
+1: Slightly Improved
+2: Moderately Improved
+3: Markedly Improved

From Sant GR, Propert KJ, Hanno PM, et al. A pilot clinical trial of oral pentosan polysulfate and oral hydroxyzine in patients with interstitial cystitis. J Urol 2003:170:810–15.

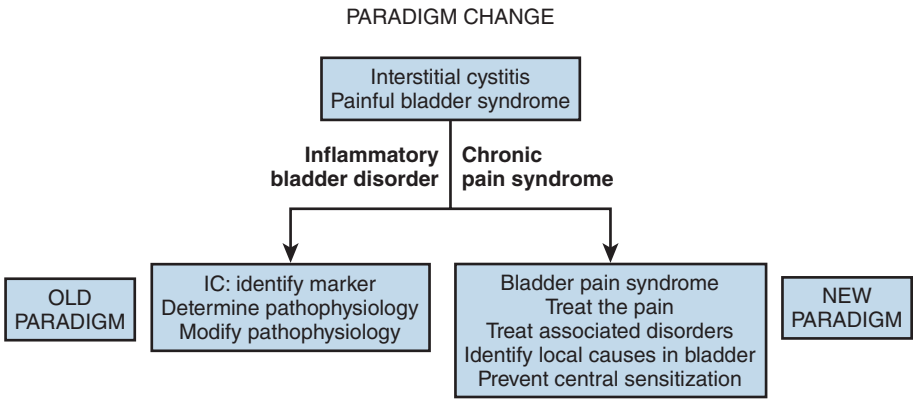


Figure 12–13. Paradigm change: interstitial cystitis (IC) evolves into painful bladder syndrome evolves into bladder pain syndrome. (From Hanno PM. Proceedings of the International Consultation on Interstitial Cystitis. Japan: Comfortable Urology Network; 2008. p. 2–9.)

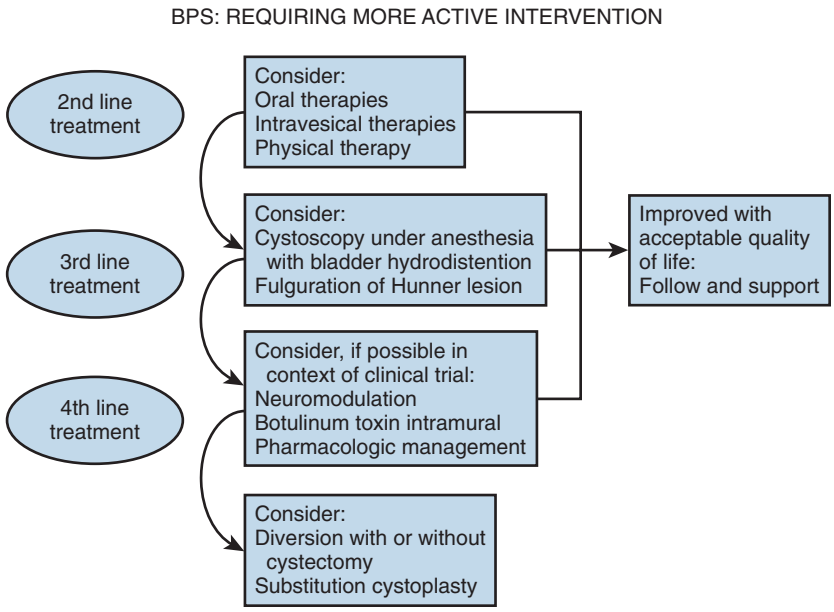


Figure 12–14. Diagnostic and treatment algorithm for bladder pain syndrome (BPS). (From International Consultation on Incontinence 2008, Paris.)

Table 12–19.

Principles of Management from the International Consultation on Incontinence, 2008

Definition

Bladder Pain Syndrome (in the absence of a universally agreed definition, the European Society for the Study of Interstitial Cystitis—ESSIC definition is given along with a slight modification made at a recent international meeting held by the Society for Urodynamics and Female Urology—SUFU)

ESSIC: *Chronic pelvic pain, pressure or discomfort of greater than 6 months duration perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or urinary frequency. Confusable diseases as the cause of the symptoms must be excluded.*

Consensus Definition from SUFU International Conference (Asia, Europe, North America) held in Miami, Florida February 2008: *An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptom(s) of more than 6 weeks duration, in the absence of infection or other identifiable causes.*

Bladder Pain Syndrome (BPS)

NOMENCLATURE (see Fig. 12–13)

The scientific committee of the International Consultation voted to use the term "bladder pain syndrome" for the disorder that has been commonly referred to as interstitial cystitis (IC). The term painful bladder syndrome was dropped from the lexicon. The term IC implies an inflammation within the wall of the urinary bladder, involving gaps or spaces in the bladder tissue. This does not accurately describe the majority of patients with this syndrome. Painful Bladder Syndrome, as defined by the International Continence Society, is too restrictive for the clinical syndrome. Properly defined, the term Bladder Pain Syndrome appears to fit in well with the taxonomy of the International Association for the Study of Pain (IASP), and focuses on the actual symptom complex rather than what appears to be long-held misconception of the underlying pathology.

HISTORY/INITIAL ASSESSMENT

Males or females with pain, pressure, or discomfort that they perceive to be related to the bladder with at least one urinary symptom, such as frequency not obviously related to high fluid intake, or a persistent urge to void should be evaluated for possible bladder pain syndrome (see Fig. 12–9). The presence of commonly associated disorders including irritable bowel syndrome, chronic fatigue syndrome, and fibromyalgia in the presence of the cardinal symptoms also suggests the diagnosis. Abnormal gynecologic findings in women and well-characterized confusable diseases that may explain the symptoms must be ruled out.

The initial assessment consists of a frequency/volume chart, focused physical examination, urinalysis, and urine culture. Urine cytology and cystoscopy are recommended if clinically indicated. Patients with urinary infection should be treated and reassessed. Those with recurrent urinary infection, abnormal urinary cytology, and hematuria are evaluated with appropriate imaging and endoscopic procedures, and only if findings are unable to explain the symptoms, are they diagnosed with BPS.

INITIAL TREATMENT

Patient education, dietary manipulation, nonprescription analgesics, and pelvic floor relaxation techniques comprise the initial treatment of BPS. The treatment of pain needs to be addressed directly, and in some instances referral to an anesthesia/pain center can be an appropriate early step in conjunction with ongoing treatment of the syndrome. When conservative therapy fails or symptoms are severe and conservative management is unlikely to succeed, oral medication, intravesical treatment, or physical therapy can be prescribed. It is recommended to initiate a single form of therapy and observe results, adding another modality or substituting another modality as indicated by degree of response or lack of response to treatment. Excellence can be the enemy of good.

SECONDARY ASSESSMENT

If initial oral or intravesical therapy fails, or before beginning such therapy, it is reasonable to consider further evaluation which can include urodynamics, pelvic imaging, and cystoscopy with bladder distention and possible bladder biopsy under anesthesia (see Fig. 12–14). Findings of bladder overactivity suggest a trial of antimuscarinic therapy. Findings of a Hunner's lesion suggest therapy with transurethral resection or fulguration of the lesion. Distention itself can have therapeutic benefit in 30%-50% of patients, though benefits rarely persist for longer than a few months.

REFRACTORY BPS

Those patients with persistent, unacceptable symptoms despite oral and/or intravesical therapy are candidates for more aggressive modalities. Many of these are best administered within the context of a clinical trial if possible. These may include neuromodulation, intradetrusor botulinum toxin, or newly described pharmacologic management techniques. At this point, most patients will benefit from the expertise of an anesthesia pain clinic. The last step in treatment is usually some type of surgical intervention aimed at increasing the functional capacity of the bladder or diverting the urinary stream. Urinary diversion with or without cystectomy has been used as a last resort with good results in selected patients. Augmentation or substitution cystoplasty seems less effective and more prone to recurrence of chronic pain in small reported series.

Philosophy of Management

This author believes that, because of the natural history of the disorder, it is best to cautiously progress through a variety of treatments. Whereas the shotgun approach, starting newly diagnosed patients on a variety of simultaneous medications, seems to have many adherents, employing one treatment at a time makes the natural history of the disease itself an ally in the treatment process. One should encourage patients to maximize their activity and live as normal a life as possible, not becoming a prisoner of the condition. Although some activities or foods may aggravate symptoms, nothing has been shown to negatively affect the disease process itself. Therefore, patients should feel free to experiment and judge for themselves how to modify their lifestyle without the guilt that comes from feeling they have harmed themselves if symptoms flare. Dogmatic restriction and diet are to be avoided unless they are shown to improve symptoms in a particular patient.

In the near future, phenotyping of patients with BPS/IC may improve treatment outcomes but only time and future studies will determine if this is true (Baranowski et al, 2008). To answer the perennial question, "Can we, as health care providers, make evidence-based decisions for BPS/IC at this time?" the answer seems to be a qualified *sometimes* (Fall et al, 2008).

SUGGESTED READINGS

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chapter
13

Sexually Transmitted Infections

Tara Lee Frenkl, MD, MPH ● Jeannette M. Potts, MD

Epidemiology and Trends
Genital Ulcers
Herpes Simplex Virus Infection
Chancroid
Syphilis
Lymphogranuloma Venereum
Chlamydia trachomatis Infection
Gonorrhea
Trichomoniasis
Genital Warts
Molluscum Contagiosum
Scabies
Pediculosis Pubis
Overview of Other Sexually Associated Infections

Screening and detecting sexually transmitted infections (STIs) is a form of secondary prevention that interrupts further transmission as well as progression of the infection and its sequelae. Unfortunately, primary prevention, by means of education and safe sex practices, has not been enough to significantly curb the prevalence and high cost of STIs.

People at high risk of contracting STIs are young adults between the ages of 18 and 28. It is also important to bear in mind that STIs rank among the top five risks of international travelers, along with diarrhea, hepatitis, and motor vehicle accidents (Mawhorter, 1997).

The brunt of the STI burden, both in risk and consequence, falls on women. When exposed to STIs, women are more likely to become infected and are much more likely to be asymptomatic. STIs can cause pelvic inflammatory disease, with subsequent risks of chronic pain syndromes, ectopic pregnancy, and infertility. Unfortunately there is very little evidence that treatment will reverse the sequelae.

A urologist should have a high index of suspicion for underlying STI in women who present with recurrent urinary tract infections (UTIs) and in those who are symptomatic with sterile urine cultures. Up to 50% of women with signs of UTI during emergency department examination had subsequent positive cultures for STI (Berg et al, 1996). Physicians should maintain the same level of vigilance when treating women who have sex with women. Genital human papillomavirus (HPV) has been identified along with squamous intraepithelial lesions among lesbians and occurs among those who have not had sexual relations with men (Marrazzo et al, 1998).

Proctitis may occur in women and men who have anal sex. Causative organisms include *Neisseria gonorrhoeae, Chlamydia trachomatis, Treponema pallidum,* and herpes simplex virus (HSV). A discussion of human immunodeficiency virus (HIV) is beyond the scope of this chapter (see Chapter 14); however, **it is important to remember that STIs—especially the ulcerative types—facilitate the transmission and infection of HIV.** HSV type 2, in particular, may play a role in the transmission of HIV because it has been identified more frequently than other STIs among HIV-concordant couples. Increased risk of HIV concordance has also been observed among couples who both have *Mycoplasma genitalium* antibodies (Perez et al, 1998).

Evidence is available that has shown that the spermicide nonoxynol-9 is not preventive against STIs and that its frequent use may actually be detrimental by increasing the rate of genital ulceration and HIV transmission (Richardson, 2002).

It is imperative that the physician treating STIs make special efforts to be sure that his or her methods of diagnosis and treatment reflect the latest knowledge. To that end, the Centers for Disease Control and Prevention (CDC) periodically updates recommendations for STI treatment, which can be retrieved easily by checking the CDC website. Changes that occur in the interim will need to come from a review of current literature. The accurate diagnosis and treatment of a patient with an STI will allow the physician to treat not only the patient but also the sexual partner and possibly the couple's unborn children.

The most common STIs are discussed in this chapter and include HSV infection, chlamydial urethritis/cervicitis, lymphogranuloma venereum, syphilis, gonorrhea, chancroid, trichomoniasis, HPV infection, and scabies. Other sexually associated pathogens, which cause urethritis and vaginitides, are also discussed briefly.

EPIDEMIOLOGY AND TRENDS

It is estimated that more than 19 million new cases of STIs are reported each year and more than 65 million people are infected with incurable viral STIs (CDC, 2010b; American Social Health Association, 1998). Approximately two thirds of cases occur in adolescents and young adults. The most common STIs are HPV and HSV infections. **Of the top 10 nationally notifiable infectious diseases in the United States in 2008, 4 were STIs** (CDC, 2008). This does not include HPV and HSV infections because they are not reportable diseases.

The prevalence of infection with HPV in the United States is approximately 20 million, and the incidence is 6.2 million (Catea,

1999; Weinstock, 2004). At least 50% of sexually active men and women acquire genital HPV infection at some point in their lives. By age 50, at least 80% of women will have acquired genital HPV infection (STD Facts, 2005).

In 2009, only 28 cases of chancroid were reported, down from 67 cases in 2002 (CDC, 2010b). Interestingly, 71% were reported from the three states of Tennessee, Wisconsin, and Texas. Overall, the rate of reported cases has declined 99% since 1987. *Haemophilus ducreyi* is difficult to culture, and therefore the infection could be underdiagnosed. Improved diagnostic testing by means of polymerase chain reaction (PCR) testing is now commercially available and may increase diagnostic capability.

The incidence of infection with *Chlamydia* has continued to rise since it became a notifiable disease in 1995. In 2009, over 1.2 million cases were reported to the CDC (CDC, 2010b). The reported number of cases of chlamydial infection was about four times greater than the reported cases of gonorrhea. It is probable that this incidence is at least in part secondary to improved diagnostic ability and growth and implementation of routine screening programs in women. Now that highly sensitive nucleic acid amplification tests (NAATs) for urine are available, the diagnosis of chlamydial infection is increasing in both symptomatic and asymptomatic men. From 2005 to 2009, the rate of chlamydial infection among men increased 37.6% compared with 20.3% among women.

The rate of gonorrhea was fairly stable from 1996-2006 at approximately 115 cases per 100,000 population, and then decreased from 2006-2009 to a rate of approximately 99.1 per 100,000 population in 2009 (CDC, 2009). The incidence rate is highest in persons aged 15 to 24 and is particularly high for non-Hispanic blacks (20 times higher than for non-Hispanic whites). Rates are particularly higher for non-Hispanic blacks (which is 20 times the rate for non-Hispanic whites) and for men who have sex with men (Fox et al, 2001; CDC, 2010b). There has also been a significant increase in quinolone-resistant *N. gonorrhoeae,* such that **fluoroquinolones are no longer recommended for treatment in the United States** (CDC, 2007).

The rate of syphilis increased yearly during 2001-2009, primarily among men (3.0 cases per 100,000 population in 2001 compared to 7.8 cases in 2009). The rate among women increased from 0.8 cases in 2004 to 1.4 cases in 2009 (CDC, 2010b). It has been proposed that this is secondary to outbreaks among males having sex with males in urban areas with high rates of coinfection with HIV and high-risk sexual behavior (CDC, 2004b). Rates continue to be particularly high in southern states and among African-Americans. There is no evidence that screening high-risk individuals, including those with HIV or other STIs, or the general population reduces morbidity or mortality from syphilis. However, it has been shown that screening pregnant women reduces the prevalence of congenital syphilis (Coles et al, 1998).

Expedited Partner Therapy

A common dilemma for physicians treating patients with an STI is how to expeditiously extend treatment to the partner to prevent complications from infection, such as pelvic inflammatory disease, and prevent the spread of disease. Expedited partner therapy (EPT) is the practice of treating the sexual partners of patients with STI by providing the patient with a prescription or medication to take to his or her partner without an intervening clinical evaluation or professional prevention counseling.

In the past, once an STI was reported to the health department the health department notified past and present sexual partners of the patient. However, the increased incidence of HIV and threats of bioterrorism are competing for health department resources and many departments now only notify partners of patients with HIV or syphilis (Erbelding and Zenilman, 2005). Patients are now requested to notify their own partners, who are then expected to go for evaluation and treatment themselves. The problems with this proposal are evident, and already this concept has been shown to be ineffective (Macke and Maher, 1999). Golden and colleagues (2003) reported their success implementing an expedited treatment plan for partners that did not require medical evaluation. This was a randomized controlled trial in which patients in the expedited treatment group were given a "partner packet" of therapy to deliver to the partner themselves or, if they were unwilling to do so, the partner was notified by the physician staff and the packet was delivered by mail or could be picked up at a participating pharmacy. Both the patients and partners in the expedited treatment group had better outcomes than the control group. Although this approach is sensible, effective, and progressive, legal and clinical barriers may unfortunately prevent the widespread acceptance of this approach.

In 2006 the CDC concluded that EPT has been shown to be at least equivalent to patient referral in preventing persistent or recurrent gonococcal or chlamydial infection in heterosexuals and released guidelines for the uses of EPT (CDC, 2006). The guidelines recommend that EPT should be implemented only when other management strategies are impractical or unsuccessful. All recipients should be encouraged to seek medical attention in addition to accepting therapy by EPT, through counseling of the index case, written materials, and/or personal counseling by a pharmacist or other personnel. However, EPT should not be used routinely in men who have sex with men because of a lack of data to confirm efficacy in this population and the high risk of comorbidity, especially with undiagnosed HIV. Similarly, EPT should not be used for partners of women with trichomoniasis because of the high risk of comorbidity with chlamydial or gonococcal infection or in the management of patients with infectious syphilis.

The CDC collaborated with the Center for Law and the Public's Health at Georgetown and Johns Hopkins Universities to assess the legal framework concerning EPT in all 50 states, the District of Columbia, and Puerto Rico. The objective of the research was to conceptualize and identify legal provisions that implicate a clinician's ability to execute EPT. As of January 2011, EPT is allowable in 27 states, potentially allowable in 15 states including the District of Columbia and Puerto Rico, and legally prohibited in 8 states. The results of the research, explanation, and up-to-date legal status for each state can be found at the CDC website (CDC, 2010; www.cdc.gov/std/ept/legal).

GENITAL ULCERS

Several sexually transmitted infections are clinically characterized by genital ulcers and most commonly include HSV infection or syphilis. Other STIs that may manifest with ulcer include chancroid and granuloma inguinale.

Although specificity for clinical diagnosis of genital ulcer disease is good (94% to 98%), sensitivity is quite low (31% to 35%) (DiCarlo and Martin, 1997). Inguinal lymph node findings did not contribute to diagnostic accuracy. Patients with genital, perianal, or anal ulcers should undergo a diagnostic evaluation for HSV and serologic testing for syphilis. Testing for *Haemophilus ducreyi* should be conducted in areas where chancroid is prevalent. Specifically, the CDC recommends (1) serology and either darkfield examination or direct immunofluorescence for *Treponema pallidum,* (2) culture or PCR test for HSV, and (3) serologic testing for

Table 13–1.

Genital Ulcer Disease

DISEASE	LESIONS	LYMPHADENOPATHY	SYSTEMIC SYMPTOMS
Primary syphilis	Painless, indurated, with a clean base, usually singular	Nontender, rubbery, nonsuppurative bilateral lymphadenopathy	None
Genital herpes	Painful vesicles, shallow, usually multiple	Tender, bilateral inguinal adenopathy	Present during primary infection
Chancroid	Tender papule, then painful, undermined purulent ulcer, single or multiple	Tender, regional, painful, suppurative nodes	None
Lymphogranuloma	Small, painless vesicle or papule progresses to an ulcer	Painful, matted, large nodes develop, with fistulous tracts	Present after genital lesion heals



Figure 13–1. Typical vesicular eruption of herpes simplex virus.



Figure 13–2. Herpes simplex virus infection on the penis.

type-specific HSV antibody (CDC, 2010c). **One should bear in mind that patients may have more than one STI. Approximately 10% of patients with chancroid also have HSV infection or syphilis.** HIV testing should also be considered in the management of patients with confirmed STI. Clinical characteristics of sexually transmitted genital ulcers are summarized in Table 13–1. Other causes that are not sexually transmitted, such as Behçet syndrome, drug reaction, erythema multiforme, Crohn disease, lichen planus, amebiasis, trauma, and carcinoma, must also be considered. **Empirical treatment for the most likely cause based on history and physical examination should be initiated as laboratory test results are pending.** If ulcers do not respond to therapy or appear unusual, a biopsy should be performed.

HERPES SIMPLEX VIRUS INFECTION

Diagnosis. Genital herpes infection is common, afflicting more than 50 million people in the United States (Xu et al, 2006). It is caused by HSV type 2 (HSV-2) in 85% to 90% of cases and HSV type 1 (HSV-1) in 10% to 15% of cases. HSV-1 is responsible for common cold sores but can be transmitted via oral secretions during oral-genital sex. Silent infection is common and may account for more than 75% of viral transmission (Langenberg et al, 1999). Up to 80% of women with HSV-2 antibodies have no history of clinical infection (White and Wardropper, 1997). The incubation period ranges from 1 to 26 days but is usually short, approximately 4 days. Nongenital infection of HSV-1 during childhood may be protective to some extent against subsequent genital HSV-2 infection in adults. When exposed to HSV-2, women with negative HSV-1 antibodies had a 32% risk of infection per year whereas women with positive antibodies had a 10% risk of infection per year (Baker, 1997).

Primary infection manifests as painful ulcers of the genitalia or anus and bilateral painful inguinal adenopathy. The initial presentations for HSV-1 and HSV-2 are the same. A group of vesicles on an erythematous base that does not follow a neural distribution is pathognomonic (Figs. 11–1 to 11–3). The differential diagnosis includes other STIs, such as primary syphilis and chancroid, as well as noninfectious disorders such as Crohn disease, trauma,



Figure 13–3. Vulvovaginal herpes simplex virus infection.

contact dermatitis, erythema multiforme, Reiter syndrome, psoriasis, and lichen planus.

The initial infection is often associated with constitutional flulike symptoms. Sacral radiculomyelopathy is a rare manifestation of primary infection that has a greater association with primary anal HSV. Genital lesions, especially urethral lesions, may cause transient urinary retention in women. Recurrent episodes are usually less severe, involving only ulceration of the genital or anal area. Severe disease and complications of herpes include pneumonitis, disseminated infection, hepatitis, meningitis, and encephalitis. **Asymptomatic viral shedding can take place for up to 3 months after clinical presentation, thereby perpetuating the risk of transmission** (Baker, 1997).

The diagnosis of genital herpes should not be made on clinical suspicion alone because the classic presentation of the ulcer occurs in only a small percentage of patients. **Women especially may present with atypical lesions such as abrasions, fissures, or itching** (ACOG Practice Bulletin, 2004). Viral culture with subtyping has been the gold standard of diagnosis of herpes infection. Viral subtype should be determined in every patient because it is important for prognosis and counseling. Women with HSV-2 have an average of four recurrences within the first year, and women with HSV-1 have one recurrence in the first year. After the first year, HSV-1 rarely recurs whereas the rate of HSV-2 decreases but slowly (Bendedetti et al, 1994). Viral culture can generally isolate the virus in 5 days, is relatively inexpensive, and is highly specific. However, the sensitivity of viral culture ranges from 30% to 95%, depending on the stage of the lesion and whether it is the primary infection or a recurrence. Viral load is highest when the lesion is vesicular and during primary infection. Therefore, viral culture has the highest sensitivity at these times and declines sharply as the lesion heals.

There are currently three U.S. Food and Drug Administration (FDA)-approved type-specific antibody assays (HerpeSelect HSV-1 and HSV-2 ELISA, HerpeSelect HSV-1 and HSV-2 Immunoblot, and Captia ELISA). These tests identify antibodies to HSV glycoproteins G-1 and G-2, which evoke a type-specific antibody response (Wald and Ashley-Morrow, 2002). These tests may also be able to identify recently acquired versus established HSV infection based on antibody avidity (Morrow et al, 2004).

Antigen detection kits are available but cannot distinguish reliably between HSV-1 and HSV-2. PCR testing has been shown to be 1.5 to 4 times as sensitive as viral culture. Samples are easy to attain and more stable than samples for viral culture. PCR testing will most likely replace viral culture as its availability increases and cost decreases.

Table 13–2.

Recommended Oral Treatment for Genital Herpes Simplex Virus Infection

AGENT	FIRST CLINICAL EPISODE	EPISODIC THERAPY	SUPPRESSIVE THERAPY
Acyclovir	400 mg tid for 7-10 days *or* 200 mg five times a day for 7-10 days	400 mg tid for 5 days *or* 800 mg tid for 2 days *or* 800 mg bid for 5 days	400 mg bid
Famciclovir	250 mg bid for 7-10 days	125 mg bid for 5 days *or* 1000 mg bid for 1 day *or* 500 mg once, followed by 250 mg bid for 2 days	250 mg bid
Valacyclovir	1 g bid for 7-10 days	500 mg bid for 3 days *or* 1 g sid for 5 days	500 mg sid *or* 1 g sid

Adapted from Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2010. MMWR 2010;59(RR-12):21–2.

Treatment. Antiviral therapies approved for treatment include those using oral acyclovir, valacyclovir, and famciclovir (Table 13–2). **Topical antiviral medications are not effective.** Recurrences can be treated with an episodic or suppressive approach. When used for episodic treatment, medication must be initiated during the prodrome or within 1 day of the onset of lesions. Daily suppressive therapy has been shown to prevent 80% of recurrences and is an option for patients who suffer from frequent recurrences. It has been shown to decrease the frequency and duration of recurrences as well as viral shedding and therefore reduce the rate of transmission. The safety and efficacy of daily suppressive therapy has been well documented.

CHANCROID

Diagnosis. Chancroid, caused by *Haemophilus ducreyi,* is the most common ulcerative STI worldwide but is rare in the United States. It affects men three times more often than women. The incubation period ranges from 1 to 21 days. It causes a painful, nonindurated ulcer on the penis or vulvovaginal area. The ulcer has a friable base covered with a gray or yellow purulent exudate and a shaggy border. It can spread laterally by apposition to inner thighs and buttocks, especially in women. **It is associated with inguinal adenopathy that is typically unilateral and tender with a tendency to become suppurative and fistulize** (Figs. 13–4 and 13–5). *H. ducreyi* is fastidious and difficult to culture. The special culture media is not widely available, and sensitivity of culture remains less than 80%. Gram stain of a specimen obtained from the undermined edge of the ulcer may be more helpful in identifying the short, fine, gram-negative streptobacilli, which are usually arranged in short, parallel chains. Recently, PCR assays have been shown to be a sensitive and specific means of detecting *H. ducreyi.* Although no PCR test is currently FDA approved, testing can be performed by commercial agencies. HIV and syphilis screening should be performed at the time of diagnosis and 3 months after treatment if initial results are negative.



Figure 13–4. Chancroid with regional adenopathy.



Figure 13–5. Chancroid lesion.

Treatment. Single-dose treatments consist of azithromycin, 1 g orally, or ceftriaxone, 250 mg intramuscularly. Alternative regimens include ciprofloxacin, 500 mg twice daily for 3 days, or erythromycin base, 500 mg by mouth three times daily for 7 days. However, antibiotic susceptibility varies geographically. Resistance has been reported to ciprofloxacin and erythromycin in some regions. Ciprofloxacin is contraindicated during pregnancy and lactation. Subjective improvement should be noted within 3 days, and ulcers generally heal completely in 7 to 14 days. Healing may be slower in uncircumcised men with ulcers below the foreskin and in patients with HIV (Schmid, 1999). Patients should be reexamined in 5 to 7 days. Sexual partners should be examined and treated if sexual relations were held within 2 weeks before or during the eruption of the ulcer. Symptomatic relief of inguinal tenderness can be provided by needle aspiration or incision and drainage of the buboes.



Figure 13–6. Syphilis with vulvar chancre.

SYPHILIS

Diagnosis. Syphilis is caused by the spirochete *Treponema pallidum*. Incubation periods range between 10 and 90 days. It is spread through contact with infectious lesions or body fluids. It can also be acquired in utero and through blood transfusion. Syphilis has been categorized into overlapping stages based on clinical signs and symptoms to guide diagnosis and treatment. Primary syphilis is characterized by a single painless, indurated ulcer occurring at the site of inoculation that appears about 3 weeks after inoculation and persists for 4 to 6 weeks (Figs. 13–6 and 13–7). The ulcer is typically found on the glans, corona, or perianal area on men and on the labial or anal area on women. It is often associated with bilateral, nontender inguinal or regional lymphadenopathy. Because the ulcer and adenopathy are painless and heal without treatment, primary syphilis often goes unnoticed.

Secondary syphilis usually begins 4 to 10 weeks after the appearance of the ulcer but may present as long as 24 months after the initial infection. Secondary syphilis manifests as mucocutaneous, constitutional, and parenchymal signs and symptoms (Figs. 13–8 and 13–9). Frequent early manifestations consist of maculopapular rash, which is commonly seen on the trunk and arms, and generalized nontender lymphadenopathy. After several days or weeks, a papular rash may accompany the primary rash. These papular lesions are associated with endarteritis and may therefore become necrotic and pustular. The distribution widens and commonly affects the palms and soles. **In the intertriginous areas these papules may enlarge and erode to produce condyloma lata, which are particularly infectious.** Less common manifestations of secondary syphilis include hepatitis and immune complex–induced glomerulonephritis (Goldmeier and Guallar, 2003).



Figure 13–7. Syphilis with penile chancre.



Figure 13–9. Secondary syphilis affecting the soles of the feet.



Figure 13–8. Secondary syphilis affecting the genitalia.

Approximately one third of untreated patients will develop tertiary syphilis. It is very rare in industrialized countries, except for occasional cases reported in HIV patients. **Syphilis is a systemic disease that can affect almost any organ or system, especially the cardiovascular, skeletal, and central nervous systems, and skin.** Neurosyphilis can occur at any stage. **Aortitis, meningitis, uveitis, optic neuritis, general paresis, tabes dorsalis, and gummas of the skin and skeleton are just some of the sequelae associated with tertiary syphilis.**

Latent syphilis is defined as seroreactivity with no clinical evidence of disease. Early latent syphilis is latent syphilis acquired within the past year. All other latent syphilis is either referred to as late latent syphilis or latent syphilis of unknown duration.

Darkfield microscopy and direct fluorescent antibody (DFA) tests can be performed on specimens obtained from primary or secondary lesions. Darkfield microscopy is not widely available, but DFA testing of a fixed smear from a lesion can be performed at many commercial laboratories. Nontreponemal serologic testing with rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) are the most common methods of screening suspected individuals. Sensitivity is 78% and 86% for RPR and VDRL, respectively, in primary syphilis, 100% for both in secondary syphilis, and over 95% in tertiary syphilis (Hart, 1986). The false-positive rate is 1% to 2% and may be secondary to a large variety of causes (Golden et al, 2003). **Therefore, all positive tests should be confirmed with treponemal testing using *T. pallidum* particle agglutination (TP-PA) or fluorescent treponemal antibody absorbed (FTA-ABS) testing.** HIV can cause false-negative results by both treponemal and nontreponemal methods (Hicks et al, 1987; Erbelding et al, 1997). Positive treponemal antibody tests usually remain positive for life and do

not correlate with disease activity. Nontreponemal antibody titers, RPR and VDRL, correlate with disease activity. These tests usually become negative 1 year after treatment. A low percentage of patients remain "serofast," never regaining a negative titer. A fourfold difference in titer is reflective of a clinically significant difference. A fourfold increase after therapy is indicative of ineffective therapy or reinfection (Johnson and Farnie, 1994). A fourfold decrease represents successful treatment. Following disease activity, the same test, either RPR or VDRL, should be performed at the same laboratory because the results are not interchangeable and may vary from laboratory to laboratory.

The U.S. Preventive Services Task Force recommends that pregnant women and people who are at higher risk for syphilis infection receive screening tests for the disease (Calonge, 2004). People at higher risk for syphilis include men who have sex with men and engage in high-risk sexual behavior, commercial sex workers, persons who exchange sex for drugs, and those in adult correctional facilities. The CDC recommends that HIV testing should be considered in the initial evaluation of all patients with syphilitic infection and that screening for hepatitis B and C, gonorrhea, and chlamydial infection also should be considered. The presence of chancres increases the risk of HIV acquisition twofold to fivefold (Greenblatt et al, 1988; Stamm et al, 1988).

Treatment. Benzathine penicillin G (2.4 million units intramuscularly as a single dose) remains the treatment of choice for adults with primary, secondary, or early latent syphilis. Other parenteral preparations or oral penicillin are not acceptable substitutes. The **Jarisch-Herxheimer reaction** is a reaction consisting of headache, myalgia, fever, tachycardia, and increased respiratory rate that occurs within the first 24 hours after treatment with penicillin. Patients should be warned about the reaction, and it is usually managed with bed rest and nonsteroidal anti-inflammatory agents. It may cause fetal distress and preterm labor in pregnant women. If the patient has penicillin allergy, doxycycline, 100 mg by mouth twice daily for 14 days, or tetracycline, 500 orally for 14 days, have been used as alternatives. Close follow-up of patents receiving alteratives to the recommended benzathine penicillin regimen is critical.

For late latent syphilis, latent syphilis of unknown duration, or tertiary syphilis with no evidence of neurosyphilis, benzathine penicillin, 2.4 million units intramuscular injection should be repeated weekly for a total of three doses (total dose of 7.2 million units) or doxycycline therapy extended for a total of 4 weeks. In pregnancy, the alternative regimens of doxycycline and tetracycline should not be used and desensitization to penicillin is recommended if the patient has a penicillin allergy. Small studies have shown that azithromycin or ceftriaxone may be potential alternatives for early syphilis, but insufficient data are available to make definitive recommendations (Augenbraun and Workowski, 1999; Gruber et al, 2000; Hook et al, 2002).

Neurosyphilis and syphilitic eye disease are treated with aqueous crystalline penicillin G, 3 to 4 million units intravenously every 4 hours for 10 to 14 days, or with procaine penicillin G, 2.4 million units intramuscularly once daily, plus probenecid, 500 mg orally four times daily, with both drugs given for 10 to 14 days. Probenecid cannot be used in patients with an allergy to sulfa. The CDC recommends consideration of treatment with benzathine penicillin, 2.4 million units intramuscularly once a week for 3 weeks after completion of the neurosyphilis treatment regimen, to provide total duration of therapy comparable to that of late syphilis.

Patients should be followed with nontreponemal antibody titers at 6 and 12 month. Patients with HIV should be followed at 3, 6, 9, 12, and 24 months. A fourfold decrease in antibody titer is usually reflective of cure. The rate of treatment failure ranges from 4% to 21% (Parkes et al, 2004). Patients with treatment failure should be re-treated, and cerebrospinal fluid should be examined to exclude neurosyphilis. Patients with neurosyphilis require repeat examination of cerebrospinal fluid 3 to 6 months after therapy and every 6 months afterward until normal results are achieved.

LYMPHOGRANULOMA VENEREUM

Diagnosis. Lymphogranuloma venereum is caused by *Chlamydia trachomatis* types L1, L2, and L3 and is extremely rare in the United States. It still persists in parts of Africa, Asia, South America, and the Caribbean (Mabey and Peeling, 2002). The incubation period ranges from 3 to 30 days. The initial manifestation of infection is usually a single, painless ulcer on the penis, anus, or vulvovaginal area that goes unnoticed. **Patients usually present with painful unilateral suppurative inguinal adenopathy and constitutional symptoms that occur 2 to 6 weeks after resolution of the ulcer** (Figs. 13–10 and 13–11). Women and homosexual men may present with proctocolitis and perirectal or deep iliac lymph node enlargement if the primary lesion



Figure 13–10. Lymphogranuloma venereum.



Figure 13–11. Lymphogranuloma venereum with inguinal adenopathy.

arises from the rectum or cervix. Significant tissue injury and scarring may occur, leading to labial fenestration, urethral destruction, anorectal fistulae, and elephantiasis of the penis, scrotum, or labia.

The diagnosis is mainly clinical and cultures are positive in only 30% to 50% of cases. Complement fixation or indirect fluorescence antibody titers can confirm diagnosis. A complement fixation titer greater than 64 is diagnostic of infection. Other causes of inguinal adenopathy should be excluded.

Treatment. Antibiotic therapy for 3 weeks is necessary, using either doxycycline, 100 mg twice daily, or erythromycin base, 500 mg four times daily. Doxycycline is contraindicated in pregnant and lactating women. Patients should be followed clinically until symptoms resolve. Sexual partners should be examined, tested for urethral or cervical infection, and treated if sexual relations occurred within 30 days of the onset of symptoms.

CHLAMYDIA TRACHOMATIS INFECTION

Diagnosis. Infection with *C. trachomatis* is the most common bacterial STI in the United States and the most common worldwide. In the United States it is most prevalent in sexually active adolescents and young adults. Virulent serotypes include D, E, F, G, H, I, J, and K. The incubation period ranges from 3 to 14 days.

The majority of both men and women are asymptomatic. Approximately 50% of men experience lower urinary tract symptoms attributed to urethritis, epididymitis, or prostatitis and may notice clear or white urethral discharge. ***C. trachomatis* is the most common cause of epididymitis in young men.** Approximately 75% of women are asymptomatic, and 40% with untreated infection will develop pelvic inflammatory disease (Rees, 1980). **The squamous cells of vaginal epithelium are relatively resistant to infection with *C. trachomatis,* but the columnar cells of the cervix are not. A mucopurulent endocervical discharge may be present.** Scarring of the fallopian tubes from chlamydial infection puts patients at risk for recurrent pelvic inflammatory disease with vaginal flora, ectopic pregnancy, pelvic pain, and infertility (Simms and Stephenson, 2000).

Chlamydia may also be transmitted to newborns during vaginal birth through exposure of the mother's infected cervix. Neonates may contract ocular, oropharyngeal, respiratory, urogenital, or rectal infection.

Selective screening has been shown to reduce the incidence of pelvic inflammatory disease (Scholes et al, 1996). Sexually active women should be screened annually until age 26. Older women should be screened if risk factors such as a new sexual partner are present. In women, screening may be accomplished by (1) a nucleic acid amplification test (NAAT) performed on an endocervical swab specimen, if a pelvic examination is acceptable; otherwise, an NAAT may be performed on urine; (2) an unamplified nucleic acid hybridization test, an enzyme immunoassay, or direct fluorescent antibody test performed on an endocervical swab specimen; or (3) culture performed on an endocervical swab specimen. In men, the options remain the same: using intraurethral samples or urine.

NAATs utilizing PCR assays for urine are a highly sensitive and noninvasive means of screening men and women for chlamydial infection. NAATs have doubled the detection rate for asymptomatic infections compared with culture and antigen tests (Black et al, 2002; Watson et al, 2002). **This method should not replace pelvic examination or endocervical culture in symptomatic women because antibiotic sensitivity cannot be determined.** Specimens for culture can be obtained from urethral or cervical swabs, urine, or prostatic fluid. However, NAAT remains an alternative in patients when culture is not possible due to logistics or noncompliance. Urine NAAT is only slightly less sensitive than endocervical swab and because of its noninvasive nature can be used in venues where pelvic examinations are not performed, such as schools and prisons (Black et al, 2002). NAATs may be used with urine or vaginal specimens but not oral or rectal samples. NAATs to test for cure should not be performed less than 3 weeks after treatment has been completed because dead organisms that may still be present will yield a false-positive test. NAATs are available that test for infection with both *Chlamydia* and *N. gonorrhoeae* from one sample; however, a positive result is nondiscriminatory between the two diseases and therefore further testing would be needed to determine which disease is present.

Treatment. Azithromycin, 1 g by mouth as a single dose, or doxycycline, 100 mg twice daily for 7 days, is the primary treatment and both are equally effective (Lau and Qureshi, 2002). Alternative therapies include erythromycin base, 500 mg four times daily, erythromycin ethylsuccinate, 800 mg four times daily, ofloxacin, 300 mg twice daily, or levofloxacin, 500 mg once daily for 7 days. Doxycycline, erythromycin estolate, and ofloxacin are contraindicated during pregnancy. Erythromycin base, erythromycin ethylsuccinate, and azithromycin are safe during pregnancy. Another alternative in pregnant women includes amoxicillin, 500 mg three times per day for 7 days. Partners should be examined, tested, and treated. Patients should refrain from sexual intercourse until both their and their partner's treatment is completed or 7 days after single-dose therapy. Reculture for cure is not needed for patients treated with doxycycline or a quinolone antibiotic. Reculture is recommended 3 weeks after treatment with erythromycin because cure rates are lower with this regimen, in pregnant women, or if the patient has persistent symptoms. However, patients with *Chlamydia* are at high risk for reinfection and should be rescreened 3 to 4 months after treatment.

All sexual partners who came in contact with the patient within 60 days of diagnosis or symptom onset should be evaluated, tested, and treated for both *N. gonorrhoeae* and *C. trachomatis.* If more than 60 days has passed, the most recent sexual partner should be evaluated and treated. Sexual activity should be avoided until both partners complete treatment and are symptom free.

GONORRHEA

Diagnosis. Gonorrhea is caused by the gram-negative diplococcus *Neisseria gonorrhoeae.* The incubation period ranges from 3 to 14 days. Risk of infection after one exposure is 10% in men and 40% in women. Men will usually experience lower urinary tract symptoms attributed to urethritis, epididymitis, proctitis, or prostatitis, with associated mucopurulent urethral discharge. Women are frequently asymptomatic but may have symptoms of vaginal and pelvic discomfort or dysuria. **As with *C. trachomatis* the vaginal epithelium is resistant to infection with *N. gonorrhoeae* but the cervix is not. A mucopurulent endocervical discharge may be present** (Table 13–3). Both symptomatic and asymptomatic infections can lead to pelvic inflammatory disease and its subsequent complications. Manifestations of gonococcal dissemination are rare today and include arthritis, dermatitis, meningitis, and endocarditis.

The U.S. Preventive Services Task Force recommends screenings for gonorrhea to those at increased risk for

Table 13–3.
Differential Diagnosis of Sexually Transmitted Infections in Women

	VAGINAL DISCHARGE	pH	WBC	MICROSCOPY	SYMPTOMS
Normal	White, thick, smooth	≤4.5	Absent	Lactobacilli	None
Candidiasis	White, thick, curdlike	≤4.5	Absent	Mycelia	Vulvar pruritus, external or superficial dysuria
Trichomoniasis	Frothy or purulent	≥4.5	Present	Mobile trichomonads present Amine odor	Vulvar erythema and edema, punctate strawberry lesions on cervix
Neisseria gonorrhoeae infection	None or mucopurulent discharge from cervicitis	≥4.5	Present	Gram-negative diplococci within or adjacent to polymorphonuclear leukocytes on Gram stain	Vaginal and pelvic discomfort, dysuria, most often asymptomatic
Chlamydia trachomatis infection	None or mucopurulent discharge from cervicitis	≥4.5	Present	Organisms not visualized	Vaginal and pelvic discomfort, dysuria, most often asymptomatic
Bacterial vaginosis	Thin, white homogeneous	≥4.5	Absent	Paucity of lactobacilli (75% of patients) Amine odor Clue cells	Fishy odor and increased vaginal discharge

infection, including women with previous gonorrhea infection or other STIs; women with new or multiple sex partners, inconsistent condom use, sex, and drug use; and women in certain demographic groups and those living in high-prevalence areas. Screening may be done by endocervical culture or can be performed with newer screening tests, including NAAT and nucleic acid hybridization tests using vaginal, urethral (men only), or urine specimens (U.S. Preventative Services Task Force, 2005; CDC, 2010b). In case of suspected or documented treatment failure, culture and sensitivity are important to monitor antibiotic susceptibility and resistance. Culture may be performed on urethral exudates if present. Patients found to have gonorrhea should be tested for other STIs, including chlamydia, syphilis, and HIV.

Treatment. The most highly recommended treatment for gonorrhea is ceftriaxone, 250 mg intramuscularly as a single dose. It produces high, sustained blood levels that result in cure in about 99% of uncomplicated cases at all anatomic sites, including the pharnyx, which often goes undiagnosed. If treatment with ceftriaxone is not possible, a single oral dose of cefixime (400 mg) is an acceptable alternative that provides a high cure rate for uncomplicated urogenital and anorectal infection but is less effective for pharyngeal infection. Other single-dose cephalosporins, including ceftizoxime 500 mg IM, cefoxitin 2 g IM with probenacid 1 g orally, and cefotaxime 500 mg IM, have been shown to be effective as alternative regimens for uncomplicated urogenital or anorectal infection but offer no advantage over the recommended regimens.

The CDC no longer recommends quinolones for the treatment of gonorrhea in the United States based on data indicating widespread resistance.

Spectinomycin (not available in the United States), 2 g intramuscularly, can be used as an alternative in patients allergic to cephalosporins and during pregnancy. In the United States, azithromycin 2 g orally can be considered for pregnant women who cannot tolerate cephalosporins. It is not considered effective for pharyngeal infection.

Patients with gonorrhea are often coinfected with *C. trachomatis*. **It has been recommended that patients undergo simultaneous dual treatment because the cost of treatment is less than that of chlamydial testing.** Single-dose regimens given in the office also ensure compliance in patients who may otherwise not be able to afford the medication, comply with treatment, or return for follow-up. Patients undergoing dual therapy for chlamydial infection should receive azithromycin, 1.0 g as a single dose, or doxycycline, 100 mg twice a day for 7 days (or other acceptable treatment regimen) in addition to one of the previously mentioned regimens for infection with *N. gonorrhoeae*.

All sexual partners who came in contact with the patient within 60 days of diagnosis or symptom onset should be evaluated, tested, and treated for both *N. gonorrhoeae* and *C. trachomatis*. If more than 60 days has passed, the most recent sexual partner should be evaluated and treated. Sexual activity should be avoided until both partners complete treatment and are symptom free.

TRICHOMONIASIS

Diagnosis. Trichomoniasis is one of the most common STIs, with approximately 174 million new cases reported worldwide each year and more than 8 million new cases reported yearly in North America (WHO, 1999). There is an increased incidence in developing countries and in women who have had multiple sexual partners. It is caused by the flagellated protozoan *Trichomonas vaginalis,* which can inhabit the vagina, urethra, Bartholin glands, Skene glands, and prostate. It does not infect the mouth, and rectal prevalence is low. The human is its only known host. The incubation period ranges from 4 to 28 days.

Trichomoniasis is typically asymptomatic in men but may produce short-lived symptoms of urethral discharge, dysuria, and urinary urgency. **Fifty percent of women are asymptomatic.** When present, clinical manifestations in women include the sudden onset of a frothy white or green, foul-smelling vaginal discharge, pruritus, and erythema. Other symptoms include dyspareunia, suprapubic discomfort, and urinary urgency. It has been associated with premature labor in pregnant women and with increased risk of HIV transmission (Cotch et al, 1997; Sorvillo et al, 1998).

Clinical examination in women may reveal a frothy discharge and the characteristic "strawberry vulva" or "strawberry cervix." However, clinical assessment alone is not specific enough for diagnosis. Typically, the vaginal discharge has an elevated pH. The motile protozoa, which are one to four times the size of polymorphonuclear cells, can also be seen on vaginal wet-mount smear or microscopic examination of urine. In men, the diagnosis can be made with urethral, urine, or semen culture or microscopic

examination of the urine (preferably voiding bottle No. 1). Standard culture, transport culture kits, enzyme immunoassay, nucleic acid amplification, and immunofluorescence techniques are also available for confirmatory testing. Nucleic acid amplification tests have the highest sensitivity for diagnosis in men (Nye et al, 2009).

Treatment. Infected individuals and their sexual partners should be treated to prevent recurrence of infection. Recommended regimens include a single oral 2.0 g dose of either metronidazole or tinidazole. The 2 g metronidazole regimen may be used during pregnancy; however, the safety of tinidazole in pregnancy has not been established. For nonpregnant treatment failures a longer course of metronidazole, 500 mg twice daily for 7 days, is recommended. The dosing regimens appear equally effective, but side effects, especially gastrointestinal side effects, are more common with the high-dose single therapy. Patients must abstain from alcohol consumption during therapy and for 24 hours after completion of metronidazole and for 72 hours after completion of tinidazole. Repeat testing at 5 to 7 days and 30 days should be performed if symptoms fail to resolve and treatment failure is suspected, and a course of metronidazole, 500 mg orally twice a day for 7 days, should be repeated, or 2 g oral treatment with tinidazole or metronidazole once daily for 5 days may be tried. Metronidazole gel for intravaginal application is available but is less than 50% as effective as oral treatment. Patients allergic to metronidazole should be desensitized. Clotrimazole and other agents have been tried as local intravaginal applications but have not been found to be effective (duBouchet et al, 1997).



Figure 13–12. Meatal wart caused by human papillomavirus.

GENITAL WARTS

Diagnosis. Genital warts (condylomata acuminata) are caused by HPV. HPV is a DNA-containing virus that is spread by direct skin-to-skin contact. Over 100 types of HPV exist, and over 30 types can infect the genital area. Risk factors for acquiring HPV include multiple sexual partners, early age at onset of sexual intercourse, and having a sexual partner with HPV. Most infections are subclinical and asymptomatic. It has been shown that 60% of a group of female college students followed by Papanicolaou smear every 6 months for 3 years were infected with HPV at some point. The median duration of HPV infection was 8 months, with only 9% remaining infected after 2 years (Ho et al, 1998).

External visible warts are typically caused by HPV types 6 and 11. Patients may be infected with more than one type of HPV. Genital warts may appear anywhere on the external genitalia (Figs. 13–12 to 13–14). It has been suggested that inoculation occurs at the site of genital microtrauma (Frydenberg and Malek, 1993). HPV has also been found on the cervix, vagina, urethra, anus, and mucous membranes such as the conjunctiva, mouth, and nasal passages. Intra-anal warts are contracted via receptive anal sex. However, perianal warts are contracted by skin-to-skin contact and not exclusively through receptive anal intercourse.

Types 6 and 11 HPV are low risk for conversion to invasive carcinoma of the external genitalia. Some other types present in the anogenital region. Types 16, 18, 31, 33, 35, 39, 45, and 51 have been associated with cervical dysplasia and neoplasm in women and squamous intraepithelial neoplasia in men (Syrjanen 1981; Adam et al, 2000; Kulasingam et al, 2002). Over 99% of cervical cancers and 84% of anal cancers are associated with HPV, most commonly HPV 16 and 18 (Frisch et al, 1997; Walboomers et al, 1999; Kulasingam et al, 2002). **Because HPV progresses rapidly in HIV-infected women, cervical cancer is considered one of the illnesses that defines the acquired**



Figure 13–13. Penile warts.



Figure 13–14. Vaginal condylomata caused by human papillomavirus.

immunodeficiency syndrome (AIDS). Smoking may increase the risk of dysplastic progression and malignancy in both men and women.

In women, HPV may be associated with nonspecific symptoms, such as vulvodynia or pruritus. Malodorous vaginal discharge may also be a presenting sign, and the high rate of coinfection with other STIs observed in this setting may be a contributing factor.

The diagnosis is usually made through the visualization or palpation of nontender papillomatous genital lesions. Acetowhitening with 3% to 5% acetic acid placed on a towel and wrapped around the genitalia may show subclinical, flat condylomata appearing as whitish areas; however, because it is not specific for HPV infection, it is not recommended as a routine screening procedure. When this method was used it was shown that 50% to 77% of steady male partners of women with HPV infection and/or cervical neoplasia had subclinical HPV infection (Schneider et al, 1988). Conversely, female partners of men with genital warts have a high incidence of HPV infection (Campion et al, 1985). The benefit of evaluating and treating asymptomatic sexual partners of women with genital warts or abnormal Papanicolaou smears remains unclear. Therefore, routine androscopy is not recommended. **Biopsies of genital warts are not routinely needed but should be undertaken in all instances of atypical, pigmented, indurated, fixed, or ulcerated warts.** In addition, biopsy should be performed if the lesions persist or worsen after treatment and in immunocompromised patients.

Treatment. The CDC currently recommends that patients with genital warts be informed that HPV and recurrence is common among sexually active persons, the incubation period can be long and variable, and duration of infection and methods of prevention are not definitively known. The choice of therapy for genital warts depends on several factors, including wart size, number, and location and patient and physician preference. Because genital warts spontaneously resolve with time, observation remains an option. Therapy can be patient applied or provider applied. Patient-applied therapies are less expensive and may be more effective than provider-applied therapy (Langley et al, 1999; Arican et al, 2004). Patients must be able to identify and access the lesion and be capable of carefully following the product instructions.

Recommended treatment choices for patient-applied therapy include podofilox 0.5% solution or gel, imiquimod 5% cream, or sinecatechins 15% ointment. Podofilox solution should be applied every 12 hours for 3 days, then off for 4 days with the option to repeat the treatment cycle four times. The total volume of solution used should not exceed 0.5 mL/day, and the total wart area should not be greater than 10 cm^2. It may be helpful to demonstrate the first application in the office. Imiquimod cream should be applied three times per week at bedtime for up to 16 weeks. The area should be thoroughly washed 6 to 10 hours after application. Imiquimod should not be used on vaginal lesions because it has been reported to cause chronic ulceration. Sinecatechin ointment (0.5 cm strand of ointment) should be applied three times daily using a finger to ensure a thin film of ointment until the wart completely clears, but no longer than 16 weeks. It should not be washed off after use. In addition, sinecathecin should not be used in immunocompromised persons, HIV-infected persons, or persons with genital herpes because the safety and efficacy in these populations has not been established. The safety of podofilox, imiquimod, and sinecatechin in pregnancy is unknown. Both imiquimod and sinecatechin may weaken condoms and vaginal diaphragms.

Options for provider-applied therapy include cryotherapy with liquid nitrogen, electrosurgery, laser therapy, podophyllin resin 10% to 25%, trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80% to 90%, or surgical excision. Surgical excision may be accomplished by electrocautery or sharply with a tangential incision. Bleeding can generally be controlled with electrocautery or silver nitrate application. Surgical therapies appear to be equally effective with regard to clearance rates (Wiley et al, 2002). The advantages of surgical excision are that large warts or large areas can be addressed at one time. Carbon dioxide laser therapy is an alternative option for treatment.

Podophyllin 10% to 25% in compound tincture of benzoin is applied once and washed thoroughly 1 to 4 hours after treatment. Treatment may be repeated weekly as needed. The total volume of solution used should not exceed 0.5 mL, and the total wart area treated should not be greater than 10 cm^2 per session. In addition, the area being treated should not contain any open wounds or lesions. Podophyllin is contraindicated during pregnancy. TCA and BCA should be carefully applied with a cotton-tipped applicator only to the warts at 1- to 2-week intervals. Patients will complain of a burning sensation, which should resolve in 2 to 5 minutes. Acid that does not react should be removed with baking soda or talc. TCA and BCA are not recommended for keratinized or large warts. TCA is not absorbed and may be used during pregnancy.

Women with genital warts or a history of exposure should seek prompt gynecologic evaluation of the vagina and cervix. In the past, extensive vulvar lesions were treated with 5-fluorouracil cream but it was reported to cause ulceration and acquired adenosis and its use is no longer recommended.

Large or extensive lesions surrounding the urethral meatus may herald the presence of urethral or bladder condylomata, warranting cystourethroscopy. Urethral or bladder lesions should be cystoscopically excised. Intraurethral 5%

5-fluorouracil cream used twice weekly may be useful. However, its use is limited by the great amount of inflammation produced. Cystoscopic evaluation should be considered with caution because of the risk of transmitting the infection beyond the urethra and into the bladder. Considerations might include many and proximal urethral condylomata or other factors that would heighten suspicion for intravesical papillomas. We try to avoid traversing the external sphincter when performing limited urethroscopic examinations for the diagnosis of urethral condyloma or for the treatment of more distal lesions. Frequent serial ultrasound examinations of the distended bladder have been used for long-term surveillance of patients to check for recurrence of urethral condylomata.

HPV Vaccine. Two virus-like particle vaccines for the prevention of HPV-associated conditions are availble. Gardasil (Merck and Co., Inc.) is a quadrivalent vaccine against HPV types 6, 11, 16, and 18 and is approved by the FDA for use in males and females for the prevention of HPV-associated conditions such as cervical cancer, cervical cancer precursors, anal cancer and associated precancerous lesions, and anogenital warts. Cervarix (GlaxoSmith-Kline, PLC.), a bivalent vaccine against HPV types 16 and 18, is approved for use in females for the prevention of cervical cancer and associated precancerous lesions.

Both vaccines demonstrate good efficacy against cervical cancer and high-grade cervical intraepithelial neoplasia caused by HPV 16 and HPV 18, if administered before the initial exposure to these HPV types (Harper et al, 2004; Villa et al, 2005; FUTURE II Study Group, 2007; Garland et al, 2007). In addition, the quadrivalent vaccine protects against condylomata acuminata caused by HPV 6 and 11 and vulvar and vaginal precancerous lesions (FUTURE II Study Group, 2007; Joura et al, 2007).

The Advisory Committee on Immunization Practices (ACIP) recommends vaccination with either vaccine for the prevention of cervicial cancer and precancers. The quadrivalent vaccination may also be used for prevention of genital warts and other HPV-associated conditions such as vulvar cancers and precancers. The vaccines are most effective when all doses are administered before sexual contact. Either vaccine is recommended for 11- and 12-year-old girls and for females aged 13 to 26 years who did not receive or complete the vaccine series when they were younger. Vaccination may begin at age 9 when appropriate. The quadrivalent vaccine can be used in males age 9 to 26 years old to prevent genital warts (CDC, 2010). The length of immunity has not been definitively determined, but in phase 2 follow-up studies both the quadrivalent and bivalent vaccines demonstrated high immunogenic levels for more than 5 years (Villa et al, 2006; Harper et al, 2008). Further research will determine how long immunity will last and if a booster dose will be needed. Vaccination provides less protection to those who have already been infected with one or more of the four vaccine HPV types; however, vaccination is still recommended for protection against the other vaccine subtypes. Unlike the CDC's guidelines, the American Cancer Society does not recommend universal vaccination among women aged 19 to 26 years because of a probable reduction in efficacy as the number of lifetime sexual partners rises (Saslow et al, 2007). It is important to inform girls and women that they should continue cervical Pap screening even if they have been vaccinated.

MOLLUSCUM CONTAGIOSUM

Diagnosis. Molluscum contagiosum virus (MCV) is a double-stranded DNA virus that belongs to the Poxviridae family and has worldwide geographic distribution. There are four known subtypes of MCV, but the subtype does not appear to influence disease presentation or course (Nakamura et al, 1995). MCV-1 is the most prevalent in the United States, whereas types 2 and 3 are more prevalent in Europe, Australia, and in HIV-infected patients (Thompson et al, 1990, 1992; Porter and Archard, 1992). The incubation period ranges from 14 to 50 days (Fenner et al, 2001). MCV may be transmitted by skin-to-skin contact, fomites, or self-inoculation. It was once believed to cause only a benign, self-limiting childhood syndrome but is now also considered an STI in adolescents and adults. In children, lesions usually occur in clusters on the face and neck, chest, back, and extremities. In adults and adolescents it is most commonly transmitted by sexual contact, and lesions most frequently appear in the genital and inguinal regions, the inner thighs, and perineum. It less commonly affects mucosal areas such as the conjunctiva and oral mucosa. In children it may spread by self-inoculation to the genital area.

MCV primarily infects the squamous epithelium and manifests as smooth, round, pearly papules that are 2 to 5 mm in diameter, with a subtle central umbilication (Figs. 13–15 and 13–16). The lesions may have an erythematous or hypopigmented halo at the base. The papules are typically asymptomatic but may be associated with an eczematous, pruritic reaction. Giant lesions, more than 5 mm, can occur and seem to be more common in immunocompromised patients. In immunocompetent persons the lesions usually spontaneously resolve within a few months



Figure 13–15. Molluscum contagiosum on abdomen.



Figure 13–16. Molluscum contagiosum affecting penis.

and usually by 1 year but may take up to 5 years (Gottlieb and Myskowski, 1994; Smith et al, 1999).

Diagnosis is usually made on clinical suspicion and may be incidental. If confirmation is necessary, hematoxylin and eosin staining of a biopsy specimen may be performed. The presence of acidophilic, hyaline-filled Henderson-Patterson bodies, also known as molluscum contagiosum bodies, are pathognomonic. A squash preparation with methylene blue will also reveal the molluscum contagiosum bodies. It is recommended that the patients be tested for other STIs such as gonorrhea, chlamydial infection, and syphilis and carefully examined for coexistent condylomata acuminata and pediculosis pubis (Waugh, 1998). Careful consideration should also be given to HIV testing in patients with extensive multisite lesions, especially those involving the head and neck, and in lesions with a poor response to treatment.

Treatment. In most cases, MCV is benign and self-limiting and therefore requires no treatment. If the patient desires or if spread is of particular concern, destructive therapy with cautery, curettage, or cryotherapy with liquid nitrogen are sound options. All of these methods cause discomfort and may result in scarring. Lidocaine/prilocaine cream applied in an occlusive manner before the procedure should assist with discomfort. A topical antibiotic preparation should be applied afterward to prevent secondary infection.

Other topical therapies such as TCA, cantharidin, tretinoin, and podophyllotoxin have been reported for the treatment of MCV (Smith and Skelton, 2002). None is approved by the U.S. FDA for this indication, and all may result in pain and inflammation, especially in the genital area. Immunotherapy with imiquimod cream, either 1% or 5%, applied to lesions three times daily has been shown to be effective and appears especially useful in patients infected with HIV (Syed et al, 1998; Liota et al, 2000). Small studies in HIV-infected patients with recalcitrant lesions have also reported success with 1% cidofovir cream (Calista, 2000; Torro et al, 2000). Currently cidofovir is commercially available only in an intravenous preparation.

SCABIES

Diagnosis. Scabies is caused by the mite *Sarcoptes scabiei*. In adults, scabies is usually sexually transmitted, but this is not the case in children. The incubation period ranges from 2 to 6 weeks. Wavy, elongated papules are characteristic of the mite burrow. Eruption with pruritus is caused by an immune reaction to the mites, their eggs, and their feces. Susceptible areas include the penile shaft and glands, areolae, finger webs, and auxiliary folds (Fig. 13–17). Confirming the diagnosis may require microscopic evidence of the mite or eggs, which is retrieved by scraping the burrow with a scalpel blade coated with mineral oil. It can also usually be demonstrated if a thin shaving of skin from a papule is removed and placed on a glass slide and digested with heat and 10% potassium hydroxide.

Norwegian scabies, also known as crusted scabies, is caused by the same mite but occurs in immunocompromised or debilitated persons. The parasite burden is much greater, resulting in many severe, deep, hyperkeratotic crusts that are characteristically less pruritic, most likely secondary to the host's immune compromise. The incubation period is shorter in patients with Norwegian scabies—usually less than 2 weeks (Kolar and Rapini, 1991).

Treatment. Permethrin cream (5%) should be applied to all areas of the body from the neck down and washed off 8 to 14 hours later. An alternative to permethrin cream is oral ivermectin, 200 µg/kg in a single dose, repeated 2 weeks later. Ivermectin therapy has been shown to be equally effective as permethrin cream and lindane lotion but is more expensive (Wendel and Rompalo, 2002). For intolterance to permethrin or ivermectin, or treatment failure, the alternative is lindane (1%) lotion or cream applied in a similar fashion and removed after 8 hours. If necessary, treatment may be repeated in 1 week. **Lindane should not be used after a bath and is contraindicated in children younger than 2 years of age, pregnant and lactating women, and patients with extensive dermatitis.** Serious adverse side effects from lindane include seizures and aplastic anemia. For young children or pregnant/lactating women, sulfur (3% to 6%) applied on 3 consecutive nights is an option. Sexual partners and close contacts should also be treated. Treatment of Norwegian scabies may require combined oral and topical therapy or repeated treatments. Lindane should be avoided in these patients because of their excessive dermatitis, which may lead to increased absorption.



Figure 13–17. Scabies affecting shaft of penis.

Clothing or bed linen that may have been contaminated should be washed and dried by machine on a hot cycle or dry cleaned and removed from body contact for at least 72 hours. It should be noted that itching may persist for 2 to 3 weeks after adequate therapy.

PEDICULOSIS PUBIS

Diagnosis. Pediculosis pubis infection (phthiriasis, pubic lice) is caused by infection with the human louse *Phthirus pubis*. This species of lice has a proclivity for the pubic area, but the nits and lice can be seen in other areas with hair, such as the axilla, eyelashes, or scalp hair. The saliva of the lice causes a maculopapular or urticarial reaction in sensitized people and results in intense itching of the affected area. The presence of eggs (nits) attached to the hair shaft near the skin surface or the actual presence of an imbedded louse in the hair follicle is diagnostic. These lice can often be seen with the naked eye or with low-power magnification.

Treatment. Recommended regimens include permethrin cream rinse (1%) or pyrethrins with piperonyl butoxide applied to affected areas of the body and washed off 10 minutes later. Alternative regimen in the case of patients who cannot tolerate the recommended regimens or for treatment failure, by patients with extensive dermatitis, include malathion 0.5% lotion applied for 8 to 12 hours and then washed off, or ivermectin 250 mcg/kg orally, repeated in 2 weeks. Although topical insecticidal preparations are

the preferred treatment, trimethoprim-sulfamethoxazole can eliminate infections (Hutchinson and Farquhar, 1982). Pediculosis of the eyelashes is treated by applying an occlusive ophthalmic ointment, such as sterile petrolatum, to the eyelid margins two times a day for 10 days. The medicated topical agents described above cannot be used on or near the eyes. Sexual partners within the past 30 days should also be treated. Clothing or bed linen that may have been contaminated should be washed and dried by machine on a hot cycle or dry cleaned and removed from body contact for at least 72 hours.

OVERVIEW OF OTHER SEXUALLY ASSOCIATED INFECTIONS

Mollicutes

Ureaplasma urealyticum, Mycoplasma hominis, and *Mycoplasma genitalium* are considered commensal organisms of the genital tract in both men and women. At least 60% of asymptomatic women have been shown to harbor *Ureaplasma* in their genital tract. **However, these organisms have also been implicated in cases of chronic prostatitis in men, urgency/frequency syndromes in women, and up to 40% of nongonococcal urethritis cases.** They have been isolated as the sole pathogen in symptomatic patients, who respond to antimicrobial therapy targeting these mollicutes. Women, especially young sexually active women, with urgency-frequency syndrome with or without dysuria who have repeatedly negative urine cultures may benefit from culture and subsequent treatment for *Mycoplasma* and *Ureaplasma*. Culturing for this organism should also be considered in men with symptoms previously attributed to prostatitis or in men with prior history of STI exposure or infection.

Mollicutes have complex nutritional requirements and will not grow on routine culture medium. They cannot be visualized well with Gram stain. Confirming the presence of the organism from cervical, urethral, or urine specimens requires the visualization of characteristic colonies on specialized agar and color changes of urea broth. The organisms are highly sensitive to drying and must be promptly placed in the proper medium and delivered to the laboratory. If cultures are positive, treatment is recommended with subsequent surveillance for improvement in symptoms. Sexual partners should be evaluated and treated and no sexual activity is advised for 2 weeks during treatment.

Historically this group of organisms was highly sensitive to tetracycline. Today, however, up to 30% of strains may be resistant, which may explain persistent symptoms in those patients treated empirically for nongonococcal urethritis or presumed *Chlamydia* infection. Most tetracycline-resistant strains remain sensitive to erythromycin. Currently, the initial recommended therapy is doxycycline, 100 mg twice daily for 2 weeks, or a single 1-g dose of azithromycin, which can be repeated after 10 to 14 days if needed. Other alternatives include erythromycin, 500 mg four times daily, or ofloxacin, 300 mg twice daily for 10 to 14 days. Sexual partners should be evaluated and treated as well as refrain from sexual activity for 2 weeks during treatment.

Bacterial Vaginosis

Diagnosis. Bacterial vaginosis is caused by the overgrowth of *Gardnerella vaginalis,* anaerobic organisms, and *Mycoplasma hominis* and inhibition of normal vaginal flora, particularly *Lactobacillus*. The cause of disruption in the microflora has not been elucidated. Bacterial vaginosis increases a woman's risk of contracting infection with HIV, is associated with increased complications in pregnancy, and may be involved in the pathogenesis of pelvic inflammatory disease.

Patients may complain of a malodorous vaginal discharge, particularly after sexual intercourse, and nonspecific low-grade genital discomfort. Risk factors for bacterial vaginosis include an increased number of sexual partners, douching, abnormal uterine bleeding, and contraceptive use.

To examine vaginal discharge, a wet mount is performed by adding 2 drops of normal saline to the vaginal discharge on one microscope slide and 2 drops of 10% potassium hydroxide to another sample on a second slide. The whiff test is performed immediately after adding the potassium hydroxide. A fishy odor secondary to the release of amines is suggestive of bacterial vaginosis. The slide is then examined under the microscope using low and high power. Clue cells are white blood cells with bacteria attached to the cell membrane. Three of four of the following factors must be met to confirm the diagnosis: (1) thin, white vaginal discharge that covers the vagina, (2) vaginal pH greater than 4.5, (3) clue cells, and (4) positive whiff test. Vaginal cultures are not helpful in this setting; however, a Gram stain of the vaginal discharge can identify the relative change in concentrations of normal bacterial flora. There are commercially available DNA probes and card tests that can be useful for office diagnosis. Routine operative prophylaxis with metronidazole before hysterectomy has been shown to reduce postoperative infectious complications.

Treatment. Recommended primary therapy includes metronidazole, 500 mg twice daily for 7 days; clindamycin cream, 2% (5 g) intravaginally at bedtime for 7 days; or metronidazole gel, 0.75% (5 g) intravaginally at bedtime for 5 days. Alternative regimens include clindamycin, 300 mg orally twice daily for 7 days; clindamycin ovules, 100 g intravaginally at bedtime for 3 days; tinidazole, 2 g orally once daily for 2 days; or tinidazole, 1 g orally once daily for 5 days. Clindamycin cream and ovules may weaken latex condoms and diaphragms. Factors that disrupt the normal vaginal flora, such as douching, should be avoided. Treatment of the sexual partner has not been shown to prevent recurrence in two randomized trials and is therefore not recommended (Vejtorp et al, 1988; Colli et al, 1997).

Vulvovaginal Candidiasis

Vaginitis caused by *Candida albicans* is the most common type seen in the clinical setting, but other species of *Candida* may also cause infection. The organism is present in the normal vagina and can also be found in the coronal sulcus of the penis. Sexual transmission with subsequent colonization and infection is possible. Predisposing factors for active infection include hormonal changes resulting from pregnancy or contraception, antibiotic use, systemic corticosteroids, or antimetabolites. Complicated vulvovaginal candidiasis is defined as recurrent, severe, non–*C. albicans* infections occurring in patients with altered immunity or pregnancy. Characteristically, thick, cheesy vaginal discharge is usually associated with vulvar irritation and itching. Patients may also experience vaginal discomfort, burning, dyspareunia, and external dysuria.

Diagnosis can be confirmed in a woman with signs and symptoms by findings of yeast or pseudohyphae on a wet preparation slide or Gram stain of the vaginal discharge. Often the yeast and pseudohyphae are seen better when 10% potassium hydroxide is used. The pH of the vaginal discharge should be normal

Key Points

- Bacterial STIs are decreasing in prevalence whereas the prevalence of viral STIs has increased significantly in recent years.
- The differential diagnosis for genital ulcers includes the following STIs: syphilis, chancroid, lymphogranuloma venereum, and herpes simplex virus. Other causes also include diseases not transmittable through sexual activity: Behçet syndrome, drug reaction, erythema multiforme, Crohn disease, lichen planus, amebiasis, trauma, and carcinoma.
- Sensitivity of diagnosis made solely on the appearance of genitourinary ulcers is 35% at best.
- Confirmatory testing made by cultures, PCR, or serologic studies is important for appropriate treatment and eradication of the disease in both patients and their partner(s).
- Empirical treatments for vaginitides should be done with caution because the differential diagnosis is quite extensive. Women with chronic lower urinary tract symptoms should be thoroughly examined to exclude the possibility of vaginal pathology and/or STIs.
- The physician treating STIs should make special efforts to be sure that his or her methods of diagnosis and treatment reflect the latest knowledge. The CDC periodically updates its website with recommendations for STI treatment, because this topic has rapidly changing epidemiologic characteristics and treatment trends based on newly resistant strains.

(<4.5). A vaginal culture may also be performed and is advised in patients with recurrent infections. Recurrent vulvovaginal candidiasis is defined as four or more episodes per year, and in 10% to 20% of patients *C. glabrata* and other candidal species are found.

Treatment. Over-the-counter antifungal vaginal creams, tablets, or suppositories of the topical azole class are generally effective, requiring 1- to 7-day regimens depending on the agent and dosage form. Over-the-counter treatment agents include butoconazole, clotrimazole, miconazole, and tioconazole. The vaginal preparations may weaken latex condoms. Prescription intravaginal agents include butoconazole, nystatin, and terconazole. An alternative to vaginal creams that is both effective and economical is fluconazole, 150 mg, as a single oral dose (Miller, 1997).

Recurring infections or complicated vulvovaginal candidiasis may require extended treatment of 14 days with vaginal preparations or oral fluconazole therapy repeated every 3 days (day 1, 4, and 7) for a total of three doses prior to starting an antifungal maintenance regimen. Patients suffering from recurrent candidal vulvovaginitis require further evaluation to exclude HIV infection, diabetes, or other immune-compromised states, although in most women no cause is found. These patients often do well with maintenance therapy, but 30% to 40% will have recurrence once maintenance therapy is stopped. Treatment of sexual partners is not suggested in general but may be considered in patients with recurrent infections.

SUGGESTED READINGS

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The complete reference list is available online at www.expertconsult.com.

chapter 14

Urologic Aspects of AIDS and HIV Infection

Thomas J. Walsh, MD, MS ● John N. Krieger, MD

HIV/AIDS Epidemiology
HIV Virology and Targets for Antiviral Therapy
Pathogenesis of HIV Infection
Tests to Diagnose and Monitor HIV Infection: What the Urologist Should Know
Urologic Manifestations of HIV Infection
Occupational Risks for HIV Infection in Urology
Antiretroviral Therapy

The acquired immunodeficiency syndrome (AIDS) is the most severe manifestation of infection with human immunodeficiency virus (HIV). **AIDS is defined by development of serious opportunistic infections, neoplasms, or other life-threatening conditions resulting from progressive immunosuppression caused by HIV infection.**

After AIDS was described in 1981 the number of cases increased rapidly (Steinbrook, 2004; World Health Organization, 2004). An estimated 30.6 million to 36.1 million people worldwide are living with HIV infection. More than 20 million have died of AIDS (Joint United Nations Program on HIV/AIDS, 2004; UNAIDS/WHO, 2008). In 2007 alone, 2.5 million people were infected and 2.1 million died of AIDS. Of all people 15 to 49 years of age worldwide, 1.1% are now infected with HIV (Steinbrook, 2004).

HIV/AIDS EPIDEMIOLOGY

In less than 15 years HIV infection reached pandemic proportions, with AIDS reported in over 190 countries (UNAIDS/WHO, 2008). The impact of HIV infection is much different in the developing world than in the industrialized world. **At one time AIDS was the leading cause of death among 25- to 44-year old men in Western European and North American cities and was the third most common cause of death among young women** (Carael et al, 2004; Steinbrook, 2004). **With effective antiretroviral therapy, deaths attributed to AIDS are declining rapidly.** Worldwide, AIDS-related deaths declined from 2.9 million to 2.1 million from 2004 to 2007 (UNAIDS/WHO, 2008).

In contrast, in many African cities AIDS represents the leading cause of death and of years of potential lost in men and the second most important cause of death in women. Life expectancy in the most affected sub-Saharan countries was reduced as much as 15 years by the year 2000, compared with projections of life expectancy in those not infected with HIV.

Worldwide Perspective

The three main modes of HIV transmission have changed little: unprotected intercourse, contact with blood, and transmission from mother to child. Direct blood contact, such as sharing drug-injection equipment, results in the most efficient transmission. Globally, "unprotected" sexual intercourse between men and women is the predominant mode of HIV transmission (World Health Organization, 2004).

The burden of HIV infection is greatest in the developing world (Steinbrook, 2004). Two thirds of HIV-infected persons are in Africa, where the epidemic exploded during the 1990s, and one fifth are in Asia, where the epidemic has been growing steadily (Steinbrook, 2004). Eight of nine countries with the most HIV-infected people are in sub-Saharan Africa. Estimates for India range from 2.2 to 7.6 million, and for China they are from 430,000 to 1.5 million. In comparison, an estimated 1.2 million people are living with HIV in the United States, 860,000 in the Russian Federation, and 680,000 in Brazil. Statistics highlight global disparities in availability of therapy. Overall, 1.6 million people died of AIDS in sub-Saharan Africa in 2007. By comparison, in Western and Central Europe, only 12,000 people died of AIDS in 2007 (Table 14–1) (Joint United Nations Program on HIV/AIDS, 2004; UNAIDS/WHO, 2007; Quinn, 2008).

Developed World Perspective

The prevalence of HIV has continued to rise in the United States with estimates as high as 1.2 million Americans living with HIV, nearly 75% of whom are adult men (Carael et al, 2004; Centers for Disease Control and Prevention, 2004; Steinbrook, 2004; Heyns et al, 2009). Early in the epidemic most infections occurred among men who have sex with men, but the incidence in this group leveled off by 1985-1987. However, HIV prevalence levels of 7% to 9% are still found among young homosexual and

Table 14–1.

The Global HIV-AIDS Epidemic at the End of 2007

REGION	NO. OF PEOPLE LIVING WITH HIV-AIDS	PREVALENCE OF HIV-AIDS AMONG ADULTS (%)	NO. OF NEW HIV INFECTIONS IN 2003	NO, OF DEATHS DUE TO AIDS IN 2003
TOTAL	33.2 million	0.8	2.5 million	2.1 million
Sub-Saharan Africa	22.5 million	5.0	1.7 million	1.6 million
South and Southeast Asia	4 million	0.3	340,000	270,000
Latin America	1.6 million	0.5	100,000	58,000
Eastern Europe and Central Asia	1.6 million	0.9	150,000	55,000
North America	1.3 million	0.6	46,000	21,000
East Asia	800,000	0.1	92,000	32,000
Western and Central Europe	760,000	0.3	31,000	12,000
North Africa and Middle East	380,000	0.3	35,000	25,000
Caribbean	230,000	1.0	17,000	11,000
Oceania	75,000	0.4	14,000	1,200

Data from UNAIDS/WHO. AIDS epidemic update. Geneva: UNAIDS/WHO; 2007.

bisexual men in cities such as San Francisco and New York. The largest decline in the proportion of AIDS cases in the United States has occurred among homosexual and bisexual men, whereas cases acquired by heterosexual transmission have increased. Despite antiretroviral therapy, blood screening, and treatment of sexually transmitted infections the number of infections has remained at a plateau of 40,000 new HIV infections per year in the United States over the past decade (Mayer and Safren, 2004).

The HIV prevalence among injecting drug users has been increasing steadily, but with large regional differences (Carael et al, 2004). Since the late 1980s on the U.S. west coast about 90% of people with AIDS are men who have sex with men, whereas on the northeastern coast most new HIV infections occurred among injecting drug users. Young adults belonging to ethnic minorities (including men who have sex with men) are at considerably greater risk of infection than they were 5 years ago. For example, African-Americans make up only 12% of the U.S. population but were affected in 47% of AIDS cases reported in 2000.

Table 14–2.

HIV Infection Risk Associated with Sexual Behaviors Compared with Blood Exposure

ROUTE/TYPE OF EXPOSURE	RISK OF INFECTION MEAN/RANGE (%)
Transfusion of contaminated blood	84-100
Intravenous drug use (needle sharing)	0.8
Receptive anal intercourse	0.3-0.8
Insertive anal intercourse	0.04-0.1
Occupational needlestick exposure	0.28-0.33
Insertive vaginal intercourse	0.03-0.09
Receptive vaginal intercourse	0.005-0.02
Insertive oral intercourse	0.003-0.008
Receptive oral intercourse	0.006-0.02

Data from Henderson et al, 1986; Kaplan and Heimer, 1994; Royce et al, 1997; Varghese et al, 2002; and Henderson, 2004.

Dynamics of the HIV Epidemic: Importance of Urologic Risk Factors

HIV epidemics may occur suddenly, reflecting circumstances that are not fully understood (Carael et al, 2004). For example, HIV seroprevalence among injecting drug users in Bangkok increased from zero in 1985-1986 to 16% in 1988 and 40% to 60% in 1992.

A number of the major risk factors are urologic (Table 14–2) (Carael et al, 2004). Early epidemiologic studies identified major risk factors, especially unprotected sexual intercourse with multiple partners or an infected partner, presence of sexually transmitted infections (STIs), or a history of STIs (Van de Perre et al, 1985; Kreiss et al, 1986; Cameron et al, 1989; Laga et al, 1994). More recent studies have highlighted sex differences in HIV transmission. For many monogamous women the main risk factor may be the sexual behavior of their steady partner (UNAIDS/WHO, 2008).

Variable Rates of Sexual Transmission

Multiple cofactors affect HIV transmission, which is why estimates vary on the relative risk for specific exposures (see Table 14–2) (Royce et al, 1997; Vernazza and Eron, 1997). The probability of HIV transmission associated with unprotected vaginal sexual intercourse is not constant from one contact to another: estimates range from 0.0005 to 0.002 per episode, in the absence of cofactors (Carael et al, 2004).

A recent meta-analysis of observational studies provided risk estimates for per sexual act transmission of HIV-1 among heterosexuals (Boily et al, 2009). The study included 43 publications, based on work in 25 different study populations. The pooled risk estimates suggest that female-to-male (0.04% per act [95% confidence interval [CI] 0.01-0.14]) and male-to-female (0.08% per act [95% CI 0.06-0.11]) HIV transmission rates are low in high-income countries. In contrast, much higher HIV transmission rates occur in low-income countries with female-to-male (0.38% per act [95% CI 0.13-1.10]) and male-to-female (0.30% per act [95% CI 0.14-0.63]) HIV transmission rates, even in the absence of commercial sex exposure. In multivariate analyses, transmission rates were influenced by gender, setting (high- vs. low-income countries), and antenatal HIV prevalence. As expected, the pooled risk estimate was higher for receptive anal intercourse (1.7% per act [95% CI 0.3-8.9]) and for the presence or history of genital ulcers in either couple member (5.3% per act [95% CI 1.4-19.5]).

Sexually Transmitted Infections

The presence of STIs suggests a marked risk of concurrent HIV. First, the modes of transmission of HIV and other STIs are similar.

Second, genital ulcers as well as nonulcerative STIs facilitate HIV transmission (Cameron et al, 1989). Ulcerative STIs, including herpes, syphilis, and chancroid, enhance susceptibility to HIV per sexual act. Nonulcerative STIs, including gonorrhea, chlamydial infections, and trichomoniasis, are independent risk factors for HIV, with relative risks of 2.7 to 3.5 (Laga et al, 1994). Because syphilis facilitates acquisition and transmission of HIV, recent outbreaks of syphilis among men who have sex with men in major U.S. cities and reported increases in sexual behavior have raised concerns about potential increases in HIV transmission (Centers for Disease Control and Prevention, 2004).

Several studies report conflicting results for aggressive diagnosis and treatment of STIs to limit HIV infection in high-risk populations. One study from Uganda employed syndromic management of STIs in an area where the epidemic was in its early stages with less than 1% of the adult population being infected at study inception. HIV incidence decreased in communities where the intervention was undertaken compared with control communities (Grosskurth et al, 1995). Different findings were reported in a study from Tanzania that employed periodic mass STI treatment of at-risk adults. This study found no decrease in HIV incidence (Wawer et al, 1999). In the later study the epidemic was more advanced with more than 16% of the adult population being infected at study inception. In addition there was a high rate of concomitant genital herpes that was not treated. Taken together, these findings suggest that efforts to decrease HIV spread through treating STIs should focus on specific treatment for individual patients, with aggressive diagnosis and treatment of STIs that are common in the community. The potential benefit of STI control programs may also prove greatest in areas of lower HIV prevalence. In communities where the epidemic is widespread, the likelihood of encountering a new partner who is HIV infected may be substantial, so the benefit of modifying a cofactor may be more limited (Mayer and Safren, 2004).

Antiretroviral Therapy and Genital Secretions

Only a small proportion of sexual exposures result in HIV transmission (Anderson and May, 1988). Transmission may occur by exposure to cell-free or cell-associated virus, and different factors may affect expression of virus concentrations in different body fluids (i.e., blood, semen, or cervicovaginal secretions) (Krieger et al, 1998; Chakraborty et al, 2001; Mayer and Safren, 2004). Although lower blood HIV levels are associated with lower transmission rates (Quinn et al, 2000), antiretroviral therapy may not make HIV-infected people noninfectious. In fact, sexual transmission of multidrug-resistant HIV has been well documented (Boden et al, 1999; Little et al, 1999). These observations underscore the need for HIV-infected patients to practice safer sex even if they are on therapy.

Circumcision Status

Three lines of evidence support the conclusion that circumcised men are at lower risk for HIV infection: biologic evidence, data from observational studies supported by meta-analyses, and the results of three randomized clinical trials supported by meta-analyses (Table 14–3) (Weiss et al, 2000).

The biologic mechanisms that could explain the increased risk of HIV among uncircumcised men include an increased rate of inflammatory conditions, susceptibility of the mucosal surface of the prepuce to trauma, and the longer survival of pathogens in the warm, moist subpreputial space. The inner foreskin is particularly susceptible to HIV infection owing to lack of keratinization and the high density of HIV target cells that are readily accessible (Patterson et al, 2002; Soilleux and Coleman, 2004; McCoombe and Short, 2006).

The hypothesis that male circumcision might protect against HIV infection was first suggested in 1986 (Fink, 1986). Subsequent support was provided by ecologic studies in areas with low prevalence of male circumcision and high HIV prevalence in sub-Saharan Africa in the late 1980s (Moses et al, 1999) and later across 118 developing countries (Drain et al, 2006). Further evidence comes from two systematic reviews of the observational study data comparing HIV infection rates in circumcised and uncircumcised men from the same populations (Weiss et al, 2000; Siegfried, 2005). One review was restricted to 27 studies from sub-Saharan Africa (Weiss et al, 2000), and the other was a global review including 37 studies (Siegfried, 2005). Circumcised men had substantially lower risk of HIV infection. Meta-analysis of the 15 studies that adjusted for potential confounders showed this reduction to be large and highly significant (adjusted risk ratio of 0.42, 95% CI 0.34-0.54) (Weiss et al, 2000). Subsequent studies have found similar large risk reductions among circumcised men (Weiss et al, 2008).

Although provocative, observational studies cannot prove causality. Three randomized clinical trials of adult male circumcision among consenting, healthy men in South Africa (Auvert et al, 2005), Kenya (Bailey et al, 2007), and Uganda (Gray et al, 2007) were started in 2002-2003. All three trials were stopped early after recommendations by independent data and safety monitoring boards when interim analyses found highly significant decreases in HIV infection risk among participants randomly assigned to circumcision.

The three trials enrolled a total of 10,908 uncircumcised, HIV-negative adult men. Participants were randomly assigned to circumcision or control arms and then observed for up to 2 years. Retention rates were high (86% to 92%). Subsequent meta-analysis using a random-effects model of the trial results, following the QUORUM statement recommendations, found no evidence of heterogeneity among the trials (Weiss et al, 2008). The overall risk ratio was 0.42 (95% CI 0.31-0.57), corresponding to a protective effect of 58% (95% CI 43%-69%), which was identical to that found in the observational studies (58%, 95% CI 46%-66%).

The true protection provided by male circumcision may be better estimated by an "as-treated" analysis, assigning outcomes according to the actual circumcision status of participants. All participants did not adhere to the study arm to which they were randomly assigned. Meta-analysis of the "as-treated" results of the three trials shows even stronger protection against HIV infection in the circumcision group (summary risk ratio of 0.35; 95% CI 0.24-0.54) (Weiss et al, 2008). Additional data have suggested that circumcision is both highly effective at reducing costs of HIV and AIDS and has a very low complication rate (Krieger et al, 2005, 2007; Gray et al, 2007). In summary, the positive findings in the male circumcision trials are in contrast to recent negative results with other HIV prevention interventions, including microbicides, the female diaphragm and gel, treatment to suppress genital herpes infections, and, most recently, an adenovirus-based HIV vaccine. **There is a need to provide safe male circumcision services for high-risk populations because this is one of few proven HIV prevention strategies.** In addition to other health benefits, male circumcision provides a much-needed addition to the limited HIV prevention armamentarium. Male circumcision is possibly the oldest and the most common surgical procedure. The evidence from biologic studies,

Table 14–3.

Evidence Table for Studies of Male Circumcision and HIV Infection Risk That Include Original Data, Systematic Reviews or Meta-Analysis, Expert Opinion, or Other Human Data (1999-2008)

STUDY TYPE	DESIGN	LEVEL OF EVIDENCE POSITIVE (FAVORING CIRCUMCISION) OR NEGATIVE	REFERENCE
Systematic reviews, meta-analyses and modeling	Meta-analysis of 29 published articles with serious technical flaws	4, Negative	Van Howe, 1999
	Meta-analysis of 33 diverse observational studies, stratifying by study type	2, Positive	O'Farrell and Egger, 2000
	Systemic review and meta-analysis of 27 studies	2, Positive	Weiss et al, 2000
	Systematic reviews	3, Positive	Siegfried et al, 2003; Siegfried, 2005
	Stochastic prevention trial simulator and RCT* data	2, Positive	Desai et al, 2006
	Dynamical simulation models using country level data	2, Positive	Williams et al, 2006
	Country-specific data from 118 developing countries evaluated with multivariate linear regression	2, Positive	Drain et al, 2006
	Individual-based stochastic model fitted to characteristics for urban African populations	3, Positive	Orroth et al, 2007
	Mathematical model parameterized RCT findings	3. Positive	Hallet et al, 2008
	Mathematical model simulated observed levels of HIV prevalence in sub-Saharan Africa	3, Positive	Londish and Murray, 2008
	Systematic review and meta-analysis of the three RCTs	1, Positive	Weiss et al, 2008
Randomized-controlled trials	3274 uncircumcised men randomized 1:1	1, Positive	Auvert et al, 2005
	2784 uncircumcised HIV-negative men randomized 1:1	1, Positive	Bailey et al, 2007
	4996 uncircumcised, HIV-negative men randomized 1:1	1, Positive	Gray et al, 2007
Nonrandomized cohort studies	Survey of 6821 men aged 15-59 years in rural Uganda	3, Positive	Kelly et al, 1999
	415 Ugandan couples in which one partner was HIV positive and one was initially HIV negative followed prospectively for up to 30 months	2, Positive	Quinn et al, 2000
	Prospective study of 2298 HIV-negative men attending sexually transmitted infection clinics in India	2, Positive	Reynolds et al, 2004
	150 Kenyan sex partners of women with genital symptoms	3, Positive	Meier et al, 2006
	Prospective cohort of 1378 men in rural Kenya followed for 2 years	2, Positive	Shaffer et al, 2007
	Respondent-driven sampling of 1154 black and 1091 Latino men who have sex with men in the United States	3, Negative	Millet et al, 2007
Case-control studies	Random population samples from two circumcising African populations compared with 2 noncircumcising populations (approximately 4000 men)	3, Positive	Auvert et al, 2001
	38 HIV-positive and 94 HIV-negative Kenyan men with genital ulcers	3, Positive	MacDonald et al, 2001
	Rural Uganda	3, Positive	Gray et al, 2004
	398 circumcised and 447 uncircumcised Kenyan men	3, Positive	Agot et al, 2004
	1277 sexually experienced men from 70 villages in South Africa	3, Positive	Jewkes et al, 2006
	Community-based study of 1418 women and 566 of their regular male partners in Tanzania	3, Positive	Kapiga et al, 2006
	Cross-sectional, population-based survey including 2941 Kenyan men	3, Positive	Johnson and Way, 2006
	Probability sample of homeless men aged in Kolkata, India	3, Positive	Talukdar et al, 2007
	Data from eight national surveys in sub-Saharan Africa	3, Positive	Mishra et al, 2007
	National probability sample of the general population in Slovenia	3, Negative	Klavs and Hamers, 2008
	Population-based study of Kenyan men	3, Positive	Foglia et al, 2008
	Cross-sectional nationally representative survey 10,227 women and 8298 men in Uganda	3, Positive	Mermin et al, 2008
Pertinent biologic studies	Immunologic and in-vivo infection of human foreskins	4, Positive	Patterson et al, 2002
	HIV-receptor studies of human foreskins	4, Positive	Soilleux and Coleman, 2004
	HIV-receptor studies of human foreskins	4, Positive	McCoombe and Short, 2006

observational studies, randomized controlled clinical trials, meta-analyses, and cost-effectiveness studies is conclusive; the challenges of implementation in high-risk populations must now be faced.

Gynecologic Factors

Female genital tract tissues vary in susceptibility to HIV infection. The stratified vaginal epithelium contains fewer cells with coreceptors that can bind HIV (Patterson et al, 1998). Thus, vaginal mucosa is less susceptible to HIV infection than the endocervix, which has a thinner, highly vascular layer, containing a much higher concentration of HIV-binding cells. Physiologic events that result in ectropion (i.e., increased exposure of the endocervix), such as the use of hormonal contraceptives or occult *Chlamydia trachomatis* infection, increase susceptibility to HIV (Mostad et al, 2000; Moscicki et al, 2001).

Specific Sexual Behaviors

Calculation of the precise risk for infection for each type of exposure is imprecise because many cofactors alter the amount of HIV in the genital tract (Mayer and Safren, 2004). Factors such as a source with a high plasma viral load (Quinn et al, 2000) or concomitant STI can greatly increase the average per-contact risk (Cohen et al, 1997; Wawer et al, 1999). Data used to generate per-contact risks are often based on cohort studies in which individuals recollect their risk during previous time intervals (often every 3 to 6 months). Recollections are often obtained about behaviors under the influence of drugs or alcohol.

Data from the developed world suggest that men are more likely to transmit HIV to their female partners (see Table 14–2) (Mayer and Safren, 2004). However, studies from Africa suggest that rates of male-to-female and female-to male transmission were similar (Quinn et al, 2000). Reasons for this apparent difference in the efficiency of female-to-male transmission may include different rates of male circumcision or the prevalence of other STIs. For anal intercourse the insertive partner is less likely to acquire HIV from an infected receptive partner than vice versa but there appear to be sufficient susceptible cells in the distal male urethra and foreskin such that an insertive partner is still at substantial risk. One study suggested that, on average, receptive anal intercourse was more than seven times as efficient at transmitting HIV as insertive anal intercourse (DeGruttola et al, 1989).

Oral intercourse, either fellatio or cunnilingus, is a much less efficient way to acquire HIV. However, case reports show that oral exposure to ejaculate may transmit HIV (Mayer and Safren, 2004). The efficiency of oral transmission is less than that of unprotected vaginal intercourse, in the realm of less than 1 per 1000 contacts. However, animal studies demonstrate that HIV can be transmitted orally via lymphoid tissue in the oropharynx. Although HIV has been identified in pre-ejaculatory secretions there are no reliable case reports of HIV transmission through exposure to pre-ejaculate without exposure to semen.

HIV VIROLOGY AND TARGETS FOR ANTIVIRAL THERAPY

The Virion

Although there are two HIV viruses, in this chapter the focus is on HIV-1 because there have been very few cases of HIV-2 in the developed world. HIV-2 is transmitted less readily than HIV-1 and the virus is less virulent. In this review, the term *HIV* refers to the clinical manifestations of infection caused by HIV-1.

HIV has a spherical shape with an outer envelope, variable surface projections, and an icosahedral capsid containing ribonucleoprotein complexed with a core shell (Fig. 14–1) (Liang and Wainberg, 2004). The HIV projections consist of envelope glycoproteins loosely associated with a lipid bilayer. Beneath the lipid layer the matrix protein covers the internal surface of the viral coat. The capsid protein constitutes the shell of the cone-shaped core, and the nucleocapsid protein forms part of a nucleoid structure that also consists of reverse transcriptase, integrase, and two copies of the single-stranded viral genomic RNA (Liang and Wainberg, 2004).

HIV Replication Cycle

The HIV replication cycle is diagrammed in Figure 14–2 (Liang and Wainberg, 2004).

Viral Attachment, Fusion, and Uncoating

HIV initially attaches to the CD4 receptor on susceptible host cells. High-affinity interactions occur between the viral envelope glycoprotein and a specific region of the CD4 molecule (Pollard and

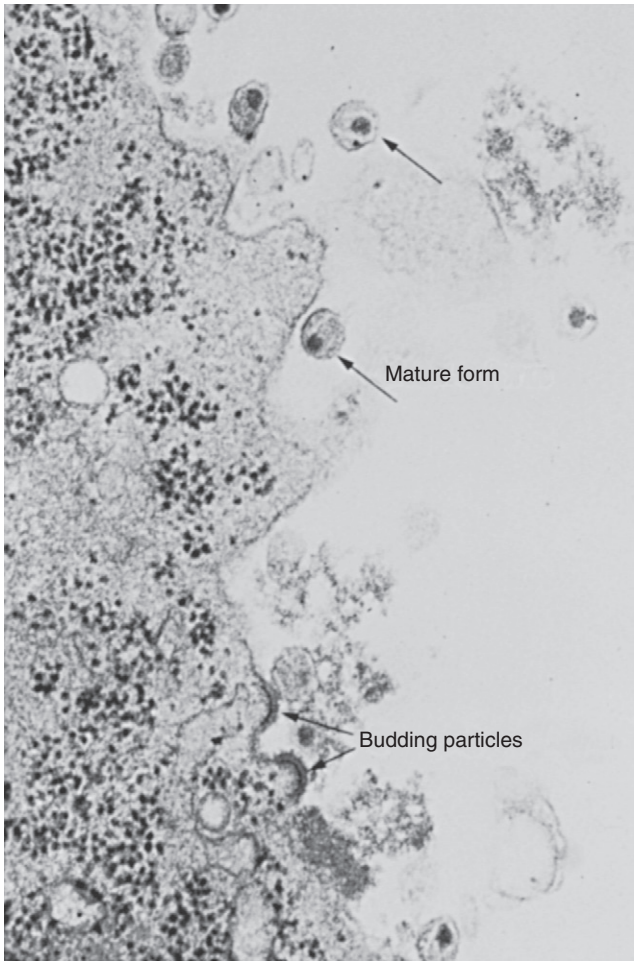


Figure 14–1. HIV virion. HIV has a spherical shape, an outer envelope, variable surface projections, and an icosahedral capsid containing ribonucleoprotein complexed with a core shell. (Electron micrograph courtesy of the Centers for Disease Control and Prevention.)

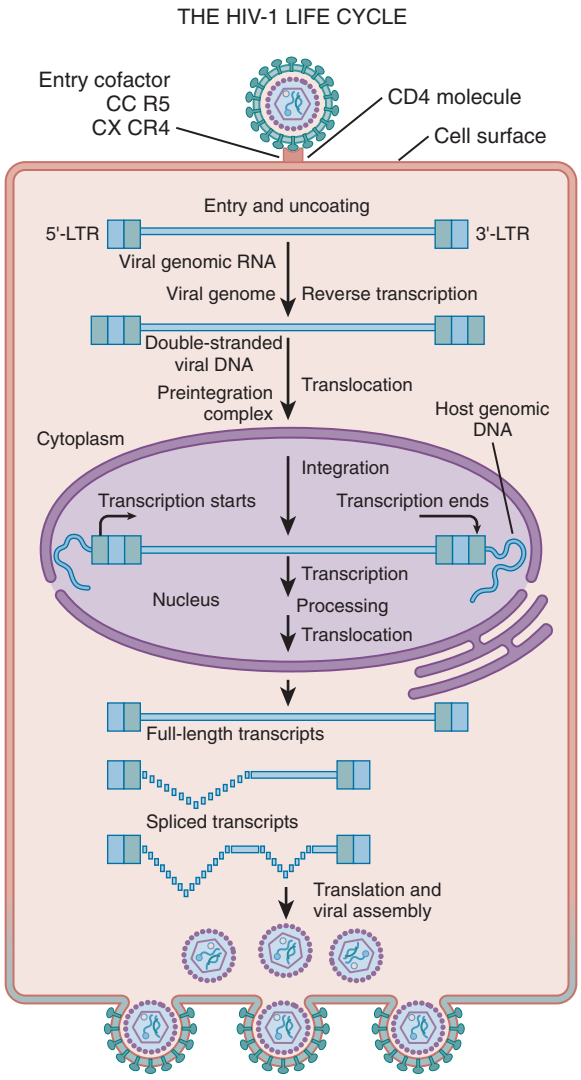


Figure 14–2. HIV replication cycle. The diagram illustrates the stages of HIV replication, including viral entry, uncoating, reverse transcription, integration, expression of proviral genome, viral assembly, and particle release. (From Liang C, Wainberg MA. Virology of HIV. In: Cohen J, Powderly WG, Berkley SF, et al, editors. Infectious diseases. vol. 2, 2nd ed. Edinburgh: Mosby; 2004. p. 1251–5.)

Malim, 1998) on the surface of immature T cells and mature CD4+ T-helper cells. In addition to CD4, a variety of coreceptors and host immune cell membrane proteins may promote HIV entry into target cells after the initial binding (Cocchi et al, 1996; Liang and Wainberg, 2004).

Efforts are underway to develop compounds that antagonize HIV entry into susceptible cells by interfering with either the CD4 receptor or the coreceptors. Cell entry probably occurs by fusion of viral and cell membranes mediated by the viral transmembrane protein. **Following fusion the virion is uncoated by a proteolytic event mediated by the virion-encoded protease. A number of protease inhibitors that inhibit this step have proven very effective antiretroviral agents.**

Reverse Transcription

After entry, viral RNA is converted into DNA, which is then integrated into host cell chromosomal DNA. This process of reverse transcription occurs within 4 to 6 hours of infection and takes place mainly in the cytoplasm catalyzed by virion-encoded reverse transcriptase. The final products of reverse transcription are double-stranded viral DNA molecules. This distinctive viral reverse transcription step has been the target of a number of effective antiretroviral agents.

Integration

The newly transcribed double-stranded DNAs are then transported into the nucleus where viral DNA is integrated into host cell chromosomal DNA, a process catalyzed by viral integrase. After integration, HIV proviral DNA remains permanently associated with the host genetic material for as long as the cell lives. The viral integrase is currently under active investigation as a potential target for antiretroviral therapy.

Viral Gene Expression, Packaging, and Assembly

HIV exploits the host cell transcription and translation machineries to generate its own gene products. The primary RNA transcripts of the provirus are made by host cell RNA polymerase II. Cellular activation and proliferation signals result in the binding of transcription factors to the long terminal repeat and lead to increased rates of initiation of transcription. Tat and Rev are two key virion-encoded proteins that upregulate viral gene expression and replication, whereas HIV accessory proteins, including Nef, Vif, Vpu, and Vpr, are crucial determinants of HIV virulence (Emerman and Malim, 1998). Host cellular ribosomes translate proviral mRNA into viral proteins (Liang and Wainberg, 2004). The HIV glycosaminoglycan proteins are the driving force for virus assembly.

Therapeutic Considerations

Viral reverse transcriptase and protease enzymes have been the main targets of anti-HIV therapy. Viral reverse transcriptase has an exceedingly high error rate (i.e., about one mutation/virus replication event) (Liang and Wainberg, 2004); thus mutants are constantly generated that have the potential for drug resistance. Drug resistance to HIV occurs when these mutations result in altered forms of HIV reverse transcriptase and protease that function yet are not inhibited by antiviral agents.

PATHOGENESIS OF HIV INFECTION

The prognosis and outcome of HIV infection changed dramatically with availability of highly active antiretroviral combination therapy (HAART). HAART has delayed the natural history and rate of progression, prolonging survival. However, initial optimism for immune reconstitution has been thwarted by information about HIV's pathogenic mechanisms and the limitations of HAART. It is now clear that eradication of the virus is not possible with available antiviral drugs.

Natural History of HIV Infection

The course of HIV infection is highly variable. In the absence of treatment the typical course occurs over 8 to 12 years. Three distinct phases have been defined: primary infection, chronic asymptomatic infection, and overt AIDS (Pierre-Alexandre and Pantaleo, 2004).

Primary HIV Infection

Primary HIV infection is a transient symptomatic illness of variable severity. This acute syndrome occurs in 40% to 90% of patients. Clinical signs and symptoms generally appear 2 to 4 weeks after infection. The clinical presentation may mimic acute

mononucleosis or other acute febrile illnesses, emphasizing the nonspecific nature of these symptoms and the difficulty of early diagnosis. The self-limited syndrome generally lasts less than 14 days.

Diagnosis of primary HIV infection depends on diagnostic testing. There are three laboratory characteristics: high plasma viremia often greater than 1 million HIV RNA copies/mL, a decrease in the blood CD4+ T-cell count, and large increase in the blood CD8+ T-cell count. Subsequently, a marked decline in plasma viremia coincides with resolution of the clinical syndrome (Kahn and Walker, 1998). This decrease in viral load also correlates with the appearance of the virus-specific immune responses, particularly HIV-specific cytotoxic T cells, indicating that immune responses downregulate virus replication (Pantaleo et al, 1994; Musey et al, 1997). Standard laboratory assays used to diagnose HIV infection are usually negative during acute infection.

Chronic Asymptomatic HIV Infection

Primary HIV infection is followed by a long phase of clinical latency, usually lasting around 10 years. During this phase patients have neither signs nor symptoms. Relatively stable HIV replication levels and CD4+ T-cell counts characterize this chronic phase.

This apparent clinical "stability" is deceptive. Although viral levels and the blood CD4 T-cell count are stable, this stability is only apparent in the blood. Virus replication and accumulation of extracellular virus trapped in the follicular dendritic cell network continue actively in the lymphoid tissue, where progressive anatomic and functional deterioration occurs, leading to impaired specific immune responses (Pantaleo et al, 1993, 1998). Eventually, immunologic deterioration is reflected by a rapid increase in viremia levels and a drop in CD4+ T-cell counts, resulting in transition to overt AIDS.

Overt AIDS

AIDS represents the end stage of HIV infection. This advanced stage of HIV disease is marked by low CD4+ T-cell counts (<2 to 300 cells/μL) and appearance of constitutional symptoms. This phase may be complicated by the development of AIDS-defining opportunistic infections or malignancies. **Without antiretroviral therapy, AIDS usually leads to death in 2 to 3 years.** The risk for death and opportunistic infections increases significantly with CD4+ T-cell counts less than 50 cells/μL.

Highly Variable Clinical Course

The clinical course of HIV infection is variable (Pierre-Alexandre and Pantaleo, 2004). Conceptually, patients may be classified in four categories: typical progressors, rapid progressors, slow progressors, or nonprogressors. **In 60% to 70% of HIV-infected patients the median time between infection and the development of AIDS is 10 to 11 years, in the absence of therapy. These infected persons are "typical progressors."** Their clinical course is described earlier.

Ten to 20 percent of HIV infections progress rapidly. These "rapid progressors" develop AIDS less than 5 years after infection. After primary infection these patients' plasma virus levels are often more than 10^5 HIV-1 RNA copies/mL and their CD4+ T-cell counts start to decrease much earlier and more rapidly. HIV-specific immune responses are either never detected or are lost rapidly after the transition from the acute to the chronic phase of infection.

At the other extreme, 5% to 15% of HIV-infected people are "slow progressors," remaining free of AIDS for more than 15 years in the absence of therapy. Their CD4+ T-cell counts remain stable, frequently greater than 500 cells/μL, and plasma HIV RNA levels are usually less than 10,000 copies/mL.

The slow progressors group includes a subgroup of long-term nonprogressors. About 1% of HIV-infected people appear to fall into this category. Long-term nonprogressors have documented HIV infections for at least 8 to 10 years without antiretroviral therapy and have no signs of disease progression (e.g., constant high CD4+ T-cell counts and either low [500 to 1000 HIV RNA copies/mL] or very low [<50 copies/mL] plasma virus levels).

Early Pathogenic Events Determine the Natural History

The most common route of HIV infection is sexual transmission at the genital mucosa (Royce et al, 1997). Animal models provide important insights into the early pathogenic events. After intravaginal infection of rhesus monkeys, tissue dendritic cells (i.e., Langerhans cells that reside in the lamina propria adjacent to the vaginal epithelium) are the first potential target cells of HIV (Spira et al, 1996). These dendritic cells constitute a complex and highly developed system of antigen-presenting cells that are able to prime naive T cells. The ability of dendritic cells to attract and prime naive T cells can be explained by expression of a type II membrane protein with an external mannose binding, C-type lectin domain, named DC-Sign (Steinman, 2000). It has been suggested that interaction between DC-Sign and the intracellular adhesion molecule-3 represents the initial contact between dendritic cells and resting T cells, a critical step for initiation of T-cell immune responses. Dendritic cells express high levels of specific chemokines that target naive rather than memory T cells (Cameron et al, 1996).

After encountering HIV below the vaginal epithelium, Langerhans cells either can be infected or can pick up HIV virions (Steinman, 2000). Thus DC-Sign–positive dendritic cells play the major role in the delivery of HIV to T cells, greatly amplifying the viral infection (Zhu et al, 1996). Subsequently dendritic cells migrate to the internal iliac lymph nodes where they target the T-cell areas and then present the viral antigens to activated virus-specific T cells. Therefore, dendritic cells play a key role, both in priming the initial HIV-specific immune response and in transporting HIV to the draining lymphoid tissue. Rapid recruitment and spreading of target cells (i.e., activated CD4+ T cells) confers a major advantage to HIV because these events occur before the appearance of virus-specific immune responses.

Within 2 days after infection, HIV can be detected in the draining lymphoid tissue. The virus then disseminates rapidly throughout the lymphoid system. Afterward, HIV enters the bloodstream, where viral replication can be detected in plasma 5 days after infection in the animal model. In humans the time from mucosal infection and initial plasma viremia varies, ranging from 4 to 11 days (Pierre-Alexandre and Pantaleo, 2004). The clinical importance of these observations is that the risk of infection is increased by conditions that decrease genital mucosal barriers, especially lesions caused by inflammatory or infectious diseases, such as cervicitis, urethritis, and genital ulcers.

Critical Role of Lymphoid Tissue in Primary HIV Infection

Events in the lymphoid tissue play a central role in HIV infection. During primary infection the peak number of virus-expressing cells in the lymph node occurs at the same time as the peak of plasma viremia or shortly precedes it (Brodie et al, 1999; Musey et al, 1999; Pierre-Alexandre and Pantaleo, 2004). With the

transition from primary to chronic infection there is a switch from individual virus-expressing cells to virus trapped by the follicular dendritic cell network of lymph node germinal centers. This trapped virus becomes the dominant form of virus in lymph nodes, and this event is associated with a dramatic decrease in the number of individual cells expressing viral RNA, reflecting the role of the host immune system in partially containing HIV infection (Pantaleo et al, 1998).

Virus Escape and Establishment of Chronic HIV Infection

Early in primary HIV infection, vigorous virus-specific immune responses may contribute to both control of the initial peak of virus replication and reduction in plasma viremia (Musey et al, 1997; Kahn and Walker, 1998; Pantaleo et al, 1993, 1998). **However, HIV-specific immune responses cannot control HIV or block the eventual progression to symptomatic disease.** HIV differs from other viruses by targeting a broad spectrum of effector components of the antiviral immune response very early after infection (during the primary phase) and by rendering these mechanisms ineffective or reshaping them (Soudeyns and Pantaleo, 1999).

HIV escapes the host immune response by both virologic and immunologic mechanisms. Virologic mechanisms include formation of a stable pool of latently infected CD4+ T cells containing HIV that is capable of replicating (Finzi et al, 1997; Wong et al, 1997), the genetic variability of HIV (Coffin, 1995), and trapping of infectious virions on the surface of follicular dendritic cells (Pantaleo et al, 1994; Chun et al, 1997; Wong et al, 1997). Initiation of HAART very early during primary HIV infection does have a significant impact on the size of this pool of CD4+ T cells. Decay of this pool of infected CD4+ T cells is very slow and not much influenced by the effective suppression of virus replication. This reservoir of replication-competent virus represents a major obstacle to HIV eradication and long-term control of virus replication (Chun et al, 1997; Finzi et al, 1997; Wong et al, 1997).

Genetic variability is another efficient mechanism by which HIV escapes the host immune response. During both primary and established chronic infection, rapid mutations ensure that the virus is able to escape both the humoral and the cell-mediated virus-specific immune responses.

HIV also reshapes antiviral mechanisms by trapping of the virus on the surface of follicular dendritic cells in lymphoid germinal centers. For most infections, formation of immune complexes and their attachment to the follicular dendritic cell network represent mechanisms leading to clearance of the pathogen and to maintenance of effective immune responses. However, with HIV infection these mechanisms lead to formation of a stable reservoir of infectious virions, representing a continuous source for infection of CD4+ T cells that ultimately results in the destruction of the lymphoid tissue (Musey et al, 1997).

HIV escapes from the immune response through multiple immunologic mechanisms that include deletion of HIV-specific CD4+ T-cell clones (Rosenberg et al, 1997), deletion of HIV-specific cytotoxic CD8+ T-cell clones, generation of virus escape mutants (Soudeyns and Pantaleo, 1999), egress of cytotoxic T cells from lymph nodes, impaired function of antigen-presenting cells (Soudeyns and Pantaleo, 1999), and interference with the humoral neutralizing response.

In summary, virus escape and establishment of chronic HIV infection reflect the ability of HIV to target the host's antiviral immune response and reshape it into a self-defense mechanism. Primary infection is critical in the pathogenesis of HIV infection because events that occur during this stage determine both the pattern and the rate of disease progression.

Virologic Set Point

During the transition from primary to chronic infection, HIV plasma RNA levels reach a virologic set point that predicts the rate of disease progression (Mellors et al, 1996). The virologic set point varies among HIV-infected individuals and tends to remain stable in the same person during the chronic phase. The virologic set point that a person attains is determined by both the mechanisms involved in the establishment of chronic infection and by host factors that can modulate the course of HIV disease. **The plasma RNA load is the most accurate predictor of disease progression** (Mellors et al, 1996). The higher the plasma viral RNA load, the greater is the risk of rapid progression to AIDS and death.

Prospects for HIV Eradication

Free HIV virions are eliminated with a half-life of 6 hours. In contrast, productively infected cells have a half-life of 1.6 days. It was hoped that HIV eradication was achievable within 2 to 3 years (Perelson et al, 1997). This goal could only be realized with complete and sustained suppression of HIV replication and if there were no pool of long-lived, latently infected cells to serve as a virus reservoir (Chun et al, 1997; Finzi et al, 1997; Wong et al, 1997).

Data from HIV-infected patients on long-term HAART significantly challenged these theories. There appears to be a pool of latent HIV–infected resting CD4+ T cells that persists in HIV-infected patients who adhered to HAART for up to 3 years (Chun et al, 1997; Finzi et al, 1997; Wong et al, 1997). This pool is composed of quiescent memory CD4+ T cells with a longer half-life than the original estimate of 1 to 4 weeks. More importantly, these cells contain replication-competent HIV proviral DNA. After activation these cells are able to support efficient viral replication.

The extent of this HIV reservoir is quantitatively limited, estimated between 50,000 and 5 million resting memory CD4+ T cells for the whole body. However, this pool of cells has a half-life of 3 to 6 months, dramatically increasing estimates of the potential time required for HIV eradication.

The reservoir of HIV-infected cells originates from productively infected cells during primary infection (Pierre-Alexandre and Pantaleo, 2004). Initiation of HAART as early as 10 days after the onset of symptoms of primary HIV infection rapidly controls plasma viremia but does not preclude generation of this viral reservoir. These observations emphasize the rapidity with which HIV viral reservoirs are established and the limited ability of HAART to interfere with this pathogenic process. This pool of HIV-infected cells represents a major obstacle to HIV eradication.

In addition to their role as a viral reservoir, HIV-infected, long-lived, resting memory CD4+ T cells possess the ability to support virus production, albeit at low levels. Patients on HAART with viral loads below detectable levels with usual clinical assays may still have viral replication detected by more sensitive tests (Pierre-Alexandre and Pantaleo, 2004). In these studies, 40% to 60% of patients still had low levels of viremia after 36 to 48 weeks of HAART.

Viral sanctuaries represent another potential source of residual HIV replication. **Sanctuaries are defined as cells and organs where the HIV can be sheltered or where HAART does not achieve therapeutic concentrations.**

Tissue sanctuaries include the lymphoid tissue, mucosa-associated lymphoid tissue, the genital organs, and the central nervous system, where the achievable concentrations of antiviral drugs (especially protease inhibitors) may be suboptimal. These sites may serve both as potential sources of low-level virus replication and as reservoirs of latently infected cells (Pierre-Alexandre and Pantaleo, 2004). Presence of viral sanctuaries, including the reproductive tract, with limited bioavailability of antiviral drugs further complicates the issue of HIV eradication. Current estimates are that it may take 5 to 10 years or more to eliminate HIV, considering a half-life of 4 months for the long-lived infected CD4+ cells and provided that effective and durable suppression of viral replication is achieved by HAART.

TESTS TO DIAGNOSE AND MONITOR HIV INFECTION: WHAT THE UROLOGIST SHOULD KNOW

HIV was first isolated in 1983, and the first diagnostic tests were marketed in 1985. Tests for diagnosis and monitoring of HIV infection have improved constantly (Kuritzkes, 2004; Reiss et al, 2004). Few areas in medicine have witnessed such rapid and widespread adaptation of molecular tools to everyday practice. Fortunately the many tests for diagnosis and monitoring HIV infection can be considered in three categories: diagnostic tests, viral load, and resistance assays.

Diagnostic Tests and Testing Algorithms

Assays have been developed to detect HIV antibodies in serum, whole blood, saliva, and urine (Kuritzkes, 2004). Most laboratories screen for anti-HIV-1 and anti-HIV-2 antibodies using an enzyme-linked immunosorbent assay (ELISA) based on antigens from viral lysates, recombinant or synthetic. Current third-generation HIV ELISAs have sensitivity and specificity approaching 100%. In contrast to earlier tests that only detected IgG antibodies these tests detect all classes of anti-HIV antibodies, substantially shortening the time to diagnosis after acute infection. A variety of rapid tests and "home tests" have also been developed.

Despite sensitivity of more than 99%, a reactive HIV ELISA has a relatively low positive predictive value in low-risk populations. Thus the current testing algorithm includes a confirmatory test to exclude false-positive results. The Western blot is most widely used for confirmation. Some laboratories prefer immunoblotting for confirmation because immunoblots are simpler to standardize and are more sensitive in cases of recent seroconversion (Kuritzkes, 2004).

Clinical Application

After acute infection, HIV RNA can be detected from day 12. HIV RNA assays (see later) **have a sensitivity of 100% in diagnosing acute infection but at the cost of lowered specificity (97%)** (Kuritzkes, 2004). **The first antibodies can generally be detected on day 21. However, development of a positive HIV antibody test can vary according to the patient and infecting strain. Beyond week 6 after infection antibodies are detectable in almost all patients** (Kuritzkes, 2004). Because reactivity by the Western blot test lags seroconversion by ELISA, a positive ELISA in a patient with a negative or evolving Western blot assay can provide evidence of recent infection.

Testing is a two-stage process. Samples positive by an initial screening assay are retested to exclude clerical or laboratory error, and then a confirmatory assay is performed on repeatedly reactive sera to verify that the antibodies are directed against HIV. Confirmation of a reactive ELISA by a positive Western blot establishes the diagnosis of HIV infection. A negative Western blot test suggests a false-positive ELISA or an acute infection.

Viral Load Monitoring

Assays to quantify HIV RNA, termed the *viral load,* led to our current understanding of HIV pathogenesis and helped establish complete suppression of HIV replication as the ultimate goal for antiretroviral therapy (Kuritzkes, 2004). These assays are now standard. Performance characteristics of the commercially available assays are similar. Current commercial assays have a lower limit of quantitation of 50 to 80 HIV RNA copies/mL.

Clinical Application

Plasma HIV RNA levels correlate with clinical stage (Kuritzkes, 2004). Patients with symptomatic HIV infection or AIDS have significantly higher virus loads than patients with asymptomatic infection. Plasma HIV RNA load is also a powerful predictor of the risk of disease progression and death at all stages of disease. Current guidelines recommend obtaining two plasma HIV RNA measurements to determine the baseline or "set point" virus load before initiating antiretroviral therapy.

After antiretroviral therapy the change in plasma HIV RNA provides important clinical information. Several large clinical trials showed significant correlations between the plasma HIV RNA reduction from baseline and the clinical benefit (Marschner et al, 1998). **The nadir in plasma HIV RNA levels is a marker for the duration of virus suppression** (Raboud et al, 1999). **The early response to treatment predicts long-term outcome. Conversely, increasing plasma HIV RNA level suggests treatment failure.**

Increasing plasma HIV RNA level is the harbinger of potential development of retroviral drug resistance (Reiss et al, 2004). This is not necessarily accompanied by an immediate decline in blood CD4+ lymphocyte numbers or by the development of clinical symptoms. Regular monitoring with plasma HIV RNA levels facilitates timely detection of drug-resistant HIV in patients on HAART.

HIV Drug-Resistance Assays

Various assays are available to assess drug resistance (Kuritzkes, 2004; Reiss et al, 2004). These assays can be considered as either genotypic or phenotypic assays. Genotypic assays evaluate HIV nucleotide sequences to detect critical drug-resistance mutations. Phenotypic assays estimate the concentration of antiviral drugs necessary to inhibit virus replication in vitro. Each approach has potential advantages and disadvantages. An important limitation is that both approaches measure characteristics of the predominant viral species but do not indicate the presence of minor species that may emerge as resistant variants during subsequent treatment.

Clinical Application

Clinical trials demonstrate the value of drug-resistance testing (Kuritzkes, 2004; Reiss et al, 2004). The risk of virologic failure during salvage therapy was reduced by 30% to 50% for each drug in the new regimen that was predicted to have activity

(De Gruttola et al, 2001; Kuritzkes, 2004). Drug-resistance remained an independent predictor of the likelihood of treatment failure even after controlling for treatment history.

Most experts recommend drug-resistance testing to guide the selection of salvage therapy for patients whose therapy is failing and in pregnant women (Hirsch et al, 2000). Resistance testing is also recommended for patients with acute HIV infection. Some experts also recommend that evidence for increasing transmission of drug-resistant HIV (Little et al, 2002) provides a rationale for testing of all patients before initiation of antiretroviral therapy where affordable (Kuritzkes, 2004).

UROLOGIC MANIFESTATIONS OF HIV INFECTION

Nonmalignant Conditions

The genitalia may be involved in either early or late stages of HIV infection (Kho et al, 2004).

Primary HIV Infection

Primary HIV infection may be characterized by an acute exanthem beginning 1 to 5 weeks after infection. Characteristic symptoms include fatigue, fever, and night sweats, accompanied by lymphadenopathy. The skin eruption consists of erythematous, round-to-oval macules and papules. The syndrome resolves with complete recovery.

Sexually Transmitted Infections

In many populations the pattern of HIV acquisition parallels that of STIs (Quinn et al, 1988). **Thus, testing for HIV is recommended in anyone with a diagnosed STI or at risk for STI** (Centers for Disease Control and Prevention, 2002). **Accurate diagnosis of STIs is of exceptional importance in individuals at high risk for HIV infection because presence of an STI increases the risk of both transmitting and acquiring HIV infection. These infections may have more atypical and prolonged clinical manifestations in people with HIV infection.**

Genital Herpesvirus. Herpes simplex virus (HSV) infection is common in HIV-infected persons (Centers for Disease Control and Prevention, 2002). In these populations HSV types 1 and 2 cause recurrent, severe, painful vesicles with an erythematous base. Untreated lesions may enlarge becoming confluent ulcerations that persist with secondary bacterial infection. Sometimes ulceration occurs without well-defined vesicles ever being noted (Kho et al, 2004). Specific diagnosis is established by viral culture, other diagnostic tests, or biopsy.

In patients with intact immune function the course of HSV is similar to that of other HSV-infected patients. Immunocompromised patients may have more prolonged and severe infections (Centers for Disease Control and Prevention, 2002). Episodic or suppressive therapy with oral antiviral agents is often beneficial (Table 14–4) (Centers for Disease Control and Prevention, 2002). Severe cases merit parenteral therapy with intravenously administered acyclovir (5 to 10 mg/kg every 8 hours) (Centers for Disease Control and Prevention, 2002).

HSV resistance should be suspected if lesions persist or recur despite antiviral therapy. Viral culture and resistance testing should be obtained if possible (Centers for Disease Control and Prevention, 2002). Patients with acyclovir-resistant HSV strains require alternative agents, such as foscarnet (40 mg/kg intravenously every 8 hours until clinical resolution) or topical cidofovir gel (1% applied to lesions daily for 5 days), which is a preparation that is not commercially available but must be compounded by a pharmacy.

Table 14–4.

Recommended Regimens for Treating Genital Herpes Virus Infections in HIV-Infected Patients

Episodic Treatment Regimens		
DRUG	DOSAGE	DURATION
Acyclovir	400 mg orally three times a day	5-10 days
Acyclovir	200 mg orally 5 times a day	5-10 days
Famciclovir	500 mg orally twice a day	5-10 days
Valacyclovir	1 g orally twice a day	5-10 days

Drug Suppressive Therapy	
DRUG	DOSAGE
Acyclovir	400-800 mg orally twice or three times a day
Famciclovir	500 mg orally twice a day
Valacyclovir	500 mg orally twice a day

From Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. MMWR Morb Mortal Wkly Rep 2002;5:1.

HSV infection increases HIV replication in persons infected with both viruses (Van de Perre et al, 2008). Studies have also shown that anti-HSV treatment with acyclovir reduced HIV in genital secretions among HIV- and HSV-coinfected persons (Dunne et al, 2008). Thus, it was disappointing that randomized clinical trials found that acyclovir as HSV suppressive therapy did not decrease the incidence of HIV infection in HSV-positive, high-risk HIV-negative women (Watson-Jones et al, 2008).

Human Papillomavirus. Warts can develop in unusual locations, such as on the lips, tongue, and oral mucosa in addition to the genitalia. Such lesions are treated using standard regimens (cryotherapy, podofilox, imiquimod, podophyllin resin, laser, or excisional surgery) (Centers for Disease Control and Prevention, 2002). However, in immunosuppressed patients genital lesions are resistant to treatment and these patients may be at higher risk for recurrence (Centers for Disease Control and Prevention, 2002).

In men, human papillomavirus (HPV) affects the penis, urethra, scrotum, perineal, and rectal mucosa as condylomata acuminata, which are usually recognized as soft sessile lesions with finger-like projections (Fig. 14–3). In women the spectrum of clinical disease is broad with vulvar, vaginal, and cervical condylomata. Other clinical presentations of HPV infection include bowenoid papulosis and epidermodysplasia verruciformis. Bowenoid papulosis presents as small, brown, flat papules affecting the perianal and genital areas. Epidermodysplasia verruciformis consists of a widespread eruption of pink-red, flat, wartlike lesions distributed mostly on sun-exposed skin (Berger et al, 1991).

HPV infection increases the risk for carcinoma, especially in HIV-infected hosts. These lesions include cervical intraepithelial neoplasia in women and squamous cell carcinoma in men. Whenever extensive warts develop the patient should be screened for HIV infection. Because there is an increased risk of anal cancer in HIV-infected homosexual men, screening for anal squamous intraepithelial neoplasia by cytology is recommended by some authorities. Until more data on the natural history of anal squamous intraepithelial neoplasia and the efficacy of treatment are available, routine screening is not recommended (Centers for

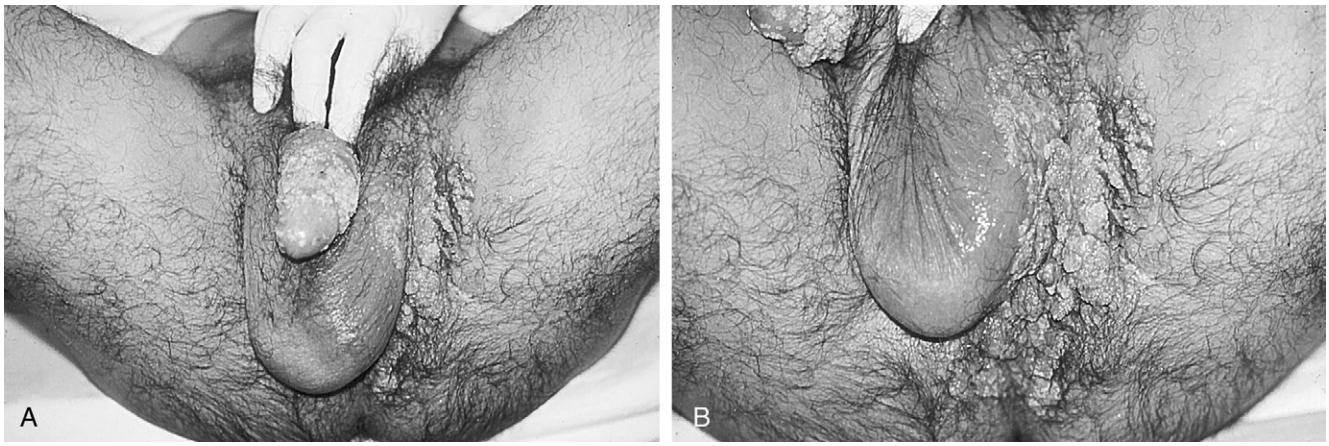


Figure 14–3. **A** and **B,** AIDS patient with five active urogenital viral infections. Extensive genital condylomata associated with areas of dysplasia and squamous intraepithelial neoplasia related to coinfection with human papillomavirus. Shedding of HIV, cytomegalovirus, and hepatitis B virus was documented in the patient's semen. Herpes simplex virus type 2 was cultured from active ulcers in the patient's inguinal crease.

Disease Control and Prevention, 2002). Differential diagnosis of atypical and/or extensive genital warts includes squamous cell carcinoma in-situ and squamous cell carcinoma. These cases are best diagnosed by biopsy. Treatment by various excisional procedures is often effective, but recurrence occurs frequently.

Syphilis. A high prevalence of syphilis is found in certain HIV-infected populations, particularly men who have sex with men (Quinn et al, 1988; Centers for Disease Control and Prevention, 2002). In HIV-infected patients, primary infection with *Treponema pallidum* presents as the typical chancre. Secondary syphilis may present in classic papulosquamous form with involvement of palms, soles, and mucous membranes, but unusual presentations are common, such as verrucous plaques, extensive oral ulcerations, keratoderma, deep cutaneous nodules, and widespread gummata (Kho et al, 2004). The disease may progress faster from secondary to tertiary syphilis in HIV-infected patients. Early central nervous system relapse also can be more common.

Unusual serologic responses have been observed among HIV-infected persons with syphilis, usually among persons with higher than expected titers. False-negative tests have also been reported (Centers for Disease Control and Prevention, 2002). Patients with clinical findings suggesting possible syphilis but with nonreactive or atypical serologic tests should have alternative diagnostic tests, such as biopsy of lesions, darkfield examination, or direct fluorescent antibody staining for diagnosis.

HIV-infected persons with early syphilis appear to be at increased risk for neurologic complications and higher risk for treatment failure with standard regimens. For primary and secondary syphilis in HIV-infected patients the current recommendation is intramuscular injection of benzathine penicillin G (2.4 million units). At least one dose is recommended and some authorities recommend three doses at weekly doses, as recommended for late syphilis. Careful follow-up is recommended with repeated serologic studies for at least 24 months after treatment.

Chancroid. In the United States, chancroid usually occurs in discrete outbreaks. Chancroid is a cofactor for HIV transmission. Definitive diagnosis requires culture of *Haemophilus ducreyi* on special culture. Although polymerase chain reaction–based tests are described, none is approved by the U.S. Food and Drug Administration. Probable diagnosis can be made if the patient has painful genital ulcers, no evidence of *Treponema pallidum* infection, and a negative test for HSV. The combination of a painful ulcer and tender inguinal adenopathy, symptoms occurring in one third of patients, suggests a diagnosis of chancroid. When accompanied by suppurative inguinal adenopathy these signs are almost pathognomonic.

Recommended regimens for chancroid in HIV-infected patients are either ciprofloxacin, 500 mg orally twice daily for 3 days, or erythromycin base, 500 mg orally three times daily for 7 days (Centers for Disease Control and Prevention, 2002). Alternative drugs are either azithromycin, 1 g orally as a single dose, or ceftriaxone, 250 mg as a single intramuscular dose. HIV-infected patients with chancroid should be monitored closely because, as a group, these patients are more likely to experience treatment failure and to have ulcers that heal more slowly. HIV-infected patients may require longer courses of therapy, and treatment failures can occur with any regimen.

Urethritis. As the first rheumatic disease reported in HIV-infected patients, Reiter syndrome, consisting of uveitis, urethritis, and arthritis often presents in incomplete form (Solomon et al, 1991). The link between Reiter syndrome and AIDS is poorly understood. The syndrome, particularly the urethral discharge, is usually refractory to antibiotic therapy.

Molluscum Contagiosum. Molluscum contagiosum is caused by a sexually transmitted poxvirus. This condition reportedly develops in 10% to 20% of AIDS patients (Kho et al, 2004). Characteristic lesions are umbilicated, dome-shaped, translucent 2- to 4-mm papules. Lesions can develop in any part of the body, especially the face and genital areas. In AIDS patients these lesions are widespread and may attain immense size (Izu et al, 1994). Most HIV-infected patients with extensive molluscum contagiosum have CD4+ counts less than 250 cells/mL. In such immunosuppressed patients the diagnosis of molluscum contagiosum should be confirmed by histologic examination because the clinical appearance may simulate more serious infections such as cutaneous pneumocystosis, histoplasmosis, *Penicillium marneffei* infection, cryptococcosis, or cutaneous mycobacterial infection. Molluscum contagiosum is treated with cryotherapy, electrodissection, curettage, or topical application of keratolytic preparations (Kho et al, 2004).

HIV-Related Genitourinary Tract Infections

The genitourinary tract may be involved as the site or sequelae of HIV-related opportunistic infections (Randazzo et al, 1986; Stamm et al, 1988; Miles et al, 1989; Shevchuk et al, 1989, 1999; Pudney and Anderson, 1991; Wilson et al, 1992; Buzelin et al, 1994;

Leibovitch and Goldwasser, 1994; Swartz et al, 1994; Trauzzi et al, 1994; Cespedes et al, 1995; Timmerman et al, 1995; Appel et al, 2004; Kuritzkes, 2004).

Renal Infections. There has been a rise in drug-resistant tuberculosis in the United States. Persons with or at risk for HIV infection appear to be at increased risk for active infection with drug-resistant strains of *Mycobacterium tuberculosis*. Persons coinfected with HIV and *M. tuberculosis* have a greater likelihood of developing clinical tuberculosis, including renal and other extrapulmonary disease, that may be more difficult to diagnose and to treat (Weiss et al, 1998).

Other renal infectious manifestations of AIDS include cytomegalovirus, *Aspergillus,* and *Toxoplasma* infections. Cytomegalovirus is a common opportunistic infection in immunocompromised patients. Renal infection is most commonly noted in widespread disease in association with acute tubular necrosis (Kwan and Lowe, 1995). Although it has been suggested that renal cytomegalovirus infection might facilitate the development of HIV-associated nephropathy (HIVAN), an autopsy study of 75 kidneys suggested that the two findings are unrelated (Nadasdy et al, 1992). Aspergillosis and toxoplasmosis are common opportunistic infections of the kidney. Both organisms are treated with systemic therapy. Serious infections such as abscesses require percutaneous drainage, open drainage, or nephrectomy.

Prostatitis. The prostate is the site for varied opportunistic infections in HIV-infected patients. In one study bacterial prostatitis was diagnosed in 17 (8%) of 209 men hospitalized for HIV (Leport et al, 1989). The clinical presentation varies based on the severity of the infection but includes fever, obstructive and irritative voiding symptoms, and a tender prostate on digital rectal examination with possible fluctuance. Superimposed urinary tract infections occurred in 22% of AIDS patients in one study (Kaplan et al, 1987). Diagnosis requires broad cultures including aerobes, anaerobes, fungi, and mycobacteria. Prostatic abscesses require open, transrectal or endoscopic drainage. Bacterial prostatitis requires prolonged courses of antibiotics with high levels of prostatic penetration. Fungal prostatitis is initially treated with two-agent therapy (amphotericin and flucytosine) or one of the newer antifungal drugs, with long-term suppression for persistent or recurrent infections.

Epididymitis and Orchitis. The most common intrascrotal pathology in AIDS is testicular atrophy secondary to endocrine imbalances, febrile episodes, malnutrition, toxic effects of therapeutic agents, and testicular infections (Leibovitch and Goldwasser, 1994). Autopsy studies have demonstrated opportunistic testicular infection in up to 39% of AIDS patients (De Paepe et al, 1990). One study (Shevchuk et al, 1989) of 80 autopsies in AIDS patients demonstrated that 2 of 11 cases with systemic toxoplasmosis involved the testes, 4 of 48 cases of systemic cytomegalovirus infection involved the prostate whereas 1 involved the testes, and 1 of 27 cases of systemic candidiasis involved the prostate. Most patients' testes exhibited marked spermatogenic arrest, germ cell degeneration, peritubular fibrosis, and Leydig cell depletion, nonspecific findings that likely reflect severe systemic disease (Shevchuk et al, 1999). Other immunocompromised patients develop symptomatic genitourinary tract infections with both common and unusual organisms, for example, epididymitis caused by *Candida* (Swartz et al, 1994) or cytomegalovirus (Randazzo et al, 1986). Patients may be less likely to respond to medical therapy and to require surgery (Coburn, 1998).

Clinically, scrotal infections usually present as epididymo-orchitis. Relapse is common and may result in persistent symptoms or fulminant infection with abscess formation. Treatment requires initial antibiotic treatment followed by long-term maintenance suppression. The differential diagnosis of epididymitis or orchitis that does not respond to conventional therapy includes fungal, mycobacterial, and other opportunistic infections, in addition to testicular tumors (see later).

Impetigo, Abscesses, Cellulitis, Lymphadenitis, and Necrotizing Fasciitis. Impetigo, usually caused by *Staphylococcus aureus*, occurs in the inguinal area as in other common sites (the face, shoulders, and axilla). Typically the infection begins with painful red macules, progressing to pustules that rupture producing a characteristic honey-colored crust (Kho et al, 2004). Soft tissue and deep-seated infections, including cellulitis, abscesses, and necrotizing fasciitis may develop in HIV-infected patients.

Necrotizing fasciitis of the genitalia, also known as Fournier gangrene, has a propensity to occur in immunocompromised hosts (Corman et al, 1999). This aggressive, progressive, necrotizing fasciitis has been documented as the presenting finding in previously undiagnosed AIDS patients (McKay and Waters, 1994). Treatment depends on rapid diagnosis, wide surgical debridement, hemodynamic support, and prolonged antibiotic therapy. Diverting colostomy and partial or complete scrotectomy may prove necessary during operative debridement.

Voiding Dysfunction

Because HIV infection affects both the central and peripheral nervous systems, voiding dysfunction is common in patients with advanced infection (Hermieu et al, 1996). Urinary retention is the most common voiding dysfunction (54%) seen by urologists, although detrusor hyperreflexia (27%) and outflow obstruction (18%) have been documented during urodynamic evaluation of AIDS patients with voiding symptoms (Travers and Huybers, 1987; Kane et al, 1996). **Standard pharmacologic measures are preferred for patients with mild dysfunction, and routine urodynamic investigation has proven to be of low yield** (Gyrtrup et al, 1995). In our experience, voiding complaints often reflect the degree of systemic impairment; such symptoms often improve substantially after effective antiretroviral therapy. For patients in urinary retention, intermittent catheterization is the treatment of choice. When the patient lacks sufficient manual dexterity, indwelling urethral or suprapubic catheterization is employed.

Urolithiasis

Urinary calculi have been associated with several treatments of HIV infection. **The strongest association is with protease inhibitors, especially indinavir** (Daudon and Jungers, 2004). Kidney and ureteral stones occur in 2% to 3% of patients taking indinavir (Lerner et al, 1998; Katner et al, 2002), but rates as high as 12% to 24% have been reported (Hermieu et al, 1999; Reiter et al, 1999; Meraviglia et al, 2002). Renal secretion appears to increase urinary supersaturation with formation of indinavir urinary crystals, especially with indinavir dosages of more than 600 mg (Vella and Floridia, 2004). **The stones are nonopaque and may be associated with minimal findings on noncontrast CT examination** (Gentle et al, 1997; Blake et al, 1998; Schwartz et al, 1999).

The authors' experience is consistent with recommendations for conservative treatment in most cases, consisting of hydration, analgesics, and temporary cessation of indinavir (Hermieu et al, 1999; Kohan et al, 1999). Indications for intervention include persistent fever, intractable pain, inability to tolerate oral hydration, or obstruction of a solitary kidney. Indinavir crystals develop at pH 7.0 and can be dissolved when the pH is lowered to 4.0.

This suggests that short-term urinary acidification may be valuable for stone dissolution (Kalaitzis et al, 2002). After resolution of the acute symptoms and passage of the stone, indinavir therapy can be restarted with aggressive oral hydration (Clayman, 1998). Urinary calculi have also been associated with use of other protease inhibitors, such as nelfinavir (Engeler et al, 2002) and saquinavir (Green et al, 1998).

HIV-infected patients on protease inhibitors also form stones that do not contain protease inhibitors. One study of 24 HIV-infected patients with urinary calculi found that only 3 (29%) of 14 on indinavir had indinavir-containing stones (Nadler et al, 2003). Of 10 patients evaluated, 8 had metabolic abnormalities. Thus metabolic evaluation may help prevent future stone episodes while avoiding the need to alter antiretroviral regimens in most patients.

Sulfadiazine therapy for toxoplasmosis has also been associated with obstructive nephropathy (Farina et al, 1995; Colebunders et al, 1999; Crespo et al, 2000). The obstructing calculi often appear radiolucent. Initial therapy should include hydration, discontinuation of the sulfadiazine, and urinary alkalinization (Crespo et al, 2000). Invasive interventions should be reserved for patients who fail such medical management (Colebunders et al, 1999).

HIV-Associated Nephropathy

AIDS-related renal failure was first reported in the 1980s and has now become known as HIV-associated nephropathy (HIVAN) (Rao et al, 1984). **This glomerular disease has emerged as a significant medical renal disease in HIV-infected patients. The high prevalence and severity of HIVAN among certain populations has made this diagnosis almost synonymous with HIV-associated chronic kidney disease** (Appel et al, 2004; Winston et al, 2008). More recently the clinical course of HIVAN has been substantially improved by the widespread use of HAART (Lucas et al, 2004). Nonetheless, HIVAN remains a significant cause of morbidity and mortality among infected individuals.

Epidemiology. HIVAN has been reported more often on the U.S. east coast than the west coast. In urban east coast populations the prevalence of HIVAN approached 90% in nephrotic HIV-infected patients compared with 2% in San Francisco, where most patients were white homosexuals (Appel et al, 2004; Ross and Klotman, 2004).

HIVAN occurs more frequently among HIV-infected black patients, with a black-to-white ratio of 12:1, and represents the third leading cause of end-stage renal disease among 20- to 64-year-old blacks (following only diabetes and hypertension). Blacks also appear to have more severe renal disease with heavier proteinuria, higher rate of the nephrotic syndrome, and greater renal insufficiency. Intravenous drug use has been the most common risk factor associated with HIVAN, but the disease has been seen in all HIV risk groups (Appel et al, 2004). There is no relationship between HIVAN and patient age, duration of HIV infection, or types of opportunistic infections or malignancies (Appel et al, 2004). The prevalence of HIVAN is reported to be 3.5% in HIV-infected clinic patients and 6.9% in autopsy series of HIV-infected patients (Shahinian et al, 2000). As expected, hypertension and diabetes mellitus remain the most common risk factors for the development of chronic kidney disease, leading to a 10-fold increased risk of chronic kidney disease and accounting for more than 70% of cases of end-stage renal disease. Data from the Multicenter AIDS Cohort Study suggest that HIV-infected individuals are four times more likely to have diabetes compared with control subjects. Thus the association between HIV, HIVAN, and chronic kidney disease is complex (Brown et al, 2005; Winston et al, 2008).

Clinical Presentation. **HIVAN usually occurs in patients with low CD4 counts, but overt AIDS is not a prerequisite** (Appel et al, 2004). **HIVAN typically presents as nephrotic range proteinuria and renal insufficiency** (Appel et al, 2004). Other characteristics typical of the nephrotic syndrome are common in some series, including edema, hypoalbuminemia, hypercholesterolemia, and hypertension. Patients may also present with sub–nephrotic-range proteinuria and urinary sediment findings of microhematuria and sterile pyuria. Renal ultrasound evaluation shows echogenic kidneys with preserved or enlarged size despite severe renal insufficiency (Appel et al, 2004).

Pathology and Pathogenesis. Diagnosis of HIVAN is based on a renal biopsy specimen showing characteristic focal segmental glomerulosclerosis with collapsing features and related mesangiopathies (Appel et al, 2004). Patients with HIVAN have a higher percentage of glomerular collapse, less hyalinosis, and greater visceral cell swelling than patients with classic, idiopathic focal segmental glomerulosclerosis or heroin nephropathy.

There are conflicting data on the potential for direct HIV infection of renal glomerular cells in vivo, but HIV appears to be able to infect glomerular endothelial cells and to a lesser degree mesangial cells in vitro (Marras et al, 2002; Appel et al, 2004). HIV replication may not be necessary for development of HIVAN, and it is likely that a viral gene product or indirect effects on host cytokine production are involved in the pathogenesis.

Course and Treatment. During the early years of the epidemic HIVAN was characterized by rapid progression to end-stage renal disease (Appel et al, 2004). There was an almost universal requirement for dialysis within 1 year of diagnosis (Appel et al, 2004).

With the introduction of HAART the rise in new cases of end-stage renal disease due to HIVAN slowed markedly (Kirchner, 2002; Appel et al, 2004). There are reports of patients with biopsy-documented or presumed HIVAN who experienced dramatic resolution of nephrotic syndrome and improved glomerular filtration rate on therapy (Appel et al, 2004). **Antiretroviral therapy also appears to delay progression of HIVAN to end-stage renal disease. Thus antiretroviral therapy is recommended for patients with early histologic lesions and milder proteinuria without renal deterioration. Antiretroviral drugs need to be selected with caution given their propensity to cause or potentate nephrotic syndrome and must be dose adjusted in cases of renal insufficiency** (Winston et al, 2008). Other therapies that have been recommended include angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and immunosuppressive therapy in selected patients (Appel et al, 2004).

Abnormal Urinalysis

Abnormalities on urinalysis are relatively common in HIV-infected persons. These findings include hematuria, pyuria, bacteriuria, and proteinuria. One study suggests that hematuria occurs in 25% of HIV-infected persons (Cespedes et al, 1995). Although hematuria may be related to many causes, genitourinary tumors appear to be uncommon, particularly in young men. Thus, complete urologic evaluation may safely be omitted in young men with asymptomatic microscopic hematuria (Cespedes et al, 1995). In contrast, the authors have seen a number of HIV-infected patients with urologic malignancies, including bladder, renal, and other tumors, presenting with hematuria. These observations suggest that complete investigation is indicated in older patients and

those with significant hematuria. Proteinuria is also common in certain populations of HIV-infected patients (see earlier).

Neoplasms

Many neoplasms occur in HIV-infected patients (Kho et al, 2004; Tirelli and Vaccher, 2004). Vascular and lymphoreticular neoplasms have been associated most strongly with HIV infection, particularly Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL) (Cadogan and Dalgleish, 2008). The risks of KS and NHL are increased 1000- and 100-fold, respectively, among HIV-infected patients compared with the general population (Tirelli and Vaccher, 2004). KS, primary central nervous system lymphoma, systemic intermediate/high-grade B-cell NHL, and invasive cervical cancer have been designated as AIDS-defining illnesses. Other malignancies reported to be associated with HIV infection include Hodgkin disease, high-grade anal epithelial lesions, nonmelanomatous skin cancer, myeloma, and lung and testicular carcinoma (International Collaboration on HIV and Cancer, 2000; Tirelli and Vaccher, 2004). HAART radically changed the clinical spectrum of HIV infection in industrialized countries. During the mid 1990s, rates of opportunistic infections, KS, primary central nervous system lymphoma, and NHL decreased significantly (International Collaboration on HIV and Cancer, 2000; Grulich et al, 2001).

Kaposi Sarcoma

KS is the most common vascular neoplasm and a significant cause of morbidity and mortality in certain HIV-infected populations (Cockerell, 1996).

Classification and Clinical Presentation. KS is classified into classic and epidemic forms. The classic form was first described in 1827 (Kho et al, 2004) and occurs mainly in elderly Mediterranean men, black equatorial Africans, and patients with lymphoma or immune deficiencies. In contrast, epidemic KS is associated with AIDS.

KS ranges from an indolent to an aggressive disease with substantial morbidity and mortality. **Typical patients present with disseminated skin lesions, often with lymph node and visceral involvement** (Tirelli and Vaccher, 2004). Any skin area may be involved, including the genitalia. Three types of skin lesions are described: macule or patch, plaque, and nodule (Kho et al, 2004). Typical macules are oriented along skin cleavage lines and may be mistaken for blushes, purpura, or nevi. With time the lesions darken and develop into raised, firm, indurated, purplish plaques reflecting the presence of abundant blood vessels, extravasated erythrocytes, and siderophages. Some lesions may ulcerate. Nodular lesions are dome-shaped elevated lesions that are usually purple. On palpation they are firm and may be ulcerated.

Epidemiology. KS incidence rates started to decline in the late 1980s and then dramatically lessened with the introduction of HAART in the mid 1990s (International Collaboration on HIV and Cancer, 2000; Grulich et al, 2001; Tirelli and Vaccher, 2004). Meta-analysis of 47,936 HIV-infected individuals from North America, Europe, and Australia found that the KS rate ratio for 1997-1999 versus 1992-1996 was 0.3 (International Collaboration on HIV and Cancer, 2000). The risk of KS among male homosexuals is more than 100,000-fold higher than other HIV-infected populations (Tirelli and Vaccher, 2004).

A new herpesvirus, called KS-associated herpesvirus or human herpesvirus 8 (Chang et al, 1994), **is essential for all forms of KS.** KS-associated herpesvirus transmission correlates with a history of STIs and number of male sexual partners. Coinfection with HIV and KS-associated herpesvirus increases the risk of developing KS 10,000-fold compared with KS-associated herpesvirus infection alone. The probability of developing KS after coinfection with both KS-associated herpesvirus and HIV approaches 50% over 10 years (Chang et al, 1994).

Pathology and Pathogenesis. KS is an proliferative disease characterized by angiogenesis, endothelial spindle cell growth (KS cells), inflammatory cell infiltration, and edema (Tirelli and Vaccher, 2004). These lesions reflect immune dysregulation characterized by CD8+ T-cell activation, production of T-helper-1 cytokines, and angiogenic factors. This process induces generalized activation of endothelial cells.

Diagnosis and Management. An experienced observer can often make a presumptive diagnosis but skin biopsy is necessary to confirm the diagnosis of KS.

No specific therapy is curative (Tirelli and Vaccher, 2004). Treatment needs to be individualized, based on the patient's clinical and immunologic status. HAART results in clinical improvement of KS lesions and prolongation of time to treatment failure (Lebbe et al, 1998; Levine and Tulpule, 2001). Numerous anecdotal reports document KS regression on HAART alone. Anti-KS activity of HAART appears to reflect immune system reconstitution and, to a lesser extent, suppression of HIV replication. HIV protease inhibitors are also potent antiangiogenic molecules that may affect KS pathogenesis (Sgadari et al, 2002).

Localized, cutaneous KS lesions can be treated using radiation, laser, cryotherapy, or intralesional injections of antineoplastic drugs (Levine and Tulpule, 2001). Cytotoxic chemotherapy is indicated for patients who do not respond to HAART and patients with life-threatening or visceral disease. A wide variety of drugs, including *Vinca* alkaloids (vincristine, vinblastine), bleomycin, and doxorubicin individually and in combination have produced tumor regression in 21% to 59% of patients, with lower rates for monotherapy. Paclitaxel is the newest systemic agent approved for use in the patient in whom KS has relapsed (Levine and Tulpule, 2001). Corticosteroid therapy should be avoided because they induce development of KS and may worsen preexisting KS lesions.

Prognosis for HIV-infected patients with KS depends primarily on their immune status and, secondarily, on the clinical stage of the KS lesions. Median survival of patients with CD4+ T-cell counts greater than or equal to 150/μL and early-stage disease is 35 months. Patients with CD4+ T-cell counts less than 150/μL have poor median survival (13 months for early-stage disease and 12 months for advanced-stage disease, respectively) (Levine and Tulpule, 2001).

Non-Hodgkin Lymphoma

A number of lymphoreticular malignancies of both B and T cells develop in HIV-infected patients. Most are based in the lymph nodes and reticuloendothelial system. The genital skin and genitourinary organs may be involved primarily or secondarily (Mearini et al, 2002; Kho et al, 2004; Tirelli and Vaccher, 2004). Patients usually present with advanced disease associated with a short median survival time. NHL is the most common lymphoreticular neoplasm.

Epidemiology and Clinical Presentation. NHL incidence decreased significantly after the introduction of HAART (Tirelli and Vaccher, 2004). Systemic NHL incidence decreased less than KS and later than the other AIDS-defining illnesses. Consequently, lymphoma has become the most common AIDS-associated cancer among patients receiving HAART (International Collaboration on HIV and Cancer, 2000; Grulich et al, 2001; Tirelli and Vaccher, 2004).

HIV-infected patients characteristically have widespread disease at presentation (Tirelli and Vaccher, 2004). They frequently have

systemic symptoms, including fever, night sweats, and weight loss of more than 10%. At diagnosis of NHL, approximately 75% of HIV-infected patients have advanced disease with frequent involvement of extranodal sites. Any body site may be affected, including the genitourinary tract.

Diagnosis and Treatment. NHL should be diagnosed by histologic examination of an incisional or excisional biopsy specimen. Treatment consists of the usual therapy for systemic lymphoma. Optimal therapy has not been defined, and whether intensive or conservative chemotherapy regimens are indicated remains controversial. Prognosis for HIV-infected patients with lymphoma is poor, with a median survival of 5 to 10 months after diagnosis (Tirelli and Vaccher, 2004).

Squamous Genital Cancers: Role of Human Papillomavirus

HIV infection is associated with HPV-related anogenital neoplasms (Tirelli and Vaccher, 2004). **These lesions include cancers and precancerous lesions of the cervix, vulva, anus, and penis.** The risk of all HPV-associated cancers and their in-situ precursor lesions in both women and men is elevated across all HIV exposure categories (Tirelli and Vaccher, 2004). Risk factors include multiple sexual partners, cigarette smoking, and STIs, particularly HPV infection.

HPV sequences are found in more than 99% of cervical squamous cell carcinomas and in most anal cancers, with HPV type 16 present in 50% and types 18, 31, and 45 present in another 30%. High-grade intraepithelial precursor lesions have comparable rates of similar HPV types. HPV-associated oncogenesis results from upregulated expression of viral-encoded transforming proteins, particularly E6 and E7. These proteins interact with and inactivate the host cell tumor suppressor gene products, including retinoblastoma and TP53. This results in upregulated cell cycle progression, deficient DNA repair, and, eventually, malignant transformation (Tirelli and Vaccher, 2004). The degree of HIV-related immunosuppression corresponds with the occurrence and severity of these anogenital tumors.

Testicular Cancer

There may be an increased incidence of germ cell and non–germ cell testicular tumors associated with HIV infection (Wilkinson and Carroll, 1990; Wilson et al, 1992; Kwan and Lowe, 1995). Retrospective review of 3000 patients enrolled in an HIV clinic found a 50 times greater rate of testicular neoplasms than in the general population (Wilson et al, 1992). Compared with HIV-uninfected patients there is a greater risk of tumor bilaterality and a greater risk of high-grade testicular lymphoma (Armenakas et al, 1992). **More recent data suggest that the increased risk of testicular germ cell tumors is more modest, whereby HIV-infected men are approximately two times more likely to develop seminoma (Standardized Incidence Ratio 1.9, 95% CI 1.6-2.2) but not more likely to develop nonseminomatous tumors** (Goedert et al, 2007).

The therapeutic dilemma is that all accepted treatments for testicular neoplasms, except surveillance, cause additional immune suppression. Furthermore, patients with advanced HIV/AIDS often tolerate radiation and chemotherapy poorly. This may require major modifications of standard treatment protocols, resulting in decreased effectiveness. Despite these limitations, most experts recommend that HIV-infected patients with testicular neoplasms should receive standard treatment, as indicated by the tumor histology and stage (Wilkinson and Carroll, 1990).

OCCUPATIONAL RISKS FOR HIV INFECTION IN UROLOGY

For reasons that are not completely understood, occupational HIV infection remains relatively uncommon (Henderson, 2004b).

Epidemiology

The Centers for Disease Control and Prevention has recorded only 57 instances of documented occupational HIV infection. For each case the worker sustained an occupational exposure, had a negative baseline serum sample, and then developed serologic evidence of HIV infection. In addition there have been 138 instances of probable or possible occupational HIV infection among U.S. health care workers (Centers for Disease Control and Prevention, 2004). Of adults with AIDS, 5.1% have occurred in health care workers, including 122 surgeons. Approximately 60 cases of "possible or probable" occupational infection have been reported from outside the United States (Henderson, 2004b). There were no documented cases of occupationally acquired AIDS/HIV infection among surgeons and 6 possible cases of occupational transmission among surgeons.

Risks Associated with Specific Exposures

Of the 57 health care workers who seroconverted following occupational exposures 48 (84%) had percutaneous (puncture/cut injury) exposures; 5 (9%) had mucocutaneous (mucous membrane and/or skin) exposures; 2 (4%) had both percutaneous and mucocutaneous exposure; and 2 (4%) had an unknown route of exposure. Forty-nine health care workers were exposed to HIV-infected blood, 3 to concentrated virus in a laboratory, 1 to visibly bloody fluid, and 4 to an unspecified fluid (Centers for Disease Control and Prevention, 2004).

Many occupational cases of HIV transmission share common features. Most are percutaneous exposures, especially injection needlestick injuries. All clinical cases occurred after exposure to blood or grossly blood-stained fluids from HIV-infected patients. As yet, no case has been documented following a needlestick injury with a solid surgical needle (Henderson, 2004b).

A retrospective, case-control study from the United States, France, and the United Kingdom identified **five risk factors for occupational infection: deep as compared with superficial exposure** ($P < .0001$), **blood visible on the device causing the exposure** ($P = .0014$), **placement of the device in a source-patient's vein or artery** ($P = .0028$), death of **the source-patient within 60 days of the exposure** ($P = .0011$), **and no postexposure chemoprophylaxis with zidovudine** ($P = .0026$) (Cardo et al, 1997). The first four factors are likely related to an increased inoculum.

The importance of an inoculum effect is supported by other data. Transfusion of a unit of blood from an HIV-infected donor is associated with virtually 100% risk for infection (Ward et al, 1987). The depth of a percutaneous exposure was an independent risk factor for occupational HIV infection (Cardo et al, 1997). In addition, all needlestick exposures associated with occupational transmission have been caused by hollow-bore needles (i.e., injection as compared with suturing needles), which contain more blood than solid needles.

Table 14–5.
Risk for HIV Infection Associated with Occupational Exposure

TYPE OF EXPOSURE	PERCUTANEOUS	MUCOUS MEMBRANE
No. of longitudinal studies	27	21
No. of exposures	6807	2761
No. of documented infections	21	0/1
Infection rate per exposure	0.031%	0-0.11%

From Henderson DK: Preventing occupational infection with HIV in the health care environment. In Cohen J, Powderly WG, Berkley SF, et al, editors. Infectious diseases. 2nd ed, vol. 22. Edinburgh: Mosby; 2004. p. 1217–22.

Combining available data, health care workers have sustained more than 6800 percutaneous exposures to sharp devices contaminated with blood or other blood-stained body fluids from HIV-infected patients (Ippolito et al, 1999; Henderson, 2004b). Twenty-one occupational HIV infections were documented, resulting in a risk of transmission per injury of 0.31% (Table 14–5). Thus, 1 in 324 parenteral exposures resulted in occupational HIV infection.

Other exposures represent a lower risk for infection. In rare circumstances, mucous membrane or cutaneous exposures may produce occupational infection (Chamberland et al, 1995). To date, more than 2700 exposures have been followed prospectively, with only one seroconversion (Ippolito et al, 1993). Thus, a maximum risk estimate for HIV infection is 0.11% per mucous membrane exposure. Occupational exposures other than percutaneous and mucous membrane exposures are even less likely to result in infection. Prospective studies (Friedland et al, 1990; Gershon et al, 1990) that include hundreds of person-years of follow-up have not identified a single instance of HIV transmission. Although exposures to other fluids are likely to be associated with some occupational risk, this risk is below measurable limits.

Interventions to Decrease Occupational Risk

Adherence to current guidelines might prevent one third of parenteral occupational exposures (Marcus, 1988). Universal Precautions are based on the principle that health care workers should treat blood and blood-stained body fluids from all patients as potentially infectious (Centers for Disease Control and Prevention, 1988). The CDC also recommends Standard Precautions, focusing on the bidirectional spread of organisms to and from patients and health care providers. The recommendations emphasize that blood and blood-containing body fluids represent risks to health care workers and that health care workers should use barriers and take precautions to prevent occupational exposures. These recommendations are effective. For example, the act of piercing a latex glove with a needle covered with blood may reduce the blood inoculum by as much as 50% (Henderson, 2004b).

Once exposure to HIV has occurred, the exposed site should be allowed to bleed freely and first aid should be administered. The wound should be cleansed and decontaminated as soon as patient safety permits. Wounds should be washed with soap and water and then irrigated with sterile saline, a disinfectant, or other suitable solution.

Postexposure Prophylaxis

Data support postexposure chemoprophylaxis to reduce the risk of occupational HIV transmission. Postexposure prophylaxis has proven effective in animal models (Henderson and Gerberding, 1989; Henderson, 2004a). The case-control study described earlier found that zidovudine chemoprophylaxis was associated with an 80% reduction in the risk for occupational infection (Cardo et al, 1997).

Current recommendations include a three-drug regimen for the most severe occupational exposures (i.e., zidovudine, lamivudine, and one of four additional agents) and a two-drug regimen for lesser exposures (i.e., zidovudine plus lamivudine or one of two other alternative two-drug regimens) (Centers for Disease Control and Prevention, 2001). If the source patient is (or recently has been) receiving antiretroviral therapy, some authorities recommended use of alternative regimens (Henderson, 2004a).

There are two major problems with antiretroviral prophylaxis following occupational exposure to HIV. First, these drugs have substantial toxicity. Data on healthy individuals, especially for the newer agents, are extremely limited (Henderson, 2004a). Studies of antiretroviral prophylaxis after occupational HIV exposures in health care workers have demonstrated substantial side effects, often limiting completion of the regimen. Recently, use of nevirapine has been contraindicated because of the risk of severe liver toxicity, including hepatic failure. Virtually all marketed antiretroviral agents have potential for carcinogenicity, teratogenicity, and mutagenicity. Second, there have been documented failures of antiretroviral prophylaxis. Cases of zidovudine chemoprophylaxis failure (eight of which have clinical relevance) have appeared in the literature (Henderson, 2004a). Thus, the potential risks and benefits of post-exposure prophylaxis must be considered on a case-by-case basis.

ANTIRETROVIRAL THERAPY

A diagram of antiretroviral therapy in HIV infection is presented in Figure 14–4 (Vella and Floridia, 2004).

Suppression of HIV replication is associated with a significant delay in the progression to AIDS and increased survival. Thus, the goal of antiretroviral treatment should be to obtain maximal and sustained suppression of HIV replication (Vella and Floridia, 2004).

The main tools for monitoring antiretroviral treatment are the plasma HIV RNA level and CD4+ T-cell count (O'Brien et al, 1996). **Previously untreated patients should reach undetectable plasma HIV RNA levels within 4 to 6 months accompanied by a concomitant rise in CD4+ counts. In this context "undetectable plasma HIV RNA level" does not mean eradication of the virus at other sites (lymphoid tissues, central nervous system, or genital tract)** (Perelson et al, 1997). Eradication of HIV from these viral reservoirs and sanctuaries is not yet a realistic goal.

From Monotherapy to Highly Active Antiretroviral Therapy (HAART)

In 1987 zidovudine, the first effective antiretroviral drug and prototype of the nucleoside reverse transcriptase inhibitors (NRTIs), was introduced. Zidovudine monotherapy remained the mainstay of treatment until it became evident that benefit was limited (Concorde, 1994). Clinical trials demonstrated that two-drug

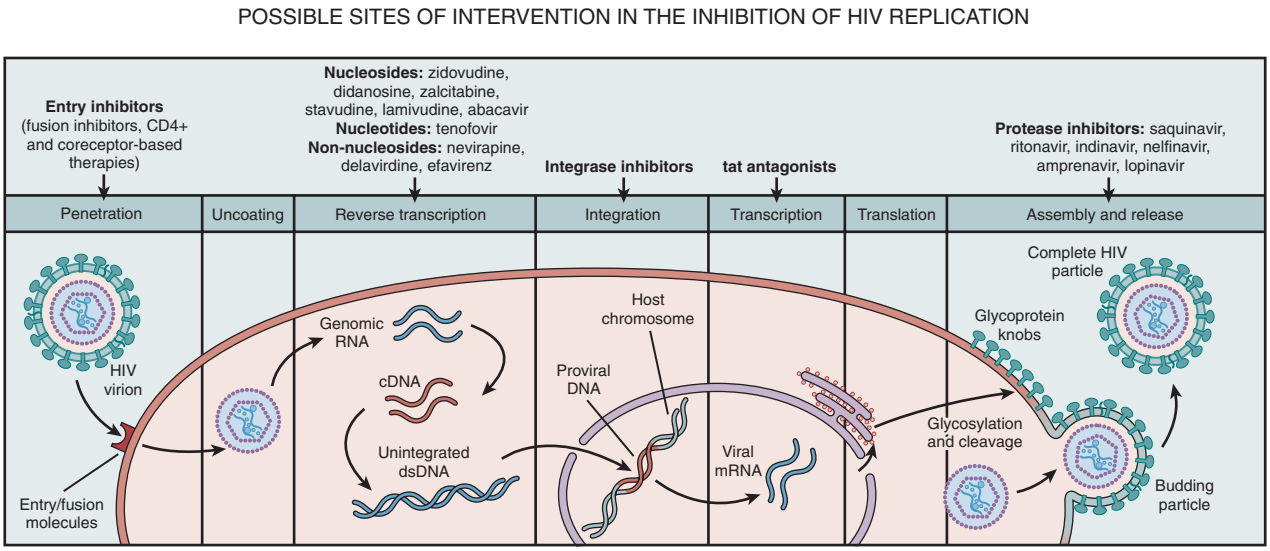


Figure 14–4. Antiretroviral therapy for HIV infection. Diagram illustrating potential sites of action for drug therapy. (From Vella S, Florida M. HIV therapy: antiviral therapy. In: Cohen J, Powderly SF, Berkley SF, et al, editors. Infectious diseases. 2nd ed, vol. 2. Edinburgh: Mosby; 2004. p. 1387–98).

regimens induced a more profound and prolonged effect on viral load, CD4+ T-cell counts, delayed clinical progression, and increased patient survival (Hammer et al, 1996; Deeks et al, 1997). In 1995 protease inhibitors became available. Combined with NRTIs, protease inhibitors produced a further reduction of HIV replication, often to undetectable levels (Deeks et al, 1997). Non-nucleoside reverse transcriptase inhibitors (NNRTIs), introduced after 1996, also proved highly effective. Availability of a rapidly increasing number of drugs and the evolving information has made HIV treatment extremely complex. The objective of antiretroviral therapy is to prevent disease progression and prolong survival while maintaining quality of life. Long-term nonprogression will be achieved by reducing plasma viral load below 50 copies/mL on a long-term basis. Combinations of antiretroviral agents with minimal or no overlapping toxicity and demonstrated antiviral additive to synergistic effect is recommended to maximize the antiviral response (Montaner et al, 2004). Current recommendations from the International AIDS Society-USA Panel note that the initial treatment regimen must be individualized but should generally include a protease inhibitor (efavirenz) plus two NRTIs (tenofovir/emtricitabine or abacavir/lamivudine) (Hammer et al, 2008).

Available Drugs

The optimal treatment of HIV infection is a potent combination of drugs, termed highly active antiretroviral therapy (HAART). Most HAART regimens are based on a dual nucleoside "backbone" plus an NNRTI or a protease inhibitor (with the option of adding low-dose ritonavir to another protease inhibitor for pharmacoenhancement.) Three-nucleoside regimens including abacavir are increasingly used because these regimens are easy to administer and are dual-class sparing (i.e., allow deferred use of protease inhibitors and NNRTIs).

Currently antiretroviral drugs include 7 NRTIs (zidovudine, didanosine, zalcitabine, stavudine, lamivudine, emtricitabine, and abacavir), 1 NRTI (tenofovir disoproxil fumarate), 3 NNRTIs (nevirapine, delavirdine, and efavirenz), and 10 HIV protease inhibitors (saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, fosamprenavir, tipranavir, darunavir, atazanavir, and lopinavir). Other drugs have recently been approved by the U.S. Food and Drug Administration for treating HIV. These drugs may prove particularly useful in cases of viral resistance to standard regimens and include a fusion inhibitor (enfuviritide), an entry inhibitor (maraviroc), and an HIV integrase strand transfer inhibitor (raltegravir) (Table 14–6) (He et al, 2008; Hicks and Gulick, 2009; Hunt and Romanelli, 2009).

Nucleoside Reverse Transcriptase Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors

NRTIs act through at least two mechanisms. First, as "chain terminators," they block viral DNA elongation, stopping addition of further nucleosides. This mechanism depends on intracellular phosphorylation of NRTIs to the corresponding triphosphates. Second, they act by competition/binding of the reverse transcriptase; NNRTIs act only through this mechanism and not as "chain terminators."

Protease Inhibitors

Protease inhibitors act by binding to the catalytic site of HIV aspartic protease. This enzyme is critical for post-translational processing of the polyprotein products into the functional core proteins and viral enzymes. By inhibiting this step, protease inhibitors release immature, noninfectious viral particles. However, unlike the NRTIs, which provide no protection in established HIV infection, protease inhibitors are also active in chronically infected cells. Protease inhibitors are combined with NRTIs or with other protease inhibitors, taking advantage of a boosting effect on drug concentrations that occurs when protease inhibitors are administered together.

Significant Urologic Side Effects

Of the NRTIs, zalcitabine is associated with peripheral neuropathy and painful penile ulcers. Of the protease inhibitors, ritonavir should be used with caution among patients at high risk of bleeding. Indinavir is a potent protease inhibitor that has been associated with urolithiasis (see earlier). In addition to drug-specific adverse events, long-term use HAART has highlighted a number

Table 14–6.

Antiviral Drugs Available for HAART Combination Regimens

CLASS	DRUG	TRADE NAME
Nucleoside reverse transcriptase inhibitors (NRTIs)	Zidovudine (AZT)	Retrovir*†
	Didanosine (ddI)	Videx
	Zalcitabine (ddC)	Hivid
	Lamivudine (3TC)	Epivir*†
	Stavudine (d4T)	Zerit
	Abacavir (ABC)	Ziagen†
	Emtricitabine (FTC)	Emtriva‡
Nucleotide reverse transcriptase inhibitors	Tenofovir	Viread
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Delaviridine (DLV)	Rescriptor
	Nevirapine (NVP)	Viramune
	Efavirenz (EFV)	Sustiva
Protease inhibitors	Saquinavir (SAQ)	Invirase
	Ritonavir (RTV)	Norvir
	Nelfinavir (NFV)	Viracept
	Indinavir (IDV)	Crixivan
	Amprenavir (APV)	Agenerase
	Fosamprenavir (FOS-APV)	Lexiva
	Lopinavir (LPV)	Kaletra§
	Tipranavir (TPV)	Aptivus
	Darunavir	Prezista
	Atazanavir (ATV)	Reyataz
Fusion inhibitors	Enfuviritide (T-20)	Fuzeon
Entry inhibitors	Maraviroc	Selzentry
HIV integrase strand transfer inhibitors	Raltegravir	Isentress

*Also available as Combivir (300 mg AZT + 150 mg 3TC).
†Also available as Trizivir (300 mg AZT + 150 mg 3TC + 300 mg ABV).
‡Also available as Truvada (300 mg FTC + 200 mg tenofovir).
§Only available as Kaletra (133.3 mg lopinavir +33.3 mg ritonavir).
From Vella S, Floridia M. HIV therapy: antiviral therapy. In: Cohen J, Powderly WG, Berkley SF, et al, editors. Infectious diseases. 2nd ed, vol. 2. Edinburgh: Mosby; 2004. p. 1387–98.

of previously unrecognized adverse events. Some appear to be associated with a specific class of drugs, such as mitochondrial toxicity and lactic acidosis with NRTIs or hypoglycemia with protease inhibitors. Fat distribution changes (commonly described as lipodystrophy) represent a major clinical event. This syndrome presents as atrophic changes (peripheral fat loss involving face and limbs resembling Cushing disease), hypertrophic changes (visceral or dorsocervical fat accumulation, breast enlargement), or both.

New Investigational Agents

Even with potent, multidrug regimens, virologic failure is frequent. This may depend on various factors, including low adherence, drug-resistant HIV strains, low drug levels in the plasma or tissues, and other undetermined factors. Targeted strategies are being developed to improve treatment efficacy, including development of new drugs with improved formulation and administration schedules, increased potency, and reduced toxicity. A number of agents in each of the available drug classes as well as drugs with novel mechanisms of action are being developed. Desirable characteristics of this new generation of drugs include easier administration schedule, perfected pharmacokinetics, potency, tolerability, and the ability to inhibit HIV viruses that are resistant to the existing agents.

Evolving HIV Treatment Strategies

Growing appreciation of the difficulties of taking antiretroviral therapy on a long-term basis, the adverse effects of many regimens, and their negative impact on quality of life have led to reevaluation of this early intervention strategy. Because "eradication" of HIV is not on the horizon, the goal of therapy must now be redirected toward the long-term management of a chronic infection (Vella and Floridia, 2004).

The decision to start treatment is now based first on the patient's disease stage, because it is clear that a symptomatic patient should be treated. For an asymptomatic patient, the decision is often driven by the CD4+ lymphocyte count and the plasma HIV RNA level (Montaner et al, 2004). **The CD4+ T lymphocyte count can be regarded as an immediate predictor of prognosis, whereas the plasma HIV RNA level indicates the level of actual HIV replication.** Other elements include the patient's commitment to therapy and knowledge of the limitations of current regimens.

Despite the effectiveness of HAART the optimal time to initiate therapy remains unclear. Although current antiviral therapies have proven ability to suppress viral load and improve immune system function, several questions remain. Specific concerns remain about early initiation of HAART and patient compliance, drug toxicities, drug resistance, and the marked costs associated with prolonged therapy (Wilkin and Gulick, 2008). Despite the absence of randomized clinical trials, several large cohort studies have demonstrated decreased AIDS-related morbidity and mortality when HAART is started early in the course of infection, when CD4 cell counts are higher. Recent data from the ART Cohort Collaboration suggest that individuals in whom therapy is initiated with a CD4 count of 200 to 350 cells/μL have a 5-year mortality rate that is 40% higher than those in whom therapy is started with counts greater than 350 cells/μL (May et al, 2007). The rationale for early therapy is augmented by studies suggesting decreased rates of non–AIDS-defining conditions, such as cancers, neuropathy, and anemia when antiviral medications are initiated at these higher CD4 levels. Fear that early therapy may increase costs of HIV treatment prompted multiple studies of the cost-effectiveness of early antiviral treatment, with sensitivity analyses using varying CD4 count levels. These studies suggest that early treatment is cost effective and offers significant improvements in quality-adjusted life years (Wilkin and Gulick, 2008).

Strategies on the Horizon

In addition to a plethora of new antiretroviral agents targeting the HIV replication cycle there are a number of strategies under active investigation to prevent HIV infection or to improve therapy. Two promising approaches are development of immune-based strategies and vaccines.

Immune-Based Strategies That May Be Combined with HAART. Because eradication of HIV with HAART probably cannot be achieved in less than 50 to 60 years (Montaner et al, 2004) the possibility of adding additional treatment to ensure immune restoration holds considerable appeal (Pollard and Onorato, 2004). Various strategies are under investigation to both enhance HIV-specific immune responses and to stimulate the general immune responses, such as therapeutic vaccination, structured treatment interruption, transfer of HIV-specific cell populations to enhance cell-mediated immunity, and transfer of pooled immune sera from donors who have HIV infection or of monoclonal antibodies directed against HIV. Such strategies may be of particular value for treating patients with later-stage infection, whose high levels of

viremia and previous exposure to therapy place them at greatest risk of developing resistance to therapeutic agents (Pollard and Onorato, 2004).

Vaccines to Prevent HIV Infection. Considerable efforts are being expended to develop an effective vaccine to prevent HIV infection (Rosenberg et al, 1997; Amara et al, 2001; Shiver et al, 2002; Fast et al, 2004). HIV represents a formidable challenge. Its immune evasion mechanisms include molecular tricks to avoid neutralization by antibody, downregulation of immune functions, direct destruction of the CD4 T cells that support both antibody and effector T-cell responses, and a very rapid mutation rate that gives rise to virus strains lacking the antigenic sites to which effective immune responses are directed.

Nevertheless, several lines of evidence suggest that vaccines may prove effective in preventing HIV infection or in preventing progression to AIDS (Fast et al, 2004). First, HIV infection occurs after only a small fraction of all exposures, suggesting that a modest immune defense might be effective. Second, the natural history of HIV infection is that after an initial phase of rapid viral replication immune responses may control HIV replication and slow its pathogenic effects for many years. Third, in primate models some vaccines can prevent infection or slow viral replication and disease progression. Immunization that induces mucosal responses is particularly effective against mucosal challenges, as would occur with sexual exposure (Amara et al, 2001; Shiver et al, 2002). A number of vaccines have been tested and, lacking credible immunogenicity data, abandoned. Several more promising vaccines have recently entered trials or are expected to do so soon.

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chapter
15

Cutaneous Diseases of the External Genitalia

Richard Edward Link, MD, PhD

Introduction to Basic Dermatology
Dermatologic Therapy
Allergic Dermatitis
Papulosquamous Disorders
Vesicobullous Disorders
Noninfectious Ulcers
Infections and Infestations
Neoplastic Conditions
Benign Cutaneous Disorders Specific to the Male Genitalia
Common Miscellaneous Cutaneous Disorders

The diagnosis and treatment of cutaneous diseases of the external genitalia remains an important element of urologic practice. Often overlooked during formal urology residency training, this topic lies at the interface of three specialties: urology, infectious disease, and dermatology.

INTRODUCTION TO BASIC DERMATOLOGY

Dermatology is the clinical discipline focused on the biology and pathology of the skin. The diagnosis of skin disease depends critically on the history and physical examination, with laboratory testing often relegated to a peripheral and confirmatory role. In many cases, visual inspection alone will suffice to narrow the diagnosis significantly.

The skin is divided into three layers: the epidermis, dermis, and subcutaneous tissue. The epidermis, composed of stratified squamous epithelium, can vary in thickness from 0.05 mm to 1.5 mm, depending on location. The dermis, composed of collagen, elastin, and reticular fibers, can be divided into two layers: the thin superficial layer (papillary dermis) and thicker deeper layer (reticular dermis).

Literally hundreds of cutaneous diseases exist involving the external genitalia. In addition, within each disease there may be significant variation in appearance and symptoms as the process evolves. For this reason, a methodical and systematic approach is essential to reach a rational diagnosis. The dermatologic history should focus on the duration, rate of onset, location, symptoms, family history, allergies, occupation, and previous treatment of the condition (Habif, 2004). Common symptoms include pruritus (itching), burning, and pain.

The physical examination should address the distribution of primary and secondary skin lesions. **It is important to perform a thorough skin survey and not focus solely on the area of affected genital skin.** Most skin conditions begin with a characteristic primary lesion that is an important key to diagnosis. Precise description of this lesion includes documenting its color (red, brown, black, yellow, blue, or green) and morphology (macule, papule, plaque, nodule, pustule, vesicle, bulla, or wheal; Table 15–1) (Habif, 2004). Because of the mucosal nature of genital skin, papular and macular lesions may present as erosions in this area (Margolis, 2002). Secondary skin lesions develop as the skin condition evolves or are caused by scratching or superinfection. A secondary lesion should also be classified morphologically as a scale, crust, erosion, ulcer, atrophy, or scar (Table 15–2).

Once gross morphology is determined, laboratory testing may serve to confirm the diagnosis. To identify cutaneous fungi such as dermatophytes and *Candida* species, potassium hydroxide (KOH) or periodic acid–Schiff (PAS) staining may be applied to scraped or touched skin specimens. KOH dissolves keratin, leaving fungal hyphal walls prominently visible under the microscope. Likewise, Tzanck preparations may aid in identifying viral agents such as herpes simplex, varicella zoster, and molluscum contagiosum.

For difficult cases or those in which malignancy is suspected, skin biopsy may be indicated. A variety of techniques exists for this purpose, including curettage, punch, shave, incisional, and complete excisional biopsies. For small scrotal or phallic shaft lesions, these techniques can often be performed in the office setting under local anesthesia. For larger lesions or those involving the glans penis or urethral meatus, biopsy in the operating room is recommended.

DERMATOLOGIC THERAPY

Medical therapy for dermatologic conditions consists of a broad range of topical and systemic compounds.

For systemic therapy, useful drug classes include antibiotics, antifungals, antivirals, anti-inflammatories, and antipruritics. Less commonly used agents, including chemotherapeutic drugs (e.g., methotrexate, cyclophosphamide),

Table 15–1.

Primary Cutaneous Lesions

PRIMARY LESION	DESCRIPTION
Flat	
Macule	A circumscribed, **flat** discoloration that may be brown, blue, red, or hypopigmented
Elevated Solid	
Papule	An **elevated, solid** lesion up to 0.5 cm in diameter of variable color. Papules may become confluent to become plaques
Nodule	A circumscribed, **elevated solid** lesion >0.5 cm in diameter
Plaque	A circumscribed, **elevated**, superficial, **solid** lesion >0.5 cm in diameter
Fluid-Filled	
Vesicle	A circumscribed **collection of free fluid** up to 0.5 cm in diameter
Bulla	A circumscribed **collection of free fluid** >0.5 cm in diameter
Pustule	A circumscribed collection of leukocytes and free fluid (**pus**)
Wheal (hive)	A firm **erythematous plaque** resulting from **infiltration** of the dermis with fluid (may be transient)

From Habif TP. Clinical dermatology: a color guide to diagnosis and therapy. Edinburgh: Mosby; 2004.

Table 15–2.

Secondary Cutaneous Lesions

SECONDARY LESION	DESCRIPTION
Scale	Excess dead epidermal cells that are produced by abnormal keratinization and shedding
Crust	A collection of dried serum and cellular debris (a scab)
Erosion	A focal loss of epidermis. Erosions do not penetrate below the dermoepidermal junction and heal without scarring
Ulcer	A focal loss of epidermis and dermis which heals with scarring
Fissure	A linear loss of epidermis and dermis with sharply defined, vertical walls
Atrophy	A depression in the skin resulting from thinning of the epidermis or dermis
Scar	An abnormal formation of connective tissue implying dermal damage

From Habif TP. Clinical dermatology: a color guide to diagnosis and therapy. Edinburgh: Mosby; 2004.

immunosuppressants (e.g., azathioprine, cyclosporine, tacrolimus), and hydroxyurea, will be covered under specific disease entities.

A lack of familiarity with cutaneous diseases affecting the genitalia may lower the threshold that leads urologists to prescribe systemic antibiotics for these conditions. Unfortunately, these agents carry significant greater risks than topical preparations, including promotion of resistant organisms, interaction with other medications, and disruption of the normal bowel and vaginal flora. Similar caveats apply to systemic antifungal agents such as ketoconazole and fluconazole. Superficial dermatophytes, such as those causing tinea cruris, generally respond well to topical antifungal preparations. **Systemic antifungals are indicated for local infection with an extensive area of skin involved, disseminated mycoses with skin involvement, infection involving the hair follicles, or fungal infections in immunocompromised individuals** (Lesher and McConnell, 2003). In some cases, even in immunocompetent individuals, systemic antifungals are necessary to treat infections resistant to local therapy (Lesher, 1999).

Systemic anti-inflammatory agents, particularly the glucocorticosteroids (GCS), deserve additional attention. Oral GCS are absorbed in the jejunum, with peak plasma concentrations occurring in 30 to 90 minutes (Lester, 1989). Despite short plasma half-lives of 1 to 5 hours, the duration of effect of GCS lasts between 8 and 48 hours, depending on the agent (Nesbitt, 2003). These drugs have **widespread** anti-inflammatory effects. They release neutrophils from bone marrow but inhibit their movement to sites of inflammation in tissue. They also impair both T-cell activation and antigen presentation by dendritic cells (Nesbitt, 2003). **For short-term (≤3 weeks) treatment of dermatologic conditions such as allergic contact dermatitis** (Feldman, 1992), **a single morning dose of GCS is given to minimize suppression of the hypothalamic-pituitary-adrenal axis** (Myles, 1971). Prednisone is generally the GCS of choice due to its low cost, intermediate duration of action, and variety of dosage forms, although methylprednisolone may be substituted to reduce mineralocorticoid effects (Wolverton, 2001). **Longer-term treatment with systemic GCS may lead to a wide variety of adverse effects, including osteoporosis, cataract formation, hypertension, obesity, immunosuppression, and psychiatric changes** (Nesbitt, 2003).

Topical preparations are the mainstay of therapy for a wide range of cutaneous diseases affecting the genitalia. Urologists tend to be less familiar with the use of these medications than dermatologists. **Topical medications can be broken down into five general classes: emollients, anti-inflammatories, antibiotics, antifungals, and chemotherapeutic agents.**

Topical preparations have both active ingredients and a vehicle, which determines the rate at which the active ingredients are absorbed by the skin. Emollients restore water and lipids to the epidermis and are useful for dry skin diseases. Emollients should be applied to moist skin for maximal effect, such as after bathing. Preparations containing urea (e.g., Carmol, vanodine) or lactic acid (Lac-Hydrin, AmLactin) may be particularly potent hydrating agents (Habif, 2004).

Topical corticosteroids are potent anti-inflammatory agents available in a myriad of preparations and strengths. A detailed review of the use and dosing of topical corticosteroids is beyond the scope of this chapter, and the reader is directed to several excellent dermatology textbooks for more detail (Habif, 2004). **It is important to recognize that even topical corticosteroids can have significant adverse effects, from both systemic and local absorption. Local effects include epidermal atrophy, dermal changes (telangiectasias, hypopigmentation), allergic reactions, and alteration in the usual course of skin infections and infestations** (Burry, 1973). In most cases, atrophy is a reversible process that can be expected to resolve over the course of several months (Sneddon, 1976). Atrophy is particularly troublesome if corticosteroids are applied under the foreskin, which can serve as an occlusive "dressing" and enhance penetration of the drug (Fig. 15–1) (Goldman and Kitzmiller, 1973).

A variety of physical modalities have also been applied to treat dermatologic problems, including ultraviolet light therapy,



Figure 15–1. Steroid atrophy of penile shaft skin after application of corticosteroid under the foreskin for 8 weeks. (From Habif TP. Clinical dermatology. Edinburgh: Mosby; 2004. p. 36.)



Figure 15–2. Eczema involving the vulva. (From du Vivier A. Atlas of clinical dermatology. London: Churchill Livingstone; 2002. p. 687.)

Table 15–3.

Differential Diagnosis of Allergic Dermatitis

Eczema
Allergic dermatitis
Seborrheic dermatitis
Intertrigo
Contact dermatitis
Irritant dermatitis
Balanoposthitis
Zoon balanitis
Candidal-related illness
Impetigo
Herpes simplex
Herpes zoster
Drug reaction

From Margolis DJ. Cutaneous disease of the male external genitalia. In: Walsh PC, editor. Campbell's urology. Philadelphia: WB Saunders; 2002.

photodynamic therapy, laser therapy, and cryosurgery. Ultraviolet light therapy with UVB has been used to treat psoriasis, atopic dermatitis, and seborrheic dermatitis (Honigsmann and Schwarz, 2003). Psoralens, when combined with long-wave UVA radiation (PUVA therapy), generate a phototoxic effect beneficial for treating psoriasis (Honigsmann, 2001; Stern, 2007), vitiligo (Honigsmann and Schwarz, 2003), atopic dermatitis (Morison, 1992), and lichen planus (Honigsmann and Schwarz, 2003). Photodynamic therapy (PDT) involves the use of cytotoxic oxygen radicals generated from photoactivated molecules to achieve a therapeutic response (Tope and Shaffer, 2003; Braathen et al, 2007). PDT is a new arena of dermatologic therapy and holds promise for treating a variety of inflammatory and malignant skin conditions. Laser and cryosurgery play a relatively small role in the management of genital lesions, although the CO_2 laser has been used effectively to manage genital condyloma acuminata.

ALLERGIC DERMATITIS

Allergic or "eczematous" dermatitis consists of a group of allergy-mediated processes leading to pruritic skin lesions (Table 15–3).

Atopic Dermatitis (Eczema)

Atopic dermatitis (AD) is a chronic relapsing dermatitis with a predilection for skin flexures that is associated with intense pruritus and damage to the epidermis (Williams, 2005). **The characteristic lesions are erythematous papules and thin plaques with secondary excoriations** (Fig. 15–2) (Kang et al, 2003). In general, the lesions do not have a precise border as is common for papulosquamous disorders (Margolis, 2002). Although any age can be affected, 90% of AD patients manifest their condition before the age of 5 years (Rajka, 1989). AD is associated with susceptibility to irritants and proteins as well as the tendency to develop asthma and allergic rhinitis.

The genetic susceptibility to AD has been extensively explored. In a study of 372 AD patients, 73% had a positive family history for atopy. Likewise, twin concordance studies have demonstrated a risk of 0.86 for monozygotic twins to have AD as compared with only 0.21 for dizygotic twins. These findings have spurred an intense search for genes involved in atopy and AD (Wollenberg and Bieber, 2000), although, to date no single gene serves as a unique marker for the disease (Kang et al, 2003).

Intense pruritus is the hallmark of AD, and controlling the patient's urge to scratch is critical for successful treatment (Przybilla et al, 1994). Itching is often worse during evening hours and can be exacerbated by sweat or wool clothing

(Kang et al, 2003). Scratching of lesions may contribute to the clinical complications of AD, including superinfection with *Staphylococcus aureus* species (Ogawa et al, 1994). There is growing evidence that bacterial toxins may serve as superantigens that drive an inflammatory cascade sustaining AD (Skov and Baadsgaard, 2000; Skov et al, 2000).

Clinically, there is no pathognomonic laboratory test, biopsy result, or single clinical feature that allows the definitive diagnosis of AD. The association with a personal or family history of atopy is a critical clue to the diagnosis (Kang et al, 2003). For patients presenting with genital findings, extragenital involvement is commonplace.

A variety of "trigger factors" have been implicated in the exacerbation of AD, including chemicals, detergents, and household dust mites. Removal of these factors from the environment may be beneficial on an individualized basis. Dust mite exposure, in particular, has received significant attention in the literature. Although several studies have demonstrated modest improvement in AD with mite reduction (Kubota et al, 1992; Tan et al, 1996), others report that reduction is associated with no significant clinical benefit (Colloff et al, 1989; Gutgesell et al, 2001).

Treatments for AD include gentle cleaning with nonalkali soaps and the frequent use of emollients. Evaporation of liquid from the skin may trigger AD (Kang et al, 2003); thus very frequent bathing is not encouraged. Soaking may be helpful during episodes of bacterial super-infection but should be discontinued once the infection has resolved (Margolis, 2002). Topical corticosteroids may be needed to control pruritus but should only be used for short courses with a rapid taper to avoid local complications of skin atrophy and pigment changes. Topical macrolide immunomodulatory agents such as tacrolimus and pimecrolimus have shown efficacy in the treatment of AD (Meagher, et al, 2002; Nghiem et al, 2002; Luger and Paul, 2007; Leung et al, 2009), and may decrease the need for corticosteroids during long-term therapy (Zuberbier et al, 2007). Antihistamines such as diphenhydramine may be helpful in breaking the "itch-scratch cycle" in AD, particularly when given before bedtime (Kang et al, 2003). Oral antistaphylococcal drugs have not been shown to significantly improve AD in a recent randomized, double-blind trial (Ewing et al, 1998). Systemic treatment with corticosteroids, cyclosporine, methotrexate, or azathioprine may be indicated rarely for severe, widely disseminated cases (Cooper, 1993; Salek et al, 1993).

Contact Dermatitis

Contact dermatitis can be broken down into two distinct entities: irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). Although the mechanisms differ significantly, the clinical presentation of ICD and ACD may be similar. Most notably, the affected area is usually sharply limited to an area of skin exposure to an allergen or irritating chemical. The primary mode of treatment is to identify and reduce exposure to the offending agent.

ICD results from a direct cytotoxic effect of an irritant chemical touching the skin and is responsible for approximately 80% of contact dermatitis cases (Marks et al, 2002). Examples of offending agents include soaps, solvents, metal salts, and acid- or alkali-containing compounds. Occupational ICD is a serious public health problem and contributes to costs on the scale of $1 billion annually in the United States (Cohen, 2000). The clinical manifestations of ICD depend on the identity of the irritating substance as well as the duration of contact, concentration, temperature, pH, and location of exposure. Acute ICD, such as might be result from an occupational accident, generally peaks within minutes to hours after exposure and then begins to heal. Symptoms of burning, stinging, and soreness may be accompanied by erythema, edema, bullae, or frank necrosis in a sharply defined area corresponding to the exposed skin (Cohen and Bassiri-Tehrani, 2003). There are also a variety of subacute forms of ICD that result from repeated subthreshold skin insults. Pruritus is much more common in these more chronic conditions and the skin lesions are less well demarcated. The mainstay of treatment for ICD lies in avoiding skin contact with the causative irritants through the use of protective clothing, safe occupational practices, and the use of skin barriers such as ointments or emollients (Berndt et al, 2000).

In contrast, allergic contact dermatitis (ACD) represents a local type IV hypersensitivity reaction to a skin allergen to which an individual has been previously sensitized. The typical appearance is a well-demarcated pruritic eruption, which may manifest blistering or weeping in the acute phase or the development of scaly plaques more chronically (Mowad and Marks, 2003). In 2003 and 2009, the North American Contact Dermatitis Group (NACDG) reported a long list of common allergens implicated in ACD based on patch testing results (Zug et al, 2009). Patch testing is a simple technique of exposing an area of skin to a variety of potential allergens in a grid template (Fig. 15–3). Generally performed by dermatologists, patch testing can help to confirm the diagnosis of ACD and the allergen involved. The most common sensitizing allergen identified by the NACDG was nickel sulfate (Zug et al, 2009), which is a common component of costume jewelry and belt buckles (Fig. 15–4). Although traditionally a cause of earlobe dermatitis from pierced earrings, nickel sensitivity may be a potential cause of genital ACD due to the increasing prevalence of genital piercing. Other important allergens include textile dyes, topical antibiotics, perfumes, and topical corticosteroids. Oral



Figure 15–3. An example of patch testing with a positive response to nickel. (From Bolognia JL, Jorizzo JL, Rapini RP. Dermatology. Edinburgh: Mosby; 2003. p. 233.)



Figure 15–4. Contact dermatitis from belt buckle due to nickel allergy. (From Habif TP. Clinical dermatology, Edinburgh: Mosby; 2004. p. 94.)

antihistamines may be helpful for the symptomatic control of ACD in combination with removal of the inciting allergen.

Erythema Multiforme and Stephens-Johnson Syndrome

Erythema multiforme (EM) is a generalized skin disease that may involve the genitalia. **EM can be subdivided into minor and major forms.**

EM minor was first described in 1860 by an Austrian dermatologist, Ferdinand von Hebra (von Hebra, 1860). **It is an acute, self-limited skin disease characterized by the abrupt onset of symmetrical fixed red papules that may evolve into target lesions** (Weston, 1996). EM is a clinical rather than a histologic diagnosis. Papules and target lesions are usually grouped and can be present anywhere on the body, including the genitalia (Fig. 15–5A). There is also a predilection for involvement of the oral mucous membranes.

The majority of cases of EM minor are precipitated by herpesvirus type I and II (Schofield et al, 1993; Nikkels and Pierard, 2002), **with herpetic lesions usually preceding the development of target lesions by 10 to 14 days** (Lemak et al, 1986). Although continuous suppressive acyclovir may prevent EM episodes in patients with herpes infection (Tatnall et al, 1995), administration of the drug after development of target lesions is of no benefit (Huff, 1988). The natural history of EM minor is spontaneous resolution after several weeks without sequelae (Schofield et al, 1993), although recurrences are common (Huff and Weston, 1989). Oral antihistamines may provide symptomatic relief. For immunosuppressed patients, the time course of

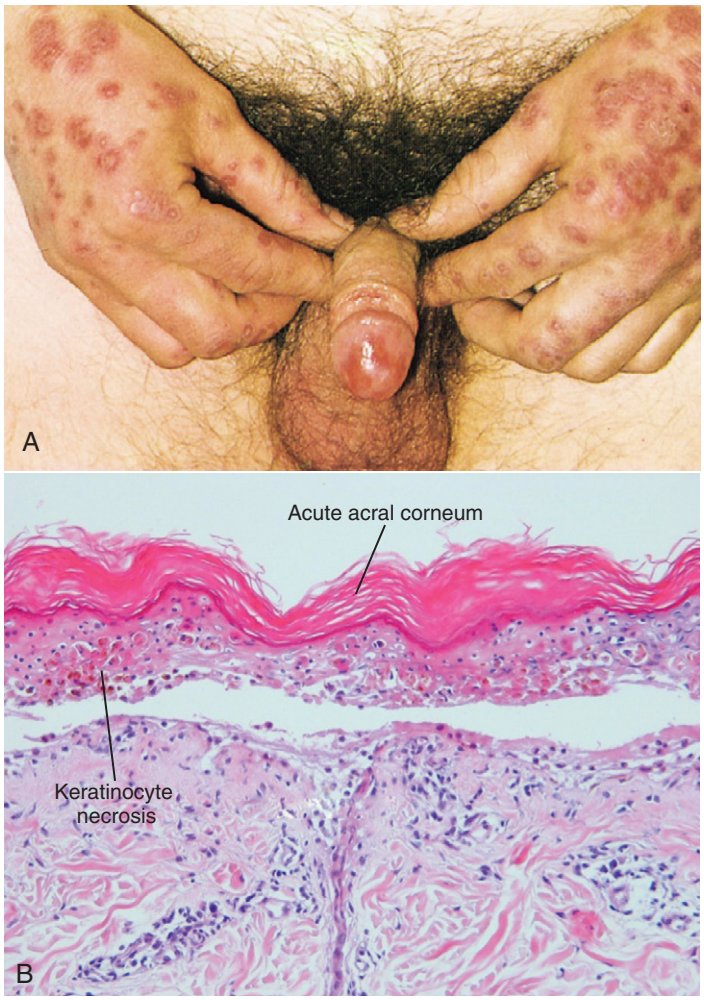


Figure 15–5. Erythema multiforme. **A,** Targetoid lesions of the hands and penis. **B,** Typical microscopic picture of erythema multiforme with a normal stratum corneum, necrotic keratinocytes in the epidermis and a lymphoid infiltrate. (**A,** From Korting GW. Practical dermatology of the genital region. Philadelphia: WB Saunders; 1981. p. 16; **B,** from Elston DM, Ferringer T. Dermatopathology. Edinburgh: WB Saunders; 2009. p. 147.)

EM minor outbreaks may be longer, and the frequency of recurrence may be greater (Schofield et al, 1993).

The major form of EM has been called Stevens-Johnson syndrome (SJS) in the past, although there remains some controversy as to whether EM major and SJS are distinct entities (Bachot and Roujeau, 2003; Williams and Conklin, 2005). SJS is a much more serious illness than EM minor with features similar to extensive skin burns (Parrillo, 2007). In its more severe forms, SJS may mimic life-threatening toxic epidermal necrolysis. Admission to the intensive care unit or burn unit may significantly reduce morbidity and mortality in this condition (Wolf et al, 2005). **Most patients with SJS have a prodromal upper respiratory illness (fever, cough, rhinitis, sore throat, and headache) that progresses after 1 to 14 days to the abrupt development of red macules with blister formation and areas of epidermal necrosis. Genital involvement includes erythema and erosions of the labia** (Fig. 15–6), **penis, and perianal region.**

A vast array of inciting factors has been implicated in the development of SJS, with drug exposures being the most commonly



Figure 15–6. Labial erosions in a case of Stevens-Johnson syndrome. (From Bolognia JL, Jorizzo JL, Rapini RP. Dermatology. Edinburgh: Mosby; 2003. p. 319.)

identified. Nonsteroidal anti-inflammatory agents are the most frequent offending agents followed by sulfonamides, tetracycline, penicillin, doxycycline, and anticonvulsants (Chan et al, 1990). In contrast to EM minor, there is rarely an association with an infectious agent (Weston, 2003). **SJS generally has a protracted course of 4 to 6 weeks and may have a mortality rate approaching 30%. Severe scarring of denuded skin may result in a range of complications including joint contractures, vaginal stenosis, urethral meatal stenosis, and anal strictures** (Brice et al, 1990; Weston, 2003). Treatment involves immediate removal of the offending drug and supportive care similar to the management of severe burns. There is currently no strong evidence for any specific therapy for SJS (Weston, 2003), and the role of systemic corticosteroids in treating SJS remains controversial (Rasmussen, 1976; Tripathi et al, 2000; Weston, 2003).

PAPULOSQUAMOUS DISORDERS

Papulosquamous disorders are a disparate group of diseases that share a common primary lesion: scaly papules and plaques (Table 15–4).

Psoriasis

Psoriasis is a common disease affecting up to 2% of the population (Christophers, 2001; Nestle et al, 2009). For patients with a predisposition, which is likely polygenic in nature, triggering factors such as trauma, infection, psychological stress, or new medications can elicit a flare up in the psoriatic phenotype. One third of affected patients have a family history of psoriasis (Melski and Stern, 1981; Hensler and Christophers, 1985; Margolis, 2002).

The characteristic lesion is a sharply demarcated erythematous plaque with silvery-white scales (van de Kerkhof, 2003). Its pattern can be limited to the elbows or knees,

Table 15–4.

Differential Diagnosis of Papulosquamous Lesions

Psoriasis
Seborrheic dermatitis
Dermatophyte infection
Erythrasma
Secondary syphilis
Pityriasis rosea
Discoid lupus
Mycosis fungoides
Lichen planus
Fixed drug eruption
Reiter syndrome
Pityriasis versicolor
Bowen disease
Extramammary Paget disease

From Margolis DJ. Cutaneous disease of the male external genitalia. In: Walsh PC, editor. Campbell's urology. Philadelphia: WB Saunders; 2002.

or distributed over the entire surface of the skin. Although psoriasis can appear at any age, two peaks of onset have been identified: 20 to 30 and 50 to 60 years of age. Patients complain of a significant impairment in their quality of life due to pruritus and the cosmetic impact of these visible plaques.

Psoriatic involvement of the genitalia is relatively common, although usually within the context of a generalized cutaneous disorder. **Patients may present with concerns for malignancy or sexually transmitted infection when psoriatic lesions are present on the genitals.** The presence of characteristic lesions on the elbows, knees, buttocks, nails, scalp, and umbilicus may help direct the diagnosis (Fig. 15–7A) (Margolis, 2002). When lesions are present in the inguinal folds and intergluteal cleft, scaling may be absent (so-called "inverse psoriasis") (Goldman, 2000). When evaluating nonscaling erythematous plaques in the inguinal folds, the diagnosis of fungal involvement (i.e., tinea or *Candida*) should be considered. In circumcised men, psoriatic plaques are often present on the glans and corona, whereas in uncircumcised men, lesions are commonly hidden under the preputial skin (Buechner, 2002). In some cases, however, psoriasis involves the entire penis and scrotum (Fig. 15–8).

Psoriasis is a chronic disease with a relapsing and remitting course. A variety of topical and systemic therapies have been developed and applied to this difficult problem. However, despite these therapies, as many as 40% of psoriasis sufferers express frustration with the ineffectiveness of current treatments (Krueger et al, 2001). **For genital psoriasis, the mainstay of therapy is the use of low-potency topical corticosteroid creams for short courses.** Examples include a preparation of 3% liquor carbonis detergens in 1% hydrocortisone cream (Fisher and Margesson, 1998). These preparations should not be used continuously for more than 2 weeks on thin genital skin or in areas occluded by skin folds (Margolis, 2002). Other topical therapies for psoriasis include vitamin D_3 analogues, dithranol, and retinoids, although these agents may be too irritating for genital skin application. Photochemotherapy combining an ingested psoralen with ultraviolet radiation (PUVA) has been used extensively to treat psoriasis (Stern, 2007). However, a dose-dependent increase in the risk of genital squamous cell carcinoma has been associated with high-dose PUVA therapy for psoriasis elsewhere on the body (Stern, 1990; Stern et al, 2002). Genital shielding during PUVA therapy is strongly recommended; therefore this modality is contraindicated for treating psoriatic lesions localized to genital skin.

For patients with extensive psoriasis, systemic therapy with methotrexate, cyclosporine, or retinoids may be appropriate. Experimental therapies that have shown promise in treating psoriasis include the 308-nm excimer laser (Gerber et al, 2003), vitamin D receptor ligands (Bos and Spuls, 2008), and antibodies or antisense oligonucleotides against T-lymphocyte surface molecules (Gottlieb et al, 2000a, 2000b), tumor necrosis factor (Chaudhari et al, 2001; Bos and Spuls, 2008), or intracellular adhesion molecules (Gottlieb et al, 2000a, 2000b).



Figure 15–7. Psoriasis. **A,** Silver scales on an erythematous base. **B,** Alternating neutrophils and parakeratosis in the stratum corneum of plaque psoriasis (sandwich sign). (**A,** From Callen JP, Greer DE, Hood AF, Paller AS. Color atlas of dermatology. Philadelphia: WB Saunders; 1993. p. 320; **B,** from Elston DM, Ferringer T. Dermatopathology. Edinburgh: WB Saunders; 2009. p. 152.)

Reiter Syndrome

This is a syndrome composed of urethritis, arthritis, ocular findings, oral ulcers, and skin lesions. The skin findings, particularly when present on the genitalia, may be mistaken for psoriatic lesions (Fig. 15–9). Reiter syndrome is more common in men than in women and is rarely diagnosed in children. **It is generally preceded by an episode of either urethritis (*Chlamydia, Gonococcus*) or gastrointestinal infection (*Yersinia, Salmonella, Shigella, Campylobacter, Neisseria,* or *Ureaplasma* species) and is more common in HIV-positive patients** (Rahman et al, 1992; Margolis, 2002; Wu and Schwartz, 2008). **There is a strong genetic association with the HLA-B27 haplotype.** Whether cross reactivity between bacterial antigens and HLA-B27 leads to autoimmunity in Reiter syndrome remains controversial (Ringrose, 1999; Yu and Kuipers, 2003).

Conjunctivitis is the most common ocular manifestation, although iritis, uveitis, glaucoma, and keratitis may occur. Polyarthritis and sacroiliitis are the most common orthopedic complaints and may lead to chronic disability in a small minority of cases (van de Kerkhof, 2003). Psoriasiform skin lesions present on



Figure 15–8. Psoriasis involving the entire penis and scrotum. (From Bolognia JL, Jorizzo JL, Rapini RP. Dermatology. Edinburgh: Mosby; 2003. p. 130.)

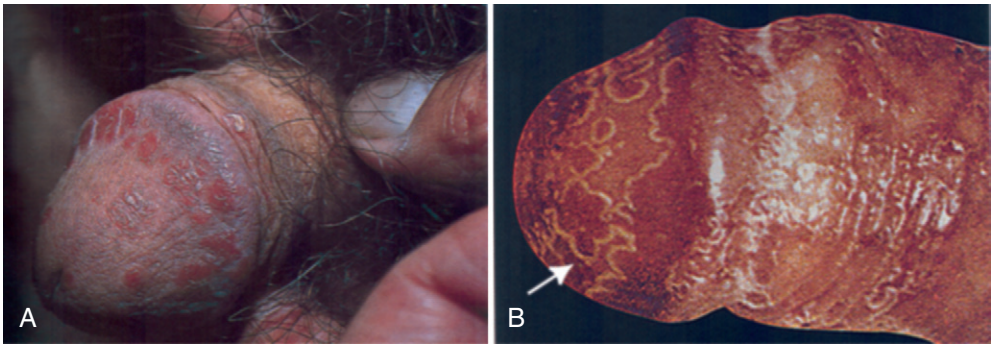


Figure 15–9. Comparison of psoriasis (**A**) and Reiter syndrome (**B;** *balanitis circinata*) involving the glans penis. Note the highly characteristic coalescence of lesions in this case of Reiter syndrome forming a wavy pattern (*white arrow*). (From Habif TP. Clinical dermatology. Edinburgh: Mosby; 2004. p. 217.)

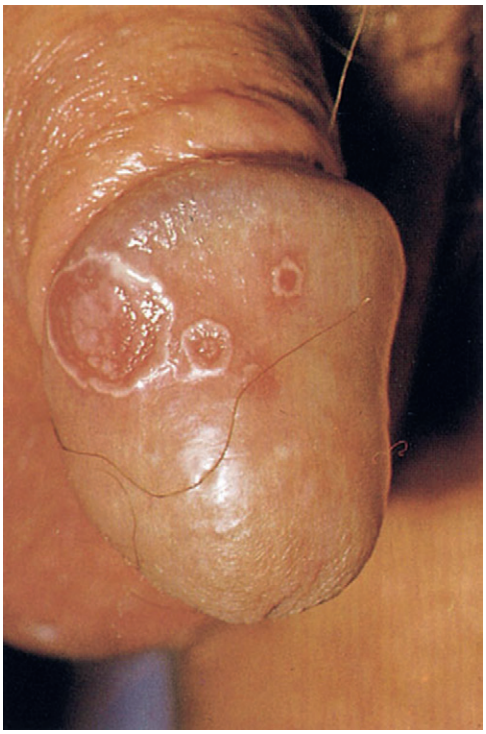


Figure 15–10. Erosive psoriasiform lesions of the glans penis (Reiter syndrome; *balanitis circinata*) may also lack the wavy pattern, making them difficult to differentiate from genital psoriasis. (From Callen JP, Greer DE, Hood AF, Paller AS. Color atlas of dermatology. Philadelphia: WB Saunders; 1993. p. 160.)

the penis are referred to as *balanitis circinata* (Fig. 15–10). **These lesions may be difficult to differentiate from psoriasis, and histologic analysis of biopsy specimens cannot consistently differentiate the two conditions** (Margolis, 2002). The course of Reiter syndrome involving the genitalia is usually self-limited, lasting a few weeks to months. Lesions may respond to topical corticosteroids, and systemic therapy is rarely required.

Lichen Planus

Lichen planus (LP), the prototype of the lichenoid dermatoses, is an idiopathic inflammatory disease of the skin and mucous membranes. The characteristic "lichenoid tissue reaction" is characterized by epidermal basal cell damage that is associated with a massive infiltration of mononuclear cells in the papillary dermis (Shiohara and Kano, 2003). Cutaneous LP may affect up to 1% of the adult population (Boyd and Neldner, 1991), and oral lesions may be present in as many as 4% (Scully et al, 1998). The pathogenesis of LP appears to be related to an autoimmune reaction against basal keratinocytes that express altered self-antigens on their surfaces (Morhenn, 1986).

The primary lesion of LP is a small, polygonal-shaped, violaceous, flat-topped papule. These lesions may be widely separated or coalesce into larger plaques, which may ulcerate, particularly on mucosal surfaces. LP commonly involves the flexor surfaces of the extremities, the trunk, the lumbosacral area, the oral mucosa, and the glans penis (Margolis, 2002). **On the genitalia, the clinical presentation of LP can be quite variable and includes isolated or grouped papules, a white reticular pattern, or an annular (ringlike) arrangement with or without ulceration** (Fig. 15–11). In some cases, the lesions appear to form linear patterns related to skin trauma (the so-called Koebner phenomenon; also seen with psoriasis). The differential diagnosis of LP includes squamous cell carcinoma, Bowen disease, Zoon balanitis, psoriasis, secondary syphilis, and lupus erythematosus, and biopsy may be necessary to establish the diagnosis, particularly when the lesions are ulcerated (Shiohara and Kano, 2003). Lichenoid reactions can also occur in response to ingested drugs and contact allergens, and a careful search for potential offending agents is appropriate.

The natural history of LP is benign, and the spontaneous resolution of cutaneous lesions has been observed in up to two thirds of cases after one year (Shiohara and Kano, 2003), **although the oral form may persist significantly longer** (Mignogna et al, 2000). Although bothersome pruritus is common with LP, asymptomatic lesions on the genitalia do not require treatment. The primary modality of treatment for symptomatic cutaneous LP is topical corticosteroids, with the caveats mentioned previously about their use on genital skin. There also appears to be a role for topical calcineurin inhibitors in the management of LP (Luger and Paul, 2007). For severe cases, systemic corticosteroids (15 to 20 mg per day; 2- to 6-week course [Boyd and Neldner, 1991]) have been shown to shorten the clearance time of LP lesions from 29 to 18 weeks (Cribier et al, 1998). Other systemic therapies for severe LP include cyclosporine, tacrolimus, griseofulvin, metronidazole, and acitretin (Ho et al, 1990; Boyd and Neldner, 1991; Cribier et al, 1998; Buyuk and Kavala, 2000; Madan and Griffiths, 2007), although randomized trials demonstrating efficacy are generally lacking.

Lichen Nitidus

Lichen nitidus (LN) is an unusual inflammatory eruption characterized by tiny, discrete, flesh-colored papules arranged in large clusters. Although there is some debate whether LN may represent a variant of LP (Aram, 1988), the two entities are histologically distinct. LN has a dense, well-circumscribed, lymphohistiocytic infiltrate closely apposed to the epidermis (Shiohara and Kano, 2003). Commonly involved sites include the flexor aspects of the upper extremities, the genitals, trunk, and dorsal aspects of the hands. Nail involvement is common. Similar to LP, the natural history of LN is one of spontaneous resolution, with the majority of patients (69%) manifesting disease for less than one year (Lapins et al, 1978). Patients should be reassured that these genital lesions are not infectious and should resolve with time. For symptomatic pruritus, genital lesions usually respond to topical corticosteroids and oral antihistamines (Shiohara and Kano, 2003).

Lichen Sclerosus

Lichen sclerosus et atrophicus (LS) is a chronic inflammatory disease with a predilection for the external genitalia. LS is 6 to 10 times more prevalent in women than in men, generally presenting around the time of menopause (Wojnarowska and Cooper, 2003). For patients with genital LS, 15% to 20% have extragenital disease (Powell and Wojnarowska, 1999). LS is a scarring disorder characterized by tissue pallor, loss of architecture, and hyperkeratosis (Fig. 15–12). It tends to affect older men (>60 years of age) (Ledwig and Weigand, 1989) and can be associated with pain during voiding or erection (Margolis, 2002). The glans penis and foreskin are usually affected, and the perianal involvement common in women is usually absent. Preputial scarring from LS can lead to phimosis, and circumcision is usually curative, although recurrence in the circumcision scar may occur. The late stage of this



Figure 15–11. Lichen planus. Various presentations of lichen planus on the male genitalia. **A** and **B,** Both individual and grouped purple papules on the penile shaft; some oriented in a linear pattern. **C,** A white reticular pattern sometimes seen in lichen planus. **D,** An annular (ring-like) arrangement with a shiny surface. **E,** Histologically, lichen planus is characterized by destruction of the basal layer, a sawtooth rete ridge pattern, the presence of Civatte bodies, and dermal melanocytes, and the absence of parakeratosis or eosinophils. (**A,** From Korting GW: Practical dermatology of the genital region. Philadelphia: WB Saunders; 1981. p. 29; **B** to **D,** from du Vivier A: Atlas of clinical dermatology. London: Churchill Livingstone; 2002. p. 100); **E,** from Elston DM, Ferringer T. Dermatopathology. Edinburgh: WB Saunders; 2009. p. 137.)

disease is called *balanitis xerotica obliterans*, which can involve the penile urethra and result in troublesome urethral stricture disease.

Despite the similarities in name, LS shares little in common with LP and LN other than pruritus and a predilection for the genital region. **Another critical distinction is that LS has been associated with squamous cell carcinoma of the penis, particularly those variants not associated with human papillomavirus, and may represent a premalignant condition** (Velazquez and Cubilla, 2003; Bleeker et al, 2009). LS has specific histologic features, including basal cell vacuolation, epidermal atrophy, dermal edema, collagen homogenization, and focal perivascular infiltrate of the papillary dermis, and plugging of the ostia of follicular and eccrine structures (Margolis, 2002). Biopsy is worthwhile both to confirm the diagnosis and exclude malignant change (Powell and Wojnarowska, 1999).

From a management standpoint, long-term follow-up of patients with LS is important due to the association with squamous cell carcinoma. The application of potent topical steroids (such as clobetasol propionate 0.05%) for long courses (3 months) is well established as a treatment for LS in women and may both improve symptoms and reverse the disease process (Dalziel et al, 1991) This regimen is contrary to the usual policy of avoiding long courses of steroid application to genital skin. The efficacy of similar approaches has not been confirmed in adult men, although benefits have been demonstrated in the pediatric age group (Kiss et al, 2001). A recent European, multicenter, phase II trial also

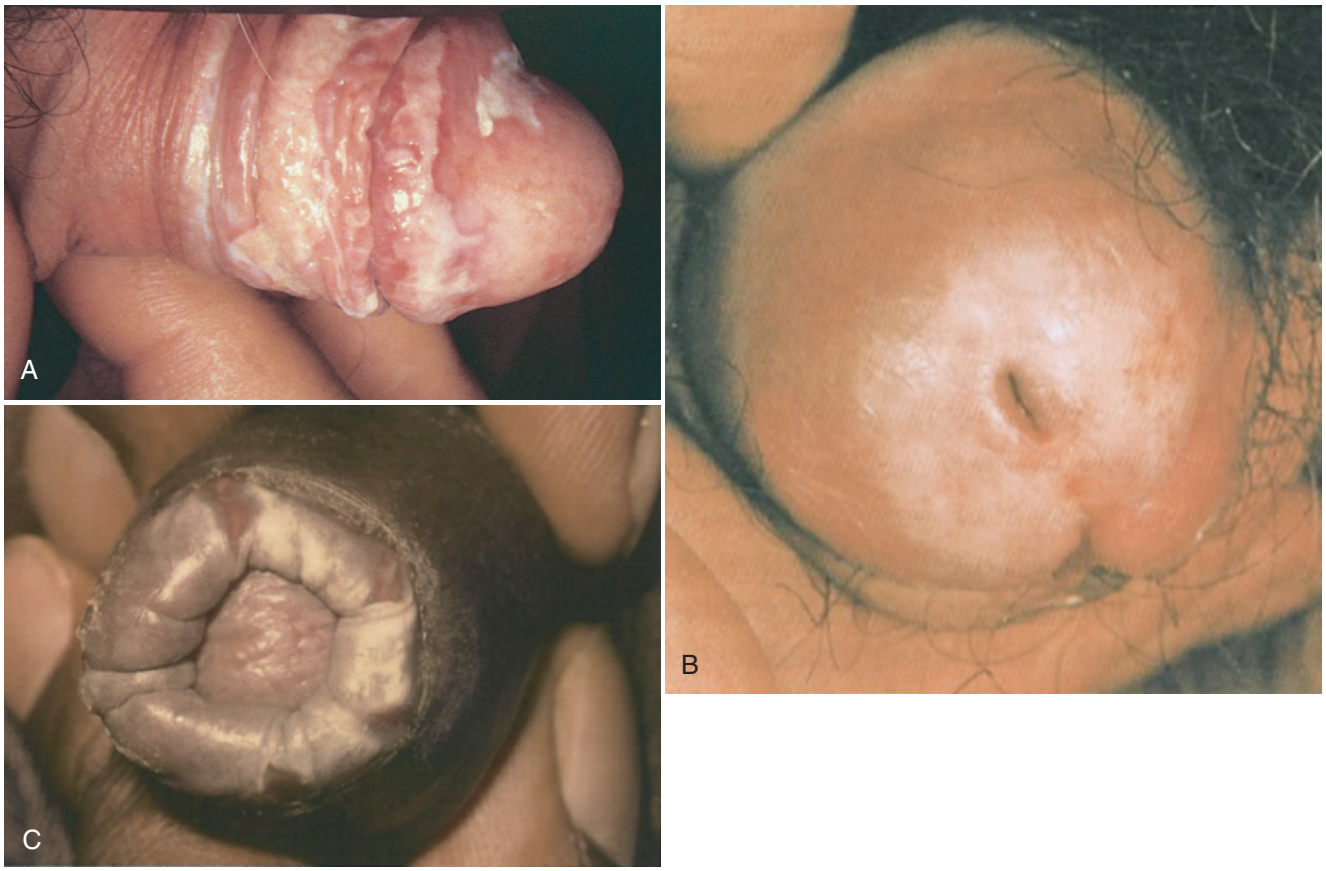


Figure 15–12. **A** to **C,** Lichen sclerosis et atrophicus (balanitis xerotica obliterans) of the penis. Note the erythematous and white plaques involving the penile shaft, preputial skin, and glans. (**A,** From Callen JP, Greer DE, Hood AF, Paller AS: Color atlas of dermatology. Philadelphia: WB Saunders; 1993. p. 327; **B,** from du Vivier A. Atlas of clinical dermatology. London: Churchill Livingstone; 2002. p. 716; **C,** from Bolognia JL, Jorizzo JL, Rapini RP. Dermatology. Edinburgh: Mosby; 2003. p. 1101.)

supported the safety and efficacy of topical tacrolimus in the treatment of long standing LS (Hengge et al, 2006).

Fixed Drug Eruption

A fixed drug eruption occurs in response to oral medications, usually 1 to 2 weeks after the first exposure, and commonly involves the lips, face, hands, feet, and genitalia (Fig. 15–13). After subsequent re-exposure to the drug, the reaction presents in the exact same location, usually within 24 hours (hence the term "fixed"). The most common medications causing this reaction are sulfonamides, nonsteroidal anti-inflammatory agents, barbiturates, tetracyclines, carbamazepine, phenolphthalein, salicylates, oral contraceptives, and salicylates (Kauppinen and Stubb, 1985; Stubb et al, 1989; Thankappan and Zachariah, 1991).

When present on the penile shaft or glans, these lesions are usually solitary inflammatory plaques, which may be erosive and painful (Margolis, 2002). On the genitalia, the differential diagnosis includes herpes simplex infection or an insect bite. Removing the offending agent usually results in resolution of the lesion, although postinflammatory brown pigmentation may remain.

Seborrheic Dermatitis

This is a common skin disease characterized by the presence of sharply demarcated pink-yellow to red-brown plaques with a flaky scale. It shares a variety of features in common with eczematous dermatitis and could easily be grouped in that category. Common dandruff is a mild form of seborrheic dermatitis (SD) localized to the scalp. It has a predilection for areas rich in sebaceous glands and is generally present only during the first few months of life or post-puberty, when sebaceous glands are active. Common areas affected include the scalp, eyebrows, nasolabial folds, ears, and chest although the anus, penis, and pubic areas may also be involved (Margolis, 2002). Circumcision may be somewhat protective against the development of SD. In one study of 357 patients, the risk of developing penile SD was 2.5 times greater in the uncircumcised state (Mallon et al, 2000).

Adult SD has a chronic relapsing course (Webster, 1991). **This condition is particularly common in patients with Parkinson disease, and up to 83% of AIDS patients may manifest SD** (Froschl et al, 1990; Gupta and Bluhm, 2004). SD may involve a significant proportion of the body surface area, particularly in immunosuppressed individuals. **Extensive and/or severe SD should raise concerns for possible underlying HIV infection** (Fritsch and Reider, 2003). SD may be pruritic, and differentiation from psoriasis may occasionally be problematic. Unlike psoriasis, however, SD rarely involves the nails and tends to have a thinner associated scale.

Controversy concerning the etiology of SD revolves around a possible autoimmune response to a component of normal skin flora, the yeast *Malassezia furfur* (*Pityrosporum ovale*). Although *M. furfur* can be isolated from the lesions of SD, the number of organisms is only about twice that observed in normal control skin (Nenoff et al, 2001). Likewise, severely SD-affected HIV patients do not harbor more organisms than HIV patients without

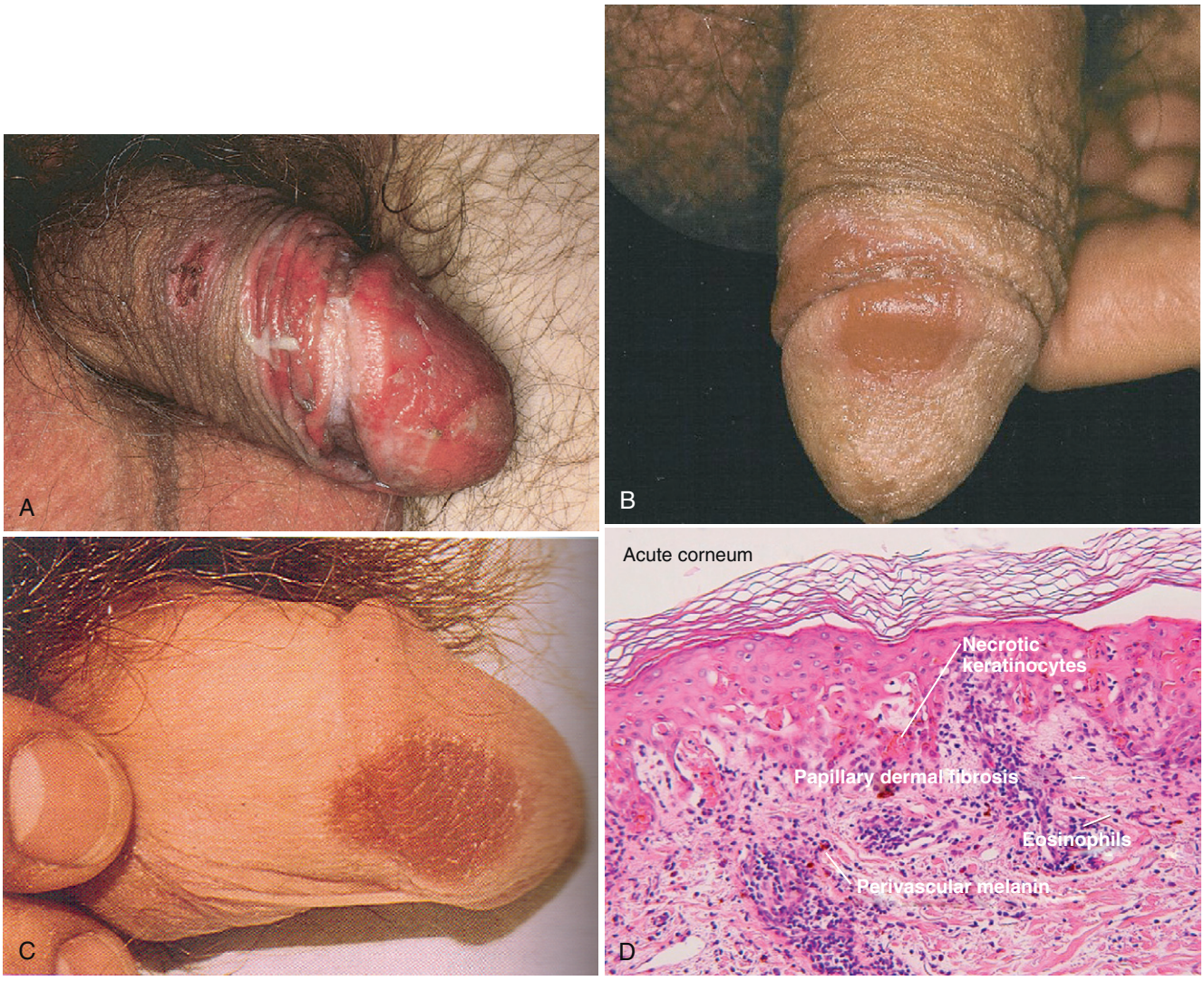


Figure 15–13. Fixed drug eruptions. **A** to **C,** Involvement of the penis. **D,** Histologic features include a normal stratum corneum with chronic changes in the superficial dermis including an eosinophilic infiltrate. (**A,** From Callen JP, Greer DE, Hood AF, Paller AS. Color atlas of dermatology. Philadelphia: WB Saunders; 1993. p. 160; **B,** from Bolognia JL, Jorizzo JL, Rapini RP. Dermatology. Edinburgh: Mosby; 2003. p. 345; **C,** from Habif TP: Clinical dermatology. Edinburgh: Mosby; 2004. p. 492; **D,** from Elston DM, Ferringer T. Dermatopathology. Edinburgh: WB Saunders; 2009. p. 149.)

manifestations of SD (Pechere et al, 1999). Another factor potentially linked to SD is an elevated level of triglycerides and cholesterol at the skin surface (Fritsch and Reider, 2003).

Creams containing topical antifungals (i.e., ketoconazole) are the mainstay of SD treatment on the body and have a 75% to 90% response rate (Faergemann, 2000; Fritsch and Reider, 2003). For hair-bearing areas, "antidandruff" shampoos containing zinc, salicylic acid, selenium sulfide, tar, ciclopirox olamine, or ketoconazole are effective (Margolis, 2002; Squire and Goode, 2002). Because of the relapsing nature of SD, treatment often must be repetitive. Low-potency topical corticosteroids may play a role during the initial treatment of severe cases but should not be the primary mode of treatment for this chronic condition due to local steroid side effects.

VESICOBULLOUS DISORDERS

Vesicobullous disorders are uncommon conditions often characterized by autoimmune damage to the epidermis or basement membrane (Table 15–5). On the genitalia, the rupture of blisters and bullae may leave behind erosions (Margolis, 2002).

Pemphigus Vulgaris

Pemphigus is a family of autoimmune blistering diseases characterized by intraepidermal blisters due to the loss of keratinocyte cell–cell adhesion (Martel and Joly, 2001). These blisters are located in the deep epidermis close to the basal cell layer. The proposed immunopathology includes the development of autoantibodies directed against keratinocyte cell surface markers and desmosomes (Amagai et al, 1996; Zhou et al, 1997; Joly et al, 2000).

Almost all pemphigus patients will have painful oral mucosal erosions, and over half will have cutaneous blisters that may involve the genitalia. Characteristic oral lesions are, therefore, an important clue to the diagnosis (Fig. 15–14). The cutaneous blisters are thin-walled and easily broken, leaving behind a painful erosion. The loss of epidermal cohesion seen in pemphigus leads to the characteristic

Table 15–5.

Differential Diagnosis of Vesicobullous Disorders

Bullous pemphigoid
Pemphigus vulgaris
Pemphigus foliaceus
Zoon balanitis
Behçet syndrome
Contact dermatitis
Dermatitis herpetiformis
Porphyria cutanea tarda
Herpes zoster
Herpes simplex
Lymphangioma circumscriptum
Impetigo
Fixed drug eruption
Factitial
Innocent trauma
Benign familial pemphigoid (Hailey-Hailey disease)

From Margolis DJ. Cutaneous disease of the male external genitalia. In: Walsh PC, editor. Campbell's urology. Philadelphia: WB Saunders; 2002.

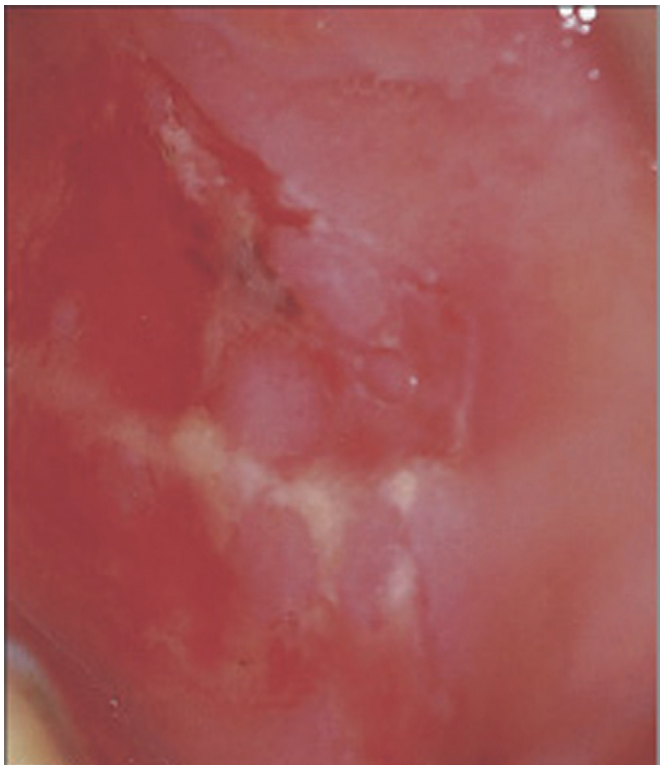


Figure 15–14. Characteristic painful oral mucosal erosions in pemphigus vulgaris. (From Bolognia JL, Jorizzo JL, Rapini RP. Dermatology. Edinburgh: Mosby; 2003. p. 455.)

Asboe-Hansen sign: spreading of fluid under the adjacent normal-appearing skin away from the direction of pressure on the blister (Amagai, 2003). In severe cases, without appropriate treatment, pemphigus may be fatal due to the loss of the epidermal barrier function of large areas of affected skin. Treatment for pemphigus usually depends on systemic corticosteroids, although minimization of steroid dose is an important goal to limit side effects. The addition of immunosuppressive agents such as azathioprine and cyclophosphamide may be beneficial due to their corticosteroid-sparing effect (Amagai, 2003).

Bullous Pemphigoid

Bullous pemphigoid (BP) is a subepidermal blistering disease that is more common in men and generally afflicts patients older than 60 years of age (Rzany and Weller, 2001). There is enrichment for specific HLA class II alleles in BP patients as compared with normal controls (Delgado et al, 1996), supporting an autoimmune mechanism of pathogenesis. In BP, autoantibodies against specific proteins involved in cell–cell adhesion (BP180, BP230) are present. These proteins are components of hemidesmosomes, structures that mediate epidermal–stromal adhesion. Binding of autoantibodies to these structures leads to complement activation and a cascade of events resulting in tissue damage, epidermal–dermal separation and blister formation (Kitajima et al, 1994; Lin et al, 1997).

Clinically, the presentation of BP can be highly variable. It generally begins with a non-bullous phase characterized by severe itching and nonspecific skin findings. As the disease progresses to the bullous phase, vesicles and blisters appear on normal skin or areas containing confluent erythematous plaques. The blisters are tense, tend to form on flexor surfaces, and may involve the inner thighs and genitalia (Fig. 15–15A). Mucous membranes may also be involved, although less commonly than in pemphigus. **The diagnosis is made by a combination of clinical, histologic, and, often most importantly, immunohistochemical features such as the deposition of IgG antibodies along the basement membrane** (Fig. 15–15B) (De Jong et al, 1996). Treatment of BP is similar to that described for pemphigus, with systemic corticosteroids and immunosuppressants playing primary roles (Kirtschig and Khumalo, 2004). For treatment-resistant cases, intravenous immunoglobulin or plasmapheresis may be beneficial (Hatano et al, 2003; Lee et al, 2003; Ruetter and Luger, 2004; Wetter et al, 2005).

Dermatitis Herpetiformis and Linear IgA Bullous Dermatosis

Both of these entities are blistering autoimmune skin diseases associated with the deposition of IgA antibodies at the basement membrane.

Dermatitis herpetiformis (DH) is a cutaneous manifestation of celiac disease and is generally associated with gluten sensitivity (Karpati, 2004). It is most commonly found in people of Northern European origin. There is a close association of DH with certain HLA class II DQ2 alleles (DQA1*0501, DQB1*02) (Reunala, 1998). Pruritic plaques, papules, and vesicles in a symmetrical distribution characterize DH. These vesicles may form "herpetiform" groups on an erythematous base. Patients may also complain of pain and burning over the lesions. Diagnosis can be confirmed by biopsy and direct immunofluorescence, which shows a granular pattern of IgA deposition at the basement membrane. Treatment includes the use of dapsone and a strict gluten-restricted diet (Frodin et al, 1981; Andersson and Mobacken, 1992).

Linear IgA bullous dermatosis (LABD), in contrast, is not associated with celiac disease. As the name implies, a linear pattern of antibody deposition at the basement membrane is found on immunohistochemistry testing in LABD (Fig. 15–16). Characteristic clinical features include vesicles and bullae arranged in a combination of circumferential and linear orientations. Treatment with either sulfapyridine or dapsone is usually effective in controlling LABD, and long-term spontaneous remission rates of 30% to 60% have been described (Wojnarowska et al, 1988).

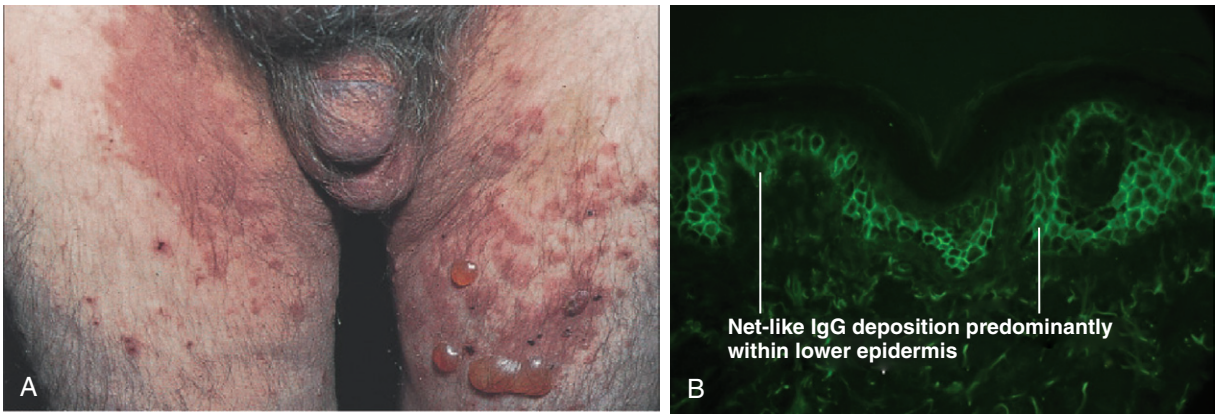


Figure 15–15. Bullous pemphigoid. **A,** Involvement of the inner thighs. Note the confluent plaques and tense blisters in the inguinal area. **B,** Direct immunofluorescence of bullous pemphigoid showing deposition of autoantibodies (IgG) at the dermoepidermal junction. (**A,** From Bolognia JL, Jorizzo JL, Rapini RP. Dermatology. Edinburgh: Mosby; 2003. p. 465; **B,** from Elston DM, Ferringer T. Dermatopathology. Edinburgh: WB Saunders; 2009. p. 169.)

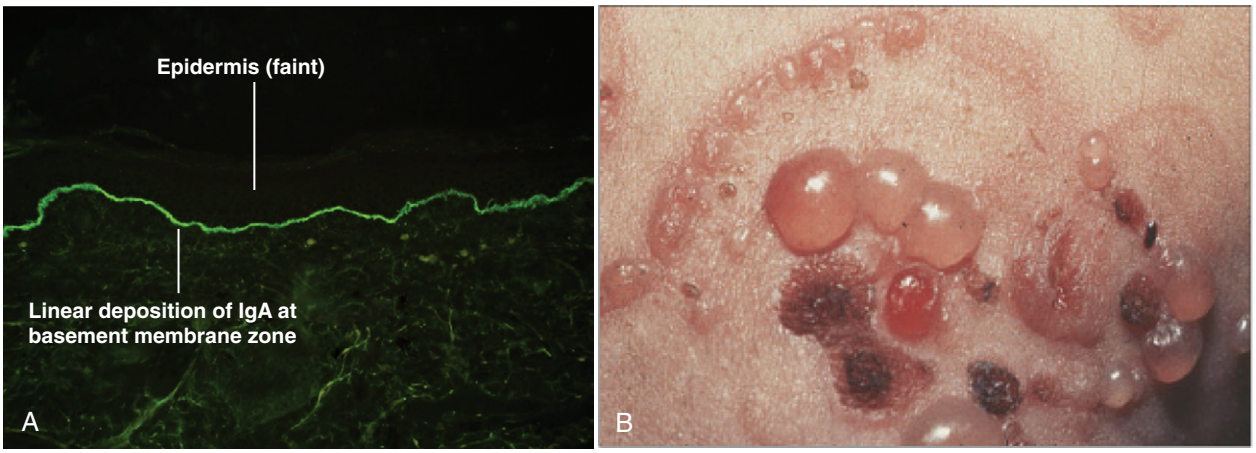


Figure 15–16. Linear IgA bullous dermatosis. **A,** Direct immunofluorescence showing linear deposition of IgA along the dermoepidermal junction. **B,** Typical circumferential and linear patterns of vesicles. (**A,** From Elston DM, Ferringer T. Dermatopathology. Edinburgh: WB Saunders; 2009. p. 170; **B,** from Bolognia JL, Jorizzo JL, Rapini RP. Dermatology. Edinburgh: Mosby; 2003. p. 485.)

Hailey-Hailey Disease

Hailey-Hailey disease (HH) is an autosomal-dominant blistering dermatosis that usually develops within the second or third decade of life (Burge, 1992). **It has a predilection for the intertriginous areas, including the groin and perianal region** (Fig. 15–17). In women, disease in the inframammary folds is common, although vulvar disease is unusual (Wieselthier and Pincus, 1993). Symptoms include an unfortunate combination of pruritus, pain, and a foul odor. As heat and sweat exacerbate the condition, HH tends to worsen during the summer months (Burge, 1992). Skin findings include confluent areas of vesicles and fragile blisters, which form due to aberrant keratinocyte cell adhesion. Lesions may be confined to the axilla or groin, and superinfection with yeast or bacteria may compound the problem. Histologic examination may be helpful in differentiating HH from impetigo, pemphigus, intertrigo, and Darier disease (Margolis, 2002). **Treatment includes wearing lightweight, breathable clothing to avoid friction and sweating. Lesions may respond to topical or intralesional corticosteroids, with the caveats mentioned previously about the use of these agents on intertriginous skin. For disease resistant to medical therapy, wide excision and skin grafting have been effective, as have local ablative techniques such as dermabrasion and laser vaporization** (Hamm et al, 1994; Christian and Moy, 1999; Hohl et al, 2003).

NONINFECTIOUS ULCERS

Genital ulcers can be a result of both infectious and noninfectious causes (Table 15–6).

Aphthous Ulcers and Behçet Disease

Aphthous ulcers are small, painful erosions that commonly involve the oral cavity but can occasionally be present on the genitalia. **When oral and genital aphthous ulcers are coexistent, the clinician should consider the diagnosis of Behçet disease (BD).** BD is a generalized relapsing and remitting, ulcerative, mucocutaneous disease that probably involves a genetic predisposition and an autoimmune mode of pathogenesis (Sakane, 1997; Mendes et al, 2009). Oxidative stress related to overproduction of superoxide radicals by neutrophils has also been implicated in the development of this condition (Freitas et al, 1998; Najim et al, 2007). BD has a high prevalence in Turkey (80 per 100,000) and Japan (10 per 100,000) but is quite rare in



Figure 15–17. Genital presentations of Hailey-Hailey disease. **A,** The vulva and groin are covered in a vesicular eruption which has become confluent and macerated. **B,** Erythematous plaque with maceration of the inguinal canal and scrotum. (**A,** From du Vivier A. Atlas of clinical dermatology. London: Churchill Livingstone; 2002. p. 688; **B,** from Bolognia JL, Jorizzo JL, Rapini RP. Dermatology. Edinburgh: Mosby; 2003. p. 830.)

Table 15–6.

Differential Diagnosis of Ulcers

Syphilis
Chancroid
Herpes simplex
Crohn disease
Aphthous ulcer
Behçet disease
Granuloma inguinale
Lymphogranuloma venereum
Factitial dermatitis
Wegener granulomatosis
Leukocytoclastic vasculitis
Pyoderma gangrenosum

From Margolis DJ. Cutaneous disease of the male external genitalia. In: Walsh PC, editor. Campbell's urology. Philadelphia: WB Saunders; 2002.

the United States (0.12 per 100,000) (Arbesfeld and Kurban, 1988). Affected individuals may also suffer from epididymitis, thrombophlebitis, aneurysms, and gastrointestinal, neurologic, and arthritic problems (Koc et al, 1992; Tuzun et al, 1997; Cetinel et al, 1998; Krause et al, 1999; Aykutlu et al, 2002; Margolis, 2002).

Mucocutaneous lesions of the oral cavity and genitalia (Fig. 15–18) **and ocular involvement (uveitis) form a triad of clinical features in BD. The genital lesions are larger and generally more painful than the oral lesions.** Optic involvement occurs in 90% of cases and may lead to blindness (Moschella, 2003). The Behçet's International Study Group has defined the diagnosis as recurrent oral ulceration plus any two of the following: recurrent genital ulceration, eye lesions, cutaneous lesions, and skin sensitivity to needle puncture (pathergy test) ("Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease," 1990). Other causes for genital ulceration, however, including aphthous ulcers, syphilis, herpes simplex, and chancroid must be considered before a diagnosis of BD is made (Margolis, 2002). The clinical course of BD is protean, and randomized controlled trials in support of specific therapy are currently limited (Kaklamani and Kaklamanis, 2001). A wide range of topical and systemic agents has been applied to treat BD with variable success, including corticosteroids, dapsone, colchicine, and immunosuppressants (Kose et al, 2009).

Pyoderma Gangrenosum

Pyoderma gangrenosum (PG) is an ulcerative skin disease associated with systemic illnesses including inflammatory bowel disease, arthritis, collagen vascular disease, and myeloproliferative disorders (Moschella, 2003). **It most commonly affects women between the second and fifth decade of life and likely has an autoimmune pathogenesis, given its association with other autoimmune diseases.** Between 20% and 50% of cases, however, are idiopathic.

The classic morphologic presentation of PG is painful cutaneous and mucous membrane ulceration, often with extensive loss of tissue and a purulent base (Fig. 15–19). Although unusual, PG can involve the penis, scrotum, vulva, and peristomal sites (Cairns et al, 1994). As with BD, no specific diagnostic laboratory test or histopathologic feature is pathognomonic for PG, although a history of underlying systemic disease may raise suspicion. Treatment includes a combination of local and systemic corticosteroid therapy with or without adjunctive immunosuppressants (i.e., cyclosporine) (Chow and Ho, 1996).

Traumatic Causes

Cutaneous lesions of the genitalia, including ulceration, can be caused by local trauma, which should be included in the differential diagnosis. **This can be either accidental ("innocent**



Figure 15–18. Scrotal (**A**), perianal (**B**), and (**C**) oral ulcers seen in Behçet disease. (**A,** From du Vivier A. Atlas of clinical dermatology. London: Churchill Livingstone; 2002. p. 713; **B** and **C,** from Bolognia JL, Jorizzo JL, Rapini RP. Dermatology. Edinburgh: Mosby; 2003. p. 419.)

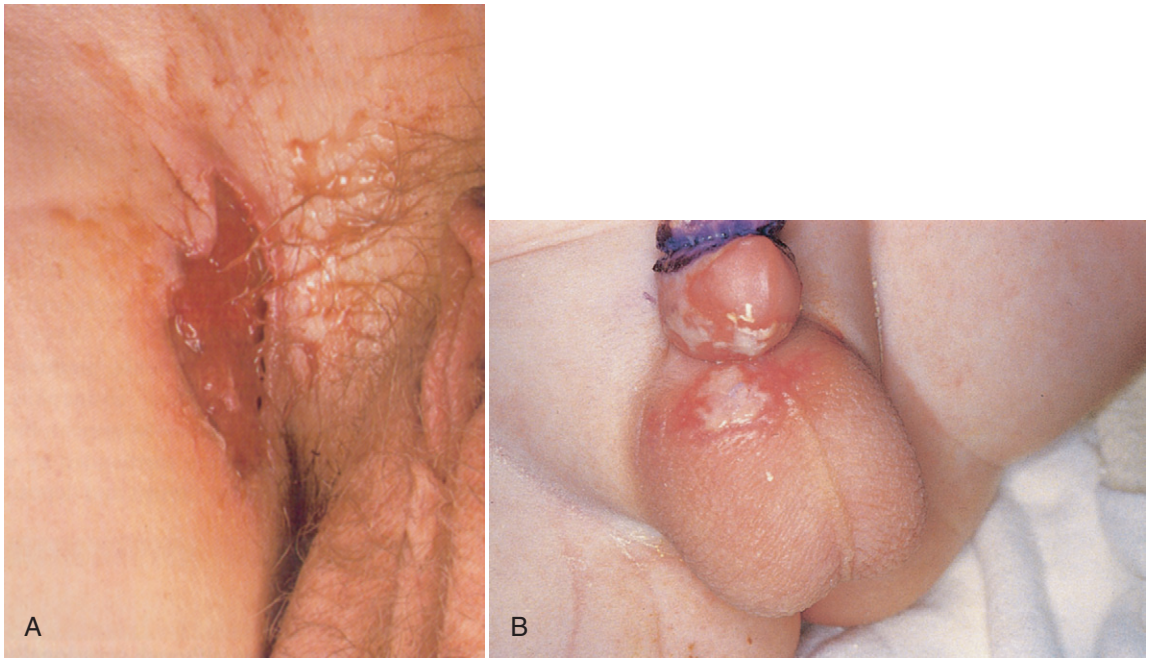


Figure 15–19. Pyoderma gangrenosum involving the inner thigh of a woman with rheumatoid arthritis (**A**) and (**B**) the penis and scrotum. (**A,** From du Vivier A. Atlas of clinical dermatology. London: Churchill Livingstone; 2002. p. 387; **B,** from Callen JP, Greer DE, Hood AF, Paller AS. Color atlas of dermatology. Philadelphia: WB Saunders; 1993. p. 330.)

trauma") or self-inflicted ("factitial dermatitis"). Accidental injuries may be a result of trauma during sexual practices, ornamentation (i.e., piercing) or unusual hygiene practices (i.e., cleaning) (Margolis, 2002). **Factitial dermatitis is a psychocutaneous disorder in which the individual self-inflicts cutaneous lesions usually for an unconscious motive.** An association between factitial dermatitis and borderline personality disorder appears to exist (Koblenzer, 2000). Other disorders to be considered include Munchausen syndrome by proxy and malingering, if secondary gain issues exist.

INFECTIONS AND INFESTATIONS

Sexually Transmitted Infections

Sexually transmitted infections with genital cutaneous manifestations include lymphogranuloma venereum, granuloma inguinale, herpes simplex, chancroid, molluscum contagiosum, human papillomavirus, and syphilis (Fig. 15–20). These conditions are covered in detail in Chapter 13.

Balanitis and Balanoposthitis

Balanitis is an inflammatory disorder of the glans penis. When the process involves the preputial skin in uncircumcised men it is termed balanoposthitis. In children, bacterial infections are the predominant cause. In adult men, the cause may be intertrigo, irritant contact dermatitis, local trauma, or candidal and bacterial infections (Fig. 15–21). Treatment includes removal of irritating agents, improved hygiene, topical antibiotics, and antifungals and, occasionally, short courses of low-potency topical corticosteroids (Margolis, 2002). When treatment fails, the differential should include neoplastic diseases, Zoon balanitis, psoriasis, and alternative infectious agents such as papillomavirus (Wikstrom et al, 1994). Balanoposthitis tends to occur in patients with phimosis, and circumcision may be curative in select recurrent cases.

Cellulitis and Erysipelas

Cellulitis is an infection of the deep dermis and subcutaneous tissues most commonly caused by gram-positive organisms (*S. pyogenes* and *S. aureus*) (Lewis, 1998). In immunocompetent individuals, organisms usually gain entry to the site of infection through a break in the skin barrier. In immunocompromised patients, a blood-borne route of infection is more common. Systemic signs of illness include fever, chills, and general malaise. Local signs include erythema (rubor), warmth (calor), pain (dolor), and swelling (tumor) at the site with indistinct borders (Fig. 15–22). Treatment includes systemic antibiotics with activity against *S. pyogenes* and *S. aureus* species. In cases associated with diabetes, mixed flora may be present and antibiotic coverage should be broadened. Marking the zone of cellulitis at the onset of therapy is an important step to allow progression and resolution of cellulites to be monitored during therapy.

Erysipelas is a superficial bacterial skin infection limited to the dermis with lymphatic involvement. It is commonly a disease at the extremes of age and often involves the face. In contrast to the cutaneous lesion of cellulitis, erysipelas generally has a raised and distinct border at the interface with normal skin. The causative organism is usually *S. pyogenes*.



Figure 15–20. Genital lesions associated with sexually transmitted infections. **A,** Herpes simplex virus. **B,** Molluscum contagiosum. **C,** Syphilitic chancre. **D,** Granuloma inguinale. **E,** Chancroid. **F,** Lymphogranuloma venereum. **G,** Condyloma acuminata. (From Callen JP, Greer DE, Hood AF, Paller AS. Color atlas of dermatology. Philadelphia: WB Saunders; 1993. p. 48, 328, 329, 233, 177, 331, and 330.)

Fournier Gangrene (Necrotizing Fasciitis of the Perineum)

Fournier gangrene (FG) is a potentially life-threatening progressive infection of the perineum and genitalia (Morpurgo and Galandiuk, 2002). In the genital region, most cases of FG are caused by mixed bacterial flora, which include gram-positive, gram-negative, and anaerobic bacteria. Risk factors for developing FG include alcoholism, diabetes, malnutrition, advanced age, and peripheral vascular disease. However, group A streptococcal necrotizing fasciitis can occur in healthy immunocompetent individuals.

The hallmark of FG is a rapid progression from the signs and symptoms of cellulitis to blister formation and foul-smelling necrotic lesions (Fig. 15–23). **Infection may spread along fascial planes, and hence the exterior skin findings may represent only a small proportion of the underlying infected and necrotic tissue. The diagnosis of FG is a surgical emergency as progression from genitalia to perineum to abdominal wall may occur extremely rapidly (often within hours). The exclusion of FG, therefore, should be a priority during every consultation for soft tissue infection of the genitalia.** Pain out of proportion to the visible extent of infection should raise suspicion for FG. The skin may also have a grayish cast or fetid odor uncharacteristic of uncomplicated genital cellulitis. Imaging of the genitalia with



Figure 15–21. Candidal balanoposthitis. (From Korting GW. Practical dermatology of the genital region. Philadelphia: WB Saunders; 1981. p. 159.)



Figure 15–22. Penoscrotal cellulitis. (From Korting GW. Practical dermatology of the genital region. Philadelphia: WB Saunders; 1981. p. 37.)

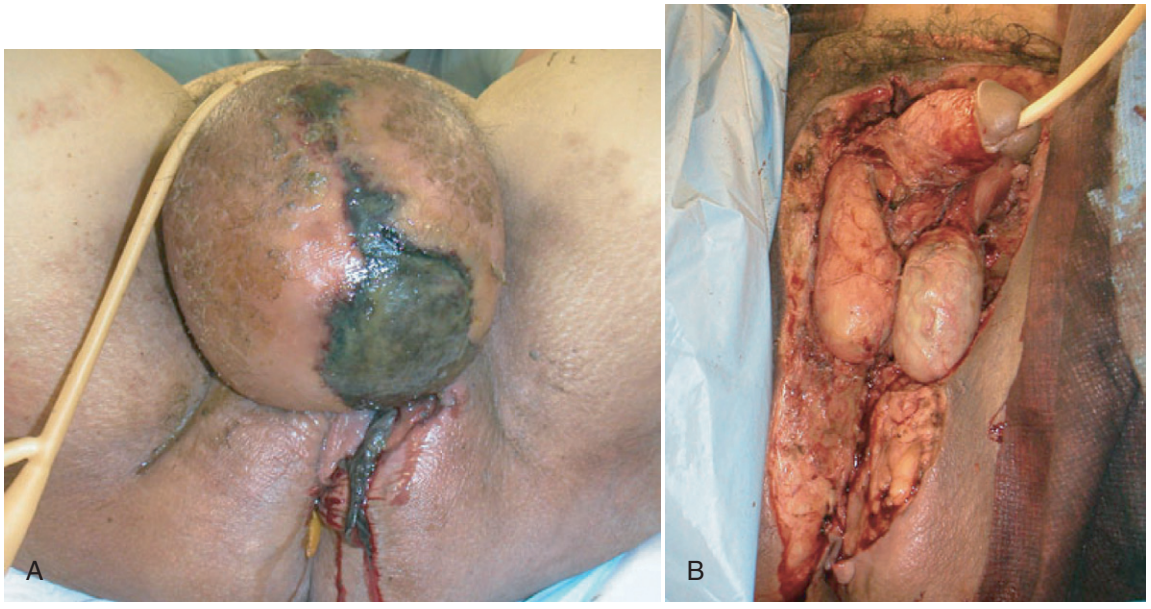


Figure 15–23. Fournier gangrene of the scrotum. **A,** Surface appearance of scrotum and perineum showing area of frank necrosis. **B,** Extent of soft tissue debridement required to achieve margins of viable tissue. Note that the testes within their tunica vaginalis compartment are spared.

plain radiographs or computed tomography (Amendola et al, 1994) may demonstrate gas bubbles within the tissue, although the delay associated with imaging should not delay surgical intervention in obvious cases.

Treatment involves a combination of broad-spectrum antibiotics and extensive surgical debridement to margins of healthy bleeding tissue. These patients will often require a second-look operation after 24 to 48 hours to exclude further disease progression (Gurdal et al, 2003). During surgical debridement for scrotal FG, the testicles and other structures within the tunica vaginalis can almost always be spared, although loss of tissue in the abdominal wall may be extensive due to bacterial spread along fascial planes. The indications for adjunctive hyperbaric oxygen therapy in FG remain controversial, although several groups have reported favorable results (Dahm et al, 2000; Eke, 2000; Jallali et al, 2005). There may also be a potential benefit to the use of vacuum-assisted closure devices in FG (Czymek et al, 2009). However, despite aggressive modern management, the mortality of FG may be as high as 16% to 40% (Dahm et al, 2000; Eke, 2000; Blume et al, 2003; Yeniyol et al, 2004; Sorensen et al, 2009).

Folliculitus

Folliculitis is a common disorder characterized by perifollicular pustules on an erythematous base (Kelly, 2003). It occurs most frequently in heavily hair-bearing areas such as the scalp, beard, axilla, groin, and buttocks, and can be exacerbated by local trauma from shaving, rubbing, or clothing irritation (Margolis, 2002). Patients may complain of pruritus or pain over the area or symptoms may be absent. Cultures are generally negative, although a variety of infectious organisms have been associated with folliculitis, including *S. aureus*, *Pseudomonas* sp., fungi, and herpes simplex virus. Folliculitis has also been associated with the use of contaminated hot tubs and swimming pools, with the offending organism usually *Pseudomonas aeruginosa* (Fig. 15–24) (Gregory and Schaffner, 1987; Rolston and Bodey, 1992). Treatment for folliculitis includes good hygiene, removal of offending irritants, and appropriate topical or systemic antiviral, antibiotic, or antifungal agents.



Figure 15–24. Pseudomonal folliculitis caused by the use of a hot tub. (From Bolognia JL, Jorizzo JL, Rapini RP. Dermatology. Edinburgh: Mosby; 2003. p. 554.)

Furunculosis

Both furuncles and abscesses are walled-off collections of pus. **Although abscesses can occur anywhere on the body, a furuncle is by definition associated with a hair follicle.** Furuncles tend to occur in areas prone to minor trauma, including the groin and buttocks (Fig. 15–25). *S. aureus* is the most common causative organism, although anaerobes may be present. Risk factors include diabetes mellitus, obesity, poor hygiene, and immunosuppression (Brook and Finegold, 1981). Warm compresses may be beneficial, and larger lesions may require incision and drainage as for any abscess. When there is associated cellulitis, a systemic antibiotic with activity against staphylococci should be given.



Figure 15–25. A large furuncle located on the buttocks. (From Habif TP. Clinical dermatology. Edinburgh: Mosby; 2004. p. 284.)

Hidradenitis Suppurativa (Acne Inversa)

Hidradenitis suppurativa (HS) is a chronic disease of apocrine gland-bearing skin with a predilection for the axillae and anogenital regions (Kelly, 2003; Alikhan et al, 2009). **It generally begins after puberty and a familial form with an autosomal-dominant pattern of inheritance has been described** (Von Der Werth et al, 2000). Originally believed to be a disease of apocrine glands, HS is now thought to be an epithelial disorder of hair follicles (Jansen et al, 2001). Although superinfection of HS lesions may occur, bacterial infection does not appear to be the primary initiator. During the pathogenesis of HS, hair follicles become plugged and swollen. **Rupture of follicular contents (including bacteria and keratin) into the surrounding dermis initiates a marked**

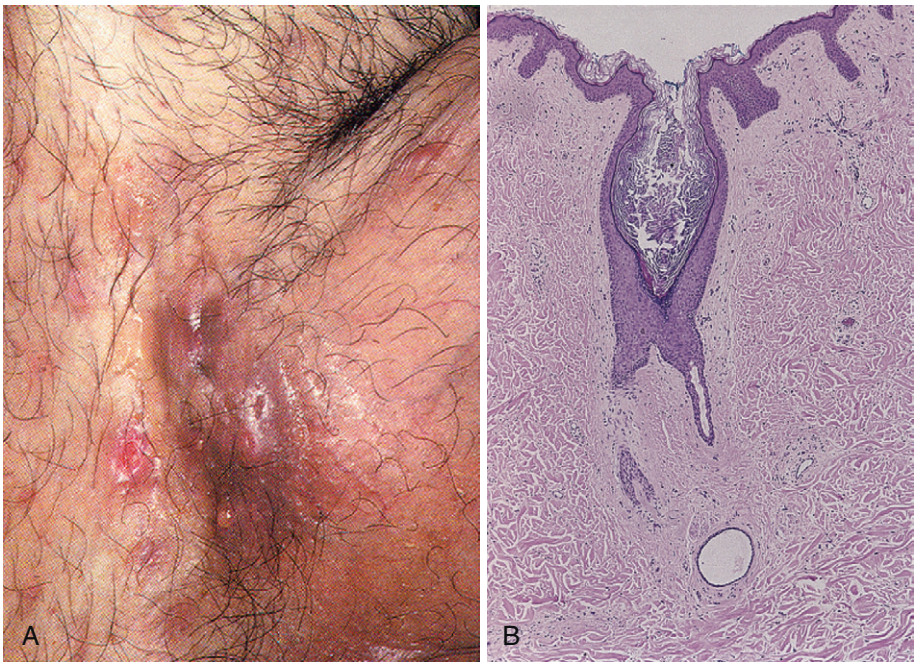


Figure 15–26. Hidradenitis suppurativa. **A,** Characteristic painful papules and draining sinus tracts. **B,** Histology shows follicular plugging and connection to a dilated apocrine duct. (**A,** From du Vivier A. Atlas of clinical dermatology. London: Churchill Livingstone; 2002. p. 712; **B,** from Bolognia JL, Jorizzo JL, Rapini RP. Dermatology. St. Louis: Elsevier; 2008. Figure 39.13.)

inflammatory response with the formation of abscesses and sinus tracts (Slade et al, 2003).

The clinical features of HS include painful inflammatory nodules and sterile abscesses developing in the axillae, groin, perianal, and inframammary areas (Fig. 15–26) (Kelly, 2003). Over time, draining sinus tracts and hypertrophic scars develop. Serious complications of HS can occur, including hypoproteinemia, secondary amyloidosis, the development of fistulae to the urethra (Gronau and Pannek, 2002); bladder, peritoneum, and rectum (Nadgir et al, 2001); and squamous cell carcinoma in areas of heavy scarring (Altunay et al, 2002; Rosenzweig et al, 2005).

Treatment of HS includes improvement in hygiene, weight reduction, and efforts to minimize friction and moisture in affected areas (i.e., loose undergarments, absorbent powder) (Kelly, 2003). Topical clindamycin or the combination of oral clindamycin and oral rifampicin may be beneficial in some patients (Gener et al, 2009). In a double-blind randomized trial, systemic therapy with tetracycline was no more effective than topical clindamycin in HS (Jemec and Wendelboe, 1998). Systemic corticosteroids may improve HS, but relapse is the rule after cessation of therapy (Slade et al, 2003). Lithium may exacerbate HS or limit its response to conventional medical therapy (Gupta et al, 1995). Although recurrent incision and drainage of HS lesions is discouraged, wide excision and skin grafting has been effective (Rompel and Petres, 2000; Bocchini et al, 2003). A variety of new approaches, including the use of the CO_2 and Nd:YAG lasers to treat HS, are under investigation (Lapins et al, 1994; Madan et al, 2008; Tierney et al, 2009).

Corynebacterial Infection (Trichomycosis Axillaris and Erythrasma)

Trichomycosis axillaris (TA) is a superficial bacterial infection of axillary and pubic hair caused by *Corynebacteria*. Yellow, red, or black nodules are visible on the hair shafts (Fig. 15–27), and there is frequently a characteristic odor (Blume et al, 2003). There is an association with hyperhidrosis (Margolis, 2002). The differential diagnosis includes infestation with pediculosis pubis or fungal infection (piedra) (Avram et al, 1987), although examination with magnification can generally distinguish TA from these conditions. Shaving can provide immediate improvement, and antibacterial soaps may prevent further infection (Blume et al, 2003). For pubic TA, clindamycin gel, bacitracin, and oral erythromycin have also proven effective (Bargman, 1984; Blume et al, 2003).

Erythrasma is a *Corynebacterium minutissimum* infection of the skin that results in sharply bordered, red-brown, scaling eruptions in moist areas including the groin and axilla. These lesions may be pruritic or asymptomatic and may be confused with dermatophyte infection (tinea cruris) (Sindhuphak et al, 1985). Under a Wood light, the lesions show a characteristic bright coral-red fluorescence (see Fig. 15–27) (Halprin, 1967). Effective treatments include antibacterial soaps, topical aluminum chloride, topical clindamycin, miconazole cream, and oral erythromycin (Holdiness, 2002).

Ecthyma Gangrenosum

Ecthyma gangrenosum (EG) is a rare cutaneous manifestation of pseudomonal septicemia that presents most commonly on the anogenital area in debilitated or immunosuppressed patients. The lesions of EG are tender, grouped, erythematous macules that may progress to form bullae or rupture to produce a gangrenous ulcer (Fig. 15–28) (Blume et al, 2003). On histologic examination, necrotizing vasculitis and gram-negative organisms are present. The differential diagnosis includes pyoderma gangrenosum, necrotizing vasculitis, cryoglobulinemia, and septic emboli containing other organisms, including *Candida, Aspergillus, Citrobacter, Escherichia coli, Aeromonas hydrophila,* and *Fusarium* (Altwegg and Geiss, 1989; Martino et al, 1994; Gucluer et al, 1999; Reich et al, 2004). Consistent with the underlying sepsis, EG carries a poor prognosis, and immediate treatment with intravenous antipseudomonal antibiotics is indicated. Wound debridement may also be necessary (Collini et al, 1986).



Figure 15–27. Corynebacterial infections of the skin. **A,** Trichomycosis axillaris. **B** and **C,** Erythrasma under white light (**B**) and Wood lamp (**C**) showing coral-red fluorescence. (From Bolognia JL, Jorizzo JL, Rapini RP. Dermatology. Edinburgh: Mosby; 2003. p. 1128–9.)

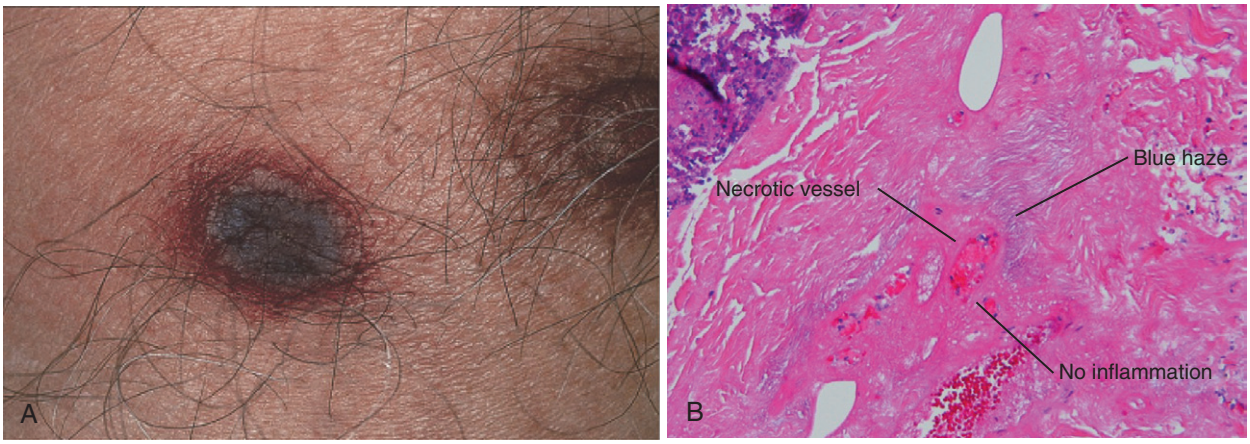


Figure 15–28. Ecthyma gangrenosum. **A,** Involvement on the chest wall. Note the necrotic center and erythematous border around the lesion. **B,** Histologically, ecthyma gangrenosum is characterized by necrotic vessels surrounded by a "blue haze" of organisms. (**A,** From Bolognia JL, Jorizzo JL, Rapini RP. Dermatology. Edinburgh, Mosby, 2003. p. 1132; **B,** from Elston DM, Ferringer T. Dermatopathology. Edinburgh, WB Saunders, 2009. p. 263.)



Figure 15–29. Candidal intertrigo with erythema, areas of tissue maceration and satellite lesions. (From Callen JP, Greer DE, Hood AF, Paller AS. Color atlas of dermatology. Philadelphia: WB Saunders; 1993. p. 318.)

Candidal Intertrigo

Fungal infection of macerated skin folds can occur with candidal species and involve the finger webs and intertriginous areas. Affected pruritic skin is reddened, and there may be characteristic satellite lesions present (Fig. 15–29). The differential diagnosis includes dermatophyte infection (tinea cruris), pemphigoid, psoriasis, seborrheic dermatitis, and contact dermatitis (Margolis, 2002). Fungal forms can be seen in scraped skin preparations after treatment with KOH, and culture is usually unnecessary. Topical treatment with imidazoles for at least 2 weeks is usually necessary for intertrigo, and occasionally oral antifungals are required (Cullin, 1977). Maneuvers to decrease moisture and skin maceration, such as the use of drying powders and loose clothing, may also help prevent relapse.

Dermatophyte Infection

Dermatophytes are fungi of three genera (*Trichophyton, Microsporum, Epidermophyton)* that have the propensity to invade and grow within keratinized tissues such as the skin, hair, and nails. These fungi produce keratinases that break down keratin and facilitate invasion (Viani et al, 2001). In addition, mannans in the cell wall of some dermatophytes have immunoinhibitory effects (Dahl, 1994).

Tinea cruris is the term given to dermatophyte infection of the groin and genital area and is commonly known as "jock itch." More common in males than females, this condition is favored by hot, humid environments and concomitant dermatophyte infection of the feet (*tinea pedis)*. Obesity may also be a significant risk factor (Scheinfeld, 2004). The inner thighs and inguinal region are the most commonly affected areas, and the scrotum and penis are usually spared in men. **Significant scrotal involvement should raise suspicion for cutaneous candidiasis as an alternative diagnosis** (Sobera and Elewski, 2003). Characteristic lesions in tinea cruris are sharply demarcated with a raised erythematous border (Fig. 15–30) and may be intensely pruritic. A variety of disorders can mimic dermatophytes infection, including seborrheic dermatitis, psoriasis, contact dermatitis, and erythrasma. The diagnosis of fungal infection can be confirmed with skin scrapings and a KOH preparation.

Good hygienic practices can be beneficial in preventing recurrent disease, including wearing loose clothing, cleaning of contaminated garments, weight reduction, and the use of topical powders to keep the intertriginous areas dry (Sobera and Elewski, 2003). Topical antifungal preparations are the primary agents for treatment, with the powdered forms having the added benefit of drying moist areas. **Care should be taken to treat only active disease and not the postinflammatory hyperpigmentation that can occur with recurrent chronic dermatophyte infection** (Margolis, 2002). Systemic antifungals are rarely necessary to treat groin infection with dermatophytes.

Infestation

Pediculosis pubis and scabies (*Sarcoptes scabiei*) are the most common infestations involving the genital region.

Infestation with the crab louse (*Phthirus pubis)* causes pediculosis pubis, a pruritic disorder of the genitalia that may coexist with other sexually transmitted infections (Opaneye et al, 1993; Varela et al, 2003). In one study of adolescent males, patients with pediculosis pubis had a more than twofold-higher risk of concomitant gonorrhea or chlamydial infection than normal controls (Pierzchalski et al, 2002). Louse infestation is not limited to the genitals and may involve other hair-bearing areas such as the eyelashes, beard, and axillae (Meinking, 1999). The diagnosis is confirmed by identification of crab lice attached to hairs (Fig. 15–31), often with associated perifollicular erythema. **Transmission of pediculosis pubis is usually through sexual contact, although contaminated clothing, bedding, and towels have also been implicated in some cases** (Meinking, 1999). **The standard treatment is application of 5% permethrin cream overnight to all affected hair-bearing areas with a repeat application one week later** (Meinking et al, 2003). Note that the second application of permethrin is important, as the rate of treatment success with a single application may be as low as 57% (Kalter et al, 1987). For rare cases refractory to topical therapy, or those involving the eyelashes (*tinea palpebrum)*, the addition of oral ivermectin may be curative (Burkhart and Burkhart, 2000).

Another important infestation involving the genitalia is scabies, caused by the female itch mite *Sarcoptes scabiei*. **Scabies is a worldwide problem, and factors such as overcrowding, delayed treatment of primary cases, and poor public awareness encourage spread** (Meinking et al, 2003). Transmission is common between close contacts and family members (Burkhart et al, 2000). The number of mites living on an immunocompetent host is usually small (<100) (Arlian et al, 1988), although far greater numbers may be recovered in cases of immunosuppression (so-called "crusted scabies"). The incubation period before symptoms develop after infestation can vary from days to months in duration.

Severe pruritus is the hallmark of scabies, often accentuated at night or after bathing (Meinking et al, 2003). In both sexes, the genital areas are commonly affected. Small



Figure 15–30. Dermatophyte infection. **A,** *Tinea cruris* showing areas of postinflammatory hyperpigmentation and active infection at the border of the lesions. **B,** Histologically, fungal hyphae are localized within a compact stratum corneum layer. **C,** A KOH preparation from a scraping showing fungal forms. (**A,** From Callen JP, Greer DE, Hood AF, Paller AS. Color atlas of dermatology. Philadelphia: WB Saunders; 1993. p. 318; **B** and **C,** from Elston DM, Ferringer T. Dermatopathology. Edinburgh: WB Saunders; 2009. p. 275.)



Figure 15–31. Pediculosis pubis. Several crab lice are visible. (From du Vivier A. Atlas of clinical dermatology. London: Churchill Livingstone; 2002. p. 338.)

erythematous papules are present and excoriations with secondary bacterial infection may occur (Fig. 15–32). **Thin, gray or white burrows may be visible and are pathognomonic for scabies infestation.** In the absence of visible burrows, a broad differential must be considered, including atopic dermatitis, pyoderma, psoriasis, and other insect bites. As with pediculosis pubis, the treatment of choice for scabies is 5% permethrin cream applied to the entire body overnight with a second application 1 week later. An alternative scabicide, lindane, is not favored due to both central nervous system (CNS) toxicity in children and a rising rate of resistance among mites (Purvis and Tyring, 1991; Elgart, 1996; Boix et al, 1997). Oral ivermectin is an alternative regimen that has been successfully used to treat scabies (Chouela et al, 2002; Heukelbach et al, 2004; Karthikeyan, 2005). **Note that pruritus may persist for several weeks despite successful treatment and that intimate contacts should also be treated to prevent reinfestation.**

NEOPLASTIC CONDITIONS

Squamous Cell Carcinoma In Situ

Squamous cell carcinoma in situ (SCCis) is a full-thickness intraepidermal carcinoma (Miller and Moresi, 2003). Bowen originally described this condition in 1912, hence the term "Bowen disease" (Bowen, 1912). On extragenital sites, there is a strong association between SCCis and ultraviolet light exposure (Reizner et al, 1994). **Commonly presenting in the seventh decade of life with a slight female predominance** (Hemminki and Dong, 2000; Arlette, 2003), **SCCis usually has an indolent clinical course and rarely progresses to invasive disease. When it occurs on mucosal surfaces of the male genitalia, most notably the glans penis of uncircumcised men, this entity is referred to as erythroplasia of Queyrat** (Fig. 15–33). In that location, coinfection with human papilloma virus types 8, 16, 39, and 51 has been identified (Wieland et al, 2000). Other risk factors for SCCis include ionizing radiation, immunosuppression, thermal injury, arsenic exposure, chronic dermatoses, and lichen sclerosis of the glans penis (Euvrard et al, 1995; Nasca et al, 1999; Powell et al, 2001; Centeno et al, 2002; Arlette, 2003).

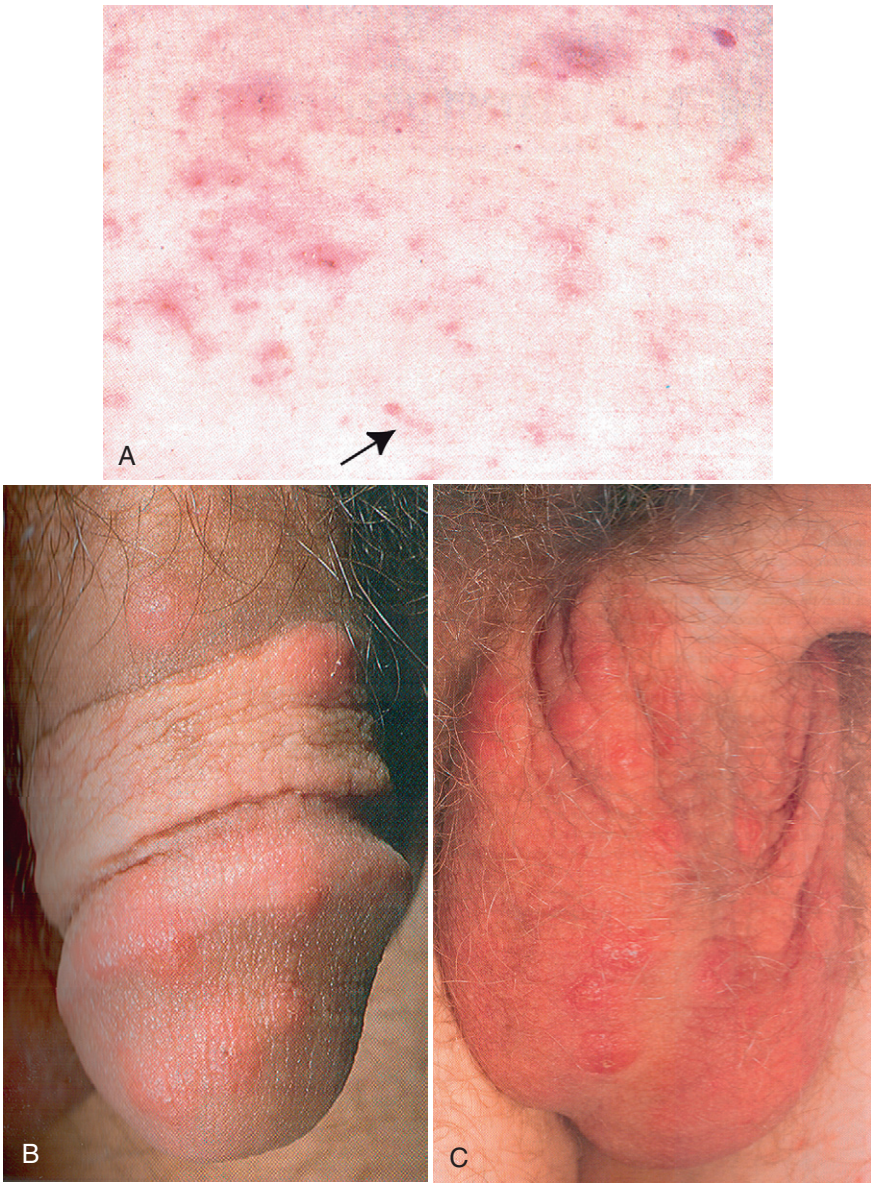


Figure 15–32. Scabies. **A,** A papular eruption with characteristic burrows visible (*arrow*). **B** and **C,** Classic established genital scabies with eroded papules on the glans penis and scrotum. (**A,** From du Vivier A. Atlas of clinical dermatology. London: Churchill Livingstone; 2002. p. 332; **B** and **C,** from Habif TP. Clinical dermatology. Edinburgh: Mosby; 2004. p. 501.)

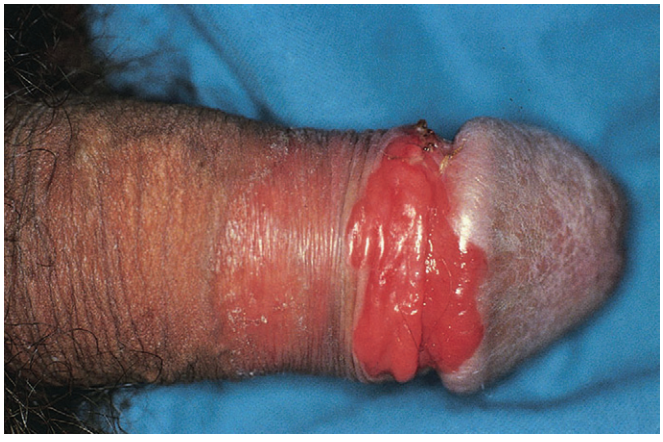


Figure 15–33. Erythroplasia of Queyrat. Squamous cell carcinoma involving the glans penis. (From Callen JP, Greer DE, Hood AF, Paller AS. Color atlas of dermatology. Philadelphia: WB Saunders; 1993. p. 330.)

SCCis lesions are sharply demarcated, solitary, pink to red, scaly plaques that may be confused with basal cell carcinoma, eczema, or psoriasis. When localized to the penile shaft, SCCis may have a more thickened, verrucoid appearance. Although usually asymptomatic, these lesions may also be pruritic or painful. The diagnosis is confirmed by histologic evaluation, and several areas should be sampled to exclude the presence of dermal invasion (Margolis, 2002).

Primary treatment of SCCis involves either surgical excision or tissue ablation. For accessible areas, such as the scrotum, simple excision with a 5-mm margin is favored (Bissada, 1992; Margolis, 2002). For areas where tissue preservation is more critical, Mohs microsurgery, laser therapy and cryoablation may have a role (Sonnex et al, 1982b; van Bezooijen et al, 2001; Leibovitch et al, 2005). Topical treatment with either 5-fluorouracil or imiquimod has also proven effective for management of selected cases of SCCis involving the genitalia (Gerber, 1994; Arlette, 2003; Micali et al, 2003).

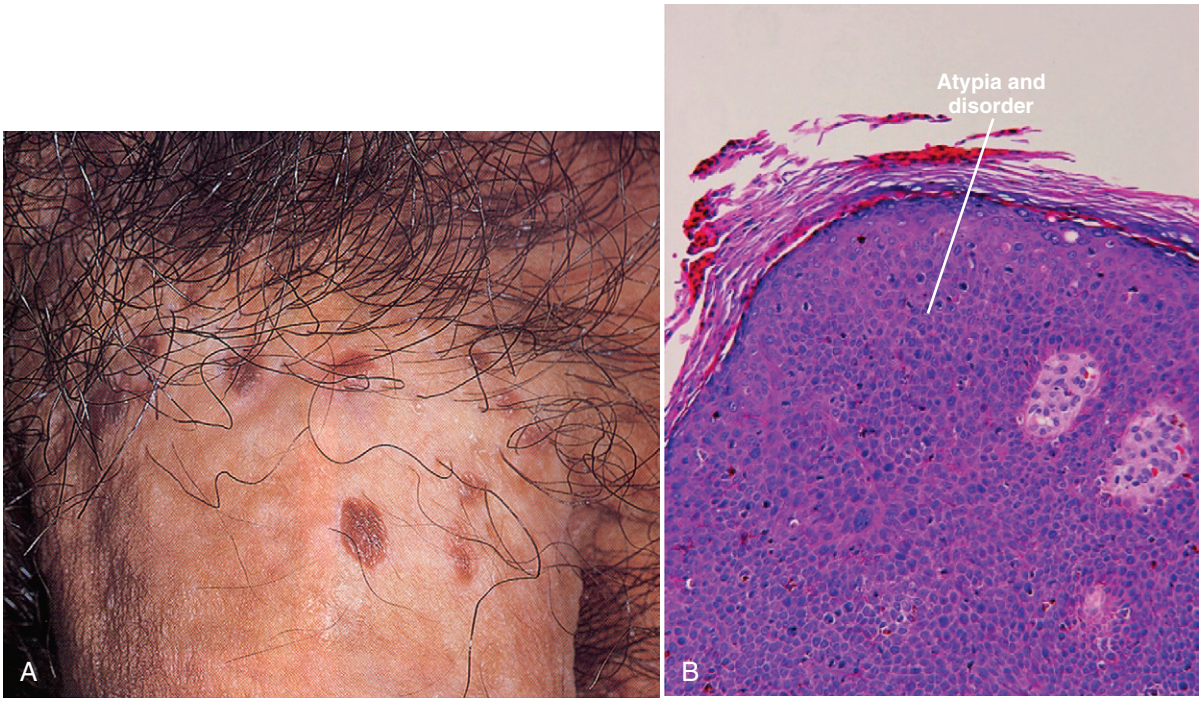


Figure 15–34. Bowenoid papulosis. **A,** Involvement of the penile shaft. Note multiple brown verrucous papules on the penile shaft. **B,** Characteristic full thickness atypia, which may be mistaken for Bowen disease. (**A,** From Habif TP. Clinical dermatology. Edinburgh: Mosby; 2004. p. 343; **B,** from Elston DM, Ferringer T. Dermatopathology. Edinburgh: WB Saunders; 2009. p. 293.)

Bowenoid Papulosis

Bowenoid apulosis (BP) is an uncommon condition found on the penis and vulva of sexually-active adults, with a peak incidence in the third decade (Schwartz and Janniger, 1991). **It histologically resembles Bowen disease, except that the abnormal keratinocytes are spread discontinuously throughout the epidermis** (Margolis, 2002). Typical lesions are multiple small erythematous papules that may coalesce to form plaques with a verrucous surface similar to a genital wart (Fig. 15–34). There is a clear association with HPV type 16. **Female partners of men with BP have an increased risk of cervical neoplasia and should have close cervical follow-up** (Rosemberg et al, 1991). In men, however, BP generally has a benign course and spontaneous regression may occur (Eisen et al, 1983; Giam and Ong, 1986). Therefore conservative local therapy with observation, topical agents (5-fluorouracil or imiquimod), or ablative measures (electrodissection, cryotherapy, laser therapy) is usually appropriate (Margolis, 2002).

Squamous Cell Carcinoma

Invasive squamous cell carcinoma involving the genitalia (Fig. 15–35) is covered in detail in Chapter 83.

Verrucous Carcinoma (Buschke-Lowenstein Tumor)

Verrucous carcinoma (VC) is a locally aggressive, exophytic, low-grade variant of squamous cell carcinoma that has little metastatic potential (Habif, 2004). **The Buschke-Lowenstein tumor is a VC of the anogenital mucosal surface and may represent up to 24% of all penile tumors** (Schwartz, 1995). It most commonly occurs in uncircumcised men on the glans or prepuce, although similar lesions can be found on the vulva, vagina cervix, or anus. VC has been associated with human papilloma virus types 6 and 11 infection, but not with the more classically oncogenic types 16 and 18 (Yasunaga et al, 1993; Chan et al, 1994; Margolis, 2002; Ahmed et al, 2006).

VC lesions have a warty appearance and are often large and fungating when presenting on the genitalia (Fig. 15–36). Aside from genital sites, these lesions can also present within the oral and nasal cavities and plantar surfaces of the feet. They are slow-growing and locally destructive, often extending deeply into underlying tissue. Treatment is preferably by local excision. **Primary radiotherapy is relatively contraindicated due to the potential for anaplastic transformation with a subsequent increase in metastatic potential** (Stehman et al, 1980; Andersen and Sorensen, 1988; Fukunaga et al, 1994; Vandeweyer et al, 2001).

Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common cutaneous neoplasm, arising most often on areas of chronically sun-exposed skin such as the head and neck. Genital BCC has also been described as a rare entity, most commonly involving the scrotal skin in the male and vulva in the female (Nahass et al, 1992; Benedet et al, 1997; Esquivias Gomez et al, 1999; Kinoshita et al, 2005). Several subtypes of BCC have been defined including nodular, superficial, micronodular, and infiltrating. The nodular variant accounts for 60% of all BCCs and presents as a pearly, skin-toned papule or plaque, often with telangiectasias overlying the tumor (Fig. 15–37) (Miller and Moresi, 2003). These lesions may ulcerate and have a very low metastatic potential. Treatment is by local excision.



Figure 15–35. Squamous cell carcinoma. **A,** Exophytic erosive lesion on the glans with evident keratinization. **B,** Atypical keratinocytes invading the dermis in squamous cell carcinoma. (**A,** From Callen JP, Greer DE, Hood AF, Paller AS. Color atlas of dermatology. Philadelphia: WB Saunders; 1993. p. 129; **B,** from Elston DM, Ferringer T. Dermatopathology. Edinburgh: WB Saunders; 2009. p. 57.)

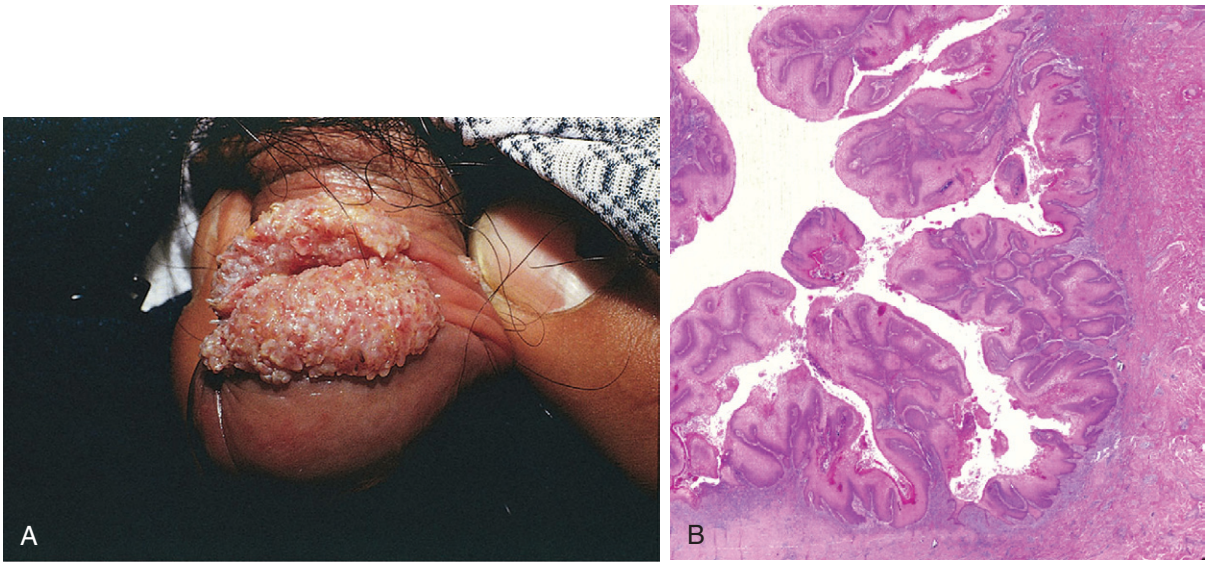


Figure 15–36. Verrucous carcinoma of the penis (Buschke-Lowenstein tumor). **A,** Note the exophytic and wart-like appearance. **B,** Histologic features of verrucous carcinoma. (**A,** From Callen JP, Greer DE, Hood AF, Paller AS. Color atlas of dermatology. Philadelphia: WB Saunders; 1993. p. 330; **B,** Elston DM, Ferringer T. Dermatopathology. Edinburgh: WB Saunders; 2009. p. 58.)

Kaposi Sarcoma

Kaposi sarcoma (KS) is a disease of endothelial cell origin. Whether KS is a neoplastic or hyperplastic process remains controversial, and evidence exists both for and against clonal expansion (Rabkin et al, 1997; Gill et al, 1998). Prior to the onset of the AIDS epidemic, KS was considered a chronic disease afflicting elderly men of Jewish, Mediterranean, or Eastern European descent ("classic KS") (Safai, 1987). However, infection with HIV-1 has increased the incidence of KS by more than 7000-fold (Miles, 1994; Margolis, 2002). KS generally affects HIV-infected patients with advanced immune impairment (CD4+ T-cell counts of <500 cells/mm) (Tappero et al, 1993). Approximately 40% of homosexual men with AIDS have developed KS as compared with less than 5% in other risk groups (Rogers et al, 1987; North et al, 2003). There is also a clear association between infection with human herpesvirus 8 and the development of KS (Boshoff and Weiss, 1997; Weiss et al, 1998).

Classic KS in immunocompetent individuals presents as slowly growing blue-red–pigmented macules on the

lower extremities. Although oral and gastrointestinal lesions may occur, the genitalia are seldom involved. This is in contrast to AIDS, ("epidemic KS") in which a solitary genital lesion may be the first manifestation of KS (Lowe et al, 1989). **The clinical features of KS in AIDS patients are diverse, ranging from a single lesion to disseminated cutaneous and visceral disease** (Fig. 15–38). Lesions may coalesce to cover large areas of skin and may result in lymphatic or venous blockage leading to local edema (Margolis, 2002). When these lesions involve the glans penis, they can cause obstruction at the urethral meatus or fossa navicularis (Swierzewski et al, 1993).

Treatment must be tailored to the individual clinical case and complete cure may be an unrealistic goal. For solitary lesions, local therapy such as surgical excision, laser treatment, cryotherapy, or intralesional injection of chemotherapeutic agents (i.e., vinblastine) may be beneficial (Chun et al, 1999; Schwartz, 2004; Heyns and Fisher, 2005). For extensive locoregional disease, radiotherapy (15 to 30 Gy) has an objective response rate of >90% (Kirova et al, 1998; Cattelan et al, 2002). For widely disseminated KS, systemic chemotherapy with vincristine, doxorubicin, and bleomycin is the treatment of choice (Aversa et al, 1999).



Figure 15–37. Basal cell carcinoma involving the vulva. (From du Vivier A. Atlas of clinical dermatology. London: Churchill Livingstone; 2002. p. 688.)

Pseudoepitheliomatous, Keratotic, and Micaceous Balanitis

Pseudoepitheliomatous, keratotic, and micaceous balanitis (PEKMB) is a rare entity characterized by the development of a thick, hyperkeratotic plaque on the glans penis of older men (Fig. 15–39). The term *micaceous* refers to the white, scaly appearance of the lesions (Child et al, 2000). PEKMB was originally thought to be a purely benign process, although several case reports have documented the presence of concurrent verrucous carcinoma associated with this lesion (Child et al, 2000). There remains controversy as to whether PEKMB is a premalignant condition (Read and Abell, 1981; Beljaards et al, 1987; Jenkins and Jakubovic, 1988). Histologic examination is essential to exclude the presence of squamous cell carcinoma and verrucous carcinoma (Margolis, 2002). PEKMB is characterized on histology by a hyperplastic epidermis with ridges extending deeply into the dermis (Jenkins and Jakubovic, 1988). These lesions should be treated locally either by surgical excision or ablative techniques, and close



Figure 15–38. Kaposi sarcoma. Classic macular lesions seen on the back (**A**) and glans penis (**B**). (**A,** From Callen JP, Greer DE, Hood AF, Paller AS. Color atlas of dermatology. Philadelphia: WB Saunders; 1993. p. 220; **B**, from du Vivier A. Atlas of clinical dermatology. London: Churchill Livingstone; 2002. p. 716.)



Figure 15–39. Pseudoepitheliomatous, keratotic and micaceous balanitis. The glans becomes covered with mica (asbestos-like) scales and horny crusts. (From du Vivier A. Atlas of clinical dermatology. London: Churchill Livingstone; 2002. p. 717.)

follow-up is essential (Read and Abell, 1981; Bargman, 1985). There are also anecdotal reports of successful treatment using topical 5-fluorouracil cream (Bargman, 1985; Krunic et al, 1996).

Melanoma

Malignant melanoma is a neoplasm arising from melanocytes. The incidence of melanoma has risen 3% to 7% over the past several decades (Nestle and Kerl, 2003). Risk factors for development of the disease include family history, certain genetic markers, fair skin, and ultraviolet radiation exposure. Primary melanoma of the male genitalia is an uncommon entity with only approximately 100 cases reported in the literature (Sanchez-Ortiz et al, 2005), and melanoma of the male urethra is even rarer (Oliva et al, 2000).

Genital melanoma usually presents as a pigmented macule or papule with an irregular border, although unpigmented lesions and ulceration may also be present (Margolis, 2002). **Early diagnosis is critical because local treatment of superficial lesions with wide local excision or partial penectomy can provide excellent disease control** (Stillwell et al, 1988; Sanchez-Ortiz et al, 2005). **In contrast, patients with biopsy-proven metastatic disease have a universally poor prognosis despite aggressive surgical management and multiagent cytotoxic chemotherapy.**

Extramammary Paget Disease

Extramammary Paget disease (EPD) is an uncommon intraepithelial adenocarcinoma of sites bearing apocrine glands (Zollo and Zeitouni, 2000). The majority of patients with EPD are elderly white females, and involvement of the male penis and scrotum is exceedingly rare (Park et al, 2001; van Randenborgh et al, 2002; Yang et al, 2005). The vulva is the most commonly involved genital site in women, followed by the perianal region in men (Wojnarowska and Cooper, 2003). **There is an important association between EPD and another underlying malignancy in 10% to 30% of cases** (Payne and Wells, 1994, Ng et al, 2001; Margolis, 2002). **In the male, associations between urethral, bladder, rectal, and apocrine malignancies with EPD have been described** (Hayes et al, 1997; Salamanca et al, 2004). It is critical, therefore, to perform a systematic evaluation for underlying carcinoma in cases of EPD.

The lesion in EPD is usually an erythematous plaque with a sharp border between normal and involved skin (Fig. 15–40). It may be asymptomatic, pruritic, or associated with burning pain. The diagnosis is confirmed histologically by the presence of vacuolated Paget cells in the epidermis, which stain for glandular cytokeratins, epithelial membrane antigen, and carcinoembryonic antigen (Wojnarowska and Cooper, 2003). Treatment generally involves surgical excision or Mohs micrographic surgery, although radiotherapy and topical imiquimod or 5-fluorouracil have also been used successfully (Sillman et al, 1985; Bewley et al, 1994; Brown et al, 2000; Brown et al, 2002; Guerrieri and Back, 2002; Moreno-Arias et al, 2003; Qian et al, 2003; Lee et al, 2009).

Cutaneous T-Cell Lymphoma

Cutaneous T-cell lymphoma (CTCL) represents a group of related neoplasms derived from T cells that home to the skin. It includes a variety of conditions including mycosis fungoides, Sezary syndrome, lymphoid papulosis, and pagetoid reticulosis (Willemze, 2003). There is an increased risk of CTCL associated with HIV infection (Biggar et al, 2001). Although these disorders may involve the genitalia of both sexes, extragenital disease is usually also present. CTCL accounts for the majority of primary cutaneous lymphomas, with B-cell–derived lymphomas accounting for only 20% to 25% (Willemze et al, 1997; Willemze et al, 2005). Definitive diagnosis depends on biopsy histopathology.

CTCL generally presents with pruritus, which must be differentiated from a variety of benign dermatoses including psoriasis, eczema, superficial fungal infections, and drug reactions. Patients may subsequently develop hematologic involvement (Sezary syndrome) and cutaneous plaques, erosions, ulcers, or frank skin tumors (Fig. 15–41) (Margolis, 2002). CTCL is a chronic condition that may progress over many years. Topical treatments include corticosteroids, nitrogen mustard, and carmustine with complete remission rates of approximately 60% (Vonderheid et al, 1989; Zackheim et al, 1998). Other treatments include radiotherapy, phytotherapy (PUVA), and systemic treatment with chemotherapy, interferons, or retinoids (Hoppe et al, 1990; Olsen and Bunn, 1995; Diederen et al, 2003; Querfeld et al, 2005).

BENIGN CUTANEOUS DISORDERS SPECIFIC TO THE MALE GENITALIA

Angiokeratoma of Fordyce

Angiokeratomas of Fordyce (AF) are vascular ectasias of dermal blood vessels, which may be visible on the penis and scrotum of adult men (Bechara et al, 2002). These lesions appear as 1- to 2-mm red or purple papules (Fig. 15–42A), and there may be associated generalized scrotal redness (Miller and James, 2002). This is usually a benign condition without systemic manifestations, although it may rarely be a source of troublesome scrotal bleeding (Taniguchi et al, 1994; Hoekx and Wyndaele, 1998). Similar lesions can be observed in Fabry disease (Fig. 15–42B), which is a rare glycogen storage deficiency. Although treatment is usually unnecessary for AF, several authors have reported success using erbium:YAG, Nd:YAG, KTP, and argon laser photocoagulation in select cases (Occella et al, 1995; Bechara et al, 2004; Ozdemir et al, 2009).

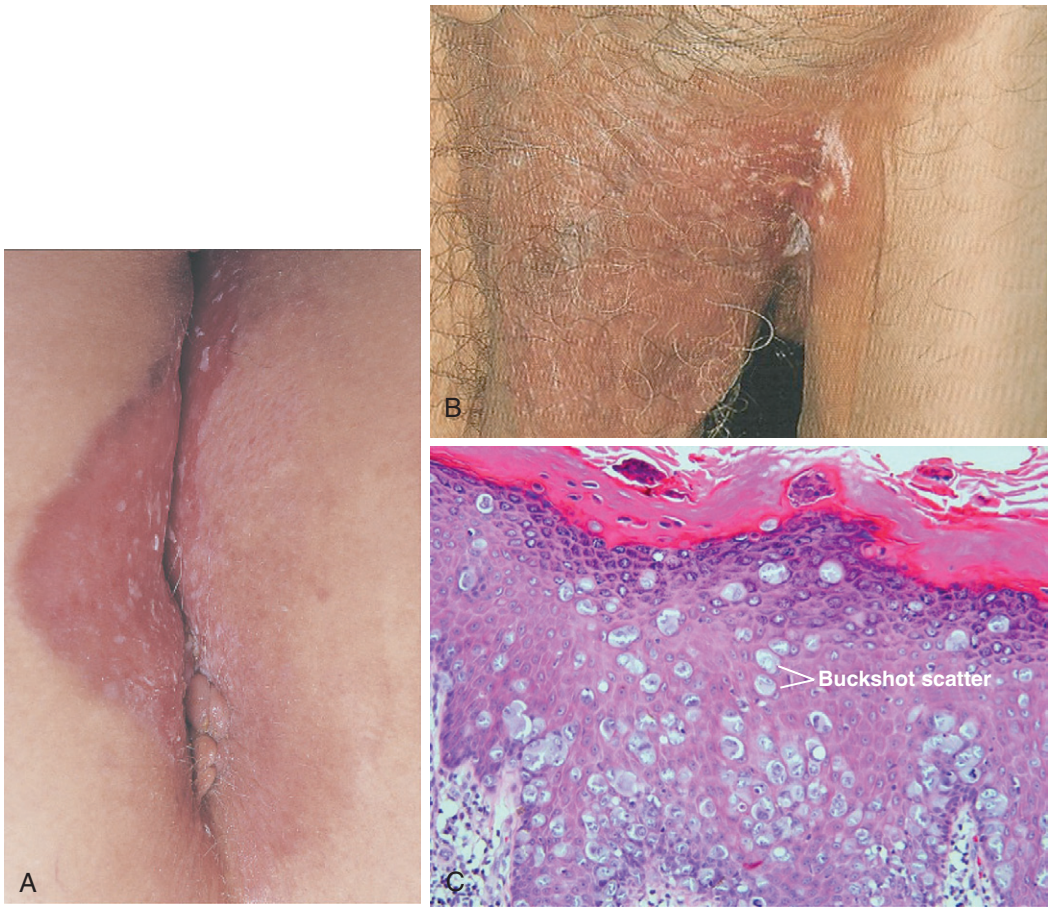


Figure 15–40. Extramammary Paget disease involving (**A**) the vulva and (**B**) base of scrotum. Note the well-demarcated border between the lesion and normal adjacent skin. **C,** Tumor cells distributed throughout the epidermis ("buckshot scatter"). (**A,** From Habif TP. Clinical dermatology. Edinburgh: Mosby; 2004. p. 764; **B,** from Bolognia JL, Jorizzo JL, Rapini RP: Dermatology. Edinburgh: Mosby; 2003. p. 1108; **C,** from Elston DM, Ferringer T. Dermatopathology. Edinburgh: WB Saunders; 2009. p. 66.)

Pearly Penile Papules

Pearly penile papules (PPP) are white, dome-shaped, closely spaced small papules located on the glans penis (see Fig. 15–42). They are often arranged circumferentially at the corona. PPP are very common lesions found in up to 14% to 48% of young postpubertal adults, particularly if the penis is not circumcised (Rehbein, 1977; Khoo and Cheong, 1995; Sonnex and Dockerty, 1999). **Although PPP may occasionally be misdiagnosed as condyloma, the available evidence does not support a role for human papilloma virus in causing PPP, and no association with cervical intraepithelial neoplasia in female partners has been demonstrated** (Hogewoning et al, 2003). Patients should be reassured that this is a benign condition that does not usually require treatment. If treatment is desired due to cosmetic concerns, local destruction with either the CO_2 laser or cryotherapy has been applied successfully (Ocampo-Candiani and Cueva-Rodriguez, 1996; Lane et al, 2002). **Histologically, these lesions are angiofibromas similar to the lesions seen on the face in tuberous sclerosis.**

Zoon Balanitis

Zoon balanitis, also called plasma cell balanitis, occurs in uncircumcised men from the third decade onward (Pastar et al, 2004). Smooth, moist, erythematous, well-circumscribed plaques on the glans penis characterize the disease (see Fig. 15–42). Shallow erosions may also be present (Yoganathan et al, 1994), and the lesions can be quite large (up to 2 cm in diameter) (Margolis, 2002). Squamous cell carcinoma and extramammary Paget disease should be excluded, often by biopsy. Circumcision appears to be proof against development of the disease and can be performed to cure the majority of cases (Sonnex et al, 1982a; Ferrandiz and Ribera, 1984). For patients averse to circumcision, topical corticosteroids may provide symptomatic relief, and topical tacrolimus and laser therapy may also have a role (Baldwin and Geronemus, 1989; Tang et al, 2001; Albertini et al, 2002; Retamar et al, 2003; Wojnarowska and Cooper, 2003; Rallis et al, 2007).

Sclerosing Lymphangitis

Nonvenereal sclerosing lymphangitis is a rare penile lesion consisting of an indurated, slightly tender cord involving the coronal sulcus and adjacent penile skin (Gharpuray and Tolat, 1991; Rosen and Hwong, 2003). It is usually flesh-colored but may occasionally be red. A mechanism related to thrombosis of lymphatic vessels has been proposed. There is an association with vigorous sexual activity and resolution usually occurs within several weeks (Sieunarine, 1987; Margolis, 2002).

Median Raphe Cyst

Median raphe cysts occur in young men on the ventral aspect of the penis, most commonly near the glans (Stone, 2003). Although



Figure 15–41. Mycosis fungoides (a cutaneous T-cell lymphoma) involving the buttocks. **A,** Limited plaque stage. **B,** A more advanced case with plaques, patches, and tumors present. (From Bolognia JL, Jorizzo JL, Rapini RP. Dermatology. Edinburgh: Mosby; 2003. p. 1926, 1927.)

these cysts are believed to develop from aberrant urethral epithelium, they do not communicate with the urethra (Asarch et al, 1979). Treatment is by surgical removal.

Ectopic Sebaceous Glands

Ectopic sebaceous glands on the penile shaft may be visible as pin-sized popular lesions that may be mistaken for verruca (see Fig. 15–42) (Margolis and Wein, 2002).

COMMON MISCELLANEOUS CUTANEOUS DISORDERS

Skin Tag

Skin tags (acrochordons, fibroepithelial polyps) are soft, skin-colored, pedunculated lesions that can be present anywhere on the body. Although usually asymptomatic, these lesions may be painful secondary to local trauma or torsion and infarction in rare cases. These are common lesions and up to 50% of all individuals may have at least one skin tag (Banik and Lubach, 1987). **It is important to distinguish these lesions from the hamartomatous skin lesions (multiple fibrofolliculomas) associated with Birt-Hogg-Dube syndrome, which are histologically distinct from common skin tags** (De la Torre et al, 1999).

Epidermoid Cysts

Epidermoid or epidermal-inclusion cysts (EC) are the most common cutaneous cysts, and these lesions can be found anywhere on the body, including the genitalia. They are particularly common on the scrotum (Fig. 15–43). **The term "sebaceous cyst" should be avoided because the contents of these cysts are not derived from a sebaceous origin** (Stone, 2003). Although not painful at baseline, rupture of the cyst wall can lead to a severe inflammatory reaction that is extremely painful. Definitive treatment requires surgical excision of the entire cyst wall to prevent cyst recurrence. Inflamed or superinfected epidermoid cysts may require incision and drainage, and antibiotic therapy if there is adjacent cellulitis. Dystrophic calcification of scrotal epidermoid cysts may be a cause of scrotal calcinosis (Dare and Axelsen, 1988; Michl et al, 1994).

Seborrheic Keratosis

Seborrheic keratoses are very common brown macules, plaques, and papules affecting individuals over 30 years of age and that increase in frequency with advancing age. They are most common on the face, neck, and trunk, although any body site except the palms, soles, and mucous membranes may be affected. The degree of pigmentation can vary significantly, and darker lesions may be confused with melanoma or warts (Pierson et al, 2003). **These lesions have a waxy, "stuck-on" appearance** (see Fig. 15–43), **and patients may note that they drop off spontaneously and regrow** (Margolis, 2002). Treatment by shave excision or destruction with liquid nitrogen is usually performed for cosmetic reasons. **An abrupt increase in the size and number of multiple seborrheic keratoses has been termed Leser-Trelat syndrome and has been implicated as a cutaneous marker of internal malignancy** (Chiba et al, 1996; Heaphy et al, 2000; Vielhauer et al, 2000; Ginarte et al, 2001).

Lentigo Simplex

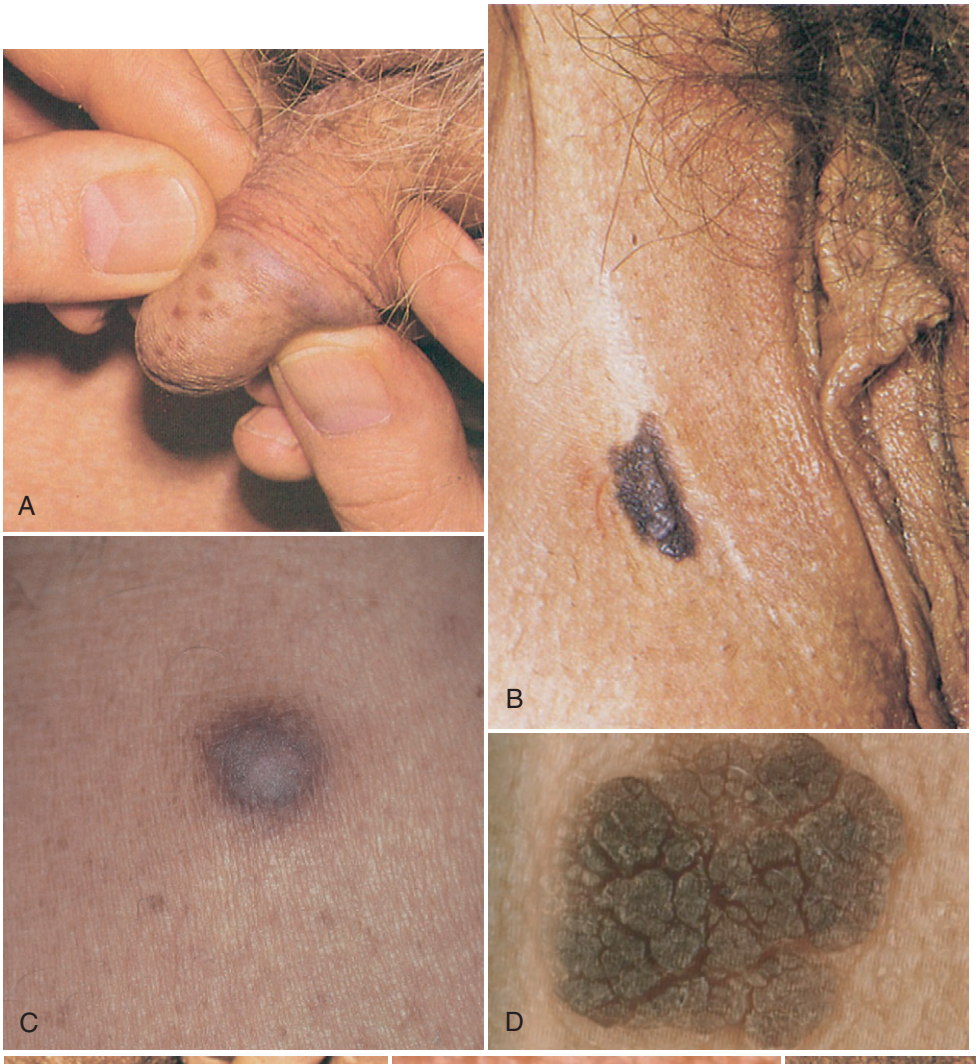
Lentigo simplex is a condition characterized by the presence of brown-pigmented macules unrelated to sunlight exposure (see Fig. 15–43). These lesions can be found anywhere on the body, including the mucous membranes and nail beds. In the genital area (genital lentiginosis), these lesions present commonly on the labia, vaginal introitus, perineum, and glans penis (penile melanosis). The lesions of lentigo simplex are usually smaller than those seen in melanocytic nevi. Although usually benign, the lesions of lentigo simplex may deserve biopsy evaluation in cases with atypical shape or coloration. **Finally, the combination of multiple pigmented lesions associated with intestinal polyposis should raise suspicion for Peutz-Jeghers syndrome.**

Mole (Nevus)

A mole, or nevus of the skin, is composed of slightly altered melanocytes called "nevus cells" arranged in a cluster. The location of the cluster determines the type of nevus. Junctional nevi are located between the epidermis and dermis and are usually flat, tan to black in coloration, small (<5 mm), and sharply bordered (Margolis, 2002). Intradermal nevi have clusters within the dermis and are usually small (<5 mm) and lighter in coloration with sharp borders. Compound nevi have clusters in both locations and are usually darker and raised, as for a papule (see Fig. 15–43). As for



Figure 15–42. Benign cutaneous disorders specific to the male genitalia. **A,** Angiokeratoma of Fordyce showing purple scrotal vascular malformations. **B,** Fabry disease: a glycogen storage deficiency with associated purple vascular malformations on the penile shaft. **C,** Pearly penile papules located on the corona of the glans penis. **D,** Zoon balanitis of the glans penis. **E,** Ectopic sebaceous glands on the penile shaft. (**A, B,** and **E,** From Callen JP, Greer DE, Hood AF, Paller AS. Color atlas of dermatology. Philadelphia, WB Saunders, 1993. p. 328, 327, and 3; **C** and **D,** from Korting GW. Practical dermatology of the genital region. Philadelphia: WB Saunders; 1981. p. 5 and 159.)



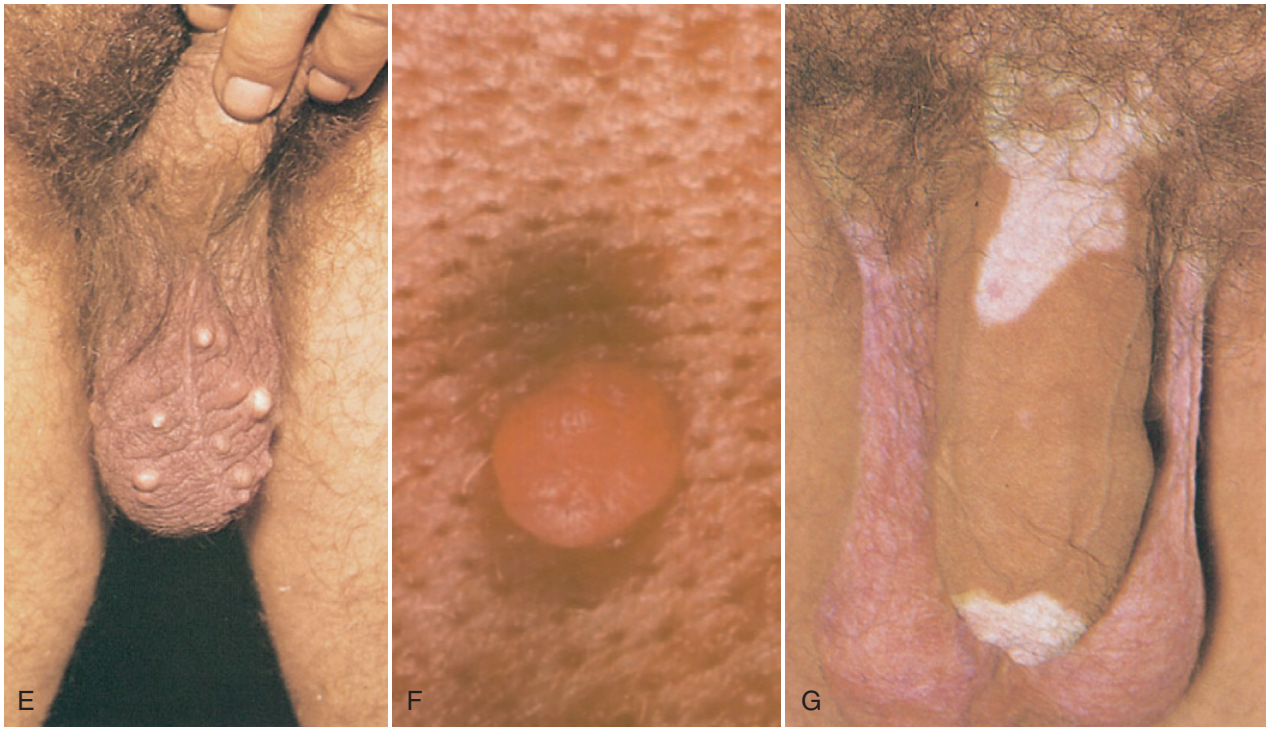


Figure 15–43. Miscellaneous cutaneous disorders. **A,** Lentigo simplex involving the glans penis (penile melanosis). **B,** A compound melanocytic nevus in the inguinal crease. **C,** A dermatofibroma on the lower extremity. **D,** A characteristic seborrheic keratosis showing the "stuck-on" waxy appearance. **E,** Epidermoid cysts of the scrotum. **F,** Pedunculated neurofibroma. **G,** Vitiligo involving the penile shaft. (**A, B, E,** and **G,** From Korting GW. Practical dermatology of the genital region. Philadelphia, WB Saunders, 1981. p. 85, 121, 115, and 88; **C,** from Bolognia JL, Jorizzo JL, Rapini RP. Dermatology. Edinburgh: Mosby; 2003. p. 1865; **D,** from Habif TP. Clinical dermatology. Edinburgh: Mosby; 2004. p. 700.)

any pigmented lesion, irregularity in coloration or border and rapid change over time are indications for excisional biopsy.

Dermatofibroma

Dermatofibromas are small hyperpigmented nodules that occur most commonly on the lower extremities and occasionally on the genitalia. Pinching of these lesions causes a downward movement of the tumor (the so-called "dimple sign") (Kamino and Pui, 2003). These are benign lesions with a characteristic histologic pattern of spindle-shaped fibroblasts and myofibroblasts arranged in fascicles. Treatment by surgical excision is usually unnecessary and may leave a scar that is cosmetically inferior to the original lesion (Kamino and Pui, 2003).

Neurofibroma

Neurofibromas are common tumors composed of neuromesenchymal tissue with residual nerve axons. They can be present anywhere on the body including the labia and scrotum (Yoshimura et al, 1990; Singh et al, 1992; Mishra et al, 2002; Kantarci et al, 2005). They are usually skin-colored, soft or rubbery, nodular lesions, which may be pedunculated. **Digital pressure on the lesion causes invagination or so-called "button-holing"** (Habif, 2004). These can be solitary lesions or multiple, which should raise suspicion for neurofibromatosis or von Recklinghausen disease.

Capillary Hemangioma

Capillary hemangiomas are proliferations of blood vessels that are either present at birth or develop rapidly during the neonatal period. These lesions can involve the anogenital region and lead to bleeding or cause obstruction of the urethra, vagina, or anus (Sharma et al, 1981; Roberts and Devine, 1983). The majority will involute during childhood or early adolescence (Margolis, 2002).

Vitiligo

Vitiligo is an acquired disorder of skin depigmentation that affects 0.5% to 2% of the population (Ortonne, 2003). It may present at any age and the pathogenesis of vitiligo remains a topic of intense research effort. Large patches of skin become completely amelanotic, appearing white although the tissue is otherwise normal. The borders with unaffected skin are usually sharp and well defined. This condition is particularly noticeable in darker skinned individuals and on body sites that are normally hyperpigmented. Vitiligo limited to the genitalia has been observed in less than 0.3% of the male population (Moss and Stevenson, 1981). Lesions have a tendency to enlarge circumferentially over time and may develop at sites of local trauma (Koebner phenomenon). Genital vitiligo must be differentiated from lichen sclerosis and postinflammatory hypopigmentation (Margolis, 2002). Treatments include repigmentation with topical cosmetics, ultraviolet light exposure, PUVA therapy, and skin grafting.

Key Points

- The diagnosis of cutaneous diseases of the external genitalia depends critically on a thorough history and physical examination. Extragenital findings may provide the key to diagnosis. The urologist should perform a thorough skin survey and not focus solely on the area of affected genital skin.
- The side effects of topical corticosteroids are significant, both from systemic absorption and locally. Adverse effects may be worsened if these agents are applied under the foreskin, which may serve as an occlusive dressing. In general, when applied to genital skin, only low-potency topical corticosteroids should be used for short treatment courses.
- Cutaneous disorders of the external genitalia can be broken down into the general categories of allergic, papulosquamous, vesicobullous, ulcerative, infectious, neoplastic, and miscellaneous diseases.
- Histopathologic analysis of biopsy specimens plays an important role in differentiating cutaneous diseases with similar clinical features and in excluding malignancy.
- Local treatment modalities, including the use of laser energy, photodynamic therapy, ultraviolet radiation, and cryotherapy are being applied successfully to a variety of genital cutaneous disorders and offer an alternative to surgical excision in some cases.

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chapter
16

Tuberculosis and Other Opportunistic Infections of the Genitourinary System

Islam A. Ghoneim, MD, PhD • John C. Rabets, MD • Steven D. Mawhorter, MD, DTM&H

Genitourinary Tuberculosis

Parasitic Diseases of the Genitourinary System

Other Parasitic Diseases of the Genitourinary Tract

GENITOURINARY TUBERCULOSIS

Tuberculosis has been one of the great imitators of all time, and only a few years ago was thought to be a disease of the past. Tuberculosis (TB) is a deadly infectious disease with a rising incidence worldwide. The urologist's awareness of the clinical features of genitourinary (GU) TB is necessary to effectively treat patients with this disease. A review of the literature will reveal that the clinical features and pathology of genitourinary tuberculosis described in the earlier part of the 20th century has remained essentially valid to date. Current research focuses on epidemiology of the new resurgence of the disease, as well as rapid diagnostic modalities and new treatment regimens to combat multidrug-resistant TB.

History

Akhenaton, a Pharaoh of the eighteenth dynasty of Egypt, and his wife Nefertiti both are believed to have died from tuberculosis, and evidence indicates that hospitals for tuberculosis existed in Egypt as early as 1500 BCE (Madkour, 2003). Signs of the disease have also been found in the spines of Egyptian mummies dating between 3000 and 2400 BCE (Zink et al, 2003).

Tuberculosis became known as "the consumption" during the 1700s in Europe when infections reached epidemic proportions, causing one fourth of the deaths in England (Daniel, 2000). The bacillus causing tuberculosis, *Mycobacterium tuberculosis,* was identified and described on March 24, 1882 by Robert Koch. He demonstrated that *Mycobacterium* was the single cause of tuberculosis in all of its forms. His conclusion was based on the observations that *Mycobacterium* was found in all cases of the disease, could be prepared as a pure culture, and the original infection could be reproduced in an inoculated animal, from which it could be cultured again (Koch, 1882). These observations lead to postulates that have become known as the "Koch postulates," and they form the basis for the study of all infectious diseases. March 24th has become "World Tuberculosis Day."

Epidemiology

Incidence

The World Health Organization (WHO) estimates that 9.27 million new cases of TB occurred in 2007, compared with 9.24 million new cases (140 per 100,000) in 2006. An estimated 1.37 million (14.8%) of the cases in 2007 were HIV-positive (World Health Organization and Global Tuberculosis Programme, 2008).

In the United States, the incidence of TB showed a resurgent peak in 1992 after having continually declined until 1985, coinciding with the emergence of HIV-AIDS. In 2008, 12,904 cases were reported (4.2 cases per 100,000), representing a decline of 2.9% compared with 2007.

The trend of the declining annual case rate has slowed, from an annual average decline of 5.6% for 1993 through 2002 to an annual average decline of 2.6% for 2003 through 2008.

Genitourinary TB

Extrapulmonary sites account for 10% of tuberculosis cases. Genitourinary TB accounts for 30% to 40% of all extrapulmonary TB, second only to lymphonodal affection (Eastwood et al, 2001). In developed countries, urogenital tuberculosis occurs in 2% to 10% of cases of pulmonary tuberculosis, while in developing countries it occurs in as many as 15% to 20% of cases.

Transmission and Development of Disease

Controversy existed as early as the latter part of the 19th century as to whether pulmonary tuberculosis spread to the genitourinary tract by bacterial retrograde ascent or hematogenous dissemination. In 1885, injection of the renal artery with TB bacillus was shown to produce renal tuberculosis in the kidney of an experimental animal. Ekehorn, in 1908, postulated that TB bacilli lodged in renal glomeruli flourished into renal infection. These suspicions were confirmed in 1949 by Medlar and associates, proving that

renal cortical TB was a "metastatic" infection spread by the hematogenous route (Medlar et al, 1949).

The kidney, epididymis in men, and fallopian tubes in women are the primary landing sites for hematogenous spread of TB. The prostate is also considered one of the sites for hematogenous spread, though its involvement with TB bacilli in urine is more common. Other genitourinary organs are involved by direct, endoluminal, or lymphatic spread from these sites.

Immunology and Pathogenesis

In the lung, inhaled tubercle bacilli implant in the respiratory bronchioles and alveoli. The interaction between bacterial virulence and host immunity determines whether an infection is established or aborted (Dannenberg, 1993). If infection occurs, the mycobacteria slowly divide within alveolar macrophages. Two to 12 weeks often ensue before mycobacterial numbers are sufficient to mount a clinically detectable cellular immune response (Dannenberg, 1994).

The interval before the development of cellular immunity is when tubercle bacilli spread through the lymphatics to the hilar lymph nodes and ultimately through the bloodstream to seed distant organs. Mycobacteria deposited in the upper lung zones, kidneys, bones, and brain find such environments favorable, and bacterial multiplication may occur before specific cellular immunity can limit bacterial activity.

In the presence of intact cell-mediated immunity, macrophages, T lymphocytes, B lymphocytes, and fibroblasts aggregate to form a granuloma, with lymphocytes surrounding the infected macrophages and organisms localized in the center of the granuloma. This pathognomonic lesion prevents dissemination of the mycobacteria. Immune cells communicate through cytokines within the milieu of the granuloma. T lymphocytes secrete interferon gamma, which induces intracellular killing of mycobacteria within infected macrophages (Kaufmann, 2002). An antibody response against *M. tuberculosis* has been demonstrated but does not appear to be protective (Abebe and Bjune, 2009). Tubercle bacilli often remain viable within the tubercle, become dormant, and finally result in a latent infection.

The risk of reactivation of dormant TB foci increases with diabetes mellitus and diseases associated with immunosuppression, e.g., HIV infection and malignancies, as well as by use of corticosteroids, chemotherapy, and other immunosuppressive drugs.

Pathologic Features

Kidney

The kidneys are the primary site of hematogenous spread of TB. Mycobacteria lodge in the renal capillaries causing microscopic foci near the glomeruli bilaterally, the cortex being favored due to its greater blood supply and higher oxygen tension (Pasternak, 2001). An initial acute inflammatory response ensues, resulting in polymorphonuclear leukocytes infiltration. Over the following 3 to 6 weeks cell-mediated immunity developing in macrophages may inhibit the *M. tuberculosis* by containing the bacterial replication and halting the disease in the renal cortex, leading to the formation of dormant TB foci.

Upon activation of the disease, a chronic inflammatory process arises with the subsequent development of characteristic granulomata, tubercles consisting of multinucleated Langhans giant cells, lymphocytes, and fibroblasts. Central caseous necrosis builds up within the tubercles, and neighboring tuberculous foci coalesce to form confluent areas of caseation. With progression of the disease, inflammatory changes extend into the renal tubules and medulla with further tubercle formation and caseous necrosis. Renal papilla involvement results in sloughing and caseous material gaining access to the collecting system by calyceal ulceration (Medlar, 1926). Renal tuberculosis often becomes clinically evident at this stage. Extensive fibrosis accompanying healing tubercles results in cicatricial complications, such as calyceal infundibular narrowing, ureteropelvic junction scarring, and disfiguration leading to segmental or generalized hydronephrosis respectively, and adds an obstructive element to the ongoing renal damage (Medlar, 1926).

Adrenal

Adrenal tuberculosis is seen in less than 6% of active TB cases. The lesion may be unilateral, but is usually bilateral. Tuberculosis causes necrosis of the adrenal gland, which manifests as Addison disease. Primary caseous tuberculosis of the adrenals is probably the most common lesion seen. The glands are enlarged, surrounded by a thickened capsule, and have irregular nodular surfaces with infrequent calcifications. Caseous cavitary destruction is found upon section. As a result, up to 56% of patients with adrenal TB will have a subnormal cortisol response to corticotrophin stimulation (Hawken et al, 1996).

Ureter

Tuberculosis of the ureter is almost always a direct extension of TB of the kidney. The passage of caseous material rich in mycobacteria leads to tubercle formation within the ureteric mucosa. This usually affects the lower ureter, commonly the ureterovesical junction, less commonly the middle and upper ureter (Shin et al, 2002). Tubercle formation is soon followed by ulceration of the mucosa and subsequent fibrosis and scarring, leading to ureteric stricture disease and obstruction. Lesions extending into the ureteric wall will also initiate a dense fibrosis on the ureteric serosa, leading to encasement of the ureter and angulation by contracted cicatricial bands (Johnson, 1911).

Bladder

Tuberculosis of the bladder occurs secondary to TB of the kidney. The bladder urothelium is very resistant to infection by TB bacilli. Urine of renal tuberculosis patients may contain mycobacteria for years prior to the involvement of the bladder. The most common sites affected by TB are the areas surrounding the ureteric orifices and the trigone. The urothelium is initially swollen and inflamed, following the formation of tubercles within the bladder mucosa. The ureteric orifice may be completely obscured by the swollen mucosa. In modern times the progression to the stage of mucosal ulceration is rare. However, if it does occur, the coalescence of tubercles will lead to larger areas of caseated mucosa, the top of which ulcerates leading to the formation of a classical undermined tuberculous ulcer with "worm-eaten" ragged edges (Johnson, 1911).

Epididymis, Vas, and Testis

Tubercle bacilli reach the epididymis by hematogenous spread. The disease initially affects the more vascular globus minor. Tubercles form within the epididymal epithelium eliciting a chronic inflammatory reaction that subsequently leads to fibrous narrowing and possible obliteration of the lumen. With disease progression, large caseous foci may form leading to a nodular epididymis. These lesions may become adherent to the overlying skin and ulcerate through giving the classic picture of a tuberculous sinus that is typically located on the posterior surface of the scrotum. Spread of the infection along the lumen, with the flow of

secretion, will lead to affection of the vas deferens in a similar pattern. The classical finding is that of a beaded vas as a result of tubercles eventually inducing dense fibrosis.

Tuberculosis of the testis is secondary to that of the epididymis and is due to direct extension of the disease. Tubercles form within the seminiferous tubular epithelium as well as in the connective tissue septa of the testis. As a result the affected testicular tissue is eventually replaced by caseous material and fibrosis. Such lesions may be clinically difficult to distinguish from a testicular tumor.

Prostate and Seminal Vesicles

The prostate is rarely affected, it is however one of the sites of hematogenous spread of TB. The lesions are often incidentally found on TUR specimens. In cases where progression occurs, caseous destruction of prostatic tissue ensues that may be significant enough to cause a noticeable reduction in semen volume (Marconi et al, 2009). Densely fibrotic nodules may form and are indistinguishable from cancer.

Tuberculosis of the seminal vesicle is rarely seen in modern times. The bacilli can reach the seminal vesicles through the vas deferens in cases of tuberculosis of the testis or epididymis, or through the urethra and ejaculatory duct because of tuberculosis of the kidneys, bladder, or prostate. Caseous masses develop in the walls, and the lumen may be filled caseation.

Penis and Urethra

Tuberculosis of the penis in adults is very rare and is secondary to infection of the kidney and bladder. It starts as a chronic process, by the formation of infected granulation tissue, which gradually infiltrates the glanular and cavernous tissues and may invade the whole thickness of the penis. As the infection progresses, isolated pea-sized masses can be felt in the cavernous bodies and urethra, and in some cases directly under the skin. On pathologic section, these lesions are found to be masses of caseous tubercles.

One rare presentation is an ulcerative lesion of the glans. This *primary* infection can be acquired by sexual relations with partners having genital or perineal tuberculous lesions (Angus et al, 2001). Several cases of primary TB of the penis were reported in young Jewish boys following circumcision. Hemorrhage was stopped by sucking the penis with the mouth. Rabbis with open pulmonary TB transmitted the infection through infected sputum. Urethral tuberculosis is rare, often only seen at the meatus. Small miliary tubercles are seen over the surface and throughout the urethra. Late cases may have advanced fibrotic strictures.

Clinical Manifestations

In the words of Chang: "the kidney is an inarticulate organ; its vocal cords are the bladder" (Chang, 1976). Tuberculosis can often mimic a wide range of nonspecific urologic symptoms. It is thus, no wonder that many cases of genitourinary TB are easily overlooked. A high index of clinical suspicion of TB is required to further investigate cases of unexplained symptoms in the urinary tract. This is especially important when there is a failure to respond to initial treatments given for lower urinary tract symptoms or when urinalysis and routine culture reveal "sterile pyuria." The fact that 18 out of 25 physicians with renal TB presented only after cavitary lesions developed is a measure of how silently the destructive process occurs (Lattimer, 1965).

Genitourinary TB is more commonly seen in men (male : female ratio of 2 : 1), usually presenting in the fourth decade of life. Lower urinary tract symptoms are the most common presentation, with over 50% of patients presenting with storage symptoms. Hematuria and loin pain are the presentation in one third of cases (Figueiredo et al, 2008). Passage of caseous material, necrotic renal papillary tissue, clots, or stones account for renal colic in 10% of patients (Simon et al, 1977). Less than 20% of cases will present with constitutional symptoms of fever, anorexia, weight loss, and night sweats. The presence of these symptoms, however, can alert to the presence of active TB elsewhere in the body (Simon et al, 1977).

Physical examination is often of limited value in the diagnostic process, because physical signs develop late in the disease. The most common physical finding is an abnormal scrotal exam in about half the patients (Figueiredo et al, 2008). Epididymal hardening, modularity, or scrotal fistulae are among the signs seen. A chronic renal fistula tract, often with a history of prior renal surgery is another late physical sign. Enlarged, firm seminal vesicles, or prostatic nodules on rectal examination, though nonspecific, should arouse suspicion in clinically suggestive cases. It remains a fact that up to 25% of patients will present only with sterile pyuria and 13% might have gross or microscopic hematuria as their only presentation (Wise and Shteynshlyuger, 2008). Functional loss of the affected kidney can be present in up to 25% of cases, and renal failure is present in 7.4% of cases (Figueiredo et al, 2008). Genitourinary TB may be diagnosed during a workup for infertility as a cause of epididymal and vasal obstruction (Paick et al, 2000). TB should be considered in all cases of recurrent hemospermia. Adrenal tuberculosis may present with an addisonian type of clinical picture.

Diagnosis

Urinalysis and Culture

Historically, the diagnosis of genitourinary TB has relied on the identification of *Mycobacterium tuberculosis* in the urine. Unlike sputum examination, Ziehl-Neelsen staining of concentrated urine samples for acid-fast bacilli is often negative. Of note, a large majority of patients with genitourinary TB have "sterile pyuria," often accompanied by hematuria and proteinuria, whereas up to 20% may have superimposed bacterial infection (Gow and Barbosa, 1984).

Urine cultures are carried out on standard solid media optimized for mycobacterial growth, namely egg-based (Löwenstein-Jensen) or agar-based (e.g., Middlebrook 7H10) media. Optimizing factors include aniline dyes, such as malachite green, that inhibit growth of bacterial contaminants. Agar-based media are transparent and facilitate earlier visualization of micro-colonies by approximately 1 week. Intermittent release of the organism in urine makes multiple sampling necessary. Three to five early-morning urine samples should be cultured soon after collection rather than 24-hour samples, because exposure to urine acidity for prolonged periods retards mycobacterial growth (American Thoracic Society [ATS] and Centers for Disease Control and Prevention [CDC], 2000; Sommers, 1979). One other caveat is that chronic renal lesions may no longer discharge tuberculous material in urine due to dense fibrosis that is a barrier to the collecting system. In such cases diagnostic methods other than urine testing must be applied. Notably, cultures optimized for mycobacterial growth will favor the growth of mycobacterial contaminants as well as TB. Species identification is done using growing colonies tested with DNA strip assays. These provide rapid confirmation of pathogenic *Mycobacterium* TB in culture (Piersimoni et al, 2002).

Urine cultures are sensitive in 80% to 90% of cases and have a specificity of nearly 100% (Sorlozano et al, 2009). However, they

may take up to 6 weeks to yield clinically reliable results. Radiometric detection of mycobacterial activity in liquid culture media allows a more rapid diagnosis. Inoculation of specimens in broth with radiolabelled ^{14}C-palmitate results in liberation of $^{14}CO_2$ by mycobacterial metabolism, which is then detected by a radiometric analyzer. Mycobacterial detection and drug sensitivity testing using this method is possible as early as 7 to 14 days after inoculation (Watterson and Drobniewski, 2000; Sorlozano et al, 2009). One of the most popular systems using this principle is the BACTEC 460TB (Becton, Dickinson, Franklin Lakes, NJ). Nonradiometric methods using advanced fluorometric technology to detect O_2 consumption also yield rapid detection of mycobacteria without the use of radiation. One example of this detection method is the mycobacterial growth indicator tube (MGIT; Becton, Dickinson; Watterson and Drobniewski, 2000).

Antibiotic sensitivity testing (AST) is also done using traditional and rapid culture methods.

Purified Protein Derivative–Tuberculin Test—Mantoux Test

Charles Mantoux, a French physician who developed on the work of Koch, described this test in 1907. Purified protein derivative (PPD) tuberculin is a precipitate of non–species-specific molecules obtained from glycerol extracted filtrates of sterilized, concentrated cultures of tubercle bacilli. In the United States, a standard dose of 5 tuberculin units (0.1 mL) is injected intradermal (between the layers of dermis) into the volar or dorsal surface of the forearm and read 48 to 72 hours later. T-cell–mediated delayed-type hypersensitivity reaction to this intradermal antigen is the principle of the test. Antigen stimulation of memory cells leads to cytokine release that induces induration via local vasodilatation, fibrin deposition, and recruitment of other inflammatory cells into the area. These begin to accumulate within 24 hours and reach their peak after 48 to 72 hours, hence the timing of test interpretation. Patients who have been exposed to TB are expected to mount an immune response to PPD (Daniel, 1980).

Tuberculin test is nondiagnostic, and is of value only if positive. Three distinct cut points for positivity have been defined to optimize sensitivity and specificity for the test in different patient populations. The test must be interpreted in light of the recommendations in Table 16–1.

It is important to note that prior vaccination with bacillus Calmette-Guérin (BCG) may lead to a false-positive tuberculin test. Interestingly, a PPD skin test done before initiation of BCG therapy for superficial bladder cancer converted from negative to positive in 68% of patients (Bilen et al, 2003).

Nucleic Acid Amplification (NAA) Testing—PCR

Nucleic acid amplification tests (NAAT), such as the polymerase chain reaction (PCR) and other methods for amplifying DNA and RNA, facilitate rapid detection of microorganisms, particularly those difficult to culture. The high sensitivity of PCR is particularly useful in non-pulmonary tuberculosis where discharge of the organism is sporadic and present in small amounts (Manjunath et al, 1991). Multiple sampling is also necessary for this method. The PCR test has been extensively studied and has shown reliably high sensitivity, specificity, and rapid results. In various studies, data show sensitivity ranging from 87% to 95% (usually >90%) and specificity from 92% to 99.8% (usually >95%) as compared to culture. Staining for acid-fast bacilli, bladder biopsies, and intravenous pyelography (IVP) examinations all yielded inferior results (Hemal et al, 2000b; Moussa et al, 2000). Numerous commercial tests and kits are available with near-equivalent quality.

Table 16–1.

Interpretation of Tuberculin Test: ATS and CDC Guidelines

- *Five millimeters or more* of induration is considered positive in persons with the highest likelihood of developing active disease. These include patients with HIV infection, organ transplants, and immunosuppression (equivalent to taking more than 15 mg/day of prednisone for at least one month), as well as those having close contact with persons having active tuberculosis cases or radiographic findings consistent with old tuberculosis.
- *Ten millimeters or more* of induration is considered positive in those who do not meet the preceding criteria but who are at high risk for tuberculosis. These include HIV-negative injection drug users; residents and employees of high-risk congregate settings, such as prisons, nursing homes, health care facilities, residential facilities for persons with HIV/AIDS, drug treatment centers, and homeless shelters; laboratory personnel dealing with mycobacterial samples; recent (<5 years) immigrants from countries where tuberculosis is prevalent; persons with high-risk medical conditions, including silicosis, diabetes, chronic renal failure, leukemias and lymphomas, carcinoma of the head or neck and lung, more than 10% loss of ideal body weight, gastrectomy, and jejunoileal bypass; children under 4 years of age; infants, children, and adolescents exposed to high-risk adults; those with a recent (within 2 years) conversion of their skin test result; and any other locally identified high-prevalence population.
- Fifteen millimeters or more of induration is considered positive in anyone.

From American Thoracic Society and Centers for Disease Control and Prevention. Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med 2000;161(4 Pt. 1):1376–95.

Some caveats exist in the interpretation of NAAT results, because they are best used in conjunction with clinical judgment and TB cultures. Urine is known to have naturally occurring enzyme inhibitors in up to 10% of cases, which suppress the enzymatic reactions of DNA/RNA amplification (van Vollenhoven et al, 1996). This may result in false-negative tests (Moussa et al, 2000). It is thus important to corroborate with the laboratory that appropriate measures have been done to confirm a PCR result as negative rather than an inhibited reaction, especially in clinically suspicious cases. Moreover, NAA tests can amplify nucleic acids from dead organisms, thus yielding positive results even after effective chemotherapy. Thus they should be used for diagnosis only and not as a follow-up to treatment (ATS and CDC, 2000).

Rapid molecular testing for drug resistance is available by detecting resistance mutations in three *Mycobacterium* TB genes. Results are available in 1 to 2 days (Barnard et al, 2008).

Radiography and Endoscopy

A wide spectrum of imaging findings has been described. Though each finding is nonspecific, multiple findings are common and are collectively suggestive of tuberculosis.

Plain Radiograph

Plain radiographic findings in genitourinary tuberculosis may be seen in the GU tract, surrounding tissues, and up to 50% of patients may show positive findings on chest radiograph. Disparity in renal size on plain films may indicate early increase in size of the affected kidney due to caseous lesions or a shrunken fibrotic kidney of autonephrectomy. Calcifications are seen in 30% to 50%



Figure 16–1. Kidney-ureter-bladder radiographic view in a patient with left renal tuberculosis with associated calcifications.



Figure 16–2. Occluded calyx.

of cases (Roylance et al, 1970). Focal calcifications occur within the caseating lesions (Fig. 16–1). A characteristic diffuse, uniform, extensive parenchymal, putty-like calcification, forming a lobar cast of the kidney is seen with autonephrectomy (Muttarak et al, 2005). Calculi may also be seen in the collecting system or ureter secondary to stricture formation. Ureteral calcifications are rare and are characteristically intraluminal as opposed to the mural calcifications of schistosomiasis. Bladder wall calcifications are not very common except in late cases of bladder contraction. Calcifications of the prostate and seminal vesicles are seen in 10% of cases (Burrill et al, 2007).

Plain film findings suggestive of tuberculosis may be seen in surrounding tissues such as erosions of the vertebral bodies or calcifications in a cold abscess of the psoas muscle (Burrill et al, 2007).

Intravenous Urography (IVU)

The majority of cases will show positive findings on excretory urography, the most common findings being hydrocalycosis, hydronephrosis, or hydroureter due to stricture formation (Wang et al, 2003). Early signs include the moth-eaten appearance of calyceal erosion and papillary irregularity. These signs are best seen on early excretory films, because they are often masked by increasing density of the contrast on later films of the IVU. Cavitary lesions communicating with the collecting system are characteristic of TB. These lesions eventually enlarge as parenchymal destruction ensues, and a picture similar to chronic pyelonephritis may be seen. Fibrotic distortion of the collecting system and ureter is also seen. Calyceal obliteration and amputation, hydrocalycosis, segmental or total hydronephrosis, and a shriveled reduced-capacity renal pelvis may all be signs of renal tuberculosis (Figs. 16–2 and 16–3). Scarring and angulation of the ureteropelvic



Figure 16–3. Severe calyceal and parenchymal destruction.



Figure 16–4. Stricture at the distal left ureter.

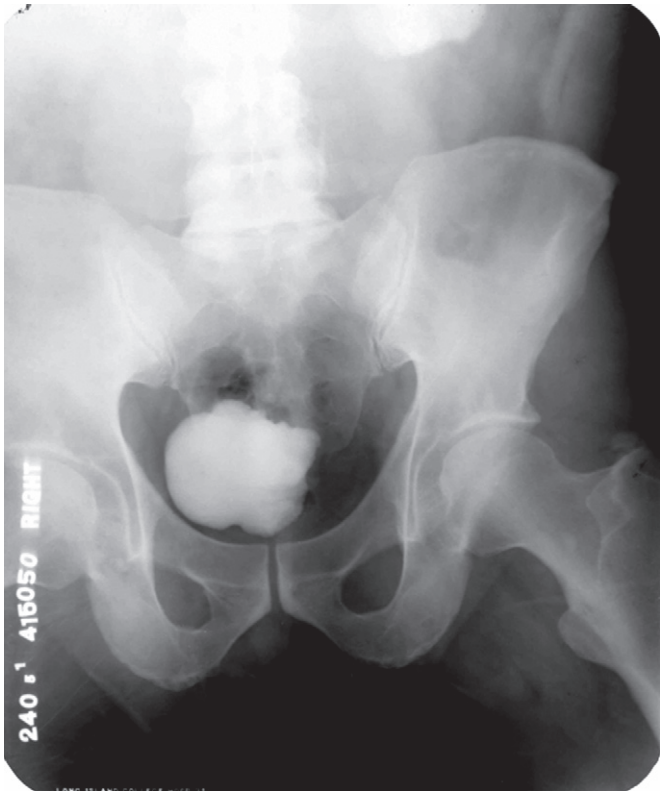


Figure 16–5. The cystogram portion of an intravenous pyelogram in a patient with left renal tuberculosis. Note the contracted left side of the bladder that is secondary to fibrosis from the tuberculosis.

junction (UPJ) may also occur, the so-called "Kerr's kink" (Matos et al, 2005). Ultimately diminished or absent function and extensive calcification may be seen with autonephrectomy. If nonvisualized on IVU, the kidney is best evaluated by computed tomography (CT) or ultrasonography.

Tuberculosis of the ureter is commonly seen as a rigid, straightened "pipe-stem" ureter. A beaded, corkscrew appearance is sometimes also seen. Ureterovesical junction obstruction is caused by tuberculous cystitis or strictures of the distal third of the ureter (Fig. 16–4). Secondary stone formation on top of this stricture is an occasional finding. The cystogram films may show a small contracted bladder due to excessive fibrosis (Fig. 16–5). Of note, although IVU is being phased out by CT-urography in many developed countries (Stacul et al, 2008), IVU continues to be a reliable imaging modality for genitourinary TB in most parts of the world.

Computed Tomography

The most common findings on contrast-enhanced CT include renal parenchymal masses and scarring, thick urinary tract walls (ureter and bladder) and extraurinary tubercular manifestations particularly in miliary TB (Wang et al, 2003). Coalescence of caseating granulomata may lead to a renal mass (tuberculoma), which must be differentiated from renal cell carcinoma. CT allows for evaluation of renal function, grading of hydronephrosis and parenchymal scarring (Fig. 16–6). CT is most sensitive in detecting renal calcifications (Premkumar, et al, 1987). Most CT findings are in themselves nonspecific, and the collective interpretation of multiple findings in conjunction with the clinical picture is the best option in decision making (Wang et al, 2003).

CT is also helpful in the diagnosis of adrenal tuberculosis, which may appear as bilaterally enlarged glands with areas of necrosis (caseation) early in the disease. Dotlike calcifications and atrophy of the adrenal gland are common late findings (Wang, et al, 1998).

Tuberculosis of the prostate or seminal vesicles may lead to calcification, caseation, and necrosis causing hypoattenuation or cavity formation that can be visualized on contrast-enhanced CT scan of the pelvis. However, in the absence of calcification,



Figure 16–6. CT after oral contrast medium in a patient with bilateral tuberculosis. The right kidney is hydronephrotic secondary to infundibular stenosis but has retained good function. The left kidney is an end-stage nonfunctioning atrophic kidney with calcification.

tuberculous prostatic lesions may mimic a pyogenic abscess or carcinoma, especially that prostate-specific antigen (PSA) may be elevated in one third of cases (Lee et al, 2001). Needle biopsy may be needed in these cases.

Ultrasonography

Ultrasonography has a limited role in diagnosis because it provides nonspecific findings. However, it may be used to follow up cases

presenting with hydronephrosis during the course of treatment; fibrotic scarring during healing may lead to worsening of hydronephrosis, thus requiring surgical attention. Ultrasonography is useful in the demonstration of epididymal and testicular lesions. Transrectal ultrasonography may also show seminal vesicular and prostatic lesions. All findings are nonspecific and should be interpreted in light of the clinical picture.

Retrograde Pyelogram and Antegrade Pyelogram

Diagnosis using contrast studies by directly injecting a contrast medium, whether using endoscopy or percutaneous puncture, have largely been superseded by noninvasive imaging techniques such as CT urography and magnetic resonance imaging (MRI). The value of these modalities lies in the ability to obtain a urine sample from the upper tract, particularly where it is important to identify the affected side (as in surgical planning). Percutaneous puncture is particularly useful in cases where fibrosis has sealed the affected side, such that organisms are no longer discharged in urine. A ureteric stent or nephrostomy tube may be placed, at that time, to bypass a stricture or drain infected material in a septic patient.

Cystoscopy and Ureteroscopy

Endoscopy plays a limited role in the diagnosis of TB. Despite direct visualization of lesions, there are no pathognomonic findings that are specific for tuberculosis. Ulcerative lesions may mimic malignancy. A "golf-hole" ureteric orifice is suggestive of tuberculosis, and, when found, upper tract imaging or endoscopy should be obtained (Fig. 16–7). A positive urine culture or stain for acid-fast bacilli obviates the need for a biopsy, especially because it is diagnostic in only 18% to 45% of cases (Wong et al, 1984; Hemal et al, 2000b). However, a biopsy should be done when in doubt of malignancy.

Treatment

Successful treatment of genitourinary tuberculosis relies on the early diagnosis and the prompt initiation of an adequate drug regimen. Prior to successful antituberculous chemotherapy extirpative surgery was the initial form of treatment. Currently surgical treatment is reserved for advanced cases, often to correct the obstructive effects of fibrosis and scarring rather than the removal of infected tissues. Thus the balanced medical-surgical approach is ideally aimed at the preservation of renal (organ) function and eradication of mycobacteria. Despite standardized regimens and surgical indications, treatment must also be individualized; "No disease process is as atypical as a typical tuberculous process" (Cooper and Robinson, 1972).

Medical Therapy

On November 20, 1944, streptomycin was administered for the first time to a critically ill TB patient. His advanced disease was clearly arrested, and mycobacteria disappeared from his sputum. A succession of antimycobacterial agents rapidly appeared in the years that followed.

The principle underlying medical treatment is the effective eradication of the slowly dividing mycobacteria from tissues and urine. To understand the basis for modern-day multidrug regimens for tuberculosis, it is important to contemplate the following dilemma: Mycobacteria exist in several different environments in genitourinary tract TB. The largest population is the more actively dividing extracellular mycobacteria that exist within cavitary lesions, often at a neutral or alkaline pH. Another population exists in the intracellular acidic environment within macrophages. A smaller population of slowly dividing organisms can be found enclosed within caseous material at a neutral pH or freely in the acidic pH of urine (Dutt and Stead, 1982). The differential ability of various antimycobacterial drugs to penetrate tissues, inherent effects on the tubercle bacillus (bactericidal vs. bacteriostatic), and their levels of activity in the wide range of pH required to manage genitourinary TB (as discussed under the individual drugs below), dictates the use of a multidrug regimen. This is in addition to the standard principle of lowering the emergence of drug-resistant strains.

Genitourinary TB can safely be managed with short-course chemotherapy (Dutt et al, 1986; Small and Fujiwara, 2001). This treatment is effective because there are fewer organisms in genitourinary lesions; isonicotinic acid hydrazide (isoniazid, INH) and rifampicin have good penetration of lesions at lethal concentrations; and isoniazid, rifampicin, and pyrazinamide attain high concentrations in urine (Gow and Barbosa, 1984).

Classically, antimycobacterial regimens rely on a first line of drugs, namely, rifampicin, INH, pyrazinamide, and ethambutol. A second line of drugs is reserved for cases that fail to respond to first-line therapy or in drug-resistant cases. Finally, it is important to acknowledge the rising incidence of multidrug resistant (MDR-TB) and extensively drug resistant TB (XDRTB) infections, and the resultant implications for the drug regimens used (Johnston et al, 2009).

A standard treatment regimen for tuberculosis requires 6 months of therapy. The first 2 months involve three to four drugs: Rifampicin, isoniazid, and pyrazinamide are administered daily; ethambutol is added if drug resistance to isoniazid is suspected. An additional 4 months of rifampicin and isoniazid daily, twice per week, or three times per week are used (Small and Fujiwara, 2001). The intensive 2-month, three-drug regimen targets rapid multipliers, and the prolonged 4-month, two-drug regimen eradicates slow, sporadic multipliers and persistent bacteria. Directly observed therapy is often best to ensure patient compliance and completion of treatment.

It is important to obtain adequate specimens for culture and susceptibility testing before treatment is initiated. Ethambutol can be stopped if lack of resistance is demonstrated. Baseline measurements of hepatic enzymes, bilirubin, and creatinine, and a complete blood count with a platelet count, should be performed. During treatment, all patients should be monitored for adverse effects on a monthly basis. Routine follow-up of liver enzymes is important to detect hepatotoxicity of rifampicin. If pyrazinamide is used, uric acid levels should be measured, and if ethambutol is given, visual acuity and red-green color perception should be monitored (Small and Fujiwara, 2001) (Tables 16–2 and 16–3).

Antituberculous Drugs

Isoniazid

Isoniazid (INH) acts by inhibition of cell wall lipid synthesis, depletion of nucleic acid pools, and metabolic depression in mycobacteria (Timmins and Deretic, 2006). It penetrates caseous material and is active within the macrophages. INH is rapidly and completely absorbed orally; this may be slowed by food. It is widely distributed in the body, and tissue levels are similar to serum levels. Seventy percent of all administered INH is excreted by the kidneys, most in an inactive form. Dose modification in renal failure is usually not necessary but is recommended

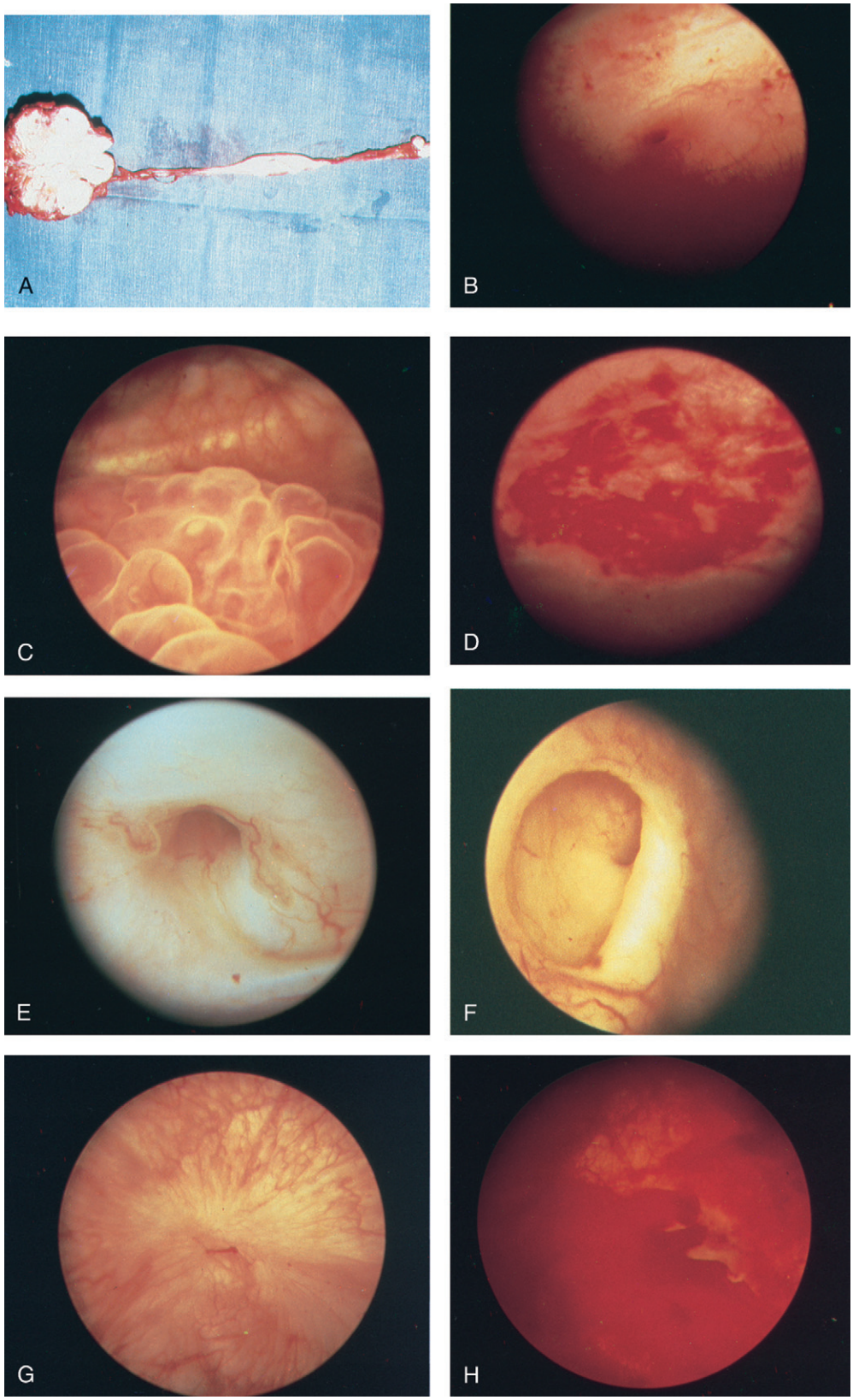


Figure 16–7. **A,** Extensive tuberculosis of the kidney and ureter with calcification and stricture formation. **B,** Acutely inflamed ureteric orifice. **C,** Tuberculous bullous granulations. **D,** Acute tuberculous ulcer. **E,** Tuberculous golf-hole ureter. **F,** Tuberculous golf-hole ureter, severely withdrawn. **G,** Healed tuberculous lesion. **H,** Acute tuberculous cystitis with ulceration.

Table 16–2.

First-Line Antituberculous Drugs

DRUG/FORMULATION	ADULT DOSAGE (DAILY)*	ADULT DOSAGE (INTERMITTENT)†	MAIN ADVERSE EFFECTS
Isoniazid (INH)‡ 100, 300 mg tabs 50 mg/5 mL syrup 100 mg/mL injection	5 mg/kg (max 300 mg) PO, IM, IV	15 mg/kg (max 300 mg) 2-3 times/week	Hepatic toxicity, peripheral neuropathy
Rifampin (Rifadin, Rimactane) 150, 300 mg caps 600 mg injection powder	10 mg/kg (max 600 mg) PO, IV	10 mg/kg (max 600 mg) 2-3 times/week	Hepatic toxicity, flulike syndrome, pruritus, drug interactions
Rifabutin§ (Mycobutin) 150 mg caps	5 mg/kg (max 300 mg) PO	5 mg/kg (max 300 mg) 2-3 times/week	Hepatic toxicity, flulike syndrome, uveitis, neutropenia, drug interactions
Rifapentine (Priftin) 150 mg tabs		10 mg/kg/wk PO (max 600 mg) continuation phase only	Similar to rifampin
Pyrazinamide 500 mg tabs	20-25 mg/kg PO	30-50 mg/kg 2-3 times/week (max 4 g); 3 times/week (max 3 g)	Arthralgias, hepatic toxicity, pruritus, rash, hyperuricemia, gastrointestinal upset
Ethambutol¶ (Myambutol) 100, 400 mg tabs	15-25 mg/kg PO	20-50 mg/kg 2-3 times/week (max 4 g); 3 times/week (max 2.4 g)	Decreased red-green color discrimination, decreased visual acuity, optic neuritis

*5 times/week regimen may be done with direct observed therapy.
†Intermittent therapy is started after a few weeks or months of daily treatment.
‡Pyridoxine, 25 to 50 mg, should be given to prevent neuropathy in malnourished or pregnant patients and those with HIV infection, alcoholism, or diabetes.
§For use with amprenavir, fosamprenavir, nelfinavir, or indinavir, the rifabutin dose is 150 mg/day or 300 mg two to three times a week. For use with atazanavir, ritonavir alone or combined with other protease inhibitors, and lopinavir/ritonavir, the rifabutin dose is further decreased to 150 mg every other day or three times weekly. For use with efavirenz, the rifabutin dose is increased to 450 to 600 mg/day or 600 mg two to three times weekly. Not recommended with saquinavir alone or delavirdine.
¶Some clinicians use 25 mg/kg/day during the first 1 or 2 months, or longer if organism is isoniazid resistant. Decrease dosage if renal function diminished.
From The Medical Letter. Drugs for tuberculosis. Treat Guidel Med Lett 2009;7(86):75–82; quiz 2 (after p. 82).

Table 16–3.

Some Second-Line Antituberculous Drugs

DRUG/FORMULATION	ADULT DOSAGE (DAILY)	MAIN ADVERSE EFFECTS
Streptomycin*	15 mg/kg IM, IV (max 1 g)	Vestibular and auditory toxicity, renal damage
Capreomycin (Capastat)	15 mg/kg IM, IV (max 1 g)	Auditory and vestibular toxicity, renal damage, electrolyte imbalance
Kanamycin (Kantrex and others)	15 mg/kg IM, IV (max 1 g)	Auditory toxicity, renal damage
Amikacin (Amikin)	15 mg/kg IM, IV (max 1 g)	Auditory toxicity, renal damage
Cycloserine† (Seromycin and others)	10-15 mg/kg in two doses (max 500 mg bid) PO	Psychiatric symptoms, seizures
Ethionamide (Trecator-SC)	15-20 mg/kg in two doses (max 500 mg bid) PO	Gastrointestinal and hepatic toxicity, hypothyroidism
Levofloxacin (Levaquin)	500-1000 mg PO, IV	Nausea, abdominal pain, restlessness, confusion, rash dysglycemia
Moxifloxacin (Avelox)	400 mg PO, IV	Nausea, abdominal pain, restlessness, confusion, rash dysglycemia
Aminosalicylic acid (PAS; Paser)	8-12 g in 2-3 doses PO	Gastrointestinal disturbance

*Streptomycin is generally given 5 to 7 times per week (15 mg/kg, or a maximum of 1 g per dose) for an initial 2- to 12-week period and then, if needed, two to three times per week (20 to 30 mg/kg, or a maximum of 1.5 g per dose). For patients >59 years old, dosage is reduced to 10 mg/kg/day (max 750 mg/day). Dosage should be decreased if renal function is diminished.
†Some authorities recommend pyridoxine, 50 mg, for every 250 mg of cycloserine to decrease the incidence of adverse neurologic effects.
From The Medical Letter. Drugs for tuberculosis. Treat Guidel Med Lett 2009;7(86):75–82; quiz 2 (after p. 82).

in hepatic failure, especially in persons who are slow hepatic acetylators.

INH is associated with hepatic toxicity in 10% to 20% of patients, usually in the form of asymptomatic elevations of transaminase levels. This occurs after 6 to 8 weeks of therapy and may normalize with continued INH treatment. Baseline liver function tests should be obtained, and INH should be stopped if the aminotransferase level triples or if symptoms suggestive of hepatitis develop (fatigue, nausea, anorexia), because severe hepatic necrosis has been reported. Peripheral neuropathy due to INH can be prevented by supplementation with pyridoxine (vitamin B_6) 20 to 50 mg/day. INH is an inhibitor of the hepatic cytochrome P-450

system; thus it increases serum levels of anticonvulsants, warfarin, benzodiazepines, haloperidol, theophylline, tacrolimus, and ketoconazole.

Rifampicin

Rifampicin acts by inhibiting the β-subunit–dependent DNA-directed RNA polymerase of mycobacteria, leading to suppression of DNA synthesis (Sousa et al, 2008). The drug is lipid soluble, enters macrophages, and is excreted in the urine.

Hepatotoxicity is the major adverse reaction to rifampicin. Liver failure requires a moderate reduction in dosage, but full doses can be given with renal insufficiency. Rifampicin decreases serum levels of digoxin, verapamil, diltiazem, warfarin, sulfonylureas, progestins, theophylline, diazepam, corticosteroids, and several other drugs.

Streptomycin

Streptomycin is an aminoglycoside and binds to the S12 protein of the 30S unit of the bacterial ribosome, interfering with bacterial protein synthesis. It penetrates the walls of tuberculous abscesses at lethal concentrations, even in caseous material, and is active mainly against extracellular tubercle bacilli because its penetration into cells is poor. High concentrations are obtained in the urine. Isolates resistant to streptomycin are not resistant to other aminoglycosides. It must be given intramuscularly because it is very poorly absorbed orally. Streptomycin is ototoxic, causing vertigo and hearing loss. It is also nephrotoxic. Toxicity is dose related, and the risk is increased in the elderly; dose adjustment according to renal function is necessary.

Pyrazinamide

Pyrazinamide is a derivative of nicotinamide. Its target and mechanism of action are not fully known. Being highly active at pH 5.5 makes it suitable for genitourinary tuberculosis. It is readily taken up by macrophages and is active in the acidic intracellular milieu against mycobacteria within lysosomes. Gastrointestinal disturbances, hepatotoxicity (in 1% to 5% of patients), arthralgias, and hyperuricemia are some of its side effects.

Ethambutol

Ethambutol halts mycobacterial cell wall synthesis by inhibition of arabinosyl transferases. It is active against *M. tuberculosis* strains resistant to INH and other commonly used antituberculous drugs. It is well absorbed after oral administration. Up to 80% is excreted in the urine as active unchanged drug; dosage should be reduced in renal failure. Ethambutol rarely causes retrobulbar neuritis and should be discontinued if ocular changes occur. Changes in visual acuity and red-green color perception are early findings, and these parameters should be tested at baseline and monthly therafter.

Corticosteroids

Steroids have a limited role in management of genitourinary TB. The general rational behind their use is lowering the host immune response that is responsible for the tissue destruction and subsequent scarring. In cases of severe acute tuberculous cystitis, steroids may reduce mucosal inflammation and improve symptoms. Of note, higher doses of oral steroids are needed because rifampicin will increase their hepatic metabolism.

Multidrug-Resistant TB

Drug-resistant tuberculosis is defined as *M. tuberculosis* that is resistant to one of the first-line antituberculosis drugs (isoniazid, rifampin, pyrazinamide, or ethambutol).

Multidrug-resistant tuberculosis (MDR-TB) refers to *M. tuberculosis* that is resistant to at least isoniazid *and* rifampin, and possibly additional chemotherapeutic agents.

Extensively drug-resistant tuberculosis (XDR-TB) refers to *M. tuberculosis* that is resistant to at least isoniazid and rifampin, and is additionally resistant to fluoroquinolones and either aminoglycosides (amikacin, kanamycin) or capreomycin, or both (Centers for Disease Control and Prevention [CDC], 2007). Typical MDR-tuberculosis regimens can consist of up to five drugs, used for a minimum of 18 months after culture conversion to negative. XDR tuberculosis requires individualized treatment based on drug-susceptibility testing of the particular organism (Rich and World Health Organization, 2006). Drug regimens combining linezolid with other companion drugs selected according to individual drug history, and tailored to the susceptibility results of each isolate, are currently being evaluated (Schecter et al, 2010).

Surgical Therapy

About 55% of patients with genitourinary TB will require surgical intervention. This rate is lower in areas where the disease is diagnosed early, while still asymptomatic. In developing countries, where the disease is diagnosed in late stages, often after examination of nephrectomy specimens, this rate maybe as high as 95% (Figueiredo et al, 2008). The role of surgery has changed in the era of effective antitubercular treatment. Surgical intervention compliments medical treatment in preservation and restoration of organ function. Ablative surgery is performed less commonly and should be considered carefully. The earlier diagnosis and chemotherapy have allowed reconstructive procedures to be performed more commonly today, even in advanced cases. Currently, more than half of surgeries performed for TB are reconstructive (Gupta et al, 2006). Moreover, surgical treatment is best carried out after an initial 3 to 6 weeks of medical treatment. This interval allows intense inflammatory changes to resolve and lesions to stabilize, permitting a better assessment of the extent of destruction, and hence doing the appropriate procedure. In the setting of obstruction and deteriorated kidney function, initiation of medical treatment can temporize definitive surgical intervention until renal function recovers, provided that measures are taken to relieve the obstruction (e.g., ureteric stenting or percutaneous nephrostomy).

Indications for surgical management follow broad lines: procedures to relieve obstruction and drain infected material, definitive local treatment, upper urinary tract reconstruction, lower urinary tract reconstruction, and surgery for genital TB.

Procedures to Relieve Obstruction

The prompt relief of obstruction is emergently required in cases of uremia or sepsis. Bilateral hydronephrosis or unilateral hydronephrosis of a solitary or functionally solitary kidney is often the cause of renal failure. Early ureteral stenting or percutaneous nephrostomy (PCN) for tuberculous ureteral strictures have been demonstrated to decrease the loss of renal function and increase the opportunity for later reconstructive surgery (Shin et al, 2002). In such cases, temporary and immediate drainage of hydronephrosis, preferably by retrograde ureteric stenting if possible, is required. An indwelling double J stent can be left until the patient's condition is optimized. Retrograde placement is successful in 41% of cases (Ramanathan et al, 1998). When this is not technically feasible, percutaneous puncture of the hydronephrotic kidney is done to pass an antegrade stent. If that also fails, a percutaneous tube is left until definitive management is done. In cases of

segmental hydronephrosis, more than one PCN may be required to achieve adequate drainage (Carl and Stark, 1997). It is important to understand that PCN placement must be followed by correcting the cause of obstruction. A tuberculous cutaneous fistula invariably develops if the PCN is simply removed. If the renal unit is deemed unsalvageable or shows no function, a nephrectomy is inevitable to prevent this complication. One pitfall to avoid during stent placement is the use of high-contrast injection pressures, because this may lead to possible dissemination of infection (Salem, 2008).

Nephrectomy

Upfront (primary) nephrectomy to remove an infected kidney or debride caseous tissue is no longer the preferred line of treatment of genitourinary TB in the era of modern antitubercular chemotherapy. Today, the decision for a nephrectomy is based upon the extent of renal parenchymal destruction and, more importantly, the function of the kidney (Ramanathan et al, 1998). The indications for nephrectomy have thus been reduced to the excision of a renal unit that is nonfunctioning despite adequate drainage and medical treatment (Gupta et al, 2006). Other indications include extensive parenchymal destruction involving the whole kidney associated with hypertension (Flechner and Gow, 1980). Coexisting renal carcinoma also mandates nephrectomy. The current paradigm implies that chemotherapy is sufficient to render lesions free of mycobacteria even in nonfunctioning kidneys. However, removal of a calcified nonfunctioning kidney may be curative in patients with persistent symptoms (predominantly those of cystitis), because up to 50% of cases may still discharge mycobacteria in urine despite adequate chemotherapy (Fischer and Flamm, 1990).

A standard lumbar incision provides adequate exposure sufficient to carry out the dissection and control of the kidney. Every effort should be taken to avoid inadvertent entry into the peritoneal or pleural cavities. It is often possible to preserve the adrenal gland. In rare cases, the perinephric fat may appear to have tubercles or caseous cavities. These should not be dissected from the kidney and should be removed with the specimen. Dense fibrosis, due to healing of such lesions after chemotherapy, is more commonly encountered in the perirenal tissues or surrounding the renal pedicle. Control of the renal artery and vein, separately, may be difficult in these cases, and the pedicle may be controlled in toto by suture ligation. Routine removal of the ureter is not necessary. Retroperitoneoscopic nephrectomy has been attempted successfully for tuberculous kidneys (Hemal et al, 2000a).

Partial Nephrectomy

Partial nephrectomy is permissible only where parenchymal destruction is clearly localized, such as a calcified polar cavitary lesion or localized lesions that progress to calcification despite 6 weeks of adequate chemotherapy. Early localized lesions are adequately managed by medical treatment. It is prudent to ensure that no obstruction is present at the level of the renal pelvis or ureter to avoid tuberculous fistula formation.

Ureteropelvic and Ureteral Surgery

Strictures of the UPJ and ureter may be temporarily stented, as mentioned above, to allow improvement of renal function, after which a definitive decision on the appropriate management of the stricture is made. Upper and midureteric strictures are rare and may be amenable to endourologic treatment. Lower ureteric strictures are the commonest form and will often require surgical intervention. Additionally, the length of a stricture, whether it is passable or not, and renal function are important factors to be considered.

Endoscopic Management. Several options are available for the endourologic management of ureteric strictures. Tuberculous ureteric strictures are characterized by mucosal ischemia and dense fibrosis. Hence, success rates of endoscopic management of strictures due to other etiologies may not necessarily apply to TB strictures. Generally, short, passable strictures, with good renal function yield the best endoscopic outcome.

Strictures forming during medical treatment and managed by early stenting (double J placement) have been shown to stabilize and require no further treatment (Shin et al, 2002). Balloon dilatation by retrograde or antegrade access has been described for TB strictures of the ureter, UPJ, and calyceal infundibula (Murphy et al, 1982; Kim et al, 1993). A stent is left after dilatation. Due to high failure rates, repeated procedures are needed.

Follow-up of all cases of ureteric strictures by imaging (ultrasonography or IVU), especially those managed endoscopically, is needed because some strictures will worsen during the healing process due to fibrosis and cicatrization. Corticosteroids may be added if deterioration is detected. Consequently, up to 72% of cases will show relief of obstruction (Horne and Tulloch, 1975), and stent placement, if still needed, is often possible at this time. Failure to respond or progression after 6 weeks is an indication for definitive management.

Surgical Options. Long, complex strictures require surgical repair. It must be kept in mind that due to loss of elasticity, fibrosis, and reduced vascularity, mobilization of structures may be difficult, and thus the surgeon should be open to alternative options.

Repair of the ureteropelvic junction scarring is more challenging in TB cases than for congenital stenosis. The choice of procedure largely depends on the degree of scarring and contraction of the pelvis. Dismembered pyeloplasty is feasible for extrarenal pelvis with short segment scarring. Nondismembered (flap) pyeloplasty is preferred for longer strictures, but may not be feasible due to excessive scarring of the pelvis. When anatomic reconstruction is not possible, ureterocalicostomy (ureter to the lower pole calyx) is an option. It is important to cover the exposed lower pole parenchyma (using preserved capsule or omentum) to avoid fibrosis and constriction around the anastomosis (Carl and Stark, 1997).

Upper and middle ureteric strictures can be managed by excision of the diseased segment and, with adequate mobilization, a primary tension-free ureteroureterostomy can be performed if endourologic management has failed. Alternatively, lysis of adhesions and intubation (Davis intubated ureterotomy) may be done.

Lower ureter strictures requiring surgery are best managed by complete excision of the entire affected ureteric segment back to healthy ureteric mucosa having good blood supply. Affection of the bladder around the ureteric orifice is also common, and the area of anastomosis must also be healthy. The main focus then becomes to bridge the resultant gap with a tension-free, well-vascularized anastomotic technique. An array of ureteroneocystostomy procedures exist to bring the bladder closer to the ureteric end. Salient points are discussed briefly here; surgical details can be found under ureteroneocystostomy. Simple mobilization of the lateral attachments of the bladder on the contralateral side, accompanied by dividing the superior vesical artery, may provide 2 to 3 cm of length to bridge a small gap. In patients with good bladder capacity, a psoas hitch may also be performed. The genitofemoral and femoral nerves are close in the vicinity, and care must be taken to avoid their injury when placing these sutures. A well-performed psoas hitch can bridge a gap of up to 5 cm.

Constructing a Boari flap is another method of bridging a longer gap of up to 10 cm, and may also be performed in combination with a psoas hitch. It is important to note that a poorly executed Boari flap can compromise bladder capacity. In addition, small or contracted fibrotic bladders of tuberculous cystitis may not have sufficient wall area to allow flap creation. Finally, ileal interposition (ileal ureteric replacement) can be done in cases of multiple or recurrent strictures, where the native ureter is no longer an adequate conduit.

Bladder Surgery

Augmentation cystoplasty and bladder substitution are options in the management of the tuberculous contracted bladder. A capacity of less than 100 mL is commonly the indication to augment. Extremely contracted bladders (thimble bladders of 20 mL capacity) are best managed by orthotopic bladder substitution (Hemal and Aron, 1999). Various bowel segments have been used, and the general rules of incorporating the bowel into the urinary tract apply, such as thoroughly evaluating renal functions, reconfiguring a low pressure reservoir (de Figueiredo et al, 2006), patient education, and long-term follow-up.

Prostate and Urethra

Bladder neck contracture or severe granulomatous prostatitis is best managed endoscopically by transurethral incision of the contracture or resection of the prostate. A tuberculous prostatic abscess can be managed by transurethral drainage or aspiration with ultrasound guidance.

Urethral strictures may also be managed endoscopically and will often require repeated procedures. Tuberculous urethral fistulae are best managed by initiation of medical therapy and suprapubic bladder drainage. Delayed reconstruction is preferred.

Drainage of a seminal vesicle TB cavity into the bladder by cold knife incision has been reported (Dewani et al, 2006).

Genital TB

Surgery is considered only for established male genital tuberculosis when symptoms have failed to respond to chemotherapy and for nonresolving caseating abscesses. Surgical options involve excision of the diseased tissue. Involvement of the epididymis without clear affection of the testis is often the case, and every effort should be made to perform an epididymectomy rather than excision of the testis. Preserving testicular blood supply is important during the tedious dissection of the epididymis. Initiating dissection at the globus minor after ligation of the vas facilitates excision. If testicular involvement is evident, a scrotal orchiectomy is done. Involvement of the vas deferens by TB is usually distal to the external ring and ligation of at the level of the ring is possible and sufficient.

Management of Genitourinary TB in Special Situations

Pregnancy and Lactation

Females of the childbearing age should be advised to avoid pregnancy while on antituberculous treatment. If the diagnosis is discovered during pregnancy, prompt treatment is initiated because risks to the fetus from TB outweigh the risk of adverse drug effects. Pregnancy is allowed to continue, and a drug regimen consisting of isoniazid, ethambutol, and rifampicin, in addition to pyridoxine supplements, is started and should continue for 9 months.

During lactation, pyridoxine should be given while on isoniazid because this drug is significantly excreted in breast milk. Ethambutol is sparsely excreted in milk, and risk of ocular toxicity is rare.

HIV Infection

Patients diagnosed with TB should be tested for HIV infection. HIV-positive individuals with recent contact with a TB case should receive empiric treatment of latent TB, regardless of screening test results. Patients on maintenance treatment for active TB should be placed on daily or three times a week regimens rather than weekly regimens to avoid the emergence of drug-resistant strains, particularly in patients with CD4 counts <100 cells/mm^3 (Nettles et al, 2004). Treatment should continue for a minimum of 9 months. Drug interactions with components of a highly active antiretroviral (HAART) regimen should be taken into consideration. Rifampicin may decrease the serum levels of HAART drugs to possibly ineffective levels. Dose increases may be needed to compensate for this effect.

Renal Transplant Recipients

Tuberculosis should be considered in the differential evaluation of a recipient with unexplained fever and constitutional manifestations. The risk is highest in recipients born in or who live in endemic areas, and the peak incidence occurs during the first year after transplantation (el-Agroudy et al, 2003). Urinary tract involvement occurs in up to 50% of cases. PPD skin testing may be falsely negative in 70% of cases due to anergy. A repeat test after one week may increase the diagnostic yield by 10%. Thus PCR analysis, or DNA probing, of urine is the recommended method of detection. Rejection may also complicate the presentation of allograft tuberculosis.

PPD-positive patients in pretransplantation evaluation should receive isoniazid prophylaxis for at least 6 months. Four drug regimens are used for treatment, which typically lasts for 18 months. Rifampicin induces the hepatic P-450 microsomal enzyme and may substantially decrease serum levels of cyclosporine, tacrolimus, and prednisolone below therapeutic levels, necessitating dose increases and frequent monitoring of serum drug levels. Rifampicin-free regimens have also been used (Khaira et al, 2009).

Renal Failure

Renal failure patients, particularly those on chronic dialysis, have a markedly increased risk for TB. Early diagnosis prevents a high mortality associated with this presentation (Hussein et al, 2003). Most antitubercular drugs need dose adjustments in the presence of various degrees of renal failure and in patients on hemodialysis and chronic ambulatory peritoneal dialysis. Reference should be made to dosing methods (interval increase or dose reduction) and clearance on dialysis of each drug.

PARASITIC DISEASES OF THE GENITOURINARY SYSTEM

Parasitic diseases remain a significant health problem, especially in resource-poor countries. The human urogenital tract is typically only affected by a few species of parasites (Richens, 2004; Kehinde, 2008). This chapter will discuss in detail *Schistosoma haematobium*, a blood trematode that causes severe genitourinary tract disease, and the filarial helminth infections of the generas *Wuchereria*, *Brugia*, and *Onchocerca*, which may result in hydrocele, chyluria, funiculoepididymitis, and genital elephentiatis. Involvement of the genitourinary tract by other parasites (except sexually

transmitted protozoa) is either subordinate to systemic manifestations or rare.

Billions of people harbor parasites, yet symptomatic infections are substantially less common. Parasitic infection does not always result in parasitic disease, depending on the intensity and duration of infection, as well as the contributing sequelae of inflammatory responses to the presence of parasites and/or their biologic products.

Increasing international travel, globalization of the economy, and jet travel increasingly results in uncommon and tropical diseases presenting in the offices of physicians far from endemic areas. The most important requirement for recognition of parasitic infections is awareness, based on knowledge of common clinical presentations, pathogenesis, and geographic distribution of parasitic diseases. The importance of careful history-taking should include questions of recent and remote travel. Additional probing can assist in establishing the likelihood of specific parasitic infections. Helpful cogent information on parasitic infections is available from the Centers for Disease Control and Prevention at www.dpd.cdc.gov/dpdx/. One of the best available resources for current knowledge on available drug therapies for parasitic infections is available from The Medical Letter (2010) (www.themedicalletter.com).

Urinary Schistosomiasis

History

Schistosomiasis is a chronic infection caused by the digentic parasitic trematodes of the genus *Schistosoma*. Human infection begins with free-swimming cercariae penetrating the skin and eventual development of the adult male and female worms. The threadlike female schistosome lies within a cleft in the body of the male worm, remaining in a state of permanent copulo for many years. The paired adult worms reside in the venous plexuses of the abdominal viscera. *S. mansoni* and *S. japonicum* reside in the mesenteric veins, leading to gastrointestinal and/or hepatic disease, while *S. haematobium* dwells principally in the perivesical venous plexus, resulting in urinary schistosomiasis.

Urinary schistosomiasis has been a scourge of the Middle East and Africa for millennia and remains a major cause of morbidity and mortality in these areas. Egyptian physicians of the twelfth dynasty (1900 BC) recognized hematuria as the cardinal sign and symptom of this disease. Theodore Bilharz, a German pathologist working in Cairo in 1852, first described worm pairs in mesenteric veins at autopsy and linked these to eggs found in human excreta.

Biology and Life Cycle

The life cycle of *S. haematobium* is outlined in Fig. 16–8 (King, 2006). The male and female worm pair and attach to the blood vessel endothelia, producing and depositing 200 to 500 eggs per day. The estimated common life span of 3 to 6 years (Butterworth et al, 1988) means a single worm pair can produce 250,000 to 600,000 eggs. Rare cases of long-lived worm pairs, of up to 30 years, are capable of inducing greater pathology (De Gentile et al, 1988).

According to experimental data, the majority of eggs microembolize in the microvasculature of the lungs, liver, and other sites (Cheever and Anderson, 1971), while 20% of the eggs cross into the lumina of the hollow viscera near the adult pair. Hence, for *S. haematobium* the eggs are predominantly excreted in the urine with some finding their way into the feces. The eggs entrapped in tissue become calcified and accumulate in the viscera at a rate of 90 to 100 per worm pair per day (Cheever et al, 1977). These eggs are destroyed by the host gramulomitis immune response which may result in clinical morbidity and possible mortality.

S. haematobium eggs measure 80 to 150 μm, are ovoid, and have a small spine at their terminal end. This differentiates them from the laterally spined *S. mansoni* eggs. *S. chyponecum* has a tiny lateral spine. The only other schistosome that is pathogenic for humans and has a terminally spined egg, *S. interculotum*, is rarely seen outside limited foci in the Republic of Congo, Gabon, and Cameroon (WHO, 1993). Diagnostic terminally spined eggs can be found in the urine, feces, or human tissue especially intestinal or bladder wall biopsy. Due to the ongoing nature of infection and egg production, all egg stages are seen during active infection. Once the infection is treated, only degenerated or calcified eggs can be found.

If viable eggs are placed in fresh water, the miracidia emerge as short-lived ciliated larvae that swim to seek intermediate snail hosts. For *S. haematobium* snails of the *Bulinus* species (Ross et al, 2002) can perpetuate the life cycle. The miracidia migrate through tissues and then transform into successive generations of sporocysts. An amplification cascade finds each miracidium developing into a sporocyst, which produces 20 to 40 daughter sporocysts, which each in turn produce 200 to 400 cercariae. The cercariae escape the daughter sporocyst, migrate to the snail surface, and emerge into the surrounding fresh water. This enormous asexual multiplication from a single miracidium to 10^5 cercariae compensates for the attrition during aquatic parts of the life cycle. The cercariae must penetrate unbroken skin of appropriate hosts within a few hours or they die. For *S. haematobium*, the developmental process from cercarial body to schistosomulum to adult pair may require 80 to 110 days.

Epidemiology

Of the 200 million persons afflicted with schistosomiasis, 80 to 90 million are infected with *S. haematobium* (Mahmoud and Abdel Wahab, 1990; WHO, 1998, 2002; Engels et al, 2002), and as many as 10 to 40 million have obstructive uropathy or other complications secondary to this parasitic disease. Transmission of *S. haematobium* occurs in many countries in the Middle East and in most of the African continent. In Southwest Asia, the disease is found in Southern Yemen, Yemen, Saudi Arabia, Lebanon, Syria, Turkey, Iraq, and Iran (WHO, 1998).

Clinical and autopsy studies have demonstrated a correlation between the prevalence of infection and its intensity with levels of egg excretion or tissue egg burden (Smith et al, 1974b). The tissue egg burden is related to the severity of the disease and to the frequency of complications. Autopsy studies have shown that severe urinary pathology is uncommon when the frequency of infection in a population is less than 30%, but increases linearly after this threshold is exceeded (Cheever et al, 1978).

Pathogenesis and Pathology

Schistosomal disease results directly from the granulomatous host response to schistosome eggs (Phillips and Colley, 1978; Cheever et al, 1985; Waine and McManus, 1997). During ongoing human infections all stages of granulomas are simultaneously present; whereas, in treated or burned-out infection the granulomas are uniform (Cheever et al, 1985). Four factors contribute to this spectrum of significant disease related to *S. haematobium*: intensity, duration, activity, and focality. These factors also determine the morbidity, mortality, and treatment of urinary schistosomiasis.

Though *S. haematobium* adult worm pairs are widely distributed in the pelvic venous plexuses, egg-laying occurs mainly in the lower urinary tract, the site of pathologic manifestations (Cheever

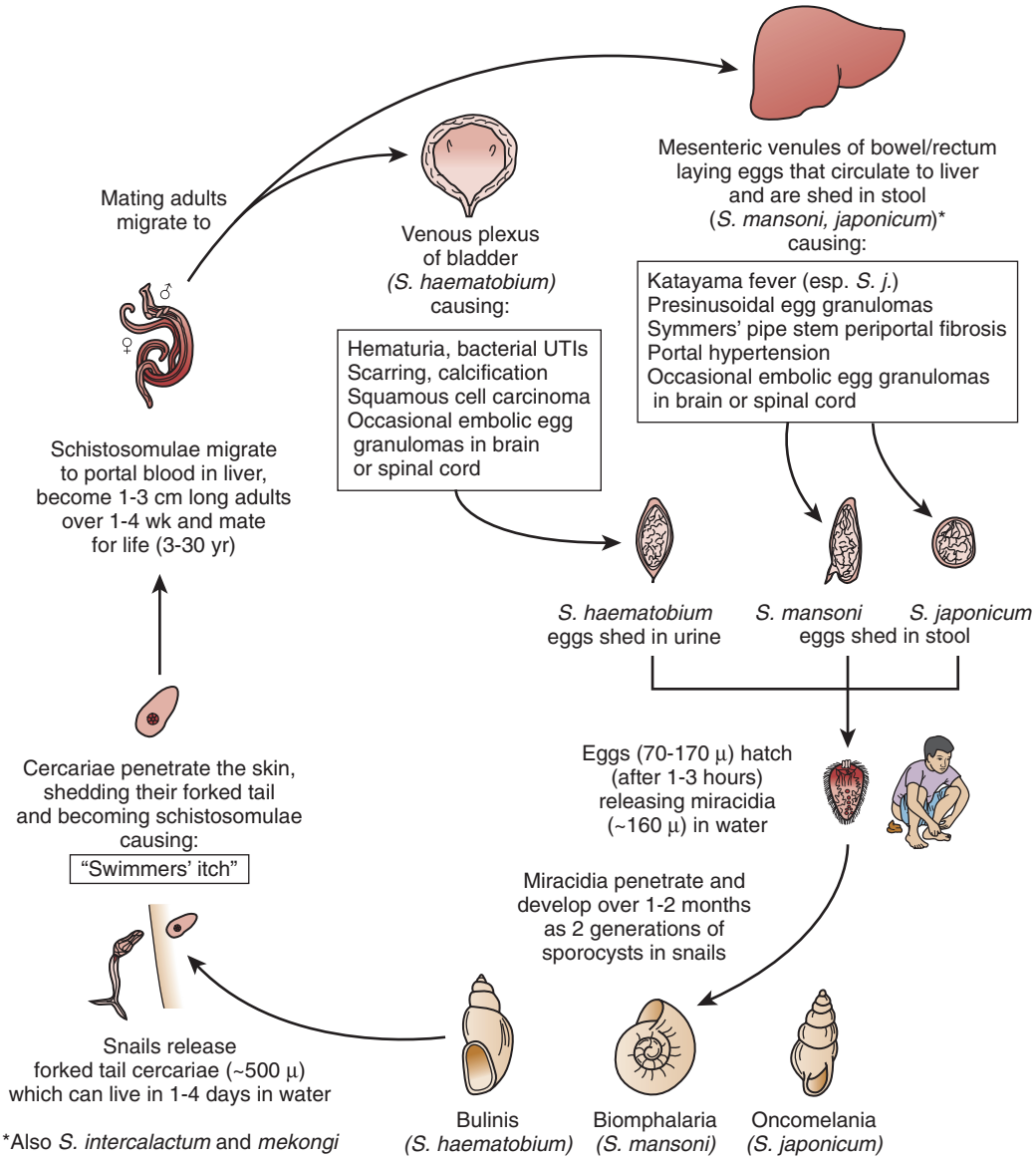


Figure 16–8. Life cycle of a schistosome. UTIs, urinary tract infections. (From King CH. Schistosomiasis. In: Guerrant RL, Walker DH, Weller PF, editors. Tropical infectious diseases, principals, pathogens, and practice. 2nd ed. Philadelphia: Elsevier Churchill Livingstone; 2006. p. 1341–8.)

et al, 1977). It is typical to see composite granulomas in tissue rather than a small single granuloma, because *S. haematobium* eggs are deposited in groups more often than singly. Even though *S. mansoni* may lay eggs in the lower urinary tract, no lesions have been ascribed solely to *S. mansoni* (Cheever et al, 1978).

The immune response to *S. haematobium* is complex and multifaceted. The embolized eggs induce a vigorous eosinophilic and granulomatous immune response. Significant cellular and humoral host responses develop (Phillips and Colley, 1978; Butterworth, 1993; Mwatha et al, 1998; De Jesus et al, 2002; Pearce and MacDonald, 2002; Leutscher et al, 2005). These immune responses partially abrogate (but do not eliminate) subsequent reinfection in human hosts (Hagan et al, 1985, 1987, 1991; Woolhouse et al, 1991). Areas of the world endemic for schistosomiasis often have very high rates of HIV coinfection. Egg excretion in HIV-seronegative persons is significantly higher than HIV-seropositive individuals, though circulating schistosomal antigen levels are similar (Karanja et al, 1997). These observations are compatible with the hypothesis that the transit of schistosome eggs through the tissue is facilitated by a competent immune system.

Microscopic examination of tissue shows polypoid patches consisting of scattered and massed composite granulomas separated by edematous granulation tissue diffusely infiltrated by eosinophils, lymphocytes, and plasma cells. On gross examination, the areas of granulomatous inflammation result in large, bulky, hyperemic, and polypoid masses projecting into the lumen (Fig. 16–9). In the active stage of disease, schistosomiasis is characterized by multiple large inflammatory polyps related to the heavy localized egg burden (Smith et al, 1977c). In the endemic areas, these polypoid patches occur mainly in children through their early teens. However, up to 60% of urinary bladder polypoid lesions in patients with schistosomiasis result from conditions other than schistosomiasis, such as polypoid cystitis (Smith et al, 1974a).

Inactive urinary schistosomiasis, occurs after adult worms have died, and is characterized by the absence of viable eggs in tissue or urine and the presence of "sandy patches"—relatively flat, tan



Figure 16–9. Intravenous urogram in an Egyptian boy shows scalloping of the bladder and right lower ureter by schistosomal polypoid lesions.

mucosal lesions of various depth, with somewhat ill-defined borders (Fig. 16–10). These patches are formed as the inflammation associated with active egg-laying wanes. The remaining entrapped eggs are destroyed or calcified and the tissues undergo fibrotic reaction, which is the histologic characterization of the sandy-patch lesions. Urinary excretion of dead or calcified eggs is rare. However, the bladder may contain a sufficient number of calcified eggs to result in a thin outline of the bladder on plain radiographs.

The clinical pathology of chronic schistosomiasis is often the development of obstructive uropathy. There are two components to schistosomal obstructive uropathy: obstruction and its effect on the proximal ureter. Schistosomal obstructive uropathy is usually asymmetric (Smith et al, 1974a). The location of the obstruction varies from the urethral meatus (1%), interstitial ureter (10% to 30%), juxtavesical ureter (20% to 60%), lower third of the ureter (15% to 50%), or a contiguous combination of these areas (30% to 60%) (Gelfand, 1948; Smith et al, 1977b; Al-Shukri and Alwan, 1983). Three types of hydroureter are associated with obstructive schistosomiasis: segmental (i.e., cylindrical or fusiform), tonic, and atonic (Smith et al, 1977b). Approximately 25% of obstructive uropathy cases involve segmental ureteral dilation, with 80% of those cases occurring in the lower ureter. The dilations occur above areas of concentric ureteral muscular obliteration associated with fibrosis and sandy patches. It is rare for segmental lesions to cause significant hydronephrosis. Up to 30% of obstructive uropathy is due to tonic hydroureter. This is characterized by dilated, tortuous, thick-walled, and trabeculated ureters with marked ureteral muscular hypertrophy and decreased peristaltic action. Typically, the entire ureter proximal to an obstructive lesion is involved, creating a functional stenosis. This is usually accompanied by significant hydronephrosis, which is reversible if the obstruction is relieved (Smith et al, 1977b). Atonic hydroureters are found in the remaining patients with schistosomal obstructive uropathy. This form is characterized by markedly dilated, very tortuous, thin-walled ureters, without peristalsis and associated with atrophic fibrotic ureteral muscle.

Hydroureter usually precedes hydronephrosis (Lehman et al, 1973; Smith et al, 1974a, 1977b; Cheever et al, 1978). Left untreated, schistosomal hydronephrosis advances from progressive renal pelvic dilation to medullary atrophy to near total medullary effacement before cortical atrophy ensues (Smith et al, 1974a, 1977b). This specific pathophysiology explains the abrogation of tubular function (especially maximal urine concentration) before compromise of glomerular function (Lehman et al, 1971, 1973).

Bladder cancer is the final pathologic sequela of schistosomiasis. Linkage between urinary schistosomiasis and the development of bladder cancer has been postulated since the end of the nineteenth century. Bladder cancer in the setting of *S. haematobium* has an early onset (40 to 50 years) and a high frequency of squamous cell carcinomas (60% to 90%), with 5% to 15% adenocarcinomas (Cheever, 1978; Lucas, 1982; Al-Shukri et al, 1987; Thomas et al, 1990; Bedwani et al, 1998). More than 40% of schistosomiasis-associated squamous cell carcinomas of the bladder are well-differentiated or verrucous carcinomas that are exophytic and carry an overall good prognosis. Tumors are found on the posterior wall about 50% of the time and on the lateral wall roughly 30% of the time. Exophytic tumors constitute about two thirds of schistosomal bladder cancers, while one third are ulcerative endophytic tumors. Mass schistosomiasis treatment campaigns in Egypt are associated with an overall reduction of all bladder cancers (27.6% to 11.7%) and a shift to more transitional cell carcinoma from squamous cell carcinoma (Gouda et al, 2007). Although less frequent transitional cell carcinomas of the bladder are associated with *S. haematobium* infection (Michaud, 2007), some epidemiologists feel the relatively high rate of smoking in this region may increase the risk of bladder cancer. Notably, however, some unselected autopsy series from the same regions have shown similar frequencies of bladder cancers in patients without schistosomiasis (Smith et al, 1977a; Cheever et al, 1978).

Clinical Manifestations

Acute Schistosomiasis. Acute schistosomiasis is also referred to as Katayama fever, rarely found among endemic populations. First coined about *S. japonicum* infection, it refers to a first, and presumably heavy, exposure of a noninfected individual that leads to fever, lymphadenopathy, splenomegaly, eosinophilia, urticaria, and other manifestations of a serum sickness–like disease (Doherty et al, 1996; De Jesus et al, 2002). This presentation is relatively rare in *S. haematobium* and more common in *S. japonicum,* which is probably the result of the significantly greater egg fecundity of *S. japonicum*. Acute schistosomiasis generally occurs 3 to 9 weeks after infection, coinciding with the onset of egg-laying, but may be delayed for up to 4 months (Young et al, 1986). Of note, this symptomatic phase often precedes the occurrence of eggs in the urine. Hematuria is the first sign of established *S. haematobium* infection, often appearing 10 to 12 weeks after infection (Kehinde et al, 2008).

Acute schistosomiasis is rarely associated with atopic egg-laying because worms meander toward the pelvic venous plexuses and become delayed or lost. These ectopic eggs incite an intense granulomatous inflammatory reaction in aberrant sites such as the skin (Edington et al, 1975), epididymis (Elem et al, 1989), or spinal cord or nerve roots or both (Pitella, 1997).

Chronic Schistosomiasis. Chronic schistosomiasis is far more common than acute disease and has several different clinical

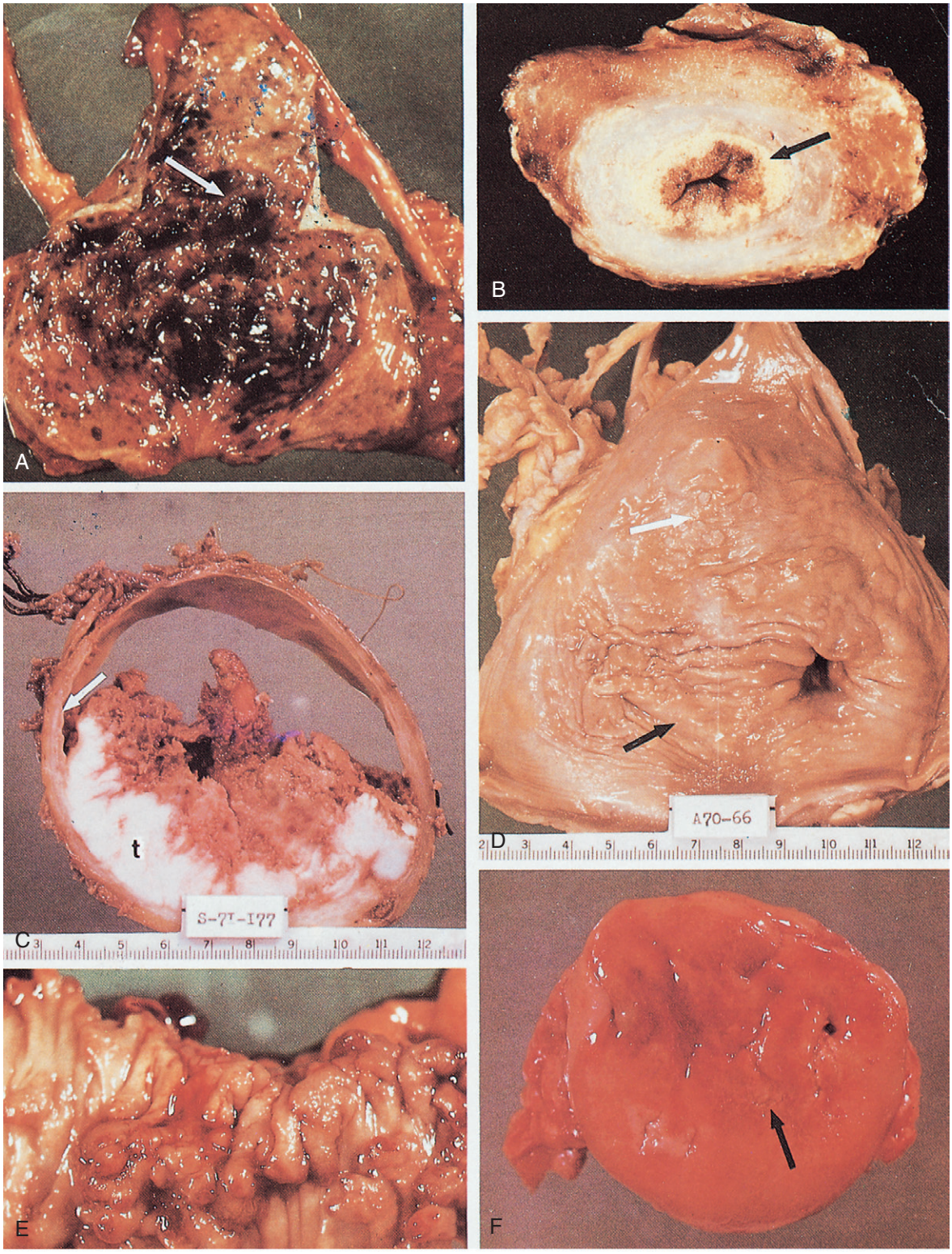


Figure 16–10. Macroscopic appearance of human urinary schistosomiasis. **A,** Urinary bladder opened with an anterior Y incision. The posterior and apical walls have many erythematous, granular, sessile, and pedunculated polyps *(arrow),* characteristic of the early active stage of urinary schistosomiasis. **B,** Coronal section through the apex of a formalin-fixed urinary bladder. The lamina propria has been expanded and is replaced by a yellow-tan, finely granular, sandy patch *(arrow),* which is characteristic of chronic inactive foci. Small sandy patches are sprinkled through the fibrotic, atrophic detrusor muscle, even in perivesical fat. The more superficial erythematous portion of the lamina propria contains some viable eggs with granulomatous response (chronic active stage of urinary schistosomiasis). **C,** Coronal section through the middle of a urinary bladder after formalin inflation and fixation. The lamina propria *(arrow)* has been replaced by a concentric sandy patch, most prominent at the margin of the exophytic, moderately differentiated squamous cell carcinoma. The bladder wall is attenuated except for the tumor (*t*). No evidence of recent oviposition was found in the lower urinary tract (chronic inactive stage of urinary schistosomiasis, usually found with the bilharzial bladder cancer syndrome). **D,** Urinary bladder opened with anterior Y incision shows several features of severe chronic inactive urinary schistosomiasis. The entire lamina propria has been replaced by a sandy patch. Foci of epidermization are seen at or near the *white arrow*. The left ureteral orifice *(right)* is markedly dilated (the so-called golf-hole ureter of schistosomal uropathy). The right ureteral orifice *(point of black arrow)* is markedly stenotic. **E,** Rectosigmoid colon with polyposis. Numerous sessile and pedunculated polyps are seen. Many are erythematous, indicative of active oviposition with granuloma formation. Some have necrotic hemorrhagic tips. **F,** Mucosal surface of partial cystectomy specimen (4- to 5-cm ellipse) from a patient with the chronic inactive stage of the disease. There is a stellate chronic schistosomal ulcer. Despite the inactivity of the disease, these ulcers may bleed profusely. Pale mucoid flecks at the margin of the ulcer *(arrow)* are areas of adenoid (goblet cell) metaplasia.

manifestations. The prepatent period, between penetration of the cercariae and onset of egg deposition in the tissues, is usually 2 to 3 months but may last more than 7 months (Young et al, 1986). The most typical presentation of active schistosomiasis is hematuria with terminal dysuria. This hematuria can be sufficient to induce anemia (Wilkins et al, 1985). Some patients develop early polypoid lesions of the bladder that result in urethral or ureteral obstruction or develop heavy bleeding, enough to produce clot retention. Because water contact is essentially universal, active schistosomiasis usually begins in childhood. In some cultures, hematuria in males may be seen as a sign of puberty. In this active infection stage, eggs are deposited in the tissues, traverse the bladder or rectosigmoid mucosa, and are excreted in the urine (or less commonly in the feces). This provides an opportunity for diagnosis.

S. haematobium egg burdens of the seminal vesicles and the ejaculatory ducts are high, and either blood and schistosome eggs or both may appear in the ejaculate before they appear in the urine. Patients with involvement of these genitourinary structures often present with scrotal pain or a testicular mass. Egg burdens of the uterus, vagina, and testes are lower than those of the epididymis, ovaries, and fallopian tubes (Cheever et al, 1977, 1978; Helling-Giese et al, 1996).

S. haematobium causes genital disease in 30% of infected women (Poggensee and Feldmeier, 2001; Kjetland et al, 2005). Schistosomal cervicitis and vaginitis may be asymptomatic or have clinical manifestations similar to cervicitis and vaginitis due to other causes (Williams, 1967). A routine Papanicolaou smear may reveal diagnostic eggs of *S. haematobium* infection. Similar to other ulcerating sexually transmitted infections, schistosomal lesions of the vagina and cervix may predispose patients to the acquisition of HIV infection (Feldmeier et al, 1994). Histologic evaluation of the placenta and amniotic fluid at term has shown schistosome eggs in these structures, but there are no documented reports of fetal schistosomiasis.

Over time, a late, chronic, active stage develops when egg burdens in the tissue are at their highest. Clinically constant, deep lower abdominal and pelvic pain with associated urinary urgency, frequency, and incontinence are noted with the "schistosomal contracted bladder" (Duvie, 1986). Anatomically, the trigone appears normal or minimally hyperemic and edematous, while the detrusor muscle is indurated and thickened, along with the entire bladder wall. The bladder lumen is reduced to as little as 50 mL of functional capacity.

After some years, the active infection enters a more quiescent period, in which egg deposition and excretion continue at a lower rate and symptoms are diminished. Over 30% of light infections "resolve" spontaneously in some endemic areas (Rutasitara and Chimbe, 1985). The painful presentations of acute schistosomiasis are typically absent at this point. However, silent obstructive uropathy may develop throughout this phase as fibrosis replaces polypoid lesions and the bladder and ureters undergo irreversible damage. A slow, insidious evolution may result in enormous hydroureters and hydronephrosis with few symptoms.

Patients finally enter a chronic inactive phase, in which viable eggs are no longer detected in urine or tissues. Signs and symptoms at this stage are caused by sequelae and complications of the immune reaction to the eggs rather than the schistosomal infection itself. Unfortunately, among patients with schistosomal obstructive uropathy, 40% to 60% present to urologists at this stage of their disease (Smith and Christie, 1986). In heavily endemic areas, it is common to find nonfunctioning kidneys in patients who are otherwise apparently well. About 50% of patients will develop chronic or acute bacterial urinary tract infection complications superimposed on their schistosomal obstructive uropathy. The bacterial organisms associated with schistosomiasis are the same organisms that cause infections in patients without schistosomiasis. Some series have noted an association of chronic or recurring urinary tract infections caused by *Salmonella* species, often associated with intermittent bacteremia in some patients with urinary schistosomiasis (King, 2001). *Salmonella* organisms reside in the apical invaginations of the schistosome tegument, where they are protected from host defenses and antibiotics. Awareness of this association can lead to treatment of both conditions with good response. Antibiotics alone do not fully resolve this process.

Another manifestation of schistosomal disease is the development of bladder ulcers, which are usually of two types (Smith et al, 1977a). Acute schistosomal ulcers will rarely present in the active stage, when a necrotic polyp sloughs into the urine. The more common chronic schistosomal ulcer is a late sequela of heavy infection. This lesion is associated with a constant "burning" micturition and intense pelvic and suprapubic pain. Over 90% of these patients have a history of previous urinary schistosomiasis, 20% have histories of previous sequelae and complications, and 10% have had previous surgical intervention for urinary schistosomiasis. Gross hematuria and gross pyuria are found in more than half of these patients.

Diagnosis

The presence of terminally spined eggs in the urinary sediment is diagnostic of active *S. haematobium* infection. The eggs of *S. mansoni* and *S. japonicum* have a lateral spine. Eggs may also be seen in the rectal stool samples examined for ova and parasites. If eggs are not found in the urine or stool, a rectal biopsy should be attempted before a bladder biopsy, because eggs are nearly as common in the rectum mucosa and the risk of a urinary tract infection is avoided. A squash preparation of the biopsy specimen between glass slides is better than histopathologic analysis, because it is more sensitive and allows determination of egg viability. Ova are excreted in the urine in proportion to the viable worm burden in the lower urinary tract tissues (Smith et al, 1974b; Smith and Christie, 1986). The intensity of the current infection in its early stages can be estimated by the examination of urine and quantitative urinary egg count. This also has some prognostic significance. Moderate to heavy infections will reveal eggs in almost all routine examinations of the urinary sediment, although lighter infections may require filtration or concentration of the urine (Mott, 1983). *S. haematobium* egg excretion peaks between 10 AM and 2 PM. Interestingly, this circadian phenomenon reverses in night-shift workers without the variation induced by athletic activity or water loading (McMahon, 1976).

Serology tests of the blood that combine a FAST-ELISA followed by Western blot analysis are available at the CDC (Wilson et al, 1995; Al-Sherbiny et al, 1999). In cases where the diagnosis is highly suspected but eggs are not present, the serologic tests can be useful, but do not distinguish between acute and chronic disease. Antibody titers can remain positive even after curative treatment. Although serologic testing is a valuable diagnostic and epidemiologic tool, finding eggs is the gold standard for diagnosis of active infection. Chronic inactive urinary schistosomiasis is characterized by the lack of egg secretion even in patients with severe clinical sequelae. When tissue biopsies are taken, up to 10^6 eggs/g of tissue have been found (Smith et al, 1974b). Real-time

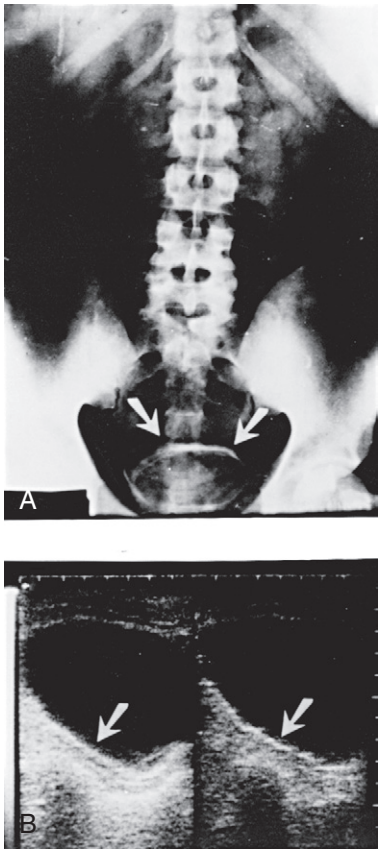


Figure 16–11. Bladder calcification in a 30-year-old Egyptian farmer. **A,** Plain x-ray film of the abdomen shows a rim of calcification surrounding the urinary bladder *(arrows)*. **B,** Abdominal ultrasound study shows a bright line surrounding the bladder with a definite dark rim behind it *(arrows)*. (**A** and **B,** Courtesy of G. Thomas Strickland, MD. From Abdel-Wahab MF, Ramzy I, Esmat G, et al. Ultrasonography for detecting *Schistosoma haematobium* urinary tract complications: comparison with radiographic procedures. J Urol 1992;148:346.)

PCR of the urine is in developmental testing, and may hold some promise in the future. Specificity of nearly 100% is better than sensitivity of 89% in studies, consistent with other nucleic acid–based diagnostic assays (Obeng et al, 2008). Radiography is an important diagnostic tool in the evaluation of sequelae and complications of urinary schistosomiasis. A plain radiograph of the abdomen may reveal calcifications in the urinary tract. The classic presentation of a calcified bladder, which may even look like a fetal head in the pelvis, is pathognomonic of chronic urinary schistosomiasis (Fig. 16–11). The seminal vesicles, prostate, posterior urethra, distal ureters, and, in rare instances, the colon may also show calcified lesions. The earliest radiographic changes appear to be striations in the ureters and renal pelvis (Hugosson, 1987). Ureteral calcification is typically mural, and the ureter is dilated. This differs from the calcification seen in tuberculosis, which forms a cast of a nondilated ureter.

Hydroureter, hydronephrosis, nonfunctioning kidney, ureteral stenosis, and bladder and ureteral filling defects caused by polypoid lesions are readily observed on a standard intravenous urogram. Similar lesions can also be seen with ultrasonography. In the presence of severe obstructive uropathy, delayed films are often needed to discern distended ureters and kidneys. Postvoid films may indicate bladder neck obstruction with retention. Fluoroscopy can differentiate tonic and atonic ureters (Abdel-Halim et al, 1985) and identify nonstenotic, immotile ureters. Computer tomography (CT) scans have the advantage of being able to detect both obstructive uropathy and calcified lesions in the urinary tract and colon (Jorulf and Linstedt, 1985), giving them advantage over the intravenous urogram. MRI scanning has been tried but so far has not shown significant enhanced diagnostic ability to warrant the additional expense (Kohono et al, 2008).

Another useful imaging modality is vesicocystourethrography. It indicates the presence of vesicoureteral reflux, which occurs in 25% of infected ureters. Abdominal ultrasound is a useful method to detect focal thickening of the bladder wall and polypoid lesions of the urinary tract. It also detects hydroureter, hydronephrosis, and heavily calcified patches (Medhat et al, 1997).

Treatment

Medical Management. The development of safe and effective antischistosomal drugs has dramatically changed the management of schistosome infections (WHO, 1993; Richter, 2003; Berhe et al, 2008). All patients with schistosomiasis should be treated regardless of the intensity or apparent activity of their infection. Praziquantel is the drug of choice for all schistosoma species (The Medical Letter, 2010). It is active against all clinical forms and stages of the disease after the first 3 to 4 weeks of infection, because it works better in the presence of antibodies against schistosomal organisms. Praziquantel interferes with the ion transport in the schistosome tegument, resulting in calcium and sodium fluxes, metabolic alterations, and sudden contraction of the parasite's musculature. Cure rates for *S. haematobium* infections are 73% to 100% (Mott et al, 1985; Leutscher et al, 2008). The drug also has activity against most other flukes and tapeworms, which is a great advantage in the developing world. The current recommendation is 2 oral doses of 20 mg/kg (or a single 40 mg/kg dose) in 1 day for *S. haematobium* (The Medical Letter, 2010). Praziquantel is extremely well tolerated, with occasional gastrointestinal complaints noted as the more common side effects. Headache, dizziness, and fever have occasionally been reported. The lack of serious side effects has made it an excellent agent of choice in mass chemotherapy campaigns (King et al, 1990).

Surgical Management. The efficacy and ease of current drug therapy for schistosomiasis, together with the possible reversibility of disease (Berhe et al, 2008) provides rationale for medical therapy trials prior to elective surgical approaches for genital urinary disease associated with schistosomal infection (Cioli et al, 1995). In general, surgery is reserved for complications that have not responded to adequate medical treatment within a reasonable follow-up time, or for those settings where immediate surgical intervention is necessary. Obstructive neuropathy is the most common chronic condition requiring surgery with severe bladder hemorrhage, the most common cause for urgent surgical intervention.

Significant prostatitis and hypertrophy are uncommon in schistosomiasis. There is no evidence of bladder outlet obstruction in *S. haematobium* infections in multiple autopsy studies (Smith et al, 1974a; Cheever et al, 1977, 1978). However, clinical studies consistently report cystoscopic (Fam, 1964), urodynamic (Sabha and Nilsson, 1988), and postvoid residual urine, which are evidence of functional bladder outlet obstruction that occasionally requires surgical intervention in patients with severe inactive urinary schistosomiasis (Abdel-Halim, 1984). Due to scrotal pain, induration, and enlargement associated with schistosomal

epididymitis, surgery is often performed for the suspicion of a testicular tumor.

As previously discussed, schistosomal disease of the urinary bladder leads to a spectrum of clinical outcomes, including schistosomal polyposis, sandy patches, contracted bladder, schistosomal ulceration, urothelial hyperplasia, metaplasia, dysplasia, and bladder cancer. In particular instances, such as the chronically contracted bladder, surgical intervention is indicated and takes the form of vesical denervation, urinary diversion, ileocystoplasty, or hydrodistention. Any treatment, however, must be done in conjunction with medical chemotherapy. Chronic deep bladder ulcers may necessitate a partial cystectomy, because fulguration rarely produces either symptomatic relief or healing of the ulcer. Urothelial hyperplasia is strongly associated with severe urinary schistosomiasis, whereas urothelial metaplasia and dysplasia commonly accompany schistosomal bladder cancer (Khafagy et al, 1972). Treatment of bladder cancer secondary to schistosomiasis is usually surgical and discussed elsewhere in this textbook.

The most common sequelae of urinary schistosomiasis result from ureteral involvement causing obstructive uropathy (Lehman et al, 1973; Smith et al, 1974a; Cheever et al, 1978; Smith and Christie, 1986). Hydroureter and hydronephrosis are related to the intensity of *S. haematobium* infection. **Because ureteral obstruction seen during active schistosomiasis is most often caused by concentric or hemiconcentric polypoid lesions that "girdle" the ureteral muscle in the intramural and adjacent extravesical ureter, it responds well to medical management alone.** Complete resolution of deteriorated renal function occurs within 1 to 2 months of antischistosomal chemotherapy when obstruction is caused by active disease (Lehman et al, 1973). One study reported that chemotherapy not only reverses schistosomal obstructive uropathy but also prevents it, even in persons who continue to become reinfected (Subramanian et al, 1999). In late chronic active and inactive urinary schistosomiasis, on the other hand, anatomic obstruction is more prominent.

Anatomic ureteral stenosis, with or without calculi, has been identified in up to 80% of obstructions (Lehman et al, 1973; Smith et al, 1977b; Al-Shukri and Alwan, 1983; El-Nahas et al, 2003). **Therefore when there is residual ureteral stenosis after successful chemotherapy it is usually amenable to surgical intervention. Depending on the extent and location of the stricture, procedures involving excision or dilatation have been used.** Balloon dilatation has reportedly proved effective with anatomic stenosis (Jacobsson et al, 1987), but mechanical dilatation is frequently followed by repeat stenosis (Wishahi, 1987). When the ureteral meatus, intermural ureter, ureterovesical junction, or lower ureter is involved, a variety of plastic operations to reconstruct a functional valve are available. Most of these procedures are variants of the Leadbetter-Politano operation (Politano and Leadbetter, 1958; Leadbetter and Leadbetter, 1961). Although highly effective for some patients (Smith et al, 1977b; Al-Shukri and Alwan, 1983), other authors have noted restenosis (Umerah, 1981).

In long or multisegmental lesions, excision of the affected portion leaves an inadequate residual ureter for reimplantation; in these cases, surgeons have successfully employed the Boari-Ockerblad bladder flap, Boari-Küss flap, ileal conduit, suprapubic intravesical ureterostomy, and ureteroileocystostomy, taking care to have an isoperistaltic direction of the ileal segment (Abdel-Halim, 1980, 1984; Al-Shukri and Alwan, 1983; Abu-Aisha et al, 1985). Isolated meatal stenosis may be amenable to simple meatoplasty (Al-Shukri and Alwan, 1983). When a ureter is hopelessly obstructed, long-term nephrostomy drainage or creation of an ileal ureter can provide relief.

Prognosis

Tens of millions of people are infected with *S. haematobium,* but **most have mild infections, and good prognosis. However, the morbidity and mortality of schistosomiasis are determined by the overall intensity of infection.** No mortality was observed in areas in which the prevalence of schistosomiasis and frequency and severity of schistosomal obstructive uropathy were low (Nigeria). Yet when Egypt had a prevalence of 50%, attributable mortality approached 10% (Smith et al, 1974a; Cheever et al, 1978). **Among patients with severe disease, mortality reached 50% in 2 to 5 years** (Lehman et al, 1970).

Patients who die of schistosomal obstructive uropathy (bilateral end-stage hydronephrosis) are usually in their 20s, have early-stage disease, and have heavy total egg burdens. Patients who develop the complications of pyelonephritis and urothelial cancer are usually older than age 40, consistent with time- and intensity-linked pathology (Christie et al, 1986; Smith and Christie, 1986).

The prognosis for persons with demonstrable urinary tract lesions has dramatically improved with praziquantel therapy. In children with obstructive polyps, the uropathy usually completely resolves within 2 to 6 weeks of treatment. For patients with chronic obstructive uropathy due to sandy patches and fibrosis, the prognosis is less clear. Some individuals tolerate advanced obstructive uropathy with little, if any, deterioration in renal function. **Schistosomal obstructive uropathy, urolithiasis, bladder outlet obstruction, and bacterial cystitis all predispose to pyelonephritis.** Bacterial superinfection is a serious prognostic event and should be treated as vigorously and as soon as possible. Furthermore, for **those who develop a bladder malignancy, their prognosis is dependent on the aggressiveness of their tumor.**

Prevention and Control

Travelers in endemic areas should be advised of the hazard of infected fresh water streams, rivers, ponds, and lakes and should avoid contact with such water. Boiling water kills the cercariae. Measures of control in endemic areas have utilized several approaches: destruction of the snail host, elimination of urine and fecal contamination of water, and reduction of contact with infected water (WHO, 1993). In many endemic areas, such measures are expensive, unfeasible, or poorly tolerated by the local population. Therefore mass therapy by drugs has been emphasized, and all major control campaigns today include drug treatment as a major component, often age-directed or annual or both (King et al, 1991; Engels et al, 2002; WHO, 2002). Vaccines to prevent disease or to reduce infection are not currently available (Pearce, 2003).

Genital Filariasis

In broad terms, filarial diseases are classified as lymphatic and nonlymphatic. *Wuchereria bancrofti* accounts for 90% of the cases of human lymphatic filariasis, notably widespread throughout tropical regions of the world. This human parasite has no animal reservoir. *Brugia malayi* and *B. timori* cause human lymphatic filariasis in the Far East, but also have primate and feline reservoirs. Nonlymphatic filariasis is caused by *Onchocerca volvulus*, *Loa loa* or

Mansonella perstans. *O. volvulus*, the agent of river blindness, is found predominantly in Africa with small scattered foci in South and Central America. Although dermatitis, keratitis, and chorioretinitis are the common features of *O. volvulus* infection (Freedman, 2006); subcutaneous nodules and massive inguinal lymphadenopathy may result in "hanging groin" and scrotal elephantiasis.

Very rarely, *Loa loa* or *M. perstans* have been isolated from ovarian follicular fluid and associated with infertility (Chang et al, 2008; Bazi et al, 2006).

Lymphatic Filariasis

The symptoms of bancroftian and brugian filariasis range from acute lymphatic inflammation characterized by fever, localized lymphangitis, and transitory lymphadenopathy to chronic lymphatic dilation with hydrocele, elephantiasis of the limbs, and chyluria (Ottesen, 1989; Dreyer et al, 2000). Lymphatic filariasis affects 120 million people living in 73 countries, with India accounting for 40% of the global infections (Ramaiah et al, 2000).

Biology and Life Cycle. The lymphatic filariae are elongated (100 × 0.3 mm for female and 40 × 0.1 mm for male *W. bancrofti*) nematodes. **Their cycle proceeds from human to mosquito and back.** The most common urban vectors of *W. bancrofti* are the ubiquitous *Culex pipiens* complex, but filariae have adapted to a wide variety of mosquitoes in different areas. Only small portions of mosquito bites (1%) are infective, even in hyperendemic areas. Typically, obstructive lymphatic disease occurs in people repeatedly infected over many years.

Female mosquitoes ingest microfilariae with their blood meals. These rapidly become infective larvae and go to the mosquitoes' salivary glands. The infective larvae are then deposited on the skin during the next mosquito feeding. Although unable to traverse unbroken skin, the infective larvae can enter the bite site or can cross the normal conjunctiva or buccal mucosa (Ah et al, 1974; Sullivan and Chernin, 1976). **The adult filaria then migrates to and lives in the larger lymphatic vessels. *W. bancrofti* adults have a predilection for periaortic, iliac, inguinal, and intrascrotal lymph vessels, whereas *B. malayi* prefers inguinal and more distal lymphangioles.**

Most of the mature *Wuchereria* female is composed of the uterus, which contains all stages, from eggs to mature microfilariae. Microfilaria discharge into the blood is regulated by a feedback system that maintains a constant level of microfilaremia. There is, however, no constant relationship between the number of worms and the level of microfilaremia. Indeed, microfilaremia is found in only 30% to 40% of all infections. The timing of peak microfilaremia in each endemic focus corresponds to the peak feeding period of local mosquito vectors.

Pathology and Pathogenesis. Epidemiologic findings and animal experiments clearly indicate that host reactions to microfilariae differ from those to adult worms. Although pathologic and clinical features differ between patients from endemic and from nonendemic areas, significant humoral and cellular immune responses develop in both groups (Steel et al, 1996). Filaria-specific IgE titers rise, and IgE-eosinophil–mediated killing of microfilariae has been noted in vitro. However, patients from endemic regions manifest IgG_4-blocking antibodies and antigen-specific suppressor T cells. The extent of immune down regulation correlates with an absence of pathologic sequelae and the presence of microfilaremia (Piessens, 1982; Davis, 1989; Ottesen, 1989).

Early Infection. **Lesions of established infection do not remit, but either persist actively or result in significant scarring and lymphatic obstruction. Lesions may appear at the worms' nesting areas (funiculoepididymitis, orchitis, filarial lymphangitis, filarial abscess), in their lymphatic distribution (e.g., hydrocele, lymphadenitis, genital edema), or both.** Dying or dead adult filariae are often detected in surgically excised tissue, which suggests that worm death provokes the inflammatory response.

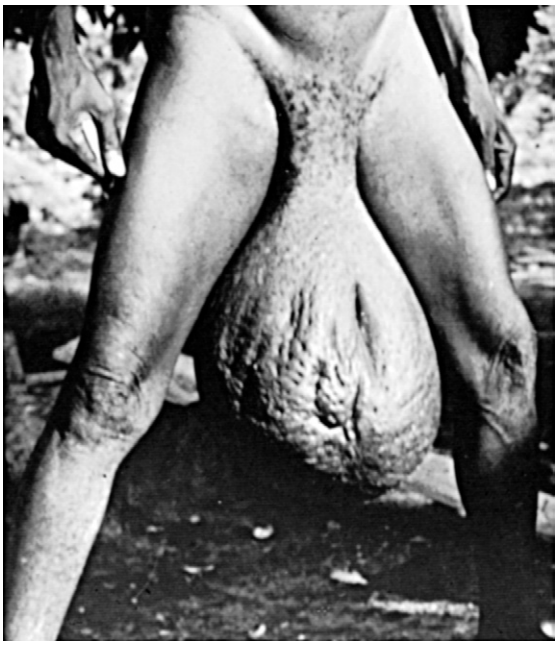


Figure 16–12. Huge hydrocele and scrotal elephantiasis. (Courtesy of Dr. B.H. Kean. From Zaiman H. A pictorial presentation of parasites, Valley City, ND.)

The lesions vary from nodular inflammation, simulating neoplasm, to suppuration, simulating acute bacterial disease. Histologically, nodular lesions show massive granulomas around cuticular fragments or necrotic filaria. **Tissue eosinophilia is a useful diagnostic hint but may be absent.** The most acute subcutaneous filarial lesions simulate fluctuant abscesses with bacteriologically sterile but purulent exudate that surrounds a dying worm (O'Connor and Hulse, 1935).

Episodic filarial inflammation eventually abates, leaving obliterated lymphatics surrounded by poorly organized scar tissue. A palpable mass or indurated cord may develop. The consequences of lymphatic obstruction vary with the location of the obstruction, but the common feature is the accumulation of lymphedema or hydrocele fluid associated with lymphoid infiltrates.

Late Infection. The complications of late infection include huge hydroceles and scrotal and penile elephantiasis (Fig. 16–12). **Lymphangiographic studies reveal that the initial obliteration of lymphatic vessels is bypassed by collateral formation. As these collaterals become progressively obstructed, lymph dilatation follows.** Lymphangiograms in late filariasis show poorly draining networks of communicating lymph vessels extending through lymphedematous tissues into superficial dermal layers (Kanetkar et al, 1966).

Patients demonstrating chyluria and filarial hydrocele rarely experience bacterial super-infection. In contrast, elephantiasis and lymphedematous scrotum are often superinfected (Olszewski et al, 1997). Further supporting the role of infection in classic elephantiasis is noted by the ability to prevent this manifestation when patients with lymphedema are instructed to use antiseptic soap on a regular basis and treated with antibiotics (Maher and Ottesen,

2000). Bacterial superinfections are thus considered an additional contributing factor to the development of sequelae from filarial infection (Dreyer et al, 2000).

Serial autopsy studies of men show that the tail of the epididymis and the lower spermatic cord are the most constant locations of worms (Galindo et al, 1962). Correspondingly, funiculoepididymitis and hydrocele are the most common consequences of bancroftian filariasis. Assuming that heavy infections saturate the preferred habitat and compel adult filariae to spread centrifugally to increasingly distant sites, saturation of inguinal lymphatic trunks (yielding scrotal edema) initiates encroachment into femoral lymphatics (causing elephantiasis of lower extremities) and proximally to renal lymphangioles (producing lymph varices whose intrapelvic rupture causes chyluria).

Clinical Manifestations. Clinical lymphatic filariasis manifests as one of four forms:

Asymptomatic Infection. Persons in endemic areas may have positive serology or skin test reactivity to filarial antigens but no microfilaremia and no clinical evidence of filariasis. Asymptomatic microfilaremia may occur in patients with downregulated effector immune responses (Ottesen, 1989). Such individuals probably developed tolerance to filarial antigens in utero (Weil et al, 1983). In addition, generation of elevated levels of interleukin-12 has been noted in individuals with chronic microfilaremia (King et al, 1995).

Filarial Fevers. Patients with "filarial fever" sustain episodic fevers, lymphangitis-lymphadenitis, funiculoepididymitis, transient edema, and small acute hydroceles. **They are typically amicrofilaremic.** Patients with endemic filarial fever usually inexorably progress due to ongoing reinfection and persistent inflammatory reaction. Expatriates who may experience parasite-related fevers will abate after repatriation and treatment.

Chronic Filariasis. Early established filariasis progresses to the late chronic stage with a series of **progressive lesions: funiculoepididymitis, hydrocele, orchitis, scrotal and penile elephantiasis, lymph scrotum, and chyluria. These do not resolve with treatment, reflective of the chronic tissue changes induced by earlier inflammatory reaction. This pathology alters local lymph fluid drainage** (Fan et al, 1995).

Funiculoepididymitis. Most symptomatic cases of filarial funiculoepididymitis appear before patients' fourth decade. The attack may be isolated, with remission, or may be repetitive and progressive. Pain radiating to the testis and simulating ureteral colic may accompany the systemic symptoms.

Palpable cordlike swelling may mimic an intrascrotal tumor or torsion of the cord and be accompanied by hydrocele or soft tissue edema. Eosinophilia is common because of the persistent tissue migratory nature of this parasitic infection. Varicocele, or thrombosis of the pampiniform plexus, may complicate inflammation, increasing pain and swelling. Bacterial superinfection of acute filarial corditis, is a rare but often lethal complication, with exquisite pain and septic thrombophlebitis as a contributing cause.

Mild cases may involute spontaneously, but, in an endemic setting, they more often point to future recurrences or the development of chronic lymphedema or both (Kazura et al, 1995). The disease frequently simulates malignancy, and many patients ultimately undergo operations including orchiectomy. Even in severe filarial funiculitis, the spermatic cord is usually intact and patent. Sterility and orchitis due to filariasis are rare.

Hydrocele. In endemic areas, differentiation of filarial from idiopathic hydrocele is difficult on either clinical or laboratory grounds. Microfilariae or adult worms are rarely detected in the hydrocele fluid, but a milky or sediment-rich hydrocele fluid suggests a filarial origin. Hydrocele accompanied by nodules in the cord or epididymis and a history of travel to or residence in an endemic area suggests filariasis. Discovery of a thick, fibrous tunica, especially with cholesterol or calcium deposits, should also suggest a diagnosis of filariasis. Tunical calcification is very rare in idiopathic hydrocele.

Scrotal and Penile Elephantiasis. Mild scrotal edema is not unusual during early infection or with established hydrocele. Penile edema, on the other hand, is unusual, and the monstrous elephantine enlargements of the scrotum or penis depicted in textbooks occur largely in populations without access to medical care. Elephantiasis of the limbs poses the differential diagnosis between filarial and other causes, but genital elephantiasis is rarely due to other causes, such as malignancy.

Chyluria. Chyluria occurs with or without microfilaremia, usually in young adults. It occurs earlier in the natural history of filariasis than does genital elephantiasis. Dying worms provoke lymphatic obstruction with proximal lymphangiolar dilatation. Rupture of a lymphatic varix into the urinary collecting system has been demonstrated by lymphangiography. Chyluria may initially alarm patients but often is disregarded and may result in severe protein loss, leading to hypoalbuminemia and anasarca. Chyluria is usually intermittent and may spontaneously remit with bed rest.

Tropical Pulmonary Eosinophilia. Tropical pulmonary eosinophilia occurs in patients with an allergic response to microfilarial antigens; such patients are amicrofilaremic (Ong and Doyle, 1998). This syndrome is characterized by marked, sustained peripheral eosinophilia, only temporarily affected by corticosteroids but responsive to antifilarial drugs. There is an absence of classic filarial lesions, such as lymphedema or funiculoepididymitis. However, the presence of lymphadenopathy that can be marked enough to mimic lymphoma and symptomatic pulmonary infiltrates suggests asthma (Danaraj et al, 1966). Patients develop very high levels of filaria-specific IgE and pulmonary reticulonodular densities on chest radiographs that reveal an eosinophilic interstitial pneumonitis on biopsy. The frequency of this syndrome varies markedly between endemic foci and is most common in southern India and Singapore.

Diagnosis. Careful history-taking and physical examination are paramount in suggesting a filarial lymphedema. TB, *S. haematobium*, and gonorrhea may also produce funiculoepididymitis. Idiopathic hydrocele with or without varicocele or hernia is common in tropical and nontropical areas. However, hydrocele occurs at an earlier age and in greater frequency in areas of endemic filariasis (Jachowski et al, 1962).

The histologic finding of adult worms is a diagnostically definitive but insensitive technique. The presence of microfilariae in peripheral blood, chylous urine, or hydrocele fluid is also diagnostic. Blood samples must be taken when peak microfilaremia occurs (e.g., midnight in the case of nocturnal periodic *W. bancrofti*). Peripheral blood is best examined by the thick-drop technique with Giemsa stain. It is important to remember that filaremia may be absent in both early and late filariasis, after treatment with a microfilaricide, and in tropical pulmonary eosinophilia. Immunoassays for measuring antibody and circulating antigens, as well as molecular biologic assays for detecting parasite DNA, have been developed (McCarthy, 1996; Harnett et al, 1998; Mishra, 2005).

Direct ultrasonographic observation of adult filariae has been reported in lymph vessels of microfilaremic and otherwise asymptomatic patients, made possible by energetic movements of the

worms ("filarial dance sign") (Amaral et al, 1994; Chaubal et al, 2003). Lymphangiography may distinguish filariasis from other causes of lymphatic obstruction, especially in conditions with reduced numbers and competence of lymph vessels. Plain radiographs may reveal calcified worms, which are diagnostic.

Treatment and Prevention. There is continual development of new control strategies and treatment programs for filariasis. The new methodology of control leverages the benefits of mass treatment programs and individual patient treatment to dramatically reduce transmission (Ottesen et al, 1997). Four drugs are now used singly or in various combinations and doses: diethylcarbamazine (DEC), ivermectin, albendazole, and doxycycline (Shenoy et al, 1999; Taylor et al, 1999; Mand et al, 2009). DEC has been used for over 50 years and is predominantly effective against adult worms. Ivermectin has efficacy against microfilaremia, but is relatively ineffective against adult parasites. The objective of therapy is to kill adult worms and abolish microfilaremia. Unfortunately, patients may have prominent immune reactions to the enhanced antigenic exposure associated with dying filariae, the severity directly proportional to the magnitude of the microfilaremia. Patients with high microfilarial counts should start with lower doses when DEC is used for the first several days to minimize these reactions. Some treatment protocols include premedication with corticosteroids or antihistamines to reduce the inflammatory symptoms. Additional treatment-related effects, including fever, headache, nausea, vomiting, and arthralgias, may occur in the first few days of treatment.

Ivermectin is used in a single dose of 200 to 400 μg/kg. The microfilaricidal effect is comparable to that of DEC. There is no effect on adult filariae. In contrast, albendazole kills both adults and microfilariae in lymphatic disease (Ottesen et al, 1999; Bookaire et al, 2002; Gardon et al, 2002). These medications are the cornerstone of mass treatment programs; they successfully interrupt transmission by reducing the microfilariae available for the arthropod vectors in endemic areas.

The recognition that all human pathogenic filariae harbor the bacterial endosymbiont (*Wolbachia* spp.) has led to trials of doxycycline, which kills the filarial by killing the *Wolbachia*. Subsequent use of the three classic antifilarial agents may still have a role in full eradication (Coulibaly et al, 2009; Mand et al, 2009). Three-week doxycycline therapy for *W. bancrofti* cases followed by a single dose of DEC has been shown to reduce or resolve lymphatic pathology in GU filariasis (Mand et al, 2009).

Use of elastic stockings and elevation of extremities are important adjunctive measures in reducing lymphedema. Meticulous skin care and aggressive treatment of secondary infections may halt or even reverse the lymphedema and prevent the development of elephantiasis (Ottesen et al, 1997). Abdominal binders have been used to increase intra-abdominal pressure in an effort to stop chyluria but are controversial because they may increase chyluria in some patients (Ahrens, 1970). Finally, diagnostic retrograde lymphangiography curatively sclerosses lymphatic fistulas in 48% of patients (Gandhi, 1976). Thus **surgical correction is unnecessary in many of these cases, and operative intervention is challenging because the varices are hard to identify and eliminate.**

Genital elephantiasis is rarely amenable to surgery. Additionally, procedures such as lymphadenectomy may further compromise lymph drainage and exacerbate complications. There are, however, a few instances when surgical intervention is necessary to treat the complication of filariasis. For example, patients with filarial funiculoepididymitis should first undergo a thorough workup for malignant, filarial, and bacterial causes of their symptoms. Then, appropriate antibiotics should be prescribed for bacterial disease, and treatment of the filariasis may require surgical decompression or excision of filarial nodules, preserving the testis and cord. When funiculoepididymitis is recurrent, painful, and deforming or complicated by blood vessel involvement, more radical surgery is warranted. Next, for the treatment of large or symptomatic hydroceles, hydrocelectomy is indicated. Excision of the intact hydrocele sac is the treatment of choice; an alternative method is inversion with partial excision (Jachowski et al, 1962). Small hydroceles that do not enlarge can be ignored. Finally, a variety of procedures have been devised to remove redundant tissue and to reconstruct the scrotum or vulva.

For prevention of disease, DEC has been used as a prophylactic drug, given as an annual dose of 6 mg/kg. Trials with prophylactic ivermectin have had similar beneficial effects. Major control methods, however, depend on the use of residual insecticides, domestic mosquito netting, and the reduction of mosquito breeding sites.

Onchocerciasis

Onchocerca volvulus is the agent of river blindness and of severe, debilitating, chronic dermatitis. Onchocerciasis is **common throughout tropical Africa, and endemic foci also exist in Central and South America.** This filaria differs sharply from *Brugia* and *Wuchereria:* (1) It is transmitted by black flies of the *Simulium* species; (2) adult worms inhabit subcutaneous tissue and cause palpable fibrous nodules in which they are encapsulated; and (3) microfilariae travel through the dermis (and the eye) but are not in the peripheral blood. Diagnosis and estimation of infection intensity are made by microscopic examination of skin snips immersed in normal saline solution for 20 to 30 minutes under a coverslip on a slide, or with Giemsa stain. Serologic and antigen detection tests have also been developed (Vincent et al, 2000; Pischke et al, 2002).

In late stages, onchocerca infection may produce "hanging groin" or scrotal elephantiasis. Histology demonstrates atrophy and fibrosis of the inguinal lymph nodes with subcutaneous edema and fibrosis superimposed on the typical onchocercal dermatitis (Connor et al, 1970). In addition, onchocerciasis is occasionally accompanied by giant inguinal lymphadenopathy, which can also produce "hanging groin."

A single oral dose of ivermectin (150 μg/kg) repeated every 2 to 6 months until the patient is asymptomatic (resolution of pruritis and rash) has proved to be a successful onchocercal microfilaricide with few side effects (Greene et al, 1985; The Medical Letter, 2010). **DEC should not be used for treatment of this disease,** because of the severe allergic immune responses to microfilariae dying in the skin and other sites (the Mazzotti reaction). Ivermectin distribution has been successfully used for curbing *O. volvulus* transmission in an international campaign against African river blindness under the auspices of the WHO (Dull and Meredith, 1998). An advance with potential therapeutic implications is the demonstration that a 6-week course of doxycycline renders the female worm sterile by reducing the symbiotic *Wolbachia* endobacteria (Hoerauf, 2003).

OTHER PARASITIC DISEASES OF THE GENITOURINARY TRACT

This section describes parasitic infections that are rare, or in which urogenital manifestations are overshadowed by diseases and other organs. They are, nonetheless, occasionally clinically important

for individual patients. The organisms involved include the intestinal helminth *Enterobius;* the larval tapeworm of hydatid disease, *Echinococcus; Entamoeba histolytica; Gnathostomiasis; Trichomonas vaginalis; Plasmodium falciparum; Strongyloides stercoralis;* and, very rarely, locally inoculated fly larvae.

Enterobiasis

The common **intestinal pinworm *Enterobius vermicularis,* which is ubiquitous worldwide,** occasionally migrates from its nocturnal swarming site, the anus, upward into the vagina, reaching the peritoneal cavity through the uterus and fallopian tubes. In that unnatural habitat, worm movement and egg-laying may continue, producing inflammation of the pelvic peritoneum with pain, fever, simulated acute appendicitis, or other lesions. Dead worms and eggs incite granulomas and adhesions. Careful searching for enterobiasis eggs in vaginal secretions may properly diagnose a persistent vaginal discharge that was originally thought to be caused by more typical organisms. Treatment of pelvic enterobiasis is with pyrantel pamoate, mebendazole, or albendazole (The Medical Letter, 2010).

Hydatid Disease

No part of the human anatomy is invulnerable to hydatid cysts, but renal hydatids occur in only about 2% of cases (Musacchio and Mitchell, 1966; Kehinde et al, 2008). **The hydatid is the larval form of *Echinococcus granulosus,* whose definitive host is the dog, and whose principal intermediate host is the sheep.** The major endemic loci of hydatid disease are sheep-herding areas, such as Australia, Argentina, Greece, Spain, and the Middle East. In addition, feral life cycles lead to sporadic human cases in sites without sheep. Echinococcal cysts of other species are found in Alaska, Siberia, parts of Europe *(Echinococcus multilocularis)* (Rausch, 1967), and Central America *(Echinococcus vogeli)* (D'Alessandro, 1979). In each instance, humans acquire the cysts by accidentally eating eggs excreted in the feces of dogs or alternative feral hosts.

In the kidney and other sites, hydatid cysts evolve by slow, asymptomatic, concentric growth over years and may invoke pressure symptoms or flank pain, depending on their location and size. Cysts can reach over 20 cm in diameter (Fig. 16–13). A host fibrous shell with scant inflammatory reaction envelops the cyst. They often enlarge 1 to 2 cm per year.

The most common urologic presentation is of chronic dull flank or lower back discomfort from cystic pressure (Gogus et al, 2003). The cysts seldom affect renal function. Diagnosis can be made by plain film radiography, ultrasonography, or CT, which shows a thick-walled, fluid-filled spherical cyst, often with a calcific cyst wall (Horchani et al, 2001; Turgut et al, 2009). Serologic testing (available through state laboratories or the CDC) has proved useful but has a sensitivity of only 60% to 90%. **Albendazole, 400 mg twice daily for 1 to 6 months, is the recommended medical therapy. Some patients may require surgical excision of their cysts because of the size or location of the lesions** (Handa and Harjai, 2005). **Praziquantel and albendazole have been recommended preoperatively for 7 to 10 days to minimize or prevent secondary seeding by daughter cysts if they accidentally contaminate the operative field** (The Medical Letter, 2010). Spillage of cystic products into the peritoneum or the bloodstream may result in metastatic infection. Rupture of cysts may result in systemic anaphylaxis.



Figure 16–13. Echinococcosis of the human kidney.

Amebiasis

***E. histolytica* is a rare cause of renal abscess** (Brandt and Perez Tamayo, 1970). Liver abscesses invariably accompany the abscess. The right kidney is more frequently involved. Hematuria may be a prominent manifestation, especially if the abscess induces renal vein thrombosis. Medical therapy (metronidazole or tinidazole) must be promptly instituted (The Medical Letter, 2010). Surgery, if necessary, should be delayed until drug therapy has been initiated; otherwise, disastrous spread of amebic infection is likely (Grigsby, 1969). Good reviews on the pathology (Brandt and Perez Tamayo, 1970), surgery (Grigsby, 1969), and medical management of amoebiasis (Ravdin and Stauffer, 2005) are available.

Gnathostomiasis

Gnathostomiasis is a food-borne zoonotic nematode. *Gnathostoma spinigerum* is the most common species to infect humans. Disease is acquired by consumption of infected fish when eaten raw or undercooked. Humans represent an accidental host, which means the parasite is unable to reach full maturity. It wanders through tissues resulting in local symptoms, depending on location, and typically a very predominant eosinophilia (often greater than 50%) (McCarthy and Moore, 2000). While the disease typically has superficial subcutaneous manifestations, deeper visceral tissues may be involved. Very rare genitourinary cases have been reported (Rusnak and Lucey, 1993).

Serologic assays have been developed with sensitivity and specificity of 93% and 98%, respectively, but are not readily available.

The definitive treatment is surgical excision when possible. Albendazole is a safe and well-tolerated medical treatment that is often successful (Kraivichian et al, 1992).

Trichomoniasis

Trichomonas vaginalis is a flagellate protozoal organism, commonly found in the secretions of inflamed genital surfaces, such as the vagina or the preputial skin or the urethral mucosa (Kehinde, et al, 2008). Infection from this parasite is most commonly transmitted through intimate sexual contact and may involve the Cowper or Skeen glands. In women, the prevalence of trichomoniasis is estimated to be 3% to 48% in various studies (Sena et al, 2007). Vaginitis is the most frequent manifestation; however, it has been associated with preterm delivery in pregnant women (Cotch et al, 1997). The majority of male partners of women with trichomoniasis are infected even when the men are asymptomatic. Men may experience urethritis, epididymitis, prostatitis, and infertility, probably through infection of the seminal vesicles.

Diagnosis can be relatively straightforward if secretions are examined under a microscope and the highly active motile flagellum is visualized. However, the sensitivity of this diagnostic step is limited. Newer nucleic acid amplification tests have been developed with sensitivities ranging from 85% to 100% (Kaydos et al, 2002).

Malaria

Plasmodium falciparum is a protozoal parasite that causes severe malaria. The urogenital manifestation is through the phenomenon of black water fever due to hemoglobinuria (Kehinde et al, 2008). This is a rare manifestation involving a complement-mediated immune reaction found in patients who have resided 2 to 3 months in endemic areas, and who have also been treated with inadequate doses of antimalarial medication. The treatment includes appropriate full-course doses of effective antimalarials together with supportive medical care if the hemoglobinuria has resulted in acute renal tubular necrosis.

Strongyloidiasis

Strongyloides stercoralis is the fourth most important intestinal nematode infection in the world, with distribution throughout the tropical and temperate world. The parasite has the capacity for autoreinfection, which perpetuates infection for decades after exposure (Siddiqui et al, 2006). Typically, *S. stercoralis* infection produces an asymptomatic chronic upper gastrointestinal infection. However, in immunocompromised individuals, especially those receiving corticosteroids, strongyloides hyperinfection can develop with dissemination of the larvae to extraintestinal organs with mortality rates as high as 85%. Genitourinary infection is extremely rare and is usually an indication of disseminated disease. Motile larvae are rarely visible on urinalysis (Rifaat et al, 1973). The migrating worms carry gram-negative bacteria on their coat, which may result in bacteremia or infection of the genitourinary system if the parasites accidentally migrate to the genitourinary organs.

Diagnosis is usually best accomplished with blood serology, although the high sensitivity decreases in the face of immunosuppression. The organism exists as worms and larvae in typically low numbers, making direct observation challenging. The high numbers seen in disseminated infection can increase this sensitivity. Ivermectin represents the treatment of choice at a dose of 200 μg/kg daily for 2 days in normal hosts. Longer courses of treatment may be necessary in patients with disseminated disease. Of note, thiabendazole, the historical drug of choice, should no longer be used due to its prominent gastrointestinal and neuropsychologic side effects. Albendazole has some activity but a lower cure rate than ivermectin (The Medical Letter, 2010).

Key Points

- The symptoms of bancroftian and brugian filariasis range from acute lymphatic inflammation characterized by fever, localized lymphangitis, and transitory lymphadenopathy to chronic lymphatic dilatation with hydrocele, elephantiasis of the limbs, and chyluria.
- Schistosomiasis and filariasis parasites can survive in a host for up to 10 years. *Strongyloides* species can survive for many decades. A careful social history is essential to determine exposure, thus leading to thoughtful diagnostic testing and helping to understand if such infections may explain the presenting GU symptoms.
- When schistosomiasis is diagnosed during active infection (before scarring), treatment with praziquantel may reverse significant GU changes caused by infection and inflammatory reaction to the parasite.
- For schistosomiasis, although serologic testing is a valuable diagnostic and epidemiologic tool, finding eggs is the gold standard for diagnosis of active infection. If not found in urine or stool, tissue biopsy of the bladder or rectum may reveal eggs and aid in diagnosis.
- To minimize the risk of seeding new metastatic infection in the case of spillage of cyst contents, praziquantel or albendazole have been recommended for 7 to 10 days before any procedure on an echinococcal cyst.

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chapter 17

Basic Principles of Immunology in Urology

Stuart M. Flechner, MD, FACS ● James H. Finke, PhD ● Robert L. Fairchild, PhD

Innate Immunity
Adaptive Immunity
Molecules of the Adaptive Immune System
Lymphocyte Activation
Activation of B Cells
Cell Signal Transduction
T-Cell Maturation to Effector Function
Apoptosis-Programmed Cell Death
Lymphocyte Tolerance
Adhesion Molecules and Control of Lymphocyte Trafficking
Tumor Immunology
Immunotherapy
Immunity to Infections
Molecular Immunology

The immune system was initially described as the collection of cells, tissues, and molecules that provide resistance to infections. However, we now know it is essential for the maintenance of health and for combating a broad range of diseases. Various immune mechanisms are involved in urologic disorders including infections of the urinary tract, urologic cancers, the rejection of transplanted organs, the transfusion of blood products, and abnormalities of male reproduction. The immune response, once a set of clinical observations, has now been traced to unique cell populations, their secretory and membrane products, and the very intracellular machinery unlocking these responses. This has come about due to rapid advances in molecular immunology, including the development of monoclonal antibodies, the ability to clone cell populations, recombinant gene technology, and the ability to place genes into (transfect) or eliminate them from (knockout) animals. Nevertheless, the immune response remains identified by a set of unique characteristics that help explain its utility and adaptability against many different foreign invaders. **These include (1) the ability to identify self from nonself, (2) specificity, (3) memory, and (4) rapid amplification.** What we describe today as the immune system represents the interplay between two separate biologic responses, those that are **innate** and those that are acquired, or **adaptive.** In this chapter we will describe the nuts and bolts of the immune response and how they interact in various states of disease. This will often be presented in the context of an invading microbe and how it engenders immunity.

Immune mechanisms rely upon the interactions between diverse cell populations, which at any point in time are in various stages of differentiation. In contemporary terms immunity can be divided into two separate responses. **Cell-mediated immune responses describe those primarily directed by cell-to-cell contact, and humoral immune responses describe those primarily due to the production of antibody (immunoglobulin).** In fact, most responses involve both cellular and humoral events, which are mediated by several different types of immune competent cells. Although the small lymphocyte is the backbone of the immune response, several other bone marrow–derived cells are needed for a mature immune response. **These cells "talk" to each other and their surroundings through receptors that they express on their surface, and through cytokines, which are small peptides that they secrete locally** (Clark and Ledbetter, 1994). The receptors are usually glycoproteins that extend from the cell surface as single chains or double chains called dimers, which are often designated alpha and beta. A nomenclature has developed to describe these markers, at international workshops, comparing several monoclonal antibodies from different laboratories. When a cluster of monoclonals are found to react with the same surface polypeptide, it is designated with a CD number (cluster of differentiation). The number of CD specificities on leukocytes is now in the hundreds, and Table 17–1 provides the ones more commonly associated with immune responses. **A cell surface receptor bound by its ligand will often trigger downstream intracellular events, thereby activating the cell to either produce specific cytokines, express other surface markers required for immune interactions, or enter cell cycle progression and proliferation.** Many of the small peptide cytokines that directly influence immune responses will be described further in this chapter, and are represented in Table 17–2.

INNATE IMMUNITY

The innate immune responses are constitutive and do not improve on repeated contact with the same offending agent. An invading microbe first encounters innate immune responses. **Innate**

Table 17–1.

Some of the Major Cell Surface CD (Cluster of Differentiation) Markers

CD NO.	CELLULAR ASSOCIATION	MEMBRANE COMPONENT/LIGAND
CD2	T cells, NK cells	Receptor for LFA3 (CD58), sheep RBC rosettes
CD3	T cells	Component of T-cell receptor, signal transduction
CD4	Helper T cells	Receptor for MHC class II and HIV virus
CD5	T cells, thymocytes	Signaling molecule, binds CD72
CD8	Cytotoxic T cells	Receptor for MHC class I
CD11a	Leukocytes	Adhesion binds ICAMs (CD50, 54, and 102)
CD16	PMN, NK, macrophages	Fcγ receptor, phagocytosis, and ADCC
CD18	All leukocytes	Integrin beta chain
CD19	B cells	Pan–B-cell marker
CD20	B cells	Role in B-cell activation
CD25	Activated T and B cells, macrophages	IL-2 receptor, also called Tac
CD28	T cells	Costimulator ligand for B7.1 (CD80) and B7.2 (CD86)
CD40	B cells, APCs	Receptor for CD40 ligand (CD154), B-cell costimulator
CD44	Leukocytes	Proteoglycan binding receptor,
CD45	Leukocytes	Leukocyte common antigen, tyrosine phosphatase
CD45RO	Activated and memory T and B cell subset, monocytes, macrophages	Isoform of CD45, CD45RO memory cells; high MW CD45RA naive cells; low MW
CD52	T and B cells, some monocytes, macrophages	CAMPATH-1, unknown function
CD54	Dendritic, macrophages, B cells	Leukocyte adhesion, also called ICAM-1
CD55	Most cells	Decay accelerating factor (DAF), binds C3b
CD56	NK, few T cells	Adhesion
CD58	Broad	Binds CD2 (called LFA-3)
CD62L	B and T cells, monocytes, PMN	L-Selectin, endothelial adhesion, homing of naive T cells to lymph nodes
CD69	Activated leukocytes	Activation inducer molecule (AIM), signal transduction
CD71	Erythroid cells	Transferrin receptor, iron uptake
CD80	Dendritic, macrophages, B cells	Ligand for CD28, also B7.1, T-cell costimulator
CD86	Dendritic, macrophages, B cells	Ligand for CD28 and CD152 (CTLA-4), also B7.2 T-cell costimulator
CD152	Activated T cells	Also called CTLA-4; negative regulation of costimulation; binds CD80 (B7.1) and CD86 (B7.2)
CD154	Activated CD4+ T cells	CD40 ligand, activates B cells

AM, adhesion molecules; MW, molecular weight; NK cells, natural killer cells; PMN, polymorphonuclear leukocytes; RBC, red blood cells.

Table 17–2.

Representative Cytokines

CYTOKINE	CELLULAR SOURCE	MAJOR ACTIVITIES
IL-1	MØ, EC, keratinocytes	Upregulation of AM expression, stimulation of CK production, activation of MØ and T cells
IL-2	T cells	Activation of NK cells, T-cell growth factor
IL-4	Type 2 CD4+ and CD8+ T cells	T-cell growth factor, B-cell growth factor, Ig class switching to IgE
IL-5	Type 2 CD4+ and CD8+ T cells	Stimulation of eosinophil development
IL-6	Type 2 CD4+ T cells, MØ	Stimulation of acute phase proteins, activation of lymphocytes
IL-7	Stromal cells bone marrow	Stimulates survival and expansion of immature T and B cells
IL-10	Th2 and Th3 T cells, MØ	Immunosuppression
IL-12	MØ, DC	Stimulation of IFN-γ production
IL-13	Type 2 CD4+ T cells	Allergic inflammation, upregulation of VCAM-1 expression
IL-15	Fibroblasts, EC, DC	CD8+ T-cell growth factor
IL-17	CD4+ T Cells	Promotes inflammatory responses; may trigger autoimmunity
TNF-α	T cells, NK cells, MØ	Upregulation of AM expression, stimulation of CK production, inflammation
TNF-β	Type 1 CD4+ and CD8+ T cells	MØ activation, cytolysis
IFN-γ	Type 1 CD4+ and CD8+ T cells, NK cells	MØ activation, upregulation of AM expression, production of T-cell chemoattractants, inhibition of Th2 cells
GM-CSF	T cells, NK cells, B cells, MØ	Stimulation of MØ and granulocyte development
TGF-β	T cells, B cells, mast cells, MØ	Immunosuppression

AM, adhesion molecules; CK, chemokines; DC, dendritic cells; EC, endothelial cells; MØ, macrophages; NK cells, natural killer cells.

defense mechanisms represent nonspecific barriers to invaders, which rely primarily on physical barriers, phagocytic cells, natural killer cells, complement, acute phase proteins, lysozyme, the interferons, and defensins. Innate immunity also underlies most inflammatory responses; these are initially triggered by macrophages, polymorphonuclear leukocytes, and mast cells through their germline-encoded innate immune receptors (Janeway and Medzhitov, 2002).

Barrier Function

The body's first line of defense includes mechanical, chemical, and biologic barriers that lie external to the basement membrane of the skin and mucous membranes of the respiratory, alimentary, and urinary tract. The epithelial surface of tissues exposed to the environment provides a barrier to infection. This is most clearly demonstrated by the increased susceptibility to infection at sites where the epithelial barrier is breached, such as occurs in open wounds. In addition, the epithelial cells protecting the internal portion of the body produce mucus that prevents microbial adherence to the epithelium. Hairs and cilia serve to filter and sweep out microbes. The strong periodic flushing of the urinary tract helps to limit bacterial ascension to the kidneys. Cells composing most areas of the epithelial barrier also produce small, positively charged antibacterial peptides called **defensins.**

Defensins

Defensins are small cysteine-rich peptides of 18 to 45 amino acids that are found in both vertebrates and invertebrates (Klotman and Chang, 2006). They are active against bacteria, fungi, and both enveloped and nonenveloped viruses. Cells of the immune system contain these peptides to assist in killing phagocytized bacteria—for example, in neutrophilic granulocytes and almost all epithelial cells. Most defensins function by binding to microbial cell membranes, and once embedded, forming porelike membrane defects. These defects allow the efflux of essential ions and nutrients, resulting in microbial death.

Phagocytosis

Phagocytosis is a nonspecific innate response of circulating neutrophils and macrophages that actively ingest microbes and secrete antimicrobial toxins. Phagocytosis also includes reticuloendothelial cells such as Kupffer cells in the liver and bronchial alveolar macrophages. **The macrophage advances pseudopodia over the microbe, which is internalized into a phagocytic vacuole that fuses with a lysosomal vacuole.** This fusion vacuole results in the degradation of the microbe or particle as digestive enzymes are released. Killing is mediated by reactive oxygen intermediates and hydrogen peroxide (Underhill and Ozinsky, 2002).

Opsonization

The term opsonization describes the process of tagging microbes with macromolecules, or "opsonins," that promotes their elimination by phagocytosis. **Opsonins can be complement fragments (C3b) or antibodies such as IgG, which can be recognized by surface receptors on neutrophils and macrophages.** When antibodies bind to a microbe, their Fc regions project outward and can engage the high-affinity receptor for the Fc regions of γ chains called FcγR1 (CD64), which is expressed on neutrophils and macrophages. The engagement of antibody Fc tails to these receptors will trigger the intracellular machinery that begins phagocytosis, because FcγR1 contains various signaling chains that are necessary for activation.

Granulocytes

The polymorphonuclear leukocyte (PMN) shares a common stem cell precursor with the other formed blood elements, and is the predominant cell type, comprising 60% to 75% of the circulating white blood cells. The name derives from its multilobed nucleus, and the cytoplasm is filled with granules. The granules are often lysosomal and contain the enzymes necessary to digest engulfed microorganisms. Based on the histologic appearance of the granules, they are identified as neutrophils, eosinophils, or basophils, and are about 16 to 18 microns in diameter. **The PMNs are phagocytic and can be attracted to a local site by chemotactic factors such as complement C5a.** The eosin-staining granules of eosinophils contain cationic peptides that are toxic to surrounding tissues. The number of eosinophils increases during allergic reactions and during parasitic infestations. Basophil granules stain with basic dyes and contain heparin, histamine, and proteases. Surface receptors bind IgE with high affinity**. Binding of antigens to the surface IgE on basophils cause them to degranulate, resulting in immediate (type I) hypersensitivity. When basophils are fixed in the tissues they are called mast cells.**

Monocytes and Macrophages

Bone marrow–derived mononuclear phagocytic cells circulate in the blood for 1 to 2 days, and then migrate and attach to tissues where they mature and become macrophages**. They usually occupy perivascular areas and can be called Kupffer cells in the liver, alveolar macrophages in the lung, and histiocytes in connective tissue, brain microglia, or kidney glomerular mesangial cells.** They are relatively large, 15 to 25 microns, and have abundant lysosomes and digestive enzymes required for phagocytosis. These cells have a variety of cell surface receptors that enable them to bind to carbohydrates and protein molecules, such as immunoglobulins (Fc receptor) and complement (CR 1 and 3). Mononuclear phagocytes also secrete a rich array of cytokines, such as tumor necrosis factor alpha (TNF-α), IL-1, IL-6, prostaglandins, and some complement proteins. Activated macrophages can also express cell surface major histocompatibility complex (MHC) class I and II molecules, which play an important role in antigen presentation.

Natural Killer Cells

These are large granular lymphocytes that can destroy various nucleated cells including tumors and virus-infected cells. They are an important component of innate immunity and do not require prior contact with antigen, nor are they MHC-restricted. NK cells release cytotoxic factors such as perforin, serine proteases called granzymes, and tumor necrosis factor beta (TNF-β). They can also trigger apoptosis in their targets. Interferons seem to augment their activity. They also participate in antibody-dependent cell-mediated cytotoxicity (ADCC), by the binding of their cell surface Fc receptor (CD16) to the Fc portion of antibody-coated cells. The precise lineage of NK cells is not known. Characterized by the presence of CD16 and CD56, and the absence of CD3, they have IL-2 receptors and respond to exogenous IL-2. Although their

T-cell receptor (TCR) genes are not rearranged, they seem to be related to T cells (Yokoyama et al, 2004).

Toll-Like Receptors

Toll receptors were originally identified as transmembrane receptors required for the establishment of polarity in the developing *Drosophila* embryo, but also were shown to be essential in protecting flies from infection. The mammalian counterpart, a family of 10 structurally similar proteins has been identified and named Toll-like receptors (TLRs 1 to 10). Most tissues express at least one TLR, but phagocytes, in particular, show abundant expression of all known TLRs. The mRNA of TLRs has been found in monocytes and macrophages, dendritic cells, mast cells, B cells, and epithelial cells of the respiratory and intestinal tract. Different TLRs respond to different products of microbes, but all of the TLRs activate similar signaling mechanisms, resulting in cellular responses that are central to innate immunity. The TLRs can be present on the cell surface, where they recognize the extracellular products of microbes, and other TLRs are actually part of intracellular endosomes where microbes are ingested. Once TLRs are engaged, they activate transcriptional factors that signal the expression of genes that encode various enzymes, proteins, and cytokines that focus on the antimicrobial functions of phagocytes and dendritic cells (see Immunity to Infections).

Pattern Receptors

Various components of innate immunity recognize structures that are shared by many microbes but are not present on host cells. Examples are bacterial lipopolysaccharide (endotoxin), terminal mannose residues typical of bacterial but not mammalian glycoproteins, double-stranded RNA (viral), and certain unmethylated oligonucleotides seen in microbial DNA**. The receptors that recognize these shared but different structures are referred to as pattern recognition receptors. Many pattern receptors have evolved to recognize structures that are essential for the survival and infectivity of the microbes.** The receptors of innate immune system are encoded in the germline, have a predetermined specificity, and have evolved as a protective mechanism against invading microbes. Thus all macrophages may recognize one microbial pattern receptor. The innate immune system does not react against "self" because the inherent specificity of its receptors are coded for microbial structures, and there are regulatory molecules that control reactions. Thus the innate immune system responds the same way to repeat encounters with a microbe. This is in distinct contrast to the adaptive immune system, which is produced by somatic recombination of genes.

Complement

A major component of innate immunity is the collection of about 20 soluble proteins referred to as complement. Complement, once activated, can directly lyse invading bacteria or viruses, and several of its components are important in the regulation of immune responsiveness (Carroll, 2004). **Complement activation results in a cascade phenomenon where the product of one reaction is the enzyme catalyst of the next.** Each component is described by the letter "C" and a number, more closely reflecting the sequence of discovery rather than sequence of action. The split components are designated with an a or b. The most critical component is C3, which has a molecular weight of about

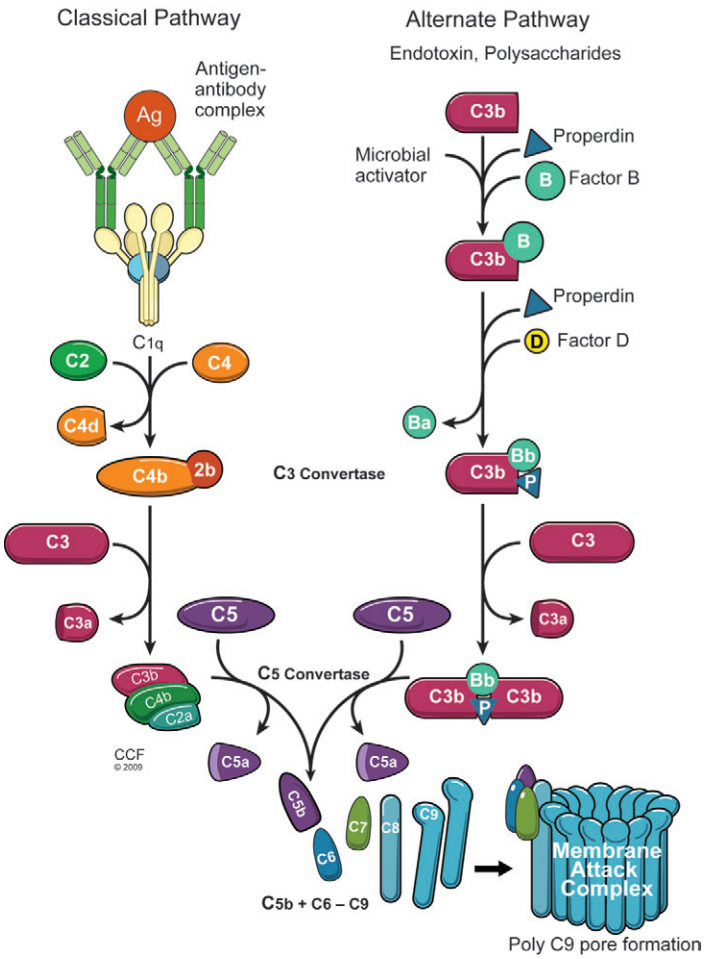


Figure 17–1. The classical and alternative complement pathways. Each component protein labeled "C" acts as an enzyme catalyst for a subsequent product in a ever-expanding cascade. The process can be initiated when an antigen-antibody complex fixes the first component C1q to the cell surface. Alternatively, the cascade can be initiated by microbial products and properdin that can directly activate C3. In addition to forming the membrane attack complex, complement fragments C3b can function as opsonins, and C3a and C5a function as anaphylatoxins. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2009-2011. All Rights Reserved.)

195 kD. Once complement proteins and a target substance interact, a C3 convertase is activated, which splits C3 into C3a and C3b fragments (Fig. 17–1). The C3b bound to the target becomes a component of the convertase for C5. The union of C5b with C6-C9 generates the membrane attack complex (MAC), which integrates with the lipid bilayer of the target cell. The MAC produces cell membrane lesions that permit loss of potassium and ingress of salt and water leading to hypotonic lysis (Walport, 2001).

Complement plays an important role in the elimination of microbes and invaders during both innate and adaptive immune responses. Three important mechanisms can be identified. **(1) Opsonization and phagocytosis:** Not all C3b produced becomes a component of the C5 convertase. Some binds directly to the cell membrane and coats microbes, acting as an **opsonin** for phagocytes such as neutrophils and macrophages that have receptors for C3b. **(2) Complement-mediated cytolysis**: C3b bound directly to a microbe can trigger late complement components and formation of the MAC, leading to osmotic lysis. **(3) Augmentation of inflammation:** Fragments C3a and C5a serve as powerful **anaphylatoxins** that degranulate mast cells

with the release of histamine, which enhances vascular permeability and smooth muscle contraction. The C5a fragment is also a chemoattractant for PMNs and macrophages, which are recruited and activated at inflammatory sites.

Multiple substances may trigger the complement system, which has two pathways of activation. **The classical pathway is a mechanism to activate C3 using the serum proteins C1, C4, and C2. The process is initiated when an antigen-antibody complex fixes the first component C1q, which results in the cascade C1qrs, 4, 2, 3, 5, 6, 7, 8, 9 to produce lysis**. Complement fixation requires one IgM or several IgG antibody molecules. **The alternative pathway is non–antibody dependent, and does not require C1, C4, and C2 to initiate the process.** It is dependent upon bacterial products such as endotoxin and microbial polysaccharides and a serum globulin called **properdin,** which activates C3 directly. An alternative C3 convertase is formed that triggers the sequence leading to cell lysis. The complement system is regulated by endogenous inhibitors that protect the host from continuous activation. These complement regulatory proteins, such as decay accelerating factor (DAF), membrane cofactor protein (MCP, CD46), and CD59, are glycoproteins found on erythrocytes, platelets, neutrophils, and on selected mucosal epithelial and endothelial cells. For example, the membrane protein DAF disrupts the binding of factor B to C3b, or the binding of C4b2a to C3b, which terminates both the classical and alternate activation pathways. MCP serves as a necessary cofactor for the proteolysis of C3b into inactive fragments.

Recently, complement activity has become an important target for immune responses to transplanted organs. The human gene for DAF has been transfected into pigs in an attempt to control complement activation during a pig-to-primate xenograft rejection model. In addition, the complement protein split product C4d has been proposed as a reliable marker for antibody-mediated rejection of renal allografts. Antibody-mediated activation of the classical complement pathway leads to the formation of C4d, which covalently binds to the endothelial surface of the kidney peritubular capillaries, thus leaving an imprint of antibody activity that persists for days to weeks (Collins, 1999). C4d-staining in the kidney correlates with the presence of circulating donor-specific antibody in the recipient.

ADAPTIVE IMMUNITY

Specifically acquired, or **adaptive,** responses result from repeated exposure to invading microbes, and rely primarily on large populations of lymphocytes, each with its own individual (clonal) specificity for an invader. **In addition, the clonal expansion of specific lymphocyte populations after first contact with a foreign molecule confers memory and the ability to elicit a more vigorous response upon subsequent exposure to the same foreign molecule.**

Unlike innate immune pattern receptors, which are encoded in the germline, the adaptive immune system is produced by somatic recombination of genes during maturation, which can generate many more structurally different receptors on lymphocytes such as antibodies and T-cell receptors. This provides for more **diversity** of adaptive responses that are capable of recognizing many more chemically distinct structures. **It is estimated that the entire lymphocyte population can recognize more than a billion different antigens, while innate immune receptors recognize less than a thousand microbial patterns.** Adaptive responses are purged of self-reacting lymphocytes during their first encounter with self-antigens.

Lymphoid Organs and the Lymphatic System

Although descriptions of immune responses are often presented as individual events, in vivo they take place within the organized architecture of lymphoid tissue. **Bone marrow stem cells differentiate into immunocompetent T and B cells in the primary lymphoid organs, and then colonize the secondary lymphoid tissues where the immune responses take place.** The primary lymphoid organs are the thymus, responsible for the selection and education of T cells, and the bone marrow, responsible for the education of B cells. Secondary or peripheral lymphoid tissue includes the spleen, lymph nodes, and unencapsulated tissues lining the alimentary, respiratory, and urogenital tracts (Drayton, 2006). B lymphocytes seed the secondary lymphoid tissues where they form follicles. **The spleen filters the blood, the lymph nodes drain local body tissues, and the unencapsulated tissues associated with mucosal surfaces can secrete IgA antibodies.** The lymphoid tissues communicate through a network of lymphoid ducts that drain all the viscera and return through the thoracic duct to the circulation (Fig. 17–2). This communication is maintained by populations of

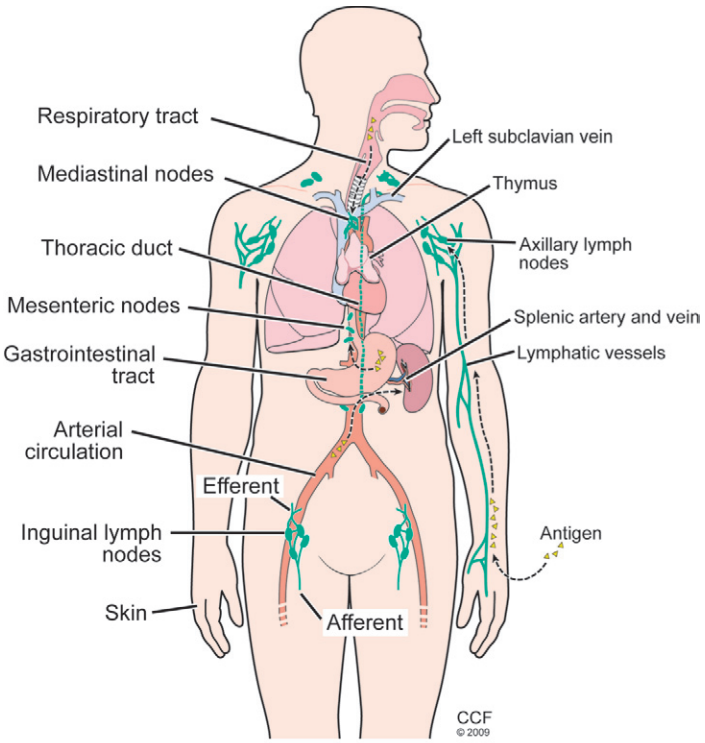


Figure 17–2. The lymphatic system. A major function of the lymphatic system is to collect antigens from their portals of entry and deliver them to lymph nodes where they first interact with immunoresponsive cells of the host. Numerous lymphatic capillaries in the periphery absorb and drain interstitial fluid (lymph) that flows into convergent, ever-larger, central lymphatic vessels. Ultimately the large central thoracic duct drains into the superior vena cava returning the lymph to the circulation. Lymph nodes are interposed along lymphatic vessels and act as filters that sample the lymph at numerous points before it reaches the circulation. The course of antigens (Δ) entering in the periphery or the gastrointestinal tract are followed. Lymphatic vessels that carry lymph into a lymph node are referred to as afferent, and those that drain lymph from the node are called efferent. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2009-2011. All Rights Reserved.)

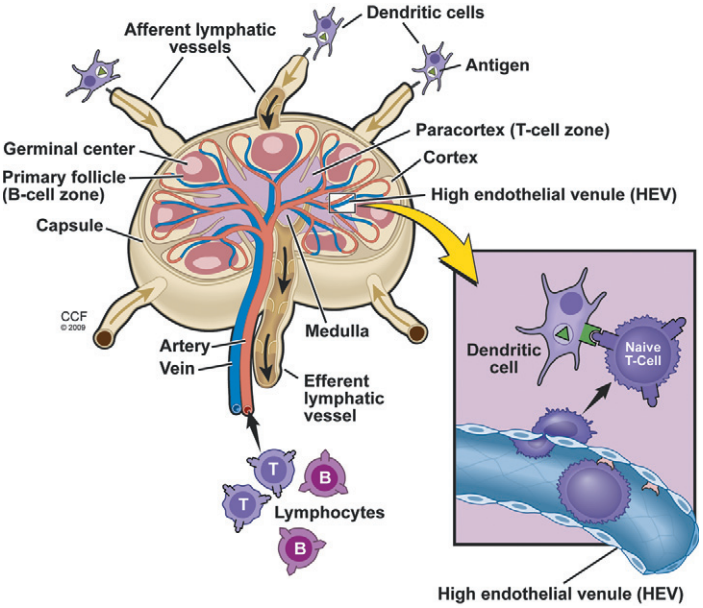


Figure 17–3. Representative morphology of a lymph node. Lymph nodes reside in the periphery connected by lymphatic channels. Each has its own arterial and venous circulation. Afferent lymphatic vessels carry lymph fluid into the node, and efferent lymphatic vessels carry lymph fluid out of the node, eventually reaching the circulation through the thoracic duct. The node is organized into a cortex and medulla. The T lymphocytes aggregate into the paracortical areas and the B lymphocytes form follicles with germinal centers in the periphery of the node. Naive lymphocytes first encounter antigen displayed by dendritic cells in the lymph nodes. Once activated, lymphocytes exit through the efferent lymphatic vessels. Specialized high endothelia venules form a gate for lymphocyte entry into the node. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2009-2011. All Rights Reserved.)

recirculating lymphocytes, which can travel from the blood into the spleen, lymph nodes, and peripheral tissues, and return. **This traffic, or recirculation, of lymphocytes between the peripheral tissues, lymph nodes, and bloodstream enables the immune system to function as a single organ.** Antigen-responsive cells can be recruited to peripheral sites for initial activation, and memory cells can be disseminated to these sites to amplify ongoing responses.

The lymph nodes, located along lymphatic channels throughout the body, are the primary nexus where naive immunocompetent cells meet a foreign antigen (Fig. 17–3). Fluid draining from various epithelial cells, tissues, and organs (called lymph), is collected through lymph channels and funneled to lymph nodes through their afferent lymphatic vessels. The assorted antigen-presenting cells (APC) residing in the nodes can then sample the various antigens, particles, and microbes present in the lymph fluid. In addition, dendritic cells can directly transport digested antigenic particles through lymph fluid to the nodes. Naive T and B lymphocytes enter the nodes through the arterial circulation and migrate through specialized high endothelial venules (HEVs) to reside in the node where they encounter antigens. The lymph nodes are organized into various compartments that concentrate the different lymphocyte subsets. T cells migrate to the paracortical areas of the nodes where they encounter antigens that are displayed by dendritic cells. The B cells form follicles at the periphery of the nodes that often contain germinal centers in which rapid B-cell maturation and proliferation occurs. Once activated, lymphocytes exit the lymph nodes through efferent lymph channels to reach the circulation and migrate to the periphery at sites of inflammation and infection.

Cellular immune traffic is also highly organized and restricted, with certain cell populations directed to specific sites. For example, lymphoblasts and memory cells display tissue-restricted migration to extralymphoid sites such as the skin or mucosal surfaces, while lymphocytes, neutrophils, and monocytes, target and migrate to sites of inflammation in response to local mediators. Such directed movement of immune cells is termed homing, and results from the interaction of various homing receptors that recognize their complementary ligands on the surface of specialized vascular endothelium in selected tissues (Salmi and Jalkanen, 1997). Much of this directional trafficking is orchestrated by two families of G protein–coupled receptors: chemokine receptors and sphingosine-1-phosphate (S1P) receptors (Cyster, 2005). For example, in the spleen, lymphocytes enter the lymphoid area (white pulp) from the arterioles, pass to the sinusoids of the erythroid area (red pulp), and leave by the splenic vein.

Dendritic Cells

Dendritic cells originate in the bone marrow but are dispersed and populate the epithelium of common sites of entry for microbes, such as the respiratory and gastrointestinal tracts and the skin. In the skin, epidermal dendritic cells are called Langerhans cells. They are also dispersed throughout most solid organs. They are characterized by thin membranous projections, which are helpful for capture of large protein antigens. **Dendritic cells are commonly referred to as "professional antigen-presenting cells (APCs)," because they display antigens and provide activating signals to T and B lymphocytes.** Dendritic cells not only capture antigens, but also transport them to peripheral lymphoid tissues where they encounter lymphocytes. During their migration to lymph nodes, dendritic cells mature by increased synthesis and expression of MHC and surface costimulatory molecules needed for T-cell activation (Villadangos and Schnorrer, 2007). In addition, dendritic cells play a central role in the differentiation of naive T cells into their various subsets.

Lymphocytes: T and B Cells

T lymphocytes originate in the bone marrow and migrate to the thymus where they undergo a complex process of maturation. Mature T cells are responsible for cell-mediated cytotoxicity, providing help to antibody-producing B cells, delayed-type hypersensitivity, and play specific roles in immune regulation. Stem cells first enter the outer cortical thymus and mature as they pass to the thymic medulla. During this migration, the critically important surface T-cell receptor (TCR) genes are rearranged, and the CD3, CD4, and CD8 surface molecules appear (Starr et al, 2003). **During maturation CD4–CD8– (double-negative) T cells develop into CD4+CD8+ (double-positive) T cells, and then become single-positive CD4–CD8+ (cytotoxic/suppressor) or CD4+CD8– (helper/inducer) T-cell precursors. Each retains the pan–T-cell CD3 marker, which is a signal-transducing component of the TCR.** Thymic T-cell maturation also involves the critical initial process of self-recognition, which is a consequence of the interaction between maturing T cells and the surrounding thymic cortical epithelium. This leads to the selection of those T cells that are to be saved. **Negative selection** occurs when CD4+CD8+ TCR+ thymocytes recognize self-peptide–MHC complexes on thymic epithelium with high avidity, which leads to apoptosis or deletion of these clones. The

majority of cortical thymocytes are killed during the selection process, thus preventing the development of autoimmune T cells. During **positive selection** CD4+CD8+ TCR+ thymocytes recognize self-peptide–MHC complexes on thymic epithelial cells with low avidity. This saves them from programmed cell death. **The resulting T-cell populations are self-MHC restricted and tolerant to self-antigens, but are capable of reacting to foreign antigens.** Cells leaving the thymus migrate to the peripheral lymphoid organs and seed the T-dependent regions of lymph nodes, spleen, and lymphoid follicles (Przylepa et al, 1998).

B lymphocytes are responsible for the production of immunoglobulin or antibody. They are so named because they mature in hindgut lymphoid tissue called the bursa of Fabricius in birds. In mammals the bone marrow serves as their point of origin and maturation. Immature B cells express immunoglobulin in their cytoplasm, and mature B cells express immunoglobulin on their cell surface. **Cell surface immunoglobulin, both IgD and IgM, serves as the antigen receptor on B cells. Each B cell has about 10^5 identical antibody molecules on its surface. Once activated by antigen bound to its surface antibody, B cells mature to become plasma cells, which secrete the specific antibody. That is, a single B cell produces only one antibody specificity that recognizes only one antigenic determinant (epitope).** B cells also express receptors for the Fc portion of antibody (FcR), which serves to concentrate antigen-antibody complexes on their cell surface. In addition, B cells also express receptors for the third component of complement (C3R). Plasma cells develop from B cells and are large, ellipsoid in shape with an eccentric nucleus, and about 15 to 20 microns in diameter. They are factories for antibody production, although they do not express surface antibody, complement receptors, or CD19 and CD20.

Trafficking of Naive T Cells

Rather than remain passively in the lymphoid tissues, naive or antigen inexperienced T cells circulate through the secondary lymphoid tissues using the lymphatic and blood vessels (Picker and Butcher, 1992). From the blood vessels, T cells enter secondary lymphoid tissues using specialized carbohydrate binding proteins termed selectins. Naive T cells express high levels of L-selectin (CD62L) that mediates binding to its ligand, peripheral lymph node vascular addressin (PNAd). PNAd is expressed by specialized postcapillary venules, called high endothelial venules (HEV), draining the lymphoid node. CD62L-PNAd engagement ceases the circulation of the T cells, allowing the T cells to traverse the HEV barrier and enter the cortical areas of the lymph node. The cortical areas of lymphoid tissues are rich in professional antigen-presenting cells such as macrophages and dendritic cells (see Fig. 17–3). As the naive T cells percolate through this area the T-cell receptors on each cell can survey the surface of these APCs for recognition of the specific peptide-MHC ligand, leading to cellular activation. This restricted circulation of naive T cells optimizes the chance of T-cell encounters with dendritic cells presenting the specific ligand, and is critical for efficient immune surveillance in light of the low number of T cells specific for any particular antigen-MHC complex (approximately 1 in every 10^5 to 10^6 cells). Unless the T cell encounters the appropriate activating complex presented by an antigen-presenting cell, the naive T cells exit the lymph node through the efferent lymphatics and are eventually carried into the thoracic duct. The thoracic duct drains into the blood vessels, and the pattern of naive T-cell circulation through the secondary lymphoid tissues continues.

MOLECULES OF THE ADAPTIVE IMMUNE SYSTEM

Major Histocompatibility Complex

The MHC describes a region of genes, located on chromosome 6 in man, that encodes proteins responsible for the rejection of tissue between different species or members of the same species. More importantly, these cell surface proteins serve as identity markers on cells interacting with T lymphocytes carrying out specific immune functions. The cell surface MHC markers are called human leukocyte antigens (HLA), because they were first identified on white blood cells. There are two major types of HLA antigens termed class I and class II. Interestingly, a heterogeneous group of protein products that track with the MHC termed class III have immune-related functions and include some complement proteins and tumor necrosis factors. **Virtually all nucleated cells express HLA class I antigens, while class II antigens are primarily found on B cells, monocytes, macrophages, and antigen-presenting cells.** Many other cells can express class II antigen once activated, such as renal tubular epithelium during kidney allograft rejection. Interferon is a cytokine that can upregulate different cells to express class II antigens during activation. **Each individual inherits two class I and one class II antigen(s) from each parent, so six HLA antigens constitute an individual's tissue type (three from each parent).** The HLA molecules are polymorphic, based on multiple alleles (alternative genes at each locus) with over 150 now serologically defined. Therefore it is very unusual if two unrelated individuals have the same tissue type of six HLA antigens.

Both class I and II molecules are dimers with an α and a β chain (Fig. 17–4). The class I alpha chain has three domains of amino

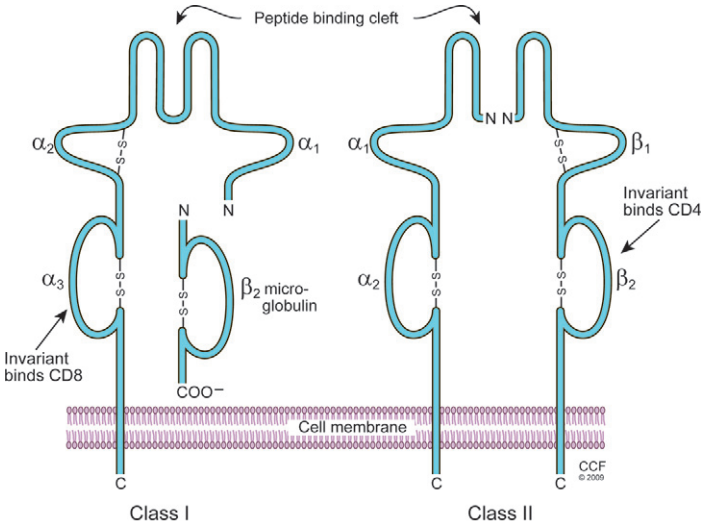


Figure 17–4. Schematic diagram of major histocompatibility complex (MHC) class I and class II molecules. Both are cell surface glycoprotein dimers with the carboxyl terminus directed towards the plasma membrane. Class I molecules (left) have an alpha chain with three domains and an invariant beta chain with a solitary domain. Class II molecules (right) have two alpha- and two beta-chain domains. Both molecules have polymorphic Ig-like regions that extend off the cell surface and form a cleft in which small peptides can bind. A peptide residing in an MHC molecule cleft provides signal 1 to the receptor of a naive T cell during activation. The nonpolymorphic Ig-like domains of MHC molecules contain binding sites for the T-cell molecules CD4 and CD8. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2009-2011. All Rights Reserved.)

acids and a constant β chain called β-2 microglobulin, which is the same in all class I molecules and does not insert into the cell membrane (Bjorkman, 1987). The class II molecules have two domains for each chain, and both chains insert into the cell membrane. **The alpha-1 and -2 domains of class I molecules and the alpha-1 and beta-1 domains of the class II molecules form a unique antigen peptide–binding cleft that cradles the antigen and is essential for antigen presentation.** Analysis of peptides eluted from the binding groove of MHC class I molecules revealed that a maximum of 8 to 10 amino acids will fit, while the groove for the MHC class II molecule is larger and allows a peptide of 12 to 28 amino acids in length. The β-2 microglobulin domain of the class I and the alpha-2 and beta-2 domains of the class II molecules are fairly invariant, so the diversity of the different HLA antigen molecules resides in the domains that define the peptide-binding groove.

T-Cell Receptor

The TCR is that cell surface structure responsible for the initial steps in T-cell activation upon encounter with antigen. The TCR comprises at least seven receptor subunits whose production is encoded by six separate genes that are precisely assembled (Davis and Bjorkman, 1988). The TCR is composed of the clonotypic α and β chains that are responsible for antigen binding and are noncovalently associated with the invariant CD3-γ, -δ, -ε, and TCR ζ chains. The cytoplasmic tails of the CD3 and TCR ζ chains contain a critical amino acid sequence known as the immunoreceptor tyrosine–based activation motif (ITAM) that includes two tyrosine residues. The CD3 chains contain one ITAM, while the TCR ζ chain contains three ITAM sequences (Fig. 17–5). **CD3 is commonly called the pan–T-cell marker, present on all T cells. There are generally two types of TCRs named TCR1 and TCR2. The TCR1 consists of a γδ heterodimer, appears first in ontogeny, and represents about 5% of circulating T cells in an adult. The TCR2, representing 95% of peripheral blood T cells, has an αβ heterodimer. Each of the two polypeptides comprising each receptor has a constant and a variable region (similar to immunoglobulin). Antigen recognition takes place at the variable αβ heterodimer, resembling an antibody Fab antigen–binding fragment.** The relatively invariant transmembrane CD3 complex transmits the signal to the cell interior. Reminiscent of the diversity of antibody molecules produced by rearrangements of variability, diversity, and joining genes, the TCRs can likewise identify a large number of antigenic specificities, estimated to be 10^{10} to 10^{12} epitopes (Davis et al, 1998). The affinity of TCR binding to APCs is rather weak, which is why additional adhesion molecules are required to strengthen the interaction.

B-Cell Receptor

The functional B-cell receptors are the IgD and IgM immunoglobulin molecules on the surface of B cells. These antibodies are anchored to the B-cell plasma membrane by the C-terminal ends of their heavy chains. The surface antibodies provide antigen specificity through the variable regions of both heavy and light chains, which face outward from the cell surface. The variable regions usually have three hypervariable or complementarity-determining regions (CDRs) that make direct contact with antigens. The CDRs form a loop structure that is complementary to the three-dimensional structure of the antigen. The antigen

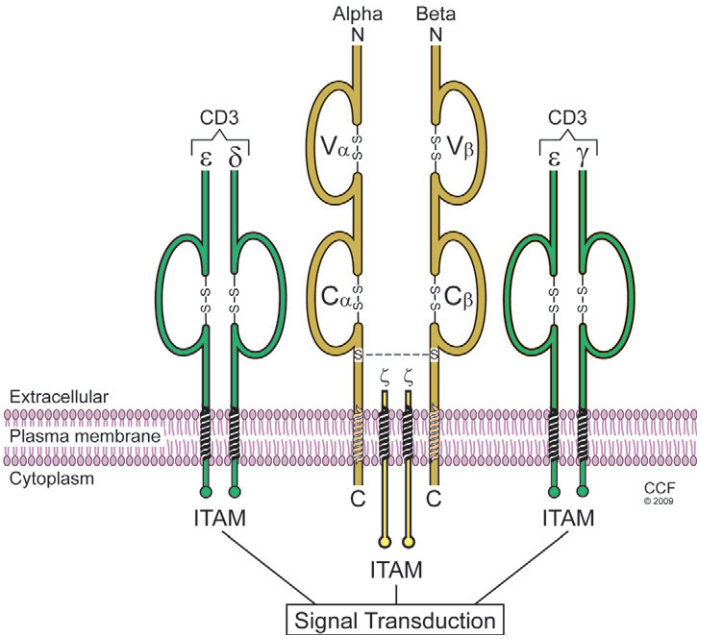


Figure 17–5. Schematic diagram of the T-cell receptor (TCR). The receptor is a complex of two main glycoprotein alpha and beta chains (defining an αβ TCR) noncovalently linked to the CD3 proteins (γ, δ, ε) and the ζ chain. As in other Ig superfamily products disulfide bonds form domains and the carboxyl terminus of each chain is inserted into the plasma membrane. The amino terminus extracellular domains are variable in amino acid sequence, and form the site of recognition of MHC-peptide complexes. The CD3 and ζ chains have intracytoplasmic ends (○) with signaling functions termed immunoreceptor tyrosine based activation motifs (ITAMs). The phosphorylation of the tyrosines in ITAMs represent the initial intracellular signaling events induced by TCR interaction with antigen. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2009-2011. All Rights Reserved.)

receptors of B cells can recognize a wide variety of macromolecules, such as proteins, polysaccharides, lipids, and nucleic acids. This broad specificity of B cells gives antibodies a wide net to recognize microbes and toxins in their native form. However, very large proteins are not able to bind B-cell receptors, and a full B-cell response requires help from CD4+ T cells. B cells can ingest protein antigens, which are processed and displayed as peptides with MHC molecules for recognition by helper T cells.

LYMPHOCYTE ACTIVATION

Presentation of Antigen

An essential requirement of immunity is that the system cannot be continuously triggered by self-antigens. As described previously, an early process of selection of T cells during maturation in the thymus deletes many offending clones, and selects those for future antigen response by utilizing MHC restriction. **The TCR2 T cells bearing αβ receptors only respond when the antigen-presenting cells express the same MHC molecules as the host from which the T cells were derived (the MHC molecules that first primed the T cell).** The types of responses are also controlled by the specificity of the MHC antigens on the APCs themselves. **Those T cells bearing CD8 that are programmed to be cytotoxic require APCs to present antigen in the context of MHC class I molecules, while those helper T cells expressing CD4 require antigen to be**

associated with MHC class II molecules on the APC for activation (Micelli and Parnes, 1993).

An additional layer of control is also imbedded in this system. Antigen must be processed into smaller pieces, linear 8 to 20 amino acid sequences, so it can fit precisely into a groove created by the outermost domains of the class I and class II MHC molecules (Germain, 1994). The result is that the T cell must recognize both MHC and peptide in a particular arrangement for antigen-specific activation to take place (Madden, 1995). **Antigen processing necessitates the conversion of native proteins to peptide-MHC complexes. This involves uptake by the cell, proteolysis, and additional mechanisms for the repackaging and transport of the MHC-peptide complex to the cell surface**. In general, peptides associated with MHC class I are derived from proteins synthesized within the cell on cytosolic ribosomes, such as viral and oncogenic products, whereas those peptides associated with MHC class II molecules often originate from extracellular fluids, such as bacterial products and toxins, and are taken up by receptor-mediated endocytosis.

Antigen-Presenting Cells

An antigen-presenting cell (APC) is a cell that can process a protein antigen, breaking it into peptides and then presenting it in conjunction with MHC molecules on the cell surface, where it may interact with appropriate T-cell receptors. Macrophages, monocytes, some B cells, Langerhans cells of the skin, dendritic reticulum cells, and vascular endothelium can process and present antigen. **The most efficient are the dendritic cells, which have a characteristic starfish shape and line the epithelial layer of exposed surfaces.** Once mature, they travel to the periphery to pick up antigen, then process and present it to naive T cells in the lymphoid tissues. These cells ingest proteins and split them into small peptides in endosomes. The peptides are then transported to the cell surface and assembled in the peptide-binding groove on the MHC molecules for presentation (Trombetta and Melman, 2005). **The peptides presented by APCs must be assembled with self-MHC molecules, forming the basis of MHC restriction in the immune response.** CD4+ T cells will recognize antigens only in the context of self-MHC class II molecules on the surface of the APCs. Again, cells that can initiate an immune response, such as dendritic cells, macrophages and some B cells, are often referred to as "professional APCs."

Three Signals

T cells become activated when the TCR engages an antigen for which it is specific; however, the TCR must "see" the antigen peptide presented in the groove of an MHC molecule on an APC. The interaction of one TCR and a peptide-MHC is of surprisingly low affinity and must be stabilized by an appropriate coreceptor–CD4 for MHC class II and CD8 for MHC class I molecules (Fig. 17–6). This initial step is called **signal 1.** Although triggering by signal 1 is necessary, it is not sufficient for T-cell activation alone. In fact, stimulation by signal 1 alone leads to a state of anergy, whereby the T cell becomes unresponsive to antigen. **Activation requires costimulation by proteins on the APC that engage specific receptors on the T-cell surface, referred to as signal 2.** The major APC molecules providing signal 2 are B7.1 (CD80) and B7.2 (CD86), but a number of other accessory molecules may support or enhance costimulation, such as CD2 engaging LFA-3 (CD58) and

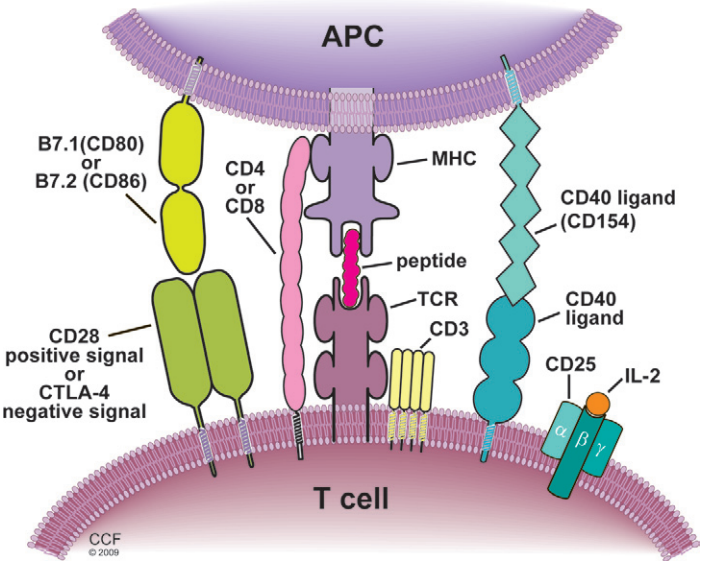


Figure 17–6. The immune synapse: T-cell activation requires three signals. Activation is initiated at the cell surface between an antigen-presenting cell (APC) and a T cell bearing a T-cell receptor (TCR). Signal 1 is delivered by an APC by a major histocompatibility complex (MHC) molecule with bound peptide to a tight-fitting TCR. This interaction is stabilized by a T-cell CD4 during presentation by MHC class II molecules, and stabilized by CD8 for presentation by MHC class I molecules. Activation will not proceed without the delivery of a second signal, which is required for further intracellular signal transduction. The second signal may be delivered by one of several glycoproteins, such as B7 (CD 80/86) and CD40, to their T-cell ligands CD28 and CD40 ligand (CD 154), respectively. The necessary signal 3 is delivered by interleukin-2 (IL-2) and other cytokines (IL-15) to their respective receptors. This leads to activation of various cyclins and the target of rapamycin, resulting in T-cell proliferation. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2009-2011. All Rights Reserved.)

LFA-1 engaging ICAM. These molecules engage the T-cell surface glycoprotein CD28, and when combined with signal 1, leads to activation of calcium-calcineurin phosphatase, mitogen-activated protein (MAP) kinase, and protein kinase C pathways, which in turn initiate transcription (Dustin, 2005) (see Signal Transduction). **Completion of activation requires the delivery of growth factors (interleukin [IL]-2 and -15), using phosphoinositide-3-kinase (PI-3K) and the target of rapamycin (mTOR) pathways, referred to as signal 3, thus initiating the cell cycle.**

Recognition of Alloantigen

The MHC was originally defined by its ability to provoke and sustain the rejection of organs and tissues between members of the same species (the allograft response). This response can be very rapid and intense, because individuals have a very high frequency of potentially alloreactive T cells. **As previously described, only a small fraction of T cells are specific for a single peptide, yet more than 10% of the T-cell population can react with alloantigens. Why is this so? Alloantigens create a unique potential for T-cell activation, because they serve both as immunogens as well as participants in the activation of the immune response in the host.** When an allograft kidney, heart, or liver is transplanted into a recipient, it brings an array of tissue-bound cell-surface class I and II MHC antigens that are foreign to the host. In addition,

the grafted organs transport large numbers of "passenger leukocytes" that can be both adherent to the blood vessels as well as within the interstitial tissues. As a "passenger leukocyte" the mononuclear dendritic cell is particularly suited to augment the alloimmune response, because it functions as an APC and can traffic from the graft to recipient secondary lymphoid tissues to interact with immune-competent cells. **Remember that the requirements for T-cell activation are dependent on both the presentation of peptide-MHC complexes and the costimulatory signals provided by professional APCs.**

The immune response is provided by two distinct pathways for allograft recognition (Gould and Auchincloss, 1999). In the **direct recognition** pathway, recipient T cells engage peptide-MHC molecules expressed on allogeneic cells. **The direct pathway is mainly responsible for the initiation of acute cellular rejection of allografts, and evidence suggests that passenger leukocytes (dendritic cells) play a key role.** These donor APCs must express both MHC class II and the appropriate costimulatory molecules, because the depletion of either will prevent an immune response from taking place. The peptides sitting in the MHC groove may be derived from endogenous proteins of either the donor or the recipient. Thus the foreign MHC molecules presented to the recipient can be a myriad of alloantigens, including the allogeneic MHC molecule itself plus the many different peptides derived from endogenous proteins. There is also evidence that recipient T cells can recognize allo-MHC molecules that are empty, with no peptide in the binding groove. These observations help explain why so many recipient T cells can become alloreactive and rapidly destroy a graft.

The immune response is also provided an indirect recognition pathway for alloantigens, whereby T cells recognize processed alloantigens presented by recipient APCs in association with self-MHC class II molecules. Mechanistically, this pathway requires the uptake and processing of the donor MHC molecules (to form peptide fragments) by the APCs of the recipient. **The evidence for such an indirect pathway comes from observations that rejection can take place even if donor and recipient share most, if not all, MHC antigens.** During indirect pathway recognition, recipient APCs migrate to the graft and take up soluble donor MHC molecules for processing. The actual T-cell activation occurs in recipient secondary lymphoid tissues, similar to activation in the direct pathway. Because the indirect pathway results in T cells that are self-MHC–restricted, their numbers are much smaller than those produced from direct pathway recognition, which predominates during the initiation of acute allograft rejection. However, the direct route becomes less important with time as the number of donor APCs diminish by senescence. The ready supply of recipient APCs involved in the indirect pathway is never depleted and can continuously process and present donor antigens. **For this reason, indirect recognition is thought to be more closely linked to chronic rejection of an allograft.**

Lymphocyte Precursor Frequency

The magnitude of the responses produced by various subsets of lymphocytes is closely related to the absolute number of precursor cells capable of responding. Thus the frequency of precursor cells can determine the robustness of an antigen-specific response in culture. Simply counting cells with a particular marker (i.e., CD4) may over- or underestimate the number of cells able to perform the function associated with cells bearing that marker. So, a technique called limiting dilution analysis (LDA) is used to measure the abundance of cells able to perform a particular function. The particular function can be CD4+ helper-cell proliferation measured by ^{3}H-thymidine incorporation, or CD8+ CTL lytic activity of chromium-labeled targets. The LDA procedure involves setting up cell cultures with graded dilutions of cell suspensions (peripheral blood lymphocytes) to be tested. If the quantity of active cells in the suspension is so high that each culture is positive for the specificity being tested, then all the cultures will be positive. If the concentration of cells is very low, then only rarely will a positive culture be found. Between these extremes, the response can be quantified as a function of cell dose. The analysis follows a Poisson distribution in that the dilution at which 37% of the aliquots give negative responses will contain one precursor cell per aliquot. From this concentration one can calculate the precursor frequency for the original cell suspension (Lefkovits and Waldmann, 1979).

Regulation of T-Cell Activation

Until they are activated through TCR-mediated engagement of a specific antigen-MHC complex on professional APCs, T cells are immunologically quiescent and do not express immune functions. **Activation of specific T cells and the generation of an immune response require transport of antigenic components to the lymphoid tissue. For the induction of most T-cell–mediated immune responses, the critical antigen-presenting cell is the dendritic cell, which is interspersed throughout peripheral tissues (Shortman and Naik, 2007).** As situated in the peripheral tissues, dendritic cells exist in an immature state and must be activated to perform the immune functions of antigen processing, presentation, and trafficking to the lymphoid tissue.

The immune system has evolved with highly regulated components to control the activation of dendritic cells and the transport of antigenic material to the lymphoid tissue. **Tissue trauma and/or the deposition of antigenic material in peripheral tissues, such as from a microbial infection, vaccination, or an organ allograft, induces a local inflammatory response. This inflammation is initiated by the production of TNF-α and IL-1 in response to tissue trauma and/or recognition of microbial products (Tracey and Cerami, 1994). Microbial products such as flagellin, unmethylated CpG of DNA, lipopolysaccharide, or single- or double-stranded RNA are potent activators of cells through innate pattern recognition and Toll-like receptors. In addition, endogenous stress molecules released by a variety of cells during tissue injury include HMGB1, heparin sulfate, and hyaluronan fragments bind to TLR2 and TLR4 to activate cells.** An important consequence of this response is that inflammation is stimulatory for antigen capture, processing, and transport to the lymphoid tissues. **Interstitial dendritic cells are activated by TNF-α to become phagocytic cells and ingest pieces of foreign material and tissue debris. The ingested material is processed or degraded within specialized intracellular compartments, and peptides and glycolipids are presented as complexes in association with class I or class II MHC–encoded proteins. TNF-α produced during tissue inflammation also stimulates the dendritic cells to downregulate the expression of molecules retaining or tethering dendritic cells in parenchymal tissues, and to upregulate expression of receptors for chemoattractant cytokines, or chemokines, that direct trafficking of the dendritic cells through the afferent lymphatic vessels**

and into the T-cell rich areas of lymphoid tissues draining the tissue site (Saeki et al, 1999).

Following trafficking to the lymphoid tissue, dendritic cells presenting peptide-MHC complexes secrete proteins that attract naive T cells to survey or sample the dendritic cell surface. **During antigen presentation in the lymphoid tissues, T cells expressing receptors with specificity for peptides presented in association with class II MHC molecules (i.e., CD4+ T cells) and/or T cells with specificity for peptides presented in association with class I MHC molecules (i.e., CD8+ T cells) are stimulated to develop into effector cells (Germain and Margulies, 1993).** In addition to TCR engagement of peptide-MHC complexes, activation of naive T cells to functional activity requires other receptor–ligand interactions (Schwartz, 1992). This costimulation is provided by several complementary sets of molecules. During the initial period of T-cell priming, TCR engagement of peptide–class II MHC complexes on the dendritic cell stimulates the CD4+ T cell to express the ligand CD154, which binds to a costimulatory molecule, CD40, constitutively expressed by dendritic cells. Engagement of this ligand–receptor pair stimulates the dendritic cell to upregulate expression of the CD80/B7-1 and/or CD86/B7-2 costimulatory molecules that bind to a constitutively expressed molecule, CD28, on the T-cell surface.

CD8+ T cells do not express CD154 during peptide–class I MHC interaction for the generation of many immune responses. However, other costimulatory molecules, such as 4-BB1, have been identified for CD8+ T cells, and these molecules may in some circumstances substitute for the absence of CD154 expression. Similar to the activation of CD4+ T cells, most CD8+ T-cell responses are dependent on B7-mediated costimulation during priming. **It is also important to note that the generation of many CD8+ T cell–mediated responses requires provision of CD4+ T-cell helper signals. The CD4+ T-cells help is not provided through production of cytokines for antigen-specific CD8+ T-cell growth but through delivery of signals to the antigen-presenting dendritic cells that "license" the dendritic cell to activate the CD8+ T cell.** CD40–CD154 interactions appear to be important signaling components in dendritic cell licensing to activate CD8+ T cells, and CD4+ T-cell help can be replaced by agonist anti-CD40 antibodies. CD4+ T-cell helper–dependent CD8+ T-cell responses include most CD8+ T-cell responses to viruses and to solid organ allografts, whereas CD4+ T cell–independent responses include CD8+ T-cell responses to skin allografts and to contact allergens.

During T-cell priming by dendritic cells in the lymphoid tissues, many regulated events occur that promote the optimal development of T cell–mediated immune responses. These events include (1) the expression of growth factor receptors on the T cell, (2) the production of appropriate growth factors, (3) the expression of molecules which direct trafficking of the primed T cells to inflammatory sites, (4) the production of effector molecules mediating the immune response following the arrival of T cells at the peripheral site of inflammation, and (5) the interaction with cells expressing the target peptide-MHC complex.

ACTIVATION OF B CELLS

Antibody Production

Although the thrust of this chapter focuses on cell-mediated immunity, a brief description of antibody structure follows. Antibodies are glycoprotein molecules of the globulin fraction, produced by plasma cells in response to stimulation with an immunogen. They are also called immunoglobulins and constitute 1% to 2% of the total serum proteins. The term antigen is used to describe a molecule capable of being recognized by an antibody or a T-cell receptor. **The immunoglobulin molecule consists of two identical heavy (H) and two light (L) chains held together by disulfide bonds** (Fig. 17–7). There are five antibody classes termed isotypes, so named by their different heavy chains and designated IgM, IgG, IgA, IgD, and IgE. Two types of light chains, kappa and lambda, are present in all five antibody classes, although only one is present in a specific molecule. **The basic structure is Y shaped with a hinge region rich in proline, stabilized by the disulfide bridges and noncovalent forces. Both H and L chains have constant amino acid sequences at their carboxy terminus and variable sequences at their amino terminus** (Alzari et al, 1988).

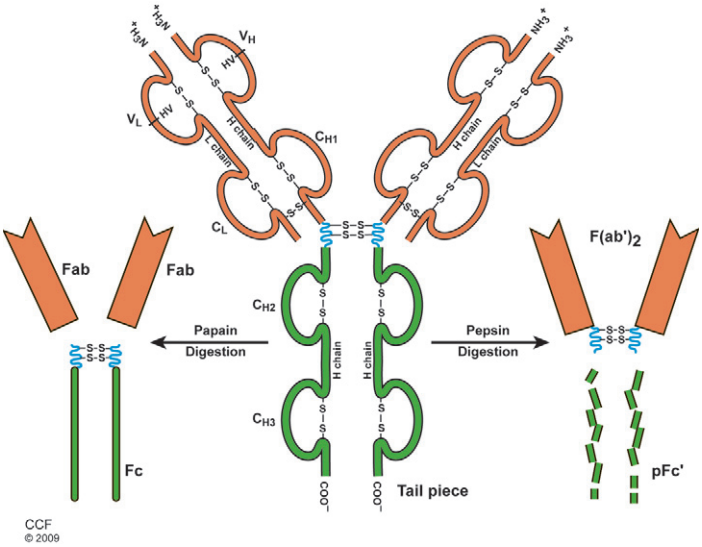


Figure 17–7. Schematic diagram of a typical IgG antibody molecule. Antibodies are dimers of two identical amino acid chains joined by disulfide bonds. These bonds provide the alignment of the two heavy and light chains and the formation of domains. The domains at the carboxyl-terminal ends are generally uniform or constant in sequence. The domains at the amino-terminal ends are variable and unique for each antibody molecule. There are usually three constant domains in heavy chains (C_H) and one in light chains (C_L). The antigen binding sites are formed by the juxtaposition of variable light chain (V_L) and variable heavy chain (V_H) domains. Enzymatic digestion with pepsin results in a divalent antigen binding fragment termed F(ab')$_2$. Digestion with papain results in three functional fragments; two (Fab) that bind antigen, and an Fc that identifies the different antibody isotypes. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2009-2011. All Rights Reserved.)

Much has been learned about antibody structure and binding after digestion experiments using the proteolytic enzymes papain and pepsin (see Fig. 17–7). Digestion with papain yields two Fab (antibody binding) and one Fc (crystallizable) fragment(s). Each Fab fragment has one antibody-binding site. The Fc fragment does not bind antibody, but is responsible for fixation to complement and attachment of the molecule to the cell surface. Digestion with pepsin cleaves the molecule toward the carboxyl-terminal side of the disulfide bonds, resulting in a single F(ab')$_2$ fragment with two antigen-binding sites and a functionless heavy chain segment. **These experiments confirmed that specific antigen binding occurs at the Y limb of the molecule, and that**

the nonspecific functions of each antibody isotype reside in the Fc end (Harris et al, 1999).

Each antibody H and L chain also conforms to several domains of 110 amino acid residues that form loops linked by disulfide bonds. In a typical IgG molecule, an H chain will have four domains, and an L chain two domains. Three of the H chain domains and one of the L chain domains are usually invariable in amino acid sequences and are called the constant regions. **The amino terminus domain on the H and L chains contains unique sequences for each molecule and is called the variable region. Several sites within the variable region are even more unique and are referred to as hypervariable. These hypervariable sequences govern both the conformation and specificity of the antigen-binding site of an antibody molecule.** The part of the hypervariable regions on the antibody that contacts the antigen is called the **paratope,** and the part of the antigen that is in contact with the **paratope** is called the **epitope.** Today, the nomenclature complementarity-determining region (CDR), rather than paratope, is more commonly used to describe these amino acid sequences. Both the variable and constant regions of each antibody molecule are encoded by specific gene sequences. The term **idiotype** is used to describe the unique antigen-binding site of each antibody molecule formed by a unique clone of lymphocytes.

Monoclonal Antibodies

The in vivo antibody response to an antigen is polyclonal in that many different antibody molecules are generated that will bind to the antigen. Each antibody originates from a specific clone of plasma cells, and binds to a different antigenic determinant or epitope. **Monoclonal antibodies are synthesized from a single clone of cells. The identical copies produced contain only one class of H chain and one type of L chain.** They are produced by fusing antigen-primed splenic B cells with an immortal myeloma cell line to create a hybridoma (Kohler and Milstein, 1975). Polyethylene glycol is used to effect the cell fusion. The antibody-producing B cell provides the specificity, and the myeloma cell provides the immortality to the hybridoma, which can generate large quantities of the monoclonal antibody. For clinical practice, murine-derived monoclonal antibodies can be engineered by "humanizing" the sequences of the constant regions of the light and heavy chains or with recombinant technology actually fusing human constant regions to murine variable regions to create a "chimeric" antibody. This is done to minimize undesired reactions of the human host to the murine sequences, which may trigger inflammatory responses such as fever, chills, nausea, vomiting, joint pains, hypotension, tremors, seizures, or visual disturbances.

Allogeneic B-Cell Activity

B cells often require the help of CD4+ T cells to proliferate and differentiate into plasma cells that synthesize and secrete specific antibody (Parker, 1993). This is especially true when B cells encounter alloantigens from an organ transplant. After B-cell immunoglobulin receptors react with donor protein antigens, the antigens are endocytosed, processed, and transported to the cell surface for presentation to resting T cells, only in the context of MHC class II molecules on the B-cell surface. The helper CD4+ T-cell TCR is engaged and stabilized by its CD4 molecule, which leads to T-cell activation and secretion of lymphokines including IL-2 (see Fig. 17–6). These lymphokines promote B-cell growth and differentiation into plasma cells that secrete specific antibodies. **B-cell activation also requires the presence of a second costimulatory signal to complete the process. In this case, a marker on the B-cell surface, CD40, must be engaged by its ligand CD40L on the surface of the helper T cell** (Foy et al, 1996)**. T cells are also required for isotype switching that occurs during some immune responses** (Stavnezer, 1996). Plasma cells often secrete IgM antibodies after primary antigen exposure. Secondary responses (after reexposure to the same antigen) usually results in the production of IgG or IgA antibodies by B cells with the same antibody-binding variable regions.

It should be emphasized that B and T cells usually recognize different antigens and/or different epitopes on the same antigen. **B cells usually recognize native proteins, peptides, or denatured proteins through their surface immunoglobulin receptors, whereas T cells are more complex in their recognition system in that smaller peptides are only recognized when processed and presented to T cells by APCs in context of MHC class I or II molecules.** However, B cells can recognize certain antigens without T-cell help. These so-called **T cell–independent antigens** are large macromolecules with repeating segments, such as bacterial polysaccharides and lipopolysaccharides that can cross-link many B-cell receptors. These antigens can bypass the second costimulatory signal (CD40), elicit a weaker response with poor memory, and usually cause only a polyclonal IgM response. **T cell–dependent antigens** are smaller and more complex, and elicit a more specific antibody response with durable memory. All antibody classes can be generated, but this process remains dependent upon the delivery of two signals for T-cell help.

CELL SIGNAL TRANSDUCTION

The response of cells to external stimuli, typically through surface receptors, results in the conversion of that signal into intracellular biochemical events, which ultimately leads to the expression of a variety of genes that are critical for cell function and growth.

TCR-Signaling Proximal Events

Activation of T cells is dependent on the signaling events transmitted by the TCR to the cytoplasm and the nucleus (Fig. 17–8)**. The initial intracellular signaling events, after lymphocyte detection of specific antigen, begin with the CD3 molecules (CD3ε, γ, and δ) and their corresponding motifs termed ITAMs (immunoreceptor tyrosine-based activation motifs), which are phosphorylated following TCR ligation** (van Leeuwen and Samelson, 1999; Kane et al, 2000; Myung et al, 2000; Smith-Garvin et al, 2009). Phosphorylation of ITAMs is mediated by two Src family kinases: Lck, which constitutively associates with CD8 and CD4 molecules, and Fyn, which interacts with the cytoplasmic domains of the CD3ε and ζ chain after receptor engagement. The phosphotyrosines produced by tyrosine kinases form binding sites for protein domains referred to as SH2 domains (Src homology 2 domains) that are present in a number of signaling molecules. The interaction of SH2 domains with the phosphotyrosines provides an important way to recruit signaling proteins to the activated receptors. TCR signaling can also be negatively regulated by the protein tyrosine kinase Csk, which alters the phosphorylation status of the Src kinases. The kinase domain of the Src kinase contains two tyrosine residues, where one provides an activation signal while the other inactivates the

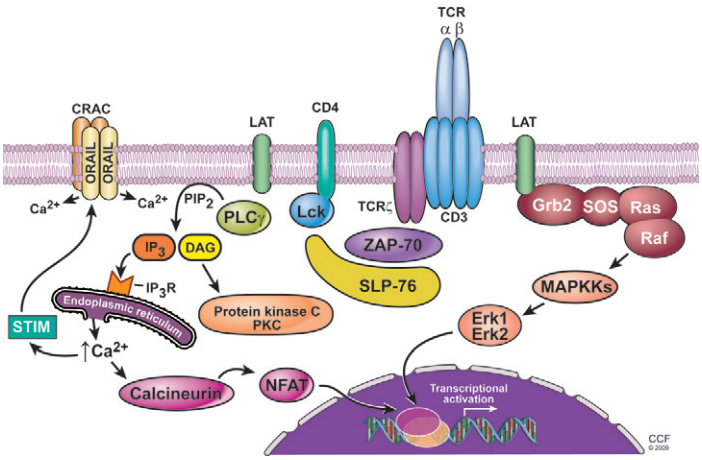


Figure 17–8. Signaling pathway induced by the T-cell receptor (TCR). The binding of antigen to the α/β chains of the TCR causes activation of Lck, which in turn results in the phosphorylation of TCR ζ and the recruitment and activation of another tyrosine kinase ZAP-70. This kinase phosphorylates the adaptor molecules LAT and SLP-76 that are the backbone of a complex that interacts with and orients different effector molecules, allowing activation of multiple signaling pathways. LAT then recruits PLCγ to the membrane where it cleaves its substrate PIP_2 into IP_3 and diaclyglycerol (DAG). IP_3 stimulates Ca^{2+}-permeable ion channel receptors (IP_3R) causing a release of Ca^{2+} into the cytosol from ER storage sites raising the intracellular levels of Ca^{2+}. The depletion in ER Ca^{2+} induces an influx of extracellular Ca^{2+} by the activation Ca^{2+} release-activated Ca^{2+} (CRAC) channels. The pore-forming units of the channel were determined to be a transmembrane molecule termed Orail. These events are regulated by stromal interaction molecule (STIM). The increase in Ca^{2+} activates the phosphatase calcineurin, which dephosphorylates the transcription factor NFAT allowing it to migrate to the nucleus. DAG release leads to the activation of protein kinase-C (PKC). Phosphorylated LAT also binds Grb2 that recruits the guanine-nucleotide exchange factor SOS that activates RAS. Activated Ras then recruits Raf-1 to the membrane where it is activated. Raf-1 then phosphorylates and activates MAPK kinases (MAPKKs), which initiates the activation of other kinases (Erk-1 and Erk-2) in this pathway. The end result is the activation of a number of transcription factors that initiate gene expression. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2009-2011. All Rights Reserved.)

enzyme. In resting cells, the Csk kinase phosphorylates the inhibitory tyrosine that maintains the Src enzymes in an inactive state. The negative effect of Csk on Src kinase function can be reversed by the protein tyrosine phosphatase CD45, which is involved in receptor signaling in T cells. This involves the removal of the phosphate group from the inhibitory tyrosine residue of the Src kinase.

The most effective activation of the TCR requires interaction with the coreceptor molecules CD4 and CD8, which serves to bring Lck in close proximity to the cytoplasmic domains of the TCR complex (van Leeuwen and Samelson, 1999; Kane et al, 2000; Myung et al, 2000). Once activated, Lck phosphorylates the tyrosine residues in the ITAMS of the CD3 and TCR ζ chains, which then provide the docking site for the tyrosine kinase ZAP-70. After recruitment to the TCR, ZAP-70 becomes activated as a result of its phosphorylation on multiple tyrosine residues by either Lck or Fyn kinases. Activated ZAP-70 then leads to the activation of the adaptor molecule LAT (linker of activation in T cells) and SLP-76. LAT is a transmembrane protein expressed in T cells and NK cells. It is a critical SH2 domain–binding protein involved in transmitting the signal from the membrane to downstream targets. LAT is essential for coupling the TCR to the PLC-γ1–Ca^{2+} and the Ras signaling pathways. SLP-76 is another adaptor protein that is also important for efficient TCR-induced tyrosine phosphorylation of PLC-γ1, inositol phosphate accumulation, Ca^{2+} mobilization, and Ras activation. **Thus the proximal signaling complex composed of the adaptor molecules along with a growing number of effector molecules is responsible for promoting the TCR–phosphotyrosine kinase (PTK) signal into multiple distal signaling pathways** (Smith-Garvin et al, 2009).

Activation of Intracellular Calcium and Protein Kinase C (PKC)

Phosphorylation of the enzyme phospholipase C–γ (PLC-γ) is a critical event in transmitting the activation signal from the membrane downstream (Myung et al, 2000). After TCR ligation, PLC-γ is present in the proximal signaling complex bound to SLP-76 and LAT where it is phosphorylated, an event that is dependent on several kinases (Lck, ZAP-70, Itk, and a Tec kinase family member, Rlk). The activated PLC-γ then hydrolyzes membrane-bound phospholipid phosphatidylinositol bisphosphate (PIP_2) into two active components, inositol triphosphate (IP_3) and diacylglycerol (DAG).

IP_3 stimulates Ca^{2+}-permeable ion channel receptors (IP_3R), resulting in the release of Ca^{2+} into the cytosol from storage sites within the endoplasmic reticulum (Oh-hora and Rao, 2008) which raises the intracellular levels of Ca^{2+}. The reduction in endoplasmic reticulum (ER) Ca^{2+} stimulates a sustained influx of extracellular Ca^{2+} via the activation of plasma membrane Ca^{2+} release–activated Ca^{2+} (CRAC) channels. Recent studies have identified the sensor for the depletion of ER Ca^{2+} stores and the activator of CRAC as an ER transmembrane protein referred to as stromal interaction molecule (STIM) (Roos et al, 2005). **Elevated μCa^{2+} results in the activation of multiple transcription factors along with various signaling molecules. This includes the Ca^{2+} enzyme calcineurin, a cytosolic serine/threonine protein phosphatase that regulates the activation of an important family of transcription factors, termed NFAT (nuclear factor of activated T cells).**

NFAT transduces Ca^{2+} signals not only in T lymphocytes but also in B cells, NK cells, monocytes, and nonhematopoietic cells, including those of the cardiac and nervous system (Zhu and McKeon, 2000). Four separate genes are present that encode different NFATs: NFAT1/p, NFAT2.c, NFAT3, and NFAT4. **NFAT, along with other transcription factors, play a critical role in T-cell activation and clonal expansion through their activation of the interleukin-2 gene.** The inactive form of NFAT is retained in the cytoplasm, unable to translocate to the nucleus because its nuclear localization sequence (NLS) is phosphorylated on serine/threonine. Calcineurin is composed of a catalytic subunit and a regulator subunit and is activated by the recruitment of Ca^{2+}-bound calmodulin. The association of calmodulin with calcineurin alters the structure of catalytic subunit, leading to activation of its phosphatase activity. Calcineurin then dephosphorylates the NLS of NFAT, allowing the transcription factor to translocate into the nucleus.

NFAT is important for T-cell activation; and because of its role in the regulation of critical genes in this process (e.g., IL-2, proto-oncogenes c-*myc* and cytokine receptors), it is a target for immune suppression in the allotransplant setting (Matsuda and Koyasu, 2000). **The immunosuppressive drugs cyclosporine and tacrolimus function by blocking the NFAT pathway.** Cyclosporine is a small, cyclic, fungus-derived peptide that is immunosuppressive once it has formed a complex with its

cytoplasmic receptor, cyclophilin, a ubiquitous cytosolic protein. The activity of tacrolimus also is dependent on binding to its receptor, FK-binding protein 12 (FKBP12). **The active complexes, cyclosporine/cyclophilin and tacrolimus/FKBP12, are known to block NFAT nuclear translocation by binding to the catalytic subunit of calcineurin and inhibiting its phosphatase activity.** The major inhibitory activity of cyclosporine and tacrolimus is thought to be their suppression of the growth factor IL-2. **Actually, the induction of IL-2 gene expression along with other T-cell activation genes involves stimulation of NFAT/AP-1 transcription factors and Ras signaling while NFAT activity in the absence of AP-1 stimulation induces a gene expression pattern that promotes T-cell anergy** (Macian et al, 2002)**.**

The cleavage of the PIP_2 by the PLC-γ enzyme also results in the formation of diacylglyerol (DAG), which remains attached to the inner surface of the plasma membrane (Myung et al, 2000). **DAG is involved in the activation of protein kinase C (PKC), a serine/threonine protein kinase that regulates the nuclear translocation of various transcription factors, including NFκB.** Recent studies have detailed how PKC activation leads to nuclear import of NFκB via the phosphorylation of a multiple protein complex (Matsumoto et al, 2005). PKC can be further activated by the increase in Ca^{2+} resulting from the release of IP_3. Beside activation of the PKC pathway, TCR-induction of DAG leads to activation of the Ras pathway.

Ras Pathway

Activation of the TCR-associated tyrosine kinases involves the small guanosine triphosphate (GTP)-binding protein Ras (Ebinu et al, 2000; Genot and Cantrell, 2000). **Ras proteins are proto-oncogenes that were initially discovered because of their effect on tumor cell growth, but it is now known that Ras plays an important role in lymphocyte activation.** Ras is involved in the activation the AP-1 family of transcription factors, which are composed of heterodimers of the oncogenes *fos* and *jun*. It also regulates other transcription factors such as NFAT, Elk-1, and the serum response factor (SRF). Ras also mediates TCR signals important to thymocyte and B-cell development. Defects in the activation of Ras have been linked to the development of T-cell anergy. Ras is a guanine-nucleotide binding protein that rapidly cycles from an inactive guanosine diphosphate (GDP) form to an active GTP-bound state. Ras activation is enhanced by two different proteins (SOS and RasGRP) and is suppressed by GTPase-activating proteins (Smith-Garvin et al, 2009). The activation of Ras induces a cascade of protein kinases referred to as the mitogen-activated protein kinases (MAP kinase). One of the best characterized Ras effector pathways is mediated by the MAP kinase Raf-1. Activation through the TCR results in the tyrosine phosphorylation of LAT that binds to Grb2 and recruits the guanine-nucleotide exchange factor SOS that activates the G protein, Ras. Activated Ras recruits Raf-1 to the plasma membrane, where Raf-1 is activated. Raf-1 then phosphorylates and activates the kinase MAPKKS, which then activates the MAPKs Erk1 and Erk2. These events ultimately lead to the activation of a variety of transcription factors.

Actin and Cytoskeletal Changes

The interaction between TCR and APCs results in the rearrangement of the actin cytoskeletal compartment that leads to polarization and activation of T cells with a reduction in cellular motility. As part of this process, there is movement of the microtubular organizing center toward the site of contact between T-cells and APC (Jacobelli et al, 2004). **At this contact site, an organized structure develops that is referred to as the immunologic synapase (IS)** (Monks et al, 1998; Smith-Garvin et al, 2009) **and is composed of two concentric regions, the central and peripheral supramolecular activation clusters (cSMAC and pSMAC).** Although much remains to be determined, it is thought that the start of TCR signaling is in the peripheral microclusters containing the TCR and associated signaling molecules (LAT, SLP-76, and Ca^{2+}). The cSMAC is thought to be the site of TCR signaling prolongation and, ultimately, degradation (Varma et al, 2006). TCR signaling is also important for the activation of integrins that are receptors responsible for cell–cell and cell–matrix adhesions. Relevant integrins include leukocyte function–associated antigen-1 (LFA-1) and very late antigen–4 (VLA-4) that bind their respective ligands intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM) (Menasche et al, 2007). A critical regulator of these interactions is the small GTPase Ras-proximity-1 (Rap1) molecule, because mutations in Rap-1–initiated integrin interaction is associated with leukocyte adhesion deficiency syndrome.

B-Cell Signaling

The receptor on B cells that recognizes antigen and transmits signal to the nucleus for gene expression is composed of a cell surface immunoglobulin containing heavy and light chains with variable regions (Janeway and Medzhitov, 2002). The immunoglobulin molecule is linked to two proteins (Iga and Igb) that consist of a single amino-terminal Ig-like domain and a transmembrane domain linked to a cytoplasmic tail. Iga and Igb are involved in signaling and contain one ITAM each. The Src kinases Fyn, Blk, and Lyn are associated with the B-cell receptor and are responsible for the phosphorylation of the ITAM after antigen engagement. The phosphatase CD45 is likely involved in removing inhibitory phosphates from the Src kinases and thus allowing their activation. Signaling, by the immunoglobulin receptors, is facilitated by coreceptor molecules that include CD19, CD21, and CD81. CD21 is a receptor for complement fragments that can recognize complement associated with antigen bound to the immunoglobulin receptor. These complexes cross-link CD21, which then induces phosphorylation of the cytoplasmic tail of CD19, allowing other Src kinases to bind and thus enhance receptor signaling. The next protein tyrosine kinase involved in the B-cell pathway is Syk, which induces the activation of phospholipase C-γ, leading to an increase in Ca^{2+} levels and activation of PKC. The tyrosine kinases are also responsible for activating the Ras pathway. Activation of these various pathways leads to induction of transcription factors that initiate gene expression required for B-cell proliferation and effector function.

JAK/STAT Signaling Pathway

The Janus family of kinases (Jak kinases) and the STAT (signal transducers and activators of transcription) proteins constitute one of the main signaling pathways that regulate cytokine gene expression (Schindler, 1999; Imada and Leonard, 2000). In mammals there are four Jak kinases, Jak1, Jak2, Jak3, and Tyk2, which are constitutively associated with many different cytokine receptors. However, different cytokine receptors are regulated by select kinases. For example, 1 and Tyk2

are required for IFN-γ/β signaling, whereas IFN-γ is dependent on Jak1 and Jak2. On the other hand, cytokines whose receptors share γc (IL-2, IL-4, IL-7, IL-9, and IL-15) use Jak1 and Jak3, except IL-13, which uses Jak1, Jak2, and Tyk2. Cytokines whose receptors share βc (IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor [GM-CSF]) use 2. Ligand binding causes dimerization of receptor chains, leading to activation of the Jaks and phosphorylation of the receptors that provide docking sites for the STAT proteins. The recruited STATs are phosphorylated by the Jaks and then translocate to the nucleus, where they initiate transcription. Seven different STAT proteins have been identified. Differences in the SH2 domains of the different STAT proteins determine their selectivity to various cytokine receptors.

The biologic importance of different Jaks and STATs has been revealed by deficiencies in these proteins in both humans and animal models (Imada and Leonard, 2000). **Mutations in Jak3 have resulted in patients having severe combined immunodeficiency (SCID), which is similar to X-linked SCID, which occurs because of a mutation in the common cytokine receptor γ chain. Jak3 activation is necessary for normal development and survival of T and B cells but not for dendritic cells (DCs)** (Yamaoka et al, 2005; Ross et al, 2007). Most mice deficient in Jak1 die perinatally and have defects in lymphoid development, except that Jak1 is not necessary for late stages of thymocyte maturation (Roberts et al, 2004; Ross et al, 2007). On the other hand, Jak2-deficient mice result in embryonic lethality due to loss of erythropoiesis, but Jak2 is not required for survival and function of lymphoid progenitors. Mice deficient in Tyk2 demonstrated only a reduced response to IFN-α/β and IL12. STAT1-deficient mice demonstrate a significant defect in IFN-dependent antiviral and antimicrobial immune responses. Although STAT2 KO mice develop normally, they are susceptible to viral infections. STAT4-deficient mice confirm that STAT4 is only activated by IL-12, because T cells from these mice were unresponsive to IL-12 and were defective in Th1 development. As expected, the STAT4-deficient mice showed an increase in IL-1/IL-10–producing Th2 cells. It has also been noted that STAT6-deficient mice are impaired in the development of a Th2 immune response as predicted, because IL-4 and IL-13 activate STAT6. Although there are no apparent immune deficits in either STAT5a–/– or STAT5b–/– mice, double KO mice exhibited severe impairment in T-cell function (Moriggl et al, 1999).

T-CELL MATURATION TO EFFECTOR FUNCTION

Clonal Expansion of Specific T Cells

Because the frequency of naive T cells for a particular peptide–self-MHC complex is very low (e.g., 1 in 10^5 to 10^6 T cells), the pool of reactive T cells needs to be expanded during priming in order to mount an effective immune response. **Most naive or quiescent T cells constitutively express the common cytokine receptor γ chain that is a component of the receptor for many cytokines, including IL-2, IL-4, IL-7, IL-9, and IL-15** (Leonard, 1996). The common γ chain is the target defect in X-linked severe combined immunodeficiency. In addition to the common γ chain, most naive T cells constitutively express the IL-2 receptor β chain. The combination of the β and γ chains form a receptor complex with low affinity for IL-2. **TCR engagement of a specific ligand, with delivery of costimulation during CD4+ T-cell priming, induces the expression of the IL-2 receptor α chain (called CD25) on the T cells. In combination, the α, β, and γ chains constitute the high-affinity IL-2 binding receptor.** TCR engagement plus costimulation also stimulates the CD4+ T cells to produce IL-2, which binds to the high-affinity IL-2 receptor and stimulates clonal proliferation of the CD4+ T cells in an autocrine manner (Fig. 17–9). This series of events results in rapid expansion of the reactive CD4+ T-cell pool. In many immune responses, activation of naive CD8+ T cells does not induce expression of the IL-2 receptor α chain. **Although CD8+ T-cell expansion can be promoted in vitro during culture with IL-2, a different growth factor, IL-15, appears to be critical for naive CD8+ T-cell proliferation during antigen priming in vivo** (Kennedy et al, 2000). **For expansion of reactive CD8+ T cells, TCR engagement of peptide–class I MHC complexes stimulates the upregulated expression of the α chain of the IL-15 receptor**. Rather than T cells, IL-15 is produced by a number of nonlymphoid cells, including fibroblasts, epithelial cells, and dendritic cells.

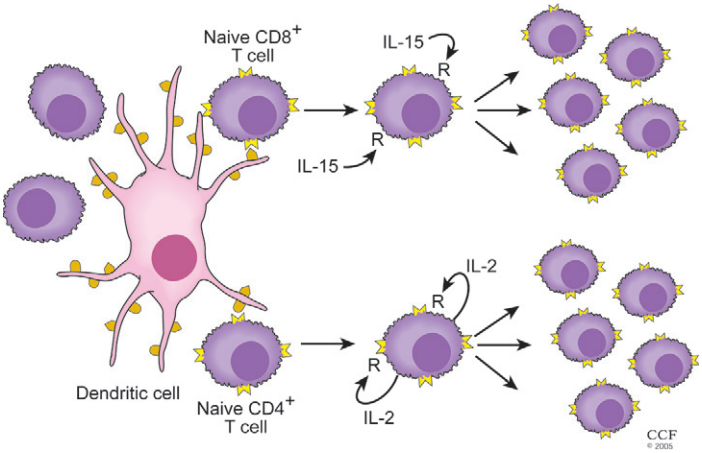


Figure 17–9. Activation of naive CD4+ and/or CD8+ T cells by dendritic cells results in proliferation of the reactive T-cell clones. Following emigration from the peripheral tissues to lymphoid tissues, dendritic cells presenting foreign peptides in the context of class I and/or class II major histocompatibility complex (MHC) molecules activate CD8+ and CD4+ T cells bearing receptors with specificity for the peptide-MHC complex. This activation includes the upregulation of growth factor receptor components that increase the affinity of the growth factor receptor. In addition to the expression of CD25 and high-affinity interleukin-2 (IL) receptors, activated CD4+ T cells produce IL-2, which is used in an autocrine manner to drive clonal proliferation of the activated CD4+ T cell. During activation, CD8+ T cells are stimulated to express the α chain of the IL-15 receptor that forms the high-affinity receptor for this growth factor. In contrast to IL-2–mediated expansion of CD4+ T cells, IL-15 is not produced by the CD8+ T cell but is produced by the dendritic cell and stromal cells in the lymphoid tissue. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2009-2011. All Rights Reserved.)

It is also important to note that maintenance of specific numbers of T cells occurs through homeostatic mechanisms that control the levels of the proliferative cytokine IL-7. This cytokine maintains the viability of naive, unstimulated T cells in the secondary lymphoid organs (the spleen, lymph nodes, and Peyer patches). The introduction of naive T cells into a lymphopenic environment results in the rapid proliferation of T cells (homeostatic proliferation), and their differentiation into effector and memory T cells. Homeostatic proliferation requires TCR engagement of MHC molecules and IL-7, or other proliferative cytokines. Because homeostatic proliferation

requires MHC stimulation of T cells, the importance of homeostatic proliferation arises in expansion of donor-reactive T cells in cases of intentional lymphodepletion for bone marrow or solid organ transplantation. Such conditioning can be achieved clinically with monoclonal or polyclonal anti–T-cell antibodies such as muromonab-CD3, alemtuzumab, or thymoglobulin.

Following initial priming and expansion of the peptide-MHC–reactive T-cell pool, T cells develop into cells with effector function. **Effector T cells mediate and regulate immune responses through two activities: cytokine production and expression of cytolytic function.** These effector functions are then expressed by antigen-primed T cells following interaction with target cells expressing the specific peptide-MHC ligand in peripheral tissues during elicitation of the immune response.

Cytokine-Producing T-Cell Phenotypes

During antigen priming CD4+ T cells develop into: (1) cells producing type 1 cytokines (e.g., Th1 cells), (2) cells producing type 2 cytokines (e.g., Th2 cells), (3) cells producing IL-17 and IL-21 (Th17 cells), or (4) cells that express regulatory function (O'Garra, 1998; Korn et al, 2009). **Type 1 cytokines include IFN-γ and TNF-β (also called lymphotoxin) and are critical components of cell-mediated immune responses, particularly responses to intracellular parasites and tuberculin delayed-type hypersensitivity** (see Table 17–2). The prototypic type 1 cytokine IFN-γ induces a number of proinflammatory events, including stimulating increased class I and class II MHC expression, stimulating production of intracellular molecules required for antigen processing and presentation, and stimulating macrophage proinflammatory activities such as superoxide and nitric oxide (NO) production, which render macrophages engulfing bacteria competent to kill the bacteria. These inflammatory functions are also important components of many organ-specific autoimmune diseases. **Type 2 cytokines include IL-4, IL-5, IL-6, IL-9, and IL-10 and are critical components of allergic responses and immune responses to extracellular parasites such as helminths.** These activities include the stimulation of eosinophil and mast cell growth and function, including the release of histamine and other molecules involved in allergic responses. IL-4 is also an important stimulus of B-cell growth. **IL-17 and IL-21 are important cytokines amplifying inflammation by inducing the recruitment and activation of innate immune cells, particularly neutrophils. Recent studies have also documented the critical role of IL-17 in the elicitation of autoimmune disease.**

The type 1 and type 2 cytokines also influence the isotype of antibody produced by B cells during an immune response. In general, the type 1 cytokines direct antibody responses to those fixing complement and participating in cell-mediated immune responses, such as opsonization, that are critical for protection against intracellular pathogens. In contrast, type 2 cytokines stimulate IgE production and other antibodies involved in allergic reactions. Obviously, the phenotype of T-cell cytokine production will have an important impact on the course of immune responses to infectious agents, as well as the sequelae of the response.

The most important factor influencing the development of CD4+ T cells to a particular functional phenotype is the cytokine environment present during priming by the antigen-presenting cell (Fig. 17–10). This polarization can occur within 48 hours of initial priming by dendritic cells.

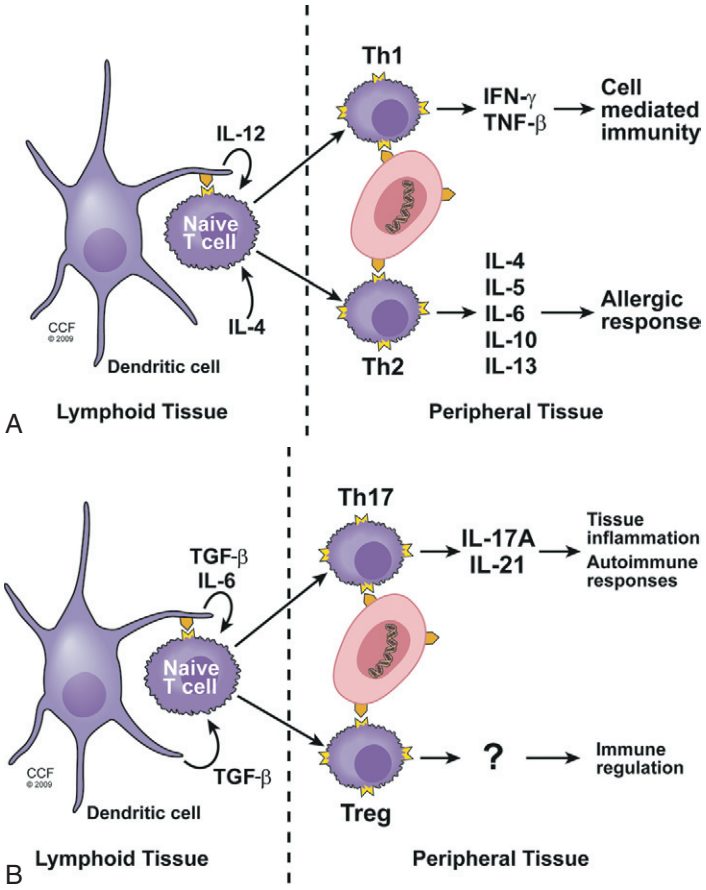


Figure 17–10. The cytokine environment during peptide–class II major histocompatibility complex (MHC) priming influences skewing of CD4+ T-cell development to Th1, Th2, Th17 or Treg cells. Following emigration from the peripheral tissues to lymphoid tissues, dendritic cells presenting foreign peptide in the context of class II MHC molecules activate specific CD4+ T cells to develop into immune effector T cells. **A,** The production of interleukin-12 (IL-12) by the dendritic cell or the presence of IL-12 during CD4+ T-cell priming skews the CD4+ T cells to develop into Th1 cells. Upon encounter with the specific peptide–class II MHC complex in the periphery, the Th1 cells are activated to produce type 1 cytokines, such as interferon-γ (IFN-γ) or tumor necrosis factor-β (TNF-β), during the elicitation of the immune response. The presence of IL-4 in the priming environment skews the CD4+ T cells to develop into Th2 cells. Upon encounter with the specific peptide–class II MHC complex in the periphery, the Th2 cells are activated to produce type 2 cytokines, such as IL-4, IL-5, or IL-13, that promote allergic-type immune responses. **B,** Similarly, the presence of both transforming growth factor-β (TGF-β) and IL-6 in the priming environment skews antigen-reactive CD4+ T cells to develop into Th17 cells, and upon encounter with the antigen in the periphery these T cells are activated to produce IL-17A and IL-21, cytokines that mediate inflammation by recruiting and activating neutrophils, as well as playing key roles in the elicitation of responses in autoimmune disease. When TGF-β is present in the absence of IL-6 in the priming environment, CD4 T cells develop into T-regulatory cells. Many different effector mechanisms have been ascribed to the functions of Tregs to mediate regulation of immune responses. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2009-2011. All Rights Reserved.)

Production of the cytokine IL-12 by antigen-presenting dendritic cells is a critical factor in guiding CD4+ T-cell development to the type 1 cytokine-producing phenotype (Gately et al, 1998). IL-12 is a 75-kD disulfide-linked dimer of p35 and p40 subunits. Many cells constitutively produce the p35 subunit, whereas production of the p40 subunit is restricted

to macrophages and dendritic cells. Induction of p40 expression and IL-12 heterodimer production by these cells is stimulated by microbial or endogenous stress products binding to TLR and/or by CD40 ligation during interaction with T cells. In the absence of IL-12 and in the presence of IL-4, CD4+ T-cell development is guided to the type 2 cytokine–producing phenotype. The source of this IL-4 during priming of the Th2 cells is not clear but may be provided by cells that express at least some properties of NK cells and some properties of T cells, thus classified as NK T cells. The development of CD4+ T cells to Th17 cells during antigen priming occurs in the presence of TGF-β and IL-6. In addition, the p19/p35 heterodimer, IL-23, stabilizes the phenotype and function of the IL-17/IL-21–producing cells. Finally, the presence of TGF-β and IL-2 in a priming environment in which there is no IL-6 can promote CD4+ T-cell development to CD4+CD25+FoxP3+ T-regulatory cells. The skewed development of CD4+ T cells to a specific functional phenotype occurs through the induced expression of specific transcription factors. IL-12 stimulates T-cell production of the transcription factor T-Bet which promotes IFN-γ production during Th1 development, whereas IL-4 stimulates production of the transcription factors c-Maf and GATA-3, which promote IL-4 production. The combination of TGF-β and IL-5 leads to the activation of ROR_{gt}, the transcription factor required for differentiation to Th17 cells. Other factors may also influence CD4+ T-cell development–the antigen dose and the type of costimulation provided during priming.

An important facet of the immune system is that type 1 and type 2 cytokines are counter-regulatory (Sher and Coffman, 1992). **IFN-γ inhibits IL-4 production, as well as the development of CD4+ T cells to the type 2 or Th17 cytokine–producing phenotypes. Similarly IL-4 inhibits the development of CD4+ T cells to IFN-γ cytokine–producing cells.** During T-cell cytokine–dendritic cell interactions, many cytokine-mediated regulatory events occur. For example, the presence of IL-12 induces the production of IFN-γ that, in turn, stimulates increased expression of the inducible IL-12 β2 receptor component. Alternatively, the presence of IL-4 downregulates the expression of the β2 receptor subunit and the T-cell development is skewed to the type 2 cytokine-producing phenotype. **In addition to the Th1 and Th2 populations of cytokine-producing T cells, a novel population of CD4+ T cells that produce IL-10, and TGF-β has been identified in some experimental systems and in humans** (Groux et al, 1997). **These cytokines, and therefore these T cells, have potent down-regulatory activities for Th1- and Th2-mediated responses.**

Antigen priming of CD8+ T cells in vivo usually induces IFN-γ–producing cells. In contrast to CD4+ T cells, CD8+ T-cell development to IFN-γ–producing cells is not dependent on the presence of IL-12 during priming. In vitro, development of CD8+ T cells to type 1 versus type 2 production can be promoted during antigen stimulation in the presence of IL-12 or IL-4, respectively. CD8+ T cells producing IL-4 and IL-5 have been isolated from patients with the tuberculoid form of leprosy or AIDS, which may indicate that the induction of type 2–producing CD8+ T cells in vivo is limited to certain disease states.

T Cell–Mediated Cytolysis of Target Cells

The development of CD8+ T cells with cytolytic function is a critical component of many immune responses to tumors, viruses, and other intracellular parasites. Cytolysis of infected target cells is an efficient mechanism for inhibiting the replication of intracellular parasites. **There are two major mechanisms used by CD8+ T cells to mediate cytolysis of cells expressing the target peptide–class I MHC complex** (Fig. 17–11)**. During priming in the lymphoid tissue, CD8+ T cells may develop into cells containing intracellular granules containing a protein called perforin, and a family of serine esterases of which granzyme B is the prototype enzyme** (Shi et al, 1997). Following TCR engagement of the specific peptide–class I MHC complex on a target cell the CD8+ T cell becomes activated to release these granules toward the target cell. The perforin monomers polymerize in the membrane of the target cell forming a pore. Granzyme B then enters the target cell and enzymatically activates intracellular caspases, such as caspase 10, leading to the induction of apoptosis. Perforin/granzyme B–mediated cytolysis is also an important function

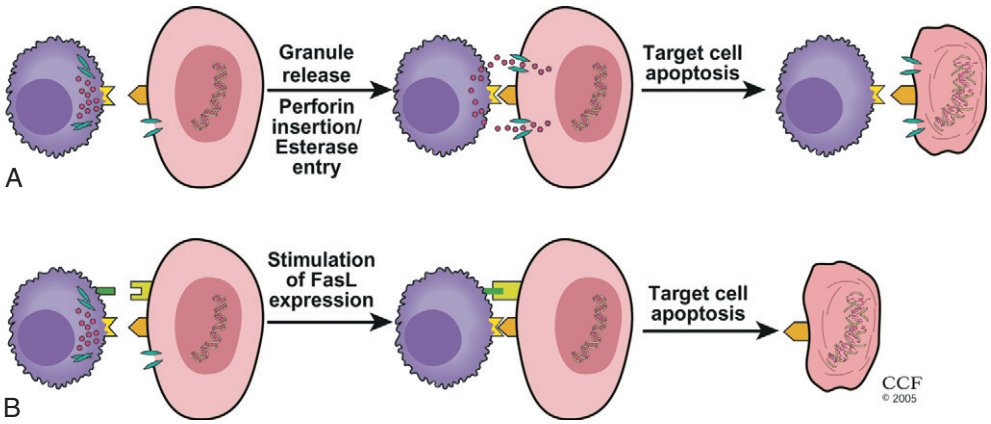


Figure 17–11. Two pathways used by CD8+ T cells to mediate cytolysis of target cells. Following priming by peptide–class I MHC complexes presented by dendritic cells in the lymphoid tissues, CD8+ T cells enter peripheral tissues and mediate cytolysis of target cells expressing the priming peptide–class I MHC complex. **A,** Following recognition of the target complex on target cells, the CD8+ T cell is activated to release cytotoxic granules containing perforin and serine esterases, such as granzymes A and B. The perforin monomers form a complex in the cell membrane of the target cell allowing the serine esterases to enter the target cell. The enzymes activate caspases, which promote apoptosis of the target cell. **B,** Following recognition of the target complex on target cells, the CD8+ T cell is activated to express FasL. The interaction of FasL with Fas on the surface of the target cell stimulates the induction of the apoptotic pathway and the death of the target cell. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2009-2011. All Rights Reserved.)

expressed by NK cells during innate immune responses and immune surveillance. Another lytic protein in T-cell and NK-cell granules, granulysin, is an important component of CD8+ T cell–mediated responses to intracellular microbial infections (Stenger et al, 1998). **The second major cytolytic mechanism is mediated through expression of Fas ligand (FasL), a member of the TNF family of proteins** (Sabelko-Downes and Russell, 2000). **FasL is induced on T cells following TCR recognition of the specific peptide-MHC complex. Engagement of FasL with the Fas receptor expressed by the target cell transduces apoptotic signaling resulting in target cell death.** Although cytolytic function has been primarily attributed to CD8+ T cells during immune responses, there is considerable evidence for CD4+ T-cell expression of perforin/granzyme B- and FasL-mediated lytic function, which may be an important component of immune responses to class II MHC–bearing target cells. Expression of mRNA encoding perforin and FasL is observed during rejection of renal allografts and is a reliable indicator of an ongoing acute rejection response.

Phenotypic Changes during TCR-Mediated Activation

In addition to alterations in immune function, priming induces many phenotypic changes in T cells. As discussed above, the expression of high-affinity receptors for growth factors is necessary for clonal expansion of reactive T cells and for their development to cells with immune effector function. An activation antigen, CD69, is expressed within hours of TCR engagement, and this expression disappears within 18 hours of its initial appearance. **Once T cells have been primed to the specific peptide-MHC complex, it is essential that they be able to get to sites in the peripheral tissue where an immune response is needed. During activation, T cells down modulate expression of CD62L, a receptor that facilitates T-cell entry into lymph nodes. Activation also stimulates T cells to express adhesion molecules and chemokine receptors that direct the cells to inflammation in the vascular endothelium.** Phenotypic analysis of circulating T cells is often used in diagnosis of ongoing immune responses, such as during an infection or autoimmune disease.

Memory Cells

During activation and clonal expansion of specific T cells, a portion of the pool develops into a population of memory T cells (Dutton et al, 1998). **In contrast to the effector T cells developing during the course of a primary immune response, the memory T-cell population is long-lived.** Memory cells survive even after an infection is eradicated or the inciting antigen is no longer present. This results in an increased frequency of reactive T cells, when compared with the original naive progenitor T cells. Whether memory T cells originate from specific precursor cells or from a set of long-lived primary effector T cells is still not clear and is under investigation in many laboratories. **Phenotypically, memory T cells express a high molecular-weight form of CD45, CD45RO, whereas naive T cells express the low molecular-weight form, CD45RA. Memory T cells have a lower threshold of activation and require less antigen-MHC complex to become activated. In addition, memory T cells use different costimulatory pathways than do naive T cells for activation, which may complicate the use of costimulatory blockade strategies to inhibit T cell–mediated responses in sensitized patients.** Following reencounter with a specific ligand, memory T cells will more quickly expand and develop to effector T cells than will naive T cells. In contrast to effector T cells generated during a primary immune response, memory T cells may also express multiple immune effector functions. It is also important to note that during differentiation to memory cells, some memory T cells express chemokine receptors and integrins, directing their trafficking to peripheral tissue such as the skin, gut, and lung, and they are termed effector memory T cells—those situated for rapid response in the peripheral tissue. In contrast, central memory cells are those that express receptors and integrins, directing their trafficking to secondary lymphoid tissues where antigens and antigen-presenting dendritic cells from the periphery drain.

Similar to T cells, naive B-cell activation results in the development of a memory B-cell pool. Subsequent activation of memory B lymphocytes results in more rapid generation of antibody responses than during primary antibody responses. **In contrast to memory T cells, the antibody produced by memory B cells is of increased affinity that is the result of somatic hypermutation of the V-region genes of the memory B cell** (Wagner and Neuberger, 1996). **Furthermore, the isotypes of antibody produced by memory B cells (e.g., IgG and IgA) are different from those produced during primary B-cell responses (e.g., primarily IgM with some IgG).** The purpose of vaccination is to induce populations of memory T and B cells so that upon infection with the microbial agent, a protective immune response is quickly mounted and consists of a broader range of protective effector mechanisms.

APOPTOSIS-PROGRAMMED CELL DEATH

Death Receptor Pathway

Apoptosis is a mechanism by which an organism deletes aged, damaged, and autoimmune cells, or cells that are no longer required in subsequent stages of differentiation (Ashkenazi and Dixit, 1998; Scaffidi et al, 1999). There are many stimuli that induce apoptosis and numerous intracellular pathways that lead from these to the final effector phase of the process. The proteins responsible for executing the suicide program, the caspases, are essentially common to all the stimuli and pathways and mediate the nuclear and cytoplasmic alterations characteristic of apoptotic cell death. **The specific roles of each member of the caspase cascade are gradually becoming defined. Caspase-8 and -10 are the initiator caspases that are involved in apoptosis mediated by the extrinsic pathway through the activation of different death receptors, Fas (CD95), TNFR (CD120a), and DR4 (TRIAL-R1) and DR5 (TRAIL-R2)** (Fig. 17–12). **Caspase-9 is the initiator for the intrinsic pathway (mitochondrial pathway). Caspases-3, -6 and -7 typically function to carry out the final steps of the committed apoptotic program** (Danial and Korsmeyer, 2004; Aslan and Thomas, 2009; MacFarlane, 2009).

The death receptor pathway is initiated by the Fas ligand (FasL/CD95-L) binding to Fas (CD95) or the ligand TRAIL (TNF-related apoptosis-inducing ligand) binding to cells that express one of two proapoptotic receptors, DR4 (TRIAL-R1) and DR5 (TRAIL-R2). These receptors

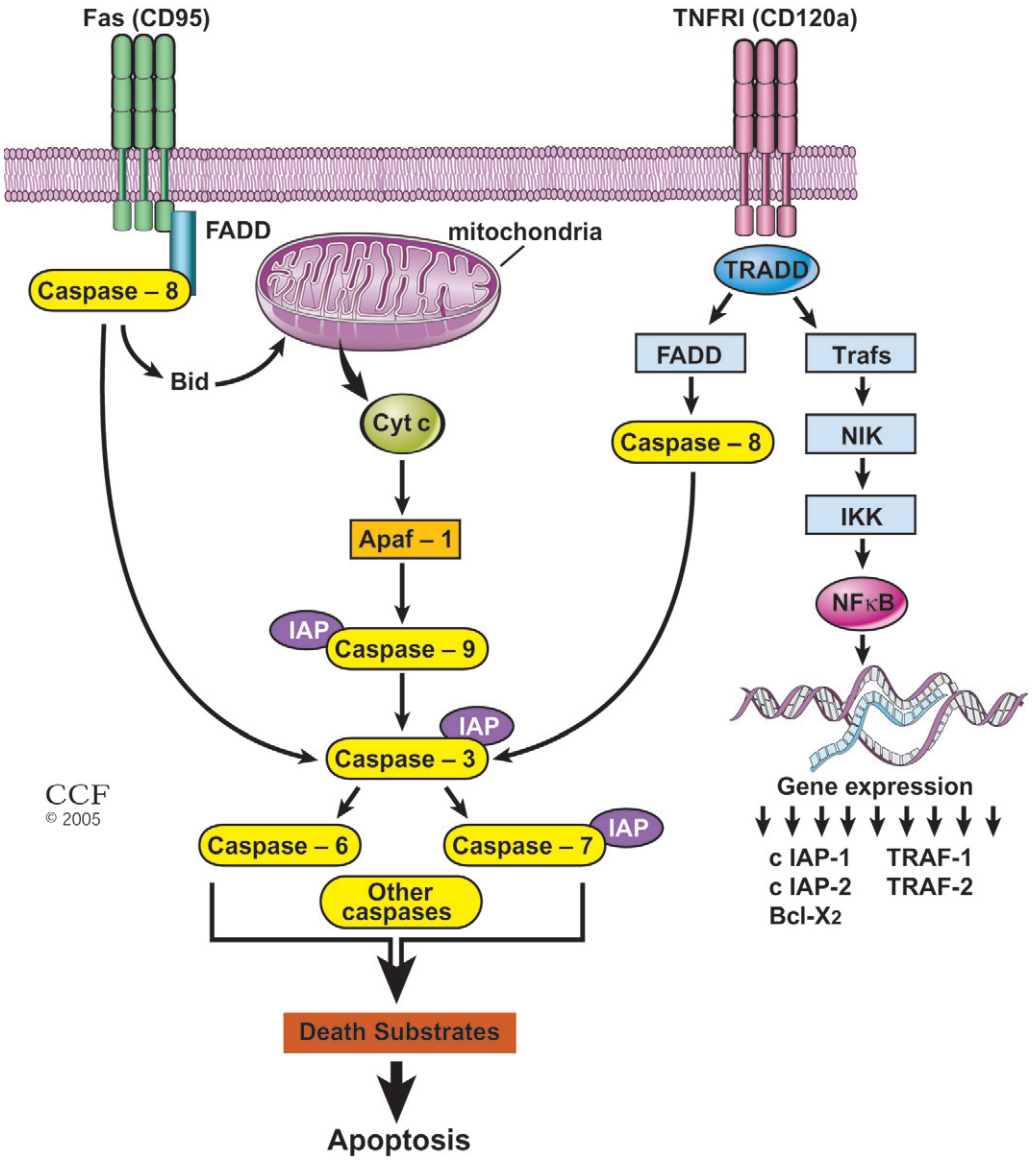


Figure 17–12. Scheme of Fas and TNFR1 activation leading to apoptosis. Ligation of Fas results in FADD binding to the death domains of the Fas receptor. FADD then recruits and activates caspase-8, which, in turn, activates downstream caspases in this pathway. Caspase-8 can also cleave Bid, which induces the release of cytochrome *c* from the mitochondria. Cytochrome *c* binding to Apaf-1 results in caspase-9 activation, which then initiates the caspase cascade to apoptosis. A similar extrinsic pathway is induced by the TNF-related apoptosis-inducing ligand (TRAIL/Apo2L) upon binding to its proapoptotic receptors DR4 (TRAIL-R1) and DR5 (TRAIL-R2) (not shown). TNFR1 ligation can also initiate the death pathway through the activation of caspase-8. It also activates the signaling pathway for the activation of the transcription factor NFκB. NFκB regulates the expression of a number of antiapoptotic genes (e.g., cIAP) some of which can bind to and inhibit the activity of caspases. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2009-2011. All Rights Reserved.)

contain a cytoplasmic sequence termed the death domain (Danial and Korsmeyer, 2004; MacFarlane, 2009). The death domains enable the death receptors to engage the cells' apoptosis machinery. Interaction between the Fas receptor (Apo-1/CD95) and its ligand is known to regulate several types of physiologic apoptosis. Fas-L is used by lymphocytes not only as a cytotoxic effector mechanism to induce apoptosis in Fas-expressing targets but also to diminish the immune response, once the targeted antigen has been eliminated. Fas/Fas-L–mediated induction of apoptosis is also an effective mechanism of T-cell homeostasis whereby self-reactive clones can be eliminated. Fas/Fas-L is also involved in killing of inflammatory cells at immune-privileged sites. **Oligomerization of Fas or DR4/DR5 as a consequence of ligand binding results in the recruitment of the Fas-associated death domain (FADD), thus forming a death-inducing signaling complex (DISC), which in turn activates caspase-8 and -10 triggering of apoptosis** (Danial and Korsmeyer, 2004; MacFarlane, 2009). Using selective inhibitors, a branched protease cascade was revealed in the Fas pathway, in which caspase-8 activates caspases-3 and -7, and caspase-3 activates caspase-6. Caspases-3 and -6 have specific roles in the nuclear changes accompanying apoptosis, whereas caspase-7 is responsible for the mitochondrial permeability transition and cytoplasmic shrinkage. **The formation of the DISC can be impaired by the protein c-FLIP, which is structurally similar to caspase-8 but is enzymatically inactive, and/or by decoy receptors (DcR3), which can bind ligand but do not signal apoptosis** (MacFarlane, 2009).

The engagement of TNFR1 by its ligand TNF activates the transcription factors NFκB and AP-1, leading to the induction of proinflammatory and immunomodulatory genes that are critical to the development of an immune response. **In contrast to Fas, TNF does not induce apoptosis by TNFR1 unless protein synthesis is blocked, suggesting that preexisting antiapoptotic genes can block the apoptotic pathway.**

The molecular events that modulate apoptosis vary depending on cell type. Cells that use the type 1 pathway can stimulate the initiator caspases directly to activate the executioner caspases, independent of the mitochondria. In contrast, type II cells have the initiator caspases that stimulate the executioner caspase, through Bcl-2 proteins such as the death agonist Bid (BH3-interacting–domain), which facilitates the release of cytochrome *c* through mitochondria membrane permeabilization (MMP).

Mitochondrial Pathway

In many apoptosis scenarios, changes in mitochondria play an integral role in the cell death process (Green and Reed, 1998). **Although the caspases can be characterized as the molecules that directly mediate apoptotic cell death, the Bcl-2 family of proteins regulates apoptosis at the mitochondrial level. The antiapoptotic members of this group (Bcl-2 and Bcl-X_L) buffer some of the signals that initiate the sequence to cell destruction, whereas others in the family (BAD, BAX) are proapoptotic** (Adams and Cory, 1998). The antiapoptotic and proapoptotic members act by differentially modulating cytochrome *c* release from mitochondria. Binding of cytochrome *c* to Apaf-1 causes a conformational change that results in the interaction of Apaf-1 with procaspase-9, and the ultimate activation of the latter to initiate a caspase cascade. Some proapoptotic members of the Bcl-2 family bind and destabilize the mitochondrial membrane directly, whereas others heterodimerize to and antagonize the anti-apoptotic membrane–spanning proteins. In addition to stabilizing the mitochondrial membrane to prevent cytochrome *c* release, Bcl-2 also acts cytoplasmically to inhibit activation of caspase-9. Overexpression of Bcl-2 and Bcl-X_L by gene transfer acts dominantly to prevent the activity of expressed proapoptotic Bcl family members. As mentioned above the mitochondria pathway can be induced after activation of the death receptors (Fas). The linkage between these pathways is the protein Bid, which is inactive in the cytosol but can be cleaved into an active form by caspase-8. The active fragment of Bid travels to the mitochondria and induces cytochrome *c* release, resulting in the activation of downstream effector caspases (Luo et al, 1998).

NFκB Regulation of Apoptosis

The importance of NFκB in host survival has been elucidated from studies using knockout mice having deletions of individual NFκB family members (Barkett and Gilmore, 1999). Cells deficient in RelA are much more sensitive to TNF-α–mediated apoptosis as compared with the wild type. This increased sensitivity to apoptosis is reversed by overexpression of RelA.

The increased susceptibility to apoptosis in NFκB defective cells probably results from the fact that NFκB regulates the expression of antiapoptotic genes (Deveraux and Reed, 1999). This includes TRAF-1 and TRAF-2, which associate with the cytoplasmic regions of TNFR family members. TRAF-2 interacts with downstream signal transducers that activate NFκB, while TRAF-1 is required for the recruitment of the NFκB-inducible cellular inhibitors of apoptosis proteins (cIAP-1 and cIAP-2). The cIAPs can directly bind and neutralize caspases-3, -7, and -9, and are thought to have other downstream antiapoptotic roles as signal transducers. Overexpression of TRAF-1, TRAF-2, cIAP-1, and cIAP-2 by transfection can together inhibit the apoptosis observed when NFκB activation is suppressed in TNF-sensitive cells. IEX-1L is another NFκB-dependent gene whose transfection into NFκB-defective mutants also provides protection against apoptosis in some systems.

Other antiapoptotic molecules with NFκB-dependent expression include Bcl-2, Bcl-X_L, and Bfl-1/A1 members of the Bcl family of proteins. Although some members of the family are proapoptotic, these molecules are known to protect against apoptosis induced by mediators of the mitochondrial permeability transition and also have been found to inhibit the activation of caspase-9.

LYMPHOCYTE TOLERANCE

The recombinatorial mechanisms generating receptors on T- and B-lymphocyte precursors result in the appearance of cells expressing receptors with reactivity to self-proteins. If allowed to mature and become activated in peripheral tissues, self-reactive lymphoid cells could cause considerable harm by mediating autoimmune disease. In addition to the generation of T- and B-cell clones with reactivity to a great number of different antigens, an essential feature of the immune system is the presence of mechanisms to remove or inactivate those cells with specificity for self-peptides. The development of autoimmune disease represents the failure of mechanisms maintaining nonresponsiveness or tolerance to self-proteins. Formally, tolerance may be defined as the inability of the immune system to react to a specific determinant following an initial encounter with that determinant. Thus the development of tolerance results in the absence of lymphocyte reactivity to receptor-reactive ligands that have been previously encountered by the immune system. The immune system has evolved with several mechanisms to circumvent the activation of antigen-reactive T and B lymphocytes. As will be briefly discussed below, mechanisms mediating tolerance to self-proteins may be manipulated in the design of strategies to induce tolerance to exogenous antigens such as alloantigens expressed by organ allografts.

Central Tolerance

An important mechanism mediating tolerance to self-proteins is the deletion of self-reactive T cells and B cells during maturation (see T and B cells). This mechanism is termed central tolerance. Maturation of T cells occurs in the thymus, and those cells that undergo a process termed positive selection are given signals to leave the thymus and seed the peripheral lymphoid tissues, whereas those with high reactivity for self are deleted or negatively selected (Sebzda et al, 1999). These selection processes begin when T-cell precursor cells originating from the fetal liver (in preborn and neonates) and the bone marrow traffic to the thymus. Three potential outcomes arise from these interactions. Those T cells expressing receptors that do not engage peptide-MHC complexes in the thymus undergo apoptosis due to the absence of survival signals delivered from the thymic cells. Those T cells expressing receptors with moderate reactivity to self-peptide–MHC complexes, presented by cortical epithelial cells in the thymus, receive signals to survive, and these are the cells that are positively selected to emigrate from the thymus and seed the peripheral lymphoid tissues to form the peripheral T-cell

repertoire. In contrast, those T cells expressing receptors with very high reactivity to complexes of self-peptides and class I or class II MHC molecules receive signals to undergo programmed cell death and are negatively selected or deleted from the repertoire. Recent studies have also identified a population of thymic medullary epithelial cells that express a set of peripheral tissue-specific antigens (TSA), including insulin, glutamic acid decarboxylase (GAD), and many other organ-specific proteins, under control of the *AIRE* (autoimmune regulator) gene and mediate the deletion of T cells with receptors specific for the TSA (Mathis and Benoist, 2009). The transcriptional activator AIRE was first identified and cloned from patients with autoimmune polyendocrinopathy-candidiases-ectodermal dystrophy (APECED). Rodent models have directly demonstrated that the deletion of AIRE and/or other defects in the deletion of self-reactive T cells results in the development of overt autoimmune disease.

Immature B-cell precursors expressing surface immunoglobulin receptors with reactivity to self-proteins are deleted during maturation in the bone marrow similar to the way T cells are negatively selected in the thymus (Nemazee, 2000). Deletion of self-reactive B cells in the bone marrow is dependent on cell-associated rather than soluble antigen.

Peripheral Tolerance

Negative selection does not result in deletion of all self-reactive T and B lymphocytes during maturation. One factor accounting for the incompleteness of this mechanism is that not all self peptides may be presented with MHC molecules by cells in the thymus. The escape of self-reactive T and B cells from the thymus and the bone marrow imparts the need for mechanisms to mediate tolerance of self-reactive lymphocyte clones in the periphery. Compensating for the incomplete deletion of self-reactive lymphocytes during maturation are mechanisms mediating deletion (e.g., clonal exhaustion and veto cell–mediated deletion) or inactivation (clonal anergy and active suppression) of peripheral T and B cells.

Peripheral Deletion of T Cells

Several mechanisms mediate deletion of antigen-specific T cells in the periphery. **Administration of large antigen doses stimulates the rapid proliferation of reactive T cells, but this is quickly followed by apoptosis of the reactive cells. This form of deletion due to "clonal exhaustion" has been shown experimentally in mouse models using virus infections and is thought to be operative in removing viral antigen-reactive CD8+ T cells during HIV infections** (Moskophidis et al, 1993). Clonal exhaustion is likely to occur in response to the large amount of self-proteins in the periphery, acting as a backup to remove self-reactive T cells that escaped negative selection during maturation in the thymus

An active mechanism of T-cell deletion in the periphery is mediated through stromal cells in the lymph nodes expressing AIRE (Gardner et al, 2008). Interestingly, the set of TSA expressed under the control of AIRE in the periphery is distinct from that expressed by thymic medullary epithelial cells.

Clonal Anergy

Clonal anergy of T cells is induced by TCR engagement of peptide-MHC complexes in the absence of costimulatory signals (Schwartz, 1997). In the two-signal model of naive T-cell activation, signal one (e.g., TCR-mediated stimulation) is delivered in the absence of signal two (e.g., B7/CD40–mediated costimulation). The major consequence of clonal anergy induction is the inability of the anergized T cell to produce IL-2 in response to subsequent encounters with the specific peptide-MHC ligand. Thus these T cells are unable to clonally expand and differentiate into effector cells. In at least some experimental model systems, T cells rendered anergic are able to proliferate when provided with exogenous growth factors such as IL-2, and their continued proliferation in the presence of growth factors promotes development to effector function such as IFN-γ production.

Clonal anergy of T cells can be induced by TCR engagement of specific antigen-MHCs presented by nonprofessional APCs that do not express costimulatory molecules; by resting professional APCs that do not express costimulatory molecules, by interaction with chemically fixed APCs, or by blocking-mediated costimulatory interactions, particularly CD28- and/or CD154-mediated costimulation. In some instances costimulation may also be delivered by other receptor ligand interactions during naive priming by professional antigen-presenting cells. Administration of antibodies to adhesion molecules, such as ICAM-1 and LFA-1, and to CD45RB during antigen priming induces clonal anergy of specific T cells. The ability to induce clonal anergy using these strategies emphasizes the importance of a highly regulated process of antigen capture, processing, and presentation by professional APCs having the ability to deliver the necessary costimulatory signals during T-cell priming. Anergy of B cells is also induced by antigen binding to surface immunoglobulins in the absence of costimulatory signals that are required for complete activation and development to antibody-producing cells.

Blockade of costimulation delivery during TCR interaction with peptide-MHC results in the alteration of many intracellular biochemical events observed during TCR-mediated activation of T lymphocytes. These events include absence of kinase activation (including the LCK and ZAP-70 kinases), absence of phosphorylation of CD3 components, and absence of activation of transcription factors including AP-1 and NF-AT. These intracellular signaling alterations suggest that the induction of clonal anergy is an active process. The ability of many immunosuppressants to block clonal anergy during naive T-cell interaction with peptide-MHC complexes in the absence of appropriate costimulation is consistent with clonal anergy induction as an active process.

In addition to the removal or inactivation of autoreactive lymphocytes through TCR engagement in the absence of costimulation, it is obvious that this feature of the immune system can be manipulated to induce tolerance and promote the survival of allografts or to ameliorate active autoimmune disease (Larsen et al, 1996). **The induction of clonal anergy by costimulation blockade forms the basis of several immunosuppressive strategies currently under investigation in clinical studies of transplantation and autoimmune disease. Many of these studies have used CTLA-Ig that binds to B7-1 and B7-2 molecules with high affinity and blocks interaction with CD28 expressed by T cells in combination with anti-CD154 monoclonal antibodies** (Leonard et al, 1996). Preclinical studies testing this approach have shown considerable promise in prolonging allografts in nonhuman primate models. In addition, strategies combining costimulatory blockade with injection of donor bone marrow at the time of allograft transplantation appear to be effective in inducing recipient tolerance to graft alloantigens.

Regulatory T Cells

An active mechanism of tolerance mediated by T cells with suppressive or downregulatory activities may also

be induced to inhibit immune responses to self- and exogenous antigens. The concept of T cells with suppressive or downregulatory function was originally conceived by Gershon in experiments using mouse models (Gershon, 1975). Mice primed with high doses of antigen were not only rendered unresponsive to subsequent challenges with the original antigen, but the tolerant state was transferable to naive animals by T cells from the tolerant animals. Treatment with nondepleting anti-CD4 monoclonal antibodies during antigen priming also induces a population of CD4+ T cells that can transfer tolerance to naive animals. **More recent studies have identified a population of CD25+ CD4+ T cells that inhibit the activation of peripheral T cells to self-antigens. Depletion or removal of these regulatory T cells promotes the development of autoimmune disease in animal models of colitis and diabetes** (Salomon et al, 2000). Similar populations of regulatory CD4+ T (also termed Th3 cells) have been identified in humans. The forkhead/winged helix transcription factor FOXP3 is required for the development of CD4+CD25+ regulatory T cells, and FOXP3 is currently used as a reliable marker of these cells. The immunosuppressive functions expressed by these regulatory T cells appear to be many and may be mediated at least in part through production of the immunosuppressive cytokines IL-10 and TGF-β, which may inhibit antigen-presenting cell function during T-cell priming. Other mechanisms expressed by these regulatory cells may be mediated through expression of FasL and deletion of antigen-presenting cells during effector T-cell priming. **An important consequence of tolerance mediated by regulatory T cells specifically is the ability to inhibit immune responses to an irrelevant antigen when that (irrelevant) antigen and the regulatory T cell–specific antigen are presented by the same APC. This form of so-called "linked immunosuppression" may be further manipulated in future strategies to inhibit responses to self- and allogeneic antigens.**

Tolerance in Human Organ Transplantation

Currently, patients transplanted with organs from MHC-mismatched donors to treat end-stage organ failure must take a potent immunosuppression regimen to prevent rejection of the graft. The immunosuppression currently used renders the recipient susceptible to infection, tumors, and renal fibrosis. The design and implementation of a strategy that would induce donor-specific tolerance would obviate the need for this immunosuppression and the accompanying side effects. Seminal experiments by Billingham, Brent, and Medawar using rodent models demonstrated that introduction of allogeneic cells during the development of the immune system generated tolerance to the donor alloantigens, first suggesting that the manipulation of recipients to become tolerant to alloantigens was possible (Billingham et al, 1953). **Based on this original premise, a nonmyeloablative conditioning regimen that includes a donor bone marrow infusion to induce a period of mixed chimerism has recently been used clinically in a small cohort of adult recipients of single HLA single-haplotype–mismatched kidney grafts to induce tolerance and allow complete withdrawal of immunosuppressive drugs** (Kawai et al, 2008). **Furthermore, recent studies have also demonstrated a time window after birth in which neonates can be transplanted with ABO-incompatible heart allografts and induce deletion of B cells producing antibodies to the ABO-incompatible carbohydrate moieties** (Fan et al, 2004).

ADHESION MOLECULES AND CONTROL OF LYMPHOCYTE TRAFFICKING

A critical feature of the immune system is the restriction imposed on the migration of T lymphocytes through lymphoid versus peripheral tissues, which is dependent on the stage of T-cell development or activation. Trafficking of naive T cells is restricted to primary lymphoid tissues. It is in these tissues that the chances of encountering dendritic cells presenting foreign peptide-MHC complexes are highest (see Trafficking of Naive T Cells). In contrast, T-cell activation results in the ability of the T cells to recognize and stop at sites of vascular inflammation. This allows the T cells to traverse the endothelium barrier and enter peripheral tissues where the effector functions of primed T cells may be needed during an immune response.

Upregulated Adhesion Molecule Expression

TCR engagement of a specific ligand in association with appropriate costimulation from professional APC leads to T-cell activation. Activation induces two phenotypic changes that alter the migration pattern of the T cell. First, the expression of the lymph node homing receptor CD62L is downregulated. This decreases the ability of the T cells to traffic into the lymph nodes and promotes T-cell circulation through the blood vessels. Second, expression of molecules that facilitate localization of antigen-primed T cells to inflammatory sites in the vascular endothelium is stimulated. T cells and other leukocytes travel through the circulation under extremely high shear forces. **The expression of these adhesion molecules is critical for mediating the arrest of the activated cells on the vascular endothelium under this high shear force and facilitates T-cell entry into the peripheral tissues** (Springer, 1994). Complementary sets of receptors on leukocytes and endothelial cells help mediate the arrest of activated T cells and other leukocytes at inflammatory foci on the vascular endothelium. These molecules include the selectins and their ligands, the addressins, and the integrins and their ligands, which are members of the Ig superfamily.

The principal adhesion molecules upregulated during cellular activation of leukocytes are the integrins, a family of noncovalently associated dimers composed of an α chain and a common β chain (Table 17–3). On T cells, antigen priming stimulates increased expression of CD11a, which associates with CD18 to form the integrin LFA-1 (leukocyte functional antigen–1) or $\alpha_L\beta_2$. T-cell activation also induces expression of the integrin VLA-4 (very late activation antigen–4) or $\alpha_4\beta_1$. **In addition to their adhesive functions, integrin ligation may deliver costimulatory signals during T-cell interaction with antigen-presenting cells** (Ni et al, 1999). **Integrins also bind to extracellular matrix proteins, and this engagement may augment T-cell effector function during the elicitation of an immune response.** Activation of leukocytes including T cells also upregulates expression of a proteoglycan binding

Table 17–3.
Representative Integrins

α/β CHAINS	COMMON NAME	CD DESIGNATION	LIGAND
αLβ2	LFA-1	CD11a/CD18	ICAM-1; ICAM-2; ICAM-3
αMβ2	MAC-1	CD11b/CD18	ICAM-1; Fibronectin
α4β1	VLA-4	CD49d/CD29	VCAM-1; Fibronectin
α5β1	VLA-5	CD49e/CD29	Fibronectin
α4β7	LPAM-1	CD107a	VCAM-1; MAdCAM-1

receptor, CD44. Macrophages and neutrophils also express LFA-1 as well as CD11b in association with CD18 ($\alpha_M\beta_2$), commonly called Mac-1.

In addition to integrins, T cells and other leukocytes express selectin binding molecules that direct cells to inflammatory sites in the vascular endothelium. **The P-selectin glycoprotein ligand (PSGL-1) is expressed by granulocytes and T lymphocytes and is the major ligand for P-selectin on endothelial cells** (Kansas, 1996). Expression of these ligands may also direct the T cells to distinct tissue sites. Activated T cells that are programmed to traffic to the skin also express cutaneous lymphoid antigen (CLA), which binds to E-selectin. In contrast, T cells trafficking to the gut mucosa are stimulated to express $\alpha_4\beta_7$ during priming.

Adhesion Molecule Expression on Endothelial Cells

Vascular endothelial cells normally express low levels of ligands for integrins and other adhesion molecules. **During tissue inflammation, endothelial cells are activated to produce several cytokines including TNF-α and IL-1** (Pober et al, 1986). **These cytokines stimulate the endothelial cells to express several classes of adhesion molecules.** Endothelial cells express two different selectins that facilitate the localization of activated T cells and other leukocytes to the vascular endothelium surface. P-selectin is preformed in specialized vacuoles called Weibel-Palade bodies, and surface expression is mobilized following activation of the endothelial cells. In contrast, endothelial cell activation initiates transcription and expression of E-selectin. During activation, endothelial cell expression of adhesion molecule members of the super-Ig family is also upregulated. These molecules include intercellular adhesion molecule (ICAM) -1 and very late cell adhesion molecule (VCAM) -1. Another member of this family, ICAM-2, is constitutively expressed on the endothelial cell surface and is not upregulated by proinflammatory cytokines such as TNF-α and IL-1 during inflammatory processes.

T-Cell–Endothelial Cell Interactions

The localization of T cells and other leukocytes in response to inflammation on the vascular endothelium is a highly regulated process (Ebnet et al, 1996). This localization begins with the regulated expression of adhesion molecules and their ligands on the leukocytes and endothelial cells. As the leukocytes are circulating through a vessel, engagement of selectins tether the cells and slow their movement to rolling along the endothelial surface (Fig. 17–13). **After cell movement is slowed by selectin-mediated tethering, the binding of integrins to Ig superfamily counter-receptors mediates the arrest of the T cells on the vascular endothelium. During this process, leukocyte engagement of cytokines produced by endothelial cells, including IL-8 and TARC, is required to trigger activation of the integrins**

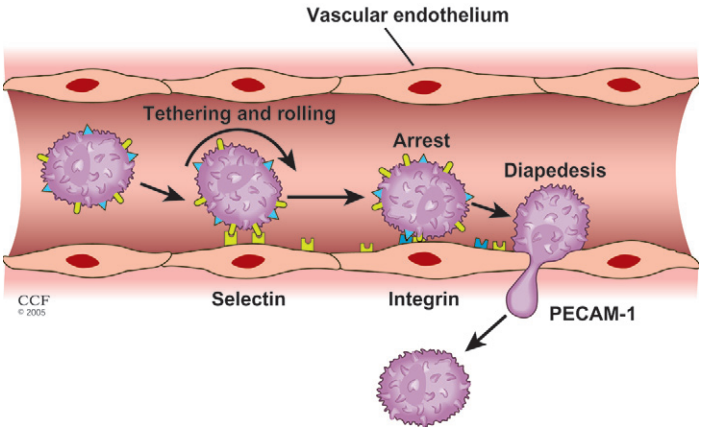


Figure 17–13. Localization of leukocytes to sites of vascular inflammation. During inflammation, vascular endothelial cells are activated to express adhesion molecules, such as selectins and ligands for integrins and several different chemokines. Under high shear forces, leukocytes in the circulation are slowed down by selectin-mediated tethering on the endothelium. As the leukocytes are rolling along the vascular endothelial surface, expressed integrins are activated by endothelial chemokines and the interaction of the integrins with their ligands results in leukocyte arrest. Through the homotypic interactions of platelet–endothelial cell adhesion molecule–1 (PECAM-1) on the leukocyte and endothelial cell surfaces, the leukocyte transmigrates across the vascular endothelial cell barrier. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2009-2011. All Rights Reserved.)

(Campbell et al, 1996). Binding of these cytokines through specific G protein–coupled receptors induces a conformational change to a high-affinity binding molecule and mediates arrest of the leukocytes on the vascular endothelium. As leukocyte movement is arrested, there is a considerable amount of "cross-talk" between the leukocyte and the endothelial cell. Activation of macrophages, neutrophils, and possibly other leukocytes at the endothelial cell surface stimulates the leukocytes to produce TNF-α, which provides continued stimulation to express increased levels of VCAM-1 and ICAM-1 on the endothelial cell surface. Furthermore, antigen-primed T-cell recognition of specific peptide-MHC complexes on the endothelial cell surface stimulates the T cells to express immune function such as cytokine production. T-cell production of IFN-γ stimulates endothelial cells to upregulate expression of MHC molecules and to produce chemoattractant cytokines, which amplifies T-cell recruitment and the immune response to localized areas in the endothelium.

Traversing the Endothelial Barrier

Following the arrest of the leukocyte on the vascular endothelium, the cell traverses the endothelial barrier into the peripheral tissue, a process termed diapedesis. Platelet–endothelial cell adhesion molecule–1 (PECAM, CD31) is expressed on endothelial cells and is concentrated at the cell junctions in a vessel (Muller and Randolph, 1999). This molecule is also expressed on the surface of leukocytes. A critical property of PECAM-1 is the ability to bind to another PECAM-1 molecule, a process called homophilic adhesion. During diapedesis, PECAM-1 on the leukocyte binds to a PECAM-1 molecule at an endothelial cell junction, and the leukocyte begins to traverse the endothelial barrier. In addition to these interactions, other molecules including CD99 and JAM (junctional adhesion molecule) are expressed by leukocytes and endothelial cells and coordinate with PECAM-1 interactions to guide the leukocyte

through the endothelium, and the leukocyte enters the peripheral tissue. Following TCR-mediated activation, the T cell expresses immune function such as cytokine production or target cell cytolysis.

Chemokines and Peripheral Tissue Recruitment of Leukocytes

Cytokines with chemoattractant properties, chemokines, are also critical in mediating localization and trafficking of leukocytes to tissue sites during physiologic processes, including inflammation and homeostasis (Rollins, 1997). Chemokines are a superfamily of small (<14 kD), heparin-binding proteins. More than 50 chemokine proteins have been identified and are grouped into four families based on a cysteine motif in the amino-terminal area of the protein (Table 17–4). The C-X-C chemokines, in which these cysteines are separated by a single amino acid, are attractant for neutrophils and include IL-8 and GROα. The CXC chemokines also include three members, IP-10 (IFN-γ–inducible protein), Mig (monokine induced by IFN-γ), and I-TAC (interferon-inducible T-cell alpha chemoattractant), which are chemoattractant for activated T cells. The C-C chemokines, in which the two cysteines are adjacent, are chemoattractant for a variety of leukocytes including monocytes, eosinophils, T lymphocytes, NK cells and dendritic cells. Representative C-C chemokines include MIP (macrophage inflammatory protein)-1α, MIP-1β, and monocyte chemoattractant protein–1 (MCP-1). The C family consists of a single cytokine, lymphotactin, which is chemotactic for NK cells and T cells. The C-X_3-C family also contains a single chemokine, fractalkine, which is on a membrane-bound mucin stalk and has adhesive and chemoattractant properties for IL-2–activated NK cells and CD8+ T cells.

Under appropriate stimulatory conditions, such as inflammation, virtually all cells produce specific chemokines. **Chemokine production is primarily regulated by the cytokine environment.** TNF-α and IL-1 induce many different cell types to produce neutrophil (e.g., IL-8 and GROα) and macrophage (e.g., MCP-1) chemoattractants. IFN-γ stimulates many different cells to produce the T-cell attractants IP-10, Mig, and ITAC. Cytokines including IL-4, IL-10, and IFN-γ inhibit production of specific chemokines during many processes.

Chemokines play a major role in tissue pathology by directing receptor-bearing leukocytes to tissue sites of inflammation. The hepta-transmembrane–spanning chemokine receptors are linked to G-coupled proteins, which transduce intracellular signals following ligand binding. Because chemokines bind to glycosaminoglycans on cell surfaces and to extracellular matrix proteins, leukocytes expressing the appropriate receptors likely bind chemokines as solid-phase (nonsoluble), proteins during infiltration into inflammatory tissue sites, and this solid-phase binding may be required to augment intracellular signaling. Some leukocyte populations constitutively express chemokine receptors, but cellular activation is required for expression of chemokine receptors on other types of cells. The expression of chemokine receptors such as CXCR3, the ligand for IP-10 and Mig, on T cells is induced by antigen priming and/or cytokines. There is considerable experimental and clinical evidence indicating that populations of CD4+ T cells producing type 1 (e.g., Th1 cells) versus type 2 (e.g., Th2 cells) cytokines express unique patterns of chemokine receptors (Bonecchi et al, 1999). TNF-α stimulates the expression of CCR7 on interstitial dendritic cells and directs their migration through the afferent lymphatics into the draining lymphoid tissue, where they prime peptide-MHC–specific T cells.

The critical role of chemokines during inflammatory processes has been clearly demonstrated in animal models where neutralization of specific chemokines results in inhibition of leukocyte infiltration and tissue pathology (Huffnagle et al, 1995; Koga et al, 1999). Chemokines are produced by all renal cell types and promote tubulointerstitial and glomerular pathology (Segerer et al, 2000). **In addition to leukocyte recruitment, many chemokines stimulate other proinflammatory activities, which may amplify the function of target leukocyte populations in vivo and intensify tissue inflammation.** These activities include the ability of specific chemokines to: (1) trigger the arrest of monocytes and T lymphocytes rolling on endothelial surfaces under physiologic shear conditions in an adhesion molecule–dependent manner; (2) stimulate increased integrin expression and cell adhesion; (3) stimulate the release of granules by neutrophils and granulocytes; and, (4) amplify CD8+ T cell and NK cell–mediated cytotoxicity. Each of these processes has a critical impact on the intensity and duration of inflammation and is likely to be augmented by specific chemokines.

Chemokines also play a crucial role in immune homeostasis (Cyster, 1999). For example, chemokines such as B lymphocyte chemoattractant (BLC) direct newly matured B lymphocytes to form follicles in the secondary lymphoid tissue. The localization of immature dendritic cells in peripheral tissues, where they will function as antigen-processing and -presenting cells during the initiation of immune responses, is also directed by specific chemokines.

Table 17–4.
Representative Chemokines and Receptors

FAMILY	CHEMOKINE	RECEPTOR	RESPONSIVE LEUKOCYTE POPULATIONS
CXC	IL-8	CXCR1, CXCR2	Neutrophils
	GROα	CXCR2	Neutrophils
	IP-10	CXCR3	Activated T cells
	MIG	CXCR3	Activated T cells
	SDF	CXCR4	Naive T cells, B cells, Dendritic cells, MØ
	BLC	CXCR5	B cells
CC	MIP-1α	CCR1, CCR5	T cells, NK cells, MØ
	MCP-1	CCR2, CCR10	MØ
	TARC	CCR4	T cells
	Eotaxin	CXCR3	Eosinophils
	RANTES	CCR1, CCR3, CCR5	T cells, MØ, NK cells
	MIP-3α	CCR6	Immature dendritic cells
	SLC	CCR7	Mature dendritic cells, T cells
C	Lymphotactin	XCR1	T cells, NK cells
CX_3C	Fractalkine	CX_3CR1	CD8+ T cells, NK cells

MØ, macrophages; NK cells, natural killer cells.

TUMOR IMMUNOLOGY

The concept that the immune system protects the host from cancer dates back to 1909, and was refined in the 1950s (Bhardwaj, 2007) when it was proposed that immune cells eliminate tumors by an "immune surveillance" mechanism. **This concept was challenged in the 1980s but has regained favor and has**

now been expanded based on additional findings. We now describe "cancer immunoediting" that encompasses three different phases (Dunn et al, 2004). The initial phase of editing involves immune cell elimination of tumor cells, supported by a greater incidence of tumor development in mice deficient in immune cells (RAG-2 mice deficient in T, B, and NK cells) or immune-related molecules (IFN-γ–deficient mice). In the second phase, there is modification of tumors by immune cells, leading to persistence and the establishment of an equilibrium between the tumor and the immune systems. In the third phase, the tumors escape the immune system by various mechanisms, resulting in tumor progression. Thus the challenge is to develop a greater understanding of each of these phases, which in turn should lead to more effective ways to stimulate potent T-cell antitumor immunity and, at the same time, define new approaches to modify or eliminate the mechanisms by which tumors can escape the immune system.

Role of T Cells

T lymphocytes are central to the generation of an effective tumor immune response (Cheever and Chen, 1997). In fact, most approaches to immunotherapy center on stimulating a potent T-cell response**.** The importance of T cells in tumor eradication is illustrated by the demonstration that adoptive transfer of tumor-reactive T cells into syngeneic murine tumor models, and in melanoma patients, can lead to the rejection of established tumors. Furthermore, the in-vivo deletion of T cells using antibodies to CD8 and, in some cases, to CD4, will eliminate antitumor activity normally induced by various forms of immunotherapy.

Activation of CD8+ T cells that recognize tumor-associated antigens (TAA) presented by MHC class I molecules and CD4+ T cells that respond to TAA presented by MHC class II molecules represents the most effective tumor immune response (Robbins and Kawakami, 1996). Dendritic cells present in tumors and draining lymph nodes are critical for the presentation of processed tumor antigen peptides to the T cells and their subsequent activation (Schuler and Steinman, 1997). Tumor cells are generally considered to be poor stimulators of T cells, owing in part to the lack of expression of MHC class II molecules and their variable expression of MHC class I molecules. After T-cell activation, tumor rejection is thought to occur by several mechanisms that may vary depending on the effectors generated and the sensitivity of the tumors (Kagi et al, 1996). Cytotoxic CD8+ T cells (CTL) destroy tumor cells by elaboration of cytoplasmic granules containing the pore-forming protein perforin, resulting in plasma membrane disruption, or by the upregulation of Fas ligand that can bind to Fas (on the tumors) to induce apoptosis. CD4+ T cells are important for the generation of memory CD8+ T-cell responses (Ossendorp et al, 1998; Janssen et al, 2003), which are typically the effector cells associated with tumor rejection (Matsui et al, 1999). However, antitumor CD4+ T effector cells also have the capacity to mediate the regression of MHC class I–loss tumors that are resistant to CD8+ CTLs (Surman et al, 2000). Additionally, the quality of antitumor CD4+ T-cell responses appears to be a prognostic indicator of disease progression and immunotherapeutic responsiveness. For example, renal cell carcinoma (RCC) patients whose tumor environment is biased towards a type 1 immune response have a more favorable prognosis (Kondo et al, 2006). **Moreover, the production of Th1 cytokines, such as IFN-γ, produced by both CD4+ and CD8+ T cells is known to be critical** (Brunda et al, 1995). Although IFN-γ production is necessary, it is not sufficient for tumor rejection. Other T1 cytokines, such as IL-2 and IL-12, are involved in antitumor response primarily through their ability to activate effector T cells and induce their clonal expansion (Burke, 1999). The secretion of select chemokines is also necessary for the recruitment of additional T cells and dendritic cells to the tumor site (Tannenbaum et al, 1998). In contrast, Th2 CD4+ T cells produce cytokines such as IL-4, IL-5, IL-6, and IL-10, which lead to a humoral immune response but are not typically targeted for cellular immunotherapy. The third subset of CD4+ T cells produce IL-17 and is a major effector cell in autoimmunity. **Although present in human and murine tumors, the role that Th17 cells play in tumor immunity is unclear because there are opposing data.** One study showed that in IL-17 deficient mice the growth of B16 melanoma and MB49 bladder carcinoma tumors was reduced, which was significantly enhanced, however, in IFN-γ knockout mice where IL-17 expression was increased within the tumor (Wang et al, 2009). Others, however, show that tumor growth and lung metastasis were increased in IL-17–deficient mice, which was associated with decreased expression of IFN-γ–producing NK cells and tumor-specific T cells (Kryczek et al, 2009). The latter findings suggest that the induction of IL-23/IL-6 and IL-17 pathways may not always lead to tumor progression. Thus further studies are needed to define the role of Th-17 T-effector cells in the tumor-bearing host.

Tumor Antigens

The initial gene encoding a human tumor associated antigen (TAA) recognized by MHC restricted T cells was the melanoma antigen-1 (MAGE-1) (van der Bruggen et al, 1991). **Subsequently over 300 TAAs have been identified along with their HLA class I and II restrictions** (Novellino et al, 2005). Peptide epitopes for a number of the TAAs have been identified, which can serve to stimulate T-cell immunity. Many of the TAAs that have been identified are expressed on melanomas, which is attributable to the ease with which it has been possible to isolate and detect MHC-restricted melanoma-specific T cells from this patient population. TAAs are expressed by a variety of different tumor types, including urologic tumors such as RCC and prostate. An updated peptide database for T cell–defined tumor antigens is available (van der Bruggen et al, 2001).

Four main groups of TAAs have been identified, and three of these represent shared antigens present on multiple tumor types. **One group is the shared tumor-specific antigens that are encoded by a family of genes that include *BAGE-1, MAGE-1, MAGE-2 LARGE-1, NY-ESO-1,* and *RAGE* (cancer-testis genes)** (Table 17–5). These antigens are expressed on a variety of human tumors but not by most normal tissues, with the exception of testis and placenta. **Their tumor expression includes melanomas, lung tumors, breast tumors, head and neck tumors, RCC, and bladder cancer** (Robbins and Kawakami, 1996; Bellone et al, 1999). **A second group of shared TAAs is the differentiation antigens, which are also expressed by normal tissue from which the tumor was derived** (van der Bruggen et al, 2001). These include antigens that are encoded by genes such as MART-1/MelanA (GP100 along with tyrosinase), a melanocyte lineage protein that is a key enzyme in pigment synthesis. Other differentiation antigens that are recognized by T cells include the gut carcinoma antigen CEA, (along with kallikrein 4 and PSA) expressed by prostate cancer, and NY-Br-1 (expressed on some breast cancers). These antigens are not tumor specific and some may result in an autoimmune response that can be mild in the case of tyrosinase or more severe in the

Table 17–5.
Human Tumor Antigens Recognized by T Cells

	EXPRESSED BY RENAL CELL CARCINOMA
Tumor Specific (Widely Expressed)	
MAGE-1	
MAGE-3/MAGE-6	+
BAGE	
GAGE-1, -2	
RAGE-1	+
Tissue Specific (Melanocyte Lineage)	
PG100	
MART-1	
TRP-1 (GP75)	+
Tyrosinase	
Mutated or Overexpressed	
Cyclin-dependent kinase (CDK4)	
β-catenin	
P53	
Carcinoembryonic antigen	
G250	+
Intestinal carboxyl esterase	+
HTERT (mutant HSP70)	+
HER2/NEU	+
MUC-1 (mucin)	+
PRAME	+
Oncogenic viral antigens	
E7, human papilloma virus	

case of CEA. **A third group of shared TAAs is represented by proteins that are overexpressed in the tumor compared to normal tissue.** Included in this group are BCLx, expressed on colon, breast, and melanoma tumors; CALCA expressed on thyroid tumors; and some lung carcinomas as well as G250 (CAIX), expressed on stomach; RCC; and liver tumors. HER2/NEU is another protein that is present in normal tissues at low levels but is overexpressed in some tumors, particularly breast and ovarian carcinomas. There are other antigens that have been identified that can serve as potential targets for immunotherapy. This includes MUC-1, a cell surface protein composed of multiple tandem repeats that can be recognized by T cells, which is directed against breast, ovarian, and pancreatic tumors. The risk of autoimmune responses is also possible with some of the antigens in this group. **The fourth group is composed of antigens that arise from point mutations in genes that are ubiquitously expressed.** These antigens are tumor specific and usually limited to a small subset of patients. **Because of their restricted expression, many of these may not be the best candidate antigens targeted for immunotherapy.** This group of TAAs includes BCL-ABL fusion protein, CDC-27, P53, K-RAS, and HSP70. Thus a significant number of human tumor antigens have been identified that are recognized by T cells and many are currently being evaluated for their ability to stimulate antitumor immune responses in mouse models and cancer patients.

RCCs have the potential to stimulate an immune response (Bukowski, 2000) **as evident by the isolation and expansion of CD4+ and CD8+ T-cell lines, along with clones from patients that produce IFN-γ and mediate lysis in response to autologous tumor cells.** RCCs express a number of TAAs that could serve as targets for immunotherapy. These include RAGE-1, HER2/NEU, G250, PRAME, PG75, MUC-1, and the receptor tyrosine kinase, EPHA2. There is considerable variation in the level of expression and percentage of cells expressing these antigens among renal tumors. For example, RAGE is expressed on 2% to 20% of renal cell carcinomas, whereas most renal cell carcinomas (75%) express carboxyl esterase. Recently, MAGE-6 was shown to be expressed on 30% of RCCs, whereas the receptor kinase EPHA2 was expressed on 90% of RCCs and is associated with a more aggressive phenotype (Tatsumi et al, 2002; Herrem et al, 2005). The demonstration of TAAs on RCCs is an important step toward developing vaccine strategies for this disease. **There are also a number of TAAs expressed on prostate cancers that can serve as potential targets for different immunotherapy approaches.** This includes prostate specific membrane antigen (PSMA), prostate stem cell antigen, MUC1, epidermal growth factor receptor, and urokinase plasminogen activator and its receptor (Mohebtash et al, 2009; Li et al, 2010).

Role of Innate Immunity

NK cells represent part of the host immune response against neoplastic cells (Basse et al, 2000). NK cells can recognize and destroy some tumors, particularly those of lymphoid origin, without any exogenous activation. However, the lysis of many freshly isolated solid tumors requires activation of these cells by IL-2; thus NK cells have been referred to as lymphokine-activated killer (LAK) cells. **The destruction of tumor target cells by NK cells does not involve MHC restriction, and, in fact, these cells are considered most effective against tumor cells that express low to no MHC class I antigens. Indeed, the ability of NK cells to kill tumor cells is regulated by several receptors with unique specificity for different MHC class I antigens, and are collectively referred to as killer–Ig-like receptors (KIR)** (Moretta, 2007). Although the interaction of different KIRs with their corresponding HLA–class I molecules is a major regulator of NK activation, the activation of these cells is dependent on activation receptors that recognize unique ligands on target cells (Moretta et al, 2004). Several receptors have been identified (NK-46, NKp30, and NKp44) and are referred to as natural cytotoxicity receptors (NCR). Usually the ligands recognized by the NCRs are not expressed by normal cells but are highly expressed by tumor cells and virally infected cells. **NK cells can also kill tumor targets by antibody-dependent cell-mediated cytotoxicity.** In this setting, there is redirected lysis because the specificity of tumor recognition resides in the variable region of the antibody. While the Fab portion of the antibody binds to its tumor antigen, the Fc portion of the immunoglobulin engages the Fc receptor on an NK cell, which in turn activates the cells lytic machinery. **The relevance of NK cells in defense against cancer cells has been demonstrated by evidence that the depletion of this population in some tumor models by anti-NK antibodies reduces or eliminates antitumor activity.**

Tumor Evasion of the Immune System

Although most solid tumors, including RCCs, express TAAs that can be recognized by T cells, the immune response that develops is insufficient to impair tumor progression (Finke, 2004). There is growing evidence to suggest that the absence of a strong antitumor response in vivo is partly attributable to the tumor promoting an immunosuppressive environment. Indeed**, it has been shown that T cells infiltrating many tumors are functionally**

impaired, as demonstrated by their diminished ability to proliferate in response to a variety of stimuli and their diminished cytotoxic activity. Dendritic cells within the tumor have been shown to be impaired in their antigen-presenting function, which may contribute to the immune dysfunction noted in the tumor microenvironment. **The immune dysfunction is not restricted to tumor infiltration of lymphocytes because tumor-specific CD4+ T cells in the peripheral blood of RCC and melanoma patients display a Th2 bias in response to dendritic cells pulsed with peptides to either MAGE-6 or EPHA2.** However, in patients who have no evidence of disease MAGE-6–specific and EPHA2-specific IFN-γ–producing T cells were predominant (Tatsumi et al, 2002; Tatsumi et al, 2003). Thus the tumor microenvironment may shift the balance from a Th1 cytokine response, which is known to be important for the rejection of tumors in animal models, to a Th2 cytokine response, which is primarily effective at promoting a humoral immune response. There is also evidence that increased apoptotic activity within T cells from cancer patients may also contribute to the immune dysfunction that could be mediated by Fas/FasL interaction or by other tumor products (Gastman et al, 2000; Das et al, 2008).

The following describes several different mechanisms that are thought to play important roles in tumor evasion of the immune system (Fig. 17–14). Most of these mechanisms are supported by substantial experimental data derived from murine tumor models and cancer patients.

Impaired Antigen Presentation

The recognition of tumor cells by T cells may be impaired because of defective antigen processing and presentation (Pawelec et al, 1997; Seliger et al, 1997). Reduced or loss of MHC class I and class II expression by tumors, including RCCs, has been well documented. In some tumors there is also decreased expression of transporter proteins associated with antigen processing (TAP proteins), as well as deficient levels of LMP proteosomal complexes. A reduction in mRNA and protein levels of these molecules appears more pronounced in RCC cells that have acquired metastatic potential, suggesting that the process of malignant transformation may include progressive loss of TAP and LMP. Increasing the levels of TAP in tumors, either by stimulation by IFN-γ or by transfection with TAP-1 cDNA, results in higher expression of MHC class I molecules on the tumor cell surface and enhanced tumor-specific, class I–restricted cytotoxic T-cell recognition.

Regulatory T Cells

Regulatory T cells (Tregs) are divided into two subsets, which include natural/intrinsic and adaptive/induced populations (Shevach, 2002; Fontenot and Rudensky, 2005). The natural subset, is characterized as CD4+, interleukin (IL)-2 receptor–α (CD25)+, FOXP3 (transcription factor)+, and is thought to be a distinct T-cell lineage originating from the thymus, representing 1% to 3% of CD4+ T cells in healthy individuals. This Treg subset is the most

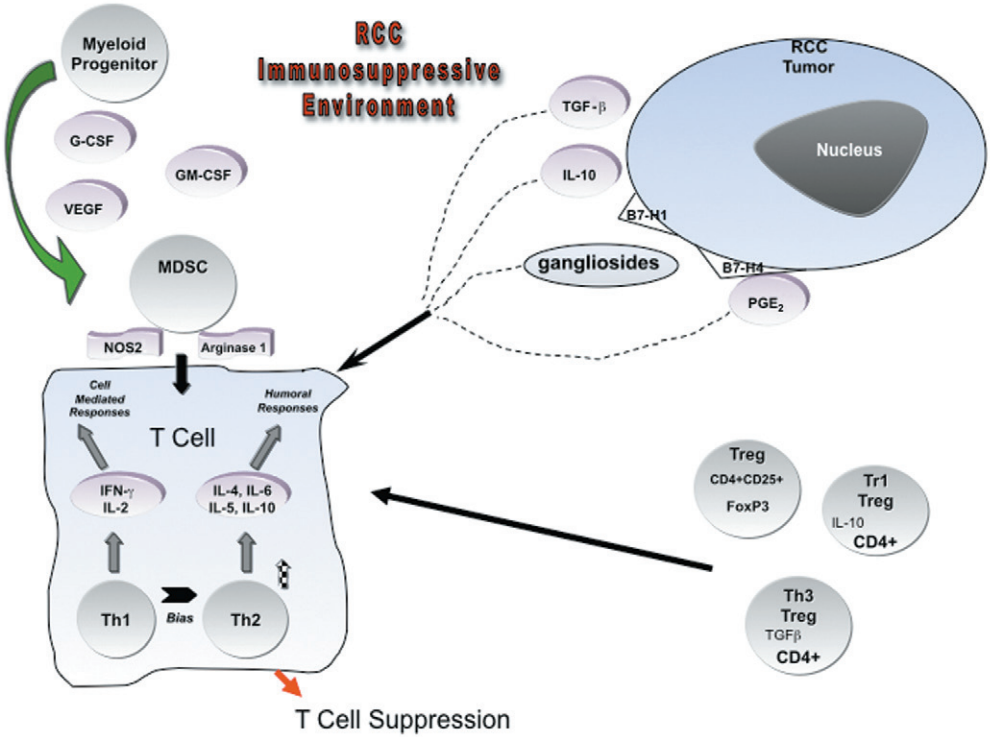


Figure 17–14. Scheme showing the mechanisms by which tumor cells can induce immune dysfunction in T cells. Tumor cells produce a variety of immunosuppressive products that include interleukin-10 (IL-10), gangliosides, transforming growth factor-β (TGF-β), and prostaglandins, which can directly suppress T-cell function. B7-H1 and B7-H4 ligands expressed on tumor cells, including renal cell carcinoma (RCC), can promote T-cell anergy or cell death by engaging its receptor PD-1 on T cells. Tumor cells can also indirectly suppress T-cell function by promoting the activation and expansion of T-regulator cells, and by producing cytokine (G-CSF, VEGF, GM-CSF) that can stimulate myeloid-derived suppressor cell (MDSC) accumulation. These suppressive cells and secreted products have the ability to inhibit the development of a type 1 T-cell response (interferon-γ [IFN-γ] production) that is critical for development of antitumor immunity. The tumor environment can, in some cases, increase a type 2 response resulting in a Th2 bias. NOS2, nitric oxide synthase 2; PGE_2, prostaglandin E_2.

characterized of the T-regulatory cells and has emerged as another mechanism that promotes immune suppression in a tumor-bearing host. This occurs by inhibiting the proliferation of CD4+ T-helper cells, as well as their ability to produce the cytokines IFN-γ and IL-2 (Curiel et al, 2004). It also appears that the cytokine IL-2 produced by T-helper cells may promote the growth of T-regulatory cells (Antony and Restifo, 2005). The adaptive subset is not characterized by a specific marker, but by the immunosuppressive cytokines they produce. The adaptive subset includes Tr1 Tregs that produce IL-10, while Th3 Tregs produce TGF-β. Adaptive Tregs appear to originate from naive T cells after interaction with dendritic cells (Shevach, 2002; Fontenot and Rudensky, 2005).

Tregs appear to preferentially migrate to and accumulate in tumors and ascites of cancer patients. The expression of Tregs in cancer patients may have a negative impact on clinical outcomes. For some tumor types, including ovarian, breast cancer, and hepatocellular carcinomas, the accumulation of Tregs (FOXP3+) in the tumor microenvironment correlates inversely with patient survival (Curiel et al, 2004; Bates et al, 2006; Kobayashi et al, 2007). In a study of ovarian cancer, an increase in Tregs was associated with inhibition of tumor-specific cytotoxic T-cell activity and cytokine production. Conversely, it appears that in follicular and Hodgkin lymphoma the increased numbers of Tregs (FOXP3+) can be correlated with improved patient survival (Alvaro et al, 2005; Carreras et al, 2006).

Metastatic RCC patients have a significant increase in Tregs (FOXP3+) in their peripheral blood (Cesana et al, 2006; Griffiths et al, 2007; Finke et al, 2008), which are able to inhibit T-effector cell proliferation. Furthermore, Griffith and colleagues found that increased Tregs (FOXP3+) numbers in the peripheral blood of metastatic RCC patients correlated with poor clinical outcomes. However, an analysis of RCC patients with localized disease (tumor tissue) found that the FOXP3– (Tr1) rather than the FOXP3+ subset of Tregs was significantly associated with poor outcomes and death from RCC (Siddiqui et al, 2007). Based on these findings, it is clear that additional studies are needed to define the role of Tregs in urologic cancers such as RCC.

Tregs are beginning to be examined as therapeutic targets. One study used DAB389IL-2, a recombinant IL-2–diphtheria toxin conjugate, to remove Tregs in cancer patients (including RCC) and the reduction of Tregs coincided with an augmented T-cell response to tumor antigens after vaccination. These findings suggest that Tregs in RCC patients are directly contributing to the immunosuppressive environment that is allowing tumor cells to thrive, and that they can be reduced in numbers by targeting the IL-2 receptor. It is also interesting to note that the tyrosine kinase inhibitor, sunitinib, used in the treatment of RCC can also cause some reduction in Tregs in RCC patients (Finke et al, 2008) and murine tumor models (Ozao-Choy et al, 2009).

Myeloid-Derived Suppressor Cells

Myeloid-derived suppressor cells (MDSC) represent a heterogeneous group of immature myeloid cells (monocytic/macrocytic, granulocytic, and dendritic) at various stages of maturation, which accumulate in tumor-bearing hosts as result of tumor-induced alterations in myelopoiesis. These cells suppress the antitumor T-cell response by several mechanisms such that their removal facilitates tumor rejection in mouse tumor models (Marigo et al, 2008; Gabrilovich and Nagaraj, 2009). They are broadly defined in mouse models as CD11b+Gr–1+ cells with T-cell suppressive function; and granulocytic (Ly6G+) and monocytic (Ly6G–) subsets have recently been reported (Marigo et al, 2008; Movahedi et al, 2008; Gabrilovich and Nagaraj, 2009). In the peripheral blood of cancer patients, MDSC that are immature (Lin–CD33+HLADR–), granulocytic (CD33+CD15+CD14–), and monocytic (CD33+CD14+HLADR–/dim) have all been reported (Almand et al, 2001; Zea et al, 2005; Hoechst et al, 2008; Marigo et al, 2008; Gabrilovich and Nagaraj, 2009). MDSC are not only implicated in immune dysfunction, but they have also been shown to directly promote tumor-dependent angiogenesis.

The suppressive mechanisms of MDSC may largely be grouped into L-arginine–dependent and –independent ones. MDSCs metabolize L-arginine by two main pathways: arginase 1 (ARG1) and/or nitric oxide synthase 2 (NOS2). ARG1 activation occurs in response to type 2 cytokines (IL-4, IL-13), IL-10, TGF-β, GM-CSF, and PGE_2 among others (Hesse et al, 2001). ARG1 upregulation leads to the depletion of environmental L-arginine, and consequently compromises TCR-mediated T-cell activation, proliferation, and cytokine production (Rodriguez et al, 2009). Arginine metabolism by upregulated levels of NOS2 in MDSC occurs in response to prostaglandin E_2, and inflammatory cytokines such as IFN-γ, TNF-α, or IL-1–α. Whereas L-arginine is depleted by arginase, NOS2 metabolizes arginine to produce superoxide and NO, which rapidly combine to form highly reactive peroxynitrites that disrupt downstream JAK/STAT proteins required for normal T-cell function (Marigo et al, 2008). In this regard, ARG1 and NOS2 pathways can actually operate in parallel and synergize to inhibit T-cell function.

Targeting MDSC in mouse tumor models to reverse T-cell suppression and promote antitumor immunity has been achieved by treating tumor-bearing mice with anti-Gr1 antibody (Marigo et al, 2008; Gabrilovich and Nagaraj, 2009). In cancer patients, treatment with all-trans-retinoic acid has been shown to improve T-cell response and also reduced MDSC levels (Mirza et al, 2006). Recently it was observed that sunitinib, which is front-line therapy for RCC, significantly reduced the number of MDSC and restored a Th1 T-cell response in the treated patients (Ko et al, 2009).

B7-H1– and B7-H4–Mediated Immune Suppression

The costimulatory molecule, B7-H1 (PD-L1) is a B7 family member that has been reported to provide either a positive or negative signal for the generation of T-effector function (Greenwald et al, 2005; Flies and Chen, 2007). Recent studies have implicated B7-H1 as a potent negative regulator of antitumor immunity (Greenwald et al, 2005; Flies and Chen, 2007). B7-H1 expression on tumors interacts with the corresponding receptor PD-1 (programmed death receptor–1, CD279) on T cells to enhance either apoptosis or decrease TCR-mediated proliferation and cytokine production. Similarly, B7-H1 expressed on activated T cells has been demonstrated to impair both T-cell function and survival. Consistent with these observations, in-vivo monoclonal antibody blockade of B7-H1 has been shown to potentiate antitumor responses in several murine cancer models, presumably by blocking the interaction of B7-H1 with its receptor (Dong et al, 2002; Iwai et al, 2002).

Constitutive expression of B7-H1 has been found in a number of human cancers, including melanoma glioblastoma along with carcinomas of the lung, ovary, colon, bladder, breast, cervix, and liver (Greenwald et al, 2005; Flies and Chen, 2007). B7-H1 is also expressed in both primary and metastatic renal cell carcinoma (RCC), and patients with tumors expressing high levels of B7-H1 were at significant risk for disease progression, cancer-specific death, and overall mortality (Thompson et al, 2004). Additionally, B7-H1 expression by clear cell RCC tumors (or infiltrating mononuclear cells) correlates with aggressive pathologic features,

including advanced tumor-node-metastasis stage, tumor size, higher nuclear grade, and coagulative necrosis (Thompson et al, 2004). B7-H1, along with other negative regulators of T-cell activation, may act in concert to thwart host antitumor immunity in patients with RCC and also other forms of malignancy. Thus tumor-associated B7-H1 has recently garnered attention as a potential inhibitor of host antitumor immunity. B7-H4 expression was also associated with adverse clinical and pathologic features (including lymphocytic infiltration), as well as an increased risk of death from RCC and disease progression after surgical removal of localized RCC (Kryczek et al, 2009).

Based on the all the available data, B7-H1 expressed by RCC tumor tissue and infiltrating lymphocytes may serve to facilitate tumor progression by inhibiting the generation of host anti-tumor T cell–mediated immunity. Thus blocking B7-H1 may be a relevant strategy for improving the development of an effective antitumor immune response in patients with metastatic RCC.

Immunosuppressive Cytokines

Several molecules with known immunosuppressive activity are present within the tumor microenvironment (see Fig. 17–14). These products may be secreted by the tumor cells themselves or by surrounding mononuclear inflammatory infiltrates (Pawelec et al, 1997). **Among the best-studied immunosuppressive molecules overexpressed in the tumor microenvironment is the Th2 cytokine IL-10** (Pawelec et al, 1997). **The primary inhibitory effect of this cytokine relates to downregulation of MHC class II expression on monocytes/dendritic cells, resulting in diminished antigen presentation.** The immunosuppressive properties of IL-10 may be partly attributable to its ability to inhibit activation of the transcription factor NFκB, which regulates a number of genes important to tumor immunity development. Although it is clear that IL-10 is immunosuppressive, its impact on the generation of an antitumor immune response is complex. In knockout mice deficient in IL-10, tumor growth is either reduced or prevented when compared with tumor growth in IL-10–producing mice. However, tumor cells genetically modified to overexpress IL-10 are found to be less tumorigenic than wild-type tumors (Halak et al, 1999).

TGF-β contributes to the suppression of tumor immunity (Pawelec et al, 1997). **TGF-β is produced by a variety of tumors, including RCC, and increased levels of this cytokine have been reported in the serum of patients with kidney tumors. TGF-β is a potent inhibitor of IL-2–dependent T-cell proliferation affecting both helper and cytotoxic lymphocyte populations.** TGF-β appears to suppress T-cell growth by blocking TCR- and IL-2R–mediated tyrosine phosphorylation, thereby impairing downstream signaling events central to the control of cell cycle progression.

Prostaglandin E_2 (PGE_2) is frequently present in the tumor bed and is known to regulate T-cell function (Menetrier-Caux et al, 1999; Ochoa et al, 2007). PGE_2 can block T-cell proliferation by several mechanisms, which include increasing the levels of the intracellular second messenger cyclic adenosine monophosphate, inhibiting the DNA-binding activity of NFκB, and blocking IL-2–dependent G1–S transition. PGE_2 can promote a Th2 response and MDSC accumulation. Prostaglandins may also adversely affect the function of NK cells.

Gangliosides Contribute to the Immune Suppression

Gangliosides are structurally diverse acidic glycosphingolipids present in the outer leaflet of the plasma membrane that are involved in cell–cell interactions and membrane receptor modulation (Deng et al, 2000). Importantly, they also act as inhibitors of the host immune response. Select gangliosides are increased in expression and shed into the tumor microenvironment. For example, in malignant melanomas and neuroblastomas, there is overexpression of GD3, GD2, and GM2 (Hakomori, 1996). Rapid progression of tumors and lower survival rates were related to higher GD2 levels in patients with neuroblastomas. Recent findings also show increased expression of GD1a, GM1, and GM2 in RCCs as compared with normal kidney tissue (Biswas et al, 2006). Gangliosides isolated from different tumor types, such as neuroblastoma, lymphoma, and melanoma, all can inhibit immune responses. **Gangliosides have been shown to interfere with proliferation, antigen presentation, cytotoxic effector function, and IL-2 and IFN-γ production by T cells, without affecting production of the Th2 cytokine IL-10.** Animal studies have shown that the administration of tumor-derived GM1b inhibits the in-vivo development of antitumor immunity (McKallip et al, 1999). Thus mediators within the tumor environment may diminish effective antitumor immunity through a number of mechanisms that result from select alterations in signal transduction pathways critical for normal T-cell activation. TNF-α can increase the expression of gangliosides on tumor cells, thereby enhancing ganglioside-mediated immune suppression.

IMMUNOTHERAPY

Adoptive Cell Therapy

The transfer of tumor-reactive T cells has been shown to protect animals from tumor challenges and to cause rejection of established tumors (Cheever and Chen, 1997). T-cell transfer has been used primarily for the treatment of metastatic melanoma. This has included the administration of tumor-infiltrating lymphocytes (TIL) that have been expanded ex vivo with IL-2 (Rosenberg et al, 1994). **Efficacy of adoptive T-cell therapy has been improved by lymphocyte depletion with cyclophosphamide and fludarabine, which allows the transferred T cells to undergo increased expansion in response to growth factors** (Dudley et al, 2002; Gattinoni et al, 2006). T cells expanded from draining lymph nodes of patients with renal cell carcinoma, and vaccinated with irradiated autologous tumor cells plus GM-CSF, have antitumor activity in a small subset of patients even in the absence of IL-2 administration (Plautz et al, 1999). New directions in adoptive T-cell therapy include the use of gene therapy where melanoma cancer patients' peripheral lymphocytes are transduced with high-affinity T-cell receptors recognizing shared tumor antigens (Johnson et al, 2009). Approaches to enhancing the survival and functionality of adoptively transferred T cells will likely include transfecting (or cotransfecting) the tumor-reactive T cells with genes encoding proteins such as costimulatory molecules, chemokine receptors, and antiapoptotic and survival molecules (Charo et al, 2005; Gattinoni et al, 2006).

Cytokines and Interferons

Some patients have benefited from cytokine therapy (Bukowski, 2000). **The use of natural and recombinant cytokines has been investigated over the past 2 decades, with IFN-α and IL-2 being the only agents appearing to at least reproducibly cause tumor regressions in 10% to 15% of patients**

with renal cell carcinoma. Responses to IFN-α occur most frequently in patients with pulmonary metastases and good performance status, where the median response duration is between 6 to 10 months (Bukowski, 2000). Randomized trials in metastatic disease comparing IFN-α with other therapeutic approaches do suggest IFN-α may enhance survival in patients with metastatic RCC, but the effect is only modest at best. IL-2 was approved for use in renal cell carcinoma by the U.S. Food and Drug Administration on the basis of demonstrated safety and efficacy in clinical studies. Use of high-dose IL-2 appears to cure a small percentage of highly selected patients (Klapper et al, 2008). However, toxicity, including hypotension, dyspnea, thrombocytopenia, malaise, and disorientation, associated with high-dose IL-2 treatment represents a serious obstacle to this single-agent therapy.

A number of studies have tested whether combining IL-2 with IFN-α would improve the therapeutic activity over either agent alone. This combination of cytokines caused only a modest increase in response rates, and no effects on survival were evident. Other combinations are currently being tested in phase I/II trials, and this includes IL-12 combined with IFN-γ and the triple combination of IL-2, GM-CSF, plus IFN-α. It is clear from these and other studies that a subset of individuals with metastatic renal cancer do respond favorably to cytokine therapy; however, they represent a minority of patients (<15% response rate).

Cancer Vaccines

Several different vaccine approaches are underway to stimulate the immune response in patients with existing tumors. **The injection of irradiated tumors genetically engineered to secrete various immunostimulatory cytokines, such as IL-2, IL-4, IFN-γ, IL-12, and GM-CSF, demonstrated some antitumor activity** (Sogn, 1998; Burke, 1999). Also, different chemokines (e.g., IP-10 and MIG) have been overexpressed in tumors as a means of attracting T cells, as well as APCs, into the tumor microenvironment. Many of the chemokines and cytokines secreted by the tumor cells decreased tumorigenicity, and some could protect animals from subsequent challenge with the parental tumor. The inhibition in tumor growth occurred through a variety of mechanisms, including, in some cases, the generation of an antitumor T-cell response. Although the transfer of this technology to cancer patients has been difficult, some clinical trials using gene-modified tumor cells have been used as vaccines. Thus far, technical problems that have hindered the use of gene therapy in cancer patients, include the low efficiency of transfections, the safety issues of infecting with retroviral vectors, and the development of antiviral responses to adenoviral constructs that may compromise the immune response generated to the tumor.

Synthetic peptides corresponding to defined TAAs (e.g., MART-1) have been used as vaccines in cancer patients with melanoma, lung carcinoma, pancreatic cancer, and prostate carcinomas (Robbins and Kawakami, 1996; Bellone et al, 1999). The defined peptides have been given in the absence and presence of adjuvants, or pulsed on autologous monocytes or dendritic cells. In some cases, vaccination with defined TAAs has led to induction of a TAA peptide–specific T-cell response in cancer patients. **After immunization, increases in peptide-specific CD8+ T cells from the peripheral blood and draining lymph nodes have been detected by their binding to MHC class I tetramer complexes containing the appropriate TAA peptide. Increases in antigen-specific cytokine-secreting T cells have been detected by the use of enzyme-linked immunosorbent spot (ELISPOT) assays. Unfortunately, there has been a poor correlation between induction of specific T cells and the clinical responses. A limitation to immunization with a single TAA is the potential to generate antigen-loss variants that are not recognized by the specific T cells. To minimize this problem, some studies are using combinations of peptides that should evoke a broader range of tumor-reactive T cells.** Another approach is to use tumor cell lysates that contain a wide variety of peptides for the pulsing of dendritic cells (DC). Indeed, antitumor responses have been seen in melanoma and renal cell carcinoma patients immunized with dendritic cells pulsed with whole tumor cell lysates. However, in many clinical trials, DC-based vaccines as monotherapy have had limited therapeutic success (Bhardwaj, 2007). Another approach for immunizing patients with multiple peptides has been to electrofuse the patients' own dendritic cells to tumors and thus generate dendritic cell–tumor hybrids for T-cell activation. This is currently being tested in renal cell carcinoma patients with metastatic disease (Avigan et al, 2007).

Different vaccine strategies are under investigation in patients with prostate cancer. One approach selectively targets the prostate-specific antigen (PSA) and is produced by ex-vivo exposure of dendritic cell precursors to PA2024, a recombinant fusion protein composed of the PAP target fused to granulocyte-macrophage colony-stimulating factor (GM-CSF) (termed Sipuleucel-T; Dendreon, Seattle, WA) (Ward and McNeel, 2007). Other vaccines that are in phase II/III clinical trials include immunization with two allogeneic prostate cancer cell lines transduced with the GM-CSF (termed GVAX; Cell Genesys, Hayward, CA) (Ward and McNeel, 2007) and Prostvac-VF (Cell Genesys), a vaccinia-plus fowlpox-based vector containing the transgenes for PSA and the multiple T-cell costimulatory molecules TRICOM (Madan et al, 2009). The real potential of these vaccines in prostate cancer are yet to be determined.

Combinational approaches to immunotherapy are now receiving significant attention. This includes combining vaccines with Toll-like receptor (TLR) agonists that include oligodeoxynucleotides containing one or more unmethylated CpG dinucleotides (CpG, ODN), which can activate B cells and plasmacytoid DC, and promote T-cell immunity (Bhardwaj, 2007). Another approach is to combine immunotherapy with tyrosine kinase inhibitors (TKI) such as sunitinib, which is front-line therapy for RCC. Sunitinib monotherapy in metastatic RCC patients has shown to significantly reduce the number of MDSC and Tregs while at the same time increasing the type 1 T-cell response (Finke et al, 2008; Ko et al, 2009). Similar findings have been reported in several murine tumor models, and one study showed that sunitinib would enhance the therapeutic activity of IL-12 and 4-1BB (Ozao-Choy et al, 2009).

Monoclonal Antibodies for Cancer Therapy

There is interest in monoclonal antibodies for the treatment of select tumors. Antibodies to CD20 have produced meaningful responses in a number of patients with B-cell lymphoma patients who were refractory to chemotherapy (Maloney et al, 1997). The Food and Drug Administration (FDA) has also approved an antibody to HER2/NEU for the treatment of patients with breast cancer. **Additional antibodies are being tested that can reduce immune suppression by targeting CTLA4, PD1 receptor, and B7-H1** (Iwai et al, 2002; Hodi et al, 2003).

IMMUNITY TO INFECTIONS

The immune system provides protection against the ubiquitous numbers of infectious microbes that surround us at all times. They can range in size from 10^{-4}-mm viruses to 10^{3}-mm worms. **The initial barrier to these pathogens is the skin and external body fluids described previously under innate immunity.** If penetration occurs, organisms can be killed by soluble factors such as lysozyme, which is an antibacterial enzyme present in the tears, saliva, and phagocytic cells that digests peptidoglycans in bacterial cell walls. **Neutrophils and macrophages provide phagocytosis, killing, and digestion of bacteria and fungi.** Killing is accomplished by digestive enzymes and by oxygen-free radicals and other reactive oxygen species generated by the nicotinamide adenosine diphosphate (NADPH) oxidase, and oxidized halides produced by myeloperoxidase. The oxidase pumps electrons into phagocytic vacuoles, which produces conditions conducive to microbial killing and digestion by enzymes released into vacuoles from the cytoplasmic granules (Soehnlein et al, 2008). **This process is greatly enhanced by the complement proteins that are not only cytotoxic but are attractants for phagocytic cells, and that facilitate inflammation and cell adhesion.** The combination of innate and adaptive immunity is required for complete eradication of the offending organisms (Janeway, 2002). However, the burden of invading microbes may be large and overwhelm immune mechanisms so that drainage or (surgical) removal, and the use of antimicrobial drugs to diminish replication, may be required for complete elimination of the invading organisms.

Bacterial Infections

Extracellular Bacteria Are Susceptible to Killing by Phagocytosis and Complement

Bacteria try to evade these mechanisms by surrounding themselves with capsules that do not readily adhere to phagocytic cells, by secreting exotoxins that can impede host responses, or by proliferating in relatively inaccessible locations. For example, some gram-positive bacteria have developed capsules that do not favor stable binding of the complement C3 convertase, or prevent the insertion of the lytic C5b-9 membrane attack complex. To overcome this, host antibodies can override some of these mechanisms by directly binding to bacterial exotoxins and "neutralizing" them. They can also bind to the encapsulated bacteria, which will permit ingestion by PMNs and macrophages. **These coated bacteria become "opsonized" as the Fc portion of the antibody permits binding to high-affinity receptors on phagocytes and also can fix complement.** In addition, secretory IgA (and some IgM) antibodies can afford protection in the tears, saliva, gut, vaginal mucosa, and lung by preventing bacterial adherence to these epithelial surfaces. Opsonized bacteria too large for phagocytosis can also be killed because the Fc portion of antibody can attract "killer" lymphocytes by the process called antibody-dependent cell-mediated cytotoxicity (ADCC).

Some bacteria, such as the bacilli that cause tuberculosis, leprosy, listeriosis, and brucellosis, try to escape the immune system by growing within macrophages (Schaible et al, 1997). They defy the innate killing mechanisms by blocking macrophage activation, scavenging oxygen radicals, or inhibiting lysosomal fusion with the phagocytic vacuole. These organisms develop strong lipid outer coats and can escape from the phagosome into the cytoplasm of the macrophage and there proliferate. **Clearance of these intracellular microbes is directly dependent upon T-cells, which in turn must activate the infected macrophages. Specifically primed T cells react with processed antigen derived from the intracellular bacteria in association with MHC class II antigens on the macrophage surface.** The subsequent T-cell release of lymphokines, such as INF-γ and other macrophage activating factors, up regulate the macrophage killing mechanisms. These include the formation of nitric oxide and other reactive oxygen intermediates within the macrophage.

Chronic Inflammation

The character of the immune response can change during persistent infections or when the immune response is ineffective or unable to clear the offending microbe. In these instances, the site of infection becomes dominated by macrophages in various stages of activation. These cells may fuse and appear as "giant cells" or line up in arrays called "epitheliod cells." Macrophages bearing bacterial antigens on their surface may actually become targets of cytotoxic T cells and be destroyed. Lymphocytes in various stages of activation will also be present. This combination of immune-activated cell types is also associated with proliferating fibroblasts and areas of necrosis. **This reaction represents an attempt by the body to wall off a site of persistent infection, and the site is referred to as a granuloma**. **Such a response can also arise from the persistence of undigested inorganic materials or antigen–antibody complexes.**

Viral Infections

Viruses are subject to the same mechanisms of immune clearance as other microbes but attempt to avoid the immune system by altering their surface antigens. **Minor changes in surface antigens due to point mutations in the viral genome is called antigenic drift, while major changes arising from exchanges of large portions of the viral genome with other viruses is called antigenic shift. Influenza viral epidemics often result from such antigenic shifts, which act like new infections and bypass host immune memory and recall.** Viruses can use certain host receptors (the CD4 molecule by HIV) to gain entry into the host cell. Altered viral epitopes can inhibit the triggering of the host T-cell receptors, block complement components, and prevent antigen processing by APCs. The viral genome may encode proteins similar to host cytokines and their receptors that subvert immune activation (Watts and Bertram, 2004). **As with bacterial infection, host antibody is essential for eliminating extracellular viral particles, and cell-mediated responses are necessary for those that are intracellular.** Antibodies can neutralize viruses by blocking their surface receptors, activating the classical complement pathway, and clumping or aggregating the viral particles for enhanced phagocytosis. These responses are especially effective when the virus has to travel in the bloodstream to reach its target, such as the poliovirus, which enters through the gut and travels to the nervous system. When the target organ is at the portal of entry, such as the gut or lung, rapid release of local interferon and recruitment of NK cells is essential for immune clearance.

Toll-Like Receptors and Microbial Killing

The first mammalian TLR identified, TLR4, was shown to induct the genes for several inflammatory cytokines and costimulatory molecules. Therefore it was anticipated that the TLRs might be

Table 17–6.
Toll-Like Receptors (TLRs) and Their Ligands

TLR FAMILY	LIGANDS (ORIGIN)
TLR1	Triacyl lipopeptides (bacteria, mycobacteria)
	Soluble factors (*Neisseria meningitides*)
TLR2	Lipoprotein/lipopeptides (a variety of pathogens)
	Peptidoglycan (gram-positive bacteria)
	Lipoteichoic acid (gram-positive bacteria)
	Lipoarabinomannan (mycobacteria)
	A phenol-soluble modulin (*Staphylococcus epidermidis*)
	Zymosan (fungi)
	HSP70 (host)
TLR3	Double-stranded RNA (virus)
TLR4	LPS (gram-negative bacteria)
	Taxol (plant)
	Fusion and envelope protein (RSV)
	HSP60 and HSP70 (*Chlamydia,* host)
	Type III domain A of fibronectin (host)
	Oligosaccharides of hyaluronic acid (host)
	Polysaccharide fragments of heparan sulfate (host)
	Fibrinogen (host)
TLR5	Flagellin (bacteria)
TLR6	Diacyl lipopeptides (mycoplasma)
TLR7	Synthetic compounds
TLR9	CpG DNA (bacteria)
TLR 8 and 10	??

involved in immune responses, especially in the activation of innate immunity (Takeda et al, 2003). TLR4 was then shown to be involved in the recognition of lipopolysaccharide (LPS), a major cell wall component of gram-negative bacteria. Subsequently, other members of the TLR family have been shown to be essential for the recognition of a wide range of microbial components (including double-stranded RNA), flagellin, taxol, fibrinogen, peptidoglycan, and various other viral and fungal envelope proteins and products (Table 17–6). TLRs also recognize some endogenous ligands such as heat-shock proteins. A wide variety of stressful conditions, such as heat shock, ultraviolet radiation, and viral and bacterial infection, induce the increased synthesis of heat-shock proteins, which can activate macrophages and dendritic cells to secrete proinflammatory cytokines and to express costimulatory molecules.

Expression of TLRs is modulated by a variety of factors such as microbial invasion, microbial components, cytokines (such as colony-stimulating factor 1), and macrophage migration inhibitory factor (MIF). Upon recognition of their cognate ligands, TLRs induce the expression of a variety of host defense genes. These include inflammatory cytokines and chemokines, interferons, antimicrobial peptides, costimulatory and MHC molecules, and other effectors necessary to arm the host cell against the invading pathogen (Zhang et al, 2007). The pathways that transduce TLR signals in mammals are highly homologous to that of the IL-1R family, and ultimately lead to the activation of two distinct signaling pathways, JNK and NFκB (Barton and Kagan, 2009). Once freed from inhibitors NFκB translocates into the nucleus and turns on transcription of target genes. Not surprisingly, NFκB is critical in the function and development of dendritic cells. Both TLR and IL-1R interact with an adaptor protein MyD88, which is critical to the production of inflammatory cytokines induced by the TLR family. Indeed, no activation of NFκB was observed in macrophages of MyD88-deficient mice, which were found to be susceptible to infection by *Staphylococcus aureus*.

Recognition of microbial components by TLRs triggers activation of not only innate immunity but also adaptive immunity, which is largely provided by dendritic cells. Immature dendritic cells residing in the periphery have a high capacity for endocytosis, which facilitates antigen uptake. They are activated by various microbial components to undergo maturation and express many of the TLRs. TLR-mediated recognition of microbial components by dendritic cells induces the expression of costimulatory molecules such as CD80/CD86, and production of inflammatory cytokines such as IL-12. Once matured, dendritic cells lose their capacity for endocytosis and migrate into the draining lymph nodes. Here they present microorganism-derived peptide antigens expressed on the cell surface with MHC class II antigen to naive T cells, thereby initiating an antigen-specific adaptive immune response. In addition to controlling the development of adaptive immunity, activation of TLRs appears to be directly involved in antimicrobial activity. TLR2 activation leads to nitric oxide–dependent and –independent killing of intracellular *Mycobacterium tuberculosis* in macrophages. TLR2 confers LPS- and lipoprotein-induced apoptosis of macrophages, indicating the possible involvement of TLRs in infection-induced cell death.

Passive and Acquired Immunity

Protection against a specific infection can be passively transferred from one individual to another by serum containing preformed antibodies. This type of passive immunity is generally short lived because the half-life of immunoglobulins is generally 1 to 2 weeks. Patients with immunodeficiency diseases may actually be sustained by regular treatments with pooled nonspecific human gamma globulin treatments. High-titer, pooled, specific antibodies to agents such as the cytomegalovirus can be given as prophylaxis or treatment of the viral infection. Equine globulin raised against diphtheria and tetanus toxin has also been effective, although globulin from nonhuman species tends to be more toxic and presents the risk of serum sickness. Passive immunity is also transferred from mother to child by the placental transfer of IgG during gestation and the intestinal absorption of secretory IgA in the mother's milk.

The most durable form of protection from infection results from active immunization. This can arise from an acquired infection that results in host immunity, or vaccination by intentional exposure to either killed or attenuated live organisms. **Attenuated organisms, which cause only a very mild form of the natural disease, yet retain the antigenic specificity of the organism, are most effective.** Attenuated organisms replicate, which provides for a larger dose, and the immune response is produced at the site of natural infection. The objective is to provide effective immunity by establishing adequate levels of antibody and a primed population of memory cells, which can rapidly expand upon rechallenge with the offending agent. To be most effective, successful immunization requires a combination of specific antibody, macrophage-activating cell-mediated immunity, and the generation of cytotoxic T-cells.

MOLECULAR IMMUNOLOGY

"Omics" Era of Biology

During the past decade the first version of the complete human genome has been sequenced and published (www.ornl.gov/scitechresources/Human_Genome/home.shtml), which has unlocked a remarkable potential for discoveries in human biology

and medicine. In parallel, recent advances in molecular biologic techniques have permitted the profiling of the global mRNA transcript, which encompasses the cell's transcription of activated genes that drive the subsequent events of protein translation, modification, and metabolism—creating the complex functions of any biologic system. **These emerging technologies have set the stage for the "omics" era of biology in which cellular events are described in terms of the transcriptome (mRNA transcripts), the proteome (proteins); the metabolome (metabolic products), and glycomics (carbohydrate modifications to proteins).** These technologies offer immense potential because they provide a global view of changes in gene expression in the tissue or organ studied. The changes can be profiled to differentiate normal or healthy states from diseased ones. This genome-wide approach can describe both the expression of known genes and mechanistic pathways, as well as the discovery of yet unknown genes and pathways. These newly identified genes and proteins may provide the key targets for future therapies. Such genomic profiling can also identify prognostic biomarkers to diagnose, classify, and guide the treatment of disease. Several clinical fields related to urology have begun to explore these technologies, which include oncology, immunology, and transplantation biology. The initial foray into these technologies has been the analysis of gene expression profiles using DNA microarrays.

Gene Chip

cDNA Arrays and Oligonucleotide Arrays

Although earlier estimates suggested that the linear sequence of 3 billion base pairs in human DNA encoded over 100,000 genes, the numbers have now been downsized by more than half. High-throughput technologies are now in place to identify most of the known genes that have been previously identified and annotated. **The basic principle involves the "spotting," on a glass support, of a nucleotide sequence that represents a particular gene (a probe) to which a complementary nucleotide sequence (a target) will hybridize according to molecular attraction (A-T and G-C). The probe is generally a piece of complementary DNA (cDNA) several hundred nucleotides in length that is generated as a polymerase chain reaction (PCR) product from a known cDNA library. More recently, machine-synthesized oligonucleotides of between 25- to 75-mer length have been used as probes. When thousands of these probes are spotted, they are described as a DNA microarray, or a DNA gene chip.** The target can come from any tissue or cell type of interest by first extracting its total RNA, then labeling the mRNA fraction with a fluorescent isotope. The relative amount of labeled target that hybridizes to the DNA on the chip provides a signal captured by a laser scanner, and the signal reflects the expression level of the corresponding gene. Using the current version of a commercially produced human DNA microarray (U133A Plus 2.0; Affymetrix, Santa Clara, CA), about 47,000 transcripts, representing 38,500 well-characterized genes, can be screened on one chip, now referred to as a whole genome-wide array. Such large data sets were originally generated from publicly available (on the Internet) gene sequence databases. Once such a large volume of raw data is generated, computerized bioinformatics is necessary to identify relationships. A commonly used technique is hierarchical clustering of up- or downregulated genes comparing experimental groups to controls.

Gene Expression Profiling in Urologic Oncology

Although costs and labor have been reduced with production efficiency, DNA microarray analysis remains expensive, labor intensive, and cumbersome. However, a number of initial experiences provide exciting future possibilities. **Gene expression profiling has the potential to significantly advance the diagnosis and classification, prognosis, and treatment of urologic cancers.** Creating gene lists from high-throughput microarrays can establish gene profiles of different tumor types. Such profiling has been used to distinguish the various histologic subtypes of renal cell carcinomas (RCCs), each with a unique molecular signature (Yang et al, 2006). For example, microarrays identified strong alpha-methylacyl coenzyme A racemase in 41/41 papillary RCCs, including 6 with metastases; while this gene was only weakly found in less than 15% of all other renal cancers tested (Tretiakova et al, 2004). Clear cell renal cancers commonly express glutathione-S-transferase alpha, while carbonic anhydrase II is upregulated in chromophobe renal cancers; neither enzyme is expressed in oncocytomas. For these reasons, it has been suggested that gene expression profiling may someday permit the use of renal biopsy to accurately diagnose radiographic renal masses such as oncocytomas from carcinomas (Rohan et al, 2006). In addition, DNA microarray analysis of benign prostatic hyperplasia (BPH) versus prostate adenocarcinoma has revealed 402 genes in BPH and 141 genes in cancer, which were up- or downregulated at least fivefold (Endo et al, 2009).

Some have proffered that gene expression profiling could help quantify the malignant potential of specific cancers. Two studies reported a 40-gene and a 45-gene cluster associated with poor cause-specific survival for clear cell RCC, and suggested that vascular cell adhesion molecule–1 may be a useful prognostic marker (Takahashi et al, 2001; Vaselli et al, 2003). Recently, data-mining with DNA microarray analysis of bladder cancer tissue and voided urine identified differential expression according to tumor grade. A more select cluster of eight genes was then used to demonstrate tumor progression (Mengual et al, 2009). However, such analysis is often retrospective and complex, as evidenced, in one study, by the lack of association of gene expression profiles for predicting metastases from penile cancer (Kroon et al, 2008). In future studies, the combination of genomics and proteomics may further refine the molecular analysis of specific tumors (Seliger et al, 2009). Lastly, gene expression profiling can also identify targets for therapeutic intervention. Topoisomerase II, identified as being highly upregulated in aggressive Wilms tumors, has also been found in renal medullary cancers, making it an early molecular target for therapeutic interventions.

Gene Expression Profiling in Transplantation

Another area explored with DNA microarray technology has been renal transplantation, in particular the gene profiles associated with allograft rejection and renal dysfunction. Using a spotted cDNA array consisting of about 12,440 selected genes created at Stanford University; 67 pediatric renal allograft biopsies were profiled. **Hierarchical clustering of gene expression demonstrated three patterns of acute rejection that also correlated with 2-year graft survival, and suggested a previously unknown correlation with genes linked to B cell–mediated immunity** (Sarwal et al, 2003). Two reports

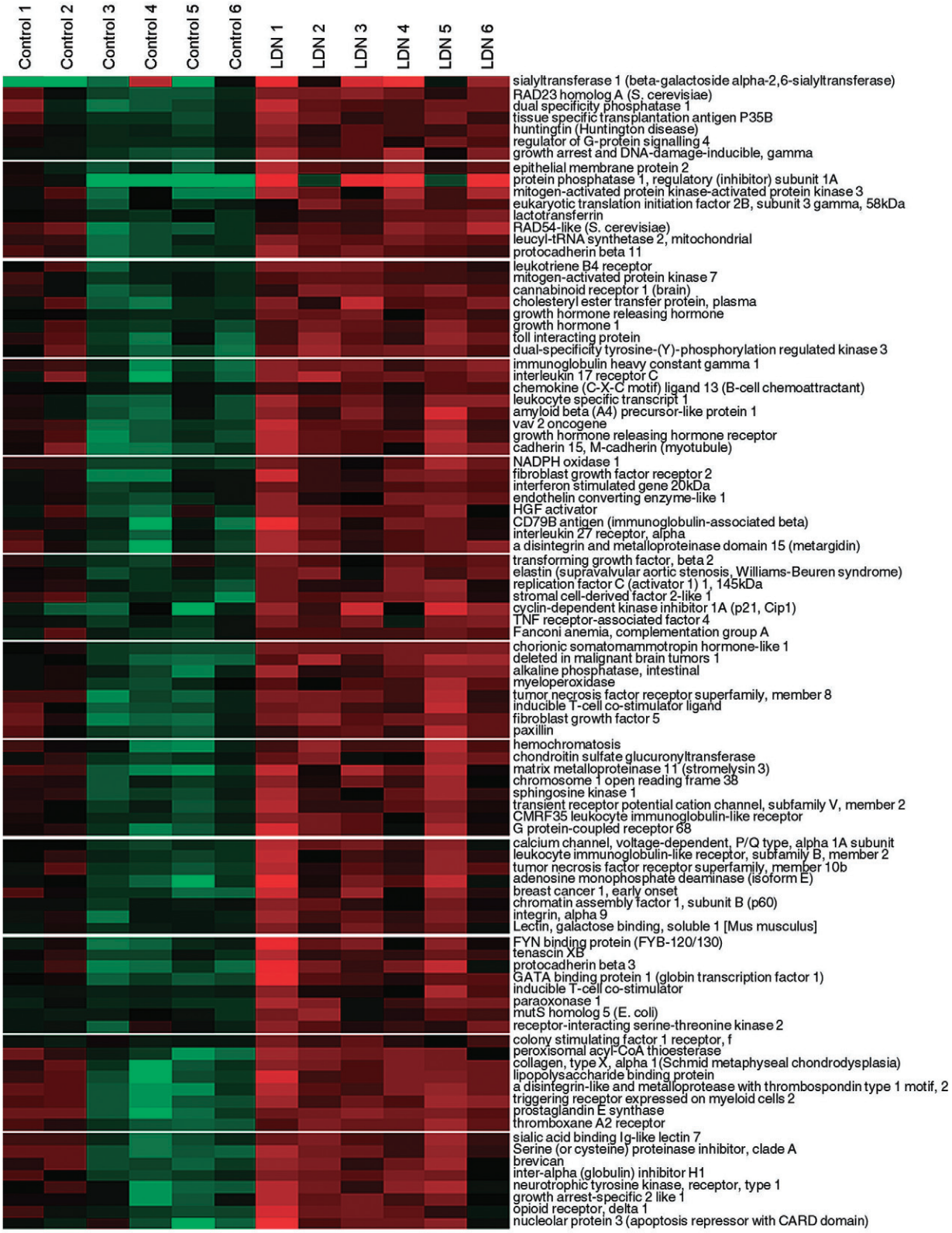


Figure 17–15. Heat map representing the relative signal intensities of a subset of 95 differentially expressed genes selected from a class comparison of the gene expression profiles between control and laparoscopic donor kidneys. Control biopsies were obtained prior from open nephrectomies prior to surgical manipulation. Genes were selected based on association with ischemia, tissue injury, and stress from a literature search using publicly available databases.

describe the use of high-density oligonucleotide arrays to define molecular signatures for transplant kidney biopsies, as well as peripheral blood lymphocytes (PBL). Affymetrix HG-U95Av2 GeneChips (over 22,600 genes) were used in four groups of transplant patients: normal donors, recipients with well-functioning kidneys, patients with acute rejection, and patients with renal dysfunction but no rejection. Distinct gene expression profiles were identified for both kidney biopsies and PBL that correlated and classified each of the four groups of patients (Flechner et al, 2004). **Interestingly, the genes upregulated in the PBL did not overlap with the biopsies associated with acute rejection, suggesting that the PBL and the transplanted kidney represent two distinct compartments regarding the immune mechanisms involved.** In another study, the same group compared the gene expression profiles from 2-year kidney biopsies in recipients treated with or without a calcineurin inhibitor (CNI) drug. The authors showed that the patients on the CNI-free immunosuppressive protocol had better renal function and a significantly diminished prevalence of chronic allograft nephropathy by histology. **Gene expression profiles of kidneys that were graded with higher Banff scores for chronic allograft nephropathy showed a marked upregulation of genes that were involved in immune//inflammation and tissue injury/remodeling and fibrosis** (Flechner et al, 2004). Another group has used DNA microarrays in an attempt to separate histologic grades of severity in the rejection of kidneys (Mueller et al, 2007). cDNA microarrays can also be used to study specific mechanisms of renal transplant physiology by comparing the gene expression profiles from laparoscopically removed donor kidneys (Kurian et al, 2005), and from the glomeruli and tubulointerstitium obtained by microdissection of biopsies from both deceased and live-donor kidneys (Kainz et al, 2004). One can see that several hours of pneumoperitoneum and laparoscopic surgery causes a specific signature of up- and down-regulated genes compared with controls (Fig. 17–15). **Such gene expression patterns can be used to identify which compartments in the kidney may be most susceptible to ischemia, and which biologic products may be targets to help minimize injury.** Lastly, hierarchical clustering of genes from a DNA microarray can be used to establish the state of degeneration or cyst formation in the end-stage kidney, such as those found with adult polycystic kidney diseases (Schieren et al, 2006).

Key Points

- The immune response is identified by unique characteristics that explain its utility and adaptability against numerous foreign invaders and substances. These include (1) the ability to identify self from non-self, (2) specificity, (3) memory, and (4) rapid amplification.
- Innate immune responses are constitutive and do not improve on repeated contact. Innate defense mechanisms represent nonspecific barriers to invaders, which rely primarily on physical barriers, phagocytic cells, natural killer cells, complement, acute phase proteins, lysozyme, interferons, defensins, and germline-encoded innate immune receptors.
- Adaptive or specifically acquired immune responses result from repeated exposure to invading microbes and rely primarily on large populations of lymphocytes, each with its own individual specificity. The clonal expansion of specific lymphocyte populations after first contact confers memory and the ability to elicit a more vigorous response upon subsequent exposure.
- T-cell activation requires costimulation. Initial engagement of the TCR with MHC-peptide on an antigen-presenting cell (signal 1) alone will result in anergy. Additional engagement with accessory molecules on the APC (signal 2) is necessary for further intracellular signal transduction leading to T-cell activation.

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chapter
18

Molecular Genetics and Cancer Biology

Mark L. Gonzalgo, MD, PhD ● Alan Keith Meeker, PhD, MA

Basic Molecular Genetics
Tumor Suppressor Genes and Oncogenes
The Cell Cycle
DNA Methylation
DNA Damage and Repair
Chromosomal Abnormalities and Genetic Instability
Telomeres and Telomerase
Apoptosis
Stem Cells and Cancer

Despite decades of intensive biomedical research, cancer remains a significant cause of morbidity and mortality worldwide. In part, this is due to the complexity inherent in this disease, which is, in fact, not truly a single disease at all, but well over 100 separate subtypes, all grouped together under the single term, "cancer."

In the United States alone, cancer strikes over half a million victims annually and is currently the second leading cause of death, poised to become the leading cause of death in the near future, should recent trends continue. **Genitourinary (GU) malignancies comprise 28% (413,700) of all cancer cases in the United States (nonmelanoma skin cancers excluded) and 15% of all cancer deaths** (Jemal et al, 2009). However, significant advances in the diagnosis and treatment of certain GU cancers have been made. For example, the cure rate for testicular cancer now approaches 100% (Einhorn, 2002; Horwich et al, 2006). Unfortunately, this cancer is unusual in its responsiveness to therapy and is relatively uncommon. We have had less success with the more prevalent GU malignancies, such as prostate, bladder, and renal cancers—the second, eighth and tenth most common cancers, respectively. Encouragingly, however, mortality figures for these malignancies have shown a slow but steady decline over the past decade, and there is every reason to believe that these trends will continue and even accelerate in the future.

Much of our current understanding of cancer is the direct result of the molecular biology (Table 18-1) revolution that developed rapidly following the elucidation of the molecular structure of deoxyribonucleic acid (DNA) by Watson and Crick in 1953. In subsequent years, the field of molecular genetics has complemented and greatly expanded upon knowledge gleaned by other disciplines, such as biochemistry and cell biology, providing important insights, at the molecular level, regarding the abnormalities present in cancer cells. Thus a great deal is now known concerning the numerous molecular signaling pathways that provide both positive and negative regulatory signals that stringently control cell proliferation in normal cells, such that any losses in cell number are precisely counterbalanced by cell proliferation, thereby maintaining tissue and organ homeostasis. Renegade populations of autonomously proliferating cells represent a serious threat to survival of the organism, particularly to large, long-lived species such as ourselves; therefore, we have evolved multiple barriers to prevent such outbreaks from occurring. This means that incipient cancer cells must overcome several hurdles on the way to becoming fully malignant—a multistep process that takes many years or even decades to complete. Consequently, it has been recognized that **cancer cells need to acquire several key attributes in order to make the transition from a normal cell to a malignant tumor. These attributes include (1) genetic instability, (2) autonomous growth, (3) insensitivity to internal and external antiproliferative signals, (4) resistance to apoptosis and other forms of induced cell suicide, (5) unlimited cell division potential, (6) the ability to induce new blood vessel formation, a process termed angiogenesis, (7) locally invasive behavior, which uniquely distinguishes malignant from benign neoplasms, and (8) evasion of the immune system.** In addition, cancer cells need to cope with various cellular stresses that are byproducts of their abnormal physiology. **Finally, many cancers develop an additional, lethal attribute—the ability to leave the site of the primary tumor to colonize and thrive in distant organs or tissues as metastases** (Hanahan and Weinberg, 2000; Solimini et al, 2007; Luo et al, 2009).

This chapter outlines fundamental concepts of molecular genetics that are directly related to human cancer in general, with an emphasis on genitourinary malignancies in particular. Spurred by recent technological advances such as high-throughput DNA sequencing, genome-wide assessment of DNA polymorphisms and DNA copy number changes, as well as array-based gene expression profiling methods, our knowledge of the molecular genetics of cancer is rapidly expanding, providing new insights that are just beginning to be successfully exploited for use in novel diagnostic, prognostic, and therapeutic applications.

Table 18–1.

Molecular Biology: Glossary of Terms

Allele: An alternative form of a gene.
Amplification: Additional copies of a chromosomal sequence; these sequences may include genes and may be extrachromosomal or intrachromosomal.
Aneuploid: Deviation in chromosomal number from the usual diploid state (e.g., tetraploidy)
Annealing: The pairing of two single strands of complementary DNA sequences to form a double helix.
Alternative splicing: A mechanism by which variations in the incorporation of a gene's coding regions during mRNA maturation leads to the production of multiple related forms of a gene.
Base pair: The physical relationship between adenine/thymidine and guanine/cytosine within the double helix of DNA. Abbreviated as bp, it provides the unit of measurement for DNA. Each base pair is stabilized by hydrogen bonds.
cDNA: A segment of DNA complementary to an RNA sequence.
Centromere: An essential structural element of chromosomes consisting of repetitive, non-coding DNA to which the spindle microtubules attach during mitosis.
Chromosome: A distinct segment of linear DNA containing a large number of genes. In humans there are 23 such segments, each containing hundreds to thousands of genes.
Codon: Three sequential nucleotides in protein coding genes that specify a particular amino acid in the protein or a STOP translation signal.
Deletion: The removal of a segment of DNA, with rejoining of the ends.
Diploid: A set of chromosomes containing two complete copies of the organism's genomic DNA.
Dominant: Allele determining the phenotypic manifestation of a gene.
Endonuclease: An enzyme that cuts DNA or RNA within the nucleotide chain.
Epigenetic: Nongenetic information, such as methylation or acetylation of histone proteins that modifies gene expression.
Exon: A sequence of DNA that is represented with a complementary RNA sequence, also known as the coding sequence.
Expression vector: A vector designed to encode a particular DNA sequence or gene for transcription and translation into RNA or protein.
FISH: Fluorescence in situ hybridization. A technique in which a fluorescently-labeled nucleic acid probe is hybridized to its complementary target sequence in the genome, allowing localization and enumeration of the target.
Frameshift mutation: A deletion or insertion of DNA that shifts the normal codons into a different order for translation into protein.
Gene: A segment of DNA that contributes to the formation of a protein, including both the introns (noncoding regions) and the exons (coding regions), as well as the regulatory regions preceding and following the coding regions.
Genetic code: The correspondence between triplets of DNA or RNA (codons) and amino acids making up proteins.
Genotype: The genetic makeup of an organism as reflected in its DNA sequence.
Haplotype: A group of alleles in relative close proximity on a chromosome that are inherited together.
Hemizygote: Having only one copy of a gene owing, for example, to the loss of chromosomal material or an entire chromosome.
Heterozygote: Having two different copies (alleles) of a gene.
Homozygote: Having two identical copies (alleles) of a gene.
Hybridization: The physical pairing of complementary RNA and/or DNA sequences.
Intron: A segment of DNA that is transcribed but is removed by the splicing together of the exons on either side; part of the noncoding sequences of a gene.
Karyotype: A catalogue of all the chromosomes within a particular cell. Typically accomplished by isolation and staining of metaphase chromosomes.
Linkage: The tendency for genes in proximity to one another on a chromosome to be inherited together.
Locus: The position of a particular gene on a particular chromosome.
Loss of heterozygosity (LOH): Deletion or mutation of a gene creating a hemizygous state or, if the remaining allele is duplicated, a homozygous state. In cancers arising in cancer predisposition syndromes caused by an inherited gene mutation, the remaining wild-type allele is often lost by LOH.
Methylation: The addition of a methyl group to a molecule. Methylation of the nucleotide cytosine in the promoter regulatory region of a gene is often associated with decreased transcription of that gene.
Micro-RNA: (miRNA); small, single-stranded RNA molecules, 21 to 23 nucleotides in length, that function to negatively regulate transcribed genes for which they have sequence complementarity.
Mutation: Any change in the sequence of genomic DNA.
Northern blotting: A technique of transferring RNA from an agarose gel to a nitrocellulose filter for hybridization with a complementary DNA.
Oncogenes: Genes that encode for proteins that have the ability to transform normal cells into cancerous cells.
Phenotype: The appearance or function of an organism, reflecting the contributions of the genotype and the environment.
Ploidy: The number or copies of entire chromosome complements (genomes) within a cell; diploid has two copies, triploid has three copies, tetraploid has four copies, etc.
Point mutation: A change in a DNA sequence involving a single base pair.
Polymerase chain reaction (PCR): A technique using sequential temperature cycles favoring DNA denaturation, annealing of primer sequences, and primer extension with DNA polymerase to amplify a large number of copies of a particular sequence of DNA. This technique can be used to detect very small amounts of DNA by creating a huge number of identical copies.
Polymorphism: A difference in normal DNA sequence between individuals. It can be a repetitive element or a single nucleotide polymorphism (SNP).
Promoter: The region of DNA in a gene where RNA polymerase binds and gene transcription begins. This region is often the sequence of DNA 100 to 500 base pairs immediately before the initiation site of the protein coding portion of the gene.
Recessive: An allele that is not represented phenotypically in the presence of a dominant allele.
Reporter gene: A gene encoding for a new or foreign protein that can easily be detected. For example, the luciferase gene, encoding the light-producing proteins of the firefly, is introduced into cells that do not express this gene.

Continued

Table 18–1.

Molecular Biology: Glossary of Terms—cont'd

Restriction enzyme: An enzyme recognizing specific short sequences of DNA (e.g., 4 or 6 base pairs); these enzymes cut the DNA at a particular location.
Silent mutation: An alteration in a DNA sequence that does not change the protein product of the gene.
Small interfering RNA: (siRNA); small double-stranded RNA molecules, 20 to 25 nucleotides in length, that promote degradation of mRNA molecules to which they have complementarity, thus downregulating expression of the corresponding gene—often employed by researchers as a means of reducing expression of specific genes.
Southern blotting: A technique of transferring denatured DNA from an agarose gel to a nitrocellulose filter for hybridization with complementary DNA.
Splicing: The removal of introns (spliced out) and the connection of exons (spliced together) in mRNA.
Telomere: An essential structural element of chromosomes consisting of repetitive, noncoding DNA and associated telomere-specific binding proteins that cap and stabilize the chromosomal termini.
Transcription: Synthesis of RNA on a DNA template.
Transfection: The introduction of DNA sequences into a cell.
Transgenic animals: Animals created by the introduction of new DNA into the germ line (into the egg).
Translation: Synthesis of protein from the messenger RNA (mRNA) template.
Vector: A plasmid, bacteriophage, or virus that carries new DNA into a cell. Vectors are often designed to produce large amounts of protein encoded by the gene within the host cell.

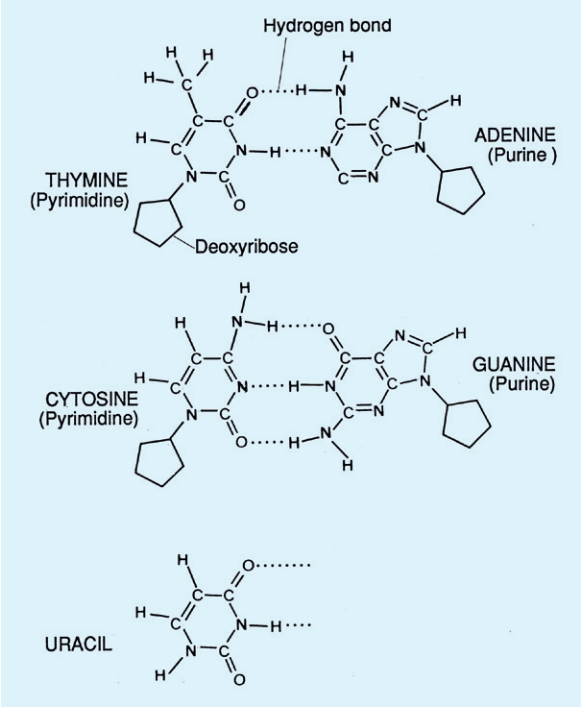


Figure 18–1. The nucleic acid alphabet consists of four bases: the purines adenine (A) and guanine (G), and the pyrimidines thymine (T) and cytosine (C). Uracil (U) is substituted for thymine in the case of RNA. The combination of a base and a sugar (deoxyribose) is referred to as a *nucleoside*.

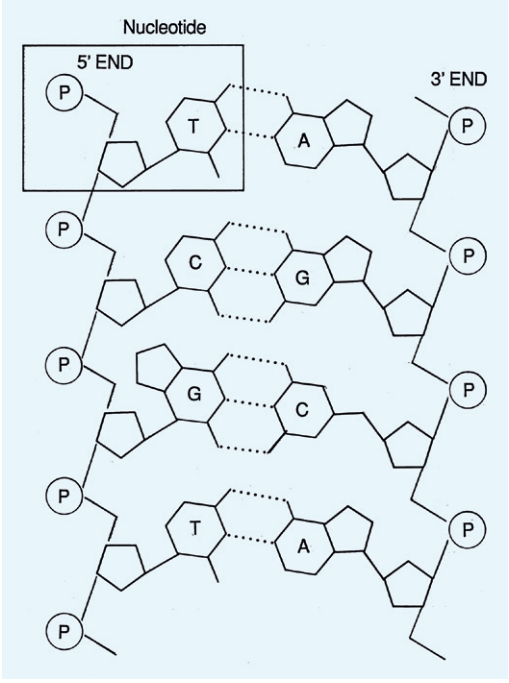


Figure 18–2. The combination of a sugar phosphate group and a base constitutes a *nucleotide*. The double helix is made from two polynucleotide chains, each of which consists of a series of 5'– to 3'–sugar phosphate links that form a backbone from which the bases protrude. The double helix maintains a constant width because purines always face pyrimidines in complementary A-T and G-C base pairs, respectively.

BASIC MOLECULAR GENETICS

DNA

The molecular characteristics of DNA were first described in 1953 (Watson and Crick, 1953). This molecule serves as the blueprint for determination of structure and function of all living organisms. **DNA is composed of three basic components: a pyrimidine or purine base, a sugar (2-deoxyribose), and a phosphate** (Fig. 18–1). The connection between repeating phosphates and sugars creates a helical chain. The DNA structure exists as a double helix in which one strand of bases is ordered in one direction and the other strand is ordered in the opposite direction. The two strands are held together by hydrogen bonds and are organized by complementary base pairing. The four bases that primarily comprise DNA are adenine, cytosine, guanine, and thymine. There is a fifth base that can be found in DNA known as 5-methylcytosine (5-mC). Uracil is substituted for thymine in ribonucleic acid (RNA). **Hydrogen bonding occurs specifically between the purine adenine (A) and the pyrimidine thymine (T) and between the purine guanine (G) and the pyrimidine cytosine (C)** (Fig. 18–2). **In the RNA molecule, adenine base pairs with uracil (U).**

During the process of replication, each strand of the DNA double helix acts as a template for generation of the new strand of DNA. The precise ordering of DNA base pairs results in a code

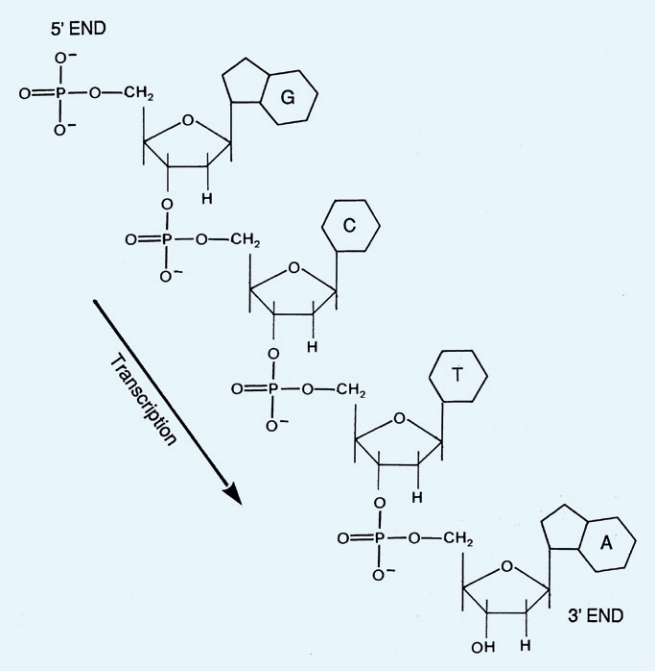


Figure 18–3. During transcription, a section of one DNA strand, or the other, is used as a template for the synthesis of messenger RNA. This synthesis always occurs in a 5′ to 3′ direction.

that will be processed to ultimately generate proteins responsible for a variety of cellular functions. Each single-stranded DNA molecule has two nonidentical ends referred to as the 5′ (5 prime) and 3′ (3 prime) termini. The 5′ and 3′ numbering refers to the carbon atoms in the deoxyribose sugar. The 5′ carbon of one deoxyribose is linked to the 3′ carbon of another deoxyribose by a phosphate group. Each strand will end with part of the sugar ring exposed based on these connections.

Transcription

During the process of transcription, linear DNA is converted to linear messenger RNA (mRNA). The process of translation consists of the conversion of linear mRNA to a linear set of amino acids that will eventually form a functional protein (Fig. 18–3). Transcription is the first step in converting DNA into protein. A single strand of RNA is copied from one of the strands of DNA. The sugar element in the RNA molecule is ribose and the pyrimidine uracil substitutes for thymine. RNA polymerase II is the enzyme that synthesizes the first copy of RNA, which is a complementary strand of the DNA template. This primary strand of RNA is called heterogeneous nuclear RNA (hnRNA) and contains coding sequences (exons) of DNA and noncoding sequences (introns).

The pre-mRNA molecule undergoes three major modifications: 5′ capping, 3′ polyadenylation, and RNA splicing. These processes occur in the nucleus before the RNA molecule is translated into protein. A guanine is added to the 5′ end of the molecule which results in the formation of a methylated cap (Perry, 1981). A long chain of approximately 200 adenine residues forms what is called a poly(A) tail that is added to the 3′ end of the mRNA and may provide stability to the molecule (Jackson and Standart, 1990). RNA splicing is a dynamic process that can result in the formation of different peptide sequences. A primary RNA transcript is converted into a mature mRNA prior to protein synthesis. **The process known as alternative RNA splicing is how a single gene can encode for multiple unique proteins by including or excluding certain exons in the mRNA transcript** (Sharp, 1987). The sequences contained within introns are not essential for protein synthesis; therefore introns are spliced out and exons are spliced together to generate the functional message known as mRNA. **Exons are sequences of DNA that have corresponding sequences in the mRNA, and introns are regions of DNA sequence that are not represented in mRNA** (Witkowski, 1988).

RNA Interference

Post-transcriptional gene regulation can occur by a mechanism involving the expression of noncoding RNAs that have the capability of binding to and degrading messenger RNAs. RNA interference (RNAi) was first discovered in *Caenorhabditis elegans,* but exists as a means of post-transcriptional regulation in a wide variety of organisms (Fire et al, 1998). RNAi are double-stranded RNAs that are transcribed from cellular genes or infecting pathogens. A double-stranded RNA species is reduced in size by a ribonuclease (RNAse) III–like enzyme, known as Dicer, into 21– to 23–base pair (bp) products with two-nucleotide 3′ overhangs known as small (or short) interfering RNA (siRNA) (Bernstein et al, 2001). These short RNA molecules are homologous to the gene that is being suppressed. The antisense strand of the siRNA is incorporated into a multicomponent nuclease called "RNA-induced silencing complex" (RISC) to destroy specific mRNAs (Gregory et al, 2005).

RNAi has been used to investigate gene function in the laboratory. Long micro-RNAs contain self-complementary regions resulting in the formation of hairpin loops that are cleaved by two RNAse III–like enzymes. The enzyme called Drosha cuts the long hairpin to generate a short hairpin RNA (shRNA) molecule. The shRNA is then processed by Dicer to produce double-stranded miRNA capable of binding target genes for destruction. Synthetic siRNA and shRNA species can be generated to target and knock-down specific gene expression. For example, this technique has been used to study the role of the androgen receptor (AR) in the progression of castrate-resistant prostate cancer. Expression of AR was knocked down using an shRNA in prostate cancer xenografts and cell lines, demonstrating that AR was necessary and sufficient for tumor growth, thereby implicating continued AR function as an essential component in both hormone-dependent and castrate-resistant prostate cancer (Chen et al, 2004).

Protein Translation

Translation of mRNA into protein occurs in the cytoplasm where ribosomes are located. The mRNA message is translated in segments of three adjacent nucleotides called a codon. Each codon is translated into one of 20 amino acids (Fig. 18–4). A total of 64 different codons can be generated from the four bases found in RNA. Due to redundancy, more than one codon can encode for a single amino acid (Fig. 18–5). Genetic mutations or alterations can have a profound effect on protein translation of mRNA. For example, a single base insertion or deletion results in a frame-shift mutation and often results in a nonfunctioning protein product. In contrast, a single base substitution may or may not result in a change in the amino acid sequence to alter protein function.

Two other forms of RNA are important for protein translation: transfer RNA (tRNA) and ribosomal RNA (rRNA). Transfer RNA is a small (75 to 85 bases long) adapter molecule that is covalently linked to a single

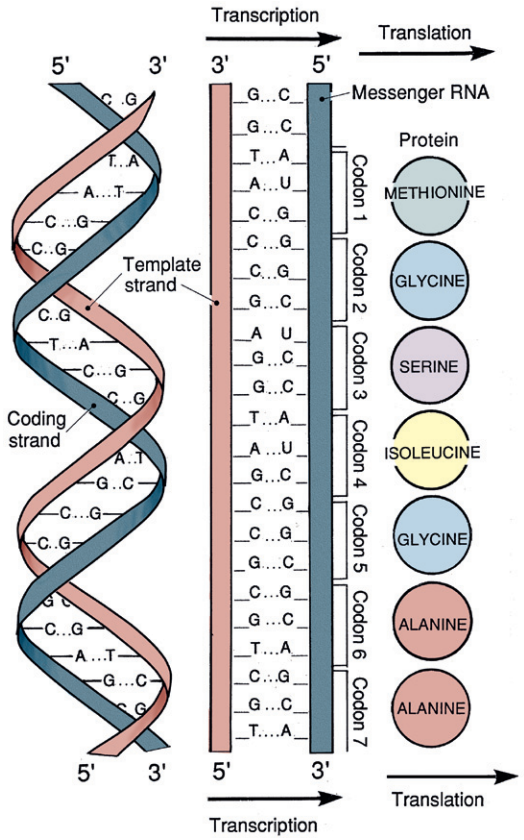


Figure 18–4. During transcription, the coding strand conveys its message through the template strand to make messenger RNA that is eventually translated into polypeptides by ribosomes. The relationship between a DNA sequence and the corresponding protein is called the *genetic code*, which is read in nucleotide triplets, or codons, specifying amino acids or protein translational start and stop signals. The code is degenerate, in that multiple codons may code for the same amino acid.

amino acid at one end and an anticodon in the middle of the chain. The anticodon is composed of three nucleotides that are complementary to the codon representing a particular amino acid. Ribosomal RNA comprises approximately 80% of the RNA within a cell and makes up part of the ribosome that is responsible for protein synthesis.

The three major stages of protein synthesis are: initiation, elongation, and termination. Initiation is frequently the rate-limiting step in translation (Merrick, 1992). During the process of initiation, the 40S ribosome binds to mRNA and forms an initiation complex that binds a tRNA with an amino acid attached. All new proteins start with methionine because the initiation codon is AUG. During elongation, amino acids are sequentially added to the peptide chain, and the ribosome moves along the mRNA chain similar to beads on a string. Elongation is the most rapid phase of protein synthesis. For any given mRNA transcript, multiple ribosomes can simultaneously move along the chain to generate new polypeptides (Rich et al, 1963). Termination is the last stage of protein synthesis and is signaled by one of three "stop" codons (Tate and Brown, 1992). The release factor is a cytoplasmic protein that binds to the stop codon and catalyzes the hydrolysis of the aminoacyl linkage that releases the carboxyl end of the polypeptide chain (Merrick, 1992). The ribosome releases from the mRNA and dissociates into two subunits after termination.

Chromosomes and Gene Structure

The long strands of DNA responsible for the genetic makeup of eukaryotic cells are organized together with specialized proteins to form chromosomes. Eukaryotic cells contain large linear chromosomes that are packaged by proteins into a condensed structure called chromatin. The chromatin structure varies depending upon the phase of the cell cycle. During interphase, euchromatin consists of DNA that is actively being expressed as protein. Heterochromatin is composed of inactive DNA that may serve a structural support role.

First base	Second base U	C	A	G	Third base
U	Phenylalanine	Serine	Tyrosine	Cysteine	U
	Phenylalanine	Serine	Tyrosine	Cysteine	C
	Leucine	Serine	Stop	Stop	A
	Leucine	Serine	Stop	Tryptophan	G
C	Leucine	Proline	Histidine	Arginine	U
	Leucine	Proline	Histidine	Arginine	C
	Leucine	Proline	Glutamine	Arginine	A
	Leucine	Proline	Glutamine	Arginine	G
A	Isoleucine	Threonine	Asparagine	Serine	U
	Isoleucine	Threonine	Asparagine	Serine	C
	Isoleucine	Threonine	Lysine	Arginine	A
	Methionine	Threonine	Lysine	Arginine	G
G	Valine	Alanine	Aspartic acid	Glycine	U
	Valine	Alanine	Aspartic acid	Glycine	C
	Valine	Alanine	Glutamic acid	Glycine	A
	Valine	Alanine	Glutamic acid	Glycine	G

Figure 18–5. RNA codon table. The 20 amino acids found in proteins are listed. All 64 possible 3-letter combinations of the RNA coding units U, C, A, and G are used to encode an amino acid or one of the 3 stop codons. Note: The codon AUG codes for methionine and also serves as an initiation site (the first AUG in the mRNA coding region where translation into protein is initiated).

Key Points: Basic Molecular Genetics

- The information contained in DNA is transcribed into RNA and then translated into protein.
- Transcription of RNA is tightly regulated and is tissue specific.
- A single gene can encode for multiple unique proteins by including or excluding certain exons in the mRNA transcript by alternative splicing.
- Post-transcriptional gene regulation can occur by a mechanism involving the expression of noncoding RNAs that have the capability of binding to and degrading messenger RNAs.

TUMOR SUPPRESSOR GENES AND ONCOGENES

Tumor Suppressor Genes

Tumor suppressor genes regulate cellular growth and play a critical role in the normal processes of the cell cycle. These genes are also important for DNA repair and cell signaling. The absence of tumor suppressor gene function may lead to dysregulation of normal growth control and malignancy. **Loss of function of both alleles of a tumor suppressor gene is typically required for carcinogenesis. This functional loss can occur by (1) homozygous deletion, (2) loss of one allele and mutational inactivation of the second allele, (3) mutational events involving both alleles, and (4) loss of one allele and inactivation of the second allele by DNA methylation.** Classic tumor suppressor genes discussed later in this chapter are the retinoblastoma gene (*RB*) and *TP53* (see The Cell Cycle).

The "two-hit" hypothesis was first proposed in cases of retinoblastoma, which required mutations in both alleles for disease manifestation (Knudson, 1971). This is because if just one allele is inactivated, the remaining allele could produce a sufficient amount of the correct protein to maintain the normal state (Fig. 18–6). **Specific types of mutations in certain genes, however, may not follow this two-hit rule and can function as dominant negative mutations that produce altered protein.** Mutant protein products have been reported to inhibit function of normal protein from unaltered alleles (Baker et al, 1990). Mutation of a single allele may result in haploinsufficiency, causing increased carcinogen susceptibility as in the case of the TP27Kip1 gene (Fero et al, 1998). Abnormally low levels of the TP27 protein were frequently observed in human cancers; however, homozygous inactivating mutations of the *TP27* gene were infrequent. Both *Tp27* nullizygous and *Tp27* heterozygous mice were predisposed to developing tumors when exposed to radiation or a chemical carcinogen. **The assumption that null mutations in tumor suppressor genes are recessive excludes genes that exhibit haploinsufficiency** (Fero et al, 1998).

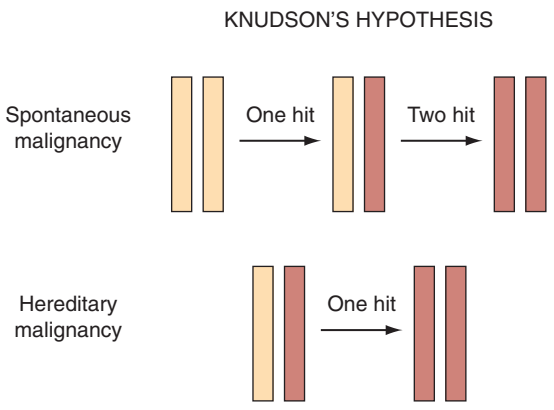


Figure 18–6. Knudson's hypothesis was that inactivation of the same gene was responsible for both sporadic and hereditary malignancies. Patients with sporadic tumors had two normal copies of the gene, and therefore the sporadic tumors required inactivation of both copies of the gene. Patients with hereditary tumor syndromes were born with only one functioning copy of the gene of interest, and therefore the hereditary tumors required inactivation of only one copy.

Oncogenes

Oncogenes are associated with cellular proliferation and are the mutated form of normal genes (proto-oncogene). A number of oncogenes were initially identified by their presence in retroviruses that were capable of inducing malignant transformation of normal cells (Martin, 1970). Two oncogenes that have been found to be overexpressed in a variety of cancers include c-*MYC* and c-*MET* (Wong et al, 1986; Bottaro et al, 1991). The proto-oncogene, c-*MYC*, encodes an early-response gene product that is a transcription factor responsible for regulating cellular proliferation. Amplification of c-*MYC* is a frequent event in prostate cancer and expression of c-*MYC* in human prostate epithelial cells has been associated with immortalization (Gil et al, 2005).

Hepatocyte growth factor acts through a receptor that is encoded by the proto-oncogene c-*MET* (Bottaro et al, 1991). Hepatocyte growth factor plays a role in normal development of the kidney, acts as a mitogen for renal tubular cells, and is capable of inducing tubulogenesis of renal cells in vitro (Montesano et al, 1991; Santos and Nigam, 1993). Increased expression of c-*MET* has been reported in renal cell carcinoma and is also more frequent in higher grade cancers (Pisters et al, 1997). Missense mutations of the *MET* proto-oncogene may also result in constitutive activation of the MET protein in tumors associated with hereditary renal cell carcinoma (Schmidt et al, 1997).

Mechanisms by which a proto-oncogene can be converted to an oncogene are by (1) mutation of the proto-oncogene resulting in an activated form of the gene, (2) gene amplification, and (3) chromosomal rearrangement. A mutation occurring within the coding sequence of a gene can lead to a continuous proliferation signal. The proto-oncogene *ERBB* encodes for the epidermal growth factor receptor (EGFR), and mutations of *ERBB* can result in overexpression of a receptor form that is constitutively active (Downward et al, 1984). Errors that occur during chromosomal replication may result in gene amplification and aneuploidy. An increase in gene copy number can produce an increased number of mRNA transcripts and overproduction of protein. For example, certain types of bladder cancer have been found to over-express c-*MYC* by this mechanism (Christoph et al, 1999). Immunohistochemical staining of bladder cancer specimens has demonstrated overexpression of c-MYC protein in more than half of papillary and invasive tumors (Schmitz-Drager et al, 1997). Finally, chromosomal rearrangements such as translocation events can result in the formation of an oncogene. This has been classically described in chronic myelogenous leukemia in which the Philadelphia chromosome is formed by reciprocal translocation between chromosome 9 and 22 (Nowell and Hungerford,

1960). A portion of the breakpoint cluster region (*BCR*) gene from chromosome 22 (region q11) is juxtaposed to the *ABL1* gene on chromosome 9 (region q34) to form a constitutively active *BCR-ABL* transcript.

Key Points: Tumor Suppressor Genes and Oncogenes

- Mutations in DNA can lead to changes in protein function or expression that increase the potential for cancer initiation, progression, or metastasis.
- Tumor suppressor genes regulate and control cellular growth. Oncogenes promote cell growth.
- Loss of tumor suppressor gene function can occur primarily by (1) homozygous deletion, (2) loss of one allele and mutational inactivation of the second allele, (3) mutational events involving both alleles and (4) loss of one allele and inactivation of the second allele by DNA methylation.
- Certain tumor suppressor genes do not follow the "two-hit" hypothesis and may be inactivated by dominant negative mutations or haploinsufficiency.
- Proto-oncogenes can be converted to oncogenes by (1) mutation of the proto-oncogene resulting in an activated form of the gene, (2) gene amplification, and (3) chromosomal rearrangement.

THE CELL CYCLE

Apart from development and growth, **cell division is tightly regulated such that the production of new cells precisely balances those lost during normal wear and tear, thus maintaining tissue and organ homeostasis.** Unlike single-celled eukaryotes, individual human cells are not allowed to make autonomous decisions regarding their proliferation. Rather, **a complex series of external growth inhibitory and growth stimulatory signals are integrated by the cell, resulting in either cell division or quiescence. Many activated oncogenes and inactivated tumor suppressor genes contribute to the deregulated growth phenotype of cancer cells by altering the balance between these signals such that proliferation is continuously favored.**

Quiescent cells are considered to be out of cycle, in a reversible state known as "G_0," which is the default state for most cells (Fig. 18–7). When signaled to proliferate, cells activate their **cell cycle** machinery, initiating **an orderly, unidirectional, series of events resulting in (1) accurate duplication of the cell's genome during the DNA synthetic phase (S phase), followed by (2) accurate segregation of each genomic complement to each of two resulting daughter cells, a process referred to as mitosis (M phase).** These two critical phases are **separated by two so-called "gap" phases (G_1 and G_2).** Throughout the cell cycle, which takes approximately 24 hours to complete, each sequential step is dependent upon completion of the prior step before progressing further (Hartwell et al, 1974). In addition, **checkpoint mechanisms closely monitor DNA integrity as well as certain critical cell cycle events. If problems are detected (e.g., DNA damage), the cell cycle will pause to allow repair** (Hartwell and Weinert, 1989). **If repair is not possible, normal cells often will commit cellular suicide through an active process termed apoptosis.** In addition to proliferative signaling networks, **many oncogenes and tumor suppressors exert their effects by interfering with cell cycle checkpoints and apoptotic pathways, allowing cancer cells to divide continuously and accumulate. Loss of the ability to respond appropriately to damaged DNA is particularly dangerous, because it fosters genetic instability, a key attribute of cancer cells. Loss of DNA damage checkpoint controls results in an increased mutation rate, accelerating the mutation of cancer-associated genes, thus contributing to carcinogenesis and disease progression** (Bartek et al, 1999).

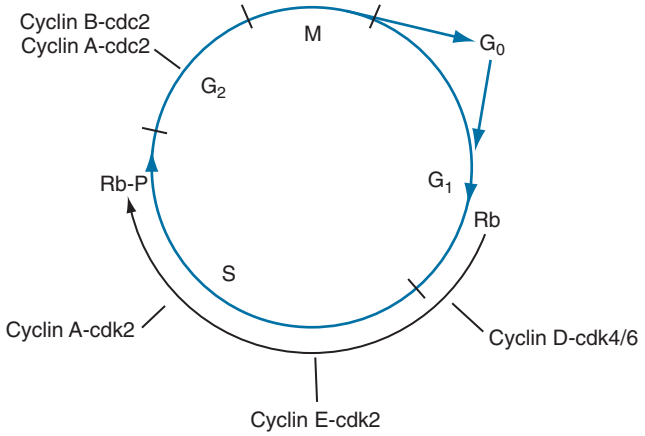


Figure 18–7. A schematic drawing of the cell cycle. Sequential activation of cyclin-CDK complexes is critical to the orderly progression of cell replication.

Cyclin-Dependent Kinases and Cyclins

The temporal sequence of events occurring throughout the cell cycle are effected by a highly conserved set of serine- and threonine-specific protein kinases termed cyclin-dependent kinases or CDKs for short (Meyerson et al, 1992). CDKs phosphorylate specific protein substrates involved in executing the phase-specific activities of the cell cycle. As their name implies, **the enzymatic activities of the CDKs are dependent upon a class of regulatory proteins called cyclins,** of which there are 12 known in mammals (Morgan, 1995). Cyclins, so named because the abundance of specific cyclins within the cell was found to be highly dynamic and tightly linked to specific phases of the cell cycle, physically associate with and activate CDK enzymatic activity (De Bondt et al, 1993; Jeffrey et al, 1995) (Fig. 18–7). Additionally, cyclins also assist in guiding CDK substrate specificity. Thus **depending largely on the transitory presence of particular cyclins, which are rate-limiting, specific cyclin/CDK complexes form and act during restricted periods within the cell cycle to initiate and regulate the events required during these precise phases, after which each cyclin is typically degraded by polyubiquitination of specific lysine residues that serve as the signal for proteosomal degradation, thereby inactivating its CDK partner** (Sherr, 1993; van den Heuvel and Harlow, 1993). The rapid, phase-specific destruction of cyclins also underlies the irreversible nature of the cell cycle. CDKs are also regulated by specific sites of phosphorylation on the CDKs themselves (Lundgren et al, 1991). For example, activation of the cyclin-dependent kinase CDK2 is dependent upon phosphorylation, by CDK-activating kinase (CAK), of threonine 160, which

moves a regulatory loop away from the CDK2 catalytic active site, thereby allowing access to substrate. In contrast, phosphorylation of tyrosine 15 on CDK2 (effected by kinases WEE1 or MIK1) acts to inhibit CDK2 enzymatic activity. In addition, removal of this inhibitory phosphate group can occur by the phosphatase CDC25 (Sebastian et al, 1993). Finally, a group of proteins termed cyclin-dependent kinase inhibitors (CDKIs) exist that can bind to and directly inhibit CDK activity or their activating phosphorylations (Peter and Herskowitz, 1994; Sherr and Roberts, 1995). Thus, although cyclins play major regulatory roles in orchestrating CDK activities, **CDKs are subject to additional levels of control** and, as might be expected, these processes are also commonly altered in cancer cells.

Cell Cycle Entry

Under normal conditions a cell will be induced to proliferate when the balance between growth-stimulatory signals received from its environment (e.g., soluble growth factors in the extracellular space) outweighs growth inhibitory signals (e.g., TGF-β). If the cell was in the G_0 state, it will proceed into **G_1, the first gap phase of the active cell cycle, during which sufficient macromolecules and organelles are synthesized to support cell replication.** Growth stimulatory signaling pathways (e.g., the RAS/RAF/MEK pathway) promote expression of the main G_1 cyclins, cyclin D and cyclin E, leading to their association with CDK4 and CDK6 kinases, thus activating these CDKs (Baldin et al, 1993; Winston and Pledger, 1993; Sherr et al, 1994). **Throughout early and mid-G_1, progress through the cell cycle remains sensitive to external signals, largely because persistent mitogenic stimulation is required for sustained expression of cyclin D** (Matsushime et al, 1991). Cyclin D is the main cyclin functioning early in G_1. Cyclin E is expressed later in G_1, peaking at the G_1S boundary, where its presence is required for S-phase entry (Dulic et al, 1992; Koff et al, 1992; Ohtsubo et al, 1995).

The Retinoblastoma Protein and the Restriction Point

Due to the dependence of cyclin D on the continued presence of mitogens and other favorable conditions (e.g., attachment to the substratum), the cell cycle remains responsive to external signals throughout early and mid-G_1 (Guadagno et al, 1993). However, **if the decision is made in late G_1 to continue on with cell division, then the subsequent phases of the cell cycle (S, G_2, and M) proceed in an autonomous fashion. This key point in time in late G_1, after which the cell cycle becomes insensitive to extracellular signals, is termed the restriction point (R point)** and is highly regulated (Pardee, 1974).

The retinoblastoma susceptibility protein, pRB, plays a central role in controlling the R point, and the inappropriate, continuous proliferation of cancer cells is largely due to a loss of R-point control, typically the result of functional inactivation of the RB pathway (Pardee, 1989). pRB is a member of a protein family termed pocket proteins that includes the closely related proteins TP107 and TP130. pRB is a substrate of G_1 cyclin/CDK complexes and its activity is critically dependent on its phosphorylation state (Buchkovich et al, 1989; Mittnacht et al, 1994; Sherr, 1994). **In nondividing cells, pRB is unphosphorylated and in this state pRB and the other pocket proteins physically associate with members of the E2F family of transcription factors, inhibiting their transcriptional activation of target genes required for cell cycle progression into S phase** (Lai et al, 1999b). In addition, pRB recruits proteins such as histone deacetylases (HDACs) to E2F target genes promoting the formation of repressive heterochromatin at these sites and pRB itself may play a role in maintaining this repressive chromatin state, further suppressing E2F target genes (Lai et al, 1999a, Gonzalo and Blasco, 2005). However, **during G_1, pRB becomes progressively phosphorylated, on 8 different sites, by cyclin D-CDK4/6 and cyclin E-CDK2 complexes, creating hyperphosphorylated pRB, causing its dissociation from E2F** (Fig. 18–8). The liberated E2F proteins, of which there are at least seven, heterodimerize with one of three DNA polymerase (DP) subunits (DP1-3) and activate transcription of target genes, including essential S-phase genes (e.g., DNA polymerase and S-phase cyclins) (Dyson, 1998). Notably, the cyclin E gene is an E2F target gene; thus once E2Fs become activated, a positive feedback loop is initiated, with further production of cyclin E reinforcing pRB hyperphosphorylation, which, in turn, frees additional E2F. In addition, activated E2F increases transcription of its own gene, thus providing another positive feedback loop. These autocatalytic cycles represent the molecular core of the R point. Beyond this point, pRB remains inactivated and the remaining cell cycle phases are unresponsive to either external mitogenic or antiproliferative signals. Once the cell cycle is complete, pRB returns to its unphosphorylated state, once more suppressing E2F until cell division is once again signaled (Ludlow et al, 1993).

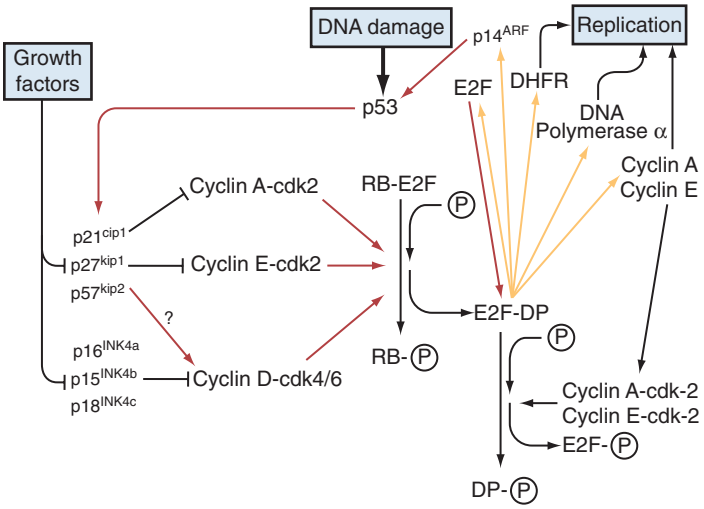


Figure 18–8. Schematic representation of the stimulatory and inhibitory cascade at the G_1S boundary. This finely tuned system takes advantage of multiple negative and positive feedback loops.

The *pRB* gene was initially characterized as the tumor suppressor gene responsible for disease susceptibility in familial retinoblastoma (thus the name) and, as is the case with many cancer predisposition genes, was also found to be compromised in sporadic retinoblastoma as well (Friend et al, 1986; Knudson, 1993). As outlined above, its central role as the gatekeeper of the R point in the cell cycle explains why pRB is also commonly altered in other cancers besides retinoblastoma. In fact, **it has been suggested that RB, or components of the regulatory pathway it is associated with (e.g., cyclins D and E, CDK4, E2F, TP16 and TP27), are likely to be altered in virtually all human cancers** (Sherr, 1996; Hanahan and Weinberg, 2000).

There are many ways, both direct and indirect, in which cancer cells inactivate pRB's function, including mutation or deletion of the *pRB* gene itself, silencing of the *pRB* gene by promoter DNA hypermethylation, overexpression of proteins such as cyclin D and E2F (in some cases due to increased copy number of the gene; gene amplification), as well as mutational inactivation, deletion, or promoter methylation of genes encoding specific CDK inhibitors (described below).

Retinoblastoma Protein and Genitourinary Malignancies

pRB gene mutations have been identified in approximately one third of bladder tumors (Horowitz et al, 1990), and reintroduction of the *pRB* gene into bladder carcinoma cell lines has been found to inhibit cell growth in vitro and tumor formation in vivo (Takahashi et al, 1991). Altered expression of pRB protein has been also identified in approximately one third of bladder carcinomas (Logothetis et al, 1992), and altered expression has been correlated with higher-stage disease and decreased patient survival (Cordon-Cardo et al, 1992).

Prostate carcinoma has not been as strongly linked to *pRB*. Although *pRB* mutations are present in 10% to 30% of prostate cancer specimens (Bookstein et al, 1990; Kubota et al, 1995), decreased expression is not consistently identified with high-risk patients or recurrent disease (Kibel and Isaacs, 2000). In other studies, no correlation was found between expression and grade or stage (Ittmann and Wieczorek, 1996), but Theodorescu and colleagues (1997), reported that low pRB protein expression correlated with decreased disease-specific survival in univariate and multivariate analysis.

Renal carcinoma has not been clearly linked to *pRB*. *pRB* is rarely inactivated in renal carcinoma cell lines or tumors (Ishikawa et al, 1991), and analysis of clinical specimens has not demonstrated a clear association between prognosis and *pRB* expression (Lipponen et al, 1995).

Cell Cycle Progression through S phase

During S phase, a normal cell replicates its diploid genome once and only once. S-phase genes are activated as a result of cyclin A replacing cyclin E to form cyclin A-CDK2 complexes in early S phase, and later by cyclin A associating with CDK1 forming cyclin A-CDK1 complexes in late S phase (Girard et al, 1991; Pagano et al, 1992). Upon completion of S phase, cyclin A-CDK2 phosphorylates E2F-DP heterodimers, thus terminating E2F's activity (Dynlacht et al, 1994). At the end of S phase, cyclin B replaces cyclin A, forming cyclin B-CDK1 complexes that move the cell into the second gap phase of the cell cycle, G_2, and on into mitosis (Pines and Hunter, 1989). It should be noted that the above description, although correct in outline, has been simplified. For example, there are actually multiple closely related cyclins within each cyclin class; thus there are actually three D-type cyclins (D1, D2, and D3), two E-type cyclins (E1 and E2), two A-type cyclins (A1 and A2), and two B-type cyclins (B1 and B2).

Mitosis

Although mitosis is the shortest of the cell cycle phases (lasting approximately 1 hour), it is one of the most complex and dramatic (Alberts, 2007). **During mitosis, the two genomic complements present following S phase are precisely partitioned into what will become two separate daughter cells.** The proper functioning of many of the proteins participating in mitosis depends upon phosphorylation of these substrates by cyclin B-CDK1. Early in mitosis, the chromosomes condense through the activity of condensin proteins. Each chromosome is tightly associated along its length with its corresponding S-phase copy, termed the sister chromatid, through cohesin proteins. When isolated and stained, these condensed metaphase chromosomes are used in karyotyping studies to look for numerical and structural chromosome aberrations. During this time also, two structures called centrosomes, which act as microtubule organizers, migrate to opposite poles of the nucleus and assemble spindle microtubules that radiate through the nucleus and attach to the condensed chromosomes at constriction sites termed centromeres, through complex protein matrices termed kinetochores. The nuclear envelope and supporting intermediate filament proteins, the nuclear lamins, dissociate in response to phosphorylation by cyclin B-CDK1. Balanced tension along the spindle microtubules causes all of the chromosomes to align along the cell midline, creating a hallmark stage of mitosis termed metaphase. Once all metaphase chromosomes are properly aligned, a protein complex termed the anaphase promoting complex (APC, not to be confused with the adenomatous polyposis coli gene, which is commonly mutated in colon cancer) is activated by cyclin B-CDK1. The APC, in turn, ubiquitinates a protein called securin, targeting it for destruction, which liberates separase protease from securin's inhibitory influence (Nasmyth et al, 2000). Once activated, separase functions to cleave the cohesin complexes, thus liberating the sister chromatids from one another, allowing microtubule-associated motors on the spindle microtubules to pull each diploid chromosome complement apart toward the centrosomes at opposite poles, a key mitotic event termed anaphase. One of the APC's substrates is cyclin B itself; thus by activating the APC, cyclin B initiates its own destruction (Deshaies, 1995). Lastly, two new nuclei are assembled around the two separated chromosome complements, which decondense, and two separate daughter cells are formed in a cell-splitting process termed cytokinesis.

Mitotic abnormalities are commonly seen in human cancers and were noted by David Hanseman in the late 1800s, soon after the discovery of chromosomes, and, in 1914, the eminent German biologist Theodor Boveri proposed that such abnormalities might underlie tumor formation (Harris, 2008).

Cyclin-Dependent Kinase Inhibitors

In addition to their dependence on cyclins and regulation by specific phosphorylations, CDK **activities are also subject to negative regulation by a set of seven proteins termed cyclin-dependent kinase inhibitors (CDKIs)**. CDKIs belong to either of two different classes: the CIP/KIP family, which includes the proteins TP21 (*CDKN1A*), TP27 (*CDKN1B*), and TP57 (*CDKN1C*); and the INK4 (*in*hibit CD*K4*) family, which includes TP15 (*INK4B*), TP16 (*INK4A*), TP18 (*INK4C*), and TP19 (*INK4D*). The CIP/KIP proteins are broadly acting, able to inhibit multiple cyclin-CDK complexes throughout the cell cycle (Clurman and Porter, 1998), while the members of the INK4 group are more restricted in their activities, inhibiting CDK4 and CDK6-containing complexes; thus they are critical regulators of the R point and the G_1S transition because they can block pRB phosphorylation (Fig. 18–8). **Increased expression and accumulation of CDKIs is used by the cell as a means of halting the cell cycle in response to various stresses.** For example, TP21 expression is

increased in response to DNA damage (el-Deiry et al, 1993). CDKIs function in nonstress situations as well. For example, TP27 levels are high in quiescent cells, and all of the CIP/KIP proteins appear to play some role in maintenance of the G_0 state in terminally differentiated cells (Halevy et al, 1995; Matsuoka et al, 1995). Interestingly, mice engineered with a homozygous deletion of the *TP27* gene grow more quickly, exhibit hyperplasia in multiple organs, and are cancer prone (Fero et al, 1996). In addition to increased expression in order to inhibit cell cycle progression, CDKIs can also be oppositely regulated by proteolytic degradation—for example, the targeted elimination of *TP27* upon mitogenic stimulation (Ohtsubo et al, 1995).

Among the *INK4* family, inactivating mutations and abnormal methylation of *TP15* and *TP16* have been strongly implicated in cancer in general (Kamb et al, 1994; Hirama and Koeffler, 1995) and specifically in genitourinary malignancies (Cairns et al, 1995; Herman et al, 1995). The best studied of the INK4 proteins is TP16. The gene was initially found mutated and deleted in a wide variety of tumors including bladder and kidney (Kamb et al, 1994). Subsequent analysis has demonstrated that **inactivation often occurs by DNA hypermethylation at the *TP16* promoter,** an alternative method of gene inactivation (Merlo et al, 1995). Interestingly, the same *CDKN2A* locus codes for an entirely different gene product, $TP14^{ARF}$, the coding sequence of which partially overlaps with the *TP16* coding sequence but uses a separate gene promoter and is translated using an alternate reading frame (Quelle et al, 1995). **TP14 modulates the TP53 tumor suppressor pathway, serving to stabilize TP53 protein** by inhibiting the ubiquitin ligase HDM2 (Mdm2 in the mouse) which normally tags TP53 for destruction. TP14 binds to HDM2 directly inhibiting it, as well as sequestering it in the nucleolus, a subcompartment within the cell nucleus (Honda and Yasuda, 1999; Llanos et al, 2001). In addition, TP14 can also bind to E2F transcription factors, inhibiting them and inducing their degradation (Rizos et al, 2007). The *TP15* gene lies just adjacent to the *TP16* gene on the short arm of chromosome 9 (9p21), and therefore was deleted in many of the same tumors and cell lines that lost *TP16* (Hannon and Beach, 1994). However, *TP15* does not appear to play as strong a role in tumorigenesis as *TP16* (Stone et al, 1995).

The *TP16* gene is frequently inactivated by deletion in bladder carcinomas (Cairns et al, 1995; Williamson et al, 1995). Importantly, despite its proximity, the *TP15* gene was ruled out as the primary tumor suppressor at this site because it was not within the deletion interval. A study by Orlow and colleagues (1999) found that deletion and methylation of the *TP16* gene occurred frequently in superficial bladder carcinoma, but only those deletions that affect both the *TP16* and *TP14*ARF genes correlated with a decrease in disease-free survival.

Mutational inactivation of *INK4* family members appears to be rare in prostate carcinoma. Komiya and associates (1995) identified a mutation of *TP16* in only 1% of clinical specimens. Park and associates (1997) examined primary prostate carcinomas for mutations in *TP16, TP15,* and *TP18* and identified one mutation in *TP16*. In contrast, inactivation of *TP16* by hypermethylation has been implicated in prostate cancer. Herman and associates (1996; 1995) demonstrated hypermethylation of *TP16* in 60% of prostate cancer cell lines, whereas *TP15* was rarely inactivated. However, these results are tempered by observations that *TP16* gene silencing by promoter hypermethylation often occurs during the establishment of cell lines.

Despite the critical role that CIP/KIP family members play in G_1S cell cycle arrest, they are rarely mutated in a wide variety of malignancies, including genitourinary tumors, and there are only rare reports of promoter hypermethylation (Shiohara et al, 1994; Kawamata et al, 1995). However, expression of this family of CDK inhibitors plays an important role in cancer in general (Catzavelos et al, 1997; Loda et al, 1997; Yatabe et al, 1998), and in genitourinary carcinomas in particular. Stein and associates (1998) found increased expression of *TP21* in 64% of bladder tumors and that increased expression was associated with decreased probability of tumor recurrence and improved patient survival. Decreased *TP27* expression has also been linked to increasing tumor grade, pathologic stage, and poor survival in bladder carcinoma (Del Pizzo et al, 1999).

The expression of *TP21* in prostate cancer has not demonstrated a clear correlation with advanced disease or poor outcome (Kibel and Isaacs, 2000). However, specific genetic polymorphisms in *TP21* and *TP27* have been associated with advanced disease (Kibel et al, 2003), and altered expression of *TP27* has been implicated in aggressive disease in multiple studies. Cordon-Cardo and colleagues (1998) examined radical prostatectomy specimens and found that absent or low *TP27* expression by immunohistochemistry was an independent risk factor for decreased disease-free survival by multivariate analysis. Cote and colleagues (1998) found that decreased *TP27* nuclear staining not only correlated with decreased disease-free survival but also overall survival in radical prostatectomy patients, while Freedland and colleagues (2003) found that *TP27*-positive cells in the prostate needle-biopsy specimen had a 2.5-fold increased risk of biochemical recurrence (prostate-specific antigen [PSA] relapse).

The relevance of TP27 to prostate cancer is also supported by studies of mouse models. For example, mice deficient in TP27 develop prostate hyperplasia, confirming the potential importance of this gene in prostate tissue homeostasis (Cordon-Cardo et al, 1998). More excitingly, studies have shown that mice deficient in both TP27 and Pten have a high incidence of prostate cancer (Di Cristofano et al, 2001).

Cell Cycle Checkpoints

Although beyond the R point the cell cycle functions autonomously, in a unidirectional manner, the cell is still capable of halting its progress at various points should adverse conditions arise. Thus **a number of so-called "checkpoints," first discovered in yeast, have been identified, the two primary ones being the G_1S, and G_2M checkpoints** (Weinert and Hartwell, 1988). These checkpoints are primarily **tasked with monitoring the completion of key events in the cell cycle, although genomic integrity is also closely monitored** (Hartwell et al, 1994). **Loss of checkpoint control can allow inappropriate cell division to occur and also facilitates genetic instability, two key contributors to cancer progression. Indeed, inherited mutations in several of the genes involved in cell cycle checkpoint control (e.g., *TP53* and *ATM*) cause familial cancer predisposition syndromes.**

The G_1S Checkpoint

As previously mentioned, the expression of cyclin D during G_1 is dependent upon the integration of both pro- and antiproliferative signals received from the extracellular environment (e.g., mitogens, nutrient and oxygen availability, etc.); thus the cell will not fully commit to division unless it receives a sustained signal to do so and conditions remain favorable (Matsushime et al, 1991).

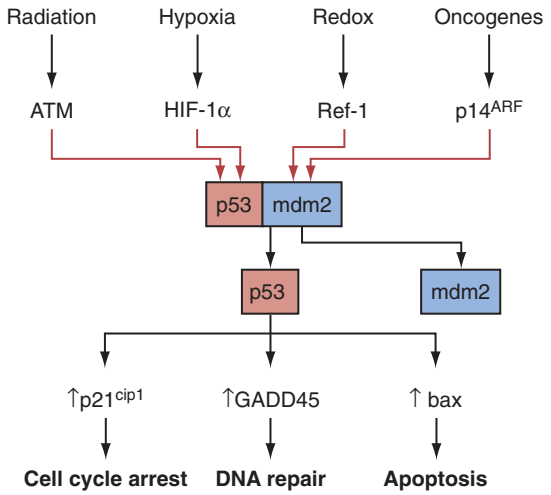


Figure 18–9. TP53 plays a central role in the cell's response to extracellular stimuli. Radiation, hypoxia, redox reactions, and oncogenes can all increase TP53 activity through different mechanisms. In response, the cell initially stops dividing and then attempts to repair the DNA damage. If it fails to repair the DNA, it undergoes apoptosis (programmed cell death). These functions are mediated through transcriptional activation of a variety of genes, some examples of which are indicated in the figure.

A critical contributor to the G_1S checkpoint is the TP53 protein. As discussed elsewhere in more detail, **the TP53 tumor suppressor is a pleiotropic transcription factor that receives signals from multiple types of cell stress and damage and, in response, activates genes that function variously in cell cycle arrest, DNA damage repair, and apoptosis (programmed cell death), thus highlighting the link between cell cycle arrest and DNA repair** (Elledge, 1996) (Fig. 18–9). DNA damage has obvious relevance for the G_1S checkpoint because a normal cell will not proceed to S phase if the genomic template DNA is damaged, thus **intact checkpoint controls represent important antitumor mechanisms acting to limit the proliferation of cells bearing potentially oncogenic mutations.** During the cellular response to damaged DNA, specific kinases are activated that phosphorylate the TP53 protein, thereby protecting it from HDM2 ubiquitin ligase–mediated degradation (Momand et al, 1992). The accumulated TP53 undergoes further modifications that serve to activate it and facilitate its translocation to the nucleus, where it induces various checkpoint and DNA repair proteins. TP53 target genes that facilitate the G_1S checkpoint include *TP21* and *14-3-3-sigma*, which cause cell cycle arrest by inactivating or sequestering G_1 CDK complexes (Giaccia and Kastan, 1998). **If the cell cannot arrest growth and/or repair the DNA damage, TP53 often induces apoptosis** (Levine, 1997).

S-Phase Arrest

Whereas S phase is not considered to have a checkpoint per se, such as those recognized during G_1S and G_2M, the cell does maintain the ability to arrest the cell and repair DNA damage through two mechanisms, both mediated through the ATM kinase. In response to genotoxic insults, CDC25A is ubiquitinated through an ATM-dependent cascade, resulting in a rapid decrease in CDC25A levels. Because CDC25 family members normally activate CDK2, the loss of CDC25A function maintains CDK2 in its inactive form, preventing its phosphorylation of substrates required for DNA synthesis. Inactive CDK2 prevents CDC45 from recruiting DNA polymerase. Thus this cascade pauses the cell in S phase, ostensibly to allow time for DNA repair (Bartek et al, 2004).

The second mechanism mediated by ATM in response to DNA damage is phosphorylation of DNA repair enzymes (see DNA Repair). These two parallel pathways further highlight the interaction between DNA repair and checkpoint control. It is not surprising that such S-phase control has been documented in response to DNA-damaging agents, because it is the last opportunity to repair DNA damage before replication (Falck et al, 2002; Pichierri and Rosselli, 2004). Notably, the cascade does not appear to be mediated by TP53 and therefore is an intriguing potential target for therapy in the future (Kastan and Bartek, 2004).

G_2M Checkpoint

The G_2M checkpoint is a second major point of control during cell division. Unlike the G_1S checkpoint, which responds to a variety of extracellular signals in addition to DNA damage, **the G_2M checkpoint appears to be similar to S-phase arrest and responds only to DNA damage. It therefore serves as an important monitor of DNA replication errors** (Weinert, 1997; Bartek et al, 1999).

DNA damage secondary to radiation is believed to induce G_2M arrest through ATM. ATM activates CHK1 and CHK2 kinases in response to DNA damage, and these, in turn, inactivate the CDC25 family proteins through phosphorylation, which causes 14-3-3-sigma to bind and sequester it (Hermeking et al, 1997; Sanchez et al, 1997). There are three CDC25 proteins, primarily functioning at the G_1M and S-phase checkpoints as outlined previously, whereas CDC25B and CDC25C primarily function at the G_2M checkpoint. CDC25B/C phosphorylation disallows their activation of CDC2, therefore inhibiting the cyclin B and cyclin A-CDC2 complexes (Mailand et al, 2002; Donzelli and Draetta, 2003).

It has become apparent that, at least in part, G_2M arrest may also be mediated by TP53 and the BRCA1 tumor suppressor (Bunz et al, 1998; Xu et al, 2001). Transcriptional upregulation of cell cycle inhibitors (e.g., TP21, GADD45, and 14-3-3-sigma) by TP53 helps maintains the cell in G_2M arrest (Nyberg et al, 2002). As a result, **it appears that TP53 mediates both G_1S and G_2M arrest, consistent with its critical role in preserving genomic integrity.**

Mitotic Arrest: Spindle Assembly Checkpoint

As detailed earlier, **one of the key events in mitosis is the proper attachment of each and every chromosome to the spindle microtubule apparatus.** It is critical that all chromosomes are attached before proceeding into anaphase where the chromosome complements are pulled apart. Failure of one or more chromosomes to attach leads to chromosome nondisjunction, wherein one daughter cell receives an extra copy of the chromosome, becoming trisomic for that chromosome, while the other receives one copy too few, becoming monosomic. Both cases are abnormal and fall under the category of aneuploidy, a nearly universal characteristic of human solid tumors. Gene expression patterns often correlate with gene copy number; thus the widespread change in gene dosage due to gains or losses of entire chromosomes can lead to profound imbalances in the expression

of hundreds or thousands of genes and, as such, it has been proposed that aneuploidy may be a major contributor to cancer initiation and progression (Duesberg et al, 1999; Duesberg, 2005). **The mitotic checkpoint (spindle assembly checkpoint) apparatus monitors chromosome attachment and receives a "not ready" signal from any unattached chromosomes, preventing activation of the APC complex, thus blocking the transition from metaphase to anaphase until all chromosomes are attached** (Chan et al, 1999; Holland and Cleveland, 2009). Although mutations have been identified in specific mitotic checkpoint genes, such as hBUBR1, in some cancers (Cahill et al, 1998), subsequent studies have shown these to be relatively rare (Wang et al, 2008b). Additional studies have found aberrant expression levels of mitotic checkpoint proteins, which may better explain the mitotic instability frequently observed in cancer cells (Yuan et al, 2006), including reports of reduced levels of the checkpoint proteins MAD1 and MAD2 in renal cell carcinoma (Pinto et al, 2007) and reduced MAD2 in testicular cancer (Fung et al, 2007).

Key Points: The Cell Cycle

- The cell cycle consists of an ordered, unidirectional series of events, the main goal of which is to replicate the cell's genome and partition one copy into each of two resulting daughter cells.
- The cell cycle is divided up into 4 phases; G_1, S, G_2, and M phase. The transition from G_1 into S is critically dependent on phosphorylation of the pRB tumor suppressor protein. Mutations in *pRB* are common in some urologic malignancies.
- Phase-specific phosphorylation of substrate proteins by cyclin-dependent kinases (CDK) orchestrate progression through the cell cycle.
- The activities of CDKs are dependent upon their association with specific cyclin proteins. Cyclins accumulate and are rapidly degraded in a phase-specific manner, thus assuring the proper sequencing and irreversibility of key events throughout the cell cycle.
- Primary points of cell cycle control are the G_1S and G_2M checkpoints. Checkpoints employ cyclin-dependent kinase inhibitor proteins (CDK1) to pause the cell cycle in response to a variety of stress signals, including DNA damage, cell–cell contact, cytokine release, and hypoxia.
- The TP53 tumor suppressor protein is a key player in cell cycle checkpoints, responding to DNA damage by signaling cell cycle arrest and repair of the damage. If the DNA damage cannot be repaired, TP53 may trigger cell death (apoptosis).
- *TP53* is the most commonly mutated gene in cancer and plays a prominent role in genitourinary malignancies.
- Defects in cell cycle checkpoints lead to unregulated cell proliferation and genetic instability.

DNA METHYLATION

The covalent modification of the C-5 position of cytosine is mediated by DNA (cytosine-5) methyltransferase, resulting in the formation of 5-methylcytosine. This enzymatic conversion is an epigenetic modification of DNA that occurs in vertebrates and is essential for normal embryonic development (Jones, 1986; Bird, 1992). Methylation of cytosine occurs primarily at the CpG palindrome in DNA. The presence of 5-methylcytosine at CpG dinucleotides has resulted in a significant depletion of this sequence from the genome during the course of vertebrate evolution (Schorderet and Gartler, 1992). This reduction in frequency of CpG dinucleotides in the genome is the result of spontaneous deamination of 5-methylcytosine to thymine (Rideout et al, 1990; Sved and Bird, 1990). Certain areas of the genome do not show a depletion of the CpG dinucleotide and contain the expected frequency of this sequence. These regions are referred to as CpG islands and comprise approximately 1% of vertebrate genomes, yet account for approximately 15% of the total number of CpG dinucleotides in DNA (Bird, 1986; Gardiner-Garden and Frommer, 1987). CpG islands are typically located upstream of many housekeeping and tissue-specific genes. Methylation of cytosines within CpG islands is believed to affect gene function by altering transcription (Cedar, 1988). Hypermethylation of CpG islands results in transcriptional downregulation, while hypomethylation of these regions may increase the potential for gene activity.

CpG islands located in the promoter regions of tumor suppressor genes are normally unmethylated. Abnormal methylation of these regions may result in a progressive reduction in gene expression, thus altering normal cellular growth control. Methylation of CpG islands may lead to decreased gene expression by mechanisms including: disruption of local chromatin structure, inhibition of transcription factor binding, or exclusion of transcriptional machinery from methylated promoter DNA (Bird and Wolffe, 1999). The epigenetic properties of methylation may therefore affect gene activity without altering the DNA sequence.

Changes in global levels and regional patterns of DNA methylation are among the earliest and most frequent events known to occur in human cancer (Jones and Baylin, 2002). Alterations in DNA methylation have a direct impact on mutational and epigenetic components that may contribute neoplastic transformation. **Three major pathways by which DNA methylation may result in genetic dysregulation in human caner include (1) inherent mutational effects of 5-methylcytosine, (2) epigenetic effects of promoter methylation on gene transcription, and (3) potential gene activation and induction of chromosomal instability by DNA hypomethylation** (Gonzalgo and Jones, 1997; Jones and Gonzalgo, 1997).

DNA Methylation and Prostate Cancer

Glutathione-S-transferases belong to a superfamily of enzymes responsible for detoxification of a wide range of xenobiotics. These enzymes catalyze the nucleophilic attack of reduced glutathione on electrophilic compounds. **Aberrant methylation of the CpG island at the glutathione-S-transferase Pi (*GSTP1*) locus is the most frequent somatic genome alteration reported in prostate cancer** (Lee et al, 1994; Jeronimo et al, 2001). Methylation of *GSTP1* has been detected in greater than 90% of prostate carcinomas and approximately 70% of prostatic intraepithelial neoplasin (PIN) lesions, but is not present in normal prostate tissue or benign prostatic hyperplasia (Lee et al, 1994). In normal prostate tissue, expression of *GSTP1* is limited to basal cells, but it can be upregulated in columnar epithelial cells exposed to oxidative stress. Increased levels of DNA methylation have also been associated with worse clinical outcomes in patients with prostate cancer (Maruyama et al, 2002).

The *RAS* association domain family protein 1, isoform A (*RASSF1A*) gene is located on chromosome 3p21. *RASSF1A* is a

tumor suppressor gene that is frequently altered in a variety of human cancers. Abnormal methylation of *RASSF1A* has been reported to occur in 60% to 70% of prostate carcinomas (Kuzmin et al, 2002). Loss of heterozygosity (LOH) of the 3p21 region is associated with methylation and silencing of the remaining *RASSF1A* allele during tumorigenesis. Methylation of *RASSF1A* has been observed more frequently in higher grade prostate cancers compared with less aggressive tumors (Liu et al, 2002).

Role of DNA Methylation in Bladder Cancer

The *TP53* tumor suppressor gene plays a critical role in a variety of growth regulatory mechanisms involving cell cycle, apoptotic, senescence, and angiogenic pathways (Smith et al, 2003). Mutations of the *TP53* gene are present in more than half of all human malignancies. Approximately 24% of point mutations in the *TP53* gene are C→T transitions located at CpG dinucleotides (Greenblatt et al, 1994). Many of the mutational hotspots found in the *TP53* gene occur at CpG dinucleotides that are methylated, thus implicating 5-methylcytosine as an endogenous mutagen in the genome (Rideout et al, 1990; Tornaletti and Pfeifer, 1995). Mutational inactivation of *TP53* is a frequent event in urothelial dysplasia, carcinoma in situ (CIS), and invasive bladder cancer (Spruck et al, 1994b).

The presence of DNA methylation at CpG dinucleotides within the *TP53* gene is associated with many mutational hotspots found within this gene. The contribution of DNA methylation to these mutational events is be variable depending upon the type of bladder cancer and the etiologic agent believed to be responsible for tumor formation (Jones et al, 1998). Urothelial carcinomas in Western countries and Japan have relatively few mutations at CpG sites, suggesting that DNA methylation may not play a major role in inducing these changes. In contrast, a higher frequency of mutations at CpG dinucleotides consistent with 5-methylcytosine deamination is observed in patients with squamous cell carcinoma, and urothelial carcinoma with a history of exposure to phenacetin or arsenic (Jones et al, 1998). Although the exact mechanisms responsible for variability of the *TP53* mutational spectra are not fully understood, these observations highlight the potential mutagenic effects of DNA methylation upon the genome and the contribution of methylation to *TP53* inactivation during bladder carcinogenesis.

TP16 Methylation in Bladder Cancer

The cyclin-dependent kinase inhibitor 2A (*TP16/CDKN2A/INK4a*) is a tumor suppressor gene found on chromosome 9p21. The protein product TP16 binds to cyclin-dependent kinases 4 and 6 and inhibits their interaction with cyclin D1, which normally mediates passage through G_1 phase of the cell cycle by phosphorylation of the protein product of the retinoblastoma gene (*RB*) (Serrano et al, 1993). Unphosphorylated RB exerts its cell cycle inhibitory effects through binding of regulatory proteins that normally stimulate genes required for cellular proliferation. Inactivation of the *TP16* may occur by a variety of mechanisms including deletion, mutation, and promoter methylation (Spruck et al, 1994a; Gonzalez-Zulueta et al, 1995; Herman et al, 1995). Mutation or deletion of one *TP16* allele and concurrent methylation of the remaining allele may result in loss of functional activity. Methylation of *TP16* has been observed in 27% to 60% of primary urothelial carcinomas (Chan et al, 2002; Chang et al, 2003). Epigenetic changes are among the earliest molecular events associated with transformation and may therefore precede morphologic alterations in cellular architecture.

The first detailed study investigating the effects of *TP16* promoter methylation on transcriptional activity was performed in bladder cancer cells (Gonzalgo et al, 1998). A reduction in *TP16* expression was associated with higher levels of methylation in the upstream promoter region. Methylation of specific CpG sites in the *TP16* promoter was shown to significantly down regulate transcriptional activity in a chloramphenicol acetyltransferase (CAT) assay (Gonzalgo et al, 1998). Administration of the demethylating agent 5-aza-2′-deoxycytidine (5-aza-CdR) was capable of reactivating *TP16* expression in bladder cancer cells that were previously shown to contain methylated alleles of the gene. Methylation in exon 2 of the *TP16* gene is also a frequent occurrence in a variety of cancers and is an excellent marker for transformation. Presence of methylation in this region of the *TP16* gene, however, does not affect *TP16* transcription in bladder cancer cells (Gonzalgo et al, 1998).

Hypermethylation of Genes in Bladder Cancer

The E-cadherin (*CDH1*) gene encodes a transmembrane glycoprotein that modulates calcium-dependent intercellular adhesion in epithelial tissues. Methylation of the CpG island located in the *CDH1* promoter is associated with decreased gene expression in high-grade urothelial carcinoma, including disease associated with carcinoma in situ (Graff et al, 1995; Horikawa et al, 2003). *CDH1* methylation has also been reported in histologically normal urothelium; however, many of these cases were from patients older than 70 years of age and may be related to a potential link between methylation and aging (Ahuja and Issa, 2000; Bornman et al, 2001). Lower levels of *CDH1* expression resulting from promoter hypermethylation may increase β-catenin/TCF activity and proliferation in urothelial carcinomas (Maruyama et al, 2002; Thievessen et al, 2003).

Methylation of *RASSF1A* has been reported in up to 97% of primary bladder tumors (Lee et al, 2001). High tumor grade, nonpapillary growth pattern, and muscle invasive disease are associated with *RASSF1A* promoter methylation in bladder cancer (Maruyama et al, 2001). Downregulation of *RASSF1A* expression in bladder cancer cell lines and primary tumors by aberrant promoter hypermethylation suggests that epigenetic inactivation of this gene may play an important role in bladder carcinogenesis.

Hypomethylation in Bladder Cancer

Global DNA hypomethylation and gene-specific hypermethylation are frequent events in tumorigenesis (Jones and Baylin, 2002). **Hypomethylation may result in genomic instability through alterations in chromatin structure, recombination between repetitive elements, or reexpression of retrotransposons** (Baylin et al, 2001). Methylation of CpG sites is normally maintained by the enzymatic activities of DNA methyltransferase 1 (DNMT1), while de novo methylation of CpG sites is mediated by DNA methyltransferases 3A and 3B (DNMT3A, DNMT3B) (Jones and Baylin, 2002). **One important role for methylation is genomic imprinting, which results in monoallelic gene expression without altering the genetic sequence.** Loss of imprinting (LOI) is a reduction in the methylation of the normally methylated allele, which can

lead to activation of the normally silent copy of a growth-promoting gene (Feinberg and Tycko, 2004). This phenomenon has been reported for the human insulin-like growth factor-2 gene (*IGF2*) in a variety of cancers (Woodson et al, 2004; Sakatani et al, 2005).

Methylation of long interspersed nuclear element (L1 LINE) sequences is reduced in bladder cancer cell lines and primary tumors compared with normal bladder mucosa (Jurgens et al, 1996). DNA methyltransferase expression, however, did not correlate with methylation status of cell lines, and methyltransferase activity was reduced in quiescent cells suggesting that aberrant expression of *DNMT1* does not account for the altered methylation patterns found in urothelial carcinoma (Jurgens et al, 1996). Decreased *DNMT1* expression and induction of *DNMT3A* and *DNMT3B* in bladder cancer has also been reported (Kimura et al, 2003). These data suggest that downregulation of *DNMT1* expression may be at least partly responsible for hypomethylation of repetitive elements in bladder cancer. Although the exact mechanisms underlying the dysregulation of methyltransferase activity during malignant transformation are not well defined, the enhanced cellular proliferation observed in bladder cancer does not appear to be accompanied by an appropriate increase in *DNMT1* expression. Dysregulation of this process in combination with other factors may determine the extent of DNA hypomethylation during cancer development.

Key Points: DNA Methylation

- Methylation occurs specifically at CpG dinucleotides in the genome. The presence of 5-methylcytosine in DNA can result in spontaneous deamination to thymine and formation of C→T transition mutations.
- DNA methylation can affect gene function by mutational events or epigenetic mechanisms. Methylation of CpG islands associated with the promoter region of genes may result in down-regulation of transcription and suppression of gene expression.
- Loss of methylation of normally methylated genes can lead to the potential for gene expression.

DNA DAMAGE AND REPAIR

Cancer is fundamentally a genetic disease. Alterations in numerous genes provide the malignant cell the means to activate cancer-associated pathways and inactivate tumor suppressive barriers, making possible the acquisition of the key set of attributes associated with the cancer phenotype. **The intrinsic accuracy of DNA polymerase coupled with associated error-correction mechanisms keeps the error rate during DNA replication to an astonishingly low estimated value of approximately three incorrect bases per cell division, this in a genome of over three billion bases! And yet, cancer causing changes occur in oncogenes and tumor suppressor genes by epigenetic, mutational, and copy number alterations.** Many of these genetic changes are thought to result from a variety of endogenous (e.g., mitochondrial respiratory byproducts) and exogenous (e.g., chemicals, radiation, etc.) DNA-damaging agents that constantly assault the genome (Ames and Gold, 1991, 1998). To counter these threats, our cells employ a plethora of defensive mechanisms, including free-radical scavengers such as alpha-tocopherol, vitamin C, carotenoids, bilirubin and urate, as well as protective enzymes such as superoxide dismutases, glutathione peroxidases, and glutathione transferases that serve to detoxify a wide range of carcinogens (Mates and Sanchez-Jimenez, 1999; Finkel and Holbrook, 2000). Loss of expression, due to promoter hypermethylation, of the glutathione-S-transferase Pi enzyme encoded by the *GSTP1* gene is observed in the vast majority of prostate cancer cases (Lee et al, 1994; Lin et al, 2001), and recent studies have found associations between genetic polymorphisms in GSTs and the risk of biochemical recurrence in prostate cancer patients (Nock et al, 2009). Epidemiologic and retrospective studies on prostate cancer risk have found a protective effect for selenium, which is used as a cofactor by glutathione peroxidases (Lowe and Frazee, 2006; Colli and Amling, 2009), raising hope that dietary intervention might be protective against prostate cancer. However, a recent large clinical trial showed no benefit for dietary supplementation with selenium (Hatfield and Gladyshev, 2009), and it now appears that selenium's observed protective effects may be limited to men with low selenium levels at baseline. Results from other clinical chemoprevention trials in prostate cancer have, unfortunately, been similarly disappointing (Gaziano et al, 2009).

Despite the presence of detoxification systems such as those just described, DNA damage routinely occurs. For example, it has been estimated that each cell's genome experiences on the order of 10,000 lesions per day from reactions with oxidative species alone (Ames et al, 1993). Other processes, such as spontaneous loss of individual DNA bases (depurination and depyrimidination), as well as spontaneous deamination of bases, also occur at appreciable rates. **Thus, in addition to damage prevention, the cell employs a host of DNA repair systems as well.** The set of pathways dealing with DNA damage recognition and repair is **referred to as the DNA damage response, or DDR,** and encompasses a plethora of genes whose protein products are involved in ensuring the fidelity of DNA replication. The DDR includes the replication machinery itself (with its associated proofreading capability), as well as the many components of specific DNA repair systems such as base-excision repair, nucleotide-excision repair, double-strand break repair, and mismatch repair described in detail below (Loeb, 1998; Schmutte and Fishel, 1999) (Fig. 18–10).

As previously mentioned, **the cell cycle and the DDR are closely integrated. In response to DNA damage, the first step is to arrest the cell cycle so that the DNA can be repaired. It is therefore not surprising that there is substantial overlap between the initiators of DNA repair and cell cycle arrest** (Kastan and Bartek, 2004). For example, ATM and ATR kinases are both activated in response to DNA damage, and both activate TP53, CHK1, and other proteins critical to cell cycle arrest (Bartek and Lukas, 2003). In addition, both recruit and activate various DNA repair factors, such as MRE11, BLM, NBS1, BRCA1, BRCA2, RAD51, FANCD2, and RPA to sites of damage (Zou and Elledge, 2003; Kitagawa et al, 2004).

Considering the number of genetic changes calculated to be required for cancer development, as well as the large number of changes actually observed in cancer cells, and also taking into account the extraordinarily low spontaneous mutation rates in normal human cells, Loeb and colleagues concluded that the spontaneous mutation rate is insufficient to explain the number of mutations observed in the majority of human cancers. Loeb hypothesized that early in the process of tumorigenesis

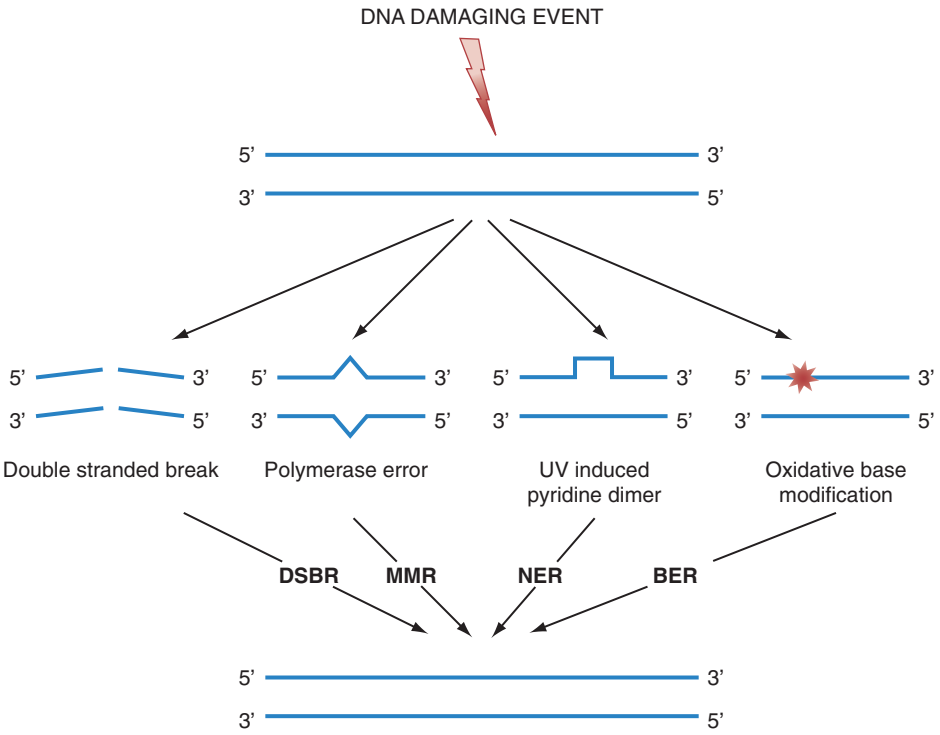


Figure 18–10. Schematic of different DNA damaging events and repair mechanisms.

preneoplastic cells might develop defects in one or more of the genes responsible for the fidelity of DNA replication (Loeb et al, 1974; Loeb, 1991; Cheng and Loeb, 1993). Such a defect would then lead to an increased mutation rate resulting in a so-called "mutator phenotype." This hypothesis gains further support from observations that most cells of proliferating tissues, such as epithelial tissues (the source of the vast majority of human cancers), are relatively short lived, being eliminated either by cell shedding or apoptosis. Thus the target population of cells at risk for becoming cancerous is far less than the total number of cells in the body, yet cancers are certainly not uncommon. In addition, cells with a "hypermutable" phenotype are often more difficult to treat because the selection pressure of therapy may rapidly select tumor cells with mutations conferring resistance (Tlsty et al, 1989).

The term mutator phenotype is generally used to refer to defects in the DNA replication and repair proteins, resulting in relatively small-scale errors in the DNA sequence, such as single base substitutions, deletions, and duplications. Despite (or perhaps because of?) the many potential targets for mutator genes, few such genes have been found to be consistently mutated in significant proportions of common human cancers, a notable exception being the mismatch repair pathway. Mismatch repair defects are the underlying cause of hereditary nonpolyposis colorectal cancer (HNPCC) (Aaltonen et al, 1993), and have also been reported in as many as 15% of sporadic colon cancers (Liu et al, 1995). There have been reports of mismatch repair defects (usually gauged by measuring instability in so-called microsatellite sequences) in cancers other than colon cancer (Eshleman and Markowitz, 1995), but, as yet, it remains to be determined to what extent mismatch repair defects contribute to the overall development of sporadic tumors. Indeed, the relevance of the postulated mutator phenotype itself, as originally outlined, remains a hotly debated topic, with authors such as Tomlinson and Bodmer 1999 arguing that clonal expansion and selection in the absence of any raised mutation rate are sufficient to account for the number of mutations observed in cancer cells (Tomlinson et al, 1996). Furthermore, other researchers have calculated higher basal spontaneous mutation rates than those which led Loeb to consider the need for a mutator phenotype (Simpson, 1997). It is intriguing however that **many recessively inherited cancer predisposition syndromes (e.g., xeroderma pigmentosum, Bloom syndrome, Werner syndrome, ataxia telangiectasia, hereditary breast and colon cancer syndromes, etc.) are caused by defects in genes involved with DNA maintenance and repair, thus strongly implicating hypermutability in cancer causation** (Modrich, 1994; Sancar et al, 1996; Patel et al, 1998).

Although defects in DNA repair genes in sporadic malignancies, including genitourinary tumors, have been identified, Loeb's concept of the mutator phenotype, as originally stated, has yet to be fully evaluated, and it currently appears that it may not be a major player in the development of the majority of common sporadic human cancers. **If, however, one broadens the mutator concept to include systems involved in *chromosomal* stability, then it may become widely applicable**. At any rate, **the current consensus is that genetic instability of *some* sort is required for cancer development.**

Nucleotide Excision Repair

NER is a major defense against DNA damage caused by ultraviolet (UV) radiation and chemical exposure. NER acts on a wide range of alterations that result in large local distortions in DNA, by recognizing distortions in the DNA helix, excising the damaged DNA, and replacing it with the correct sequence (Wood, 1997).

The study of three syndromes—xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy—associated with inborn defects in proteins essential to NER has been critical to expanding our understanding of this pathway (Hoeijmakers,

2001). Patients with xeroderma pigmentosum, caused by defects in one of eight distinct genes, have a risk of skin cancer that approaches 100% by 20 years of age. The increased cancer risk is linked to exposure to ultraviolet radiation. That these patients are at such a profound risk for developing malignancies demonstrates the fundamental importance of NER in protecting DNA from cancer-causing mutations (Kraemer, 1997). In contrast, skin cells of patients with Cockayne syndrome and trichothiodystrophy are particularly sensitive to lesion-induced apoptosis. Intriguingly, the result is accelerated aging but no predisposition to cancer (Hoeijmakers, 2001).

NER requires at least a dozen proteins in humans, including: RPA, XPA-XPG, and TFIIH (Mu et al, 1997; Sancar et al, 2004). DNA damage that produces a substantial distortion in the DNA helix, such as UV-induced thymidine dimers, is recognized by XPA, which binds to the damaged DNA and recruits the other enzymes critical for DNA repair. XPA forms a complex with replication protein A (RPA) and then recruits the transcription complex TFIIH. This protein complex has helicase activity, which allows the complex to unwind the damaged DNA. A 24- to 32-bp segment of DNA is then excised by exonucleases, and the excised sequence is replaced by DNA polymerase delta or epsilon. The newly synthesized DNA is then ligated into place (Wood, 1997; Sancar et al, 2004). A special subtype of NER called transcription-coupled repair (TCR) focuses on the template strand of actively transcribed genes.

Base Excision Repair

The BER pathway repairs damage caused by a variety of events including spontaneous deamination of bases, radiation, oxidative stress, alkylating agents, or replication errors. In particular, the pathway is critical for repair of oxidative lesions caused by reactive oxygen species (ROS). Unlike NER, lesions recognized by BER do not tend to create major distortions in the DNA molecule. Because ROS are a normal byproduct of metabolism, loss of BER repair is particularly detrimental in the fidelity of DNA. ROS react with DNA to produce DNA base modifications, and the modified bases often mispair during DNA replication, resulting in mutations (Croteau and Bohr, 1997).

As the name implies, the initial step in BER is the removal of a base rather than a nucleotide. The key element of the repair is the recognition of the modified bases by one of several DNA glycosylases (Krokan et al, 1997). Many DNA glycosylases are nonspecific and remove several structurally different damaged bases while others have specific substrates. Each glycosylase identifies the damaged base, cleaves the N-glycosidic bond between the target base and the DNA deoxyribose backbone, thus releasing the damaged base, leaving an apurinic/apyrimidinic (AP) site (Wyatt et al, 1999; Bruner et al, 2000).

There are two forms of BER: short patch repair and long patch repair. In a short patch repair of one nucleotide, a 5′ endonuclease termed APE1 and the 3′ phosphodiesterase activity of polymerase-β excise the remaining base-free sugar, and then DNA polymerase-β fills in the single nucleotide gap (Beard and Wilson, 2000). Lastly, a DNA ligase (LIG3/XRCC1 complex) ligates the inserted nucleotide (Cappelli et al, 1997). An alternative BER mechanism is called long patch repair. This allows insertion of a 2- to 10-bp sequence beginning at the damaged nucleotide. It is most useful in cases in which the damaged moiety is refractory to polymerase-β excision (Gary et al, 1999). APE1 again makes a 5′ incision next to the damaged nucleotide, but, in this case, recruits DNA polymerase-δ or -ε, PCNA, and FEN1. A 2- to 10-bp patch is then synthesized, which displaces the damaged nucleotide, along with adjacent nucleotides, and then is ligated by LIG1 (Klungland and Lindahl, 1997; Levin et al, 1997).

Mouse models provide some insight into associations between components of the BER pathway and cancer risk. Whereas loss of some glycosylases can increase the risk of developing malignancies when exposed to mutagens (Elder et al, 1998), in general, loss of individual glycosylases does not cause an overt phenotype, probably due to overlapping function among the many glycosylases. On the other hand, core BER enzymes appear to be essential, because inactivation in knockout mice is embryonic lethal (Friedberg et al, 1998). In human cancers, mutations in the MUTYH glycosylase are associated with colorectal carcinoma. This glycosidase functions with OGG1 to correct A/G and A/C mismatches (Al-Tassan et al, 2002). Interestingly, polymorphic variants of OGG1 have been implicated in genitourinary malignancies (Xu et al, 2002b).

Mismatch Repair

MMR removes nucleotides mispaired by DNA polymerases and insertion/deletion loops (ranging from 1 to 10 or more bases) that result from slippage during replication of repetitive sequences or during recombination.

The MMR pathway functions primarily to reverse incorporation errors made by DNA polymerase. Defects in MMR compromise DNA replication fidelity by approximately two orders of magnitude, thus dramatically increasing mutation rates. Although DNA polymerases have the ability to identify and correct their own errors, some mistakes are not identified. Several of the proteins responsible for MMR (*MSH2, MSH3, MLH1, PMS1, PMS2, and MSH6*) have been identified through the study of the hereditary nonpolyposis colon cancer (HNPCC) syndrome, in which the adenoma-to-carcinoma transition is greatly accelerated. The MMR process has been elucidated in large part by studying the proteins responsible for MMR in bacteria (Modrich, 1997). MMR defects cause high rates of mutation in genes that contain microsatellite repeats within their coding sequences. For example, one study of colon cancer cell lines found mutated TGF-β receptors, which carry a run of 10 adenines in a row, in 9/11 cell lines examined (Carethers and Pham, 2000). TGF-β signaling is a major inhibitor of the cell cycle in epithelial cells, with signal transduction occurring from the TGF-β receptor to the nucleus through SMAD transcription factor proteins. **Activated TGF-β signaling can have multiple antiproliferative effects** including induction of TP15, TP21, and TP27 expression, as well as inhibition of CDK4 translation (Laiho et al, 1990; Ewen et al, 1993; Hannon and Beach, 1994; Koff et al, 1993). Cancer cells that abrogate this pathway become refractory to TGF-β's inhibitory effects.

Once an error has been detected, it is critical for the MMR proteins to distinguish the newly synthesized strand of DNA, that is, the strand that contains the error, from the original template strand. The mechanism for strand distinction has not been well elucidated in eukaryotes, but in *Escherichia coli* the parental strand is methylated, which allows identification of the daughter strand (Modrich, 1997).

The MMR proteins form heterodimers, each of which is responsible for detecting specific DNA replication errors. The MSH2/MSH3 heterodimer (MutSβ) mediates repair of insertions and deletions whereas the MSH2/MSH6 heterodimer (MutSα) recognizes single nucleotide mismatches in addition to insertions and deletions. Once the error has been detected, MutSα and MutSβcomplex with the MLH1/PMS2 heterodimer (MutLα) to direct the repair process. The newly synthesized strand containing the incorrect base(s) is degraded along with surrounding nucleotides. DNA

polymerase then replaces the degraded DNA using the parental strand as a template (Kolodner and Marsischky, 1999; Jiricny, 2000).

The MutSα and MutSβ complexes have also been found to play a role in cell cycle arrest (Meyers et al, 1997) and apoptosis (Tominaga et al, 1997). This is a further example of the integration that exists between cell cycle arrest, DNA repair, and apoptosis that is critical to protecting the fidelity of the DNA.

The critical role of MMR in protecting the cell from mutations that may lead to tumorigenesis is highlighted by their role in HNPCC, studies of sporadic tumors, and evidence from knockout mice. Inherited mutations in *MSH2, MLH1, PMS1, PMS2,* and *MSH6* have all been linked to an increased risk of malignancy (Fishel et al, 1993; Nicolaides et al, 1994; Papadopoulos et al, 1994; Wijnen et al, 1999). Genetic inactivation of MMR genes, particularly *MLH1,* is a frequent event in sporadic colon carcinoma (Veigl et al, 1998) and has been implicated in prostate (Boyer et al, 1995) and bladder carcinoma (Christensen et al, 1998). The finding that MMR knockout mice are cancer prone provides additional evidence that defects in MMR repair can contribute substantially to tumorigenesis (Friedberg et al, 1998).

Double-Stranded Break Repair

DNA double-strand breaks (DSBs) arise from a variety of causes including ionizing radiation or x-rays, free radicals, reactive chemical species, as well as during replication of DNA containing single-strand breaks. After DSB detection, a complex cascade of reactions is triggered that halts the cell cycle and recruits specific repair factors (Kastan and Bartek, 2004). **Double-stranded breaks have the potential to be the most disruptive form of DNA damage. If they are not repaired, the cell will oftentimes undergo apoptosis. This apoptotic response process to double-stranded DNA breaks is the basis of radiation therapy and many chemotherapeutic agents that function primarily by inducing double-strand breaks. Thus cancer cells that have abrogated this response may exhibit increased resistance to such therapies.** Incorrectly repaired DNA can lead to DNA mutations, deletions, and structural chromosomal rearrangements, which are nearly ubiquitous in human solid tumors. There are two DSB repair pathways: homologous recombination (HR) and nonhomologous end joining (NHEJ) (Sancar et al, 2004).

The ATM kinase is a key player in DSB repair (Berkovich et al, 2007). By mechanisms that are still unclear, DSBs are quickly recognized, leading to rapid ATM activation by phosphorylation. In turn, activated ATM phosphorylates and activates TP53 and kinases CHK1 and CHK2, which, among other things, act to halt cell cycle progression to allow DNA repair (Fig. 18–11). ATM also activates many genes involved in DSB repair, such as the histone H2A variant *H2AX* (Rogakou et al, 1998; Lukas et al, 2003), *NBS1, BRCA1,* and *SMC1* (Kitagawa et al, 2004). Phosphorylated H2AX (also known as gamma H2AX) binds at the breakpoint and also occupies a sizeable stretch of DNA (up to 30 Mbp) on either side of the break, where it serves to recruit other DDR factors creating so-called repair foci (Rogakou et al, 1999; Bassal and El-Osta, 2005). Activated NBS1-MRE11-RAD50 (MRN) complex can then bind to RAD52 and the broken chromosomal ends (Lobachev et al, 2004). RAD51, along with the breast cancer susceptibility gene products, BRCA1 and BRCA2, plus the BRCA1-associated–RING-domain 1 protein (BARD1) then participate in replicating the undamaged region from the sister chromosome template (Welcsh et al, 2000; Sancar et al, 2004). Homologous recombination involves the transfer of genetic information between sister chromatids. Essentially, **homologous repair allows the normal undamaged sister chromatid to act as a template to allow precise repair of a damaged segment of DNA** (Johnson et al, 1999). It should be noted that use of the sister chromatid is only an option following S phase into G_2, before mitosis has occurred.

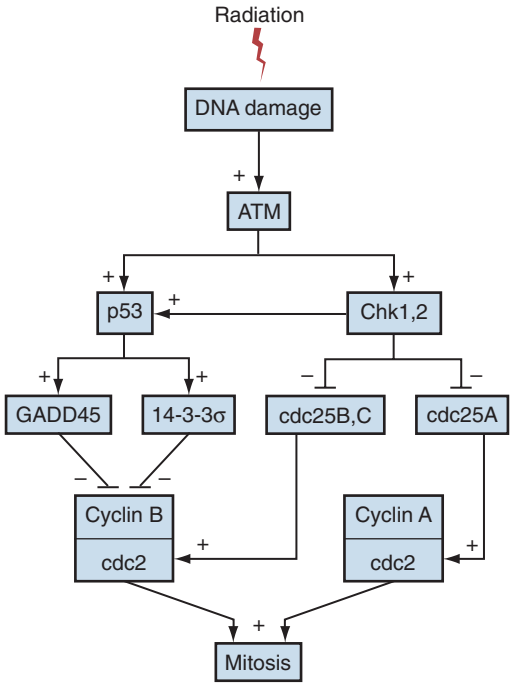


Figure 18–11. Schematic representation of the cascade at the G_2M checkpoint in response to genotoxic events such as radiation. Increased ATM kinase activity eventually leads to inhibition of cyclin B through TP53 and decreased stimulation of CDC2 through CHK1 and CHK2. This leads to cell cycle arrest.

NHEJ is the more extreme of the two DSB repair pathways. In this instance, broken ends are brought together and ligated, often with a loss of some nucleotides at the resulting joint. In addition, the potential exists for incorrectly joining broken DNA ends that were not originally juxtaposed in the genome, thus creating chromosomal rearrangements such as chromosomal translocations. The KU protein is a heterodimer consisting of KU70 and KU80 subunits that initiates NHEJ by binding to the broken ends of the DNA (Tuteja and Tuteja, 2000). KU complexes with DNA-dependent protein kinase (DNA-PK), and in doing so activates DNA-PK's kinase activity (Anderson, 1993). Active DNA-PK phosphorylates a large number of proteins involved in the repair process, including KU and also H2AX. Phosphorylated KU uses its helicase activity to unwind the damaged DNA and allows the ligase 4/XRCC4 heterodimer to repair the break (Tuteja and Tuteja, 2000).

Similar to other DNA repair mechanisms, defects in DSB repair have clearly been linked to cancer. *BRAC1* and *BRAC2* are associated with familial breast and ovarian cancer (Miki et al, 1994; Wooster et al, 1995). Patients with Nijmegen breakage syndrome have mutation in *NBS1* and are predisposed to leukemia, lymphoma, and breast carcinoma (Varon et al, 1998). Patients with mutations in *MRE11* are also predisposed to cancer (Stewart et al, 1999). These inherited cancer predisposition syndromes further highlight the existing link between genomic instability and cancer causation.

Key Points: DNA Damage and Repair

- DNA damage does not often lead to malignancy, because the cell possesses multiple repair mechanisms.
- Defects in DNA repair facilitate the accumulation of the mutations critical for tumor formation and progression.
- The cell cycle and the DDR are closely integrated. In response to DNA damage, the first step is to arrest the cell cycle so that the DNA can be repaired. TP53 plays a key role at this interface.
- Nucleotide excision repair (NER) is a major defense against DNA damage caused by ultraviolet radiation and chemical exposure.
- Base excision repair (BER) repairs damage caused by spontaneous deamination of bases, radiation, oxidative stress, alkylating agents, and replication errors.
- Mismatch repair (MMR) removes nucleotides mispaired by DNA polymerase.
- Double-stranded break repair (DSBR) is a major defense against DNA damage caused by ionizing radiation, free radicals, and chemicals.
- Many syndromes involving inherited defects in DNA repair exhibit marked increases in cancer susceptibility; strongly linking genomic instability and cancer.

CHROMOSOMAL ABNORMALITIES AND GENETIC INSTABILITY

Research by many different groups on several different tumor types has strongly implicated genetic instability as an important determinant of tumorigenesis, although the ultimate source of genetic instability in cancer is still not entirely clear (Loeb, 1991; Hartwell, 1992). As mentioned above, although certainly important in specific instances, such as inherited cancer susceptibility syndromes, deficiencies in genes involved in the replication, maintenance, and repair of DNA have not yet been shown to play a major direct role in the genesis of most sporadic human cancers. On the other hand, because there are so many proteins involved in these various pathways, it is conceivable that efforts such as the comprehensive cancer genome sequencing projects now underway may find that such defects are widespread. **Recent studies on a limited number of colon and breast cancers found that the genomes of each cancer do indeed have numerous mutations (90 mutant genes per tumor, on average) in gene coding sequences, although deciphering how many of these are truly oncogenic changes ("driver mutations") versus merely irrelevant secondary changes ("passenger mutations") remains a challenge** (Sjoblom et al, 2006).

Apart from the simple sequence alterations predicted to arise from the original mutator phenotype concept, *chromosomal* instability leads to gross changes in chromosome number and/or structure. The spectrum and severity of such chromosomal alterations may differ for different tumor types. For instance, **hematological malignancies often present with simple diploid or near-diploid karyotypes with only one or very few detectable, often balanced, chromosomal rearrangements** (see later). However, as a class these cancers only account for about 10% of all human cancers. **In stark contrast, the presence of large variations in chromosome numbers and complex structural rearrangements, as well as intratumoral variation in these aberrations, are hallmarks of most human solid tumors,** which represent the bulk of human malignancies. Important exceptions include certain tumors deficient in MMR. Thus Lengauer and colleagues (1997), observed an intriguing exclusivity between microsatellite instability (MIN) and chromosomal instability (CIN) in colorectal cancer cells. These authors proposed that while this finding supports the necessity of genetic instability in cancer, it may manifest itself in various forms.

In prostate cancer, as well as most human tumor types and transplantable tumor models, the extent of chromosomal abnormalities correlates with disease severity and aggressiveness, pointing to a role for these changes in cancer progression—running from pre-malignant lesions to localized primary tumors, and, finally, to metastatic disease to which patients typically succumb (Brothman et al, 1990; Lundgren et al, 1992; Sandberg, 1992; Isaacs et al, 1995; Bostwick et al, 1996).

The chromosomal changes seen in solid tumors can be broken down into two main classes: changes in the number of whole chromosomes and changes in chromosomal structure. Numerical chromosomal alterations can be further subdivided into changes in the numbers of specific individual chromosomes (aneusomies, e.g., monosomies and trisomies) and changes in the number of copies of the entire diploid set of chromosomes (ploidy changes, e.g., tetraploidy, octaploidy, etc.). Possible mechanisms responsible for such numerical changes include nondisjunction, endoreduplication (an abrupt doubling of the chromosome complement without cell division) cytokinesis defects, and cell fusion events. Likewise, structural changes can be subdivided into several distinct types of chromosomal aberrations as listed in Table 18–2. Over the years, painstaking dissection of chromosomal regions that are repeatedly found to undergo alteration in specific tumor types or subtypes has led to the discovery of hundreds of individual cancer-associated genes. Typically, genomic loci that are frequently lost tend to harbor tumor

Table 18–2.

Gross Chromosomal Abnormalities Frequently Observed in Cancer

Numerical Abnormalities
Aneuploidies
Abnormal numbers of whole chromosome complement (triploidy, tetraploidy, etc.)
Losses or gains of single chromosomes (monosomy, trisomy, etc.)
Structural Abnormalities
Rearrangements
Inversions
Translocations (either balanced or unbalanced)
Chromosomal fusions
End-to-end fusion = dicentric chromosome
Intrachromosomal fusion = ring chromosome
Deletions (from small segments up to entire chromosome arms)
Duplications, amplifications
Double minutes (often containing amplified sequences)
Isochromosomes (loss of one chromosomal arm, replaced by duplication of the remaining arm)
Complex (a variety of combinations of the above abnormalities)

suppressor genes, while those loci exhibiting copy number gains (e.g., gene amplification) point towards oncogenes (Snijders et al, 2005). Examples of genes frequently amplified in cancers include members of the *MYC*, *RAS*, *EGFR* and *FGF* gene families, as well as cell cycle regulatory genes such as *CCND1* (cyclin D gene), *CDK4* and *HDM2*. **Gene amplifications in cancer are usually seen either as multiple small extrachromosomal copies, called double minutes, or as amplified regions within chromosomes, so-called homogeneous staining regions or (HSRs)** (Cowell, 1982).

Specific Chromosomal Translocations Are Frequently Observed in Leukemias, Lymphomas, and Sarcomas

In contrast to numerical changes, the genesis of most structural changes requires that one or more DNA double-strand breaks occur. As outlined previously, normal cells are extremely intolerant of double-strand breaks, and if these are not resolved by HR or NHEJ repair processes, the cell typically commits suicide by apoptosis. Uncovering precisely what has gone wrong within the cancer cell that allows it to generate, as well as tolerate, such gross chromosomal changes is currently an intensive area of research.

As previously mentioned, cancer-associated chromosomal changes were recognized as early as the 1900s by Boveri, who proposed that such abnormalities might be involved in cancer causation. Much later, Klein put forth the idea that chromosomal rearrangements affect the expression of cancer-related genes located near the observed chromosomal breakpoints (Klein, 1981). This hypothesis has been validated over the ensuing years, in large part due to studies showing consistent chromosomal changes found in hematologic malignancies and soft tissue sarcomas, these studies eventually leading to the isolation and cloning of the resident genes involved (Nowell, 1994). A classic example of such a discovery is that involving the chromosomal translocation associated with chronic myelogenous leukemia (CML). An abnormal derivative chromosome, first identified by the karyotyping of metaphase chromosomes (the so-called "Philadelphia chromosome"), was found to be the result of a translocation between chromosomes 9 and 22, formally designated t(9;22)(q34;q11). This rearrangement brings together two genes, *BCR* and the *ABL* proto-oncogene, with the result that a chimeric fusion protein is expressed from the juxtaposition of these two genes (Rowley, 1990; Look, 1997). The net result is inappropriate functioning of the ABL tyrosine kinase portion of the chimeric protein product, which is an oncogenic event in the hematopoietic cell lineage giving rise to CML. A similar scenario is played out in greater than 50% of all leukemias and many lymphomas and sarcomas; involving a host of translocation partner genes. **In general, these involve the juxtaposition of known proto-oncogenes (often protein kinases or nuclear transcription factors) with other genes featuring strong tissue-specific promoters (such as an immunoglobulin or T-cell receptor locus), such that the oncogene is overexpressed or constitutively activated in the context of a fusion protein. Assaying for specific translocations has clinical utility in diagnosis, and in many cases they provide significant prognostic information as well, thus helping to guide treatment decisions** (Pui, 1995).

Specific Chromosomal Rearrangements in Genitourinary Malignancies

Recurrent Gene Rearrangements in Prostate Cancer

Although they are much less frequently observed in common adult solid tumors, recurrent translocations do occur, often amid the backdrop of a sea of numerical and structural abnormalities (Sandberg, 1985). **One of the most exciting recent findings in prostate cancer research has been the discovery of recurrent structural rearrangements in the majority of prostate cancer cases involving oncogenic ETS transcription factor family members.** The initial report by Tomlins and colleagues (2005), described the use a novel bioinformatic approach that led to the identification of recurrent gene fusions between the upstream regulatory region of the androgen-regulated gene *TMPRSS2* and *ERG*, an ETS family member previously known to be involved in Ewing sarcoma and various leukemias. These two genes reside 3 Mb apart on chromosome 21 (*TMPRSS2*, 21q22.3; *ERG* 21q22.2), and detailed molecular analysis revealed that in the majority of cases (approximately two thirds) the gene fusion occurs by deletion of the intervening sequence, with the remaining fusions due to more complex, translocation-type of rearrangements (Tomlins et al, 2005; Perner et al, 2007). In either case, **the net result is to place a known oncogenic transcription factor under the control of an androgen-regulated promoter, resulting in androgen-driven expression of the fusion transcript,** of which there are greater than 20 splice variants (Wang et al, 2008a). As expected, increased *ERG* transcription is positively correlated with presence of the gene fusion. In addition to splice variants, there are multiple forms of the genomic rearrangement, the most common one being a fusion between exon 1 of *TMPRSS2* to exon 4 of *ERG*. **These gene rearrangements can be readily detected, either by assaying for the presence of the fusion transcripts by real-time polymerase chain reaction (RT-PCR), or by assaying for the rearrangement directly by multiprobe, multi-color fluorescence in-situ hybridization (FISH), and such approaches are being evaluated for potential use in noninvasive diagnostic applications (e.g., in urine or blood).**

Since the publication of the initial report by Tomlins and colleagues (2005), several large retrospective studies have been preformed assessing these fusions in localized prostate cancers in PSA-screened cohorts. These studies confirmed the initial finding and found the prevalence of *TMPRSS2-ERG* fusion in prostate cancer to be in the range of 40% to 60%, making this one of the most common somatic genetic alteration in prostate cancer (Mehra et al, 2007; Nam et al, 2007; Perner et al, 2007; Tu et al, 2007; Wang et al, 2008a; Gopalan et al, 2009b; Mosquera et al, 2009). One intriguing exception is cancer originating in the transition zone of the prostate, which appears to completely lack *TMPRSS2-ERG* gene rearrangements (Guo et al, 2009).

As assessed by FISH in tissue sections, the *TMPRSS2-ERG* fusion has not been observed in benign prostate epithelial or stromal cells, although it has been reported to be present in high-grade prostatic intraepithelial neoplasia (HG-PIN), the presumptive precursor lesion for prostate adenocarcinoma, at frequencies between 15% to 20%, which is about one half the frequency observed in localized PSA-detected cancers (Cerveira et al, 2006; Perner et al, 2007; Mosquera et al, 2008; Han et al, 2009). This finding indicates that, at least in a subset of cases, the rearrangement may be an early event in prostate tumorigenesis. **With the important**

exceptions of transition zone cancers and HG-PIN, the prevalence and high degree of specificity of the *TMPRSS2-ERG* fusion for prostate cancer makes this a potentially useful biomarker for diagnosis and disease monitoring, one that could be used in conjunction with current markers such as serum PSA, which have limited specificity.

Apart from its promising potential as a diagnostic prostate cancer marker, it is as of yet unclear if additional clinical information might be provided by determining a patient's *TMPRSS2-ERG* gene fusion status. In 111 tissue specimens obtained by transurethral resection in a population-based Swedish cohort undergoing expectant management for prostate cancer, the presence of *TMPRSS2-ERG* rearrangement was found to be significantly associated with cancer-specific death, leading the authors to suggest that fusion positivity may mark a more aggressive form of the disease (Demichelis et al, 2007). Interestingly, the frequency of fusions detected in this cohort (≈15%) was significantly lower than the range reported for tissues obtained from radical prostatectomy in PSA-screened populations. In two other population-based studies, the frequency of fusion-positive cases ranged between 30% to 35%, higher than that found in the Demichelis study but still lower than that typically found in PSA-screened prostatectomy series, which average around 50% fusion-positivity (Attard et al, 2008a; Fitzgerald et al, 2008). Despite these intriguing reports, **the prognostic significance of fusion status in prostate cancer remains uncertain.** Thus while several studies have reported associations between *TMPRSS2-ERG* rearrangement and various indicators of disease aggressiveness, including higher stage, presence of metastases, and disease-specific mortality (Demichelis et al, 2007; Mehra et al, 2007; Nam et al, 2007; Perner et al, 2007; Rajput et al, 2007; Attard et al, 2008a; Cheville et al, 2008), other studies did not observe such associations (Yoshimoto et al, 2006; Lapointe et al, 2007; Tu et al, 2007; Dai et al, 2008; Rouzier et al, 2008; Albadine et al, 2009; Darnel et al, 2009; Gopalan et al, 2009b; Lotan et al, 2009). In addition, one study reported a link between gene fusion and *favorable* prognosis (Saramaki et al, 2008), and Petrovics and colleagues (2005) have reported that higher levels of *ERG* mRNA expression appeared to be associated positively with disease-free survival. The precise reasons for these conflicting results are not apparent. A number of variables differ between many of these studies, including the nature the study cohorts, sample sizes, methods of cancer detection, how the tissues were obtained, how the gene fusions were detected (e.g., PCR or FISH), length of patient follow-up, and the clinical end points assessed. Further research in this area is clearly warranted in order to better resolve these issues.

Following the report of *TMPRSS2-ERG* rearrangements, further study revealed additional gene fusions in prostate cancer. Thus the *TMPRSS2* gene can fuse to other ETS family member genes including *ETV1, ETV4,* and *ETV5* (Tomlins et al, 2005; Tomlins et al, 2006; Helgeson et al, 2008). These additional translocations are much rarer than the *TMPRSS2-ERG* rearrangement, which is estimated to represent greater than 90% of all fusions involving *ETS* genes in prostate cancer (Kumar-Sinha et al, 2008). In addition, fusions involving upstream fusion partners other than *TMPRSS2* have also been found, including the fusions *SLC45A3-ETV5, SLC45A3-ERG, SLC45A3-ELK4,* and *HNRPA2B1-ETV5*; however, these are also relatively rare (Mehra et al, 2007; Attard et al, 2008a; Attard et al, 2008b; Hermans et al, 2008; Maher et al, 2009; Rickman et al, 2009). **In total, greater than 70% of prostate cancers are now thought to harbor some form of recurrent gene fusion, and this number continues to increase as novel fusion partners are discovered.**

Recurrent Gene Rearrangements in Renal Cancer

Recently, a novel subtype of renal cell carcinoma (RCC), MITF/TFE family translocation carcinoma, was described that features chromosomal translocations involving one of two members of the micropthalmia transcription factor (MITF) family (Hemesath et al, 1994; Argani et al, 2005). The first involves the *TFE3* gene on chromosome Xp11.2, which translocates to one of several partner genes including *PRCC* (1q21), *ASPL* (17q25), *PSF* (1p34), *NONO* (Xq12; rearranged by inversion), and an unknown gene at 3q23 (Sidhar et al, 1996; Weterman et al, 1996; Argani et al, 2001a; Argani et al, 2001b; Argani et al, 2005; Argani and Ladanyi, 2005; Martignoni et al, 2009). These translocations place the *TFE3* gene under the control of strong promoters that then drive inappropriate expression of TFE3 (or a TFE3-containing fusion protein). In these cancers, TFE3 protein is readily detectable in the nucleus by immunohistochemical (IHC) staining with anti-TFE3 antibody, thus aiding in diagnosis. TFE3 renal cell carcinomas are primarily found in children and adolescents and account for the majority of pediatric RCC cases (Argani and Ladanyi, 2005). It has recently been reported that activation of the *MET* proto-oncogene may play a role with *TFE3* in these tumors (Tsuda et al, 2007), which is of interest because these tumors display papillary histological architecture, and mutations in the *MET* gene are the underlying cause of hereditary papillary renal cell carcinoma (Jeffers et al, 1997).

A second class of *MITF/TFE* family translocation carcinomas contain a specific translocation between the *TFEB* gene on 6p21 and the *ALPHA* gene on 11q12 (Argani et al, 2005). Like the *XP11* translocation RCCs, this entity is also most commonly found in children and adolescents and shares many other features with the *TFE3* translocation tumors. In addition to IHC staining for TFE3 and TFEB proteins, it was recently demonstrated that these tumors are also marked by staining for the protein cathepsin K, whose gene is a shared transcriptional target gene of these transcription factors (Martignoni et al, 2009). The use of such markers or PCR to detect these specific gene fusions may have clinical importance because, as the cathepsin K example shows, these tumors likely are controlled by a different transcriptional program than conventional RCC, thus therapeutic targets used against these cancers may not be effective against translocation RCCs.

Recurrent Gene Rearrangements in Testicular Cancer

In testicular germ cell tumors (TGCT), gain of the short arm of chromosome 12 is a nearly universal finding, with the notable exception of the rare spermatocytic seminoma subtype (Atkin and Baker, 1982; Rodriguez et al, 1993; Rosenberg et al, 1998; Verdorfer et al, 2004). In the majority of cases (≈80%), this occurs through a structural rearrangement producing an isochromosome 12p, that is, a version of chromosome 12 consisting of two p-arms and no q- (long) arm. In the remainder of cases 12p material is gained through more complex chromosomal rearrangements (Rosenberg et al, 2000; Ottesen et al, 2003; Looijenga et al, 2007). More detailed analyses have revealed amplification of specific regions on 12p, including the area 12p11-12p13. One common region of amplification at 12p11.2-12p12.1 contains 22 potential genes, including *KRAS*, a promising candidate TGCT gene, which also undergoes activating

mutations in TGCTs (Moul et al, 1992; Olie et al, 1995; Rodriguez et al, 2003; Zafarana et al, 2003; Goddard et al, 2007). An additional region of interest lies at 12p13.31, where the so-called "stem cell cluster region" resides. This region contains several stem cell–related genes including *CD9, EDR1, GDF3, SCNN1A, NANOG,* and *STELLAR,* which exhibit coordinate overexpression (Clark et al, 2004; Korkola et al, 2006).

Other Recurrent Structural Genomic Alterations in GU Malignancies

Apart from chromosomal translocations, which are primarily specific changes in the spatial organization of the genome, an overall derangement of the chromosomal complement is nearly universal in human cancer, particularly in carcinomas; cancers that originate from epithelial cells and represent the vast majority of adult GU malignancies. Such abnormalities are wide ranging, affecting the genome at multiple scales, including losses and gains of entire chromosomes or chromosomal arms, as well as deletions and amplifications of chromosomal regions both large and small. **These changes are generically referred to as copy number alterations (CNA) that, in addition to mutations, structural rearrangements, and epigenetic changes, are yet another reflection of the underlying genomic instability inherent in cancer cells and responsible for the large number of genetic changes required for malignant transformation.** This instability generates a great degree of genetic heterogeneity. For instance, when metaphase chromosomes of tumor cells are examined during karyotypic analysis, a bewildering array of chromosomal aberrations is typically observed, such that no two karyotypes within a given cancer cell population are exactly the same. However, within this seemingly random assortment of alterations, there are some changes that are seen in multiple different cells and multiple tumor samples, providing a strong indication that a gene (or genes) located in the region undergoing recurrent alteration is involved in the pathogenesis of the disease. Over the past several decades, using ever more sophisticated and higher-resolution molecular methods, many such changes have been cataloged and candidate cancer genes identified. Two general approaches are used here. In the first, inherited (germ-line) defects in genes that cause hereditary cancer predisposition syndromes are sought, often by performing genetic linkage analysis in affected and nonaffected family members in an attempt to find genetic loci that track in a mendelian fashion with disease status. Several familial cancer predisposition syndromes are now understood in significant detail, some featuring GU malignancies, others not (Tables 18–3 and 18–4). In the second approach, a variety of techniques are employed to discover disease-associated genes in sporadic cancers that lack a strong familial component (caused by somatic rather than germ-line genetic alterations). **The detection of copy number alterations in a particular gene (or region containing the gene), coupled with mutations in the other allele is persuasive evidence for that gene functioning as a disease-relevant oncogene**

Table 18–3.
Tumor Syndromes Associated with Genitourinary Malignancies

SYNDROME	TUMOR	CHROMOSOME(S)	GENE(S)	(FUNCTION)
Wilms' tumor	Wilms' tumor	11p13	*WT1*	(Transcriptional repressor)
Beckwith-Wiedemann	Wilms' tumor	11p15	*CDKN1C*	(Cell cycle regulator)
von-Hippel-Lindau	Clear cell renal carcinoma Pheochromocytoma	3p25	*VHL*	(Transcriptional elongation and ubiquitination)
Hereditary papillary renal cancer	Papillary renal carcinoma	7q31	*MET*	(Receptor tyrosine kinase)
Birt-Hogg-Dubé	Papillary renal carcinoma Oncocytoma	17p11.2	*FLCN*	(Unknown function)
Multiple endocrine neoplasia type II	Pheochromocytoma	10q11	*RET*	(Receptor tyrosine kinase)
Hereditary nonpolyposis colorectal cancer	Upper tract transitional cell carcinoma	2p22, 3p21.3, 2p18, 2q31-q33, 7p22, 14q24.3	*MSH2, MLH1, MSH6, PMS1, PMS2, MLH3*	(DNA mismatch repair)
Hereditary prostate cancer	Prostate cancer	1q24-25, 1p36, 1q42-43, 8p22-23, 17p11, 20q13, Xq27-28	*RNASEL, MSR1, ELAC2*	(Endoribonuclease, macrophage-specific receptor, cell cycle regulator)

Table 18–4.
Selected Tumor Syndromes Not Strongly Associated with Genitourinary Malignancies

SYNDROME	PRIMARY TUMOR	CHROMOSOME(S)	GENE(S)	(FUNCTION)
Familial retinoblastoma	Retinoblastoma	13q14	*pRB*	(Transcriptional regulation)
Li-Fraumeni	Sarcoma, breast carcinoma	17p13 22q12	*TP53* *hCHK2*	(Transcription factor, serine kinase)
Familial adenomatous polyposis	Colorectal carcinoma	5q21	*APC*	(Regulates β-catenin activity)
Familial breast carcinoma	Breast carcinoma	17q21, 13q12	*BRCA1, BRCA2*	(DNA double-strand break repair)
Cowden's disease	Breast carcinoma	10q23	*PTEN*	(Phosphatase; TPI3K antagonist)
Multiple endocrine neoplasia type I	Pancreatic islet cell carcinoma	11q13	*MEN1*	(Transcription factor)

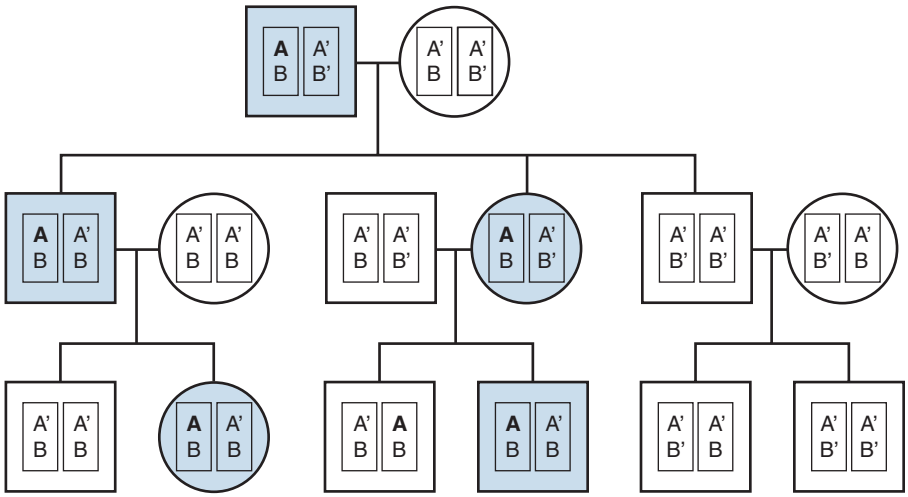


Figure 18–12. The familial tumor syndrome is passed from generation to generation. Genotyping demonstrates that the polymorphic marker A *(bold)* is passed also from generation to generation in concert with the phenotypic disease. Presumably, a gene responsible for the syndrome is located near marker A. Linkage analysis is complicated by incomplete penetrance (not all members of the family with the allele get the disease), phenocopies (family members who have sporadic disease), inability to get DNA from all family members, and the large number of markers being simultaneously analyzed.

(with activating mutations) or tumor suppressor gene (featuring inactivating mutations). In the case of cancer-related genes identified in hereditary predisposition syndromes, one hopes that alterations of genes discovered in familial forms of the disease are also relevant to their more common sporadic counterparts. In a number of instances, this has been found to be the case; for example, gene abnormalities linked to certain familial forms of kidney cancer are also involved in sporadic forms of the disease. In the following sections we describe some of the recurrent genetic changes identified in familial and sporadic forms of genitourinary malignancies.

Hereditary Prostate Cancer

Family history is one of the strongest prostate cancer risk factors (Steinberg et al, 1990), and criteria defining a hereditary form of the disease have been established (Carter et al, 1993). Twin studies have estimated a heritable risk for prostate cancer of approximately 50% (Page et al, 1997; Lichtenstein et al, 2000). Initial genome-wide searches in HPC families uncovered evidence for susceptibility loci on chromosome 1q, 4q, 5p, 7p, 13q, and Xq (Smith et al, 1996). The first strong candidate locus, *HPC1,* was localized to the region 1q24.25 (Gronberg et al, 1997) and a gene, *RNASEL*, was later identified at this locus (Carpten et al, 2002; Rokman et al, 2002). Although this linkage was replicated in some studies, it was not confirmed in others (Cooney et al, 1997; McIndoe et al, 1997; Eeles et al, 1998; Bergthorsson et al, 2000). Similarly, a failure to consistently confirm linkage has plagued other candidate HPC loci/genes as well, highlighting the difficulty in conducting such studies, because prostate cancer is a relatively common disease, HPC families are contaminated with sporadic cases ("phenocopies"). Furthermore, it has become apparent that familial prostate cancer lacks the type of high-risk susceptibility genes such as *BRCA1* or *BRCA2* that are clearly linked to hereditary forms of breast and ovarian cancers (Simard et al, 2003). Among other considerations, these facts underline the need for large, well-defined HPC cohorts, making genetic studies difficult to perform. Other candidate HPC susceptibility genes include *ELAC2* (*HPC2*), macrophage scavenger receptor-1 (*MSR-1*), and *PODXL* (Tavtigian et al, 2001; Xu et al, 2003; Nupponen et al, 2004; Casey et al, 2006). It is intriguing that two of the HPC candidates, *RNASEL* and *MSR-1* are both associated with functions of the immune response, as inflammation is currently considered a likely contributor to the pathogenesis of prostate cancer (De Marzo et al, 2007b).

Traditional linkage analysis is well suited to identifying highly penetrant genetic alterations (Fig. 18–12). **The overall low yield and irreproducibility seen in HPC linkage studies has led to the conclusion that rather than being caused by a few high-impact genes, HPC is likely, instead, to be dependent upon alterations in many genes, each of which has only a modest effect** (Easton et al, 2003; Schaid, 2004).

Sporadic Prostate Cancer

In sporadic prostate cancer, initial studies found recurrent changes involving losses of genetic material at 6q, 7q, 8p, 10q, 13q, 16q, 17p, 17q, and 18q; however, in most cases, the precise genes involved have yet to be identified (Karan et al, 2003). **Changes in chromosome 8, typically loss of the p-arm and gain of the q-arm, or portions of these arms, are the most frequently observed genetic alterations.** At least two to three separate regions are deleted on 8p, implying the existence of multiple tumor suppressor genes (TSG). **8p22 is commonly deleted, with frequencies of 32% to 65% reported in primary tumors and 65% to 100% in metastases. *MSR-1* lies in this region,** and sequence variants in *MSR-1* have been found to be associated with increased disease risk; however, mutations in *MSR-1* have not been reported in sporadic prostate cancers (Xu et al, 2002a; Nupponen et al, 2004; Wiklund et al, 2009). **Another promising candidate, *TSG* on 8p, is the prostate-restricted homeobox gene *NKX3.1* at 8p21** (He et al, 1997). Mice engineered with a loss of a single allele of *NKX3.1* develop prostate hyperplasia and PIN, an example of haploinsufficiency, wherein a phenotypic effect is observed due to the loss of a single allele (Bhatia-Gaur et al, 1999; Abdulkadir et al, 2002).

8q gain, often involving the entire chromosomal arm, is the most common chromosomal abnormality found in advanced prostate cancer (e.g., hormone-refractory lymph node metastases) and is correlated with disease progression and resistance to hormone deprivation or blockade (Alers et al, 2000; Isaacs, 2002; van Dekken et al, 2003). **The proto-oncogene c-*MYC* at 8q24 is a likely candidate gene on 8q,** but the observed gains are large and more work is required to properly assess this possibility. Elevated expression of another gene in

this region, *EIF3S3*, has been documented in cancer compared to benign prostatic hyperplasia (Savinainen et al, 2004). Mouse models lend support for a linkage to *MYC*, because transgenic mice with forced prostate-specific expression of human c-*MYC* develop PIN and invasive adenocarcinomas (Ellwood-Yen et al, 2003). Furthermore amplification at the c-*MYC* locus has been reported in some human prostate cancers and is associated with a poor prognosis (Jenkins et al, 1997; Sato et al, 1999).

Chromosome 7 abnormalities are also frequently observed in prostate cancer. Aneusomy of the entire chromosome (trisomy 7) has been reported in both PIN and cancer and has been associated with advanced stage and a poor prognosis (Arps et al, 1993; Macoska et al, 1993; Alcaraz et al, 1994; Zitzelsberger et al, 1994; Qian et al, 1995). Apart from whole chromosome gains, losses involving 7q31.1 have been documented, suggesting a tumor suppressor resides here (Takahashi et al, 1995; Zenklusen et al, 1994). A potential candidate TSG in this region is *CAV1*, which encodes caveolin, whose expression is reportedly decreased in cancer (Bender et al, 2000; Wiechen et al, 2001). On the other hand, positive IHC staining for caveolin has been associated with *poor* prognosis; thus its role in prostate cancer remains unclear (Yang et al, 1999; Tahir et al, 2001). Another attractive candidate gene in this region is *EZH2*, which codes for a histone methyl-transferase involved in gene silencing. In microarray analyses *EZH2* has been found to be overexpressed in prostate cancer metastases, and its expression in primary tumors is associated with disease (PSA) recurrence (Varambally et al, 2002; Rhodes et al, 2003; Lapointe et al, 2004).

Chromosome 10 also undergoes alteration in prostate cancer, with deletions observed at 10p11.2 and 10q23-q24 (Ittmann, 1996; Trybus et al, 1996). **The tumor suppressor gene *PTEN*, a TPI3 kinase antagonist, maps to this second region and has been linked to human prostate cancer in a number of studies** (Li et al, 1997a; Ayala et al, 2004). *PTEN* undergoes homozygous (both copies) deletion, loss of heterozygosity (LOH), promoter hypermethylation, and is also mutated in prostate cancer. **Overall, *PTEN* is more frequently altered in advanced disease** (reported rates of 60% to 100%) compared with primary tumors (Cairns et al, 1997; Pesche et al, 1998; Whang et al, 1998; Han et al, 2009; Sarker et al, 2009). Interestingly, the frequency of *PTEN* LOH greatly exceeds *PTEN* mutation; therefore it is suggested that another gene or genes may be targeted for deletion in this region of chromosome 10. One possibility is the *MXI1* gene, whose protein product binds to and antagonizes c-*MYC*. In the mouse, *Pten* deficiency exhibits synergy when combined with other mouse models of prostate cancer (Di Cristofano et al, 2001; Kim et al, 2002; Chen et al, 2006).

LOH on 13q has been reported in greater than 50% of prostate cases examined. Three separate regions of loss have been identified, containing the potential cancer genes *BRCA2*, *RB1*, *EDNRB,* and *KLF5* (Cooney et al, 1996b; Hyytinen et al, 1999; Chen et al, 2003). High rates of *pRB* loss (up to 80%) have been reported in advanced cancers (Cher et al, 1996); however, the *pRB* mutation rate is relatively low, and *pRB* expression is not well correlated with the gene dosage or disease status (Bookstein et al, 1990; Kubota et al, 1995; Ittmann and Wieczorek, 1996; Kibel and Isaacs, 2000). However, Theodorescu and colleagues (1997) reported that low RB protein expression was correlated with decreased disease-specific survival in univariate and multivariate analysis.

Losses on 16q have been observed with reported frequencies ranging from 30% to 56% of prostate cancer cases, being more commonly seen in advanced cancer and also associated with a poor prognosis (Carter et al, 1990; Bergerheim et al, 1991; Suzuki et al, 1996; Elo et al, 1997; Li et al, 1999). A common region of loss at 16q22-q24 contains two likely candidate genes, the *CDH1* gene at 16q22.1, coding for the calcium-dependent cell–cell adhesion protein E-cadherin (Morton et al, 1993; Umbas et al, 1994; Murant et al, 2000; Rubin et al, 2001), and the *ATBF1* gene at 16q22, coding for an AT-sequence–binding transcription factor (Sun et al, 2005). Loss of *CDH1* has been associated with metastatic prostate cancer; however, IHC staining studies have produced mixed results, and reports of mutation or LOH of E-cadherin are lacking. Therefore *CDH1* may not be the primary target of the 16q deletion. The *ATBF1* gene, on the other hand, has been reported to be mutated in 40% of prostate cancers (Sun et al, 2005).

Reports of LOH on 6q range from 30% to 50%, with a minimal region of loss at 6q14-q22, although no strong candidate gene has been identified in this region (Cooney et al, 1996a; Hyytinen et al, 2002).

Allelic losses of a region on 17p that includes the *TP53* gene have been documented, but are relatively infrequent in primary prostate cancer compared with more advanced disease (Brooks et al, 1996). This matches findings of mutational analyses where *TP53* mutations are rarely found in primary tumors but are reported in up to 40% of advanced disease (Visakorpi et al, 1992; Bookstein et al, 1993; Navone et al, 1993). A recurrent region of loss on 17q is located near the *BRCA1* gene at 17q21; however, the identified common area of loss does not include this critical tumor suppressor gene (Brothman et al, 1995; Williams et al, 1996).

Deletions on 18q are mainly observed in advanced prostate cancer, with a common region of deletion encompassing the known cancer-related genes *DCC*, *SMAD2,* and *SMAD4* (Ueda et al, 1997; Yin et al, 2001).

Loss of the cell cycle regulatory gene *CDKN2A* on 9p21, which encodes the cyclin-dependent kinase inhibitor TP16, has been reported in 20% of prostate cancers, and at twice this frequency in advanced disease (Cairns et al, 1995; Jarrard et al, 1997). As discussed previously, this locus also contains the *TP14* and *TP15* genes as well, making it difficult to pinpoint the exact target(s) of genetic loss in this region. Reduced expression and LOH of another CDKI gene, *CDKN1B* on 12p13.1-p12 which encodes the TP27 protein, are also found in prostate cancer and are associated with more advanced disease (Guo et al, 1997; Kibel et al, 1998; Yang et al, 1998).

One additional locus that has particular relevance for prostate cancer is the androgen receptor (AR) gene located on Xq12. **The region Xq11-q13 containing *AR* is amplified in up to 30% of cases of advanced disease failing hormonal ablation therapy, in stark contrast with untreated (hormonally naive) cases that do not show *AR* amplification** (Visakorpi et al, 1995; Linja and Visakorpi, 2004; Wang et al, 2004; Mellado et al, 2009). AR mutations, which often act to broaden the receptor's ligand specificity or otherwise provide a gain of function, occur in both advanced as well as lower stage cancer, although they are rarely found in cases untreated by androgen deprivation therapy (Newmark et al, 1992; Taplin et al, 1995; Tilley et al, 1996; Culig et al, 2001; Hara et al, 2003; Gottlieb et al, 2004). Even in the absence of gene amplification, AR protein levels have been seen elevated in prostate cancer (Latil et al, 2001; Linja et al, 2001), further emphasizing the importance of AR hyperactivation in this disease.

Subsequent studies using the comparative genomic hybridization (CGH) technique—in which competitive reactions between differentially labeled tumor-derived versus normal-derived

genomic DNA highlight regions lost or gained in the tumor sample—have largely confirmed and also extended the genomic alterations previously uncovered using LOH analysis. These CGH studies indicate that the number of different alterations is increased in advanced disease and that losses are more frequent than gains in early stages of the disease, with gains and genetic amplifications more commonly seen in advanced hormone-refractory disease (Visakorpi et al, 1995; Cher et al, 1996; Nupponen and Visakorpi, 2000). Recently, Sun and colleagues reviewed all published prostate cancer CGH studies (Sun et al, 2007). Overall, 13 regions were found to be altered in at least 10% of prostate cancer cases, with 8 regions showing deletion and 5 regions showing copy number gain. An additional 6 regions (3 with gains, 3 with losses) were found to be altered in greater than 10% of advanced cancers. In agreement with earlier studies, 8p was the most frequent region of genomic loss (with a peak at 8p21.3), being observed in one third of all cases and one half of advanced disease. Likewise, 8q was gained most often (bimodal peaks at 8q22.2 and 8q24.13), being observed in one quarter of all cases versus one half of cases with advanced disease (Sun et al, 2007). The other regions commonly lost, in decreasing order of frequency, included 13q21.q31, 6q14.1-q21, 16q13-q24.3, and 18q12.1-q23, while regions exhibiting gain included 7q11.21-q32.3, Xq11.1-q23, 17q24.1-q25.3, and 3q26.23-q33. Also, in keeping with the general observation that more aggressive and advanced cancers typically harbor more genetic abnormalities than their lower-grade and lower-stage counterparts, advanced prostate cancers displayed two- to three-fold more copy number alterations.

The application of modern high-resolution methods for assessing CNA, such as representational oligonucleotide microarray analysis (ROMA) and single nucleotide polymorphism (SNP) mapping arrays, will vastly improve our ability to detect CNA, particularly smaller alterations below the resolution limit of CGH, as well as aid in the identification of the resident oncogenes and tumor suppressor genes (Lucito et al, 2003; Sebat et al, 2004; Slater et al, 2005; Zhao et al, 2005; Liu et al, 2006).

Recently, high-density single nucleotide polymorphism (SNP) microarrays have been used in genome-wide–association studies (GWAS), high-resolution–association studies examining the relationship between common DNA sequence variants (SNPs) and cancer risk. Unlike the more traditional linkage analyses of the past, the new platform is amenable to very large cohorts and is better able to detect genetic variations with small to moderate effects on disease risk (Risch and Merikangas, 1996; Jorgenson and Witte, 2007). To date, several GWAS studies have been published on prostate cancer, resulting in the identification of 20 SNPs that are associated with the risk of developing prostate cancer (Amundadottir et al, 2006; Duggan et al, 2007; Gudmundsson et al, 2007; Haiman et al, 2007; Witte, 2007; Eeles et al, 2008; Gudmundsson et al, 2008; Thomas et al, 2008; Breyer et al, 2009; Yeager et al, 2009). Interestingly, most of the SNPs are not located in or even near genes previously shown to be involved in prostate cancer pathogenesis. Notably, three independent loci were identified on 8q24, all contained within a 1-Mb DNA segment; however, no genes have yet been identified to account for these risk alleles (Cheng et al, 2008). Although the *MYC* gene is in this vicinity, it is still 200 Kb away from the nearest SNP; thus its relevance, if any, remains uncertain. Importantly, unlike the loci identified in earlier linkage studies in HPC families, the risk alleles identified in these GWAS studies have been independently confirmed. As predicted, the risk attributable to each locus is small to modest, yet, due to the large cohorts studied, each association is highly statistically significant, and each has been shown to confer risk independent of the other loci; thus these risk alleles act in a fairly additive fashion (Kote-Jarai et al, 2008; Zheng et al, 2008; Witte, 2009). However, **although men in the top decile, in terms of number of combined risk alleles, have a two- to fourfold increased risk for prostate cancer compared with the bottom decile. The numbers of men harboring such large numbers of risk alleles is small; thus these SNPs are unlikely to have utility for population screening purposes.** An important facet to these studies is that so far none of these prostate cancer risk alleles appear to be associated specifically with risk for aggressive disease (Kader et al, 2009; Wiklund et al, 2009). This is unfortunate, because the lack of strong prognostic markers is a key shortcoming in the field that desperately needs to be resolved. **The current GWAS studies all used case-control designs; therefore it will likely require new case-case studies, comparing aggressive versus nonaggressive disease, to uncover new SNPs informative for disease aggressiveness. Recently identified SNPs are therefore thought to be more likely related to prostate cancer initiation rather than to progression. One alternative approach, which has had some early success in other cancers, is to use gene expression array data to develop "gene signatures" able to predict aggressive behavior** (Cheville et al, 2008; Mucci et al, 2008; Setlur et al, 2008).

Renal Cancer

Renal cell carcinoma (RCC) includes a spectrum of subtypes and can be subdivided into at least five different categories: clear cell RCC (ccRCC), which accounts for the majority (70% to 80%) of adult cases; papillary RCC, which accounts for most of the remaining 10% to 20%; chromophobe RCC; collecting duct RCC; and the MITF/TFE family translocation carcinomas described earlier. In addition, there are more than four inherited forms of RCC. **Importantly, the genes discovered to have germ-line mutations that cause these familial forms of the disease have also been found to play important roles in sporadic RCC as well** (Coleman, 2008).

Patients with von Hippel-Lindau syndrome are predisposed to a number of tumor types, notably ccRCC (Coleman, 2008). The finding of consistent losses of 3p in this disease led to the identification of the *VHL* gene located at 3p25-p26; the germ-line mutation causes VHL disease (Zbar et al, 1987; Tory et al, 1989; Latif et al, 1993; Stolle et al, 1998). **Once the *VHL* gene was identified, its status was assessed in sporadic (nonfamilial) RCC, where it was found to be mutated in over half of sporadic ccRCC cases** (Gnarra et al, 1994; Shuin et al, 1994). To date, over 300 different *VHL* mutations have been cataloged, and ccRCC cases not harboring *VHL* mutations often undergo LOH (deletion) or silencing of the gene by promoter hypermethylation. Thus, altogether, the vast majority of ccRCCs have compromised *VHL*. **The VHL protein normally functions as part of a multiprotein complex with elonginB, elonginC, CUL-2 (cullin-2), and RBX1 (ring box-1), which exhibits E3 ubiquitin ligase activity and targets subunits of the hypoxia-inducible factor-1 (HIF-1) transcription factor for ubiquitination and subsequent proteosomal destruction** (Kibel et al, 1995; Iliopoulos et al, 1996; Pause et al, 1997; Kamura et al, 1999; Kaelin, 2002). **HIF-1 functions as a master regulator of the cellular response to low oxygen levels.** Under normal conditions, specific proline amino acid residues in

the two HIF-1 subunits, HIF-1α and HIF-1β, are hydroxylated by the oxygen-dependent proline hydroxylase enzymes EGLN1-3. This oxygen-dependent modification signals HIF-1's ubiquitination, and thus HIF-1 is rapidly turned over (Maxwell et al, 1999; Bruick and McKnight, 2001; Ivan et al, 2001; Jaakkola et al, 2001). **Under conditions of oxygen deprivation (hypoxia) the prolyl hydroxylases fail to act; thus HIF-1 is spared and accumulates, allowing its translocation to the nucleus where it activates a number of target genes,** including the glucose transporter GLUT-1, the proangiogenic growth factors PDGF and ***VEGF,*** the chemokine CXCL-1 and its receptor CXCL-4, TGF-α, and the HGF receptor MET (Wykoff et al, 2001; Igarashi et al, 2002; Hu et al, 2003; Staller et al, 2003; Linehan et al, 2007). That the HIF-1 pathway is activated in ccRCCs is supported by the highly vascular nature of these tumors and that expression of HIF-1 target genes is found to be elevated. Thus **in ccRCCs, the loss of VHL function leads to a state of "pseudohypoxia" in which the cells respond as if they are being starved for oxygen.**

Several of the genes activated by HIF-1 have been singled out for therapeutic targeting, and positive results in clinical trials have led to Food and Drug Administration (FDA) approval of some of these agents (Linehan, 2002; Hansel and Rini, 2008). For example, the monoclonal anti-VEGF antibody bevacizumab, and the small molecule kinase inhibitors sunitinib and sorafenib, which inhibit both VEGF and PDGF, have all shown improvements in progression-free survival in clinical trials for metastatic RCC, leading to FDA approval in the latter two cases (Hansel and Rini, 2008).

The VHL/sporadic ccRCC example epitomizes the potential for translational application of cancer molecular genetics, beginning with studies on a familial cancer (then translated to the sporadic form of the disease), culminating in the rational design of therapeutic agents against revealed molecular targets having a positive impact in the clinic.

A second familial form of RCC is hereditary papillary renal carcinoma (HPRC), whose cause has been pinpointed to activation of the proto-oncogene tyrosine kinase c-MET, which is the cell surface receptor for the growth factor HGF (Jeffers et al, 1997). The *MET* gene is located at 7q31-q34, which is notable because the vast majority of sporadic papillary RCC cases show trisomy of chromosome 7 (Kovacs, 1993). In addition, activating mutations, typically affecting the tyrosine kinase domain and leading to a constitutively active receptor, have also been found in sporadic cases (Schmidt et al, 1997).

A third type of hereditary renal cell cancer predisposition is Birt Hogg Dube (BHD) syndrome. Individuals with BHD most commonly develop chromophobe RCC, but other forms, such as clear cell RCC, papillary RCC, and benign oncocytomas are also observed (Pavlovich et al, 2002; Pavlovich et al, 2005). The *BHD* gene underlying the disease is located at 17p11.12 and codes for the protein folliculin (Schmidt et al, 2001). A spectrum of disruptive mutations and gene deletions support a tumor suppressor gene function for folliculin (Khoo et al, 2002; Nickerson et al, 2002; Schmidt et al, 2005; Vocke et al, 2005); however, the precise function of this protein has not been elucidated, although evidence indicates it impacts both the ERK and AKT/mTOR signaling pathways (Baba et al, 2008).

A fourth familial RCC subtype, albeit rare, is hereditary leiomyomatosis RCC (HLRCC), featuring an aggressive form of papillary RCC (Kiuru and Launonen, 2004; Merino et al, 2007; Sudarshan et al, 2007). The cause of HLRCC has been traced to the fumarate hydratase gene at 1q42.3-q43, whose protein product acts to convert fumarate to malate in the Krebs cycle. Once again, the HIF-1 pathway is implicated in RCC tumorigenesis, because the resulting accumulation of fumarate acts as a competitive inhibitor of the prolyl hydroxylase *EGLIN1-3*, preventing modification of HIF-1 subunits, prolonging their half-lives, and leading to a pseudohypoxic state, as was the case for mutated VHL. In support of this pathogenetic scheme, increased expression of VEGF and a high microvessel density have been found in HLRCC tumors (Isaacs et al, 2005; Pollard et al, 2005).

Bladder Cancer

Although first degree relatives of patients with bladder cancer are at increased risk of developing the disease, high-risk families are very rare and lack clear mendelian inheritance patterns, precluding classical linkage analysis. Bladder cancer is therefore not considered a familial disease. Instead, it has been proposed that there likely exist many susceptibility genes with small to moderate effects on disease risk (Aben et al, 2006; Kiemeney, 2008). Recent attention has therefore turned to the use of GWAS, which are better suited to the discovery of low penetrance susceptibility loci. The first such studies have been published, and reported susceptibility loci include 8q24.21, near the *MYC* proto-oncogene; 3q28, associated with the *TP53* relative *TP63;* and at 5p15.33, which is near the *HTERT* gene coding for the cancer-associated telomere maintenance enzyme telomerase (Kiemeney et al, 2008; Kiemeney et al, 2009; Rafnar et al, 2009; Wang et al, 2009a). Notably, gain of 5p15.33 had previously been identified as being associated with bladder cancer progression (Yamamoto et al, 2007), and reduced or absent *TP63* expression has been associated with disease progression and poor prognosis (Urist et al, 2002; Koga et al, 2003). An additional GWAS, reported by Wu and colleagues found a missense variant in the prostate stem cell antigen (*PSCA*) gene to be associated with bladder cancer risk (Wu et al, 2009). This mutation is predicted to result in truncation of the first nine amino acids of the PSCA protein, and earlier studies reported that PSCA mRNA and protein levels are increased in bladder cancer compared with normal urothelium, with mRNA expression serving as an independent predictor of recurrence in superficial bladder cancer (Amara et al, 2001; Elsamman et al, 2006). The increased risk of bladder cancer engendered by these risk alleles uncovered by GWAS range from 16% to 22%, and further studies are currently underway.

The majority (75% to 85%) of bladder cancer and cancer-associated lesions seen in the clinic are of superficial type (stages pTa, pTis, pT1). Recurrences following therapy are frequent, requiring diligent surveillance by urine cytology and cystoscopy, resulting in frequent resections. In addition, the risk of progression is likewise high. Accurate assessment of risk for recurrence and progression to muscle-invasive disease are critical needs for which current predictive schemes based on histopathologic features are suboptimal. Hopefully, information at the molecular level will help improve current methods of risk stratification.

Much work has been done to identify genetic alterations in bladder cancer. In general, changes observed fall into two groups, those that are mostly unrelated to clinical subtype (e.g., changes in chromosome 9 and *RAS* mutations), and those that are related to specific grades and/or stages of the disease (e.g., *FGFR3* mutations in superficial pTa disease; *TP53* and *pRB* alterations in muscle-invasive disease) (Knowles, 2008).

Greater than half of urothelial cell carcinomas of all grades show chromosome 9 alterations; commonly these

are losses of the entire chromosome or entire chromosomal arms, while LOH events of more restricted regions are also seen, leading to the current consensus that there are multiple tumor suppressor genes located on both chromosomal arms (Tsai et al, 1990; Cairns et al, 1993; Linnenbach et al, 1993). In otherwise near-diploid tumors, complete loss of one copy (monosomy 9) is the only karyoptypic abnormality seen (Gibas et al, 1984; Fadl-Elmula et al, 2000). **The region at 9p21 containing the genes for the CDKI proteins TP15 and TP16, which suppress the pRB pathway, as well as harboring the TP53-stabilizing gene *TP14*^{ARF}, is a strong candidate for the bladder cancer *TSG* locus.** This region commonly undergoes LOH or homozygous deletion in bladder cancers, including low-grade and low-stage tumors (Devlin et al, 1994; Orlow et al, 1995; Williamson et al, 1995; Berggren et al, 2003), and mutations have been associated with high-grade disease and tumor progression (Orlow et al, 1999).

At least three different regions of loss have been mapped on 9q, and candidate bladder cancer TSGs have been proposed, including the patched gene (*PTCH*) at 9q22, which shows mutations and LOH in up to 40% of cancers (McGarvey et al, 1998; Aboulkassim et al, 2003); the region termed DBC1 at 9q32-q33, which exhibits deletion and silencing in approximately 50% of cases (Habuchi et al, 1998; Nishiyama et al, 1999); and 9q34, which exhibits LOH and contains the gene *TSC1* (tuberous sclerosis gene 1), a strong candidate bladder TSG due to finding *TSC1* mutations in conjunction with LOH (Hornigold et al, 1999; Adachi et al, 2003; Knowles et al, 2003). The *TSC1* gene encodes the protein hamartin, which is a phosphorylation target of AKT and functions in negative regulation of mTOR (mammalian target of rapamycin), a downstream target of the *PI3K* pathway, which is also dysregulated in bladder cancer by inactivation of the *PI3K* antagonist *PTEN*, as well as mutational activation of the TP110 catalytic subunit of PI3 kinase; *PIK3CA* (Cairns et al, 1998; Aveyard et al, 1999; Wang et al, 2000).

Noninvasive (superficial, pTa) papillary urothelial cell carcinoma (UCC) represents a major bladder cancer subgroup at diagnosis. Apart from changes involving chromosome 9, these tumors appear relatively stable with respect to chromosomal structural changes, with losses and gains reported for approximately a dozen different chromosomal locations, most in 20% or fewer of cases examined (Koed et al, 2005; Knowles, 2008). More subtle genetic alterations in oncogenes and tumor suppressor genes also occur with varying frequencies. As recently reviewed by Knowles (2008), activating mutations in the *RAS* family of proto-oncogenes (*H-, K-*, and *NRAS*) have been reported in up to 15% of cases, mutations in *PIK3CA* in 16% of cases, and amplification/overexpression of *CCND1* and *HDM2* have been reported in 10% to 20% and approximately 30% of cases, respectively.

In addition to oncogene activation, inactivation of several tumor suppressor genes by either deletion or promoter hypermethylation has been reported in superficial papillary UCC. These genes include several genes on chromosome 9 such as *CDKN2A* (*TP16*), affected in 30% to 60% of cases; *PTCH*, the *DBC1* locus, and *TSC1*, all reportedly affected in 60% of cases (Knowles, 2008).

The most frequently altered TSG in superficial Ta disease is the fibroblast growth factor receptor 3 (*FGFR3*), with mutation frequencies approaching 90% of cases reported (Cappellen et al, 1999; Billerey et al, 2001; Sibley et al, 2001; Tomlinson et al, 2007). The most common *FGFR3* mutation is a serine to cysteine mutation at amino acid 249 that has been shown to cause constitutive ligand-independent receptor activation due to induced receptor dimerization by intermolecular cys–cys disulfide bonding (Li et al, 2006). **The frequency of *FGFR3* mutations is much lower in higher-stage, invasive bladder cancers, and mutations are lacking in the superficial Tis stage (carcinoma in situ, CIS) that have a high propensity for recurrence and progression to invasive disease.** In addition, in Ta disease there is a strong inverse correlation between mutation and tumor grade (Billerey et al, 2001). The high preferential prevalence of *FGFR3* mutations in Ta disease suggests an association with low-risk bladder cancer (Tomlinson et al, 2007). In this respect, it is noteworthy that *FGFR3* mutations are also associated with benign tumors of the skin (seborrheic keratoses) (Logie et al, 2005; Hafner et al, 2006). In a recent prospective study, Hernandez and colleagues (2006) concluded that *FGFR3* mutations are associated with a subgroup of tumors having good prognosis, and Burger and colleagues (2008) reported *FGFR3* status is useful in risk stratification for patients with high-grade non–muscle-invasive UCC. Finally, there are indications that *FGFR3* mutations and *RAS* family mutations are mutually exclusive (Jebar et al, 2005; Logie et al, 2005; Hafner et al, 2006). These findings may be rationalized by considering that *FGFR3* itself is known to activate the *RAS/RAF/MEK/ERK* pathway (Choi et al, 2001). Likewise, reports of mutational exclusivity have been made regarding *FGFR3* and *TP53*, which is only mutated in about 5% of pTa cases, and is associated with higher-grade disease (Bakkar et al, 2003; Zieger et al, 2005). Interestingly, in pT1 disease, the frequency of *FGFR3* mutations is lower, *TP53* mutation frequency is higher, and, unlike pTa disease, these mutations are not necessarily mutually exclusive (Bakkar et al, 2003; van Rhijn et al, 2004; Tomlinson et al, 2007).

Although the frequency of chromosome 9 alterations and *RAS* family mutations are comparable across all grades and stages of bladder cancer, **muscle-invasive urothelial carcinomas (stage pT2 and higher) exhibit more genetic alterations (both qualitatively and quantitatively) than lower-stage disease in keeping with the general observation that more aggressive cancers tend to exhibit evidence of greater genetic instability than their less aggressive counterparts.** Invasive bladder tumors exhibit a wide range of copy number alterations across virtually every chromosome, although the gene targets of these changes are largely unknown at present (Koed et al, 2005). In a similar vein, Blaveri and colleagues (2005), used cluster analysis of array CGH (aCGH) data to successfully separate bladder tumors of differing stages and grades from one another. In addition, a quantitative measure of the fraction of genome altered (FGA) was shown to be inversely related to patient survival time in cases with muscle-invasive cancer. Ploidy, another reflection of genomic instability, has been found to be associated with progression from noninvasive to invasive bladder cancer (Holmang et al, 2001). Mutational inactivation of *TP53* is seen in greater than 40% of invasive pT2 tumors, in sharp contrast to the low mutational rate seen in pTa disease, where *TP53* mutation is associated with risk for progression (Fujimoto et al, 1992; Spruck et al, 1994b; Uchida et al, 1995; George et al, 2007). Likewise, inactivation of *RB,* either by LOH or through *TP16* inactivation, is common in invasive bladder cancer but is infrequent in pTa tumors (Cairns et al, 1991; Benedict et al, 1999; Chatterjee et al, 2004; Shariat et al, 2004). Loss of the region of 10q harboring the *PTEN* tumor suppressor gene is also more frequent in muscle-invasive bladder cancer than in lower stage pTa tumors (Cappellen et al, 1997; Kagan et al, 1998; Aveyard et al, 1999).

Genetic Alterations in Bladder Preneoplasia

Urothelial hyperplasias with flat or papillary histomorphology have been proposed as precursors of low-grade bladder cancers, although this concept is somewhat controversial (Chow et al, 2000). In support, Hartmann et al (1999) reported that, when present, genetic alterations (assayed at 9q21, 9q22, and 17p13) in hyperplasias were also found in superficial papillary tumors from the same patient. Genetic studies on hyperplasias have reported moderate to high frequencies of chromosome 9 alterations, whereas other genetic changes that are associated with aggressive forms of bladder cancer are reportedly infrequent (Chow et al, 2000). Dysplastic urothelial lesions have been found to have frequent changes in chromosome 9, frequent aneuploidy, and approximately half are *TP53*-mutated (Hartmann et al, 2002; Mallofre et al, 2003). The prevalence of changes seen in low-grade intraurothelial neoplasia was lower than that observed in high-grade (CIS) lesions (Hartmann et al, 2002). CIS lesions (pTis) are aggressive, high-grade precursor lesions, exhibiting high rates of recurrence and progression to invasive disease. In contrast to superficial papillary lesions, CIS exhibits frequent (50% to 70% range) genetic alterations (LOH) of 4q, 8p, 11p, 13q, and 14q, in addition to several other chromosomal alterations observed at lower but still significant frequencies (Rosin et al, 1995). CIS lesions may be subdivided into primary lesions that are isolated without associated cancer and cancer-associated secondary lesions. It has been reported that chromosome 9 changes are infrequent in primary lesions, whereas the majority of secondary lesions exhibit deletions on chromosome 9 (Spruck et al, 1994b; Billerey et al, 2001; Hartmann et al, 2002; Hopman et al, 2002).

As expected, given their aggressive nature, *FGFR3* mutation rates are low in CIS, while the *TP53* pathway shows frequent alterations. *TP53* mutation occurs in over half of CIS lesions and is correlated with strong nuclear TP53 staining by IHC (Hartmann et al, 2002; Hopman et al, 2002). Nuclear *TP53* expression in transitional cell carcinoma (TCC) has been associated with increased risk of recurrence and death, independent of tumor grade, stage, and lymph node status in TCC patients (Lipponen, 1993; Sarkis et al, 1993; Esrig et al, 1994).

Genetic Alterations in Normal and Benign Bladder Urothelium

Given the propensity of bladder cancer to recur, plus that it is often multifocal, there are proposals that genetic changes may occur in broad areas of the urothelium. Such a hypothesis concurs with the "field cancerization" concept (also known as "field effect"), first put forward by Slaughter and colleagues, in 1953, to help explain the multifocal nature and high local recurrence rates of cancers of the oral cavity, as well as the finding of histologically abnormal epithelium in areas adjacent to cancer. These authors proposed that multiple cancer foci arose within a wider field of abnormal epithelium that had been preconditioned by some prior carcinogenic insult(s), a process they termed field cancerization. Genetic changes have been detected in samples of histologically normal-appearing urothelium obtained from surgical samples from cancer patients. For example, Muto and colleagues (2000) found shared instances of LOH, as well as promoter hypermethylation of the *TP16* gene, between normal-appearing and tumor areas from the same case. Likewise, Stoehr and colleagues (2005) performed LOH analyses on a large number of cases in which normal-appearing epithelium was isolated by laser capture microdissection. These authors also reported cancer-associated genetic changes in the normal-appearing urothelium which, in some cases, matched the changes found in concurrent cancers in the same case. However, caution is warranted when assessing such results, given the possibility of contamination of the normal areas sampled by small multifocal cancer lesions or by pagetoid spread of tumor cells (Junker et al, 2003). On the other hand, a study by Obermann and colleagues (2004), using interphase FISH in tissue sections detected losses involving chromosome 9 in normal-appearing cells, that, from a technical standpoint, should be effective at excluding possible confounding microscopic foci of cancer cells.

Inverted papillomas of the urinary bladder are considered benign entities. In keeping with this, they exhibit infrequent LOH at cancer-associated chromosomal loci, as well as infrequent (less than 10%) mutations of *FGFR3* (Sung et al, 2006; Eiber et al, 2007). In contrast to inverted papillomas, papillary urothelial neoplasia of low malignant potential (PUN-LMP) exhibit high rates (85%) of *FGFR3* mutation (van Rhijn et al, 2002), a genetic alteration that is strongly associated with bladder tumors of low stage and low grade, as described above. However, a study by Cheng and colleagues (2004) found frequent LOH at several loci that typically undergo LOH in advanced (greater or equal to pT2).

Molecular Genetic-Based Assays for Bladder Cancer Detection and Surveillance

The large amount of data concerning common genetic alterations in bladder cancer has been exploited to aid in detecting the presence of bladder cancer. One widely used test termed Urovysion (Vysis/Abbott Molecular, Abbott Park, IL) is a multiplex, multicolor FISH-based assay that features a cocktail of four hybridization probes that assess the status of four chromosomes (Bubendorf et al, 2001; Halling, 2003). Probes specific for the centromeres of chromosomes 3, 7, and 17 provide information on cancer-associated gains of these chromosomes, while the fourth probe is specific for 9p21, which harbors the *TP14* and *TP16* genes that are often deleted in bladder cancers. This test, approved by the FDA in 2005, is used in conjunction with standard urine cytology in diagnosing suspected cases, as well as monitoring for local recurrence in patients previously diagnosed and treated (Halling et al, 2000; Hajdinjak, 2008). In addition, the test may have utility in monitoring response in patients with superficial bladder cancer treated with intravesical bacillus Calmette-Guérin (BCG) therapy (Kipp et al, 2005), and may also be useful in distinguishing inverted papillomas from urothelial carcinoma with inverted growth pattern (Jones et al, 2007).

Currently there are six FDA-approved urine-based molecular tests for bladder cancer focused on either genetic or immunochemical targets, and many other potential markers are under development (van Rhijn et al, 2005; Herman et al, 2008; Zwarthoff, 2008; Sullivan et al, 2009). **However, notably, although these new tests improve upon standard urine cytology, they do not supplant it.**

Finally, a recent study by Wang and colleagues (2009b), reported the development of a quantitative-PCR (Q-PCR) gene signature for predicting progression in cases of non–muscle-invasive bladder cancer.

Testicular Cancer

Testicular germ cell tumors (TGCT) are a fascinating set of malignancies possessing many unique features (Oosterhuis and Looijenga, 2005). These cancers appear to originate from totipotent stem cells, with evidence strongly supporting TGCT initiation in utero, whereby abnormal primordial germ cells (PGC), or gonocytes, are blocked in their differentiation, remaining dormant until puberty. This is supported by expression in TGCT of markers closely associated with PGC, including placental alkaline phosphatase (PLAP), the stem cell factor tyrosine kinase receptor c-KIT, and the transcription factors OCT3/4 and NANOG, which are involved in maintenance of pluripotency or "stemness." The presumptive common precursors to TGCT are the intratubular germ cell neoplasia unclassified (ITGCNU), which closely resemble PGC, sharing many of the same markers (PLAP, c-KIT, OCT3/4) (Skakkebaek et al, 1987). ITGCNU, also traditionally referred to as CIS (carcinoma in situ), although this nomenclature is technically inaccurate, have a very high rate of progression to invasive disease, estimated to be essentially 100% if allowed sufficient time (Linke et al, 2005).

TGCT are classified into two main categories: seminomas and the nonseminomas. A third type, the so-called spermatocytic seminomas, is extremely rare and will not be discussed here (Ulbright, 1993). **Like the TGCT precursor ITGCNU, seminomas closely resemble PGC/gonocytes, both morphologically as well as in their expression of molecular markers** (positive expression of PLAP, c-KIT, OCT3/4, NANOG, STELLAR, and SOX-17) (Sperger et al, 2003; de Jong et al, 2008). **Nonseminomatous TGCTs resemble embryonic and extra-embryonic tissues that have undergone varying extents of differentiation.** The non-seminomas include four subtypes. Embryonal carcinomas (EC) are similar, in many respects, to embryonic stem cells, or perhaps primitive ectoderm, and express *OCT3/4, NANOG,* and *STELLAR,* as well as *SOX-2* (Gopalan et al, 2009a). Extraembryonic differentiation is apparent in the yolk sac tumors (YST) and choriocarcinoma (CC), while somatic tissue differentiation is found in the teratomas.

Beside their unique pathogenesis, TGCT are also unique in their responsiveness to treatment modalities that induce DNA damage (e.g., ionizing radiation and cis–platin-based chemotherapy). Thus the vast majority of patients are currently curable, even those with advanced disseminated disease (Einhorn, 2002). This extreme sensitivity to DNA damage is thought to be related to the origins of TGCT (their normal stem cell counterparts are poised to undergo apoptosis in response to DNA damage), and the observation that **most TGCT maintain wild-type *TP53,* and apparently intact DDR** (Kersemaekers et al, 2002; Gorgoulis et al, 2005; Bartkova et al, 2007). Interestingly, responsiveness to therapy in TGCT is the inverse of that seen in most other cancers, that is, sensitivity decreases with increasing differentiation state, such that ITGCNU are eliminated with low-dose radiation while teratomas exhibit resistance to radiation and chemotherapy.

Family history is a strong risk factor for the development of TGCT, stronger than that found in most other cancers (Forman et al, 1992; Westergaard et al, 1996; Czene et al, 2002; Mai et al, 2010). Despite this, initial reports of an association between specific losses on Yq and risk of TGCT were not later confirmed (Krausz and Looijenga, 2008). Genetic polymorphisms in CAG-tract length, which codes for polyglutamine repeats in the androgen receptor, were assessed but were not found to be associated with disease risk (Rajpert-De Meyts et al, 2002; Giwercman et al, 2004; Garolla et al, 2005). Furthermore, **linkage and more recent GWAS analyses have not revealed evidence for major TGCT-related genetic loci, implying instead the existence of multiple loci having modest influence** (Lutke Holzik et al, 2005; Crockford et al, 2006; Rapley, 2007). **However, a very recent GWAS study by Kanetsky and colleagues reported that common genetic variants at 5q31.3 and in the *KITLG* gene region (c-KIT ligand, also known as stem cell factor or steel factor) on 12q22 are significantly associated with TGCT risk,** including both seminomas and nonseminomas (Kanetsky et al, 2009).

Spontaneous (as opposed to inherited) genetic alterations have been catalogued in TGCTs. Apart from aneuploidy, there are relatively few genetic changes or gene mutations found in TGCT, giving an overall picture of a relatively low level of genetic instability, which may be in large part due to the aforementioned intact DDR and predominately wild-type *TP53* status in these cancers (Bignell et al, 2006; Greenman et al, 2007). One recurrent, nearly universal genetic alteration in TGCT (excluding the rare spermatocytic seminomas) is the previously described gain of 12p that may involve the *KRAS* gene or genes such as *NANOG* and *STELLAR,* located in the stem cell cluster region at 12p13.31. Additional evidence for *KRAS* involvement in TGCT include reports of activating mutations in up to 40% of cases, as well as increases in expression in concert with increased gene copy number. Interestingly, *BRAF* mutations have also been identified in TGCT but are seen to be mutually exclusive to *KRAS* overexpression (McIntyre et al, 2005b; Sommerer et al, 2005).

Other changes that have been reported in sporadic TGCT include gains of material on chromosomes 1, 5, 7, and X; losses on 18 in both ITGCNU as well as invasive cancer; and losses from chromosomes 4 and 13, plus gain of 2p, which were more restricted to invasive cancers (Summersgill et al, 2001).

In seminomas, recurrent gains of 4q12, 16p13, and Xq22, plus losses of 3q29, 11q12.1, and 14q13.2 have been reported (Goddard et al, 2007). The c-*KIT* gene, whose protein product is a receptor tyrosine kinase also known as CD117, is located at 4q12, and c-*KIT* amplifications have been reported in 24% of seminomas and 17% of gene-specific amplifications, but these changes were lacking in nonseminomas and ITGCNU (McIntyre et al, 2005a). Also, mutations in c-*KIT* represent the most common somatic mutations found in seminomas (25% of cases), but are rarely found in nonseminomas (Forbes et al, 2006; Coffey et al, 2008). Despite the apparent lack of c-*KIT* gene amplifications in ITGCNU, activating mutations in c-*KIT* have been reported, and IHC staining is positive for this entity as well as seminomas, while it is not seen in nonseminomas or spermatocytic seminomas (Tian et al, 1999; Przygodzki et al, 2002; Looijenga et al, 2003; Kemmer et al, 2004; Goddard et al, 2007).

Gains of 17q11.2-q21 have been reported in TGCT, and this region contains the *ERBB2* receptor tyrosine kinase gene as well as the *GRB7* adaptor protein gene. *ERBB2* ties into the RAS pathway, while GRB7 binds to and likely regulates c-KIT, ERBB2, and RAS and is reportedly overexpressed in TGCT and their ITGCNU precursor (Kraggerud et al, 2002; Skotheim et al, 2003).

The above results create an emerging picture of derangement of growth stimulatory protein kinase signaling pathways in TGCT, including activations in the RAS and KIT pathways in most seminomas and nonseminomas (Kemmer et al, 2004; Sommerer et al, 2005). Activated AKT has also been observed concomitant with **both RAS and KIT activation of the PI3K/AKT pathway** (Kemmer et al, 2004). In addition, **the PI3K antagonist PTEN is reported to**

be frequently inactivated by either mutation or deletion in both seminomas and nonseminomas, further suggesting an important role for activated PI3K/AKT pathway in TGCT (Teng et al, 1997; Di Vizio et al, 2005).

Normal PGC undergo programmed erasure of DNA CpG methylation marks and thus a loss of imprinting. Recent IHC studies using an anti–5-methylcytosine antibody to assess global methylation status in situ have confirmed and extended prior reports focusing on specific loci. These new studies found very low to absent 5-methylcytosine in the vast majority of ITGCNU and seminoma compared to robust detection of 5-methylcytosine in nonseminomas (Peltomaki, 1991; Smiraglia et al, 2002; Zhang et al, 2005; Netto et al, 2008). These results are supportive of a model for TGCT pathogenesis in which ITGCNU is derived from retained abnormal PGC that have matured to the point of 5-methylcytosine erasure, but prior to the point in normal PGC development where epigenetic marks are reestablished by de novo DNA methylation. Notably, such observed changes in global methylation do not necessarily rule out the existence of hypermethylation at specific gene promoters. For instance, epigenetic silencing of specific genes, such as the tumor suppressor *RASSF1A,* has been reported in seminoma (Koul et al, 2002; Honorio et al, 2003).

Key Points: Chromosomal Abnormalities and Genetic Instability

- Large variations in chromosome numbers and complex structural rearrangements, as well as intratumoral heterogeneity in these aberrations, are hallmarks of most human solid tumors.
- The extent of chromosomal abnormalities typically correlates with disease severity and aggressiveness.
- Recurrent structural rearrangements occur in prostate (*ETS* family gene fusions), renal (*MITF/TFE* family translocation carcinomas), and testicular cancers (isochromosome 12p).
- Copy number alteration in a particular gene, coupled with changes in the other allele is strong evidence for that gene functioning as a disease-relevant oncogene or tumor suppressor gene.
- Genes discovered to have germ line mutations that cause familial forms of cancer may also be involved in the sporadic form of the disease (e.g., *VHL* in ccRCC).
- High-density single nucleotide polymorphism (SNP) microarrays have been used in genome-wide association studies (GWAS) to identify DNA sequence variants associated with cancer risk.

TELOMERES AND TELOMERASE

As we have seen, **cancer cells exhibit marked genetic, morphologic, and behavioral heterogeneity, a reflection of their underlying genetic instability. In addition, most cancers display a strong positive association with increasing age.** As discussed previously, it has been persuasively argued that an increase over the extremely low baseline mutation rate (a mutator phenotype) is needed for accrual of sufficient mutations to bring about malignant transformation (Loeb, 1991).

Cancer genomes exhibit clear evidence of instability; however, defective DNA maintenance and repair genes do not appear to be major contributors to the development of most sporadic cancers. Thus the source of the genetic instability involved in the majority of cancers has been unclear. This has been particularly true of chromosomal instability, a nearly ubiquitous feature of carcinomas. Although alterations in chromosome number may arise through defects in centrosomes or the mitotic spindle checkpoint, very little information exists regarding the origins of structural chromosomal abnormalities (Pihan et al, 2003; Roh et al, 2003). **An attractive candidate for the source of chromosomal instability in cancer is telomere dysfunction. Telomeres may provide a common link between genetic instability, cellular proliferation, and ageing** (Shay, 1997; DePinho, 2000).

Telomeres and Chromosomal Instability

Telomeres are structures composed of specialized repetitive DNA complexed with telomere-specific binding proteins, located at the ends of every human chromosome where they function to stabilize and protect the ends (Blackburn, 1991). Telomeric DNA is noncoding and consists of tandem repeats of the 6–base pair sequence TTAGGG (Moyzis et al, 1988; Meyne et al, 1989). In normal human cells, telomere lengths typically range from 6 to 12 kilobases per chromosome. **Telomeres that are too short are dysfunctional ("uncapped"), causing chromosomal destabilization** (Karlseder, 2003; Saldanha et al, 2003).

Importantly, telomeres are dynamic; shortening by approximately 100 base pairs each time a cell divides due to inability of DNA polymerases to completely replicate terminal DNA sequences (Harley et al, 1990; Lindsey et al, 1991). **Thus telomere length is inversely correlated with the number of times a cell has divided** (Hastie et al, 1990; Levy et al, 1992). Telomere shortening may also occur due to unrepaired single-strand breaks caused by oxidative damage to telomeric DNA (Kruk et al, 1995; von Zglinicki et al, 2000). Conversely, telomeres may be elongated through the action of the telomere synthetic enzyme telomerase or, uncommonly, by a poorly characterized telomerase-independent genetic recombination mechanism termed alternative lengthening of telomeres (ALT) (Greider and Blackburn, 1985; Reddel et al, 2001).

Chromosomes with short, dysfunctional telomeres are prone to fusion, leading to the formation of dicentric chromosomes that mis-segregate or break in mitosis during anaphase. The newly generated chromosomal breaks are themselves fusogenic, thus perpetuating a cycle of chromosome fusion and breakage (McClintock, 1941; Lo et al, 2002). In this way, critically short telomeres initiate chromosomal instability (Artandi et al, 2000; Feldser et al, 2003; Vukovic et al, 2007). **Numerous studies support the link between telomere dysfunction and chromosomal instability in human cancers.** For example, in head and neck tumors, chromosomes bearing severely short telomeres are associated with chromosomal fusions, rearrangements, anaphase bridges, and multipolar mitoses (Gisselsson et al, 2000).

Telomere Shortening Acts as a Tumor Suppressive Mechanism in Normal Cells

Normal cells closely monitor their telomere lengths. Moderate telomere shortening either signals entry into an irreversible cell cycle arrest termed replicative senescence, or initiates programmed

cell death—responses thought to have evolved as tumor suppressive barriers against abnormal clonal expansion and the development of excessive telomere shortening that would accompany further cell division, were it allowed to continue (Wright and Shay, 2001). Thus **progressive telomere shortening acts as a "mitotic clock," counting down cell divisions and signaling cell cycle exit once one or more telomeres reaches a threshold length** (Harley et al, 1990).

Forced expression of the enzyme telomerase in presenescent cells counteracts telomere shortening, thus preventing replicative senescence and endowing the cells with unlimited cell division potential or "immortalization" (Bodnar et al, 1998; Vaziri and Benchimol, 1998). In normal somatic human cells, telomerase activity is stringently repressed; thus telomere length will decrease in proliferating cells and can be used as a signal to halt further expansion. **Although the precise mechanism(s) by which short telomeres trigger senescence and apoptosis are still under study, evidence, to date, implicates the tumor suppressors TP53 and pRB as being involved in the response to shortened telomeres** (Vaziri and Benchimol, 1999). Importantly, abrogation of this telomere length checkpoint allows continued cell division and, in the absence of telomerase, severe telomere shortening beyond the minimum length required for proper telomere function, therefore causing telomere uncapping and chromosomal destabilization (Counter et al, 1992).

In summary, **telomere shortening presents two important barriers to incipient cancer cells. First, moderate shortening instigates the senescence cell cycle exit. Second, extreme telomere shortening causes chromosomal instability that, although it increases the mutation rate, will also tend to result in lethal genetic abnormalities** (Fig. 18–13).

Cancers and Premalignant Lesions Possess Abnormally Short Telomeres

The majority of human cancer tissues and cancer-derived cell lines examined to date have been found to contain abnormally short telomeres (Hastie et al, 1990; Mehle et al, 1996; Takagi et al, 1999; Furugori et al, 2000; Remes et al, 2000). For example, prostate carcinomas typically have shorter-than-normal telomeres. Using a Southern blot technique for bulk telomere length assessment, Koeneman and colleagues (1998) and Sommerfeld and colleagues (1996) observed telomere shortening in primary prostate cancer tissues compared with matched adjacent or nearby normal-appearing and benign proliferative hyperplasia (BPH) areas in radical prostatectomy specimens. Furthermore, results from direct telomere length assessment in archival tissue samples using FISH are also in agreement with the previous telomere length analyses, with shorter telomeres found in prostate cancer cells when compared with their normal epithelial cell counterparts within the same tissue samples (Meeker et al, 2002a).

When examined using high-resolution telomere-specific FISH, it has been found that **pre-malignant lesions, including those of bladder and prostate cancer, tend to have abnormally short telomeres** (van Heek et al, 2002; Meeker et al, 2004; Meeker and Argani, 2004; Hansel et al, 2006; Kawai et al, 2007). This finding indicates that **telomere loss occurs early in the disease process**, at the intraepithelial neoplasia (IEN) stage, **strongly implying a causal role for telomere shortening in carcinogenesis through the initiation of chromosomal instability** (O'Shaughnessy et al, 2002). In the prostate, the premalignant precursor is high-grade prostatic intraepithelial neoplasia (HGPIN) (Bostwick et al, 1996), the majority of which (93%) were found to harbor abnormally short telomeres by FISH (Meeker et al, 2002b). Notably, in this study,

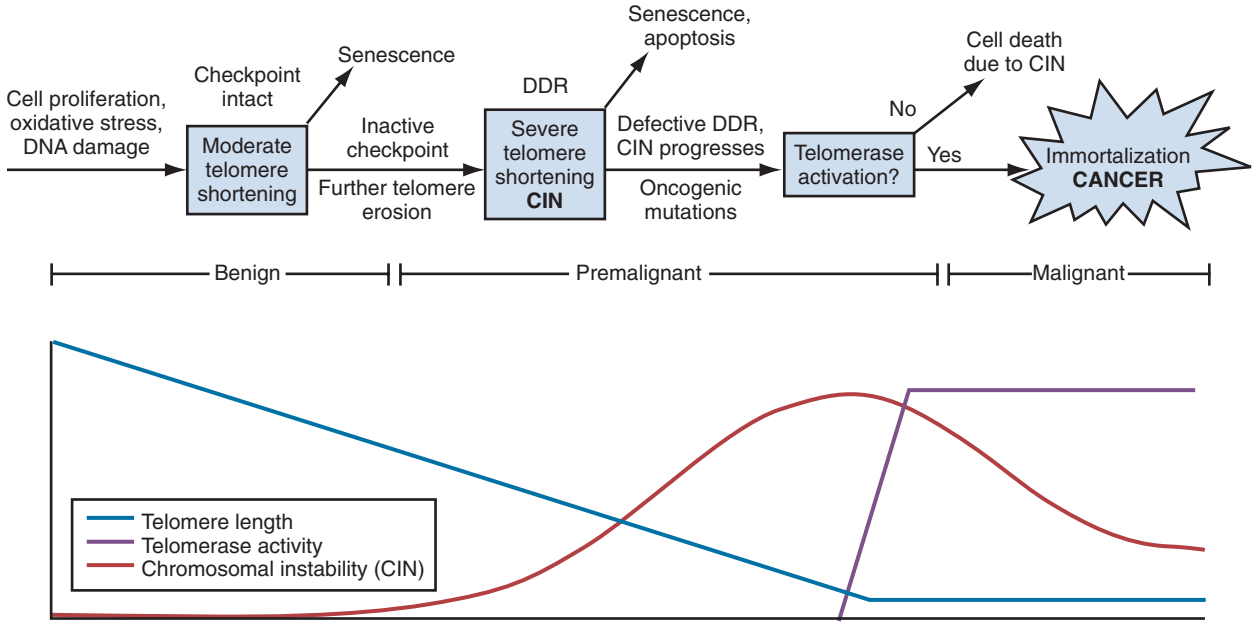


Figure 18–13. Contributions of telomere loss and telomerase activation to oncogenesis. Bypass of the normal telomere length-sensitive cell senescence checkpoint allows severe telomere loss that initiates chromosomal instability (CIN). Defective DNA damage response (DDR) allows CIN to continue, generating potentially oncogenic mutations but also producing intolerable levels of genomic damage. Transformed cells may proceed through this second barrier by activating telomerase, which stabilizes the telomeres and also provides an unlimited proliferative potential ("immortalization").

telomere shortening in HGPIN foci was restricted to the *luminal* secretory epithelial cells only, while the underlying basal epithelial cells and surrounding stromal cells displayed normal telomere lengths. In a separate independent study, Vukovic and colleagues (2003), reported significant shortening in 63% of HGPIN overall, with a higher rate of telomere shortening (80%) reported for foci situated near (within 2 mm) adenocarcinoma within the same tissue sample. When studying a cohort of men with a diagnosis exclusively of HGPIN (using prostate needle biopsies), Joshua and colleagues (2007), reported an association between short telomeres in the PIN lesions, or surrounding stromal cells, and eventual diagnosis of prostate cancer, as well as time to diagnosis.

The level of telomere shortening observed in PIN exceeds that which would normally elicit a cell cycle checkpoint response, thus implying that the telomere checkpoint tumor suppression system is defective in PIN lesions. Similar levels of telomere shortening have been correlated with markers of chromosomal instability in other organ systems (O'Sullivan et al, 2002; Meeker et al, 2002b; Meeker and Argani, 2004; Montgomery et al, 2004). One candidate element of an abrogated checkpoint response in PIN is 13-3-3-sigma. This protein is normally induced by *TP53* in response to DNA damage and leads to G_2M cell cycle arrest (Hermeking, 2003). Lodygin et al (2004), found the promoter of this gene to be hypermethylated in prostate cancer cell lines and 100% of primary prostate cancers assayed. Decreased 13-3-3-sigma protein expression was also seen in 91% of prostate cancers, while normal, atrophic, and BPH areas showed high levels of expression in both luminal and basal epithelial cells. Interestingly, 13-3-3-sigma protein expression levels were also low in the luminal cells of PIN lesions, whereas basal cells retained robust expression, matching the aforementioned pattern of telomere shortening seen in HGPIN (Lodygin et al, 2004). **Because the majority of PIN lesions are not thought to progress to invasive cancers, intact telomere-based replicative senescence or apoptosis checkpoints may represent a critical bottleneck restraining the outgrowth of most PIN lesions. Even if incipient cancer cells manage to abrogate these checkpoints, as described below, they would still need to activate telomerase to avoid intolerable levels of genetic instability and provide an immortalized phenotype.**

A consideration of telomere biology as outlined above leads to the conclusion that telomeres can play opposing roles in the development of cancer. On the one hand, telomere shortening places strict limits on the proliferative capacity of a given cell lineage, thus serving to prevent the expansion of potentially malignant (initiated) cells. This is supported by mouse models engineered with combinations of telomere dysfunction and cancer predisposition, where the overall tumor incidence is decreased in the short telomere background (Karlseder et al, 1999; Farazi et al, 2003; Wong et al, 2003). On the other hand, critically short telomeres can promote carcinogenesis by initiating chromosomal instability (Artandi et al, 2000; Feldser et al, 2003). In keeping with this, the frequency of *initiated* lesions is increased in the aforementioned combined mouse models, despite the decrease in overall tumor incidence (Karlseder et al, 1999; Farazi et al, 2003; Wong et al, 2003). The deciding factor in determining which of these opposing outcomes wins appears to be the status of the cellular checkpoint pathways that monitor telomere length. Thus, telomerase deficient mouse models support a tumor suppressive role for telomere shortening only if cellular checkpoints are intact; particularly the Tp53 tumor suppressor pathway. Research on mice doubly deficient for telomerase and Tp53 has revealed a key role for dysfunctional telomeres in the development of epithelial cancers in the setting of defective checkpoints, and tumors arising in such a background of short dysfunctional telomeres display the types of complex karyotypic abnormalities typically seen in human carcinomas but usually lacking in mouse models of human cancer (Artandi et al, 2000; O'Hagan et al, 2002).

The root cause of the telomere shortening that occurs during malignant transformation in humans is unknown. Because telomeres shorten during cell division, one possibility is that telomeres are progressively lost through normal division as cells are replaced during ageing. This would help explain the strong dependence of cancer on age (Hsing et al, 2000). On the other hand, in an organ such as the prostate, the normal rate of cell division is relatively low; thus it may be that other processes serve to accelerate cell turnover and/or telomere loss. One such process may be inflammation, a common histologic finding in the prostate that also increases with age (De Marzo et al, 2007a). Locally, the inflammatory response generates genotoxic chemical species such as oxy-radicals as part of the host defense mechanism against pathogens. Exposure to these chemicals causes co-lateral host cell killing leading to compensatory proliferation in order to replace the lost cells. Furthermore, oxidative stress itself is able to cause rapid loss of telomere DNA (von Zglinicki, 2002). Additionally, **chronic inflammation not only increases cell turnover and perhaps telomere loss, but the accompanying genotoxic stress may impair telomere-sensitive senescence/apoptosis checkpoints, as well as DNA damage-sensitive checkpoints, perhaps in cells whose genomic protection is already crippled**—for instance, due to epigenetic downregulation of glutathione-S-transferase Pi (Nakayama et al, 2003; Nelson et al, 2003).

Telomerase Activity Restabilizes Chromosomes and Allows Unlimited Replication

Although dysfunctional telomeres may help initiate cancer formation, if left unchecked continued telomere shortening in premalignant lesions and cancers would cause increasing levels of genetic instability ultimately becoming lethal to the tumor. Cancer cells overcome this problem by restabilizing their telomeres, primarily through activation of the enzyme telomerase, a specialized reverse transcriptase that adds back telomere DNA repeats to chromosome ends (Greider and Blackburn, 1987). Telomerase provides at least two critical functions to the tumor cell—namely, quelling chromosomal instability and supplying the capacity for unlimited replication ("immortalization") (Shay and Wright, 1996; Greider, 1998). Research has revealed that telomere length maintenance appears to be a necessary step for human cells to become malignant; confirming the long-held belief that cellular immortalization is a key attribute of cancer cells (Hahn et al, 1999; Elenbaas et al, 2001). Thus **at least 85% of human epithelial cancers have measurable telomerase activity** (Kim et al, 1994; Meeker and Coffey, 1997; Shay and Bacchetti, 1997). **In contrast to cancer cells, telomerase activity is stringently repressed in most normal human somatic cells, thus allowing telomere loss to act as the counting element of the tumor-suppressive mitotic clock** (telomere length checkpoint) (Shay, 1997; Harley, 2002). A subset of normal cells do express some telomerase, including activated lymphocytes; subpopulations of highly proliferative tissues, such as in the hematopoietic system

and testes; and proliferative zones in renewal tissues, such as the intestinal crypts and the basal layer of the skin and cervix, plus hormonally-responsive cells of the female breast and endometrium, as well as the prostate (Broccoli et al, 1995; Harle-Bachor and Boukamp, 1996; Hiyama et al, 1996; Meeker et al, 1996; Weng et al, 1996; Wright et al, 1996; Yasumoto et al, 1996; Kyo et al, 1997). Notably, the activity detected in these normal tissues is either transient or much weaker than that found in malignant tumors of the same tissue of origin.

Although telomerase activity appears to be the preferred way cancer cells stabilize their telomeres, approximately 15% of human cancer cases lack detectable telomerase activity. At least a subset of these, particularly certain tumors of mesenchymal origin, maintain their telomeres through a telomerase-independent pathway known as alternative lengthening of telomeres (ALT), the details of which are still being uncovered (Reddel, 2003).

Several studies have reported on telomerase activity in clinical prostate samples, with positivity ranging from 47% to 100%, whereas normal and BPH tissues taken from prostates without evidence of cancer are typically negative for telomerase activity (Kim et al, 1994; Sommerfeld et al, 1996; Engelhardt et al, 1997; Kallakury et al, 1997; Lin et al, 1997; Koeneman et al, 1998; Zhang et al, 1998; Wullich et al, 1999; Caldarera et al, 2000; Kamradt et al, 2003). Although two of these studies found a positive correlation between either the presence or level of telomerase activity and tumor grade, four other studies found no correlation with grade, stage, or preoperative PSA levels. However, the number of cases in many of these studies was small. Furthermore, the situation is complicated by the observation that a tumor initially lacking telomerase could conceivably acquire it at a later time.

Telomerase Activity as a Potential Diagnostic Marker

Although there are potential confounding factors when assaying telomerase activity (e.g., activity in activated lymphocytes, intratumoral heterogeneity of activity, etc.), the high prevalence and relatively strong activity found in prostate cancers compared with normal tissue, plus the very high sensitivity of the standard telomerase activity assay has led to evaluation of the telomerase activity assay as a potential diagnostic marker for prostate cancer. In the prostate, activity assays have been performed using prostate needle biopsy samples (Scates et al, 1997; Takahashi et al, 1997; Lin et al, 1998; Bertaccini et al, 1999; Muller, 1999; Wymenga et al, 2000; Chieco et al, 2001; Wang et al, 2001). In these studies, activity was detected in over half of all cancer cases (range 58% to 91%), with most reporting telomerase activity in greater than 80% of cases with cancer. In two of five studies that also tested normal prostate tissue, no activity was detected in normal tissue. However, the remaining three studies found activity in 11% to 17% of samples lacking prostate cancer. Likewise, two studies that included BPH tissues detected activity in 12% and 38% of cases, although, in the former, the activity seen was very weak, and cancer was later detected in these patients by repeat biopsy (Wymenga et al, 2000). This study also found a trend for increased activity levels in cancers of higher Gleason grade, although this did not reach statistical significance in this small study. Lin and colleagues (1998) and Wang et al (2001) also noted a positive correlation between either activity levels or telomerase detection rates and pathologic grade. Using a split biopsy approach, Lin and colleagues (1998), showed that differences in activity levels they observed were not simply due to different amounts of cancer in the needle biopsy samples. Similarly, using a touch preparation method, Chieco and colleagues (2001) found no association between activity detected and either area of cancer or extent of inflammation on the needle biopsy.

In addition to tissue biopsy samples, noninvasive detection of telomerase enzyme components and enzymatic activity has been attempted. Overall, the potential utility of aiding cancer diagnosis appears limited, primarily due to problems with both false-negative and false-positive results seen with the technically demanding assay. False-negative results may occur due to inactivation of the labile enzyme during isolation, while false-positive results may stem from the presence of inflammatory cells in the sample (Meeker and Coffey, 1997). One avenue showing some early promise is the detection of bladder cancer in voided urine and bladder washings. Bladder cancer diagnosis and surveillance is currently conducted by a combination of cystoscopy and urine cytology; however, cytology provides suboptimal sensitivity in low-grade disease. Detection of telomerase components by RT-PCR in urine provides some improvement in the sensitivity and specificity compared with urine cytology in bladder cancer detection, particularly in low-grade disease (Eissa et al, 2007). However, van Rhijn and colleagues (2005) recently reviewed the literature on urinary molecular markers for bladder cancer detection and concluded that other markers (e.g., microsatellites, FISH, and cytokeratin 20) outperform telomerase.

In an intriguing study, Wu and colleagues (2003) **found that shorter telomeres in peripheral blood leukocytes (PBL), as measured with telomere-specific Q-PCR, were associated with increased risk for a number of cancers, including bladder and renal cancer**. Similar associations between short telomeres and bladder cancer risk were observed when telomere lengths were measured in either buccal cells or PBL (Broberg et al, 2005; McGrath et al, 2007). **However, no association was observed between PBL telomere length and prostate cancer risk in a recent study** (Mirabello et al, 2009). Interestingly, a recent report by Svenson and colleagues found that patients with the longest PBL telomeres had a significantly worse prognosis compared with patients with shorter PBL telomeres (Svenson et al, 2009). The variations in the PBL telomere lengths measured in these studies are thought to be due to inherited interindividual differences in telomere lengths modified by changes occurring postnatally, perhaps due to diet and lifestyle factors. It is often assumed that telomere lengths obtained in PBL reflect those in other tissues throughout the body, although this remains to be rigorously shown.

Potential Prognostic Value of Telomere Length in Prostate Cancer

Telomere shortening has been found to be predictive of poor prognosis in several cancers including those of the lung, endometrium, breast, and neuroblastoma (Smith and Yeh, 1992; Hiyama et al, 1995a; Hiyama et al, 1995b; Griffith et al, 1999; Bisoffi et al, 2006). A potential link between telomere length and prostate cancer prognosis was first reported by Donaldson et al (1999), using a slot blot method devised by Bryant and colleagues (1997), which measures relative telomeric DNA content, a surrogate for telomere length. In this retrospective case-control study, both biochemical recurrence and overall survival were significantly correlated with tumor telomere content. Specifically, all seven prostatectomy patients, whose tumor telomeric DNA contents were less than that of control samples (placental DNA),

showed evidence of biochemical recurrence (elevated PSA) within 10 years after surgery (Donaldson et al, 1999). Of the nine patients with short tumor telomeres, seven died within 10 years, in contrast with 100% ten-year survival for patients with normal-to-long tumor telomeres. Additionally, these patients also showed no evidence of biochemical recurrence. Potential drawbacks of this study include a small sample size (18 cases; only seven of nine men in the short telomere category underwent surgery), and that it was not known whether the deaths observed were due specifically to prostate cancer. In a more recent retrospective study using 77 prostatectomy samples and a more sensitive chemiluminescent slot blot assay, Fordyce and colleagues (2002) reported that less-than-normal telomere content in primary prostate cancers was associated with recurrence, independent of patient age, grade (Gleason sum), and regional lymph node status (Fordyce et al, 2005). The magnitude of the relative hazard for disease recurrence associated with low telomere content (RH = 5.02) was on par with that of Gleason grade and nodal status. Interestingly, a positive correlation was found between telomere content of the tumor and that of the surrounding normal-appearing prostate tissue within the same prostatectomy samples. An association was also found between telomere content of these normal-appearing prostate tissues and 72-month recurrence-free survival. The authors postulated that telomere loss in morphologically normal tissue represent areas at heightened risk for genetic instability. This is reminiscent of the so-called "field effect" phenomenon that has long been discussed in the cancer literature (Crissman et al, 1993; Bostwick et al, 1998; Foster et al, 2000; Yuen et al, 2004). The authors further proposed that cancers arising in such areas may show greater genotypic and phenotypic heterogeneity, and thus be more prone to behave aggressively due to a greater level of chromosomal instability caused by short telomeres (Fordyce et al, 2005).

Telomerase-Based Opportunities for Therapy

Because the majority of human tumors rely on telomerase for immortalization and genomic stabilization, this enzyme is an attractive target for anticancer therapy. There are two overall strategic paradigms for therapeutic targeting of telomerase in cancer. The first involves taking advantage of the tumor's dependence on telomerase enzymatic activity for survival. This strategy includes approaches aimed at directly inhibiting telomerase enzymatic activity or blocking its expression. The second approach attempts to exploit the observation that the telomerase gene (*HTERT*) promoter is selectively active in cancer cells. For example, the telomerase promoter could be used to drive oncolytic virus or gene therapy vectors and thus limit their replication or expression to tumor cells. Also, immunotherapy could be directed against cells expressing HTERT protein.

Many of these approaches have undergone preclinical testing using prostate cancer cell lines and xenografts, and some are currently in early clinical trials. One point of concern with anti-telomerase therapies relates to their selectivity of action against tumor cells versus normal telomerase-positive cells, such as the stem cells of the hematopoietic system and those within tissues with high turnover rates. This is of particular importance for those approaches in which telomerase-positive cells are actively targeted for destruction, including immunotherapy, gene therapy, and oncolytic viral therapies. Encouragingly, work to date describing the treatment of human tumor xenografts in mice have, in general, not produced major toxicity in normal tissues.

Key Points: Telomeres and Telomerase

- Telomeres contain stretches of terminal, noncoding, repetitive DNA that cap the ends of each chromosome, thereby stabilizing them.
- Telomere DNA repeats are progressively lost as cells divide and as a result of oxidative DNA damage at the telomeres.
- Normal cells monitor their telomere lengths and permanently exit the cell cycle (cellular senescence) or commit suicide (apoptosis) in response to telomere shortening. This tumor-suppressive telomere length checkpoint involves *TP53* and *pRB*.
- Loss of telomere length checkpoints can lead to critical telomere shortening that initiates chromosomal instability, thus contributing to carcinogenesis.
- A majority of cancers and premalignant lesions have abnormally short telomeres.
- Most cancers express the enzyme telomerase, which restabilizes the telomeres and allows unlimited cell division potential ("immortalization"), thus telomerase represents an attractive therapeutic target.

APOPTOSIS

Apoptosis, also known as programmed cell death, is a tightly regulated process used by multicellular organisms to eliminate unwanted cells. For example, apoptosis is used in tissue remodeling during development, and in the immune system to eliminate self-reactive T cells (Kerr et al, 1972; Ashkenazi and Dixit, 1998). **Apoptosis contrasts sharply with necrosis, a nonprogrammed form of cell death** in which cells that are acutely injured (e.g., by physical trauma) swell and burst, abruptly releasing their contents, which act as potent inducers of the inflammatory response. **Apoptosis is a more orderly, energy-requiring process in which the dying cell's contents are degraded and neatly packaged into so-called apoptotic bodies, which are then engulfed by neighboring cells or macrophages, a process which does not elicit a strong inflammatory response** (Fadok et al, 1992).

Apoptosis and Cancer

Unlike unicellular organisms, cancer poses a risk to multicellular life forms; thus a variety of abnormalities linked to tumorigenesis can signal a cell to eliminate itself as a potential threat by apoptosis. For example, if a cell suffers DNA damage (potentially mutagenic), but fails to make repairs, it will be eliminated and replaced from the organism's pool of undamaged cells. **Depending on the location, environment, or extent of damage, apoptosis may even be the primary response to DNA damage** (Evan and Littlewood, 1998). Other potentially oncogenic abnormalities that can signal apoptosis include excessive *E2F* transcriptional activity, loss of cell contact to other cells and the basement membrane, hypoxia and activated oncogenes (e.g., c-*MYC*). Therefore, it is not surprising that aberrations of apoptosis can be detrimental, and that failure of dividing cells to initiate apoptosis contributes to cancer (Ashkenazi and Dixit, 1998).

Abnormalities in the apoptotic machinery have implications for malignancy beyond an individual cell's ability to respond appropriately to cell physiologic stresses such as DNA damage. First, **the apoptosis cascade is critical to the immune system's**

ability to eliminate cancer cells (Nagata, 1997). This has clear implications for both the organism's intrinsic immunosurveillance for malignancy and the tumor's response to extrinsic immunotherapy. Second, because cytotoxic cancer therapies depend in large part on inducing apoptosis, **defects in the apoptotic cascade can profoundly influence tumor responses to chemotherapy and radiotherapy** (Walton et al, 1993; Bostwick et al, 1998; Thornberry, 1998).

Apoptosis Is an Evolutionarily Conserved Process

Apoptosis is tightly regulated by an evolutionarily conserved system of positive and negative signals, the balance of which determines whether the cell will undergo apoptosis. These signals ultimately converge upon an important family of proteases named caspases ("cysteine proteases with aspartic acid specificity"), key components of the apoptotic machinery (Thornberry and Lazebnik, 1998). Caspases, of which there are at least 13, are **broadly categorized as either initiator caspases (e.g., caspases-8, -9, and -10) or executioner caspases (e.g., caspases-3, -6, and -7).** Caspases are synthesized as larger, inactive forms called procaspases, which **require specific proteolytic cleavage to become active proteases themselves.** Often a procaspase is activated by another caspase, setting in motion a sequential, amplifying, proteolytic cascade. **Initiator caspases begin the cascade that ultimately leads to activation of executioner caspases downstream. Once activated, the executioner caspases attack several intracellular protein targets.** One of the initial targets of executioner caspases is procaspase-8, activation of which serves to accelerate the apoptotic process by a positive feedback loop. Executioner caspases cleave antiapoptotic proteins, such as BCL-2 and BCL-X_L, which not only destroys their antiapoptotic function but actually releases proapoptotic carboxyl-terminal fragments, further stimulating cell death (Wolf and Green, 1999). Executioner caspases then target proteins critical to cell survival, from DNA to the extracellular matrix. Cleavage of DNA repair and replication proteins, such as DNA-PK_{cs} and replication factor C, leads to nuclear dysregulation. Nuclear structural proteins such as lamins NuMA and SAF-A are fragmented, contributing to dissolution of the nucleus and nuclear condensation, a hallmark of apoptosing cells. Proteolysis of cytoskeletal proteins, such as fodrin, keratin, and actin, leads to destruction of the internal structural integrity of the cell. Lastly, cleavage of proteins critical to cell–cell interaction, such as β-catenin and focal adhesion kinase (FAK), precipitates the specific and irreversible phenotypic changes associated with apoptosis (Orth et al, 1996; Wen et al, 1997; Wolf and Eastman, 1999). **The end result is a stereotypical death in which the cytoplasm shrinks, the cell membrane blebs, and the nuclear chromatin condenses. The entire apoptotic process can be completed in just 60 minutes** (Thornberry, 1998).

Intrinsic Apoptotic Pathway

Apoptosis can be initiated by two different routes: the intrinsic and the extrinsic apoptotic pathways (Fig. 18–14). **The intrinsic apoptotic pathway monitors conditions within the cell, responding to various forms of stress.** Proapoptotic signals may arise due to unrepaired DNA damage or from a lack of prosurvival signals transduced from cell-surface receptors, such as when cell–cell or cell–extracellular matrix (ECM) contact is disrupted or soluble factors such as hormones or growth factors are withdrawn.

The mitochondrion is the main site of the intrinsic pathway, including the conserved protein family BCL-2. BCL-2 family members include both pro- and antiapoptotic proteins. The proapoptotic group consists of at least a dozen members, including BAX, BAK, BOK, BIK, BAD, BID, and BIM. There are at least a half dozen antiapoptotic (prosurvival) BCL-2 family members, including BCL-2 itself, BCL-X_L, BCL-W, and MCL1 (Adams and Cory, 1998). All members contain one or

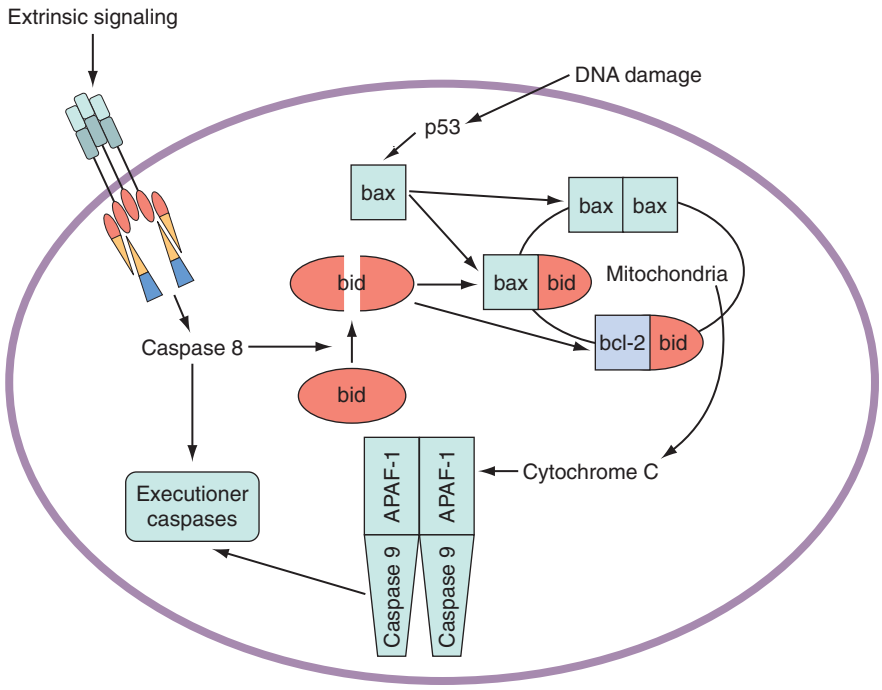


Figure 18–14. Cascade of extrinsic and intrinsic mechanisms of apoptosis. The extrinsic system depends on ligand-induced activation of executioner caspases, whereas the intrinsic system depends on the dimerization of BCL2 family members to alter mitochondrial membrane permeability.

more BCL-2 homology domains (BH1 to BH4) that allow members of the family to heterodimerize with each other. BCL-2 family members regulate each other's function through these BH domains (Chittenden et al, 1995; Cheng et al, 1996). Whereas each pro-apoptotic BCL-2 family member responds to different stimuli, **the principal mechanism by which they induce cell death is by increasing mitochondrial membrane permeability** (Kroemer and Reed, 2000). When apoptosis is signaled by the intrinsic pathway, the balance between BCL-2 family members shifts in favor of pro-apoptotic proteins that increase the permeability of the mitochondrial outer membrane, facilitating the release of cytochrome *c* from the intermembrane space into the cytoplasm (Jurgensmeier et al, 1998; Wolf and Eastman, 1999). **Once in the cytoplasm, cytochrome *c* molecules bind to APAF-1 proteins, forming a complex known as the apoptosome. The apoptosome activates caspase-9, one of the initiator caspases, thus beginning the caspase cascade as described above** (Li et al, 1997b).

Antiapoptotic BCL-2 family members block apoptosis by inhibiting the proapoptotic family members and, in doing so, decreasing mitochondrial permeability (see Fig. 18–14) (Li et al, 1997b; Srinivasula et al, 1998).

BAX is the best-studied proapoptotic BCL-2 family member. It is transcriptionally activated by TP53. Once activated, BAX dimerizes at the mitochondrial membrane. The dimer forms a channel that facilitates the release of cytochrome *c* from the mitochondria. BCL-2 is the best-studied antiapoptotic BCL-2 family member. It functions by binding to BAX and, in doing so, blocks BAX-induced mitochondrial permeability (Miyashita et al, 1994; Adams and Cory, 1998).

Other proapoptotic family members are activated by a variety of stimuli. Often they function not by inducing mitochondrial permeability directly but by activating or inhibiting other BCL-2 family members. The first example is BID. BID is regulated by initiator caspases. Cytosolic BID is activated by caspase-8 (see Fig. 18–14). This allows dimerization of BID with either BAX or BCL-2. This dimerization activates BAX activity and inhibits BCL-2. The net result is to tip the balance in favor of apoptosis (Li et al, 1998). Because BID is activated by caspases, it provides a link between the ligand-induced apoptotic machinery of the extrinsic pathway (described below) and BCL-2 family members.

A second example is BAD. BAD is not regulated by transcription or by cleavage but by AKT-dependent phosphorylation. In tumors with activation of the TPI3 kinase pathway, the resulting AKT activation leads to BAD phosphorylation, which is prosurvival. In contrast, removal of growth factors has been demonstrated to deactivate AKT, which leads to dephosphorylation of BAD. BAD can then bind to and inactive BCL-2, the net result being proapoptotic (Kroemer and Reed, 2000).

An additional level of regulation is provided by inhibitor of apoptosis proteins (IAPs), a family of proteins which act to prevent apoptosis by inhibiting specific caspase proteases, either directly or by inhibiting the conversion from the procaspase to the active form (Deveraux et al, 1998).

Extrinsic Apoptotic Pathway

In addition to the intrinsic pathway, a second pathway termed the extrinsic pathway mediates apoptosis following receipt of extracellular signals from cell surface receptors called "death receptors," such as the tumor necrosis factor receptor, TNFR1, and the FAS receptor (Fig. 18–15). These receptors belong to the tumor necrosis factor superfamily and contain a ligand-specific extracellular domain and an intracellular "death domain." The binding of extracellular signaling molecules to the receptor activates the receptor, which then signals through the death domain located on the cytoplasmic portion of the receptor. The death domain allows the receptor to bind to intracellular adaptor proteins that also contain a death domain (e.g., RIP, TRADD, FADD). In addition to their own death domain, the adaptor proteins have a death effector domain that allows the adaptor protein to bind to the caspase recruitment domain (CARD) of initiator caspases (Ashkenazi and Dixit, 1998). Once bound, the initiator caspases undergo self-cleavage and are then capable of activating effector caspases by the caspase cascade. (Li et al, 1998; Muzio, 1998).

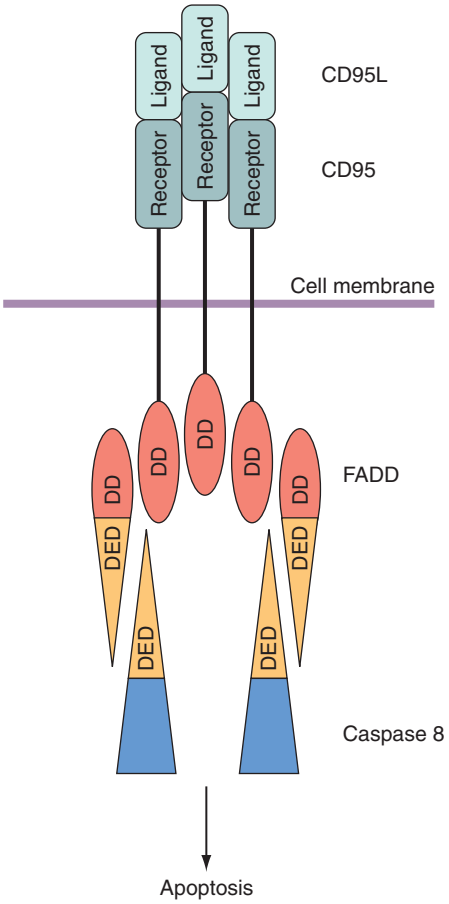


Figure 18–15. Example of death receptor–mediated activation of initiator caspases.

The best-characterized death receptor is CD95, or FAS, which appears to play an important role in cancer immunosurveillance (Ashkenazi and Dixit, 1998). The ligand CD95L (also known as FAS ligand or FASL) forms a trimer that binds three CD95 receptors (Nagata, 1997). The clustering of CD95 allows the adaptor protein FADD to bind to CD95 by their death domains (see Fig. 18–15). In turn, procaspase-8, or FLICE, binds to FADD by the death effector domain. Procaspase-8 oligomerization promotes autoactivation to active caspase-8 (Muzio, 1998). Other initiator procaspases, such as procaspase-10, are activated through similar mechanisms (Vincenz and Dixit, 1997). Negative regulatory molecules, such as FLIP, bind to FADD and, in doing so, inhibit procaspase-8 binding and therefore apoptosis (Irmler et al, 1997).

A second important death receptor is TRAIL (Mariani et al, 1997). In contrast to CD95L, which is predominantly expressed on activated T lymphocytes and natural killer cells (Nagata, 1997), TRAIL's receptors, DR4 and DR5, are expressed in many human tissues, including the prostate. Similar to CD95L-mediated apoptosis, TRAIL induces cell death through caspase activation. Again, negative regulatory elements, such as the decoy receptor TRID, play an important role in modifying the ligand's activity. TRID binds to TRAIL, but because it lacks a death domain, it is unable to bind adaptor proteins and therefore blocks the pathway (Pan et al, 1997).

The death receptor pathway does not appear to have a direct role in the etiology of cancer. Patients with hereditary defects in this system and knockout mice are both characterized by T-cell abnormalities and fatal autoimmune syndromes, but not hereditary tumor syndromes (Nagata, 1997). **However, the identification of ligand-dependent apoptosis receptors may have a profound impact on therapy. Most cancer therapies (i.e., chemotherapy and external-beam radiation therapy) depend on *TP53* to induce apoptosis in the cancer cell. Because *TP53* is mutated in over half of malignancies** (Hollstein et al, 1991), ***TP53*-independent pathways for apoptosis are of great clinical interest. Because the ligand-dependent apoptosis described earlier is independent of *TP53*, this makes these receptors and ligands attractive novel treatment targets.** Unfortunately, compounds that bind to the receptors are extremely toxic (Nagata, 1997). Hopefully, novel compounds will have improved toxicity profiles.

Role of TP53 in Apoptosis

In addition to the key roles played by the TP53 tumor suppressor in cell cycle arrest and DNA damage repair, TP53 can also induce apoptosis (May and May, 1999). TP53-induced apoptosis is mediated through the BCL-2 family by the intrinsic pathway, and dysregulation of this apoptotic pathway has direct relevance to the etiology of cancer. The mechanism by which TP53 induces cell cycle arrest or apoptosis is still not well understood, but in both cases recognition of physiologic cell stresses, such as DNA damage, triggers TP53 activation (Sabbatini et al, 1995; Attardi et al, 1996). TP53-induced apoptosis is mediated by transcriptional activation of genes that initiate the apoptotic cascade and inhibition of genes that block the cascade (Miyashita et al, 1994; Miyashita and Reed, 1995; Oda et al, 2000) TP53-induced apoptosis is dependent of the APAF-1/caspase-9 activation pathway (Soengas et al, 1999) (see Fig. 18–14). Whereas the BCL-2 family member BAX has been implicated as the primary factor responsible for TP53 induction of this cascade (Miyashita and Reed, 1995), BAX is not essential for TP53-dependent apoptosis (Knudson et al, 1995). It is possible that inhibition of BCL-2 (Miyashita et al, 1994) or upregulation of the proapoptotic BCL-2 family member noxa, may allow cells lacking BAX to still undergo TP53-dependent apoptosis (Oda et al, 2000).

Considering the role of TP53 in multiple tumor suppressive pathways (DNA damage response, cellular senescence, and apoptosis), it is not surprising that it is so frequently mutated in cancer.

Apoptosis and Genitourinary Malignancies

Because a tumor cell's inability to undergo apoptosis is a hallmark of malignancy, multiple groups have attempted to characterize the apoptotic response of genitourinary malignancies. Because cells undergoing apoptosis undergo a stereotypical death, global analysis of apoptosis is possible using assays designed to detect hallmarks of the apoptotic process, such as the fragmentation of DNA characteristic of the process, as well as assays designed to detect abnormalities in specific apoptotic proteins.

Global Defects in Apoptosis

Both high-grade prostatic intraepithelial neoplasia (HGPIN) and prostate carcinomas actually have significantly higher levels of apoptosis than normal prostatic epithelium. The level of apoptotic activity is relatively low compared with other malignancies and is balanced by increased replication. Importantly, many prostate cancer cells can be induced to undergo apoptosis in response to androgen withdrawal, which represents a front-line therapy for patients with advanced disease (Kyprianou et al, 1990; Isaacs, 1994; Tu et al, 1996; Denmeade and Isaacs, 1996). Unfortunately, clearly not all of a patient's cancer cells succumb, as recurrences inevitably arise. As the tumor progresses to androgen independence, it is unclear if the androgen-resistant cells have an increased or decreased rate of apoptosis, because studies have demonstrated both in hormone-refractory disease (Berges et al, 1995; Koivisto et al, 1997). The conflicting data may reflect both the tumor's dynamics and the effect of therapy. There is a clear survival advantage for the advanced cancer cell that can protect itself from apoptosis. However, **a rapidly growing, infiltrative, advanced tumor, which is outgrowing its blood supply and mutating its DNA, may have a high apoptotic rate despite protective mechanisms acquired by the tumor's cells.**

Studies of apoptosis in bladder carcinoma have demonstrated an association with aggressive, high-grade, advanced disease but not with decreased disease-free survival (Lipponen and Aaltomaa, 1994; King et al, 1996). External-beam radiation therapy has been associated with a modest improvement in survival for tumors with high apoptotic rates, possibly reflecting that effective external-beam radiation therapy requires an intact apoptotic mechanism (Rodel et al, 2000).

As previously mentioned, **most testicular germ cell tumors maintain intact DDR and wild-type *TP53* and thus display high cure rates in response to therapies inducing DNA damage** (Einhorn, 2002; Kersemaekers et al, 2002; Gorgoulis et al, 2005; Bartkova et al, 2007).

Individual members of the apoptotic machinery have been studied frequently. However, all these studies suffer from an inability to assay all elements of the apoptotic machinery simultaneously, and therefore to globally assess the tumor's ability to undergo programmed cell death.

***TP53* mutations and abnormalities in expression are among the most frequent in cancer and have been identified in prostate, bladder, and renal cancers** (Hollstein et al, 1991; Sidransky et al, 1991; Reiter et al, 1993). Abnormalities in *TP53* cause dysregulation of the cell cycle and DNA repair mechanisms in addition to apoptosis and are covered in more detail in the section The Cell Cycle.

BCL-2 family members have been studied in genitourinary malignancies. **Elevated levels of BCL-2 have been identified in the majority of hormone-refractory prostate tumors, reflecting the tumor's relative resistance to apoptosis in the advanced state** (McDonnell et al, 1992; Colombel et al, 1993). Both increased and decreased levels of BCL-2 have been identified in localized prostate tumors, and few studies have found a correlation with grade, stage, and progression (Byrne et al, 1997; Lipponen and Vesalainen, 1997; Theodorescu et al, 1997). Other

antiapoptotic members of the BCL-2 gene family, BCL-X_L and MCL1, may also be linked to prostate carcinoma (Krajewska et al, 1996). Analysis of bladder carcinoma has demonstrated similar results. BCL-2 levels are higher in more aggressive bladder carcinoma, but expression of BCL-2 had no effect on treatment outcome (King et al, 1996; Rodel et al, 2000). As noted earlier, phosphorylation of BAD by AKT can also tilt the scales toward cell survival, especially in concert with elevated levels of BCL-2. AKT activation is commonly seen in many urologic malignancies and can result from loss of the tumor suppressor *PTEN,* mutation and constitutive activation of TPI3 kinase, and/or activation of tyrosine kinase receptors such as HER2/NEU, EGFR, and the insulin-like growth factor receptor (IGFR).

Other BCL-2 family members have not been as well studied. Loss of BAX expression is apparently not a common mechanism for the development of prostate carcinoma (Krajewska et al, 1996; Johnson and Hamdy, 1998) but may play a role in progression of localized bladder carcinoma (Ye et al, 1998).

In summary, deficiencies in signal transduction pathways leading to apoptosis clearly play a role in the initiation and progression of malignancy. It is unclear if expression analysis of the apoptotic machinery will provide additional prognostic information other than that derived from traditional histochemical analysis. However, it is clear that effective chemotherapy and radiation therapy is, in large part, dependent on apoptosis. Additionally, in the future, the apoptotic machinery may be manipulated using novel ligands that bind to death receptors and promote *TP53*-independent cancer cell death.

Alternative Regulators of Apoptosis in Genitourinary Malignancies

In addition to the classic regulators of apoptosis, a number of other pathways for cell survival and death play key roles in urologic cancer. Some of these pathways are being actively explored as targets for cancer therapy. Miyake and colleagues (2000) mapped a detailed gene profile of prostate tumors treated with neoadjuvant hormonal ablation therapy to identify key regulators of cell death and survival after castration. In addition to BCL-2, which is upregulated in surviving cancer cells, they have also reported on clusterin and HSP27. **Clusterin, or TRPM2 (testosterone repressed prostate message–2), is upregulated, both in patient samples after hormone ablation as well as in the Shionogi and CWR-22 xenograft models of hormone-sensitive tumors. Although its precise function is not known, a large body of evidence suggests that clusterin is induced by stress and functions to stabilize the cell during periods of stress** (Miyake et al, 2000). In this model, clusterin is believed to act like heat shock proteins, whose role as a protein chaperone is also to stabilize client proteins. Clusterin is activated by heat shock protein–1 (HSP1). Functional evidence of clusterin's role comes from studies in which clusterin is either overexpressed or knocked down using antisense strategies. In the first scenario, clusterin expression promotes hormone-refractory cell growth and prevents androgen withdrawal–induced apoptosis. In the second scenario, treatment of hormone-refractory cells with antisense clusterin promotes apoptosis (July et al, 2002; Miyake et al, 2004; Gleave and Miyake, 2005). This same group of investigators has also reported that the heat shock protein HSP27 is also frequently overexpressed in hormone-refractory prostate cancers. Similar experiments using overexpression and antisense strategies have suggested that targeting HSP27 may influence the course of hormone-refractory cancers, in particular in combination with cytotoxic chemotherapies (Rocchi et al, 2004).

Another family of cellular signaling molecules that play a role in the regulation of cell survival and apoptosis is that of sphingolipids. Sphingolipids are one of three major constituents of the cell membrane, along with phospholipids and cholesterol. Sphingolipid generation is regulated by a large cast of enzymes—notably, the sphingomyelinases, ceramide synthase, and the ceramidases. Ceramide is produced from sphingomyelin by sphingomyelinase, and from sphinganine by ceramide synthase. Ceramidases, on the other hand, degrade ceramide and lead to formation of sphingosine and sphingosine-1-phosphate. Ceramide is a potent proapoptotic molecule that can promote apoptosis through the classical mitochondrial activation of caspases, or through a nonclassical caspase-independent form of apoptosis (Kolesnick and Fuks, 2003). Sphingosine-1-phosphate, in contrast, is a powerful antiapoptotic molecule that may modulate the degree of apoptosis, similar to a rheostat (Maceyka et al, 2002).

The importance of ceramide to genitourinary tumors is its role as a key modulator of radiation-induced tissue damage and apoptosis. As with clusterin and other heat shock proteins, ceramide appears to be a critical mediator of stress response in cells, in this case promoting apoptosis as opposed to cell survival. Studies supporting the role of ceramide in radiation-induced apoptosis are manifold, including studies demonstrating the direct cell death signal induced by exogenous treatment of cells with ceramide, studies of radiation response in mouse knockout models, and studies of radiation response in the presence and absence of inhibitors of sphingolipid metabolism. Hopefully, therapeutics that increase ceramide production and promote apoptosis can be developed. The role of sphingolipid-1-phosphate has also emerged from these studies, and recent work suggests that this molecule is a promising target for cancer therapy (Gulbins and Kolesnick, 2003; Kester and Kolesnick, 2003; Perry and Kolesnick, 2003).

STEM CELLS AND CANCER

Stem cells are found in multicellular organisms and are characterized by the ability of self-renewal through mitotic cell division and differentiation into a diverse range of specialized cell types. **Common properties of stem cells include the ability of self-renewal, generation of cellular progeny, localization within specialized niches, and the ability to give rise to all cell types within an organ.** Prostate stem cells are believed to be localized within the basal epithelium and give rise to a hierarchy of progenitor cells that may differentiate into secretory or neuroendocrine cells (Burger et al, 2005; Xin et al, 2005). Cancer stem cells are tumorigenic and possess characteristics associated with normal stem cells, including the ability to give rise to all cell types found in a particular cancer.

Recent studies suggest that neoplastic cells mimic normal tissue development and may arise from and are dependent on a small population of stem cells. **The cancer stem cell hypothesis argues that cancers arise from transformation of stem or progenitor cells that are capable of multilineage differentiation.** Cancer stem cells may account for only a small percentage of any tumor, but this small population of cells is critical for tumor survival. Initial evidence to support the cancer stem cell hypothesis is based on observations in leukemia, breast, and neurologic cancers. A CD44+/CD24low/– population of cells in primary breast tumors were specifically capable of tumor

Key Points: Apoptosis

- Apoptosis is a rapid, orderly, programmed form of cell death that is used by multicellular organisms to eliminate unwanted cells. Through this process, cells are preprogrammed to commit suicide in response to various internal and external signals.
- Apoptosis is believed to play an important role in tumor suppression because many of the signals that induce apoptosis arise from potentially tumorigenic cell stresses such as DNA damage.
- Cancer is characterized by interruptions in the normal process of apoptosis, resulting in inappropriate cell survival.
- Apoptosis is mediated by a conserved family of proteases known as caspases. *Initiator caspases* begin caspase proteolytic cascades that result in the activation of downstream *executioner caspases,* which, in turn, target several cellular proteins.
- Two main apoptotic pathways have been identified. In the *intrinsic pathway,* BCL-2 family members modulate the release of cytochrome *c* from mitochondria, which then participates in the activation of initiator caspases. The *extrinsic pathway* activates caspases in response to signals from extracellular "death receptors."
- In addition to its functions in cell cycle arrest and DNA repair, *TP53* also plays a key role in apoptosis.
- BCL-2 is a classic inhibitor of the mitochondrial pathway of apoptosis and is overexpressed in some genitourinary malignancies.
- Therapeutic response is often dependent upon the integrity of apoptotic pathways in cancer cells. Most TGCT retain intact DDR, wild-type *TP53*, and apoptotic responses, providing high cure rates with DNA-damaging agents.
- Novel agonists and antagonists of apoptosis, such as ceramide and clusterin, may be successfully controlled to combat cancer.

formation when engrafted into nude mice (Dontu et al, 2003). Similar reports about glioblastomas suggest that the putative stem cells are CD133 positive (Singh et al, 2003; Dirks, 2005).

The hedgehog (HH) signaling pathway is required for regeneration of prostate epithelium and has been implicated in transformation of prostate progenitor cells (Karhadkar et al, 2004). Elevated HH pathway activity has been shown to distinguish metastatic prostate cancer from localized disease. This pathway was activated in response to endogenous expression of HH ligands and was shown to be dependent upon expression of Smoothened which is an essential response component that is not expressed in benign prostate epithelial cells (Beachy et al, 2004; Karhadkar et al, 2004).

A tumor-initiating cell (T-IC) subpopulation has also been identified in human bladder cancer. This group of cells was found to express CD44+/CK5+/CK20– markers similar to normal bladder basal cells (Chan et al, 2009). The bladder T-IC subpopulation was also capable of forming xenografted tumors in vivo that recapitulated characteristics of the original tumor. Furthermore, CD47 was highly expressed in this group of cells, and blockade of CD47 resulted in macrophage engulfment of bladder cancer stem cells in vitro. This finding suggests a potential role for therapeutic targeting of CD47 and the T-IC subpopulation in bladder cancer (Chan et al, 2009).

Key Points: Cancer Stem Cells

- Stem cells are defined by their ability to differentiate along multiple lineages and their immortality.
- Cancer is believed to be a stem cell disease in which a small population of cancer stem cells maintains the larger tumor.
- The hedgehog signaling pathway is required for regeneration of prostate epithelium and has been implicated in transformation of prostate progenitor cells.
- Cancer may ultimately be eradicated by targeting only the cancer stem cell.

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chapter 19

Regenerative Medicine in Urology: Stem Cells, Tissue Engineering, and Cloning

Anthony Atala, MD

Regenerative Medicine: Strategies for Tissue and Organ Reconstitution
Sources of Cells for Therapy
Biomaterials for Genitourinary Regenerative Medicine
Regenerative Medicine of Urologic Structures
Other Applications of Genitourinary Regenerative Medicine
Summary

"So the Lord God caused the man to fall into a deep sleep, and while he was asleep, He took part of the man's rib, and closed up the place with flesh. Then the Lord God made a woman from the part He had taken out of the man, and He brought her to the man."

—*Genesis 2:21*

Four medical firsts are described in the passage cited above: the use of anesthesia, surgery, cloning, and tissue engineering. Even three decades ago, the performance of two of these, tissue engineering and cloning, was not possible. The use of one body part for another or the exchange of parts from one person to another was mentioned in the medical literature even in antiquity and captured the imagination of many over time. The maintenance of organs in culture was a major area of inquiry in the early 1900s. Charles Lindbergh, the first pilot to successfully fly across the Atlantic in the 1920s, joined forces with Alexis Carrel, a Nobel Prize winner in the field of medicine, to investigate the potential of keeping organs alive ex vivo long-term (Carrel et al, 1935).

The field of urology was the earliest to gain from the advent of transplantation, with the kidney being the first entire organ to be replaced in a human, in 1955 (Guild et al, 1955). In the early 1960s, Joseph Murray, who later received the Nobel Prize for his work, performed a nonrelated kidney transplantation from a nongenetically identical patient into another. This transplant, which overcame the immunologic barrier, marked a new era in medical therapy and opened the door for use of transplantation as a means of therapy for different organ systems. However, lack of good immune suppression and the ability to monitor and control rejection, as well as a severe organ donor shortage, opened the door for other alternatives.

As times evolved, synthetic materials were introduced to replace or rebuild diseased tissues or parts in the human body. The advent of new manmade materials, such as tetrafluoroethylene (Teflon) and silicone, opened a new field that included a wide array of devices that could be applied for human use. Although these devices could provide for structural replacement, the functional component of the original tissue was not achieved.

Simultaneous with this development was an increased body of knowledge of the biologic sciences that included new techniques for cell harvesting, culture, and expansion. The areas of cell biology, molecular biology, and biochemistry were advancing rapidly. Studies of the extracellular matrix and its interaction with cells, and with growth factors and their ligands, led the way to a further understanding of cell and tissue growth and differentiation. The concept of cell transplantation took hold in the research arena, and culminated with the first human bone marrow cell transplant in the 1970s.

In the 1970s, a natural evolution occurred wherein researchers started to combine the field of devices and materials sciences with cell biology, in effect starting a new field called *tissue engineering*. As more scientists from different fields came together with the common goal of tissue replacement, the field of tissue engineering became more formally established. Tissue engineering was defined as "an interdisciplinary field which applies the principles of engineering and life sciences towards the development of biological substitutes that aim to maintain, restore or improve tissue function" (Atala et al, 2001). The first use of the term "tissue engineering" in the literature can be traced to a reference dealing with corneal tissue in 1985 (Wolter et al, 1985).

The field of stem cells also received a large boost with the discovery of mouse embryonic stem cells in the early 1980s (Martin,

1981). However, the field remained relatively dormant until the description of human embryonic stem cells in 1998 (Thomson et al, 1998). The description of these cells led to one of the most contested ongoing ethical debates in the field of medicine. Just a year later, in 1999, the world awoke to the startling media announcement of the creation of the first cloned mammal, a sheep named Dolly (Wilmut et al, 1997). Although cloning, or nuclear transfer, had been done in amphibians and other animal models for years, this accomplishment in a mammal showed once again that concepts believed to be scientifically prohibitive were indeed possible.

The fields of cell transplantation, tissue engineering, and nuclear transfer all had one unifying concept—the regeneration of living tissues and organs. Thus in 1999, William Haseltine, then the scientific founder and Chief Executive Officer of Human Genome Sciences, coined the term "regenerative medicine," in effect bringing all these areas under one defining field (Haseltine, 1999). Soon, the first online journal for the new field of tissue engineering, *Regenerative Medicine*, was formed, along with The Regenerative Medicine Society.

Organ transplantation remains a mainstay of treatment for patients with severely compromised organ function. Despite initiatives to increase the availability of transplant organs, however, the number of patients in need of treatment far exceeds the organ supply, and this shortfall is expected to worsen as the global population ages. One alternative treatment approach is regenerative medicine. In the last two decades, scientists have attempted to grow native and stem cells, engineer tissues, and design treatment modalities using regenerative medicine techniques for virtually every tissue of the human body. This chapter reviews some of the progress that has been achieved in the field of genitourinary regenerative medicine.

REGENERATIVE MEDICINE: STRATEGIES FOR TISSUE AND ORGAN RECONSTITUTION

Regenerative medicine follows the principles of cell transplantation, materials science, and engineering toward the development of biologic strategies that can restore and maintain normal function. Regenerative medicine strategies usually fall into one of three categories: cell-based therapies, the use of biomaterials (scaffolds) alone, wherein the body's natural ability to regenerate is used to orient or direct new tissue growth, or the use of scaffolds seeded with cells to create tissue substitutes.

SOURCES OF CELLS FOR THERAPY

Stem Cells

The cells used for regenerative medicine can be autologous or heterologous, and from either native or stem cell sources. In general, there are three broad categories of stem cells obtained from living tissue that are used for cell therapies. Embryonic stem cells are obtained through the aspiration of the inner cell mass of a blastocyst or, more recently, a single cell from this mass. Fetal and neonatal amniotic fluid and placenta may contain multipotent cells that may be useful in cell therapy applications. Adult stem cells, on the other hand, are usually isolated from organ or bone marrow biopsies. Stem cells are defined as having three important properties: the ability to self-renew, the ability to differentiate into a number of different cell types, and the ability to easily form clonal populations (populations of cells derived from a single stem cell). Many techniques for generating stem cells have been studied over the past few decades. Some of these techniques have yielded promising results, but others require further research. The main techniques are discussed in detail below, and their advantages and limitations are summarized in Table 19–1.

Embryonic Stem Cells

In 1981 pluripotent cells were found in the inner cell mass of the human embryo, and the term "human embryonic stem cell" was coined (Martin, 1981). These cells are able to differentiate into all cells of the human body, excluding placental cells (only cells from the morula are totipotent; that is, able to develop into all cells of the human body). These cells have great therapeutic potential, but their use is limited by both biological and ethical factors.

The political controversy surrounding stem cells began in 1998 with the creation of human embryonic stem (hES) cells derived from discarded embryos. hES were isolated from the inner cell mass of a blastocyst (an embryo 5 days postfertilization) using an immunosurgical technique. Given that some cells cannot be expanded ex vivo, ES cells could be an ideal resource for regenerative medicine because of their fundamental properties: the ability to self-renew indefinitely and the ability to differentiate into cells from all three embryonic germ layers. Skin and neurons have been

Table 19–1.
Summary of Alternate Methods for Generating Pluripotent Stem Cells

METHOD	ADVANTAGES	LIMITATIONS
Somatic cell nuclear transfer	Customized stem cells Has been shown to work in nonhuman primates	Requires oocytes Has not been shown to work in humans
Single cell embryo biopsy	Patient-specific to embryo Does not destroy or create embryos Has been done in humans	Allogeneic cell types Is not known if single cells are totipotent Requires coculturing with a previously established human embryonic stem cell line
Arrested embryos	Cells obtained from discarded embryos Has been done in humans	Allogeneic cell types Quality of cell lines might be questionable
Altered nuclear transfer	Customized stem cells	Ethical issues surround embryos with no potential Modified genome Has not been done with human cells
Reprogramming	Customized stem cells No embryos or oocytes needed Has been done with human cells	Retroviral transduction Oncogenes

formed, indicating ectodermal differentiation (Reubinoff et al, 2001; Schuldiner et al, 2001; Zhang et al, 2001). Blood, cardiac cells, cartilage, endothelial cells, and muscle have been formed, indicating mesodermal differentiation (Kaufman et al, 2001; Kehat et al, 2001; Levenberg et al, 2002). Pancreatic cells have been formed, indicating endodermal differentiation (Assady et al, 2001). In addition, as further evidence of their pluripotency, embryonic stem cells can form embryoid bodies, which are cell aggregations that contain all three embryonic germ layers while in culture, and can form teratomas in vivo (Itskovitz-Eldor et al, 2000). These cells have demonstrated longevity in culture and can maintain their undifferentiated state for at least 80 passages when grown using current published protocols (Reubinoff et al, 2000; Thomson et al, 1998).

However, in addition to the ethical dilemma surrounding the use of embryonic stem cells, their clinical application is limited because they represent an allogenic resource and thus have the potential to evoke an immune response. New stem cell technologies (such as somatic cell nuclear transfer and reprogramming) promise to overcome this limitation.

Single Cell Embryo Biopsy. Because a major objection to hES cell research for some persons is that it results in the destruction of embryos, a method of isolating these cells without destroying the embryo would be advantageous. In 2006, Chung and colleagues were the first authors to report the generation of mouse embryonic stem cell lines in this manner. Their method was based on a technique used to obtain a single cell embryo biopsy for preimplantation genetic diagnosis. Cells were taken from eight-cell blastomeres rather than from blastocysts. The cells differentiated into derivatives of all three embryonic germ layers in vitro, and as well as into teratomas in vivo. In addition, the mouse embryos that resulted from the biopsied blastomeres developed to term without a reduction in their developmental potential.

Obtaining Cells from Arrested Embryos. hES cell lines can also be derived from arrested embryos (Zhang et al, 2006a). During in vitro fertilization, only a small proportion of zygotes produced will develop successfully to the morula and blastocyst stages. Over half the embryos stop dividing (Hardy, 1993; Geber et al, 1999) and are, therefore, considered dead embryos (Landry et al, 2004). Such embryos have unequal or fragmented cells and blastomeres and are usually discarded. Not all the cells within these arrested embryos, however, are abnormal (Martinez et al, 2002; Zhang et al, 2006a), and these embryos might be a source of hES cells. More studies are needed to characterize the full proliferation and differentiation potential of embryonic stem cells derived from arrested embryos.

Altered Nuclear Transfer. Altered nuclear transfer is a variation of somatic cell nuclear transfer (SCNT) in which a genetically modified nucleus from a somatic cell is transferred into a human oocyte. This embryo, which contains a deliberate genetic defect, is capable of developing into a blastocyst, but the induced defect prevents the blastocyst from implanting in the uterus. This process has the potential to generate customized hES cells from the blastocyst stage (Hurlbut, 2005). Human embryos with this genetic defect might lack the capacity to develop into viable fetuses, as a result of their inability to implant, thus providing a source of stem cells without destroying viable embryos. Proof of concept was obtained in mice by Meissner and Jaenisch (2006) by using embryos lacking the *CDX2* homeobox gene.

The viability of human embryos lacking the *CDX2* gene is unclear, as is whether this mutation restricts human developmental potential into certain lineages. Although much research must be done before therapeutic strategies based on this technique could ever enter the clinic, at this time, hES cells derived from altered nuclear transfer can provide opportunities to study pluripotency in hES cells without the need for destruction of viable embryos. The exact effects of *CDX2* gene knockout on the development of human embryos are not well known. The effects of this gene however, have been thoroughly investigated in the gastric and intestinal epithelium (Benahmed et al, 2008; Vauhkonen et al, 2008).

Therapeutic Cloning (Somatic Cell Nuclear Transfer)

Somatic cell nuclear transfer, or therapeutic cloning, entails the removal of an oocyte nucleus in culture, followed by its replacement with a nucleus derived from a somatic cell obtained from a patient. Activation with chemicals or electricity stimulates cell division up to the blastocyst stage.

At this point, it is extremely important to differentiate between the two types of cloning that exist: reproductive cloning and therapeutic cloning. Both involve the insertion of donor deoxyribonucleic acid (DNA) into an enucleated oocyte to generate an embryo that has identical genetic material to its DNA source. However, the similarities end there. In reproductive cloning, the embryo is then implanted into the uterus of a pseudopregnant female to produce an infant that is a clone of the donor. A world-famous example of this type of cloning resulted in the birth of a sheep named Dolly in 1997 (Wilmut et al, 1997). However, there are many ethical concerns surrounding such practices, and as a result, reproductive cloning has been banned in most countries.

Although therapeutic cloning also produces an embryo that is genetically identical to the donor, this process is used to generate blastocysts that are explanted and grown in culture, rather than in utero. Embryonic stem cell lines can then be derived from these blastocysts, which are only allowed to grow to a 100-cell stage. At this time the inner cell mass is isolated and cultured, resulting in ES cells that are genetically identical to the patient. This process is detailed in Fig. 19–1. It has been shown that nuclear-transferred ES cells derived from fibroblasts, lymphocytes, and olfactory neurons are pluripotent and can generate live pups after injection into blastocysts. This shows that cells generated by SCNT have the same developmental potential as blastocysts that are fertilized and produced naturally (Hochedlinger et al, 2002; Eggan et al, 2004; Brambrink et al, 2006). In addition, the ES cells generated by SCNT are perfectly matched to the patient's immune system, and no immunosuppressants would be required to prevent rejection should these cells be used in regenerative medicine applications.

Although ES cells derived from SCNT contain the nuclear genome of the donor cells, mitochondrial DNA (mtDNA) contained in the oocyte could lead to immunogenicity after transplantation. To assess the histocompatibility of tissue generated using SCNT, Lanza and colleagues (2002b) microinjected the nucleus of a bovine skin fibroblast into an enucleated oocyte. Although the blastocyst was implanted (reproductive cloning), the purpose was to generate renal, cardiac and skeletal muscle cells, which were then harvested, expanded in vitro, and seeded onto biodegradable scaffolds. These scaffolds were then implanted into the donor steer from which the cells were cloned to determine if cells were histocompatible. Analysis revealed that cloned renal cells showed no evidence of T-cell response, suggesting that rejection will not necessarily occur in the presence of oocyte-derived mtDNA. This finding represents a step forward in overcoming the histocompatibility problem of stem cell therapy.

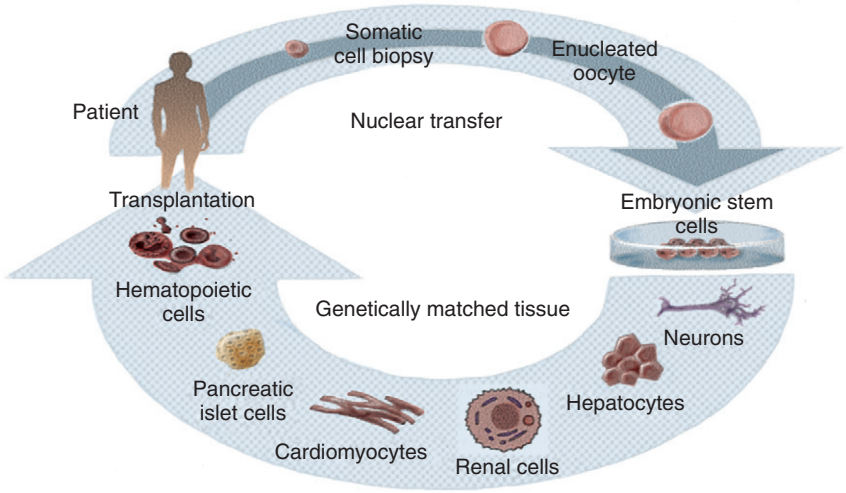


Figure 19–1. Therapeutic cloning strategy and its application to the engineering of tissues and organs.

Although promising, SCNT has certain limitations that require further improvement before its clinical application, in addition to the ethical considerations regarding the potential of the resulting embryos to develop into cloned embryos if implanted into a uterus. In addition, to date this technique has not been shown to work in humans. The initial failures and fraudulent reports of nuclear transfer in humans reduced enthusiasm for human applications (Simerly et al, 2003; Hwang et al, 2004; Hwang et al, 2005), although it was recently reported that nonhuman primate ES cell lines were generated by SCNT using nuclei from adult skin fibroblasts (Byrne et al, 2007; Mitalipov, 2007).

Before SCNT-derived ES cells can be used as clinical therapy, careful assessment of quality of the lines must be determined. For example, some cell lines generated by SCNT have contained chromosomal translocations, and it is not known whether these abnormalities originated from aneuploid embryos or if they occurred during ES cell isolation and culture. In addition, the low efficiency of SNCT (0.7%) and the inadequate supply of human oocytes further hinder the therapeutic potential of this technique. Still, these studies renew the hope that ES cell lines could one day be generated from human cells to produce patient-specific stem cells with the potential to cure many human diseases that are currently untreatable.

Reprogramming (Induced Pluripotent Stem Cells)

Recently, reports of the successful transformation of adult cells into pluripotent stem cells through a type of genetic "reprogramming" have been published. Reprogramming is a technique that involves de-differentiation of adult somatic cells to produce patient-specific pluripotent stem cells, eliminating the need to create embryos. Cells generated by reprogramming would be genetically identical to the somatic cells (and thus, the patient who donated these cells) and would not be rejected. Yamanaka's group was the first to discover that mouse embryonic fibroblasts (MEFs) and adult mouse fibroblasts could be reprogrammed into an "induced pluripotent state" (iPS) (Takahashi and Yamanaka, 2006). These iPS cells possessed the immortal growth characteristics of self-renewing ES cells—expressed genes specific for ES cells, and generated embryoid bodies in vitro and teratomas in vivo. When iPS cells were injected into mouse blastocysts, they contributed to a variety of cell types. However, although iPS cells selected in this way were pluripotent, they were not identical to ES cells. Unlike ES cells, chimeras made from iPS cells did not result in full-term pregnancies. Gene expression profiles of the iPS cells showed that they possessed a distinct gene expression signature that was different from that of ES cells. In addition, the epigenetic state of the iPS cells was somewhere between that found in somatic cells and that found in ES cells, suggesting that the reprogramming was incomplete.

These results were improved significantly by Wernig and colleagues in July 2007 (Wernig et al, 2007). In this study, DNA methylation, gene expression profiles, and the chromatin state of the reprogrammed cells were similar to those of ES cells. Teratomas induced by these cells contained differentiated cell types representing all three embryonic germ layers. Most importantly, the reprogrammed cells from this experiment were able to form viable chimeras and contribute to the germ line like ES cells, suggesting that these iPS cells were completely reprogrammed.

It has recently been shown that reprogramming of human cells is possible (Yu et al, 2007). Yamanaka's group generated human iPS cells that are similar to hES cells in terms of morphology, proliferation, gene expression, surface markers, and teratoma formation. These were generated via retroviral transduction of the stem cell markers *OCT4, SOX2, NANOG, and LIN28* (Takahashi et al, 2007). However, in both studies, the human iPS cells were similar but not identical to hES cells. Although reprogramming is an exciting phenomenon, our limited understanding of the mechanism underlying it currently limits the clinical applicability of the technique, but the future potential of reprogramming is quite exciting.

Amniotic Fluid– and Placenta-Derived Stem Cells

The amniotic fluid and placental membrane contain a heterogeneous population of cell types derived from the developing fetus (Priest et al, 1978; Polgar et al, 1989). Cells found in this heterogeneous population include mesenchymal stem cells (in 't Anker et al, 2003b; Tsai et al, 2004). In addition, the isolation of multipotent human and mouse amniotic fluid– and placenta-derived stem (AFPS) cells that are capable of extensive self-renewal and give rise to cells from all three germ layers was reported in 2007 (De Coppi et al, 2007a). AFPS cells represent approximately 1% of the cells found in the amniotic fluid and placenta. The undifferentiated stem cells expand extensively without a feeder cell layer and double every 36 hours. Unlike human embryonic stem cells, the AFPS cells do not form tumors in vivo. Lines maintained for over 250 population doublings retained long telomeres and a normal complement of chromosomes. AFPS cell lines can be induced to differentiate into cells representing each embryonic germ layer, including cells of adipogenic, osteogenic, myogenic,

endothelial, neural-like and hepatic lineages. In addition to the differentiated AFPS cells expressing lineage-specific markers, such cells can have specialized functions. Cells of the hepatic lineage secreted urea and α-fetoprotein, while osteogenic cells produced mineralized calcium. In this respect, they meet a commonly accepted criterion for multipotent stem cells, without implying that they can generate every adult tissue.

AFS cells represent a new class of stem cells with properties somewhere between those of embryonic and adult stem cell types. They are probably more agile than adult stem cells, but less so than embryonic stem cells. Unlike embryonic and induced pluripotent stem cells, however, AFPS cells do not form teratomas, and if preserved for self-use, avoid the problems of rejection. The cells could be obtained either from amniocentesis or chorionic villous sampling in the developing fetus, or from the placenta at the time of birth. They could be preserved for self-use, and used without rejection, or they could be banked. A bank of 100,000 specimens could potentially supply 99% of the U.S. population with a perfect genetic match for transplantation. Such a bank may be easier to create than with other cell sources, because there are approximately 4.5 million births per year in the United States.

Since the discovery of the AFPS cells, other groups have published on the potential of the cells to differentiate to other lineages, such as cartilage (Kolambkar et al, 2007), kidney (Perin et al, 2007), and lung (Warburton et al, 2008). Muscle differentiated AFPS cells were also noted to prevent compensatory bladder hypertrophy in a cryoinjured rodent bladder model (De Coppi et al, 2007b).

Adult Stem Cells

Adult stem cells, especially hematopoietic stem cells, are the best understood cell type in stem cell biology (Ballas et al, 2002). However, adult stem cell research remains an area of intense study, because their potential for therapy may be applicable to a myriad of degenerative disorders. Within the past decade, adult stem cell populations have been found in many adult tissues other than the bone marrow and the gastrointestinal tract, including the brain (Taupin, 2006), skin (Jensen et al, 2008; Jiao et al, 2008), and muscle (Crisan et al, 2008). **Many other types of adult stem cells have been identified in organs all over the body and are thought to serve as the primary repair entities for their corresponding organs** (Weiner, 2008) (Fig. 19–2). The discovery of such tissue-specific progenitors has opened up new avenues for research.

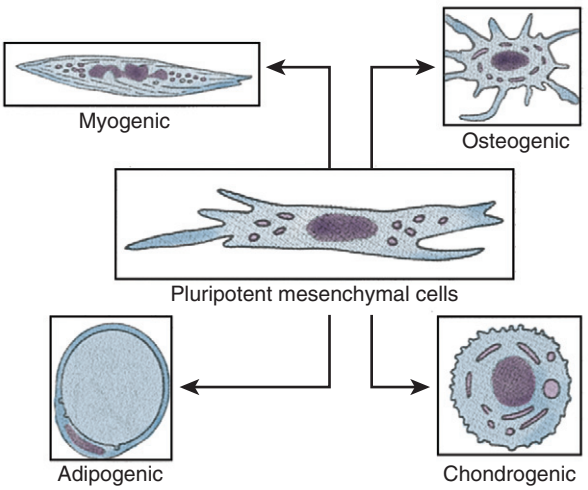


Figure 19–2. Schematic diagram of pluripotential stem cell lineages that can be derived from postnatal tissue.

A notable exception to the tissue specificity of adult stem cells is the mesenchymal stem cell, also known as the multipotent adult progenitor cell. This cell type is derived from bone marrow stroma (Devine, 2002; Jiang et al, 2002). Such cells can differentiate in vitro into numerous tissue types (Caplan, 2007; da Silva Meirelles et al, 2008) and can also differentiate developmentally if injected into a blastocyst. Multipotent adult progenitor cells can develop into a variety of tissues including neuronal (Duan et al, 2007), adipose (Crisan et al, 2008), muscle (Crisan et al, 2008; Luttun et al, 2006), liver (Ikeda et al, 2008; Mimeault et al, 2008), lungs (Nolen-Walston et al, 2008), spleen (in 't Anker et al, 2003a), and gut tissue (Jiang et al, 2002), but notably not bone marrow or gonads.

Research into adult stem cells has, however, progressed slowly, mainly because investigators have had great difficulty in maintaining adult nonmesenchymal stem cells in culture. Some cells, such as those of the liver, pancreas, and nerve, have very low proliferative capacity in vitro, and the functionality of some cell types is reduced after the cells are cultivated. Isolation of cells has also been problematic, because stem cells are present in extremely low numbers in adult tissue (Hristov et al, 2008; Mimeault et al, 2008). Although the clinical utility of adult stem cells is currently limited, great potential exists for future use of such cells in tissue-specific regenerative therapies. The advantage of adult stem cells is that they can be used in autologous therapies, thus avoiding any complications associated with immune rejection.

Native Targeted Progenitor Cells

In the past, one of the limitations of applying cell-based regenerative medicine techniques to organ replacement was the inherent difficulty of growing certain human cell types in large quantities. Native targeted progenitor cells, or native cells, are tissue specific unipotent cells derived from most organs. The advantage of these cells is that they are already programmed to become the cell type needed, without any extralineage differentiation. By noting the location of the progenitor cells, as well as by exploring the conditions that promote differentiation and/or self-renewal, it has been possible to overcome some of the obstacles that limit cell expansion in vitro. One example is the urothelial cell. Urothelial cells could be grown in the laboratory setting in the past, but only with limited success. It was believed that urothelial cells had a natural senescence that was hard to overcome. Several protocols have been developed over the last two decades that have improved urothelial growth and expansion (Cilento et al, 1994; Liebert et al, 1997; Scriven et al, 1997; Puthenveettil et al, 1999). A system of urothelial cell harvesting was developed that does not use any enzymes or serum and has a large expansion potential. Using these methods of cell culture, it is possible to expand an urothelial strain from a single specimen that initially covers a surface area of 1 cm^2 to one covering a surface area of 4202 m^2 (the equivalent area of one football field) within 8 weeks (Cilento et al, 1994).

An additional advantage in using native cells is that they can be obtained from the specific organ to be regenerated, expanded, and used in the same patient without rejection, in an autologous manner (Atala et al, 1992b, 1993b, 1993c, 1994, 1995b, 1997, 1998; Cilento et al, 1994; Yoo et al, 1997; Fauza et al, 1998a, 1998b; Machluf et al, 1998; Yoo et al, 1998b; Amiel et al, 1999; Kershen et al, 1999; Oberpenning et al, 1999; Park et al, 1999).

Bladder, ureter, and renal pelvis cells can equally be harvested, cultured, and expanded in a similar fashion (Fig. 19–3). Normal human bladder epithelial and muscle cells can be efficiently

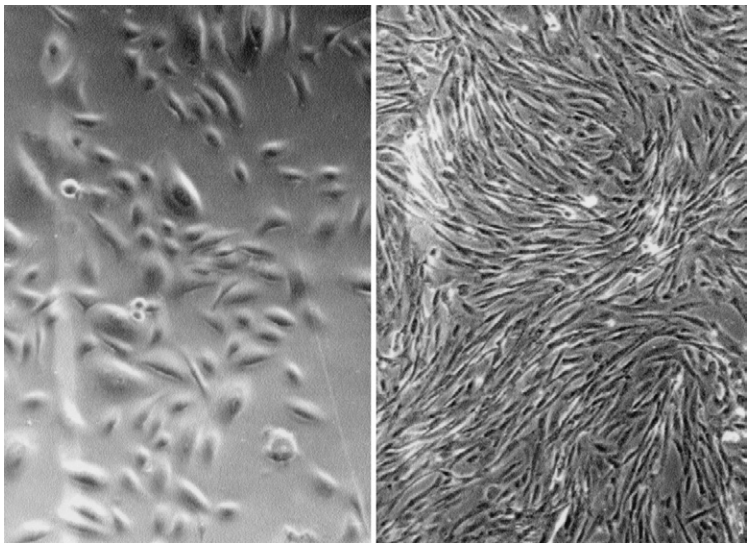


Figure 19–3. Urothelial *(left panel)* and bladder muscle *(right panel)* cells growing in vitro.

harvested from surgical material, extensively expanded in culture, and their differentiation characteristics, growth requirements, and other biologic properties can be studied (Liebert et al, 1991; Cilento et al, 1994; Tobin et al, 1994; Harriss, 1995; Freeman et al, 1997; Liebert et al, 1997; Fauza et al, 1998a, 1998b; Lobban et al, 1998; Solomon et al, 1998; Nguyen et al, 1999; Puthenveettil et al, 1999; Rackley et al, 1999). Major advances in cell culture techniques have been made within the past decade, and these techniques make the use of autologous cells possible for clinical application. However, even now, not all human cells can be grown or expanded in vitro. Liver, nerve, and pancreas are examples of human tissues where the technology is not yet advanced to the point where these cells can be grown and expanded.

When cells are used for tissue reconstitution, donor tissue is dissociated into individual cells that are either implanted directly into the host or expanded in culture, then attached to a support matrix or reimplanted after expansion. The implanted tissue can be heterologous, allogeneic, or autologous. Ideally, this approach allows lost tissue function to be restored or replaced in toto, and with limited complications (Atala, 1997). **Native cells and tissues are usually preferable for reconstruction.** In most cases, the replacement of lost or deficient tissues with functionally equivalent cells and tissues would improve the outcome for these patients. This goal may be attainable with the use of regenerative medicine techniques.

BIOMATERIALS FOR GENITOURINARY REGENERATIVE MEDICINE

Synthetic materials have been used widely for urologic reconstruction. **The most common type of synthetic prostheses for urologic applications is made of silicone.** Silicone prostheses have been used for the treatment of urinary incontinence with the artificial urinary sphincter and detachable balloon system, for treatment of vesicoureteral reflux with silicone microparticles, and for impotence with penile prostheses (Atala et al, 1992a; Riehmann et al, 1993; Levesque et al, 1996; Buckley et al, 1997). There has also been a major effort directed toward the construction of artificial bladders made with silicone. In some disease states, such as urinary incontinence or vesicoureteral reflux, artificial agents (Teflon paste, glass microparticles) have been used as injectable bulking substances; however, these substances are not entirely biocompatible (Atala, 1994).

For regenerative medicine purposes, there are clear advantages in using degradable, biocompatible materials that can function as cell delivery vehicles, and/or provide the structural parameters needed for tissue replacement. **Biomaterials in genitourinary regenerative medicine function as an artificial extracellular matrix (ECM) and elicit biologic and mechanical functions of native ECM found in tissues in the body.** Native ECM brings cells together into tissue, controls the tissue structure, and regulates the cell phenotype (Alberts et al, 1994). Biomaterials facilitate the localization and delivery of cells and/or bioactive factors (e.g., cell adhesion peptides, growth factors) to desired sites in the body; define a three-dimensional space for the formation of new tissues with appropriate structure; and guide the development of new tissues with appropriate function (Kim et al, 1998). Direct injection of cell suspensions without biomaterial matrices has been used in some cases (Ponder et al, 1991; Brittberg et al, 1994), but it is difficult to control the localization of transplanted cells. In addition, the majority of mammalian cell types is anchorage-dependent and will die if not provided with a cell-adhesion substrate.

Design and Selection of Biomaterials

The design and selection of the biomaterial is critical in the development of engineered genitourinary tissues. The biomaterial must be capable of controlling the structure and function of the engineered tissue in a predesigned manner by interacting with transplanted cells and/or host cells. Generally, the ideal biomaterial should be biocompatible, promote cellular interaction and tissue development, and possess proper mechanical and physical properties.

The selected biomaterial should be biodegradable and bioresorbable to support the reconstruction of a completely normal tissue without inflammation. Such behavior of the biomaterials avoids the risk of inflammatory or foreign-body responses that may be associated with the permanent presence of a foreign material in the body. The degradation rate and the concentration of degradation products in the tissues surrounding the implant must be at a tolerable level (Bergsma et al, 1995).

The biomaterials should provide an appropriate regulation of cell behavior (e.g., adhesion, proliferation, migration, differentiation) to promote the development of functional new tissue. Cell behavior in engineered tissues is regulated by multiple interactions with the microenvironment, including interactions with cell-adhesion ligands (Hynes, 1992) and with soluble growth factors (Deuel, 1997). Cell adhesion–promoting factors (e.g., arg-gly-asp [RGD]) can be presented by the biomaterial itself or incorporated into the biomaterial to control cell behavior through ligand-induced cell receptor signaling processes (Barrera et al, 1993; Cook et al, 1997). The biomaterials provide temporary mechanical support sufficient to withstand in vivo forces exerted by the surrounding tissue and maintain a potential space for tissue development. The mechanical support of the biomaterials should be maintained until the engineered tissue has sufficient mechanical integrity to support itself (Atala, 2007). This potentially can be achieved by an appropriate choice of mechanical and degradative properties of the biomaterials (Kim et al, 1998).

The biomaterials need to be processed into specific configurations. A large ratio of surface area to volume is often desirable to allow the delivery of a high density of cells. A high-porosity, interconnected pore structure with specific pore sizes promotes tissue ingrowth from the surrounding host tissue. Several techniques, such as electrospinning, have been developed that readily control porosity, pore size, and pore structure (Lee et al, 2007; Yoo et al, 2007; Choi et al, 2008; Lee et al, 2008a, 2008b, 2008c).

Types of Biomaterials

Generally, three classes of biomaterials have been used for engineering of genitourinary tissues: naturally derived materials, such as collagen and alginate; acellular tissue matrices, such as bladder submucosa and small-intestinal submucosa; and synthetic polymers, such as polyglycolic acid (PGA), polylactic acid (PLA), and poly(lactic-co-glycolic acid) (PLGA). These classes of biomaterials have been tested in regard to their biocompatibility with primary human urothelial and bladder muscle cells (Pariente et al, 2001). Naturally derived materials and acellular tissue matrices have the potential advantage of biologic recognition. Synthetic polymers can be produced reproducibly on a large scale with controlled properties of strength, degradation rate, and microstructure.

Collagen is the most abundant and ubiquitous structural protein in the body, and it may be readily purified from both animal and human tissues with an enzyme treatment and salt/acid extraction (Li, 1995). Collagen has long been known to exhibit minimal inflammatory and antigenic responses (Furthmayr et al, 1976), and it has been approved by the U.S. Food and Drug Administration (FDA) for many types of medical applications, including wound dressings and artificial skin (Cen et al, 2008). Intermolecular cross-linking reduces the degradation rate by making the collagen molecules less susceptible to an enzymatic attack. Intermolecular cross-linking can be accomplished by various physical (e.g., ultraviolet radiation, dehydrothermal treatment) or chemical (e.g., glutaraldehyde, formaldehyde, carbodiimides) techniques (Li, 1995). Collagen contains cell-adhesion domain sequences (e.g., RGD) that exhibit specific cellular interactions. This may help to retain the phenotype and activity of many types of cells, including fibroblasts (Silver et al, 1992) and chondrocytes (Sams et al, 1995). This material can be processed into a wide variety of structures such as sponges (Fig. 19–4, top) fibers, and films (Yannas et al, 1980a, 1980b; Cavallaro et al, 1994).

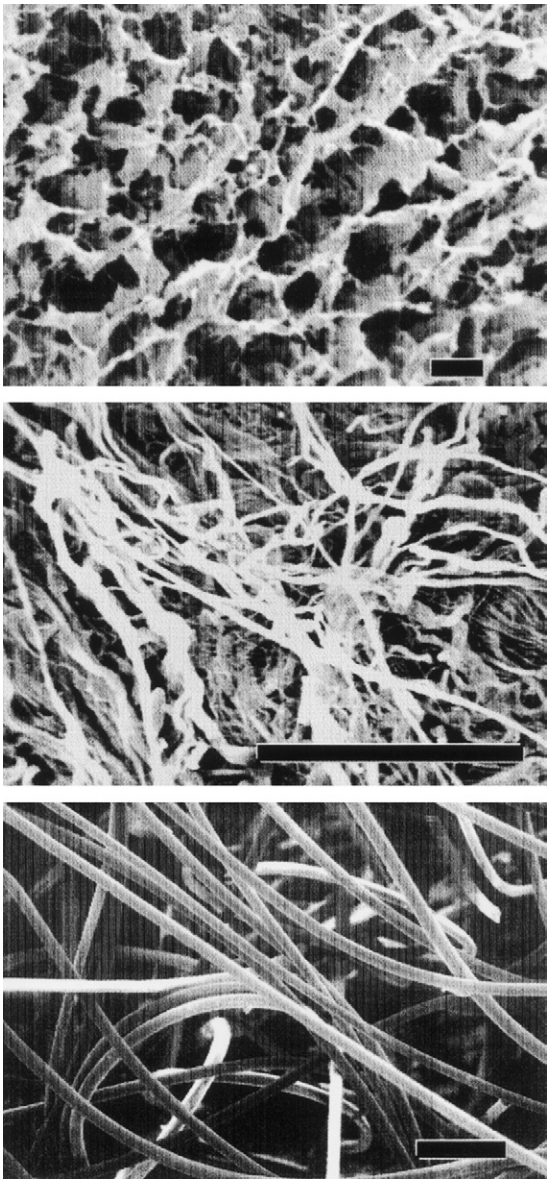


Figure 19–4. Scanning electron micrographs of biomaterials: collagen sponge *(top)*, acellular matrix prepared from pig bladder submucosa *(center)*, and polyglycolic acid fiber-based matrix *(bottom)*. (Size bars = 100 µm.)

Alginate, a polysaccharide isolated from seaweed, has been used as an injectable cell delivery vehicle (Smidsrod et al, 1990) and a cell immobilization matrix (Lim and Sun, 1980) owing to its gentle gelling properties in the presence of divalent ions such as calcium. Alginate is a family of copolymers of D-mannuronate and L-guluronate. The physical and mechanical properties of alginate gel are strongly correlated with the proportion and length of the polyguluronate block in the alginate chains (Smidsrod et al, 1990). Efforts have been made to synthesize biodegradable alginate hydrogels with mechanical properties that are controllable in a wide range by intermolecular covalent cross-linking and with cell-adhesion peptides coupled to their backbones (Rowley et al, 1999).

Recently, natural materials such as alginate and collagen have been used as "bio-inks" in a newly developed bioprinting technique based on inkjet technology (Boland et al, 2006; Campbell et al, 2007). Using this technology, these scaffold materials can be "printed" into a desired scaffold shape using a modified

inkjet printer. In addition, several groups have shown that living cells can also be printed using this technology (Laflamme et al, 2005; Nakamura et al, 2005). This exciting technique can be modified so that a three-dimensional construct containing a precise arrangement of cells, growth factors, and extracellular matrix material can be printed (Roth et al, 2004; Ilkhanizadeh et al, 2007; Xu et al, 2009). Such constructs may eventually be implanted into a host to serve as the backbone for a new tissue or organ.

Acellular tissue matrices are collagen-rich matrices prepared by removing cellular components from tissues (Fig. 19–4, center). The matrices are often prepared by mechanical and chemical manipulation of a segment of bladder tissue (Dahms et al, 1998; Piechota et al, 1998; Yoo et al, 1998b; Chen et al, 1999). The matrices slowly degrade after implantation and are replaced and remodeled by ECM proteins synthesized and secreted by transplanted or ingrowing cells. Acellular tissue matrices have been proved to support cell ingrowth and regeneration of genitourinary tissues, including urethra and bladder, with no evidence of immunogenic rejection (Probst et al, 1997; Chen et al, 1999). Because the structures of the proteins (e.g., collagen, elastin) in acellular matrices are well conserved and normally arranged, the mechanical properties of the acellular matrices are not significantly different from those of native bladder submucosa (Dahms et al, 1998).

Polyesters of naturally occurring α-hydroxy acids, including PGA, PLA, and PLGA, are widely used in regenerative medicine. These polymers have gained FDA approval for human use in a variety of applications, including sutures (Gilding, 1981). The degradation products of PGA, PLA, and PLGA are nontoxic, natural metabolites that are eventually eliminated from the body in the form of carbon dioxide and water (Gilding, 1981). Because these polymers are thermoplastics, they can easily be formed into a three-dimensional scaffold with a desired microstructure, gross shape, and dimension by various techniques, including molding, extrusion (Freed et al, 1994), solvent casting (Mikos et al, 1994), phase separation techniques, and gas foaming techniques (Harris et al, 1998). More recently, techniques such as electrospinning have been used to quickly create highly porous scaffolds in various conformations (Han et al, 2006; Choi et al, 2008; Lee et al, 2008a; Lee et al, 2008b).

Many applications in genitourinary regenerative medicine require a scaffold with high porosity and a high ratio of surface area to volume. This need has been addressed by processing biomaterials into configurations of fiber meshes (Fig. 19–4, bottom) and porous sponges using the techniques described previously. A drawback of the synthetic polymers is lack of biologic recognition. As an approach toward incorporating cell recognition domains into these materials, copolymers with amino acids have been synthesized (Barrera et al, 1993; Intveld et al, 1994; Cook et al, 1997). Other biodegradable synthetic polymers, including polyanhydrides and polyortho-esters), can also be used to fabricate scaffolds for genitourinary regenerative medicine with controlled properties (Peppas et al, 1994).

Nanotechnology, the ability to use small molecules that have distinct properties in a small scale, has been used to create "smart" biomaterials for regenerative medicine (Boccaccini et al, 2005; Harrison et al, 2007). Nanoscaffolds have been manufactured specifically for bladder applications (Harrington et al, 2006). The manufacturing of biomaterials can also lead to enhanced cell alignment and tissue formation (Choi et al, 2008).

Vascularization

The goals in regenerative medicine include the replacement of damaged, injured or missing body tissues with biological compatible substitutes. **A limiting factor for the engineering of tissues is that cells cannot be implanted in volumes exceeding 3 mm^3** (Folkman et al, 1973)**. Nutrition and gas exchange is limited by this maximal diffusion distance. If cells were implanted in volumes exceeding 3 mm^3, only the cells on the surface would survive, and the central cell core would undergo necrosis resulting from a lack of vascularity.** Therefore a critical obstacle in regenerative medicine is the ability to maintain large masses of cells alive upon transfer from the in vitro culture conditions into the host (in vivo) (Mooney et al, 1999). To achieve the goals of engineering large complex tissues, and possibly internal organs, vascularization of the regenerating cells is essential.

Formation of new blood vessels and capillaries comprises two different processes: vasculogenesis, the in-situ assembly of capillaries from undifferentiated endothelial cells (EC), and angiogenesis, the sprouting of capillaries from preexisting blood vessels. The formation of the first capillaries takes place mostly during the early stages of embryogenesis (Folkman et al, 1996; Yancopoulos et al, 1998).

Vasculogenesis can be divided into five consecutive steps: (1) EC are generated from precursor cells, called angioblasts, in the bone marrow; (2) EC form the vessel primordia and aggregates that establish cell-to-cell contact but have no lumen; (3) a nascent endothelial tube is formed, composed of polarized EC; (4) a primary vascular network is formed from an array of nascent endothelial tubes; and (5) pericytes and vascular smooth muscle cells are recruited (Drake et al, 1998).

Angiogenesis is a morphogenic process, which describes the formation of new blood capillaries from EC of preexisting vessels. There are six basic steps in angiogenesis: (1) vasodilatation of the parental vessel, reducing the contact between adjacent EC, (2) degradation of the basement membrane of a parental vessel by secretion and activation of a wide range of proteolytic enzymes, (3) EC migration and proliferation to form a leading edge of the new capillary, (4) generation of the capillary lumen and formation of a tube-like structure, (5) basement membrane synthesis, and (6) recruitment of pericytes and vascular smooth muscle cells (Folkman et al, 1992).

When converting to the angiogenic stage, EC will capture new properties that enable them to neovascularize the tissue (Hanahan et al, 1996). When the new vessels are in place and the vascular network matures, the neovascular EC resume their quiescent phenotype (Darland et al, 1999). Several growth factors serve as stimuli for EC conversion to the angiogenic phenotype (Battegay, 1995). Vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) are two well-characterized and important angiogenic molecules that have a direct effect on EC.

The understanding of the angiogenic process and the isolation of potent and specific angiogenic growth factors has encouraged the use of these factors therapeutically (Loges et al, 2009; Phelps et al, 2009). Efforts have been aimed at incorporating the knowledge acquired in angiogenesis of ischemic tissues into practical approaches to vascularize bioengineered tissues (Stosich et al, 2009). Bioengineered tissues are usually supported by scaffolds of biocompatible matrices made from natural or artificial sources (Hubbell et al, 1991). Successful vascularization is dependent on the porosity of the supporting matrix. A positive correlation between the pore size of poly-L-lactic acid (PLLA) implants and the rate of vascularization has been observed (Mikos et al, 1993).

Three approaches have been used for vascularization of bioengineered tissue: (1) incorporation of angiogenic factors in the bioengineered tissue, (2) seeding EC with other cell types in the bioengineered tissue, and (3)

prevascularization of the matrix prior to cell seeding. Angiogenic growth factors may be incorporated into the bioengineered tissue before implantation, to attract host capillaries and to enhance neovascularization of the implanted tissue. Angiogenic growth factors can be embedded in specific biomaterials, and can be controlled for slow release (Eiselt et al, 1998). Cells can also be genetically engineered to secrete high levels of angiogenic proteins (Springer et al, 1998).

Another approach for enhancing angiogenesis employed cultured EC, which are incorporated into the bioengineered tissue prior to implantation. Human penile corpus cavernosum–derived smooth muscle cells and EC were seeded on biodegradable polymer scaffolds, in order to reconstruct penile corporeal tissue in vitro and in vivo (Park et al, 1999). The use of EC improved the formation of the engineered tissue. In another study, the addition of both EC and angiogenic growth factors (VEGF) accelerated the formation of engineered muscle tissue (De Coppi et al, 2005). An alternative direction in vascularization of bioengineered tissue is the prevascularization of the supporting polymer prior to cell seeding. In this manner, the bioengineered tissue will be organized around the vascular network, providing sufficient tissue perfusion (Fontaine et al, 1995).

Despite the successes in bioengineering tissues consisting of thin layers of cells such as skin, a major challenge for regenerative medicine in the future is the production of larger organs with more complex structures like the kidney. Tissues with a large mass of cells will require a vascular network of arteries, veins, and capillaries to deliver nutrients to each cell. The development of efficient methods to vascularize bioengineered tissues is critical for a successful outcome. There are many obstacles to overcome before large entire tissue-engineered solid organs are produced. Recent developments in angiogenesis research may provide important knowledge and essential.

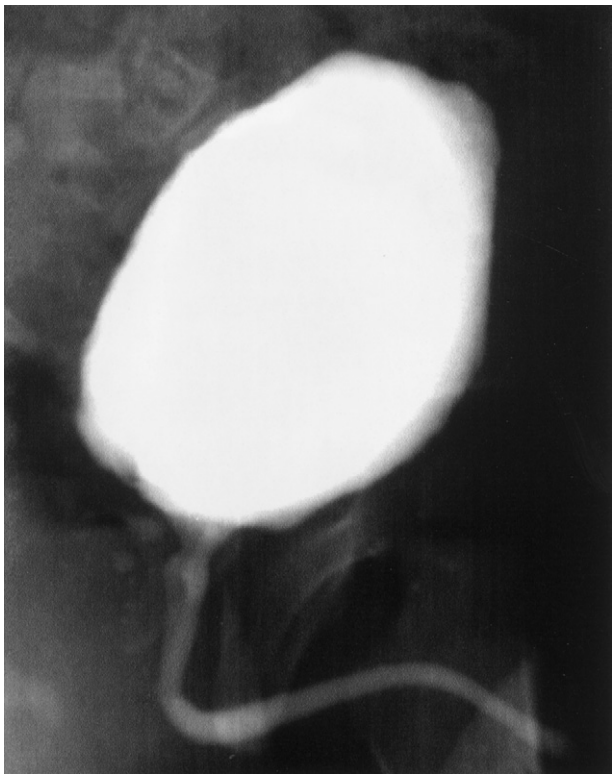


Figure 19–5. Urethrogram 6 months after surgery in a patient who had a portion of his urethra replaced with the use of regenerative medicine techniques.

REGENERATIVE MEDICINE OF UROLOGIC STRUCTURES

Urethra

Various strategies have been proposed over the years for the regeneration of urethral tissue. Woven meshes of PGA without cells (Bazeed et al, 1983; Olsen et al, 1992) or with cells (Atala et al, 1992b) were used to regenerate urethras in various animal models. Naturally derived collagen-based materials, such as bladder-derived acellular submucosa (Chen et al, 1999), and an acellular urethral submucosa (Sievert et al, 2000), have also been tried experimentally in various animal models for urethral reconstruction.

The bladder submucosa matrix (Chen et al, 1999), proved to be a suitable graft for repair of urethral defects in rabbits. The neourethras demonstrated a normal urothelial luminal lining and organized muscle bundles. These results were confirmed clinically in a series of patients with a history of failed hypospadias reconstruction wherein the urethral defects were repaired with human bladder acellular collagen matrices (Atala et al, 1999). The neourethras were created by anastomosing the matrix in an onlay fashion to the urethral plate. The size of the created neourethra ranged from 5 to 15 cm. After a 3-year follow-up, three of the four patients had a successful outcome in regard to cosmetic appearance and function (Fig. 19–5). One patient who had a 15-cm neourethra created developed a subglanular fistula. The acellular collagen-based matrix eliminated the necessity of performing additional surgical procedures for graft harvesting, and both operative time and the potential morbidity from the harvest procedure were decreased. Similar results were obtained in pediatric and adult patients with primary urethral stricture disease using the same collagen matrices (El-Kassaby et al, 2003). Another study in 30 patients with recurrent stricture disease showed that a healthy urethral bed (two or fewer prior urethral surgeries) was needed for successful urethral reconstruction using the acellular collage-based grafts (El Kassaby et al, 2008). **More than 200 pediatric and adult patients with urethral disease have been successfully treated in an onlay manner with a bladder-derived collagen-based matrix. One of its advantages over nongenital tissue grafts used for urethroplasty is that the material is "off the shelf."** This eliminates the necessity of additional surgical procedures for graft harvesting, which may decrease operative time as well as the potential morbidity due to the harvest procedure.

The above techniques, using nonseeded acellular matrices, were applied experimentally and clinically in a successful manner for onlay urethral repairs. However, when tubularized urethral repairs were attempted experimentally, adequate urethral tissue regeneration was not achieved, and complications ensued, such as graft contracture and stricture formation (De Filippo et al, 2002). Autologous rabbit bladder epithelial and smooth muscle cells were grown and seeded onto preconfigured tubular matrices. Entire urethra segments were resected and urethroplasties were performed with tubularized collagen matrices, either seeded with cells or without cells. The tubularized collagen matrices seeded with autologous cells formed new tissue that was histologically similar to native urethra. The tubularized collagen matrices without cells led to poor tissue development, fibrosis, and stricture formation. These findings were confirmed clinically. A clinical trial using tubularized nonseeded small intestinal submucosa (SIS) for

urethral stricture repair was performed with eight evaluable patients. Two patients with short inflammatory strictures maintained urethral patency. Stricture recurrence developed in the other six patients within 3 months of surgery (le Roux, 2005). Other cell types have also been tried experimentally in acellular bladder collagen matrices, including foreskin epidermal cells and oral keratinocytes (Fu et al, 2007; Li et al, 2008). Vascular endothelial growth factor gene–modified urothelial cells have also been used experimentally for urethral reconstruction (Guan et al, 2008).

The normal wound-healing response to injury has been studied extensively, and this knowledge has been helpful in maximizing success for the engineering of tissues. At the time of tissue injury, cell ingrowth is initiated from the wound edges to cover the tissue defect. **The cells from the edges of the native tissue are able to traverse short distances without any detrimental effects. If the wound is large, more than a few millimeters in distance or depth, increased collagen deposition, fibrosis, and scar formation ensue. Matrices implanted in wound beds are able to lengthen the distances that cells can traverse without initiating an adverse fibrotic response. However, these distances are also limited. The maximum distance that adjacent cells from the wound edge have to travel to create normal tissue over a biologic matrix is approximately 1 cm** (Dorin et al, 2008). **Tissue defects greater than 1 cm, which are treated with a matrix alone (without cells), usually have increased collagen deposition, increased fibrosis, and scar formation. Cell-seeded matrices implanted in wound beds are able to further lengthen the distance for normal tissue formation without initiating an adverse fibrotic response. Studies in the field of regenerative medicine have shown that very large defects (>30 cm), can be successfully treated using cell-seeded scaffolds. This explains the described experimental and clinical results noted with urethral repair. Nonseeded matrices are able to replace urethral segments when used in an onlay fashion, because of the short distances required for tissue ingrowth. However, if a tubularized urethral repair is needed, the matrices need to be seeded with autologous cells in order to avoid the risk of stricture formation and poor tissue development.**

Bladder

Currently, gastrointestinal segments are commonly used as tissues for bladder replacement or repair. However, gastrointestinal tissues are designed to absorb specific solutes, whereas bladder tissue is designed for the excretion of solutes. **When gastrointestinal tissue is in contact with the urinary tract, multiple complications may ensue, such as infection, metabolic disturbances, urolithiasis, perforation, increased mucus production, and malignancy** (McDougal, 1992; Atala et al, 1993a; Kaefer et al, 1997, 1998). Because of the problems encountered with the use of gastrointestinal segments, numerous investigators have attempted alternative reconstructive procedures for bladder replacement or repair. These include autoaugmentation (Cartwright et al, 1989a, 1989b) (Fig. 19–6) and ureterocystoplasty (Bellinger, 1993; Churchill et al, 1993; Adams et al, 1998). In addition, alternative methods for bladder reconstruction have been explored, such as the use of tissue expansion and regenerative medicine with cell transplantation.

Tissue Expansion for Bladder Augmentation

A system of progressive dilation for ureters and bladders has been proposed but has not been attempted clinically (Lailas et al, 1996; Satar et al, 1999). In an animal experiment, rabbits underwent

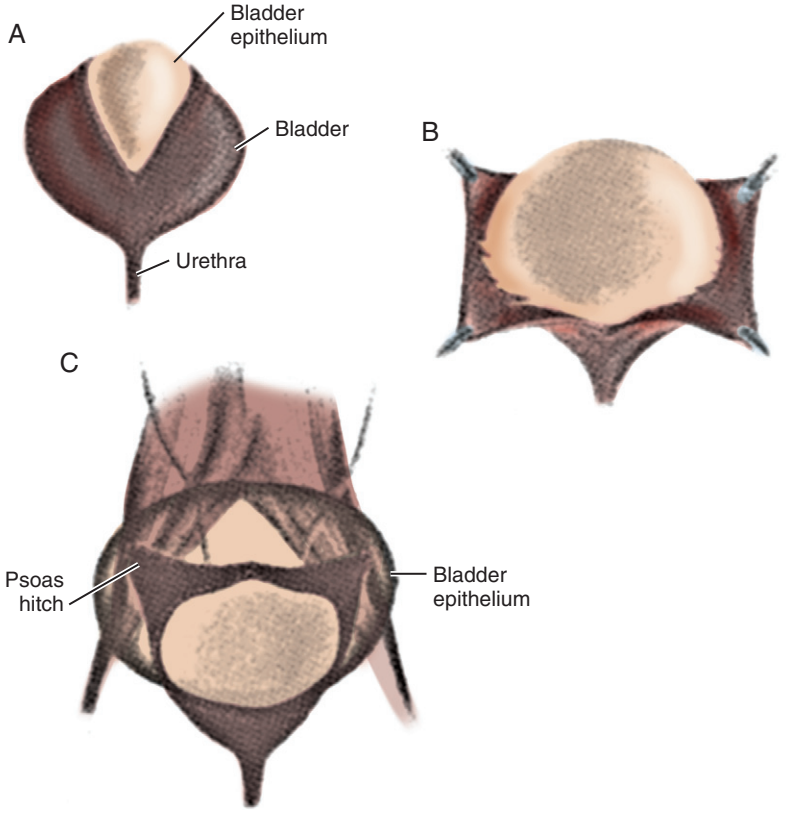


Figure 19–6. Autoaugmentation is performed by incising the detrusor **(A)** and stripping it from intact bladder epithelium **(B),** which allows the urothelial layer to bulge with bladder filling **(C).** (From Cartwright PC, Snow BW. Bladder autoaugmentation: early clinical experience. J Urol 1989;142:505.)

unilateral ureteral ligation at the ureterovesical junction. A catheter was threaded into the proximal ipsilateral ureter and connected to an injection port that was secured subcutaneously. A saline-antibiotic solution was injected daily subcutaneously into the injection port. After 1 month of daily saline-antibiotic–solution injections, the ureteral units were dilated at least 10-fold, and the diameter exceeded that of adjacent colon in each instance (Fig. 19–7). Augmentation cystoplasty was performed with the reconfigured dilated ureteral segment, resulting in an increased bladder capacity ranging from 190% to 380% (Lailas et al, 1996). In a similar system, a dilating indwelling catheter was used to dilate ureteral tissue in pigs (Ikeguchi et al, 1998).

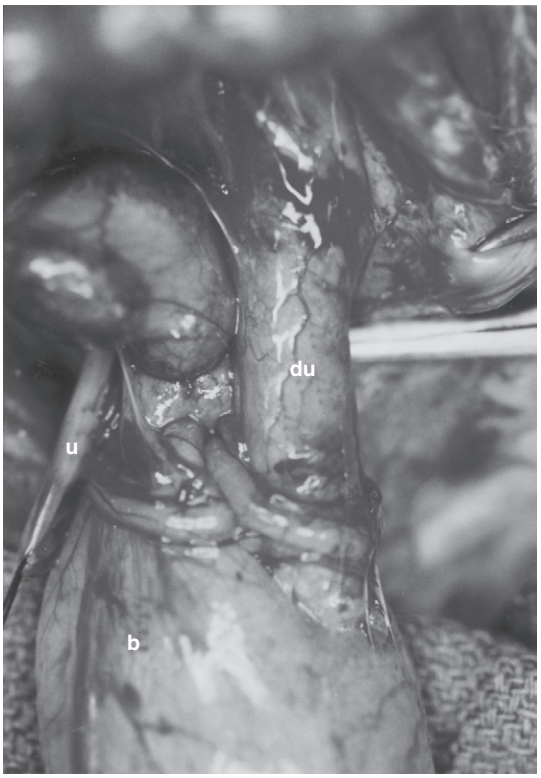


Figure 19–7. Progressive dilation can be performed in a normal-caliber ureter, which can be subsequently used for ureterocystoplasty. After placement of a ureteral dilation device, comparison is made of progressively dilated ureter (du) and native undilated ureter (u) coming off the bladder (b).

A system for the progressive expansion of native bladder tissue has also been used for augmenting bladder volumes (Satar et al, 1999). Beagle dog bladders were divided horizontally into two segments: a superior bladder neoreservoir, and an intact smaller bladder inferiorly with both ureters left intact and draining. A Silastic catheter was threaded into the newly formed, superiorly located neoreservoir and connected to an injection port, which was secured subcutaneously. Four weeks after surgery, a saline-antibiotic solution was injected daily into the palpable injection port, dilating the neoreservoir through the Silastic catheter. Within 30 days after progressive dilation, the neoreservoir volume was expanded at least 10-fold (Fig. 19–8). Urodynamic studies showed normal compliance in all animals, and microscopic examination of the expanded neoreservoir tissue showed a normal histology. A series of immunocytochemical studies demonstrated that the dilated bladder tissue maintained normal phenotypic characteristics (Satar et al, 1999).

Ideally, bladder tissue expansion could be performed with an indwelling dilation catheter, similar to a Foley catheter with a large balloon. In the future, one could foresee placing a dilating catheter intravesically in a patient who requires augmentation, either in an intermittent fashion (e.g., four times daily) or left indwelling. An expanding balloon within the catheter could then be filled progressively, with either continuous or intermittent filling until the desired bladder volume is achieved.

Matrices for Bladder Regeneration

Over the last few decades, several bladder wall substitutes have been attempted with both synthetic and organic materials. Synthetic materials that have been tried in experimental and clinical settings include polyvinyl sponge, Teflon, collagen matrices, Vicryl (PGA) matrices, and silicone. Most of these attempts have failed because of mechanical, structural, functional, or biocompatibility problems. **Usually, permanent synthetic materials used for bladder reconstruction succumb to mechanical failure and urinary stone formation, and use of degradable materials leads to fibroblast deposition, scarring, graft contracture, and a reduced reservoir volume over time** (Atala, 1995a, 1998).

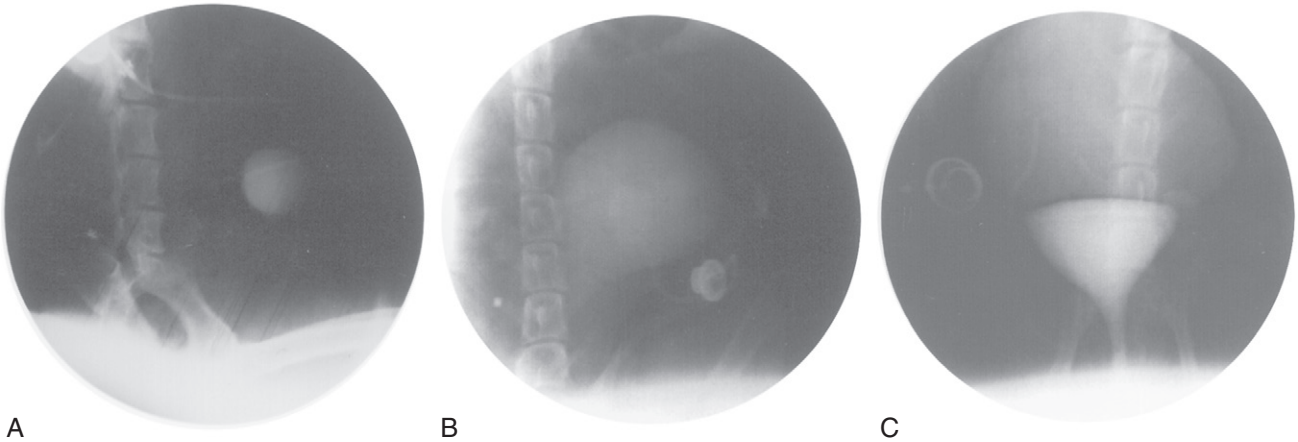


Figure 19–8. Progressive bladder dilation can be performed with adequate increases in capacity. Cystography of bladder neoreservoir before progressive dilation **(A)** is compared with cystography results after progressive dilation **(B)** and with cystogram showing dilated neoreservoir and intact bladder segment **(C).**

There has been a resurgence in the use of various collagen-based matrices for tissue regeneration. Nonseeded allogeneic acellular bladder matrices have served as scaffolds for the ingrowth of host bladder wall components. The matrices are prepared by mechanically and chemically removing all cellular components from bladder tissue (Sutherland et al, 1996; Probst et al, 1997; Piechota et al, 1998; Yoo et al, 1998b; Wefer et al, 2001). The matrices serve as vehicles for partial bladder regeneration, and relevant antigenicity is not evident.

Cell-seeded allogeneic acellular bladder matrices were used for bladder augmentation in dogs (Yoo et al, 1998b). The regenerated bladder tissues contained a normal cellular organization consisting of urothelium and smooth muscle and exhibited a normal compliance. **Biomaterials preloaded with cells before their implantation showed better tissue regeneration compared with biomaterials implanted with no cells, in which tissue regeneration depended on ingrowth of the surrounding tissue.** The bladders showed a significant increase (100%) in capacity when augmented with scaffolds seeded with cells, compared to scaffolds without cells (30%) (Fig. 19–9). The acellular collagen matrices can be enhanced with growth factors to improve bladder regeneration (Kikuno et al, 2008).

SIS, a biodegradable, acellular, xenogeneic collagen-based tissue-matrix graft, was first described by Badylak and colleagues in the 1980s as an acellular matrix for tissue replacement in the vascular field (Badylak et al, 1989). It has been shown to promote regeneration of a variety of host tissues, including blood vessels and ligaments (Badylak, 2002). The matrix is derived from pig small intestine in which the mucosa is mechanically removed from the inner surface, and the serosa and muscular layer are removed from the outer surface. Animal studies have shown that the nonseeded SIS matrix used for bladder augmentation is able to regenerate in vivo (Kropp et al, 1996a, 1996b). Histologically, the transitional layer was the same as that of the native bladder tissue, but, as with other nonseeded collagen matrices used experimentally, the muscle layer was not fully developed. A large amount of collagen was interspersed among a smaller number of muscle bundles. A computer-assisted image analysis demonstrated a decreased muscle-to-collagen ratio with loss of the normal architecture in the SIS-regenerated bladders. In-vitro contractility studies performed on the SIS-regenerated dog bladders showed a decrease in maximal contractile response by 50% from those of normal bladder tissues. Expression of muscarinic, purinergic, and α-adrenergic receptors and functional cholinergic and purinergic innervation were demonstrated (Kropp et al, 1996b). Cholinergic and purinergic innervation also occurred in rats (Vaught et al, 1996).

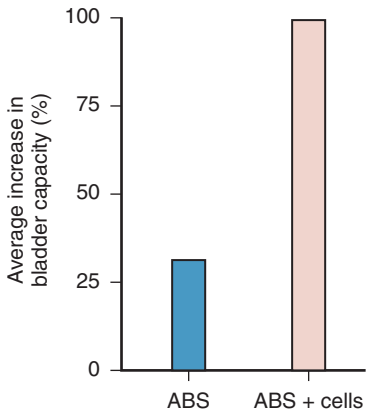


Figure 19–9. Bladders augmented with a collagen matrix derived from bladder submucosa seeded with urothelial and smooth muscle cells (allogenic bladder submucosa [ABS] + cells) showed a 100% increase in capacity compared with bladders augmented with the cell-free ABS, which showed only a 30% increase in capacity within 3 months after implantation.

Bladder augmentation using laparoscopic techniques was performed on mini-pigs with porcine bowel acellular tissue matrix, human placental membranes, or porcine SIS. At 12 weeks postoperatively, the grafts had contracted to 70%, 65%, and 60% of their original sizes, respectively, and histologically the grafts showed predominantly only mucosal regeneration (Portis et al, 2000). The same group evaluated the long-term results of laparoscopic hemicystectomy and bladder replacement with SIS with ureteral reimplantation into the SIS material in mini-pigs. Histopathology studies after 1 year showed muscle at the graft periphery and center, but it consisted of small fused bundles with significant fibrosis. Nerves were present at the graft periphery and center, but they were decreased in number. Compared with primary bladder closure after hemicystectomy, no advantage in bladder capacity or compliance was documented (Landman et al, 2004). More recently, bladder regeneration has been shown to be more reliable when the SIS was derived from the distal ileum (Kropp et al, 2004).

In multiple studies using various materials as nonseeded grafts for cystoplasty, the urothelial layer was able to regenerate normally, but the muscle layer, although present, was not fully developed (Kropp et al, 1996b; Probst et al, 1997; Sutherland et al, 1996; Jayo et al, 2008b; Yoo et al, 1998b; Zhang, 2008). Studies involving acellular matrices that may provide the necessary environment to promote cell migration, growth, and differentiation are being conducted (Chun et al, 2007). With continued bladder research in this area, these matrices may have a clinical role in bladder replacement in the future.

Regenerative Medicine for Bladder Using Cell Transplantation

Regenerative medicine with selective cell transplantation may provide a means to create functional new bladder segments (Atala, 1997). The success of cell transplantation strategies for bladder reconstruction depends on the ability to use donor tissue efficiently and to provide the right conditions for long-term survival, differentiation, and growth. Various cell sources have been explored for bladder regeneration. Native cells are currently preferable due to their autologous source, wherein they can be used without rejection (Cilento et al, 1994). It has been shown experimentally that the bladder neck and trigone area has a higher propensity of urothelial progenitor cells (Nguyen et al, 2007), and these cells are localized in the basal region (Kurzrock et al, 2008). Amniotic fluid and bone marrow–derived stem cells can also be used in an autologous manner and have the potential to differentiate into bladder muscle (De Coppi et al, 2007a; Shukla et al, 2008) and urothelium (Anumanthan et al, 2008). Embryonic stem cells also have the potential to differentiate into bladder tissue (Oottamasathien et al, 2007).

Formation of Bladder Tissue. Human urothelial and muscle cells can be expanded in vitro, seeded onto polymer scaffolds, and allowed to attach and form sheets of cells. The cell-polymer scaffold can then be implanted in vivo. Histologic analysis indicated that viable cells were able to self assemble back into their respective tissue types, and would retain their native phenotype (Atala et al, 1993c). These experiments demonstrated,

for the first time, that composite layered tissue-engineered structures could be created de novo. Before this study, only nonlayered structures had been created in the field of regenerative medicine.

In order to determine the effects of implanting engineered tissues in continuity with the urinary tract, animal models of bladder augmentation were used (Yoo et al, 1998b). Partial cystectomies were performed in dogs. The animals were divided into two experimental groups. One group had their bladder augmented with a nonseeded bladder-derived collagen matrix, and the second group had their bladder augmented with a cell-seeded construct. The bladders augmented with matrices seeded with cells showed a 100% increase in capacity compared with bladders augmented with cell-free matrices, which showed only a 30% increase in capacity (see Fig. 19–9).

Most of the free grafts (without cells) used for bladder replacement in the past were able to show adequate histology in terms of a well-developed urothelial layer, but they were associated with an abnormal muscular layer that varied in terms of its full development (Atala, 1995a, 1998).

It has been well established for decades that the bladder is able to regenerate generously over free grafts. Urothelium is associated with a high reparative capacity (de Boer et al, 1994). Bladder muscle tissue is less likely to regenerate in a normal fashion. Both urothelial and muscle ingrowth are believed to be initiated from the edges of the normal bladder toward the region of the free graft (Baker et al, 1958; Gorham et al, 1989). Usually, however, contracture or resorption of the graft has been evident. The inflammatory response toward the matrix may contribute to the resorption of the free graft. It was hypothesized that building the three-dimensional structure constructs in vitro, before implantation, would facilitate the eventual terminal differentiation of the cells after implantation in vivo and would minimize the inflammatory response toward the matrix, thus avoiding graft contracture and shrinkage. The dog study demonstrated a major difference between matrices used with autologous cells (tissue-engineered matrices) and those used without cells (Yoo et al, 1998b). **Matrices implanted with cells for bladder augmentation retained most of their implanted diameter, as opposed to matrices implanted without cells for bladder augmentation, in which graft contraction and shrinkage occurred. The histomorphology demonstrated a marked paucity of muscle cells and a more aggressive inflammatory reaction in the matrices implanted without cells.** Epithelial-mesenchymal signaling is important for the differentiation of bladder smooth muscle (Master et al, 2003).

The results of initial studies showed that the creation of artificial bladders may be achieved in vivo; however, it could not be determined whether the functional parameters noted were caused by the augmented segment or by the intact native bladder tissue. To better address the functional parameters of tissue-engineered bladders, an animal model was designed that required a subtotal cystectomy with subsequent replacement with a tissue-engineered organ (Oberpenning et al, 1999).

Cystectomy-only and nonseeded controls maintained average capacities of 22% and 46% of preoperative values, respectively. An average bladder capacity of 95% of the original precystectomy volume was achieved in the cell-seeded tissue engineered bladder replacements. These findings were confirmed radiographically (Fig. 19–10). The subtotal cystectomy reservoirs that were not reconstructed and the polymer-only reconstructed bladders showed a marked decrease in bladder compliance (10% and 42% total compliance). The compliance of the cell-seeded tissue-engineered bladders showed almost no difference from preoperative values that were measured when the native bladder was present (106%). Histologically, the nonseeded scaffold bladders presented a pattern of normal urothelial cells with a thickened fibrotic submucosa and a thin layer of muscle fibers. The retrieved tissue-engineered bladders showed a normal cellular organization, consisting of a trilayer of urothelium, submucosa, and muscle (Fig. 19–11). Immunocytochemical analyses confirmed the muscle and urothelial phenotype. S-100 staining indicated the presence of neural structures (Oberpenning et al, 1999). These studies, performed with polyglycolic acid–based scaffolds, have been repeated by other investigators, showing similar results in large numbers of animals long-term (Jayo et al, 2008a, 2008b). The strategy of using biodegradable scaffolds with cells can be pursued without concerns for local or systemic toxicity (Kwon et al, 2008). However,

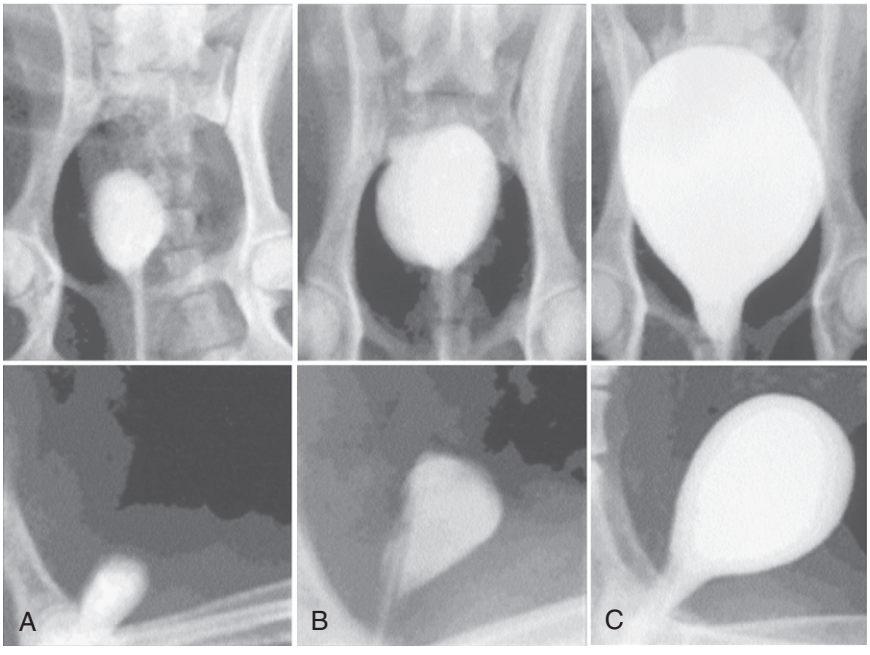


Figure 19–10. Radiographic cystograms in beagles 11 months after subtotal cystectomy without reconstruction **(A);** with reconstruction using a polymer without cells **(B);** and with reconstruction with a polymer and cell-seeded tissue-engineered organ **(C).** Organs after trigone-sparing cystectomy retained a small-sized reservoir. Tissue-engineered neobladders showed a normal configuration and a larger capacity than the trigones grafted with polymer only.

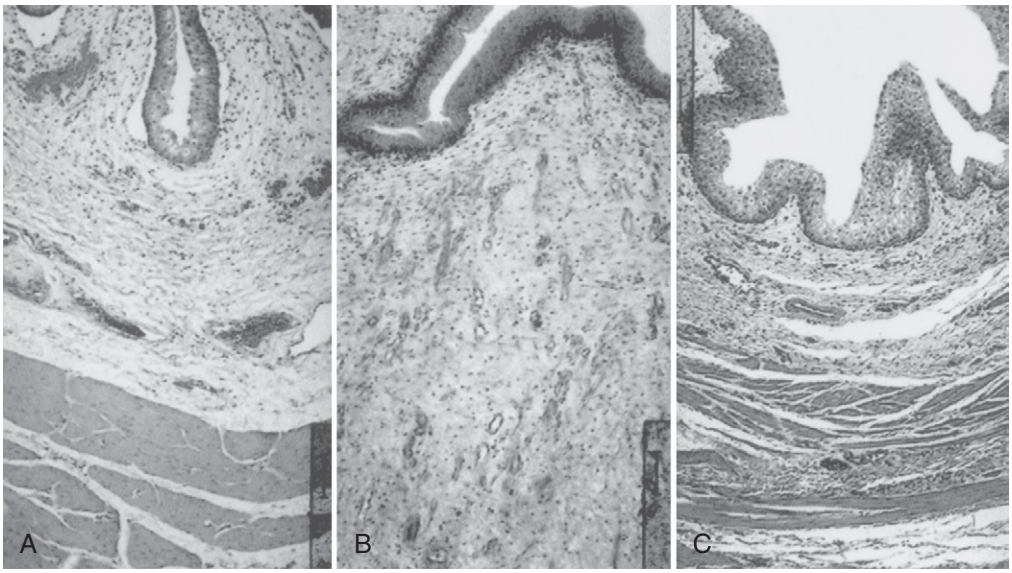


Figure 19–11. Hematoxylin and eosin staining shows histologic results 6 months after surgery (original magnification, ×250). **A,** Normal canine bladder. **B,** The bladder dome of the bladder reconstructed with cell-free polymer consists of normal urothelium over a thickened layer of collagen and fibrotic tissue; only scarce muscle fibers are apparent. **C,** The tissue-engineered neo-organ has a histomorphologically normal appearance. A trilayered architecture consisting of urothelium, submucosa, and smooth muscle is evident.

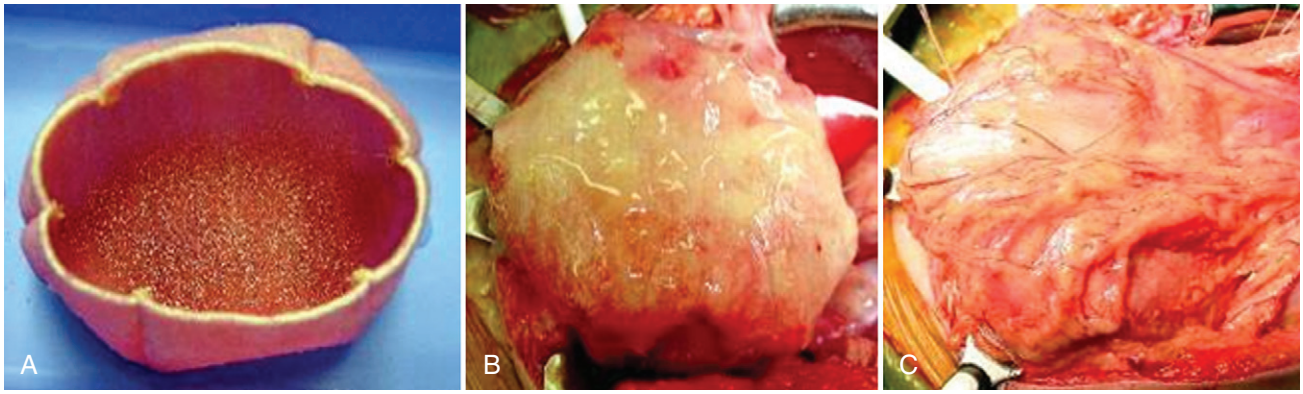


Figure 19–12. Construction of engineered bladder. **A,** Scaffold material seeded with cells for use in bladder repair. **B,** The seeded scaffold is anastomosed to native bladder with running 4-0 polyglycolic sutures. **C,** Implant covered with fibrin glue and omentum.

not all scaffolds perform well if a large portion of the bladder needs replacement. In a study using SIS for subtotal bladder replacement in dogs, both the unseeded and cell-seeded experimental groups showed graft shrinkage and poor results (Zhang et al, 2006b). The type of scaffold used is critical for the success of these technologies. The use of bioreactors, wherein mechanical stimulation is started at the time of organ production, has also been proposed as an important parameter for success (Farhat et al, 2008).

A clinical experience involving engineered bladder tissue for cystoplasty reconstruction was conducted starting in 1998. A small pilot study of seven patients was reported, using a collagen scaffold seeded with cells either with or without omentum coverage, or a combined PGA-collagen scaffold seeded with cells and omental coverage (Fig. 19–12). The patients reconstructed with the engineered bladder tissue created with the PGA-collagen cell-seeded scaffolds with omental coverage showed increased compliance, decreased end-filling pressures, increased capacities, and longer dry periods over time (Atala et al, 2006). It is clear from this experience that the engineered bladders continued their improvement with time, mirroring their continued development. Although the experience is promising in terms of showing that engineered tissues can be implanted safely, it is just a start in terms of accomplishing the goal of engineering fully functional bladders. This was a limited clinical experience, and the technology is not yet ready for wide dissemination, because further experimental and clinical studies are required. FDA Phase II studies have now been completed.

An area of concern in the field of tissue engineering in the past was the source of cells for regeneration. The concept of creating engineered constructs involves initially obtaining cells for expansion from the diseased organ. How can one be assured that the cell population that is obtained and being expanded for later autologous implantation is normal and will lead to normal tissue formation? For example, if one is dealing with a patient, will the cells obtained from a neuropathic bladder lead to the engineering of another neuropathic bladder? Cultured neuropathic bladder smooth muscle cells possess and maintain different characteristics than normal smooth muscle cells in vitro, as demonstrated by growth assays, contractility, adherence tests, and microarray analysis (Lin et al, 2004; Dozmorov et al, 2007; Hipp et al, 2008). However, when neuropathic smooth muscle cells were cultured in

vitro, and seeded onto matrices and implanted in vivo, the tissue engineered constructs showed the same properties as the tissues engineered with normal cells (Lai et al, 2002). **The progenitor cells, which reside within stem cell niches within each organ, are responsible for new cell differentiation and tissue formation during the normal process of tissue regeneration due to natural turnover, ageing, and tissue injury. It is known that genetically normal nonmalignant progenitor cells, which are the reservoirs for new cell formation, are programmed to give rise to normal tissue, regardless of whether the niche resides in either normal or diseased tissues** (Faris et al, 2001; Lai et al, 2002; Haller et al, 2005). Therefore although the mechanisms for tissue self-assembly and regenerative medicine are not fully understood, it is known that the progenitor cells are able to "reset" their program for normal cell differentiation. The stem cell niche and its role in normal tissue regeneration remains a fertile area of ongoing investigation.

From the above studies, it is evident, as with the urethral studies, that the use of cell-seeded matrices is superior to the use of nonseeded matrices for the creation of engineered bladder tissues. Although advances have been made with the engineering of bladder tissues, many challenges remain. Current research in many centers is aimed at the development of biologically active and "smart" biomaterials that may improve tissue regeneration.

Ureters

Collagen tubular sponges have been used to transplant bladder cells for replacement of ureteral segments in dogs. The study showed severe stricture formation and papillary mucosal thickening at the anastomotic sites. In addition, muscle regeneration into the collagen grafts was not evident (Tachibana et al, 1985).

Ureteral decellularized matrices have been used as a scaffold for both the ingrowth of ureteral tissue (Dahms et al, 1997) and as a cell delivery vehicle using urothelial and bone marrow–derived cells (Matsunuma et al, 2006). Laparoscopic segmental ureteral replacement with an acellular matrix prepared from ureters and small-intestinal submucosa was performed in mini-pigs (Shalhav et al, 1999). At 12 weeks, all animals had complete obstruction at the level of the replacement. Ureteral replacement with polytetrafluoroethylene (Teflon) grafts was attempted in dogs, also with poor functional results (Baltaci et al, 1998). Nonseeded ureteral collagen acellular matrices were tubularized and used to replace 3 cm segments of canine ureters. At the time of sacrifice, there was moderate to marked hydroureteronephrosis above the level of the new tube in all dogs with significant narrowing of the ureteral lumen, up to complete occlusion (Osman et al, 2004).

Cell-seeded biodegradable polymer scaffolds have been used as cell transplantation vehicles to reconstruct ureteral tissues. In one study, urothelial and smooth muscle cells isolated from bladders and expanded in vitro were seeded onto PGA scaffolds with tubular configurations and implanted subcutaneously into athymic mice. After implantation, the urothelial cells proliferated to form a multilayered luminal lining of tubular structures, while the smooth muscle cells organized into multilayered structures surrounding the urothelial cells. Abundant angiogenesis was evident. The degradation of the polymer scaffolds resulted in the eventual formation of natural urothelial tissues (Atala et al, 1993c). This study suggested that it was possible to engineer urologic tissues containing multiple cell types. This approach was expanded to replacement of ureters in dogs by transplantation of smooth muscle cells and urothelial cells on tubular polymer scaffolds (Yoo et al, 1995). The limitations of transferring this technology to humans are the small number of patients requiring this type of tissue, and the large investment that would be required for regulatory approval.

Genital and Reproductive Tissues

Reconstructive surgery is required for a wide variety of pathologic penile conditions, including penile carcinoma, trauma, severe erectile dysfunction, and congenital conditions such as ambiguous genitalia, hypospadias, and epispadias. One of the major limitations of phallic reconstructive surgery is the availability of sufficient autologous tissue. Nongenital autologous tissue sources have been used for decades. Phallic reconstruction was initially attempted in the late 1930s, with rib cartilage used as a stiffener for patients with traumatic penile loss (Frumpkin, 1944; Goodwin et al, 1952). This method, involving multiple staged surgeries, was soon discouraged due to the unsatisfactory functional and cosmetic results. Silicone rigid prostheses were popularized in the 1970s and have been used widely (Small et al, 1975; Bretan, 1989). However, biocompatibility issues have been a problem in selected patients (Thomalla et al, 1987; Nukui et al, 1997). Tissue transfer techniques with flaps from various nongenital sources, such as the groin, dorsalis pedis, and forearm, have been used for genital reconstruction (Jordan, 1999). However, operative complications such as infection, graft failure, and donor site morbidity are not negligible. Phallic reconstruction with autologous tissue, derived from the patient's own cells, may be preferable in selected cases.

Reconstruction of Corporeal Tissues

Reconstruction of Corporeal Smooth Muscle. One of the major components of the phallus is corporeal smooth muscle. The creation of autologous functional and structural corporeal tissue de novo would be beneficial. Initial experiments showed that cultured human corporeal smooth muscle cells may be used in conjunction with biodegradable polymers to create corpus cavernosum tissue de novo (Kershen et al, 2002). **When grown on collagen, corporeal cavernosal endothelial cells formed capillary structures that created complex three-dimensional capillary networks** (Fig. 19–13). In a subsequent study, human corporeal smooth muscle cells and endothelial cells seeded on biodegradable polymer scaffolds were able to form vascularized

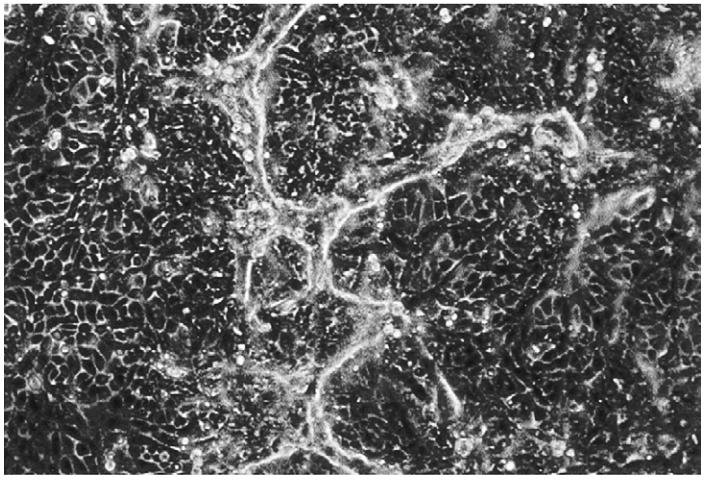


Figure 19–13. Human corporal cavernosal endothelial cells form capillary-like structures in vitro (original magnification, ×100).

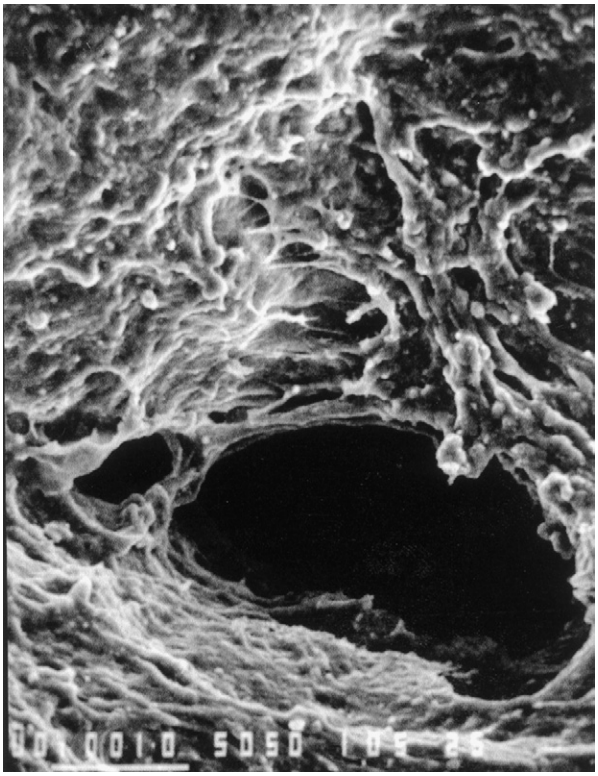


Figure 19–14. Scanning electron microscopy of human cavernosal smooth muscle and endothelial cells seeded on acellular matrices.

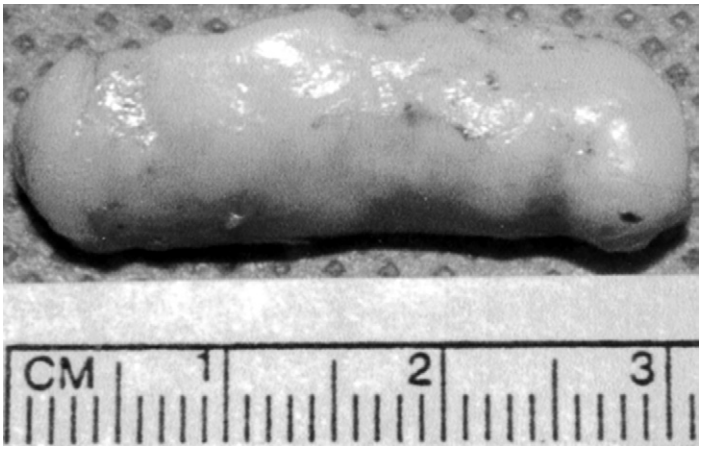


Figure 19–15. Cylindrical polymer scaffolds seeded with chondrocytes and implanted in vivo formed milky-white, rod-shaped, solid cartilaginous structures.

cavernosal muscle when implanted in vivo (Park et al, 1999). A naturally derived acellular corporal tissue matrix that possesses the same architecture as native corpora was developed (Fig. 19–14). Acellular collagen matrices were derived from processed donor rabbit corpora using cell lysis techniques. Human corpus cavernosal muscle and endothelial cells were derived from donor penile tissue, and the cells were expanded in vitro and seeded on the acellular matrices (Fig. 19–15). The matrices were covered with the appropriate cell architecture 4 weeks after implantation (Falke et al, 2003). The use of these tissue-derived matrices as cell-delivery scaffolds allowed the development of adequate structural and vascular corpora cavernosa constructs.

To look at the functional parameters of the engineered corpora, acellular corporeal collagen matrices were obtained from a donor rabbit penis, and autologous corpus cavernosal smooth muscle and endothelial cells were harvested, expanded, and seeded on the matrices. An entire cross-sectional segment of protruding rabbit phallus was excised, leaving the urethra intact and the cell-seeded matrices were interposed into the excised corporal space. Functional and structural parameters (cavernosography, cavernosometry, mating behavior, and sperm ejaculation) were followed, and histochemical, immunocytochemical and Western blot analyses were performed up to 6 months after implantation. The engineered corpora cavernosa achieved adequate structural and functional parameters (Kwon et al, 2002). This technology was further confirmed when the entire rabbit corpora was removed and replaced with the engineered scaffolds. The experimental corporeal bodies demonstrated intact structural integrity by cavernosography and showed similar pressure by cavernosometry when compared with the normal controls. The control rabbits without cells failed to show normal erectile function throughout the study period. Mating activity in the animals with the engineered corpora appeared normal by 1 month after implantation. The presence of sperm was confirmed during mating, and was present in all the rabbits with the engineered corpora. The female rabbits mated with the animals implanted with engineered corpora and also conceived and delivered healthy pups. Animals implanted with the matrix alone were unable to demonstrate normal mating activity and failed to ejaculate into the vagina. Grossly, the corporeal implants with cells showed continuous integration of the graft into native tissue. Histologically, sinusoidal spaces and walls, lined with endothelium and smooth muscle, were observed in the engineered grafts. Grafts without cells contained fibrotic tissue and calcifications with sparse corporal elements. Each cell type was identified immunocytochemically and by Western-blot analyses. The engineered corporeal tissues were able to contract and relax in response to electric field and pharmacologic stimulation, and the contractile response reached levels similar to normal corpora by 6 months after implantation (Chen et al, 2005). Dynamic cell seeding using bioreactor systems have been shown to enhance cell penetration in the acellular tissue-derived matrices (Eberli et al, 2008b).

The above series of studies demonstrate that penile corpora cavernosa tissue can be engineered. The engineered tissue is able to achieve adequate structural and functional parameters sufficient for erection, copulation, ejaculation, conception, and delivery in rabbits. Further studies will be needed to confirm the long-term functionality of these organs. In addition, further studies are needed to show that human structures can also be engineered.

Engineered Penile Prostheses. **Although silicone is an accepted biomaterial for penile prostheses, biocompatibility is a concern** (Thomalla et al, 1987; Nukui et al, 1997). The use of a natural prosthesis composed of autologous cells may be advantageous. A feasibility study for the creation of natural penile prostheses made of cartilage was performed initially (Yoo et al, 1998a).

Cartilage, harvested from the articular surface of calf shoulders, was isolated, grown, and expanded in culture. The cells were seeded onto preformed cylindrical polyglycolic acid polymer rods and implanted in mice. At retrieval, all polymer scaffolds seeded with cells formed milky-white, rod-shaped, solid cartilage structures, maintaining their preimplantation size and shape (see Fig. 19–15). In a subsequent study using an autologous system, the feasibility of applying the engineered cartilage rods in situ was

investigated (Yoo et al, 1999). Autologous chondrocytes harvested from rabbit ear were grown and expanded in culture. The cells were seeded onto biodegradable poly-L-lactic acid coated polyglycolic acid polymer rods and implanted into the corporal spaces of rabbits. Examination at retrieval showed the presence of well-formed, milky-white cartilage structures within the corpora at 1 month. The animals were able to copulate and impregnate their female partners. In another study, human cartilage rods were engineered in vitro for potential use as penile prostheses. Chondrocytes isolated from human ear were seeded on rod-shaped biodegradable polymer scaffolds (1.2 cm in diameter, 6.0 cm long). The engineered human cartilaginous rods were flexible, elastic, and able to withstand high degrees of compressive forces. The mechanical properties were comparable to those of commercially available silicone prostheses (Kim et al, 2002).

Testis

Leydig cells are the major source of testosterone production in males. Patients with testicular dysfunction require androgen replacement for somatic development. Conventional treatment for testicular dysfunction consists of periodic intramuscular injections of chemically modified testosterone or, more recently, skin patch applications. However, long-term nonpulsatile testosterone therapy is not optimal and can cause multiple problems, including erythropoiesis and bone density changes.

A system was designed wherein Leydig cells were microencapsulated for controlled testosterone replacement. **Microencapsulated Leydig cells offer several advantages, such as serving as a semipermeable barrier between the transplanted cells and the host's immune system, as well as allowing for the long-term physiologic release of testosterone.** Purified Leydig cells were isolated and encapsulated in an alginate-poly-L-lysine solution (Fig. 19–16). The encapsulated Leydig cells were injected into castrated animals, and serum testosterone was measured serially; the animals were able to maintain testosterone levels in the long term (Machluf et al, 1998). These studies suggest that microencapsulated Leydig cells may be able to replace or supplement testosterone in situations where anorchia or testicular failure is present. A novel technique to isolate Leydig stem cells and to study Leydig cell development has also been described (Lo et al, 2004). The successful transplantation of functional Leydig stem cells into a hypogonadal recipient showed that the de novo synthesis of testosterone is possible.

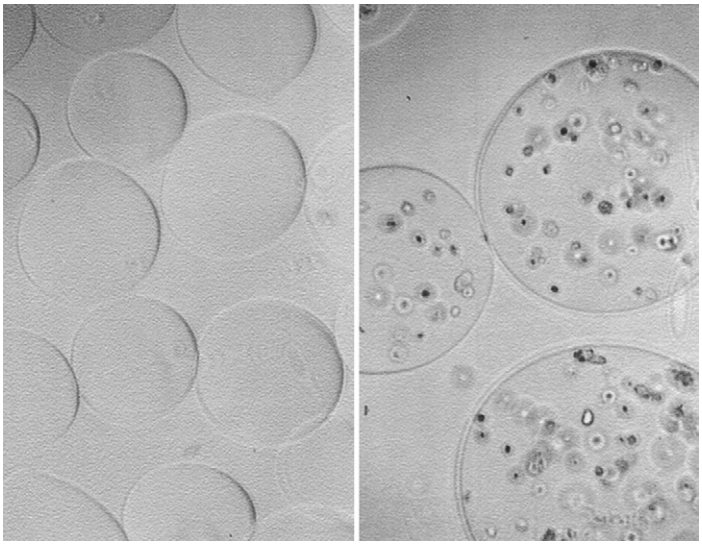


Figure 19–16. *Left,* Hydrogel microcapsules without cells. *Right,* Leydig cells encapsulated in hydrogel microcapsules secrete testosterone in vitro and in vivo.

Further studies showed that testicular prostheses created with chondrocytes in bioreactors, could be loaded with testosterone. The prostheses were implanted in athymic mice with bilateral anorchia, and testosterone was released long term, maintaining the androgen level at a physiologic range (Raya-Rivera et al, 2008). One could envision combining the Leydig cell technology described above with engineered prostheses for the long-term functional replacement of androgen levels. The ability to have spermatogenesis for infertility purposes has been a major area of interest in the last decade. Spermatogonial transplantation and reconstitution of donor cell spermatogenesis was shown in recipient mice (Nagano et al, 1998). The same group was able to show the restoration of fertility in mice with the transplantation of male germ-line stem cells (Ogawa et al, 2000). Spermatogonial stem cells can be isolated and enriched with specific markers (Lo et al, 2005). Sertoli cells, the main component of the testicular germ-cell niche, were recovered and dissociated from testes of donor male mice and microinjected into recipient testes, forming mature seminiferous tubule structures, and supporting spermatogenesis (Shinohara et al, 2003). The germ-line niche transplantation was also able to restore fertility in mice (Kanatsu-Shinohara et al, 2005).

Female Genital and Reproductive Tissues

Congenital malformations of the uterus may have profound implications clinically. Patients with cloacal exstrophy and intersex disorders may not have sufficient uterine tissue present for future reproduction. We investigated the possibility of engineering functional uterine tissue using autologous cells (Wang et al, 2003). Autologous rabbit uterine smooth muscle and epithelial cells were harvested, then grown and expanded in culture. These cells were seeded onto pre-configured uterine-shaped biodegradable polymer scaffolds, which were then used for subtotal uterine tissue replacement in the corresponding autologous animals. Upon retrieval 6 months after implantation, histological, immunocytochemical, and Western-blot analyses confirmed the presence of uterine tissue components. Biomechanical analyses and organ bath studies showed that the functional characteristics of these tissues were similar to those of normal uterine tissue. Breeding studies using these engineered uteri are currently being performed.

Similarly, several pathologic conditions, including congenital malformations and malignancy, can adversely affect normal vaginal development or anatomy. Vaginal reconstruction has traditionally been challenging due to the paucity of available native tissue. Acellular materials have been used experimentally for vaginal reconstruction in rats (Wefer et al, 2002). The feasibility of engineering vaginal tissue with cells in vivo was also investigated (De Filippo et al, 2003). Vaginal epithelial and smooth muscle cells of female rabbits were harvested, grown, and expanded in culture. These cells were seeded onto biodegradable polymer scaffolds, and the cell-seeded constructs were then implanted into mice. Functional studies in the tissue-engineered constructs showed similar properties to those of normal vaginal tissue. When these constructs were used for autologous total vaginal replacement in a rabbit model, patent functional vaginal structures were noted in the tissue-engineered specimens, while the non–cell-seeded structures were noted to be stenotic (De Filippo et al, 2008) (Fig. 19–17) These studies indicated that a regenerative medicine approach to clinical vaginal reconstruction would be a realistic possibility. Clinical trials are currently being conducted.

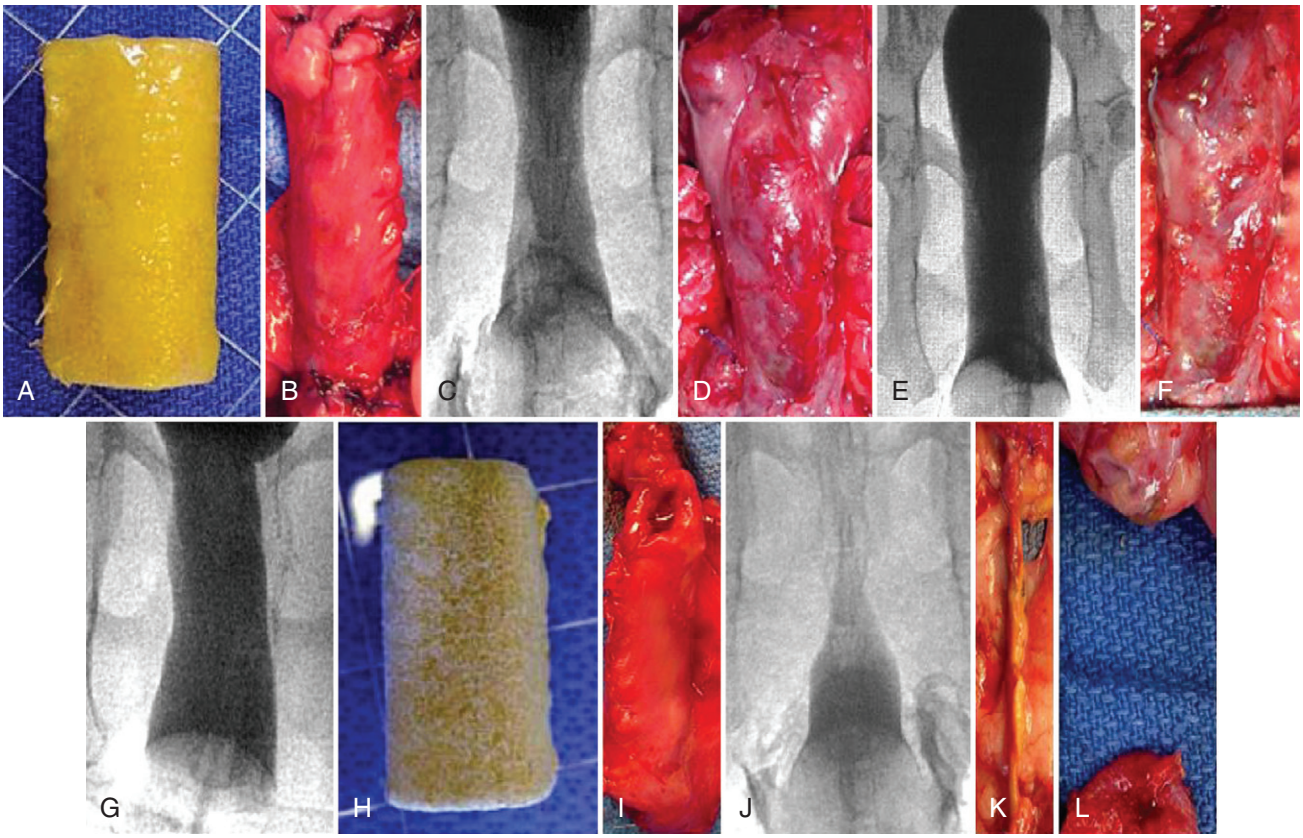


Figure 19–17. Appearance of tissue engineered neovaginas. **A,** Tubular polymer scaffold after cell seeding and 1-week in vitro culture, prior to implantation in vivo. **B, D,** and **F** indicate gross appearance and **C, E,** and **G** show vaginography of cell-seeded constructs 1, 3, and 6 months, postimplantation, respectively. **H,** Unseeded control scaffold prior to implantation. **I, K,** and **L,** Gross appearance of unseeded construct at 1, 3, and 6 months postimplantation. **J,** Vaginography of unseeded graft at 1 month.

Renal Structures

Although the kidney was the first organ to be substituted by an artificial device and the first successfully transplanted organ (Guild et al, 1955), current modalities of treatment are far from satisfactory. Renal tissue is arguably one of the most difficult tissues to replicate in the laboratory. The kidney is a complex organ and the unique structural and cellular heterogeneity present within this organ creates many challenges. The system of nephrons and collecting ducts within the kidney is composed of multiple functionally and morphologically distinct segments. For this reason, appropriate conditions must be provided to ensure the long-term survival, differentiation and growth of many types of cells. Efforts in the area of kidney tissue regeneration have focused on the development of a reliable cell source (Prockop, 1997; Kale et al, 2003; Lin et al, 2003; Ikarashi et al, 2005; Lin et al, 2005; Yokoo et al, 2005). Moreover, optimal growth conditions have been extensively investigated to provide adequate enrichment to achieve stable renal cell expansion systems (Milici et al, 1985; Carley et al, 1988; Humes et al, 1992; Schena, 1998).

Isolation of particular cell types that produce specific factors may be a good approach for selective cell therapies. For example, cells that produce erythropoietin have been isolated in culture, and these cells could eventually be used to treat anemia that results from end stage renal failure (Aboushwareb et al, 2008). Other more ambitious approaches involve working towards the goal of total renal function replacement. To create kidney tissue that would deliver full renal function, a culture containing all of the cell types comprising the functional nephron units should be used. Optimal culture conditions to nurture renal cells have been extensively studied and cells grown under these conditions have been reported to maintain their cellular characteristics (Lanza et al, 2002a). Cells obtained through the initial process of nuclear transfer were retrieved and expanded from cloned tissue. Moreover, renal cells placed in a three-dimensional culture environment are able to reconstitute into renal structures.

Recent investigative efforts in the search for a reliable cell source have been expanded to stem and progenitor cells. Use of these cells for tissue regeneration is attractive due to their ability to differentiate and mature into specific cell types needed. This is particularly useful in instances where primary renal cells are unavailable due to extensive tissue damage. Bone marrow–derived human mesenchymal stem cells have been shown to be a potential source due to their ability to differentiate into several cell lineages (Prockop, 1997; Kale et al, 2003; Ikarashi et al, 2005). These cells have been shown to participate in kidney development when they are placed in a rat embryonic niche that allows for continued exposure to a repertoire of nephrogenic signals (Yokoo et al, 2005). These cells, however, were found to contribute mainly to regeneration of damaged glomerular endothelial cells after injury. The major cell source of kidney regeneration was found to originate from intrarenal cells in an ischemic renal injury model (Lin et al, 2005). Systemic administration of bone marrow–derived mesenchymal stem cells in mice has led to prevention of nephropathy in a diabetic model, the acceleration of acute renal injury, and to angiogenesis and vasculogenesis in a renal injury model (Humphreys et al, 2008; Lin, 2008).

Another potential cell source for kidney regeneration is circulating stem cells, which have been shown to transform into tubular and glomerular epithelial cells, podocytes, mesangial cells, and interstitial cells after renal injury (Ito et al, 2001; Poulsom et al, 2001; Gupta et al, 2002; Iwano et al, 2002; Kale et al, 2003; Lin et al, 2003; Rookmaaker et al, 2003). Other stem cell types, such as human embryonic stem cells (Lin, 2006), and the more recently discovered human amniotic fluid and placental stem cells can also lead to renal differentiation (Perin et al, 2007). These observations suggest that controlling stem and progenitor cell differentiation may lead to successful regeneration of kidney tissues.

Although isolated renal cells are able to retain their phenotypic and functional characteristics in culture, transplantation of these cells in vivo may not result in structural remodeling. In addition, cell or tissue components cannot be implanted in large volumes due to limited diffusion of oxygen and nutrients (Folkman et al, 1973). Thus a cell-support matrix, preferably one that encourages angiogenesis, is necessary to allow diffusion across the entire implant. A variety of synthetic and naturally derived materials has been examined in order to determine the ideal support structures for regeneration (Tachibana et al, 1985; Atala, 1995b; Oberpenning et al, 1999; El-Kassaby et al, 2003; Atala et al, 2006). Biodegradable synthetic materials, such as poly-lactic and polyglycolic acid polymers, have been used to provide structural support for cells. Synthetic materials can be easily fabricated and configured in a controlled manner, which make them attractive options for regenerative medicine. However, naturally derived materials, such as collagen, laminin, and fibronectin, are much more biocompatible and provide a similar extracellular matrix environment to normal tissue. For this reason, collagen-based scaffolds have been used increasingly in many applications (De Filippo et al, 2002; El-Kassaby et al, 2003; Falke et al, 2003; Atala et al, 2006; Murray et al, 2006).

Developmental Approaches to Kidney Regeneration

Transplantation of a kidney precursor, such as the metanephros, into a diseased kidney has been proposed as a possible method for functional restoration. In an animal study, human embryonic metanephroi, transplanted into the kidneys of an immune-deficient mouse model, has developed into mature kidneys (Dekel et al, 2003). The transplanted metanephroi produced urine-like fluid, however, failed to develop ureters. This study suggests that development of an in-vitro system in which metanephroi could be grown may lead to transplant techniques that could produce a small replacement kidney within the host. In another study, the metanephros was divided into mesenchymal tissue and ureteral buds, and each of the tissue segments was cultured in vitro (Steer et al, 2002). After 8 days in culture, each portion of the mesenchymal tissues had grown to the original size. A similar method was used for ureteral buds, which also propagated. These studies were expanded further by staging renal structure reconstitution in vitro and later implanting these structures in vivo in a mouse model (Rosines et al, 2007). These studies indicate that if the mesenchyme and ureteral buds were placed together and cultured in vitro, a metanephros-like structure would develop and suggest that the metanephros could be propagated under an optimal condition.

In another study, transplantation of metanephroi into a nonimmunosuppressed rat omentum showed that the implanted metanephroi are able to undergo differentiation and growth that is not confined by a tight organ capsule (Rogers et al, 1998). When the metanephroi with an intact ureteric bud were implanted, the metanephroi are able to enlarge and become kidney shaped tissue within 3 weeks. The metanephroi transplanted into the omentum were able to develop into kidney tissue structure with a well-defined cortex and medulla. Mature nephrons and collecting system structures are shown to be indistinguishable from those of normal kidneys by light or electron microscopy (Hammerman, 2002a, 2002b). Moreover, these structures become vascularized by arteries that originate at the superior mesenteric artery of the host (Hammerman, 2002a, 2002b). It has been demonstrated that the metanephroi transplanted into the omentum survive for up to 32 weeks postimplantation (Rogers et al, 1999). These studies show that developmental approach may be a viable option for regenerating renal tissue for functional restoration.

Regenerative Medicine Approaches to Kidney Regeneration

The ability to grow and expand renal cells is one of the essential requirements in engineering tissues. The feasibility of achieving renal cell growth, expansion, and in-vivo reconstitution using regenerative medicine techniques was investigated (Atala, 1995b). Donor rabbit kidney cells, including distal tubules, glomeruli, and proximal tubules were plated separately in vitro and, after expansion, were seeded onto biodegradable polyglycolic acid scaffolds and implanted subcutaneously into host athymic mice. This included implants of proximal tubular cells, glomeruli, distal tubular cells, and a mixture of all three cell types. Histologic examination demonstrated progressive formation and organization of the nephron segments within the polymer fibers with time. BrdU incorporation into renal cell DNA was confirmed. These results demonstrated that renal specific cells can be successfully harvested and cultured, and can subsequently attach to artificial biodegradable polymers. However, it was unclear whether the tubular structures reconstituted de novo from dispersed renal elements, or if they merely represented fragments of donor tubules that survived the original dissociation and culture processes intact. Further investigation was conducted in order to examine the process (Fung, 1996). Mouse renal cells were harvested and expanded in culture. Subsequently, single isolated cells were seeded on biodegradable polymers and implanted into immune competent syngeneic hosts. Renal epithelial cells were observed to reconstitute into tubular structures in vivo. Sequential analyses of the retrieved implants over time demonstrated that renal epithelial cells first organized into a cordlike structure with a solid center. Subsequent canalization into a hollow tube could be seen by two weeks. Histologic examination with nephron segment-specific lactins showed successful reconstitution of proximal tubules, distal tubules, loop of Henle, collecting tubules, and collecting ducts. These results showed that single suspended cells are capable of reconstituting into tubular structures, with homogeneous cell types within each tubule.

In a subsequent study mouse renal cells were harvested, expanded in culture, and seeded onto a tubular device constructed from polycarbonate (Yoo et al, 1996). The tubular device was connected at one end to a Silastic catheter that terminated into a reservoir. The device was implanted subcutaneously in athymic mice. Histological examination of the implanted device demonstrated extensive vascularization, as well as formation of glomeruli (Fig. 19–18) and highly organized tubule-like structures. Immunocytochemical staining with antiosteopontin antibody, which is secreted by proximal and distal tubular cells and the cells of the thin ascending loop of Henle, stained the tubular sections. Immunohistochemical staining for alkaline phosphatase stained

proximal tubule-like structures. Uniform staining for fibronectin in the extracellular matrix of newly formed tubes was observed. The fluid collected from the reservoir was yellow and contained 66 mg/dL uric acid (compared with 2 mg/dL in plasma), suggesting that these tubules are capable of unidirectional secretion and concentration of uric acid. The creatinine assay performed on the collected fluid showed an 8.2-fold increase in concentration when compared with serum. These results demonstrated that single cells form multicellular structures can become organized into functional renal units that are able to excrete high levels of solutes through a urine-like fluid (Yoo et al, 1996).

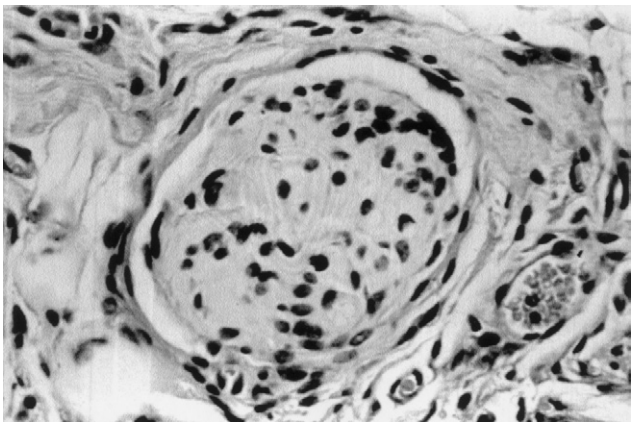


Figure 19–18. Retrieved tissue-engineered renal units demonstrate formation of glomeruli (hematoxylin and eosin stain; original magnification, ×400).

To determine whether renal tissue could be formed using an alternative cell source, nuclear transplantation (therapeutic cloning) was performed to generate histocompatible tissues, and the feasibility of engineering syngeneic renal tissues in vivo using these cloned cells was investigated (Lanza et al, 2002a) (Fig. 19–19). Nuclear material from bovine dermal fibroblasts was transferred into unfertilized enucleated donor bovine eggs. Renal cells from the cloned embryos were harvested, expanded in vitro, and seeded onto three-dimensional renal devices. The devices were implanted into the back of the same steer from which the cells were cloned, and were retrieved 12 weeks later. This process produced functioning renal units. Urine production and viability were demonstrated after transplantation back into the nuclear donor animal. Chemical analysis suggested unidirectional secretion and concentration of urea nitrogen and creatinine. Microscopic analysis revealed formation of organized glomeruli and tubular structures. Immunohistochemical and real-time polymerase chain reaction (RT-PCR) analysis confirmed the expression of renal mRNA and proteins. These studies demonstrated that cells derived from nuclear transfer can be successfully harvested, expanded in culture, and transplanted in vivo with the use of biodegradable scaffolds on which the single suspended cells can organize into tissue structures that are genetically identical to that of the host. These studies were the first demonstration of the use of therapeutic cloning for regeneration of tissues in vivo.

A naturally derived tissue matrix with existing three-dimensional kidney architecture would be preferable to the artificial matrix used in the above experiments, because it would allow transplantation of a larger number of cells, resulting in greater renal tissue volumes. Thus an acellular collagen-based kidney matrix, which

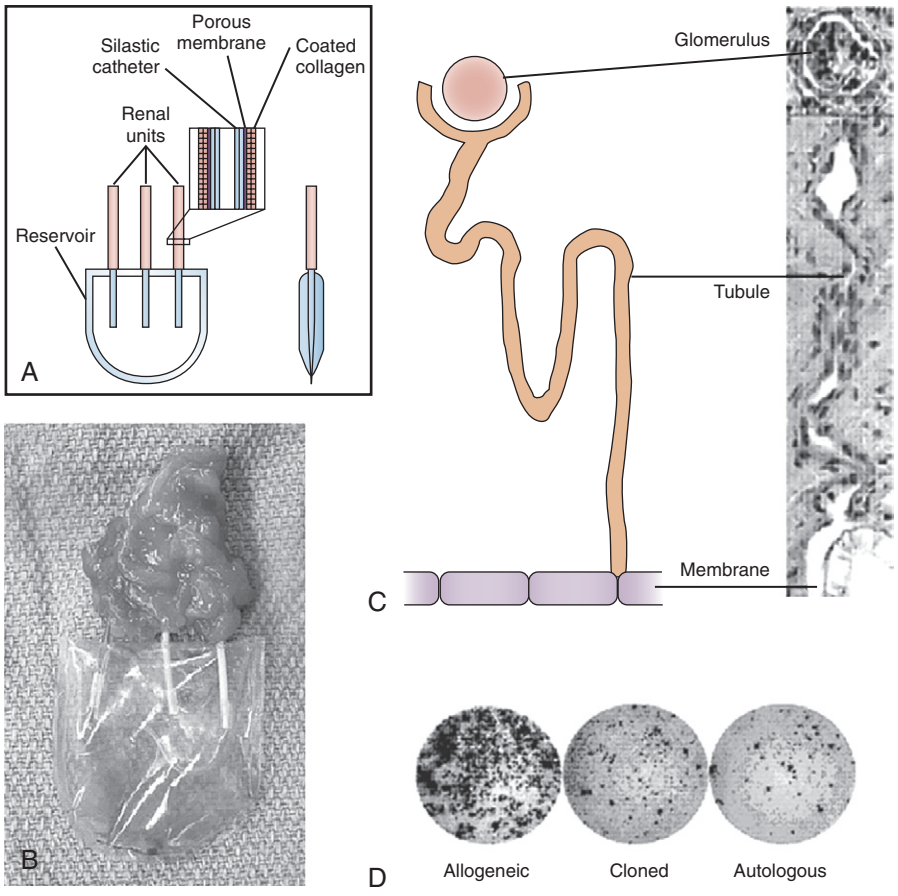


Figure 19–19. Production of kidney tissue by therapeutic cloning and regenerative medicine. **A,** Illustration of the tissue-engineered renal unit. **B,** Renal unit seeded with cloned cells, three months after implantation, showing the accumulation of urine-like fluid. **C,** There was a clear unidirectional continuity between the mature glomeruli, their tubules, and the polycarbonate membrane. **D,** ELISPOT analyses of the frequencies of T cells that secrete interferon-γ after primary and secondary stimulation with allogeneic renal cells, cloned renal cells, or nuclear donor fibroblasts.

is similar to the native renal architecture, was developed. In a subsequent study, it was investigated whether these collagen-based matrices could accommodate large volumes of renal cells and form kidney structures in vivo (Amiel et al, 2000).

Acellular collagen matrices, derived from porcine kidneys, were obtained through a multistep decellularization process. During this process, serial evaluation of the matrix for cellular remnants was performed using histochemistry, scanning electron microscopy (SEM), and RT-PCR. Mouse renal cells were harvested, grown, and seeded on decellularized collagen matrices. Cell matrix constructs grown in vitro and implanted in the subcutaneous space of 20 athymic mice were analyzed over time. Renal cells seeded on the matrix adhered to the inner surface and proliferated to confluency by 7 days after seeding. Renal tubular and glomerulus-like structures were observed 8 weeks after implantation.

OTHER APPLICATIONS OF GENITOURINARY REGENERATIVE MEDICINE

Please see the Expert Consult website for this section, including Figure 19–20.

Key Points

- New advances in the ability to expand cells in vitro, to use smart biomaterials, and new techniques for vascularization are allowing more complex organs to be engineered.
- Tissue injury can be repaired with minimal fibrosis by the natural wound-healing response for small defects, by the use of nonseeded matrices for defects up to 1 cm from any edge and by the use of cell-seeded matrices for defects greater than 1 cm.
- Stem cells may provide large repositories of different cell types for tissue and organ repair. Embryonic and induced pluripotent stem cells differentiate easily but may form tumors and may require immunosuppression. Fetal stem cells replicate readily and do not form tumors but may be more limited than embryonic stem cells in their differentiation potential. Adult stem cells do not form tumors or require immunosuppression, but they may not replicate readily.
- Nuclear transfer can be used for either reproductive cloning or for therapeutic cloning.

SUMMARY

Regenerative medicine efforts are currently being undertaken for every type of tissue and organ within the urinary system. Most of the efforts expended in the genitourinary field have occurred within the last two decades. Regenerative medicine strategies involve the use of biomaterials alone, as has been accomplished clinically in patients with urethral disease; biomaterials with cells, as is currently being tested clinically with bladder and vaginal tissues; and cell therapies alone, as those applied clinically for urinary incontinence, initially with chondrocytes and now with muscle cells. Regenerative medicine is a multidisciplinary field that requires expertise in a wide variety of scientific disciplines, including cell and molecular biology, physiology, pharmacology, chemical engineering, biomaterials, nanotechnology, and clinical sciences. Although, to date, modest clinical success has been achieved in specific areas, the field is still in its infancy. Long-term studies are still essential to assure safety and efficacy before these technologies have widespread clinical application.

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chapter 20

Male Reproductive Physiology

Paul J. Turek, MD, FACS, FRSM

Hypothalamic-Pituitary-Gonadal Axis
The Testis
The Epididymis
Ductus (Vas) Deferens
Seminal Vesicle and Ejaculatory Ducts
Spermatozoa

The male reproductive axis of hormones and organs is a remarkably efficient, well-orchestrated, and precisely managed biological system that has evolved over millions of years. It is responsible for reproductive tract formation and development, maturation of fertility potential at puberty, and the maintenance of maleness in the adult. This chapter explores our current understanding of this complex system by defining the anatomy and physiology of its component parts, including the hypothalamic-pituitary-gonadal hormonal axis, spermatogenesis and androgen production within the testicle, and maturation and transport of sperm in the excurrent ductal system. In addition, new concepts in genetic infertility, stem cell science, and the physiology of ejaculation are introduced and explained. Through such rigorous intellectual dissection, the true beauty and sophistication of the reproductive process is realized and appreciated.

HYPOTHALAMIC-PITUITARY-GONADAL AXIS

The hypothalamic-pituitary-gonadal (HPG) axis plays a critical role during development and adulthood in four physiological processes: 1) **phenotypic gender** development during embryogenesis, 2) **sexual maturation** at puberty, 3) testis endocrine function—**testosterone production,** and 4) testis exocrine function—**sperm production.**

Basic Endocrine Concepts

Two classes of hormones mediate communication in the reproductive axis: peptide and steroid. **Peptide hormones are small, secretory proteins that act through cell surface receptors.** Hormone signals are transduced by one of several second-messenger pathways (Fig. 20–1). Ultimately, most peptide hormones induce phosphorylation of proteins that alter cell function. Examples of peptide hormones are luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In contrast, **steroid hormones are derived from cholesterol. They are not stored in secretory granules; consequently, steroid secretion rates directly reflect rates of production.** In plasma, these hormones are usually bound to carrier proteins, and because they are lipophilic, steroid hormones are cell membrane–permeable. After binding to intracellular receptors, steroids are translocated to nuclear DNA recognition sites and regulate the transcription of target genes. Examples of reproductive axis steroid hormones are testosterone and estradiol.

Hormonal signaling within the HPG axis is hierarchically governed by a **free-running pulse generator** within the hypothalamus. The specific amplitude and frequency with which hormone secretions occur within the reproductive axis determine downstream organ responsiveness. Feedback control is the principal mechanism through which hormonal regulation occurs in the HPG axis (Fig. 20–2). With feedback control, a hormone can regulate the synthesis and action of itself or of another hormone. **In the HPG axis, negative feedback activity is primarily responsible for minimizing hormonal perturbations and maintaining homeostasis.**

Components of the Reproductive Axis

Hypothalamus

As the integrative center of the HPG axis, the hypothalamus receives neuronal input from the amygdala, thalamus, pons, retina, olfactory cortex, and many other areas (see Fig. 20–2). The pulse generator for the cyclical secretion of pituitary hormones, **the hypothalamus, is anatomically linked to the pituitary gland by both a portal vascular system and neuronal pathways.** By avoiding the systemic circulation, the portal vascular system allows direct delivery of hypothalamic hormones to the anterior pituitary.

The most important hypothalamic hormone for reproduction is gonadotropin-releasing or LH-releasing hormone (GnRH or LHRH), a 10–amino acid peptide secreted from the neuronal cell bodies in the preoptic and arcuate nuclei. **Currently, the only known function of GnRH is to stimulate the secretion of luteinizing hormone (LH) and follicle-stimulating hormones (FSH) from the anterior pituitary.** GnRH has a plasma half-life of approximately 5 to 7 minutes, and is almost entirely removed on the first pass through the pituitary either by receptor internalization or enzymatic degradation. GnRH secretion results from integrated input from the effects of stress, exercise, and diet from higher brain centers, gonadotropins secreted from the pituitary, and circulating gonadal hormones. Substances known to regulate GnRH secretion are listed in Table 20–1. In Kallman syndrome, characterized by congenital hypogonadotropic hypogonadism, the GnRH precursor neurons fail to migrate normally with a subsequent absence of

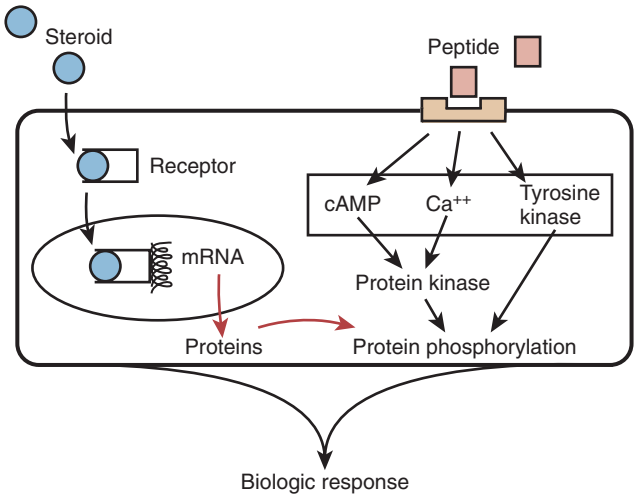


Figure 20–1. Two kinds of hormones classes mediate intercellular communication in the reproductive hormone axis: peptide and steroid. (Adapted from Turek PJ. Male infertility. In: Tanagho EA, McAninch JC, editors. Smith's urology. 16th ed. Stamford, CT: Appleton & Lange; 2008 [chapter 44–1].)

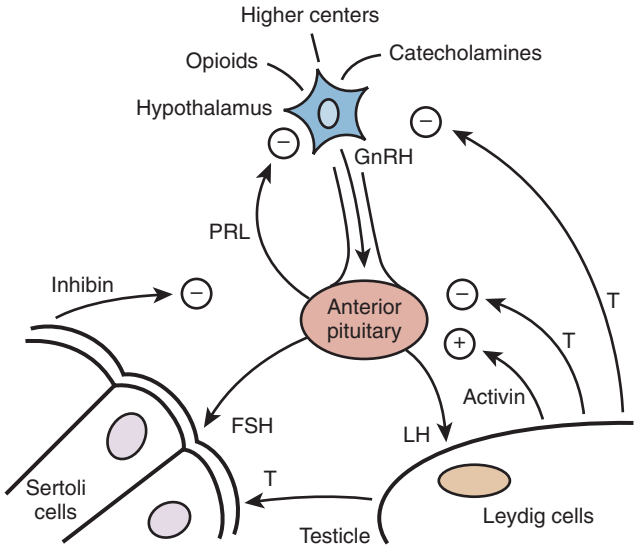


Figure 20–2. Diagram of the hypothalamic-pituitary-testis hormonal axis. +, positive feedback; –, negative feedback; FSH, follicle-stimulating hormone; GnRH, gonadoatrophin releasing hormone; LH, luteinizing hormone; PRL, prolactin; T, testosterone. (Adapted from Turek PJ. Male infertility. In: Tanagho EA, McAninch JC, editors. Smith's urology. 16th ed. Stamford, CT: Appleton & Lange; 2008 [chapter 44–2].)

Table 20–1.

Substances That Modulate GnRH Secretion

GnRH MODULATOR	TYPE OF FEEDBACK	EXAMPLES
Opioids	Negative	β-Endorphin
Catecholamines	Variable	Dopamine
Peptide hormones	Negative	FSH, LH
Sex steroids	Negative	Testosterone
Prostaglandins	Positive	PGE_2
Insulin	Positive	Insulin
Kisspeptins	Positive	Kisspeptin (puberty)
Leptins	Positive	Leptin

FSH, follicle-stimulating hormone; LH, luteinizing hormone; PGE_2, prostaglandin E_2.

hypothalamic secretion of GnRH (Bick et al, 1992; Dode et al, 2003). Affected individuals present with delayed puberty or infertility due to lack of testosterone production.

GnRH output exhibits several types of rhythmicity: seasonal, on a time scale of months and peaking in the spring; circadian, resulting in higher testosterone levels during the early morning hours; and pulsatile, with GnRH peaks occurring every 90 to 120 minutes on average. The importance of a pulsatile GnRH secretory pattern in normal HPG axis function is aptly demonstrated by the ability of exogenously given GnRH agonists (leuprolide acetate) to stop testicular testosterone production by changing pituitary exposure to GnRH from a cyclic to a constant pattern.

Anterior Pituitary

Located within the bony sella turcica of the cranium, the pituitary has two lobes: posterior and anterior. The posterior lobe, or neurohypophysis, secrets two hormones, oxytocin and vasopressin, and is driven by neural stimuli. In contrast, **the anterior pituitary or adenohypophysis is regulated by blood-borne factors and is the site of action of GnRH** (see Fig. 20–2). GnRH stimulates the production and release of FSH and LH by a calcium flux–dependent mechanism. The sensitivity of the pituitary gonadotrophs for GnRH varies with patient age and hormonal status. **LH and FSH are the primary pituitary hormones that regulate testis function.** They are glycoproteins composed of two polypeptide chain subunits, termed α and β, each coded by a separate gene. The α subunit of each hormone is identical and is similar to that of all other pituitary hormones; biologic and immunologic activities are conferred by the unique β subunit. Both subunits are required for endocrine activity. Sugars linked to these peptide subunits, consisting of oligosaccharides with sialic acid residues, differ in content between FSH and LH and likely account for differences in plasma clearance of these hormones. Secretory pulses of LH vary in frequency from 8 to 16 pulses in 24 hours and vary in amplitude by one- to threefold. These pulse patterns closely reflect GnRH release. **Both androgens and estrogens regulate LH secretion through negative feedback.** On average, FSH pulses occur approximately every 1.5 hours and vary in amplitude by 25%. The FSH response to GnRH is more difficult to measure than that of LH for two reasons: (1) FSH has a smaller amplitude response and a longer serum half-life, (2) **the gonadal proteins inhibin and activin may affect FSH secretion and are thought to account for the relative secretory independence of FSH from GnRH secretion.**

FSH and LH are only known to act in the gonads. They activate adenylate cyclase, which leads to increases in intracellular cAMP. In the testis, LH stimulates steroidogenesis within Leydig cells by inducing the mitochondrial conversion of cholesterol to pregnenolone and testosterone. **FSH binds to Sertoli cells and spermatogonial membranes within the testis and is the major stimulator of seminiferous tubule growth during development. FSH is essential for the initiation of spermatogenesis at puberty.** In the adult, the major physiologic role of FSH is to stimulate quantitatively normal levels of spermatogenesis.

A third anterior pituitary hormone, prolactin, can also affect the HPG axis and fertility. Prolactin is a large, globular protein of 199 amino acids (23 kD) that is responsible for milk synthesis during pregnancy and lactation in women. No human mutations have been found in either the human prolactin gene or its receptor (Goffin et al, 2002). **The normal role of prolactin in men is less clear, but it may increase the concentration of LH**

receptors on Leydig cells and sustain normal, high intratesticular testosterone levels. It may also potentiate the effects of androgens on the growth and secretions of the male accessory sex glands (Wennbo et al, 1997; Steger et al, 1998). Normal prolactin levels may be important to maintain libido. Although low prolactin levels are not necessarily pathologic, hyperprolactinemia abolishes gonadotropin pulsatility by interfering with episodic GnRH release. In addition, the anterior pituitary contains cells that secrete other glycoprotein hormones: adrenocorticotropic hormone (ACTH), growth hormone (GH), and thyroid-stimulating hormone (TSH). These glycoprotein hormones can also have significant effects on male reproductive function.

Testis

Normal male virility and fertility requires the collaboration of the exocrine and endocrine testis (see Fig. 20–2). The interstitial compartment, composed mainly of Leydig cells, is responsible for steroidogenesis. The seminiferous tubules produce spermatozoa.

Normal testosterone production in men is approximately 5 g/day, and secretion occurs in a damped, irregular, pulsatile manner (nyctehemeral). Testosterone is metabolized into two major active metabolites in target tissue: (1) the major androgen **dihydrotestosterone (DHT)** from the action of 5α-reductase and (2) the estrogen **estradiol** through the action of aromatases. DHT is a much more potent androgen than is testosterone. In most peripheral tissues, testosterone reduction to DHT is required for androgen action, but in the testis and skeletal muscle, conversion to DHT is not essential for hormonal activity.

The primary site of FSH action is on Sertoli cells within seminiferous tubules. In response to FSH, Sertoli cells produce androgen-binding protein, transferrin, lactate, ceruloplasmin, clusterin, plasminogen activator, prostaglandins, and growth factors. Through these FSH-mediated factors, seminiferous tubule growth is stimulated during development, and sperm production is initiated during puberty. Interestingly, mice FSH knockout studies suggest that FSH is not essential for spermatogenesis, because affected mice can be fertile (Levallet et al, 1999). In humans, it is thought that FSH is required for normal spermatogenesis (Tapanainen et al, 1997).

The testis also produces the protein hormones inhibin and activin (Itman et al, 2006). Inhibin is a 32-kD protein made by Sertoli cells that inhibits FSH release from the pituitary. Within the testis, **inhibin production is stimulated by FSH and acts by negative feedback at the pituitary or hypothalamus. Activin, a testis protein with close structural homology to transforming growth factor–β, exerts a stimulatory effect on FSH secretion.** Activin receptors are found in a host of extragonadal tissues, suggesting that this hormone may have growth factor or regulatory roles in the body.

Negative feedback suppression of GnRH release by testosterone occurs through androgen receptors (AR) present in hypothalamic neurons and in the pituitary. **In studies of genetic mutations, it is clear that both testosterone and estrogen participate in negative feedback** (Shupnik and Schreihofer, 1997). Steroid negative feedback results mainly from AR binding to testosterone, with a smaller contribution from estradiol binding. **Testosterone feedback occurs mainly at the hypothalamus, whereas estrogens feedback to the pituitary** (Santen, 1975). It also appears that although testosterone is the primary regulator of LH secretion, estradiol (along with inhibin from Sertoli cells) is the predominant regulator of FSH secretion (Hayes et al, 2001).

Development of the HPG Axis

Sex determination is genetically determined in humans. **A critical gene for sex determination is *SRY* (sex-determining region Y gene) on the short arm of the Y chromosome.** The *SRY* gene product is a protein with a high mobility group box (HMG) sequence, a highly conserved DNA-binding motif that kinks DNA. This DNA bending effect alters gene expression, leading to testis formation and subsequently to the male phenotype. However, the *SRY* gene does not act in isolation to determine human sex. *DAX1*, a nuclear hormone receptor gene, can alter *SRY* activity during development by suppressing genes downstream to *SRY* that would normally induce testis differentiation. A second gene, *WNT4*, largely confined to the adult ovary, may also serve as an "antitestis" gene. The discovery of these genes has significantly altered theories of sex determination. In the past, the female genotype was considered the "default," *SRY*-negative, developmental pathway. **It is now clear that genes such as *WNT4* and *DAX1* can proactively induce female gonadal development, even in the presence of *SRY*** (DiNapoli and Capel, 2008).

Once gonadal sex is determined, Leydig cells make **testosterone** that induces development of the **internal genitalia** (Fig. 20–3). Leydig cells also synthesize **insulin-like-3** to promote **transabdominal testis migration** into the scrotum. **DHT** masculinizes the genital anlage to form the **external genitalia** (see Fig. 20–3). In addition, Sertoli cells within the developing testis synthesize **müllerian-inhibiting substance (MIS, AMH)** that **prevents the müllerian duct from developing into uterus and fallopian tubes and keeps the early germ cells quiescent** in the testis (Fig. 20–4). Deficiencies in these developmental pathways generally result in either birth defects or intersex disorders.

The hormonal feedback relationships within the HPG axis also become established during gestation. **The expression of kisspeptin protein is in part responsible for activating GnRH neurons and triggering GnRH release.** In addition, SF-1, an orphan nuclear receptor, is secreted by developing Sertoli cells and contributes to HPG axis development (Val et al, 2003). After the withdrawal of placental steroids at birth, there is a period of high

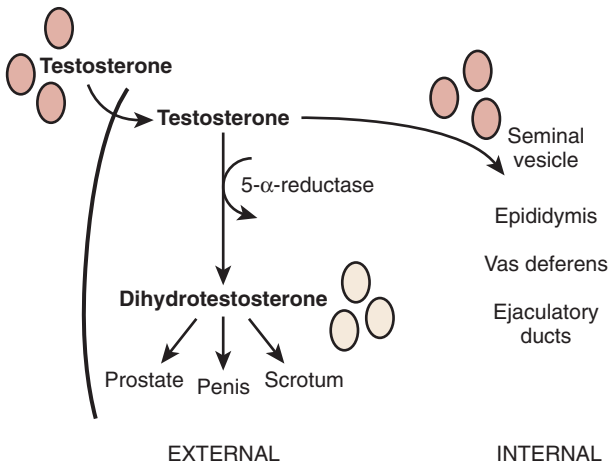


Figure 20–3. Diagram of internal and external genitalia development. Testosterone is the main androgenic steroid responsible for the developing male external genitalia, whereas dihydrotestosterone is the main androgen responsible for development of male internal genitalia.

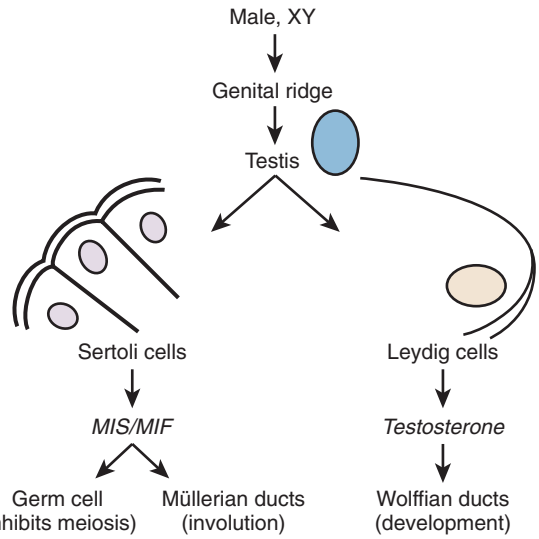


Figure 20–4. Early differentiation pathway of the male. *MIF/MIS,* müllerian inhibiting factor/substance. (Adapted from Turek PJ: Male infertility. In: Tanagho EA, McAninch JC, editors. Smith's urology. 16th ed. Stamford, CT: Appleton & Lange; 2008 [chapter 44–13].)

gonadotropin secretion in the neonate. Subsequently, as axis sensitivity to gonadotropins increases, FSH and LH secretions fall to the low levels characteristic of childhood. Puberty begins with GnRH pulsing, leading gonadotropins to increase to adult levels and, subsequently, to increase sex hormones. **The hypothalamic capacity to generate GnRH pulses arises at puberty, usually starting around the 12th year. Puberty begins at critical growth, weight, and nutritional rates for boys and girls, and is likely initiated by kisspeptin, melatonin, and leptin** (Clement et al, 1998). The adipocyte hormone leptin is the body's regulatory signal governing the size of the fat stores, and there is increasing evidence that leptin modulates hypothalamic and pituitary activity (Caprio et al, 1999; Kiess et al, 1999; Quinton et al, 1999).

Aging and the HPG Axis

A progressive decline in testosterone and sperm production occurs with age, such that men in the 7th decade have mean plasma testosterone levels 35% lower than young men (Vermeulen et al, 1995). The consequence of this is a phenomenon has been variously termed **male menopause, male climacteric, andropause, or, more appropriately, partial androgen deficiency in the aging male (PADAM).** The changes to the seminiferous epithelium with age include decreases in seminiferous tubule volume and length. **An age-related decrease in sperm production in older testes appears to stem from a decrease in germ cell proliferation rather than cellular degeneration. Correspondingly, FSH levels also increase with age, with mean values threefold higher in older than younger men.** The etiology of the age-related decline in HPG axis function is multifactorial. Testosterone production is reduced because of decreased numbers of Leydig cells and an increase in testosterone binding proteins. Diurnal variation of testosterone secretion is also lost in elderly men. There is also evidence for a blunted HPG feedback response to low testosterone (despite generally high levels of gonadotropins) and to GnRH stimulation. Finally, normal pulsatile GnRH release is replaced by irregular pulses that are less effective in stimulating gonadotropin release (Mulligan et al, 1997). A combination of these effects is likely responsible for diminished HPG axis function with age in men.

Key Points: HPG Axis

- Normal testosterone and sperm production by the testis depends on the pulsatile secretion of hypothalamic GnRH and LH and FSH from the anterior pituitary gland.
- Regulation of HPG axis hormones occurs primarily through negative feedback.
- The determination of maleness is derived from the *SRY* gene on the Y chromosome. Other developmental genes such as *WNT4* and *DAX1* are considered "antitestis" genes and can proactively induce female gonadal development.
- Changes that occur to the HPG axis with paternal age include lower testosterone levels, blunted HPG axis feedback, and irregular hormone pulsatility.

THE TESTIS

Gross Architecture

The testis is a white, ovoid organ that is normally 15 to 25 mL in volume (Prader, 1966) and has a length of 4.5 to 5.1 cm (Tishler, 1971; Winter and Faiman, 1972). The tunica albuginea has smooth muscle cells that course through predominantly collagenous tissue (Langford and Heller, 1973). These smooth muscle cells may impart contractile capability to the capsule (Rikmaru and Shirai, 1972), may affect blood flow into the testis (Schweitzer, 1929), and promote the flow of seminiferous tubule fluid out of the testis (Davis and Horowitz, 1978).

The testis parenchyma is divided into compartments separated by septa. Each septum divides seminiferous tubules into lobes that each contain a centrifugal artery. **Individual seminiferous tubules harbor developing germ cells and interstitial tissue. Interstitial tissue is composed of Leydig cells, mast cells, macrophages, nerves, and blood and lymph vessels. In humans, interstitial tissue comprises 20% to 30% of total testicular volume** (Setchell and Brooks, 1988). The relationship between seminiferous tubules and interstitial tissue anatomy is demonstrated in Fig. 20–5. Seminiferous tubules are long, highly coiled, and looped. Both ends usually terminate in the rete testis. **It is estimated that the combined length of the 600 to 1200 tubules in the human testis is approximately 250 meters** (Lennox and Ahmad, 1970) (Fig. 20–6). The "hub" of the testis, also termed the rete testis, coalesces to form 6 to 12 ductuli efferentes that carry testicular fluid and spermatozoa into the caput epididymis (see Fig. 20–6).

The arterial supply to the testis and epididymis is derived from three sources: the internal spermatic artery, the deferential (vasal) artery, and the external spermatic (or cremasteric) artery (Harrison and Barclay, 1948). The internal spermatic artery arises from the abdominal aorta and is intimately associated with the pampiniform plexus of veins. The vascular arrangement within the pampiniform plexus, with the counterflowing artery and veins, facilitates the exchange of heat and small molecules. For example, testosterone passively diffuses

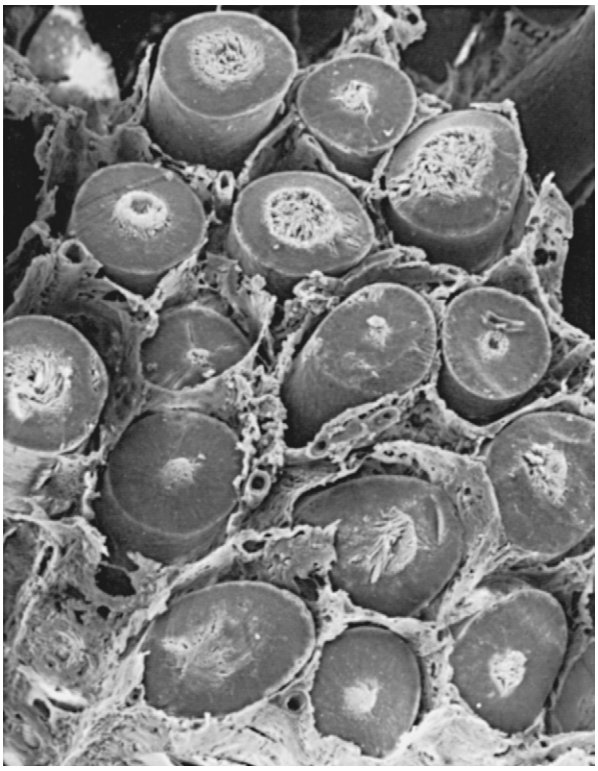


Figure 20–5. Scanning electron micrograph of the cut surface of the human testis. Note the relationship of interstitial tissue to seminiferous tubules. (From Christensen AK. Leydig cells. In: Greep RO, Astwood EB, editors. Handbook of physiology. Washington, DC: American Physiology Society; 1975. p. 57–94.)

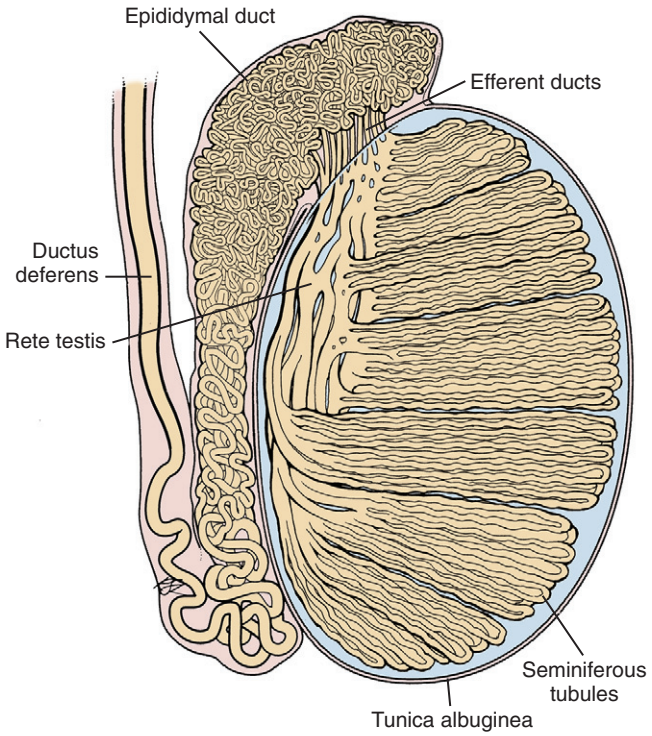


Figure 20–6. Drawing of the human testis showing the seminiferous tubules (250 meters length), epididymis (3 to 4 meters length), and vas deferens. (Based on Hirsh AV. The anatomical preparations of the human testis and epididymis in the Glasgow Hunterian Collection. Hum Reprod Update 1995;1:515–21.)

from veins to the artery in a concentration-limited manner (Bayard et al, 1975). **The countercurrent heat exchange supplies arterial blood to the testis that is 2° C to 4° C lower than the rectal temperature in normal men** (Agger, 1971). A loss of the temperature differential is associated with testicular dysfunction in men with varicocele (Goldstein and Eid, 1989) and cryptorchidism (Marshall and Edler, 1982). As the spermatic cord is commonly dissected during varicocele repair, it is surgically relevant to know that a single artery is observed in 50% of spermatic cords, with two arteries in 30% and three arteries in 20% of cases (Beck et al, 1992).

Inferior to the scrotal pampiniform plexus and near the mediastinal testis, the spermatic artery is highly coiled and branches before entering the testis. Extensive interconnections, especially between the internal spermatic and deferential arteries, allow maintenance of testis viability even after division of the internal spermatic artery (Fig. 20–7). From angiographic studies, a single artery enters the testis in 56% of cases; two branches enter in 31% of cases and three or more branches in 13% of testes (Kormano and Suoranta, 1971). In men with a single testicular artery, its interruption can result in testicular atrophy (Silber, 1979). The testicular arteries penetrate the tunica albuginea and then travel

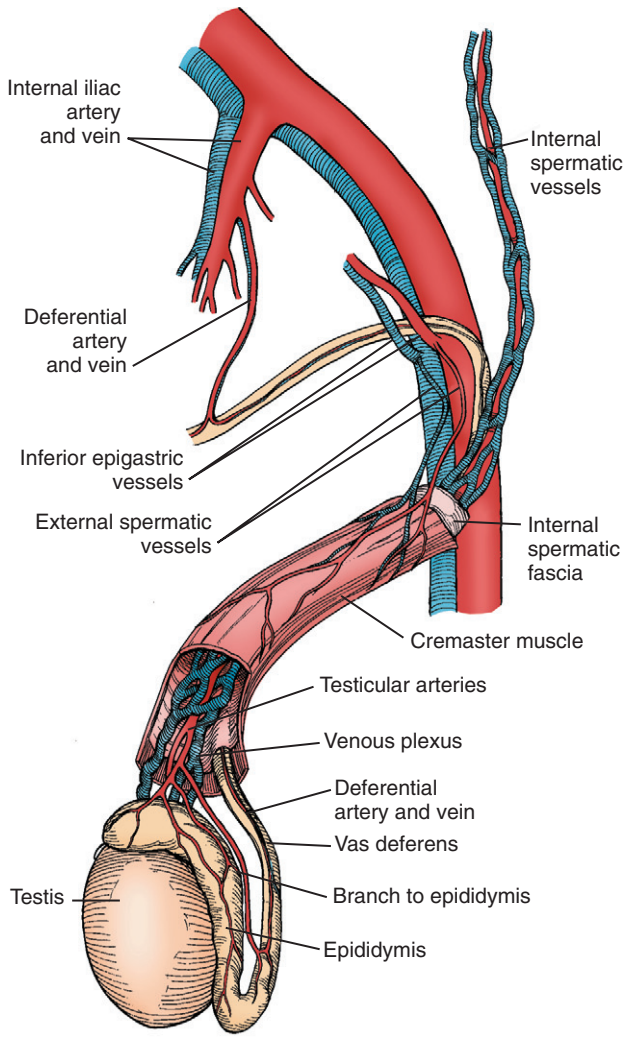


Figure 20–7. Schematic illustration of the interconnections between internal spermatic, external spermatic (cremasteric), and deferential vessels in the peritesticular region and spematic cord.

inferiorly along the posterior surface of the testis within the parenchyma. Branching arteries pass anteriorly over the testicular parenchyma. Major testicular artery branches also travel over the inferior pole of the testis, pass anteriorly and branch out over the surface of the testis. The location of these vessels is clinically important, because they may be injured during orchiopexy or testis biopsy procedures (Jarow, 1991; Schlegel and Su, 1997). **The midsection of the testis has relatively fewer vessels compared with superior or inferior areas of the testis.** Individual arteries to the seminiferous tubules, termed centrifugal arteries, travel within the septa that contain tubules. Centrifugal artery branches give rise to arterioles that supply individual intertubular and peritubular capillaries (Muller, 1957). The intertubular capillaries are located within the columns of interstitial tissue, whereas the ladder-like capillaries running near the seminiferous tubule are called peritubular capillaries. Through this vascular complex, the human testis is provided with 9 mL of blood per 100 g of tissue per minute (Pettersson et al, 1973).

Veins within the testis are unusual in that they do not run with the corresponding intratesticular arteries. Small parenchymal veins empty into either the veins on the testis surface, or into a group of veins near the mediastinum testis that travels along the rete testis (Setchell and Brooks, 1988). These two sets of veins join together with deferential veins to form the pampiniform plexus as they ascend into the scrotum. Pampiniform plexus veins are thin walled, which likely contributes to the passive diffusion of testosterone and temperature exchange with the closely associated spermatic artery.

The testis has no known somatic innervation. It receives autonomic innervation primarily from the intermesenteric nerves and renal plexus (Mitchell, 1935). These nerves run along the testicular artery into the testis. It appears that testicular adrenergic innervation is restricted primarily to small blood vessels that supply Leydig cell clusters that may regulate Leydig cell steroidogenesis (Baumgarten et al, 1968; Turnbull and Rivier, 1997). It is thought that vascular tone in the testis may involve regulation at several levels (Linzell and Setchell, 1969), including autoregulation of capsular arteries (Davis et al, 1990), regional variation based on local metabolic need and governed by peptides such as atrial natriuretic peptide (Collin et al, 1997), and assisted transport of molecules such as LH across the vascular endothelium (Milgrom et al, 1997). Indeed, these observations suggest a highly specialized function for the microvasculature of the testis (see review by Desjardins [1989]).

Prominent lymphatics can be observed within the spermatic cord (Hundeiker, 1971). Obstruction of these ducts results in dilatation of the testis interstitium but not the seminiferous tubules, suggesting that the interstitial space is drained by lymphatics, but the seminiferous tubules are not. **Lymphatic obstruction can also result in hydrocele formation, a known complication of certain varicocelectomy and herniorrhaphy procedures.** The sperm containing intratubular fluid that baths Sertoli cells flows from the seminiferous tubules into the rete testis and, subsequently, into the caput epididymis. This fluid, isosmotic with plasma, is thought to be mainly of seminiferous tubule origin (Setchell and Brooks, 1988). **Reabsorption of this fluid within the rete testis and efferent ductules is regulated by estrogens** (Lee et al, 2000). Tubular fluid composition is markedly different from blood plasma or lymphatics, suggesting that substances are not freely diffusible into and out of the tubules (Setchell and Waites, 1975). This has led to the concept of a "blood-testis barrier" to be discussed later.

Testis Cytoarchitecture

Interstitium

Leydig Cells. The testis interstitium contains blood vessels, lymphatics, fibroblasts, macrophages, mast cells, and Leydig cells (Fig. 20–8). **Leydig cells are responsible for the bulk of testicular steroid production. Leydig cells differentiate from mesenchymal precursor cells by the 7th week of gestation.** The activation of Leydig cell steroidogenesis correlates with the onset of androgen-dependent differentiation of the male reproductive system. Although it is apparent that Leydig cells express steroidogenic enzymes before becoming responsive to LH (El-Gehani et al, 1998; Majdic et al, 1998), they also differentiate from precursor cells under the influence of LH, placental-derived human chorionic gonadotropin (HCG), and from the effect of local paracrine factors such as IGF-1 (Huhtaniemi and Pelliniemi, 1992; Teerds and Dorrington, 1993; Le Roy et al, 1999). **At 2 to 3 months after birth, a second wave of Leydig cell differentiation occurs in response to gonadotropin production from the pituitary, briefly elevating testosterone levels in infants.** Androgen produced during the the early male neonate's life is thought to hormonally imprint the hypothalamus, liver, and prostate such that they respond appropriately to androgen stimulation later in life. **After reactivation of the HPG axis at puberty, stereologic analysis has revealed that a single testis from a young adult contains approximately 700 million Leydig cells** (Kaler and Neaves, 1978).

Testosterone. **Testosterone, synthesized from cholesterol, is the principal steroid produced by the testis** (Lipsett, 1974). In addition, numerous C_{18}, C_{19}, and C_{21} steroids are also produced (Lipsett, 1974; Ewing and Brown, 1977). Cholesterol must be transported into Leydig cell mitochondria, where the cholesterol side-chain cleavage enzyme converts it to pregnenolone. The three main sources of cholesterol in the Leydig cell are (1) externally, from blood-borne lipoprotein and internalization of cholesterol-lipoprotein receptor complexes, (2) from de novo synthesis from acetate, and (3) from stored cholesterol esters in lipid droplets. Maintenance of cholesterol stores is part of the normal resting function of the Leydig cell; LH stimulation evokes cholesterol mobilization through cholesterol esterase activity. Pregnenolone is transported out of the mitochondrial membrane into the smooth endoplasmic reticulum, where it is converted into testosterone. Testosterone diffuses across the cell membrane and is trapped within the extracellular fluid and blood plasma by steroid-binding proteins.

Cholesterol transport to the inner membrane of the mitochondrion is regulated by two transport proteins: steroid acute regulatory protein (StAR) and peripheral benzodiazepine receptor (PBR). LH binding elicits protein synthesis in the Leydig cell, and the newly-synthesized StAR contains a signal sequence that enables it to be threaded through the outer mitochondrial membrane to faciliate cholesterol transport (Stocco, 2000). PBR forms a channel for cholesterol in the mitochondrial membrane (Culty et al, 1999), but it is not clear whether PBR functionally interacts with StAR (West et al, 2001).

The four major enzymes participating in testosterone biosynthesis from pregnenolone are cholesterol side-chain cleavage enzyme, 3β-hydroxysteroid dehydrogenase, cytochrome P450 17α-hydroxylase/$C_{17\text{-}20}$-lyase, and 17β-hydroxysteroid dehydrogenase. The enzymology, chromosomal locations, and molecular genetics of these enzymes are well described (Payne and Hales,

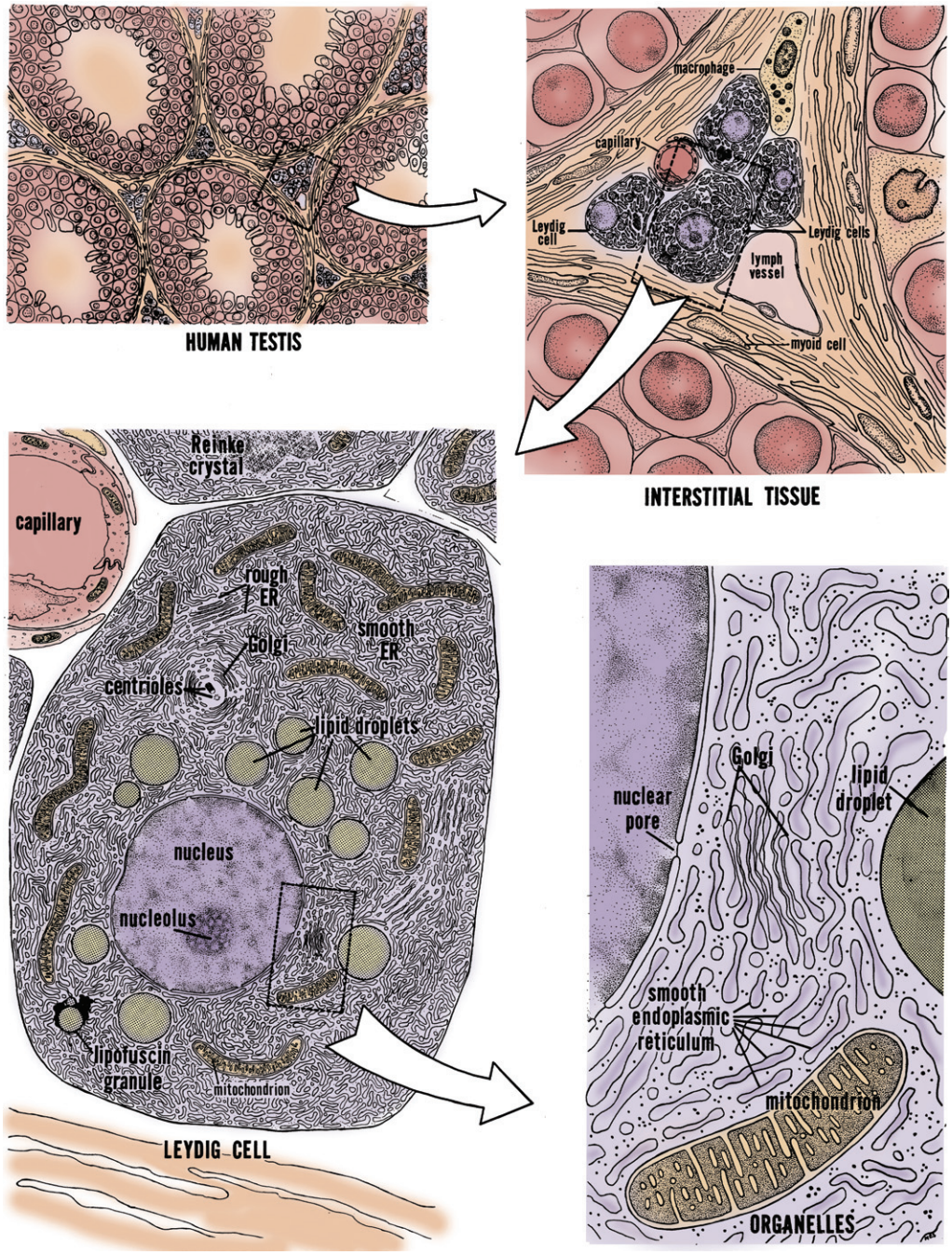


Figure 20–8. Fine structure of human Leydig cells. Leydig cells occur in clusters in the interstitium between seminiferous tubules *(upper left)*. Interstitial tissue *(upper right)* contains macrophages and fibroblasts and capillaries and lymph vessels. The most abundant organelle within the Leydig cell cytoplasm is the smooth endoplasmic reticulum *(lower left)*. Organelles seen in greater detail *(lower right)*. (From Christensen AK. Leydig cells. In: Greep RO, Astwood WB, editor. Handbook of physiology, section 7, Endocrinology. Baltimore: Williams & Wilkins; 1975. Copyright 1975, The American Physiological Society, Bethesda, MD.)

2004). Gene mutations in the genes encoding these enzymes have been described and the resulting disorders of androgen biosynthesis are a relatively rare cause of sexual ambiguity in chromosomally normal males (Miller, 2002).

Control of Testosterone Synthesis. The control of Leydig cell steroidogenesis is complex and involves both pituitary and nonpituitary factors (Payne and Youngblood, 1995). **The most important regulator of testosterone production is LH. LH binding, through the second messenger cyclic adenosine monophosphate (cAMP), initiates transport of cholesterol into mitochondria.** Pituitary peptides other than LH (e.g., FSH and prolactin) modify the response to LH (Ewing, 1983). Other, nonpituitary factors capable of modifying steroid production by Leydig cells include **GnRH** (Sharpe, 1984), **inhibin and activin** (Bardin et al, 1989), **epidermal growth factor (EGF), IGF-1, and transforming growth factor-β (TGF-β)** (Ascoli and Segaloff, 1989; Saez et al, 1991), prostaglandins (Eik-Nes, 1975), and adrenergic stimulation (Eik-Nes, 1975). Moreover,

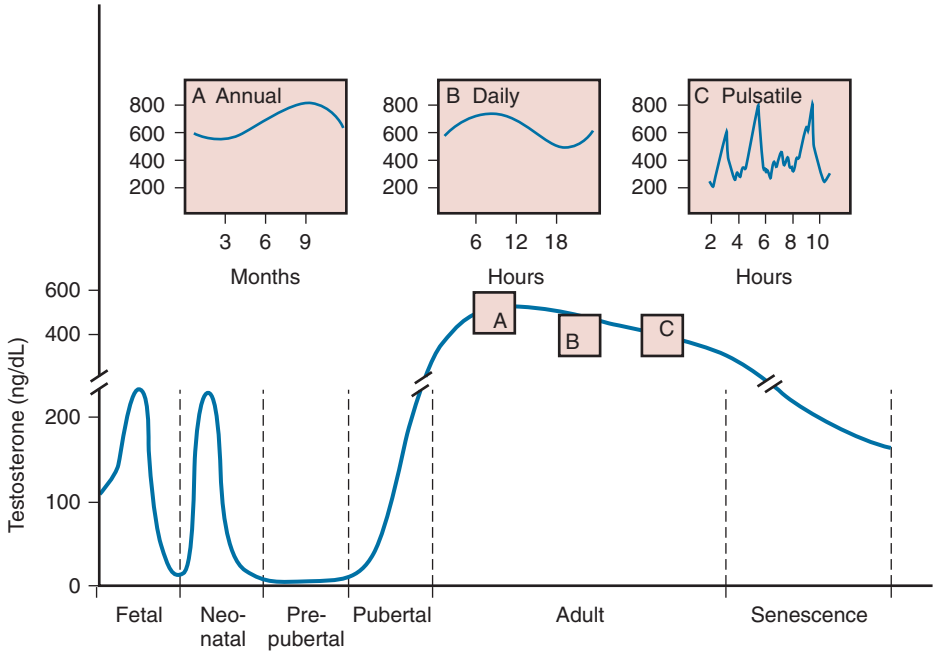


Figure 20–9. Peripheral blood testosterone levels in the human male during the life cycle. The fetal testosterone peak occurs between 12 and 18 weeks of gestation *(lower left corner; gestational age not shown)*. The neonatal peak occurs at approximately 2 months of age. Testosterone declines to low levels during the prepubertal period. The pubertal increase in testosterone occurs between 12 and 17 years of age. Testosterone concentration in the adult reaches its maximum during the second or third decade of life and then declines slowly through the 5th decade. Testosterone declines dramatically during senescence. *Inset A* shows the annual rhythm in testosterone concentration in the human male. The peak and nadir occur in the fall and spring, respectively. *Inset B* shows the daily rhythm in testosterone concentration. The peak and nadir occur in the morning and evening, respectively. *Inset C* shows the frequent and irregular fluctuations in testosterone concentration. (From Ewing LL, Davis JC, Zirkin BR. Regulation of testicular function: a spatial and temporal view. In: Greep RO, editor. International review of physiology. Baltimore: University Park Press; 1980. p. 41.)

direct inhibition of Leydig cell steroidogenesis may also occur through **estrogens and androgens** (Ewing, 1983; Darney et al, 1996).

Testosterone Cycles. Testosterone blood levels change dramatically during human fetal, neonatal, and adult life. Fig. 20–9 shows that a testosterone peak occurs in the human fetus between 12 and 18 weeks of gestation. Another testosterone peak occurs at approximately 2 months of age. A third testosterone peak occurs during the 2nd or 3rd decade of life. After this, there is a plateau, and then a slow decline with age. Superimposed on this, there are annual and daily rhythms of testosterone production (see Fig. 20–9, insets A and B) and irregular daily fluctuations in testosterone (see Fig. 20–9, inset C). These temporal changes in testosterone production during human life reflect a complex interaction between the pituitary gland and the testis. **The testosterone peaks correspond temporally to the following developmental events: (1) the differentiation and development of the fetal reproductive tract, (2) the neonatal organization or "imprinting" of androgen-dependent target tissues, (3) the masculinization of the male at puberty, and (4) the maintenance of growth and function of androgen-dependent organs in the adult.** This topic has been reviewed thoroughly by Swerdloff and Heber (1981).

Seminiferous Tubules

The seminiferous tubules consist of germ cells and supporting cells and are a unique environment for gamete production. Support cells include the Sertoli cells and fibrocyte and myoid cells of the basement membrane. The germ cells include a slowly dividing stem cell population, more rapidly proliferating spermatogonia and spermatocytes, and metamorphosing spermatids.

Sertoli Cells. The seminiferous tubules are lined with Sertoli cells that rest on the tubular basement membrane and extend cytoplasmic ramifications into its lumen (Fig. 20–10). The ultrastructural features of Sertoli cells are well described (Bardin et al, 1994). They have irregularly shaped nuclei, prominent nucleoli, low mitotic index, and exhibit unique **tight junctional complexes** between adjacent Sertoli cells. **These tight junctions are the strongest intercellular barriers in the body. They divide the seminiferous tubule space into basal (basement membrane) and adluminal (lumen) compartments** (see Fig. 20–10). This anatomic arrangement forms the basis for the **"blood-testis barrier"** and allows spermatogenesis to occur in an immunologically privileged site. **Sertoli cells serve as "nurse" cells for spermatogenesis, nourishing developing germ cells that are arranged between Sertoli cell cytoplasmic projections. The undifferentiated spermatogonia are near the basement membrane of the tubule, whereas the more advanced spermatocytes and spermatids are located near the luminal surface.** Thus the Sertoli cell is a polarized epithelium in which the base approximates the plasma environment, and its apex harbors an environment unique to the seminiferous tubule (Ewing et al, 1980).

Sertoli cells nurture germ cell development by: (1) providing a specialized adluminal microenvironment, (2) supporting germ cells through gap junctions between Sertoli and germ cells, and (3) allowing migration of developing germ cells within the tubule (see Fig. 20–10). The tight junctions between Sertoli cells are constantly remodeled to allow "opening" and "closing" necessary for germ cell interaction and migration (Mruk and Cheng, 2004). Ligand-receptor complexes, such as c-kit and kit ligand, are likely involved in

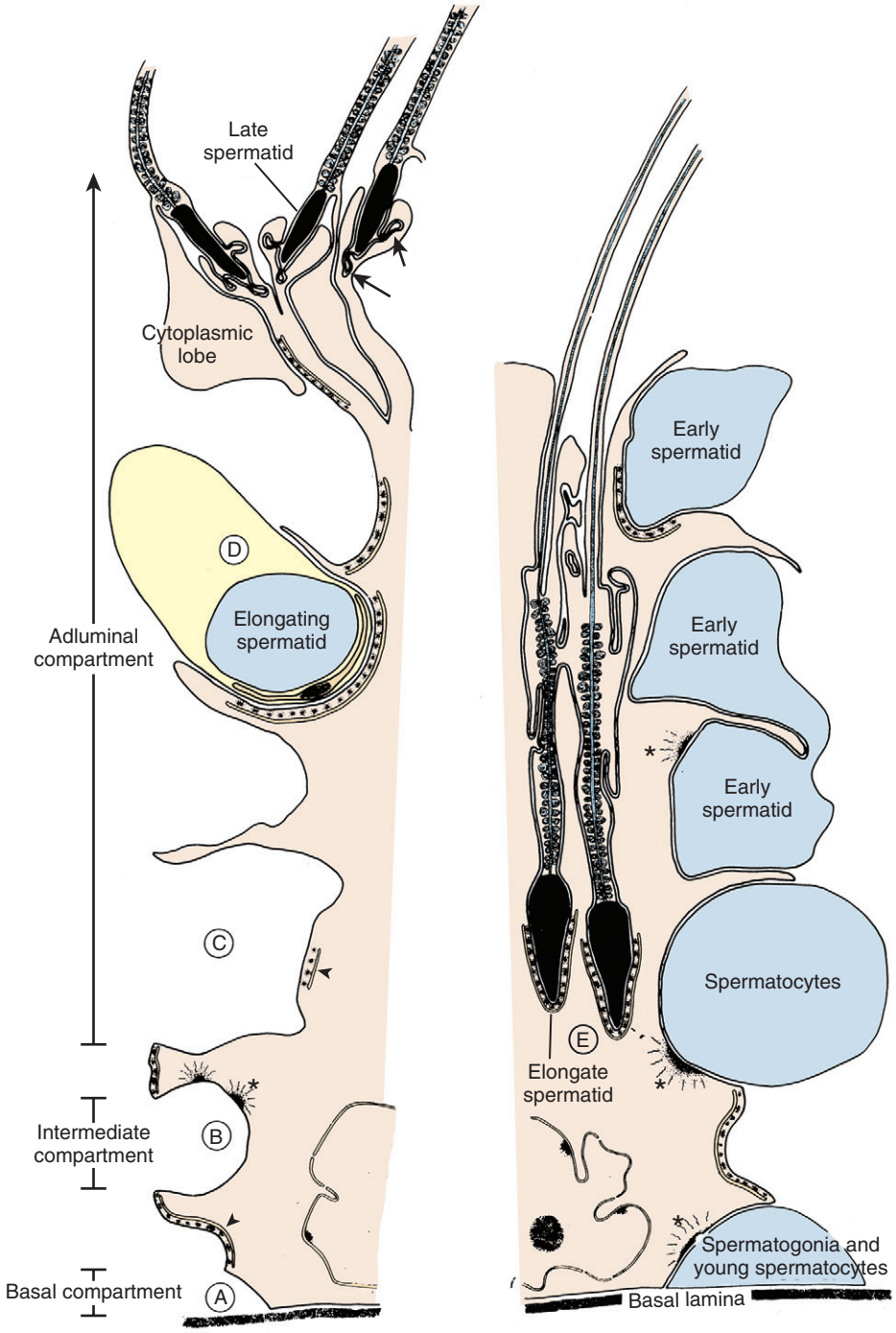
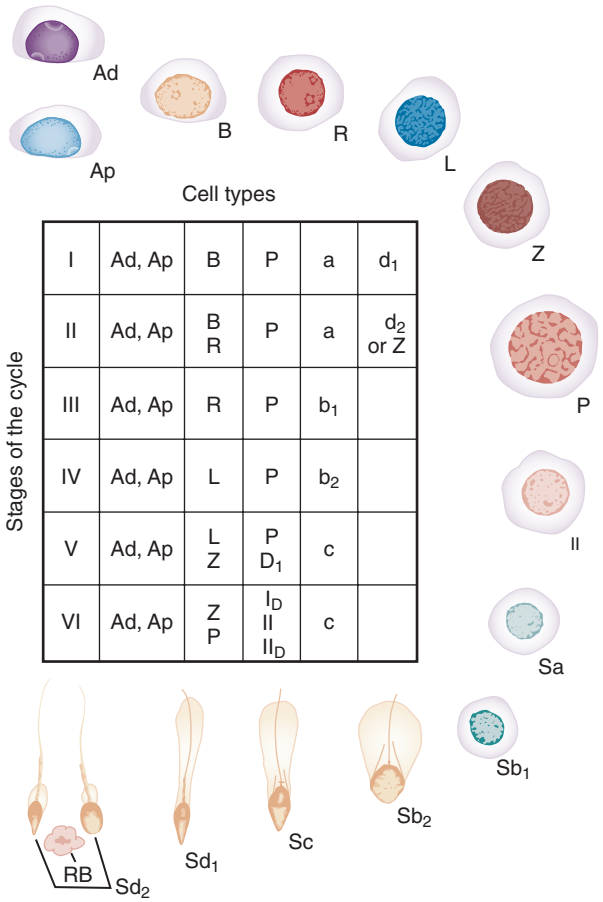


Figure 20–10. Representation of the tree-shaped Sertoli cell with a thickened central portion, or "trunk," and more delicate processes, or "limbs." The major configurational changes that occur during spermatogenesis are noted. Note the basal, intermediate, and adluminal compartments of the seminiferous epithelium. **A**, Spermatogonia and early spermatocytes share positions on the basal lamina and are enveloped by adjacent Sertoli cells that join to form tight junctional complexes (site of blood-testis barrier). **B**, Sertoli cells form junctional complexes both above and below leptotene-zygotene spermatocytes as they translocate from the basal to adluminal compartments. **C**, The spermatocytes enter the adluminal compartment when Sertoli tight junctions dissociate. **D**, The elongating spermatid is situated within a narrow recess of the Sertoli cell trunk. **E**, As the spermatid elongates further, the cell becomes lodged within the body of the Sertoli cell. The advanced spermatid moves toward the lumen of the epithelium in preparation for spermiation. Only the sperm head remains in intimate contact with the Sertoli cell. Specialized cell-to-cell contacts: *asterisks,* desmosome-gap junction complex; *arrowheads,* ectoplasmic specializations; *isolated arrows,* tubulobulbar complexes. (From Russell L. Sertoli-germ cell interactions: a review. Gamete Res 1980;3:179.)

mediating communication between germ and Sertoli cells. Sertoli cells also participate in germ cell phagocytosis and produce and secrete fluid and important effector molecules. Androgen-binding protein (ABP) is one of earliest described Sertoli cell secretory products (Hansson and Djoseland, 1972). ABP is an intracellular carrier of androgen within the Sertoli cell. **By binding testosterone, ABP maintains high levels of androgen (50-fold, as observed in serum) within the seminiferous tubules.** Testosterone also plays an important role in the regulation of Sertoli cell function, including ABP production (Griswold, 1988). Inhibin is Sertoli cell–derived and plays an important regulatory role in the negative feedback loop of FSH secretion. Inhibin B is emerging as an important endocrine marker of Sertoli cell function in the male infertility evaluation.

As keepers of the immunological sanctuary in the testis, Sertoli cells maintain a germ cell microenvironment entirely distinct from that of plasma. As such, Sertoli cells secrete numerous other products including extracellular matrix components (lamin, collagen type IV, and collagen type I) and proteins such as ceruloplasmin, transferrin, glycoprotein 2, plasminogen activator, somatomedin-like substances, T proteins, H-Y antigen, clusterin, cyclic proteins, growth factors, and somatomedin (Mruk and Cheng, 2004). Steroids, such as DHT, testosterone, androstenediols, 17β-estradiol, and numerous other C_{21} steroids are also produced by Sertoli cells



Cell types

Stages of the cycle

I	Ad, Ap	B	P	a	d_1
II	Ad, Ap	B R	P	a	d_2 or Z
III	Ad, Ap	R	P	b_1	
IV	Ad, Ap	L	P	b_2	
V	Ad, Ap	L Z	P D_1	c	
VI	Ad, Ap	Z P	I_D II II_D	c	

Figure 20–11. The steps of spermatogenesis in man. Ad, dark type A spermatogonium; Ap, pale type A spermatogonium; B, type B spermatogonium; II, secondary spermatocyte; L, leptotene spermatocyte; P, pachytene spermatocyte; R, resting or preleptotene primary spermatocyte; Rb, residual body; Sa(a), $Sb_1(b_1)$, $sb_2(b_2)$, Sc(c), $sd_1(d_1)$, $Sd_2(d_2)$, spermatids; Z, zygotene spermatocyte. The table shows cells that make up the six stages of the "cycle" of the seminiferous epithelium (I to VI): D_1, diakenesis; ID and IID, first and second maturation divisions of spermatocytes. (Modified from Clermont Y. Renewal of spermatogonia in man. Am J Anat 1966;118:509.)

(Ewing et al, 1980; Mather et al, 1983). Although the function of many Sertoli cell– and peritubular-derived substances is unclear, further research will enlighten our understanding of how Sertoli cells orchestrate and support spermatogenesis.

Germ Cells. Within the human seminiferous tubule, germ cells give rise to approximately 123×10^6 (range: 21 to 374×10^6) spermatozoa daily (Amann and Howards, 1980). This equates to the production of about 1200 sperm per heartbeat. Within the seminiferous tubule, germ cells are arranged in a highly ordered sequence from the basement membrane to the lumen. **Morphologic analysis of the various germ cells reveals at least 13 recognizable germ cell types in the human testis** (Clermont, 1963; Heller and Clermont, 1964) (Fig. 20–11). Each cell type is thought to represent a different step in the spermatogenic process. Proceeding from the least to the most differentiated, based on morphologic appearance, they have been named **dark type A spermatogonia (Ad); pale type A spermatogonia (Ap); type B spermatogonia (B); preleptotene (R), leptotene (L), zygotene (z), and pachytene primary spermatocytes (p); secondary spermatocytes (II); and Sa, Sb, Sc, Sd_1, and Sd_2 spermatids.** The tight junctions maintain

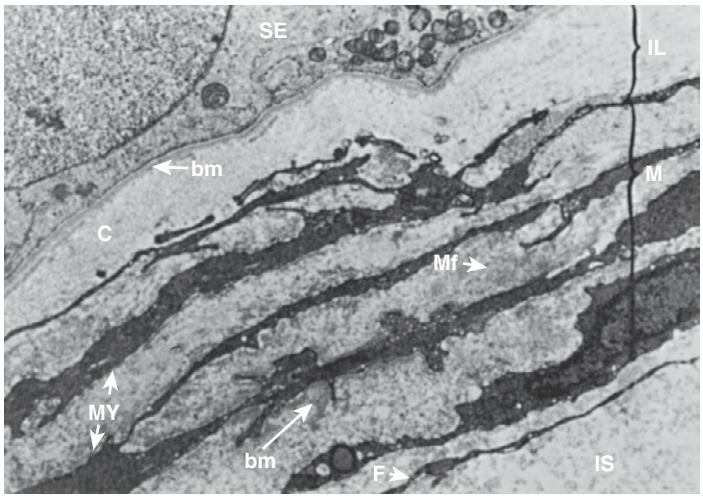


Figure 20–12. Low-power electron micrograph of human peritubular testis tissue. Peritubular tissue lies between the basement membrane (bm) of the seminiferous epithelium (SE) and the interstitial tissue (IS). Peritubular tissue has three zones: the inner lamella (IL); the myoid layer (M), containing myoid cells (MY) with abundant microfibrils (Mf); and an adventitial layer containing fibroblasts (F). (From Hermo L, Lalli M, Clermont Y. Arrangement of connective tissue elements in the walls of seminiferous tubules of man and monkey. Am J Anat 1977;148:433–46.)

spermatogonia and early spermatocytes within the basal compartment and all subsequent germ cells in the adluminal compartment.

Peritubular Structure

The human seminiferous tubule is surrounded by several layers of peritubular tissue (Hermo et al, 1977) (Fig. 20–12). The outer adventitial layer consists of fibrocytes. In the middle layer are myoid cells interspersed with connective tissue lamellae. The inner layer consists of a collagen matrix. In humans the peritubular myoid cells are thought to have contractile function (Toyama, 1977). Myoid cells actively secrete extracellular matrix components fibronectin and collagen type I, and produce the inner collagenous layer (Tung et al, 1984). Myoid cells may also affect Sertoli cell function and are known to associate with Sertoli cells in a precise mesenchymal-epithelial interaction. Skinner and coworkers (1988) isolated a paracrine factor produced by myoid cells, P-Mod-S (peritubular modifies Sertoli), that profoundly affects Sertoli cell synthetic and differentiation functions in vitro. Human peritubular cells have also been shown to secrete testosterone, and exert regulatory Sertoli cell secretory activity (Cigorraga et al, 1994).

Blood Testis Barrier

Dyes and other substances, when injected into the bloodstream of animals, will rapidly appear throughout all body tissues but fail to penetrate regions of the brain and testis. From this observation, the concept of a "blood-testis barrier" was derived. **More appropriately termed the "blood–seminiferous tubule barrier," the barrier has two components: an anatomic or mechanical element and functional elements.** The mechanical barrier is created, in part, by muscle-like myoid cells that surround seminiferous tubules (Dym and Fawcett, 1970; Fawcett et al, 1970). Regulation of molecular traffic also occurs at the level of capillary endothelial cells. However, the most important component of this barrier is the synaptic tight junctions between Sertoli

cells that preclude the passage of large molecules and lymphocytes. These anatomical elements of the blood-testis barrier are necessary but not sufficient for maintaining the immunologic "sanctuary" status within the tubule, because they are not observed in other "protected" areas of the reproductive tract (Tung et al, 1971; Brown et al, 1972).

Thus, although the mechanical barrier contributes to the isolation of the testis, other "functional" components must also exist that suppress the normal immune response. Several mechanisms likely work in concert to protect sperm from destruction. First, lymphocytes are diverted by the vascular endothelium and are excluded from anatomically vulnerable regions in the germinal epithelium (Mahi-Brown et al, 1988). Second, these vulnerable regions harbor mainly T-suppressor cells (el-Demiry et al, 1985; Anderson and Hill, 1988). Due to deficiencies in antigen–HLA association, there may be a lack of sperm antigen presentation to lymphocytes, impairing the immune response (Jenkins et al, 1987; Anderson and Hill, 1988). There is also evidence to suggest that immunologic tolerance plays a role in the functional blood-testis barrier. Tung and colleagues have proposed that within the anatomically weaker areas (rete testis, efferent tubule, epididymis), there is a small, continuous leak of sperm antigens (Tung, 1980). This leak generates T-suppressor cells and immune tolerance, similar to desensitization protocols for common environmental allergens. However, with larger antigenic challenges, a true immune response results (Turek, 1997). Cytokines may contribute to immune tolerance, including interferon gamma, soluble Fc receptor, and transforming growth factor–β (Perussia et al, 1987; Ben Rafael, 1992; Turek, 1997). In addition, androgens have mild immunosuppressive activity and also appear to help regulate immunity (Diemer et al, 2003).

Why does the blood-testis barrier exist? Since it develops at spermarche, when spermatogenesis begins at puberty (Kormano, 1967), it is likely important for meiosis. In addition, it may immunologically isolate developing male gametes that are not recognized as "self" by the adult male immune system. In this sense, **the value of a blood-testis barrier is fully realized after puberty, because foreign "antigens" on postmeiotic germ cells only exist after spermarche. A testicular insult such as biopsy, torsion, or trauma will not induce antisperm antibodies if it occurs before puberty.** After puberty, however, immunologic infertility is a known risk (Turek, 1997). Clinically, the blood-testis barrier may also limit chemotherapy access to cancer cells sequestered behind it and result in isolated cancer recurrence within the testis.

Spermatogenesis

Spermatogenesis is a remarkably complex and specialized process of DNA reduction and germ cell metamorphosis. Older studies have estimated that the entire process in humans requires approximately 64 days (Clermont, 1972). **However, a recent in-vivo kinetic study in healthy men revealed that the total time to produce an ejaculated sperm ranges from 42 to 76 days, suggesting that the duration of spermatogenesis can vary widely among individuals** (Misell et al, 2006) (Fig. 20–13). **Spermatogenesis involves (1) a proliferative phase** as spermatogonia divide to replace their number (self-renewal) or differentiate into daughter cells that become mature gametes; (2) **a meiotic phase** when germ cells undergo a reduction division, resulting in haploid (half the normal DNA complement) spermatids; and (3) **a spermiogenesis phase** in which spermatids undergo a profound metamorphosis to become mature spermatozoa. (For excellent reviews, see Steinberger, 1976, and de Kretser and Kerr, 1988.)

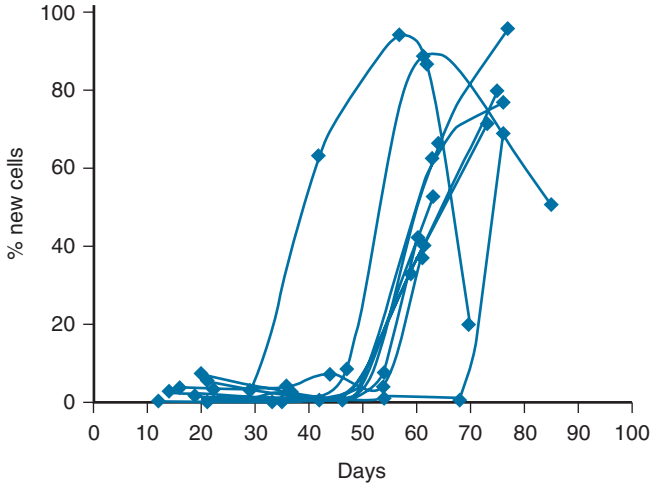


Figure 20–13. Time to make and ejaculate human sperm. Combined spermatocyte labeling curves for 11 individuals with normal semen quality who ingested 50 mL of ^2H_2O twice daily for 3 weeks. Note that new ejaculated sperm was found as soon as 42 days after ingesting the label, and that there is considerable interindividual variation in the time to make and ejaculate sperm among normal men. (From Misell LM, Holochwost D, Boban D, et al. A stable isotope/mass spectrometric method for measuring the kinetics of human spermatogenesis in vivo. J Urol 2006;175: 242–46.)

A cycle of spermatogenesis involves the division of primitive spermatogonial stem cells into subsequent germ cells. **Several cycles of spermatogenesis coexist within the germinal epithelium at any one time, and they are described morphologically as stages.** If spermatogenesis is viewed from a single fixed point within a seminiferous tubule, six recognizable cellular associations or stages exist in a predictable and constant fashion in humans (Heller and Clermont, 1964) (see Fig. 20–11). **In addition, there is also a specific organization of spermatogenic cycles within the tubular space, termed spermatogenic waves.** The best evidence suggests that human spermatogenesis exists in a spiral or helical cellular arrangement that ensures sperm production is a continuous and not a pulsatile process (Schulze, 1989) (Fig. 20–14).

Testis Stem Cell Migration, Renewal, and Proliferation

Testis Stem Cell Migration. During early prenatal development, **primordial germ cells** migrate to the gonadal ridge and associate with Sertoli cells to form primitive testicular cords (Witschi, 1948). These primitive germline stem cells are termed **gonocytes** after the gonad differentiates into a testis by forming seminiferous cords. They are called **spermatogonia** after migration to the periphery of the tubule (Gondos and Hobel, 1971). **Interestingly, these early migrating germ cells have properties very similar to embryonic stem cells and are likely the source of adult seminoma germ cell tumors** (Ezeh et al, 2005).

Testis Stem Cell Renewal. Spermatogonia within the testis stem cell niche are replenished in a process termed stem cell renewal. The growth factor-receptor kit ligand/c-kit receptor system and the niche factor glial cell line-derived neurotrophic factor (GDNF) appear to be involved in this process (Oatley and Brinster, 2008). In fact, the c-kit receptor is a marker of spermatogonial stem cells

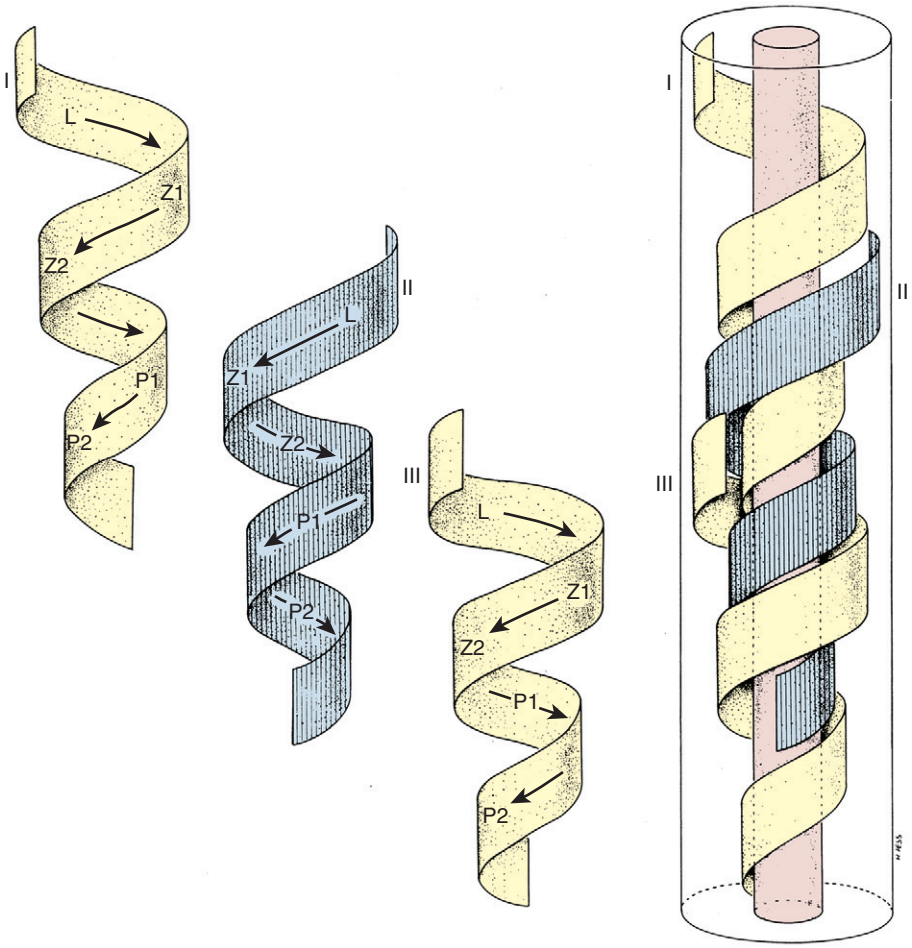


Figure 20–14. Helical configuration of seminiferous tubule epithelial cycles in man, forming overlapping "waves" of spermatogenesis that keep sperm production constant. (From Schulze W, Rehder U. Organization and morphogenesis of the human seminiferous epithelium. Cell Tissue Res 1984;237:395–407.)

in rats (Dym, 1994) and spermatogenesis in the rat is a c-kit–dependent process, whereas spermatogonial stem cell renewal may be c-kit–independent (Yoshinaga et al, 1991). **Recent studies have also shown that human spermatogonial stem cells can be reprogrammed in vitro to become embryonic-like stem cells** (Conrad et al, 2008; Kossack et al, 2009) (Fig. 20–15). Obtained from adult testis biopsies, the embryonic-like cells express distinct markers of pluripotency (*OCT-4, SOX-2, STELLAR, GDF-3*), can form all three germ layers, maintain a normal karyotype, form teratomas, and express appropriate levels of epigenetic markers and telomerase (Kossack et al, 2009). This finding suggests that, in the future, the testis may be a source of patient-specific, embryonic stem cells for cell-based therapy.

Testis Stem Cell Proliferation. In the human, pale type A (Ap) spermatogonia in the basal, stem cell niche of the seminiferous tubule divide at 16-day intervals (Clermont, 1972) to form B spermatogonia. B spermatogonia are committed to become spermatocytes, but the cytoplasm between spermatogonial daughter cells remains conjoined after mitosis, forming cytoplasmic bridges between adjacent cells. These **cytoplasmic bridges are observed between all classes of germ cells throughout spermatogenesis** (Ewing et al, 1980). These bridges could be important for synchronized cellular proliferation and differentiation, and possibly for regulation of gene expression.

Meiosis

Somatic cells replicate by mitosis, in which genetically identical daughter cells are formed. **Germ cells replicate by meiosis, in which the genetic material is halved to allow reproduction.** Meiosis generates genetic diversity, providing a richer source of material on which natural selection can act. Cell replication by mitosis is a precise, well-orchestrated sequence of events involving duplication of the genetic material (chromosomes), breakdown of the nuclear envelope, and equal division of the chromosomes and cytoplasm into two daughter cells. **The essential difference between mitotic and meiotic replication is that a single DNA duplication step is followed by only one cell division in mitosis, but two cell divisions in meiosis (four daughter cells).** Consequently, daughter cells contain only half of the chromosome content of parent cells. Thus a diploid ($2n$) parent cell becomes a haploid (n) gamete. Other major differences between mitosis and meiosis are outlined in Table 20–2. Recent research has shown that small RNA molecules (small RNAs), including small interfering RNAs (siRNAs), microRNAs (miRNAs), and piwi-interacting RNAs (piRNAs), are important regulators of gene germ cell expression at the post-transcriptional or translation level (Tolia and Joshua-Tor, 2007; He et al, 2009).

Spermatogenesis begins with type B spermatogonia dividing mitotically to form primary spermatocytes within the adluminal compartment. **Mature spermatocytes are the first germ cells to undergo meiosis** (Kerr and de Kretser, 1981). In this process, a meiotic division is followed by a typical mitotic reduction division, resulting in daughter cells with a haploid chromosome complement. In addition, as a consequence of chromosomal recombination, each daughter cell contains different genetic information. The resultant cell is the Sa spermatid (see Fig. 20–11).

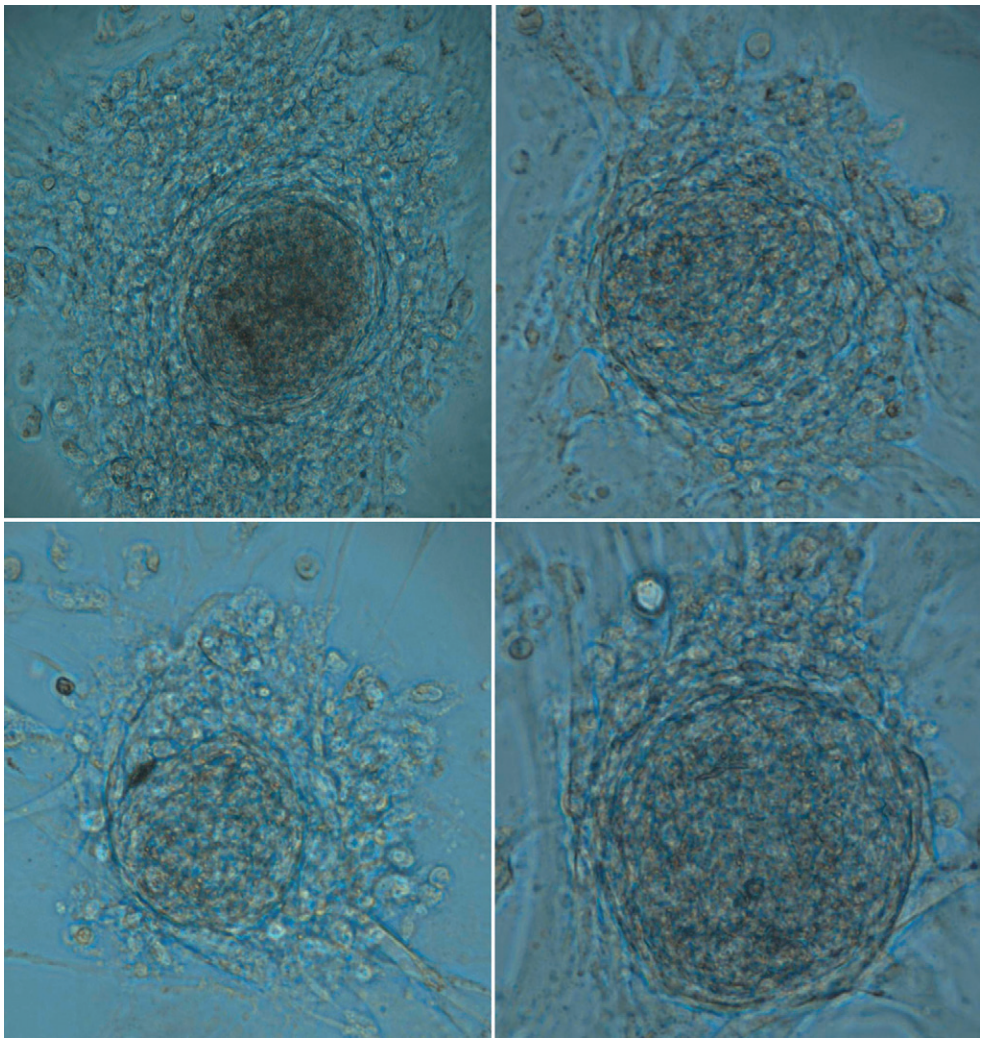


Figure 20–15. Microphotograph of four different colonies of adult testis spermatogonial–derived stem cells. These cell clusters are the result of reprogramming of adult spermatogonia in culture conditions used for human embryonic stem cells (HESCs). They exhibit the typical "cobblestone" appearance of HESCs and have also been shown to be functionally multipotent and even pluripotent.

Table 20–2.

Essential Differences: Mitosis and Meiosis

MITOSIS	MEIOSIS
Occurs in somatic cells	Occurs in sexual cells
1 cell division, 2 daughter cells	2 cell divisions, 4 daughter cells
Chromosome number maintained	Chromosome number halved
No pairing, chromosome homologs	Synapse of homologs, prophase I
No crossovers	>1 crossover per homolog pair
Centromeres divide, anaphase	Centromeres divide, anaphase II
Identical daughter genotype	Genetic variation in daughter cells

Chromosomal recombination, the defining feature of mammalian meiosis, ensures that haploid gametes differ genetically from their adult precursors and is the real engine of genetic diversity and evolution. During meiotic prophase, there is formation of a synaptonemal complex with pairing of homologous (maternal and paternal) chromosomes, and physical interaction and exchange of DNA through reciprocal sites of crossing over **(chiasmata)** between homologs. Recent research has shown that defects in the fidelity of recombination within human male germ cells can cause azoospermia and male infertility (Walsh et al, 2009). **In one study, 10% of nonobstructive azoospermic men had significant defects in recombination compared to men with normal spermatogenesis** (Gonsalves et al, 2004). In addition, among men with maturation arrest pattern on testis biopsy, faulty recombination was observed in about half of cases, providing evidence that faulty recombination is linked to poor sperm production (Gonsalves et al, 2004). Variations in recombination also have implications for sperm aneuploidy, because alterations in crossover position are risk factors for chromosomal nondisjunction. **Indeed, molecular evidence suggests that the correlation of faulty recombination and sperm aneuploidy in azoospermic men is strong enough to explain the higher de novo rate of chromosomal abnormalities in offspring conceived with in-vitro fertilization–intracytoplasmic sperm injection (IVF-ICSI)** (Sun et al, 2008).

Spermiogenesis

During spermiogenesis, round Sa spermatids mature into spermatozoa (see Fig. 20–11). During this maturation sequence, cell division does not occur, but there are extensive changes to the

spermatid nucleus and cytoplasm**. These include the loss of cytoplasm, migration of cytoplasmic organelles, formation of the acrosome from the Golgi apparatus, formation of the flagellum from the centriole, nuclear compaction to about 10% of former size, and reorganization of mitochondria around the sperm midpiece** (Kerr and de Kretser, 1981). The nucleus of the round spermatid changes from spherical to asymmetrical as chromatin condenses. Many cellular elements contribute to the reshaping process, including chromosome structure, associated chromosomal proteins, the perinuclear cytoskeletal theca layer, the manchette of nuclear microtubules, subacrosomal actin, and Sertoli cell interactions. With completion of spermatid elongation, the Sertoli cell cytoplasm retracts around the developing sperm, stripping it of all unnecessary cytoplasm and extruding it into the tubule lumen. The mature sperm has remarkably little cytoplasm, and it is an elaborate, specialized cell produced in massive quantity—up to 300 per gram of testis per second.

Sertoli Cell–Germ Cell Interaction

A complex network of cell–cell interactions exists within the testis between Leydig cells and Sertoli cells, between Leydig cells and peritubular cells, between Sertoli and peritubular cells, and between Sertoli cells and germ cells. There are several kinds of Sertoli cell–germ cell associations in mammalian testes as illustrated in Figure 20–10 (Russell and Clermont, 1976; Romrell and Ross, 1979; Skinner, 1995). Physical contact between these cells plays a role in propelling the germ cell toward the tubule lumen and casting off of the residual cytoplasm from the spermatid. Lastly, there are factors that can reversibly disrupt the blood-testis barrier, including transforming growth factor–β3 (TGF-β3) and tumor necrosis factor–α (TNF-α). These substances act by reducing the levels of occludin and zonula occludens-1 (ZO-1) in the barrier through a p38 mitogen-activated protein (MAP) kinase signaling pathway (Xia et al, 2009). This represents only a piece of the remarkably complex and highly interactive process that characterizes spermatogenesis.

Genetics

Genetic causes of abnormal spermatogenesis have been identified as point mutations in single genes inherited in mendelian fashion (e.g., cystic fibrosis), and as chromosomal disorders, in which segments of (or entire) chromosomes have structural or numerical abnormalities. The reader is referred to Turek and Reijo Pera (2002) for a comprehensive review of such disorders. The postulation that deletions in the long arm of the Y chromosome cause azoospermia was made over thirty years ago (Tiepolo et al, 1976). Based on cytogenetic analysis, this theoretical region was termed the azoospermia factor (AZF). **Currently, the positional patterns of deletions (termed "microdeletions") in the AZF region are used to subdivide this region into AZFa, b, and c subregions** (Vogt et al, 1996). **Regional deletions of the Y chromosome, termed Yq microdeletions, occur in 6% to 8% of severely oligospermic men and in up to 15% of azoospermic men** (Reijo et al, 1996). Taken together, such deletions are the most commonly defined molecular cause of male infertility (Kostiner et al, 1998).

There is emerging literature addressing the prognostic value of specific AZF deletions. In contrast to partial and complete AZFc-deletion patients, in which sperm is often found on semen analysis or testis biopsy, the chance of finding ejaculated or testis sperm in men with complete AZFa or AZFb deletions is highly unlikely (Hopps et al, 2003). Complete AZFa deletions are associated with germ cell aplasia or Sertoli cell–only histology. Complete AZFb deletions are generally associated with maturation arrest at the primary spermatocyte (early) or spermatid (late) stages. AZFc deletions are associated with hypospermatogenesis or a Sertoli cell–only pattern with foci of spermatogenesis. Sperm have been detected in ejaculates of men with presumed and confirmed partial AZFa and AZFb deletions (Foresta et al, 2001). Similarly, ejaculated sperm in men with AZFa + b, and AZFb + c deletions (presumably partial deletions) has also been reported, but the finding of AZFa–c deletions has been associated with azoospermia and no sperm on testis biopsy.

More recently, it has become clear that the X chromosome may also be important for spermatogenesis. Insight into the role of the X chromosome in male infertility has been garnered mainly from rodent studies. In 2001, Wang and colleagues reported on a systematic search for genes expressed exclusively in mouse spermatogonia (Wang et al, 2001). Twenty-five genes were identified by complementary DNA (cDNA) subtraction, of which 10 (9 novel) localized to the X chromosome, suggesting that the X chromosome may have a key role in premeiotic stages of spermatogenesis. Further, human homologues of six of these genes were mapped to chromosomal regions of conserved synteny between mouse and human genomes. Thus, similar to genes on the Y chromosome, it is possible that these X chromosome genes may also prove to be sites of mutation in cases of human spermatogenic failure. Studies have also examined mutations in X-linked genes in male infertility patients, including the *SOX3* gene (sex determining region Y box 3) and the *FATE* gene (Olesen et al, 2003; Raverot et al, 2004). Although not commonly identified at this point, mutations on X chromosome genes will likely prove to contribute significantly to human male infertility in the future.

Genetics and Paternal Age

Age-Related Sperm Chromosomal Anomalies. The aneuploidy and polyploidy status of sperm were first investigated due to concern that advanced paternal age was associated with increased cases of trisomy, especially trisomy 21 or Down syndrome in offspring. With fluoresence in-situ hybridization technology (FISH), subtle paternal-age effects on sperm aneuploidy have been detected. **The paternal age effect appears to increase the fraction of sperm with sex chromosomal aneuploidies** (Wyrobek et al, 1996). **However, there is little evidence to support a paternal age–related increase in aneuploid births, except for possibly trisomy 21 and disomy 1 (very rare).** Examining sperm chromosome structural abnormalities, Martin and Rademaker (1987) found that a highly significant linear relationship exists between paternal age and the frequency of structural anomalies in sperm ($r = 0.63$). **One explanation for this association may be that continued cell division during spermatogenesis places germ cells at risk for chromosomal injury, especially with advanced paternal age.** Except for reciprocal translocations, however, there is little evidence to indicate that this association leads to an increased frequency of offspring with de novo structural chromosomal anomalies.

Age-Related Sperm Genetic Mutations. Single gene defects in sperm result from errors in DNA replication. To date, it has been difficult to assess the presence or absence of such defects in sperm. However, the effect of advanced paternal age on cases of conditions associated with single-gene deletions has been studied extensively. These disorders are listed in Table 20–3 and consist of autosomal dominant diseases that have known associations with advanced paternal age. They are termed "sentinel phenotypes" because they are disorders of significant frequency and low fitness,

Table 20–3.

Selected Genetic Disorders Associated with Advanced Paternal Age

Achondroplasias
Aniridia
Apert syndrome
Bilateral retinoblastoma
Crouzon syndrome
Fibrodysplasia ossificans
Hemophilia A
Lesch-Nyhan syndrome
Marfan syndrome
Neurofibromatosis
Oculodentodigital syndrome
Polycystic kidney disease
Polyposis coli
Progeria
Treacher Collins syndrome
Tuberous sclerosis
Waardenburg syndrome
Schizophrenia (postulated)
Autism (postulated)

and occur sporadically due to highly penetrant mutations. **One mechanism for the development of new single-gene mutations with age implicates the characteristic and continuous process of spermatogonial cell division in spermatogenesis.** By puberty, 30 cell divisions of spermatogonia have occurred, resulting in a large pool of undifferentiated cells. After puberty, 23 divisions per year occur in these cells. **The simple fact that the spermatogonia of older men have undergone numerous cell divisions may make them more likely to harbor errors in DNA transcription, the source of single-gene defects.** Formal risk estimates exist for the contribution of advanced paternal age to autosomal dominant mutations: In men <29 years old, the risk of a mutation occurring in offspring is 0.22 per 1000. This risk doubles (0.45 per 1000) at paternal ages 40 to 44, and then climbs to 3.7 per 1000 at ages >45 (Friedman, 1981).

Key Points: Testis

- The testis contains 250 meters of seminiferous tubules and 700 million Leydig cells in the young adult male.
- Spermatogenesis occurs in stages, cycles, and waves to ensure constant sperm production.
- Genes on the X, as well as the Y, chromosome control spermatogenesis and can contribute to male infertility.
- With paternal age, there are increases in structural chromosomal abnormalities in sperm and autosomal dominant mutations leading to "sentinel phenotypes" in offspring.

THE EPIDIDYMIS

Gross Architecture

The epididymis is a comma-shaped organ located along the posterolateral surface of the testis. **Passage through the epididymis induces many changes to newly formed sperm,**

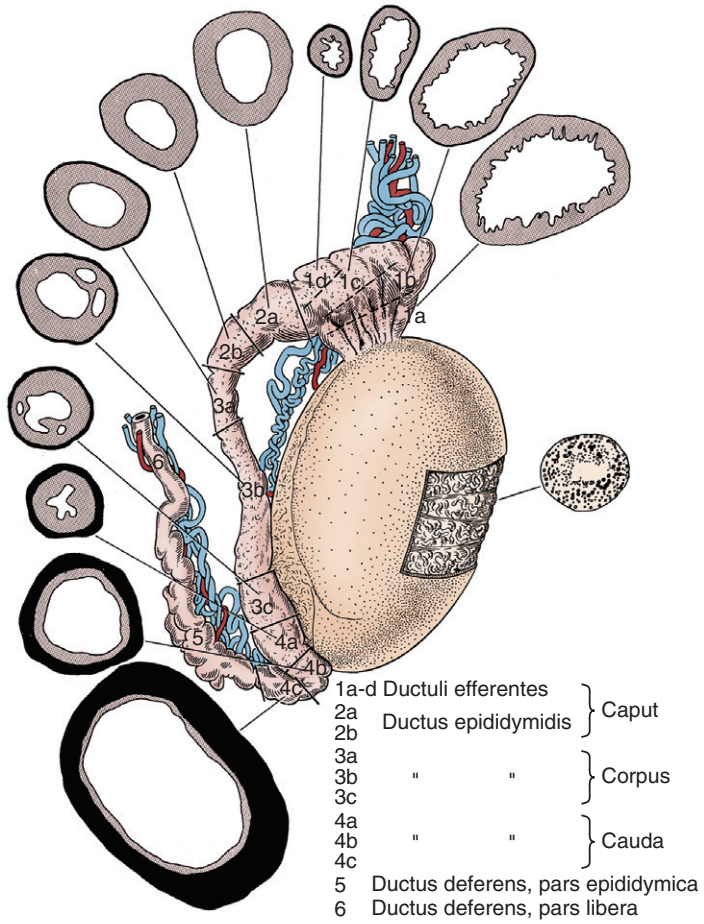


Figure 20–16. Drawing of the human epididymis showing regionalization of the ductal epithelium and muscle layer. Epididymal segment locations are shown in cross section and are identified by number. (From Baumgarten HG, Holstein AF, Rosengren E. Arrangement, ultrastructure, and adrenergic innervation of smooth musculature of the ductal efferentes, ductus epididymidis, and ductus deferens in man. Z Zellforsch Mikrosk Anat 1971;120:37.)

including a gain in functional motility, and alterations in surface charge, membrane proteins, immunoreactivity, phospholipids, fatty acid content, and adenylate cyclase activity. These changes improve cell membrane structural integrity, increase fertilization ability, and improve motility. Spermatozoa within the testis have very poor or no motility. They become progressively motile and functional only after traversing the epididymis. The transit time of sperm through the epididymis is thought to take up to 12 days in humans (Johnson and Varner, 1988).

The epididymis is a tubule or duct that is 3 to 4 meters in length and is tightly coiled and encapsulated within the sheath of connective tissue of the tunica vaginalis (Lanz and Neuhauser, 1964; Turner et al, 1978). Extensions from the sheath enter interductal spaces and form septa that divide the duct into histologically characteristic regions (Kormano and Reijonen, 1976). **Anatomically, these are classically divided into three regions: caput or head, corpus or body, and cauda (or tail)** (Fig. 20–16). The caput epididymis consists of 8 to 12 ductuli efferentes from the testis. The lumen of the ductuli efferentes is large and somewhat irregular in shape near the testis, becoming narrow and oval near the junction with the ductus epididymis. Distal to this junction, the duct diameter increases

slightly and, thereafter, remains constant in the corpus epididymis. In the bulky cauda epididymis, the tubule diameter enlarges substantially and acquires an irregular shape. Progressing distally, the tubule gradually assumes the characteristic appearance of the vas deferens.

Vascular and Lymph Supply

In humans, the caput and the corpus epididymis receive arterial blood from a branch of the testicular artery (see Fig. 20–7). It subsequently divides into superior and inferior epididymal branches (MacMillan, 1954). The epididymis also receives blood from branches of the deferential arteries (artery of the vas deferens), and collateral vessels connect the deferential artery to the testicular blood supply. The cauda epididymis is supplied by branches of the deferential artery. **The deferential and cremasteric arteries serve as collateral sources to the epididymis, when the main testicular artery is obstructed or ligated.** The arterial branches within the epididymis enter along septa formed from the connective tissue sheath. These vessels coil extensively before transforming into the straight vessels of the microvascular bed (Kormano and Reijonen, 1976). Microvascularization density varies significantly along the length of the epididymis, with the proximal caput containing the densest subepithelial capillary network, and the more distal segments harboring less dense vascularization. From animal studies, the epididymal capillary network is under hormonal control. For example, in rabbits, bilateral hormonal castration results in progressive deterioration and eventual disappearance of the epididymal capillary network (Clavert et al, 1981). It is not clear whether vascularization in the human epididymis is similarly controlled.

According to MacMillan (1954), venous drainage from the corpus and cauda epididymis joins to form the vena marginalis epididymis of Haberer. These veins drain into the pampiniform plexus through the vena marginalis testis, or through the cremasteric or deferential veins. Lymphatic drainage of the epididymis occurs through two routes (Wenzel and Kellermann, 1966). Lymph from the caput and corpus epididymis is removed through the same route as that described for the testis. These vessels course beside the internal spermatic vein and ultimately terminate in the preaortic nodes. Lymph vessels from the cauda epididymis join those draining the vas deferens and terminate in the external iliac nodes.

Innervation

The innervation of the human epididymis is derived primarily from the intermediate and inferior spermatic nerves that arise from the superior portion of the hypogastric plexus and pelvic plexus, respectively (Mitchell, 1935). The ductuli efferentes and the proximal segments of the epididymis are sparsely innervated by sympathetic fibers (Baumgarten and Holstein, 1967; Baumgarten et al, 1968). In these regions, the fibers are observed in a peritubular plexus and are principally associated with blood vessels. Many more fibers are observed in the midcorpus epididymis, and their density increases progressively with distal progression along the epididymis, coincident with the appearance and proliferation of smooth muscle cells in these areas (Baumgarten et al, 1971). The distribution of contractile cells and sympathetic nerves within the epididymis may explain the rhythmic peristaltic movements of the ductuli efferentes and initial epididymal segments, as well as the intermittent contractile activity of the cauda epididymis and the vas deferens during emission (Risely, 1963). These physiologic contractions are critical to the movement of sperm through the epididymis.

Cytoarchitecture

Epididymal Epithelium

The histology of the human epididymis has been reviewed by Holstein (1969) and Vendrely (1981). It consists of two main cells types: **principal cells and basal cells** (seen at low ultrastructural magnification in Fig. 20–17). Principal cells vary in height along the length of the epididymis due to the length of stereocilia (microvilli, not cilia). Tall stereocilia (120 μm) are generally found in the proximal epididymis, and smaller or shorter stereocilia (50 μm) are observed in more distal regions. The nuclei in principal cells are elongated and often possess large clefts and one or two nucleoli. Consistent with the idea that principal cells carry out both absorptive and secretive processes, their cellular apices have numerous coated pits, micropinocytotic vesicles, multivesicular bodies, irregularly shaped membranous vesicles, and an extensive Golgi apparatus. Because these cytologic features vary along the length of the epididymis, it suggests that there is varying absorptive and secretory capacity along the length of the duct (Vendrely and Dadoune, 1988).

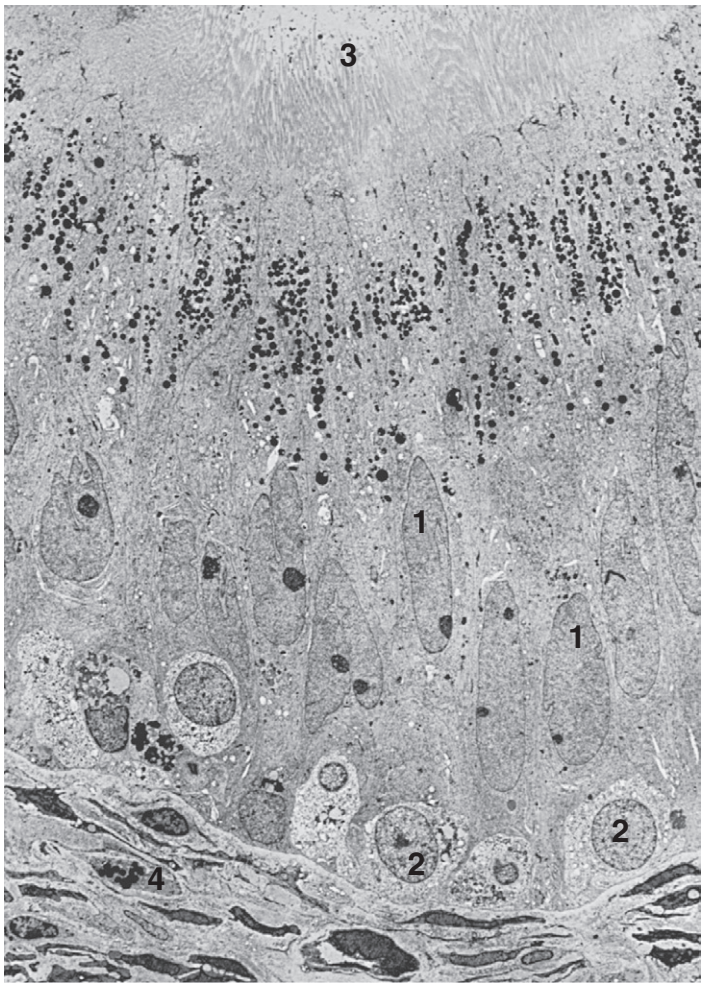


Figure 20–17. Electron micrograph of a human epididymis in cross section. Major components of the luminal epithelium are principal cells (1), basal cells (2), stereocilia (3), and myofilaments (4). Magnification approximately ×1800. (From Holstein AF. In: Hafez ESE, editor. Human semen and fertility regulation in men. St Louis: Mosby; 1976.)

There are far fewer basal cells than principal cells lining the epididymal epithelium, and they are dispersed among the more numerous principal cells. Tear-shaped basal cells rest on the basal lamina and extend approximately 25 µm toward the lumen, their apices forming threads between adjacent principal cells. They are thought to be derived from macrophages. Unlike the principal cells, the morphology of basal cells remains relatively constant throughout the epididymal duct. They are thought to be the precursors of the principal cells.

Overall, the epithelium of the epididymis exhibits regional differences along the length of the duct. Within the epididymis proper, the epithelium is pseudostratified in nature and consists of principal and basal cells as described above. More proximally, at the junction of the rete testis and ductuli efferentes, there is a distinct transition from a low to a high cuboidal epithelium. The epithelium in the ductuli efferentes appears uneven and consists of ciliated and nonciliated cells (Holstein, 1969). The ciliated cells are dispersed throughout the epithelium and conduct sperm from the efferent ducts into the epididymis. The nonciliated cells with protruding apices are likely secretory in nature and predominate in the proximal ductuli efferentes (Vendrely, 1981). Other nonciliated cells have microvilli suggestive of resorptive activity and predominate in the distal ductuli efferentes. Nonciliated cells likely are involved in testis fluid reabsorption. Both nonciliated and ciliated cells are joined apically through junctional complexes. This suggests the existence of a blood-epididymis barrier analogous to the blood-testis barrier (Suzuki and Nagano, 1978; Hoffer and Hinton, 1984). **Although not as dense as the blood-testis barrier, the blood-epididymis barrier extends from the caput to the cauda epididymis and may play an important role in influencing the composition of fluid within different segments of the epididymal lumen** (Turner, 1979).

Epididymal Contractile Tissue. Peripheral to the basal lamina of the ductuli efferentes and the epididymal tubule, there are various contractile cells (Baumgarten et al, 1971) (see Fig. 20–17). In the ductuli efferentes (distal regions of the caput and the proximal corpus epididymis), the contractile cells form a loose layer, two to four cells deep, around the tubule. These cells contain myofilaments and are connected by numerous nexus-like junctions. In the distal corpus epididymis, there are larger contractile cells with fewer nexus-like intracellular junctions that resemble thin smooth muscle cells. In the cauda epididymis, the thin contractile cells are replaced by thick smooth muscle cells that form three layers—the outer two layers oriented longitudinally and the central layer circularly. This distal contractile layer increases in thickness as it forms the vas deferens. The contractile tissue throughout the epididymis is likely involved in sperm transport.

Epididymal Function

Described variations in the anatomy and histology of the epididymal tubule from the caput to cauda regions suggest that the epididymis is actually several different functional tissues (Vendrely, 1981). It is clear that sperm transport and storage, sperm-fertilizing ability, and motility maturation are several consequences of passage through this organ. This is addressed more fully in reviews by Robaire and Hermo (1988), and Moore and Smith (1988).

Sperm Transport

Sperm transport through the human epididymis has been calculated to take from 2 to 12 days (Johnson and Varner, 1988). **Sperm transit time through the caput-corpus epididymis is roughly similar to the transit time through the cauda epididymis and is more likely related to daily testicular sperm production rather than a man's age or the frequency of ejaculation** (Amann, 1981; Johnson and Varner, 1988). In one study, sperm epididymal transit time averaged 2 days in men with a high daily rate of sperm production (137 million per testis), compared with 6 days in men with low daily sperm production (34 million per testis) (Johnson and Varner, 1988). Although the frequency of sexual activity does not affect sperm transit time through the caput and corpus epididymis, "recent emissions" can reduce transit time through the cauda epididymis by 68% (Amann, 1981).

Because normal human testicular sperm are immotile as they enter the epididymis, and remain relatively immotile within the caput, **mechanisms other than sperm motility must exist to transport sperm through the epididymis.** Animal studies have been very revealing in this regard (Bedford, 1975; Hamilton, 1977; Courot, 1981; Jaakkola and Talo, 1982; Jaakkola, 1983). Initially, sperm are carried into the ductuli efferentes by rete testis fluid, and **fluid flow is facilitated by fluid resorption by ductal epithelial cells mediated by the estrogen receptor. Motile cilia and myoid cell contractions within the ductuli efferentes also assist with sperm movement. Within the epididymis proper, the principal mechanism responsible for sperm transport is likely the spontaneous, rhythmic contraction of the contractile cells surrounding the epididymal duct.**

Sperm Storage

After migrating through the caput and corpus epididymis, sperm are retained in the cauda epididymis for varying lengths of time, depending on the frequency of sexual activity. In men 21 to 55 years of age, **an average of 155 to 209 million sperm are present in each epididymis** (Amann, 1981; Johnson and Varner, 1988), **and approximately half are stored in the caudal region.**

Spermatozoa stored in the cauda epididymis, unlike testicular sperm, are capable of progressive motility and are able to fertilize eggs. The exact amount of time that sperm can remain fertile within the epididymis is unclear, but animal studies have shown that sperm can remain viable for several weeks within the cauda epididymis after vas deferens ligation (Hammond and Asdell, 1926; Young, 1929). However, it is also clear that sperm fertility measured in vivo diminishes when sperm are maintained in the epididymis for prolonged periods of time (Cooper and Orgebin-Crist, 1977; Cuasnicu and Bedford, 1989). In humans, sperm aging as a result of extended epididymal transit time and prolonged storage may contribute to reduced fertility (Johnson and Varner, 1988).

The exact fate of unejaculated epididymal sperm is unknown. In animals, sperm are lost through spontaneous seminal discharge, oral self-cleaning (Martan, 1969), through urine (Lino et al, 1967), or by epididymal reabsorption (Amann and Almquist, 1961). Phagocytosis of spermatozoa by macrophages (spermiophages) within the epididymal lumen has been observed in humans after ligation of the vas deferens (Alexander, 1972). However, whether this mechanism can remove large numbers of spermatozoa from the epididymis of unvasectomized men is unclear.

Sperm Maturation

Sperm Motility. Sperm gain an increased capacity for motility with migration through the epididymis. This is observed as both a change in the pattern of motility, and

as an increase in the proportion of sperm exhibiting "mature" motility patterns. Bedford and coworkers (1973) first observed that the majority of sperm from the ductuli efferentes, when placed in culture medium, are immotile or show only weak, twitching movement. Occasionally, they also observed sperm showing "immature" tail movements characterized by "thrashing" beats in wide arcs that result in little forward progression. The proportion of sperm with this immature motility pattern increased within the initial epididymal segment. However, in the corpus region, the proportion of sperm exhibiting this motility pattern decreased. Within the corpus region, there was an increase in the fraction of sperm with a "mature" motility pattern characterized by high-frequency, low-amplitude beats that result in progressive motility (Fig. 20–18). Within the cauda epididymis, >50% of sperm had a mature motility pattern, with the remainder either immotile or showing the immature motility patterns described earlier. Moore and colleagues (1983) also formally demonstrated the increased capacity of human sperm to show progressive forward motility with epididymal transit. When placed in buffer in vitro, 0%, 3%, 12%, 30%, and 60% of sperm were motile from the efferent ducts, caput, proximal corpus, distal corpus, and cauda epididymis, respectively (Fig. 20–19).

The relative importance of overall epididymal contact time versus region-specific maturation to the gain in mature sperm motility patterns is unknown. Animal studies indicate that motility maturation may, in part, be an intrinsic sperm process that occurs independent of specific epididymal interactions. For example, although hamster and rabbit sperm are generally immotile within the caput epididymis, motile sperm are found in this region (albeit developing motility far more slowly and persisting for shorter periods than in the normal system) after epididymal duct ligation within the corpus region (Orgebin-Crist, 1969; Horan and Bedford, 1972). Human studies in obstructed patients with congenital absence of the vas deferens or epididymal obstruction also frequently report poor motility in spermatozoa aspirated from the distal epididymis, and better sperm motility in the proximal epididymis (Silber, 1989; Matthews et al, 1995). When combined, **these observations suggest that spermatozoa are able to develop motility based on contact time with the proximal epididymal epithelium.** However, this maturation process may not be the same as that which occurs through sperm interaction with the epididymis during migration through all ductal regions.

Sperm Fertility. Testicular sperm are incapable of fertilizing eggs unless injected into them with micromanipulation (Orgebin-Crist, 1969; Bedford, 1974; Yanagimachi, 2005). In most animals, the ability of sperm to fertilize eggs is acquired gradually as the sperm pass through the distal epididymis (see Fig. 20–19). Indeed, it has been shown in rabbits that sperm from the caput, corpus, and cauda epididymis can fertilize 1%, 63%, and 92% of rabbit eggs, respectively (Orgebin-Crist, 1969). Human in-vitro experiments using zona pellucida–free hamster eggs have corroborated these findings (Moore et al, 1983). In a study that assessed the fertilizing capacity of human epididymal sperm, Hinrichsen and Blaquier (1980) demonstrated that although sperm from the proximal epididymis are able to bind to zona-free eggs, only sperm from the cauda epididymis can both bind and penetrate eggs. **Thus sperm fertility maturation is, for the most part, achieved at the level of the late corpus or early cauda epididymis.**

Recent clinical observations, however, challenge the idea that fertility maturation requires sperm migration through the entire epididymis. Indeed, patients with epididymal obstruction or congenital absence of the vas deferens can achieve natural pregnancies after vasoepididymostomy at the level of the ductuli efferentes (Schoysman and Bedford, 1986; Silber, 1989). This suggests that obstruction induces proximal "skewing" of the maturation sequence along the epididymal duct, or that there may be a

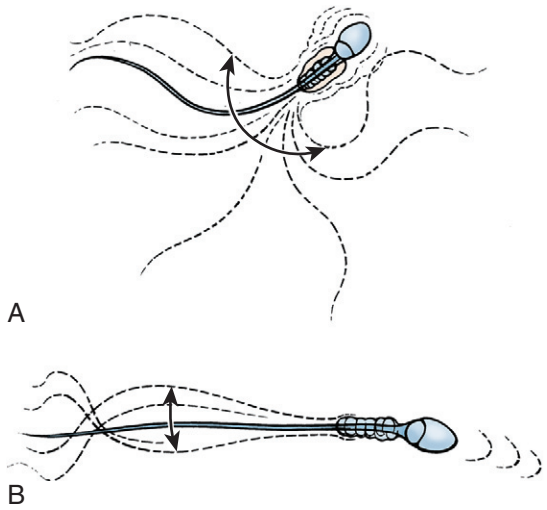


Figure 20–18. Patterns of tail movement of human epididymal sperm. **A,** The pattern shown by sperm taken from proximal epididymis is characterized by high-amplitude, low-frequency beats producing little forward movement. **B,** In contrast, tail movement in a large proportion of sperm from the cauda epididymis is characterized by low-amplitude, rapid beats with forward progression. (From Bedford JM, Calvin HI, Cooper GW. The maturation of spermatozoa in the human epididymis. J Reprod Fertil 1973;18:199–213.)

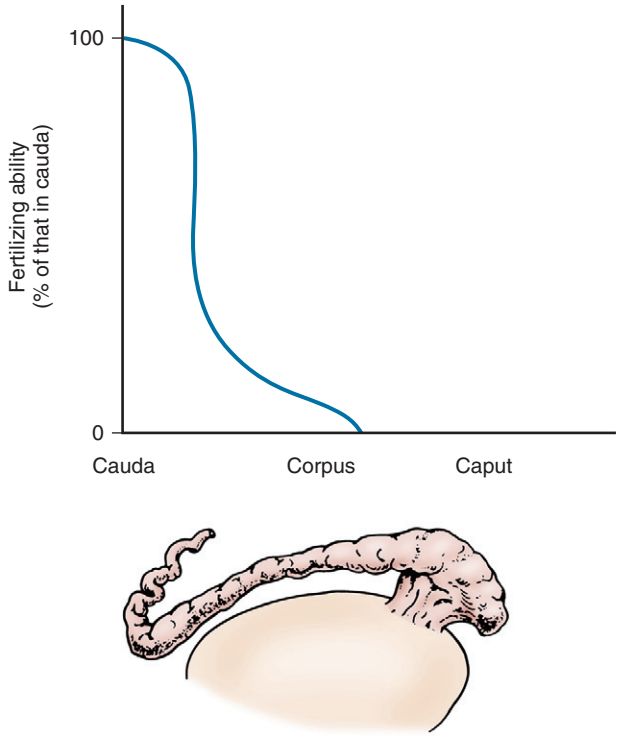


Figure 20–19. Sperm fertility maturation in the human epididymis. Sperm fertilizing ability was assessed using zona pellucida–free hamster eggs and by changes in motility. (From Bedford JM. The bearing of epididymal function in strategies for in vitro fertilization and gamete intrafallopian transfer. Ann N Y Acad Sci 1988;541:284–91.)

reduced flow of sperm through the epididymis after such bypass procedures, allowing more contact time and sperm maturation (Orgebin-Crist, 1969; Turner and Roddy, 1990). Despite this observation, **is it generally believed that the likelihood of fertility is greater as the surgical anastomosis is performed more distally in the epididymis** (Thomas, 1987).

Sperm Biochemical Changes. Sperm undergo many biochemical changes with passage through the epididymis (Brooks, 1983). Although human information is limited, **epididymal sperm transit induces a net negative surface membrane charge** (Bedford et al, 1973) **and sperm membrane sulfhydryl groups oxidize to disulfide bonds, improving sperm structural rigidity necessary for progressive motility and egg penetration** (Bedford et al, 1973; Reyes et al, 1976). Other post-testicular modifications of sperm membranes include changes in sperm lectin-binding properties (Courtens and Fournier-Delpech, 1979; Olson and Danzo, 1981), phospholipid and lipid content (Nikolopoulou et al, 1985), glycoprotein composition (Brown et al, 1983), immunoreactivity (Tezón et al, 1985), and iodination characteristics (Olson and Danzo, 1981). **Overall, these membrane modifications during epididymal passage may enhance sperm adherence to the egg zona pellucida** (Orgebin-Crist and Fournier-Delpech, 1982; Blobel et al, 1990). Sperm also undergo numerous metabolic changes during epididymal transit (Dacheux and Paquignon, 1980). These include gaining an increased capacity for glycolysis (Hoskins et al, 1975), changes in intracellular pH and calcium content, modification of adenylate cyclase activity (Casillas et al, 1980), and alterations in cellular phospholipid and phospholipid-like fatty acid content (Voglmayr, 1975).

Regulation of Epididymal Function

Sperm changes within the epididymis are likely influenced by fluids and secretions within the epididymal lumen (Robaire and Hermo, 1988; Blaquier et al, 1989). The biochemical composition of epididymal fluid not only differs from that of serum, but there are also regional differences in the osmolarity, electrolyte content, and protein composition of epididymal fluid (Robaire and Hermo 1988). These differences are likely the consequence of variations in vascularization, blood-epididymis barrier activity, and selective absorption and secretion of fluid constituents such as glycerylphosphorylcholine (GPC), carnitine, and sialic acids along the epididymal duct. Proteins within the epididymal fluid that are known to have physiologic effects on sperm in vitro include forward motility protein (Brandt et al, 1978), sperm survival factor (Morton et al, 1978), progressive motility sustaining factor (Sheth et al, 1981), sperm motility-inhibiting factor (Turner and Giles, 1982), acidic epididymal glycoprotein (Pholpramool et al, 1983) and the EP2-EP3 proteins that induce sperm binding to zona pellucida (Cuasnicu et al, 1984; Blaquier et al, 1988). Thus variations in epididymal tubule fluid characteristics play an important role in sperm maturation during epididymal transit. It is not surprising, then, that epididymis is a potentially important source of sperm dysfunction and male infertility.

Epididymal function is hormonally regulated. Testosterone and DHT are found in very high concentrations within the epididymis, and there are no regional gradients in androgen levels (Leinonen et al, 1980). This suggests the importance of androgens for epididymal function, a finding confirmed in animal studies (Brooks and Tiver, 1983). Bilateral castration results not only in the loss of androgen-dependent epididymal proteins but also losses in epididymal weight, changes in luminal histology, and alterations in the synthesis and secretion of epididymal fluid GPC, carnitine, and sialic acid. Ultimately, the castrated epididymis loses the ability to sustain sperm motility, fertility maturation, and sperm storage capacities, but most of these degenerative processes are reversed with androgen replacement.

Compared with other accessory sex glands, the epididymis requires relatively higher levels of androgen for maintenance of its structure and function (Prasad and Rajalakshmi, 1976). **Androgen effects on the epididymis appear to be mediated mainly through dihydrotestosterone (DHT), the primary androgen in epididymal tissue extracts** (Pujol et al, 1976) and/or 5α-androstane-3α, 17β-diol (3α-diol) (Orgebin-Crist et al, 1975). Indeed, this is corroborated by the fact that the enzymes Δ4-5α-reductase (catalyzes the DHT formation from testosterone), and 3α-hydroxysteroid dehydrogenase (converts DHT to 3α-diol) that produce these testosterone metabolites are also found in the human epididymis (Kinoshita et al, 1980; Larminat et al, 1980).

Epididymal function is also influenced by temperature (Foldesy and Bedford, 1982; Wong et al, 1982). Chronic exposure of the epididymis to elevated temperatures, by placing them within the abdomen, results in the loss of sperm storage and electrolyte transport functions. The influence of temperature on epididymal function in humans may be an important consideration for how varicocele and cryptorchidism induce male infertility. Abnormalities in epididymal myoid cell contractility may also influence epididymal function. In the rat, partial surgical denervation of the epididymis results in an abnormal accumulation of sperm within the cauda epididymis and a decrease in the swimming speed of retained sperm (Billups et al, 1990). These findings certainly have implications for infertility due to neuropathic causes such as spinal cord injury and diabetes mellitus.

Key Points: Epididymis

- The epididymis consists of principal cells, with absorptive and secretory function, basal cells derived from macrophages, and contractile cells that facilitate sperm transport.
- During passage through the epididymis, sperm mature by gaining progressive motility and the ability to bind to and penetrate the egg zona pellucida.
- Epididymal function is temperature- and androgen- (mainly DHT) dependent, important considerations for cryptorchidism and varicocele.

DUCTUS (VAS) DEFERENS

Gross Architecture

The vas deferens is a tubular organ derived from the mesonephric (wolffian) duct. In humans, the vas deferens is 30 to 35 cm long, beginning at the cauda epididymis and terminating in the ejaculatory duct, medial to the seminal vesicle and posterior to the prostate. It is classically divided into 5 regions: (1) the sheathless epididymal segment contained within the tunica vaginalis, (2) the scrotal segment, (3) the inguinal segment, (4) the retroperitoneal or pelvic portion, and (5) the ampulla (Lich et al, 1978). In cross section, the vas deferens consists of an outer adventitial connective tissue sheet containing blood vessels and small nerves, a muscular coat that consists of a middle circular layer surrounded by inner and outer longitudinal muscle layers, and an inner mucosal layer with an epithelial lining (Neaves, 1975). The outer

diameter of the vas deferens varies from 1.5 to 3 μm, and the lumen of the unobstructed vas deferens varies from 200 to 700 mm in diameter (Middleton et al, 2009).

The vas deferens receives its blood supply from the deferential artery, a branch of the superior vesicle artery. Venous drainage corresponds to arterial supply. The vas deferens receives innervation from both the sympathetic and the parasympathetic nervous systems (Sjostrand, 1965). The cholinergic supply does not appear important for motor activity of the vas deferens (Baumgarten et al, 1975). There is a rich supply of sympathetic adrenergic nerves derived from hypogastric nerve coursing via the presacral nerve (Batra and Lardner, 1976; McConnell et al, 1982). Adrenergic nerve fibers have been observed in all three layers of the vas tunica muscularis, with the greatest concentration in the outer longitudinal layer (McConnell et al, 1982). The vas deferens also receives a short adrenergic nerve (Sjostrand, 1965) and has an abundance of ligand-gated, purinergic receptors in its smooth muscle membranes, suggesting sympathetic and purinergic cotransmission in sperm transport and ejaculation (Gur et al, 2007). Neurons containing other neurotransmitters, including neuropeptide Y, enkephalin, galanin, somatostatin, vasoactive intestinal polypeptide, and nitric oxide, have also been identified; however, their role in vas deferens function is unknown (Dixon et al, 1998). Interestingly, observations from human vas deferens specimens obtained at vasovasostomy from 1 to 15 years after vasectomy show a marked reduction in the density of muscular noradrenergic and subepithelial secretomotor nerves in testicular compared to abdominal segments. These changes after vasectomy may influence subsequent sperm maturation and transport, and hence procedural success after vasectomy reversal (Dixon et al, 1998).

Cytoarchitecture

The human vas deferens is lined by pseudostratified epithelium (Paniagua et al, 1981). The height of the epithelium decreases along the length of the vas deferens from the testis to the seminal vesicle. In addition, the longitudinal epithelial folds are simpler proximally near the testis and become more complex distally. The pseudostratified epithelium lining of the vas deferens is composed of basal cells and three types of tall, thin columnar cells (Hoffer 1976; Paniagua et al, 1981). The columnar cells, extending from the epithelial base to the lumen, include principal cells, but also pencil cells and mitochondria-rich cells. All columnar cells exhibit stereocilia and irregular convoluted nuclei. Principal cells are the most frequent columnar cell type in the proximal vas deferens, whereas both pencil cells and mitochondria-rich cells increase in density distally. The thickness of the total muscle layer gradually decreases along the length of the vas deferens. This complex cytoarchitecture strongly suggests that the vas deferens is more than simply a passive conduit for sperm transport.

Vas Deferens Function

Sperm Transport

Sperm transport through the vas deferens is influenced by several physiologic processes. First, **the human vas deferens exhibits spontaneous motility** (Ventura et al, 1973). **It also has the capacity to respond when stretched** (Bruschini et al, 1977). **Finally, fluid within the vas deferens can be propelled into the urethra by strong peristaltic contractions elicited either by electrical stimulation of the hypogastric nerve** (Bruschini et al, 1977) or by adrenergic neurotransmitters (Bruschini et al, 1977; Lipshultz et al, 1981). This suggests that immediately before emission, with sympathetic stimulation, rapid transport of sperm from the distal epididymis through the vas deferens to the ejaculatory duct occurs. **This rapid transport ability is consistent with the vas deferens having the greatest muscle to lumen ratio (≈10:1) of any hollow viscus in the body.**

Sperm reserves in the vas deferens have been estimated at approximately 130 million, suggesting that a significant proportion of human ejaculated sperm is stored in the vas deferens (Amann and Howards, 1980). In addition, vasal sperm quality, as assessed from fertile men at the time of vasectomy, is very similar to that of the ejaculate, with 71% motility and 91% viability (Bachtell et al, 1999). In the rabbit, it has been shown that during sexual rest, epididymal sperm are transported through the vas deferens and leak into the urethra in small amounts and at irregular intervals (Prins and Zaneveld, 1979, 1980a, 1980b). This suggests that the vas deferens is involved in ridding the epididymis of excess, stored sperm. Upon sexual stimulation, rabbit sperm are transported through the vas deferens similar to humans. **After sexual stimulation, however, the vas deferens contents are propelled proximally toward the epididymis as the distal vas deferens contracts with greater amplitude, frequency, and duration than the proximal segment** (Prins and Zaneveld, 1980a). Notably, with prolonged sexual rest, excess epididymal sperm are once again transported distally, supporting the idea that the vas deferens is important not only for sperm transport, but also for the maintenance of epididymal sperm reserves.

Absorption and Secretion

Based on its cytoarchitecture, it has been suggested that the human vas deferens has both absorptive and secretory functions (Hoffer 1976 and Paniagua et al, 1981). The principal cells are typical of cells that synthesize and secrete glycoproteins, as has been demonstrated in the rat model (Gupta et al, 1974; Bennett et al, 1974). The stereocilia, apical blebbing, and primary and secondary lysosomes within principal cells are also characteristic of cells involved in absorptive function (Murakami et al, 1988), which has also been confirmed in the rat (Friend and Farquhar, 1967). Lastly, spermiophagy by epithelial cells in the ampullary vas deferens has been observed with scanning electron microscopy in both men and monkeys (Murakami et al, 1988). **Importantly, normal vas deferens function is likely to be androgen dependent because the vas deferens actively converts testosterone to DHT** (Dupuy et al, 1979). Castration causes atrophy of—and testosterone treatment, restoration of—monkey vas cytoarchitecture (Dinakar et al, 1977), and spontaneous and α- and β-adrenergic–stimulated contractions of the rat vas deferens are altered by castration (Borda et al, 1981). Thus, although once thought to be a simple muscular conduit for sperm, the vas deferens is now viewed as a complex reproductive organ.

SEMINAL VESICLE AND EJACULATORY DUCTS

Gross and Cytoarchitecture

Seminal Vesicle

In the adult, the seminal vesicles are paired, elongated, hollow viscous organs located posterior to the prostate and bladder. Each

seminal vesicle is 5 to 7 cm long and up to 1.5 cm wide. Each seminal vesicle actually consists of a tubule that is 15 cm long and highly coiled and convoluted. **The tubule itself is composed of three layers: The inner lining is a moist and folded mucous membrane; the middle layer is largely collagenous; and the outer layer consists of circular and longitudinal muscles layers that constitute 80% of the wall thickness** (Nguyen et al, 1996). The mucosa of the seminal vesicle, mainly nonciliated, pseudostratified columnar or cuboidal cells, is notable for many thin, complicated folds that produce numerous crypts. The excretory duct of the seminal vesicle opens into the ampullary vas deferens as it enters the prostate gland.

The blood supply to the seminal vesicle arises from the internal iliac artery and inferior vesicular artery through the prostatovesicular branch (Clegg, 1955). The prostatovesicular artery can also arise from the superior vesicular artery or from the pudendal artery. Most commonly, the prostatovesicular artery has anterior and posterior branches that supply the respective surfaces of the seminal vesicle. The lymphatic drainage of the seminal vesicle is through the internal iliac lymph nodes. The seminal vesicles are innervated through sympathetic nerves from the superior lumbar and hypogastric nerves. Parasympathetic innervation occurs through the pelvic plexus.

Ejaculatory Ducts

The ejaculatory ducts are paired, collagenous, tubular structures that commence at the junction of the vas deferens and seminal vesicle, course through the prostate, and empty into the prostatic urethra at the verumontanum. Histologically, the ejaculatory ducts are a continuation of the seminal vesicle, except that the outer circular muscle layer does not extend into the ducts (Nguyen et al, 1996). There are three distinct anatomic regions to the ejaculatory duct: the proximal, extraprostatic portion; the middle intraprostatic segment; and a short distal segment incorporating the lateral aspect of the verumontanum in the urethra (Nguyen et al, 1996) (Fig. 20–20). Although the ejaculatory duct contains an outer muscular layer in its extra- and intraprostatic segments, as the duct courses distally, the outer muscular layer dissipates, and **there is no valvelike, muscular "sphincter" at the ejaculatory duct orifice,** as was once thought (Nguyen et al, 1996) (Fig. 20–21). Instead, urinary reflux is prevented and ejaculatory continence is maintained by the acute angle of duct insertion into the urethra. The inner epithelial layer of the ejaculatory ducts is also complex and folded, and consists of simple and pseudostratified columnar cells. The ejaculatory ducts receive their blood supply from branches of the inferior vesicle artery and are innervated through the pelvic plexus.

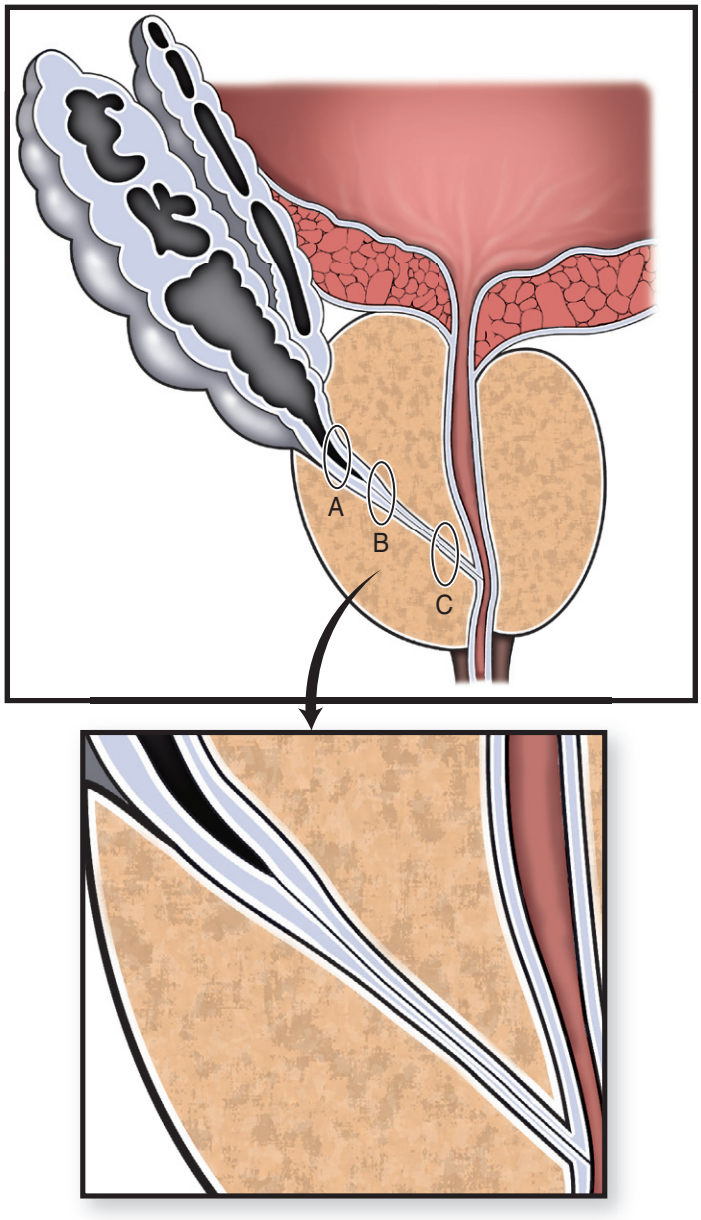


Figure 20–20. Schematic anatomy of the human ejaculatory duct complex. *A,* Proximal, *B,* intraprostatic or middle, and *C,* distal ejaculatory duct regions. The *inset* shows how the muscle layer thins out in the middle segment. (From Nguyen HT, Etzell J, Turek PJ, et al. Normal human ejaculatory duct anatomy: a study of cadaveric and surgical specimens. J Urol 1996;155:1639–42.)

Seminal Vesicle and Ejaculatory Duct–Unit Function

Animal studies suggest that the seminal vesicle and ejaculatory ducts are functionally similar to the bladder and urethra (Turek et al, 1998). **The seminal vesicle is a contractile, compliant, smooth muscular organ with dynamic properties analogous to those of the bladder, and the ejaculatory ducts serve as a urethra-like conduit. This theory allows the classification of ejaculatory duct obstruction into two types of disorders, analogous to bladder outlet obstruction: (1) obstruction resulting from physical blockage of the ducts, similar to bladder outlet obstruction, and (2) "functional" obstruction of the seminal vesicle, similar to voiding dysfunction due to bladder myopathy.** In addition, this has implications for the diagnosis of ejaculatory duct disorders because "static" anatomical imaging, such as transrectal ultrasonography, may not be sufficient to differentiate between these disorders, and medications and conditions (such as diabetes) might predispose the system to seminal vesicle dysfunction (Smith et al, 2008).

Seminal Vesicle Function

The seminal vesicles secrete a significant proportion (80%) of the seminal fluid, and these secretions are found in later fractions of the ejaculate, after the sperm-rich

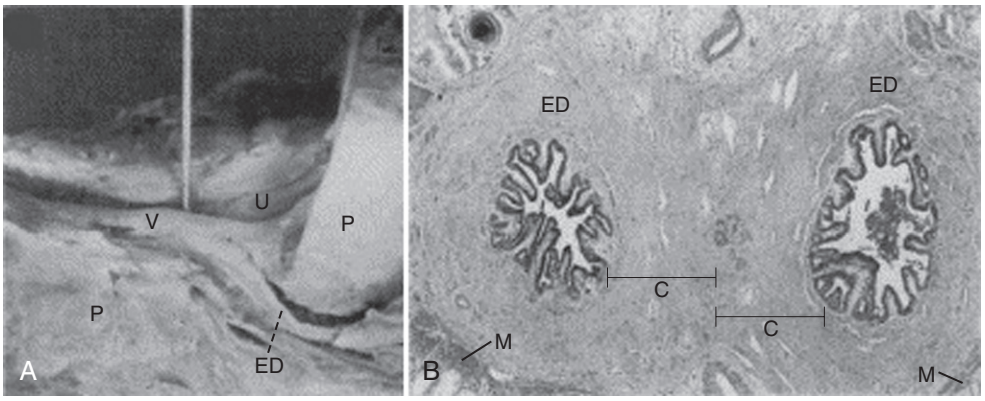


Figure 20–21. Human ejaculatory duct gross and microscopic anatomy from cadaver specimens. **A,** Shows sagital section through the midline with pin in ejaculatory duct orifice and ejaculatory duct (ED) and veru (V), urethra (U), and prostate (P) visible. **B,** Microphotograph of the paired ejaculatory ducts in the middle intraprostatic segment showing the thick collagenous layer (label C) surrounding the mucosa with a thin, outer muscular layer (label M). (From Nguyen HT, Etzell J, Turek PJ, et al. Normal human ejaculatory duct anatomy: a study of cadaveric and surgical specimens. J Urol 1996;155:1639–42.)

epididymal, and prostatic secretions. After ejaculation, sperm pass into and through the female cervical mucus and, subsequently, the uterus to enter the oviduct, where fertilization occurs. During residence in the female reproductive tract, sperm must undergo capacitation prior to oocyte fertilization. Capacitation occurs at different rates for individual sperm. During capacitation, the acrosome reaction and development of hyperactivated motility occurs (Yanagimachi, 1994). It is not clear if prostatic or seminal vesicle secretions contribute to capacitation.

In fact, the exact physiologic role of seminal vesicle fluid is not clear, although in rodents it functions as a plug or barrier that reduces the chances for sperm from a subsequent male to fertilize the oocyte. Before ejaculation, semen is a liquid, and after all components mix with the seminal vesicle secretions, it coagulates. The major component of the coagulum is **semenogelin I, a 52-kD protein expressed exclusively in the seminal vesicles** (Robert et al, 1999). **Through coagulating semen, seminal vesicle secretions may promote sperm motility, increase stability of sperm chromatin, and suppress immune activity in the female reproductive tract.** The best-elucidated function of human semen appears to be its ability to provide antioxidative protection to sperm. Semen is rich in antioxidant enzymes, including glutathione peroxidase, superoxide dismutase, and catalase (Yeung et al, 1998). In addition, the antioxidant molecules taurine, hypotaurine, and tyrosine are present in high concentrations (van Overveld et al, 2000). Lipofuscin granules from dead epithelial cells give seminal vesicle secretions a yellow-white color. In addition, seminal vesicle secretions are alkaline and contain fructose, mucus, vitamin C, flavins, phosphorylcholine, and prostaglandins. High fructose levels provide nutrient energy for the sperm when studied in vitro. The mixing of seminal vesicle with prostatic secretions results in human semen having a mildly alkaline pH. Acidic ejaculate (pH <7.2) is associated with blockage or absence of seminal vesicles (Turek, 2005).

Key Points: Vas Deferens, Seminal Vesicle, and Ejaculatory Ducts

- The vas deferens is of wolffian (mesonephric) duct origin and serves to transport sperm from the cauda epididymis to the ejaculatory duct during seminal emission.
- The seminal vesicle and ejaculatory duct–unit is analogous to the bladder and urethra, and is subject to both physical blockage and functional disorders that result in infertility.

SPERMATOZOA

Anatomy and Physiology

The human spermatozoon is approximately 60 μm in length and is divided into 3 morphological sections: head, neck, and tail (Fig. 20–22). The oval **sperm head,** about 4.5 μm long and 3 μm wide, contains a nucleus with highly compacted **chromatin,** and an **acrosome,** a membrane-bound organelle that harbors enzymes required for penetration of the outer vestments of the egg before fertilization (Yanagimachi, 1978). The **sperm neck** maintains the connection between the sperm head and tail. It consists of the **connecting piece** and **proximal centriole.** The **axonemal complex** extends from the proximal centriole through the sperm tail. The **tail** harbors the **midpiece, principle piece, and end piece** (Zamboni, 1992). The midpiece is 7 to 8 μm long and is the most proximal segment of the tail, terminating in the annulus. It contains the axoneme, which is the **9 + 2 microtubule arrangement,** and surrounding **outer dense fibers** (Fig. 20–23). It also contains the **mitochondrial sheath,** which is helically arranged around the outer dense fibers. The outer dense fibers, rich in disulfide bonds, are not contractile proteins but are thought to provide the sperm tail with the elastic rigidity necessary for progressive motility (Oko and Clermont, 1990). Similar in structure to the midpiece, the principal piece has several columns of outer dense fibers that are replaced by the fibrous sheath. The fibrous sheath consists of **longitudinal columns** and **transverse ribs.** The sperm terminates in the endpiece, the most distal segment of the sperm tail, and contains axonemal structures and the fibrous sheath. Except for the end-piece region, the sperm is enveloped by a highly specialized plasma membrane that regulates the transmembrane movement of ions and other molecules (Friend, 1989).

The spermatozoon is a remarkably complex metabolic and genetic machine. **The 75 sperm mitochondria that surround the axoneme contain enzymes required for oxidative metabolism and produce adenosine triphosphate (ATP), the primary energy molecule for the cell.**

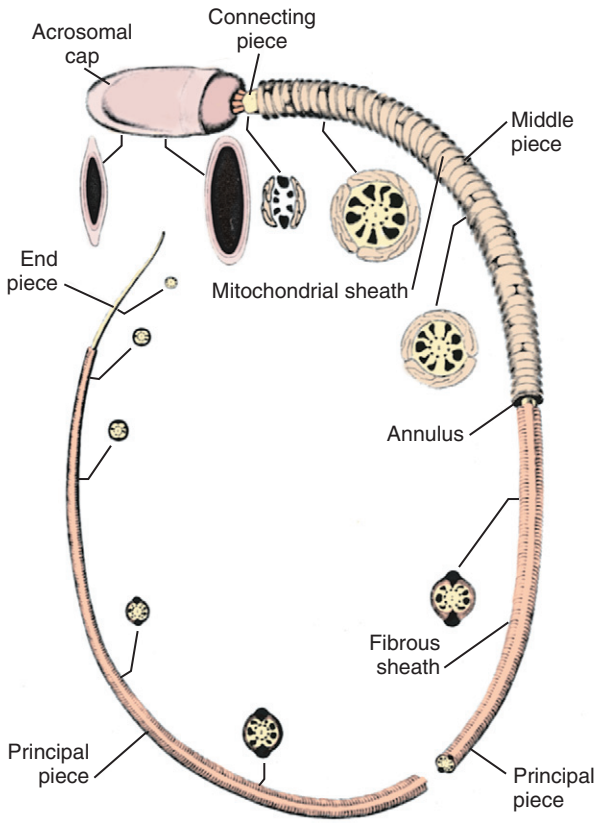


Figure 20–22. Diagram of a typical mammalian spermatozoon. The plasma membrane is omitted to illustrate the major cellular components. Cross-sectional insets show the orientation of the internal cell structures. (From Fawcett DW. The mammalian spermatozoon. Dev Biol 1975;44:394–436.)

Mitochondria are semiautonomous organelles that produce cellular energy and can also cause apoptotic cell death through the release of cytochrome *c*. Mitochondria are composed of outer and inner membranes. As an organelle, the mitochrondrion has two compartments: the space between the outer and inner membranes, the intermembrane space, and the space surrounded by the inner membrane, termed the matrix. The inner membrane forms deep folds into the matrix, called the cristae, which make the surface area of the inner membrane larger than that of the outer membrane. Five distinct respiratory chain complexes span the width of the inner membrane and are necessary for oxidative phosphorylation: the nicotinamide adenosine diphosphate (NADPH) dehydrogenase, succinate dehydrogenase, cytochrome *bc1*, cytochrome *c* oxidase, and ATP synthase complexes. Contained within the matrix are citric acid cycle, fatty acid and amino acid oxidative enzymes, newly made ATP, mitochondrial DNA (mtDNA), and ribosomes. From animal studies, it is clear that the plasma membrane covering the sperm-head region harbors specialized proteins that participate in sperm–egg interaction (Saling, 1989). Indeed, carbohydrate-binding proteins on the sperm membrane interact with the species-specific ZP3 protein in the egg zona pellucida, resulting first in sperm binding to the zona and, subsequently, to induction of the acrosome reaction (Shabanowitz, 1990). Another sperm membrane protein, PH30, is present on testicular sperm and is modified during sperm migration through the epididymis and function as a fusion protein between the sperm and egg membranes at fertilization (Primakoff, 1987; Blobel et al, 1990).

Physiologically, the axoneme is the true motor assembly and requires 200 to 300 proteins for proper function. Among these, the microtubules are the best-understood components. **Sperm microtubules are arranged in the classic "9 + 2" pattern of 9 outer doublets encircling an inner central doublet** (Fig. 20–23). The complex protein dynein extends from one microtubule doublet to the adjacent doublet, and forms both the inner and outer "arms" of the axoneme. **The sperm axoneme contains the enzymes and structural proteins necessary for the chemical transduction of ATP into mechanical movement and motility.** Dynein is large (2000 kD), Mg^{+}-stimulated, ATPase responsible for ATP-generated microtubule sliding that causes axonemal bending and, ultimately,

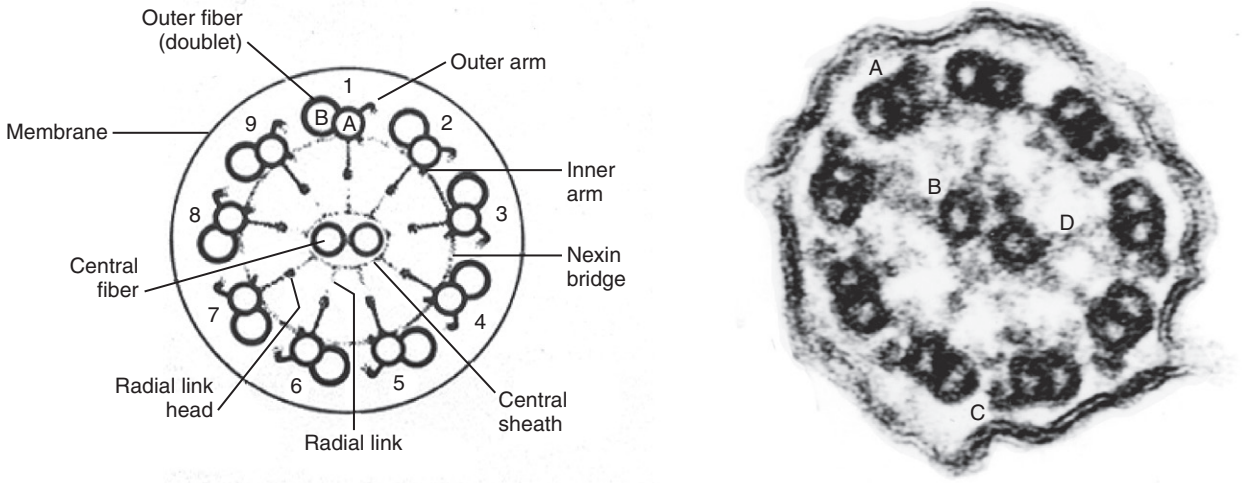


Figure 20–23. The "9 + 2" sperm axonemal structure. *Left:* schematic cross section of axoneme, demonstrating microtubule arrangement. *Right:* electron micrograph of axoneme. *(A)* outer doublet; *(B)* inner central doublet; *(C)* outer dynein arm; *(D)* radial link.

sperm flagellar movement. The dynein structure has 2 to 3 globular, outer (heavy) chain heads (500 kD) joined to a common stem. The heads control movement along the microtubules. The inner (light) chain arms (14 to 120 kD) are the primary effectors of movement and are associated with the radial spokes of the dynein assembly. Sperm with outer arm mutants have reduced motility, and those with inner arm mutants have no motility. Radial links or spokes connect a microtubule of each doublet to the central inner doublet and consist of a complex of proteins. The central inner doublet is surrounded by a ringlike helical sheath to which the radial links from the outer doublets are attached. Tektins are proteins associated with the outer microtubular doublets, and nexin links are proteins that connect the outer doublets to each other and maintain the cylindrical axonemal shape.

The human mitochondrial DNA (mtDNA) is distinct from the sperm nuclear DNA. It consists of a circular, histone-free chromosome of 16,569 bp of DNA arranged in a single heavy and single light strand. **MtDNA encodes 13 respiratory-chain-complex subunit proteins, 2 mitochondrial rRNAs, and 22 tRNAs used for protein synthesis.** These genes have no introns. Expression of mtDNA genes are regulated by strand-specific, but not gene-specific, promoters in response to activation of a transcription factor (mtTFA). MtDNA is also far more susceptible to mutations than is nuclear DNA (estimated 40 to 100 times higher). Reasons for this may include the fact that mitochondria are near respiratory-chain complexes and may be easily attacked by reactive oxygen species. **In addition, mtDNA is not coated with protective histones, and mitochondria have very limited DNA repair mechanisms** (Hirata et al, 2002). **The fact that mitochondria rapidly accumulate mutations suggests the necessity of degrading all paternal mtDNA in the fertilized egg.** This degradation is likely mediated by the small proteolytic polypeptide ubiquitin that regulates proteolysis in many tissues (Sutovsky et al, 1999).

The phenotype of defective sperm structure has been recognized as ciliary dyskinesia. Although infertility is the rule with ciliary dyskinesias, ejaculated sperm can be motile and sperm concentrations can be normal. With ICSI, clinical pregnancies and live births have been reported using affected sperm (Cayan et al, 2001). Because the inheritance is usually recessive, normal offspring are likely. Patients suspected of harboring sperm structural defects generally exhibit severely compromised sperm motility (<10%). Sperm electron microscopy can reveal ultrastructural or functional abnormalities of the sperm. Sperm structural abnormalities are currently categorized by Chemes (2000) as follows:

1. **Nonspecific flagellar anomalies.** The most frequent flagellar anomaly underlying severely low motility with a structural phenotype of random, heterogeneous, microtubular alterations. They are sometimes due to correctable disorders such as varicocele, reactive oxygen species, and gonadotoxin exposure. There is no evidence of familial occurrence.
2. **Dysplasia of the fibrous sheath.** This condition is a systematic sperm abnormality, usually associated with near-total or total immotility. It has a more homogenous and distinctive phenotype characterized by sperm fibrous sheath, axonemal, and periaxonemal distortions. A subset of these patients exhibits the classical ciliary dykinesias (formerly immotile cilia syndrome), in which sperm immotility is associated with respiratory disease and dextrocardia. There is a strong familial incidence of these conditions, suggesting that they are genetic in origin.

Key Points: Sperm

- Sperm are ciliated cells that possess a "9 + 2" axonemal structure that allows motility.
- It is estimated that 200 to 300 genes regulate sperm motility.
- Sperm motility defects, termed ciliary dyskinesias, are common and can be either correctable (nonspecific flagellar anomalies) or genetic (dysplasia of the fibrous sheath).
- Human sperm mitochondrial DNA (mtDNA) is a circular, histone- and intron-free DNA ring that encodes for respiratory-chain-complex proteins and is very susceptible to mutations.

SUMMARY

Spermatogenesis is a remarkably intricate and complex process that is driven by precisely regulated and pulsatile secretions of GnRH, LH, and FSH from the hypothalamic-pituitary-gonadal axis. Pertubations in this hormonal milieu are common causes of male infertility. Sperm production occurs in the testis, a specialized structure that functions optimally at 2° C to 4° C below body temperature and generates a mature human sperm in 64 days. Well-integrated cycles and waves of spermatogenesis ensure that human sperm production is constant at about 1200 sperm per second. Spermatogenesis is an androgen-dependent process that occurs with very high intratesticular levels of testosterone. The product of spermatogenesis, the spermatozoa, leave the testis as immotile cells with limited capacity to fertilize an oocyte. After epididymal transit, sperm are typically motile and capable of fertilization. During ejaculation, sperm are rapidly transported through the ejaculatory ducts into the urethra from the distal epididymis. The ejaculate itself supports sperm metabolism, motility, serves as an antioxidant, and serves as a barrier to exclude subsequent gamete deposits from gaining access to the egg.

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chapter
21

Male Infertility

Edmund Sabanegh, Jr., MD ● Ashok Agarwal, PhD

Introduction: Definition and Demographics of Infertility
History and Review of Systems
Physical Examination
Laboratory Evaluation of Male Infertility
Other Testing
Diagnostic and Treatment Categories of Male Infertility
Assisted Reproduction

INTRODUCTION: DEFINITION AND DEMOGRAPHICS OF INFERTILITY

Over the past 50 years, we have witnessed dramatic advances in the understanding and treatment of male fertility. The introduction of intracytoplasmic sperm injection (ICSI) in 1992 (Palermo et al, 1992), a technique of in-vitro fertilization using direct insertion of a single sperm into an egg, offered the ability to bypass even some of the most severe etiologies of male subfertility but raised a variety of cost and safety issues. Growing understanding of the genetics of fertility, environmental influences on gonadocytes, and the endocrine basis for germ cell development holds promise to allow more targeted diagnostic and therapeutic interventions. Unlike many other disease states, fertility represents a complex interaction between two individuals involving multiple organ systems. Attempts to isolate pathology to one gender are confounded by the fact that male fertility is not a clearly quantifiable parameter but is dependent on requirements of the individual female reproductive system. Older studies have related 20% of cases of infertility to purely male factor etiology, while an additional 30% to 40% involve both male and female factor pathology (Simmons, 1956). Newer studies have shown little change in this distribution with more than 50% attributable to male factor, despite advances in the diagnosis and management of infertility (Mosher and Pratt, 1991; Thonneau et al, 1991).

Knowledge of the inherent inefficiency of normal human reproduction is critical before we can define infertility. Studies of conception in normal couples reveal that 60% to 75% will conceive within 6 months of unprotected intercourse and 90% by 1 year (Tietze et al, 1950; Spira, 1986). On the basis of this, the classic definition of infertility became the absence of conception after 12 months of regular, unprotected intercourse, a definition supported by the Practice Committee of the American Society for Reproductive Medicine (ASRM). Because a small number of normal couples will conceive between 1 and 2 years, the World Health Organization (WHO) recommends 24 months of unprotected intercourse as the preferred definition of infertility (Rowe, 1993). Geographically diverse population-based studies have reported a remarkably consistent 15% to 20% incidence of infertility (WHO, 1991; Gunnell and Ewings, 1994; Philippov et al, 1998). Although the classic definition of infertility would suggest deferring medical assessment until 12 months of unprotected intercourse, we support performance of a basic, cost-effective evaluation of both partners at the time of presentation for evaluation. Current recommendations by the Practice Committees of the American Urological Association and the American Society for Reproductive Medicine (Male Infertility Best Practice Committee Report, 2006a, 2006b) recommend infertility evaluation before 1 year if (1) male infertility risk factors such as a history of bilateral cryptorchidism are known to be present, (2) female infertility risk factors including advanced female age (older than 35 years) are suspected, or (3) the couple questions the male partner's fertility potential. A timely but limited evaluation provides early identification and correction of factors that may reduce fertility, as well as reassurance in an emotionally difficult situation for couples. Alleviation of anxiety related to infertility may in itself provide therapeutic value.

Perhaps more than in many other medical assessments, evaluation of infertility requires a methodic approach involving a comprehensive medical history, review of systems, targeted physical examination, and basic laboratory tests. An effective initial approach should be rapid, cost-effective, and noninvasive. Concurrent basic evaluation of the female partner is prudent given the multifactorial etiology of infertility, as well as the potential need for assisted reproductive technologies (ARTs) to treat the male factor. Initial male factor evaluation may suggest the need for more advanced semen, genetic, endocrine, or radiologic tests to arrive at the correct diagnostic and treatment plan.

Whenever possible, treatment should involve correction of a specific problem rather than blanket application of costly assisted reproductive technologies. ART use for male factor infertility in the United States has been estimated to cost almost $18 billion dollars in 1 year alone (Meacham et al, 2007), underscoring the need for addressing the specific cause of male factor infertility. More importantly, ART application without attention to the male factor may mask potentially significant and even life-threatening conditions present in the infertile male, conditions that may occur in up to 1.3% of men and that would only have been diagnosed with a complete medical evaluation (Kolettis and Sabenegh, 2001). However, ART retains an important role in the management of male factor infertility, especially where no etiology for infertility can be identified or in the setting of noncorrectable causes. In

addition to assisted reproduction, donor sperm insemination and adoption remain excellent options for the management of noncorrectible infertility.

HISTORY AND REVIEW OF SYSTEMS

Successful diagnosis and treatment of infertility requires careful attention to obtaining a thorough history. A diverse variety of specific factors can affect subsequent fertility or sexual function (Table 21–1). Although focus may be on long-term factors that can affect fertility, human spermatogenesis is estimated to involve a 64-day cycle with an additional 5 to 10 days of epididymal transit time on the basis of radioisotope labeling studies (Clermont and Heller, 1963; Franca et al, 2005; Misell et al, 2006). Factors such as fever, illness, or drug use in the several months before semen testing should prompt repeat testing after an additional 3 months to rule out transient detrimental effects.

Table 21–1.

Pertinent History in Evaluation of the Infertile Male

- Infertility history
  - Duration
  - Prior conceptions
    - Current or previous partner
    - Outcome
  - Previous fertility evaluation and treatment
- Sexual history
  - Erectile function
  - Lubricants
  - Frequency/timing of intercourse
- Past history
  - Childhood
    - Cryptorchidism
    - Onset of puberty
    - Testicular pathology
      - Torsion
      - Trauma
    - Midline defects (cleft palate)
  - Medical
    - Diabetes mellitus
    - Neurologic disease
      - Spinal cord injury
      - Multiple sclerosis
    - Infection
      - Urinary infections
      - Sexually transmitted disease
      - Epididymitis/prostatitis
      - Tuberculosis
      - Mumps orchitis
      - Recent viral/febrile illness
    - Renal disease
    - Cancer
      - Chemotherapy/radiotherapy
  - Surgical
    - Orchidopexy
    - Retroperitoneal/pelvic surgery
    - Herniorrhaphy
    - Vasectomy
    - Bladder neck/prostatic surgery
  - Medications
  - Gonadotoxins
    - Environmental exposures (pesticides, heavy metals)
    - Radiation
    - Habits (tobacco, recreational drugs, anabolic steroids)
- Family history
  - Infertility
  - Cystic fibrosis
  - Androgen receptor deficiency

Reproductive history is of particular importance in the initial evaluation. Details regarding any prior conceptions the patient may have caused with his present or prior partner, duration of infertility, method of reproductive timing, and prior contraceptive history should be obtained. Primary infertility is defined as the failure to conceive at any time in the past with any prior partner, whereas secondary infertility indicates a prior conception with the current or previous partner. This simple classification can be helpful in narrowing the differential diagnoses because those with secondary infertility are presumed to have normal embryologic development of their reproductive tract and genetic complement.

The timing and frequency of intercourse are an important component of the reproductive history. In recent years, the ease and availability of ovulation predictor kits, which measure midcycle urinary luteinizing hormone (LH) surge as a predictor of impending ovulation, have allowed couples to approach reproductive timing in a more informed and effective fashion. However, many couples are not aware of the viability of spermatozoa within the female reproductive tract with sperm surviving between 2 and 5 days in favorable cervical mucus (Wilcox, 1995). This finding is the basis for the widely offered recommendation of intercourse frequency every 2 days near the time of ovulation, maximizing the chance that viable sperm are available to the oocyte (Tur-Kaspa et al, 1994). Intercourse that is too frequent does not allow replenishment of adequate numbers of spermatozoa within the epididymis, whereas infrequent intercourse may miss the potential window for fertilization. An assessment of erectile and ejaculatory function is also germane to the initial evaluation.

Use of vaginal lubricants is commonplace in reproductive-aged couples with almost one half of couples reporting intermittent use (Oberg et al, 2004). A number of commercially available lubricants that are not marketed as spermicidal agents have been shown to adversely affect sperm motility (Miller, 1994; Kutteh et al, 1996; Anderson et al, 1998) and sperm deoxyribonucleic acid (DNA) integrity (Agarwal et al, 2008). Although some lubricants such as vegetable oil, raw egg white, and Pre-Seed have minimal spermicidal effect (Goldenberg and White, 1975; Edvinsson et al, 1983; Agarwal et al, 2008), it remains optimal to avoid lubricant use if possible and to use minimal concentrations of the least toxic lubricant available, if required.

A variety of pediatric conditions including cryptorchidism, postpubertal mumps orchitis, and testicular torsion or trauma can have significant implications on eventual fertility. Although prepubertal mumps is unlikely to have detrimental effects on fertility, mumps occurring in the postpubertal timeframe is associated with unilateral or bilateral orchitis in up to 40% of children (Werner, 1950) with potentially devastating testicular damage. Testicular torsion or trauma can result in testicular atrophy, as well as the development of antisperm antibodies, which are detrimental to sperm function and motility (Bronson et al, 1984; Puri et al, 1985).

The timing of the onset of puberty may suggest underlying endocrinologic abnormalities. A history of delayed puberty, especially in conjunction with anosmia, is associated with the diagnosis of Kallmann syndrome, or primary hypogonadotropic hypogonadism. On the other hand, precocious puberty may be secondary to congenital adrenal hyperplasia, which may affect future fertility.

Prior scrotal, inguinal, or retroperitoneal surgeries can obstruct the ductal system or interfere with emission or ejaculation of

sperm. Classic retroperitoneal lymphadenectomy for testicular cancer frequently results in sympathetic nerve injury leading to anejaculation or retrograde ejaculation (Kedia et al, 1977). Fortunately, with modifications in the surgical template and intentional nerve sparing, ejaculation can be preserved in almost all patients with low-stage disease and in selected patients with more advanced disease (Donohue et al, 1990). Bladder neck surgery and transurethral resection of the prostate can lead to retrograde ejaculation due to bladder neck incompetence. In selected patients, transurethral incision of the prostate can allow preservation of antegrade ejaculation. Vasal injuries from inguinal surgery have seen resurgence with the popularity of polypropylene mesh hernia repairs, which can induce dense fibroblastic reactions leading to vasal obstruction (Shin, 2005).

Systemic diseases in adulthood can affect fertility through a number of different mechanisms. Diabetes mellitus, spinal cord injuries, and multiple sclerosis exert effects through impairment of both ejaculatory and erectile function (Sønksen and Biering-Sørenson, 1992; Sexton and Jarow, 1997). Diseases of the thyroid, both hyper and hypo function, affect both steroid hormone metabolism and sperm quality and have been associated with subfertility (Velazquez and Bellabarba, 1997; Abalovich et al, 1999; Krassas et al, 2002). Subclinical hypothyroidism does not produce significant seminal abnormalities (Trummer et al, 2001).

Neoplasms in general can induce marked impairment of spermatogenesis due to endocrine disturbances, malnutrition, hypermetabolism with associated fever, and immunologic factors (Costabile and Spevak, 1998; Wong et al, 2000). In addition to the global effects of malignancy on reproductive health, specific malignancies such as Hodgkin disease (HD) and testicular germ cell tumors produce significant direct gonadotoxic effects (Petersen et al, 1999; Rueffer et al, 2001). Pretreatment testicular dysfunction associated with HD has been postulated to be due to a variety of mechanisms including genetic abnormalities at the germ cell level, endocrinopathies, systemic release of cytokines injurious to both the seminiferous tubules and the Leydig cells, and negative local effects from intratesticular lymphatic tissue. Testicular tumors impair spermatogenesis by the destruction of surrounding tissue, local secretion of HCG and other paracrine factors, intrascrotal temperature elevation, and alterations in the local blood flow. Cancer treatments including chemotherapy and radiation produce direct toxicity on surviving germ cells, potentially depressing spermatogenic function for many years if recovery occurs at all (Nalesnik et al, 2004; Ståhl et al, 2006).

A detailed history should include a comprehensive assessment of medications, recreational, environmental, and occupational exposures that can impact fertility. Medications can impair fertility by direct toxic effects on gonadocytes, disturbance of the hypothalamic-pituitary-gonadal axis, disruption of ejaculatory or erectile function, and inhibition of libido. Antibiotics including nitrofurantoin, erythromycin, tetracycline, and gentamycin exhibit direct gonadotoxicity or impair sperm function. Androgen production is inhibited by spironolactone, ketoconazole, and cimetidine (Griffin and Wilson, 1991). Treatments for ulcerative colitis such as sulfazalazine are associated with reversible reductions in sperm concentration and motility (Toth, 1979). α Blockers, which are commonly used for treatment of benign prostatic hypertrophy and hypertension, are associated with retrograde ejaculation, an effect that may be more prominent with tamsulosin than with other selective α blockers (Giuliano, 2006). 5-α reductase inhibitors such as finasteride and dutasteride inhibit conversion of testosterone to the metabolically active dihydrotestosterone and are commonly used for treatment of benign prostatic hypertrophy. Use of these agents has been associated with reductions in semen volume, as well as erectile and ejaculatory dysfunction (Giuliano, 2006). Psychotherapeutic medications including the selective serotonin reuptake inhibitors (SSRI), monoamine oxidase inhibitors, phenothiazines, and lithium can suppress the hypothalamic-pituitary-gonadal axis, impair ejaculation and erectile function, and reduce libido (Nudell et al, 2002). Exogenous testosterone and steroid supplementation, whether medically prescribed or used for recreational purposes, can have the most profound detrimental effects on spermatogenesis of the medical agents. Androgenic agents induce hypogonadotropic hypogonadism leading to azoospermia, which can last 6 months or more after cessation of the supplements and, on occasion, may be irreversible (Sigman et al, 2006). Testosterone replacement therapy in hypogonadal men desiring fertility should be avoided, and alternate regimens such as antiestrogens (clomiphene citrate, tamoxiphene) should be considered instead. Recreational drugs have also been implicated as gonadotoxic agents. Marijuana use is associated with gynecomastia, reductions in serum testosterone, decreased sperm counts, and elevated seminal leukocytes (Harmon and Aliapoulios, 1972; Hembree et al, 1979; Close et al, 1990). Abnormal sperm morphology, decreased motility, and low sperm concentrations have been associated with cocaine use (Bracken et al, 1990; Hurd et al, 1992). Although long-term abuse of alcohol is associated with global suppression of the hypothalamic-pituitary gonadal axis and spermatogenesis, moderate intake is not associated with significant deterioration in fertility (Muthusami and Chinnaswammy, 2005).

Although the role of smoking in lung and heart diseases is widely established, the adverse effect of tobacco on male reproductive health is less well known by the general public. Smoking is associated with declines in basic semen parameters such as sperm concentration, viability, forward motility, and morphology (Vine et al, 1996; Künzle et al, 2003), as well as declines in sperm penetration ability and hence fertilization rates (Sofikitis et al, 1995). Defects in these parameters not only affect normal fecundity but also lower assisted reproduction success rates (Joesbury et al, 1998; Zitzmann et al, 2003).

The impacts of environmental and occupational exposures on spermatogenesis are more difficult to prove and quantify. Certain agents such as heavy metals, pesticides such as dibromochloropropane, organic solvents, and heat have been widely associated with gonadotoxicity (Lipshultz and Corriere, 1980; Moreira and Lipshultz, 2008). Industrial lead exposure exerts direct negative effects on both seminiferous tubules and the hypothalamic pituitary axis, resulting in asthenospermia, oligospermia, teratospermia, and ultimately reduced fertility (McGregor and Mason, 1990; Gennart et al, 1992; Shiau et al, 2004).

Inflammatory diseases can have profound effects on the patency of the genital tract and function of the spermatozoa. Infectious diseases such as prostatitis or sexually transmitted infections such as *Chlamydia* or *Neisseria gonorrhea* are associated with elevated seminal oxidative stress and leukocytospermia, resulting in abnormal bulk semen parameters, elevated sperm DNA fragmentation, and reduced fertility (Trum, 1998; Pasqualotto, 2000; Aitken et al, 2007). A history of bilateral epididymitis with subsequent azoospermia suggests the possibility of epididymal obstruction. Epididymal granuloma may result from noninfectious diseases such as sarcoidosis (Rao, 2009) or from the sequelae of an active tuberculosis infection. Epididymal sarcoidosis has been associated with azoospermia, which may be reversible with corticosteroid treatments (Svetec, 1998).

Questions regarding a family history of infertility are an underemphasized component of the initial assessment because of a misperception that genetic conditions that cause infertility are inherently nontransmissible. A family history of cystic fibrosis may suggest the diagnosis of congenital bilateral absence of the vas deferens (CBAVD) with its associated vasal, epididymal, and seminal vesicle anomalies. Abnormalities of the androgen receptors should be considered in the setting of a family history of intersex disorders. Today's widespread use of assisted reproductive technologies such as ICSI allow us to overcome subtle genetic abnormalities that may account for many cases of idiopathic male subfertility. With up to 2% to 4% of European and more than 1% of U.S. children born today (Wright et al, 2007) as a result of these technologies, we would expect the genetic causes of infertility to represent a growing etiology of infertility as these men attempt to conceive in the future, further reinforcing the importance of obtaining a comprehensive family history.

Finally, a complete history should also include an assessment of female factor fertility issues because almost two thirds of infertility can be attributed to the female side, either wholly or in combination with male factors. Failure to incorporate these considerations into the evaluation and management can result in ineffective and unnecessarily expensive treatment courses. Risk factors for female subfertility include but are not limited to advanced age, irregular menstrual cycles, and a history of pelvic pathology including endometriosis and pelvic infections. Fecundity begins to decline sharply after age 35 and is less than 5% by age 40 (Robins and Carson, 2008). Ovulatory dysfunction occurs in 40% of infertile women, accounting for the largest single cause of female infertility (Mosher and Pratt, 1991). A variety of tools are used to assess ovulation; these include basal body temperature charts, midluteal serum progresterone levels, endometrial biopsy, urinary LH prediction kits and transvaginal sonographic detection of ovarian follicles. Tests of ovarian reserve involve an assessment of remaining ovulatory capability and a de facto assessment of ovarian aging. Standard testing includes basal hormone measurements of follicle-stimulating hormone (FSH) and estradiol, as well as dynamic ovarian testing, which involves stimulation of ovulation using clomiphene citrate or gonadotropin (Hofmann et al, 1996). Abnormalities of uterine cavity or tubal anatomy occur in up to 25% of infertile women (Thonneau et al, 1991). Uterine and tubal patency can be assessed with hysterosalpingography (HSG) or laparoscopy with chromotubation. HSG testing involves transcervical injection of contrast material allowing assessment of intrauterine and tubal anatomy. In addition, a number of reports have suggested that the use of oil-based contrast materials may be therapeutic, in addition to the diagnostic value (Al-Fadhli et al, 2006; Luttjeboer et al, 2007). Laparoscopy allows confirmation of HSG findings by direct observation of free spill of contrast (methylene blue or indigo carmine introduced via cervix) and detection of other pathologies such as endometriosis, fibrial phimosis, or peritubular adhesions. At the time of laparoscopy, tubal reconstruction and surgical ablation of endometriosis may be undertaken.

PHYSICAL EXAMINATION

General Examination

Because fertility issues can be a reflection of the general health, the physical examination should be comprehensive with special attention to the genital examination. Body habitus provides clues to the adequacy of virilization with androgen deficiency suggested by decreased body hair, absence of temporal pattern balding, gynecomastia, and eunuchoid proportions. Abnormalities in these areas suggest possible endocrinopathies to include low serum testosterone, hyperprolactinemia, abnormalities in the estrogen to testosterone ratio, adrenal dysfunction, and genetic syndromes associated with subvirilization to include Klinefelter syndrome (KS). Low androgen levels at the time of puberty may cause disproportionately long extremities due to delayed closure of the epiphyseal plates. Palpation of the thyroid gland will occasionally disclose nodules suggesting hyperfunction or hypofunction, which can affect fertility. Hepatomegaly on abdominal examination raises suspicion for hepatic dysfunction, which may induce altered sex steroid metabolism.

Genital Examination

Genital examination starts with a careful examination of the phallus. Penile curvature, chordee, or hypospadias may interfere with semen deposition in the vaginal vault. A careful examination of the scrotal contents is the most critical part of the examination. The testes should be examined with the patient in both supine and standing positions in a warm room to assist relaxation of the cremasteric muscle. The entire testicular surface should be carefully palpated to assess consistency and rule out masses because infertility has been consistently established as a risk factor for testicular carcinoma (Kolettis and Sabanegh, 2001). Testicular size should be assessed with either an orchidometer, calipers, or sonographic measurement. Normal adult testicular measurements have been established to be at least 4 × 3 cm or 20 mL in volume (Charny, 1960). Because 85% of the testicular volume involves sperm production, decreased testicular size portends impaired spermatogenic potential (Lipshultz and Corriere, 1977). The epididymides should be carefully palpated for enlargement or induration, which can indicate downstream obstruction or inflammatory conditions such as epididymitis. Granulomatous changes of the epididymis have been associated with tuberculosis, bacile Calmette-Guerin (BCG) treatments, and sarcoidosis. Small cystic lesions of the epididymis are common and are usually spermatoceles, which are often nonobstructing. Papillary cystadenomas are less commonly seen and may present in conjunction with von Hippel-Lindau (VHL) disease.

Examination of the spermatic cord in the supine and standing position allows the detection of varicoceles, defined as abnormally dilated scrotal veins. Varicoceles are detected by palpation for assymetry of the spermatic cord, or an impulse, during the Valsalva maneuver. Gentle traction on the testis during this examination can be helpful in more difficult examinations such as patients with high riding testes or exaggerated cremasteric muscle response to Valsalva. Varicoceles are present in 15% of normal males, 19% to 41% in men presenting with primary infertility, and up to 81% of men with secondary infertility (Agarwal et al, 2007). Varicoceles are graded by size with small grade I varicoceles, which are detectable only during the Valsalva maneuver; moderate size grade II varicoceles, which can be palpated without Valsalva; and the large grade III varicoceles, which are visible through the scrotal skin and classically described as feeling like a "bag of worms." Due to the right-angle insertion of the left gonadal vein into the renal vein with the resulting turbulent flow, varicoceles are more prevalent on the left side with almost 90% presenting on the left side alone. Large unilateral right-side varicoceles and varicoceles that fail to decompress with the supine position suggest the possibility of retroperitoneal or caval pathology such as renal neoplasms and warrant dedicated imaging. A variety of ancillary procedures including ultrasonography with and without Doppler

examination, radionucleotide scans such as technetium 99m pyrophosphate, thermography, and venography have been used to corroborate clinical examination findings. In the absence of physical examination findings, varicoceles detected by these procedures alone are considered subclinical and not of clinical significance.

Careful palpation of the vas deferens is also a critical component of the spermatic cord assessment. Inability to palpate the vas deferens is consistent with unilateral or bilateral vasal agenesis and may have genetic or renal implications, which are discussed later in this chapter. Nodularity of the vas is also observed from prior infections such as tuberculosis. Vasal thickening is associated with prior scrotal surgery or downstream obstructions such as inguinal vasal obstruction, potentially from prior surgery or ejaculatory duct obstruction.

Finally, a rectal examination should be performed to evaluate prostatic anatomy for midline cysts such as müllerian duct cysts, which can obstruct the ejaculatory ducts. Prostatic induration or tenderness may be seen in acute or chronic prostatitis. Under normal conditions, the seminal vesicles may not be palpable but may be prominent in the setting of ejaculatory duct obstruction. After obtaining a thorough history and a comprehensive physical examination, the clinician has a number of available tools to further evaluate the infertile male, ranging from the basic semen analysis to testicular biopsy, as well as imaging studies.

LABORATORY EVALUATION OF MALE INFERTILITY

Semen Analysis

Semen analysis is one of the most important predictors in determining the fertility potential of a man. Appropriate laboratory testing of semen plays a key role in evaluation of men presenting with infertility. However, semen analysis does not allow for the definitive separation of patients into fertile and sterile, in case of azoospermia. It is important to understand that although the statistical chance of conception decreases as the semen quality declines, it does not reach zero. The basic semen testing is inexpensive and determines the quality and the quantity of the spermatozoa. More advanced testing is available to patients who suffer from idiopathic infertility in order to determine specific causes. The analysis of semen evaluates a variety of parameters including characteristics of spermatozoa, seminal plasma, and non–sperm cells.

Collection and Timing

Physicians should provide patients with standard guidelines for the collection of semen because suboptimal sperm collection remains a frequent cause of error in semen analysis. There should be 2 to 7 days of sexual abstinence before collection. Two separate samples at least 7 days apart should be analyzed (Rowe, 2000; Jeyendran, 2003). The duration of abstinence should be constant, if possible, because each additional day can add as much as 25% in sperm concentration (Carlsen et al, 2004). Lubricants should be avoided because they may interfere with motility results. Coitus interruptus should be discouraged because it often leads to inaccurate results (i.e., the first part of the ejaculate, which contains most of the sperm, may be lost).

Masturbation in a clinical setting is the recommended procedure. Collection is done in a private room in the same facility where the semen will be analyzed. The glans and the penis should be cleaned with a wet paper towel (soap should be avoided). Lubricant use is discouraged but, if necessary, should not be applied to the glans. A clean, sterile container should be used for specimen collection. The container should be provided by the laboratory to avoid contamination or spermicidal effects. The main advantages of this collection method are its simplicity, noninvasiveness, and inexpensiveness (Jeyendran, 2003).

Some men may not be able to achieve adequate erection and ejaculation. Assistance can be provided to them by oral medications such as phosphodiesterase type 5 inhibitors given 30 to 60 minutes before collection. Cavernosal and subcutaneous injections of prostaglandins are less popular but remain possible options for patients who have erectile dysfunction. Seminal pouches that do not contain any spermicides allow the patient to engage in sexual activity if he is incapable of or uncomfortable producing specimens by masturbation. Vacuum erection devices can also be used to obtain erection by creating a vacuum around the penis, generating a pressure differential that fills the corpora with blood. Vibratory stimulation may be used for patients who have suffered spinal cord injury, if the spinal cord lesion is T8 and above (Brown et al, 2006). Rectal probe electro-stimulation induces ejaculation by stimulation of the efferent fibers of the hypogastric plexus. Precautions for autonomic dysreflexia should be taken while doing these procedures because some patients with high spinal cord lesions (T6 and above) can have life-threatening hypertension (Jeyendran, 2003).

In order to allow liquefaction and mixing, semen is placed in a 37° C gently shaking incubator for 30 minutes. The semen sample should be examined within 1 hour of production and receipt in the laboratory. Some of the semen parameters can be affected by a delay in assessment. Motility decreases significantly after 2 hours and progressively diminishes afterwards as free radical activity increases.

The semen analysis characteristics can be classified into two groups: macroscopic and microscopic.

Macroscopic Assessment

The five macroscopic measurements in a standard sperm analysis have remained fairly constant, with the normal values remaining relatively unchanged since the inception of the semen analysis in the 1950s (Table 21–2). Normal human semen is an off-white to grayish-yellow opalescent fluid. In event of urine contamination, the semen sample has a yellow discoloration. The semen may appear pink in patients with urethral bleeding and yellowish in jaundice patients. During the time of ejaculation, the spermatozoa are suspended in the secretions of prostate, seminal vesicles, bulbo-urethral glands, and other accessory glands that form a coagulum. The specimen usually liquefies within 30 minutes. However, semen obtained from patients with congenital bilateral absence of the vas usually does not form a coagulum and is acidic. Liquefaction is aided by the proteolytic enzyme fibrinolysin, secreted by the prostate. Improper or prolonged liquefaction indicates an ejaculatory duct obstruction or poor prostatic secretion. Viscosity and nonliquefaction are two different phenomena often confused. Viscosity relates to the fluid nature of the sample. It is measured by dropping the semen sample into a container using a pipette and observing the length of the thread formed. Increased viscosity is often associated with infertility because it is known to impair sperm movement. Semen samples that are highly viscous can be treated with enzymes such as trypsin before they are processed for therapeutic purposes. Measurement of pH is a standard component of semen analysis and is largely determined by the

Table 21–2.

Macroscopic Features of Semen Analysis

PARAMETERS	NORMAL VALUES	ABNORMALITIES	CLINICAL SIGNIFICANCE
Ph	7.8	Acidic: <6.5-7	With low volume and noncoagulation: congenital bilateral absence of vas deferens Ejaculatory duct obstruction Partial retrograde ejaculation
Coagulation/ liquefaction	Coagulates and liquefies within 20 minutes at room temperature of 37° C	No coagulation Prolonged liquefaction	Congenital absence of the seminal vesicles Poor prostatic secretions
Color	Whitish-gray; pearl-white	Yellowish color Reddish brown	Jaundice, carotenemia, drugs Haemato-spermia secondary to urethral bleeding or inflammation of the seminal vesicles, exclude genitourinary tumors
Viscosity	4-mm threading	>6 mm No threading	Important when associated with low motility
Volume	2-4 mL	0 (aspermia) <2 mL (hypospermia) >4 mL	Retrograde ejaculation Incomplete collection Partial retrograde ejaculation Short duration of sexual abstinence Prolonged sexual abstinence

secretions from the seminal vesicles and the prostate. The normal range of pH has been defined as 7.2 to 8.0. Because the secretions of seminal vesicles are alkaline, acidic pH indicates congenital absence of the vas with the associated seminal vesicle hypoplasia seen in azoospermic patients (WHO, 1999).

Microscopic Assessment

Sperm Agglutination. The microscopic examination starts with the creation of a wet smear by placing a drop of semen on a slide covered with a cover slip and observing it under 1000× magnification. Sperm agglutination, sperm presence, and subjective motility can be assessed by this method. Sperm adhesion to nonsperm elements (nonspecific agglutination) may indicate accessory gland infection. Sperm-to-sperm agglutination (site-specific agglutination) can be secondary to antisperm antibodies; however, it should be kept in mind that a small degree of agglutination is normal (WHO, 1999). When agglutination is observed, semen cultures and antibody assessment should be performed.

Count and Concentration. Assessment of sperm concentration (number of sperm per milliliter) and sperm count (number of sperm per ejaculate) is conducted after liquefaction. Multiple counting chambers are used for sperm count determination where sperm are counted within a grid pattern. The normal sperm concentration is reported as greater than or equal to 20 million sperm/mL. Attention should be given to collection problems in order to rule out incomplete collection or a short abstinence period before starting evaluation of oligospermia (<20 million sperm/mL). Azoospermia (absence of sperm) may be the result of abnormal spermatogenesis, ejaculatory dysfunction, or obstruction. These specimens should be centrifuged and the pellet examined for the presence of any sperm. Polyspermia (abnormally elevated sperm concentration), although rare, may be caused by a long period of abstinence and is often associated with sperm of poor quality.

When oligospermia is reported, the levels of motility and morphology become especially important. Total motile sperm counts guide decisions on appropriate therapies including the use of ARTs. In cases of azoospermia and severe oligospermia, hormonal evaluation (FSH and testosterone) should be requested. Karyotyping and Y microdeletion may provide valuable information regarding the etiology of the patient's abnormal semen parameters and important information if in-vitro fertilization (IVF) is being entertained as a treatment option. Foci of microdeletions in the Y chromosome are associated with impaired spermatogenesis and, depending on their location, may predict poor sperm retrieval even with testicular biopsy. Karyotyping may also detect autosomal or X-linked genetic aberrations causing infertility. Knowledge of the chromosome status is important because male offspring conceived with intracytoplasmic sperm insemination (ICSI) or even natural conception most likely will inherit the same microdeletion (Krausz et al, 2000).

Motility. Motility is recognized as the most important predictor of the functional aspect of spermatozoa. Sperm motility is a reflection of the normal development of the axoneme and the maturation that it undergoes within the epididymis. This parameter is subject to significant potential for technical mistakes in the laboratory. The method most commonly employed by laboratories is the simple estimation of the motility of sperm on several fields. This subjective assessment is prone to inaccuracy. Moreover, in-vitro motility of sperm may not reflect the true motility within the female reproductive tract. The sperm motility is graded according to the WHO as follows: A—Rapid forward progress motility; B—Slow or sluggish progressive motility; C—Nonprogressive motility; and D—Immotility. The cutoff value for normal is 50% grade A+B or 25% grade A motility (Rowe, 2000). In addition to organic causes, asthenospermia (sperm motility less than the WHO cutoff levels) can also be artifactual when spermicides, lubricants, or rubber condoms are used. Occasional clumps of agglutinated sperm are of no consequence. However, more than 10% to 15% of clumping of spermatozoa is indicative of antisperm antibodies (ASAs). ASA is known to reduce sperm motility and cause a peculiar shaking pattern that prevents spermatozoa from penetrating through the cervical mucus. ASA testing must be performed to rule out the presence of antibodies. Other potential causes of asthenospermia include prolonged abstinence periods, genital tract infection, partial ductal obstruction, and varicocele. Loss of motility in all spermatozoa or less than 5% to 10% motility can be caused by ultrastructural defects such as absence of axonemal dynein arms or dead sperm (necrospermia) (McLachlan, 2003).

Morphology. Sperm morphology is the most subjective and most difficult-to-standardize semen parameter. Accurate

assessment of morphology is critical in the evaluation of an infertile male because it can be a significant predictor of pregnancy. Normal sperm possess an oval head with a well-defined acrosomal region composing 40% to 70% of the head area. The dimensions of the head are 4 to 5.5 µm in length and 2.5 to 3.5 µm in width. The normal sperm are free from head, midpiece, or tail defects. Head defects include microcephalic head (approximately half the size of a normal sperm head), megalocephalic head (one-and-a-half times the size of a normal sperm head), tapered head, round sperm (missing acrosome), and bicephalic or multicephalic head. Neck defects include no tail or improper tail insertions. Midpiece defects comprise elongated, distended, thin, or bent midpieces. Some of the tail defects commonly noted are short, multiple, bent, or broken tails. One common defect includes coiled tail, which is indicative of osmotic stress (McLachlan, 2003).

Sperm morphology is expressed as percentage of abnormal forms present in the semen. The two most common classifications used for the assessment of sperm morphology are the WHO criteria and Kruger's strict criteria (Table 21–3). When correctable causes of male infertility are not identified, couples with teratozoospermia (<15% normal morphology by WHO method) may be directed to proceed with IVF and ICSI as compared with intrauterine insemination (IUI). Teratozoospermia may occur due to several factors such as fever, varicocele, and stress. Some drugs that affect spermatogenesis are also known to cause morphologic abnormalities. With the advent of ICSI, which requires only one morphologically and functionally normal spermatozoa to fertilize an oocyte, morphologic assessment is losing its significance (Zinaman, 2000).

Viability. When the motility is reported as less than 5% to 10%, viability testing is recommended because profoundly low motility may indicate dead sperm or necrospermia (McLachlan, 2003). The most common viability assessment involves staining with Eosin Y followed by counter staining with Nigrosin. The viable sperm with its intact cell membrane will not take up the dye and will remain unstained. This test will differentiate necrospermia from immotile sperm secondary to ultrastructural defects such as in Kartagener syndrome and primary cilia dyskinesia.

Hypo-osmotic swelling test (HOST) is an alternative method to assess sperm viability. It is based on the principle that viable sperm have intact cell membranes. Exposure of the sperm to hypo-osmotic fluid will cause water to flow into the viable cells seen as swelling of the cytoplasmic space and curling of the sperm tail. Nonviable sperm with nonfunctional cell membranes will not exhibit this effect because they cannot maintain an osmotic gradient. This reproducible and relatively inexpensive test aids in selection of viable sperm for use in IVF or ICSI, especially when no motile sperm are seen in the cryopreserved specimens (Check, 2002).

Nonsperm Cells. Several nonsperm elements noted on seminal microscopic examination are immature germ cells, epithelial cell, and leukocytes (Branigan et al, 1995; Fedder, 1996). Epithelial cells when present in high numbers are indicative of poor collection. Leukocytes are the most significant nonsperm cellular elements in the semen and are a frequent finding in patients who have unexplained infertility (Branigan et al, 1995). However, in the initial microscopic analysis, the immature spermatozoa may be confused with leukocytes. To confirm the presence of leukocytes, additional testing is therefore required when there are greater than five round cells per high-power field (HPF). Immunocytochemistry is the procedure of choice, but given its expense, it is not widely used in most laboratories. The Endtz test is a reliable alternative because it allows accurate identification of leukocytes that contain enzymes that will react with peroxide and can be visualized with the orthotoluidine dye (Shekarriz et al, 1995). Initially considered solely as a marker of genital tract infection, contemporary research has shown that leukocytes can be present in the absence of other signs of infection or immune response (Lackner et al, 2006) and that they have intimate links with reactive oxygen species (ROS) (Aitken et al, 1994; Sharma et al, 2001; Saleh et al, 2002; Lackner et al, 2006). The WHO has defined leukocytospermia as levels above 1×10^6 WBC/mL. Studies have shown, however, that ROS levels are elevated even at WBC counts of less than 0.2×10^6/mL, suggesting that much lower levels of leukocytes are pathologic (Sharma et al, 2001; Athayde et al, 2007). In a 12-month follow-up, men who had a negative Endtz test (zero) had a 23.7% chance of initiating pregnancy, whereas leukocytes levels of less than 1×10^6/mL lowered the chances to 15.5% (Athayde et al, 2007). In many andrology laboratories, leukocytospermia

Table 21–3.
Sperm Morphology Classification

	WORLD HEALTH ORGANIZATION 3RD	STRICT WORLD HEALTH ORGANIZATION 4TH (KRUGER)
Normal reference range	>30%	>14%
Head		
Shape	Oval	Oval, smooth borders
Acrosome	40%-70% of head surface	40%-70% head surface
Size	4-5.5 mm length 2.5-3.5 mm width Length/width 1.5-1.75	3-5 mm length 2-3 mm width
Vacuoles	<20% head area	Up to 4
Midpiece		
Shape	Straight regular outlined Axially arched	Slender, straight, regular outline Axially arched
Size	<⅓ of head area	<1 mm wide Length 1.5 × head
Cytoplasmic droplet	<⅓ of head area	<½ of head area
Tail		
Appearance	Slender, uncoiled	Uniform, uncoiled
Width		Thinner than midpiece
Length	>45 mm	10 × head

determination still has to be requested separately. However, its significance and the ease of determination should place this test among the standard testing that accompanies a basic semen analysis. When leukocytospermia is identified, semen cultures should be performed. Furthermore, red blood cells (RBCs) are also often present in semen. Although small amounts are usually a normal finding, they can be indicative of infection, inflammation, ductal obstruction, or rarely vascular abnormalities.

Computer-Assisted Sperm Analysis

Computer-assisted sperm analysis (CASA) is a semiautomated technique that provides data on sperm density, motility, straight-line and curvilinear velocity, linearity, average path velocity, amplitude of lateral head displacement, flagellar beat frequency, and hyperactivation. It has two distinct advantages over traditional manual analyses: high precision and quantitative assessment of sperm kinematics. Sperm concentration, samplepreparation, and frame rate can, however, affect accuracy of the CASA (Mortimer, 1994). The use of some stains has also affected the accuracy of determining the sperm morphology. Although this technology has theoretic advantages, it has not translated into benefits in clinical practice. This test requires expensive equipment and still requires the active participation of a technician. Therefore at present, these machines are found commonly in andrology laboratories, not in general pathology laboratories, where most of the initial semen analyses are analyzed (Amann and Katz, 2004). Presently, the most important role of CASA is to provide standardized aids in quality control and quality assurance in andrology laboratories, as the emerging use of ICSI has diminished the role of motility assessment in sperm selection (Amann and Katz, 2004).

Limitations of Semen Analysis

The true litmus test for male fertility remains the ability to cause pregnancy in vivo. Although the semen analysis is used as a surrogate measure of a man's fertility potential, it is not a direct measure by any means. Clinical research has shown that normal semen analysis may not reflect defects in sperm function (idiopathic infertility), and men with poor sperm parameters still may cause spontaneous pregnancies. Only 50% of infertile men have recognizable causes detectable by the basic semen analysis (MacLachlan, 2003). The presence of several criteria further reinforces the emerging opinion that the current standards do not reflect the true fertility potential of subjects. The current normal values fail to satisfy clinical and statistical standards (McLachlan, 2003; Nallella et al, 2006) and pose the risk of misclassifying a subject's true fertility status. In fact, 20% of 18-year-olds would be classified as subfertile using the WHO cutoff of 20×10^6 sperm/mL (Andersen et al, 2000). Studies on semen donors with known fertility status have revealed a significant overlap in the sperm characteristics between fertile and subfertile men (Li et al, 2006; Nallella et al, 2006). Guzick and colleagues (2001) in a study of 1461 men found different cutoff levels in sperm concentration ($<13.5 \times 10^6$ in subfertile and 48×10^6 in fertile men), percent motility (<32% in subfertile and >63% in fertile men), and normal morphology (<9% in subfertile and >12% in fertile men). Nallella and colleagues in 2006 did a similar study ($n = 572$) and used the WHO and Tygerberg criteria on subjects with known fertility. They noted that there is low sensitivity (0.48) in detecting subfertile subjects using WHO reference values for sperm concentration and low sensitivity (0.83) using Tygerberg criteria for percentage of normal morphology. Among the variables, motility had the least overlap range and gave the best prediction of the subject's fertility potential. This is in contrast with the earlier study by Guzick and colleagues, where morphology was reported to provide the highest discriminating power in detecting subfertility among all the semen variables. Clearly, each variable alone is neither a powerful sole discriminator nor a predictor of fertility status, and they must be considered in the context of other parameters and the clinical setting. There remains a need for further studies in larger populations and different demographics before a consensus can be reached on the necessity of resetting current values to increase the predictiveness and utility of the semen analysis (Table 21–4).

Sperm Function Assessment

Sperm-Mucus Interaction/Postcoital Test

Cervical mucus is a heterogenous fluid that is composed of 90% water. In order to reach the site of fertilization, the spermatozoon must be able to successfully traverse the cervix and the cervical mucus. In-vitro penetration of spermatozoa through cervical mucus is comparable to in-vivo conditions. The cervical mucus is shown to demonstrate cyclical changes in consistency and to be highly receptive around the time of ovulation. Increase in penetrability is often observed one day before the LH surge. Cervical mucus has been shown to protect the spermatozoa from the hostile environment of the vagina. The penetrability of the spermatozoa through the cervical mucus can be detected by the cervical mucus migration assay. Some methods by which migration can be detected include the postcoital test (PCT). This test can assess cervical environment as a cause of infertility. Accurate timing is crucial because it must be conducted when the cervical mucus is thin and clear just before ovulation. In this test, cervical mucus is examined 2 to 8 hours after normal intercourse. Progressively motile sperm greater than 10 to 20 per HPF is designated as normal. Practical guidelines of the American Society of Reproductive Medicine recommend PCT in the setting of hyperviscous semen, unexplained infertility, or low-volume semen with normal sperm count (Van der Steeg et al, 2004). Medical history and semen analysis can predict PCT results in half of the infertile couples. Poor-quality semen most likely will have poor PCT. Therefore it is not recommended routinely for men who have abnormal semen analyses. Couples who show defective sperm mucus interaction may be advised to proceed with IUI because additional tests are unlikely to affect the management (Guzick et al, 2001). However, abnormal PCT may result from inappropriate timing of the test. Other causes of abnormal PCT include anatomic abnormalities, semen or cervical mucus antisperm antibodies, inappropriately performed intercourse, and abnormal semen. Persistently abnormal PCT in the presence of reasonably good semen parameters should indicate poor cervical mucus quality. The finding of good-quality mucus with nonmotile spermatozoa or immobilized

Table 21–4.

Characteristics of Normal Semen (World Health Organization, 1999)

Color	White, opalescent
Specific gravity	1.028
pH	7.35-7.50
Volume	2-6 mL
Count	2×10^6 spermatozoa/mL or more
Motility	≥50% motile (grades A + B) or 25% with progressive motility (grade A)
Morphology	>30% sperm with normal morphology
Viability	≥50% viable sperm
Pus cells	$<1 \times 10^6$/mL of semen

sperm demonstrating shaking motion should lead to the evaluation of both partners for the presence of antisperm antibodies. Although it has fallen out of favor, this test may be useful in patients who are unable or unwilling to produce an ejaculate.

Acrosome Reaction

The Acrosome is a membrane-bound organelle that covers the anterior two thirds of the sperm head. Acrosome reaction is an important prerequisite for successful fertilization. It is an exocytotic event that involves fusion of outer acrosomal membrane and sperm plasma membrane, which enables the exposure of acrosomal contents through the formation of vesicles. The two important acrosomal enzymes that are required to digest the oocyte cumulus cells and zona pellucida include acrosin and hyaluronidase. Acrosome reaction testing is not widely practiced in laboratories and only remains a research interest. However, this test may be recommended in cases of profound abnormalities of head morphology or in the setting of unexplained fertility in patients with poor IVF pregnancy rates. Normal semen samples demonstrate spontaneous acrosome reaction rates of less than 5% and induced acrosome reaction rates of 15% to 40%. Infertile populations have shown high spontaneous rates of acrosome-reacted sperm and low rates of induced acrosome reactions. Although not widely practiced due to its cost and labor, the structure of the acrosome can be studied under transmission electron microscopy. Other techniques such as fluorescence microscopy and beads coated with antiacrosomal antibodies have been developed, but these tests are also not readily available in standard laboratories.

Sperm Penetration Assays/Sperm Zona Binding Tests

The sperm penetration assay (SPA) or the hamster egg penetration assay (HEPT) determines the functional capacity of the spermatozoa necessary to fertilize an oocyte. It is based on the principle that normal spermatozoa can bind and penetrate the oocyte membrane, which is a prerequisite for the fusion of sperm and the oocyte. Zona pellucida is the outermost layer protecting the cytoplasm of the oocyte. It plays an important role in the fertilization process and is shown to be the only physiologic inducer of acrosome reaction. Sperm binds to the species-specific receptor, ZP3, which is found on the zona pellucida of the oocyte. The zona-free hamster oocytes, in which the zona pellucida is stripped, are used to allow cross-species fertilization. Human sperm penetration assay with zona-free hamster eggs determines the ability of sperm to successfully undergo capacitation, acrosome reaction, membrane fusion with oocytes, and chromatin decondensation. The assay is performed by incubating zona-free hamster oocytes in sperm droplets for 1 to 2 hours. The oocytes are examined microscopically for sperm penetration. Penetrations are indicated by swollen sperm heads within the oocyte cytoplasm. Normally, 10% to 30% of ova are penetrated (WHO, 1999). Oligozoospermic and severely teratospermic men have a higher number of defective sperm-zona pellucida interactions, which may account for their low fertility potential in both spontaneous and IVF pregnancies (Liu and Baker, 2004). Despite its low predictive power, SPA is correlated positively with spontaneous pregnancy outcomes (Corson et al, 1988). Sperm capacitation index (SCI) is a variant of the SPA test, assessing the mean number of penetrations per ovum. ICSI has been recommended for couples with an SCI less than 5 instead of standard IVF procedures (Ombelet et al, 1997). Compared with SPA, the zona binding test uses oocytes that failed to fertilize in IVF clinics. The need for human oocyte supply, however, remains a limitation to the use of this test.

Advanced Semen Testing

Antisperm Antibody Testing

The tight Sertoli-cell junctions provide the testis with a barrier that prevents the immune system from coming in contact with the post-meiotic germ cells. However, in certain conditions such as testicular torsion, vasectomy, and testicular trauma, this unique barrier can be violated, resulting in an immune response to sperm, displayed as antisperm antibodies (ASABs). These antisperm antibodies can be several types—sperm agglutinating, sperm immobilizing, or spermotoxic. The sperm agglutinating type causes agglutination of spermatozoa, which reduces the availability of motile spermatozoa penetrating the cervical mucus. Sperm-immobilizing antibodies induce loss in motility of the sperm, which can be identified by the characteristic "shaking" pattern in motility on postcoital test. The spermotoxic type of ASAB causes a complement-dependent loss in viability of spermatozoa.

Approximately 10% of infertile men will present with ASA as compared with 2% of fertile men (Guzick et al, 2001). Sperm parameters are often normal in men with ASA (Munuce et al, 2000). Hence it has been suggested to be tested routinely in all men undergoing infertility work-ups (McLachlan, 2003). Excessive sperm agglutination or an abnormal PCT can suggest the presence of ASA.

The direct ASA test detects sperm-bound immunoglobulins. Indirect testing detects the biologic activity of circulating ASA. False positives can result from nonimmunologic factors (Francavilla et al, 2007). Because only antibodies present on the sperm surface are clinically significant, most investigators prefer direct assays that determine sperm-bound antibodies instead of indirect detection of serum antisperm antibodies. IgG-MAR (mixed antiglobulin reaction) and Sperm MAR are recommended screening tests that are economical and readily available. Immunobead Test (IBT), which measures IgG, IgA, and IgM, may be additionally recommended when either of the previous tests gives a positive result in order to determine if IgA are bound to sperm surface. Acceptable normal values by WHO (1992) standards include less than 10% (IgG MAR) or 20% (IBT) of spermatozoa with adherent particles.

Clinical implications of ASA on male infertility are varied. A weakly positive IgG MAR/IBT in men who have low motile sperm rules out immunologic factors, and no further testing is necessary (Francavilla et al, 2007). ASA are present in 34% to 74% of vasectomized men and persist in 38% to 60% after vasectomy reversal (Broderick et al, 1989; Francavilla et al, 2007). Routine ASA testing is not recommended in this setting because it is of uncertain significance and usually does not affect the decision to do a vasectomy reversal. There are conflicting reports regarding ASA levels after orchidopexy for cryptorchidism (Mirilas et al, 2003). In genitourinary infections, ASA is thought to be a consequence of the inflammatory process rather than cross reactivity to the microorganism (Francavilla et al, 2007).

The decision to proceed with IUI versus ICSI in immunologic infertility can be aided by a zona pellucida (ZP) test. If the sperm exhibit inability for ZP binding, ICSI is the procedure of choice. Presently, flow cytometry techniques are being developed to quantify ASA in individual spermatozoa (Shai et al, 2005). These techniques are also being explored to identify sperm surface antigens for possible immunocontraceptive development.

Electron Microscopy

Spermatozoa may test positive for viability even in the presence of ultrastructural defects. Ultrastructural details of the sperm can

only be seen under the electron microscope (EM). Patients who have low sperm motility (<5% to 10%) with high viability (as determined by HOST or Eosin-Nigrosin staining) and density may be appropriate candidates for EM assessment. Subfertile men may demonstrate more serrated and blurred circular sulcus, less intact acrosome membrane, a bigger proportion of the spermatic head, and more droplets attached to the acrosome membrane. Mitochondrial and microtubular defects that are not visible under the usual Papanicolaou smear can be detected.

Biochemical Tests

Acrosin is a serine protease-like enzyme that exhibits a lectin-like carbohydrate binding activity to the zona pellucida glycoproteins. Low acrosin activity has been associated with low sperm density, motility, and poor normal morphology (Xu and Zhan, 2006).

Zinc is necessary for chromatin stability and decondensation, as well as for head–tail detachment during fertilization. It is measured by colorimetric methods with a reference value of 13 mmoL per ejaculate (WHO, 1999). Reports on the effects of zinc in sperm function and semen parameters are quite conflicting. Mankad and colleagues (2006) reported positive correlations between seminal zinc levels, alpha glucosidase, and sperm count; however, there are other reports that showed no significant changes in sperm count and motility with variations in zinc concentration (Abou-Shakra et al, 1989; Lewis-Jones et al, 1996; Sorensen et al, 1999). Zinc levels in seminal plasma are decreased, but spermatozoal zinc levels are increased in asthenozoospermic and oligoasthenozoospermic men (Zhao and Xiong, 2005). A low zinc-to-calcium ratio has been shown to be associated with better motility than high ratio (Sorensen et al, 1999). However, dietary supplementation of zinc did not improve semen variables (Agarwal and Said, 2004).

The seminal vesicles contribute to the bulk of seminal fluid that serves as the transport medium for sperm and contribute to the nutrition in the form of fructose. There is a positive correlation between sperm motility and seminal fructose levels (Lewis-Jones, 1996). Low or absent fructose is seen in ductal obstruction and congenital conditions like CBAVD. Semen fructose testing may be requested when hypo-functioning seminal vesicles are suspected, although morphometric analysis of seminal vesicles using transrectal ultrasound (TRUS) is the recommended test nowadays.

L-carnitine is secreted by the epididymis and is concentrated in the seminal plasma at up to 10 times the serum levels. It has a role in sperm maturation. Low L-carnitine levels are found in oligoasthenozoospermic men (Agarwal and Said, 2004; Sigman et al, 2006). The levels of carnitine can possibly serve as indicators of the level of obstruction in the ductal system. Extremely low concentrations of L-carnitine are found in azoospermic men who have postepididymal obstructions, whereas normal levels are found in azoospermic men who have intratesticular obstructions (Agarwal and Said, 2004). Administration of L-carnitine supplements did not improve sperm density, but contrasting results have been reported for sperm motility changes (Sigman et al, 2006). L-carnitine determinations remain far from becoming mainstream tests in male infertility until significant well-designed studies are conducted.

Alpha glucosidase, tested by fluorimetric methods, has been used to distinguish nonobstructive from obstructive azoospermia. It is used as a specific marker for epididymal function and is believed to play a role in sperm maturation in the epididymis. A cutoff value of 12 mIU/mL distinguishes ductal obstruction from primary testicular failure (Comhaire et al, 2002). The usefulness of this test was questioned by Krause and Bohring (1999), but Comhaire and colleagues (2002), in their review, showed a strong association between α-glucosidase and semen parameters. The cutoff level had 95% specificity in identifying obstructive azoospermia. This suggests that the test can predict IUI response (higher pregnancy rate >78 U per ejaculate) because high levels indicate better zona-binding capacity (Comhaire et al, 2002). The presence of commercial test kits using colorimetric methods promises to make testing accessible and affordable.

Reactive Oxygen Species

Research conducted during the past decade has provided growing support for the concept that excessive production of reactive oxygen species (ROS) is related to abnormal semen parameters and sperm damage. Routine semen analysis remains the backbone of clinical evaluation in male infertility, and determining the levels and sources of excessive ROS generation in semen is currently not included in the routine evaluation of subfertile men. However, the diagnostic and prognostic capabilities of seminal oxidative stress measurement exceed the capabilities of conventional sperm quality tests. An oxidative stress test may accurately discriminate between fertile and infertile men and identify those with a clinical diagnosis of male factor infertility who are likely to initiate a pregnancy if they are followed over a period of time. In addition, such a test can help select subgroups of patients with infertility in which oxidative stress is an important factor and who may benefit from antioxidant supplementation. Although consensus is still required about the type and dosage of antioxidants to be used, rationale and evidence exist supporting their use in infertile men with elevated oxidative stress (Deepinder et al, 2008).

Currently, clinical practice as to the inclusion of ROS measurement is variable, primarily because of the lack of standardization of ROS analytic methods, equipment, and range of normal levels of ROS in semen. The evidence defining high ROS levels as a cause or an effect of abnormal semen parameters and sperm damage is still insufficient on both sides of the question. However, it has been reported that a high level of ROS is an independent marker of male factor infertility in leukocytospermic samples after adjustment for semen characteristics. This finding suggests that ROS may play an important role in the etiology of male factor infertility and encourages the use of ROS measurement as a diagnostic tool in clinical practice, particularly in cases of idiopathic infertility. Although numerous assays for ROS measurement have been introduced, the chemiluminescence assay, determining ROS levels in neat semen, has proven to be an accurate and reliable test for evaluating oxidative stress status. This technique accurately represents an individual's true in vivo oxidative stress status and overcomes the drawbacks of earlier methods that involve processing semen, a step that may generate ROS by itself. The ROS level for healthy donors with normal standard semen parameters is 1.5×10^4 cpm/20 million sperm/mL. Using this value as a cutoff, infertile men can be classified as either oxidative stress positive ($>1.5 \times 10^4$ cpm/20 million sperm/mL) or oxidative stress negative ($\leq 1.5 \times 10^4$ cpm/20 million sperm/mL), regardless of their clinical diagnosis or standard semen analysis results (Deepinder, et al, 2008).

Sperm DNA Damage

DNA fragmentation was initially described in 1993 and has since been researched as a test to aid fertility prediction in subfertile males. The spermatozoal chromatin is a tightly packed structure because of the disulfide cross linkages between protamines that allow compaction of the nuclear head and protect the DNA fragments from stress and breakage. DNA damage is multifactorial and theories on its etiology include protamine deficiency and mutations that may affect DNA packaging or compaction during spermiogenesis (Agarwal and Said, 2003). Various factors found to be

associated with increased sperm DNA damage include tobacco use, chemotherapy, testicular carcinoma, and other systemic cancers (Agarwal and Said, 2003). DNA damage is correlated positively with poor semen parameters, especially low sperm concentration and low sperm motility, leukocytospermia, and oxidative stress (Erenpreiss et al, 2002; Agarwal and Said, 2003; Zini and Libman, 2006). Approximately 8% of subfertile men who have normal semen parameters will have high abnormal DNA (Aitken et al, 1991).

Many tests of sperm DNA damage are now available (Table 21–5). The use of these tests has been driven largely by the growing use of assistive reproductive technologies and awareness that the integrity of the male genome plays an important role in IVF. Sperm DNA damage can be measured directly (fragmentation, oxidation) or indirectly (sperm chromatin compaction). Direct assessment of DNA damage can be obtained by means of single-cell gel electrophoresis assay or "comet" assay (electrophoresis causes DNA fragments to migrate away from the central DNA core, revealing a "comet"), terminal deoxynucleotidyl transferase-mediated dUTP-nick end-labeling or "TUNEL" assay (the ends of fragmented DNA are tagged), and liquid chromatography to measure DNA oxidation levels. DNA damage can also be assessed indirectly by means of sperm chromatin integrity assays and by evaluation of nuclear protein levels. Sperm chromatin integrity assays include slide-based sperm nuclear protein stains (e.g., aniline or toludine blue [detects histones], CMA3 [detects underprotamination]) and DNA stains (e.g., acridine orange [detects denatured or single-stranded DNA]). The sperm chromatin structure assay (SCSA) uses flow cytometry to estimate the percentage of spermatozoa with DNA denaturation (spermatozoa are stained with acridine orange). A cutoff rate of greater than 30% has been shown to be associated with a significant decrease in in-vivo fertilization rates (Evenson and Wixon, 2002). A DNA fragmentation index (DFI) of greater than 30% has a sensitivity of 15% and a specificity of 96%. Meta-analyses by Evenson and Wixon (2002) and Li and colleagues (2006) showed that couples are twice as likely to become pregnant with regular IVF methods if the DFI is less than 30%. Contrasting reports, however, have failed to show significant correlation between DNA damage and idiopathic infertility (Verit et al, 2006). In addition, significant intraindividual variation exists making conclusions using SCSA problematic (Erenpreiss et al, 2006). There is a higher rate of DNA damage in ejaculated or epididymal sperm than in intratesticular spermatozoa. Hence the use of intratesticular spermatozoa from high DFI men is recommended for ICSI (Steele et al, 1999; Greco et al, 2005). ICSI is advised when DFI is above cutoff levels. DNA fragmentation testing can help couples decide on what fertility modality and possible lifestyle modifications they can employ to increase their chances of conception.

Table 21–5.

Commonly Used Tests of Sperm DNA Damage

TEST	MEASURES	CHARACTERISTICS
Sperm chromatin structure assay	Susceptibility of sperm DNA to denaturation	Objective, flow cytometry–based, indirect assay, complex analysis, used clinically
Nuclear protein composition (by protein separation)	Sperm histone and protamine levels	Objective, gel electrophoresis assay, indirect assay, labor intensive
Sperm nuclear maturity test (by nuclear staining)	Chromatin compaction, protamine content	Simple, semiquantitative, slide-based, indirect assay
Comet assay (by single-cell gel electrophoresis)	Double-stranded DNA breaks (neutral assay)	Objective, quantitative, direct assay, complex image analysis
TUNEL assay	Double-stranded DNA breaks	Semiquantitative, direct assay, quantitative if flow cytometry based
DNA oxidation	8-hydroxy-2-deoxyguanosine	Quantitative, direct assay, labor intensive

Endocrine

Although an uncommon cause of male subfertility, up to 3% of infertile men will have an underlying endocrinopathy (Sigman et al, 1997). Although some authors recommend routine screening of the male hypothalamic-pituitary-gonadal axis in all patients, the consensus opinion favors endocrine evaluation in men with (1) an abnormally low sperm concentration, especially if less than 10 million/mL; (2) impaired sexual function; or (3) other clinical findings suggestive of endocrinopathy such as marked reduction in testicular size or gynecomastia (AUA/ASRM Practice Committee Recommendations, 2006).

Initial endocrine evaluation in those with indications for testing should include serum follicle-stimulating hormone (FSH) and morning serum testosterone measurements. Gonadotropins and testosterone are secreted in a pulsatile manner, and some advocate pooled specimens drawn at 15 minute intervals to increase accuracy, although most recommend screening with a single morning specimen. Morning specimens are preferred due to a normal physiologic decline in testosterone levels throughout the day. Table 21–6 demonstrates commonly observed endocrine patterns associated with various clinical diagnoses. Under normal conditions, FSH secretion is under negative feedback control via inhibin B, which is produced by the Sertoli cells (Fig. 21–1). Elevations in serum FSH are indicative of disturbances in spermatogenesis such as primary testicular failure (hypergonadotropic hypogonadism), although normal FSH levels do not rule out spermatogenic failure. Obstructive azoospermia is usually associated with normal gonadotropin and testosterone levels. Low serum testosterone levels may indicate hypogonadism of pituitary or hypothalamic origin, as well as primary testicular failure. If initial testing is abnormal, further endocrine testing should be obtained to include a repeated testosterone assay including free and total testosterone levels, serum luteinizing hormone (LH), and serum prolactin levels. Low FSH and LH levels indicate hypogonadotropic hypogonadism such as Kallman syndrome and warrant a complete pituitary hormonal assessment including thyroid stimulating hormone (TSH), adrenal corticotropic hormone (ACTH), and growth hormone assays. Direct measurement of serum inhibin levels may provide a more accurate assessment of spermatocytic health than FSH levels, although most find that the cost of this assay and lack of widespread availability limit its clinical utility (Sussman et al, 2008).

Hyperprolactinemia is usually associated with low serum testosterone often without associated increases in LH levels, suggesting that the hypothalamic-pituitary axis is unresponsive in the setting of elevated serum prolactin levels (Carter et al, 1978). Prolactin tests should be repeated due to marked physiologic variability in serum prolactin levels. Mild serum prolactin elevations (<50 ng/mL) may be seen with medications, stress, and renal insufficiency or may be idiopathic. However, if the prolactin level is persistently elevated, a pituitary tumor such as a prolactinoma should be ruled

Table 21–6.

Patterns of Endocrine Testing by Diagnosis

DIAGNOSIS	FSH (mIU/mL)	LH (mIU/mL)	TESTOSTERONE (ng/dL)
Normal	Normal	Normal	Normal
Obstruction	Normal	Normal	Normal
Primary Testicular Failure Histology			
Hypospermatogenesis	High	Normal or high	Normal or low
Germinal cell aplasia	Very high	High	Low
Maturation arrest	Normal	Normal	Normal
Klinefelter syndrome	Very high	High	Low
Hypogonadotropic Hypogonadism	Low	Low	Low

FSH, follicle-stimulating hormone; LH, luteinizing hormone.

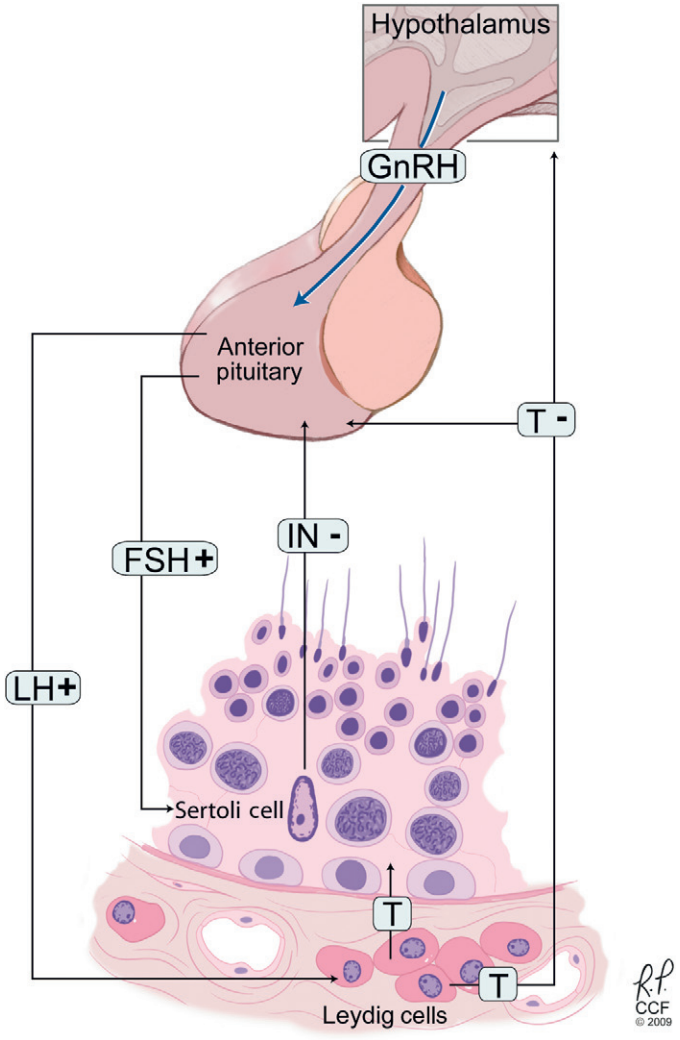


Figure 21–1. The hypothalamic-pituitary-testicular axis. Gonadotropin-releasing hormone (GnRH) is released from the hypothalamus, stimulating luteinizing hormone (LH) and follicle-stimulating hormone (FSH) release. The gonad is stimulated with FSH inducing stimulation of germinal cell epithelium and LH inducing testosterone production by the Leydig cells. Both testosterone (T) and inhibin (IN) downregulate gonadotropin release.

out with a focused neurologic examination including visual field testing and magnetic resonance imaging of the pituitary fossa.

Estrogen excess may be manifested by gynecomastia, decreased libido, erectile dysfunction, and low serum testosterone levels. Although elevated serum estradiol levels may be from exogenous

Table 21–7.

Factors That Impact Sex Hormone Binding Globulin Levels

INCREASE	DECREASE
Estrogen	Obesity
Medications	Medications
Anticonvulsants	Progestins
Thyroid replacement	Insulin
	Glucocorticoids
Hyperthyroidism	Hypothyroidism
Cirrhosis	Acromegaly
Aging	Nephrotic syndrome

intake, they are more commonly associated with morbid obesity due to the peripheral aromatization of testosterone to estradiol in adipose cells. Estradiol stimulates sex steroid hormone binding globulin (SHBG) production in the liver, which reduces levels of bioavailable testosterone. SHBG levels are also influenced by a number of other conditions (Table 21–7).

On rare occasions, endocrinopathies involving adrenal or thyroid functions may present with male subfertility. Patients with congenital adrenal hyperplasia (CAH) present with a history of precocious puberty and short stature due to premature closure of the epiphyseal plates. The common variant involving 21-hydroxy deficiency will have elevated serum levels of 17-hydroxyprogesterone and urinary pregnanetriol. Although CAH patients may retain fertility, many will have reduced testicular function due to suppression of gonadotropin levels from direct feedback inhibition of the pituitary from the excessive adrenal androgens.

Thyroid disease, both hyperfunction and hypofunction, may occasionally be associated with male factor infertility, although subclinical hypothyroidism does not impact semen parameters (Trummer et al, 2001). Thyroid function testing of the infertile male is not justified for routine screening but should be reserved for patients with clinical symptoms of thyroid dysfunction.

Genetic Testing

Genetic testing is important for establishment of the etiology of infertility, identification of potential future medical issues for the patient, prediction of therapeutic efficacy from various fertility interventions such as varicocele repair and sperm retrieval, and counseling information to couples regarding transmission risk to offspring. Clinically relevant genetic testing for the infertile male include karyotype and y-linked microdeletion assessment, which are used for evaluation of both nonobstructive azoospermia (NOA)

and severe oligospermia, as well as the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which is assessed in men with obstructive azoospermia due to CBAVD. Almost 7% of infertile men will have structural or numeric chromosomal abnormalities. The incidence of karyotype anomalies is inversely proportional to the sperm concentration with a prevalence of 10% to 15% in azoospermia, 5% in oligospermia, and less than 1% in patients with normal sperm counts (De Braekeleer and Dao, 1991; Samli et al, 2006). Microdeletions of the Y chromosome have been described in 10% to 15% of patients with severe oligospermia or azoospermia (Pryor et al, 1997). CFTR mutations have been identified in 88% of patients with CBAVD (Ratbi, 2007). Specific genetic syndromes are reviewed later in this chapter.

OTHER TESTING

Imaging Studies

Radiographic evaluation of the infertile male focuses on identification of patients with genital tract obstruction in the vas deferens or ejaculatory duct, as well as ruling out associated pathologies in certain individuals such as testicular masses or renal anomalies. The tests described here are not required in most individuals but should be used judiciously in those with appropriate indications.

Transrectal Ultrasonography

TRUS provides excellent definition of the prostate, seminal vesicles, ampulla of the vas deferens, and the ejaculatory ducts. TRUS is primarily employed to examine patients suspected to have ejaculatory duct obstruction (EDO). These patients usually have low-volume azoospermia (volume <1 mL) with acidic pH and negative semen fructose. TRUS typically employs the 5- to 7-MHz endocavitary probe with scanning in both the longitudinal and transverse planes. Careful examination of verumontanum may identify midline prostatic cysts such as müllerian or wolffian duct cysts or stones obstructing the ejaculatory duct (Fig. 21–2). Often the ejaculatory duct may not be well visualized, but dilation of the seminal vesicles serves as a de facto sign of ejaculatory duct obstruction. Although not always present with ejaculatory duct obstruction, seminal vesicle width in excess of at least 12 to 15 mm or ejaculatory duct diameter greater than 2.3 mm is considered suggestive of obstruction (Carter et al, 1989; Vazquez-Levin et al, 1994; Smith et al, 2008).

Seminal vesicle aspiration using a 20-gauge needle at the time of TRUS has been used to further increase the specificity of the diagnostic techniques. Significant quantities of sperm are not normally present in the seminal vesicles. Findings of three or more sperm per HPF in the seminal vesicle aspirate support the diagnosis of EDO (Jarow, 1994). Test accuracy is improved by performing aspiration within 24 hours of ejaculation (Jarow, 1996).

Seminovesiculography using transrectal injection of radiopaque contrast (50% renograffin) into the seminal vesicles under TRUS guidance with postinjection radiographs can provide excellent anatomic detail of the seminal vesicles and ejaculatory ducts. Seminal vesicle chromotubation is a variation of seminovesiculography using the injection of dilute indigo carmine or methylene blue (1:5 dilution with saline) into the seminal vesicles via TRUS guidance followed by cystoscopic inspection of the ejaculatory ducts in the prostatic urethra to confirm patency. The dynamic tests of chromotubation and seminal vesiculography offer higher specificity for detection of EDO than static TRUS imaging alone (Purohit et al, 2004). The newest adjunctive technique, ejaculatory duct manometry, involves hydraulic assessment of the ejaculatory ducts at the time of seminal vesicle chromotubation, noting that men with EDO have higher mean ejaculatory duct opening pressures, 116 cm H_2O versus 33 cm H_2O in fertile controls (Eisenberg, 2008). Despite these advances in diagnostic techniques, criteria for diagnosis of complete EDO remain unclear and those for partial EDO remain controversial.

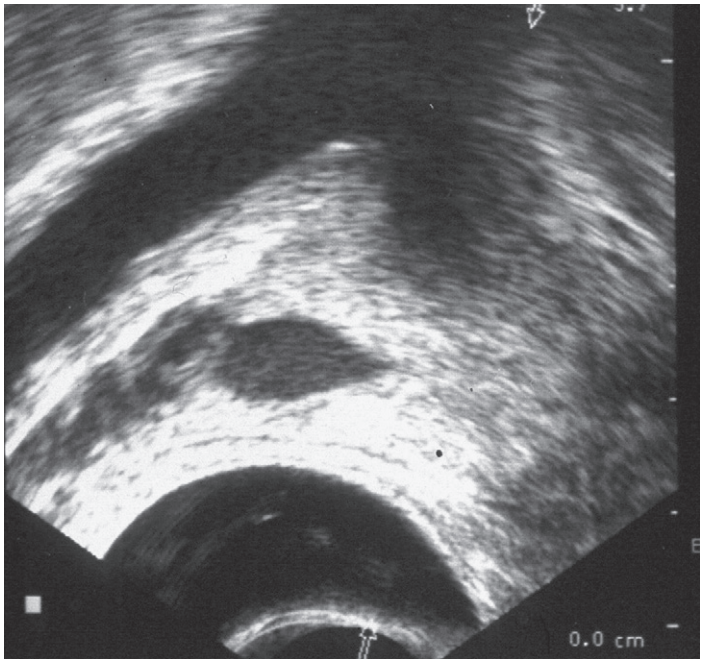


Figure 21–2. Transrectal ultrasound (sagittal image) demonstrating a dilated ejaculatory duct culminating in an ejaculatory duct cyst.

Scrotal Ultrasonography

Scrotal ultrasound for the infertile male is primarily used to confirm the presence of clinical varicoceles, although it also provides high-quality imaging of scrotal contents that offers the advantage of widespread availability without exposure to ionizing radiation. Although clinical varicoceles do not require confirmation with ultrasound examination, color Doppler ultrasound may be required when the clinical examination is difficult due to body habitus or when the examination is equivocal. Demonstration of reversal of venous blood flow with the Valsalva maneuver or spermatic vein diameters of 3 mm or greater (Fig. 21–3A and B) support the diagnosis of varicocele (Meacham et al, 1994). Scrotal ultrasound is not recommended for screening for subclinical varicoceles because repair of these has not been demonstrated to be of clinical benefit.

In addition, ultrasound examination provides excellent anatomic details of the epididymis and testis, potentially disclosing a number of conditions that may affect fertility. Epididymitis is associated with epididymal enlargement with diffuse hypoechogenicity and is often associated with a reactive hydrocele. Doppler ultrasound will often reveal increased vascularity in the involved epididymis or adjacent testicular region. Epididymal cysts or spermatoceles appear as simple or minimally complex cysts and may cause epididymal outflow obstruction. Testicular germ cell tumors are noted with increased frequency in the subfertile population, and even small, nonpalpable lesions (<0.5 cm) are well visualized with ultrasonography (Fig. 21–4). Testicular microlithiasis are diffuse 1- to 2-mm hyperechogenic nonshadowing foci and have been reported in 3% of subfertile men (Thomas et al, 2000).

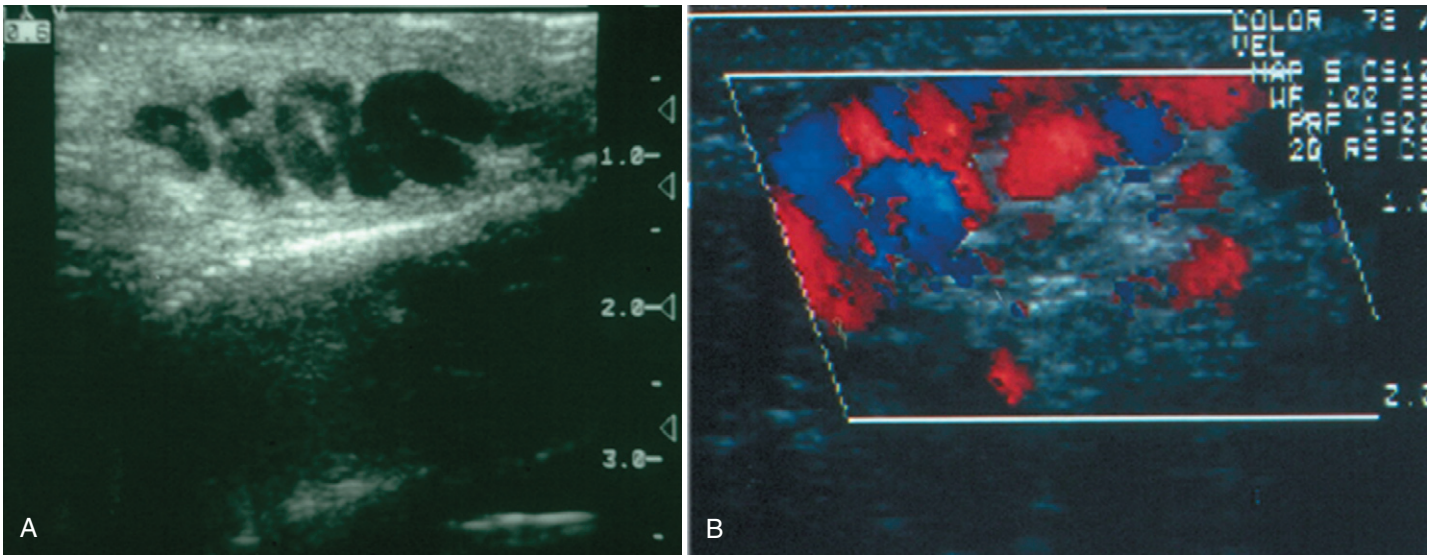


Figure 21–3. Scrotal ultrasound of varicocele. **A,** Dilated veins in spermatic cord. **B,** Color Doppler image revealing typical venous reflux with Valsalva maneuver.

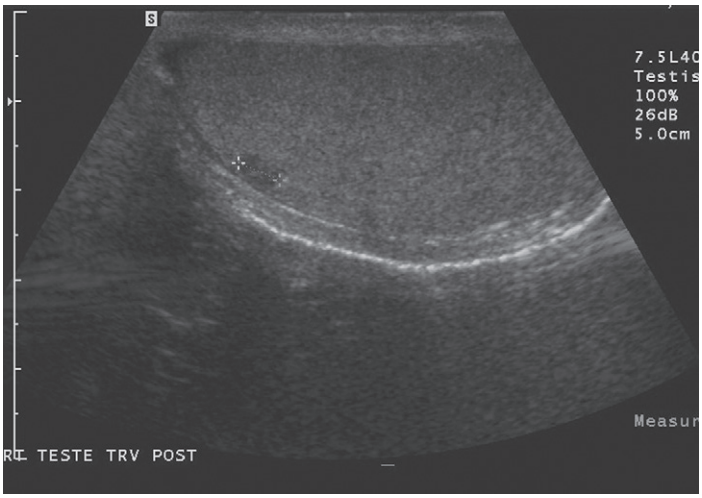


Figure 21–4. Testicular ultrasound—small nonpalpable testicular mass (seminoma) noted on fertility evaluation.

Although originally thought to represent a radiologic precursor to the development of germ cell tumors, it is now known that testicular microlithiasis is common and does not represent a risk factor for germ cell tumor development or necessitate continued medical surveillance (Costabile and Spevak, 1998).

Abdominal Ultrasonography

Abdominal ultrasound imaging in the infertile male is primarily indicated to rule out associated renal anomalies in patients with vasal agenesis. Vasal agenesis is theorized to result from one of two mechanisms—either mutations in the CFTR gene that do not incur associated renal anomalies or improper morphogenesis of the mesonephric duct before week 7 of gestation, which causes vasal agenesis and unilateral renal agenesis.

The CFTR gene is responsible for regulation of chloride ion transport across epithelial cell membranes. Dysfunction in this transport results in abnormal luminal fluid quality during vasal morphogenesis with resulting vasal agenesis (Oates and Amos, 1993). In patients with proven CFTR gene mutation in association with CBAVD, renal anomalies are unlikely and routine abdominal imaging is not indicated. However, up to 20% of men with CFTR mutation-negative vasal agenesis will have ipsilateral renal anomalies, most commonly renal agenesis, and should have routine abdominal ultrasonography as part of their evaluation.

Vasography

Vasography remains the gold standard test for assessing the patency of the male ductal system. Although procedures such as TRUS, seminal vesicle aspiration, and seminal vesiculography offer minimally invasive imaging to diagnose obstruction, properly performed vasography provides unequalled anatomic detail of the vas deferens, seminal vesicles, and ejaculatory ducts. Vasography is indicated for determination of the site of obstruction in the azoospermic patient with confirmed normal spermatogenesis on testis biopsy. On occasion, it may be used for the severely oligospermic patient in whom there is a high clinical suspicion of unilateral vasal obstruction from iatrogenic injury such as prior inguinal hernia repair (Matsuda, 2000). Vasography may also be used to rule out ejaculatory duct obstruction in the setting of ejaculatory pain. However, it should be emphasized that vasography is not necessary in oligospermic patients who do not have clinical evidence or history (i.e., inguinal surgery) that suggests unilateral obstruction.

Vasography is ideally performed at the time of anticipated reconstruction due to the potential to cause vasal scarring at the vasogram site, although this complication has not been observed in large series (Payne et al, 1985). For antegrade vasography, the straight portion of the vas deferens is isolated in the scrotal region, immediately adjacent to the convoluted vas to allow maximum length of vas deferens if a reconstruction such as a vasoepididymostomy is eventually required. Either a puncture or vasotomy technique may be used to inject contrast into the vas deferens. The puncture technique is preferred if possible because it avoids a full-thickness vasotomy, which necessitates subsequent microsurgical closure, although it is technically more difficult to enter the vasal lumen than with the vasotomy method. With the puncture procedure, a 30-gauge lymphangiogram needle is inserted directly into the proximal vas lumen and contrast is injected in an antegrade fashion (Fig. 21–5A). Alternatively, a microsurgical

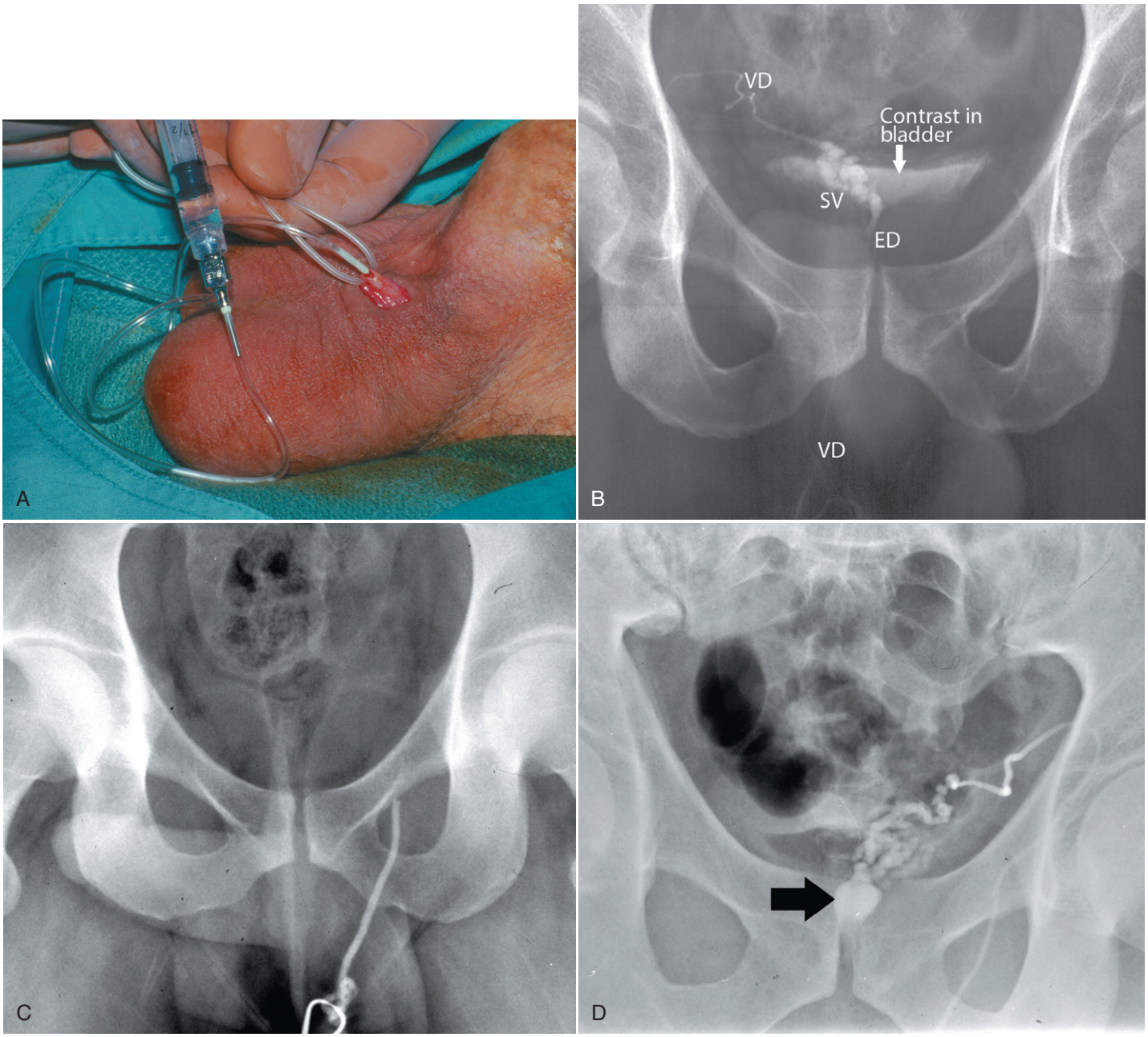


Figure 21–5. Vasography—examples of technique and findings. **A,** Technique for antegrade injection of contrast into proximal vas deferens. **B,** Normal vasogram with clearly defined vas deferens (VD), seminal vesicles (SV), ejaculatory duct (ED), and contrast spilling into bladder. **C,** Obstruction of left inguinal vas deferens due to prior herniorrhaphy. **D,** Ejaculatory duct obstruction with large cyst *(arrow)*.

scalpel may be used to make a hemivasotomy incision through the anterior wall of the vas deferens to expose the vasal lumen and allow placement of a 25-gauge angiocatheter for contrast injection (Fig. 21–5B). This techique allows examination of the intravasal fluid for presence of sperm to confirm epididymal patency. If a hemivasotomy technique is used for the vasogram, the vas will require reconstruction at the end of the procedure with 9-0/10-0 nylon interrupted sutures using standard microsurgical technique. Once the vasal lumen has been intubated, 5 to 10 mL of full- or half-strength contrast (Renografin) is injected in an antegrade fashion. Retrograde injection is not recommended due to the potential for subsequent epididymal scarring or obstruction. Vasography images are obtained using either standard radiographs or fluoroscopy. Methylene blue or indigo carmine may be mixed with contrast (1:10 dilution) to guide the depth of transurethral resection if the vasogram is performed at the time of ejaculatory duct resection. On occasion, contrast will not flow and a 2-0 monofilament suture may be passed in an antegrade fashion to identify the level of obstruction.

A properly performed vasogram will opacify the scrotal and inguinal portions of the vas deferens with subsequent filling of the ipsilateral seminal vesicle and the bladder (Fig. 21–5C). Failure to opacify the bladder represents either insufficient injection of contrast or evidence of obstruction (Fig. 21–5D).

Venography

Venography of the internal spermatic veins has been used to diagnose and treat varicoceles. As a diagnostic test, venography is

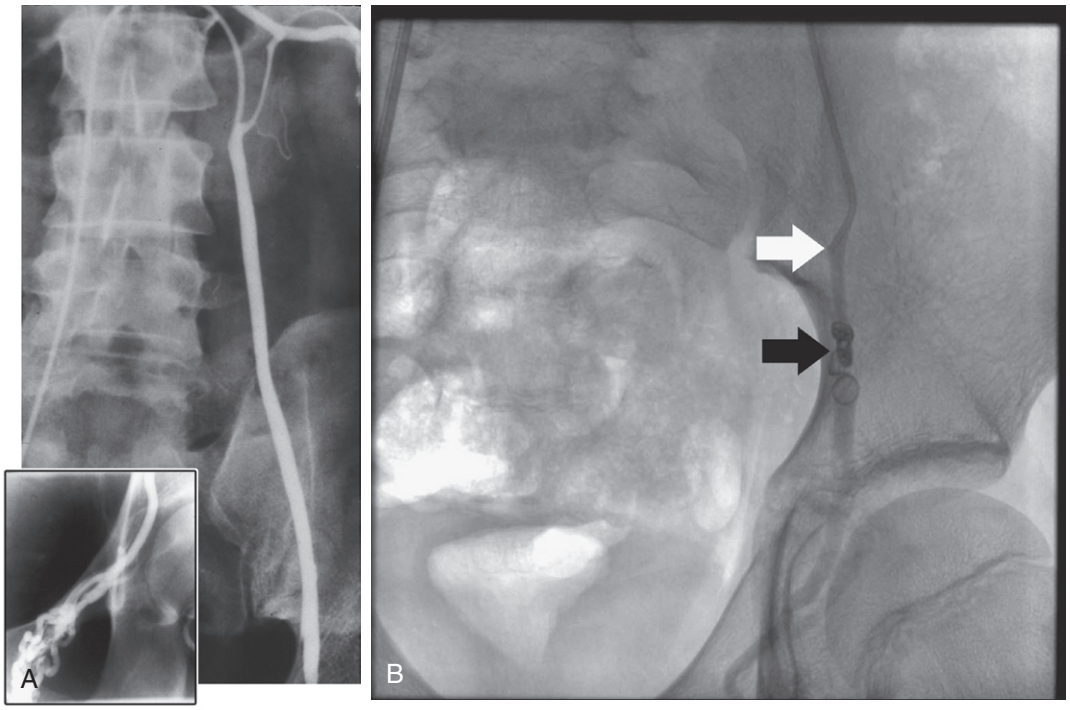


Figure 21–6. Venography for evaluation and treatment of varicoceles. **A,** Venogram demonstrates reflux through incompetent venous valves of the left internal spermatic vein consistent with left varicocele. *Inset* reveals inguinal plexis of gonadal veins. **B,** Venous embolization procedure with catheter tip *(white arrow)* and deployed coils *(black arrow)*.

arguably the most sensitive imaging modality but specificity remains its limitation. Although nearly 100% of clinical varicocele patients will demonstrate reflux on venographic examination, left internal spermatic vein reflux has been reported in up to 70% of patients without a palpable varicocele (Ahlberg et al, 1966; Narayan et al, 1980). False-positive studies may be due to examination technique factors such as high-pressure contrast instillation or placement of the catheter tip through a valve in the proximal portion of the internal spermatic vein. Because of the high false-positive rate and the invasive nature of the test, venography is not indicated for routine screening in the subfertile male. It does have utility in patients with presumed postvaricocelectomy recurrence both for confirmation of the diagnosis and embolization of persistent vessels (Fig. 21–6A and B).

Percutaneous embolization of varicoceles has been described using deployed coils, balloons, and sclerotherapy. Although it may be used for initial treatment, higher recurrence rates than surgical repair and unsuccessful procedure rates support embolization as a second-line therapy (Khera and Lipshultz, 2008). In addition, rare safety issues such as balloon migration, femoral vein injury, and anaphylactic reactions to contrast material further reinforce the recommendation that embolization is not the initial procedure of choice (Matthews et al, 1992; Zini et al, 1997). However, embolization does have a role in the management of patients with a persistent or recurrent varicocele after varicocele ligation. Antegrade scrotal sclerotherapy has also been described as first-line varicocele therapy with success rates as high as 95%, although this technique awaits validation with larger series and with long-term follow-up (Tauber and Johnson, 1994; Ficarra et al, 2002).

Testicular Biopsy

Testicular biopsy has two roles in the management of male infertility: diagnostic for the differentiation of obstruction from nonobstructive testicular pathology and therapeutic for sperm harvest with the intention of use for ICSI. Sperm retrieval techniques are discussed later in the chapter and reviewed in detail in Chapter 22.

Diagnostic testicular biopsy is primarily indicated for evaluation of the azoospermic patient presenting with a clinical picture suggestive of obstruction to include normal testicular size and consistency and normal serum FSH levels. Although some have suggested testicular biopsy for moderate oligospermia (<5 to 10 million/mL), most clinicians do not find that this provides useful prognostic or therapeutic information. On occasion, a diagnostic biopsy may be performed in a patient with clinical evidence of testicular failure (small-volume testes, high serum FSH level) to assess ability to perform sperm harvest for ICSI in the future. However, in this setting, a diagnostic biopsy should be coupled with sperm retrieval and cryopreservation to mitigate the need for a repeat biopsy in the future. Men with known obstructive etiologies such as prior vasectomy or vasal agenesis do not require routine testicular biopsy. Unilateral testicular biopsy is usually sufficient to assess the azoospermic patient for obstruction. Bilateral biopsy may be performed if there is suggestion of asymmetric pathology such as unilateral testicular failure from a situation such as cryptorchidism and contralateral obstruction such as from prior inguinal surgery with vasal injury. Although testicular biopsy may be performed concurrently with planned reconstruction, reconstruction is often performed at a later surgery to allow permanent section analysis of the tissue by pathologists. Frozen sections of the testis or touch preparations of testicular tissue have less accuracy for identification of normal spermatogenesis than permanent sections. Testicular biopsy specimens should be placed in specific solutions such as Bouin's, Zenker's, or buffered glutaraldehyde because the normal formalin tissue preservative will introduce distortion artifacts into the specimen, making histologic analysis less accurate.

Interpretation of testicular biopsies requires an experienced pathologist because analysis is descriptive rather than quantitative in nature. Electron microscopy of the germinal epithelium has not been shown to provide clinical benefit over standard light microscopy. A variety of objective histologic scoring methods have been described in an effort to quantify spermatogenesis and predict outcomes from surgical reconstruction for obstruction, but these have not gained widespread acceptance due to the time-consuming nature of the analysis and the lack of validated studies (Johnsen, 1970; Silber and Rodriguez-Rigau, 1981). DNA flow cytometry has also been employed to quantify spermatogenesis, but this has not gained popularity for similar reasons (Kaufman and Nagler, 1987; Hellstrom et al, 1990). At the present time, the most commonly used system for analysis of testicular biopsy remains the histologic classification across a spectrum of standard patterns ranging from normal to germ cell aplasia with hypospermatogenesis and maturation arrest in between. Although single patterns may be seen throughout the biopsy, multiple patterns may often be identified.

Normal

More than 85% of testicular volume consists of seminiferous tubules made up of progressively maturing germ cells and their supporting Sertoli cells. Blood vessels and Leydig cells in the interstitial areas provide the rest of the cellular complement. Spermatogenesis proceeds in an orderly fashion from spermatogonia along the basement membrane to spermatocytes and finally mature spermatozoa adjacent to the tubular lumen (Fig. 21–7A). Type A spermatogonia provide the stem cell complement and have a diploid complement of chromosomes (2N). These cells undergo a mitotic division to replenish the stem cell complement and

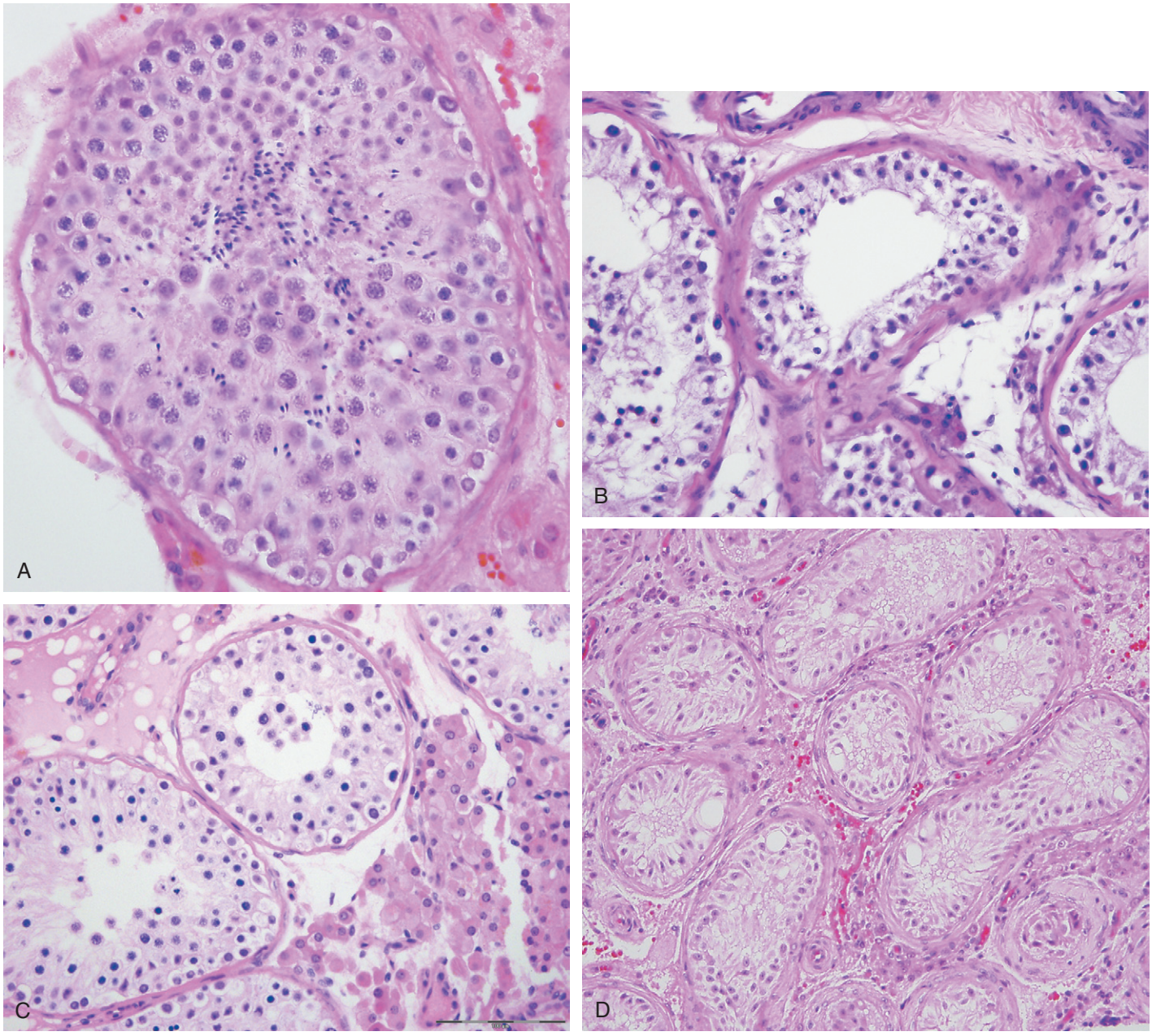


Figure 21–7. Diagnostic findings on testicular biopsy. **A,** Normal. **B,** Hypospermatogenesis. **C,** Maturation arrest. **D,** Germinal cell aplasia (Sertoli cell–only pattern).

provide type B spermatogonia (2N). Type B spermatogonia undergo DNA synthesis, resulting in spermatocytes that have a tetraploid complement of chromosomes (4N). Two subsequent meiotic divisions result in spermatids with the final haploid number of chromosomes (1N). Further maturation results in a progression from round to elongated spermatids and then to the final product, mature spermatozoa. Human testes exhibit multiple stages of spermatogenesis in a single tubular section (patchwork pattern), unlike other mammalian testes, which produce waves of spermatogenesis progressing along a tubule.

In the setting of azoospermia, a normal testicular biopsy is considered pathognomonic of ductal obstruction. Although focal areas of hypospermatogenesis and maturation arrest have been observed in the presence of obstruction, particularly in the setting of prior vasectomy, these are not classic findings for obstruction (Joshi et al, 1972; Perera, 1978). Dilated tubules with intraluminal debris are also commonly noted in patients exhibiting obstruction.

Hypospermatogenesis

Hypospermatogenesis is associated with reduced numbers of all germ cells, but all stages of spermatogenesis remain present in the histologic section (Fig. 21–7B). The degree of reduction determines whether the patient is oligospermic or azoospermic. A critical level of sperm production is required before sperm can be detected in the ejaculate, accounting for the common observation of hypospermatogenesis in the azoospermic patient.

Maturation Arrest

As the name suggests, maturation arrest involves a block of sperm maturation at a specific stage anywhere along the path of spermatogenesis (Fig. 21–7C). Maturation arrest most commonly occurs at the primary spermatocyte or late spermatid stages. Late maturation arrest may be difficult to distinguish from a normal biopsy, but the presence of mature sperm on testicular touch prep supports the diagnosis of normal spermatogenesis. Complete maturation arrest will produce azoospermia, whereas patients with partial maturation arrest may present with severe oligospermia. The remaining testicular architecture including the Sertoli and Leydig cells, as well as the basement membranes, are usually normal. Interestingly, maturation arrest is often associated with normal endocrine profiles such as FSH and inhibin levels due to an intact hypothalamic-pituitary-gonadal negative feedback system. Thus the clinical presentation of maturation arrest and ductal obstruction may be similar because both are associated with normal testicular volume and similar endocrine profiles.

Germinal Aplasia

Germinal aplasia, also called Sertoli cell-only syndrome, has small seminiferous tubules that are completely devoid of germ cells (Fig. 21–7D). The interstitial component, as well as the Sertoli cells and basement membranes, are normal. The diagnosis of germinal aplasia is suggested in an azoospermic patient with small-volume testes and elevated levels of FSH consistent with primary testicular failure. Although there are no current treatments to repopulate the testis with germ cells, low levels of spermatogenesis may be seen in other areas of the testis, which forms the basis for the use of microsurgical dissection testis biopsy (micro-TESE) to retrieve sperm in some of these patients for eventual ICSI use.

End-Stage Testes

Thickened basement membranes, tubular and peritubular sclerosis, and absence of both germ cells and Sertoli cells are characteristic histologic findings for end-stage testes. These patients will have azoospermia with profoundly small, soft testes (2- to 3-mL volume). Although this is characteristic of KS, some patients may still have small foci of retained spermatogenesis, which may be identified by micro-TESE. This histology may also be seen with cryptorchid testes.

DIAGNOSTIC AND TREATMENT CATEGORIES OF MALE INFERTILITY

Upon completion of a focused physical and laboratory examination, patients may be grouped into common patterns on the basis of seminal parameters (Table 21–8) and etiologic categories (Table 21–9). In the following sections, we review diagnostic criteria and appropriate therapy for specific diseases.

The goal of the infertility evaluation is to cause a successful pregnancy in the safest, most natural, expeditious, and cost-effective manner possible. Although advanced ART technologies such as ICSI are helpful tools in the armentarium for the management of infertility, all attempts should be made to correct underlying male factor etiologies before proceeding with these treatments. The high cost of these technologies, the shifting of treatment burden of male factor to the female partner, and intrinsic safety issues with ICSI mandate a complete exploration of correctable male factor issues before proceeding with ICSI.

Table 21–8.

Distribution of Seminal Parameters in Patients Presenting for Infertility Evaluation

TYPE	INCIDENCE (%)
Abnormal semen parameter	37
Motility	26
Asthenospermia	24
Oligospermia	8
Agglutination	2
Volume	2
Morphology	1
Azoospermia	8
All parameters normal	55

From Lipshultz L. Subfertility. In: Kaufman JJ, editor. Current urologic therapy. Philadelphia: WB Saunders; 1980.

Table 21–9.

Distribution of Etiology of Male Infertility

CATEGORY	NUMBER	PERCENT (%)
Varicocele	603	42.2
Idiopathic	324	22.7
Obstruction	205	14.3
Normal/female factor	119	7.9
Cryptorchidism	49	3.4
Immunologic	37	2.6
Ejaculatory dysfunction	18	1.3
Testicular failure	18	1.3
Drug/radiation	16	1.1
Endocrinopathy	16	1.1
Others (all <1%)	31	2.1

Data from Nagler HM, Martinis FG. Varicocele. In: Lipshultz LI, Howards S, editors. Infertility in the male. St. Louis: Mosby Year Book; 1997. p. 336–59.

Semen Parameter Categories

Azoospermia

Azoospermia is defined as the absence of sperm in the ejaculate and is identified in 10% to 15% of infertile males (Jarow et al, 1989). Before proceeding with further diagnostic procedures, the diagnosis of azoospermia should be confirmed with at least two centrifuged semen specimens to rule out severe oligospermia. The finding of even small quantities of sperm in the centrifuged specimen rules out complete ductal obstruction such as CBAVD and also offers the potential for immediate sperm cryopreservation for ICSI cycles.

Although there is a myriad of causes of azoospermia, etiologies fall into three general categories: pretesticular, testicular, and posttesticular. Causes can usually be differentiated on the basis of semen volume (low vs. normal), physical exam findings of testicular volume and presence of vas deferens as well as serum FSH level (Fig. 21–8).

Pretesticular causes, also called *secondary testicular failure,* are usually endocrine in nature and relate to either congenital (Kallman syndrome) or acquired hypogonadotropic hypogonadism, which are addressed in detail later in this chapter.

Testicular etiologies, broadly termed as *primary testicular failure,* are intrinsic disorders of spermatogenesis. Direct testicular pathology may derive from genetic abnormalities such as Y-chromosome

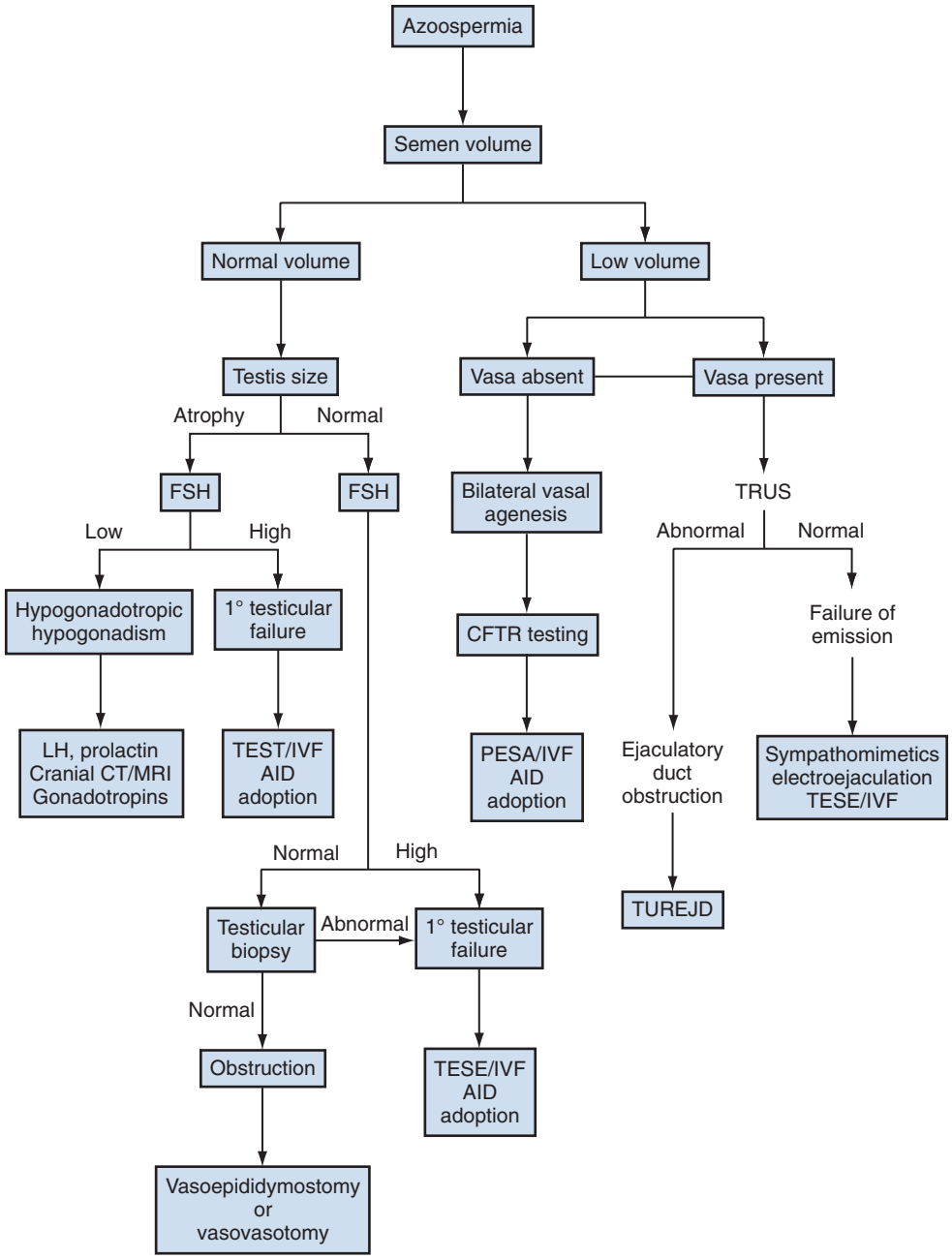


Figure 21–8. Algorithm for evaluation and treatment of azoospermia. AID, artificial insemination by donor semen; CFTR, cystic fibrosis transmembrane conductance regulator; CT/MRI, computed tomography/magnetic resonance imaging; FSH, follicle-stimulating hormone; IVF, in-vitro fertilization; LH, leuteinizing hormone; PESA, percutaneous epididymal sperm aspiration; TESE, testicular sperm extraction; TRUS, transrectal ultrasound; TUREJD, transurethral resection of the ejaculatory ducts.

microdeletions or chromosomal abnormalities, varicocele-induced testicular damage, gonadotoxic effects from medications or environmental exposures, and idiopathic infertility, which constitute the majority.

Ejaculatory dysfunction or obstruction of the genital tract account for the post-testicular pathologies, which constitute 40% of cases of azoospermia (Best Practice Committees of American Urological Association and American Society for Reproductive Medicine, 2006). Pretesticular and post-testicular causes are often amenable to treatment, which may restore fertility, whereas the success rates for intervention in testicular pathology are much more modest.

Although both primary and secondary testicular failure will be associated with marked reduction in testicular volume, these entities can be distinguished by serum endocrine testing to include FSH, LH, testosterone, and prolactin levels. High serum FSH levels, typically greater than two times normal, are indicative of primary testicular failure, and diagnostic testicular biopsy is not required to rule out obstructive etiologies. Primary testicular failure in conjunction with azoospermia, commonly termed *nonobstructive azoospermia* (NOA), is best managed with testicular sperm harvest for eventual ICSI. The absolute degree of serum FSH elevation has not proven predictive of success rates for sperm retrieval (Vernaeve et al, 2004; Hibi et al, 2005; Harris and Sandlow, 2008). Azoospermic patients with normal testicular size, palpable vas deferens, and normal serum FSH levels require a diagnostic testicular biopsy to differentiate genital tract obstruction from disorders of spermatogenesis such as maturation arrest.

Obstructive azoospermia accounts for 40% of cases of azoospermia (Practice Committee, American Society of Reproductive Medicine, 2008). A normal testicular biopsy is pathognomonic for genital tract obstruction. If these patients desire restoration of patency, they will require scrotal exploration and vasography at the time of planned reconstruction to identify the site of obstruction. Genital tract obstruction may occur anywhere along the sperm transport system to include the rete testis, efferent ductules, epididymis, vas deferens, or ejaculatory ducts. Obstruction at the level of the epididymis or vas deferens may be successfully treated with microsurgical reconstruction, either vasoepididymostomy for epididymal obstruction or vasovasostomy for vasal obstruction. Elective vasectomy remains the leading cause of obstructive azoospermia and subsequent infertility. In the absence of prior injury to the vas either intentionally from vasectomy or iatrogenic injury of inguinal vas from hernia repair, most men with idiopathic ductal obstruction will be obstructed at the level of the epididymis. Epididymal obstruction may be due to prior trauma, infection, or the result of downstream vasal obstruction from an elective vasectomy. Although vasectomy usually results in a single obstructive site, the development of high intraluminal pressures after a vasectomy can result in rupture of the delicate epididymal tubule with secondary obstruction in the epididymis. Epididymal obstruction rarely occurs within 4 years of a vasectomy but is present in more than 60% of patients on one or both sides after 15 years of vasal obstruction (Fuchs and Burt, 2002). The absence of proximal vasal fluid or thick, viscous, pastelike fluid is indicative of a concurrent epididymal obstruction and such patients will require a vasoepididymostomy for their reconstruction. The outcome of reconstruction in vasectomized men depends on a number of factors including the obstructive interval, the quality of the fluid from the proximal vas at the time of surgery, and the surgeon's microsurgical experience (Sabanegh, 2009).

Azoospermia in conjunction with low semen volumes and palpable vas deferens is most likely caused by ejaculatory duct obstruction (EDO), although rarely, ejaculatory dysfunction can cause a similar presentation. Disorders of ejaculation such as retrograde ejaculation will more frequently cause oligospermia in conjunction with low semen volume and are readily diagnosed by the presence of sperm in a postejaculation urine specimen. The diagnosis of EDO is suggested by low semen volume with acidic pH and absent semen fructose. TRUS will often reveal midline prostatic cysts, dilated ejaculatory ducts, or dilated seminal vesicles (>1.5 cm in width), and seminal vesicle aspiration may produce large numbers of sperm. Ultimately, EDO may be confirmed by vasography at the time of planned transurethral resection of the ejaculatory ducts (TUREJD) to relieve the obstruction.

Oligospermia

Oligospermia is defined as a sperm density of less than 20 million/mL. Unlike the situation with azoospermia, the number of potential diagnoses causing oligospermia can be quite vast and the etiology is often idiopathic. Oligospermia is rarely seen as an isolated seminal abnormality but is usually associated with disturbances in motility and morphology. Endocrinopathies are rarely observed in patients with concentrations higher than 10 million/mL, so routine endocrine screening with serum testosterone and FSH levels are reserved for counts lower than 10 million (Sigman and Jarow, 1997). Testis biopsy is not indicated in the setting of mild to moderate oligospermia, although it can be considered in patients with sperm concentrations under 1 million/mL in whom ductal obstruction is considered on the basis of history or physical examination findings.

Seminal Quality Abnormalities

Isolated defects may occur in motility or morphology, known as *asthenospermia* or *teratospermia,* respectively, while global sperm quality abnormalities are described with the term *oligoasthenoteratospermia* (OAT). Asthenospermia may be iatrogenic from delayed processing in the laboratory or may be due to a prolonged abstinence period. Persistent asthenospermia in a properly processed specimen, while often idiopathic, may be seen in association with varicoceles, genital tract infections, ultrastructural cilia abnormalities such as immotile cilia syndrome, and immunologic infertility in association with antisperm antibodies.

Teratospermia is a common finding, especially with use of the strict morphologic criteria (Tygerberg or Kruger) applied by many andrology laboratories. Bizarre morphologies of the sperm head such as pinhead sperm, multiheaded sperm, or round-headed sperm, which suggest acrosome deficiency, undoubtedly have clinical significance, although there is growing controversy regarding the predictive utility of abnormal morphology in general, largely due to the subjective nature of the test making it difficult to standardize (Agarwal et al, 2008). Abnormal sperm morphology has not been correlated with recurrent spontaneous miscarriages or abnormalities in offspring (Rosenbusch et al, 1992; Hill et al, 1994).

Low ejaculate volume may also be a contributing factor to subfertility. Reduction in ejaculate volume is most commonly due to improper specimen collection but may be associated with CBAVD with associated hypoplasia of the seminal vesicles, hypoandrogenism, retrograde ejaculation, or obstruction of the ejaculatory duct. Relative acidity of the seminal pH and low semen fructose suggest absence of seminal vesicle contribution to the semen, pointing to either CBAVD or EDO as lead possible causes of subfertility.

Normal Bulk Semen Parameters

Up to 50% of men presenting for an infertility evaluation will have normal bulk semen parameters, representing a particularly

difficult population to be assigned an etiology for subfertility and reinforcing the inherent inability of standard semen analyses to assess sperm function. In these couples, particular attention should be given to identifying occult female factor fertility issues, as well as assessing coital frequency to optimize reproductive timing for conception. On occasion, antisperm antibodies in the cervical mucus may inhibit sperm motility in vivo and prevent fertilization. This situation can be quantified with indirect antisperm antibody testing of the cervical mucus, although an in-vivo assessment of compatibility of sperm with the cervical mucus can be provided with the postcoital test (PCT). Couples with an abnormal PCT may benefit from intrauterine insemination, which bypasses the hostile cervical factors.

Varicocele

Varicoceles represent the most common attributable cause of primary and secondary infertility in the male (see Table 21–9). Although there is a large body of research on varicoceles dating back to Tulloch's first report of varicocele ligation for male infertility in 1955, much of the subsequent research has suffered from methodologic flaws, lack of standardized definitions for varicoceles, and failure to control confounding issues such as concurrent female factor infertility. Despite these limitations, varicocele treatment remains the most commonly performed surgery for the correction of male factor subfertility.

Varicoceles have been attributed to turbulent venous flow related to the right angle insertion of the left testicular vein into the left renal vein, an explanation supported by the left-sided predominance of these lesions. The insertion of the right testicular vein directly into the inferior vena cava is believed to provide less flow turbulence and back pressure, which translates into a lower incidence of venous dilation in the right spermatic cord. In addition, incompetent or absent venous valves in the gonadal veins allow retrograde reflux of blood into the scrotum with the standing position (Braedel et al, 1994). On rare occasions, a "nutcracker phenomenon" has been described where the left renal vein may be compressed between the superior mesenteric artery and the aorta producing elevated pressure in the left gonadal vein and resulting in a varicocele.

The mechanism of varicocele-induced impairment of spermatogenesis remains the subject of much debate. The lead theory postulates that testicular cellular processes are exquisitely temperature dependent. Venous pooling from a varicocele produces elevated intrascrotal temperature resulting in reductions in testosterone synthesis by Leydig cells, injury to germinal cell membranes, altered protein metabolism, and reduced Sertoli cell function (Khera and Lipshultz, 2008). Varicocele ligation has been demonstrated to be associated with reductions in intrascrotal temperature (Wright et al, 1997). It has also been suggested that free reflux of renal and adrenal metabolites from the left renal vein are directly gonadotoxic. Spermatic cord blood catecholamine and prostaglandin levels appear elevated in varicocele patients, although the direct gonadotoxic effects of these compounds remain to be established in humans (Comhaire et al, 1974; Ito et al, 1982). Other proposed mechanisms for varicocele-induced subfertility include impaired venous drainage with resulting hypoxia, poor clearance of gonadotoxins, and elevated levels of oxidative stress. The level of seminal oxidative stress correlates with varicocele grade and improves with treatment of the varicocele (Allamaneni et al, 2004; Khera et al, 2007). Although conflicting evidence exists for each theory, it appears that the mechanism of varicocele damage is multifactorial.

Treatment of varicoceles in the subfertile patient has produced variable results on the basis of the definition of the varicocele (subclinical vs. clinical) and the method of intervention used. The various methods of varicocele treatment all involve ligation or occlusion of dilated gonadal veins. Surgical ligation has been approached through retroperitoneal, inguinal, and subinguinal dissection, whereas embolization is a radiologic procedure. These techniques are discussed in depth in a later chapter. The most current guidelines in 2008 by the Best Practice Committee of the American Society for Reproductive Medicine recommend treatment of a varicocele in the infertile patient when all of the following conditions are met: (1) varicocele is palpable on physical examination; (2) the couple has known infertility; (3) the female partner has normal fertility or a potentially treatable cause of infertility; and (4) the male partner has abnormal semen parameters or abnormal results from sperm function tests. Patients with subclinical varicoceles are not candidates for varicocele treatment due to a lack of demonstrated efficacy in this population (Yamamoto et al, 1996). On occasion, large varicoceles will produce clinical symptoms such as dull hemiscrotal discomfort or sense of heaviness and these patients will benefit from varicocele treatment.

Adolescent males with unilateral or bilateral clinical varicoceles and ipsilateral testicular hypotrophy are also candidates for varicocele repair. Although there remains controversy with the threshold for testis size reduction to support varicocele intervention in the adolescent, authors have suggested 2-mL volume or 20% volume decrement from the contralateral testis as evidence of significant varicocele-induced damage (Gargollo and Diamond, 2009). Further support can be provided by pretreatment semen analysis, although this can be challenging to obtain in the adolescent patient. Recovery of testicular volume, so called "catch-up growth," has been reported to occur in up to 80% of boys with grade II or III varicoceles (Kass and Belman, 1987; Gershbein et al, 1999), although this has been challenged by a more recent study that suggests testicular growth will occur spontaneously in conservatively managed patients with varicoceles (Kolon et al, 2008). In the absence of testicular growth retardation, adolescents with varicoceles should be followed with annual testicular size assessments, as well as semen analysis if possible to assist early identification and intervention of varicocele-induced testicular damage.

Outcomes of varicocele treatment remain the subject of some controversy, although substantial evidence exists to support intervention in patients with clinical varicoceles and abnormal semen quality. The bulk of studies (Table 21–10) has shown improvements in seminal parameters with varicocele repair (Schlesinger et al, 1994) and specific functional testing to include sperm penetration assay (Ohl et al, 2007), sperm DNA fragmentation levels (Zini et al, 2005), and oxidative stress levels (Mostafa et al, 2001). A recent meta-analysis incorporating studies using current clinical guidelines for varicocele repair reported mean increases in sperm density of 9.7 million/mL, motility increases of 9.9%, and WHO sperm morphology improvement by 3% (Agarwal et al, 2007). Semen quality has been reported to improve in 51% to 78% of infertile men after varicocele treatment (Turek, 2005). The impact of varicocele grade on post-treatment semen quality remains unclear, although the bulk of studies suggests that larger varicoceles produce more significant impairment in semen parameters and the repair of bilateral varicoceles produced increased benefit over the repair of unilateral varicoceles (Richardson et al, 2008). In the setting of underlying genetic abnormalities associated with the subfertility, varicocele treatment does not appear to produce significant improvement in outcomes (Cayan et al, 2001). Azoospermic patients with varicoceles have shown some potential for

Table 21–10.

Outcomes of Varicocele Treatment in Nonazoospermia Men (Controlled Trials) for Clinical Varicoceles

STUDY	PATIENTS (No.)	VARICOCELE GRADE	PREGNANCY RATE (%) TREATMENT	PREGNANCY RATE (%) CONTROL	ODDS RATIO
Nilsson (1979)	96	III	8	18	0.394
Baker (1985)	651	I-III	47	21	3.37
Madgar (1995)	45	II-III	60	40	13.5
Nieschlag (1998)	125	I-III	29	25	1.20
Grasso (2000)	68	I	3	6	0.485
Krause (2002)	67	I-III	16	18	0.875

Table 21–11.

Outcomes of Varicocele Treatment in Azoospermic Men

STUDY	PATIENTS (No.)	MEAN POSTOPERATIVE SPERM CONCENTRATION (MILLION/mL)	PREGNANCY RATE (%)
Matthews (1998)	22	2.2	14
Kim (1999)	28	1.2	NR
Pasqualotto (2003)	15	2.54	7
Esteves (2005)	17	1.5	NR
Gat (2005)	32	3.81	NR
Pasqualotto (2005)	28 Germinal cell aplasia	12.05	53.8
	32 Maturation arrest	24.76	25

NR, not reported.

return of sperm to their ejaculate after varicocele treatment (Table 21–11), although studies have been relatively small with modest conception results. The vast majority of azoospermic patients with return of sperm postvaricocele treatment will still require advanced ART such as in-vitro fertilization to obtain conception.

Spontaneous pregnancy rates after varicocele treatment have been reported to average between 30% and 50% in the larger series (Abdulmaaboud et al, 1998; Segenreich et al, 1998; Perimenis et al, 2001) with pregnancies occurring at an average of 8 months after treatment (Pryor, 1987). A recent meta-analysis after surgical varicocelectomy noted that the odds of spontaneous pregnancy were 2.87 times higher over the nontreatment group (Marmar et al, 2007). Cost-benefit analyses have generally been supportive of varicocele treatment over ART techniques (Schlegel, 1997). In addition, 30% to 50% of couples who are felt to require ART due to low semen quality may be able to avoid this after varicocele treatment (Cayan et al, 2002) or have improved efficacy with post-treatment intrauterine insemination (Daitch et al, 2001).

Cryptorchidism

Cryptorchidism is a relatively common condition noted in 2.7% of newborns and up to 0.8% of 1 year olds (Score, 1964). It is a well-known etiology for subfertility and has been associated with reduced testicular size and sperm concentration, as well as reductions in serum inhibin and elevations in serum FSH levels (de Gouveia Brazao et al, 2003; Caroppo et al, 2005). It is important to distinguish cryptorchid testes from retractile testes, a condition involving hyperactive cremasteric muscles causing the testis to periodically reside in the inguinal canal or high scrotum. Although retractile testes have been associated with depressed spermatogenesis, more severe reductions in semen quality have been identified in cryptorchid patients (Caroppo et al, 2005). Suggested mechanisms for cryptorchidism-induced subfertility include testicular dysgenesis, impaired endocrine axis, immunologic damage, and obstruction. Controversies remain as to the exact effect on fertility from unilateral versus bilateral cryptorchidism and the protective effect and timing of orchidopexy. Early studies reported significant detrimental effects on semen parameters with even unilateral cryptorchidism (Kogan, 1985; Cendron, 1989), but newer work suggests that unilateral cryptorchidism may be associated with modest or no significant impact on fertility (Lee, 2005; Murphy, 2007). The level of the cryptorchid testis is predictive of spermatogenic impairment with germinal cell aplasia found in 20% to 40% of inguinal testes versus 90% of intra-abdominal testes (Hadziselimovic, 1984). One epidemiologic study comparing fertility in men with either unilateral or bilateral cryptorchidism versus age-matched controls reported paternity rates of 89% in unilateral cryptorchidism, 93% in age-matched controls, and 65% in patients with a history of bilateral cryptorchidism (Lee, 2005). Some studies have suggested that orchiopexy at younger ages, typically younger than 4 years of age, is associated with improved fertility outcomes (Coughlin et al, 1999; Lee, 2002), although the question still awaits large longitudinal studies.

Endocrinopathies

Endocrine-derived causes of infertility may occur at the hypothalamic, pituitary, or gonadal levels. Originally believed to be a rare cause of infertility, growing evidence suggests that hypogonadism, as defined by the U.S. Food and Drug Association (FDA), established normal testosterone level of 300 ng/dL may be highly prevalent in infertile males, occurring in 45%, 43%, and 35% of men with nonobstructive azoospermia, oligospermia, and normal semen parameters, respectively (Sussman et al, 2008).

Primary hypogonadism, also called *primary testicular failure* or *hypergonadotrophic hypogonadism,* is defined as low serum testosterone and elevated gonadotropin level consistent with organ function failure at the level of the testes.

Secondary hypogonadism, also called *hypogonadotropic hypogonadism,* has low testosterone levels in conjunction with low gonadotropin levels.

The time of onset of hypogonadism induces variable clinical presentations. Failure of testosterone surge at the expected time of puberty produces delayed or absent puberty, growth retardation, and small, soft testis. Patients with onset of hypogonadism after puberty will have normal secondary sexual characteristics and body habitus but small firm testis consistent with possible fibrosis after normal testicular development.

Hypogonadotropic Hypogonadism

Isolated gonadotropin deficiency or hypogonadotropic hypogonadism (HH) is a relatively rare cause of subfertility accounting for less than 1% of cases of male infertility and may be congenital or acquired (Sigman and Jarow, 1997).

Acquired causes of hypogonadotropic hypogonadism include pituitary disease, which may result from prior surgery, infarction, tumors, or infection; metabolic disorders; and a variety of other medical conditions (Table 21–12).

Although variants of congenital hypogonadotropic hypogonadism have been described (Table 21–13), the anosmic form or Kallman syndrome is the most commonly reported, occurring in between 1:10,000 and 1:60,000 births (Oates, 1997). In addition to the anosmia and azoospermia noted with Kallman syndrome, other clinical features may include midline facial defects such as cleft palate; gynecomastia; neurologic abnormalities (mental retardation, oculomotor defects, deafness, and synkinesia); unilateral renal agenesis; cryptorchidism; micropenis; and pes cavus (Sussman et al, 2008). Kallman syndrome results from failure to secrete gonadotropin-releasing hormone (GnRH) by the hypothalamus, leading to low gonadotropin levels and ultimately, failure to transition the prepubertal testis to postpubertal level of function. The GnRH deficiency noted with Kallman syndrome is the result of failed embryonic migration of neuroendocrine GnRH cells from the olfactory epithelium to the forebrain. Absence or hypoplasia of the olfactory bulbs accounts for the concurrent anosmia. Kallman syndrome represents a genetically diverse group of diseases with both X-chromosome linked inheritance via mutations in the *KAL1* gene, as well as autosomal dominant inheritance via mutations in the fibroblast growth factor receptors 1 and 8 (*FGFR1, FGFR8*), the prokineticin receptor-2 (*PROKR2*), and the prokineticin-2 *(PROK2)* genes. Mutations in these five genes are found in less than 30% of Kallman syndrome patients reinforcing the need for further genetic study on these complex patients (Dode, 2009).

Prader-Willi syndrome (PWS), another form of congenital hypogonadotropic hypogonadism, has features that include infantile hypotonia, obesity, cryptorchidism, short stature, and mental retardation. It is caused by microdeletions or mutations on the paternal chromosome 15 at the q11 or q13 location (Smeets et al, 1992). Because of concurrent medical problems in these patients, most do not seek treatment for infertility.

Hypogonadotropic hypogonadism usually presents in the late teenage years when the patient fails to undergo the usual pubertal changes with secondary virilization. It is of critical importance to distinguish HH from constitutional delay of growth and puberty (CGDP) because they share many clinical and hormonal features and yet require markedly different treatments. Usually, CGDP patients will attain spontaneous puberty by age 18 or may require transient androgen replacement for puberty induction but then will progress through normal development and fertility. HH patients will require lifelong androgen replacement for maintenance of virilization and episodes of exogenous gonadotropin treatment off androgen therapy for fertility induction as described later. Because differentiation is not always possible on the basis of serum testosterone and gonadotropin levels, a number of physiologic and stimulatory tests have been described to discriminate these conditions to include serial serum LH measurements, prolactin response to TRH, and GnRH and human chorionic gonadotropins (HCG) stimulation tests (Segal, 2009). Patients with CGDP often demonstrate LH pulses with serial overnight blood draws and gonadotropin surge in response to GnRH stimulation. HH patients have minimal variability in LH levels and do not demonstrate significant increases in gonadotropins levels with administration of GnRH.

In general, treatment of HH syndromes is directed to two ultimate goals: (1) induction of normal serum androgen levels to allow appropriate virilization and bone growth and (2) the induction of spermatogenesis and, ultimately, fertility. During adolescence, puberty and virilization are usually initiated with exogenous androgen treatment. Various effective methods of testosterone replacement therapy exist including intramuscular testosterone enanthate or cypionate (200 mg every 2 weeks), transdermal patches (5 to 10 mg/day), testosterone gel, or buccal tablets. Adequacy of replacement can be assessed by serum testosterone levels, which should be within the midrange of normal, and observation of the desired phenotypic response to therapy. Exogenous

Table 21–12.

Acquired Causes of Hypogonadotropic Hypogonadism

Central nervous system (CNS) derived
CNS developmental abnormalities
Head trauma
Pituitary tumors
Autoimmune disease
Parasitic diseases
Crohn disease
Beta-thalassemia/hemoglobinopathy
Hemochromatosis
Disorders of lipid metabolism

Table 21–13.

Variants of Congenital Hypogonadotropic Hypogonadism

Congenital idiopathic hypogonadism
Anosmic (Kallman syndrome)
Nonanosmic
Congenital adrenal hypoplasia
Fertile eunuch syndrome
Genetic defects of the gonadotropin subunits
Follicle-stimulating hormone–β mutations
Luteinizing hormone–β mutations
Mutations in leptin and leptin receptor genes
Hypogonadotropic hypogonadism with other associated pituitary hormone deficiencies
PROP-1 mutations
HERS1 mutations
Syndromes associated with hypogonadotropic hypogonadism
Prader-Willi syndrome
Congenital spherocytosis
Moebius syndrome
Cerebellar ataxia
Retinitis pigmentosa

From Sussman EM, Chudnovsky A, Niederberger CS. Hormonal evaluation of the infertile male: has it evolved? Urol Clin North Am 2008;35(2):147–55.

testosterone is effective in induction of virilization but will inhibit spermatogenesis, so alternate therapies will be required when the patient desires fertility.

Induction of spermatogenesis in the HH patient requires the maintenance of intratesticular testosterone levels that are exponentially higher than that obtainable with conventional androgen replacement therapy. To obtain such levels, the usual first-line therapy for HH involves treatment with human chorionic gonadotropin (hCG), which is biologically similar to LH, inducing Leydig cell production of testosterone. hCG is administered subcutaneously at a dose of 1500 to 2000 IU two to three times per week for 4 to 6 months. When testicular volume and serum testosterone levels are stable without significant further improvement, FSH stimulation is added to the treatment regimen to induce spermatogenesis. FSH may be administered in the form of human menopausal gonadotropin (hMG), a compound that contains both FSH and LH in equal doses or with recombinant human FSH formulations. Human menopausal gonadotropin is administered at a dose of 75 IU two to three times per week, and recombinant FSH usually uses doses of 37.5 to 75 IU three times per week. FSH therapy is continued until attainment of sperm concentrations of at least 5 million per mL in the ejaculate or pregnancy is obtained. The vast majority of patients will be able to conceive after gonadotropin therapy, although 71% of the patients with subsequent fertility have sperm concentrations considerably lower than normal, suggesting that these patients are often able to conceive with low counts (Burris et al, 1988). Interestingly, 10% of patients may maintain normal serum testosterone levels after cessation of all endocrine therapy, implying that HH may be reversible in some patients (Raivio et al, 2007). Prior treatment of HH patients with testosterone does not affect success with future gonadotropin therapy (Ley and Leonard, 1985; Hamman and Berg, 1990).

Hypogonadotropic hypogonadism patients with intact pituitary function can also be effectively treated with pulsatile GnRH therapy supplied via subcutaneous infusion from portable pump or intranasal administration (Klingmuller, 1985; Aulitzky, 1988). Although direct GnRH therapy is effective, inconvenience of administration and expense do not justify this choice over traditional gonadotropins therapy at the present time (Liu, 1988). In addition, selected patients with HH presenting after puberty with intact pituitary function may respond to clomiphene citrate, an antiestrogen therapy (Whitten et al, 2006).

Androgen Excess

Excess systemic levels of androgen paradoxically inhibit spermatogenesis due to direct feedback inhibition of gonadotropin secretion at the level of the hypothalamus and pituitary. This ultimately results in low intratesticular levels of testosterone, which are inadequate for the maintenance of spermatogenesis, an observation that provides the impetus for growing research examining the potential contraceptive role of exogenous testosterone.

Excess states may result from either endogenous production or exogenous administration of androgens. Elevations in endogenous production of androgens may be caused by congenital abnormalities of steroid metabolism such as congenital adrenal hyperplasia or androgen-producing tumors of the testis or adrenal gland. Congenital adrenal hyperplasia (CAH), the most common endogenous etiology of androgen excess, encompasses a variety of specific enzyme defects in cortisol and aldosterone synthesis. Inadequate systemic cortisol levels result in excessive pituitary release of ACTH leading to hyperstimulation of the adrenal gland with subsequent release of adrenal androgens and suppression of pituitary gonadotropin release. Deficiency in the 21-hydroxylase enzyme accounts for 90% of cases of CAH. Although severe deficiency in 21-hydroxylase activity can present in the neonatal period with salt wasting, milder deficiencies present more commonly in childhood with phallic enlargement, precocious puberty, and advanced skeletal maturation. Elevated levels of serum 17-hydroxyprogesterone (often >1000 ng/dL) and urinary pregnanetriol support the diagnosis of 21-hydroxylase deficiency. The impact on subsequent fertility is variable, depending on the degree of androgen excess. Treatment for CAH consists of glucocorticoid replacement, which reduces ACTH levels and adrenal androgen production. In one small series of adult patients with CAH, 60% of men were able to cause pregnancies either with treatment or even in the absence of CAH treatment (Urban, 1978).

Anabolic steroids represent a growing etiology of male subfertility with a similar mechanism of spermatogenic disruption to that observed with CAH. It remains problematic to accurately predict the impact of these agents because of the variety of performance-enhancing substances used, as well as the variation in doses employed. Older studies of semen quality in athletes using high doses of anabolic steroids revealed severe impairment of sperm concentration, motility, and morphology (Knuth et al, 1989). Although cessation of use allowed normalization of seminal parameters in an average of 4 months, cases of persistent azoospermia have been reported occurring more than 1 year later (Jarow, 1990). To avoid the fertility-related side effects, anabolic steroid users have employed modified regimens that add hCG with steroid to protect spermatogenesis. These combinations, although causing transient impairment in semen quality, seem to allow preservation of spermatogenesis in some patients (Karila et al, 2004). In patients with persistent azoospermia or severe oligospermia after steroid abuse, hCG alone or in combination with hMG has been successfully used to restore spermatogenesis (Pundir, 2008).

Hyperprolactinemia

Because of its low yield, screening serum prolactin measurements in the infertile male is not indicated unless associated with erectile dysfunction, low serum testosterone levels, or decreased libido. Although often idiopathic, hyperprolactinemia can be associated with medications, physiologic stress, and pituitary tumors. Because of the marked physiologic variability noted with serum prolactin levels, elevated levels should be confirmed by at least one additional measurement. If elevated prolactin levels are confirmed (>18 ng/dL), anatomic imaging of the sella turcica is required, usually with magnetic resonance imaging with gadolinium contrast. Although macroadenomas may require surgical excision, microadenomas are usually responsive to dopamine agonist therapy with either bromocriptine or cabergoline. Cabergoline offers advantages over bromocriptine to include longer half-life, allowing less frequent dosing and an improved side effect profile without compromising therapeutic efficacy. Despite limited data on the therapeutic efficacy of dopamine agonist therapy for the infertile male with hyperprolactinemia, several small studies have reported improvements in sperm concentration and motility, as well as normalization of serum prolactin levels with treatment (Laufer et al, 1981; Mancini et al, 1984).

Estrogen Excess

Regardless of the source of the estrogen excess, estrogens inhibit GnRH secretion by the hypothalamus and gonadotropin release by the pituitary. In addition to the effects on the hypothalamic-pituitary-gonadal axis, elevations in serum estrogen levels produce direct deleterious effects on spermatogenesis (Hammoud et al, 2008). Hormonal evaluation in the infertile patient will reveal low

levels of serum FSH, LH, and testosterone with elevations in serum estrone and estradiol (E_2).

In the male, hyperestrogenemia may result from hepatic disease, estrogen-producing tumors, or, most commonly, obesity. Sertoli or Leydig cell testicular tumors and adrenal cortical tumors may rarely produce elevated estrogen levels. In the obese patient, elevations in serum estrogen derive from elevated peripheral aromatization of androgen to estrogen occurring in adipose tissue via an aromatase enzyme. The level of serum androgen inversely correlates with the degree of obesity (Giagulli et al, 1994; Tchernof et al, 1995). This provides the scientific basis for the use of selective medical therapy with aromatase inhibitors in men with reduced testosterone-to-estrogen ratios, which are discussed later in this chapter. In the obese patient, weight loss and bariatric surgery have been associated with improvements in endocrine profiles (Kaukua et al, 2003; Globerman et al, 2005), although the ultimate effect on fertility remains subject to further study.

Genetic Syndromes

Disorders of Sex Chromosome Number and Structure

Klinefelter Syndrome (47,XXY). KS, or 47,XXY male syndrome, is the most common genetic cause of nonobstructive azoospermia (NOA), accounting for up to 10% of these cases (Oates, 2003; Visootsak and Graham, 2006). It has been reported to occur in between 1:500 and 1:1000 live male births (Nielsen and Wohlert, 1991; Simpson et al, 2003). The majority of KS patients have a pure 47,XXY karyotype due to nondisjunction during the meiotic phase of the parental gametes, although 10% of patients are mosaic if the nondisjunction occurs during the mitotic cell division of embryogenesis (Therman et al, 1993). The extra X chromosome may be of maternal or paternal origin, but advancing paternal age is a risk factor for sperm with an XY complement and subsequent KS offspring. The frequency of XY sperm was reported to be 10%, 31%, and 160% higher in men in their 30s, 40s, and 50s, respectively, as compared with men in their 20s (Lowe et al, 2001; Eskenazi et al, 2002).

Although the exact mechanism of the subfertility induced by the supernumerary X chromosome remains to be defined, this karyotype results in severe spermatogenic and androgenic failure. In 1942 Klinefelter originally described a triad of gynecomastia, hypergonadotropic hypogonadism, and infertility (Klinefelter et al, 1942). Since the original report, KS has been identified with a wide spectrum of clinical presentations. The most severe form presents with delayed or absent puberty, incomplete virilization, and eunuchoid appearance. These patients tend to have tall, slender statures with long legs, narrow shoulders, and proportionately shorter torsos. Often they present for medical attention during adolescence and may be placed on testosterone replacement to induce puberty. On the other end of the developmental spectrum are patients who have adequate androgen levels to induce puberty but are noted to have KS during a fertility evaluation in their adulthood. Both extremes of presentation share common features of small testicular size (<8 to 10 mL testis volume), elevated serum gonadotropin levels, and azoospermia, although mosaic patients may occasionally have rare sperm identified in semen.

In addition to the detrimental effects on testicular function, KS is associated with significant developmental, neoplastic, and metabolic implications. Early studies suggested severe cognitive and behavioral abnormalities in KS patients, yet more recent reports have identified only mild cognitive impairment with speech and language deficiencies, as well as fine motor developmental delays (Youings et al, 2000; Fales et al, 2003). KS patients have been described to have as much as a 50-fold increased risk of breast cancer development reinforcing the need for monthly breast self-examination and screening in this population (Swerdlow et al, 2005). They have also been noted to have an increased risk of non-Hodgkin lymphoma and extragonadal mediastinal germ cell tumors (Aguirre et al, 2006; Oates, 2008). The underlying hypogonadism in KS patients predisposes them to the development of metabolic syndrome with the associated findings of abdominal obesity, hyperlipidemia, diabetes mellitus, and cardiovascular disease with an associated increase in risk of mortality from diabetic or cardiovascular complications (Lanfranco et al, 2004; Ishikawa, 2008).

Although most KS patients will present with azoospermia, rare cases of unassisted paternity in these patients exist, reinforcing the need for careful semen analysis of centrifuged specimens to assess for severe oligospermia, or cryptospermia. The predominant testicular histology in these patients is germinal cell aplasia with seminiferous tubular sclerosis, but there can be small areas of residual complete spermatogenesis. Advances in testicular biopsy techniques including microsurgical dissection have allowed successful sperm retrieval in up to 69% of KS patients (Denschlag et al, 2004; Gonsalves et al, 2005; Schiff et al, 2005). These techniques are covered in detail in Chapter 22. Sperm retrieved from KS patients is associated with high fertilization rates with ICSI, although there have been isolated reports of KS genotypes in offspring (Ron-El et al, 2000; Komori et al, 2004; Okada et al, 2005). This reinforces the need for all KS patients to be offered genetic counseling before proceeding with surgical sperm retrieval, both for their own health issues and the potential implications for offspring.

46,XX Male Syndrome. Also called the *sex reversal syndrome,* 46,XX male syndrome has an incidence of 1:20,000 male babies (de la Chapelle, 1972). Although sharing some similarities in presentation with KS including small testicular size, gynecomastia, and azoospermia, these patients have shorter stature than average men, an increased incidence of hypospadias, and normal levels of cognitive function (Vorona et al, 2007). In 90% of these patients, the testis-determining *(SRY)* gene including a small distal portion of the short arm of the Y chromosome (Yp) has been translocated to either one of the X chromosomes or to an autosome allowing differentiation of the bipotential gonads into testes (Schiebel et al, 1997). In the remaining 46,XX men, the *SRY* gene is not identified and it is presumed that other Y-chromosome genes have translocated to an autosome (Rajender et al, 2006). Unlike KS patients, these men are missing the *AZFa, AZFb,* and *AZFc* genetic regions, resulting in a complete absence of spermatogenesis. At the current time, there are no reports of successful sperm harvest and testicular biopsy is not recommended for prognostic or therapeutic purposes.

47,XYY Syndrome. Found in 0.1% of male births, the 47,XYY karyotype is characterized by a normal male phenotype and endocrine profile (Oates, 2002). This syndrome has been associated with reduced intelligence and antisocial behavior, although its mechanism has been controversial (Oates, 1997). These patients typically retain some degree of spermatogenesis, although they may have severe oligospermia or complete azoospermia. Fortunately, only a small percentage of spermatogonia have an abnormal genetic complement (0.35% 24,XY; 0.43% 24,YY) suggesting a low risk of genetic abnormalities in spontaneous or ICSI-derived offspring of these patients (Egozcue et al, 2000). It is still recommended that these patients receive genetic counseling before any testicular sperm harvest or ART procedure.

Noonan Syndrome. Noonan syndrome (NS) is commonly referred to as *male Turner syndrome* because both syndromes share numerous clinical features. Unlike the female Turner syndrome (45X0), the inheritance pattern for NS is autosomal dominant with a normal 46,XY karyotype. Although the exact chromosomal locus remains to be determined, studies have implicated chromosome 12 in some cases (Jamieson et al, 1994; Robin et al, 1995). The syndrome is characterized by short stature, webbing of the neck, cubitus valgus, pulmonary stenosis, hypertrophic cardiomyopathy, low-set ears, and ptosis. Fertility may be normal, but 77% of these patients will have cryptorchidism with resulting spermatogenic failure and elevated gonadotropin levels (Sharland et al, 1992).

Y-Linked Microdeletions. Testing for Y chromosome microdeletion is indicated in men with presumed nonobstructive etiology of azoospermia and severe oligospermia (concentration < 5 million/mL) to assess the prognosis for surgical sperm retrieval and to assist genetic counseling for affected couples. Normal molecular anatomy of the Y chromosome is critical both for gonadal development and function. The Y chromosome is an acrocentric chromosome with an off-center centromere creating asymmetric short (Yp) and long (Yq) arms incorporating 60 million base pairs (Morton, 1991). The Y chromosome has two important regions—the euchromatic zone, which includes Yp, the centromere, and the proximal portion of Yq, and the heterochromatic zone, which comprises the distal Yq. The heterochromatic region does not appear to have transcriptional function, while the euchromatic zone has a number of important genetic loci that are critical to the development of normal spermatogenesis (Fig. 21–9). Of particular importance is the sex-determining region Y (SRY) gene located on Yp, which is critical in initiating the cascade that converts the embryonic bipotential gonad to the eventual testis.

Deletions or mutations of critical areas of the Y chromosome may cause profound disruption of spermatogenesis. Early cytogenetic analysis of infertile men suggested the presence of a specific region on Yp termed the *azoospermia factor* (AZF), which is of paramount importance for normal spermatogenesis (Tiepolo and Zuffardi, 1976). Subsequent advances in chromosomal molecular mapping allowed the identification of three regions of Y-chromosome microdeletion: AZFa, AZFb, and AZFc (Vogt, 1998). Deletions in the AZFa region have been reported in 1% of men with nonobstructive azoospermia. This region contains two genes, DDX3Y (also known as DBY) and USP9Y, which are felt to be important for normal spermatogenesis (Kamp et al, 2000). AZFa microdeletion is associated with germinal cell aplasia histology of the testis, and current literature suggests that an attempt at testicular sperm retrieval (TESE) is not indicated because the success rate is poor (Blagosklonova et al, 2000; Hopps et al, 2003; Oates, 2008).

Like AZFa, microdeletions in the AZFb region are uncommon and are associated with poor surgical sperm retrieval success rates, especially if associated with concurrent microdeletion in other loci. The critical spermatogenic gene in the AZFb region is the RNA-binding motif (RBM) gene, which produces an RNA-binding protein localized to germ cell nuclei (Ma et al, 1993). Microdeletion in the AZFc region is the most most commonly noted, in up to 13% and 6% of azoospermic and severely oligospermic men, respectively (Reijo et al, 1996). The AZFc region is the location for the Deleted in Azoospermia (DAZ) gene, which encodes an RNA-binding protein noted primarily in spermatogonia (Saxena et al, 2000; Collier et al, 2005). Isolated AZFc microdeletion portends a better prognosis because more than 50% of azoospermic men will have successful sperm retrieval (Silber et al, 1998; Oates 2002).

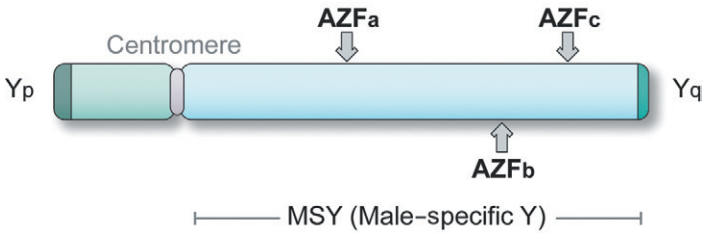


Figure 21–9. Y chromosome with azoospermia factor (AZF) region.

Considering the fact that Y chromosome microdeletions do not have direct health implications to patients other than in the fertility arena, couples should receive genetic counseling before obtaining and using surgically retrieved sperm for ICSI. The male offspring of these patients will be phenotypically normal but will harbor the father's microdeletion and thus are expected to have similar fertility challenges in their adulthood (Silber and Repping, 2002).

Disorders of Internal Ductal Development

Congenital Bilateral Absence of the Vas Deferens. CBAVD represents the mildest phenotypic presentation of cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction with cystic fibrosis at the severe end of the spectrum (Oates, 2008). The cystic fibrosis (CF) gene is located on chromosome 7 and encodes for CFTR, a membrane-spanning protein that assists transmembrane chloride ion transport, which is critical for the maintenance of epithelial-lined lumen. If only one CF allele is mutated, the patient may present with CBAVD without the pulmonary and pancreatic manifestations described in classic cystic fibrosis. However, if both alleles manifest mutations and critically reduce the CFTR reserve, patients may exhibit full-blown CF, although the degree of dysfunction depends on the nature of the CF gene mutations involved.

CBAVD accounts for 6% of cases of obstructive azoospermia. The descriptive name incorporates only a portion of the associated anomalies because these patients will also have a prominent caput with absence of the distal two thirds of the epididymis, atrophy, or hypoplasia of the seminal vesicles in addition to the characteristic vasal agenesis. In the absence of seminal vesicle contributions, the ejaculate will be azoospermic with low volume (typically <0.5 mL) and acidic pH (6.5) due to unbuffered scant prostatic secretions. Although TRUS can be used to confirm the seminal vesicle anomalies, the diagnosis of CBAVD can usually be made on the basis of clinical and semen findings. Spermatogenesis is normal and biopsy is not required unless undertaken for sperm retrieval for eventual ICSI. Renal anatomy is usually normal except in cases of non-CF mutation CBAVD, as discussed later.

Development of vasal agenesis is secondary to one of two genetic transmission patterns, either CF gene mutation or aberrant development of the early mesonephric duct. Almost 80% of men with CBAVD will have at least one detectable CF mutation with more than 500 types identified to date (Claustres, 2005). The most common mutation observed in CBAVD patients is a three-base pair deletion called delta-508, which accounts for almost 70% of CFTR mutations (Kerem et al, 1989). In CBAVD men without identifiable CF mutation, the syndrome is probably secondary to yet unidentified CF mutations or to improper morphogenesis of the mesonephric duct. These patients should be screened with a renal imaging study because up to 40% will have renal agenesis or fusion anomalies (Oates, 2002). Renal screening is not necessary for CBAVD patients testing positive for CF mutations. Clearly, all

patients with CBAVD should have thorough genetic counseling before proceeding with fertility treatment.

Because spermatogenesis is usually normal in these patients, sperm retrieval techniques via a percutaneous or open surgical route from either the caput epididymis or testis are usually successful in extracting excellent quality spermatozoa for ICSI (Phillipson, 2000). Cryopreserved sperm from these patients produce equally high pregnancy rates with ICSI similar to those observed with fresh specimens (Oates, 1996).

Ultrastructural Sperm Anomalies

Primary Ciliary Dyskinesia. Primary ciliary dyskinesia (PCD), also known as the *immotile cilia syndrome,* encompasses a spectrum of disorders involving ultrastructural abnormalities of the flagellum affecting all ciliated cells including the lining of the respiratory and sinus tracts, as well as sperm motility. Normal ciliary axonemal structure involves a 9 + 2 microtubular arrangement with 9 pairs surrounding a central doublet with axonemal bridges that connect the outer doublet to the central pair. Movement generation requires intact ATPase function that localizes to the dynein complex located in the peripheral doublets. Electron microscopy studies have demonstrated a variety of abnormalities in PCD including absence of outer and inner dynein arms, radial spokes, and central doublet. Of these, the lack of both dynein arms is the most commonly observed deficiency (Rott, 1979).

Typically, affected patients may rarely present with infertility as their initial complaint. They will rather initially present in childhood with chronic bronchiectasis and sinusitis due to dysfunctional movement of mucus through the upper airways and sinuses.

Kartagener syndrome is a variant of PCD with three components including chronic sinusitis and bronchiectasis, situs inversus, and infertility as manifested by low or absent sperm motility. The prevalence of PCD and Kartagener syndrome are 1 in 20,000 and 1 in 40,000, respectively (McClure, 1997). Ciliary dyskinesia has also been described in association with retinitis pigmentosa, presumably due to the axonemal support requirements of retinal cells (van Dorp et al, 1992). The genetic basis for PCD has been elusive due to the heterogeneous nature of the syndrome and the multitude of substructures required for ciliary function. Most cases appear to be inherited in an autosomal recessive pattern, although there have been isolated reports of autosomal dominant or X-linked transmission (Yokota et al, 1993; Narayan et al, 1994; Blouin et al, 2000). Diagnosis can be confirmed by electron microscopy examination of ciliary axonemal structure. Although there is no cure for the ultrastructural defects, sperm have been used successfully for ICSI with resulting normal births (Kay and Irvine, 2000). Genetic counseling is highly recommended before pursuing ICSI in these patients.

Globozoospermia. Globozoospermia, also called the *round-headed sperm syndrome,* is an unusual condition noted in less than 0.1% of infertile males (Dam et al, 2007a). Although sperm concentration and motility are normal, spermatozoa have a characteristic circular head due to the absence of the acrosomal cap and enzyme package including acrosin. This deficiency prevents the sperm from penetrating the zona pellucida and outer investment of the oocyte and from obtaining fertilization. Morphologic abnormalities have also been described in the nuclear chromatin, midpiece, and mitochondrial sheath. Familial studies strongly argue for genetic transmission with some evidence suggesting a mutation in the *SPATA16* gene, which is a spermatogenesis-specific locus, although the exact mode remains to be described (Carrell et al, 1999; Dam et al, 2007b). Standard ICSI has been successfully used for these patients, although some authors have suggested that it be combined with calcium ionophore oocyte activation to improve fertilization rates (Rybouchin et al, 1997; Kilani et al, 1998; Dirican et al, 2007).

Fibrous Sheath Dysplasia. Fibrous sheath dysplasia (FSD), also known as the *Stump-tail syndrome,* describes a malformation of the fibrous sheath investing the sperm tail, resulting in structural and functional impairment (Rawe et al, 2001). Spermatozoa have a distinctive morphologic appearance with coiled or markedly shortened tails and are immotile. Although the genetic basis of FSD has not yet been established, there are troubling reports that the sperm have higher rates of diploidy and sex chromosomal disomy, suggesting the need for genetic counseling before proceeding with fertility treatment (Baccetti et al, 2005; Moretti and Collodel, 2006). Despite these concerns, ICSI has been used successfully for patients with FSD (Olmedo et al, 2000).

Ejaculatory Dysfunction

Although an uncommon cause of male infertility, ejaculatory dysfunction is responsive to a variety of therapies allowing restoration of fertility in most patients. Ejaculation is a complex process requiring coordinated inputs from both the central and peripheral neural systems to produce expulsion of semen from the urethra. There are three distinct phases of semen production: emission, closure of the bladder neck, and ejaculation. In response to visual or sensory erotic stimulation to the cerebral cortex, signals are conducted down the thoracolumbar sympathetic nerves, resulting in contraction of prostatic smooth muscle, seminal vesicles, and the vas deferens and allowing deposition of pre-ejaculatory fluid into the posterior urethra, a process called *emission.* Bladder neck closure occurs concurrently with emission in response to sympathetic innervations. Finally, semen is propelled in an antegrade fashion from the posterior urethra in response to rhythmic contractions of the periurethral and pelvic floor muscles.

Various classifications of ejaculatory dysfunction have been described, but three broad categories account for most of the disturbances observed in the infertile male: functional, neurogenic, and retrograde.

Functional Ejaculatory Dysfunction

Functional disorders include premature and delayed ejaculation. Premature ejaculation (PE) is a common form of male sexual dysfunction, occurring in more than 30% of men between the ages of 18 and 60 (Laumann et al, 1999). PE may cause significant emotional distress in couples, yet the vast majority of patients will still have intravaginal ejaculation minimizing the infertility implications of this condition. If ejaculation is consistently occurring before intromission, semen may be collected by the couple and used for intravaginal insemination at home.

Delayed ejaculation is defined as persistent difficulty or inability to ejaculate despite the presence of sexual desire and erection. No clear neurologic basis for this condition has yet been established and it is widely believed to represent a psychogenic issue (Ohl et al, 2008). Some authors have described an association with strict religious upbringing and frequent use of masturbation (Stewart and Ohl, 1989; Perelman, 2006). Some men may benefit from sex therapy or vibratory stimulation to induce ejaculation, but many will require electroejaculation or surgical sperm retrieval for eventual fertility.

Neurogenic Anejaculation

Neurogenic anejaculation is usually the result of a spinal cord injury (SCI). In addition to the ejaculatory dysfunction in these

patients, many will also have erectile dysfunction and deficiencies in spermatogenesis related to thermal dysregulation of the testes, stasis of spermatozoa, and chronic genital tract infections. Oral therapies are rarely of value in these patients and most require penile vibratory stimulation (PVS), electroejaculation (EEJ), or surgical sperm retrieval to circumvent the lack of ejaculation.

Penile vibratory stimulation involves direct vibratory stimulation of the penile frenular region using specially designed equipment. Specific vibratory parameters including a vibration amplitude of 2.5 at 100 Hz appear optimal for ejaculation induction in SCI men (Sønksen, 1994). The best candidates for PVS are patients with complete SCI who have an intact ejaculatory reflex system: Specifically, patients with complete upper motor neuron lesions above T10 with preservation of sacral efferents, thoracolumbar sympathetic outflow, and intact communication between sacral and thoracolumbar segments will exhibit the best response to PVS because approximately 70% of these patients will have ejaculation in response to treatment (Ohl et al, 1996; Bird et al, 2001). Men with incomplete spinal cord lesions may have poor response to PVS because of cortical inhibition of the reflex arc preventing ejaculation. In addition, patients with lower spinal cord lesions or peripheral neural root injuries are unlikely to respond to PVS. The most serious adverse event associated with both PVS and EEJ is autonomic dysreflexia, a massive sympathetic discharge generally associated with SCI above the T6 level. Blood pressure monitoring is essential during any procedure on SCI patients. Men who are prone to autonomic dysreflexia may be given sublingual nifedipine, 10 to 20 mg 10 minutes before the procedure to minimize the blood pressure elevation (Steinberger et al, 1990). In general, PVS is well tolerated and can even be performed by the patient at home in the absence of autonomic dysreflexia. Sønksen reviewed the efficacy of PVS in SCI men reporting 102 pregnancies in 619 couples using home vaginal insemination or clinic intrauterine insemination (Sønksen and Biering-Sørenson, 1992). PVS remains the first-line therapy for SCI patients, producing better ejaculate quality than noted with EEJ procedures (Brackett et al, 1997; Ohl et al, 1997).

Electroejaculation may be used for SCI men who have failed a trial of PVS and is usually effective for any level of spinal cord injury, as well as in men with anejaculation from a variety of other mechanisms including retroperitoneal nerve injury from prior surgery such as retroperitoneal lymphadenectomy, diabetic neuropathy, multiple sclerosis, spina bifida, and psychogenic anejaculation. In the EEJ procedure, a rectal probe is inserted and pulsed direct electrical stimulation is applied to induce ejaculation. Although SCI patients often do not require an anesthetic during the procedure, men who retain normal pelvic and perirectal sensation will need general or spinal anesthesia. Because retrograde ejaculation often results, patients should have bladder catheterization before the procedure to minimize urine contact with the ejaculate. In addition, instillation of a sperm-friendly buffered medium into the bladder, systemic alkalinization with sodium bicarbonate, and hydration before the procedure will improve sperm survival in the bladder. Antegrade ejaculate is collected and the patient is again catheterized at the end of the procedure to recover any retrograde ejaculate. Sigmoidoscopy is also performed before and after the procedure to evaluate for preexisting rectal pathology that could interfere with the EEJ procedure, as well as identify any injuries resulting from the electrical stimulation of the rectal wall. Rectal injuries are rare, occurring in less than 0.1% of EEJ procedures, but they require prompt identification and treatment to minimize morbidity (Ohl and Sønksen, 1997). Electroejaculation procedures have been reported to produce ejaculates adequate for intrauterine insemination in 71% of men with SCI and 87% of patients with anejaculation postretroperitoneal lymph node resection (Ohl, 1989, 1995).

Regardless of the etiology of anejaculation, surgical sperm retrieval via either percutaneous or open biopsy of the epididymis or testis remains an effective option for management. One study conducted a cost-benefit analysis of EEJ coupled with intrauterine insemination versus ICSI using surgical sperm retrieval in SCI patients, noting that EEJ was the cost-effective approach if the procedure could be performed without anesthesia. However, in those patients requiring anesthesia for the EEJ, the cost-benefit analysis favored surgical sperm retrieval via local anesthetic followed by ICSI (Ohl, 2001).

Retrograde Ejaculation

Retrograde ejaculation occurs when seminal fluid preferentially flows into the bladder, instead of the normal antegrade direction due to failure of the bladder neck to close. The diagnosis is confirmed by identification of 10 to 15 sperm per HPF in a centrifuged specimen of postejaculation urine. The causes of retrograde ejaculation include incompetence of the bladder neck usually from prior surgery such as transurethral resection of the prostate gland, medications including α blockers and antidepressants, and diseases causing neurologic pathology such as diabetes and multiple sclerosis. Before initiating therapy, potential reversible etiologies such as medications should be removed if possible. In the absence of correctible etiologies, a trial of sympathomimetic medication therapy may be useful in increasing sympathetic tone of the bladder neck and vas deferens, especially in patients with slowly progressive disease such as diabetic neuropathy or in those with failure of emission due to disruption of retroperitoneal sympathetic innervation from prior surgery. Table 21–14 lists some of the standard medication regimens described. Medical therapy can produce a spectrum of results including conversion of retrograde to antegrade ejaculation, increase in ejaculatory volume, and development of retrograde ejaculation in a previously anejaculatory patient (Brooks et al, 1980; Kamischke and Nieschlag, 2002). These regimens must be used judiciously because side effects include tachycardia and hypertension, which may be particularly concerning in the diabetic patient at risk for occult cardiovascular disease.

Patients with retrograde ejaculation who do not respond to medical therapy may have sperm recovered from the bladder for use in intrauterine insemination as detailed earlier. With proper preparation of the bladder to retain sperm viability and laboratory sperm processing, this technique is an effective and economical method of treatment (Van der Linden, 1992).

Immunologic Infertility

Immunologic mechanisms of infertility remain poorly understood and controversial, both in cause and treatment. The development

Table 21–14.

Medication Regimens for Treatment of Retrograde Ejaculation

MEDICATION	DOSE
Phenylpropanolamine	75 mg po bid
Ephedrine	25-50 mg po qid
Pseudoephedrine	60 mg po qid or 120 mg po bid
Imipramine	25 mg po bid

of antisperm antibodies (ASA) results from a variety of conditions that cause disruption of the blood-testis immune barrier, resulting in exposure of sperm antigens to the systemic immune system. Elevated levels of ASA have been associated with gonadal trauma, testicular torsion, cryptorchidism, varicocele, genital infections, and prior testicular biopsy, although it has long been recognized that many patients will have no clear inciting event (Ansbacher and Gangai, 1975; Koskimies and Hovatta, 1982; Witkin and Toth, 1983; Golomb et al, 1986). Prior vasectomy is a leading cause of clinically significant immunologic infertility with ASA development reported in 34% to 74% of vasectomized men and persisting in 38% to 60% after vasectomy reversal (Broderick et al, 1989; Francavilla et al, 2007). The potential detrimental effects of ASA depend on the location of binding to the sperm and include impaired sperm motility, reduced binding and penetration of the zona pellucida, inhibition of the acrosome reaction, and reduced sperm survival in the female reproductive tract. The degree of fertility impairment is related to the amount of antibody binding, with one series noting IVF fertilization rates of 27% in men with 80% or more of sperm bound with IgG or IgA versus 78% in patients with less than 80% binding (Clarke et al, 1985).

A critical assessment of effective treatment options for immunologic infertility is hampered by a lack of controlled, prospective studies and the absence of a standard definition of the disease. Current treatment strategies use two main approaches: immunosuppressive therapy or assisted reproduction using laboratory techniques to lower antibody levels. Immunosuppression using corticosteroid therapy remains the most commonly used therapeutic approach with reported pregnancy rates ranging from 6% to 50% despite consistent reductions in antibody titers (Turek and Lipshultz, 1994). Many different regimens have been employed in uncontrolled studies, making it difficult to critically compare results. Hendry conducted a 6-month randomized trial using high-dose prednisolone given on days 1 through 10 of the female partner's cycle followed by a rapid taper over 2 days (Hendry et al, 1990). Pregnancy rates were 31% in the treatment group compared with 9% in the untreated men. A more recent double-blind, placebo-controlled study using methylprednisolone treatment for three cycles reported a significant reduction in sperm-associated IgG titers but no significant improvement in pregnancy rates in the treated group (Haas and Manganiello, 1997). Although therapy may be helpful in some patients, this therapeutic benefit must be weighed against the potential risks of steroid treatment including fluid retention, bone loss, gastrointestinal bleeding, and aseptic necrosis of the femoral head (Naz, 2004).

Assisted reproduction strategies for immunologic infertility have centered on using semen processing techniques to attempt removal of ASA for IUI and IVF. Simple sperm wash and percoll gradient methods of sperm preparation do not reliably remove ASA attached to the sperm surface (Haas and D'Cruz, 1988; Windt et al, 1989; Almagor et al, 1992). Despite the persistent presence of ASA after sperm processing, studies have suggested that IUI may be an effective and economical treatment for ASA-mediated infertility in some couples. One series reported a pregnancy rate of 64% after three cycles of IUI in men with ASA who produced ejaculate into a sterile medium (Ombelet et al, 1997). These results were considerably better than the conception rates per cycle of 3% to 10% reported in ASA-positive men using untreated sperm (Haas,1991; Francavilla et al, 1992). Intracytoplasmic sperm injection appears to be an effective treatment for ASA-mediated infertility when IUI fails, although there have been some concerning reports regarding postfertilization development. Fertilization and cleavage rates with ICSI treatment appear to be similar in ASA-positive and ASA-negative men (Lahteenmaki et al, 1995). However, ASA may have direct negative effects on developing embryos as manifested by higher embryonic degeneration and miscarriage rates than those observed in ASA-negative men (Naz, 2004).

Idiopathic Infertility

Despite the diagnostic advances in the field of male infertility, more than 30% of patients will still have no discernible cause for abnormal semen analyses (Nieschlag, 1997). Although it is anticipated that future developments will allow identification of the etiology for subfertility in these patients, at present they are considered idiopathic disorders that defy specific treatment recommendations. In the absence of obvious causality, therapy involves the employment of empiric medical therapy or assisted reproductive techniques to be discussed later. Empiric pharmacologic treatments have usually involved endocrine agents, with a variety of different tested therapies (Table 21–15). Although small series provide support for some empiric therapies, large placebo-controlled trials are lacking in this area, further confounding decision making in this difficult population, especially in the context of a 26% background pregnancy rate for untreated couples with abnormal semen parameters (Collins et al, 1983; Siddiq and Sigman, 2002).

Empiric Medical Therapy

Gonadotropin-Releasing Hormone Agonists. The justification for use of gonadotropin-releasing hormone agonists (GnRHs) involves the observation that these agents are effective for treatment of hypogonadotropic hypogonadism, implying that stimulation of FSH elevation may be beneficial even in the absence of known deficiency. Although multiple studies of empiric GnRH therapy have yielded conflicting results, two small controlled studies failed to show significant improvements in semen parameters (Badenoch et al, 1988; Crottaz et al, 1992). In addition, most studies have not shown significant increases in pregnancy rates, further reinforcing the conclusion that the expense of the therapy is not justified by improvements in fertility outcomes.

Table 21–15.

Empiric Pharmacologic Therapy

Gonadotropin-releasing hormone
Gonadotropins
Luteinizing hormone (human chorionic gonadotropin)
Follicle-stimulating hormone (human menopausal gonadotropin)
Antiestrogens
Clomiphene citrate
Tamoxifen citrate
Aromatase inhibitors
Testolactone
Anastrozole
Other
Antioxidant vitamins
L-carnitine
Kallikrein
Thyroid hormone
Dopamine agonist for hyperprolactin-associated infertility
Bromocriptine
Cabergoline

Gonadotropins. Multiple studies employing various formulations to include hCG, hMG and recombinant forms of gonadotropins have yielded conflicting results. A Cochrane meta-analysis suggested a modest 9% increase in pregnancy rates in the 3-month GnRH treatment group over controls, although even this analysis was underpowered to allow definitive assessment of impact due to lack of studies meeting selection criteria (Attia et al, 2006). Studies of GnRH treatment in men before ICSI have not shown significant improvements in pregnancy rates (Ashkenazi et al, 1999; Baccetti et al, 2004).

Antiestrogens. Antiestrogens remain the most commonly employed medical therapy for idiopathic male infertility. The two main formulations, clomiphene citrate and tamoxifen citrate, are nonsteroidal selective estrogen receptor modulators. By blocking the estrogen receptors at the hypothalamus and pituitary levels, this class of agents minimizes the estrogenic-mediated inhibition of gonadotropin release, resulting in elevation of gonadotropin levels. Numerous clinical trials with both agents have been conducted with conflicting results. Although some controlled studies with clomiphene citrate have shown improvement in semen parameters (Ronnberg, 1980; Wang et al, 1983; Micic and Dotlic, 1985), others have failed to show significant changes (Abel et al, 1982; Sokol et al, 1988; WHO, 1992). A meta-analysis of available studies did not reveal a significant improvement in pregnancy rates with clomiphene therapy (Liu, 2003). Similar randomized controlled trials using tamoxifen therapy have not conclusively supported efficacy in either improved semen parameters or pregnancy rates (Torok, 1985; Krause et al, 1992). A Cochrane meta-analysis combining 10 clomiphene and tamoxifen randomized controlled studies failed to show improvements in pregnancy rates with therapy (Vandekerckhove et al, 2000). A more recent study examined combination therapy with tamoxifen (20 mg/day) and testosterone replacement (120 mg/day testosterone undecanoate) for patients with idiopathic oligoteratospermia, noting improvements in semen parameters and pregnancy rates (Adamopoulos et al, 2003). These results remain to be confirmed in other large controlled studies. Other investigators used clomiphene therapy for men with nonobstructive azoospermia, titrating the dose to elevate serum testosterone levels to between 600 and 800 ng/dL (Hussein et al, 2005). In this noncontrolled trial, 64% had spontaneous return of sperm to the ejaculate with mean density of 3.8 million/mL. In those with persistent azoospermia, testicular biopsy was successful in retrieving sperm for ICSI in all cases.

Aromatase Inhibitors. Aromatase inhibitors suppress the activity of aromatase, a cytochrome P-450 enzyme concentrated in the testes, liver, brain, and adipose tissue. Aromatase is responsible for the conversion of testosterone to estradiol, so blockade produces functional effects similar to the antiestrogen class of medications. Aromatase inhibitors have been postulated to have incremental benefit over antiestrogens in patients with lower serum testosterone to estradiol ratios (<10) and in obese patients. Testolactone and anastrozole are the two main agents that have been used for the treatment of idiopathic infertility. Although one study using testolactone noted improvement in semen parameters in men with severe idiopathic oligospermia (Pavlovich et al, 2001), a controlled crossover trial failed to identify treatment benefit over placebo (Clark and Sherins, 1989). A newer study by Raman examined subgroups of infertile men with abnormal testosterone to estradiol (T/E2) ratios treated with either testolactone or anastrozole (Raman and Schlegel, 2002). Men in both treatment groups had significant improvements in their T/E2 ratios, sperm concentration, morphology, and motility, although pregnancy rates were not reported. Although these reports are intriguing, the expense of these agents and the absence of large controlled studies will limit use until further study.

Antioxidant Therapy. With growing awareness of the role of oxidative stress in idiopathic male infertility, antioxidant supplementation has become a common form of empiric therapy. The antioxidant vitamins α-tocopherol (vitamin E), ascorbic acid (vitamin C), and the retinoids (vitamin A), as well as L-carnitine, an amino acid important for mitochondrial metabolism, have all been postulated to have therapeutic benefit for male subfertility. Various studies of antioxidant vitamin supplementation have yielded conflicting conclusions on both semen parameter and pregnancy rate results (Suleiman et al, 1996; Rolf et al, 1999; Keskes-Ammar et al, 2003). More recent studies in infertile men with elevated levels of sperm DNA fragmentation revealed improvements in fragmentation rates and increased rates of ICSI-derived pregnancy following vitamin C and E supplementation (Greco et al, 2005a-c). Randomized double-blind studies examining the effect of L-carnitine administration in men with idiopathic asthenospermia have yielded contrasting results on post-treatment semen parameters, preventing definitive conclusions on the efficacy of supplementation (Balercia et al, 2005; Sigman et al, 2006).

ASSISTED REPRODUCTION

Assisted reproductive techniques have become increasingly popular for the management of idiopathic male infertility, unexplained infertility, or in cases in which no therapy is available or has effectively resulted in conception. These techniques involve the manipulation of sperm, ova, or both in an attempt to improve the chances of conception. Controlled ovarian hyperstimulation is used to induce simultaneous development of multiple ova in females by giving oral clomiphene citrate or parenteral gonadotrophins.

Artificial Insemination

Artificial insemination is an assisted conception method that can be used to alleviate infertility in selected couples. The rationale behind the use of artificial insemination is to increase the gamete density near the site of fertilization. Several different techniques have been used for artificial insemination. The original technique used for more than a century was intravaginal insemination, where an unprocessed semen sample is placed high in the vagina. In the latter half of the 20th century, the cervical cap was developed to maintain the highest concentration of semen at the external os of the cervix. It was soon discovered that placing the semen sample into the endocervix (intracervical insemination) resulted in pregnancy rates similar to that obtainable using a cervical cap and superior to those seen with high vaginal insemination.

The effectiveness of artificial insemination has been clearly established in specific subsets of infertile patients such as those with idiopathic infertility, infertility related to a cervical factor, or a mild male factor infertility (Keck et al, 1997; Cohlen, 2004). An accepted advantage of artificial insemination is that it is generally less expensive and less invasive than other assisted reproductive technology (ART) procedures (Goverde et al, 2000). The source of semen for artificial insemination can be either from the woman's male partner or a donor, who usually remains anonymous. In the past, the only available options for couples with severe male factor infertility including severe oligospermia or failure to conceive using partner insemination were either donor insemination or

adoption. Since the widespread availability of IVF using ICSI, many couples with severe male factor infertility have chosen to procreate their own genetic children using these techniques. However, donor insemination remains an option when IVF/ICSI has been unsuccessful. Alternatively, many candidates for IVF/ICSI initially choose donor insemination because it is less invasive and ultimately more likely to achieve pregnancy for couples with limited resources. Some women choose donor insemination because they are not candidates for IVF/ICSI. Perhaps the most obvious situation is women without male partners who seek pregnancy. The use of donor insemination is also indicated when the male partner has no viable sperm or when IVF/ICSI fails to achieve fertilization. Finally, men with a known genetic disorder often choose donor insemination to avoid transmission to their children.

Thorough evaluation of all potential sperm donors other than sexually intimate partners is necessary to avoid inadvertent transmission of sexually transmitted diseases or known genetic syndromes (ASRM, 1990). All donors should undergo a review of relevant medical records, personal and family history, and a physical examination. Determination of normal semen characteristics is extremely important. In addition, blood grouping and karyotyping are performed. Each donor must be screened for risk factors and clinical evidence of communicable diseases including human immunodeficiency virus types 1 and 2; human T-lymphotropic virus types I and II; hepatitis B and C; cytomegalovirus; human transmissible spongiform encephalopathy (including Creutzfeldt-Jakob disease); *Treponema pallidum; Chlamydia trachomatis;* and *Neisseria gonorrheae*. If the donor is deemed acceptable and is aware of the ethical and legal implications, semen can be collected. All donor semen samples are cryopreserved and quarantined for 6 months. Before a donor sample is used for insemination, the donor is retested and his eligibility is determined.

Presently, there is no general consensus as to the best sperm preparation technique for IUI. In general, swim-up, simple sperm washing, density gradient centrifugation, and glass wool filtration methods all effectively produce adequate sperm samples. However, some preparation techniques appear better suited for particular types of samples; thus the technique chosen should be tailored to individual samples. The preparation techniques most commonly used today are the double-density gradient centrifugation and the glass wool filtration sperm washing techniques. These techniques have been shown to improve the number of morphologically normal spermatozoa with grade A motility and normal chromatin condensation in the prepared sample (Erel et al, 2000; Sakkas and Tomlinson, 2000; Hammadeh et al, 2001). In addition, these techniques best reduce the amount of reactive oxygen species and leukocytes in the prepared sample and provide spermatozoa with minimal chromatin and nuclear DNA anomalies and high nuclear maturity rates. For semen samples with normal or near-normal sperm parameters, it has been shown that swim-up and density gradient techniques result in higher pregnancy rates compared with the washing, swim-down, and refrigeration/heparin techniques (Carrell et al, 1998). For poor samples, the density gradient centrifugation and glass wool filtration techniques appear to be superior. In cases of very low sperm counts, simple sperm washing will recover the highest number of sperm, both motile and nonmotile.

In-Vitro Fertilization/ICSI

IVF involves using controlled ovarian hyperstimulation to recruit multiple oocytes during each cycle from the female partner. Follicular development is monitored ultrasonically, and ova are harvested before ovulation with the use of ultrasound-guided needle aspiration. The recovered oocytes are mixed with processed semen to perform in-vitro fertilization. The developing embryos are incubated for 2 to 3 days in culture and then placed transcervically into the uterus. Generally, only 20% to 30% of transferred embryos result in clinical pregnancies.

Notwithstanding the broad success of in-vitro fertilization (IVF), failure to achieve fertilization still plagues a substantial group of patients, with sperm abnormalities being the main culprit. In the 1980s, several micromanipulation procedures were adopted from animal husbandry to assist gamete interaction, and this resulted in the development of intracytoplasmic sperm injection (ICSI), a procedure through which an oocyte can be fertilized independently of the morphology and/or motility of the single spermatozoon injected. The procedure was first used in cases of fertilization failure after standard IVF or when an inadequate number of sperm cells were available. The consistency of fertilization independent of the functional quality of the spermatozoon has extended the application of ICSI to immature spermatozoa retrieved surgically from the epididymis and testis. Moreover, the need to denude the oocyte has allowed assessment of the nuclear maturity of the oocyte. ICSI is also preferred in conjunction with preimplantation genetic diagnosis and has recently been used to treat HIV-discordant couples, where there is a pressing need to minimize the exposure of the oocyte to a large number of spermatozoa. For all ages and with all the different sperm types used, fertilization after ICSI is at approximately 70% to 80% and it ensures a clinical pregnancy rate of up to 45%. These results have made ICSI a procedure comparable in popularity with IVF and have minimized the need for couples suffering from all forms of male infertility to resort to adoption or the use of donor sperm (Palermo et al, 2009).

Key Points

- Male factor infertility accounts for almost 50% of infertility.
- There are three different approaches to treat male infertility depending on the cause:
  - Treat the man to maximize his fertility
  - Extract sperm for use in assisted reproduction if optimization is not possible
  - Use donor sperm or adoption
- Comprehensive male factor evaluation is critical to identify factors that may affect the man's health, as well as that of his offspring.

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chapter
22

Surgical Management of Male Infertility

Marc Goldstein, MD, DSc (Hon)

Surgical Anatomy
Testis Biopsy
Vasography
Vasovasostomy
Surgery of the Epididymis
Transurethral Resection of the Ejaculatory Ducts
Electroejaculation
Sperm Retrieval Techniques
Varicocelectomy
Orchiopexy in Adults

Since the previous edition, the indications for and techniques of surgery for male infertility have been significantly refined, resulting in substantially increased success in the management of male factor infertility. These advances include (1) increasing use of genetic and molecular biologic markers (see Chapters 20 and 21) to better select patients for surgical treatment; (2) improved techniques for microsurgical reconstruction for obstruction; (3) the use of varicocelectomy for enhancement of spermatogenesis in azoospermic or severely oligospermic men (Matthews et al, 1998; Kim et al, 1999); and (4) refined microsurgical techniques for sperm retrieval combined with in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) for men with nonobstructive azoospermia. Even **men with nonobstructive azoospermia due to Klinefelter syndrome, once regarded as hopeless cases, can now father biologic offspring with assisted reproductive techniques** (Tournaye et al, 1996; Palermo et al, 1998; Ramasamy et al, 2009).

Use of transrectal high-resolution ultrasound, as well as scrotal ultrasound with color flow Doppler, has substantially improved our diagnostic and therapeutic abilities. Transrectal ultrasound of the seminal vesicles provides not only diagnostic information but ultrasound-guided aspiration of the seminal vesicles that allows retrieval of sperm to be used for IVF with ICSI (Jarow, 1996). Power Doppler may allow identification of pockets of sperm production in the testis, which may help guide sperm retrieval in men with nonobstructive azoospermia (Har-Toov et al, 2004; Herwig et al, 2004; Tunc et al, 2005).

IVF with ICSI has expanded our ability to treat even the most severe forms of male-factor infertility such as unreconstructable reproductive tract obstruction and nonobstructive azoospermia. It is, however, a costly procedure and an intense process for the female partner, with associated risks of complications including ovarian hyperstimulation, multiple gestations, and complications of the procedures for oocyte retrieval. Furthermore, as ICSI bypasses all natural biologic barriers, it raises realistic concerns of passing genetic abnormalities to the offspring (Kim et al, 1998; Foresta et al, 2005). Thus proper selection of couples for advanced assisted reproductive technology, along with adequate genetic counseling, is mandatory.

On the other hand, recent analyses clearly indicate that **specific treatments for male-factor infertility such as microsurgical reconstruction for obstructive azoospermia and varicocelectomy for impaired testis function, in properly selected patients, remain the safest and most cost-effective ways of managing infertile men** (Kolettis and Thomas, 1997; Pavlovich and Schlegel, 1997; Lee et al, 2008). Specific treatment aimed at correcting or enhancing male infertility can upgrade a couple from intensive levels of assisted reproduction to simpler methods or even to naturally conceived pregnancies.

For men with unreconstructable obstruction, as well as men with nonobstructive azoospermia, surgical retrieval of sperm to achieve fertilization, pregnancy, and live birth with IVF and ICSI is a feasible management option. The development and recent refinement of the various techniques of surgical sperm retrieval, from testes, epididymides, or seminal vesicles with percutaneous or open surgical approaches, have expanded the armamentarium of urologists treating infertile men. In particular, the employment of the operating microscope to evaluate and identify individual seminiferous tubules more likely to contain sperm has significantly improved the success of testicular sperm extraction (Schlegel, 1999) while minimizing morbidity significantly (Tsujimura et al, 2002; Ramasamy et al, 2005).

The use of microsurgical techniques has also been extended to varicocelectomy. Varicoceles have long been known to be associated with male infertility and have now clearly been shown to result in progressive, duration-dependent testicular injury (Russell, 1957; Lipshultz and Corriere, 1977; Nagler et al, 1985; Gorelick and Goldstein, 1993; Sigman and Jarow, 1997). **Furthermore, microsurgical varicocelectomy, previously reserved only for men with oligospermia, has now been applied to men with nonobstructive azoospermia, resulting in**

induction of spermatogenesis and successful return of sperm to the ejaculate in many cases (Matthews et al, 1998; Kim et al, 1999; Pasqualotto et al, 2003; Pasqualotto et al, 2006; Ishikawa et al, 2008). Although varicocelectomy has historically been reserved for the treatment of infertile men and varicocele-induced pain, there is an emerging concept of **early repair of varicoceles to prevent both future infertility and Leydig cell dysfunction.** Substantial evidence has accumulated suggesting that varicocele adversely affects Leydig cell function, resulting in lower serum testosterone levels when compared with age-matched controls without varicocele. Varicocelectomy can halt and even partially reverse this decline (Castro-Magana et al, 1989; Su et al, 1995; Cayan et al, 1999). **In selected men, varicocelectomy may be an effective treatment for symptomatic, age-related androgen deficiency** (Tanrikut et al, 2011) **a condition increasingly referred to as andropause or testosterone deficiency syndrome (TDS). Thus with safer and more effective microsurgical techniques, early varicocelectomy has expanded the urologist's role from that of salvaging remaining testicular function to that of preventing future infertility and TDS.**

When surgery for male infertility is undertaken, only rarely is the life (or death) of the patient at stake. What is at stake when the surgery described in this chapter is undertaken is new life, with the potential for altering not only the quality of a couple's life but the future of our species. The responsibilities assumed by the surgeon in these circumstances demand the utmost in judgment and skill. **Many of the procedures described in this chapter are among the most technically demanding in all of urology.** Acquisition of the skills required to perform them demands intensive laboratory training in microsurgery and a thorough knowledge of the anatomy and physiology of the male reproductive system. **Attempting such surgery only occasionally and without proper training is a terrible disservice to the patient, the couple, and future humanity.**

SURGICAL ANATOMY

The scrotal contents are unique in their accessibility for physical examination, imaging modalities, and surgical intervention. The success of surgery for male infertility and scrotal disorders is predicated on selection of the correct operation and the most appropriate surgical approach. The details of the history and careful physical examination followed by confirmatory, judiciously selected laboratory and imaging procedures are presented in Chapter 21. When surgical intervention for diagnostic or therapeutic purposes is indicated, a thorough understanding of the anatomy (see Chapter 2) and physiology (see Chapter 20) of the male reproductive system is requisite for planning and carrying out a surgical procedure with the highest probability of success and lowest morbidity.

The key points of surgical anatomy follow.

Testicular Blood Supply

The main blood supply to the testis is from the testicular (internal spermatic) artery arising directly from the aorta (Table 22–1). A second blood supply comes from the artery of the vas deferens (deferential artery), which derives from the hypogastric (internal iliac) artery or the superior vesicle artery (also a branch of the hypogastric). The third blood supply, primarily to the tunica vaginalis but with branches going to the testes, comes from the cremasteric (external spermatic) artery, which derives from the inferior epigastric artery. **The testicular artery is the main blood supply to the testes.** Its diameter exceeds the diameter of the deferential (vasal) artery plus the cremasteric artery combined (Raman and Goldstein, 2004). Although vasal and cremasteric arteries can provide adequate blood supply to the testes in the event that the testicular artery is ligated, especially in children, **atrophy and/or azoospermia has resulted from testicular artery ligation both in adults and children.** Experience with the one-stage Fowler-Steven operation for orchiopexy, in which the testicular artery is intentionally ligated, indicates that 20% to 40% of such testes atrophy, although the rate of atrophy is lower in the staged procedure.

Special attention should be paid to men who have undergone vasectomy because the vasal artery has likely been compromised. In these men, maintaining the integrity of the testicular artery in any future operations such as varicocelectomy is critical (Lee JS et al, 2007).

Table 22–1.

Blood Supply to Testis, Epididymis, and Vas Deferens

Testis

1. Testicular (internal spermatic) artery from aorta (main blood supply)
2. Deferential artery from internal iliac (hypogastric) artery/superior vesicle artery
3. Cremasteric (external spermatic) artery from inferior epigastric artery

Epididymis

1. Superior epididymal artery derived from testicular artery
2. Inferior epididymal artery derived from vasal (deferential) artery

Vas Deferens

1. Seminal vesicle end: deferential artery
2. Testicular end: deferential artery and inferior epididymal artery

Epididymal Blood Supply

The epididymis has a rich blood supply (see Table 22–1). The superior and medial epididymal arteries derive from the testicular artery. The blood supply to the cauda (inferior pole) of the epididymis derives from the vasal (deferential) artery. The two main blood supplies to the epididymis, running superiorly and inferiorly, form an extensive interconnection such that if the vasal artery is ligated from previous vasectomy, the blood supply to the epididymis from the testicular artery is more than adequate. In addition, in preparation for vasoepididymostomy or vasovasostomy, the epididymis can be intentionally dissected off of the testis and mobilized to the caput (see Technique When Vasal Length Is Severely Compromised) with the inferior and medial epididymal arteries intentionally ligated without adverse consequence. **As long as the superior epididymal artery remains intact, the blood supply to the epididymis will be adequate.**

Blood Supply of the Vas Deferens

The vas deferens obtains its blood supply from two sources (see Table 22–1). The seminal vesical (abdominal) end of the vas derives

its blood supply from the deferential (vasal) artery, a branch of the internal iliac (hypogastric) artery or of its branch, the superior vesicle artery. The testicular end of the vas receives additional blood supply from the inferior epididymal arterial interconnections, which extends onto the vas deferens. The two blood supplies to the vas deferens freely anastomose with each other. **After vasectomy, if the vasal vessels are ligated, the testicular end of the vas receives all of its blood supply from branches of the testicular artery and epididymal artery, whereas the seminal vesical (abdominal) end of the vas receives all of its blood supply from the deferential artery. The vas deferens receives no blood supply from the surrounding cremaster muscle or from any blood vessels from the spermatic cord. Therefore if the vas deferens is sectioned or obstructed in two different locations, the intervening segment will fibrose due to lack of blood supply. Therefore two simultaneous vasovasostomies cannot be safely performed on the same vas if the vasal vessels have been interrupted in both locations.**

Anatomy of the Excurrent Ducts

Sperm and testicular fluid exit the testes through 7 to 11 tiny efferent ducts. These ducts become convoluted when they exit the testes and form the caput of the epididymis (see Chapter 20). At that level, they freely anastomose with each other. They all coalesce at the distal caput to form a single epididymal tubule from the caput-corpus junction all the way to the vas deferens. Therefore **if the epididymis is accidentally injured or ligated distal to the caput, the entire system on that side will be completely obstructed.** This is an important consideration when performing epididymal surgery or surgery near the epididymis. **Hydrocelectomy** is a common surgical procedure that can result in **iatrogenic injury to the epididymis.** In long-standing large hydroceles, the epididymis is often splayed out and difficult to identify. **Generous margins from the epididymis should be allowed when performing hydrocelectomy** (see Chapter 37). Orchiopexy for torsion can also result in inadvertent injury to the epididymis. **A single stitch through an epididymal tubule in the corpus or cauda will result in complete obstruction** of that side. Because there are multiple lobules at the levels of the caput, **puncture of a single tubule for sperm aspiration can be safely performed at the most proximal region of the caput** without significantly compromising the flow of sperm into the corpus. Multiple punctures of many tubules at the caput, or any puncture distal to the caput, however, can cause obstruction.

Ejaculatory Ducts

The left and right ejaculatory ducts enter the prostatic urethra at the level of the utricle. Obstruction of ejaculatory ducts can lead to azoospermia. Transurethral resection of the ejaculatory ducts (TURED) can relieve the obstruction. TURED should not be considered a benign procedure because it is occasionally associated with significant morbidity (see Transurethral Resection of the Ejaculatory Ducts later). Normally, the ejaculatory ducts contain a valvelike mechanism that prevents reflux of urine into the ejaculatory duct. **After transurethral resection of the ejaculatory ducts, a significant percentage of men will develop reflux of urine up the excurrent ductal system** (Vazquez-Levin et al, 1994), **causing chemical and/or bacterial epididymitis.**

TESTIS BIOPSY

Indications

The indications for testis biopsy are detailed in Chapter 21. Briefly, **testis biopsy is indicated in azoospermic men with testis of normal size and consistency, palpable vasa deferentia, and normal serum follicle-stimulating hormone (FSH) levels.** Under these circumstances, **biopsy will distinguish obstructive from nonobstructive azoospermia.** In men with **congenital absence of vasa and normal serum FSH levels,** biopsy always reveals spermatogenesis (Goldstein and Schlossberg, 1988) and **biopsy is not necessary** before definitive sperm aspiration and IVF with ICSI. **Diagnostic biopsy should usually be performed bilaterally irrespective of the size discrepancy of the two testes.** Good spermatogenesis is sometimes found in small, firm testes, whereas biopsies of large, healthy testes may reveal maturation arrest.

The ability to achieve pregnancy with only a single testicular sperm has turned biopsy into a potentially therapeutic, as well as diagnostic, procedure. Even men with markedly elevated serum FSH levels and small, soft testes (meaning certain testicular failure) often harbor rare mature sperm in their testes. These sperm can be extracted using techniques described later (see Testicular Sperm Extraction) and employed for IVF with intracytoplasmic injection of testicular sperm.

The recently discovered heterogeneity of the testes of men with nonobstructive azoospermia, coupled with the ability of testicular sperm to acquire motility (Jow et al, 1993), has resulted in changes in the techniques of testis biopsy. **Examination of fresh, unfixed tissue for the presence of sperm with tails** and possible motility, **as well as examination of multiple samples if sperm are not found initially, are now recommended. Furthermore, optimal care requires the availability, at the time of biopsy, of an andrology laboratory capable of processing and cryopreserving any sperm found at the time of biopsy.**

Open Testis Biopsy—Microsurgical Technique

Open biopsy remains the gold standard because it provides an optimal amount of tissue both for accurate diagnosis and retrieval of sperm for IVF (Rosenlund et al, 1998; Schlegel, 1999; Dardashti et al, 2000). Open testis biopsy may be performed using either general, spinal, or local anesthetic. Although local anesthesia of just the skin and tunicas without a cord block is uncomfortable, local anesthesia with spermatic cord block can be effective and comfortable. However, there are limitations of the cord block. In animal studies, the incidence of accidental damage to the testicular artery during blind cord block is 5% (Goldstein et al, 1983). In addition, if there has been previous scrotal surgery with scar or adhesions and more extensive dissection and manipulation may be required, the author prefers to use general or spinal anesthetic.

The surgeon's goals when performing a testis biopsy are to provide an optimal tissue sample, avoid trauma to the specimen, and avoid injury to the epididymis or testicular blood supply. Open biopsy under magnification (preferably with an operating microscope) satisfies these requirements.

An assistant stretches the scrotal skin tightly over the anterior surface of the testis and confirms that the epididymis is posterior.

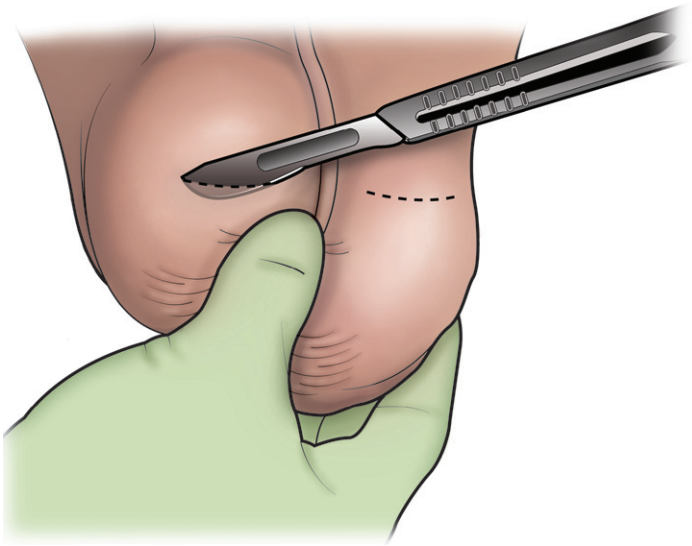


Figure 22–1. Bilateral 1-cm incisions made on each hemiscrotum.

Bilateral 1-cm transverse scrotal incisions provide good exposure with a minimum of scrotal bleeding (Fig. 22–1). Alternatively, a single vertical incision in the median raphe may be employed. The incision is carried through the skin and dartos muscle, and the tunica vaginalis is opened. **If the anatomy is distorted from previous surgery, the epididymis cannot be clearly palpated posteriorly. If the tunica albuginea cannot be clearly identified, the incision should be enlarged and the testis delivered.** The edges of the tunica vaginalis are held open with hemostats and any bleeding vessels are cauterized. **Use of loupes or, better yet, the operating microscope allows ready identification of a spot on the tunica albuginea relatively free of visible surface vessels.** The wound should be dry before incising the tunica albuginea to prevent saturation of the biopsy with blood. A 3- to 4-mm incision is made in the tunica albuginea with a 15-degree microknife (Fig. 22–2A). Small crossing vessels are cauterized with bipolar cautery and divided before excising a pea-sized sample of seminiferous tubules with razor-sharp iris scissors (Fig. 22–2B). **When handling testis biopsy material for permanent fixation, avoid tissue handling in any way (including with forceps) because this may traumatize and distort the testicular architecture.** The specimen is then deposited directly into Bouin, Zenker, or collidine-buffered glutaraldehyde solution. **Formalin fixation** results in distortion of testicular histology and **should not be used for testis biopsy. A touch-prep is made by blotting the cut surface of the testis several times with a glass slide** (Fig. 22–2C) **and adding a drop of saline, lactated Ringer, or human tubal fluid with IVF medium and a cover slip. Examination under high power using a light microscope with or without phase contrast will reveal the presence of sperm with tails and allow assessment of motility** (Fig. 22-2D). If no sperm are found in the touch prep, a second specimen may be cut for a wet squash prep. In this case the specimen is placed on a slide, a drop of saline is added, and the specimen is crushed under a coverslip (Jow et al, 1993). If no sperm are found, the tunica is closed with two to three interrupted sutures of 5-0 Vicryl (Fig. 22-2E) and another area is biopsied through the same skin incision. As described later in this chapter, **use of an operating microscope providing 10× to 25× magnification may allow selective biopsy of larger seminiferous tubules more likely to contain sperm** (Schlegel, 1999). **If sperm are identified,** the slide and additional **tissue removed are sent for cryopreservation** in the andrology laboratory. The location of the biopsy site where sperm were found is noted, and the tunica albuginea is closed with two to three interrupted sutures of 6-0 nylon. This assists identification of sites of spermatogenesis for future testicular sperm extraction for IVF/ICSI.

The tunica vaginalis is closed with 5-0 Vicryl suture for hemostasis. **Careful closure will assist structural identification in any future scrotal explorations such as epididymal reconstruction, aspiration, or testicular sperm retrieval** at the time of IVF with ICSI. The skin is closed with a subcuticular 5-0 Monocryl suture. The wounds are covered with Bacitracin ointment and a fluff-type dressing secured with a snug scrotal support. Antibiotics are unnecessary.

Percutaneous Testis Biopsy

Percutaneous testis biopsy using the same 14-gauge biopsy gun employed for prostatic biopsy is a blind procedure and could result in unintentional injury to either the epididymis or testicular artery. This technique should not be used when previous surgery has resulted in scarring and obliteration of normal anatomy. Diagnostic specimens obtained in this way often contain few tubules with poorly preserved architecture. When performed under local anesthesia, a cord block is necessary to minimize pain. The technique of percutaneous biopsy is described later in Testicular Sperm Extraction. As a therapeutic tool for sperm retrieval, percutaneous biopsy is most useful for fresh sperm retrieval for IVF/ICSI in men with obstructive azoospermia and normal spermatogenesis.

Percutaneous Testicular Aspiration

Testicular aspiration performed with a 23-gauge needle or angiocath sheath (Marmar) is probably less invasive and less painful than percutaneous biopsy. Although flow cytometric evaluation of this material can distinguish haploid from diploid cells and therefore confirm the presence or absence of late stages of spermatogenesis (Chan et al, 1984), direct wet examination of the aspirate for sperm and assessment of motility provide the most practical clinical information. Three or four aspirations can be performed until sperm are identified. In cases of obstructive azoospermia, these sperm can be used for IVF with ICSI (Craft et al, 1995) when sperm cannot be retrieved from the epididymis (see Testicular Sperm Extraction).

Complications of Testis Biopsy

Carefully performed, testis biopsy is associated with few complications (Schlegel and Su, 1997; Dardashti et al, 2000). **The most serious complication associated with testis biopsy is inadvertent biopsy of the epididymis.** If histologic evaluation of the biopsy material reveals epididymis with sperm within the epididymal tubule, obstruction of the epididymis at the site of the biopsy is certain. If, however, there are no sperm within the epididymal tubules, the patient is either obstructed above the level of the epididymal biopsy or has primary seminiferous tubular failure and no harm has been done.



Figure 22–2. **A,** A 3- to 4-mm incision is made in the tunica albuginea with a 15-degree ultrasharp microknife. **B,** Small crossing vessels are cauterized with bipolar cautery, and a pea-sized sample of seminiferous tubules are taken with a no-touch technique. **C,** A touch-prep is made by blotting the cut surface of the testis several times with a glass slide. **D,** Examination under high power using a light microscope will reveal the presence of sperm and allow assessment of motility. **E,** The biopsy site is closed with two to three interrupted sutures of 6-0 nylon.

The most common complication of testis biopsy is hematoma. Hematomas can be quite large and may require drainage. Use of magnification to avoid vessels and a bipolar cautery for hemostasis will help prevent this complication. Proper closure of the well-vascularized tunica vaginalis with a continuous suture of 5-0 Vicryl will minimize bleeding and adhesions.

With the rich blood supply of the scrotum and its contents, wound infection is rare in the absence of hematoma and antibiotics are unnecessary.

VASOGRAPHY

Indications

The absolute indications for vasography are as follows:

1. Azoospermia, plus
2. Complete spermatogenesis with many mature spermatids on testis biopsy, plus
3. At least one palpable vas

Relative indications for vasography are as follows:

1. Severe oligospermia with normal testis biopsy.
2. High level of sperm-bound antibodies that may be due to obstruction (Lee et al, 2009).
3. Low semen volume and poor sperm motility (partial ejaculatory duct obstruction).

Vasography should answer the questions:

1. Are there sperm in the vasal fluid?
2. Is the vas obstructed?

If the testis biopsy reveals many sperm, consider the following:

1. **Absence of sperm in vasal fluid indicates** obstruction proximal to the vasal site examined, most likely an **epididymal obstruction.** Vasography is done in this case with saline or indigo carmine to confirm patency of the seminal vesicle (distal) end of the vas before vasoepididymostomy.
2. **Copious vasal fluid containing many sperm indicates vasal or ejaculatory duct obstruction,** and formal contrast vasography is performed as described later to document the exact location of the obstruction.
3. **Copious thick white fluid without sperm in a dilated vas indicates secondary epididymal obstruction** in addition to a potential vasal or ejaculatory duct obstruction.

Vasography with radiographic contrast media and intraoperative radiograph are rarely indicated. There is no need to perform vasography at the time of testis biopsy for azoospermia unless immediate reconstruction is planned and the touch/wet prep biopsy reveals mature sperm with tails. If not meticulously performed, vasography can cause stricture or even obstruction at the vasography site, which can complicate subsequent reconstruction (Howards et al, 1975a; Poore et al, 1997). In addition, vasography is of no value in making the diagnosis of epididymal obstruction and the majority of nonvasectomy-related obstructions are epididymal.

If testis biopsy reveals normal spermatogenesis and the vasa are palpable, vasography, if necessary, should be performed only at the time of definitive repair of obstruction. General anesthesia provides the most flexibility for scrotal exploration, vasography, and repair of obstruction. Although local anesthesia can provide adequate analgesia, patients are often unable to lie still through several hours of microsurgery. Long-acting hypobaric spinal or continuous epidural anesthesia can be satisfactory alternatives.

Technique of Vasography and Interpretation of Findings

Inguinal hernia repair, particularly when performed in childhood, is known to be associated with vasal injury leading to obstruction. If there is no previous inguinal incision and the side of obstruction is unknown, the testis is delivered through a high vertical scrotal incision (see Scrotal later). The vas deferens is identified and isolated at the junction of the straight and convoluted portions of the vas deferens. Using an operating microscope and 10-power magnification, the vasal sheath is longitudinally incised and the vasal vessels carefully preserved (Fig. 22–3A).

A clean segment of bare vas is delivered and surrounded with a vessel loop. A straight clamp is placed beneath the vas to act as a platform. Under 25-power magnification, a 15-degree microknife is used to hemitransect the vas until the lumen is revealed (Fig. 22–3B). **Any fluid exuding from the lumen is placed on a slide, mixed with a drop of saline, and sealed with a coverslip for microscopic examination. If the vasal fluid is devoid of sperm with repeated sampling** after milking the epididymis and convoluted vas, **epididymal obstruction is present.** The end of the vas toward the seminal vesicles is then cannulated with a 24-gauge angiocatheter sheath and injected with 1 mL of lactated Ringer solution with a 1-mL tuberculin syringe to confirm its patency (Fig. 22–4). If the Ringer passes easily, formal vasography is not necessary. If further proof of patency of the vas deferens is desired, 1 mL of 50% dilute indigo carmine may be injected and the bladder catheterized. The presence of blue/green dye in the urine confirms patency of the vas. Indigo carmine diluted 50/50 with lactated Ringer solution is preferred instead of methylene blue because, even at low concentrations, methylene blue kills sperm and renders them useless for cryopreservation or for immediate IVF/ICSI (Chang et al, 1998; Sheynkin et al, 1999b; Wood et al, 2003). **If motile sperm are found in the vas, the testicular end should be gently barbotaged with 0.2 mL of human tubal fluid media and the fluid processed by the andrology laboratory for**

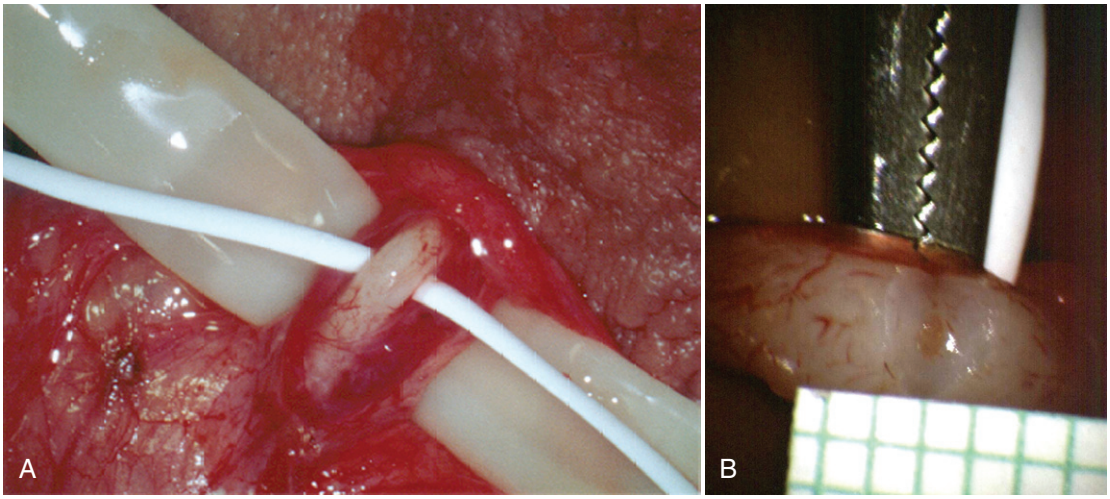


Figure 22–3. **A,** Using an operating microscope and 10× magnification, the vasal sheath is longitudinally incised and vasal vessels carefully preserved. **B,** Under 25× magnification, a 15-degree microknife is used to hemitransect the vas until the lumen is revealed.

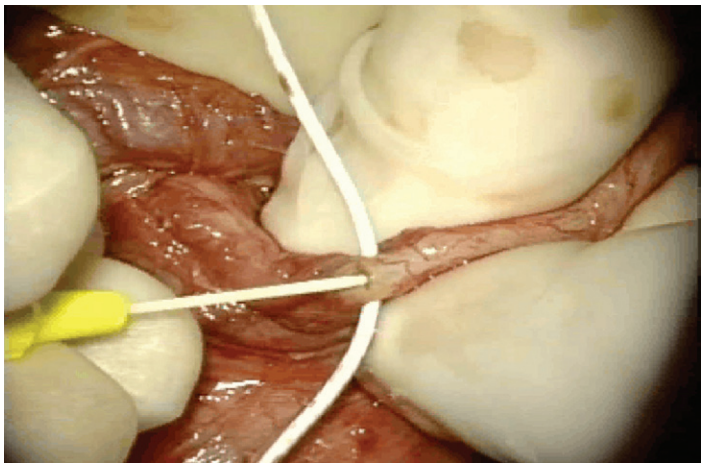


Figure 22–4. The end of the vas toward the seminal vesicles is cannulated with a 24-gauge angiocatheter and then injected with 1 mL of lactated Ringer solution with a 1-mL tuberculin syringe to confirm its patency.

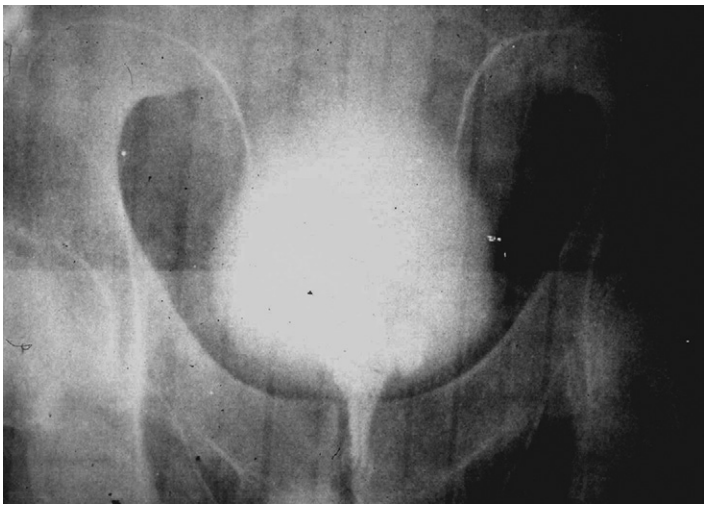


Figure 22–5. Placing the balloon on gentle traction before vasography prevents reflux of contrast into the bladder, which can obscure detail.

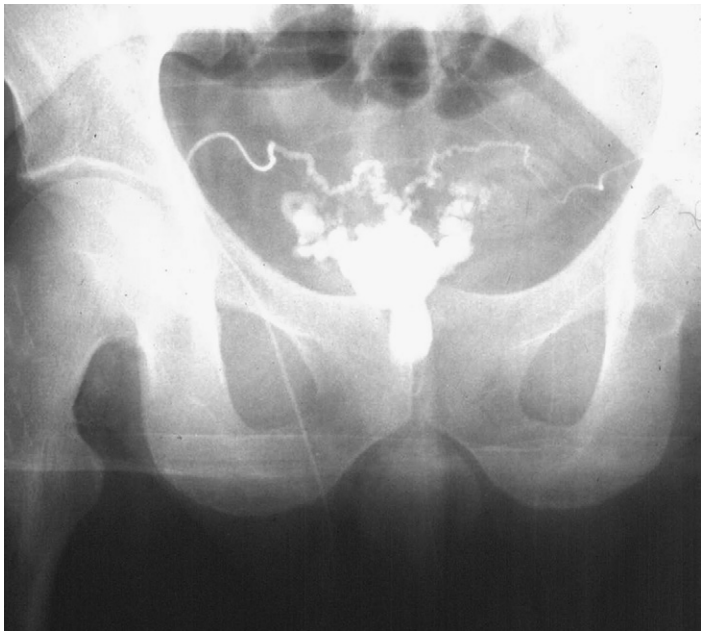


Figure 22–6. Vasograms are performed with 0.5 mL of water-soluble contrast media.

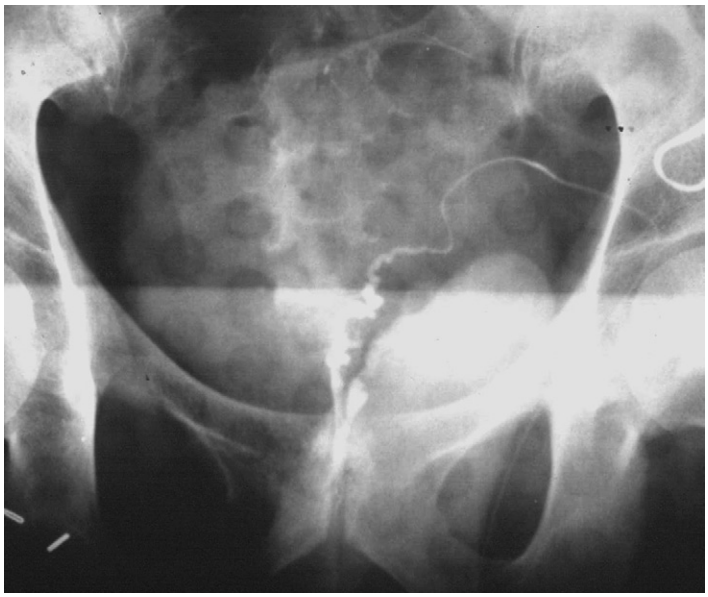


Figure 22–7. Vasography reveals obstruction at the site of the ejaculatory ducts.

sperm cryopreservation for potential future use for IVF/ICSI. This should be done before injection with indigo carmine or x-ray contrast material (Sheynkin et al, 1999a).

If a large amount of fluid is found in the vasal lumen and microscopic examination reveals the presence of sperm, the obstruction is toward the seminal vesicle end of the vas. In these cases the vas is usually markedly dilated. A 2-0 Proline suture can be passed toward the seminal vesicle end of the vas and a clamp placed on the Proline when the suture passes no farther. This is particularly useful for delineating the site of inguinal obstruction from prior groin surgery. If the obstruction is proximal to the inguinal scar, formal vasography is performed by passing a No. 3 whistle-tip ureteral catheter toward the seminal vesicle end of the vas. A 16-Fr Foley catheter is placed in the bladder, and the balloon is filled with 5 mL of air. Placing the balloon on gentle traction before vasography prevents reflux of contrast into the bladder, which can obscure detail (Fig. 22–5). The air-filled balloon also identifies the location of the bladder neck relative to any obstruction. After the vasa have been cannulated, vasograms are performed with the injection of 0.5 mL of water-soluble contrast media (Fig. 22–6). **If vasography reveals obstruction at the site of the ejaculatory ducts** (Fig. 22–7), **indigo carmine is injected in both vasa to assist a transurethral resection (TUR) of the ejaculatory ducts** (see Diagnosis later). If both vasa are visualized after injection of contrast into only one vas (Fig. 22–8), it means both vasa empty into a single cavity, usually a midline ejaculatory duct cyst.

Vasography may reveal the vas deferens ending blindly, far from the ejaculatory ducts (Fig. 22–9). This finding indicates congenital partial absence of the vas deferens, and these patients should be tested for cystic fibrosis mutations (see Chapter 21). If this is found bilaterally (Fig. 22–10), reconstruction is impossible but vasal or epididymal sperm can be aspirated into standard laboratory



Figure 22–8. Both vasa are visualized after injection of contrast into one vas only, revealing distal obstruction.



Figure 22–10. Vasogram demonstrating partial absence of the vas deferens.

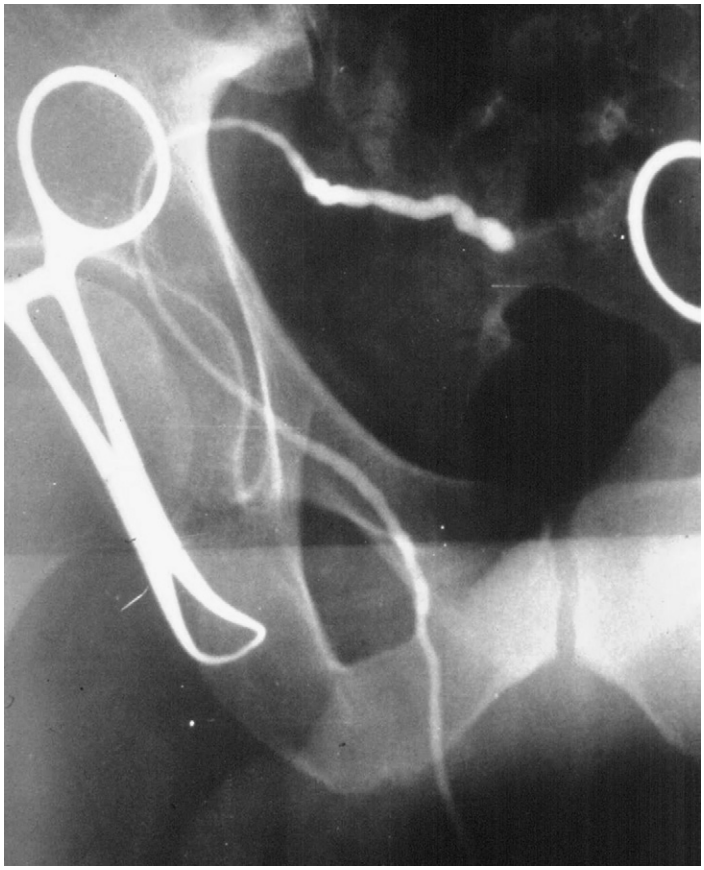


Figure 22–9. Vasography reveals a blind-ending vas deferens far from the ejaculatory duct.

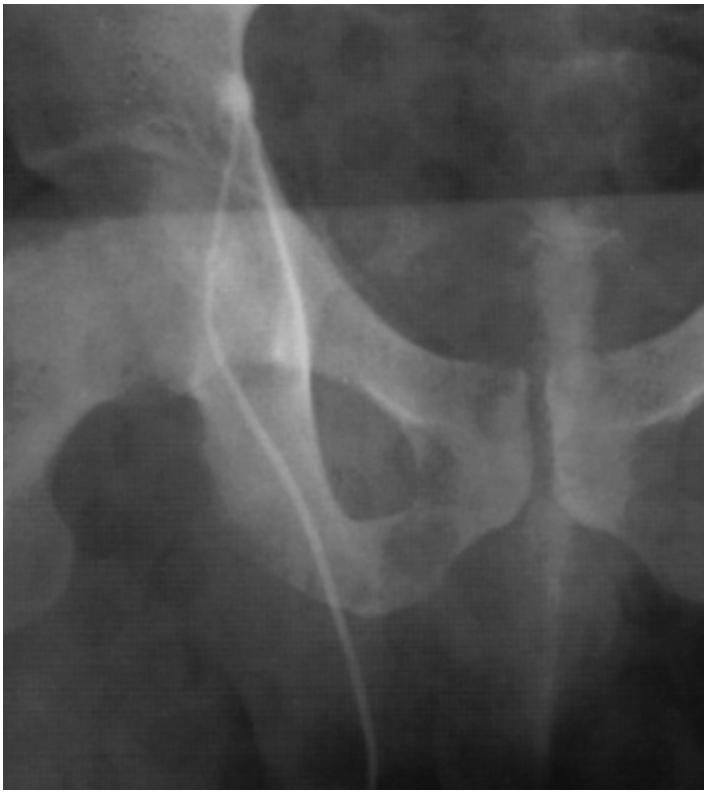


Figure 22–11. Vasography reveals an obstruction in the inguinal region.

pipettes (see Microsurgical Epididymal Sperm Aspiration Techniques later) and cryopreserved for future IVF with ICSI. If vasography reveals obstruction in the inguinal region (Fig. 22–11), either inguinal vasovasostomy or crossed transeptal vasovasostomy, using the contralateral unobstructed vas (see Crossed Vasovasostomy later), may be performed. **The hemitransected vasography sites are carefully closed microsurgically** using two or three interrupted 10-0 monofilament nylon for the mucosa and 9-0 for the muscularis and adventitia (see Microsurgical Multilayer Microdot Method later).

If the vasal fluid reveals no sperm and vasography confirms patency of the seminal vesicle end of the vas, the vas is completely transected and the seminal vesicle end is prepared for

vasoepididymostomy (see Vasoepididymostomy later). If the vasal fluid reveals many sperm and vasography is normal, either retrograde ejaculation, lack of emission, or aperistalsis of the vas (Tiffany and Goldstein, 1985; Tillem and Mellinger, 1999) is the cause of the azoospermia.

Fine-Needle Vasography

Exposure of the vas in its straight portion may allow vasography to be performed with a fine needle, obviating the need for hemitransection of the vas. Dewire and Thomas (1995) employed a 30-gauge lymphangiogram needle attached to Silastic tubing. When the sensation of puncture of the lumen is detected, 50% water-soluble contrast is injected to confirm patency radiographically. This has proven to be a difficult technique for even experienced microsurgeons to master. Accurate evaluation of vasal fluid for sperm is difficult because it is so scant. If barbotage with saline or lactated Ringer solution reveals the presence of sperm, then epididymal obstruction has been excluded and contrast can be injected. Collection of vasal sperm for cryopreservation is difficult with this technique. Percutaneous vasography through the scrotal skin has been successfully performed in China (Li) using the same ringed percutaneous fixation clamp employed for the no-scalpel vasectomy. After fixation of the vas beneath the scrotal skin, the vas lumen is punctured with a 22-gauge sharp needle and cannulated with a 24-gauge blunt needle through which vasography is performed. This technique is even more difficult than the direct-vision technique with a fine needle.

Complications of Vasography

Stricture

Multiple attempts at percutaneous vasography using sharp needles can result in stricture or obstruction at the vasography site. Imprecise closure of a vasotomy can also result in stricture and obstruction (Howards et al, 1975b; Poore et al, 1997). Non-water-soluble contrast agents may also result in stricture and should not be employed for vasography.

Injury to the Vasal Blood Supply

If the vasal blood supply is injured at the site of vasography, vasovasostomy proximal to the vasography site may result in ischemia, necrosis, and obstruction of the intervening segment of vas.

Hematoma

A bipolar cautery should be used for meticulous hemostasis at the time of vasostomy to prevent hematoma in the perivasal sheath.

Sperm Granuloma

Leaky closure of a vasography site may lead to the development of a sperm granuloma, which can result in stricture or obstruction of the vas. The microsurgical technique for closure of vasography sites is identical to that employed for vasovasostomy described later in this chapter.

Transrectal Vasography and Seminal Vesiculography

If transrectal ultrasound reveals markedly dilated seminal vesicles and/or a midline müllerian duct cyst in a man with obstructive azoospermia, transrectal aspiration followed by instillation of indigo carmine mixed with radiographic contrast is a useful diagnostic maneuver (Jarow, 1994; Katz et al, 1994; Riedenklau et al, 1995).

The same bowel prep and antibiotic coverage used for transrectal prostate biopsy is employed. The fine-needle aspirate is examined for sperm. If sperm are present it means at least one vas and epididymis are patent. One-half mL of indigo carmine is diluted with 1.5 mL of 50% water-soluble contrast and instilled. If a flat plate reveals a potentially resectable lesion, a TUR of the ejaculatory ducts is performed (see Transurethral Resection of the Ejaculatory Ducts later). Visualization of blue dye effluxing from the ejaculatory ducts or an unroofed cyst aids in determining the adequacy of the resection (Cornel et al, 1999).

This technique obviates the need for formal open scrotal vasography in men with transrectally accessible lesions. If sperm are found in the aspirate, a TUR may immediately be undertaken without violating the scrotum. Sperm-laden aspirates may be frozen for future IVF with ICSI if surgery fails.

If no sperm are found in the aspirated fluid, it suggests that secondary epididymal obstruction exists. Simultaneous TUR of the ejaculatory ducts and vasoepididymostomy is rarely successful. In the face of both ejaculatory duct obstruction and bilateral epididymal obstruction, the best option would be epididymal sperm aspiration for cryopreservation for future IVF/ICSI.

Summary

1. **Perform vasography only if testicular biopsy confirms spermatogenesis consistent with obstructive azoospermia.**
2. **Perform vasography only at the time of planned reconstruction.**
3. **Always sample vasal fluid first to allow cryopreservation of motile sperm if found.**
4. **Use indigo carmine instead of methylene blue to confirm patency.**
5. **Formal vasography with x-ray contrast is only needed to locate obstructions proximal to the internal inguinal ring.**
6. **If transrectal ultrasound reveals dilated seminal vesicles and/or a midline (Mullerian duct) cyst, transrectal fine needle aspiration followed by instillation of contrast and indigo carmine should be performed. If motile sperm are found they should be cryopreserved.**

VASOVASOSTOMY

Introduction

The number of American men who undergo vasectomy has remained stable at about 500,000 per year, as has the divorce rate of 50%. Surveys suggest that 2% to 6% of vasectomized men will ultimately seek reversal. Furthermore, obstructive azoospermia can be the result of iatrogenic injuries to the vas deferens, usually from hernia repair, in 6% of azoospermic men (Sheynkin et al, 1998a; Shin et al, 2005).

Preoperative Evaluation

Before attempted surgical reconstruction of the reproductive tract, adequate spermatogenesis should be documented. A prior history

of natural fertility prevasectomy is usually adequate. In other cases a testicular biopsy may be indicated to confirm the presence of spermatogenesis.

Physical Examination

a. Testis: Small or soft testes suggest impaired spermatogenesis and predict a poor outcome.
b. Epididymis: An indurated, irregular epididymis often predicts secondary epididymal obstruction, necessitating vasoepididymostomy.
c. Sperm granuloma: **A sperm granuloma at the testicular end of the vas suggests that sperm have been leaking at the vasectomy site. This vents the high pressures away from the epididymis and is associated with a better prognosis for restored fertility** regardless of the time interval since vasectomy.
d. Vasal gap: When a destructive vasectomy has been performed, most of the scrotal straight vas may be absent or fibrotic and the patient should be advised that inguinal extension of the scrotal incision will be necessary to mobilize adequate length of vas to enable a tension-free anastomosis.
e. Scars from previous surgery: Operative scars in the inguinal or scrotal region should alert the surgeon to the possibility of iatrogenic inguinal (hernia repair), vasal, or epididymal obstruction (hydrocelectomy, orchiopexy) (Sheynkin et al, 1998a; Hopps and Goldstein, 2006).

Laboratory Tests

a. **Semen analysis with centrifugation and examination of the pellet for sperm should be performed preoperatively. Complete sperm with tails are found in 10% of preoperative pellets a mean of 10 years after vasectomy** (Lemack and Goldstein, 1996). **Under these circumstances sperm are certain to be found in the vas on at least one side, indicating a favorable prognosis for restored fertility.** Men with a low semen volume should have a transrectal ultrasound to alert one to the possibility of an additional ejaculatory duct obstruction.
b. Serum and antisperm antibody studies: **The presence of serum antisperm antibodies corroborates the diagnosis of obstruction and the presence of active spermatogenesis** (Lee et al, 2009). At present this test is of unknown prognostic value and is optional.
c. Serum FSH: Men with small soft testes should have serum FSH measured. An elevated FSH predicts impaired spermatogenesis and a poorer prognosis.
d. Prostate-specific antigen (PSA): All vasectomy reversal candidates older than age 40 should have serum PSA measured.

Anesthesia

General anesthesia is preferred. Slight movements are greatly magnified by the operating microscope and disturb performance of the anastomosis. In cooperative patients regional or even local anesthesia with sedation can be employed if the vasal ends are easily palpable, a sperm granuloma is present, and/or the time interval since vasectomy is short, decreasing the likelihood of secondary epididymal obstruction. When large vasal gaps are present, extensions of the incisions high into the inguinal canal may be necessary. Furthermore, if vasoepididymostomy is necessary, the operating time could exceed 4 or 5 hours. **Local anesthesia limits the options available to the surgeon.**

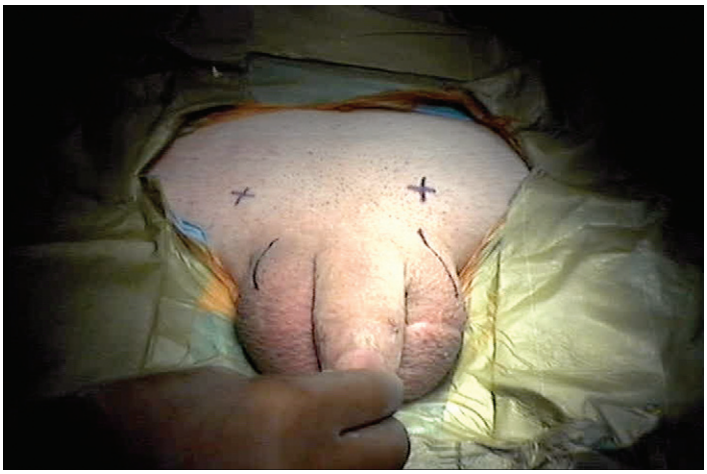


Figure 22–12. The X's mark the locations of the external ring. Incisions are marked on the hemiscrotums.

Hypobaric spinal anesthesia with long-acting agents such as Marcaine can provide 4 to 5 hours of anesthesia time and has the advantage of eliminating lower body motion. Epidural anesthesia with an indwelling catheter can be equally effective.

Surgical Approaches

Scrotal

Bilateral high vertical scrotal incisions provide the most direct access to the obstructed site in cases of vasectomy reversal. Length is usually a problem on the abdominal end but not on the testicular end. Mark the location of the external inguinal ring (Fig. 22–12). **If the vasal gap is large or the vasectomy site is high, this incision can easily be extended toward the external ring.** If the vasectomy site is low, it is easy to pull up the testicular end. This incision should be made at least 1 cm lateral to the base of the penis. **The testis should be delivered with the tunica vaginalis left intact.** This provides excellent exposure of the entire scrotal vas deferens and, if necessary, the epididymis.

Infrapubic Incision

An infrapubic incision provides excellent exposure when the abdominal end of the vas is short but awkward when vasoepididymostomy is necessary. In addition, surgeons should be cautious that, when vasal gaps are large, tension on the anastomosis may not be apparent during the surgery until an attempt is made to place the testis back into the scrotum. Overall this incision has no advantage over inguinal extension of a high scrotal incision.

Inguinal Incision

An inguinal incision is the preferred approach in men when obstruction of the inguinal vas deferens from prior herniorrhaphy or orchiopexy is strongly suspected. Incision through the previous scar usually leads directly to the site of obstruction. If the obstruction turns out to be scrotal or epididymal, it is a simple matter to deliver the testis through the inguinal incision or through a separate scrotal incision to perform the anastomosis.

Preparation of the Vasa

The vas is grasped above and below the site of obstruction with two Babcock clamps. Penrose drains replace the Babcock clamps and assist the dissection. The vasal vessels and periadventitial sheath are included. **Transillumination of the periadventitial sheath,** by properly adjusting the operating light, **allows clear visualization of the blood vessels, which facilitates dissection of the periadventitial sheath and prevents damage to the vasal vessels.** The vas is mobilized enough to allow a tension-free anastomosis. In order to preserve good blood supply **the vas should not be stripped of its sheath.** The obstructed segment and, if present, sperm granuloma at the vasectomy site should be dissected out and excised. By staying right on the vas and/or sperm granuloma during this dissection, the risk of injuring the testicular artery is reduced. **Injury to adjacent cord structures, especially the testicular artery, is likely to result in testicular atrophy because the vasal artery has usually been interrupted at the vasectomy site.**

When large vasal gaps are present, a gauze-wrapped index finger is used to bluntly separate the cord structures from the vas. Blunt finger dissection through the external ring will free the vas to the internal inguinal ring if additional abdominal side length is necessary. These maneuvers will leave all the vasal vessels intact. **When the vasal gap is extremely large, additional length can be achieved by dissecting the entire convoluted vas free of its attachments to the epididymal tunica** (Fig. 22–13), allowing the testis to drop upside down. These maneuvers can provide an additional 4 to 6 cm of length. In order to maintain the integrity of the vasal vessels, this dissection is best performed using magnifying loupes or the operating microscope under low power. If the amount of vas removed is so large that even these measures fail to allow a tension-free anastomosis, the incision can be extended to the internal inguinal ring, the floor of the inguinal canal cut, and the vas rerouted under the floor, as in a difficult orchiopexy. An additional 4 to 6 cm of length can be obtained by dissecting the epididymis off of the testis from the vasoepididymal junction to the caput epididymis (Fig. 22–14A and B). The superior epididymal vessels are left intact and provide adequate blood supply to the testicular end of the vas. With this combination of maneuvers, up to 10 cm gaps can be bridged.

After the vasa have been freed, the testicular end of the vas is cut transversely. An ultrasharp knife drawn through a slotted 2-, 2- to 5-, or 3-mm diameter nerve holding clamp (Accurate Surgical

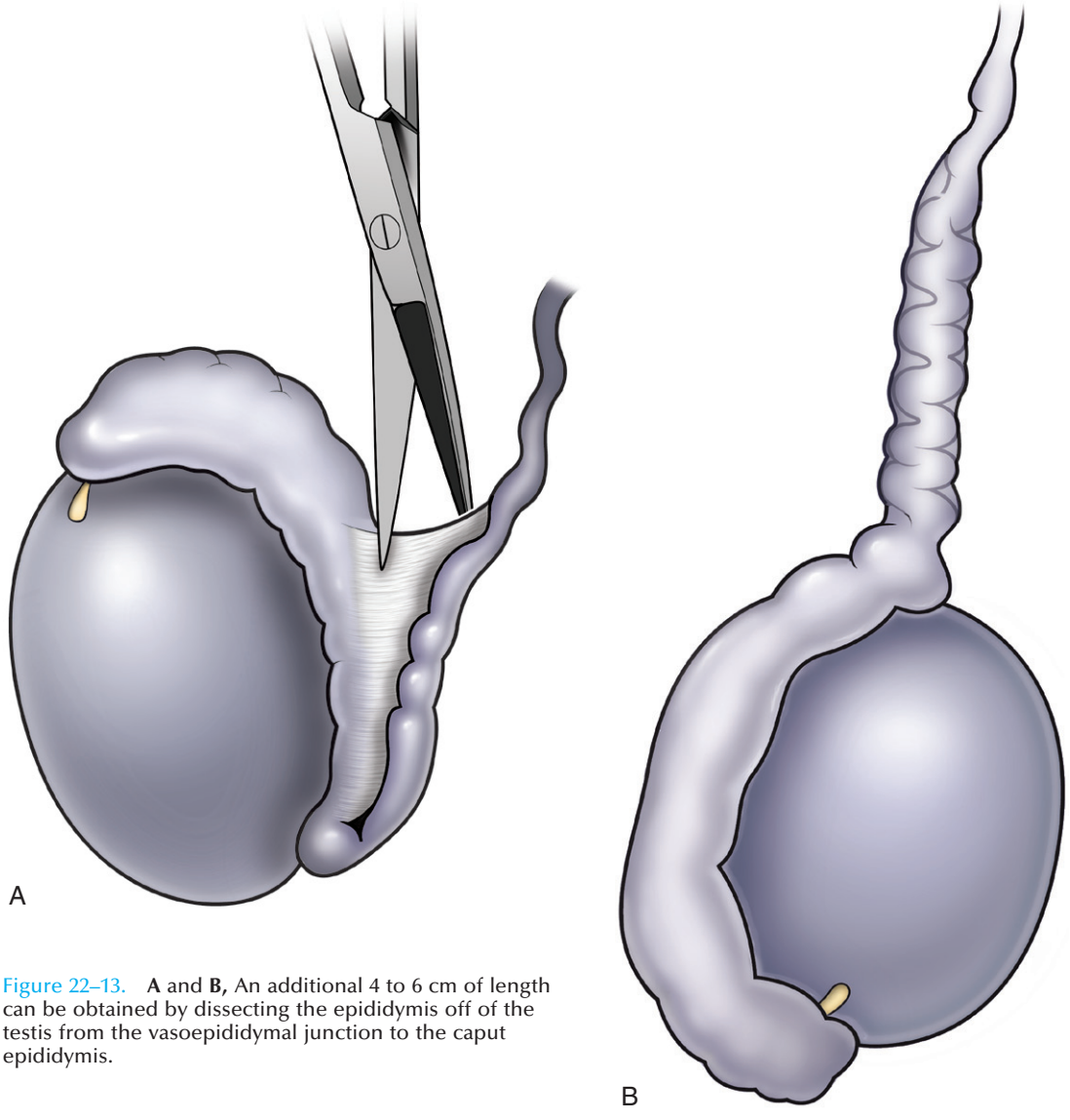


Figure 22–13. **A** and **B,** An additional 4 to 6 cm of length can be obtained by dissecting the epididymis off of the testis from the vasoepididymal junction to the caput epididymis.

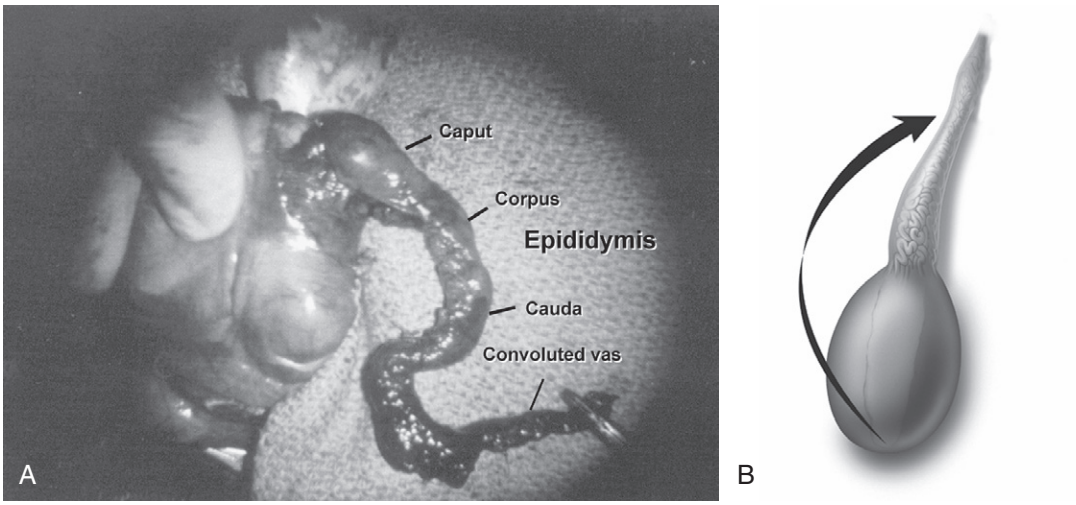


Figure 22–14. **A** and **B,** An additional 4 to 6 cm of length can be obtained by dissecting the epididymis off of the testis from the vasoepididymal junction to the caput epididymis.

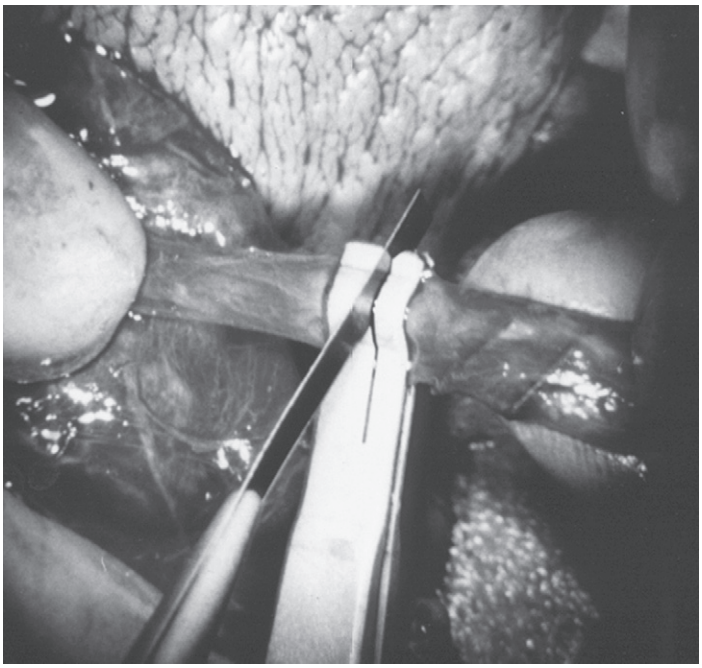


Figure 22–15. An ultrasharp knife drawn through a slotted 2.5- or 3-mm diameter nerve-holding clamp (Accurate Surgical and Scientific Instrument Corp., Westbury, NY) yields a perfect 90-degree cut.

and Scientific Instrument Corp., Westbury, NY) yields a perfect 90-degree cut (Fig. 22–15). The cut surface of the testicular end of the vas deferens is inspected using 15- to 25-power magnification. **A healthy white mucosal ring that springs back immediately after gentle dilation should be seen. The muscularis should appear smooth and soft. A gritty-looking muscularis layer indicates the presence of scar/fibrotic tissues.** The cut surface should look like a bull's-eye with the three vasal layers distinctly visible. Healthy bleeding should be noted from both the cut edge of the mucosa and the surface of the muscularis. If the blood supply is poor or the muscularis is gritty, the vas is recut until healthy tissue is found. The vasal artery and vein are then clamped and ligated with 6-0 nylon. Small bleeders are controlled with a microbipolar forcep set at low power. Once a patent lumen has been established on the testicular end, the vas is milked and a clean glass slide is touched to its surface. The vasal fluid is immediately mixed with a drop or two of saline or lactated Ringer solution and preserved under a cover slip for microscope examination. The abdominal end of the vas deferens is prepared in a similar manner, and the lumen gently dilated with a microvessel dilator and cannulated with a 24-gauge angiocatheter sheath. Injection of saline or lactated Ringer solution confirms its patency. After the Ringer injection and a test dilation, the vas is recut to obtain a fresh surface. **A minimum of instrumentation of the mucosa should be performed.**

After preparation, the ends of the vasa are stabilized with a Microspike approximating clamp (Goldstein, 1985) to remove all tension before performing the anastomosis. Isolating the field through a slit in a rubber dam prevents microsutures from sticking to the surrounding tissue. A sterile tongue blade covered with a large Penrose drain is placed beneath the ends of the vasa to provide a platform on which to perform the anastomosis.

When to Perform Vasoepididymostomy

The gross appearance of fluid expressed from the testicular end of the vas is usually predictive of findings on microscopic examination (Table 22–2). If microscopic examination of the vasal fluid reveals the presence of sperm with tails, vasovasostomy is performed. If no fluid is found, a 24-gauge angiocatheter sheath is inserted into the lumen of the testicular end of the vas and barbotaged with 0.1 mL of saline while the convoluted vas is vigorously milked. The barbotage fluid is expressed onto a slide and examined. **Men with large sperm granulomas often have virtually no dilation of the testicular end of the vas and little or no fluid initially; however, with barbotage and vigorous milking, sperm can invariably be found in this scant fluid.** If there is no sperm granuloma and the vas is absolutely dry and spermless after multiple samples are examined, vasoepididymostomy is indicated. If the fluid expressed from the vas is found to be thick, white, water insoluble, and like toothpaste in quality, microscopic examination rarely reveals sperm. Under these circumstances, the tunica vaginalis is opened and the epididymis inspected. If clear evidence of obstruction is found (i.e., an epididymal sperm granuloma with dilated tubules above and collapsed tubules below), vasoepididymostomy is performed.

Table 22–2.
Relationship between Gross Appearance of Vasal Fluid and Microscopic Findings

VASAL FLUID APPEARANCE	MOST COMMON FINDINGS ON MICROSCOPIC EXAMINATION	SURGICAL PROCEDURE INDICATED
Copious, crystal clear, watery	No sperm in fluid	Vasovasostomy
Copious, cloudy thin, water soluble	Usually sperm with tails	Vasovasostomy
Copious, creamy yellow, water soluble	Usually many sperm heads; occasionally sperm have short tails	Vasovasostomy
Copious, thick, white toothpaste-like, water insoluble	No sperm	Vasoepididymostomy
Scant white thin fluid	No sperm	Vasoepididymostomy
Dry spermless vas—no granuloma at vasectomy site	No sperm	Vasoepididymostomy
Scant fluid, granuloma present at vasectomy site	Barbotage fluid reveals sperm	Vasovasostomy

When in doubt or if not experienced with vasoepididymostomy, vasovasostomy should be performed. However, only 15% of men with bilateral absence of sperm in the vasal fluid after barbotage and an intensive search will have sperm return to the ejaculate after vasovasostomy (Sheynkin et al, 2000).

When copious, crystal-clear, water-like fluid squirts out from the vas and no sperm are found in this fluid, a vasovasostomy is performed because the likelihood is that sperm will return to the ejaculate after vasovasostomy is performed.

Multiple Vasal Obstructions

If saline injection reveals that the abdominal end of the vas deferens is not patent, a 2-0 nylon or polypropylene suture is gently threaded into the vas lumen to determine the site of obstruction. If the obstruction is within 5 cm of the original vasectomy site, the abdominal end of the vas deferens may be dissected to this site and excised. The incision should then be extended inguinally to free the vas up extensively toward the internal inguinal ring. The testicular end then should also be freed up to the vasoepididymal junction. If the site of the second obstruction is so far from the vasectomy site that two vasovasostomies are necessary, a single crossed vasovasostomy should be performed to yield one good system (see Crossed Vasovasostomy earlier). If this is not possible, vasal or epididymal sperm is aspirated into micropipets and cryopreserved for future IVF with ICSI (see Sperm Retrieval Techniques later). **Simultaneous vasovasostomies at two separate sites may lead to devascularization of the intervening segment with fibrosis and necrosis.**

Varicocelectomy and Vasovasostomy

When men presenting for vasovasostomy or vasoepididymostomy are found to have significant varicoceles on physical examination, it is tempting to repair the varicoceles at the same time. **When varicocelectomy is properly performed, all spermatic veins are ligated and the only remaining avenues for testicular venous return are the vasal veins. In men who have had vasectomy and are presenting for reversal, the vasal veins are likely to be compromised from either the original vasectomy or the reversal itself. Furthermore, the integrity of the vasal artery in those men is also likely to be compromised. Varicocelectomy in such men requires preservation of the testicular artery as the primary remaining testicular blood supply, as well as preservation of some avenue for venous return.**

Microscopic varicocelectomy can assure preservation of the testicular artery in most cases. Deliberate preservation of the cremasteric veins provides venous return. In one series of 570 men presenting for vasectomy reversal, 19 had large varicoceles (20 left, 7 bilateral). Microsurgical varicocelectomy was performed at the same time as vasovasostomy. The cremasteric veins and the fine network of veins adherent to the testicular artery were left intact for venous return and to minimize the chances of injury to the testicular artery. Postoperatively 5 of 26 varicoceles recurred (22%) (Goldstein, 1995). This compares with a recurrence rate of less than 1% in 2700 varicocelectomies performed by the author in nonvasectomized men in whom the vasal vessels were intact and the cremasteric veins and periarterial venous network were ligated. However, Mullhall and colleagues performed a series of simultaneous microsurgical vasovasostomies and varicocelectomies without intentionally preserving the cremasteric and periarterial network. They reported a low recurrence rate and no cases of atrophy (Mulhall et al, 1997). Interestingly, the increase in recurrences when the cremasteric veins and periarterial venous network were left intact suggests that these veins contribute to a significant proportion of varicocele recurrences.

If varicocelectomy is performed at the same time as vasovasostomy or vasoepididymostomy, it is important that a microscope be used and the testicular artery preserved. A safer approach is to do the vasovasostomy or vasoepididymostomy first. The semen quality is then assessed postoperatively. **If necessary, varicocelectomy can be safely performed 6 months or more later when venous and arterial channels have formed across the anastomotic line.** This two-stage delayed approach has been completed a dozen times with no atrophy or recurrence.

Anastomotic Techniques: Keys to Success

All successful vasovasostomy techniques depend on adherence to surgical principles that are universally applicable to anastomoses of all tubular structures.

These include the following:

1. **Accurate mucosa to mucosa approximation.**
   In human vasovasostomy, the lumen on the testicular side is usually dilated, often to diameters two to five times that of the abdominal side. Techniques that work well with lumina of equal diameters may be less successful when applied to lumina of markedly discrepant diameters.
2. **Leakproof anastomosis.**
   Sperm are highly antigenic and provoke an inflammatory reaction when they escape from the normally intact lining of the excurrent ducts of the male reproductive tract. Extravasated sperm adversely influence the success of

vasovasostomy (Hagan and Coffey, 1977). **Unlike blood vessel anastomoses, in which platelets and clotting factors seal the gaps between sutures, vasal and epididymal fluid contain no platelets or clotting factors, so the water-tightness of the anastomosis is entirely dependent on the mucosal sutures.**

3. **Tension-free anastomosis.**
   When an anastomosis is performed under tension, sperm may appear in the ejaculate for several months after surgery. Ultimately, sperm counts and motility will decrease and azoospermia may ensue. At re-exploration only a thin fibrotic band is found at the anastomotic site. This can be prevented by adequately freeing up the vasa and placement of re-enforcing sutures in the sheath of the vas.
4. **Good blood supply.**
   If the cut vas exhibits poor blood supply, it should be recut until healthy bleeding is encountered. If extensive resection is necessary, additional length should be obtained using the techniques previously described.
5. **Healthy mucosa and muscularis.**
   If the mucosa or cut surface of the vas exhibits poor distensibility after dilation, peels away from the underlying muscularis, or shreds easily, then the vas should be cut back until healthy mucosa is found. Surgeons should be aware that if a needle electrocautery was used in vasectomy, the area of damage to the mucosa and muscularis by the electric current may extend far beyond the tip of the needle cautery. If the muscularis is found to be fibrotic or gritty, the vas must be recut until healthy tissue is found.
6. **Good atraumatic anastomotic technique.**
   If multiple surgical errors occur during the procedure such as inadvertent cutting of the mucosa with the needles when placing sutures, tearing through of sutures, or backwalling of the mucosa, the anastomosis should be resected and redone immediately.

Setup

An operating microscope providing variable magnification from 6 to 32 power is employed. A diploscope providing identical fields for both surgeon and assistant is preferred. Foot pedal controls for a motorized zoom and focus leave the surgeon's hands free.

Both surgeon and assistant should be comfortably seated on microsurgical chairs that stabilize the chest and arms. This dramatically improves stability and accuracy. An inexpensive alternative is a simple rolling stool with a round bean bag (meditation pillow) taped on top for padding. Two arm boards, placed on either side of the surgeon and built up to the appropriate height with folded blankets taped to the board, provide excellent arm support. **A right-handed surgeon should sit on the patient's right side** so that his or her forehand stitch is always on the smaller, more difficult abdominal-side lumen.

Microsurgical Multilayer Microdot Method

This method of vasovasostomy can handle lumina of markedly discrepant diameters in the straight or convoluted vas. **The microdot technique ensures precise suture placement by exact mapping of each planned suture. The microdot method separates the planning from the placement** (Goldstein et al, 1998). This allows focus on only one task at a time and results in substantially improved accuracy.

A microtip marking pen (Devon Skin Marker Extra Fine No. 151) is used to map out planned needle exit points. **Exactly six mucosal sutures are used for every anastomosis** because it is easy to map out and always results in a leakproof closure even when the lumen diameters are markedly discrepant.

Immediately after drying the cut surface of the testicular end of vas with a Weck cell, a dot is made at 3 o'clock halfway between the mucosal ring and the outer edge of the muscle layer. A line is extended out from this dot to serve as a reference point. The second dot is made at 9 o'clock, and a line is extended from this dot as well. Additional dots are placed at 11, 1, 5, and 7 o'clock for a total of six. The abdominal end of the vas is marked in the same way to exactly match the testicular end (Fig. 22–16). Monofilament 10-0 nylon sutures, double-armed with 70-µm diameter taper-point needles bent into a fish hook configuration (available from Sharpoint and Ethicon), are used. **Double-armed sutures allow inside-out placement** (Fig. 22–17), **eliminating the need for manipulation of the mucosa and the possibility of back-walling.** If the mucosal rings are not sharply defined, stain the cut surfaces of the vasal ends with indigo carmine to highlight the mucosa (Sheynkin et al, 1999a). The anastomosis is

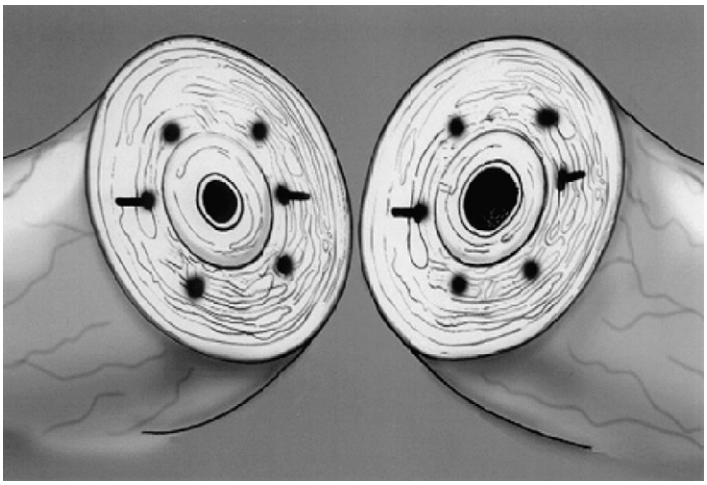


Figure 22–16. The abdominal end of the vas is marked in the same way to exactly match the testicular end.

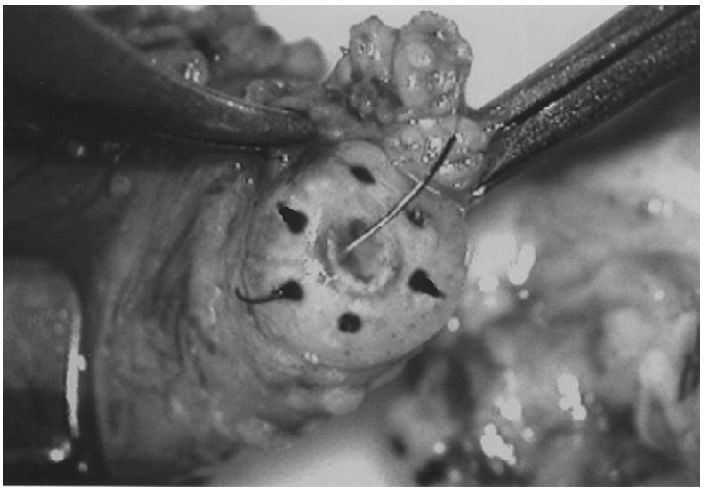


Figure 22–17. Double-armed sutures allow inside-out placement.

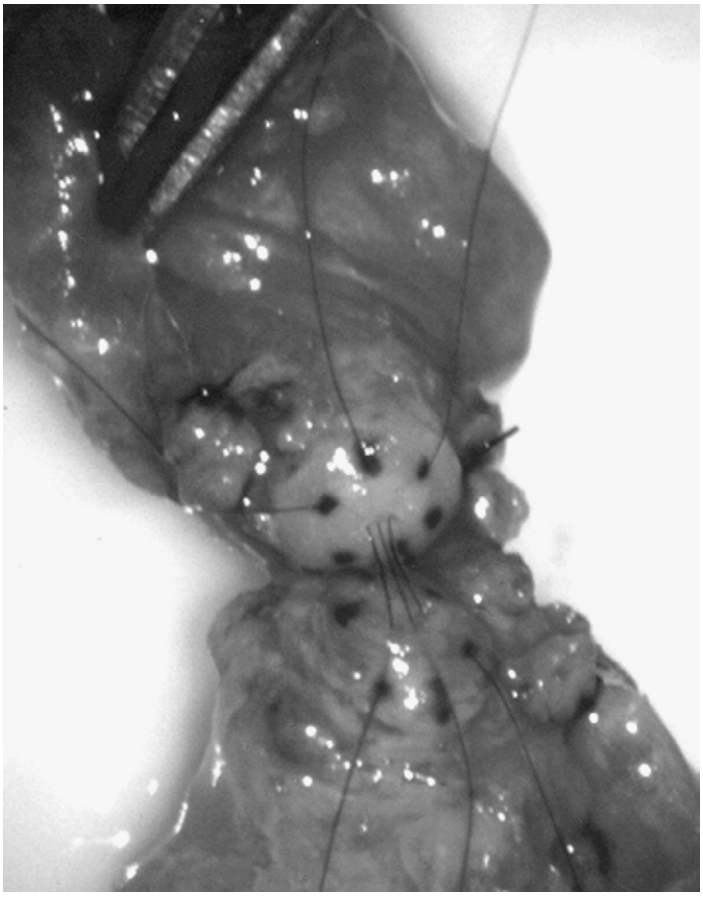


Figure 22–18. The anastomosis is begun with the placement of three 10-0 mucosal sutures anteriorly.

begun with the placement of three 10-0 mucosal sutures anteriorly (Fig. 22–18). **On the small abdominal side lumen, gently and momentarily dilate the lumen with a microvessel dilator just before placement of the sutures.** For accurate mucosal approximation, include only a small amount of mucosa but one-third to one-half the muscle wall thickness. **Include exactly the same amount of tissue in the bites on each side. The needle should exit through the center of each dot.** After placement, tie the three mucosal sutures. Place two 9-0 monofilament nylon deep muscularis sutures exactly in between the previously placed mucosal sutures, just above, but not through the mucosa (Fig. 22–19) and then tie them. These sutures seal the gaps between the mucosal sutures without trauma to the mucosa from the larger 100-µm diameter cutting needle required to penetrate the tough vas muscularis and adventitia. Rotate the vas 180 degrees (Fig. 22–20) and place three additional 10-0 sutures through each microdot and then tie them to complete the mucosal portion of the anastomosis (Fig. 22–21). Just before tying the last mucosal suture, irrigate the lumen with heparinized Ringer solution to prevent the formation of clot in the lumen. After completion of the mucosal layer (Fig. 22–22), place four more 9-0 deep muscularis sutures exactly in between each mucosal suture, just above but not penetrating the mucosa. Place four to six 9-0 nylon interrupted sutures, between each muscular suture. This is a purely adventitial layer that covers the underlying mucosal suture. Finish the anastomosis by approximating the vasal sheath with six interrupted sutures of 8-0 nylon completely covering the anastomosis and relieving it of all tension (Fig. 22–23).

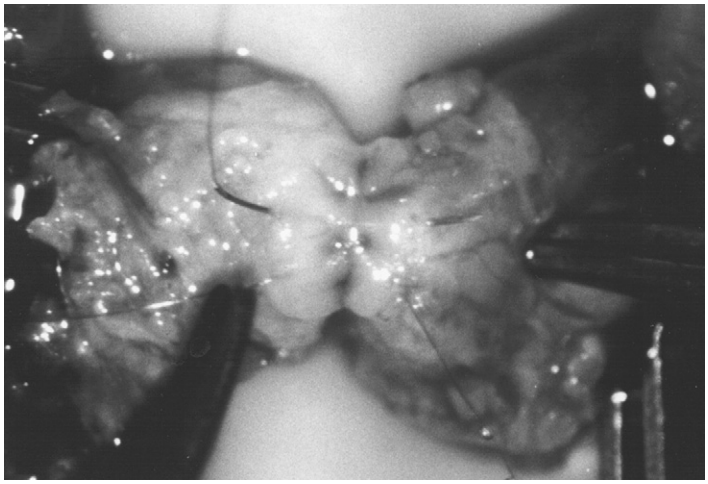


Figure 22–19. Place two 9-0 monofilament nylon deep muscularis sutures exactly in between the previously placed mucosal sutures, just above, but not through, the mucosa.

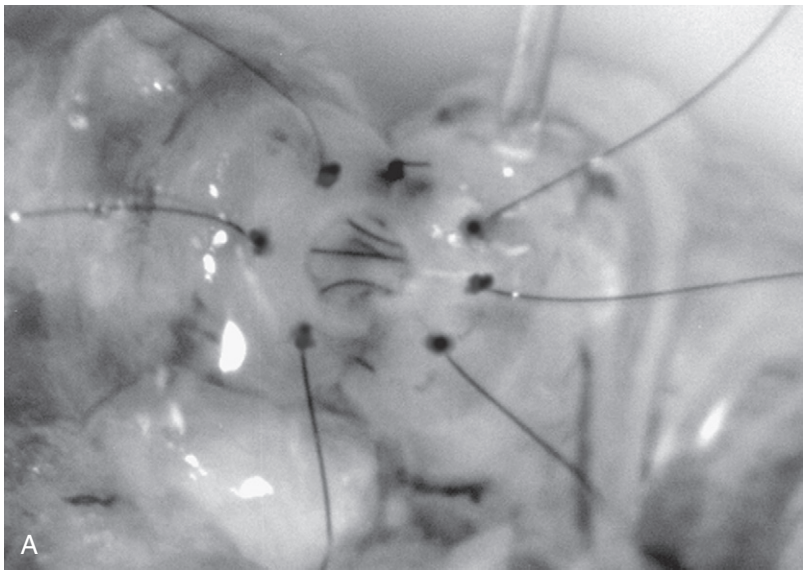
Anastomosis in the Convoluted Vas

Vasovasostomy performed in the convoluted portion of the vas deferens is technically more demanding than anastomoses in the straight portion. **Fear of cutting back into the convoluted vas in order to obtain healthy tissue may lead surgeons to complete an anastomosis in the straight portion when the testicular end of the vas has poor blood supply, unhealthy or friable mucosa, or gritty fibrotic muscularis.** Adherence to the following principles will enable anastomosis in the convoluted vas to succeed as often as those in the straight portion.

1. **A perfect transverse cut yielding a round ring of mucosa and a lumen directed straight down is essential.** An oblique lumen with a thin flap of muscle and mucosa on one side is not acceptable (Fig. 22–24). The vas should be recut at 0.5-mm intervals until a perfect cut with good blood supply and healthy tissue is obtained. A slotted nerve clamp 2.5 or 3 mm in diameter and ultrasharp knife assists this part of the procedure (see Fig. 22–15). Often the vas must be recut two or three times until a satisfactory cut is obtained.
2. **The convoluted vas should not be unraveled.** This disturbs the blood supply at the anastomotic line.
3. The sheath of the convoluted vas may be carefully dissected free of its attachments to the epididymal tunica (see Fig. 22–13). This will minimize disturbance of its blood supply and provide the necessary length to perform a tension-free anastomosis.
4. Care must be taken to avoid taking large bites of the muscularis and adventitial layers on the convoluted side to prevent inadvertent perforation of adjacent convolutions.
5. Reinforce the anastomosis by approximating the vasal sheath of the straight portion to the sheath of the convoluted portion with six interrupted sutures of 7-0 nylon. This will remove all tension from the anastomosis.

Crossed Vasovasostomy

This is a useful procedure that often provides an easy solution for otherwise difficult problems (Lizza et al, 1985; Hamidinia, 1988;



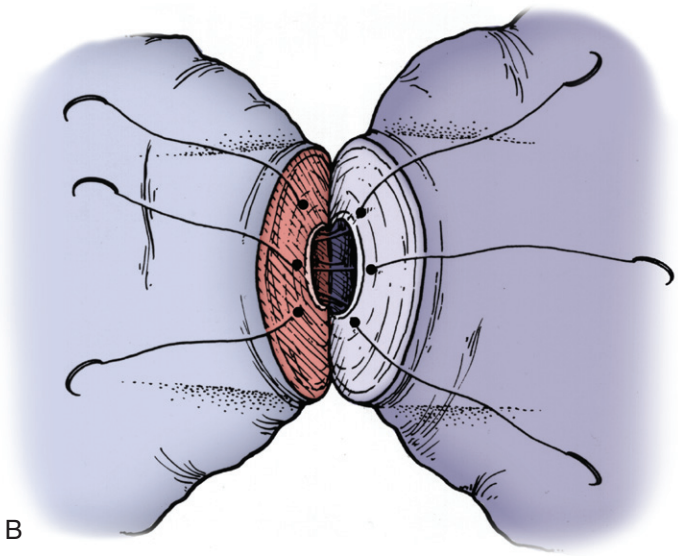


Figure 22–20. **A** and **B,** Rotate the vas 180 degrees and then place three more 10-0 sutures through the remaining microdots.

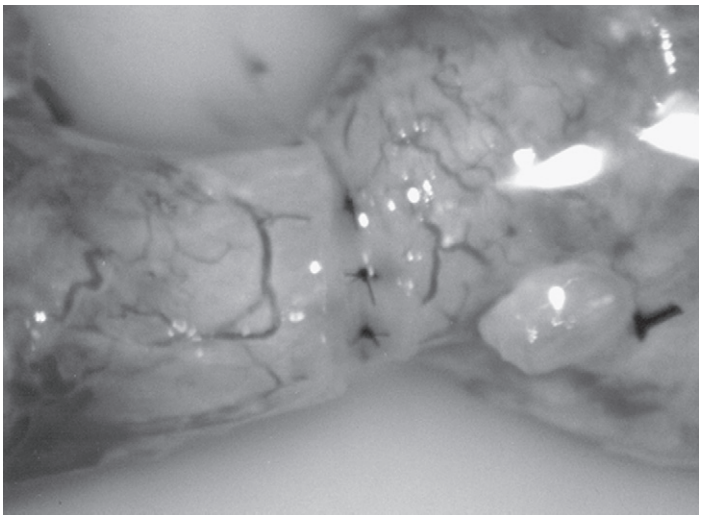


Figure 22–21. The mucosal layer is complete.

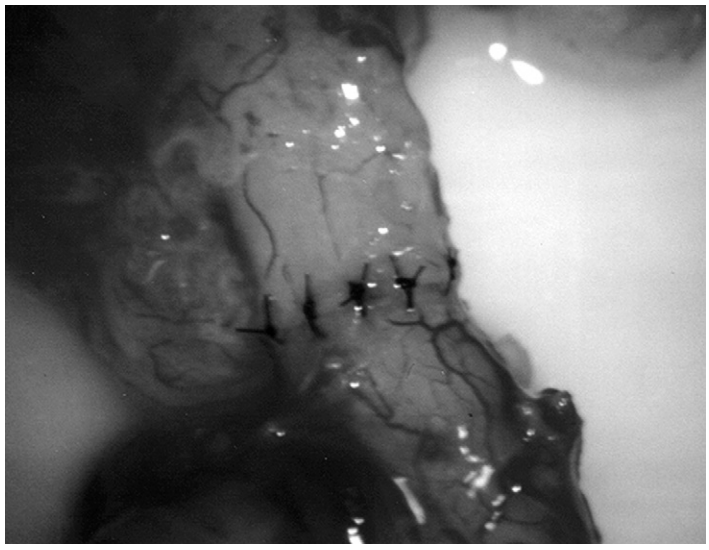


Figure 22–22. Additional sutures are placed in between the mucosal sutures, completing the anastomosis.

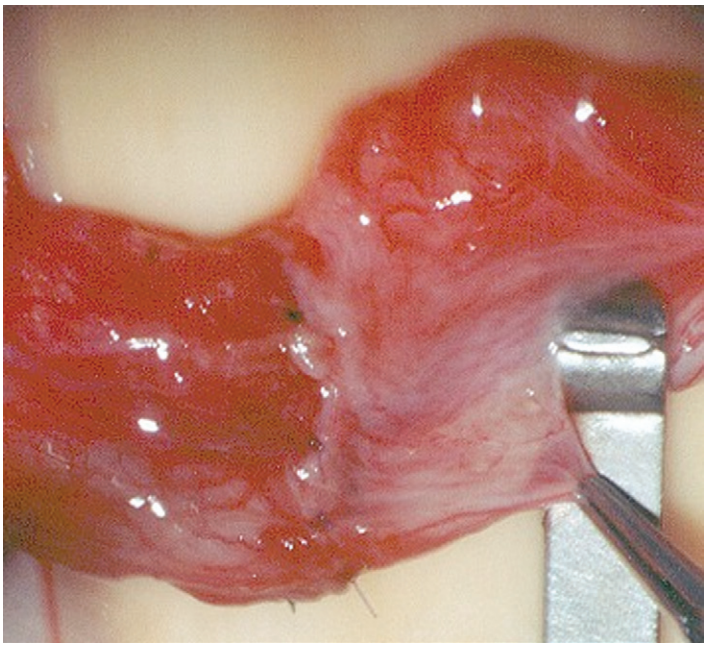


Figure 22–23. Finish the anastomosis by approximating the vasal sheath with six interrupted sutures of 7-0 polydioxanone, completely covering the anastomosis and relieving it of all tension.

Sheynkin et al, 1998a). **Crossover is indicated in the following circumstances:**

1. **Unilateral inguinal obstruction of the vas deferens associated with an atrophic testis on the contralateral side. A crossover vasovasostomy should be performed to connect a healthy testicle to the contralateral unobstructed vas.**
2. **Obstruction or aplasia of the inguinal vas or ejaculatory duct on one side and epididymal obstruction on the contralateral side.**

It is preferable to perform one anastomosis with a high probability of success (vasovasostomy) rather than two operations with a much lower chance of success (i.e., unilateral vasovasoepididymostomy and contralateral transurethral resection of the ejaculatory ducts).

Technique

Transect the vas attached to the atrophic testis at the junction of its straight and convoluted portion and confirm its patency with a Ringer or indigo carmine vasogram (Fig. 22–25). Dissect the contralateral vas with the normal testis toward the inguinal obstruction. Clamp and transect it as high up as possible with a right-angle clamp. Cross the testicular end of the vas through a capacious opening made in the scrotal septum and proceed with vasovasostomy as described earlier. This procedure is much easier than inguinal vasovasostomy, which requires finding both ends of the vas within the dense scar of a previous inguinal operation.

Transposition of the Testis

Occasionally when vasal length is critically short, a tension-free crossed anastomosis can best be accomplished by testicular transposition (Fig. 22–26). The spermatic cord is always longer than the vas. The testes will comfortably cross through a generous opening in the septum and sit nicely in the contralateral scrotal compartment.

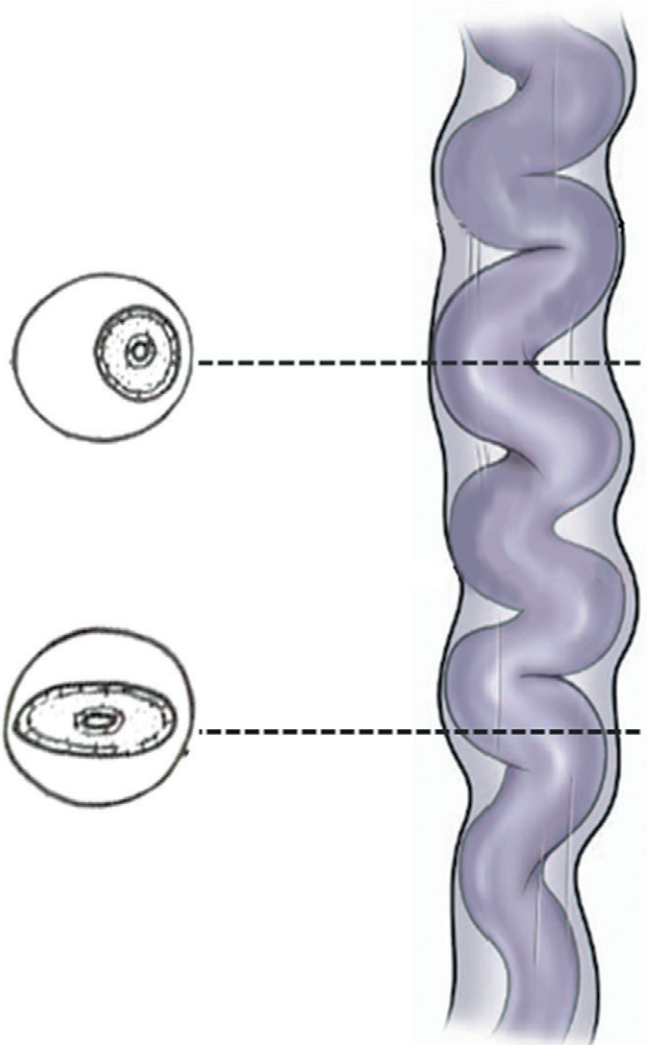


Figure 22–24. An oblique lumen with a thin flap of muscle and mucosa on one side is not acceptable.

Wound Closure

If the vasal dissection was extensive, Penrose drains are brought out the dependent portion of the right and left hemiscrota and fixed in place with sutures and safety pins preferably before beginning the anastomosis. Placement of drains at the end of the procedure may potentially disturb the anastomosis. The dartos layer is approximated with interrupted 4-0 absorbable sutures and the skin with subcuticular sutures of 5-0 Monocryl. The wound heals with a fine scar. The use of through-and-through skin closures, which give an unacceptable railroad-track-looking scar, should be avoided. **Virtually all of our procedures are performed on an ambulatory basis.** If drains were placed, the patients are given detailed instructions (with explicit drawings) on how to remove the drains the next morning.

Postoperative Management

Sterile fluff gauze dressings are held in place with a snug-fitting scrotal supporter. Only perioperative antibiotics are used. Patients are discharged with a prescription for acetaminophen with codeine. They shower 48 hours after surgery. **They wear a scrotal supporter at all times (except in the shower),**

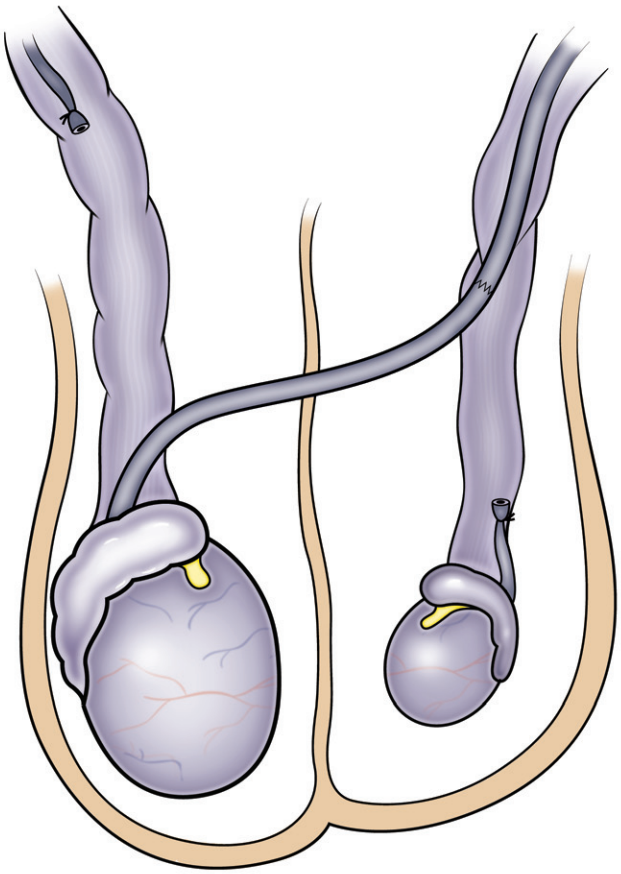


Figure 22–25. A crossed vasovasostomy can be done in cases with a unilateral atrophic testis.

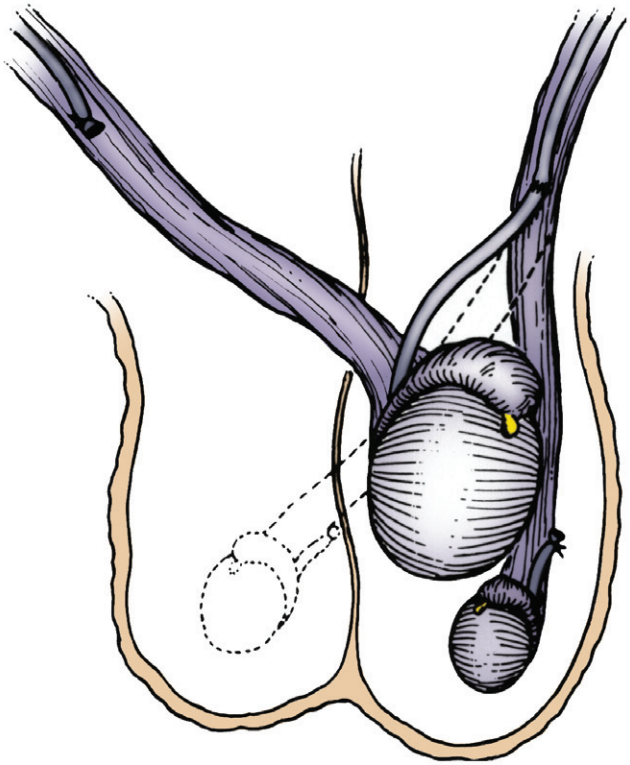


Figure 22–26. Occasionally, when vasal length is critically short, a tension-free crossed anastomosis can best be accomplished by testicular transposition.

even when sleeping, for 6 weeks postoperatively. Thereafter a scrotal supporter is worn during athletic activity until pregnancy is achieved. Desk work is resumed in 3 days. No heavy work or sports are allowed for 3 weeks. **No intercourse or ejaculation is allowed for 4 weeks postoperatively.** Semen analyses are obtained at 1, 3, and 6 months postoperatively and every 6 months thereafter. If azoospermia persists at 6 months, a redo vasovasostomy or vasoepididymostomy will be necessary.

Postoperative Complications

The most common complication is hematoma. In 2500 operations seven small hematomas occurred. None required surgical drainage. Most were walnut sized and perivasal. They take 6 to 12 weeks to resolve. Wound infection has not occurred. Late complications include sperm granuloma at the anastomotic site (≈5%). This is usually a harbinger of eventual obstruction. Late stricture and obstruction are disappointingly common (see later). **Progressive loss of motility followed by decreasing counts indicates stricture.** Our recent change from Proline to **nylon sutures** (Sheynkin et al, 1999a), **use of the microdot system to prevent leaks, extensive dissection of the vas until healthy mucosa and muscularis are identified, constant attention to the preservation of good blood supply, as well as generous use of scrotal support until pregnancy is established, has reduced the incidence of late obstruction from 12%** (Matthews et al, 1995) **to 5%** (Kolettis and Thomas, 1997) **at 18 months after surgery. Because of the risk of late stricture and obstruction, we strongly encourage cryopreservation of semen specimens as soon as motile sperm appear in the ejaculate.**

Long-Term Follow-Up Evaluation after Vasovasostomy

When sperm are found in the vasal fluid on at least one side at the time of surgery, the anastomotic technique described results in appearance of sperm in the ejaculate in 99.5% of men (Goldstein et al, 1998). Pregnancy has occurred in 52% of couples followed for at least 2 years and 63% when female factors are excluded with outcomes dependent on the time since vasectomy and female partner age (Kolettis et al, 2003; Boorjian et al, 2004; Kolettis et al, 2005; Gerrard et al, 2007).

SURGERY OF THE EPIDIDYMIS

Introduction

Detailed knowledge of epididymal anatomy and physiology (presented in Chapters 2 and 20) is essential before undertaking surgery of this delicate but important structure. Sperm motility and fertilizing capacity progressively increase during passage through the 200-µm diameter, 12- to 15-foot-long, tightly coiled single tubule. When the epididymis is obstructed and functionally shortened after vasoepididymostomy, even short lengths of epididymis are able to adapt and allow some sperm to acquire motility and fertilizing capacity (Silber, 1989a, 1989b; Jow et al, 1993). Adaptation may gradually continue up to 2 years after surgical reconstruction, with progressive improvement in the fertility and motility of sperm. Nevertheless, preservation of the greatest possible length of functional epididymis is most likely to result in the best sperm quality after vasoepididymostomy (Schoysman and

Bedford, 1986; Schlegel and Goldstein, 1993). Furthermore, because the wall of the epididymis is thinnest in the caput region and gradually thickens, due to the increasing numbers of smooth muscle cells in its more distal (inferior) end, anastomoses are technically easier to perform and more likely to succeed in distal regions. **Because the corpus and cauda epididymis is a single tubule with a small diameter, injury or occlusion of a tubule anywhere along its length will lead to total obstruction of outflow at that level.** For these reasons, **magnification, with loupes for macrodissection and with the operating microscope for anastomosis, is essential for performing all epididymal surgery.**

Fortunately, the epididymis is blessed with a rich blood supply derived from the testicular vessels superiorly and the deferential vessels inferiorly (see Testicular Blood Supply earlier and Chapter 2). Because of the extensive interconnections between these branches, either the testicular or deferential branches (but not both) to the epididymis may be divided without compromising epididymal viability.

Conversely, because the epididymal branches of the testicular artery are medial to and separate from the main testicular artery and veins, surgical procedures may be performed on the epididymis without compromise to testicular blood supply.

Table 22–3.

Comparison of Three Common Techniques for Vasoepididymostomy

TECHNIQUES	ADVANTAGES	DISADVANTAGES
Intussusception	2-3 sutures placed in the epididymal tubule provide 4 and 6 points of fixation. Virtually bloodless anastomosis.	Cannot assess tubular fluid for sperm before anastomosis setup.
End-Side	Virtually bloodless anastomosis. Epididymal fluid can be examined before anastomosis.	Difficult suture placement to a collapsed tubule.
End-End	Epididymal fluid can be examined before anastomosis. Easy and rapid identification of the level of obstruction in the epididymis. Allows upward mobilization of epididymis to bridge a large vasal gap.	Difficult hemostasis on transected epididymis. Difficult to identify the proper tubule for anastomosis. Difficult outer-layer closure. Vasal blood supply from inferior epididymal artery is sacrificed.

Vasoepididymostomy

Introduction

Before the development of microsurgical techniques, accurate approximation of the vasal lumen to that of a specific epididymal tubule was not possible. Vasoepididymostomy was performed by aligning the vas deferens adjacent to a slash made in multiple epididymal tubules and hoping a fistula would form. Results with this primitive technique were poor. Microsurgical approaches allow accurate approximation of the vasal mucosa to that of a single epididymal tubule (Silber, 1978), resulting in marked improvement in the patency and pregnancy rates (Schlegel and Goldstein, 1993; Chan et al, 2005). **Microsurgical vasoepididymostomy,** however, **is the most technically demanding procedure in all of microsurgery.** In virtually no other operation are results so dependent on technical perfection. **Microsurgical vasoepididymostomy should only be attempted by experienced microsurgeons who perform the procedure frequently.**

Indications

The indications for vasoepididymostomy at the time of vasectomy reversal are reviewed in Vasovasostomy earlier. For obstructive azoospermia not due to vasectomy, **vasoepididymostomy is indicated when the testis biopsy reveals complete spermatogenesis and scrotal exploration reveals the absence of sperm in the vasal lumen with no vasal or ejaculatory duct obstruction.** The preoperative evaluation is identical to that described in the previous section on vasovasostomy.

Microsurgical End-to-Side Vasoepididymostomy

End-to-side techniques of vasoepididymostomy have the advantage of being minimally traumatic to the epididymis and relatively bloodless (Table 22–3) (Wagenknecht et al, 1980; Krylov and Borovikov, 1984; Fogdestam et al, 1986; Thomas, 1987). The end-to-side technique does not disturb the epididymal blood supply. When the level of epididymal obstruction is clearly demarcated by the presence of markedly dilated tubules proximally and collapsed tubules distally, the site at which the anastomosis should be performed is readily apparent. The end-to-side approach has the advantage of allowing accurate approximation of the muscularis and adventitia of the vas deferens to a precisely tailored opening in the tunica of the epididymis. This is the preferred technique when vasoepididymostomy is performed simultaneously with inguinal vasovasostomy because it is possible to preserve the vasal blood supply deriving from epididymal branches of the testicular artery (Fig. 22–27). This provides blood supply to the segment of vas intervening between the two anastomoses. Maintenance of the deferential artery's contribution to the testicular blood supply is also important in situations where the integrity of the testicular artery is in doubt due to prior surgery such as orchiopexy, nonmicroscopic varicocelectomy, or hernia repair.

The testis is delivered through a 3- to 4-cm-high vertical scrotal incision. The vas deferens is identified, isolated with a Babcock clamp, and then surrounded with a Penrose drain at the junction of the straight and convoluted portions of the vas deferens. Using 8- to 15-power magnification provided by the operating microscope, the vasal sheath is longitudinally incised with a microknife and a bare segment of vas stripped of its carefully preserved vessels is delivered. The vas is hemitransected with the ultrasharp knife until the lumen is entered (Fig. 22–28). **The vasal fluid is sampled. If microscopic examination of this fluid reveals the absence of sperm, the diagnosis of epididymal obstruction is confirmed.** Patency of the vas and ejaculatory ducts is confirmed by cannulating the abdominal end of the vas with a 24-gauge angiocatheter sheath and gently injecting lactated Ringer solution with a 1-mL tuberculin syringe (see Fig. 22–4). Further confirmation of patency may be obtained by injecting indigo carmine, catheterizing the bladder, and observing blue-tinged urine. The vas is then completely transected using a 2.5-mm slotted nerve clamp (see Fig. 22–28), and the vas is prepared as for vasovasostomy as described earlier (see Preparation of the Vasa).

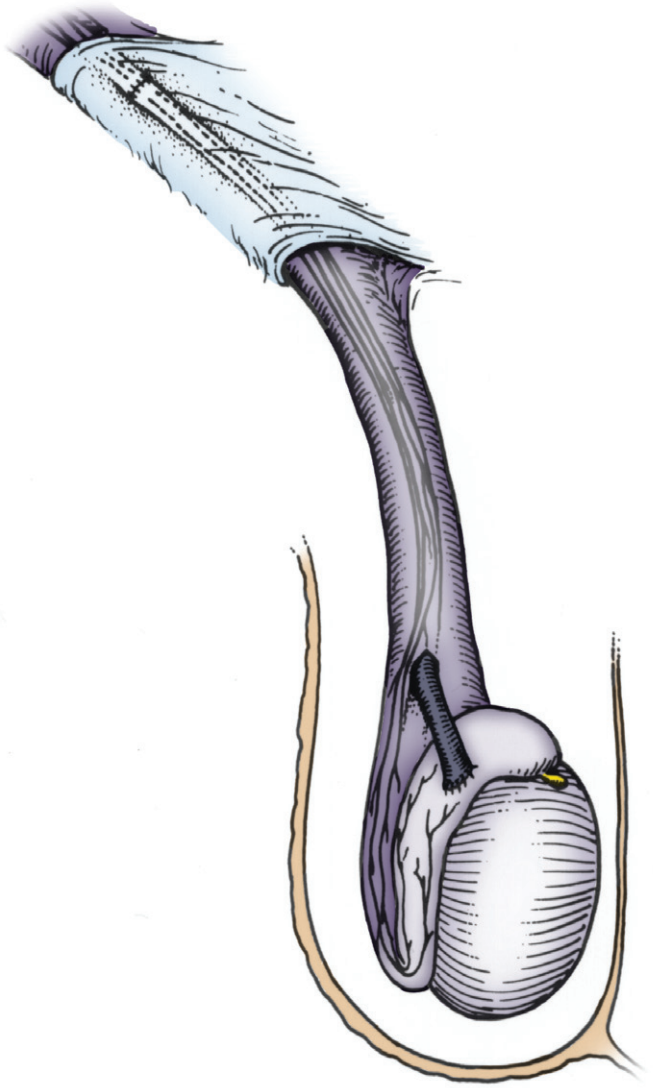


Figure 22–27. A diagram of a finished vasoepididymostomy.

After opening the tunica vaginalis, the epididymis is inspected under the operating microscope. An anastomotic site is selected above the area of suspected obstruction, proximal to any visible sperm granulomas, where dilated epididymal tubules are clearly seen beneath the epididymal tunica (Fig. 22–29). A relatively avascular area is grasped with sharp jeweler's forceps and the epididymal tunica tented upward. **A 3- to 4-mm buttonhole is made in the tunica with microscissors to create a round opening that matches the outer diameter of the previously prepared vas deferens.** The epididymal tubules are then gently dissected with a combination of sharp and blunt dissection until dilated loops of tubule are clearly exposed (Fig. 22–30). **If the level of obstruction is not clearly delineated after the buttonhole opening is made in the tunic, a 70-µm diameter tapered needle from the 10-0 nylon microsuture is used to puncture the epididymal tubule beginning as distal as possible and fluid is sampled from the puncture site. When sperm are found, the puncture sites are sealed with microbipolar forceps, a new buttonhole is made in the epididymal tunic just proximally, and the tubule is prepared as described previously.**

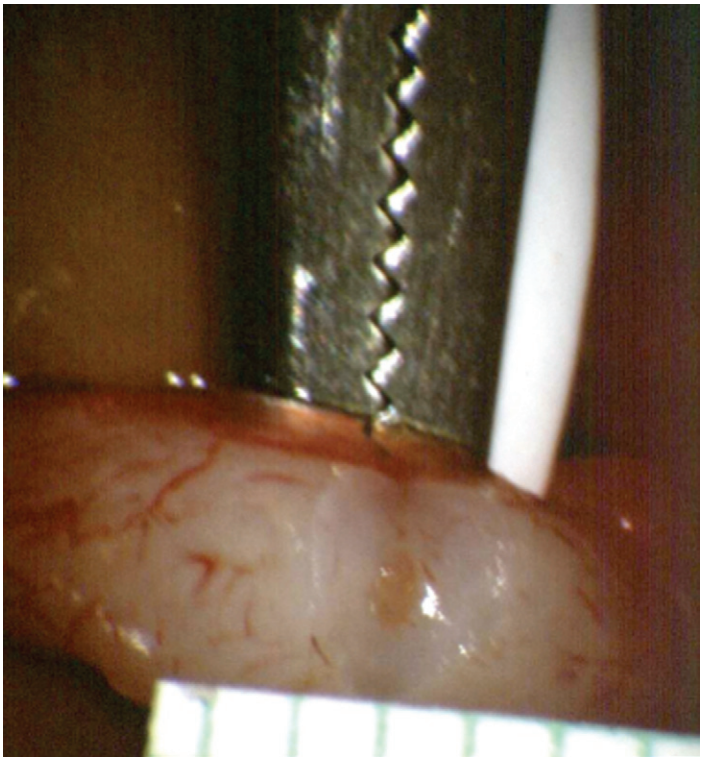


Figure 22–28. The vas is hemitransected with the ultrasharp knife until the lumen is entered.

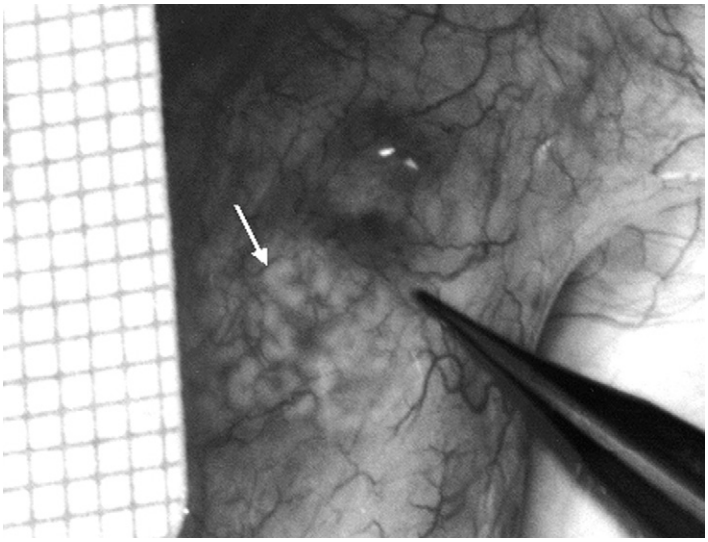


Figure 22–29. An anastomotic site is selected above the area of suspected obstruction, proximal to any visible sperm granulomas, where dilated epididymal tubules are clearly seen beneath the epididymal tunica, as marked by an *arrow*.

The vas deferens is drawn through an opening in the tunica vaginalis and secured in proximity to the anastomotic site with two to four interrupted sutures of 6-0 polypropylene placed through the vasal adventitia and the tunica vaginalis. **The vasal lumen should reach the opening in the epididymal tunica easily, with length to spare.** The posterior edge of the epididymal tunica is then approximated to the posterior edge of the vas muscularis and adventitia with two to three interrupted sutures of double-armed 9-0 nylon (Fig. 22–31). This is done in

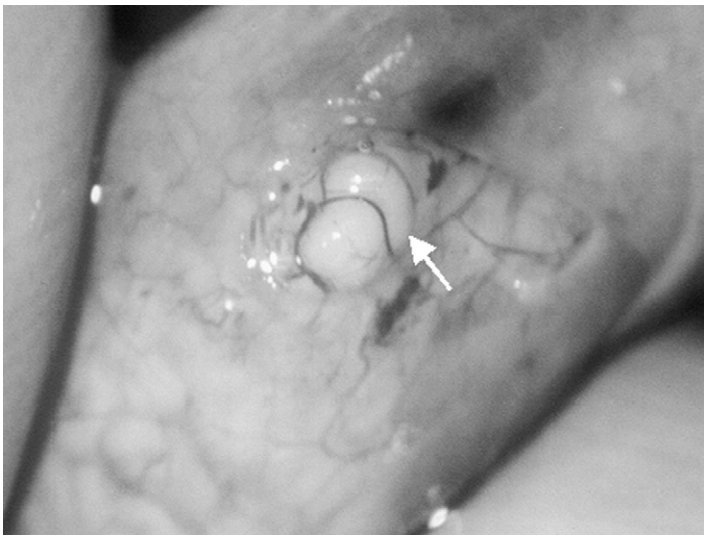


Figure 22–30. The epididymal tubules are then gently dissected with a combination of sharp and blunt dissection until dilated loops of tubule are clearly exposed.

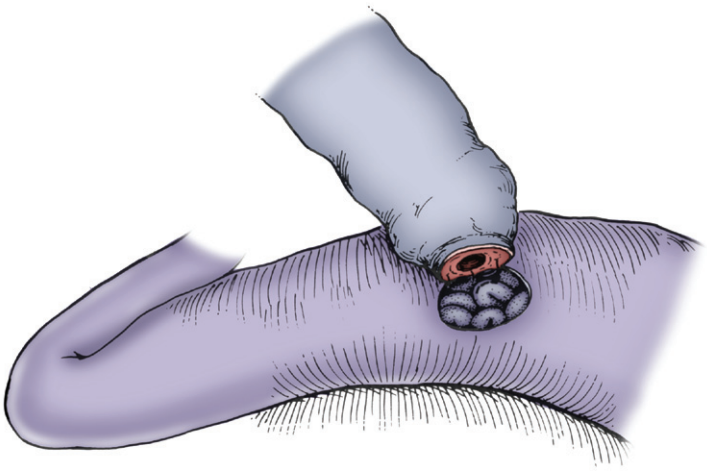


Figure 22–31. The posterior edge of the epididymal tunica is then approximated to the posterior edge of the vas muscularis and adventitia with two to three interrupted sutures of double-armed 9-0 nylon.

such a way as to bring the vasal lumen in close approximation to the epididymal tubule selected for anastomosis.

Classic End-to-Side Technique

Under 25× to 32× magnification, using small curved microscissors or a 15-degree microknife, an opening about 0.3 to 0.5 mm in diameter is made in the selected tubule. Epididymal fluid is touched to a slide, diluted with saline or lactated Ringer solution, and inspected under the microsope for sperm. If no sperm are found, the opening in the tubule is closed with 10-0 sutures, the vas is detached, and the tunica incision is closed with 9-0 nylon. The procedure is then repeated more proximally in the epididymis.

Once sperm are identified, they are aspirated into glass capillary tubes and flushed into media for cryopreservation (Fig. 22–32) (see Open Tubule Technique later) (Matthews et al, 1995). **Indigo carmine solution is dripped on the cut tubule to outline the mucosa.** Methylene blue kills sperm instantly even when diluted, rendering the sperm useless for

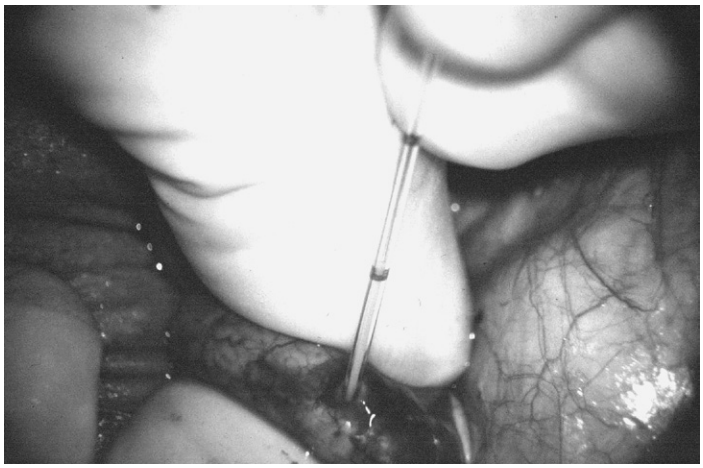


Figure 22–32. Once sperm are identified, they are aspirated into glass capillary tubes and flushed into media for cryopreservation.

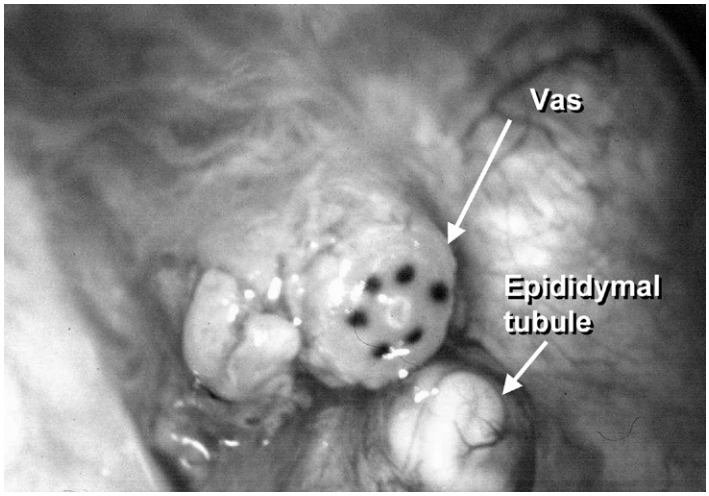


Figure 22–33. The posterior mucosal edge of the epididymal tubule is approximated to the posterior edge of the vasal mucosa with two interrupted sutures of 10-0 monofilament nylon sutures double-armed with a fish-hook 70-µm diameter tapered needles.

cryopreservation (Sheynkin et al, 1999b). Indigo carmine, diluted 50%, is safe for sperm. The posterior mucosal edge of the epididymal tubule is approximated to the posterior edge of the vasal mucosa with two interrupted sutures of 10-0 monofilament nylon sutures double armed with fish-hook 70-µm diameter tapered needles (Fig. 22–33). The lumen is irrigated with lactated Ringer solution just before placement of each suture to keep the epididymal lumen open. The lumen is irrigated with heparinized saline just before tying the last mucosal suture to prevent clots from obstructing the lumen. Unlike blood vessels, there are no platelets and fibrinogen to seal a leaky anastomosis and no clot lysis factor to dissolve clots. After these mucosal sutures are tied, the anterior mucosal anastomosis is completed with two to four additional 10-0 sutures. The outer muscularis and adventitia of the vas are then approximated to the cut edge of the epididymal tunica with 6 to 10 additional interrupted sutures of 9-0 nylon double armed with 100-µm diameter needles (Fig. 22–34A and B). The vasal sheath is secured to the epididymal tunica with three to five sutures of 9-0 nylon. The testis and epididymis are gently returned to the tunica vaginalis, which is closed with 5-0 Vicryl. Penrose drains are usually not necessary. The scrotum is closed as previously described for vasovasostomy.

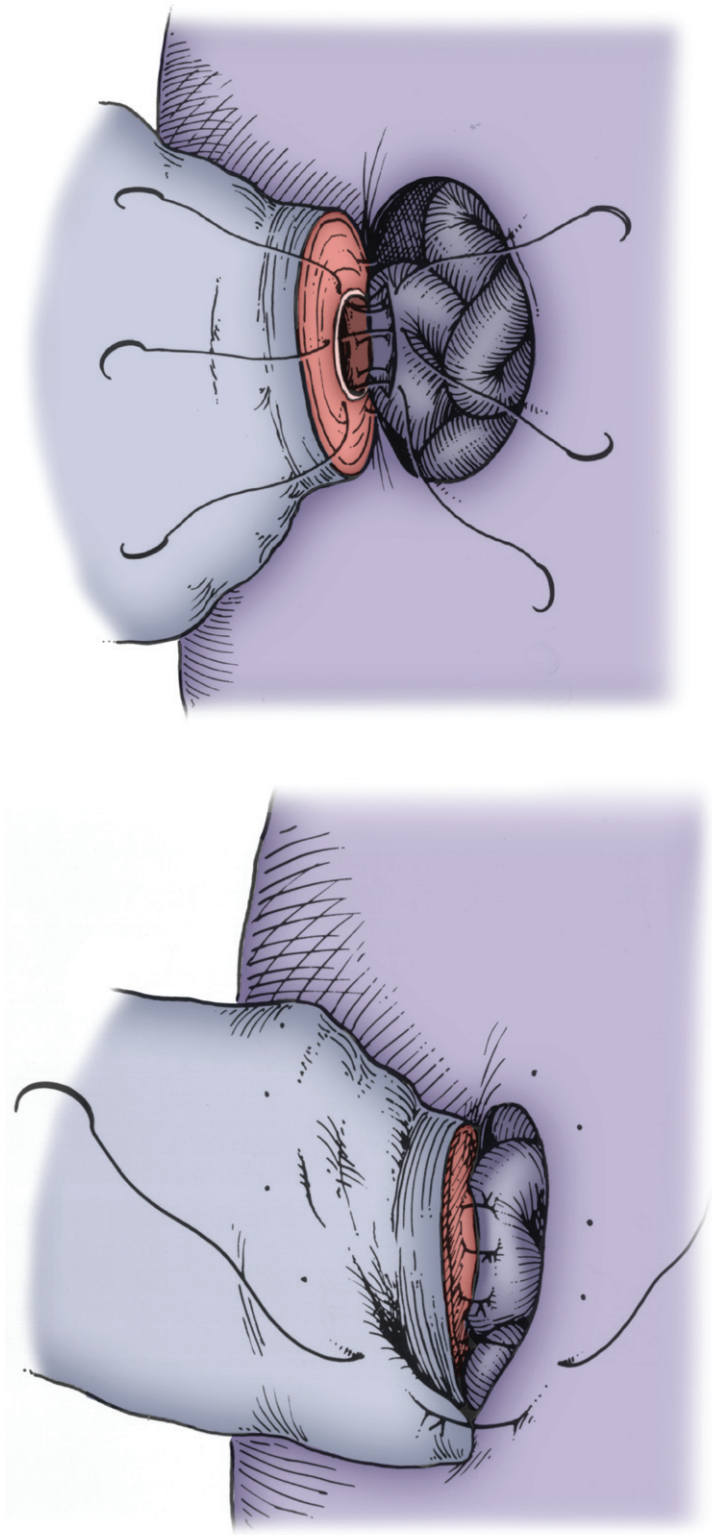


Figure 22–34. The outer muscularis and adventitia of the vas are then approximated to the cut edge of the epididymal tunica with 6 to 10 additional interrupted sutures of 9-0 nylon double-armed with 100-µm diameter needles.

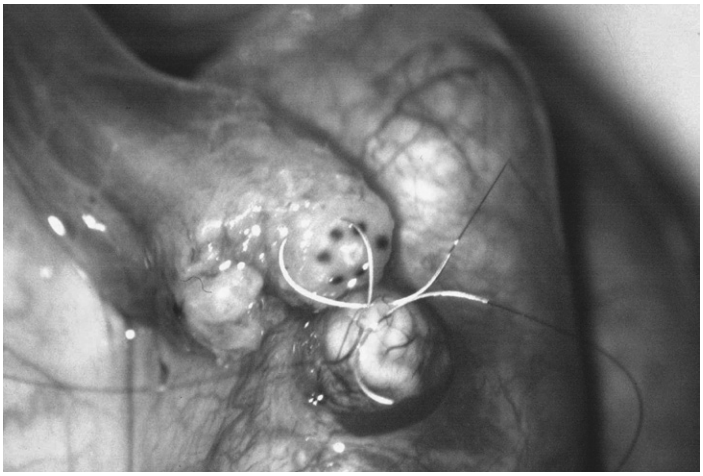


Figure 22–35. The needles are not pulled through but left in situ, creating a triangle of needles.

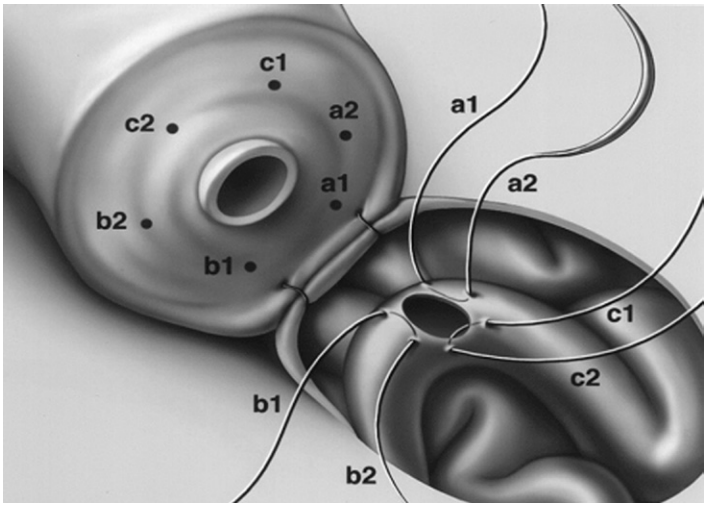


Figure 22–36. Using a 15-degree microknife with the blade pointing upward, a generous opening is made in the epididymal tubule in the center of the triangle created by the three needles.

End-to-Side Intussusception Techniques

This method, originally described as the triangulation technique, was introduced by Berger (1998). There are several advantages of the methods over previous techniques (see Table 22–3) (Goldstein, 1999). The setup is identical to that for the classical end-to-side vasoepididymostomy. After the vas is fixed to the opening in the epididymal tunica, six microdots are placed on the cut surface of the vas in an identical fashion to that described for vasovasostomy. The epididymal tubule selected is dissected with blunt microscissors and the micro needle holder until it is free of surrounding tissue and prominent. The tubule is then stained with indigo carmine. Using 10-0 monofilament nylon sutures approximately 2 inches in length, double armed with 70-µm diameter fish hook–shaped tapered needles, three sutures are placed in the epididymal tubule in a triangulation fashion. The apex of the triangle faces the inferior edge of the vasal mucosa. **The needles are not pulled through but left in situ,** creating a triangle of needles (Fig. 22–35). Using a 15-degree microknife with the blade pointing upward, a generous opening is made in the epididymal tubule in the center of the triangle created by the three needles (Fig. 22–36).

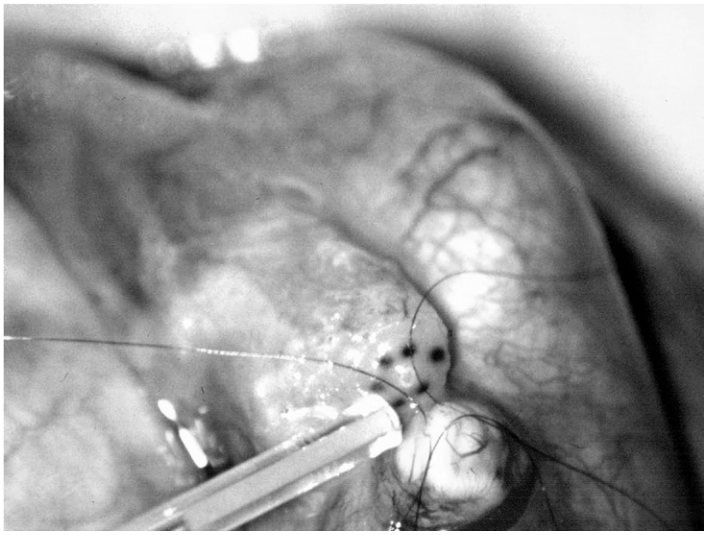


Figure 22–37. Sperm are aspirated into micropipets first.

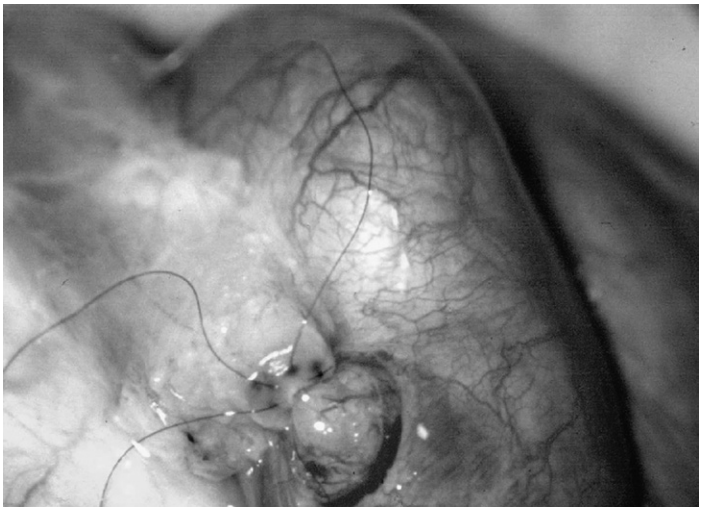


Figure 22–38. After abundant sperm have been aspirated into micropipets and cryopreserved, the six needles are passed inside out the vas deferens, exiting through the six previously placed microdots in the order indicated in Fig 22-36.

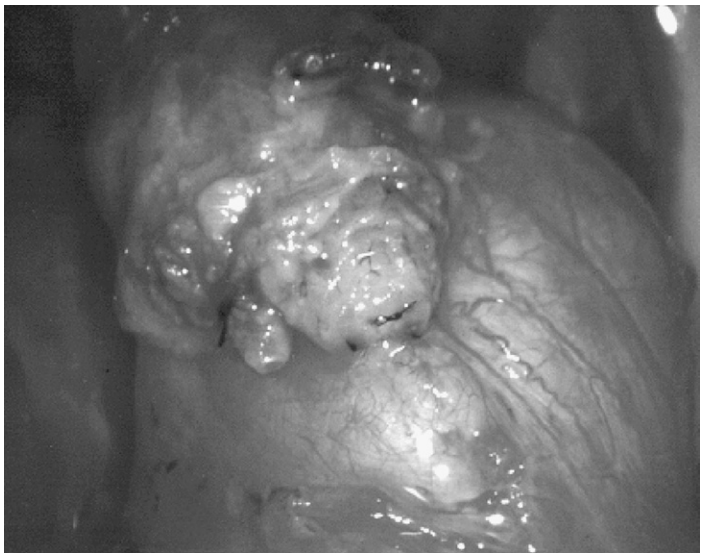


Figure 22–39. Tying of these sutures intussuscepts the epididymal tubule into the vas lumen.

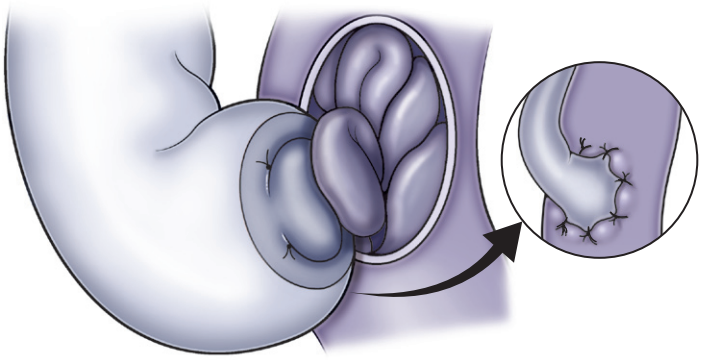


Figure 22–40. This creates a water-tight closure.

The three needles are then pulled through. The six needles are now laid out so as to avoid a spaghetti-like tangle. A glass slide is touched to the fluid exuding from the opening in the epididymal tubule and mixed with human tubal fluid media, covered with a coverslip, and examined by the surgeon using the separate bench microscope under 400-power magnification. If sperm are present (whether motile or not), the decision is made to proceed with the anastomosis. Sperm are aspirated into micropipets first (Fig. 22–37) and expressed into human tubal fluid media and sent for cryopreservation if motility is observed. Sperm that initially appear immotile, when mixed with human tubule fluid, often regain motility adequate for successful cryopreservation. Even immotile sperm should be placed in the media and evaluated for potential cryopreservation. **If the needles are pulled through before placing the microsurgical sutures or before making an opening in the epididymal tubule, epididymal fluid and sperm would immediately leak through the suture hole, causing the tubule to collapse.** This makes placement of subsequent sutures and creation of the opening in the tubule considerably more difficult. **Leaving the needles in the epididymal tubule before making the opening also prevents accidental cutting of the sutures when making the opening in the center of the triangle.** After abundant sperm have been aspirated into micropipets and cryopreserved, the six needles are passed inside out the vas deferens exiting through the six previously placed microdots in the order indicated (Fig. 22–38). Each pair of sutures is then sequentially tied beginning with suture a1 and a2, then b1 and b2, and finally c1 and c2. Tying of these sutures intussuscepts the epididymal tubule into the vas lumen (Fig. 22–39). This creates a water-tight closure (Fig. 22–40). In addition, the flow of epididymal fluid from the epididymal tubule into the vas deferens tends to plaster the edges of the epididymal tubule against the mucosal walls of the vas deferens, further helping create a leakproof closure. The second layer of the anastomosis is completed in an identical fashion to that described for the classical end-to-side operation described earlier (Fig. 22–41A and B).

Two-Stitch Variation of the Intussusception Technique (Preferred Technique)

For anastomoses to small epididymal tubules such as those found in the caput or to the efferent ductules (Chan et al, 2005), the three-stitch triangulation technique may be impossible. **We now**

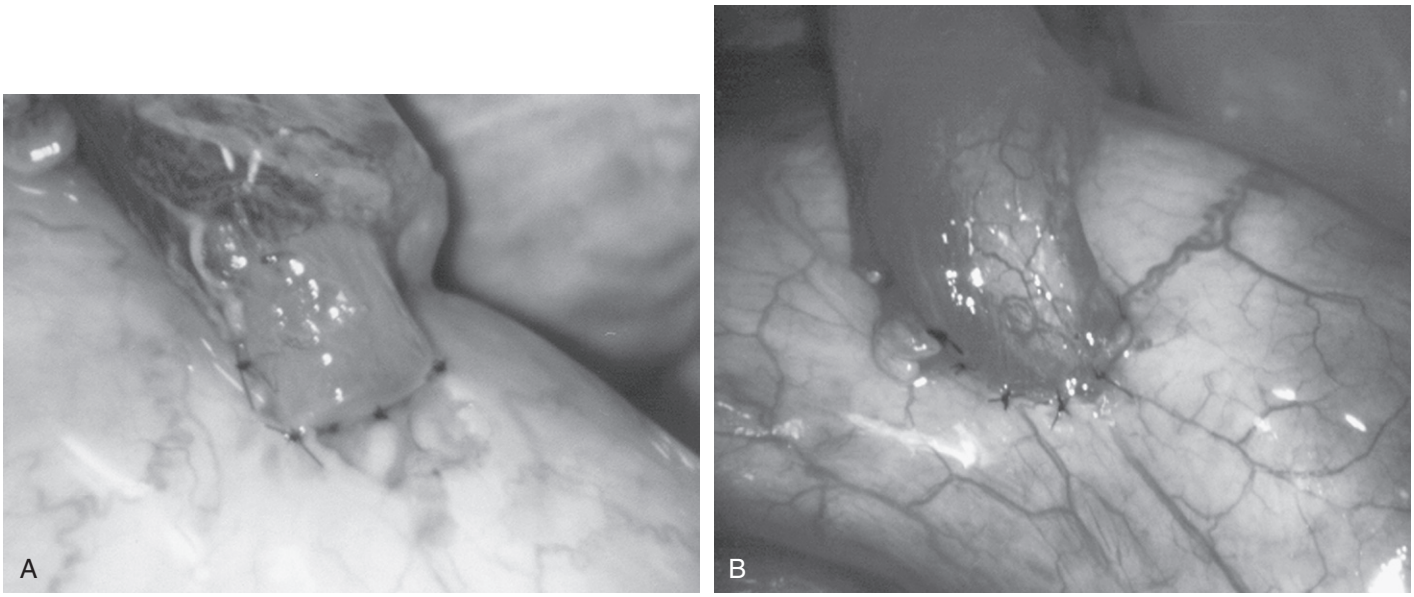


Figure 22–41. **A** and **B,** The second layer of the anastomosis is completed in an identical fashion to that described for the classical end-to-side operation described earlier.

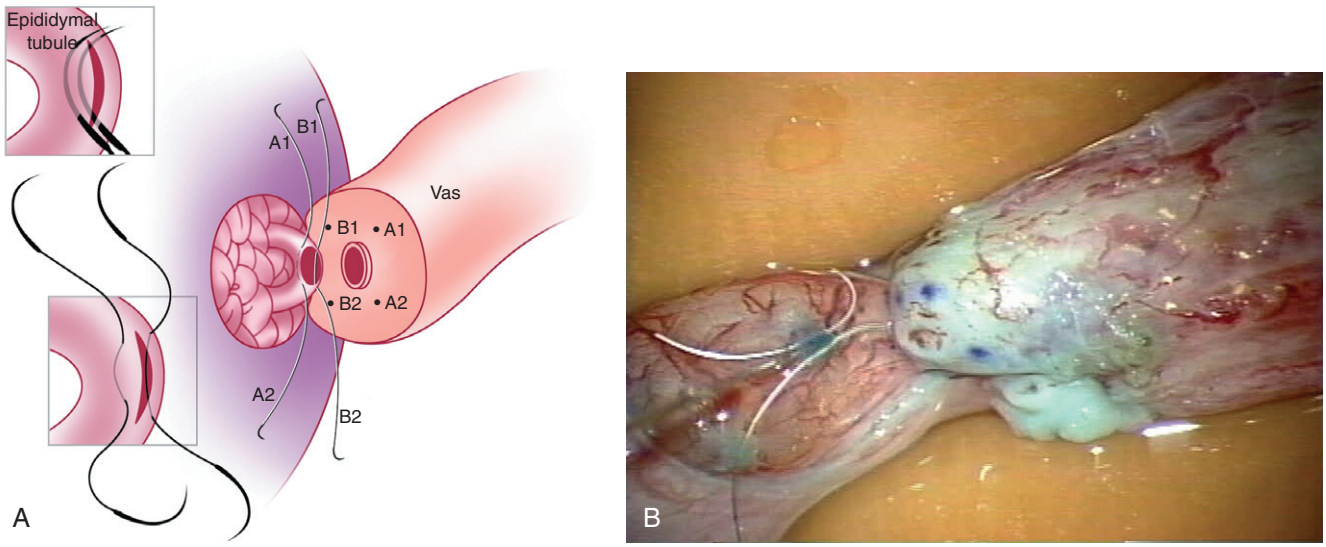


Figure 22–42. **A** and **B,** With this method, four microdots are marked on the cut surface of the vas deferens and two parallel sutures are placed in the distended epididymal tubule longitudinally, but not pulled through.

employ a two-stitch longitudinal intussusception technique for all vasoepididymostomies. It is much easier to perform and is even more successful. With this method, four microdots are marked on the cut surface of the vas deferens and two parallel sutures are placed in the distended epididymal tubule longitudinally, but not pulled through (Fig. 22–42A and B). Marmar suggests mounting two needles in the needle holder and placing them simultaneously transversely in the tubule. However, if the needles are not pulled through to avoid leakage of fluid and tubular collapse, they can be placed one at a time with greater control and accuracy (Chan et al, 2005; Schiff et al, 2005). Using a 15-degree microknife, an opening is made exactly between and parallel to the two previously placed sutures. Of note, we have also developed a single-arm technique of vasoepididymostomy, which is almost as effective as the double-arm technique (Fig. 22–43) (Monoski et al, 2007). This technique is valuable when double-armed sutures are not available.

Technique When Vasal Length Is Severely Compromised

When there is inadequate length of the vas deferens to reach the dilated epididymal tubule without tension, the epididymis can be dissected down to the vasoepididymal junction and then dissected off the testes as in the older end-to-end operation.

After the vas has been prepared, the tunica vaginalis is opened and the testis is delivered. Inspection of the epididymis under the operating microscope may reveal a clearly delineated site of obstruction. Often, a discrete yellow sperm granuloma is noted, above which the epididymis is indurated and the tubules are dilated and below which the epididymis is soft and the tubules

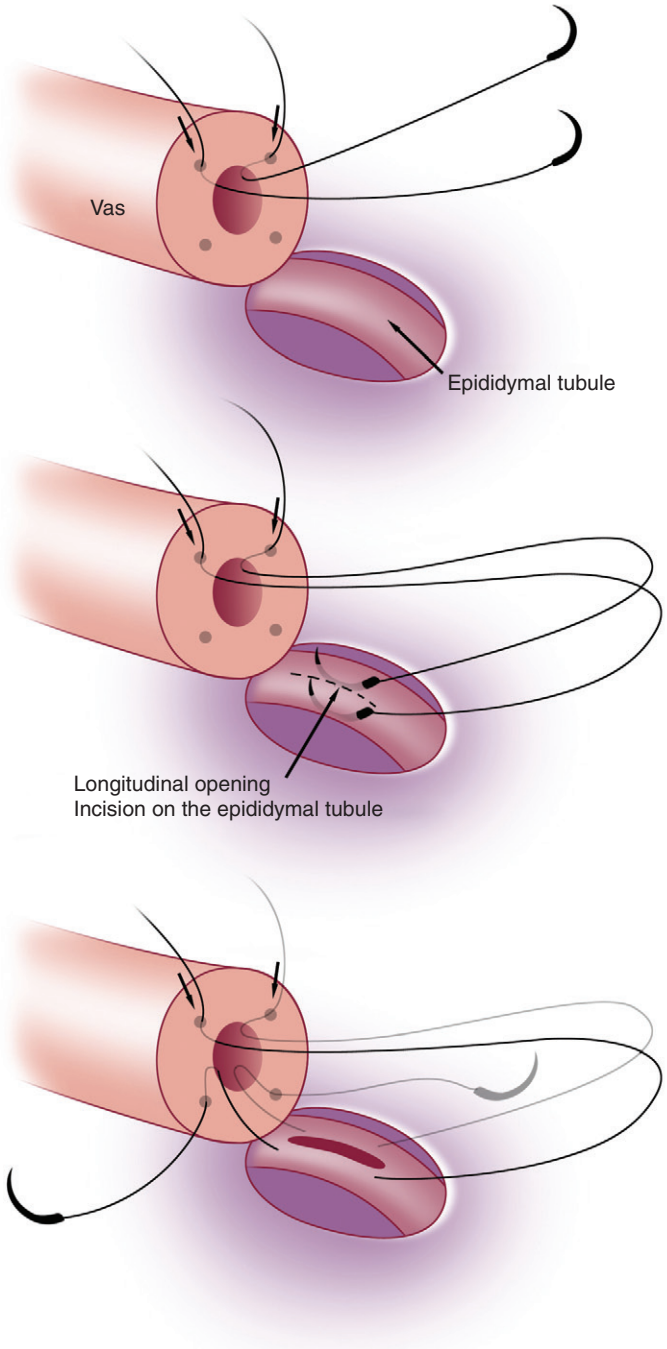


Figure 22–43. Of note, we have also developed a single-arm technique of vasoepididymostomy, which is almost as effective as the double-arm technique.

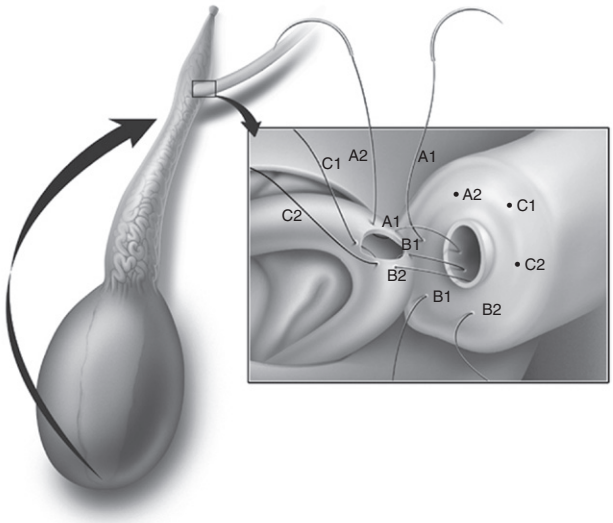


Figure 22–44. In addition, if vasal length is compromised, the epididymis can be dissected to the caput by ligating the inferior and medial epididymal vessels and flipping the epididymis up, providing additional length.

are collapsed. **If the level of obstruction is not clearly delineated, a 70-μm tapered needle from the 10-0 nylon microsuture is used to puncture the epididymal tubule beginning as distal as possible and fluid is sampled from the puncture site until sperm are found. At that level the puncture is sealed with microbipolar forceps, and the epididymis is ligated just proximal to the puncture site with a 6-0 nylon. The epididymis is then dissected off the testis and flipped up to obtain additional length** (Fig. 22–44). To do this, the epididymis is encircled with a small Penrose drain at the level of obstruction and, using 2.5-power loupe magnification, dissected off of the testis for 3 to 5 cm, yielding sufficient length to perform the anastomosis. Usually a nice plane can be found between the epididymis and testis, and injury to the epididymal blood supply can be avoided by staying right on the tunica albuginea of the testis. The inferior and, if necessary, middle epididymal branches of the testicular artery are ligated and divided to free up an adequate length of epididymis. The superior-epididymal branches entering the epididymis at the caput are always preserved and can provide adequate blood supply to the entire epididymis. The tunica vaginalis in then closed over the testis with 5-0 Vicryl. This prevents drying of the testis and thrombosis of the surface testicular vessels during the anastomosis. The dissected epididymis remains outside the tunica vaginalis.

If the epididymis is indurated and dilated throughout its length, it is dissected to the vasoepididymal (VE) junction. This dissection is often assisted by first dissecting the convoluted vas to the VE junction from below, and then, after encircling the epididymis with a Penrose drain, dissecting the epididymis to the VE junction from above. In this way the entire VE junction can be freed up. This will allow preservation of maximal epididymal length in cases of distal obstruction near the VE junction. After the epididymis is dissected off of the testis and flipped up, a three-stitch end-to-side intussusception anastomosis is performed as described earlier.

Long-Term Follow-Up—Evaluation and Results

Microsurgical vasoepididymostomy in the hands of experienced and skilled microsurgeons will result in the appearance of sperm in the ejaculate in 50% to 85% of men. Patency rates with the intussusception technique can exceed 80% (Berger, 1998; Brandell, 1999; Marmar, 2000). With the classic end-to-side or older end-to-end method, the patency rate is about 70% and 43% of men with sperm will impregnate their wives after a minimum follow-up of 2 years (Schlegel and Goldstein, 1993; Pasqualotto et al, 1999). With the intussusception techniques, patency rates

are 70% to 90% (Kolettis and Thomas, 1997; Chan et al, 2005; Schiff et al, 2005). Regardless of technique, pregnancy rates are higher the more distal the anastomosis is performed (Silber, 1989a). **With the older end-to-end or end-to-side methods, at 14 months after surgery 25% of initially patent anastomoses have shut down** (Matthews et al, 1995). **With intussusception technique, the late shut-down rates appear to be less than 10%** but long-term follow-up with these techniques has not been reported. **Nevertheless, we recommend banking sperm both intraoperatively** (Matthews and Goldstein, 1996) **and as soon as they appear in the ejaculate postoperatively after vasoepididymostomy, regardless of technique employed.** In men with low counts or poor sperm quality postoperatively and men who remain azoospermic, the sperm intraoperatively cryopreserved can be used for IVF with intracytoplasmic sperm injection. Persistently azoospermic men without cryopreserved sperm can opt for either a redo vasoepididymostomy and/or microscopic epididymal sperm aspiration combined with IVF and intracytoplasmic sperm injection (see Microsurgical Epididymal Sperm Aspiration Techniques).

TRANSURETHRAL RESECTION OF THE EJACULATORY DUCTS

Ejaculatory duct obstruction is usually a congenital anomaly that represents the opposite end of the spectrum of excurrent ductal system anomalies that begin with congenital complete absence of the vas deferens and most of the epididymis. When the aplastic segment occurs at the terminal end of the vas, where the ejaculatory duct enters the urethra, it is potentially correctable by transurethral resection (Paick et al, 2000; Schroeder-Printzen et al, 2000; Kadioglu et al, 2001; Ozgok et al, 2001; Yurdakul et al, 2008). Occasionally ejaculatory duct obstruction results from chronic prostatitis or extrinsic compression of the ejaculatory ducts by prostate or seminal vesical duct cysts (Cornel et al, 1999; Paick et al, 2000; Kadioglu et al, 2001). Higher ejaculatory duct pressures have been directly measured in men with ejaculatory duct obstruction (Eisenberg et al, 2008).

Diagnosis

The workup leading to the diagnosis of probable ejaculatory duct obstruction is covered in Chapter 21. Briefly, **ejaculatory duct obstruction is suspected in azoospermic or severely oligospermic and/or asthenospermic men with at least one palpable vas deferens, a low semen volume, acid semen pH and negative, equivocal, or low semen fructose levels.** If these men have normal serum levels of FSH and testis biopsy reveals normal spermatogenesis, the diagnosis of ejaculatory duct obstruction is entertained.

Digital rectal examination may reveal a midline cystic structure. **Transrectal sonography is key for the diagnosis and treatment of ejaculatory duct obstruction.** A midline cystic lesion or dilated ejaculatory ducts and seminal vesicles can be visualized sonographically. As described in Transrectal Vasography and Seminal Vesiculography earlier in this chapter, **transrectal ultrasound-guided aspiration of the cystic or dilated ejaculatory ducts or seminal vesicles is performed** (Jarow, 1994). **The aspirate is examined microscopically and if motile sperm are found, they are cryopreserved and 2 to 3 mL indigo carmine diluted with water-soluble radiographic contrast are instilled. If a radiograph confirms a potentially resectable lesion, TUR of the ejaculatory ducts is performed without the need for prior vasography** because the presence of sperm in the seminal vesicles indicates that at least one epididymis is patent and that the cyst or dilated ejaculatory duct communicates with a nonobstructed vas. The instillation of indigo carmine assists in localizing the opening of the ejaculatory duct and confirms when resection has successfully opened the obstructed system. **Transrectal sonography with aspiration should be performed immediately before anticipated surgery and employs the same bowel prep and antibiotic prophylaxis used for transrectal prostate biopsy.**

If no sperm are found in the aspirate, vasography, as described earlier in Technique of Vasography and Interpretation of Findings, is necessary. **If no sperm are found in either vas when the vasotomy is made and vasography reveals ejaculatory duct obstruction, it is best to abandon attempts at reconstruction and simply perform microsurgical epididymal sperm aspiration and cryopreservation for future IVF/ICSI. Simultaneous vasoepididymostomy and TUR of the ejaculatory ducts rarely works.** If ejaculatory duct obstruction is confirmed by vasography employing a 50% water-soluble contrast medium and sperm are present in the vasa, the 3-Fr whistle-tip ureteral vasography stents are left in place so that a dilute indigo carmine solution can be injected by the assistant to aid resection.

Technique

Cold knife incision alone almost always leads to reobstruction. The resectoscope, with the 24-Fr cutting loop, is engaged with a finger placed in the rectum providing anterior displacement of the posterior lobe of the prostate. The ejaculatory ducts course between the bladder neck and the verumontanum and exit at the level of and along the lateral aspect of the verumontanum (Fig. 22–45). **Resection of the veru will often reveal the dilated ejaculatory duct orifice or cyst cavity. Resection should be**

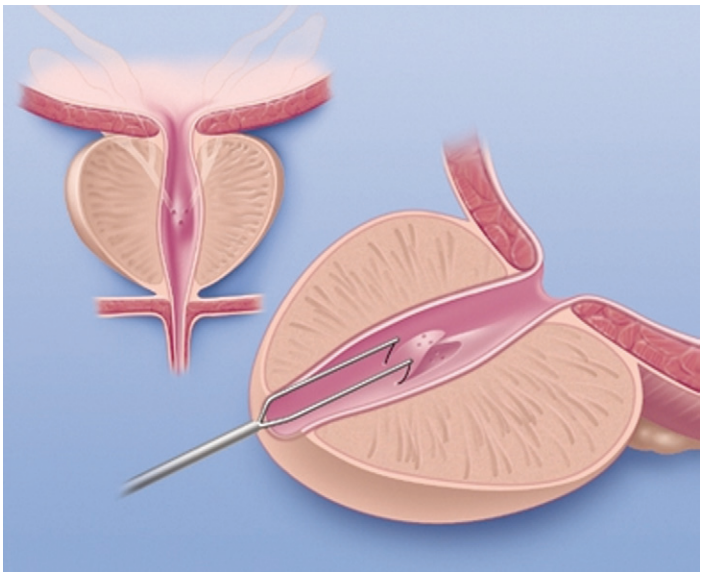


Figure 22–45. The ejaculatory ducts course between the bladder neck and the verumontanum and exit at the level of and along the lateral aspect of the verumontanum.

carried out in this region with great care in order to preserve the bladder neck proximally, the striated sphincter distally and the rectal mucosa posteriorly. Efflux of indigo carmine from dilated orifices confirms adequate resection. **Avoid excessive coagulation.** If formal vasography was performed, the hemivasotomies are carefully closed employing microsurgical technique. A Foley catheter is left overnight and the patient receives an additional 7 days of oral antibiotics.

Complications

Reflux

Reflux of urine into the ejaculatory ducts, vas, and seminal vesicles occurs after a majority of resections. This can be documented by voiding cystourethrography or measuring semen creatinine levels (Malkevich et al, 1994). Contamination of semen by urine impairs sperm quality.

Epididymitis

Reflux can lead to acute and chronic epididymitis. Recurrent epididymitis often results in epididymal obstruction. The incidence of epididymitis after TUR is probably underestimated. Symptomatic chemical epididymitis may occur from refluxing urine. **Chronic low-dose antibacterial suppression such as that employed for vesicoureteral reflux may be necessary until pregnancy is achieved.** If epididymitis is chronic and recurrent, vasectomy or even epididymectomy may be necessary.

Retrograde Ejaculation

Even when care has been taken to spare the bladder neck, retrograde ejaculation is common after TUR. Pseudoephedrine 120 mg orally, 90 minutes before ejaculation, or Ornade Spansules (chlorpheniramine and phenylpropanolamine) twice a day for a week may prevent this. If this is not successful, sperm can be retrieved from alkalinized urine and used for either intrauterine insemination or IVF with ICSI.

Results

TUR of the ejaculatory ducts results in increased semen volume about two thirds of the time and appearance of sperm in the ejaculate in about 50% of previously azoospermic men. Pregnancy rates are based on case reports and small series (Goldwasser et al, 1985; Paick et al, 2000; Ozgok et al, 2001; Fuse et al, 2003; Yurdakul et al, 2008). If viable sperm appear in the ejaculate but the quality is poor, IVF with ICSI is recommended. This approach currently yields delivery rates of up to 38.5% per attempt. Because of the potential for serious complications, **TUR should only be performed in azoospermic men or in severely oligoasthenospermic men and only after the couple has stated they are unwilling to do IVF and have been fully apprised of the risks of TUR.**

ELECTROEJACULATION

Men with neurologic impairments in sympathetic outflow such as seen in traumatic spinal cord injury, demyelinating neuropathies (multiple sclerosis), and diabetes following retroperitoneal lymph node dissection frequently have abnormalities in or absence of seminal emission. **Ejaculation can be induced in most of these men, especially those with high spinal cord injury, with vibratory stimulation** (Schellan, 1968; Brindley, 1981; Bennett et al, 1987; Brackett et al, 1997; Ohl et al, 1997). **For those men that do not respond to vibratory stimulation, electroejaculation has proven to be a safe and effective means of obtaining motile sperm suitable for assisted reproduction techniques (IUI, IVF/ICSI).**

The procedure is performed under general anesthesia except for men with a complete spinal cord injury, who do not require anesthesia. **In men with a high thoracic spinal cord lesion (above T6) or in those men with prior history of autonomic dysreflexia, pretreatment, 15 minutes before the procedure, with 20 mg of sublingual nifedipine is employed.** These men should have intravenous access and their blood pressure and pulse should be monitored every 2 minutes before, during, and for 20 minutes following electroejaculation. In the event of a sympathetic outflow (autonomic dysreflexia), termination of the procedure should be sufficient to break the response. However, intravenous access allows for delivery of sympatheticolytic agents should they become necessary.

Before placing the patient in the lateral decubitus position, the bladder is catheterized and emptied. A 12-Fr or 14-Fr Silastic catheter lubricated with a small amount of mineral oil is used because commonly employed lubricants are spermicidal. Ten mL of buffer (HEPES-BSA) is instilled into the bladder. Before the electroejaculation sequence, a digital rectal examination and anoscopy are performed. A rectal probe with three large horizontal stripes is well lubricated, inserted with the electrodes facing anteriorly and applied against the posterior aspect of the prostate and seminal vesicles. The probe is connected to a variable-output power source that simultaneously records probe temperature through a thermistor in the rectal probe. Electrostimulation is started at 3 to 5 volts and increased in 1-volt increments with each stimulation (Ohl et al, 2001). An assistant records probe temperatures and number of stimulations to full erection and ejaculation and collects the ejaculate in a sterile wide mouth plastic container. The number of stimulations and maximum voltage required are variable and the ejaculate may be retrograde. If probe temperature rises rapidly or above 40° C, stimulation is suspended until the temperature falls below 38° C or probes are changed. At the completion of stimulation, anoscopy is again performed to check for rectal injury. The bladder is recatheterized to obtain any retrograde-ejaculated sperm. The specimens are then delivered to the laboratory for processing. **A second electroejaculation sequence can be immediately performed under the same anesthetic to obtain additional sperm.**

Employing this technique, sperm can be recovered in more than 90% of men. Overall pregnancy rates of up to 40% can be achieved after multiple cycles with intrauterine insemination. Use of IVF with ICSI will yield 50% live delivery rates for a single (albeit costly) procedure if motile sperm are obtained.

SPERM RETRIEVAL TECHNIQUES

Men with congenital absence or bilateral partial aplasia of vas deferens, or those with failed or surgically unreconstructable obstructions, can now be treated by using sperm retrieval techniques in conjunction with in vitro fertilization (Table 22–4) (Temple-Smith et al, 1985; Silber et al, 1990; Schlegel et al, 1994; Craft et al, 1995; Sheynkin et al, 1998b; Janzen et al, 2000; Levine et al, 2003; Qiu et al, 2003; Anger et al, 2004). These techniques are also useful for intraoperative retrieval of sperm during reconstructive procedures such as vasoepididymostomy, which have significant failure rates. The intraoperatively retrieved sperm may

Table 22–4.

Surgical Techniques for Sperm Retrieval

	ADVANTAGES	DISADVANTAGES
MESA (microsurgical epididymal sperm aspiration)	Microsurgical procedure allows lower complication rate. Epididymal sperm has better motility than testicular sperm. Large number of sperm can be harvested for cryopreservation of multiple vials in a single procedure.	Requires anesthesia and microsurgical skills. Not indicated for nonobstructive azoospermia.
PESA (percutaneous epididymal sperm aspiration)	No microsurgical skill required. Local anesthesia. Epididymal sperm has better motility than testicular sperm.	Complications include hematoma, pain, and vascular injury to testes and epididymis. Variable success in obtaining sperm. Small quantity of sperm obtained than with MESA. Not indicated in nonobstructive azoospermia.
TESA (testicular sperm aspiration)	No microsurgical skill required. Local anesthesia. Can be used for obstructive azoospermia.	Immature or immotile testicular sperm. Small quantity of sperm obtained. Poor results in nonobstructive azoospermia. Complications include hematoma, pain, and vascular injury to testes and epididymis.
TESE (testicular sperm extraction)	Low complication rate if performed microsurgically. Preferred technique for nonobstructive azoospermia.	Requires anesthesia and microsurgical skills.

be used immediately if the wife has been prepared for IVF or may be cryopreserved for a future IVF with ICSI cycle in the event the reconstructive surgery is unsuccessful. Sperm obtained from chronically obstructed systems usually have poor motility and decreased fertilizing capacity. **The use of intracytoplasmic sperm injection (ICSI) combined with IVF is essential to achieve optimal results.**

Microsurgical Epididymal Sperm Aspiration Techniques

Open Tubule Technique

The technique described here can be employed for either intraoperative sperm retrieval at the time of vasoepididymostomy or as an isolated procedure in men with congenital absence of the vas or unreconstructable obstructions (Matthews and Goldstein, 1996; Nudell et al, 1998). A median raphe approach through two small transverse scrotal incisions within the scrotal skin folds is used. After delivery of the testis, the tunica vaginalis is opened and the epididymis inspected under 16× to 25× magnification using the operating microscope. The epididymal tunica is incised over a dilated tubule as described previously for vasoepididymostomy. Meticulous hemostasis is obtained using the bipolar cautery. A dilated tubule is isolated and incised with a 15-degree microknife. The fluid is touched to a slide, a drop of human tubal fluid media is added, a coverslip is placed, and the fluid examined. If no sperm are obtained, the epididymal tubule and tunica are closed with 10-0 and 9-0 monofilament nylon sutures, respectively, and an incision is made more proximally in the epididymis or even at the level of the efferent ductules until motile sperm are obtained.

As soon as motile sperm are found, a dry micropipet (5 µL; Drummond Scientific Co., Broomall, PA) is placed adjacent to the effluxing epididymal tubule (Fig. 22–46). A standard hematocrit pipette is less satisfactory but can be used if micropipets are not available. **Sperm are drawn into the micropipet by simple capillary action.** Negative pressure, as is generated by action of an in-line syringe, should not be applied during sperm recovery because this may disrupt the delicate epididymal mucosa. Two micropipets may be employed simultaneously to increase the speed of sperm recovery.

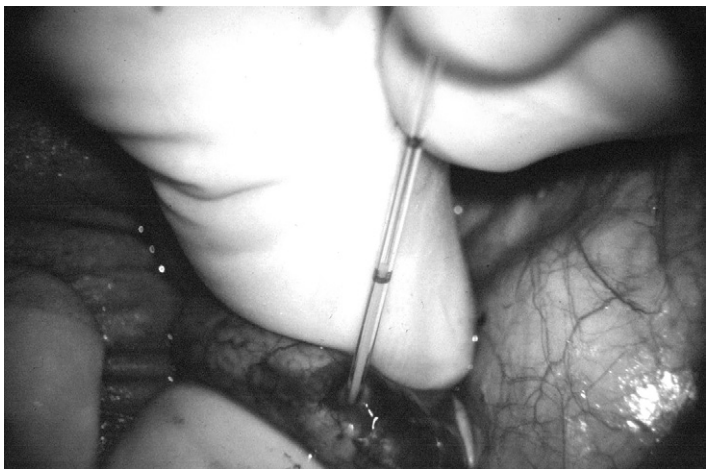


Figure 22–46. As soon as motile sperm are found, a dry micropipet (5 µL; Drummond Scientific Co., Broomall, PA) is placed adjacent to the effluxing epididymal tubule.

The highest rate of flow is observed immediately following incision of the tubule. Progressively better-quality sperm are often found following the initial washout. **Gentle compression of the testis and epididymis enhances flow from the incised tubule.** With patience, 10 to 20 µL of epididymal fluid can be recovered.

The micropipet is connected to a short (3 to 5 cm) segment of medical-grade silicone tubing (American Scientific Products; McGaw Park, IL). Alternatively, the tubing attached to a 22-gauge butterfly needle may be employed. A 20-gauge needle fitted to a Luer-tip syringe is then placed in line. The fluid is flushed with IVF media (0.5 to 1.0 mL) into a sterile container. Once a micropipet has been used, it is discarded. Residual fluid in the pipette

will disrupt capillary action. A typical procedure requires 4 to 12 micropipets. The sperm bank should be instructed to cryopreserve the aspirate in multiple vials (aliquots) so that several IVF cycles may be attempted if required (Janzen et al, 2000; Anger et al, 2004).

Experience with the technique has revealed that, **paradoxically, in obstructed systems, sperm motility is better more proximally in the epididymis with the most motile sperm often found in the efferent ductules** (Fig. 22–47). Motility immediately after aspiration and, consequently, fertilization rates are highest in men who have the longest length of epididymal tubule available. Even when packed with debris distally, the epididymal tubule may be capable of secreting substances that can diffuse proximally and benefit sperm motility and fertilizing capacity.

Employing ICSI, ongoing pregnancy or delivery rates exceeding 60% have been achieved with this technique using either fresh or cryopreserved epididymal sperm (Schlegel et al, 1995; Nudell et al, 1998). **Epididymal sperm aspiration can be done electively, with the cryopreserved sperm used for multiple future IVF cycles** (Janzen et al, 2000; Anger et al, 2004).

Percutaneous Epididymal Sperm Aspiration

Percutaneous puncture of the epididymis with a fine needle (Fig. 22–48) has been successfully employed to obtain sperm and achieve pregnancies (Shrivastav et al, 1994; Craft and Tsirigotis, 1995; Levine et al, 2003; Qiu et al, 2003; Lin et al, 2004). The technique is less reliable than the open retrieval, and the small quantities of sperm obtained are sometimes inadequate for cryopreservation. Reported pregnancy rates are half those achieved with open techniques (Sheynkin et al, 1998b). In view of the enormous costs and effort involved in IVF, epididymal sperm retrieval under direct vision is the preferred technique.

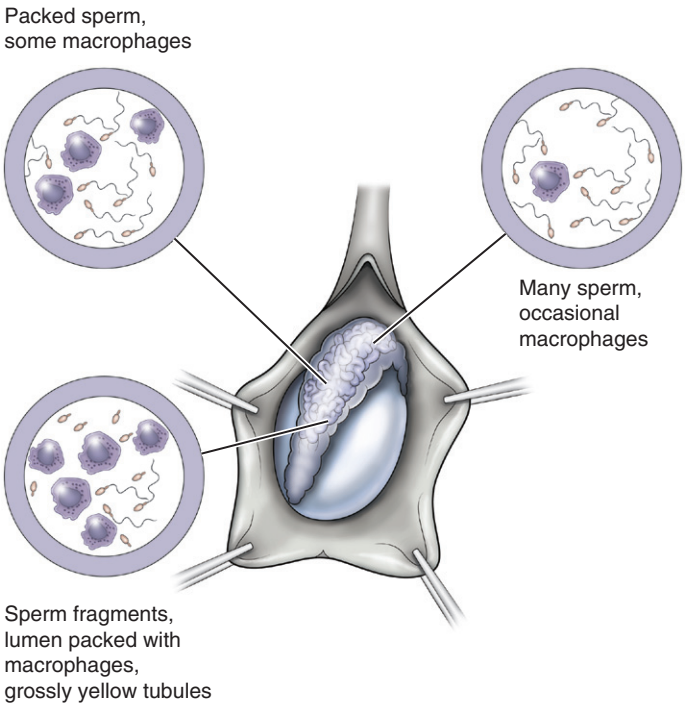


Figure 22–47. Experience with the technique has revealed that, paradoxically, in obstructed systems, sperm motility is better more proximally in the epididymis with the most motile sperm often found in the efferent ductules.

Testicular Sperm Extraction

The indications for testicular sperm extraction (TESE) are:

1. **Failure to find sperm in the epididymis** in the presence of the spermatogenesis or complete absence of the epididymis.
2. **Nonobstructive azoospermia** (Schlegel et al, 1997; Ostad et al, 1998; Su et al, 1999; Tsujimura et al, 2002).

Testicular sperm has been retrieved employing one of three techniques:

1. **Open testicular sperm extraction**—allows retrieval of the largest member of sperm with potential for cryopreservation; this **is the best technique in men with nonobstructive azoospermia.**
2. Percutaneous core biopsy; uses the same 14-gauge biopsy gun used for prostate biopsy (Fig. 22–49).
3. Percutaneous aspiration (testicular sperm aspiration—TESA) with a high-suction glass syringe and a 23-gauge needle. This is the least invasive but requires 10 to 20 passes to obtain an adequate yield (Fig. 22–50) (Rajfer and Binder, 1989; Harrington et al, 1996; Friedler et al, 1997; Sheynkin et al, 1998b; Mercan et al, 2000; Carpi et al, 2005).

The percutaneous methods are most appropriate in men with normal spermatogenesis and obstructive azoospermia in whom adequate numbers of sperm can be retrieved in a small amount of tissue (Craft et al, 1995). The pros and cons of these three methods are discussed earlier in Testis Biopsy.

Microsurgical Testicular Sperm Extraction

The use of an operating microscope for standard open diagnostic testes biopsy allows identification of an area in the tunica albuginea free of blood vessels (Fig. 22–51), minimizing the risk of injury to testicular blood supply and allowing a relatively blood-free biopsy specimen (Dardashti et al, 2000). Employing the microscope for testis biopsy, Schlegel (1999) discovered that in men with nonobstructive azoospermia, some of the tubules were larger than others. **The larger tubules are more likely to**

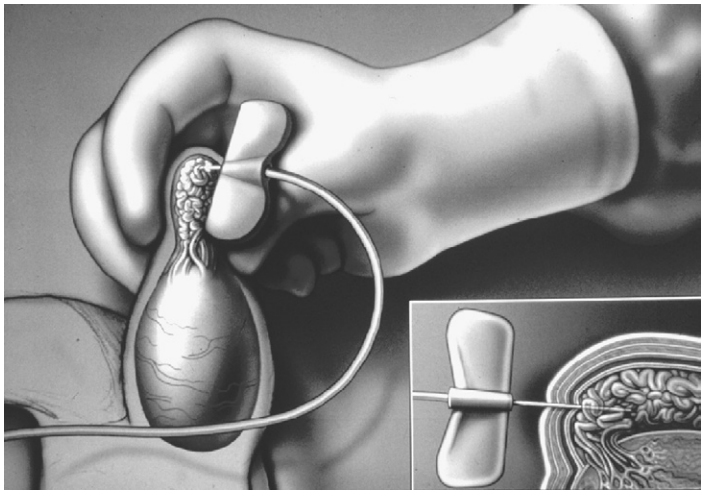


Figure 22–48. Percutaneous puncture of the epididymis with a fine needle.

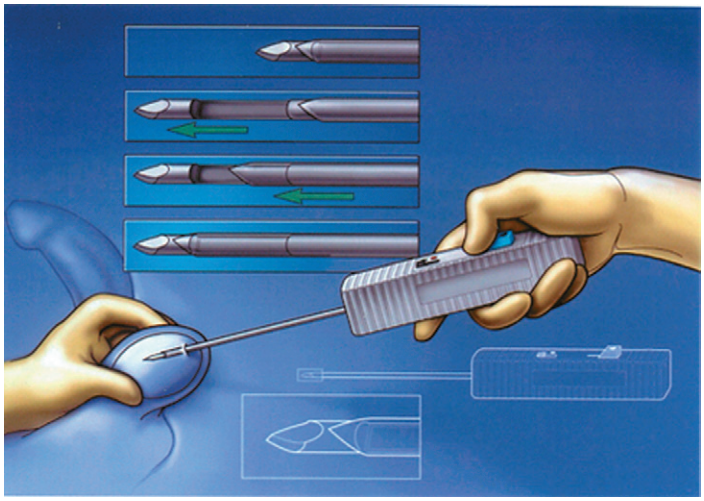


Figure 22–49. Percutaneous core biopsy; uses the same 14-gauge biopsy gun used for prostate biopsy.

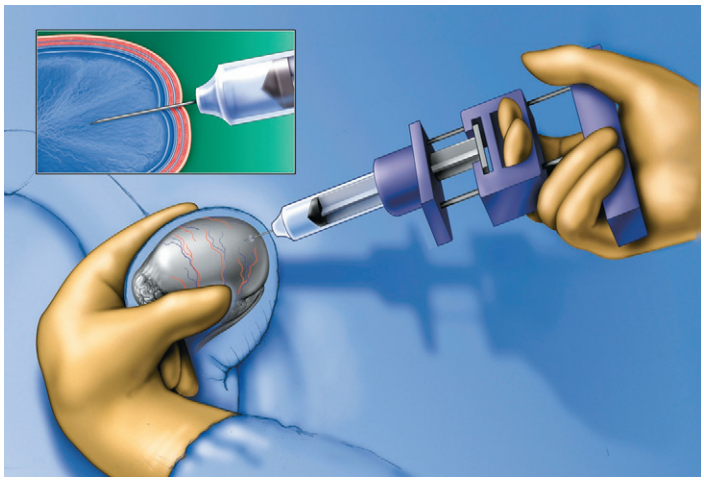


Figure 22–50. Percutaneous aspiration (testicular sperm aspiration) with a high-suction glass syringe and a 23-gauge needle. This is the least invasive but requires 10 to 20 passes to obtain an adequate yield.

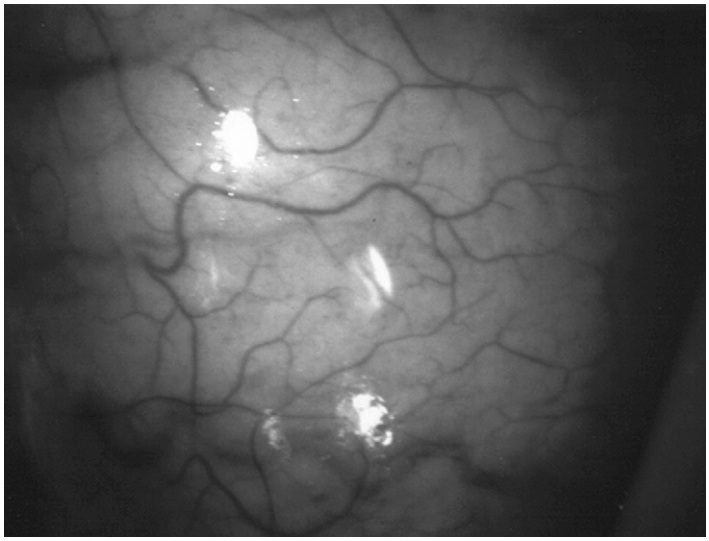


Figure 22–51. The use of an operating microscope for standard open diagnostic testes biopsy allows identification of an area in the tunica albuginea free of blood vessels.

yield sperm. Previous studies revealed that testicular biopsy in men with nonobstructive azoospermia display considerable heterogeneity. Examination of permanently fixed biopsy specimens that display heterogeneity reveal that **tubules with spermatogenesis are of considerably larger diameter than tubules composed of Sertoli cells only. This difference can be readably observed under the operating microscope** (Fig. 22–52).

Technique. With the patient under general or regional anesthetic, the testes are exposed through either a single midline median raphe incision or two transverse incisions within the skin lines and between the scrotal blood vessels. The testes are delivered into the wound. The tunica vaginalis is opened, and the operating microscope is brought into the field. Using 10-power magnification, an avascular plane is identified on the anterior surface of the tunica albuginea. Using a 15-degree microknife, a generous transverse incision is made between the blood vessels through the tunica albuginea. Small blood vessels that are seen coursing across the incision are coagulated with the microbipolar cautery prior to incising them. This yields a blood-free field. The seminiferous tubules are observed. **Sertoli-cell-only tubules tend to be thin, white, and stringy. Tubules with active spermatogenesis are larger, plumper, and somewhat yellow.** Using a micro needle holder, the seminiferous tubules are dissected in an attempt to identify larger tubules. If such a tubule is found, a sharp curved iris scissor is used to selectively excise these tubules. The sample is placed in human tubal fluid media, microdissected, and immediately examined by an andrology laboratory technician present in the operating room. After sperm have been found, hemostasis is obtained with the microbipolar cautery. The incision in the tunica albuginea is closed with a 6-0 nylon suture. The testis is returned to the tunica vaginalis, which is closed with a continuous suture of 5-0 Vicryl. If necessary, the opposite testis is explored.

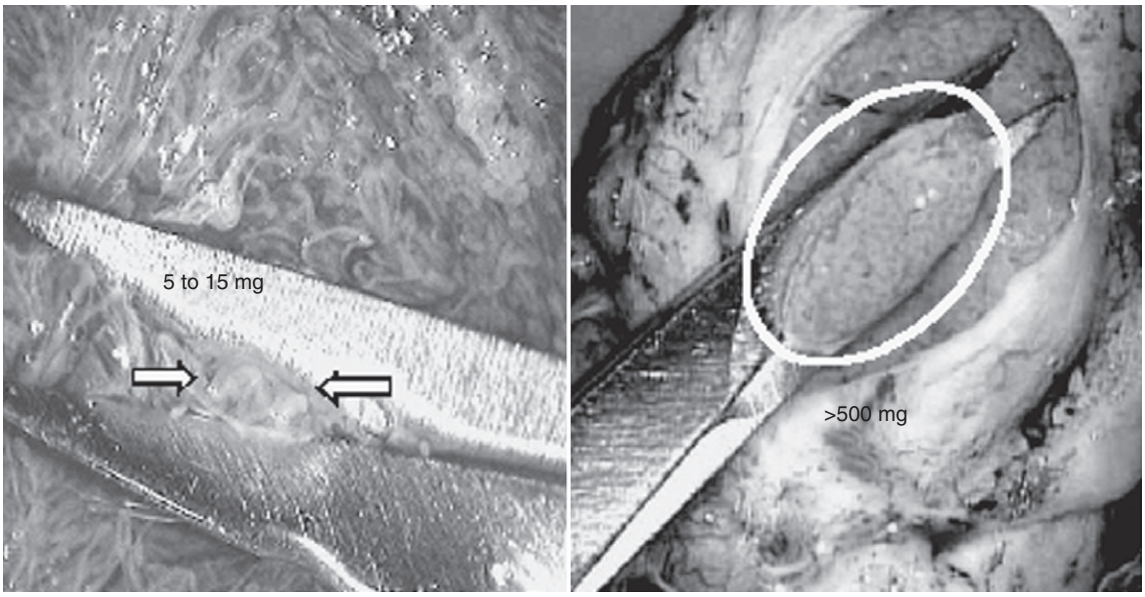
Results. Using the microdissection technique, sperm have been identified in 50% of men explored. In those men in whom sperm are found, a pregnancy rate of 50% has been achieved at Cornell using IVF/ICSI. The spontaneous abortion rate is 19%. The high rate of spontaneous abortion is probably owing to the increased incidence of chromosomal abnormalities and DNA damage in the sperm of men with nonobstructive azoospermia (Rucker et al, 1998). Even in severe cases of congenital or acquired testicular failure, as in Sertoli-cell-only syndrome (Su et al, 1999), postchemotherapy azoospermia (Chan et al, 2001) and nonmosaic (47XXY) Klinefelter syndrome (Palermo et al, 1998; Ramasamy et al, 2009) sperm have been found and pregnancy and live births achieved (Table 22–5).

Table 22–5.

Testicular Sperm Extraction Outcomes by Diagnosis from Schlegel

CONDITION	RETRIEVAL
Klinefelter syndrome	68%
AZFc deletions	70%
Sertoli cell only	37%
Postchemotherapy	53%
Cryptorchidism (postorchiopexy)	74%
Maturation arrest	40%
AZFa, AZFb deletions	0%

From Chan et al, 2001; Hopps et al, 2003b; Raman and Schlegel, 2003; Hung et al, 2007; Ramasamy and Schlegel, 2007; and Ramasamy et al, 2009.



Microsurgical testicular sperm extraction, x25 Conventional testicular sperm extraction, x8

Figure 22–52. Tubules with spermatogenesis are of considerably larger diameter than tubules that are Sertoli-cell only. This difference can be readily observed under the operating microscope.

Postmortem Sperm Retrieval

Postmortem sperm retrieval and cryopreservation (but no pregnancies) were initially reported by Rothman in 1980 and employed removal and mincing of the epididymis. The retrieved sperm can be frozen and subsequently used to achieve pregnancy. Pregnancy has now been achieved with sperm retrieved postmortem using IVF with ICSI (Tash et al, 2003; Dostal et al, 2005; reviewed in Benshushan and Schenker, 1998).

Retrieval of sperm from the vas can be performed using the technique described previously for vasography. Once the vas has been delivered, a hemivasotomy is made with a 15-degree microknife (as described earlier in Technique of Vasography and Interpretation of Findings). The testicular end of the vas is cannulated with a 22-gauge angiocatheter and the vas irrigated with a 0.2-mL volume of human tubal fluid medium while the convoluted vas and epididymis are massaged.

Twenty-four million sperm with 70% grade 1 motile sperm were retrieved 13 hours after death with this technique (Schlegel, personal communication). The ethical appropriateness of such retrieval is the most important issue surrounding its use.

VARICOCELECTOMY

Introduction

Varicocele is by far the most commonly performed operation for the treatment of male infertility. **Varicocele is found in approximately 15% of the general population, 35% of men with primary infertility, and 75% to 81% of men with secondary infertility.** Animal and human studies have demonstrated that **varicocele is associated with a progressive and duration-dependent decline in testicular function** (Russell, 1957; Lipshultz and Corriere, 1977; Nagler et al, 1985; Harrison et al, 1986; Kass and Belman, 1987; Hadziselimovic et al, 1989; Chehval and Purcell, 1992; Gorelick and Goldstein, 1993; Witt and Lipshultz, 1993).

Repair of varicocele will halt any further damage to testicular function (Kass and Belman, 1987; Gorelick and Goldstein, 1993) and, in a large percentage of men, result in improved spermatogenesis (Dubin and Amelar, 1977; Schlegel and Goldstein, 1992), as well as enhanced Leydig cell function (Su et al, 1995). The potentially important role of urologists in preventing future infertility underscores the importance of using a varicocelectomy technique that minimizes the risk of complications and recurrence. Table 22–6 summarizes the pros and cons of various methods of varicocele repair.

Scrotal Operations

Various surgical approaches have been advocated for varicocelectomy. The earliest recorded attempts at repair of varicocele date to antiquity and involved external clamping of the scrotal skin including the enlarged veins. In the early 1900s an open scrotal approach was employed, involving the mass ligation and excision of the varicosed plexus of veins. At the level of the scrotum, however, the pampiniform plexus of veins are intimately entwined with the coiled testicular artery. Therefore **scrotal operations are to be avoided because damage to the arterial supply of the testis frequently results in testicular atrophy and further impairment of spermatogenesis and fertility.**

Retroperitoneal Operations

Retroperitoneal repair of varicocele involves incision at the level of the internal inguinal ring (Fig. 22–53), splitting of the external and internal oblique muscles, and exposure of the internal spermatic artery and vein retroperitoneally near the ureter. This approach has the advantage of isolating the internal spermatic veins proximally, near the point of drainage into the left renal

Table 22–6.
Techniques of Varicocelectomy

TECHNIQUE	ARTERY PRESERVED	HYDROCELE (%)	FAILURE (%)	POTENTIAL FOR SERIOUS MORBIDITY
Retroperitoneal	No	7	15-25	No
Conventional inguinal	No	3-30	5-15	No
Laparoscopic	Yes	12	3-15	Yes
Radiographic	Yes	0	15-25	Yes
Microscopic inguinal or subinguinal	Yes	0	1.0	No

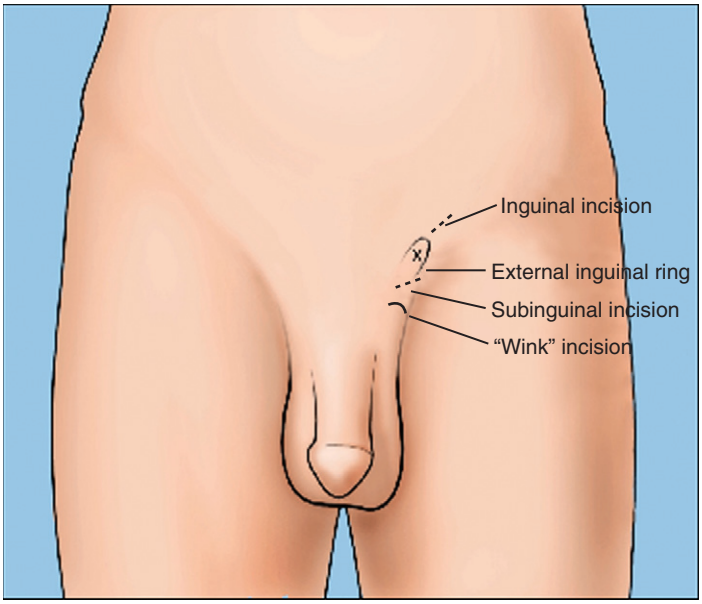


Figure 22–53. Retroperitoneal repair of varicocele involves incision at the level of the internal inguinal ring.

vein. At this level, only one or two large veins are present and, in addition, the testicular artery has not yet branched and is often distinctly separate from the internal spermatic veins. Retroperitoneal approaches involve ligation of the fewest number of veins. This approach is still a commonly employed method for the repair of varicocele, especially in children.

A disadvantage of a retroperitoneal approach is the high incidence of varicocele recurrence, especially in children and adolescents, when the testicular artery is intentionally preserved. Recurrence rates after retroperitoneal varicocelectomy are in the range of 15% (Homonnai et al, 1980; Rothman et al, 1981; Watanabe et al, 2005). Failure is usually due to preservation of the periarterial plexus of fine veins (venae comitantes) along with the artery. These veins have been shown to communicate with larger internal spermatic veins. If left intact, they may dilate and cause recurrence. Less commonly, failure is due to the presence of parallel inguinal or retroperitoneal collaterals, which may exit the testis and bypass the ligated retroperitoneal veins, rejoining the internal spermatic vein proximal to the site of ligation (Sayfan, 1981; Murray et al, 1986). Dilated cremasteric veins, another cause of varicocele recurrence (Sayfan et al, 1980), cannot be identified with a retroperitoneal approach. Positive identification and preservation of the 1.0- to 1.5-mm testicular artery via the retroperitoneal approach is difficult, especially in children where the artery is small. The operation involves working in a deep hole. Because at this level the internal spermatic vessels cannot be delivered into the wound, they must be dissected and ligated in situ in the retroperitoneum. In addition, the difficulty in positively identifying and preserving lymphatics using this approach results in postoperative hydrocele formation after 7% to 33% of retroperitoneal operations (Szabo and Kessler, 1984). The incidence of recurrence appears to be higher in children, with rates reported between 15% and 45% in adolescents (Gorenstein et al, 1986; Levitt et al, 1987; Reitelman et al, 1987). Kass (1992) reports that **recurrence can be markedly reduced in children and adolescents by intentional ligation of the testicular artery** (Kass and Marcol, 1992). This assures ligation of the periarterial network of fine veins. Although reversal of testicular growth failure has been documented with intentional testicular artery ligation at the time of retroperitoneal repair in children, **the effect of artery ligation on subsequent spermatogenesis is uncertain.** In adults bilateral artery ligation has been documented to occasionally cause azoospermia and testicular atrophy. At least **it is inarguable that testicular artery ligation will not enhance testicular function.**

Laparoscopic Varicocelectomy

Laparoscopic repair is in essence a retroperitoneal approach and many of the advantages and disadvantages are similar to those of the open retroperitoneal approach (Donovan and Winfield, 1992; Hagood et al, 1992; Enquist et al, 1994; Hirsch et al, 1998; Riccabona et al, 2003; Watanabe et al, 2005).

Using the laparoscope, the internal spermatic vessels and vas deferens can be clearly visualized through the laparoscope as they course through the internal inguinal ring. **The magnification provided by the laparoscope allows visualization of the testicular artery. With experience, the lymphatics may be visualized and preserved as well** (Glassberg et al, 2008). With laparoscopic varicocelectomy the internal spermatic veins are ligated at the same level as the retroperitoneal (Palomo) approach described earlier in Retroperitoneal Operations. Laparoscopic varicocelectomy should allow preservation of the testicular artery in a majority of cases, as well as preservation of lymphatics. The incidence of varicocele recurrence would be expected to be similar to that associated with the open retroperitoneal operations. These recurrences would be due to collaterals joining the internal spermatic vein near its entrance to the renal vein, or entering the renal vein separately.

Currently reported series of laparoscopic varicocelectomy report a recurrence rate of 2.9% to 4.5% in most recent series (May et al, 2006; Glassberg et al, 2008; Barroso et al, 2009), but up to 17% in some (Al-Said et al, 2008). An artery ligation but lymphatic-sparing

laparoscopic technique has markedly reduced the incidence of postoperative hydrocele formation in children (Glassberg et al, 2008). The potential complications of laparoscopic varicocelectomy (injury to bowel, vessels or viscera, air embolism, peritonitis) are significantly more serious than those associated with the open techniques. Furthermore, laparoscopic varicocelectomy requires a general anesthetic. The microsurgical techniques described next can be performed using local or regional anesthesia and employ an incision of 2.5 to 3 cm for unilateral repair. This is equal to or less than the sum of incisions employed for a laparoscopic approach. Postoperative pain and recovery from the laparoscopic technique are the same as those associated with subinguinal varicocelectomy (Hirsch et al, 1998). Finally, laparoscopic varicocelectomy is less cost-effective than open varicocelectomy. In the hands of an experienced laparoscopist, the approach is a reasonable alternative for the repair of bilateral varicoceles (Donovan and Winfield, 1992; Diamond et al, 2009; Mendez-Gallart et al, 2009; Tong et al, 2009).

Microsurgical Inguinal and Subinguinal Operations: Preferred Approaches

Introduction

Inguinal and subinguinal varicocelectomy are currently the most popular approaches. They have the advantage of allowing the spermatic cord structures to be pulled up and out of the wound so that the testicular artery, lymphatics, and small periarterial veins may be more easily identified. In addition, **an inguinal or subinguinal approach allows access to external spermatic and even gubernacular veins,** which may bypass the spermatic cord and result in recurrence if not ligated. Lastly, an inguinal or subinguinal approach allows access to the testis for biopsy or examination of the epididymis for obstruction.

Traditional approaches to inguinal varicocelectomy involve a 5- to 7-cm incision made over the inguinal canal, opening of the external oblique aponeurosis, and encirclement and delivery of the spermatic cord. The cord is then dissected, and all the internal spermatic veins are ligated (Dubin and Amelar, 1977). The vas deferens and its vessels are preserved. An attempt is made to identify and preserve the testicular artery and, if possible, the lymphatics. In addition, the cord is elevated and any external spermatic veins that are running parallel to the spermatic cord or perforating the floor of the inguinal canal are identified and ligated. Compared with retroperitoneal operations, conventional nonmagnified inguinal approaches lower the incidence of varicocele recurrence but do not alter the incidence of either hydrocele formation or testicular artery injury. **Conventional inguinal operations are associated with an incidence of postoperative hydrocele formation varying from 3% to 15% with an average incidence of 7%** (Szabo and Kessler, 1984). Analysis of the hydrocele fluid has clearly indicated that hydrocele formation following varicocelectomy is due to ligation of the lymphatics (Szabo and Kessler, 1984). The incidence of testicular artery injury during nonmagnified inguinal varicocelectomy is unknown. Case reports, however, suggest that this complication may be more common than realized. It can result in testicular atrophy and, if the operation is performed bilaterally, azoospermia may ensue in a previously oligospermic man. Furthermore, Starzl and his transplant group reported a 14% incidence of testicular atrophy and 70% incidence of hydrocele formation when the spermatic cord was divided and only the vas and vasal vessels were preserved (Penn et al, 1972).

The introduction of **microsurgical technique** to varicocelectomy **has resulted in a substantial reduction in the incidence of hydrocele formation** (Goldstein et al, 1992; Marmar and Kim, 1994; Matthews et al, 1998; Cayan et al, 2000). This is **because the lymphatics can be more easily identified and preserved.** Furthermore, the use of **magnification enhances the ability to identify and preserve the 0.5- to 1.5-mm testicular artery, thus avoiding the complications of atrophy or azoospermia.**

Advocates of nonmicrosurgical techniques contend that the deferential (vasal) artery and, if preserved, the cremasteric artery, will provide adequate blood supply to the testes to prevent atrophy. However, anatomic studies have known that the diameter of the testicular artery is greater than the diameter of the deferential artery and cremasteric artery combined (Raman and Goldstein, 2004). **The testicular artery is the main blood supply to the testis.** Experience with the one-stage Fowler and Steven orchiopexy, in which the testicular artery is intentionally ligated, reveals that a substantial percentage of such procedures results in an atrophic testis. Also, animal models indicate that artery preservation varicocelectomy results in improved testicular ultrastructure, whereas artery ligation resulted in further deterioration of ultrastructure (Zheng et al, 2008). At the very least, it is inarguable that **ligation of the testicular artery is unlikely to enhance testicular function.**

Anesthesia

If the testis is delivered, as described later, regional or light general anesthesia is preferred. If only the cord is delivered, local anesthesia with a 50/50 combination of 0.25% bupivacaine and 1% lidocaine is satisfactory with adjunctive intravenous heavy sedation. After infiltration of the skin and subcutaneous tissues, the cord is infiltrated before delivery. Blind cord block carries with it a small risk of inadvertant testicular artery injury (Goldstein, 1983). A 30-gauge needle should therefore be employed for cord block to minimize the risk of injury and hematoma.

Inguinal and Subinguinal Approaches

The introduction of the subinguinal approach, just below the external inguinal ring (Marmar et al, 1985) obviates the need for opening any fascial layer and is associated with less pain and a rapid recovery comparable with laparoscopic procedures. At the subinguinal level, however, significantly more veins are encountered, the artery is more often surrounded by a network of tiny veins that must be ligated, and the testicular artery has often divided into two or three branches, making arterial identification and preservation more difficult (Hopps et al, 2003a).

Subinguinally, the arterial pulsations are often dampened by compression on the edge of the external ring, making its identification somewhat more difficult than when the external oblique is opened. Table 22–7 summarizes the criteria for performing the operation inguinally (external oblique opened) versus subinguinally (fascia intact). **In general, it is best to use a subinguinal approach in men with a history of any prior inguinal surgery.** Under these circumstances the cord is usually stuck to the undersurface of the external oblique and opening the fascia risks injury to the cord. A subinguinal approach is easier in obese men in whom opening and closing the fascia is difficult through a small incision. A subinguinal approach is easier in men with high, lax, capacious external rings and in men with long cords and low-lying testes. In these men the level of the external ring is fairly proximal to the testis and opening the fascia will not result

Table 22–7.

Indications for Inguinal (External Oblique Opened) versus Subinguinal (Fascia Intact) Varicocelectomy

INGUINAL	SUBINGUINAL
Children or prepubertal adolescents	Prior inguinal surgery
Solitary testis	Obesity
Tight, low external ring	Lax, capacious external ring High external ring
Short cord, high-lying testis	Long cord with low-lying testis
Less experienced with microsurgical repair	Very experienced with microsurgical repair

in a significant diminution in the number of veins to be ligated or in the branching of the testicular artery.

Always open the external oblique in children or prepubertal adolescents without prior inguinal surgery. In children the testicular artery is very small and systemic blood pressure is low, making identification of the artery difficult in a subinguinal approach. The fascia should also be opened in men with a solitary testis in whom preservation of the artery is critical. Exposure of the cord more proximally (at the inguinal level) allows identification of the artery before it has branched, where clear pulsations are more readily observed.

Open the fascia in thin men with tight low external rings, high-riding testes, and short cords. The microdissection will be quicker and easier and it is easy to open and close the fascia in thin men. **A subinguinal operation is significantly more difficult than a high inguinal operation and should only be used by surgeons who perform the operation frequently. An inguinal operation is employed when simultaneous ipsilateral hernia repair is performed.**

Before making the incision, the location of the external inguinal ring is determined by invagination of the scrotal skin and marked. The size of the incision is determined by the size of the testis when delivery of the testis (see later) is planned. Atrophic testes can be delivered through a 2- to 2.5-cm incision. Large testes require a 3-cm incision. The incision is made within Langer lines to minimize scarring.

If the decision is made to perform an inguinal operation and thus to open the fascia, the incision is begun at the external ring and extended laterally 2 to 3.5 cm along Langer lines (Fig. 22–54). If the operation is to be performed subinguinally, the incision is placed in the skin lines just below the external ring (Fig. 22–55).

Camper fascia and Scarpa fascia are divided with the electrocautery between the blades of a Crile clamp. The superficial epigastric artery and vein, if encountered, are retracted or, alternately, clamped, divided, and ligated.

If an inguinal approach is selected, the external oblique aponeurosis is cleaned and opened the length of the incision to the external inguinal ring in the direction of its fibers. A 3-0 absorbable suture placed at the apex of the external oblique incision assists later closure.

The spermatic cord is grasped with a Babcock clamp and delivered through the wound. The ilioinguinal and genital branches of the genitofemoral nerve are excluded from the cord, which is then surrounded with a large Penrose drain. If a subinguinal incision was made, Camper and Scarpa fascia are incised as described earlier. An index finger is introduced into the wound and along the cord into the scrotum. The index finger is then hooked under the external inguinal ring, retracting it cephalad. A small



Figure 22–54. If the decision is made to perform an inguinal operation, and thus to open the fascia, the incision is begun at the external ring and extended laterally 2 to 3/5-cm along Langer lines.

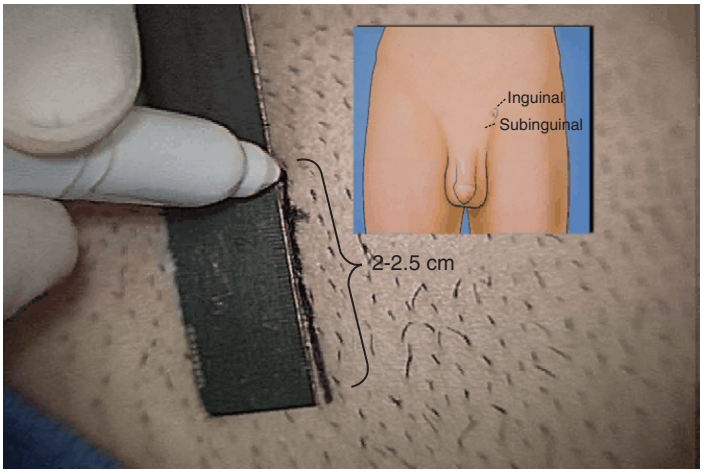


Figure 22–55. If the operation is to be performed subinguinally, the incision is placed in the skin lines just below the external ring.

Richardson retractor is slid along the back of the index finger and retracted caudad over the cord toward the scrotum (Fig. 22–56). The spermatic cord will be revealed between the index finger and retractor. The assistant grasps the cord with a Babcock clamp and delivers it through the wound. The cord is surrounded with a large Penrose drain.

Dissection of the Cord

The operating microscope is then brought into the field. Under 10-power magnification, the external and internal spermatic fascias are opened (Fig. 22–57A and B). The magnification is increased to 10 to 25 power and, after irrigation with 1% papaverine solution, the cord is inspected for the presence of pulsations

revealing the location of the testicular artery**. A micro-Doppler is extremely useful in identifying arteries** (Fig. 22–58). **Once the testicular artery is identified, it is dissected free of all surrounding tissue, tiny veins, and lymphatics using a fine-tipped nonlocking micro needle holder and microforceps.** The artery is encircled with a vessel loop for positive identification and gentle retraction (Fig. 22–59). The suspected artery is tested by elevating the artery with the tips of the micro needle holder until it is completely occluded and then slowly lowering it until a pulsating blush of blood appears just over the needle holder. If the artery is not immediately identified, the cord is carefully dissected beginning with the largest veins. The veins are stripped clean of adherent lymphatics (Fig. 22–60) and the underside of the largest veins inspected for an adherent artery. **In approximately 50% of cases the testicular artery is adherent to the undersurface of a large vein** (Beck et al, 1992). All veins within the cord, with the exception of the vasal veins, are doubly ligated with either hemoclips (Fig. 22–61A) or by passing two 4-0 silk ligatures, one black and one white, beneath the vein (Fig. 22–61B). These are then tied, and the vein is divided.

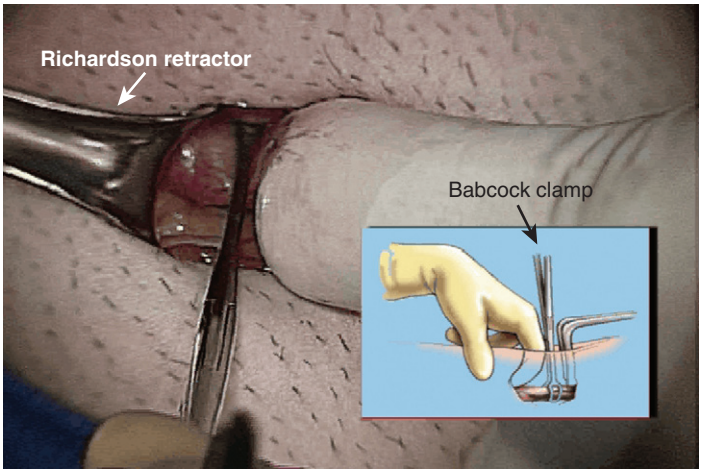


Figure 22–56. A small Richardson retractor is slid along the back of the index finger and retracted caudad over the cord toward the scrotum.

Medium hemoclips are used for veins 5 mm or larger, small automatic hemoclips for veins 1 to 5 mm, and 4-0 silk for veins smaller than 2 mm. **The use of an automatic clip applier** (Ligaclip small size, Ethicon, Somerville, NJ) **significantly reduces operating time.** The bipolar cautery can be used for veins smaller than 0.5 mm. The vasal veins are preserved providing venous return. If the vas deferens is accompanied by dilated veins greater than 3 mm in diameter, they are dissected free of the vasal artery and ligated. The vas deferens is always accompanied by two sets of vessels. **As long as at least one set of vasal veins remains intact, venous return will be adequate.** At the completion of the dissection, the cord is run over the index finger and inspected to verify that all veins have been identified and ligated. Small veins adherent to the testicular artery are dissected free and ligated or, if smaller than 1 mm, cauterized using a bipolar unit with a jeweler's forcep tip and divided. Cremasteric arteries are found (usually between and adherent of two cremasteric veins) and preserved in at least 90% of cases. Recent studies employing power-Doppler in men with nonobstructive azoospermia undergoing testicular sperm extraction have found that tubules containing sperm are most likely to be found in areas of the testis with the greatest blood supply. Therefore logic would dictate that preservation of maximum testicular blood supply including both testicular and cremasteric arteries would be beneficial to testicular function. **At the completion of the dissection, only the testicular arteries, cremasteric arteries, cremaster muscle fibers, nerves, lymphatics, and vas deferens with its vessels remain** (Fig 22–62). After adequate hemostasis is achieved, the cord is returned to its bed.

Delivery of the Testis

Delivery of the testis through a small inguinal or subinguinal incision guarantees direct visual access to all possible avenues of testicular venous drainage. Delivery of only the cord allows access to most external spermatic collaterals but may miss those close to the testis and will not allow access to scrotal or gubernacular collaterals, which have been demonstrated radiographically to be the cause of 10% of recurrent varicoceles (Kaufman et al, 1983). With gentle upward traction on the cord and upward pressure on the testis through the invaginated scrotum, the testis is easily delivered through the wound. All

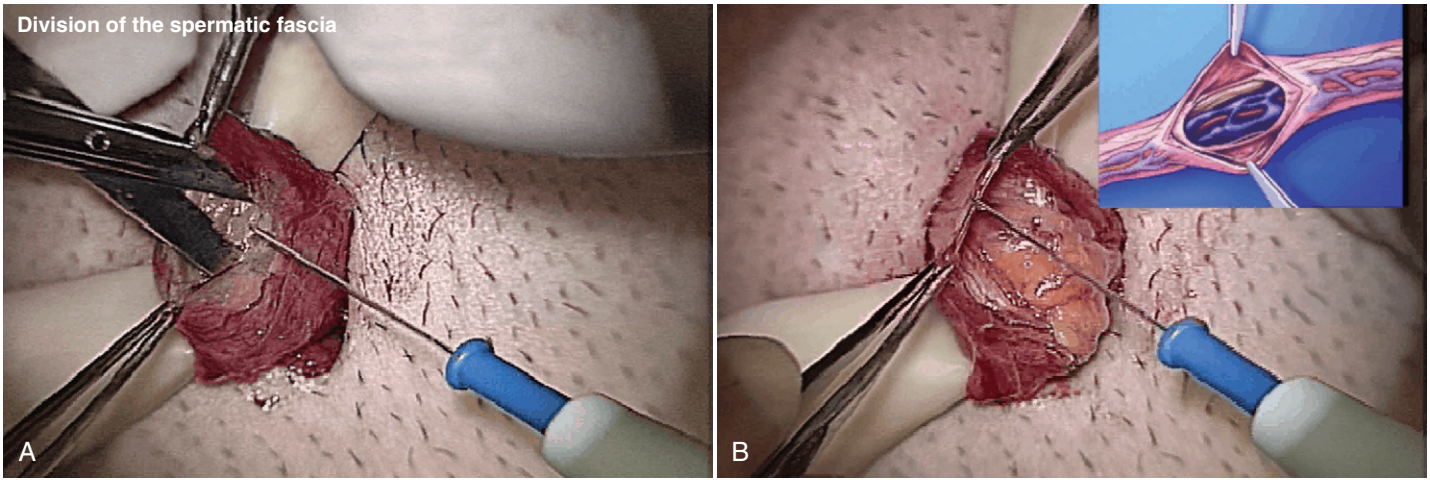


Figure 22–57. **A** and **B,** The operating microscope is then brought into the field. Under 4- to 6-power magnification, the external and internal spermatic fascias are opened.

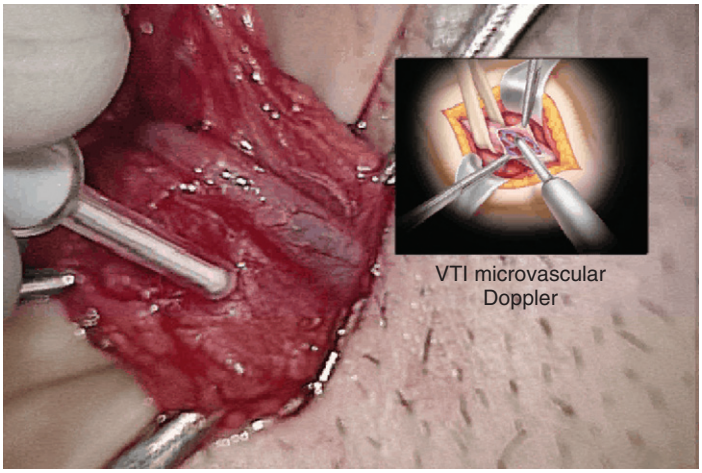


Figure 22–58. A micro-Doppler is extremely useful in identifying arteries.

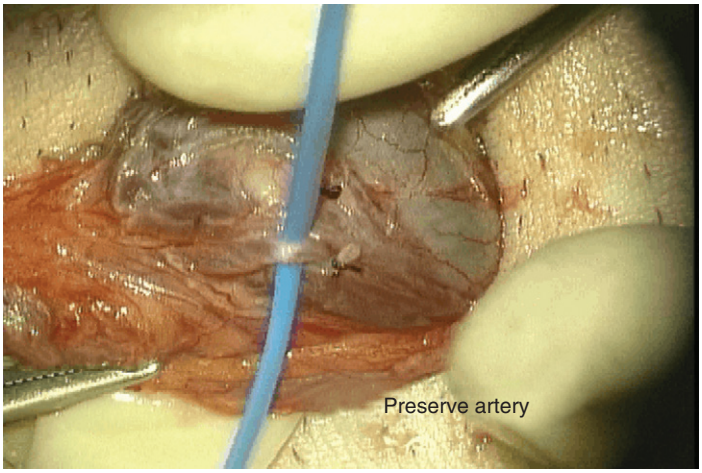


Figure 22–59. The artery is encircled with a vessel loop for positive identification and gentle retraction.

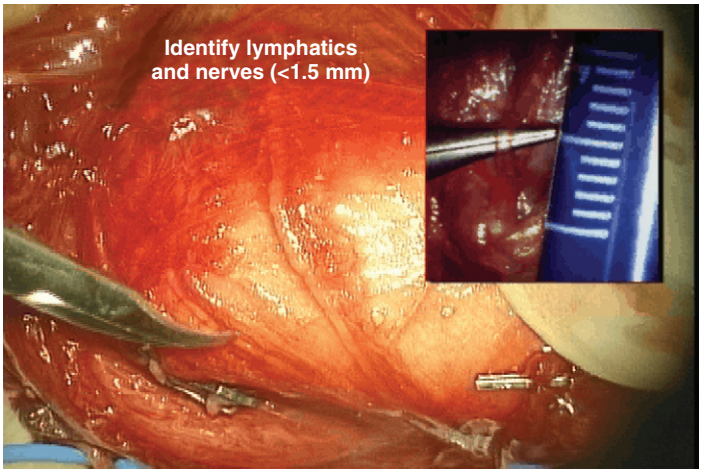
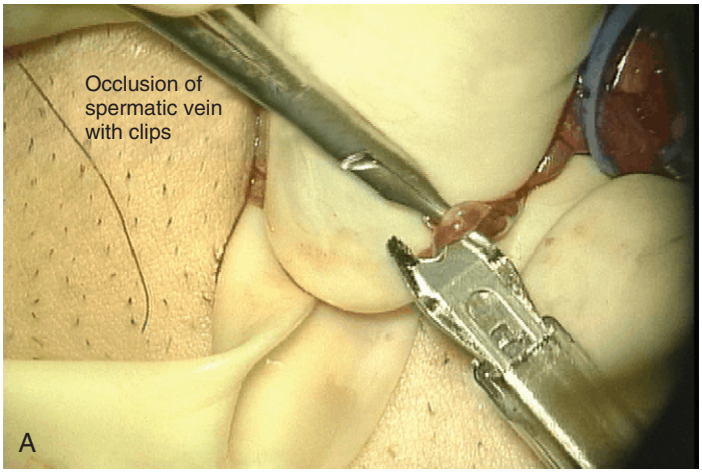


Figure 22–60. If the artery is not immediately identified, the cord is carefully dissected, beginning with the largest veins. The veins are stripped clean of adherent lymphatics.



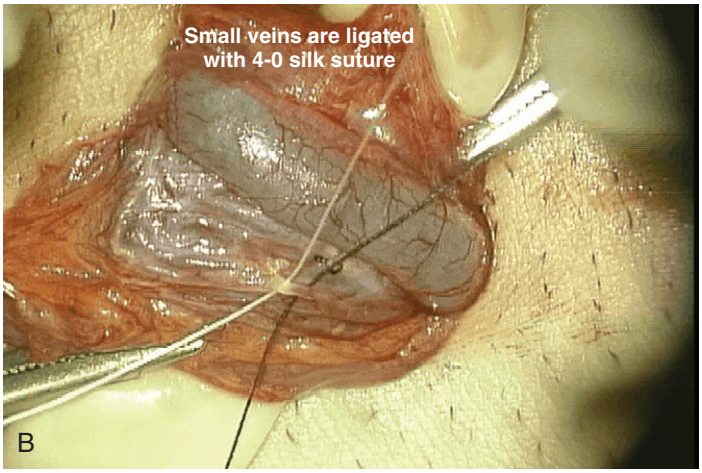


Figure 22–61. All veins within the cord, with the exception of the vasal veins, are doubly ligated, either with hemoclips **(A)** or by passing two 4-0 silk ligatures, one black and one white, beneath the vein **(B).**

external spermatic veins are identified and doubly ligated with hemoclips and divided (Fig. 22–63). The gubernaculum is inspected for the presence for veins exiting from the tunica vaginalis. These are either cauterized or doubly clipped and divided. **When this step is completed, all testicular venous return must be within the Penrose-surrounded cord.**

Hydroceles are found in 15% of testes associated with varicoceles. **As little as 3 mL of hydrocele fluid can significantly alter testicular temperature regulation** (Wysock et al, 2009). If a hydrocele is noted when the testis is delivered, it is repaired. Small ones may be treated with excision of a segment of the hydrocele sac and cauterization of the edges. Larger hydroceles are treated with either a bottleneck or excision technique. **The temporary high-venous pressure immediately after varicocelectomy can make good hemostasis difficult to achieve after excisional hydrocelectomy. Therefore there should be no hesitation to employ a scrotal Penrose drain placed in the dependant portion of the scrotal for 24 hours after combined varicocelectomy and excisional hydrocelectomy.** The testis is then returned to the scrotum, and the Penrose drain is left beneath the cord structures.

The external oblique aponeurosis, if opened, is reapproximated with continuous suturing using the previously placed 3-0 suture.

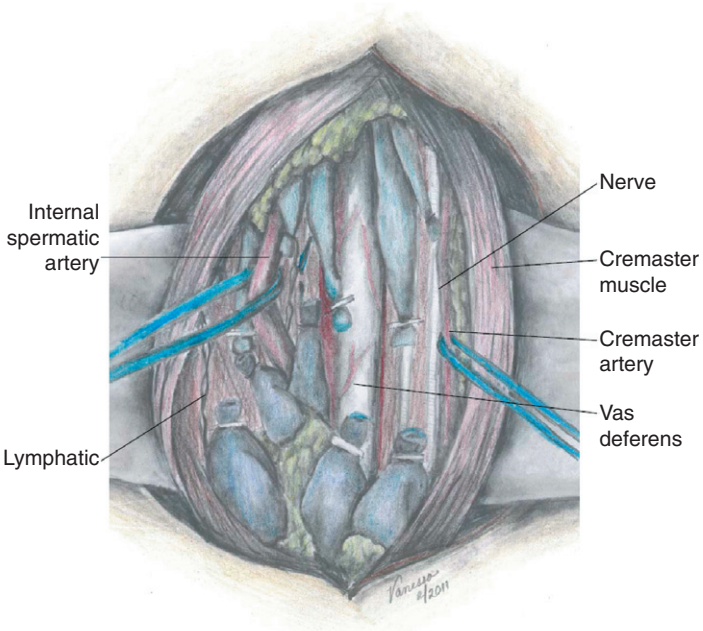


Figure 22–62. At the completion of the dissection, only the testicular arteries, cremasteric arteries, cremaster muscle fibers, nerves, lymphatics, and vas deferens with its vessels remain.

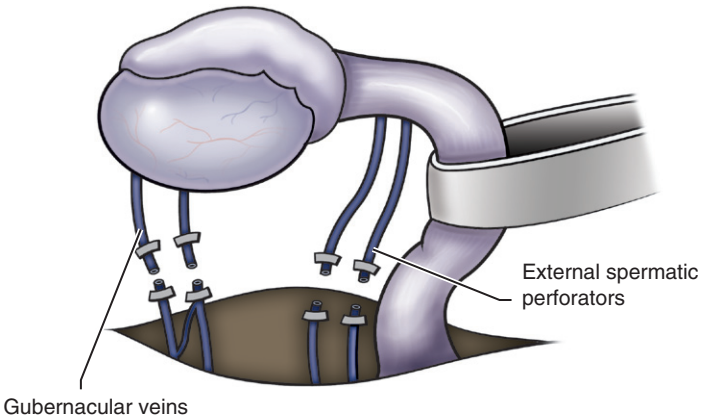


Figure 22–63. All external spermatic veins are identified and doubly ligated with hemoclips and divided.

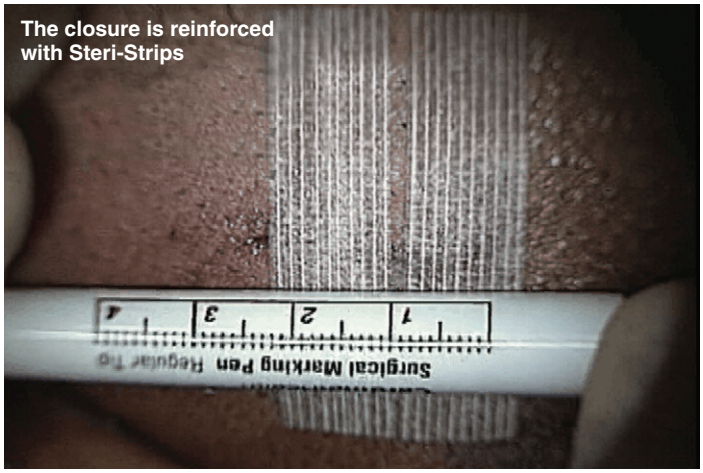


Figure 22–64. Scarpa fascia and Camper fascia are reapproximated with a single or continuous 3-0 monocryl suture, and the skin is approximated with a 5-0 monofilament absorbable subcuticular suture, reinforced by two to three sterile adhesive strips (Steri-Strips).

Scarpa fascia and Camper fascia are reapproximated with a single or continuous 3-0 plain catgut suture, and the skin is approximated with a 5-0 monofilament absorbable subcuticular suture reinforced by two to three sterile adhesive strips (Steri-Strips) (Fig. 22–64). A scrotal supporter is applied and stuffed with fluff-type dressings. The patient is discharged on the day of surgery with a prescription for Tylenol with codeine. Light work may be resumed in 2 or 3 days.

Radiographic Occlusion Techniques

Intraoperative venography has been employed to visualize the venous collaterals, which if left unligated, may result in varicocele recurrence (Sayfan, 1981; Belgrano et al, 1984; Levitt et al, 1987; Zaontz and Firlit, 1987). Intraoperative venography does reduce the incidence of varicocele recurrence, but the two-dimensional view afforded often does not enable the surgeon to identify the location of all collaterals.

Radiographic balloon or coil occlusion of the internal spermatic veins has been successfully employed for varicoceles (Lima et al, 1978; Walsh and White, 1981; Weissbach et al, 1981). These techniques are performed under a local anesthetic through a small cut-down incision over the femoral vein. The recurrence rate after balloon occlusion was originally 11% and more recently is reportedly as low as 4% (Kaufman et al, 1983; Mitchell et al, 1985; Murray et al, 1986; Matthews et al, 1992). Failure to successfully cannulate small collaterals and external spermatic veins results in recurrence. **Venographic placement of a balloon or coil in the internal spermatic vein is successfully accomplished in 75% to 90% of attempts** (White et al, 1981; Morag et al, 1984; Winkelbauer et al, 1994; Sivanathan and Abernethy, 2003). **Therefore a significant number of men undergoing attempted radiographic occlusion will ultimately require a surgical approach.** In addition, the radiographic techniques take between 1 and 3 hours to perform compared with 25 to 45 minutes required for surgical repair. Although rare, serious complications of radiographic balloon or coil occlusion have included migration of the balloon or coil into the renal vein, resulting in loss of a kidney, pulmonary embolization of the coil or balloon (Matthews et al, 1992), femoral vein perforation or thrombosis, and anaphylactic reaction to radiographic contrast medium. Antegrade scrotal sclerotherapy via cannulation of a scrotal vein has been employed in Europe (Tauber and Johnsen, 1994; Ficarra et al, 2002; Minucci et al, 2004). The recurrence rate is similar to balloon or coil techniques. Long-term follow-up is not available, and the consequence of escape of the sclerosing agent into the renal vein and vena cava is unknown. In addition, the larger the varicocele, the higher the failure and recurrence rate with this technique. **We have seen many men referred with late (2 to 5 years) recurrence after radiographic occlusion. They typically present as slow-filling veins that become prominent at the end of the day. Initial cursory physical examination can miss these recurrences. We believe these recurrences are likely due to recanalization**

through the coils because, unlike surgical repair, the veins are not ligated and divided.

Complications of Varicocelectomy

Hydrocele

Hydrocele formation is the most common complication reported after nonmicroscopic varicocelectomy. The incidence of this complication varies from 3% to 33%, with an average incidence of about 7%. Analysis of the protein concentration of hydrocele fluid indicates that **hydrocele formation after varicocelectomy is due to lymphatic obstruction** (Szabo and Kessler, 1984). At least half of postvaricocelectomy hydroceles grow to a size large enough to warrant surgical excision due to the discomfort and growth of the hydrocele to a large size. The effect of hydrocele formation on sperm function and fertility is uncertain. It is known that men with varicocele have significantly elevated intratesticular temperatures (Zorgniotti et al, 1979; Goldstein and Eid, 1989), and this appears to be an important pathophysiologic phenomenon mediating the adverse effects of varicocele on fertility (Saypol et al, 1981). The development of a large hydrocele creates an abnormal insulating layer that surrounds the testis. This may impair the efficiency of the counter-current heat exchange mechanism and therefore obviate some of the benefits of varicocelectomy (Wysock et al, 2009).

Use of magnification to identify and preserve lymphatics can virtually eliminate the risk of hydrocele formation after varicocelectomy (Goldstein et al, 1992; Marmar and Kim, 1994; Glassberg et al, 2008). The management of postvaricocelectomy hydrocele is identical to that for other forms of hydrocele (see Chapter 37).

Testicular Artery Injury

The diameter of the testicular artery in humans is 1.0 to 1.5 mm. The testicular artery supplies two thirds of the testicular blood supply, and the vasal and cremasteric arteries supply the remaining one third (Raman and Goldstein, 2004). Microdissections of the human spermatic cord have revealed that the testicular artery is closely adherent to a large internal spermatic vein in 40% of men. In another 20% of men the testicular artery is surrounded by a network of tiny veins (Beck et al, 1992). During the course of cord dissection for varicocelectomy, the artery may go into spasm and even in its unconstricted state is often difficult to positively identify and preserve. **Injury or ligation of the testicular artery carries with it the risk of testicular atrophy and/or impaired spermatogenesis.** Starzl's transplant group (Penn et al, 1972) reported a 14% incidence of frank testicular atrophy when the testicular artery was purposely ligated. The actual incidence of testicular artery ligation during varicocelectomy is unknown, but some studies suggest it is common (Wosnitzer and Roth, 1983). Animal studies indicate that the risk of testicular atrophy after testicular artery ligation varies from 20% to 100% (MacMahon et al, 1976; Goldstein, 1983). In humans, atrophy after artery ligation is probably less likely due to the contribution of the cremasteric and vasal arterial supply (Raman and Goldstein, 2004). **In children the potential for neovascularization and compensatory hypertrophy of the vasal and cremasteric vessels is probably greater than in adults, making atrophy after testicular artery ligation less likely.** Use of magnifying loupes, or preferably an operating microscope and/or a fine-tipped Doppler probe, assists identification and preservation of the testicular artery and therefore minimizes the risk of testicular injury. Radiographic balloon or coil occlusion techniques also eliminate this risk.

Varicocele Recurrence

The incidence of varicocele recurrence following surgical repair varies from 0.6% to 45% (Barbalias et al, 1998; Lemack et al, 1998; Cayan et al, 2000; Al-Kandari et al, 2007). Recurrence is more common after repair of pediatric varicoceles. Radiographic studies of recurrent varicoceles visualize periarterial, parallel inguinal or midretroperitoneal collaterals, or, more rarely, transcrotal collaterals (Kaufman et al, 1983). **Retroperitoneal operations miss parallel inguinal collaterals.** Nonmagnified inguinal operations have a lower incidence of varicocele recurrence but fail to address the issue of scrotal collaterals or small veins surrounding the testicular artery. The microsurgical approach with delivery of the testis lowers the incidence of varicocele recurrence to less than 1% compared with 9% using conventional inguinal techniques (Goldstein et al, 1992; Marmar and Kim, 1994).

Results

Varicocelectomy results in significant improvement in semen analysis in 60% to 80% of men. Reported pregnancy rates after varicocelectomy vary from 20% to 60% (Marmar et al, 2007). A randomized controlled trial of surgery versus no surgery in infertile men with varicoceles revealed a pregnancy rate of 44% at 1 year in the surgery group versus 10% in the control group (Abdel-Meguid, 2010). In our series of 1500 microsurgical operations 43% of couples were pregnant at 1 year (Goldstein and Tanrikut, 2006) and 69% at 2 years when couples with female factors were excluded. **Microsurgical varicocelectomy results in return of sperm to the ejaculate in up to 60% of azoospermic men with palpable varicoceles** (Matthews et al, 1998; Kim et al, 1999; Pasqualotto et al, 2006; Lee et al, 2007; Ishikawa et al, 2008).

The results of varicocelectomy are also related to the size of the varicocele. **Repair of large varicoceles results in a significantly greater improvement in semen quality than repair of small varicoceles** (Steckel et al, 1993; Jarow et al, 1996). In addition, large varicoceles are associated with greater preoperative impairment in semen quality than small varicoceles, and consequently overall pregnancy rates are similar regardless of varicocele size. Some evidence suggests that the younger the patient is at the time of varicocele repair, the greater the improvement after repair and the more likely the testis is to recover from varicocele-induced injury (Kass et al, 1987). Varicocele recurrence, testicular artery ligation, or postvaricocelectomy hydrocele formation are often associated with poor postoperative results. **In infertile men with low serum testosterone levels, microsurgical varicocelectomy alone results in substantial improvement in serum testosterone levels** (Su et al, 1995; Cayan et al, 1999; Younes, 2003; Rosoff et al, 2009).

Summary

Varicocele is an extremely common entity, present in 15% of the male population. Varicoceles are found in approximately 35% of men with primary infertility but 75% to 81% of men with secondary infertility. Mounting evidence clearly demonstrates that varicocele causes progressive duration-dependent injury to the testis. Larger varicoceles appear to cause more damage than small varicoceles and, conversely, repair of large varicoceles results in greater improvement of semen quality. **Varicocelectomy can halt the**

progressive duration-dependent decline in semen quality found in men with varicoceles. The earlier the age at which varicocele is repaired, the more likely is recovery of spermatogenic function. **Variococelectomy can also improve Leydig cell function, resulting in increased testosterone levels** (Su et al, 1995; Cayan et al, 1999; Younes, 2003).

The most common complications after varicocelectomy are hydrocele formation, testicular artery injury, and varicocele persistence or recurrence. **The incidence of** these **complications can be reduced by employing microsurgical techniques, inguinal or subinguinal operations, and exposure of the external spermatic and scrotal veins.** Employment of these advanced techniques of varicocelectomy provide a safe, effective approach to elimination of varicocele, preservation of testicular function, and, in a substantial number of men, an increase in semen quality and likelihood of pregnancy (Abdel-Meguid, 2010).

ORCHIOPEXY IN ADULTS

It is well known that cryptorchidism is associated with a high incidence of infertility even when unilateral. Long hot baths and saunas in humans, on a regular basis, have been shown to impair spermatogenesis. Elevated testicular temperature is also thought to be the primary pathophysiology feature of varicocele (Zorgniotti, 1980; Saypol et al, 1981; Goldstein and Eid, 1989; Wright et al, 1997). Spermatogenesis is exquisitely temperature sensitive. Both animal and human studies have shown that artificial elevation of testicular temperature results in impaired spermatogenesis (Shin et al, 1997; Perez-Crespo et al, 2008; Shiraishi et al, 2009). It will also preserve testicular hormonal function. The technique of orchiopexy in adults is identical to that employed for children. Even with a normal contralateral testis, orchiopexy is worthwhile to bring down a unilateral undescended testis to, if possible, a scrotal location where it can be examined. Leydig cell function in undescended testis can be retained. Orchiopexy in adults with bilateral undescended testes can induce spermatogenesis and allow pregnancy (Shin et al, 1997). Even **a solitary cryptorchid testis, when properly placed in scrotum, can provide enough testosterone to obviate the need for hormone replacement. When orchiopexy is performed in adults, regular self-examination and yearly sonography are mandatory.**

Retractile Testes in Adults

Retractile testes in boys are usually not surgically repaired if the testes can be manually manipulated to stay down into the scrotum either in the office or under anesthesia. The fate of persistently retractile testis in adults is unknown. A subset of infertile men have retractile testis (Caucci et al, 1997). The semen analyses of these men often demonstrate a typical stressed pattern similar to those of men with varicoceles. These men, however, do not have palpable varicoceles. They all have at least one and frequently both testes that retract out of the scrotum and into the abdomen and remain there for an hour or more a day. In some men these testes remain in the abdomen virtually all the time, except when in a warm shower or under anesthesia. It is likely that these testes will suffer from impaired temperature regulation and impaired spermatogenesis. Scrotal orchiopexy can improve the semen quality and fertility of some of these men.

When scrotal orchiopexy is performed for retractile testis, a dartos pouch operation should be performed. Simple suture orchiopexy of the tunica albuginea of the testis to the dartos, such as is performed sometimes to prevent torsion, will not prevent retraction of these testes into the groin. Creation of a dartos pouch will keep the testis well down into the scrotum and permanently prevent retraction. **This is also the most reliable and safest technique for the prevention of testicular torsion** (Redman and Barthold, 1995).

A 3- to 4-cm transverse incision is made in the low scrotal skin folds overlying the testis. **The incision is kept superficial, just through the dermis and not into the dartos. A large pouch must be created to accommodate the adult testis.** The place of dissection is above the dartos and just below the skin, which is kept thin.

After a capacious pouch is created, the dartos and underlying tunica vaginalis are vertically incised and the testis delivered. The cremasteric fibers overlying the spermatic cord are divided and ligated to minimize the tendency of the testis to retract. The opening in the dartos is closed around the cord (but not too tightly) to prevent the testis from falling out of the pouch. The cut edge of the everted tunica is approximated to the opening in the dartos with interrupted synthetic monofilament absorbable sutures. This allows placement of the testis in the pouch without the need for fixation sutures in the tunica albuginea (Redman and Barthold, 1995). The skin is closed over the testis with interrupted sutures of 4-0 chromic catgut. This technique obviates the risk of inadvertent injury to and bleeding from the testicular artery, which courses just under the tunica albuginea (Jarow, 1990).

Acknowledgments

I thank Vanessa L. Dudley and Philip Shihua Li, MD, for their immeasurable assistance in the preparation of this manuscript.

Special thanks to Wayland Hsiao, MD, who critically reviewed this manuscript and provided invaluable suggestions resulting in substantial improvement in its content.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter
23

Physiology of Penile Erection and Pathophysiology of Erectile Dysfunction

Tom F. Lue, MD, ScD (Hon), FACS

Physiology of Penile Erection
Pathophysiology of Erectile Dysfunction
Perspectives

"The penis does not obey the order of its master, who tries to erect or shrink it at will. Instead, the penis erects freely while its master is asleep. The penis must be said to have its own mind, by any stretch of the imagination."

—*Leonardo da Vinci*

PHYSIOLOGY OF PENILE ERECTION

Historical Aspects

The first description of erectile dysfunction (ED) dates from about 2000 BC and was set down on Egyptian papyrus. Two types were described: natural ("the man is incapable of accomplishing the sex act") and supernatural (evil charms and spells). Later, Hippocrates reported many cases of male impotence among the rich inhabitants of Scythia and ascribed it to excessive horseback riding. Aristotle stated that three branches of nerves carry spirit and energy to the penis and that erection is produced by the influx of air (Brenot, 1994). His theory was well accepted until Leonardo da Vinci (1504) noted a large amount of blood in the erect penis of hanged men and cast doubt on the concept of the air-filled penis. His writings, however, were kept secret until the beginning of the 20th century (Brenot, 1994). Nevertheless, in 1585, in *Ten Books on Surgery* and the *Book of Reproduction,* Ambroise Paré gave an accurate account of penile anatomy and the concept of erection. He described the penis as being composed of concentric coats of nerves, veins, and arteries and of two ligaments (corpora cavernosa), a urinary tract, and four muscles. "When the man becomes inflamed with lust and desire, blood rushes into the male member and causes it to become erect," Paré wrote. The importance of retaining blood in the penis was stressed by Dionis (1718; quoted by Brenot, 1994), who attributed this to the muscles cramping the veins at the proximal end, and by Hunter (1787), who thought that venous spasm prevented the exit of blood.

Modern investigations of penile hemodynamics began in the 1970s with xenon washout and cavernosography studies in human volunteers exposed to audiovisual sexual stimuli. These studies yielded conflicting results: Shirai and associates (1978) concluded that penile venous flow is increased during erection, but markedly increased arterial flow compensates for this; in contrast, Wagner (1981) also demonstrated increased arterial flow but concluded that venous drainage is decreased during erection.

Much of the current understanding of erectile physiology was gained in the 1980s and 1990s. In addition to the role of smooth muscle in regulating arterial and venous flow, the three-dimensional structure of the tunica albuginea and its role in venous occlusion were elucidated. An important breakthrough in the understanding of neural influences was the identification of nitric oxide (NO) as the major neurotransmitter for erection and of phosphodiesterases (PDEs) for detumescence. The role of endothelium in regulating smooth muscle tone and of the intercellular links affected by gap junctions has been uncovered. Furthermore, the importance of ion channels (potassium and calcium) and Rho/Rho kinase pathways in contraction and relaxation of smooth muscle has been shown. In pathophysiology, changes in smooth muscle, nerve endings, endothelium, and the fibroelastic framework associated with disease have been identified. These developments are discussed in detail in this chapter.

Functional Anatomy of the Penis

The penis is composed of three cylindrical structures: the paired corpora cavernosa and the corpus spongiosum (which houses the urethra), covered by a loose subcutaneous layer and skin. Its flaccid length is controlled by the contractile state of the erectile smooth muscle and varies considerably, depending on emotion and outside temperature. In one study, penile length, measured from the pubopenile junction to the meatus, was 8.8 cm flaccid, 12.4 cm stretched, and 12.9 cm erect, with neither age nor the size of the flaccid penis accurately predicting erectile length (Wessells et al, 1996). In another study, the author concluded that about 15% of men have a downward curve during erection; erect angle is below horizontal in one quarter; and shorter erect lengths (from 4.5 to 5.75 inches) occur in 40% of men (Sparling, 1997).

Table 23–1.

Penile Length in Adults

FIRST AUTHOR	YEAR OF REPORT	NUMBER OF SUBJECTS	AGE IN YEARS (RANGE)	FLACCID LENGTH (cm)	STRETCHED (S) OR ERECT (E) LENGTH (cm)	COUNTRY
Kinsey	1948	2770	20-59	9.7	15.5 (E)	USA
Bondil	1992	905	17-91	10.7	16.74 (S)	France
Wessells	1996	80	21-82	8.85	12.45 (S), 12.89 (E)	USA
Ponchietti	2001	3300	17-19	9	12.5 (S)	Italy
Ajmani	1985	320	17-23	8.16	NA	Nigeria
Schneider	2001	111	18-19	8.6	14.48 (E)	Germany
		32	40-68	9.22	14.18 (E)	
Awwad	2005	271 (N)	17-83	9.3	13.5 (S)	Jordan
		109 (ED)	22-68	7.7	11.6 (S)	

E, erect length; ED, erectile dysfunction; N, normal; NA, not available; S, stretch length.

Modified from Awwad Z, Abu-Hijleh M, Basri S, et al. Penile measurements in normal adult Jordanians and in patients with erectile dysfunction. Int J Impot Res 2005;17:191–5.

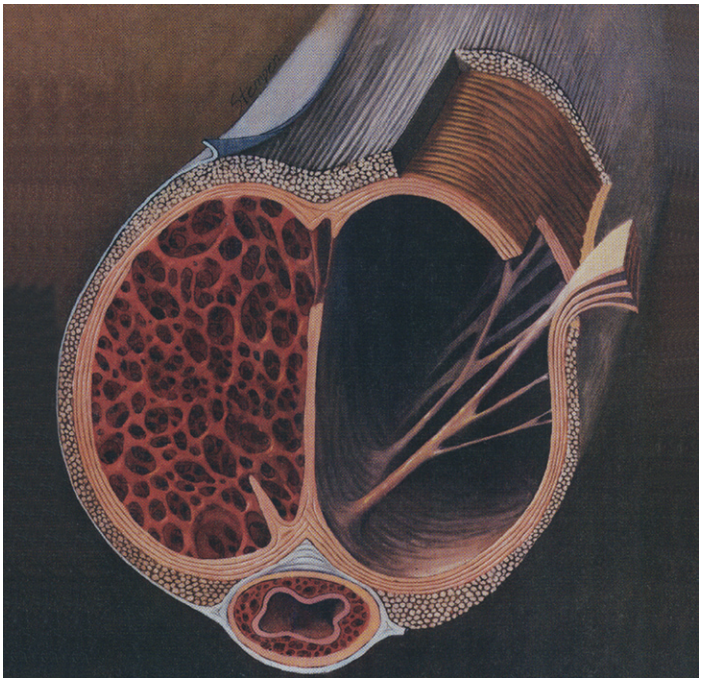


Figure 23–1. Artist's cross-sectional drawing of the penis, depicting the inner circular and outer longitudinal layers of the tunica albuginea, as well as the intracavernous pillars. The longitudinal layer is absent in the ventral groove housing the corpus spongiosum. (From Lue TF, Akkus E, Kour NW. Physiology of erectile function and dysfunction. Campbell's Urology Update 1994;12:1–10.)

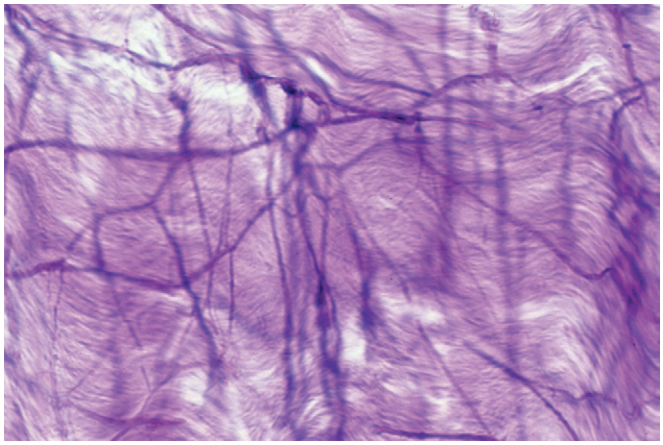


Figure 23–2. Micrograph of the human tunica albuginea, showing the interwoven elastic fibers and the finer collagen fibers (Hart stain ×100).

Since then, more studies have been reported from several countries (Awwad et al, 2005) (Table 23–1). Regarding penile morphology and erection, one study showed that, during erection, the penile buckling forces are dependent not only on intracavernous pressures but also on penile geometry and erectile tissue properties. The authors concluded that, in patients with normal penile hemodynamics but without adequate rigidity, structural causes should be investigated (Udelson et al, 1998).

Tunica Albuginea

The tunica affords great flexibility, rigidity, and tissue strength to the penis (Hsu et al, 1992) (Fig. 23–1). **The tunical covering of the corpora cavernosa is a bilayered structure with multiple sublayers. Inner-layer bundles support and contain the cavernous tissue and are oriented circularly. Radiating from this inner layer are intracavernous pillars that act as struts to augment the septum and provide essential support to the erectile tissue. Outer-layer bundles are oriented longitudinally, extending from the glans penis to the proximal crura; they insert into the inferior pubic rami but are absent between the 5 and the 7 o'clock positions. In contrast, the corpus spongiosum lacks an outer layer or intracorporeal struts, ensuring a low-pressure structure during erection.**

The tunica is composed of elastic fibers that form an irregular, latticed network on which the collagen fibers rest (Fig. 23–2). The detailed histologic composition of the tunica varies with anatomic location and function. Emissary veins run between the inner and outer layers for a short distance, often piercing the outer bundles obliquely. However, the cavernous artery and the branches of the dorsal artery that give additional blood supply to the corpus cavernosum take a more direct route and are surrounded by a periarterial soft-tissue sheath, which protects the arteries from occlusion by the tunica albuginea during erection.

The outer tunical layer appears to play an additional role in compression of the emissary veins during erection. It also

determines, to a large extent, the variability in tunical thickness and strength (Hsu et al, 1992). Between the 6 and 7 o'clock positions, the tunical thickness is 0.8 ± 0.1 mm; at the 9 o'clock position, 1.2 ± 0.2 mm; and at the 11 o'clock position, 2.2 ± 0.4 mm. At the 3, 5 to 6, and 1 o'clock positions, the measurements are nearly identical in mirror-image fashion. (Differences at specific locations have been found to be statistically significant.)

The stress on the tunica before penetration has been measured as $1.6 \pm 0.2 \times 10^7$ N/m^2 between the 6 and 7 o'clock positions, $3.0 \pm 0.3 \times 10^7$ N/m^2 at the 9 o'clock position, and $4.5 \pm 0.5 \times 10^7$ N/m^2 at the 11 o'clock position. **The strength and thickness of the tunica correlate in a statistically significant fashion with location. The most vulnerable area is located on the ventral groove (between the 5 and 7 o'clock positions), where the longitudinal outer layer is absent; most prostheses tend to extrude here** (Hsu et al, 1994).

The tunica albuginea is composed of fibrillar collagen (mostly type I, but also type III) in organized arrays interlaced with elastin fibers. Although collagen has a greater tensile strength than steel, it is unyielding. In contrast, elastin can be stretched up to 150% of its length. It is the elastin content that allows tunical expansion and helps to determine stretched penile length.

External penile support consists of two ligamentous structures: the fundiform and suspensory ligaments. The fundiform ligament arises from Colles' fascia and is lateral, superficial, and not adherent to the tunica albuginea of the corpora cavernosa. The suspensory ligament arises from Buck fascia and consists of two lateral bundles and one median bundle, which circumscribe the dorsal vein of the penis. Its main function is to attach the tunica albuginea of the corpora cavernosa to the pubis, and thus it provides support for the mobile portion of the penis (Hoznek et al, 1998). In patients with congenital deficiency or in whom this ligament has been severed in "penile elongation" surgery, the erect penis may be unstable or droop.

Corpora Cavernosa, Corpus Spongiosum, and Glans Penis

The corpora cavernosa comprise two spongy, paired cylinders contained in the thick envelope of the tunica albuginea. Their proximal ends, the crura, originate at the undersurface of the puboischial rami as two separate structures but merge under the pubic arch and remain attached up to the glans. **The septum between the two corpora cavernosa is incomplete in men but is complete in some species such as the dog.**

The corpora cavernosa are supported by a fibrous skeleton that includes the tunica albuginea, the septum, the intracavernous pillars, the intracavernous fibrous framework, and the periarterial and perineural fibrous sheath (Goldstein and Padma-Nathan, 1990; Hsu et al, 1992). Within the tunica are the interconnected sinusoids separated by smooth muscle trabeculae surrounded by elastic fibers, collagen, and loose areolar tissue. The terminal cavernous nerves and helicine arteries are intimately associated with the smooth muscle. Each corpus cavernosum is a conglomeration of sinusoids, larger in the center and smaller in the periphery. In the flaccid state, the blood slowly diffuses from the central to the peripheral sinusoids and the blood gas levels are similar to those of venous blood. During erection, the rapid entry of arterial blood to both the central and the peripheral sinusoids changes the intracavernous blood gas levels to those of arterial blood (Sattar et al, 1995).

The structure of the corpus spongiosum and glans is similar to that of the corpora cavernosa, except that the sinusoids are larger; the tunica is thinner in the spongiosum (with only a circular layer [see earlier]) and is absent in the glans (Table 23–2).

Table 23–2.

Penile Components and Their Function during Penile Erection

Corpora cavernosa	Support corpus spongiosum and glans
Tunica albuginea (of corpora cavernosa)	Contains and protects erectile tissue Provides rigidity of the corpora cavernosa Participates in veno-occlusive mechanism
Smooth muscle	Regulates blood flow into and out of the sinusoids
Ischiocavernosus muscle	Pumps blood distally to hasten erection Provides additional penile rigidity during rigid erection phase
Bulbocavernosus muscle	Compresses the bulb to help expel semen
Corpus spongiosum	Pressurizes and constricts the urethral lumen to allow forceful expulsion of semen
Glans	Acts as a cushion to lessen the impact of penis on female organs Provides sensory input to facilitate erection and enhance pleasure Facilitates intromission because of its cone shape

Arteries

The source of penile blood is usually the internal pudendal artery, a branch of the internal iliac artery (Fig. 23–3A). **In many instances, however, accessory arteries exist, arising from the external iliac, obturator, and vesical and femoral arteries, and they may in some men constitute the dominant or only arterial supply to the corpus cavernosum** (Breza et al., 1989). **In a study of 20 fresh human cadavers,** Droupy and colleagues (1997) reported three patterns of penile arterial supply: type I arising exclusively from internal pudendal arteries (3/20); type II arising from both accessory and internal pudendal arteries (14/20); and type III arising exclusively from accessory pudendal arteries (3/20). Nehra and colleagues (2008) **studied 79 consecutive patients with a history of erectile dysfunction (ED) and noted that 35% had an accessory pudendal artery, typically arising from the obturator artery. In these men, the accessory pudendal was the dominant blood supply in 54% and the only corporal blood supply in 11%. The importance of accessory pudendal artery preservation during radical prostatectomy was demonstrated by Mulhall and colleagues, who reported more rapid recovery of sexual function in men who underwent artery-sparing radical prostatectomy** (Mulhall et al, 2008).

The internal pudendal artery becomes the common penile artery after giving off a branch to the perineum. The three branches of the penile artery are the dorsal, bulbourethral, and cavernous. Distally, they join to form a vascular ring near the glans. The dorsal artery is responsible for engorgement of the glans during erection. The bulbourethral artery supplies the bulb and corpus spongiosum. The cavernous artery effects tumescence of the corpus cavernosum and enters it at the hilum of the penis, where the two crura merge. Along its course, it gives off many helicine

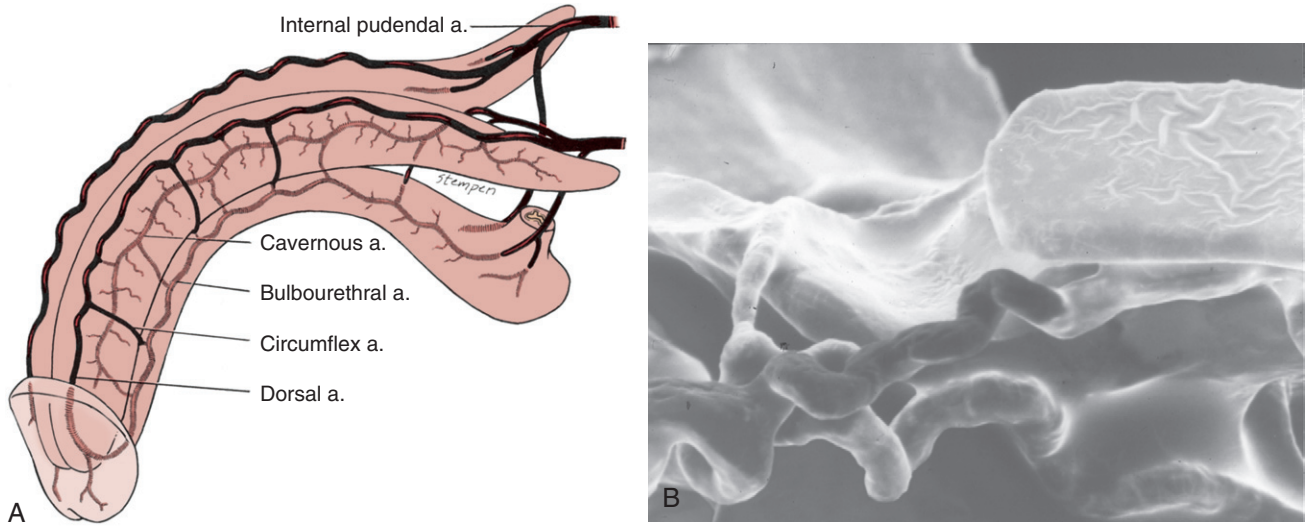


Figure 23–3. **A,** Penile arterial supply. **B,** Scanning electron micrograph of a human penile cast showing helicine arteries opening directly into the sinusoids without intervening capillaries.

arteries, which supply the trabecular erectile tissue and the sinusoids (Fig. 23–3B). These helicine arteries are contracted and tortuous in the flaccid state and become dilated and straight during erection.

Veins

The venous drainage from the three corpora originates in tiny venules leading from the peripheral sinusoids immediately beneath the tunica albuginea. These venules travel in the trabeculae between the tunica and the peripheral sinusoids to form the subtunical venous plexus before exiting as the emissary veins (Fig. 23–4A). Outside the tunica albuginea, venous drainage is as follows:

Skin and Subcutaneous Tissue. Multiple superficial veins run subcutaneously and unite near the root of the penis to form a single (or paired) superficial dorsal vein, which in turn drains into the saphenous veins. Occasionally, the superficial dorsal vein may also drain a portion of the corpora cavernosa.

Pendulous Penis. The emissary veins from the corpus cavernosum and spongiosum drain dorsally to the deep dorsal, laterally to the circumflex, and ventrally to the periurethral veins. Beginning at the coronal sulcus, multiple venous channels coalesce to form the deep dorsal vein, which is the main venous drainage of the glans penis and distal two thirds of the corpora cavernosa. Usually a single vein, but sometimes more than one deep dorsal vein, runs upwards behind the symphysis pubis to join the periprostatic venous plexus. There are also small venous channels accompanying the paired dorsal artery. In addition, many veins also travel longitudinally within the layers of the tunica albuginea to join the dorsal vein or Santorini plexus proximally (Hsu et al, 2003). These become enlarged after the deep dorsal vein is ligated and may be the cause of recurrent leakage in venogenic ED (Chen et al, 2005).

Infrapubic Penis. Emissary veins draining the proximal corpora cavernosa join to form cavernous and crural veins. These join the periurethral veins from the urethral bulb to form the internal pudendal veins.

The veins of the three systems communicate variably with each other. Indeed, variations in the number, distribution, and termination of these venous systems are common (Fig. 23–4B and C).

Hemodynamics and Mechanism of Erection And Detumescence

Corpora Cavernosa

The penile erectile tissue, specifically the cavernous smooth musculature and the smooth muscles of the arteriolar and arterial walls, plays a key role in the erectile process. **In the flaccid state, these smooth muscles are tonically contracted, allowing only a small amount of arterial flow for nutritional purposes.** The blood partial pressure of oxygen (pO_2) is about 35 mm Hg (Sattar et al, 1995). The flaccid penis is in a moderate state of contraction, as evidenced by further shrinkage in cold weather and after phenylephrine injection.

Sexual stimulation triggers release of neurotransmitters from the cavernous nerve terminals. This results in relaxation of these smooth muscles and the following events (Fig. 23–5): **(1) dilation of the arterioles and arteries by increased blood flow in both the diastolic and systolic phases; (2) trapping of the incoming blood by the expanding sinusoids; (3) compression of the subtunical venous plexuses between the tunica albuginea and the peripheral sinusoids, reducing venous outflow; (4) stretching of the tunica to its capacity, which occludes the emissary veins between the inner circular and outer longitudinal layers and further decreases venous outflow to a minimum; (5) an increase in Po_2 (to about 90 mm Hg) and intracavernous pressure (around 100 mm Hg), which raises the penis from the dependent position to the erect state (the full-erection phase); and (6) a further pressure increase (to several hundred millimeters of mercury) with contraction of the ischiocavernosus muscles (rigid-erection phase).**

The angle of the erect penis is determined by its size and attachment to the puboischial rami (the crura) and the anterior surface of the pubic bone (the suspensory and funiform ligaments). In men with a long heavy penis or a loose suspensory ligament, the angle usually will not be greater than 90 degrees, even with full rigidity.

Three phases of detumescence have been reported in an animal study (Bosch et al, 1991). The first entails a transient

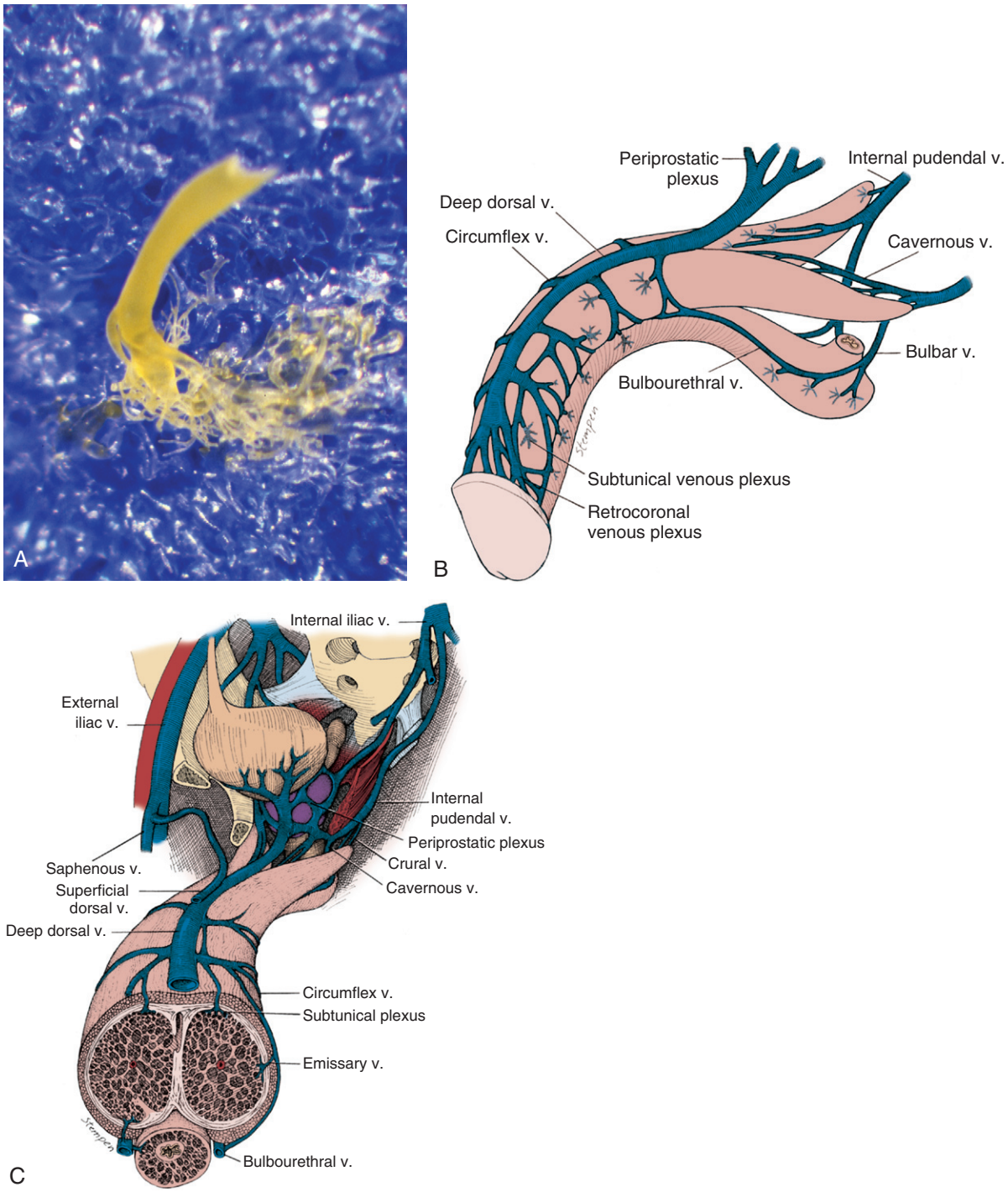


Figure 23–4. **A,** Photograph of an emissary vein with subtunical venous plexus of a human penile cast. The cast was made by injecting blue material into the corpus cavernosum and yellow material into the deep dorsal vein. The skin and tunica albuginea were then digested away with KOH solution. **B** and **C,** Penile venous drainage.

intracorporeal pressure increase, indicating the beginning of smooth muscle contraction against a closed venous system. The second phase shows a slow pressure decrease, suggesting a slow reopening of the venous channels with resumption of the basal level of arterial flow. The third phase shows a fast pressure decrease with fully restored venous outflow capacity.

Erection thus involves sinusoidal relaxation, arterial dilation, and venous compression (Lue et al, 1983). The importance of smooth muscle relaxation has been demonstrated in animal and human studies (Saenz de Tejada et al, 1989a; Ignarro et al, 1990). To summarize the hemodynamic events of erection and detumescence, seven phases have been observed in animal experiments that reflect the changes in and the relationship between penile arterial flow and intracavernous pressure (Fig. 23–6).

Corpus Spongiosum and Glans Penis

The hemodynamics of the corpus spongiosum and glans penis are somewhat different from those of the corpora cavernosa. **During erection, the arterial flow increases in a similar manner;**

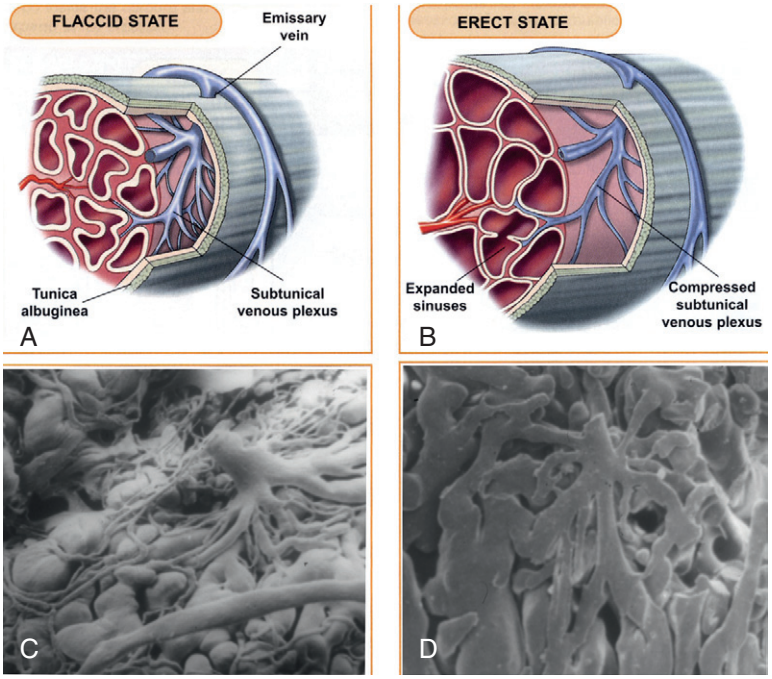


Figure 23–5. The mechanism of penile erection: **A,** In the flaccid state, the arteries, arterioles, and sinusoids are contracted. The intersinusoidal and subtunical venous plexuses are wide open, with free flow to the emissary veins. **B,** In the erect state, the muscles of the sinusoidal wall and the arterioles relax, allowing maximal flow to the compliant sinusoidal spaces. Most of the venules are compressed between the expanding sinusoids. The larger venules are sandwiched and flattened between the distended sinusoids and the tunica albuginea. This effectively reduces the venous capacity to a minimum. **C** and **D,** Scanning electron micrographs of casts of a canine subtunical venous plexus in the flaccid and erect states, respectively. (**A** and **B,** From Lue TF, Giuliano F, Khoury S, Rosen R. Clinical manual of sexual medicine: sexual dysfunction in men. Paris: Health Publications; 2004.)

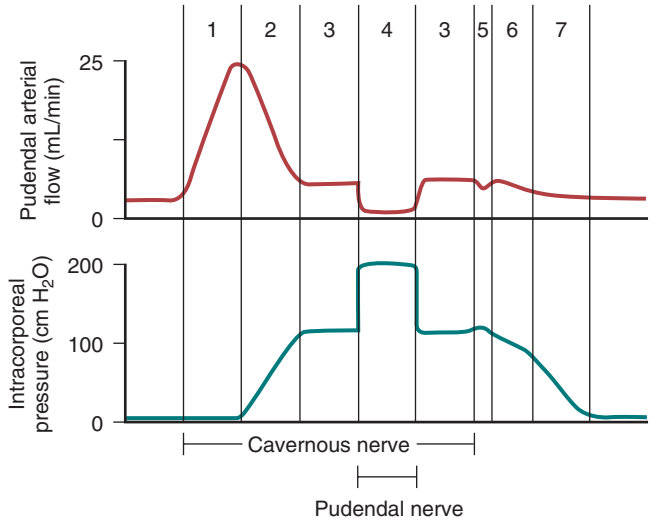


Figure 23–6. Blood flow and intracavernous pressure changes during the seven phases of penile erection and detumescence: 0, flaccid; 1, latent; 2, tumescence; 3, full erection; 4, rigid erection; 5, initial detumescence; 6, slow detumescence; 7, fast detumescence.

however, the pressure in the corpus spongiosum and glans is only one-third to one-half that in the corpora cavernosa because the tunical covering, which is thin over the corpus spongiosum and virtually absent over the glans, ensures minimal venous occlusion. During the full-erection phase, partial compression of the deep dorsal and circumflex veins between Buck fascia and the engorged corpora cavernosa contributes to glanular tumescence, although the spongiosum and glans essentially function as a large arteriovenous shunt during this phase. In the rigid-erection phase, the ischiocavernosus and bulbocavernosus muscles forcefully compress the spongiosum and penile veins, resulting in further engorgement and increased pressure in the glans and spongiosum (Table 23–3).

Table 23–3.

Comparison of Corpus Spongiosum and the Glans

	CORPUS SPONGIOSUM	GLANS PENIS
Tunica albuginea	Thin (circular layer only)	Absent
Main blood supply	Bulbal and spongiosal arteries	Dorsal artery
Venous occlusion during erection	No	No
Compression by skeletal muscle	Yes (ischiocavernosus, bulbocavernosus)	No

Neuroanatomy and Neurophysiology of Penile Erection

Spinal Centers and Peripheral Pathways

The innervation of the penis is both autonomic (sympathetic and parasympathetic) and somatic (sensory and motor) (Fig. 23–7). From the neurons in the spinal cord and peripheral ganglia, the sympathetic and parasympathetic nerves merge to form the cavernous nerves, which enter the corpora cavernosa and corpus spongiosum to modulate the neurovascular events during erection and detumescence. The somatic nerves are primarily responsible for sensation and the contraction of the bulbocavernosus and ischiocavernosus muscles.

Autonomic Pathways. The sympathetic pathway originates from the 11th thoracic to the 2nd lumbar spinal segments and passes through the white rami to the sympathetic chain ganglia. Some fibers then travel through the lumbar splanchnic nerves to the inferior mesenteric and superior hypogastric plexuses, from which fibers travel in the hypogastric nerves to the pelvic plexus. In humans the T10 to T12 segments are most often the origin of the sympathetic fibers, and the chain ganglia cells projecting to the penis are located in the sacral and caudal ganglia (de Groat and Booth, 1993).

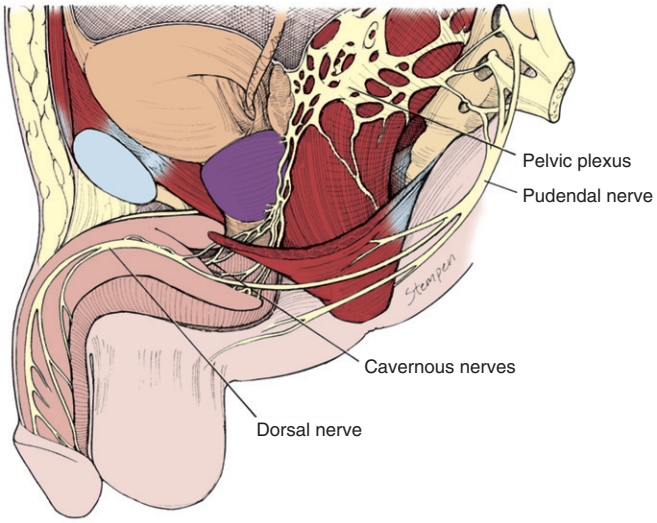


Figure 23–7. Penile neuroanatomy.

The parasympathetic pathway arises from neurons in the intermediolateral cell columns of the second, third, and fourth sacral spinal cord segments. The preganglionic fibers pass in the pelvic nerves to the pelvic plexus, where they are joined by the sympathetic nerves from the superior hypogastric plexus. The cavernous nerves are branches of the pelvic plexus that innervate the penis. Other branches innervate the rectum, bladder, prostate, and sphincters. The cavernous nerves are easily damaged during radical excision of the rectum, bladder, and prostate. A clear understanding of the course of these nerves is essential to the prevention of iatrogenic ED (Walsh et al, 1990). Human cadaveric dissection has revealed medial and lateral branches of the cavernous nerves (the former accompanying the urethra and the latter piercing the urogenital diaphragm 4 to 7 mm lateral to the sphincter) and multiple communications between the cavernous and dorsal nerves (Fig. 23–8) (Paick et al, 1993). In addition to the cavernous nerve proper, pelvic ganglion cells also exist in and along the nerve components and pelvic viscera. These are seen at the bladder/prostate junction, the dorsal aspect of the seminal vesicles, and along the prostate. Takenaka and colleagues (2005) reported individual variations in distribution of these extramural ganglion cells in the male pelvis, which may complicate nerve-sparing efforts.

Stimulation of the pelvic plexus and the cavernous nerves induces erection, whereas stimulation of the sympathetic trunk causes detumescence. This clearly implies that the sacral parasympathetic input is responsible for tumescence and the thoracolumbar sympathetic pathway is responsible for detumescence. In experiments with cats and rats, removal of the spinal cord below L4 or L5 reportedly eliminated the reflex erectile response, but placement with a female in heat or electrical stimulation of the medial preoptic area (MPOA) produced marked erection (Giuliano et al, 1996; Sato and Christ, 2000). Paick and Lee (1994) also reported that apomorphine-induced erection is similar to psychogenic erection in the rat and can be induced by means of the thoracolumbar sympathetic pathway in case of injury to the sacral parasympathetic centers. In man, many patients with sacral spinal cord injury retain psychogenic erectile ability even though reflexogenic erection is abolished. These cerebrally elicited erections are found more frequently in patients with lower motoneuron lesions below



Figure 23–8. Drawing from a human cadaveric dissection shows the medial *(red arrow)* and lateral *(green arrow)* bundles of the cavernous nerve distal to the prostate. (Reprinted with permission from Paick JS, Donatucci EF, Lue TF. Anatomy of cavernous nerves distal to prostate: microdissection study in adult male cadavers. Urology 1993;42:145–9, with permission from Exerpta Medica, Inc.)

T12 (Courtois et al, 1999); no psychogenic erection occurs in patients with lesions above T9. The efferent sympathetic outflow is thus suggested to be at the levels T11 and T12 (Chapelle et al, 1980). These authors have also reported that, in patients with psychogenic erections, lengthening and swelling of the penis are observed but rigidity is insufficient.

It is therefore possible that, for rigid-erection production in normal men, cerebral impulses travel as follows: inhibiting the sympathetic pathway and thus decreasing norepinephrine release; through the parasympathetic, releasing NO and acetylcholine; and the somatic, releasing acetylcholine. In patients with a sacral cord lesion, the cerebral impulses can still travel by means of the sympathetic pathway to inhibit norepinephrine release, and NO and acetylcholine can still be released through synapse with postganglionic parasympathetic and somatic neurons. Because the number of these synapses is less than in men with an intact sacral spinal cord, the resulting erection will not be as strong.

Somatic Pathways. The somatosensory pathway originates at the sensory receptors in the penile skin, glans, and urethra and within the corpus cavernosum. In the human glans penis are numerous afferent terminations: free nerve endings and corpuscular receptors in a ratio of 10:1. The free nerve endings are derived from thin myelinated A_d and unmyelinated C fibers and are unlike any other cutaneous area in the body (Halata and Munger, 1986). The nerve fibers from the receptors converge to form bundles of the dorsal nerve of the penis, which joins other nerves to become the pudendal nerve. The latter enters the spinal cord via the S2-S4 roots to terminate on spinal neurons and interneurons in the central gray region of the lumbosacral segment (McKenna, 1998).

Table 23–4.

Spinal Reflexes Involved in Stimulation of Penile Dorsal Nerve

STIMULATION	SPINAL CENTER	EFFERENT	EFFECT
Noxious, abrupt stimulation	Sacral motor neurons	Pudendal nerve (motor)	Bulbocavernous reflex
Low-intensity continuous (e.g., vibratory, manual)	Sacral parasympathetic neurons and interneurons	1. Pelvic nerves 2. Cavernous nerve	1. Bladder inhibition and closure of bladder neck 2. Penile erection
High-intensity continuous	Sacral motor and parasympathetic Thoracolumbar sympathetic neurons	Pudendal, pelvic, and cavernous nerves	Ejaculation

Activation of these sensory neurons sends messages of pain, temperature, and touch by means of spinothalamic and spinoreticular pathways to the thalamus and sensory cortex for sensory perception.

The dorsal nerve of the penis used to be regarded as purely somatic; however, nerve bundles testing positive for NO synthase (NOS), which is autonomic in origin, have been demonstrated in the human by Burnett and colleagues (1993) and in the rat by Carrier and colleagues (1995). Giuliano and colleagues (1993) have also shown that stimulation of the sympathetic chain at the L4-L5 level elicits an evoked discharge on the dorsal nerve and that stimulation of the dorsal nerve evokes a reflex discharge in the lumbosacral sympathetic chain of rats. These findings clearly demonstrate that the dorsal nerve has both somatic and autonomic components that enable it to regulate both erectile and ejaculatory functions.

The Onuf nucleus in the second to fourth sacral spinal segments is the center of somatomotor penile innervation. These nerves travel in the sacral nerves to the pudendal nerve to innervate the ischiocavernosus and bulbocavernosus muscles. **Contraction of the ischiocavernosus muscles produces the rigid-erection phase. Rhythmic contraction of the bulbocavernosus muscle is necessary for ejaculation.** In animal studies, direct innervation of the sacral spinal motoneurons by brainstem sympathetic centers (A5-catecholaminergic cell group and locus ceruleus) has been identified (Marson and McKenna, 1996). This adrenergic innervation of pudendal motoneurons may be involved in rhythmic contractions of perineal muscles during ejaculation. In addition, oxytocinergic and serotonergic innervation of lumbosacral nuclei controlling penile erection and perineal muscles in the male rat has also been demonstrated (Tang et al, 1998).

Depending on the intensity and nature of genital stimulation, several spinal reflexes can be elicited (Table 23–4). The best known is the bulbocavernosus reflex, which is the basis of genital neurologic examination and electrophysiologic latency testing. Although impairment of bulbocavernosus and ischiocavernosus muscles may impair erection, the significance of obtaining a bulbocavernosus reflex in overall sexual dysfunction assessment is controversial.

Table 23–5.

Brain Centers Involved in Sexual Function

LEVEL	REGION	FUNCTION
Forebrain	Medial amygdala Stria terminalis	Control sexual motivation
	Pyriform cortex	Inhibits sexual drive (hypersexuality when destroyed)
	Hippocampus	Involved in penile erection
	Right insula and inferior frontal cortex	Increased activity during visually evoked sexual stimulation (sexual arousal)
	Left anterior cingulate cortex	
Hypothalamus	Medial preoptic area (MPOA) Lateral preoptic area (LPOA)	Ability to recognize a sexual partner, integration of hormonal and sensory cues Control nocturnal penile tumescence in rats
	Paraventricular nucleus (PVN)	Facilitates penile erection (via oxytocin neurons to lumbosacral spinal autonomic and somatic efferents)
Brainstem	Nucleus paragigantocellularis	Inhibits penile erection (via serotonin neurons to lumbosacral spinal neurons and interneurons)
	A5-catecholaminergic cell group Locus ceruleus	Major noradrenergic center
Midbrain	Periaqueductal gray	Relay center for sexually relevant stimuli

Supraspinal Pathways and Centers

Integration and processing of afferent inputs (e.g., visual, olfactory, imaginative, genital stimulation) in the supraspinal centers are essential in the initiation and maintenance of penile erection. Many brain areas have been found to be associated with sexual function including the medial amygdala, the medial preoptic area (MPOA), the paraventricular nucleus (PVN), the periaqueductal gray, and ventral tegmentum (Table 23–5). Marson and colleagues (1993) injected pseudo-rabies virus into the rat corpus cavernosum and traced labeled neurons from major pelvic ganglia to neurons in the spinal cord, brainstem, and hypothalamus. Mallick and colleagues (1994) also showed that stimulation of the dorsal nerve in the rat influenced the firing rate of about 80% of the neurons in the MPOA but not in other areas of the hypothalamus. Efferent pathways from the MPOA enter the medial forebrain bundle and the midbrain tegmental region (near the substantia nigra). Pathologic processes in these regions such as Parkinson disease or cerebrovascular accidents are often associated with erectile dysfunction. Axonal tracing in monkeys, cats, and rats has shown direct projection from hypothalamic nuclei to the lumbosacral autonomic erection centers. The neurons in these hypothalamic nuclei contain peptidergic neurotransmitters including oxytocin and vasopressin, which may be involved in penile erection (Sachs and Meisel, 1988). Several brainstem and medullary centers are

also involved in sexual function. The A5-catecholamine cell group and locus ceruleus have been shown to provide adrenergic innervation to the hypothalamus, thalamus, neocortex, and spinal cord. Projections from the nucleus paragigantocellularis, which provides inhibitory serotonergic innervation, have also been demonstrated in the hypothalamus, limbic system, neocortex, and spinal cord.

Central Neural Activation during Arousal. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have allowed a greater understanding of brain activation during human sexual arousal by demonstrating increases in regional cerebral blood flow or changes in regional cerebral activity during a particular moment in time. Generally, in young heterosexual men sexual arousal is triggered with sexually explicit pictures or videos. Scanned brain images taken during arousal are compared with images taken in response to sexually neutral media (e.g., documentaries or humorous video clips). Centers of activation and deactivation can be demonstrated. Although the simplicity of these study designs is elegant, multiple factors are involved in sexual arousal—especially when triggered by visual clues. The authors of these studies have placed many necessary conditions in an attempt to standardize the methods and participants; however, the complexity of human emotion and sexual response is extremely difficult to regulate.

In 1999 Stoléru and colleagues studied eight healthy right-handed heterosexual men with PET during visually evoked sexual arousal (Stoléru et al, 1999). Regions of brain activation were correlated with testosterone plasma levels and penile tumescence. Significant activation was seen in the bilateral inferior temporal cortices, right insula, right inferior frontal cortex, and left anterior cingulate cortex. From this landmark study a tentative model was introduced, suggesting that **visually evoked sexual arousal has three components associated with neuroanatomic regions: (1) a perceptual-cognitive component that recognizes the visual stimuli as sexual and is performed in the bilateral inferior temporal cortices; (2) an emotional/motivational component that processes sensory information with motivational states and is performed in the right insula, right inferior frontal cortex, and left cingulate cortex (paralimbic areas); and (3) a physiologic component that coordinates the endocrine and autonomic functions and is performed in the left anterior cingulate cortex.**

Bocher and colleagues (2001) demonstrated increased activation in the inferior lateral occipital cortex, bilateral posterior temporal cortices (right greater than left), right inferior lateral prefrontal cortex, left postcentral gyrus, bilateral inferior parietal lobules, left superior parietal lobules, frontal pole (Brodmann area 10), left prefrontal cortex, and midbrain regions. They also noted deactivation in the medial frontal and anterior cingulate, contrary to Stoleru's report. Again, visual association centers were noted to be activated, in particular the posterior temporal cortices and postcentral gyrus. Interestingly, the midbrain activation seen in this study correlates with the location of the dopaminergic neurons. It was not demonstrated in other studies, but that may owe to these authors' use of prolonged provocation: the visual sexual stimulus was a 30-minute continuous video clip, whereas other studies used brief visual stimuli (2 to 10 minutes).

Park and colleagues studied 12 healthy men with fMRI (Park et al, 2001) in response to erotic and nonerotic film clips. With the former, regional brain activation was generally seen in the inferior frontal lobe, cingulate gyrus, insular gyrus, corpus collosum, thalamus, caudate nucleus, globus pallidus, and inferior temporal lobes. Some activation regions were similar to those in other studies, in particular the inferior frontal lobes, inferior temporal lobes, and insular gyrus.

In a well-designed study with fMRI and visual stimuli, correlated with penile turgidity, Arnow and colleagues demonstrated a significant region of activation in the right subinsular/insular region, including the claustrum (Arnow et al, 2002), a response also seen in previous studies with PET (Stoléru et al, 1999; Redouté et al, 2000). This region has been associated with sensory processing, and this activation may represent somatosensory processing and recognition of erection. Other brain regions activated during visual sexual stimuli were the right middle gyrus, right temporal gyrus, left caudate and putamen, bilateral cingulate gyri, right sensimotor and premotor regions. Also, a lesser activation was seen in the right hypothalamus. (Dopamine is projected to the hypothalamus, and the evidence that dopamine assists male sexual behavior is substantial.) The activation of the right middle temporal gyrus is probably associated with visual processing.

In 2003 Mouras and colleagues studied eight men with fMRI. Video clips were not used; rather, still photographs (neutral and sexually arousing) were shown quickly. The authors believed that, by using shorter visual sexual stimuli, early neural responses would be generated instead of responses to the perception of penile tumescence. Again, activation of the middle and inferior occipital gyri was demonstrated, most likely linked to the visual stimuli, but not necessarily to the sexual component. In addition to multiple brain centers that showed activation with visual sexual stimuli (bilateral parietal lobules, left inferior parietal lobule, right postcentral gyrus, right parieto-occipital sulcus, left superior occipital gyrus, bilateral precentral gyrus), the cerebellum demonstrated activation in three subjects and deactivation in four. As many other reports have demonstrated activation of the cerebellum in response to erotic films and pictures of love partners (Garavan et al, 2000; Beauregard et al, 2001), visual sexual stimuli likely promote activation in regions within the cerebellum.

With the advances with fMRI, detailed comparisons of brain activation in response to visual sexual stimuli have been performed on varied groups. Stoléru and colleagues (2003) compared healthy men with men with hypoactive sexual desire disorder (HSDD) and reported that the left gyrus rectus, a portion of the medial orbitofrontal cortex, remained activated in the latter group in contrast to its deactivation in healthy men. This region is believed to mediate inhibition of motivated behavior, and its continued activation may help explain the pathophysiology of HSDD. Montorsi and colleagues (2003) compared men with psychogenic ED and potent controls after the administration of apomorphine. During visual sexual stimulation, the former group evidenced extended activation of the cingulated gyrus, frontal mesial, and frontal basal cortex, suggesting an underlying organic cause for psychogenic ED. However, their fMRI images after apomorphine were similar to those of the potent controls. Apomorphine caused additional activation of foci in the psychogenic ED patients (seen in the nucleus accumbens, hypothalamus, mesencephalon), and it was significantly greater in the right hemisphere than in the left. This greater right-sided activation is a common finding in sexually evoked brain activation studies.

Brain scanning with PET and fMRI has become a powerful tool in the study of central activation of sexual arousal, with many brain regions of activation demonstrated in these reports (Table 23–6). Psychogenic ED, premature ejaculation, sexual deviations, and orgasmic dysfunction are just a few conditions that may

Table 23–6.

Common Brain Activation Regions with Visual Sexual Stimuli*

BRAIN ACTIVATION REGIONS	FUNCTIONAL ASSOCIATION
Bilateral inferior temporal cortex (right > left)	Visual association area
Right insula	Processes somatosensory information with motivational states
Right inferior frontal cortex	Processes sensory information
Left anterior cingulate cortex	Controls autonomic and neuroendocrine function
Right occipital gyrus	Visual processing
Right hypothalamus	Male copulatory behavior
Left caudate (the striatum)	Processes attention and guides responsiveness to new environmental stimuli

*These regions demonstrate activation with visual sexual stimuli in multiple studies.

Table 23–7.

Brain Centers of Orgasm

	BRAIN AREAS	RELEVANCE
Increased activity Primary area	Mesodiencephalic transition zone (including the ventral tegmental area)	"Reward" center also activated by opioid
Increased activity Secondary areas	Midbrain lateral central tegmental field, the zona incerta, subparafascicular nucleus, ventroposterior, midline, and intralaminar thalamic nuclei	
	Lateral putamen and adjoining parts of the claustrum	
	Brodmann areas 7/40, 18, 21, 23, and 47, exclusively on the right side	
Increased activity Other area	Cerebellum	Emotional processing
Deceased activity	Amygdala and adjacent entorhinal cortex	

accompany alterations in higher brain function and perhaps now can be studied. As we begin to understand brain function with normal sexual response and arousal, the causes of dysfunction may be elucidated.

The structures discussed earlier are responsible for the three types of erection: psychogenic, reflexogenic, and nocturnal. **Psychogenic erection is a result of audiovisual stimuli or fantasy. Impulses from the brain modulate the spinal erection centers (T11-L2 and S2-S4) to activate the erectile process. Reflexogenic erection is produced by tactile stimulation of the genital organs. The impulses reach the spinal erection centers; some then follow the ascending tract, resulting in sensory perception, while others activate the autonomic nuclei to send messages via the cavernous nerves to the penis to induce erection. This type of erection is preserved in patients with upper spinal cord injury. Nocturnal erection occurs mostly during rapid-eye-movement (REM) sleep. PET scanning of humans in REM sleep shows increased activity in the pontine area, the amygdalae, and the anterior cingulate gyrus but decreased activity in the prefrontal and parietal cortex. The mechanism that triggers REM sleep is located in the pontine reticular formation; the cholinergic neurons in the lateral pontine tegmentum are activated, while the adrenergic neurons in the locus ceruleus and the serotonergic neurons in the midbrain raphe are silent.** This differential activation may be responsible for these nocturnal erections. In rats, the area of the brain that appears to control nocturnal penile tumescence is the lateral preoptic area (LPOA) (Schmidt et al, 2000).

The brain centers activated during orgasm and ejaculation have also been studied. Holstege and colleagues (2003) used positron emission tomography (PET) to measure increases in regional cerebral blood flow during ejaculation versus sexual stimulation without orgasm in heterosexual male volunteers. Manual penile stimulation was performed by the volunteer's female partner. Primary brain activation was found in the mesodiencephalic transition zone (including the ventral tegmental area), an area frequently activated with "reward" behaviors and with injection of opioids such as heroin. Other activated mesodiencephalic structures included the midbrain lateral central tegmental field, the zona incerta, the subparafascicular nucleus, and the ventroposterior, midline, and intralaminar thalamic nuclei. Increased activation was also observed in the lateral putamen and adjoining parts of the claustrum. Neocortical activity was found in Brodmann areas 7/40, 18, 21, 23, and 47, exclusively on the right side. Conversely, in the amygdala and adjacent entorhinal cortex, a decrease in activation was observed. Remarkably strong blood flow increases were observed in the cerebellum. These findings corroborate the notion that the cerebellum plays an important role in emotional processing. Although activation of these particular areas is of great interest, it is apparent that further studies are necssary to truly understanding the neurobiologic basis of orgasm, ejaculation, and sexual satisfaction in men (Table 23–7).

Neurotransmitters

Peripheral Neurotransmitters and Endothelium-Derived Factors

Flaccidity and Detumescence. **α-Adrenergic nerve fibers and receptors have been demonstrated in the cavernous trabeculae and surrounding the cavernous arteries, and norepinephrine has generally been accepted as the principal neurotransmitter to control penile flaccidity and detumescence** (Hedlund and Andersson, 1985; Diederichs et al, 1990). Receptor-binding studies have shown the number of α adrenoceptors to be 10 times higher than the number of β adrenoceptors (Levin and Wein, 1980). Currently, it is suggested that sympathetic contraction is mediated by activation of postsynaptic α_{1a}- and α_{1d}-adrenergic receptors (Christ et al, 1990; Traish et al, 1995) and modulated by presynaptic α_2-adrenergic receptors (Saenz de Tejada et al, 1989b). Contraction mediated by α_2 receptors depends on the entry of calcium from the extracellular compartment, while the activation of α_1 receptors provokes the release of intracellular calcium, initially, with subsequent extracellular calcium entry for the maintenance of the contractile tone.

Endothelin, a potent vasoconstrictor produced by the endothelial cells, has also been suggested to be a mediator for detumescence (Holmquist et al, 1990; Saenz de Tejada et al, 1991a). Endothelin-1 is a member of a family of three peptides and is a

potent constrictor synthesized by the sinusoidal endothelium (Holmquist et al, 1990; Saenz de Tejada et al, 1991a). Its presence in human cavernous tissue suggests the participation of this peptide in the regulation of trabecular smooth muscle. Endothelin also potentiates the constrictor effects of catecholamines on trabecular smooth muscle (Christ et al, 1995b). Two receptors for endothelin, ETA and ETB, mediate the biologic effects of endothelin in vascular tissue: ETA receptors mediate contraction, whereas ETB receptors induce relaxation.

Several constrictor prostanoids including prostaglandin I2 (PGI2), $PGF2_{\alpha}$, and thromboxane A2 (TXA2) are synthesized by the human cavernous tissue. In-vitro studies have demonstrated that prostanoids are responsible for the tone and spontaneous activity of isolated trabecular muscle (Christ et al, 1990). Functional characterization of prostanoid receptors in human trabecular and arterial penile smooth muscle has revealed that only TP receptors mediate contractile effects of prostanoids in these tissues (Angulo et al, 2002). Also, it has been observed in vitro that constrictor prostanoids, simultaneously released with NO, attenuate the dilator effect of the latter (Azadzoi et al, 1992; Minhas et al, 2001).

The renin-angiotensin system may also play a significant role in the maintenance of penile smooth muscle tone. Angiotensin II has been detected in endothelial and smooth muscle cells of human corpus cavernosum (Kifor et al, 1997) and evokes contraction of human (Becker et al, 2001a) and rabbit (Park et al, 1997) corpus cavernosum in vitro. This contractile effect is mediated by interaction with AT-I subtype receptors (Park et al, 1997). Intracavernous injection of angiotensin II reverses spontaneous erections in dogs, while the AT-I receptor antagonist, losartan, increases the intracavernous pressure (Kifor et al, 1997). Finally, intracavernous blood levels of angiotensin II, which are higher than in systemic peripheral blood, increase in the detumescence phase (Becker et al, 2001b). Thus local production of angiotensin II may increase penile smooth muscle contractility by way of AT-I receptors, assisting penile detumescence. In addition, the endothelium has been shown to release potent vasoconstrictors including endoperoxides, thromboxane A2, and superoxide anions.

The current consensus holds that the maintenance of the intracorporeal smooth muscle in a semicontracted (flaccid) state likely results from three factors: intrinsic myogenic activity (Andersson and Wagner, 1995); **adrenergic neurotransmission; and endothelium-derived contracting factors such as angiotensin II, $PGF2_{\alpha}$, and endothelins. On the other hand, detumescence after erection may be a result of cessation of NO release, the breakdown of cyclic guanosine monophosphate (cGMP) by phosphodiesterases, and/or sympathetic discharge during ejaculation.**

Erection. Acetylcholine has been shown to be released with electrical field stimulation of human erectile tissue (Blanco et al, 1988). Traish and colleagues (1990) reported the density of muscarinic receptors in cavernous tissue to range from 35 to 65 fmol/mg protein and in endothelial cell membrane from 5 to 10 fmol/mg protein. However, intravenous or intracavernous injection of atropine has failed to abolish erection induced in animals by electrical neurostimulation (Stief et al, 1989a) and in men by erotic stimuli (Wagner and Uhrenholdt, 1980). **Although acetylcholine is not the predominant neurotransmitter, it does contribute indirectly to penile erection by presynaptic inhibition of adrenergic neurons and stimulation of NO release from endothelial cells** (Saenz de Tejada et al, 1989a).

Most researchers now agree that NO released from nonadrenergic/noncholinergic (NANC) neurotransmission and from the endothelium is the principal neurotransmitter mediating penile erection. NO increases the production of cGMP, which in turn relaxes the cavernous smooth muscle (Ignarro et al, 1990; Holmquist et al, 1991; Kim N et al, 1991; Pickard et al, 1991; Burnett et al, 1992; Knispel et al, 1992; Rajfer et al, 1992; Burnett et al, 1993; Trigo-Rocha et al, 1993a). The consensus is that NO derived from nNOS in the nitrergic nerves is responsible for the initiation and majority of the smooth muscle relaxation whereby NO from eNOS contributes to the maintenance of the erection (Hurt et al, 2002). (For a fuller discussion of NO, see specific "Nitric Oxide" sections later.)

Aside from its role in releasing vasoconstrictors, the endothelium can also release factors that induce smooth muscle relaxation including carbon monoxide, endothelium-derived hyperpolarizing factor (EDHF), prostacyclin (PGI2), and endothelin (which may induce relaxation via activation of ETB receptors).

Interactions among Nerves and Neurotransmitters. Acetylcholine, by acting on the presynaptic receptors on adrenergic neurons, has been shown to modulate the release of norepinephrine (Saenz de Tejada et al, 1989b), which also can be inhibited by PGE_1 (Molderings et al, 1992). In the human corpus cavernosum, noradrenergic responses are under nitrergic control. Conversely, adrenergic neurons, through prejunctional α2 receptors, can also regulate the release of NO.

Several studies have demonstrated that the interaction between the two systems also occurs in the smooth muscle (Brave et al, 1993; Angulo et al, 2001). The NO-cGMP-PKGI pathway can lead to inhibition at several sites on the noradrenergic contractile pathway in the vascular smooth muscle, impairing IP3 production by phospholipase C (Hirata et al, 1990), IP3 receptor activity (Schlossmann et al, 2000), and the RhoA/Rho-kinase pathway (Sauzeau et al, 2000). However, interaction sites have not yet been identified in penile smooth muscle. A nitrergic-noradrenergic imbalance owing to defective nitrergic neurotransmission has been implicated in penile tissue from patients and in animal models with erectile dysfunction (Christ et al, 1995a; Cellek et al, 1999). Similar to the interaction between nitrergic and noradrenergic pathways, vasoconstrictive actions of endothelin have been shown to be inhibited by NO during erection (Mills et al, 2001).

A number of factors have been reported to increase both NOS activity and NO release. These include molecular oxygen, androgen, chronic administration of L-arginine, and repeated intracavernous injection of PGE1 (Kim N et al, 1993; Escrig et al, 1999; Marin et al, 1999). Decreased NOS activity has been associated with castration, denervation, hypercholesterolemia, and diabetes mellitus. Interaction of different types of NOS may also occur. For example, nNOS activity has been to shown to decrease and iNOS levels to increase after injection of transforming growth factor (TGF)-β1 into the penis (Bivalacqua et al, 2000), and eNOS levels are reportedly significantly higher in nNOS-knockout mice (Burnett et al, 1996).

In a study of neurotransmitters in human corpus cavernosum and spongiosum, Hedlund and colleagues (2000) reported that vesicular acetylcholine transporter (VAChT), vasoactive intestinal polypeptide (VIP), and neuronal nitric oxide synthase (nNOS) are found in the same nerve terminals. Tyrosine hydroxylase (TH) positive nerves do not contain VAChT, VIP, or NOS. Heme oxygenases (HO-1 and HO-2) and eNOS are localized to the endothelium. Interaction of these neurotrasmitters may modify the effect of parasympathetic and sympathetic activation on penile function.

Role of Caveolae. Caveolae are invaginated microdomains of plasma membrane that are rich in eNOS and caveolins, as well as cholesterol, sphingolipids, and glycosylphosphatidylinositol-linked proteins. In addition, caveolae contain numerous other signaling proteins such as receptors with seven-transmembrane domains, G-proteins, adenylyl cyclase, phospholipase C, protein kinase C, calcium pumps, and calcium channels. Decreased caveolin-1 expression has been reported in the cavernous smooth muscle of aged rat (Bakircioglu et al, 2001). Linder and colleagues (2006) demonstrated that penile erection requires association of soluble guanylyl cyclase with endothelial caveolin-1 in rat corpus cavernosum. Shakirova and colleagues (2009) reported that nerve-mediated relaxation of penile tissue from caveolin-1 deficient mice was impaired. Caveolon-1 in the cavernous smooth muscle and endothelium are both decreased after bilateral cavernous nerve injury (Becher et al, 2009). These reports strongly suggest that the caveolae and caveolin are involved in the regulation of penile function.

Central Neurotransmitters and Neural Hormones. **A variety of neurotransmitters (dopamine, norepinephrine,5-hydroxytestosterone [5-HT], and oxytocin) and neural hormones (oxytocin, prolactin) have been implicated in regulation of sexual function. It is suggested that dopaminergic and adrenergic receptors may promote sexual function and 5-HT receptors inhibit it** (Foreman and Wernicke, 1990).

Dopamine. There are many dopaminergic systems in the brain with ultrashort, intermediate, and long axons. The cell bodies are located in the ventral tegmentum, substantia nigra, and hypothalamus. One of these dopaminergic systems, the tuberoinfundibular system, secretes dopamine (DA) into the portal hypophysial vessels to inhibit prolactin secretion (Ganong, 1999a). Five different DA receptors have been cloned (D1 to D5), and several of these exist in multiple forms (Ganong, 1999b). **In men, apomorphine, which stimulates both D1 and D2 receptors, induces erection that is unaccompanied by sexual arousal** (Danjou et al, 1988). In male rats, Hull and colleagues (1992) have found that low levels of dopaminergic stimulation through the D1 receptor increase erection; higher levels or prolonged stimulation produces seminal emission through D2 receptors. The erectile response induced by injection of apomorphine into the paraventricular area can be suppressed by blockers of both DA and oxytocin receptors (Melis et al, 1989). Injection of oxytocin into the paraventricular area also induces erection, but this cannot be blocked by DA receptor blockers. These findings suggest that dopaminergic neurons activate oxytocinergic neurons in the paraventricular area and that the release of oxytocin produces erection (Melis et al, 1992).

In general terms, DA is supportive of copulation and 5-HT is inhibitory. DA is released in the MPOA at the time of ejaculation (5-HT is not), and changes in DA and 5-HT in different areas of the brain may promote copulation and sexual satiety, respectively (Hull et al, 1999). Testosterone enhances DA release in the MPOA at rest and with sexual challenge, possibly by upregulating NOS, which increases NO and thereby increases DA release. The same pattern of copulatory activity promoting DA release in the MPOA and the enhanced effect of the presence of sex hormones is seen in female rats. Longer-lasting changes may be seen through the postcopulatory effects of gene expression, and this expression increases with increased sexual experience, effectively changing the phenotype of certain cells in sexually experienced animals. Cells of the MPOA have high densities of α_2-noradrenergic receptors, as well as DA receptors, and the effects of DA in the MPOA are most likely assisted by the activation of α_2 (inhibition) and α_1 (excitation) adrenoceptors owing to cross-talk within central nervous system (CNS) catecholamine systems (Cornil et al, 2002).

DA agonists (apomorphine and pergolide) and DA uptake inhibitors (nomifensine and bupropion) have been reported to enhance sexual drive (Stimmel and Gutierrez, 2006). Sublingual apomorphine is available for the treatment of ED in many countries but its utility is limited due to emetic side effects. A selective DA D4 receptor agonist, ABT-724, has been shown to assist penile erection in a dose-dependent fashion in conscious rats; interestingly, this drug lacked emetic effects in a ferret model (Brioni et al, 2004; Osinski et al, 2005). A similar compound, ABT-670, with superior oral bioavailability has also been identified for potential clinical use (Patel et al, 2006).

Serotonin. Neurons containing 5-HT have their cell bodies in the midline raphe nuclei of the brainstem and project to a portion of the hypothalamus, limbic system, neocortex, and spinal cord (Ganong, 1999a). Currently, 5-HT receptors 1 to 7 have been cloned and characterized. Within the 5-HT1 group are the 5-HT1 A, B, D, E, and F subtypes. Within the 5-HT2 group are the 5-HT2 A, B, and C subtypes. There are two 5-HT5 subtypes, 5-HT5 A and B (Ganong, 1999b). **General pharmacologic data indicate that 5-HT pathways inhibit copulation, but 5-HT may have both facilitory and inhibitory effects on sexual function, depending on the receptor subtype, the receptor location, and the species investigated** (de Groat and Booth, 1993). Andersson and Wagner (1995) have summarized the results of administration of selective agonists and antagonists as follows: 5-HT1A receptor agonists inhibit erectile activity but assist ejaculation; stimulation of 5-HT2C receptors causes erection; and 5-HT2 agonists inhibit erection but assist seminal emission and ejaculation. Steers and de Groat (1989) have also shown increased firing of the cavernous nerve and erection when *m*-chlorophenylpiperazine, a 5-HT2C receptor agonist, is given to rats. Applying a novel 5-HT2c receptor agonist (YM348) and antagonist SB242084, Kimura and colleagues (2006) confirmed the pro-erectile effect of the 5-HT2c receptor stimulation in rats. Stimulation of both 5-HT2 and 5-HT2C receptors has also been reported to increase oxytocin secretion (Bagdy et al, 1992). In addition, 5-HT may also affect the spinal reflex because Marson and McKenna (1992) have reported that endogenous 5-HT may act in the lumbar cord to inhibit sexual reflexes.

5-HT is believed to be an inhibitory transmitter in the control of sexual drive (Foreman et al, 1989). Suppressed libido has been reported in patients taking fenfluramine, a 5-HT-releasing agent, but elevated libido occurred in patients taking buspirone, a 5-HT neuron suppressor (Buffum, 1982).

Norepinephrine. The cell bodies of the norepinephrine-containing neurons are located in the locus ceruleus and the A5-catecholaminergic cell group in the pons and medulla. The axons of these noradrenergic neurons ascend to innervate the paraventricular, supraoptic, and periventricular nuclei of the hypothalamus, the thalamus, and neocortex. They also descend into the spinal cord and the cerebellum. **Central norepinephrine transmission seems to have a positive effect on sexual function.** In both humans and rats, inhibition of norepinephrine release by clonidine, an α_2-adrenergic agonist, is associated with a decrease in sexual behavior, and yohimbine, an α_2-receptor antagonist, has been shown to increase sexual activity (Clark et al, 1985). β Blockers have also been implicated in sexual dysfunction, probably because of their central side effects such as sedation, sleep disturbances, and depression.

γ-Aminobutyric Acid. γ-Aminobutyric acid (GABA) activity in the PVN provides a mechanism to balance (inhibit) proerectile signaling. Agonism for the type A receptor for GABA in the PVN can reduce both pharmacologically (apomorphine) and physiologically induced erections (Melis et al, 2001).

Opioids. Endogenous opioids are known to affect sexual function, but the mechanism of action is far from clear. Injection of small amounts of morphine into the MPOA assists sexual behavior in rats. Larger doses, however, inhibit both penile erection and yawning induced by oxytocin or apomorphine. It is suggested that endogenous opioids may exert an inhibitory control on central oxytocinergic transmission (Argiolas, 1992). Injection of morphine into the paraventricular nucleus of the hypothalamus prevents noncontact penile erections and impairs copulation in rats. It is speculated that intracellular nitric oxide may be involved in this process (Melis et al, 1999).

Cannabinoids. Cannabinoid CB_1 receptor activation inhibits sexual function by modulating the paraventricular oxytocinergic neurons, which mediate erection. Antagonism of CB_1 receptors in the paraventricular nucleus of male rats induces penile erection, which seems to involve glutamic acid and nitric oxide (Melis et al, 2004, 2006).

Oxytocin. Oxytocin is a neural hormone secreted by the neurons into the circulation. These are found in the posterior pituitary gland, but, because they are also found in the neurons projecting from the PVN to the brainstem and spinal cord, oxytocin can also function as a neurotransmitter. The blood level is increased during sexual activity in humans and animals and, when injected into the paraventricular area in rats, oxytocin produces yawning and penile erection. Calcium has been suggested as the second messenger mediating oxytocin-induced penile erection. Oxytocin release following stimulation of dompamine receptors in the paraventricular nucleus influences the appetitive and reinforcing effects of sexual activity (Succu et al, 2007). Because neurons in the paraventricular area have been shown to contain NOS, and NOS inhibitors prevent apomorphine- and oxytocin-induced erection, it is suggested that oxytocin acts on neurons whose activity is dependent on certain levels of NO (Vincent and Kimura, 1992; Melis and Argiolas, 1993).

Nitric Oxide. Nitric oxide (NO) is a gaseous molecule produced from various tissues, in particular the endothelium and nerve. It mediates penile erection at the level of the PVN (Melis et al, 1998) and at other levels of the neural pathway supporting sexual response. The presence of NO and the soluble guanylyl cyclase needed to generate cGMP is seen throughout the human brain. The NO/cGMP pathway (see later) is affected by aging in the brain and offers a potentially significant but unexplored site for mediating the deleterious effects of age on sexual function (Ibarra et al, 2001). Reduced nNOS protein within the PVN leading to blunting of the erectile response has been reported in streptoxotosin-induced diabetic rats (Zheng et al, 2007). Testosterone or its metabolite dihydrotestosterone (DHT) downregulates NOS activity and mRNA expression and the number of nNOS-containing neurons (Singh et al, 2000). Direct evidence of the importance of NO in central signaling related to erectile function resulted from a series of experiments designed to alter CNS NO activity (Sato et al, 2001): Manipulation of NO or cGMP levels altered MPOA-triggered intracavernous pressure response through CNS, not peripheral, mechanisms.

Melanocortins. Melanocortin-4 receptor (MC4R), implicated in the control of food intake and energy expenditure, also modulates erectile function and sexual behavior. Evidence supporting this notion is based on several findings: (1) a highly selective nonpeptide MC4R agonist augments erectile activity initiated by electrical stimulation of the cavernous nerve in wild-type, but not MC4R-null, mice; (2) copulatory behavior is enhanced by administration of a selective MC4R agonist and is diminished in mice lacking MC4R; (3) RT-PCR and non-PCR-based methods demonstrate MC4R expression in the rat and human penis and rat spinal cord, hypothalamus, brainstem, and pelvic ganglion (major autonomic relay center to the penis) but not in rat primary corpus cavernosum smooth muscle cells; and (4) in situ hybridization of glans tissue from the human and rat penis reveals MC4R expression in nerve fibers and mechanoreceptors in the glans. Collectively, these data implicate MC4R in the modulation of penile erectile function and provide evidence that MC4R-mediated proerectile responses may be activated through neuronal circuitry in spinal cord erectile centers and somatosensory afferent nerve terminals of the penis (Van der Ploeg et al, 2002).

Prolactin. **Increased levels of prolactin suppress sexual function in men and experimental animals. In rats, high levels of prolactin decrease the genital reflex and disturb copulatory behavior** (Rehman et al, 2000). **It is suggested that the mechanism of prolactin's action is through inhibition of dopaminergic activity in the MPOA and decreased testosterone. In addition, prolactin may have a direct effect on the penis through its contractile effect on the cavernous smooth muscle** (Ra et al, 1996). In a study of sexual activity of married men with ED, men with sexual inactivity were noted to have a significanly higher mean prolactin level (Paick et al, 2006) (Table 23–8).

Smooth Muscle Physiology

Spontaneous contractile activity of cavernous smooth muscle has been recorded in vitro and in vivo. In isolated strips of rabbit corpus cavernosum, Mandrek (1994) demonstrated spontaneous mechanical activity with a frequency of 6 to 30 contractions per minute accompanied by fluctuations in membrane potential. In a human study, Yarnitsky and colleagues (1995) found two types of electrical activity recorded from the corpus cavernosum:

Table 23–8.
Central Neurotransmitters and Their Function

NEUROTRANSMITTER	RECEPTOR AND FUNCTION
Dopamine	D1 and D4 receptor—enhances erection D2 receptor—enhances seminal emission
Serotonin (5HT)	5HT—inhibits sex drive and spinal sexual reflex 5HT1A—inhibits erection, facilitates ejaculation 5HT2C—enhances erection
Norepinephrine	Enhances sexual function
Gamma-aminobutyric acid	Inhibits erectile signals
Opioids	Inhibit penile erection
Cannabinoids	Inhibit sexual function
Oxytocin	Enhances appetitive and reinforcing effects of sexual activity
Nitric oxide	Mediates erection at paraventricular nucleus
Melanocortins	McR4—enhances erection
Prolactin	Suppresses sexual function

spontaneous and activity induced. Levin and colleagues (1994) reported that in-vitro spontaneous contractile activity is correlated with a phasic increase in intracellular calcium and a biphasic change in the NADH/NAD ratio, suggesting an initial increase and then a decrease of intracellular energy. Italiano and colleagues (1998) suggested that phasic contraction of the penis is through the enzyme Na-K-ATPase and the resting tone is mediated by the endothelium through the release of $PGF2_a$. Field stimulation results in a decrease in tension and intracellular calcium at low frequencies and an increase in tension and intracellular calcium at high frequencies. In general, the response to pharmacologic agents correlates with the change in intracellular calcium: for example, phenylephrine produces muscle contraction and an increase in intracellular calcium, whereas nitroprusside causes the opposite.

In a study of myosin isoforms in smooth muscle cells in the corpus cavernosum, DiSanto and colleagues (1998) reported their overall composition to be between that in aorta and bladder smooth muscles, which generally express tonic- and phasic-like characteristics, respectively. Further studies of isoform changes may elucidate the increased contractility or impaired relaxation of the cavernous smooth muscle in pathologic conditions.

Molecular Mechanism of Smooth Muscle Contraction

Smooth muscle contraction and relaxation are regulated by intracellular free calcium (Ca^{2+}) acting through calmodulin. Calcium-bound calmodulin undergoes a conformational change, increasing its affinity for myosin light chain kinase (MLCK). MLCK is activated by binding of the calcium-calmodulin complex, leading to phosphorylation of the serine-19 residue of regulatory myosin light chain MLC_{20}. In the presence of ATP, this phosphorylation enables actin to activate the myosin ATPase and initiates cross-bridge cycling. Hydrolysis of ATP by ATPase supplies the energy for the contractile process (Fig. 23–9).

Regulatory Molecules Affecting Smooth Muscle Contraction. The muscle contractile process ends when MLC_{20} is dephosphorylated (inactivated) by myosin light chain phosphatase (MLCP). MLCP is a holoenzyme consisting of a type 1 phosphatase (PP1c), a myosin-targeting subunit (MYPT1), and a 20 kD subunit of unknown function (Hersch et al, 2004; Ito et al, 2004). Theoretically, MLCP inhibition may lead to enhanced smooth muscle contraction. This is also termed "calcium sensitization" pathway. The activity of MLCP can be modulated by Rho/Rho-kinase pathway (Fig. 23–10). Rho-kinase can phosphorylate multiple substrates including MYPT1, the 17 kD protein kinase C-potentiated inhibitor protein (CPI-17), and MLC_{20}. Phosphorylation of MYPT1 and CPI-17 results in the inhibition of PP1c phosphatase activity. RhoA and Rho-kinase have been shown to be expressed in penile smooth muscle (Rees et al, 2002; Wang et al, 2002). Interestingly, the amount of RhoA expressed in the cavernous smooth muscle is 17-fold that in vascular smooth muscle (Wang et al, 2002). A selective inhibitor of Rho-kinase has been shown to elicit relaxation of human corpus cavernosum in vitro and to induce erection in animal models (Chitaley et al, 2001; Rees et al, 2001). The emerging consensus is that phasic contraction of penile smooth muscle is regulated by an increase in cytosolic Ca2+ and that tonic contraction is governed by the calcium-sensitizing pathways (Cellek et al, 2002). The presence of CPI-17 protein has been detected in human and rabbit penile corpus cavernosum (Wang et al, 2002), but its functional significance remains to be determined.

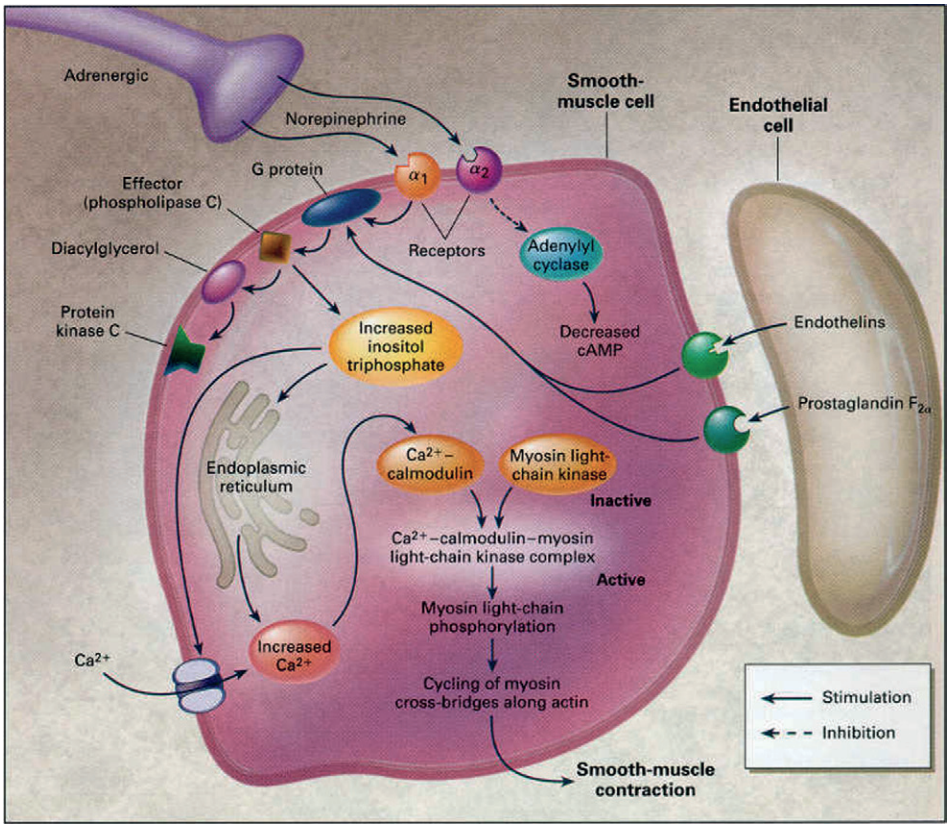


Figure 23–9. Molecular mechanism of penile smooth muscle contraction. Norepinephrine from sympathetic nerve endings and endothelins and prostaglandin $F_{2\alpha}$ from the endothelium activate receptors on smooth muscle cells to initiate the cascade of reactions that eventually result in elevation of intracellular calcium concentrations and smooth muscle contraction. Protein kinase C is a regulatory component of the Ca^{2+}-independent, sustained phase of agonist-induced contractile responses. (From Lue TF. Erectile dysfunction. N Engl J Med 2000;342:1802–13.Copyright © 2000 Massachusetts Medical Society. All rights reserved.)

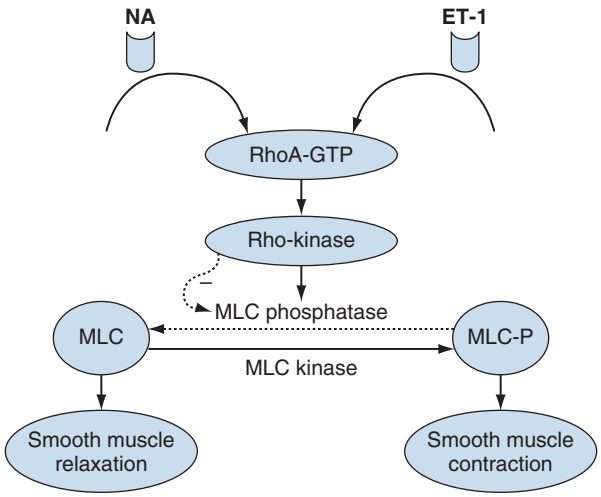


Figure 23–10. RhoA/Rho kinase pathway: the calcium sensitization pathway. ET-1, endothelin receptor 1; GTP, guanosine triphosphate; MLC, myosin light chain; MLC-P, phosphorylated myosin light chain; NA, noradrenalin.

Latch State—a Unique Characteristic of Smooth Muscle Contraction. Smooth muscle has the ability to maintain tension for prolonged periods with minimal energy expenditure. This efficiency has been termed the ***latch*** state and is critical for sustaining the "basal" tone of the smooth muscle. It has been proposed that dephosphorylated myosin remains bound to actin in the high-affinity state to help stabilize the latch state. Others have proposed that calponin participates in the latch state by simultaneously binding actin and myosin to stabilize cross-bridge interactions and slow the rate of detachment (Szymanski, 2004).

Pathways Involving IP_3, DAG, and PKC. Vasoconstrictor agonists such as norepinephrine (α_1-adrenergic receptors), endothelin-1 (ET_A receptors), angiotensin II (AT1 receptors), prostaglandin $F_{2\alpha}$ (FP receptors), and thromboxane A_2 (TP receptors) bind their respective receptors to activate Gq, which in turn stimulates phospholipase C beta (PLC-β). This membrane-bound enzyme hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) to liberate inositol 1,4,5-trisphosphate (IP_3) and 1,2-diacylglycerol (DAG). IP_3 binds to specific receptors (IP_3R) on the smooth endoplasmic reticulum (SER) to stimulate the release of Ca^{2+} from intracellular stores. Binding of IP_3 to these receptors not only activates the channel but also increases the sensitivity of the IP_3R to Ca^{2+} and assists ***calcium-induced calcium release*** (CICR).

Another mechanism of increased intracellular Ca^{2+} is by permitting entry of extracellular Ca^{2+} through ***receptor-operated channels*** without a change in membrane potential (Large, 2002). Norepinephrine, endothelin, vasopressin, and angiotensin II cause the opening of Ca^{2+}-permeable, nonselective cation channels.

Molecular Mechanism of Smooth Muscle Relaxation

After contraction, relaxation of the muscle follows a decrease of free Ca^{2+} in the sarcoplasm. Calmodulin then dissociates from myosin light-chain kinase and inactivates it. Myosin is dephosphorylated by myosin light-chain phosphatase and detaches from the actin filament, and the muscle relaxes (Walsh, 1991) (Fig. 23–11).

Another mechanism of smooth muscle relaxation is through cyclic adenosine monophosphate (cAMP) and cGMP, which are the two major second messengers involved in smooth muscle relaxation. They activate cAMP- and cGMP-dependent protein kinases, which in turn phosphorylate certain proteins and ion channels, resulting in (1) opening of the potassium channels and hyperpolarization; (2) sequestration of intracellular calcium by the endoplasmic reticulum; and (3) inhibition of voltage-dependent calcium channels, blocking calcium influx. The consequence is a drop in cytosolic free calcium and smooth muscle relaxation.

Cyclic AMP-Signaling Pathway. Cyclic-AMP-signaling molecules include adenosine, calcitonin gene–related peptides (CGRPs), prostaglandins, and vasoactive intestinal peptide (VIP).

Adenosine. Adenosine is released from a variety of cells as a result of increased metabolic rates, and its actions on the vasculature are most prominent when oxygen demand is high (Tabrizchi and Bedi, 2001). However, the vascular response to the action of adenosine can be either relaxation or constriction, depending on which type of adenosine receptor is activated. Currently four AR subtypes (A1, $A2_A$, $A2_B$, and A3) belonging to the gene protein–coupled receptor (GPCR) superfamily have been recognized (Tabrizchi and Bedi, 2001). In general, the A1 receptor is believed to be coupled to G_i and G_o proteins, and its activation results in inhibition of adenylyl cyclase (AC) and activation of phospholipase C, both of which lead to vasoconstriction. The A2 receptors are coupled to the G_s proteins, and their activation stimulates AC and thus vasorelaxation. The A3 receptor is coupled to G_i and G_q proteins, and its activation results in the activation of phospholipase C/D and the inhibition of AC, leading to vasoconstriction. The differential distribution of these adenosine receptor subtypes largely determines whether a particular vessel relaxes or contracts as a result of adenosine stimulation (Tabrizchi and Bedi, 2001). Whether adenosine plays a role in physiologic erection is unclear. **Nevertheless, excessive adenosine accumulation in the penis, coupled with increased A(2B)R signaling, contributes to priapism in two independent lines of mutant mice. One is adenosine deaminase (ADA)-deficient mice (the only animal displaying spontaneously prolonged penile erection), and the other is sickle cell disease (SCD) transgenic mice, a well-accepted animal model for priapism** (Bivalacqua et al, 2009; Dai et al, 2009).

Calcitonin Gene–Related Peptide Family. Calcitonin gene–related peptide, amylin, and adrenomedullin are members of the CGRP family. These short-chain peptides are potent vasodilators released from perivascular nerve fibers. They act through the calcitonin receptor–like receptor (CRLR), which belongs to the GPCR superfamily (Conner et al, 2002).

In rats the CGRP levels in the penis, bladder, kidney, testis, and adrenal gland were found to increase gradually up to maturity and then rapidly decline (Wimalawansa, 1992). In ED patients given CGRP intracavernously, a dose-related increase in penile arterial inflow (and erection) occurred (Stief et al, 1991). Adenovirus-mediated gene transfer of CGRP also enhanced erectile responses in aged rats, apparently through an increase of cAMP levels in the corpora cavernosa (Bivalacqua et al, 2001). Intracavernous administration of adrenomedullin also results in cavernous relaxation; however, the effect is through an NO-cGMP, rather than cAMP, pathway (Nishimatsu et al, 2001).

Prostaglandins. Prostaglandins (PGs) are a family of eicosanoids capable of initiating numerous biologic functions. The prime mode of PG action is through specific PG receptors that all belong to the GPCR family. There are at least nine known PG receptor subtypes in mouse and humans, as well as several additional splice

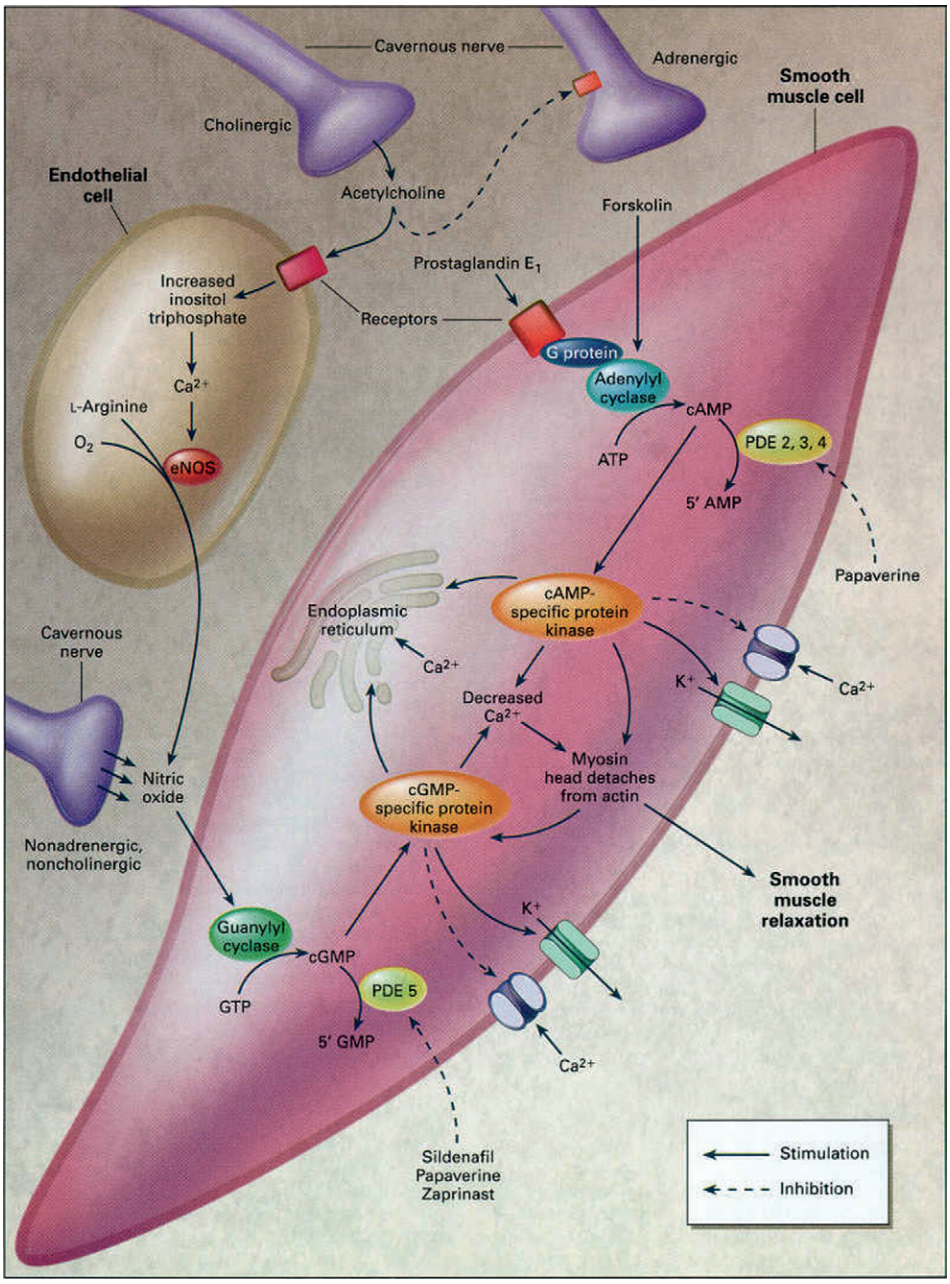


Figure 23–11. Molecular mechanism of penile smooth muscle relaxation. The intracellular second messengers mediating smooth muscle relaxation, cAMP and cGMP, activate their specific protein kinases, which phosphorylate certain proteins to cause opening of potassium channels, closing of calcium channels, and sequestration of intracellular calcium by the endoplasmic reticulum. The resultant fall in intracellular calcium leads to smooth muscle relaxation. Sildenafil inhibits the action of PDE5 and thus increases the intracellular concentration of cGMP. Papaverine is a nonspecific phosphodiesterase inhibitor. eNOS, endothelial nitric oxide synthase; GTP, guanosine triphosphate. (From Lue TF. Erectile dysfunction. N Engl J Med 2000;342:1802–13. Copyright © 2000 Massachusetts Medical Society. All rights reserved.)

variants with divergent carboxyl termini (Narumiya and FitzGerald, 2001). Four of the subtypes (EP1-EP4) bind PGE2, two (DP1 and DP2) bind PGD2, and the other three subtypes (FP, IP, and TP) bind $PGF2_{\alpha}$, PGI2, and TXA2, respectively. On the basis of signaling attributes, the PG receptors are classified into three types. The "relaxant" receptors IP, DP1, EP2, and EP4 are coupled to an α_s-containing G-protein and therefore are capable of stimulating AC to increase intracellular cAMP. The "contractile" receptors EP1, FP, and TP are coupled to an α_q-containing G-protein, which activates phospholipase C instead of AC. These contractile receptors therefore do not signal through the cAMP pathway, and their signaling outcome is an increase of intracellular calcium. The EP3 receptor is also a contractile receptor, but it is coupled to an α_i-containing G-protein that inhibits AC to result in a decrease of cAMP formation.

Animal and human corpora cavernosa produce several PGs including $PGF2_{\alpha}$, PGE2, PGD2, PGI2, and TXA2 (Moreland et al, 2001). In studies in isolated human penile tissue, different PGs have been shown to elicit different effects in human corpus cavernosum, corpus spongiosum, and cavernous artery (Hedlund and Andersson, 1985). Although $PGF2_{\alpha}$, PGI2, and TXA2 contract the corpus cavernosum and corpus spongiosum, PGE1 and PGE2 (but not PGI2) relax the corpus cavernosum and spongiosum that have been precontracted with noradrenaline or $PGF2_{\alpha}$. Therefore although PGI2 is the predominant vasorelaxant in blood vessels, its action in the erectile tissue is either contractile or neutral. This disparity in the action of PGI2 between blood vessels and the erectile tissue and the difference between the effects of PGI2 and PGE1/2 in the erectile tissue are most likely due to differences in the distribution of PG receptors. Indeed, recent

studies have shown that, in the corpus cavernosum, the relaxant effects of prostanoids are mediated by EP2 and/or EP4 receptors (for PGE1 and PGE2) but not IP receptor (for PGI2) (Angulo et al, 2002).

Although the production of PGs and the expression of PG receptors in the erectile tissue have been clearly demonstrated, their roles in physiologic erection are yet to be defined. On the other hand, **the erectogenic effects of PGE1 as a pharmaceutic agent have been extensively documented. First described in 1998, intracavernous injection of PGE1 is one of the safest and most effective treatments for ED** (Stackl et al, 1988). Transurethral application is an effective alternative.

Vasoactive Intestinal Peptide. The human or animal penis is richly supplied with nerves containing VIP (Andersson, 2001). Two subtypes of VIP receptors, VPAC1 and VPAC2, belonging to the GPCR family have been cloned from human and rat tissues. VPAC2, but not VPAC1 mRNA, has been identified in cultured rat cavernous smooth muscle cells (CSMCs) (Guidone et al, 2002). In the dog, intracavernous VIP injection has been found to induce penile erection (Juenemann et al, 1987); in men, it has not produced rigid erection but can improve success rates when combined with papaverine and phentolamine (Kiely et al, 1989). However, it has been shown that VIP release is not essential for neurogenic relaxation of human cavernous smooth muscle (Pickard et al, 1993), and VIP failed to stimulate cAMP production in cultured human CSMCs (Palmer et al, 1994).

Adenylyl Cyclase. Signaling molecules in the cAMP pathway bind to and activate specific cytoplasmic membrane receptors that, through their coupled G-proteins, activate ACs. To date, nine membrane-bound isoforms and one soluble form of mammalian AC have been cloned and characterized (Patel et al, 2001). Although different membrane-bound ACs are regulated differently, they are all stimulated by the GTP-bound form of the G_α subunit and are all (except AC9) stimulated by forskolin.

In rabbits with alloxan-induced diabetes, cAMP formation in the corpus cavernosum in response to forskolin has been shown to be reduced, suggesting impaired AC function in diabetes mellitus (Sullivan et al, 1998).

Protein Kinase A. PKA, also called cAMP-dependent kinase (cAK), is the principal receptor for cAMP, and it mediates the vast majority of the cellular effects of cAMP by phosphorylating a wide variety of downstream targets in both the cytoplasmic and nuclear compartments (Johnson et al, 2001). PKA is composed of two regulatory (R) and two catalytic (C) subunits that form a tetrameric holoenzyme R_2C_2. Binding of cAMP to the R subunits causes the holoenzyme to dissociate into an $R_2(cAMP)_4$ dimer and two free catalytically active C subunits. The presence of multiple C subunit genes further adds to the diversity and complexity of the various holoenzyme complexes, which differ in biochemical and functional properties, as well as patterns of expression and localization. These differences among the isozymes contribute to the broad specificity of PKA in a wide variety of physiologic processes in response to cAMP signaling.

More than 100 different cellular proteins have been identified as physiologic substrates of PKA, with more than 90% (135 of 145) being phosphorylated at serine and the remainder at threonine (Shabb, 2001). The predominant target sequence (>50%) is Arg-Arg-X-Ser, in which Ser is the phosphate acceptor. Three PKA substrate proteins have been identified in penile tissue: PDEs, cAMP-responsive element-binding protein (CREB), and ATP-sensitive potassium (K_{ATP}) channel.

Cyclic GMP-Signaling Pathway. Signaling molecules in the cGMP pathway include nitric oxide, carbon monoxide, and natriuretic peptides.

Nitric Oxide (NO). Because of its small size, NO can diffuse inside its target cell, where it interacts with molecules that contain iron in either a heme or iron-sulfur complex. The most physiologically relevant receptor for NO is soluble guanylyl cyclase (sGC), and the NO-sGC-cGMP pathway is responsible for the vasorelaxing effect of many endothelium-dependent vasodilators including histamine, estrogens, insulin, corticotrophin-releasing hormone, nitrovasodilators, and acetylcholine. This pathway is also principally responsible for erection.

Synthesis of NO is catalyzed by NOS, which converts L-arginine and oxygen to L-citruline and NO. NOS exists as three isoforms in mammals: nNOS and eNOS are preferentially expressed in neurons and endothelial cells, respectively, and iNOS in virtually all cell types. All three NOS isoforms have been identified in the corpus cavernosum, with nNOS and eNOS being considered responsible for initiating and sustaining erection, respectively (Hurt et al, 2002). Downregulation of nNOS expression has been found in the corpus cavernosum of aging rats (Carrier et al, 1997), a model in which corpus cavernous smooth muscle relaxation is impaired (Cartledge et al, 2001). Despite its secondary role in erectile function, the endothelium-dependent cavernous smooth muscle relaxation is attenuated in the aging rabbit, and this age-related defect is paradoxically accompanied with upregulated eNOS expression in both the endothelium and cavernous smooth muscle (Haas et al, 1998; Bakircioglu et al, 2001). A contradictory observation, however, was made in another study, which showed downregulation of eNOS in the corpus cavernosum of aging rats (Rajasekaran et al, 2002).

Gene transfer of nNOS or eNOS to the penis has been shown to augment erectile responses in aging rats (Champion et al, 1999; Magee et al, 2002), and gene transfer of iNOS has enhanced intracavernous pressure (Chancellor et al, 2003). However, despite these encouraging results, it should be noted that mice with disrupted nNOS or eNOS gene have normal erectile function (Burnett et al, 1996; Burnett et al, 2002). Compensatory mechanisms, alternative splicing of the disrupted gene (Ferrini et al, 2003), and/or other unknown mechanisms are possibly involved in the preservation of erectile function in the NOS-knockout mice.

Carbon Monoxide (CO). CO is a gaseous second messenger that occurs in biologic systems during the oxidative catabolism of heme by the heme oxygenase (HO) enzyme. HO exists as constitutive (HO-2, HO-3) and inducible isoforms (HO-1). The latter is upregulated in response to multiple stress stimuli. HO-1 confers protection in vitro and in vivo against oxidative cellular stress. CO regulates vascular processes such as vessel tone, smooth muscle proliferation, and platelet aggregation and may function as a neurotransmitter. The neurotransmitter effect of CO is dependent on the activation of guanylate cyclase by direct binding to the heme moiety of the enzyme, stimulating the production of cyclic AMP. Recent research indicates that CO exerts novel anti-inflammatory and anti-apoptotic effects dependent on the modulation of the p38 mitogen–activated protein kinase (MAPK)–signaling pathway. By virtue of these effects, CO confers protection in oxidative lung injury models and likely plays a role in HO-1–mediated tissue protection (Ryter et al, 2002).

Natriuretic Peptides. The natriuretic peptide family is involved in the regulation of cardiovascular homeostasis and consists of atrial (ANP), brain (BNP), and C-type (CNP) natriuretic peptides (Matsuo, 2001). Whereas ANP and BNP are ligands for the NPR-A

receptor, CNP is a ligand for the NPR-B receptor. Both receptors are members of the guanylyl cyclase (GC) family and are therefore also called GC-A and GC-B.

The effects of ANP, BNP, and CNP on cGMP production and smooth muscle relaxation in isolated human and animal corpus cavernosum and in cultured CSMCs have been investigated (Kim et al, 1998; Guidone et al, 2002; Kuthe et al, 2003). The results indicate that CNP is the most potent natriuretic peptide and that it relaxes the isolated cavernous smooth muscle by binding to NPR-B. However, whether CNP and NPR-B play a role in physiologic erection remains to be seen.

Guanylyl Cyclase. In mammals, seven membrane-bound (particulate) GC isoforms (GC-A to GC-G) and one soluble isoform (sGC) have been identified (Andreopoulos and Papapetropoulos, 2000). On the basis of their ligand specificity, the particulate GCs (pGCs) have been classified as (1) natriuretic peptide receptors (GC-A and GC-B), which are activated by natriuretic peptides including ANP, BNP, and CNP; (2) intestinal peptide receptor (GC-C), which is activated by intestinal peptides including guanylin, uroguanylin, and lymphoguanylin; and (3) orphan receptors (GC-D, -E, -F, and -G). Although the membrane-bound GC system is not known to play a role in physiologic erection, expression of GC-B in human and rat corpus cavernosum and induction of cavernous smooth muscle relaxation by CNP (ligand for GC-B) have been demonstrated recently (Guidone et al, 2002; Kuthe et al, 2003).

The soluble isoform sGC plays a pivotal role in erectile function because it provides the link between NO and cGMP, which represent the extracellular and intracellular signaling molecules, respectively, in physiologic erection (Andersson, 2001). A heterodimeric protein, sGC consists of α and β subunits, each of which exists in two isoforms (α1, α2, and β1, β2) that are encoded by two separate genes (Andreopoulos and Papapetropoulos, 2000). Messenger RNAs of these four subunits have been detected in human corpus cavernosum (Behrends et al, 2000). In animal studies, sGC activator YC-1 has been shown to cause erectile responses (Mizusawa et al, 2002). However, mmunohistochemical examination has found sGC expression to be similar in the corpus cavernosum of potent and impotent patients (Klotz et al, 2000).

Protein Kinase G. Protein kinase G (PKG), also called cGMP-dependent kinase (cGK), is the principal receptor and mediator for cGMP signals. In mammals, PKG exists in two major forms, PKG-I and PKG-II, which are encoded by two separate genes. In smooth muscle, only PKGI is expressed and exists as two splice variants (PKG-Iα and PKG-Iβ). Immunoprecipitation studies in smooth muscle indicate that PKG-Iβ is associated with IP_3R and a 125 kD protein known as ***IP_3R-associated PKG substrate*** (IRAG), both of which act as substrates for the kinase (Schlossmann et al, 2000). Phosphorylation of IP_3R and IRAG decreases agonist-induced Ca^{2+} release from the smooth endoplasmic reticulum (SER). Deletion mutation studies demonstrate that IRAG is a critical protein in mediating cGMP-dependent relaxation of smooth muscle (Geiselhöringer et al, 2004). In addition, PKG-I is known to phosphorylate phospholamban, a small membrane-associated protein (6 kD homopentamer) that constitutively inhibits SER. Phosphorylation of phospholamban inactivates its inhibitory control of SER Ca^{2+}-ATPase pump (SERCA) and increases Ca^{2+} reuptake into the SER, where Ca^{2+} is bound by proteins such as calsequestrin and calreticulin. Interestingly, cAMP-mediated relaxation is unaffected by mutated, nonfunctional IRAG (Geiselhöringer et al, 2004), whereas PKA can phosphorylate phospholamban to increase Ca^{2+} reuptake (Raeymaekers et al, 1988) Thus the combined actions of PKG-I and PKA inhibit Ca^{2+} release from intracellular stores and stimulate Ca^{2+} reuptake.

Additionally, and perhaps of equal importance, cGMP and/or PKGI may induce relaxation via activation of the plasma membrane Ca^{2+}-ATPase pump, inhibition of IP_3 generation, inhibition of Rho-kinase, stimulation of MLCP, and phosphorylation of heat shock proteins (Carvajal et al, 2000; Lincoln et al, 2001). These mechanisms have been demonstrated in various cells, but their relevance to smooth muscle cells in genital tissues has not been explicitly shown. The PKG-I polypeptide contains three functional domains: the N-terminal, the regulatory, and the catalytic. The N-terminal domain has three functions: dimerization, autoinhibition, and localization. The regulatory domain contains two tandem cGMP-binding sites, and the catalytic domain catalyzes the transfer of the γ phosphate from ATP to a serine/threonine residue of the substrate protein.

Cavernous smooth muscle strips from PKG-I knockout mice cannot be relaxed by agents that raise cGMP levels, and these mice have a low ability to reproduce, presumably owing to ED (Hedlund et al, 2000). This observation further affirms the essential role of the cGMP/PKG-I pathway in physiologic erectile function.

Cross-Activation. Increased levels of intracellular cAMP and cGMP cause the activation of ***cAMP-dependent*** and ***cGMP-dependent protein kinases*** (PKA and PKG). Each cyclic nucleotide-dependent kinase can be activated by either cAMP or cGMP, although cross-activation requires an approximately 10-fold higher concentration of cyclic nucleotide (Walsh, 1994). Although PKA and PKG may phosphorylate a number of common substrates, several lines of evidence indicate that the activation of PKG by cGMP and cAMP is the predominant mechanism by which cyclic nucleotides decrease intracellular Ca^{2+} to cause vascular smooth muscle relaxation (Lincoln et al, 1990; Jiang et al, 1992; Komalavilas and Lincoln, 1996). On the other hand, PKA (but not PKG) can inhibit Ca^{2+}-calmodulin activation of MLCK by phosphorylation and may play an important role in Ca^{2+} desensitization of the contractile apparatus (Hathaway et al, 1985).

Phosphodiesterase. In each episode of cyclic nucleotide signaling, the increase of intracellular cAMP or cGMP concentration is typically twofold to threefold baseline (Francis et al, 2001). Decline occurs rapidly and often during the continued presence of the signaling hormone (Francis et al, 2001). Termination of cyclic nucleotide signals is principally carried out by PDEs, which catalyze the hydrolysis of cAMP and cGMP to AMP and GMP, respectively. Feedback mechanisms that increase PDE activities and/or expression by the increased cyclic nucleotide level assist cyclic nucleotide degradation (Corbin et al, 2000; Lin et al, 2001a, 2001b).

The superfamily of mammalian PDEs consists of 11 families (PDE1 to PDE11) that are encoded from 21 distinct genes (Lin et al, 2003; Montorsi et al, 2004). Each PDE gene usually encodes more than one isoform through alternative splicing or from alternate gene promoters. Phosphodiesterase-1, PDE3, PDE4, PDE7, and PDE8 are multigene families, whereas PDE2, PDE5, PDE9, PDE10, and PDE11 are unigene families. PDE1, PDE2, PDE3, PDE10, and PDE11 hydrolyze both cAMP and cGMP; PDE4, PDE7, and PDE8 hydrolyze cAMP; and PDE5, PDE6, and PDE9 are specific for cGMP.

With the exception of PDE6, which is specifically expressed in photoreceptor cells, all PDEs have been identified in the corpus cavernosum (Küthe et al, 2001). However, there is ample evidence that **PDE5 is by far the principal PDE for the termination of cavernous cGMP signaling** (Fig. 23–12) (e.g., inhibition of

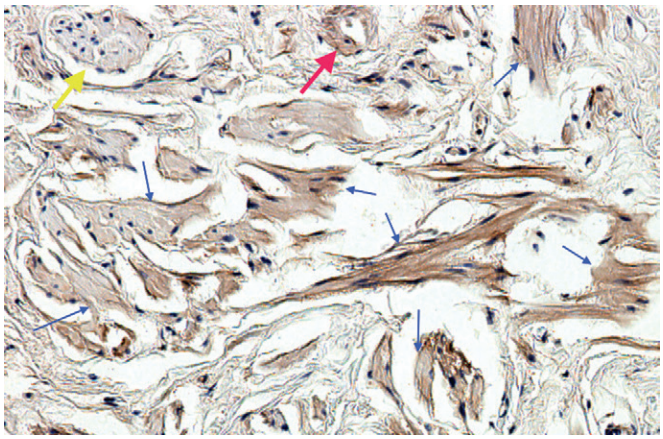


Figure 23–12. Immunohistochemistry of human penile tissue, showing positive PDE5 staining of cavernous smooth muscle fibers *(small blue arrows),* nerve *(yellow arrow),* and blood vessel wall *(red arrow)* (×100).

the cGMP-catalytic activity of PDE5 by specific inhibitors has been shown to be highly effective in treating ED) (Eardley et al, 2002).

Phosphodiesterase-3 also appears to play a role in erection, as demonstrated by the erectogenic effect of a PDE3-specific inhibitor, milrinone (Kuthe et al, 2002). Furthermore, although direct inhibition of PDE5 is the main mechanism through which sildenafil exerts its erectogenic effect, it has been shown that sildenafil also significantly increases cAMP concentration in isolated human cavernous tissue strips (Stief et al, 2000). This effect is thought to involve PDE3 because cGMP, which is accumulated as a result of PDE5 inhibition by sildenafil, is capable of preventing cAMP degradation by competing for the same catalytic sites on the PDE3 molecules (Francis et al, 2001). This attenuating effect of cGMP on the cAMP-catalytic activity of PDE3 is also believed to explain why inhibition of PKG could suppress the relaxing effect of forskolin in isolated human cavernous smooth muscle (Uckert et al, 2004).

Ion Channels. In general, there are four major types of ion channels: (1) external ligand-gated, which open to a specific extracellular molecule (e.g., acetylcholine); (2) internal ligand-gated, which open or close in response to an intracellular molecule (e.g., ATP); (3) voltage-gated, which open in response to a change in membrane potential (e.g., sodium, potassium, and calcium channels); and (4) mechanically gated, which open in response to mechanical pressure.

Smooth muscle has neither a T-tubule system nor a well-developed sarcoplasmic reticulum. Therefore extracellular calcium plays an important role, and calcium must enter the cytoplasm through the plasma membrane during an action potential. Three transmembrane proteins are known to regulate calcium inflow and outflow: Calcium channels are the major inflow regulators, whereas the calcium-sodium exchanger and calcium-ATPase regulate calcium exit from muscle cells. The presence of voltage-dependent L-type calcium channels (long-duration current, slow calcium channel) in isolated cavernous smooth muscle and cultured muscle cells has been documented. Christ and colleagues (1993) have reported that both calcium influx through calcium channels and mobilization of intracellular calcium stores are involved during phenylephrine- and endothelin-induced contraction, but only calcium channel influx is apparent for potassium chloride-induced contraction.

Studies have shown at least four types of potassium channel subtypes in the cavernous smooth muscle: (1) the calcium-sensitive potassium channel (e.g., maxi-K); (2) the metabolically regulated potassium channels (K_{ATP}); (3) the delayed rectifier; and (4) the fast transient A current (IA) (Christ et al, 1993a; Fan et al, 1995). The calcium-sensitive potassium channels may be involved in cAMP-mediated smooth muscle relaxation. Decreased intracytosolic potassium and altered potassium conductance have been shown to occur in acetylcholine- and sodium nitroprusside-treated corpus cavernosum smooth muscle (Seftel et al, 1996). A stretch-sensitive chloride channel has also been demonstrated in CSMCs (Fan et al, 1999).

Hyperpolarization of the Smooth Muscle Cells. Hyperpolarization causes closure of voltage-dependent calcium channels, a decrease in the intracellular free calcium concentration, and relaxation of the smooth muscle. One of the hyperpolarization mechanisms is through the opening of potassium channels. The opening of ATP-sensitive K+ channels (KATP) and Ca^{2+}-activated K+ channels (KCa) causes hyperpolarization and relaxation of vascular smooth muscle. These two types of channels are present in human corpus cavernosum smooth muscle (Christ et al, 1993b), and pharmacologic stimulation of KATP channels induces penile smooth muscle relaxation (Venkateswarlu et al, 2002). Furthermore, PNU-83757, an opener of KATP channels, has been shown to induce erection when given intracavernously to patients with ED (Vick et al, 2002). The opening of large-conductance KCa channels, also known as *maxi-K,* has been found to hyperpolarize and relax human corpus cavernosum (Spektor et al, 2002). The opening of K+ channels can be stimulated by PKA, PKG, or cGMP.

Hyperpolarization of penile smooth muscle is also important in endothelium-dependent relaxation of human penile arteries, in which significant relaxation remains despite blockade of NO and prostaglandin synthesis (Angulo et al, 2003). This activity has been attributed to the endothelium-derived hyperpolarizing factor (EDHF), which opens KCa channels and produces hyperpolarization and vasodilation. The nature of EDHF remains undetermined.

Molecular Oxygen as a Modulator of Penile Erection. The pO_2 level of cavernous blood in the flaccid state is similar to that of venous blood (≈35 mm Hg). During erection, the large inflow of arterial blood raises pO_2 to approximately 90 mm Hg (Sattar et al, 1995). Molecular oxygen is a substrate, together with L-arginine, for the synthesis of NO by NOS. In the flaccid state the low oxygen concentration inhibits NO synthesis; during erection, the higher level of substrate induces NO synthesis. It has been estimated that the minimal concentration of oxygen in the cavernous bodies necessary to reach full NOS activity is 50 to 60 mm Hg (Kim et al, 1993).

Similarly, prostaglandin H synthase is also an oxygenase (cyclooxygenase) and uses oxygen as substrate for the synthesis of prostanoids. Production of PGE1 has been shown to be inhibited in flaccidity and stimulated during erection. Endothelin synthesis is also modulated by oxygen: a low oxygen concentration promotes production, whereas a high concentration inhibits it.

Intercellular Communication. During erection and detumescence, communication should exist among cavernous smooth muscles to mediate synchronized relaxation and contraction (Christ et al, 1991). **Several studies have demonstrated the presence of gap junctions in the membrane of adjacent muscle cells. These intercellular channels allow exchange of ions such as calcium and second-messenger molecules** (Christ et al, 1993a). The major component of gap junctions is connexin-43, a membrane-sparing protein of less than 0.25 μm

that has been identified between smooth muscle cells of human corpus cavernosum (Campos de Calvalho et al, 1993). Cell-to-cell communication through these gap junctions most likely explains the synchronized erectile response, although their pathophysiologic impact is still unclear.

Intracavernous Tissue Architecture

The trabeculae of the corpora cavernosa provide the structural support and regulatory mechanism for the endothelial-lined sinusoidal spaces, as well as the conduit for blood vessels and nerves. Relaxation of the trabeculae allows the expansion and filling of the sinuoids by the incoming blood, while "recoil" of the trabeculae expels blood to the emissary veins and returns the penis to a flaccid state. In 24 men undergoing penile prosthesis implantation for severe ED, Nehra and colleagues (1996) categorized the smooth muscle content of the corpus cavernosum into four groups: high (39% to 42%), intermediate (30% to 37%), low (13% to 29%), and normal (42% to 50%) and reported that increasing degree of venous leakage correlates with decreasing muscle content. Costa and colleagues (2006) showed that the major constituents of the trabeculae are collagen fibers (40.8%), smooth muscle (40.4%), and elastic fibers (13.2%) in specimens from six men who died of nongenital causes. Interestingly, in seven men undergoing penile prosthesis implantation, the content of the three components were collagen fibers (41.6%), smooth muscle (42%), and elastic fibers (9.1%); the only significant change in ED compared with normals was a reduction of elastic fibers. From these two reports, it seems likely that the histologic changes associated with ED consist primarily of decline in either smooth muscle or elastic fibers.

The complex architecture of the penis is maintained by the dynamic expression and interaction of numerous trophic factors. One of them is sonic hedgehog (SHH), which plays a key role in regulating vertebrate organogenesis such as the growth of digits on limbs and organization of the brain. SHH remains important in the adult. It controls cell division of adult stem cells and has been implicated in development of some cancers. SHH has been identified in the penis; inhibition of SHH in the adult rat leads to rapid atrophy and disorganization of the corpus cavernosum (Podlasek et al, 2003, 2005). **In addition, SHH has been shown to stimulate the expression of vascular endothelial growth factor (VEGF) and nitric oxide synthase (NOS) in the penis** (Podlasek et al, 2005) (Table 23–9).

Key Points: Smooth Muscle Physiology

- Relaxation of the cavernous smooth muscle is the key to penile erection.
- Nitric oxide released by nNOS contained in the terminals of the cavernous nerve initiates the erection process, whereas nitric oxide released from eNOS in the endothelium helps maintain erection.
- Upon entering the smooth muscle cells, NO stimulates the production of cGMP.
- Cyclic GMP activates protein kinase G, which in turn opens the potassium channels and closes the calcium channels.
- Low cytosolic calcium favors smooth muscle relaxation.
- The smooth muscle regains its tone when cGMP is degraded by phosphodiesterase.

Table 23–9.

Key Molecules Involved in the Physiologic Regulation of Cavernous Smooth Muscle

Contraction	
NAME	FUNCTION
High cytosolic calcium	Binds calmodulin to activate MLC kinase
MLC kinase	Converts MLC to active form, MLCp
Phosphorylated MLC (MCLp)	Cycling of myosin cross-bridges along actin results in muscle contraction
MLC phosphatase	Dephosphrylate MLCp to inactive form, MLC
Rho kinase	Inhibits MLC phosphatase to enhance contraction (calcium sensitization pathway)
Relaxation	
NAME	FUNCTION
Nitric oxide	Bind soluble guanylyl cyclase to produce cGMP
cGMP	Activate protein kinase G
Protein kinase G	Opens potassium channels and closes calcium channels
Low cytosolic calcium	Calcium dissociates from calmodulin, muscle relaxes

PATHOPHYSIOLOGY OF ERECTILE DYSFUNCTION

Incidence and Epidemiology

The increasing incidence of impotence with age was noted by Kinsey and colleagues in 1948: only 1 of 50 men at age 40 years, but 1 in 4 by age 65. In 1990 Diokno and colleagues reported that 35% of married men aged 60 years and older suffer from erectile impotence.

Modern probability sampling techniques were used by two surveys obtaining prevalence data of ED in the United States: the Massachusetts Male Aging Study (MMAS) and the National Health and Social Life Survey (NHSLS). The MMAS consisted of 1709 noninstitutionalized men between the ages of 40 and 70 years living in the greater Boston area first surveyed between 1987 and 1989 and resurveyed between 1995 and 1997 (Feldman et al, 1994; Johannes et al, 2000). Extensive physiologic measures, demographic information, and self-reported ED status (nine items related to potency on a questionnaire) were components of this report. The MMAS was the first cross-sectional, community-based, random-sample, multidisciplinary epidemiologic survey on ED and its physiologic and psychosocial correlates in men in the United States. **From the prevalence rates reported in the MMAS study, between the ages of 40 and 70 years, the probability of complete ED increased from 5.1% to 15%, moderate dysfunction increased from 17% to 34%, and mild dysfunction remained constant at about 17%.**

The NHSLS was a national probability survey of men ($N = 1410$) and women between the ages of 18 and 59 years living in households in the United States in 1992 (Laumann et al, 1999) and was principally a broad-ranging inquiry into sexual practices and beliefs within that age group. Therefore the survey collected only limited information on sexual function broadly defined. The following prevalence rates for ED were reported (responses to questions regarding obtaining and maintaining erection): 7% for ages 18 to 29 years, 9% for ages 30 to 39, 11% for ages 40 to 49, and 18% for ages 50 to 59.

Regarding worldwide prevalence of ED, 24 international studies were reported between 1993 and 2003 (Lewis et al, 2004). All that were stratified by age showed a rising prevalence of ED. Below age 40 the rate was 1% to 9%, from 40 to 59 it ranged from 2% to 9% to as high as 20% to 30%, with some studies showing marked differences between the 40 to 49 and the 50 to 59 groups. The 50- to 59-year groups showed the greatest range of reported prevalence rates. For the group from 60 to 69 years, most of the world showed a rather high rate (20% to 40%), with some increasing after age 65, except for the Scandinavian reports, in which the 70s and older were the time of major rate change. Almost all of the reports showed high prevalence rates for men in their 70s and 80s, ranging from 50% to 75%.

Incidence Studies

The MMAS (Johannes et al, 2000) is the only longitudinal study conducted in the United States (1987-1989 and 1995-1997). Analyses were performed on 847 of the 1297 men without ED at baseline (1987-1989) and with follow-up information from 1995 to 1997. The average age of these men at baseline was 52.2 years (range, 40 to 69 years). **From this group of patients, the crude incidence rate of impotence in white men in the United States was 25.9 cases/1000 man-years (95% confidence interval [CI], 22.5 to 29.9). The annual incidence rates increased with each decade (per 1000 man-years): 12.4 cases for 40 to 49 years; 29.8 cases for 50 to 59 years; and 46.4 cases for 60 to 69 years. Age-adjusted risk (per 1000 man-years) of ED was higher for men with diabetes mellitus (50.7 cases), treated heart disease (58.3 cases), and treated hypertension (42.5 cases). By using these data and the known population of the United States, it was estimated that, for white men, the new cases in the 40- to 69-year age group would be 617,715 per year** (Lewis et al, 2000). **Rates reported from Europe and Brazil also suggest an incidence of 25 to 30/1000 man-years** (Moreira et al, 2003; Schouten et al, 2005). A study using a validated questionnaire in a random sample of 2213 men conducted in Olmsted County, MN, from 1996 to 2004 revealed that the five sexual function domains change together over time in this community-based cohort. Erectile function, ejaculatory function, and sexual drive decrease over time with greater rates of decline for older men. However, older men are less likely to perceive these declines as a problem and are less likely to express dissatisfaction referable to them (Gades et al, 2009).

Risk Factors

Common risk factor categories associated with sexual dysfunction include the following: general health status, diabetes mellitus, cardiovascular disease, concurrence of other genitourinary disease, psychiatric/psychologic disorders, other chronic diseases, and socio-demographic conditions. In a study of race/ethnicity and socioeconomic status in 2301 men aged 30 to 79 years from the city of Boston, it is reported that men in the low socioeconomic status (SES) category had a greater than twofold increase in risk of ED (adjusted odds ratio of 2.26, 95% confidence interval 1.39, 3.66). The increased risk of ED in Black and Hispanic men in this study was thought to be associated with differences in SES rather than biologic factors (Kupelian et al, 2008).

For ED, smoking, medications, and hormonal factors also serve as well-defined risk-factor-associated conditions. In men, diabetes has been associated with a greater prevalence of decreased desire and orgasmic dysfunction, as well as ED. A higher odds ratio is seen with insulin-dependent diabetes mellitus; diabetes present for more than 10 years; fair or poor control based on glycosylated hemoglobin; management by means other than diet; a history of diabetes-related arterial, renal, or retinal disease and neuropathy; and concurrent cigarette smoking. Endothelial dysfunction is a condition present in many cases of ED, and thus there are common etiologic pathways for other vascular disease states (Lewis et al, 2004).

Classification

Many classifications have been proposed (Fig. 23–13). Some are based on the cause (diabetic, iatrogenic, traumatic) and some on the neurovascular mechanism (failure to initiate [neurogenic], failure to fill [arterial], and failure to store [venous] [I. Goldstein, personal communication, 1990]). A classification recommended by the International Society of Impotence Research is shown in Table 23–10 (Lizza and Rosen, 1999).

Psychogenic

Previously, psychogenic impotence was believed to be the most common, thought to affect 90% of impotent men (Masters and Johnson, 1965). This belief has given way to the realization that **ED is usually a mixed condition that may be predominantly functional or physical.**

Sexual behavior and penile erection are controlled by the hypothalamus, limbic system, and cerebral cortex. Therefore stimulatory or inhibitory messages can be relayed to the spinal erection centers to assist or inhibit erection. **Two possible mechanisms have been proposed to explain the inhibition of erection in psychogenic dysfunction: direct inhibition of the spinal erection center by the brain as an exaggeration of the normal suprasacral inhibition** (Steers, 2000); **and excessive sympathetic outflow or elevated peripheral catecholamine levels, which may increase penile smooth muscle tone to prevent its necessary relaxation.** Animal studies demonstrate that the stimulation of sympathetic nerves or systemic infusion of epinephrine causes detumescence of the erect penis (Diederichs et al, 1991a, 1991b). Clinically, higher levels of serum norepinephrine have been reported in patients with

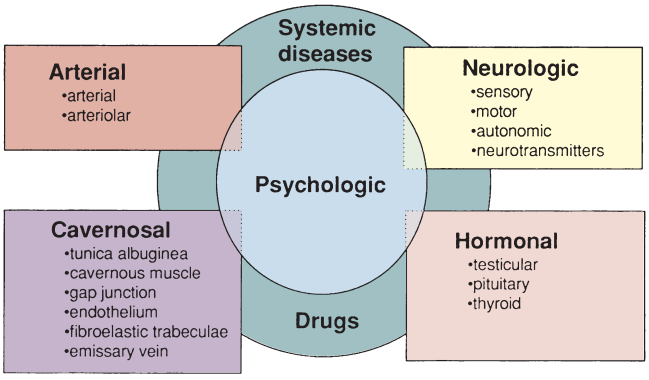


Figure 23–13. A functional classification of impotence. Note that it is unlikely for an individual patient's impotence to derive solely from one source. Most cases have a psychogenic component of varying degree, and systemic diseases and pharmacologic effects can be concomitant and causative. (Modified from Carrier S, Brock G, Kour NW, Lue TF. Pathophysiology of erectile dysfunction. Urology 1993;42:468–81, with permission of Exerpta Medica, Inc.)

Table 23–10.

Classification of Male Erectile Dysfunction

Organic

I. Vasculogenic
  A. Arteriogenic
  B. Cavernosal
  C. Mixed
II. Neurogenic
III. Anatomic
IV. Endocrinologic

Psychogenic

I. Generalized
  A. Generalized unresponsiveness
    1. Primary lack of sexual arousability
    2. Aging-related decline in sexual arousability
  B. Generalized inhibition
    1. Chronic disorder of sexual intimacy
II. Situational
  A. Partner-related
    1. Lack of arousability in specific relationship
    2. Lack of arousability owing to sexual object preference
    3. High central inhibition owing to partner conflict or threat
  B. Performance-related
    1. Associated with other sexual dysfunction/s (e.g., rapid ejaculation)
    2. Situational performance anxiety (e.g., fear of failure)
  C. Psychologic distress or adjustment related
    1. Associated with negative mood state (e.g., depression) or major life stress (e.g., death of partner)

psychogenic ED than in normal controls or patients with vasculogenic ED (Kim and Oh, 1992).

Bancroft and Janssen theorized that male sexual response depends on the balance between excitatory and inhibitory impulses within the CNS (Bancroft and Junssen, 2000). One example is the high prevalence of sexual/erectile dysfunction in men with psychiatric disorders. Mosaku and Ukpong (2009) surveyed patients (mean age 39.6, standard deviation [SD] = 11.6 years) carrying the diagnosis of schizophrenia, bipolar affective disorder, recurrent depressive disorder, and/or substance use disorder with mean duration of illness of 10.24 years (SD 8.2 years) who were attending a psychiatry clinic. In this population the prevalence of ED was 83%; older age, unmarried status, use of medications, and the presence of comorbid medical conditions were significantly predictive of ED.

Neurogenic

It has been estimated that 10% to 19% of ED is neurogenic. If one includes iatrogenic causes and mixed ED, the prevalence is likely much higher. The presence of a neurologic disorder or neuropathy does not exclude other causes, and confirming that ED is neurogenic can be challenging. Because erection is a neurovascular event, **any disease or dysfunction affecting the brain, spinal cord, and cavernous or pudendal nerves can induce dysfunction.**

As discussed earlier, the MPOA, the PVN, and the hippocampus have been regarded as important integration centers for sexual drive and erection (Sachs and Meisel, 1988), and pathologic processes in these regions such as **Parkinson disease, stroke, encephalitis, or temporal lobe epilepsy are often associated with ED.** Parkinsonism's effect may result from the imbalance of the dopaminergic pathways (Chaudhuri and Schapira, 2009). **Other brain lesions associated with ED are tumors, dementias, Alzheimer disease, Shy-Drager syndrome, and trauma.** In studies of sexual function in men after stroke, lack of sexual desire was found to be common (Jung et al, 2008). ED is more prevalent in patients who have cerebrovascular accident lesions in the thalamic area (Jeon et al, 2009).

In men with a **spinal cord injury,** its nature, location, and extent will largely determine erectile function. In addition to ED, they may also have impaired ejaculation and orgasm. **Reflexogenic erection is preserved in 95% of patients with complete upper-cord lesions but in only about 25% of those with complete lower-cord lesions** (Biering-Sørensen and Sønksen, 2001). Sacral parasympathetic neurons are important in the preservation of reflexogenic erection, although the thoracolumbar pathway may compensate for sacral loss through synaptic connections. In these patients, minimal tactile stimulation can trigger erection, albeit of short duration and requiring continuous stimulation. **Other disorders at the spinal level** (e.g., spina bifida, disc herniation, syringomyelia, tumor, transverse myelitis, and multiple sclerosis) **may affect the afferent or efferent neural pathway in a similar manner.**

Because of the close relationship between the cavernous nerves and the pelvic organs, the incidence of iatrogenic impotence from pelvic surgical procedures is reportedly high: radical prostatectomy, 43% to 100% (Walsh and Donker, 1982; Borchers et al, 2006), and abdominal perineal resection, 15% to 100% (Weinstein and Roberts, 1977).

An improved understanding of the neuroanatomy of the pelvic and cavernous nerves (Walsh and Donker, 1982) has resulted in modified surgery for cancer of the rectum, bladder, and prostate, producing a lower incidence of iatrogenic impotence. For example, the introduction of nerve sparing has reduced the incidence of impotence after radical prostatectomy to 30% to 50% (Catalona and Bigg, 1990; Quinlan et al, 1991) and less than 10% after radical rectal surgery (Liang et al, 2008).

In cases of **pelvic fracture,** ED can be a result of cavernous nerve injury or vascular insufficiency or both. In men with posterior urethral injury, early realignment has been associated with better potency preservation rate relative to delayed anastomosis (ED rate 34% vs. 42%) (Mouraviev et al, 2005). In **diabetics,** impairment of neurogenic and endothelium-dependent relaxation results in inadequate NO release (Saenz de Tejada, 1989a). Because autonomic penile innervation cannot be tested directly, clinicians should be cautious in diagnosing neurogenic ED. A corpus cavernosum electromyograph has been developed and refined for diagnosis of various conditions affecting the penis (including autonomic neuropathy), but the clinical utility of this device is still under investigation (Meuleman et al, 2007).

A decrease in penile tactile sensitivity with increasing age was also reported by Rowland and colleagues (1993). Sensory input from the genitalia is essential to achieve and maintain reflexogenic erection, and the input becomes even more important when older people gradually lose psychogenic erection. Therefore sensory evaluation should be an integral part of the evaluation for ED in all patients with or without an apparent neurologic disorder.

Endocrinologic

Hypogonadism is a frequent finding in the impotent population. Androgens influence the growth and development of the male reproductive tract and secondary sex characteristics; their effects on libido and sexual behavior are well established. In a review of published articles from 1975 to 1992, Mulligan and

Schmitt (1993) **concluded that testosterone (1) enhances sexual interest; (2) increases the frequency of sexual acts; and (3) increases the frequency of nocturnal erection, but has little or no effect on fantasy-induced or visually stimulated erections.** Granata and colleagues (1997) have reported that the threshold level of testosterone for normal nocturnal erections is about 200 ng/dL. In a population-based, observational survey conducted in the Boston area, Araujo and colleagues (2007) reported a 5.6% prevalence of symptomatic androgen deficiency in men between the ages of 30 and 79 years, with older men at greater risk. Prevalence of symptoms were low libido (12%), erectile dysfunction (16%), osteoporosis/fracture (1%), and two or more nonspecific symptoms (20%); however, it is noteworthy that many men with low testosterone levels are asymptomatic. In a study of patients presented with ED, Köhler and colleagues (2008) reported androgen deficiency symptoms in 47%, 33%, 23%, and 7% in men with testosterone levels of less than 200, less than 300, less than 346, and less than 400 ng/dL, respectively. Age, the presence of uncontrolled diabetes, high total cholesterol, and anemia all correlated with significantly decreased testosterone levels in men with ED. In another report from the same group, waist circumference was noted to be the most important predictor of low testosterone and symptomatic androgen deficiency (Hall et al, 2008). In men with BMI of more than 30 kg/m^2, total testosterone was subnormal in 57.5% and free testosterone subnormal in 35.6% of the subjects. Most of these men had isolated hypogonadotropic hypogonadism (Hofstra et al, 2008). In a comprehensive literature review, Traish and colleagues (2009) noted that low testosterone precedes elevated fasting insulin, glucose, and hemoglobin A1c (HbA1C) values in men who develop diabetes, suggesting that hypogonadism may be a sentinel event in the development of diabetes. **The authors further suggest that androgen deficiency is associated with insulin resistance, type 2 diabetes, metabolic syndrome, and increased deposition of visceral fat. Visceral fat may serve as an endocrine organ, producing inflammatory cytokines and thus promoting endothelial dysfunction and vascular disease.**

The mechanism of androgen's effect has been examined by several investigators. Beyer and González-Mariscal (1994) have reported that testosterone and dihydrotestosterone (DHT) are responsible for male pelvic thrusting and estradiol or testosterone is responsible for female pelvic thrusting during copulation. Androgens have beneficial effects on endothelial cells and smooth-muscle cells: androgens promote endothelial cell survival, reduce endothelial expression of proinflammatory markers, and inhibit proliferation and intimal migration of vascular smooth-muscle cells. Low androgen levels are associated with apoptosis of endothelial cells and smooth-muscle cells. Moreover, low androgen levels impair proliferation, migration, and homing of endothelial progenitor cells, as well as myogenic differentiation of mesenchymal progenitor cells (Mirone et al, 2009). Testosterone and dihydrotestosterone may also relax penile artery and cavernous smooth muscle through their nongenomic effects (Waldkirch et al, 2008). In rats, castration has been reported to decrease arterial flow, induce venous leakage, and reduce the erectile response to stimulation of the cavernous nerve by about 50% (Mills et al, 1994; Penson et al, 1996). Castration also increases α-adrenergic responsiveness of penile smooth muscle (Traish et al, 1999). Clinically, many men on long-term androgen ablation therapy for prostate cancer have reported poor libido and ED.

Any dysfunction of the hypothalamic-pituitary axis can result in hypogonadism. Hypogonadotropic hypogonadism can be congenital or caused by a tumor or injury; hypergonadotropic hypogonadism may result from a tumor, injury, surgery, or mumps orchitis.

Hyperprolactinemia, whether from a pituitary adenoma or drugs, results in both reproductive and sexual dysfunction. Symptoms may include loss of libido, ED, galactorrhea, gynecomastia, and infertility. Hyperprolactinemia is associated with low circulating levels of testosterone, which appear to be secondary to inhibition of gonadotropin-releasing hormone secretion by the elevated prolactin levels (Leonard et al, 1989). Interestingly, in a study of subjects consulting for sexual dysfunction, prolactin in the lowest quartile levels was noted to be associated with metabolic syndrome and arteriogenic ED, as well as with premature ejaculation and anxiety symptoms (Corona et al, 2009).

ED may also be associated with both hyperthyroidism and hypothyroidism. The former is commonly associated with diminished libido (which may be caused by the increased circulating estrogen levels) and less often with ED. In hypothyroidism, low testosterone secretion and elevated prolactin levels contribute to ED.

Arteriogenic

Atherosclerotic or traumatic arterial occlusive disease of the hypogastric-cavernous-helicine arterial tree can decrease the perfusion pressure and arterial flow to the sinusoidal spaces, thus increasing the time to maximal erection and decreasing the rigidity of the erect penis. In the majority of patients with arteriogenic ED, the impaired penile perfusion is a component of the generalized atherosclerotic process. Common risk factors associated with arterial insufficiency include hypertension, hyperlipidemia, cigarette smoking, diabetes mellitus, blunt perineal or pelvic trauma, and pelvic irradiation (Feldman et al, 1994; Martin-Morales et al, 2001). Shabsigh and colleagues (1991) reported that abnormal penile vascular findings increased significantly as the number of risk factors for ED increased. On arteriography, bilateral diffuse disease of the internal pudendal, common penile, and cavernous arteries has been found in impotent patients with atherosclerosis. Focal stenosis of the common penile or cavernous artery is most often seen in young patients who have sustained blunt pelvic or perineal trauma (Levine et al, 1990). **Long-distance cycling is also a risk factor for vasculogenic and neurogenic ED.** The impact of cycling on penile circulation seems to depend on the rider position and the seat design (Cohen and Gross, 2005; Dettori and Norvell, 2006; Gemery et al, 2007; Schrader et al, 2008).

Erectile dysfunction and cardiovascular disease share the same risk factors such as hypertension, diabetes mellitus, hypercholesterolemia, and smoking (Feldman et al, 1994; Martin-Morales et al, 2001). Lesions in the pudendal arteries are much more common in impotent men than in the general population of similar age. Interestingly, natural remission and progression do occur in a substantial number of men with erectile dysfunction. The association of body mass index with remission and progression, as well as the association of smoking and health status with progression, offer potential avenues for facilitating remission and delaying progression using lifestyle intervention (Travison et al, 2007).

Atherosclerosis/Cardiovascular Diseases. High prevalence of ED has been reported in men with coronary, cerebral, and peripheral vascular diseases (Kloner et al, 2003; Montorsi et al, 2003; Bener et al, 2008; Chai et al, 2009). Among men

with coronary arterial disease, the prevalence of ED increases as the severity of coronary arterial lesions increases (Montorsi et al, 2006). Similarly, cardiovascular diseases are also prevalent in men with ED, and ED tends to manifest before other signs of cardiovascular disease. In patients with chronic coronary disease who also had ED, onset of sexual dysfunction occurred before CAD onset in 93%, with a mean time interval of 24 (12 to 36) months (Montorsi et al, 2006). This has led some to advocate screening for ED as a means to identify men at risk for cardiovascular disease (Jackson, 2008).

Hyperlipidemia. Erectile dysfunction has been associated with a high prevalence of hyperlipidemia and coronary heart disease (Roumeguere et al, 2003). Hypercholesterolemia at baseline was also shown to be a predictor of subsequent ED over the course of 25 years in 570 male patients included in the Rancho Bernardo Study (Fung et al, 2004). On the other hand, a survey of 1899 men aged 30 to 79 in the Boston area did not show an association between untreated hyperlipidemia and ED (Hall et al, 2009). Although several reports suggest an association of ED and dyslipidemia, there is no consistency in the involvement of the different lipid fractions. Therefore a subcommittee of the Sexual Medicine Society of North America has suggested a more precise analysis of hyperlipidemia as an independent risk factor for ED (Mulhall et al, 2006).

The effect of hypercholesterolemia on erectile function has been studied in different experimental models. In hypercholesterolemic rabbits, examination of the corpus cavernosum ultrastructure revealed an early atherosclerotic process in the sinusoids (Kim et al, 1994). Although the endothelial NO/cGMP pathway is impaired in this model, neuronal vasodilation does not appear affected (Azadzoi et al, 1998). The NO/cGMP pathway effect likely owes to increased superoxide production (Kim et al, 1997) or endogenous NOS inhibitors such as NG-monomethyl-L-arginine monoacetate (L-NMMA) and asymmetric dime thylarginine (ADMA). L-arginine supplementation reverses endothelium-dependent relaxation impairment (Azadzoi et al, 1998). Vascular endothelial growth factor (VEGF) is an important angiogenic factor for maintenance of endothelial health. Ryu and colleagues (2006) reported that VEGF and VEGF receptor 2 (VEGFR-2) are downregulated in the corporal tissue of rats eating a 4% cholesterol diet for 3 months. In rabbits fed with 1% cholesterol diet, Xie and colleagues (2005) also noted that levels of VEGF mRNA are reduced with subsequent observation of impaired endothelium-dependent relaxation.

Studies have also been conducted in apolipoprotein E knockout mice. After being fed a moderate- to high-cholesterol diet, these mice developed atherosclerosis and ED with reduced endothelium-dependent and endothelium-independent relaxation, as well as alteration of structure of the cavernosal tissue (Behr-Roussel et al, 2006; Xie et al, 2007).

In a more severe ischemic experimental model, rabbits underwent balloon de-endothelization of the iliac arteries followed by a high-cholesterol diet (Azadzoi et al, 1992). They developed both penile arterial insufficiency and veno-occlusive dysfunction owing to decreased expandability of the cavernous smooth muscle (Azadzoi et al, 1997; Nehra et al, 1998). Changes in iliac and penile vasculature were noted, associated with decreased NOS activity and reduced endothelium-dependent and neurogenic NO-mediated relaxation of the cavernous tissue (Azadzoi et al, 1999). As a result of the impaired NO activity, production of contractile thromboxane and prostaglandin increased, leading to potentiation of neurogenic contractions of the cavernous smooth muscle (Azadzoi et al, 1998, 1999).

In large arteries in rabbits, oxidized low-density lipoproteins (ox-LDLs) inhibited endothelium-dependent NO-mediated relaxation (Murohara et al, 1994). Enhanced corpus cavernosum muscle contractility by ox-LDL has also been reported by Ahn and colleagues (1999).

Hypertension. **Hypertension is an independent risk factor for ED** (Feldman et, 1994; Johannes et al, 2000), **and its consequent cardiovascular complications such as ischemic heart disease and renal failure are associated with even higher ED prevalence** (Feldman et, 1994; Kaufman et al, 1994; Johannes et al, 2000). **However, in hypertension, the increased blood pressure itself does not impair erectile function; rather, the associated arterial biochemical and structural changes are thought to be the causes** (Hsieh et al, 1989; Behr-Roussel et al, 2005).

In two analyses including more than 270,000 men with ED from a U.S. care claim database, the prevalence of hypertension in men with and without ED were 41.2% versus 19.2%, respectively (Seftel et al, 2004; Sun and Swindle, 2005).

The potential determinants for ED in hypertensive men include older age, longer duration of disease, greater severity of hypertension, and the use of antihypertensive medications (Doumas et al, 2006). Other researchers have studied arterial function and intima/media thickness in hypertensive men with ED and have suggested that high levels of the endogenous inhibitor of eNOS, asymmetric dimethylarginie (ADMA), are a potential marker of endothelial dysfunction (Vlachopoulos et al, 2008).

In animal models of spontaneously hypertensive rats (SHR) and DOCA-salt hypertensive rats, intracavernous pressure was decreased in two studies when expressed as a percentage of mean arterial pressure (Dorrance et al, 2002; Behr-Roussel et al, 2005). However, the absolute increases in intracavernous pressure did not appear different. Interestingly, in the longitudinal study of the SHR rats, the impairment of cavernosal endothelium-dependent and independent relaxation occurred before systemic vascular alteration, suggesting that corporal vascular tissue is affected early in the disease process (Behr-Roussel et al, 2005). In SHR rats, the impairment appears to involve both NO-mediated and carbon monoxide (CO)-mediated relaxation (Ushiyama et al, 2004). Treating these rats with an antioxidant, alpha-tocopherol, enhanced both NO- and CO-mediated relaxation, as well as endothelial function, suggesting that oxidative stress may play a significant role in this condition (Ushiyama et al, 2008). Increased activity of angiotensin II–mediated NADPH-oxidase in hypertensive rats is suggested to be the cause of increased superoxide anions (Jin et al, 2008).

Mechanism of Vascular Erectile Dysfunction

Structural Changes. In arteriogenic ED, oxygen tension in corpus cavernosum blood is less than that in psychogenic ED (Tarhan et al, 1997). Formation of PGE_1 and PGE_2 is oxygen dependent, and, in rabbit and human corpus cavernosum, increased oxygen tension was associated with elevation of PGE_2 and suppression of TGF-β1-induced collagen synthesis (Moreland et al, 1995; Nehra et al, 1999). A decrease in oxygen tension may diminish cavernous trabecular smooth muscle content and lead to diffuse venous leakage (Saenz de Tejada et al, 1991; Nehra et al, 1998).

A narrowed lumen or increased wall-to-lumen ratio in the arteries contributes to increased peripheral vascular resistance in hypertension. Increased resistance has also been found in the penile vasculature of SHR—an alteration ascribed to structural changes of the arterial and erectile tissue (Gradin et al, 2006; Arribas et al, 2008). Mitochondrial damage (in both smooth muscle and endothelial cells) and nerve degeneration have been described in SHR

rats (Jiang et al, 2005). Partial success in the prevention/reversal of the structural changes has been described when rats are treated with type 1 angiotensin II receptor (AT1) blocker, AT1 blocker with phosphodiesterase type 5 inhibitor, and a selective β_1 blocker, nebivolol (Mazza et al, 2006; Toblli et al, 2006).

Enhanced Smooth Muscle Contraction and Vasoconstriction. Enhanced basal and myogenic tone has been observed in arteries from hypertensive rats (Schubert and Mulvany, 1999). The RhoA/Rho kinase calcium sensitization pathway is responsible for maintenance of muscle tone. Both hypercholesterolemia and hypertension enhance smooth muscle tone via RhoA/Rho kinase activity (Morikage et al, 2006; Fibbi et al, 2008). Interestingly, both statins and Rho kinase inhibitors enhance the erectile effect of PDE 5 inhibitors in hypertensive rats (Wilkes et al, 2004; Fibbi et al, 2008).

Endothelin-1 (ET-1) levels are elevated in plasma of men with atherosclerosis, hypertension, and hypercholesterolemia. Men with organic ED have higher venous and cavernous blood levels of ET-1 as well (Nohria et al, 2003; El Melegy et al, 2005). Despite this, a pilot study using an ETa receptor antagonist as a treatment for men with ED did not produce positive results (Kim et al, 2002). On the other hand, angiotensin type 1 receptor antagonist and angiotensin conversion enzyme inhibitor have shown promise in the treatment of men with ED hypertension and atherosclerosis, respectively (Speel et al, 2005; Baumhakel et al, 2008).

Impaired Endothelium-Dependent Smooth Muscle Relaxation. Endothelial dysfunction has been proposed as the common link between cardiovascular disease and ED (Brunner et al, 2005). Impairment of endothelium-dependent flow-mediated dilation (FMD) of the brachial artery has been reported in men with ED, and the degree of impairment correlates with the severity of ED (Kovacs et al, 2008). On the other hand, a plethysmography device designed to assess endothelium-dependent vasodilation of the penis did not find a correlation between brachial and penile arteries in ED men (Vardi et al, 2009).

Endothelial progenitor cells (EPCs) are regenerative cells produced in bone marrow that migrate to peripheral vessels to repair endothelial defects. The number of EPCs is reduced in men with ED and coronary heart disease, as well as in overweight men (Foresta et al, 2005; Baumhakel et al, 2006; Esposito et al, 2009). Importantly, both acute and chronic administration of PDE 5 inhibitors increases the number of circulating EPCs and improves both endothelial and erectile function (Foresta et al, 2005, 2009).

In SHR, the relaxing effect of acetylcholine is blunted in corporeal strips (Behr-Roussel et al, 2003). Impairment of endothelium-dependent relaxation in arteries from SHR could be ascribed to angiotensin II (Rajagopalan et al, 1996), thromboxane, and superoxide (Cosentino et al, 1998) or to high blood pressure per se (Paniagua et al, 2000) (Table 23–11).

Table 23–11.

Vascular and Structural Changes Leading to Erectile Dysfunction (ED)

PENILE STRUCTURE	CHANGES IN ED
Cavernous artery	Increased vascular resistance, narrow lumen
Smooth muscle	Increased tone (hypertonicity)
	Decreases muscle content
	Alteration of K channels and GAP junctions
Erectile tissue	Fibrosis
	Impaired veno-occlusive mechanism
Endothelium	Impaired endothelium dependent relaxation
Tunica albuginea	Alteration of elastic and collagen fibers
Neurotransmitters	Decreased nNOS, eNOS

Cavernous (Venogenic)

Failure of adequate venous occlusion has been proposed as one of the most common causes of vasculogenic impotence (Rajfer et al, 1988). **Veno-occlusive dysfunction may result from a variety of pathophysiologic processes: degenerative tunical changes; fibroelastic structural alterations; insufficient trabecular smooth muscle relaxation; and venous shunts.**

Degenerative changes (Peyronie disease, old age, and diabetes) or traumatic injury to the tunica albuginea (penile fracture) can impair the compression of the subtunical and emissary veins (Gonzalez-Cadavid, 2009). **In Peyronie disease, the inelastic tunica albuginea may prevent the emissary veins from closing** (Metz et al, 1983). Chiang and colleagues (1992) have postulated that a decrease in the elastic fibers of the tunica albuginea and an alteration in its microarchitecture may contribute to impotence in some men. Changes in the subtunical areolar layer may impair the veno-occlusive mechanism, as is occasionally seen in patients after surgery for Peyronie disease (Dalkin and Carter, 1991).

Structural alterations in the fibroelastic components of the trabeculae, cavernous smooth muscle, and endothelium may result in venous leakage. Insufficient trabecular smooth muscle relaxation, causing inadequate sinusoidal expansion and insufficient compression of the subtunical venules, may occur in anxious individuals with excessive adrenergic tone or in patients with inadequate neurotransmitter release. It has been shown that alteration of an α adrenoceptor or a decrease in NO release may heighten smooth muscle tone and impair relaxation in response to endogenous muscle relaxant (Christ et al, 1990).

Acquired venous shunts—the result of operative correction of priapism—may cause persistent glans/cavernosum or cavernosum/spongiosum shunting.

Fibroelastic Component. Loss of compliance of the penile sinusoids associated with increased deposition of collagen and decreased elastic fiber may be seen in diabetes, hypercholesterolemia, vascular disease, penile injury, or old age. Sattar and colleagues (1994) have reported significant differences in the mean percentage of penile elastic fibers: 9% in normal men; 5.1% in patients with venous leakage; and 4.3% in patients with arterial disease. In an animal model of vasculogenic ED, Nehra and colleagues (1998) demonstrated that cavernous expandability correlates with smooth muscle content and may be used to predict trabecular histology. Moreland and colleagues (1995) have shown that PGE1 suppresses collagen synthesis by TGF-β1 in human cavernous smooth muscle, which implies that intracavernous injection of PGE1 may be beneficial in preventing intracavernous fibrosis.

Smooth Muscle. Because corporeal smooth muscle controls the vascular events leading to erection, a change in smooth muscle content and ultrastructure can be expected to affect erectile response. In a study of human penile tissue, Sattar and colleagues (1996) demonstrated a significant difference between the mean percentage of cavernous smooth muscle in normal potent men, stained with antidesmin (38.5%) or antiactin (45.2%), and that in a venogenic group (antidesmin, 27.4%; antiactin, 34.2%) or arteriogenic group (antidesmin, 23.7%, antiactin, 28.9%). An in-vitro biochemical study has shown impaired neurogenic and

endothelium-related relaxation of penile smooth muscle in impotent diabetic men (Saenz de Tejada et al, 1989a). In vasculogenic and neurogenic ED, the damaged smooth muscle can be a key factor, aggravating the primary cause (Mersdorf et al, 1991). Pickard and colleagues (1994) have also shown impairment of nerve-evoked relaxation and α-adrenergic-stimulated contraction of cavernous muscle, as well as reduced muscle content in men with venous or mixed venous/arterial impotence.

Ion channels are intimately involved in the biochemical events of muscle function. Fan and colleagues (1995) reported an alteration of the maxi-K^+ channel in cells from impotent patients and suggested that this might contribute to decreased hyperpolarizing ability, altered calcium homeostasis, and impaired smooth muscle relaxation. In animal studies, Junemann and colleagues (1991) showed significant smooth muscle degeneration with loss of cell-to-cell contact in rabbits fed a high-cholesterol diet for 3 months. In a rabbit model of vasculogenic impotence, Azadzoi and colleagues (1997) demonstrated that veno-occlusive dysfunction could be induced by cavernous ischemia. Cavernous nerve injury may also affect cavernous smooth muscle relaxation, as demonstrated in neurotomized dogs (Paick et al, 1991).

Gap Junctions. These intercellular communication channels are responsible for synchronization and coordination of the erectile response (Christ et al, 1991). In severe arterial disease, the presence of collagen fibers between cell membranes reduces or abolishes their contact (Persson et al, 1989). In aged and streptozotocin-induced diabetic rats, Suadicani and colleagues (2009) reported a significant decrease of gap junction protein connexin 43 in the corpus cavernosum.

Endothelium. By release of vasoactive agents, the endothelium of the corpus cavernosum can modify the tone of adjacent smooth muscle and affect the development or inhibition of erection. NO, prostaglandins, and the polypeptide endothelins have been identified in endothelial cells (Ignarro et al, 1990; Saenz de Tejada et al, 1991a, 1991b). Activation of cholinergic receptors on endothelial cells by acetylcholine or the cells' expansion as a result of increased blood flow may elicit underlying smooth muscle relaxation through the release of NO (Saenz de Tejada et al, 1988). Diabetes and hypercholesterolemia have been shown to alter the function of endothelium-mediated relaxation of the cavernous muscle (Azadzoi et al, 1991) and impair erection. In a study of cell junction proteins in hypercholesterolemic mice, Ryu and colleagues (2009) reported downregulation of endothelium-specific cell-to-cell junction proteins including claudin-5, VE-cadherin, and PECAM-1, as well as decreased endothelial content, which may contribute to ED in these mice.

Maintenance of Structural Integrity. Sonic hedgehog homolog (SHH) is one of three proteins in the mammalian hedgehog family, the others being desert hedgehog (DHH) and Indian hedgehog (IHH). SHH is the best studied ligand of the hedgehog signaling pathway. It plays a key role in regulating vertebrate organogenesis, such as in the growth of digits on limbs and organization of the brain. SHH remains important in the adult. It controls cell division of adult stem cells and has been implicated in development of some cancers. SHH has been shown to regulate cavernous smooth muscle apoptosis in response to signals from cavernous nerve. In an animal model of neurogenic ED, SHH protein treatment of the penis prevents cavernous nerve (CN) injury–induced apoptosis and structural changes (Podlasek, 2009).

Markers of Erectile Function. Variable coding sequence protein A1 (Vcsa1) has been proposed as a marker of erectile function in rats. Vcsa1 is downregulated in animal models of neurogenic, diabetic, and aging-associated ED. In rat models of ED treated with human Ca2+-activated K+ channels (hslo) and tadalafil, the erectile function improved and the gene expression of Vcsa1 was also upregulated (Calenda et al, 2009). The Vcsa protein product sialorphin is an endogenous neutral endopeptidase inhibitor. Tong and colleagues (2008) proposed that downregulation of sialorphin could result in prolonged activation of G-protein activated signaling pathways by their peptide agonists and thus heighten the cavernous smooth muscle tone. In humans, there are at least three homologues to the Vcsa1 gene (hSMR3A, hSMR3B, and PROL1). Downregulation of hSMR3A has been reported in men with ED (Davies and Melman, 2008).

Drug-Induced

ED is common among older men and therefore will inevitably coexist with other conditions that are themselves risk factors for ED such as depression, diabetes, and cardiovascular disease (Feldman et al, 1994). In addition, sexual symptoms related to medication can involve a combination of complaints concerning desire, arousal, and orgasm rather than being limited to impaired function. Self-reported and questionnaire data concerning ED as a side effect of medication should be interpreted with caution.

Antihypertensive Agents. Almost all antihypertensive drugs have ED listed as a potential side effect, nevertheless, recent well-designed controlled clinical trials have clarified some myths.

Diuretics. Thiazide diuretics are carbonic anhydrase inhibitors that alkalinize cells and causes vasodilation. Nevertheless, the predominant activity of thiazide diuretics is to inhibit a directly coupled Na-Cl cotransporter (NCC) along the distal convoluted tubule of the kidney. Acutely, when ECF volume depletion occurs because of salt wasting, cardiac output tends to decline, resulting in reactive vasoconstriction. Chronically, however, cardiac output is regulated according to metabolic needs and vasodilation supervenes, returning cardiac output toward baseline; this transforms hypotension from hypovolemic to vasodilatory (Ellison et al, 2009).

This class of drug has been extensively studied. Data from a large U.K. trial showed that twice as many men taking thiazides for mild hypertension reported ED than did those treated with propranolol or placebo—the most common reason for withdrawal from the bendrofluazide arm of the study (Medical Research Council, 1981).

Similar findings were documented from the Treatment of Mild Hypertension Study (TOMHS), where the prevalence of ED at 2 years in men taking low-dose thiazide was twice that of those on placebo or alternative agents (Grimm et al, 1997). Interestingly, after 4 years of treatment, the prevalence of ED in the placebo group approached that of the thiazide group, a finding not fully explained by dropouts. It may be that thiazide therapy, rather than causing ED directly, unmasks it at an earlier stage. A study comparing sexual side effects of thiazide, placebo, or atenolol in hypertensive patients also found a higher rate of ED in the thiazide group, although this was ameliorated by weight loss (Wassertheil-Smoller et al, 1991). The mechanism of diuretic-induced ED remains to be elucidated.

β-Adrenergic Blockers. Receptor studies show that only 10% of adrenoceptors in the penile tissue are of the β type, and their stimulation is thought to mediate relaxation (Andersson and Wagner, 1995). This response is attenuated in vitro by nonselective drugs such as propranolol, possibly via a prejunctional β_2-receptor effect (Srilatha et al, 1999), but not by cardiac-selective agents such as practolol. Beta antagonists also exert an inhibitory effect within the CNS, perhaps leading to lowered sex hormone levels (Suzuki et al, 1988).

The differential effects of β-adrenoceptor antagonists on erectile function may be explained by whether they are general antagonists, selective antagonists, or possess vasodilatatory properties. **Nonselective drugs such as propanolol are associated with higher prevalence of ED** compared with what is observed in patients treated with placebo or angiotensin-converting enzyme (ACE) inhibitors (Croog et al, 1986). Later trials using **agents with higher selectivity for the β_1 adrenoceptor such as acebutolol have shown a substantial reduction in ED** with no difference between placebo and ACE inhibitor groups (Grimm et al, 1997). Carvedilol, a general β-adrenoceptor antagonist that also causes vasodilation by blocking α_1 adrenoceptors, has been associated with worsening sexual function (Fogari et al, 2001). Some recently introduced β_1-adrenoceptor antagonists, such as nebivolol, have vasodilatatory effects mediated by release of nitric oxide (Reidenbach et al, 2007). In cross-over studies using nebivolol versus the selective β_1-adrenoceptor antagonists metoprolol and atenolol, nebivolol did not decrease sexual intercourse activity in hypertensive men and in some cases had positive effects on erectile function (Boydak et al, 2005; Brixius et al, 2007).

α-Adrenoceptor Blockers. Animal studies have demonstrated a positive effect on erection for α antagonists, particularly those acting on the α_1 receptor, by increasing or prolonging the relaxant response of cavernous smooth muscle (Andersson and Wagner, 1995). In addition, prejunctional α_2-receptor activation modulates the release of noradrenaline, suggesting a putative relaxant role for α_2 blockers. In clinical observations, **drugs such as doxazosin,** used to treat hypertension (Grimm et al, 1997) or lower urinary tract symptoms (Flack, 2002), **were not associated with complaints of ED** and indeed had lower rates than in placebo groups. Not surprisingly, **drugs stimulatory to the α_2 receptor such as clonidine do result in diminished erectile function,** both clinically and experimentally, by peripheral and central mechanisms (Srilatha et al, 1999). The centrally acting drug, **methyldopa, has also been associated with ED** in controlled trials comparing it with placebo and other antihypertensive agents (Croog et al, 1988,) and it may act by antagonizing hypothalamic α_2 adrenoceptors.

Angiotensin-Converting Enzyme Inhibitors. **These drugs lack any easily appreciated peripheral or central effect that would interfere with sexual function.** An in-vivo experiment showed that the ACE inhibitor captopril did not cause any significant adverse effect on sexual function in awake normotensive rats (Srilatha et al, 1999). In three clinical studies of hypertension treatment comparing an ACE inhibitor with other agents and placebo, all found either no difference from placebo or improved sexual function over baseline when compared with other agents (Croog et al, 1988; Suzuki et al, 1988; Grimm et al, 1997).

Angiotension II Type 1 (AT_1) Receptor Antagonist. In studies of hypertensive or aging normotensive animals, the AT_1 receptor antagonists (e.g., losartan, valsartan, candesartan) reverse structural changes in the penile vasculature and appear to conserve erectile function (Hale et al, 2001, 2002; Park et al, 2005; Hannan et al, 2006). Moreover, in clinical cross-sectional studies, AT_1 receptor antagonists, in contrast to other antihypertensive drugs, seem to improve erectile function (Doumas et al, 2006). In a cross-over study comparing valsartan with the β-adrenoceptor antagonist carvedilol, valsartan had a beneficial effect on preexisting sexual dysfunction and had no adverse sexual effects during 12 months of treatment (Fogari et al, 2001). Three-month treatment with losartan has also been reported to improve sexual function (Llisterri et al, 2001).

Calcium-Channel Blockers. Clinical studies have demonstrated **no adverse effect on erection;** ejaculatory complaints, which may owe to decreased force of bulbocavernous muscles, seem short-lived (Suzuki et al, 1988). In the TOMHS study there was no ED increase over placebo in the amlodipine group (Grimm et al, 1997). Another study also showed no increase in the prevalence of ED when hypertension was treated with diltiazem alone or in combination with an ACE inhibitor (Cushman et al, 1998).

Aldosterone Receptor Antagonist. Spironolacotone and eplerenone are mineralocorticoid-blocking agents used for their ability to block both the epithelial and nonepithelial actions of aldosterone. Spironolactone is a nonselective mineralocorticoid receptor antagonist with moderate affinity for both progesterone and androgen receptors. The latter property increases the likelihood of endocrine side effects including loss of libido, gynecomastia, and impotence. Eplerenone is a next-generation aldosterone receptor antagonist selective for aldosterone receptors alone. It has less affinity for progesterone and androgen receptors (Sica, 2005).

Summary. Treatment of mild to moderate hypertension requires agents with an acceptable side effect profile to minimize noncompliance. Thiazide diuretic is associated with higher rates of ED, although this may be reduced by combination therapy and weight loss. α_1 Blockers and angiotensin II receptor blockers both tend to improve sexual functioning during treatment and may therefore be useful when commencing antihypertensive therapy in men with preexisting ED (Khan et al, 2002) (Table 23–12).

Psychotrophic Medication. As with hypertension, the underlying disorder may be more relevant for ED than the medication. On the other hand, **receptor complexity and interrelation of pathways within the CNS make it extremely likely that neurons and ganglia involved in sexual functioning will be affected by psychotropic drugs, leading to functional changes that may be positive or negative.** One example is the loss of sexual desire among nonmedicated patients with schizophrenia, while those on antipsychotic drugs have shown greater desire but increased erectile and ejaculatory disturbance (Aizenberg et al, 1995).

Table 23–12.

Effect of Antihypertensive Agents on Sexual Function

AGENT	EFFECT	MECHANISM
Diuretics	ED (twice as placebo)	Unknown
β blocker (nonselective)	ED	Prejunctional α_2-receptor inhibition
β_1 blocker (selective)	None	
α_1 blocker	Decreases ED rate but may cause retrograde ejaculation	Failure of sympathetically induced closure of internal sphincter and proximal urethra during ejeculation
α_2 blocker	ED	Inhibition of central α_2 receptor
Angiotensin-converting enzyme inhibitor	None	
Angiotensin II receptor blocker	Decreases ED rate	
Calcium channel blocker	None	

Antipsychotics. Members of this class of drug have many effects on CNS receptors and may also act peripherally. Their therapeutic effect is thought to relate to doperminergic receptor blockade within the limbic and prefrontal areas of the brain. Their unwanted effects owe to β-adrenergic blockade and anticholinergic properties, as well as to antidopaminergic actions within the basal ganglia, causing extrapyramidal side effects that commonly produce sexual symptoms (Sullivan and Lukoff, 1990).

The occurrence of extrapyramidal effects differentiates the older "typical" antipsychotics, with which they are frequent, from the newer "atypical" antispychotics, with which they are less common. This difference probably relates to differential affinities for particular classes of receptor (Strange, 2001) or avidity for particular areas of the cerebral cortex (Westerink, 2002). An additional effect of DA blockade, hyperprolactinaemia, which also alters sexual function by reducing DA release in permissive cerebral centers, is more common with older "typical" agents (Smith and Talbert, 1986).

Animal experiments, chiefly in the rat, show that D1-receptor activation in the MPOA of the hypothalamus facilitates erection through intermediary oxytocinergic and spinal cholinergic pathways. It is also possible that activation of D2 receptors in this area has the opposite effect (Zarrindast et al, 1992). Older agents such as haloperidol and flupenthixol have been shown to reduce apomorphine-induced erections in experimental animals by means of D1-receptor antagonism (Andersson and Wagner, 1995). In addition, systemic administration of antipsychotic agents in the rabbit produced erection by a local nondoperminergic action, possibly involving anatagonism of α_1 adrenoceptors (Naganuma et al, 1993). Therefore **the clinical effect of antipsychotics on sexual function will vary according to their affinity for particular receptors.**

In a nonrandomized comparative study of antipsychotic medications, the prevalence of sexual dysfunction ranged from 40% to 70% (Wirshing et al, 2002). Newer agents such as clozapine showed a lower reduction in sexual desire, and the group taking risperidone had the greatest decrease in erectile frequency.

Antidepressants. Sexual side effects in both men and women are varied but are important factors governing compliance because these drugs are commonly prescribed to younger and middle-aged adults. **In a Cochrane review of 15 randomized trials, besides changing medications, addition of bupropion or a phosphodiesterase 5 inhibitor (PDE5I) to antidepressant seems to be an effective method to correct antidepressant-associated erectile dysfunction** (Rudkin et al, 2004).

Tricyclics act by inhibiting the reuptake of catecholamines in the CNS. **Their sexual side effect profile is thought to relate to peripheral anticholinergic and β-adrenergic effects.** It is also possible that they antagonize 5-HT receptors. Controlled clinical studies suggest that **orgasmic disorders in both sexes are frequent,** explaining the use of these drugs as inhibitors of ejaculation (Harrison et al, 1986; Monteiro et al, 1987).

Monoamine oxidase inhibitors are associated with **higher rates of orgasmic dysfunction** in controlled trials (Harrison et al, 1986), but the nature of the central or peripheral mechanisms involved is uncertain.

Selective serotonin reuptake inhibitors (SSRIs) are the class of drug commonly used to treat depression at the present time. They inhibit the reuptake of 5-HT into CNS neurons and can therefore produce stimulatory effects on various 5-HT receptors. It is estimated that **up to 50% of patients taking these drugs experience a change in sexual function** (Rosen et al, 1999; Keltner et al, 2002). Possible mechanisms include stimulation of 5-HT2 and 5-HT3 receptors, which may inhibit erectogenic pathways within the spinal cord (Tang et al, 1998), decreased DA release in the MPOA (Maeda et al, 1994), inhibition of NOS, and lower serum levels of LH, FSH, and testosterone (Safarinejad, 2008). A controlled clinical study suggested that the improvement in sexual function resulting from SSRIs' alleviation of clinical depression outweighed any negative effect (Michelson et al, 2001). However, other placebo-controlled randomized studies revealed increased sexual dysfunction, mainly anorgasmia, in the SSRI-treated group (Labbate et al, 1998; Croft et al, 1999). Further studies have suggested that **these adverse effects can be modified by cotreatment with other drugs such as sildenafil** (Fava et al, 2006) **or mianserin** (Aizenberg et al, 1997).

SSRIs differ in their ability to cause ED. A high incidence has been observed in patients treated with paroxetine (Kennedy et al, 2000), while a lesser impact has been reported with citalopram (Mendels et al, 1999). This suggests that mechanisms other than inhibition of serotonin reuptake may be involved, which is supported by a report that acute or chronic paroxetine, but not citalopram, caused ED in rats by inhibiting NO production (Angulo et al, 2001). Indeed, the inhibitory effects induced by acute paroxetine on erectile function in the rat can be prevented by inhibition of PDE5 with vardenafil (Angulo et al, 2003).

Other Antidepressants. Animal experiments suggest that stimulation of 5-HT-1 receptors within the CNS modulates sexual function, with the 5-HT-1A subtype increasing ejaculation and the 5-HT-1C subtype improving erection. Recently developed antidepressants such as mirtazapine and nefazodone tend to have beneficial effects on sexual function, possibly by activating the 5-HT-1C receptor, which augments sexual response (Stancampiano et al, 1994), although they may also antagonize the 5-HT-2C receptor (Millan et al, 2000). The isolated reports of priapism seen with a prototype agent, trazodone, may be related to the 5-HT-1C erectogenic effect seen with its primary metabolite, *m*-chlorophenylpiperazine, in experimental animals (Andersson and Wagner, 1995). In a clinical study, trazodone was shown to increase nocturnal erectile activity, despite reducing REM sleep (Ware et al, 1994).

Anxiolytics. Although not previously associated with ED, anxiolytics have been implicated in sexual problems by the MMAS study (Derby et al, 2001). Benzodiazepines are thought to potentiate the action of GABA in the reticular and limbic system, but they may also affect the serotonin and dopaminergic pathways. Experimental studies suggest that GABA-ergic drugs inhibit erection induced by apomorphine, a DA agonist (Zarrindast and Farahvash, 1994). A controlled clinical study demonstrated that a combination of lithium and benzodiazepine was associated with a significantly higher rate of sexual dysfunction than treatment with lithium alone (Ghadirian et al, 1992). More recent anxiolytic agents such as bupropion, acting mainly by inhibiting DA reuptake, and buspirone, acting on 5-HT-1A receptors, were not associated with sexual side effects in placebo-controlled trials (Coleman et al, 2001) and can be used to alleviate sexual symptoms caused by other antidepressant medication (Gitlin et al, 2002).

Anticonvulsants. Epileptic discharges may affect the function of the hypothalamic-pituitary axis and thus the level of hormones important for sexual function (Morris et al, 2005). Sexual function, bioavailable testosterone levels, and gonadal efficiency in men with epilepsy who take lamotrigine are comparable with control

and untreated values and significantly greater than in men treated with carbamazepine or phenytoin (Herzog et al, 2004). Orgasmic dysfunction is common in patients who receive carbamazepine therapy, and loss of sexual desire is common in men treated with valproate (Kuba et al, 2006). There are reports of improved sexual function and hypersexuality in patients treated with lamotrigine (Gil-Nagel et al, 2006; Grabowska-Grzyb et al, 2006).

Antiandrogens

Androgens are believed to modify sexual behavior by modulating AR within the CNS. **Antiandrogens cause partial or near-complete blockade of androgen's action by inhibiting production of or antagonizing the androgen receptor (AR).** The effects of androgen deficiency on sexual activity are variable, ranging from complete loss to normal function. Experimental studies in humans suggest that nocturnal erections during REM sleep are androgen dependent, while erections in response to visual sexual stimulation are independent (Andersson and Wagner, 1995). An additional peripheral effect has been suggested from animal experiments in which castration decreased nitric oxide synthase (NOS) activity within the rat corpus cavernosum, leading to reduced erectile activity. Testosterone restored NOS activity, but treatment with finasteride prevented this recovery, suggesting that dihydrotestosterone (DHT) may be the important androgen in penile tissue (Lugg et al, 1995).

Indeed, the 5-α-reductase inhibitor, finasteride, is the antiandrogen with the least effect on circulating testosterone. In randomized placebo-controlled studies of patients given finasteride (5 mg daily) for prostatic symptoms, approximately **5% complained of decreased desire and ED compared with 1% in the placebo group** (Gormley et al, 1992). At the lower dose used to treat male-pattern alopecia (1 mg daily), no sexual dysfunction was seen (Tosti et al, 2001).

More complete androgen ablation is achieved by competitive antagonism at the AR, thus preventing signal transduction of testosterone and DHT. Nonsteroidal drugs such as flutamide and bicalutamide have relatively pure effects on the AR. The steroidal antiandrogen cyproterone acetate also has inhibitory effects on the hypothalamus. These drugs are used in the palliative treatment of locally advanced and metastatic prostate cancer, either alone or in combination with a luteinizing hormone-releasing hormone (LHRH) agonist. When used alone, nonsteroidal antiandrogens are associated with a rise in serum testosterone levels; when combined with an LHRH agonist, they reduce testosterone to the castrate range. The main effect is a reduction of sexual desire, which occurs in up to 70% (Iversen et al, 2001).

In a clinical trial with larger sample size and longer duration, treatment with bicalutamide alone resulted in a lesser decrease in sexual desire than did castration (Iversen et al, 2000). However, in another large controlled trial, treatment with either flutamide or cyproterone resulted in a gradual loss of sexual desire over 2 to 6 years in approximately 80% (Schroder et al, 2000). In a placebo-controlled study, half the patients on bicalutamide therapy suffered loss of erectile function, even at a low dose of 50 mg (Eri and Tveter, 1994).

The near-complete androgen deprivation achieved by medical castration with LHRH agonists results in a profound loss of sexual desire, which is usually accompanied by ED (Basaria et al, 2002). This was objectively confirmed by nocturnal penile tumescence (NPT) monitoring before and after initiation of therapy in a small study (Marumo et al, 1999).

Miscellaneous Drugs. Many other drugs are suggested as having sexual side effects, in particular that of ED in men, but these contentions are usually based on anecdotal case reports or postmarketing drug alerts rather than controlled trials.

Digoxin. In an experimental in-vitro study with isolated human corpus cavernosum tissue, digoxin attenuated the relaxant response to acetylcholine and intrinsic nerve stimulation; this was linked to findings of reduced penile rigidity not seen in men given a placebo after visual sexual stimulation (Gupta et al, 1998). A randomized clinical study confirmed a negative effect on general sexual functioning linked to a decrease in plasma testosterone (Neri et al, 1987). However, others did not find change in sex and adrenal hormone levels in men taking digitalis (Kley et al, 1984).

Statins. **Statins** are used to lower lipid levels and thus are commonly used in men likely to have established risk factors for sexual dysfunction, particularly ED. In a single placebo-controlled trial, the rate of ED was twice as high (12% vs. 6%) in men taking a statin, despite improvement in other parameters of hyperlipidemic endothelial dysfunction (Bruckert et al, 1996). In another study of 93 men attending cardiovascular risk clinics, after 6 months of statin therapy, the mean IIEF scores were reduced from 21 to 6.5 (range 0 to 25) ($p < 0.001$), and 22% experienced new-onset ED. The authors suggest that ED following statin therapy is more likely in patients with severe endothelial dysfunction due to established cardiovascular risk factors including age, smoking, and diabetes (Solomon et al, 2006). In contrast, in the large Scandinavian simvastatin survival study, 4444 patients with coronary arterial disease were randomized to treatment with simvastatin or placebo for up to 6 years. ED was found in 28 placebo-treated patients (8 resolved) and in 37 simvastatin-treated patients (14 resolved) (Pedersen and Faergeman, 1999). Therefore the **underlying disease process appears to be the cause of ED in men treated with statins rather than the drug itself.**

Regarding sexual side effects, the most studied statin is atorvastatin. In clinical studies, atorvastatin has been reported to have the following positive effects: (1) improvement in nocturnal penile activity and mean scores on the Sexual Health Inventory in Men (SHIM) questionnaire from 14.2 to 20.7 in hyperlipidemic patients treated for 4 months (Saltzman et al, 2004); (2) when combined with the ACE inhibitor quinapril, positive effects on ED in men with established penile disease and suboptimal response to phosphodiesterase inhibitors (Bank et al, 2006); (3) improvement in the response to sildenafil in men with ED not initially responsive to sildenafil (Herrmann et al, 2006); (4) when combined with sildenafil, improvement in erectile function recovery in men who had undergone bilateral nerve-sparing radical prostatectomy (Hong et al, 2007); and (5) positive effect on International Index of Erectile Function (IIEF) questionnaire scores in patients with hyperlipidemia followed for 12 months (Dogru et al, 2008).

Statins are classified as natural (lovastatin), semisynthetic (simvastatin), and synthetic (atorvastatin, cerivastatin) and are structurally heterogenous. Therefore the statins may have different effects on sexual function, which remain to be elucidated.

Histamine H_2 Receptor Antagonists. Cimetidine and ranitidine were widely prescribed for prophylaxis and treatment of peptic ulcer disease. Case reports suggested that cimetidine was associated with ED. A single in-vitro animal study suggested that H_2 receptor stimulation causes cavernous relaxation, possibly via endothelial release of NO (Andersson and Wagner, 1995).

Opiates. Long-term intrathecal administration of opiates results in hypogonadatropic hypogonadism and associated sexual dysfunction that can be restored with appropriate supplementation (Abs et al, 2000). However, administration of opioid antagonists to older men with ED was not found to improve erectile function

measured objectively by NPT monitoring (Billington et al, 1990). Opioids do have a generalized depressant effect on sexual function when directly administered to the MPOA in rat brain, but treatment with the opioid receptor antagonist naloxone had no sexual effect on healthy male volunteers (Andersson and Wagner, 1995).

Antiretroviral Agents. Hypogonadism and erectile dysfunction (ED) appear to be more common among men infected with HIV compared with age-matched men within the general U.S. population (Crum et al, 2005). **Sexual dysfunction seems to be a common event after the introduction of highly active antiretroviral therapy** (HAART). The average prevalence is erectile dysfunction (46%), decreased libido (44%), ejaculatory disturbances (39%), and orgasmic disorders (27%) (Collazos, 2007). These disturbances seemed to be more common in patients treated with protease inhibitors. Because these patients may have diseases involving several organ systems and taking multiple drugs, the precise mechanism is difficult to determine.

Tobacco. **Cigarette smoking may induce vasoconstriction and penile venous leakage because of its contractile effect on the cavernous smooth muscle** (Juenemann et al, 1987). In an NPT study in cigarette smokers, Hirshkowitz and colleagues (1992) reported an inverse correlation between nocturnal erection (both rigidity and duration) and the number of cigarettes smoked per day: Men who smoked more than 40 cigarettes had the weakest and shortest nocturnal erections. **The Boston Area Community Heath (BACH) survey** used a multistage stratified random sample to recruit 2301 men, aged 30 to 79 years, from the city of Boston. The authors' report **indicates a dose-response association between smoking and ED with a statistically significant effect observed with 20 or more pack-years of exposure.** Passive smoking is associated with a small, statistically insignificant increase in risk of ED comparable with approximately 10 to 19 pack-years of active smoking (Kupelian et al, 2007). In an experiment to elucidate the mechanisms of tobacco use–associated ED, nicotine- and tar-free cigarette smoke extract (CSE) was injected subcutaneously into adult male rabbits once a day for 5 weeks. The authors reported impaired NO production from blunted NOS activity, downregulation of nNOS protein, accumulation of endogenous NOS inhibitors, enhanced arginase activity, and upregulation of arginase I protein in cavernous tissue. CSE also caused accumulation of endogenous NOS inhibitors due to impaired dimethylarginine dimethylaminohydrolase (DDAH) activity and decreased expression of DDAH I protein. These alterations may be relevant to erectile dysfunction following CSE (Imamura et al, 2007).

Alcohol. Alcohol in **small amounts improves erection and sexual drive because of its vasodilatory effect and suppression of anxiety;** however, **large amounts can cause central sedation, decreased libido, and transient ED.** In the Western Australia Men's Health Study, Chew and colleagues (2009) reported that, compared with never-drinkers, the age-adjusted odds of ED were lower among current, weekend, and binge drinkers and higher among exdrinkers.

Chronic alcoholism may result in liver dysfunction, decreased testosterone and increased estrogen levels, and alcoholic polyneuropathy, which may also affect penile nerves (Miller and Gold, 1988). In an in-vitro study of rabbits given 5% alcohol for 6 weeks, Saito and colleagues (1994) reported augmented smooth muscle contraction and relaxation to both electrical field stimulation and vasoconstrictors such as phenylephrine and potassium chloride, but not to sodium nitroprusside, suggesting changes in neurovascular function. In a study of subacute alcohol effect, mice were exposed to alcohol vapor for 7 or 14 days. The authors reported impaired endothelium-dependent relaxation of cavernous smooth muscle, as well as damage of endothelium in 14-day exposure group of mice but not the 7-day group (Aydinoglu et al, 2008) (Table 23–13).

Table 23–13.

Drug-Induced Erectile Dysfunction (ED) and Suggested Alternatives

CLASS	KNOWN TO CAUSE ED	SUGGESTED ALTERNATIVES
Antihypertensives	Thiazide diuretics General β blockers	α blockers Calcium channel blockers Specific β blockers Angiotensin-converting enzyme inhibitors Angiotenin II receptor antagonists
Psychotropics	Antipsychotics Antidepressants Anxiolytics	Newer anxiolytics (bupropion, buspirone)
Antiandrogen	Androgen receptor antagonists LHRH agonists 5-α reductase inhibitors	
Opiates		
Antiretroviral agents		
Tobacco		Quit smoking
Alcohol	Large amount	Small amount

Aging, Systemic Disease, and Other Causes

A number of studies have indicated a progressive decline in sexual function in "healthy" aging men. Masters and Johnson (1977) **noted a number of changes in older men including greater latency to erection, less turgidity, loss of forceful ejaculation and decreased volume, and a longer refractory period. Decreased frequency and duration of nocturnal erection with increasing age were reported in a group of men who had regular intercourse** (Schiavi and Schreiner-Engel, 1988). Other research has also indicated a decrease in penile tactile sensitivity with age (Rowland et al, 1989). A heightened cavernous muscle tone may also contribute to the decreased erectile response in older men (Christ et al, 1990). In one study, a decrease in testosterone in aging impotent men in association with relatively normal gonadotropins was reported, suggestive of hypothalamic-pituitary dysfunction (Kaiser et al, 1988). Penile structural and functional changes have been documented in various animal studies. Costa and Vendeira (2008) reported progressive decline of smooth muscle content and increase in the caliber of vascular spaces in the corpus cavernosum with increasing age in Wister rats. This may be due to increases in smooth muscle cell apoptosis due to oxidative stress and/or increase in caspase 2-mediated intrinsic pathway signaling (Braga et al, 2008). Suadicani and colleagues (2009) showed a significant decrease in gap junction protein connexin 43 and purinoceptor subtypes P2X1R and an increase in P2X7R in the corpus cavernosum of aging Fischer-344 rats. Change of nitric oxide expression or activity has also been reported. Numao and colleagues (2007) have demonstrated attenuated neuronal nitric oxide synthase protein expression and accelerated arginase

activity. Ferrini and colleagues (2001a and b) reported an increase of inducible nitric oxide, peroxynitrite formation, and elevation of apoptotic index in the corpus cavernosum and hypothalamic regions. The increased contractile property of the erectile tissue associated with aging may be due to elevated RhoA/Rho-kinase activity (Jin et al, 2006), enhanced rennin-agniotension system (Park et al, 2005) or impaired angiotensin-(1-7)-mediated relaxation (Yousif et al, 2007).

Diabetes Mellitus. Diabetes mellitus is a common chronic disease, affecting 0.5% to 2% of worldwide population. The **prevalence of ED is three times higher in diabetic men (28% vs. 9.6%)** (Feldman et al, 1994), **occurs at an earlier age, and increases with disease duration,** being approximately 15% at age 30 and rising to 55% at 60 years (McCullough et al, 1980, 1984). Erectile dysfunction among men with diabetes is **more frequent in those with coexisting neuropathy.** In a study of men presenting with ED, the authors found a twofold increase of hypogonadism in men with diabetes (24% vs. 12%) (Corona et al, 2006). **The presence of ED is associated with more than 14 times higher risk for silent coronary artery disease, higher major cardiovascular morbidity, and mortality in diabetic men** (Gazzaruso et al, 2004). This evidence indicates the presence of ED in diabetic patients could predict the future major cardiovascular events. Diabetes mellitus may cause ED by affecting one or a combination of the following: psychologic well-being, CNS function, androgen secretion, peripheral nerve activity, endothelial cell function, and smooth muscle contractility (Dunsmuir and Holmes, 1996).

In 12% of diabetic men, deterioration of sexual function can be the first symptom. Duplex ultrasound after intracavernous injection has revealed a high prevalence (>75%) of penile arterial insufficiency among diabetic men with ED (Wang et al, 1993). Pathologic changes in the cavernous arteries (Michal, 1980), ultrastructural changes in the cavernous smooth muscle (Mersdorf et al, 1991), and impaired endothelium-dependent relaxation of the corporeal smooth muscle (Saenz de Tejada et al, 1989a) have also been noted in penile specimens from diabetic men with ED. Hirshkowitz and colleagues (1990) have reported that impotent men with diabetes have fewer sleep-related erections, shorter tumescence time, diminished penile rigidity, decreased heart rate response to deep breathing, and lower penile blood pressure than do age-matched nondiabetic men.

A number of type 1 and type 2 diabetic animal models have been used to study the basic mechanisms of diabetes-induced ED. In these animals, diabetes causes endothelial cell dysfunction, resulting in an increased prevalence of vascular disease. Other effects include decreased nNOS, reduced activity of eNOS, oxidative stress, increased advanced glycation endproducts (AGEs), decreased elastin, reduced vascular endothelial growth factor (VEGF), hypercontractility of cavernous erectile tissue, and decreased smooth muscle/collagen ratio leading to impairment of the veno-occlusive mechanism. Summaries of mechanistic studies in humans and animal models, derived from the committee report of the Second International Consultation of Sexual Medicine (Saenz de Tejada et al, 2005), are shown in Tables 23–14 and 23–15.

Metabolic Syndrome. The metabolic syndrome (MetS) includes glucose intolerance, insulin resistance, obesity, dyslipidemia, and hypertension. Higher prevalence of ED (26.7%) in men with MetS relative to controls (13%) has been reported. Furthermore, the prevalence of ED increases as the number of MetS components increases (Esposito et al, 2005). **In an analysis of the Baltimore Longitudinal Study of Aging, in which men were followed for a mean of 5.8 years, Rodriguez and colleagues** (2007) **confirmed that the prevalence of MetS increases with age and is associated with lower androgen levels. They also found that lower total T levels, along with lower sex hormone binding globulin (SHBG) levels, predicts a higher incidence of MetS. Men with MetS have an increased prevalence of ED, reduced endothelial function score, and higher circulating concentrations of**

Table 23–14.

Summary Findings of Studies in Diabetic Patients

FOCUS	FINDING
Anatomic	More atheromatic lesions in large vessels and stenosis in pudendal and iliac arteries
Functional	Decreased number and rigidity of nocturnal erections
	Lower penile rigidity after intracavernous injection of vasodilators
	High prevalence of penile arterial insufficiency studied with duplex ultrasound
Cavernous Tissue Studies	
A. Ultrastructural	Decreased smooth muscle content, increased collagen, thickening of basal lamina, and loss of endothelial cells (more severe in men with diabetes)
B. Functional	• Reduced endothelial and neurogenic NO-mediated penile smooth muscle relaxation, but not nitroprusside-induced relaxation (suggesting impaired NO release or synthesis) • Increased advanced glycation end products (AGEs) in cavernous tissue • Contractile response to α-adrenergic agonist is higher in type 1 but not type 2 diabetics • In human penile arteries, EDHF-mediated endothelium-dependent relaxation is significantly reduced in penile resistance arteries from diabetic patients • Exposure to hyperglycemia induces increased expression of collagen, decreased proliferation, and increased programmed cell death (apoptosis). Expression of TNF_{α} is also increased • Insulin is thought to enhance NOS activity by increasing transport of L-arginine into the cell and furnishing greater quantities of the essential co-factor NADPH. These effects are reversed in insulin deficiency or insulin resistance in diabetes. • The inducible form (arginase II) of arginase, an enzyme that competes with NOS for the substrate L-arginine, is overexpressed in corpus cavernosum from diabetic patients, where inhibition of arginase restores NOS activity

EDHF, endothelium-derived hyperpolarizing factor; NOS, nitric oxide synthase.

Table 23–15.

Summary Findings of Studies in Diabetic Animal Models

MODEL	FINDING
Streptozocin-induced diabetic rats or mice	• Increased activity of AC and GC, resulting in production of more cAMP and cGMP in response to prostaglandin E1 and nitroprusside, respectively • Decreased endothelial and neurogenic NO-mediated cavernous muscle relaxation • Increased prostacyclin synthesis • Increased cavernous muscle tone owing to upregulation of endothelin ETA receptors • Increased contractile prostaglandins and free oxygen radicals in hyperglycemic state, resulting in reduced response to acetylcholine (reversed by indomethacin and antioxidants) • Increased levels of oxygen free radicals and oxidative stress injury. Preventive treatment with an antioxidant prevented the appearance of endothelial dysfunction in cavernosal tissue, whereas restorative treatment with same antioxidant only partially reversed the impairment of endothelium-dependent relaxation • Increased glycated hemoglobin, which impairs endothelium-dependent relaxation in aorta and corpus cavernosum from diabetic rats. This effect is reversed by superoxide dismutase (SOD), the scavenger of superoxide anions • Inhibition of AGE formation improves endothelium-dependent relaxation and restores erectile function in diabetic rats • Impaired responses attributable to endothelium-derived hyperpolarizing factor (EDHF) in the vasculature of diabetic animals • Plasma concentration and vascular content of L-arginine are reduced in diabetic rats • NO-dependent selective nitrergic nerve degeneration in diabetes
Diabetic rabbit	• Production of cAMP in response to PGE_1 or forskolin is reduced after 6 months, but not 3 months • Increased glucose-induced production of PKC mediated by oxidative stress in rabbit corpus cavernosum smooth muscle cells • Oxidative stress interferes with endothelial function in diabetic erectile tissue. This is supported by the potentiating effect of SOD or the natural antioxidant, vitamin E, on endothelium-dependent relaxation of corpus cavernosum from rabbits

C-reactive protein compared with men without metabolic disorders (Esposito et al, 2005). **Low levels of androgens in men with erectile dysfunction and obesity were also reported by Corona and colleagues (2008).**

Chronic Renal Failure. Sexual dysfunction is common in men with chronic renal failure. In a survey of 69 men on hemodialysis, only 55% were sexually active and the predominant sexual dysfunctions were loss of or diminished sexual needs (84.7%), erectile dysfunction (44.5%), and inhibited or lack of ejaculation (51.5%) (Lew-Starowicz and Gellert, 2009). Similarly, ED was reported in 52% of men undergoing peritoneal dialysis (Lai et al, 2007). The presence of depressive symptoms, highly prevalent in hemodialysis patients, is an independent factor of sexual dysfunction in male hemodialysis patients (Peng et al, 2007). Significant improvement of sexual function has been reported after kidney transplantation (Tavallaii et al, 2009). Nevertheless, in a report of 182 men who had undergone kidney transplantation, Espinoza and colleagues (2006) noted that 49% of men continued to have erectile dysfunction, whereas 33% of men had normal sexual function and 18% had no sexual activity. Many of the effects of uremia can potentially contribute to the development of ED including disturbance of the hypothalamic-pituitary-testis sex hormone axis, hyperprolactinemia, accelerated atheromatous disease, and psychologic factors (Ayub and Fletcher, 2000).

Bagcivan and colleagues (2003) suggest that ED may be due to either decreased production or reduced bioavailability of endogenous NO (Bagcivan et al, 2003). Evidence from animal models of chronic uremia therefore suggests that a decrease in functional NO may be responsible for vascular side effects including ED. Several putative mechanisms may lead to such a deficiency such as reduced bioavailability of the NO substrate L-arginine, reduced expression of NOS isoforms in the relevant organs, rapid quenching of NO by reactive oxygen species known to be increased in chronic renal failure, and the accumulation of uremic inhibitors of NOS (Vaziri, 2001).

Evidence of autonomic neuropathy as a factor contributing to ED in men with chronic renal failure comes from studies that found a high rate of abnormality in vascular and bulbocavernous reflexes, suggesting nerve dysfunction (Campese et al, 1982; Vita et al, 1999). Neuropathy is a common complication of end-stage kidney disease (ESKD), typically presenting as a distal symmetric process with insidious onset progressing over months. Neuropathy has been estimated to occur in 60% to 100% of patients on dialysis. Nerves of uremic patients have been shown to exist in a chronically depolarized state before initiation of dialysis, with subsequent improvement and normalization of resting membrane potential after initiation of dialysis. The degree of depolarization correlates with serum K(+), suggesting that chronic hyperkalemic depolarization plays an important role in the development of nerve dysfunction in ESKD (Krishnan and Kiernan, 2007). Investigation of cavernous vascular function in 20 men undergoing renal replacement therapy showed that 80% had both arterial insufficiency and veno-occlusive dysfunction (Kaufman et al, 1994). A link between impairment of the NO-cGMP pathway relating to failure of cavernous relaxation is provided by the finding of increased serum levels of asymmetric dimethylarginine (ADMA) in uremic patients (Kielstein and Zoccali, 2005).

Patients with severe pulmonary disease often fear aggravating dyspnea during sexual intercourse. Patients with angina, heart failure, or myocardial infarction can become impotent from anxiety, depression, or arterial insufficiency. Other systemic diseases such as cirrhosis of the liver, scleroderma, chronic debilitation, and cachexia are also known to cause ED.

Primary Erectile Dysfunction

Primary ED refers to a **life-long inability to initiate and/or maintain erections beginning with the first sexual encounter.** Although most cases owe to psychologic factors, a small number of afflicted men do have a physical cause resulting from maldevelopment of the penis or the blood and nerve supply. Primary psychologic dysfunction is usually related to anxiety about sexual performance stemming from adverse childhood events, traumatic early sexual experience, or misinformation. Endocrine abnormalities, particularly low testosterone levels, may also be implicated in primary ED, although lowered sex drive is likely to be the main symptom. Evidence to support these concepts is confined to observation studies with varying numbers of cases. The largest study described 67 patients, of whom 10 (15%) had a predominantly psychologic cause (Stief et al, 1989b). Those with physical abnormalities had a variety of neurologic, arterial, and veno-occlusive dysfunction.

Micropenis. Symmetric hypoplasia of the phallus, micropenis, is often related to urethral developmental abnormalities such as hypospadias and epispadias (Reilly and Woodhouse, 1989) or endocrine deficiency. The erectile tissue in such cases often functions normally; sexual dysfunction usually relates to lack of penile length or the degree of chordee, rather than to ED (Woodhouse, 1998).

Vascular Abnormalities. Primary ED in the presence of an externally normal phallus is unusual. Authors have described structural abnormalities of the cavernous tissue such as absence (Teloken et al, 1993) or replacement by fibrous tissue (Aboseif et al, 1992). Others have found vascular abnormalities including hypoplasia of the cavernous arteries (Montague et al, 1995) or veno-occlusive dysfunction owing to aberrant cavernous venous drainage (Lue, 1999). The underlying cause of these congenital abnormalities is unknown. Treatment in most cases has been vascular surgery or implantation of a penile prosthesis.

Key Points: Other Causes of Erectile Dysfunction

- Aging is the single most important contributing factor to ED. The aging process can affect the central regulatory mechanism, hormonal and neural function, and penile structure.
- Diabetes mellitus and metabolic syndrome may affect multiple organ systems and cause premature aging of both central and peripheral structures and molecules that regulate erectile process.
- The diseases that cause chronic renal failure may also cause ED, and the condition may persist in spite of successful renal transplantation.
- Primary ED may be due to psychogenic cause, inexperience, congenital arterial insufficiency or abnormal venous channels.

PERSPECTIVES

The past two decades have seen a continuing explosion of new information on the physiology of penile erection and the pathophysiology of ED. These new discoveries not only enhance our understanding of the disease process but also provide a solid basis for improving our diagnosis and treatment. We can expect that the application of new research tools and information in molecular biology, signal transduction, growth factors, microarrays, and stem cells will bring the investigation of erectile function and dysfunction to an even higher level in the near future.

Key Points: Pathophysiology

- The prevalence of ED increases with age and concomitant medical diseases. The incidence is about 25 to 30 cases per thousand person-years.
- ED is a symptom of many underlying conditions and diseases.
- Any condition that affects penile nerve, artery, endothelium, smooth muscle, or tunica albuginea can cause ED.
- Endothelial dysfunction seems to be a common final pathway to ED in patients with hyperlipidemia, diabetes mellitus, hypertension, and chronic renal failure.
- Drugs most commonly associated with ED include antiandrogens, antidepressants, and antihypertensives.

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chapter 24

Evaluation and Management of Erectile Dysfunction

Arthur L. Burnett, MD, MBA, FACS

Historical Perspective
Public Health Significance
Management Principles
Diagnostic Evaluation
Specialized Evaluation and Testing
Treatment Considerations
Future Directions

HISTORICAL PERSPECTIVE

Over just the past quarter century, the clinical management of erectile dysfunction (ED) has changed remarkably (Table 24–1). This comment relates to the success of greatly improved therapeutic options in the field, well demonstrated by oral phosphodiesterase type 5 (PDE5) inhibitor pharmacotherapy. Previously, ED management was mostly empirical and frequently used options were psychoanalysis, sex therapy, and endocrine treatments. Other notional prescriptions ranged from aphrodisiacs and erection enhancement pills to penile rigidity-inducing devices and surgically implanted penile prosthetics.

The modern management of ED marks a surge in the science of penile erection and a trend toward applying an evidence-based methodology (guided by outcomes from controlled and systematic scientific research) in the evaluation and institution of clinical therapies. Movement in this direction was witnessed in the early 1970s with the development of penile revascularization as a plausibly curative intervention for ED, which hinged on new insights regarding the vascular etiopathology of the problem. Although the place of the surgery is today relegated to select ED clinical presentations, it nonetheless ushered in a new era for therapies having an evidentiary basis. This era espoused therapeutic applications based on real scientific advances, from deciphering the pathophysiologic grounds for ED to elucidating the essential biochemical and molecular factors governing the erectile response. Additionally, efficacies of treatments were demonstrated by way of proper clinical investigation. Innovative pharmacologic delivery routes including intracavernosal, intraurethral, and oral treatments were similarly devised and introduced successively in the 1980s, mid-1990s, and late 1990s.

Besides advances in its therapeutic dimension, the field emerged overall as a recognized clinical discipline. Additional highlights in this regard included reaffirmations of its nosological foundations and its principles of practice for the patient with ED. Physiologic penile erection and its impairment were described within the context of the male sexual response cycle, and the historically pejorative and ambiguous term "impotence" was replaced with the more euphemistic and well-defined term "erectile dysfunction." Along the way, the importance of the patient's subjective claim of the existence of the problem was fully recognized, with emphasis given to the roles of both the patient and partner in its evaluation and management. Lue originally proposed the concept of the "goal-directed approach" for the management of ED, recognizing that lesser-invasive, reversible therapeutic methods had become available by the 1980s that did not require extensive and costly diagnostic testing before their implementation (Lue, 1990). The approach pronounced the imperative role of the clinician in performing a standard evaluation on the basis of a thorough and adequate sexual, medical, and psychosocial history in combination with a focused physical examination and select laboratory testing. However, it also acknowledged that diagnostic and therapeutic decisions should rely on the goals and preferences of the patient (and partner). This manner emphasizes the "patient-centered" intent brought to ED management (Rosen et al, 2004c).

The clinician's responsibility in recognizing and managing ED, as for all sexual dysfunctions, has gained the support of many thought leaders in the field of sexual medicine. Guidelines for the management of sexual dysfunctions with worldwide acceptance have resulted from numerous consensus meetings. Prominent among these were the series of International Consultations on Sexual Medicine (ICSM), cosponsored variously by the World Health Organization, International Consultation on Urological Diseases, American Urological Association, Société Internationale d'Urologie, and the International Society for Sexual Medicine, the first held in July 1999 with subsequent conferences convened in July 2004 and in July 2009 (Jardin et al, 2000; Lue et al, 2004; Montorsi et al, 2010). **Published proceedings from these congresses established diagnostic and therapeutic algorithms, which were founded on the principles of the goal-directed clinical management approach and obliged the trained clinician/physician to assess the patient and couple completely and prescribe therapy appropriately. They have also proclaimed that sexual medicine should be practiced in accordance with the highest standards of ethics, quality, safety and cost-effectiveness.**

Table 24–1.
Evolution in the Management of Erectile Dysfunction

	DIAGNOSTICS	TREATMENTS	GUIDES
Pre-1970	Psychosexual history	Psychosexual therapy Herbal supplements	Studies of Masters and Johnson
1970's	Medical and psychosexual history Nocturnal penile tumescence testing	Penile prosthesis surgery Penile revascularization	International Conferences on Corpus Cavernosum Revascularization
1980's	Physical examination Endocrine evaluation Penile duplex ultrasonography DICC	Oral medications Intracavernous pharmacotherapy Vacuum device therapy	Goal-directed management
1990's	Combined intracavernous injection and stimulation	Intraurethral pharmacotherapy Oral phosphodiesterase type 5 therapy	NIH Consensus Statement Process of Care Model
2000-Present	Biomarkers of vascular health Neuroimaging	?Gene therapy ?Stem cell therapy ?Tissue engineering	ICUD algorithms (patient-centered approach) AUA Practice Guidelines (evidence-based approach)

DICC, dynamic infusion cavernosometry and cavernosography; ICUD, International Consultation on Urological Diseases; NIH, National Institutes of Health.

PUBLIC HEALTH SIGNIFICANCE

ED is a medical condition of major health significance, with implications that extend beyond treating the occasionally presenting patient who possesses a problem of seemingly non-life-threatening magnitude. **The value of properly assessing and managing ED relates not only to affected individuals and their partners but also to society as a whole, and its scope encompasses physical and mental wellness aspects related to addressing (or failing to address) the sexual dysfunction, concurrent disease management issues, and socioeconomic burden.**

Epidemiology

Epidemiologic investigation, which specifies that study results are readily generalized to the overall male population, has provided powerful information regarding the nature, etiology, and prognostic ramifications of ED. **The most thoroughly studied sexual dysfunction in the context of epidemiologic research, ED is estimated to carry an overall adult male (older than 20 years of age) prevalence rate of 10% to 20% worldwide, with the majority of studies reporting a rate closer to 20%** (Derogatis and Burnett, 2008). It was estimated that there were more than 152 million men worldwide who experienced ED in 1995, with a projection of the prevalence reaching approximately 322 million men having ED by 2025 (Aytac et al, 1999). This trend is maintained irrespective of racial/ethnic background or geographic region. **Current data have also confirmed that the prevalence of ED mounts with increasing age and the presence of comorbid medical conditions, which include type 2 diabetes mellitus, obesity, cardiovascular disease, hypertension, dyslipidemia, depression, and prostate disease/benign prostatic hypertrophy (BPH)** (Braun et al, 2000; Martin-Morales et al, 2001; Nicolosi et al, 2004; Rosen et al, 2004b; Saigal et al, 2006; Laumann et al, 2007; Selvin et al, 2007). This correlation has supported the premise that ED and comorbid medical conditions share pathophysiologic mechanisms such as endothelial dysfunction, arterial occlusion, and systemic inflammation (Solomon et al, 2003; Montorsi et al, 2004; Billups, 2005; Ganz, 2005; Kloner, 2005; Guay, 2007).

Although they are few in number, prospectively conducted longitudinal studies have documented the true incidence and disease risk relationships for ED. In one study, a crude ED incidence rate was 25.9 cases/1000 man-years among men aged 40 to 69 years (Johannes et al, 2000). According to another study, incident ED statistics were 57% at 5 years and 65% at 7 years in men 55 years or older (Thompson et al, 2005). **Such studies have uniquely affirmed predictors for the development of ED, which include age, lower education, diabetes, cardiovascular disease, hypertension, cigarette smoking, cigar smoking, passive exposure to cigarette smoke, and overweight condition** (Feldman et al, 2000; Johannes et al, 2000; Inman et al, 2009).

However, the strength of the risk association is also gauged from the opposite analytic direction, and incident ED may indeed inform the risk of subsequent disease morbidity and mortality. This relationship has been best demonstrated so far with respect to cardiovascular disease. The placebo arm of the Prostate Cancer Prevention Trial found that ED is a sentinel for future risk of cardiovascular events, comparable with that of current cigarette smoking or a family history of myocardial infarction (Thompson et al, 2005). This study established that men with ED were 45% more likely than men without ED to experience a cardiac event after 5 years of follow-up (Thompson et al, 2005). In another population-based study of community-dwelling men followed longitudinally, ED was associated with an approximately 80% higher risk of subsequent coronary artery disease at 10 years (Inman et al, 2009). In a long-term follow-up (15 years) of the Massachusetts Male Aging Study (Feldman et al, 1994), ED was found to be positively associated with subsequent all-cause and cardiovascular disease mortality and constituted a risk in this regard similar to that of conventional risk factors such as increased body mass index, diabetes, and hypertension (Araujo et al, 2009). **These compelling data, considered alongside results generated from multiple smaller clinical cohort studies in the field, have contributed profoundly toward the understanding that the diagnosis of ED represents a clinical barometer of overall male health status and further serves to catalyze efforts to prevent disease, promote health and, moreover, improve survival.**

Health Policy

Sexual dysfunctions and ED specifically have taken on increasing importance with respect to their socioeconomic impact. **Besides its medical comorbidity associations, ED is recognized to**

adversely affect quality of life, decrease occupational productivity, and increase health care resource utilization (Krane et al, 1989; Litwin et al, 1998). Because of the heightened ease of use and availability of effective first-line treatments combined with a growing societal awareness of ED and acceptance of its treatment, it is understandable that a trend toward increased health care services utilization surrounding ED has been observed (Wessells et al, 2007).

ED can be included among a host of urologic diseases having a substantial burden on the public financially. Total expenditures for outpatient clinical management of ED (exclusive of pharmaceutical costs) in the United States in 2000 approximated $330 million, ranking ninth most costly among most frequent urologic diagnoses (Litwin et al, 2005). By contrast, this cost was approximately $185 million in 1994 (Wessells et al, 2007). Individual-level expenditures on an annual basis associated with an ED diagnosis (inclusive of pharmaceutical costs) among affected 18- to 64-year-old males in the United States in 2002 were calculated to be $1107 (Wessells et al, 2007). These data have enormous implications for governmental, as well as nongovernmental agencies in the United States and worldwide, whose work must consider the practical distribution and fiscal allocation of health care services for ED.

Key Points: Epidemiology and Health Policy

- Approximately 20% of adult men worldwide experience ED.
- Risk factors for ED include increasing age and presence of comorbid medical conditions such as type 2 diabetes mellitus, obesity, cardiovascular disease, hypertension, dyslipidemia, depression, and prostate disease/BPH.
- Between 1994 and 2000, expenditures solely for outpatient clinical management of ED in the United States nearly doubled from $185 million to $330 million.
- ED ranks among the top 10 most costly urologic diagnoses in the United States and must be included in considerations for fiscal allocation of health care services.

MANAGEMENT PRINCIPLES

The approach to the evaluation and treatment of ED is most assuredly different from that of many other urologic diseases in several basic respects. The diagnosis of ED customarily involves an acknowledgment of the subjective complaint of erectile inability by the patient (or patient and partner), and extensive diagnostic procedures are generally not required to proffer the diagnosis. Additionally, current first-line intervention in the form of effective oral pharmacotherapy is easily prescribed and administered and is frequently successful for the majority of patients. **However, notwithstanding the semblance that the management of ED is fairly uncomplicated, it is a structured process that critically incorporates several clinical practice concepts for bringing the best therapeutic outcomes to patients.**

Early Detection

Epidemiologic and clinical investigation has suggested that many patients with ED retain adverse clinical conditions and also lifestyle factors (e.g., diabetes, cardiovascular disease, prostate disease, overweight condition, current cigarette smoking, physical inactivity) that potentially compromise erectile function (Saigal et al, 2006; Laumann et al, 2007; Selvin et al, 2007). It is estimated that as much as 75% of men with diabetes have ED to some degree (Hakim and Goldstein, 1996). Similar rates of ED diagnoses are described for men presenting clinically with other chronic diseases, which constitute risk factors for ED (Jackson, 1999; Burchardt et al, 2000; Montorsi et al, 2003b; Solomon et al, 2003).

In addition to adverse health conditions having risk associations with ED, medication use has also been associated with ED in up to 25% of presentations (Keene and Davies, 1999; Francis et al, 2007). The most commonly implicated classes of drug include antihypertensive drugs such as thiazide diuretics and β-adrenoceptor antagonists and psychotherapeutic drugs, particularly selective serotonin reuptake inhibitor (SSRI) antidepressants. Table 24–2 lists several drug classes commonly associated with ED. It is importantly recognized that medications may affect other components of the male sexual response cycle including sexual desire, arousal, and orgasm, which secondarily hampers erectile function. Of additional importance, the assignment of causation of ED for any particular medication is conditional, requiring that an increased prevalence exists in the target population compared with the placebo group after stratification for known risk factors or compared with another drug with an equivalent therapeutic effect, and further, a credible physiologic mechanism should be established experimentally (Sáenz de Tejada et al, 2005).

Calculated odds ratios underscore the extent to which various ED risk factors correlate with ED (Table 24–3). **These data**

Table 24–2.
Drugs Associated with Erectile Dysfunction

CLASS	SPECIFIC AGENTS
Antihypertensives	Thiazide diuretics, nonselective β-blockers
Antidepressants	Tricyclics; selective serotonin reuptake inhibitors
Antipsychotics	Phenothiazines
Antiandrogens	Nonsteroidal (flutamide); steroidal (cyproterone acetate); luteinizing hormone-releasing hormone analogues
Antiulcer drugs	Histamine H_2 receptor antagonists (cimetidine)
Cytotoxic agents	Cyclophosphamide, methotrexate
Opiates	Morphine

Table 24–3.
Major Erectile Dysfunction Risk Factors

CONDITION	MULTIVARIATE ADJUSTED ODDS RATIO
Diabetes mellitus	2.9
Hypertension	1.6
Cardiovascular disease	1.1
Hypercholesterolemia	1.0
Benign prostate enlargement	1.6
Obstructive urinary symptoms	2.2
Increased body mass index (>30 kg/m^2)	1.5
Physical inactivity	1.5
Current cigarette smoking	1.6
Antidepressant use	9.1
Antihypertensive use	4.0

From Selvin E, Burnett AL, Platz EA. Prevalence and risk factors for erectile dysfunction in the US. Am J Med 2007;120:151–57; and Francis ME, Kusek JW, Nyberg LM, Eggers PW. The contribution of common medical conditions and drug exposures to erectile dysfunction in adult males. J Urol 2007;178:591–6.

support the contention that patients with identifiable ED risk factors likely experience the sexual dysfunction currently or will eventually develop it at some time. Clinical screening of such patients based on these indications may allow advantageous opportunities to diagnose and treat ED.

Goal-Directed Management

A goal-directed approach to the management of patients with ED has largely been practiced in the field over the past two decades since Lue's original description (Lue, 1990). The approach dictates that the diagnostic evaluation and therapeutic plan relates to the individual patient's presentation and manner of deriving satisfaction, in accordance with a patient-centered framework (Hatzichristou et al, 2010). **The basic aim of goal-directed management is to allow the patient or couple to make an informed selection of the preferred therapy for sexual fulfillment on the basis of a sound understanding of all treatment options after completing a thorough discussion with the treating clinician. The approach recognizes that patients vary in their acceptance of their sexual disorders and in their interest to pursue management. Their decisions accordingly follow individual preferences, needs, and expectations regarding management options.** Evaluations of this approach have affirmed its utility and demonstrated that patient therapeutic preferences accord with the least invasive forms of therapy (Jarow et al, 1996; Hanash, 1997).

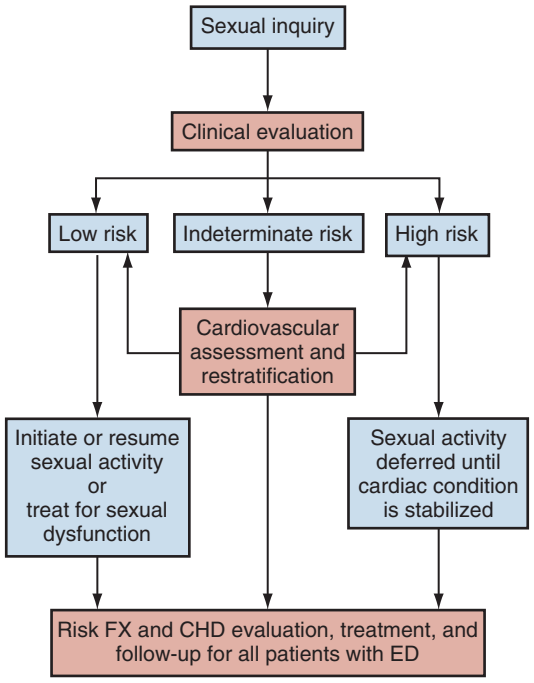


Figure 24–1. Algorithm for evaluation of the patient with cardiovascular disease recommended by the Second Princeton Panel. CHD, coronary heart disease; ED, erectile dysfunction; FX, factors.

Role of Partner Interview

The partner interview is a critical component in initiating management of ED. Partner interviews have been shown to impact diagnosis and treatment in up to 58% of cases (Tiefer and Schuetz-Mueller, 1995; Chun and Carson, 2001). **The partner may be the source of important information that guides optimal intervention and response to therapy. The partner may share a new and different perspective on sexual issues affecting the couple, provide insight into the quality of the couple's relationship, and relate his/her role in the sexual dysfunction** (Speckens et al, 1995; Fisher et al, 2009). **The partner's involvement and attitude may also affect the patient's initiation of and adherence to therapy** (Jackson and Lue, 1998; Fisher et al, 2005).

An important additional consideration is that partners' well-beings may be affected by the patients' ED conditions. Studies have shown that women partners of men with ED are themselves more likely to have sexual dysfunction or to cease sexual activity entirely (Ichikawa et al, 2004; Montorsi and Althof, 2004; Fisher et al, 2005; Sand and Fisher, 2007). This observation further prompts the facilitatory role of the partner in ED management, which maximizes the success of therapy and inherently satisfaction of the couple.

In practice, additional office visits as needed, in which the partner accompanies the patient, and the communication of educational information to the partner via the patient are recommended techniques for involving partners in ED management (Dean et al, 2008).

Cardiac Risk Assessment

The frequent coexistence of ED and cardiovascular disease, as established by clinical epidemiologic study and by basic science research, has steered ED management to include procedures that account for the ED patient's cardiovascular health risks. The second Princeton Consensus Guidelines Panel reinforced the linkage between sexual activity and cardiac risk, which was acknowledged with the first conference (DeBusk et al, 2000), and pronounced that all men with ED, even in the absence of manifesting cardiac symptoms, should be regarded as having potential risks for cardiovascular disease (Kostis et al, 2005; Jackson et al, 2006).

ED patients are recommended to undergo a full medical assessment with stratification of cardiovascular risk as high, medium, or low (Fig. 24–1). **Patients classified as having high risk would be those with unstable or refractory angina, a recent history of myocardial infarction, certain arrhythmias, or uncontrolled hypertension. For these patients, sexual activity with any particular ED therapy should be deferred until the cardiac condition is stabilized. Such patients should ideally undergo cardiologic referral for cardiovascular stress testing and subsequent risk reduction therapy. Importantly, even patients at low risk for cardiovascular events should receive the minimum recommendations of cardiovascular disease management.** Basic intervention includes counseling for lifestyle modifications such as increased physical activity and improved weight control combined with regular health monitoring by the patient's general practitioner (Kostis et al, 2005).

Step-Care Approach

Practitioners of ED management have always sought a rational approach for implementing diagnostic and therapeutic options. The "Process of Care Model for Erectile Dysfunction" was proposed as a stepwise methodology, combining processes, actions,

and outcomes in the management of the ED patient (Process of Care Consensus Panel, 1999). **It specified an algorithm for therapeutic decision making that takes into account patient needs and preferences (goal-directed management), although it was also based on specific criteria such as ease of administration, reversibility, relative invasiveness, and cost of therapies. This algorithm presented a strategy of staged therapy (i.e., first-, second-, and third-line interventions), which ranged from lifestyle modification to surgery.** In concept, the scheme has been borrowed and endorsed by other consensus panels, which acknowledged the purpose of patient education and counseling along with medical therapies as initial forms of ED management in common practice (Montague et al, 2005; Hatzichristou et al, 2010).

Shared Decision Making and Treatment Planning

The therapeutic plan may vary for each patient and couple and ultimately depends on a host of factors including patient considerations and clinical indications and contraindications. **An informed decision-making process should dictate the best therapeutic option. It follows a balanced and thorough discussion led by the clinician of all treatment options, both medical and nonmedical, and their expected advantages and disadvantages. Perceived risks and benefits, which may be influenced by the individual clinical situation, should be weighed.** It is understood that the patient may appropriately select a preferred treatment option without necessarily adhering to a strictly prescribed succession of attempted therapies. Indeed, the patient may elect to defer treatment altogether. Whatever the patient (or couple) chooses, this option can then be pursued within the boundaries of safety, under the supportive partnership of his clinician.

Specialist Referral

The advent of effective oral pharmacotherapy for ED has recently enabled many primary practitioners to feel comfortable with managing the majority of clinical presentations of ED. At the same time, it is understood that situations arise in which the patient or primary practitioner may request the assistance of a consultant/specialist (e.g., cardiologist, endocrinologist, psychologist, urologist) for further diagnostic evaluation and treatment beyond the boundaries of initial management (Process of Care Consensus Panel, 1999). **Such referrals may be required for individuals with complicated or atypical presentations of ED, representing diagnostic challenges that exceed common clinical practices of nonspecialists. Specialized evaluation and management potentially offer improved therapeutic outcomes for these presentations.**

Generally recommended indications for specialized evaluations and associated consultants are failure of initial treatment, referred to a urologist; younger patients with a history of pelvic or perineal trauma, referred to a urologist; patients with significant penile deformity (e.g., Peyronie disease, congenital chordee), referred to a urologist; complicated endocrinopathies (e.g., secondary hypogonadism, pituitary adenoma), referred to an endocrinologist; complicated psychiatric or psychosexual disorders (e.g., refractory depression, hypoactive sexual desire), referred to a psychiatrist; presentations requiring vascular or neurosurgical intervention (e.g., aortic aneurysm, lumbosacral disc disease), referred to a vascular surgeon or neurosurgeon, respectively; medicolegal reasons (e.g., workman's compensation claims), referred to a urologist.

A caveat is that effort should be taken at the time of referral to be sure that patients are fully informed about the rationale, costs, potential risks, and potential outcomes of the referral and possible additional procedures. This recommendation is made in accordance with the principles of patient-centered medicine, by which patients (and partners where possible) should be included in the decision-making process.

Follow-up Care

Follow-up care is an essential part of ED management and should not be overlooked. The objectives of this action are manifold. **A primary basis is to ensure continual success with the therapeutic outcome. It has been shown that treatment discontinuation occurs at high rates among patients who are not reassessed regularly** (Albaugh et al, 2002). Additional purposes are to reassess medical and psychosocial conditions adversely impacting ED and success of therapy, evaluate the need for dosage titration or treatment substitution, and monitor adverse drug interactions or drug interaction effects. As always, follow-up attention offers educational opportunities for patient and partner with regard to addressing sexual health concerns, as well as lending guidance for related health care matters.

DIAGNOSTIC EVALUATION

The cornerstone in the evaluation of ED involves a detailed case history, preferably taken from patient and partner, physical examination, and proper laboratory tests (Fig. 24–2). **The diagnosis can be submitted on the basis of an individual's report of consistent inability to attain and maintain an erection of the penis sufficient to permit satisfactory sexual intercourse** (NIH Consensus Statement, 1992; Lewis et al, 2004). It is noteworthy that the original National Institutes of Health definition did not specify a parameter for the duration of symptoms to accept the diagnosis. Subsequent organizational statements did apply a 3-month interval as a minimal requirement diagnostically, except for cases of trauma or surgically induced ED (Lewis et al, 2004).

Sexual, Medical, and Psychosocial History

The comprehensive assessment of any sexual problem begins with the performance of a detailed case history including sexual, medical, and psychosocial components. The clinician may employ brief checklists or questionnaires for the purpose of recognizing the problem and initiating its evaluation, although he or she should standardly perform a detailed interview to understand the nature of the sexual complaint. The sexual history component in particular should be elicited with utmost sensitivity, given the intrapersonal and interpersonal aspects of sexual dysfunction (Rosen et al, 2004c). Additional emphasis has recently been given to providing cultural competence when interacting with patients (Hatzichristou et al, 2010). **All discussion of sexual matters is done privately and**

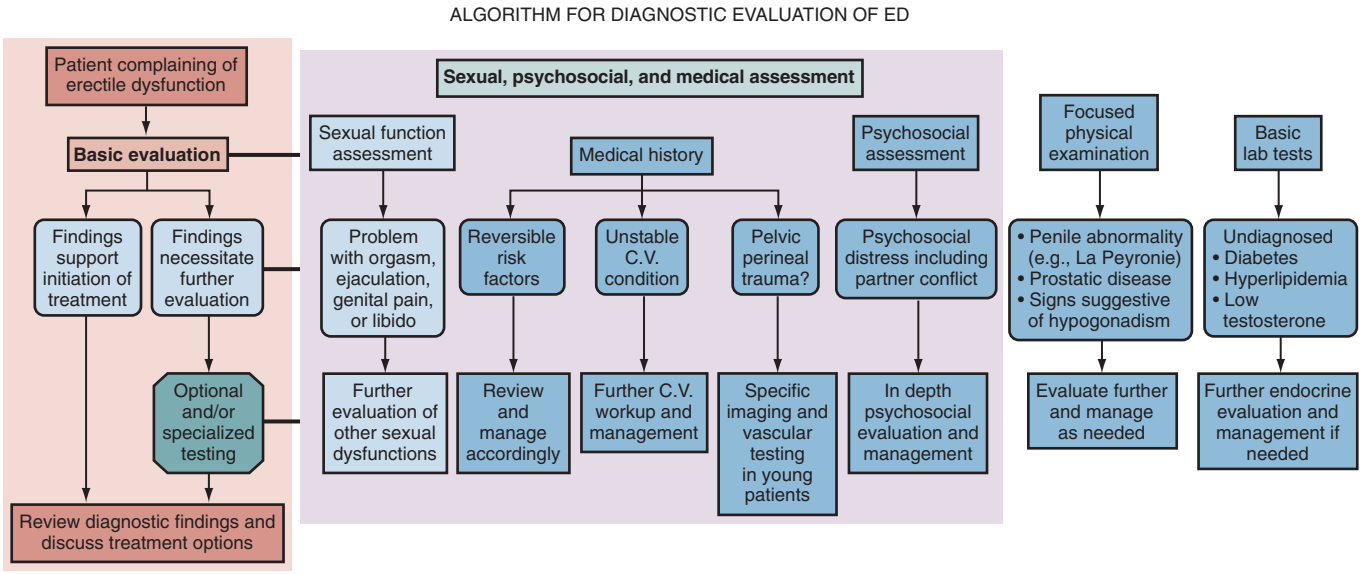


Figure 24–2. Diagnostic algorithm for erectile dysfunction (ED) recommended by the International Consultations on Sexual Medicine.

confidentially, and the clinician is required to express trust and concern, as well as a nonjudgmental manner that epitomizes the doctor-patient relationship. The clinician should not assume that every patient is involved in a monogamous, heterosexual relationship. However, the situation may be presented whereby the partner can be interviewed, and this opportunity may be used, with the approval of the patient, to corroborate aspects of the clinical history and confirm mutual therapeutic goals.

Sexual History

The sexual history is the central component of the clinical history and serves to confirm the patient's sexual dysfunction complaint of ED. **Objectives of the interview are also to delineate the problem according to such features as its onset, duration, conditions, severity, and etiology. The conditions of the problem are often determined by reviewing circumstances that facilitate or hinder erectile function.** Circumstances for achievable erections include stimuli used during sexual encounters, erections on awakening, and the role of self-stimulation. Circumstances associated with erectile difficulty include performance anxiety, inability to perform with a designated partner, and motivational factors affecting lovemaking. Other pertinent issues include availability, interest and health of the partner, changes in medical status or other events relating to the onset of ED, and prior attempts to manage the problem by the patient or another caregiver.

The severity of ED can be defined as mild, moderate, or severe/complete, according to increasing degrees of loss of penile rigidity and the associated interference with sexual activity. For instance, mild ED may refer to minimally decreased ability to attain and/or maintain an erection with intermittent satisfactory sexual performance, moderate ED may refer to minimally decreased ability to attain and/or maintain an erection with infrequent satisfactory sexual performance, and severe ED may refer to substantially decreased ability to attain and/or maintain an erection with rare or absent satisfactory performance.

The potential etiology of ED is commonly probed and may be categorized as psychogenic, organic, or mixed according to whether there is a presumed psychologic or interpersonal determinant (psychogenic); a specific endocrinologic, neurologic, or cardiovascular cause (organic); or coexistence of psychologic or relationship factors and organic causes (mixed) (Table 24–4) (Ralph and McNicholas, 2000). It is accepted that ED many times cannot be fully dichotomized into psychogenic and organic categories. However, its characterization by a predominant etiologic basis may nonetheless assist therapeutic objectives. The interview should also assess whether ED is the primary source of the presenting complaint or secondary to some other aspect of the sexual response cycle (e.g., desire, ejaculation, orgasm) that may also relate to the clinical presentation (Rosen et al, 2004c). The association of decreased arousal, if present, may be explored as well and evaluated as to whether it preceded or was incidental to the development of ED.

Table 24–4.
Classification of Erectile Dysfunction

PSYCHOGENIC	ORGANIC
Sudden onset	Gradual onset
Complete immediate loss	Incremental progression
Situational dysfunction	Global dysfunction
Waking erections present	Waking erections poor/absent

Adapted from Ralph D, McNicholas T. UK management guidelines for erectile dysfunction. BMJ 2000;321:499–503.

Medical History

The medical history primarily serves to identify and evaluate predictors and risk factors associated with ED. **The main objective is to explore the role of possibly related or underlying medical conditions and to ascertain the existence of comorbidities. Recognition of the association between medical conditions and ED not only may lend insight into the possible basis for the ED, which may guide choice of therapy, but it may also specify reversible or treatable factors associated with ED that may be**

corrected with an expectation of improving the level of erectile function.

Medical conditions associated with ED include disease states (e.g., type 2 diabetes mellitus, cardiovascular disease, hypertension, dyslipidemia, neurologic disease, hypogonadism, thyroid disorders); consequences of trauma involving aspects of the body, pelvis, or genitalia (e.g., spinal cord injury, pelvic surgery or radiation, sexual injury); and side effects of medications or recreational substances that disturb biochemical processes of penile erection. Age is recorded, in accordance with the well-known association between aging and ED. Comorbidities (e.g., depression, anxiety, anger) are importantly registered because of their bidirectional relationship with ED.

Psychosocial History

The intake of psychosocial history is a necessary part of the clinical history. **The very best sexual performance most assuredly implies wellness of mind and body acting together, and unstable psychosocial circumstances of both intrapersonal and interpersonal contexts may adversely affect sexual function.** Accordingly, the presence and interaction of mental health problems, emotional stressors, and interpersonal relationship difficulties, both past and present, should be ascertained. Additional questions may be asked relating to occupational status, financial security, family life, and social support, which may also influence sexual function.

Physical Examination

The physical examination is a necessary component of the comprehensive assessment of sexual dysfunctions and complements the clinical case history. It may reveal possible etiologies for ED.

This evaluation consists of basic anthropometrics (i.e., height, weight, waist circumference); assessment of body habitus (appearance of secondary sexual characteristics); and examination of relevant body parts pertaining to cardiovascular, neurologic, and genital systems, with a particular focus on the external genitalia. The observation of a classically distinctive body habitus consistent with Kallman or Klinefelter syndrome or obvious physical signs of hypogonadism such as gynecomastia and general poor masculine development may suggest an endocrinologic basis for ED.

Findings of obesity, elevated blood pressure, or abnormal femoral or pedal pulses—all signs representative of cardiovascular disease—convey a potential vascular causation. Findings of abnormal genital and perineal sensation or bulbocavernosus reflex, indicative of a peripheral neuropathy, suggest the involvement and effects of a neurologic disorder or diabetes.

Detection of a penile deformity such as micropenis, congenital chordee, or Peyronie disease–related fibrous plaques in the corpora cavernosa supports the possibility that a physical impediment accounts for ED. Genital examination findings of abnormal position, size, and consistency of testes may also suggest hypogonadism and suggests that ED exists on endocrinologic grounds.

Questionnaires and Sexual Function Symptom Scores

Self-administered ED questionnaires are extremely useful adjuncts to the case history, and they concur with the patient's self-report in establishing the diagnosis. Early supplied questionnaires in the field such as the Derogatis Sexual Function Inventory (245 items) (Derogatis and Melisaratos, 1979) and the Golombok Rust Inventory of Sexual Satisfaction (GRISS) (28 items) (Rust and Golombok, 1986) were detailed, and they commonly aimed to differentiate psychogenic and nonpsychogenic ED or evaluate sexual functioning in the context of the couple. More recently developed instruments were implemented primarily in clinical trials associated with new drug development, and they captured particular efficacy end points including sexual interest, performance, and satisfaction. However, as part of practice pattern shifts that have occurred in ED management in recent years, there has been a growing emphasis on and application of patient self-reported instruments for clinical practice. **These self-report measures have been meant to be brief and practical and to serve in documenting the presence, severity, and responsiveness to treatment of ED.**

The most widely referenced instruments include the International Index of Erectile Function (IIEF) by Rosen and colleagues (1997), the Brief Male Sexual Function Inventory (BMSFI) by O'Leary and colleagues (1995), the Center for Marital and Sexual Health Sexual Functioning Questionnaire by Glick and colleagues (1997), the Changes in Sexual Functioning Questionnaire by Clayton and colleagues (1997), and the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) by Althof and colleagues (1999). The IIEF, which contains 15 items that address and quantify five domains—erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction—is the most widely used questionnaire (Fig. 24–3). An abridged five-item version of this instrument, the IIEF-5, has been useful to clinicians in routine clinical practice specifically for the evaluation of ED (Rosen et al, 1999). The instrument classifies ED severity into five categories: severe (5 to 7), moderate (8 to 11), mild to moderate (12 to 16), mild (17 to 21), and no ED (22 to 25). The Male Sexual Health Questionnaire offers another instrument that assesses core components of male sexual function (i.e., desire, erection, ejaculation, satisfaction) and has utility in both clinical and research settings (Rosen et al, 2004a). The Sexual Experience Questionnaire has also recently been developed as a tool for evaluating health-related quality of life concepts and comprises erection, individual satisfaction, and couple satisfaction domains (Mulhall et al, 2008).

A known limitation of self-administered questionnaires is that they do not distinguish an etiologic basis for ED, that is, they do not differentiate among the various causes of ED (Blander et al, 1999; Kassouf and Carrier, 2003). **Further, they may not sufficiently indicate the severity of ED that is evidenced on objective grounds** (Tokatli et al, 2006). Although the exact nature of the ED diagnosis arguably is not absolutely necessary to initiate ED treatment today with current management options, it is understood that further clinical evaluation with diagnostic tests may be required to discern the basis and extent of the ED by system (e.g., vascular, neurologic, endocrinologic) and take action that may be most effective and possibly corrective.

Laboratory Tests

Appropriate laboratory testing can be considered part of a systematic clinical evaluation for individuals presenting with ED. **Such evaluation may confirm or define etiologic medical conditions associated with the sexual dysfunction. At times, it may identify treatable conditions or previously undetected disease states that may contribute to ED.** A

Patient Name: _____ **MR#:** _____ **Date:** _____

OVER THE PAST 4 WEEKS

1. How often were you able to get an erection during sexual activity?
   0 = No sexual activity
   1 = Almost never/never
   2 = A few times (much less than half the time)
   3 = Sometimes (about half the time)
   4 = Most times (much more than half the time)
   5 = Almost always/always

2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?
   0 = No sexual activity
   1 = Almost never/never
   2 = A few times (much less than half the time)
   3 = Sometimes (about half the time)
   4 = Most times (much more than half the time)
   5 = Almost always/always

3. When you attempted sexual intercourse, how often were you able to penetrate (enter)?
   0 = Did not attempt intercourse
   1 = Almost never/never
   2 = A few times (much less than half the time)
   3 = Sometimes (about half the time)
   4 = Most times (much more than half the time)
   5 = Almost always/always

4. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) you partner?
   0 = Did not attempt intercourse
   1 = Almost never/never
   2 = A few times (much less than half the time)
   3 = Sometimes (about half the time)
   4 = Most times (much more than half the time)
   5 = Almost always/always

5. During sexual intercourse, how difficult was it to maintain your erection to complete intercourse?
   0 = Did not attempt intercourse
   1 = Extremely difficult
   2 = Very difficult
   3 = Difficult
   4 = Slightly difficult
   5 = Not difficult

6. How many times have you attempted sexual intercourse?
   0 = No attempts
   1 = One to two attempts
   2 = Three to four attempts
   3 = Five to six attempts
   4 = Seven to ten attempts
   5 = Eleven or more attempts

7. When you attempted sexual intercourse, how often was it satisfactory to you?
   0 = Did not attempt intercourse
   1 = Almost never/never
   2 = A few times (much less than half the time)
   3 = Sometimes (about half the time)
   4 = Most times (much more than half the time)
   5 = Almost always/always

8. How much have you enjoyed sexual intercourse?
   0 = No intercourse
   1 = No enjoyment
   2 = Not very enjoyable
   3 = Fairly enjoyable
   4 = Highly enjoyable
   5 = Very highly enjoyable

9. When you had sexual stimulation or intercourse, how often did you ejaculate?
   0 = No sexual stimulation/intercourse
   1 = Almost never/never
   2 = A few times (much less than half the time)
   3 = Sometimes (about half the time)
   4 = Most times (much more than half the time)
   5 = Almost always/always

10. When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?
    0 = No sexual stimulation/intercourse
    1 = Almost never/never
    2 = A few times (much less than half the time)
    3 = Sometimes (about half the time)
    4 = Most times (much more than half the time)
    5 = Almost always/always

11. How often have you felt sexual desire?
    1 = Almost never/never
    2 = A few times (much less than half the time)
    3 = Sometimes (about half the time)
    4 = Most times (much more than half the time)
    5 = Almost always/always

12. How would you rate your level of sexual desire?
    1 = Very low/none at all
    2 = Low
    3 = Moderate
    4 = High
    5 = Very high

13. How satisfied have you been with your overall sex life?
    1 = Very dissatisfied
    2 = Moderately dissatisfied
    3 = About equally satisfied and dissatisfied
    4 = Moderately satisfied
    5 = Very satisfied

14. How satisfied have you been with your sexual relationship with your partner?
    1 = Very dissatisfied
    2 = Moderately dissatisfied
    3 = About equally satisfied and dissatisfied
    4 = Moderately satisfied
    5 = Very satisfied

15. How do you rate your confidence that you could get and keep an erection?
    1 = Very low
    2 = Low
    3 = Moderate
    4 = High
    5 = Very high

Figure 24–3. International Index of Erectile Function Questionnaire.

standardized panel of tests can be offered for the man presenting routinely with sexual dysfunction including ED. Further laboratory testing can be tailored to the clinical situation. Similarly, specialized endocrinologic assessment can be performed when indicated for select clinical presentations.

Recommended laboratory tests for men with sexual problems typically include serum chemistries, fasting glucose, complete blood count, lipid profile, and serum total testosterone. Total testosterone, measured from a morningtime blood draw, serves to screen androgenic status and, if

abnormally low, serum-free (or bioavailable) testosterone and leutinizing hormone should be measured. Prolactin measurement may also be done for hormonal assessment. Thyroid function tests may be performed at the clinician's discretion. Serum PSA testing is performed as needed if prostate pathology is suspected that might be promoted by exogenously administered testosterone. Dipstick analysis of urine may reveal glucosuria, which suggests the diagnosis of diabetes.

SPECIALIZED EVALUATION AND TESTING

The implicit goal of specialized evaluations in medicine in general is to improve diagnostic accuracy and direct successful therapy on the basis of the specific diagnosis. A similar principle applies to sexual medicine. However, at the present time, despite the availability of various technologies that may specify and define the causation for ED (i.e., vasculogenic, neurogenic, endocrinogenic, psychogenic), the treatment plan for this sexual dysfunction can often be formulated without carrying out extensive diagnostic testing. **Nonetheless, such testing is frequently applied for diagnostic precision, typically by specialists, particularly in settings of complex clinical presentations.** Table 24–5 summarizes the most frequently used evidence-based test procedures for diagnostic evaluations of ED (Rosen et al, 2004c).

Vascular Evaluation

The vascular evaluation for ED conceptually connotes surveying the vascular requirements of the sexual organ for the erectile response: arterial blood inflow, blood engorgement, and blood retention within the corporal structures. **From a diagnostic standpoint, the studies aim to assist in deriving the classical diagnoses of arterial impairment and veno-occlusive dysfunction.** As for all diagnostic testing, hemodynamic tests of the penis require that the patient is counseled regarding the purpose, alternatives, risks, and benefits of any procedure before its implementation.

Combined Intracavernous Injection and Stimulation

The CIS test serves as a first-line evaluation of penile blood flow because of its basic manner of administration and assessment. **The test involves the intracavernous injection of a vasodilatory drug or drugs as a direct pharmacologic stimulus, combined with genital or audiovisual sexual stimulation, and the erectile response is observed and rated by an independent assessor** (Donatucci and Lue, 1992; Katlowitz et al, 1993). **The test is designed to bypass neurologic and hormonal influences involved in the erectile response and allows the clinician to evaluate the vascular status of the penis directly and objectively.**

The clinician may decide the protocol for using vasodilator drugs. Alternative regimens include alprostadil alone (Caverject or Edex, 10 to 20 μg), a combination of papaverine and phentolamine (Bimix, 0.3 mL), or a mixture of all three of these agents (Trimix, 0.3 mL). The procedure requires a syringe with a ⅝-inch needle (27 to 29 gauge), which is inserted at the lateral base of the penis directly into the corpus cavernosum for medication delivery. After needle withdrawal, manual compression is applied to the injection site for 5 minutes to prevent local hematoma formation. The assessment is done periodically afterwards to rate both rigidity and duration of response. Repeated dosing may be performed if the initial erectile response is poor. Return to penile flaccidity is required before allowing the patient to leave the office, and if detumescence does not occur spontaneously in approximately an hour after dosing, intracavernous injection of a diluted phenylephrine solution (500 μg/mL) can be done every 3 to 5 minutes until flaccidity returns.

A normal CIS test, based on the assessment of a sustainably rigid erection, is understood to signify normal erectile hemodynamics. Alternative diagnoses of psychogenic, neurogenic, or endocrinogenic ED may then be considered. However, it is known that false-positive results may occur in up to 20% of patients with borderline arterial inflow (as defined by the measurement of 25 to 35 cm/sec peak cavernous artery systolic

Table 24–5.
Evidence-Based Tests for Organic Erectile Dysfunction and Recommendations

TEST	RECOMMENDATION*
Vascular	
Dynamic infusion cavernosometry and cavernosography (DICC)	B
Intracavernous injection pharmacotesting (ICI)	B
ICI and color duplex ultrasound	B
Arteriography	C
Computed tomography angiography	D
Magnetic resonance imaging (MRI)	D
Infrared spectrophotometry	D
Radioisotope penography	D
Audiovisual Sexual Stimulation (AVSS)	
Independent or jointly with vascular testing	C
With or without: pharmacologic stimulation (oral, ICI)	C
Neurophysiologic	
Nocturnal penile tumescence and rigidity (NPTR)	B
Erectiometer/rigidometer	D
Biothesiometry (vibratory thresholds)	C
Dorsal nerve conduction velocity	C
Bulbocavernosus reflex latency	B
Plethysmography/electrobioimpedance	D
Corpus cavernosum electromyography (CC-EMG)	C
MRI or positron emission tomography scanning of brain (during AVSS)	D

*Grades of recommendation:
A: At least one meta-analysis, systematic review, or randomized controlled trial with a low level of bias and directly applicable to the target population.
B: A body of evidence including high-quality systematic reviews of case-control or cohort studies directly applicable to the target population and demonstrating overall consistency of results.
C: A body of evidence including well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal, directly applicable to the target population, with overall consistency of results.
D: Nonanalytic studies (e.g., case reports, case series, expert opinion).
Modified from Rosen RC, Hatzichristou D, Broderick G, et al. Clinical evaluation and symptom scales: sexual dysfunction assessment in men. In: Lue TF, Basson R, Rosen F, et al, editors. Sexual medicine: sexual dysfunctions in men and women. Paris: Health Publications; 2004. p. 173–220; and Harbour R, Miller J. A new system for grading recommendations in evidence-based guidelines. BMJ 2001;323:334–6.

flow on duplex ultrasound) (Pescatori et al, 1994). False-negative results are also possible and occur most commonly because of patient anxiety, needle phobia, or inadequate dosage.

Duplex Ultrasonography (Gray Scale or Color Coded)

Duplex ultrasound of the penis following pharmacostimulation or CIS represents second-line evaluation of penile blood flow. **However, it is the most reliable and least invasive diagnostic modality for assessing ED. The test adds an imaging dimension and a quantification component to the evaluation of blood flow in the penis distinct from first-line evaluation, which relies on the assessor's judgment alone.**

The technique consists of high-resolution (7 to 10 MHz) real-time ultrasonography and color pulsed Doppler, which serves to visualize the dorsal and cavernous arteries selectively and to perform hemodynamic blood flow analysis (Lue et al, 1989). Scanning is applied to the surface of the penis and may include the entire penis from the crura in the perineum to the tip. Color-coded duplex ultrasound indicates the direction of blood flow within vessels, with red designating direction toward the probe and blue designating direction away from the probe (Broderick and Arger, 1993; Herbener et al, 1994). Flow velocities are measured at baseline before injection and commonly every 5 minutes afterwards up to 20 minutes. Cavernous arterial diameters may also be measured. Vascular anatomic communications between the paired cavernous arteries or between the dorsal and cavernous arteries should be noted (Fig. 24–4). Erection quality should also be simultaneously assessed and rated. An observed poor erection, possibly associated with patient anxiety, should prompt vasodilator redosing as recommended for the CIS test.

A standard pattern of Doppler waveforms occurs with hemodynamic changes in corporeal pressure during progression to normal full erection (Fig. 24–5) (Schwartz et al, 1991). In the filling phase when sinusoidal resistance is low (within 5 minutes after vasodilator injection), the waveform increases in size consistent with high forward flow during both systole and diastole. As intracavernous pressure increases, diastolic velocities decrease. With full erection, the systolic waveforms sharply peak and may be slightly less than during full tumescence. At maximal rigidity, when intracavernous pressure exceeds systemic diastolic blood pressure, diastolic flow may be zero. The sonographic color pattern of the cavernous artery may demonstrate an impressive shift from red to blue in association with the reversal of diastolic flow.

Normative values have been described for peak systolic velocity (PSV) and diameter of the cavernous arteries during increases in arterial inflow to the penis. Early studies documented that the PSV of the cavernous arteries consistently exceeded 25 cm/sec within 5 minutes of vasodilator injection in patients with nonarteriogenic causes of ED (i.e., psychogenic, neurogenic) (Lue et al, 1985; Mueller and Lue, 1988). Investigators subsequently confirmed mean PSV of cavernous arteries after pharmacostimulation to range from 35 cm/sec to 47 cm/sec in normal subjects (Benson and Vickers, 1989; Shabsigh et al, 1990). A cut point at 25 cm/sec

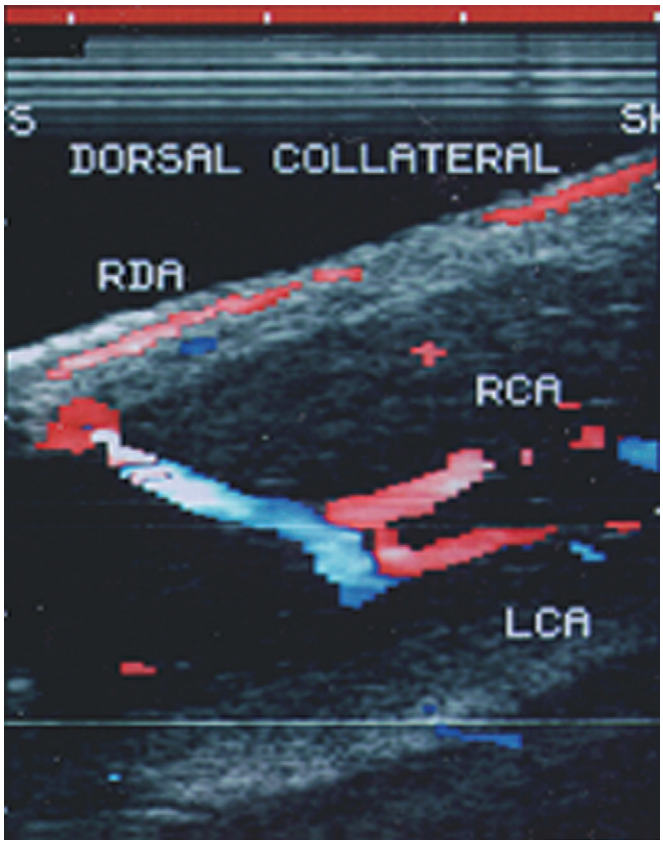


Figure 24–4. Collateral circulation connecting the right dorsal artery (RDA) to the right cavernous artery (RCA) and the left cavernous artery (LCA) is shown by color duplex ultrasound in a longitudinal view.

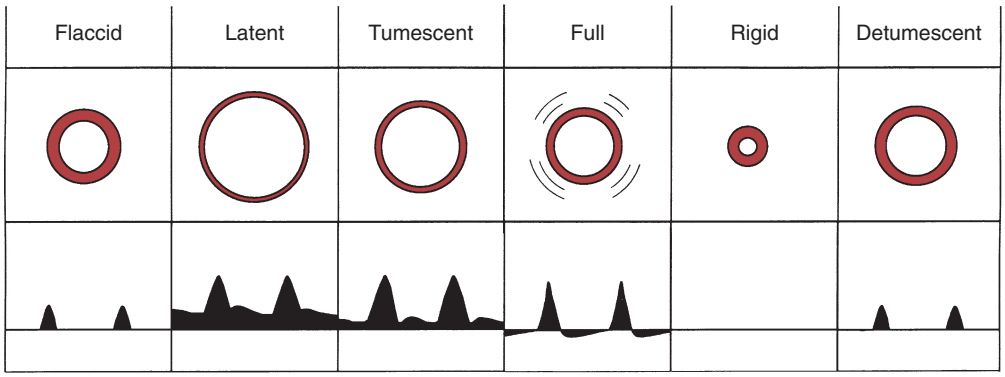


Figure 24–5. Artist's conception of the changes in diameter and flow waveform in the cavernous arteries induced by intracavernous injection of prostaglandin E_1 in a potent young man as demonstrated by duplex ultrasound. Forceful concentric pulsations are particularly noticeable during full erection.

had a sensitivity of 100% and a specificity of 95% in patients with abnormal pudendal arteriography (Quam et al, 1989). Diameter changes of the cavernous artery after vasodilator injection were found to increase less than 75% and rarely exceed 0.7 mm in patients with severe vascular ED (Lue and Tanagho, 1987; Mueller and Lue, 1988). Importantly, unlike PSV changes, percentage of cavernous arterial vasodilation was not found to correlate well with findings on pudendal arteriography (Jarow et al, 1993).

Vascular arterial anatomic variants may confound the interpretation of duplex ultrasonography (Breza et al, 1989; Jarow et al, 1993). Early cavernous arterial branching or the presence of multiple such branches may affect blood flow velocity determinations of the main cavernous artery. The presence of distal arterial perforators extending from the dorsal or spongiosal arteries also may alter the measurement of cavernous arterial blood flow velocity. Accordingly, the clinician must recognize these variants to avoid making the incorrect diagnosis of arteriogenic ED. On the other hand, asymmetric blood flow of the cavernous arteries may have diagnostic significance. The findings of dissimilar cavernous artery velocity measurements, which are greater than 10 cm/sec between sides, or reversal of flow across a collateral may suggest a significant atherosclerotic lesion (Benson et al, 1993).

Duplex ultrasound measurements are informative for diagnosing vasculogenic ED (Rosen et al, 2004c). **Cavernous arterial insufficiency is suggested when PSV is less than 25 cm/sec; a PSV consistently greater than 35 cm/sec defines normal cavernous arterial inflow.** Cavernous artery acceleration time (i.e., PSV divided by systolic rise time) greater than 122 msec may also indicate this diagnosis. Cavernous veno-occlusive dysfunction, which refers to failure of erection maintenance despite adequate cavernous arterial inflow, is suggested by assorted sonographic parameters. Generally meaningful at 15 to 20 minutes after stimulatory onset, these parameters include persistent high systolic flow velocities (i.e., PSV > 25 cm/sec) and high end-diastolic flow velocities (EDV > 5 cm/sec), accompanied by rapid detumescence, following stimulatory onset. In addition, vascular resistive index (RI), based on the formula: RI equals PSV minus EDV that is then divided by PSV, has had tremendous diagnostic utility in this regard. The parameter is based on the concept that, as penile intracavernous pressure during erection achievement equals or exceeds diastolic pressure, diastolic flow in the corporal bodies will approach zero and the value for RI will approach one. **An RI greater than 0.9 has been associated with normal penile vascular function, and that less than 0.75 is consistent with veno-occlusive dysfunction** (Naroda et al, 1996).

Several technical modifications of sonographic evaluation of the penis have been described. A portable Midus pulsed Doppler unit connected to a laptop computer for in-office testing reliably records the Doppler waveform of the cavernous arteries despite not providing a real-time ultrasound image (Metro and Broderick, 1999). Power Doppler offers an even more specialized technique to visualize distal ramifications of the main cavernous artery down to the level of arterioles (Sarteschi et al, 1998; Golubinski and Sikorski, 2002). A somewhat more invasive approach that evaluates the integrity of cavernosal arterial flow involves the measurement of the cavernous artery systolic occlusion pressure (CASOP) by a Doppler transducer during saline intracavernous infusion (Rhee et al, 1995). As a variation on the stimulatory component of penile sonographic testing, a combination of an oral PDE5 inhibitor in association with visual erotic stimulation has been shown to be an effective, noninvasive method (Bacar et al, 2001; Speel et al, 2001). Sonographically measured postocclusive vasodilation of the cavernous arteries, which is believed to relate to the level of intact endothelial function in the penis, has been found to be diagnostic for organic ED (Virag et al, 2004). Cavernous artery intima media thickness as demonstrated by high-resolution echo color Doppler ultrasound has been suggested to be more accurate than PSV in predicting vasculogenic ED (Caretta et al, 2009).

Dynamic Infusion Cavernosometry and Cavernosography

Cavernosometry and cavernosography, precisely referring to functional hemodynamic and radiographic assessments of the corpora cavernosa, represents third-line evaluation of the vascular integrity of the penis. **The testing is indicated for select patients who are suspected to have a site-specific vasculogenic leak resulting from perineal or pelvic trauma or who have had life-long ED (primary ED). When used, it generally precedes consideration for corrective penile vascular surgery.**

The technique involves two needles inserted into the penis for simultaneous saline infusion and intracavernous pressure monitoring following intracavernous pharmacologic injection. The testing requires complete trabecular smooth muscle relaxation to avoid erroneous results, and repeated and maximal pharmacologic dosing protocols are recommended (Hatzichristou et al, 1995). Measurements of maintenance flow rate, pressure drop, and CASOP are done to verify complete smooth muscle relaxation (Fig. 24–6).

Dynamic infusion cavernosometry and cavernosography evaluate the penile venous outflow system. **The existence of veno-occlusive dysfunction is indicated by the failure to increase intracavernous pressure to the level of the mean systolic blood pressure with saline infusion or the demonstration of a rapid drop of intracavernous pressure after cessation of saline infusion** (Puyau and Lewis, 1983; Rudnick et al, 1991; Shabsigh et al, 1991; Motiwala, 1993). The flow rate required to maintain erection at an intracavernous pressure of more than 100 mm Hg is normally less than 3 to 5 mL/min, and the pressure decrease in 30 seconds from 150 mm Hg is normally less than 45 mm Hg. **Cavernosography follows cavernosometric evaluation and is intended to reveal the site of venous leakage** (Fig. 24–7). With normal veno-occlusive function, there should be opacification of the corpora cavernosa with minimal or no visualization of venous structures or corpus spongiosum. With impaired veno-occlusive function, leakage may be identified into such sites as the glans, corpus spongiosum, superficial dorsal veins, and cavernous and crural veins. More than one site is visualized in the majority of patients (Lue et al, 1986; Rajfer et al, 1988; Shabsigh et al, 1991).

Penile Angiography

Penile angiography essentially refers to an anatomic study of the arterial vasculature of the penis and also represents third-line evaluation of the penile vascular system. **It is commonly reserved for the young patient with ED secondary to a traumatic arterial disruption or the patient with a history of penile compression injury, who is being considered for penile revascularization surgery.**

The procedure involves selective cannulation of the internal pudendal artery and injection of radiographic contrast. The intracavernous injection of a vasodilating agent is optimally used to induce maximal vasodilation of the penile arterial supply. The anatomy and radiographic appearance of the iliac, internal

pudendal, and penile arteries are then evaluated and documented (Fig. 24–8). The inferior epigastric arteries are frequently studied as well to determine their suitability for use in surgical revascularization. It should be recognized that significant variation of the intrapenile arterial anatomy exists, challenging the angiographer to differentiate congenital variations from acquired abnormalities and establish their clinicopathologic relevance (Bähren et al, 1988; Benson et al, 1993).

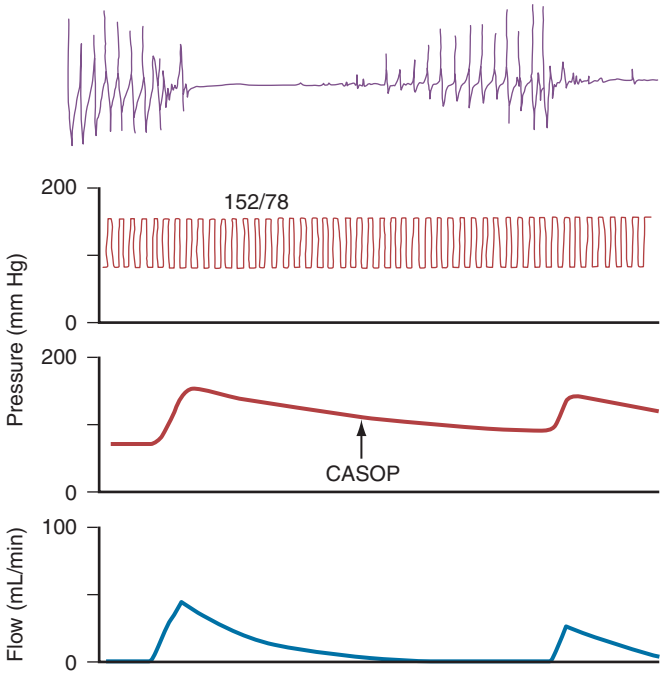


Figure 24–6. This tracing depicts four simultaneous variables obtained during the third phase of dynamic infusion cavernosometry and cavernosography. Top to bottom, Cavernosal artery flow recorded by using a continuous-wave Doppler ultrasound probe; systemic brachial systolic and diastolic arterial blood pressure (150/87 mm Hg); intracavernosal pressure, which varied from 70 to 160 mm Hg in this tracing; and intracavernosal heparinized saline inflow. The intracavernosal pressure at which the cavernosal artery pulsations returned, the effective cavernosal artery systolic occlusion pressure (CASOP), was 108 mm Hg. The gradient between the brachial and the cavernosal artery systolic occlusion pressures was 150 to 108, or 42 mm Hg, which is abnormal.

Historical and Investigational Studies of Penile Blood Flow

Penile Brachial Pressure Index

This test refers to the penile systolic blood pressure divided by the brachial systolic blood pressure. The technique involves applying a small pediatric blood pressure cuff to the base of the flaccid penis and measuring the systolic blood pressure with a continuous-wave Doppler probe. A PBI of 0.7 or less has been used to indicate arteriogenic ED (Metz and Bengtsson, 1981). **The technique has not been found to be valid, basically because it does not assess the hemodynamic properties of a functionally relevant, induced erection, and thus it is not recommended for use** (Aitchison et al, 1990; Mueller et al, 1990).

Penile Plethysmography (Penile Pulse Volume Recording)

This test evaluates arterial pressure waveforms in the penis with an aggregate of the contributions of all penile vessels (Kedia, 1983). It requires the application of a 2.5- or 3-cm cuff connected to an air plethysmograph applied to the base of the penis, inflating the cuff to a pressure above brachial systolic pressure, and then decreasing the pressure by 10–mm Hg increments while recording pressure waveform tracings. Abnormal pressure waveforms by diagnostic criteria have been used to indicate vasculogenic ED (Doyle and Yu, 1986). **Because this study is done in the flaccid penis like the PBI, its clinical relevance has been questioned.** Despite this concern, a technical modification that measures postischemic flow-mediated dilation was introduced as being informative regarding penile vascular endothelial function (Dayan et al, 2005; Vardi et al, 2009).

Radioisotopic Penography

This test quantifies changes in penile blood volume after intracavernous injection of a vasoactive agent using ^{99m}Tc-labeled red blood cells (Shirai et al, 1976). Extremely low flow is understood to mean arteriogenic ED (Smith et al, 1998). An evaluation comparing color Duplex ultrasound and radionuclide penography showed poor correlation (Glass et al, 1996).

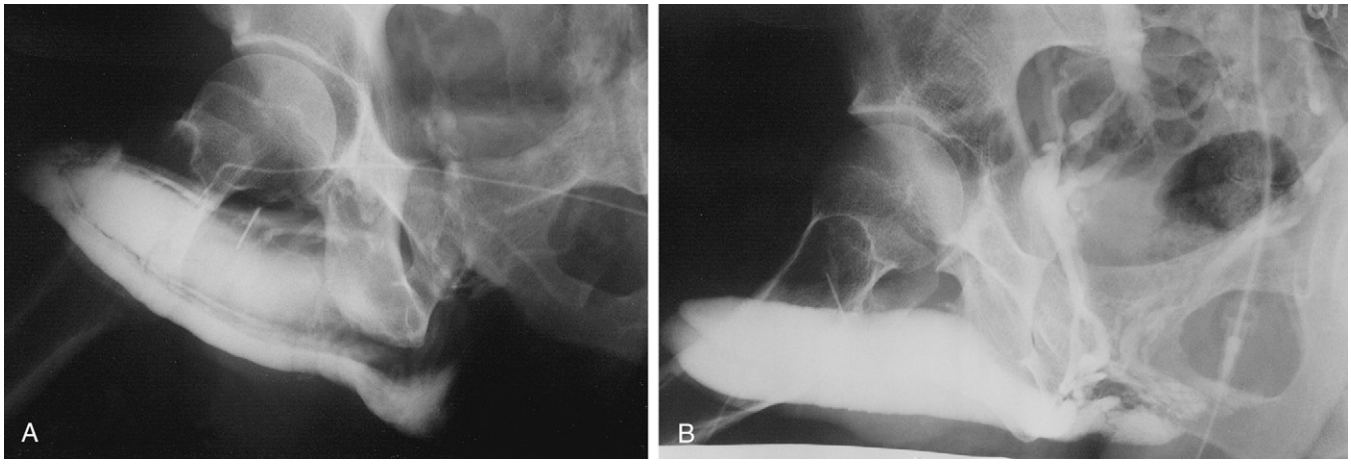


Figure 24–7. Pharmacologic cavernosography. **A,** In a patient 1 year after a penile fracture, a communication between the corpus cavernosum and the spongiosum is seen. **B,** In a 27-year-old man with primary impotence, venous leakage from the crura is seen.

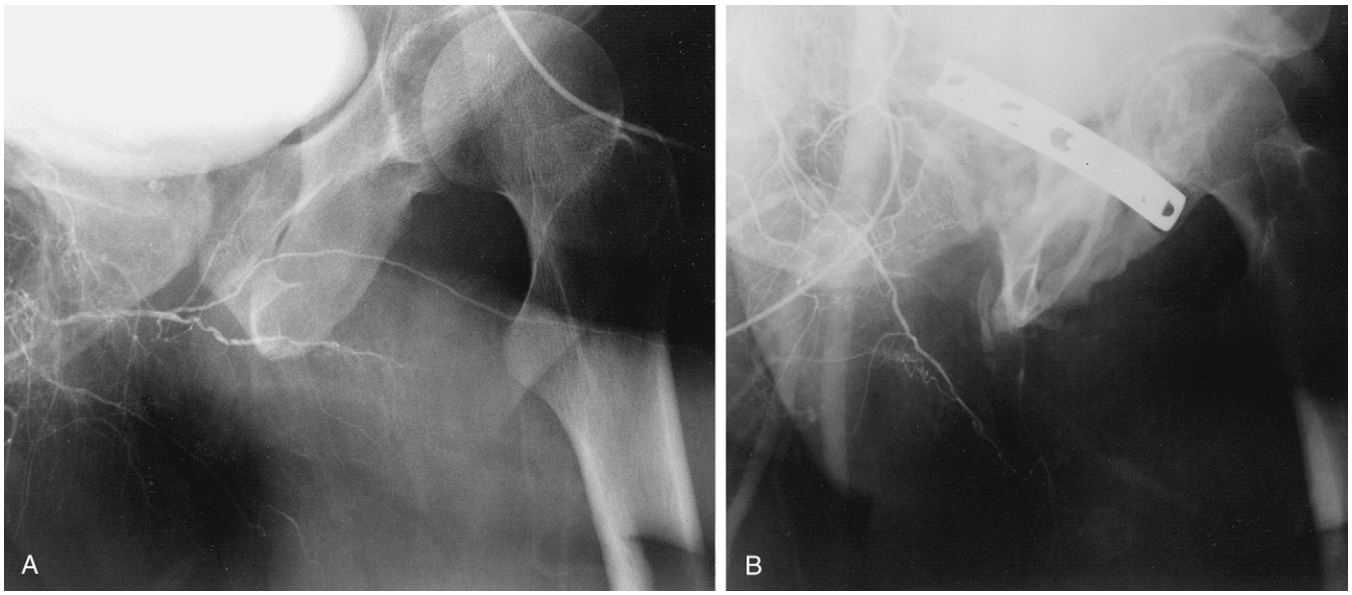


Figure 24–8. In this patient with a pelvic injury, pharmacologic penile arteriography (after intracavernous injection of 60 mg of papaverine) shows patent common penile, dorsal, and cavernous arteries **(A)** and nonvisualization of the common penile artery and its branches **(B)**.

Penile Magnetic Resonance Imaging

This test has significant potential applications for the assessment of anatomic details of the penis and penile microcirculation. Angiographic techniques may be combined with it to evaluate the anatomic condition of the internal iliac and penile vasculature. Magnetic resonance angiography has been shown to have good correlation with color duplex ultrasound testing (Stehling et al, 1997; John et al, 1999).

Penile Near-Infrared Spectrophotometry

This test provides continuous, quantitative measurements of penile blood flow using a specialized near-infrared spectrophotometry instrument (Burnett et al, 2000). It may be applied with an erectile stimulus and documents the hemodynamic phenomena of erection. Penile spectrophotometry has been further investigated in combination with intraurethral pharmacotherapy documenting blood flow increase to the penis with this erectogenic modality (Padmanabhan and McCullough, 2007). Further investigation of this technique is necessary to establish its clinical utility.

Cavernous Smooth Muscle Content

This test evaluates the smooth muscle composition of the corporeal tissue by light microscopic and computed morphometric assessment of biopsies of the penis and may serve adjunctively in the diagnosis of vasculogenic ED (Wespes et al, 1992). A reduced proportion of corporeal smooth muscle (and correspondingly increased collagen) has been observed in older men with venoocclusive dysfunction (19% to 36% smooth muscle) and arteriogenic ED (10% to 25%), compared with that of young, healthy men with normal erections and penile curvature (40% to 52%) (Wespes et al, 1991). In part because of its invasiveness, the test is controversial and thus it remains investigational at present.

Psychophysiologic Evaluation

The psychophysiologic evaluation of ED seeks to evaluate the erectile response applying techniques that directly measure penile tumescence and rigidity. From the historical perspective of ED diagnostics, testing was applied primarily to differentiate psychogenic from organic ED. In general, the documentation of a full erection indicates functional integrity of the neurovascular axis regulating penile erection and thereby raises suspicion of a psychogenic etiology. There are several approaches to perform this evaluation. Importantly, the psychophysiologic evaluation does not currently represent first-line evaluation for ED, largely because of technical and cost limitations associated with current techniques. When considered to undergo any of these tests as part of a diagnostic plan, patients are counseled with regard to their expected utility and risks and benefits.

Penile Tumescence and Rigidity Monitoring

Nocturnal penile tumescence (NPT) monitoring, which describes the study of erections that occur with nighttime sleep, was classically described as a technique offering assessment of physiologic erectile ability (Wasserman et al, 1980). **Standardly, sleep laboratory nocturnal penile tumescence and rigidity (NPTR) testing applies nocturnal monitoring devices that measure the number of episodes, tumescence (circumference change by strain gauges), maximal penile rigidity, and duration of nocturnal erections** (Kessler, 1988). The conventional approach is to perform monitoring in conjunction with electroencephalography, electro-oculography, and electromyography (EMG), with nasal airflow and with oxygen saturation to document rapid eye movement (REM) sleep and the presence or absence of hypoxia (sleep apnea). Importantly, documentation of REM sleep is done because of the observation that true erectile phenomena occurring during sleep are associated with the REM sleep phase (Fisher et al, 1965). Sleep movement patterns are also monitored because periodic limb movement disorders are associated with abnormal NPT. Axial rigidity is measured along with photography of the erect penis on awakening the patient at maximal tumescence; a buckling device is applied to the tip of the penis to measure resistance (500 g minimum for vaginal penetration, 1.5 kg suggestive of complete rigidity) (Karacan et al, 1977). NPT has traditionally been performed over two to three nights to

overcome the so-called first-night effect when REM sleep is inconsistent. Formal testing, which involves a specially equipped sleep laboratory staffed with trained observers, is costly. The monitoring of diurnal penile tumescence, in reference to monitoring performed during daytime napping, has served alternatively as an in-office evaluation (Morales et al, 1994).

Rigiscan (Timm Medical Technologies, Inc. Minneapolis, MN) is an automated, portable device used for NPTR, which combines the monitoring of radial rigidity, tumescence, number, and duration of erectile events (Bradley et al, 1985). The device employs two loops, one placed at the base of the penis and the other placed at the coronal sulcus (respectively, base and tip recording sites), which record penile tumescence (circumference) and radial rigidity with timed, standardized constrictions of the loops. A baseline initialization is done with the patient in the office, and then it is calibrated for home use. At home, registrations of penile rigidity are done every 3 minutes and increased to every 30 seconds when the base loop detects a circumference increase of greater than 10 mm (Fig. 24–9). **Recommended criteria for normal NPTR include four to five erectile episodes per night, mean duration longer than 30 minutes, an increase in circumference of more than 3 cm at the base and more than 2 cm at the tip, and maximal rigidity above 70% at both base and tip** (Cilurzo et al, 1992). A computerized program has yielded standardized data measurements according to cumulative distribution of time-intensity measures, defined as tumescence activity units (TAU) and radial rigidity activity units (RAU) (Burris et al, 1989; Levine and Carroll, 1994). Potential limitations of Rigiscan include that radial rigidity does not accurately predict axial rigidity (Allen et al, 1993; Licht et al, 1995) and considerable variability apparently exists even in normal subjects (Levine and Carroll, 1994). Further, the manner of testing does not allow verification of the presence of REM sleep.

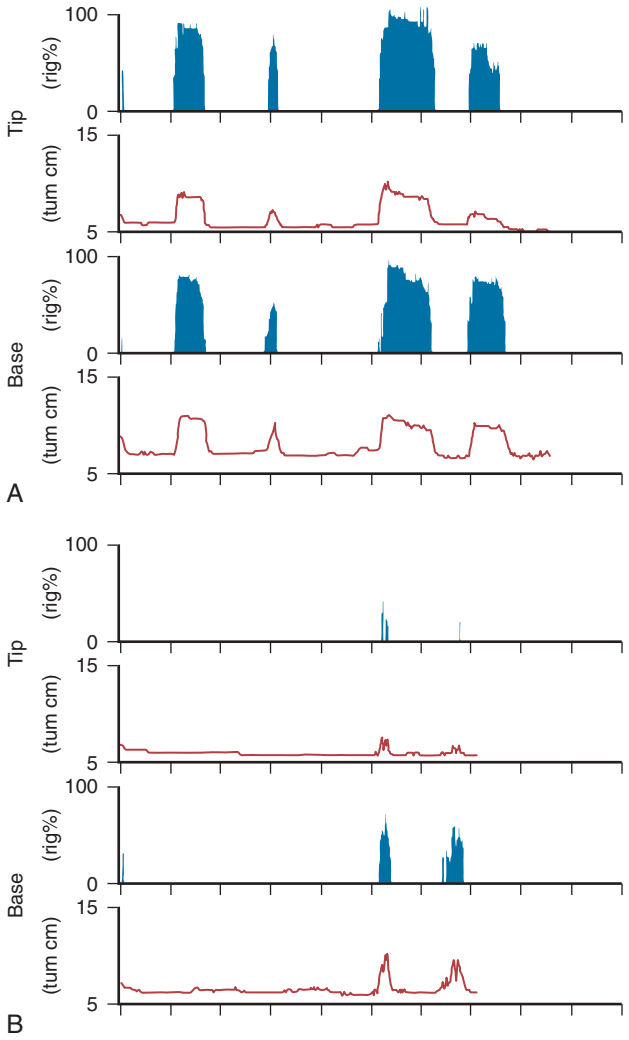


Figure 24–9. The RigiScan device has been designed to measure penile rigidity during home nocturnal monitoring. **A,** A study in a patient with at least two episodes of well-sustained, completely rigid nocturnal erections. **B,** A study with two episodes of poorly sustained, poorly rigid nocturnal erections. Such home studies fail to document sleep quality.

NPT electrobioimpedance (NEVA, American Medical Systems, Inc., Minnetonka, MN) is a more recently introduced device that assesses volumetric changes in the penis during nocturnal erections (Knoll and Abrams, 1999). The device consists of three small electrode pads applied to the hip and the penile base and glans and a small recording device attached to the patient's thigh. In operation, an undetectable alternating current is transmitted from the glans electrode to the hip ground, and the penile base electrode measures impedance and changes in penile length. Impedance measures decrease in concert with increases in cross-sectional area of the penis during nocturnal tumescence. Further investigation is necessary to establish the relationship of volumetric changes and rigidity of the penis. Similar to Rigiscan, the technique does not include REM sleep monitoring and correlations.

In summary, NPTR monitoring is an attractive approach for objectively evaluating the somatic basis of erectile ability, theoretically devoid of psychologic interference. However, it has several apparent shortcomings, which limit its routine use for diagnostic purposes (Jannini et al, 2009). Central issues are that the testing does not indicate the cause and severity of ED and that it may be poorly reproducible. A fundamental issue, too, is whether the testing appropriately evaluates wakeful, sexually relevant erections. Indeed, erections observed during NPTR monitoring do not unequivocally equate with erections sufficient for sexual performance, and false-positive results are possible for various clinical situations (e.g., multiple sclerosis). False-negative results may occur in aging patients and in patients with depression or anxiety, which may conditionally affect the physiology of sleep-related erectile phenomena. Nonetheless, NPTR monitoring may be considered in special circumstances such as when the cause of ED is obscure and noninvasive testing is desirable.

Audiovisual and Vibratory Stimulation

Alternative erectogenic methods can be used in conjunction with diagnostic testing of erectile function. **Erotic stimulation by explicit videotape material with monitoring has been used as a reliable and time- and cost-effective alternative to NPTR for differentiating between organic and psychogenic ED presentations** (Sakheim et al, 1987; Bancroft et al, 1991). **It is also considered more physiologic, consistent with erectile behavior when awake.** The testing has potential limitations, with possible false-negative responses occurring in the presence of endocrine abnormalities (Carani et al, 1992; Greenstein et al, 1995) and false-positive responses occurring in psychologic situations such as erotic excitement inhibition (Chung and Choi, 1990). As one may infer, these methods can be applied in conjunction with other stimulatory conditions (e.g.,

pharmacologic erection testing), as well as erectile function assessment approaches (e.g., Rigiscan monitoring) (Katlowitz et al, 1993; Martins and Reis, 1997).

Neuroimaging

Diagnostic techniques to evaluate central mechanisms of male sexual arousal have contributed to the psychophysiologic investigation of ED. Positron emission tomography (Miyagawa et al, 2007) and functional magnetic resonance imaging (Park et al, 2001; Montorsi et al, 2003; Mouras et al, 2003; Ferretti et al, 2005) have been used in association with video sexual stimulation or an erectogenic pharmacologic stimulus (e.g., oral apomorphine). Studies have documented key brain regions associated with sexual arousal that induce penile erection (i.e., anterior cingulate, insula, amygdala, hypothalamus, and secondary somatosensory cortices). Interestingly, functional abnormalities in the brain have been shown in patients with psychogenic ED, suggesting that this diagnosis may be attributable to an actual biologic basis. More investigation in this area is necessary before determining its clinical role.

Psychologic Evaluation

The psychologic evaluation of ED addresses psychogenic contributions to clinical presentations, essentially psychologic and interpersonal factors interfering with erectile function. These aspects should not be underestimated, and it is well documented in population studies that ED is associated with anxiety, depression, low degrees of self-esteem, negative outlook on life, self-reported emotional stress, and a history of sexual coercion (Feldman et al, 1994; Laumann et al, 1999). The urologist's role in initiating a psychologic evaluation is not necessarily complicated, and a basic attempt employing queries about a patient's psychologic health is useful in assessing sexual health (Rowland et al, 2005).

The diagnostic interview is central to the psychologic evaluation, and this process should be done straightforwardly. **Immediately discernible causes of sexual dysfunction may be elicited such as fear of failure; performance anxiety (for widowers, this may include complex interactions of dating, new partners, and unresolved mourning/guilt); insufficient sexual stimulation; loss of attraction for the partner; adjustment to a chronic illness or surgery; and relationship conflicts.** Less immediately discernible causes may be identified as well to include unresolved parental attachments, sexual identity issues, history of sexual trauma, occurrence of extramarital affairs, and cultural-religious taboos (Leach and Bethune, 1996; Laumann et al, 1999).

The interviewer should be mindful of the possibility of a primary psychogenic ED presentation (Turnbull and Weinberg, 1983). **In the absence of organic risk factors, a primary psychogenic ED causation may be suspected. Further support for the diagnosis may follow the confirmation of noncoital erections (i.e., masturbatory, nocturnal or on awakening).** Clinical subtypes of psychogenic ED may be further identified: (1) generalized versus situational and (2) lifelong (primary) versus acquired (secondary including substance abuse or major psychiatric illness).

The interviewer should also inquire about relationship factors (Rosen, 2001). Relationship conflicts may be the source of psychogenic ED or otherwise may exacerbate organic ED. Couple's issues include intimacy and trust, status and dominance, loss of sexual attraction, ability to achieve sexual satisfaction without erection, and communication problems. Important information may derive not just from interviewing the patient alone, and interviews both with the couple together and of partners separately may prove insightful.

Complex intrapsychic causes of sexual dysfunction are often relevant for the ED presentation and may become evident during the diagnostic interview. The clinical history may reveal a significant traumatic life experience, cultural or religious strife, compulsive sexual behavior, or neurotic process. It may suggest the presence of serious psychiatric comorbidities such as substance abuse, depressive symptoms, anxiety disorder, or personality disorder. It is recognized that the urologist may not have the professional background, comfort, or time to address these issues definitively, and a referral to a psychologic expert for further attention would certainly be appropriate.

Neurologic Evaluation

The neurologic evaluation of ED is concerned with neurogenic associations with ED presentations. **The importance of testing for deficits in the neurologic system relates to the principal regulatory role of this system for governing erectile function. Target sites for evaluation include peripheral, spinal, and supraspinal centers, as well as both somatic and autonomic pathways involved in this biologic response.** In line with this purpose, several diagnostic tests have been introduced. However, thus far they have had limited impact on routine clinical management decisions, and much of the available testing in this realm is reserved for research protocols and medicolegal investigations. Additionally, fundamental problems surround the lack of sensitivity, reproducibility, reliability, and validity for many of these tests. This concern is particularly so for autonomic function tests, distinct from somatic function testing, which has been shown to be reproducible and valid. Otherwise, tests that could be most useful for evaluating penile erection (e.g., neurotransmitter release) await development altogether.

Somatic Nervous System

Biothesiometry. This test represents a technique to assess afferent sensory function of the penis (Padma-Nathan, 1988). Testing involves a hand-held electromagnetic device placed on the pulp of the index fingers, both sides of the penile shaft, and the glans penis. Measurements of sensory perception threshold are obtained in response to various amplitudes of vibratory stimulation. Investigators have questioned the utility of penile glans biothesiometry, which does not accurately portray neurophysiologic function of the dorsal penile nerve because of limitations in recording responses to vibratory stimuli of glanular skin (Bemelmans et al, 1995).

Sacral Evoked Response—Bulbocavernosus Reflex Latency. This test is used to assess the somatosensory reflexogenic mechanism of penile erection. Testing consists of a direct-current stimulator, which delivers square-wave impulses via two stimulating ring electrodes placed around the penis, one secured near the corona and the other secured 3 cm more proximally, and a recorder, which gauges responses via concentric needle electrodes placed in the right and left bulbocavernous muscles. Latency period is measured as the interval from the beginning of each stimulus to the beginning of each response. An abnormal latency time, defined as a value more than three standard deviations above the mean (30 to 40 msec), indicates a high probability of neuropathology (Padma-Nathan, 1988). However, the utility of this test has been

questioned, and it has been shown that a full battery of electrophysiologic tests evaluating limb nerve function is more sensitive in diagnosing neuropathy than such tests specific to pudendal nerve function alone (Vodusek et al, 1993; Ho et al, 1996).

Dorsal Nerve Conduction Velocity. This test in concept extends from pudendal nerve function reflex testing and involves electrophysiologic stimulation with two stimulating electrodes placed at the glans and the base of the penis for obtaining two bulbocavernosus reflex latency measurements. Conduction velocity of the dorsal nerve is represented by dividing the distance between the two stimulating electrodes by the difference in latency times recorded from both sites. An average conduction velocity of 23.5 m/sec with a range of 21.4 to 29.1 m/sec is found in normal subjects (Gerstenberg and Bradley, 1983). Abnormal nerve conduction velocities were found to be diagnostic for neurogenic ED in patients with diabetes (Kaneko and Bradley, 1987).

Genitocerebral Evoked Potential. This test is designed to assess afferent sensory mechanisms and stimulus processing at spinal and supraspinal nervous system levels. The testing requires complex electronic equipment for recording the evoked potential waveforms overlying the sacral spinal cord and cerebral cortex in response to dorsal penile nerve electrical stimulation (Spudis et al, 1989). Central conduction time is recorded as the difference between the latency times after stimulation of the first replicated spinal response and the first replicated cerebral response (Padma-Nathan, 1988). The test has been questioned as having poor discriminatory value of response latencies (Pickard et al, 1994). However, it may still serve as an objective tool to define characteristics of afferent penile sensory dysfunction in patients with subtle abnormalities on neurologic examination.

Autonomic Nervous System

Heart Rate Variability and Sympathetic Skin Response. The test of heart rate control (mainly parasympathetic) consists of measuring heart rate variations during quiet breathing, deep breathing, and in response to raising the feet. Normative parameters have been documented. The test of sympathetic skin response involves producing an electrical shock stimulus at a certain location (e.g., median or tibial nerve) and recording the evoked potential elsewhere (e.g., contralateral hand or foot or penis). Recording from the penis is considered to be a potentially useful method of testing penile autonomic innervation (Daffertshofer et al, 1994).

Penile Thermal Sensory Testing. This test serves to assess the conductance of small sensory nerve fibers, which are affected by autonomic disturbances consistent with neuropathy. The testing measures thermal threshold. In studies of the penis, it seems to correlate very well with the clinical determination of neurogenic ED (Lefaucheur et al, 2001; Bleustein et al, 2003).

Corpus Cavernosum Electromyography (CC-EMG) and Single Potential Analysis of Cavernous Electrical Activity. This test offers a direct recording of cavernous electrical activity, which varies between penile flaccidity and tumescence (Wagner et al, 1989). In the normally flaccid penis, electrical activity is described to have a rhythmic slow wave with intermittent bursts of activity. As penile tumescence occurs (such as in response to visual sexual stimulation or after intracavernous injection of a smooth muscle relaxant), this activity ceases. During detumescence, the baseline electrical activity returns. Patients with suspected autonomic neuropathy were demonstrated to display a discordant pattern, having continued electrical activity during erectogenic stimuli (Wagner et al, 1989). Recording techniques have been standardized, and normative values have been defined to include maximum peak-to-peak amplitudes between 120 and 500 mV and mean potential durations of 12 seconds (Stief et al, 1994). However, its clinical utility remains in question (Kellner et al, 2000; Jiang et al, 2003).

Hormonal Evaluation

The hormonal evaluation for ED explores an endocrinologic basis for the sexual dysfunction and recognizes accumulating evidence that endocrinopathies potentially affect the physiology of penile erection (Traish and Guay, 2006; Mirone et al, 2009). **Several endocrine conditions are particularly relevant in this regard: hypogonadism (decrease or absence of hormonal secretion from the gonads), hyperthyroidism (excessive thyroid hormone release), and diabetes (altered modulation of androgen function). The diagnostic evaluation may be undertaken in view of their possible influences on erectile function.** The clinical history may raise suspicion of the diagnosis, although the clinical presentation of an endocrinopathy may be quite variable. Several questionnaires have been proposed for use in screening, particularly with respect to hypogonadism (Morley et al, 2000; Daig et al, 2003; Heinemann, 2005). However, their general lack of specificity for most presentations and lack of sensitivity for some others has limited their widespread applications (Morales et al, 2007). The central feature of this evaluation involves biochemical testing for serum hormonal levels.

Serum Testosterone Measurements

Much focus in assessing the impact of endocrinopathies on male sexual function has centered on the role of androgens. Androgen deficiency or low testosterone levels are observed in as low as 2% and as high as one-third of men presenting clinically with ED (Korenman et al, 1990; Citron et al, 1996; Soran and Wu, 2005). Differences in patient populations under study likely account for the variation in statistics. In acknowledgment that aging may represent the primary cause of declining androgens, thought leaders have variously applied such terms as androgen deficiency of the aging male (ADAM), partial androgen deficiency of the aging male (PADAM), hypoandrogenism, symptomatic late-onset hypogonadism (SLOH), and andropause to designate this association.

It is important to understand the biology of testosterone production and function in order to proceed with its laboratory evaluation. **Testosterone circulates in three fractions: free (0.5% to 3%), tightly bound to sex hormone binding globulin (SHBG) (≈30%), and loosely bound to albumin and other serum proteins (≈67%)** (Basaria and Dobs, 2001; Freeman et al, 2001). **Free testosterone and albumin-bound portions comprise the bioavailable testosterone fraction. The relative concentrations of the carrier proteins (SHBG and albumin) serve to modulate androgen function.** Numerous conditions can alter the SHBG fraction and accordingly affect bioavailable testosterone to some extent even if the total testosterone measurement is unchanged (Bhasin et al, 2006). Decreased SHBG is associated with moderate obesity, nephrotic syndrome, and hypothyroidism, as well as use of glucocorticoids, progestins, and androgenic steroids, and it produces an elevation in bioavailable testosterone. Increased SHBG is associated with aging, hepatic cirrhosis, hyperthyroidism, human immunodeficiency virus infection, and use of anticonvulsants and estrogens, and it produces a lowering in bioavailable testosterone. Despite the observation that lower levels of SHBG are associated with insulin resistance (Stellato et al, 2000), variable SHBG levels have been documented in diabetic men, possibly because of confounding obesity and aging factors, and the diagnosis of hypogonadism

in this population should rely on the measurement of a low bioavailable testosterone level (see later) (Kapoor et al, 2007).

Theoretically, the unbound or free fraction measurement of testosterone offers the most relevant determination of testosterone bioavailability. However, commercial assays for free testosterone are known to be inconsistent and have been considered to be invalid by some investigators (Vermeulen et al, 1999). **The best indicator of androgen status is the calculated bioavailable testosterone (free testosterone and albumin-bound testosterone).** A formula for this calculation is found on the website of the International Society for the Study for the Aging Male at http://www.issam.ch/freetesto.htm and requires entries for the values of total testosterone and SHBG. In men with serious liver disease or hypoalbuminemia, entry of the serum albumin value may be useful for obtaining the best calculation.

For screening purposes, measurement of total serum testosterone level is generally sufficient. It is recommended that the blood draw be done between 7 and 11 AM, when there is a peak serum testosterone level, accounting for the fact that diurnal variation occurs in younger and middle-aged men (Wang et al, 2009). **The typical reference range for the total testosterone measurement is 280 to 1000 ng/dL. It is recognized that because of individual variability the normal range for testosterone beyond which replacement therapy should be initiated remains unresolved.** If the testosterone level is below or at the low limit of normal, it should be repeated for confirmation. On the other hand, a mildly abnormal testosterone may be found to be normal in 30% of patients on repeat testing (Bhasin et al, 2006). The clinical scenario, such as the presence of conditions that alter testosterone carrier proteins, may prompt further testing and assessment decisions.

Serum Gonadotropin Measurements

When proceeding with a second total testosterone determination, assessment of leutinizing hormone (LH) and prolactin should also be included. Measurement of serum gonadotropins will help to localize the source of the hypogonadism. It is understood that testosterone release involves the integrative activity of the hypothalamic-pituitary-gonadal axis and its regulatory feedback mechanisms, and disruption at any level of this axis may account for hypogonadism (Bhasin et al, 2006). Low testosterone results in decreased negative feedback to the hypothalamus and pituitary, causing increased secretion of LH and follicle-stimulating hormone (FSH). Elevated serum LH and FSH releases are appropriate pituitary responses to low serum testosterone levels, which is consistent with testicular failure (primary hypogonadism). In contrast, normal or low serum LH and FSH releases in the setting of low serum testosterone levels indicate an inappropriate response and suggest a central disorder (secondary hypogonadism).

Serum Prolactin Measurement

Hyperprolactinemia causes hypogonadism by suppression of gonadotropin-releasing hormone from the hypothalamus, which impairs pulsatile LH secretion required for serum testosterone production by the gonads (Morales et al, 2004). An additional possible mechanism for sexual dysfunction, specifically loss of sexual libido, in patients with hyperprolactinemia independent of the circulating level of testosterone relates to an interference of the peripheral conversion of testosterone to dihydrotestosterone (Lobo and Kletzky, 1983). **Suspicion of hyperprolactinemia is raised in the patient with low serum testosterone and low or inappropriately normal LH.** However, controversy surrounds the consideration of routine determinations of prolactin in men with ED, with some indicating the low yield in doing so (Johnson and Jarow, 1992; Govier et al, 1996) and others finding that low serum testosterone or low sexual desire does not always coincide with the diagnosis (Buvat and Lemaire, 1997; Johri et al, 2001). Causes of the condition include various medications such as antipsychotic agents, tricyclic depressants and opiates, prolactin-secreting tumors, hypothyroidism, hypothalamic lesions, renal insufficiency, cirrhosis, and chest wall lesions (Zeitlin and Rajfer, 2000; Molitch, 2005).

Magnetic Resonance Imaging Scans

Cases of central (hypogonadotropic) hypogonadism and unexplained hyperprolactinemia prompt central imaging of the pituitary. This evaluation commonly involves magnetic resonance imaging, which can identify structural abnormalities (Citron et al, 1996; Petak et al, 2002; Rhoden et al, 2003). **Generally accepted guidelines provide indications for pituitary imaging: cases of severe central hypogonadism (testosterone <150ng/dL) and suspicion of pituitary disease (i.e., panhypopituitarism, persistent hyperprolactinemia, or symptoms of tumor mass effect).**

Serum Thyroid Function Tests

Hyperthyroidism is associated with ED, possibly by increasing aromatization of testosterone into estrogen (which raises levels of SHBG) (Morales et al, 2004) **or by increasing adrenergic tone (which causes smooth muscle contractile effects or exerts psycho-behavioral effects)** (Carani et al, 2005). Symptoms of hyperthyroidism such as hyperactivity, irritability, heat intolerance, palpitations, fatigue, and weight loss are often reported, and physical signs such as tachycardia, tremor, goiter, and eyelid retraction are often identified. **The diagnosis is made biochemically by measurement of high levels of thyroid hormone (total or free T4 or T3) with a low serum thyroid-stimulating hormone level.**

Key Points: Diagnostic Evaluation

- The basic evaluation of ED consists of a detailed case history, physical examination, and proper laboratory tests.
- The sexual history should define the characteristics of the ED presentation according to such features as its onset, duration, conditions, severity, and etiology.
- Cardiac risk assessment and risk reduction interventions are appropriate when necessary for all patients presenting for ED evaluations.
- The hormonal evaluation for ED explores an endocrinologic basis for the disorder, with special consideration given to hypogonadism, hyperthyroidism, and diabetes as possible influences.
- Questionnaires and other patient self-report measures offer practical utility in documenting the presence, severity, and responsiveness to treatment of ED.
- Specialized evaluation and testing may be required for individuals with complicated or atypical presentations of ED and potentially offer improved therapeutic outcomes for these presentations.

TREATMENT CONSIDERATIONS

The treatment of ED axiomatically follows an appropriate diagnostic workup. Although current interventions are both etiologically specific and nonspecific, an intervention that is specific for the cause of ED ideally offers the opportunity to treat ED with a corrective purpose in mind. **Current recommendations adhere to a patient goal-directed focus to therapy and specify that therapeutic options are presented according to a step-care clinical management approach** (Fig. 24–10) (Montague et al, 2005; Hatzichristou et al, 2010).

Lifestyle Modification

The risk of developing ED is highly associated with the presence of comorbid health conditions such as diabetes, cardiovascular disease, and metabolic syndrome that are either preventable or to a minimal extent treatable in the endeavor to optimize health status (Kostis et al, 2005). It stands to reason that optimization of these diseases offers opportunities to prevent the development of ED or ameliorate its extent.

Epidemiologic studies have examined potentially modifiable risk factors and in some instances provided support that risk modification may indeed improve erectile function. For instance, several reports have suggested that discontinuation of cigarette smoking results in a recovery of functional erection status (Mannino et al, 1994; Feldman et al, 2000; Bacon et al, 2006). A beneficial role of increasing exercise for those with sedentary lifestyle in men with ED was also shown (Feldman et al, 1994; Derby et al, 2000). In a recent prospective study, obese men with moderate ED and no overt symptoms of cardiovascular disease showed significant improvements in IIEF scores after exercise and weight control compared with a control group, which followed an educational program alone (Esposito et al, 2004). Significant changes in body mass index, C-reactive protein and physical activity scores were observed in the intervention group compared with the control group. Mediterranean-style diets and a reduction in caloric intake have been found to improve erectile function in men with metabolic syndrome (Esposito et al, 2006). A change to a no-nose saddle from a conventional saddle was shown to recover erectile function, presumably by alleviating perineal trauma, in a short-term interventional study of men with ED associated with occupational bicycle riding (Schrader et al, 2008).

Reports indicating that ED is potentially ameliorated by lifestyle modifications of risk factors that predispose this sexual dysfunction are most illuminative. **More definitive clinical and basic science evidence is certainly necessary to evaluate biologic mechanisms associated with these risk factors and affirm the benefits of risk modification.** However, current knowledge about these risks still prompts recommendations for a healthy and fit lifestyle for maximal erectile function preservation.

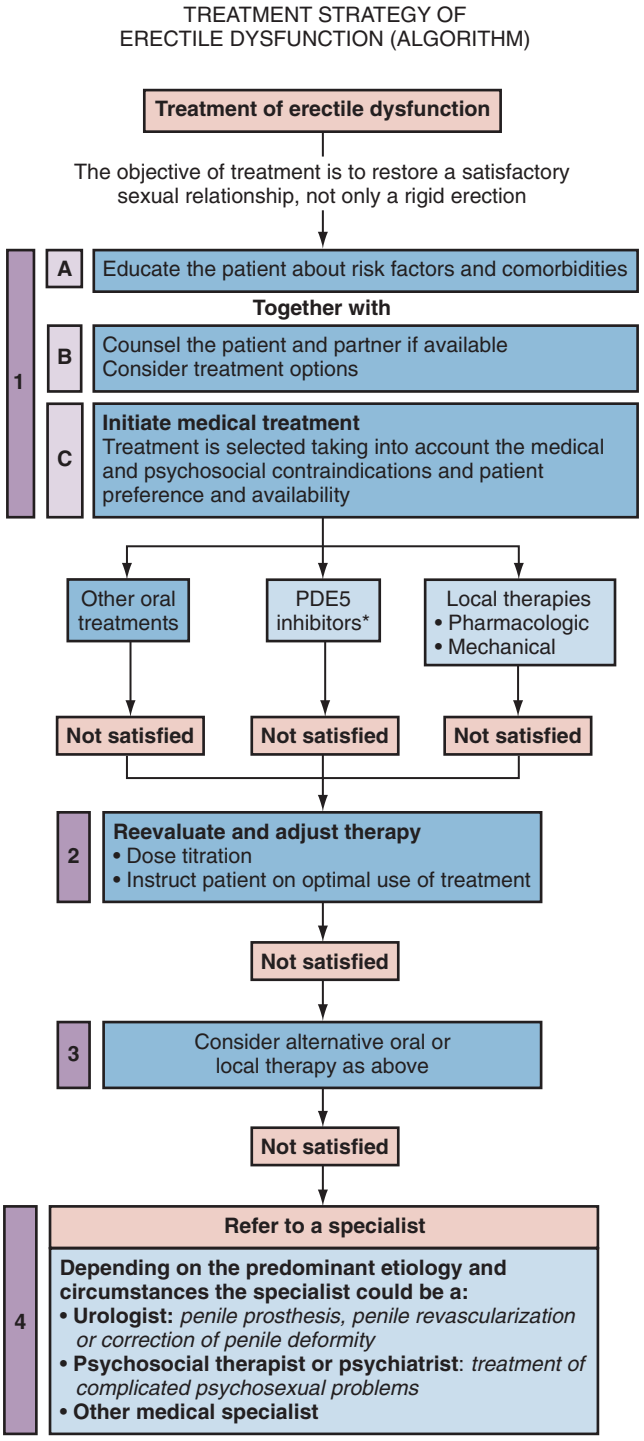


Figure 24–10. Treatment algorithm for erectile dysfunction recommended by the International Consultations on Sexual Medicine.

Medication Change

It is quite possible that a certain medication is an offending factor resulting in the clinical presentation of ED. After this inference is made, an appropriate next step would be to change to a different dose or type of medication entirely considering that this action may reverse ED in some patients (Ralph and McNicholas, 2000). For instance, switching antihypertensive therapies from thiazide diuretics and β-blockers to calcium channel blockers and renin-angiotensin system inhibitors (i.e., angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) may recover erectile function in men developing ED in this clinical setting. Similarly, in patients suffering adverse sexual dysfunction effects from use of selective serotonin reuptake inhibitors (SSRI) (e.g., ED, retarded ejaculation), such treatment strategies as drug substitution (e.g., bupropion, nefazodone, buspirone, mirtazapine), drug holidays, SSRI dosage reduction, watchful waiting, and administration of PDE5

inhibitors have enabled sexual function recovery (Rosen et al, 1999; Nurnberg et al, 2001).

Psychosexual Therapy

Because of the frequent interplay of psychologic and interpersonal factors in clinical presentations of ED, it is hardly surprising to consider that psychosexual therapy should be included in the therapeutic armamentarium for this sexual dysfunction. A strong limitation of this area is that evidence-based investigation and well-controlled, large-scale outcome research documenting the efficacy of interventions are generally lacking. In practice, psychosexual therapy does represent an ill-defined combination of interventions and interpretations on the basis of behavioral, relational, psychoanalytic, and cognitive psychology concepts. **A variety of interventions are used: systematic anxiety reduction/desensitization, sensate focus, interpersonal therapy, cognitive-behavior therapy, sex education, couples' communication and sexual skills training, and masturbation exercises** (Althof et al, 2005). **Integrated treatments, which combine psychosexual interventions with medical therapies such as oral therapy, intracavernosal injection, or vacuum device therapy have been successful, too, in managing ED presentations, particularly those associated with motivational obstacles** (Hawton, 1998; Althof et al, 2005). For urologists, collaborative efforts with other specialists who have expertise in psychosexual therapy may be advantageous to provide effective, comprehensive treatment.

Hormonal Therapy

A prescription of hormonal therapy is considered for the patient in whom a hormonal disturbance is identified to affect the clinical presentation of ED. The urologist's role is fitting for the treatment of primary hypogonadism and hyperprolactinemia, whereas endocrinologists would be considered foremost consultants for other endocrinopathies.

Testosterone Replacement

Androgen replacement straightforwardly addresses the clinical complaint that is associated with hypogonadism. As a general principle of sex steroid replacement therapy, serum hormone levels to be achieved over the 24 hours of the day should ideally achieve normal reference values and resemble the normal diurnal pattern. **Evaluating serum testosterone levels both before and during treatment is imperative, although the efficacy of testosterone supplementation is best judged by clinical response rather than a precise testosterone determination. Current recommendations suggest that a short (e.g., 3-month) therapeutic trial is justified, and in the absence of a response testosterone administration should be discontinued** (Wang et al, 2009). Potential adverse effects of androgen therapy (i.e., erythrocytosis, sleep apnea, urinary symptoms, prostate cancer progression risk, gynecomastia, acne) should be recognized (Morales et al, 2004; Wald et al, 2006). **Monitoring of patients on therapy consists of a baseline assessment that includes digital rectal examination and serum PSA testing along with laboratory evaluation (i.e., hemoglobin/hematocrit levels, liver function tests, cholesterol level, and lipid profile) followed by assessment of treatment efficacy after 1 to 3 months and annually thereafter to assess symptom response and any adverse events** (Morales et al, 2004; Bhasin et al, 2006). Short-acting preparations may be preferred over long-acting depot preparations in the initial treatment of patients so that therapy can be discontinued on the occasion of an adverse event (Wang et al, 2009).

For the treatment of hypogonadism, several testosterone preparations are offered and can be delivered by various routes: injectable, subcutaneous, transdermal (patch and gel), buccal, and oral (Edelstein et al, 2006; Morgentaler et al, 2008; Wang et al, 2009). A brief description of available therapies follows (see also Table 24–6).

Injectable. Testosterone enanthate, an injectable depot preparation of testosterone, is delivered by deep intramuscular injection 150 to 300 mg every 2 to 4 weeks). The schedule of therapy results in supraphysiologic levels of testosterone for 72 hours with a steady exponential decline to subphysiologic levels by 10 to 12 days. Alternative dosing of 100 mg every 7 to 10 days can be considered in situations when patients experience symptomatic mood or sexual fluctuations associated with documented early hypogonadal troughs. Another parenteral preparation, testosterone cypionate, is also delivered intramuscularly at a dosage 200 mg every 2 to 3 days because of its shorter half-life, and it may also display serum testosterone fluctuations. Testosterone undecanoate (TU), as a depot formulation consisting of 750 mg or 1000 mg dosages administered at 10-week dosing intervals, has been used in Europe since 2003 but is not yet available in the United States.

Subcutaneous. Pellets offer a subcutaneous, long-acting depot formulation of testosterone. Testopel is a pellet containing 75 mg of testosterone. Dosing usually requires two to six pellets (150 to 450 mg testosterone) implanted subcutaneously every 3 to 6 months.

Transdermal. Transdermal delivery options comprise patches and gels, with a delivery approach that intendedly simulates normal circadian levels of testosterone. When patients apply medication in the morning, higher initial absorption will mimic normal diurnal variation.

Testoderm was approved initially as a daily administered scrotal patch without adhesive (4 to 6 mg), but it came under disuse because of difficulties with its application and the requirement for scrotal shaving, as well as finding that it significantly produced high levels of dihydrotestosterone (DHT) by conversion by 5α-reductase activity that is plentiful on scrotal skin. Testoderm TTS represented an alternative formulation avoiding the inconveniences of the scrotal application. Its application is to the arm, back, or buttock as a 5-mg patch. Androderm, an alternative product, delivers 2.5 or 5 mg testosterone daily. Both patches have been associated with itching, chronic skin irritation, and allergic contact dermatitis. The skin irritation is alleviated by local application of cortisone cream. Patients are advised to alternate application sites and avoid sun-exposed areas.

AndroGel (testosterone gel) 1% gel pack is a topical gel, which contains 50, 75, or 100 mg of testosterone, with only 10% of the drug being absorbed during a 24-hour period. Testim, also providing 1% testosterone, is an alternative product packaged as a 5-g tube containing 50 mg of testosterone. Both are similarly applied once daily in the morning to clean, dry skin over the shoulders, upper arms, or abdomen and allowed to dry before dressing.

Buccal. Striant refers to a tablet-like, mucoadhesive treatment system (30 mg of testosterone) that continuously delivers medication. It is applied twice daily to the gum tissue above the incisors, allowing testosterone to be absorbed through the buccal mucosa.

Oral. Oral testosterone preparations are limited. Concern is associated with the liver toxicity of testosterone (i.e., hepatitis, cholestatic jaundice, hepatomas, hemorrhagic liver cysts, and hepatocellular carcinoma) related to large doses necessary to

Table 24–6.

Testosterone Preparations

PREPARATION	DOSE	ROUTE	SCHEDULE
Oral			
Methyltestosterone (Metandren)	10-30 mg	Sublingual	Daily
Testosterone undecanoate (Andriol)	120-160 mg	Oral	Daily
Fluoxymesterone (Halotestin)	5-20 mg	Oral	Daily
Methandrostenolone	5-10 mg	Oral	Daily
Buccal			
Striant	30 mg	Buccal	q 12 hr
Transdermal Patches			
Testoderm TTS	5 mg	Skin	Daily
Testoderm	4-6 mg	Scrotum	Daily
Androderm	2.5-5 mg	Skin	Daily
Transdermal Gel			
Androgel 1%	5 g	Skin	Daily
Testim 1%	5 g	Skin	Daily
Intramuscular			
Cypionate (Depo-testosterone)	150-300 mg	IM	q 2-4 wk
Enanthate (Delatestryl)	150-300 mg	IM	q 2-4 wk
Pellet			
Testopel	150-450 mg	SC	q 3-6 mo

Modified from Maas D, Jochen A, Lalande B. Age-related changes in male gonadal function. Drugs Aging 1997;11:45–50.

achieve normal serum levels (Bagatell and Bremner, 1996). Large doses (>200 mg/day) are required orally because much of the administration is rendered metabolically inactive during the "first pass" circulation through the liver. Chemical modifications of oral testosterone have been explored to overcome adverse reactions. Both 17α-methyltestosterone and fluoxymesterone have been formulated, but because of their patient variability of effect with potential liver toxicity risk, they should not be prescribed (Wang et al, 2009). TU, as an oral formulation in oleic acid, is safe by partly escaping hepatic inactivation (Köhn and Schill, 2003). However, it has shown a large individual variability for the time of maximal responses, as well as when maximal serum testosterone is attained. Oral TU remains unapproved in the United States.

Alternative Hormone Treatments

Alternative hormonal replacement therapies have been suggested, and they have posed certain desirable features and caveats. DHT as a direct mode of therapy is attractive because of its action as a pure androgen that is not aromatizable to estradiol, and accordingly it has been demonstrated that the hormone does not exert adverse estrogenic effects on prostate growth or lipid profile measurements (Kunelius et al, 2002; Sakhri and Gooren, 2007). A therapeutic DHT gel is available at a dose of 125 to 250 mg/day, yielding plasma DHT levels comparable with physiologic testosterone levels (Kunelius et al, 2002). Dehydroepiandrosterone (DHEA), a hormone supplement with androgen-like and estrogen-like effects, has been used although limited evidence exists showing it improves sexual function (Baulieu et al, 2000; Morales et al, 2004). Importantly, the treatment cannot be considered harmless, and the potential exists for DHEA and other non-testosterone androgen precursor preparations (e.g., DHEA-S, androstenediol, androstenedione) to stimulate hormone-sensitive diseases such as breast or prostate cancer. Human chorionic gonadotropin (HCG) has been found to increase total and free testosterone and estradiol 50% above baseline and conceivably would benefit hypogonadal men similar to effects of androgen administration. Clinical investigation of HCG has shown some anthropometric effects (i.e., decrease in fat mass, increase in lean body mass) and improvements in serum testosterone concentrations in androgen deficient men without documented benefits for sexual function (Liu et al, 2002; Tsujimura et al, 2005). Anti-estrogens and aromatase inhibitors have been shown to increase endogenous testosterone levels, and selective androgen receptor modulators are under development. Because of insufficient evidence about the therapeutic benefits and adverse effects of alternative replacement therapies in older men with hypogonadism, they are not currently recommended for use (Wang et al, 2009).

Hyperprolactinemia Treatments

The treatment of hyperprolactinemia is undertaken acknowledging that testosterone replacement therapy is neither corrective nor sufficient to improve sexual function. The therapeutic objective, rather, is to identify and address the underlying cause, which may then ameliorate ED. Offending drugs such as estrogens, morphine, sedatives, and neuroleptics should be discontinued (Molitch, 2008). A prolactin-secreting adenoma should be treated medically and, if necessary, surgically. Bromocriptine, a dopamine agonist that lowers prolactin level and restores testosterone production to normal, serves to reduce the size of the tumor. Neurosurgical ablation becomes necessary if the therapeutic response to medication does not occur or visual effects are noted in association with optic nerve compression (Gillam et al, 2006). Erection recovery is most evident after treatment of men with significant serum elevations of prolactin (>40 ng/mL) (Netto Júnior and Claro, 1993).

Pharmacologic Therapies

The premise of pharmacologic therapies is that they simulate the biochemical and molecular mechanisms of action naturally

governing the erectile response. **Conceptually, erectogenic therapies serve strategically either to promote proerectile mechanisms or oppose antierectile mechanisms, at both peripheral and central levels of the neurovascular axis responsible for penile erection** (Rowland and Burnett, 2000). At a peripheral level, these mechanisms influence corporal smooth muscle tone. Promotion of proerectile mechanisms is achieved by either inducing corporal smooth muscle activation through cell-receptor agonists or effectors of tissue relaxant pathways (e.g., stimulating second messenger cyclic nucleotide [cyclic guanosine monophosphate, cGMP or cyclic adenosine monophosphate, cAMP] synthesis) or inhibiting the deactivation of smooth muscle relaxation pathways (e.g., inhibiting phosphodiesterases), whereas opposition of antierectile mechanisms are achieved by decreasing smooth muscle contraction through receptor antagonists of tissue contractile pathways (e.g., α_1-adrenergic inhibitors). At a central nervous system level (i.e., brain or spinal cord), neuronal pathways are affected and potential opportunities exist to promote proerectile pathways (e.g., agonists of dopaminergic D_2 receptors in the medial hypothalamus) or oppose antierectile pathways (e.g., antagonists of 5-$HT_{1A/2}$ [serotonergic] receptors in the spinal cord).

Diverse therapies have been touted over time, although their efficacy and safety characteristics have not always been clearly defined. Current standards of regulatory agency approval have helped to clarify the qualifications of commercially developed and marketed therapies (Hirsch et al, 2004).

Oral Therapy

Orally administered medication for ED meets many of the attributes of "ideal therapy," which include convenience, simplicity, and noninvasiveness (Morales et al, 1995). Oral therapies are increasingly demanded to meet the therapeutic objective of clinical efficacy as well.

Phosphodiesterase Type 5 Inhibitors. This class of medication was famously inaugurated as an effective ED treatment in the United States following U.S. Food and Drug Administration (FDA) approval of sildenafil citrate (Viagra, Pfizer, Inc, New York) in 1998 and vardenafil hydrochloride (Levitra, Bayer Schering Pharma AG, Berlin) and tadalafil (Cialis, Lilly LLC, Indianapolis, IN) in 2003 (Burnett, 2005). **PDE5 inhibitors similarly work to block the catalytic action of the enzyme that degrades cGMP, the downstream effector of the erection mediator nitric oxide, which then facilitates the signal transductional mechanisms of corpus cavernosal smooth muscle relaxation required for penile erection. It is important to recognize that the medications augment but do not induce the erectile response and the induction of penile erection requires the release of nitric oxide from penile nerve endings and vascular endothelium under the influence of sexual stimulation.** The high concentration of PDE5 in the smooth muscle of the penile corpora cavernosa accounts for the selectivity of their effect.

Despite their similar modes of actions, PDE5 inhibitors differ somewhat in their biochemical properties, pharmacokinetic profiles, and clinical performances (Table 24–7). The chemical structures of sildenafil and vardenafil are similar, unlike that for tadalafil, and this difference does explain some phenomenological differences observed between the agents (Corbin and Francis, 1999). **Distinct from the action of tadalafil, sildenafil and vardenafil cross-react slightly with phosphodiesterase (PDE) type 6, which is expressed in the retina, and this difference may explain the complaint of visual disturbances observed with sildenafil and vardenafil use.** Tadalafil minimally cross-reacts with PDE type 11, unlike the other two PDE5 inhibitors, although the significance of this effect is unclear. The remaining side effects commonly observed with PDE5 inhibitor treatment are associated with inhibition of PDE5 localized in other target tissues such as vascular and gastrointestinal smooth muscle. Tadalafil possesses a longer half-life of elimination than the other two PDE5 inhibitors. This feature suggests a longer therapeutic window uniquely afforded for tadalafil, which may translate into increased convenience for couples to have sexual intercourse with this agent.

All three PDE5 inhibitors have demonstrated equivalent efficacy and tolerability in clinical trials for the treatment of ED of varying severity and cause (Carson and Lue, 2005; Hellstrom, 2007; Giuliano et al, 2009). Trial designs for the three PDE5 inhibitors have differed, limiting useful comparisons between them, and in the absence of directly comparative studies superiority cannot be claimed for any particular agent (Carson and Lue, 2005). **In general, the agents effectively achieve successful sexual intercourse rates of approximately 70%** (Carson and Lue, 2005). A somewhat reduced intercourse success rate of 40% to 50%

Table 24–7.

Comparison of Three PDE5 Inhibitors Currently Available in the United States

	SILDENAFIL	VARDENAFIL	TADALAFIL
Cmax (ng/mL)	450	20.9	378
Tmax (hr)	0.8	0.7-0.9	2
Onset of action (min)	15-60	15-60	15-120
Half-life (hr)	3-5	4-5	17.5
Bioavailability	40%	15%	Not tested
Fatty food	Reduced absorption	Reduced absorption	No effect
Recommended dosage	25, 50, 100 mg	5, 10, 20 mg	5, 10, 20 mg
Side effects:			
Headache, dyspepsia, facial flushing	Yes	Yes	Yes
Backache, myalgia	Rare	Rare	Yes
Blurred/blue vision	Yes	Rare	Rare
Precaution with antiarrhythmics	No	Yes	No
Contraindication with nitrates	Yes	Yes	Yes

Cmax, maximal plasma concentration; Tmax, time required to attain Cmax; Half-life, time required for elimination of one half of the medication from plasma.

has been reported in diabetic patients with ED (Fonseca et al, 2004; Safarinejad, 2004) and in patients with ED associated with radical prostatectomy in general (Hatzimouratidis et al, 2009). However, the intercourse success rate for patients specifically after bilateral nerve-sparing radical prostatectomy is somewhat better than for the entire group, and reports have commonly documented rates of functional erections with therapy that approach 60% to 70%.

According to standard dosing recommendations, patients are instructed to take the medications on demand approximately an hour before intended sexual activity. This lead-time interval is specified to take advantage of the duration by which the medications achieve peak serum concentrations (i.e., approximately 1 hour for sildenafil and vardenafil and 2 hours for tadalafil). Although the onset of activity has been documented to occur possibly within 20 minutes for each agent, this characteristic is less important to patients than erection hardness and maintenance of erections with therapy (Claes et al, 2008). A daily dosing regimen has been approved for tadalafil as an alternative treatment schedule to afford patients greater convenience in having sexual intercourse while using this agent (Porst et al, 2006; Shabsigh et al, 2010). **Optimization of effect for all PDE5 inhibitors is also achieved by properly applying sexual stimulation as a prerequisite for nitric oxide release; reducing food intake, which may delay drug absorption; escalating drug dosing as needed; and repeating attempts with the medications several times (up to 9 or 10 attempts affords maximal probability of success)** (McCullough et al, 2002; Barada, 2003; Shindel, 2009). **Correcting or improving adverse health conditions (e.g., glycemic control, hyperlipidemic control, androgen replacement), which affect drug efficacy, has also been demonstrated to be potentially beneficial** (Guay, 2003; Sadovsky et al, 2009). As evidence of therapeutic efficacy, patient and partner satisfaction with therapy (as shown for sildenafil) has been well demonstrated (Montorsi and Althof, 2004). Suboptimal acceptance or lack of long-term adherence to therapy (up to 47% of patients) has been reported, which may indicate the influence of psychosocial factors or challenges of a treatment that requires repeated dosing (Seftel, 2002; Al-Shaiji and Brock, 2009).

Patients using PDE5 inhibitors should be thoroughly counseled regarding precautions (Table 24–8). Cardiovascular safety using the medication has been well demonstrated, although it should be emphasized that given the cardiovascular risks of sexual activity and potential for adverse drug interactions with this therapy, cardiovascular risk assessment and stabilization should be considered for all men before institution of PDE5 inhibitor therapy. **Controlled and postmarketing studies involving these agents have shown that they do not cause an increase in myocardial infarction or death rates when compared with expected rates in study control populations** (Jackson et al, 2006; Hellstrom, 2007; Nehra, 2009). In addition, patients with known coronary artery disease or heart failure receiving PDE5 inhibitors did not exhibit worsening ischemia, coronary vasoconstriction, or worsening hemodynamics on exercise testing or cardiac catheterization. Caution is advised for the use of PDE5 inhibitors in patients with certain conditions: aortic stenosis, left ventricular outflow obstruction, hypotension, and hypovolemia. The agents have a minimal effect on QTc interval (Morganroth et al, 2004). Vardenafil among PDE5 inhibitors is not recommended in patients who take type-1A antiarrhythmics (e.g., quinidine or procainamide) or type-3 antiarrhytmics (e.g., sotalol, amiodarone) or in patients with congenital prolonged QT syndrome.

Table 24–8.

Warnings and Drug Interactions

The package inserts of all three PDE5 inhibitors warn against the use in patients with severe cardiovascular diseases and left ventricular outflow obstruction (e.g., aortic stenosis, idiopathic subaortic stenosis), those with severely impaired autonomic control of blood pressure, and patients not studied in clinical trials (U.S. prescribing information of Viagra, Cialis, and Levitra, August 2009). These include patients with:

- Myocardial infarction, stroke, or life-threatening arrhythmia within the previous 6 mo
- New York Heart Association class II or greater heart failure or coronary artery disease causing unstable angina
- Resting hypotension (<90/50 mm Hg) or hypertension (>170/100 mm Hg)
- Known hereditary degenerative retinal disorders including retinitis pigmentosa
- Severe hepatic impairment (Child-Pugh C) or end-stage renal disease requiring dialysis

Certain drugs such as ketoconazole and itraconazole and protease inhibitors such as ritonavir can impair the metabolic breakdown of PDE5 inhibitors by blocking the CYP3A4 pathway. Such agents may increase blood levels of inhibitors, requiring a PDE5 dose reduction. On the other hand, agents such as rifampin may induce CYP3A4, enhancing the breakdown of inhibitors and requiring higher PDE5 doses. Kidney or hepatic dysfunction may require dose adjustments or warnings.

Nitrate use in any form (e.g., sublingual nitroglycerin, isosorbide dinitrate, other nitrate preparations used to treat angina, amyl nitrite, and amyl nitrate "poppers") represents an absolute contraindication. Past use of nitrates (more than 2 weeks before the use of PDE5 inhibitors) is not considered a contraindication. **If angina occurs during sexual activity having used a PDE5 inhibitor, patients should cease this activity and seek emergency care immediately.** They should inform medical personnel that a PDE5 inhibitor was taken and avoid nitroglycerin use for a period of 24 hours for sildenafil and vardenafil and 48 hours for tadalafil (Cheitlin et al, 1999). If acute myocardial infarction occurs with the use of PDE5 inhibitors, usual therapies with the exception of organic nitrates may be administered. If hypotension results from PDE5 inhibitor use, patients should be placed in the Tredelenburg position and given intravenous fluids along with administration of α-adrenergic agonists (e.g., phenylephrine) as needed. Refractory hypotension warrants intra-aortic balloon counterpulsation, as specified by the American College of Cardiology/American Heart Association guidelines. **No pharmacologic antidote to the PDE5 inhibitor/nitrate interaction exists. Caution is advised when PDE5 inhibitors are coadministered with α-adrenergic blockers because both agents are vasodilators with blood pressure–lowering effects.**

Side effects observed with PDE5 inhibitor therapy include headache (15% to 16%), dyspepsia (4% to 10%), flushing (4% to 10%), myalgia/back pain (0% to 3%), nasal congestion (3% to 4%), and visual disturbances (e.g., photophobia, blue vision) (0% to 3%). Randomized, controlled trials have documented that flushing and visual side effects are more common in patients receiving sildenafil or vardenafil, whereas back pain/myalgia is more common in patients receiving tadalafil. These events have been found to be mild, abate with time, and prompt discontinuation in few patients (Hellstrom, 2007). **The concern of the development of nonarteritic anterior optic neuropathy (NAION), which can cause blindness, with PDE5 inhibitor therapy has been posed,**

although a careful review of pooled data from clinical trials for all three agents did not demonstrate an increased risk of NAION or other adverse ocular events associated with their use (Laties, 2009). Affected patients in postmarketing reports possibly carried risk factors for blindness to include hypertension, diabetes, and hyperlipidemia. At this time, despite the absence of a proven link between PDE5 inhibitor use and serious ocular disorders, physicians should continue to advise patients to stop use of PDE5 inhibitors and seek immediate medical attention as a safety measure in the event of a sudden loss of vision (Laties, 2009).

The interest to extend the utility of PDE5 inhibitors beyond an on-demand erectogenic role and rather apply them to recover or maintain the natural vitality of the penis in the face of an ED-associated disease state or condition has been investigated. This proposal has been considered particularly in the clinical context of radical prostatectomy and introduced as a therapeutic strategy à la "penile rehabilitation," by which the medications are taken in some regularly scheduled fashion to promote the recovery of spontaneous erectile function. Presently, this role remains unclear. Opposing outcomes were found in two controversial albeit well-designed and conducted (i.e., randomized, controlled) clinical trials of PDE5 inhibitor use after bilateral nerve-sparing radical prostatectomy. In one trial involving sildenafil treatment of 36 weeks starting 4 weeks after the surgery, 27% of patients using the agent recovered erections defined as "good enough for sexual activity" compared with 4% of patients on placebo at about 1 year after surgery (Padma-Nathan et al, 2008). In another trial involving vardenafil treatment of 9 months either on demand or daily starting 14 days after surgery, erection recovery was no different in patients administered vardenafil by either form of administration or placebo at about 1 year after surgery (Montorsi et al, 2008). Randomized, controlled trials in other ED contexts have also failed to show sustained natural erectile function improvement after discontinuing continuous regimens of PDE5 inhibitor therapy (Zumbé et al, 2008; Burnett et al, 2009).

The notion to combine PDE5 inhibitors with other ED therapies such as vasoactive penile pharmacotherapies has been proposed (Lau et al, 2006; McMahon et al, 2006). This strategy is to be considered "off label," and clinical precautions are advised.

α-Adrenoceptor Antagonists. Phentolamine mesylate is a nonspecific α-adrenergic receptor antagonist with equal affinity for blocking both α_1- and α_2-adrenoreceptors. Its mode of action presumably is to produce corporal smooth muscle relaxation by blocking the (antierectile) postsynaptic α_1-adrenergic receptor (Juenemann et al, 1986). Clinical trials suggested an efficacy rate in men with minimal ED of approximately 40% (Goldstein, 2000). The drug was considered to be relatively safe, with less than 10% of patients using the 40-mg dosage experiencing headaches, facial flushing, or nasal congestion. However, further investigation is required before determining whether it will produce erectile responses of sufficient quality for reliable sexual intercourse, particularly in men with more severe ED.

Yohimbine hydrochloride (Yocon), an indolalkylamine alkaloid derived from the bark of the yohimbe tree, reportedly exerts central effects on the mediation of penile erection operating as an α_2-adrenoreceptor antagonist (Clark, 1991; Giuliano and Rampin, 2000). Originally proposed to be an erectogenic and aphrodisiac agent, the drug has been investigated recently as an authentic ED treatment. It is conventionally prescribed orally at a dosage of 5.4 mg three times daily with observation for improvement over at least a month. A meta-analysis of all randomized, placebo-controlled trials involving yohimbine suggested a superior effect for the medication compared with placebo (Ernst and Pittler, 1998). **However, the drug does not appear to enable successful sexual intercourse any better than placebo in men with confirmed organic ED** (Montague et al, 1996; Teloken et al, 1998). Adverse effects appear to be relatively infrequent but include hypertension, anxiety, tachycardia, and headache. Although yohimbine may be well tolerated, its modest results suggest that it may be best limited to men with psychogenic ED.

Dopaminergic Agonists. Apomorphine (Uprima, TAP Pharmaceutical Products Inc, Lake Forest, IL) is a dopaminergic agent activating D_1 and D_2 receptors at a central level within the paraventricular nucleus of the brain, indicating its particular relevance in the treatment of men with psychogenic ED (Lal et al, 1987). The medication is taken in sublingual form, having a dosage range of 2, 4, and 6 mg, and it has no erectile efficacy if it is swallowed (Heaton, 2000). It has a rapid onset of action, with a mean time to erection of 12 minutes. Apomorphine achieves a maximal plasma concentration in 50 minutes, although its window of opportunity extends for approximately 2 hours from administration. In clinical trials involving men with ED of varying severities and etiologies, the drug achieved a successful sexual intercourse rate of 50.6% at the 4-mg dosage compared with the 33.8% placebo rate (Heaton, 2000). Side effects include nausea (16.9%), dizziness (8.3%), yawning (7.9%), somnolence (5.8%), sweating (5%), and emesis (3.7%). Syncope occurred in 0.6% of patients using the medication at the highest recommended dosage and was accompanied by a prodrome consisting of nausea, vomiting, sweating, dizziness, and light-headedness but no cardiac sequelae. Side effects were minimized when patients were titrated from higher to lower dosages. The drug achieved regulatory approval for commercialization by European authorities in early 2001, but it has not been so approved in the United States.

Melanocortin-Receptor Agonists. Melanocortin analogues (e.g., melanotan II, PT-141) have been studied showing efficacy in inducing erectile responses in early clinical trials (Wessells et al, 2000; Diamond et al, 2004). These drugs operate centrally at melanocortin-4 receptors, which have been implicated in controlling food intake and energy expenditure, as well as modulating erectile function and sexual behavior. Flushing and nausea have been reported as side effects. The drugs have not achieved regulatory approval for the treatment of ED.

Serotonin-Receptor Effectors. Trazodone (Desyrel) is an antidepressant that has been associated with priapism, prompting its "off-label" investigation as a possible treatment for ED (Lal et al, 1990). It is purported to work through mechanisms at the spinal cord level with multiple serotonergic effects (Allard and Giuliano, 2001). The active metabolite of trazodone acts as an agonist of the proerectile 5-HT_{2C} receptor through reuptake inhibition, with some affinity for the 5-HT_{2A} receptor, although it may also operate as an antagonist of antierectile 5-HT_{1A} receptors (Andersson and Wagner, 1995). Rigorous recent evaluations have not shown clinical efficacy that exceeds placebo responses in eliciting penile erection (Costabile and Spevak, 1999). Given its potential side effects (i.e., drowsiness, nausea, emesis, blood pressure changes, urinary retention, and priapism) and general lack of effect, this medication would appear to have a limited role for ED treatment.

Other Oral Therapies. Additional possibilities for the oral treatment of ED including L-arginine (the amino acid precursor of nitric oxide), L-dopa (dopamine precursor), limaprost (prostaglandin E_1), and naltrexone (opioid antagonist) have been proposed

(Burnett, 1999). Each of these agents has a plausible mechanism of action to induce erections. However, they remain insufficiently studied and their clinical roles remain unclear.

Intracavernous Injection

The discovery in 1982 that vasoactive agents, delivered by injection into the penis, induced erections is credited with launching the movement toward medical therapies for the treatment of ED (Virag, 1982; Zorgniotti, 1985). **Since that time, there has been an explosion of basic scientific and clinical research leading to the development and use of various locally administered vasoactive medications having mechanisms of action that result in corporal smooth muscle relaxation.** Although a host of medications have been explored for this purpose, three medications are used regularly in clinical practice: alprostadil, papaverine, and phentolamine (Table 24–9). **These have been administered clinically as a single agent (i.e., monotherapy) or in various combinations (e.g., bi-mix, tri-mix). Combination therapy offers a synergistic mechanism of the vasoactive agents to elicit maximal erectile responses, particularly among patients who have failed monotherapy** (Zorgniotti and Lefleur, 1985; Bennett et al, 1991; Floth and Schramek, 1991). This alternative may also be used to circumvent side effects of a certain agent (e.g., penile pain associated with alprostadil).

A general rule of thumb is to start with a small dose of medication, especially in patients with nonvasculogenic forms of ED. In-office self-injection training and education are recommended before home injection, and this opportunity may also be used to titrate medication toward a dosage that safely yields an erection of sufficient rigidity for sexual intercourse yet lasts no more than an hour (Benard and Lue, 1990; Fallon, 1995). **The therapy is contraindicated for men with psychologic instability, a history or risk for priapism, histories of severe coagulopathy or unstable cardiovascular disease, reduced manual dexterity (although the partner can be trained in the injection technique), and use of monoamine oxidase inhibitors (because of the risk of precipitating a life-threatening hypertensive crisis in the event that an intracavernosal α-adrenergic agonist is used to reverse a priapic episode)** (Sharlip, 1998).

Table 24–9.

Intracavernous Pharmacotherapies

TRADE NAME	DRUG	DOSAGES	EFFICACY (INTERCOURSE)
Caverject	Alprostadil (Prostin VR)	5-40 µg/mL	≈70%
Edex	Alprostadil (Prostin VR)	5-40 µg/mL	≈70%
Bi-mix	Alprostadil + phentolamine	20 µg/mL + 0.5 mg/mL	≈90%
Bi-mix Androskat (EU)	Papaverine + phentolamine	30 mg/mL + 0.5 mg/mL	≈90%
Tri-mix	Alprostadil + papaverine + phentolamine	10 µg/mL + 30/mg/mL + 1.0 mg/mL	≈90%
Invicorp	VIP + phentolamine	NA	≈80%
Thymoxamine	Moxisylyte	NA	≈70%

EU, European Union; VIP, vasoactive intestinal polypeptide.

Alprostadil. Alprostadil (Prostin VR) is a synthetic form of a naturally occurring fatty acid, prostaglandin E_1, which binds with specific receptors on smooth muscle cells and activates intracellular adenylate cyclase to produce cAMP, which in turn induces tissue relaxation through a second messenger system (Palmer et al, 1994). Currently it is the only FDA-approved injectable medication for ED, and it is marketed for this purpose by the trade names Caverject (Pfizer Inc, New York) and Edex (Schwarz Pharma, Milwaukee, WI) (Linet and Ogrinc, 1996; Porst, 1996; Buvat et al, 1998). After intracavernous injection, the medication is locally metabolized by 96% within 60 minutes and does not appreciably enter the peripheral circulation (Van Ahlen et al, 1994). **At dosages of 10 to 20 µg, alprostadil produces full erections in 70% to 80% of patients with ED** (Linet and Neff, 1994). Side effects of treatment are most commonly pain at the injection site or during erection (in 11% of patients), hematoma/ecchymosis (1.5%), prolonged erection/priapism (1% to 5%), and penile fibrotic lesions (2%) (Linet and Ogrinc, 1996). **Perceived advantages of alprostadil for intracavernous pharmacotherapy relative to other agents are lower incidences of prolonged erection, systemic side effects, and penile fibrosis. Disadvantages include a higher incidence of painful erection and higher cost, and once reconstituted into liquid from powder it has a shortened half-life if not refrigerated.**

Papaverine. Papaverine, an alkaloid isolated from the opium poppy, is a nonspecific PDE inhibitor, which prevents the degradation of cAMP and cGMP so that these cyclic nucleotides accumulate in smooth muscle cells and thereby increasingly promote tissue relaxation (Kukovetz et al, 1975). The compound also blocks voltage-dependent calcium channels along the membrane wall, thus impeding calcium influx to the cell, a process known to trigger smooth muscle contraction (Brading et al, 1983; Sunagane et al, 1985). Papaverine is metabolized in the liver, and the plasma half-life is 1 to 2 hours. Its general efficacy in promoting penile erection after intracavernous administration is less than 55%. The drug is inexpensive and stable at room temperature. However, disadvantages of commonly observed liver enzyme elevations, priapism risk (up to 35%), and penile fibrosis risk (1% to 33%) have led to its abandonment as monotherapy (Lakin et al, 1990; Fallon, 1995; Porst, 1996; Moemen et al, 2004).

α-Adrenoceptor Antagonists. Besides its purported oral role for ED therapy, phentolamine mesylate is more familiarly applied as an intracavernous agent (Regitine). Although its erectogenic effect is mediated by blocking the (antierectile) postsynaptic α_1-adrenergic receptor (Sironi et al, 2000), because of its potential inhibition of the prejunctional α_2-adrenergic receptor, which interferes with norepinephrine reuptake, the drug's tissue relaxant effect for penile erection is believed to be antagonized (Juenemann et al, 1986). This dual effect of the drug probably accounts for its limited success when administered intracavernously as a sole agent (Blum et al, 1985). It has a short plasma half-life (30 minutes). Common side effects associated with the drug include systemic hypotension, reflex tachycardia, nasal congestion, and gastrointestinal upset. Moxisylyte (Thymoxamine) is a competitive blocker of α_1-adrenoceptors with impressive erectogenic effects (Buvat et al, 1989). Its availability is restricted in the United States.

Vasoactive Intestinal Polypeptide. Vasoactive intestinal polypeptide (VIP), a hormone having 28 amino acids originally isolated from the small intestine, was proposed early on to be the elusive nonadrenergic noncholinergic (NANC) mediator of penile

erection because of its potent vasodilatory effects in various tissues (Adaikan et al, 1986). Its mechanism of action in smooth muscle is achieved through specific protein receptor binding and activation of adenylate cyclase, therebypromoting synthesis of cAMP and subsequent tissue relaxation (Andersson and Wagner, 1995). The drug has had disappointing effects when administered alone, although in separate combination with other drugs such as papaverine and phentolamine, erection responses were elicited (Kiely et al, 1989; Dinsmore and Wyllie, 2008). VIP in combination with phentolamine (Invicorp) is currently being sought for regulatory approval in the United States.

Intraurethral Suppositories

The administration of vasoactive drugs via the urethral channel of the penis was introduced with the hope of affording a less invasive procedure than intracavernous needle injections to induce penile erection. **This technique relies on the absorption of medication through the mucosal lining into the surrounding corpus spongiosum, with passage via small vascular channels into the main erectile bodies, the corpora cavernosa.** The transfer of drug from the urethra to the cavernous tissue varies across men according to anatomic variability. Following an initial trial that demonstrated prostaglandin E_2 was effective in inducing full tumescence in 30% of patients and partial tumescence in 40% of patients (Wolfson et al, 1993), a synthetic formulation of prostaglandin E_1 was developed and FDA approved in November 1996 as MUSE (Medicated Urethral System for Erection, Vivus, Menlo Park, CA) (Hellstrom et al, 1996; Padma-Nathan et al, 1997). MUSE employs a suppository inserted into the urethral opening that dispenses a semisolid pellet (1 × 3 mm) of alprostadil (125, 250, 500, and 1000 μg dosages) into the distal urethra (3 cm from the external urethral meatus). Several technical procedures optimize the success of the treatment including properly depositing and manually distributing the medication into the penis and the patient's remaining in the upright position for several minutes after its application. In-office training and monitoring of initial response may afford advantages for optimizing technique and making dosage adjustments before performing treatment at home.

A calculated final responder rate to MUSE is approximately 50%, and among responders approximately 70% of administrations result in sexual intercourse (Hellstrom et al, 1996; Padma-Nathan et al, 1997; Guay et al, 2000). The combined use of an adjustable penile constriction band (ACTIS) was designed and FDA approved to enhance the local retention and effect of the medication (Lewis, 2000). A transurethral bi-mix consisting of alprostadil and α_1-adrenergic antagonist prazosin (ALIBRA) was introduced and in a multicenter trial of nearly 400 patients was shown to increase the at-home responder rate for successful sexual intercourse from 47% with alprostadil alone to 70% with ALIBRA (Qureshi, 2001).

The most common side effects of MUSE include local urogenital pain (approximately one third of patients) and minor urethral bleeding (5%) (Padma-Nathan et al, 1997; Guay et al, 2000). Other complications such as hypotension (3%), dizziness (4%), and priapism (0.1%) have been observed as well. MUSE is contraindicated in patients with known hypersensitivity to alprostadil, abnormal penile anatomy, and conditions that increase the risk of priapism. MUSE seems safe for female partners, producing only a 5.8% incidence of vaginal burning or itching, although it should not be used for intercourse with a pregnant woman without a condom.

Transdermal/Topical Pharmacotherapy

The notion to apply vasoactive drugs directly to the surface of the penis is consistent with the general appeal of many transdermal therapies (e.g., gels, creams) in medicine on the basis of their delivery route: convenience, simplicity, and putatively limited systemic adverse effects. Several topical therapies have been explored for ED treatments, although certain obstacles have limited their widespread use. Nitroglycerine, a nitric oxide donor formulated as a 2% paste, was found to produce tumescence but rarely penile rigidity sufficient for sexual intercourse (Owen et al, 1989). This relative inefficacy combined with its headache side effects for both patient and partner following absorption and action of the drug as a potent systemic vasodilator have precluded its use in clinical practice. Papaverine, formulated as a gel, was investigated but then abandoned as a topical ED treatment on finding that its large molecular size (molecular weight 376 Da) interfered with its transdermal absorption (Kim et al, 1995).

Alprostadil has been a more promising prospect, subjected to commercial development by two companies for penile glans administration in combination with transdermal delivery enhancers: alprostadil 1% + SEPA (soft enhancer of percutaneous absorption), referred to as Topiglan (Macrochem, Lexington, MA), and alprostadil + NexACT, referred to as Alprox-TD (NexMed, Inc., Robbinsville, NJ). Applied intrameatally, both agents in clinical trials have shown efficacy with rates of vaginal penetration and intercourse success that were small but significantly greater than placebo rates and caused minor side effects of site-specific burning or warmth that were comparable with placebo rates (McVary et al, 1999; Goldstein et al, 2001; McMahon, 2002; Padma-Nathan and Yeager, 2006; Rooney et al, 2009). Prostaglandin E_1 ethyl ester, which is a prodrug of prostaglandin E_1, is believed to possess an improved transdermal permeation and less skin irritation than enhancing agents because of its esterification (Schanz et al, 2009). Applied to the shaft of the penis in early clinical trials, this drug achieved significantly higher rigidity scores than placebo. In general, transdermal therapy with alprostadil is likely to meet similar clinical roles as that assigned to transurethral pharmacotherapy. Further clinical trials will be useful to define and establish their place in the treatment of ED.

Medical Devices

In patients who do not respond to or decline oral or local vasoactive pharmacotherapeutic options, vacuum erection device therapy may be alternatively explored. **The principle of vacuum erection device therapy is to mechanically create negative pressure surrounding the penis in order to engorge it with blood and then restrain blood egress from the organ to maintain the erection-like effect** (Broderick et al, 1992). Although the treatment does not produce a truly physiologic erection and the engorged blood predominantly consists of venous blood (Bosshardt et al, 1995), the effect resembles a normal erection and is sufficient for coitus. A particular feature is that the glans penis, and not solely the corpora cavernosa, is engorged with blood by the treatment, such that the treatment is further advantageous for patients experiencing glanular insufficiency.

The vacuum erection device standardly consists of a usually clear plastic suction cylinder and vacuum-generating source (manual or battery-operated pump) in one piece. It is placed directly over the flaccid penis and operated, and after the penis is erected an elastic constriction ring or band is positioned at

the base of the penis; then the vacuum is released and the device is removed (Montague et al, 1996; McMahon, 1997). The cylinder has a pressure release valve designed to prevent penile injury from excessive negative pressure. Sexual intercourse may then ensue, although it is recommended that the ring should not be left in place for longer than 30 minutes. Prescription devices are advised, and metal or other inelastic rings are contraindicated.

Efficacy rates in achieving satisfactory erections of 67% to 90% have been reported for ED associated with various severities and etiologies, but satisfaction rates with the device are lower, ranging from 34% to 68% (Hellstrom et al, 2010). Attrition is reported to occur and may relate to lack of efficacy with more severe forms of ED, although long-term continuation rates have ranged from 19% to 42%. Success is limited in patients with severe vascular abnormalities such as proximal venous leakage or arterial insufficiency or fibrosis secondary to priapism or prosthesis infection (Marmar et al, 1988). Patient preferences also dictate long-term success. The device is more acceptable to older men in a steady relationship compared with young, single men.

Among basic expectations of the treatment, patients should be informed of possible local discomfort or pain associated with the constriction band, a pivoting effect of the penis because turgidity exists only distal to the band's location, a cyanotic discoloration and coolness of the penis resulting from extracorporeal congestion, and trapping of the ejaculation caused by urethral constriction (Witherington, 1989; Sidi et al, 1990; Cookson and Nadig, 1993). Common complications are minor and include penile pain and numbness, difficult ejaculation, ecchymosis, and petechiae, and major complications (e.g., penile skin necrosis, urethral varicosities, Fournier gangrene) are infrequent. Patients receiving anticoagulant therapy (e.g., aspirin, warfarin) and patients with bleeding disorders should use the device with caution (Limoge et al, 1996).

Special uses for this therapy have been sought. It has been successfully combined with oral, intracavernous, and intraurethral pharmacotherapies to produce erectile responses (Marmar et al, 1988; Chen et al, 1995; John et al, 1996; Chen et al, 2004; Canguven et al, 2009). The device has enhanced erectile effects in the presence of a malfunctioning penile prosthesis (Sidi et al, 1990; Korenman and Viosca, 1992). Further, it may offer a means to preserve the elasticity of penile tissues after priapism or penile prosthesis explantation (Moul and McLeod, 1989; Soderdahl et al, 1997) or after surgical correction of Peyronie disease (Yurkanin et al, 2001), and it has been suggested to facilitate erection recovery after treatments for prostate cancer (Raina et al, 2006; Kohler et al, 2007).

Surgery

Surgical interventions have always served an important role in the armamentarium of ED treatments. **Often, they are applied in the face of penile injury resulting from genital or pelvic trauma, penile structural deformity occurring in association with Peyronie disease, or possibly cavernosal fibrosis secondary to prolonged ischemic priapism or infection. They are also considered when medical therapy for ED is contraindicated, unsuccessful, or undesirable.**

Penile Prosthesis Surgery

Penile prosthesis or implant surgery is a mechanism for creating penile rigidity that differs from a physiologic or pharmacologically induced erection. Both malleable (semi-rigid) and inflatable (hydraulic) devices are currently available for this purpose. Details of this treatment option are presented elsewhere.

Penile Revascularization Surgery

On the basis of the requirements of inflow of blood and its retention in the penis for penile erection to occur, it is hardly a wonder to think that vascular surgeries have aggressively been pursued to facilitate or restore these biologic processes.

Arterial Revascularization. In concept, arterial revascularization surgery was designed to create arterial inflow to the corpora cavernosa, in turn addressing the presentation of arteriogenic ED. Several procedures have been described to meet this objective, similarly creating an anastomosis of the inferior epigastric artery either to the corpus cavenosum directly or to vascular conduits of the penis such as the dorsal artery (i.e., revascularization), the deep dorsal vein (i.e., arterialization), or the deep dorsal vein with venous ligation (i.e., arterialization with venous reconstruction) (Hellstrom et al, 2010). Success of these surgeries has been variable and depends on careful patient selection. Penile arteriography is required to establish a penile arterial anatomic defect, and other organic causes of ED (e.g., venous incompetence) that would limit surgical success should be excluded. **According to the current literature, the following inclusion criteria should be met to select patients for arterial surgery: age younger than 55 years, nonsmoker, nondiabetic, absence of venous leakage, and radiographic confirmation of stenosis of the internal pudendal artery** (Hellstrom et al, 2010). **The highest success rates are reported in young men (younger than 30 years of age) with isolated arterial stenosis following perineal or pelvic trauma** (Babaei et al, 2009). Complications of arterial revascularization surgery include glans hyperemia (13%), shunt thrombosis (8%), and inguinal hernias (6.5%) (Manning et al, 1998; Kawanishi et al, 2004).

Venous Reconstruction. Venous reconstruction was proposed to prevent the pathologic blood egress from the penis, understandably serving to correct veno-occlusive ED. Most surgical procedures have centered on ligating or embolizing penile veins (e.g., superficial dorsal vein, deep dorsal vein, crural vein) or surgically compressing the penile crura (e.g., crural plication/ligation, pericavernoplasty) (Hellstrom et al, 2010). **Success with these surgeries has not been affirmed, owing primarily to inaccurate or deficient methods for diagnosing and correcting the relevant anatomic defect. The optimal surgical approach remains to be defined, and thus venous reconstructive surgery is presently considered investigational** (Montague et al, 2005; Hellstrom et al, 2010). Reported complications of this surgery include glanular hypoesthesia/anesthesia, skin necrosis, wound infections, penile curvature/shortening, and glans hyperemia.

Combination Therapies

It is well recognized that many patients with ED will not respond acceptably to monotherapy. Some patients indeed may achieve optimal therapeutic responses by combining treatment options. In addition, it is possible that a dose-limiting adverse effect is associated with ED monotherapy such that combined treatments may then seem advantageous. Multiple combinations may certainly be proposed for ED treatment. The extant literature describes several successful combinations: oral PDE5 inhibitors with psychosocial counseling (Althof et al, 2005), oral PDE5 inhibitors with

testosterone replacement therapy (Shabsigh et al, 2004), oral PDE5 inhibitors with transurethral alprostadil (Mydlo et al, 2000; Nehra et al, 2002), oral PDE5 inhibitors and intracavernous pharmacotherapy (McMahon et al, 1999), oral PDE5 inhibitors and vacuum erection device (Chen et al, 2004; Canguven et al, 2009), intracavernous pharmacotherapy and vacuum erection device (Chen et al, 1995), transurethral pharmacotherapy and vacuum erection device (John et al, 1996), and transurethral pharmacotherapy and penile prosthesis surgery (Benevides and Carson, 2000). **Caution is advised when initiating combination therapy to observe for potential complications that may be compounded by combined treatments, and in-office evaluations before continuing treatments at home may be considered to offer an additional measure of safety.**

Alternative Therapies

Alternative therapies have long been considered for the treatment of ED, from herbs, ointments, and concoctions of antiquity to vitamins, nutraceuticals, and dietary supplements in commercial supply today. The movement toward alternative medicines in this field actually gained momentum over the past decade with the emergence of effective oral therapy in the form of PDE5 inhibitors, which created avenues for producing PDE5 inhibitor-like counterfeit and imitation substances and promoting regulatory agency unapproved products in general. Indeed, the true efficacies of proposed alternative therapies (e.g., ginkgo biloba, L-arginine, Korean red ginseng) remain uncertain in the absence of evidenced benefit in randomized, controlled clinical trials (Moyad et al, 2004). The success of these products is ascribed in some measure to the known placebo effect of agents to treat ED, which has been observed to amount to as much as 25% to 50% in properly conducted clinical trials. **Before the use of alternative therapies can be advocated, further research that demonstrates their mechanisms of action and meaningful efficacies must be done.**

Key Points: Treatment Considerations

- An informed decision-making process that combines goals and preferences of the patient (and partner) and balanced and thorough guidance of the clinician should dictate the best therapeutic option.
- Although definitive evidence is necessary to affirm the benefits of risk modification for preserving erectile health, recommendations are offered to maintain a healthy and fit lifestyle for this purpose.
- Patient education and counseling and application of medical therapies as initial forms of ED management constitute basic management in common practice.
- Psychosexual therapy offers a role in the integrative management of ED.
- Several pharmacotherapies administered by various modalities including oral, intracavernous, intraurethral, and transdermal/topical routes are successfully applied or are under study as ED treatments.
- Vacuum erection device therapy offers an alternative to oral or local vasoactive pharmacotherapeutic options for ED.
- Surgical intervention, principally penile prosthesis surgery, represents an important ED treatment and may be considered when medical (nonsurgical) therapy is contraindicated, unsuccessful, or undesirable.
- Arterial revascularization surgery is offered only to select patients with ED meeting stringent clinical and radiographic criteria for surgical success.

FUTURE DIRECTIONS

The National Urology Research Agenda Summit Meeting, which was convened in the fall of 2009 and sponsored by the American Urological Association Foundation, included sexual dysfunctions among its priority research areas for advancing urologic health. Among the assembly of scientific experts and leaders in urologic research, the working group on sexual medicine enumerated several broad thematic categories of research for advancing ED management. These categories encompassed all subject areas of epidemiology, basic scientific research, and clinical investigation. Five top recommendations were submitted.

First, the epidemiologic relationships and pathogenic mechanisms linking ED and its comorbidity risk factors should be further clarified. It was considered that the definition and implementation of health prevention efforts for ED and for general health disorders have potentially mutual gains and should predictably improve overall health and longevity outcomes for patients.

Second, further research emphasis should be given to understanding and addressing iatrogenic ED. This objective recognizes that ED is a complication associated with numerous medical and surgical treatments that are performed in urology and in other disciplines. The scope in urology includes treatments for prostate cancer, benign prostate conditions, voiding dysfunctions, and possibly even pelvic pain disorders.

Third, basic scientific research in such areas as endothelial mechanisms, smooth muscle biology, and neurobiology referable to the sexual organ system must be supported with the understanding that research discoveries are the foundation for continued advances in the clinical practice of sexual medicine. Interdisciplinary research collaborations and interactions with researchers in other urologic research fields in particular are likely to facilitate the translational purpose of this objective.

Fourth, research focus should be given to the development of innovative therapeutics for ED. It is recognized that today's advances in oral pharmacotherapy, despite their noted advantages, do not fully achieve goals of ideal therapy. Ideal therapy for ED management should go further, such as to restore function or improve it effectively for the long term. This prospect underscores the purpose of molecular and cellular therapeutic targeting, which is specific for etiopathogenic factors underlying ED. Exciting directions, from up-and-coming pharmacotherapeutics and technologies to futuristic approaches such as gene therapy, stem cell therapies, and tissue engineering, are all worth investigating.

Fifth, outcomes research is highly relevant for this field. This objective pertains to the rigorous evaluation of diagnostic assessments and treatments associated with ED management to ascertain their roles. It also applies to clinical contexts in which accurate erectile function assessments such as outcome reporting for pelvic surgery are necessary. This research area will profit from the ongoing development, validation and proper use of questionnaires, biomarkers, and other specialized clinical tools.

SUGGESTED READINGS

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chapter 25

Priapism

Gregory A. Broderick, MD

Defining Priapism
Priapism: Historical Perspectives
Epidemiology and Pathophysiology of Priapism
Molecular Basis of Ischemic and Stuttering Priapism
Evaluation and Diagnosis of Priapism
Medical Treatments
Surgical Management of Ischemic Priapism
Interventional Angiography in the Management of Arterial (Nonischemic, High-Flow) Priapism
Surgical Management of Arterial (Nonischemic, High-Flow) Priapism
Conclusions and Recommendations for Research in Priapism

Priapism describes a persistent erection arising from dysfunction of the mechanisms regulating penile tumescence, rigidity, and flaccidity. A correct diagnosis of priapism is a matter of urgency requiring identification of the underlying hemodynamics.

Scientific organizations have recommended guidelines for the management of priapism including the American Urological Association in 2003 (www.auanet.org) and the International Society for Sexual Medicine in 2006 (www.issm.info). Both groups have noted that the literature on priapism is composed mainly of small case series and individual case reports and includes inconsistent definitions and methodologies with little long-term erectile function outcome data. Recent case series have included detailed methodology including duration of priapism, etiology of priapism, and erectile function outcomes. The basic science on the pathogenesis of priapism and clinical research supporting the most effective treatment strategies are summarized in this chapter. Recommendations for best clinical practice and suggestions for research are made.

DEFINING PRIAPISM

Priapism is a full or partial erection that continues more than 4 hours beyond sexual stimulation and orgasm or is unrelated to sexual stimulation.

Ischemic Priapism (Veno-Occlusive, Low-Flow)

Ischemic priapism is a persistent erection marked by rigidity of the corpora cavernosa and little or no cavernous arterial inflow. In ischemic priapism there are time-dependent changes in the corporal metabolic environment with progressive hypoxia, hypercarbia, and acidosis. The patient typically complains of penile pain after 6 to 8 hours, and the examination reveals a rigid erection. The condition is analogous to a muscle compartment syndrome, with initial occlusion of venous outflow and subsequent cessation of arterial inflows. Well-documented histologic changes occur within the corporal smooth muscle as a consequence of prolonged ischemia. **Interventions beyond 48 to 72 hours of onset may help relieve erection and pain but have little benefit in preserving potency.** Histologically by 12 hours corporal specimens show interstial edema, progressing to destruction of sinusoidal endothelium, exposure of the basement membrane, and thrombocyte adherence at 24 hours. After 48 hours thrombus can be found in the sinusoidal spaces and smooth muscle necrosis with fibroblast-like cell transformation is evident (Spycher, 1986). Ischemic priapism is an emergency. **When left untreated, resolution may take days and erectile dysfunction (ED) invariably results** (Fig. 25–1A and B).

Stuttering Priapism (Intermittent)

Stuttering priapism characterizes a pattern of recurrence. The term has historically described recurrent unwanted and painful erections in men with sickle cell disease (SCD) (Serjeant, 1985). Patients typically awaken with an erection that persists for several hours. Unfortunately, males with SCD may experience stuttering priapism from childhood; in these patients the pattern of stuttering may increase in frequency and duration, leading up to a full episode of unrelenting ischemic priapism. Unfortunately, any patient who has experienced an episode of ischemic priapism is also at risk for stuttering priapism.

Nonischemic Priapism (Arterial, High-Flow)

Nonischemic priapism is a persistent erection caused by unregulated cavernous arterial inflow. Typically, the corpora are tumescent but not rigid and the penis is not painful. A history of blunt trauma to the penis or an iatrogenic needle injury is common. Whatever the mechanism of injury, the result is a disruption of the cavernous arterial anatomy creating an arteriolar-sinusoidal fistula. **The cavernous environment does not become ischemic and cavernous blood gases do**

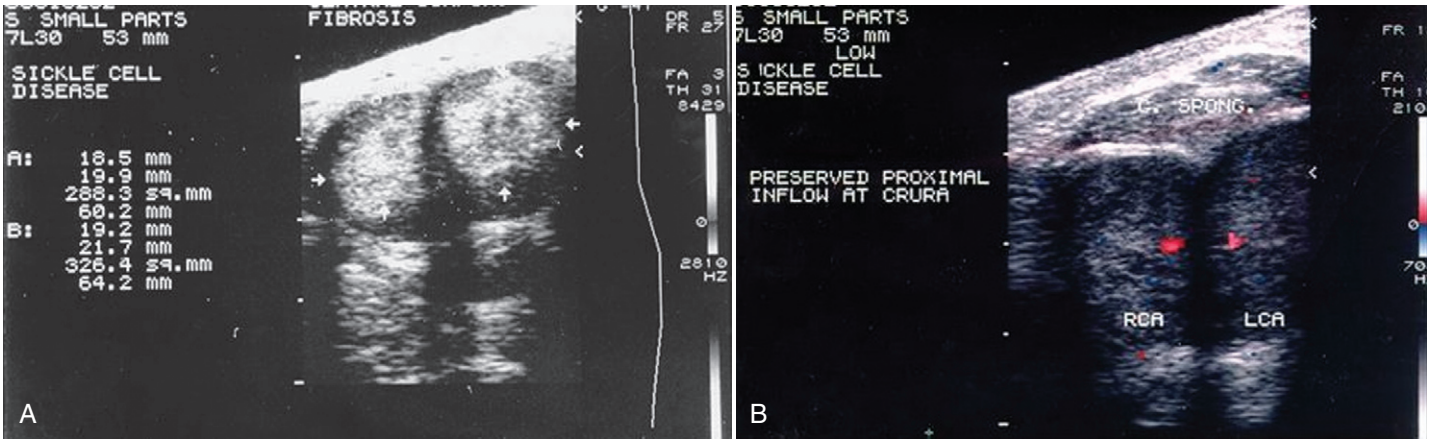


Figure 25–1. **A,** Transverse gray-scale ultrasound image of pendulous penis in a 30-year-old sickle cell disease patient, with history of multiple episodes of priapism, shows hyperechoic corporal fibrosis replacing normal tissues *(arrows)*. **B,** Color duplex Doppler in same patient following intracavernous injection of alprostadil. The right and left (RCA, LCA) cavernous arteries show preservation of blood flow only at the base of the penis.

not show hypoxia, hypercarbia, or acidosis. This type of priapism, once properly diagnosed, does not require emergent intervention. Beyond the acute trauma, patients do not complain of pain. Normal erectile function has been reported after recovery from the initial event, despite persistence of nonsexual partial erection.

PRIAPISM: HISTORICAL PERSPECTIVES

The term *priapism* has its origin in reference to the Greek god Priapus, who was worshipped as a god of fertility and protector of horticulture. Priapus is memorialized in sculptures for his giant phallus. The first recorded account of priapism in English medical literature appears in the *Lancet* and is attributed to Tripe (1845). Historically the most commonly cited observation on this condition in North American literature is Frank Hinman Senior's landmark article describing the natural history of priapism (Hinman, 1914). Subsequently in 1960 his son Frank Hinman Jr. proposed that venous stasis, increased blood viscosity, and ischemia were responsible for priapism and emphasized that failure to correct these abnormalities in the penile environment was essentially responsible for treatment nonresponse (Hinman, 1960). Advances in our understanding of the physiology of erection and the pathophysiology of ED substantiated early hypotheses that prolonged veno-occlusion within the corporal bodies is analogous to a compartment syndrome. Hauri demonstrated the radiologic differences between veno-occlusive and arterial priapism (1983).

Frank Hinman (1914) first described "acute transitory attacks of priapism" as opposed to persistence or rapid recurrence of a single episode. The actual term of stuttering priapism is attributed to Emond and colleagues (1980) in observations of patients with SCD in a Jamaican clinic. Stuttering priapism episodes were seen to increase in frequency and length, leading to major, unrelenting occurrence of ischemic priapism. Attempts to manage SCD patients with stuttering ischemic priapism resulted in the early recommendation for hormonal suppression of nocturnal erections and stuttering with estrogen (Serjeant, 1985).

Nonischemic priapism is described far less commonly than ischemic priapism in the urologic literature. Nonischemic priapism is invariably associated with antecedent perineal or penile trauma. It was first described in the English literature by Burt (1960).

Key Points: Priapism Definitions

- Priapism is a full or partial erection that continues more than 4 hours beyond sexual stimulation and orgasm or is unrelated to sexual stimulation.
- Ischemic priapism (low-flow) is a persistent erection marked by rigidity of the corpora cavernosa, with little or no cavernous arterial inflow.
- Nonischemic priapism (arterial, high-flow) is a persistent erection caused by unregulated cavernous arterial inflow. The corpora are tumescent but not rigid, and the erection is not painful.
- Stuttering priapism describes a pattern of recurrence. The term has traditionally described recurrent prolonged and painful erections in men with SCD.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF PRIAPISM

Etiology of Ischemic Priapism (Veno-Occlusive, Low-Flow)

Ischemic priapism accounts for the majority of cases described in the literature. The erection of ischemic priapism may begin with sexual stimulation or the administration of pharmacologic agents. Once an erection persists beyond 4 hours and is not relieved by cessation of sexual stimulation or orgasm, the physiologic phenomena of ischemic priapism have begun. Erections lasting up to 4 hours are by consensus defined as "prolonged"; manufacturers of erection-facilitating pharmacotherapies (oral, injectable, and intraurethral) recommend that the patient seek emergent medical consultation for prolonged erection.

Population-based studies estimate cases per 100,000 person-years (the number of patients with a first episode of priapism divided by the accumulated amount of person-time in the study population). Cases per 100,000 person-years have been calculated in several countries; these data depend on recording of presentations to clinics and hospitals where cases are registered. Kulmala and colleagues (1995) calculated the cases per 100,000

person-years to be 0.34 to 0.52 from 1975-1990 in Finland; Eland and colleagues (2001) calculated the cases in the Netherlands to be 1.5/100,000 person-years; Earle and colleagues (2003) calculated 0.84/100,000 person-years in Australia from 1985-2000. These reported incidences were statistically significantly impacted by the introduction and proliferation of intracavernous vasoactive injections for the management of erectile dysfunction; in Finland during the last 3 years of the study the incidence of priapism doubled to 1.1 cases/100,000 person-years. These and other reports on the epidemiology and etiology of priapism are also greatly influenced by the prevalence of SCD in the populations described. **The life-time probability of a man with SCD developing ischemic priapism ranges from 29% to 42%** (Emond, 1980).

In 1986 Pohl and colleagues reported on 230 cases. The etiology of priapism was identified as idiopathic in the majority, and 21% of cases were associated with alcohol or drug use/abuse, 12% with perineal trauma, and 11% with SCD (Pohl, 1986). Although SCD is a predominant etiology of veno-occlusive priapism cases in the literature, there is a wide variety of reported associations from urinary retention to insect bites (Hoover, 2004). Priapism has even been reported following spider bites and envenomation from the "Brazilian banana spider," *Phoneutria nigriventer* (Andrade, 2008; Villanova, 2009). The genus *Phoneutria* (Greek for murderess) has eight species. *P. nigriventer* is known to hide in dark and moist places, wander the jungle floor, and stowaway within banana shipments. *P. nigriventer* is blamed for most cases of envenomation in Brazil; the venom contains a neurotoxin that has calcium channel blocking properties, inhibits glutamate release, and inhibits calcium reuptake and glutamate reuptake. Bites can cause intense pain, loss of muscle control—paralysis, breathing problems—asphyxiation, and priapism (www.wikipedia.org). Two peptides isolated from the venom of *P. nigriventer* have been directly linked with the induction of persistent and painful erections in mammals (Tx2-5 and TX2-6). The protein has been named *eretina* and has been shown to have highly specific interference at the molecular level with nitric oxide pathway (NO). Penile erection has been induced in vivo with eretina by direct intraperitoneal injection with a minimum effective dosage of 0.006 mcg/kg (Andrade, 2008).

Hematologic dyscrasias are a major risk factor for ischemic priapism. Priapism has been described as a complication of SCD, thalasssemia, hemoglobin Olmsted, and thrombophilia (Burnett, 2005). **Thrombotic disease states have also been cited as precipitants of ischemic priapism:** asplenism, erythropoietin use, hemodialysis with heparin use, and cessation of coumadin therapy. Intracavernous heparin given as a therapy for priapism due to rebound hypercoagulable states has actually worsened the condition (Fassbinder et al, 1976; Bschieipfer, 2001). **Priapism may occur in patients with excessive white blood cell counts.** The incidence of priapism in adult male patients with leukemia is 1% to 5% (Chang et al, 2003). Hyperleukocystosis causes priapism in these patients; it is believed that mechanical pressure on abdominal veins secondary to splenomegaly causes congestion of cavernous outflow and sludging of leukemic cells within the corpora cavernosa. When priapism presents in the oncology setting, evaluation and management of the predisposing condition must accompany interventions directed at the penis. In hematologic malignancies, leukaphresis and cytotoxic therapy (hydroxurea, ctosine arabinoside) may reduce the numbers of circulating white blood cells (Ponniah et al, 2004; Manuel et al, 2007). **Priapism secondary to metastatic infiltrating solid lesions rather than leukemoid reaction is extremely rare.** In most case reports of metastatic priapism, the primary malignancy is genitourinary (prostate and bladder). Metastatic infiltration of the penis may proceed with solid replacement or focal deposits within the corpora cavernosa, glans, and corpus spongiosum. Theoretically, metastatic deposits within the corpora could obstruct venous outflow resulting in ischemic priapism. Depending on the status of the patient, metastatic lesions may be managed expectantly, with partial or total penectomy, chemotherapy, or irradiation. These cases are too rarely and poorly described to define best practice recommendations (Robey, 1984; Chan, 1998; Guvel, 2003; Celma-Domenech, 2008) (Table 25–1).

Sickle Cell Disease

Blood dyscrasias are a risk factor for ischemic priapism. **SCD priapism has traditionally been ascribed to stagnation of**

Table 25–1.
Etiologies of Priapism

α-Adrenergic Receptor Antagonists
Prazosin, terazosin, doxazosin, tamsulosin

Antianxiety Agents
Hydroxyzine

Anticoagulants
Heparin, warfarin

Antidepressants and Antipsychotics
Trazodone, bupropion, fluoxetine, sertraline, lithium, clozapine, resperidone, olazapine, chlorpromazine, thoridazine, phenothaizines

Antihypertensives
Hydralazine, guanethidine, propanolol

Drugs (Recreational)
Alcohol, cocaine (intranasal and topical), crack cocaine, marijuana

Genitourinary
Straddle injury, coital injury, pelvic trauma, kick to penis/perineum, arteriovenous or arteriocavernous bypass surgery, urinary retention

Hematologic Dyscrasias
Sickle cell disease, thalassemia, granulocytic leukemia, myeloid leukemia, lymphocytic leukemia, multiple myeloma, haemoglobin Olmsted variant, fat emboli associated with hyperalimentation, hemodialysis, glucose 6-phosphate dehydrogenase deficiency

Hormones
Gonadotropin-releasing hormone, testosterone

Infectious (Toxin Mediated)
Scorpion sting, spider bite, rabies, malaria

Metabolic
Amyloidosis, Fabry disease, gout

Neoplastic (Metastatic or Regional Infiltration)
Prostate, urethra, testis, bladder, rectal, lung, kidney

Neurogenic
Syphilis, spinal cord injury, cauda equina compression, autonomic neuropathy, lumbar disk herniation, spinal stenosis, cerebral vascular accident, brain tumor, spinal anesthesia, cauda equina syndrome

Vasoactive Erectile Agents
Papaverine, phentolamine, prostaglandin E_1, oral phosphodiesterase type 5 inhibitors, combination intracavernous therapy

Modified from Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction and priapism. In: Walsh PC, Retik AB, Vaughan ED, et al, editors. Campbell's urology. Philadelphia: WB Saunders; 2002. p. 1610–96.

blood within the sinusoids of the corpora cavernosa during physiologic erection, secondary to obstruction of venous outflow by sickled erythrocytes (Lue, 2002). Nelson and Winters described a series of cases in which SCD was the primary etiology of ischemic priapism in 23% of adults and 63% of children (Nelson, 1977). **Sickle cell hemoglobinopathy accounts for at least a third of all cases of priapism,** and indeed prevalence of ischemic priapism will vary significantly with the population of males in a community with SCD. **From** Emond and colleagues' 1980 **observational study comes the most commonly quoted incidence: Among 104 men attending an outpatient sickle cell clinic in Kingston, Jamaica the incidence of priapism in men with homozygous sickle cell (SS) disease was 42%** (Emond, 1980). In a U.S. clinical series, Tarry and Duckett (1987) found that 6.4% of male children in an outpatient sickle cell clinic had history of priapism (Tarry, 1987). Adeyoju and colleagues (2002), in an international multicenter observational study of SCD, mailed or interviewed 130 patients attending SCD clinics in the United Kingdom and Nigeria. Respondents ranged in age from 4 to 66 years old with the mean age of 25. The authors cited mean age of onset of priapism as 15 years, with 75% of patients having their first episode before age 20 and rare first-time presentations by the third decade of life. In the questionnaires a clear distinction was made between acute severe prolonged priapism lasting longer than 24 hours requiring emergency attention and stuttering recurrent priapism of shorter and self-limiting duration. In this population the incidence of acute priapism was 35%; of these patients 72% gave a history of stuttering. The median frequency of occurrence of stuttering priapism was three times per month; the median duration of each espisode was 1.2 hours, with the longest being 8 hours. Precipitating events reported from greatest to least were sexual arousal/intercourse, fever, sleep, cold weather, and dehydration. Self-administered regimens were analgesics, drinking water, and exercise. Twenty-one percent of patients reporting history of priapism also reported erectile dysfunction. Only 7% of young men who had not experienced priapism were even aware that priapism was a potential complication of their SCD. On the basis of the World Health Organization global prevalence map of SCD, Aliyu (2008) estimates that 20 to 25 million individuals worldwide have homozygous SCD: 12 to 15 million in sub-Saharan Africa, 5 to 10 million in India, and 3 million in other world regions. Aliyu (2008) also found that 70,000 patients with SCD live in the United States.

The sickle cell genetic mutation is the result of a single amino acid substitution in the beta-globin subunit of haemoglobin. The clinical features are seen in homozygous SCD patients: chronic hemolysis, vascular occlusion, tissue ischemia, and end-organ damage. HbS polymerizes when deoxygenated, injuring the sickle erythrocyte, activating a cascade of hemolysis and vaso-occlusion. Membrane damage results in dense sickling of red cells, causing adhesive interactions among sickle cells, endothelial cells, and leukocytes. Hemolysis releases hemoglobin into the plasma. Free Hbg reacts with nitric oxide (NO) to produce methemoglobin and nitrate. This is a scavenging reaction; the vasodilator NO is oxidized to inert nitrate. Sickled erythrocytes release arginase-I into blood plasma, which converts L-arginine into ornithine, effectively removing substrate for NO synthesis. Oxidant radicals further reduce NO bioavailability. The combined effects of NO scavenging and arginine catabolism result in a state of NO resistance and insufficiency termed *hemolysis-associated endothelial dysfunction* (Morris, 2005; Rother, 2005; Kato, 2007; Aliyu, 2008).

Contemporary science implicates hemolysis and reduced nitric oxide in the pathogenesis of pulmonary hypertension, leg ulcers, priapism, and stroke in SCD patients. Increased blood viscosity is believed to be responsible for painful crises, osteonecrosis, and acute chest syndrome. SCD patients with priapism have a fivefold greater risk of developing pulmonary hypertension. SCD priapism is also associated with reduced hemoglobin levels and increased hemolytic markers: reticulocyte count, bilirubin, lactate dehydrogenase, and aspartate aminotransferase (Kato, 2006). Cerebral vascular accidents are more frequent, close to episodes of full-blown priapism; the ASPEN syndrome (priapism, exchange transfusion, and neurologic events) describes cerebral vascular accidents in SCD patients who have received exchange transfusions (Siegel, 1993; Merritt, 2006). Sickle cell trait is considered a benign condition; a few complications have been associated with extreme physical exertions. There have been case reports of sickle cell trait as the predisposing factor to ischemic priapism (Larocque, 1974; Birnbaum, 2008).

Iatrogenic Priapism: Intracavernous Injections

Prolonged erection is more commonly reported than is priapism, following therapeutic or diagnostic injection of intracavernous vasoactive medications (Broderick, 2002). Despite the introduction of effective oral medications for ED in 1998, ICI remains an important therapeutic option for men with severe ED failing a phosphodiesterase type-5 inhibitor or for men who cannot take PDE-5 inhibitors because they require or carry nitrates. In many communities patients receiving intracavernous medications for ED will outnumber patients with SCD. **Priapism following intracavernous injection (ICI) is a problem all urologists will encounter and must be prepared to manage.** In a review of worldwide reports on intracavernous injection (ICI) programs, Junemann and colleagues (1990) noted that diagnostic injection resulted in 5.3% of men getting ischemic priapism and 0.4% of men reported priapism after injecting at home (Junemann, 1990). In papaverine-based ICI programs, reports of prolonged erections and priapism are poorly distinguished and range from 0% to 35% (Broderick, 2002). In worldwide clinical trials of the Alprostadil Study Group, prolonged erection (defined as 4 to 6 hours) was 5%, and priapism (>6 hours) was described in 1% of subjects (Porst, 1996). In papaverine/phentolamine/alprostadil ICI programs prolonged erections have been reported in 5% to 35% of patients (Broderick, 2002).

Iatrogentic Priapism: Oral Phosphodiesterase Type 5 Inhibitors

All PDE5 inhibitors have similar side effects related directly to their mode of action, tissue content of substrate, and pharmacologic selectivity for type 5 inhibition versus other phosphodiesterase enzymes. Those side effects include headache, flushing, dyspepsia, rhinitis, light sensitivity, and myalgia. Morales and colleagues (1998) analyzed data from 4274 men who received double-blind treatment with sildenafil or placebo for up to 6 months and 2199 who received long-term open-label sildenafil for up to 1 year (Morales, 1998). No cases of priapism (erection lasting >4 hours) were reported. No cases of priapism were reported by Montorsi and colleagues (2004) in a multicenter, open-label, 24-month extension of 8- or 12-week double-blind, placebo-controlled studies assessing the long-term efficacy, safety, and tolerability of tadalafil in 1173 men with ED (Montorsi, 2004). Nonetheless, the **INDICATION and USAGE section of the U.S. Food and Drug Administration (FDA)-approved product labeling**

for PDE type 5 inhibitors (USPI) does contain this warning: **There have been rare reports of prolonged erection greater than 4 hours and priapism (painful erections >6 hours duration) for this class of compounds.** Both the USPI and European Summary of Product Characteristics label information contain warning or precautionary language about the use of these agents in men who have conditions predisposing them to priapism. Tadalafil has recently been approved in many regions of the world for daily dosing in the management of ED and is currently being studied for use in the management of symptoms due to benign prostatic hypertrophy. Tadalafil 5-mg daily dosing caused no priapism in a phase II clinical study of 281 men with history of lower urinary tract symptoms secondary to benign prostatic hyperplasia for 6 weeks, followed by dosage escalation to 20 mg once daily for 6 weeks (McVary, 2007).

From 1999-2007 there have been at least nine case-based reports of oral phosphodiesterase type 5 inhibitor dosing and adult priapism and at least one pediatric case: Aoyagi (1999), Sur (2000), Kassim (2000), Goldmeier (2002), McMahon (2003), Wilt (2004), Gallati (2005), King (2005), Kumar (2005), and Wills (2007). **The majority of cases reports detailing priapism following a PDE type 5 inhibitor reveal histories of men with increased risk for priapism: SCD, spinal cord injury, men who used PDE5 inhibitor recreationally, men who used PDE5 inhibitor in combination with intracavernous injection, men with history of penile trauma, men on psychotropic medications, and men abusing narcotics.** Wills (2007) described a 19-month-old male child weighing 10 kg who accidentally ingested up to 6 tablets of sildenafil 50 mg. The child presented with persistent sinus tachycardia and partial erection for 24 hours; the authors presume this was a high-flow priapism (HFP) because the shaft was neither completely rigid nor painful. Erection in the child subsided spontaneously after overnight intravenous hydration and observation.

Key Points: Ischemic Priapism as a Complication of Erectile Dysfunction Therapy

- Prolonged erection is more commonly reported than is priapism, following therapeutic or diagnostic injection of intracavernous vasoactive medications.
- In worldwide clinical trials of alprostadil, prolonged erection (defined as 4 to 6 hours) occurred in 5% of administrations and priapism (>6 hours) in 1%.
- In clinical practice, intracavernous injection of trimix (papaverine/phentolamine/alprostadil) results in prolonged erections in 5% to 35% of administrations.
- Few case reports have documented priapism following a PDE type 5 inhibitor therapy. These reports suggest men were at increased risk for priapism: SCD, spinal cord injury, men who used PDE5 inhibitor recreationally, men who used a PDE type 5 inhibitor in combination with intracavernous injection, men with a history of penile trauma, men on psychotropic medications, and men abusing narcotics.

Etiology of Stuttering (Intermittent) Priapism

Stuttering (intermittent) priapism describes a pattern of recurrent priapism. The term has traditionally been used to describe recurrent unwanted and painful erections in men with SCD. **Patients typically awaken with an erection that persists up to 4 hours and becomes progressively painful secondary to ischemia. SCD patients may experience stuttering priapism from childhood. Any patient who has experienced ischemic priapism is at risk for stuttering priapism. Patients with stuttering priapism will experience repeated painful intermittent attacks up to several hours before remission.** Affected young men suffer embarrassment, sleep deprivation, and performance anxiety with sexual partners (Chow, 2008). In a study of 130 patients with SCD, Adeyoju and colleagues (2002) reported that 46 (35%) had a history of priapism and, of these, 33 (72%) had a history of stuttering priapism. In 75% of patients the first episode of stuttering occurred before the age of 20. Two thirds of males presenting with SCD ischemic priapism will describe prior stuttering attacks (De Jesus, 2009). **Commonly reported precipitants of full-blown SCD priapism are stuttering nocturnal/early morning erections, dehydration, fever, and exposure to cold.**

Etiology and Pathophysiology of Nonischemic (Arterial, High-Flow) Priapism

HFP is a persistent erection caused by unregulated cavernous arterial inflow. The epidemiologic data on nonischemic priapism is almost exclusively derived from small case series or individual case reports**. Nonischemic priapism is much rarer than ischemic priapism, and the etiology is largely attributed to trauma. Forces may be blunt or penetrating, resulting in laceration of the cavernous artery or one of its branches within the corpora. The etiology most commonly reported is a straddle injury to the crura. Other mechanisms include coital trauma, kicks to the penis or perineum, pelvic fractures, birth canal trauma to the newborn male, needle lacerations, complications of penile diagnostics, and vascular erosions complicating metastatic infiltration of the corpora** (Witt, 1990; Brock, 1993; Dubocq, 1998; Burgu, 2007; De Jesus, 2009). Although accidential blunt trauma is the most common etiology, **HFP has been described following iatrogenic injury: cold-knife urethrotomy, Nesbitt corporoplasty, and deep dorsal vein arterialization** (Wolf, 1992; Liguori, 2005). Any mechanism that lacerates a cavernous artery or arteriole can produce unregulated pooling of blood in sinusoidal space with consequent erection. Nonischemic priapism is typically delayed in onset compared with the episode of blunt trauma (Ricciardi, 1993). Sustained partial erection may develop 24 hours following perineal or penile blunt trauma. It is believed that the hemodynamics of a nocturnal erection disrupts the clot and the damaged artery/arteriole ruptures; the unregulated arterial inflow creates a sinusoidal fistula. As healing progresses with clearing of clot and necrotic smooth muscle tissue, the fistula forms a pseudocapsule. **Formation of a pseudocapsule at the site of fistula may take several weeks to months.**

Contemporary reports suggest that HFP may have a unique subvariety. **Several authors have noted that following either aggressive medical management of ischemic priapism or surgical shunting, priapism may rapidly recur with conversion from ischemia to high flow.** HFP has been reported after aspiration and injection of α-adrenergics in the

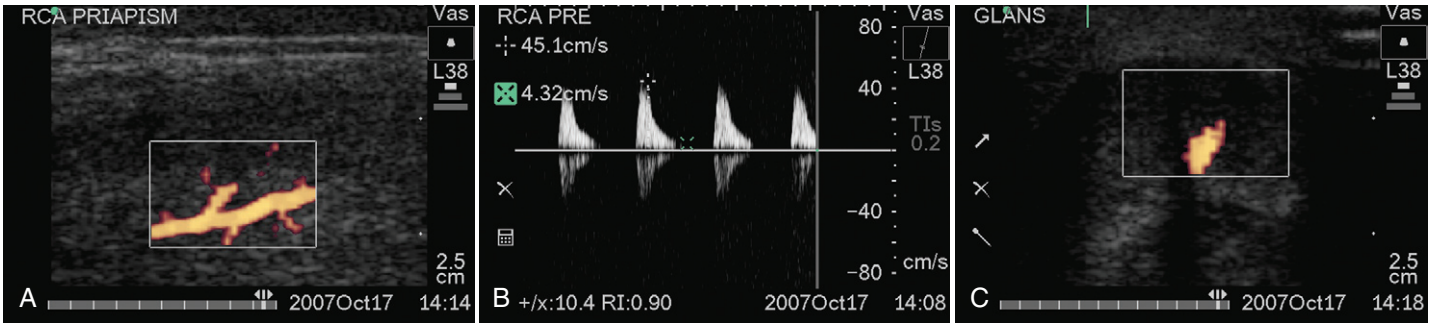


Figure 25–2. **A,** Color duplex Doppler ultrasound, showing right cavernous arterial inflow (RCA). The patient had a 30-hour ischemic priapism reversed with a Winter shunt. He developed a persistent partial erection, converting from ischemia to high-flow priapism. **B,** Peak systolic velocity in right cavernous artery is 45 cm/sec. **C,** Arterial sinusoidal fistula has formed at the site of the previous Winter shunt, as shown in this transverse color Doppler image of the glans penis.

management of ischemic priapism (McMahon, 2002; Rodriguez, 2006; Bertolotto, 2009). Color Doppler ultrasound has shown formation of an arteriolar-sinusoidal fistula at the site of intervention (needle laceration or shunt site) (Fig. 25–2A to C). On rare occasion following reversal of ischemic priapism, a new high-flow hemodynamic state of the cavernous arteries occurs with no evidence of fistula. **This presentation of HFP should be suspected in cases where rapid recurrence, persistence of erection with partial penile rigidity, or stuttering priapism not associated with pain is evident.** Nonfistula type of arterial priapism is the result of dysregulation of cavernous inflows. Nonfistula arterial priapism is a rare complication following management ischemic priapism (Seftel, 1998; Cruz-Guerra, 2004; Wallace, 2009). Penile tenderness to palpation is easily confused with the ongoing ache of persistent ischemia. Soft tissue edema and ecchymosis render the physical examination equivocal after medical and surgical maneuvers to alleviate priapism. **Dysregulated arterial inflows with or without a fistula can best be distinguished from persistent ischemic priapism by color Doppler ultrasound.**

Key Points: High-Flow Priapism

- Nonischemic priapism is much rarer than ischemic priapism.
- HFP results from laceration or disruption of a cavernous artery or arteriole.
- The most common cause is a straddle injury to the crura.
- Other mechanisms include coital trauma, kicks to the penis or perineum, pelvic fractures, birth canal trauma to the newborn male, needle lacerations, complications of penile diagnostics, and vascular erosions complicating metastatic infiltration of the corpora.
- HFP has been described following iatrogenic trauma: cold-knife urethrotomy, corporoplasty, and penile revascularization procedures.

Priapism in Children

Priapism in children and adolescents is most commonly related to SCD. The literature suggests that the incidence of priapism in pediatric sickle cell clinics is 2% to 6% (Tarry and Duckett, 1987; De Jesus, 2009). The majority of SCD priapism is ischemic. In the newborn period, fetal hemoglobin predominates, not hemoglobin S (Burgu, 2007). SCD phenotypes related to ischemic or occlusive crises are unlikely to be evident while fetal hemoglobin persists. Newborn priapism is an extremely rare phenomenon with only limited case reports and rare application of contemporary diagnostic modalities. Erection is frequently elicited in males during the newborn period. In newborn males simple tactile stimulation such as diaper changing, bathing, and urethral catheterization may result in erection; the erection quickly subsides following cessation of stimuli. Fewer than 20 cases of newborn priapism have been reported in the literature; rarely has etiology been defined: polycythemia, blood transfusion, and birth canal trauma (Amlie, 1977; Leal, 1978; Shapiro, 1979; Walker, 1997). The majority of cases have been conservatively managed with spontaneous resolution reported from hours to days. Minimally invasive diagnostics (color Doppler ultrasound) should be performed (Pietras, 1979; Meijer, 2003). In children who develop priapism following straddle trauma, every effort should be made to localize the arteriolar-sinusoidal fistula. Hatzichristou and colleagues (2002) reported that identification of the fistula by Doppler ultrasound coupled with direct manual compression softens the high-flow erection and may speed spontaneous resolution. They suggested that this noninvasive therapy likely works in children and not adults because the perineum has considerably less subcutaneous fat and crural bodies are more easily compressed (Hatzichristou, 2002).

MOLECULAR BASIS OF ISCHEMIC AND STUTTERING PRIAPISM

Advances in our understanding of the molecular basis of priapism have drawn significantly from both in vitro and in vivo experimental studies using animal models. Data on the true inciting mechanisms involved in ischemic priapism are emerging. **Ischemic priapism consists of an imbalance of vasoconstrictive and vasorelaxatory mechanisms predisposing the penis to hypoxia and acidosis. In-vitro studies have demonstrated that when corporal smooth muscle strips and cultured corporal smooth muscle cells are exposed to hypoxic conditions, α-adrenergic stimulation fails to induce corporal smooth muscle contraction** (Broderick, 1994; Saenz de Tejada, 1997; Muneer, 2005). Extended periods of severe anoxia significantly impair corporal smooth muscle contractility and cause significant apoptosis of smooth muscle cells and, ultimately, fibrosis of the corpora cavernosa.

In experimental animal models of ischemic priapism, lipid peroxidation, an indicator of injury induced by reactive oxygen

species (ROS), and increased hemo-oxygenase expression occurs in the penis during and after ischemic priapism (Munarriz, 2003; Jin, 2008). Additional pathophysiologic mechanisms involved in the progression of ischemia-induced fibrosis are the upregulation of hypoxia-induced growth factors. TGF-β is a cytokine that is vital to tissue repair. However, excess amounts may induce tissue damage and scarring. Upregulation of TGF-β occurs during hypoxia and in response to oxidative stress (Moreland, 1995; Jin, 2008). It is hypothesized that TGF-β may be involved in the progression of the corporal smooth muscle to fibrosis (Bivalacqua, 2000; Jeong, 2004).

Transgenic mouse models of SCD manifest priapism (Beuzard, 1996; Bivalacqua, 2009). There have been two major discoveries in elucidation of the molecular mechanism of ischemic priapism. Mi and colleagues (2008) have shown that transgenic sickle cell mice corpora cavernosa have enhanced smooth muscle relaxation to electrical field stimulation. Transgenic sickle cell mice and mice lacking endothelial nitric oxide synthase (eNOS) gene expression display supraphysiologic erections and spontaneously phasic priapic activity in vivo (Bivalacqua, 2006, 2007).

Endothelial cells actively regulate basal vascular tone and vascular reactivity, by responding to mechanical forces and neurohumoral mediators with the release of a variety of relaxing and contracting factors. In the penis the vascular endothelium is a source of vaso-relaxing factors such as NO and adenosine, as well as vaso-constrictor factors such as RhoA/Rho-kinase. Recent evidence suggests that in states of priapism there may be aberrant NO and adenosine signaling, thus identifying a potential role for NO/cGMP, as well as adenosine and RhoA/Rho-kinase signaling in the pathophysiology of ischemic priapism (Champion, 2005; Mi, 2008; Bivalacqua, 2009).

eNOS–/– mutant mice have an exaggerated erectile response to cavernous nerve stimulation and have phenotypic changes in erectile function consistent with priapism (Champion, 2005; Bivalacqua, 2006). Mice lacking the eNOS gene manifest a priapism phenotype through mechanisms involving defective phosphodiesterase type 5 (PDE5) regulatory function in the penis, resulting from altered endothelial nitric oxide/cGMP signaling in the organ (Lin, 2003; Bivalacqua, 2006). Supporting this hypothesis, PDE5 expression is significantly reduced in corpora cavernosa smooth muscle cells (CCSMC) grown under anoxic and hypoxic cell culture conditions (Lin, 2003). **In the context of molecular dysregulation, the cyclic nucleotide cGMP is produced in low steady-state amounts under the influence of priapism-related destruction of the vascular endothelium and thus reduced endothelial nitric oxide activity; this situation thereby downregulates the set point of PDE type 5 function, secondary to altered cGMP-dependent feedback control mechanisms** (Champion, 2005; Bivalacqua, 2006; Burnett, 2007). **Under these conditions, when NO is neuronally produced in response to an erectogenic stimulus or with nocturnal erections, cGMP production surges in a manner that leads to excessive erectile tissue relaxation because of basally insufficient PDE type 5 enzyme to degrade the cyclic nucleotide. Additionally, reduced Rho-kinase activity (contractile mediator) may contribute to the susceptibility of corporal tissue to excessive relaxation via two distinct molecular mechanisms. These two distinct molecular mechanisms may act in concert to promote stuttering ischemic priapism: enhanced vaso-relaxation by uninhibited cGMP and diminished contractile effects of Rho-kinase.** Transgenic sickle cell mice also have significant reductions in penile NO/cGMP signaling leading to deficient PDE5 expression/activity, as well as reduced RhoA/Rho-kinase expression from which they manifest enhanced erectile responses and recurrent priapism (Champion, 2005). Another potential cause of enhanced corporal smooth muscle relaxation in SCD-associated priapism is elevated penile adenosine levels, thus causing the corpora cavernosa to be in a chronically vasodilated state (Mi, 2008). **Taken together, these data suggest that ischemic priapism and most importantly stuttering priapism is a direct result of NO imbalance resulting in aberrant molecular signaling, PDE5 dysregulation, adenosine overproduction, and reductions in Rho-kinase activity, translating into enhanced corporal smooth muscle relaxation and inhibition of vasoconstriction in the penis.**

Key Points: Sickle Cell Disease and Priapism

- Sickle cell hemoglobinopathy accounts for at least a third of all cases of ischemic priapism.
- The sickle cell genetic mutation is the result of a single amino acid substitution in the β-globin subunit of hemoglobin.
- Clinical features are seen in homozygous SCD patients: chronic hemolysis, vascular occlusion, tissue ischemia, and end-organ damage.
- Hemolysis and reduced nitric oxide are central in the pathogenesis of pulmonary hypertension, leg ulcers, priapism, and stroke in SCD patients.
- Increased blood viscosity is responsible for painful crises, osteonecrosis, and acute chest syndrome.
- SCD patients may experience stuttering priapism from childhood.
- SCD patients with stuttering priapism will experience repeated painful intermittent attacks up to several hours before remission.
- Stuttering priapism in SCD is the result of molecular dysregulation with enhanced corporal smooth muscle vaso-relaxing forces and inhibition of vasocontractile forces in the penis.

EVALUATION AND DIAGNOSIS OF PRIAPISM

History

In order to initiate appropriate management, the physician must determine whether the underlying priapism hemodynamics are ischemic or nonischemic. Emergency management of ischemic priapism is recommended. **Ischemia should be suspected when** the patient has progressive penile pain, associated with the duration of erection; has used a known drug associated with priapism; has SCD or another blood dyscrasia; or has a known neurologic condition, especially those affecting the spinal cord. Stuttering priapism history is one of recurrent episodes of prolonged erections, usually nonresolving morning erections. **Nonischemic priapism should be suspected when** there is no pain and the erection duration has not been accompanied by progressive discomfort. There is a history of straddle injury, coital trauma, blunt trauma to the penis or perineum, penile injection, penile surgery or a diagnostic procedure of the pelvic and penile vessels. The onset of post-traumatic HFP in adults and children

may be delayed by hours to several days following the initial injury (Table 25–2).

Physical Examination

Inspection and palpation of the penis is recommended to determine the extent and degree of tumescence and rigidity; the involvement of the cavernous bodies; the presence of pain; and the evidence of trauma to the perineum. In ischemic priapism the corporal bodies will be completely rigid; the glans penis and corpus spongiosum are not. Although malignancies rarely cause priapism, examination of the abdomen, testicles, perineum, rectum, and prostate may help identify a cancer primary. Malignant infiltration of the penis causes indurated nodules within or replacing corporal tissue. The subtle differences in the penile examination may be apparent to the experienced urologist but can be overlooked by emergency personnel on initial evaluation (Fig. 25–3A and B). If physical examination reveals the penis is nontender, tumesced, or partially erect, nonischemic priapism is suspected. In nonischemic priapism the corpora will be tumescent but not completely rigid. In children and adults with high-flow priapism, depending on the location of trauma and time since the traumatic event, there may be residual bruising at the perineum from straddle injury (Table 25–3).

Laboratory Testing

Evaluation should include a CBC, WBC with blood cell differential, platelet count, and coagulation profile to assess anemia, rule out infection, detect hematologic abnormalities, and ensure that the patient can safely tolerate surgical interventions should initial medical management fail. **In African-Americans a sickle cell prep and hemoglobin electrophoresis should be requested.** Other hematologic abnormalities may cause priapism and should be sought if etiology is not evident: leukemia, platelet abnormalities, and thalassemia. An elevated reticulocyte count is nonspecific and may be elevated in both priapism due to SCD and thalassemia. Urine and serum toxicology panels should be done if recreational narcotic or prescription psychoactive drugs are suspected from the history**. A corporal blood gas by aspiration is recommended in the emergency evaluation of priapism. The corporal blood aspirate differentiates ischemic from nonischemic priapism. Aspiration may be both diagnostic and therapeutic. Visual inspection of the color and consistency of an initial penile aspirate will reveal dark deoxygenated blood, with a "crankcase oil" appearance in ischemic priapism. The initial corporal apirate may be sent for blood gas testing to document pH, Po_2, and Pco_2** (Table 25–4). **Color duplex Doppler ultrasonography should be initiated if the history suggests penile/perineal**

Table 25–2.

Elements in Taking the History of Priapism

Duration of erection
Presence of pain
Previous episodes of priapism and method of treatment
Baseline erectile function
Use of any erectogenic therapies (both prescription and nutritional supplements)
Medications and recreational drugs
Sickle cell disease, hemoglobinopathies, hypercoagulable states
Trauma to the pelvis, perineum, or penis

Table 25–3.

Key Findings in Priapism

FINDINGS	ISCHEMIC PRIAPISM	NONISCHEMIC PRIAPISM
Perineal trauma	Seldom	Usually
Hematologic abnormalities	Usually	Seldom
Recent intracorporal injection	Sometimes	Sometimes
Corpora cavernosa fully rigid	Usually	Seldom
Penile pain	Usually	Seldom
Abnormal penile blood gas	Usually	Seldom
Cavernous inflow (by Doppler)	Seldom	Usually

Modified from Montague DK, Jarow J, Broderick GA, et al. American Urological Association guideline on the management of priapism. J Urol 2003;170: 1318–24.

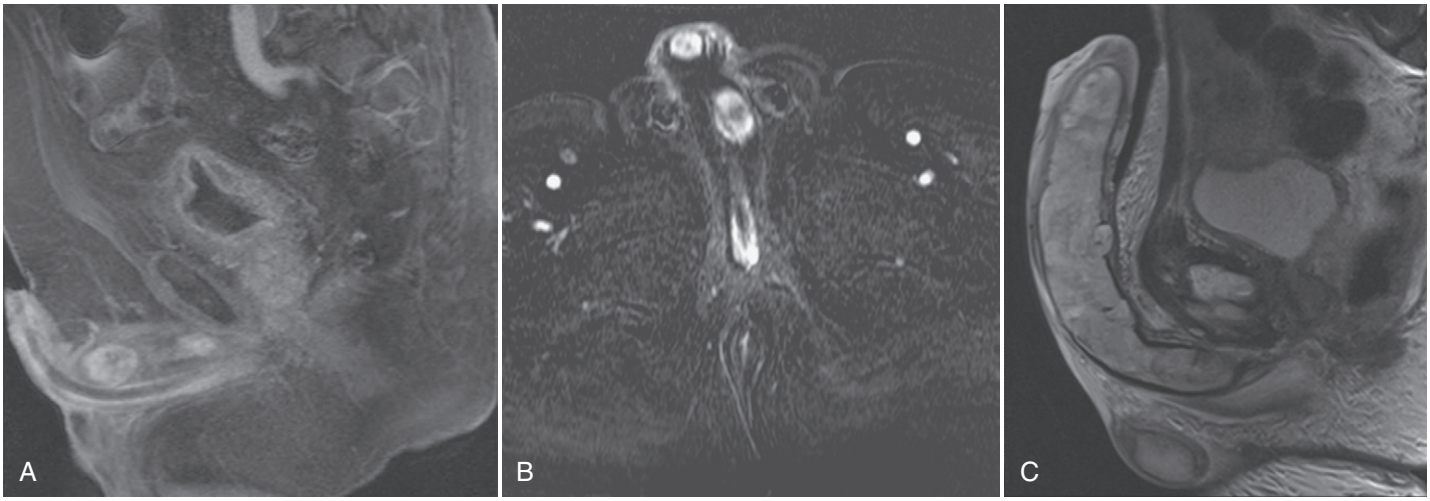


Figure 25–3. **A,** Saggital MRI of the penis showing metastatic deposits of prostate cancer to the corpus cavernosum. **B,** Coronal MRI of the same patient. Note the proximal and distal metastic deposits of prostate cancer. **C**, T2-weighted MRI showing chondrosarcoma replacing corpus cavernosum. (Courtesy of David Ralph.)

trauma or if the corporal aspirate reveals well-oxygenated blood (Fig. 25–4A and B).

Penile Imaging

Color duplex Doppler ultrasonography (CDU) of the penis and perineum is recommended in the evaluation of priapism. CDU is an adjunct to the corporal aspirate in differentiating ischemic from nonischemic priapism. **Patients with prolonged ischemic priapism will have no blood flow in the cavernous arteries;** the return of the cavernous artery waveform will accompany successful detumescence. **Patients with nonischemic priapism have normal to high blood flow velocities** detectable in the cavernous arteries; an effort should be made to localize the characteristic blush of color emanating from the disrupted cavernous artery/arteriole (Broderick, 2002). Examination of the entire penile shaft and perineum is recommended; this can be done with the patient supine but frog legged (Fig. 25–5). **Penile arteriography should be reserved for the management of high-flow priapism, when embolization is planned; arteriography is too invasive as a diagnostic procedure to differentiate ischemic from nonischemic priapism** (Burnett, 2004). The data from penile blood gas assessments become confusing following interventions. **Color Doppler ultrasound should always be considered in the evaluation of a full or partial erection after treatments for ischemic priapism.** The differential diagnosis includes resolved ischemia with penile edema, persistent ischemia, and conversion to high-flow state. Chiou and colleagues (2009) have recommended that to accurately categorize presentations as nonischemic or ischemic, careful interpretation of color Doppler ultrasound hemodynamics must be done in conjunction with the clinical assessment. They describe eight patients with priapism following intracavernous injection (duration ≤7 hours), all of whom showed presence of cavernous arterial inflows with varied peak systolic velocities and end-diastolic velocities. They concluded that most patients with priapism following ICI (and duration <7 hours) have a hemodynamic picture of mixed arteriogenic and veno-occlusive priapism. In their series, men with idiopathic ischemic priapism longer than 20 hours showed no detectible cavernous arterial inflows.

There have recently been reports on the use of magnetic resonance imaging in priapism. Kirkam and colleagues (2008) noted that there are **three possible roles for magnetic resonance imaging (MRI)** to help in the assessment of priapism; the primary role would be in the **imaging of a well-established arteriolar-sinusoidal fistula** (Kirkham, 2008). The authors acknowledge a limitation of MRI is resolution; MRI cannot demonstrate small vessels as clearly as high-frequency Doppler sonography or angiography. The second would be in ischemic priapism

Table 25–4.

Typical Blood Gas Values

SOURCE	Po_2 (mm Hg)	Pco_2 (mm Hg)	pH
Normal arterial blood (room air)	>90	<40	7.40
Normal mixed venous blood (room air)	40	50	7.35
Ischemic priapism (first corporal aspirate)	<30	>60	<7.25

Modified from Montague DK, Jarow J, Broderick GA, et al. American Urological Association guideline on the management of priapism. J Urol 2003;170: 1318–24.

Key Points: Priapism Imaging

- Color Doppler ultrasound (CDU) is an adjunct to the corporal aspirate in differentiating ischemic from nonischemic priapism.
- CDU imaging should include corporal shaft and transperineal assessment of the crural bodies when there is a history of penile trauma or straddle injury.
- CDU should always be considered in the evaluation of a persistent or partial erection after treatments for ischemic priapism.
- Penile arteriography is too invasive as a diagnostic procedure to differentiate ischemic from nonischemic priapism.
- MRI has three possible roles: imaging of a well-established arteriolar-sinusoidal fistula, identifying corporal thrombus, and identifying corporal metastasis.

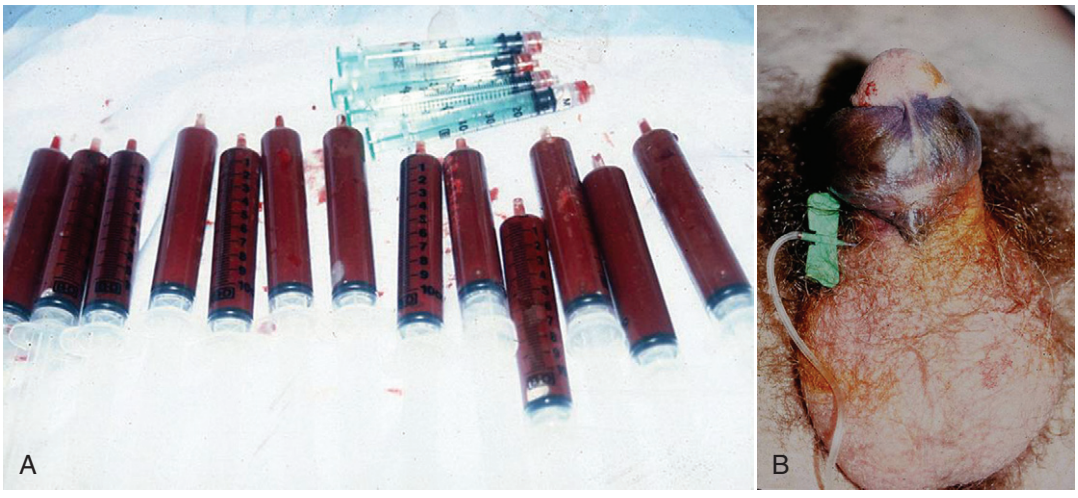


Figure 25-4. **A,** Initial corporal aspirate in ischemic priapism show dark, deoxygenated blood. Subsequent aspirations will show brighter blood as corpus cavernosum is reoxygenated by inflow. Empty syringes are from successive injections of phenylephrine. **B,** A butterfly needle for aspiration and injection should be placed at the penoscrotal junction. Initial failed efforts in the emergency room were due to distal placement of butterfly needle and failure to repeat aspirations.

to **demonstrate the presence and extent of tissue thrombus and corporal smooth muscle infarction.** Ralph (2009) used MRI in the prospective management of 50 patients with refractory ischemic priapism failing medical/surgical management from 24 to 72 hours. Patients underwent MRI to characterize the extent of smooth muscle necrosis before placement of penile prosthesis (Fig. 25–6A and B). The third role for MRI would be in the **imaging of corporal metastasis** mimicking priapism, or causing true ischemic priapism by obstruction of venous outflow.

MEDICAL TREATMENTS

Ischemic Priapism

Historically, first aid was applied by the patient or recommended by a health practitioner unfamiliar with the hemodynamics of priapism; these interventions included ejaculation, ice packs, cold baths, and cold water enemas. Each of these remedies was thought to end erection by inducing vasoconstriction. Some historical reports advised voiding and exercise. Oral sympathomimetic drugs (etilefrine, pseudoephedrine, phenylpropanolamine, and terbutaline) have been reported to effectively reverse prolonged erection (<4 hours) initiated by intracavernous injection therapies with efficacies of 28% to 36% (Lowe, 1993). Lowe and Jarow (1993) compared oral terbutaline with pseudoephedrine or placebo in 75 patients with prolonged erection induced by intracavernous injection of Alprostadil; they reported detumescence in 38% of cases following terbutaline, 28% following pseudoephedrine, and 12% following placebo. In a follow-up study Priyadarshi (2004) specifically investigated the efficacy of oral terbutaline in the management of prolonged erection following intracavernous injections (papaverine/chlorproamazine); he administered oral terbutaline 5 mg or placebo to men with persisting erection for more than 2.5 hours. Detumescence was acheieved in 42% and 15% of cases, respectively, treated with terbutaline/placebo. Terbutaline treatment was unsuccessful in 58% of cases; all of those patients responded to intracavernous injection of an α-adrenergic. In this author's experience, when diagnostic injections result in prolonged erections with duration from 2 to less than 4 hours, aspiration may not be necessary. An ultrafine needle and 1-mL syringe (phenylephrine 200 μg) may be used for single injection of α-adrenergic.

Oral agents are not recommended in the management of acute ischemic priapism (>4 hours). The recommended initial treatment of ischemic priapism is the decompression of the corpora cavernosa by aspiration. Aspiration will immediately soften the erection and relieve pain. Aspiration alone may relieve priapism in 36% of cases. The AUA Guidelines Panel (2003) advised that there were not sufficient data to conclude that aspiration followed by saline intracorporal irrigation was any more effective than aspiration alone (Montague, 2003). Subsequently, Ateyah (2005) reported that a combination of corporal blood aspiration and cold saline irrigation effectively terminated priapism in 66% of cases compared with aspiration alone (24%). Data to support the efficacy of cold saline are limited. **Aspiration should be repeated until no more dark blood can be seen coming out from the corpora and fresh bright red blood is obtained. This process leads to a marked decrease in the intracavernous pressure, relieves pain, and resuscitates the corporal environment removing anoxic, acidotic, and hypercarbic blood.** A single, large-bore, 19-gauge needle should be inserted at the peno-scrotal junction at 3 or 9 o'clock, to avoid piercing the dorsal neurovascular bundle. The surgeon should compress the penile shaft between the thumb and first digit, just below the 19-gauge needle, aspirating the shaft until it is soft. Leaving the needle in place, the shaft is permitted to refill. Compression is reapplied and aspiration repeated. These maneuvers may need to be serially repeated. Several small, empty syringes should be available (3-mL to 12-mL syringes).

Corporal aspiration, if unsuccessful, should be followed by α-adrenergic injection or irrigation. Aspiration followed by the intracavernous injection of sympathomimetic drugs is recommended by the AUA Guidelines Panel, 2003 (Montague, 2003). Sympathomimetic drugs (phenylephrine, etilephrine, ephedrine, epinephrine, norepinephrine, metaraminol) cause cavernous smooth muscle (CSM) contraction. In the laboratory, normal CSM preparations from humans, rabbits, and rodents show concentration-dependent contractions on exposure to phenylephrine, if the corporal environment is well oxygenated and has a normal pH (Broderick, 1994; Muneer, 2008). Broderick and Harkaway (1994) described time-dependent changes in the corporal environment beginning within 6 hours of persistent erection (Broderick, 1994) in humans. Animal models of

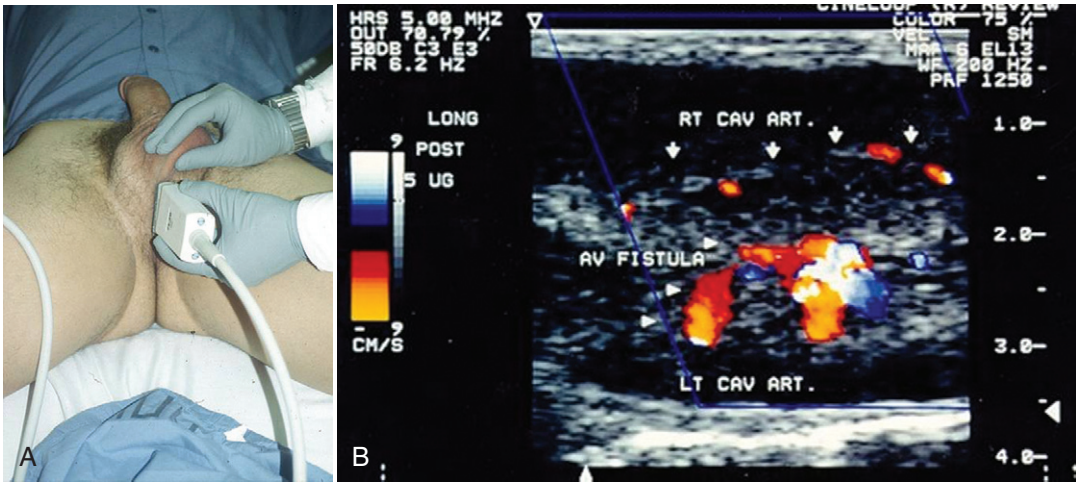


Figure 25–5. **A,** Examination of the crural bodies is required when searching for arterial sinusoidal fistula following straddle injury. **B,** Color Doppler image of arterial sinusoidal fistula of left cavernous artery.

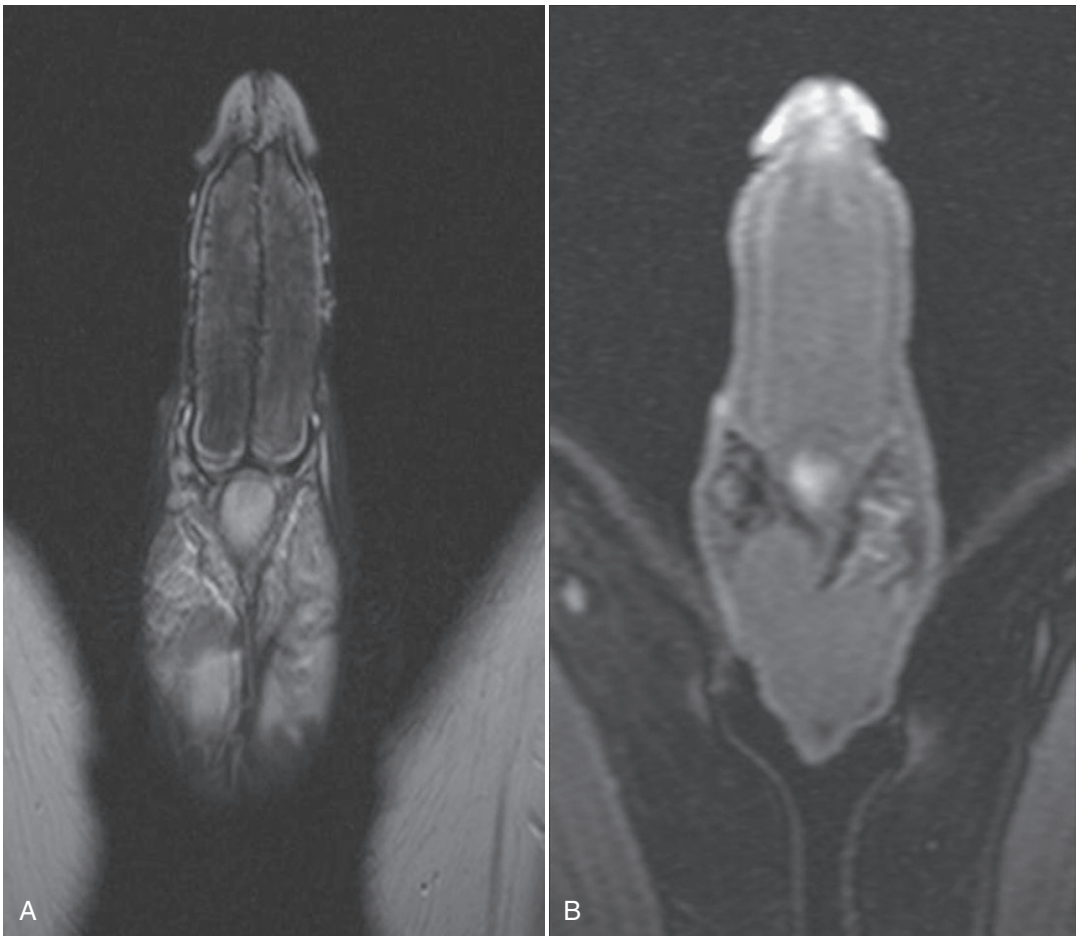


Figure 25–6. **A,** T2-weighted MRI showing cavernous body thrombosis. **B,** Same patient. There is no enhancement following gadolinium infusion. At operation, extensive smooth muscle necrosis and thrombus was found. Patient had untreated ischemic priapism lasting several days. (Courtesy of David Ralph.)

ischemic priapism have demonstrated impairment in smooth muscle contraction with progressive acidosis, hypoxia, and glucopenia (Broderick, 1994; Saenz de Tejada, 1997; Munnarriz, 2006; Muneer, 2008). Corpus cavernosum specimens from patients presenting with prolonged priapism show no contractions to high-dose phenylephrine in vitro.

Phenylephrine is a selective α_1-adrenergic receptor agonist without β-mediated ionotropic and chronotropic cardiac effects; it is the agent of choice by AUA consensus recommendation (Montague, 2003; Pryor, 2004). There are no comparative trials of sympathomimetics in the management of priapism, nor are there dosage-tolerating studies to report. Case reports vary in efficacy from 43% to 81%, with time-dependent efficacies for each agent reported. Phenylephrine is usually diluted in normal saline with a concentration of 100 to 500 μg/mL and given in 1-mL dosages every 3 to 5 minutes. Dosing should be intermittent over the course of an hour. **In this author's experience phenylephrine can be concentrated as 200 μg/mL in saline and administered intermittently as 0.5 mL to 1.0 mL, every 5 to 10 minutes to a maximum dosage of 1 mg. This will permit up to 10 separate injections of 0.5 mL (100 μg each) or 5 separate injections of 1 mL (200 μg each). Aspirate the penis between successive injections by tightly pinching the shaft at the peno-scrotal junction, just below the site of needle insertion. Aspirate until distal shaft is empty. Then inject phenylephrine, releasing the compression at the peno-scrotal junction, allowing the shaft to refill with fresh blood.** Extremes of age and preexisting cardiovascular diseases should be taken into consideration before intracavernous sympathomimetic dosing. **Serial monitoring of blood pressure and pulse should be performed during and immediately following intracavernous injection of sympathomimetic drugs. Potential side effects of intracavernous sympathomimetics include headache, dizziness, hypertension, reflex bradycardia, tachycardia, and irregular cardiac rhythms.** Davila (2008) reported subarachnoid hemorrhage in a case of SCD ischemic priapism. The patient was a 24-year-old African-American male who reported sudden and severe headache immediately following phenylephrine intracorporal dosing of 500 μg/mL repeated every 3 minutes for a total 4 mL (2000 μg = 2 mg). In 2005 in its Patient Safety News: Caution on Fatal Dosing Errors with Epinephrine (#35), the FDA reported a case of a 16-year-old boy who received 4 mL of undiluted 1:1000 epinephrine solution intracavernously to treat priapism. A 1:1,000,000 solution should have been used, so the boy received a massive overdosage; he arrested and could not be resuscitated (www.fda.gov/psn). **Whichever intracavernous sympathomimetic agent is chosen for the management of ischemic priapism, urologists are well advised to consult their pharmacies and develop clear mixing and dosing protocols for safe administration** (Fig. 25–7).

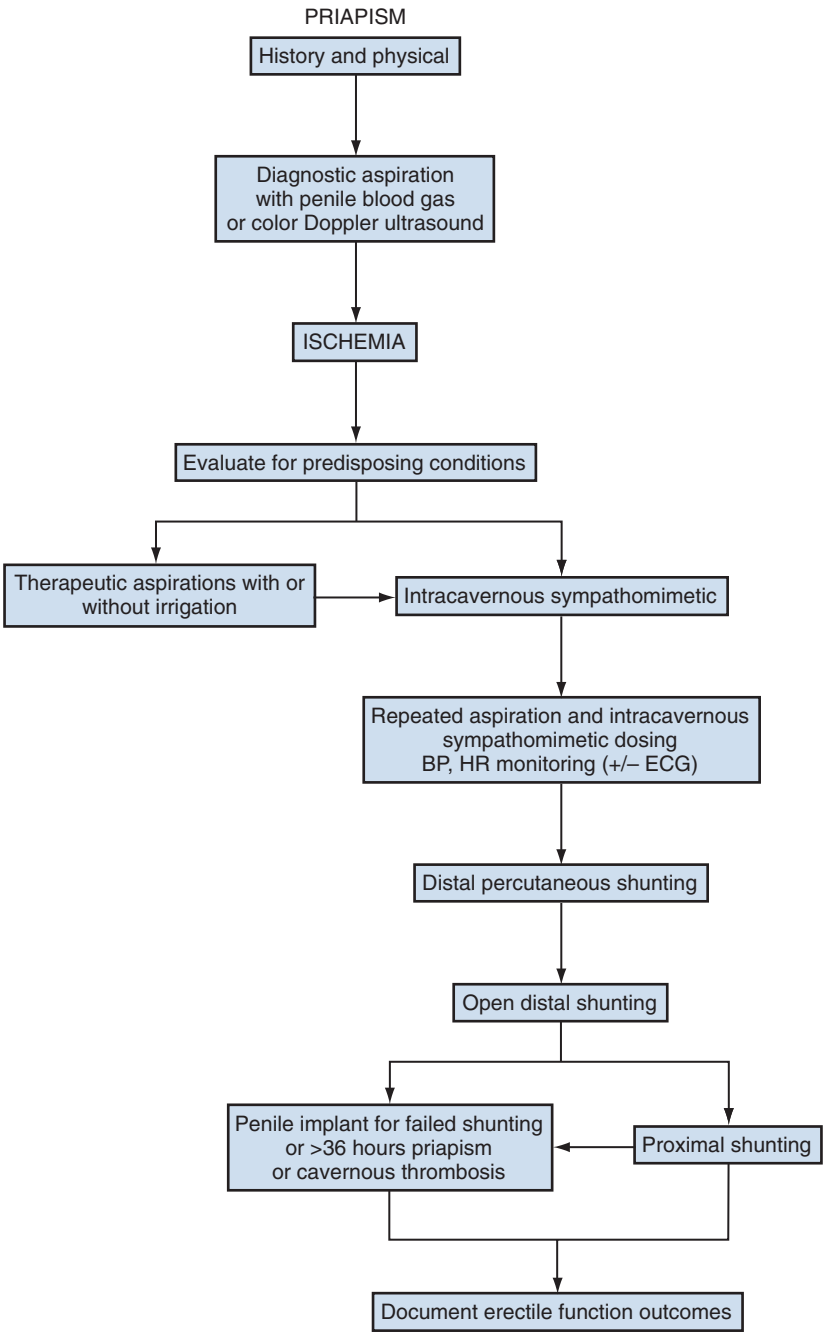


Figure 25–7. Algorithm for managing ischemic priapism.

SCD and hematologic malignancies are rare but important causes of ischemic priapism. Classically, treatment of SCD-induced ischemic priapism involved analgesics, hydration, oxygen, bicarbonate, and blood transfusion. However, **systemic therapy alone is not effective management of SCD priapism** (Rogers, 2005). A recent report suggested that blood transfusion may have no effective role in the treatment of sickle cell-induced priapism (Merritt, 2006). **Reports from hematology centers suggest high success rates using penile aspiration/injection/irrigation of intracavernous sympathomimetics for SCD priapism** (Mantadakis, 2000). Mantadakis and colleagues (2000) conducted a prospective trial for the management of children with SCD presenting with prolonged erection, ages 3 to 18 years (no placebo group). For erections lasting longer than 4 hours and less than 12 hours, emergency department interventions were local anesthetic, cavernous aspiration, and irrigation with 10 mL of a 1:1,000,000 solution of epinephrine. If detumescence lasted for 30 minutes, patients were discharged to home. They described 15 patients receiving 39 interventions, of which 37 were successful; 67% required only one aspiration and irrigation treatment. **In the management of SCD pediatric patients with stuttering priapism, several levels of escalating intervention are necessary with parental and emergency department staff education comprising the first level.** Gbadoe and colleagues (2001) described the treatment of 11 SCD patients (ages 30 months to 15 years) who presented with acute ischemic priapism or stuttering priapism. In their series of cases if the patient presented with priapism lasting less than 6 hours, aspiration and injection of 5 mg of etilefrine was given in the emergency department; for stuttering priapism, patients were

given oral etilefrine 0.5 mg/kg nightly for 1 month, or 0.25 mg/kg twice daily. Patients (parents) also administered injections at home to reverse painful erection lasting longer than 1 hour. The authors reported no significant hypertension and only one case of "agitation" attributed to daily dosing.

Key Points: Medical Management of Ischemic Priapism

- Oral therapy is not recommended for the treatment of acute ischemic priapism.
- The initial treatment of ischemic priapism is decompression by aspiration.
- Aspiration should be repeated until oxygenated blood is seen to refill the corpora.
- Aspiration should be followed by the intracavernous injection (or irrigation) of a diluted α-adrenergic drug.
- Worldwide availability of adrenergic agents varies; effective reversal of priapism has been documented with dilute injections of ephedrine, epinephrine, etilefrine, metaraminol, or phenylephrine.
- Clinicians are advised to consult their pharmacies and develop clear mixing and dosing protocols for safe administration of adrenergic solutions.
- Phenylephrine is a sympathomimetic drug with selective α_1 adrenergic receptor actions; it lacks β-mediated ionotropic and chronotropic cardiac effects. As such, if available it is the recommended agent for intracavernous management of ischemic priapism (AUA Guidelines, 2003).
- Phenylephrine should be concentrated as 200 μg/mL in normal saline and administered intracavernously as 0.5 mL to 1 mL. Lower concentrations should be used in children and adults with cardiovascular disease. Dosing and aspiration may need to be repeated. No recommendations can be made about maximum safe dosing. Hypertensive stroke has been reported as a complication of cumulative dosing of 2 mg.
- Some sympathomimetic drugs are activators of both α- and β-adrenergic receptors. Physicians should monitor patients for subjective complaints and objective findings consistent with known undesirable effects: headache, chest discomfort, acute hypertension, reflex bradycardia, tachycardia, palpitations, and cardiac arrhythmia. Patients and parents should be informed about these potential complications.
- Blood pressure monitoring is recommended if repeated sympathomimetic dosing is given. In patients with significant cardiovascular risks, electrocardiogram monitoring is recommended.
- Ischemic priapism associated with SCD requires intracavernous treatment. A hematologist may provide concurrent systemic therapies, but the best resolution rates are achieved with therapies directed at the penis.

Stuttering Priapism

Various factors need to be considered when treating stuttering priapism. **Although an episode may last less than 4 hours, increasing frequency or duration of stuttering episodes may herald a major ischemic priapism.** Multiple frequent visits to the emergency department to resolve the priapism are disruptive to the patient's life and embarrassing. If attacks follow sexual activity, patients may become sexually avoidant (Adeyoju, 2002; Chow, 2008). Safety and efficacy of various treatments are poorly characterized in the literature. The side effects of recommended medications should be understood by the patient. Patients on chronic medical therapy to decrease the frequency of stuttering episodes may significantly benefit from performing a single sympathomimetic intracorporal injection at home as part of a personal treatment algorithm (Virag, 1996; Teloken, 2005). Multiple treatment options have been described: oral and injectable α-adrenergic agonists, terbutaline, digoxin, antisickling agent hydroxacabamide, estrogens, GnRH analogues, antiandrogens, baclofen, gabapentin, and recently phophodiesterase type 5 inhibitors (Chow, 2008).

Etilefrine is an α agonist available as an oral or injectable treatment in some European countries. Maximum oral dosing is 100 mg in 24 hours (Okpala, 2002). Okpala (2002) followed 18 adults (17 SCD patients and one with sickle trait), all with history of stuttering priapism. Patients were given oral etilefrine in escalating dosages from 25 mg at bedtime to a maximum of 100 mg each day. Stuttering episodes were reduced in frequency and duration in 72%. A small series of six SCD children were followed with dosing twice daily with 0.25 mg/kg of etilefrine (Gbadoe, 2002). **The experience of multiple investigators using oral α-adrenergic dosing in the management of SCD stuttering ischemic priapism suggests that oral α-adrenergics at limited daily dosing should be considered in the management of stuttering priapism; drug therapy is typically initiated at bedtime.**

Hormonal Therapies

The primary action of systemic hormonal therapy in stuttering priapism is the suppression of the androgenic effects on penile erection. Attempts to treat stuttering priapism with hormones have exploited known regulators of male sexual function by targeting the pituitary gland (GnRH agonists), suppressing pituitary function through feedback inhibition (diethylstilbestrol), blocking androgen receptors (antiandrogens), and reducing testicular and adrenal synthesis (ketoconazole). In the only randomized placebo-controlled trial, a synthetic estrogen, diethylstilbestrol (DES), caused termination of the stuttering episodes in all patients subjected to treatment (Chinegwundoh, 2004). However, in more than 50% of patients (five of nine) priapism recurred after treatment cessation. Similar results are described by others in case reports (Gbadoe, 2002; Shamloul, 2005). Long-term estrogen therapy is not recommended due to the potential cardiovascular side effects. GnRH analogues, goserelin acetate and leuprolide acetate, have been described in case reports (Levine, 1993; Shamloul, 2005). Chronic dosing with GnRH analogues in combination with penile injection of alpha adrenergics as needed have been reported in the management of ischemic stuttering priapism (Steinberg, 1995). Discontinuation of GnRH analogues typically leads to stuttering resumption. Antiandrogens carry their actions by direct suppression of the penile androgen receptors. These agents including flutamide, bicalutamide, and chlormadinone have been able to cause considerable relief of stuttering priapism in a number of case reports; antiandrogens may have benefit to the patients over the GnRH analogues—orally administered patients have reported continued ability to have sexually stimulated erections (Costabile, 1998; Dahm, 2002; Yamashita, 2004). Rachid-Filho and colleagues (2009) have recently described the efficacy of oral finasteride in the management of sickle cell stuttering priapism. They administered

finasteride to 35 patients over 120 days in dosages that decreased monthly from 5 mg/day to 3 mg/day and then 1 mg/day in the final month. This was not a controlled trial, but careful observation of stuttering episodes was made; they found at the beginning of treatment the mean episode of stuttering priapism per patient was 22.7, and at the end of 4 months the mean episodes per patient were 2.1. The optimal effects were found at 5- and 3-mg daily dosing. Finasteride is a 5-α-reductase inhibitor approved in the United States for management of symptomatic benign prostatic hyperplasia and male pattern alopecia; it is not approved for use in stuttering ischemic priapism, and this was not a placebo-controlled trial. Six of 35 patients in this study developed painless gynecomastia. Abern and Levine (2009) used nightly dosing with oral ketoconazole and prednisone to suppress nocturnal erections as a preventive strategy for recurrent ischemic priapism; their protocol required titrating dosages and monitoring of nocturnal erections and serum testosterone levels.

Baclofen

Studies in both rats and humans suggest that baclofen inhibits penile erection and ejaculation, through GABA receptor activity. In rats, stimulation of $GABA_B$ receptors in the lumbosacral spinal cord inhibits erection (Bitran, 1988; Paredes, 1995; Vaidyanathan, 2004). Denys and colleagues (1998) reported on nine men with multiple sclerosis or spinal cord injuries who were treated for 44 months with intrathecal baclofen for muscle spasticity; eight of nine reported decreased erectile function, which reversed on cessation of baclofen. Rourke and colleagues (2002) first reported on the use of oral nightly baclofen 40 mg in the management of recurrent priapism in patients with neurologic lesions. D'Aleo and colleagues (2009) were the first to report on the use of an intrathecal pump dosing baclofen 180 μg daily for the management of skeletal muscle spasm and recurrent priapism in a patient with spinal cord injury; the patient was refractory to treatment with oral dosing of 75 mg/day but responded to a test dosage of 25 μg intrathecally. The neurologic literature generally fails to categorize these erectile events as ischemic or nonischemic. Triggering events may be tactile nonsexual stimulation causing repeated reflexogenic erections. Better characterization of these unwanted reflexogenic erections is necessary to appreciate hemodynamics, inciting events, duration, and impact on erectile function. In nonneurogenic patients baclofen daily dosing is associated with drowsiness, nausea, complaints of fatigue, and ED. Recurrent reflexogenic erections are clearly an unwanted condition associated with muscle spasticity in men with spinal cord lesions and neurologic disease, but it remains to be demonstrated that the duration and hemodynamics of such erectile events are similar to ischemic stuttering priapism in SCD.

Phophodiesterase Type 5 Inhibitors in the Management of Stuttering Priapism: a Counter-Intuitive Treatment Strategy

Bialecki and Bridges (2002) first reported on sildenafil having a paradoxical effect in controlling stuttering priapism in three patients with SCD (Bialecki, 2002). Although this proposal would immediately seem illogical on the basis of the understanding that PDE5 inhibitors exert erectogenic effects, there is a scientific basis for using these agents to treat priapism.

In a small case series, Burnett and colleagues have shown that daily sildenafil or tadalafil therapy reduces ischemic priapism episodes in men with stuttering priapism (Burnett, 2006). **When used in long-term dosing regimens unassociated with erection stimulatory conditions, PDE5 inhibitor therapy alleviates recurrent priapism episodes in men with SCD-associated priapism without affecting normal erectile capacity** (Burnett, 2006; Bivalacqua, 2009). The working theory is that surges of cGMP go unchecked because of down-regulated levels of PDE type 5; this results in stimuli like nocturnal erection, which causes unchecked corporal smooth muscle relaxation. In initial series, the short-acting PDE5 inhibitor sildenafil citrate was given in a dose of 25 mg oral daily, with escalation to 50 mg daily. Subsequently these investigators have reported on tadalafil at a dose of 5 or 10 mg oral dosage taken three times weekly. Multicenter, randomized, double-blind, placebo-controlled clinical trials are under way. PDE5 Inhibitors should be started under conditions of complete penile flaccidity, not during a stuttering episode. Efficacy is seen after a week or more of dosing.

Key Points: Medical Management of Stuttering Priapism

- The goals of managing a patient with stuttering priapism (SP) include prevention of future episodes, preservation of erectile function, and balancing the risks versus benefits of various treatment options.
- A trial of daily oral α-adrenergic may be used in the management of patients (adults and children) with SP associated with hemoglobinopathies. Dosing efficacy should be monitored for frequency and duration of stuttering episodes, blood pressure, and normal erectile capacity.
- A trial of daily oral PDE5 inhibitor therapy may be used in the management of patients (adults and children) with SP associated with hemoglobinopathies. Dosing should be initiated under conditions of complete penile flaccidity. Dosing efficacy should be monitored for frequency and severity of stuttering episodes, as well as PDE5 inhibitor side effects and normal erectile capacity.
- A trial of gonadotropin-releasing hormone (GnRH) agonists or antiandrogens may be used in the management of adult patients with SP. Hormonal agents should not be used in patients who have not achieved full sexual maturation and adult stature. Chronic GnRH or antiandrogen dosing in adult males may affect libido, may affect fertility, cause gynecomastia, cause hot flushes, promote osteoporosis, and worsen sexual function.
- When administered at home for prolonged morning erections, an injection of an intracavernous α-adrenergic may overt a full-blown episode of ischemic priapism. Intracavernous injection of phenylephrine (by the adult patient or parent) should be considered as an adjunct to daily systemic therapies in patients with SP.

SURGICAL MANAGEMENT OF ISCHEMIC PRIAPISM

Surgical management of ischemic priapism is indicated after repeated penile aspirations and injections of sympathomimetics have failed or if such an attempt has resulted in a significant cardiovascular side effect. At present there is a paucity of data regarding the timing of surgical intervention following initiation of medical treatment, although the 2004 International Consultation on Sexual Medicine in Paris

recommended corporal aspiration and α-adrenergic agonists for at least 1 hour before consideration of surgery (Pryor, 2004). Early surgical intervention may be preferable in patients with malignant or poorly controlled hypertension or for men who are using monoamine oxidase inhibitor medications contraindicating α-adrenergic therapies. A comprehensive discussion and documentation that includes baseline erectile function, duration of priapism, risks and benefits of the surgery, and ED should be held with the patient/guardian and an informed consent form signed by the patient/guardian.

Shunting

It is generally accepted that the longer an episode of ischemic priapism lasts, the greater the likelihood of compromised erectile function will be in the future. Previous reviews have concluded that priapism lasting longer than 24 hours was associated with a 90% ED rate (Pryor, 1982). Kulmala and colleagues (1995) reported 92% erectile function preservation among patients with ischemic priapism reversed in less than 24 hours, but only 22% preservation of erectile function among men with priapism lasting longer than 7 days. Recommendations based on well-documented erectile function outcomes are few. One recent study does document erectile function outcomes by contemporary standards (International Index of Erectile Function). Bennett and Mulhall (2008) carefully documented 39 cases of SCD priapism presenting to their emergency department over 8 years; men were routinely interviewed for erectile function status within 4 weeks of priapism/interventions. Of the 39 African-American men followed, 73% acknowledged prior episodes of stuttering; 85% had previously been diagnosed with SCD; and only 5% had been counseled in SCD clinics or were aware that priapism was a complication of SCD. A standard protocol of aspiration and phenylephrine injection was performed; shunting for failure of medical management was performed in 28%. In those patients where priapism was reversed, spontaneous erections (with or without use of sildenafil) were reported in 100% of men when priapism was reversed by 12 hours; 78% when reversed by 12 to 24 hours; and 44% when reversed by 24 to 36 hours. No patient reported spontaneous erections after priapism duration of longer than 36 hours. **The International Society for Sexual Medicine Standards Committee (expert opinion) stated that shunting is to be considered for ischemic priapism events lasting 72 hours or less.** Consideration should be given to foregoing a shunt in priapism events lasting longer, in particular where cavernous thrombosis is evident and no blood can be aspirated from the corporal bodies (Pryor, 2004; Mulhall, 2006).

The objective of shunt surgery is reoxygenation of the cavernous smooth muscle. The shared principle of shunt procedures is to reestablish corporal inflow by relieving venous outflow obstruction; this requires creation of a fistula between the corpora cavernosa (CC) and glans penis, CC and corpus sponsigosum, or CC and dorsal/saphenous veins. Shunt procedures are subdivided on the basis of anatomic location on the penis (Lue, 2006) (Figs. 25–8 and 25–9).

- Percutaneous distal shunts—Ebbehoj (1974), Winter (1976), or T-shunt (Brant, 2009)
- Open distal shunt—Al-Ghorab (Hanafy, 1976; Borrelli, 1983) or Corporal Snake (Burnett, 2009)
- Open proximal shunt—Quackles (1964) or Sacher (1972)
- Saphenous vein—Grayhack (1964)
- Deep dorsal vein shunt—Barry (1976)

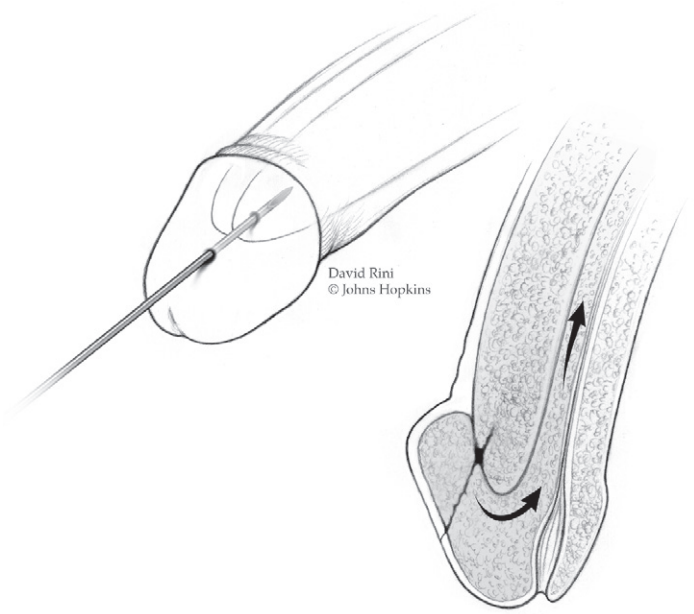


Figure 25–8. Winter shunt. A distal cavernoglanular shunt procedure is depicted by the transglanular placement of a large-bore needle or angiocatheter in the distal glans and corpus cavernosum. (© Brady Urological Institute.)

A distal cavernoglanular shunt should be the first choice of shunting procedures because it is technically easier to perform than proximal shunting. Percutaneous distal shunting is less invasive than open distal shunting and can be performed with local anesthetic in the emergency department. The most recently described distal shunt (Brant, 2009) creates a T-shaped shunt between the CC and glans penis. Brant (2009) describes 13 men with priapism durations longer than 24 hours (6 of 13 had failed other distal or proximal shunt procedures). All T shunts were performed following penile anesthetic block; 12 of 13 patients were successfully reversed by initial intervention. In T shunting a No. 10 blade is placed vertically through the glans 4 mm away from the meatus; the blade pierces through the glans to CC and is rotated 90 degrees away from the urethra and removed. Deoxygenated blood is milked out of the wound. The glans is then sutured with absorbable suture. The authors recommend discharge home if the penis remains flaccid for 15 minutes. If erection returns or persists, a second T shunt is recommended on the opposite side of the meatus. In those cases where ischemic priapism has been present for more than 36 hours, the authors recommend immediate bilateral T shunts with passage of 20-Fr dilators into the fistula tract and well into the CC down to the crus. This technique is more traumatic and will require anesthetic. Burnett and Perorazio (2009) have described a similar technique to resolve ischemic priapism refractory to first-line interventions. Their procedure known as the "corporal snake" is a modification of the Al-Ghorab corporoglanular shunt (Fig. 25–10). Under general anesthetic, a 2-cm transverse incision is made on the glans; the distal tips of the rigid CC are incised and grasped with 2-0 stay sutures or Kocher clamps. Deoxygenated blood is milked out of the CC, but rather than excising a wedge of tunica and underlying CC muscle, a 7/8 Hegar dilator is advanced through each of the tunica windows proximally several centimeters to release blood and thrombus. The penis is made flaccid by repeated manual compression and release; the glans skin is then approximated with 4-0 chromic sutures;

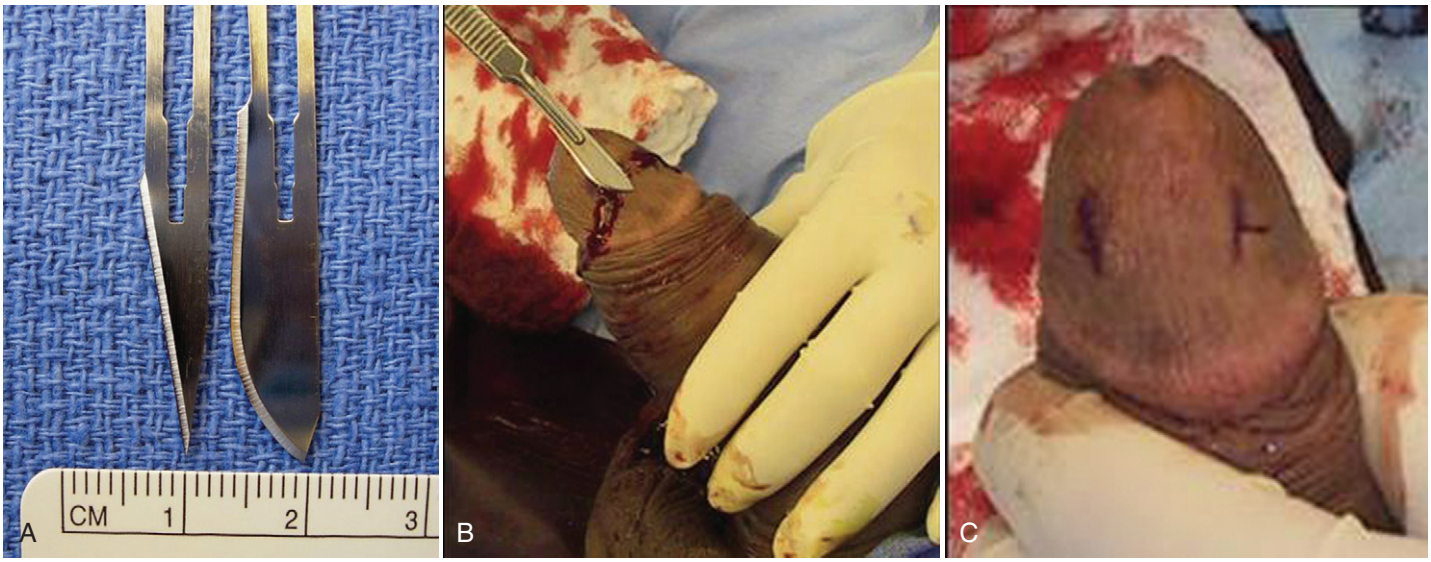


Figure 25–9. **A,** A No. 11 blade is used for an Ebbehoj percutaneous cavernoglanular shunt, and a No. 10 blade is used for a T shunt. **B** and **C,** Note the differences between the Ebbehoj and T shunts. In the Ebbehoj technique the No. 11 blade leaves a straight incision into the glans and corporus cavernosum. In the creation of a T shunt the No. 10 blade is rotated 90 degrees after insertion and withdrawn. In both the percutaneous techniques deoxygenated blood is milked out of the open wounds; once bright red blood is seen, the skin is closed, leaving the deeper incision as the open fistula. In either procedure the maneuver may be repeated on the opposite corpora. (Courtesy of Tom Lue.)

Table 25–5.

Assessing Corpora Cavernosa Shunt Patency

Visualization of bright red blood in corporal aspirate
Corporal blood gas
Color Doppler ultrasound
Measurement of intracavernous pressure
Penile compression maneuver (squeeze and release)

urethral catheter is placed and lightly compressive dressing is applied to the genitalia.

The key factors determining successful surgical reversal of ischemic priapism are evacuation of thrombus, reestablishing cavernous inflow, and patency of shunt. Theoretically, larger open shunt procedures are likely to result in higher shunt patency rates; there are no data comparing percutaneous and open distal shunts. The surgeon must be guided by familiarity with various techniques: percutaneous shunting, open distal shunting, proximal shunting, and vein shunting. Although distal shunting can be performed with penile block and sedation in the emergency department, open shunting, especially that requiring passage of dilators into the CC, will likely require general anesthesia and an operating room suite. At the completion of the shunt, patency can be verified in the operating room and subsequently recovery room in a number of ways: bright oxygenated blood should be seen emanating from the corporal bodies; intracavernous pressures should fall; the penis should detumesce and refill with sequential compression and release; and color Doppler ultrasound will show resumption of cavernous artery inflow (Lue, 2002; Nixon, 2003; Chiou, 2009) (Table 25–5). Complications of shunting include penile edema, hematoma, infection, urethral fistula, penile necrosis, and pulmonary embolism.

The most commonly described proximal shunt is the unilateral shunt, described by Quackles in 1964 (Fig. 25–11). Proximal corpus cavernosum to spongiosum (CC-CS) shunt procedures require a transscrotal or transperineal approach (Quackles, 1964). There are no data comparing bilateral (Sacher, 1972) and unilateral CC-CS shunts (Quackles, 1964). Typically, bilateral shunts are staggered; the right side and left side are separated by a distance of at least 1 cm in an effort to minimize the risk of urethral stricture at the point of CC-CS communication (Fig. 25–12). In cases where proximal shunt fails, some have advocated saphenous vein bypass or deep dorsal vein shunt (Fig. 25–13A and B). A wedge of tunica albuginea is removed and the vein is anastamosed end to side of CC. There are no comparative trials of vein shunting for ischemic priapism. Authors have described a significant risk of sapheno-femoral vein thrombus and pulmonary embolism with vein shunting (Kandel, 1968).

Immediate Implantation of Penile Prosthesis

Unfortunately **the natural history of untreated ischemic priapism or priapism refractory to interventions is severe fibrosis, penile length loss, and complete ED** (see Fig. 25–1). Kelami (1985) described the implantaion of the Small-Carrion penile prosthesis through an infrapubic incision in the management of postpriapic erectile dysfunction. Bertram and colleagues (1985) described six postpriapic cases of penile prosthesis; five of six men had successful implantation of semirigid prostheses. Both groups described extensive corporal fibrosis and suggested that semirigid implants were preferable because inflatable implants would not overcome the corporal fibrosis sufficiently to erect the penis. Douglas and colleagues (1990) reported on penile prosthesis in five SCD postpriapic men; they described a surgical technique of tunneling and corporal excavation. Inadvertent damage to the tunica albuginea was common, as was subsequent migration of hardware; 11 additional procedures were required following the initial implants. The average time from priapism to implant in Douglas's series was 4 years. Monga and colleagues (1996) described implants in young SCD patients (six patients, average age 26); inflatable implants were placed to both treat ED

Key Points: Surgical Management of Ischemic Priapism

- Shunt surgery should be considered for all cases of ischemic priapism (IP) failing aspiration and intracavernous injection of α-adrenergics.
- Patients should be counseled that erectile function outcomes decline significantly when IP has lasted longer than 24 hours and that complete ED is anticipated if IP persists for longer than 36 hours.
- The objective of shunt surgery is reoxygenation of the cavernous smooth muscle.
- The key factors determining successful surgical reversal of IP are evacuation of thrombus, patency of shunt, and resumption of cavernous inflow.
- A distal cavernoglanular shunt should be the first choice of shunting procedures.
- Percutaneous distal shunting is less invasive than open distal shunting and may be performed with local anesthetics.
- There are a number of distal shunting procedures and the surgeon should be familiar with these procedures and their complications.
- Open distal shunting should be considered if percutaneous shunting fails. There are no comparative trials of safety, efficacy, or erectile function outcomes for percutaneous versus open distal shunting techniques.
- If distal shunting fails, then proximal shunting is recommended. Proximal shunting establishes a communication between the corpora cavernosa and spongiosa at the base of the penis. The surgeon must be aware of the unique anatomic relationship between the corpus spongiosum and urethra.
- Shunting may also be accomplished with vein grafting to the corpora cavernosa. Venous shunts have increased the risk of thromboembolism.
- Following medical or surgical reversal of IP, penile tumescence rather than complete flaccidity may be evident. A phenomenon of conversion from IP to HFP has been described. In cases where the examination may be equivocal, color Doppler ultrasonography or cavernous blood gas is recommended to demonstrate patency of shunt and restoration of cavernous inflows.
- After shunting, follow up with the patient on erectile function and any subsequent ED therapies.

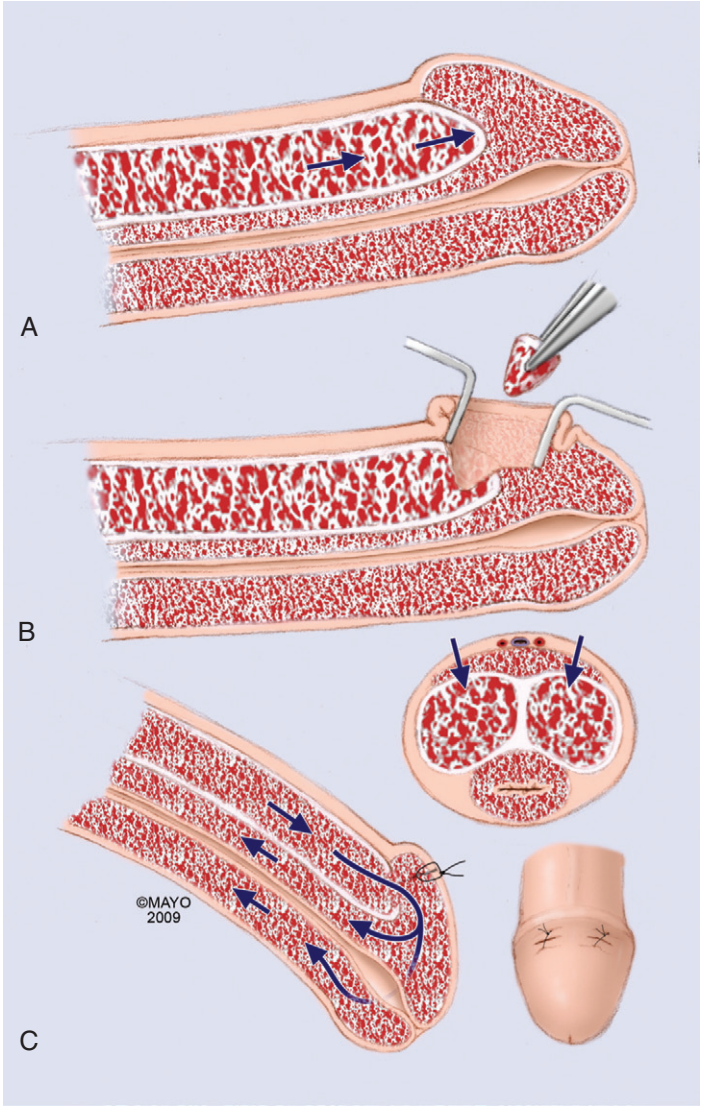


Figure 25–10. **A-C,** An open corporoglanular shunt is indicated if percutaneous shunting fails to reestablish cavernous blood inflow. The Al-Ghorab shunt requires the excision of circular cone segments of the distal tunica albuginea (5 × 5 mm). (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

and circumvent ongoing episodes of stuttering priapism. They suggested that both potency and recurrent episodes of ischemic priapism could be managed by "early" implantation. **Some have suggested performing immediate penile prosthesis in the acute management of ischemic priapism, when the patient has failed sympathomimetic intracavenous therapies and shunting** (Rees et al, 2002). There are two distinct advantages to immediate implantation: corporal fibrosis is not yet established, and penile length may be preserved. **The exact time point at which prosthetic insertion becomes a reasonable option for managing ischemic priapism is unclear.** Should medical management of ischemic priapism be followed by distal percutaneous shunt, by open distal shunt, and subsequently by proximal shunting before penile implant? Should men with delayed presentation of ischemic priapism and evident corporal thrombus be triaged to immediate penile implant? What is clear is that any discussion pertaining to early prosthesis insertion should be documented and include a comprehensive review of the theoretic advantages and actual risks. Compared with prosthesis insertion in a typical patient with erectile dysfunction, **there are significantly higher rates of complications noted in priapism cases: infection, urethral injury, device migration, device erosion, and revision surgeries.** The surgeon must be familiar with the additional technical concerns posed by weaknesses in the tunica albuginea in the region of prior shunts.

The advantages of early penile implantation in the acute management of ischemic priapism are preservation of penile length and technically easier implant insertion. Delayed placement of penile prosthesis is technically challenging due to corporal fibrosis. Ralph (2009) reported on 50 patients with ischemic priapism. All patients failed conservative management with the instillation of α-adrenergic agents (200 μg phenylephrine repeated to a maximum dosage of 1500 μg). Unsuccessful shunts were performed in 13 of 50 cases

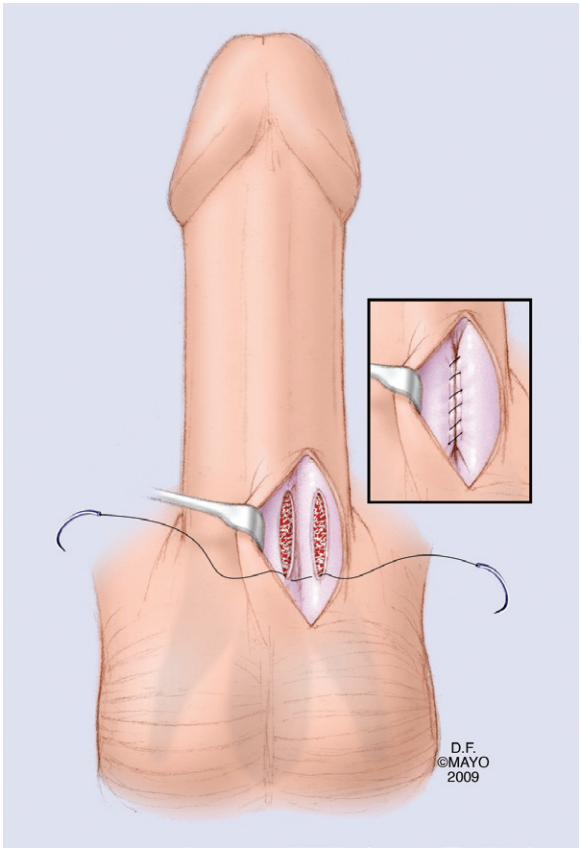


Figure 25–11. The proximal open shunt technique to establish communication between the corpus spongiosum and corpus cavernosum was first described by Quackles in 1964. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

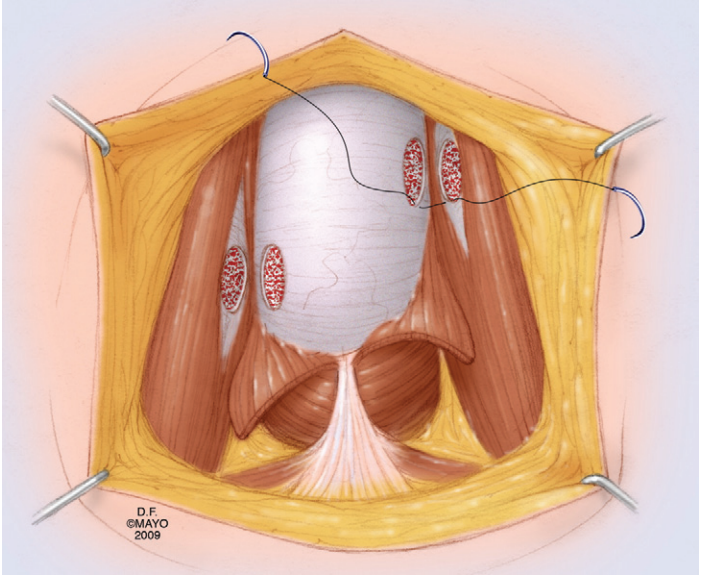


Figure 25–12. Bilateral shunts are staggered. The right and left sides are separated by a distance of at least 1 cm in an effort to minimize the risk of urethral stricture at the point of corpus cavernosum to spongiosum communication (Sacher, 1972). (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

(Ralph, 2009). Mean duration of priapism was 209 hours (range 24 to 72 hours). All patients had evidence of cavernous thrombus and smooth muscle necrosis on MRI and all 50 underwent insertion of penile prosthesis in the acute setting of refractory ischemic priapism. Revision rates were significantly high 24% (12 of 50 patients). The infection rate of 6% was also notably high and likely related to multiple factors including ischemic tissues and preceding penile interventions.

Key Points: Surgical Management of Ischemic Priapism with Immediate Penile Implant

- The natural history of untreated IP or priapism refractory to interventions is severe fibrosis, penile length loss, and complete erectile dysfunction.
- The advantages of early penile implantation in the acute management of IP are preservation of penile length and easier insertion.
- Document baseline erectile function, duration of priapism, history of stuttering, and prior interventions.
- Consider penile prosthesis if:
  - The patient has failed aspiration and sympathomimetic intracavernous injection.
  - The patient has failed distal and proximal shunting.
  - Ischemia has been present for longer than 36 hours.
- Consider an MRI before surgery or corporal biopsy at the time of implant to document corporal smooth muscle necrosis.
- There are higher rates of revision surgery and complications noted in priapism cases due to infection, urethral injury, device migration, and device erosion.

INTERVENTIONAL ANGIOGRAPHY IN THE MANAGEMENT OF ARTERIAL (NONISCHEMIC, HIGH-FLOW) PRIAPISM

Arterial priapism is not an emergency. Spontaneous resolution or response to conservative therapy has been reported in up to 62% of published series (Montague et al, 2003; Pryor et al, 2004). Persistent partial erection from HFP may be evident for months to years, without adverse impact on erectile function (Bastuba et al, 1995). Kumar et al (2006) described a case of HFP in a 24-year-old patient 10 days after straddle injury on a bicycle. The patient had no erection for the first 4 days following injury. Examination revealed a tumescent penis that was compressible. Penile aspiration and blood gas analysis revealed oxygenated corporal blood. Color Doppler ultrasound of the cavernous artery revealed arterio-sinusoidal fistula. Partial erection spontaneously resolved 4 days after diagnostic evaluation, with the patient reporting normal erections 2 weeks later. The authors hypothesized that in cases of blunt penile and perineal trauma an arterio-lacunar fistula forms; these fistulae, unlike arteriovenous communications, may spontaneously resolve as the less rigid walls of the lacunae are prone to spontaneous thrombosis.

There are no comparative outcome studies of intervention versus conservative management in high-flow priapism; there are sufficient case descriptions, especially in children, to recommend initial watchful waiting (Nehra, 2006). Initial

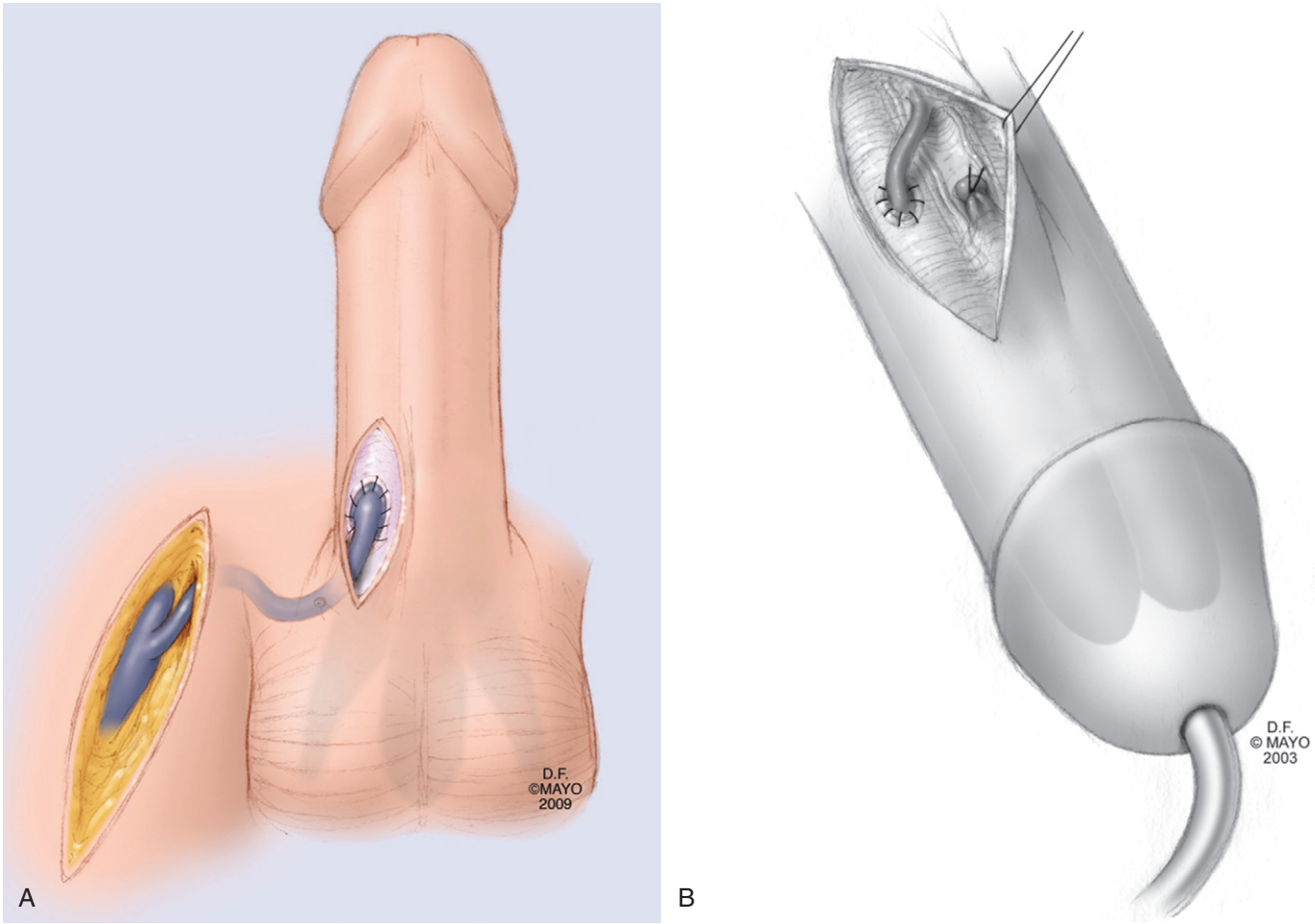


Figure 25–13. **A,** Venous bypass to control ischemic priapism was first described by Grayhack in 1964. The Grayhack shunt mobilizes the saphenous vein below the junction of the femoral vein and anastamoses the vein end to side into the corpus cavernosum. **B,** Deep dorsal vein (DDV) shunt with distal ligation of DDV and anastamosis of proximal DDV to corpus cavernosum. A wedge of tunica albuginea is removed. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

observation is recommended for this type of priapism. Conservative measures include ice applied to the perineum and site-specific compression. **Cavernous aspiration has only a diagnostic role in high-flow priapism. Repeated aspirations, injection, and irrigation with intracavernous sympathomimetics have no role in the treatment of nonischemic priapism.**

Patients demanding immediate relief can be offered selective arterial embolization. The pathognomonic arteriographic finding is an arterial-lacunar fistula; a characteristic intracavernosal cone-shaped blush of contrast is seen at the site of the cavernous artery or arteriole laceration (Fig. 25–14). Selective internal pudendal catheterization and subsequent embolization have been reported with various agents: microcoils, polyvinyl alcohol, N-butylcyanoacrylate, gel-foam, and autologous blood clot (Kuefer, 2005). Permanent materials pose a greater theoretic risk of erectile dysfunction; many authors recommend use of autologous blood clot and absorbable gels (Pryor, 2004; Kim, 2007). Autologous blood clot has a low risk of foreign body reaction, or antigenicity; it is a temporary occlusive agent and should permit recanalization of the cavernous artery (Park, 2001). The success rates with selective pudendal artery catherterization followed by embolization are quite high (89% to 100%), regardless of the embolization material used (Kuefer, 2005; Numan, 2008). Similar results have been reported by others (Savoca, 2004; Alexander, 2006). Normal postembolization erectile function has been reported in 75% to 86% of patients (Cakan, 2006; Numan, 2008). **It should be noted that a single treatment of embolization carries a recurrence rate of 30% to 40%** (Ciampalani, 2002; Gandini, 2004; Ozturk, 2009). **Although ultimately successful, embolization of HFP may require retreatment**. **The most notable side effect of arterial embolization is erectile dysfunction.** Although it was previously reported that nonpermanent embolization materials cause less ED than permanent ones (5% vs. 39%), recent reports employing International Index of Erectile Function in evaluation of postembolization erectile function describe similar rates of erectile dysfunction, 15% and 20% (Savoca, 2004; Alexander, 2006). Other reported adverse effects include penile gangrene, gluteal ischemia, purulent cavernositis, and abscess of the perineum (Hakim, 1996; Sandock, 1996) (Fig. 25–15).

Puppo (1985) compared perineal duplex ultrasound and selective internal pudendal arteriography showing excellent sensitivity in detecting the arterial-lacunar fistula on ultrasound that is seen angiographically (12 of 12 cases). Several reports describe combined ultrasound-guided compression with selective arterial embolization to increase success rates in the treatment of nonischemic priapism (Hatzichristou, 2002; Bartsch, 2004; Cakan, 2006).

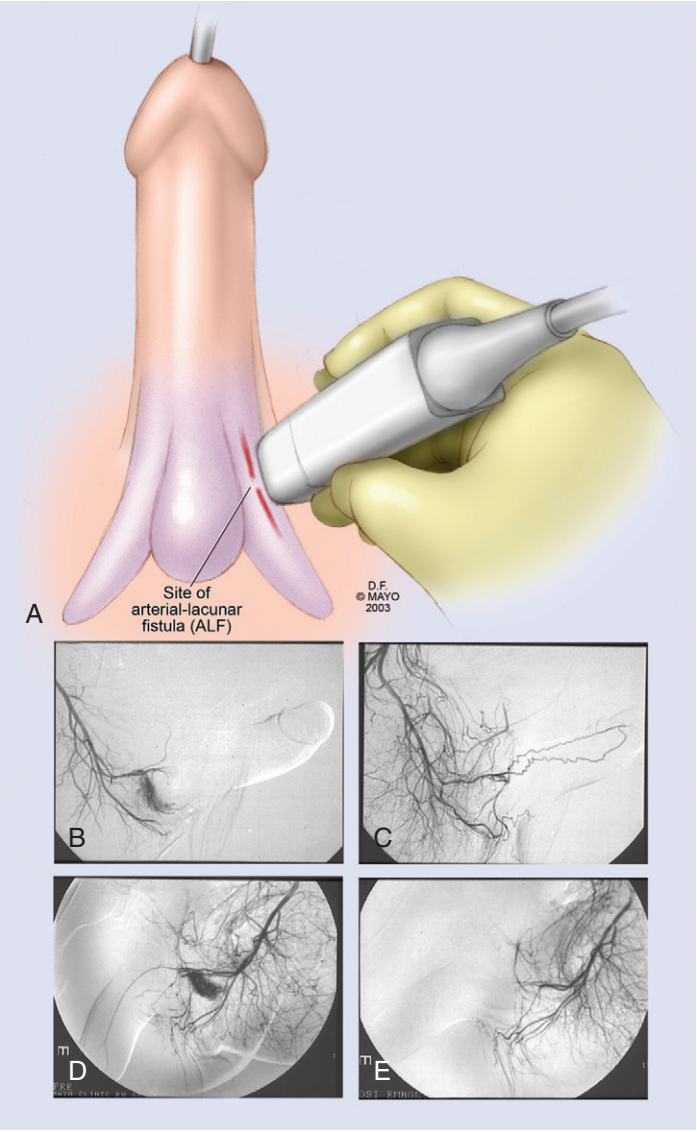


Figure 25–14. Color Doppler ultrasonography of the penis and perineum is recommended in the evaluation of priapism, when the history or examination suggests penile trauma (**A**). Doppler sonography for localization of a fistula correlates well with selective pudendal angiography (**B, C, D, E**); a characteristic fistula blush is shown (**B, D**), along with normal arteriograms (**C, E**). (**A,** By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

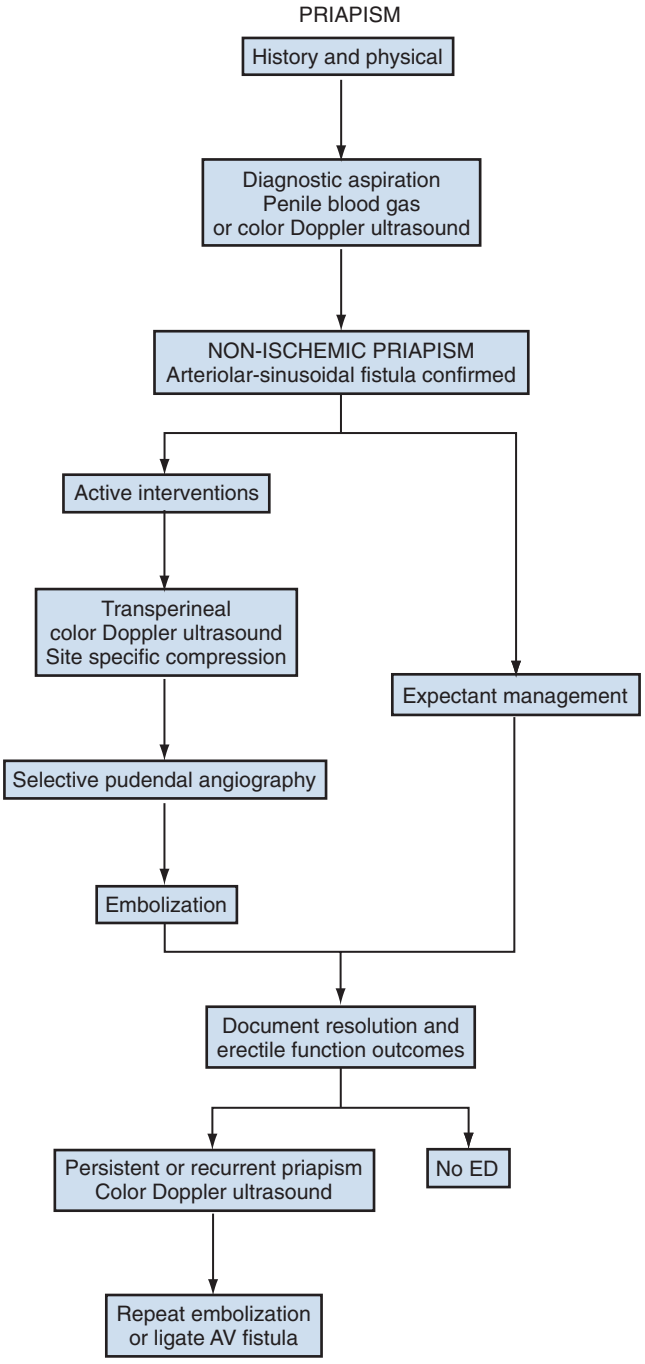


Figure 25–15. Algorithm for managing high-flow priapism. AV, arteriovenous; ED, erectile dysfunction.

If the follow-up clinical examination is equivocal for recurrence of high-flow priapism, a perineal duplex Doppler ultrasound can determine the need for repeat arteriography and embolization (Kim, 2007).

SURGICAL MANAGEMENT OF ARTERIAL (NONISCHEMIC, HIGH-FLOW) PRIAPISM

Arterial priapism is not a urologic emergency. HFP is painless and there have been reports of partial erection persisting for years (Nehra, 2006). Any intervention must follow a comprehensive discussion with the patient regarding risks and benefits of any of the procedures advocated by the clinician. **In cases of long-standing arterial priapism where a pseudocapsule around the fistula has developed, surgical ligation has been reported to be successful. Formation of a pseudocapsule may take weeks to months following trauma. Corporal exploration before the formation of a pseudocapsule may result in ligation of cavernous artery rather than selective ligation of the fistula.** Currently this intervention is reserved for patients who do not wish to pursue expectant management or who are poor candidates for angio-embolization. It is also reserved for patients who refuse the procedure; for patients in places where technology is not available; and for patients whose angio-embolization failed (Ji, 1994; Berger, 2001; Mulhall, 2006). The surgical approach is transcorporal. Intraoperative Doppler ultrasound guidance is recommended.

Key Points: Evaluation and Management of High-Flow Priapism

- Arterial priapism is not an emergency and may be managed expectantly.
- Diagnosis of HFP is best made by penile/perineal color Doppler ultrasound.
- Penile aspiration and injection of α-adrenergic agents is not recommended for HFP.
- Angio-embolization should be preceded by a thorough discussion of chances for spontaneous resolution, risks of treatment-related ED, and lack of significant consequences expected from delaying interventions.
- Overall success rates with embolization are high, although a single treatment carries a recurrence rate of 30% to 40%.
- Where angio-embolization fails or is contraindicated, surgical ligation is reasonable.
- Formation of a pseudocapsule at the site of a sinusoidal fistula may take weeks to months following trauma.
- Color Doppler ultrasound guidance is recommended during exploration to locate fistula.

CONCLUSIONS AND RECOMMENDATIONS FOR RESEARCH IN PRIAPISM

Prompt diagnosis and appropriate management of priapism are necessary to spare patients ineffective interventions and optimize erectile function outcomes. Future research is necessary to understand each type of priapism: (a) corporal smooth muscle pathology associated with genetic and acquired conditions that result in ischemic priapism; (b) the molecular mechanisms involved in the pathogenesis of stuttering ischemic priapism; (c) documentation of onset of HFP in relation to time of injury and response to conservative management versus angiographic or surgical interventions. Future research should include animal models to study the physiology of ischemic priapism. These models should examine the clinical observation that interventions for ischemic priapism may result in a phenomenon of conversion to high flow. Specific questions need to be addressed: Is cavernous arterial dysregulation a normal postischemic response? When does postischemic high flow resolve? Sickle cell patients should receive education on priapism and its management. Recent studies suggest that only 5% of SCD patients recalled learning that priapism was a complication of SCD. Urologists preparing case reports should document pre-priapism erectile function, duration of priapism with respect to initiation of each intervention, history of stuttering priapism, and recovery of erectile function using standardized questionnaires. Documenting erectile function outcomes on the basis of duration of ischemic priapism, time to interventions, and types of interventions will establish evidence-based guidance on how and when to apply those interventions.

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chapter
26

Premature Ejaculation

John P. Mulhall, MD, MSc (Anat)

Physiology of Ejaculation
Definition of Premature Ejaculation
Epidemiology
Pathophysiology of Premature Ejaculation
Patient Evaluation
Treatment Overview

PHYSIOLOGY OF EJACULATION

Alongside developments in the field of erectile physiology and pathophysiology, the past decade has witnessed increased understanding of central and peripheral mechanisms involved in ejaculatory control. **Usually accompanied by orgasm, ejaculation constitutes the final phase of the sexual response cycle in the male and represents a reflex comprising sensory stimuli, cerebral and spinal control centers, and efferent pathways. Ejaculation is a reflex, which requires a complex interplay among somatic, sympathetic, and parasympathetic pathways involving predominantly central dopaminergic and serotonergic neurons** (McMahon et al, 2004). In antegrade ejaculation, two basic phases are involved: emission and expulsion (Giuliano, 2005). **Emission,** as the first phase of ejaculation, is a sympathetic spinal cord reflex and defined as the deposition of seminal fluid into the posterior urethra. **Expulsion** is due to the combined action of sympathetic and somatic pathways. **An antegrade ejaculation requires a synchronized interplay between periurethral muscle contractions and bladder neck closure, contemporaneous with the relaxation of the external urinary sphincter. Orgasm,** generally associated with ejaculation, is a pleasurable sensation resulting from cerebral processing of the increased pressure in the posterior urethra and contraction of the bulbar urethra bulb and accessory sexual organs.

Coordination of Ejaculation

Peripheral and central centers, as well as sympathetic, parasympathetic, and somatic pathways, participate in the physiologic control of the ejaculatory reflex (Fig. 26–1 on Expert Consult website). A normal ejaculatory response requires synchronized neurochemical interplay coordinated at different levels of the nervous system (Giuliano, 2005). In humans, the composition of the ejaculate is released from participating organs in a particular order. **The first portion of the ejaculate is provided by the bulbourethral glands followed by some fluid from the prostate. Afterwards, the main fraction of the ejaculate including the bulk of the spermatozoa is contributed by the epididymis and vas deferens, along with prostate and seminal vesicle contributions.**

Adequate sensory stimulation of the dorsal penile nerve and posterior urethral distention appears to be sufficient to trigger an ejaculatory response. McKenna, describing a urethrogenital reflex, showed that urethral distension in anesthetized rats induced contractions of the striated perineal muscles (McKenna et al, 1991). The **emission of the seminal fluid is controlled by the sympathetic nervous system activating propulsive contraction of the smooth muscle of the prostate, vas deferens, and seminal vesicles, as well as prostatic glandular secretion. Clear clinical evidence for a functional role of parasympathetic innervation involved in the ejaculatory process is missing** thus far (Giuliano, 2005). The important role of the sympathetic system in the ejaculatory process in humans is emphasized by the fact that an **interruption of the innervation of the bladder neck, vas deferens, and prostate might lead to a retrograde ejaculation or failure of emission.** Protection of sympathetic efferents during surgical procedures in the retroperitoneum or in the pelvis preserves normal ejaculatory function. In patients with spinal cord injury, ejaculation can be achieved acquiring a semen sample with electric stimulation of the hypogastric plexus activating sympathetic efferents (Ohl et al, 1997, 2001).

The somatic nervous system (represented by the pudendal nerve) is exclusively responsible for the expulsion phase of the ejaculate. The synchronous activation of ischiocavernosus, bulbospongiosus, and levator ani muscles as the perineal striated muscles and the anal and urethral external sphincters innervated by the pudendal nerve causes the expulsion of seminal fluid from the urethra. Patients with sacral spinal cord injuries (pudendal nerve arises from sacral segments S2-4) after trauma or patients with neuropathies (e.g., diabetes) typically show a dribbling ejaculation due to the missing motor innervation of the propulsive pelvic musculature.

Using positron emission tomography (PET) scanning, the areas of the brain most activated during ejaculation include the mesodiencephalic transition zone including the ventral tegmental area (VTA), medial and lateral thalamus, and SPFp (Holstege et al, 2003). Other PET and functional magnetic resonance imaging (MRI) studies have suggested that there is intense activation of the parietal cortex during ejaculation (Arnow et al, 2002; Holstege et al, 2003). This site appears to receive sensory signals from the pudendal sensory nerve fibers (Perretti et al, 2003). The VTA zone

contains A10 dopaminergic neurons, purported to be involved in rewarding behaviors (also activated by cocaine).

Neuropharmacology of Ejaculation

Experimental studies in animals advocate **a fundamental role for dopamine (D) and serotonin** (5-hydroxytryptamine, 5-HT) in the regulation of ejaculation. Cerebral serotonin (5-HT) plays an inhibitory role in ejaculation, demonstrated in several animal studies in rats (Giuliano and Clement, 2006). Within the group of 14 different 5-HT receptor subtypes, some subtypes may have proejaculatory and other antiejaculatory effects. **Current literature supports at least the involvement of 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2C} receptors in ejaculatory control** (Waldinger et al, 2004a). **The stimulation of 5-HT_{1A} receptors at various places including cerebral, spinal, or peripheral autonomic ganglia has a generally positive effect on ejaculation, whereas stimulation of 5-HT_{2C} has the opposite effect.** Activation of 5-HT_{1A} autoreceptors has resulted in shortening of the ejaculatory latency time. On the other hand, the stimulation of presynaptic 5-HT_{1B} autoreceptors and postsynaptic 5-HT_{2C} receptors has shown an inhibition of ejaculatory behavior in male rats. Serotonergic neurons originate adjacent to the reticular formation in the brainstem and are self-regulated via a negative feedback system.

Serotonin is released into the synapse by the presynaptic neuron (Fig. 26–2). **Once in the synapse, serotonin binds to receptors located on the postsynaptic membrane. Following this, serotonin returns to the presynaptic neuron. The return of serotonin to the presynaptic neuron is assisted by serotonin transporters. Selective serotonin reuptake inhibitor (SSRI) medications block serotonin transporters, thus preventing the reabsorption of serotonin into the presynaptic neuron. In the immediate term, there are increased levels of serotonin in the synapse. Due to this increased synaptic serotonin level, 5-HT_{1A} receptors and 5-HT_{1B} receptors on the postsynaptic and presynaptic membranes, respectively, become activated, resulting in a reduction in secretion of serotonin into the synapse. These receptors then become desensitized (failure of inhibition of serotonin secretion from the presynaptic neuron), resulting in the serotonin release into the**

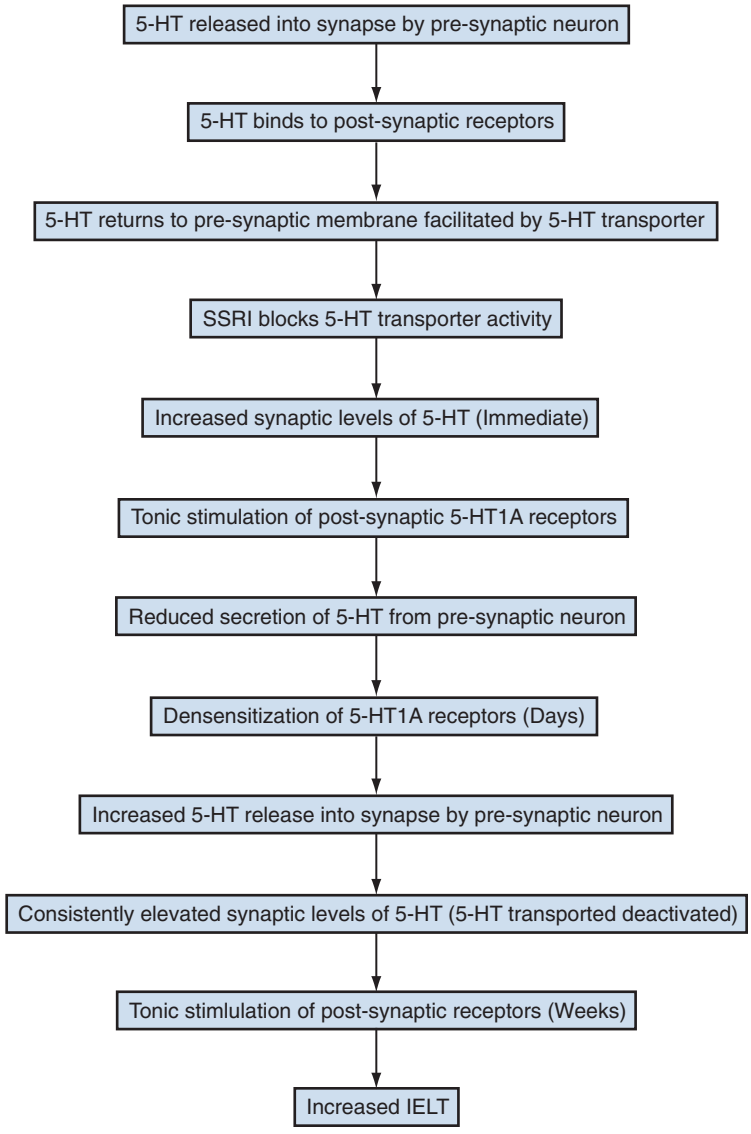


Figure 26–2. Schema depicting the effect of selective serotonin reuptake inhibitor (SSRI) medications on intravaginal ejaculatory latency time (IELT).

synapse, but this time because of transporter inhibition by the SSRI, the synaptic serotonin levels remain high, resulting in persistent activation of postsynaptic receptors, which translates into the clinical effects of SSRI medications including prolongation of ejaculatory latency time.

- Ejaculation is a reflex, requiring a complex interplay among somatic, sympathetic, and parasympathetic pathways involving predominantly central serotonergic neurons.
- The somatic nervous system represented by the pudendal nerve is exclusively responsible for the expulsion phase of ejaculation.
- Current literature supports the concept that stimulation of 5-HT_{1A} receptors shortens ejaculatory latency time and stimulation of 5-HT_{2C} prolongs ejaculatory latency time.
- SSRI-induced elevated levels of serotonin in the synapse result in prolongation of ejaculatory latency time.

DEFINITION OF PREMATURE EJACULATION

In 1943 Shapiro published the first report on premature ejaculation (PE; synonyms *rapid ejaculation, ejaculatio praecox*), reporting on more than 1000 men with this condition (Optale, 1943). Between then and the publication of Seaman's seminal paper (Semans, 1956), little appeared in the literature. **Since that time, the definition of PE has been a source of debate for clinicians and researchers and has undergone radical review in the past few years, culminating in a new definition developed by a consensus panel of the International Society for Sexual Medicine (ISSM)** (McMahon et al, 2008). Shapiro discussed PE of types A and B in his 1943 article. These types became retermed in 1989 as *life-long* (also termed *primary*) and *acquired* (also termed *secondary*) by Godpodinoff (1989). Historically, there are numerous definitions, some defined by individuals, some by professional organizations (Table 26–1). **The two definitions for PE that have been used most often have come from the American Psychiatric Association and the World Health Organization. Both groups used expert panels to arrive at their definitions, and both were devoid of any evidence-based medicine to support such definitions.** In the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) overseen by the American Psychiatric Association, the PE definition has as its core element the concept of "patient distress or interpersonal difficulty." **According to the International Classification of Diseases (ICD-10), a time cutoff is used and the time limit arrived at was 15 seconds, without any validation of this time point.**

No single factor defines PE, and the definition should involve multiple dimensions such as time, perceived control over ejaculation, personal and partner distress, reduced sexual satisfaction, and relationship difficulty (Waldinger, 2007a). **Time is measured by the intravaginal ejaculatory latency time** (IELT, also known as *IVELT*), the duration in seconds or minutes that pass from the first moment of vaginal penetration to ejaculation/orgasm. Waldinger has made a cogent argument that there is a difference between a disorder (all men with PE) and a dysfunction (those bothered by their PE) (Waldinger, 2007a). Thus given that previous definitions are based on expert opinion and are not based on epidemiologic or controlled studies, the ISSM set forth to convene a panel of experts in 2007 to review the current medical literature and to arrive at a functional definition for lifelong PE. **The panel defined PE as having three components: (1) ejaculation that always or nearly always occurs before or within about 1 minute of vaginal penetration, (2) the inability to delay ejaculation on all or nearly all vaginal penetrations, and (3) negative personal consequences such as distress, bother, frustration, and/or the avoidance of sexual intimacy.**

A recent proposal has been put forth by Waldinger to categorize PE into four subtypes: lifelong, acquired, natural variable PE, and premature-like ejaculatory dysfunction (Table 26–2) (Waldinger, 2007a). This subcategorization has clinical utility because as a group these categories describe nearly all patients seen in clinical practice.

Table 26–1.

Definitions of Premature Ejaculation

ORGANIZATION	PUBLICATION	YEAR	DEFINITION
ISSM	J Sex Med	2008	• Ejaculation within about a minute • Inability to delay ejaculation • All or nearly all vaginal penetrations • Negative personal consequences
WHO	ICD-10	2004	• Inability to delay ejaculation • Sufficient to enjoy lovemaking • Ejaculation before/soon after beginning of intercourse (15 sec)
AUA	J Urol	2004	• Ejaculation occurring sooner than desired • Before or shortly after penetration • Causes distress to one/both partners
EAU	Website	2001	• Inability to control ejaculation for sufficient time before vaginal penetration
APA	DMS-IV-TR	2000	• Persistent or recurrent ejaculation • Minimal sexual stimulation • Before, on, or shortly after penetration • Before the person wishes it
Masters & Johnson	Human Sexual Inadequacy		• Inability to control ejaculation for sufficient time during intercourse • Inability to satisfy partner on at least 50% of intercourse attempts

APA, American Psychiatric Association; AUA, American Urological Association; EAU, European Association of Urology; ISSM, International Society for Sexual Medicine; WHO, World Health Organization.

Table 26–2.
Variations of Premature Ejaculation

TYPE	FEATURES
Lifelong	• PE at all or nearly all intercourse attempts • With all or nearly all women • In majority of cases within 1 minute • Consistent during life • Inability to control ejaculation may be lacking (not obligatory)
Acquired	• Rapid ejaculation occurring at some point in life • Normal ejaculation before onset of premature ejaculation • Often source of problem identifiable (organic, psychologic) • Inability to control ejaculation may be lacking (not obligatory)
Natural variable	• Rapid ejaculation inconsistent and irregular • Inability to control ejaculation may be lacking (not obligatory)
Premature-like ejaculatory dysfunction	• Subjective perception of rapid ejaculation • Intravaginal ejaculatory latency time in normal range • Preoccupation with imagined rapid ejaculation • Preoccupation with poor control of ejaculation • Preoccupation not accounted for by another mental disorder • Inability to control ejaculation may be lacking (not obligatory)

Adapted from Waldinger MD. Premature ejaculation: state of the art. Urol Clin North Am 2007;34:591–9, vii–viii.

EPIDEMIOLOGY

Prevalence

In the Multicountry Concept Evaluation and Assessment of PE (MCCA-PE) study, **the self-reported time taken for an average man to ejaculate varied greatly from 7 to 14 minutes** (Montorsi, 2005). These figures were highly geography dependent, being shorter in Germany (7 minutes), longer in the United States (14 minutes), and average in England, France, and Italy (10 minutes). Furthermore, the partners' estimates were also country dependent with North American women estimating coital times lower than that of their male partners and German women estimating coital times higher than their partners.

Over the course of the past 5 years our understanding of the epidemiology of PE has been expanded significantly by several prospectively conducted studies. Further discussion and data on this topic (including Fig. 26–3 and Table 26–3) are included on the Expert Consult website.

Impact of Premature Ejaculation

PE burdens the patient on two different levels: emotional and relational (Sotomayor, 2005). Men have a sense of shame and embarrassment at not being able to satisfy their partner and they often have low self-esteem and feelings of inferiority. These findings are supported by the study of Symonds and colleagues (2003), which conducted 28 in-person interviews of men with self-reported PE in the United States. The main concern for these patients was erosion of sexual self-confidence, and two thirds of the interviewees mentioned that sexual and general confidence was affected by their PE. Anxiety was also common in these PE patients with one third of interviewees specifically linking their anxiety to PE. The Global Study of Sexual Attitudes and Behaviors demonstrated that PE may result in depressive symptoms in some men (Laumann et al, 2005).

The impact of PE on relationships is an important consideration for men with PE and a significant driver for treatment seeking. Rowland and colleagues (2007) reported that men with PE are more likely to report being dissatisfied with their sexual relationship compared with men without PE. The PE patients may find it difficult to initiate and maintain relationships. Women's feelings about their partners' PE range from understanding and support to anger and frustration. Often the man is perceived as selfish, and women have difficulty realizing that many men have poor control over their ejaculation and that they feel badly about the condition. Rowland and colleagues, in a subanalysis of the original Patrick data, assessed the psychologic burden of PE. In this analysis, a number of questionnaires were administered to patients including the Premature Ejaculation Profile (PEP) and the Self-Esteem And Relationship (SEAR) questionnaire. Overall, all inventory scores indicated significantly worse sexual functioning and satisfaction in men with PE compared with those without PE.

In the Patrick study the PRO inventory (Patrick et al, 2009) used demonstrated higher levels of distress in men with PE compared with those without PE (Patrick et al, 2005). Distress was also experienced by partners. These findings were confirmed in the counterpart European study (Giuliano et al, 2008). In an earlier U.S. Internet-based survey, men with PE reported that they had difficulty relaxing in sexual situations and were more anxious about sexual intercourse compared with a non-PE group (Rowland et al, 2004). The PEPA study (Porst et al, 2007) showed a greater percentage of men with PE reported anxiety, depression, and psychologic distress compared with men who did not have PE.

It is clear from the current literature that PE has a significant negative impact on the psychologic status of the sufferer and his partner.

PATHOPHYSIOLOGY OF PREMATURE EJACULATION

As the biologic mechanisms involved in ejaculatory function and dysfunction become clearer, a greater understanding of the pathophysiology of PE is being appreciated. Although there has been significant research in this area in recent times, a complete understanding of the pathophysiologic mechanisms involved in PE has not yet been achieved. **The final common pathway in the genesis of PE appears to be either a hyposensitivity of 5-HT_{2C} receptors or a hypersensitivity of the 5-HT_{1A} receptors** (Waldinger, 2002). It is believed that the ejaculatory threshold for men with low 5-HT levels and/or 5-HT_{2C} receptor hyposensitivity may be genetically set at a lower point, resulting in more rapid ejaculation. In contrast, men with a high set point may experience delayed ejaculation. This theory is supported in part by research that has demonstrated the efficacy of SSRI medications in inhibiting PE.

A number of potential explanations have been postulated for the genesis of PE including **(1) genetic etiologies, (2) psychologic causes, (3) hormonal aberrations, (4) penile sensory changes, and (5) chronic prostatitis.**

Genetic Factors

Recently, research has been conducted into serotonin transporter (5-HTT) promoter region polymorphisms. 5-HTT is a specific protein transporter that permits serotonin reuptake from the synapse and is the target of SSRI medications. Having a high affinity for serotonin, 5-HTT controls the duration, availability, and signaling capacity of 5-HT in the synapse. If short IELT values in men with PE are associated with diminished synaptic 5-HT neurotransmission, an increase in the function of 5-HTT may be related to PE development and such an increase in 5-HTT function might be related to genetic polymorphisms of the protein. Further discussion and data on this topic are included on the Expert Consult website.

Psychologic Factors

Despite decades of discussion regarding psychologic mechanisms involved in PE development, there is as of yet no definitive evidence to prove such a link. Further discussion and data on this topic are included on the Expert Consult website.

Hormone Alterations

At this time, the role of hormones in the genesis of PE is not completely understood. Ongoing research is aimed at elucidating the role of thyroid hormones and androgens in ejaculatory control and dysfunction. Further discussion and data on this topic are included on the Expert Consult website.

Penile Sensitivity and Circumcision Status

Although the link between circumcision status and sexual function has been studied extensively, in the final analysis the data are conflicting and no definitive link can be declared. Further discussion and data on this topic are included on the Expert Consult website.

Chronic Prostatitis

A number of studies suggest that chronic prostatitis is more prevalent among men with a diagnosis of PE. Screponi and colleagues (2001) studied 46 patients with PE and compared them with 30 healthy volunteers.

The mechanism behind the link between chronic prostatitis and PE and the mean by which antibiotic treatment improved IELT are at this point unclear. Further discussion and data on this topic are included on the Expert Consult website.

- The definition of PE revolves around rapid ejaculation (consistently within about a minute of penetration) combined with negative personal effects (bother, frustration, interpersonal difficulty).
- Epidemiologic studies demonstrate that PE is common, affecting up to 30% of men of all ages.
- PE is more common in younger men when adjusted for acquired premature ejaculation in older men resulting from erectile dysfunction.
- PE often has significant negative consequences on the patient's relationship, sexual and otherwise, and this represents a major driver for treatment seeking.
- Accumulating evidence supports roles in the genesis of PE for genetic factors, hyperthyroidism, and chronic prostatitis. However, the link between circumcision status and premature ejaculation is incompletely defined.

PATIENT EVALUATION

Sexual History and Physical Examination

In spite of the negative effect of sexual dysfunction on life satisfaction and perceived quality of life, it has been well documented that men and women are rarely asked by their physicians about their sexual health. The GSSAB suggested that in North America less than 15% of patients were asked about their sexual health by their physician in the preceding 12 months (Laumann et al, 2005). The PEPA study showed that 80% of men with PE who sought treatment reported that they had to initiate the conversation about PE with their physician (Porst et al, 2007). Another survey found that 90% of physicians state that conversations about sexual problems occur rarely during patient visits. Thus the data suggest that routine office visits rarely include physician inquiries about sexual function including PE.

The American Urological Association (AUA) guidelines on PE management state that clinicians should "explicitly communicate the circumstances of the condition" because it is the "fundamental basis of assessment with time to ejaculation (IELT) as the most important feature" (Montague et al, 2004). **In addition to evaluation of IELT, the AUA recommends the following be taken into consideration: (1) the duration and frequency of PE, (2) the rate of occurrence of PE with some or all sexual encounters and partners, (3) the degree to which sexual stimuli cause PE, and (4) the nature and frequency of sexual activity including foreplay, masturbation, and intercourse.**

Although numerous definitions of PE exist and it is likely that the recently developed ISSM definition (see Table 26–1) will become the de facto definition, IELT measurement in clinical practice is difficult (McMahon et al, 2008). In contrast to clinical trials where partner-held stopwatch assessment of IELT is routine, the clinician generally must rely on a patient's self-reported IELT to define PE. However, IELT should not be taken into account alone and other key factors including perceived control over ejaculation, bother experienced by the patient because of the rapidity of ejaculation, and the impact on the patient's sexual relationship should be considered. So **a simple PE history algorithm that can be undertaken is as follows: (1) asking how long he has experienced PE,** that is, whether it is lifelong or more recently acquired. Because lifelong PE is believed to be a potential neuroendocrine problem with alterations in serotonin levels or serotonin receptor sensitivity, most of these men are not considered curable, although they are eminently treatable. On the other hand, men with PE related to the presence of ED or some underlying medical comorbidity, as has been previously outlined, or related to a major life stressor may be potentially curable; **(2) defining the IELT from a patient is useful, appreciating that some men overestimate this.** If a partner is present, seeking corroboration of the estimated IELT is helpful; urologists

have all been faced with the young man presenting to the office complaining of PE with an estimated IELT of 30 minutes. Most would agree that treating this man for PE with pharmacologic therapy is not indicated and referral to a mental health professional is likely to be the best choice of treatment. Likewise, we see men who on review of systems declare IELT values of 1 minute yet do not believe that they have PE. These scenarios are in keeping with the Patrick study demonstrating significant overlap in IELT values between those with self-declared PE and those without, as well as the classification system proposed by Waldinger (see Table 26–2); **(3) asking the patient to define whether his control over ejaculation is good, fair, or poor** is another useful step; irrespective of his IELT, if a man expresses good control over his ejaculation, treatment for PE is not indicated. Some men ejaculate quickly routinely because of partner issues (including rapid orgasm on behalf of the partner). Men with IELT values of 5 minutes or more who express poor control over ejaculation present a challenge and are often best managed by combined short-term pharmacotherapy of PE and mental health evaluation. Many of these men have acquired PE and for much of their lives were able to keep IELT values of 10 minutes plus and have more recently had shortening of their IELT; and **(4) assessing the bother related to PE and the impact PE has on his relationship.** As with control, low bother and little impact on the relationship usually translate into no need for treatment, whereas high-bother, high-negative impact on the relationship irrespective of IELT or sense of control may warrant treatment.

Using Waldinger's model for variations of PE, in which four variations exist (lifelong, acquired, natural variable, and premature-like ejaculatory dysfunction), the clinician can discuss this problem with the patient. **For many men with natural variable PE, rapid ejaculation occurs inconsistently or irregularly and control over ejaculation may be fair or even good in these patients. Premature-like ejaculatory dysfunction is also a common presentation in which men have a subjective perception of rapid ejaculation despite having IELT values well within the normal range.** These men may also have a preoccupation with imagined rapid ejaculation and poor control over ejaculation.

Finally, from a patient history standpoint it is critically important to be able to differentiate PE from ED. Both are common conditions and may coexist in the same patient. However, there are many patients who have ED, specifically with loss of sustaining capability, who are erroneously diagnosed with PE and vice versa. Indeed, some patients have undergone penile implant surgery because of complaints of inability to sustain erectile rigidity, while in fact, PE was the cause for his rapid penile detumescence. The critical point in the history is defining the onset of the patient's problem. For example, there are many patients who have ED and develop secondary PE. This is commonly seen in men who have loss of sustaining capability, whether organically or psychologically based, who condition themselves to ejaculate more rapidly so that they can achieve orgasm before loss of erectile rigidity. This patient clearly has primary erectile problems with secondary ejaculatory problems and his treatment should be aimed at his ED first. Doing this often translates into improvement not only of his erectile problems but also of the acquired PE. On the other hand, there are patients who have lifelong PE who develop ED as they age. Although the treatment of the latter patient may commence with erectogenic pharmacotherapy, it is likely that his eventual management, if the patient's bother is high, will require pharmacologic therapy for his PE as well.

Although it is recommended that a physical examination be conducted, more often than not it yields little information pertaining to the patient's PE complaint. Such examination should include an assessment of signs and symptoms of conditions believed to be associated with PE such as thyroid dysfunction and chronic prostatitis. A routine urologic genital examination should be conducted, and some recommend assessment of the sacral reflexes and lower limb neuromuscular evaluation. It must be stated, however, that **it is rare to find anything on physical examination that would help define the etiology of the patient's PE or that would change the management plan.** No specific investigations have been designed for the patient with PE, and any adjuvant testing should be aimed at confirming findings uncovered by the history and physical examination such as thyroid dysfunction or prostatitis.

A number of instruments have been developed to assess the impact of treatment on men with PE including the Premature Ejaculation Profile (PEP) (Patrick et al, 2009) developed by Johnson & Johnson, the Index of Premature Ejaculation (IPE) (Althof et al, 2006), the Male Sexual Health Questionnaire-Ejaculation (MSHQ-EjD) (Rosen et al, 2007), and the Premature Ejaculation Diagnostic Tool (PEDT) (Althof et al, 2006; Symonds et al, 2007) developed by Pfizer. All of the aforementioned questionnaires have been validated and have demonstrated robust psychometrics, although they have yet failed to infiltrate their way into routine clinical practice. Although other questionnaires exist such as the PEQuest (Hartmann et al, 2005) and the Yonsei-Sexual Function Inventory (Lee et al, 1996), no validation information can be found in the literature for these measures. As with the ED, the impetus behind the development of these questionnaires has largely been industry investigation of potential candidate agents for the treatment of PE.

TREATMENT OVERVIEW

Behavioral Therapy

Behavioral psychosexual therapies are a well-recognized treatment for PE, and their use predates the use of pharmacologic agents by decades. Interestingly, the earliest method of behavioral therapy was described by urologist James Semans from Duke University in 1956. The maneuver he described involved the partner stimulating the man's penis until he has the sensation of almost climaxing (inevitable orgasm), at which time stimulation is abruptly stopped until this feeling disappeared. The partner must repeat this cycle until the ejaculation can be controlled voluntarily. This technique became known as the "stop-start" technique. In 1970 Masters and Johnson reported a similar maneuver in which the partner is advised to squeeze the penile frenulum or glans, just on cessation of penile stimulation at the time of inevitable orgasm, and then the female partner restarts the stimulation at least 30 seconds later. This is known as the "squeeze" technique.

Both methods focus on distraction and a reduction of excitement or stimulation, which may also detract from overall sexual satisfaction, and are based on the theory that the reason PE occurs is that the patient fails to pay sufficient attention to preorgasmic levels of sexual tension (Althof, 2006). **The main goal of traditional psychosexual treatment for PE is to help men identify the premonitory sense of ejaculation/orgasm and work with the patient to improve self-control.** Secondary benefits may include improved sexual self-confidence, less anxiety, resolution

of any interpersonal difficulties, and increased couple communication. **Although behavioral therapy has been shown to have success rates between 45% and 65%, the benefits are generally short-lived** (De Amicis et al, 1985; Hawton, 1988). Hawton and colleagues (1988) reported that 75% of men with PE who initially responded to behavioral therapy showed no long-lasting improvement after 3 years of follow-up. De Amicis and colleagues (1985) also found that although men treated for PE with couples' therapy experienced significant immediate benefits, these gains were not maintained when measured at a follow-up visit 3 years later.

Currently, a combination of pharmacotherapy and psychotherapy is suggested as the modern approach to PE treatment. The severe PE patient may often require greater levels of intervention than drugs alone (Althof, 2006). Clinicians and sex therapists can work as one team to manage such severe PE patients and have obtained better results than monotherapy (Althof, 2006).

Oral Agents

Centrally Acting Agents

The agents with proven efficacy in the treatment of PE include clomipramine and the older SSRI agents paroxetine, fluoxetine, sertraline, and citalopram. Newer agents fluvoxamine and venlafaxine (Kilic et al, 2005) have not demonstrated any significant effectiveness in the treatment of PE. No pharmacologic therapy has been approved by the U.S. Food and Drug Administration, but in Europe a novel SSRI (Dapoxetine) has been approved (Pryor et al, 2006).

Clomipramine. Clomipramine is a tricyclic antidepressant (TCA) that inhibits the uptake of noradrenaline and 5-HT by adrenergic and 5-HT neurons. Eaton (1973) published the first report on the use of clomipramine in PE, and numerous subsequent publications have confirmed its efficacy. In a randomized, placebo-controlled crossover trial in 36 men with PE, daily use of clomipramine significantly increased stopwatch-measured IELT compared with a placebo (Kim and Seo, 1998). A meta-analysis has shown that, on daily use, clomipramine increases IELT more than fourfold, similar in magnitude to sertraline and fluoxetine (Haensel et al, 1998; Waldinger et al, 2004a). On-demand dosing with clomipramine has significantly increased IELT compared with placebo (Haensel et al, 1998; Strassberg et al, 1999; Waldinger et al, 2004a). In three double-blind, placebo-controlled, crossover studies, on-demand use of clomipramine (25 mg, 12 to 24 hours before intercourse) increased IELT fourfold in PE patients (Haensel et al, 1998; Strassberg et al, 1999; Waldinger et al, 2004a).

Selective Serotonin Reuptake Inhibitors. The ability of SSRIs to delay ejaculation was accidentally discovered when these drugs were being evaluated for the treatment of depression in the 1970s. **Although none of these agents have received U.S. Food and Drug Administration approval for PE treatment, the current guidelines from AUA** (Montague et al, 2004) **and recommendations of the 2009 International Consultation on Sexual Medicine (ICSM) suggest the off-label use of SSRI for managing PE.** Prolongation of IELT is seen as early as a few days after treatment initiation but is maximized and plateaus at 2 to 4 weeks with an average of a twofold to eightfold increase in IELT depending on the agent and the study analyzed (Table 26–4) (McMahon et al, 2004).

In one study using a daily treatment regimen, paroxetine showed the highest efficacy (IELT fold increase of nine), followed by sertraline (four) and fluoxetine (four). This increase was significantly greater than placebo (1.5-fold) (Waldinger, 2007b). The aforementioned meta-analysis on SSRI use in PE focused on eight randomized, double-blind studies of the SSRI and clomipramine for treatment of PE including stopwatch assessment of IELT. The rank order of efficacy of IELT increase was paroxetine, sertraline, clomipramine, fluoxetine, and placebo. Of note, the IELT-prolonging capability of SSRI was noted to be less in the randomized controlled trials than in the noncontrolled studies (Waldinger et al, 2004b).

Only a small number of studies address on-demand use of SSRI agents. Waldinger and colleagues (2004a) investigated the ejaculation delay induced by on-demand treatment of paroxetine and clomipramine in a randomized, double-blind, fixed-dose study of 30 PE patients. It was found that on-demand treatment of 20 mg of paroxetine did not cause clinically relevant delay in ejaculation, but with the daily use of the same SSRI for 6 weeks, the IELT increased significantly. The issue of daily versus on-demand SSRI use remains unanswered, and further well-designed studies are required to address this issue.

SSRI medications are associated with well-recognized side effects. The most common short-term adverse effects are yawning, mild nausea, excessive sweating, fatigue, and changes in bowel function. Loss of bone mineral density is the most concerning adverse effect of long-term treatment (Haney et al, 2007). **Sexual side effects such as reduced libido and erectile rigidity decrease have been reported** (Montejo-Gonzalez et al, 1997). These adverse effects are usually mild, and some patients experience gradual disappearance with continued use of the medications over the first month of utilization. **A sudden reduction or cessation of long-term treatment of SSRIs can lead to the "SSRI discontinuation syndrome," a group of symptoms including nausea, vomiting, dizziness, headache, ataxia, drowsiness, anxiety, and insomnia. These symptoms begin 1 to 3 days after the drug cessation and may continue for more than a week in some patients. This syndrome is usually reversible by SSRI reintroduction** (Giuliano and Clement, 2006). **Thus it is recommended that SSRI agents should be gradually withdrawn over a 2- to 4-week period, and all patients using SSRI for PE should be forewarned about this.**

Drug-drug interactions with SSRI is common (Table 26–4), **leading potentially to the "serotonin syndrome," a group of serious, persistent symptoms including myoclonus, hyperreflexia, sweating, shivering, motor discoordination, and mental status changes** (Giuliano and Clement, 2006).

Dapoxetine. Given side effects and the need for daily use of SSRI, the search for short-acting SSRI agents that could be used on demand has been conducted in earnest over the past 5 years (Giuliano, 2007). An example of such a drug is dapoxetine. Available research suggests that dapoxetine is a powerful inhibitor of serotonin transporter (Andersson et al, 2006). Although its pharmacologic activity is similar to clomipramine, as well as conventional SSRI, its pharmacokinetic profile differentiates it from other SSRI agents (Andersson et al, 2006). **Dapoxetine has a time to maximum serum concentration (Tmax) of 1.3 hours and a short half-life (T½) of 1.5 hours** (Andersson et al, 2006).

Two placebo-controlled trials were conducted in the United States in almost 3000 men who (1) met the DSM-IV-TR criteria for PE, (2) had an IELT of less than or equal to 2 minutes in 75% or more intercourse episodes in a 2-week baseline period, and (3)

Table 26–4.

Characteristics of the Most Commonly Used Oral Agents for Premature Ejaculation Treatment

AGENT	TRADE NAME	STANDARD DAILY DOSE	T½H	ADVERSE EFFECTS	CONTRAINDICATION	DDI
Clomipramine	Anafranil	25-50 mg/day	19-37	Dry mouth, constipation	MAOI	Anticholinergics, antipsychotics, barbiturates, charcoal, cimetidine, clonidine oral contraceptives
Fluoxetine	Prozac Sarafem	5-20 mg/day	36	Nausea, anxiety, insomnia, anhidrosis, libido loss, ED	MAOI	5-HT1 agonists, benzodiazepines, β blockers, buspirone, carbamazepine, clozapine, cyclosporine, cyproheptadine haloperidol, hydantoins, lithium, sympathomimetics TCA
Paroxetine	Paxil Seroxat Pexeva	10-40 mg/day	21	Nausea, anxiety, insomnia, anhidrosis, libido loss, ED	MAOI	Alcohol, anticoagulants, cimetidine, cyclosporine, cyproheptadine, drugs metabolized by CYP2D6, digoxin, phenobarbital, phenytoin, procyclidine, St. John's wort, sympathomimetics, theophylline, thioridazine, TCA, tryptophan, zolpidem
Sertraline	Zoloft	25-200 mg/day	26	Nausea, anxiety, insomnia, anhidrosis, libido loss, ED	MAOI	Alcohol, cimetidine, clozapine, disulfiram, hydantoins, pimozide, St. John's wort, sympathomimetics, tolbutamide, TCA, antiarrhythmics (1C), zolpidem
Dapoxetine*	Priligy	15-60 mg†	1.5	Nausea, diarrhea, headache, dizziness, somnolence	MAOI	Ketoconazole, lithium, linezolid, nefazadone protease inhibitors, tryptophan St. John's wort, thioridazine, tramadol, sumatriptan
Tramadol	Ultram	25-50 mg†	5-7	Nausea, dizziness, insomnia, dyspepsia, seizures	MAOI SSRI TCA	Digoxin, erythromycin, ketoconazole, quinidine, rifampin, St. John's wort, tegretol, warfarin

*Not currently FDA approved but approved in Europe.
†For on-demand use.
ED, erectile dysfunction; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; T½H, half-life; TCA, tricyclic antidepressants.

reported a PE severity of moderate or severe. On-demand administration (within 1 to 4 hours of the sexual encounter) of dapoxetine 30 or 60 mg significantly improved outcomes compared with placebo. The IELT was significantly increased 3.5-fold from baseline compared with 2-fold for placebo. Patient-reported perception of control over ejaculation and satisfaction with sexual intercourse was also significantly better compared with both baseline values and end of treatment with placebo (Pryor et al, 2006). The most common adverse events with dapoxetine 30 and 60 mg compared with placebo were, respectively, nausea (9%, 20%, 2%); diarrhea (4%, 7%, 1.5%); headache (6%, 7%, 4%); and dizziness (3%, 6%, 1%). About 5% of all subjects discontinued because of adverse events (Andersson et al, 2006).

A second randomized, double-blind, multicenter, placebo-controlled, phase III, randomized, clinical trial involving 618 men with PE was conducted (Buvat et al, 2009). Dapoxetine 30 mg, 60 mg, and placebo groups were studied. IELTs and PROs improved significantly in the treatment arm versus placebo. Results from a 9-month, open-label extension study that assessed dapoxetine 60 mg showed that the most common adverse events were nausea, dizziness, and headache.[120]

Tramadol. **Tramadol is a synthetic opioid analgesic** (Frink et al, 1996; Lintz et al, 2000). Tramadol has been used for many years for pain control and has a recognized safety profile. The mechanism of action of tramadol in PE is not fully understood. From animal experiments, inhibition of norepinephrine and serotonin reuptake may be the main mechanism (Salem et al, 2008). Two recently published studies have assessed the effectiveness of on-demand use of tramadol for the treatment of PE (Safarinejad and Hosseini, 2006; Salem et al, 2008). In a double-blind, placebo-controlled study, on-demand use study, tramadol 50 mg, taken 2 hours before sexual intercourse, was associated with clinically discernible ejaculation delay with 28% of patients reporting adverse effects. The most common side effects were nausea (15%), vomiting (6%), and dizziness (6%) but were reported as being mild. Another study by Sharon and colleagues was a single-blind, placebo-controlled, crossover, two-period prospective study to evaluate on-demand tramadol 25 mg treatment. The treatment group experienced a sixfold increase in IELT compared with approximately a twofold increase for the placebo group. Thirteen percent of patients reported adverse effects with tramadol including dyspepsia and mild sleepiness. Further studies are required to define the role of tramadol in PE treatment.

Phosphodiesterase-5 Inhibitors (PDE5i). At least 30% of men with PE have coexisting erectile dysfunction (ED) (Laumann et al, 1999, 2005, 2006, 2007). It is generally believed that PE secondary to ED is a psychogenic issue (Jannini et al, 2005). The efficacy of PDE5i alone (Abdel-Hamid, 2004; McMahon et al, 2005) or in combination with SSRI (Abdel-Hamid et al, 2001; Salonia et al, 2002) for the treatment of PE has been explored. In PDE5i monotherapy, a single placebo-controlled, parallel group study of sildenafil citrate for treatment of PE has been conducted. This study demonstrated that although there was no significant improvement in IELT compared with placebo, the sildenafil group had a

statistically significant increase in self-report ejaculation control (McMahon et al, 2005). In another study, on-demand sildenafil use increased vibrator-assisted ejaculation time compared with placebo group.

In an open-label comparison trial, Abdel-Hamid and colleagues (2001) showed superiority of combining sildenafil to the stop-start technique over SSRI therapy. However, the magnitude of effect has not been replicated and may have been due to a significant number of men with combined PE and ED. An industry-sponsored, double-blind, placebo-controlled study showed no significant difference in IELT when sildenafil was compared with placebo. In men with IELT less than 1 minute, on-demand administration of sildenafil 50 mg combined with 20 mg paroxetine (1 hour before planned sexual intercourse) after 21 days of daily administration of 10 mg paroxetine alone showed superiority compared with daily administration of 10 mg paroxetine alone for 21 days and on-demand dosing of 20 mg paroxetine 3 to 4 hours before intercourse (Salonia et al, 2002). Patients in the sildenafil group had a higher incidence of headache and flushing compared with those in the paroxetine-only group. In another study, men with PE who were dissatisfied with lidocaine ointment were given 20 mg paroxetine daily for 30 days and 20 mg paroxetine combined with 25 to 100 mg sildenafil 7 hours before intercourse. Psychologic and behavioral counseling was also provided throughout the study. Sildenafil combined with paroxetine and psychologic and behavioral counseling alleviated PE in nearly all patients, by significantly improving the grade of PE and increasing IELT (Chen et al, 2003).

A recent systematic review of published reports of PDE5i in PE treatment has concluded that there is limited evidence to support the role of PDE5i monotherapy in PE treatment, although some evidence suggests that PDE5i might benefit men with concomitant PE and ED (McMahon et al, 2006). **Thus at this time, the weight of the evidence would suggest that PDE5i monotherapy for PE treatment has no solid foundation. However, in difficult-to-treat cases the addition of a PDE5i to an SSRI may offer select patients some benefit.**

α_1-Adrenoceptor Antagonist. In an effort to modulate sympathetic tone, α blockers have been studied in a limited fashion (Kim et al, 2004). In a single clinical study of an α_1-adrenergic receptor antagonist, significant improvement was seen in 50% of PE patients who failed to respond to psychotherapy alone (Cavallini, 1995). This drug class will require significant further exploration before its role as a first line therapy in PE is defined.

Topical Agents

Sixty years ago Schapiro described local anesthetic agent use for PE (Optale, 1943). Currently, such off-label topical treatment is widespread. Compared with systemic therapy in PE management, there is the palatability of local treatment because of its immediacy and minimal systemic side-effect profile. **However, the application of a local anesthetic agent on the penis still has a number of potential drawbacks such as the loss of penile sensitivity, ED, female genital anesthesia, and skin irritation. The topical drugs for PE treatment include the SS cream, lidocaine alone, and lidocaine-prilocaine combinations.**

Severance Secret-Cream

Severance secret-cream (SS-cream) (CJ Co Ltd, Seoul, Korea), developed at Yong-Dong Severance Hospital in Korea, is made with the extracts of nine natural products. It is applied on the penis 1 hour before sexual intercourse and washed off before sexual intercourse. SS cream is available only in Korea and is not approved for use in Europe or the United States. After applying SS-cream, sensory thresholds have been shown to increase (Xin et al, 1996, 2000). Xin and colleagues (1997) reported ejaculation latency was significantly prolonged more than 2 minutes in 89% of patients using SS-cream. In a multicenter, double-blind study involving 106 cases, the use of the SS-cream was reported to increase the mean stopwatch-measured IELT from a baseline value of 1.5 to 11 minutes, compared with end-of-treatment IELT with placebo of 2.5 minutes (Choi et al, 2000). The main disadvantage of SS-cream is an unpleasant odor, which makes it unpalatable to many patients. The main challenge for this agent is the absence of large, randomized, controlled trials using standardized end points. Furthermore, the failure to disseminate publicly the constituents of this product has raised concerns regarding the reproducibility of the published data.

Lidocaine

This topical agent has been available for more than 25 years. Reliable data from clinical trials is absent; therefore its efficacy and safety cannot be assessed (Morales, 2000, 2007).

Lidocaine-Prilocaine

EMLA (AstraZeneca, United Kingdom) is a local anesthetic cream containing 2.5% lidocaine-prilocaine for topical use that can anaesthetize intact skin. Published studies of lidocaine-prilocaine cream use in PE are scarce. The first pilot study of lidocaine-prilocaine cream evaluation in the treatment of PE included 11 men only (Berkovitch et al, 1995). Nine of 11 cases reported their performance as "excellent" or "better," and all 11 partners were satisfied with the treatment. A placebo-controlled study reported by Atikeler and his colleagues (2002) showed that the best application time was 20 minutes before sexual relations. The largest double-blind clinical trial of lidocaine-prilocaine cream included 42 cases and demonstrated a 5.5-fold increase in IELT in the treatment arm. However, only 29 of 42 participants completed the study. Sixteen percent of patients reported adverse effects including penile numbness, retarded ejaculation, penile irritation, and decreased vaginal sensitivity (Busato and Galindo, 2004).

The topical eutectic mixture for PE (TEMPE, also known as *PST-502*, Sciele Pharma, Inc.) is a recently developed metered-dose spray of lidocaine and prilocaine. The metered-dose aerosol-delivery system is specifically designed for use in PE. The system delivers 7.5 mg lidocaine plus 2.5 mg prilocaine per spray. The mixture is alcohol free and can easily be wiped off if necessary, so no condom is required (Henry and Morales, 2003). The product is incapable of penetrating keratinized skin, hence only anesthetizing the glans and reducing the incidence of penile shaft numbness-related ejaculatory failure. The first open-label pilot study involved 11 men whose IELT was recorded by stopwatch at baseline and on five subsequent encounters when using the spray 15 minutes before intercourse. The average IELT increased from 1.5 minutes to 11 minutes, which was equivalent to a mean eightfold increase over baseline. In addition, 8 of 11 patients and 7 of 11 partners reported their sexual satisfaction as "better" or "much better." In a phase II, placebo-controlled trial (Dinsmore et al, 2007; Dinsmore and Wyllie, 2009), 54 men reported prolongation of their IELT from a baseline of 1 minute to 5 minutes at end of treatment. It is a well-tolerated treatment, having a low incidence of penile hypoesthesia and erectile impairment.

Key Points

- The diagnosis of premature ejaculation is based on taking a thorough sexual history.
- It is critically important to differentiate premature ejaculation from erectile dysfunction when loss of sustaining capability is the primary issue.
- Besides assessing patient self-reported ejaculatory latency time, defining the patient's perceived control over ejaculation, his level of bother, and the bother level of his partner are important.
- Validated instruments for the evaluation of premature ejaculation exist but to date have largely been confined to research use.
- Behavioral approaches as monotherapy have been associated with poor long-term benefits.
- Combining pharmacotherapy and psychotherapy is the modern approach to PE treatment.
- SSRI agents are the first-line (albeit off-label) pharmacotherapeutic approach to the treatment of premature ejaculation.
- There is little evidence for the effective use of other oral agents (tramadol, PDE5 inhibitors).
- Properly formulated transdermal agents are of benefit to some patients with premature ejaculation.

Intracavernosal Injection Therapy

In cases refractory to first-line and combination therapy, intracavernosal injection (ICI) has been used for years to increase sexual satisfaction in men with recalcitrant PE. Fein (1990) reported on eight patients who used this strategy. The patients reported improved sexual confidence, and although they ejaculated early, they maintained their erections, which permitted them to continue penetrative relations. Of note, three of the eight patients were cured of their PE, suggesting these men had acquired PE.

Surgical Treatment

Although there are mixed data on the issue of the link between penile sensation and PE, some Asian workers have explored the role of surgery, specifically dorsal penile nerve division, in the management of PE. Shi and colleagues (2008) studied 483 patients with lifelong PE who underwent selective resection of branches of the dorsal penile nerve and were followed for up to 3 years after surgery. The authors report decreased penile sensitivity in all patients and significantly prolonged ejaculation latency in 352 (73%) patients. In a more recent study, Zhang and colleagues (2009) reported on a total of 314 men with lifelong premature ejaculation who underwent selective neurectomy of the dorsal penile nerve (Zhang et al, 2009). This operative intervention achieved an intravaginal ejaculation latency of 4.5 minutes compared with 1.5 minutes before surgery. **Such seemingly radical therapeutic approaches have not gained any significant traction in the United States or Europe and given the absence of definitive data linking penile sensitivity issues to PE development, it is not likely that such an approach will be accepted in the near future.**

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chapter
27

Prosthetic Surgery for Erectile Dysfunction

Drogo K. Montague, MD

Types of Prostheses
Preoperative Patient-Partner Counseling
Surgical Approaches
AMS 700 LGX Inflatable Penile Prosthesis Implantation by a Combined Longitudinal-Transverse Penoscrotal Approach
Postoperative Care
Complications
Penile Prosthesis Implantation in Special Cases
Results

Three sentinel events define the history of the treatment of erectile dysfunction (ED): the **introduction of the inflatable penile prosthesis** (Scott et al, 1973); **intracavernous injection therapy** (Virag, 1982); and effective **systemic therapy** with sildenafil citrate (Goldstein et al, 1998). Today the treatment of ED can be compared with the treatment of osteoarthritis, another common disorder that also becomes more prevalent with age. In both, a progressive treatment model may be employed (Table 27–1). Most men with ED will initially be offered systemic therapy with a PDE5 inhibitor. If that fails and the men want to continue treatment, second- and third-line therapies should be discussed. If these fail or are rejected, penile prosthesis implantation is usually appropriate.

TYPES OF PROSTHESES

Currently available penile prostheses in the United States are shown in Table 27–2. Malleable prostheses are semirigid devices with a central core that allows the penis to be bent down for dressing and bent upward for coitus. However, for most men this malleable core does not maintain these positions well. Malleable devices have the advantage of low mechanical failure rates and ease of use. Disadvantages include constant penile rigidity and an increased risk of erosion (Steidle and Mulcahy, 1989; Zermann et al, 2006).

The positionable penile prosthesis (Dura II) is a semirigid device with a central series of articulating segments held together with a spring on each end. This device, compared with malleable prostheses, is better able to maintain its upward and downward positions.

The two-piece inflatable penile prosthesis (AMS Ambicor) consists of two cylinders connected to a small scrotal pump (Levine et al, 2001; Lux et al, 2007). Squeezing this pump transfers a small volume of fluid from the rear tip reservoirs of the cylinders into a nondistensible central chamber producing rigidity comparable with that of a malleable device. When the device is deflated, the central chamber partially collapses, providing better flaccidity than a malleable implant. The two-piece prosthesis has as its primary advantage ease of implantation because there is no third piece (abdominal fluid reservoir). A disadvantage compared with malleable devices is the increased risk of mechanical failure. Excel, a two-piece inflatable prosthesis (Coloplast), is not available in the United States.

The ideal prosthesis would provide its recipient with a penis that resembles as closely as possible normal penile flaccidity and erection. Only three-piece inflatable devices that transfer a large volume of fluid into the penile cylinders for erection and out of the cylinders for flaccidity approach this ideal. Three-piece prostheses have paired corporeal cylinders, a scrotal pump, and an abdominal fluid reservoir. An example of a three-piece inflatable prosthesis is the *Coloplast Titan Inflatable Penile Prosthesis* (Fig. 27–1). All three-piece devices provide penile girth expansion and rigidity similar to that of a normal erection. One device, the *AMS 700 LGX Inflatable Penile Prosthesis*, also provides length expansion (Fig. 27–2).

PREOPERATIVE PATIENT-PARTNER COUNSELING

Ideally, discussions regarding the treatment of ED should include the partner; however, this is not always possible. Once a decision has been made that penile prosthesis implantation should be considered, it is important to inform the patient about alternative treatments and the advantages and disadvantages of each. By this time the patient has either failed or is not a candidate for systemic treatment with PDE5 inhibitors. He should be aware that in addition to penile prosthesis implantation, therapies with vacuum constriction devices, intraurethral prostaglandin, and intracavernous injection are available. **An option such as penile prosthesis implantation should not be considered to treat a man with erectile dysfunction that is situational, the result of a relationship conflict, or one that is potentially reversible. For these men and their partners, psychologic consultation and sex therapy are more appropriate.**

Table 27–1.

Progressive Treatment Model

	OSTEOARTHRITIS	ERECTILE DYSFUNCTION
First-line therapy	NSAIDs	PDE5 inhibitors
Second-line therapy	Joint injections	VCDs, IUD
Third-line therapy	Arthroscopic surgery	Intracavernous injections
Fourth-line therapy	Prosthetic joint replacement	Penile prosthesis implantation

IUD, intraurethral drugs; NSAIDs, nonsteroidal antiinflammatory agents; PDE5, type 5 phosphodiesterase; VCDs, vacuum constriction devices.

Table 27–2.

Penile Prosthesis Types

PROSTHESIS TYPE	AMERICAN MEDICAL SYSTEMS*	COLOPLAST CORPORATION†
Semirigid rod	AMS Malleable 600 AMS Malleable 650	Genesis
Positionable	Dura II	
Two-piece inflatable	AMS Ambicor	Excel‡
Three-piece inflatable	AMS 700 CX	Titan
	AMS 700 CXR	Titan Narrow Base
	AMS 700 LGX	

*American Medical Systems (AMS), Minnetonka, MN.
†Coloplast Corporation, Minneapolis, MN.
‡Not available in the United States.



Figure 27–1. Coloplast Titan three-piece inflatable penile prosthesis. (Courtesy of Coloplast Corp., Minneapolis, MN.)



Figure 27–2. AMS 700 LGX three-piece inflatable penile prosthesis. (Courtesy of American Medical Systems, Inc., Minnetonka, MN.)

The various types of penile prostheses along with their advantages and disadvantages (see above) should be explored. Most penile prosthesis implantation is done under spinal or general anesthesia on an outpatient basis with discharge on the same or next day. The intensity and duration of postoperative pain is variable. Most men require oral narcotics for about 1 week. After that pain can often be managed with a nonsteroidal antiinflammatory agent. When an abdominal fluid reservoir has been placed, strenuous activity and heavy lifting are proscribed for 4 weeks. Patients can drive and return to nonstrenuous work once they are no longer taking narcotics. Coitus is usually possible in 4 to 6 weeks.

The patient should understand that penile prostheses produce an erection-like state. The following considerations refer to the three-piece inflatable devices. With the prosthesis deflated most men feel comfortable in a locker room situation. With inflation the erection-like state produces girth expansion and rigidity that for most men approaches that of a normal erection. **The glans, however, is not included in the erection, and for most men the erection will be shorter than their normal erection. We demonstrate to men their stretched penile length and tell them that this will be the approximate length of their prosthetic erection.** One device, the *AMS 700 LGX* (formerly the *AMS 700 Ultrex*), produces both girth and length expansion with length expansion ranging from 1 to 4 cm (mean 1.9 cm) (Montague and Lakin, 1992).

Many men with ED have normal libido, and most have normal penile sensation and orgasm with ejaculation. If present, penile prosthesis implantation will preserve orgasm and ejaculation but not restore them if absent.

The patient should be informed that infection will probably require complete removal of the implant with resulting scarring of the corporeal smooth muscle. With prosthesis reimplantation after infection, the penis is frequently smaller and cylinder implantation is usually difficult. On rare occasions reimplantation may not be possible. Erosion of the prosthesis through the skin or into the urethra also requires device removal. **The potential implant recipient should understand that mechanical failure is possible and correcting this requires device revision or replacement.**

Key Points: Patient Expectations

- The glans penis does not increase in size with a prosthetic erection.
- A prosthetic erection is usually shorter than a normal erection and is about equal to the patient's stretched penile length.
- Using AMS LGX cylinders in appropriately selected patients can provide an additional 2 cm of penile length with device inflation.

Table 27–3.

Comparison of Infrapubic and Penoscrotal Implant Approaches

	INFRAPUBIC APPROACH	PENOSCROTAL APPROACH
Advantages	Reservoir placement under direct vision	Better corporeal exposure No dorsal nerve injury Pump fixation possible
Disadvantages	Limited corporeal exposure Possible dorsal nerve injury Inability to anchor pump	Blind reservoir placement

SURGICAL APPROACHES

Surgical approaches for penile prosthesis implantation include subcoronal (used only for implantation of malleable or positionable devices), infrapubic, and penoscrotal. We prefer the penoscrotal approach for the reasons listed in Table 27–3. When corporeal fibrosis is present, the penoscrotal incision can be extended to expose almost the entire extent of both corpora cavernosa.

A potential disadvantage of the penoscrotal incision not listed in Table 27–3 is the presence of excess tubing in the scrotum or at the base of the penis. We avoid this by implanting the preconnected cylinders and pump first using a penoscrotal incision with a transverse flap through the deep layers of dartos fascia. A second incision is made through dartos fascia in the midline of the scrotum to develop a pouch for the pump. A stab incision is then made deep through the back wall of the pouch (the transverse dartos flap), and the pump is brought through this to place it into the pouch. This helps anchor the pump in the pouch and buries the tubing in the upper scrotum. This is advantageous not only from a cosmetic standpoint but also because it reduces the risk of device infection. **If a superficial penoscrotal wound infection occurs and the fascia is intact, a deep infection in the space around the prosthesis, which would require device removal, is not likely to occur.**

Increasingly, men who have had radical prostatectomy require penile prosthesis implantation. Some question the feasibility of three-piece inflatable prosthesis implantation in this group because of scarring of the lower abdominal fascia and concern regarding scarring in the retropubic (prevesical) space. Lane and colleagues (2007) reported 115 consecutive implants of three-piece inflatable penile prostheses done through a single transverse penoscrotal incision with no reservoir-related complications. The use of LGX cylinders in men who have had radical prostatectomy may be of particular benefit because radical prostatectomy has been shown to result in a loss of penile length in many individuals (Gontero et al, 2007; Mulhall, 2005; Savoie et al, 2003).

AMS 700 LGX INFLATABLE PENILE PROSTHESIS IMPLANTATION BY A COMBINED LONGITUDINAL-TRANSVERSE PENOSCROTAL APPROACH

The authors perform this procedure with the patient in the supine position under either spinal or general anesthesia. Shaving of the skin is done in the operating room to avoid bacterial colonization of small skin breaks that might occur if shaving were done before the surgery. A 10-minute skin prep is performed. Paper drapes are used because when cloth drapes become wet, they do not provide a good bacterial barrier. We do not place a urethral catheter at this point because it is easier to judge the quality of the erection when a catheter is not present.

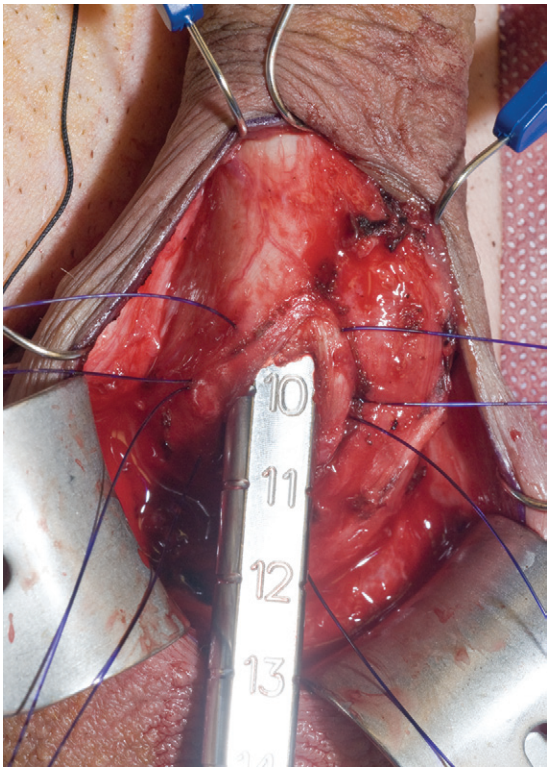


Figure 27–3. The distal measurement is 10 cm.

A longitudinal penoscrotal incision is made, and the superficial layers of dartos fascia are divided longitudinally. At the penoscrotal junction the deep layers of dartos fascia are divided transversely. This transverse incision through the fascia should be directed toward the urethra and corporeal bodies rather than toward the scrotum. Allis clamps are placed on the lower margin of the fascia, and the underside of dartos fascia is dissected off the urethra and the proximal corpora (crura). This combined longitudinal-transverse penoscrotal incision provides a transverse dartos flap to bury tubing in the upper scrotum with the cosmetic advantages of a skin incision along the midline penoscrotal raphe. The authors use a ring retractor they have modified by placing slits in it so that exposure may be maintained by a combination of hook stays and retractor blades.

Two-centimeter corporotomies are made, and two horizontal mattress sutures of 2-0 PDS II (polydioxanone, Ethicon, Inc., Somerville, NJ) are placed on each side of the corporotomy. These sutures are used as guide sutures during corporeal dilation and measurement, and they are also used to close the corporotomy after the cylinders are placed (Montague, 1993). Dilation starts with an 8-mm Hegar dilator and proceeds to 16 mm proximally and 14 mm distally. The greater proximal dilation is necessary to accommodate both the cylinder and cylinder tubing. If dilation to these diameters is not possible, the smaller-diameter AMS 700 CXR or the Mentor Titan Narrow Base prosthesis should be used.

Using a sizing instrument, the distal measurement taken from the distal end of the corporotomy is 10 cm (Fig. 27–3), and the

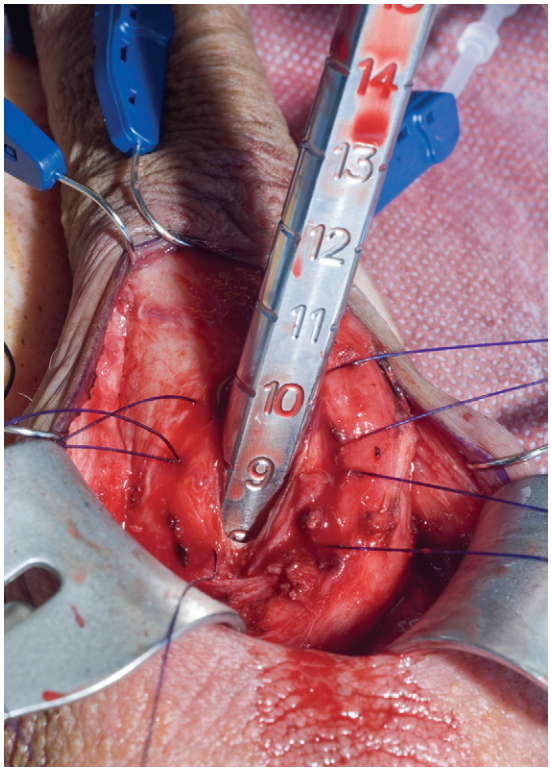


Figure 27–4. The proximal measurement is 8 cm.

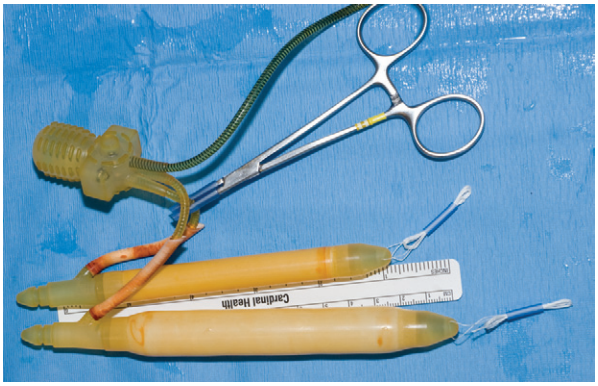


Figure 27–5. The prosthesis components prepared for implantation. One cylinder is inflated to demonstrate its girth- and length-expanding properties. It is deflated before insertion.

proximal measurement taken from the proximal end of the corporotomy is 8 cm (Fig. 27–4). **It is important to size cylinders exactly to fill the entire corpora. Cylinders should be neither too short, producing the supersonic transporter (SST) deformity (Ball, 1980), nor too long, producing bucking within the corpora. We do not include the 2-cm corporotomy in the measurement because we believe that surface sizing with a rigid measuring tool introduces a 2-cm measuring error** (Montague et al, 2003). With standard measuring techniques from a midcorporotomy reference point, the cylinder placed is about 2 cm too long. When the length-expanding LGX cylinder is used, this leads to the so-called S-shaped cylinder deformity (Wilson et al, 1996). Although no data support this, the authors believe that with non–length-expanding cylinders, a too-long cylinder may cause premature failure (cylinder failures are most common in the area where the buckling with a too-long cylinder occurs).

After corporeal measurements are taken, the appropriate cylinder size is selected. LGX and CX cylinders come in the following lengths: 12, 15, 18, and 21 cm. Adjustments between these sizes are made by the addition of rear tip extenders. The cylinders are filled with normal saline, and the authors inject saline until the cylinders are full (rounded) but not inflated under pressure. Having the cylinders full rather than collapsed makes it easier to judge whether the cylinder fit following insertion is correct. The pump is filled by cycling the pump while the pump tubes are submersed in a basin of normal saline. The reservoir is filled with normal saline to displace air; the saline is then removed because the reservoir will be filled after it is implanted. In this case the total corporeal length was 18 cm (10 cm + 8 cm), and the authors elected to use 15-cm LGX cylinders with 3-cm rear tip extenders. Figure 27–5 shows the filled prosthesis components ready for implantation. For illustrative purposes one cylinder is inflated to show both its girth and length expansion. It will be deflated before implantation.

Distal cylinder insertion is aided by the use of the Furlow cylinder inserter (American Medical Systems, Minnetonka, MN). The guide sutures in the tip of the cylinder are threaded through the needle provided in the accessory package, and this needle with its sutures is placed into the distal end of the inserter. The inserter is then placed to the distal end of the corpus cavernosum. The plunger of the cylinder inserter is pushed in delivering the needle and guide sutures through the tip of the corpus cavernosum and out through the glans. The guide sutures are used to pull the distal cylinder into the distal corpus cavernosum. If rear tip extenders are necessary, they are added now and the proximal portion of the cylinder is manually inserted. If the cylinder fit is proper, the proximal portion will be all the way down to the attachment of the crus to the pelvic bone, and the distal portion will be in the distal corpus cavernosum under the mid glans penis. When these conditions have been met, the rounded visible portion of the cylinder will lie flatly in the open corporotomy (Fig. 27–6). The penis should then be released from the retractor, and the distal position of the cylinders and glans support should be evaluated (Fig. 27–7). If the cylinder is too long or too short, the proximal portion can be removed and length adjustment can be made by adding or removing rear tip extenders. The corporotomies are closed by tying the proximal ends and then the distal ends of the preplaced horizontal mattress sutures (Montague, 1993).

In preparation for pump placement, a second incision through dartos fascia is made in the scrotal septum. A deep septal pouch is developed with ring forceps. A passage way is made with a right angle clamp through the back wall of this pouch deep in the scrotum, and the pump is brought through this passage way into the pouch (Fig. 27–8). After irrigation with antibiotic solution, the second dartos incision is closed with running 3-0 Dexon II (polyglycolic acid suture, United States Surgical, Tyco Healthcare Group, Norwalk, CT).

A 50-mL syringe filled with normal saline, which serves as a temporary reservoir, is then connected to the reservoir tube from the pump. The pubis to glans tip penile length measurement is 15 cm with the cylinders deflated (Fig. 27–9) and 17 cm with the cylinders inflated (Fig. 27–10). **The use of a device with LGX cylinders in this patient has given him a prosthetic erection that is 2 cm longer than that obtainable with any other inflatable device.**

Safe reservoir insertion into the retropubic space through the primary penoscrotal incision is possible

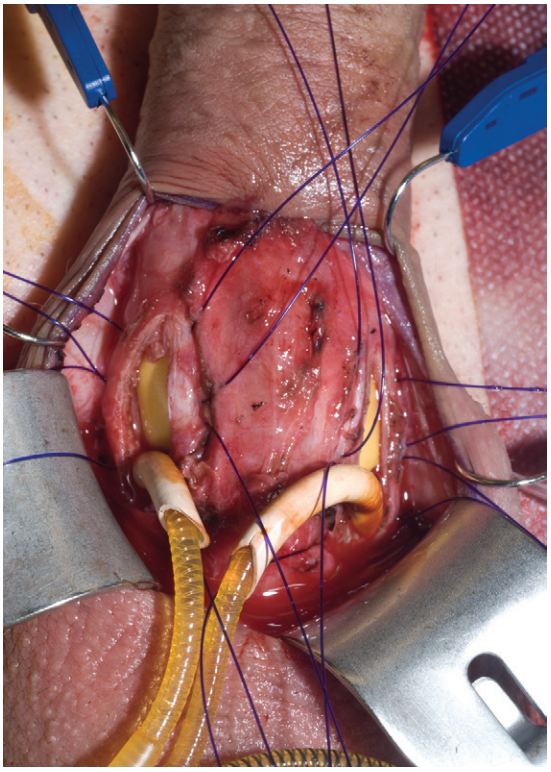


Figure 27–6. The cylinders, which have been correctly sized, lie flat within the corpora.



Figure 27–7. The penis has been released from the retractor. Both cylinder tips reach the ends of the corpora and provide excellent glans support.

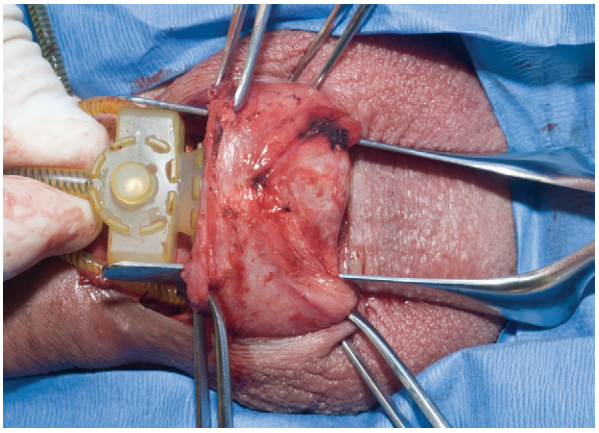


Figure 27–8. The pump is brought through a stab incision deep through the back wall of the subdartos pouch.



Figure 27–9. The length of the penis with the cylinders deflated is 15 cm.

only if the bladder is completely empty. The authors insert an 18-Fr urethral catheter attached to closed gravity drainage and apply suprapubic pressure over the bladder until it is empty. The surgeon introduces his or her finger into the incision and moves this up to the external inguinal ring on either side. If the external ring is not palpable, a point just above the pubic tubercle is chosen. Metzenbaum scissors or a Kelly clamp is used to perforate the transversalis fascia. **If all layers of the fascia are perforated, the surgeon's index finger enters the retropubic space. Correct entry is confirmed if the back of the symphysis pubis and the balloon in the empty bladder are palpated.** A nasal speculum with long blades is substituted for the finger; this maintains the fascial opening (Fig. 27–11). The empty reservoir is introduced into the retropubic space; the



Figure 27–10. The length of the penis with the cylinders inflated is 17 cm.

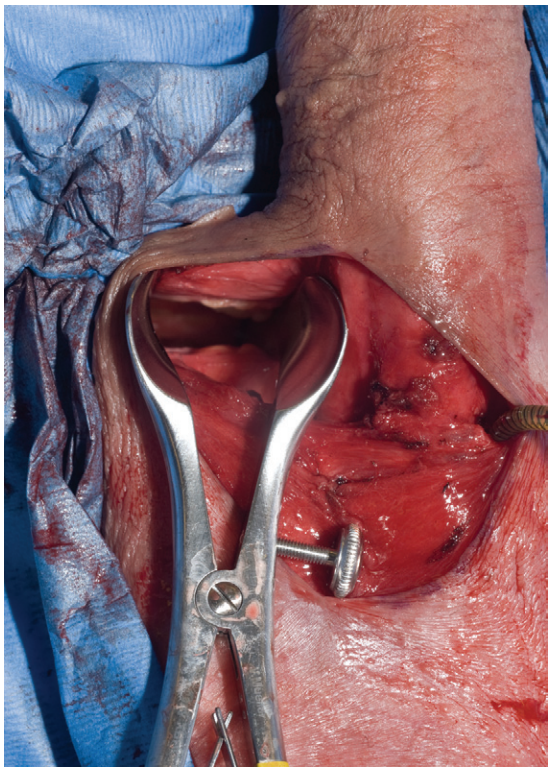


Figure 27–11. A nasal speculum maintains the fascial opening for reservoir insertion.

hublike junction between the reservoir and the tube should be located in the fascial defect.

The AMS reservoirs are available in two sizes: 65 mL and 100 mL. The former is recommended for all cylinder sizes except for the 18- and 21-cm LGX cylinders, which require the 100-mL reservoir size. The reservoir is then filled with the requisite amount of normal saline, and then the position of the reservoir is confirmed by palpation. The reservoir itself, which is below the fascia, should not be palpable. The tubing hub should be palpable as it protrudes through the fascia. A back pressure test is done; if fluid exits under pressure, as little as 85 mL can be left in a 100-mL reservoir and as little as 50 mL can be left in a 65-mL reservoir. The reservoir tubing is brought down into the incision in the upper scrotum, where a connection to the pump-reservoir tubing is made over a sutureless straight connector.

A long right-angle clamp is introduced through the incision to the inguinal area on the side of the reservoir. A stab incision is made and through this a closed-suction type of drain is introduced. The drain is brought down to the base of the penis, where it will lie on top of the tubes and connectors. Dartos fascia is then closed transversely with running 3-0 Dexon. The skin is closed with running subcuticular 4-0 Vicryl.

POSTOPERATIVE CARE

The urethral catheter and the closed suction drain are removed the next morning after an overnight stay in the ambulatory surgery center. Most men require an oral narcotic for about 1 week. After that a nonsteroidal antiinflammatory agent will usually suffice. If an abdominal fluid reservoir has been placed, lifting and other activities that might result in reservoir displacement from the retropubic space into the inguinal area are proscribed for 1 month. The patient is instructed to keep his penis up on the lower abdomen pointing to the umbilicus. If the penis is worn in a downward position as healing takes place, ventral curvature of the penis may result.

One month after surgery most men are ready for instructions on cycling the device. We instruct the patient to fully inflate and deflate his device twice daily for 1 month. This serves a dual purpose: practice on cycling, as well as activity that stretches the pseudo capsule that by now has formed around the cylinders. In the beginning pumping requires considerable force, but with time it becomes much easier.

The patient is given permission to begin coitus whenever inflation can be accomplished without discomfort. Because anxiety on the part of the partner may inhibit vaginal lubrication, the couple is advised to use a water-soluble lubricant at least initially. **Retarded ejaculation (failure to reach orgasm) may occur when men first use their prosthesis for coitus. To avoid this, the couple is counseled to have adequate foreplay so that both partners are sexually aroused before intromission.**

COMPLICATIONS

Infection

Infection in the periprosthetic space usually does not cause significant illness; however, to eradicate the infection, removal of all components of the prosthesis is almost always required. Therefore infection is considered by many to be the most significant complication of genitourinary prosthetic surgery.

Penile prosthesis implantation should be delayed in patients with urinary tract infections or cutaneous infections in the operative area. Shaving of the operative area is done just before surgery to avoid bacterial colonization of small skin breaks that might occur if shaving was done before the day of surgery. The operative

area is prepared with a 10-minute skin prep. Broad-spectrum prophylactic antibiotics are given 1 hour before the case begins so that adequate tissue levels are present when the incision is made. We use gentamicin and vancomycin for this purpose. Paper rather than cloth drapes are used because the latter are permeable to bacteria when wet. The prosthesis is kept in its sterile package until it is ready to be filled and implanted. It is then submersed in an antibiotic solution unless it has an antibiotic coating, in which case it is placed in a sterile basin and covered with a paper towel. Silicone has a positive charge and attracts air borne particles; therefore as it is placed in the body, it is irrigated with antibiotic solution and irrigated again as tissues are closed over it. For our antibiotic solution we use 50,000 units of bacitracin in a liter of normal saline.

Infections occurring after penile prosthesis are either early (in the first few weeks following implant) or late (6 months to 1 or 2 years after implant). The former are often associated with gram-negative bacteria. whereas the latter are usually associated with gram-positive bacteria such as *Staphylococcus epidermidis* (Kabalin and Kessler, 1988; Licht et al, 1995). Infections with other organisms such as fungi (Peppas et al, 1988) and gonococci (Nelson and Gregory, 1988) have also been rarely reported. It was originally believed that all infections originated from the time of surgery. Carson showed that late prosthetic infections can occur by hematogenous spread from a distant source (Carson and Robertson, 1988). The authors have shown that late infection can also arise after a mechanical malfunction (fluid leak) from a prosthetic device (Milbank et al, 2004). Fluid leak likely disrupts the balance with a biofilm, favoring bacterial growth (Silverstein et al, 2003). Alternatively, the fluid itself could be a bacterial reservoir.

Evidence is divided as to whether men with diabetes mellitus are at increased risk for infection following penile prosthesis implantation and whether the degree of diabetes control at the time of surgery is related to the risk of infection. In one study four infections occurred in 13 diabetics with a glycosylated hemoglobin above 11.5%, whereas in 19 diabetics with a glycosylated hemoglobin under 11.5%, only one infection occurred (Bishop et al, 1992). In another study of penile prosthesis recipients, infections occurred in 10 of 114 diabetics (8.7%) and in 11 of 275 nondiabetics (4%). However, there was no statistically significant increased infection rate with increased levels of glycosylated hemoglobin (Wilson et al, 1998). In a study of 556 prosthesis recipients, there was no significant difference in the incidence of infection in diabetic versus nondiabetic patients (Montague et al, 2001).

In a study looking at the surgical approach for penile prosthesis implantation, 4 of 139 devices implanted via the infrapubic approach became infected (2.9%), whereas 2 of 221 implanted via the penoscrotal approach became infected. This difference was not statistically significant (Garber and Marcus, 1998).

Early infections are likely to be evident by swelling, erythema, tenderness, possible purulent drainage, and occasionally fever. Late infections may only be manifested by persistent or recurrent long-term pain. With long-term infections the scrotal skin may be adherent to the pump. Infections are sometimes evident by erosion, particularly of the pump through the scrotum (Fig. 27–12). **This should never be considered infection of the pump alone. All components of the device are connected by tubing, and the entire device is considered to be infected.**

Treatment of a prosthetic infection with appropriate antibiotics usually results in clinical improvement; however, antibiotic treatment will rarely permanently eradicate this type of infection. This

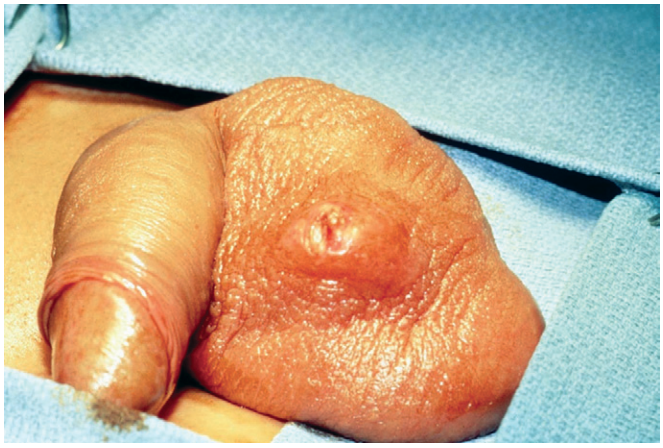


Figure 27–12. Impending scrotal pump erosion in a patient with an infected prosthesis.

is thought to be due to the harboring of microorganisms within a biofilm that is adherent to the device (Abouassaly et al, 2004). **For this reason, when a prosthetic infection is present, all components of the prosthesis should be removed.**

Penile prosthesis reimplantation following infected device removal presents certain difficulties. Pump and reservoir reimplantation is seldom a problem. However, after infected device removal, the corporeal smooth muscle becomes replaced in varying degrees with scar. In the past reimplantation was often delayed as long as a year. During this time the scar within the corpora would mature, resulting in contraction, a smaller penis size, and more difficulty with dilation before cylinder reimplantation. **To minimize loss of penile size and to facilitate corporeal dilation, the authors now perform prosthesis reimplantation as soon as possible after device removal for infection.** Once all incisions have healed and postoperative edema has resolved (usually 6 to 12 weeks after device removal), reimplantation is advised because early fibrosis is easier to dilate and the scar contraction that leads to shortening has not yet occurred.

Mulcahy introduced the concept of prosthesis salvage for infection in 1996 (Brant et al, 1996), and he updated his experience with this in 2000 (Mulcahy, 2000). His protocol involves removal of all prosthetic components and foreign bodies followed by irrigation with seven antibacterial solutions. A new device is implanted, and the patient is placed on antibiotics. In 55 patients available for follow-up, 45 (82%) were free of infection with follow-up ranging from 6 to 93 months. **When salvage procedures are successful, they maintain penile size and correct the problem with only one operation.**

Recent advances in prosthetic design have been made in attempts to reduce infection. A surface treatment combining rifampin and minocycline (InhibiZone) was introduced in 2001 by American Medical Systems for its three-piece inflatable penile prosthesis product line. In a report comparing 2261 rifampin-minocycline–coated devices with 1944 controls, the infection rate at 180 days was 0.68% in the treated group compared with 1.61% in the control group (Carson, 2004).

Mentor (now Coloplast) introduced a hydrophilic surface coating for their three-piece inflatable prosthesis in 2002 (Coloplast Titan). This coating, polyvinylpyrrolidone (PVP), reduces bacterial adhesion and absorbs the antibiotics in which the prosthesis is submerged by the surgeon just before implantation. In a report comparing 2357 hydrophilic-coated devices with 482 controls, the infection rate was 2.07% in the treated group

compared with 1.06% in the control group (Wolter and Hellstrom, 2004).

The incidence of infection during first-time penile prosthesis implantation ranges from 1% to 3%, whereas with revision surgery it is considerably higher (7% to 18%) (Kabalin and Kessler, 1988; Wilson and Delk, 1995; Jarow, 1996; Henry et al, 2005). In the early days of penile prosthesis surgery, mechanical failures were common and frequently occurred within the first few years following device implantation. The reports of increased infection rates following prosthesis revision occurred when only the failed component of the prosthesis was replaced. **If the entire device is explanted and all prosthesis compartments are thoroughly irrigated before a new prosthesis is implanted, the infection rate is not significantly different from the rates seen with first-time prosthesis implantation** (Montague et al, 2001; Henry et al, 2005).

Mechanical failures today are less common and typically occur more than 5 years after implantation.

Key Points: Prosthesis Infections

- Primary prosthesis infection rates range from 1% to 3%. Revision surgeries for penile prostheses have similar infection rates if all prosthesis components are removed and replaced with new ones.
- In surgery for infected penile prostheses, all prosthetic components and associated prosthetic material should be removed.
- Salvage surgery for infected penile prostheses is successful in approximately 80% of cases and avoids loss of penile length.
- Early (1- to 3-month) penile prosthesis reimplantation after removal of an infected penile prosthesis minimizes loss of penile length.

Perforation and Erosion

Perforation is an event that occurs intraoperatively; whereas erosion is an event that occurs or is only recognized postoperatively. When the surgeon is dilating the proximal corpora (crura), a sudden give of the dilator suggests the crus has been perforated on its medial aspect near its attachment to the pelvic bone. The dilator, almost always a smaller size, travels out into the soft tissues of the perineum. Although Mulcahy (1987) suggested the "wind sock" correction for this, it is rarely necessary if the perforation is recognized and larger-diameter dilators are used to dilate the correct tract. When the proximal portion of the cylinder is inserted, it will stay within the crus and the small area of perforation will heal over it.

With distal dilation, crossover to the opposite side may occur or the urethra may be perforated. **If urethral perforation occurs, the implant procedure should be abandoned and a urethral catheter should be left in for 7 to 10 days.** Prosthesis reimplantation may be done at a later date. To avoid urethral perforation, the surgeon should keep the tip of the dilator under the dorsolateral surface of the corpus cavernosum. This maneuver also helps to prevent crossover to the opposite side. After the first cylinder is implanted, the surgeon should resound the other side both proximally and distally to see if crossover in either direction has occurred.

Erosion of the distal cylinder lateral to the distal corpus cavernosum is usually most effectively corrected by a technique described by Mulcahy (1999). With this approach the distal cylinder is removed (folded back) and an incision through the back wall of the capsule of the cylinder compartment is made in an area proximal to the site where the erosion has occurred. This allows distal dilation within the true corpus cavernosum. Using the Furlow cylinder inserter, the distal cylinder is then reimplanted within the distal corpus cavernosum.

Erosion of the distal end of the prosthesis may occur into the urethra, in which case it is visible through the meatus. This occurs more commonly after semirigid rod implantation, presumably due to constant internal pressure from the rod device (Steidle and Mulcahy, 1989). It also occurs more commonly in men with spinal cord injury because of their lack of sensation (Zermann et al, 2006). In the case of a semirigid rod device, only the eroded side needs to be removed and this can usually be done in the office by grasping the distal end of the rod with a towel clip and then pulling it out. In the case of urethral erosion, a urethral catheter is placed for 10 days to allow urethral healing. Many patients can have adequate coitus with only one rod in place; hence a procedure to reimplant the second rod is usually unnecessary.

In the case of erosion of one cylinder of an inflatable device into the meatus or through the glans, this cylinder should be removed as soon as possible to avoid spread of bacteria along the cylinder to its tubing and thus to the rest of the prosthesis. After the cylinder is removed, an implantable plug (supplied by the device manufacturer) is placed in the pump tubing that led to that cylinder. Again, many men can have coitus with only one inflatable cylinder; thus a later procedure to reimplant the second cylinder is not always necessary.

Poor Glans Support

Poor support of the glans penis by cylinder or rod tips leads to a drooping appearance of the glans, which is commonly referred to as the "SST deformity" after the supersonic transport (Concorde) nose appearance on takeoff and landing (Ball, 1980). This may result from inadequate distal dilation; too short cylinders; or in the case of minor deformity, variations in anatomy.

Correction of this deformity can be done in one of two ways. The definitive correction involves removing both cylinders, perforating the distal capsule with Metzenbaum scissors, redilating the distal corpora, resizing, and then inserting longer cylinders or the same cylinders with longer rear tip extenders. Alternatively, dorsal plication of the glans back onto the shaft of the penis can be performed (Fig. 27–13) (Ball, 1980; Mulhall and Kim, 2001). This latter procedure is preferable when there are minor but otherwise bothersome degrees of SST deformity.

Oversized Cylinder or Rod

When a semirigid rod prosthesis that is too long is implanted, the patient may complain of pain that does not subside as healing takes place following device implantation. Alternatively, this may lead to erosion of the rod either into the meatus or through the glans. Reoperation with placement of smaller rods will usually relieve the pain and avoid impending erosion.

As already discussed, cylinders that are too long may result in a sigmoid (S) penile deformity in the case of Ultrex or LGX cylinders. In the case of non–length-expanding cylinders, usually there is no problem, although theoretically it might lead to premature cylinder failure.

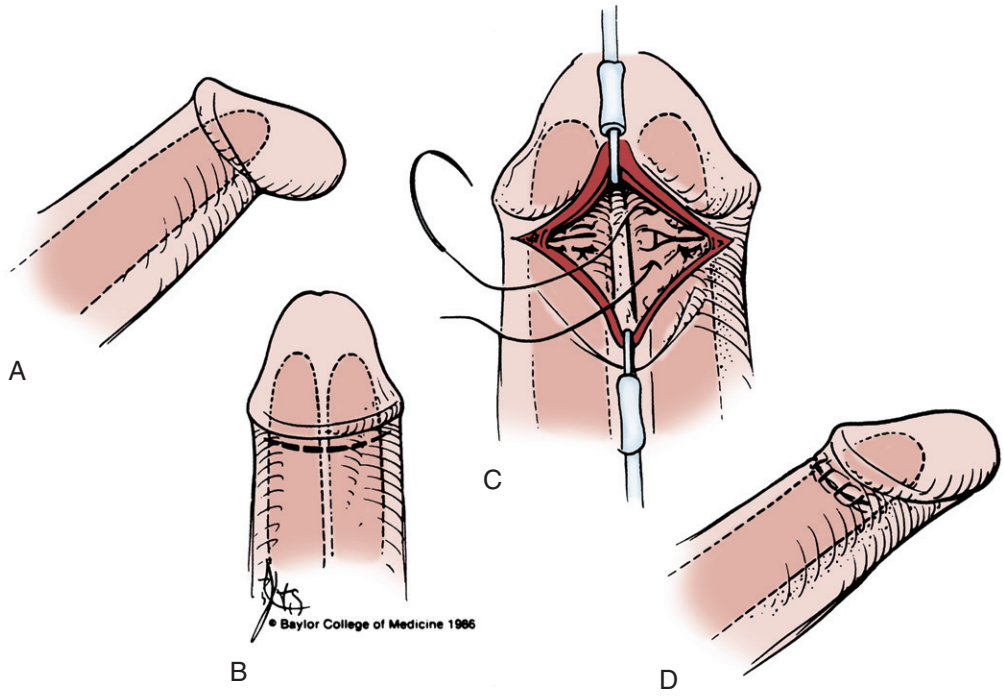


Figure 27–13. Plication sutures pull the dorsal aspect of the glans back onto the corporeal bodies to correct an SST (supersonic transporter) deformity. (© Baylor College of Medicine.)

Pump Complications

The technique for pump implantation discussed earlier helps to avoid upward pump migration, which tends to take place during healing because of the action of the cremasteric muscles. If upward pump migration occurs, the pump may impinge on the base of the penis, making use of the pump difficult and also interfering with intromission. Revision is sometimes necessary, at which time the pump is relocated to its correct position.

The pump may also be difficult to use if a hematoma or seroma forms around it. These may reabsorb with time; if they do not, pump revision may be necessary.

Autoinflation

Autoinflation occurs when the inflatable penile prosthesis partially inflates with physical activity. This can be minimized by placing the reservoir in the prevesical (retropubic) space and by performing the back pressure test as described earlier. The cylinders should also be kept deflated during healing after surgery and when the prosthesis is not being used.

The Coloplast Titan prosthesis has a reservoir with a lock-out valve in the stem. Initial experience with this device suggests that it reduces the incidence of this complication (Hollenbeck et al, 2002; Wilson et al, 2002). The MS pump of the AMS 700 series three-piece inflatable penile prostheses has a lock-out valve in the top, deflation portion of the pump.

PENILE PROSTHESIS IMPLANTATION IN SPECIAL CASES

Peyronie Disease

Men who have acquired erectile deformity secondary to Peyronie disease along with significant ED may be candidates for penile prosthesis implantation. When prosthesis implantation by itself does not produce satisfactory straightening of the penis, a corporoplasty may also be necessary (Mulcahy and Wilson, 2002). Corporoplasty was frequently necessary when girth- plus length-expanding Ultrex cylinders were used and not necessary when girth-only expanding CX cylinders were used (Montague et al, 1996). Wilson showed that modeling or forcefully bending the penis with the cylinders inflated usually obviated the need for corporoplasty (Wilson et al, 2001).

Multiple relaxing incisions to correct curvature and increase penile length have been used in men with Peyronie disease undergoing penile prosthesis implantation (Montorsi et al, 2001; Rajpurkar et al, 1999). When a relaxing incision leaves a gap greater than 1 cm, covering the defect to prevent herniation of the cylinder is recommended. Materials used to cover the defect include human cadaveric dura mater (Fallon, 1990), polytetrafluoroethylene (Fig. 27–14) (Herschorn and Ordorica, 1995), human cadaveric pericardium (Palese and Burnett, 2001), and porcine small intestinal submucosa (Knoll and Center for Urological Treatment, 2002).

Cavernosal Fibrosis

In contrast to Peyronie disease, in which scarring is present in the tunica albuginea, scarring may occur in the cavernosal smooth muscle that forms much of the contents of the corporeal bodies. **Cavernosal fibrosis is most often seen after removal of an infected penile prosthesis; it also occurs in men with ED as a result of ischemic priapism. In both cases, the penis is often significantly smaller owing to decreased volume of the corpora cavernosa. Dilation of the corpora and placement of semirigid rods or cylinders is also frequently quite difficult.**

In preparing the corpora for cylinder implantation, the authors start with a 2-cm standard corporotomy. If the corpora cannot be

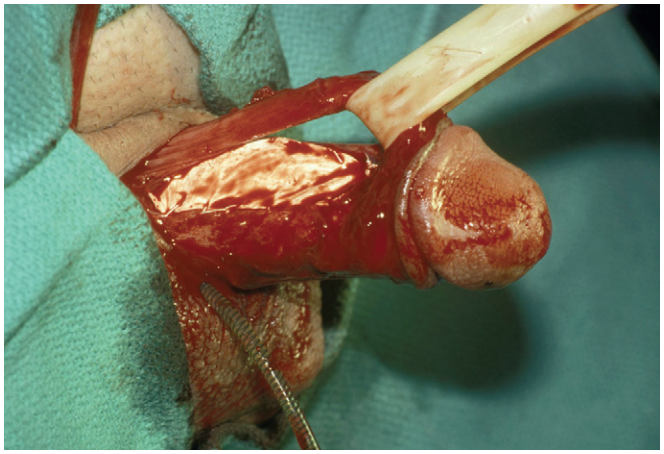


Figure 27–14. After inflatable penile prosthesis implantation, a large plaque required excision. The exposed cylinders are covered with a polytetrafluoroethylene patch.

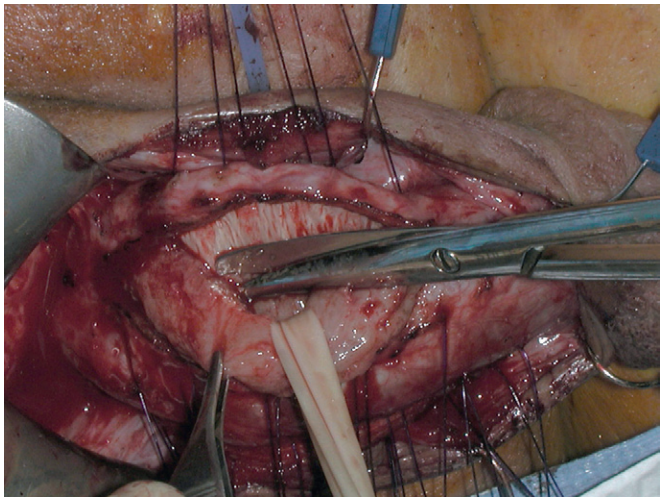


Figure 27–16. A Penrose drain is used to place traction of the fibrotic core, facilitating further dissection.

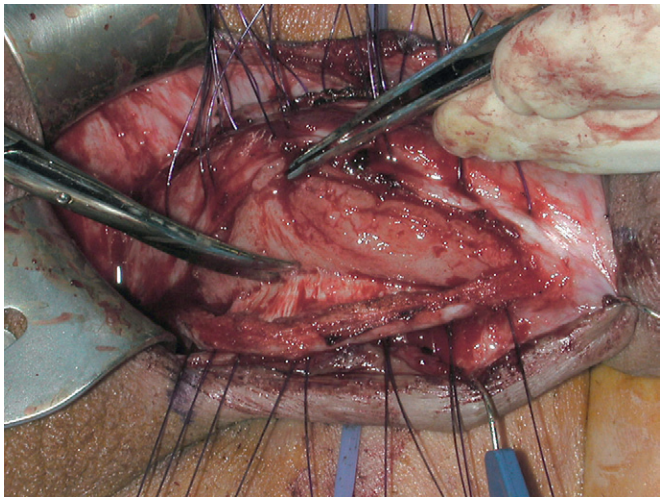


Figure 27–15. A plane of dissection is established between the fibrotic core and the inner surface of the tunica albuginea.



Figure 27–17. The excised core of fibrotic tissue.

dilated without force, they abandon the use of Hegar dilators and instead use Metzenbaum scissors with rounded tips. Gently spreading the tips as the scissors are advanced is often effective. After the scissors tips reach the distal and proximal ends of the corpora, dilation with special cutting dilators is helpful (Mooreville et al, 1999).

If these maneuvers are not successful, the authors extend the penoscrotal incision to the frenulum. Extended corporotomies are made permitting either dilation with more control or resection of scar tissue by establishing a plane between the fibrotic core and the inner surface of the tunica albuginea (Fig. 27–15), and this is facilitated by placing a Penrose drain around the core (Fig. 27–16) (Montague and Angermeier, 2006). The result is removal of the fibrotic contents of the corpus cavernosum (Fig. 27–17). Multiple horizontal mattress sutures of 2-0 PDS are then placed along the edges of the tunica albuginea (Fig. 27–18). The prosthetic cylinder can then be laid into the empty corporeal shell (Fig. 27–19), with primary closure of the tunica albuginea being possible (Fig. 27–20).

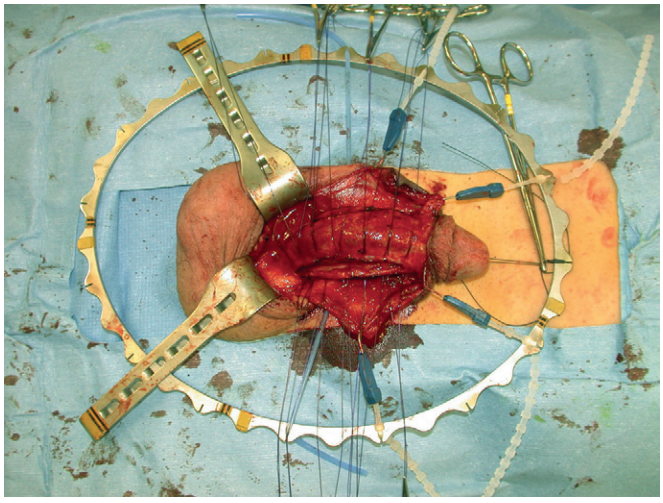


Figure 27–18. Multiple horizontal mattress sutures are placed along the cut edges of the tunica albuginea.

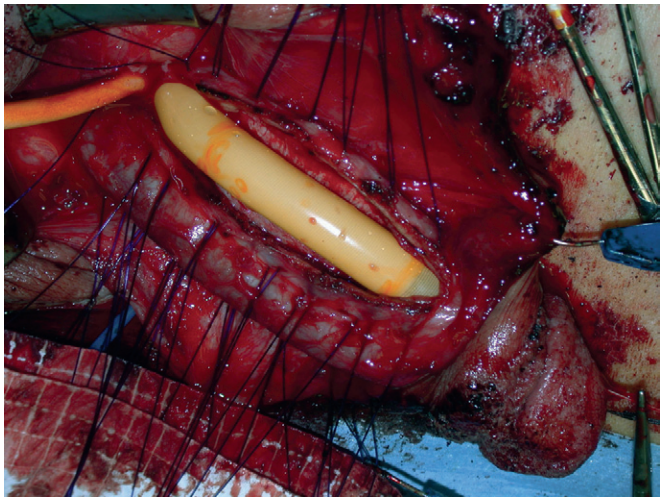


Figure 27–19. The cylinder can be laid into place.

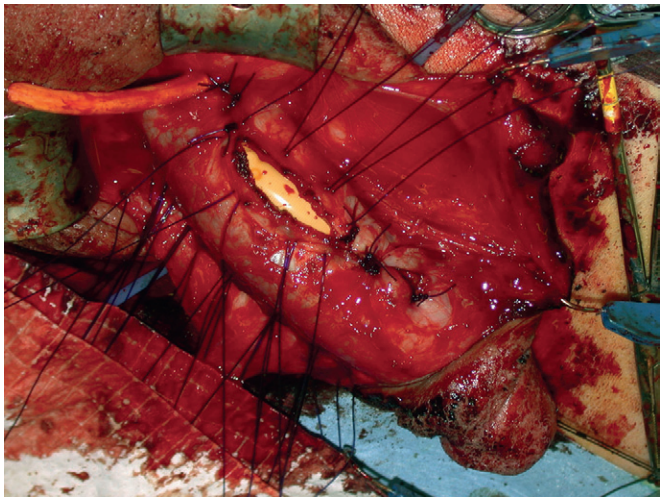


Figure 27–20. Partial primary closure over the cylinder.

Table 27–4.

Inflatable Penile Prostheses: Survival Free of Mechanical Failure*

REFERENCE	NO. PATIENTS	FOLLOW-UP MONTHS RANGE (MEAN)	DATA PREMODIFICATION OR POSTMODIFICATION	% OF DEVICES FREE OF MECHANICAL FAILURE†
AMS 700 CX/CXM (Not Modified)				
(Deuk Choi et al, 2001)	273	6-100 (49)	NA	90.4
(Carson et al, 2000)	372	38-134 (57)	NA	86.2
(Montorsi et al, 2000)	90	(60)	NA	93.1
(Daitch et al, 1997)	111	1-112 (47.2)	NA	90.8
(Dubocq et al, 1998)	103	(66 across 3 groups)	NA	83.9‡
(Dhar et al, 2006)	455	0.49-231 (median 91.5)	NA	81.3§
AMS 700 Ultrex (Modified 1993)				
(Montorsi et al, 2000)	110	(58)	Both	79.4
(Dubocq et al, 1998)	103	(66 across 3 groups)	Both	84.2‡
(Milbank et al, 2002)	85	<1-136 (75)	Pre-1993	64.7
(Milbank et al, 2002)	52	<1-92 (46)	Post-1993	93.7
Mentor α-1 (Modified 1992)				
(Goldstein et al, 1997)	434	<1-44 (22)	Both	85¶
(Dubocq et al, 1998)	117	(66 across 3 groups)	Both	95.7‡
(Wilson et al, 1999)	410	Not specified	Pre-1992	75.3
(Wilson et al, 1999)	971	Not specified	Post-1992	92.6

NA, not applicable.
*With permission from AUA Erectile Dysfunction Guidelines Update Panel.
†Kaplan-Meier survival estimates; 5-year estimates unless otherwise noted.
‡63-month estimate.
§3-year estimate.
¶10-year estimate.

RESULTS

Mechanical Failure Rates

Much of the early reporting of penile prosthesis results in terms of survival free of mechanical failure was limited because of data that usually gave only the range and mean follow-up for the entire series. It was not possible with this type of reporting to meaningfully compare different devices or the same device in different series because of failures to take into account differences in follow-up. **Contemporary reporting standards should require reporting device survival free of mechanical failure by using Kaplan-Meier projections** (Kaplan and Meier, 1958; Montague et al, 2005).

The results reported herein are limited to the three-piece inflatable penile prostheses available today (the AMS 700 CX/CXM, the AMS 700 Ultrex, and the Mentor Alpha-1) and include only those studies that report Kaplan-Meier projections. Eight such studies were found (Table 27–4). The AMS 700 CX/CXM prosthesis was introduced in 1987; no significant design changes have occurred with this device since its introduction. Five studies with a total of 949 implant recipients reveal that freedom from mechanical failure ranges from 83.9% (63 months) to 93.1% (5 years).

The AMS 700 Ultrex prosthesis was introduced in 1990, and the cylinders were modified in 1993. Results from two studies (Dubocq et al, 1998; Montorsi et al, 2000) with a total of 213 device recipients included both pre- and post-1993 Ultrex modified devices. Survival free of mechanical failure ranges were 79.4% (5 years) and

84.2% (63 months). One study compared 5-year device survival before the 1993 cylinder modification (64.7%, $N = 85$) to after the 1993 cylinder modification (93.7%, $N = 52$) (Milbank et al, 2002).

The Mentor Alpha-1 prosthesis introduced in 1989 underwent pump modification in November 1992. Two studies with a total of 55l implant recipients included both prepump and postpump modification devices. Survival free of mechanical failure was 85% at 3 years (Goldstein et al, 1997) and 95.7% at 63 months (Dubocq et al, 1998). One study compared 5-year device survival before pump modification (75.3%, $N = 410$) and after pump modification (92.6%, $N = 971$) (Wilson et al., 1999).

Dhar and colleagues reported on 455 men implanted with CX/CXM devices. Median follow-up was 91.5 months. Ten-year Kaplan-Meier estimates of freedom from mechanical failure were 81.3% (95% CI, 75.7 to 87.3) (Dhar et al, 2006).

Patient (Partner) Satisfaction

Early satisfaction studies were retrospective and used nonstandardized questionnaires. In one such study of the AMS 700 inflatable (pre-CX and pre-Ultrex) prosthesis, 387 recipients were mailed questionnaires and 272 were returned. This retrospective review showed that 83% of the men and 70% of their partners were satisfied with the use of this device (McLaren and Barrett, 1992). In another retrospective study of 145 AMS 700 Ultrex inflatable penile prosthesis recipients using a nonstandardized questionnaire, 85% of the men and 76% of their partners were satisfied (Holloway and Farah, 1997).

Prospective studies using structured questionnaires can provide more useful information regarding patient and partner satisfaction following penile prosthesis implantation. In one such study a psychosexual questionnaire containing 13 questions scored on a scale of 1 to 5 was administered to 35 inflatable penile prosthesis recipients preoperatively and again at 3, 6, and 12 months after surgery. This study demonstrated significant improvements in the psychosexual well-being of these prosthesis recipients with attainment of a high level of patient satisfaction up to 1 year after surgery. This study permitted these results to be broken down into erectile ability, libido, frequency of sexual activity, satisfaction with sexual activity, and a decrease in feelings of sadness, depression, anxiety, anger, frustration, and embarrassment related to sexual activity (Tefilli et al, 1998).

In another prospective study of 96 inflatable penile prosthesis recipients, the International Index of Erectile Function (IIEF) (Rosen et al, 1997) and the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) (Althof et al, 1999) were administered preoperatively and 3, 6, and 12 months postoperatively (IIEF) and 3, 6, and 12 months postoperatively (EDITS). All 12 month scores were significantly higher than baseline scores, and the 12-month scores were significantly higher than the 6-month scores for the IIEF satisfaction domain and for EDITS (Mulhall et al, 2003).

One study compared penile prosthesis implantation to penile injection therapy. In this retrospective study a structured telephone questionnaire was administered to 115 intracavernosal injection patients and 65 penile prosthesis recipients. Mean follow-up of all patients was 5.4 years. At the time of contact 70% of the patients with prostheses were still sexually active, whereas only 41% of the penile injection patients were sexually active (Sexton et al., 1998).

Another retrospective study compared erectile function status and satisfaction in patients receiving treatment with sildenafil citrate, intracavernous injection therapy, and inflatable penile prosthesis implantation. The patients were administered EDITS and the erectile function domain of the IIEF. There were 31 patients in the sildenafil citrate group, 22 in the penile injection therapy group, and 32 who had received a penile prosthesis. At a mean follow-up of 19.54 months, penile prosthesis recipients had significantly better erectile function and treatment satisfaction than did patients in the other two groups (Rajpurkar et al, 2003).

In a study of 114 penile prosthesis recipients, IIEF was administered preoperatively and IIEF, EDIT, and a Global Satisfaction Questionnaire were given at least 6 months postoperatively (Akin-Olugbade et al, 2006). Subgroups evaluated included recipients with Peyronie disease, body mass index (BMI) greater than 30 $kg \cdot m^2$, radical prostatectomy, and patient age older than 70 years. All groups showed significant improvement in IIEF and EDITS scores. Men with Peyronie disease, radical prostatectomy, and BMI greater than 30 had lower satisfaction rates than the general penile implant group.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter
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Peyronie's Disease

Gerald H. Jordan, MD, FACS, FAAP (Hon), FRCS (Hon) ●
Kurt A. McCammon, MD, FACS

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Credit for the first description of Peyronie's disease is given to François Gigot de la Peyronie in 1743 (Peyronie, 1743). Fallopius, however, first reported the entity in 1561. Peyronie's disease is also known as induratio plastica of the penis. **In most patients, reassurance is sufficient and a necessity.** For others, medical therapy is useful. Fortunately, only a minority of patients will have deformity that precludes them from having intercourse. **Most of the patients with Peyronie's disease do not require surgery. Surgery, at best, can be viewed as palliation for the mechanical effects of Peyronie's disease and erectile dysfunction.**

The literature associates Peyronie's disease with many entities. Some have stood the test of time; in others, the association has not. In a study by Nyberg and colleagues (1982), **Peyronie's disease was associated with Dupuytren disease. Dupuytren disease has a familial pattern known to be transmitted in an autosomal dominant pattern. Thirty percent to 40% of men with Peyronie's disease will also have Dupuytren disease** (Nyberg et al, 1982; Ralph et al, 1997). **Other associated fibrotic conditions are contracture of the plantar fascia (Ledderhose disease) and tympanosclerosis.** Peyronie's disease is also reported to occur in patients after external trauma to the penis (e.g., seat belt injuries). To the authors' knowledge, no reported incidence rate appears in the literature for such patients. However, all urologists who see any volume of patients with Peyronie's disease will inevitably encounter one or two such patients a year who can attribute the onset of Peyronie's disease only to an incident of external trauma to the penis. The relationship of Peyronie's disease to diabetes mellitus likewise remains unclear. Certainly if one accepts the notion that erectile dysfunction can be an inciting event for the development of Peyronie's disease, the relationship with diabetes mellitus will follow. To date, however, the incidence of Peyronie's disease as associated with diabetes mellitus has not been defined, although patients with diabetes mellitus were shown to have statistically significant more curvature and worse vascular status compared with patients without diabetes mellitus (Kendirci et al, 2007; El-Sakka and Tayeb, 2009). The relationship to gout can only be regarded as anecdotal.

The relationship with Paget disease of the bone, however, was noted in a nicely done study reported by Lyles (1997) in which patients with Paget disease were noted to have Peyronie's disease at an incidence rate higher than that quoted for the population in general. Certain human leukocyte antigen subtypes have been incriminated as being causally related to the development of Peyronie's disease. However, for a subtype to be positively linked to the development of Peyronie's disease, a study of many thousands of patients would be required. Nyberg and associates, in 1982, Leffell, in 1997, and Ralph and colleagues, in 1997, suggested an association.

The use of β-adrenergic blockers has been causally incriminated with regard to the development of Peyronie's disease. However, the association was made when first-generation β blockers had just been released to the market. Like diabetes mellitus, those first-generation β blockers were also causally associated with erectile dysfunction. Thus, as possibly the case with diabetes mellitus and hypertension, the same relationship could hold true for the relationship to β blockers. Further study substantiating the relationship to diabetes exists (Lindsay et al, 1991; Kendirci et al, 2007; El-Sakka and Tayeb, 2009).

Urethral instrumentation has been implicated as a cause of Peyronie's disease. Any urologist who sees a large volume of patients with Peyronie's disease will encounter, on a one or two per year basis, patients who had straight erections before transurethral surgery but with the resumption of intercourse after surgery noted curvature. Most of these patients do not complain of ventral curvature. This association should not be confused with Kelami syndrome, which is fibrosis of the corpus spongiosum so severe that it limits expansion of the ventral corpora cavernosa. Again, to the authors' knowledge, no incidence figures exist for the relationship to urethral instrumentation (Carrieri et al, 1998).

A prime example of an association that has never stood the test of time is the association with phenytoin. In the postmarketing study for phenytoin there were patients taking phenytoin who developed Peyronie's disease. Because phenytoin is associated with hyperplastic tissue growth phenomena (gingival hyperplasia) the association of Peyronie's disease with phenytoin was thought logical and published in the *Physicians' Desk Reference*. No other report of a causal relationship, and in fact no other report linking phenytoin use with Peyronie's disease, has been published.

The symptomatic incidence of Peyronie's disease has been estimated at 1%. In white men the average age at onset of Peyronie's disease is 53 years. The asymptomatic prevalence is estimated at 0.4% to 1.0%. In a study of 100

men without known Peyronie's disease, at autopsy 22 were found to have fibrotic lesions of the tunica albuginea compatible with Peyronie's disease (Smith, 1969; Gelbard et al, 1990; Lindsay et al, 1991; Carson et al, 1999; Greenfield and Levine, 2005). Clearly, many think that the clinical incidence of Peyronie's disease is increasing. The increase, however, may be associated with, and seems to coincide with, the increased use of erection-enhancing medications. The phosphodiesterase-5 (PDE5) inhibitor medications and the approved intracavernosal injection agents are not indicated for Peyronie's disease. That does not mean that they are contraindicated but that during the final phase studies reviewed for drug approval that patients with Peyronie's disease were excluded. **To the authors' knowledge there has never been any suggestion that PDE5 inhibitors are in any way directly causally related to the development of Peyronie's disease nor is there suggestion that their use would worsen the course of Peyronie's disease** (Jalkut et al, 2003). Data are emerging to suggest that certain endothelial impairment may be reversed with the initiation of PDE5 inhibitor therapy. However, the concept of "endothelial rehabilitation" with PDE inhibitor therapy should be considered as suggested only (Rosano et al, 2005). Rajfer's work suggests the opposite. PDE5 therapy or therapy with other promoters of cyclic guanosine monophosphate (cGMP) (pentoxifylline) actually suggests that in the animal model cGMP functions as an antifibrotic and thus PDE5 medication and pentoxifylline therapy may actually counter the fibrotic process. Likewise, it is the authors' belief that the scarring seen with intracavernosal injection therapy is related not to the medications necessarily but rather to the injection technique. There are certainly patients who can recall a given event in which they used their injection medication. The injection was accompanied by undue pain, a good erection was not achieved, and the patient then noticed an area of induration in the penis. After that, patients often notice deformity of the penis. Also, it could be theorized that the repetitive trauma of the needle may initiate a "Peyronie's-like process." The prolonged use of papaverine and phentolamine (Regitine) has been implicated as a cause of intracorporeal fibrosis, which is different from the fibrotic process of the tunica albuginea that is recognized as Peyronie's disease.

Key Points: Epidemiology

- Peyronie's disease presents as a variety of deformities of the penis. The symptomatic incidence has been estimated at 1%, but most think that the incidence is increasing and now can be conservatively estimated at 4% to 5%. Fortunately, most patients do not require surgery. Most do require reassurance and education. Surgery for Peyronie's disease is considered palliation for the mechanical effects of the disease.
- Peyronie's disease has been related to a number of conditions. The strongest relation is to Dupuytren disease.
- Although the increased incidence of Peyronie's disease seems to correspond with the use of pharmacotherapy for the management of erectile dysfunction, to the authors' knowledge there has never been any suggestion that PDE5 inhibitors are in any way directly causally related to the development of Peyronie's disease nor is there any evidence that intracavernosal injection therapy is directly implicated in the process of Peyronie's disease. The development of Peyronie's disease does seem to be related to the unique anatomy of the tunica albuginea and its relationship to the septal fibers.

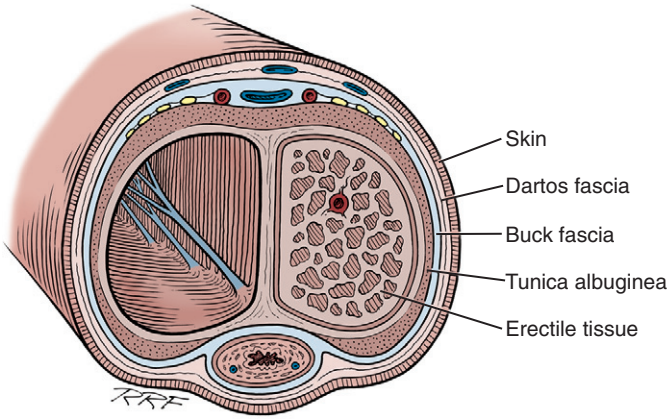


Figure 28–1. Diagram of the penis. The fibers of the septum are attached to the inner layer of the tunica albuginea of the corpora cavernosa along the dorsal and ventral midlines. Plaques of Peyronie's disease occur in the tunica albuginea at the site of attachment of the septal fibers.

ANATOMIC CONSIDERATIONS AND ETIOLOGIC FACTORS

In examining the etiology of Peyronie's disease it is important to review some facts concerning the anatomy of the corpora cavernosa (Fig. 28–1). The tunica albuginea is bilaminar throughout most of its circumference. It is composed of an outer longitudinal layer and an inner circular layer. The corpora are separated by an incompetent septum. In the pendulous portion of the penis there are intracavernous supporting fibers that anchor the inner layer of the corpora cavernosa at the 2-o'clock and 6-o'clock positions. The tunica albuginea varies in thickness from 1.5 to 3.0 mm, depending on the position on the circumference. The outer longitudinal layer attenuates in the ventral midline, and thus the tunica is monolaminar at that point. The outer longitudinal layer is thickest on the ventrum adjacent to the corpus spongiosum and on the dorsum and thinnest on the lateral aspects (El-Sakka et al, 1998b). **Most patients with Peyronie's disease demonstrate lesions dorsally.** Because the tunica albuginea is bilaminar on the dorsum it is possible that these layers might delaminate with buckling trauma. Also, on the ventrum, the longitudinal layer is absent, thus potentially allowing dorsal buckling more easily (Devine and Horton, 1988; Border and Ruoslahti, 1992; Brock et al, 1997; Devine et al, 1997; Jarow and Lowe, 1997). The authors, as have others, note that in the case of calcified plaques the calcification seems to involve the inner circular lamina and, in fact, can be removed, leaving the outer lamina intact. The outer lamina is not normally compliant, but the predilection for calcification of the inner lamina calls to question the preciseness of the typical delamination hypothesis.

Somers and Dawson (1997), **in studies, have shown that Peyronie's disease most likely begins with buckling trauma that causes injury to the septal insertion of the tunica albuginea.** Intravasation of blood occurs with activation of fibrinogen (Fig. 28–2). The body responds to the effects of trauma; and macrophages, as well as neutrophils and mast cells, migrate to the area. Platelets are present because of the intravasation of blood, and fibrin becomes incarcerated in the healing process. Platelets, neutrophils, and mast cells secrete cytokines, autacoids, and vasoactive factors, many of which become involved in fibrosis. Platelets release serotonin and platelet-derived growth

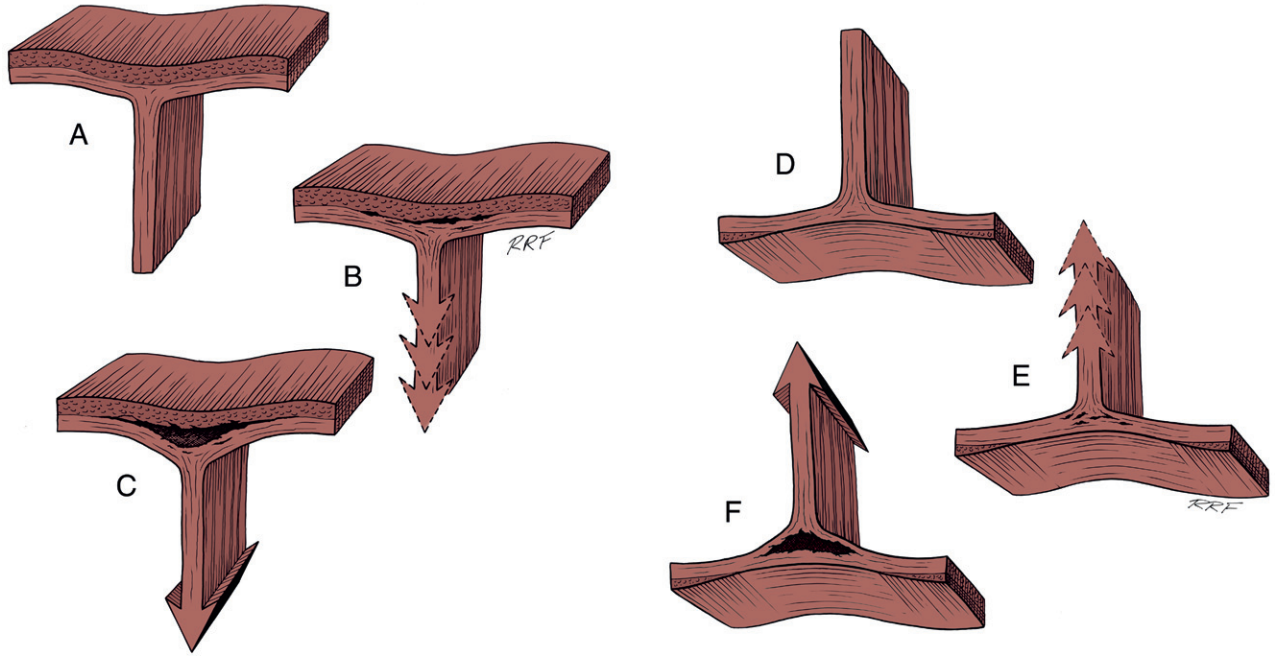


Figure 28–2. Demonstration of the mechanism of injury during buckling injuries to the penis. **A,** Fibers of the septal strands dorsally fan out and are interwoven with the inner circular lamina fibers of the tunica albuginea. The outer lamina consists of longitudinal fibers. **B,** In the chronic mechanism of Peyronie's disease, less turgid erections allow flexion of the penis during intercourse, producing elastic tissue fatigue, further reducing elasticity of the tissue and leading to multiple smaller ruptures of the fibers of the tunica with smaller collections of blood, possibly producing multiple scars. **C,** In the acute mechanism of Peyronie's disease, bending the erect penis out of column produces tension on the strands of the septum, delaminating the layers of the tunica albuginea. Bleeding occurs, and the space fills with clot. The
scar generated by the response of the tissue to this process becomes the Peyronie's disease plaque. **D,** Illustration of the situation on the ventrum of the penis, where the bilaminar arrangement of the tunica albuginea becomes thinned, with the midline being monolaminar. The fibers of the septal strands fan out and are interwoven with the inner circular layer. There is no outer circular layer. **E,** In the chronic

factors as well as transforming growth factors. The formation of thrombus leads to the deposition of fibronectin, which binds a number of growth factors, keeping them localized to the area of injury. Fibrinogen leakage leads to the deposition and incarceration of fibrin (Fig. 28–3).

It has been proposed that the avascular nature of the tunica albuginea may impede clearance of many of these growth factors. The transforming growth factors, particularly transforming growth factor-β (TGF-β), are capable of autoinducement. Thus, the accumulation of TGF-β1 is capable of inducement of further accumulation. The presence of TGF-β stimulating further release of TGF-β1 could possibly lead to an ongoing, smoldering, inflammatory process ending with disordered healing. There is good reason to suspect TGF-β1 as possibly involved with the formation of Peyronie's plaque because it has been implicated in a number of soft tissue fibroses as well as with erectile dysfunction (Border and Ruoslahti, 1992; Border and Noble, 1994; Davis, 1997; Diegelmann, 1997; Van De Water, 1997; Moreland, 1998; Mulhall et al, 2001b).

TGF-β1 is synthesized as a latent peptide by many cells; those pertinent to this discussion are platelets, macrophages, and fibroblasts. On activation, TGF-β1 binds to cell surface receptors and eventually results in synthesis of connective tissues with inhibition of collagenase (El-Sakka et al, 1997a, 1997b, 1998a). Also noted was that the expression and activity of Smad transcription factors of the TGF-β pathway is increased in fibroblasts of patients with Peyronie's disease. The net result of this trauma with disordered healing is the formation of plaques that appear as scars and impede expansion of the tunica albuginea during erection, which results in curvature, and/or indentation, and/or foreshortening (Fig. 28–4). On histologic examination there is aberrant cicatrization with nonpolarization of collagen and diminished and erratic distribution of the elastin fibers (Fig. 28–5).

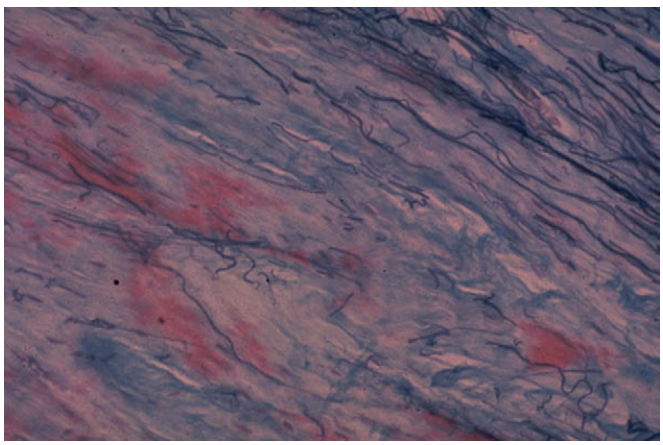


Figure 28–3. Photomicrograph of Peyronie's plaque demonstrating entrapped fibrin. The fibrin stains pink; the collagen fibers stain prussian blue.

Recent work at the University of California, San Francisco, has examined the role of matrix metalloproteinase in this abnormal

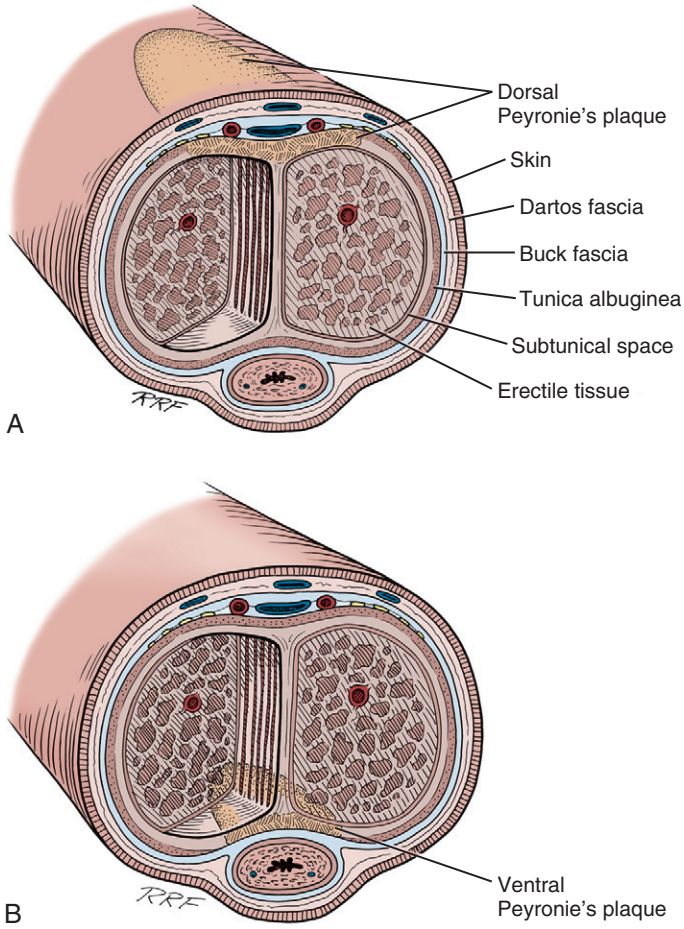


Figure 28–4. **A** and **B,** Under the influence of inflammation and cytokines the disease progresses through an active or immature phase during which there appears to be disordered healing that eventually leads to a scar, which almost always is associated with the septal fibers.

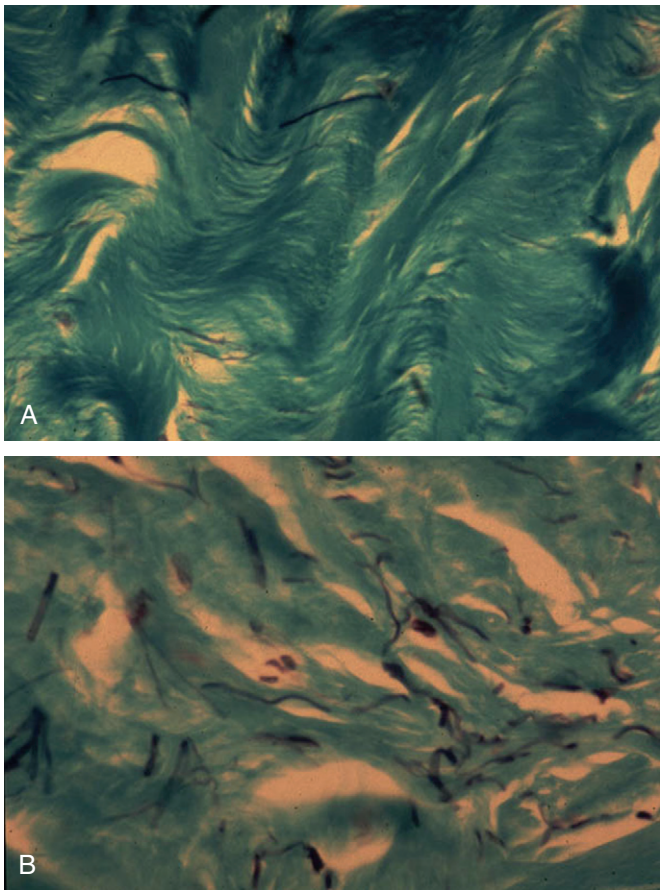


Figure 28–5. Photomicrographs of the tunica albuginea. **A,** Normal tunica albuginea demonstrating the polarized arrangement of collagen. **B,** Peyronie's plaque demonstrating the nonpolarized arrangement of collagen and the haphazard arrangement of elastin. Collagen stains green; the elastin stains black.

scarring process. Matrix metalloproteinases are enzymes that are involved in the remodeling of extracellular matrix proteins. These remodeling enzymes are regulated by tissue inhibitors of metalloproteinase. **Failure or downregulation of matrix metalloproteinase has been implicated in a number of disease processes. In the case of Peyronie's disease, if matrix metalloproteinases are downregulated that could function as a possible mechanism for the scarring process in Peyronie's disease.** In the studies, image analyses were used to examine the cavernosal tissues of Peyronie's disease patients compared with control subjects having only prosthetic placement for other reasons. Those analyses showed a higher expression of the tissue inhibitors of metalloproteinase in all of the components of the Peyronie's plaques compared with the control subjects. **Thus, inhibition of antiscarring enzymes can perhaps represent another facet of the etiology of the lesion that is recognized as the Peyronie's plaque** (Grazziotin et al, 2004).

In a similar vane, Hauck and coworkers (2004) examined the role of α_1-antitrypsin, which is a proteinase inhibitor, as a possible factor in the development of Peyronie's disease. Reduction in α_1-antitrypsin levels could result in a change in collagen metabolism. Previous work had suggested diminished levels, and such diminished levels could be associated with diminished tissue degradation (remodeling) and hence increased cicatrization. Hauck and coworkers did find diminished α_1-antitrypsin levels in patients with Peyronie's disease; however, compared with age-matched controls the levels were not diminished in Peyronie's disease with regard to the control subjects. **Thus α_1-antitrypsin levels may vary with age but the association with Peyronie's disease was not made.**

Studies also demonstrate the role of oxidative stress in addition to cytokine release in the development of Peyronie's disease plaques. Acting as profibrotic factors, they interact with antifibrotic defense mechanisms, which, as already mentioned, may be inhibited. Oxidative stress intensifies in the fibroblasts of human Peyronie's disease plaques and rat-modeled fibrosis (Ferrini et al, 2002; Vernet et al, 2002; Valente et al, 2003). Reactive oxygen species trigger profibrotic processes in a number of disease processes (Becker et al, 2001; Intengan et al, 2001). There is interplay between a number of mechanisms as they relate to fibrosis. Possibly of particular importance as previously mentioned is cGMP, one of the mediators of penile erection. cGMP has been found to be antifibrotic in Peyronie's disease plaques. Long-term administration of PDE5 inhibitors prevents plaque formation in rat fibrosis models. PDE5 is expressed in tunical and Peyronie's disease fibroblasts (Valente et al, 2003). Thus, as previously mentioned, the use of PDE5 inhibitors and cGMP promoters in patients with Peyronie's disease may be helpful in a number of ways.

Key Points: Etiologic Factors

- Buckling trauma of the penis, usually occurring during intercourse, has been implicated in the development of Peyronie's disease. TGF-β has been found to be related to the disordered healing process that leads to the scarring of the Peyronie's plaque. In addition, failure of downregulation of a number of "antifibrotic" factors has been implicated.
- Basic science research into the etiology of Peyronie's disease is limited by the failure, to date, to develop a true animal model of Peyronie's disease. There are animal models and models of fibrosis, however, that have led to a number of interesting proposals, many of which are becoming translational with therapeutic options.

PATHOPHYSIOLOGY AND NATURAL HISTORY

Basic science research into the etiology of Peyronie's disease is limited by the failure, to date, to develop a true reliable animal model of Peyronie's disease. A couple of animal models have examined the injection of cytomodulin, a TGF-β promoter, and the injection of blood. Clearly, in both models, fibrotic lesions were produced. Whether these represent true models of Peyronie's disease remains to be proved or disproved. These models of fibrosis, however, have led to interesting research regarding the pathogenesis of Peyronie's disease. In addition, a number of cell culture models have been proposed and have allowed significant enlightenment with regard to cell cycle regulators and gene expression. The obvious comment about these models is that, of course, these do enlighten us with regard to the essential cell aberrations; however, most probably fail to truly represent what would be the in-vivo condition. They do allow, however, investigation with regard to agents that potentially can manipulate the behavior of the individual cell (El-Sakka et al, 1999; Perinchery et al, 2000; Bivalacqua et al, 2001; Mulhall et al, 2001a; Ferrini et al, 2002; Gonzalez-Cadavid et al, 2002; Lin et al, 2002; Magee et al, 2002; Hauck et al, 2003b; Kim et al, 2004; Piao et al, 2008).

Several studies have examined the natural history of Peyronie's disease (Hellstrom, 2003). **In most cases there are two phases. The first is an active phase, which not uncommonly is associated with painful erections and changing deformity of the penis. This is followed by a quiescent secondary phase, which is characterized by stabilization of the deformity, with disappearance of painful erections, if they were present, and, in general, stability of the process. Up to a third of patients, however, present with what appears to be sudden development of painless deformity.** It has been said that Peyronie's disease totally resolves in some patients, but this is probably a misstatement. Clearly there are some patients who traumatize their penises and then develop curvature secondary to the inflammatory process and its associated loss of compliance. In some, the inflammation resolves without seeming to enter into the phase of smoldering inflammation that ends in disordered healing and scar formation. Thus the process is resolved. Semantically, however, these patients probably cannot be said to have resolved Peyronie's disease; rather, the trauma has resolved without the development of Peyronie's disease. In Mulhall's study of men diagnosed promptly after development of Peyronie's disease symptoms and findings who elected to avoid all therapy, few were found to show much improvement in curvature during a period of 12 months (O'Brien et al, 2004). Obviously this study could be faulted for not having observed the patients longer, but the point is made that "spontaneous resolution" of Peyronie's disease is an infrequent occurrence.

When the urologist is confronted with a patient with Peyronie's disease it is imperative that he or she understand the mindset of that patient and indeed of the couple. It has been shown that couples in which the man has Peyronie's disease, compared with age-matched adult couples, seem to engage in more frequent and more vigorous intercourse and often use positions that are potentially traumatic to the penis. These couples seem to relate by intercourse. It could be stated that Peyronie's disease is a disease of aging tissue in a patient with a youthful libido (Williams and Thomas, 1970; Gelbard et al, 1990; Carson et al, 1999; Rosen et al, 2008). An association to trauma and position of intercourse has been proposed for some time, based on the assumption that certain positions of intercourse can be traumatic to the penis. However, this premise has not been well verified. The hypothesis is that patients with Peyronie's disease have a higher incidence of penile trauma associated with intercourse (Jarow, 1997; Zargooshi, 2004). It has also been proposed that patients with Peyronie's disease use positions of intercourse that are different and varied compared with a "control population" and may have less firm erections than a "control population," therefore creating a situation in which intercourse could traumatize the penis.

A study at the Eastern Virginia Medical School examined these hypotheses. Control subjects and Peyronie's disease patients were aged matched. Peyronie's disease patients had a higher incidence of Dupuytren disease as well as Ledderhose disease. It was found that patients with Peyronie's disease reported traumatic intercourse in a much higher rate than control subjects, and this was highly statistically significant. However, compared with the control population in this study, Peyronie's disease patients seemed to have firmer erections. When positions of intercourse were looked at, with the female superior position being believed to be potentially traumatic, Peyronie's patients and control patients used different positions of intercourse at almost an identical rate. Further studies are obviously required (Logan et al, 2008).

The relationship of erectile dysfunction with Peyronie's disease is a difficult one to ascertain. Mention of erectile dysfunction after surgery begins with the first report of surgery for Peyronie's disease (Lowsley and Boyce, 1950) using excision and grafting. In that series, erectile dysfunction postoperatively was a major source of failure. Interestingly, patients with ventral curvature were singled out as particularly at risk for postoperative problems with erectile dysfunction. The poor prognosis for that group of patients seems to persist into current series. Returning to articles concerning the natural history (Williams and Thomas, 1970; Gelbard et al, 1990), erectile dysfunction again is prominently mentioned. In Gelbard and colleagues' manuscript (1990), a large number of patients discussed poor erections and erectile dysfunction. In the authors' experience, erectile dysfunction precedes the onset of Peyronie's disease in many patients. In an analysis in 1993 (Jordan and Angermeier, 1993) it was clear that erectile dysfunction is a significant factor in patients examined preoperatively. A review by Mulhall further clarifies the association of erectile dysfunction with Peyronie's disease (Palese et al, 2004). In that analysis a large cohort of men were questioned with the International Index of Erectile Function, Erectile Function domain (IIEF/EF). The data showed that one third of men with Peyronie's disease presented with erectile dysfunction at the time that they presented with Peyronie's

disease. Furthermore, a significant percentage of them had erectile dysfunction that preceded their notice of the onset of Peyronie's disease and its diagnosis. The investigators also examined patients with dynamic infusion cavernosometry and cavernosography and found that venous leak is seen more commonly in men who develop erectile dysfunction with Peyronie's disease; however, site-specific venous leak was not noted. There also was the confusing factor of those men with normal vascular parameters who by questionnaire had erectile dysfunction. This further emphasizes the strong psychological component seen in these patients and also the role of destabilization of rigidity by curvature and indentation.

In that analysis, almost 80% of the patients complained of "the psychological effects" of Peyronie's disease. Of note is that of those 80%, 70% complained that their psychological complaints did not improve despite the fact that their disease went into a quiescent phase. A major failure of the literature is that patients are not stratified with regard to functional issues versus organic issues as they relate to erectile dysfunction. Nelson and associates (2008) using validated instruments showed that 48% of patients with Peyronie's disease were shown to have clinically meaningful depression.

Since Brock and Lue's analysis (1993) **there are now a number of reports that have attempted to stratify patients preoperatively with functional testing. In those articles there is wide variance of opinion concerning the coexistence of erectile dysfunction with Peyronie's disease.** Jordan and Angermeier (1993) showed erectile dysfunction in almost 100% of patients; Jarow and Lowe (1997) showed that 76 of 95 patients were impotent by testing; and Ralph and coworkers (1992) showed that of 20 patients with erectile dysfunction who were studied with duplex ultrasonography, 90% had complaints of erectile dysfunction because of functional, not organic, causes. In Mulhall's study cited earlier, by IIEF/EF criteria, 30% of that cohort had erectile dysfunction associated with Peyronie's disease (Palese et al, 2004). Hellstrom's analysis of more than 500 men, all evaluated with duplex ultrasonography, showed a significant relationship between the type of penile deformity and penile hemodynamics. The study showed that patients with hourglass deformity most commonly had arterial insufficiency. Veno-occlusive dysfunction was most prevalent in patients with ventral curvature. This fact makes Lowsley's final statement in his 1950 paper almost prophetic: "Patients with ventral curvature do not do well with graft operations." However, Hellstrom's study did not demonstrate any statistical relationship between the type of deformity and the frequency of erectile dysfunction. All patients were evaluated with the IIEF/EF questionnaire (Kendirci et al, 2005).

Thus what is in the literature is not clear other than the fact that patients preoperatively complain in large numbers of the psychological impact of their Peyronie's disease and that those psychological aspects continue to plague good surgical results (Jones, 1997).

On the basis of a study still to be published, men with and without Peyronie's disease participated in a series of focus groups that were conducted in several cities. Most men indicated that the impact Peyronie's disease has had on their life has been severe (Rosen et al, 2008). **The emotions expressed by many of the men who were interviewed ranged from anger to frustration to hopelessness.** Although many men—even those not in a steady relationship—were still having sex, most of those who were still having sex said that it was different from what it used to be and many were concerned that their condition would worsen and that they would not be able to have sexual intercourse in the future. In every focus group, most men said they had become resigned to the fact that there was nothing that could be done. Additional work is being done to develop a questionnaire to measure the impact of Peyronie's disease on various aspects of a man's life (Rosen et al, 2008).

Jones (1997) deals best with the counseling issues of men with sexual dysfunction resulting from Peyronie's disease. His comments are based on interviews of more than 1500 men with Peyronie's disease. **He describes counseling a patient with Peyronie's disease as being much the same as counseling a person who has suffered a death and is grieving.** As with death, grieving is complicated by denial, ambivalence, anxiety, depression, shame, embarrassment, and, in the case of this particular group of patients, self-disgust. Most of these patients are not good talkers. Jones (1997) suggests that these patients tend not to like to talk about their problems with their spouses and initially spurn counseling in many instances.

A major point made by Jones (1997) **in dealing with patients with Peyronie's disease is that to avoid or to limit emotional factors patients and their partners need to hear the suggestion that they must "keep sexual expression alive, be active to whatever degree possible at every stage of the progression or regression of their Peyronie's disease course."** Patients' understanding of Peyronie's disease is made worse many times by the comments of urologists and primary care physicians, who in general do not understand the disease. Many patients have been told that Peyronie's disease is probably the end of their sex life. Many of these couples have related by the belief that "sex is intercourse." Thus, when coitus is precluded, they avoid all sexual activity. Most men with Peyronie's disease have ignored, at one point, the plea of their partners who have asked for intimacy regardless of whether there was intercourse. As mentioned, the relationship of the functional

Key Points: Pathophysiology and Natural History

- Studies that examine the natural history of Peyronie's disease show that Peyronie's disease presents usually as two phases. The first is an active phase; the second is a quiescent phase. Thus studies to evaluate the efficacy of pharmacotherapy are difficult; when the disease process enters the quiescent phase, many things noted during the acute phase disappear or become less apparent.
- The relationship of Peyronie's disease to erectile dysfunction has been difficult to determine. Studies estimate the occurrence of simultaneous erectile dysfunction with Peyronie's disease to be in some cases as high as 100%. A study showed that one third of a cohort of patients with Peyronie's disease presented with erectile dysfunction at the time they presented with Peyronie's disease. A significant percentage of them noted that the erectile dysfunction preceded their notice of Peyronie's disease.
- Older articles fail to stratify patients with regard to their erectile function, and this has led to the variance of opinion concerning the relationship of erectile dysfunction with Peyronie's disease. It is clear that the issues of erectile dysfunction make the psychological effects of Peyronie's disease worse. Recent data suggest that one major concern of patients with Peyronie's disease is that the condition will worsen and eventually they will completely lose the ability to have sexual intercourse. Patients must be encouraged to keep their sexual expression alive.

aspects to the organic aspects remains elusive. To define these aspects there must be uniformity in history-taking; there must be uniformity in preoperative assessment with regard to erectile function; and, in failures, there must be uniformity in postoperative assessment with regard to erectile dysfunction.

SYMPTOMS

The presenting symptoms of Peyronie's disease include, in many patients, penile pain with erection; penile deformity, both flaccid and erect; shortening with and without an erection; plaque or indurated areas in the penis; and, in many patients, erectile dysfunction. On physical examination, virtually all patients have either a well-defined plaque or an area of induration that is palpable. The plaque is usually on the dorsal surface of the penis, intimately associated with the insertion of the septal fibers. Patients not uncommonly can remain sexually active with significant dorsal curvature (up to 45 degrees). Patients with lateral components or ventral Peyronie's disease tolerate the deformity far less well. Mulhall's analysis of the natural history of Peyronie's disease in a group of men who avoided treatment but were observed carefully documents the frequent occurrence of penile shortening in this population (O'Brien et al, 2004).

An interesting variant of Peyronie's disease has been reported by Brock, who has coined the term *septal-only Peyronie's disease*. In his description (cited in Bella, 2007), patients had nonpalpable scarring of the penile septum that caused deformity of the erect penis. In the authors' experience there is palpable scarring; however, the scarring appears to be in the substance of the corpora cavernosa as opposed to the tunica albuginea associated with the insertion as is usually seen. In septal-only disease, the authors have found it difficult to tell whether the scarring is indeed Peyronie's disease or perhaps a Peyronie's lookalike. Fortunately, tumors of the erectile tissue of the corpora cavernosa are quite rare, but it is the authors' practice to evaluate these patients with magnetic resonance imaging (MRI).

Pain may be persistent in the inflammatory stage of the disease; it is usually not severe, but it can interfere with sexual function. Some patients also complain of being awakened in the morning or at night with pain during erection. **Spontaneous improvement in pain virtually always occurs as the inflammation resolves.** A small group of patients with extensive disease will have "circumferential plaques" and an unstable penis owing to the resulting hinge effect. Most patients complain of distal flaccidity. In dynamic infusion cavernosometry and cavernosography it was found, however, that the pressures were equal proximal and distal to the plaque (Jordan and Angermeier, 1993). Opinions vary with regard to the cause of distal tip flaccidity; one ultrasound study seemingly showed cavernosal fibrosis that ostensibly could interfere with distal perfusion of the corpus cavernosum (Ralph et al, 1992). However, in the authors' experience, the fibrotic process is limited to the tunica albuginea, although the process can clearly involve the septal fibers and thicken them appreciably. Thus there is no corroboration of the finding of diffuse cavernosal fibrosis when these patients are taken to the operating room (Ralph et al, 1996).

EVALUATION OF THE PATIENT

When the urologist is confronted with the patient with Peyronie's disease the medical history should include the mode of onset (sudden vs. gradual) and time at onset. The course of disease is helpful with regard to determining the phase the patient is in. The history is obtained of prior penile surgery, urethral instrumentation or external trauma, medication or drug abuse, and fibromatosis including Dupuytren disease and Ledderhose disease. Family history of the other fibromatoses is revealing. **Because most patients with Peyronie's disease have an element or at least the aura of erectile dysfunction, risk factors for erectile dysfunction should also be assessed.** The recent literature suggests that erectile dysfunction may be a sensitive hallmark of many vasculopathic conditions. Endothelial dysfunction is an important abnormality contributing to a decrease in penile vascular responses to sexual stimuli. Vascular disease has been shown to be the most common cause of erectile dysfunction. Cardiovascular disease and erectile dysfunction share a host of risk factors, including age, smoking, hyperlipidemia, hypertension, and diabetes mellitus. Furthermore, the severity of coronary artery disease has been shown to correlate with the severity of erectile dysfunction (Feldman et al, 1994; Greenstein et al, 1997; Lue, 2000; Martin-Morales et al, 2001; Roumeguere et al, 2003). Thus, in addition to trying to glean factors from the patient about smoking, hypertension, diabetes mellitus, and other suggestions of vascular disease, the inquiries must also extend to the patient's family with regard to those same issues. Likewise, because a few of these patients will require surgery, the surgeon must carefully assess the need for screening with regard to a patient's total vascular health.

A detailed psychosexual history is imperative. In the authors' opinion, photographs of the patient's erect penis are helpful in identifying the direction of curvature and degree of curvature and they provide some information about the patient's erectile function.

The penis should be examined on stretch. This amplifies the plaque and often allows the examiner to feel plaques that are not obvious when the penis is examined in the nonerect state. The location and size of the plaque as well as the consistency (e.g., tender, indurated) are better defined. Most of the recent clinical trials examining intralesional injection have included a diagram in the chart. The diagram illustrates the plaque or plaques both longitudinally and in cross section. Most of these protocols emphasize the need to measure total penile length (pubis to mid glans coronal margin) as well as length of the plaque. It can certainly be argued that measuring the length of the plaque really does not offer much clinical information because plaques that are indurated tend to feel much larger and more prominent than mature plaques; thus the actual diagram of the plaque may be more useful in tracking the course of the disease. The hands and feet must be examined; and in the rare patient examination of the ears will identify tympanosclerosis. Although many patients will have thickening in the palmar area of the dominant hand, except in manual laborers, callus formation in the palmar area of the nondominant hand is indicative of noncontractile Dupuytren disease. Contractile Dupuytren disease is obvious. Examination of the feet for Ledderhose disease often will reveal nodules compatible with plantar fascial involvement. Whether Ledderhose disease is just a manifestation of plantar fasciitis remains to be seen, and certainly the authors' experience would suggest that in the current American population an element of plantar fasciitis is almost a ubiquitous finding in well more than half of men older than age 50 years.

Imaging of the plaque is important for one purpose only, that is, the demonstration of calcification. Imaging to record plaque size is probably as useful as measuring plaque size and recording it on a diagram. **Demonstration of calcification is easily**

accomplished with ultrasound examination. The calcified plaque will be shown as shadowed areas (Fig. 28–6). The plaque itself will be prominently imaged (Altaffer and Jordan, 1981; Balconi et al, 1988; Hauck et al, 2003a). **Plain radiography is also equally effective in demonstrating calcification within the plaque** (Fig. 28–7). The authors use a high-definition film (Kodak X-Omat ready-pack 8 × 10). This is accurate in imaging the calcification and allows minimal radiation exposure (20 mA at 49 kV). The testes are shielded with a lead sheet. Zero radiography is an effective way of demonstrating the plaque; however, the technology is not readily available with the increase in other imaging modalities. **Computed tomography has no place in the examination of the penis for Peyronie's disease.** However, MRI, which does not effectively demonstrate plaque calcification, does image the plaque well. **There is not universal agreement about the use of MRI for imaging of the plaque** (Helweg et al, 1992; Vosshenrich et al, 1995; Andresen et al, 1998; Hauck et al, 2003a; Moncada, 2003; Perovic, 2003). In the authors' opinion, at present, MRI evaluation is probably excessive; however, for the purposes of assessing the results of clinical trials MRI may have a place.



Figure 28–6. B-mode ultrasound examination of calcified Peyronie's plaque. The plaque is imaged as an echodense area (1); the area of calcification is accompanied by shadowing (2).

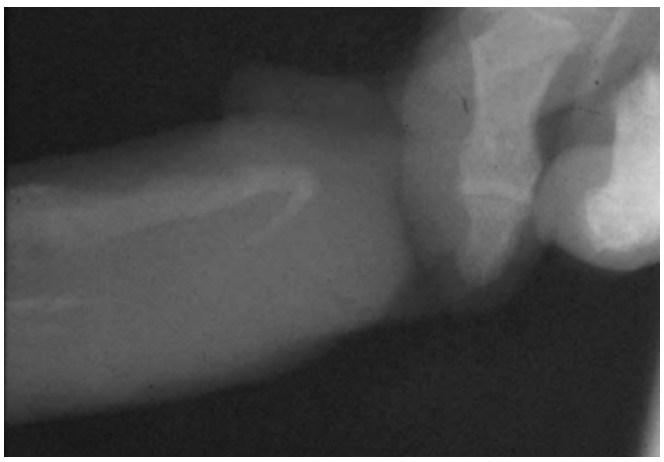


Figure 28–7. Radiograph of an extensively calcified dorsal plaque.

The place of vascular testing is not clearly defined. Currently the use of vascular testing is variable. Some centers perform duplex ultrasound testing on all patients with Peyronie's disease; other centers do not perform vascular testing at all, despite that patients are routinely operated on for Peyronie's disease and, in some cases, receive prostheses as the primary treatment option (Kendirci et al, 2004, 2005; Pak et al, 2004). At the authors' center, vascular testing is done on all patients who are prospective surgical candidates and who indicate motivation for the option of surgery. Initially, these patients are examined with color Doppler ultrasonography. If the peak systolic velocity, end-diastolic velocity, and resistive index are normal the patients are not further tested. If the end-diastolic velocity and the resistive indices are not normal, the patients are tested with dynamic infusion cavernosometry and cavernosography. Our studies have reported that there is a linear association between preoperative erectile function and postoperative results (Jordan and Angermeier, 1993). The authors thus lean heavily on these results in discussing potential options for surgical management. One group of patients whose results are clear outliers are those with ventral Peyronie's disease. As mentioned, in the authors' experience and that of many others, patients with ventral Peyronie's disease do not do well with surgery that involves grafting. In Hellstrom's analysis of the relationship of penile deformity to the vascular status of Peyronie's patients, patients with ventral curvature have the greatest likelihood of having cavernous veno-occlusive dysfunction (Lowsley and Boyce, 1950; Jordan and Angermeier, 1993; Kendirci et al, 2005).

There are a number of proposed treatment protocols or algorithms. The original classification system proposed by Kelami sought to include all categories of importance in evaluation of the patient with Peyronie's disease. Indeed, most of the important entities were included with the exception of erectile dysfunction (Kelami, 1983). In 1993, Gelbard, as part of the original collagenase intralesional injection protocol, used a modification of the Kelami classification. Several other treatment algorithms have been proposed (Gelbard, 1993; Novak et al, 2001; Levine and Greenfield, 2003; Bokarica et al, 2005; Viviano and Honig, 2005). It is imperative to understand that these algorithms serve only as guidelines. **Individualization with regard to patients' requirements and their findings and assessments is imperative.** This individualization will allow us to determine which patients require only reassurance, which need vigorous investigation, which are appropriately treated with medical management, and which few patients are appropriately treated with surgery. Shabsigh and colleagues (2003) published a Peyronie's disease index that is derived from a standardized patient questionnaire. That questionnaire seeks to specifically address issues most pertinent to the patient with Peyronie's disease. Issues such as duration of disease, recollection of injury, and presenting symptom or symptoms are addressed. Strategies to ideally assess degree and direction of curvature could include the use of visual analog scales. In association with future studies to examine intralesional injection protocols, a validated questionnaire has been developed. Interviews with Peyronie's disease patients have highlighted areas of concern, and the questions have been or are in the process of being validated for various populations (Moncala-Iribarren et al, 2004; Fragas, 2004; Rosen et al, 2008).

Key Points: Evaluation of the Patient

- Patients with Peyronie's disease present with a variety of deformities of the penis. In addition, most have noted an indurated area in the penis that has been identified as the plaque. Many patients have noticed erectile dysfunction. It is important to understand that pain with erection, if it is present, inevitably disappears as patients progress to the quiescent stage. It is not unusual for the deformities to be migratory before stabilizing.
- All patients must be evaluated with a medical history as well as a detailed psychosexual history. Approximately one third of the patients will develop dystrophic calcification in the plaque that can be demonstrated by ultrasonography or plain radiography. The place for MRI in the evaluation of Peyronie's plaque has not been defined, nor has the place for vascular testing been clearly defined. However, most investigators now would agree that in patients who are to be operated on, vascular testing to stratify the vascular parameters of erectile function is a necessity. Once all of the data have been assembled, individualization with regard to the patient's requirements, findings, and assessment is imperative.

MANAGEMENT

Medical Management

Any section on the medical management of Peyronie's disease must begin with the disclaimer that few medical methods of management have been subjected to double-blind drug testing. The use of vitamin E was proposed by Scardino and Scott (1949). Vitamin E, a tocopherol, is an antioxidant. In 1983, Pryor and Farrell convened a randomly allocated placebo-controlled study. Men were randomized to vitamin E, 200 mg three times a day, versus placebo for a 3-month course. Basic disease status was assessed, with particular emphasis on pain and deformity. In that study, no difference was found between vitamin E and placebo. In 1990 Gelbard and associates also conducted a controlled study, and again that study failed to demonstrate any significant difference between vitamin E and placebo with regard to overall disease status and in particular pain and curvature. A placebo-controlled study comparing vitamin E and propionyl-L-carnitine, separately or in combination, showed no significant improvement in pain, curvature, or plaque size in patients with Peyronie's disease (Safarinejad et al, 2007). That said, however, vitamin E is inexpensive and probably safe. Recent cautions have been raised about the use of high-dose vitamin E. It has long been recognized that vitamin E in high dose, in some individuals, can have a significant warfarin effect. Interestingly, however, in the moderate dose range, vitamin E has been implicated as causing thrombolytic phenomena and thus is of concern to cardiologists and neurologists. If one chooses to use vitamin E for Peyronie's disease it should be used in divided doses of 800 to 1000 units a day. Treatment should be continued for no longer than 3 to 6 months, and patients must be cautioned about the possibility of anticoagulative side effects and/or thrombolytic effects. Should they notice anticoagulative effects, the vitamin E should be stopped and the physician should be notified. As mentioned, in addition, concerns have been raised about general cardiac health and vitamin E. That stated, it is still probably a reasonable treatment to initiate during the early phases of the disease.

Zarafonetis and Horrax (1959) published an article on the use of potassium aminobenzoate (Potaba). This drug has been looked at in a small blinded study that showed it to be efficacious (Hasche-Klunder, 1978). Two subsequent reports examining the use of potassium aminobenzoate for Peyronie's disease have been published. First, a multicenter study with random allocation between 12 g of *p*-aminobenzoate and matching placebo showed little benefit to treatment with the exception possibly of improving pain (Shah et al, 1983). A subsequent randomized placebo-controlled double-blind prospective multicenter trial showed no improvement with regard to pain but less worsening of other symptoms. A study by Weidner and colleagues (2005) enrolled 103 patients, with 75 completing follow-up. Many were excluded because of side effects (predominantly gastrointestinal side effects) or noncompliance for reasons not stated. Fifty-one patients were randomized against 52 patients receiving placebo control. Patients received potassium aminobenzoate or placebo at a dose of 3 g, four times a day. End points studied were plaque regression and reduction of curvature. No reduction in curvature was noted; however, regression of plaque size was noted to be significantly better in the treatment group. Interestingly, progression of curvature or "deterioration of disease" was noted at a significantly increased rate in the placebo group. The dosage of potassium aminobenzoate is 12 g/day in 4 to 6 doses. The literature supports the fact that **potassium aminobenzoate is poorly tolerated by many patients because of gastrointestinal upset and is relatively expensive. The use of potassium aminobenzoate cannot be strongly advocated on the basis of the evidence to date.**

Jordan (personal experience) has used terfenadine (Seldane) and now fexofenadine (Allegra). Its use is clearly anecdotal. It is used as a nonspecific antihistamine and has been used in patients who have had an unusually long, painful course. The medication is expensive; it is well tolerated and, if used, should be in a dosage of 60 mg twice a day.

Ralph and coworkers (1992) have suggested the use of oral tamoxifen. Tamoxifen, it is believed, facilitates the release of TGF-β from fibroblasts. Teloken and coworkers (1996, 1999), **in a small controlled report, used tamoxifen versus a placebo and did not demonstrate a therapeutic advantage.** Should one desire to prescribe tamoxifen, it is used at a dosage of 20 mg twice daily.

The use of colchicine was originally proposed by Gelbard (personal communication, 1995). There are no blinded or controlled studies that have examined the use of colchicine. Akkus and coworkers (1994), in an uncontrolled study of 24 patients, reported some efficaciousness for colchicine. The patients were in the early phase of disease and received colchicine at a dose of 0.6 mg three times a day. **In that study, diminished plaque size and improved penile curvature were reported in approximately 50% of the patients.** Four actions are attributed to colchicine. Colchicine binds tubulin and causes it to depolymerize; thus, it inhibits mobility and adhesion of leukocytes as well as wound contracture. It inhibits cell mitosis by disrupting spindle cell fibers and thus functions as a potent anti-inflammatory agent. It blocks the lipoxygenase pathway of arachidonic acid metabolism, furthering its anti-inflammatory effect. It interferes with the transcellular movement of protocollagen. Colchicine is reasonably well tolerated. Approximately one third of patients, however, will have diarrhea. It is inexpensive. If it is used, the dosage is 0.6 mg three times per day with meals.

Biagiotti and Cavallini (2001) convened a study of 48 patients with Peyronie's disease, approximately one third in the acute phase and two thirds in the chronic phase. The groups were randomized between tamoxifen, 20 mg twice daily for 3 months, and acetyl-L-carnitine, 1 g twice daily for 3 months. Oral carnitine is thought to have several mechanisms of action involving free radical metabolism. It has been useful in degenerative oxidative diseases and vasculitides. **The authors found that the carnitine was more effective in reducing pain and seemed to inhibit disease progression. Thus they thought it was more effective and safer than tamoxifen in the treatment of Peyronie's disease.** Propionyl-L-carnitine in the same dose can also be used for oral therapy.

Nonsteroidal anti-inflammatory drugs and corticosteroids have been used anecdotally on the basis of the belief that inflammation is integral to the development of Peyronie's disease. No studies support an indication for the use of these drugs.

A number of intralesional injection protocols have been examined. Teasley (1954) reported the use of intralesional corticosteroids, as did others (Bodner et al, 1954). **It is the recommendation of the consensus committee on penile curvatures that the use of intralesional corticosteroids be eliminated or at least initiated with extreme caution because of the significant local side effects, the inconsistent pattern of improvement in well-established curvature, the lack of studies showing proven efficacy, and the reports of patients who believed that their condition deteriorated after the injections** (Jardin et al, 2000).

The calcium antagonist verapamil was first used as intralesional therapy by Levine and colleagues (1994). Verapamil is thought to have efficacy on the basis of its ability to inhibit the exocytosis of collagen, fibronectin, and glycosaminoglycans. This inhibition works at the basic metabolic step involved with the manufacture of collagen and hence is thought to inhibit the ultimate formation of scar. Since that report, several observational studies have been performed. **A single-blind controlled study comparing verapamil with saline showed a diminished plaque volume but no change in deformity** (Rehman et al, 1998). **In a prospective study of 156 patients, of those who completed the protocol 60% had a decrease in curvature and 80% reported improvement in tip flaccidity** (Levine et al, 2002). A number of injection protocols have been discussed. A "full course" could consist of 12 injections (10 mg/10 mL) given once every 2 weeks, although Cavallini and colleagues (2002) showed that patients receiving verapamil, 10 mg/20 mL, had significant improvement in plaque size and penile curvature compared with 10 mg/10 mL. In many hands, up to that total dose, injections are discontinued when satisfactory improvement is noted. Patients must understand that improvement may not be noted immediately, and hence they must be prepared to proceed with the entire 12-injection series. **The use of intralesional verapamil for patients with acute disease is thought reasonable on the basis of the available data to date. At the authors' center they have combined intralesional injection of verapamil with daily use of a vacuum erection device and have noted improved outcomes compared with using each individually. At present, however, these findings are anecdotal at best and need to be substantiated with controlled studies.**

The use of purified clostridial collagenase was first studied in vitro by Gelbard and associates (1982, 1983, 1993). Collagenase is a naturally occurring enzyme that has been found to be intimately involved with the process of scar remodeling. Simply stated, the use of collagenase as an intralesional agent is thought to create "chemical incisions," thus initiating areas of remodeling. **Collagenase has since been subjected to two double-blind studies and an additional small pilot study using intralesional collagenase combined with modeling** (Gelbard, 1993; Glina et al, 2007). **In that study, 25 patients were enrolled and were treated with three intralesional injections of 10,000 in 0.25 mL over 7 to 10 days. A significant decrease from baseline was seen in mean deviation angle and plaque length and width at 3 and 6 months; it also was noted that more than 50% of patients were much improved** (Glina et al, 2007). **Ten patients were enrolled, and 9 completed follow-up; improvement was noted in curvature in all 9, as judged by photographs submitted at intervals by the patients and questionnaire end points** (Jordan, unpublished). A double-blind, placebo-controlled, multicenter study has just been completed but the data are not yet available. Intralesional collagenase is thus currently available only on study protocol.

The use of interferons as intralesional therapy for Peyronie's disease was reported in 1991 by Duncan and associates. Interferons are thought to have action based on their abilities to inhibit the synthesis of collagen, fibronectin, and glycosaminoglycans (Hakim and Khater, 2004). Thus, the mechanism of action of interferon is thought to be similar to that proposed for verapamil. An observational study using interferon alfa enrolled 35 patients. Some of the patients received a 12-week course and some a 24-week course. **Seventy-five percent of the patients reported treatment satisfaction as judged by improvement in their ability to have intercourse.** The authors thought that treatment with interferon can be done safely and is reasonable to offer patients (Hellstrom et al, 2006).

A number of topical therapies have been reported, with delivery often combined with iontophoresis or electromotive therapy. Agents used are orgotein (recently withdrawn from all markets), steroids, verapamil, and β-aminopropionitrile, either singly or as "cocktails." A single blinded study showed efficacy for verapamil. Further studies have not verified the findings of that study (Montorsi et al, 2000a; Levine et al, 2002; Fitch et al, 2007). These are only single observational reports. Corticosteroids have been used in association with ultrasound (iontophoresis). Again, no blinded studies have shown statistical improvement.

Radiation therapy has been proposed as a treatment of Peyronie's disease. In recent years, radiation therapy was proposed for the treatment of pain that was thought to be "abnormally persistent." In 1975, a retrospective study examined the use of radiation therapy and found it to be no more effective than "no treatment." **It is the consensus of the World Health Organization committee that radiation therapy be avoided because of potential risk of malignant change and the potential for increasing the risk of erectile dysfunction in aging patients** (Lue et al, 2004).

Extracorporeal shockwave therapy has been proposed as a treatment of Peyronie's disease since 1989 (Lebret et al, 2002). There has been little standardization with regard to the treatment (varying dosages and machines) (Butz and Teichert, 1998; Colombo et al, 1999; Gianneo et al, 1999; Lebret et al, 2002; Manikandan et al, 2002; Sytenko, 2004). **There are no controlled trials, but one case-controlled trial reported favorable results** (Hauck et al, 2000). No studies examining the efficacy of extracorporeal shockwave lithotripsy in the treatment of Peyronie's disease have been convened in the United States.

The vacuum erection device or traction devices have been proposed as a treatment of Peyronie's disease. Kirsch-Noir and coworkers (2004) examined six patients with Peyronie's disease treated with the vacuum erection device and concluded that the vacuum device might limit penile fibrosis, but no comment was made concerning plaque volume or curvature. Verheyden is quoted as stating that in a series of patients treated with vacuum therapy for Peyronie's disease at the Andrology Unit, Department of Urology, Antwerp, Belgium, more than 50% stated that their plaques softened and they noted improvement in curvature (Augusta Medical Systems, product information, 2005). Moncada (2007) has examined the use of penile traction in both the preoperative and postoperative patient with Peyronie's disease. He believes strongly that, with grafting surgery, traction to keep the graft distended is essential to maximizing results.

Levine, in 2008, looked at penile traction therapy as a treatment for patients with Peyronie's disease in 10 patients. All patients noted subjective improvement in curvature penile length and girth; objective improvements were seen in reduction in curvature (average 33%), increased penile stretched length, and improvement in IIEF. **Treatment of Peyronie's disease with the vacuum erection or penile traction device alone thus has not been adequately studied.**

A number of studies have examined combined medical management. These include a study of intralesional injection and oral therapy with interferon alfa-2b plus vitamin E (Novak et al, 2001). Another study examined the use of oral vitamin E plus colchicine (Prieto Castro et al, 2003), and another series of studies of intralesional injection and oral therapy looked at the combination of verapamil with carnitine and verapamil with tamoxifen (Cavallini et al, 2002). These single observational studies represent the thrust of current work with regard to medical management. Rajfer has proposed the use of PDE5 inhibitors. As briefly discussed earlier there is an interplay between oxidative and nitrosative mechanisms in fibrosis that is not restricted to Peyronie's disease fibroblasts. cGMP, the mediator of penile erection, is produced by nitric oxide activation of guanylate cyclase, which is also antifibrotic in Peyronie's disease plaques. Long-term administration of sildenafil, a phosphodiesterase inhibitor that impedes guanosine monophosphate breakdown, has prevented Peyronie's disease plaque formation in rat models (Gonzalez-Cadavid and Rajfer, 2005). Unfortunately, in the authors' opinion, the future of nonoperative therapy in Peyronie's disease lies in multimodal therapy. However, such studies probably have little hope of being accomplished within the confines of U.S. Food and Drug Administration oversight.

Key Points: Medical Management

- The efficacy of medical management of Peyronie's disease is difficult to determine because, in the past, few studies were properly done. Vitamin E has been used historically. Potassium aminobenzoate, in a small study, was found to reduce plaque size, not curvature, and thus in that study was found "efficacious." However, the side effects make it difficult to tolerate. From an intellectual standpoint, the use of colchicine makes a great deal of sense in patients with Peyronie's disease who are in the acute phase. For the most part, colchicine is reasonably well tolerated. Tamoxifen, in a small controlled study, was not found to demonstrate any therapeutic advantage. The neutraceutical carnitine, in either its propionyl or acetyl ester, in preliminary studies was thought to be effective for certain disease parameters.
- A number of intralesional protocols have been proposed. The use of verapamil as an intralesional agent has been studied. A prospective study did show decrease in curvature in about 80% of the patients. The use of collagenase as an intralesional agent has been subjected to a number of double-blind placebo-controlled protocols, and, in all, efficacy was suggested. However, collagenase is currently available only as part of clinical trials.
- Radiation therapy should be avoided.
- The vacuum erection device has not been adequately studied.
- Penile traction has not been adequately studied.
- The place of extracorporeal shockwave therapy has likewise not been adequately determined.

Surgical Management

For a patient to be a surgical candidate his disease must be stable and mature. In review, the signs of disease stability (quiescence) include resolution of pain and stabilization of curvature or other deformity. Likewise, the experienced examiner will recognize the palpatory findings of a mature plaque. Most investigators arbitrarily impose a 12- to 18-month period from onset of disease. Most suggest a period of at least 6 months of disease stability (i.e., stable deformity). Indications for surgery include deformity that precludes intercourse and/or erectile dysfunction that precludes intercourse.

Surgical Correction of Peyronie's Disease

A number of surgical procedures have been used for the straightening of the deformity of Peyronie's disease. Pryor and Fitzpatrick (1979) described a procedure of excision and plicating closure of the aspect opposite the Peyronie's lesion. This procedure counteracted the effects of the inelastic lesion by shortening the opposite, more compliant aspect of the corpora cavernosa.

Lue performs a correction in which he omits the excision of the tunica albuginea and merely plicates the opposite aspect of the corpora cavernosa (Akkus et al, 1997; Gholami and Lue, 2002). Although this technique historically did not yield durable results in patients with congenital curvature, in the patient with Peyronie's disease, in whom accumulated intracavernosal pressures are probably less, it possibly can be expected to be more effective. Lue emphasizes the use of permanent suture that is "loosely tied" to correct the deformity. Although the techniques of both Pryor and Fitzpatrick (1979) and Lue are valid in some patients, many patients are already concerned by the shortening of their penis as a result of Peyronie's disease; thus, surgery that offers the suggestion of further shortening of the penis is unacceptable to them. The use of permanent suture as described by Lue is also not well accepted by some patients.

The procedure described by Yachia (1993) (see Chapter 36) represents a corporoplasty technique that can be effectively used for curvatures associated with Peyronie's disease. Plication and corporoplasty techniques seem to be useful especially for patients with associated erectile dysfunction, in whom grafting procedures could be expected to cause further deterioration of erectile function. The authors rely on this procedure for those patients with ventral curvature for reasons already discussed. The perceived shortening associated with these procedures in a number of studies, in properly selected patients, is not clinically significant

(Klevmark et al, 1994; Nooter et al, 1994; Sulaiman and Gingell, 1994; Kummerling and Schubert, 1995; Poulson and Kikeby, 1995; Ralph et al, 1995; Porst, 1997; Savoca et al, 2000; Chahal et al, 2001; Gholami and Lue, 2002; Van Drift et al, 2002; Lucas et al, 2004; Seipp and Schukfeh, 2004).

Gelbard (1989) described a surgical technique that involved incising the plaque of Peyronie's disease. He reported a series of patients in whom incisions were made in the plaque and grafts of temporalis fascia were used to fill the defects. His technique was based on the theory that by making a number of incisions, thus expanding the scar, and then filling them with compliant material, a smoother correction of curvature would result. He has reported good results with this procedure.

Das and Amar (1982) described a procedure in which the plaque is excised and the corporotomy defect is grafted with tunica vaginalis. They believed that the tunica vaginalis is an easy donor site for the urologist and that it gives the same results as the dermal graft. The authors' experience has been that tunica vaginalis is a suitable substitute for dermis in select patients with well-defined, small lesions. In patients in whom the corporotomy defect is large, however, the authors have not been pleased with the use of tunica vaginalis. A report has described tunica vaginalis double folded to limit the problem with larger corporotomy defects. In an observational series the authors reported acceptable results (Geavlete et al, 2004).

Lockhart has employed a procedure in which the plaque is excised and the corporotomy defect is closed with tunica vaginalis as an island based on a dartos fascial and cremasteric flap (cited in Helal et al, 1995). He found that his results were better with the improved vascularity of the tunica vaginalis transposed as a paddle on a flap.

Buncke (cited in Stefanovic et al, 1994) reported an experimental animal series in which the lesion is excised and the corporotomy defect is replaced with temporalis fascia transferred to the area of the penis as a microvascular free transfer flap. To date, this procedure has not been reported in humans.

El-Sakka and colleagues (1998b) have also described a procedure using incisions but patching the corporotomy defects with vein grafts. They initially believed that the excised deep dorsal vein provided an adequate donor site for the vein grafts. With time, however, it was found that the donor site offered inadequate amounts of donor tissue, and later the saphenous vein was harvested to design the vein graft patches. Lue believes that the intracorporeal space represents a large vessel and therefore a patch of vessel wall represents a physiologic procedure (Brock et al, 1993). He reports good results with this procedure. Montorsi and colleagues (2000b) reported a series of 50 men treated with plaque incision and vein grafting for Peyronie's disease. All patients were evaluated preoperatively with sexual history, examination, determination of penile length and degree of curvature, dynamic color power Doppler ultrasonography of the penile vessels, and three nights of nocturnal RigiScan. All were evaluated postoperatively with the same variables, including color duplex sonography and RigiScan. These researchers reported either complete or adequate straightening in 94% of patients. Penile rigidity was equal to that preoperatively in 94% of patients. Power Doppler imaging showed vascular impairment in 10% of patients, and RigiScan revealed significant decrease in nightly erections in 10% of patients. They concluded, thus, that plaque incision with vein grafting achieved satisfactory results in the majority of patients with severe and stable Peyronie's disease who have intact penile rigidity preoperatively. Akkus and colleagues (2001) quoted a series of 58 patients who were similarly evaluated with history, counseling, and duplex ultrasound examination. They reported complete or adequate straightening in 95% of patients and preservation of preoperative erectile function in 93%. They concluded that plaque incision with venous patch grafting is a satisfactory surgical method for the treatment of the curvature in Peyronie's disease.

Krishnamurti (1995) reported the use of de-epithelialized penile skin as a paddle carried on the dartos fascia. He cited increased dependability of flaps, not a fact that is totally validated in the literature. The authors have attempted to "de-epithelialize" penile skin with the dermabrader as described by Krishnamurti. However, histologic evaluation of these "de-epithelialized islands" actually shows many areas where the entire thickness of the skin has been removed. Thus, in the authors' minds, the precise histologic composition of Krishnamurti's de-epithelialized islands is not clear.

Hellstrom (1994) has reported the use of a number of nonautologous grafts. Hellstrom and Reddy (2000) reported the use of cadaver pericardium in a small series. Chun and associates (2001) compared the results of plaque incision or excision and grafting with either dermal or cadaveric pericardial graft techniques, and they suggest that the minimal preoperative preparation and decreased patient morbidity with cadaveric pericardium makes it a more efficacious and appropriate graft compared with dermis. They do not report that the graft provides clinical results superior to those of dermis. Levine and Estrada, in 2003, reported results of the use of human cadaveric pericardial graft for the surgical correction of Peyronie's disease in a retrospective evaluation of 40 men. Postoperatively, all patients reported sufficient rigid erection for coitus after the procedure; however, many required intracorporeal injection of papaverine. Thus, a 98% success with penile straightening and a 95% success with intercourse as previously described were reported; 70% of the patients had unaided full erections, and 30% required pharmacologic assistance. Palese and Burnett (2001) reported the use of pericardial allograft in patients requiring complex penile prosthetic surgery. Hellstrom thought that the pericardial graft essentially serves as an inert collagen matrix or scaffold for the adjoining tunica albuginea. As the graft is overgrown or ingrown and the new tissues are vascularized, the graft is enzymatically dissolved (Leungwattanakij et al, 2001). Egydio and colleagues (2002) reported the results of their series using plaque incision with bovine pericardial graft; they described 33 patients. It is unclear in the report how the patients were stratified preoperatively with regard to erectile function. They reported a good correction of deformity in 88% of cases with adequate correction in the rest of their series, and they stated that all recovered their ability to "penetrate with no difficulty." They thus think that the procedure is an effective one.

Knoll, in 2001, reported the use of a porcine small intestinal submucosal graft in the surgical management of Peyronie's disease. His initial report was of 12 patients, the majority of whom had adequate straightening and adequate preservation of erectile function. He later described 162 patients with curvatures of 60 degrees or more secondary to Peyronie's disease. Some patients were preoperatively stratified with color Doppler ultrasonography; the majority were evaluated with examination by intracavernous injection. Knoll reported successful correction of curvature in 91% of patients. Mean follow-up was 38 months. Preservation of erectile function is not clearly stated. Although results appear promising with a small intestinal submucosal graft (Knoll, 2003) there have been others who have not experienced the same success. Breyer and colleagues reported on 19 patients who underwent tunical grafting with a 1-ply small intestinal submucosal graft and found a recurrence of the curvature in 37% of patients and a recurrence of the Peyronie's plaque in 26%. Their complication rate was 37%,

with 26% of patients having a hematoma at the graft site and 5% developing graft infection. As the authors began to use this grafting procedure more and dermal grafts less, they were interested in comparing results. Fifty-eight patients were evaluated, and these patients all had an identical operation for their Peyronie's disease, but some had a small intestinal submucosal graft and some had a dermal graft. The patient ages were relatively matched, as was the mean degree of penile curvature. At the time of the analysis, 15 patients had the small intestinal submucosal graft and 45 had been treated with a dermal graft. The series was small, but dermal and small intestinal submucosal grafts in this analysis had equivalent success rates. Obviously the use of the small intestinal submucosal graft saved operative time and avoided donor site morbidity. Throughout the entire group, 91% were satisfied with the results of their surgery (Eltahawy, 2006). The authors believe that the small intestinal submucosal graft offers a good alternative, but larger and longer studies are needed. In the authors' experience foreign material "grafts" (e.g., Silastic, Gore-Tex, Dacron), in the absence of concomitant prosthetic implantation, inevitably yield poor results (Devine, 1997; Brannigan et al, 1998).

Devine and Horton (1974) described a procedure for correction of deformity of Peyronie's disease in which the plaque is excised and replaced with a dermal graft. This procedure continues to be used selectively in the authors' center. The use of dermal graft for corporoplasty has been variously applied. Austoni and coworkers (1995) reported a large series of 418 men. In this series, 17% required further surgery for curvature and 20% had troublesome postoperative erectile dysfunction. However, what one must realize is that Austoni and coworkers used an aggressive dissection of the penis, in many patients disassembling the glans from the tip of the corporeal bodies. Thus the results may not be a fair representation of the procedure of excision of Peyronie's plaque with dermal graft in general. The World Health Organization consensus (Lue et al, 2004) reports that the operation of excision of Peyronie's plaque with dermal graft is regarded as outmoded. The authors disagree. The procedure selectively still has use; however, there are many suitable alternatives.

In addition, the authors now have a relatively large series of patients who have been treated by incisions through the plaque and patching of the corporotomy defects with dermis. With the exception of those patients with severely calcified plaques, the authors have preferentially used the technique of incision with dermal grafting and more recently with porcine intestinal submucosal grafting. Early results indicate that the technique of plaque incision is at least as successful as the technique of plaque excision; however, it has not yet been determined whether there is a difference between the techniques with regard to preservation of erectile function or limitation of graft-induced veno-occlusive dysfunction. Likewise, early analysis, as described previously, of the porcine intestinal submucosal graft has been promising. The advantage of an off-the-shelf graft cannot be overemphasized.

The initial skin incision is dependent on the location of the lesion or the location of the proposed intervention; patients with ventral plaques or those who will have corporeal plication can be approached through a midline incision of the ventral aspect of the penis, and dorsal plaques are most effectively approached by a circumferential incision. In the patient who has been previously circumcised the incision should be placed through the original circumcision incision (Fig. 28–8). In many patients the circumcision scar may be displaced far down the shaft of the penis. The authors have not encountered any problems, however, with reapproaching the penis through the circumcising incision, even when this is the case.

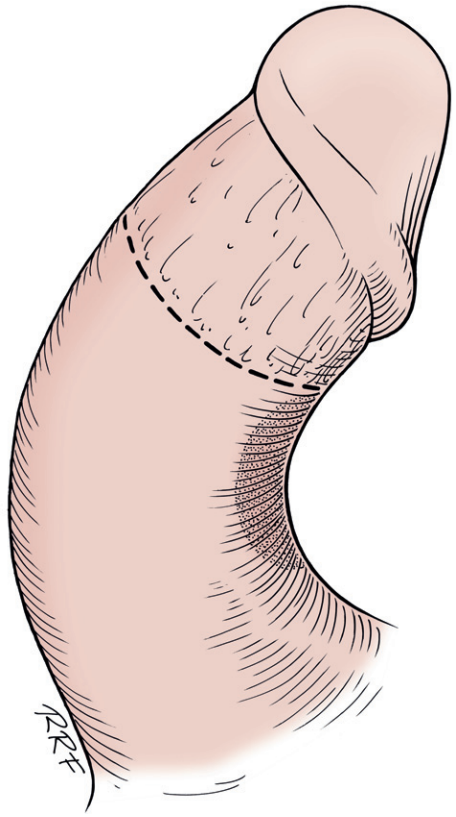


Figure 28–8. An erection demonstrates the dorsal curvature of the penis caused by the inelastic scar tissue in a dorsal plaque of Peyronie's disease. The incision to be made in the scar of the previous circumcision has been marked.

The shaft of the penis is then degloved to its base. This maneuver gives good exposure for midshaft and distal lesions. For proximal plaques or in patients who have relatively redundant foreskin, a second peripenile periscrotal incision is made. After the shaft of the penis is degloved it is delivered into the periscrotal incision; the shaft skin is laid aside and covered with a warm sponge. This protects the penile skin from trauma until the end of the procedure, when it is returned to the shaft. Optionally, a counterincision can be made at the penoscrotal junction in the scrotal raphe.

The dorsal neurovascular bundle is elevated in concert with the Buck fascia. This can be accomplished by several techniques. Incisions can be made just lateral to the corpus spongiosum, with the Buck fascia and the dorsal neurovascular bundle dissected off the lateral and dorsal aspects of the corpora cavernosa. Alternatively, the authors currently approach dorsal plaques by dissecting sharply through the bed of the deep dorsal vein and perform a modified vein dissection (Figs. 28–9 to 28–12). Initially this approach was used to investigate the potential effect of a modified vein dissection with regard to limitation of graft-induced veno-occlusive dysfunction. Although the beneficial effects of this are yet to be proved, approaching the dorsal plaque through the bed of the dorsal vein appears to be a superior approach technically.

In the past, if preoperative testing suggested veno-occlusive dysfunction, the authors proceeded with a formal vein dissection, ligation, and excision. More recent experience has shown, however, that vein dissection does not offer durable results in patients with Peyronie's disease, and it is currently believed that patients who demonstrate severe veno-occlusive dysfunction are better treated by a surgical approach or modeling to straighten the

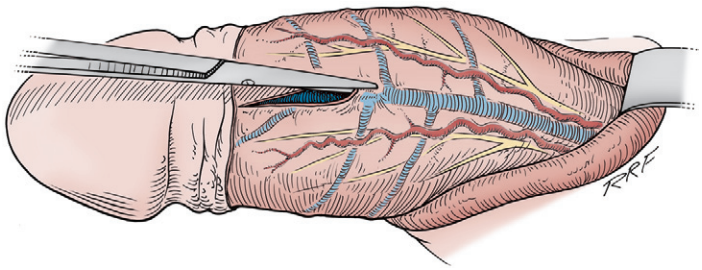


Figure 28–9. The skin has been degloved to the base of the penis by dissection in the layer immediately superficial to the Buck fascia. An incision in the dorsal midline of the Buck fascia exposes the deep dorsal vein. The coiled dorsal arteries and the circumflex veins are demonstrated.

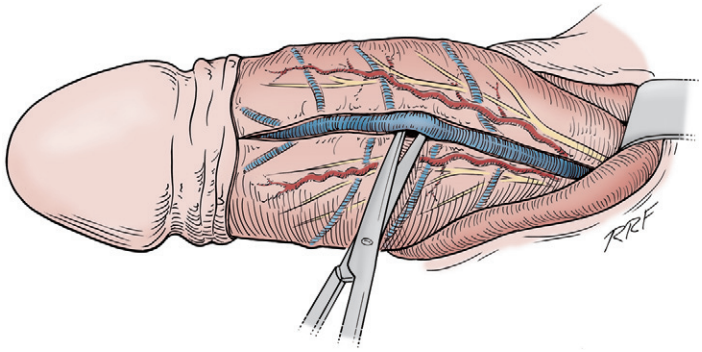


Figure 28–10. The deep dorsal vein is mobilized.

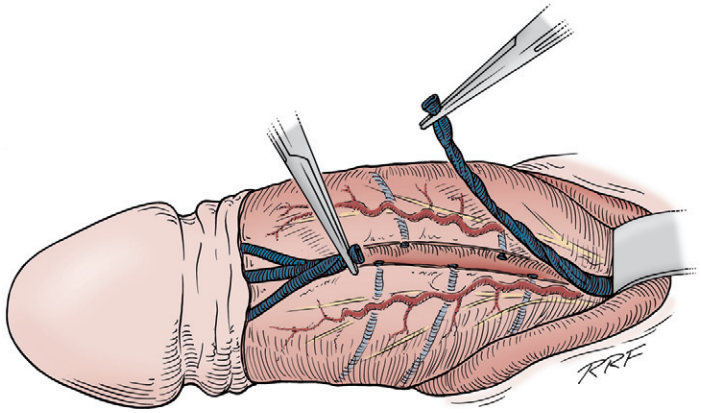


Figure 28–11. After the deep dorsal vein is divided it is dissected proximally; the emissary veins are divided and ligated. The subcoronal veins and the dorsal vein proximally are suture ligated.

penis and provided prosthetic implantation for their erectile dysfunction (Wilson and Delk, 1994). Some patients might do well with a plication or corporoplasty technique and then postoperatively undergo management of the erectile dysfunction pharmacologically.

After dorsal exposure of the tunica (see Fig. 28–12) the inelasticity of the plaque will be evident, and its extent can be delineated by feeling the surface of the tunica albuginea. An artificial erection accurately defines the curvature. Incisions are then planned either to incise or to excise the plaque. The authors place Prolene stay sutures in the midline, proximal and distal to the plaque, and mark the planned incisions. Depending on the technique selected, the plaque can be excised or incised. The use of a tourniquet for either control of bleeding or induction of an artificial erection is not advised because tourniquets can conceal proximal curvatures.

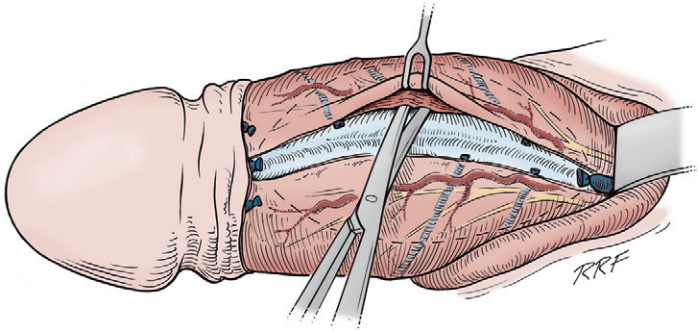


Figure 28–12. Buck fascia is elevated from the Peyronie's plaque. The area of dissection is outlined by the *dashed line*, continued far enough proximally, distally, and laterally to allow excision of the plaque without distraction or stretching of the nerves in the fascia.

Once the plaque has been excised or incisions have been made, the defect is measured, stretching the penis to ensure accurate coverage. The dermal graft, if that is what is being used, is then outlined on the donor site. The authors prefer to use the skin of the abdomen just above the iliac crest, lateral to the hairline, as the donor site for the dermal graft. The donor site is closed per primam by subcuticular sutures, with use of either a pull-out or the newer absorbable long-acting monofilament suture.

If a dermal graft is used it is carefully tailored to measure approximately 30% larger in all dimensions than the corporotomy defect and placed into either the incisional or the excisional defect. The graft, when it is released from the inherent tissue tension at the donor site, "contracts" about 30%. This should not be confused with graft contraction during "take." After completing the graft inlay with polydioxanone suture, another artificial erection is performed to demonstrate that the penis is straight and the suture lines are watertight. If there are leaks, they are oversewn. If the penis is not straight during surgery, it will not be straight postoperatively. If curvature persists, therefore, further modification by means of incisions and grafting or "touch-up" plications is necessary.

After completion of the dermal graft inlays the penis is closed. Buck fascia is reapposed with polydioxanone suture, and small suction drains are placed superficial to this fascia but deep to the dartos layer. The skin incisions are coapted with either chromic or small Vicryl sutures. If a ventral midline incision was made that crosses the penoscrotal junction, a Z-plasty should be used to prevent penoscrotal tethering.

Vein has also been used as a graft; however, the authors have never used or found the dorsal vein to be suitable but instead use the proximal saphenous vein. Use of this donor site has been criticized by some, the objection being the use of the donor site for a coronary artery graft. As an alternative, the distal vein can be used, beginning the dissection at the ankle. The vein must be turned into a "quilt," because the vein is rarely wide enough to adequately fill the corporotomy defect/defects even for incisions.

Beginning in 1998, in suitable patients, the authors further modified our technique of plaque incision. The technique of incision was described by Lue. In this technique the plaque is exposed as already illustrated and discussed. Artificial erection is used to identify the curvature and the point of maximal curvature. At that point, an H-shaped incision is made; the flaps are elevated, allowed to slide (Figs. 28–13 to 28–16), and sutured, leaving an

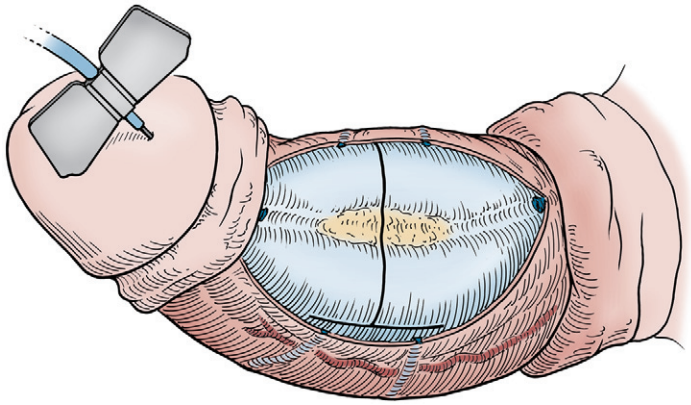


Figure 28–13. Illustration of "sliding H" technique of incision. The dorsal tunica and plaque are exposed as already described. An H-shaped incision is marked at the site of maximal curvature.

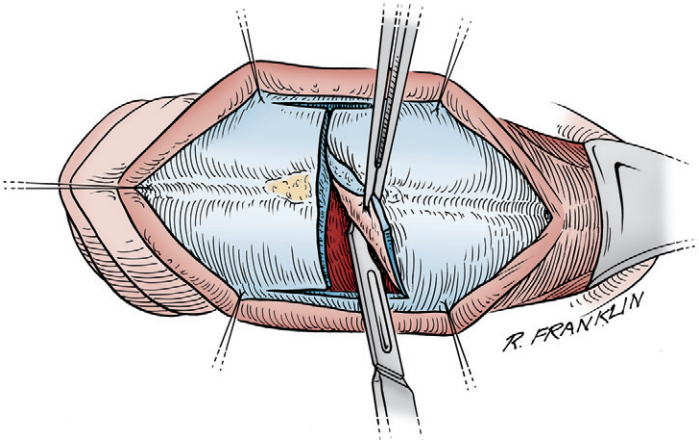


Figure 28–14. The flaps of the H are incised and elevated from the underlying erectile tissue. The septal fibers are divided. The septal fibers are detached back to the point of normal tunica albuginea both proximally and distally. This maneuver is extremely important in achieving straightening with this technique.

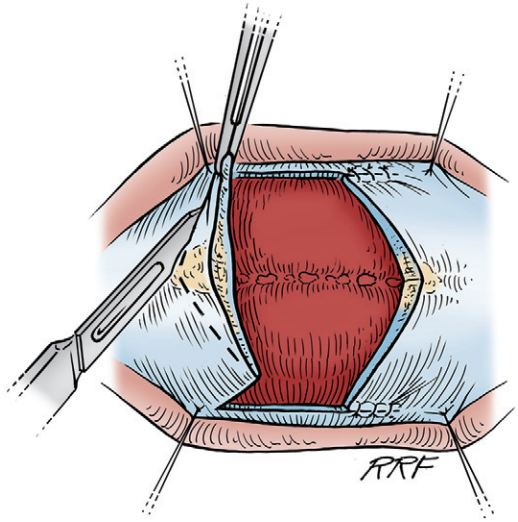


Figure 28–15. The flaps are elevated, and darting incisions are marked to allow some expansion of the defect circumferentially.

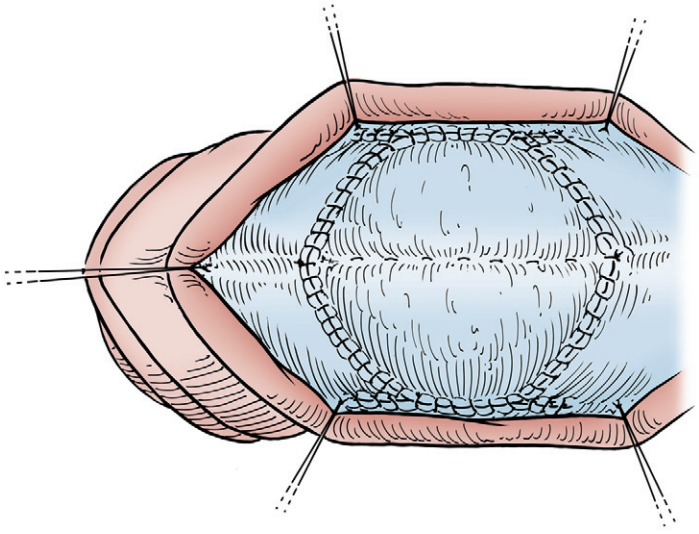


Figure 28–16. The flaps are sutured in place, creating a square corporotomy defect. Appearance with either dermis or small intestinal submucosa.

approximately square defect. Since 2001, the sliding-H incision has been modified. At the point of maximal curvature, which can be accurately identified during artificial erection, a stitch is placed and a strip of tunica albuginea is excised. This indeed does make a larger corporotomy defect; however, the corporotomy defect remains approximately square and the graft inlay can be placed without difficulty. After either H-shaped incision is made the sliding flaps are sutured. If there is indentation, the flaps are darted, allowing expansion. A graft is then sutured into the defect, and preferentially since 2003 the authors have used the small intestinal submucosal graft; however, dermis or vein can also be used (Fig. 28–17; see also Fig. 28–16). It is clear that the penis can be effectively straightened with this incision and graft technique alone in about 70% of patients. The addition of the small strip excision allows straightening in almost all patients. Only about 5% of patients will require touch-up plication, and generally that is for persistent tilt of the glans, as mentioned. Beginning about 2 years ago the modified sliding-H technique (excision of a small strip across the midline) has been used. With this technique touch-up plications are usually not required (Figs. 28–18 to 28–20). It is also clear that the sliding-H technique limits graft size, whether it is dermis, vein, or small intestinal submucosal graft. It is not clear whether this technique is more reliable or effective with regard to preservation of erectile function. It is the authors' distinct early impression that the small intestinal submucosal graft is clearly as efficacious as dermis or vein, and perhaps superior, and they continue to compare the small intestinal submucosal graft results to those of a series having an identical operation with the exception of the use of dermis versus small intestinal submucosa.

The penis is dressed with a Bioclusive dressing that is loosely applied and extending from the base of the penis to the level of the mid glans. A mildly compressing Kling dressing is wrapped over the Bioclusive dressing to limit edema and to allow better collapse of the surgical spaces around the suction drains. The Kling dressing is left in place for 4 hours, during which the glans is checked every 30 minutes. A No. 14-Fr Foley catheter is left until the patient ambulates on the morning after surgery. The suction drains are removed on the first postoperative day, and usually the patient is discharged on that day. Erections are suppressed with diazepam and amyl nitrite.

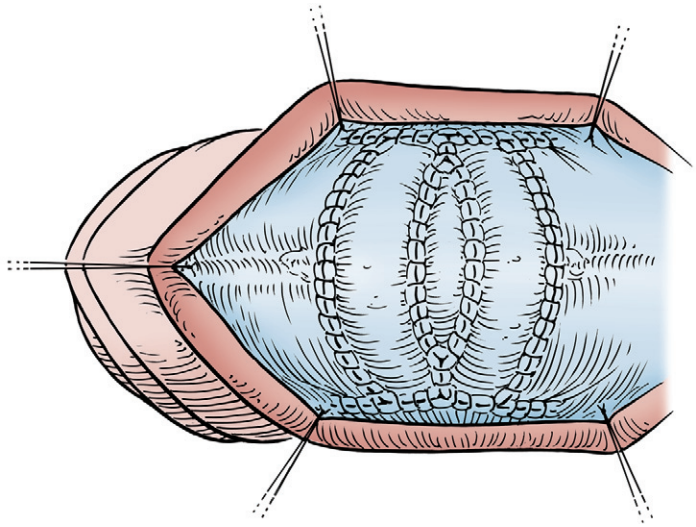


Figure 28–17. Alternatively, the corporotomy defect can be replaced with a vein graft. Notice that the vein graft is oriented so that the circumferential distensibility allows long axial lengthening.

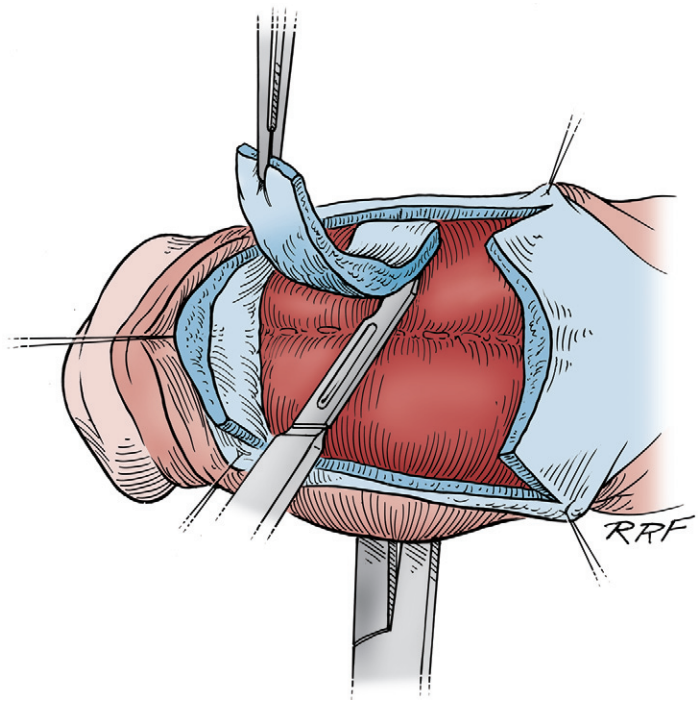


Figure 28–20. The transverse strip is excised; the H-shaped flaps are then sutured as discussed in Figure 28–15. The flap can be darted if lateral expansion is needed.

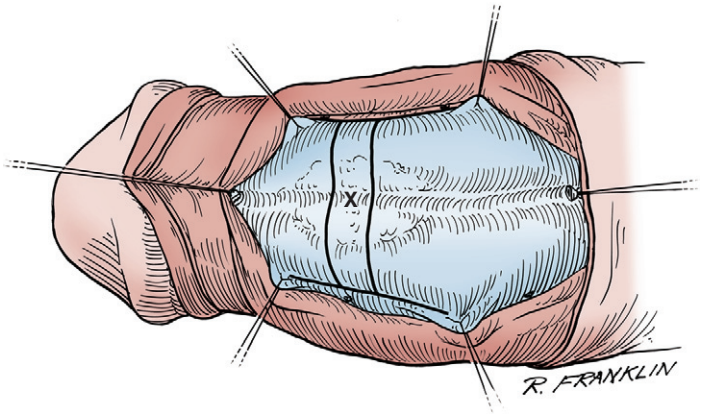


Figure 28–18. Modification of the "sliding H" technique, in which a small strip is excised at the point of maximal curvature. The stitch marks that point.

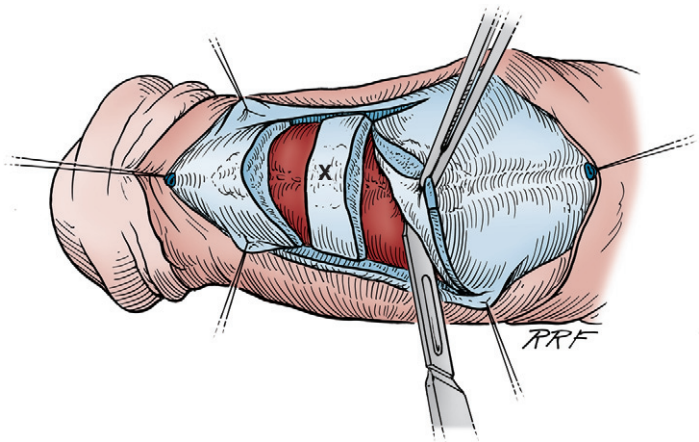


Figure 28–19. The incisions are made; the H-shaped flaps are elevated extensively as discussed in Figure 28–14. Note the expansion of the corporotomy defect.

Dermal grafts mature in the same manner as other grafts do: first nourished by imbibition of tissue fluids while inosculation occurs from adjacent blood vessels. Increased compliance is noted during the late phase of maturation, with the graft tending first to contract and then to become compliant. In the first 3 months the graft may contract enough to re-create some of the curvature, but as the graft softens, straightening occurs. This is seen less in patients who have had incisions as opposed to excisions. Patients should be forewarned of this sequence of events to avoid undue anxiety. With vein and also small intestinal submucosal grafts, this initial contraction can be seen, but seemingly less often and less severely.

After the first 2 weeks patients are encouraged to have erections but discouraged from intercourse. During this time, it is desirable for the penis to be manipulated so that the skin does not adhere to the deeper layers of the penis. In addition, erections stretch the graft and aid in the maturation phases of graft take. In some patients, the use of the vacuum erection device without the constriction ring is encouraged as a means of distending and stretching the graft.

Recently, the authors have placed Tisseel (Baxter Biosurgery, Deerfield, IL) beneath the small intestinal submucosal graft. Others have done this and believe that hematoma formation under the graft is less frequently encountered. The authors have not used this long enough or in a sufficient number of patients to say whether their current results are altered with this modification.

Penile Prosthesis in Peyronie's Disease

It is the consensus of the committee on Peyronie's disease at the World Health Organization Second International Consultation on Sexual Dysfunctions that the penile prosthesis is a reliable option for the older man with vascular impairment, erectile dysfunction, and acquired deformity of the penis (Lue et al, 2004). It is thus not the only treatment for Peyronie's disease but rather a prudent

Key Points: Surgical Correction

- For a patient to be a surgical candidate, his disease must be stable and mature. Most investigators consider curvature or erectile dysfunction that precludes intercourse the indication for surgery. The surgeon must consider all options of surgical therapy. Plication and corporoplasty techniques can be grouped under those operations that shorten the less involved side, and the application of those techniques is preferential in many patients. Procedures that incise or excise the plaque require the use of graft materials, and a number of graft materials have been successfully employed.
- Overall, plication or corporoplasty techniques seem to preserve the patient's erectile function more effectively; however, excellent results can be achieved with incision and grafting techniques. The use of a prosthesis for all Peyronie's disease patients is condemned.

treatment for the patient with significant erectile dysfunction in association with Peyronie's disease. In past years, semirigid devices have been preferred; however, with improvement in the three-piece hydraulic devices, these would appear to be preferable (Marzi et al, 1997; Ghanem, 1998). In 1993, Montorsi published a study that showed greater patient and partner dissatisfaction with semirigid devices when they were used for the treatment of erectile dysfunction combined with Peyronie's disease. Before 1994, correction of the curvature of Peyronie's disease, at the time of prosthesis placement, was accomplished by degloving of the penis and incision of the tunica albuginea in the area of curvature. In 1994, however, Wilson and Delk advised the modeling procedure. Since that report the modeling procedure has proved to be an excellent means for straightening the penis in the majority of patients. However, when the patient is to undergo this procedure, it is imperative to explain that urethral injury at the time of modeling is possible. This can occur with the extension of the modeling into the urethra at the point of maximal curvature, or the tips of the prosthesis can actually be forced through the tip of the corporeal bodies and into the urethra in some cases. If modeling does not work, one can resort to what was previously applied and that is incision with or without grafts as described earlier. In 1996, Montague and associates published a comparative study of the AMS CX cylinders versus the AMS Ultrex cylinders in Peyronie's disease. In that study it was found that the CX cylinders were superior. The message is that a controlled expansion cylinder provides better results; thus, the AMS 700CX or the Mentor Alpha I/Titan system would be preferable (Wilson and Delk, 1994; Montague et al, 1996). If incisions are required, the authors recommend closing the incisions with a synthetic patch. Gore-Tex was used in the past but now small intestinal submucosal graft is preferred. The AMS Ultrex cylinders have been redesigned to be controlled expansion cylinders. Milam reported favorable results in a series of about 35 patients with Peyronie's disease all treated with the AMS-LGX prosthesis with modeling (Whittam, 2009). To date, however, no comparative study of the AMS-LGX compared with the AMS 700CX prosthesis or the Coloplast Titan prosthesis has been undertaken.

The recent publications showing superiority of the antibiotic-coated prostheses or the hydrophilic-coated prosthesis with regard to infection rate suggest to the authors that in cases of Peyronie's disease, the antibiotic-coated devices should be used (Carson, 2004; Wolter and Hellstrom, 2004) unless there are concerns regarding antibiotic allergy. Wilson reported the use of the Ambicor prosthesis in Peyronie's patients. A series of 77 consecutive patients were studied. Primary implants were used in 32; of these patients, 20 had bothersome Peyronie's disease. Thirty-four were replacement devices for a malfunctioning AMS 700CX prosthesis, and many of these patients had Peyronie's disease. All of the Peyronie's patients had satisfactory straightening without another adjunctive procedure. There were no infections reported in the series. Thus, it was concluded that the Ambicor two-piece inflatable prosthesis has good patient satisfaction even when it is implanted for Peyronie's disease and in patients who have had previous three-piece devices (Scarzella and Wilson, 2004).

Key Points: Penile Prosthesis

- The consensus committee on Peyronie's disease at the World Health Organization Second International Consultation on Sexual Dysfunctions stated that the penile prosthesis is a reliable option for the older man with vascular impairment, erectile dysfunction, and acquired deformity of the penis.
- It is not the only treatment of Peyronie's disease but rather a prudent treatment for the patient with significant erectile dysfunction in association with Peyronie's disease. Hydraulic prostheses are preferred, and those prostheses that have true controlled expansion cylinders have been shown to provide better results.

CONCLUSION

Peyronie's disease is not the "terminal/no hope" diagnosis that many patients believe it is. These patients and their partners must be educated about what is happening and what might happen. They must be told that in the majority of cases their sexual relationship can be adequately restored. They must also understand that for most cases, all we have to offer will, at best, make their sex lives adequate. There is not one best operation or approach but rather a menu of options that for a given individual will have benefits and disadvantages. With counseling, they must match their "have to haves and can't stand to haves" to those advantages and disadvantages. This approach, in the authors' experience, will lead to the best management for most.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter
29

Androgen Deficiency in the Aging Male

Alvaro Morales, MD, FACS, FRCS

Definition
Historical Perspective
Epidemiology of Hypogonadism in Aging
Physiologic Principles
Diagnosis
Treatment of Testosterone Deficiency Syndrome
Recommendations and Guidelines

DEFINITION

Normal aging frequently results in a progressive functional dwindling of the hypothalamic-pituitary-gonadal axis (Liu et al, 2007). In men this process exhibits significant interindividual variability in the age at onset and speed and depth of the decline. The syndrome is variously known as andropause, androgen decline in the aging male (ADAM), late-onset hypogonadism (LOH), or, more accurately, testosterone deficiency syndrome (TDS). It is characterized by multiple clinical manifestations (Table 29–1) (Liu et al, 2004). Urologists often see the same presentation more acutely and dramatically in men subjected to medical or surgical castration for advanced prostate cancer (Shahani et al, 2008).

HISTORICAL PERSPECTIVE

Aging and Hormones: From Antiquity to the 21st Century

The importance of the gonads in the maintenance of homeostasis has been recognized since antiquity. The association of advancing age with hypogonadism has been widely acknowledged since the end of the 19th century with the report in the scientific literature by Brown-Séquard on his observations about the improvement in his own physical strength and intellectual capacity after administration of a *liquid testiculaire* prepared by him from animal gonads. These reports gave origin to a series of medical claims that exploited testicular extracts and heterologous transplants as effective treatments for the infirmities of aging. They were eventually exposed as hoaxes (Current Comment, 1927).

Concurrently with the pseudoscience at the turn of the last century, serious investigators were exploring the effects of substances produced and secreted by the testes, eventually resulting in the isolation of androsterone and testosterone by Laqueur (David et al, 1935). By 1935, almost simultaneously and independently, three research teams led by Adolf Butenandt, Kàroly Gyula, and Leopold Ruzicka, who were individually sponsored by three different corporations (Schering, Organon, and Ciba, respectively), synthesized the more powerful testicular hormone, ultimately named testosterone (T). **For this work, Butenandt and Ruzicka received the Nobel Prize for Chemistry in 1939.** After synthesis of the hormone, injectable preparations for human use were developed, and shortly before the onset of World War II clinical trials on T were under way. Interest grew in the use of T for a variety of ailments, ranging from sexual difficulties to the prevention of benign prostatic hyperplasia (Cuneo and Jomain, 1938). By the end of World War II the clinical picture of a syndrome named "male climacteric" associated with low T levels was fully recognized (Werner, 1946). T substitution became so widely used that warnings about the indiscriminate use and abuse of the hormone were already sounded by the 1940s (Thompson, 1946).

Key Point: Testosterone Deficiency Syndrome

- TDS is a clinical and biochemical syndrome frequently associated with advancing age and characterized by a deficiency in serum testosterone levels with or without changes in receptor sensitivity to androgens. It may affect the function of multiple organ systems and result in a significant detriment in the quality of life.

EPIDEMIOLOGY OF HYPOGONADISM IN AGING

The mean life span in Imperial Rome was about 20 years. United Nations estimates and projections of world population trends over a 75-year period showed that in the last decade of the 20th century the number of humans increased by 1 billion, and it will become close to 2 billion over the next 25 years. More importantly, life expectancy over this period will increase by more than 30 years (United Nations Secretariat, 2008). It follows that the prevalence of hormonal alterations in general and hypogonadism in particular is bound to rise significantly in the first half of this century.

The global prevalence of TDS is not accurately known, but it can be inferred from population projections that it is on the rise.

Table 29–1.

Clinical Manifestations of Late-Onset Hypogonadism and Their Anticipated Response to Treatment

SYSTEM/FUNCTION	AGING	RESPONSE TO TESTOSTERONE
Erectile function	↓	↑
Sexual desire	↓	↑
Mood/cognition	→/↓	↑*
Tiredness/lack of motivation	↓	↑
Sleep disturbances	→/↓	→
Spatial cognition	↓	↑*
Vasomotor (hot flashes)	↑	↓
Quality of life	↓	↑
Hematocrit	↓	↑
Leptin production	↑	↓
LDL and HDL cholesterol	→	↓
Fat mass	↑	↓
Muscle mass	↓	↑
Bone mass	↓	↑
Hair and skin changes	↓	→

↑ increases/improves; ↓ decreases/deteriorates; → no change; ↑* suspected/not proved.
HDL, high-density lipoprotein; LDL, low-density lipoprotein.

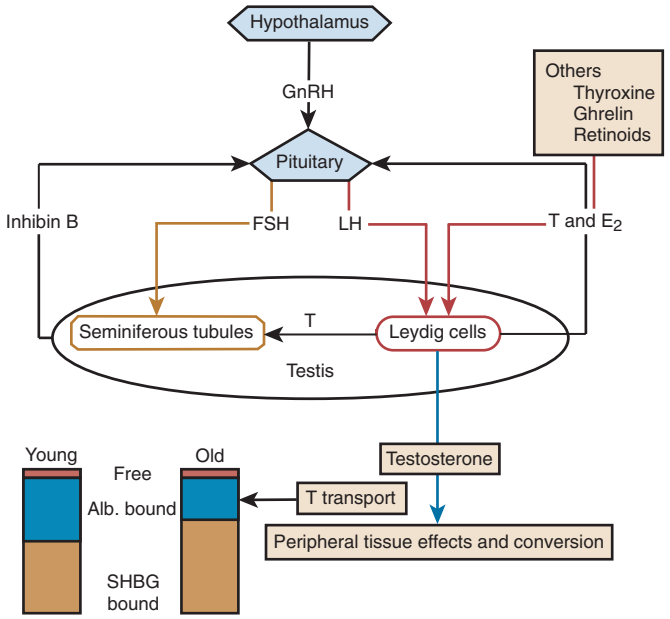


Figure 29–1. Effect of aging on the production, transport, and metabolism of testosterone (T). Luteinizing hormone (LH) is the major but not the only regulator of T production. Aging of the hypothalamus and the pituitary results in decreased production of gonadotropin-releasing hormone (GnRH) and LH, respectively. T circulates free (2%) or is bound to albumin or sex hormone–binding globulin (SHBG). Binding of T to SHBG renders it unavailable to most tissues. SHBG increases with aging. Bioavailable T (free and albumin-bound fractions) is metabolically active and can be converted to other hormones (dihydrotestosterone, dehydroepiandrosterone, estradiol [E_2]). FSH, follicle-stimulating hormone.

In an attempt to alleviate the scarcity of descriptive epidemiology of androgen deficiency, the Massachusetts Male Aging Study (MMAS) reported a crude incidence rate of 12.3 per 1000 person-years, leading to a prevalence of 481,000 new cases of TDS per year in American men 40 to 69 years old (Araujo et al, 2004). Further assessment with data from the Boston Area Community Health (BACH) survey documented a prevalence of symptomatic T deficiency in men 30 to 70 years of age of 5.6% (Araujo et al, 2007). These observations are further confirmed by an Australian study (Liu et al, 2007) and the European Male Aging Study with larger populations of very different geographic, cultural, and ethnic backgrounds (Wu et al, 2008).

PHYSIOLOGIC PRINCIPLES

Regulation of Testosterone Production—Central Mechanisms

Luteinizing hormone (LH) modulates T biosynthesis by Leydig cells and also controls their population (Habert et al, 2001). An example exists in aged animals, in which "hibernation" of Leydig cells develops after prolonged LH suppression (Chen and Zirkin, 1999). **In rodents, aging of the hypothalamus results in an apoptotic process leading to decreased production of gonadotropins** (Morales and Heaton, 2003). **Although not proved in humans, this process may explain a fundamental cause of TDS.** In the testis the local cellular environment has the potential for impact on regulation and function in a paracrine fashion, mostly in the form of T acting in seminiferous tubules (Fig. 29–1). Sertoli cells do not appear to have a major impact as long as LH control is active (Young et al, 2000). **Neural influences on Leydig cells have been demonstrated, independent of the pituitary, in the paraventricular nucleus of the hypothalamus** (Selvage and Rivier, 2003), and the peptide ghrelin actively regulates Leydig cell activity (Barreiro et al, 2004). These findings have implications for T production independent of central endocrine mechanisms.

Androgen Production in Aging—Peripheral Mechanisms

T and dihydrotestosterone (DHT) are the main androgens playing the key regulatory roles in determining and later supporting the male phenotype. Androgen effects require the delivery of androgens to the site of action, penetration into the cells, metabolic conversion where necessary, and action with the androgen receptor (AR) on the genome. T is the predominant circulating androgen; the adrenal cortex secretes 19-carbon steroids with weak androgenic activity that serve as precursors for estrogens and active androgens such as T. Very small amounts of steroids are produced in brain cells, but local production may be functionally important (King et al, 2002) and not be represented in serum-based measurements. **Leydig cells decrease in numbers in the testes of older men and these men have less T secreted per burst and a decline in secretory bursts in response to LH, suggesting partial desensitization of Leydig cells to LH with aging.** Taken together, these studies demonstrate that a component of the decline in T with aging in men is due to testicular failure.

Transport and Metabolism of Testosterone

T is exchanged readily through cellular membranes with the extracellular environment. The passive transfer of T through membranes means that serum concentrations reflect general tissue androgen levels except where local sources of production or conversion exist. Circulating T is 98% bound to proteins (sex

hormone–binding globulin [SHBG] and albumin (see Fig. 29–1), in which form it is relatively spared hepatic metabolism. The binding to SHBG and that to albumin have different affinities, providing the concept of bioavailable T; T bound to albumin is more readily unbound for use.

T levels are determined by the relative rates of production and metabolism. T can be aromatized to 17β-estradiol or reduced to 5α-DHT. Aromatization by cytochrome P450 arom and the supply of T substrate determine estrogen availability in estrogen-dependent cells such as those in the testis, fat, liver, hair follicles, and brain (de Ronde et al, 2003). There are two isoforms of 5α-reductase, and the cellular availability of 5α-DHT depends on T reduction and the rate of DHT metabolism. **The balance between T and DHT metabolic enzyme activity is more critical to the cells in which it is occurring than to the overall rate of T metabolism.** With aging, changes occur in enzyme functions that can potentially skew cellular activities in a way that is hidden from any systemic measures of androgen status. T catabolism takes place mostly in the liver, prostate, and skin, and catabolic products are largely excreted in the urine.

Androgen Receptor

T and DHT act through the androgen receptor (AR), which is a ligand-inducible transcription factor. The AR structure includes a COOH-terminal ligand binding domain, a DNA binding domain, a hinge region, a variable-length CAG repeat region, and an NH_2-terminal transactivation domain (Glass et al, 1997). Most of the transactivational activity is associated with the NH_2 terminus. The CAG repeat stretch is maximal in man (about 22 triplets) and decreases with evolutionary distance from man (Choong and Wilson, 1998). The hinge region is responsible for nuclear function after hormone binding. The ligand binding domain acts with the help of molecular chaperones, which increase the affinity for the hormone of the unbound AR.

T is transported through the cellular membrane, binds to the inactive AR complex, and is translocated to the nucleus. The binding of T to DNA activates the basal transcription machinery, thus regulating the transcription of target genes. Although the time frame for this genomic activity is 30 to 60 minutes there are nongenomic actions that take place too rapidly to follow this pathway. These rapid actions may be due to activation or possibly binding to undetermined membrane-bound receptors. **The AR may be activated without the presence of ligand, for example, by protein kinase C, a factor that has great importance in the androgen interaction with prostate cancer cells** (Culig, 2004).

CAG Repeat Polymorphism and Aging

The CAG repeat lengths of the AR vary from 6 to 39, depending on race (Valdehuis et al, 2005). In general, increased androgenic effect is seen at any level of T in men with shorter CAG repeat length. In older men, lower T is associated with fewer CAG repeats. The association of polymorphic AR with TDS manifestations showed that older men with more than 23 CAG repeats had less elevated LH, normal T, and less decreased potency but more depression, more anxiety, more deterioration of general well-being, and decreased beard growth (Harkonen et al, 2003; Lapauw et al, 2007). Changes in the AR can play a major role in the symptomatic response to T, potentially explaining some of the variability in clinical presentation in men with similar serum T. To complicate the picture, the AR CAG repeat length has been reported to correlate not only with serum T but also with estradiol in aging males (Huhtaniemi et al, 2009).

Androgen Actions

T actions on sexual function, spermatogenesis, and the prostate are discussed in other chapters. Action of T in other systems (i.e., musculoskeletal) is discussed later.

Testosterone and Glucose Metabolism

The metabolic syndrome is a complex association of several interrelated abnormalities that increase the risk for cardiovascular disease and progression to type 2 diabetes mellitus. Insulin resistance is the key factor for the clustering of risk factors (Grossman et al, 2008). Hypogonadism is seen frequently in association with the metabolic syndrome (Dandona et al, 2008), and several studies show that the fundamental cardiovascular risk parameters can be improved by the administration of T to these men. Hypogonadal men have increased leptin, obesity, and insulin levels that become normal with exogenous T treatment, which also reduces abdominal fat mass and improves insulin action (Zitzmann and Nieschlag, 2003). T administration to older men is associated with decreased visceral fat and glucose concentrations and increased insulin sensitivity (Bhasin, 2003). Hypogonadism correlates with high serum glucose, high triglycerides, high body mass, high waist-to-hip ratio, high total body fat mass, and high fasting insulin resistance index. Treatment with T improves the metabolic syndrome, especially in overweight older men (Schroeder et al, 2004).

Androgens and the Brain

A relationship between hypogonadism and depression has not been conclusively established. Although castration for the treatment of advanced cancer of the prostate has been shown to correlate with an increase in psychiatric illness, mostly depression (DiBlasio et al, 2008), there are studies showing improvements in measures of mood and well-being in aging men with hypogonadism (Almeida et al, 2008). There are well-researched gender differences in selected areas of cognition such as verbal skills and spatial tests that point to the developmental influence of T. Studies of hypogonadal men suggest that some cognitive skills can be improved with replacement therapy (Zitzmann, 2006), but this is not invariably seen because there are clearly many potential causes of impaired cognition.

DIAGNOSIS

Clinical Diagnosis

Clinical diagnosis of TDS is challenging because neither a low serum T level nor symptoms are truly diagnostic of the condition. The presence of symptoms, however, is a sine qua non for diagnosis and should be coupled with a low or borderline-low objective biochemical measure of T. In practice this ideal is not always achievable. Thus it was suggested that (Black et al, 2004) **in the presence of symptoms but without strong biochemical support that a therapeutic trial would be an acceptable diagnostic approach; it should be noted that a sustained placebo response can be observed for up to a year** (Haren et al, 2005). Morley (2007) **further advanced this notion by suggesting that the diagnosis of TDS requires the presence of symptoms, a low level of serum T, *and a positive response to treatment.* The concept was further supported by a recent set of multidisciplinary recommendations** (see Recommendation 4 later; Wang et al, 2009).

Table 29–2.

Spectrum and Severity of Late-Onset Hypogonadism Symptoms*

SYMPTOM (N = 52)	MINIMALLY TO MILDLY PROBLEMATIC	MODERATELY PROBLEMATIC	VERY PROBLEMATIC
Loss of energy	10 (19%)	17 (33%)	19 (36%)
Diminished libido	14 (27%)	10 (20%)	8 (15%)
Lack of motivation	9 (18%)	12 (23%)	8 (15%)
Irritability	4 (8%)	10 (20%)	11 (20%)
Sleepiness after meal	6 (12%)	5 (10%)	12 (23%)
Inability to concentrate	14 (26%)	4 (8%)	4 (8%)
Hot flashes	10 (20%)	2 (4%)	2 (4%)
Muscular aches	2 (4%)	0	6 (12%)

*Symptoms appearing after discontinuation of treatment with depot subdermal administration of testosterone (see text for details).

Adapted from Kelleher S, Conway AJ, Handelsman DJ. Blood testosterone threshold for androgen deficiency symptoms. J Clin Endocrinol Metab 2004;89:3813–17.

Table 29–3.

The Androgen Deficiency in Aging Male (ADAM) Questionnaire

Yes	No	1. *Do you have a decrease in libido (sex drive)?*
Yes	No	2. *Do you have a lack of energy?*
Yes	No	3. *Do you have a decrease in strength and/or endurance?*
Yes	No	4. *Have you lost height?*
Yes	No	5. *Have you noticed a decreased enjoyment of life?*
Yes	No	6. *Are you sad and/or grumpy?*
Yes	No	7. *Are your erections less strong?*
Yes	No	8. *Have you noticed a recent deterioration in your ability to play sports?*
Yes	No	9. *Are you falling asleep after dinner?*
Yes	No	10. *Has there been a recent deterioration in your work performance?*

If you answered Yes to questions 1 or 7 or any 3 other questions, you may be experiencing androgen deficiency (low testosterone level).

The clinical picture is well recognized (see Table 29–1). **Among the most prominent symptoms are tiredness, hypoactive sexual desire, and dysphoria.** Erectile dysfunction (ED) is, however, the most frequent reason for consultation. These manifestations generally correlate with the degree of T deficiency (Zitzmann et al, 2006) but need not all be present to identify the syndrome. In addition, the severity of one or more of them does not necessarily match the severity of the others, nor do we yet understand the uneven appearance of these manifestations. **TDS symptoms recur after discontinuation of therapy at highly reproducible intraindividual T levels, but the trigger level differs widely among individuals** (Table 29–2) (Kelleher et al, 2004). The increasingly recognized association of TDS and ED and cardiovascular disease (Billups et al, 2008) has brought to the forefront of clinical practice the need for a more in-depth assessment of men presenting with TDS-ED (Corona et al, 2009).

The **physical examination** suffers the same shortcomings as the history, mainly lack of specificity. Testicular atrophy may be present together with a decrease in pubic and facial hair. Sarcopenia and increase in visceral fat can also be part of the findings. The sequelae of osteoporosis become evident in long-standing cases. None of these is, alone or in combination, sufficient to make a definitive diagnosis, although the composite of history and findings on examination provides a strong case for a presumptive diagnosis of the syndrome.

Screening Questionnaires for TDS

Three questionnaires have been developed to detect hypogonadism in adult men: (1) St. Louis University's ADAM, (2) the Aging Male Survey (AMS), and (3) the MMAS. The first two are symptom questionnaires, and the last one represents a mixture of symptoms and epidemiologic findings. The ADAM questionnaire (Table 29–3) in the original validation had a sensitivity and specificity of 88% and 60%, respectively, against serum bioavailable T (BT) levels (Morley et al, 2000). In a follow-up study, BT and calculated free T (cFT) were lower in ADAM-positive men than in ADAM-negative men. The effectiveness of the ADAM questionnaire as a screening tool has been confirmed by most independent investigators (Tancredi et al, 2004). The AMS (Fig. 29–2) (Moore et al, 2004), in the author's hands, has sensitivity (83%) and specificity (39%) similar to those of the ADAM, but in a European study none of the three AMS domains correlated significantly with serum levels of total, bioavailable, or free T in men older than 70 (T'Sjoen et al, 2004). In contrast, the MMAS showed a sensitivity of 60% and a specificity of 59%. **These questionnaires are useful as screening tools but fall short of expectation for diagnostic purposes.** Their value as outcome measures after treatment with T remains undetermined (Morales et al, 2007).

Biochemical Diagnosis

T values decline while SHBG levels increase with aging. In young men, about 60% of circulating T is bound to SHBG, 38% is bound to albumin, and 1% to 2% is free (see Fig. 29–1). **The T that is free and bound to albumin is considered to be capable of entering tissues and to be responsible for the actions of T. SHBG-bound T is inaccessible to tissues and not active. In some tissues, such as the prostate, T bound to SHBG can activate SHBG receptors and produce effects within the cell** (Rosner et al, 1999). The active component (free plus albumin bound) is called bioavailable T (BT). Epidemiologic studies suggest that BT correlates better with symptoms associated with T deficiency than total T.

Assays for Testosterone

Establishing the presence of hypogonadism on a purely clinical basis is difficult. Only the most severe cases bring up clinical suspicion. The support of the biochemical evaluation is, therefore, fundamental in the diagnosis of the condition.

Although testosterone measurements should be restricted to morning hours at all ages (Brambilla et al, 2009), the importance of repeated measurements when the values are not conclusive cannot be emphasized enough. The biologic variation of repeated measurements of T is about 20%. **Values between 250 and 360 ng/dL (9 to 12 nmol/L) are considered "borderline." In the presence of a clear picture of TDS, a therapeutic trial of 3 months is justified** (see Fig. 29–3).

The urologist should become familiar with the range and quality of the T assays offered by the local laboratory as well as the intraindividual and interindividual variations in serum T levels. Assay techniques have

AMS Questionnaire

Which of the following symptoms apply to you at this time? Please mark the appropriate box for each symptom. For symptoms that do not apply, please mark "none."

Symptoms Score =	None 1	Mild 2	Moderate 3	Severe 4	Extremely severe 5
1. **Decline in your feeling of general well-being** (general state of health, subjective feeling)	☐	☐	☐	☐	☐
2. **Joint pain and muscular ache** (lower back pain, joint pain, pain in a limb, general back ache)	☐	☐	☐	☐	☐
3. **Excessive sweating** (unexpected/sudden episodes of sweating, hot flushes independent of strain)	☐	☐	☐	☐	☐
4. **Sleep problems** (difficulty in falling asleep, difficulty in sleeping through, waking up early and feeling tired, poor sleep, sleeplessness)	☐	☐	☐	☐	☐
5. **Increased need for sleep, often feeling tired**	☐	☐	☐	☐	☐
6. **Irritability** (feeling aggressive, easily upset about little things, moody)	☐	☐	☐	☐	☐
7. **Nervousness** (inner tension, restlessness, feeling fidgety)	☐	☐	☐	☐	☐
8. **Anxiety** (feeling panicky)	☐	☐	☐	☐	☐
9. **Physical exhaustion/lacking vitality** (general decrease in performance, reduced activity, lacking interest in leisure activities, feeling of getting less done, of achieving less, of having to force oneself to undertake activities)	☐	☐	☐	☐	☐
10. **Decrease in muscular strength** (feeling of weakness)	☐	☐	☐	☐	☐
11. **Depressive mood** (feeling down, sad, on the verge of tears, lack of drive, mood swings, feeling nothing is of any use)	☐	☐	☐	☐	☐
12. **Feeling that you have passed your peak**	☐	☐	☐	☐	☐
13. **Feeling burnt out, having hit rock-bottom**	☐	☐	☐	☐	☐
14. **Decrease in beard growth**	☐	☐	☐	☐	☐
15. **Decrease in ability/frequency to perform sexually**	☐	☐	☐	☐	☐
16. **Decrease in the number of morning erections**	☐	☐	☐	☐	☐
17. **Decrease in sexual desire/libido** (lacking pleasure in sex, lacking desire for sexual intercourse)	☐	☐	☐	☐	☐

Have you got any other major symptoms? Yes..... ☐ No..... ☐

If Yes, please describe: _____

_____

Thank you very much for your cooperation

Figure 29–2. The Aging Male Survey (AMS). This questionnaire has three domains: Psychological (questions 6, 7, 8, 11, 13); Somatovegetative (questions 1, 2, 3, 4, 5, 9, 10); and Sexual (questions 12, 14, 15, 16, 17). The minimum and maximum scores are 5 and 25, respectively, for the Psychological and Sexual domains and 7 and 35 for the Somatovegetative domain. The higher the score, the more severe are the symptoms.

improved greatly, but many laboratories have paid scant attention to the accuracy or the normal range of their assays. Three assays for measurement of total T are commonly used: (1) radioimmunoassay, (2) nonradioactive immunoassay kits, and (3) automated platform assays that use chemiluminescent detection. There is significant interassay variability: a value of 297 ng/dL (10.3 nmol) showed a variation from 160 to 508 ng/dL (5.5 to 17.6 nmol). In addition, the coefficients of variation ranged from 5.1% to 22.7%. Fortunately, most of the assay techniques had regression slopes close to 1 and correlation coefficients of 0.92 to 0.97 compared with liquid chromatography/tandem mass spectroscopy (Wang et al, 2004a).

In young men, but much less in older men, there is a substantial circadian rhythm, with higher values being obtained in the morning. In addition, in all men there is substantial variability (±20%) from week to week (Morley et al, 2002). **Thus, two samples obtained a week or two apart, ideally in the morning, would seem to be a minimal criterion. The assays that more closely reflect tissue available T are (1) free T only if measured by**

Key Point: Biochemistry

- In patients at risk for or suspected of having hypogonadism, the following investigations should be done: (1) T determination from blood taken between 7:00 and 11:00 AM. For screening purposes total T determination is usually sufficient. (2) If T levels are below or at the lower limit of the accepted normal values, it is prudent to confirm the results with a second determination together with assessment of gonadotropins (LH) and prolactin. (3) In the younger male, low levels of T (<12 nmol/L or <350 ng/dL) with chronically elevated gonadotropins make a clear diagnosis of primary hypogonadism. (4) In an older man the diagnostic lines are not as clearly defined and additional information may be needed (see Fig. 29–3).

ultracentrifugal ultrafiltration or dialysis techniques, (2) BT, generally measured by an ammonium sulfate precipitation technique, and (3) calculated free T or BT that can be obtained by measuring T and SHBG with or without an albumin level (see later).

Assays for BT and free T are cumbersome, costly, and not readily available. Vermeulen and colleagues (1999) provided a solution for situations in which the more reliable BT or free T determinations are not accessible: a calculation can be made from the values obtained for total T and the determination of SHBG. It has become known as calculated free T, or simply cFT. This method provides a good correlation with the values of nonbound T. (The formula is available at http://www.issam.ch.) Although this approach, in general, works well, there are pitfalls: (1) different SHBG levels varying up to twofold with different assays and (2) altered binding characteristics (either SHBG or serum) related to aging or illness. The relative advantages, drawbacks, and usefulness of the various assays are given in Table 29–4.

Because of the controversial nature of the biochemical assessment, when the biochemistry does not support a

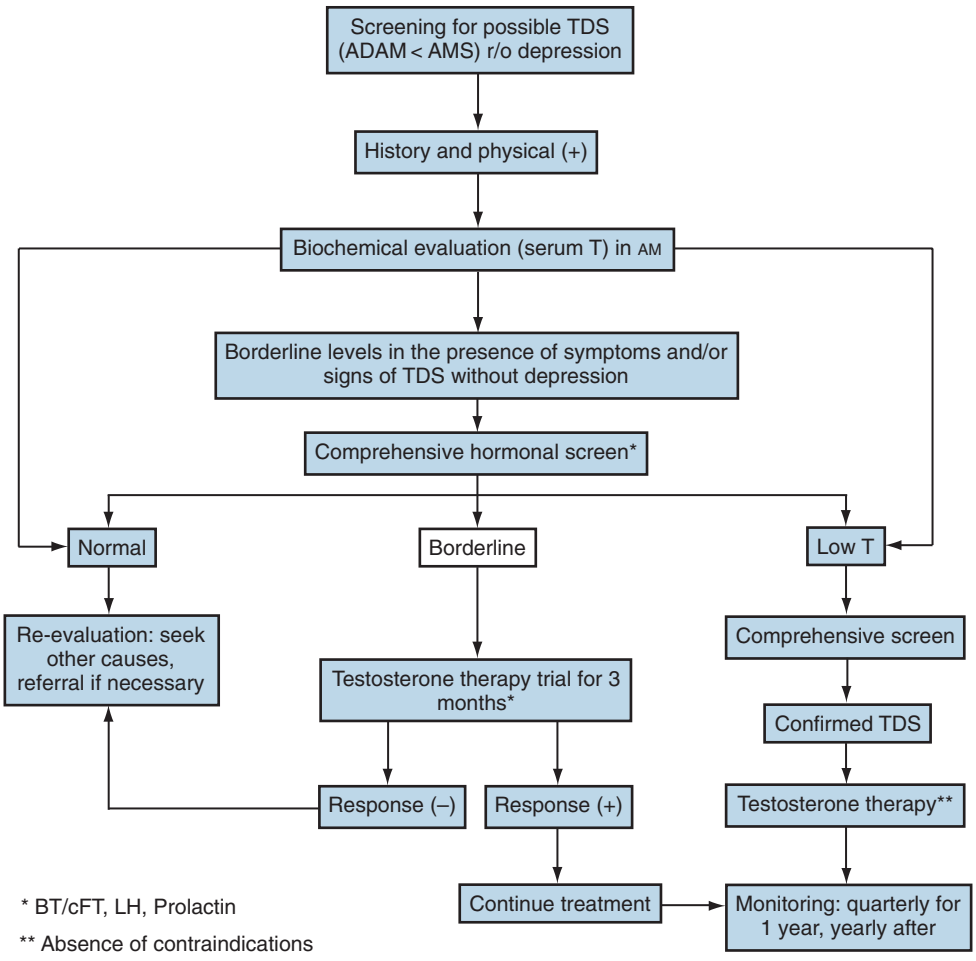


Figure 29–3. Diagnostic algorithm for testosterone deficiency syndrome (TDS). Screening questionnaires are appropriate for initial assessment. A comprehensive hormonal screen includes either a repeated measurement of total testosterone (T) or bioavailable or calculated free T (BT/cFT) to assess the non–sex hormone–binding globulin fraction. A basic evaluation of the pituitary (prolactin, luteinizing hormone) is indicated in the presence of low T levels. Evaluation of other hormones (dihydrotestosterone, dehydroepiandrosterone, growth hormone, melatonin) is not generally necessary. ADAM, Androgen Deficiency in Aging Male questionnaire; AMS, Aging Male Survey; r/o, rule out.

Key Point: Inappropriate Assay

- The assay that should not be used is commonly available and frequently ordered: direct radioimmunoassay of free T using a labeled T analog with low affinity for SHBG and albumin that binds to an immobilized antibody that is specific for T. This assay has poor accuracy and precision. It is most closely related to the measurement of total T. Clinicians are thus misled to believe that true "free T" is being measured.

Table 29–4.

Assays for Testosterone and Their Attributes

ASSAY	UTILITY	COMMENTS
Total testosterone	Low/intermediate	Variable normal ranges; below 200 ng/dL very likely to be hypogonadal; above 600 ng/dL unlikely to be hypogonadal
Free testosterone		
Dialysis	High	Difficult to do; requires ^{3}H-T
Ultrafiltration	High	
Analog	Poor	Commonly available in NA
Calculated free	Intermediate	Requires SHBG and T measurements
Bioavailable testosterone		
Ammonium sulfate	High	Easier to do than free T; excellent precipitation assay; good correlation with symptoms
Calculated bioavailable	Intermediate	Requires SHBG and T measurements
Free androgen index		
Testosterone/SHBG	Poor	Requires SHBG and T measurements
Salivary testosterone	Undetermined	Uncertain value

NA, North America; SHBG, sex hormone–binding globulin; T, testosterone.

strong clinical picture, other causes have been ruled out, and no contraindications exist, a 90-day therapeutic/diagnostic trial of T administration is justified (Black et al, 2004; Morley, 2007) (see Fig. 29–3).

Other Hormones

It is important to dispel the concept that endocrinopathies resulting from the normal process of aging in men are narrowly focused on sex steroids. Although hypotestosteronemia is most widely recognized, the production of several other hormones is also profoundly affected by age (Table 29–5).

Dehydroepiandrosterone (DHEA)

Production of DHEA reaches a peak in the second to third decade of life and decreases steadily afterward, to very low values (<30% of those in the young) by the age of 70 (Vermeulen, 1995). The finding of a putative specific DHEA receptor on the plasma membrane of bovine aortic endothelial cells (Liu and Dillon, 2002) changed our understanding of the role of DHEA in many functions, particularly in the vascular system. Kawano and colleagues (2003) and Simoncini and associates (2003) have documented an improvement in vascular endothelial function in middle-aged men with a variety of vascular problems with DHEA supplementation. These findings may have direct and significant implications for the mechanisms of sexual function. DHEA may have a dual role in sexual function: an indirect endocrinologic and a direct vascular role. The preponderance of the evidence, however, is that DHEA plays a minor, if any, role in improving quality of life (Nair et al, 2006) in men with DHEA deficiency but might be beneficial in those with Addison disease (Gurnell et al, 2008).

Table 29–5.

Hormones, Other Than Testosterone, Most Commonly Affected by the Aging Process*

HORMONE	PRODUCTION	FUNCTION AND REAL/PUTATIVE EFFECTS
DHEA	↓	Neurosteroid; regulation of vascular endothelium
Growth hormone	↓	Somatic growth; anabolic effects mediated by IGF-1 (protein synthesis and cell proliferation)
Melatonin	↓	Regulation of biorhythms and sleep patterns. Prevention of oxidative stress
Thyroxine	↓	
Leptin	↗	Regulation of appetite and fat distribution. Receptor expressed in prostate gland

*For most, their functions are not fully understood in most cases. It is known, however, that there is a great deal of cross talk among them in their production, function, and activity.

DHEA, dehydroepiandrosterone; IGF, insulin-like growth factor.

Growth Hormone (GH)

Production of GH also decreases with age, about 14% per decade. This reduction is associated with changes in lean muscle mass, bone density, hair distribution, and the pattern of obesity described also in hypogonadal states. **Administration of GH reverses these alterations** (Götherström et al, 2009) **and does it more efficiently in eugonadal men than in their hypogonadal counterparts.** Although the body of evidence favors the use of androgens in the treatment of some of the manifestations of TDS, more recent studies clearly indicate that elderly patients respond to GH administration alone (Gola et al, 2005) as well as those with other hormone deficiencies (Lo et al, 2008). Some of the concerns about androgen supplementation in elderly men (e.g., prostate health) also may be shared with GH administration. Although no changes in prostate-specific antigen (PSA) were found in adults receiving injectable GH (Colao et al, 2003), the simultaneous administration of GH and T may lead to significant increases in prostate size (Vance, 2003).

Melatonin

Melatonin production decreases with age. The pineal gland is involved in gonadal function and regulation of biorhythms.

However, the popular enthusiasm about the hormone has a precarious scientific basis. It is likely that administration of melatonin may improve sleep disorders, frequently seen in elderly persons, but profound hypogonadism is associated with alterations in melatonin production, making it difficult to attribute some symptoms exclusively to deficits of one or the other hormone. Evidence is emerging of a wide range of direct and indirect activities of melatonin on many human organ systems (Reiter and Tan, 2004), although its role in sleep disturbances in the aging population has been challenged (Tozawa et al, 2003).

Thyroxine, Prolactin, and Leptin

Changes occur with aging in the hypothalamic-pituitary-thyroid axis resulting in the development of hypothyroidism, which may reach an incidence of close to 20% in the elderly population (Leitolf et al, 2002). The production of prolactin, corticosteroids, and estradiol (E_2) in males remains fairly constant throughout life. **Hyperprolactinemia secondary to a pituitary adenoma should be ruled out in men with diminished sexual desire and/or hypogonadism. It may also be drug induced (metoclopramide).** Leptin is altered in hypotestosteronemia, which explains, in part, some of the changes in fat distribution observed in these men. Levels of leptin can be brought down by androgen supplementation (Luukkaa et al, 1998), which usually results in an improvement in obesity. **The linkage between obesity and prostate cancer is of interest. Obesity contributes to a higher risk for prostate cancer incidence and mortality as well as its aggressiveness and recurrence** (Ribeiro et al, 2004). It appears that the relationship is not simply due to the excess fats. The leptin receptor is expressed in prostatic tissue, leptin promotes prostate growth during puberty, and it might stimulate cancer development by a direct effect on the gland (Stattin et al, 2001). It has been shown that there exists an inverse correlation between plasma leptin and T levels in men with advanced prostate cancer. Equally relevant is the finding that leptin is capable of inducing proliferation of androgen-independent prostate cancer cells. The role of leptin in prostate cancer remains to be fully explored (Behre et al, 1997).

TREATMENT OF TESTOSTERONE DEFICIENCY SYNDROME

The clinical picture of TDS or LOH is not specific, and some manifestations can be effectively treated with methods other than sex hormone administration. Changes in lifestyle (smoking and alcohol abuse cessation) should be advised to all patients. Diet and exercise do decrease visceral obesity and improve muscle strength and sensation of well-being. Bisphosphonates are effective drugs for osteoporosis, and antidepressants and counseling work well for dysphoria. However, programs of lifestyle changes are characterized by a high dropout rate or only intermittent adherence. In most cases, in the presence of confirmed hypogonadism, the administration of T alone results in significant improvement in many of the signs and symptoms of the condition. That better results are achieved with lifestyle changes and additional nonhormonal medications is not debatable.

In clinical practice there are few valid and specific reasons to withhold T treatment in men with TDS. The case for treatment is compelling. It was suggested that hypogonadism did not influence life expectancy, as reported in a historical analysis of castration (n = 50) (Nieschlag et al, 2004). A retrospective study (Tomlinson et al, 2001) suggests a more realistic view: standardized mortality ratio is significantly higher in men with untreated gonadotropin deficiency compared with those treated with sex steroids and healthy control subjects. Hypogonadism was associated with increased mortality in males (Shores et al, 2006) and, more recently, TDS was found to be clearly associated with increased risk of death independently of multiple risk factors and preexisting conditions (Laughlin et al, 2008).

Options for Treatment with Testosterone

There is an ever-increasing selection of T delivery formulations available, of which the vast majority is safe and effective. Currently obtainable preparations of T are listed in Table 29–6.

Table 29–6.

Most Frequently Used Testosterone Preparations

	GENERIC NAME	TRADE NAME	DOSE	COMMENTS
Injectable	Testosterone cypionate	Depo-Testosterone cypionate	200-400 mg q 3-4 wk	Supraphysiologic levels Roller-coaster effect
	Testosterone enanthate	Delatestryl	200-400 mg q 4 wk	Same as cypionate
	Testosterone undecanoate*	Nebido	700-1000 mg q 12-14 wk*	Stable levels; unavailable in North America
Oral/buccal	Buccal tabs	Striant	30 mg bid	Inconvenient
	Methyltestosterone†	Metandren	10-30 mg/day	Liver toxicity
	Testosterone undecanoate	Andriol Testocaps	120-160 mg/day	Not available in United States
Transdermal	Testosterone patch	Androderm	5 mg/day	Skin reactions Visible
		Testoderm	10-15 mg/day	Skin reactions
	Testosterone gel	Androgel/Testim	5-10 g/day	Good tolerability. Reproduces circadian rhythm. Variable sites for application.
		Axiron (axillary application)	30-90 mg/day	
		Fortesta (thigh application)	40 mg/day	

*Requires a loading dose of 3 × 1000 mg every 6 weeks for naive patients or of 2 × 1000 mg every 8 weeks for those switching from a different testosterone formulation.
†As 17α-alkylated testosterone products, both fluoxymesterone and methyltestosterone are associated with potential for serious liver toxicity.

Intramuscular Injections

Intramuscular injections of T are long acting and reach a maximum concentration at about 72 hours. They do not provide normal circadian patterns of serum T. Levels of DHT are usually normal, but E_2 levels may become excessive in some men. In the first few days after injection, supraphysiologic serum T levels occur. These injections are commonly administered every 10 to 21 days to maintain normal average T levels; baseline values are reached at approximately 21 days. These T preparations are cost efficient and proven effective (Amory et al, 2004). Injectable T undecanoate (Nebido) is a newcomer. After a loading dose, administration of 750 to 1000 mg every 12 weeks resulted in stable serum levels within the normal range (Morales et al, 2006; Morgentaler et al, 2008). This product is not yet available in North America.

Oral Preparations

Oral agents include the alkylated preparations, which are generally associated with erratic androgenic effects, significant changes in lipid profile, and a risk of liver toxicity. They are not recommended. Although not available in the United States, oral T undecanoate (Andriol) is commonly used throughout the world. It is free of liver toxicity but may result in supraphysiologic levels of DHT (Gooren, 1994). It is taken daily with meals containing more than 20 g of fat for T to be absorbed. Cost considerations make it impractical to treat severe hypogonadism.

Buccal and Nasal Methods

A mucoadhesive delivery system (Striant) can be placed against the gum twice a day (30 mg). To diminish the incidence of local irritation (about 9%), the site of application should be alternated. It is somewhat inconvenient. The nasal route for T administration is being investigated with encouraging results (Mattern et al, 2008).

Transdermal Testosterone Therapy

Transdermal T therapy is available in patches and gels. Both result in normal serum T levels and reproduce the diurnal physiologic variations with normal E_2 and DHT levels. Drawbacks of the patches include their visibility and skin reactions (Jordan and Atkinson, 1998). **Transdermal T gel preparations are better tolerated (minimal skin irritation).** All require daily application to upper abdomen, chest, or upper arms, avoidance of showers or baths for 2 to 4 hours (residence required for absorption), as well as direct skin-to-skin contact with other persons to prevent transfer of T. They improve sexual function and mood and increase lean body mass and muscle strength and decrease fat mass (Wang et al, 2004b). The studies, however, are limited in the size of the sample, the age range of the participants, and the length of follow-up. A newer adhesive matrix patch formulation is available only in Europe. In the fourth quarter of 2010, two newer transdermal formulations were approved by the FDA: Axiron for axillary application and Fortesta for application on the thighs.

Dihydrotestosterone

The use of DHT as an alternative to T appears occasionally in the literature (Kunelius et al, 2002). **The main argument for the use of DHT is that it is not aromatizable and, as such, may prevent prostate enlargement (believed to require both androgens and estrogens).** The transdermal DHT preparation is easy to use, but long-term studies are still lacking and its use outside proper trials is not recommended (Wang and Swerdloff, 2002).

7α-Methyl-19-Nortestosterone

Effective androgens that spare the adverse effects of T are of interest. Among the drugs better recognized is 7α-methyl-19-nortestosterone (MENT). It has high biopotency per molecule (about 10 times more than T), does not undergo 5α reduction, but retains its capacity to be aromatized to E_2. It has antigonadotropic properties and anabolic effects on muscles, and its effects on the prostate are less pronounced than those of T (Kumar et al, 1999).

Selective Androgen Receptor Modulators

The therapeutic potential of selective estrogen receptor modulators (SERMs) in women has set the stage for the development of selective androgen receptor modulators (SARMs). The availability of these molecules with their diversity of ligands provides the opportunity to explore the utility and activities of SARMs (Negro-Vilar, 1999). Various SARMs are under active investigation.

Key Point: Choice of Preparation

- The choice among T preparations depends on **A**vailability, **S**afety, **T**olerability, **E**fficacy, and **P**reference (by patient and physician): **ASTEP.**

Objective Effects of Testosterone

Administration of T to hypogonadal men results in a variety of positive effects (see Table 29–1).

Body Composition and Strength

Studies consistently report changes in body composition with T therapy (Snyder et al, 1999). The magnitude of the fat mass changes in older men appeared similar to that seen with T replacement in young hypogonadal men, whereas the lean body mass changes produced were usually less dramatic. In terms of strength changes, the effects are more limited in older men. Most studies noted an increase in grip strength with T treatment (Vermeulen, 2002); **the effects are significant even when T is administered with finasteride, indicating that DHT is not necessary for these positive actions** (Page et al, 2005). The preservation of the anabolic effects of T while safeguarding prostate health by inhibition of conversion of T to DHT with the simultaneous use of T and finasteride is an important observation. It has been documented in animal studies (Borst et al, 2007) as well as human clinical trials (Page et al, 2005; Jacobsen et al, 2008).

Bone

A number of studies have evaluated the effects of T therapy on bone mineral density or biochemical parameters of bone turnover in older men. These studies have lasted from 3 to 36 months, with the shorter-term trials evaluating only bone turnover parameters. **T therapy was reported to slow the rate of bone degradation and significantly increase bone mineral density, especially in the lumbar spine** (Szulc et al, 2003). **No study has yet conclusively demonstrated the effect of T therapy in the prevention of osteoporotic fractures.**

Cardiovascular System

Most epidemiologic studies have shown that higher serum T levels correlate with lower, rather than higher, cardiovascular disease risk in men (Rosano et al, 2007). Cardiovascular disease risk factors that might be affected by sex steroids include serum lipoprotein profiles, vascular tone, platelet and red blood cell clotting parameters, and the direct process of atherogenesis commonly leading to ED (Corona et al, 2008). The effects on serum lipoprotein levels in older men are the one area in which T therapy has been more extensively evaluated (Jockenhovel et al, 1999). In general, **T therapy in older men leads to a decrease in total and low-density lipoprotein cholesterol levels with no change or a small decrease in high-density lipoprotein cholesterol levels. These lipoprotein changes are modest, and the ultimate impact on cardiovascular disease is unknown.**

Sexual Function

The efficacy of T administration to men with sexual dysfunction needs to be discussed in two different areas: sexual desire and erectile function.

Sexual Desire. Hypogonadal men frequently experience hypo active sexual desire disorder (HSDD). The threshold of serum androgen levels for adequate libido, however, exhibits large interindividual variability and is largely dependent on a number of intrapsychic and environmental factors (Morley, 2003). As monotherapy, T administration is successful in a majority of patients but it is difficult to assess outcomes of sexual interest and there is a need for large controlled studies in this area. It is, however, widely recognized that HSDD and low serum T levels clearly indicate a need for therapy (Zitzmann et al, 2006).

Erectile Dysfunction. An adequate amount of T is essential for the cascading of mechanisms driving the penile erectile response: production of nitric oxide synthase, release of nitric oxide, and augmentation of the synthesis of cyclic guanine monophosphate leading to arteriolar dilatation and relaxation of the corporeal smooth muscle. **When a critical low-androgen milieu is reached, this complex process is blunted or fails altogether.** The critical androgen level for adequate maintenance of the process remains to be determined, but, undoubtedly, it exhibits large interindividual (and possibly some intraindividual) inconsistency. For this reason, **in the presence of a combination of erectile insufficiency and hypotestosteronemia, a tr ial of supplemental androgen is justified. If no success is evident, other causes need to be explored** (Morales et al, 2004).

Synergism of Testosterone with Phosphodiesterase-5 Inhibitors

In cases of recalcitrant ED, a multipronged pharmacologic approach may be more effective than the single-agent management. Specifically in cases of ED and hypogonadism the available evidence is encouraging. Aversa and associates (2003) showed in a small, controlled, randomized study that hypogonadal patients in whom sildenafil failed could be rescued by the administration of T. The proposed mechanism of action in the study was vascular because increased arterial dilatation was documented by Doppler ultrasonography. These findings have been supported by the report of Shabsigh and coworkers (2004) that showed a significantly better response in the erectile function domains for the combination of T plus sildenafil compared with sildenafil alone in hypogonadal men. Kalinchenko and colleagues (2003) treated a group of type 2 diabetics with sildenafil. In the group of hypogonadal patients who had initially failed a trial of sildenafil alone, 70% responded to the combination of sildenafil and oral T undecanoate. Further exploration of class agents (i.e., phosphodiesterase-5 inhibitors, dopaminergic agonists) in combination with androgens should be pursued.

Adverse Effects of Testosterone Treatment

The presence of prostate or breast carcinoma is an absolute contraindication for T treatment. However, T administration can result in adverse effects that are particularly significant in elderly persons.

Fluid retention is rarely seen. In the chronically ill or frailer older man, fluid retention might pose a concern.

Liver toxicity is not a problem with modern T preparations.

Sleep apnea has been reported to be exacerbated by T therapy. A 36-month trial of T in older men found no effect on apneic or hypoapneic episodes (Luboshitzky et al, 2002).

Gynecomastia occurs rarely because of the relatively greater increase in serum E_2 levels. Often this side effect can be overcome with a downward adjustment of the T dose.

Prostate

The main concern about T supplementation relates to prostate safety. Both benign prostatic hyperplasia and prostate cancer are diseases common in older men and believed to be promoted by androgens, although endogenous levels do not correlate with prostatic cancer (Roddam et al, 2008). **Androgen deprivation therapy has been used for the treatment of both of these processes, but whether T therapy for an older man places him at increased risk for developing clinically significant prostate disease from a preexisting but subclinical condition is unknown.** There have been at least 22 T replacement trials, involving a total of 583 men aged 45 to 89 years, in which serum PSA levels were measured. Sixteen of the 22 studies showed no increase in PSA with T therapy. In the six studies showing a PSA rise with T, the average PSA change was 0.48 ng/mL and the average PSA velocity was 0.52 ng/mL/yr. Seven T replacement trials in older men have evaluated prostate size, maximum urine flow rates, and International Prostate Symptom Scores. None of them showed any change in these parameters with treatment (Morales, 2002). The data suggest that, in the short term (up to 3 years), T therapy in the older man has little effect on the prostate. **If T promotes prostate growth, how does one manage T deficiency in the presence of a normal PSA?** The evidence remains sparse, but two studies provide guidance in this regard. Morgentaler and colleagues (2006) showed an increased risk of prostate cancer in association with the severity of the hypogonadism in men with PSA levels of 4 ng/mL or less. Another study (Rhoden et al, 2008) showed that a low ratio of T to PSA is an independent predictor of prostate cancer in men with TDS; ratios of less than 1.8 were associated with greater than a threefold increase in cancer risk. **Taken together, these studies would suggest that a more aggressive approach to rule out prostate cancer is warranted in men with hypogonadism in the presence of a normal digital rectal examination and PSA test result. However, because both prostate cancer and benign prostatic hyperplasia are diseases with long natural histories and the observation time to date with T therapy in older men is limited to less than 900 man-years, it is possible that T therapy might have long-term effects on the prostates of older men.**

T supplementation after successful treatment of prostate cancer is now under investigation. Although the numbers are small, the limited evidence in cases of radical prostatectomy, brachytherapy, or external-beam radiation (Morales et al, 2008) is comforting. All studies have used standard PSA measurements as parameters to initiate therapy and to follow these patients. The ultrasensitive assay may permit early initiation of T supplementation after radical prostatectomy. After brachytherapy and external-beam radiotherapy the situation is more complex because in these situations the PSA may not reach undetectable levels. A stable nadir may prove to be acceptable.

Polycythemia

T therapy in older men can often result in a significant increase in red blood cell mass and hemoglobin levels. This may lead to termination of therapy, a decrease of dose, or a switch to a different formulation of T. The method of T replacement may affect the magnitude of the change in red blood cell mass.

RECOMMENDATIONS AND GUIDELINES

Despite the long time since the synthesis and initial use of T in clinical practice there is a scarcity of credible, well-designed trials to document its safety and efficacy. The completion of large studies on hormone replacement in postmenopausal women brought into sharp focus the inadequacy of limited trials (Writing Group for the Women's Health Initiative Investigators, 2002). **It is, however, unhelpful and misleading to assume that the results of the Women's Health Initiative on hormone replacement therapy (HRT: estrogen ± progesterone) in postmenopausal women apply equally to the men's situation; such an assumption does not take into consideration the large differences in the molecular structures and actions of the hormones themselves and the gender responses to them** (Goderie-Plomp et al, 2004). Although it is tempting to equate the possible effects of HRT in the development of breast cancer to androgen replacement therapy (ART) in prostate cancer, the biologic behavior and clinical management of the two tumors are markedly dissimilar. It is estimated (Bhasin et al, 2003) that some 5000 hypogonadal men receiving T supplementation for a period of 5 years are needed to have a study of the magnitude of the Women's Health Initiative. Alternatives to such a difficult and unrealistic study are currently under scrutiny.

The Institute of Medicine Report

In an extensive and comprehensive publication, a committee of the Institute of Medicine (IOM) analyzed the current status of androgen therapy in men. The report (available on the Internet at http://www.iom.edu or in hard copy) (Liverman et al, 2004) contains several recommendations (Table 29–7). The gist of the report is that initially the efficacy of T treatment should be assessed in a limited trial. Only if a positive response is found should the investigations proceed to the large studies designed to evaluate safety. **Although no one would question the need for and importance of these studies, it is also clear that reliable answers will not be available for at least 10 to 15 years after the completion of the efficacy studies and the subsequent safety trials.** For the practicing physician, it is not logical to wait that long until all conclusive evidence is complete. When indicated, action needs to be taken on the basis of the most reliable information at hand regarding the advantages and drawbacks of T treatment and guidelines and recommendations available from professional societies.

Table 29–7.

Summary of the Institute of Medicine Recommendations

Need for clinical trials exists.
Focus on populations most likely to benefit.
Use for treatment not for prevention.
Focus on clinical outcomes with preliminary evidence of benefit.
Begin with short-term efficacy trials.
Conduct longer-term studies if short-term efficacy is established.
Ensure safety of research participants.

Endocrine Society Guideline and the European Association of Urology Recommendations

The Endocrine Society Guideline is an important document that became the standard practice because of the reliability of the evidence-based criteria used and the high credibility of the sponsoring society. However, the document was "developed to be of assistance to endocrinologists…" (Bhasin et al, 2010) and does not contemplate several issues of importance for the urologist. For this reason, the Recommendations, jointly sponsored, among others, by the European Association of Urology, the International Society for the Study of the Aging Male and the International Society of Andrology (Wang et al, 2009) are included here, replacing the ones from the previous edition.

The recommendations that follow have been adapted (mostly because of space restrictions) from the ones published recently (Wang et al, 2009). They are categorized by the level of evidence and grade of recommendation according to the U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research (1992).

Recommendation 1: Definition

- TDS/LOH is a clinical *and* biochemical syndrome associated with advancing age and characterized by symptoms *and* a deficiency in serum T levels. It may result in significant detriment in the quality of life and adversely affect the function of multiple organ systems.

Recommendation 2: Clinical Diagnosis

- 2.1. The diagnosis of TDS requires symptoms and signs suggestive of T deficiency (level 3, grade A). Most common symptom is low libido (level 3, grade A). Others include ED, sarcopenia, osteopenia/osteoporosis, increased body fat, decreased vitality, and low mood. None of them is specific for T deficiency and must be corroborated with a low T level (level 3, grade A).
- 2.2. Questionnaires such as AMS and ADAM are not recommended for diagnosis of hypogonadism because of low specificity (level 3, grade B).

Recommendation 3: Laboratory Diagnosis

- 3.1. Patients suspected of TDS need a biochemical workup (level 4, grade A). Risk factors for hypogonadism in older men include chronic illnesses (diabetes, chronic

obstructive lung disease, and renal and HIV-related diseases), obesity, metabolic syndrome, and hemochromatosis (level 4, grade A).

- 3.2. A sample for T determination should be obtained between 7:00 and 11:00 AM (level 2a, A). The most widely accepted test is serum total T. Generally levels above 12 nmol/L (350 ng/dL) do not require substitution. Men with T levels below 8 nmol/L (230 ng/dL) usually benefit from T treatment. If the levels are between 8 to 12 nmol/L, repeating the measurement of total testosterone once or twice may be helpful.
- 3.3. Measurement of free or bioavailable T should be considered when the total T is not diagnostic, particularly in obese men.
- 3.4. Equilibrium dialysis is the gold standard for free T measurement. Free T assays based on immunoassays are widely available but do not give an accurate measurement of free T; thus they should not be used. Calculated free T correlates well with free T by equilibrium dialysis (level 2b, grade A).
- 3.5. Salivary T may be a reliable substitute for free T measurements but cannot yet be recommended because the methodology has not been standardized (level 3, grade B).

Recommendation 4: Assessment of Treatment Outcome and Decisions on Continued Therapy

- Improvement in TDS manifestations should be sought. Failure to benefit within a reasonable interval (3 months is adequate for sexual function, others require a longer interval) should result in discontinuation of treatment. Seeking other causes of symptoms is then mandatory (level 1b, grade A).

Recommendation 5: Body Composition

- T administration improves body composition in hypogonadal men (decrease fat mass, increase lean body mass) (level 1b, grade A).

Recommendation 6: Bone Density and Fracture Rate

- Osteopenia/osteoporosis and fracture prevalence rates are greater in hypogonadal men. Bone density in hypogonadal men increases under T treatment (level 1b, grade A).

Recommendation 7: Testosterone and Sexual Function

- 7.1. The initial assessment of all men with ED and/or diminished libido should include determination of serum T. These dysfunctions, with or without T deficiency might be related to comorbidities or medications (level 2a, grade A).
- 7.2. Men with ED and/or diminished libido and documented T deficiency are candidates for therapy (level 2a, grade A). An inadequate response to treatment requires reassessment of the causal mechanisms.
- 7.3. In the presence of a TDS picture and borderline serum T levels, a short (e.g., 3 months) therapeutic trial may be justified. An absence of response calls for discontinuation of T administration. A satisfactory response might be placebo generated so that continued assessment is advisable before long-term treatment is recommended (level 2a, grade B).
- 7.4. There is evidence suggesting therapeutic synergism with combined use of T and phosphodiesterase-5 inhibitors in hypogonadal men (level 1b, grade B). These observations require additional study. It is unclear whether men with hypogonadism and ED should be treated initially with phosphodiesterase-5 inhibitors, T, or the combination of the two.

Recommendation 8: Testosterone and Obesity, Metabolic Syndrome, and Type 2 Diabetes

- Several components of the metabolic syndrome are also present in hypogonadal men. Epidemiologic studies have established a close relationship between obesity and low T in healthy men. T should be measured in men with type 2 diabetes mellitus with manifestations of TDS (level 2b, grade A).

Recommendation 9: Carcinoma of the Prostate and Benign Prostatic Hyperplasia

- 9.1. There is no conclusive evidence that T therapy increases the risk or carcinoma of the prostate or benign prostatic hyperplasia. There is also no evidence that T treatment will convert subclinical prostate carcinoma to clinically detectable disease (level 4, grade C). However, there is unequivocal evidence that T can stimulate growth and aggravate symptoms in men with locally advanced and metastatic prostate carcinoma (level 2a, grade A). Adequately powered and optimally designed long-term prostate disease data are not available to determine whether there is any additional risk from T replacement. Patients should be counseled on the potential risks and benefits of T replacement before treatment and carefully monitored for prostate safety during treatment (level 3, grade A).
- 9.2. Prior to therapy with T, the risk of carcinoma of the prostate must be assessed using, as a minimum, direct rectal examination and PSA screening. Ultrasound examination or biopsies are not recommended as routine requirements.
- 9.3. During treatment, patients should be monitored for prostate disease at 3 to 6 months, 12 months, and at least annually thereafter (level 3, grade C). If the patient's risk of prostate carcinoma is high (changes in the direct rectal examination or PSA value) transrectal ultrasound-guided biopsies of the prostate are indicated (level 2b, grade A).
- 9.4. Severe lower urinary tract symptoms (>21 in IPSS) due to benign prostatic hyperplasia represent a temporary contraindication (level 3, grade C). After successful treatment of these symptoms this contraindication is lifted (level 4, grade C)
- 9.5. Men successfully treated for prostate carcinoma and suffering from confirmed TDS are potential candidates for T treatment after a prudent interval if there is no clinical or laboratory evidence of residual cancer. Because long-term outcome data are not available, clinicians must exercise good clinical judgment together with adequate knowledge of advantages and drawbacks of testosterone therapy in this situation (level 2b, grade C). The risks and benefits must be clearly discussed with and understood by the patient, and the follow-up must be particularly careful.

Recommendation 10: Treatment and Delivery Systems

- 10.1. Available intramuscular, subdermal, transdermal, oral and buccal preparations of testosterone are safe and effective (level 1b, grade A). The treating physician should have sufficient knowledge and adequate understanding of the pharmacokinetics as well as of the advantages and drawbacks of each preparation. The selection of the preparation

should be a joint decision of an informed patient and his physician.

- 10.2. Inadequate data are available to determine the optimal serum T level for efficacy and safety. Mid to lower young adult male levels seem appropriate as the therapeutic goal. No evidence exists for or against the need to maintain a circadian rhythm (level 3, grade B).
- 10.3. 17α-Alkylated preparations such as 17α-methyl-T should no longer be prescribed because of their potential liver toxicity (level 2b, grade A).

Recommendation 11: Adverse Effects and Monitoring

- 11.1. T treatment is contraindicated in men with prostate or breast cancer (level 3, grade A). T is relatively contraindicated in men at high risk of developing carcinoma of the prostate (family history).
- 11.2. Men with significant erythrocytosis (level 3, grade A), untreated obstructive sleep apnea (level 3, grade B), and untreated severe congestive heart failure should not be treated with T until resolution of the comorbid condition (level 3, grade B).
- 11.3. Erythrocytosis might develop during treatment, especially with injectable preparations. Periodic hematologic assessment is indicated. Dose adjustments and/or periodic phlebotomy may be necessary (level 3, grade A).

Recommendation 12: Age

- Age is not a contraindication to initiate testosterone treatment. Individual assessment of comorbidities and potential risks versus benefits of treatment is particularly important in elderly men (level 2a, grade A).

SUGGESTED READINGS

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chapter 30

Female Sexual Function and Dysfunction

Courtenay Kathryn Moore, MD

Female Sexual Anatomy and Physiology
Endocrine Factors
Physiology of Female Sexual Response Cycle
Classification and Epidemiology
Diagnosis
Treatment
Conclusion

"I think sex is here to stay."

—*Groucho Marx*

Urologists are well versed in the diagnosis and treatment of male sexual dysfunction. However, what is less commonly recognized but demonstrated in several studies is that male erectile dysfunction negatively impacts female sexual function and sexual quality of life (Fisher et al, 2005; Rosen et al, 2007). It was not until recently that urologists actually began to consider female sexual function as relevant to their practice. Based on the National Health and Social Life Survey, sexual dysfunction is actually more prevalent in women (43%) than in men (31%). Other studies suggest female sexual dysfunction (FSD) affects 25% to 76% of women in the United States. In one study, 98% women seeking routine gynecologic care had sexual concerns (Nusbaum et al, 2000).

Despite the high prevalence of sexual problems among women, physicians and patients alike are hesitant to initiate conversations about female sexual health. In a study of 471 physicians, only 22% stated they always screen for FSD whereas 55% screen most of the time and 23% never or rarely screen their patients (Pauls et al, 2005). Physicians cited various reasons for their lack of screening for FSD, the most common being lack of time. The majority of respondents (69%) underestimated the prevalence of FSD in their patient population. Fifty percent believed that their training and ability to treat FSD was unsatisfactory. Bachmann (2006) conducted a similar survey among physicians and health care providers attending the annual meetings of four specialty societies. Of the 1946 participants 42% did not inquire about FSD, citing limitations in time and training, embarrassment, and the absence of effective treatments as obstacles to discussing FSD. Sixty percent of participants rated both their knowledge and comfort level with FSD as fair or poor, whereas 86% rated treatment options as fair or poor.

Over the past 5 years the urologic literature has shown that a significant number of women with female pelvic floor disorders also report FSD. The aim of this chapter is to characterize female sexual function and dysfunctions while making urologists aware of the magnitude of FSD and providing them with information to diagnose and treat FSD in patients suffering from urologic conditions.

FEMALE SEXUAL ANATOMY AND PHYSIOLOGY

Genital Anatomy

The organs of the female reproductive tract are classically divided into the external and the internal genitalia. The external genital organs include the mons pubis, clitoris, urethral meatus, labia majora, labia minora, vestibule, Bartholin glands, and Skene glands. The internal genital organs are located in the true pelvis and include the vagina, uterus, cervix, oviducts, ovaries, and surrounding supporting structures.

The *vulva* is a collective term for the female external genitalia. The vulva consists of the mons pubis, labia majora, labia minora, hymen, clitoris, vestibule, urethra, Skene glands, Bartholin glands, and vestibular bulbs. The boundaries of the vulva extend from the mons pubis anteriorly to the rectum posteriorly and laterally to the genitocrural folds.

The labia majora are two large, longitudinal, cutaneous folds of adipose and fibrous tissue that extend from the mons pubis to the posterior fourchette. The skin of the outer convex surface of the labia majora is pigmented and covered with hair follicles. The inner surface does not have hair follicles but has many sebaceous glands. Histologically the labia majora have both sweat and sebaceous glands. The labia majora are homologous to the scrotum in the male. The labia minora, which are homologous to the penile urethra, are two smaller folds located between the labia majora and the vaginal orifice. Anteriorly they divide at the clitoris to form the prepuce superiorly and the frenulum of the clitoris inferiorly. Histologically they are composed of dense connective tissue with erectile tissue and elastic fibers rather than adipose tissue. The skin of the labia minora is less cornified and has many sebaceous glands but no hair follicles or sweat glands (Katz et al, 2007). The labia minora surround a space called the vestibule, into which the orifices of the urethra, vagina, and Bartholin glands open.

Bartholin glands are vulvovaginal glands located on the posterolateral aspect of the vaginal orifice at the 4- and 8-o'clock positions. Bartholin ducts open into the groove between the hymen and the labia minora and are homologous to Cowper glands in the male.

Skene glands, or paraurethral glands, are tubular glands adjacent to the distal urethra. Skene ducts run parallel to the long axis of the urethra for approximately 1 cm before opening into the distal urethra (Katz et al, 2007). Skene glands are homologous to the prostate in the male.

Lying anteriorly to the urethra is the clitoris. The average length of the clitoris is 1.5 to 2 cm. The clitoris consists of the glans, the body, and two crura, which attach to the periosteum of the symphysis pubis. The glans is the visible external portion of the clitoris. The clitoral body has two cylindrical corpora cavernosa composed of thin-walled, vascular channels that function as erectile tissue. The clitoris is the female homologue of the penis in the male.

Deep to the labia, immediately below the bulbocavernous muscle, are two erectile bodies called the vestibular bulbs. Each bulb is attached to the inferior surface of the perineal membrane and covered by the bulbocavernosal muscle. During sexual arousal the bulbs become engorged, thereby narrowing the vaginal opening.

Central and Peripheral Nervous System

The innervation of the internal genitalia is primarily by the autonomic nervous system. The sympathetic portion of the autonomic nervous system originates in the thoracic and lumbar portions of the spinal cord, and sympathetic ganglia are located adjacent to the central nervous system. In contrast, the parasympathetic portion originates in cranial nerves and the middle three sacral segments of the cord and the ganglia are located near the visceral organs. As a broad generalization, sympathetic fibers in the female pelvis produce muscular contractions and vasoconstriction whereas parasympathetic fibers cause the opposite effect on muscles and vasodilation.

The pudendal nerve and its branches supply the majority of both motor and sensory fibers to the muscles and skin of the vulvar region. The pudendal nerve arises from the second, third, and fourth sacral roots. As the pudendal nerve reaches the urogenital diaphragm it divides into three branches: the inferior hemorrhoidal, the deep perineal, and the superficial perineal. The dorsal nerve of the clitoris is a terminal branch of the deep perineal nerve.

The skin of the anus, clitoris, and medial and inferior aspects of the vulva is supplied primarily by distal branches of the pudendal nerve. The vulvar region receives additional sensory fibers from three nerves. The anterior branch of the ilioinguinal nerve sends fibers to the mons pubis and the upper part of the labia majora. The genital femoral nerve supplies fibers to the labia majora, and the posterior femoral cutaneous nerve supplies fibers to the inferoposterior aspects of the vulva.

The female sexual response is mediated primarily via spinal cord reflexes that are under descending control from the brainstem. The nucleus paragigantocellaris, which projects directly to the pelvic efferent neurons and interneurons in the lumbosacral spinal cord, is believed to play a role in female orgasm (Meston, 2000; Meston and Frohlich, 2000). The pelvic efferent neurons and interneurons in the lumbosacral spinal cord contain the neurotransmitter serotonin (Walsh et al, 2002). Serotonin applied to the spinal cord inhibits spinal sexual reflexes and may explain selective serotonin reuptake inhibitor (SSRI)-induced anorgasmia (Meston, 2000). The raphe nuclei and pallidus, the magnus and parapyramidal region, and the locus ceruleus all project to the lumbosacral spinal cord and are believed to play a role in sexual function with the periaqueductal gray area acting as a relay center for sexual stimuli (Meston, 2000; Meston and Frohlich, 2000).

In males the hypothalamic medial preoptic area, which has widespread connections to the limbic system and brainstem, functions in the ability to recognize a sexual partner. In female animals, lesions to this area increase not only lordosis but also avoidance (Meston, 2000). During orgasm and arousal oxytocin is released from neurons in the paraventricular nucleus of the hypothalamus.

c-FOS staining during copulatory testing in animals has identified the medial amygdala and the red nucleus of the stria terminalis of the forebrain as playing a role in female sexual function. Stimulation of these areas results in subjective pleasurable responses in both males and females.

More recently functional magnetic resonance imaging (MRI) studies have been used to identify specific patterns of brain activation in the female sexual response. A study by Park and coworkers (2001) reported significant activation of the inferior frontal lobe, cingulate gyrus, insula, hypothalamus, caudate nucleus, globus pallidus, and inferior temporal lobe in women watching erotic films. In another study Jeong and associates (2005) compared brain activation in premenopausal and postmenopausal women watching erotic videos. Premenopausal women were found to have greater activity in whole brain and limbic, temporal, and parietal lobes whereas postmenopausal had greater activation in the superior frontal gyrus. A study by Arnow and associates (2009) compared functional MR images after erotic videos in women with and without a history of hypoactive sexual desire disorder (HSDD) and reported significantly greater activity in the entorhinal cortex in women with no history of sexual dysfunction and higher activation in the medial frontal gyrus and putamen in women with HSDD. These findings suggest that women with HSDD have a shift in attentional focus from erotic cues to a self-monitoring of sexual response and performance concerns, underscoring the neural correlates of heightened self-focus that clinically characterizes women with HSDD (Arnow et al, 2009).

ENDOCRINE FACTORS

Estrogen and Progesterone

Traditionally three sex steroids have been implicated in female sexual behavior: estrogens, progestins, and androgens. In premenopausal woman, with normal ovulation, estrogen and progesterone levels are maintained until menopause. In premenopausal women the primary source of estradiol production is from the ovaries, under the control of follicle-stimulating hormone and inhibin produced by the pituitary gland, with less contributed from the adrenal gland and ovarian androgen precursors (Simpson, 2000; Davis et al, 2004; Giraldi et al, 2004). During the late follicular phase and in the luteal phase of the menstrual cycle there is a rise in estradiol. During the luteal phase there is also a rise in progesterone. Estradiol and progesterone levels fall abruptly at the time of menopause when ovulation ceases (Simpson, 2000; Davis et al, 2004; Giraldi et al, 2004).

Recent research suggests that estrogen and progesterone have little direct influence on female desire. Schreiner-Engel and

coworkers (1989) found no significant difference in the estrogen levels of women with and without clinically diagnosed HSDD. Numerous studies have also shown no change in sexual desire with the administration of exogenous estrogen therapy alone in women (Furuhjelm et al, 1984; Nathorst-Boos et al, 1993a, 1993b). However, administration of both estrogen and androgen in natural and surgically menopausal woman has been shown to restore normal levels of sexual desire (Sherwin and Gelfand, 1985a). Although lack of estrogen may not directly impair female arousal and desire, it can indirectly impair sexual function by decreasing vasocongestion and lubrication and vaginal epithelial atrophy. Because estrogen plays a role in the regulation of vaginal and nitric oxide synthase expression, both naturally and surgically induced menopause result in decreased vaginal and nitric oxide synthase expression, resulting in apoptosis of the vaginal wall, smooth muscle, and epithelium. Treatment with estrogen therapy increases nitric oxide synthase expression, restores vaginal lubrication, and decreases dyspareunia, resulting in improved female sexual satisfaction.

In general, progestins do not have a direct impact on female sexual function. Although oral contraceptives that increase progesterone levels have been associated with decreased sexual desire and interest, treatment with progesterone alone has not been shown to improve sexual desire in either premenopausal or menopausal women (Persky, 1976; Schreiner-Engel et al, 1981; Leiblum et al, 1983; Sherwin and Gelfand, 1985b). Indirectly, progesterone may affect female sexual behavior by increasing depressive moods. It is believed that progesterone and estradiol compete for receptors in the central nervous system, and higher ratios of progesterone to estradiol correlate with unpleasant feelings and depressive moods (Persky et al, 1982).

Testosterone

Premenopausal women also produce 0.3 mg of testosterone daily. Unlike in men, 50% of testosterone production in women comes directly from the ovaries and the adrenal glands, with the remaining 50% produced by testosterone precursors such as androstenedione and dehydroepiandrosterone (DHEA) in peripheral tissues (Walsh et al, 2002). Only 2% of the total testosterone is free, whereas 98% is bound to albumin or sex hormone–binding globulin (SHBG). Fluctuations in SHBG alter the bioavailability of free testosterone. The administration of exogenous estrogens, such as oral contraceptives, increases hepatically synthesized SHBG, thereby reducing the bioavailability of free testosterone. Oral contraceptives also diminish follicle-stimulating hormone and luteinizing hormone levels, thereby suppressing ovulation and inhibiting androgen production. The combination of these two mechanisms may lead to very low circulating levels of free and bioavailable testosterone. Several studies have documented the negative effects of oral contraceptives on sexual function, including diminished sexual interest and arousal, suppression of female-initiated sexual activity, and decreased frequency of sexual intercourse and sexual enjoyment (Basson et al, 2004; Davis et al, 2004; Nappi et al, 2005). In premenopausal women with regular menstrual cycles, testosterone and androstenedione rise in the late follicular and luteal phases (Vierhapper et al, 1997). In premenopausal women there is also a diurnal variation in testosterone, with levels peaking in the morning (Vierhapper et al, 1997).

Unlike estrogen and progesterone levels, which fall abruptly with menopause, testosterone levels diminish gradually throughout life. Between the ages of 30 and 60, total and free testosterone levels decrease by 50% (Basson, 2008). In addition, adrenal precursors, DHEA and DHEA sulfate, decrease with increasing age (Baulieu, 1996; Baulieu et al, 2000). Decreased androgen levels associated with aging have been associated with decreased libido, arousal, orgasm, and genital sensations.

In addition to aging there are several clinical conditions in premenopausal women that are associated with low testosterone levels. Hyperprolactinemia and adrenal insufficiency can cause hypogonadotropic hypogonadism and loss of libido. Cushing disease or endogenous or exogenous glucocorticosteroid excess leads to adrenal suppression and androgen insufficiency and indirectly inhibits sexual function. Symptoms of androgen insufficiency include diminished sense of well-being or dysphoria; unexplained fatigue; decreased libido, sexual receptivity, and pleasure; and vasomotor instability or decreased vaginal lubrication despite adequate estrogen treatment. Bone loss, decreased muscle strength, and changes in memory or cognitive function are also possible as a result of diminished androgen production.

In studies of both naturally and surgically menopausal women the administration of testosterone alone, without estrogen replacement therapy, has been shown to improve desire, arousal, and sexual fantasies (Leiblum et al, 1983; McCoy and Davidson, 1985; Sherwin and Gelfand, 1985a). However, the effect of relationship between testosterone levels and desire in premenopausal women is less well defined. Several studies have failed to find differences in testosterone levels in premenopausal women with and without HSDD (Stuart et al, 1987; Schreiner-Engel et al, 1989). New data suggest that testosterone is beneficial in premenopausal women with HSDD who have low circulating testosterone levels (Schwenkhagen and Studd, 2009). Women placed on testosterone supplementation must be counseled regarding the potential risks and side effects of therapy, which include acne, hirsutism, male pattern baldness, clitoral hypertrophy, and increased triglyceride levels.

PHYSIOLOGY OF FEMALE SEXUAL RESPONSE CYCLE

Although detailed writings of female anatomy date back to medieval times it was not until the 1900s that female sexuality and the physiology of the female sexual response cycle were described. Prior to 1900 female sexuality was demonized and deemed inappropriate unless procreatory or tied to pleasuring one's husband. It was also widely believed that mental diseases in females resulted from abnormalities or excitation of the female external genitalia. It was not until 1953 when Arthur Kinsey published the controversial *Sexual Behaviour in the Human Female,* the first book to candidly report on female orgasm, masturbation, premarital sex, and infidelity, that the many myths surrounding female sexuality were dispelled.

Masters and Johnson were the first to study and report on sexual function and dysfunction. Published in 1966, the *Human Sexual Response* described the male and female sexual response cycle as four linear, successive phases: excitement, plateau, orgasm, and resolution. In females, the excitement phase begins with engorgement of the vaginal mucosa, thickening of the vaginal walls, and transudation of fluid into the vagina. There is engorgement of labia, clitoris, and vagina, with a resultant increase in vaginal and clitoral length. The breast become slightly enlarged from engorgement and the areolae become erect. Muscular tension, heart rate, and blood pressure rise slightly. In the plateau phase the labia become more engorged, the clitoris retracts, the outer one third of the vagina becomes more congested and narrow while the inner two thirds expand, and pelvic floor muscle tension builds. Orgasm

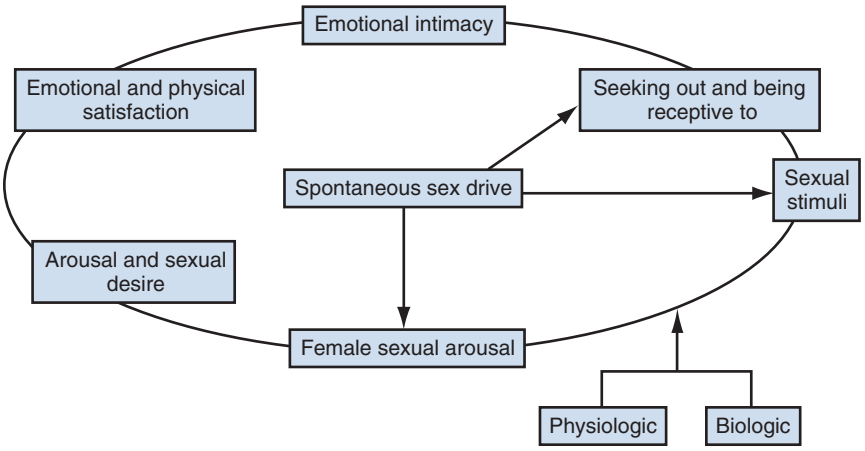


Figure 30–1. Female sexual response cycle.

is characterized by rhythmic contractions of levator ani, vagina, and uterus with massive release of muscular tension. During the resolution phase there is gradual diminishing of sexual muscular tension and detumescence of the labia, clitoris, and vagina.

In response to much criticism, Basson, in 2000, described a more contemporary nonlinear model of female sexual response, integrating emotional intimacy, sexual stimuli, and relationship satisfaction (Fig. 30–1). This model recognizes that female sexual functioning is more complex and is less linear than male sexual functioning. It also emphasizes that many women initially begin a sexual encounter from a point of sexual neutrality, with the decision to be sexual stemming from the conscious need for emotional closeness or as a result of seduction from a partner. As demonstrated by the model, arousal stems from intimacy and seduction and often precedes desire. This model emphasizes that women have many reasons for engaging in sexual activity other than spontaneous sexual drive. Sexual neutrality or being receptive to, rather than initiating sexual activity, is considered a normal variation of female sexual functioning.

CLASSIFICATION AND EPIDEMIOLOGY

Unlike male erectile dysfunction, female sexual disorders are more difficult to assess, diagnose, and treat. One of the initial barriers in the field of FSD was the lack of consensus of the definitions and criteria of these disorders. In 1998 the American Foundation of Urologic Disease Consensus convened to create a classification system and common terminology. It was at this conference that FSD was divided into four categories: sexual desire disorders, sexual arousal disorders, orgasmic disorders, and sexual pain disorders. In 2000 the panel reconvened and changed the classification schema to add "causing personal distress" as a criterion for diagnosis (Basson et al, 2000). This distinction is important because many studies on the prevalence of FSD have not qualified if the sexual symptoms reported caused "personal distress." In 2004 the Second International Consensus of Sexual Medicine, consisting of over 200 multidisciplinary experts from 60 countries, convened and revised the definitions for FSD (Table 30–1).

Estimates on the prevalence of FSD varies greatly depending on the definitions, the assessment tool used, and the demographics of the population (age, race, educational and marital status). Hayes and colleagues (2008) compared the difference in the prevalence of the types of FSD among 356 women using four different instruments and found that the prevalence varied substantially depending on the instrument used, leading to the conclusion that the instrument chosen to assess for FSD significantly affects prevalence estimates. U.S. population census data suggest that roughly 10 million American women aged 50 to 74 years self report complaints of diminished lubrication, pain during intercourse, decreased arousal, and difficulty achieving orgasm (Salonia et al, 2004).

Several studies have shown that the prevalence of FSD varies depending on age, with women older than age 45 years at an increased risk of having FSD (Shifren et al, 2008). Among women

Table 30–1.

Revised Definitions for Female Sexual Dysfunction from the Second International Consensus of Sexual Medicine

Hypoactive Sexual Desire Disorder: Absent or diminished feelings of sexual interest or desire, absent sexual thoughts or fantasies, and a lack of responsive desire. Motivations for attempting to become sexually aroused are scarce or absent. The lack of interest is considered to be beyond the normal decrease experienced with increasing age and relationship duration.

Subjective Sexual Arousal Disorder: Absent or markedly diminished feelings of sexual arousal from any type of sexual stimulation. However, vaginal lubrication or other signs of physical response still occur.

Genital Sexual Arousal Disorder: Complaints of impaired genital sexual arousal, which may include minimal vulvar swelling or vaginal lubrication from any type of sexual stimulation and reduced sexual sensations from caressing genitalia. However, subjective sexual excitement still occurs with nongenital sexual stimuli.

Combined Genital and Subjective Arousal Disorder: Absent or markedly diminished feelings of sexual arousal from any type of sexual stimulation plus complaints of absent or impaired genital sexual arousal.

Persistent Sexual Arousal Disorder: Spontaneous, intrusive, and unwanted genital arousal in the absence of sexual interest and desire. Arousal is unrelieved by orgasms and the feelings of arousal persist for hours or days.

Women's Orgasmic Disorder: Despite the self-report of high sexual arousal or excitement, there is either lack of orgasm, markedly diminished intensity of orgasmic sensations, or marked delay of orgasm from any kind of stimulation.

Dyspareunia: Persistent or recurrent pain with attempted or complete vaginal entry and/or penile-vaginal intercourse.

Vaginismus: Persistent or recurrent difficulties to allow vaginal entry of a penis, finger, or other object, despite the woman's desire to participate.

Sexual Aversion Disorder: Extreme anxiety or disgust at the anticipation of or attempt at any sexual activity.

aged 40 and older, the most common reported sexual problem was low desire (38.7% to 54%), difficulty with lubrication (21.5% to 39%), and inability to orgasm (20.5% to 34%) (Shifren et al, 2008).

Female pelvic floor disorders (incontinence, lower urinary tract symptoms, and pelvic organ prolapse) have also been shown to have a negative impact on female sexual function. Women with incontinence are up to three times more likely to experience decreased arousal, infrequent orgasms, and increased dyspareunia (Handa et al, 2004; Hansen, 2004; Laumann et al, 1999; Salonia et al, 2004). Several recent large studies have found a statistically significant improvement in sexual function scores among women who underwent successful surgery for incontinence and prolapse (Brubaker et al, 2009; Handa et al, 2007).

DIAGNOSIS

The first step in diagnosing FSD is to identify women with the problem. Plouffe (1985) and colleagues found three simple questions as effective at identifying sexual problems as a lengthy interview (Kammerer-Doak and Rogers, 2008).

1. Are you sexually active?
2. Are there any problems?
3. Do you have pain with intercourse?

Validated questionnaires are also valuable tools to help identify the presence or absence of a sexual problem. A list of questionnaires recommended by the 4th International Consultation on Incontinence for evaluation of sexual function and health in women with urinary symptoms by grade is shown in Table 30–2. For additional information regarding commonly used and validated sexual function assessment tools the reader is referred to the Baylor College of Medicine website (http://femalesexualdysfunctiononline.org/resources/) (Kingsberg and Janata, 2007).

After identifying patients at risk for FSD, the diagnosis of a problem relies on a careful clinical evaluation consisting of a detailed history, which includes sexual, medical, surgical, and

Key Points: Physiology

- Sex steroid hormones are critical for normal female sexual structure and function.
- Androgen sex steroid hormone values decline gradually in menopausal women whereas estrogen and progesterone decrease abruptly.
- Lack of estrogen may not directly impair female arousal and desire, but it can indirectly impair sexual function by decreasing vasocongestion and lubrication and vaginal epithelial atrophy.
- Progestins do not have a direct impact on female sexual function, but they may indirectly affect female sexual behavior by increasing depressive moods. Progesterone and estradiol compete for receptors in the central nervous system, and higher ratios of progesterone to estradiol correlate with unpleasant feelings and depressive moods.
- Decreased androgen levels associated with aging have been associated with decreased libido, arousal, orgasm, and genital sensations.
- Studies have also shown no change in sexual desire with the administration of exogenous estrogen therapy alone in women.
- The administration of testosterone alone, without estrogen replacement therapy, in both naturally and surgically menopausal women has been shown to improve desire, arousal, and sexual fantasies. However, the effect of relationship between testosterone levels and desire in premenopausal women is less well defined.
- Female pelvic floor disorders (incontinence, lower urinary tract symptoms, and pelvic organ prolapse) have also been shown to have a negative impact on female sexual function. Women with incontinence are up to three times more likely to experience decreased arousal, infrequent orgasms, and increased dyspareunia.

Table 30–2.

Questionnaires Recommended by the 4th International Consultation on Incontinence for Evaluation of Sexual Function and Health in Women with Urinary Symptoms

QUESTIONNAIRE	GRADE	NO. OF QUESTIONS	GOAL
Golombok-Rust Inventory of Sexual Satisfaction (GRISS)	A	28	Self-administered questionnaire assessing quality of heterosexual relationships and function in women currently in relationships
ICIQ-FLUTSsex (BFLUTS)	A	4	Self-administered questionnaire to assess affect of urinary symptoms on sexual function
Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ)	A	31	Self-administered questionnaire to assess sexual function in women with pelvic organ prolapse or incontinence
Brief Index of Sexual Function for Women (BISF-W)	B	22	Self-administered questionnaire to assess sexual function and satisfaction
Female Sexual Function Index (FSFI)	B	19	Self-administered questionnaire assessing six domains of sexual function
Sexual Quality of Life-Female (SQOL-F)	B	18	Self-administered questionnaire to assess impact of female sexual dysfunction on womens' quality of life
McCoy Female Sexuality Questionnaire (MFSQ)	C	19	Self-administered questionnaire to assess aspects of sexual function in postmenopausal women

Grade A: highly recommended indicating that the questionnaire is valid, reliable, and responsive to change following psychometric testing.
Grade B: valid and reliable.
Grade C: valid or reliable.

psychosocial history; medications (including over-the-counter medications and supplements); physical examination; and validated questionnaires. At times blood tests and specialized laboratory tests may be appropriate. Although FSD can be purely physiologic, many cases are multifactorial owing to a combination of physiologic and psychological/social factors. It is advised that women with sexual health concerns undergo a separate and concomitant psychological interview by a psychologically focused health care professional (Basson, 2000; Basson et al, 2003, 2004).

History

If a problem is elicited a detailed and more thorough sexual history is warranted and should include past and present assessment of physiologic sexual responses (desire, arousal, and orgasm) to determine the following:

- What the sexual problem is
- When it began
- How often it occurs
- If it occurs only with the current partner or also with previous partners
- If there were any precipitating events (physiologic or psychologic)
- If sex is associated with pain, whether the problem occurs both with a partner and with self-stimulation
- Whether the onset of the problem temporally coincides with starting a new medication or the diagnosis of any disease/condition
- If there are new significant life stressors
- Whether the patient's partner has any sexual problems
- Whether either the patient or her partner has received any treatment (medications, surgery, counseling)
- If there is any history of sexual or emotional abuse

The medical history should include focused questions on the patient's medical conditions, surgeries, and medication use. Current and medical history should focus on the following:

- Reproductive history: age of menarche and menses, use of chronic birth control, number of pregnancies, obstetric trauma, infertility, sexually transmitted diseases, sexual abuse
- Chronic medical conditions: diabetes, renal failure, congestive heart failure, hypertension, coronary artery disease, atherosclerosis, hyperlipidemia
- Neurologic conditions: multiple sclerosis, spinal cord injuries, spina bifida
- Endocrinologic illnesses: hypogonadism, thyroid disorders
- Pelvic/genital trauma: pelvic fractures, female mutilation
- Urologic history: incontinence, prolapse, interstitial cystitis, urinary tract infections, fecal incontinence, pelvic surgery
- Psychiatric history: anxiety, depression
- Medications that have been found to negatively affect sexual function (Table 30–3): hormones, prescription drugs, and over-the-counter and recreational drugs including alcohol, marijuana, cocaine, steroids, street drugs

See Tables 30–4 and 30–5 for the components of a complete patient history.

Table 30–3.

Medications with Known Sexual Side Effects

Amphetamines
Antidepressants and mood stabilizers
Selective serotonin reuptake inhibitors (SSRIs)
Serotonin-norepinephrine reuptake inhibitors (SNRIs)
Tricyclic antidepressants
Monoamine oxidase inhibitors (MAOIs)
Antipsychotics
Benzodiazepines
Anticonvulsants
Antiepileptics
Antihypertensives
β blockers
α blockers
Diuretics
Cardiovascular agents
Lipid-lowering agents
Digoxin
Histamine-2 receptor
Hormones
Oral contraceptive pills
Estrogens
Progestins
Gonadotropin-releasing hormone agonists
Narcotics
Psychotropic drugs
Recreational drugs
Cocaine
Alcohol
Marijuana
Steroids

Table 30–4.

Components of Comprehensive Sexual History

1. Establish the sexual difficulty in the patient's own words.
2. Are there problems with arousal, desire, or orgasm?
3. How long has the problem been present?
4. Was the onset acute or gradual?
5. Is the problem specific to a certain situation or partner or is it generalized?
6. Was there a precipitating event—physical or psychological?
7. Are there current life stressors that may be contributing to the sexual problem(s)?
8. Is the problem temporally related to starting a new medication?
9. Is intercourse associated with pain?
10. Is there any history of physical, emotional, or sexual abuse?
11. Does the partner have any sexual problems?
12. Have you received any previous treatment—medical or psychological for the problem?

Physical Examination

The goals of the physical examination in women with sexual concerns are to confirm normal anatomy, assess for abnormalities, and reproduce and/or localize pain or tenderness (if tolerable). Given the intimate nature of the physical examination it is recommended that it be conducted in the presence of a female chaperone.

Although the physical examination of a woman with sexual concerns should focus on the genital examination, the examination should also include vital signs, particularly blood pressure, peripheral pulses, and a neurologic evaluation, including a sensory assessment. For women with neurologic disorders, anal and vaginal tone, voluntary tightening of the anus, and bulbocavernosal reflexes should be evaluated.

The genital examination should begin with visual inspection. Atrophy, abnormal discharges, signs of vaginitis, vulvar skin

Table 30–5.

Components of Comprehensive Medical and Surgical History

1. Past medical history
   a. Endocrinologic diseases (diabetes, thyroid dysfunction)
   b. Neurologic diseases (multiple sclerosis, spinal cord injuries)
   c. Cardiovascular disease (hypertension, chronic obstructive pulmonary disease, atherosclerosis)
   d. Pelvic trauma
2. Past surgical history, with emphasis on urologic and gynecologic surgeries
3. Current health status
4. Reproductive history
   a. Age at menarche and menopause
   b. Number of pregnancies, miscarriages, abortions
   c. History of sexually transmitted diseases
   d. Infertility
   e. Birth control use
5. Psychiatric illnesses

abnormalities, Bartholin or Skene gland cysts, urethral diverticuli, and signs of former episiotomy scars should be noted. The clitoris should be exposed to inspect for adhesions.

The second portion of the physical examination is palpation. The levator ani muscles should be palpated to assess for vaginismus and levator ani myalgia. A bimanual examination should be done to assess for motion tenderness, adnexal masses, endometriosis, and fibroids. Finally, a speculum examination should be performed to evaluate for pelvic organ prolapse. Table 30–6 is a list of physical examination findings that may impair female sexual function.

Table 30–6.

Physical Examination Findings That May Impair Female Sexual Function

EXAMINATION	CONDITION	SEXUAL SYMPTOMS
Inspection of Genitalia		
Vaginal or labial atrophy	Low estrogen levels	Decreased arousal, dyspareunia
Sparse pubic hair	Low androgen levels	Decreased desire
Vulvar skin lesions	Lichen sclerosis, *Candida*, sexually transmitted infections	Dyspareunia
Vaginal discharge	Infection	Dyspareunia
Hypertonic muscle tone	Vaginismus, vestibulitis	Dyspareunia
Clitoral hood retraction	Adhesions	Anorgasmia
Vaginal wall cysts	Infected Bartholin or Skene gland	Dyspareunia
Manual Examination		
Urethral fullness	Urethral diverticulum	Dyspareunia
Levator tenderness	Levator ani myalgia	Vaginismus, deep dyspareunia
Fixed retroverted uterus	Endometriosis, masses	Deep dyspareunia
Narrowed vaginal canal	Stricture/stenosis	Dyspareunia
Speculum Examination		
Pelvic organ prolapse		Dyspareunia, decreased desire
Stress incontinence		Vaginitis, decreased desire

Data from from Kingsberg, 2007, and Frank, 2008.

Laboratory Testing

Vaginal pH

Vaginal pH should be measured in women with vaginal discharges, odors, or atrophic vaginitis. Normal vaginal pH in women is 3.5 to 4.5. An acidic pH rules out a bacterial vaginitis other than candidiasis. A pH of 4.5 or more is suggestive of vaginitis, vaginosis, and/or atrophic vaginitis.

Wet Mount Testing

During the speculum portion of the examination samples should be taken of any abnormal discharge for wet mount and culture. Normal vaginal secretions are odorless and are not associated with the clinical complaint of itching or irritation.

Clue cells on wet mount are suggestive of bacterial vaginosis. Women diagnosed with bacterial vaginosis should be treated with oral or vaginal administration of metronidazole (Flagyl). Partners do not require treatment. If a patient is diagnosed with bacterial vaginosis it is important to also screen for gonorrhea and chlamydia.

The observation of an increased white blood cell count on a wet mount, more than 1 white blood cell per epithelial cell, may occur under the following conditions: vaginitis secondary to *Trichomonas,* yeast, and/or atrophy; cervicitis secondary to gonorrhea, chlamydia, and/or herpes; and upper genital/reproductive tract disease such as endometritis and/or pelvic inflammatory disease (Haefner, 1999; Anderson et al, 2004).

Blood Testing

Currently there are no recommended routine laboratory tests for women with sexual concerns. Therefore laboratory testing should be tailored to the results of the history and physical examination.

There are 10 sex steroids, including 7 androgens and 3 estrogens. Measurement of multiple sex steroids may be of clinical relevance to gain a better understanding of the hormonal integrity in a woman with sexual health concerns. Certain clinical scenarios might suggest checking estrogen (estradiol and estrone) and androgen values (DHEA sulfate, androstenedione, total testosterone, free testosterone, SHBG, and dihydrotestosterone). For example, measuring SHBG values might be of value in a premenopausal woman on oral contraceptive therapy with sexual complaints or measuring dihydrotestosterone levels in a woman who develops acne or alopecia after treatment with testosterone.

There are multiple concerns and limitations in determining serum hormone levels in women with sexual health concerns (Södergård et al, 1982; Zumoff et al, 1995; Shifren et al, 2000; Basson et al, 2004; Davis et al, 2005; Davison et al, 2005). First, although two studies have suggested normative ranges of androgens in women, the Endocrine Society's Clinical Guidelines on Androgen Therapy in Women state that there are insufficient data to determine normal ranges of testosterone concentration values for women of different ages (Guay et al, 2004; Davison et al, 2005;

Wierman et al, 2006). Second, the accuracy, precision, and reliability of the assays used to measure testosterone levels in women are not uniformly sensitive or reliable to accurately measure the low serum concentrations typically found in women (Wierman et al, 2006). However, newer testosterone assays, using mass spectroscopy, have shown promise in measuring testosterone more accurately and precisely (Rosner et al, 2007). Free testosterone is more important than total testosterone in sexual function. Only 1% to 2% of testosterone is found in its free biologically available form, with the remainder bound to either SHBG or albumin (Shufelt and Braunstein, 2002). The gold standard for measuring free testosterone is equilibrium dialysis. DHEA is usually measured in the sulfated form because it is easier to measure and does not vary during the menstrual cycle. Several studies have shown a consistent, age-related decline in DHEA sulfate levels (Zumoff et al, 1995; Munarriz et al, 2002; Basson et al, 2004). If low levels of DHEA sulfate are found, a morning cortisol level should be drawn to rule out adrenal insufficiency.

Specialized Testing

Vascular Testing

The female sexual response cycle is a complex interplay of physiologic, hypothalamic and emotive factors that relies on an intact neurovascular system. During sexual arousal, engorgement of the clitoral, labial, and vaginal erectile tissues occurs as a result of increased blood flow through the iliohypogastric-pudendal arterial bed. Just as atherosclerosis can cause impotence in men it can also cause sexual dysfunction in women. Diminished genital blood flow to the iliohypogastric-pudendal arterial bed secondary to atherosclerosis resulting in clitoral and vaginal vascular insufficiency syndromes can lead to decreased engorgement and arousal (Goldstein and Berman, 1998). In return, diminished blood flow and atherosclerotic changes lead to clitoral fibrosis, which interferes with normal smooth muscle relaxation and dilation to sexual stimulation (Tarcan et al, 1999).

Therefore Doppler ultrasonography, vaginal and clitoral photoplethysmography, and selective pudendal arteriography have all been used to assess the integrity of the female pelvic vascular supply. However, none of these measures has been validated or standardized. In addition, no normative data for control subjects exist for comparison. Therefore the clinical relevance of diagnostic hemodynamic investigations in women with sexual dysfunction has not yet been established (Basson et al, 2004).

Indications for vascular testing include (1) women with sexual arousal disorders who have exposure to multiple vascular risk factors, (2) women who have suffered pelvic fractures, and (3) women with sexual arousal disorders unresponsive to other therapies.

Vaginal photoplethysmography, the most commonly used noninvasive vascular testing in women with FSD, measures vaginal blood flow and vaginal pulse amplitude, thereby providing quantitative data on the extent of vaginal engorgement (Pasqualotto et al, 2005). However, this test has many drawbacks, including movement artifact (not suitable for use during stimulation or orgasm), the fact that it provides arbitrary rather than absolute units of measure, and that it provides no anatomic information (Verit et al, 2006).

Duplex Doppler ultrasonography before and after stimulation—visual, vibratory, or after topical alprostadil—has been used to record vaginal, clitoral, and labial blood flow during arousal. It also can be used to obtain changes in peak systolic velocity that occur in the vaginal, clitoral, cavernosal, and labial arteries during sexual arousal as well as the changes in clitoral and labial diameter associated with sexual stimulation. Drawbacks include paucity of "control" of duplex Doppler ultrasound values in women without sexual dysfunction and lack of standardized technique (Akkus et al, 1995; Khalife et al, 2000; Bechara et al, 2003; Munarriz et al, 2003; Pasqualotto et al, 2005).

MRI is one of the newest technologies being used to assess sexual function and arousal in women. MRI provides noninvasive, unparalleled multiplanar high-resolution imaging of the female pelvic floor without ionizing radiation. It can also be used to obtain dynamic quantitative physiologic information regarding changes in tissue volume, regional blood flow changes, and regional metabolite composition. **MRI can be used to define the normal anatomic relationships of the female genital structures in vivo,** providing a more accurate picture and a better understanding of the functional anatomy of women compared with cadaveric studies (Deliganis et al, 2002; Maravilla et al, 2002; Suh et al, 2003, 2004). During arousal, MR images show characteristic engorgement that is most pronounced in the clitoris, especially in the crura and body of the clitoris. The vaginal mucosa does not show any increase in size and signal intensity because it is only a few cell layers thick, below the limit of resolution of the MRI technique (Suh et al, 2003).

Functional brain imaging or functional MRI represents the ability to observe anatomic sites of brain activation in response to a specific task performed by a subject using rapid dynamic MRI. This technique is an experimental tool for exploring brain function associated with emotional attraction, feelings of pleasure, and even sites of activation associated with sexual arousal. There have been a number of studies applying functional MRI techniques to the evaluation of sexual arousal or emotional response in women. Brain regions that activated with sexual arousal were related with visual association areas (posterior temporo-occipital cortices, paralimbic areas, anterior cingulate cortex) (Komisaruk and Whipple, 2005).

As discussed earlier, a study by Arnow and associates (2009), comparing functional MRI in women with HSDD with women without sexual dysfunction found greater activation in the bilateral entorhinal cortex in women without FSD but greater activation of the medial frontal gyrus, right inferior frontal gyrus, and bilateral putamen in women with HSDD, suggesting that women with HSDD shift focus from erotic cues to self-monitoring of sexual response and performance concerns.

TREATMENT

The treatment of FSD is complicated owing to the many causes for these disorders. Optimal female sexual health requires physical, emotional, and mental well-being, which often makes medical treatment alone insufficient. Therefore, treatment requires a multimodal approach, often involving a multidisciplinary team of urologists and a mental health specialist with expertise in sexual medicine/sex therapy. Known anatomic, metabolic, and infectious causes should be corrected first. After correcting medical causes, treatment should begin with patient education.

Women should be educated about average sexual behaviors and frequencies (Kammerer-Doak and Rogers, 2008). Often women are led to believe they have a sexual dysfunction based on misinformation about what is "normal." Behavioral changes such as changes in sexual practices and routine (e.g., initiating a sexual encounter in the morning instead of when exhausted at the end of a long day), smoking cessation, a healthy diet, and adequate

rest and exercise should be discussed. Psychological referrals should be made to those providers who specialize in sexual disorders.

Once these issues have been addressed the use of pharmacotherapy should be discussed when appropriate. It is important to inform patients that to date the only U.S. Food and Drug Administration (FDA)–approved pharmacologic treatment of any female sexual disorder is that of conjugated estrogens (Premarin Vaginal Cream) for moderate to severe dyspareunia.

Hypoactive Sexual Desire Disorder

HSDD is defined as the absence or diminution of sexual interest or desire, absence of sexual thoughts or fantasies, and a lack of responsive desire. This is the most common type of female sexual disorder, and the cause can be physiologic, psychological, or both (Laumann et al, 1999; Nicolosi et al, 2004).

Although desire disorders are the most common sexual disorder they are challenging for physicians to treat. Desire is a complex concept composed of three discrete yet interrelated components: drive, cognition, motivation (Althof et al, 1992; Kingsberg and Althof, 2009). It is imperative for physicians to determine which component or components are causative because the treatments for impaired sex drive are different from those of impaired motivation.

Drive, the biologic component of desire, is based on neuroendocrine function and manifested by spontaneous sexual interest: sexual fantasies, dreams, and thoughts. Cognition is the woman's sexual expectations, beliefs, and values. The third component of desire is motivation or the willingness to engage in sexual activity and is commonly related to psychosocial factors.

Treatment should begin with educating the patient that it is normal for drive to decline with increasing age, which reflects decreased androgen and testosterone production.

If desire is diminished secondary to psychosocial factors the patient should be referred to a sex therapist or psychologist to discuss lifestyle changes, stress management, or couples therapy.

If the cause appears to be related to drive, exogenous testosterone therapy with tibolone (a synthetic steroid with selective estrogenic, androgenic, and progesterogenic properties) may be an appropriate option, particularly for postmenopausal women. Centrally acting agents also are being investigated for the treatment of HSDD in both premenopausal and postmenopausal women.

Androgens for the Treatment of Desire Disorders

Despite testosterone being one of the most commonly prescribed drugs for desire disorders, its use is controversial and not FDA approved in women. Although testosterone is linked to sexual desire, studies have shown that low serum testosterone levels are not predictive of low desire nor do they correlate well with the likelihood of a therapeutic response (Davis et al, 2005).

In 2005 a Cochrane review of 23 trials with 1957 participants looking at the benefits of adding testosterone to hormonal therapy in perimenopausal and postmenopausal women concluded that although there was insufficient evidence in perimenopausal women, postmenopausal women did experience improved sexual function with the addition of testosterone to hormonal therapy (Somboonporn et al, 2005).

Several subsequent randomized controlled trials in postmenopausal women and surgically castrated women have shown that the addition of testosterone to hormonal therapy improved not only desire but also arousal and orgasm (Shifren et al, 2000, 2006; Braunstein et al, 2005; Davis et al, 2005).

The data regarding testosterone therapy in premenopausal women is lacking owing to a paucity of studies, but in two studies an improvement in sexual desire in premenopausal women with low libido treated with transdermal testosterone was suggested (Goldstat et al, 2003; Davis et al, 2005).

When prescribing testosterone therapy physicians must be aware of the potential adverse side effects and contraindications. Complications include acne, hirsutism, seborrhea, menstrual irregularities, virilization, hyperlipidemia, liver dysfunction, and male pattern baldness. Transdermal preparations may minimize adverse effects. Any patient on testosterone should be seen and have laboratory studies done routinely to avoid having levels reach superphysiologic levels.

Contraindications to testosterone therapy include androgenic alopecia, hirsutism, seborrhea or acne, polycystic ovary syndrome, liver dysfunction, and estrogen depletion (Basson et al, 2004).

For the androgen precursors DHEA and DHEA sulfate there are limited data regarding their effectiveness. One small retrospective study showed DHEA (50 mg/day) to improve desire, arousal, orgasm, and sexual satisfaction in both premenopausal and postmenopausal women (Munarriz et al, 2002).

Other Medication for the Treatment of Desire Disorders

Tibolone, a synthetic steroid, has been used in Europe for more than 20 years given its positive effects on sexual function. In one randomized control study of postmenopausal women with arousal and desires disorders, tibolone in combination with hormonal therapy was shown to significantly improve sexual function scores and increase clitoral circulation.

Arousal Disorders

Sexual arousal disorders can be treated, depending on the etiology, with counseling to change sexual practice patterns, medical therapy, or a combination of the two.

Estrogen replacement therapy has shown beneficial effects in women with postmenopausal arousal disorder by improving vaginal lubrication and blood flow.

Bupropion, an aminoketone antidepressant, has been shown to improve arousal in both premenopausal and postmenopausal women and both depressed and nondepressed women with arousal disorder (Modell et al, 2000; Segraves et al, 2001, 2004).

Alprostadil, a topically applied prostaglandin applied to the external genitalia, is currently under investigation for use in women given its beneficial effects on male arousal.

Arginmax, a nutritional supplement containing L-arginine, a precursor of nitric oxide, showed an increase in sexual arousal in both premenopausal and postmenopausal women in two small randomized control studies (Ito et al, 2001, 2006).

Zestra, botanical massage oil applied to the vulva, has been shown in one randomized control trial to significantly improve arousal in women with arousal disorders (Ferguson et al, 2003).

Phentolamine and yohimbine are α-androgenic antagonists that cause vasodilatation through smooth muscle relaxation. Although phentolamine has been shown to improve arousal and lubrication for menopausal women with arousal disorder, yohimbine failed to show any clinical improvement in arousal (Raina et al, 2007).

Sildenafil, a selective phosphodiesterase-5 inhibitor used to treat erectile dysfunction in men via smooth muscle relaxation, has also been used in women with arousal disorder with mixed results. Kaplan and colleagues (1999) reported no overall improvement in

33 postmenopausal women with arousal disorder treated with 50 mg of sildenafil despite improved vaginal lubrication and clitoral sensitivity. Basson and associates (2002) also reported no improvement in 781 premenopausal and postmenopausal women with arousal disorder with sildenafil. However, several studies have shown significant improvement in sexual arousal, orgasm, and overall satisfaction in women with arousal disorders treated with sildenafil (Caruso et al, 2001; Berman et al, 2003).

The EROS clitoral therapy device, an FDA-approved device that applies gentle suction to the clitoris, enhancing clitoral engorgement, has proven beneficial in women with arousal disorders (Wilson et al, 2001).

Orgasmic Disorders

Orgasmic disorders can be classified as primary or secondary. Primary orgasmic disorders are typically the result of sexual inexperience and are treated using cognitive behavioral therapy, directed masturbation, and sex education. Permission giving by the physician regarding sexual exploration and masturbation is hugely helpful to women with anorgasmia. Secondary anorgasmia, or acquired anorgasmia, is often the result of antidepressant medications. This can be treated by stopping the offending medication.

Dyspareunia and Vaginismus

The treatment of sexual pain disorders is often challenging, given the paucity of controlled trials as well as the multiple causes. Ideally, treatment should involve a multidisciplinary team that can address the physiologic, emotional, relational, and psychological factors. Pelvic floor physical therapy with biofeedback, pelvic floor electrical stimulation, perineal ultrasonography, and vaginal dilators have all been used with reported clinical benefit but without scientific evidence (Basson et al, 2004).

Pharmacotherapy for sexual pain disorders is routed in treating the underlying condition. Postmenopausal women with pain secondary to atrophic vaginitis should be treated with topical estrogen whereas women with vulvovaginitis should be treated with oral or transvaginal antifungal agents.

Tricyclic antidepressants, SSRIs, and corticosteroids have been used to treat vulvar vestibulitis, but data supporting their use are limited.

SSRI-Related Sexual Dysfunction

Selective phosphodiesterase-5 inhibitors have been used in therapy for SSRI-induced sexual function. In several studies, women with SSRI-induced sexual dysfunction reported significant improvements in overall sexual function and satisfaction on sildenafil (Nurnberg et al, 1999, 2008; Salerian et al, 2000; Basson et al, 2004). Some reports suggest that bupropion may be an effective antidote for SSRI-induced sexual dysfunction; however, the data on restoring normal sexual functioning in this patient population are mixed (Clayton et al, 2004; DeBattista et al, 2005).

Surgical Therapy

Sexual Pain Disorders

The role of surgery in the treatment of female sexual pain disorders should be considered only in patients who have failed conservative medical and psychological therapy.

Vulvar Vestibulectomy. Vulvar vestibulectomy has been used in women with refractory vulvar vestibulitis syndrome and in women with various conditions such as lichen sclerosis or posterior fourchette fissures that have destroyed the normal vulvar architecture. Since first described in 1981, the surgery has undergone several modifications and variations. A complete vulvar vestibulectomy involves anterior, posterior, and lateral vaginal mucosa with a posterior vaginal advancement flap. In a modified vulvar vestibulectomy, only the posterior vaginal mucosa is excised (Kehoe and Luesley, 1999).

It is imperative to map the painful vestibular areas preoperatively. With the patient under general anesthesia, the previously mapped areas are infiltrated with lidocaine and epinephrine (1:200,000 units) for hydrodissection. A No. 15 blade is then used to excise the vestibular mucosa. The defect is then closed using 3-0 or 4-0 Vicryl sutures. Attention should be paid to the location of the Bartholin gland, which should be avoided to prevent postoperative cyst formation (Kehoe and Luesley, 1999).

Postoperatively, patients should be instructed to avoid vaginal penetration and limit physical activity for a minimum of 4 weeks. At 4 weeks patients should begin a physical therapy regimen, which may include biofeedback and vaginal dilators.

In 2008 Landry and colleagues conducted a review of the treatment of vestibulodynia. Of the 38 studies reviewed only 5 were randomized controlled studies and the majority of the studies had several methodologic weaknesses, including absence of a control group, pretreatment pain evaluation, validated questionnaires assessing pain and sexual function, and standard surgical technique.

Yet based on these limited prospective studies and the randomized clinical trials, vestibulectomy was the most efficacious treatment to date, achieving a high rate of patient satisfaction and greater than 50% resolution of dyspareunia (Landry et al, 2008).

Drainage of Sebaceous Cysts or Infected Bartholin or Skene Gland Cysts. If conservative therapy fails, incision and drainage and, at times, marsupialization of the cyst is indicated.

Female Pelvic Floor Disorders

Although female pelvic organ prolapse, incontinence, and overactive bladder have all been shown to have a negative impact on female sexual function, surgical restoration of normal anatomy with alleviation of symptoms does not consistently improve female sexual outcomes.

Key Points: Diagnosis and Treatment

- A detailed history (including medical, sexual, and psychiatric history), medication list, and thorough physical examination are imperative to diagnosing female sexual dysfunction.
- Currently there are no recommended routine laboratory tests for women with sexual concerns. Therefore laboratory testing should be tailored to the results of the history and physical examination.
- In women with FSD, known anatomic, metabolic, and infectious causes should be corrected first.
- To date the only FDA-approved pharmacologic treatment of any female sexual disorder is conjugated estrogens (Premarin Vaginal Cream) for moderate to severe dyspareunia.

CONCLUSION

Despite our increasing knowledge base, female sexual disorders still remain a challenge to physicians and patients alike. Much of this is based on both physician and patient avoidance of the topic. Sexual health is as important to the quality of lives of women as it is to men, and female patients expect that their physicians will address their sexual concerns. The goal of this chapter was to equip the urologist with the tools to screen, diagnose, and collaborate with a multidisciplinary team to adequately address the complexity of female sexual disorders.

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The complete reference list is available online at www.expertconsult.com.

chapter 31

Neoplasms of the Testis

Andrew J. Stephenson, MD, FACS, FRCSC • Timothy D. Gilligan, MD, MS

Germ Cell Tumors

Non–Germ Cell Tumors

Tumors of the Testicular Adnexa

Neoplasms of the testis comprise a morphologically and clinically diverse group of tumors, **95% of which are germ cell tumors (GCTs). GCTs are broadly categorized as seminoma and nonseminoma (NSGCT) owing to differences in natural history and treatment. GCTs are relatively rare malignancies, accounting for 1% to 2% of cancers among men in the United States,** with an incidence of approximately 5 cases per 100,000. Approximately 90% of GCTs arise in the testis and 2% to 5% are extragonadal (the retroperitoneum and mediastinum are the most common sites). With the development of cisplatin-based chemotherapy and the integration of surgery, GCTs have become a model of a curable neoplasm and serve as a paradigm for the multidisciplinary treatment of cancer (Einhorn, 1981). Before therapy with cisplatin was introduced the cure rate for patients with advanced GCT was 5% to 10%. Currently the long-term survival for men with metastatic GCT is 80% to 90%. With the successful cure of patients (even those with advanced disease), an important treatment objective is minimizing treatment-related toxicity without compromising curability. Mortality from GCT is due to inherent resistance to platin chemotherapy and the failure to fully eradicate residual disease elements in the early course of therapy.

Non-GCTs of the testis are rare and include sex cord/stromal tumors, lymphoid and hematopoietic tumors, tumors of the collecting duct and rete testis, and tumors of the testicular adnexa. A classification of neoplasms of the testis is provided in Table 31–1.

GERM CELL TUMORS

Epidemiology

As of 2010 in the United States it was estimated that 8400 men would develop testicular cancer and 380 would die of this disease (Jemnal et al, 2010). **In the United States, testicular cancer is the most common malignancy among men aged 20 to 40 years and the second most common cancer after leukemia among males aged 15 to 19 years** (Horner et al, 2009). Testicular tumors have three age model peaks: infancy, ages 30 to 34 years, and approximately age 60. **The incidence of bilateral GCT is approximately 2%** (Fossa et al, 2005). **Testicular lymphoma is less common than GCT but accounts for the majority of testicular tumors in men older than 50 years of age** and is more likely to have a synchronous bilateral presentation.

The incidence of testicular cancer varies significantly according to geographic region: **rates are highest in Scandinavia, Germany, Switzerland, and New Zealand; intermediate in the United States and Great Britain; and lowest in Africa and Asia. The incidence of testicular cancer in the United States in non-Hispanic whites is five times higher than the incidence in African-Americans, four times higher than the incidence in Asians, and 78% higher than in Hispanics** (Horner et al, 2009).

The incidence of GCT appears to be increasing worldwide (McKiernan et al, 1999; McGlynn et al, 2005; Purdue et al, 2005). In the United States, the age-adjusted incidence rate for males aged 15 to 49 years increased from 2.9 per 100,000 in 1975 to 5.1 per 100,000 in 2004 (Holmes et al, 2008). Over this time period incidence rates have increased substantially more for seminoma than NSGCT (McGlynn et al, 2005; Powles et al, 2005). **A stage migration of GCT has been observed in several countries owing, in part, to increased awareness and earlier diagnosis.** Between 1973 and 2001 the percentage of tumors diagnosed at a localized stage increased from 55% to 73% in the United States among white males. The stage distribution for African-American males remained stable during this time (McGlynn et al, 2005). **Only 10% to 30% of men will present with distant metastatic disease.** In the United Kingdom the change in stage distribution over time is largely restricted to an increase in localized seminoma and a decrease in metastatic NSGCT; rates of localized NSGCT and metastatic seminoma are largely unchanged (McGlynn et al, 2005). **Currently, localized seminoma is the most common presentation of GCT, representing approximately 50% of all men with GCT** (Powles et al, 2005). Thus, contemporary testicular germ cell tumors have more favorable prognostic features on average compared with those diagnosed in the 1970s and 1980s.

Risk Factors

There are four well-established risk factors for testicular cancer: cryptorchidism, family history of testicular cancer, a personal history of testicular cancer, and intratubular germ cell neoplasia (ITGCN). Infertile men also have a higher incidence of testicular cancer. **Numerous studies have reported that recent increases in the incidence of testicular cancer can be largely attributed to birth-cohort effects, which implies that diet and/or other environmental factors play a major role in GCT carcinogenesis** (Liu et al, 1999; Huyghe et al, 2003; McGlynn et al, 2003; Richiardi et al, 2004; Bray et al, 2006; Verhoeven et al, 2008).

Males with cryptorchidism are four to six times more likely to be diagnosed with testicular cancer, but the relative risk (RR) falls to 2.0 to 3.0 if orchidopexy is

Table 31–1.

World Health Organization Classification of Testicular Tumors

Germ Cell Tumors

Precursor lesions—intratubular malignant germ cells (carcinoma in situ)
Tumors of one histologic type (pure forms)
- Seminoma
  - Variant—seminoma with syncytiotrophoblastic cells
- Spermatocytic seminoma
  - Variant—spermatocytic seminoma with sarcoma
- Embryonal carcinoma
- Yolk sac tumor
- Polyembryoma
- Trophoblastic tumors
  - Choriocarcinoma
  - Choriocarcinoma with other cell types
  - Placental site trophoblastic tumor
- Teratoma
  - Mature teratoma
  - Dermoid cyst
  - Immature teratoma
  - Teratoma with malignant areas

Tumors of more than one histologic type (mixed forms)—specify types and estimate percentage

Sex Cord/Gonadal Stromal Tumors

Pure forms
- Leydig cell tumor
- Sertoli cell tumor
  - Large-cell calcifying Sertoli cell tumor
  - Lipid-rich Sertoli cell tumor

Granulosa cell tumor
- Adult-type granulosa cell tumor
- Juvenile-type granulosa cell tumor

Tumors of thecoma/fibroma group
Incompletely differentiated sex cord/gonadal stromal tumors
Mixed forms

Unclassified Forms

Tumors Containing Both Germ Cell and Sex Cord/Gonadal Stromal Elements

Gonadoblastoma
Mixed germ cell–sex cord/gonadal stromal tumors, unclassified

Miscellaneous Tumors

Carcinoid tumor
Tumors of ovarian epithelial types

Lymphoid and Hematopoietic Tumors

Lymphoma
Plasmacytoma
Leukemia

Tumors of Collecting Ducts and Rete

Adenoma
Carcinoma

Tumors of the Tunica, Epididymis, Spermatic Cord, Supporting Structures, and Appendices

Adenomatoid tumor
Mesothelioma
- Benign
- Malignant

Adenoma
Carcinoma
Melanotic neuroectodermal
Desmoplastic small round cell tumor

Soft Tissue Tumors

Unclassified Tumors

Secondary Tumors

Tumor-like Lesions

Nodules of immature tubules
Testicular lesions of adrenogenital syndrome
Testicular lesions of androgen-insensitivity syndrome
Nodular precocious maturation
Specific orchitis
Nonspecific orchitis
Granulomatous orchitis
Malakoplakia
Adrenal cortical rest
Fibromatous peritonitis
Funiculitis
Residue of meconium peritonitis
Sperm granuloma
Vasitis nodosa
Sclerosing lipogranuloma
Gonadal splenic fusion
Mesonephric remnants
Endometriosis
Epidermal cyst
Cystic dysplasia
Mesolithial cyst
Others

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performed before puberty (Dieckmann and Pichlmeier, 2004; Wood and Elder, 2009). Although most of the increased risk reflects an increased risk of cancer in the undescended testis, **a meta-analysis of cryptorchidism studies reported that the contralateral descended testis is also at slightly increased risk** (RR 1.74 [95% CI, 1.01 to 2.98]) (Akre et al, 2009). Men with a first-degree relative with testicular cancer have a substantially increased risk, and the median age at diagnosis in these men is 2 to 3 years younger than in the general population (Mai et al, 2009). An individual's RR for testicular cancer is 8.0 to 12.0 with an affected brother compared with 2.0 to 4.0 in those with an affected father (Westergaard et al, 1996; Sonneveld et al, 1999; Hemminki and Chen, 2006). Men with a history of testicular cancer are at a 12-fold increased risk of developing GCT in the contralateral testis, but the 15-year cumulative incidence is only 2%. The risk is higher in patients who are younger when testicular cancer is diagnosed and in men whose initial GCT is seminoma (Theodore et al, 2004; Fossa et al, 2005). A population-based study of contralateral testicular cancer reported that a man younger than the age of 30 with a testicular seminoma has a 3.1% risk of developing a contralateral testicular cancer (Fossa et al, 2005). The same study reported that 10-year overall survival after diagnosis with a second primary (i.e., contralateral) testicular cancer was 93%.

Most GCTs arise from a precursor lesion called intratubular germ cell neoplasia (ITGCN) (which is also referred to as carcinoma in situ). Men with ITGCN have a

significantly increased risk of developing invasive GCT. **ITGCN is present in adjacent testicular parenchyma in 80% to 90% cases of invasive GCT and is associated with a 50% risk of GCT within 5 years and a 70% risk within 7 years** (Skakkebaek et al, 1982; Dieckmann and Skakkebaek, 1999; Montironi, 2002). **Between 5% and 9% of patients with GCT have ITGCN within the unaffected contralateral testis, although the incidence of contralateral ITGCN increases to about 36% in men with testicular atrophy or cryptorchidism** (Dieckmann and Loy, 1996; Dieckmann and Skakkebaek, 1999). Gene expression profile analysis indicates that ITGCN develops before birth from an arrested gonocyte (Hussain et al, 2008; Sonne et al, 2009). In men with a history of GCT the finding of testicular microlithiasis on ultrasound evaluation of the contralateral testis is associated with an increased risk of ITGCN (Karellas et al, 2007). **However, the significance of microlithiasis in the general population is unclear;** a study of 1500 army volunteers found a 5.6% prevalence of microlithiasis, yet fewer than 2% of those with microlithiasis developed cancer within the subsequent 5 years (DeCastro et al, 2008).

Pathogenesis and Biology

The carcinogenesis of GCTs is poorly understood. As noted earlier, testicular GCTs develop from a precursor lesion, ITGCN, which, in turn, appears to develop from arrested primordial germ cells or gonocytes that failed to differentiate into prespermatogonia (Rajpert-de Meyts and Hoei-Hansen, 2007; Hussain et al, 2008). These cells are thought to then lie dormant until after puberty when they are stimulated by increased testosterone levels.

The increased incidence of testicular cancer that started in the first half of the 20th century has been accompanied by an increased incidence of other male reproductive disorders, such as hypospadias, cryptorchidism, and subfertility (Rajpert-de Meyts and Hoei-Hansen, 2007; Sonne et al, 2008). These findings led to the hypothesis that testicular cancer and these other disorders all resulted from a testicular dysgenesis syndrome, which in turn resulted from environmental and/or lifestyle factors and genetic susceptibility. The specific environmental or lifestyle factors have not been defined. Increased prenatal estrogen exposure has been hypothesized as a risk factor, but this is controversial (Martin et al, 2008). There is stronger evidence that reduction in androgen activity can result in features of testicular dysgenesis syndrome, including cryptorchidism, hypospadias, and impaired spermatogenesis, but a direct link between reduced androgen signaling and ITGCN or GCTs remains hypothetical (Sonne et al, 2008; Hu et al, 2009).

Evidence of environmental and lifestyle factors contributing to testicular cancer includes the rapid rise in its incidence as well as findings that the risk in second-generation immigrants is similar to that in their country of birth. In addition, mothers of children with testicular cancer (but not the testicular cancer patients themselves) have been found to have higher blood levels of certain organic pollutants compared with other mothers (Sonne et al, 2008). Evidence for genetic factors includes the clustering of testicular cancer in some families, the extreme difference in the rate of testicular cancer in black and white Americans, and the finding of susceptibility loci on chromosomes 5, 6, and 12 in case-control studies (Mai et al, 2009). In addition, specific polymorphisms of certain genes, including the gene encoding c-KIT ligand, have been associated with an increased risk of testicular cancer (Blomberg Jensen et al, 2008; Kanetsky et al, 2009). Gonocytes depend on c-KIT ligand for survival, and the gene for this protein is located on the short arm of chromosome 12. **Approximately 70% of GCTs have an extra copy of chromosome 12 in the form of an isochromosome 12p (i[12p])** (Bosl et al, 1989). Thus a connection between mutations or polymorphisms in this gene and GCT has biologic plausibility.

One of the most striking features of GCTs is their sensitivity to cisplatin-based chemotherapy, which enables cure in the vast majority of patients with widely metastatic disease. The specific biologic basis of this acute vulnerability to chemotherapy remains incompletely understood but is thought to derive from the close relationship between GCTs and embryonal stem cells and gonocytes, which have a low threshold for undergoing apoptosis in response to DNA damage (Mayer et al, 2003; Schmelz et al, 2010). GCTs have high intrinsic levels of wild-type TP53 protein (which plays a role in mediating cell cycle arrest and apoptosis), and *TP53* mutations in GCTs are rare, yet differences have not been consistently found in TP53 status when comparing chemosensitive and chemoresistant germ cell tumors (Burger et al, 1998; Houldsworth et al, 1998). Similarly, expression of the antiapoptotic protein BCL2 is low in germ cell tumors but BCL2 levels do not distinguish chemosensitive and chemoresistant cell lines (Mayer et al, 2003). Gene expression analysis has found an upregulation of numerous genes that facilitate apoptosis, including *FASLG, TNFSF10,* and *BAX,* whereas *BCL2* is downregulated (Schmelz et al, 2010). Expression patterns of genes controlling the G1/S-phase checkpoint in GCTs appear to promote induction of apoptosis (Schmelz et al, 2010). In addition, GCTs lack transporters to export cisplatin from the cell and have a reduced ability to repair cisplatin-induced DNA damage (Mayer et al, 2003). Nonetheless, a small fraction of GCTs are resistant to chemotherapy and the basis of that resistance remains obscure, although DNA mismatch repair deficiency, microsatellite instability, and *BRAF* mutations have been associated with treatment failure (Honecker et al, 2009).

Up to 10% of GCTs are extragonadal and develop in midline anatomic locations. There are two main competing theories regarding the pathogenesis of extragonadal GCTs. The first hypothesizes that they originate from germ cells that mismigrated along the genital ridge and were able to survive in an extragonadal environment. The second theory proposes a reverse migration from the testis to extragonadal locations (Chaganti and Houldsworth, 2000).

Primary mediastinal NSGCTs differ in several ways from those originating in the testis or retroperitoneum. First, they are less sensitive to chemotherapy and have a poor prognosis with a 5-year overall survival of about 45% (Bokemeyer et al, 2002b). Mediastinal NSGCTs are more likely to have yolk sac tumor components and thus to be associated with elevations in serum α-fetoprotein (AFP) (Kesler et al, 2008). They are also associated with Kleinfelter syndrome and with hematologic malignancies that carry extra copies of the short arm of chromosome 12, as seen in adult GCTs (Bokemeyer et al, 2002a; McKenney et al, 2007). **In contrast, mediastinal seminomas carry a similar prognosis to testicular seminomas. Primary retroperitoneal GCTs are indistinguishable biologically from testicular GCTs and carry the same prognosis.**

Histologic Classification

The histologic classification of GCT is outlined in Table 31–2 (Sobin and Wittekind, 2002). **GCTs are broadly classified as seminoma and NSGCT, and the relative distribution of each is 52% to 56% and 44% to 48%, respectively** (McGlynn et al, 2005; Powles et al, 2005). **NSGCTs include embryonal carcinoma (EC), yolk sac tumor, teratoma, and**

Table 31–2.

World Health Organization Classification of Germ Cell Tumors

Intratubular germ cell neoplasia
Tumors of one histologic type (pure forms):
Seminoma
Seminoma with syncytiotrophoblastic cells
Spermatocytic seminoma
Embryonal carcinoma
Yolk sac tumor
Trophoblastic tumors
Choriocarcinoma
Trophoblastic neoplasms other than choriocarcinoma
Monophasic choriocarcinoma
Placental site trophoblastic tumor
Teratoma
Dermoid cyst
Monodermal teratoma
Teratoma with somatic type malignancy (malignant transformation)
Tumors of more than one histologic subtype (mixed forms)

From Sobin LH, Wittekind CH. UICC: TNM classification of malignant tumors. 6th ed. New York: Wiley-Liss; 2002.

choriocarcinoma subtypes, either alone as pure forms or in combination as mixed GCT with or without seminoma (Ulbright, 2005). Most NSGCTs are mixed tumors that are composed of two or more GCT subtypes. GCTs that contain both NSGCT subtypes and seminoma are classified as NSGCT.

Intratubular Germ Cell Neoplasia. With the exception of spermatocytic seminoma, all adult invasive GCTs arise from ITGCN. ITGCN consists of undifferentiated germ cells that have the appearance of seminoma that are located basally within the seminiferous tubules. The tubule usually shows decreased or absent spermatogenesis, and normal constituents are replaced by ITGCN. The presence of ITGCN in an orchiectomy specimen in men with testicular cancer does not carry any prognostic implications with regard to the risk of relapse of the cancer (von Eyben et al, 2004). ITGCN is much less frequent in pediatric GCTs (Cheville, 1999).

Seminoma. Seminoma is the most common type of GCT. **On average, seminomas occur at an older average age than NSGCTs, with most cases diagnosed in the fourth or fifth decade of life** (Rayson et al, 1998). Grossly, seminoma is a soft tan to white diffuse or multinodular mass (Fig. 31–1A). Necrosis may be present but is usually focal and not as prominent as other GCTs. Seminomas consist of a sheetlike arrangement of cells with polygonal nuclei and clear cytoplasm, with the cells divided into nests by fibrovascular septa that contain lymphocytes (see Fig. 31–1B) (Ulbright, 2005). Syncytiotrophoblasts, which stain positive for human choriogonadotropin (hCG), can be identified in about 15% of cases of pure seminoma but are of no clear prognostic significance (Cheville, 1999). Lymphocytic infiltrates and granulomatous reactions are often seen and seminomas appear to be associated with an increased incidence of sarcoidosis (Rayson et al, 1998; Tjan-Heijnen et al, 1998). Seminomas may be confused with solid-pattern EC, yolk sac tumor, or Sertoli cell tumors (Ulbright and Young, 2008). Although immunohistochemical staining plays a limited role in diagnosing GCTs, seminomas are typically negative for CD30, positive for CD117, and strongly positive for placental alkaline phosphatase (PLAP). Anaplastic seminoma was a previously recognized subtype of seminoma, but this distinction is of no clear biologic or clinical significance and is no longer recognized. **Seminoma arises from ITGCN and is considered to be the common precursor for the other NSGCT subtypes** (Ulbright, 2004). This ability of seminoma to transform into NSGCT elements has important therapeutic implications for the management of seminoma (discussed later) (Ulbright, 2004).

Spermatocytic Seminoma. **Spermatocytic seminoma is rare and accounts for less than 1% of GCTs.** Although classified as a variant of seminoma it represents a distinct clinicopathologic entity from other GCTs. **Unlike other GCTs, spermatocytic seminoma does not arise from ITGCN, is not associated with a history of cryptorchidism or bilaterality, does not express PLAP or i(12p), and does not occur as part of mixed GCTs** (Ulbright, 2005). Histopathologically, it differs from seminoma in that the nuclei are round, minimal lymphocytic infiltration is present, and three distinct cell types are present, including small lymphocyte-like cells, medium-sized cells with dense eosinophilic cytoplasm and a round nucleus, and large mononucleated or multinucleated cells (Aggarwal and Parwani, 2009). The peak incidence is in the sixth decade of life (Eble, 1994; Chung et al, 2004a). **It is a benign tumor (only one documented case having metastasized) and is almost always cured with orchiectomy** (Chung et al, 2004a). An exception to this is the rare case of spermatocytic seminoma with sarcoma that exhibits elements of sarcomatous differentiation and is commonly associated with widely metastatic disease and poor prognosis.

Embryonal Carcinoma. EC consists of undifferentiated malignant cells resembling primitive epithelial cells from early-stage embryos with crowded pleomorphic nuclei (Ulbright, 2005). Grossly, EC is a tan to yellow neoplasm that often exhibits large areas of hemorrhage and necrosis. The microscopic appearance of these tumors varies considerably, and they may grow in solid sheets or in papillary, glandular-alveolar, or tubular patterns (see Fig. 31–1C). In some cases, syncytiotrophoblasts are identified. EC is an aggressive tumor associated with a high rate of metastasis, often in the context of normal serum tumor markers. **EC is the most undifferentiated cell type of NSGCT, with totipotential capacity to differentiate to other NSGCT cell types (including teratoma) within the primary tumor or at metastatic sites.** As discussed later, the presence and proportion of EC has been associated with an increased risk of occult metastases in clinical stage (CS) I NSGCT. EC typically stains for AE1/AE3, PLAP, and OCT3/4 and does not stain for c-KIT.

Choriocarcinoma. Choriocarcinoma is a rare and aggressive tumor that typically presents as elevated serum hCG levels and disseminated disease. **Choriocarcinoma commonly spreads by hematogenous routes,** and common sites of metastases include lungs and brain, but eye and skin metastases have also been reported (Tinkle et al, 2001; Osada et al, 2004). Microscopically the tumor is composed of syncytiotrophoblasts and cytotrophoblasts, and the former stain positively for hCG (see Fig. 31–1D) (Cheville, 1999). Seminoma and EC may also contain syncytiotrophoblasts. Areas of hemorrhage and necrosis are prominent. As in gestational trophoblastic disease, testicular choriocarcinoma is prone to hemorrhage, sometimes both spontaneously and immediately after chemotherapy is initiated, and such bleeding can be catastrophic, particularly when it occurs in the lungs or brain (Motzer et al, 1987).

Yolk Sac Tumor. Pure yolk sac tumors (sometimes called endodermal sinus tumors) represent a very small fraction of adult-type GCTs but are more common in mediastinal and pediatric GCTs. Mixed GCTs often include elements of yolk sac tumor, which

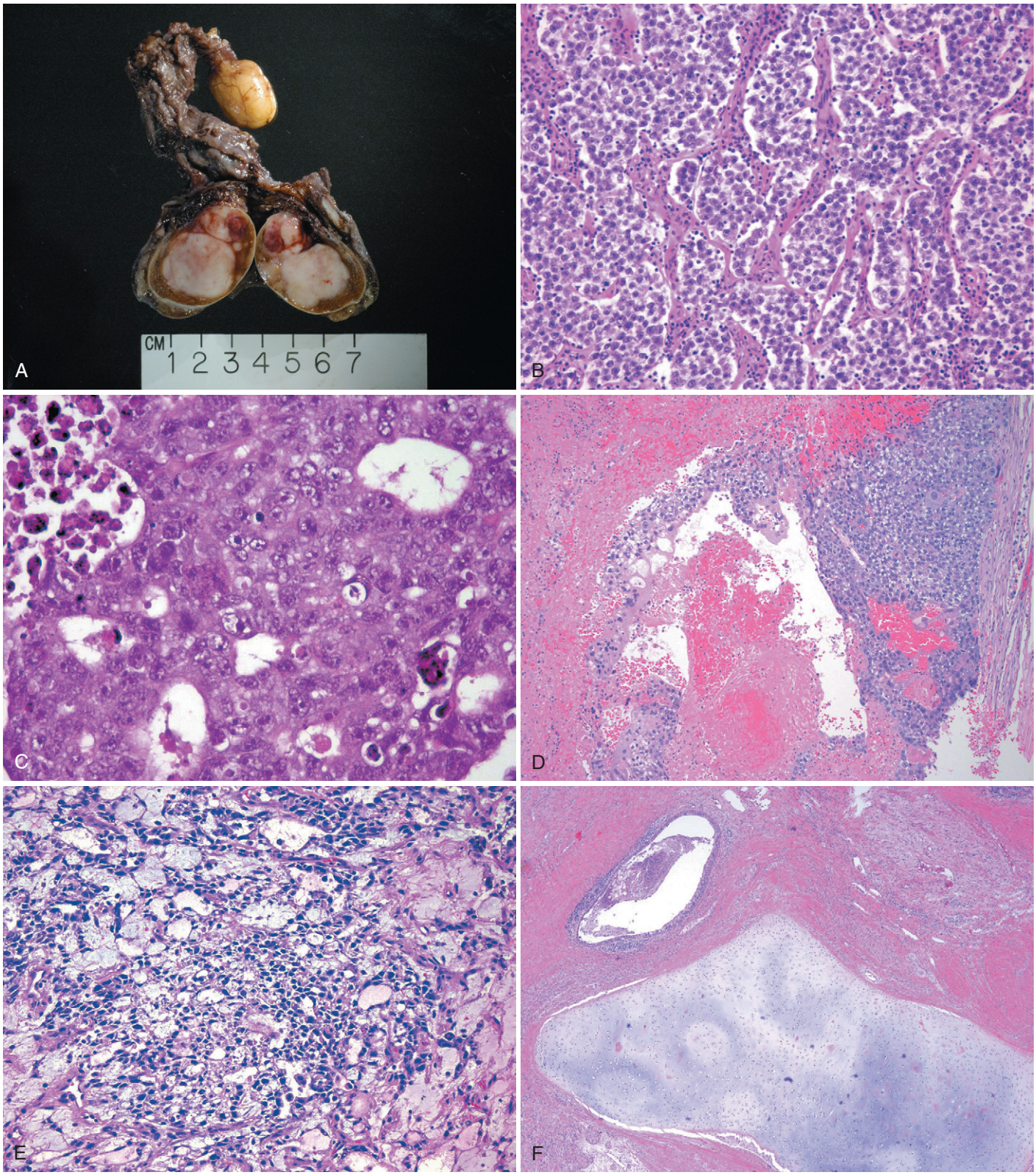


Figure 31–1. **A,** Gross section of testis containing seminoma. **B,** Seminoma (H&E stain). **C,** Embryonal carcinoma (H&E stain). **D,** Choriocarcinoma (H&E stain). **E,** Yolk sac tumor (H&E stain). **F,** Teratoma (H&E stain). (**A-F,** Courtesy of Donna E. Hansel, MD, PhD.)

consists of a reticular network of medium-sized cuboidal cells with cytoplasmic and extracytoplasmic eosinophilic, hyaline-like globules (Epstein, 2010). Hyaline globules are a characteristic feature and are present in up to 84% of cases. Yolk sac tumors may grow in a glandular, papillary, or microcystic pattern. A characteristic feature is the Schiller-Duval body, which resembles endodermal sinuses, and is seen in roughly half of cases (see Fig. 31–1E). **Yolk sac tumors almost always produce AFP but not hCG.** Among men with CS I NSGCT with normal serum tumor markers the presence of a yolk sac tumor is associated with a lower risk of

relapse, but this finding may simply be a result of serum tumor markers (i.e., AFP) having a higher sensitivity for detecting micrometastatic disease in this type of GCT (Read et al, 1992).

Teratoma. Teratomas are tumors that contain well-differentiated or incompletely differentiated elements of at least two of the three germ cell layers of endoderm, mesoderm, and ectoderm. Characteristically all components are intermixed. Well-differentiated tumors are labeled mature teratomas, whereas those that are incompletely differentiated (i.e., similar to fetal or embryonal tissue) are called immature teratomas. Mature teratomas may include elements of mature bone, cartilage, teeth, hair, and squamous epithelium, a fact that most likely explains the name teratoma, which roughly means "monster tumor," in Greek (see Fig. 31–1F). The gross appearance of teratoma depends largely on the elements within it, with most tumors having solid and cystic areas. **Teratomas are generally associated with normal serum tumor markers, but they may cause mildly elevated serum AFP levels.** Approximately 47% of adult mixed GCTs contain teratoma, but pure teratomas are uncommon. In contrast, pure teratomas comprise a sizeable fraction of pediatric GCTs (Epstein, 2010).

In adults, teratomas are histologically benign but are frequently found at metastatic sites in patients with advanced NSGCT. It is hypothesized that nonteratomatous elements (mostly EC) have the ability to mature into teratoma and that the metastases are derived from these elements before their differentiation. **Teratoma is resistant to chemotherapy.** Thus, given its frequent presence at metastatic sites in advanced NSGCT, patients with residual masses after chemotherapy require consolidative surgical resection because 40% to 50% will have residual teratoma. The inherent chemoresistance of teratoma is a limitation to treatment strategies for NSGCT that utilize chemotherapy alone.

Despite their benign histologic appearance, teratomas may contain genetic abnormalities frequently found in malignant GCT elements, including aneuploidy, i(12p), and widely variable proliferative capacity (Castedo et al, 1989; Sella et al, 1991). Studies have also shown that cystic fluid from teratoma frequently contains hCG and AFP, confirming the malignant potential of teratoma (Sella et al, 1991; Beck et al, 2004). The genetic instability of teratoma has important clinical implications. **Teratomas may grow uncontrollably, invade surrounding structures, and become unresectable (known as growing teratoma syndrome)** (Logothetis et al, 1982). **On rare occasions, teratoma may transform into a somatic malignancy such as rhabdomyosarcoma, adenocarcinoma, or primitive neuroectodermal tumor** (Little et al, 1994; Comiter et al, 1998; Motzer et al, 1998). These tumors are called "teratoma with somatic-type malignancy" or "teratoma with malignant transformation." They frequently have abnormalities of chromosome 12 or i(12p), indicating their origin from GCT. Malignant transformation is highly aggressive, resistant to conventional chemotherapy, and associated with a poor prognosis. Lastly, unresected teratoma in patients with advanced NSGCT may result in late relapse (Sheinfeld, 2003). All of these events may have lethal consequences.

Initial Presentation

Signs and Symptoms

The most common presentation of testicular cancer is a painless testicular mass. Acute testicular pain is less common and is caused by rapid expansion of the testis due to intratumor hemorrhage or infarction caused by rapid tumor growth. Pain is more commonly associated with NSGCT, because these tumors tend to be more vascular and exhibit more rapid growth compared with seminomas. Patients frequently report a history of testicular trauma, although incidental trauma is likely responsible for bringing the testicular mass to the patient's attention for the first time. Patients may also complain of vague scrotal discomfort or heaviness. **Regional or distant metastasis at diagnosis is present in approximately two thirds of NSGCTs and 15% of pure seminomas, and symptoms related to metastatic disease are the presenting complaint in 10% to 20% of patients.** Bulky retroperitoneal metastasis may cause a palpable mass, abdominal pain, flank pain due to ureteral obstruction, back pain due to involvement of the psoas muscle or nerve roots, lower extremity swelling due to compression of the inferior vena cava, or gastrointestinal symptoms. Pulmonary metastasis may present as dyspnea, chest pain, cough, or hemoptysis. Metastasis to supraclavicular lymph nodes may present as a neck mass. **Approximately 2% of men have gynecomastia,** resulting from either elevated serum hCG levels, decreased androgen production, or increased estrogen levels (most commonly seen in men with Leydig cell tumors). **Although approximately two thirds of men with GCT have diminished fertility, it is an uncommon initial presentation.**

Physical Examination

The physician should carefully examine the affected and the normal contralateral testes, noting their relative size and consistency and palpating for any testicular or extratesticular masses. Atrophy of the affected or contralateral testis is common, particularly in patients with a history of cryptorchidism. Any firm area within the testis is suggestive of malignancy and should prompt further investigations. A hydrocele may accompany a testicular cancer and impair the examiner's ability to evaluate the testis. In this case, scrotal ultrasonography to evaluate the testis is warranted. The patient should also be examined for any evidence of palpable abdominal mass or tenderness, inguinal lymphadenopathy (particularly if he has had prior inguinal or scrotal surgery), gynecomastia, and supraclavicular lymphadenopathy; and auscultation of the chest should be done in a search for intrathoracic disease.

Differential Diagnosis

The differential diagnosis of a testicular mass includes epididymo-orchitis, torsion, hematoma, or paratesticular neoplasm (benign or malignant). Other diagnostic possibilities include hernia, varicocele, or spermatocele, although these usually can be distinguished from a testicular mass by physical examination. **A firm intratesticular mass should be considered cancer until proven otherwise and should be evaluated further with scrotal ultrasonography. In patients with a presumptive diagnosis of epididymo-orchitis, patients should be reevaluated within 2 to 4 weeks of completion of an appropriate course of oral antibiotics.** A persistent mass or pain should be evaluated further with scrotal ultrasonography.

Diagnostic Delay

Although testicular cancer is the most common malignancy in young adult males, diagnostic delay is a well-recognized phenomenon of this disease, with patients and physicians contributing to this delay. Testicular cancer patients are typically young and may be less inclined to seek medical evaluation for symptoms due to denial, ignorance, or limited access. In cases of diagnostic delay,

the longest period of delay has been attributed to the physician in up to two thirds of cases. **Prior studies show that up to one third of testicular tumors are initially misdiagnosed as epididymitis or hydrocele** (Bosl et al, 1981). For patients who present with signs or symptoms from metastatic GCT, these may become the focus of the treating physician, resulting in the failure to diagnose GCT. These patients may be subjected to inappropriate treatment, diagnostic tests, and unnecessary surgery with subsequent delays in definitive therapy. Case reports describe patients undergoing exploratory laparotomy, neck dissection, or mastectomy for unsuspected metastatic GCT. The interval of delay is associated with advanced clinical stage, suboptimal response to chemotherapy, and diminished survival. Moul and colleagues (1990) reported a decrease in survival in GCT patients treated from 1970 to 1987 with a diagnostic delay greater than 16 weeks, although a significant survival difference was not observed among patients treated in the cisplatin era. Stephenson and associates (2004) reported a higher proportion of men requiring intensive chemotherapy (multiple regimens, high-dose, and salvage chemotherapy) among those with a treatment delay greater than 30 days due to unnecessary exploratory laparotomy.

Diagnostic delay can be avoided by efforts to improve patient and physician education. Physicians must consider the diagnosis of GCT in any male aged 15 to 50 years with a firm testicular mass, midline retroperitoneal mass, or mass in the left supraclavicular fossa. A thorough physical examination with appropriate serologic (serum AFP, hCG, lactate dehydrogenase [LDH]) and radiologic evaluations (testicular ultrasonography) should lead to the correct diagnosis.

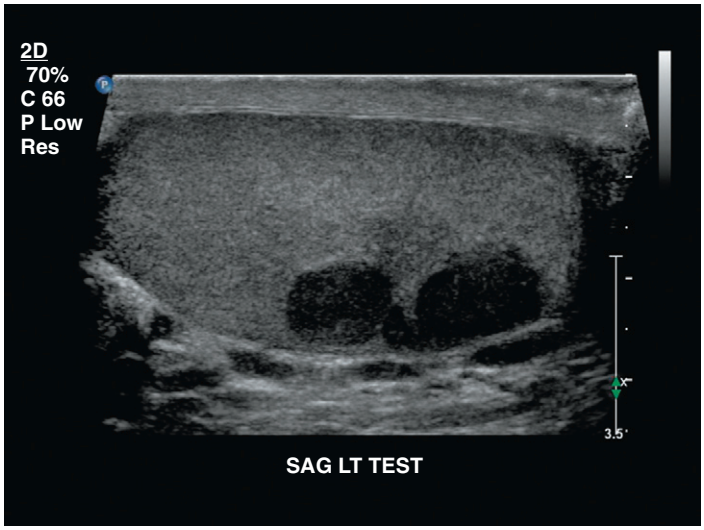


Figure 31–2. Sagittal view of left testis showing multinodular hypoechoic intratesticular lesion confirmed to be pure seminoma at orchiectomy.

Diagnostic Testing and Initial Management

Scrotal Ultrasonography

In men presenting with a testicular mass, hydrocele, or unexplained scrotal symptoms or signs, **scrotal ultrasonography should be considered an extension of the physical examination because it is widely available, inexpensive, and noninvasive.** With high-frequency transducers (5 to 10 MHz), intratesticular lesions as small as a few millimeters can be identified and readily distinguished from an extratesticular pathologic process. On ultrasonography the typical GCT is hypoechoic and two or more discrete lesions may be identified (Fig. 31–2). Heterogeneous echotexture within a lesion is more commonly associated with NSGCT, because seminomas usually have a homogeneous echotexture. The presence of increased flow within the lesion on color Doppler ultrasonography is suggestive of malignancy, although its absence does not exclude GCT. The association between testicular microlithiasis and GCT is not clearly defined, and this finding alone should not prompt further evaluation (DeCastro et al, 2008). **Given the 2% incidence of bilateral GCTs, both testes should be evaluated ultrasonographically, although bilateral tumors at diagnosis is rare (0.5% of all GCTs) and metachronous presentation is more common** (Fossa et al, 2005).

In men with advanced GCT and a normal testicular examination, scrotal ultrasonography should be performed to rule out the presence of a small, impalpable scar or calcification, indicating a "burned-out" primary testicular tumor. Radical orchiectomy should be performed in those patients with ultrasonographic evidence of intratesticular lesions. Men with advanced GCT with normal testes on physical examination and ultrasonographic evaluation are considered to have primary extragonadal GCT.

The presence of small (<10 mm), impalpable intratesticular lesions in the absence of disseminated GCT or elevated serum tumor markers represents a diagnostic dilemma. The majority of these lesions are benign (testicular cysts, small infarcts, Leydig cell nodules, or small Leydig cell or Sertoli cell tumors), although up to 20% to 40% may represent small GCTs (usually seminoma) (Hindley et al, 2003; Connolly et al, 2006; Muller et al, 2006). Management options include inguinal orchiectomy, inguinal exploration and excision (with frozen section analysis to rule out GCT), and close observation with serial ultrasonographic evaluation (with exploration of growing lesions). Intraoperative ultrasonography is useful during surgical exploration of the testis to locate the lesion. The risk of malignancy increases with the size of the lesion (Carmignani et al, 2005).

Serum Tumor Markers

Testicular cancer is one of the few malignancies associated with accurate serum tumor markers (LDH, AFP, and hCG), a finding that is essential in its diagnosis, prognosis, treatment, and monitoring. Serum tumor marker levels should be obtained at diagnosis, after orchiectomy, to monitor for response to chemotherapy, and to monitor for relapse in patients on surveillance and after completion of therapy.

At diagnosis, AFP levels are elevated in 50% to 70% of low-stage (CS I, IIA, IIB) NSGCT and 60% to 80% of advanced (CS IIC, III) NSGCT. EC and yolk sac tumors secrete AFP. Choriocarcinomas and seminomas do not produce AFP. Patients with pure seminoma in the primary tumor with an elevated serum AFP value are considered to have NSGCT. The half-life of AFP is 5 to 7 days. AFP levels may also be raised in patients with hepatocellular carcinoma and cancers of the stomach, pancreas, biliary tract, and lung. Patients with nonmalignant liver disease (infectious, drug-induced, alcohol-induced, autoimmune) may also have elevated AFP levels. Elevated serum AFP levels are also a feature of ataxic telangiectasia and hereditary tyrosinemia.

hCG levels are elevated in 20% to 40% of low-stage NSGCT and 40% to 60% of advanced NSGCT. Approximately 15% of seminomas secrete hCG. hCG is also secreted by choriocarcinoma and EC. Levels greater than 5000 IU/L are usually associated with NSGCT. The half-life of hCG is 24 to 36 hours. hCG levels may be elevated in cancers of the liver, biliary tract, pancreas, stomach, lung, breast, kidney, and bladder. The α subunit of hCG is common to several pituitary hormones, thus **immunoassays for hCG are directed at the β subunit. Cross-reactivity of the hCG assay with luteinizing hormone may cause false-positive hCG elevations in patients with primary hypogonadism.** Elevated serum hCG results caused by hypogonadism will normalize within 48 to 72 hours after the administration of testosterone, and this can be done to distinguish between true- and false-positive hCG results. Marijuana use may also cause false-positive hCG results.

LDH levels are elevated in approximately 20% of low-stage GCTs and 20% to 60% of advanced GCTs. LDH is expressed in smooth, cardiac, and skeletal muscle. Lymphoma may also cause elevated LDH levels. Of the five isoenzymes of LDH, LDH-1 is the most frequently elevated isoenzyme in GCT. LDH-1 levels are correlated with the chromosome arm 12p copy number, which is frequently amplified in GCT. The magnitude of LDH elevation correlates with the bulk of disease. As a nonspecific marker for GCT, its main use is in the prognostic assessment of GCT at diagnosis. The serum half-life of LDH is 24 hours.

Patients suspected of having a GCT should have blood drawn for serum AFP, hCG, and LDH evaluation before orchiectomy to aid in the diagnosis and to help interpret postorchiectomy tumor marker levels. For staging purposes it is relevant to know whether preorchiectomy serum tumor marker levels are declining after orchiectomy and, if so, how quickly. The results of serum tumor marker assays should not be used to guide decision making about whether to perform a radical orchiectomy, because AFP or hCG levels in the normal range do not rule out GCT. A significantly elevated serum AFP level can establish the diagnosis of NSGCT in a patient whose histopathologic diagnosis is pure seminoma because seminomas do not produce AFP. However, borderline-elevated values should be interpreted cautiously. **In rare patients who present with a testicular, retroperitoneal, or mediastinal primary tumor and whose disease burden has resulted in a need to start treatment very urgently, substantially elevated serum AFP and/or hCG levels may be considered sufficient for diagnosis of GCT.** For rare patients with medically unstable disease, treatment need not be delayed until histology results permit a tissue diagnosis. However, these patients should undergo radical orchiectomy after the completion of chemotherapy because the testis is a sanctuary site for malignant GCT owing to the blood-testis barrier and because the testis frequently contains residual invasive GCT, teratoma, and/or ITGCN (Geldart et al, 2002).

Radical Inguinal Orchiectomy

Patients suspected of having a testicular neoplasm should undergo a radical inguinal orchiectomy with removal of the tumor-bearing testis and spermatic cord to the level of the internal inguinal ring. **A transscrotal orchiectomy or biopsy is contraindicated because it leaves the inguinal portion of the spermatic cord intact and may alter the lymphatic drainage of the testis, increasing the risk of local recurrence and pelvic or inguinal lymph node metastasis.** Because of the rapid growth of GCT, orchiectomy should be performed in a timely manner and delays greater than 1 to 2 weeks should be avoided.

Radical orchiectomy establishes the histologic diagnosis and primary T stage, provides important prognostic information from the tumor histology, and is curative in 80% to 85% and 70% to 80% of CS I seminoma and CS I NSGCT, respectively.

Histopathologic examination of the testis should identify the histologic type of the tumor (see Table 31–2) (Sobin and Wittekind, 2002), tumor size, multifocality, local tumor invasion (rete testis, tunica albuginea, tunica vaginalis, epididymis, spermatic cord, scrotum), primary T stage (Table 31–3) (Sobin and Wittekind, 2002; Greene et al, 2002), presence of ITGCN, invasion of blood or lymphatic vessels (termed *lymphovascular invasion* [LVI]), and the surgical margin status. For patients with mixed GCT, each individual tumor subtype should be identified, including its relative proportion. Because of the relative rarity of GCT and the importance of primary tumor histology for treatment decision making, review of primary tumor specimens by experienced pathologists is recommended (Krege et al, 2008a). In a recent randomized, multicenter clinical trial, 5 of 382 NSGCT specimens (1.3%) were reclassified as seminomas by centralized pathologic review (Albers et al, 2008).

Testis-Sparing Surgery

Testis-sparing surgery (or partial orchiectomy) is highly controversial and has no role in the patient suspected of having a testicular neoplasm with a normal contralateral testis. However, it may be considered for organ-confined tumors of less than 2 cm in patients with synchronous bilateral tumors or tumor in a solitary testis with sufficient testicular androgen production. It may also be considered for suspected benign tumor or indeterminate lesion when serum AFP, hCG, and LDH values are normal. Testis-sparing surgery is seldom feasible for larger tumors (>2 cm) because a complete excision frequently leaves insufficient residual testicular parenchyma for preservation. **When testis-sparing surgery is performed, biopsies of the adjacent testicular parenchyma should be done to rule out the presence of ITGCN. ITGCN is present in adjacent testicular parenchyma in 80% to 90% cases of GCT and is associated with a 50% risk of GCT within 5 years and 70% within 7 years** (Skakkebaek et al, 1982; Dieckmann and Skakkebaek, 1999; Montironi, 2002). **Adjuvant radiotherapy to the residual testis using doses of 20 Gy or greater is usually sufficient to prevent the development of a GCT.** The German Testicular Cancer Study Group reported no cases of local recurrence over a median follow-up of 91 months in 46 patients with small, organ-confined tumors who underwent testis-sparing surgery and received adjuvant radiotherapy for ITGCN (Heidenreich et al, 2001).

Biopsy of the Contralateral Testis

Between 5% and 9% of patients with GCT have ITGCN in the normal contralateral testis (Dieckmann and Skakkebaek, 1999). In patients with an atrophic testis, history of cryptorchidism, or age younger than 40 years, the risk of ITGCN in the contralateral testis has been reported in up to 36% (Dieckmann and Loy, 1996). Thus an open inguinal biopsy of the contralateral testis may be considered in patients with risk factors for ITGCN or those with suspicious lesions on preoperative ultrasonography (Motzer et al, 2006).

Suspected Extragonadal GCT

Two to 5 percent of GCT are extragonadal origin (Bokemeyer et al, 2002b). Of the patients with metastatic GCT without a testicular

mass, only one third definitively has a primary extragonadal GCT, because one third has ITGCN in the testis and one third has ultrasonographic evidence of a "burned-out" primary tumor (Scholz et al, 2002). GCT should be considered in any young male with a midline mass. The presence of elevated serum AFP and/or hCG with a normal testicular evaluation is sufficient for the diagnosis of GCT, and histologic confirmation by biopsy is not necessary before starting treatment. When serum tumor markers are normal, then biopsy of the mass should be performed to confirm the diagnosis of GCT before beginning treatment. A biopsy specimen showing poorly differentiated carcinoma represents a diagnostic dilemma if a primary tumor site cannot be confirmed. In this scenario the diagnosis of extragonadal GCT with malignant transformation may be considered and supported by the expression of i(12p) in biopsy specimens.

Patients with suspected retroperitoneal extragonadal GCT should undergo inguinal orchiectomy at some point during their treatment course if the pattern of metastasis is consistent with a right- or left-sided testicular primary tumor or if there is ultrasonographic evidence of a "burned-out" primary tumor.

Table 31–3.

TNM Staging of Testicular Tumor: American Joint Committee on Cancer and Union Internationale Contre le Cancer

Primary Tumor (T)*	
The extent of primary tumor is usually classified after radical orchiectomy and, for this reason, a *pathologic* stage is assigned.	
pTx	Primary tumor cannot be assessed
pT0	No evidence of primary tumor (e.g., histologic scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma in situ)
pT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade into the tunica albuginea but not the tunica vaginalis
pT2	Tumor limited to the testis and epididymis with vascular/lymphatic invasion, or tumor extending through the tunica albuginea with involvement of the tunica vaginalis
pT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion
Regional Lymph Nodes (N)	
CLINICAL (as determined by noninvasive staging)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass, more than 2 cm, but not more than 5 cm in greatest dimension; or multiple lymph nodes, any one mass greater than 2 cm but not more than 5 cm in greatest dimension
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
PATHOLOGIC (pN) (as determined by pathologic findings of RPLND without prior chemotherapy or radiotherapy)	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and less than or equal to five nodes positive, none more than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional nodal or pulmonary metastasis
M1b	Distant metastasis at site other than nonregional lymph nodes or lung
Serum Tumor Markers (S)	
SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH < 1.5 × N† *and* hCG (MIU/mL) <5000 *and* AFP (ng/mL) <1000
S2	LDH 1.5-10 × N *or* hCG (MIU/mL) 5000-50,000 *or* AFP (ng/mL) 1000-10,000
S3	LDH >10 × N *or* hcG (MIU/mL) >50,000 *or* AFP (ng/mL) >10,000

Continued

Table 31–3.

TNM Staging of Testicular Tumor: American Joint Committee on Cancer and Union Internationale Contre le Cancer—cont'd

Stage Grouping				
GROUP	T	N	M	S (SERUM TUMOR MARKERS)
Stage 0	pTis	N0	M0	S0
Stage I	pT1-4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
Stage IS	Any pT/Tx	N0	M0	S1-3
Stage II	Any pT/Tx	N 1-3	M0	SX
Stage IIA	Any pT/Tx	N1	M0	S0
	Any pT/Tx	N1	M0	S1
Stage IIB	Any pT/Tx	N2	M0	S0
	Any pT/Tx	N2	M0	S1
Stage IIC	Any pT/Tx	N3	M0	S0
	Any pT/Tx	N3	M0	S1
Stage III	Any pT/Tx	Any N	M1	SX
Stage IIIA	Any pT/Tx	Any N	M1a	S0
	Any pT/Tx	Any N	M1a	S1
Stage IIIB	Any pT/Tx	N1-3	M0	S2
	Any pT/Tx	Any N	M1a	S2
Stage IIIC	Any pT/Tx	N1-3	M0	S3
	Any pT/Tx	Any N	M1a	S3
	Any pT/Tx	Any N	M1b	Any S

*Except for pTis and pT4, extent of primary tumor is classified by radical orchiectomy. Tx may be used for other categories in the absence of radical orchiectomy.
†N indicates the upper limit of normal for the LDH assay.
AFP, α-fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase.
Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual,* Seventh Edition (2010), published by Springer Science and Business Media, LLC, www.springer.com.
From AJCC. Testis. In: Edge SE, Byrd DR, Compton CC, editors. AJCC cancer staging manual. 7th ed. New York: Springer; 2010. p. 469–73.

Key Points: Diagnosis and Initial Management

- A solid intratesticular mass in a postpubertal male should be considered a GCT until proven otherwise.
- With rare exceptions, inguinal orchiectomy with high ligation of the spermatic cord should be performed in men suspected of having GCT. Transscrotal orchiectomy or biopsy is to be condemned.
- Testis-sparing surgery for GCT is a consideration only in highly select patients who have a small tumor in either a solitary testis or synchronous bilateral testicular masses when preservation of the affected testis will provide the patient with sufficient testicular androgen production.
- Diagnostic delay is common in GCT, and approximately one third of cases are initially misdiagnosed.
- If elevated before orchiectomy, serum tumor marker levels should be measured after orchiectomy to determine if levels are declining, stable, or rising. Preorchiectomy serum tumor marker levels should not be used in management decisions.

Clinical Staging

The prognosis of GCT and initial management decisions are dictated by the clinical stage of the disease, which is based on the histopathologic findings and pathologic stage of the primary tumor, postorchiectomy serum tumor marker levels, and presence and extent of metastatic disease as determined by physical examination and staging imaging studies. In 1997 an international consensus classification for GCT was developed by the American Joint Committee on Cancer (AJCC) and Union Internationale Contre le Cancer (UICC) (see Table 31–3). The AJCC and UICC staging systems for GCT are unique because, for the first time, a serum tumor marker category (S) based on postorchiectomy AFP, hCG, and LDH levels is used to supplement the prognostic stages as defined by anatomic extent of disease. **The AJCC and UICC staging systems were updated in 2002 and the new systems consider the presence of LVI in the primary tumor as pT2 in an otherwise organ-confined tumor.** CS I is defined as disease clinically confined to the testis, CS II indicates the presence of regional (retroperitoneal) lymph node metastasis, and CS III represents nonregional lymph node and/or visceral metastasis.

Staging Imaging Studies

GCT follows a predictable pattern of metastatic spread that has contributed to its successful management. **With the exception of choriocarcinoma, the most common route of disease dissemination is via lymphatic channels from the primary tumor to the retroperitoneal lymph nodes and subsequently to distant sites. Choriocarcinoma has a propensity for hematogenous dissemination. The retroperitoneum is the initial site of metastatic spread in 70% to 80% of patients with GCT.** Detailed mapping studies from retroperitoneal lymph node dissection (RPLND) series have increased our understanding of the testicular lymphatic drainage

and identified the most likely sites of metastatic spread (Sheinfeld, 1994). **For right testicular tumors the primary drainage site is the interaortocaval lymph nodes inferior to the renal vessels, followed by the paracaval and para-aortic nodes. The primary "landing zone" for left testicular tumors is the para-aortic lymph nodes, followed by the interaortocaval nodes** (Donohue et al, 1982). The pattern of lymph drainage in the retroperitoneum is from right to left. Thus, contralateral spread from the primary "landing zone" is common with right-sided tumors but is rarely seen with left-sided tumors and usually is associated with bulky disease. **More caudal deposits of metastatic disease usually reflect retrograde spread to distal iliac and inguinal lymph nodes secondary to large volume disease and, more rarely, aberrant testicular lymphatic drainage. Retroperitoneal lymphatics drain into the cisterna chyli behind the right renal artery and right crus of the diaphragm.** Thus, retrocrural lymph node metastasis may be visible in patients with retroperitoneal disease. From there, lymphatic spread occurs via the thoracic duct to the posterior mediastinum and left supraclavicular fossa.

Clinical Staging of the Abdomen and Pelvis. All patients with GCT should undergo staging imaging studies of the abdomen and pelvis. Computed tomography (CT) after administration of oral and intravenous contrast agents is the most effective, noninvasive means of staging the retroperitoneum and pelvis. CT also provides a detailed anatomic assessment of the retroperitoneum to identify anatomic anomalies that may complicate subsequent RPLND, such as a circumaortic or retroaortic left renal vein, lower pole renal artery, or retrocaval right ureter. Magnetic resonance imaging (MRI) is an alternative to CT. Lymphangiography has no role where transaxial imaging is available.

Enlarged retroperitoneal lymph nodes are found on CT in 10% to 20% of seminomas and 60% to 70% of NSGCT. The retroperitoneum continues to be the most difficult area to accurately stage clinically. **A consistent 25% to 35% rate of pathologically involved retroperitoneal lymph nodes has been reported for CS I NSGCT in the presence of a "normal" CT scan despite the improvements in CT over the past 4 decades** (Fernandez et al, 1994). There is no consensus regarding size criteria for retroperitoneal lymph nodes that constitutes a "normal" CT scan. A size cutoff of 10 mm is frequently used to identify enlarged lymph nodes, but false-negative rates up to 63% have been reported when this size criterion is used. Among patients with CS IIA and IIB disease, clinical overstaging by CT (i.e., pathologically negative lymph nodes at RPLND despite enlarged lymph nodes on CT) is reported in 12% to 40% of patients.

An understanding of the primary drainage sites for left- and right-sided tumors has led to efforts to increase the sensitivity of abdominopelvic CT by decreasing the size criteria for clinically positive lymph nodes in the primary "landing zone," and a size criterion as small as 4 mm has been proposed. Leibovitch and colleagues (1995) showed that using a size cutoff of 4 mm in the primary landing zone and 10 mm outside this region was associated with a sensitivity and specificity for pathologic stage II disease of 91% and 50%, respectively. In a similar study, Hilton and associates (1997) reported a sensitivity and specificity of 93% and 58%, respectively, using a cutoff of 4 mm for lymph nodes in the primary "landing zone" that were anterior to a horizontal line bisecting the aorta. **Based on this evidence, retroperitoneal lymph nodes greater than 5 to 9 mm in the primary "landing zone," particularly if they are anterior to the great vessels on transaxial CT images, should be viewed with suspicion for regional lymph node metastasis** (Fig. 31–3). Because of the rapid growth of GCT, it is advisable to base the management decision on CT studies performed within 4 weeks of the initiation of treatment.

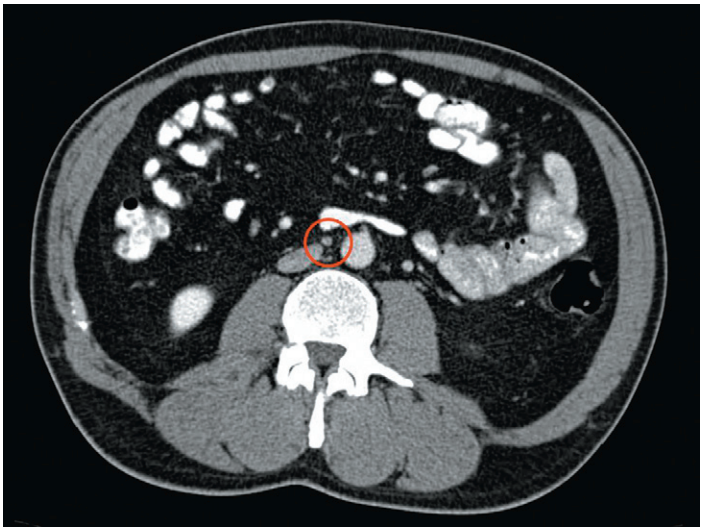


Figure 31–3. Postorchiectomy abdominopelvic CT scan in a patient with right testicular NSGCT showing a 7-mm lymph node in a primary landing zone. The lymph node was involved with teratoma at RPLND.

Malignant GCT accumulates fluorodeoxyglucose (FDG), and several studies have investigated FDG-labeled positron emission tomography (FDG-PET) in the staging of GCT at diagnosis and assessing response after chemotherapy. Several small pilot studies suggested that FDG-PET can identify retroperitoneal metastasis in low-stage seminoma and NSGCT more precisely than CT (Albers et al, 1999). In a prospective trial of centrally reviewed FDG-PET studies in 111 contemporary patients with CS I NSGCT on surveillance, relapse was observed in 33 of 87 patients who were PET negative, with an estimated relapse-free rate of 63% (Huddart et al, 2007). The investigators concluded that FDG-PET is not sufficiently sensitive to accurately stage CS I NSGCT. De Wit and associates (2008) also reported that FDG-PET yielded only slightly better results than CT as a primary staging tool for low-stage NSGCT. **Thus there is currently no role for FDG-PET in the routine evaluation of NSGCT and seminoma at the time of diagnosis.**

CS II disease is subclassified based on the size of regional lymph node(s) as determined by abdominopelvic imaging into IIA (enlarged retroperitoneal lymph nodes ≤2 cm), IIB (enlarged retroperitoneal lymph nodes >2 cm but ≤5 cm), and IIC (enlarged lymph nodes >5 cm).

Pathologic Staging of the Abdomen and Pelvis. In select centers European centers performing open RPLND and most laparoscopic RPLND series, RPLND is performed in patients with CS I or IIA NSGCT largely as a staging procedure without curative intent to identify the presence of regional lymph nodes and determine the need for subsequent chemotherapy (Nelson et al, 1999; Janetschek et al, 2000; Albers et al, 2003, 2008; Bhayani et al, 2003; Nielsen et al, 2007). Pathologic N stage differs from clinical N stage in that the former also considers the number of lymph nodes involved:

pN0: no regional lymph node metastasis
pN1: 5 or fewer lymph nodes involved, none larger than 2 cm
pN2: more than 5 lymph nodes involved and/or any lymph node of 2 to 5 cm
pN3: any lymph node larger than 5 cm

In patients with pathologic stage II disease (Any pT, pN1-3, M0), the risk of occult metastases (and relapse after RPLND) is closely related to the burden of regional lymph node metastasis (10% to 30% of pN1 vs. 50% to 80% for pN2-3). The pathologic N stage cannot be applied to RPLND specimens from patients who have received prior chemotherapy or radiotherapy.

Chest Imaging

All patients with GCT should undergo chest imaging before decisions regarding management are made. Thoracic metastasis in the absence of retroperitoneal disease and/or elevated serum tumor markers is uncommon, particularly for seminoma. Thus, routine chest CT may be associated with a high rate of false-positive findings, which may complicate subsequent therapy (Horan et al, 2007). Thus it is reasonable to perform obtain chest radiographs at the time of diagnosis as an initial staging study, and CT should be performed in patients with elevated postorchiectomy levels of serum tumor markers, evidence of metastatic disease by physical examination or abdominopelvic CT, or abnormal or equivocal findings on chest radiography. It may be reasonable to perform chest CT in patients with CS I NSGCT with evidence of LVI or EC predominance because some studies have reported a high rate of hematogenous metastasis to the lung in the setting of a negative CT for retroperitoneal metastasis (Hermans et al, 2000; Sweeney et al, 2000). Mediastinal or hilar lymphadenopathy in the absence of retroperitoneal disease should raise the index of suspicion of non-GCT etiology such as lymphoma or sarcoidosis, and histologic confirmation of GCT by mediastinoscopy and biopsy should be performed before initiating systemic therapy (Hunt et al, 2009).

Visceral metastasis to bone and brain is uncommon in GCT in the absence of symptoms or other clinical indicators of disease. As such there is no role for routine bone scintigraphy or brain CT at the time of diagnosis. A notable exception to this is brain CT for patients with a highly elevated hCG value (>10,000 IU/L) because these levels are often associated with metastati choriocarcinoma, which has a propensity for brain metastases.

Serum Tumor Markers

Postorchiectomy AFP, hCG, and LDH levels are important for staging, prognosis, and treatment selection. Thus, all patients should have blood drawn after orchiectomy to assess for appropriate decline in these markers according to half-life in those patients with elevated levels before orchiectomy. The presence of newly elevated and/or rising serum tumor marker levels after orchiectomy indicates metastatic disease, and these patients should receive induction chemotherapy as initial therapy. In the setting of a negative metastatic evaluation and slowly declining markers (i.e., not according to half-life), patients should be monitored closely and have levels checked periodically until levels normalize or begin to rise. Stable AFP or hCG levels slightly above the normal range should be interpreted cautiously, and other causes for serum tumor marker elevation should be ruled out before management decisions are made. As with staging imaging studies, management decisions should be based on serum tumor marker levels measured within 4 weeks of the initiation of treatment.

Prognostic Classification of Advanced GCT

An international, retrospective pooled analysis of 5202 patients with advanced NSGCT treated between 1975 and 1990 with platin-containing chemotherapy regimens (cisplatin or carboplatin) identified AFP, hCG, and LDH levels at the initiation of chemotherapy, the presence of nonpulmonary visceral metastasis, and primary mediastinal NSGCT as significant and independent prognostic factors for progression and survival. In 660 patients with advanced seminoma, only the presence of nonpulmonary visceral metastasis was an important predictor of progression and survival (International Germ Cell Consensus Classification, 1997).

Based on these analyses the International Germ Cell Cancer Collaborative Group (1997) **(IGCCCG) risk classification for advanced GCT was developed** (Table 31–4). **The**

Table 31–4.

International Germ Cell Cancer Collaborative Group Risk Classification for Advanced GCT

Good Prognosis	
NONSEMINOMA	SEMINOMA
Testicular/retroperitoneal primary *and* No nonpulmonary visceral metastases *and* Good markers—all of: AFP <1000 ng/mL *and* hCG <5000 IU/L (1000 ng/mL) *and* LDH <1.5 × *upper limit of normal*	Any primary site *and* No nonpulmonary visceral metastases *and* Normal AFP, any hCG, any LDH
56% of nonseminomas	90% of seminomas
5-year PFS 89%	5-year PFS 82%
5-year survival 92%	5-year survival 86%
Intermediate Prognosis	
NONSEMINOMA	SEMINOMA
Testicular/retroperitoneal primary *and* No nonpulmonary visceral metastases *and* Intermediate markers—any of: AFP ≥1000-10,000 ng/mL and ≤10,000 ng/mL *or* hCG ≥5000-50,000 IU/L and ≤50,000 IU/L *or* LDH ≥1.5 × N and ≤10 × N	Any primary site *and* Nonpulmonary visceral metastases *and* Normal AFP, any hCG, any LDH
28% of nonseminomas	10% of seminomas
5-year PFS 75%	5-year PFS 67%
5-year survival 80%	5-year survival 72%
Poor Prognosis	
NONSEMINOMA	SEMINOMA
Mediastinal primary *or* Nonpulmonary visceral metastases *or* Poor serum markers—any of: AFP >10,000 ng/mL *or* hCG >50,000 IU/L (10,000 ng/mL) *or* LDH >10 × *upper limit of normal*	No patients classified as poor prognosis
16% of nonseminomas	
5-year PFS 41%	
5-year survival 48%	

AFP, α-fetoprotein; GCT, germ cell tumor; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; PFS, progression-free survival; ULN, upper limit of normal.

From International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J Clin Oncol 1997;15:594–603.

IGCCCG risk group should be determined for each patient with metastatic GCT and this should be used to guide treatment decision making on the choice of chemotherapy (discussed later). This classification applies only to patients with advanced GCT at the time of diagnosis and is not applicable to patients with relapsed GCT. It is also based on the postorchiectomy serum tumor marker levels at the start of chemotherapy not the preorchiectomy levels.

Approximately 56%, 28%, and 16% of patients with advanced NSGCT are classified as at good, intermediate, and poor risk by IGCCCG criteria; and the 5-year progression-free and overall survival rates for these patients are 89% and 92%, 75% and 80%, and 41% and 48%, respectively. There is no poor-risk category for seminoma. Approximately 90% and 10% of patients with advanced seminoma are classified as at good and intermediate risk, respectively, by IGCCCG criteria; and the 5-year progression-free and overall survival rates for these patients are 82% and 86% and 67% and 72%, respectively. Van Dijk and coworkers (2006) published a meta-analysis of 10 studies of 1775 NSGCT patients treated after 1989 and reported pooled 5-year survival estimates of 94%, 83% and 71% for good-, intermediate-, and poor-risk patients by IGCCCG criteria. These results represent a significantly improved survival compared with the original study (particularly for those classified as poor risk) and are attributed to more effective treatment strategies and more experience in treating NSGCT patients.

The TNM system does incorporate marker levels (S0-3) and nonpulmonary visceral metastasis in the staging of testicular cancer. However, this system does not consider the differences in prognosis between seminomas and NSGCT with nonpulmonary visceral metastasis. In the TNM system these would both be classified as stage IIIC, but IGCCCG would classify the former as intermediate risk and the latter as poor risk. As such, the IGCCCG system is preferentially used for prognostic assessment and the selection of chemotherapy.

Sperm Cryopreservation

Although infertility is an uncommon presentation for GCT, up to 52% of men have oligospermia at diagnosis and 10% are azoospermic (DH Williams et al, 2009). The germinal epithelium is exquisitely sensitive to platin-based chemotherapy and radiation therapy. **Virtually all patients will become azoospermic after chemotherapy, and 50% and 80% of patients with normal semen parameters at diagnosis will return to these levels within 2 and 5 years, respectively** (Bokemeyer et al, 1996a; Feldman et al, 2008). **Recovery of spermatogenesis after radiation therapy for seminoma may take 2 to 3 years or more** (Fossa et al, 1999b). RPLND may result in ejaculatory dysfunction in 80% or more of patients undergoing a full, bilateral template dissection without nerve sparing. **Given the impact of treatments for testicular cancer on fertility, men who are undecided or are planning future paternity are recommended to undergo sperm cryopreservation before treatment is initiated.** Sperm banking can be done before or after radical orchiectomy.

Treatment

Therapeutic Principles

The management of GCTs is governed by the potential for rapid growth and for cure in essentially all patients. **This translates into a need for rapid diagnosis and staging and expeditious application of appropriate treatment so as not to have patients die unnecessarily or suffer side effects from treatment that would not have been required with earlier diagnosis and proper management.** After orchiectomy, staging imaging studies, serum tumor marker status, and treatment plans should be performed/developed as rapidly as can be reasonably accomplished.

The probability of cure even in the presence of metastatic disease has also led to an aggressive approach with regard to the administration of chemotherapy and the performance of postchemotherapy surgery (PCS) to resect residual masses. Chemotherapy is generally administered regardless of low white blood cell counts or thrombocytopenia, and nephrotoxic chemotherapy (cisplatin) is often administered even in the presence of moderate-to-severe renal insufficiency (Williams, 1987a; Einhorn et al, 1989; Bajorin et al, 1993; Loehrer et al, 1995; Bokemeyer et al, 1996b; Nichols et al, 1998; de Wit et al, 2001). Similarly, an aggressive surgical approach is taken to resect all sites of residual disease after chemotherapy for NSGCT, even if this involves multiple anatomic sites. The young age and generally good health of GCT patients permits an aggressive treatment approach if needed.

Serum tumor markers strongly influence the management of GCTs, particularly NSGCT. As discussed, **elevated serum AFP or hCG after orchiectomy indicates the presence of metastatic disease and these patients are preferentially given chemotherapy as their initial therapy.** For patients receiving chemotherapy, rising serum tumor marker levels during or after therapy generally indicate refractory or relapsed disease, respectively. As discussed, serum AFP, hCG, and LDH levels at the initiation of chemotherapy are important prognostic factors and

Key Points: Clinical Staging

- Testicular GCT follows a predictable pattern of spread from the primary tumor to retroperitoneal lymph nodes and then to distant metastatic sites.
- The primary "landing zone" for left-sided tumors is the paraaortic and left renal hilar lymph nodes, and for right-sided tumors it is the interaortocaval and paracaval lymph nodes.
- CT is the optimal modality for staging the retroperitoneum, although false-negative results occur in 25% to 35% and 14% to 20% of patients with CS I NSGCT and seminoma, respectively, when a 1-cm cutoff is used.
- Chest radiography and CT are acceptable staging modalities in the absence of retroperitoneal lymphadenopathy or elevated serum tumor marker levels.
- Rising postorchiectomy serum tumor marker levels indicate the presence of metastatic GCT, and these patients should receive chemotherapy.
- The IGCCCG risk classification is used to evaluate the prognosis of patients with metastatic GCT and dictates the selection of chemotherapy. For NSGCT, IGCCCG risk is assigned based on the postorchiectomy serum tumor marker levels, mediastinal primary tumor, and the presence of nonpulmonary visceral metastases. For seminoma, IGCCCG risk is assigned based on the presence of nonpulmonary visceral metastases only.
- Sperm cryopreservation should be offered to all patients before RPLND, chemotherapy, or radiation therapy owing to the potential effects of these treatments on fertility.

influence the selection and duration of chemotherapy regimens (International Germ Cell Consensus Classification, 1997).

Testicular cancer is a relatively rare disease, and general urologists and general oncologists do not typically treat a large volume of GCT patients. In addition, the treatment algorithms are relatively complex and nuanced and the data supporting certain treatments, such as RPLND, are based on data from a relatively small number of surgeons who have performed a large number of these operations (Donohue et al, 1993, 1995; Heidenreich et al, 2003; Stephenson et al, 2005b; SB Williams et al, 2009). The majority of urology residents in the United States complete their training having performed two or fewer RPLND procedures (Lowrance et al, 2007). Several studies have reported improved survival when the treatment was provided at high-volume institutions (Aass, et al, 1991; Harding et al, 1993; Feuer et al, 1994; Collette et al, 1999; Joudi and Konety, 2005; Suzumura et al, 2008). Therefore, whenever possible, GCT patients should be treated at a high-volume centers and RPLND should be performed by surgeons who are experienced with this operation.

Contrasting Seminoma and NSGCT

For treatment purposes the distinction between seminoma and NSGCT holds great importance. Compared with NSGCT, seminoma has a relatively favorable natural history. In general, seminoma tends to be less aggressive, to be diagnosed at an earlier stage, and to spread predictably along lymphatic channels to the retroperitoneum before spreading hematogenously to the lungs or other organs. **At diagnosis the proportion of patients with CS I, II, and III disease is 85%, 10%, and 5%, respectively, for seminoma and approximately 33%, 33%, and 33% for NSGCT** (Powles et al, 2005). **Seminoma is also associated with a lower incidence of occult metastasis among patients with CS I (10% to 15% vs. 25% to 35% for NSGCT) and a lower risk of systemic relapse after treatment of the retroperitoneum (1% to 4% after radiotherapy for seminoma versus 10% after RPLND for NSGCT),** which has important implications for the use of chemotherapy. Seminoma is less likely to have elevated serum tumor markers, and they do not range as high as in NSGCT. Serum tumor markers are also not used in the IGCCCG risk classification of seminoma.

Compared with NSGCT, **seminoma is exquisitely sensitive to radiation therapy and platin-based chemotherapy.** Regarding the former aspect, substantially lower radiation doses are required to eradicate seminoma compared with other solid tumors. As such, **radiation therapy is a standard treatment option for CS I and IIA-B seminoma but has no role in NSGCT,** with the exception of treatment for brain metastases. Seminoma only accounts for 10% of advanced GCT cases despite the fact it accounts for 52% to 56% of all GCTs. A poor prognosis IGCCCG risk category does not exist for advanced seminoma, and over 90% of metastatic cases are classified as good risk (compared with 56% for NSGCT) (International Germ Cell Consensus Classification, 1997). **The risk of teratoma at metastatic sites is generally not a consideration for advanced seminoma, which has important implications for the management of residual masses after chemotherapy. However, the potential for seminoma to transform into NSGCT elements is an important consideration in the management of patients who fail to respond to chemotherapy or who experience relapse after radiation therapy. Of patients with metastatic seminoma who experience relapse after treatment, 10% to 15% have NSGCT elements at the site(s) of relapse. An autopsy study has shown that 30% of patients who die of seminoma have NSGCT elements at metastatic sites** (Bredael et al, 1982).

The risk of teratoma at metastatic sites has a substantial effect on treatment algorithms for NSGCT and necessitates the frequent use of PCS in patients with advanced disease. The risk of teratoma in the retroperitoneum in low-stage NSGCT has also influenced many clinicians to favor RPLND over chemotherapy in situations in which the risk of occult systemic disease is low. As discussed, teratoma is not sensitive to chemotherapy and the outcome of patients with metastatic teratoma is related to the completeness of surgical resection. Although histologically benign, teratoma has an unpredictable biology with a capacity to grow rapidly, undergo malignant transformation, or result in late relapse.

Because GCTs are almost always cured, numerous clinical trials have been conducted in an attempt to minimize treatment and avoid any unnecessary therapies in an effort to reduce short-term and particularly long-term side effects and toxicity. One such approach has been to limit the number of patients who receive two interventions ("double therapy"): either surgery or chemotherapy and not both. **However, because NSGCTs are usually mixed tumors and teratoma often exists at metastatic sites with other GCT elements, "cure" often requires chemotherapy to kill the chemosensitive components and surgery to remove teratomatous components.** It is widely accepted that the successful integration of systemic therapy and PCS is a major contributing factor to the improved cure rates for metastatic GCT seen over the past several decades. Although minimizing unnecessary treatment is an important goal, chemotherapy, radiation therapy, and CT imaging are associated with an increased lifetime risk of secondary malignant neoplasms and/or cardiovascular disease (Meinardi et al, 2000; Zagars et al, 2004; Brenner et al, 2007; van den Belt-Dusebout et al, 2007; Tarin et al, 2009). In contrast, RPLND is associated with a substantially more favorable long-term toxicity profile when performed by experienced surgeons.

Key Points: Contrasting Seminoma and NSGCT

- Compared with NSGCT, seminoma is associated with an indolent natural history with a lower incidence of metastatic disease and lower rates of occult retroperitoneal and distant metastases in patients with CS I and IIA-B disease, respectively.
- No poor-risk prognostic category exists for metastatic seminoma, and substantially more patients are classified as good risk by IGCCCG criteria compared with NSGCT.
- Seminoma is associated with increased sensitivity to radiation therapy and platin-based chemotherapy compared with NSGCT.
- Serum hCG is elevated in only 15% of patients with metastatic seminoma, and serum tumor marker levels are not used to guide treatment decisions.
- Teratoma at metastatic sites is less of a concern for seminoma compared with NSGCT but should be considered in patients whose disease fails to respond to conventional therapy.

Intratubular Germ Cell Neoplasia

ITGCN is diagnosed by testicular biopsy performed for the investigation of infertility, by biopsy of the contralateral testis in a patient with GCT, or by biopsy within the affected testis in a

patient undergoing testis-sparing surgery. The rationale for treatment of ITGCN is based on the high risk of developing invasive GCT (Skakkebaek et al, 1982; Dieckmann and Skakkebaek, 1999). Treatment options include orchiectomy, low-dose radiotherapy, and close observation. The choice of therapy should be individualized based on the patient's desire for future paternity, the presence or absence of a normal contralateral testis, and the patient's desire to avoid testosterone replacement therapy. **Radical orchiectomy is the most definitive, although low-dose radiotherapy (20 Gy) is associated with similar rates of local control with the prospect of preserving testicular endocrine function owing to the relative radioresistance of Leydig cells compared with germinal epithelium** (Heidenreich et al, 2001; Montironi, 2002; Dieckmann et al, 2003). **However, testosterone replacement therapy is ultimately required in 15% to 25% of patients and patients should be monitored after radiotherapy for adequate testicular androgen production** (Heidenreich et al, 2001). To preserve testicular endocrine function, dose reductions less than 20 Gy have been investigated but cases of recurrent ITGCN have been observed (Classen et al, 2003a; Dieckmann et al, 2003). For patients who do not desire future paternity, radiotherapy is the preferred option, although radical orchiectomy and testosterone replacement therapy is a reasonable alternative. For patients with a normal contralateral testis who desire future paternity, radical orchiectomy is preferred because scatter to the contralateral testis from radiotherapy may impair spermatogenesis. For patients with semen parameters that are abnormal but sufficient for assisted reproductive techniques, close surveillance with periodic ultrasound evaluation of the testis is a reasonable strategy with deferred therapy until successful pregnancy and/or GCT. Another option for these patients is exploration of the testis, sperm harvesting and cryopreservation for assisted reproductive techniques, and radical orchiectomy followed by testosterone replacement therapy.

Patients with ITGCN scheduled to receive cisplatin-based chemotherapy represent a unique circumstance because chemotherapy may reduce (but not eliminate) the risk of GCT. A recent study estimated the risk of testicular GCT after chemotherapy in a patient with ITGCN to be 21% and 45% at 5 and 10 years, respectively (Christensen et al, 1998). These patients may be treated by low-dose radiotherapy after completion of chemotherapy or they may undergo testicular biopsy 2 years or more after chemotherapy with therapy reserved for patients with evidence of ITGCN (Krege et al, 2008a).

Key Points: Intratubular Germ Cell Neoplasia

- ITGCN is a precursor lesion for GCT and is associated with a 50% risk of developing an invasive GCT within 5 years.
- Radical orchiectomy and low-dose (20 Gy) radiation therapy are effective treatment options for ITGCN.

NSGCT

Clinical Stage I NSGCT. Approximately one third of NSGCT patients have CS I with normal postorchiectomy levels of serum tumor markers. **The optimal management of these patients continues to generate controversy because the long-term survival associated with surveillance, RPLND, and primary chemotherapy approaches 100%.** Contributing to the controversy is the fact that occult metastases in the retroperitoneum or at distant sites are present in only 20% to 30% of patients overall. Thus, any intervention after orchiectomy, with the potential for short- and long-term morbidity, represents overtreatment for the 70% to 80% of patients with disease limited to the testis. Most centers employ a risk-adapted approach based on the probability of occult metastasis, although surveillance is the preferred approach at select centers, regardless of a man's risk.

Risk Assessment. Numerous studies have attempted to identify histopathologic factors within the primary tumor that predict for the presence of occult metastasis. **The most commonly identified risk factors for occult metastasis are LVI and a predominant component of EC.** The definition of EC predominance in the literature varies from 45% to 90%. **The reported rate of occult metastasis (based on observed relapses on surveillance or lymph node metastasis at RPLND) with LVI and EC predominance varies from 45% to 90% and 30% to 80%, respectively** (Heidenreich et al, 1998; Sogani et al, 1998; Hermans et al, 2000; Sweeney et al, 2000; Alexandre et al, 2001; Roeleveld et al, 2001; Vergouwe et al, 2003; Nicolai et al, 2004; Stephenson et al, 2005a; de Wit et al, 2008). **In the absence of these two risk factors the risk of occult metastasis is less than 20%.** Other identified risk factors include advanced pT stage, absence of mature teratoma, absence of yolk sac tumor, presence of EC (regardless of the percent composition), percentage of MIB-1 staining, tumor size, and patient age. In a pooled analysis of 23 studies assessing predictors of occult metastasis in CS I NSGCT, Vergouwe and coworkers (2003) identified LVI (odds ratio [OR] 5.2), MIB-1 staining greater than 70% (OR 4.7), and EC predominance (OR 2.8) as the strongest predictors, and these factors were present in 36%, 55%, and 51% of patients, respectively.

As discussed previously, the results of abdominopelvic CT should be considered when formulating treatment recommendations because a size cutoff of 1 cm is associated with a high false-negative rate. Retroperitoneal lymph nodes greater than 5 to 9 mm in the primary "landing zone" should be viewed with suspicion of regional lymph node metastasis.

Numerous risk groups and prognostic indices have been proposed based on the presence/absence of several of these risk factors, most commonly on the basis of LVI and EC predominance (Freedman et al, 1987; Read et al, 1992; Heidenreich et al, 1998; Sogani et al, 1998; Hermans et al, 2000; Alexandre et al, 2001; Albers et al, 2003; Nicolai et al, 2004; Stephenson et al, 2005a). **Patients classified as at low versus high risk based on LVI and EC predominance applies to the risk of occult metastatic disease in patients with CS I and should not be confused with the IGCCCG risk classification for metastatic NSGCT** (discussed previously). Only one of these prognostic models has been prospectively validated, and none has considered the results of staging CT (Freedman et al, 1987; Read et al, 1992). Three recent prospective studies suggest that LVI and EC predominance may be associated with a risk of metastasis between 35% and 45%, not 50% to 70% as has been reported in most older studies. A contemporary surveillance series from Princess Margaret Hospital reported a relapse rate of 39% among patients with LVI or pure EC (Duran et al, 2007). Likewise, a population-based surveillance study from Scandinavia reported a 42% relapse rate in patients with LVI (Tandstad et al, 2009). Lastly, only 18% of CS I NSGCT patients treated by RPLND in a randomized trial had retroperitoneal lymph node metastasis despite the fact that 42% had evidence of LVI in the primary tumor (Albers et al, 2008). This lower-than-expected rate of occult metastasis may be due to greater scrutiny of staging CT for abnormal lymph nodes and/or stage migration.

Table 31–5.

Surveillance Series for Clinical Stage I NSGCT

STUDY	NO. PATIENTS	RELAPSES (%)	MEDIAN FOLLOW-UP (mo)	MEDIAN TIME TO RELAPSE (mo)	% SYSTEMIC RELAPSE*	GCT DEATHS (%)
Read et al (1992)	373	100 (27)	60	3 (1.5-20)	39%	5 (1.3)
Daugaard et al (2003)	301	86 (29)	60	5 (1-171)	66%	0
Freedman et al (1987)	259	70 (32)	30	NR	61%	3 (1.2)
Colls et al (1999)	248	70 (28)	53	NR	73%	4 (1.6)
Francis et al (2000)	183	52 (28)	70	6 (1-12)	54%	2 (1)
Gels et al (1995)	154	42 (27)	72	4 (2-24)	71%	2 (1)
Sharir et al (1999)	170	48 (28)	76	7 (2-21)	79%	1 (0.5)
Sogani et al (1998)	105	27 (26)	136	5 (2-24)	37%	3 (3)
Duran et al (2007)†	305	77 (25)	NR	7	26%	2 (0.7)
Tandstad et al (2009)	350	44 (13)	56	8	27%	0
Kollmannsberger et al (2010b)	223	59 (26)	52	NR	NR	0

*Systemic relapse defined as relapse with elevated serum tumor markers and/or relapse in tissue other than retroperitoneal lymph nodes.
†Unpublished.
NR, not reported.

Surveillance. **The rationale for surveillance is based on the fact that 70% to 80% of patients with CS I NSGCT are cured by orchiectomy alone and the ability to salvage virtually all relapsing patients with chemotherapy based on the long-term cure rates achieved for chemotherapy for good-risk metastatic NSGCT** (International Germ Cell Consensus Classification, 1997). Surveillance offers the potential of reducing treatment-related toxicity by restricting treatment to those with a proven need for it. Surveillance series have reported overall and disease-specific survival rates indistinguishable from those seen with RPLND and primary chemotherapy. As a result, initial surveillance is regarded as a standard treatment option for CS I NSGCT. **The disadvantages of surveillance are that it is associated with the highest risk of relapse, the need for long-term (>5 years) surveillance, the potential for secondary malignant neoplasms due to intensive surveillance CT** (Brenner and Hall, 2007; Tarin et al, 2009), **and more intensive therapy required to treat patients at the time of relapse than if they had received treatment at diagnosis.**

Published surveillance series have reported results on more than 2500 men, with a mean relapse risk of 28% and a 1.2% cancer-specific mortality. The 10 largest series are summarized in Table 31–5 (Freedman et al, 1987; Read et al, 1992; Gels et al, 1995; Sogani et al, 1998; Colls et al, 1999; Sharir et al, 1999; Francis et al, 2000; Daugaard et al, 2003; Duran et al, 2007; Tandstad et al, 2009; Kollmannsberger et al, 2010b). **More than 90% of relapses occur within the first 2 years, but late relapses (>5 years) are found in up to 1% of patients (as many as 5% in some reports)** (Daugaard et al, 2003). In older surveillance series, relapse at systemic sites or with elevated serum tumor markers was common and only 30% to 40% of relapses were restricted to the retroperitoneum. In more contemporary series, 65% to 75% of relapses are contained in the retroperitoneum, with or without elevated serum tumor markers (Duran et al, 2007; Tandstad et al, 2009). **Induction chemotherapy is the most common treatment used for relapse because most patients will have bulky (>3 cm) retroperitoneal lymphadenopathy, elevated serum tumor marker levels, or distant metastasis. However, patients with normal serum tumor marker levels and relapses limited to nonbulky (<3 cm) retroperitoneal lymphadenopathy may be managed initially with RPLND** (Stephenson et al, 2007).

The surveillance schedule employed in published series is highly variable and no schedule has been demonstrated to be superior to another in terms of survival. Given that the vast majority of relapses will occur within the first 2 years, surveillance imaging and testing is intense in years 0 to 2, with less frequent testing in years 3 to 5. The risk of late relapse mandates surveillance beyond 5 years. The frequency of abdominopelvic CT varies across multiple series from 2 to 13 or more scans within the first 5 years of follow-up. A randomized trial of 2 versus 5 CT scans in years 1 and 2 reported no significant differences in survival, IGCCCG risk category at relapse, or clinical stage at relapse (Rustin et al, 2007). Noncompliance with the prescribed surveillance schedule has been reported in 35% to 80% of patients in published series (Howard et al, 1995; Hao et al, 1998). Although these patients are at risk for advanced NSGCT at relapse, excellent survival rates are achieved with surveillance despite issues with compliance.

Retroperitoneal Lymph Node Dissection. **The rationale for RPLND for CS I NSGCT is based on several factors:** (1) the retroperitoneum is the most common site of occult metastatic disease and the risk of associated systemic disease is low; (2) 15% to 25% incidence of retroperitoneal teratoma (which is resistant to chemotherapy) in those with occult metastasis; (3) low risk of abdominopelvic recurrence after full, bilateral template RPLND thereby obviating the need for routine surveillance CT; (4) high cure rates after RPLND alone for patients with low-volume (pN1) retroperitoneal malignancy and teratoma (pN1-3); (5) avoidance of chemotherapy in more than 75% or more of patients if adjuvant chemotherapy is restricted to those with extensive retroperitoneal malignancy (pN2-3); (6) high salvage rate of relapses with good-risk, induction chemotherapy; and (7) low short- and long-term morbidity when a nerve-sparing RPLND is performed by experienced surgeons. **In low-stage NSGCT the therapeutic focus is the retroperitoneum, for which RPLND provides most the effective control with the lowest rates of serious long-term morbidity. The disadvantages of RPLND are that all patients undergo major abdominal surgery, it requires the availability of experienced surgeons and thus may not be deliverable to all patients, and it is associated with the highest rate of double therapy.**

A summary of the seven largest RPLND series for CS I NSGCT is listed in Table 31–6 (Richie, 1990; Donohue et al, 1993; Hermans et al, 2000; Nicolai et al, 2004; Stephenson et al, 2005b; Albers et al, 2008; SB Williams et al, 2009). The rate of pathologic stage

Table 31–6.

Summary of Published Series of RPLND for Clinical Stage I NSGCT

	NO. PATIENTS	PS II (%)	% TERATOMA IN RETROPERITONEUM	% RELAPSE, PS I	% RELAPSE, PS II	% ADJUVANT CHEMOTHERAPY	GCT DEATHS (%)
Donohue et al (1993)	378	113 (30)	15%	12%	34%	13%	3 (0.8)
Hermans et al (2000)	292	67 (23)	NR	10%	22%	12%	1 (0.3)
Nicolai et al (2004)	322	61 (19)	NR	NR	27%	NR	4 (1.2)
Stephenson et al (2005)	297	83 (28)	15%	6%	19%	15%	0
Williams et al (2009)	76	37 (49)	NR	5%	11%	NR	0
Albers et al (2008)	173	31 (19)	NR	9%	NR	19%	0
Richie et al (1990)	99	35 (35)	NR	6%	15%	15%	0

PS, pathologic stage; NR, not reported.

II in these series ranges from 19% to 28%, and an estimated 66% to 81% of these patients were cured after RPLND alone (where adjuvant chemotherapy was not dictated by protocol) (Donohue et al, 1993; Hermans et al, 2000; Sweeney et al, 2000; Rabbani et al, 2001; Nicolai et al, 2004; Stephenson et al, 2005b). **The long-term cancer-specific survival with RPLND (± adjuvant chemotherapy) approaches 100%, and the risk of late relapse is negligible. Most RPLND series have reported retroperitoneal recurrences in less than 2% of patients, demonstrating its efficacy for control of the retroperitoneum** (Donohue et al, 1993; Hermans et al, 2000; Stephenson et al, 2005b).

A full, bilateral template dissection is associated with the lowest risk of abdominopelvic recurrence (<2%) and the highest rate of antegrade ejaculation (>90%) when nerve-sparing techniques are employed (Jewett, 1990; Donohue et al, 1998; Stephenson et al, 2005b; Eggener et al, 2007b; Subramanian et al, 2010). For this reason it is now considered by many to be the standard of care for primary RPLND (Stephenson and Foster, in press). A recent randomized trial of primary RPLND (+ adjuvant bleomycin-etoposide-cisplatin [BEP]×2 for pathologic stage II) versus BEP×1 chemotherapy for CS I NSGCT showed a significant improvement in 2-year progression-free survival with chemotherapy (99% vs. 92%), although no GCT deaths were observed in either arm (Albers et al, 2008). The local recurrence rate was 11% in patients with histologically negative retroperitoneal lymph nodes at RPLND, which was substantially higher than the local recurrence rate among patients treated at high-volume centers. It is noteworthy that the 191 patients undergoing RPLND in this trial were treated at 1 of 61 centers in Germany. Thus, the relative inexperience of surgeons and unilateral templates likely contributed to these poor results. **Thus, patients who opt for RPLND should have this procedure performed by an experienced surgeon with a full, bilateral template dissection. Otherwise, patients should go on surveillance or receive primary chemotherapy.**

RPLND is a curative procedure in 60% to 90% of patients with pN1 disease and up to 100% of patients with teratoma only (regardless of the extent of lymph node involvement) (Pizzocaro and Monfardini, 1984; Williams et al, 1987b; Richie and Kantoff, 1991; Rabbani et al, 2001; Sheinfeld et al, 2003; Stephenson et al, 2005b). The risk of relapse in patients with pN2-3 disease is greater than 50% (Vogelzang et al, 1983; Williams et al, 1987b; Socinski et al, 1988; Stephenson et al, 2005b). With two cycles of adjuvant chemotherapy (most commonly BEP×2 or EP×2), relapses are reduced to 1% or less (Behnia et al, 2000; Albers et al, 2003; Kondagunta et al, 2004). **A randomized trial of adjuvant chemotherapy versus observation after RPLND for pathologic stage II showed a significant reduction in the risk of relapse (6% vs. 49%) but no difference in overall survival** (Williams et al, 1987b). Adjuvant chemotherapy and observation are acceptable treatment options for patients with pathologic stage II disease, and patients should be informed of the risk of relapse after RPLND and the potential benefits and risks of these approaches.

Primary Chemotherapy. In distinction to adjuvant chemotherapy given for pathologic stage II disease after RPLND, primary chemotherapy refers to treatment administered to men with CS I NSGCT after orchiectomy. The goal of primary chemotherapy is to minimize the risk of relapse and to allow men to avoid RPLND and induction chemotherapy (for those who experience relapse on surveillance). The rationale for primary chemotherapy is based on the efficacy of two cycles of chemotherapy to eradicate micrometastatic disease when given as adjuvant therapy after RPLND and the 20% to 25% need for chemotherapy despite RPLND (either as adjuvant or for treatment of relapse) (Donohue et al, 1993; Hermans et al, 2000; Nicolai et al, 2004; Stephenson et al, 2005a). **Primary chemotherapy offers patients the greatest chance of being relapse free with any single treatment modality, and it can be delivered at community-based institutions** (Tandstad et al, 2009). **The disadvantages of primary chemotherapy are (1) it does not treat retroperitoneal teratoma and thus exposes patients to the potential for chemoresistant and/or late relapse (see later), (2) long-term surveillance CT of the retroperitoneum is required, and (3) all patients are exposed to chemotherapy and the potential risk of late toxicity (cardiovascular disease and secondary malignant neoplasms among others).** The risk of late toxicity from two cycles of chemotherapy is poorly defined, although there appears to be no safe lower limit.

Primary chemotherapy has been investigated in 11 published series, the majority of which have used BEP×2 (Table 31–7) (Abratt et al, 1994; Cullen et al, 1996; Pont et al, 1996; Ondrus et al, 1998; Bohlen et al, 1999; Amato et al, 2004; Chevreau et al, 2004; Oliver et al, 2004; Dearnaley et al, 2005; Albers et al, 2008; Tandstad et al, 2009). In men with LVI and/or EC predominance, it is possible to reduce the recurrence rate to 2% to 3% with BEP×2 chemotherapy. In 7 of the 11 series, no deaths from GCT have been observed over an average median follow-up of 5 years. In the other four studies totaling 406 patients, 13 relapses (3%) have been observed and 6 (46%) of these relapsing patients have died of GCT. **Thus, although primary chemotherapy is associated with the lowest risk of relapse, these relapses are less amenable to salvage therapy because they are chemoresistant. In contrast, patients who experience relapse after RPLND or on surveillance are chemotherapy naive**

Table 31–7.
Published Series of Primary Chemotherapy for Clinical Stage I NSGCT

	NO. PATIENTS	REGIMEN	MEDIAN FOLLOW-UP (mo)	RELAPSES	TIME TO RELAPSE (mo)	GCT DEATHS (%)
Abratt et al (1994)	20	BEP×2 (E: 360)	31	0		0
Cullen et al (1996)	114	BEP×2 (E: 360)	48	2	7, 18	2 (1.8)
Pont et al (1996)	29	BEP×2 (E: 500)	79	2	8, 27	1 (3.5)
Ondrus et al (1998)	18	BEP×2 (E: 360)	36	0		0
Amato et al (2004)	68	CEB×2 (E: 360)	38	1	21	0
Bohlen et al (1999)	58	BEP×2 (E: 360) PVB×2 (20 pts)	93	2	22, 90	0
Chevreau et al (2004)	40	BEP×2 (E: 360)	113	0		0
Oliver et al (2004)	148	BEP×1 (n = 28); BEP×2 (n = 46); BOP×2 (n = 74). (E: 360)	33	6	Not reported	2 (1.4)
Dearnaley et al (2005)	115	BOP×2	70	3	3, 6, 26	1 (0.9)
Albers et al (2008)	191	BEP×1 (E: 500)	56	2	15, 60	0
Tanstad et al (2009)	382	BEP×1 (n = 312) BEP×2 (n = 70) (E: 500)	56	7	Range: 8-36	0

E: 360, etoposide dose of 360 mg/m^2/cycle; E: 500, etoposide dose of 500 mg/m^2/cycle.

and are cured with chemotherapy in virtually all cases. Although relapses are uncommon with primary chemotherapy, virtually all occur in the retroperitoneum. This mandates the use of surveillance abdominopelvic CT in the follow-up of these patients. Many European institutions prefer BEP×2 to RPLND, because the RPLND is primarily used as a staging procedure and performed without curative intent (Krege et al, 2008a; Schmoll et al, 2009a).

A recent randomized trial and a population-based study have investigated the use of BEP×1 as primary chemotherapy for CS I NSGCT (Albers et al, 2008; Tandstad et al, 2009). Over a median follow-up of less than 5 years in both studies the risk of relapse after BEP×1 ranged from 1% to 3% and the cancer-specific survival approached 100% in both studies. BEP×1 needs to be compared with BEP×2 in a randomized trial to verify its safety and efficacy.

Treatment Selection for Clinical Stage I NSGCT. There are no randomized trials that compare the standard treatment approaches for CS I NSGCT. A recent phase III, randomized trial compared BEP×1 versus unilateral, modified-template RPLND (with BEP×2 for patients with pathologic stage II disease) (Albers et al, 2008). Although a statistically significantly reduced risk of relapse was reported with BEP×1, no cancer-specific deaths were reported in either arm. This trial has been criticized because it compared two nonstandard treatment approaches for CS I NSGCT (Sheinfeld and Motzer, 2008).

Given the excellent long-term survival with surveillance, RPLND, and primary chemotherapy, it is inappropriate to recommend any specific treatment option because there are relative advantages and disadvantages of each approach in terms of treatment-related toxicity, the need for subsequent treatment, and intensity of surveillance testing and imaging. Likewise, patient preferences may vary and should be considered. **Several clinical practice guidelines for CS I NSGCT have been published, and surveillance is generally recommended to low-risk patients and either surveillance, RPLND, or primary chemotherapy to those at high risk** (Albers et al, 2005; Motzer et al, 2006; Hotte et al, 2008; Krege et al, 2008a; Schmoll et al, 2009a; Stephenson et al, in press). Nguyen and associates (2010) have developed a decision-analysis model that considered cancer outcomes, treatment-related toxicity, and patient preferences for important post-treatment outcomes to define the optimal treatment for CS I NSGCT. Surveillance is associated with the highest quality-adjusted survival when the estimated risk of relapse is less than 33% to 37%, and active treatment (RPLND or primary chemotherapy) is favored when the risk of relapse is greater than 46% to 54%.

Clinical Stage IS NSGCT. CS IS is defined as the presence of elevated postorchiectomy serum tumor markers without clinical or radiographic evidence of metastatic disease. Studies of primary RPLND for CS IS NSGCT have reported that 37% to 100% of patients subsequently required chemotherapy for retroperitoneal metastasis, persistently elevated serum tumor markers, or relapse (Davis et al, 1994; Saxman et al, 1996). **There is consensus that these patients should be treated similar to those with CS IIC-III and receive induction chemotherapy.** The cancer-specific survival after chemotherapy for CS IS is greater than 90% (Culine et al, 1996; International Germ Cell Consensus Classification, 1997). Slightly elevated and stable serum tumor marker levels after orchiectomy in patients without clinical evidence of disease should be interpreted cautiously because they may represent false-positive results for disseminated NSGCT.

Clinical Stage IIA and IIB NSGCT. The optimal management of CS IIA-B NSGCT is controversial. **RPLND (± adjuvant chemotherapy) and induction chemotherapy (± postchemotherapy RPLND) are accepted treatment options, with survival rates exceeding 95%.** There are no randomized trials comparing these treatment approaches. In a prospective, multicenter, nonrandomized trial of RPLND and two cycles of adjuvant chemotherapy versus induction chemotherapy, no significant differences in recurrence (7% for RPLND vs. 11% for chemotherapy) or overall survival were observed (Weissbach et al, 2000). A single-institution, nonrandomized, retrospective comparison of RPLND (and two cycles of adjuvant chemotherapy for pathologic stage II) and induction chemotherapy reported a significant reduction in the risk of recurrence with induction chemotherapy (98% vs. 79%), but cancer-specific survival approached 100% with both modalities (100% vs. 98%), RPLND patients received fewer cycles of chemotherapy (mean 4.2 vs. 1.4), and 51% of RPLND patients avoided chemotherapy (Stephenson et al, 2007).

The arguments in favor of RPLND for CS IIA-B are (1) 13% to 35% of patients have pathologically negative lymph nodes and thus avoid chemotherapy (Pizzocaro, 1987; Donohue et al, 1995; Weissbach et al, 2000; Stephenson et al, 2007; (2) approximately 30% have retroperitoneal teratoma that is resistant to chemotherapy (Foster et al, 1996; Stephenson et al, 2007); (3) long-term cancer-specific survival is 98% to 100% with RPLND ± adjuvant chemotherapy (Pizzocaro, 1987; Donohue et al, 1995; Weissbach et al, 2000; Stephenson et al, 2007); (4) 10% to 52% avoid any chemotherapy (Pizzocaro, 1987; Donohue et al, 1995; Weissbach et al, 2000; Stephenson et al, 2007); and (5) ejaculatory function is preserved in 70% to 90% of patients (Richie and Kantoff, 1991; Donohue et al, 1995; Weissbach et al, 2000). **The disadvantages of RPLND are** (1) additional therapy is required in 48% or more of patients; (2) 13% to 15% have persistence of disease after RPLND and require a full induction chemotherapy regimen, and (3) high-quality RPLND may not be deliverable at all institutions (Weissbach et al, 2000; Stephenson et al, 2007).

The arguments in favor of induction chemotherapy are (1) 60% to 78% of patients achieve a complete response and avoid PCS; (2) treatment can be delivered at community-based institutions, and (3) cancer-specific survival is 96% to 100% (Peckham and Hendry, 1985; Logothetis et al, 1987; Socinski et al, 1988; Ondrus et al, 1992; Horwich et al, 1994; Lerner et al, 1995; Culine et al, 1997; Debono et al, 1997; Weissbach et al, 2000; Stephenson et al, 2007). **The disadvantages of chemotherapy are** (1) all patients are exposed to the risk of long-term toxicity of chemotherapy and (2) those who do not undergo post-chemotherapy RPNLD are at risk of relapse with chemorefractory GCT.

Given that 13% to 35% of patients with CS IIA NSGCT have pathologically negative lymph nodes (thus, a false-positive CT result), patients with indeterminate lesions on staging abdominopelvic CT who are at otherwise low risk for metastatic disease may be observed closely initially to clarify subsequent treatment decisions.

Treatment considerations for CS IIA-B NSGCT include the risk of occult systemic disease, risk of retroperitoneal teratoma, short- and long-term treatment-related morbidity, and need for double therapy. The last consideration is of least importance but has strongly influenced opinion regarding the optimal treatment of these patients. As discussed earlier, because metastatic NSGCT frequently exists as chemosensitive malignant GCT and chemoresistant teratoma, "cure" often requires the combination of chemotherapy and surgery.

Experience with primary RPLND in low-stage NSGCT for over the past 2 decades has identified parameters associated with systemic relapse. As with CS IS NSGCT, the presence of elevated postorchiectomy AFP and hCG are associated with an increased risk of systemic relapse after RPLND. Rabbani and associates (2001) reported relapses after RPLND in 4 of 5 patients (80%) with elevated postorchiectomy AFP or hCG compared with 7 of 45 (16%) patients with normal serum tumor markers. Stephenson and coworkers (2005b) identified the presence of elevated serum tumor markers (hazard ratio [HR] 5.6, $P < .001$) and retroperitoneal lymphadenopathy greater than 3 cm (hazard ratio [HR] 12.3, $P < .001$) as significant predictors of systemic relapse after RPLND in multivariable analysis adjusting for treatment year and the use of adjuvant chemotherapy. **Thus there is consensus that CS IIA-B NSGCT patients with elevated AFP or hCG or bulky lymph nodes (>3 cm) should receive induction chemotherapy.**

The presence of retroperitoneal teratoma is a limitation to any strategy for metastatic NSGCT that uses chemotherapy alone because it is resistant to chemotherapy. Overall, approximately 20% of CS IIA-B patients have retroperitoneal teratoma, and this increases to 30% to 35% in those with teratoma in the primary tumor (Donohue et al, 1995; Foster et al, 1996; Stephenson et al, 2005b). Residual microscopic teratoma may remain dormant and clinically silent throughout a patient's lifetime. It may also exhibit slow growth that can be detected on surveillance CT and is amenable to cure by surgical resection. However, growing teratoma syndrome, malignant transformation, and late relapse are the most serious (though rare) sequelae of unresected teratoma. **Thus RPLND is preferred as initial therapy in those patients at risk for retroperitoneal teratoma who are at otherwise low risk for systemic disease (normal serum tumor markers, lymphadenopathy <3 cm).**

Investigators at Memorial Sloan-Kettering reported the impact of these selection factors (primary chemotherapy for elevated serum tumor markers or bulky retroperitoneal lymphadenopathy and RPLND for all others) on the outcome of patients with CS IIA-B. Before these selection factors were applied, 62% of patients were treated by RPLND but 68% of patients received primary chemotherapy after these selection criteria were rigorously applied. The impact of these selection factors on outcome was a significantly improved 5-year progression-free survival (98% vs. 84%, $P = .004$) without a significant increase in the proportion of patients receiving any chemotherapy (79% vs. 70%, $P = .16$) (Stephenson et al, 2007).

Clinical Stage IIC and III NSGCT. Induction chemotherapy with cisplatin-based multiagent regimens is the initial approach used for the treatment of CS IIC and CS III NSGCT. As discussed previously, induction chemotherapy is also the preferred approach for CS IS and CS IIA-B with elevated postorchiectomy AFP and hCG. The specific regimen and number of cycles is based on the IGCCCG risk stratification (see Table 31–4) (International Germ Cell Consensus Classification, 1997).

The development of cisplatin-based chemotherapy represents the most important advancement in the treatment of GCT. Before the identification of cisplatin, complete responses to chemotherapy were achieved in 10% to 20% of patients and the cure rate was only 5% to 10% (Einhorn, 1990). Long-term cure is now anticipated in 80% to 90% of patients with metastatic GCT. Randomized trials have evaluated the efficacy and safety of various drug combinations to determine the optimal regimen based on the IGCCCG risk (International Germ Cell Consensus Classification, 1997).

The initial landmark study was conducted at Indiana University using cisplatin-vinblastine-bleomycin (PVB×4) in the 1970s and reported complete responses in 74% of patients and over 70% long-term survivors (Einhorn, 1990). When it was demonstrated that etoposide could cure some patients with relapse after PVB chemotherapy, PVB×4 was compared with bleomycin-etoposide-cisplatin (BEP×4) in a multicenter randomized trial. No significant difference in overall survival was seen between the two regimens (2-year survival 80%, $P = .11$), but BEP×4 was associated with less neuromuscular toxicity and was subsequently adopted as the standard regimen (Williams et al, 1987a).

Chemotherapy for Good-Risk NSGCT

After BEP×4 became the standard regimen for advanced GCT, subsequent trials focused on reducing toxicity for patients with good-risk features and improving outcomes for those with intermediate- and poor-risk disease. **For patients at good risk, two randomized trials have shown that BEP×3 is not inferior to BEP×4** (Einhorn et al, 1989; Saxman et al, 1998; de Wit et al,

2001). With 184 patients enrolled in the U.S. study, 92% of patients in each study arm were continuously disease free with a minimum follow-up of 1 year, and 4 deaths in each study arm at 10 years were reported (Einhorn et al, 1989). Similarly, an international European trial comparing BEP×3 versus BEP×4 in more than 800 IGCCG good-risk patients reported similar outcomes with respect to 2-year progression-free (90% vs. 89%) and overall survival (97% in each arm) (de Wit et al, 2001). With these studies, BEP×3 became the standard regimen for good-risk GCT.

To reduce toxicity, investigators have studied the effect of omitting bleomycin and substituting carboplatin for cisplatin. **All of the randomized trials in which a cisplatin regimen has been compared with a carboplatin regimen have reported superior outcomes with cisplatin** (Bajorin et al, 1993; Bokemeyer et al, 1996b, 2004; Horwich et al, 1997, 2000). **The issue of whether bleomycin can be safely omitted from cisplatin-based regimens in good-risk patients is much less clear and is one of the few remaining controversies in the management of advanced GCT.** The rationale for omitting bleomycin is based on the risk of pulmonary complications (including pulmonary fibrosis) and Raynaud phenomenon. All of these studies have shown a trend toward superiority for the bleomycin-containing regimen, although no significant survival advantage has been shown in any of the trials (Bosl et al, 1988; Levi et al, 1993). EP×3 is inferior to BEP×3 (Loehrer et al, 1995). A European randomized trial comparing BEP×4 to EP×4 (with reduced doses of etoposide) reported a significantly higher complete response rate (95% vs. 87%, $P = .008$) with BEP×3 but no difference in overall survival (de Wit et al, 1997). Most recently, a French randomized trial comparing BEP×3 with EP×4 (using conventional doses of etoposide) failed to show a statistically significant difference in the risk of relapse or survival between the two regimens (Culine et al, 2007). **Thus BEP×3 and EP×4 are both accepted regimens for advanced GCT patients with good-risk features by IGCCCG criteria, and the 5-year overall survival is 91% to 94%** (International Germ Cell Consensus Classification, 1997; van Dijk et al, 2006).

Chemotherapy for Intermediate- and Poor-Risk NSGCT. **BEP×4 has been the standard regimen for advanced GCT with intermediate- and poor-risk features since 1987, and the corresponding 5-year survival rate is 79% and 48%, respectively** (International Germ Cell Consensus Classification, 1997). Ifosfamide-based regimens using either etoposide-ifosfamide-cisplatin (VIP×4) and vinblastine-ifosfamide-cisplatin (VeIP×4) have been investigated in randomized trials compared with BEP×4 (de Wit et al, 1998; Nichols et al, 1998; Hinton et al, 2003). The multicenter U.S. trial reported results on nearly 300 men with advanced GCT, with 13%, 23%, and 64% classified as at good, intermediate, and poor risk by IGCCCG criteria, respectively (Nichols et al, 1998; Hinton et al, 2003). Comparing BEP×4 with VIP×4, the 2-year survival was 71% versus 74% and the 5-year survival was 57% versus 62%, neither of which was significantly different (Nichols et al, 1998). The European study closed prematurely because the results of the U.S. study became available. Nevertheless, with 84 patients enrolled and more than 7 years median follow-up there were 2 deaths in the BEP×4 arm and 1 in the VIP×4 arm, and overall survival at 5 years exceeded 80% (de Wit et al, 1998). Thus, in both BEP×4 versus VIP×4 trials there were more deaths with BEP×4 but the differences were not significantly different. **Because VIP×4 resulted in more high-grade hematologic and genitourinary toxicity, BEP×4 has remained the standard regimen for intermediate- and poor-risk GCT.** However, these studies showed that comparable cancer outcomes could be achieved when ifosfamide is substituted for bleomycin. **Thus, VIP×4 may be substituted for BEP×4 in patients with compromised pulmonary function and to patients in whom extensive chest surgery will likely be performed to remove residual disease after chemotherapy** (Kesler et al, 2008).

High-dose chemotherapy (HDCT) using carboplatin-etoposide–based regimens with autologous stem cell support (also termed *stem-cell rescue*) has been investigated as an alternative to BEP×4 in patients with poor prognosis GCT. The rationale for HDCT is the hypothesis that increasing dosage may overcome chemotherapy resistance. The most widely studied regimens have included carboplatin-etoposide alone or in combination with cyclophosphamide, ifosfamide, paclitaxel, or thiotepa (Beyer et al, 1996; Bokemeyer et al, 2002a; Einhorn et al, 2007; Kondagunta et al, 2007; Lorch et al, 2007; Kollmannsberger et al, 2009). Carboplatin is used in HDCT regimens because of dose-limiting nephrotoxicity and neuropathy with cisplatin. A randomized trial in 219 patients with intermediate- (21%) and poor-risk GCT (79%) randomized to BEP×4 versus BEP×2 followed by two cycles of high-dose carboplatin-etoposide-cyclophosphamide and autologous stem cell support showed no significant difference in the 1-year durable complete responses rate (48% vs. 52%, $P = .5$) or overall survival (Motzer et al, 2007). The 2-year and 5-year survival for patients in both arms was 83% and 71%, respectively. However, toxicity was more severe for patients receiving HDCT. A smaller randomized trial also failed to demonstrate an improved survival with HDCT compared with standard-dose regimens as first-line therapy for patients with poor-prognosis metastatic GCT (Droz et al, 2007). **As a result, BEP×4 remains the standard first-line regimen in patients with intermediate- and poor-risk disease.**

Although the standard chemotherapy for men with poor-risk disease has not changed in more than 20 years, the outcome of these men appears to have improved over time. In the original IGCCCG analysis, the 5-year overall survival for poor-risk patients was 48% whereas survival rates of 60% or better have been reported in subsequent multicenter randomized trials (Hinton et al, 2003; Droz et al, 2007; Culine et al, 2008). Moreover, a meta-analysis of 10 studies enrolling a total of 1775 disseminated NSGCT patients (including 456 poor-risk patients) reported that the pooled 5-year survival estimate for poor-risk patients was 71% (van Dijk et al, 2006). To what extent this improvement in reported outcomes reflects more effective treatment, prognostic-category migration due to improved staging tests, or patient selection bias is impossible to know.

Management of Postchemotherapy Residual Masses in NSGCT. To assess the response to first-line, cisplatin-based chemotherapy, patients are restaged with serum tumor markers and imaging studies of the chest-abdomen-pelvis (including other sites of disease if present before chemotherapy). **Patients are classified into the following categories based on their response to chemotherapy:** (1) complete response (CR), defined by normalization of serum tumor markers and resolution of radiographic disease (usually defined as residual masses ≤1 cm); (2) normalization of serum tumor markers with persistent radiographic tumor (partial remission–marker negative); (3) partial remission–marker positive; and (4) disease progression. **Five to 15 percent of patients fall into categories 3 and 4 and are typically managed with second-line (also termed *salvage*) chemotherapy** (Einhorn et al, 1989; Mead et al, 1992; Debono et al, 1997; de Wit et al, 1997). **There is clear consensus that patients with residual masses larger than 1 cm should undergo PCS** (Albers et al, 2005; Motzer et al, 2006; Krege et al,

2008b; Schmoll et al, 2009a). The management of patients with complete serologic and radiographic response is controversial, with some guidelines advocating close observation and others recommending PCS if prechemotherapy mass size is greater than 3 cm (Albers et al, 2005; Motzer et al, 2006; Krege et al, 2008b; Schmoll et al, 2009a).

The role of PCS for residual masses in metastatic NSGCT is well established and its rationale is based on several factors. **Multiple large series of patients undergoing PCS for residual masses after first-line chemotherapy have consistently reported evidence of persistent GCT elements in the resected specimens in 50% or more. On average, histology of resected specimens will demonstrate necrosis, teratoma, and viable malignancy (with or without teratoma) in 40%, 45%, and 15% of cases, respectively** (Table 31–8) (Toner et al, 1990; Gerl et al, 1995; Steyerberg et al, 1995, 1998; Debono et al, 1997; de Wit et al, 1997; Hartmann et al, 1997b; Sonneveld et al, 1998; Stenning et al, 1998; Hendry et al, 2002; Albers et al, 2004; Spiess et al, 2006b; Carver et al, 2007a). The 5-year overall survival of patients with complete resection of viable malignancy (with or without further chemotherapy postoperatively) ranges from 45% to 77% (Toner et al, 1990; Fox et al, 1993; Gerl et al, 1995; Hartmann et al, 1997b; Donohue et al, 1998; Stenning et al, 1998; Fizazi et al, 2001, 2008; Spiess et al, 2006a; Carver et al, 2007a). In contrast, if left unresected, residual viable malignancy is destined to relapse and only 25% to 35% of patients will achieve durable remissions to second-line chemotherapy.

As discussed earlier, teratoma is resistant to chemotherapy and is present at metastatic sites in 15% of more of patients with disseminated NSGCT. The presence of metastatic teratoma is a limitation to any strategy for NSGCT that utilizes chemotherapy alone and necessitates the integration of chemotherapy and PCS in the majority of patients with metastatic GCT. Unresected teratoma has the potential to exhibit rapid growth (growing teratoma syndrome), undergo malignant transformation, or cause late relapse, all of which may have lethal consequences. **The outcome of metastatic teratoma is related to the completeness of surgical resection, and long-term survival is reported in 75% to 90% of patients who undergo PCS for residual teratoma** (Toner et al, 1990; Hartmann et al, 1997b; Sonneveld et al, 1998; Stenning et al, 1998; Carver et al, 2007c). Lastly, infield retroperitoneal relapse occurs in fewer than 1% of patients after a full, bilateral template RPLND, largely eliminating the need for radiographic surveillance of the abdomen and pelvis (Carver et al, 2007b).

Six to 8 percent of PCS specimens will contain evidence of non-GCT malignancy, arising from malignant transformation of teratoma (Toner et al, 1990; Little et al, 1994; Carver et al, 2007c). The most common histology is rhabdomyosarcoma, and the presence of i(12p) or abnormalities of chromosome 12 in most specimens confirms its origin from GCT (Motzer et al, 1998). **As with teratoma, the outcome of patients with malignant transformation is related to the completeness of surgical resection because they are generally resistant to GCT-specific chemotherapy regimens.** With complete resection 50% to 66% of patients will survive, whereas the vast majority of patients with incomplete resection will experience rapid progression and death from GCT (Little et al, 1994; Comiter et al, 1998; Motzer et al, 1998; Lutke Holzik et al, 2003; Carver et al, 2007c). Chemotherapy specific to the transformed histology (e.g., sarcoma-specific regimen) has been investigated in two small series in select patients with measurable disease limited to one histology. Partial responses are observed in a total of 11 of 24 patients, 6 of whom are alive with PCS (Donadio et al, 2003; El Mesbahi et al, 2007).

Patients with necrosis only in the PCS specimens have a favorable prognosis, with relapse rates of 10% or less reported in most series (Toner et al, 1990; Hartmann et al, 1997b; Stenning et al, 1998; Carver et al, 2007a). However, PCS is a staging procedure only for these patients and they derive no therapeutic benefit. Investigators have sought to identify factors that reliably predict for a high probability of necrosis to obviate the need for PCS in all patients with residual masses. In an early study Donohue and colleagues (1987) reported that none of 15 patients without teratoma in the primary tumor and who achieved a 90% or greater reduction in the size of the residual mass with chemotherapy had any evidence of viable malignancy or teratoma at PCS. In contrast, 7 of 9 patients (78%) with teratoma in the primary tumor experiencing a similar reduction in the size of the metastasis with chemotherapy had evidence of viable malignancy and/or teratoma. **The absence of teratoma in the primary tumor, the percentage reduction in the retroperitoneal mass with chemotherapy, and the size of the residual mass have consistently been identified as predictors of necrosis in PCS specimens** (Toner et al, 1990; Stomper et al, 1991; Fossa

Table 31–8.

Histology of Postchemotherapy Residual Masses

	NO. PATIENTS	NECROSIS	VIABLE MALIGNANCY ± TERATOMA	TERATOMA ONLY
Steyerberg et al (1995)	556	45%	13%	42%
Carver et al (2007a)	504	49%	11%	39%
Hendry et al (2002)	330	25%	9%	66%
Debono et al (1997)	295	25%	7%	67%
Spiess et al (2006b)	236	41%	17%	42%
Albers et al (2004)	232	35%	31%	34%
Toner et al (1990)	185	47%	16%	37%
Steyerberg et al (1998)	172	45%	13%	42%
Stenning et al (1998)	153	29%	15%	55%
deWit et al (1997)	127	35%	9%	56%
Oechsle et al (2008)	121	45%	21%	34%
Sonneveld et al (1998)	113	46%	9%	45%
Gerl et al (1995)	111	47%	12%	41%
Hartmann et al (1997b)	109	52%	21%	27%

et al, 1992; Steyerberg et al, 1995, 1998; Albers et al, 2004). However, despite statistical modeling using these and other factors, a consistent false-negative rate for necrosis of 20% has been reported (Steyerberg et al, 1995, 1998; Vergouwe et al, 2001). **Thus, the presence of necrosis only in the retroperitoneum cannot be predicted with sufficient accuracy to safely obviate the need for PCS in patients with residual masses. An important concept is that the absence of teratoma in the primary tumor does not reliably exclude its presence in the retroperitoneum** (Toner et al, 1990; Beck et al, 2002). Investigators have also investigated the utility of FDG-PET in the prediction of the histology of residual masses after first-line chemotherapy. The utility of FDG-PET in the prediction of retroperitoneal histology for NSGCT is limited by the fact that teratoma is not FDG avid. In a prospective study of 121 patients with residual masses after induction chemotherapy, the predictive accuracy of FDG-PET (56%) for viable malignancy or teratoma was no better than that of CT (55%) or postchemotherapy serum tumor markers (56%) (Oechsle et al, 2008). **Thus FDG-PET has no role in the assessment of NSGCT patients with residual masses after chemotherapy.**

Twenty-six to 62 percent of patients will experience a serologic and radiographic complete response to first-line chemotherapy (Einhorn et al, 1989; Dearnaley et al, 1991; Mead et al, 1992; Debono et al, 1997; Stenning et al, 1998; Ehrlich et al, 2010; Kollmannsberger et al, 2010a). **The optimal management of these patients is controversial.** Advocates of PCS for these patients argue that residual mass size (or percentage reduction with chemotherapy) cannot be used to reliably exclude the presence of residual disease within the retroperitoneum. **Numerous studies have demonstrated that, on average, patients with residual masses 20 mm or smaller have a 30% and 6% incidence of teratoma and viable malignancy, respectively** (Table 31–9) (Fossa et al, 1989b, 1992; Toner et al, 1990; Stomper et al, 1991; Steyerberg et al, 1995; Beck et al, 2002; Oldenburg, et al, 2003; Stephenson et al, 2007). In an analysis of 295 patients with GCT managed at Indiana University where those with a complete serologic and radiographic response to chemotherapy (group A; 26%) and 90% or greater reduction in mass size without evidence of teratoma in the primary tumor (group B; 9%) were observed and those with residual masses (group C; 47%) underwent PCS, Debono and coworkers (1997) reported an improved survival for those patients in group C (94%) compared with those in group B (78%), despite the fact that the latter had a more favorable response to chemotherapy. This result highlights the therapeutic benefit of PCS for patients with residual masses. However, **Debono and colleagues** (1997) **reported a 92% survival for patients in group A, suggesting that patients who achieve a serologic and radiographic complete response can be observed. Patients in group A represented only 26% of the overall population, indicating that observation is a reasonable option for only a select group of patients.** Recently, two studies have confirmed the low risk of relapse (4% to 10%) and 97% to 100% cancer-specific survival in patients with residual masses less than 1 cm who were observed without PCS (Ehrlich et al, 2010; Kollmannsberger et al, 2010a). However, the majority of these patients were considered at good risk by IGCCCG criteria and did not have teratoma in the primary tumor, highlighting their select nature.

Approximately one third of patients will have residual masses at multiple anatomic sites (the retroperitoneum, chest, and left supraclavicular fossa are the most common), and these patients should undergo resection of all sites of measurable residual disease (Toner et al, 1990; Gerl et al, 1995; Hartmann et al, 1997a; McGuire et al, 2003). Although some centers have described performing simultaneous RPLND, thoracotomy, and/or neck dissection, the authors' practice is to perform infradiaphragmatic and supradiaphragmatic resections as separate procedures. **Discordant histology between anatomic sites is reported in 22% to 46% of cases, and different histologies in each lung have also been reported in patients undergoing bilateral thoracotomies for residual lung masses** (Toner et al, 1990). In general, the histology of PCS specimens from nonretroperitoneal sites is more likely to show necrosis (60%) and less likely to show viable malignancy (10%) and teratoma (30%) (Toner et al, 1990; Gerl et al, 1994; Hartmann et al, 1997a; Steyerberg et al, 1997). In addition to the size of residual masses and the number of anatomic sites, the presence of necrosis in postchemotherapy RPLND specimens is highly predictive of necrosis at other sites (Steyerberg et al, 1997). Of patients undergoing PCS for residual masses at different sites, only 19 of 159 (12%) who had necrosis in the RPLND specimen had either viable malignancy or teratoma at other sites (Tiffany et al, 1986; Gerl et al, 1994; Brenner et al, 1996; Steyerberg et al, 1997; Tognoni et al, 1998; McGuire et al, 2003). **Thus RPLND should be performed before PCS at other sites because the probability of residual disease in the retroperitoneum is highest and RPLND histology is a strong predictor of histology at other sites. Observation of small residual masses at other sites is a reasonable option if the histology of the RPLND specimen is necrosis.**

As mentioned, the 5-year survival for patients with viable malignancy in PCS specimens is 45% to 77%. The role of postoperative chemotherapy in this setting is controversial. Fox and colleagues (1993) reported that 14 of 27 patients (70%) undergoing PCS for viable malignancy were free of

Table 31–9.
Histology of Postchemotherapy Residual Masses Less Than 20 mm

	NO. PATIENTS	SIZE	NECROSIS	VIABLE MALIGNANCY ± TERATOMA	TERATOMA ONLY
Steyerberg et al (1995)	275	≤20 mm	65%	5%	30%
Steyerberg et al (1995)	162	≤10 mm	72%	4%	24%
Oldenburg et al (2003)	87	≤20 mm	67%	7%	26%
Fossa et al (1992)	78	<20 mm	68%	4%	29%
Fossa et al (1989a)	37	≤10 mm	67%	3%	30%
Stephenson et al (2007)	36	≤5 mm	69%	6%	25%
Toner et al (1990)	21	≤15 mm	81%	7%	12%
Stomper et al (1991)	14	≤20 mm	36%	14%	50%

recurrence with adjuvant chemotherapy versus none of 7 patients who were observed. In an international pooled analysis of 238 patients with viable malignancy in PCS specimens, Fizazi and associates (2001) identified prechemotherapy IGCCCG intermediate- and poor-risk disease, incomplete resection, and greater than 10% viable malignancy in PCS specimens as important prognostic factors. Patients with none, one, and two to three risk factors had a 5-year overall survival of 100%, 83%, and 51%, respectively. Overall, a significant improvement in 5-year relapse-free survival was observed with postoperative chemotherapy (73% vs. 64%, $P < .001$) but no difference in 5-year overall survival (74% vs. 70%, $P = .7$). In a subset analysis, patients with one risk factor had an improved 5-year survival with postoperative chemotherapy (88% vs. 56%, $P = .02$) but those with none (100% survival, with or without chemotherapy) and two to three risk factors (55% vs. 60%) did not. In a confirmatory study this prognostic index was validated for relapse-free and overall survival and no significant difference in these end points was observed among the patients who did and did not receive postoperative chemotherapy (Fizazi et al, 2008). **A complete resection of residual masses is the most critical determinant of outcome for patients with viable malignancy in PCS specimens after first-line chemotherapy. Immediate postoperative chemotherapy or surveillance may be reasonable options depending on the completeness of resection, IGCCCG risk group, and percent of viable cancer.** There is no consensus on the appropriate chemotherapy regimen and the number of cycles that should be used in this setting. The most common practice reported is two cycles of therapy using a second-line regimen. However, many centers favor using the same induction regimen (often omitting bleomycin) and up to four cycles of therapy are given.

The importance of PCS was highlighted in a randomized trial of BEP×3 versus EP×4 in 257 men with good-risk metastatic NSGCT (Culine et al, 2007). As part of this trial, PCS was not dictated by protocol and only 52% underwent PCS, which frequently involved resection of residual mass only. Overall, 14 of 20 (70%) patients with relapse of their disease and 7 of 14 (50%) of those who died of GCT either did not undergo PCS or experienced relapse in the retroperitoneum after an inadequate RPLND. **These results suggest a substantial proportion of deaths from GCT may be prevented by the appropriate integration of chemotherapy and surgery.**

Relapsing NSGCT. The treatment of relapsing NSGCTs depends on what treatment the patient has previously received and, in certain cases, the location of the relapse. Patients who have never received chemotherapy have a much more favorable prognosis than patients who have already been treated with chemotherapy for disseminated disease.

Chemotherapy-Naive NSGCT Relapse. Chemotherapy-naive relapses occur in men with CS I NSGCT managed with either surveillance or RPLND and in the men with CS IIA-B NSGCT treated with RPLND alone. Serum tumor markers are elevated 60% to 75% of the time in CS I NSGCT patients who experience relapse on surveillance (Read et al, 1992; Gels et al, 1995; Sharir et al, 1999; Alexandre et al, 2001). **In general these patients are treated with induction chemotherapy, with the specific regimen and duration of therapy determined by IGCCCG risk, and cure rates exceed 95%. Select CS I NSGCT patients on surveillance who experience relapse in the retroperitoneum with nonbulky (<3 cm) disease and normal serum tumor markers may be treated by induction chemotherapy or RPLND (particularly if teratoma was present in the primary tumor)** (Stephenson et al, 2007). The rationale for RPLND is to avoid or minimize the toxicity of chemotherapy, and long-term cure rates approach 100% with RPLND ± adjuvant chemotherapy (Stephenson et al, 2007). CS I, CS IIA, and CS IIB patients who experience relapse after RPLND will usually do so in the lungs or mediastinum. Virtually all of these patients are cured with first-line chemotherapy. The vast majority of relapses during surveillance or after RPLND occur within the first 2 years (Freedman et al, 1987; McLeod et al, 1991; Read et al, 1992; Albers et al, 1995; Gels et al, 1995; Sogani et al, 1998; Sharir et al, 1999; Colls et al, 1999; Francis et al, 2000; Daugaard et al, 2003; Stephenson et al, 2005b; Albers et al, 2008; SB Williams et al, 2009; Zuniga et al, 2009; Kollmannsberger et al, 2010a). For the rare patient experiencing relapse more than 2 years after orchiectomy or RPLND with normal tumor markers, biopsy or surgical resection should be strongly considered because of the likelihood of teratoma (Michael et al, 2000; Oldenburg et al, 2006). **Although the time to relapse is an important determinant of outcome in relapsing patients who have received prior chemotherapy, chemotherapy-naive patients who experience relapse more than 2 years after initial treatment have a similar prognosis to those who experience relapse earlier.**

Postchemotherapy NSGCT Relapse—Early. Men who experience relapse after previously receiving first-line chemotherapy are treated with second-line (also termed *salvage*) chemotherapy. **The majority of relapses will occur within 2 years of completing initial treatment, and these are classified as early relapse** (de Wit et al, 1997; Nichols et al, 1998; Michael et al, 2000; Culine et al, 2007; Motzer et al, 2007). **Relapses occurring more than 2 years after the completion of initial therapy are classified as late relapse and differ substantially in terms of prognosis and therapy** (discussed later). A subset of early relapsing patients who appear to have a particularly unfavorable prognosis are those who fail to achieve a complete response to first-line therapy or who experience relapse within 6 months of achieving a complete response; these patients are frequently termed *incomplete responders* (Fossa et al, 1999c). **In an international, pooled analysis of 1984 patients from 38 centers with relapse after first-line chemotherapy, incomplete response to induction chemotherapy (HR 1.4-1.9), primary mediastinal NSGCT (HR 3.0), nonpulmonary visceral metastasis (HR 1.3), and elevated AFP (HR 1.3-2.0) and hCG (HR 1.5) were associated with increased risk of progression with second-line chemotherapy. Overall, the 3-year progression-free and overall survival was 38% and 51%, respectively** (International Prognostic Factors Study Group et al, 2010). Second-line chemotherapy has not been investigated as extensively as first-line chemotherapy, but there is one randomized controlled trial and numerous single-arm studies that have defined current standards of care (McCaffrey et al, 1997; Loehrer et al, 1988, 1998; Mead et al, 2005; Einhorn et al, 2007; Kondagunta et al, 2005; Pico et al, 2005).

As discussed earlier, etoposide and ifosfamide were demonstrated to have substantial activity in patients with relapse after first-line chemotherapy and this led to the investigation of VIP×4 as a second-line regimen for relapse GCT after PVB×4 (Loehrer et al, 1986; Einhorn et al, 1990). VeIP×4 was also studied as a second-line regimen in men who had received prior etoposide from BEP regimens (Loehrer et al, 1988). Studies of VIP×4 and VeIP×4 reported long-term remission rates of 23% to 35% and overall survival rates of 32% to 53% (McCaffrey et al, 1997; Loehrer et al, 1998; Pico et al, 2005). Studies of paclitaxel in the early 1990s showed activity in relapsed GCT. This led to the

development of the paclitaxel, ifosfamide, and cisplatin (TIP) regimen, and relapse-free survival has been reported in 36% to 47% of patients (Kondagunta et al, 2005; Mardiak et al, 2005; Mead et al, 2005). **TIP×4, VIP×4, and VeIP×4 have never been compared in a randomized trial, and all are considered standard second-line regimens.**

HDCT has also been investigated as a second-line (and third-line) regimen in patients with GCT relapse, although its role as second-line therapy is controversial. Indiana University has amassed the largest, single-institution series involving 184 consecutive patients with metastatic GCT that progressed after first- (73%) or second-line chemotherapy (27%), 94% of whom received two or more courses of HDCT (Einhorn et al, 2007). Over a median follow-up of 4 years, 63% of patients were continuously disease free, including 70% and 45% of patients who received HDCT as second- and third-line therapy, respectively. Unfavorable prognostic variables on multivariate analysis included receiving HDCT as third-line therapy, cisplatin-refractory disease, and poor-risk disease at diagnosis by IGCCCG criteria. In an international matched-pair analysis comparing 74 patients treated at a single institution who received two to three cycles of VIP followed by one cycle of HDCT using carboplatin-etoposide-ifosfamide with 119 patients treated at multiple centers throughout Europe who received standard-dose, second-line chemotherapy using a variety of regimens, a 10% improvement was reported in event-free and overall survival with HDCT (Beyer et al, 2002). HDCT was compared to standard-dose, second-line chemotherapy in a randomized controlled trial enrolling 280 patients from 43 institutions. Patients in the standard-dose arm received VIP×4 or VeIP×4, depending on whether they received prior etoposide during first-line therapy. Patients in the HDCT study arm received VIP/VeIP×3 followed by one cycle of high-dose carboplatin-etoposide-cyclophosphamide (Pico et al, 2005). Over a median follow-up of 45 months there were no significant differences in complete and partial response rates (56% in both study arms) or the 3-year event-free (35% vs. 42%, $P = .16$) and overall survival (53% in both study arms).

There are several potential explanations for the lack of benefit of HDCT in the randomized trial despite the favorable results reported in the two nonrandomized studies. First, the results from single-arm trials may be subject to selection bias from differences in case mix. In addition, the results achieved at high-volume institutions with unique experience with HDCT may not be reproducible at other institutions. Alternatively, the treatment strategy employed in the randomized trial may have been suboptimal in that three cycles of standard-dose chemotherapy and only one cycle of HDCT were given. The treatment philosophy at Indiana University is to take patients to HDCT as quickly as possible, limit the number of cycles of standard-dose chemotherapy so patients are able to better tolerate HDCT, and to give 2 cycles of HDCT. In the randomized trial, only 73% of patients assigned HDCT were able to receive it and toxic deaths of patients in the HDCT study arm were twice as common as those in the standard-dose study arm (7% vs. 3%). In the Indiana University series 94% of patients were able to receive two cycles of HDCT and the treatment-related death rate was 2.7%. **Although HDCT as second-line therapy can cure a significant number of patients, the failure to demonstrate an improvement in survival compared with standard-dose regimens in three randomized trials (two as first-line therapy and one as second-line therapy) suggests it should not be considered a standard approach.** Currently, HDCT should only be offered at specialized centers with extensive experience.

Treatment options for high-risk patients with relapse (e.g., incomplete responders) include standard-dose, second-line chemotherapy or HDCT (if administered at a specialized, high-volume institution). Standard-dose, second-line chemotherapy is the preferred approach for patients who relapse more than 6 months after first-line chemotherapy. **Special mention is made of patients with declining or normalized serum tumor markers during first-line chemotherapy with enlarging (usually cystic) masses. These patients are considered to have growing teratoma syndrome. In these rare cases, chemotherapy is temporarily interrupted and patients are taken for surgical resection. With complete surgical resection the long-term prognosis for these patients is favorable** (Logothetis et al, 1982; Andre et al, 2000; Spiess et al, 2007).

Management of Post–Salvage Chemotherapy Residual Masses. **Patients with serologic complete response to second-line chemotherapy with residual masses should undergo post–salvage chemotherapy surgical resection (PSCS).** Patients undergoing PSCS differ from those undergoing PCS of residual masses after first-line chemotherapy in several ways. A complete resection of residual masses is feasible in only 56% to 72% of patients (compared with 85% or more after first-line therapy) (Fox et al, 1993; Debono et al, 1997; Hartmann et al, 1997b; Stenning et al, 1998; Eggener et al, 2007a). The histology of PSCS specimens is characterized by higher rates of viable malignancy (53%) and lower rates of necrosis (26%) and teratoma (21%) compared with those after first-line chemotherapy. The long-term survival of patients is also substantially poorer with 5-year survival rates of 44% to 61% in most series (Fox et al, 1993; Hartmann et al, 1997b; Donohue et al, 1998; Stenning et al, 1998). **Patients with viable malignancy in PCSC specimens have a particularly poor prognosis, and their survival is not improved with the use of postoperative chemotherapy.**

Desperation Surgery. The vast majority of patients with progressive disease despite first- and second-line chemotherapy have a dismal prognosis. **However, a highly select group of patients with rising serum tumor markers who are deemed to have resectable disease limited to a single site (usually the retroperitoneum) may be candidates for salvage surgery, commonly referred to as "desperation surgery."** Although published studies are limited to small, single-institution case series, 47% to 60% will have normalization of serum tumor marker levels postoperatively and long-term survival is reported in 33% to 57% of patients after desperation surgery ± postoperative chemotherapy (Wood et al, 1992; Murphy et al, 1993; Eastham et al, 1994; Albers et al, 2000; Beck et al, 2005).

Postchemotherapy NSGCT Relapse—Late. **Late relapse after chemotherapy is defined as that occurring more than 2 years after treatment.** Roughly 3% of NSGCT patients experience a late relapse (Ronnen et al, 2005; Oldenburg et al, 2006). Because late relapse is rare, a biopsy should be performed to confirm the diagnosis, particularly when serum AFP and hCG values are normal. **Late relapses can be divided into three histopathologic categories: viable malignancy (54% to 88%; yolk sac tumor most common), teratoma (12% to 28%), and malignant transformation (10% to 20%; adenocarcinoma most common)** (Baniel et al, 1995; Gerl et al, 1997; Michael et al, 2000; George et al, 2003; Sharp et al, 2008).

Risk factors for late relapse have not been definitively identified but a history of prior relapse and presence teratoma in PCS specimens (potentially for incomplete resection) are associated with an increased risk (Gerl et al,

1997; Sharp et al, 2008). Most men with a late relapse have only one site of disease. The majority of late relapses occur in the retroperitoneum (50% to 72%), 17% occur in the lungs, 9% in the mediastinum, 7% in the neck, and 4% in the pelvis (Baniel et al, 1995; Gerl et al, 1997; George et al, 2003; Dieckmann et al, 2005; Oldenberg et al, 2006; Sharp et al, 2008). **Thus failure to control the retroperitoneum in the initial treatment phase is a major risk factor for late relapse.** Serum AFP and hCG values are elevated in about 50% and 25% of late relapses (Oldenberg et al, 2006). Patients with elevated serum tumor marker levels as the only manifestation of late relapse should be monitored closely until there is measurable disease (George et al, 2003).

Until recently, late relapse has been associated with a worse prognosis than early relapses, although contemporary data suggest these patients may have a similar probability of cure. **In general, late relapse is resistant to chemotherapy and the outcome is related to the ability to render patients disease free by complete surgical resection** (Gerl et al, 1997; Shahidi et al, 2002; George et al, 2003; Dieckmann et al, 2005; Oldenberg et al, 2006; Sharp et al, 2008).

The importance of surgery is related to the fact that teratoma and malignant transformation are inherently chemoinsensitive and viable malignancy is usually present in the setting of prior chemotherapy (thereby, platin resistant). Of 32 patients with late relapse at Indiana University who received chemotherapy, only 6 (19%) achieved a complete response and 5 of these are in complete remission (3 of whom were chemotherapy naive). PCS successfully rendered 18 (69%) of the remaining 26 patients free of disease, 12 (46%) of whom remained in complete remission. Thus, 72% of patients treated with chemotherapy (± surgery) were rendered disease free and 53% are in complete remission. Of the 49 patients treated initially with surgery, 45 (92%) were rendered free of disease overall (22 [45%] by surgery alone) and 29 (59%) are in complete remission. Overall, 69 (85%) patients achieved a disease-free state and 58% are disease free over a median follow-up of 25 months (George et al, 2003). In the Memorial Sloan-Kettering experience, the 5-year cancer-specific survival was 60% and

Key Points: NSGCT

- The optimal management of CS I NSGCT is controversial. Surveillance, primary RPLND, and primary chemotherapy with BEP×2 are accepted treatment options, with long-term survival rates approaching 100% for each.
- A risk-adapted approach for CS I NSGCT based on the presence of LVI and EC predominance is recommended. Surveillance is recommended to patients without these risk factors and active treatment (RPLND or BEP×2) is recommended to those with LVI and/or EC predominance. A non–risk-adapted approach is employed at some centers, whereby surveillance is the recommended approach for all patients with CS I NSGCT.
- Surveillance is not recommended to patients who are anticipated to be poorly compliant with follow-up imaging and clinical evaluation. The standard treatment approach to patients who relapse on surveillance is induction chemotherapy based on the IGCCCG risk. However, select patients with normal serum tumor marker levels and nonbulky (<3 cm) retroperitoneal adenopathy may also be managed by RPLND.
- BEP×2 is the standard regimen used for patients with CS I NSGCT who choose to receive chemotherapy. There is insufficient evidence at this time to support BEP×1 as an acceptable alternative.
- A full, bilateral template with nerve sparing is the recommended approach for primary RPLND. Attempts at preserving ejaculatory function should not compromise oncologic efficacy. RPLND should be performed only by surgeons experienced with the procedure.
- Adjuvant chemotherapy after primary RPLND for pathologic stage II disease is associated with a reduced risk of relapse but no difference in long-term survival compared with an observational strategy with induction chemotherapy at the time of relapse. Adjuvant chemotherapy is usually recommended to patients with extensive retroperitoneal metastasis (pN2-3) and those anticipated to be noncompliant with postoperative cancer surveillance imaging and testing.
- Induction chemotherapy and primary RPLND are accepted treatment options for patients with CS IIA-B NSGCT, with long-term cure in 95% of more. Induction chemotherapy is favored in patients with a high risk of occult metastasis disease on the basis of elevated postorchiectomy serum tumor markers and/or bulky (>3 cm) retroperitoneal lymphadenopathy.
- The management of patients with CS IS, IIC, and III NSGCT is induction cisplatin-based chemotherapy. The specific regimen and number of cycles is dictated by IGCCCG risk criteria. Patients with good-risk disease should receive BEP×3 or EP×4, and those with intermediate- and poor-risk disease should receive BEP×4. With risk-appropriate chemotherapy and PCS, the survival of patients with good-, intermediate- and poor-risk disease is 89% to 94%, 75% to 83%, and 41% to 71%, respectively.
- Postchemotherapy resection of all residual masses is based on the incidence of residual cancer (either viable malignancy or teratoma) in 50% or more of patients.
- The use of adjuvant chemotherapy is controversial in patients with viable malignancy in residual masses after first-line chemotherapy. The outcome of patients with viable malignancy and/or teratoma in residual masses after chemotherapy is primarily influenced by the completeness of surgical resection.
- Neither the absence of teratoma in the primary tumor, size of the residual mass, nor percentage reduction in the size of the mass after first-line chemotherapy can be used to reliably exclude the presence of viable malignancy or teratoma in residual masses after first-line chemotherapy.
- The standard approach to patients who experience relapse within 2 years after first-line chemotherapy is conventional-dose, second-line chemotherapy with ifosfamide-containing regimens. HDCT should not be given outside of specialized centers. All patients with residual masses should undergo postchemotherapy resection given the 70% to 80% incidence of residual disease (viable malignancy and teratoma).
- The standard approach to patients with relapse 2 years or more after initial therapy is surgical resection of all sites of disease if feasible.

patients who had a complete surgical resection at the time of late relapse (60%) had a significantly improved survival compared with those without complete resection (40%) (79% vs. 36%, $P < .001$) (Sharp et al, 2008). The presence of symptoms and of multifocal disease at late relapse was associated with inferior survival. In a German study of 72 NSGCT patients with late relapse (51 [71%] of whom had received prior chemotherapy), 35 (49%) were in complete remission at last follow-up, most of whom were treated with a combination of chemotherapy and surgery (Dieckmann et al, 2005). The most favorable chemotherapy results for late relapse are with the TIP regimen. A study from Memorial Sloan-Kettering reported that 7 of 14 patients achieved a durable complete response to TIP plus surgical resection (Kondagunta et al, 2005). In the absence of data from randomized trials it is impossible to define optimal management, but an aggressive surgical approach to resect all disease is appropriate either as the primary treatment or, in the setting of unresectable disease, after chemotherapy. Given the rarity and complexity of these cases, referral to a specialized center is encouraged.

Seminoma

Clinical Stage I Seminoma. Approximately 80% of patients with seminoma have CS I disease, and this is the most common presentation of testicular cancer. **The management of these patients has undergone substantial changes over the past 2 decades, and surveillance, primary radiotherapy, and primary chemotherapy with single-agent carboplatin are now accepted treatment options.** Recent efforts have focused on reducing the therapeutic burden. **Platin-based chemotherapy and infradiaphragmatic radiotherapy are associated with an increased risk of late cardiovascular toxicity and secondary malignant neoplasms** (Zagars et al, 2004; Travis et al, 2005; van den Belt-Dusebout, 2007). Minimizing target volume and dose have been investigated to reduce the toxicity of radiotherapy. Carboplatin is associated with less neurotoxicity, ototoxicity, and nephrotoxicity compared with cisplatin, but the risks of cardiovascular disease and secondary malignant neoplasms are largely unknown. In many instances, the short-term efficacy and safety of these approaches has been validated by randomized trials. **The long-term cancer control with each of these modalities approaches 100%.**

Primary Radiotherapy. Until recently the mainstay of treatment for CS I seminoma for the past 4 decades had been primary radiotherapy to the retroperitoneum and ipsilateral pelvis, termed *dog-leg configuration*. Published series of radiotherapy for CS I are listed in Table 31–10 (Fossa et al, 1989a, 1999b; Warde et al, 1995, 2005; Classen et al, 2004; Jones et al, 2005; Oliver et al, 2005). **The optimal radiation dose has not been defined, and most centers use 25 to 35 Gy in 15 to 20 daily fractions** (Fossa et al, 1989a, 1999b; Warde et al, 1995). Long-term cancer-specific survival approaches 100%, and progression-free probability between 95% and 97% is reported (Fossa et al, 1989a, 1999b; Warde et al, 1995, 2005). **In-field recurrence after dog-leg radiotherapy is less than 1%,** obviating the need for routine surveillance abdominal-pelvic CT imaging. Inguinal metastases are uncommon in those without prior inguinal or scrotal surgery. **The most common sites of recurrence are the thorax and left supraclavicular fossa. Virtually all recurrences are cured with first-line chemotherapy.** Select patients with isolated inguinal relapse may be salvaged with radiotherapy or surgical resection. **The surveillance of patients after dog-leg radiotherapy consists of regular clinical assessment, chest radiography, and serum tumor markers.**

Most patients experience some acute side effects with adjuvant radiotherapy, which typically include transient nausea, vomiting, and diarrhea that are usually mild and self-limited. Acute grade II-IV hematologic toxicity occurs in 5% to 15% (Fossa et al, 1999b). Moderate and severe late gastrointestinal toxicity (usually chronic dyspepsia or peptic ulcer disease) is reported in 5% and less than 2% of patients, respectively. The testicular germinal epithelium is exquisitely sensitive to ionizing radiation, and scatter dose to the contralateral testis may be significant despite protective shielding. After dog-leg radiotherapy, persistent oligospermia is reported in 8% (Fossa et al, 1999b). The issue of late cardiac toxicity and secondary malignant neoplasms is particularly germane for these patients given the long anticipated life expectancy. **The actuarial risk of developing secondary malignant neoplasms is estimated to be 18% at 25 years after radiotherapy for seminoma** (Travis et al, 2005). Secondary leukemia is linked with radiotherapy and chemotherapy, whereas an excess of the upper gastrointestinal tract, bladder, and possibly pancreas cancers is associated with radiotherapy.

To reduce the toxicity of radiotherapy, efforts to minimize the target volume and dose have been evaluated in randomized trials. The Medical Research Council (MRC; United Kingdom) conducted a randomized trial of dog-leg versus para-aortic radiotherapy for CS I seminoma (Fossa et al, 1999b). The rationale for omitting radiotherapy to the ipsilateral pelvis is based on the low rate (1% to 3%) of pelvic lymph node involvement in patients without prior inguinal or scrotal surgery. Restricting radiotherapy to the para-aortic strip may reduce the risk of secondary malignant neoplasms and improve the recovery of spermatogenesis. The 3-year

Table 31–10.

Summary of Radiation Therapy Series for Clinical Stage I Seminoma

	NO. PATIENTS	MEDIAN FOLLOW-UP (mo)	TARGET VOLUME	MEDIAN DOSE (Gy)	GCT DEATHS (%)	RELAPSE (%)	IN-FIELD RELAPSE (%)	PELVIC RELAPSE (%)
Fossa et al (1989)	365	109	Dog leg	40	4 (1)	13 (4)	1 (0.3)	0
Warde et al (1995)	194	97	Dog leg	25	0	11 (6)	0	0
Warde et al (2005)	282	106	Dog leg	25	0	14 (5)		
Fossa et al (1999b)	242	54	Dog leg	30	0	9 (4)	0	0
Fossa et al (1999b)	236	54	Para-aortic	30	1	9 (4)	2 (0.8)	4 (1.7)
Classen et al (2004)	721	61	Para-aortic	26	2 (0.3)	26 (4)	8 (1.1)	13 (1.8)
Jones et al (2005)	313	61	Para-aortic	30	1 (0.3)	10 (4)	3 (1)	6 (2)
Jones et al (2005)	312	61	Para-aortic	20	0	11 (4)	2 (0.6)	3 (1)
Oliver et al (2005)	904	48	Para-aortic	20-30	1 (0.1)	32 (4)	3 (0.3)	10 (1.6)

GCT, germ cell tumor.

relapse-free survival (96% vs. 97%) and overall survival (99% vs. 100%) in the para-aortic versus dog-leg study arms were similar, but patients receiving para-aortic radiotherapy had an improved short-term recovery of spermatogenesis (although no difference was seen at 3 years). However, those in the para-aortic study arm experienced a significant increase in the rate of pelvic recurrence (2% vs. 0%, $P = .04$). The small but significant risk of pelvic recurrence necessitates the use of routine surveillance pelvic CT with the associated increased cost and radiation exposure (Brenner and Hall, 2007).

The MRC and the European Organisation for the Research and Treatment of Cancer (EORTC) also conducted a randomized trial of 20-Gy versus 30-Gy PA radiotherapy for CS I seminoma (Jones et al, 2005). The 5-year relapse-free survival (96% vs. 97%) and overall survival (99.6% vs. 100%) were similar, but patients receiving 20 Gy experienced less acute gastrointestinal toxicity, leukopenia, and lethargy (although results were similar at 12 weeks). Further follow-up is necessary to assess the durability of these results.

Surveillance. Given the potential for late toxicity with dog-leg radiotherapy, the 80% to 85% cure rate after orchiectomy, and the more than 90% cure rates achieved with platin-based chemotherapy for advanced seminoma, surveillance has been evaluated at several centers. **Compared with NSGCT, surveillance for CS I seminoma is complicated by the limited utility of serum tumor markers to detect relapse and the need for long-term surveillance CT because 10% to 20% of relapses occur 4 years or more after diagnosis** (Chung et al, 2002).

The largest surveillance series for CS I seminoma are listed in Table 31–11 (Horwich et al, 1992; von der Maase et al, 1993; Warde et al, 1995, 2005; Aparicio et al, 2003, 2005; Choo et al, 2005; Daugaard et al, 2003). **The 5-year relapse-free survival ranges from 80% to 86%, and cancer-specific survival approaches 100%. Eighty-four to 100 percent of patients experience relapse in the retroperitoneum, and 18% to 24% of patients have bulky retroperitoneal disease and/or distant metastases at the time of recurrence** (Horwich et al, 1992; von der Maase et al, 1993; Warde et al, 1995; Aparicio et al, 2003). Dog-leg radiotherapy is employed for treatment of relapse in 73% to 88% of patients, and cure rates of 70% to 90% are reported. Virtually all patients who experience relapse of disease outside the retroperitoneum are cured with first-line chemotherapy.

To detect and treat recurrences at an early stage, patients on surveillance should be followed with clinical assessment, chest radiography, serum tumor marker evaluation, and abdominopelvic CT. Surveillance schedules employ assessments every 2 to 4 months in years 1 to 3, every 6 months in years 4 to 7, then annually thereafter. The necessary frequency of CT is poorly defined, and centers perform this every 4 to 6 months in years 1 to 3, every 6 months in years 4 to 7, then annually thereafter. A recent MRC trial suggested that the frequency of surveillance CT in low-risk CS I NSGCT in years 0 to 2 may be safely reduced from 5 to 2 without affecting survival or burden of therapy (Rustin et al, 2007). It is unclear whether these findings can be safely applied to surveillance for seminoma. Long-term follow-up is mandatory given the higher incidence of relapse after 5 years compared with NSGCT (Chung et al, 2002).

To better select patients for active treatment, investigators have endeavored to identify prognostic factors for occult metastasis. **In a pooled analysis of three large surveillance series from the 1980s, tumor size greater than 4 cm and invasion of the rete testis were significant predictors of relapse in multivariable analysis** (Warde et al, 2002). **Unlike NSGCT, LVI has not been identified as a significant predictor of relapse for CS I seminoma.** The 5-year relapse rate for patients with 0, 1, and 2 risk factors was 12%, 16%, and 32%, respectively. Twenty-one percent of patients in this cohort had both invasion of the rete testis and tumor size greater than 4 cm. Primary radiotherapy or carboplatin for all "high-risk" patients would still expose two thirds of CS I seminoma patients (who are cured by orchiectomy) to unnecessary therapy. However, prospective validation of these risk factors is currently lacking.

Primary Chemotherapy with Single-Agent Carboplatin. **Primary chemotherapy with one to two cycles of single-agent carboplatin** has also been investigated as an alternative to primary radiotherapy with the potential for reduced late toxicity. The rationale for single-agent carboplatin is based on the 65% to 90% reported complete response rates observed among patients with advanced seminoma (Horwich et al, 2000) and its reduced toxicity compared with cisplatin. Oliver and associates (1994) first described the use of one to two cycles of carboplatin in 78 patients and reported only two relapses and no deaths. The published studies of carboplatin in CS I seminoma are listed in Table 31–12 (Dieckmann et al, 2000; Reiter et al, 2001; Steiner et al, 2002; Aparicio et al, 2003, 2005; Oliver et al, 2005). No deaths from seminoma have been observed and 3- to 5-year relapse-free rates are 91% to 100%.

The MRC and EORTC conducted a randomized, phase III clinical trial of one cycle of carboplatin versus 20- to 30-Gy para-aortic radiotherapy in 1477 patients with CS I seminoma (Oliver et al,

Table 31–11.

Summary of Surveillance Series for Clinical Stage I Seminoma

	NO. PATIENTS	MEDIAN FOLLOW-UP (mo)	GCT DEATHS (%)	RELAPSE (%)	RPN RELAPSE (%)	CS IIC-III RELAPSE (%)	SYSTEMIC RELAPSE (%)
Daugaard et al (2003)	394		0	69 (17)			
Warde et al (2005)	348	106	1 (0.3)	55 (16)			
Warde et al (1995)	172	50	1 (0.6)	27 (16)	24 (89)	5 (19)	1 (4)
von der Maase et al (1993)	261	48	1 (0.4)	49 (19)	46 (94)	12 (24)	1 (2)
Aparicio et al (2003)	143*	52	0	23 (16)	19 (84)		3 (13)
Horwich et al (1992)	103	62	0	17 (17)	17 (100)	3 (18)	1 (6)
Choo et al (2005)	88	145	0	17 (19)	15 (88)	3 (18)	2 (12)
Aparicio et al (2005)	100†	34	0	6 (7)	6 (100)		0

*Patients with lymphovascular invasion or clinical stage ≥ T2 excluded.
†Patients with tumor size >4 cm or rete testis invasion excluded.
GCT, germ cell tumor; RPN, retroperitoneal; CS, clinical stage.

Table 31–12.

Summary of Adjuvant Chemotherapy Series for Clinical Stage I Seminoma

	NO. PATIENTS	MEDIAN FOLLOW-UP (mo)	NO. CYCLES	GCT DEATHS (%)	RELAPSE (%)
Oliver et al (2005)	573	48	1	0	27 (5)
Steiner et al (2002)	108	60	2	0	2 (2)
Reiter et al (2001)	107	74	2	0	0
Dieckmann et al (2000)	93	48	1	0	8 (9)
Dieckmann et al (2000)	32	48	2	0	0
Oliver et al (1994)	78	51	2*	0	2 (2)
Aparacio et al (2003)	60	52	2	0	2 (3.3)
Aparacio et al (2005)	214	34	2	0	7 (4)

*33% of patients received 1 cycle of carboplatin.
GCT, germ cell tumor.

2005). Over a median follow-up of 4 years, the 3-year relapse-free survival was similar (96% vs. 95%) and only one death was observed in the para-aortic radiotherapy study arm. An update of this trial was recently presented in abstract form after a median follow-up of 6.5 years, and the 5-year relapse-free survival (95%) was the same in both arms of the trial (Oliver et al, 2008). The trial was designed as a noninferiority trial to exclude a risk of relapse greater than 3% with carboplatin, but the trial was only able to exclude a risk of relapse with 95% confidence greater than 3.6%; thus, the primary end point was not reached. In this trial, patients receiving carboplatin experienced less lethargy and time away from work than those receiving radiotherapy and acute grade III-IV hematologic toxicity was observed in 4% of patients.

A concern with one cycle of carboplatin is the potential for inadequate dosing, leading to an increased risk of relapse. A slightly higher relapse rate with one versus two cycles was reported in a phase 2 study, and a higher risk of relapse was reported among patients receiving an inadequate dose of carboplatin in the MRC/EORTC trial (Dieckmann et al, 2000; Oliver et al, 2008). The optimal dosing of carboplatin is calculated by the formula 7 × (glomerular filtration rate [GFR, mL/min] + 25) mg (Calvert et al, 2002). Estimated GFR using the serum creatinine level may underestimate the true GFR, leading to inadequate dosing of carboplatin. The MRC/EORTC trial calculated GFR using clearance of chromium-51–labeled ethylenediaminetetraacetic acid (EDTA) radioisotope renal scan, which is not licensed for this purpose in the United States. Available alternatives to calculate GFR include iodine-125–labeled iothalamate sodium radioisotope renal scan and 24-hour urine collection for creatinine clearance. **Carboplatin dosing should not be based on estimated GFR. Thus, it is recommended to base one cycle of carboplatin dosing on the results of radioisotope renal scans or administer two cycles of therapy.**

The equivalence of carboplatin to dog-leg radiotherapy has yet to be definitively proven, and several concerns about carboplatin approach limit its acceptance. Carboplatin is inferior to cisplatin in advanced GCT, and there is little evidence to support the notion that micrometastases will be more sensitive to carboplatin. This notion is supported by the higher risk of relapse after carboplatin for CS I seminoma (3% to 5% in most studies) compared with the 1% or less risk of relapse after two cycles of adjuvant cisplatin-based chemotherapy for pathologic stage II NSGCT after RPLND (a cohort with a substantially higher risk of relapse). Follow-up of patients treated with this approach is inadequate at this time to assess its long-term efficacy. It is also unclear whether carboplatin is associated with a substantially reduced risk of late toxicity compared with radiotherapy. Lastly, the pattern of recurrence after carboplatin is the same as that for surveillance, with the retroperitoneum being the most common (and often solitary) site of relapse (Mead et al, 2008). Thus, patients need to be followed with routine abdominopelvic CT.

Given the low overall risk of relapse with CS I seminoma, the lack of prospectively validated markers to identify a high-risk population, and the potential for late toxicity with radiotherapy and carboplatin, many clinical practice guidelines now recommend surveillance as the preferred approach (Krege et al, 2008a; Schmoll et al, 2009b). Surveillance enables 80% to 85% of patients to avoid treatment-related toxicity, and relapses are effectively salvaged with dog-leg radiotherapy in most cases. However, surveillance must be continued for more than 5 years and frequent CT imaging is required. **For noncompliant patients or those unwilling to accept surveillance, primary radiotherapy is recommended given the long-term efficacy and simplified follow-up.** The early results of single-agent carboplatin are encouraging but insufficient at this time to demonstrate equivalence with radiotherapy.

Clinical Stage IIA and IIB Seminoma. **Fifteen to 20 percent of seminoma patients have CS II disease, 70% of whom have CS IIA-B. Dog-leg radiotherapy using 25 to 30 Gy (including a 5- to 10-Gy boost to involved areas) is employed at most centers.** The higher radiation doses administered to CS IIA-B patients is generally well tolerated, with acute grade III-IV gastrointestinal toxicity reported in 8% to 10% (Classen et al, 2003b). Prophylactic radiation to the left supraclavicular fossa is no longer practiced because fewer than 3% of patients are likely to benefit (Zagars and Pollack, 2001; Chung et al, 2003). Long-term disease-free survival rates of 92% to 100% for CS IIA and 87% to 90% for CS IIB have been reported, with in-field recurrences reported in 0% to 2% and 0% to 7% of cases, respectively (Zagars and Pollack, 2001; Classen et al, 2003b; Chung et al, 2004b). **Relapses are cured in virtually all cases with first-line chemotherapy, and disease-specific survival approaches 100%. Routine surveillance CT is not necessary after complete resolution of disease.**

The Royal Marsden Hospital reported relapses in 15% and 30% of CS IIA and IIB patients, respectively with dog-leg radiotherapy alone, 87% of which occurred at distant sites (Patterson et al, 2001). To reduce the risk of relapse, the combination of single-agent carboplatin followed by 30-Gy dog-leg radiotherapy was investigated in 33 patients, and only two relapses (6%) were observed over a median follow-up of 48 months (Patterson et al,

2001). These early results are promising, but further data are required to assess the utility of this approach.

Induction chemotherapy using first-line regimens (BEP×3 or EP×4) is an accepted alternative to dog-leg radiotherapy. The Spanish Germ Cell Cancer Study Group recently reported on the use of BEP×3 or EP×4 in 72 patients with CS IIA-B seminoma (Garcia del Muro et al, 2008). Overall, 83% of patients achieved a serologic and radiographic complete response and only 1 (1.3%) had residual mass greater than 3 cm, and the 2 patients who underwent PCS for residual masses had necrosis only in the resected specimens. Overall, the 5-year relapse-free and overall survival was 90% and 95%, respectively. The rationale for chemotherapy in CS IIA-B seminoma is based on the risk of late toxicity due to dog-leg radiotherapy and the lower risk of relapse in patients with bulky retroperitoneal disease. **Induction chemotherapy is preferentially given to patients with bulky (>3 cm) and/or multiple retroperitoneal masses because the risk of relapse is lower than with dog-leg radiotherapy** (Patterson et al, 2001; Chung et al, 2004b; Garcia del Muro et al, 2008).

Clinical Stage IIC and III Seminoma. **As with NSGCT, patients with CS IIC and III seminoma are treated with induction chemotherapy, with the regimen and number of cycles determined by the IGCCCG risk. Ninety percent of patients with advanced seminoma are classified as good risk and should receive either BEP×3 or EP×4 chemotherapy.** Complete radiographic responses are reported in 70% to 90% of patients, and the 5-year overall survival is 91% (Loehrer et al, 1987; Mencel et al, 1994; International Germ Cell Consensus Classification, 1997; Gholam et al, 2003). Only 10% of advanced seminomas have nonpulmonary visceral metastasis (classified as intermediate risk by IGCCCG criteria). With BEP×4 chemotherapy, the 5-year overall and progression-free survival is 79% and 75%, respectively (International Germ Cell Consensus Classification, 1997). Single-agent carboplatin in advanced seminoma is associated with inferior survival compared with standard first-line regimens (Bokemeyer et al, 2004).

Management of Postchemotherapy Residual Masses. **After first-line chemotherapy, 58% to 80% of patients have radiologically detectable residual masses** (Motzer et al, 1987; Puc et al, 1996; Duchesne et al, 1997; Fossa et al, 1997; Herr et al, 1997; Flechon et al, 2002; De Santis et al, 2004). **Spontaneous resolution of these masses is reported in 50% to 60% of cases, and the median time to resolution is 13 to 18 months** (Flechon et al, 2002; De Santis et al, 2004). **The histology of residual masses is necrosis and viable malignancy in 90% and 10% of cases, respectively** (Puc et al, 1996; Herr et al, 1997; Ravi et al, 1999; Flechon et al, 2002; De Santis et al, 2004). **PCS for seminoma is technically difficult (and frequently not feasible) owing to the desmoplastic reaction that occurs after chemotherapy with resultant increased perioperative morbidity** (Mosharafa et al, 2003). Surgical complete resections in postchemotherapy seminoma are reported in only 58% to 74% of patients (compared with 85% or more after first-line chemotherapy for NSGCT) (Puc et al, 1996; Herr et al, 1997; Ravi et al, 1999; Flechon et al, 2002; De Santis et al, 2004). **Teratoma and malignant transformation are much less of a concern with advanced seminoma.** As such, the management of postchemotherapy residual masses differs substantially for seminoma compared with NSGCT.

Given the fact that the vast majority of postchemotherapy residual masses contain necrosis, investigators have endeavored to identify factors associated with a high risk of viable malignancy to justify PCS. **Postchemotherapy radiotherapy has no role in the management of residual masses** (Duchesne et al, 1997). **The size of residual masses is an important predictor of viable malignancy; 27% to 38% of discrete residual masses larger than 3 cm contain viable malignancy compared with 0% to 4% for masses less than 3 cm** (Puc et al, 1996; Herr et al, 1997; Flechon et al, 2002; De Santis et al, 2004). **Recently, FDG-PET has been found to be a useful adjunct to CT to select patients for PCS** (De Santis et al, 2004). FDG-PET has no role in the evaluation of residual masses in NSGCT owing to the poor uptake of FDG by teratoma; this is less of a concern with advanced seminoma. The specificity and sensitivity of a positive FDG-PET evaluation for masses greater than 3 cm were 100% and 80%, respectively. **Thus patients with discrete residual masses greater than 3 cm should be evaluated further with FDG-PET and those who are PET positive should undergo PCS. PET-negative residual masses greater than 3 cm and masses less than 3 cm should be observed.** Inflammation and residual nonviable malignancy may cause a false-positive PET result if patients are scanned too soon after completing chemotherapy. Thus FDG-PET should be delayed until at least 4 weeks after completion of chemotherapy.

Although a survival advantage associated with PCS for seminoma has yet to be definitively proven there is a therapeutic benefit because it enables an immediate assessment of tumor response and further chemotherapy can be administered in a timely fashion. PCS is also therapeutic for the rare advanced seminoma patient with teratoma at the metastatic site(s), which is reported to be present in up to one third of seminoma patients with residual masses larger than 3 cm after chemotherapy (Puc et al, 1996). In the study by Herr and colleagues (1997), all 6 patients who had complete resection of viable malignancy were disease free over a median follow-up of 45 months, including 2 patients with teratoma who were rendered disease free by resection alone. In contrast, 4 of 6 patients with unresected viable malignancy died of seminoma despite additional chemotherapy and/or radiotherapy. Although this suggests patients who undergo PCS with complete resection of residual masses have an improved survival, considering all 32 patients who had complete resection of residual masses and 72 patients with incomplete or no resection, no difference in overall survival was observed (91% vs. 93%).

Relapse Seminoma

Chemotherapy-Naive Seminoma Relapse. Chemotherapy-naïve relapse occurs in men with CS I seminoma on surveillance and in those with CS I-IIB seminoma treated with primary radiotherapy. **For the former, dog-leg radiotherapy is employed for treatment of relapse in 73% to 88% of patients and cure rates of 70% to 90% are reported. Patients with bulky (>3 cm) retroperitoneal masses and systemic relapse should receive first-line chemotherapy, and salvage rates approach 100%. First-line chemotherapy cures virtually all patients who experience relapse of their disease outside the retroperitoneum after primary radiotherapy.** Patients who experience relapse after therapy with single-agent carboplatin are considered to have a chemotherapy-naive relapse and should receive first-line cisplatin-based chemotherapy.

Postchemotherapy Seminoma Relapse—Early. **An estimated 15% to 20% of patients with advanced seminoma will experience relapse after induction chemotherapy, including 10% who achieve an initial complete response** (Loehrer

et al, 1987; Mencel et al, 1994; International Germ Cell Consensus Classification, 1997). In general, patients with an incomplete response to first-line chemotherapy or relapse after an initial major clinical response have a poor prognosis with long-term survival rates of 20% to 50% (Miller et al, 1997; Vuky et al, 2002; Gholam et al, 2003). The small number of patients with seminoma who require second-line chemotherapy has limited the evaluation of unique treatment strategies, and patients experiencing relapse of their disease are treated with regimens that were largely developed for NSGCT relapse. In two small studies the efficacy of VeIP×4 as second-line chemotherapy was evaluated in 36 patients with relapsed seminoma. Overall, 30 patients (83%) achieved a complete response to chemotherapy (with or without PCS) and 21 (53%) were continuously free of recurrence over a median follow-up of 72 to 84 months (Miller et al, 1997; Vuky et al, 2002). Vuky and colleagues (2002) also evaluated HDCT in 12 patients with advanced seminoma who had an incomplete response to first-line chemotherapy, and 6 patients (50%) achieving a complete response have remained free of recurrence. **An important consideration for patients with advanced seminoma who experience relapse after first-line chemotherapy is the potential for teratoma at the site of relapse. Thus patients with normal values of serum tumor markers should undergo biopsy before starting second-line chemotherapy.**

Postchemotherapy Seminoma Relapse—Late. In most published series, pure seminoma accounts for fewer than 8% of late relapse events (Baniel et al, 1995; George et al, 2003; Ronnen et al, 2005; Sharp et al, 2008). However, Dieckmann and coworkers (2005) reported a series of 122 patients with late relapse, of whom 50 (41%) had pure seminoma at diagnosis. Only 6 (12%) of these patients had received prior first-line chemotherapy, and the majority had received single-agent carboplatin or radiation therapy at diagnosis. Long-term cancer control was achieved in 88% of patients. **Thus late relapse of seminoma may have a favorable prognosis, particularly among patients without prior exposure to cisplatin.**

Brain Metastases

About 1% of men with disseminated GCT will have brain metastases detected before initiating chemotherapy, and between 0.4% and 3% will develop brain metastases after first-line chemotherapy (Raina et al, 1993; International Germ Cell Consensus Classification, 1997; Fossa et al, 1999a). **Brain metastases are associated with choriocarcinoma and should be suspected in any patient with a very high serum hCG level** (Fossa et al, 1999a; Kollmannsberger et al, 2000; Gremmer et al, 2008). **Choriocarcinomas are highly vascular and tend to hemorrhage during chemotherapy, and death rates of 4% to 10% due to intracranial hemorrhage have been reported** (Kollmannsberger et al, 2000; Nonomura et al, 2009). Management of these patients must consider this risk, and neurologic changes need to be evaluated expeditiously.

The 5-year overall survival in patients with brain metastases is 33% and 57% for those with disseminated NSGCT and seminoma, respectively (International Germ Cell Consensus Classification, 1997). **Men who relapse in the brain after achieving a complete response to chemotherapy appear to have a worse prognosis than those with brain involvement at diagnosis,** with overall survival rates of 39% to 44% for isolated brain metastases and 2% to 26% for those with brain metastases in association with other sites of disease (Fossa et al, 1999a; Kollmannsberger et al, 2000; Hartmann et al, 2003; Salvati et al, 2006; Gremmer et al, 2008; Nonomura et al, 2009). Case studies and pooled analyses of GCT patients with brain metastases have reported outcomes with various treatment strategies, but there are no randomized trials to clearly define optimal management (Spears et al, 1992; Fossa et al, 1999a; Kollmannsberger et al, 2000; Hartmann et al, 2003; Salvati et al, 2006; Gremmer et al, 2008; Nonomura et al, 2009). Treatment strategies have included chemotherapy, surgical resection, whole-brain radiation therapy, and stereotactic radiosurgery, with most patients receiving multimodal therapy. **Patients with brain metastases at diagnosis should receive BEP×4 chemotherapy followed by resection of residual masses.** The benefit of radiation therapy in this setting is unclear (Fossa et al, 1999a; Kollmannsberger et al, 2000; Hartmann et al, 2003). At the authors' institution radiation therapy is

Key Points: Seminoma

- The optimal management of CS I seminoma is controversial. Surveillance, primary radiotherapy (20 to 30 Gy to the para-aortic region ± ipsilateral pelvis), and primary chemotherapy with carboplatin (one to two cycles) are accepted treatment options, with long-term survival rates approaching 100% for each.
- Prognostic factors for occult metastases in CS I seminoma are not as well developed as for NSGCT. Given the overall low-risk of occult metastases (15% to 20%), the inability to identify a high-risk population on the basis of histopathologic factors in the primary tumor and the potential for late toxicity with primary radiotherapy, surveillance has become the recommended treatment approach for CS I seminoma.
- Surveillance is not recommended to patients who are anticipated to be poorly compliant with follow-up imaging and clinical evaluation. The standard treatment approach to patients who relapse on surveillance is dog-leg radiotherapy (25 to 35 Gy), although patients with bulky retroperitoneal lymphadenopathy or distant metastases should receive IGCCCG risk-appropriate first-line chemotherapy.
- Primary radiotherapy and primary chemotherapy with single-agent carboplatin are associated with similar rates of cure and survival. Para-aortic radiotherapy and carboplatin both require periodic CT in the surveillance of recurrent disease after treatment; this is not required for dog-leg radiotherapy.
- Dog-leg radiotherapy (25 to 35 Gy) and first-line chemotherapy (BEP×3 or EP×4) are accepted treatment options for CS IIA-B seminoma patients with nonbulky (<3 cm) retroperitoneal lymph node metastasis. First-line chemotherapy (BEP×3 or EP×4) is recommended for bulky (>3 cm) and/or multifocal retroperitoneal metastases.
- The treatment of patients with CS IIC and III seminoma is first-line cisplatin-based chemotherapy, and the specific regimen and number of cycles is dictated by IGCCCG risk criteria. Patients with good-risk disease should receive BEP×3 or EP×4, and those with intermediate-risk disease should receive BEP×4.
- Patients with discrete, residual masses larger than 3 cm after first-line chemotherapy should undergo further evaluation with FDG-PET. Patients with PET-positive residual masses should undergo postchemotherapy surgical resection. Residual masses that are PET negative or less than 3 cm can be safely observed after chemotherapy.

only considered for patients with unresectable residual lesions not amenable to stereotactic radiosurgery owing to the concerns of radiation-induced neurotoxicity (Doyle et al, 2008). **Patients who experience relapse in the brain after first-line chemotherapy should be treated with second-line chemotherapy followed by resection and/or radiation therapy** (Fossa et al, 1999a; Hartmann et al, 2003). For men who experience relapse in the brain and at other anatomic sites the prognosis is particularly grim, particularly if it is not the first relapse.

Key Points: Brain Metastases

- Brain metastases are associated with choriocarcinoma and should be suspected in any patient with a very high serum hCG level.
- Choriocarcinomas are highly vascular and tend to hemorrhage during chemotherapy, causing intracranial hemorrhage.

Treatment-Related Sequelae

Testicular cancer treatment sequelae can be divided into late and early complications. Complications from orchiectomy and RPLND are discussed in Chapter 32 and will not be reviewed here except to note that the main issues after RPLND are midline scar, ejaculatory dysfunction, small bowel obstruction, and perioperative complications. It is also worth noting that there is an increased incidence of hypogonadism after orchiectomy for GCT.

Early Toxicity

Cisplatin-based chemotherapy is associated with numerous early complications and side effects, including fatigue, myelosuppression, infection, peripheral neuropathy, hearing loss, diminished renal function, and death. The toxic death rate has ranged from 0% to 2.4% during chemotherapy for good-risk disease and from 3.0% to 4.4% during standard first-line chemotherapy for intermediate- and poor-risk disease (Nichols et al, 1998; de Wit et al, 2001, 2008; Toner et al, 2001; Culine et al, 2007, 2008). The impact of chemotherapy and radiation therapy on spermatogenesis has been discussed previously. Most men are able to father children after treatment for GCT, but paternity rates are lower for men treated with radiation therapy and/or chemotherapy (Huyghe et al, 2004; Brydoy et al, 2005). Early complications of radiation therapy include fatigue, nausea and vomiting, leukopenia, and dyspepsia (Fossa et al, 1999b; Jones et al, 2005; Oliver et al, 2005).

Late Toxicity

Numerous long-term sequelae have been reported in GCT survivors, including peripheral neuropathy, Raynaud phenomenon, hearing loss, hypogonadism, infertility, secondary malignant neoplasms, and cardiovascular disease (Brydoy et al, 2005, 2009; Rossen et al, 2009). Symptoms of Raynaud phenomenon and peripheral neuropathy have been reported in 20% to 45% and 14% to 43%, respectively, and the risk appears to increase with increasing cumulative doses of cisplatin (Brydoy et al, 2009; Rossen et al, 2009). Significant hearing loss and/or tinnitus after cisplatin-based chemotherapy is reported in 20% to 40% of patients and can be documented via audiometry in 30% to 75%. Hypogonadism has been documented in 10% to 20% of patients treated with orchiectomy alone, 15% of patients treated with radiation therapy, and 20% to 25% of men treated with first-line chemotherapy regimens (Nord et al, 2003; Lackner et al, 2009).

Large population-based studies of GCT survivors have reported an increased risk of death from gastrointestinal and cardiovascular diseases after radiation therapy and an increased risk of death from infections and cardiovascular and pulmonary diseases after chemotherapy (Fossa et al, 2007). Patients treated with both radiation and chemotherapy have the highest risk of death from nonmalignant causes. The increased incidence and mortality of cardiovascular disease in GCT survivors is particularly well documented (van den Belt-Dusebout et al, 2007; Meinardi et al, 2000; Huddart et al, 2003; Fossa et al, 2007, 2009). The causes of these cardiovascular complications are not well understood, but putative contributing factors are radiation- or chemotherapy-induced vascular injury, as well as chemotherapy-induced cardiac injury and metabolic syndrome (Nuver et al, 2005; Altena et al, 2009).

The risk of second malignant neoplasms is a particular concern. The incidence of non–germ cell malignancies is 60% to 100% higher in GCT survivors treated with cisplatin-based chemotherapy or radiation therapy compared with the general population and 200% higher in patients who received both radiation and chemotherapy (Travis et al, 2005; Richiardi et al, 2007). The risk of death from non–germ cell malignancies in GCT survivors treated with radiation or chemotherapy is less well defined but appears to be doubled compared with the general population (Fossa et al, 2004). The frequent use of body CT in the surveillance of patients after therapy is another source of radiation that may increase the risk of secondary malignant neoplasms (Brenner and Hall, 2007; Chamie et al, 2008; Tarin et al, 2009).

Key Points: Treatment-Related Sequelae

- All treatments for GCT (surgery, radiotherapy, and chemotherapy) are associated with risks of early and late toxicity.
- The late complications of most concern are cardiovascular disease and secondary malignant neoplasms.
- With the successful cure of patients (even those with advanced disease), an important treatment objective is minimizing treatment-related toxicity without compromising curability.

NON–GERM CELL TUMORS

Sex Cord/Stromal Tumors

Sex cord/stromal tumors are rare, comprising approximately 4% of testicular neoplasms, and the term refers to neoplasms containing Leydig cells, Sertoli cells, granulosa cells, or thecal cells.

Leydig Cell Tumors

Leydig cell tumors are the most common of the sex cord/stromal tumors. There is no association with cryptorchidism. Most of these tumors occur in adult males between age 20 and 60 years, although approximately one fourth occur in children. In adults, the most common presentation is a painless testicular mass, frequently with feminizing characteristics (as a result of androgen excess and peripheral conversion to estrogen), including gynecomastia, impotence, and decreased libido. Children usually present with a

testicular mass and isosexual precocious puberty (prominent external genitalia, pubic hair growth, and masculine voice).

Radical inguinal orchiectomy is the initial treatment of choice. Ninety percent of these tumors are benign, and 10% are malignant. Benign lesions are usually small, yellow to brown, well circumscribed, and without areas of necrosis of hemorrhage. Histologically, the tumors consist of uniform polygonal cells with round nuclei. Reinke crystals are present in 25% to 40% of cases and appear as densely eosinophilic needle-like or rhomboid structures within the cytoplasm. These tumors must be distinguished from Leydig cell hyperplasia that occur in atrophic testes and adjacent to GCTs, in which Leydig cells infiltrate between seminiferous tubules without displacing or obliterating them. **Although large size, necrosis, nuclear pleomorphism, and increased mitotic activity may occur and suggest malignant Leydig cell tumor there are no consistently reliable histologic criteria for making this judgment.** The presence of metastatic disease is the only reliable criteria for making this distinction. Malignant behavior has not been reported in a prepubertal patient. Older patients are more likely to have malignant tumors. **The most frequent metastatic sites are the retroperitoneum and lung. If the pathologic features raise the suspicion for malignancy, abdominopelvic CT and chest radiography should be performed. RPLND is reasonable in select cases with adverse features.** Surveillance of men with Leydig cell tumors is not necessary in those without clinical or pathologic features suggestive of malignancy. **Metastatic Leydig cell tumors are resistant to chemotherapy and radiation therapy.** Mitotane (Lysodren), a potent inhibitor of steroidogenesis, may produce partial responses in metastatic patients with excess androgen production, but cure is not possible (Schwarzman et al, 1989).

Sertoli Cell Tumor

These tumors comprise less than 1% of testicular neoplasms. They can occur in any age group, including infants. There is no association with cryptorchidism. Gynecomastia is evident in one third of patients. Treatment is radical inguinal orchiectomy. The tumors are well circumscribed and yellow-white or tan, with uniform consistency. Microscopically the tumors contain epithelial elements resembling Sertoli cells with varying amounts of stroma organized into tubules. **Ninety percent of tumors are benign, and 10% are malignant. Because of its rarity there are no reliable histologic criteria associated with malignancy.** The presence of metastasis is the only reliable criterion. RPLND may be considered if the suspicion of malignancy is high or if retroperitoneal adenopathy exists. Radiation therapy and chemotherapy are ineffective. Surveillance of men with Sertoli cell tumors is not necessary in those without clinical or pathologic features suggestive of malignancy.

Granulosa Cell Tumors

Granulosa cell tumors of the testis are exceedingly rare and resemble adult-type granulosa cell tumors of the ovary. Gynecomastia and increased estrogen secretion are common. Radical inguinal orchiectomy is curative because these tumors appear to have limited metastatic potential.

Gonadoblastoma

Gonadoblastoma is a mixed germ cell/sex cord/stromal tumor composed of seminoma-like germ cells and sex cord cells showing Sertoli differentiation. They occur almost exclusively in patients with dysgenic gonads and intersex syndromes. Eighty percent of affected individuals are phenotypic females, usually presenting with primary amenorrhea. The remainder of patients are phenotypic males, almost always presenting with cryptorchidism (with the dysgenic gonad in the inguinal or abdominal location), hypospadias, and some form of female internal genitalia. One third of cases are bilateral (Scully, 1970). **These tumors should be considered an in-situ form of malignant GCT, because approximately 50% will develop an invasive GCT (usually seminoma, although yolk sac tumor and EC can occur)** (Ulbright, 2004). Gonadoblastomas do not metastasize, but the malignant GCT elements may. **Bilateral orchiectomy is required because of the risk of bilateral tumors.** For patients with malignant GCT, subsequent workup for metastatic disease ± treatment should be initiated.

Miscellaneous Testicular Neoplasms

Epidermoid Cyst

These rare benign neoplasms are thought to represent monodermally differentiated mature teratoma, because a case with adjacent ITGCN has been identified and association with cryptorchidism and bilaterality have been reported (Younger et al, 2003). Grossly they are well-circumscribed cystic masses filled with keratinized debris, similar to an epidermal inclusion cyst. They have a characteristic ultrasonographic appearance. **Enucleation or partial orchiectomy may be performed, although the lesion should be thoroughly sampled by a pathologist to rule out GCT or ITGCN.**

Adenocarcinoma of the Rete Testis

Adenocarcinoma of the rete testis is a rare but highly malignant neoplasm arising from the collecting system of the testis. The usual presentation is a painless testicular mass with hydrocele. More than 50% of patients present with metastatic disease, and the overall median survival is 1 year. RPLND may be curative in patients with limited retroperitoneal lymph node metastasis. Chemotherapy and radiation therapy are ineffective.

Secondary Tumors of the Testis

Lymphoma

Primary testicular non-Hodgkin lymphoma is a rare tumor and represents only 1% to 2% of all cases of lymphoma. Most commonly, lymphoma involves the testis through dissemination from extratesticular sites (Ulbright, 2004). Eighty-five percent of cases occur in men older than age 60. **Non-Hodgkin lymphoma is the most common testicular neoplasm in men older than age 50. Bilateral testicular involvement occurs in 35% of cases.** This tumor usually presents as a painless testicular mass in an older man. Approximately 25% of men have systemic symptoms (fever, night sweats, weight loss). Central nervous system involvement at diagnosis is reported in 10% of men. The initial treatment is radical inguinal orchiectomy. Men with testicular non-Hodgkin lymphoma should be referred to hematology-oncology for staging investigations and subsequent therapy. Most cases are associated with systemic disease, and the overall prognosis is poor.

Leukemic Infiltration

The testis is a frequent site of relapse in boys with acute lymphocytic leukemia. The majority of boys are in complete

remission at the time of testicular enlargement. **The diagnosis can usually be made by biopsy, and orchiectomy is unnecessary. Local control can be achieved with low-dose radiotherapy (20 Gy), and treatment should include the contralateral testis owing to the frequent risk of bilateral involvement.** Overall the prognosis is poor because most patients have associated systemic disease.

Metastases

Metastases to the testis are rare and usually associated with diffuse metastatic disease. Bilateral involvement occurs in 15% of patients. The most common primary lesions are prostate cancer, lung cancer, melanoma, colon cancer, and kidney cancer. Although treatment is largely dictated by the primary tumor, orchiectomy may be considered for palliative reasons.

Key Points: Non–Germ Cell Tumors

- Ninety percent of Leydig cell and Sertoli cell tumors are benign, and 10% are malignant.
- There are no reliable histologic criteria to identify malignancy.
- RPLND may be considered in patients with adverse histologic features (large size, necrosis, increased mitoses, nuclear pleomorphism) and/or evidence of retroperitoneal metastases.
- Malignant tumors are resistant to chemotherapy and radiation therapy.

TUMORS OF THE TESTICULAR ADNEXA

Adenomatoid Tumor

Adenomatoid tumor is the most common paratesticular tumor, most commonly involving the epididymis (although these tumors may also arise within the testicular tunics or the spermatic cord). The most common presentation is a small (0.5 to 5.0 cm), painless paratesticular mass detected on routine examination in a male in his third or fourth decade. **These tumors are benign and managed by inguinal exploration and surgical excision.** On microscopic examination these tumors are composed of epithelial-like cells that contain vacuoles and fibrous stroma.

Cystadenoma

Cystadenoma of the epididymis corresponds to benign epithelial hyperplasia. The lesions are usually multicystic, the walls of which are studded with nodules of epithelial cells arranged in a glandular or papillary configuration. **Approximately one third of cases occur in patients with von Hippel-Lindau syndrome.** The lesions are usually small and painless and are detected on routine examination in a young adult.

Mesothelioma

Paratesticular mesothelioma arises from the tunica vaginalis and usually presents as a painless scrotal mass in association with a hydrocele. These tumors most commonly occur in older adults but may be encountered in any age group. **Both benign and malignant mesothelioma have been described, with the distinction based on atypia, mitotic activity, and invasion** (Ulbright, 2004). Malignant cases may be associated with asbestos exposure. **Treatment is radical inguinal orchiectomy.** Unsuspected cases of paratesticular mesothelioma identified at the time of scrotal hydrocelectomy should be managed by inguinal orchiectomy. RPLND may be considered in patients with malignant tumors without widespread metastatic disease. The role of chemotherapy for these tumors is poorly defined.

Sarcoma

Sarcomas of the spermatic cord, epididymis, and testis are the most common genitourinary sarcomas in adults. **Liposarcoma is the most common histologic subtype in adults,** followed by rhabdomyosarcoma, leiomyoma, malignant fibrous histiocytoma, and fibrosarcoma (Coleman et al, 2003; Ulbright, 2004; Dotan et al, 2006). **Embryonal rhabdomyosarcoma is the most common histologic subtype in men younger than age 30. Sarcomas are most often in the intrascrotal region and primary mesenchymal tumors of the testis are uncommon.** These tumors usually present as a painless, palpable mass, and most are large (>5 cm) (Dotan et al, 2006). Ultrasonography will demonstrate a solid mass, although it cannot distinguish between benign and malignant pathology. **As such, any solid mass in the scrotum external to the tunica albuginea should be explored through an inguinal approach and biopsy performed. Liposarcomas of the spermatic cord in the inguinal canal may be mistaken for inguinal hernia or lipoma, and CT or MRI is helpful to distinguish between these entities.**

Sarcomas should be managed initially through an inguinal approach with wide excision of the spermatic cord and testis with high ligation. Patients with an initial incomplete resection should undergo repeat wide excision (Coleman et al, 2003). Additional therapy is dictated by the histologic subtype and the presence of regional or distant metastases. The vast majority of patients have localized disease at diagnosis. **Liposarcomas rarely metastasize but tend to recur locally** (Montgomery and Fisher, 2003). **Thus, postoperative radiation therapy may be considered for these tumors or in those in whom the adequacy of local excision is in doubt,** although the efficacy of this approach is debated (Fagundes et al, 1996; Coleman et al, 2003). Systemic chemotherapy should be given to patients with evidence of retroperitoneal or distant metastases. **In the presence of a normal metastatic evaluation, patients with sarcomas other than liposarcoma should undergo RPLND and postoperative chemotherapy should be given to patients with retroperitoneal lymph node metastasis.** The long-term survival

Key Points: Tumors of the Testicular Adnexa

- Adenomatoid tumor is the most common paratesticular tumor. These tumors are benign and managed by surgical excision.
- The paratesticular region is the most common location for genitourinary sarcomas. The most common histology in children and young adults is embryonal rhabdomyosarcoma, and liposarcoma is the most common histology in older adults.

of men with paratesticular sarcoma is approximately 50% (Coleman et al, 2003).

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chapter 32

Surgery of Testicular Tumors

Joel Sheinfeld, MD ● George J. Bosl, MD

Management of the Primary Tumor
Retroperitoneum and Germ Cell Tumors
Retroperitoneal Lymph Node Dissection
Treatment Options for Low-Stage Germ Cell Tumors
Surgery for High-Stage Germ Cell Tumors

Each year, approximately 8000 new cases and almost 400 deaths due to testicular cancer are expected (Jemal et al, 2007). The incidence of germ cell tumors (GCTs), the most common solid tumor in men between the ages of 20 and 35 years, is rising both in the United States and Europe (Bergstrom et al, 1996; McKiernan et al, 1999).

Given the dramatic improvements in survival rates from 60% to 65% in the 1960s to more than 90% in the 1990s, the management of testicular cancer has come to represent a model in the successful multidisciplinary approach to solid tumors (Einhorn et al, 1981). Although testicular cancer is highly curable, it requires appropriate management at all stages (Bosl et al, 2000). Both the cure rate and the morbidity are highly sensitive to nuances of management. The clinician and, more importantly, the patient pay a high price for inappropriate management. Surgery remains an integral part of the management of patients with GCTs, but the advent of effective chemotherapy and improvements in clinical staging, including sophisticated imaging modalities and reliable serum tumor markers, have altered its role over the past 30 years (Sheinfeld and Herr, 1998).

In this chapter the principal indications and controversies of surgery in the management of testicular neoplasms are summarized, common surgical techniques and their associated complications are described, and established and investigational alternatives to surgery in both low- and high-stage GCTs are discussed.

MANAGEMENT OF THE PRIMARY TUMOR

Unfortunately, delays in the timely and accurate diagnosis of testicular cancer continue to be a significant problem. Moul (1994) noted a mean duration of symptoms of 26 weeks before diagnosis in a review of 4948 patients with testicular cancer, with both patient and physician factors contributing to this delay. Bosl and colleagues (1981) reported that the median interval of delay for patients with clinical stage I disease was 75 days compared with 101 and 134 days for patients with clinical stage II and III disease, respectively. Painless scrotal masses are often ignored, whereas testicular cancers presenting as scrotal pain are treated as epididymitis up to 18% to 30% of the time (Bosl et al, 1981; Prout et al, 1984). Almost 20% of patients present with signs or symptoms of metastatic disease, such as back or abdominal pain, weight loss, neck mass, and gynecomastia or breast tenderness (Bosl et al, 1981, 2000; Thornhill et al, 1987). Patients have undergone unnecessary mastectomy or laparotomy or prolonged therapy for back pain without considering the diagnosis of testicular cancer (Post and Belis, 1980; Moul and Moellman, 1992; Moul et al, 2000). Stephenson and associates (2004) reported on 40 patients with a midline retroperitoneal mass who underwent unnecessary laparotomy. At the time of laparotomy all patients had an abnormality on testicular examination or ultrasonography or an elevated serum tumor marker to suggest the diagnosis of GCT. The laparotomy contributed to therapeutic delay in a substantial number of patients and complicated their therapy.

A careful history and physical examination, as well as serum β-human chorionic gonadotropin (hCG), α-fetoprotein (AFP), and lactate dehydrogenase (LDH) levels are helpful in establishing a correct diagnosis. Scrotal ultrasonography is extremely accurate in identifying solid intratesticular lesions with greater than 95% sensitivity and specificity.

Radical Orchiectomy

A radical orchiectomy with high ligation of the spermatic cord at the level of the internal ring is the first step in the treatment of patients suspected of harboring a testicular neoplasm. This procedure provides histopathologic diagnosis and tumor (T) staging categorization, is associated with minimal morbidity and no mortality, and provides local control of the tumor in the vast majority of patients. The rare exceptions are usually due to tumor spillage, suboptimal orchiectomy, or transscrotal surgery (Whitmore et al, 1982).

The procedure is performed under general, spinal, or local anesthesia on an outpatient basis. The patient is placed in the supine position with the scrotum prepped in the sterile field. A 5- to 7-cm oblique incision is made in the inguinal area along Langerhans skin lines approximately 2 cm above the pubic tubercle. This incision can be extended onto the upper scrotum to facilitate removal of large tumors. Camper and Scarpa fascia are incised to the level of the external oblique aponeurosis, which is then incised in the direction of its fibers to the level of the internal ring (Fig. 32–1). The ilioinguinal nerve is identified, dissected free of the cord, and preserved. The spermatic cord is isolated and occluded with either a noncrushing clamp or a 0.5-inch Penrose tourniquet at the level of the internal ring. The testis and its investing tunics are delivered into a carefully draped off field as gubernacular attachments are divided in the avascular plane. **If a diagnostic biopsy or**

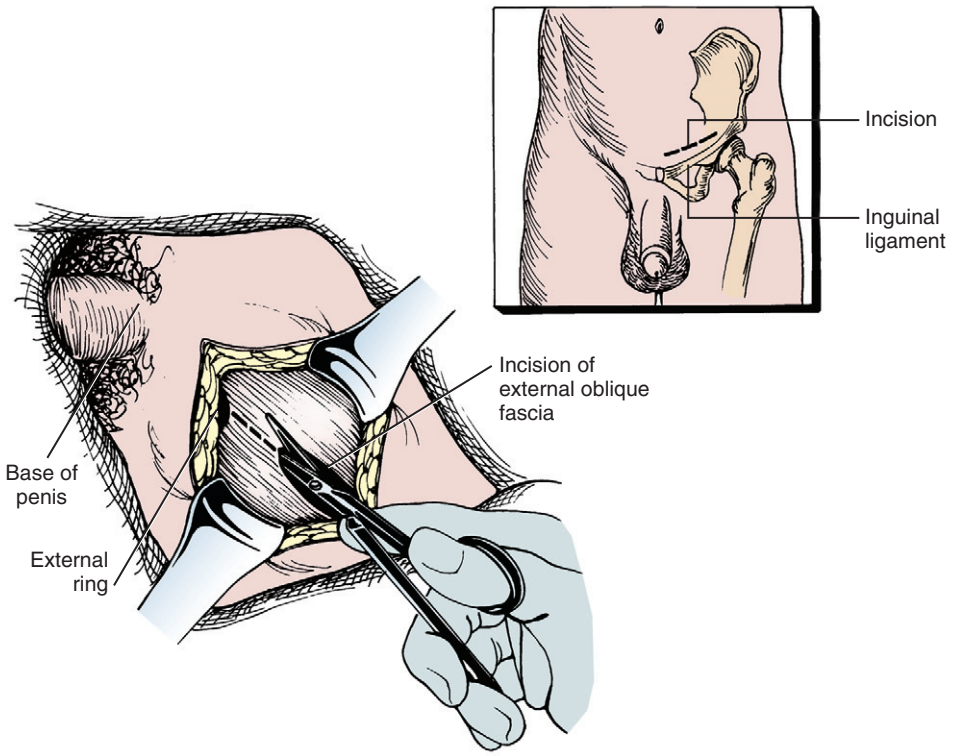


Figure 32–1. Approach for radical inguinal orchiectomy. The incision is shown in the inset. The external oblique fascia is divided in line with its fibers down to the external inguinal ring. (Adapted from Gottesman JE. In: Crawford ED, editor. Current genitourinary cancer surgery. Philadelphia: Lea & Febiger; 1990. p. 319.)

subtotal orchiectomy is planned, meticulous draping off is necessary before opening the tunica vaginalis and incising testicular parenchyma. Radical orchiectomy is completed by mobilizing the cord 1 to 2 cm inside the internal ring and individually ligating the vas deferens and the cord vessels between separate clamps (Fig. 32–2). The cord vessels are secured with silk ligatures, which can then be used to identify the stump if a retroperitoneal lymph node dissection (RPLND) is performed. The wound and scrotum are thoroughly irrigated and hemostasis is secured. A testicular prosthesis (soaked in antibiotic solution) can then be placed. The external oblique aponeurosis is closed with running 2-0 polypropylene suture. The Scarpa fascia is closed with absorbable sutures, and the skin is closed with either skin staples or a subcuticular suture. Compressive fluff dressings with a scrotal support minimize postoperative edema.

The most common complication of radical orchiectomy remains postoperative bleeding, which may occasionally result in either a scrotal or a retroperitoneal hematoma. Furthermore, significant retroperitoneal hematomas may delay further therapy or be misinterpreted as metastatic disease and result in unnecessary treatment (Bochner et al, 1995).

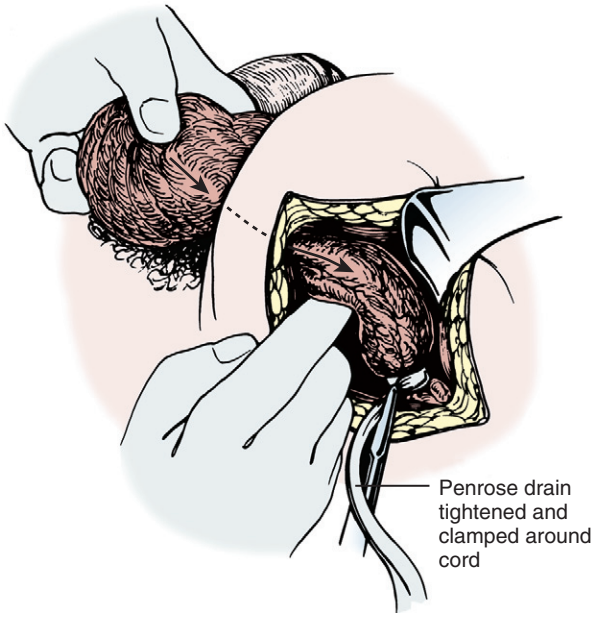


Figure 32–2. After the cord has been controlled with a tightened Penrose drain or rubber-shod clamp, the testis is mobilized out of the scrotum using blunt dissection. (Adapted form Gottesman JE. In: Crawford ED, editor. Current genitourinary cancer surgery. Philadelphia: Lea & Febiger; 1990. p 319.)

Scrotal Violation

Sayegh and associates (1966) reported that prior inguinal or scrotal surgery could alter the normal lymphatic drainage of the testis; consequently, many patients with scrotal violation have undergone extensive local surgery and/or adjuvant therapy to prevent an adverse outcome.

Suboptimal approaches to testicular neoplasms including scrotal orchiectomy, transscrotal biopsy, or fine-needle aspiration are reported from 4% to 17% of the time (Capelouto et al, 1995; Leibovitch et al, 1995a).

A recent meta-analysis of 206 cases of scrotal violation reported a local recurrence rate of 2.9% compared with 0.4% of patients treated by inguinal orchiectomy but no difference in systemic relapse or survival rates. There did not appear to be any advantage to adjuvant therapy (Capelouto et al, 1995). Others have reported an increased local recurrence rate in patients with scrotal

contamination (Giguere et al, 1988) and an 11% presence of tumor in hemiscrotectomy specimens of patients with scrotal violation. Therefore the following recommendations for patients with scrotal violation seem prudent:

1. **In patients with low stage seminoma the radiation portals should be extended to include the ipsilateral groin and scrotum.** This may result in an increased risk of azoospermia (Amelar et al, 1971).
2. **In patients with low-stage nonseminomatous GCT (NSGCT), the scrotal scar should be widely excised with the spermatic cord remnant at the time of RPLND.** Patients with clinical stage I NSGCT and scrotal violation are not good candidates for surveillance.
3. **Patients treated with full-dose platinum-based regimens should have the cord stump removed at the time of RPLND; however, given the relative absence of local relapse after systemic treatment, extensive groin dissection or hemiscrotectomy is not required.**

Partial Orchiectomy

A small subset of carefully selected patients with a solitary testis or bilateral testicular tumors, or a suspected benign lesion, may be candidates for "testis-sparing" surgery. The German Testicular Cancer Intergroup reported on 63 patients with median follow-up of 74 months and found only 4 local recurrences, all in patients with untreated intratubular germ cell neoplasia (Van der Schyff et al, 2000). Almost 90% of patients maintained normal testosterone levels. **Favorable selection criteria include organ-confined disease with a mass less than 20 mm, negative postresection biopsies of the tumor bed, and absence of intratubular germ cell neoplasia (ITGCN) in the remaining testicular parenchyma. The procedure is performed under conditions of cold ischemia with great care to avoid tumor spillage or contamination.** Biopsies of adjacent parenchyma are performed to identify ITGCN. The diagnosis of ITGCN on frozen section can be difficult due to artifact, and an experienced pathologist is particular helpful. The decision to perform completion orchiectomy in the presence of documented ITGCN is individualized based on preoperative discussion and the status of the contralateral testis. Patient compliance for rigorous follow-up must be assured, particularly because most patients with GCT have associated ITGCN.

Delayed Orchiectomy

A subset of patients with documented advanced germ cell cancer that includes histologic verification from a metastatic site undergo systemic chemotherapy without orchiectomy. Rarely, postoperative complications after orchiectomy have resulted in delays initiating chemotherapy. **The rationale for delayed orchiectomy after systemic chemotherapy is supported by data from a review of 160 patients in which 40 (25%) patients had viable cancer and 50 (31%) had teratoma in the resected testis** (Simmonds et al, 1995).

Staging

Staging evaluation must include thorough history and physical examination with particular attention to the contralateral testis. **Serum tumor markers should be repeated immediately before RPLND and should include hCG, LDH, and AFP. Computed tomography (CT) of the chest, abdomen, and pelvis is the most efficient and cost-effective means of detecting metastatic disease.** Magnetic resonance imaging (MRI) is usually reserved for the setting of major vascular involvement to assess patency of the inferior vena cava and renal vessels (Bosl et al, 2000).

In 1997 the American Joint Committee on Cancer (AJCC) and Union Internationale Contre le Cancer (UICC) adopted a comprehensive staging system that now includes serum tumor markers (TNMS). Stage I refers to disease confined to the testis, stage II implies retroperitoneal metastases, and stage III disease indicates supradiaphragmatic or visceral metastases. In the TNMS system vascular or lymphatic invasion in the primary tumor are classified in the T2 category and serum tumor markers are included because of their independent prognostic significance (AJCC, 1998). Staging systems for testicular cancer are discussed in Chapter 31.

Key Points: Demographics

- Testicular cancer is the most common solid tumor in men between the ages of 20 and 35 years.
- Approximately 8000 new cases and 400 deaths per year occur due to testicular cancer.
- Delay in diagnosis continues to be a significant problem.
- Careful history, physical examination, and serum tumor markers (hCG, AFP, and LDH) are helpful in establishing the correct diagnosis.
- Scrotal ultrasonography is extremely accurate in identifying solid intratesticular lesions, with greater than 95% sensitivity and specificity.

RETROPERITONEUM AND GERM CELL TUMORS

Natural History, Patterns of Metastasis, Anatomic Considerations

The natural history of testicular cancer provides the basis for its evaluation and management, and, in turn, is favorably influenced by effective treatment (Whitmore et al, 1982). GCTs share several features that have contributed significantly to their successful management. **These include (1) a germ cell origin, which is associated with responsiveness to irradiation (seminoma) and a number of chemotherapeutic agents, and with a potential for differentiation to histologically benign teratoma; (2) a rapid growth rate; (3) frequent production of specific tumor markers such as AFP and hCG; (4) usual occurrence in otherwise healthy young adults who can tolerate the necessary therapy; and (5) a predictable and systematic pattern of metastatic spread from the primary site to the retroperitoneal lymph nodes and subsequently to the lung and posterior mediastinum** (Whitmore et al, 1982; Richie, 1992; Sheinfeld, 1994).

Lymphatic spread is common to all forms of GCTs, although, in the case of choriocarcinoma, vascular dissemination is often a more common clinical feature. In 1899, Most was the first to accurately describe the lymphatic drainage of the testis (Most et al, 1899; Skinner and Leadbetter, 1971). Other anatomic studies in the early 20th century confirmed his findings and noted that the primary lymphatic drainage of the testis was to the area of its embryologic origin, that is, the retroperitoneal lymph nodes adjacent to the great vessels (Cuneo,

1901; Jamieson and Dobsin, 1910; Skinner and Leadbetter, 1971). **Right-sided testicular drainage included the interaortocaval lymph nodes, followed by the precaval and paracaval nodes, whereas left-sided drainage included the left para-aortic and preaortic lymph nodes** (Weinstein, 1999).

Further anatomic studies and detailed mapping studies of RPLNDs have increased our understanding of the testicular lymphatic drainage and sharpened the focus of clinical staging and treatment by identifying the most common sites of metastatic disease (Busch and Sayegh, 1963; Chiappa et al, 1966; Sheinfeld, 1994). There are four to eight lymphatic vessels that accompany the spermatic vessels through the internal ring into the retroperitoneum. Although the majority of lymphatic channels continue to accompany the spermatic vessels to the point where those vessels cross the ureter and to their origin, some may drain directly into a lymph node on the anterior surface of the proximal third of the external iliac artery. At the point where the spermatic vessels cross ventral to the ureter, lymph channels fan out medially in relation to the aorta and inferior vena cava and drain into the retroperitoneal lymph node chain extending from approximately L5 to T11 (Weinstein, 1999). Contralateral lymphatic flow is often seen, particularly for right-sided lymphatics (Weinstein, 1999).

Surgical mapping studies by Donohue and associates (1982), Weissbach and Boedefeld (1987), and Ray and colleagues (1974) divided the retroperitoneum into specific anatomic regions: right and left suprahilar, right paracaval, precaval, interaortocaval, preaortic, left para-aortic, right and left iliac, interiliac, and gonadal vessels (right or left) (Weinstein, 1999) (Fig. 32–3).

The first echelon of lymph nodes draining the right testis is located in the interaortocaval area, followed by the precaval and preaortic nodes. The primary "landing zone" for left-sided tumors includes the para-aortic and preaortic lymph nodes, followed by the interaortocaval nodes (Donohue et al, 1982). More caudal deposits of metastatic disease usually reflect retrograde spread secondary to large volume disease and, rarely, aberrant drainage. **Contralateral spread is more common with right-sided tumors, rare with left-sided tumors, and usually associated with large-volume disease** (Sogani, 1991; Richie et al, 1992).

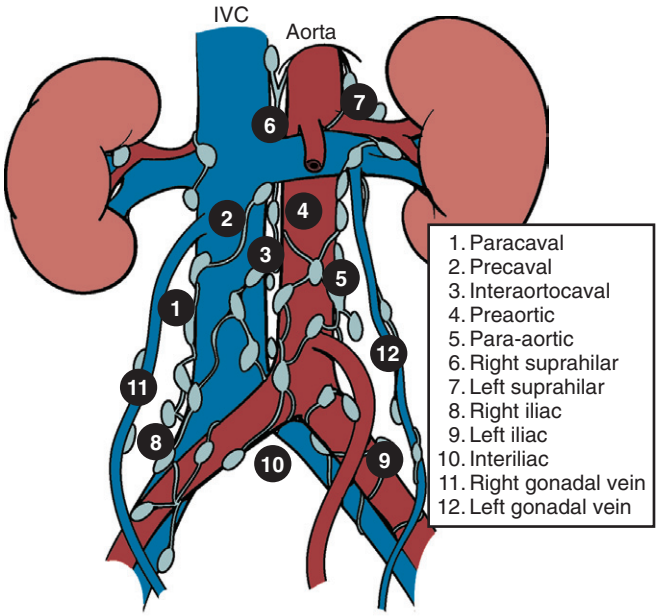


Figure 32–3. Anatomic regions of the retroperitoneum.

Testicular tumors have the capacity to spread by direct extension and involve the epididymis and/or scrotum. The lymphatic drainage of the epididymis is to the external iliac chain, whereas that of the scrotum is to the inguinal lymph nodes (Osler, 1907; Weinstein, 1999).

The rationale for treatment of the retroperitoneal lymph nodes in patients with testicular cancer is based on several factors. First, there is evidence that retroperitoneal lymph node spread is usually the first and often the only site of metastatic disease (Whitmore, 1979). This is supported by several clinical observations: (1) the survival rates in patients with retroperitoneal lymph node metastases treated by RPLND alone (Richie and Kantoff, 1991; Sheinfeld et al, 1999a; Stephenson et al, 2005); and (2) patients whose regional lymph nodes are found to be pathologically negative after adequate RPLND are usually cured by orchiectomy and the rare treatment failures in this group of patients are usually a result of pulmonary metastases and/or elevated serum tumor markers. Systemic relapse rates are declining and average approximately 10%, with disease-free survival rates ranging from 96% to 100% (Staubitz et al, 1973; Whitmore, 1979; Bredael et al, 1983; Stephenson et al, 2005).

Second, although clinical staging continues to improve through refinements of radiologic imaging such as CT (Hilton et al, 1997), in **15% to 40% of patients their disease is clinically understaged, particularly in the retroperitoneum. This is supported by the 20% to 30% incidence of pathologic stage II disease in patients with clinical stage I disease, the approximately 25% relapse rate in the retroperitoneum on surveillance protocols** (Lashley and Lowe, 1998), **and the 20% incidence of teratoma and/or viable carcinoma in resected specimens of patients with subcentimeter lymph nodes on CT after chemotherapy** (Fossa et al, 1989c; Toner et al, 1990; Sheinfeld and Bajorin, 1993; Oldenburg et al, 2003; Karellas et al, 2007).

Third, untreated retroperitoneal lymph node metastases are usually fatal (Whitmore, 1979). **Autopsy studies of patients dying with GCTs of the testis indicate that brain, liver, and bone metastases were late occurrences in the course of the disease and that most patients had concomitant and usually bulky retroperitoneal metastases** (Johnson et al, 1976; Bredael et al, 1982). Interestingly, autopsy data did not reveal any significant differences in the site or frequency of metastasis between those treated before and after introduction of cisplatin-based chemotherapy (Bredael et al, 1982). **Furthermore, the most common site of late recurrence of both teratoma and viable GCT is the retroperitoneum** (Baniel et al, 1995c; Sharp et al, 2008). **Late recurrences are usually chemorefractory, and survival rates are poor** (Borge et al, 1988; Baniel et al, 1995; George et al, 2003; Carver and Sheinfeld, 2005; Sharp et al, 2008).

RETROPERITONEAL LYMPH NODE DISSECTION

Evolution of Surgical Templates and Techniques

Although RPLND has been well established in the management of NSGCTs since 1948, both its role and the surgical template itself have undergone considerable change over the past 30 years.

Either a transabdominal or thoracoabdominal approach to the retroperitoneum for lymph node dissection may be used (Whitmore, 1962; Skinner and Leadbetter, 1971; Donohue, 1977). Initially, RPLND included bilateral suprahilar dissections as well as all the nodal tissue between both ureters down to the bifurcation of the common iliac arteries.

Given the significant limitations in clinical staging at the time, and the absence of other effective therapeutic modalities, emphasis was necessarily placed on extensive dissection of all lymph nodes. Although its therapeutic efficacy was confirmed (Skinner, 1976; Donohue, 1977; Donohue et al, 1993), extensive suprahilar dissection can result in increased pancreatic, lymphatic, and renovascular complications. **Several studies have confirmed that suprahilar metastases are rare in low-stage NSGCT, and, currently, suprahilar dissections are usually performed for residual hilar or suprahilar masses after cytoreductive chemotherapy for advanced-stage NSGCT** (Ray et al, 1974; Donohue et al, 1982). **In this setting the most common site of suprahilar disease is in the retrocrural space** (Schmeller et al, 1981).

In an effort to reduce surgical perioperative morbidity, bilateral infrahilar RPLND replaced the original suprahilar dissections (see Fig. 32–2) (Donohue et al, 1982, 1993). The procedure was associated with minimal morbidity and a mortality rate less than 1% (Baniel et al, 1994).

The most consistent long-term morbidity of a standard bilateral RPLND has been the loss of antegrade ejaculation and, consequently, potential infertility, owing to damage of sympathetic nerve fibers (Lange et al, 1983, 1984; Jewett et al, 1988). **Therefore patients are advised to complete sperm banking before the surgery.** Prior to development of nerve-sparing techniques the incidence of this complication was associated with the extent of the retroperitoneal dissection (Lange et al, 1984; Jewett et al, 1988).

The sympathetic chain, the paravertebral sympathetic ganglia, and postganglionic sympathetic fibers T2 to L4 and their convergence at the hypogastric plexus are most crucial in the preservation of antegrade ejaculation. Minimizing damage to these structures has resulted in higher rates of ejaculation (Lange et al, 1984; Sheinfeld and Herr, 1998). Two general approaches have been utilized to protect theses structures and include modified template RPLND and, more recently, nerve-sparing dissections, which can be applied to any template, including a bilateral template.

Modified Templates

Narayan and colleagues (1982) first reported that modification of surgical boundaries resulted in spontaneous return of ejaculation, with 25 of 55 patients recovering ejaculation at 3 years. Subsequently, a number of investigators have proposed a variety of modified RPLND templates for both right- and left-sided primary tumors with rates of return of ejaculation ranging from 51% to 88% (Fossa et al, 1984; Pizzocaro et al, 1985; Donohue et al, 1990; Richie, 1990).

Successful preservation of ejaculation is higher for right-sided dissections compared with left-sided ones. **In an effort to avoid disrupting the sympathetic nerves and the hypogastric plexus, all modified templates share several goals: (1) to thoroughly resect all ipsilateral lymph nodes between the level of the renal vessels and the bifurcation of the common iliac artery and (2) to minimize contralateral dissection, particularly below the level of the inferior mesenteric artery** (Sheinfeld and Herr, 1998).

These arbitrary changes were made on the basis of surgical mapping studies and overreliance of cisplatin-based chemotherapy. Initially, short-term and medium-term follow-up appeared to corroborate this approach, but long-term data (particularly late relapse and redo-RPLND studies) have since exposed some of its limitations.

Modified templates are based on mapping studies of retroperitoneal metastasis and aim to limit the extent of dissection in anatomic regions thought to be at decreased risk of metastatic spread. Unfortunately, mapping studies have several important limitations that contribute to an underestimation of the extent of retroperitoneal disease. Mapping studies often lack adequate postoperative follow-up, so the rate of recurrence outside the template region is unknown. Without appropriate follow-up, sample errors by the surgeon and/or the pathologist cannot be determined. For example, studies by Ray and associates (1974) and Donohue and coworkers (1982) did not report any follow-up data and the study by Weissbach and Boedefeld (1987) reported three retroperitoneal recurrences with a median follow-up of only 22 months in patients with pathologic stage I disease. This was a multicenter study that included 46 centers and 50 surgeons, thereby introducing significant surgical variability. Importantly, in the Weissbach and Boedefeld study it is not possible to accurately assess unresected metastatic sites in patients who subsequently received chemotherapy.

In a recent analysis of 500 patients with clinical stage I and IIA disease who underwent primary RPLND at Memorial Sloan-Kettering Cancer Center (MSKCC), Eggener and associates (2007b) reported that depending on the template applied, 3% to 23% of patients with positive nodes will have extratemplate disease, including up to 11% with low-volume retroperitoneal disease. Similarly, Carver and colleagues (2007b) reported that, of 532 patients who underwent postchemotherapy RPLND (PC-RPLND) at MSKCC, up to 32% would have had disease outside the template region, depending on the limits of the modified templates.

Both of these studies showed that the histology outside the template region was similar to that within the templates. This is an important observation, because chemoresistant teratomatous elements are present in approximately 30% of positive nodes in primary RPLND specimens and in approximately 40% of post-chemotherapy specimens. Teratoma and malignant transformation are clearly overrepresented in patients who have experienced late relapse and repeat retroperitoneal surgery and arise from unresected disease (McKiernan et al, 2003; Sheinfeld, 2007; Sharp et al, 2008). These catastrophic sequelae highlight the potential danger of a reduced surgical field and overreliance on chemotherapy.

Antegrade Ejaculation

Antegrade ejaculation requires the coordination of three separate events: (1) closure of the bladder neck, (2) seminal emission, and (3) ejaculation. The sympathetic fibers that mediate seminal emission originate primarily from the T12 to L3 levels of the thoracolumbar spinal cord. In the mid retroperitoneum after leaving the sympathetic trunk the fibers converge toward the midline and form the hypogastric plexus near the takeoff of the inferior mesenteric artery just above the aortic bifurcation. From the hypogastric plexus the sympathetic fibers travel via the pelvic plexus to innervate the seminal vesicles, vas deferens, prostate, and bladder neck (Fig. 32–4). Ejaculation is mediated by nerves originating at

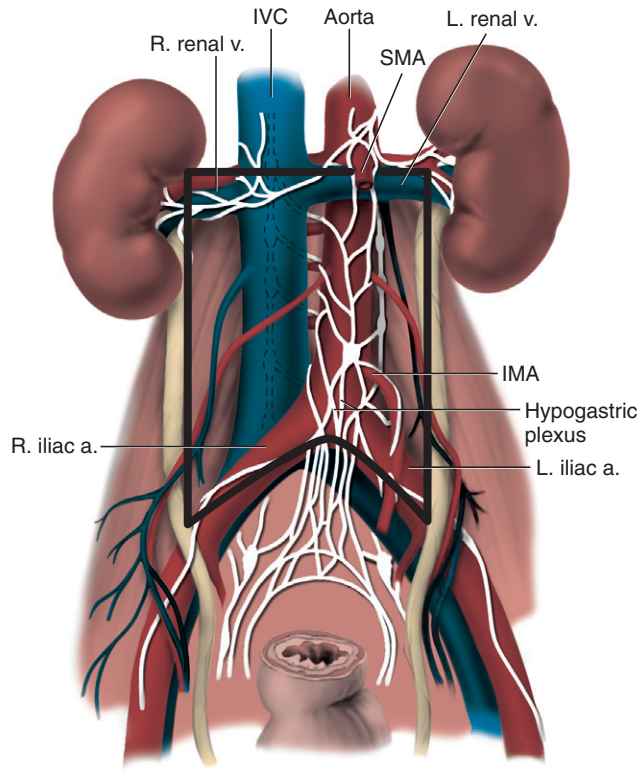


Figure 32–4. Surgical template for bilateral RPLND. IMA; inferior mesenteric artery; IVC, inferior vena cava; SMA, superior mesenteric artery.

the sacral and lumbar spinal cord levels. Sympathetic fibers tighten the bladder neck, whereas pudendal somatic innervation from S2 to S4 causes relaxation of the external urethral sphincter and rhythmic contractions of the bulbourethral and perineal muscles (Lange et al, 1983, 1984; Sheinfeld, 1994; Sogani, 1991).

Nerve-Sparing Techniques

The highest rates of preserved ejaculation are reported with nerve-sparing RPLND, in which the sympathetic chains, the postganglionic sympathetic fibers, and the hypogastric plexus are prospectively identified, meticulously dissected, and preserved (Jewett et al, 1988; Donohue et al, 1990). Nerve-sparing techniques can be utilized either in the primary or postchemotherapy setting and within standard bilateral or modified templates, depending on clinical and surgical circumstances; however, **margins of resection should never be compromised in an attempt to maintain ejaculatory function** (Bosl et al, 2000).

Surgical Technique

Strict adherence to basic surgical principles is critical to perform RPLND safely. First, it is imperative that the surgeon have an in-depth understanding of retroperitoneal anatomy and be able to recognize common variations and their potential implications. Second, excellent exposure of the retroperitoneum must be ensured to properly set up the RPLND; and, finally, a thorough lymphadenectomy using meticulous "split and roll" technique should be carried out.

Exposing the Retroperitoneum

Adequate exposure of the retroperitoneum can be accomplished with either a transabdominal or a thoracoabdominal approach.

Thoracoabdominal Approach. The extraperitoneal thoracoabdominal approach to RPLND was originally described by Cooper and later refined and popularized by Skinner and their associates (Cooper et al, 1950; Skinner et al, 1982). The main advantages of this approach are to allow easier visualization and dissection of the suprahilar lymphatic tissues and less risk of postoperative small bowel obstruction. In addition, simultaneous thoracic procedures can be performed through the same incision.

The patient is placed in the torqued position with the lower extremities and pelvis supine and the chest and upper extremities rotated medially. The operating table is hyperextended to allow exposure and retraction of the rib cage. The incision starts obliquely over the eighth or ninth rib and curves downward paramedian toward the pubic ramus. A subperiosteal rib resection is performed and the ipsilateral rectus muscle is divided. The peritoneum and contents are mobilized from the undersurface of the rectus sheath, and the diaphragm is divided and the pleural cavity is entered. The chest can be inspected and pulmonary or mediastinal procedures performed through the same incision. The retroperitoneum is exposed to the level of the contralateral ureter. Full bilateral RPLND can be performed as described for the transabdominal approach. In primary RPLND routine suprahilar dissection is not warranted, because the incidence of suprahilar or retrocrural disease is extremely low. In advanced disease, suprahilar dissection is directed by preoperative imaging studies and intraoperative palpation. The most common site of residual suprahilar disease is in the retrocrural space (Schmeller et al, 1981).

The wound is closed by reapproximation of the diaphragm with silk sutures and of the costal cartilage with polypropylene sutures. Chest tube drainage is established, and the flank is closed.

Complications specific to the thoracoabdominal approach are pulmonary, including atelectasis, prolonged chest tube drainage, and increased need for postoperative analgesia. In 1982 Skinner and colleagues described their complications with this technique in 149 patients both before and after chemotherapy. The overall operative mortality was 1.3% with both deaths due to hepatic failure. The overall complication rate was 13%, and major complications included small bowel obstruction, lymphocele, and wound dehiscence.

Transabdominal Approach. After successful induction of general endotracheal anesthesia and placement of the patient in the supine position, the skin of the chest wall, abdomen, pubis, genitalia, and upper thighs is prepared. A Foley catheter is placed and connected to closed drainage. A nasogastric tube is placed and connected to intermittent suction.

A midline incision is made from the xiphicostal junction to a point 2 cm above the symphysis pubis. It is carried down through the subcutaneous tissues, and the linea alba and peritoneum are opened. The falciform ligament is either divided between silk ligatures or excised en bloc with the preperitoneal fat. This prevents hepatic capsular tears and allows upward displacement of the liver as the wound edges are spread by two self-retaining Balfour retractors. Careful inspection of the abdomen, retroperitoneum, and pelvis is then carried out to assess resectability and the presence of metastatic disease. The greater omentum and the transverse colon are then displaced superiorly onto the chest between warm moist packs.

The small bowel is reflected to the right, and an incision is made in the posterior peritoneum medial to the inferior mesenteric vein

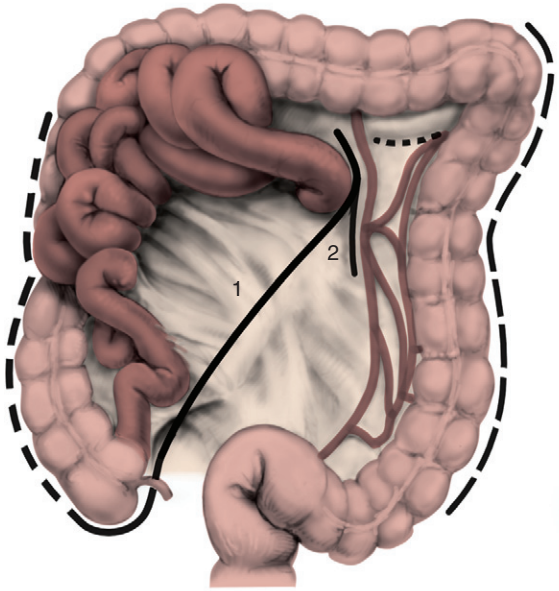


Figure 32–5. Incision of the posterior parietal peritoneum. The incision extends from the ligament of Treitz along the left side of the root of the small bowel mesentery to the ileocecal region (1). It may be extended superiorly and medially to the duodenojejunal flexure and inferolaterally around the cecum and ascending colon. The left leaf of the incised posterior peritoneum is defined (2).

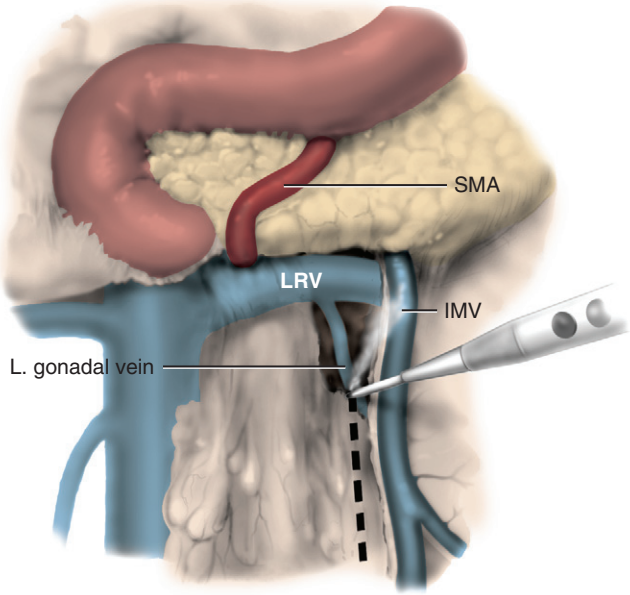


Figure 32–6. Development of the left leaf of the incised posterior peritoneum in the avascular plane between the inferior mesenteric vein (IMV) and the left gonadal vein. The colonic mesentery lies anteriorly and the para-aortic space and Gerota fascia posteriorly. SMA, superior mesenteric artery; LRV, left renal vein.

(Fig. 32–5). This incision is continued cephalad to the ligament of Treitz and is extended superiorly and medially to the duodenojejunal flexure, allowing for superior mobilization of the fourth portion of the duodenum and pancreas. The left leaf of the incised posterior peritoneum is further developed, with the colonic mesentery located anteriorly and the para-aortic retroperitoneal space posteriorly (Fig. 32–6). The proper plane of dissection is the avascular plane between the inferior mesenteric vein and the left gonadal vein. This maneuver further defines a thick condensation of fibrovascular tissue (ligament of Treitz) and several large lymphatic trunks, which should be divided between silk sutures, further mobilizing the tail of the pancreas. **Alternatively, to gain adequate exposure in the area of the left renal hilum, particularly with large postchemotherapy masses, the inferior mesenteric vein can be doubly ligated and divided.**

The incision in the posterior parietal peritoneum is continued inferiorly along the medial aspect of the small bowel mesentery, lateral to the right gonadal vein and its branches, and extended around the cecum and up the right paracolic gutter to the foramen of Winslow. The duodenum is then kocherized, allowing cephalad reflection and exteriorization of the small bowel, cecum, and right colon onto the chest wall where they can be either placed in a Lahey bag or protected by moist laparotomy pads (Fig. 32–7). To facilitate retraction of the exteriorized viscera and minimize traction when self-retaining Gallagher and large Deaver retractors are placed, careful and thorough division of attachments between the undersurface of the duodenum and pancreas and the anterior surface of the left renal vein is necessary (Fig. 32–8). It is also important to ligate or clip the numerous lymphatic vessels in this area to minimize postoperative lymphatic complications. In placing self-retaining retractors great care must be taken in identifying the superior mesenteric artery to avoid vascular compromise of the small bowel. Periodic inspection of small bowel color

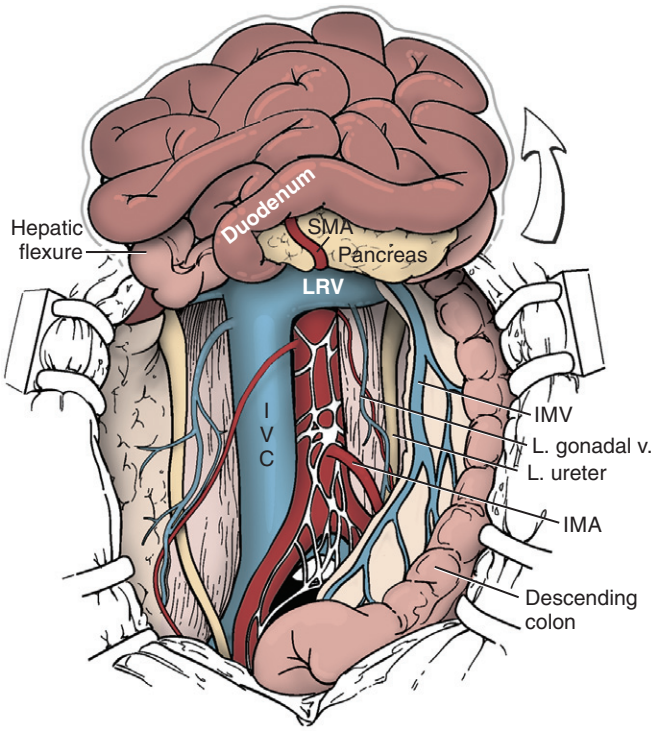


Figure 32–7. The retroperitoneal space has been exposed. The duodenum has been kocherized; its second, third, and fourth portions have been reflected superiorly along with the pancreas and superior mesenteric artery. The entire right colon has been mobilized and exteriorized. SMA, superior mesenteric artery; LRV, left renal vein; IMV, inferior mesenteric vein; IVC, inferior vena cava; IMA, inferior mesenteric artery.

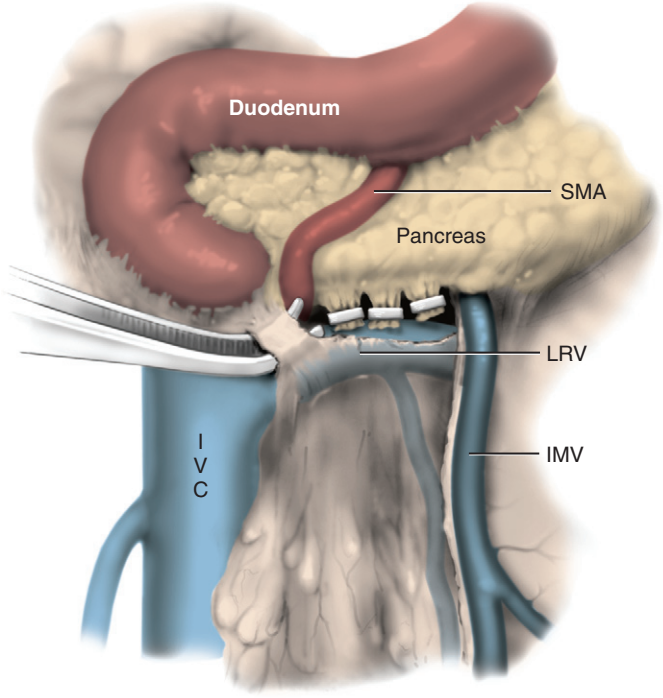


Figure 32–8. Division of attachments between undersurface of the duodenum and pancreas and the anterior surface of the left renal vein. It is important to clip or ligate the numerous lymphatic channels in this area. Prominent lacteals in the vicinity of superior mesenteric artery are often seen. SMA, superior mesenteric artery; IMV, inferior mesenteric vein; LRV, left renal vein; IVC, inferior vena cava.

or pulsation of the superior mesenteric artery is prudent. These maneuvers allow for excellent exposure of the retroperitoneal space from the level of the right and left suprahilar areas distally to the bifurcation of the right common iliac artery. **Additional exposure of the distal left para-aortic and left parailiac space can be accomplished by further extending the incision in the left leaf of the parietal peritoneum inferiorly and, if necessary, sacrificing the inferior mesenteric artery.** Alternatively, the left colon can be reflected medially by incising the left white line of Toldt and developing the plane between the colonic mesentery and the anterior surface of the Gerota fascia.

Setting Up the Dissection

Injury to important structures can be avoided by being aware of the following structures: the superior and inferior mesenteric arteries, the pancreas, the renal vessels, and the ureters. Up to 20% of patients will have accessory renal arteries and 2% to 3% of patients will have a retroaortic left renal vein. It is particularly important to recognize a retroaortic left renal vein because it may be inadvertently mistaken for a lumbar vein and ligated or, as the surgeon extends the cephalad dissection in search of the left renal vein, the pancreas and superior mesenteric artery may be injured. In the absence of a normally positioned left renal vein the attachments of the undersurface of the pancreas and duodenum may lie directly on the aorta.

Soft vessel loops are placed around the ureters as they are retracted laterally, and their medial aspect defines the lateral margins of resection. The ipsilateral gonadal vein is mobilized from its insertion in the inferior vena cava (right) or left renal vein (left) to the internal ring. It is important to encompass all the branches as well as the fibroalveolar and lymphatic tissue surrounding the gonadal vessels to avoid late paracolic recurrences from incomplete excision of the spermatic cord (Chang et al, 2002a).

Lymphadenectomy

Attention is initially directed to the left renal vein, and the renal perivascular lymphatic tissue is mobilized inferiorly. The anterior surface of the aorta is thus exposed. Then adrenal, spermatic, and lumbar branches are tied with 3-0 silk and divided. The dissection along the anterior surface of the left renal vein continues to the right until the anterior surface of the inferior vena cava is encountered and the first anterior "split" is then performed. The "split and roll" technique is illustrated in Figure 32–9. The right gonadal vein is ligated at the vena cava. Lymphatic tissue can then be rolled off the inferior vena cava laterally and medially as the dissection proceeds inferiorly. Lumbar veins are dissected, doubly ligated with 3-0 silk, and divided.

At this point, nerve-sparing techniques can be performed if clinically indicated (see later).

After control of the postganglionic sympathetic fibers has been secured with soft vessel loops as they course medially under the inferior vena cava to the anterior surface of the aorta, they are then retracted laterally. The anterior split on the surface of the aorta should then be carried inferiorly to the bifurcation of the common iliac arteries. The origin of the inferior mesenteric artery is identified. If necessary, this artery can be sacrificed without detrimental effects, provided that the marginal colonic artery is intact. The gonadal arteries should be ligated early to prevent the subadventitial hematoma that may result if they are avulsed. Following the anterior aortic split lymphatic tissue is retracted medially and laterally and lumbar arteries are dissected, doubly ligated with 3-0 silk, and divided. At this point the aorta and inferior vena cava have been separated from the retroperitoneal lymphatic tissue, which is attached to the posterior body wall and the renal arteries. The right and left renal arteries are skeletonized, and the lymphatic tissue is separated from the psoas fascia and anterior spinous ligament, which are the posterior limits of dissection. Great care should be taken to control lumbar vessels as they pass into the posterior body wall near the sympathetic chains to avoid possible injury to sympathetic innervation in attempting to control problematic bleeding.

Throughout the procedure it is important to ligate or clip the cut ends of lymphatic vessels, particularly in the region of the right renal artery and the diaphragmatic crus bilaterally, where large tributaries to the cisternae chyli are located.

Surgical margins should never be compromised in an effort to preserve ejaculation and, in the presence of documented or suspected metastatic disease in a primary RPLND, a full bilateral dissection remains the standard.

At the completion of a bilateral dissection the aorta, inferior vena cava, and renal vessels should be skeletonized and the anterior spinous ligament and psoas fascia should be visible, as should the stumps of the right and left gonadal vessels and inferior mesenteric artery.

The area of dissection is thoroughly irrigated with warm water, and lymphostasis and hemostasis must be ensured. The bowel and mesentery are inspected for injury, as are the kidneys and ureters. Intravenous indigo carmine may be given to rule out a urinary leak if ureteral integrity is in doubt. The posterior parietal

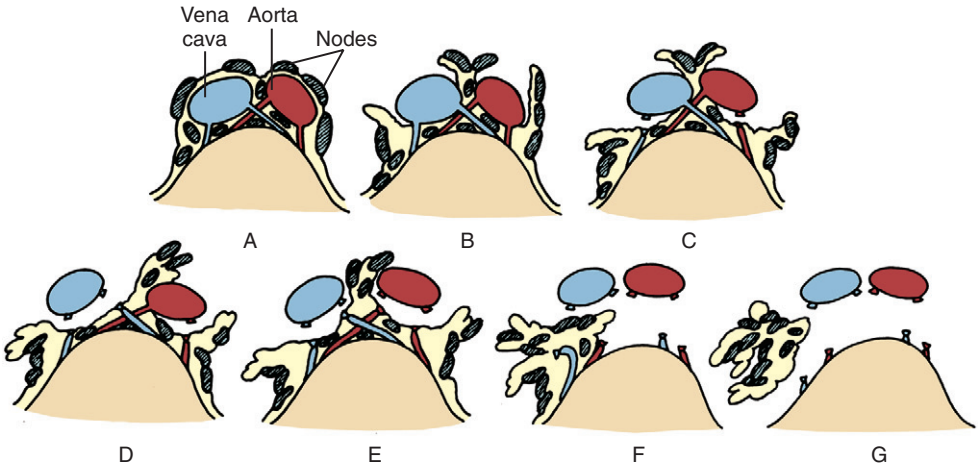


Figure 32–9. **A** to **G,** This diagram sequentially shows the "split and roll" technique that allows for en bloc removal of the nodal package. The lumbar vessels must be divided twice, first at the wall of the great vessels and again as they enter the foramina along side the vertebral bodies.

peritoneum is loosely approximated with interrupted 3-0 silk sutures to minimize the risk of small bowel obstruction and prevent direct adherence of bowel to the anterior surface of a great vessel. The abdomen is closed in a single layer with interrupted 1-0 polydioxanone suture.

Most patients can usually be extubated immediately after surgery and are managed with nasogastric tube drainage until ileus resolves. **Postoperative tachycardia is common owing to sympathetic discharge.** Fluid requirements are monitored closely and third space volume losses corrected as indicated. Diet is resumed when bowel activity returns, and volume status is monitored by pulmonary examination, net fluid balance, and daily weights. The remainder of the postoperative care is routine with average hospital stays of 5 to 7 days.

Prospective Nerve-Sparing Techniques

Appropriate candidates for nerve-sparing techniques include patients with clinical stage I and low-volume stage II NSGCT undergoing primary RPLND as well as a carefully selected subset of patients undergoing postchemotherapy lymphadenectomy (Pettus et al, 2009).

The most important aspect in performing nerve-sparing RPLND is the prospective identification and preservation of relevant sympathetic nerves, specifically (1) the sympathetic chains bilaterally, (2) the postganglionic sympathetic nerves arising from the sympathetic chains, and (3) the hypogastric plexus, which is the anastomosing network of nerve fibers anterior to the lower aorta (Fig. 32–10).

The sympathetic chains run parallel to the great vessels on either side of the spine. On the left side the sympathetic chain is lateral and posterior to the lateral border of the aorta (see Fig. 32–10) and postganglionic fibers leave at an oblique angle transversing lymphatic tissue posterolateral to the aorta as they join the hypogastric plexus (Klein, 1995). On the right side the sympathetic chain lies posterior to the inferior vena cava and the postganglionic fibers emerge from the medial edge of the vena cava and course at an oblique angle anterior to the aorta to join the hypogastric plexus. **Therefore it is important to note that an anterior "split" maneuver over the vena cava does not damage these fibers; however, dissection along the aorta before isolating and preserving these nerves individually results in their disruption** (Klein, 1995).

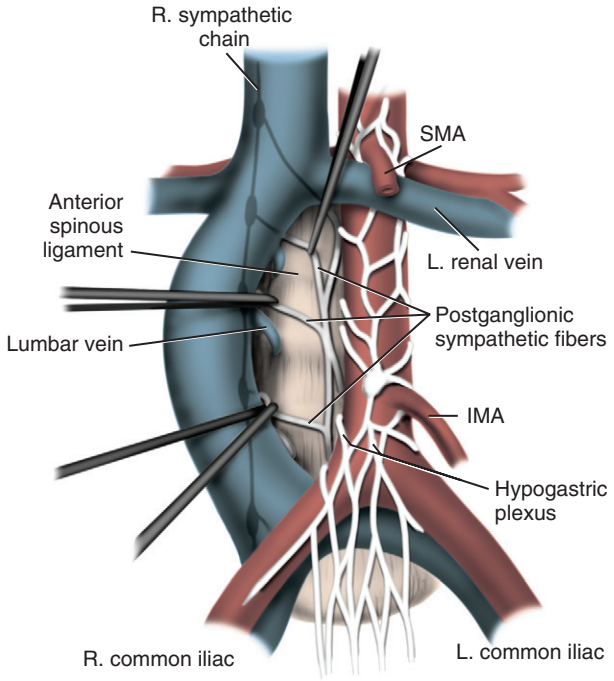


Figure 32–10. Nerve-sparing technique with soft vascular tapes around the right postganglionic branches of the sympathetic chains as they course in an oblique fashion toward the hypogastric plexus. Their relationship to the great vessels, lumbar veins, and root of the inferior mesenteric artery is shown. SMA, superior mesenteric artery; IMA, inferior mesenteric artery.

It appears that the most important nerves to preserve antegrade ejaculation are those arising from the L3 and L4 ganglia. It is often possible to preserve three or four separate nerve trunks. Nerve fibers often exit in close proximity to lumbar vessels, and great care must be taken in ligating them to avoid injury to these delicate nerve fibers.

These nerves are dissected free of surrounding fibrofatty and lymphatic tissue, encircled with soft vessel loops, and gently retracted out of harm's way. The lymphadenectomy then proceeds as described earlier within the appropriate template. Again, when performing nerve-sparing RPLND, dissection on the aorta should be done only after the nerve fibers have been isolated and

protected. Nerve-sparing techniques result in greater than 95% rates of antegrade ejaculation.

Intraoperative Neurostimulation

Several investigators have reported the use of intraoperative electrical stimulation of individual postganglionic sympathetic fibers to identify the most important nerves for antegrade emission (Recker and Tscholl, 1993; Kell and Jewett, 1999). Bladder neck closure and seminal emission can be documented endoscopically.

Laparoscopic Retroperitoneal Lymph Node Dissection

In an effort to reduce the perioperative associated with a primary RPLND, several investigators have evaluated the role of laparoscopic RPLND (L-RPLND) in the management of clinical stage I and IIA and low-volume residual disease after chemotherapy. L-RPLND has been shown to be technically feasible in the hands of dedicated experts, although it involves a steep learning curve. In addition to a faster convalescence and more favorable cosmetic results, postoperative morbidity, perioperative blood loss, and length of hospital stay appear to be reduced compared with open surgery (Janetschek et al, 1996; Nielsen et al, 2007; Rassweiler et al, 2008), although no direct comparative studies have been done and the morbidity, blood loss, and hospital stay in open RPLND have dropped significantly during the same time period (Beck et al, 2008).

However, the therapeutic efficacy of L-RPLND remains difficult to assess. First, the majority of patients with pathologic stage II disease receive chemotherapy after L-RPLND regardless of disease volume. A recent meta-analysis that included articles published since 2000 reported that 90% (126 of 140) of patients with positive nodes received postoperative chemotherapy. In spite of adjuvant chemotherapy the incidence of local and distant relapse rates were 1.4% (0.7 to 2.3) and 3.3% (1.8 to 4.6), respectively (Rassweiller et al, 2008).

Second, it remains unclear whether L-RPLND has been performed with therapeutic intent. One group reports that L-RPLND is used for diagnostic purposes only and "patients with positive nodes are definitively treated with adjuvant chemotherapy" (Janetschek et al, 2000). A second group reports that the "dissection was limited if grossly positive nodes were encountered" and the total number of nodes resected was significantly different if the nodes were positive or negative (14 ± 2 and 25 ± 3, respectively) (Nelson et al, 1999). Disappointingly, a follow-up study that combined selected data from four of the most experienced groups in the United States continued to show a higher node count in pathologic stage I disease (median 22) compared with pathologic stage II disease (median 15.5). It is counterintuitive and inappropriate to perform a more extensive and thorough dissection in the absence of disease and a more limited one in the presence of retroperitoneal metastasis (Carver and Sheinfeld, 2005). The node counts in three contemporary series appear low, with means reported of 14.4 (range 5 to 25) (Campero et al, 2009); 14 (IQR 11 to 20) (Nicolai et al, 2009); and 14 (IQR 10 to 18) (Castillo et al, 2007).

Third, there appear to be inconsistent and variable boundaries of dissection. Several laparoscopic surgeons recommend omitting dissection behind the great vessels and posterior to the lumbar vessels (Janetschek et al, 2000; Höltl et al, 2002) and advocate restricted templates even with pathologic stage II disease (Janetschek et al, 2000; Nielsen et al, 2007). The limitations of mapping studies and the incidence of extratemplate disease are discussed elsewhere in this chapter. Multifocality, contralateral, and extratemplate disease increase in pathologic stage II disease, and 20% to 30% will contain teratomatous elements, placing patients at risk for reoperative surgery, late relapse, and potentially inferior clinical outcomes (McKiernan et al, 2003; Eggener et al, 2007b). The indiscriminate use of chemotherapy is unnecessary in most cases of pN1 disease (Stephenson et al, 2005) and will not prevent relapse in cases of chemoresistant teratoma and a subset of viable cancer and increase long-term morbidity (Carver and Sheinfeld, 2005). Meinardi and colleagues (2000) reported a sevenfold increase in cardiovascular complications in men treated with cisplatin-based chemotherapy. On a positive note, a few highly specialized centers are now performing bilateral nerve-sparing RPLND, with preservation of antegrade ejaculation reported in 86% of patients. Follow-up is too short to evaluate the oncologic efficacy in pathologic stage II patients who did not receive chemotherapy (Steiner et al, 2008).

Most worrisome are patterns of relapse not seen with open RPLND. Pizzocaro and associates (2007) reported on eight patients with clinical stage IA disease, two of whom with relapsing liver disease making them at poor risk by International Germ Cell Cancer Collaborative Group (IGCCCG) criteria. Although both were salvaged, the burden of therapy is necessarily increased, as is the potential risk of subsequent failure. There have also been reports of patients with liver metastasis and diffuse abdominal and pelvic carcinomatosis after L-RPLND (Bosl, 2008; Castillo, 2008). The presumptive mechanism for this unusual pattern of metastasis is the pneumoperitoneum and positive intra-abdominal pressure required to perform L-RPLND.

Postchemotherapy Laparoscopic Retroperitoneal Lymph Node Dissection

The complication rate of L-RPLND after chemotherapy is higher than that of primary RPLND. Postchemotherapy desmoplastic reaction, as well as larger-volume residual disease requiring more extensive retroperitoneal dissection, increases the technical demands of the surgery. Nevertheless, investigators from Indiana University have reported a significant decrease in overall morbidity, major complications, and length of hospital stay (Mosharafa et al, 2004). Furthermore, for residual masses less than 2 cm, investigators from MSKCC reported a 4% major complication rate, including approximately a 2% incidence of bowel obstruction and a 1% to 2% incidence of chylous ascites (Patel et al, 2003).

In the postchemotherapy setting, with the exception of the Austrian group who report minimal morbidity in carefully selected patients with low-volume residual masses, the conversion rate to open surgery is high and very significant complications have been reported. Rassweiler and coworkers (1996) converted seven of nine (78%) postchemotherapy patients with stage II disease from L-RPLND to open RPLND, and Palese and associates (2002) reported that two (28.5%) of seven patients required open conversion. Furthermore, in the Johns Hopkins experience of seven postchemotherapy patients with L-RPLND for residual masses with a mean size of 1.9 cm, the overall complication rate was 57%. Major complications included transection of the external iliac artery requiring bypass graft in a patient with a 1.5-cm residual mass, renal artery hematoma in a patient with mild adenopathy requiring aortorenal bypass, and a 4.5-cm residual mass in a third patient who suffered renal artery thrombosis requiring nephrectomy, subsequent duodenal perforation, necrotizing fascitis, and a cerebrovascular event with neurologic sequelae (Palese et al, 2002).

The incidence of chylous ascites remains high (approximately 10%) after laparoscopic RPLND, in both the primary and the postchemotherapy setting (Wille et al, 2009). Consequently, in the postchemotherapy setting, L-RPLND cannot be endorsed as standard but rather as an operation to be evaluated in a formal prospective study by very experienced minimally invasive surgeons.

Key Points: RPLND

- Suprahilar metastasis are rare in low-stage NSGCT.
- Patients should be advised to complete sperm banking before RPLND.
- It is important to ligate or clip the cut end of lymphatic vessels.
- Surgical margins should never be compromised. In an effort to preserve ejaculation and in the presence of documented or suspected metastatic disease, bilateral RPLND remains the standard.
- Nerve-sparing techniques involve preservation of both sympathetic chains, the postganglionic sympathetic fibers, and the hypogastric plexus.
- Appropriate candidates for nerve-sparing techniques include patients with clinical stage I and low-volume stage II NSGCT undergoing primary RPLND as well as carefully selected patients undergoing PC-RPLND.
- The therapeutic impact of L-RPLND remains unknown.

TREATMENT OPTIONS FOR LOW-STAGE GERM CELL TUMORS

Clinical Stage I NSGCT

Retroperitoneal Lymph Node Dissection

In the United States and parts of Europe the conventional approach to patients with clinical stage I NSGCT has been bilateral RPLND, and it remains the standard against which all diagnostic and therapeutic alternatives must be judged (Whitmore, 1983; Hesketh et al, 1990; Chang and Sheinfeld, 2000). **As noted earlier, RPLND (1) provides the most accurate N categorization of the retroperitoneal lymph nodes that are the first site of metastatic spread in approximately 90% of GCT and (2) is curative in the majority of patients with pathologic stage I (pNO) and low-volume retroperitoneal disease (pN1) and avoids the persistence of chemorefractory teratoma in the retroperitoneum** (Sheinfeld et al, 2003). **Relapses in the retroperitoneum are rare in the hands of experienced surgeons after properly performed RPLND. Primary RPLND is associated with negligible mortality and minimal and declining morbidity rates** (Baniel et al, 1994; Stephenson and Sheinfeld, 2004; Stephenson et al, 2005; Beck et al, 2009).

Nerve-sparing techniques should be considered the operation of choice, with reported antegrade ejaculation rates greater than 95% (Donohue et al, 1990). Surgical margins should never be compromised in an attempt to preserve ejaculation, and if positive nodes are noted or suspected at the time of RPLND a bilateral dissection is warranted, particularly for right-sided primary tumors, because contralateral crossover is more common than for left-sided primary tumors.

Surveillance

The strategy of surveillance after orchiectomy was first reported by Peckham and colleagues in 1979. The rationale for surveillance protocols rests with the improved accuracy of clinical staging, the ability of cisplatin-based chemotherapy to cure early relapses, and the probability of surgical cure after radical orchiectomy alone and the possible infertility resulting from RPLND due to retrograde ejaculation (Sheinfeld, 1994; Bosl et al, 2000, 2005).

Approximately 25% of patients with T1N0M0 disease and normal serum tumor markers experience relapse while on surveillance protocols (Hoskin et al, 1986; Swanson, 1993; Lashley et al, 1998; Sogani et al, 1998). **The retroperitoneum is the most common site of relapse; the lungs or markers alone occur less frequently, and other visceral metastases are rare.** Survival rates after therapy for surveillance failures range from 96% to 100% (Hoskin et al, 1986; Swanson, 1993; Lashley et al, 1998; Sogani et al, 1998).

A number of factors predictive for retroperitoneal and/or systemic failure have been identified. The presence of lymphovascular invasion within the primary tumor (now included as T2), higher T stage (T2 to T4), that is, tumor involvement of the cord, capsule, or scrotum, and a high percentage of embryonal carcinoma are associated with a higher likelihood of relapse (Read et al, 1992; Gels et al, 1995; Nicolai et al, 1995; Heidenreich et al, 1998; Sogani et al, 1998). Approximately 50% of patients with T2 to T4 tumors experience relapse compared with 15% of patients with T1 tumors. One study from MSKCC noted that almost 80% of patients with clinical stage I and pure embryonal carcinoma who underwent RPLND had pathologic stage II disease (Pohar et al, 2003).

Patient compliance cannot be overemphasized, because strict adherence to periodic follow-up evaluations is critical. Most relapses occur within the first 2 years and are rare after 5 years (Bosl et al, 2005).

Of concern is the increased incidence of second malignancies reported in patients undergoing surveillance, presumably owing to the multiple CT scans required. Using the Surveillance Epidemiology and End Results (SEER) database, a retrospective study of, 334 patients demonstrated an odds ratio of 1.74 (1.02 to 2.95) for second malignancies associated with radiation exposure in patients on surveillance compared with those who underwent RPLND (Chamie et al, 2008). More recently, Tarin and colleagues (2009) calculated the risk of a second malignancy associated with image-related radiation during surveillance for clinical stage I NSGCT and using the National Comprehensive Cancer Network (NCCN) guidelines for CT they reported a relative risk of 15.2 compared with a single post-RPLND scan. The lifetime cancer risk ranged from 1 in 52 (1.9%) for an 18-year old to 1 in 63 (1.2%) for a 40-year old. This increases to 1 in 39 (2.6%) and 1 in 85 (1.6%), respectively, if CT of the chest is included (Tarin et al, 2009).

Chemotherapy

In an attempt to avoid the potential morbidity of an RPLND, several European groups have studied the role of two cycles of cisplatin-based adjuvant chemotherapy in high-risk clinical stage I NSGCT (Oliver et al, 1992; Cullen et al, 1995; Studer et al, 2000). More recently, investigators have examined the efficacy of one cycle of bleomycin-etoposide-cisplatin (BEP) for "high risk" clinical stage I NSGCT and reported encouraging short-term results (Albers et al, 2008; Tandstad et al, 2009). A detailed

discussion of these studies is beyond the scope of this chapter (see Chapter 31).

Although less than 5% of these patients relapse, they are exposed to both the short- and long-term toxicities of chemotherapy, such as myelosuppression, neuropathy, Raynaud phenomenon, ototoxicity, nephrotoxicity, and the risk of acute leukemia. Furthermore, given the paucity of long-term follow-up, the risk of late relapse secondary to unresected chemoresistant teratoma remains unknown.

Investigators at MSKCC reported a 21% incidence of teratoma in patients with pathologic stage II disease, including 6 of 64 (9%) with clinical stage I disease (Sheinfeld et al, 2003a). Although teratomatous elements in the orchiectomy specimen predict for teratoma in retroperitoneal metastasis, its absence in the primary tumor does not preclude its presence in the retroperitoneum (Toner et al, 1990; Foster and Donohue, 1998; Beck et al, 2002; Sheinfeld et al, 2003a).

Clinical Stage IS ("Marker Only" Disease)

Patients with persistently elevated serum tumor markers after radical orchiectomy but negative CT scans of the chest, abdomen, and pelvis should undergo primary cisplatin-based chemotherapy because systemic disease is usually present. Davis and associates (1994) reported that all 11 patients with "marker only" disease who underwent primary RPLND had persistently elevated markers postoperatively. Saxman and colleagues (1996) also reported a high rate of systemic failures in patients with "serologic disease" only after initial surgery. RPLND should be performed if there is radiographic evidence of retroperitoneal disease after chemotherapy. Dash and coworkers (2008) reported the MSKCC experience and noted that 6 of 14 (43%) patients who underwent PC-RPLND in this setting had teratoma ± viable cancer in the resected specimen.

Clinical Stage II Nonseminomatous Germ Cell Tumor

The decision to treat patients with clinical stage II NSGCT initially with either RPLND or cisplatin-based chemotherapy depends primarily on (1) extent of disease, (2) serum tumor marker status, and (3) presence or absence of tumor-related back pain (Bosl and Motzer, 1997).

Retroperitoneal Lymph Node Dissection

Patients best suited for RPLND are those with clinical stage IIA and rare, unifocal IIB tumors less than 3 cm with ipsilateral disease restricted to the primary landing zone and normal serum tumor marker levels (Bosl and Motzer, 1997; Bosl et al, 2005). **The presence of suprahilar, retrocrural, pelvic, or inguinal lymphadenopathy, contralateral or multifocal disease, or back pain implies either unresectable disease or metastases beyond the locoregional lymph nodes, and these patients should receive initial cisplatin-based chemotherapy** (Bosl et al, 2005).

Patients with clinical IIA or IIB disease and elevated serum tumor marker levels should be considered for primary cisplatin-based chemotherapy, because this usually reflects systemic disease (Sheinfeld and Motzer, 2004). Investigators at MSKCC reported that elevated serum tumor marker levels before RPLND were the most predictive factor for (1) systemic relapse in patients with low-volume (pN1) retroperitoneal disease treated without adjuvant chemotherapy and (2) for persistent NSGCT (usually persistent serum tumor marker elevation) despite complete resection of high-volume (pN2, pN3) retroperitoneal disease (Rabbani et al, 1999a, 1999b; Sheinfeld et al, 1999a, 1999b; Bosl et al, 2000; Stephenson et al, 2005, 2007).

A study of 453 patients who underwent primary RPLND at MSKCC showed that by excluding patients whose markers fail to normalize or are clinical stage IIB after 1999, the proportion of patients with pathologic stage II low-volume (pN1) retroperitoneal disease increased significantly (40% before vs. 64% after 1999, $P = .01$) without significantly affecting the rate of retroperitoneal teratoma (21% vs. 22%, $I = .89$) or pathologic stage I (56% vs. 67%, $P = .06$). For patients who did *not* receive chemotherapy, the 4-year progression-free probability improved significantly from 83% before 1999 to 96% after 1999. Consequently, for patients with normal serum tumor markers and clinical stage I to IIA the low rate of systemic progression and the 22% incidence of retroperitoneal teratoma supports the therapeutic role of RPLND (Stephenson et al, 2005).

After RPLND a meticulous pathologic assessment of the retroperitoneal lymph nodes is essential to assess prognosis and direct further therapy (Motzer and Bosl, 1993). With the exception of the Testicular Cancer Intergroup Study, most investigators have reported that the risk of relapse is related to the size and/or number of involved lymph nodes (Motzer and Bosl, 1993; Sheinfeld, 1994). Careful observation is preferred in compliant patients with fully resected low volume (pN1) disease, that is, five or fewer positive nodes *and* all nodes less than 2 cm with no evidence of extranodal extension, because these patients have a low risk of relapse (Pizzocaro et al, 1985; Richie and Kantoff, 1991; Rabbani et al, 1999a, 1999b; Stephenson et al, 2005). Three cycles of cisplatin-etoposide-bleomycin (PEB) or four cycles of etoposide-cisplatin (EP) will be necessary in the event of relapse.

Conversely, patients with high-volume nodal disease have a relapse rate or 50% to 90% (Fraley et al, 1985; Williams et al, 1987; Donohue et al, 1995); therefore patients with six or more positive nodes, any node greater than 2 cm, or any extranodal extension should be considered for two cycles of adjuvant cisplatin-based chemotherapy.

The randomized Testicular Cancer Intergroup Study showed that in patients with pathologic stage II NSGCT observation with standard treatment at relapse and two cycles of adjuvant chemotherapy resulted in equivalent survival rates (Williams et al, 1987). A number of cisplatin-based regimens have proven efficacy is preventing relapse after RPLND (Williams et al, 1987; Weissbach and Hartlapp, 1991). The PEB regimen is favored by the Indiana University group (Behnia et al, 2000); however, Kondagunta and coworkers (2004) have shown that an EP regimen was adequate in preventing relapse in patients with resected high volume disease.

Only patients who undergo complete resection and are clinically free of disease after RPLND are candidates for two cycles of cisplatin-based chemotherapy to prevent relapse. The management of patients with incompletely resected adenopathy or with any clinical evidence of disease (elevated hCG and/or AFP, lung nodule, retrocrural adenopathy) is the same as that for patients with systemic metastasis, that is, three or four cycles of cisplatin-based chemotherapy (Motzer and Bosl, 1993).

Fertility in Low-Stage Germ Cell Tumors

Up to 60% of patients diagnosed with testicular cancer have subnormal pretreatment semen analysis (Nijman et al, 1988). **When compared with healthy controls or males with lymphoma, testicular cancer patients were found to have lower total sperm counts and higher serum follicle-stimulating hormone levels. Similar findings have also been reported in patients with carcinoma in situ** (Petersen et al, 1999). These abnormal parameters before treatment suggest a primary germ cell defect in testicular cancer patients. After orchiectomy, improvement in sperm parameters is seen, implying a reversible defect in fertility that may be due to circulating hCG or psychological stress. Despite this high incidence of oligospermia at the time of diagnosis, while on surveillance 65% of men are able to achieve a pregnancy after orchiectomy (Herr et al, 1998).

Antegrade ejaculation can be preserved in 95% to 98% of patients with clinical stage I disease undergoing nerve-sparing RPLND. Paternity rates as high as 74% have been reported after RPLND for these patients (Foster et al, 1994).

Key Points: Treatment of Low-Stage NSCGT

- Patients whose tumor markers fail to normalize after radical orchiectomy should receive cisplatin-based induction chemotherapy regardless of radiographic findings.
- Bilateral RPLND is the standard template for patients with pathologic stage II NSGCT.
- Although teratoma is histologically benign, its biologic potential is unpredictable and it may grow or undergo somatic (malignant) transformation.
- Patients who have an incomplete resection with pathologic stage II NSGCT or those with any clinical evidence of disease (elevated hCG and/or AFP, lung nodules, retrocrural adenopathy) after primary RPLND require cisplatin-based induction chemotherapy.

SURGERY FOR HIGH-STAGE GERM CELL TUMORS

The initial treatment of patients with advanced GCTs is cisplatin-based combination chemotherapy (Sheinfeld, 1994; Bosl et al, 2000), and a number of effective regimens have been used over the past 30 years (Einhorn and Donohue, 1977; Bosl et al, 1988).

Preoperative Preparation and Timing of Surgery

The postchemotherapy patient mandates thorough reevaluation to assess response to therapy before surgical intervention. This must include repeat serum tumor marker evaluations, a complete blood cell count, and blood chemistries with attention directed to platelet, neutrophil, and white blood cell counts. Operative blood chemistries are checked with particular attention to serum creatinine value after cisplatin-based therapy. Repeat CT of the retroperitoneum and repeat imaging of any other site of prechemotherapy disease are done. Surgical intervention should be delayed until recovery of the white blood cell count (>3.5) and platelet count (>100,000/mm^3) into the normal range, which usually occurs 3 to 4 weeks after the final cycle of chemotherapy.

Preoperative evaluation should include pulmonary function testing in all patients treated with bleomycin. A restrictive pulmonary fibrosis due to alveolar edema and increased collagen deposition after bleomycin treatment can occur (Hay et al, 1991). **This pulmonary fibrosis is believed to increase susceptibility to alveolar edema when patients are exposed to high levels of inspired oxygen concentration and fluid overload** (Goldiner et al, 1978; Zwikler et al, 1994). Donat and Levy (1998) reviewed perioperative pulmonary complications of 77 patients treated with RPLND after bleomycin chemotherapy and found a 57% rate of pulmonary complications. Preoperative symptoms, pulmonary function testing, and history of acute bleomycin were not predictive of postoperative pulmonary complications. **The strongest risk factor for postoperative complications were overall fluid requirements and blood transfusions** (Donat and Levy, 1998). Meticulous management of intravenous fluid in the perioperative period is imperative in patients treated with bleomycin-containing chemotherapeutic regimens (Donat and Levy, 1998).

Histologic Findings and Management Controversies

Postchemotherapy surgery has evolved into an integral part of the management of patients with advanced GCTs; however, its role has undergone continued refinement over the past 2 decades (Sheinfeld et al, 1997). Prior to the development of cisplatin-based chemotherapy, surgical cytoreduction or "debulking" was followed by postoperative chemotherapy, resulting in high relapse rates, significant morbidity, and poor survival rates (Merrin et al, 1976; Donohue et al, 1980).

Improvements in staging techniques such as with CT and MRI, the reliability of serum tumor markers AFP and hCG, and the advent of effective cisplatin-based chemotherapy have led to the integration of surgery as an adjunct after cytoreductive chemotherapy (Donohue et al, 1982, 1998; Sheinfeld and Bajorin, 1993). This multidisciplinary approach has resulted in survival rates of 70% to 80% of patients with advanced GCT (Einhorn, 1981; Bosl et al, 1986, 2000).

Increased serum concentrations of AFP and hCG after primary cisplatin-based chemotherapy are often characterized by unresectable, viable GCT, and second-line "salvage" chemotherapy is usually recommended for these nonresponders (Sheinfeld and Bajorin, 1993; Bosl et al, 2000). A possible exception are patients with an increased serum AFP level, teratoma in the primary tumor, and a postchemotherapy cystic mass in the retroperitoneum. Investigators at MSKCC reported that fluid from cystic teratoma contained variably increased levels of hCG and AFP in all patients with these features and that complete resection resulted in postoperative normalization of serum AFP (Beck et al, 2004). On the other hand the recommendations for adjunctive surgery for patients who have undergone chemotherapy with appropriate normalization of serum tumor markers are variable and occasionally contradictory (Bajorin et al, 1992). Although most clinicians agree that surgical

exploration is indicated for patients with normal tumor marker levels and residual radiographic abnormalities, at the present time there are no standard guidelines for observation rather than adjunctive surgery (Bajorin et al, 1992; Sheinfeld et al, 1997, 2004). Reported variables for patients in whom surgery can be safely omitted include residual masses less than 1.5 cm (Stomper et al, 1985; Carter et al, 1987), "normal" postchemotherapy CT and absence of teratomatous elements in the primary tumor (Gelderman et al, 1988), and a greater than 90% volume reduction of the prechemotherapy mass, a residual mass less than 1.5 cm, and no teratoma in the primary tumor (Donohue et al, 1987).

Earlier published reports demonstrated that the pathologic findings at RPLND after cisplatin-based chemotherapy and normalization of serum tumor marker levels were necrosis/fibrosis, teratoma, or persistent viable carcinoma, each in approximately one third of cases (Donohue et al, 1980). More recently investigators have reported a decrease in the proportion of patients with viable GCT (Table 32–1). This is commonly attributed to stage migration and more effective chemotherapy regimens (Bosl et al, 1988; Carver et al, 2007a).

Current investigators note that, in the retroperitoneum, necrosis/fibrosis compromises 45% to 50% of pathologic findings after primary chemotherapy, teratoma another 40%, and viable GCT the remaining 10%, although variations in the various series probably reflect patient selection and stage migration (see Table 32–1). After second-line or "salvage" chemotherapy the distribution of histologic findings is markedly different, with viable GCT noted in approximately 50% of resected specimens, teratoma in 40%, and necrosis/fibrosis in only 10% of cases (Fox et al, 1993).

Table 32–1.

Postchemotherapy Pathologic Findings in Patients with High-Stage Germ Cell Tumors

AUTHOR	NO. OF PATIENTS	NECROSIS	TERATOMA	CARCINOMA
Donohue et al (1982)	51	16 (31%)	16 (31%)	19 (38%)
Bracken et al (1983)	23	9 (40%)	7 (30%)	7 (30%)
Tait et al (1984)	73	25 (34%)	32 (44%)	16 (22%)
Freiha et al (1984)	40	21 (53%)	18 (45%)	1 (2%)
Pizzocaro et al (1985)	36	16 (44%)	10 (28%)	10 (28%)
Donohue et al (1987)	80	35 (44%)	33 (41%)	12 (15%)
Gelderman et al (1988)	24	17 (71%)	7 (29%)	—
Harding et al (1989)	42	19 (45%)	14 (33%)	9 (22%)
Toner et al (1990)	122	57 (47%)	48 (39%)	17 (14%)
Mulders et al (1990)	55	31 (56%)	12 (22%)	12 (22%)
Aass et al (1991)	173	85 (49%)	50 (29%)	38 (22%)
Fossa et al (1992)	78	51 (65%)	22 (28%)	5 (7%)
Sonneveld et al (1998)*	110	49 (45%)	51 (46%)	10 (9%)
Stenning et al (1998)	153	45 (29%)	85 (56%)	23 (15%)
Donohue et al (1998)	870	221 (26%)	452 (52%)	197 (22%)
Steyerberg et al (1998)	172	77 (45%)	72 (42%)	23 (13%)
Carver et al (2008)	504	248 (49%)	199 (40%)	57 (11%)

*Three additional patients underwent exploratory laparotomy but no specimen was resected.

Viable Cancer

The patient's prognosis is related to serum marker level at the time of RPLND, prior treatment burden, and the pathologic findings of the resected specimen and completeness of resection (Donohue et al, 1998). The relapse rate of patients with necrosis/fibrosis or mature or immature teratoma is 5% to 10% after complete resection (Toner et al, 1990; Fossa et al, 1992; Donohue et al, 1998; Carver et al, 2007a); therefore additional chemotherapy is not required. However, if viable GCT is present at any site but all disease is completely resected, two additional cycles provide survival benefit in this subset of patients (Fox et al, 1993). Fox and colleagues (1993) reported that 19 of 27 (70%) patients with completely resected viable GCT after primary chemotherapy followed by two cycles of postoperative chemotherapy remained disease-free compared with none of 7 patients without additional chemotherapy. Similarly, Logothetis and Samuels (1984) and Geller and associates (1989) reported survival rates of 53% and 66%, respectively, in patients undergoing complete resection of viable GCT and additional postoperative chemotherapy. Fizazi and colleagues (2001) challenged the therapeutic benefit of additional chemotherapy in completely resected GCT after induction chemotherapy in a multicenter, retrospective analysis of 146 patients. Three independent prognostic variables for survival were identified: (1) complete resection; (2) good-risk IGCCCG classification; and (3) less than 10% viable malignant cells. Additional chemotherapy appeared to benefit only those with one risk factor but not those without risk factors or with two or more risk factors (Fizazi et al, 2001). The overall survival rates for patients with no, one, or two or three risk factors were 100%, 83%, and 51%, respectively (Fizazi et al, 2001). A follow-up study validated this prognostic index with 5-year overall survival rates of 90%, 86%, and 52% for patients with zero, one, and two or three risk factors. Again, the authors emphasized the need for a complete resection as the most important variable in achieving cure (Fizazi et al, 2008). Fox and associates (1993) reported that two additional cycles of chemotherapy did not have any therapeutic benefit after salvage chemotherapy.

Teratoma

Despite the benign histologic appearance of teratoma, its clinical behavior is unpredictable, suggesting benefit in early and complete resection.

First, teratoma may grow, obstruct or invade adjacent structures, and become either unresectable or increase the technical demands and/or morbidity of a subsequent procedure (Logothetis et al, 1982; Logothetis and Samuels, 1984; Sheinfeld and Bajorin, 1993; Carver et al, 2007c).

Second, there is the risk of somatic (malignant) transformation, that is, the development of non–germ cell malignant elements such as sarcoma or carcinoma (Little et al, 1994; Comiter et al, 1998; Motzer et al, 1998). At present there is no reliable way to predict this event; therefore, teratoma cannot be known a priori to be benign. The overall incidence is

6% to 8% but increases to almost 20% in the setting of late relapse or redo PC-RPLND (McKiernan et al, 2003; Sharp et al, 2008). The most common histologic subtypes include sarcoma, particularly rhabdomyosarcoma and carcinomas (Little et al, 1994; Motzer et al, 1998). Toner and coworkers (1990) reported that 3 of 48 (6%) patients with resected teratoma had non–germ cell elements, whereas Little and associates (1994) noted that 45 of 557 (8%) patients undergoing PC-RPLND had malignant transformation of resected teratoma. Thirteen of the 19 patients with sarcomatous elements and 10 of 18 with nonsarcomatous disease remain disease free after surgery (Little et al, 1994). Complete surgical resection is the treatment of choice for this group of chemoresistant tumors and offers patients the best chance for survival (Little et al, 1994; Comiter et al, 1998; Motzer et al, 1998).

Motzer and colleagues (1998) performed conventional cytogenetic or molecular genetic techniques on 12 patients diagnosed with teratoma with malignant transformation (TMT). The isochromosome 12p [i (12p)] was identified in 11 patients, confirming GCT clonality. Additionally, chromosomal abnormalities associated with the transformed histology are also noted.

Third, it has been shown that recurrence of teratoma is related to completeness of resection. Sonneveld and associates (2007) reported a fourfold increase in the relapse rate for patients whose tumor was incompletely resected. Loehrer and colleagues (1986) reported on 51 patients with resected teratoma after cisplatin-based chemotherapy. Twenty (39%) patients experienced relapse either with teratoma (10 patients) or visible GCT (10 patients). Predictors of relapse on univariate analysis included initial tumor burden, somatic transformation, and site of residual disease (mediastinum). In an updated series from the Indiana University group on resected teratoma greater than 10 cm 2- and 5-year disease-free survivals of 86% and 75% were reported with a mean follow-up of 42 months. The 2-year disease-free survival was 86% for patients with retroperitoneal disease only compared with 79% and 41% for patients with two to three sites and four sites, respectively ($P = .004$) (Beck et al, 2009).

A series from MKSCC on 210 patients with PC-RPLND teratoma reported a relapse rate of only 14% (30 patients), with half experiencing relapse with teratoma and 17% with somatic transformation and the remainder with viable GCT. Larger postchemotherapy size and intermediate or poor IGCCCG risk classification were independent predictors of relapse after complete resection (Carver et al, 2007c).

Given the potential for teratoma to recur adjacent to the resected specimen it is prudent that imaging with abdominal or pelvic CT should be part of the surveillance protocol for patients with resected teratomas larger that 2 cm (Einhorn, 2007).

Fourth, teratoma is associated with late recurrence (Loehrer et al, 1986; Gelderman et al, 1988; Gels et al, 1995). Loehrer and colleagues (1986) noted that 10 of 51 (19%) patients with teratoma developed late recurrence, with similar rates for mature teratoma (17%) and immature teratoma (23%). Roth and associates (1988) reported that all 7 patients with relapse after 24 months of achieving complete response had teratoma in the primary and/or retroperitoneal specimen. Furthermore, most recurrences developed locally, implying incomplete resection and foci of residual disease (Gelderman et al, 1988; Gerl et al, 1995; McKiernan et al, 2003).

Fibrosis

In an effort to reduce treatment-related morbidity, investigators have attempted to predict fibrosis and thus identify patients who could safely avoid postchemotherapy surgery. This approach is predicated on (1) the reliability of accurately predicting fibrosis; (2) comparable clinical outcomes with timely and appropriate treatment at relapse; and (3) the assumption that surgery for residual masses that yields only fibrosis is never therapeutic. Currently, fibrosis comprises 45% to 50% of resected retroperitoneal specimens after PC-RPLND.

Of 80 patients with sequential CT scans before and after chemotherapy reported from Indiana University, 15 were without teratoma in the primary tumor and at least a 90% decrease in the retroperitoneal tumor volume determined by the formula $v = 0.52d^2$ and none had viable GCT or teratoma (Donohue et al, 1987). However, in a subsequent analysis from the same institution, Debono and associates (1997) found that only 74% of patients with these same criteria who were observed were continuously free of disease and 4 of 6 experienced relapse with retroperitoneal disease. Nichols and coworkers (2008) reported on 56 patients with advanced NSGCT who were observed after a clinical complete response with induction chemotherapy: four (7%) patients experienced a relapse (median follow-up of 34 months) and were salvaged with further treatment, including PC-RPLND for retroperitoneal recurrences.

Observation has been recommended in patients whose tumor marker levels have normalized and in whom the postchemotherapy CT scan is "normal" (Debono et al, 1997; Foster and Donohue, 1998). The definition of a normal postchemotherapy CT scan varies and includes lymph node diameters of 10 mm or less (Fossa et al, 1989c) and 20 mm or less (Mead et al, 1992). A significant number of resected specimens will contain teratoma and/or viable GCT despite strict normal CT criteria (Sheinfeld et al, 1997). Fossa and associates (1989c) reported that 12 of 37 (30%) patients with normal postchemotherapy serum tumor marker levels and CT scan (≤10 mm) had teratoma and 1 patient had viable GCT. Toner and coworkers (1990) reported that 8 of 39 (21%) patients with residual masses less than 1.5 cm had residual teratoma or viable GCT. Oldenburg and colleagues (2003) reported that one third of retroperitoneal postchemotherapy masses less than 2 cm harbored either teratoma or viable GCT, including 20% in masses less than 5 mm. Debono and associates (1997) reported 5 patients (6%) with recurrence in a group of 78 patients with normal postchemotherapy CT scan who were observed.

Positron emission tomography (PET) has been studied in the evaluation of postchemotherapy residual masses in both seminoma and NSGCT (Stephens et al, 1996; Ganjoo et al, 1999). In NSGCT the major limitation is the inability to distinguish teratoma from necrosis (Stephens et al, 1996). In the nonseminoma setting, viable GCT was not reliably predicted and PET is therefore not recommended (Ganjoo et al, 1999).

Although teratoma in the primary tumor predicts the presence of teratoma and viable GCT in the postchemotherapy resection despite volume reduction of the original mass (Donohue et al, 1987; Toner et al, 1990; Fossa et al, 1992; Debono et al, 1997; Beck et al, 2002), **teratoma may be found in the retroperitoneum despite its absence in the orchiectomy specimen** (Toner et al, 1990; Beck et al, 2002). Toner and coworkers (1990) reported that of 75 patients without teratoma in orchiectomy specimen, 25 had resected teratoma after chemotherapy. Furthermore, of 17 patients with a residual mass less than 1.5 cm there was 90% or more shrinkage of the retroperitoneal mass and no evidence of teratoma in the primary specimen, 3 patients (18%) had teratoma, and 2 patients (12%) had viable GCT in the resected specimen. Beck and associates (2002) noted that 48% of patients with teratoma in the retroperitoneal specimen after

chemotherapy did not have teratomatous elements in the primary tumor.

Several logistic regression models have been developed to calculate the probability of necrosis (Toner et al, 1990; Steyerberg et al, 1995). In Steyerberg and colleagues' model, predictors of necrosis included the absence of teratoma in the primary tumor, normal prechemotherapy hCG and AFP levels, a small prechemotherapy or postchemotherapy mass, and a large volume reduction in the retroperitoneal mass.

Multiple studies show that approximately 20% of patients predicted to have fibrosis will harbor either teratoma or viable GCT (Toner et al, 1990; Steyerberg et al, 1995). **No single criterion or combination of criteria predict a negative pathology with sufficient accuracy to eliminate the risk of residual teratoma or viable GCT and thus obviate PC-RPLND** (Sheinfeld et al, 1997; Bosl et al, 2000; Carver et al, 2007c). **Therefore the decision to recommend postchemotherapy surgery depends on the frequency of viable GCT, the biologic potential of teratoma, and the morbidity of the RPLND** (Bosl et al, 2000). **If viable GCT is present, it is partially drug resistant and will progress if left unresected.** When these patients experience relapse, more intensive salvage high-dose or ifosfamide-based chemotherapy is required at the time of relapse (Motzer et al, 1992; Loehrer et al, 1988; Kondagunta et al, 2004; Einhorn, 2007). This therapy would possibly have been avoided had RPLND been performed, viable GCT identified, and two additional cycles of chemotherapy administered. The cure rate of recurrent GCT to ifosfamide-based salvage regimens is approximately 25% (Motzer et al, 1992; Loehrer et al, 1988). Conversely, if viable GCT is completely resected and two additional cycles of cisplatin-based chemotherapy are given, cure rates between 50% and 70% are likely (Toner et al, 1990; Fox et al, 1993). As noted earlier, unresected teratoma may grow rapidly ("growing teratoma syndrome"), invade or compromise local structures, become unresectable, or undergo malignant transformation (Logothetis and Samuels, 1984; Little et al, 1994; Sheinfeld and Bajorin, 1993; Motzer et al, 1998).

The data suggest that undertreatment of patients with advanced GCT after chemotherapy may result in inferior clinical outcomes compared with those who have immediate surgery. Prompt recognition and appropriate treatment of disease progression or relapse after chemotherapy do not appear to compare favorably with immediate postchemotherapy surgery. In a nonrandomized study comparing 330 patients who underwent salvage surgery after relapse, Hendry and coworkers (2002) reported lower rates of complete resection (72% vs. 87%), relapse-free survival (62% vs. 83%), and overall survival (56% vs. 89%) and higher rates of viable GCT (49% vs. 8%) and TMT (6% vs. 1%) in the salvage group. Debono and colleagues (1997) reported that 4 of 78 patients with a complete clinical response who were observed after chemotherapy subsequently died of disease and that only 78% of 27 patients with a teratoma-negative primary tumor, normal serum marker levels, and a 90% or greater radiographic response who were initially treated expectantly were free of disease. Conversely, of 140 patients with less favorable clinical parameters (less than 90% radiographic response with or without teratoma in primary tumor) who underwent immediate postchemotherapy surgery, 4 died of their disease and 94% were free of disease (Debono et al, 1997).

The concept that a pathologically negative surgical specimen (i.e., fibrosis) is of no therapeutic benefit needs to be reassessed. The cumulative experience of 187 patients who underwent PC-RPLND with elevated serum tumor marker levels showed normalization of markers in almost 90% of the 24 patients with necrosis, and they were rendered disease free (Wood et al, 1992b; Beck et al, 2005; Ong et al, 2008). This finding suggests that a subset of patients derive therapeutic benefit from surgery despite a negative pathology. Pathologic sample error may account for this observation, and step-sectioning might identify foci of previously undiagnosed disease.

Recently, investigators from Indiana University performed laser microdissection analysis and fluorescence in-situ hybridization for chromosome arm 12p in stromal cells from 27 patients whose retroperitoneal specimen revealed only fibrosis. Overall, 88% of the cases had genetic alterations as either loss of heterozygosity for genes implicated in germ cell transformation or chromosome arm 12 p abnormalities. The authors conclude that "benign-appearing fibrous lesions could represent a previously unrecognized germ cell tumor element rather than a reactive fibroproliferative response" (Cheng et al, 2007).

The debate over RPLND after chemotherapy is centered on whether residual disease less than 1 cm in diameter requires RPLND (frequently called a "complete remission," even if a small mass is visualized), particularly when there is no teratoma in the primary site. However, even in this most favorable setting, 15% to 20% of resected specimens will contain either teratoma or viable GCT. **Most authors recommend RPLND if residual retroperitoneal disease after chemotherapy measures more than 1 cm in greatest transverse diameter.** This rule of thumb should be followed in the case of these patients and patients referred to experienced urologists if necessary to minimize risk. **When metastatic disease did not initially involve the retroperitoneum, then RPLND may not be necessary after chemotherapy if imaging is normal.** Under any circumstance compliance with follow-up after chemotherapy, and surgery if required, is necessary to detect recurrent disease and minimize the risks associated with late relapse or other unfavorable settings.

Late Relapse

Finally, the data suggest that an uncontrolled retroperitoneum may be a predisposing factor for late relapse (Baniel et al, 1995a, 1995c; George et al, 2003; Carver and Sheinfeld, 2005; Sharp et al, 2008).

Late recurrence of GCT of the testis is defined as relapse after a disease-free interval of at least 2 years in the absence of a second primary testicular tumor. The reported incidence of late relapse of GCT is 2% to 4% and appears to be increasing (George et al, 2003; Carver and Sheinfeld, 2005). Almost 60% of late relapses occur beyond 10 years, emphasizing the need for prolonged follow-up. Approximately 50% of patients with late relapses will be symptomatic, and approximately 60% will have an elevated AFP level (Baniel et al, 1995a, 1995c; George et al, 2003; Carver and Sheinfeld, 2005; Dieckmann et al, 2005; Sharp et al, 2008).

Although late relapses of GCT have been reported in the chest, neck, liver, brain, and pelvis, **the most common site is the retroperitoneum,** regardless of initial stage, clinical presentation, or prior treatment. Fifty to 80 percent of late relapses occur in the retroperitoneum, which further underscores the need for initial complete surgical resection. Postoperative, cisplatin-based chemotherapy did not prevent late local recurrence in the retroperitoneum after suboptimal RPLND for initial low-stage disease (Baniel et al, 1995a, 1995c; Carver and Sheinfeld, 2005; Sharp

et al, 2008). More than 50% of patients with late relapse referred to MSKCC after induction chemotherapy for advanced disease had unresected retroperitoneal masses after chemotherapy, many with residual masses greater than 1 cm at the conclusion of chemotherapy (Sharp et al, 2008). Similarly, only 22 of 37 (59%) patients had undergone PC-RPLND in the Indiana series (Baniel et al, 1995a, 1995c). Late relapse is more common when teratoma is present in a metastatic site (Loehrer et al, 1986; Sonneveld et al, 1998).

Late relapses of GCT are usually chemorefractory, although Motzer and colleagues (2000) reported encouraging results with paclitaxel, cisplatin, and ifosfamide followed by surgery when disease is unresectable at the time of relapse presentation. **Survival rates range from 26% to 46%, and survival is rare without complete resection** (Baniel et al, 1995; George et al, 2003; Dieckmann et al, 2005; Sharp et al, 2008).

Postchemotherapy Surgery for High-Risk Patients with Nonseminomatous Germ Cell Tumors

In a review of 801 patients who underwent PC-RPLND at Indiana University between 1974 and 1994 after cisplatin-based chemotherapy, Donohue and associates (1998) identified several unfavorable subsets of patients characterized by higher relapse and lower survival rates. The overall relapse rate for all PC-RPLND (n = 801) was 27.8%. Whereas the favorable group of PC-RPLND patients (n = 414) had a relapse rate of 11.8%, 174 of 387 (45%) patients with one or more unfavorable risk factors experienced relapse and 29% died of GCT (Donohue et al, 1998).

The first high-risk group are patients undergoing PC-RPLND after salvage chemotherapy, that is, patients with advanced GCT who have a relapse or fail to achieve a complete response to standard cisplatin-based chemotherapy and receive either conventional-dose salvage therapy or high-dose chemotherapy regimens with bone marrow or stem cell support (Donohue et al, 1998). Surgery in this setting is characterized by lower rates of complete resection and a higher proportion of viable cancer (approximately 50%) (Fox et al, 1993). Recent data suggest that taxane-based salvage chemotherapeutic regimens appear to have reduced the rate of viable GCT at PC-RPLND (from 42% to 14%; $P = .01$) (Eggener et al, 2007a). Overall 5- and 10-year disease-specific survival rates were 74% (range 62% to 86%) and 70% (range 56% to 84%), respectively. Furthermore, in the salvage setting patients with resected fibrosis and teratoma had an 87% 5-year survival (Eggener et al, 2007a).

Additional standard-dose chemotherapy does not appear to benefit patients in this setting, compared with a clear benefit in the setting of complete resection of viable GCT after primary chemotherapy (Fox et al, 1993).

The second risk group comprises those with "desperation" PC-RPLND, that is, patients with an elevated serum level of a tumor marker (AFP or hCG) at the time of surgery. Historically, surgery has been avoided in patients with persistently elevated serum levels of tumor markers, because the disease is usually unresectable and thus incurable (Nijman et al, 1988). Recent studies have identified highly selected patients in this setting in whom surgery has curative potential (Wood et al, 1992b; Murphy et al, 1993; Eastham et al, 1994). Murphy and colleagues (1993) reported that 38 of 48 (79%) such patients were rendered free of disease, 29 (60%) normalized their serum tumor marker levels, and 10 (21%) remain disease free with a median follow-up of 46 months. Eastham and associates (1994) noted that 6 of 16 (31%) patients undergoing desperation PC-RPLND were cured, whereas Wood and coworkers (1992b) reported 7 of 15 (47%) patients were rendered disease free.

Beck and colleagues (2005) updated the Indiana University experience with desperation RPLND and reported a 54% survival rate. Unfavorable variables included the need for a redo PC-RPLND and viable cancer in the specimen. Ong and associates (2008) reported a 69% survival rate in patients with elevated tumor markers undergoing PC-RPLND. Favorable survival criteria included stable or declining serum levels of tumor markers, elevated AFP (vs. hCG or hCG and AFP) and complete resection. Dotan and coworkers (2005) reported the MKSCC experience and also noted that patients with rising levels of tumor markers and those with viable disease either in the retroperitoneum or in an extraretroperitoneal site fared worse.

The third high-risk group were patients whose disease was deemed to be unresectable. These patients did very poorly, with 17 of 19 (90%) patients experiencing relapse and only 4 (21%) survivors (Donohue et al, 1998).

The fourth high-risk group is the "redo" PC-RPLND, that is, patients who have undergone a prior attempt at PC-RPLND who present with recurrence in the surgical field (Donohue et al, 1998). **The importance of complete initial postchemotherapy surgery cannot be overemphasized. The data from Indiana University clearly demonstrate that patients who require repeat RPLND are severely disadvantaged, regardless of other risk factors** (Donohue et al, 1998). The relapse rates for primary versus redo PC-RPLND are 20.6% and 51.6%, and the survival rates are 55.3% for the redo group compared with 84.1% in the primary PC-RPLND group (Donohue et al, 1998).

Adjunctive procedures are sometimes necessary to ensure complete surgical resection of residual retroperitoneal masses. En-bloc nephrectomy is the most common adjunctive procedure, ranging from 5% to 20% of cases in the postchemotherapy setting (Nash et al, 1998; Stephenson et al, 2006). These are predominantly left-sided primary tumors with large volume residual disease densely adherent to the left renal vessels and/or hilum (Nash et al, 1998; Stephenson et al, 2006). The MSKCC group reported an 87% (range 69% to 100%) disease-specific survival in this group of patients (Stephenson et al, 2006). Although renal complications are rare, after adjunctive nephrectomy patients should be followed closely for evidence of microalbuminuria or a decline in the creatine clearance value. Vigilance and the early institution of appropriate preventative measures optimize long-term renal function in these patients after cisplatin-based chemotherapy (Stephenson et al, 2006).

Multiple investigators have reported en-bloc resection of a great vessel to achieve complete resection of densely adherent bulky retroperitoneal masses (Donohue et al, 1991; Kelly et al, 1995; Spitz et al, 1997; Beck et al, 1999). Long-term survivors are reported with both inferior vena cava and aortic resections (Kelly et al, 1995; Spitz et al, 1997). Of 65 patients who had a portion of the infrarenal inferior vena cava resected without reconstruction, Beck and associates (1999) reported no long-term sequelae in 75% with 7-year follow-up. However, significant morbidity with venous congestion of the lower extremities and persistent lymphatic drainage into the retroperitoneal space is possible (Waters et al, 2000). If necessary, venous reconstruction can be accomplished with synthetic graft material (Mullen et al, 1996; Spitz

et al, 1997). Similarly, aortic resection is occasionally necessary to achieve a complete resection; and, again, vascular continuity can be achieved with synthetic grafts (Kelly et al, 1995).

This aggressive surgical approach in a subset of appropriately selected patients is justified by the high proportion of teratoma or viable cancer in the resected specimen, the high survival rate of patients after complete resection, and acceptable morbidity when performed by experienced surgeons in tertiary centers (Donohue et al, 1991; Kelly et al, 1995; Spitz et al, 1997).

Postchemotherapy Retroperitoneal Lymph Node Dissection

Although many of the techniques previously described for primary RPLND are applicable in performing postchemotherapy lymphadenectomy, several important points should be emphasized. Large retroperitoneal tumors and severe desmoplastic reaction make PC-RPLND one of the most difficult and dangerous operations undertaken by urologists (Skinner and Skinner, 1992); therefore this operation should be performed by experienced surgeons in referral centers.

The choice of incision is based on tumor location and size. Large masses, located high in the retroperitoneum, may require a thoracoabdominal approach or costal extension of a midline incision. For large left-sided tumors, particularly those that cause lateral displacement of the left kidney with stretching of the renal vessels, massive suprahilar infradiaphragmatic extension is often seen. In this setting a "visceral roll" provides good exposure of the para-aortic area above the left renal artery. By incising (1) the peritoneum of the left lumbar gutter along the white line of Toldt, (2) the splenophrenic ligament, and (3) the parietal peritoneal attachments of the stomach, the descending colon, spleen, stomach, and tail of the pancreas can be reflected medially thus exposing the aorta to the level of the diaphragmatic hiatus (Whitmore and Morse, 1986).

The "split and roll" technique is used to perform the lymphadenectomy. Great care must be taken to avoid subadventitial dissection along the aorta while separating the fibrous wall of the tumor mass and lymph nodes from the great vessels. Aortic wall stripped of adventitia is not amenable to conventional suture repair and may result in delayed rupture. Direct invasion of the aorta or vena cava may require resection with graft interposition. Adjunctive procedures such as nephrectomy may be necessary to achieve complete resection particularly for left-sided tumors. Extensive violation of bowel serosa or enterotomies predispose patients to possible life-threatening fistulas, and omental interposition is advisable.

Tumor involvement of the superior mesenteric artery, celiac axis, or porta hepatis often precludes resection (Whitmore and Morse, 1986).

As noted previously, data from Indiana University and MSKCC clearly demonstrate that patients **who require repeat RPLND are at a significant disadvantage independent of other established risk factors,** and all investigators agree that the oncologic efficacy of an RPLND should not be compromised in an effort to preserve antegrade ejaculation. Importantly, in a recent study from MSKCC analyzing factors associated with the improved clinical outcome in recent years for men with advanced NSGCT, Carver and colleagues (2007a) noted that **complete RPLND superceded stage migration as the most significant variable responsible for the marked decrease in relapse rates. Furthermore, the total number of lymph nodes removed was an independent predictor for disease recurrence after PC-RPLND** (Carver et al, 2008). **Nevertheless, the extent of surgery remains highly controversial. The data suggest that resection of mass alone is inadequate and is not recommended** (Carver et al, 2007a, 2008; Kakiashvili et al, 2009). The role of modified templates in the postchemotherapy setting is less clear. In a highly select subset of 100 patients, representing less than 10% of the overall cohort of patients undergoing PC-RPLND during the study period, and with a median follow-up of 32 months, investigators from Indiana University report a 2- and 5-year disease-free survival of 95% with modified templates (Beck et al, 2009). Conversely, in a recent mapping study, investigators from MSKCC report extratemplate disease between 7% and 32%, depending on the limits of the modified template, and recommend a standard bilateral dissection as the oncologically prudent approach (Carver et al, 2007a). Recently, investigators from the Princess Margaret Hospital reported disease outside a lumpectomy or modified template in 21.4% and 4.7% of cases, respectively (Kakiashvili et al, 2009).

Appropriately selected patients are candidates for nerve-sparing PC-RPLND (Coogan et al, 1996; Pettus et al, 2009). Pettus and associates (2009) reported a single surgeon experience with nerve-sparing PC-RPLND and noted that almost 80% of carefully selected candidates had preserved antegrade ejaculation, including 4 of 9 (44%) with a mass greater than or equal to 5 cm. The 5-year relapse-free survival rate was 98%. The oncologic aspects of the procedure should not be compromised to preserve antegrade ejaculation.

Reoperative Retroperitoneal Surgery

Completeness of resection is an independent and consistent predictive variable of relapse-free survival for patients with NSGCT (Carver et al, 2007a). As noted earlier, Donohue and coworkers (1998) noted that patients undergoing "redo" PC-RPLND were significantly disadvantaged in terms of survival (55% vs. 84%) compared with those who did not require reoperation, despite controlling for marker status, histologic findings, and prior need for salvage chemotherapy. Similarly, McKiernan and associates (2003) reported the MSKCC reoperative experience and noted a 56% 5-year disease-specific survival rate in patients requiring reoperation after PC-RPLND compared with 86% in those without reoperation.

Investigators at MSKCC also showed that inadequate initial surgery in low-stage NSGCT cannot be reliably remedied by postoperative chemotherapy. Twenty (90%) of 22 patients who received cisplatin-based chemotherapy after incomplete initial RPLND and who underwent reoperative retroperitoneal surgery after primary RPLND experienced compromised survival, 86% versus 99.3% in patients not requiring reoperation (McKiernan et al, 2003). In the MSKCC series, 10 (45%) of 22 patients undergoing primary RPLND and 20 (59%) of 34 undergoing PC-RPLND had teratomatous elements present at initial surgery before local recurrence, underscoring the need for complete and meticulous resection of teratoma (McKiernan et al, 2003). Hence, tumors that are incompletely resected and require reoperative surgery after either primary or PC-RPLND result in compromised survival (Donohue et al, 1998; Sheinfeld, 2002a; McKiernan et al, 2003).

The left para-aortic region is the most common site of local recurrence prompting reoperation (McKiernan et al, 2003). This is due to the increased technical demands of obtaining adequate exposure in this area, including pancreatic mobilization and dissection of the renal vessels. Unfortunately, the preaortic and

para-aortic lymph nodes in modified templates for right-sided tumors are often not dissected (Carver et al, 2007b; Eggener et al, 2007b). Data from MSKCC and Indiana have shown that a significant subset of patients with right-sided primary NSGCT and pathologic stage II disease will have involved lymph nodes in the para-aortic area (Leibovitch et al, 1995a; Koppie et al, 2004; Carver et al, 2007; Eggener et al, 2007).

When necessary, reoperative retroperitoneal surgery is better performed with acceptable morbidity in dedicated tertiary centers with experienced surgeons (Donohue et al, 1998; McKiernan et al, 2003; Sexton et al, 2003).

Lung, Mediastinal, and Neck Resections

The indications and timing for postchemotherapy resection of residual masses in the chest are less controversial. Early investigators reported discordant histologic findings ranging from 29% to 46% between the retroperitoneum and the chest (Mandelbaum et al, 1983; Tiffany et al, 1986; Qvist et al, 1991).

Toner and associates (1990) reported on 39 patients who underwent 57 procedures for pulmonary nodules. Six of 14 patients with nodules 1 cm or smaller had either teratoma (5 patients) or viable cancer (1 patient), whereas 3 of 8 patients who underwent bilateral thoracotomies had different histologic findings in each lung.

Logistic regression analysis of multiple clinical parameters to estimate the probability of necrosis at thoracotomy found that necrosis in the retroperitoneum was the most predictive variable (Steyerberg et al, 1997). Other predictors included primary tumor histology, prechemotherapy tumor markers, change in size after chemotherapy, and the presence of a single mass (Steyerberg et al, 1997).

More recently, Tognini and coworkers (1998) reported that although retroperitoneal histology was most predictive of thoracic histology, only 31 of 40 (78%) patients with necrosis in the abdomen had necrosis in the chest. Further categorization of the RPLND as standard or complicated increased the predictive accuracy to 86%.

Finally, the recent MSKCC experience of 93 patients who had RPLND and thoracotomy revealed histologic discordance between RPLND and thoracotomy in 27 of 93 (29%) patients; 7 of 59 (14%) patients with fibrosis in the retroperitoneum had teratoma or viable cancer in the chest (McGuire et al, 2003).

Postchemotherapy thoracotomy yields important prognostic information and is therapeutic in most patients with resected teratoma and a subset of patients with viable cancer. Criteria predictive of necrosis are not sufficiently accurate to omit resection of postchemotherapy residual thoracic masses; therefore, all sites of disease should be resected regardless of size (McGuire et al, 2003). **Furthermore, investigators have demonstrated the feasibility of simultaneous RPLND and thoracic resection in experienced tertiary centers** (Brenner et al, 1996; Tognini et al, 1998; McGuire et al, 2003).

Mohseni and colleagues (2002) reported on 16 patients with a residual neck mass who underwent resection of 61 residual masses in multiple sites. Histologic discordance in different sites was seen in 7 of 16 (44%) patients, and 13 of 16 patients had teratoma (10 patients) or viable GCT (3 patients) in the neck. All 10 patients with teratoma in the residual neck mass and 1 of 3 patients with viable GCT have no evidence of disease after complete resection. There were no perioperative deaths, and no patient suffered relapse in the neck.

Key Points: High-Stage Germ Cell Tumor

- The initial treatment for patients with advanced GCT is cisplatin-based combination chemotherapy.
- Postchemotherapy pathologic findings in patients with advanced NSGCT after induction therapy is 45% to 50%; for teratoma, 40%; and for viable carcinoma, 10%.
- Variables and statistical models to predict necrosis in the retroperitoneum after induction therapy have approximately a 30% error.
- Teratomatous elements may be found in the retroperitoneum despite its absence in the orchiectomy specimen.
- Teratoma may grow and obstruct or invade local structures, undergo malignant transformation, and result in late relapse.
- Recurrence of teratoma is related to completeness of resection.
- Bilateral RPLND remains the standard template in the postchemotherapy NSGCT setting; resection of residual mass *alone* is an *unacceptable* alternative.
- Histologic discordance between different sites (e.g., retroperitoneum, thorax, neck) after postchemotherapy resection is found in approximately 30% of cases.
- Sixty percent of late relapses occur beyond 10 years, emphasizing the need for prolonged follow-up. The most common site is the retroperitoneum.
- Patients who require repeat RPLND are at a significant disadvantage independent of other risk factors.
- The para-aortic region is the most common site of local recurrence after RPLND.

Complications

The rate of complications for postchemotherapy surgery is higher than for primary RPLND (Subramanian et al, 2008). Baniel and associates (1995a, 1995b) reported 38 (8%) major complications in 478 patients who underwent primary RPLND compared with 106 (18%) in 603 patients after PC-RPLND. Furthermore, there were five deaths in the postchemotherapy group and none in the primary group. Large-volume residual disease, postchemotherapy desmoplastic reaction, prior exposure to bleomycin, and more extensive retroperitoneal resection increase the technical and perioperative demands of the procedure and result in higher morbidity rates. Fortunately, the morbidity appears to be decreasing with time. Mosharafa and associates (2004) reported that the rate of perioperative complications and length of hospital stay decreased from July 2000 to July 2002 compared with patients who underwent PC-RPLND from July 1990 to July 1992. Careful monitoring of perioperative oxygen concentrations, meticulous fluid management with strict replacement criteria, and an emphasis on colloid rather than crystalloid have reduced pulmonary toxicity. Knowledge of the retroperitoneal anatomy, careful technique, and improved perioperative management have resulted in lower morbidity when PC-RPLND is performed by experienced surgeons. Data from a retrospective analysis suggested a beneficial impact of clinical care pathways on the reduction of perioperative morbidity (Chang et al, 2002b).

Lymphatic Complications

The incidence of chylous ascites is 2% to 3%, and predisposing factors include resection of the vena cava, suprahilar dissection, or simultaneous hepatic resection.

Familiarity with retroperitoneal lymphovascular anatomy and meticulous lymphostasis with clips or ligatures will minimize this complication.

Patients with chylous ascites may present with abdominal distention, prolonged ileus, an abdominal fluid wave, a pleural effusion, or chylous leakage from the incision. Ultrasonography or CT with paracentesis is diagnostic and may provide symptomatic relief. Chylous fluid has a characteristic milky or turbid appearance with a fat content of 4 to 40 g/L and a total protein content greater than 30 g/L. Initial management is with diuretics and dietary manipulation (low-fat diet with medium-chain triglycerides) and/or total parenteral nutrition. Persistent drainage of chyle that is refractory to conservative measures may require peritoneovenous shunting (Baniel et al, 1995b, 1995d). Reoperation to repair lymphatic leakage is associated with a high failure rate and should be avoided.

Asymptomatic lymphoceles require no treatment; however, percutaneous drainage for infection, hydronephrosis, or bowel obstruction is necessary in 1% to 2% of cases. Persistent drainage may require treatment with a sclerosing agent.

Pulmonary Complications

Pulmonary complications include (1) atelectasis, which is treated by vigorous pulmonary physiotherapy; (2) pneumonia, which requires appropriate antibiotic therapy; and (3) acute respiratory distress syndrome, which often requires prolonged mechanical ventilation and corticosteroids and may be fatal. The signs and symptoms of acute respiratory distress syndrome include a dry nonproductive cough, dyspnea, rales, fever, and interstitial pneumonitis on the chest radiograph. **It is the authors' practice to judiciously monitor the perioperative fluid administered to bleomycin-treated patients and to avoid unnecessary exposure to high concentrations of inspired oxygen.**

Infectious Complications

Superficial wound infections comprise the majority of infectious problems whereas urinary tract infections account for less than 1%. *Clostridium difficile* infections require appropriate antibiotic therapy with metronidazole or vancomycin. Incidental appendectomy increases the risk of infection and is contraindicated (Leibovitch et al, 1995b).

Vascular Complications

Renovascular injury is seen in 2% to 3% of cases and can result in renovascular hypertension or require nephrectomy at the time of RPLND. Minor injury of the great vessels during dissection can be managed with 5-0 vascular sutures. Major vascular injury requiring unplanned grafting or prolonged cross-clamping are uncommon in experienced centers.

Neurologic Complications

Peripheral nerve injury due to neural compression secondary to positioning is rare and accounts for less than 1% of all complications, particularly in the transabdominal approach. Femoral and brachial neurapraxias have been reported (Baniel et al, 1995b). The more serious complication of spinal cord ischemia with aortic mobilization is encountered in less than 1% of all cases and has been associated with older age, simultaneous mediastinal and retroperitoneal dissections, previous radiotherapy, and intraoperative hypotension (Leibovitch et al, 1996). This complication can be minimized by selective preservation of lumbar arterial branches in suprahilar and thoracic dissections.

Gastrointestinal Complications

Prolonged paralytic ileus may be associated with mechanical obstruction or less commonly with retroperitoneal hematoma, pancreatitis, urinary extravasation, mesenteric hematoma, and bowel infarction (Whitmore and Morse, 1986). Small bowel obstruction is seen in 2% to 3% of all patients and can be managed conservatively with exploration being reserved for signs of toxicity or failure to respond to prolonged nasogastric tube decompression. Pancreatitis usually presents as prolonged ileus and hyperamylasemia and can be avoided by minimizing traction on the pancreas during RPLND. Therapy is usually conservative with nasogastric tube decompression and occasional need for hyperalimentation. Isolated hyperamylasemia may be seen in up to 40% of asymptomatic patients and is self-limiting (Baniel et al, 1995d). Gastrointestinal bleeding is rare and can be minimized by the use of perioperative H_2 antagonists. Sacrifice of the inferior mesenteric artery is common and is rarely associated with any lower gastrointestinal complication. Duodenal hematomas and laceration have been reported and are seen in the setting of high-volume disease behind the duodenum, making dissection in this area particularly demanding. In the past, routine appendectomy at the time of RPLND was performed; however, it has been found to be associated with an increased risk of infectious complications and therefore is no longer recommended (Leibovitch et al, 1995b).

Seminoma

The approach to the patient with pure seminoma and a residual mass after chemotherapy is controversial. **There are two important differences between seminoma and NSGCT in this setting. First, teratoma in the residual mass is very rare. Second, a complete RPLND is often not technically possible owing to obliteration of tissue planes secondary to the severe desmoplastic reaction of these tumors after chemotherapy** (Horwich et al, 1997; Sheinfeld and Herr, 1998; Bosl et al, 2000). **Consequently, perioperative morbidity is higher than for NSGCT** (Fossa et al, 1987; Ellison et al, 1988).

Several studies have evaluated the role of surgery for residual masses in seminoma patients (Fossa et al, 1987; Loehrer et al, 1987; Puc et al, 1996; Herr et al, 1997; Horwich et al, 1997). Loehrer and associates (1987) reported on 62 patients with advanced-stage seminoma who received cisplatin-based chemotherapy. Of the 13 patients who underwent attempted surgical resection, 3 (23%) had residual malignancy and the size of the residual mass was not predictive of histologic findings. Fossa and colleagues (1987) reported 39 patients with advanced-stage seminoma, 15 of whom had received prior radiation therapy; 3 of 12 patients (25%) who underwent surgical exploration had viable seminoma, and one postoperative death secondary to pulmonary toxicity was reported. Both groups concluded that observation was preferable in these patients given the significant surgical morbidity and the fact that the majority of postchemotherapy seminoma patients with residual radiographic abnormalities do not have persistent malignant disease (Fossa et al, 1987; Loehrer et al, 1987). Investigators at the Royal Marsden Hospital report only a 12% relapse rate in postchemotherapy seminoma patients with observation alone despite radiographic abnormalities in over 80% of patients (Peckham et al, 1985).

In a group of 104 postchemotherapy seminoma patients, investigators at MSKCC reported that 8 of 30 (27%) patients with a residual mass of 3 cm or larger experience relapse or had residual

seminoma whereas only 2 of 74 patients (3%) with tumors smaller than 3 cm in diameter had relapse at the site of residual disease. Of the 55 patients who underwent surgery, 32 (58%) had masses resected whereas 23 (42%) underwent multiple biopsies. There were no postoperative deaths (Puc et al, 1996; Herr et al, 1997).

Although there is general agreement that patients with residual masses less than 3 cm should be observed, management of the minority of patients with residual masses larger than 3 cm remains controversial. Investigators at MSKCC believe that resection or biopsy of residual masses larger than 3 cm is preferable to observation because it can identify residual disease and direct immediate therapy (Puc et al, 1996; Bosl et al, 2000). If viable seminoma is identified, additional chemotherapy is necessary (Puc et al, 1996). Alternatively, radiation therapy is possible; however, approximately 75% of patients will receive it unnecessarily and it did not appear to reduce the risk of relapse (Horwich et al, 1997; Bosl et al, 2000). Observation is a third option; however, ifosfamide-based salvage chemotherapy for patients who experience relapse had a low cure rate (Bosl et al, 2000).

Recently, a study of fluorodeoxyglucose (FDG)-labeled PET in 52 patients with residual masses after chemotherapy for bulky seminoma reported that all 8 positive scans and 42 of 44 negative scans correlated with clinical outcome (De Santis et al, 2004). Conversely, Daneshmand and associates (2008) reported a 50% false-positive rate in this setting.

In summary, **patients with residual masses smaller than 3 cm after chemotherapy may be observed. FDT-PET should be done for masses 3 cm or larger. A negative PET scan usually implies freedom from disease, whereas a positive PET scan is often associated with residual viable seminoma and additional therapy should be considered.** If surgical resection appears feasible, it should be done at centers with experienced surgeons (Bosl et al, 2005).

Fertility in Advanced-Stage Germ Cell Tumors

Subnormal pretreatment semen parameters in conjunction with cytotoxic chemotherapy and more extensive surgery RPLND make fertility less common in the postchemotherapy setting. Cytotoxic chemotherapy has been shown to have long-term deleterious effects on Leydig cell function (Brennemann et al, 1997; Howell et al, 1999). Platinum-based chemotherapy regimens cause both Leydig and Sertoli cell dysfunction. **After two or four cycles of platinum-based chemotherapy a nadir in spermatogenesis is reached in 10 to 14 months. The majority of patients with normal pretreatment spermatogenesis will return to baseline function by 3 years** (Brennemann et al, 1997). Overall fertility rates after chemotherapy are directly related to the total dose of platinum delivered during treatment (Pont and Albrecht, 1997). Patient age and pretreatment follicle-stimulating hormone levels are also predictive of long-term fertility after chemotherapy (Brennemann et al, 1997). Cryopreservation of sperm is now widely available and is recommended before chemotherapy for testicular cancer. However, many patients will recover adequate spermatogenesis and not require the use of cryopreserved sperm (Fossa et al, 1989a). **Despite defects in spermatogenesis and exposure to cytotoxic therapy, the incidence of birth defects is not increased in children conceived after treatment of testicular cancer** (Byrne, 1990; Hartmann et al, 1999).

Acknowledgment

The authors are grateful for the expert and invaluable assistance of Alicia Lashley in the preparation of the manuscript.

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The complete reference list is available online at www.expertconsult.com.

chapter 33

Laparoscopic Retroperitoneal Lymphadenectomy for Testicular Tumors

Mohamad E. Allaf, MD ● Louis R. Kavoussi, MD, MBA

Rationale and Evolution
Staging L-RPLND and Controversy
Duplication of Open RPLND
Surgical Technique
Postoperative Care
Prospective Nerve-Sparing Techniques
Complications
Results and Current Status
Summary

Germ cell tumors (GCTs) are the most common malignancy in men between the ages of 15 and 35 (Carver and Sheinfeld, 2005). Fortunately, testicular cancer is also one of the most curable solid organ neoplasms, owing in large part to an excellent multimodal treatment paradigm that includes effective platinum-based chemotherapy and surgery (Einhorn, 1981). **Although contemporary survival rates for GCTs are more than 90%, it is critical to note that cure rates and patient morbidity depend on selection of the management options.** Retroperitoneal lymph node dissection (RPLND) plays a major role in the management of patients with GCTs. The role of surgery continues to evolve owing to advances in chemotherapy regimens, clinical staging modalities, and continued surgical innovation (Sheinfeld and Herr, 1998; Allaf et al, 2005; Albers et al, 2008).

Whereas primary chemotherapy is favored in Europe, traditionally RPLND has been the management strategy of choice in the United States for high-risk patients with clinical stage I nonseminomatous GCT (NSGCT). The reason for this is that RPLND can accurately stage the retroperitoneum and thus positively identify those patients harboring metastases. In addition, patients with pathologic stage I disease are spared the toxicity and morbidity of any additional therapy because 90% or more experience long-term disease-free survival with surgery alone. Patients with pathologic stage II disease can learn more about the extent of their disease and make informed decisions regarding further therapy after RPLND. For patients in this group who harbor small-volume retroperitoneal disease (pN1), a properly performed RPLND can be curative in approximately 70% of men; thus chemotherapy also can be avoided in this setting (Richie and Kantoff, 1991; Donohue et al, 1993; Rabbani et al, 2001). Because the retroperitoneum is the most frequent site of chemoresistant malignant GCT and teratoma, both of these processes are minimized with RPLND (Baniel et al, 1995). Some groups advocate RPLND as the treatment of choice for all men with clinical stage I NSGCT with teratoma in the orchiectomy specimen given the increased propensity of harboring teratoma in the retroperitoneum (Sheinfeld et al, 2003). RPLND eliminates these chemoresistant elements and maximizes therapeutic efficacy.

Traditionally RPLND for GCTs has been performed via an open transabdominal or thoracoabdominal approach. Over the past 2 decades minimally invasive approaches for the treatment of various malignancies have emerged and become popular. Since the early 1990s, retroperitoneal laparoscopic surgery has been utilized with proven benefits related to reducing perioperative morbidity, improving cosmesis, and shortening convalescence without compromising oncologic efficacy (Cadeddu et al, 1998; Allaf et al, 2004; Permpongkosol et al, 2005). Laparoscopic RPLND (L-RPLND) is a technically demanding procedure that is increasingly being performed by experienced laparoscopic surgeons aiming to minimize morbidity while duplicating the open technique. **Given that untreated retroperitoneal disease and late relapses in the retroperitoneum are fatal and can be chemorefractory, it is of paramount importance that, just like in open RPLND, a complete "clean out" of lymph nodes is performed** (Whitmore, 1979; Borge et al, 1988; Baniel et al, 1995; Carver et al, 2005).

In this chapter the evolution of L-RPLND is summarized. Included is a discussion of controversies surrounding its use, surgical techniques, outcomes, and associated complications. The focus is placed on the management of low-stage NSGCTs and the role of L-RPLND in the postchemotherapeutic setting.

RATIONALE AND EVOLUTION

In an effort to decrease the morbidity associated with open RPLND, shortly after the introduction of laparoscopic renal surgery in 1991 several reports emerged documenting the feasibility of L-RPLND

in the management of clinical stage I NSGCT (Rukstalis and Chodak, 1992; Stone et al, 1993; Klotz, 1994). Larger retrospective series followed suggesting decreased blood loss, shorter hospital stays, and faster return to normal activity when compared with open RPLND, with preservation of antegrade ejaculation in more than 95% of patients (Gerber et al, 1994; Janetschek et al, 1994, 1996). An early multi-institutional retrospective analysis demonstrated preservation of antegrade ejaculation in all patients, short hospital stays (<3 days), and return to normal activity at 2 to 3 weeks postoperatively (Gerber et al, 1994). **The abbreviated convalescence allows patients who are candidates to receive chemotherapy with minimal delay.** These attractive early results encouraged others to investigate L-RPLND as a viable treatment option for low-stage NSGCT.

STAGING L-RPLND AND CONTROVERSY

Of all laparoscopic applications to surgical urology, L-RPLND has raised the most controversy. This is due to the technical difficulty of RPLND in general, the limited number of cases, as well as lack of interest at traditional centers of excellence. Laparoscopy is an access technique with the internal procedure being performed the same as that with an open incision. As such, experience drives an equivalent dissection. In all early series and some contemporary studies, L-RPLND was used as a staging procedure (Bianchi et al, 1998; Janetschek et al, 2000). Patients not harboring occult metastases were identified and spared exposure to chemotherapy without undergoing open RPLND. In this form, L-RPLND was performed without retrocaval or retroaortic dissection and chemotherapy was given to all patients harboring metastatic disease (including patients with pN1 disease). The decision to omit dissection behind the great vessels was based on the belief of a lack of isolated positive lymph nodes in this area (Holtl et al, 2002). Within this paradigm, the procedure was routinely aborted if positive lymph nodes were encountered and chemotherapy was instituted in these cases (Bianchi et al, 1998; Nelson et al, 1999). **In contemporary series this approach has been abandoned and L-RPLND has evolved into a therapeutic procedure duplicating the open approach in its intent** (Allaf et al, 2005; Steiner et al, 2008).

The use of restrictive template boundaries coupled with the universal use of chemotherapy in men harboring pathologic stage II disease generated criticism of published L-RPLND series. The controversy regarding the use of "staging" L-RPLND hinges on mapping studies demonstrating increased multifocality and contralateral disease in the presence of positive retroperitoneal nodes (Ray et al, 1974; Donohue et al, 1982; Weissbach and Boedefeld, 1987; Eggener et al, 2007). Critics argue that the liberal use of chemotherapy will not necessarily prevent relapses and compensate for incomplete resection.

DUPLICATION OF OPEN RPLND

Currently at experienced centers an exact replication of the open template is performed on all patients with NSGCT undergoing L-RPLND with wide templates and complete excision of retroaortic and retrocaval tissue, thus rendering the procedure both a staging and a therapeutic operation. Some groups perform a bilateral dissection on all patients whereas others reserve it for patients with lymph node involvement (Allaf et al, 2005; Steiner et al, 2008).

SURGICAL TECHNIQUE

L-RPLND is a technically challenging procedure associated with a steep learning curve and thus should be undertaken by experienced laparoscopic surgeons who are comfortable and adept with advanced vascular techniques and open surgery in case of conversion. The indications for primary L-RPLND are identical to those of open RPLND and include clinical stage I or IIA disease, negative serum tumor markers, and the absence of comorbidities that would preclude safe surgery. In the postchemotherapeutic setting L-RPLND has been mainly limited to small-volume residual disease; however, with experience, bulky tumors have been excised. **The surgical template for the procedure is dictated by laterality and intraoperative findings. Surgical margins should not be compromised to minimize morbidity, to preserve ejaculation, or because of technical constraints. The extent of the node dissection can be expanded based on intraoperative findings.**

Preoperative Patient Preparation and Technical Considerations

All patients considered candidates for L-RPLND must be fully informed of all treatment options, including open RPLND, chemotherapy, and surveillance. All potential complications, including bleeding requiring blood transfusion, injury to adjacent organs (liver, bowel, gallbladder, kidney, ureter, pancreas, major vascular structures), and orthopedic, neurologic, or pulmonary complications, as well as conversion to open surgery due to complications or incomplete resection, should be discussed (Allaf et al, 2005; Winfield, 1998). Patients interested in future fertility are educated regarding preoperative sperm banking. Some surgeons advocate a low-fat diet 1 to 2 weeks before surgery to reduce the risk of chylous ascites, but data regarding this practice are not definitive. Patients undergo a mechanical bowel preparation the afternoon before surgery and take only clear liquids until midnight to decompress the bowels. Preoperative antibiotics are given before surgery, and antiembolism devices are placed on the lower extremities to minimize deep vein thrombosis.

Standard laparoscopic instruments are used throughout this procedure (e.g., atraumatic graspers, scissors, clip appliers, irrigation/suction device, and laparoscopic paddle retractor). Radiolucent polypropylene clips (Hem-o-Lok, Weck Closure Systems, Triangle Park, NC) may minimize artifact on postoperative imaging of the retroperitoneum. In addition, a needle driver loaded with suture and adjunct hemostatic agents such as gelatin matrix (FloSeal Matrix Hemostatic Sealant, Fusion Medical Technologies, Fremont, CA) or oxidized cellulose (Surgicel, Ethicon, Piscataway, NJ) should be readily available in case of vascular injury. Sealing devices such as ultrasonic shears and bipolar devices should be used with caution and can be unreliable in sealing large lymphatic channels. A laparoscopic retractor is particularly useful for medial retraction of the bowel and alleviates the need to position the patient in a modified flank position. A gauze sponge placed in the abdomen can be helpful in tamponading bleeding.

Approach

Although some surgeons utilize an extraperitoneal approach (Hsu et al, 2003; Hara et al, 2004) most prefer a transperitoneal approach owing to the larger and more familiar working space. **Additionally, a transperitoneal approach facilitates bilateral**

dissection when warranted by allowing access to all four quadrants.

Patient Positioning and Port Placement

After general anesthesia is induced, an orogastric tube and Foley catheter are inserted. The patient may be placed in the modified flank position (45 degrees) with the side of dissection elevated, but the authors prefer the supine position because it makes transitioning to a bilateral dissection less cumbersome and does not require patient repositioning (Fig. 33–1). Great care is taken to pad all pressure points to minimize the risk of nerve injury or rhabdomyolysis because these surgeries may require a longer time than their open counterpart. The patient must be secured to the operating table because tilt is needed to use gravity to help shift the bowel out of the operative field.

After intraperitoneal access is achieved (via a Veress needle or Hasson technique), four equally spaced 10/12-mm laparoscopic ports are placed in the midline beginning 1 cm below the xiphoid process (Fig. 33–2). As such, the umbilicus may not necessarily be incorporated as a port site. The large port size is essential to allow for the convenient introduction of larger (10/12-mm) instruments from varying angles. An additional 5-mm port may be placed in the midaxillary line midway between the iliac crest and ribs for additional retraction if needed. The bed is rotated maximally to allow optimal medialization of the bowel away from the operative field.

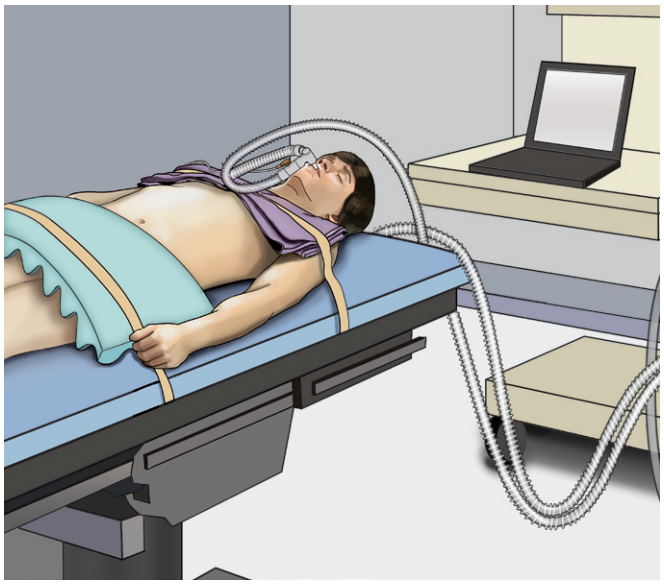


Figure 33–1. Patient positioning during laparoscopic retroperitoneal lymph node dissection. The arms are tucked, and the patient is padded and secured in a relatively supine position.

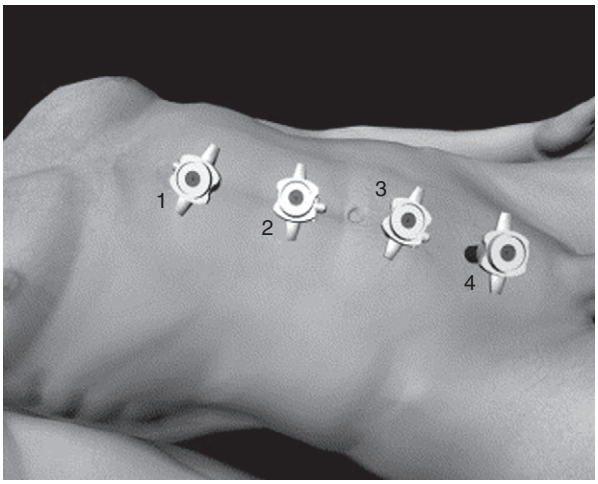


Figure 33–2. Port placement for laparoscopic retroperitoneal lymph node dissection. Four 10/12-mm equally spaced trocars are placed in the midline.

Right-Sided Dissection

The ascending colon is mobilized by incising the white line of Toldt from the pelvis and around the hepatic flexure. The second portion of the duodenum is identified and kocherized, providing exposure of the retroperitoneum including the medial para-aortic space on the left.

Spermatic Cord Dissection

The camera is moved to the second to the bottom trocar (trocar 3 in Fig. 33–2) to facilitate visualization during dissection of the spermatic cord stump. The peritoneum medial to the spermatic cord is incised, and the vas deferens is transected. The peritoneum is incised circumferentially around the inguinal ring (Fig. 33–3). With gentle traction on the cord, fibrous attachments and scar are incised until the suture on the spermatic cord is identified. The attachments are cut, and the cord is followed proximally along with surrounding nodal and fibroadipose tissue to the inferior vena cava (IVC). The ureter must be identified at all times to prevent inadvertent thermal injury. The spermatic vein and artery are both ligated proximally and transected. The specimen is placed in an endobag and dropped on the contralateral side of the abdomen.

Lymphadenectomy

Although templates should be individualized to each case, the authors advocate removal of the right common iliac, paracaval,

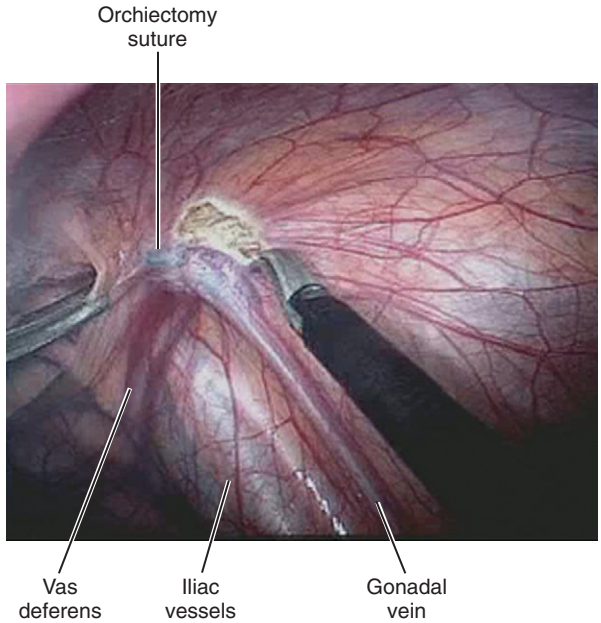


Figure 33–3. Incision of posterior peritoneum circumferentially about the inguinal ring.

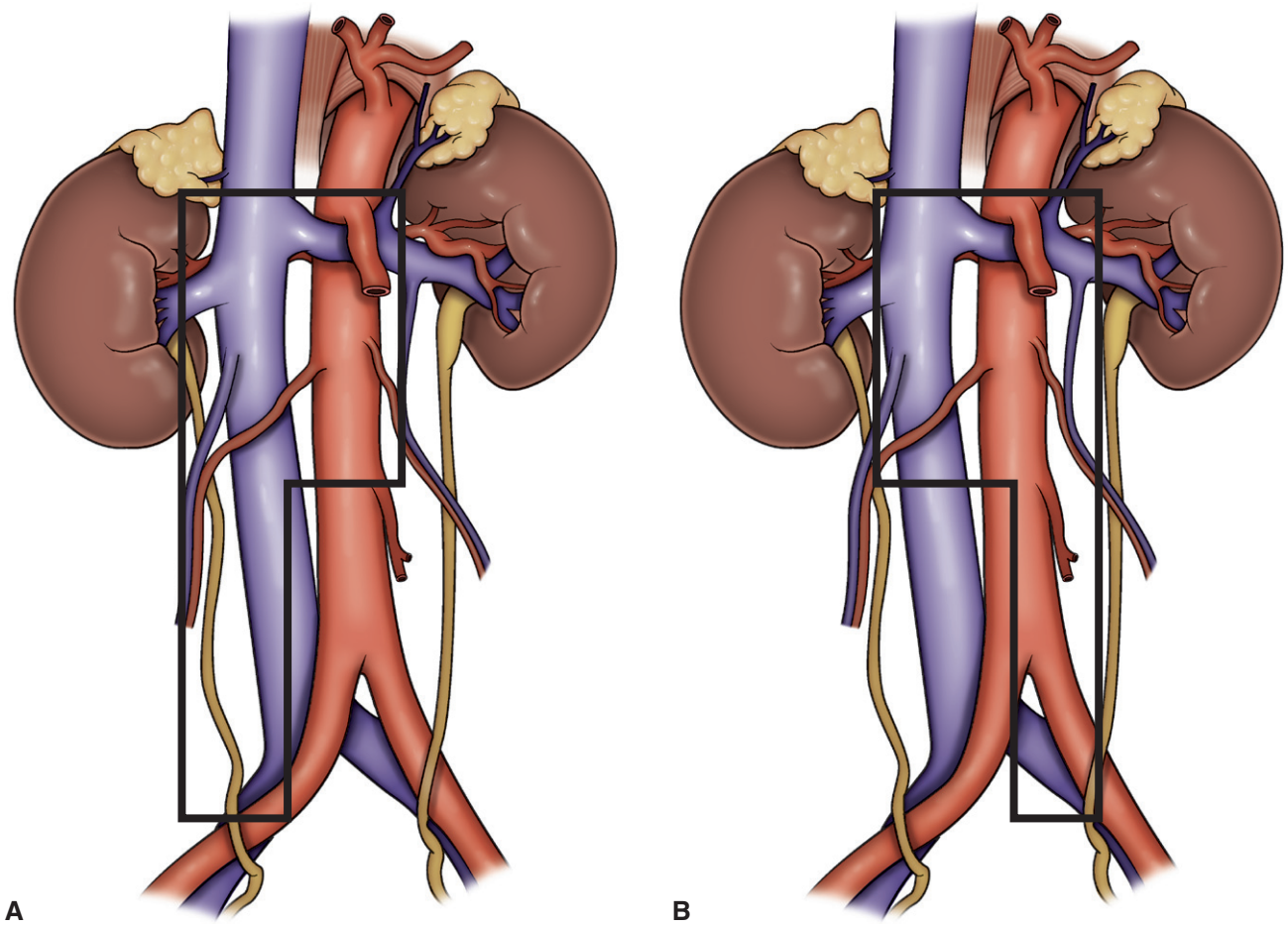


Figure 33–4. Suggested templates for right (**A**) and left (**B**) therapeutic laparoscopic retroperitoneal lymph node dissection. These templates can be expanded or contracted based on each patient's tumor.

interaortocaval, preaortic, and medial para-aortic nodes (Fig. 33–4). Occasionally in obese patients (or when performing a full bilateral dissection) the left-most border of the dissection must be performed after rotating the table contralaterally to optimize exposure. The camera should be moved to the port second from the top. A paddle retractor is placed in the lowest trocar to protect and sweep the bowel medially.

The testicular vein stump is identified and minimally manipulated to prevent pseudoaneurysm formation with subsequent rupture. The tissues overlying the IVC are gently lifted and carefully incised longitudinally (Fig. 33–5). It is swept off the IVC in a "split and roll" fashion. Blunt dissection aids in further separating these lymphatic tissues toward and overlying the common iliac vessels inferiorly and renal hilum superiorly. Care must be taken to avoid injury of lower pole renal arteries, which are present in approximately 20% of cases, and accessory vessels crossing anterior to the IVC. The renal hilum is then dissected to separate all fibroadipose tissue from the renal vein and artery as far under the IVC as possible. Next the ureter is traced to its crossing over the common iliac vessels, and thus the lymphatic packet is separated from both of these structures. The "split" tissue along the IVC is then "rolled" medially to expose the retrocaval space. Lumbar vessels are identified, clipped, and divided to allow splitting of the posterior lymphatic tissues (Fig. 33–6). Once this is accomplished the tissues are released from their attachment to the

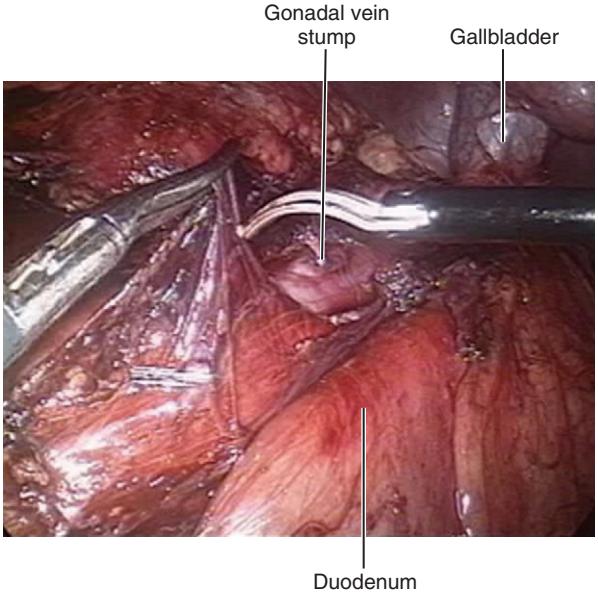


Figure 33–5. Fibrofatty tissue overlying the inferior vena cava being incised to initiate the "split and roll" technique. The duodenum has been reflected medially, and the spermatic vein stump has been clipped and divided.

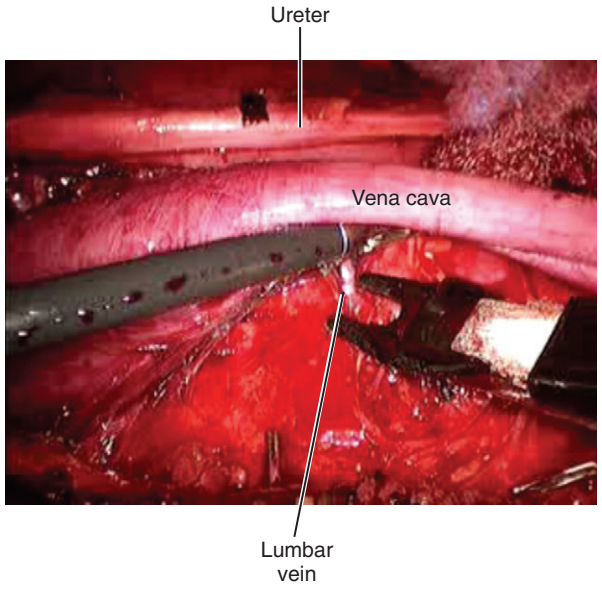


Figure 33–6. The inferior vena cava is retracted to allow for lumbar vein ligation. Paracaval and precaval lymph nodes have been cleared.

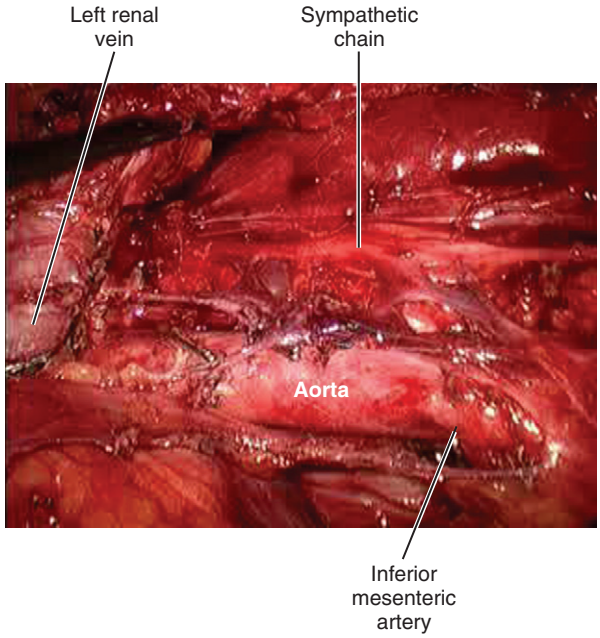


Figure 33–7. The sympathetic chain and efferent nerves are seen spared while para-aortic and preaortic lymph nodes have been removed.

spine and delivered laterally. Great care is taken to separate the lymph nodes from the sympathetic chain and postganglionic nerve fibers. Next the aorta is identified and the tissues overlying it are similarly split to the level of the inferior mesenteric artery and then rolled medially to enter the retroaortic space. The lumbar arteries may be controlled if additional mobility is needed to mobilize the interaortocaval packet posteriorly. The aorta can be medially retracted, thus facilitating para-aortic node excision with careful preservation of the sympathetic chain laterally. The interaortocaval nodes are then finally removed to complete the dissection.

An important technical point is to leave a long stump on the aorta/vena cava side when ligating lumbar vessels such that they can be grasped and controlled in the event a clip dislodges. Lumbar vessels that retract into the iliopsoas uncontrolled can usually be managed with pressure or a figure-of-eight suture placed deep into the muscle. Lacerations of the IVC and aorta may occur during this operation but in the vast majority of cases do not mandate open conversion. Direct pressure usually prevents excessive hemorrhage and can achieve hemostasis without the need for additional maneuvers. Adjunct hemostatic agents can also be used successfully in this circumstance. If the bleeding persists, or in the case of arterial bleeding, direct pressure can be used temporarily before definitive repair is undertaken with intracorporeal suturing.

Left-Sided Dissection

The peritoneum is incised lateral to the descending colon and along the splenic flexure. The colorenal ligaments are severed, and the bowel is bluntly dissected medially. The lateral attachments of the spleen are incised, and the tail of the pancreas is swept medially to ensure wide exposure of the retroperitoneum, including the medial paracaval space.

Spermatic Cord Dissection

Analogous to what is done on the right side, the spermatic cord stump suture is identified after circumscribing the peritoneum at the inguinal ring. The spermatic vein along with adjacent lymph nodes is traced proximally to the renal vein and the artery to the aorta where they are ligated and cut. The cord is then placed in an endobag for removal at the conclusion of the procedure.

Lymphadenectomy

The authors advocate removal of the left common iliac, para-aortic, preaortic, interaortocaval, and medial paracaval lymph nodes (see Fig. 33–4). The dissection can be expanded as needed. Lumbar veins draining into the renal vein are clipped and divided to allow full dissection of the renal hilum. The vein is cleaned off medially to the junction of the vena cava. A paddle retractor in the lowest trocar aids in dissection. The renal artery is completely freed of all lymphatic tissues. Again, generous use of clips is used to avoid postoperative leakage of lymph. The tissues overlying the aorta are split from the renal hilum to the level of the inferior mesenteric artery. Care should be taken to identify the right spermatic artery to avoid avulsion. In contrast to the tissues overlying the vena cava, the preaortic space may include postganglionic sympathetic nerves; thus care must be taken to separate the nodal tissue while preserving these nerves (Fig. 33–7). The ureter and common iliac vessels are separated from all fibroadipose tissue. The preaortic tissues are rolled medially down to the lumbar arteries. The lumbar vessels are controlled and cut, allowing excision of the retroaortic lymph nodes. The vena cava is identified, and using a "split and roll" approach the paracaval, precaval, and interaortocaval lymph nodes are removed in the same manner as for a right-sided dissection. Care should be taken to identify any right-sided renal arteries to avoid inadvertent ligation. In patients who have had chemotherapy it may be necessary to ligate and transect the inferior mesenteric artery. If suspect nodes are detected, the node dissection can be expanded to perform a complete bilateral dissection. This can be performed from the same side using retraction.

At the conclusion of the operation the lymph nodes are placed in an endobag and extracted. Each packet should be placed in a

separate sac during dissection to help increase yield of nodal evaluation and count. The retroperitoneum is irrigated with warm water, and lymphostasis and hemostasis are ensured. The bowel and adjacent organs (liver, gallbladder, kidneys, ureters, pancreas, and spleen) are carefully inspected for injury. The trocar sites are closed with fascial sutures using a Carter-Thomason device. A drain is not routinely used.

Bilateral L-RPLND

Bilateral dissections may be performed when necessary and can be usually undertaken without a change in patient positioning. When the side of primary tumor is completed with the templates described, a small amount of tissue is left just medial to the contralateral ureter and inferiorly toward the common iliac vessels. These tissues are dissected free, and a bilateral dissection is completed. It is easier to approach a bilateral dissection from the right side.

POSTOPERATIVE CARE

Patients are extubated and transferred to the recovery area without nasogastric tube drainage. The patient may ambulate and resume a liquid diet the night of surgery. **Postoperative tachycardia may occur due to sympathetic stimulation** (Bahnson et al, 1989). Most patients can be discharged on postoperative day 1. Some surgeons advocate consumption of a low-fat diet for 1 to 2 weeks postoperatively.

PROSPECTIVE NERVE-SPARING TECHNIQUES

As in open RPLND, nerve-sparing techniques involve prospectively identifying, dissecting, and preserving the sympathetic chains, hypogastric plexus, and postganglionic fibers. With experience these can be readily identified as more fibrous, compared with lymphatic, tissue. On the right side the postganglionic sympathetic fibers are most easily identified behind the IVC as they cross anterior to the aorta to insert in the hypogastric plexus. Their takeoff from the sympathetic chains is always near lumbar veins, so great care should be taken in clipping lumbar vessels. On the left side it is easiest to identify the postganglionic sympathetic nerves at the ganglia as they leave the sympathetic chain and then dissect them prospectively as they course anterior to the aorta before joining the hypogastric plexus. Care should be taken to avoid energy sources such as electrocautery when dissecting nerve fibers (Peschel et al, 2002; Bhayani et al, 2003; Abdel-Aziz et al, 2006; Steiner et al, 2008).

COMPLICATIONS

The most common reason for conversion to an open procedure is uncontrollable bleeding, and vascular injury is cited as the most common intraoperative complication (Bhayani et al, 2003; Abdel-Aziz et al, 2006; Neyer et al, 2007; Kenney and Tuerk, 2008). Although bleeding and open conversion occurred more frequently in older series, in more recent series this is less common. **In most contemporary series the open conversion rate is less than 5% but has been reported as high as 11.8%** (Rassweiler et al, 2000; Neyer et al, 2007; Nielsen et al, 2007; Cresswell et al, 2008; Skolarus et al, 2008). **Conversion to an open procedure should never be viewed as a failure, and surgeons should be familiar with open RPLND should it be required.** Injury to major abdominal viscera has also been reported but appears to be a rare event (Neyer et al, 2007; Kenney and Tuerk, 2008).

Postoperative complications have been reported at a rate of 9% to 25% in contemporary series (Albqami and Janetschek, 2005; Neyer et al, 2007; Nielsen et al, 2007; Cresswell et al, 2008; Skolarus et al, 2008). Reported complications include chylous ascites, ileus, lymphocele, nerve injury, pulmonary embolus, *Clostridium difficile* colitis, retroperitoneal hematoma, and ureteral injury (Kenney and Tuerk, 2008). Retrograde ejaculation is a potential long-term source of morbidity for patients undergoing both open RPLND and L-RPLND. **The rates of retrograde ejaculation have been consistently low with the laparoscopic approach and range from 0% to 14%** (Albqami and Janetschek, 2005; Neyer et al, 2007; Nielsen et al, 2007; Cresswell et al, 2008; Skolarus et al, 2008; Steiner et al, 2008). **With meticulous ligation of lymphatic channels the incidence of chylous ascites should be less than 2%.** A summary of the morbidity of L-RPLND in the management of clinical stage I NSGCT is provided in Table 33–1. Although it is difficult to compare these data retrospectively to published open RPLND series they appear to compare favorably. In one study of open primary RPLND a 6% transfusion rate with a mean length of stay of 6 days was reported (Subramanian et al, 2010). Similar to L-RPLND, vascular injury was the most common intraoperative complication (4.5% of cases) whereas 2 patients developed chylous ascites (1.8%) and 14 (12.5%) suffered from an ileus. Antegrade ejaculation in this group of patients was 80%, and 7 patients (6.3%) required reoperation (for small bowel obstruction [2 patients], incisional hernia repair [4 patients], and ureteral reconstruction [1 patient]). Interestingly, 2 patients required nephrectomy, 1 for a dysplastic kidney and the other for oncologic reasons.

The morbidity and open conversion rate of L-RPLND after chemotherapy is higher and seems to be experience dependent as well. Early series cited major complication rates of more than 50% (Palese et al, 2002) and high conversion rates (Rassweiler et al, 1996). However, similar to primary L-RPLND, more recent series from experienced centers show improvement in these parameters (Steiner et al, 2004; Permpongkosol et al, 2007). Steiner and colleagues (2004), for example, reported on 68 L-RPLND procedures performed after chemotherapy and reported no open conversions. In another more limited report including 17 patients who underwent L-RPLND after chemotherapy, the authors reported no complications, transfusions, or open conversions (Maldonado-Valadez et al, 2007). Recent studies report preservation of antegrade ejaculation with experience (LeBlanc et al, 2001; Albqami and Janetschek, 2005; Corvin et al, 2005).

RESULTS AND CURRENT STATUS

Unfortunately there are no randomized trials between open RPLND and L-RPLND. Retrospective assessments suggest that patients undergoing L-RPLND have a significantly shorter hospital stay, decreased blood loss, greater quality of life scores, and faster return to normal activities (Janetschek et al, 1996; Abdel-Aziz et al, 2006; Poulakis et al, 2006).

L-RPLND for Clinical Stage I Disease

Published reports of L-RPLND with long-term follow-up suggest that it is an effective treatment option for patients with low-stage NSGCTs (Table 33–2). The staging accuracy of

Table 33–1.

Perioperative and Morbidity Outcomes of L-RPLND for Clinical Stage I NSGCT

STUDY	NO. PATIENTS	OR TIME (MEAN, MIN)	OPEN CONVERSION	EBL (ML)	LENGTH OF STAY (DAYS)	MAJOR INTRAOPERATIVE COMPLICATIONS	MAJOR POSTOPERATIVE COMPLICATIONS	ANTEGRADE EJACULATION
Steiner et al, 2008	42*	323	0	125	4.8	0	2 (lymphoceles)	36 (85.7%)
Skolarus et al, 2008	19	250	0	145	1.5	0	4 (lymphoceles)	23/26† (88.5%)
Cresswell et al, 2008	79	177	1	NR	6	1 Bleeding with open conversion	7 (1 lymphocele, 5 ureteral stenosis/ injury, 1 pulmonary embolus)	78 (98.7%)
Albqami and Janetschek, 2005	103	217	3	144	3.6	3 Bleeding with open conversion	0	217 (100%)
Bhayani et al, 2003	29	258	2	389	2.6	2 Bleeding with open conversion	2 (1 lymphocele, 1 compartment syndrome)	28 (96.6%)
LeBlanc et al, 2001	20	230	0	<50	1.2	0	0	20 (100%)

*Data include 21 patients with clinical stage II disease.
†Ejaculation data only given as percentage of all patients (included are 7 patients with nonclinical stage I disease).
EBL, estimated blood loss; OR, operating room.

Table 33–2.

Oncologic Outcomes of Published L-RPLND Series for Patients with Clinical Stage I NSGCT

STUDY	NO. PATIENTS	FOLLOW-UP (MEAN, MONTHS)	NODE YIELD	N0/N+	NO. OF PN+ RECEIVING ADJUVANT CHEMOTHERAPY	NO. RECURRENCES*	DISEASE-FREE SURVIVAL
Steiner et al, 2008	21	17	22	N0: 16 N+: 5	0 (0%)	N0: 1 (PU) N+: 0	100%
Skolarus et al, 2008	19	23.7	23.8	N0: 13 N1: 6	5 (83.3%)	N0: 0 N+: 0	100%
Cresswell et al, 2008	79	84	14	N0: 60 N+: 19	19 (100%)	N0: 8 (3PU, 2RP, 1PS, 1BC) N+: 0	100%
Albqami and Janetschek, 2005	103	62	NR	N0: 77 N+: 26	26 (100%)	N0: 5 (3PU, 1RP, 1BC) N+: 0	100%
Bhayani et al, 2003	29	72	20	N0: 17 N+: 12	10 (83.3%)	N0: 2 (PU, BC) N+: 1 (M)	100%
LeBlanc et al, 2001	20	15	9.8 (Rt) 17.7 (Lt)	N0: 14 N+: 6	6 (100%)	N0: 0 N+: 0	100%

*Recurrences: PU, pulmonary; RP, retroperitoneal, outside of template; BC, isolated biochemical; PS, portsite.

L-RPLND has been documented and consistent with open series in that 25% to 30% of men with clinical stage I NSGCT are found to harbor occult nodal disease. **A recent study with a mean follow-up of 7 years included 87 patients with clinical stage I disease and revealed a 9% and 0% relapse rate for pN0 and pN+ patients, respectively, with all patients alive and free of disease at last follow-up** (Cresswell et al, 2008). The two retroperitoneal recurrences (2.5%) in this series occurred outside the dissection template, and all patients with pN+ disease were administered adjuvant chemotherapy. Examination of other large L-RPLND series confirms these findings, and recurrence rates and their patterns in this patient population are comparable to those of open RPLND series. The recurrence rate of those found to have negative lymph nodes at L-RPLND is reported between 0% and 10%, which compares favorably to open RPLND series (Hermans et al, 2000; Donohue et al, 1993).

Despite the favorable long-term outcomes the practice of universal chemotherapy in the adjuvant setting in patients with clinical stage I disease who are also harboring metastatic disease at L-RPLND has been the focus of critics who question the therapeutic efficacy of the technique. Interestingly, approximately 70% of men found to have pN1 disease and who undergo a properly performed RPLND are cured and can avoid chemotherapy (Richie and Kantoff, 1991; Donohue et al, 1993; Rabbani et al, 2001). However, patients found to have pN1 disease can opt to receive two cycles of chemotherapy in the adjuvant setting with excellent long-term results rather than risk receiving three or four cycles of chemotherapy should they experience relapse. Thus, the decision to administer chemotherapy to pN1 patients is a matter of preference and factors in the philosophy of the urologist and medical oncologist, as well as the patient.

A report of 120 patients undergoing L-RPLND at one of four institutions in the United States included 10 patients with pathologic stage II disease who underwent surveillance (Nielsen et al, 2007). At a mean follow-up of 34.8 months, none of the patients had experienced a retroperitoneal recurrence. **Additional recent**

reports omitting chemotherapy for patients with pN1 disease who underwent L-RPLND support its therapeutic efficacy, but further studies and follow-up are required (Skolarus et al, 2008; Steiner et al, 2008).

The adequacy of L-RPLND also can be evaluated by examining those patients found to have pathologic stage I disease. If L-RPLND was inadequate, then certain patients with pathologic stage II disease would be mislabeled as having pathologic stage I disease and a retroperitoneal recurrence would result. This supposition has not occurred, because no retroperitoneal recurrence has resulted in a series of therapeutic L-RPLND where a full dissection has been performed (Bhayani et al, 2003; Porter and Lange, 2003; Nielsen et al, 2007; Skolarus et al, 2008; Steiner et al, 2008). The therapeutic efficacy of L-RPLND will continue to be tested as more patients found to have pathologic stage II disease are choosing observation after this technique with good results.

L-RPLND for Clinical Stage II

Fewer reports exist examining the role of L-RPLND for patients with clinical stage II NSGCTs as a primary modality or in the postchemotherapeutic setting. There are limited data regarding the use of primary L-RPLND in patients with clinical stage IIA disease. Several authors have reported on the use of L-RPLND in the postchemotherapeutic setting (see Table 33–2). Albqami and Janetschek (2005) have reported their experience with 59 patients with stage IIB or IIC disease who have undergone postchemotherapy L-RPLND: of the 43 patients with preoperative stage IIB disease with a mean follow-up of 53 months, 1 experienced a recurrence 24 months postoperatively along the external iliac nodes, outside the original template. Another group (Maldonado-Valadez et al, 2007) reported on 17 patients and demonstrated the feasibility of L-RPLND after chemotherapy: viable tumor was found in 3 patients, 2 of whom experienced retroperitoneal recurrences. Full bilateral RPLND, which is typically recommended in this setting, was not performed in these series (Stephenson and Sheinfeld, 2004).

Keeping in line with the goals of open postchemotherapy RPLND, Steiner and associates (2008) have performed bilateral nerve-sparing L-RPLND on 19 postchemotherapy patients with stage IIB disease. The authors found teratoma, necrosis/fibrosis, and active tumor in 4, 14, and 1 patient, respectively. This study included 2 patients with clinical stage IIA disease who underwent L-RPLND without adjuvant chemotherapy. No retroperitoneal recurrences were noted in either group at 17 months follow-up. Longer follow-up and larger series are required to evaluate the efficacy of L-RPLND in the postchemotherapeutic setting.

SUMMARY

L-RPLND has been demonstrated to be a feasible, safe, and effective treatment option for men with clinical stage I NSGCT at large-volume institutions with experienced laparoscopic surgeons. L-RPLND has evolved into a therapeutic operation duplicating the open procedure, with reports demonstrating efficacy and minimal morbidity. Data regarding L-RPLND for clinical stage II disease and for patients who have received chemotherapy are limited and associated with a longer learning curve.



Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

SUGGESTED READINGS

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chapter 34

Tumors of the Penis

Curtis A. Pettaway, MD ● Raymond S. Lance, MD ● John W. Davis, MD

Squamous Cell Carcinoma
Surgical Management of the Primary Tumor
Treatment of the Inguinal Nodes
Radiation Therapy
Chemotherapy
Nonsquamous Penile Malignant Neoplasms

Cancers of the penis are uncommon tumors that are often devastating for the patient and frequently diagnostically and therapeutically challenging for the urologist. Although rare in North America and Europe, penile malignant neoplasms constitute a substantial health concern in many African, South American, and Asian countries.

Any discussion of penile cancers must begin by addressing both benign and malignant tumors of the penis. **Some penile lesions are strictly benign, whereas others have the potential to evolve into malignant neoplasms.** A description of these lesions serves to establish their anatomic, etiologic, and histologic relationship to squamous cell carcinoma, which is the most common malignant tumor of the penis, as well as to other malignant neoplasms that involve the penis. Developments in the etiology of various benign, premalignant, and malignant penile tumors are reviewed in this chapter.

A detailed discussion of surgical management of penile cancer is undertaken in Chapter 35. Here we review the epidemiology, etiology, and natural history of squamous carcinoma and its contemporary management. **Reports have confirmed the importance of pathologic stage and histologic features of the primary tumor as well as the presence and extent of lymph node metastasis in determining prognosis and treatment planning of penile squamous carcinoma** (Ravi, 1993b; McDougal, 1995; Theodorescu et al, 1996; Pizzocaro et al, 1997; Slaton et al, 2001). In addition, developments in staging of the disease, including novel imaging modalities and the use of lymphatic mapping, and modified surgical approaches to improve staging accuracy and reduce potential morbidities are presented. The selection of patients for organ-preserving surgical strategies is discussed.

The role of radiation therapy as both a primary treatment and a palliative measure is reviewed. Contemporary developments in chemotherapy as well as in combination therapy with multiple therapeutic modalities are also discussed. A contemporary scheme for the management of the inguinal region, based on histologic and clinical features, is presented.

Finally, the various nonsquamous malignant neoplasms that may involve the penis are reviewed and discussed.

Please see the Expert Consult website for a discussion of benign lesions, premalignant cutaneous lesions (including Figure 34–1), and virus-related dermatologic lesions.

SQUAMOUS CELL CARCINOMA

Carcinoma in Situ

Carcinoma in situ (Tis) of the penis is called erythroplasia of Queyrat by urologists and dermatologists if it involves the glans penis and prepuce or Bowen disease if it involves the penile shaft or the remainder of the genitalia or perineal region. This nomenclature has served to separate carcinoma in situ from the mainstream of thinking and reporting of penile carcinoma. However, the epidemiology and natural history of this lesion parallel those of early carcinoma of the penis, and carcinoma in situ can progress to invasive carcinoma.

The erythroplasia originally described by Queyrat in 1911 consists of a red, velvety, well-marginated lesion of the glans penis or, less frequently, the prepuce of the uncircumcised man (Aragona et al, 1985). It may ulcerate and may be associated with discharge and pain. On histologic examination the normal mucosa is replaced by atypical hyperplastic cells characterized by disorientation, vacuolation, multiple hyperchromatic nuclei, and mitotic figures at all levels. The epithelial rete extends into the submucosa and appears elongated, broadened, and bulbous. The submucosa shows capillary proliferation and ectasia with a surrounding inflammatory infiltrate that is usually rich in plasma cells. These microscopic features distinguish erythroplasia of Queyrat from chronic localized balanitis. Human papillomavirus (HPV) has been identified in penile carcinoma in situ (Pfister and Haneke, 1984). Progression to invasive carcinoma can occur in 10% to 33% of cases (Buechner, 2002; Bleeker et al, 2009).

In 1912 Bowen described an intraepithelial neoplasm of the skin associated with a high occurrence of subsequent internal malignant disease as a distinct entity. Bowen disease and erythroplasia of Queyrat are histologically similar (Graham and Helwig, 1973) (see Fig. 34–1C on the Expert Consult website). Both tumors are characterized by the noninvasive changes of carcinoma in situ. **Visceral malignant disease is not associated with erythroplasia of Queyrat, and subsequent case-control studies have shown no association of Bowen disease with internal malignant tumors** (Anderson et al, 1973). Thus penile carcinoma in situ does not in itself warrant a specific search for

internal malignant tumors. **Bowen disease is characterized by sharply defined plaques of scaly erythema on the penile shaft. Crusted or ulcerated variants can occur. The appearance can be confused with bowenoid papulosis, nummular eczema, psoriasis, and superficial basal cell carcinoma. If it is not treated then invasive carcinoma may arise in about 5% of cases** (Buechner, 2002). **When all cases of carcinoma in situ are considered, metastasis is extremely rare but has been reported** (Eng et al, 1995).

Treatment is based on proper histopathologic confirmation of malignancy with multiple biopsies of adequate depth to rule out invasion. When lesions are located on the foreskin, circumcision or excision with a 5-mm margin is adequate for local control (Bissada, 1992). In this regard, lesions on the glans penis are difficult to treat by excisional strategies while maintaining normal penile anatomy. Alternative strategies include topical 5-fluorouracil cream (Lewis and Bendl, 1971; Graham and Helwig, 1973; Goette, 1974), 5% imiquimod cream (Danielson et al, 2003), and ablation with the neodymium:yttrium-aluminum-garnet (Nd:YAG) (Landthaler et al, 1986; Frimberger et al, 2002a), potassium titanyl phosphate (KTP) 532-nm, or carbon dioxide lasers (Rosemberg and Fuller, 1980; Tietjen and Malek, 1998; van Bezooijen et al, 2001). Such strategies have been shown to produce excellent cosmetic and functional results. Radiation therapy can be used to treat tumors that are resistant to topical treatment, especially among patients who are not surgical candidates (Kelley et al, 1974; Grabstald and Kelley, 1980).

Key Points: Carcinoma in Situ

- Carcinoma in situ (Tis) is an intraepithelial malignant process.
- Progression to invasive carcinoma may occur in 5% to 33% of cases if it is not treated.
- Metastasis has rarely occurred.
- Cancer eradication with organ-preserving strategies is the goal of therapy.

Invasive Carcinoma

Penile carcinoma accounts for 0.4% to 0.6% of all malignant neoplasms among men in the United States and Europe; it may represent up to 10% of malignant neoplasms in men in some Asian, African, and South American countries (Gloeckler-Ries et al, 1990; Vatanasapt et al, 1995). **However, reports suggest that the incidence of penile cancer is decreasing in many countries, including Finland, the United States, India, and other Asian countries** (Maiche et al, 1992; Frisch et al, 1995; Vatanasapt et al, 1995; Yeole and Jussawalla, 1997). The reasons are unclear but may be related in part to increased attention to personal hygiene.

Penile cancer is a disease of older men, with an abrupt increase in incidence in the sixth decade of life (Persky, 1977). In two studies the mean age was 58 years (Gursel et al, 1973) and 55 years (Derrick et al, 1973). The tumor is not unusual in younger men; in one large series, 22% of patients were younger than 40 years and 7% were younger than 30 years (Dean, 1935); the disease has also been reported in children (Kini, 1944; Narasimharao et al, 1985). The Surveillance, Epidemiology and End Results (SEER) database reveals no racial difference in incidence of penile cancer between black and white men in the United States (incidence for white men, 0.8 of 100,000; for black men, 0.7 of 100,000) (Vatanasapt et al, 1995).

However, a study using SEER data suggested that race is associated with outcome. Rippentrop and colleagues (2004) noted there were 1605 patients diagnosed with penile cancer from 1973 to 1998, with 22.4% (360) dying of the disease. They found factors independently predictive of worsened survival to be higher stage at diagnosis, age older than 65 years, African-American ethnicity, and disease within lymph nodes. These researchers demonstrated a statistically significant disease-specific risk of death that was 2.2-fold higher in African-American patients than in white patients. Although the reason for this disparity is likely to be multifactorial, possibilities include differences in cancer biology, in health care access, or in treatment. These provocative findings clearly deserve further study.

Etiology

The incidence of carcinoma of the penis varies according to circumcision practice, hygienic standard, phimosis, number of sexual partners, HPV infection, exposure to tobacco products, and other factors (Barrasso et al, 1987; Maiche, 1992; Maden et al, 1993; Misra et al, 2004).

Neonatal circumcision has been well established as a prophylactic measure that virtually eliminates the occurrence of penile carcinoma because it eliminates the closed preputial environment where penile carcinoma develops. The chronic irritative effects of smegma, a byproduct of bacterial action on desquamated cells that are within the preputial sac, have been proposed as an etiologic agent. Although definitive evidence that human smegma itself is a carcinogen has not been established (Reddy and Baruah, 1963), its relationship to the development of penile carcinoma has been widely observed. Improper hygiene can lead to buildup of smegma beneath the preputial foreskin, with resulting inflammation. Healing by fibrosis leads to phimosis of the preputial skin, which tends to perpetuate the cycle. Phimosis is found in 25% to 75% of patients described in most large series. Reddy and associates (1984) studied the foreskins of 26 men undergoing circumcision because of phimosis and found epithelial atypia in one third of the specimens.

Carcinoma of the penis is rare among the Jewish population, for whom neonatal circumcision is a universal practice (Licklider, 1961). Similarly, in the United States, where neonatal circumcision is widely practiced, penile cancer represents less than 1% of male malignant neoplasms. Among uncircumcised tribes of Africa and within uncircumcised Asian cultures, penile cancer may amount to 10% to 20% of all male malignant neoplasms (Dodge, 1965; Narayana et al, 1982). Data from most large series show that penile cancer is rare among neonatally circumcised individuals but more frequent when circumcision is delayed until puberty (Frew et al, 1967; Gursel et al, 1973; Johnson et al, 1973). Adult circumcision appears to offer little or no protection from subsequent development of the disease (Maden et al, 1993). **These data suggest that the critical period of exposure to certain etiologic agents may have already occurred at puberty and certainly by adulthood, rendering later circumcision relatively ineffective as a prophylactic tool for penile cancer.**

Recent population-based data reveal that although neonatal circumcision is highly protective for invasive penile cancer it does not afford the same level of protection for carcinoma in situ. Schoen and colleagues (2000) evaluated the incidence of invasive penile cancer or carcinoma in situ during a 10-year period and found only 2 cases of 89 (2.3%)

occurring among neonatally circumcised men, whereas of 118 men with carcinoma in situ, 16 cases were noted in men circumcised at birth (15.7%). Considering that the protective effects of circumcision on invasive penile cancer are likely to be mediated by avoidance of phimosis, it is noteworthy that another study associated phimosis with the development of invasive penile cancer but not carcinoma in situ (Hung-fu et al, 2001).

Male circumcision has also been shown to be effective against HIV-1 infection. This effect was shown to be specific by Reynolds and colleagues (2004). There was no protective effect of circumcision for other sexually transmitted diseases, such as herpes simplex virus type 2 infection, syphilis, or gonorrhea.

HPV infection and exposure to tobacco products appear to be associated with development of penile cancer. Epidemiologic data provided the first clues to a relationship between a sexually transmitted agent and cancer by demonstrating that the wives or ex-wives of men with penile cancer had a threefold higher risk of cervical carcinoma (Graham et al, 1979). Further investigation revealed that the male partners of women with cervical intraepithelial neoplasia had a significantly higher incidence of penile intraepithelial neoplasia (Barrasso et al, 1987). These same male patients were also found to have a greater incidence of HPV infection.

Advanced molecular biologic techniques such as polymerase chain reaction and in-situ hybridization have provided increased evidence for an etiologic role of HPV by identifying specific DNA sequences from different HPV types in primary penile lesions (malignant and benign) but not in normal foreskins (Varma et al, 1991; Iwasawa et al, 1993). More than 25 types of HPV infect genital sites. HPV types 6 and 11 are most commonly associated with nondysplastic lesions such as genital warts, but these are also noted in nonmetastatic verrucous carcinomas. In contrast, HPV types 16, 18, 31, and 33 are associated with in-situ and invasive carcinomas (Wiener and Walther, 1995). **HPV-16 appears to be the most frequently detected type in primary carcinomas and has also been detected in metastatic lesions** (Varma et al, 1991; Iwasawa et al, 1993; Wiener and Walther, 1995). As noted previously, the HPV genome encodes oncoprotein E6, which complexes with the tumor suppressor protein TP53, and oncoprotein E7, which binds the retinoblastoma (RB) protein, thus affecting cell cycle regulation (Munger et al, 1989; zur Hausen, 1996; Levi et al, 1998; Griffiths and Mellon, 1999) via the $P14^{ARF}$/MDM2/p53 and $p15^{INK4a}$/cyclin D/Rb pathways (Bleeker et al, 2009). **Maden and colleagues** (1993) **found that the incidence of HPV infection directly correlated with the number of lifetime sexual partners, which was also related to risk of penile cancer.** Furthermore, Castellsague and colleagues (1997) noted a direct correlation between the number of sexual partners, HPV-infected men, and incidence of cervical neoplasia among their female partners. Thus, for both cervical and penile cancer, HPV infection represents a preventable etiology.

Poblet and coworkers (1999) reported on two cases of coexisting HIV-1 and HPV infection and postulated that HIV-1 could synergize with HPV to increase the progression of HPV penile lesions into penile carcinoma. Although there is evidence supporting this effect in cervical and anal neoplasia, definitive proof for penile cancer awaits further study (Northfelt, 1994).

Although HPV infection is probably an important factor in the development of penile cancer, its presence is not invariable (31% to 63% of patients with penile carcinoma test positive) (Wiener and Walther, 1995), **indicating that additional factors may be involved in the development of the disease or its subtypes.** Additional evidence for Rubin and associates (2001), who performed a sensitive polymerase chain reaction assay, provided this hypothesis-based essay on penile cancer specimens from the United States and Paraguay. Overall, 42% of penile carcinomas were HPV positive. However, only 34.9% and 33.3% of keratinizing and verrucous carcinomas, respectively, were positive, whereas 80% and 100% of basaloid and warty tumor subtypes, respectively, exhibited HPV DNA. Other non–HPV-dependent molecular events leading to penile carcinogenesis have been described, including silencing of the CDK2NA locus via promoter hypermethylation, the expression of genes that target the INK4a/ARF locus, other gene mutations affecting TP53, and $P14^{ARF}$ as well as MDM2 overexpression (reviewed in Ferreux et al, 2003; Bleeker et al, 2009).

Four studies have shown a significant association between exposure to cigarette smoke and development of penile cancer (Hellberg et al, 1987; Daling et al, 1992; Maden et al, 1993; Harish and Ravi, 1995). Hellberg and colleagues (1987) studied the smoking history of 244 men with penile cancer and matched controls. They found a significantly increased odds ratio for penile cancer based on whether an individual had smoked, and the risk increased with the number of cigarettes smoked. This observation held even when the presence of phimosis was controlled. **Harish and Ravi** (1995) **extended these observations by showing that all forms of tobacco products, including cigarettes, chewing tobacco, and snuff, were significantly and independently related to the incidence of penile cancer subsequent to multivariate regression analysis.** It has been hypothesized that tobacco products can act in the presence of HPV infection or bacteria associated with chronic inflammation to promote malignant transformation. These same risk factors are also common to other anogenital carcinomas (Daling et al, 1992; Maden et al, 1993).

Penile trauma may be another risk factor for penile cancer. The development of carcinoma in the scarred penile shaft after mutilating circumcision has been reported as a distinct entity (Bissada et al, 1986). Furthermore, Maden and colleagues (1993) found a greater than threefold risk of penile cancer in men with penile tears and rashes. A case-control study also revealed an odds ratio of 18:1 for the development of penile cancer for those men reporting a penile injury 2 years before the onset of the disease (Hung-fu et al, 2001).

Genital ultraviolet radiation, alone and combined with 8-methoxypsoralen, increases the risk of squamous carcinoma at genital sites. A 12-year follow-up study reported that the risk of penile and scrotal cancer was increased 286 times that of the general population for those exposed to ultraviolet A photochemotherapy and 8-methoxysoralen (PUVA) (Stern et al, 1990). The risk was dose related. For those treated with ultraviolet B exposure, the risk was 4.6-fold enhanced. Another long-term follow-up study of PUVA-associated malignant neoplasia from Sweden revealed a 30-fold increased risk for skin cancer (but not for penile cancer) among males. In this study, PUVA was also associated with respiratory and pancreatic cancers (Lindelof et al, 1991). Lichen sclerosus (also known as balanitis xerotica obliterans) is a risk factor for the development of penile cancer. **Studies have shown the incidence of subsequent cancer with long-term follow-up to be between 3% and 9% of men with lichen sclerosus** (Depasquale et al, 2000; Micali et al, 2001). Velazquez and Cubilla (2003) studied lichen sclerosus occurring in association with penile cancer and noted its presence distinctly among the subset of penile carcinomas that were not associated with HPV.

Larger studies performed in areas where the disease is endemic, incorporating the many risk factors for penile cancer into a multivariate analysis, are clearly needed to define which factors independently confer risk. Thus far, no convincing evidence has been found linking penile cancer to other factors such as occupation, other venereal diseases (gonorrhea, syphilis, and herpes), marijuana use, or alcohol intake (Maden et al, 1993).

Prevention

The role of routine neonatal circumcision as a preventive strategy for penile cancer has been, to say the least, a controversial topic. The position of the American Academy of Pediatrics has changed from one of denial of any medical benefits (Schoen et al, 1989) to the more moderate recent position stating, **"There are potential medical benefits of newborn circumcision; however, these data are not sufficient to recommend routine neonatal circumcision. In such situations where the procedure is not essential to the child's well being, parents should determine what is in the best interest of the child subsequent to being presented unbiased information"** (Shapiro, 1999).

Any argument against circumcision must consider that penile carcinoma represents the only neoplasm for which there exists a predictable and simple means of prophylaxis to spare the organ at risk (Dagher et al, 1973). Although circumcision can obviate the disease, especially where facilities for daily hygiene may be lacking, it may not be as important in countries where good hygiene is practiced. Frisch and colleagues (1995) reported a falling incidence of penile cancer (from 1.15 of 100,000 men to 0.82 of 100,000 men) in the Danish population, which has a circumcision rate of only 1.6%. They attributed this trend to improved hygiene because the incidence of dwellings having a bath facility increased from 35% in the 1940s to 90% in the 1990s. Thus, considering the benefits of circumcision (including the prevention of infections, HIV infection and its transmission, and penile and cervical cancer), enhanced education about the potential benefits of circumcision, especially in developing countries, seems rational (Schoen et al, 1989; Reynolds et al, 2004; Kinkade et al, 2005).

Although neonatal circumcision and good hygiene to prevent the occurrence of phimosis represent important prevention strategies, additional efforts to prevent malignant transformation include avoidance of HPV infection potentially through condom use, of ultraviolet light exposure, and of tobacco products. Thus, modifiable behaviors can potentially prevent penile cancer (Munger et al, 1989; Maden et al, 1993; Harish and Ravi, 1995; Levi et al, 1998; Griffiths and Mellon, 1999; Bleeker et al, 2009).

HPV vaccination could play an emerging role in the future with respect to preventing transmission of HPV between males and females and potentially penile cancer. To date two prophylactic HPV vaccines are available (HPV 16/18 vaccine Cervarix [GlaxoSmithKline] and the quadrivalent HPV 16/18/6/11 vaccine Gardasil [Sanofi Pasteur, Merck Sharpe & Dome]. The efficacy of preventing HPV infection among HPV negative women has been demonstrated (Harper et al, 2004; Villa et al, 2005). To date the safety and immunogenicity of the vaccines has also been established among adolescent boys. However, efficacy in prevention of HPV infection in such populations awaits the results of ongoing studies (Block et al, 2006; Bleeker et al, 2009).

Key Points: Epidemiology, Etiology, and Prevention

- Penile cancer is rare in developed countries and varies worldwide with age, circumcision, and hygiene practices.
- Recent epidemiologic data from the United States suggest a disparity in outcome, with African-Americans exhibiting poorer survival.
- Risk factors for development of penile cancer include lack of neonatal circumcision, phimosis, HPV infection, exposure to tobacco products, penile lichen sclerosus, and potentially penile trauma and exposure to PUVA.
- Histologic subtypes of penile cancer are correlated with HPV infection.
- Penile cancer represents a preventable disease in most cases via neonatal circumcision and/or behavior modification.

Natural History

Carcinoma of the penis usually begins with a small lesion that gradually extends to involve the entire glans, shaft, and corpora. The lesion may be papillary and exophytic or flat and ulcerative; if it is untreated, penile autoamputation may occur as a late result. The rates of growth of the papillary and ulcerative lesions are similar, but the flat, ulcerative tumor has a tendency toward earlier nodal metastasis and is associated with poorer 5-year survival rates (Dean, 1935; Marcial et al, 1962; Ornellas et al, 1994). Lesions larger than 5 cm (Beggs and Spratt, 1964) and those extending over 75% of the shaft (Staubitz et al, 1955) are also associated with an increased incidence of metastases and a decreased survival rate. However, others have not found a consistent relationship between lesion sizes, presence of metastases, and decreased survival (Ekstrom and Edsmyr, 1958; Puras et al, 1978).

Buck fascia acts as a temporary natural barrier to local extension of the tumor, protecting the corporeal bodies from invasion. Penetration of Buck fascia and the tunica albuginea permits invasion of the vascular corpora and establishes the potential for vascular dissemination. Urethral and bladder involvement are rare (Riveros and Gorostiaga, 1962; Thomas and Small, 1968).

The earliest route of dissemination from penile carcinoma is metastasis to the regional femoral and iliac nodes. A detailed description of lymphatic drainage of the penis is found elsewhere in this text and is well documented in the literature (Dewire and Lepor, 1992). Briefly, the lymphatics of the prepuce form a connecting network that joins with the lymphatics from the skin of the shaft. These tributaries drain into the superficial inguinal nodes (the nodes external to the fascia lata). The lymphatics of the glans join the lymphatics draining the corporeal bodies, and they form a collar of connecting channels at the base of the penis that drain by way of the superficial nodes. The superficial nodes drain to the deep inguinal nodes (those deep to the fascia lata). From there, drainage is to the pelvic nodes (external iliac, internal iliac, and obturator). Penile lymphangiographic studies demonstrate a consistent pattern of drainage that proceeds from superficial inguinal to deep inguinal to pelvic node sites without evidence of ipsilateral drainage (Cabanas, 1977, 1992). Multiple cross-connections exist at all levels of drainage, so that penile lymphatic drainage is bilateral to both inguinal areas.

Metastatic enlargement of the regional nodes eventually leads to skin necrosis, chronic infection, and death from inanition, sepsis, or hemorrhage secondary to erosion into the femoral vessels. Clinically detectable distant metastatic lesions to the lung, liver, bone, or brain are uncommon and are reported to occur in

1% to 10% of cases in most large series (Staubitz et al, 1955; Riveros and Gorostiaga, 1962; Beggs and Spratt, 1964; Derrick et al, 1973; Johnson et al, 1973; Kossow et al, 1973; Puras et al, 1978). Such metastases usually occur late in the course of the disease after the local lesion has been treated. Distant metastases in the absence of regional node metastases are unusual.

Carcinoma of the penis is characterized by a relentless progressive course, causing death for the majority of untreated patients within 2 years (Beggs and Spratt, 1964; Skinner et al, 1972; Derrick et al, 1973). Rarely, long-term survival occurs, even with advanced local disease and regional node metastases (Furlong and Uhle, 1953; Beggs and Spratt, 1964). No report of spontaneous remission of carcinoma of the penis is known. Five to 15 percent of patients have been reported to develop a second primary neoplasm (Buddington et al, 1963; Beggs and Spratt, 1964; Gursel et al, 1973), and one series reported secondary carcinoma in 17% of patients (Hubbell et al, 1988).

Modes of Presentation

Signs

It is the penile lesion itself that usually alerts the patient to the presence of penile cancer. The presentation ranges from a relatively subtle induration or small excrescence to a small papule, pustule, warty growth, or more luxuriant exophytic lesion. It may appear as a shallow erosion or as a deeply excavated ulcer with elevated or rolled-in edges. Phimosis may obscure a lesion and allow a tumor to progress silently. Eventually, erosion through the prepuce, foul preputial odor, and discharge with or without bleeding call attention to the disease.

Penile tumors may present anywhere on the penis but occur most commonly on the glans (48%) and prepuce (21%). Other tumors involve the glans and prepuce (9%), the coronal sulcus (6%), or the shaft (<2%) (Sufrin and Huben, 1991). This distribution of lesions may be due to constant exposure of the glans, coronal sulcus, and interior prepuce to irritants (e.g., smegma, HPV infection) within the preputial sac, whereas the shaft is relatively spared.

Rarely, a mass, ulceration, suppuration, or hemorrhage in the inguinal area may be due to nodal metastases from a lesion concealed within a phimotic foreskin. Urinary retention or urethral fistula due to local corporeal involvement is a rare presenting sign.

Symptoms

Pain does not develop in proportion to the extent of the local destructive process and usually is not a presenting complaint. Weakness, weight loss, fatigue, and systemic malaise occur secondary to chronic suppuration. On occasion, significant blood loss from the penile lesion, the nodal lesion, or both may occur. Because local disease and regional disease are usually far advanced by the time distant metastases occur, presenting symptoms referable to such metastases are rare.

Diagnosis

Delay

Patients with cancer of the penis, more than patients with other types of cancer, seem to delay seeking medical attention (Lynch and Krush, 1969). In large series, 15% to 50% of patients delayed medical care for more than a year (Dean, 1935; Buddington et al, 1963; Hardner et al, 1972; Gursel et al, 1973). Explanations include embarrassment, guilt, fear, ignorance, and personal neglect. This level of denial is substantial, given that the penis is observed and handled on a daily basis.

Delay on the part of the physician in initiating both diagnosis and treatment may also be considerable. In some instances patients have been given prolonged courses of antibiotics or topical antifungal preparations before being referred for biopsy. Although some studies show that the difference in survival rates between patients who present early and those who present later is negligible (Ekstrom and Edsmyr, 1958; Johnson et al, 1973), other series show decreased survival with longer delay (Hardner et al, 1972). It appears logical that earlier diagnosis and treatment should improve outcome.

Examination

At presentation most lesions are confined to the penis (Skinner et al, 1972; Derrick et al, 1973; Johnson et al, 1973). The penile lesion is assessed with regard to size, location, fixation, and involvement of the corporeal bodies. Inspection of the base of the penis and scrotum is necessary to rule out extension into these areas. Rectal and bimanual examination provides information about perineal body involvement and presence of a pelvic mass. Careful bilateral palpation of the inguinal area for adenopathy is extremely important.

Key Points: Natural History and Presentation

- Penile cancer often begins on the surface of the glans penis or in the preputial area, where it progressively enlarges.
- Delay in seeking medical attention and then subsequent definitive biopsy is common.
- Examination of both the penile primary tumor and the inguinal region is critical to treatment planning.
- Metastasis occurs by embolization of tumor deposits from the penile tumor through penile lymphatics to the inguinal lymph nodes.
- Distant metastases occur late in the history of the disease.

Biopsy

Confirmation of the diagnosis of carcinoma of the penis and assessment of the depth of invasion, the presence of vascular invasion, and the histologic grade of the lesion by microscopic examination of a biopsy specimen are mandatory before the initiation of any therapy. This provides insight into the therapeutic options for treatment of the primary lesion as well as the likelihood of nodal metastases in patients with no palpable adenopathy (McDougal, 1995; Lopes et al, 1996; Theodorescu et al, 1996).

Biopsy may be a separate procedure from definitive surgical treatment. A dorsal slit is frequently necessary to gain adequate exposure of the lesion for satisfactory biopsy. An alternative approach to treatment is biopsy with frozen-section confirmation followed by partial or total penectomy. Full informed consent must be obtained before the procedure. Velazquez and colleagues (2004) demonstrated the shortcomings of superficial diagnostic biopsies in a study evaluating specimens from 57 patients. There was difficulty in delineating the extent of depth in 91% of patients, discordance with the histologic grade in 30% of patients (specifically with verrucous and mixed histologic patterns), and failure to

detect any cancer in 3.5% of patients with well-differentiated cancers. The importance of obtaining an adequate biopsy specimen cannot be overemphasized.

Histologic Features

Most tumors of the penis are squamous cell carcinomas demonstrating keratinization, epithelial pearl formation, and various degrees of mitotic activity. The normal rete pegs are disrupted. Invasive lesions penetrate the basement membrane and the surrounding structures. Cubilla and associates (1993) originally divided penile cancers by growth pattern into superficially spreading squamous carcinoma, vertical growth carcinoma, verrucous carcinoma, and multicentric carcinoma. The superficially spreading carcinoma occurred most frequently, and inguinal lymph node metastases were found in 42% of patients. However, lymph node metastases were noted in 82% of patients with a vertical growth pattern, in none of those with a verrucous pattern, and in 33% of those with multicentric carcinomas. Subsequent to review of 61 cases from Memorial Sloan-Kettering Cancer Center, Cubilla and colleagues (2001) classified the histologic types as follows: usual type, 59% of cases; papillary, 15%; basaloid, 10%; warty (condylomatous), 10%; verrucous, 3%; and sarcomatoid, 3%. Of note, both the basaloid and sarcomatous types were associated with aggressive behavior; 5 of 7 patients with these histologic patterns exhibited metastasis, and 5 of 8 (63%) died. In contrast, the verruciform histologic patterns were more favorable (1 patient with metastasis and no deaths). The typical squamous histologic type was intermediate in biologic potential; 14 of 26 patients exhibited metastases, and 13 of 36 (36%) died.

The basaloid variant, in addition to its aggressive behavior as noted previously, is associated with HPV expression in approximately 80% of cases (Gregoire et al, 1995; Cubilla et al, 1998, 2001; Rubin et al, 2001).

Squamous cell carcinomas have classically been graded using the Broders classification to define the level of differentiation on the basis of keratinization, nuclear pleomorphism, number of mitoses, and several other features (Broders, 1921; Lucia and Miller, 1992). This grading system was originally designed for squamous carcinoma of the skin and has been adapted by pathologists for penile squamous carcinoma. Four grades were originally described, but it is common for authors to modify this to a three-grade system by combining grades (Maiche et al, 1991). Low-grade lesions (grade 1 and grade 2) constitute 70% to 80% of the reported cases at diagnosis, whether a three- or four-grade system is used (Maiche et al, 1991). These well-differentiated lesions show cords of atypical squamous cells projecting downward from a hyperkeratotic epidermis. The lower-grade carcinomas typically demonstrate keratin, prominent intercellular bridges, and keratin pearls, characteristics that are absent in high-grade tumors. Almost half the tumors originating in the shaft are poorly differentiated (grade 3 and grade 4, depending on scale), whereas only 10% of tumors located in the prepuce are high-grade tumors (Maiche et al, 1991). Thus, grade and stage are often correlated.

Several studies have emphasized the association of high-grade disease with regional nodal metastases (Fraley et al, 1989; Ravi, 1993b; McDougal, 1995; Theodorescu et al, 1996; Heyns et al, 1997). Overall there is a significant body of agreement as to the histologic features that characterize high tumor grade (grade 3 and grade 4) and its correlation with nodal metastasis. However, as noted previously, most tumors are of lower grades. Histologic features that would better stratify the prognosis for patients with invasive, low- to intermediate-grade penile cancers would be of value for management of patients.

Slaton and colleagues (2001) found that describing the percentage of poorly differentiated cancer in the primary penile tumor specimen correlated with lymph node metastasis. In this study, a semiquantitative system that estimated the amount of high-grade cancer (i.e., ≤50% vs. >50%) was significantly associated with nodal metastases and was more predictive than the Broders three-grade system in stratifying those with or without nodal metastasis.

Recently, however, Chaux and colleagues (2009 grade citation) questioned these findings as they examined 117 specimens among patients undergoing primary tumor therapy and lymph node dissection. Over 50% of the tumors were actually heterogeneous with respect to grade, and among these tumors any proportion of grade 3 cancer was associated with lymph node metastasis. These disparate findings point to at least three problems with respect to grading and prognosis, including (1) lack of a uniform system, (2) reproducibility of interpretation, and (3) intratumoral heterogeneity of tumor components.

Vascular invasion by tumor cells has significant prognostic importance but may not be specifically mentioned in pathology reports. When vascular invasion is present it provides valuable information. Four studies have assessed its presence or absence, and it was an important predictor of nodal metastasis in all the reports (Fraley et al, 1989; Lopes et al, 1996; Heyns et al, 1997; Slaton et al, 2001). **Thus the pathologist should specifically comment on the presence or absence of vascular invasion in the surgical specimen.**

Perineural invasion was recently found to be present in 36% of cases analyzed in a multi-institutional data set of 134 patients and was a strong predictor of lymph node metastasis (Velazquez et al, 2008).

Laboratory Studies

The results of laboratory tests in patients with penile cancer are often normal. Anemia, leukocytosis, and hypoalbuminemia may be present in patients with chronic illness, malnutrition, and extensive suppuration at the area of the primary and inguinal metastatic sites. Azotemia may develop secondary to urethral or ureteral obstruction.

Key Points: Biopsy and Histologic Features

- Adequate tumor biopsy is essential to diagnosis and treatment planning.
- Squamous carcinoma histologic subtypes include usual type, papillary, basaloid, warty, verrucous, and sarcomatoid. They vary with respect to metastatic potential.
- Pathologic description of anatomic structures invaded (i.e., stage), grade, and the status of vascular and perineural invasion provide important information to assess the risk of metastasis.

Hypercalcemia without detectable osseous metastases has been associated with penile cancer (Anderson and Glenn, 1965; Rudd et al, 1972). In a review from Memorial Sloan-Kettering Cancer Center (Sklaroff and Yagoda, 1982), 17 of 81 patients (20.9%) were hypercalcemic. Hypercalcemia seems to be largely a function of the bulk of the disease. It is often associated with inguinal metastases and may resolve after excision of involved inguinal nodes (Block et al, 1973). **Parathyroid hormone and**

related substances may be produced by both tumor and metastases that activate osteoclastic bone resorption (Malakoff and Schmidt, 1975). Medical treatment of hypercalcemia includes aggressive saline hydration to restore the extracellular fluid volume and to promote both sodium and calcium excretion. The administration of diuretics is performed if volume overload is suspected. Bisphosphonates (e.g., pamidronate, etidronate and zoledronic acid) have become first-line therapy because they possess demonstrated efficacy as antiresorptive agents and are relatively safer than mithramycin, an older agent (Videtic et al, 1997; Morton and Lipton, 2000). For severe hypercalcemia associated with neurologic manifestations, the antiresorptive bisphosphonates can be combined with an agent that produces calciuria, such as calcitonin, to rapidly lower serum calcium levels.

Radiologic Studies

Primary Penile Tumor. **In patients with penile cancer both the primary tumor and the inguinal lymph nodes are readily assessed by palpation.** However, Horenblas and associates (1991) found that physical examination incorrectly established the actual pathologic stage in 26% of cases, with understaging in 10% and overstaging in 16%. It is clear that more accurate means of staging for penile tumors is needed.

Penile ultrasonography was performed on 16 patients referred for primary therapy by Horenblas and colleagues (1994). With use of a 7.5-MHz linear array small parts transducer they found that the ultrasound appearance of cancer was invariably hypoechoic. However, ultrasound examination often underestimated the thickness of tumors and could not delineate invasion into the subepithelial connective tissue of the glans penis from corpus spongiosum involvement (i.e., glanular stage T1 vs. glanular stage T2). However, the tunica albuginea separating the corpus cavernosum from the glans was easily identified in all patients and the sensitivity for detecting corpus cavernosum invasion was 100%. This study confirmed the value of ultrasonography in assessing the primary tumor, as reported by others (Yamashita and Ogawa, 1989; Dorak et al, 1992).

Several studies have assessed the role of magnetic resonance imaging (MRI) in evaluating both the normal penis and its involvement by cancer. Vapnek and associates (1992) described the MRI appearance of the normal corpus cavernosum, corpus spongiosum, tunica albuginea, and Buck fascia. Of six patients with urethral cancer, the disease was accurately staged in five (83%). de Kerviler and colleagues (1995) used gadolinium contrast-enhanced MRI to compare both clinical and MRI findings with tumor pathologic stage. Clinical examination correctly staged six of nine tumors: MRI was correct in seven of nine cases but was not useful for clinical T1 lesions. Compared with MRI and ultrasonography, computed tomography (CT) has poor soft tissue resolution and has not been useful for imaging the extent of the primary tumor (Vapnek et al, 1992).

Lont and associates (2003) directly compared physical examination with ultrasonography and MRI to assess their ability to determine the tumor stage. They evaluated 33 patients with penile squamous cell carcinoma, all of whom underwent ultrasound examination, MRI, and physical examination of the primary tumor. Findings were correlated with histologic evaluation of the specimens obtained at surgery with a focus on determining the invasion of the corpus cavernosum. The respective positive predictive value, sensitivity, and specificity for the study were as follows—physical examination: 100%, 86%, 100%; ultrasound examination: 67%, 57%, 91%; and MRI: 75%, 100%, 91%. This comparative study concluded that physical examination is reliable in determining corporeal invasion and that additional tests are mainly of value when physical examination cannot be properly performed.

The technique of artificial erection (by intracorporeal injection of prostaglandin E_1) may augment the use of contrast-enhanced MRI in staging of the primary tumor. A study by the European Institute of Oncology evaluated nine patients to compare clinical, pathologic, and MRI staging (Scardino et al, 2004). MRI aided by artificial erection and contrast enhancement was shown to be of value as it correlated with pathologic stage in eight of nine cases, whereas physical examination correlated with only five of nine cases. These data suggest that this novel MRI approach could be beneficial in staging of glanular tumors, specifically when physical examination findings are equivocal. **Thus, for small-volume glanular lesions, imaging studies add virtually no additional information to palpation in most cases. However, for lesions thought to invade the corpus cavernosum, contrast-enhanced MRI (perhaps augmented with artificial erection) may provide unique information, especially when physical examination findings are equivocal and organ-sparing techniques are being considered.**

Inguinal/Pelvic Region. The ability to noninvasively determine the presence or absence of inguinal and pelvic metastases in patients with penile cancer remains problematic because physical examination exhibits varying reliability based on the grade and stage of the primary tumor. Historically, lymphangiography was used as an adjunct to physical examination in the identification of microscopic inguinal and pelvic nodal metastases and to direct needle biopsy (Vapnek et al, 1992). The technical difficulty of the procedure, combined with the availability of CT and MRI, has made lymphangiography obsolete in staging of this disease. Both CT and MRI techniques depend solely on lymph node enlargement for detection of metastases but are unable to define the internal architecture of normal-sized nodes. Because CT and MRI have similar accuracy in determining lymphadenopathy in other cancers, CT has often been the imaging modality chosen in penile cancer to examine the inguinal and pelvic areas as well as to rule out more distant metastases.

Horenblas and associates (1991) compared the ability of physical examination, CT, and lymphangiography to assess the inguinal region in patients who were surgically staged or had prolonged follow-up. In 102 patients with a 39% prevalence of positive nodes, the sensitivity and specificity of physical examination were 82% and 79%, respectively. Of note, both CT and lymphangiography were performed in patients who were thought to have metastases. The sensitivity of lymphangiography was only 31%, but there were no false-positive results. Similarly, the sensitivity and specificity of CT were 36% and 100%, respectively. The combination of CT and lymphangiography performed simultaneously demonstrated equally poor sensitivity. Only one fifth of patients had positive nodes detected with either test. **On the basis of these data the authors concluded that CT and lymphangiography offer no useful additional information over physical examination, especially in patients with no palpable adenopathy.** An important caveat is that CT may have a role in examination of the inguinal region in obese patients or in those who have had prior inguinal surgery, for whom the physical examination may be unreliable. In addition, in patients with known inguinal metastases, CT-guided biopsy of enlarged pelvic nodes may provide important information for consideration of neoadjuvant chemotherapeutic strategies.

Recent insights in the field of nanoparticle technology are being applied to imaging of genitourinary malignant neoplasms to

enhance detection of microscopic metastases. Ferumoxtran-10 particles (size = 35 nm), administered at a dose of 2.6 mg of iron per kilogram of body weight intravenously combined with MRI are now capable of imaging microscopic metastasis in lymph nodes that are by size criteria normal (1 cm). Tabatabaei and colleagues (2005) evaluated lymphotropic nanoparticle-enhanced MRI (LNMRI) in seven patients with penile cancer who subsequently underwent groin dissection. Five of seven patients had no palpable adenopathy. LNMRI was highly sensitive and detected positive nodes in all five of these patients. Of note the size range of the metastases was less than 1 cm in four patients.

Recently, squamous carcinoma was shown to take up the radiopharmaceutical fluorodeoxyglucose (FDG) and be amenable to detection utilizing combination positron emission tomography (PET) and CT. Scher and associates (2005) evaluated PET/CT among 13 patients with penile cancer injected FDG. Five of 13 patients had metastatic disease, and FDG-PET/CT detected it in 4 of them (80% sensitivity). Thus both LNMRI and PET/CT hold promise in the detection of microscopic inguinal disease in penile cancer but these promising initial reports will require validation among larger data sets.

In general, distant metastases occur late in the course of the disease, usually in patients with recognized significant inguinal and pelvic adenopathy. The most common metastatic sites are the lung, bone, and liver. In addition to abdominal and pelvic CT, radionuclide bone scintigraphy and chest radiography may be indicated to stage the extent of disease in patients thought to have widespread metastases (Vapnek et al, 1992).

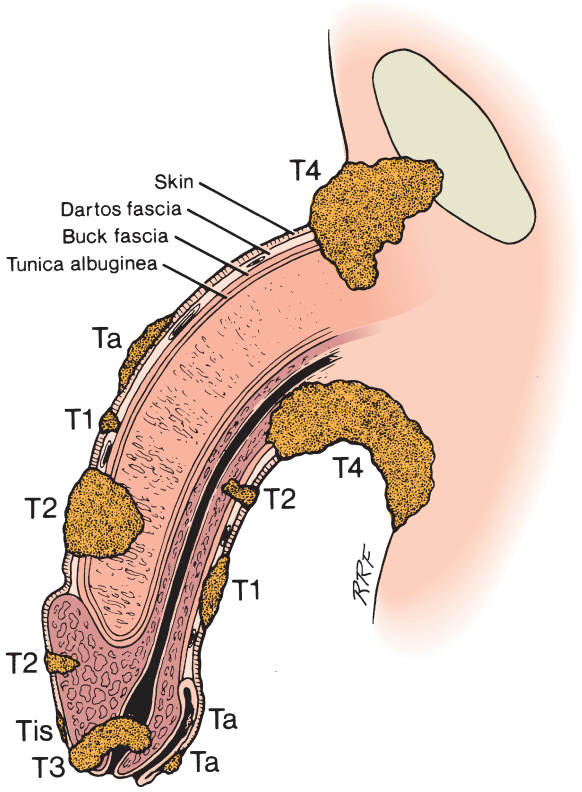


Figure 34–2. Because treatment decisions for inguinal node dissections are based on the characteristics of the primary lesion (see section on treatment of inguinal nodes), a careful assessment of the depth of invasion of the primary tumor is required. This diagram illustrates the importance of depth of invasion in assigning tumor (T) stage.

Key Points: Radiologic Studies

- Soft tissue detail of penile tumors is best imaged by ultrasonography or MRI.
- Physical examination provides the most reliable staging information for small distal lesions.
- Penile MRI performed in combination with artificial erection may provide unique staging information when physical examination findings are equivocal.
- Physical examination of the inguinal region remains the clinical gold standard for evaluating the presence of metastasis.
- CT or MRI can be useful in evaluating the inguinal region of obese patients and in those having prior inguinal surgery.
- Nanoparticle and PET/CT of the inguinal region have shown promising results in the detection of minimal inguinal metastases but validation in larger series is required.

Penile Cancer Staging

Sixth Edition TMN System. The unified Union Internationale Contre le Cancer (UICC, 1989) and American Joint Committee on Cancer (AJCC) TNM system (sixth edition) is most commonly used in contemporary series for staging penile cancer (Harmer, 1978; Fleming et al, 1997; Greene et al, 2006).

The primary tumor is staged according to histologic features and the precise anatomic structure invaded (Fig. 34–2). Experience documented in prior series has supported this system. Considering those patients with no palpable adenopathy, it is clear that patients with Tis and Ta lesions have a prognosis different from that of patients exhibiting T1 and T2 lesions (Johnson et al, 1985; Solsona et al, 1992; Gerber, 1994; Villavicencio et al, 1997). Because these histologic features are directly related to the risk of lymph node metastasis, such a staging arrangement is practical and informative with respect to surgical decision-making and prognosis.

The sixth edition TNM version also recognizes the importance of the extent of nodal involvement as a prognostic factor in survival, in that separate categories are used for patients with a single positive node (N1) versus those with bilateral nodes (N2) and deep inguinal or pelvic involvement (i.e., Cloquet or iliac nodes).

Challenges and Modifications. Horenblas and colleagues (1994) among others have challenged the utility and prognostic value of the sixth edition TMN system (Leijte et al, 2008a) based on data from several series including their own. With respect to primary tumor staging they recommended differentiating corpus spongiosum (CS) and cavernosum (CC) as separate T categories (i.e., T2 and T3, respectively) based on significant differences in both 5-year disease-specific survival (CS = 77.7% vs. CC = 52.6%) and percent of node-negative disease in the original TMN classification versus their proposed categories (current T category pT2 = 57.5%, pT3 = 57.9%; proposed T category pT2 = 65.7%, pT3 = 42.7%) (Leijte et al, 2008). Using this rationale they and others have also questioned the scientific basis for classifying isolated urethral involvement as stage T3 (Leijte et al, 2008a; Cubilla, 2009). Patients with isolated distal urethral involvement without corpus cavernosum involvement are often good candidates for organ preservation. Invasion of the prostate currently designated as stage T3 is rare, and most would concur that prostatic invasion is more

appropriately designated as pT4 related to invasion of adjacent structures rather than pT3 (i.e., same as urethral involvement in the current system).

With respect to nodal staging it is difficult to assign nodal status before definitive therapy using the sixth edition TMN "N" definitions owing to the potential for false-positive and false-negative inguinal examinations by palpation and fine-needle aspiration. In reality the current TNM staging system represents a pathologic staging system in which nodal histology must be assessed (i.e., aspiration, biopsy, lymphadenectomy). Leijte and coworkers (2008b) have proposed a clinical staging system for penile cancer based on their experience in more than 500 patients treated at the Netherlands Cancer Institute. Factors important in stratifying patient survival before definitive therapy included the presence (N+) or absence of palpable lymph nodes (N0), unilateral (N1) versus bilateral mobile nodes (N2), and a fixed inguinal mass or radiologic evidence of pelvic adenopathy (N3). The 5-year disease-specific survival (DSS) provided significantly different prognostic information for all three node positive categories (N1, N2, N3 = 77%, 54%, and 11%, respectively). Using the current N definition they could not demonstrate a significant survival difference between N1 and N2 categories (70.2% vs. 58.3%, $P = 0.176$). The proposed system if validated could represent an improvement in staging that may be more readily adapted universally (Leijte et al, 2008b).

Seventh Edition TMN Penile Staging System. A modified AJCC-UICC staging sytem has been published that addresses several inadequacies of the sixth edition TMN (Table 34–1). With respect to the primary tumor, because grade and the presence of vascular invasion are established prognostic markers in predicting the risk of subsequent inguinal metastasis the seventh edition TMN stratifies pT1 stage by their presence (i.e., high-grade tumors, vascular invasion present = pT1b) or absence (= pT1b) (Slaton et al, 2001; Solsona et al, 2004; Ficarra et al, 2005). In addition, prostatic invasion (a rare finding) is now included in the pT4 designation.

Of considerable importance is that the seventh edition has both clinical and pathologic nodal staging descriptors to facilitate both clinical and pathologic staging to better predict prognosis before definitive therapy. As pointed out by Leijte and colleagues (2008b) the prognosis worsens for patients exhibiting greater degrees of palpable adenopathy (i.e., unilateral vs. bilateral vs. a fixed mass) or positive nodes on imaging versus those with clinically negative inguinal lymph nodes. Considering pathologic nodal factors further, the seventh edition stratifies patients with a single positive node from those with multiple or bilateral nodes and further recognizes the ominous prognosis (5% to 18% 5-year survival) associated with extranodal extension of cancer (Srinivas et al, 1987; Ravi, 1993b; Lont et al, 2007).

Considering that the pathologic status of inguinal nodes is the driving factor determining survival, stage groupings (i.e., stage 0 to stage IV [see Table 34–1]) in the seventh edition TMN utilize the extent of nodal involvement as the major consideration. Thus the strength of the unified AJCC-UICC seventh edition TNM system (2009) is that it provides not only an accurate assessment of the primary tumor based on clinical staging (examination, biopsy) but also clinical and improved pathologic descriptors of lymph node status in order to predict outcome. This new TMN version, however, awaits validation using contemporary data sets.

In the 2009 AJCC-UICC TNM staging system the primary tumor stage is assigned by biopsy (or even more reliably by complete resection) and additional prognostic factors within the primary tumor now included in the TNM system (i.e., tumor grade and the presence of vascular invasion). In most cases the presence of

Table 34–1.

American Joint Committee on Cancer Staging for Penile Cancer

Primary Tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
Ta	Noninvasive verrucous carcinoma*		
T1a	Tumor invades subepithelial connective tissue without lymph vascular invasion and is not poorly differentiated (i.e., grade 3-4)		
T1b	Tumor invades subepithelial connective tissue without lymph LVI or is poorly differentiated		
T2	Tumor invades corpus spongiosum or cavernosum		
T3	Tumor invades urethra		
T4	Tumor invades other adjacent structures		
Lymph Nodes (N)			
NX	Regional nodes cannot be assessed†		
pNX	Regional nodes cannot be assessed‡		
N0	No palpable or visibly enlarged inguinal lymph nodes†		
pN0	No regional lymph node metastasis‡		
N1	Palpable mobile unilateral inguinal lymph node†		
pN1	Metastasis in a single inguinal lymph node‡		
N2	Palpable mobile multiple or bilateral inguinal lymph nodes†		
pN2	Metastasis in multiple or bilateral inguinal lymph nodes‡		
N3	Palpable fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral†		
pN3	Extranodal extension of lymph node metastasis or pelvic lymph node(s) unilateral or bilateral‡		
Distant Metastasis (M)			
M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)		
M1	Distant metastasis§		
Stage Grouping			
Stage 0	Tis	N0	M0
	Ta	N0	M0
Stage I	T1a	N0	M0
Stage II	T1b	N0	M0
	T2	N0	M0
	T3	N0	M0
Stage IIIa	T1-3	N1	M0
Stage IIIb	T1-3	N2	M0
Stage IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

*Broad pushing penetration (invasion) is permitted; destructive invasion is against the diagnosis.

†Based on palpation, imaging.

‡Based on biopsy, or surgical excision.

§Lymph node metastasis outside the true pelvis in addition to visceral or bone sites.

From Edge SB, Byrd DR, Compton CC, et al. AJCC cancer staging manual. 7th ed. New York: Springer; 2010.

Table 34–2.

Minimal Diagnostic Criteria for Carcinoma of the Penis

Primary Tumor (T)
Clinical examination
Incisional-excisional biopsy of lesion (or complete resection) and histologic examination for grade, anatomic structure invaded, and presence of vascular invasion
Regional and Juxtaregional Lymph Nodes (N)
Clinical examination
Computed tomography, if inguinal adenopathy is palpable*
Superficial inguinal node dissection (as indicated for high grade, vascular invasion, or invasive histologic pattern)
Aspiration cytology (as indicated)
Distant Metastases (M)
Clinical examination
Chest radiography
Biochemical determinations (liver functions, calcium)
Magnetic resonance imaging, bone scintigraphy (as indicated)

*Computed tomography should also be performed in obese patients and those having prior inguinal surgery, whose physical examination findings may be unreliable.

palpable adenopathy, along with the histologic features of the primary tumor, determines the need for additional imaging studies. Positive fine-needle aspiration of palpably enlarged inguinal nodes or fine-needle biopsy of pelvic adenopathy identified by CT can assist in assigning nodal stage before therapy. In those patients requiring surgical staging (palpable lymph nodes or those with adverse primary tumor histologic features), pathologic nodal status assigned according to seventh edition TNM stage provides valuable prognostic information. The suggested diagnostic criteria for current TNM staging are listed in Table 34–2.

Key Points: Staging

- The sixth edition unified TNM staging system was a pathologic system that reflected the importance of describing penile structures invaded by tumor but lacked several important descriptors of primary tumor histology and lymph node extent in determining outcome.
- Both clinical and pathologic factors related to the presence and extent of lymph node involvement determine survival and should be recorded.
- The current seventh edition unified TMN staging system represents a consensus document that includes both clinical and pathologic descriptors that provide important prognostic information. Its prognostic utility awaits further independent validation.

Differential Diagnosis

A number of penile lesions must be considered in the differential diagnosis of penile carcinoma. They include condyloma acuminatum, Buschke-Löwenstein tumor, and balanitis xerotica obliterans as well as a number of infectious lesions (e.g., chancre, chancroid, herpes, lymphopathia venereum, granuloma inguinale, and tuberculosis). These diseases can be identified by appropriate skin tests, tissue studies, serologic examinations, cultures, or specialized staining techniques.

SURGICAL MANAGEMENT OF THE PRIMARY TUMOR

Organ Preservation

Surgical amputation of the primary tumor remains the oncologic gold standard for rapid definitive treatment of the penile primary tumor; local recurrence rates range from 0% to 8% (de Kernion et al, 1973; McDougal et al, 1986; Horenblas et al, 1992). Whereas amputation is often necessary for bulky stage T2-T4 tumors, it has been shown to decrease sexual quality of life (Opjordsmoen and Fossa, 1994). This is relevant because approximately 55% of penile cancer patients are 60 years of age or younger and 30% are 55 years of age or younger (Narayana et al, 1982).

It is generally accepted that patients with penile primary tumors exhibiting favorable histologic features (stages Tis, Ta, T1; grade 1 and grade 2 tumors) are at a lower risk for metastases. These patients are also best suited for organ-sparing or glans-sparing procedures (Solsona et al, 2004). The goal of treatment is to preserve glans sensation where possible or at least to maximize penile shaft length. Such approaches include topical treatments (5-fluorouracil or imiquimod cream for Tis only), radiation therapy, Mohs surgery, limited excision strategies, and laser ablation (Sanchez-Ortiz and Pettaway, 2003; Solsona et al, 2004; Minhas et al, 2005; Crook et al, 2009). This section focuses on novel insights into surgical strategies to achieve organ preservation. Radiation-based strategies are discussed later in the section Radiation Therapy for the Primary Lesion.

Circumcision and Limited Excision Strategies

Circumcision, limited excisions of the glans, and glans removal with sparing of the penile shaft represent surgical strategies to maintain function and penile length. Historically, data on circumcision and limited excision of glanular lesions have been associated with recurrence rates from 11% to 50% (Hanash et al, 1970; Skinner et al, 1972; McDougal et al, 1986). However, the grade, size, and exact location of the lesion and the status of surgical margins were often unavailable in such reports.

Recent reports have suggested that conservative surgery may be performed safely in well-selected patients with discrete tumors by intraoperative frozen-section analysis (Davis et al, 1999; Bissada et al, 2003; Pietrzak et al, 2004; Minhas et al, 2005). **In addition, several studies have challenged the dictum establishing that a 2-cm surgical margin is required for all patients undergoing partial penectomy** (Hoffman et al, 1999; Agrawal et al, 2000). After performing a prospective histologic analysis of 64 penectomy specimens, Agrawal and associates (2000) concluded that tumor grade highly correlated with microscopic tumor spread. The maximum proximal histologic extent was 5 mm for grade 1 and grade 2 tumors and 10 mm for grade 3 tumors. Furthermore, "skip" lesions were not encountered. After performing a retrospective pathologic review of 12 penectomy specimens, Hoffman and colleagues (1999) also found 7 patients with disease of pathologic stage T1 or greater with microscopic margins measuring less than 10 mm. None of these patients had disease recurrence at a mean follow-up of 32.4 months. Pietrzak and colleagues (2004) documented the use of various techniques in a series of 39 patients to excise the

tumor and to reconstruct or graft the glans and distal penis. With a mean follow-up of 16 months, only 1 patient (2.5%) who underwent a partial glans resection had a local recurrence. There were two early complications with grafts and two late complications with graft overgrowth intruding on the urethral meatus. Minhas and associates (2005) similarly performed either wide local excision or glans penis removal in 51 patients with margins of 0 to 10 mm in 48% and less than 2 cm in 98% of patients. With a median follow-up of 26 months a local recurrence rate of 4% to 6% was noted. Limitations of this approach include proximal and distal deeply invasive tumors, high-grade tumors, and patients with poor health status who would not be candidates for salvage procedures if they experienced recurrence. Although these results seem to suggest that a 2-cm margin may not be necessary for small tumors of lower grade in the presence of a negative frozen section, these findings should be interpreted with caution owing to the relatively short follow-up of most series. Patients managed with limited excision techniques should be considered to be at a higher risk for local recurrence until longer-term follow-up of current series is available.

Mohs Micrographic Surgery

Mohs microsurgery has historically had a positive impact on the management of penile carcinoma in situ and small superficially invasive tumors. As originally described by Mohs and colleagues (1985), it involves layer-by-layer complete excision of the penile lesion in multiple sessions (fixed tissue technique), with microscopic examination of the undersurface of each layer. Its sequential microscopic guidance offers improved precision and control of the negative margin while maximizing organ preservation. In a series of 29 consecutive cases of penile squamous cell carcinoma, the primary tumor was eradicated in 23 (92%) of 25 patients available for follow-up. Local recurrences were highly associated with tumor size (3 cm), advanced stage, and failure of previous definitive therapy (Mohs et al, 1992). These excellent results using a fixed tissue technique have not been reproduced using the currently utilized frozen section methodology. Shindel and associates (2007) treated 33 patients with stage Tis (26 patients), T1 (4 patients), T2 (7 patients), and T3 (4 patients) penile cancer. Five procedures were terminated with positive margins. Of 25 patients with mean follow-up of 58 months 8 (32%) developed recurrence. However, 7 of 8 were re-treated successfully with Mohs surgery. One patient who had progression of his disease died from it. **Thus Mohs microsurgery, as currently performed, may offer no additional benefit over surgical excision with intraoperative frozen section assessment of margin status.**

Laser Ablation

The four most widely used laser energy sources are the CO_2, argon, Nd:YAG, and KTP lasers (Carpiniello et al, 1987; Malloy et al, 1988; von Eschenbach et al, 1991). Although the CO_2 laser has been widely used previously, the superficial depth of penetration (limited to 0.1 mm) makes it less than optimal for the treatment of penile carcinoma in situ or small T1 tumors. When the CO_2 laser is used, local recurrence rates have been shown to be as high as 50% (Bandieramonte et al, 1988; van Bezooijen et al, 2001). Conversely, the Nd:YAG laser results in protein denaturation at a depth of up to 6 mm by emitting at a wavelength of 1060 nm. Overall recurrence rates after laser ablation have been reported at 7.7% for penile carcinoma in situ and have ranged from 10% to 25% for T1 lesions (Malloy et al, 1988; Windahl et al, 1995; Tietjen and Malek, 1998), but results from more contemporary series using the Nd:YAG laser exclusively have been more encouraging. **Frimberger and colleagues** (2002a) **treated 29 men with carcinoma in situ and stage T1 tumors, combining Nd:YAG laser ablation with tumor base biopsies to ensure negative surgical margins. Only two recurrences (6.9%) were reported at a mean follow-up of 46.7 months, which is comparable to recurrence rates after partial penectomy.** In an effort to reduce the incidence of positive surgical margins, Frimberger and associates (2002b) have proposed the use of autofluorescence and 5-aminolevulinic acid–induced fluorescence for targeting of frozen-section biopsy specimens.

Laser ablation is feasible and may achieve results equivalent to those of extirpative surgery, especially when it is performed in well-selected patients in conjunction with frozen-section biopsies. In addition, laser ablation has been associated with high rates of resumption of sexual activity (75%) and overall satisfaction (78%) (Windahl et al, 2004). However, until additional long-term studies become available, laser ablation should be performed with the understanding that local recurrences may develop and that close surveillance and patient self-examination are necessary for early detection. Although well-selected patients who develop small recurrent lesions may be candidates for repeated laser ablation, recurrences are best treated with wide local excision or partial amputation.

Contemporary Penile Amputation

Penile amputation remains the standard therapy for patients with deeply invasive or high-grade cancers. **Partial or total penectomy should be considered in patients exhibiting adverse features for cure by organ preservation strategies. These are consistently associated with tumors of size 4 cm or more, grade 3 lesions, and those invading deeply into the glans urethra or corpora cavernosa** (Mohs et al, 1992; Gotsadze et al, 2000; Kiltie et al, 2000). Because recurrence rates are higher with organ-preserving strategies, compliance with follow-up is also a consideration in recommending organ preservation versus amputation. Fortunately most patients with recurrences that are detected and treated early are not adversely affected with respect to survival (Lont et al, 2006). On the basis of contemporary results, organ preservation strategies should be discussed with patients exhibiting optimal tumor characteristics (stages Tis, Ta, T1; grade 1 and grade 2 tumors) to assist them in making an informed decisions about therapy.

Key Points: Surgical Treatment of the Primary Tumor

- Patients with small lesions of low grade and stage (Tis, Ta, T1; grade 1 and grade 2) are the optimal candidates for organ preservation to maintain sexual quality of life.
- The goals of organ preservation are to maintain glanular tissue for sensory purposes when possible and/or to maintain penile length when glans penis preservation is not possible.
- Surgical modalities include limited excision strategies, Mohs surgery, and laser ablation.
- Local recurrence rates overall after organ preservation are higher than with traditional amputation; however, when local recurrences are detected and treated, early survival may not be adversely impacted.
- Amputation remains the standard for large or deeply invasive lesions to gain rapid tumor control.

TREATMENT OF THE INGUINAL NODES

The presence and the extent of metastasis to the inguinal region are the most important prognostic factors for survival in patients with squamous penile cancer. These findings affect the prognosis of the disease more than do tumor grade, gross appearance, and morphologic or microscopic patterns of the primary tumor.

Unlike with many other genitourinary tumors, which mandate systemic therapeutic strategies once metastasis has occurred, lymphadenectomy alone can be curative and should be performed. The biology of squamous penile cancer is such that it exhibits a prolonged locoregional phase before distant dissemination, providing a rationale for the therapeutic value of lymphadenectomy.

However, owing to the morbidity of traditional lymphadenectomy especially among those patients with clinically negative groins, contemporary controversial issues include (1) the selection of patients for lymphadenectomy versus careful observation; (2) the types of procedures to correctly stage the inguinal region with low morbidity; and (3) multimodal strategies to improve survival among patients with bulky inguinal metastases.

In this rare disease, prospective randomized trials have not been performed to answer many of these questions. However, with the use of retrospective and prospective clinicopathologic data from several centers treatment strategies are presented using the available data.

Contemporary Indications for Inguinal Lymphadenectomy

Prognostic Significance of the Presence and Extent of Metastatic Disease

Table 34–3 reveals data collected from 24 surgical series during a 37-year period. Patients proved to have no evidence of inguinal metastases on the basis of histologic examination of the inguinal nodes or repeated normal examination findings over time; the average 5-year survival rate was 73% (46% to 100%). In patients with resected inguinal metastases the 5-year survival averaged 60% (0% to 86%), but this varied widely and was directly attributable to the extent of nodal metastasis (Table 34–4). This point is illustrated in several series shown in Tables 34–2 and 34–3. Patients with minimal nodal metastases (generally fewer than two) exhibited an average 5-year survival of 77% (89 of 115 patients), compared with only a 25% survival (26 of 102 patients) when a greater degree of nodal involvement was present.

The extent of cancer in a lymph node was also of prognostic significance. Ravi (1993b) noted extranodal extension of cancer in lymph nodes 4 cm in size, and only 1 of 17 patients (6%) undergoing lymphadenectomy survived 5 years. Finally, pelvic lymph node involvement has been a particularly ominous finding with respect to long-term survival; the combined results of several small series reveal an average 5-year survival of 15% when pelvic nodal metastases are present (Table 34–5). **Taken together, these data suggest that the pathologic criteria associated with long-term survival after attempted curative surgical resection of inguinal metastases (i.e., 80% 5-year survival) include minimal nodal disease (up to two involved nodes in most series), unilateral involvement, no evidence of extranodal extension of cancer, and absence of pelvic nodal metastases.**

Presence of Palpable Adenopathy as a Selection Factor for Inguinal Dissection

One can conclude from these data that it is advantageous to find and to treat nodal metastasis at the earliest possible opportunity. Data in Table 34–3 suggest that the presence of palpable adenopathy is associated with proven nodal metastasis in about 43% of cases on average (range 8% to 64%). In the remainder, lymph node enlargement is secondary to inflammation. Persistent adenopathy after treatment of the primary lesion and 4 to 6 weeks of antibiotic therapy is most often the consequence of metastatic disease. Similarly, the development of new adenopathy during follow-up is much more likely to be due to tumor than inflammatory response. Thus historically a course of antibiotics was recommended for patients with suspicious nodes to potentially discern metastasis from cancer (Srinivas et al, 1987). However, several authors have raised the issue that this causes a significant delay and could impact survival especially among patients who are likely to be truly positive by virtue of the stage/grade of the primary tumor (Kroon et al, 2005b; Pettaway et al, 2007). An alternative approach for such patients is to perform fine-needle aspiration cytology of palpable nodes either at the time of or immediately after treatment of the primary tumor. In the case of a positive result, definite therapy can be planned without a 4- to 6-week delay. Saisorn and associates reported a 93% sensitivity and a 91% specificity in 16 patients with palpable adenopathy (mean size 1.47 cm) undergoing fine-needle aspiration before lymphadenectomy. The recommendation for this procedure among patients with palpable nodes was also incorporated in the European Association of Urology (EAU) Penile Cancer Guidelines. **Thus, although treatment of the primary tumor and a period of antibiotics is useful to help sterilize the inguinal region, this practice is no longer advocated as a tool to select patients who either should or should not undergo lymphadenectomy.** Should the fine-needle aspiration result be negative depending on clinical suspicion, close observation, repeat aspiration, or excisional biopsy is performed because the false-negative rate of fine-needle aspiration cytology was 20% to 30% in two other older series (Scappini et al, 1986; Horenblas et al, 1991).

Evolving Indications for Lymphadenectomy in Patients without Palpable Adenopathy

Immediate versus Delayed Surgery

Considering the value of early detection and treatment of metastasis, **should inguinal lymphadenectomy be routinely performed in patients with clinically normal groin examination findings at the time of presentation of the primary lesion?** This has been the most controversial issue in the management of patients with squamous penile cancer; however, the pendulum has moved toward earlier lymphadenectomy in selected patients with penile cancer. As noted, the cure rate with inguinal lymphadenectomy when nodes are positive for malignancy may be as high as 80%. A cure rate of this magnitude with surgery in the face of regional nodal metastases parallels the urologist's experience with testicular cancer, in which retroperitoneal lymphadenectomy provides cure in many patients with minimal nodal metastasis. In contrast, for other common genitourinary malignant neoplasms—bladder, prostate, and kidney—surgical cure in the presence of regional nodal metastases is rare.

Table 34–3.

Carcinoma of the Penis: Prognostic Indicators for Survival

SERIES	NO. OF PATIENTS	Clinical and Pathologic Characteristics of Inguinal Adenopathy			5-Year Survival Rates (%)	
		Percentage with Palpable Nodes	Percentage Clinically False Positive (Nodes Palpable, Histologic Findings Normal)	Percentage Clinically False Negative (Nodes Palpable, Histologic Findings Abnormal)	Inguinal Nodes Negative*	Inguinal Nodes Resected and Positive†
Ekstrom and Edsmyer, 1958	229	33	48	—	80[a]	42
Beggs and Spratt, 1964	88	35	36	20	72.5	45
Thomas and Small, 1968	190	—	64	20	—	26
Edwards and Sawyers, 1968	77	—	—	0	68	25
Hanash et al, 1970	169	—	58[b]	2[b]	77[c]	—
Kuruvilla et al, 1971	153	39	63	10	69	33
Hardner et al, 1972	100	42	41[b]	16[b]	—	—
Gursel et al, 1973	64	53	60[b]	—	58	—
Skinner et al, 1972	34	29	40	—	75	20
					87[d]	50[d]
de Kernion et al, 1973	48	54	38[b]	—	84[e]	55[e]
Derrick et al, 1973	87	29	52	—	53	22
					76[d]	55[d]
Johnson et al, 1973	153	—	—	—	64.4	21.8
Kossow et al, 1973	100	51	49	25	—	—[f]
Puras et al, 1978	576	82	47	38[b]	89	67[g]
						29[h]
Cabanas, 1977	80	96	65	100	90	70[i]
						50[j]
						20[k]
Fossa et al, 1987	79	—	—	13	90	80[l]
						20[m]
Srinivas et al, 1987	199	63	14[n]	18	74	82[o]
						54[p]
						40[q]
						12[r]
McDougal et al, 1986	65	—	—	66	100	83[s]
						66[t]
						38[u]
Young et al, 1991	34	24	27	42	77	0
Horenblas et al, 1993	110	36	26	40	100	38
Ravi, 1993b	201	53	8	16	95	81[v]
						50[w]
						86[x]
						60[y]
Ornellas et al, 1994	414	50	51[y]	39	87	29
Theodorescu et al, 1996	40	70	35	—	46	45
Puras-Baez et al, 1995	272	—	—	—	89	38

*On histologic or repeated physical examination.
†On histologic examination of adenectomy specimen.
[a]Majority of patients received prophylactic or preoperative radiation therapy to inguinal area.
[b]Histologic classification based on node biopsy, not node dissection.
[c]Corrected 5-year survival (i.e., patients dying before 5 years without evidence of disease are excluded).
[d]Patients dying free of cancer before 5 years are considered surgical cures.
[e]Three-year survival.
[f]Omitted.
[g]Positive findings in inguinofemoral nodes.
[h]Positive findings in inguinofemoral and pelvic nodes.
[i]Single inguinal node with positive findings.
[j]More than one inguinal node with positive findings.
[k]Three-year survival with positive findings in inguinal and pelvic nodes.
[l]N1-2.
[m]N3.
[n]After antibiotic therapy.
[o]One node positive.
[p]One to six nodes positive.
[q]More than six nodes positive.
[r]Bilateral nodes positive.
[s]Adjunctive adenectomy.
[t]Immediate therapeutic adenectomy.
[u]Delayed therapeutic adenectomy.
[v]One to three positive nodes.
[w]More than three positive nodes.
[x]Unilateral.
[y]Some lymph node dissection done without antibiotic pretreatment.

Given that node dissection can cure metastatic penile cancer, why is there debate about whether the procedure should be performed, especially given that regional node dissections are often advocated in other malignant neoplasms when evidence of their efficacy is marginal at best?

Morbidity versus Benefit

The reluctance to advocate automatic ilioinguinal lymphadenectomy in all patients with penile cancer stems from the substantial morbidity the procedure can produce, as opposed to the relatively limited postoperative morbidity of pelvic or retroperitoneal

Table 34–4.

Five-Year Survival Related to Extent of Nodal Metastasis

SERIES	NO. OF PATIENTS	No. of Positive Nodes ≤2	No. of Positive Nodes >2
Fraley et al, 1989	31	15/17 (88%)	1/14 (7%)
Johnson and Lo, 1984a	22	6/7 (85%)*	2/15 (13%)
Srinivas et al, 1987	119	5/6 (82%)	7/34 (20%)
			9/16 (54%)†
Fossa et al, 1987	18	11/12 (88%)‡	2/6 (33%)§
Ravi, 1993b	21	47/58 (81%)¶	5/10 (50%)¶
Horenblas et al, 1994	110	5/15 (67%)	9/23 (39%)

*Approximate.
†A subset with one to six positive nodes.
‡N1-2.
§N3.
¶One to three positive nodes.
¶More than three positive nodes.

Table 34–5.

Five-Year Survival Related to Pelvic Node Metastases

AUTHOR	NO. OF PATIENTS WITH POSITIVE NODES	5-YEAR SURVIVAL NO. (%)
de Kernion et al, 1973	2	1 (50)
Horenblas et al, 1993	2	0 (0)
Srinivas et al, 1987	11	0 (0)
Pow-Sang et al, 1990	3	2 (66)
Kamat et al, 1993	6	2 (33)
Ravi, 1993b	30	0 (0)
Lopes et al, 2000	13	5 (38)
Lont et al, 2007	25	4 (16)
Zhu et al, 2008	16	1 (6)
TOTAL	108	15 (14)

lymphadenectomies. Early complications of phlebitis, pulmonary embolism, wound infection, flap necrosis, and permanent and disabling lymphedema of the scrotum and lower limbs were frequent after both inguinal and ilioinguinal node dissections (Fig. 34–3) (Skinner et al, 1972; Johnson and Lo, 1984b; McDougal et al, 1986; Fraley et al, 1989). **Postoperative complications have been reduced by improved preoperative and postoperative care; advances in surgical technique; plastic surgical consultation for myocutaneous flap coverage; and preservation of the dermis, Scarpa fascia, and saphenous vein, as well as modification of the extent of the dissection** (Catalona, 1988; Colberg et al, 1997; Bevan-Thomas et al, 2002; Coblentz and Theodorescu, 2002; Nelson et al, 2004) (Fig. 34–4). In the University of Texas M. D. Anderson Cancer Center experience both the incidence and severity of lymphedema and skin edge necrosis were significantly decreased (Table 34–6) (Bevan-Thomas et al, 2002).

Furthermore, experience has suggested that lymphadenectomy in the setting of microscopic disease may be less likely to produce complications than node dissection in the presence of bulky nodal metastases (Fraley et al, 1989; Ornellas et al, 1994; Coblentz and Theodorescu, 2002). This is presumably due to the reduced amount of lymphatic tissue removed, preservation of venous drainage, and blood supply compromised. Together these factors affect the viability of skin flaps and lymphatic flow.



Figure 34–3. Extensive lymphedema and cutaneous changes secondary to recurrent lymphangitis and thrombophlebitis 2 years after a classic groin dissection.

Table 34–6.

Lymphadenectomy Complications in Four Surgical Series

	JOHNSON AND LO (1984a)	RAVI (1993a)	ORNELLAS ET AL (1994)	BEVAN-THOMAS ET AL (2002)
No. of dissections	101	405	200	106
Period	1948-1983	1962-1990	1972-1987	1989-1998
Complications (%)				
Skin edge necrosis	50	62	45	8*
Lymphedema	50	27	23	23†
Wound infection	14	17	15‡	10
Seroma formation	16	7	6	10
Death	0	1.3	Not stated	1.8

*Significantly lower than in the three other reported series (all $P = .0001$).
†Significantly lower than in the series of Johnson and Lo ($P = .0001$).
‡Incidence among 85 lymphadenectomies performed by Gibson-type incision.
From Bevan-Thomas R, Slaton JW, Pettaway CA. Contemporary morbidity from lymphadenectomy for penile squamous cell carcinoma: the M.D. Anderson Cancer Center experience. J Urol 2002;167:1638–42.

Mortality after inguinal lymphadenectomy has been reported in association with surgery performed concomitantly with penectomy and after palliative inguinal dissection. In both scenarios it was related to sepsis (Bevan-Thomas et al, 2002). An operative mortality of 3.3% was reported in earlier series (Beggs and Spratt, 1964). However, Johnson and Lo (1984b) and others (Ravi, 1993a;



Figure 34–4. Postoperative appearance after contemporary lymphadenectomy. The patient's status is post left ilioinguinal lymphadenectomy and right superficial inguinal dissection for stage T2N1M0 squamous penile cancer. Trace edema is visible on the left 18 months after surgery.

Ornellas et al, 1994; Coblentz and Theodorescu, 2002; Nelson et al, 2004) have reported no mortality in more recent series. Appropriate selection of patients along with routine preoperative antibiotic therapy and wound care to avoid septic complications has minimized this event.

Clearly, lymphadenectomy is not a trivial concern even though morbidity appears to be decreasing. If a policy of routine lymphadenectomy were adopted in all patients with clinically negative lymph nodes, the average risk of a false-negative examination (metastasis is actually present) would be approximately 29%, with wide-ranging variation (see Table 34–3). Stated another way, an average of 70% of patients could be subjected to the morbidity of inguinal lymphadenectomy with no benefit. Potential reasons for false-negative examinations include obesity, preexisting edema, and changes from prior therapy (radiation, inguinal surgery).

One alternative to immediate lymphadenectomy for all patients has been to observe patients with normal findings on inguinal examination. Lymphadenectomy is subsequently reserved for those patients who develop palpable lymph nodes. **The relevant question then becomes, can a delayed therapeutic dissection effectively salvage patients who have inguinal recurrence?**

Several studies have analyzed the survival of men undergoing early versus delayed lymphadenectomy according to pathologic evaluation of nodal status. McDougal and coworkers (1986) reported a series of 23 patients with invasive primary lesions and nonpalpable nodes; 9 patients were treated with immediate adjunctive lymph node dissection (6 had positive findings), and 14 were treated with surveillance and delayed lymph node dissection. The 5-year survival in the node-positive immediate adjunctive lymphadenectomy group was 83% (5 of 6 patients), whereas in the surveillance group the 5-year survival was 36% (5 of 14 patients). However, only 1 patient in the surveillance group had a node dissection. Presumably, the other 9 patients had progressed to inoperable local tumor or distant disease before presentation, emphasizing the role of careful, frequent follow-up and the difficulty of enforcing it. A third subset in this series had palpable nodes at presentation and had immediate therapeutic lymph node dissection, with 10 of 15 patients (66%) surviving 5 years (McDougal et al, 1986). The best results were from immediate adjunctive lymph node dissection (83%), with the next best from immediate therapeutic lymphadenectomy (66%). The worst results were from the surveillance and delayed lymphadenectomy group (36%), in whom dissection was delayed until palpable nodes developed. The interval of opportunity for cure in this third group appears to have been lost.

Similarly, Fraley and associates (1989) reported that immediate adjunctive lymphadenectomy resulted in a 5-year disease-free survival in 6 of 8 node-positive patients (75%) compared with 1 of 12 patients (8%) who had been observed and then treated by delayed lymphadenectomy when nodal enlargement occurred. Six other patients in that series also presented with unresectable adenopathy after initial surveillance, and all died of their disease. Although only 2 of 6 patients who had immediate lymphadenectomy had more than two positive nodes, all the patients treated by delayed lymph node dissection had three or more positive nodes.

Three other series suggest that early lymphadenectomy for varying degrees of "suspicious" or clinically positive nodes improves survival compared with the "surveillance" or delayed intervention approach in patients presenting with clinically negative nodes (Johnson and Lo, 1984a; Ornellas et al, 1994; Kroon et al, 2005b). A series from the University of Texas M. D. Anderson Cancer Center compared 5-year disease-free survival of 14 patients undergoing early lymphadenectomy for clinically suspicious and histologically node-positive disease with that of 8 patients who were observed and later underwent lymphadenectomy when clinical nodal enlargement was undisputed (Johnson and Lo, 1984a). The primary tumors were of similar stage. The 5-year disease-free survival was 57% for early lymphadenectomy compared with 13% for delayed node dissection. Of note, the number of involved nodes in the immediate lymphadenectomy group (median, two) was half that of the delayed lymphadenectomy group (median, four), and no patient with more than two positive nodes survived more than 5 years.

Kroon and associates (2005b) from the Netherlands Cancer Institute compared survival of 20 patients found to have positive lymph nodes subsequent to prophylactic dynamic sentinel node biopsy (DSNB) with that of 20 patients who underwent delayed inguinal dissection after proven nodal metastasis. The 3-year survival for those patients detected during close surveillance was only 35% compared with 84% ($P = .0017$) for those undergoing early dissection. Pathologic evaluation of involved lymph nodes revealed extranodal extension of cancer among 19 of 20 patients in the delayed group versus only 4 of 20 patients ($P = .001$) in the early group. Thus, despite careful follow-up, survival was adversely affected by the extent of cancer in involved lymph nodes.

A single large study from India disputes the magnitude of the value of early prophylactic dissection. Ravi (1993a) performed early prophylactic dissection in 113 patients with invasive penile cancer and compared the 5-year survival with that of 258 similarly staged patients who were initially observed. In the "early" group,

20 patients (18%) were found to have metastases, and all patients survived 5 years. The recurrence rate in the observed group was only 8% (21 patients). However, the 5-year survival in the patients who experienced recurrence was only 76% (compared with 100% in the early lymphadenectomy group). The enhanced survival of patients undergoing surveillance in India compared with other countries is probably attributable to patient selection factors, strict adherence to follow-up schedules, and aggressive treatment approach for recurrent disease (a combination of radiation and surgical resection) (Ravi, 1993b).

Thus, six series reveal an improvement in survival for patients undergoing early therapeutic versus delayed therapeutic dissection. Further, five of the six series show that delayed therapeutic dissection can rarely salvage patients who experience recurrence. Taken together, these data suggest that a policy of immediate adjunctive or early lymphadenectomy gives greater assurance that surgical intervention will occur when tumor volume is small (see Table 34–4) (Johnson and Lo, 1984b; Fossa et al, 1987; Srinivas et al, 1987; Fraley et al, 1989; Ravi, 1993a; Kroon et al, 2005b).

Impact of Primary Tumor Histologic Features on Predicting Occult Nodal Metastasis

Although early lymphadenectomy improves survival in patients with inguinal metastases, the challenge remains to identify those patients who are truly lymph node negative to avoid the morbidity of traditional lymphadenectomy. **Data gained from analysis of a variety of histopathologic variables within the primary penile tumor allow the classification of patients into higher and lower risk groups for lymph node metastasis** (McDougal, 1995; Lopes et al, 1996; Theodorescu et al, 1996; Solsona et al, 2001; Ficarra et al 2006).

Patients with primary tumors exhibiting carcinoma in situ or verrucous carcinoma have little or no risk for metastasis. Only two cases of metastasis in association with carcinoma in situ have been reported, and none of 47 cases of penile verrucous carcinoma has been shown to metastasize (Avrach and Christensen, 1976; Johnson et al, 1985; Seixas et al, 1994; Eng et al, 1995). Thus patients with both Tis and Ta penile cancer are included in the low-risk group for inguinal metastases (Solsona et al, 2001, 2004).

In contrast, patients with corporeal invasion (stage pT2) in the penile tumor exhibit a high risk for metastasis. The average risk for inguinal metastasis among 225 patients in seven different series was 59% (Table 34–7). **The risk for metastasis among patients exhibiting corporeal invasion was similar irrespective of whether palpable adenopathy was present.**

Stage T1 penile cancers exhibit involvement of the subepithelial connective tissue only and lack involvement of the corpus spongiosum, corpora cavernosa, or urethra (Fleming et al, 1997). Similarly staged tumors historically have been associated with a 4% to 14% incidence of nodal metastasis (Solsona et al, 1992; Villavicencio et al, 1997; Hall et al, 1998). Theodorescu and colleagues (1996) noted one exception to this relatively low rate of metastatic disease; 58% of patients (14 of 24) with pT1 primary tumors and initially negative nodes on clinical assessment subsequently developed inguinal nodal metastases. These data suggest that other variables present within the penile cancers of the cohort of patients studied (i.e., tumor grade and presence of vascular invasion) may have modified the effect of tumor stage on metastasis.

Several authors have evaluated the risk of nodal metastasis for stage T1 lesions according to tumor grade (Table 34–8). Among 73 patients with T1 grade 1 or grade 2 primary tumors, metastasis occurred in only 5 patients (7%). Recent data from Naumann and coworkers (2008), however, suggested that among T1 grade 2 tumors specifically the risk of metastases could be higher than previously described. Among three series reporting specifically on the T1 grade 2 subset, in 24 initially node-negative patients metastases occurred in 9 (38%). However, 5 patients in this subset also exhibited either lymphatic or venous invasion (an adverse prognostic feature, see later). Ficarra and colleagues (2006) developed the first penile cancer nomogram utilizing data from 175 patients. Based on tumor thickness and growth pattern, patients with T1 grade 2 tumors exhibited metastatic rates between 5% and 20%. Thus grade 2 tumors represent a heterogeneous group in which the histologic criteria used to describe grade 2 and the presence or absence of other poor prognostic features ultimately determine prognosis (Cubilla, 2009). In this regard the EAU guidelines assigned patients with T1 grade 2 tumors to the intermediate-risk category in which the risk of lymph node metastasis is greater than 16% (low risk) and less than 68% (high risk) (Solsona et al, 2004).

The presence of vascular invasion as a prognostic indicator of inguinal lymph node metastasis in squamous penile cancer is now evident (Fraley et al, 1989; Lopes et al, 1996; Heyns et al, 1997; Slaton et al, 2001; Ficarra et al, 2005). Lopes and colleagues (1996) studied the prognostic value of lymphatic invasion in 146 patients with penile cancer. In a univariate analysis, clinical nodal stage, tumor thickness, lymphatic and

Table 34–7.

Penile Carcinoma: Corporeal Invasion and Incidence of Lymph Node Metastasis

STUDY	POSITIVE NODES (%)	NO. OF PATIENTS (%)	CLINICAL N STAGE
McDougal et al, 1986	23	11 (48)	N0
Fraley et al, 1989	29	26 (90)	N0
Theodorescu et al, 1996	18	12 (67)	N0
Villavicencio et al, 1997	37	14 (38)	N0
Lopes et al, 1996	44	28 (64)	NS
Heyns et al, 1997	32	15 (47)	NS
Solsona et al, 1992	42	27 (64)	NS

N, node.

Table 34–8.

Penile Carcinoma: Incidence of Nodal Metastasis for Stage T1, Grade 1 and Grade 2 Primary Tumors

AUTHOR	STAGE AND GRADE	NO. OF PATIENTS	NO. OF PATIENTS WITH METASTASIS (%)
Theodorescu et al, 1996	T1, G1	8	2 (25)
Solsona et al, 1992	T1, G1	19	0 (0)
McDougal, 1995	T1, G1-2	24	1 (4)
Heyns et al, 1997	T1, G1-2	9	1 (11)
Hungerhuber et al, 2006	T1, G1-2	13	1 (7.7)
TOTAL		73	5 (7)
Solsona et al 1992	T1, G2	4	1 (25)
Solsona et al 2001	T1, G2	4	1 (25)
Naumann et al, 2008	T1, G2	16	7 (44)
TOTAL		24	9 (38)

Five tumors in node-positive group had lymphatic or venous invasion.

venous embolization, and urethral infiltration were all associated with lymph node metastasis. However, subsequent to multivariate analysis, only venous and lymphatic invasion remained significant predictors for positive lymph nodes. Data from the University of Texas M. D. Anderson Cancer Center revealed that vascular invasion was absent in all patients with T1 tumors (Slaton et al, 2001). These patients were also lymph node negative at surgery. In contrast, patients with stage pT2 primary tumors exhibited nodal metastasis in 75% of cases (15 of 20) when vascular invasion was present but in only 25% of cases (3 of 12) when it was absent.

Ficarra and colleagues (2005) described prognostic factors for lymph node metastasis in 175 patients undergoing surgery for penile cancer in a multicenter study from the Northeast Uro-Oncological Group from Italy. Subsequent to multivariate statistical analysis, the presence of venous or lymphatic invasion and pathologic invasion of the corpus spongiosum or urethra were the only independent risk factors for lymph node metastasis among patients who were clinically lymph node negative. Taking this a step further and including the variables of tumor thickness, growth pattern, grade, venous/lymphatic invasion, corpus spongiosum or cavernosum involvement, urethral involvement, and palpable lymph nodes Ficarra and colleagues (2006) developed a nomogram predicting inguinal lymph node involvement. The most important variables were venous/lymphatic invasion and the presence of palpable nodes in multivariate analysis. The concordance index of the nomogram was very good at 0.876. However, external validation of the nomogram is pending at this time.

The presence of perineural invasion (Velazquez et al, 2008) and the microscopic front pattern of invasion (Guimares et al, 2006) have also been shown in recent studies to provide independent information with which to stratify a patient's risk of lymph node metastasis.

Molecular Prognostic Markers

Analysis of gene expression in penile cancer may have future implications with respect to the prediction of lymph node metastasis or survival. A review by Muneer and colleagues (2009) describes the current status of several genes evaluated in tissue or serum that could have future prognostic implications with respect to predicting lymph node status or survival (Table 34–9). Presently, standardization of methodologies for assessment of gene expression and the lack of large tissue banks with well annotated clinical data for validation studies hamper efforts to rigorously evaluate the potential utility of such biomarkers. Prospective multi-institutional studies analyzing both pathologic and molecular features are needed to further validate which pathologic and molecular variables best stratify a patient's risk for metastasis and survival.

Contemporary Evolving Indications for Expectant Management of the Inguinal Region

Data reviewed in the preceding paragraphs along with consensus guidelines demonstrate that patients with primary tumors exhibiting carcinoma in situ (Tis), verrucous carcinoma (Ta), and stage T1, grade 1 tumors exhibit less than a 10% incidence of positive lymph nodes overall and are optimal candidates for watchful waiting strategies (Solsona et al, 2004). **Recommendations for management of patients with T1 grade 2 tumors vary based on quoted rates of subsequent metastases. The current EAU guideline (while classifying such patients in the intermediate risk group) recommends observation for T1 grade 2 tumors that lack vascular invasion and exhibit a superficial growth pattern (i.e., absence of any other adverse features)** (Solsona et al, 2004). Table 34–10 provides guidelines for the follow-up of such patients.

Table 34–10.

Penile Carcinoma: Suggested Follow-Up for Patients with No Evidence of Inguinal Adenopathy Who Do Not Undergo Initial Lymphadenectomy

	Interval	
YEAR	Low-Risk Group*	High-Risk Group†
1-2	3 months	2 months
3	4 months	3 months
4	6 months	6 months
5+	Annually	Annually

*Tis, Ta, and T1, grade 1 or grade 2; no vascular invasion with superficial growth pattern.

†T1, grade 2 with nodular growth or stage T2 or higher, grade 3, with vascular invasion.

Table 34–9.

Prognostic Molecular Markers of Lymph Node Status and Survival in Penile Cancer: Current Status

MARKER	ROLE	LYMPH NODE STATUS	SURVIVAL
Human papillomavirus (HPV)	High-risk types affect TP53 and RB function	Contradictory studies	Most studies show no correlation
TP53	Altered/mutated expression increased proliferation, altered Apoptosis, dedifferentiation	Preliminary data correlated with increased metastasis	Correlated with survival in T1 penile cancers only
CDKN2A	Inhibits RB function enhancing proliferation	Not established	Not established
Squamous cell carcinoma antigen (TA-4)	Serum marker function unknown	Correlates with grossly evident metastases	No role
Ki-67	Nuclear protein associated with cycling cells	Predicts increased risk	No role
E-Cadherin	Epithelial cell adhesion molecule lost in progression	Low expression associated with nodal metastasis	Low expression predicts worse survival
MMP-9	Matrix metalloproteinase family facilities invasion	No role	High expression predicts recurrence

Modified from Muneer A, Kayes O, Ahmed HU, et al. Molecular prognostic factors in penile cancer. World J Urol 2009;27:161–7.

Alternatively, all other fit patients with stage pT2 or greater or grade 3 tumors and those exhibiting vascular invasion have a greater than 50% incidence of metastasis, so prophylactic lymphadenectomy appears warranted. Although not in this high-risk group, patients with T1 grade 2 tumors with other high-risk features (tumor thickness, vertical growth) should also be considered for surgical staging owing to an intermediate risk of metastatic disease (Solsona et al, 2004). Additionally, noncompliant patients with invasive primary tumors should be offered an inguinal staging procedure versus observation. Table 34–10 provides a guideline for more intensive follow-up of high-risk patients, especially within the first 2 years. **It is imperative for both the patient and the physician to adhere to such follow-up agreements and be willing to intervene immediately if initial inguinal parameters change. Leijte and colleagues** (2008b) **have documented that only a third of patients who were initially node negative but subsequently develop an inguinal recurrence survive 5 years.**

Indications for Modified and Traditional Inguinal Procedures

Modified Procedures

In patients with no evidence of palpable adenopathy who are selected to undergo inguinal procedures by virtue of adverse prognostic factors within the primary tumor the goal is to define if metastases exist with minimal morbidity for the patient. A variety of treatment options for this purpose have been reported and include fine-needle aspiration cytology, node biopsy, sentinel lymph node biopsy, extended sentinel lymph node dissection, intraoperative lymphatic mapping, superficial dissection, and modified complete dissection. The technical aspects of many of these procedures are beyond the scope of this chapter but may be found in Chapter 35 and in the references Horenblas and colleagues (2000) and Spiess and coworkers (2009).

Fine-Needle Aspiration Cytology. The experience with aspiration of clinically negative inguinal nodes guided by either lymphangiography or ultrasonography is limited. Scappini and associates (1986) performed fine-needle aspiration cytology under pedal or penile lymphangiography for nodal localization in 29 patients. Of 20 patients who had lymphadenectomy for histologic confirmation there was complete agreement between aspiration cytology and histologic results. However, 2 of 9 patients whose cytologic analysis was negative subsequently died of metastatic disease, a presumptive 20% false-negative result. A series from Horenblas and colleagues (1991) also found that the sensitivity of fine-needle aspiration cytology was approximately 71% in 18 patients with clinically negative lymph nodes. This finding and the technical difficulty with lymphangiography make aspiration less practical as a staging technique for patients with no palpable lymph nodes. Kroon et al (2005a) described fine-needle aspiration cytology guided by ultrasonography as a preliminary study to surgical staging with DSNB. Thirty-four groins in 27 patients with clinically negative groins were found to have suspicious nodes by ultrasound examination and were aspirated. However, the sensitivity of the technique was only 39% subsequent to surgical staging. **Thus, at present, fine-needle aspiration cytology of clinically negative groins does not exhibit the sensitivity for it to be relied on as a staging modality.** However, direct aspiration of palpable inguinal nodes is easily performed, exhibited a sensitivity of 93% in a recent study, and, if positive, provides immediate information with which to advise patients about further treatment (Saisorn et al, 2006).

Sentinel Lymph Node Biopsy, Extended Sentinel Lymph Node Dissection, and Node Biopsy. The concept of sentinel lymph node biopsy as described by Cabanas (1977) is predicated on detailed penile lymphangiographic studies that have demonstrated consistent drainage of the penile lymphatics into a sentinel node or group of nodes located superomedial to the junction of the saphenous and femoral veins in the area of the superficial epigastric vein. In this series, when this sentinel node was negative for tumor, metastases to other ilioinguinal lymph nodes did not occur. Metastases to this node indicated the need for a complete superficial and deep inguinal dissection.

The accuracy of the sentinel node histology to identify inguinal node metastases was, however, questioned by a number of reports (Perinetti et al, 1980; Fowler, 1984; Wespes et al, 1986). Because nodal metastases became palpable within 1 year of sentinel node biopsy with normal findings in some patients in these series, a false-negative biopsy result must be presumed. In one large series, 5 of 41 patients (12%) with normal findings on sentinel node biopsy subsequently developed inguinal node metastases (Fossa et al, 1987). In Cabanas' series (1992), 3 of 31 patients with negative sentinel nodes died of disease, suggesting a false-negative rate for identifying metastases of 10%. McDougal and associates (1986) reported a 50% false-negative rate with inguinal node biopsy. A report by Pettaway and colleagues (1995), in which additional nodes around the sentinel node area were also removed, revealed that even this extended dissection was associated with a false-negative rate of 25%. The authors hypothesized that false-negative inguinal node biopsies were the result of anatomic variation in the position of the sentinel node within the inguinal field. **Thus, biopsies directed to a specific anatomic area can be unreliable in identifying microscopic metastasis and are no longer recommended.**

Dynamic Sentinel Node Biopsy. DSNB offers the potential for precise localization of the sentinel node with the lowest morbidity of any surgical staging technique (Kroon et al, 2005c). The goal of DSNB is to define where in the inguinal lymph node field the sentinel lymph node resides utilizing a combination of visual (vital blue dyes) or gamma emission (hand-held gamma probe) techniques at the time of surgery.

The technique has been studied in patients with malignant melanoma and breast and vulvar carcinomas who required evaluation of the regional lymph nodes (Morton et al, 1992; Levenback et al, 1994; Albertini et al, 1996; Gershenwald et al, 1999). The technique involves intradermal injection of a vital blue dye (isosulfan blue or patent blue dyes) or technetium-labeled colloid adjacent to the lesion. The dye (or radioactive tracer) is transported by the afferent lymphatics to a specific node in the regional nodal basin. This node is designated the sentinel lymph node. In Morton's series of 237 patients with melanoma, the sentinel lymph node was identified in 194 patients. These patients then underwent full regional lymphadenectomy, with a false-negative sentinel node in only 1% of cases.

Several studies evaluating the results of DSNB as a staging tool in penile cancer are now available. Kroon and associates (2004) updated the Netherlands Cancer Institute experience, describing their experience using the combination of preoperative lymphoscintigraphy and intraoperative intradermally injected blue dye in 123 patients with penile cancer. They identified a sentinel node in 98% of patients, for a sensitivity rate of 82% and a false-negative rate of 18% (6 patients). Four of the 6 patients subsequently died of disease progression. Spiess and associates (2007)

also noted a false-negative rate of 25% among 31 patients undergoing DSNB. The Netherlands Cancer Institute group subsequently instituted several changes, including (1) routine serial sectioning of the involved lymph nodes along with cytokeratin immunohistochemistry, (2) routine exploration of groins with low or no signal subsequent to preoperative or intraoperative studies, and (3) inguinal ultrasonography with fine-needle aspiration to detect subtle architectural changes (nonpalpable) in positive lymph nodes that could result in the redistribution of lymphatic flow (Kroon et al, 2005a).

In a multicenter update that included patients assessed with the modified DSNB protocol from two high-volume centers (the Netherlands Cancer Institute and St. George's Hospital in London) the false-negative rate was 7% (6 patients) among 323 patients (Leijte et al, 2009). Three of 6 patients with recurrence (50%) either died or developed distant metastases. **Thus DSNB when performed at high-volume centers using a standardized protocol has an acceptable sensitivity but deaths from penile cancer among initially node-negative patients still occurred.** This limits the applicability of this strategy to larger centers with experienced surgeons and nuclear medicine specialists.

Superficial and Modified Complete Inguinal Dissection. Both superficial inguinal and modified complete dissections have been proposed as staging tools for the patient without palpable inguinal lymphadenopathy. Superficial node dissection involves removal of those nodes superficial to the fascia lata. A complete ilioinguinal lymphadenectomy (removal of those nodes deep to the fascia lata contained within the femoral triangle as well as the pelvic nodes) is then performed if the superficial nodes are positive at surgery by frozen-section analysis. The rationale for superficial dissection is that two series have shown no positive nodes deep to the fascia lata unless superficial nodes were also positive (Pompeo et al, 1995; Puras-Baez et al, 1995). Furthermore, Spiess and colleagues (2007) showed that among the lymph node–negative cohort of patients undergoing DSNB with completion superficial dissection no patient with a negative superficial dissection recurred with more than 3-year follow-up. A complete modified inguinal dissection was originally proposed by Catalona (1988) and involves smaller skin incision, limited field of inguinal dissection, preservation of the saphenous vein, and thicker skin flaps. This technique also avoids having to transpose the sartorius muscle to cover exposed femoral vessels. Unlike in superficial dissection, deep nodes within the fossa ovalis are also removed. Two reports involving 21 patients have confirmed the value of this technique, when it is properly performed, for identifying microscopic metastases with minimal morbidity (Parra, 1996; Colberg et al, 1997).

Thus, either superficial or complete modified inguinal dissection should adequately identify microscopic metastases in patients with clinically normal inguinal examination findings, without the need for a pelvic dissection if the inguinal nodes are negative. The disadvantage of the modified dissections is the higher overall complication rate (12% to 35%) when compared with DSNB (5% to 7%) (Kroon et al, 2005c; Spiess et al, 2009).

Limited dissections have the following advantages: more information is provided than by biopsy of a single node or group of nodes; the possibility of not identifying the sentinel node is limited by removal of all potential first-echelon nodes; morbidity is minimal compared with standard lymphadenectomy; and the dissection is readily performed by any surgeon experienced in inguinal surgery without the need for specialized equipment.

Laparoscopic Inguinal Lymphadenectomy

The laparoscopic approach to the inguinal region offers the potential of removing all the inguinal lymph nodes at risk for disease while minimizing complications. The technical details of the contemporary procedure and early results have been described by two groups from South America (Sotelo et al, 2007; Tobias-Machado et al, 2007). To date among highly selected small series of patients inguinal lymph nodes removed have been comparable to open series, only a single recurrence has been reported with a 12- to 33-month follow-up, and minor complications have occurred in about 20% of patients (Sotelo et al, 2009; Spiess et al, 2009). Thus this approach, although promising, will require further validation with larger patient numbers and longer follow-up.

Traditional Inguinal and Ilioinguinal Lymphadenectomy

In patients with resectable metastatic adenopathy the potential therapeutic value of lymphadenectomy justifies the morbidity of treatment. The goals are to eradicate all obvious cancer, to provide coverage for exposed vasculature, and to provide rapid wound healing (primary closure or myocutaneous flap coverage). Several issues remain with respect to surgical decision-making.

Should inguinal lymphadenectomy be bilateral rather than unilateral for patients presenting with unilateral adenopathy at initial presentation of the primary tumor? The answer to this question is yes. The anatomic crossover of penile lymphatics is well established, and bilateral drainage is the rule. In 43 of 54 patients (79%) undergoing intraoperative lymph node mapping at the Netherlands Cancer Institute, lymphatic drainage from the penis was bilateral (Horenblas et al, 2000). The contralateral node dissection may be limited to the area superficial to the fascia lata if no histologic evidence of positive superficial nodes is found at surgery by frozen-section analysis. Clinical support for a bilateral procedure is based on the finding of contralateral metastases in more than 50% of patients so treated, even if the contralateral nodal region was normal to palpation (Ekstrom and Edsmyr, 1958).

Should bilateral inguinal lymphadenectomy be performed in patients who present with unilateral lymphadenopathy some time after the initial presentation and treatment of the primary tumor? It is generally believed that bilateral node dissection in this setting is not necessary. The recommendation of unilateral rather than bilateral node dissection with delayed presentation of unilateral lymphadenopathy is supported by the elapsed disease-free interval of observation on the normal side. If one assumes that nodal metastases will enlarge at the same rate, the clinical palpation of nodal metastases, if present in both groins, should appear at approximately the same time. The absence of clinical adenopathy on one side despite prolonged observation suggests freedom from disease on that side (Ekstrom and Edsmyr, 1958). However, this concept may not apply to all patients with delayed recurrence. Horenblas and colleagues (2000) noted that in patients with two or more unilateral metastases contralateral occult metastases were noted in 30% of cases. Thus, in patients with a bulky unilateral recurrence, a contralateral inguinal staging procedure should be considered. Considering the current treatment recommendations for bilateral inguinal staging procedures in men at high risk for metastasis and the definition of low-risk groups for metastasis by use of available prognostic markers, this scenario should rarely occur.

Should pelvic lymphadenectomy be performed in all patients with inguinal metastases considering its

potential for added morbidity and relatively low therapeutic value? This issue remains controversial. Patients with inguinal nodal metastases are at increased risk for spread to the pelvic nodes. Ravi (1993a) found no pelvic nodal metastases when inguinal nodes were negative but found positive pelvic nodes in 17 of 75 patients (22%) with one to three positive inguinal nodes and in 13 of 23 patients (57%) with more than three positive inguinal nodes. Srinivas and associates (1987) also found a similar correlation. Horenblas and colleagues (1993) showed that among patients with a single inguinal lymph node involved without extracapsular extension the incidence of pelvic metastases was rare and recommended avoiding pelvic dissection among such patients. Zhu and coworkers (2008) found that the sensitivity of CT for pelvic lymph node metastasis was only 37.5%. Defining the status of the Cloquet node in predicting a positive pelvic node was only about 30% sensitive as well. Important predictors were the number of positive nodes as well as lymph node size. Two contemporary studies addressing this issue have found a 0% to 12% incidence of pelvic lymph node metastasis when patients exhibited only one to two positive inguinal nodes especially when extracapsular extension was absent and/or size was less than 3.5 cm (Lont et al, 2007; Zhu et al, 2008). Additional factors noted in these studies included the grade of the nodal metastasis and its TP53 status. Thus patients with only a single small lymph node metastasis discovered at the time of a inguinal dissection (i.e., no extracapsular extension, not high grade) may be at very low risk for pelvic metastasis and are potentially the optimal candidates in whom pelvic lymphadenectomy can be avoided.

With respect to efficacy the 5-year survival for patients with positive pelvic nodes averages around 14% (see Table 34–5). However, data from some of the smaller series suggested that in selected instances 5-year survival can occur in patients treated with surgery alone. In the series reported by Ravi (1993a), however, even patients with a single positive pelvic node failed to survive 5 years (0 of 8 patients). The difficulty in determining the potential independent value of pelvic lymphadenectomy as a therapeutic procedure is related to the small numbers of patients reported, the coexisting extensive inguinal adenopathy in patients with resectable pelvic nodes, and the failure to specify sites of relapse in patients undergoing ilioinguinal lymphadenectomy (i.e., inguinal versus pelvic versus distant site). Although unproved, it is conceivable that patients with minimal inguinal disease who exhibit focal involvement of a pelvic node could benefit from pelvic dissection. The series reported from Lopes and coworkers (2000) provides support for this concept. Among 13 patients with pathologically proven lymph nodes, 5 of 13 (38%) were alive without disease with follow-up for more than 90 months in 4 of 5 survivors. This series is unique in that 4 of 5 survivors exhibited only a single iliac nodal metastasis and one inguinal lymph node metastasis; in fact, 1 patient with iliac metastases had no inguinal disease. This series is clearly the exception but reveals that selected patients with minimal inguinal and pelvic disease may be cured with surgery alone.

Thus in patients undergoing inguinal lymphadenectomy for curative intent (i.e., in whom preoperative studies reveal no pelvic adenopathy), pelvic lymphadenectomy should be considered in most patients with positive nodes because it can serve as an effective staging tool for identifying those patients who should receive adjuvant combination chemotherapy or radiation (Pizzocaro et al, 1997; Lont et al, 2007). It also adds to locoregional control and provides little additional morbidity to the simultaneous inguinal procedure being performed. Alternatively, if pelvic nodal metastases are proven before lymphadenectomy, consideration should be given to neoadjuvant chemotherapeutic strategies followed by surgery in those patients who respond (Pizzocaro et al, 1997; Corral et al, 1998; Bermejo et al, 2007).

Key Points: Treatment of the Inguinal Nodes

- The presence and extent of inguinal metastases determine survival in penile cancer.
- Patients with persistent palpable inguinal adenopathy should undergo an inguinal staging procedure.
- On the basis of the histologic features of the primary tumor, risk of lymph node metastases can be assessed in patients with no palpable adenopathy and lymphadenectomy or close follow-up can be recommended.
- Factors associated with cure in surgically treated patients include no more than two inguinal metastases, unilateral involvement, no extranodal extension of cancer, and absence of pelvic metastases.
- Morbidity of lymphadenectomy is decreasing in contemporary series.
- Superficial and modified inguinal dissections remain the standard dissection techniques to reliably determine the presence of microscopic inguinal metastases.
- Dynamic sentinel lymph node biopsy techniques to determine microscopic inguinal disease exhibit low morbidity, have been validated externally, and can be used in experienced centers.
- Laparoscopic lymphadenectomy is an investigational tool at this time.

Risk-Based Management of the Inguinal Region

A contemporary schema for management of the inguinal region is presented in Figure 34–5. Assumptions for these guidelines are that the primary tumor has been adequately controlled, that the pathologic stage of the primary tumor is available, and that an inguinal examination has been performed. CT of the abdomen and pelvis as well as chest radiography or other imaging studies should also be performed as clinically indicated.

Very Low-Risk Patients

Because the incidence of inguinal metastasis is anecdotal at best for patients with stage Tis or Ta primary tumors, observation is reasonable for those patients with normal inguinal examination findings (see Fig. 34–5A, left). For patients with palpable adenopathy, a course of antibiotics should reveal those whose adenopathy is related to infection versus metastasis. A persistently palpable node should undergo fine-needle aspiration cytology; if the result is negative, an excisional biopsy is recommended. If the biopsy finding is abnormal, ipsilateral ilioinguinal dissection with contralateral superficial or modified complete dissection is performed.

Low- to Intermediate-Risk Patients

Several series have combined patients with stage T1 grade 1 and grade 2 tumors and have found them to exhibit less than a 10% incidence of inguinal metastasis (see Fig. 34–5A, right; see also

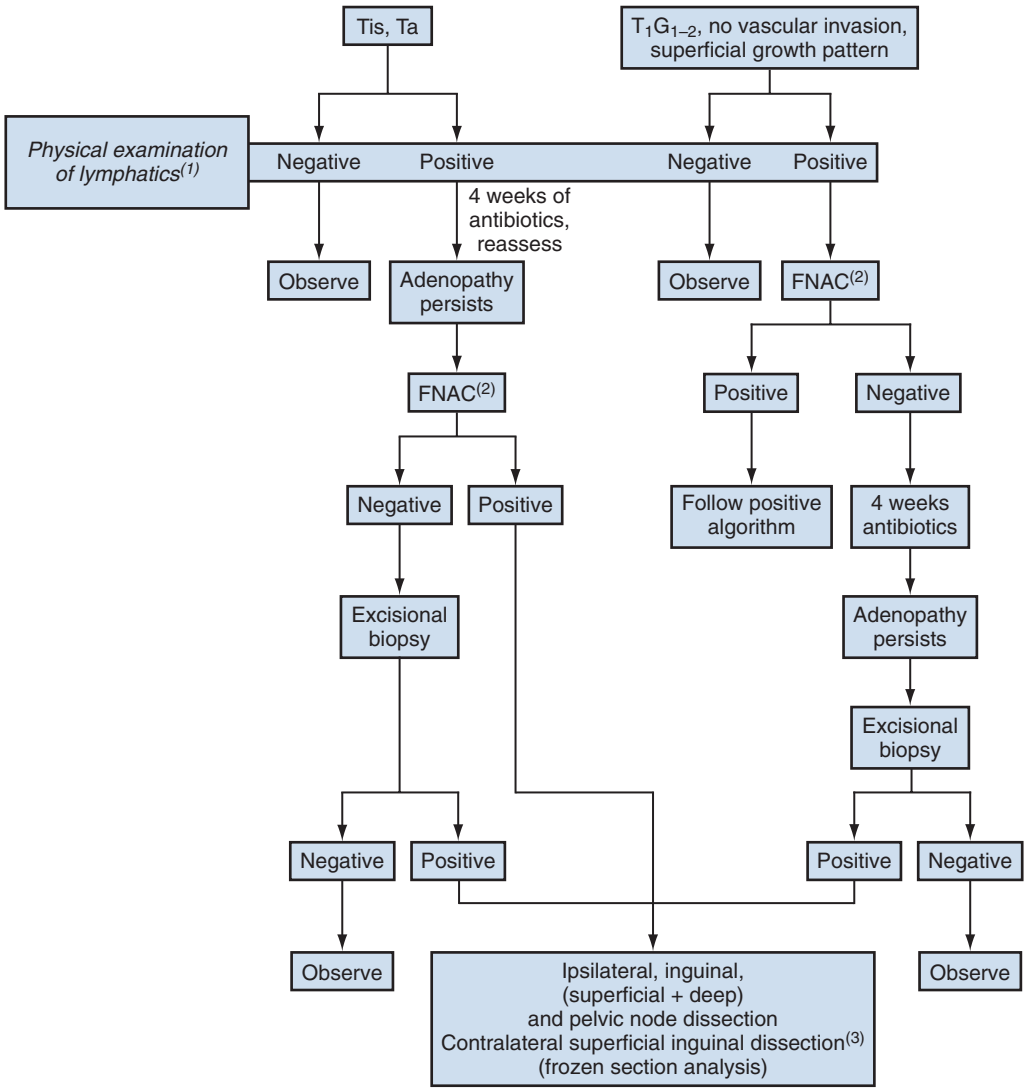


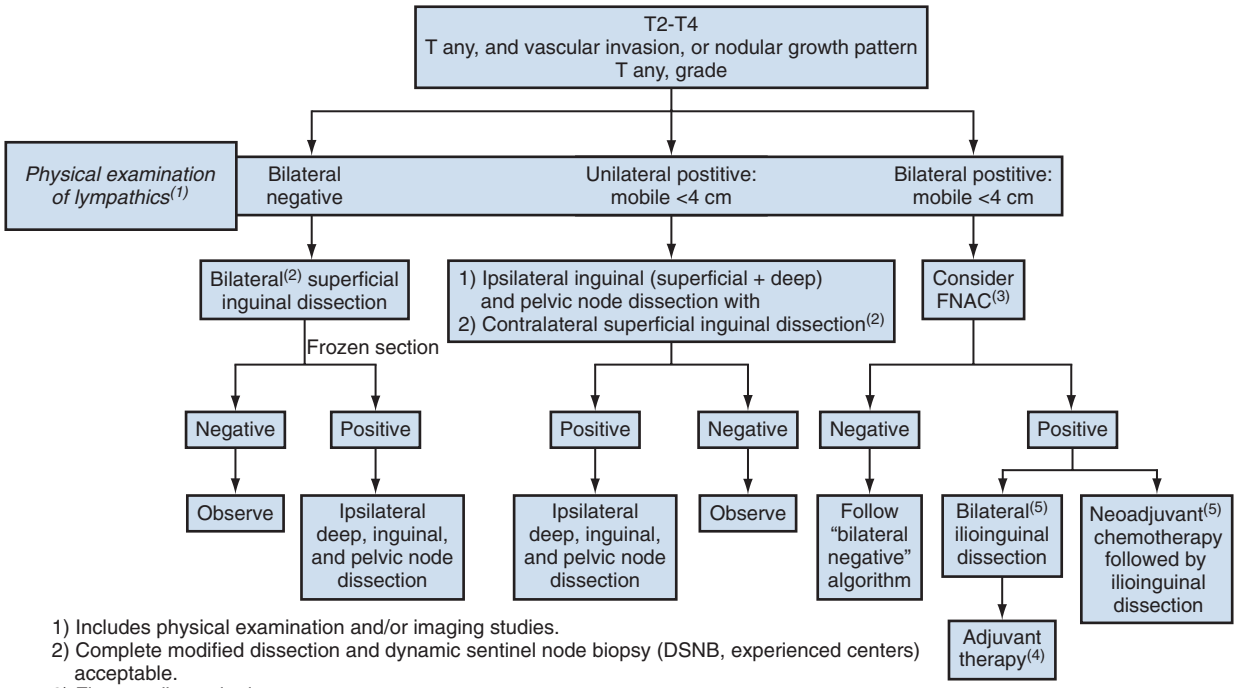
Figure 34–5. Management of regional disease. **A,** Low-risk patients. *Continued*

Table 34–8). However, the incidence of metastasis among strictly T1 grade 2 tumors (25% to 44%) may be higher and variable recommendations have been made. The recent EAU guidelines suggest that compliant patients with clinically negative lymph nodes that exhibit superficial growth and are vascular invasion negative can be observed (Solsona et al, 2004). However, similar patients with palpable nodes on initial presentation should undergo fine needle aspiration cytology. If the nodes are positive, the patients then undergo lymphadenectomy, as in Figure 34–5A. If they are negative, then a 4-week period of antibiotic therapy is reasonable. If adenopathy does not resolve, then either excisional biopsy and/or planned lymphadenectomy are reasonable options. Close follow-up is indicated for patients whose nodes resolve after antibiotic therapy, although the overall risk in this group remains low.

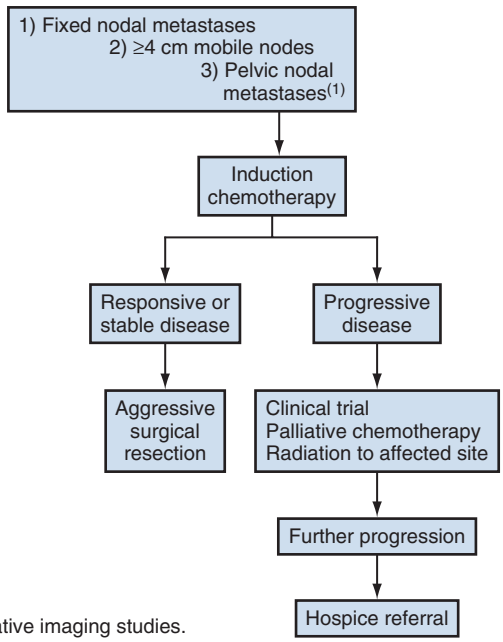
High-Risk Patients

For the high-risk cohort, the incidence of inguinal metastasis ranges from 50% to 70% (see Fig. 34–5B). According to the recent EAU guidelines, patients with T1 grade 2 tumors exhibiting a nodular growth pattern or vascular invasion are managed according to this stratification (Solsona et al, 2004). The surgical approach is designed to maximize detection and treatment for those with proven nodal metastasis while limiting the morbidity of those with negative lymph nodes at surgery. Thus surgical staging is indicated even in those patients with clinically normal inguinal examination findings. **In this setting, antibiotic use minimizes the risk of inguinal wound infections or septic complications after control of an infected primary tumor, rather than influencing the decision for surgical staging.**

Patients with normal inguinal examination findings are offered bilateral superficial dissection, complete modified dissection, or DSNB (with the last offered in experienced centers). If frozen-section results reveal no metastasis, the procedure is concluded. For DSNB the results are based on permanent sections; thus further therapy is planned at a second setting if needed. If either side is positive, an ipsilateral ilioinguinal dissection is performed.



1) Includes physical examination and/or imaging studies.
2) Complete modified dissection and dynamic sentinel node biopsy (DSNB, experienced centers) acceptable.
3) Fine needle aspiration.
4) Consider if >2 positive lymph nodes, or bilateral metastases, extranodal extension of cancer, or positive pelvic lymph nodes.
B 5) Either approach is acceptable.



C (1) Subsequent to preoperative imaging studies.

Figure 34–5, cont'd. **B,** High-risk patients. **C,** Metastatic disease. FNAC, fine-needle aspiration cytology.

Patients with unilateral resectable adenopathy that is strongly suggestive of metastasis should undergo an ipsilateral ilioinguinal dissection and a contralateral superficial or complete modified dissection. Frozen-section analysis then determines if deep inguinal or pelvic nodes should be excised. DSNB is another option in managing the contralateral node-negative side. Palpable adenopathy of less than 4 cm was arbitrarily selected as a cutoff point for surgery as monotherapy because nodal metastases larger than 4 cm are associated with extranodal extension of cancer (Ravi, 1993b).

For patients who present with bilateral palpable nodes that are strongly suggestive of metastasis, preoperative fine-needle aspiration cytology can be helpful for counseling of the patient as to the likelihood of the extent of surgery. For patients with negative results of fine-needle aspiration cytology, a staged surgical approach starting with superficial dissection is performed. Subsequent procedures in this setting depend on the results of frozen-section analysis. For patients requiring ilioinguinal lymphadenectomy because of metastases, adjuvant chemotherapy should be considered for those exhibiting more than two positive

lymph nodes, extranodal extension of cancer, or pelvic nodal metastasis.

Bulky Adenopathy and Fixed Nodal Metastasis

Survival in this cohort of patients is related to complete eradication of extensive disease (see Fig. 34–5C). **This task is difficult to achieve with surgery, chemotherapy, or radiation therapy alone. The combination of surgery and chemotherapy has shown some benefit in advanced penile carcinoma** (Pizzocaro et al, 1997; Corral et al, 1998; Bermejo et al, 2007; Leijte et al, 2007). The optimal integration and timing of such therapy are unknown. A reasonable approach in this cohort of patients is to use neoadjuvant chemotherapy followed by an aggressive surgical resection for patients demonstrating either response to therapy or stable disease. This potentially improves surgical resectability and avoids long delays in the administration of chemotherapy resulting from delays in postoperative healing. The prognosis is poor in patients exhibiting progression while they are receiving chemotherapy. Palliative groin dissection is a consideration but rarely provides significant palliation (Leijte et al, 2007). Hemipelvectomy in patients without distant metastases has been reported (Block et al, 1973). Endoluminal vascular stents have also been reported to have transient success in preventing vascular erosion by tumor (Link et al, 2004). Clinical trials of novel systemic strategies and radiation therapy to affected areas provide the next level of care. With further progression, supportive care provided by hospice services can provide valuable daily support to patients with end-stage disease.

RADIATION THERAPY

Radiation Therapy for the Primary Lesion

Primary radiation therapy has significant curative potential and may permit relative preservation of penile form and function. If local control is not achieved, salvage surgery may still be curative; thus in a subset of men with penile cancer radiation as an initial strategy represents a reasonable treatment strategy. Both external-beam radiation therapy and interstitial brachytherapy are currently utilized in treating the primary penile tumor. Before radiation therapy is performed circumcision is necessary to expose the lesion, to allow resolution of any surface infection, and to prevent maceration and preputial edema.

External-Beam Radiation Therapy

External-beam radiation therapy has several advantages: it is widely available, delivers a homogeneous dose, and does not require the same expertise with respect to technical skills required for delivery of effective brachytherapy. In their review Crook and colleagues (2009) described contemporary doses and fractions as ranging from 60 Gy in 25 fractions delivered over 5 weeks to 74 Gy in 37 fractions delivered over 7.5 weeks. This contrasts to lower doses of 50 to 55 Gy cited in older series (Neave et al, 1993; McLean et al, 1993). One of the challenges of external radiation therapy is immobilizing the penis to achieve consistent targeting of the tumor as treatment progresses. Both wax blocks along with a "see through" variant Perspex have been used for this purpose in addition to treating the patient in a prone position with the penis suspended in a small waterbath container (McLean et al, 1993; Zouhair et al, 2001; Vujovic et al, 2001).

Table 34–11 is adapted from the work of Crook and colleagues (2009) and describes the efficacy of both external-beam radiation therapy and interstitial brachytherapy with respect to local control, cause-specific survival, complications, and penile preservation. The data represent retrospective reviews of single institution series collected over many years.

Five-year local control rates among patients treated using a variety of techniques ranged from 44% to 69.7% with penile preservation rates of 50% to 65%. Thus the ability of primary external-beam radiation therapy to control the primary tumor was inferior to that of traditional surgical techniques. However, further local control in most cases was achieved by partial or total amputation. Cause-specific survival ranged from 58% to 86% depending on primary tumor stage and lymph node status.

Prognostic factors for response among patients treated with external-beam radiation therapy include dose less than 60 Gy, protracted treatment time greater than 45 days or daily fraction less than 2 Gy in addition to stage T3 disease, size greater than 4 cm, and high-grade tumors (Sarin et al, 1997; Gotsadze, et al 2000; Crook et al, 2009).

Brachytherapy

As an alternative to external-beam radiation therapy, interstitial brachytherapy with a variety of radioisotopes (radium-226, iridium-192, cesium-137) have been used. Gerbaulet and Lambin (1992), using percutaneously placed interstitial iridium-192 implants, reported successful local control in 82% of 109 patients, with long-term survivals of 75% to 80% in patients with tumor-free regional lymph nodes. Rozan and associates (1995) reviewed 259 patients from multiple centers, with 5- and 10-year disease-free survival rates of 78% and 67%, respectively. Twenty-two percent of patients also had surgery ranging from circumcision to total penectomy. Late side effects occurred in 53% of the group. Alternatively, iridium-192 wires are placed in a plastic mold worn in close apposition to the penile shaft for 12 hours or so daily for a period of 7 to 10 days for a total tumor dose of 60 Gy (El-Demiry et al, 1984; Akimoto et al, 1997).

Crook and associates (2002) initially reported a cohort (1989-2000) of 30 men with cT1-cT3 squamous cell carcinoma treated with iridium-192 delivered by 17- to 19.5-gauge steel needles held in a three-dimensional array by predrilled acrylic plastic templates. With a median of six needles, dosages of 55 to 65 Gy were delivered during an average of 93 hours. With a median 34 months of follow-up there were four local failures and four regional failures and one patient required partial penectomy for radionecrosis. The 2-year actuarial local failure-free rate was 85%, and successful penile conservation was 83%. Obviously, tumors could only be clinically staged and the authors stated that clinical distinction between cT1 and cT2 is subjective. Failure related to tumor grade but not tumor size. Kiltie and associates (2000), however, found local failures in 60% of tumors larger than 4 cm compared with 14% of tumors smaller than 4 cm. Mazeron and colleagues (1984) and Soria and coworkers (1997) both demonstrated more local failure as the tumor invaded the corpora and with tumor size larger than 4 cm. In the initial Crook series, prophylactic lymph node dissections were not routinely performed and, as one would expect, 50% of moderately or poorly differentiated tumors recurred regionally or distally. Therefore, selection of patients for prophylactic lymph node dissection should be the same as selection of patients having surgical removal of the primary tumor.

Table 34–11.

Selected Series of Studies Reporting Local Control (LC) of Disease, Cancer-Specific Survival (CSS), Complications, and Penile Preservation for Men Treated with External-Beam Radiation Therapy (XRT) or Brachytherapy (BT) as Primary Treatment for Penile Cancer

STUDY	NO. PATIENTS	TYPE OF RT	DOSE (Gy)	F/U (mo) median (range)	LC BY RT AT 5 YEARS	CSS AT 5 YEARS	COMPLICATIONS	PENILE PRESERVATION
External Beam								
McLean et al, 1993	26	XRT	35/10-60/25	116 (84-168)	61.5%	69%	7/26 unspec.	66% crude
Neave et al, 1993	20	XRT	50-55	36 mo minimum	69.7%	58%	10% stenosis	60%
Sarin et al, 1997	59	XRT	60/30	62 (2-264)	55%	66%	3% necrosis 15% stenosis	50% crude
Gotsadze et al, 2000	155	XRT	40-60	40	65%	86%	Necrosis: 1 Stenosis: 5	65%
Munro et al, 2001	13	XRT						
Zouhair et al, 2001	23	XRT						43%
Ozsahin et al, 2006	33	XRT/BT	52	62 (2-454)	44%	-	10% stenosis	52%
Mistry et al, 2007	18	XRT	55/16-50/20	62	63%	75%	2 necrosis 1 stenosis	66% crude
Brachytherapy								
Mazeron et al, 1984	50	BT	60-70	(36-96)	78% crude		3 necroses 19% stenosis	74%
Delannes et al, 1992	51	BT	50-65	65 (12-144)	86% crude	85%	23% necrosis 45% stenosis	75%
Rozan et al, 1995	184	BT	63	139	86%	88%	21% necrosis 45% stenosis	78%
Soria et al, 1997	102	BT	61-70	111	77%	72%		72% (6 years)
Chaudhary et al, 1999	23	BT	50	21 (4-117)	70% (8 years)		0 necrosis 9% stenosis	70% (8 years)
Kiltie et al, 2000	31	BT	63.5	61.5	81%	85%	8 necrosis 44% stenosis	75%
Crook et al, 2009	67	BT	60	48 (4-194)	87.5%	83.6%	12% necrosis 9% stenosis	88% 5 years 67% 10 years

The Crook series was updated in 2009 to 67 patients with a median follow-up of 4 years (range 0.2 to 16.2). At 10 years the actuarial cause-specific survival was 83.6% and three late failures were observed (42, 64, 90 months). Penectomy was performed for 8 recurrences and 2 necroses for 5- and 10-year penile preservation rates of 88% and 67%, respectively. Inguinal lymph nodes in the most recent patients were managed with the same indications as for patients undergoing primary surgery but using only biopsy information. The dominant predictor of local failure was needle spacing—an increase in spacing decreased recurrences due to the wider lateral margin achieved. **Overall local control** (see Table 34–11) **provided by interstitial brachytherapy appeared superior to that provided by external-beam radiation therapy with 5-year local control rates from 70% to 87%. Penile preservation rates are highest at 5 years (74% to 88%) with some decrease at 8 to 10 years (67% to 70%)** (Crook et al, 2009).

Adverse Effects Associated with Radiation Therapy

There are significant disadvantages to radiation therapy. Squamous cell carcinoma is characteristically radioresistant, and the dosage required to sterilize the tumor (i.e., 60 Gy) may cause urethral fistula, stricture, or stenosis, with or without penile necrosis, pain, and edema (Kelley et al, 1974). **In some instances secondary penectomy may be required** (Duncan and Jackson, 1972). Penile necrosis was seen in 0% to 23% of patients treated with external-beam or interstitial radiation therapy but appeared more common with brachytherapy (see Table 34–11). In the case of necrosis a diagnostic dilemma exists in determining whether recurrent cancer is present and biopsy may be indicated. Close follow-up and treatment with antibiotics, vitamin E, corticosteroid creams, and hyperbaric oxygen have been recommended (Crook et al, 2009). Urethral stenosis was noted in 10% to 45% of patients and may be related to increased dose per fraction in those treated with external-beam radiation therapy or needle spacing among those treated with brachytherapy. Urethral strictures often occur late and based upon severity may be managed with repeated dilation or in some cases urethroplasty.

The benefits of avoiding a mutilating surgical procedure are obvious, and although sexual function is generally reported to be preserved the side effects of radiation on sexual quality of life have not been studied with validated instruments (Crook et al, 2009). In addition, patients and physicians must carefully consider the unique acute and long-term side effects of radiation therapy. Radiation therapy is usually administered for a period of 3 to 6 weeks and is followed by several months of morbidity. This may pose a formidable burden in elderly patients. By contrast, partial penectomy offers a prompt and effective treatment, with relatively few side effects limiting activity in the postoperative period.

The organ-sparing benefits of radiation must be compared with surgical choices such as laser therapy, Mohs micrographic surgery, and reconstructive surgery, all of which can provide a surgical treatment while minimizing functional loss and potentially avoiding the long-term risks of recurrence, necrosis, and urethral stenosis that may occur after radiation therapy. Age and comorbidities may also direct treatment, with surgery as a possible solution for

the elderly patient in whom preservation of the penis is secondary, whereas radiation may be the only solution for a patient with significant comorbidities.

Finally, it must be accepted that should radiation therapy fail, prompt penectomy must be done to avoid jeopardizing survival. Careful long-term follow-up is essential to detect recurrence promptly, and it must be recognized that recurrence may develop relatively late. In one series, 7 of 11 recurrences were detected after 2 years (63%) and 2 (18%) after 5 years (Mazeron et al, 1984). In terms of salvage surgery, Crook and colleagues (2009) note that external-beam radiation therapy generally treats the entire penile shaft whereas brachytherapy tends to be best for focal disease. Therefore salvage options after brachytherapy may more likely result in a partial penectomy versus total penectomy.

Close follow-up may be difficult in a group of patients whose reliability is often poor and who have often neglected a markedly symptomatic primary lesion for an extended time before seeking treatment. Furthermore, distinguishing postirradiation ulcer, scar, and fibrosis from possible recurrent carcinoma is often impossible, and repeated biopsies of the lesions may be required.

In summary, small superficial tumors will respond well to radiation therapy and, with careful planning, complications can be minimized. Brachytherapy for tumors smaller than 4 cm may offer acceptable local control rates with faster dose delivery. The treatment of larger, invasive malignant neoplasms is less successful, may be associated with severe local complications, and theoretically may provide an interval during which metastatic dissemination may occur. For the patient who is an appropriate candidate for a radiation-based approach, the selection of external beam versus brachytherapy may depend on the skill and experience of the radiation therapist involved, with the former more widely available. Crook and colleagues' series and review (2009) would suggest that the brachytherapy technique should be expanded and studied further in a multi-institutional fashion.

Radiation Therapy for the Inguinal Areas

Assessment of the treatment of the inguinal area by primary radiation therapy is hampered by the uncertainty arising from the inaccuracy of clinical staging and the frequent lack of histologic confirmation of nodal metastases. Other objections to the treatment of inguinal node metastases are that the inguinal areas tolerate radiation poorly and are subject to skin maceration and ulceration.

Both the therapeutic and adjunctive use of radiation in the treatment of the regional nodes has fallen out of favor with little contemporary data available for review. Even if metastases were documented by node biopsy, the efficacy of subsequent radiation is impossible to judge because all tumors may have been removed by the biopsy. In one series, 70% of nodal metastases involved a single node, and survival in this group was 70% (Cabanas, 1977). Radiation therapy for inguinal metastases documented by histologic examination has been compared with surgery for the node-positive groin. A 50% 5-year survival rate was observed among the surgically treated group, and a 25% 5-year survival rate was observed among the irradiated group (Staubitz et al, 1955). Other series report that radiation to the inguinal areas has not proved therapeutically effective (Murrell and Williams, 1965; Jensen, 1977; Kulkarni et al, 1994).

Prophylactic radiation therapy to the inguinal lymph nodes in penile cancer has to date not shown benefit. In a series of 130 patients initially having clinically impalpable nodes but treated with adjuvant radiation therapy, 18 subsequently developed palpable nodal disease requiring lymphadenectomy and another 11 patients had metastases but no surgery. Therefore 29 of 130 men (22%) who received prophylactic groin irradiation subsequently developed inguinal metastases (Ekstrom and Edsmyr, 1958).

Murrell and Williams (1965) found that 3 of 11 patients (25%) who received radiation therapy to the inguinal area without initially palpable nodes subsequently developed inguinal metastases. These percentages closely approximate the incidence of subclinical metastases that are encountered if node dissection is performed when the clinical examination is normal (see Table 34–3), and they suggest that radiation therapy did not alter the course of the disease. Furthermore, because of tissue changes that follow radiation to the groin, clinical evaluation of the groin is difficult and the complications encountered with groin dissection after irradiation can be significant.

One of the largest series demonstrating a benefit of radiation therapy for lymph node metastases and/or distant metastases from penile cancer was published by Ravi and associates in 1994. One hundred and twenty patients with lymph node metastases and 9 with distant metastases were managed by radiation therapy alone (palliative) or in the preoperative or postoperative setting. Pertinent to the advanced disease presentation setting, 33 patients were treated with preoperative radiation therapy at 40 GY over 4 weeks and subsequently had inguinal lymphadenectomy. Of note, after radiation therapy and surgery only 8% had evidence of extranodal extension and 3% experienced recurrence of the disease within the groin. This is relevant because in a prior report within a contemporary time frame (Ravi, 1993b) the incidence of extranodal extension was 33% among patients treated with surgery alone and groin recurrence was noted in 19%. The difference for both extranodal extension and local recurrence were both statistically lower ($P = < .01$ and .03, respectively). The data are suggestive but not definitive that preoperative radiation therapy for nodes 4 cm or larger without skin fixation improved local control. The 5-year survival among the latter group was 70% (Ravi et al, 1994). These data are consistent with the beneficial effects seen when radiation therapy is used together with surgery or chemotherapy in management of other squamous malignancies such vulvar, cervical, or anal carcinomas (UKCCCR Anal Cancer Trial Working Party, 1996; Montana et al, 2000; Green et al, 2001). Such approaches should be further explored in the treatment of locally advanced penile cancer.

In the series by Ravi and colleagues (1994), palliative radiation therapy ameliorated symptoms in 56% of patients with fixed groin nodes, in 5 of 5 patients with painful bony metastases, and in 1 of 2 patients with spinal cord compression and paraplegia. However, pelvic and/or para-aortic radiation therapy was ineffective in patients with pelvic node metastases. Thus radiation therapy may be considered in patients presenting with inoperable fixed and ulcerative inguinal lymph nodes who are not candidates for chemotherapy. On occasion, radiation to these areas is well tolerated, may result in significant palliation, and may postpone local complications for prolonged periods (Furlong and Uhle, 1953; Staubitz et al, 1955; Vaeth et al, 1970).

An alternative use of radiation would be as adjuvant therapy for surgically treated, pN patients. In a small retrospective study from Taiwan, Chen and colleagues (2004) reported regional failure rates after positive inguinal lymph node dissections in 11% (1 of

9) versus 60% (3 of 5) with and without adjuvant inguinal radiation therapy.

In summary, radiation therapy to the inguinal area is not as effective therapeutically as lymph node dissection, but it may be useful for palliation in the situation of inoperable nodes. Based on studies in other squamous malignancies, radiation as a part of a multimodal approach with chemotherapy and surgery among patients with advanced penile cancer should be further evaluated.

Key Points: Radiation Therapy

- Primary radiation therapy for the penis may be successfully applied to select patients with T1 and T2 squamous cell carcinomas smaller than 4 cm with either external-beam or brachytherapy techniques.
- Salvage penectomy may be required after external-beam radiation therapy or brachytherapy for persistent or recurrent disease or radiation necrosis. Lifelong careful follow-up is required.
- For patients selected for radiation therapy for the primary tumor, surgical management of inguinal lymph nodes should be recommended by the same criteria as for patients selected for surgical management of the primary tumor.
- Radiation to the inguinal area is not as effective as surgery for treatment of the inguinal nodes.
- Prophylactic radiation therapy has not been shown to alter the natural history of inguinal metastases and is not recommended.
- Integration of radiation therapy with surgery and chemotherapy in advanced disease requires further study.
- Palliative radiation therapy among patients with inoperable inguinal nodes may provide some benefit.

CHEMOTHERAPY

Advanced penile cancer presenting as either bulky or unresectable regional disease or visceral metastases at initial presentation or disease recurrence is highly lethal because it is incurable in most cases with either surgery or radiation therapy alone (Ornellas et al, 1994; Ravi et al, 1994; Hegarty et al, 2006). Experience with single- or multiple-agent chemotherapy in this setting is limited because there are few phase 2 clinical trials and no randomized clinical trials. Several regimens have produced clinically meaningful responses that have occasionally resulted in clearance of disease or facilitated surgical resection.

Single-Agent Chemotherapy

Gagliano and associates (1989) from the Southwest Oncology Group treated 26 patients, 12 of whom had prior radiation, with low-dose (50 mg/m^2) cisplatin and observed a 15% response rate of 1 to 3 months' duration and a median overall survival of 4.7 months. In a study from Memorial Sloan-Kettering Cancer Center, 13 patients with extensive disease and either prior radiation therapy or chemotherapy were treated with cisplatin 70 to 120 mg/m^2 every 21 days. Three of 12 evaluable patients (25%) demonstrated responses (one complete and two partial; duration = 2 to 8 months; Ahmed et al, 1984).

Initial favorable reports from Japan suggested that bleomycin appeared to be effective in the treatment of penile and scrotal cancer. Ichikawa and associates (1969, 1977) reported a 50% response in 24 previously untreated patients with squamous cell carcinoma of the penis. A similar report from Uganda documented partial or complete tumor regression in 45% of treated patients (Kyalwazi et al, 1974). A review of 90 patients from the world literature demonstrated similar responses (Eisenberger, 1992). In the study by Ahmed and colleagues (1984) 14 patients were evaluable for response to single-agent bleomycin. There was one complete response but the patient died of bleomycin pulmonary toxicity. There were also two partial responses for an objective response rate of 21%. The median response duration was only 3 months (range 2 to 4 months).

Methotrexate produced responses in 8 of 13 patients (61%) treated at Memorial Sloan-Kettering Cancer Center (Ahmed et al, 1984), with one complete response. However, median response duration even with the high response rate was 3 months (2 to 31 months) and 1 patient died of treatment-related sepsis. Methotrexate had been shown to be active in other reports (Mills, 1972; Garnick et al, 1979). Based on the Ahmed and colleagues' study in which cisplatin (P), bleomycin (B), and methotrexate (M) were given sequentially there did not appear to be any obvious cross-resistance to the three agents. Subsequently a three-drug trial using PMB was developed.

Combination Chemotherapy

The Southwest Oncology Group reported a phase 2 study using a modified regimen that reduced the total dose of PMB. Haas and associates (1999) employed combination cisplatin, methotrexate, and bleomycin in 45 patients with locally advanced or metastatic penile cancer accrued from 31 different institutions. There were five complete and eight partial responses among 40 evaluable patients (32.5% response rate). The median duration of response was 16 weeks, with an overall survival of 28 weeks (Haas et al, 1999). Although the response rate appeared encouraging it was still within the 95% confidence intervals for single-agent cisplatin and there were five treatment-related deaths on the study (one from infection and four from pulmonary complications) (Ahmed et al, 1984; Gagliano et al, 1989; Haas et al, 1999). Thus this study failed to confirm the initial high response rate of single-agent methotrexate, which was not significantly higher than that of single-agent cisplatin; and bleomycin pulmonary toxicity was significant (Haas et al, 1999).

Two additional more contemporary trials both containing cisplatin reveal significant activity while omitting the significant toxicity associated with bleomycin and methotrexate. Theodore and coworkers (2008) reported the results of a European Organization for Research in Cancer Therapy phase 2 study in which 28 patients with stage T3/T4, N1-3, or M1 disease received combination cisplatin and irinotecan. Patients were treated in either the neoadjuvant setting for four cycles before surgery (T3N1-2) or up to eight cycles (T4N3M1 disease). Toxicity was acceptable with no treatment-related deaths. Eight responses were noted (two complete, six partial), for an objective response rate of 30.8% (80% confidence interval = 18.8% to 45%). Of note, 3 patients who underwent surgery in the neoadjuvant setting were found to have no evidence of residual disease. The authors reported the trial as negative however because it was powered to show a response rate greater than 30%.

A phase 2 clinical trial of neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy (TIP) is in progress at the University

Table 34–12.

Safety and Efficacy of Multidrug Penile Cancer Regimens without Bleomycin

	CHEMOTHERAPEUTIC REGIMEN	RESPONSE RATE	TREATMENT-RELATED DEATH	MEDIAN OVERALL SURVIVAL
Shammas et al, 1992	Fluorouracil, 1000 mg/m^2/day, days 1-5 (continuous infusion) Cisplatin, 100 mg/m^2, day 1; cycle every 3-4 weeks	25%	0/8	11.5
Pagliaro and Crook, 2009	Paclitaxel, 175 mg/m^2, day 1 Ifosfamide, 1200 mg/m^2, days 1-3 Cisplatin, 25 mg/m^2, days 1-3; cycle every 3 weeks	55%	0/20	11
Theodore et al, 2008	Irinotecan, 60 mg/m^2, days 1, 8, 15 Cisplatin, 80 mg/m^2, day 1; cycle every 4 weeks	30.8%	0/28	4.7

of Texas M. D. Anderson Cancer Center. Preliminary experience was recently published (Pagliaro and Crook, 2009). Eligible patients exhibited stage TxN2-N3 lymph node metastases, no evidence of distant metastases (M0), and no prior chemotherapy. Treatment consisted of four courses of chemotherapy followed by bilateral inguinal lymph node dissections, unilateral or bilateral pelvic lymph node dissections, and surgical control of the primary tumor when appropriate. Preliminary analysis of data from the first 20 patients revealed an objective response rate of 55% and pathologic complete responses in 10% (2 patients). Sixteen patients had residual disease at surgery, and 2 did not undergo surgery. Four patients (20%) were alive and free of disease at 23, 24, 31, and 32 months. Fifteen deaths occurred as a result of progressive disease, and one occurred from unknown causes. Toxicity was acceptable, and no treatment-related deaths occurred (Pagliaro and Crook, 2009). Thus the preliminary data using the TIP regimen suggest a response rate that may be significantly higher than that with single-agent cisplatin that is better tolerated than prior bleomycin- or methotrexate-containing regimens. However, patients treated thus far with the TIP regimen have in general had lower-stage disease and the final trial results have yet to be reported. Table 34–12 provides safety and efficacy data of cisplatin-containing chemotherapy regimens reported thus far. Treatment-related pulmonary toxicity and death were avoided with the absence of bleomycin.

Data from the just discussed two contemporary trials suggest that selected patients with advanced, unresectable primary tumors or bulky regional lymph node metastases appeared to benefit from postchemotherapy lymphadenectomy. Negative pathology in lymph nodes was seen after neoadjuvant treatment with TIP (2/20 patients) and irinotecan/cisplatin (3/7 patients). For patients with unresectable primary tumors or bulky regional lymph node metastases, neoadjuvant treatment with a cisplatin-containing regimen may be effective and may allow curative resection. The optimal chemotherapy regimen has yet to be determined.

Adjuvant Chemotherapy

Historically, combination vincristine, bleomycin, and methotrexate therapy was administered in 12 weekly courses to 17 patients in the postoperative setting (12 patients) or neoadjuvant setting (5 patients) at the Milan National Tumor Institute. The patients treated were at high risk for recurrence with surgery alone; 9 showed extranodal tumor growth, 5 had pelvic nodal involvement, and 5 had bilateral metastases. At follow-up ranging between 18 and 102 months, only one relapse had occurred (Pizzocaro and Piva, 1988). Later reports from this center further confirmed the value of adjuvant chemotherapy. Of 56 node-positive patients, 82% of the 25 patients receiving adjuvant vincristine, bleomycin, and methotrexate therapy survived 5 years, compared with 37% of 31 patients treated with surgery alone (Pizzocaro et al, 1995, 1997). In the neoadjuvant treatment group, partial responses were noted in 3 of 5 patients with extremely large (6 to 11 cm) nodal metastases. These 3 patients subsequently were underwent complete resection and were free of tumor at intervals ranging from 20 to 72 months. These data have yet to be confirmed and will probably not be further studied given the potential toxicities of bleomycin and methotrexate.

Postchemotherapy Surgical Consolidation

Shammas and coworkers (1992) reported on 8 patients treated with the combination of cisplatin and 5-fluorouracil. Seven of the patients had Jackson stage III or IV disease, and 2 in this group had either pleural or lung metastases. One of the 7 with stage III or IV disease (14%) had a partial response with disappearance of lung metastases and postsurgical consolidation and lived 32+ months; he received five cycles of therapy. Three patients with stable disease received only one to two cycles and survived 2+ to 11 months. Of note, 2 of 3 patients who ultimately had disease progression received three to four cycles of therapy and underwent surgical consolidation with survivals of 12 and 28 months after chemotherapy. Thus, 2 of 7 patients (28%) who survived 28 and 32+ months received significant palliation or cure from the combination.

Corral and colleagues (1998) reported on the long-term follow-up of a prospective group of patients treated with bleomycin, methotrexate, and cisplatin. Among the cohort, 21 patients had penile carcinoma with 10 of the 21 (48%) having either N3 or M1 disease. The remainder had either N1 or N2 nodal metastases. Objective responses were noted in 12 (57%), including 2 of 5 patients with distant metastases. Six patients in the group (28.5%) achieved disease-free status with either chemotherapy alone (2 patients) or surgery (3 patients) or radiation therapy (1 patient) with a median survival of 27.8 months. This was significantly longer than that of those not achieving disease-free status (6.7 months, $P = .004$). Thus, this prospective study showed that a multidisciplinary approach to achieve disease-free status could prolong survival. Subsequently Leijte and associates (2007) from the Netherlands Cancer Institute reviewed their experience with neoadjuvant chemotherapy in patients with initially "unresectable" penile cancer. The series included 20 patients treated with five different regimens, including (1) single-agent bleomycin; (2) bleomycin, vincristine, and methotrexate; (3) cisplatin and

5-fluorouracil; (4) bleomycin, cisplatin, and methotrexate; and (5) cisplatin and irinotecan. The objective responses were evaluable in 19 (1 patient died of bleomycin toxicity after 2 weeks) with 12 responses (63%, 2 complete, 10 partial). Surgical procedures included treatment of the primary tumor as well as inguinal and pelvic dissections. Additional soft tissue resection including bone was sometimes required. Vascularized tissue flaps were used for inguinal reconstruction. Among 12 responders only 9 went to surgery, because 2 died of bleomycin-related complications while the third was deemed unfit for surgery. Eight of 9 responding patients taken to surgery (2 were pT0) were free of disease with a median follow-up of 20.4 months. This is in contrast to 3 nonresponders who went to surgery for palliative intent: all 3 died within 4 to 8 months due to locoregional recurrence. The implications from this study indicate that response to chemotherapy together with an aggressive surgical procedure provides the optimal scenario for significant palliation or potential cure.

In a separate study Bermejo and colleagues (2007) described the surgical considerations and complications among 10 patients who had either a response or stable disease after combination chemotherapy. The regimens utilized included (1) cisplatin, methotrexate, and bleomycin (PMB); (2) paclitaxel, ifosfamide, and cisplatin (TIP); or (3) paclitaxel and carboplatin. This cohort of patients exhibited bulky inguinal or pelvic metastases, with the only exclusions being patients with fixed pelvic masses or complete encasement of the femoral vessels. In addition to ilioinguinal lymphadenectomy, resection of the inguinal ligament, the inferior aspect of the rectus abdominis or external and internal oblique muscles, the spermatic cord and ipsilateral testis, and segments of the femoral artery and vein (with subsequent patch or bypass grafting) were performed to achieve negative margins. Plastic surgery consultation was obtained for wound coverage, including the insertion of monofilament polypropylene mesh for abdominal wall defects and myocutaneous flaps of the sartorius, rectus abdominis, serratus anterior, and latissimus dorsi muscles. Of 5 patients exhibiting an objective response 3 were alive and free of disease at 48, 50, and 73 months. Two other patients died (1 of disease at 30 months, another of unknown causes at 21 months). Among the 5 remaining patients with stable disease 3 were dead of disease within 7 months and 1 patient treated with bleomycin died of "failure to thrive" at 8 months. However, another patient treated with paclitaxel and carboplatin achieving only stable disease was alive and free of disease at 84 months. These data appear to reinforce the concept that response to systemic chemotherapy before surgery enhances the chance for long-term survival among those undergoing surgical resection. Related to systemic therapy the authors reported that the TIP regimen was well tolerated and all three pT0 responses at surgery were among patients treated with TIP. This provided the rationale for the prospective phase 2 study discussed previously (Pagliaro and Crook, 2009).

Providing additional rationale to consider a taxine-based regimen in patients with advanced penile cancer as part of a multimodal strategy, Pizzocaro and associates (2009) reported on 6 patients (5 of 6 with N3 metastatic nodes) who were treated with paclitaxel (1 patient received docetaxel), cisplatin, and 5-fluorouracil. Post surgery, 3 patients exhibited a pathologic complete response. Two of the 3 received five to seven cycles of therapy and showed no evidence of disease at 25 to 27 months. The third patient tolerated only two cycles of therapy; and although he was pT0 at surgery he experienced relapse at 11 months and died. Another patient with a pathologic partial response (>90% necrosis in specimen) also received only two cycles of therapy but was without evidence of disease at 46 months. A patient with a clinical complete response refused surgical consolidation and experienced relapse and died at 6 months, as did the only remaining patient with no response to therapy (4 months survival). Taken together these data provide evidence that response to chemotherapy improves resectability and survival. Surgery among patients who do not respond to therapy may occasionally be associated with long-term survival but is more often associated with death due to either rapidly occurring locoregional recurrence or distant metastases (Bermejo et al, 2007; Leijte et al, 2007).

Key Points: Chemotherapy

- Treatment with a cisplatin-containing regimen in advanced metastatic penile cancer should be considered, because responses do occur and this may facilitate curative resection. The optimal chemotherapy regimen has yet to be determined.
- The use of bleomycin in the treatment of men with penile cancer was associated with an unacceptable level of toxicity and is discouraged as first-line therapy.
- Surgical consolidation to achieve disease-free status or palliation should be considered in fit patients with a proven objective response to systemic chemotherapy among patients who progress through chemotherapy is not recommended.

NONSQUAMOUS PENILE MALIGNANT NEOPLASMS

Nonsquamous penile malignant neoplasms are extremely rare. Pathologic descriptions and local/regional treatment options are available; however, outcomes and comparisons are limited to case reports and small retrospective series. Most reports establish the following features: (1) incidence of disease, (2) distinguishing pathologic features, (3) treatment recommendations, and (4) parallels (or lack thereof) to the same carcinoma in nongenital locations.

Basal Cell Carcinoma

Although basal cell carcinoma is frequently encountered on other sun-exposed cutaneous surfaces it is rare on the penis (Fig. 34–6A). Fewer than 30 cases have been well documented (Goldminz et al, 1989; Ladocsi et al, 1998; Nguyen, 2006). The lesion can be seen anywhere on the penis but is commonly on the penile shaft. It is slow growing, and delay in diagnosis in one series ranged from 2 months to 50 years (Kim et al, 1994). **Treatment is by local excision, which is virtually always curative** (Hall et al, 1968; Goldminz et al, 1989). Only one case report describes what the authors believe to be the only reported case of metastatic penile basal cell carcinoma (Jones, 2000). Nguyen and colleagues (2006) reported two cases of basal cell carcinoma treated by Mohs surgery.

A benign variant of basal cell carcinoma, the premalignant fibroepithelioma of Pinkus, has been reported to occur on the penile shaft (Heymann et al, 1983). Diagnosis is made at excisional biopsy. Excision has been uniformly curative.

Melanoma and basal cell carcinoma rarely occur on the penis, presumably because the organ's skin is protected from exposure

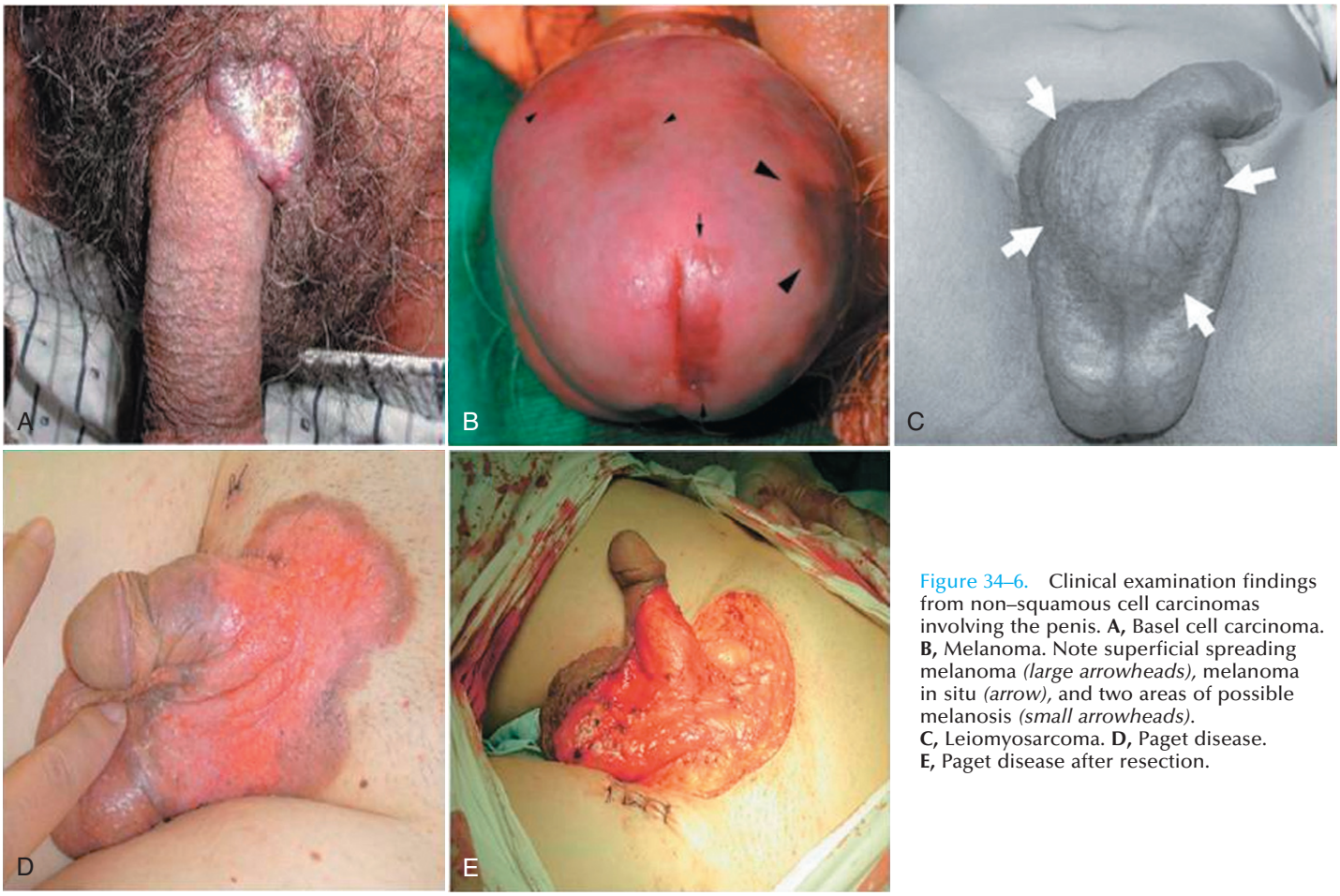


Figure 34–6. Clinical examination findings from non–squamous cell carcinomas involving the penis. **A,** Basel cell carcinoma. **B,** Melanoma. Note superficial spreading melanoma *(large arrowheads),* melanoma in situ *(arrow),* and two areas of possible melanosis *(small arrowheads).* **C,** Leiomyosarcoma. **D,** Paget disease. **E,** Paget disease after resection.

to the sun. Malignant neoplasms arising from the supporting structures of the penis are also rare and include any combination of tumors of smooth or striated muscle or of fibrous, fatty, or vascular tissue. Information about appropriate treatment of these malignant neoplasms is derived from the review of single case reports and small series (Belville and Cohen, 1992).

Melanoma

More than 150 cases of melanoma of the penis have been reported (see Fig. 34–6B). Of 1200 melanomas treated at Memorial Sloan-Kettering Cancer Center, only 2 were of penile origin (Das Gupta and Grabstald, 1965). At the University of Texas M. D. Anderson Cancer Center, less than 1% of all primary penile cancers were malignant melanomas (Johnson and Ayala, 1973; de Bree et al, 1997).

Melanoma presents as a blue-black or reddish brown pigmented papule, plaque, or ulceration on the glans penis. It occurs on the prepuce less frequently. Diagnosis is made by histologic examination of biopsy specimens, which demonstrate atypical junctional cell activity with displacement of pigmented cells into the dermis.

Prognostic characteristics that have been found significant for melanoma in other sites, such as depth of invasion (Clark staging) and thickness of the tumor (Breslow classification), have not been prospectively applied to penile lesions because experience with these lesions is limited. Sanchez-Ortiz and colleagues (2005) used the American Joint Committee on Cancer system for classifying cutaneous melanomas (Fleming et al, 1997) in the largest report to date on melanoma of the penis. This system incorporates elements of the Clark and Breslow staging systems. When this information is favorable, local excision is feasible. Distant metastatic spread has been found in 60% of patients studied (Abeshouse, 1958; Johnson et al, 1973; de Bree et al, 1997) in older series. However, Sanchez-Ortiz found that patients with early-stage melanomas had excellent outcomes if primary tumors were of low stage and regional lymph nodes were negative. Hematogenous metastases occur by means of the vascular structures of the corporeal bodies; lymphatic spread to the regional inguinal and pelvic nodes occurs by lymphatic permeation.

Surgery is the primary mode of treatment; radiation therapy and chemotherapy are of only adjunctive or palliative benefit. For stage I melanoma (localized lesion without metastases) and stage II melanoma (metastases confined to one regional area), adequate excision of the primary tumor by partial or total penile amputation together with en bloc bilateral ilioinguinal node dissection has historically been advocated (Johnson et al, 1973; Bracken and Diokno, 1974; Manivel and Fraley, 1988). In reviewing the University of Texas M. D. Anderson Cancer Center experience plus the literature to date, Sanchez-Ortiz and colleagues (2005) proposed a treatment algorithm for management of the primary tumor and inguinal lymph nodes. For tumors of the foreskin, circumcision may be adequate. For glans tumors, a partial penectomy was recommended; and for glans-shaft

tumors, a partial or total penectomy can be performed. The authors recommend bilateral modified inguinal lymph node dissections in all patients with lesions that are Breslow depth 1 mm or greater, with ulceration, or with Clark level IV or V involvement. Although sentinel lymph node biopsy techniques are increasingly utilized in more common sites of melanoma, its use in penile melanoma is unproven, and a learning curve of over 25 cases with this rare malignancy may be a barrier (Sanchez-Ortiz et al, 2006).

The prognosis for patients with penile melanoma is clearly dependent on stage of the primary tumor and the presence or absence of inguinal metastases. Contemporary staging and prognostic factors are reviewed by Sanchez-Ortiz and coworkers (2005). A report from the Netherlands (van Geel et al, 2007) focused on the concept of mucosal site penile melanomas—glans, meatus, fossa navicularis, and distal urethral. These lesions may appear more aggressive than cutaneous lesions, but greater delay in diagnosis may be a factor. In a pooled, retrospective analysis of 66 cases, the recurrence outcomes were similar for cutaneous melanomas of comparable tumor thickness.

Sarcomas

Primary mesenchymal tumors of the penis are rare. A thorough review of 46 such tumors from the Armed Forces Institute of Pathology revealed an equal number of benign and malignant lesions (Dehner and Smith, 1970). The patients ranged in age from newborn to the eighth decade of life. The presenting signs and symptoms of subcutaneous mass, penile pain and enlargement, priapism, and urinary obstruction were the same for both benign and malignant lesions. A sarcoma has been reported to masquerade as a Peyronie plaque (Moore et al, 1975).

Malignant lesions were found more frequently on the proximal shaft (see Fig. 34–6C); **benign lesions were more often located distally. The most common malignant lesions were those of vascular origin (hemangioepithelioma), followed in frequency by those of neural, myogenic, and fibrous origin** (Ashley and Edwards, 1957). Single case reports of sarcomatous lesions have been published, for example, malignant fibrous histiocytoma (Parsons and Fox, 1988), angiosarcoma (Rasbridge and Parry, 1989), leiomyosarcoma (Planz et al, 1998), epithelioid sarcoma (Leviav et al, 1988), hemangioendothelioma (Kamat et al, 2004), and osteosarcoma (Sacker et al, 1994).

Sarcomas have been classified as superficial when they arise from the integumentary supporting structures and as deep when they develop from the corporeal body supporting structures (Pratt and Ross, 1969). Wide, local surface excision and partial penile amputation for the superficial tumors have been suggested and used successfully in isolated case reports (Pak et al, 1986; Dalkin and Zaontz, 1989). Total penile amputation has been reserved for tumors of deep corporeal origin. **However, local recurrences are characteristic of sarcomas** (Dehner and Smith, 1970). Fetsch and colleagues (2004), from the Armed Forces Institute of Pathology, have updated their series of 14 cases of leiomyosarcoma with review of the literature. They concluded that small, less than 2-cm lesions were best managed with local resection whereas deeper-seated tumor often requires partial or total amputation. Deep lesions at the base of the penis have the worst prognosis.

Regional metastases are rare. Unless adenopathy is palpable, node dissections are not recommended (Hutcheson et al, 1969). Distant metastases have also been unusual (Dehner and Smith, 1970). This supports aggressive local treatment in anticipation of cure. Radiation therapy and chemotherapy have not been used extensively enough for comment on their efficacy (Fetsch, 2004)

Kaposi sarcoma, which is usually a cutaneous manifestation of a generalized lymphoreticular disorder, may produce genital lesions but is now most frequently associated with human immunodeficiency virus infection.

Extramammary Paget Disease

Extramammary Paget disease of the penis is rare with fewer than 30 cases reported (Mitsudo et al, 1981; Macedo et al, 1997) up to the late 1990s. However, more recently several larger series have been reported from China and Korea (Yang, 2005; Wang, 2008). It appears grossly as an erythematous, eczematoid, well-demarcated area that cannot be clinically distinguished from erythroplasia of Queyrat, Bowen disease, or carcinoma in situ of the penis. Clinical presentation includes local discomfort, pruritus, and occasionally a serosanguineous discharge involving the penis, scrotum or even the perianal area (see Fig. 34–6D and E). On microscopic examination, identification is clearly made by the presence of large, round or oval, clear-staining hydropic cells with hypochromatic nuclei (i.e., Paget cells). The cells often stain positively for cytokeratin 7 in addition to carcinoembryonic antigen and show gross cystic fluid protein but are S-100 protein negative (O'Connor et al, 2003). The tumor behaves as a slow-growing intraepithelial adenocarcinoma with cells derived from apocrine glands. With time the cells may become invasive with dermal tumor deposits metastasizing to regional lymph nodes via dermal lymphatics (Park et al, 2001). Of note, penoscrotal extramammary Paget disease may be associated with other malignancies of the genitourinary tract, such as prostate, bladder, and renal malignancies (Chanda, 1985; Ojeda et al, 1987; Koh, 1995; Allan et al, 1998), and should be evaluated for their presence.

Two reports from the Far East have added to the case series in the literature: 130 cases of penoscrotal Paget disease from China (Wang, 2008) and 36 from South Korea (Yang et al, 2005). In most cases only the skin and dermis must be resected with a gross margin of up to 3 cm. Positive margins may still occur, and frozen sections are recommended to guide the extent of resection. Local skin or scrotal flaps (Wang et al, 2008) can be used to cover the defects. Patients with a positive surgical margin are at a higher risk for recurrence, and additional resection is advised.

In a minority of cases, the tumor may invade deeper structures requiring more extensive resection and reconstruction, as reported in case series (Hatoko, 2002; Fujisawa, 2008). If inguinal adenopathy is present, radical node dissection is advised (Hagan et al, 1975) but prognosis is poor (Yang et al, 2005).

Adenosquamous Carcinoma

This is a rare tumor characterized by both glandular and squamous histologic elements that are independent of the urethral glands. It presents as a large (5 to 9 cm), firm, and grayish white granular exophytic mass involving the distal shaft or glans. On microscopic examination the glands contain mucin and are positive for carcinoembryonic antigen. In one reported case tumor was metastatic to a single inguinal node. This patient was managed with local excision of the primary tumor and a limited inguinal node dissection and lived 9 years after treatment. Other tumors were managed with local excision and surveillance (Cubilla et al, 1996). In only the seventh reported case (Romero, 2006), a patient with a bulky primary mass and inguinal lymph nodes underwent total

penectomy and delayed inguinal and pelvic lymphadenectomy with a final pathologic stage pT2N3M0 and free of disease at 5-year follow-up.

Lymphoreticular Malignant Neoplasm

Primary lymphoreticular malignant neoplasm rarely occurs on the penis (Dehner and Smith, 1970). **Leukemia may infiltrate the corpora, resulting in priapism** (Pochedly et al, 1974). **A thorough search for systemic disease is necessary when lymphomatous infiltration of the penis is diagnosed.** If the penile lesion is indeed a primary tumor, systemic chemotherapy may be administered. It is the most effective therapy for local disease, for potential occult deposits that may exist elsewhere, and for preservation of form and function (Marks et al, 1988). Local low-dose radiation therapy has also been reported to be successful (Stewart et al, 1985).

Metastases

Metastatic lesions to the penis are unusual with fewer than 300 cases reported in the literature (Belville and Cohen, 1992) until the early 1990s. Their infrequency is somewhat puzzling when one considers the rich blood and lymphatic supply to the organ and its proximity to the bladder, prostate, and rectum areas frequently involved with neoplasm. It is from these three organs that the majority of metastatic penile lesions originate (Abeshouse, 1961). The most likely routes of spread are by direct extension, retrograde venous and lymphatic transport, and arterial embolism. Other sources of penile metastases emanate from the gastrointestinal tract, testis, and kidney (Bellville and Cohen, 1992).

The most frequent sign of penile metastasis is priapism; penile swelling, nodularity, and ulceration have also been reported (McCrea and Tobias, 1958; Abeshouse and Abeshouse, 1961; Weitzner, 1971). Urinary obstruction and hematuria may occur. The most common histologic feature of penile invasion by metastatic lesions is the replacement of one or both corpora cavernosa, which explains the frequent occurrence of priapism. Solitary cutaneous, preputial, and glandular deposits are less common.

The differential diagnosis includes idiopathic priapism; venereal or other infectious ulcerations; tuberculosis; Peyronie plaque; and primary, benign, or malignant tumors.

Penile metastases represent an advanced form of virulent disease and usually appear rather rapidly after recognition and treatment of the primary lesion (Abeshouse and Abeshouse, 1961; Hayes and Young, 1967; Mukamel et al, 1987). On rare occasions a long period may elapse between the treatment of the primary lesion and the appearance of penile metastases (Abeshouse and Abeshouse, 1961) or the penile lesion may occur as the initial and only site of metastasis.

Because of the association of a penile metastatic lesion with advanced disease, survival after its presentation is limited, and the majority of patients die within 1 year (Robey and Schellhammer, 1984; Mukamel et al, 1987; Fischer and Patrick, 1999). Successful treatment may occasionally be possible in the case of solitary nodules or localized distal penile involvement if complete excision by partial amputation succeeds in removing the entire area of malignant infiltration (Spaulding and Whitmore, 1978). The prospect for surgical cure is minimal if proximal corporeal invasion is present. Penectomy is occasionally indicated after failure of other modalities to palliate intractable pain (Mukamel et al, 1987). Pain can also be managed by dorsal nerve section (Hill and Khalid, 1988). Radiation therapy has generally been unsuccessful, and chemotherapy has not been employed in a sufficient number of cases to warrant definitive recommendations.

Key Points: Nonsquamous Malignant Neoplasms

- Basal cell carcinoma represents a highly curable variant with low metastatic potential.
- Sarcomas are prone to local recurrence; regional and distant metastases are rare. Superficial lesions can be treated with less radical procedures.
- Melanoma is an aggressive form of cancer but can be cured if diagnosed and treated with the appropriate surgical procedure at an early stage.
- Extramammary Paget disease disseminates by intraepidermal spread. Wide local excision to achieve negative margins is the therapy of choice.
- Penile metastases most often represent spread from a clinically obvious existing primary tumor. Prognosis is poor, and therapy should be directed toward the primary tumor's histology or local palliation is advised.

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chapter
35

Surgery of Penile and Urethral Carcinoma

David S. Sharp, MD ● Kenneth W. Angermeier, MD

Penile Cancer

Male Urethral Cancer

Female Urethral Cancer

PENILE CANCER

Despite ongoing clinical experience, treatment of squamous cell carcinoma of the penis remains primarily surgical. Early meticulous surgical management with close follow-up generally provides the best opportunity for cure. A thorough understanding of the various operative procedures for treatment of the primary tumor and regional lymph nodes is therefore critical in the successful management of this condition.

Primary Tumor

Penile Biopsy

The majority of penile squamous cell carcinomas initially involve the glans penis, coronal sulcus, or inner preputial skin (Ekstrom and Edsmyr, 1958; Burgers et al, 1992). **When a suspicious lesion is identified, a biopsy is required to provide histologic confirmation of the diagnosis. It is important to include some adjacent normal tissue with the specimen to allow optimal evaluation of the depth of invasion of the cancer.** Biopsy may take the form of a punch biopsy, excisional biopsy of a relatively small tumor of the glans or foreskin, or incisional biopsy of a larger lesion that cannot be completely excised. A dorsal slit may be required to gain adequate exposure of the preputial cavity. If a lesion involves the urethral meatus, urethroscopy is indicated to evaluate the urethra, and directed biopsies are performed if any suspicious areas are noted.

Laser Therapy

Laser therapy has been extensively evaluated as a form of conservative treatment of penile squamous cell carcinoma. It is attractive because it has the potential advantage of eliminating the primary tumor with preservation of surrounding tissues and penile function. The lasers most commonly reported for this purpose are the carbon dioxide (CO_2), neodymium:yttrium-aluminum-garnet (Nd:YAG), and potassium titanyl phosphate (KTP). Circumcision is generally recommended at the time of laser therapy, if it has not already been done.

The CO_2 laser has a wavelength of 10,600 nm. The laser energy is absorbed by intracellular water, resulting in vaporization to a skin depth of 0.01 mm. Blood vessels up to 0.5 mm in size can be coagulated. For these reasons, it has been most often used as monotherapy for treatment of dysplastic lesions and squamous cell carcinoma in situ (Greenbaum et al, 1989; Tietjen and Malek, 1998; van Bezooijen et al, 2001). It remains unclear whether the CO_2 laser represents optimal therapy for carcinoma in situ; however, a local recurrence rate of up to 33% has been reported (van Bezooijen et al, 2001).

Because of its cutting properties, the CO_2 laser has been shown to be technically capable of excising small superficial lesions of the penis (Bandieramonte et al, 1987). In this study, surgical specimens were adequate for pathologic examination in 87% of cases, and three patients underwent a repeated laser procedure for a positive margin. The mean distance between the resected lesion and the incision borders was 0.6 mm. A similar technique was used to completely resect the entire surface of the glans penis in a series of patients with diffuse glanular disease: 3 with carcinoma in situ and 11 with superficially invasive squamous cell carcinoma (Bandieramonte et al, 1988). Healing time varied from 5 to 8 weeks, and cosmetic appearance was good in all cases. Following these procedures, the authors recently reported an overall 10-year tumor recurrence rate of 17.5% for patients with stage Tis and T1 penile carcinoma. Most of the recurrences were readily treated, and the penile amputation rate was 5.5% (Bandieramonte et al, 2008). The laser most commonly reported in the treatment of squamous cell carcinoma has been the Nd:YAG laser (Rothenberger, 1986; Boon, 1988; Malloy et al, 1988; von Eschenbach et al, 1991; Horenblas et al, 1992; Frimberger et al, 2002a; Windahl and Andersson, 2003). It has a depth of penetration of 3 to 6 mm and therefore is considered to potentially be more appropriate for treating small superficial penile lesions. The application of iced saline to the treatment area during laser coagulation may prevent carbonization of the surface and promote deeper penetration of the laser energy when desired. When the Nd:YAG laser is used alone for carcinoma in situ and T1 squamous cell carcinoma, the local recurrence rate has been approximately 20% (Malloy et al, 1988; von Eschenbach et al, 1991). The Nd:YAG laser has also been used in combination with surgical excision, with the hope of improving treatment efficacy. The tumor is excised initially, followed by laser coagulation of the base and margins of the defect (Rothenberger, 1986; Boon, 1988; Horenblas et al, 1992; Windahl and Andersson, 2003). With this technique, the local recurrence has been reported to be 18% to 20%.

The KTP (532-nm wavelength) laser has also been used successfully in the treatment of superficial penile carcinoma (Tietjen and

Malek, 1998). It has an intermediate depth of penetration relative to the CO_2 and Nd:YAG lasers, and better hemostasis than the CO_2 laser.

Most reports of laser therapy for penile cancer have described treatment of the lesion with a margin of 3 to 5 mm, which may underestimate the extent of the lesion in some cases. In an attempt to decrease the recurrence rate, preparation of the genital skin with 5% acetic acid has been proposed along with the use of mapping biopsies and surgical excision during the procedure (Tietjen and Malek, 1998; Frimberger et al, 2002a). The acetic acid is applied for approximately 20 minutes before the procedure, and human papillomavirus–induced areas then appear whitened. In one study, the aceto-white staining was most prominent in the periphery of the grossly visible lesions (Tietjen and Malek, 1998). Laser therapy was then carried out with elimination of all abnormal areas, with a local recurrence rate of 7% to 11%. A more recent technique intended to decrease recurrences has been described by photodynamic diagnosis with 5-aminolevulinic acid and autofluorescence to visually direct frozen-section biopsies for assessment of margin status at the time of Nd:YAG tumor ablation (Frimberger et al, 2002b).

In general, laser therapy seems to be reasonable for patients with Tis and small T1 squamous cell carcinoma of the penis, and for patients with manageable T2 tumors who refuse more aggressive surgical treatment. Disadvantages include difficulty in determining the exact depth of laser coagulation; inability to treat larger lesions; and potentially difficult healing in patients who are obese, immunocompromised, or receiving anticoagulation therapy (Tietjen and Malek, 1998). Postoperative healing generally requires 8 to 12 weeks for the Nd:YAG and KTP lasers, but overall cosmetic results are generally good. Erectile function after combined CO_2 and Nd:YAG laser treatment of penile squamous cell carcinoma was unaltered in 72% of patients in one study (Windahl et al, 2004). As with any form of conservative treatment, careful long-term surveillance is essential because of the remaining tissues of the preputial cavity that are at risk for carcinogenesis (Horenblas and Newling, 1993).

Mohs Micrographic Surgery

Mohs micrographic surgery is a technique allowing removal of penile cancer by excision of tissue in thin layers (Mohs et al, 1985). This was originally described as a fixed tissue technique, but a fresh tissue technique has increasingly been used as a result of treating smaller lesions and its shorter procedural time (Brown et al, 1988; Cottel et al, 1988; Mohs et al, 1992). Color coding of the excised layers with tissue dyes allows accurate orientation of the specimen and the creation of a tissue map. Frozen sections to evaluate the surgical margin are cut horizontally from the undersurface of the tissue specimens rather than vertically, allowing microscopic examination of the entire deep and peripheral margin. Any remaining tumor is marked on the tumor map. This is continued until the lesion is completely excised. Mohs micrographic surgery allows excellent local control rates while maximizing organ preservation. Mohs reported a cure rate of 81% for tumors on the glans or prepuce. For all tumor stages, 5-year cure rates were 100% for lesions smaller than 1 cm, 83% for lesions 1 to 2 cm, 75% for lesions 2 to 3 cm, and 50% for lesions larger than 3 cm (Mohs et al, 1985). With extended follow-up, the local control rate was 94% (Mohs et al, 1992), and this has been duplicated by others (Mikhail, 1976; Brown et al, 1988). In addition to tumor size, local recurrence has been associated with advanced stage and failure of previous definitive therapy.

Mohs micrographic surgery would seem to be best suited for patients with carcinoma in situ or small superficially invasive tumors, with cure rates comparable to partial penectomy. However, these results may be variable and dependent on the technique used and the experience of the surgeon (Cottel et al, 1988; Mohs et al, 1992). It should not be used in patients with higher-stage or large lesions. Complications of Mohs micrographic surgery may include meatal stenosis and glans disfigurement.

Conservative Surgical Excision

Conservative surgical excision is another form of tissue-sparing therapy for low-stage penile cancer. **It may be attractive in some instances when the surgeon is inexperienced regarding lasers or Mohs micrographic surgery, or when these modalities are unavailable. In addition, compared with laser therapy, excision has the advantage of providing tissue for tumor grading and assessment of margins, and it does not require the technical support necessary for Mohs micrographic surgery.** Support for a conservative approach in selected patients has been provided by studies suggesting that the traditional 2-cm surgical margin may not always be necessary for cure. Pathologic analysis of 14 patients undergoing partial or total penectomy for squamous cell carcinoma revealed a mean surgical margin of approximately 14.5 mm; seven patients had a margin of 10 mm or less. No patient in this series had a local recurrence (Hoffman et al, 1999). Microscopic extent of penile carcinoma has also been shown to be dependent on tumor grade; grade 1 and grade 2 tumors demonstrated a maximum histologic extent of 5 mm in an analysis of 64 penectomy specimens (Agrawal et al, 2000). In addition, these authors were unable to identify any tumors with a pattern of discontinuous spread. The simplest form of conservative surgical excision is circumcision. Distal preputial tumors may be effectively treated in this fashion when a surgical margin of 2 cm can be achieved (Skinner et al, 1972; McDougal et al, 1986). If the cancer is more proximal and close to the coronal sulcus; however, recurrence rates may be as high as 50% (Narayana et al, 1982), and therefore excision of additional adjacent tissue is needed to ensure an adequate surgical margin.

Local excision of glanular tumors is more difficult because of the requirement of a surgical margin that may not preserve enough tissue to allow an adequate remaining glans penis. This is most often done in the form of excisional biopsy of a lesion with negative surgical margins. In some cases, the surgical defect is small and can be closed primarily. If the defect is larger and primary closure is not possible, the area can be covered with an outer preputial skin flap (Ubrig et al, 2001) (Fig. 35–1). Alternatively, a full-thickness graft of penile skin or extragenital split-thickness skin graft may be used to reconstruct the area (Pietrzak et al, 2004) (Fig. 35–2). Local recurrence rates after conservative penile surgery have varied. Two early publications reported recurrence in 32% and 40% of patients (Hanash et al, 1970; McDougal et al, 1986). In 1999, Ficarra and colleagues noted local recurrence after conservative penile surgery in three of eight patients with Tis and T1 disease. More recent data have been a bit more favorable, with reported local recurrence rates of 8% to 11% (Banon Perez et al, 2000; Bissada et al, 2003; Pietrzak et al, 2004).

Total glansectomy for penile malignant lesions was initially described in 1996 (Austoni et al, 1996). Since that time, excellent local tumor eradication has been described in a small number of patients with verrucous carcinoma and nonsquamous penile

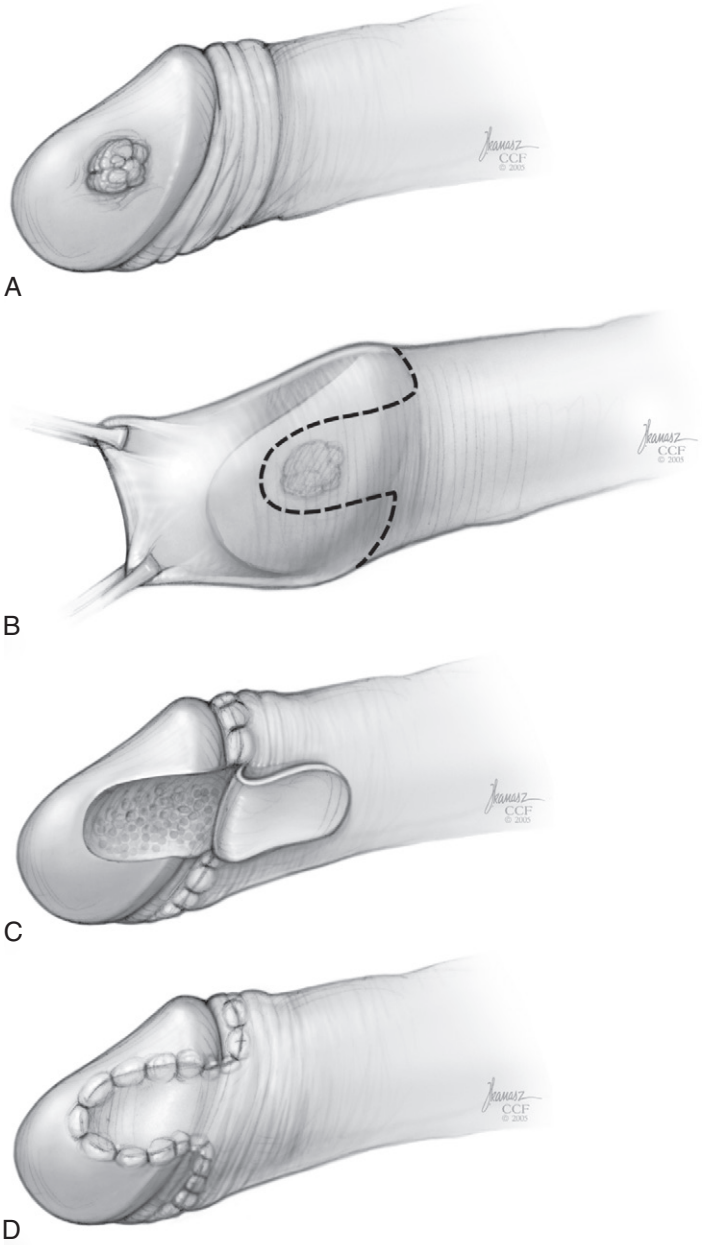


Figure 35–1. Surgical glans defect covered with outer preputial flap as described by Ubrig and colleagues. **A,** Superficial glans tumor. **B,** Outer preputial flap outlined. **C,** Tumor excised and circumcision performed. **D,** Glans defect filled with outer preputial flap. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2003-2010. All Rights Reserved.)

malignant neoplasms. Adequate voiding and erectile function was preserved in the majority of cases (Davis et al, 1999; Hatzichristou et al, 2001). In comparison, standard partial penectomy may be associated with significant impairment of sexual function (Opjordsmoen et al, 1994) and, in our experience, often results in the inability to void in a standing position with long-term follow-up. On the basis of this experience, a subsequent report described six patients with superficial, well to moderately differentiated squamous cell carcinoma limited to the glans penis who underwent glansectomy as primary therapy. With follow-up of 6 to 18 months, there were no local recurrences, and all patients



Figure 35–2. Finely meshed extragenital split-thickness skin graft quilted to glans defect after superficial tumor excision.

maintained adequate sexual function (da Fonseca et al, 2003). The procedure begins with a distal circumferential skin incision to the level of the Buck fascia. The plane under the Buck fascia is developed proximal to the corona of the glans. Laterally, there are usually only a few small vessels within the Buck fascia that may be controlled with electrocautery. Dorsally, the neurovascular structures are divided between surgical ties. Ventrally, a plane is developed under the urethra, but it is not yet divided. Dorsal dissection is commenced in the plane between the glans penis and the tunica albuginea of the corpora cavernosa, and this is continued until the glans is attached by the urethra alone. The urethra is then divided, completing the excision. Frozen-section biopsy specimens are obtained from the tips of the corpora or any other suspicious area. Reconstruction is accomplished by fixing the remaining neurovascular bundle to the tunica albuginea dorsally and the urethra ventrally if needed. The urethra is spatulated, and the penile skin is then approximated in the midline and around the neomeatus. A urethral catheter is left indwelling for 3 to 7 days.

Pietrzak and colleagues (2004) have reported the results of glansectomy or glansectomy and distal corporectomy in 29 men with primarily stage T1 and T2 squamous cell carcinoma of the glans, prepuce, and coronal sulcus. Patients undergoing glansectomy had circumcision and glans excision as described before, followed by mobilization of the urethra to allow formation of a urethrostomy near the tip of the penis. Frozen-section biopsy specimens are taken from the distal tunica albuginea and the urethral margin. The shaft skin is sutured in place approximately 2 cm from the end of the penis, leaving the corporeal tips exposed. A split-thickness skin graft is harvested and quilted to the corpora, and a urethral catheter is placed. The patient is maintained at bed rest for 5 days. If the findings on frozen-section biopsy are abnormal, distal corporectomy is performed until the margins are negative, and the corpora are reconstructed as in partial penectomy. A distal split-thickness skin graft is then used to cover the corpora and to form the neoglans. Early results were encouraging; there were no local recurrences in this initial group of patients at a mean follow-up of 16 months. These data were recently updated in a review of 72 patients treated with glansectomy and split-thickness skin graft reconstruction for stage T1 and T2 tumors limited to the glans penis. Clinical efficacy was very good with two patients requiring early repeat excision for a positive surgical margin and clinical tumor recurrence, and only three late local recurrences (4%) at a mean follow-up of 27 months (Smith et al, 2007).

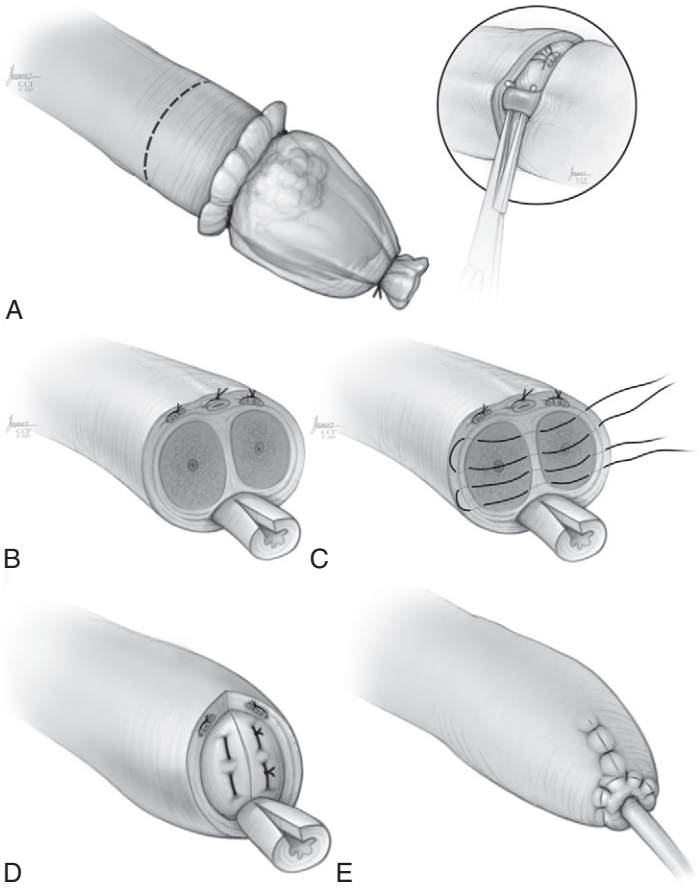


Figure 35–3. Partial penectomy. **A,** Incision with ligation and division of dorsal penile vessels within Buck fascia *(inset)*. **B,** Corpora transected and urethra spatulated. **C** and **D,** Closure of corpora cavernosa. **E,** Final closure with construction of urethrostomy. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2003-2010. All Rights Reserved.)



Figure 35–4. Penile stump after partial penectomy.

Partial Penectomy

Partial penectomy remains the most common surgical procedure for treatment of the primary tumor in patients with invasive squamous cell carcinoma. Successful local control is accomplished in the majority of patients by amputation of the penis at least 2 cm proximal to the tumor. Additional goals of the procedure are to preserve the ability to void in a standing position and possibly to allow sexual function. The lesion is initially excluded from the surgical field by a small towel or surgical glove (Fig. 35–3). Some authors have recommended the use of a tourniquet at the base of the penis, but we have not found this to be necessary. The skin and underlying dartos fascia at the proposed line of amputation are incised circumferentially to the level of the Buck fascia. The Buck fascia is incised laterally, and a plane is dissected between the tunica albuginea and the neurovascular structures dorsally. The dorsal penile vessels are sequentially ligated and divided. The corpora cavernosa are sharply divided, leaving the specimen attached only by the urethra. The urethra is dissected for a distance of 1 to 1.5 cm distal to the proximal corpora and then transected. The corpora are closed transversely with interrupted horizontal mattress sutures of 2-0 polydioxanone. The penile skin is closed in the midline over the corporeal ends with interrupted 3-0 or 4-0 chromic suture material. A ventral urethrostomy is constructed by approximating the urethra to the adjacent penile skin with interrupted 4-0 chromic sutures (Fig. 35–4). An indwelling urethral catheter is left in place for 3 to 5 days. If additional stump length is needed to increase the probability of adequate voiding function, the suspensory ligament of the penis may be divided. The proximal corpora may subsequently be dissected off of the pubic arch for a short distance as well. Scrotal flaps are used to help with skin coverage as needed, and the skin is attached to the pubic arch to preserve the dissected penile length. Division of the penoscrotal fold with a Z-plasty at the penoscrotal junction ventrally may contribute to better definition of the remaining penile stump (Parkash et al, 1986). In selected patients, glans reconstruction may be considered by covering the distal corpora with a split-thickness skin graft (de Souza, 1976) or a two-stage pedicled flap of scrotal skin (Mazza and Cheliz, 2001).

The reported local recurrence rate after partial or total penectomy has ranged from 0% to 8% (Hardner et al, 1972; de Kernion et al, 1973; McDougal et al, 1986; Horenblas et al, 1992). Two studies have suggested that recurrence rates are dependent on tumor stage, reporting a recurrence rate of 0% for patients with T1 tumors and 18% to 21% for T2 lesions (Lindegaard et al, 1996; Brkovic et al, 1997). Although one of the accepted goals of partial penectomy is to allow upright voiding, the percentage of patients able to do this after surgery has not been well documented. A 6% incidence of urethral meatal stenosis has been reported (Horenblas et al, 1992). In our experience, a significant number of men sit to void in the long term because of spraying of the urinary stream. In terms of sexual function, most published reports have indicated that approximately 20% of patients describe adequate sexual function postoperatively (Opjordsmoen et al, 1994; Ficarra et al, 1999; Mazza and Cheliz, 2001).

Total Penectomy

Total penectomy is a bit of a misnomer, because the penis is amputated at or near the level of the suspensory ligament of the penis without removal of the corpora cavernosa more proximally. **It is indicated for penile tumors whose size or location would not allow excision with an adequate surgical margin and preservation of a remnant sufficient for upright voiding.** The primary tumor is draped and an elliptical incision made around the base of the penis (Fig. 35–5). Dissection is commenced in the plane between the tunica albuginea and Buck fascia dorsolaterally, and the dorsal vessels are ligated and divided. The corporeal bodies are sharply transected, and the urethra is divided at the same level. The corpora are then closed with interrupted horizontal mattress sutures of 2-0 polydioxanone.

A perineal urethrostomy is then constructed by one of two techniques. The most commonly described method is to mobilize the urethra from the surrounding bulbospongiosus muscle and dorsally from the corporeal bodies to near the departure of the urethra from the bulb (Fig. 35–6). A small U-shaped incision is made in the perineum. The mobilized urethra is transposed through the perineal opening without angulation. The urethra is spatulated dorsally, and the skin is sutured to the full-thickness urethra with 3-0 polyglactin sutures. Alternatively, a flap inlay urethrostomy may be constructed without mobilization of the urethra. A modified lambda incision, with a short vertical limb, is made in the perineum (Fig. 35–7). The soft tissues overlying the urethra are incised, and the bulbospongiosus muscle is divided in the midline to expose the corpus spongiosum of the bulbous urethra. A 3- to 4-cm ventral urethrotomy incision is made and carried proximally to a point just distal to the bulbomembranous junction (Fig. 35–8). The lateral aspects of the corpus spongiosum in the region of the urethrotomy are fixed to the adjacent corporeal bodies with a few interrupted sutures of 4-0 polydioxanone to splay the opened urethra. The perineal skin flap is sutured to the full-thickness urethra with 3-0 polyglactin starting in the midline and working laterally as far as the flap will easily reach (Fig. 35–9). The urethrostomy is completed by approximation of the scrotal skin to the urethra dorsolaterally, and the resulting short lateral skin incisions are closed in standard fashion (Fig. 35–10).

After completion of the perineal urethrostomy, the primary skin incision is closed transversely, and a small Penrose or suction drain is placed. A urethral catheter is left indwelling for 7 to 10 days.

Radical Penectomy

Although it is not commonly done, radical penectomy with excision of the corporeal bodies in their entirety may on occasion be necessary. We have had experience with this procedure in three patients, one with epithelioid sarcoma of the penis involving multiple sites within the corpora cavernosa (Ormsby et al, 2000), and for palliation in two patients with extensive metastatic disease within the corporeal bodies related to transitional cell carcinoma of the bladder and adenocarcinoma of the rectum.

The patient is placed into lithotomy position with adjustable stirrups so that the level of the legs can be altered during the procedure as needed. The procedure begins with a peripenile incision as for total penectomy, and the corpora are mobilized off of the ischiopubic rami proximally to the point at which the dorsal vein may be seen coursing under the pubis, where it is ligated and divided (Fig. 35–11). A modified lambda incision is then made in the perineum, and the penis is maneuvered through this incision

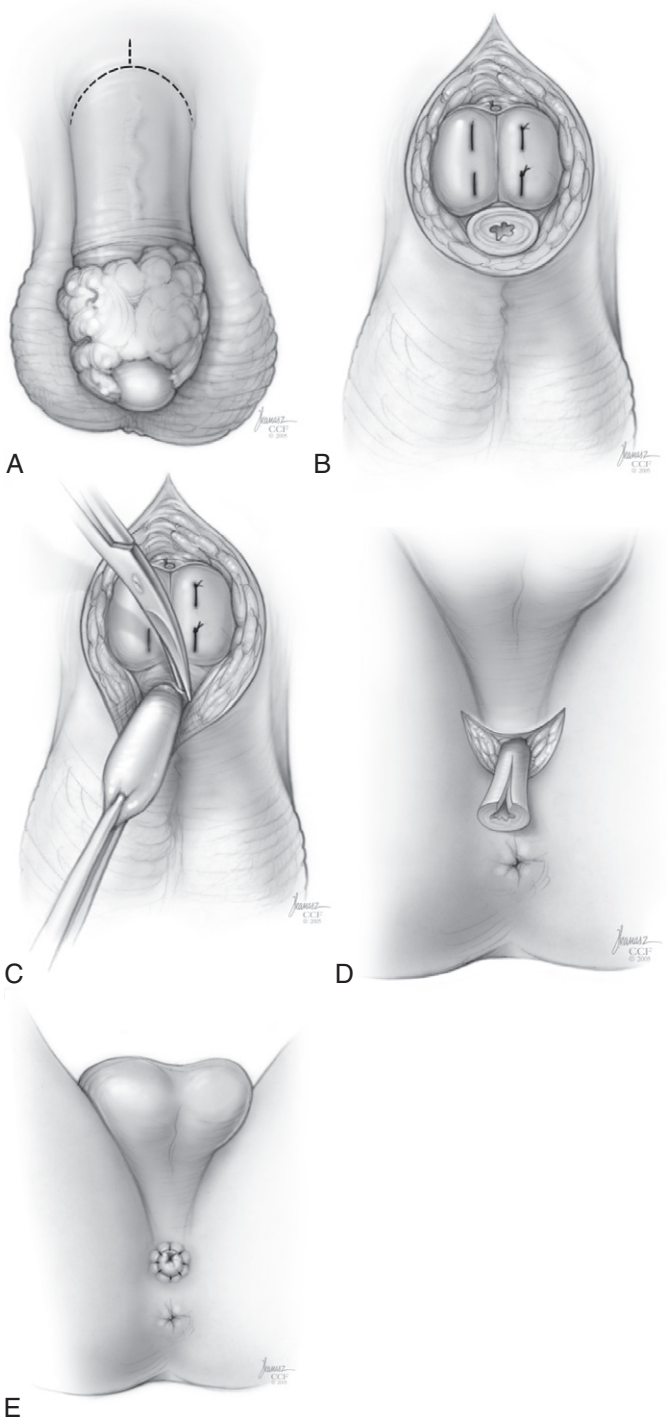


Figure 35–5. Total penectomy. **A,** Incision. **B,** Transection of the corpora near the level of the pubis. **C,** Mobilization of the remaining urethra off of the proximal corporeal bodies. **D,** Transposition of the urethra through a curvilinear perineal incision. **E,** Completion of perineal urethrostomy. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2003-2010. All Rights Reserved.)

(Fig. 35–12). Dissection of the corporeal bodies continues to the tips of the crura, which are completely excised. Suture ligatures are used to control the dorsal penile and cavernosal vasculature near the dorsal aspect of the crura, and in the penile hilum. A plane is developed between the proximal urethra and the corpora,

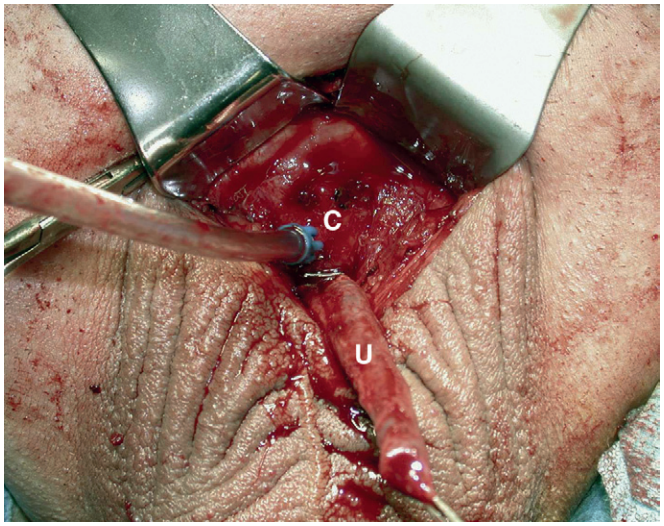


Figure 35–6. Intraoperative photograph demonstrating the bulbous urethra mobilized dorsally off of the corporeal bodies before transposition. C, proximal corporeal bodies; U, urethra.

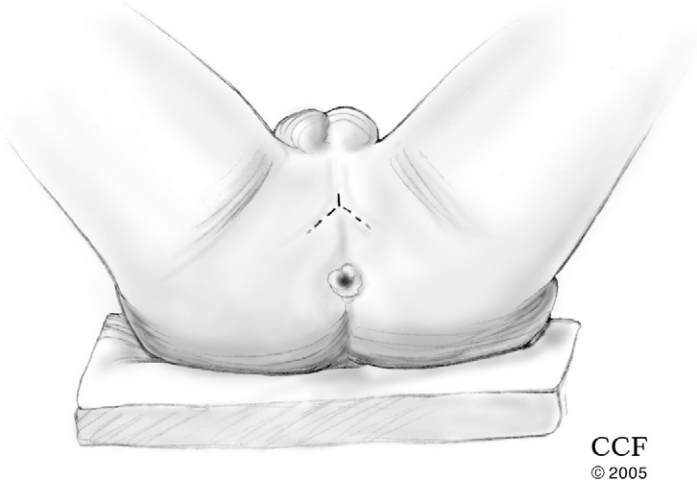


Figure 35–7. Incision for flap perineal urethrostomy. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2003-2010. All Rights Reserved.)

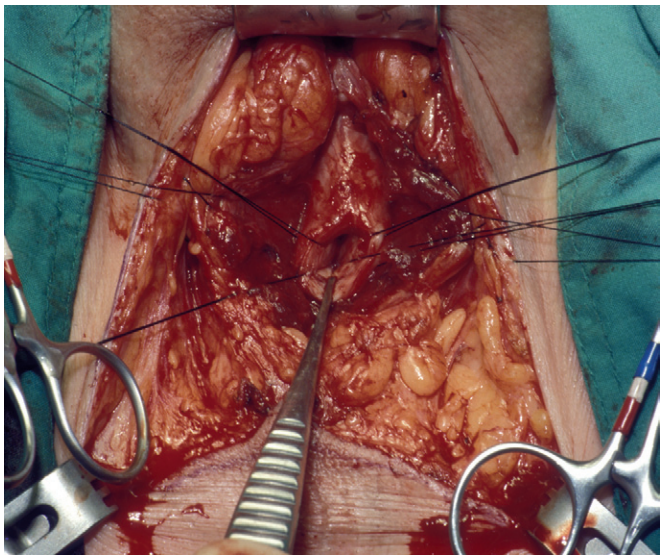


Figure 35–8. Ventral urethrotomy incision in the mid- to proximal bulbous urethra.

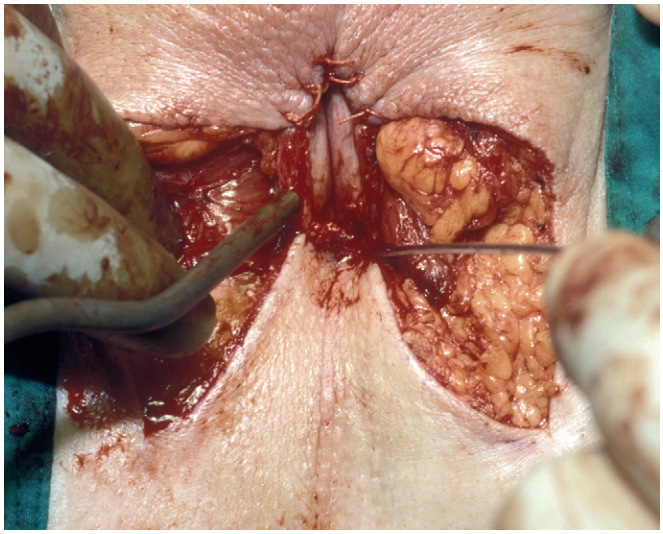


Figure 35–9. Perineal flap being sutured into place.



Figure 35–10. Completed perineal urethrostomy.

and the urethra is then transected, leaving 2 to 3 cm of urethra to form a perineal urethrostomy (Fig. 35–13). A standard flap perineal urethrostomy is then constructed. A small suction drain is placed, and the peripenile incision is closed transversely.

Regional Lymph Nodes

Squamous cell carcinoma of the penis spreads initially to regional lymph nodes before the occurrence of distant metastatic disease. Lymphatic spread occurs in a systematic

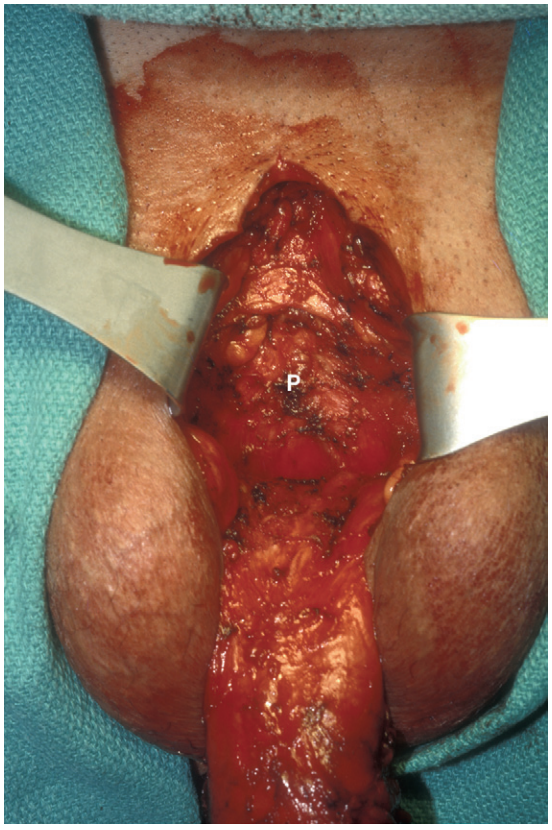


Figure 35–11. Penis retracted downward after mobilization off of the pubis (P).

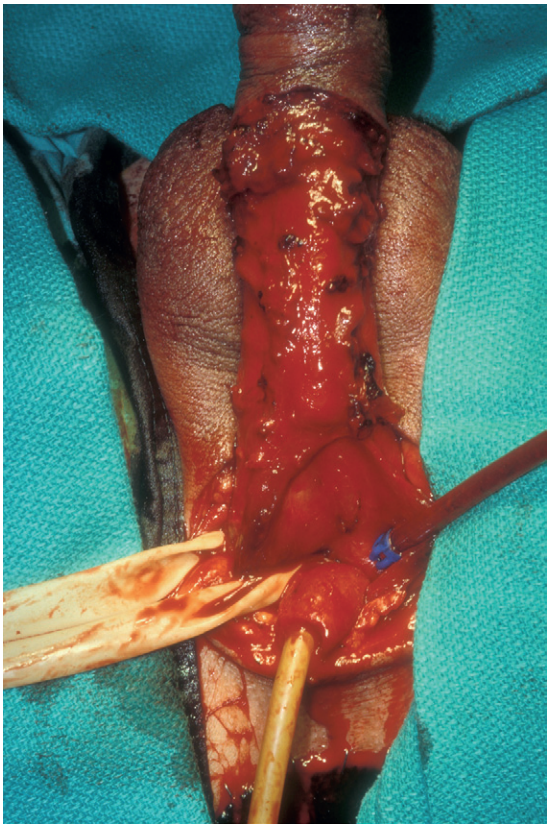


Figure 35–13. Penrose drain around right crus of the corporeal body after dissection of the urethra (with catheter indwelling).



Figure 35–12. Penis transposed through the perineal incision.

fashion along the normal route of penile lymphatic drainage. Lymphatic vessels draining the prepuce and skin of the penile shaft converge dorsally and then divide at the base of the penis to drain into the right and left superficial inguinal nodes. Drainage from the glans penis is toward the frenulum, where large trunks are formed and encircle the corona to unite with those from the other side on the dorsum. They traverse the penis to the base within the Buck fascia, draining through presymphyseal lymphatics into the superficial inguinal nodes and the deep inguinal nodes of the femoral triangle. It is not uncommon for the tumor to metastasize to the contralateral inguinal nodes. Drainage proceeds from the inguinal nodes to the ipsilateral pelvic lymph nodes. Although some anatomic texts have stated that penile lymphatics may drain directly to the external iliac nodes, we are not aware of any patients or reports in the literature in which this has occurred clinically. **Although penile carcinoma metastatic to the inguinal lymph nodes confers a poorer prognosis overall, aggressive lymphadenectomy is associated with improved long-term survival and potential cure in 30% to 60% of patients** (McDougal et al, 1986; Horenblas and van Tinteren, 1994). In addition, immediate resection of clinically occult lymph node metastases is associated with improved survival when compared with delayed resection of involved nodes at the time of clinical detection (Kroon et al, 2005). If the tumor has spread to the pelvic nodes, long-term survival is less than 10%.

Inguinal Anatomy

See Figs. 35–14 and 35–15 on the Expert Consult website.

Sentinel Node Biopsy

The concept of sentinel node biopsy in patients with invasive squamous cell carcinoma of the penis and clinically negative inguinal regions was proposed by Cabanas (1977) after extensive study of lymphangiograms and anatomic dissections. The impetus for a conservative approach to evaluate this group of patients arose from the realization that surgical treatment of inguinal metastases is desirable, and because of the significant morbidity associated with conventional inguinofemoral lymphadenectomy. A 5-cm incision is made parallel to the inguinal crease and centered two fingerbreadths lateral and inferior to the pubic tubercle. By insertion of the finger under the upper flap toward the pubic tubercle, the sentinel lymph node is encountered and excised (Fig. 35–16).

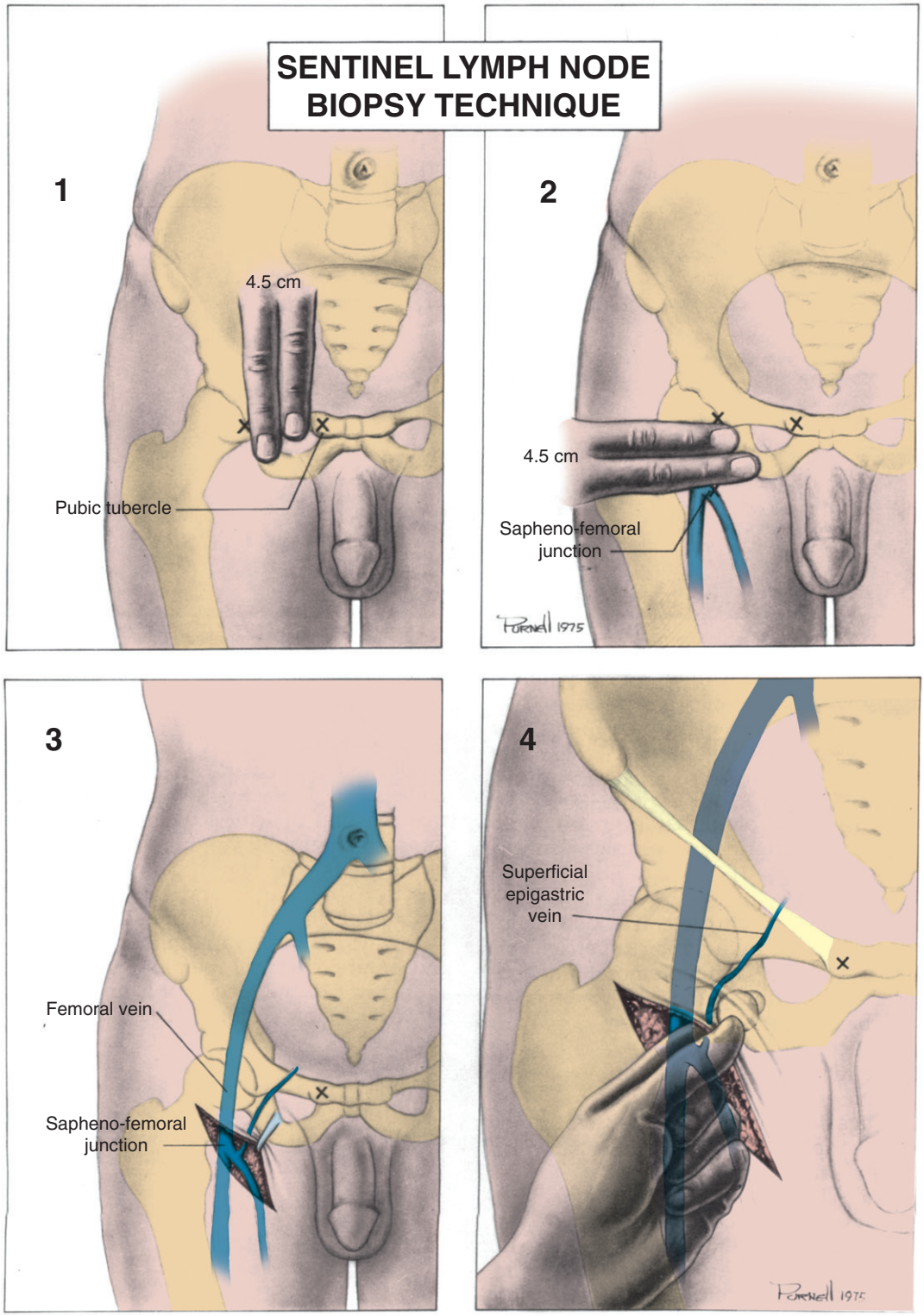


Figure 35–16. Sentinel lymph node biopsy technique as described by Cabanas. (From Cabanas RM. An approach for the treatment of penile carcinoma. Cancer 1977;39:456–66.)

Although Cabanas reported 90% survival in patients with normal findings on sentinel node biopsy, subsequent authors found the results to be less satisfactory, with reports of development of extensive regional metastases after a biopsy with normal findings (Perinetti et al, 1980; Wespes et al, 1986). As an alternative, Pettaway and colleagues (1995) evaluated extended sentinel node biopsy, during which all of the lymph nodes between the inguinal ligament and the superficial external pudendal vein were removed. This approach has also been abandoned, because it resulted in a false-negative rate of 15% to 25% (Ravi, 1993; Pettaway et al, 1995).

Efforts have been made to improve the accuracy of sentinel node biopsy. Dynamic sentinel node biopsy with lymphoscintigraphic imaging has been described on the basis of experience in other tumors (Horenblas et al, 2000). The technique starts the day before surgery with the intradermal injection of technetium Tc 99m nanocolloid at three or four sites around the primary tumor. Dynamic anterior lymphoscintigraphy is subsequently performed at defined intervals. The location of the sentinel node is marked on the skin. Shortly before surgery, 1 mL of patent blue dye is injected around the tumor in a similar fashion. The sentinel node is harvested after dissection of blue lymphatic vessels and intraoperative detection of radioactivity by use of a gamma-ray detection probe. Detection of positive nodes has also been aided by preoperative inguinal ultrasonography with fine-needle aspiration of any abnormal-appearing lymph nodes. A false-negative rate of 18% was initially reported with this approach (Kroon et al, 2004). More recently, the authors have amended their algorithm with the addition of routine inguinal exploration in the absence of radiotracer visualization, intraoperative palpation of the wound for abnormal nodes, and extended pathologic analysis of excised nodes as means of decreasing the number of false-negative biopsy results. These additional maneuvers have decreased the false-negative rate to 5% while maintaining a low risk of complications (Leijte et al, 2007).

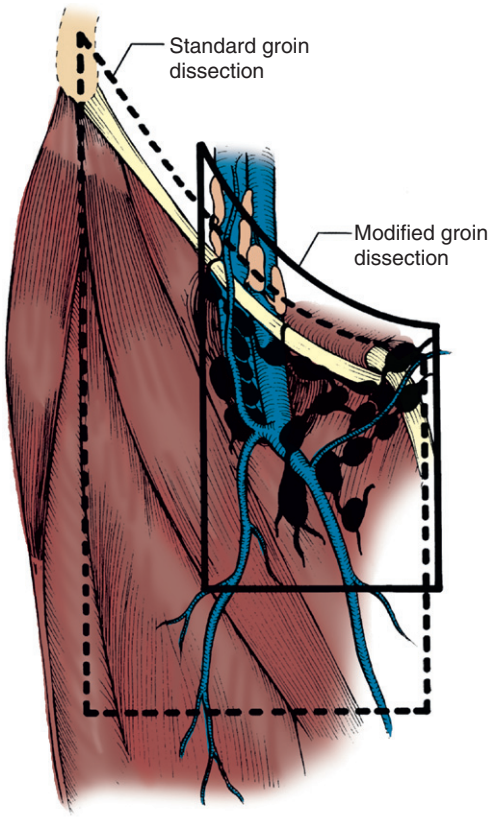


Figure 35–17. Limits of standard and modified groin dissection. (From Colberg JW, Andriole GL, Catalona WJ. Long-term follow-up of men undergoing modified inguinal lymphadenectomy for carcinoma of the penis. Br J Urol 1997;79:54–7.)

Modified Inguinal Lymphadenectomy

In 1988, Catalona proposed a technique of modified inguinofemoral lymphadenectomy designed to provide staging information and therapeutic benefit similar to standard extended lymphadenectomy with less morbidity (Fig. 35–17). **Key aspects of the procedure are (1) shorter skin incision, (2) limitation of the dissection by excluding the area lateral to the femoral artery and caudal to the fossa ovalis, (3) preservation of the saphenous vein, and (4) elimination of the need to transpose the sartorius muscle.** All of the superficial lymph nodes within the described area are removed, as are the deep inguinal nodes that are located primarily medial to the femoral vein to the level of the inguinal ligament.

The procedure begins by placing the patient into a frog-legged position. A 10-cm skin incision is made approximately 1.5 to 2 cm below the inguinal crease. Skin flaps are developed in the plane just beneath the Scarpa fascia for a distance of 8 cm superiorly and 6 cm inferiorly. The superior dissection is carried to the level of the external oblique fascia with exposure of the spermatic cord. A funiculus of lymphofatty tissue, extending from the base of the penis to the superomedial portion of the lymph node packet, is ligated and divided. Dissection commences in a caudad direction with removal of the superficial and deep inguinal nodes, with the boundaries consisting of the adductor longus muscle medially and the femoral artery laterally. The saphenous vein is identified and preserved, although a number of branches draining into it will need to be sacrificed. The nodal packet is dissected caudad to the level of the skin flap dissection (Fig. 35–18), at which point the lymphatics are carefully ligated and the specimen is delivered from the operative field (Fig. 35–19). A closed-suction drain is placed, and the incision is closed in standard fashion.

Morbidity after modified inguinal lymphadenectomy consists primarily of minor complications including seroma (25% to 27%), lymphorrhea (9% to 10%), and wound infection or skin necrosis (0% to 9%). These have been self-limited in the majority of cases (Parra, 1996; Coblentz and Theodorescu, 2002; Jacobellis, 2003; Bouchot et al, 2004; d'Ancona et al, 2004). Temporary lower extremity edema has been reported in approximately 20% of patients, and persistent edema is uncommon. Major complications are rare.

Although it is not universally accepted, the literature suggests that the primary use of modified inguinal lymphadenectomy currently is in patients with a primary tumor that places them at increased risk for inguinal metastasis and clinically negative groins on examination (stage T2 or greater, presence of vascular/lymphatic invasion, or high grade). If nodal metastasis is detected on frozen-section examination of the specimen, the procedure is converted to a standard extended lymphadenectomy. The false-negative rate for this procedure, in terms of detecting inguinal metastatic disease, ranges from 0% to 5.5% in the majority of published reports (Parra, 1996; Colberg et al, 1997; Coblentz and Theodorescu, 2002; Bouchot et al, 2004; d'Ancona et al, 2004).

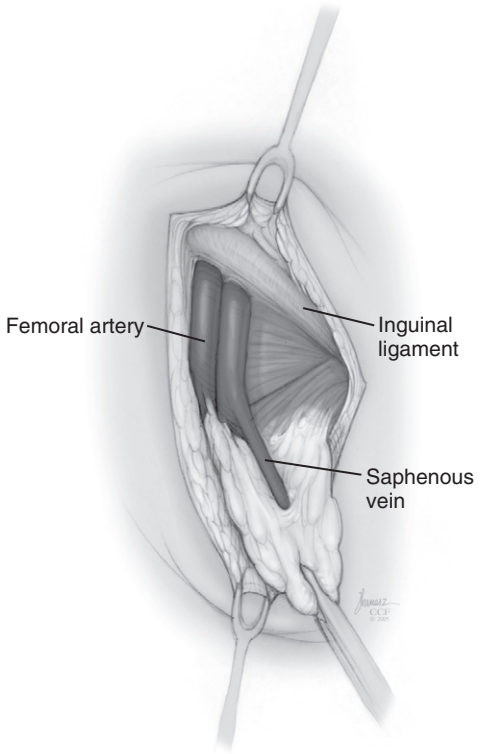


Figure 35–18. Modified inguinal lymphadenectomy. Lymph node packet is medial to the femoral artery and includes superficial and deep inguinal nodes. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2003-2010. All Rights Reserved.)

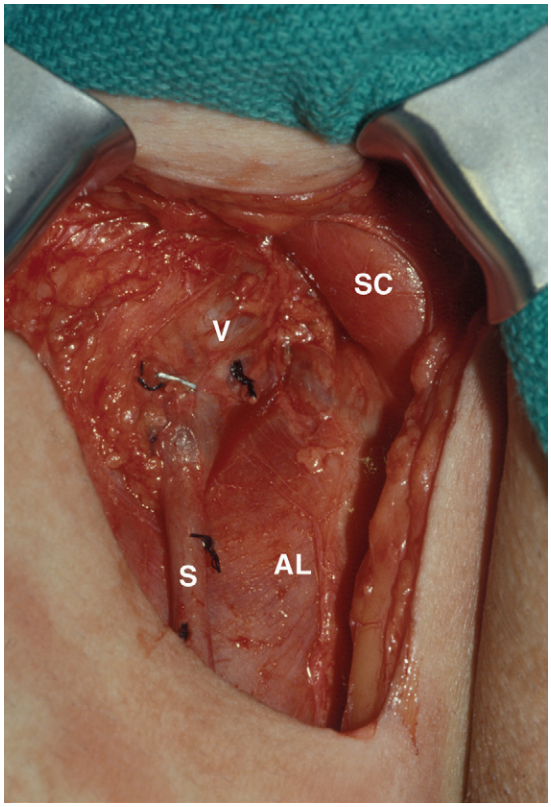


Figure 35–19. Intraoperative photograph of right inguinal region after modified lymphadenectomy. AL, adductor longus; S, saphenous vein; SC, spermatic cord; V, femoral vein.

Radical Ilioinguinal Lymphadenectomy

Radical ilioinguinal lymphadenectomy is indicated in patients with resectable metastatic adenopathy and may be curative when the disease is limited to the inguinal nodes. We have also favored its use as a palliative procedure in patients with documented inguinal metastasis who are fit for surgery. If left unchecked, cancer-bearing inguinal nodes may lead to significant complications, such as infection or abscess with chronic foul-smelling drainage or life-threatening femoral hemorrhage (Fig. 35–20). The procedure is carried out 4 to 6 weeks after surgical treatment of the primary tumor. Antibiotics are administered during this time to reduce the inflammatory component of the regional adenopathy. The patient is positioned with the involved thigh slightly abducted and externally rotated with cushioned support under the flexed knee.

The inguinofemoral dissection is designed to cover an area outlined superiorly by a line drawn from the superior margin of the external ring to the anterior superior iliac spine, laterally by a line drawn from the anterior superior iliac spine extending 20 cm inferiorly, and medially by a line drawn from the pubic tubercle 15 cm down the medial thigh. In most situations, the procedure is carried out through an oblique incision approximately 3 cm below and parallel to the inguinal ligament and extending from the lateral to the medial limit of the dissection (Fig. 35–21). If an area of the skin overlying the cancer-bearing nodes is invaded or adherent and requires excision, an elliptical incision is made around the involved skin and then extended medially and laterally. In this setting, the incision may alternatively be extended superiorly from the lateral border of the ellipse and inferiorly from the medial border to make a single S-shaped incision for the iliac and inguinofemoral dissections (Fig. 35–22).

Superior and inferior skin flaps are developed in the plane just below the Scarpa fascia. The superior flap is elevated cephalad to a point 4 cm above the inguinal ligament, and the inferior flap to the limit of the dissection. The fat and areolar tissues are dissected



Figure 35–20. Pelvic computed tomographic scan of patient with penile carcinoma demonstrating large left inguinal metastasis overlying the femoral vessels.

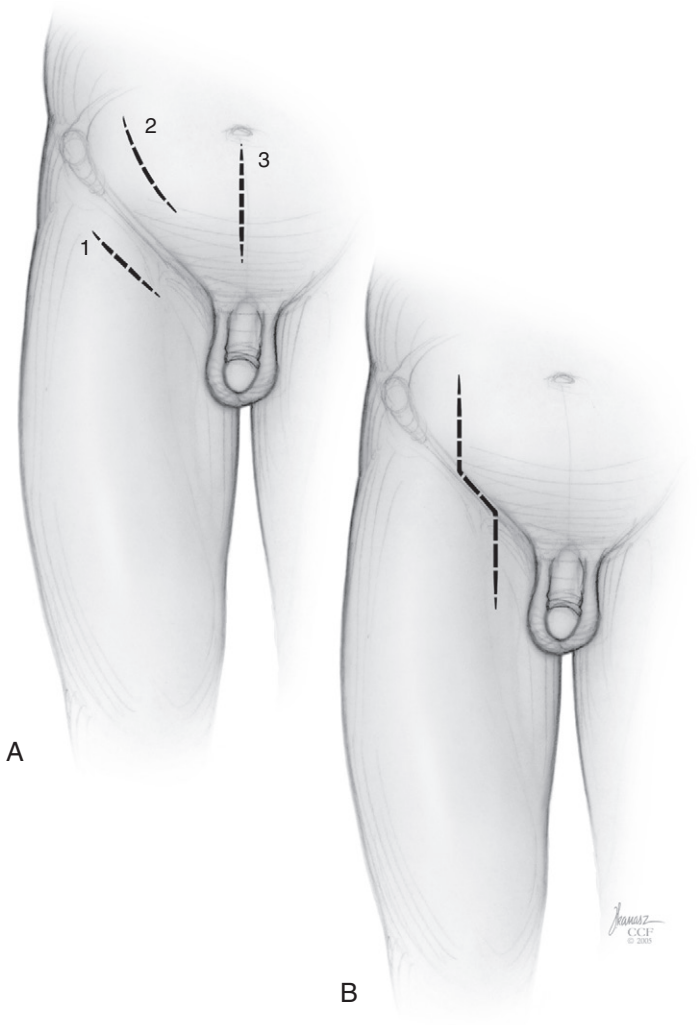


Figure 35–21. Ilioinguinal lymph node dissection. **A,** Incisions for inguinofemoral lymph node dissection (1), unilateral pelvic lymph node dissection (2), and bilateral pelvic lymph node dissection (3). **B,** Single-incision approach for ilioinguinal lymph node dissection. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2003-2010. All Rights Reserved.)

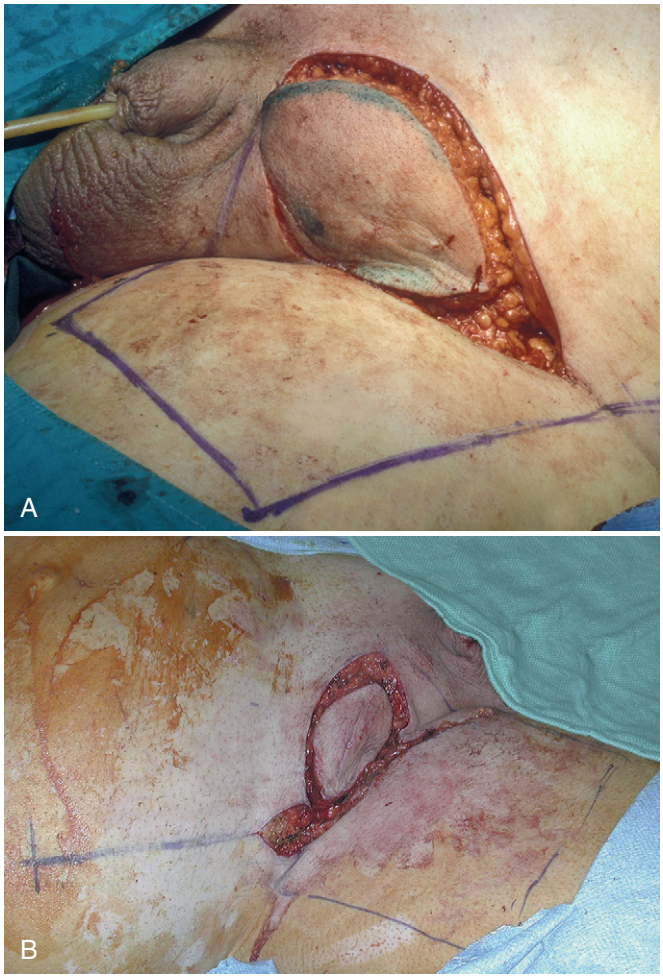


Figure 35–22. **A,** Incision and area of dissection for left inguinofemoral lymph node dissection with excision of adherent skin overlying nodal mass. **B,** Single-incision approach and area of dissection for right ilioinguinal lymph node dissection with excision of overlying skin.

from the external oblique aponeurosis and the spermatic cord to the inferior border of the inguinal ligament, forming the superior boundary of the lymph node packet (Fig. 35–23). The inferior angle of the inguinofemoral exposure is at the apex of the femoral triangle, where the long saphenous vein is identified and divided. In patients with minimal metastatic disease, it may be feasible and beneficial to spare the saphenous vein, and this should be considered (Fig. 35–24). Dissection is deepened through the fascia lata overlying the sartorius muscle laterally and the thinner fascia covering the adductor longus muscle medially. At the apex of the femoral triangle, the femoral artery and vein are identified, and dissection is continued superiorly along the femoral vessels. Superficial cutaneous perforating arteries are ligated as they are encountered on the surface of the femoral artery. The saphenous vein is divided at the saphenofemoral junction, and the dissection is continued superiorly to include the deep inguinal nodes medial and lateral to the femoral vein until continuity with the pelvic dissection is attained at the femoral canal (Fig. 35–25). The anterior aspects of the femoral vessels are dissected, but the femoral vessels are not skeletonized, and the lateral surface of the femoral artery is not exposed. This avoids injury to the femoral nerve and the profunda femoris artery, and the femoral nerve is usually not visible as it runs beneath the iliacus fascia.

After the femoral triangle is dissected (Fig. 35–26), the sartorius muscle is mobilized from its origin at the anterior superior iliac spine and either transposed or rolled 180 degrees medially to cover the femoral vessels. The muscle is sutured to the inguinal ligament superiorly, and its margins are sutured to the muscles of the thigh immediately adjacent to the femoral vessels (Fig. 35–27). The femoral canal is closed, if necessary, by suturing the shelving edge of the Poupart ligament to the Cooper ligament, being careful not to compromise the lumen of the external iliac vein or to injure the inferior epigastric vessels in the process. Primary closure of the inguinofemoral dissection is usually possible with minimal or no further mobilization of the excision margins. When circumstances demand a large area of inguinal soft tissue sacrifice, primary closure may be obtained by scrotal skin rotation flaps (Skinner, 1974), an abdominal wall advancement flap (Tabatabaei and McDougal, 2003), or a myocutaneous flap based on the rectus abdominis or tensor fascia lata (Airhart et al, 1982) for more extensive defects.

Laparoscopic inguinal lymphadenectomy has recently been shown to be technically feasible and may decrease postoperative morbidity (Sotelo et al, 2007). In one study, patients underwent

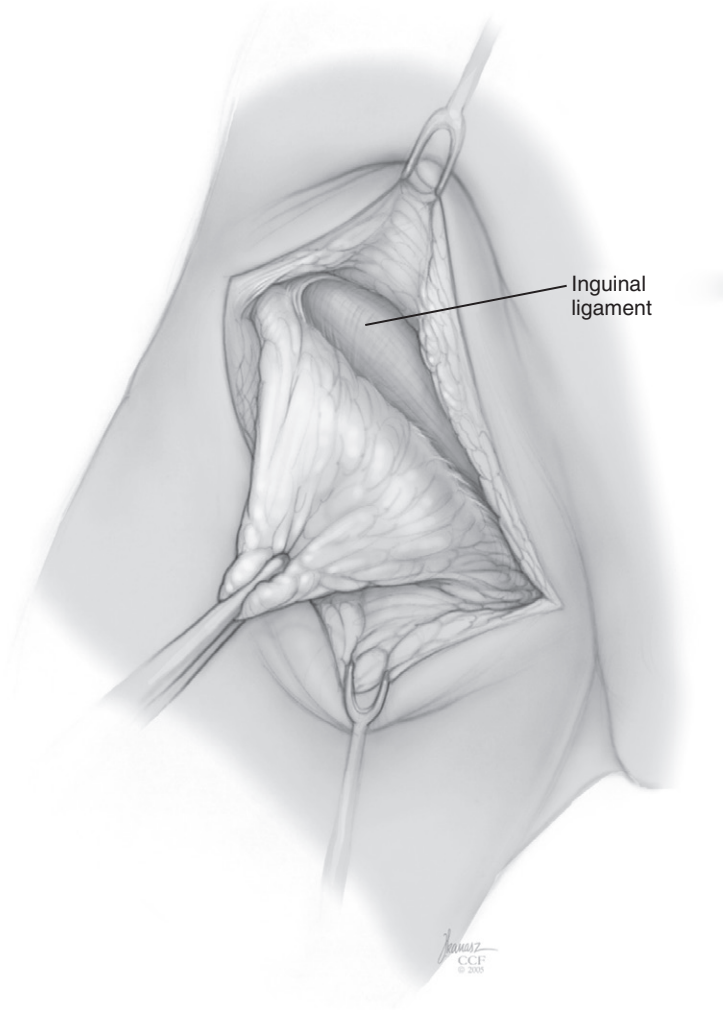


Figure 35–23. Initial dissection for radical inguinofemoral lymph node dissection with exposure of superior border defined by the external oblique fascia. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2003-2010. All Rights Reserved.)

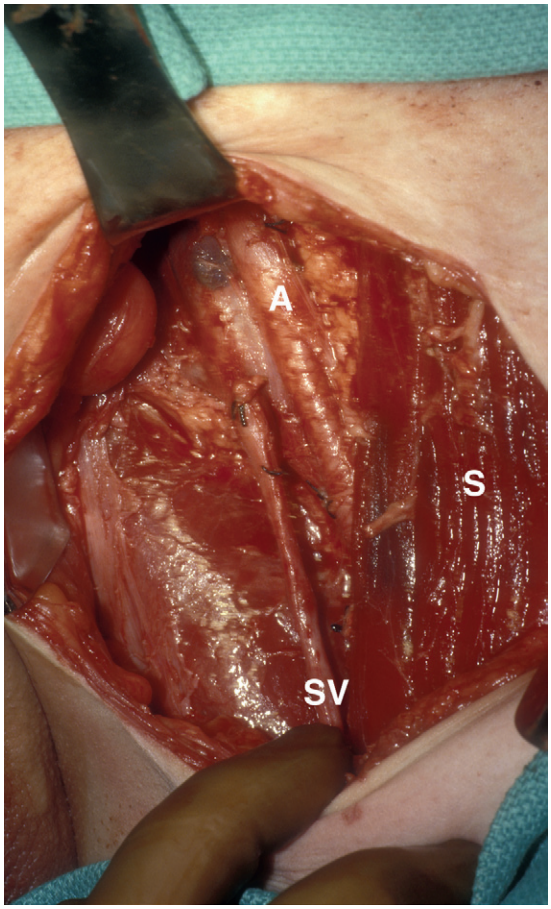


Figure 35–24. Intraoperative photograph after saphenous-sparing, radical, left inguinofemoral lymph node dissection. A, femoral artery; S, sartorius muscle; SV, saphenous vein.

open radical inguinal lymphadenectomy on one side and video endoscopic lymphadenectomy contralaterally. A similar number of lymph nodes were excised on both sides, and there were no recurrences or disease progression at a mean follow-up of 18 months (Tobias-Machado et al, 2007).

Bilateral pelvic lymphadenectomy is best accomplished by an extraperitoneal approach through a lower midline incision. If a unilateral dissection is indicated, we favor a modified Gibson incision or an S-shaped ilioinguinal incision (see Figs. 35–21 and 35–22). **Pelvic lymphadenectomy should include the distal common iliac, external iliac, and obturator nodes. No further benefit is gained from proximal iliac or para-aortic dissection.**

Closed-suction drains are placed under the subcutaneous tissue and brought out inferiorly. During closure, the skin flaps are sutured to the surface of the exposed musculature to decrease dead space. The skin is closed with absorbable subcutaneous sutures and staples. The patient is maintained at bed rest for 2 or 3 days, and pneumatic compression stockings are used. The drains are removed after 5 to 7 days, when drainage is less than 30 to 40 mL/day. Compression stockings are recommended postoperatively. We maintain the patient on a suppressive dose of a cephalosporin for

Key Points: Penile Cancer

- Early meticulous surgical management with close follow-up generally provides the best opportunity for cure of penile squamous cell carcinoma.
- In performing a penile biopsy, it is important to include some adjacent normal tissue with the specimen to allow optimal evaluation of the depth of invasion of the cancer.
- Conservative surgical approaches may be reasonable for patients with stage Tis and small T1 squamous cell carcinoma of the penis, and for patients with manageable T2 tumors who refuse more aggressive surgical treatment.
- Partial penectomy with a 2-cm surgical margin remains the most common surgical procedure for treatment of the primary tumor in patients with invasive squamous cell carcinoma and affords excellent local control in most instances.
- In patients at risk for the development of inguinal metastatic disease and with no palpable adenopathy, modified inguinal lymphadenectomy provides excellent assessment of the regional nodes and may be converted to a full lymphadenectomy if metastatic disease is detected.
- Penile cancer metastases to the pelvic lymph nodes do not occur in the setting of negative ipsilateral inguinal nodes.

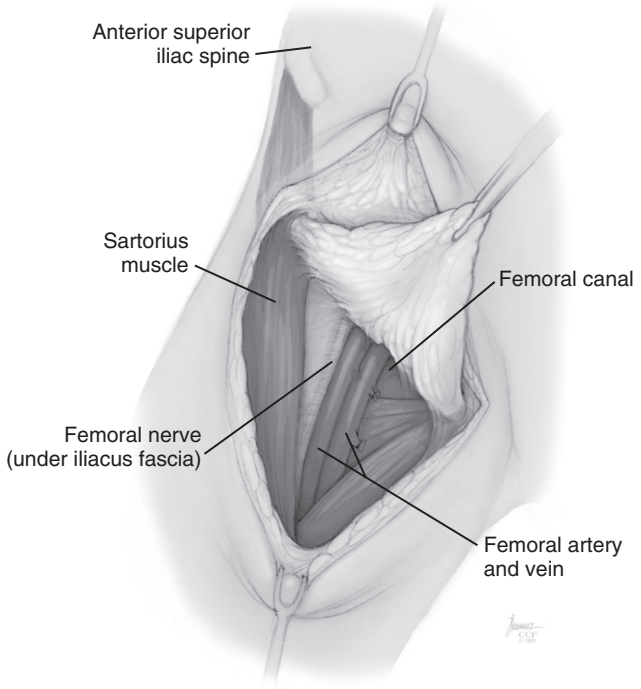


Figure 35–25. Inferior dissection during radical inguinofemoral lymph node dissection with removal of lymph node packet from the inferior border of the femoral triangle. After further lateral and medial dissection, the packet will remain in continuity with the pelvic dissection in the area of the femoral canal. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2003-2010. All Rights Reserved.)

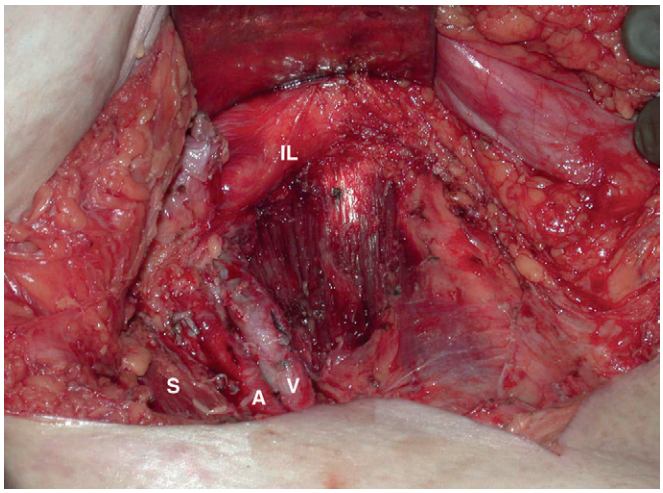


Figure 35–26. Intraoperative photograph after right radical inguinofemoral lymph node dissection in an obese patient. A, femoral artery; IL, inguinal ligament; S, sartorius muscle; V, femoral vein.

2 months to decrease the incidence of erythema and cellulitis, and this seems to improve overall wound healing.

In the past, complications related to radical ilioinguinal lymphadenectomy have been significant. In contemporary series, early minor complications have been reported in 40% to 54% of dissections (Bevan-Thomas et al, 2002; Bouchot et al, 2004; Nelson et al, 2004). These consist primarily of lymphocele, wound infection or necrosis, and lymphedema. Major complications, such as

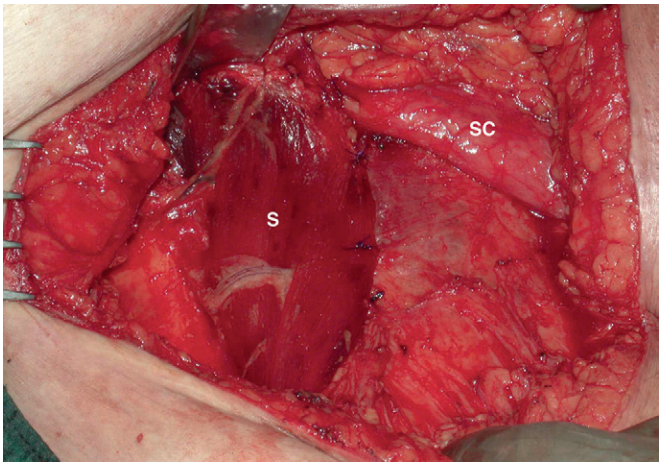


Figure 35–27. Sartorius muscle after detachment from the anterior superior iliac spine and 180-degree rotation medially, with suture fixation to the fascia of the inguinal ligament and the adductor longus. S, sartorius muscle; SC, spermatic cord.

debilitating lymphedema, flap necrosis, and lymphocele requiring intervention, occur in 5% to 21% of cases (Bevan-Thomas et al, 2002; Nelson et al, 2004). Efforts to minimize lower extremity lymphedema include the use of elastic stockings and sequential compression devices. The trend seems to be toward earlier ambulation, with the avoidance of prophylactic low-dose heparin therapy because of the possibility of an increased risk of lymphocele formation (Tomic et al, 1994).

MALE URETHRAL CANCER

General Considerations

Carcinoma of the male urethra is rare and usually presents in the fifth decade of life (Dalbagni et al, 1999). **Etiologic factors include chronic inflammation due to a history of frequent sexually transmitted diseases, urethritis, and urethral stricture, and there is likely to be a causal role for human papillomavirus 16 in squamous cell carcinoma of the urethra** (Weiner et al, 1992; Cupp et al, 1996). The onset of malignant change in a patient with chronic urethral stricture disease may be insidious, and a high index of clinical suspicion is required to diagnose these tumors expediently. More than 50% of patients have a history of urethral stricture disease, almost 25% have a history of sexually transmitted disease, and 96% are symptomatic at presentation (Dalbagni et al, 1999). The most common presenting symptoms are urethral bleeding, a palpable urethral mass, and obstructive voiding symptoms.

Pathology

Tumors of the male urethra are categorized according to location and histologic features of the cells lining the urethra (Mostofi et al, 1992) (Fig. 35–28). The bulbomembranous urethra is involved most frequently, accounting for 60% of tumors, followed by the penile urethra (30%) and the prostatic urethra (10%). Overall, 80% of male urethral cancers are squamous cell carcinoma; 15% are transitional cell carcinoma; and 5% are adenocarcinoma, melanoma, lymphoma, paraganglioma, sarcoma, or an undifferentiated tumor. The histologic subtype of urethral cancer also varies by anatomic location. Carcinomas of the prostatic urethra are of transitional cell origin in 90% and of squamous cell origin in 10%;

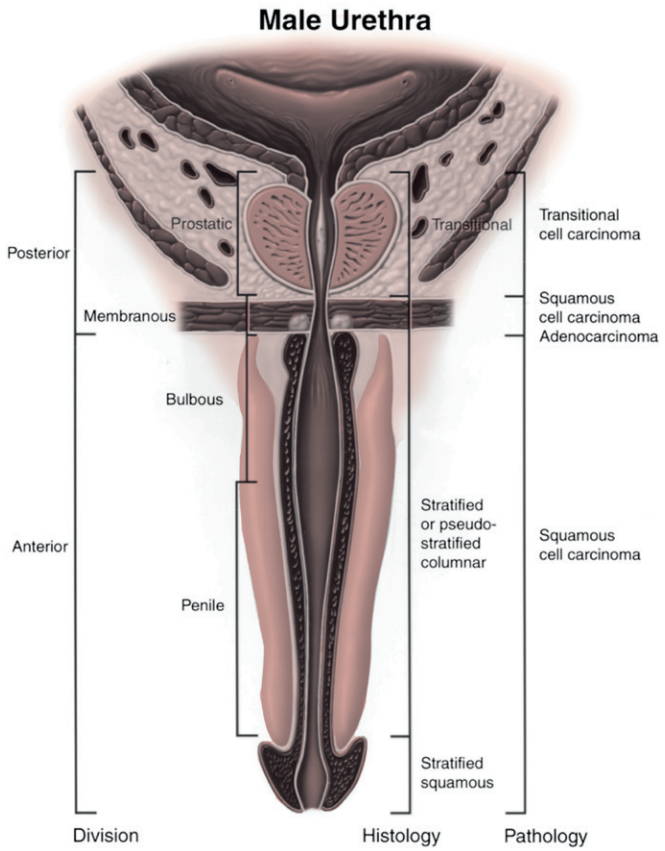


Figure 35–28. Anatomic regions of the male urethra and corresponding histology and histopathology.

carcinomas of the penile urethra are of squamous cell origin in 90% and of transitional cell origin in 10%; and carcinomas of the bulbomembranous urethra are of squamous cell origin in 80%, of transitional cell origin in 10%, and adenocarcinoma or undifferentiated in 10% (Grigsby and Herr, 2000).

Male urethral carcinoma can spread by direct extension to adjacent structures, usually involving the vascular spaces of the corpus spongiosum and the periurethral tissues, or it can metastasize through lymphatic embolization to regional lymph nodes. The lymphatics from the anterior urethra drain into the superficial and deep inguinal lymph nodes and occasionally into the external iliac lymph nodes. Tumors of the posterior urethra most commonly spread to the pelvic lymph nodes. Palpable inguinal lymph nodes occur in about 20% of cases and almost always represent metastatic disease, in contrast to penile cancer, in which a large percentage of palpable nodes may be inflammatory. Hematogenous dissemination is uncommon except in advanced disease.

Evaluation and Staging

The tumor, nodes, metastasis (TNM) staging classification is based on depth of invasion of the primary tumor and presence or absence of regional lymph node involvement and distant metastasis (Table 35–1). Examination under anesthesia, consisting of cystoscopy and bimanual palpation of the external genitalia, urethra, rectum, and perineum, aids in evaluating the extent of local involvement by tumor. Transurethral or needle biopsy of the lesion is also performed. Cytologic studies of voided urine do not seem to be a reliable method for diagnosis of primary urethral carcinoma. In one study, sensitivity was greatest in men with transitional cell carcinoma (80%) and in those with tumors involving the pendulous urethra (73%) (Touijer and Dalbagni, 2004). If rectal involvement is suspected on bimanual examination or by the patient's symptoms, an evaluation of the lower colon by barium enema study and flexible sigmoidoscopy is recommended to assist with surgical planning. Local soft tissue involvement, lymph node involvement, and bone extension are best evaluated by a computed tomographic scan of the abdomen and pelvis or by magnetic resonance imaging. Magnetic resonance imaging may be helpful for detecting invasion of the corpora cavernosa and is a useful staging modality (Vapnek et al, 1992).

Table 35–1.

Urethral Cancer TNM Staging System

Primary Tumor (T) (Male and Female)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary, polypoid, or verrucous carcinoma
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades any of the following: corpus spongiosum, prostate, periurethral muscle
T3	Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck
T4	Tumor invades other adjacent organs
Transitional Cell Carcinoma of the Prostate	
Tis-pu	Carcinoma in situ, involvement of the prostatic urethra
Tis-pd	Carcinoma in situ, involvement of the prostatic ducts
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades any of the following: prostatic stroma, corpus spongiosum, periurethral muscle
T3	Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
T4	Tumor invades other adjacent organs (invasion of the bladder)
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node, 2 cm or less in greatest dimension
N2	Metastasis in a single lymph node, more than 2 cm but less than 5 cm in greatest dimension; or in multiple nodes, none greater than 5 cm
N3	Metastasis in a lymph node greater than 5 cm in greatest dimension
Distant metastasis (M)	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Treatment

As in penile carcinoma, the primary form of treatment for men with urethral carcinoma is surgical excision. **In general, anterior urethral carcinoma is more amenable to surgical control, and the prognosis is better than that of posterior urethral carcinoma, which is often associated with extensive local invasion and distant metastasis** (Zeidman et al, 1992). A large series reported overall survival rates of 83% for low-stage tumors, 36% for high-stage tumors, 69% for anterior tumors, and 26% for those in the posterior urethra (Dalbagni et al, 1999).

Carcinoma of the Penile Urethra

Transurethral resection, local excision, or distal urethrectomy and perineal urethrostomy may be acceptable treatment in selected patients with superficial, papillary, or low-grade tumors. Long-term disease-free survival has been reported in this setting (Mandler and Pool, 1966; Konnak, 1980; Gheiler et al, 1998; Hakenberg et al, 2001). Squamous cell carcinoma in situ of the perimeatal glans may extend into the distal urethra (Fig. 35–29) and has been successfully treated with partial glansectomy and distal urethrectomy with simultaneous urethral reconstruction (Nash et al, 1996) or penile urethrostomy (Fig. 35–30). **Partial penectomy with a 2-cm negative margin is the treatment of choice for tumors infiltrating the corpus spongiosum and localized to the distal half of the penis. Excellent local control after this procedure has been documented** (Kaplan et al, 1967; Ray et al, 1977; Anderson and McAninch, 1984; Hopkins et al, 1984; Dinney et al, 1994; Gheiler et al, 1998). If invasive disease extends to or involves the proximal penile urethra, total penectomy is required to obtain an adequate margin of excision (Fig. 35–31). In the largest series to date, a local recurrence rate of 13% was reported after this procedure (Kaplan et al, 1967).

Accurate staging is important to avoid underestimation of the proximal extent of the tumor. Review of previous data would suggest that radical penectomy is an insufficient operation for bulbous urethral tumors (Zeidman et al, 1992). There have been limited reports of urethrectomy alone with perineal urethrostomy for infiltrating tumors confined to the corpus spongiosum (Hakenberg et al, 2001). The benefits of this more conservative approach need to be weighed against the probability of local relapse or dissemination of disease. **Ilioinguinal lymphadenectomy is indicated in the presence of palpable inguinal lymph nodes without evidence of metastatic disease. Benefit from prophylactic inguinal lymph node dissection has not been demonstrated in urethral cancer.**

Carcinoma of the Bulbomembranous Urethra

Early lesions of the bulbomembranous urethra have been treated successfully by transurethral resection or by segmental excision of the involved urethral segment with an end-to-end anastomosis. Unfortunately, cases appropriate for limited resection are rare. **Poor survival figures have been recorded for all forms of treatment, but it appears that radical excision offers the best opportunity for long-term disease control and the lowest incidence of local recurrence.** Radical cystoprostatectomy, pelvic lymphadenectomy, and total penectomy are usually required. Extending the operation to include in-continuity resection of the pubic rami and the adjacent urogenital diaphragm may improve the margin of resection and local control (Mackenzie and Whitmore, 1968; Shuttleworth and Lloyd-Davies, 1969; Bracken, 1982; Klein et al, 1983; Dinney et al, 1994).

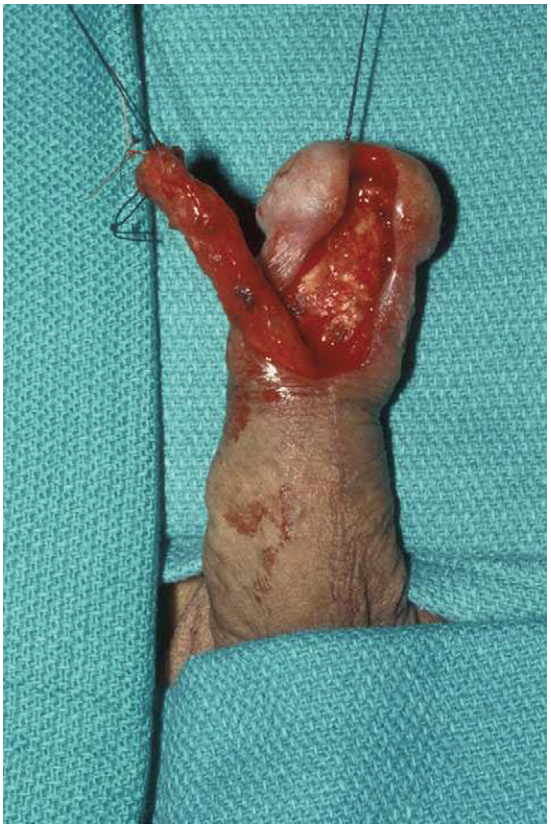


Figure 35–30. Partial glansectomy and distal urethrectomy (same patient as in Figure 35–29). After negative margins were ensured, penile urethrostomy completed the procedure.



Figure 35–29. Squamous cell carcinoma in situ (erythroplasia of Queyrat) of the glans penis surrounding the urethral meatus. The patient also had significant extension of disease into the distal urethra.



Figure 35–31. Large penile mass in a patient with transitional cell carcinoma of the penile urethra.

With the patient in low lithotomy position to allow perineal access, the standard abdominal mobilization of the bladder is completed, except for preservation of the endopelvic fascia and the anterior pubic attachments. A modified lambda or inverted U-shaped perineal incision is performed, based just medial to the ischial tuberosities, with the apex in the midperineum. The ischiorectal fossae are developed as in perineal prostatectomy, and a tunnel is bluntly dissected just anterior to the rectum, extending from one fossa to the other. The inferior skin flap is mobilized by sharply dividing the intervening subcutaneous tissue and rectourethral muscle. The superior flap is mobilized by sharply incising the subcutaneous tissue to the superficial Colles fascia and then continuing bilaterally to the adductor musculature at the inferior pubic rami. Circumferential incision of the skin and dartos fascia at the penoscrotal junction is performed, and the corporeal bodies are mobilized for a short distance proximally from the superior aspect of the symphysis pubis to allow subsequent inferior pubectomy. Care must be taken not to carry this dissection too far proximally to avoid breaching the anterior aspect of a locally advanced tumor. The penis is passed downward through the perineal incision. Wider exposure may be gained by dividing the scrotum in the midline if necessary. The scrotum can usually be preserved; however, bulky tumors may necessitate sacrifice of portions of the scrotum or perineal skin. In this setting, the testicles may be preserved in thigh pouches.

To complete the pubic arch resection, the adductor musculature is sharply divided bilaterally from the length of the inferior pubic ramus along the medial margin of the obturator foramen. A Gigli saw is passed along the inferior ramus just posterior to the origins of the transverse perineal musculature. An inferiorly beveled transection is made bilaterally to simplify perineal delivery of the specimen. Alternatively, an osteotome may be used for this purpose. The entire symphysis may be resected for bulky urethral lesions involving the presymphyseal tissues. This is accomplished by division of the superior rami at their junction with the symphysis. For most lesions, however, the bulk of the symphysis can be preserved with resection of the subsymphyseal arch. This procedure is preferred, when possible, to preserve stability of the pelvic girdle, and it results in a much smaller pelvic floor defect. A Gigli saw passed through the obturator foramina, or an osteotome is used to incise the symphysis transversely, joining the foramina (Fig. 35–32). The specimen is delivered en bloc (Fig. 35–33). After hemostasis is secure, the omentum is mobilized to cover the bowel. Large pelvic floor defects, such as occurring after total pubectomy, may be managed with a rectus abdominis muscle flap placed as a pelvic sling. Myocutaneous flaps can be fashioned to close large full-thickness perineal defects (Larson and Bracken, 1982).

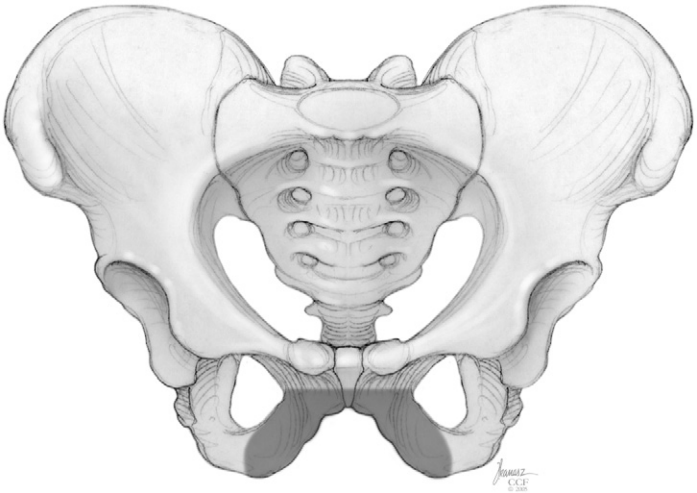


Figure 35–32. Shaded area outlines the portions of the ischiopubic rami excised at the time of inferior pubectomy during radical excision of bulbomembranous urethral cancer. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2003-2010. All Rights Reserved.)

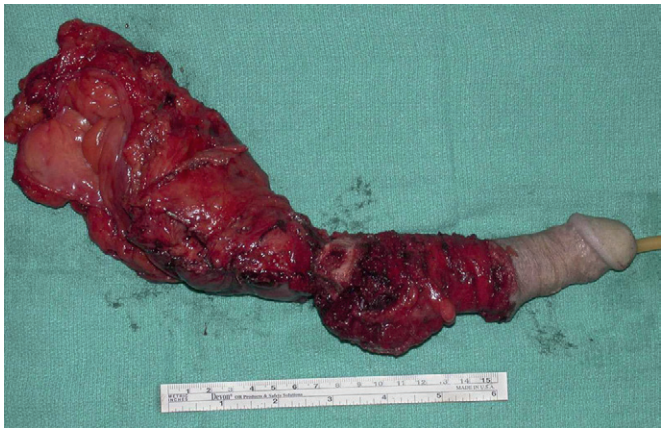


Figure 35–33. Surgical specimen after radical cystoprostatectomy, urethrectomy, penectomy, and inferior pubectomy for a large bulbomembranous squamous cell carcinoma.

Radiation Therapy and Chemotherapy

Although some instances of tumor control by irradiation have been reported, in general, radiation therapy has been reserved for patients with early-stage lesions of the anterior urethra who refuse surgery. The most commonly used technique consists of parallel opposed fields with the penis suspended vertically by a urethral catheter (Heysek et al, 1985). Radiation therapy has the advantage of preserving the penis, but it may result in skin ulceration or necrosis, urethral stricture, or chronic edema, and it does not prevent new tumor occurrence. The long-term results of radiotherapy are difficult to evaluate because few reports are available of patients treated with this modality (Raghavaiah, 1978; Forman and Lichter, 1992).

A small number of studies have reported the results of neoadjuvant and adjuvant combination chemotherapy in patients with advanced-stage or metastatic disease. A regimen including methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) has been noted to have activity against transitional cell carcinoma but was ineffective against other tumor histologic types (Scher et al, 1988). Dinney and colleagues (1994) reported long-term survival in four of eight patients who presented with metastatic urethral carcinoma and were treated with cisplatin-based chemotherapy and surgical excision. On the basis of this experience, their favored regimen consisted of cisplatin, bleomycin, and methotrexate for squamous cell carcinoma and M-VAC for transitional cell carcinoma.

The combination of chemotherapy and radiation therapy has shown some success in a small number of patients with localized and metastatic urethral cancer (Licht et al, 1995; Oberfield et al, 1996). More commonly, these forms of treatment are combined with surgery in a multimodal approach in patients with advanced stage or metastatic disease (Johnson et al, 1989; Gheiler et al, 1998; Grigsby and Herr, 2000).

Management of the Urethra after Cystectomy

General Considerations

Contemporary series have demonstrated the incidence of urethral cancer recurrence that follows cystoprostatectomy to range from 2.1% to 11.1% after cutaneous diversion (Freeman et al, 1996; Hassan et al, 2004; Nieder et al, 2004) and 0.5% to 4% after construction of an orthotopic neobladder (Freeman et al, 1996; Hassan et al, 2004; Nieder et al, 2004; Varol et al, 2004). Early studies indicated that transitional cell carcinoma involving the prostatic urethra, particularly with stromal invasion, significantly increased the probability of postoperative urethral recurrence (Hardeman and Soloway, 1990; Freeman et al, 1996). **However, the low incidence of urethral recurrence after orthotopic bladder replacement has led most surgeons to feel comfortable proceeding with this form of diversion, as long as the findings on frozen-section biopsy of the distal prostatic urethral margin are normal at the time of cystoprostatectomy** (Freeman et al, 1996; Hassan et al, 2004; Nieder et al, 2004).

Approximately 40% of urethral recurrences are diagnosed within 1 year after cystoprostatectomy, with a median time to diagnosis of 18 months (Clark et al, 2004). However, a number of cases of late urethral recurrence have been reported, indicating the need for prolonged surveillance in these patients (Schellhammer and Whitmore, 1976; Freeman et al, 1996). Urethral wash cytology has traditionally been recommended for urethral monitoring after cutaneous diversion and leads to earlier diagnosis of urethral recurrence than when evaluation is delayed until symptoms occur. However, the presumed survival benefit afforded by surveillance with urethral wash cytology over symptomatic presentation has been called into question (Lin et al, 2003). Voided urine cytology is part of standard surveillance in patients who have undergone orthotopic diversion. Patients with positive results of urine or urethral wash cytology or symptoms of urethral bleeding, discharge, or palpable mass are evaluated with cystoscopy and biopsy. Pelvic computed tomography or magnetic resonance imaging may be necessary to aid in assessment of the local extent of larger invasive tumors and to assess for metastatic disease. Patients who develop urethral carcinoma in situ after orthotopic diversion may respond to urethral perfusion with bacillus Calmette-Guérin, but this treatment is ineffective for those with papillary or invasive disease (Varol et al, 2004).

Total Urethrectomy after Cutaneous Diversion

The high or exaggerated lithotomy position provides optimal exposure for total urethrectomy, with the hips and knees gently flexed and the lower limbs abducted in boot-type stirrups. A modified lambda or midline perineal incision (Fig. 35–34) is made, and the subcutaneous tissue and bulbospongiosus muscle are then divided in the midline and retracted to expose the corpus spongiosum. The corpus spongiosum is mobilized circumferentially near the level of the mid-bulbous urethra, and traction is applied to facilitate sharp dissection of the urethra distally, thus separating the corpus spongiosum from the adjacent corpora cavernosa. As dissection proceeds distally, the penis becomes inverted, the corpora cavernosa become bowed, and the glans recedes into the phallus. The penis is essentially turned inside out onto the perineum, and the dissection is completed to the base of the glans. To excise the meatus and glandular urethra, the penis is replaced in its anatomic position, and an incision is made around the meatus and extended on each side down the ventral aspect of the glans. The distal urethra is then freed from its investments within the glans, and the isolated pendulous urethra is delivered onto the perineum. The deep spongiosum of the glans penis is reapproximated with 4-0 polydioxanone sutures in a horizontal mattress fashion; the surface layer is closed with interrupted 4-0 chromic.

Proximal sharp dissection of the urethral bulb is carried out posteriorly and laterally, staying close to the bulb but avoiding entry, if possible, because bothersome bleeding will result. The urethra is detached from the corporeal bodies anteriorly to the level of the departure of the urethra from the bulb, leaving the specimen attached only by the membranous urethra itself. The bulbar arteries are usually identified at the 4-o'clock and 8-o'clock positions just inferior to the perineal membrane after they are transected during the posterior bulb dissection. They are controlled with electrocautery or suture ligature, or they can be ligated if they are identified before transection. **Care must be exercised in completing the proximal dissection, in view of the possible postcystectomy adherence of intestine to the superior surface of the urogenital diaphragm.** This should be done under direct vision, and exposure can be aided by separating the crura of the corporeal bodies in the midline to open the intracrural space. All that remains of the membranous urethra proximally is an ill-defined fibrotic band, and it should be completely excised. Frozen-section analysis of this region adds some assurance that a negative proximal margin has been attained. A small suction drain is placed in the urethral bed and brought out through the perineum. Closure of the bulbospongiosus muscle, subcutaneous tissue, and skin with interrupted absorbable sutures completes the procedure, and a light pressure dressing is applied. Superficial hematoma, edema along the penile shaft, and infection are uncommon complications.

Total Urethrectomy after Orthotopic Diversion

Total urethrectomy after orthotopic urinary diversion is performed through an abdominoperineal approach. The patient is placed in

Key Points: Male Urethral Cancer

- Eighty percent of male urethral cancers are squamous cell carcinoma, and the region most commonly involved is the bulbomembranous urethra.
- In general, anterior urethral carcinoma is more amenable to surgical control, and the prognosis is better than that of posterior urethral carcinoma, which is often associated with extensive local invasion and distant metastasis.
- As opposed to penile carcinoma, benefit from prophylactic inguinal lymph node dissection has not been demonstrated in urethral cancer.
- The low incidence of urethral recurrence after orthotopic bladder replacement has led most authors to feel comfortable proceeding with this form of diversion, as long as the findings on frozen-section biopsy of the distal prostatic urethral margin are normal at the time of cystoprostatectomy.
- In converting a patient to cutaneous conduit urinary diversion, bowel from the existing orthotopic neobladder can often be reconfigured with its blood supply intact and used for this purpose.

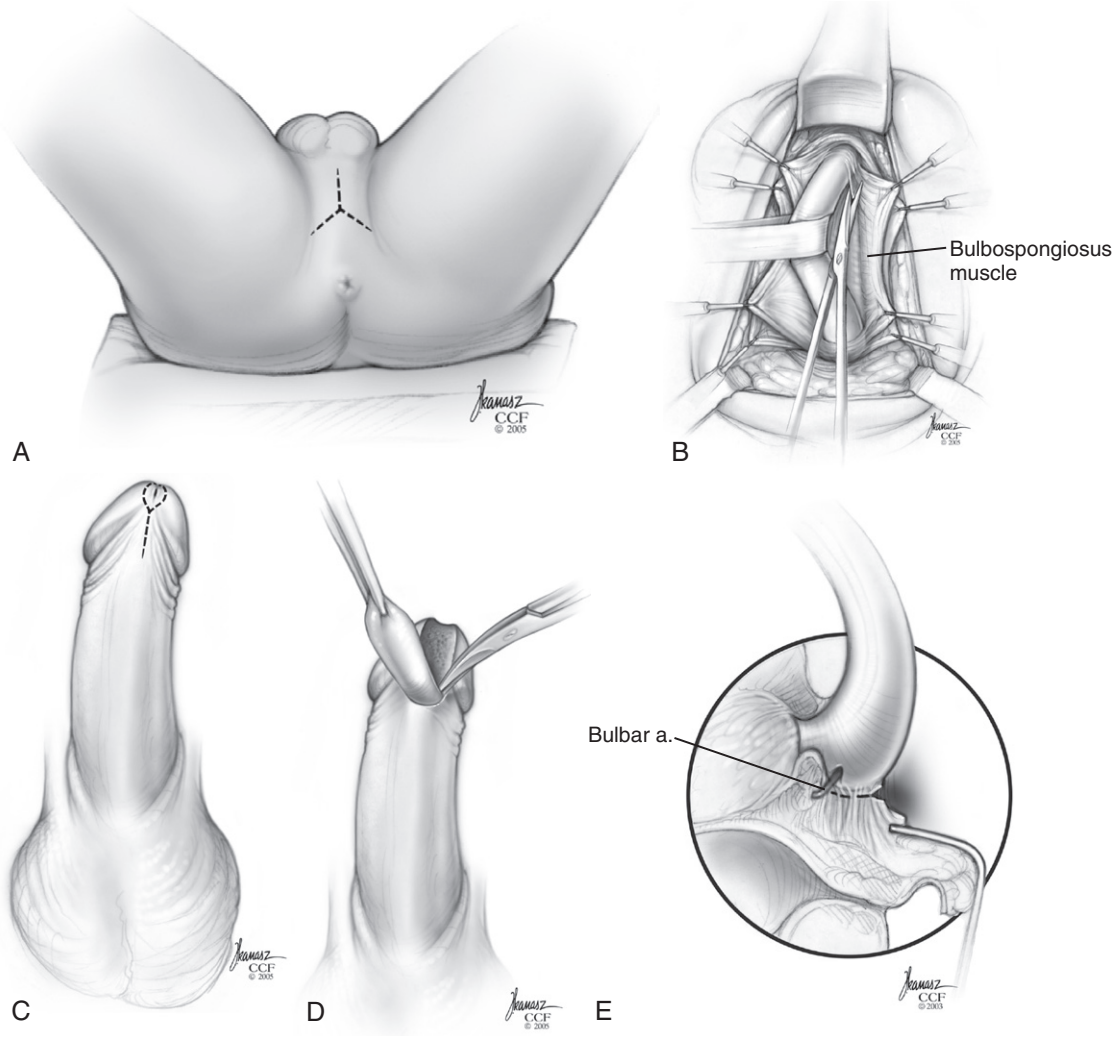


Figure 35–34. Secondary urethrectomy after previous cystoprostatectomy. **A,** Perineal incision. **B,** Division of bulbospongiosus muscle to expose the bulb of the corpus spongiosum and initial dissection of the urethra off of the corporeal bodies. **C,** Distal incision circumscribing the urethral meatus. **D,** Distal urethral dissection, which then connects to the proximal dissection at the level of the distal shaft. **E,** Sagittal view demonstrating posterior bulb dissection and location of the bulbar artery. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2003-2010. All Rights Reserved.)

lithotomy position with boot-type stirrups that can be adjusted during the procedure. Urethrectomy is carried out to the level of the membranous urethra. Abdominal exploration with lysis of adhesions and mobilization of the orthotopic neobladder is done to the level of the urethral anastomosis. Working with careful palpation from above and below, the area of the membranous urethra and the anastomosis are dissected free in their entirety. A circular area of the pouch adjacent to the anastomosis is excised to ensure an adequate surgical margin, and the specimen is delivered through the perineum. Bleeding from the musculature within the tunnel developed during excision of the membranous urethra can be bothersome and is best controlled with suture ligatures.

In most situations, urinary diversion is accomplished with an ileal conduit. **This can often be carried out with use of bowel from the orthotopic neobladder, which may be reconfigured when necessary, with care taken to incise the bowel along visible lines of previous closure with preservation of the mesenteric blood supply.** The remaining portions of the pouch are excised. If the existing diversion has an afferent limb (Studer pouch, for example), this segment can be used to construct the conduit without the need for manipulation of the ureters (Bissada et al, 2004). Conversion to a continent cutaneous diversion may also be possible in selected patients, depending on intra-abdominal anatomy and the motivation of the patient (Bartoletti et al, 1999).

FEMALE URETHRAL CANCER

Epidemiology, Etiology, and Clinical Presentation

Female urethral carcinoma is rare and accounts for approximately 0.02% of all female cancers (Fagan and Hertig, 1955) and less than 1% of cancers in the female genitourinary tract (Srinivas and Khan, 1987). More than 1200 cases are reported in the literature, most diagnosed in the fifth and sixth decades of life (Srinivas and Khan, 1987). Incidence appears to increase with age regardless of histologic subtype. Previous literature had suggested that despite the female urethra being much shorter than in the male, primary cancers of the urethra were more common than in men (Narayan

and Konety, 1992). However, a more recent study has called this into question. Swartz and colleagues studied the incidence of primary urethral carcinoma in the United States and found that based on information from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database that 1615 cases were identified between 1973 and 2002, including 1075 men and 540 women (Swartz et al, 2006). Therefore the SEER data suggests that there is a 2:1 male to female predominance. In addition, it had previously been noted that approximately 85% of urethral carcinomas occur in white women (Terry et al, 1997). However, analysis of the SEER data revealed an overall annual incidence of 1.5 cases per million women, including 4.3 cases per million African-American women and 1.3 per million white women (Swartz et al, 2006). Although it is possible that misclassification of the site of origin of tumors within the SEER database has lead to some inaccuracy in the above findings, previous studies may also be biased by the tertiary referral center populations from which they originate.

Although the cause of urethral carcinoma in women has not been identified, several factors have been implicated. **Etiologic factors associated with the development of urethral carcinoma include leukoplakia, chronic irritation, caruncles, polyps, parturition, and human papillomavirus infection or other viral infections** (Mevorach et al, 1990; Grigsby and Herr, 2000). Female urethral diverticula may also predispose the patient to malignant change, with perhaps 5% of female urethral carcinomas arising within a diverticulum (Rajan et al, 1993).

Ninety-five percent to 98% of patients are symptomatic at presentation. Many patients will present with obstructive symptoms, dysuria, urethral bleeding, urinary frequency, and often a palpable urethral mass or induration. A suspicion of a urethral tumor should be raised in any otherwise healthy middle-aged woman without prior urologic history who presents in urinary retention. Patients may also present with a small lesion prolapsing through the urethral meatus or with a small submucosal lesion on the anterior wall off the vagina. Tumors spread typically by local extension and may ulcerate as the tumor progresses to the skin and vulvar region. Proximal lesions may extend posteriorly into the vagina or proximally into the bladder. Lymphatic spread is uncommon at early stages, but clinically palpable nodes may be present in up to one third of patients at presentation and half of patients with advanced and proximal tumors (Grabstald et al, 1966). Hematogenous spread may occur to the lung, liver, bone, and brain, in order of frequency (Forman and Lichter, 1992).

Anatomy and Pathology

See Fig. 35–35 on the Expert Consult website.

Diagnosis and Staging

The evaluation of women with suspected urethral carcinoma includes cystourethroscopy, examination under anesthesia, computed tomography of the abdomen and pelvis, and chest radiography. Magnetic resonance imaging has been used to evaluate pelvic lesions and may help determine local extension. Serum prostate-specific antigen has been found to be elevated in a small number of case reports of females with adenocarcinoma, and it appears only a minority of female patients with primary adenocarcinoma of the urethra have this elevated tumor marker (Dodson et al, 1994; Pongtippan et al, 2004). TNM staging for female urethral cancer is identical to that for male urethral cancer (see Table 35–1). Clinically palpable inguinal nodes are found in 30% of patients overall, and these are confirmed to be malignant in approximately 90% of cases. Up to 50% of patients with proximal or advanced urethral cancers may have palpable nodes. Pelvic nodal metastases are also not uncommon, affecting 20% of cases. Metastasis outside of the pelvis at presentation is rare, however. During follow-up, another 15% of patients will develop metastatic nodal disease (Grigsby and Herr, 2000).

Treatment and Prognosis

Because of the rarity of this tumor and heterogeneity of disease, insufficient experience at any single institution within a reasonable period has precluded attempts to effectively define the natural history of the disease, recommendations for therapy, and follow-up of these patients (Grigsby and Herr, 2000). **Although it is conceivable that different histologic subtypes may affect prognosis and the propensity for route of disease spread, most studies have failed to detect any differences in survival based on histologic subtype** (Foens et al, 1991; Dimarco et al, 2004). Consequently, lesions of varying histologic type are often treated in a similar fashion.

Treatment recommendations are primarily dependent on tumor location and clinical stage. Local excision, which should lead to excellent functional results, may be sufficient for the relatively uncommon small, superficial, distal urethral tumors. For more proximal and advanced urethral tumors, a more aggressive approach is warranted. **Compared with proximal urethral cancers, distal lesions are associated with improved survival.** Five-year disease-specific survival is reported at 71% for distal lesions, 48% for proximal lesions, and 24% for lesions that involve the majority of the urethra (Dalbagni et al, 1998). Surgical and radiotherapy series reflect overall 5-year survival rates of 30% to 40%. Unfortunately, little improvement has been made in treatment of this disease, and survival rates have remained statistically unchanged for the last 50 years (Bracken et al, 1976; Prempree et al, 1984; Foens et al, 1991; Dalbagni et al, 1998; Dimarco et al, 2004). Options for treatment of female urethral carcinoma include surgery, radiation therapy, and chemotherapy, alone or in combination. Treatment has trended toward a multimodality approach in recent years. As representative of a heterogeneous group of studies, with varying treatment techniques and follow-up, and based on primary treatment modalities, Tables 35–2 and 35–3 summarize results for early and advanced disease, respectively, taken from study series having more than two patients.

Distal Female Urethral Carcinoma

Small, exophytic, superficial tumors arising from the urethral meatus or anterior urethra may be surgically treated with circumferential excision of the distal urethra and inclusion of a portion of the anterior vaginal wall. The distal third of the urethra may be excised while urinary continence is maintained. Frozen-section specimens of the proximal urethra should be obtained to ensure an adequate margin (Narayan and Konety, 1992). Laser coagulation of small distal tumors has been described (Staehler et al, 1985; Dann et al, 1989). In select patients with T2 or T3 cancer, bladder-sparing strategies have also been employed, if the tumor is more anterior, while an attempt is made to maintain a thorough resection. Dimarco and colleagues (2004) describe radical urethrectomy in the female patient, including excision up to the level of the bladder neck with wide resection of periurethral tissues and anterior vaginal wall. Urinary diversion is then accomplished with a catheterizable stoma (ileovesicostomy or appendicovesicostomy) to the native bladder. **Tumors in the distal urethra tend to**

Table 35–2.

Results of Various Treatment Modalities for Early Urethral Carcinoma in Women

TREATMENT	STUDY	NO. OF PATIENTS	SURVIVAL* NO. (%)
Radiotherapy	Weghaupt et al	42	30 (71)
	Pointon and Poole-Wilson	26	20 (77)[1]
	Taggart et al	15	8 (53)[2]
	Grabstald et al	11	3 (27)
	Delclos et al	11	6 (55)
	Chu	11	7 (64)
	Antoniades	8	8 (100)[3]
	Prempree et al	6	6 (100)
	Johnson and O'Connell	5	3 (60)[4]
	Klein et al	3	2 (66)[5]
	TOTAL	138	93 (67)
Surgery	Grabstald et al	14	10 (71)
	Bracken et al	3	1 (33)
	Eng et al	4	4 (100)
	TOTAL	21	15 (71)
Radiotherapy plus surgery	Grabstald et al	3	2 (67)
	TOTAL	3	2 (67)

*Five- to 6-year survival unless otherwise noted.
[1]Three-year survival.
[2]Two-year survival with no evidence of disease.
[3]One patient dead of disease at 64 months.
[4]Patients had no evidence of disease at 4 years.
[5]Patients alive at 27 and 37 months.

Table 35–3.

Results of Various Treatment Modalities for Advanced-Stage Urethral Carcinoma in Women

TREATMENT	STUDY	NO. OF PATIENTS	SURVIVAL* NO. (%)
Radiotherapy	Pointon and Poole-Wilson	52	21 (40)[1]
	Delclos et al	25	7 (28)
	Weghaupt et al	20	10 (50)
	Grabstald et al	19	1 (5)
	Antoniades	11	4 (36)[2]
	Prempree et al	7	4 (57)
	Hahn et al	8	3 (38)
	Chu	8	0 (0)
	Johnson and O'Connell	7	4 (57)[3]
	TOTAL	157	54 (34)
Surgery	Grabstald et al	13	2 (15)
	Bracken et al	7	3 (43)[4]
	Moinuddin Ali et al	3	0 (0)
	TOTAL	23	5 (22)
Radiotherapy + surgery	Grabstald et al	20	5 (25)
	Johnson and O'Connell	7	3 (43)
	Hahn et al	3	9 (0)
	Moinuddin Ali et al	4	2 (50)[5]
	TOTAL	34	19 (55)
Radiotherapy + chemotherapy ± surgery	Gheiler et al	6	3 (50)[6]
	Dalbagni et al	4	2 (50)[7]
	TOTAL	10	5 (50)

*Five- to 6-year survival unless otherwise noted.
[1]Three-year survival.
[2]Two patients dead of disease at 8 and 21 years.
[3]No evidence of disease at 1, 1, 3, and 6 years.
[4]No evidence of disease at 2 months and 3, 8, and 12 years.
[5]Alive at 48 months.
[6]No evidence of disease at 6 months and 4 years.
[7]No evidence of disease at 1.5 and 4 years.

be low stage, and cure rates of 70% to 90% have been achieved with local excision alone. However, in a study by Dimarco and colleagues (2004), 21% of patients with stage T2 tumors, or less, treated with partial urethrectomy had local recurrence. Other studies of partial urethrectomy, with or without radiation therapy, for lower-stage lesions have recurrence rates of 0% to 50% (Hahn et al, 1991; Gheiler et al, 1998). Meatal stenosis is a common complication, and incidence may be decreased by spatulation of the urethra. Approximation of the anterior vaginal wall and labia may help prevent urinary incontinence, although a sling procedure or other procedure to treat urinary incontinence may need to be subsequently performed. Many authors report minimal complications and rare incontinence from partial urethrectomy, but one series noted de novo or worsening stress urinary incontinence in 42% of patients (Dimarco et al, 2004).

Radiation therapy, as well as surgery, has proved effective for the treatment of low-stage distal urethral carcinomas. An overall 5-year actuarial survival rate of 41% was reported by Garden and colleagues (1993) in a series of 84 patients. This was subdivided into 5-year survival of 74% if only part of the urethra was involved, and 55% if the entire urethra was involved. Survival appeared to be associated with clinical stage of the tumor (Garden et al, 1993). Radiation may be delivered as external beam, brachytherapy, or combined therapy. In a series of 42 patients treated at the University of Iowa, radiotherapy delivered with combined interstitial and external beam radiation provided fewer local failures (14%) than all radiation-treated patients (36%) or those treated by surgery alone (60%). However, 5-year survival rates for irradiated and surgically treated groups are similar (Foens et al, 1991). Although doses may vary widely, a dose of between 55 and 70 Gy is reported in most series. Complication rates, now decreasing, have ranged from 20% to 40%, including urinary incontinence, urethral strictures, necrosis, fistula formation, cystitis, vulvar abscess, and cellulitis (Forman and Lichter, 1992).

Significant morbidity has been noted with ilioinguinal lymphadenectomy. In addition, female urethral carcinoma often spreads systemically without regional lymph node involvement. Although studies are small, there has been no evidence for improved survival after pelvic or inguinal lymphadenectomy (Grabstald et al, 1966; Levine, 1980; Dimarco et al, 2004). These findings, as well as the inability to prognosticate likelihood for micrometastatic lymph node involvement, have led to the recommendation against prophylactic or diagnostic lymphadenectomy. **Acknowledging that few objective data exist for making definitive decisions, recommendations for performing groin dissection have been made only for patients who present with positive inguinal or pelvic lymphadenopathy without distant metastasis, or patients who develop regional adenopathy during surveillance.** Late inguinal lymph node recurrences up to 7 years have been noted. The technique of ilioinguinal lymphadenectomy is identical to the dissection performed in men for penile cancer (Narayan and Konety, 1992; Grigsby and Herr, 2000).

In patients with recurrent or radioresistant tumors, neoadjuvant irradiation followed by local excision has resulted in a survival advantage over radiotherapy alone (Grabstald et al, 1966; Peterson et al, 1973; Allen and Nelson, 1978). Despite early and aggressive therapy for anterior lesions, local recurrence rates and mortality

remain high. Further studies are necessary to evaluate the potential role of multimodality therapy in these patients.

Proximal Female Urethral Carcinoma

Proximal female urethral carcinomas are more likely to be high stage and may extend into the bladder and vagina. Results with anterior exenteration alone resulted in a 10% to 17% 5-year survival rate and a local recurrence rate of 67% (Bracken et al, 1976; Klein et al, 1983). The poor disease-specific survival and high local recurrence rates observed with single-modality treatment of advanced female urethral carcinoma have led to the recommendation of combination therapy (Dalbagni et al, 1998, 2001; Gheiler et al, 1998). Advanced female urethral carcinoma includes tumors in a proximal location, a lesion that encompasses the entire urethra, or a locally invasive lesion that involves external genitalia, vagina, or bladder. Anterior exenteration (cystourethrectomy), pelvic lymph node dissection, and wide vaginal or complete vaginal excision are often required to obtain negative surgical margins. If the lesion extends into the external genitalia, partial vulvectomy or labial excision may be necessary. Anterior exenteration is performed as for bladder cancer in a female patient, with a more extensive perineal portion of the procedure to provide wide margins around the urethra. The margins of the lymphadenectomy should include the Cloquet node distally and otherwise retain limits identical to the dissection encouraged for lymphadenectomy in bladder cancer. Anterior exenteration includes the en bloc removal of the entire urethra and bladder, the uterus and adnexa, and the anterior and lateral vaginal walls. On occasion, the entire vagina may need to be resected. The perineal portion is initiated by completing an inverted U-shaped incision to encircle widely around the urethral meatus. It has been suggested that this incision be extended onto the posterior vaginal wall to the labia minora and continued anteriorly to beyond and including the clitoris (Narayan and Konety, 1992). En bloc resection of the pubic symphysis and inferior pubic rami may be necessary if the lesion encroaches anteriorly at the pubis, although the necessity of bone resection has been questioned in ensuring durable local control when intraoperative irradiation is added in suspect cases (Dalbagni et al, 2001).

Radiotherapy alone for proximal invasive urethral carcinoma has yielded poor local control, and 5-year survival rates of 0% to 57% are reported (Grabstald et al, 1966; Johnson and O'Connell, 1983; Prempree et al, 1984; Narayan and Konety, 1992). An improved mean survival rate of 54% at 5 years has resulted from the combination of radiation therapy and surgery for high-stage disease (Moinuddin Ali et al, 1988; Terry et al, 1997).

A combination of chemotherapy, radiation therapy, and surgery has been recommended for optimal local and distant disease control in advanced female urethral cancer. Patients whose treatment fails are thought likely to harbor micrometastatic disease at the time of primary treatment. For patients with squamous cell carcinoma, in part because of its effectiveness against anal cancers, 5-fluorouracil plus mitomycin C has been the most common empirically chosen regimen (Kalra et al, 1985). For transitional cell cancers, either M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) or a gemcitabine regimen is recommended (Grigsby and Herr, 2000). Chemotherapy given concomitantly with radiation therapy has been shown to interfere with cell repair and thus act as a radiosensitizer. It is hoped that this rationale may serve to decrease local recurrence and improve survival by eliminating micrometastatic disease and preventing progression of local failures to systemic failures. The group at Memorial Sloan-Kettering has shown early results based on six patients with advanced proximal urethral tumors treated with a multimodality approach. The authors suggest that anterior exenteration with high-dose intraoperative brachytherapy followed by external beam radiation seems to improve local control. Studies must evaluate whether combined modality therapy proves to decrease distant metastasis and improve survival (Dalbagni et al, 1998, 2001).

Urethral Recurrence after Cystectomy in Women

Orthotopic neobladder construction in women is now an established form of urinary diversion after radical cystectomy for transitional cell carcinoma. **The incidence of carcinoma involving the urethra in female patients undergoing cystectomy for bladder cancer ranges from 1% to 13%** (Coloby et al, 1994; Stein et al, 1995, 1998; Stenzl et al, 1995). There is still debate whether involvement of the bladder neck is a contraindication to orthotopic diversion; a prospective study has revealed that although all patients with urethral transitional cell carcinoma on final pathologic analysis of the cystectomy specimen had involvement of the bladder neck, more than 60% of women with bladder neck involvement had no evidence of urethral transitional cell carcinoma (Stein et al, 1998). Intraoperative frozen-section analysis of the urethral stump has been subsequently espoused by some authors to determine the feasibility of urethra-sparing cystectomy and orthotopic diversion (Stein et al, 1998).

Despite the reported incidence of urethral involvement in cystectomy patients and the increased use of orthotopic diversion in women, there are few reported cases of subsequent urethral malignant neoplasms in patients who have undergone this procedure. A review of 1054 patients undergoing radical cystectomy at a single center with a median follow-up of 10 years included 211 women, 44 of whom had an orthotopic urinary diversion. None of the 44 women developed a urethral recurrence (Clark et al, 2004). More recently, the group from the University of Southern California reported their first case of primary urethral recurrence in their series of female patients undergoing orthotopic urinary diversion. The patient remained without evidence of disease at 4 years of follow-up after total urethrectomy, resection of neobladder neck, and conversion of the orthotopic reservoir to a continent cutaneous urinary diversion (Stein et al, 2008). In a study by Ali-el-Dein and colleagues (2004), 145 women underwent orthotopic urinary diversion, 61% for squamous cell carcinoma and 21% for transitional cell carcinoma. At a median follow-up of 56 months, two patients (1.4%) developed an isolated urethral recurrence. One patient was reportedly not a surgical candidate, and the other patient underwent urethrectomy and conversion to a continent cutaneous reservoir but died 8 months later (Ali-el-Dein et al, 2004). One additional report described urethral transitional cell carcinoma in a woman after orthotopic diversion. This patient had a high-grade lesion of the bladder base with evidence of nodal metastasis. The patient was treated initially with chemotherapy, followed by urethral resection and conversion to a continent cutaneous diversion. The patient died 5 months later with visceral metastases (Jones et al, 2000). Limited experience to date precludes the ability to make definitive treatment recommendations for women with urethral cancer recurrence after orthotopic diversion. Urethrectomy and surgical resection of the area of the urethra-pouch anastomosis with conversion to a continent cutaneous urinary diversion seem feasible and reasonable in the absence of metastatic disease. Conversion to a cutaneous urinary conduit with use of reconfigured bowel from the existing orthotopic diversion is another option (Bissada et al, 2004).

Key Points: Female Urethral Cancer

- Squamous cell carcinoma is the most common histologic type of urethral cancer in women, accounting for 50% to 70% of all cases.
- Most studies have failed to detect any differences in survival based on histologic subtype.
- Compared with proximal urethral cancers, distal lesions are associated with improved survival.
- Tumors in the distal urethra tend to be low stage, and cure rates of 70% to 90% have been achieved with local excision alone.
- Proximal female urethral carcinomas are more likely to be high stage and may extend into the bladder and vagina.
- A combination of chemotherapy, radiation therapy, and surgery has been recommended for optimal local and distant disease control in advanced female urethral cancer.
- In appropriately selected women undergoing orthotopic diversion for bladder cancer, recurrence of cancer in the retained urethra is a rare event.



Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.

chapter
36

Surgery of the Penis and Urethra

Gerald H. Jordan, MD, FACS, FAAP (Hon), FRCS (Hon) ●
Kurt A. McCammon, MD, FACS

Principles of Reconstructive Surgery
Selected Processes
Trauma to the Genitalia
Urethral Stricture Disease
Pelvic Fracture Urethral Injuries
Vesicourethral Distraction Defects
Complex Fistulas of the Posterior Urethra
Curvatures of the Penis
Total Penile Reconstruction
Female-to-Male Transsexualism

Improvements in microsurgery, tissue transfer techniques, and tissue handling have expanded the repertoire of the urologic surgeon and the genitourinary reconstructive surgeon in particular. Urologists are now able to reconstruct congenital, and acquired genitourinary abnormalities with greater facility. Microvascular and microneurosurgical techniques have made it possible to construct a phallus that allows a patient to void while standing and to enjoy erotic sensibility. Because the phallus has both erotic sensibility and protective sensation, the patient can eventually have a prosthetic implantation that allows an acceptable sexual life. This chapter discusses the general principles of male genital reconstructive surgery; specifics include male urethral surgery, surgery for congenital and traumatic penile lesions, and complex fistula and obliterative issues associated with the posterior urethra.

PRINCIPLES OF RECONSTRUCTIVE SURGERY

Many techniques in reconstructive surgery require the transfer of tissue. Skin is one of those tissues, and **its properties vary from individual to individual and from place to place on the same individual.** Variable characteristics such as color, texture, thickness, extensibility, innate skin tension, and blood supply can be useful in various situations.

The term *tissue transfer* implies the movement of tissue for purposes of reconstruction. Unlike extirpative surgery, **the transfer of tissue for reconstruction requires an intimate knowledge of the anatomy of both the donor and the recipient sites, as well as of the principles that will allow that tissue to survive once it is transferred.**

The skin can be used as a model. The superficial layer of the skin is termed the epidermis (thickness, 0.8 to 1 mm). The deep layer of the skin is termed the dermis. The dermis has two layers: a superficial layer, the adventitial dermis (also called the papillary or periadnexal dermis, depending on the anatomy), and a deep layer, the reticular dermis. For genitourinary reconstruction, skin without adnexal structures is often used; thus, the papillary dermis is synonymous with the adventitial dermis. Other tissues commonly transferred for genitourinary reconstruction include bladder and oral mucosa. The bladder epithelium is the superficial layer of the bladder; the deep layer of the bladder is termed the lamina propria, with superficial and deep layers. The oral mucosa is the superficial layer of much of the oral cavity, which also has a deeper layer termed the lamina propria, again with superficial and deep layers.

All tissue has physical characteristics: extensibility, inherent tension, and the viscoelastic properties of stress relaxation and creep. The physical characteristics of a transferred unit are primarily a function of the helical arrangement of collagen along with the elastin cross-linkages. The collagen-elastin structure is suspended in a mucopolysaccharide matrix that influences the viscoelastic properties.

Tissue can be transferred as a graft (Fig. 36–1A and B). **The term *graft* implies that tissue has been excised and transferred to a graft host bed, where a new blood supply develops by a process termed take. Take requires approximately 96 hours and occurs in two phases. The initial phase, imbibition, requires about 48 hours.** During that phase, the graft survives by "drinking" nutrients from the adjacent graft host bed, and the temperature of the graft is less than the core body temperature. **The second phase, inosculation, also requires about 48 hours and is the phase in which true microcirculation is reestablished in the graft.** During that phase, the temperature of the graft rises to core body temperature. The process of take is influenced by both the nature of the grafted tissue and the conditions of the graft host bed. Processes that interfere with the vascularity of the graft host bed thus interfere with graft take.

The epidermal, or epithelial layer, is a covering, the barrier to the "outside," and is adjacent to the superficial dermis, or superficial lamina. At approximately that interface is the superficial plexus. In the case of skin, the plexus is the intradermal plexus. There are some lymphatics in the superficial dermal or tunica layer. On the undersurface of the deep dermal layer or deep lamina is the deep plexus. In the case of skin, this is the subdermal plexus. The deep dermis contains most of the lymphatics and greater collagen content than found in the superficial dermal

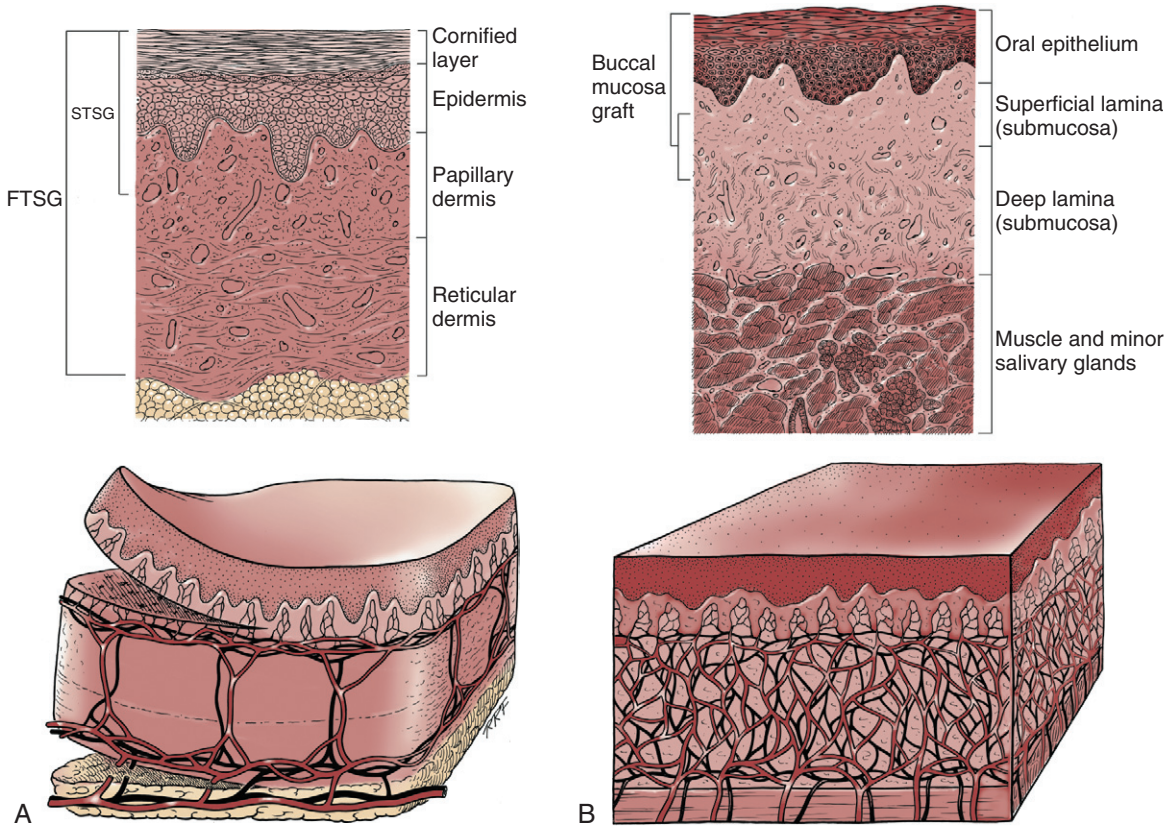


Figure 36–1. Cross-sectional diagrams (histologic appearance above, microvasculature below) of the skin. **A,** Cross-sectional diagrams of skin. **B,** Cross-sectional diagrams of oral mucosa. (From Jordan GH, Schlossberg SM. Using tissue transfer for urethral reconstruction. Contemp Urol 1993;13:23.)

layer. The deep or reticular dermis is generally thought to account for the physical characteristics of the tissue.

Thus **if a graft is a split-thickness unit, that graft carries the epidermis or the covering. That graft also exposes the superficial dermal (intradermal or intralaminar) plexus.** In most grafts, that superficial plexus is composed of small but numerous vessels. **This thus conveys favorable vascular characteristics to a split-thickness unit.** The unit has few lymphatics, and **the physical characteristics are not carried, which accounts for the tendency of split-thickness units to be brittle and less durable.** The reticular dermis is not carried with the split-thickness unit (Jordan, 1993).

The mesh graft is usually an application of the split-thickness graft. After the harvest of a sheet graft, the sheet is placed on a carrier that cuts systematically placed slits in the graft. These slits can expand the graft by various ratios (i.e., 1.5:1, 2:1, 3:1). For most genital reconstructive surgery, the slits are not for expansion but rather to allow subgraft collections to escape; in some cases, the slits allow the graft to conform better to irregular graft host beds (e.g., the testes in split-thickness skin graft scrotal construction). It has also been proposed that mesh grafts take readily because of increased levels of growth factors, possibly as a function of the slits. In general, full-thickness skin grafts are not meshed (Schreiter and Koncz, 1983; Jordan, 1993).

If a graft is a full-thickness unit, it carries the covering and the superficial dermis or lamina with all the characteristics attributable to that layer. It also, however, carries the deep dermis or deep lamina. In skin, the subdermal plexus is exposed. In most cases, **that plexus is composed of larger vessels that are more sparsely distributed. The graft is thus fastidious in its vascular characteristics.** A full-thickness unit carries most of the lymphatics, and the physical characteristics are likewise carried with the transferred tissue (Devine et al, 1976; Jordan, 1993; Wessels and McAninch, 1996). An off-the-shelf substance called Integra is currently available. Integra (Integra LifesSciences Corporation, Plainsboro, NJ 08536, 1-877-444-1122) is used to "prepare" graft recipient sites. After a period, the Integra material becomes infiltrated with granulation tissue and after about 10 days to 2 weeks can be grafted with split-thickness skin. The resultant graft is said to have both a dermal layer as well as the graft covering. We have limited experience with the material at this time.

When the grafts that are most commonly used in genitourinary reconstructive surgery are examined, **the split-thickness skin graft has favorable vascular characteristics but tends to contract** and be brittle when mature. **The full-thickness skin graft tends to have more fastidious vascular characteristics, but it does not contract as much and is more durable when mature** (see Fig. 36–1A). There is a difference between genital full-thickness skin (penile and preputial skin grafts) and extragenital full-thickness skin. This is probably a reflection of the increased mass of the graft in extragenital skin grafts. This increased mass makes the graft more fastidious, and the poor results reported with urethral reconstruction with extragenital full-thickness skin grafts are probably due to poor or ischemic take (Webster et al, 1984; Webster, 1987; Jordan, 1993). The posterior auricular graft (Wolfe graft) is an exception to the rule concerning extragenital skin. The postauricular skin is thin and overlies the temporalis fascia and is thought to be carried on

numerous perforators. The subdermal plexus of this graft thus mimics the characteristics of the intradermal plexus, and the total mass of the graft is more like that of the split-thickness unit. In the bladder epithelial graft, there is a superficial and a deep plexus; however, the plexuses are connected by many more perforators. Thus **bladder epithelial grafts tend to have more favorable vascular characteristics.** In the case of the oral **mucosal grafts, there is a panlaminar plexus.** Thus **the oral mucosal graft can be thinned somewhat, provided a sufficient amount of deep lamina is carried to preserve the physical characteristics** (see Fig. 36–1B). **The oral mucosal grafts are thought to have optimal vascular characteristics** (Humby, 1941; Memmelaar, 1947). The thinned graft diminishes the total graft mass while preserving the physical characteristics and not adversely affecting the vascular characteristics. The enthusiasm for the buccal mucosal graft thus seems well founded. The fact that the graft has a "wet epithelial" surface is likewise thought to be a favorable characteristic for many cases of urethral reconstructive surgery. The lingual, labial, and buccal grafts all vary in thickness and somewhat in substance. Because the labial mucosal grafts are thin, many surgeons prefer that donor site for reconstruction of the fossa navicularis (Jordan, 1993).

A series reporting the use of "buccal mucosal" onlay grafts with mid- and long-term results seems to suggest durability for these grafts. In that series (Fichtner et al, 2004), 67 patients were described, all with follow-up exceeding 5 years and some with 10 years of follow-up. All failures occurred within 12 months of the original procedure.

The dermal graft has been used for years to augment the tunica albuginea of the corpora cavernosa. When it is harvested, the graft exposes both the intradermal plexus and the deep dermal plexus. The dermal graft thus takes readily (is not fastidious) and has the physical characteristics normal to skin. When it is properly prepared, the tunica vaginalis graft is essentially peritoneum. The tendency of peritoneum to take readily is well documented both in the literature that examines adhesion formation and in the urology literature concerning the application of peritoneal grafts for reconstruction of the urinary tract. The literature fails to accurately define what the surgeon can expect regarding physical characteristics (Jordan, 1993). **Tunica vaginalis grafts have proved useful for small defects of the tunica albuginea of the corpora cavernosa, but there is a tendency to aneurysmal dilation when they are used for larger defects. Tunica vaginalis grafts have been tried for urethral reconstruction with uniformly poor results.**

As described in the urologic literature, vein grafts are perhaps not true grafts according to the terminology used in this chapter. Vein patches are widely used in vascular surgery. The premise is that the vein survives by endothelial direct perfusion and reestablishment of vein wall blood flow by perfusion of the vasa vasorum. The vascular literature is at odds with this concept. The intima is the endothelial layer; it is thin and easily injured during the process of vein harvest and preparation, with areas of endothelial sloughing noted. Inflammatory cells and fibrin adhere to the exposed basement membrane. However, the endothelium does regenerate in the first 6 weeks. The media is a combination of smooth muscle and interlaced collagen. After graft harvest, smooth muscle injury is prominently noted and is thought to be related to warm ischemia. In more mature grafts, much of the smooth muscle is replaced by a process of fibrous transformation with collagen deposition. The adventitia is a loose collagenous network interspersed with vasa vasorum. Mature vein grafts show evidence of take to the vasa vasorum. However, the adventitia becomes incorporated by periadventitial connective tissues. Thrombosis in the vasa vasorum, early in the process of take, is not an unusual phenomenon. When vein grafts are exposed to arterial pressure and shear stress forces, the process colloquially described as "arterialization" occurs and is associated with changes of the vessel wall elastic properties, and the graft becomes rigid with low compliance. Once these changes are noted, at least when veins are used for vessel replacement, the graft remains noncompliant throughout the remaining life of the graft (Szilagyi et al, 1973; Fuchs et al, 1978; Tolhurst and Haeseker, 1982). Vein "grafts" are currently being widely used for replacement of defects of the tunica albuginea of the corpora cavernosa. The pertinent points with regard to the transfer of vein patches to the corpora cavernosa and their long-term behavior, however, have been inferred from the current vascular literature. Dermal grafts have been tried for urethral reconstruction, also with poor results in general. **Rectal mucosal grafts have also been proposed for urethral reconstruction but little is known about their graft take. In general, the vascularity of the bowel mucosa is based on the vascularity of the underlying muscle, with the mucosa carried on perforators. Little is found in the literature regarding the process of take of these grafts.**

Tissue can be transferred as a flap. **The term *flap* implies that the tissue is excised and transferred with the blood supply either preserved or surgically reestablished at the recipient site. Flaps can be classified by a number of criteria. We can classify flaps on the basis of their vascularity and thus characterize flaps as either random flaps** (Fig. 36–2) **or axial flaps** (Fig. 36–3). **A *random flap* is a flap without a defined cuticular vascular territory.** The flap is carried on the dermal or laminar plexuses; the dimensions of random flaps can vary widely from individual to individual and from body site to body site. **The term *axial flap* means that there is a defined vessel in the base of the flap. There are three types of axial flaps. The direct cuticular axial flap is a flap based on a vessel superficial to the superficial layer of the deep body wall fascia** (see Fig. 36–3A). The classic example of a direct cuticular flap is the groin flap. **A musculocutaneous flap** (Fig. 36–4A), **on the other hand, is based on the vascularity to the muscle. The overlying skin paddle**

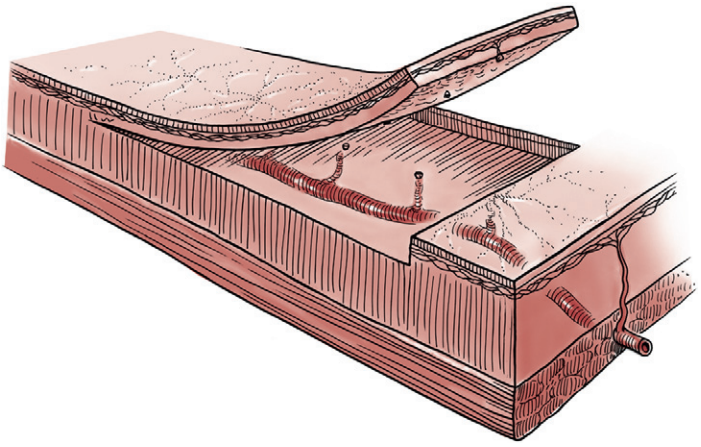


Figure 36–2. Random flap. The arterial perforators have been interrupted, and flap survival depends on the intradermal and subdermal plexuses.

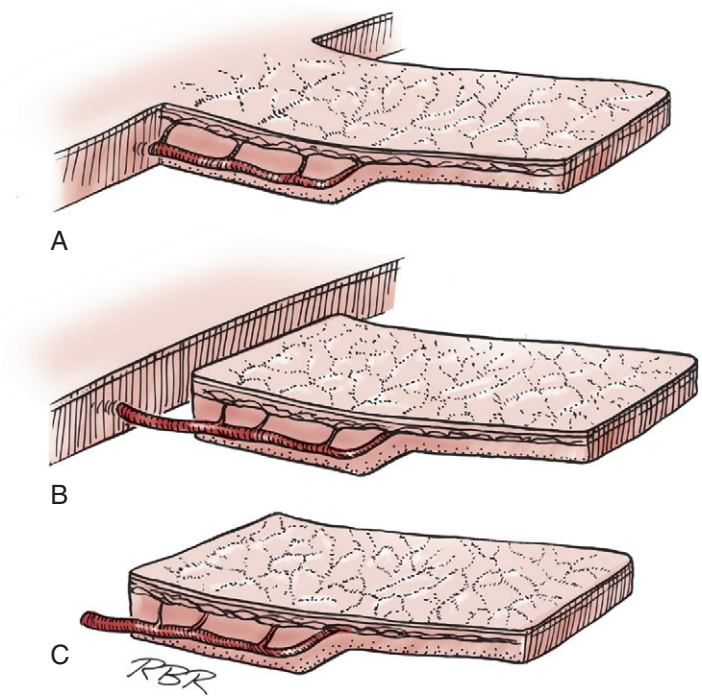


Figure 36–3. Axial flaps. Large vessels enter the base of the flaps. Survival depends on these vessels and on the random distal vascularity. **A,** Peninsula flap. The vascular continuity and the cutaneous continuity in the flap base are intact. **B,** Island flap. The vascular pedicle is intact; the cuticular continuity has been divided. These axial vessels are unsupported (dangling). **C,** Microvascular free-transfer flap. The free-flap cuticular and vascular connections are interrupted at the base of the flap. Vascular continuity is reconstituted in the recipient area by a microsurgical anastomosis. (**A** to **C,** From Jordan GH, McCraw JB. Tissue transfer techniques for genitourinary reconstructive surgery. AUA Update Series 1988;7:lesson 10.)

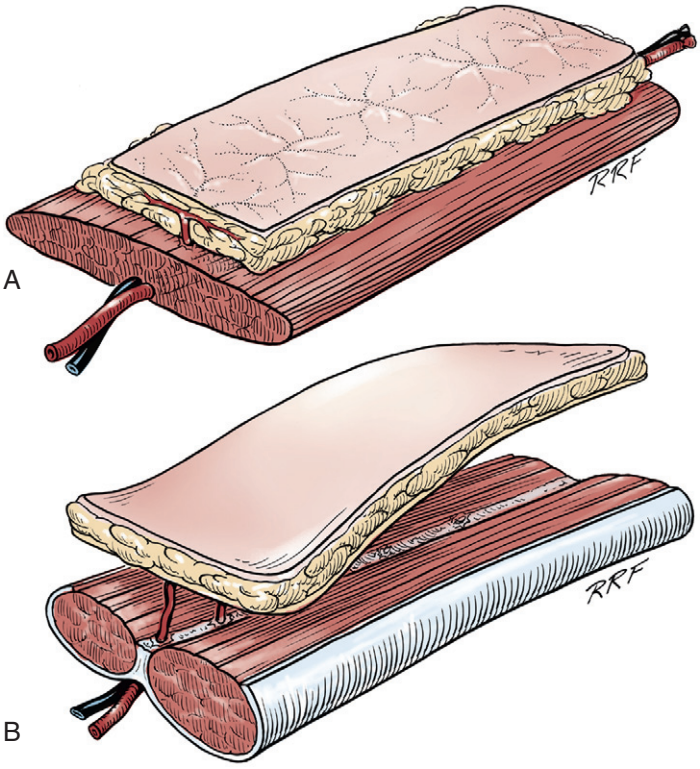


Figure 36–4. **A,** Musculocutaneous flap. Musculocutaneous perforators from the artery to a muscle vascularize the skin and overlying subcutaneous fat. They may be transferred as free flaps but are usually transferred locally, left attached to the vascular pedicle. **B,** Fasciocutaneous flap. Perforating blood vessels from rich plexuses on the superficial and deep aspects of the fascia connect to perforator vessels that communicate with the microvasculature of the overlying paddle. In genital reconstruction, these flaps are based on the dartos fascia of the penis or are free flaps from the forearm. (**A** and **B,** From Jordan GH, McCraw JB. Tissue transfer techniques for genitourinary reconstructive surgery. AUA Update Series 1988;7:lesson 10.)

is carried on perforators. If the muscle alone is carried as a flap, the overlying skin survives as a random unit. **The fasciocutaneous system of vascularity** (Fig. 36–4B) **is similar to the musculocutaneous system.** However, the deep blood supply is carried on the fascia (both deep and superficial layers), and the overlying skin paddle is based again on perforators. Thus one can transfer a fascial flap based on the deep blood supply associated with the flap; the overlying skin, if it is not carried with the flap, remains as a random unit (Ponten, 1981; Tolhurst and Haeseker, 1982; Cormack and Lamberty, 1984). It has been argued that fascia is relatively avascular and hence cannot serve as "the blood supply" to the fasciocutaneous unit. Indeed, the fascial layer, in reality, acts as a trellis—thus the vessels are carried much like the limbs of a vine (Jordan, 1993).

A flap can also be classified by the elevation technique. A peninsular flap is a flap in which the vascular continuity and the cutaneous continuity of the flap base are left intact (see Figs. 36–2 and 36–3A). **An island flap** (see Fig. 36–3B) **is a flap in which the vascular continuity is maintained; however, the cuticular continuity is divided. Thus a true island flap is elevated on dangling vessels. The microvascular free transfer flap (free flap)** (see Fig. 36–3C) **has both the vascular continuity and the cuticular continuity interrupted. The vascular continuity is then reestablished at the recipient site.**

Again, there is confusion in terminology. In genitourinary reconstructive surgical procedures, we tend to use the term *island flap*. As already mentioned, a true island flap is elevated on dangling vessels. The usual case, however, is that a skin island or paddle is elevated either on the muscle, as in the gracilis musculocutaneous flap, or on the fascia, as in local genital skin flaps. The term *island flap* is not synonymous with the terms *skin island* and *skin paddle*. The usefulness of these flaps and grafts is illustrated in the discussion of the surgical techniques in this chapter. There is continued interest in the use of tissue-cultured grafts or "manufactured" grafts. The likelihood of someday, soon, being able to successfully use off-the-shelf grafts or sheets of cultured material is right around the corner (Chen et al, 1999; Atala, 2002; Rotariu et al, 2002; El-Kassaby et al, 2003; Bhargava et al, 2004).

Anatomy of the Penis and Male Perineum

See Figs. 36–5 to 36–13 on the Expert Consult website.

Generalities of Reconstructive Surgical Techniques

With any surgical procedure, there are basic rules and surgeons' biases as to the best way to perform a certain operation. Certainly,

Key Points: Principles of Reconstructive Surgery

- Many of the techniques in reconstructive surgery require the transfer of tissue. Tissue transfer implies the movement of tissue for purposes of reconstruction. All tissue has extensibility, inherent tension, and the viscoelastic properties of stress relaxation and creep. These physical characteristics are important in predicting the behavior of transferred tissue.
- A graft is tissue that has been excised and transferred to a graft host bed, where a new blood supply develops by a process termed take. A flap is tissue that has been excised and transferred with the blood supply preserved or surgically reestablished at the recipient site. The grafts that have been successfully used for primary urethral reconstruction are the full-thickness skin graft, the bladder epithelial graft, the oral mucosal graft, and the rectal mucosal graft. Little is known about the characteristics of the rectal mucosal graft. The bladder epithelial graft and the oral mucosal graft have a number of vascular properties that make them desirable for urethral reconstruction. The issue of desiccation and hypertrophic growth, in the case of the bladder epithelial graft, has limited its use in the distal urethra.
- Full-thickness skin and split-thickness skin have been used for penile reconstruction. The results with split-thickness skin are so good that full-thickness grafts are rarely used for coverage of the penis. In complex cases, microvascular free-transfer technology has become a mainstay. For urethral reconstruction, skin islands based on the dartos fascia or tunica dartos have been effectively used. The dermal graft has been used for years to augment the tunica albuginea of the corpora cavernosa.
- The behavior of almost all forms of transfer can be predicted by examinating histologic features and recognizing which layers provide which characteristics to the tissue.

this is true for reconstructive procedures of the external genitalia. In this section, the differences are highlighted.

Reconstructive surgery is performed with all efforts aimed at minimizing tissue injury and promoting healing. Adequate visualization is essential. Surgical loupes are used by almost all surgeons performing both adult and pediatric reconstructive genital surgery. A headlight or suction with attached light often adds to visualization, especially in deep perineal surgery. **In penile cases such as reconstruction of the fossa navicularis or correction of penile curvature, bipolar cautery is used exclusively.** With cautery, the electric charge is grounded either to a pad (monopolar) or to the opposite tong of the forceps (bipolar). It is easy to see that in most instances, the field effects of the electricity are more confined with bipolar cautery. Because electricity is dissipated by conductors (in the case of human tissue, vessels and nerves), there is a possibility of damage to these delicate structures. In other cases, monopolar cautery can be used in the superficial structures, but bipolar cautery is better during dissection around the corpus spongiosum, elevation of penile and scrotal flaps, division of the perineal intracorporeal space, and dissection of the dorsal neurovascular structures.

Appropriate instruments for genitourinary reconstructive surgery can commonly be found in a plastic surgery tray or on the peripheral vascular tray in the typical operating room. Some examples are fine tenotomy scissors, fine forceps, a variety of skin hooks, and delicate needle holders. Sharp scissors that cut with minimal collateral trauma are essential. These instruments minimize tissue injury from manipulation and permit more precise dissection. For urethral surgery, a set of bougie à boule sizers is essential to check the caliber of the urethral lumen. McCrea urethral sounds are a nice addition to the typical van Buren sounds available in the usual operating room. For calibration, sounds do not replace the need for bougie à boule calibrators. For posterior urethral reconstruction, a sound to pass through the cystostomy tract and prostate to find the proximal end for the reconstruction is often helpful. We find that a Haygrove staff serves this role nicely. Some centers use the cystoscope for this purpose, and often it suffices well, whereas at other times it is not as effective as the Haygrove-style sound. The choice of suture material clearly evolves on the basis of the surgeon's experience and bias. However, there are some common principles with which most surgeons would agree. First, in urethral surgery, absorbable suture is the rule. Typical choices for most surgeons are braided absorbable sutures or the family of monofilament absorbable sutures. Chromic suture is rarely used now because the choices of other absorbable sutures seem superior in virtually all cases. Thus, in the case of tension-free closures, very small sutures can be used. In some cases, tying the suture can be awkward, and thus a larger suture may be warranted, even though the anastomosis is tension free. The caliber of suture should be the smallest possible to line up the tissue, which is typically not under tension. There is no reason to use suture that is stronger than the tissues that are being sutured. Fine suture such as 5-0 and 6-0 chromic or polyglactin can be used to suture the epithelium to the adventitia of the corpus spongiosum to control bleeding. For a flap or graft repair, 4-0 to 6-0 suture is usually adequate. For primary anastomosis of the corpus spongiosum or for a posterior urethral reconstruction, 3-0 suture may be appropriate because of tying concerns. The needle should be tapered if possible except when, as in urethroplasty, for example, severe spongiofibrosis or scarring is present. Some of the typical choices are taper needles, such as RB-1, TF, and SH-1, and cutting needles, such as P-3 and PC-3. The UR-6 half-circle taper needle that is often used in radical prostatectomy can be helpful for deep perineal anastomosis of the urethra.

Surgical position and retraction are critical to attaining good results. If possible, procedures are done with the patient supine or prone. Many procedures that previously were done with the patient in the lithotomy position can be done with the patient in the frog-leg or split-leg position. For penile surgery, a Scott retractor with stay hooks,* the Jordan-Bookwalter perineal retractor set,† or the Omni-Tract perineal retractor‡ are helpful. Lithotomy or exaggerated lithotomy positions are used only for the minimal time necessary. With appropriate padding for the foot and positioning without pressure on the back of the leg, the complications in the low lithotomy position are minimal. When the patient is in the supine, split-leg, and low lithotomy positions, venous compression stockings can be used. The controversy in positioning revolves around the use of the exaggerated lithotomy position. It is our preference to use this position for all bulbar and posterior urethral reconstructions. Other surgeons use a lower lithotomy position. We find the more exaggerated position to be safe and

*Lone Star Industries; 800-331-7427.

†C.S. Surgical, 662 Whitney Drive, Slidell, LA 70461, 985-781-8292; J. Hugh Knight Instrument Company, 226 S. Villere St., New Orleans, LA 70112, 800-535-5645.

‡Omni-Tract Surgical, Division of Minnesota Scientific Inc., 4849 White Bear Parkway, St. Paul, MN 55110; 800-367-8657.

believe that it provides unequaled access to the deep perineal structures (Angermeier and Jordan, 1994). Details of positioning, as we do it, are covered later. To minimize the patient's time in the exaggerated position, all graft harvesting or flap elevation is done with the patient in the flat supine position.

In addition to proper diagnosis and planning, the surgical technique is important for the overall success of reconstructive surgery. Unlike the results of extirpative surgery, the results of reconstructive surgery depend on methods that minimize tissue damage and maximize wound healing. The key ingredients are adequate visualization, appropriate choice of suture, delicate tissue handling, appropriate positioning, and adequate retraction.

Key Points: Reconstructive Surgical Techniques

- Reconstructive surgery is performed with all efforts aimed at minimizing tissue injury and promoting healing. Loupe magnification is used by almost all surgeons performing adult and pediatric reconstructive surgery. For deep exposure, a headlight or lighted suction is advantageous. Instruments must be delicate because reconstructive surgery uses small sutures and small needles.
- The choice of suture material clearly evolves on the basis of the surgeon's experience. However, the caliber of sutures should be the smallest possible to align the tissue, which is not typically under tension. There is no reason to use suture that is stronger than the tissues being sutured.
- The choice of surgical positioning is clearly left to the surgeon's preference.
- Proper diagnosis and planning of the surgical technique are important for the success of reconstructive surgery.

SELECTED PROCESSES

Urethral Hemangioma

Although **urethral hemangioma is a rare condition, it is usually persistent** and offers a challenge to the surgeon when excision is deemed necessary. Patients typically present with hematuria or a bloody urethral discharge and, occasionally, with obstructive symptoms. The lesions may be either single or multiple, and the urethral meatus is a common location. Although diagnosis is often made at cystoscopy, which readily visualizes the dilated blood vessels, the lesion often extends beyond the point at which it is seen with cystoscopy.

Because all reported cases of urethral hemangioma have been benign, management depends on the size and location of the lesion. Asymptomatic lesions do not require treatment and should be observed, because hemangiomas can regress spontaneously. Symptomatic lesions that require treatment must be completely excised to prevent recurrence.

Although electrofulguration has been reported as a possible treatment of urethral hemangioma, it should be used only to control an acute episode. For smaller lesions, laser treatment has been successful and produces less scarring. Lasers that are used for this purpose include argon, potassium titanyl phosphate (KTP) (532 nm), and neodymium:yttrium-aluminum-garnet (Nd:YAG). The preferred treatment of larger lesions is open excision and urethral reconstruction. This, in some cases, means circumferential reconstruction. It is clear that tubed graft reconstruction should be avoided; tubed flap reconstruction or tubed construction with mixed tissue transfer could be considered, although staged reconstruction is probably preferable. In addition, good initial success has been reported with polidocanol as a sclerosing agent for extensive urethral hemangiomas.

Reiter Syndrome

Reiter syndrome is characterized by a classic triad of arthritis, conjunctivitis, and urethritis. In addition, **some patients have had an episode of diarrhea that preceded the development of arthritis.** In most cases, however, the classic triad is not present, and patients present with only arthritis affecting the knees, ankles, and feet in an asymmetrical distribution. The history of urethritis is obtained on detailed questioning.

Urethral involvement is usually mild, self-limited, and a minor portion of the disease. In approximately 10% to 20% of patients, a glanular lesion is present. Referred to as **circinate balanitis,** this lesion **is diagnostic of Reiter syndrome** and typically appears as a shallow, painless ulcer with gray borders. On occasion, the lesion appears as small, red macules, 1 to 2 mm in diameter. When the urethritis is mild and self-limited, no treatment is necessary.

In rare cases, urethritis causes severe inflammation with necrosis of the mucosa, producing uncompromising stricture disease. We have not been successful in excision and replacement of the urethra in these cases. Alternatively, we perform a perineal urethrostomy and excise the entire distal urethra. This approach may decrease the rheumatic manifestations associated with Reiter syndrome.

Lichen Sclerosus (Balanitis Xerotica Obliterans)

Lichen sclerosus (LS) is the preferred term for what was previously known as balanitis xerotica obliterans (BXO). Lichen sclerosus is a **chronic inflammatory disorder of the skin of uknown origin.** No specific mechanism of disease has been elucidated. There are several acquired scarring disorders of the skin associated with pathology of the basement membrane, such as mucous membrane pemphigoid, that may be shown as related (Bernard et al, 1992; Akporiaye et al, 1997). The reported incidence of LS in the western population is 1 in 300; however, the worldwide prevalence may be substantially different (Wallace, 1971; Dogliotti et al, 1974; Jacyk and Isaac, 1979; Datta et al, 1993). The peak ages of recognition in women are bimodal, with many cases noted before puberty but with another peak presenting in postmenopausal women (Tasker and Wojnarowska, 2003). In men, LS seems to peak between the ages of 30 to 50; however, incidences of LS have been described in people of all ages, from infants to the elderly (Tasker and Wojnarowska, 2003). LS is commonly found at the time of circumcision when performed beyond the neonatal period (McKay et al, 1975; Rickwood et al, 1980; Garat et al, 1986; Ledwig and Weigland, 1989; Meuli et al, 1994). **The most common cause of meatal stenosis, LS appears as a whitish plaque that may involve the prepuce, glans penis, urethral meatus, and fossa navicularis. If only the foreskin is involved, circumcision may be curative** (Akporiaye et al, 1997). In the authors' experience, LS usually begins as a meatal or perimeatal process in the circumcised patient, but it may involve other areas of the preputial space in the uncircumcised patient. In uncircumcised men, the prepuce becomes edematous and thickened, and often may be adherent to the glans (Bainbridge et al, 1971).

Diagnosis is made through biopsy. Several reports have suggested the association with chronic infection by a spirochete, *Borrelia burgdorferi* (Tuffanelli, 1987; Dillon and Ghassan, 1995; Shelley et al, 1999).

The term BXO was first applied by Stühmer in 1928. Freeman and Laymon showed that BXO and LS were probably the same process (Freeman and Laymon, 1941; Laymon and Freeman, 1944). The first report of what was probably LS was published by Weir in 1875. He described a case of vulvar and oral "ichthyosis" (Weir, 1875). In 1976, the International Society for the Study of Vulvar Disease unified the nomenclature devising a new classification system and proposed the term lichen sclerosus (Friedrich, 1976). As mentioned previously, the cause of LS has not been defined. A number of mechanisms have been proposed. Koebner phenomenon relates the development of LS to trauma to an affected area (Lee and Phillips, 1994). The etiology has also been suggested to be an autoimmune disease (Goolamali et al, 1974; Marren et al, 1995). Sander hypothesized that reactive oxidative stress contributed to the sclerotic, immunologic, and carcinogenic process in LS (Sander et al, 2004). As mentioned, the infectious cause has also been implicated (Tuffanelli, 1987; Ross et al, 1990). That has been called into question because the organism has not been uniformly demonstrated in the lesions. It has also been proposed that LS has a genetic origin, based on the observation of a familial distribution of cases (Marren et al, 1995). There have been reports of concomitant existence of the disease in identical twins (Fallic et al, 1997; Thomas and Kennedy, 1986) and nonidentical twins (Cox et al, 1986), with coexistence of dermatosis. The disease has also been seen in mothers and daughters (Shirer and Ray, 1987). Studies on the human leukocyte antigen (HLA) have suggested a genetic component in patients afflicted with LS (Marren et al, 1995). The combination of topical steroids and antibiotics may help stabilize the inflammatory process. Conservative therapy may be warranted in patients whose meatus can easily be maintained at 14 to 16 French (Staff, 1970). In these cases, intermittent catheterization with lubrication of the catheter and meatal dilator with 0.05% clobetasol (brand name Temovate) may be adequate treatment. Long-term antibiotic therapy may also be helpful to improve the inflammation, because secondary infection of the inflamed tissue may occur. We have typically used tetracycline, but a trial of long-term penicillin or advanced-generation erythromycin therapy may be warranted (Shelley et al, 1999). This nonsurgical approach to treatment is used in patients who are not good surgical candidates for other medical reasons or in older patients, and in younger patients who demonstrate stable disease. Secrest has proposed a link between hypogonadism and LS in male patients. He has consistently shown diminished testosterone levels in patients afflicted with LS and has a study underway analyzing whether replacement androgen therapy may be helpful (Secrest et al, 2008).

In young patients with severe meatal stenosis, surgery is indicated. Because patients with long-standing meatal stenosis often have severe proximal urethral stricture disease, retrograde urethrography should be performed before the initiation of therapy. The etiology of stricture disease associated with LS is unclear. Possible causes include iatrogenic stricture resulting from repeated instrumentation and pressure voiding associated with meatal stenosis causing secondary intravasation of urine into the glans Littre (Fig. 36–14). In cases of early LS with only meatal involvement resulting in stenosis of the fossa navicularis, prompt reconstruction seems to be successful in the long term and seems to avoid the sequelae of panurethral stricture disease. Most surgeons now believe that because LS is a disease of genital skin, better tissue for reconstruction is the oral mucosa, and techniques are discussed later (Mundy, 1994; Bracka, 1999). Long-standing cases with a long length of urethral stricture are amenable to techniques of reconstruction but are very challenging. It is becoming clear that except in the case of urethral stricture disease confined only to the meatus and fossa navicularis, staged oral graft reconstruction, at least in the short to mid term, seems to provide superior durable results. This may also be the case in cases confined to the meatus and fossa navicularis, because a recent analysis of patients reconstructed with the ventral transverse skin island technique showed a 50% recurrence rate even in those patients. The weakness of that analysis, is that the data did not include biopsy proof that all patients had LS (Virasoro et al, 2007). We also are seeing more and more patients who present with a buried penis. This phenomenon occurs when the skin of the penile shaft has been lost because of severe inflammation, and the penis is trapped in the penopubic and scrotal area. These

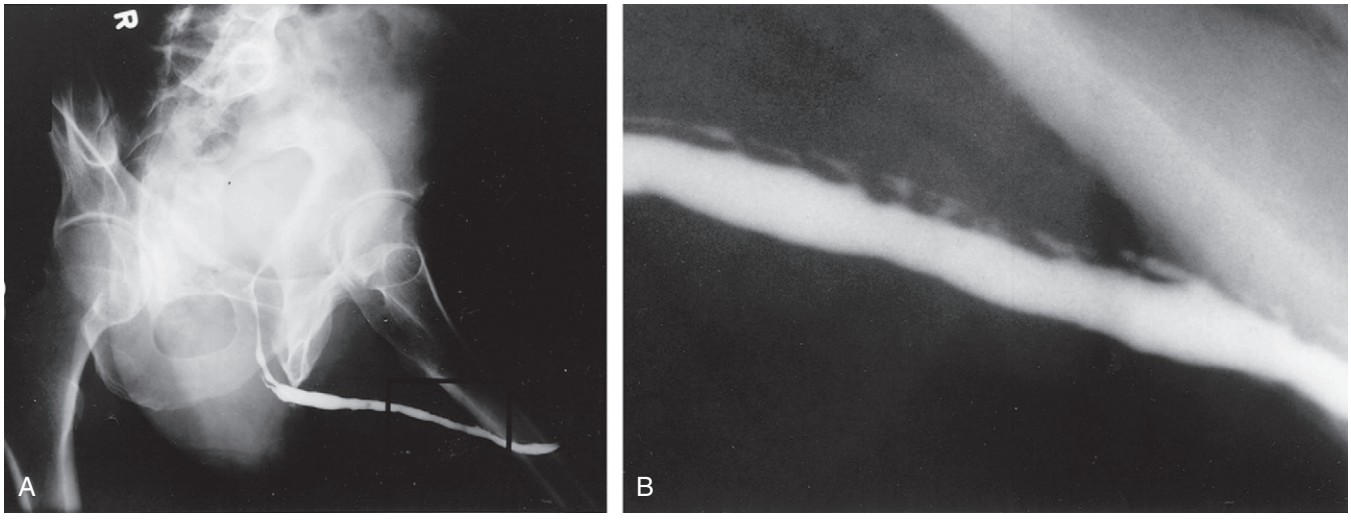


Figure 36–14. **A** and **B,** Urethrogram in a patient with urethral stricture disease associated with lichen sclerosus–balanitis xerotica obliterans. It illustrates the intravasation of contrast material into the dilated glands of Littre during voiding. (From Jordan GH. Management of membranous urethral strictures via the perineal approach. In: McAninch J, Carroll P, Jordan GH, editors. Traumatic and reconstructive urology. Philadelphia: WB Saunders; 1996.)

patients are often profoundly overweight, and many are diabetic; they have often had prior surgical procedures. Their management is complex and ultimately determined by their desire and need for functional reconstruction. In some patients with severe urethral stricture disease, we have completely reconstructed the urethra; in others, we have simply performed a perineal urethrostomy. Perineal urethrostomy is usually technically straightforward, because the rule in most patients with lichen sclerosus is to spare the proximal anterior urethra. We have proposed that, in many cases, the sparing of the proximal anterior urethra demonstrates the distribution of the glands of Littre for a given patient. Younger patients have requested mobilization and release of the penis with placement of a split-thickness skin graft. However, because the inflammation involves the glans penis (which is not removed), the secondary inflammation may also involve the skin graft. Therefore lifelong monitoring of these patients for the secondary effects of inflammation is necessary.

Several reports have suggested the development of squamous cell carcinoma in patients with a long history of lichen sclerosus (Doré et al, 1990; Pride et al, 1993).

Amyloidosis

Although a rare disease, amyloidosis of the urethra should be considered in the evaluation of any patient with a urethral mass. Patients may present with hematuria, dysuria, or urethral obstruction. Because the differential diagnosis includes urethral neoplasm, cystoscopy with transurethral biopsy is indicated. Once the diagnosis is made, treatment should be based only on symptoms. Most patients can be observed expectantly and not require aggressive treatment. Some will require treatment for urethral stricture. Progression and recurrence are rare (Walzer et al, 1983; Dounis et al, 1985; Crook et al, 2002).

Urethrocutaneous Fistula

A urethrocutaneous fistula is a tract lined with epithelium that leads from the urethra to the skin. The size of a fistula can vary from pinpoint to large. **Urethral fistulas may be a complication of urethral surgery or develop secondary to periurethral infection associated with inflammatory strictures or treatment of a urethral growth** (condyloma or papillary tumor). **Treatment of a urethral fistula must be directed not only to the defect but also to the underlying process that led to its development.** Treatment therefore varies according to the cause of the fistula. In cases of urethral reconstruction, especially reconstruction for hypospadias, fistula often occurs or recurs because of distal obstruction and high-pressure voiding. Additionally, in some cases where multiple attempts at fistula closure have been attempted and failed, the condition of the tissue adjacent to the fistula are so scarred that staged reconstruction is needed to import "better tissue."

After urethral surgery, fistulas can develop immediately or as delayed complications. An early fistula is the result of poor local healing, possibly secondary to hematoma, infection, or tension with closure. In addition, a mere breakdown of the urethral or overlying skin closure, or both, could occur. Very occasionally, with aggressive local care and continued urinary diversion, the fistula closes spontaneously.

Several techniques are used for fistula closure. Endoscopic and radiographic evaluation of the urethra must be performed before the repair in all cases. If the fistula is small and closure of the hole will not decrease the lumen of the urethra, a button of skin is removed from around the fistula, and its edges are cut flush with the urethral wall. The urethra is closed with small (6-0 or 7-0) absorbable suture, inverting the epithelial edge, and the repair is tested to ensure that it is watertight. The authors prefer either polyglycolic acid (Vicryl) or polydioxanone suture. Subsequent layers are designed and closed to avoid superimposed suture lines. Without question, the safest diversion is a suprapubic catheter. However, in many cases, a silicone stent that reduces pressure during voiding for 7 to 14 days suffices. The operating microscope can be useful for the closure of small fistulas, allowing the use of 8-0 polyglycolic acid suture and limiting the size of the associated skin incision.

If the fistula is so large that simple closure will compromise the lumen of the urethra, then often local flaps will be required. However, if the adjacent tissues are thin and poorly visualized, then closure of the fistula may become a staged urethral reconstruction as mentioned above. For larger fistulas, a suprapubic tube for diversion is probably prudent. The mobilization of flaps, such as the tunica dartos flap, may be necessary to secure adequate tissue interposition and avoidance of superimposed suture lines.

Fistulas associated with inflammatory strictures occur as periurethral tracts and develop secondary to high-pressure voiding of infected urine. As multiple tracts develop, this problem becomes what is known as a "watering pot perineum." Repair requires suprapubic drainage, and treatment of the infection requires incision and drainage of any abscesses present. We widely excise the fistula tracts and associated inflammatory tissue and wait 4 to 6 months before repairing the underlying stricture. Flap reconstruction, if donor tissues are available, may be used. However, a staged graft procedure (discussed later) is also an excellent choice. One must be cautious in the patient with urethral fistulas but without a chronic history of obstructive voiding symptoms. In many cases, fistula or periurethral abscess may be the hallmark symptom of urethral carcinoma.

Urethral Diverticulum

A congenital diverticulum is a transitional cell epithelium-lined pouch that is the result of either a distention of a segment of the urethra or the attachment of a structure to the urethra by a narrow neck (i.e., a müllerian remnant). **In males, a congenital anterior urethral diverticulum may result from incomplete development of the urethra,** with a defect in only the ventral wall and subsequent distention of this segment by the hydraulic force of the voiding stream (Valdivia et al, 1986; Bedos and Cibert, 1989; Ozgok et al, 1994). Furthermore, the downstream lip of the defect may serve as a valvular obstruction, increasing the pressure in the lumen and subsequently the diverticulum enlarges. **Another possible etiology is injury of the urethra that may cause an intraspongiosal hematoma.** This could create a paraurethral space and subsequent diverticulum or defects (fistula or diverticulum). These can also be associated with urethral strictures (Bryden and Gough, 1999). It has also been suggested that congenital diverticula may represent giant cystic dilation of Cowper ducts (Gil-Vernet, 1977; Jiminez Cruz and Rioja Sanz, 1993). We do not favor this proposed suggested etiology because the diverticula seem to be slightly more distal than the expected location of Cowper ducts, and in our experience with reconstruction of a considerable number of these diverticula, no proximal limb of the ducts seems to exist in them. In many cases, endoscopic unroofing

of the diverticulum remedies the voiding symptoms; although, after unroofing it is not uncommon for the patient to note postvoid dribbling. Open repair essentially excises the redundancy of the urethra associated with the diverticulum. If the lumen is comprised, then dorsal onlay by either graft or flap can be useful.

A congenital diverticulum in the prostatic urethra may be a large remnant of the müllerian duct associated with defects of diminished virilization. However, it often occurs in proximal hypospadias and represents an enlarged utricle (Devine et al, 1980). **These diverticula may not be demonstrated with voiding urethrography but are demonstrated with cystoscopy or retrograde urethrography.** The tip of a urethral catheter tends to catch in this opening, necessitating the use of something to direct the catheter tip toward the true lumen. Other than necessitating caution during evaluation, they do not usually cause problems or require treatment unless they are very large.

Large utricles can accumulate urine with voiding and then decompress after voiding. If they are large enough, the stasis of urine can be associated with recurrent urinary tract infection or difficult-to-manage "incontinence." A surgical approach to small lesions can be through a suprapubic incision, possibly opening the bladder to go through the center of the trigone. However, large diverticula can be approached trans-sacrally (Peña and Devries, 1982). Although this is a complex procedure, it seems to be associated with much less morbidity than an abdominal or a perineal approach and provides superior exposure. We excise the diverticulum after exposing and dissecting its communication with the urethra. After ensuring that there is no distal obstruction to interfere with healing, we close the urethra.

Diverticula of the female urethra are covered in Chapter 78.

Paraphimosis, Balanitis, and Phimosis

Paraphimosis, or painful swelling of the foreskin distal to a phimotic ring, occurs if the foreskin remains retracted for a prolonged time. Swelling is sufficient to make reduction of the foreskin over the glans difficult. **In the very young child, paraphimosis is often seen after the foreskin has been traumatically reduced during an examination, or sometimes by overzealous parental attempts at hygiene.** It serves to say that traumatic, sudden reduction of a tight foreskin should be avoided in all ages and circumstances. To reduce a paraphimosis, gentle steady pressure must be applied to the foreskin to decrease the swelling. Especially with a child, this is best accomplished in a quiet room by a parent squeezing it in the hand. Elastic wrap may be helpful in some cases. Putting an ice pack on the area for a short time before gentle compression helps, not with the swelling but as an analgesic. When the swelling has been reduced, the surgeon can push against the glans with the thumbs, pulling on the foreskin with the fingers. Because paraphimosis tends to recur, a dorsal slit at a minimum or a circumcision should be carried out as an elective procedure at a later date. An occasional patient presents with acute paraphimosis that has been present for many hours to days. This is typically seen in an adolescent who is reluctant to reveal the problem to his parents. In these cases, reduction may be impossible and should be dealt with by emergency dorsal slit or circumcision. Considerable postoperative edema is the rule in these cases.

Balanitis, or inflammation of the glans, can occur as a result of poor hygiene, from failure to retract and clean under the foreskin. The subsequent swelling makes cleaning more difficult, but the inflammation usually responds to local care and antibiotic ointment. Oral antibiotic therapy may occasionally be necessary. Balanoposthitis is a severe balanitis and occurs when the phimotic band is tight enough to retain inflammatory secretions, creating what amounts to a preputial cavity abscess. On occasion, an emergent dorsal slit is required.

Phimosis, or the inability to retract the foreskin, can result from repeated episodes of balanitis. In older patients, balanitis may be a presenting sign of diabetes**.** In these cases, circumcision may be warranted.

Urethral Meatal Stenosis

A small urethral meatus in the newborn will probably not be called to a urologist's attention unless the stenosis is associated with other congenital deformities (e.g., hypospadias) or causes voiding difficulties or urinary tract infection (Allen and Summers, 1974). If the urethral meatus of a boy appears exceptionally narrow and there are associated symptoms, a meatotomy should be considered. For this decision to be made, voiding should be observed to note that the meatus opens as a full, forceful stream is passed. If the stream is narrow and excessively forceful, stenosis is probably present. The occluding skin is generally a thin layer that can sometimes be seen to pouch out, with the meatus opening at the dorsal lip as the child voids. **Meatal stenosis in a boy appears to be a consequence of circumcision that then allows subsequent ammoniacal meatitis.** If the child is seen with ammoniacal meatitis, we usually start meatal dilation with 0.05% clobetasol cream. Within a week, the process seems to settle down. Anecdotally, the fusion of the ventral-meatal skin that causes meatal stenosis can be avoided. Parents must be counseled about the cause, that is, a wet diaper pressing for prolonged periods against the tip of the glans.

A ventral urethral meatotomy can at times be accomplished with the use of local anesthesia. In the young child, general anesthesia is the preferred approach, avoiding trauma to the child, the parents, and the urologist. It is important to insert the anesthetic needle into the skin fold from the underside, so that the tip of the needle can be observed and controlled. If insertion is done from the outside, the needle will pass through both layers of the fold, and a wheal cannot be raised because of leakage of the anesthetic solution. After the meatotomy, the edges of the cut will seal together unless they are kept open. The tip of a meatal dilator is the best instrument for this purpose. The child's parents are instructed to gently separate the edges with the tip of the dilator three times a day for 7 to 10 days. The surgeon should observe the parents carry out this procedure. Pediatric meatal dilators (see the later product reference) are available; however, the tip of an ophthalmic antibiotic tube also works well, and the antibiotic ointment can be used as the lubricant.

Meatal stenosis occurs in adults after inflammation, specific or nonspecific urethral infection, and trauma (especially in association with indwelling catheters, urethral instrumentation, or radical prostatectomy in some cases). It may also be the result of the failure of a previous hypospadias repair. To perform a ventral meatotomy in a normally developed penis in adolescents and adults, it is often necessary to place sutures to approximate the urethral mucosal edge to control bleeding. This step usually requires three sutures: one at the apex and one on either side. We have found a dilator made by Cook Urological* to be helpful in

*Cook Urological, PO Box 227, Spencer, IN 47460; 800-457-4448. Catalog No. 073406, adult 6 to 34 French; No. 073403, pediatric 6 to 10 French.

keeping the meatus open. In some cases, it may be necessary to perform a dorsal rather than a ventral meatotomy. This can be accomplished as a Y-V-plasty after the excision of any scarred ridge of neourethra. Dorsal meatotomy, although effective in opening the meatus, often creates a cosmetically less-than-optimal shape of the meatus. In the adult, it is unusual for the meatal stenosis to be an isolated finding. The stricture process usually involves the fossa navicularis to some extent as well.

Circumcision

Controversy continues about whether neonatal circumcision should or should not be performed (Poland, 1990; Schoen, 1990). Much attention has been focused on this issue, but despite this, many little boys in the United States are circumcised. Ritual circumcision will continue; however, in ritual circumcision, it is not necessary to remove the skin but only to draw blood. **It is important not to circumcise any boy with a penile abnormality (e.g., hypospadias, chordee) that may require the foreskin during repair. An indication for circumcision in the young boy presents when the child has had recurrent urinary tract infections thought to be associated with the redundant preputial skin.**

Most circumcisions performed just after birth are done with the Gomco clamp or one of the plastic disposable devices made for this purpose. Care should be taken to free the foreskin from the glans completely and to apply appropriate tension when the foreskin is pulled into the clamp. To prevent either a too generous or an inadequate circumcision, we find it useful to carefully mark the foreskin so that the correct level is ascertained. At this center, we do neonatal circumcision with a penile block for anesthesia.

The most common complication is bleeding due to inadequate control with vascular compression. Application of an epinephrine-soaked sponge may help in controlling a minimal ooze. Infection can also occur and responds to local care. Any resulting skin separation should be repaired after the inflammation resolves. Sometimes, too much skin is removed, or the urethra is included in the clamp, resulting in a fistula. In many if not most cases in which excess skin is removed, closure can still be accomplished with aggressive frenuloplasty along with remaining skin closure by transposition of the remaining skin. If the entire penis is "scalped," it may be best managed with a split-thickness skin graft or with reapplication of the excised foreskin, after it is prepared properly as a graft. In complicated cases, burying the penis in the scrotum and repairing it at a later date may be prudent. **Monopolar electrocautery should be avoided in a neonatal circumcision, because penile loss from the field distribution of the current can occur. The use of monopolar cautery with a Gomco or similar clamping device must be avoided, because devastating loss of tissue can occur.**

At present, whether a newborn who has lost his penis because of a circumcision mishap should be gender reassigned is under review by the North American Task Force on Intersexuality (Oesterling et al, 1987; Gearhart and Rock, 1989). Our experience with phallic construction now includes a number of children and youths who had been converted to a female after a circumcision accident. As they passed through puberty, they realized that this sexual assignment was wrong. We believe that with the present knowledge of reconstructive techniques, the matter is not clear, one way or the other. However, most of these boys could undergo reconstruction in such a manner as to preserve reproductive function.

In adults, circumcision can be done with local anesthesia, by blocking the dorsal nerves at the base of the penis and circumferentially infiltrating the superficial layers of the penile base. In men and older boys, we favor a sleeve circumcision. With the foreskin in its retracted position, a marking pen outlines an incision, leaving a small preputial cuff. This mark should go straight across the base of the frenulum. This incision is made and carried through the dartos fascia to the superficial lamina of the Buck fascia. The foreskin is reduced, and a second incision is marked, following the outlines of the coronal margin and the V of the frenulum on the ventral side. The frenulum usually retracts into a V. In some cases, the frenulum can be lengthened by closing the edges of the V in a longitudinal orientation for a short length (frenuloplasty). If frenuloplasty is done, the proximal incision does not need to follow the V of the retracted frenulum because the ventral skin is straight. We make the skin incision and fulgurate bleeding vessels with bipolar cautery as the incision is deepened and the skin edge mobilized. In older boys and adults, the vessels are more substantial and not easily sealed by compression, no matter how vigorous. Thus circumcision clamps can be ineffective and are not recommended even though larger sizes are available. After the sleeve of preputial skin has been removed, hemostasis is obtained and the skin edges are reapproximated.

In smaller boys, some may consider this sleeve procedure to be tedious and difficult. If this is the case, after the skin is marked, a dorsal slit is made through both layers of the prepuce back to the level of the corona. Following the marks, the two layers of the preputial skin are incised. Bleeders are controlled, and the skin edges are reapproximated.

Complications should be uncommon. Most patients develop some hyperesthesia of the glans, which resolves. A hematoma is probably the most common immediate complication. Some patients notice minor cosmetic imperfections that are functionally insignificant. One of the most distressing problems we see, however, is a patient who complains that the surgeon has removed too much skin. To avoid this unfortunate occurrence, a circumcision should be done precisely, and, whatever the procedure to be carried out, the incisions should first be marked with the skin lying undistorted on the shaft. Adults requesting circumcision must be carefully evaluated from a psychosexual standpoint because many of these patients, who are the most persistent in requesting circumcision, become the most dissatisfied after the surgery.

Circumcision has been shown now in numerous studies to provide protection for men in areas where HIV is very prevalent (Tobian et al, 2009).

Failed Hypospadias Repair

In treating a patient in whom hypospadias repair has failed, it is important to obtain all available records to help determine what may have contributed to his complications. **A hypospadias repair may fail because of an inadequate correction of chordee or an inadequate urethra, with a stricture, fistula, or diverticulum** (Winslow et al, 1986). **Many times, it is readily apparent from the records that not all aspects of the hypospadias deformity** (i.e., ventrally displaced meatus, ventral chordee, and some expression of inadequacy of ventral tissue fusion) **were addressed in the previous repairs.** Adults with urethral strictures are often seen who have had hypospadias surgery as children. Depending on the age of the patient and the preference of the treating urologist, a variety of

different techniques may have been used to repair the original hypospadias. Many of these patients have persistent chordee and a subcoronal meatus. Adults have also been seen who have had long-standing evidence of urethral fistula. In addition, some patients may have clinical findings not related to hypospadias that should have been recognized previously, especially when hypospadias is part of an overlying intersex problem. In years past, problems associated with previous failures have been caused by errors in design, technique, or postoperative care (Devine et al, 1978). **With more modern techniques available and with most hypospadias treated by surgeons with considerable experience, failures seem to be associated with perioperative infections or other factors that adversely affect wound healing.** Complex hypospadias repair failures are currently encountered with much less frequency, and most that are encountered are in patients who had previous procedures more than 15 to 20 years ago. Truly, their complications resulted not from poorly designed surgery at the time but rather from the "state of the art" at the time.

Evaluation of a failed hypospadias repair includes retrograde urethrography, voiding cystourethrography, and cystoscopy. In an older patient, a reliable preoperative assessment of residual chordee can be made on the basis of the history and photographs taken at home. In younger patients, complete evaluation of more complex situations with use of anesthesia may be necessary.

In the adult patient, a detailed discussion must occur regarding the positive and negative aspects of the various approaches. Patients who were initially operated on before the late 1970s probably underwent either a graft or some form of repair using almost exclusively ventral tissue. Some of these patients still have the remnants of a dorsal hood or enough dorsal skin for a dorsal transverse penile skin island type of reconstruction to be performed.

We believe that surgical correction of complex cases requires an aggressive approach by the surgeon (Secrest et al, 1993). However, with the advent and very common usage of the tubed incised plate repair, initially described by Snodgrass (1999), the nature of failures is different and the approaches also remarkably different. It is the authors' observation that the number of failed surgeries is less, the nature of graft salvage techniques is remarkably different, and the method of addressing residual curvature is also different. It is possible to reincise the "urethral plate" and tabularize it if the plate is not scarred, possible to graft the plate dorsally if it is, and, if the tissues are badly scarred, then the tendency to revert to staged reconstruction has now been adopted by many surgeons (Snodgrass et al, 2009). Certainly, the use of flaps has a place in corrective procedures, and the excision of scarred tissues causing residual curvature, likewise its place. However, the procedure of plication or corporoplasty techniques for correction of residual curvature has, for the most part, become the standard of care. Certainly graft techniques for correction of curvature are used, but with far less frequency than in years past.

Residual Genital Abnormality in Patients with Closed or Diverted Exstrophy

General

Residual genital defects in men who have had exstrophy repaired as children can cause functional, aesthetic, and psychologic problems. The effects of these problems are compounded in men who have undergone urinary diversion and who must wear stomal appliances, although with the improvement of continent diversions, this is less of a factor. Except in the most severe forms of bladder exstrophy or cloacal exstrophy—when the penis or the halves of the bifid penis are truly inadequate—successful reconstruction is possible. Even then, if normal testes are present, the success of newer techniques of phallic construction (see subsequent discussion) should lend support to considerating the option of raising such a child as a boy, possibly preserving his reproductive potential through puberty. In these very difficult cases, we think that the parents must be presented with both options, gender reassignment versus eventual phalloplasty. Remarkable progress has been made in the treatment of difficult cases (Johnston, 1975; Hendren, 1979; Jeffs, 1979; Snyder, 1990; Perovic et al, 1992; Gearhart et al, 1994; Mitchell and Bagli, 1996), as well as in techniques of primary closure. However, many patients need further genital surgery, because they experience the hypertrophic growth spurt of the penis associated with puberty.

The goals of reconstructive surgery in male patients with exstrophy or epispadias are to produce a dangling penis with erectile bodies of satisfactory length and shape to allow sexual function and to construct a urethra that serves as a conduit for the passage of urine and ejaculate. However, experience has shown that in the diverted exstrophy patient with only a bladder remnant, construction of a urethra that is essentially defunctionalized is difficult. These urethras all eventually seem to fibrose and stenose. The bladder neck remnant thus becomes a cyst that is often colonized. Bouts of virulent epididymitis or the formation of what is really a bladder neck remnant abscess begin to occur. We have now seen two patients who developed carcinoma of the prostate in a bladder neck remnant. The diagnosis in these patients was difficult and the resultant surgery even more difficult. Neither patient did well from the standpoint of treatment of the carcinoma. Both were seen before the aggressive use and better understanding of prostate-specific antigen.

Many patients who have undergone surgery as children do not present for correction of inadequacies of the external genitalia until after they have completed puberty and realize that their situation has not improved and is not likely to improve. Some have been in sexual situations and have encountered problems. We employ a systematic approach to accomplishing the reconstruction necessary to correct the anatomic defects in these patients (Devine et al, 1980; Winslow et al, 1988). Surgery is undertaken in a sequential fashion beginning with the simplest procedure that will achieve the desired functional result.

Lower abdominal wall scarring can be corrected or defects can be closed by fashioning peripenile flaps that are shaped like a W (see Fig. 36–19). In many patients, there may be wide diastasis recti that is really a ventral hernia. Anchoring of meshes or Gore-Tex can be difficult, and in several cases we have resorted to a fibular bone microvascular free transfer to reconstruct the continuity of the pubis, allowing effective closure of the abdominal hernia.

Surgical Technique

The adult reconstructive surgeon's place, now, with the more effective primary closures, is in the correction of hernia as mentioned above or in the patient who has an inadequate penis either due to the deformity, scarring from multiple surgeries, or has had prior gender reassignment yet recognizes and chooses their male gender.

Key Points: Selected Processes

- Urethral hemangioma is a rare condition and usually persistent. It can offer a significant challenge to the surgeon. All reported cases of urethral hemangioma have been benign, and management depends on the size and location of the lesion.
- Reiter syndrome is characterized by a classic triad of arthritis, conjunctivitis, and urethritis. Urethral involvement is usually mild, self-limited, and a minor portion of the disease.
- Lichen sclerosus was referred to in the past as balanitis xerotica obliterans. Diagnosis is made through biopsy. Lichen sclerosus is thought to be possibly premalignant for the development of squamous cell carcinoma of the glans. It is the most common cause of meatal stenosis. Management of patients with lichen sclerosus–related stricture is complex, and results to date are less than optimal. The management is determined by the desire of the patient and the need for functional reconstruction.
- Amyloidosis is a rare disease of the urethra and should be considered in the evaluation of any patient with a urethral mass. Patients present with hematuria, dysuria, or urethral obstruction.
- A urethrocutaneous fistula is a tract lined with epithelium that leads from the urethra to the skin. It may be a complication of urethral surgery or develop secondary to periurethral infection associated with inflammatory strictures or treatment of a urethral growth. Treatment of the urethral fistula must be directed not only to the defect but also to the underlying process that led to its development.
- A congenital urethral diverticulum is a transitional cell epithelium-lined pouch that is the result of either a distention of a segment of the urethra or the attachment of a structure to the urethra by a narrow neck. In males, "congenital" anterior urethral diverticulum may result from incomplete development of the urethra or may possibly be the result of straddle trauma that led to an intracorporeal spongiosal hematoma. Congenital diverticulum in the prostatic urethra is a remnant of the müllerian duct.
- Paraphimosis is a painful swelling of the foreskin distal to a phimotic ring. It occurs when the foreskin has been retracted and not reduced. Edema then forms in the distal skin.
- Urethral meatal stenosis in the young boy appears to be a consequence of circumcision. The circumcision allows the development of ammoniacal meatitis, which then can heal with a membrane across the ventral portion of the meatus. Controversy continues about whether neonatal circumcision should or should not be performed. If it is going to be performed, an adequate circumcision needs to be done. The most common complication of neonatal circumcision, in the authors' opinion, is the fact that it is inadequately done.
- A patient with failed hypospadias repair can be complex. Many are victims of the technology of the time when they had their initial reconstruction. When the urethra is involved, all should be evaluated as if they have urethral stricture disease.
- Advanced techniques for the reconstruction of exstrophy-epispadias complex have led to much better functional results and less need for secondary exstrophy reconstruction. Secondary exstrophy reconstruction is aimed at the area of the escutcheon, the dorsal base of the penis, the penile shaft, the urethra, and the penoscrotal junction.

TRAUMA TO THE GENITALIA

This topic is primarily covered in Chapter 88, but an additional description is also included in the electronic version of this chapter. Please see the Expert Consult website for this section, as well as Fig. 36–15.

URETHRAL STRICTURE DISEASE

The term *urethral stricture* refers to anterior urethral disease, or a scarring process involving the spongy erectile tissue of the corpus spongiosum (spongiofibrosis) (Fig. 36–16). The spongy erectile tissue of the corpus spongiosum underlies the urethral epithelium, and, in some cases, the scarring process extends through the tissues of the corpus spongiosum and into adjacent tissues. **Contraction of this scar reduces the urethral lumen.** For example, if a normal urethra measures 30 French, its diameter is 10 mm and the area of the lumen is approximately 78 mm^2. If scarring has resulted in a urethra that measures 15 French, the lumen is only 55 mm^2, or 29% reduced. It is therefore evident that scar contraction caused by anterior urethral stricture disease can, for a while, be asymptomatic, but because the lumen is further reduced can be associated with marked voiding symptoms.

In contrast, posterior urethral "strictures" are not included in the common definition of urethral stricture. Posterior urethral stricture is an obliterative process in the posterior urethra that has resulted in fibrosis and is generally the effect of distraction in that area caused by either trauma or radical prostatectomy. Although the distraction defect can be lengthy in some cases, the actual process involving the tissues of the urethra is usually confined. By consensus of the World Health Organization conference, the term *stricture* is limited to the anterior urethra. Distraction defects are those processes of the membranous urethra associated with pelvic fracture. Other narrowings of the posterior urethra are termed urethral contractures or stenoses (Bhargava et al, 2004).

Urethral Anatomy

Although urethral anatomy is described in the earlier section on anatomy, it is useful to re-emphasize key anatomic points. **The bulbous urethra is eccentrically placed in relation to the corpus spongiosum and is much closer to the dorsum of the penile structures** (see Fig. 36–6). As one moves distally, the pendulous or penile urethra becomes more centrally placed within the corpus spongiosum.

The genital skin has a dual (proximal and distal) and bilateral blood supply, forming a fasciocutaneous system (see Fig. 36–10). **The corpus spongiosum receives blood from the common penile artery, the terminal branch of the internal pudendal artery** (see Fig. 36–12). **The corpus spongiosum also has a dual blood supply—a proximal blood supply and a retrograde blood supply through the dorsal arteries as they arborize in the glans penis.**

Etiology

Any process that injures the urethral epithelium or the underlying corpus spongiosum to the point that healing results in a scar can cause an anterior urethral stricture. Today, most urethral strictures are the result of trauma (usually straddle trauma). This trauma to the urethra often goes

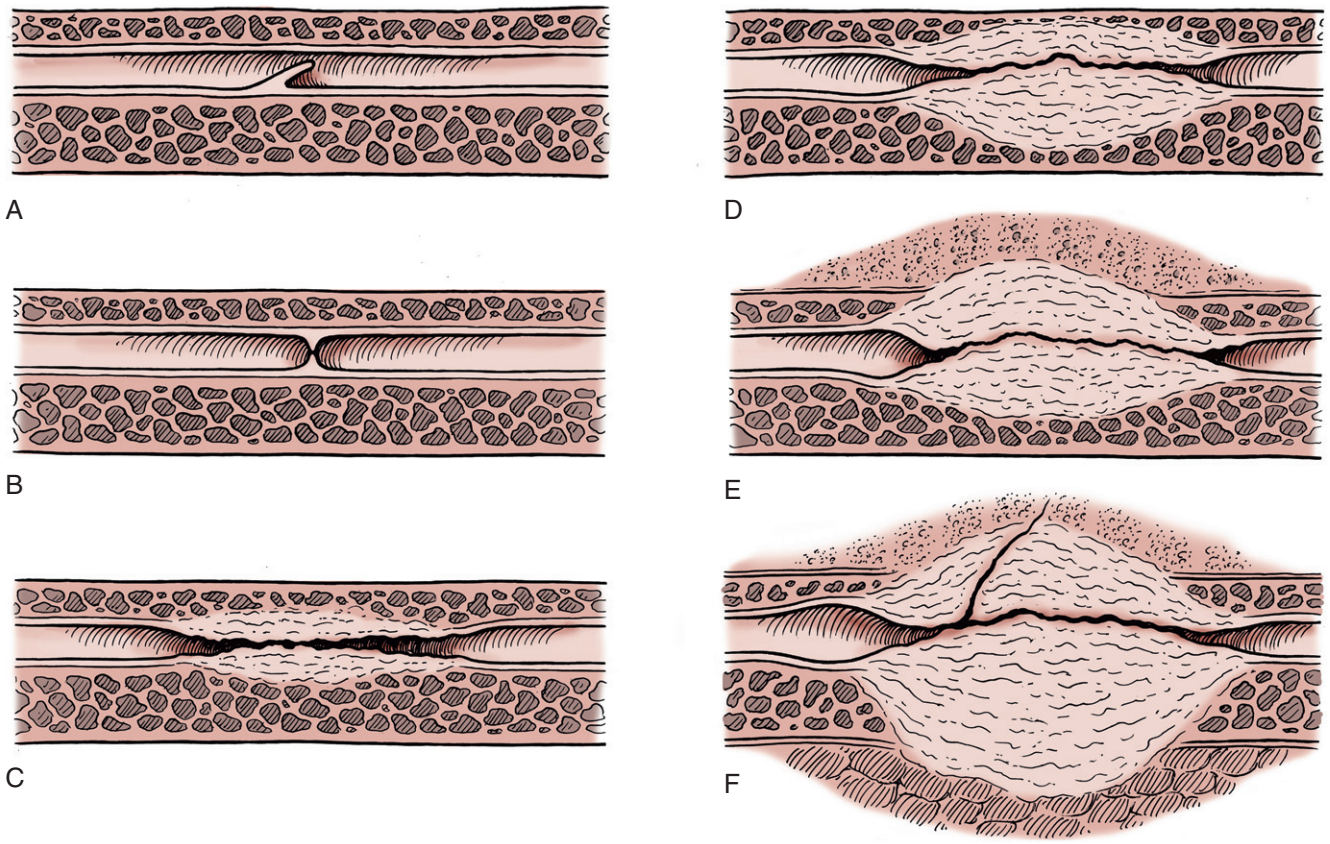


Figure 36–16. The anatomy of anterior urethral strictures includes, in most cases, underlying spongiofibrosis. **A,** Mucosal fold. **B,** Iris constriction. **C,** Full-thickness involvement with minimal fibrosis in the spongy tissue. **D,** Full-thickness spongiofibrosis. **E,** Inflammation and fibrosis involving tissues outside the corpus spongiosum. **F,** Complex stricture complicated by a fistula. This can proceed to the formation of an abscess, or the fistula may open to the skin or the rectum. (**A** to **F,** From Jordan GH. Management of anterior urethral stricture disease. Probl Urol 1987;1:199–225.)

unrecognized until the patient presents with voiding symptoms resulting from the obstruction of the stricture or scar. In most straddle trauma, the injury to the bulbous urethra is readily reconstructable (Park and McAninch, 2004). Unfortunately, iatrogenic trauma to the urethra still exists, but with the development of small endoscopes and the limitation of indications for cystoscopy in boys, we see fewer iatrogenic strictures today than in the past. The place of idiopathic urethrorrhagia with regard to strictures in children is not clear; some question whether it may be a cause of strictures in young boys irrespective of the child's having undergone an endoscopic procedure (Rourke et al, 2003). To date, no specific inciting factor has been identified as causing idiopathic urethrorrhagia. We appear to have histologic results from a patient with resolving urethrorrhagia that shows portions of tissues covered in part by squamous epithelium; other parts are covered by transitional epithelium; there are several areas of denuded epithelium with acute hemorrhage and neutrophilic infiltration; a few foci of microcalcification were shown; several mucus glands were found within the submucosal connective tissue and a few collections of amorphous material, likely mucin. These areas stain negatively, however, with a special stain for amyloid. There is no evidence of viral cytopathic effect or malignancy. Thus, what is not seen is evidence of bacterial infection, viral inclusions, and so on. We are, however, seeing an increase in strictures associated with lichen sclerosus, and those strictures clearly behave much more like inflammatory strictures than traumatically induced isolated scars. Finally, posterior urethral injuries, traumatic by definition, result in obliterative or near-obliterative defects that are associated with extensive fibrosis interposed between the distracted ends of the urethra.

On the other hand, inflammatory strictures associated with gonorrhea were the most commonly seen in the past and are less common now. With the advent of prompt and effective antibiotic treatment, gonococcal urethritis now progresses less often to gonococcal urethral strictures. The place of *Chlamydia* and *Ureaplasma urealyticum* (i.e., nonspecific urethritis) in the development of anterior urethral strictures is not clear. To date, no clear association between nonspecific urethritis and the development of anterior urethral stricture has been established.

There is, as mentioned earlier, a definite association between the development of an inflammatory stricture and lichen sclerosus–balanitis xerotica obliterans (LS-BXO). LS-BXO usually begins with inflammation of the glans and inevitably causes meatal stenosis, if not a true stricture of the fossa navicularis. The cause of this distal penile skin and urethral inflammation is not known. Literature suggests the possibility that bacterial infection is the cause of the resultant skin changes. There is some evidence to suggest that the progression of the stricture eventually to involve the anterior urethra extensively may be due to high-pressure voiding that causes intravasation of urine into the glands of Littre, inflammation of these glands, and, perhaps, microabscesses and deep spongiofibrosis. Whether the urethral changes and eventual fibrosis are also related to bacterial injury has not, to our knowledge, been well defined. Although the use of antibiotics seems, in these

patients, to limit obstructive voiding symptoms, to our knowledge the literature does not show resolution of the stricture process with the use of antibiotics.

What is known as a congenital stricture is an entity that is difficult to understand. If, in embryologic development, a stricture is found at a natural place where a fusion of structures occurs (i.e., the posterior and anterior urethra), a congenital stricture might be a reasonable assumption**.** However, the term *congenital stricture* is used by some to define a stricture for which there is no identifiable cause. We propose, however, that it is reasonable to define a stricture as congenital only if it is not an inflammatory stricture, it is a short-length stricture, and it is not associated with a history of or potential for urethral trauma. This then limits the term *congenital stricture* to strictures of the anterior urethra found in infants before they attempt erect ambulation. So defined, congenital strictures will clearly be the rarest encountered.

Diagnosis and Evaluation

Patients who have urethral strictures most often present with obstructive voiding symptoms or urinary tract infections such as prostatitis and epididymitis. Some patients also present with urinary retention. However, on close inquiry, most of these patients are found to have tolerated notable voiding obstructive symptoms for a long time before progressing to complete obstruction.

Not uncommonly, when a patient cannot void, an attempt is made to pass a urethral catheter. If the catheter does not pass, the nature of the obstruction is determined by dynamic retrograde urethrography. Thus, most cases are managed with acute dilation, and clearly there are many instances in which this is not the best course for the patient. When there is doubt, we determine the nature of the stricture when possible, and selectively place a suprapubic cystostomy catheter to treat the acute situation and allow time for a more appropriate treatment plan to be devised. The practice of blind passage of filiforms and blind dilation without knowledge of the anatomy of the urethral stricture is condemned. Although detailed imaging is not always available, flexible endoscopy is almost universally available in the United States. At the least, the stricture can be visualized and attempted guide wire placement under direct vision is attempted.

For an appropriate treatment plan to be devised, it is important to determine the location, length, depth, and density of the stricture (spongiofibrosis). The length and location of the stricture can be determined with radiography, urethroscopy, and ultrasonography. The depth and density of the scar in the spongy tissue can be deduced from the physical examination, the appearance of the urethra in contrast-enhanced studies, and the amount of elasticity noted on urethroscopy. The depth and density of fibrosis are difficult to determine objectively. The absolute length of spongiofibrosis may not be evident on ultrasound evaluation. **Ultrasound examination clearly can augment contrast-enhanced studies and is accurate in determining the length of narrow-caliber annularity** (Morey and McAninch, 1996a). Contrast studies of the urethra are best carried out by or under the direct supervision of the surgeon responsible for treatment of the patient.

In 1979, McCallum and Colapinto described the use of dynamic radiographic studies and emphasized the need for these studies to be dynamic as opposed to static (Fig. 36–17) (McCallum and Colapinto, 1979a, 1979b). At our center, imaging includes dynamic studies that are accomplished during retrograde injection of contrast material and while the patient is voiding. Even with gentle technique, extravasation during retrograde urethrography is possible in patients in whom the urethra is markedly inflamed. For this reason, contrast studies should be carried out with contrast material that is suitable for intravenous injection and used either directly from the bottle or diluted according to the manufacturers' guidelines. Contrast materials that have been thickened with lubricating jelly or anesthetic gels can be a source of problems, and offer little with regard to enhancement of radiographic studies, nor do they make the studies more comfortable. Real-time ultrasound evaluation of the urethra after it has been filled with a lubricating jelly or saline has been described by Morey and McAninch (1996a, 1996b). It is a misconception, however, that ultrasonography always directly visualizes the spongiofibrosis. However, Morey and McAninch (1996a, 1996b) believe that ultrasonography of the bulbous urethra possibly more accurately determines the length of the stricture, which could be important in considering an anastomotic repair. If the patient is not in steep lateral oblique position for retrograde urethrography, the length of the stricture will be underestimated. Finally, it should be understood that during contrast-enhanced urethrography, more than one projection may be necessary to visualize the stricture. Magnetic resonance is also being explored as an adjunct to the evaluation of urethral stricture, as well as pelvic fracture urethral injuries. In our experience, the use of magnetic resonance for routine strictures or pelvic fracture urethral distraction defects is not routinely beneficial. In the case of urethral tumors, we have found magnetic resonance to be invaluable. The experience of others is commensurate with ours (Pavlica et al, 2003). In the occasional pelvic fracture urethral distraction defect, the alignment of the two urethral ends can be nicely defined.

Endoscopic examination may be necessary after the contrast studies. The flexible cystoscope has simplified this evaluation, and when local anesthesia is used, there is little discomfort associated with it. The scope can be passed to the stricture, and many times it is not necessary to pass it beyond that level. In addition, it is not always necessary, and usually not beneficial, to dilate the stricture at the time of the initial endoscopic evaluation. Pediatric endoscopic equipment has proved to be extremely valuable for examination of the urethra proximal to a narrow-caliber area without the need to dilate the narrowest area. In the patient who cannot void and has a suprapubic tube, combined contrast studies with endoscopy are helpful in defining the stricture anatomy (Fig. 36–18).

It is imperative, however, to completely evaluate the urethra proximal and distal to the stricture with endoscopy and bougienage during surgery to ensure that all the involved urethra is included in the reconstruction. Whereas hydraulic pressure generated by voiding may keep segments proximal to the stricture patent, unless these segments are included in the repair, they are at risk for contraction after obstruction of the narrow-caliber segment is relieved with reconstruction. For this reason, any abnormal areas of the urethra that are proximal to a narrow-caliber segment of the stricture must be treated with suspicion. If the lumen does not appear to demonstrate evidence of diminished compliance, we presume that area to be uninvolved in active stricture disease. However, coning down of the urethra suggests its involvement in the scar.

In some patients, the urethra proximal to a narrow area may remain confusing with regard to its potential for continued constriction after reconstruction. In select patients, we have found it useful to place a suprapubic tube to defunctionalize the urethra. After 6 to 8 weeks, if there is to be

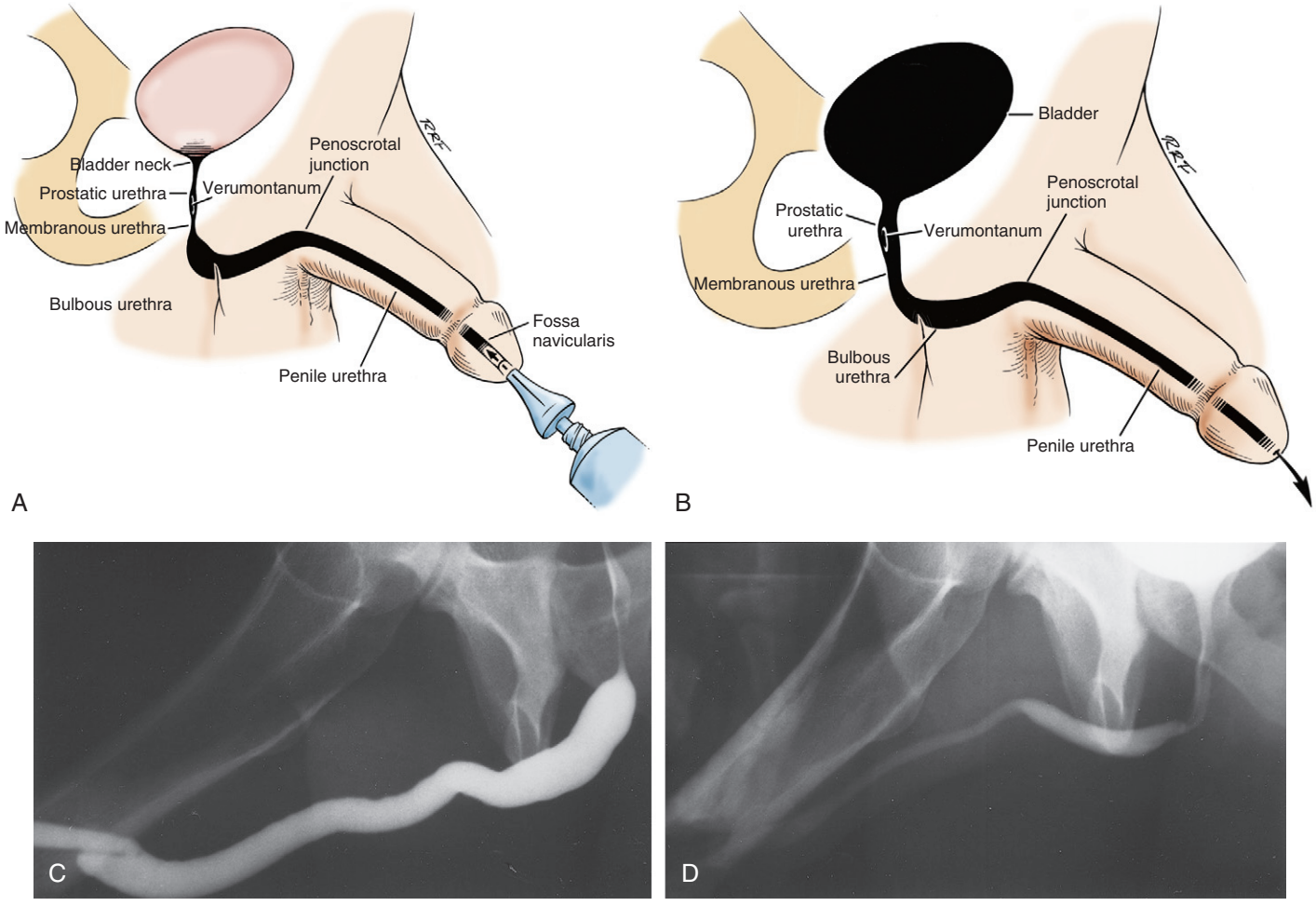


Figure 36–17. **A,** Representation of a dynamic retrograde urethrogram with the criteria of McCallum illustrated. **B,** Representation of a dynamic voiding urethrogram with the criteria of McCallum illustrated. **C,** A normal retrograde urethrogram. **D,** A normal voiding urethrogram. (**A** and **B,** Modified from McCallum RW. The adult male urethra. Radiol Clin North Am 1979;17:227–44.)

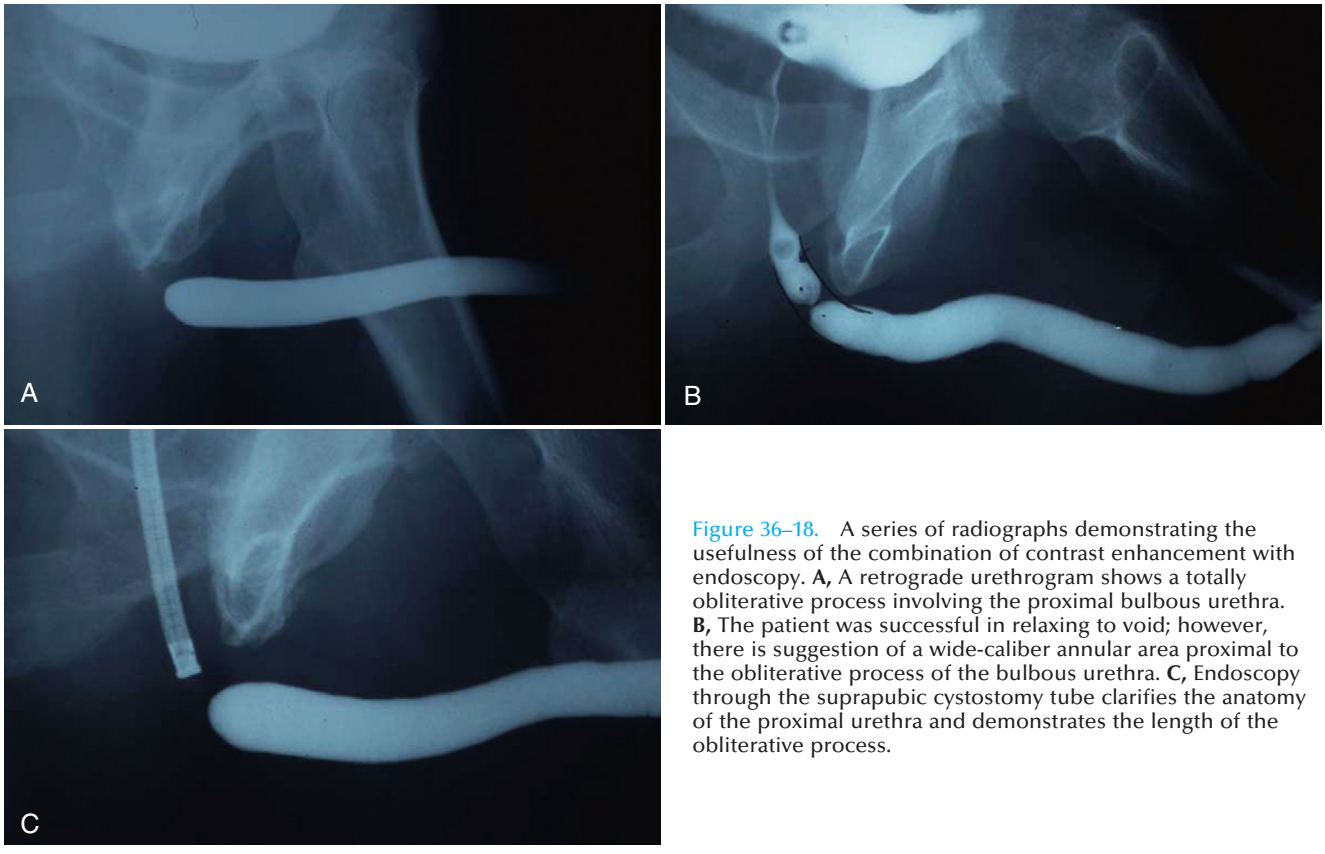


Figure 36–18. A series of radiographs demonstrating the usefulness of the combination of contrast enhancement with endoscopy. **A,** A retrograde urethrogram shows a totally obliterative process involving the proximal bulbous urethra. **B,** The patient was successful in relaxing to void; however, there is suggestion of a wide-caliber annular area proximal to the obliterative process of the bulbous urethra. **C,** Endoscopy through the suprapubic cystostomy tube clarifies the anatomy of the proximal urethra and demonstrates the length of the obliterative process.

constriction of an area that was hydrodilated with voiding, the tendency for that constriction to occur should become apparent.

Key Points: Urethral Stricture

- The term *urethral stricture* refers to anterior urethral disease and is a scarring process that involves the epithelium as well as the spongy erectile tissue of the corpus spongiosum. Contraction of the scar reduces the urethral lumen. In contrast, posterior urethral strictures are more correctly referred to as pelvic fracture urethral injuries; strictures of the prostatic urethra or bladder neck are properly referred to as contractures or stenoses.
- The anterior urethra is invested by the corpus spongiosum and as it proceeds proximally is eccentrically placed in relation to the corpus spongiosum. The genital skin has a dual and bilateral blood supply, forming a fasciocutaneous vascular system. The vascularity of the corpus spongiosum is based on the common penile artery.
- In general, most anterior urethral strictures are the result of trauma. Inflammatory strictures associated with gonorrhea are rarely seen; however, strictures associated with lichen sclerosus clearly behave like inflammatory strictures.
- Patients who have urethral strictures most often present with obstructive voiding symptoms or urinary tract infections such as prostatitis and epididymitis. Those patients who present with urinary retention, on close inquiry, have tolerated notable voiding obstructive symptoms for a long time.
- For an appropriate treatment plan to be devised, it is important to determine the length, location, depth, and density of the spongiofibrosis. This can be done with a combination of contrast-enhanced studies, endoscopy, and selective ultrasonography. It is imperative to completely evaluate the urethra proximal and distal to the stricture with endoscopy. A pediatric cystoscope is useful.

Treatment

Although the treatment of urethral stricture disease dates to the foundations of our specialty, significant progress made during the last 50 years allows many of the most complex strictures to be reliably reconstructed in one stage. In the past, a concept known as the reconstructive ladder was used as a treatment guideline for urethral strictures. That concept was based on the principle that the simplest procedure should always be attempted first, and sometimes repeated after failure, before moving on to more complex approaches. This approach is considered archaic in modern urethral reconstruction.

Both the patient and the physician must have a good understanding of the goal of treatment before the treatment choice is made. To this end, treatment options should be discussed with the patient, with care taken to emphasize the anticipated outcome with regard to potential cure. Some patients may prefer stricture management and choose to have periodic dilations in the office, at home, or in the hospital rather than undergo technically detailed open surgery. Others may have cure as a goal and choose surgical management. Many surgical procedures today have short- and midterm results approaching long-term success rates of more than 90% to 95% for many strictures.

Dilation

Urethral dilation is the oldest and simplest treatment of urethral stricture disease, and for the patient with an epithelial stricture without spongiofibrosis, it may be curative. **The goal of this treatment, a concept that is frequently forgotten, is to stretch the scar without producing more scarring.** If bleeding occurs during dilation, the stricture has been torn rather than stretched, possibly further injuring the involved area.

The least traumatic method to stretch the urethra is to use soft techniques over multiple treatment sessions. We believe that the safest method of urethral dilation currently available involves the use of urethral balloon-dilating catheters. These catheters may be attached to a filiform tip or passed over a guide wire or may come with an integral coudé tip. For initial dilation, we favor the use of balloons placed over wires that have been passed through the stricture under endoscopic control.

Dilation can be curative, and, in the literature, in correctly selected patients, has short and midterm efficacy rates equal to internal urethrotomy. Selection criteria will be discussed in the following section that discusses internal urethrotomy. The literature does not compare internal urethrotomy and dilation in randomized selection, thus we do not have a true comparison but rather comparison by retrospective analysis (Steenkamp et al, 1997).

Internal Urethrotomy

Internal urethrotomy refers to any procedure that opens the stricture by incising it transurethrally. The urethrotomy procedure involves incision through the scar to healthy tissue to allow the scar to expand (release of scar contracture) **and the lumen to heal enlarged.** The goal is for the resultant larger luminal caliber to be maintained after healing.

With epithelial apposition, wound healing occurs by primary intention. Internal urethrotomy does not provide an epithelial approximation but, rather, aims to separate the scarred epithelium so that the healing occurs by secondary intention. In healing by secondary intention, epithelialization progresses from the wound edges. As it progresses from the wound edge, epithelialization slows. In an effort to aid epithelialization, nature invokes the forces of wound contraction, not to be confused with scar contraction. Wound contraction closes the wound defect and limits the size of the area that requires epithelialization, hastening the healing of the surface defect. In the case of internal urethrotomy, however, wound contraction merely tries to reapproximate the edges of the scar, putting a race into effect. If epithelialization progresses completely before wound contraction significantly narrows the lumen, the internal urethrotomy may be a success. If wound contraction significantly narrows the lumen before completion of epithelialization, the stricture has recurred. The study by Dubey and colleagues (2005) shows the extent of luminal narrowing to be a predictor of success with internal urethrotomy: the narrower the percent of narrowing, the worse the outcome, with a cutoff of 74% narrowing.

Many surgeons have learned to perform internal urethrotomy by making a single incision at the 12-o'clock position. This location might be questioned, however, on the basis of the location of the urethra within the corpus spongiosum (see Fig. 36–25). On examination of a cross section of the corpus spongiosum, it can be seen that the thinnest portion of the anterior aspect is from 10-o'clock to 2-o'clock. The distance between the anterior wall of the urethra and the corpora cavernosa is likewise short in the bulbous urethra, and a single 12-o'clock cut could rapidly

penetrate the corpus spongiosum and extend into the triangular ligament; although it might not enter the corpora cavernosa, a deep cut could enter the intracrural space. Distally, although the anterior aspect of the corpus spongiosum is thicker, on the other hand, a deep incision in the more distal aspects of the anterior urethra will certainly enter the corpora cavernosa, and these incisions have been associated with erectile dysfunction thought to be due to local cavernosal veno-occlusive dysfunction. Vigorous incisions at 10-o'clock and 2-o'clock in the bulbous urethra risk the same problem. If deep spongiofibrosis is present, stricture cure is impossible by internal urethrotomy, and these deep incisions are therefore unnecessary.

The most common complication of internal urethrotomy is recurrence of stricture. Less commonly noted complications of internal urethrotomy include bleeding (almost always associated with erections immediately after the procedure) and extravasation of irrigation fluid into the perispongiosal tissues. These complications are rare today, however, because of the less frequent use of aggressive internal urethrotomy as a treatment modality for urethral strictures. Normal saline should be used as the irrigant when direct visual internal urethrotomy is performed. Additionally with the use of deep urethrotomy incisions, another complication can be creation of a fistula between the corpus spongiosum and the corpora cavernosa, and thus cavernosal veno-occlusive dysfunction.

A major problem with assessing the success rates of internal urethrotomy is that the nature of the strictures that have been treated with internal urethrotomy has been poorly reported. In addition, the literature is not clear regarding the goal of internal urethrotomy. For many, an internal urethrotomy is successful if it offers temporary relief. Therefore, in many cases, internal urethrotomy has been reported as successful despite the fact that it has been associated with eventual stricture recurrence. A report published by Santucci and McAninch (2001) (Rosen et al, 1994) using actuarial techniques shows the curative success rate of internal urethrotomy to be approximately 20%. Evaluations by Pansadoro and Emiliozzi (1996) and others show the curative success rate of direct visual internal urethrotomy to be approximately 30% to 35%. Their analysis also shows that there is virtually no increase in success rate with a second internal urethrotomy. **The data show that strictures at the bulbous urethra that are less than 1.5 cm in length and not associated with dense, deep spongiofibrosis (i.e., straddle injuries) can be managed with internal urethrotomy, with a 74% moderately long-term success rate.** Pansadoro's study did not have any long-term successes for treated strictures outside the bulbous urethra. The variables associated with success of internal urethrotomy have been verified by other studies (Heyns et al, 1998). A number of studies now show that the success of reconstruction is diminished by multiple prior urethral dilations and internal urethrotomy (Stone et al, 1983; Albers et al, 1996; Heyns et al, 1998; Boccon-Gibod, 2005). Success rates with internal urethrotomy are not equal to those of open urethral reconstruction (Mandhani et al, 2005). A number of analyses have sought to compare the cost effectiveness of the practice of internal urethrotomy initially prior to consideration of open reconstruction. The analyses all differ in method, and thus not surprisingly differ in findings (Rourke and Jordan, 2005; Wright et al, 2006; Wessells, 2009).

Several techniques have been employed to oppose the process of wound contraction and to prevent stricture recurrence. One method is to leave an indwelling Foley catheter for as long as 6 weeks after urethrotomy, in the hope that the urethra will mold around the catheter as it heals. Studies have shown, however, that the failure rate of long-term catheterization after internal urethrotomy is similar to that seen with 3 to 7 days of catheterization, and even 6 weeks is not sufficient time to oppose the forces of wound contraction.

Another technique used to oppose the forces of wound contraction after internal urethrotomy is home self-catheterization or home urethral obturation. After internal urethrotomy, patients generally have an indwelling catheter placed for a period of 3 to 5 days. When the catheter is removed, the patient is started on a urethral obturation regimen. Most regimens require more frequent catheterizations early in the recovery period, with a tapering schedule during the next 3 to 6 months. Anecdotally, many have reported an improved cure rate with self-catheterization in combination with internal urethrotomy. It has been our experience, however, that the stricture inevitably recurs when the patient stops self-obturation, regardless of how long it has been used. That being understood, this can effectively manage the problems when it is combined with a urethral dilating regimen in the properly motivated patient. Colchicine, because it binds tubulin, has been used along with internal urethrotomy (Carney et al, 2007). Initial findings in a nonrandomized study also suggest that, perhaps by pharmacologically blocking tubulin and thus possibly wound contracture, the results of internal urethrotomy may be better.

Urethral stents (removable or permanently implantable) are another modality used in opposing the forces of wound contraction after internal urethrotomy or dilation. Removable urethral stents are designed to prevent the process of epithelialization from incorporating the stent into the urethral wall and are left in place for as long as 6 months to 1 year before they are removed. The greatest experience with these removable stents comes from Israel (Yachia and Beyar, 1991), and centers there report good success in small series. The Memokath stent is currently being used in studies in the United States. It is a removable stent made of nitinol.

The majority of experience with permanently implantable stents comes from Europe and the United Kingdom. Milroy (1993) has reported a success rate of 84% at 4.5 years with use of the permanently implantable UroLume (Rousseau et al, 1987; Sigwart et al, 1987; Milroy et al, 1988, 1989; Sarramon et al, 1990; Ashken et al, 1991; Krah et al, 1992; Sneller and Bosch, 1992; Verhamme et al, 1993; Badlani et al, 1995; Milroy and Allen, 1996; Jordan, 1997; Tillem et al, 1997; Brandes and McAninch, 1998; Shah et al, 2003). The UroLume, made of an alloy, is designed to be incorporated into the wall of the urethra and corpus spongiosum. Available data show that the stent is best employed for relatively short strictures of the bulbous urethra associated with minimal spongiofibrosis. However, these are the strictures that are most successfully reconstructed with open techniques that offer better long-term success rates. The North American Study Group 11-year data have been published (Shah et al, 2003). Of 179 patients originally enrolled in the North American Study, 24 patients completed 11 years of follow-up. The overall success rate for all patients enrolled at 11 years is less than 30% (Shah et al, 2003). A 10-year follow-up study from the Netherlands (De Vocht et al, 2003) reported results thought to "weaken the optimistic early results"; of 15 patients implanted, only 2 were satisfied with their stent at 10 years.

Permanently implantable stents are associated with some unique complications. The stents must be **placed only in the bulbous urethra,** and when they are placed beyond the area of the scrotal urethra, placement has been associated with

pain on sitting and intercourse. Some patients (particularly young patients) **complain of perineal pain,** often with vigorous activity, even after implantation of the stent in the deep bulbous urethra. In addition, **longer, bulbous strictures require two stents that are overlapped.** These **stents can migrate** away from each other, leaving a gap between them where recurrence of stricture is inevitable. When this occurs, the stricture recurrence is excised and a third stent is placed to span the gap.

There are also **specific contraindications to the use of the UroLume.** Patients who have undergone **prior substitution urethral reconstruction,** particularly where skin has been incorporated into the urethra, have been shown to be poor candidates for implantation with the UroLume stent because contact of the stent with the skin is associated with a virulent hypertrophic reaction. These patients experience postvoid dribbling, and the hypertrophic reaction can be so severe in some cases that functional recurrence of the stricture results. Another subset of patients shown to be **poor candidates for the UroLume is those with strictures associated with deep spongiofibrosis.** Patients who fall into this category are **those who have had urethral distraction injuries and straddle injuries associated with deep fibrosis.** As of this writing, the UroLume is approved by the U.S. Food and Drug Administration. The product insert clearly contraindicates use of the UroLume in patients with pelvic fracture urethral distraction defects. Many greeted the arrival of the UroLume as a panacea. Experience is accumulating not only with use of the UroLume but also with misuse of the device, and its use should therefore be approached with the utmost caution. Some centers in Europe are now advocating use of the UroLume only in patients who are older than 50 years, or who have other significant medical problems that make the option of lengthy open urethral reconstruction less appealing. At our center, we have seen teenagers implanted, many patients implanted for pelvic fracture urethral distraction, patients with stents palpable on the shaft of the penis, and patients with both prostatic stents and urethral stents—all absolute contraindications. We have seen patients with as many as six stents in place, and although the maximal number of stents is not absolutely defined, if the first stent does not work, it is probably wise to refer the patient for reconstruction, which is possible with acceptable results (86% with mean follow-up of 25 months) (Barbagli et al, 1999). Placement of more stents, except when two stents were originally placed and then migrated from each other, is probably futile. However, in carefully selected elderly patients, the UroLume can be life changing for the patients, with minimal morbidity associated with the implantation procedure, in a situation where early and midterm success is adequate. The place of permanently implanted stents seems to be challenged as newer temporary/removable urethral stents are introduced.

Lasers

Types of lasers that have been used for the treatment of urethral stricture disease include carbon dioxide, argon, KTP, Nd:YAG, holmium:YAG, and excimer lasers. The ideal laser for use in the treatment of urethral stricture disease is one that totally vaporizes tissue, exhibits negligible peripheral tissue destruction, is not absorbed by water, and is easily propagated along a fiber. Although the carbon dioxide laser appears to be ideally suited, it must be used with a gas cystoscope, which carries the potential threat of a carbon dioxide embolus.

For both the argon and the Nd:YAG lasers, the predominant mode of action is thermal necrosis, which leads to a significant potential for peripheral tissue injury, rather than vaporization. The Nd:YAG laser has also been used with a bare fiber in the contact mode. A bare fiber carries with it a risk of forward scatter. When it is used in the contact mode, the YAG energy is transferred to a sapphire tip. Advocates of the use of a contact laser suggest that it obliterates the scar by vaporization; however, results with use of these fibers are no better than those with direct cold-knife visual internal urethrotomy.

A KTP laser is essentially an Nd:YAG laser that has passed through a KTP crystal, resulting in a reduced depth of penetration. A KTP laser urethrotomy is accomplished by passing the fiber over the scar tissue to make urethrotomy cuts. The holmium:YAG laser has properties similar to the KTP laser, and like the KTP laser, it provides both direct contact cutting and vaporization with minimal forward scatter. Experience with the holmium:YAG laser is accumulating; anecdotally, it may have a place in the management of some strictures, in particular strictures that are relatively isolated and short.

The excimer laser is a true vaporizing laser that has little forward scatter or peripheral tissue necrosis associated with it. Little experience with this laser has been reported, but future investigation is clearly warranted.

To date, the results of laser urethrotomy are mixed. With the advent of new lasers and experience with them, however, future data may show better results.

Open Reconstruction

Excision and Reanastomosis. **It has now been demonstrated with certainty that the most dependable technique of anterior urethral reconstruction is the complete excision of the area of fibrosis, with a primary reanastomosis of the normal ends of the anterior urethra** (Fig. 36–19) (Russell, 1914). The best results are achieved when **the following technical points are observed: the area of fibrosis is totally excised; the urethral anastomosis is widely spatulated, creating a large ovoid anastomosis; and the anastomosis is tension free.**

The **success of this procedure relies on vigorous mobilization of the corpus spongiosum.** With vigorous mobilization, dissection of Buck fascia to improve compliance, development of the intracrural space, and detachment of the bulbospongiosus from the perineal body, significant lengths of stricture can be excised and reanastomosed. Strictures of 1 to 2 cm are generally easily excised with reanastomosis. In some cases, strictures as long as 3 to 5 cm can be totally excised and a primary reanastomosis of the anterior urethra performed. For very proximal short-length bulbous strictures, tension-free anastomosis can be facilitated by the dissection of the membranous urethra (Fig. 36–20). As a rule, the closer the stricture is to the membranous urethra, the longer it can be and still be reconstructed with anastomotic techniques. For many proximal strictures, a single-layer anastomosis is preferable. When the length of stricture precludes total excision of fibrosis with primary anastomosis, tissue transfer is required. Morey published a series of patients who had stricture excision with anastomosis for strictures up to 5 cm. He makes the point that the younger patient has more compliant tissue, thus allowing the limits to be stretched (Morey and Kizer, 2006).

Morey also reported an interesting variant of excision with anastomosis for anterior stricture. In that case report, a patient had two independent areas of stricture apparently separated by totally normal urethra and corpus spongiosum. The authors excised both areas of stricture independently with respective anastomosis of

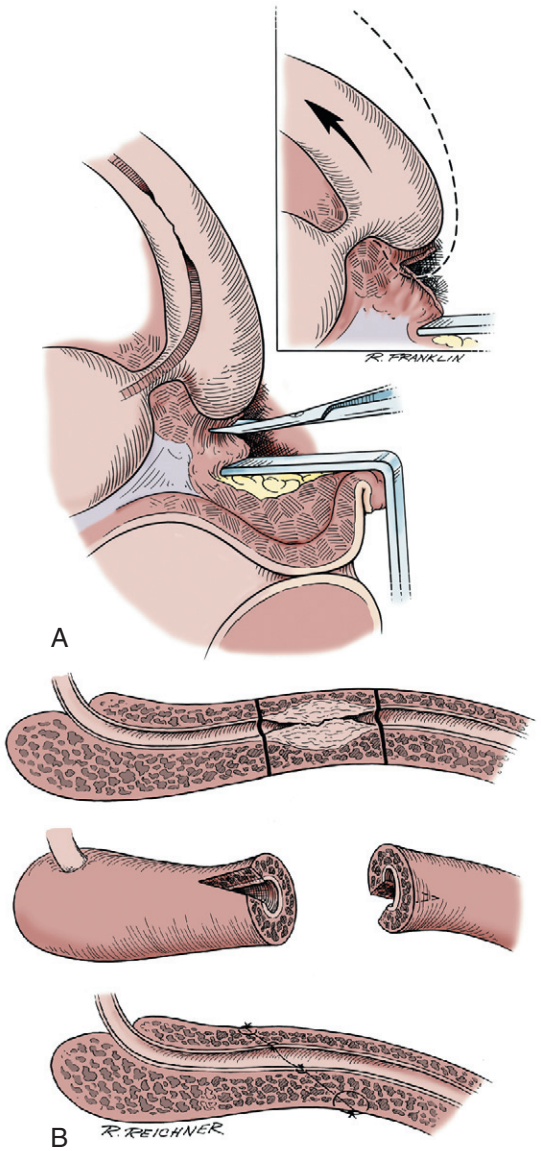


Figure 36–19. Techniques for excision and primary reanastomosis of anterior urethral stricture. **A,** The bulbospongiosus is released from its attachment to the perineal body. The arteries to the bulb are not divided. This technique allows the urethra to be mobilized distally. This technique combined with development of the intracrural space can shorten the path of the urethra by approximately 1 to 1.5 cm. **B,** Technique of a primary spatulated anastomosis after excision of an anterior urethral stricture. (**A** and **B,** From Jordan GH. Principles of plastic surgery. In: Droller MJ, editor. Surgical management of urologic disease: an anatomic approach. Philadelphia: Mosby–Year Book; 1992. p. 1218–37.)

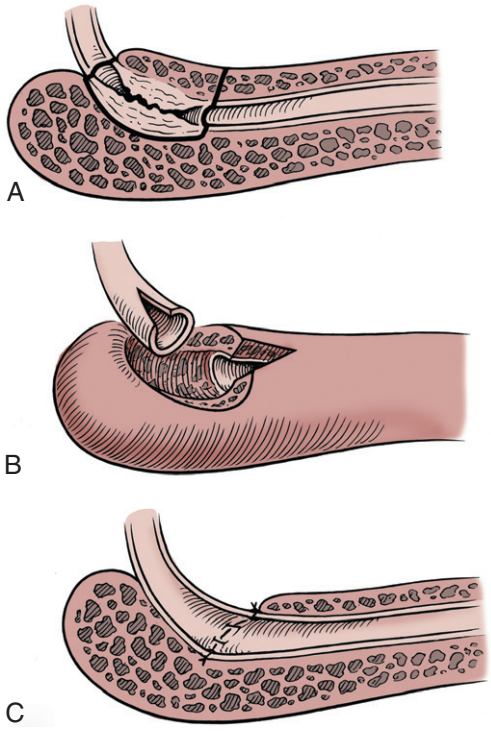


Figure 36–20. Technique of excision of very proximal bulbous urethral stricture with reanastomosis. This technique is facilitated by dissection of the membranous urethra. **A,** The area of the stricture is defined for excision. **B,** The stricture is excised and both ends of the urethra are spatulated on the dorsal aspect. **C,** The anastomosis is complete.

each site. Although this case was successful, we think that the authors' considerable experience allowed them to achieve a successful result, and a safer reconstruction with use of onlay or augmented onlay might have been better (DeCastro et al, 2002).

Jordan reported the use of a vessel-sparing excision and reanastomosis of the bulbar urethra. The dissection is similar to the standard excision and reanastomosis (Fig. 36–21), except once the triangular ligament is divided and the intracrural space developed, the space between the membranous urethra and the proximal vasculature is developed and these vessels are preserved (Fig 36–22). The urethra is then divided with the stenotic segment excised, the ends are spatulated, and then the reanastomosis is done. Advantages of preserving the proximal blood supply to the bulbar urethra include those patients whose distal blood supply is compromised by trauma, previous surgery, or hypospadias. Another theoretical advantage would be a decrease in the risk of erectile dysfunction. Further studies need to be done to confirm our initial excellent results and the above advantages (Jordan, et al 2007; Gur and Jordan, 2008).

Four grafts that have been successfully used for primary urethral reconstruction are the full-thickness skin graft, the bladder epithelial graft, the oral mucosal graft and the rectal mucosal graft. Oral mucosal grafts as mentioned can be taken from the cheek (buccal), the lip (labial), and the undersurface of the tongue (lingual). Split-thickness skin grafts have been used for staged anterior urethral reconstruction (Humby, 1941; Memmelaar, 1947; Pressman and Greenfield, 1953; Devine et al, 1976; Hendren and Crooks, 1980; Schreiter and Koncz, 1983; Webster et al, 1984; Hendren and Reda, 1986; Ransley et al, 1987; Burger et al, 1992; Jordan, 1993; El-Kassaby et al, 1996; Wessels and McAninch, 1996). The characteristics and microvascularity of some of those grafts are discussed earlier in this chapter in the section Principles of Reconstructive Surgery.

In years past, graft reconstruction of the urethra was almost abandoned in favor of flap reconstruction techniques. However, since the late 1990s, there has been a resurgence of interest in the use of grafts (Wessells and McAninch, 1996) and, specifically, the use of buccal mucosal grafts (Hellstrom et al, 1996; Weinberg et al, 2002; Barbagli et al, 2003; Elliott et al, 2003; Bhargava and Chapple, 2004; Kellner et al, 2004; Xu et al, 2004; Dubey et al,

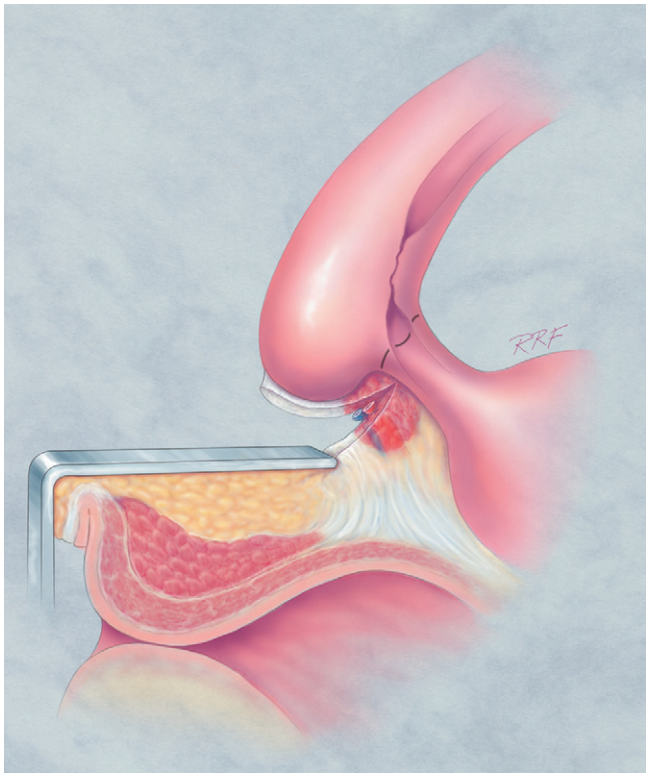


Figure 36–21. Diagrammatic representation of the dissection of the proximal corpus spongiosum, bulbospongiosum, and the membranous urethra. Illustrated is the customary technique for dividing the urethra through the juncture of the membranous urethra with the proximal bulbous urethra—to perform an excision of stricture with a primary anastomosis. In this illustration, the proximal vasculature has been ligated and divided. The urethra can then be divided at the distal most limits of the membranous urethra.

2005). **Grafts have been most successfully employed in the area of the bulbous urethra, where the urethra is invested by the bulk of the ischiocavernosus muscles. However, the use of grafts, other than in the area of the bulbous urethra, and, in some cases, the use of tubed reconstruction is reported in increasing numbers.** The grafts can be applied to the ventrum of the urethra; however, a ventral urethrotomy seems to be advantageous only if the use of the spongioplasty maneuver is contemplated (Fig. 36–23). The spongioplasty procedure requires that the corpus spongiosum adjacent to the area of the stricture be relatively normal and free of fibrosis. There are data to support the superiority of results with the dorsal onlay technique and other reports showing no difference in success. In the past, we preferred to use lateral graft onlay (see Fig. 36–23) or dorsal graft onlay (see Fig. 36–23). Placement of the urethrostomy laterally allows exposure of the urethra while cutting through the corpus spongiosum, where it is relatively thinner, thus limiting bleeding and maximizing exposure. In addition, in the bulbous urethra, the graft can be sutured to the underlying muscle bed in the hope of improving graft host bed immobilization and approximation.

The Monseur (1980) urethral reconstruction was applied in only a few select centers. In this technique, the urethrostomy was made through the stricture on the dorsal wall. The edges of the stricture were then sutured open to the underlying triangular ligament or corpora cavernosa, or both. Barbagli and associates (1995) have modified the Monseur technique (Fig. 36–24). In that modification, the urethrostomy is performed through the stricture on the dorsal wall. In the area of the urethrostomy, a graft is then applied and spread fixed to the triangular ligament or corpora cavernosa, or to both. In turn, the edges of the stricturotomy are then sutured to the edges of the graft as well as to the adjacent structures. The results of this technique are excellent. The ventral and dorsal graft onlay techniques can both be used with stricture excision and strip anastomosis (augmented anastomotic procedure) (Fig.

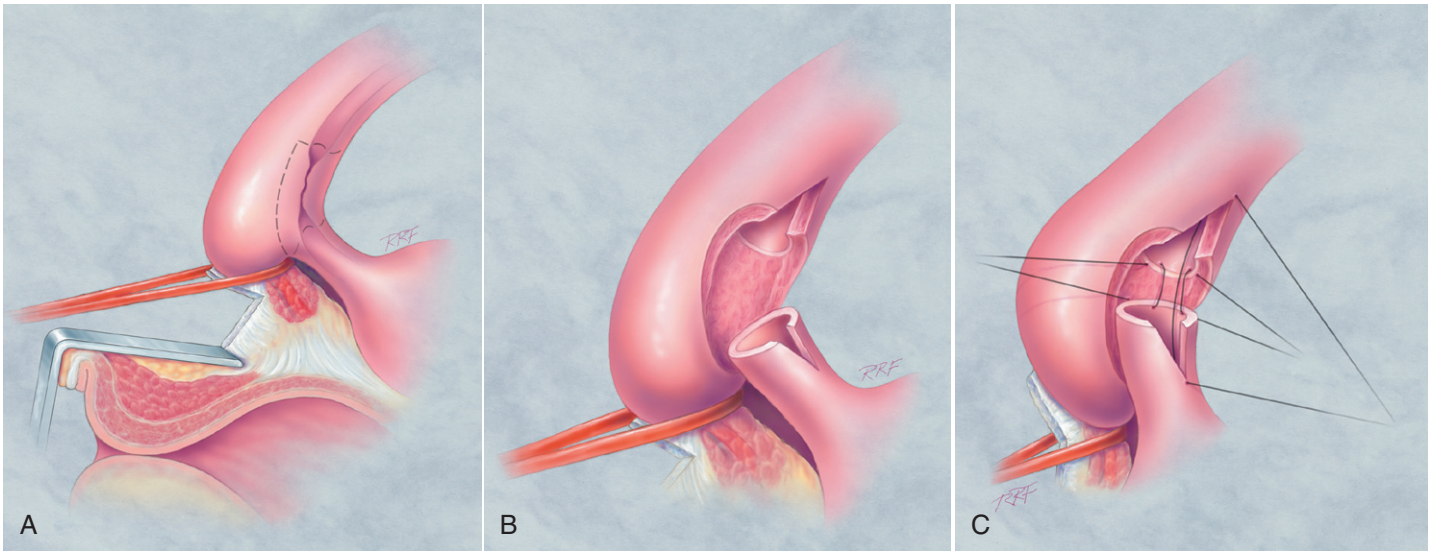


Figure 36–22. Illustrated is the technique of vessel-sparing excision with primary anastomosis. The proximal corpus spongiosum, bulbospongiosum, and area of the proximal vessels and membranous urethra have been dissected. **A,** Illustrated is the dissection of the space between the proximal vasculature and the membranous urethra. In this technique, the arteries to the bulb can be preserved, and the membranous urethra can be divided at its juncture with the bulbous urethra. The area of proximal stricture can be excised. **B,** The illustration of the stricture having been excised prior to placement of the anastomotic sutures. **C**, Anastomotic sutures are placed to effect the spatulated anastomosis. At this center, customarily we alternate polydioxanone sutures with Monocryl; however, any acceptable absorbable suture can be used. Note the membranous urethra is spatulated on the dorsum as is the proximal bulbous urethra.

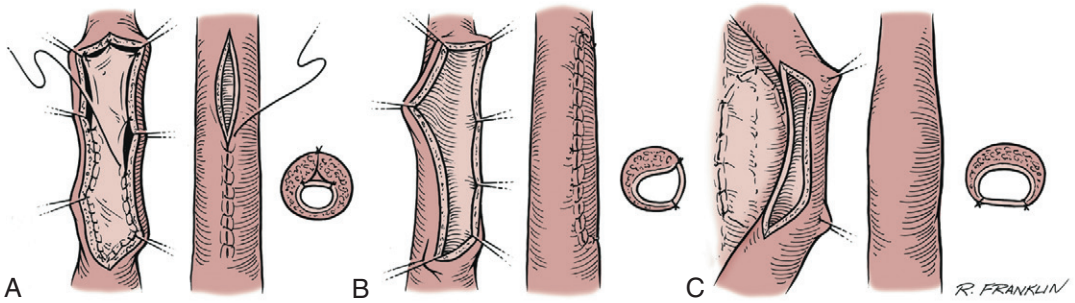


Figure 36–23. Diagram of various techniques of graft onlay. **A,** Ventral onlay with spongioplasty. **B,** Lateral onlay with quilting to the ischiocavernosus muscle. **C,** Dorsal onlay with spread fixation of the graft.

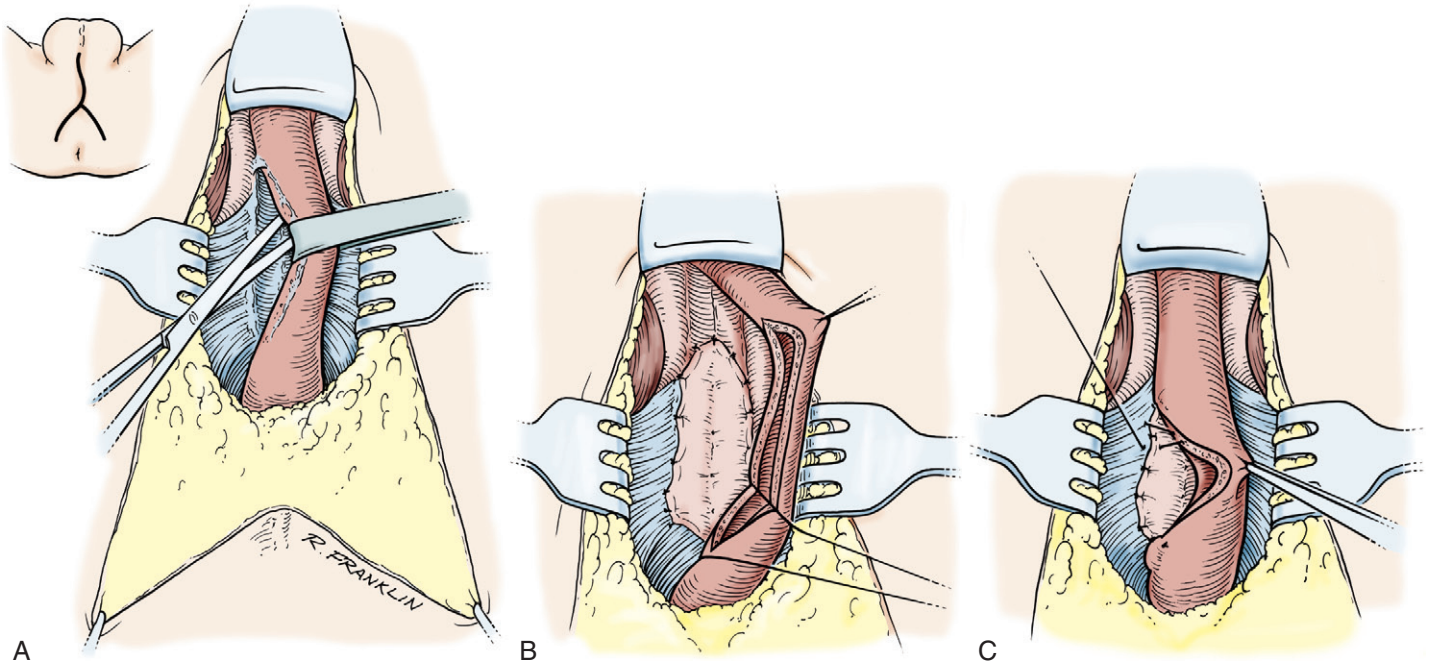


Figure 36–24. Technique of dorsal graft onlay popularized by Barbagli. **A,** The corpus spongiosum is detached from the triangular ligament and corpora cavernosa. **B,** A dorsal urethrostomy is performed. The graft is spread fixed to the corpora cavernosa. Note the pie-crusting incision. **C,** The edges of the stricturotomy are then sutured to the graft as well as to the corpora cavernosa.

36–25). For proximal strictures, the vessel-sparing technique of augmented anastomosis depends on the surgeon's ability to excise the scarred epithelium and underlying corpus spongiosum tissue without the need to completely divide the corpus spongiosum.

Another option is the two-staged application of a mesh split-thickness skin graft, buccal mucosal graft, or posterior auricular full-thickness skin graft. In the first stage of the staged graft procedure, a medium-thickness split-thickness skin graft, a buccal mucosal graft, or a Wolfe graft is placed over the dartos fascia. If the graft is placed immediately onto the tunica albuginea or corpora cavernosa, the inability to mobilize the graft makes second-stage tubularization difficult. However, there is an advantage to having at least a midline strip of the graft adherent to the corpora cavernosa. At a later date, second-stage surgery is performed to tubularize the graft. Whereas Schreiter and Noll (1989), who first described the procedure of mesh split-thickness skin graft, often proceeded to the second stage within 3 to 4 months, we wait 12 months between the first- and second-stage surgeries if a split-thickness skin graft is used. This procedure has been found useful for select cases in both the United States and Europe. In the United States, its use has mostly been confined to the most difficult cases, however, with single-stage reconstruction still applied to the majority. As already mentioned, staged graft techniques have been effectively used in the complicated hypospadias patient. Staged buccal graft operations have been successfully employed in the LS-BXO patients with midterm follow-up. In addition, in the complicated hypospadias patient, staged buccal grafts and posterior auricular skin grafts have been successfully employed (Fig. 36–26).

A number of applications of genital skin islands, mobilized on either the dartos fascia of the penis or the tunica dartos of the scrotum, have been proposed for the repair of urethral stricture disease. In the past, these "flap operations" were considered separate procedures. We suggest that all these procedures are really different applications of a single concept, as proposed by the microinjection studies of Quartey (1983). Skin islands can be viewed as passengers on fascial flaps, and the design of flaps for urethral reconstruction can be paralleled to the design of flaps for reconstruction in general.

There are **three important considerations for the use of flaps in urethral reconstruction: the nature of the flap**

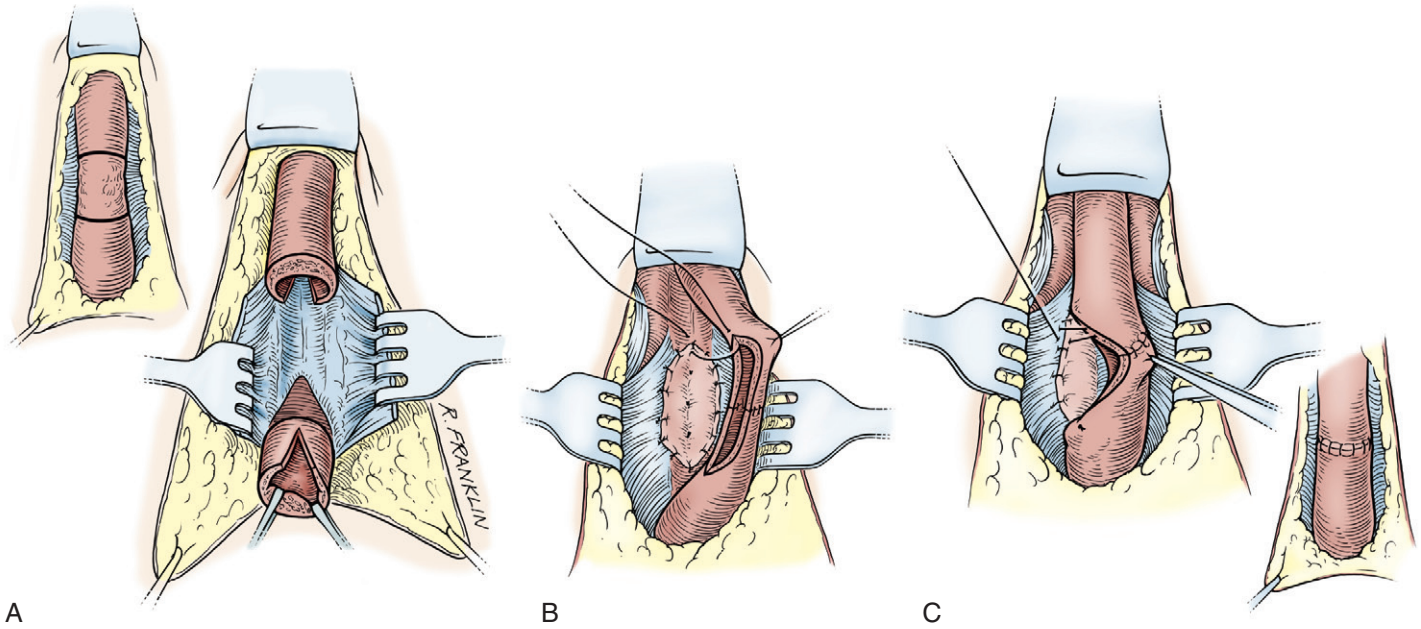


Figure 36–25. Technique of augmented anastomosis with graft onlay. **A,** The corpus spongiosum is detached from the triangular ligament and the corpora cavernosa. The area of spongiofibrosis is identified and marked, and the area of narrowest caliber stricture is excised. The urethral ends are then spatulated on the dorsum. **B,** A two-layer floor strip anastomosis is performed and the graft is spread fixed to the corpora cavernosa. Note the pie-crusting incisions and the mattress sutures. **C,** The edges of the stricturotomy are then sutured to the graft as well as to the corpora cavernosa.

tissue, the vasculature of the flap, and the mechanics of flap transfer. The skin must be nonhirsute for urethral reconstruction. **In addition, for donor site consideration, it is most convenient to use the areas of redundant nonhirsute genital skin.**

If the redundancy is dorsal, the skin island can be oriented transversely and mobilized on the dorsal dartos fascia after the techniques described by Duckett and Standoli in 1984 (Fig. 36–27) (Duckett, 1986, 1992; El-Kassaby et al, 1986; Duckett et al, 1993). If there is redundancy of the ventral skin, the skin island can be mobilized as a ventral longitudinal island. These islands can be either vigorously mobilized on a ventrolaterally oriented dartos fascial flap for transposition to the perineum or less vigorously mobilized and transposed and inverted into a pendulous urethral stricture defect (Fig. 36–28) (Orandi, 1972). Ventral islands can be oriented transversely (Fig. 36–29) as well as longitudinally. Longer skin islands can be mobilized by orienting the island both ventrally and transversely at the distal extent. This "hockey stick" orientation allows islands as long as 7 to 9 cm (Fig. 36–30). For distal strictures of the anterior urethra, including the fossa and meatus as well as the pendulous urethra, the islands can be advanced to reconstruct to the level of the meatus by either developing glans wings or elevating the ventral glans.

Where there is general redundancy to the penile skin, the islands can be oriented circumferentially. These "circular skin islands" are mobilized on the entire penile dartos fascia, and the mechanics of transposition suggest that they are most efficient when they are ventrally based, with the pedicle split dorsally. In some cases, circular skin islands as long as 15 cm can be obtained (El-Kassaby et al, 1986; McAninch, 1993; Miller and McAninch, 1993). The so-called Q flap circular island design can provide even longer islands, sometimes necessary for complex long-length anterior urethral reconstruction (Morey et al, 2000).

Many times, it is beneficial to combine the excision of the stricture with a skin island onlay (Fig. 36–31) **or a graft onlay** (see Fig. 36–25, augmented anastomosis). We have found that **segments of very narrow caliber (nearly or totally obliterating) are difficult to deal with.** These segments can often be completely excised; a roof or floor strip anastomosis of the urethra is performed, and the remaining urethrotomy defect is filled with either a graft or a skin island onlay. In some patients, there are relatively large nonhirsute areas of the scrotal skin that can be elevated on the tunica dartos of the scrotum. This flap has, in the past, been maligned in the literature. However, we and others have extensive experience with these flaps and, in select cases, have had very good results. The fascial flap must be based laterally, and so oriented, these flaps have been shown to be extremely reliable. Because the tunica dartos has a significant muscle component, the skin island must be carefully tailored. If these skin islands are correctly tailored at the outset, they are not attended with diverticular development as some have believed they were in the past. We now have used these flaps in more than 80 patients with excellent results and good long-term follow-up (>12 years at this writing). Scrotal skin islands are not our first choice; however, for difficult cases, they remain a reasonable option.

These procedures using skin islands oriented on the penile dartos fascia have also been useful for reconstruction of the fossa navicularis (Cohney, 1963; Blandy and Tresidder, 1967; Brannen, 1976; De Sy, 1984; Jordan, 1987; Armenakas et al, 1998). In the past, meatal strictures and strictures of the fossa navicularis were managed with repeated dilations or sequential meatotomies. Because these meatotomies were seldom successful in the long term, techniques were developed that allowed the spatulation of random penile skin flaps into the meatotomy defects. These procedures functionally improved the results; however, the cosmetic

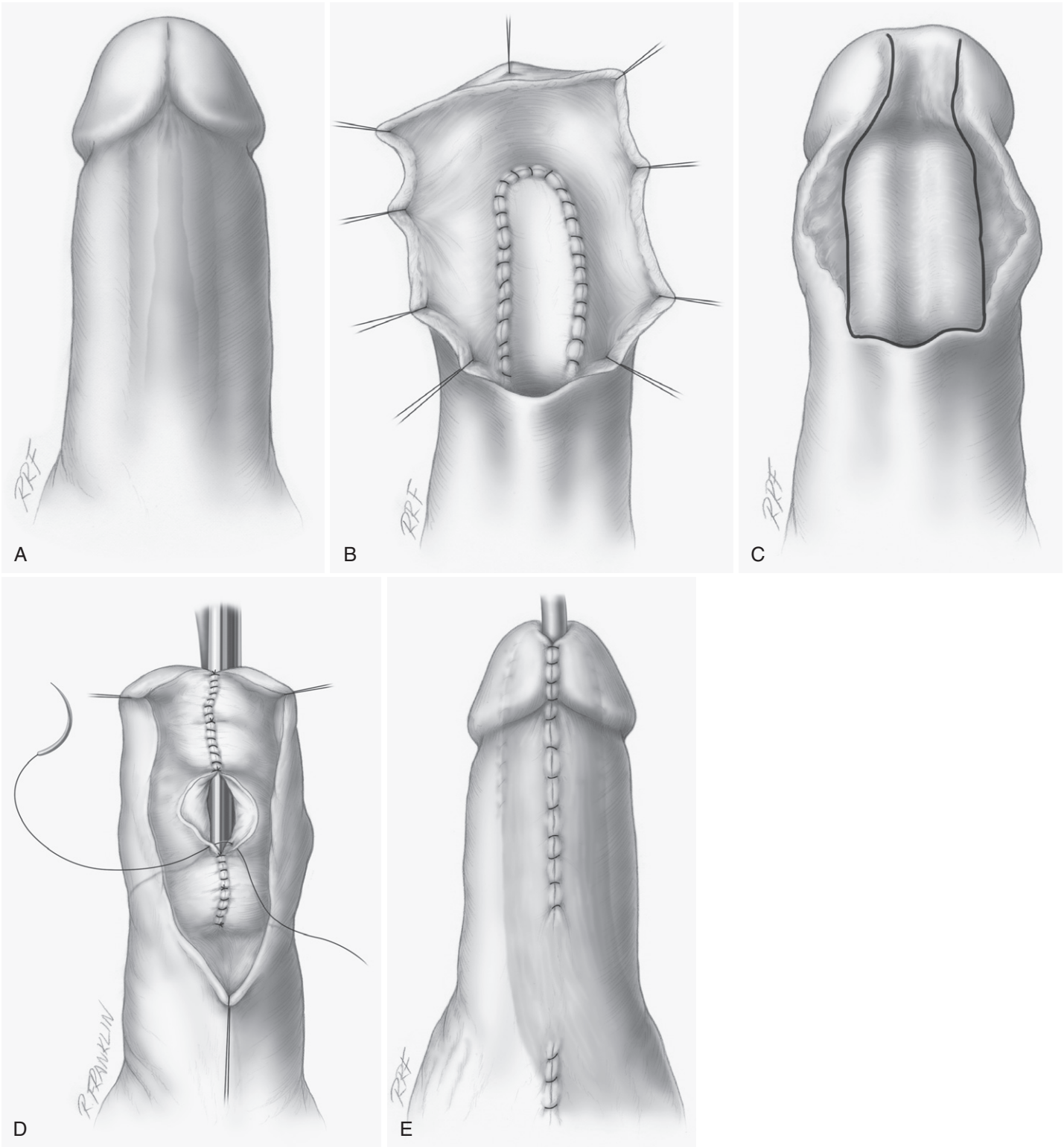


Figure 36–26. Staged reconstruction of a distal anterior urethral stricture. **A,** The appearance of the penis with the urethra (shaded area shows the location of a tight stenosis of the fossa navicularis that extends into the distal pendulous urethra). **B,** The distal narrow stricture of the fossa navicularis has been excised and stricturotomy performed into the normal urethra proximal to the excised tissue. A buccal graft has been applied to the defect, but the bolster dressing has not yet been applied. **C**, After 6 months, the graft is mature. The illustration shows a Tiersch tube ready for closure. **D**, The Tiersch tube is closed with a watertight suture line. The distal urethra is usually calibrated to create a urethral lumen of approximately 28 Fr. **E,** Glans reconstruction and closure of the distal shaft has been performed (the shaded area shows the tunica dartos flap that carries a parietal tunica vaginalis island). The flap is mobilized in this case from left hemiscrotum, and transposed to cover the entire area of the urethral reconstruction.

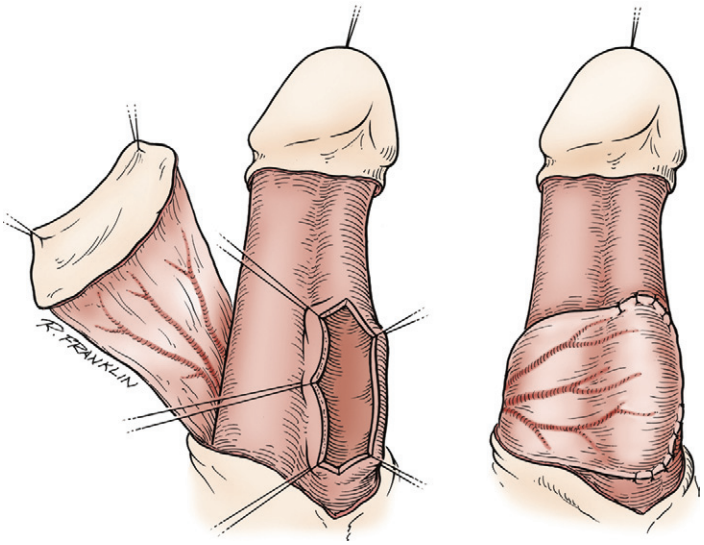


Figure 36–27. A dorsal transverse island of penile skin applied to a stricture of the urethra. The flap has been elevated on the dartos fascia, and a lateral incision has been made into the urethra. The flap is secured in place *(right)*. (From Jordan GH. Management of anterior urethral stricture disease. In: Webster GD, editor. Problems in urology. Philadelphia: JB Lippincott; 1987. p. 217.)

appearance of the penis was less than optimal. With the use of skin islands elevated on the dartos fascia, excellent functional as well as cosmetic results became the norm. Again, the design of these islands must take into consideration the location of hair on the shaft of the penis, as well as the mechanics of flap transfer (i.e., transposition versus advancement) (Figs. 36–32 and 36–33). In addition, full-thickness skin has been used to reconstruct the fossa navicularis, but when they can be avoided, skin grafts are not thought appropriate for reconstruction in cases of LS-BXO. As already mentioned, there is question about the use of skin islands in general in patients with LS-BXO.

The literature is clear that onlay procedures (graft or flap) are attended with a higher success rate than tubularized grafts or tubularized skin islands (Hendren and Crooks, 1980). **Tubularized grafts and skin islands should therefore be avoided, if possible. When tubularized segments cannot be avoided, the length of these segments can be limited by combining aggressive mobilization and excision. Without question, tubularized flaps provide better results than tubularized grafts.** Where extremely long segments of the anterior urethra require reconstruction, a flap can be used distally and augmented by graft onlay proximally (Wessells et al, 1997). Where tubed reconstruction is required, the combination of a graft spread fixed to reestablish the "urethral plate" with flap onlay, in a small series with only short follow-up, seems perhaps to be better than tubed flap reconstruction, even when it is employed in the onlay-tube-onlay configuration (Morey, 2001).

A flap procedure that can be used as an alternative to the split-thickness skin grafts when nonhirsute skin is unavailable is the epilated midline genital skin island. Like the split-thickness skin graft, this procedure must be viewed as a staged procedure, with the epilations being the initial stage or stages. Epilation can be accomplished with either a narrow-gauge needle and monopolar cautery or epilation needles and machines. The interval between the epilations must be 6 to 8 weeks, and urethral reconstruction cannot be accomplished until 10 to 12 weeks after the last

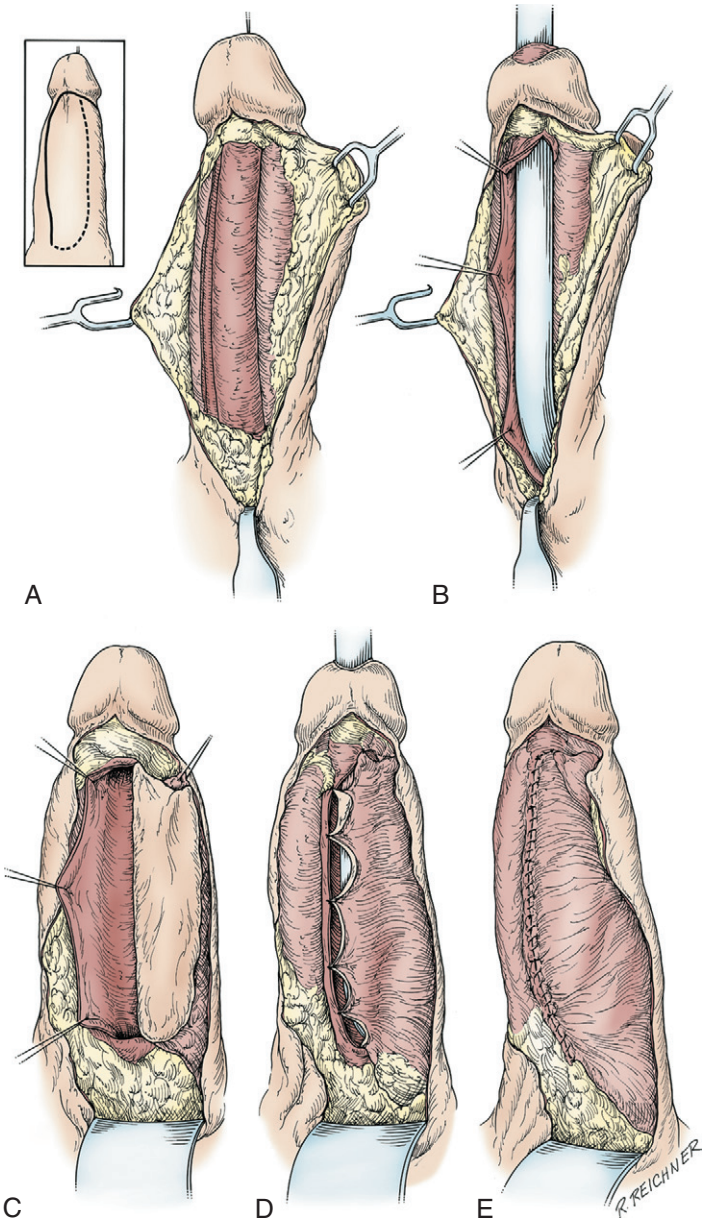


Figure 36–28. Penile longitudinal skin island. The incisions to be made to mobilize the flap are demonstrated in the inset. The heavy line is the primary incision made full thickness through the dartos fascia and superficial Buck fascia lateral to the corpus spongiosum. **A,** Dissection elevates the dartos fascial flap well past the corpus spongiosum in the midline. **B,** A lateral urethrostomy placed to face the flap has opened the entire length of the stricture. **C,** The skin paddle of the flap has been developed by making the incision outlined by the dotted line *(inset)* and undermining the skin lateral to it. The medial edge of the flap has been fixed to the edge of the stricturotomy. **D,** The flap is inverted into the defect. **E,** A watertight subepithelial suture line has been completed with a running absorbable monofilament suture. The skin will be closed with subcutaneous sutures and interrupted cutaneous sutures. (**A** to **E,** From Jordan GH. Management of anterior urethral stricture disease. In: Webster GD, editor. Problems in urology. Philadelphia: JB Lippincott; 1987. p. 214.)

epilation. The actual stricture repair involves elevation of the midline skin island, based on both the dartos fascia of the penis and the tunica dartos of the scrotum. As with nonhirsute scrotal skin islands in general, the importance of meticulous tailoring of the scrotal portion of the island cannot be overemphasized.

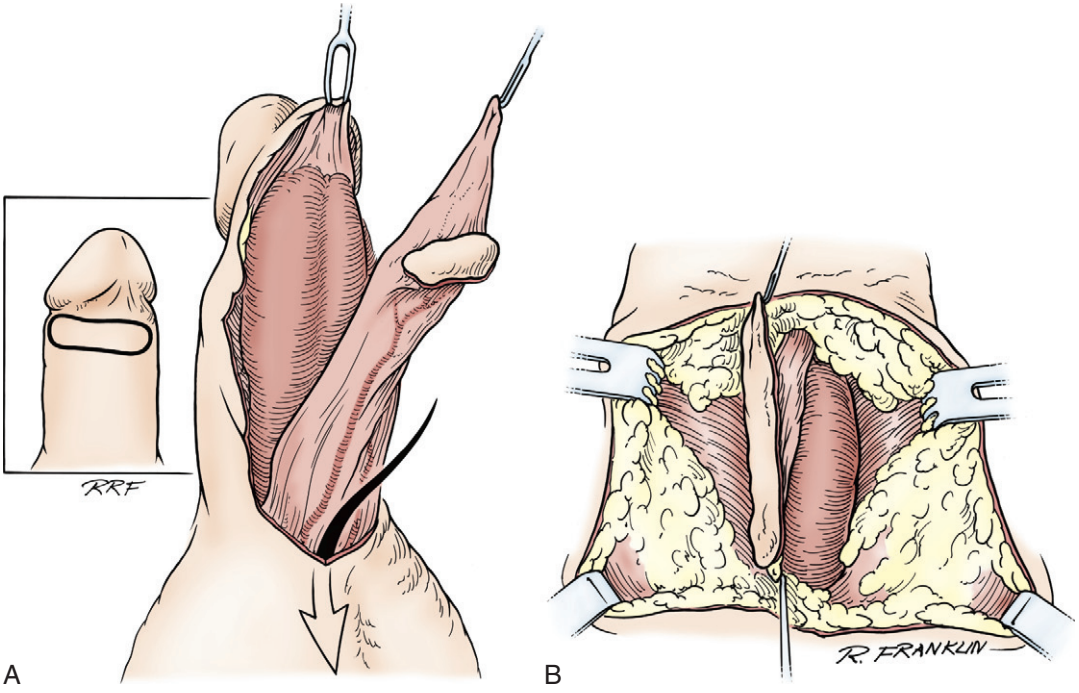


Figure 36–29. A ventral transverse skin island is elevated on the penile dartos fascia, inverted to the area of the perineum where flap onlay is accomplished. **A,** The skin island is elevated on the dartos fascia. **B,** The appearance of the flap transposed to the area of the perineum for onlay in a proximal bulbous urethral stricture.

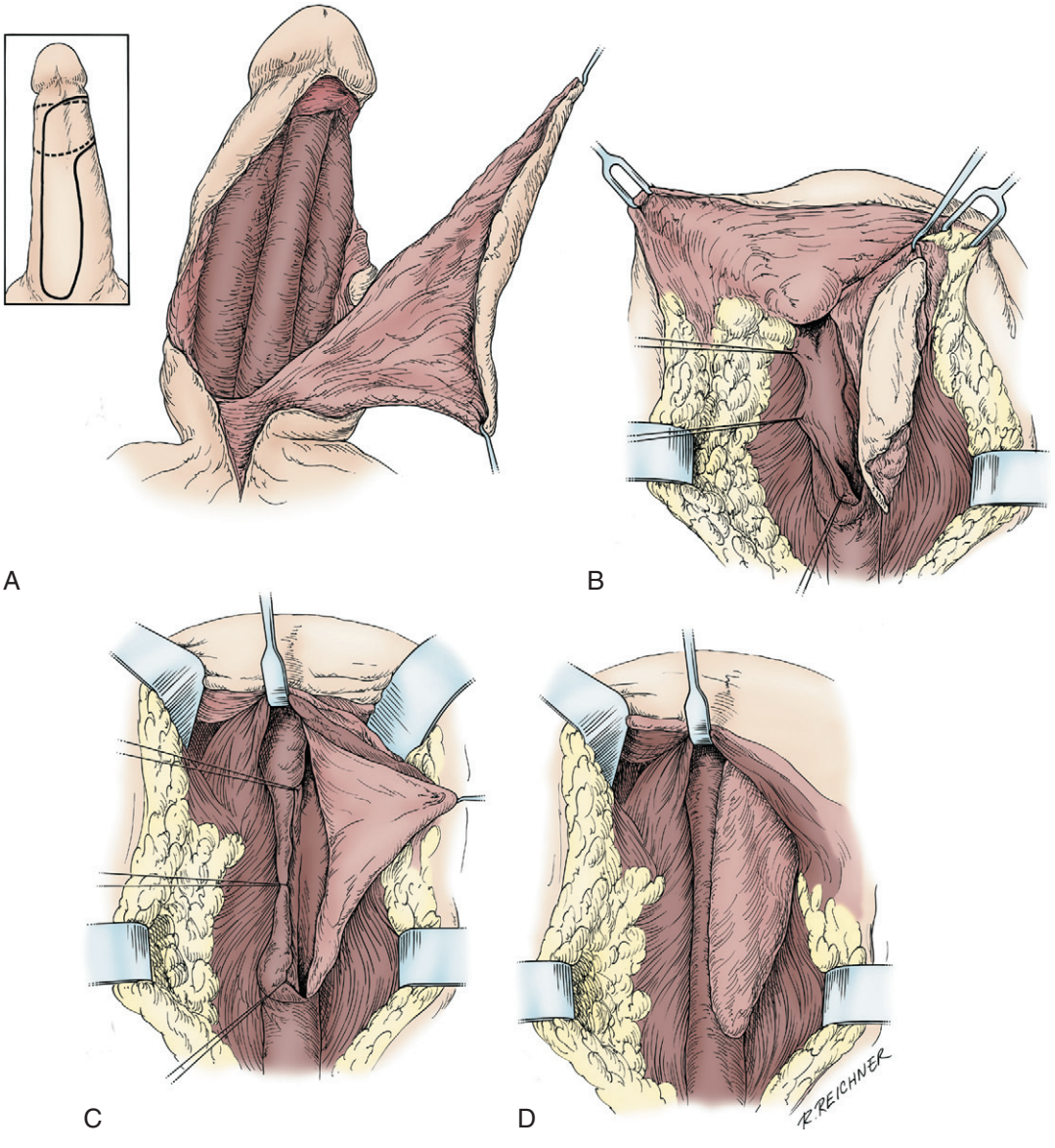


Figure 36–30. Ventral skin island for long bulbous stricture. The skin paddle of the flap is developed on the ventral midline of the penis and can be extended around the penile shaft at its distal end. **A,** The paddle of the flap has been incised and its pedicle elevated. This pedicle includes Buck fascia and dartos fascia, denuding the tunica of the corpus spongiosum and the corpora cavernosa. The pedicle (the dartos fascia bilaterally) is based on the superficial external pudendal vessels and the internal pudendal vessels in the scrotum. Development of this pedicle allows the flap to be moved to any area of the urethra. **B,** The flap has been passed through a tunnel beneath the scrotum developed by dissection along the corpus spongiosum. A laterally placed urethrostomy has opened the urethral stricture. **C,** The deep edge of the flap is secured by the suture techniques previously described. **D,** Anastomosis of the flap has been completed. The pedicle can be seen extending beneath the scrotum. (**A** to **D,** From Jordan GH, McCraw JB. Tissue transfer techniques for genitourinary surgery, part III. AUA Update Series 1988;7:lesson 11.)

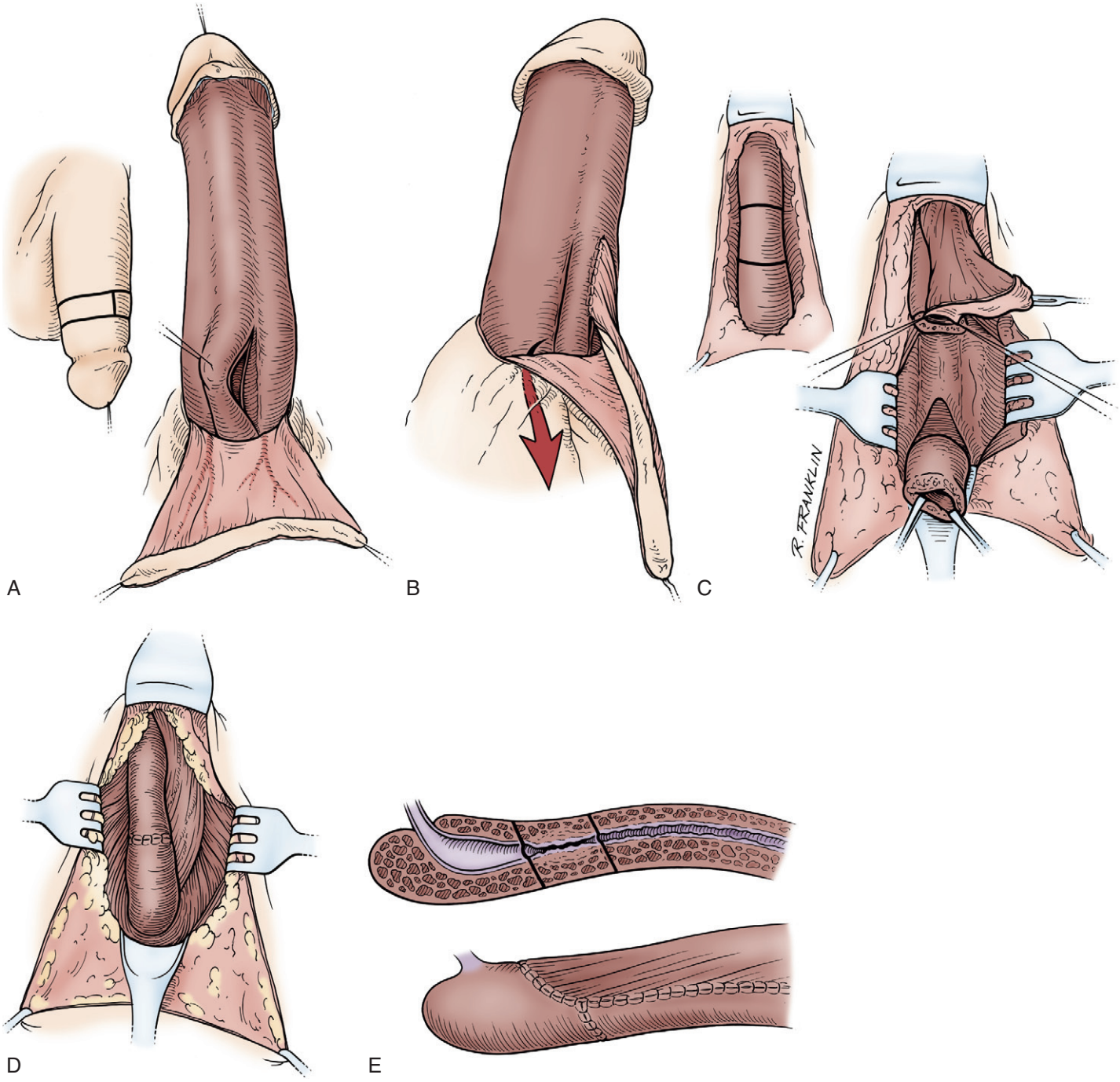


Figure 36–31. Illustration of reconstruction in a patient with a long anterior urethral stricture with a relatively short narrow-caliber section (technique of augmented anastomosis with circular skin island). **A,** A circular skin island is elevated on the dartos fascia. The patient is positioned flat on the table. **B,** The skin island onlay is begun, the rest of the flap is placed into the perineal dissection, and the penis is closed; the patient is then repositioned in the lithotomy position. **C,** The flap is retrieved through the perineal dissection. The narrow-caliber section is excised, and the urethra is spatulated on the dorsum. **D,** The onlay is completed, and the floor strip anastomosis is closed. **E,** Schematic of the surgery. (**A** to **E,** From Stack RS, Schlossberg SM, Jordan GH. Reconstruction of anterior urethral strictures by the technique of excision and primary anastomosis. Atlas Urol Clin North Am 1997;5:11–21.)

Mundy (1994) **analyzed a large series of urethral reconstructions. His data show that when follow-up is limited to 1 year, the success rate with tissue transfer clusters is about 95%. With longer follow-up, however, there is deterioration over time. With excision and primary anastomosis, the success seen at 1 year seems to be more durable, however, and does not appear to deteriorate at the same rate with time.** We have reported our long-term data for excision and primary anastomosis with anterior urethral stenosis in 220 patients with a mean follow-up of 44 months; three recurrences were noted, two within the first 6 months and a third at 4 years. The rate of postoperative erectile dysfunction is 2%, with the severe straddle population being at increased risk. Wessells and McAninch (1998), **in a meta-analysis of graft onlay procedures compared with flap procedures, showed equivalent results for graft operations and flap**

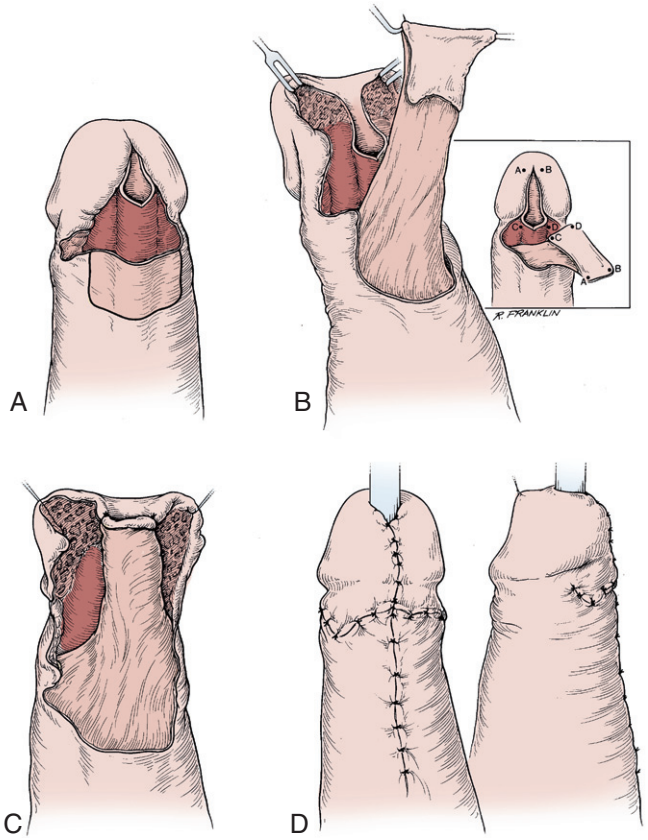


Figure 36–32. Technique of reconstruction of the fossa navicularis after Jordan. **A,** The ventral corpus spongiosum is exposed and the urethra opened ventrally through the area of stenosis. A transverse ventral skin island is outlined on the distal penile skin. **B,** The skin island is elevated on the ventral dartos fascia. **C,** The skin island is transposed and inverted into the meatotomy defect *(inset)*. **D,** The appearance of the penis closed after the procedure. (**A** to **C,** From Jordan GH. Reconstruction of the fossa navicularis. J Urol 1987;138:1210; **D,** from Jordan GH. Reconstruction of the meatus–fossa navicularis using flap techniques. In: Schreiter F, editor. Plastic-reconstructive surgery in urology. Stuttgart: Georg Thieme; 1999. p. 338–44.)

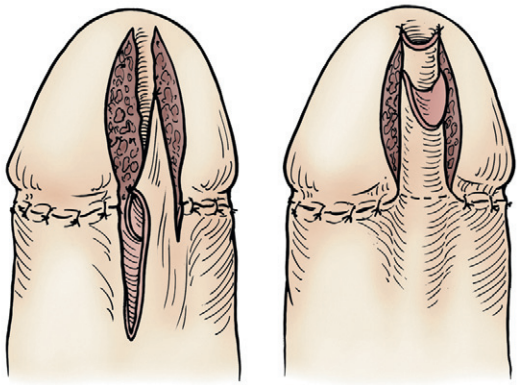


Figure 36–33. Technique after De Sy, in which a ventral longitudinal skin island is advanced into the meatotomy defect. The skin island is developed by deepithelialization of a portion of the longitudinal flap. (From Jordan GH. Management of anterior urethral stricture disease. Probl Urol 1987;1:199–225.)

procedures, and graft onlay procedures are technically far easier to perform. There clearly are some cases where flap reconstruction would be expected to provide superior results (i.e., radiation strictures, patients with multiple operations, pendulous strictures). However, with the increased knowledge gained by the enthusiastic application of graft reconstruction, there is currently a redefined paradigm for anterior reconstruction. Whereas grafts have been used successfully for all segments of the anterior urethra, many think that flaps are best suited for distal reconstruction and grafts for proximal reconstruction, all other variables equivalent (Greenwell et al, 1999).

Key Points: Treatment of Urethral Stricture

- In the treatment of urethral stricture disease, both the patient and the physician must have a good understanding of the goals of treatment before the treatment choice is made.
- Urethral dilation is the oldest and simplest treatment of urethral stricture disease. However, the goal of dilation is to stretch the scar atraumatically. Dilation is seldom used curatively.
- Internal urethrotomy refers to any procedure that opens the stricture by incising it transurethrally. The factors that contribute to success of internal urethrotomy have been defined as follows: internal urethrotomy should be reserved for strictures of the bulbous urethra; the stricture should be less than 1.5 cm in length; and the stricture should not be associated with dense deep spongiofibrosis. Repeated dilation and internal urethrotomies have been shown in a number of studies to diminish the success rate of eventual open urethral reconstruction.
- Urethral stents can be either removable or permanently implantable. The UroLume is the Food and Drug Administration–approved permanently implantable stent. The long-term data have not held up to the original enthusiasm for use of the UroLume. The greatest experience with explantable urethral stents comes from Europe. The concept of these stents is different in that they are designed to prevent epithelial incorporation.
- A number of lasers have been used for anterior urethral strictures. To date, the results of laser urethrotomy are mixed.
- Excision with primary anastomosis has proved to be the "gold standard" form of repair for anterior urethral strictures. In years past, excision with primary anastomosis was thought to be a relatively limited procedure and applicable only for strictures less than 1.5 to 2 cm. However, with better understanding of the anatomy, longer and longer strictures have been successfully addressed with excision and primary anastomosis.
- Admittedly, there are strictures that require tissue transfer, and grafts and flaps have been successfully employed. A meta-analysis by Wessells has shown that the results of graft reconstruction and flap reconstruction are equivalent. Clearly, the complexity of flap procedures is greater than that of graft procedures. The concept of augmented anastomosis can be used with both graft and flap onlay and is thought, in many cases, to provide better results than just pure onlay. When flaps are employed for urethral reconstruction, conceptually all become one operation with multidimensional application.

The issue of postoperative erectile dysfunction must be discussed. Our rates for anterior urethral anastomotic reconstruction are quoted earlier. **In an analysis by Coursey, 200 urethroplasty patients were studied. Overall, the rate of erectile dysfunction after urethroplasty was approximately equal to that with circumcision. However, longer-segment reconstructions did have a higher risk of postoperative erectile dysfunction, although in many, over time, the patient's erectile function improved** (Coursey et al, 2001).

Special mention must be made regarding reconstruction for strictures associated with LS-BXO**.** With the advent of flap techniques, many centers embraced these techniques for these strictures. However, analysis of results from these patients treated at several large centers has shown a very high recurrence rate. Consequently, these centers adjusted the techniques by applying staged graft techniques (see Fig. 36–26). Interestingly, staged graft techniques using skin grafts again had a very high recurrence rate in a number of analyses. **Theoretically, because LS-BXO is a skin condition, the use of skin as a flap, single-stage graft, or staged graft does not preclude involvement of the skin with the inflammatory process** (Lee and Phillips, 1994; Akporiaye et al, 1997). **Thus surgeons at a number of centers believe that staged oral graft techniques should be employed for reconstruction of strictures associated with LS-BXO.** Short follow-up suggests better success with this approach. Long-term follow-up is not available. In a review of our experience in patients with a fossa navicularis stricture and LS-BXO, we noted a 50% recurrence in the stricture with a ventral transverse skin island (Virasoro et al, 2007).

PELVIC FRACTURE URETHRAL INJURIES

Pelvic fracture urethral injuries are the result of blunt pelvic trauma and accompany about 10% of pelvic fracture injuries. Although it is possible to totally disrupt the urethra with a straddle injury, these injuries most commonly involve only the bulbous urethra. However, the ensuing spongiofibrosis can be associated with complete obliteration of the urethra. **Distraction injuries are for all intents unique to the membranous urethra.** Pelvic fracture distraction injuries of the membranous urethra have been compared with plucking an apple (prostate) off its stem (the membranous urethra). This analogy implies that the injury most frequently occurs at the apex of the prostate. Experience shows that this is not the case, however, and the most frequent point of distraction is at the departure of the bulbous urethra from the membranous urethra (Andrich and Mundy, 2001; Mouraviev and Santucci, 2005). The distraction can, however, involve all or any portion of the membranous urethra between the departure of the bulbous urethra and the apex of the prostate. In the postpubescent male, the injury seldom involves the prostatic urethra. In the prepubescent male, in whom the prostatic urethra is more fragile, the injury can extend into that area.

Many injuries appear not to totally distract the entire circumference of the urethra. Instead, a strip of epithelium is left intact. In these patients, the placement of an aligning catheter may allow the urethra to heal virtually unscarred or with an easily managed stenosis. Because of flexible endoscopy equipment, the placement of an aligning catheter is relatively straightforward. If distraction is complete, the catheter then serves to align the obliterated urethral ends, and reconstruction is facilitated. Because of the ready availability of flexible cystoscopes, some centers are now acutely evaluating these injuries only with endoscopy. Those enthusiastic for this approach believe that not only can the injury be completely evaluated but the entire process, including the placement of an aligning catheter, is expedited (Kielb et al, 2001). **Aligning catheters are just what the name implies—a guide, not a mechanism for placing traction on the bladder and prostate.** Aligning catheters also seem to act as a drain as the pelvic hematoma liquefies, and perhaps the presence of the catheter may allow more rapid and complete resolution of the process (Cohen et al, 1991; Herschorn et al, 1992; Rehman et al, 1998; Mouraviev et al, 2005).

Evaluation

As with the repair of any stricture or stenosis, it is important to define the precise anatomy of the pelvic fracture injury before treatment is undertaken (McCallum and Colapinto, 1979a, 1979b); **this includes the depth, density, length, and location. In pelvic fracture urethral distraction defects, the depth and density of fibrosis are predictable. Although the location of the distraction injury has been demonstrated to be an important factor in continence after reconstruction, this information should be a factor only in counseling of patients before the reconstruction and not in the treatment approach. The length of the defect is an important consideration and must be determined as precisely as possible.**

Contrast studies are a first-line tool for the evaluation of pelvic fracture urethral injury. A cystogram outlines the bladder and provides information about rostral displacement of the proximal urethra. A lack of contrast material in the posterior urethra gives some information, albeit inconclusive, about the integrity of the bladder neck.

When the patient is successful in relaxing to void and the cystogram outlines the posterior urethra, a simultaneous retrograde urethrogram nicely outlines the length of the injury defect. However, this situation is the exception rather than the rule, and retrograde urethrography is most useful for determining whether the anterior urethra is normal. If the anterior urethra is normal, **it has been our experience, as well as that of others, that a successful anastomotic repair is ensured.** In fact, a primary anastomosis has been shown to be possible even with some involvement of the anterior urethra. Even in cases of prior failed posterior urethral reconstruction, primary anastomotic repair is often feasible, although the failure rate is slightly higher in these cases (Chapple and Pang, 1999; Flynn et al, 2003; Koraitim, 2003; Shenfeld et al, 2004). **Thus primary anastomosis is unquestionably the goal in all these patients until it is proved impossible to perform.**

When the proximal urethra is not visualized on a simultaneous cystogram with urethrogram, endoscopy through the suprapubic tract in combination with retrograde urethrography can be used to outline the defect. After the endoscopic appearance of the bladder neck is assessed, the flexible endoscope can be advanced through the bladder neck and into the posterior urethra to the level of the obstruction. **The appearance of the bladder neck on contrast studies or on antegrade endoscopy does not accurately predict the ultimate function of the bladder neck after urethral reconstruction** (Iselin and Webster, 1999). A simultaneous retrograde urethrogram will then outline the anterior urethra, with the space not visualized representing the injury defect.

Some have also advocated magnetic resonance imaging for the evaluation of patients with pelvic fracture urethral injuries. We have had little experience with this modality for that purpose; however, we have found the information obtained on the few studies that we have done to be useful. In these cases, there was the question of bone interposition into the injury defect, and magnetic resonance imaging nicely outlined that. We evaluated a case in which the prostatic urethra appeared obliterated. On magnetic resonance imaging, one could easily see that the prostate was not only distracted from the membranous urethra but also distracted from the bladder. This information was essential to planning of subsequent reconstruction in this case. It would seem intuitively obvious that knowing the length of distraction would be helpful in determining the precise approach and steps necessary for reconstruction. However, the literature is not clear on this matter (Andrich et al, 2003; Koraitim, 2004), and it is our experience that the surgeon must be prepared to exercise all options of reconstruction in virtually all such cases (McCallum and Colapinto, 1979a, 1979b).

Repair

The timetable for the reconstruction of pelvic fracture urethral injuries is determined by the type and extent of associated injuries. If possible, it is desirable to proceed within 4 to 6 months after trauma. However, orthopedic injuries of the lower extremities often necessitate a delay in proceeding with urethral reconstruction (Mundy, 1991; Follis et al, 1992; Brandes and Borrelli, 2001). Most pelvic fracture patients have inferior venal caval filters placed, because of the risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) at the time of trauma. It is our practice to start all of these patients on low-dose anticoagulation and to continue it for about 10 days to 2 weeks after surgery.

In the majority of cases, pelvic fracture urethral injuries are not long, and the resultant obliteration is amenable to a technically straightforward mobilization of the corpus spongiosum with a primary anastomotic technique. The classic reconstruction consists of a spatulated anastomosis of the proximal anterior urethra to the apical prostatic urethra. Experience has demonstrated, however, that anastomosis of the proximal anterior urethra to any segment of the posterior urethra (apical, prostatic, or below) **can be successfully accomplished by a widely spatulated anastomosis in which optimal epithelial apposition is achieved.** About 10% of pelvic fracture urethral injuries are associated with more complex injuries and can be associated with fistulas (most commonly urethral rectal fistulas). Reconstruction of these injuries is technically more demanding.

Several series support the concept that the bulk of pelvic fracture urethral injuries, even the most difficult cases, can be managed by the perineal approach (Webster et al, 1983, 1990; Webster and Sihelnik, 1985; Koraitim, 1985, 1997; Morey et al, 1996; Flynn et al, 2003). In fact, a transpubic or an abdominal-perineal approach, as pioneered by Waterhouse and colleagues (1973), in our experience, is not necessary for the reconstruction of distraction injuries. In addition, pubectomy can be associated with long-term sequelae that include shortening of the penis, destabilization of erection, and destabilization of the pelvis, resulting in a chronic pain syndrome with exercise. However, there are surgeons who continue to rely heavily on the transpubic approach (Koraitim, 1997; Das et al, 2004).

Alternatively, the above-and-below approach does have merit when concomitant surgery is planned in the region of the bladder neck. We have found, and Iselin and Webster (1999) have reported that the competence of the bladder neck is difficult to assess accurately before the reestablishment of urethral continuity. In the past, great reliance was placed on whether the bladder neck was closed or open on cystography. We now know, however, that contrast material can opacify the prostatic urethra when the bladder neck is more than adequately competent for continence. Similarly, confidence has been placed in the appearance of the bladder neck on endoscopic examination through the suprapubic tube. Again, even when an obvious scar is noted to involve the bladder neck, follow-up of these patients after the urethral reconstruction establishes continuity of the urethra and finds many patients with more than adequate continence. Still other patients are believed to have incontinence due to scar incarceration of the bladder neck, caused by the extensive fibrosis left behind by resolution of the hematoma. In our experience, however, this is an infrequent occurrence, and the appearance of the bladder neck by any modality available is not predictive of continence. Therefore, it is currently our practice to reestablish the continuity of the urethra and, when there are concerns about continence, forewarn the patient before the urethral reconstruction. If these patients find that they experience less-than-adequate continence postoperatively, the problem is addressed in a subsequent procedure (Bhargava et al, 2004).

At the time of reconstruction, before the patient is placed in the lithotomy position, endoscopy is performed through the meatus and again through the suprapubic tube sinus. Endoscopy on the table is designed to ensure that there is no concomitant vesicolithiasis. This endoscopy is performed with a rigid endoscope, which is manipulated through the suprapubic tube sinus and the bladder neck and positioned against the area of total obliteration. On gentle manipulation of the endoscope, if the impulse of the endoscope tip is felt on the patient's perineum, the impulse will be palpable when the perineum is opened and an instrument is manipulated through the bladder neck during reconstruction. If the impulse is not palpable perineally at this time, it may not be palpable during dissection, and in those cases, we create a temporary vesicostomy. This allows us to position an instrument reliably through the bladder neck, because the vesicostomy allows the surgeon to palpably identify the bladder neck before instrumentation of the posterior urethra. This maneuver has eliminated the occurrence of false passages with use of a sound such as the Haygrove staff through the suprapubic site, and also has eliminated the occurrence of misanastomosis of the anterior urethra to sites other than the apical proximal urethra.

We prefer the use of the exaggerated lithotomy position for the perineal approach (Fig. 36–34). This position is safe and provides optimal exposure to the area of the membranous and apical prostatic urethra (Angermeier and Jordan, 1994; Miller et al, submitted). A custom Skytron table, modified to allow the exaggerated lithotomy position, and a Stille-Scandia table, designed to place patients in the lithotomy position, are our preferences. The legs are carefully positioned in the Allen- or Guardian-style stirrups. Care is taken to avoid pressure on the lateral aspects of the lower extremities and calf muscles. The patient's hips are elevated into position by raising the buttocks portion of the operating table. The boots are positioned to avoid stretch injuries of the common peroneal nerves (see Fig. 36–34).

After the patient is correctly positioned, the perineal approach to reconstruction begins with an incision and dissection anterior to the transverse perinei musculature (anterior perineal triangle).

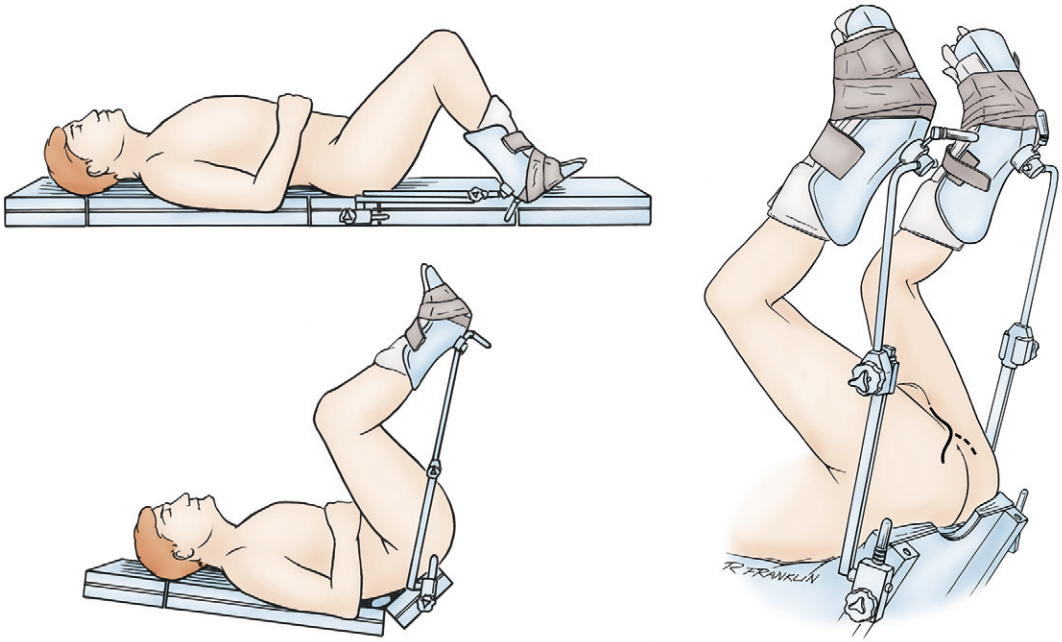


Figure 36–34. Patient placed in an exaggerated lithotomy position. The hips have been rotated into position by elevation of the buttocks portion of a specially modified table. The legs are suspended from boot-style stirrups with as little flexion of the hips and knees as allowed by the design of the stirrups. (From Angermeier KW, Jordan GH. Complications of the exaggerated lithotomy position: a review of 177 cases. J Urol 1994;151:866–8.)

This is in contrast to the approach posterior to the transverse perinei musculature (posterior anal triangle), which is useful for perineal prostatectomy. We use a λ-shaped incision (Fig. 36–35) that is carried sharply down to the midline fusion of the ischiocavernosus musculature (see Fig. 36–35A), then beneath the scrotum, to expose the uninvested portion of the corpus spongiosum. We then place a self-retaining ring retractor.

The fusion of the ischiocavernosus musculature is divided, and the musculature is cleanly dissected from the corpus spongiosum and bulbospongiosum (see Fig. 36–35B to D). The corpus spongiosum is detached from the triangular ligament and corpora cavernosa (see Fig. 36–35E), the bulbospongiosum is detached from the perineal body, and the dissection is carried farther down to the infrapubic space. Posterior detachment of the bulbospongiosum is carried anteriorly, and the dissection is eventually carried through the area of fibrosis (see Fig. 36–35F).

In some cases, the proximal blood supply is encountered and must be controlled. We have found that these arteries are easily controlled with a sharp tip hemostat and monopolar cautery. Suture ligature should be avoided in the case of the arteries to the bulbospongiosum because of their proximity to the nerves as they are coursing into the corpora cavernosa.

We then divide the triangular ligament and vigorously develop the intracrural space down to the pubis (Fig. 36–36). If the dorsal vein is encountered, it is ligated and divided. It is important to make sure that the arteries were not rolled into the intracrural space if the tissues were dislocated during trauma. It is not uncommon to see the penetration of the cavernosal arteries or the dorsal arteries, or both, into this space. If there is doubt about the nature of the vessels encountered, Doppler sonography should be used. When the pubis is exposed, the periosteal elevator can be gently introduced onto the retropubic surface, releasing and allowing the descent of the tissues from beneath the pubis.

We then introduce a Haygrove staff into the suprapubic sinus and through the bladder neck to the distal limits of the posterior urethra (see Fig. 36–35G and H). The impulse is palpated, and the fibrosis is resected until normal tissue planes are encountered. The tissue is submitted for histologic examination. The tip of the Haygrove staff is eventually concealed only by the normal urethral epithelium, at which point we open the epithelium and control it with either a skin hook or a stitch. We then perform endoscopy to ensure that the urethrotomy is at the distal limits of the posterior urethra. If a tension-free anastomosis is not thought possible, we mobilize the corpus spongiosum beneath the scrotum from its attachment to the corpora cavernosa. Aggressive mobilization of the corpus spongiosum is the last maneuver undertaken, because it is thought to have possible ill effects on the retrograde blood supply, which in the pelvic fracture patient may be tenuous. Meticulous detachment of the investment of Buck fascia from the corpus spongiosum increases the compliance of the corpus and limits the need for aggressive mobilization.

It is important to try to avoid the creation of chordee during the repair of a distraction injury. To prevent chordee, the attachment cannot be carried beyond the area of the penoscrotal attachment. It is warranted in some cases, however, to preoperatively counsel patients that they may have some chordee after aggressive mobilization that results in a primary anastomotic repair. Primary anastomotic repairs carry success rates in the high 90% range. If a technique of tissue transfer is needed, the long-term cure rates may eventually only be in the mid 80% range. Most of these patients are young. Successful, durable reconstruction is of paramount importance. If chordee results, it is most often mild and not disabling sexually; in our and other surgeons' minds, it is probably a fair trade for optimizing the urethral reconstruction. Development of the intracrural space—mobilization of the corpus spongiosum, infrapubectomy, and, if needed, rerouting of the

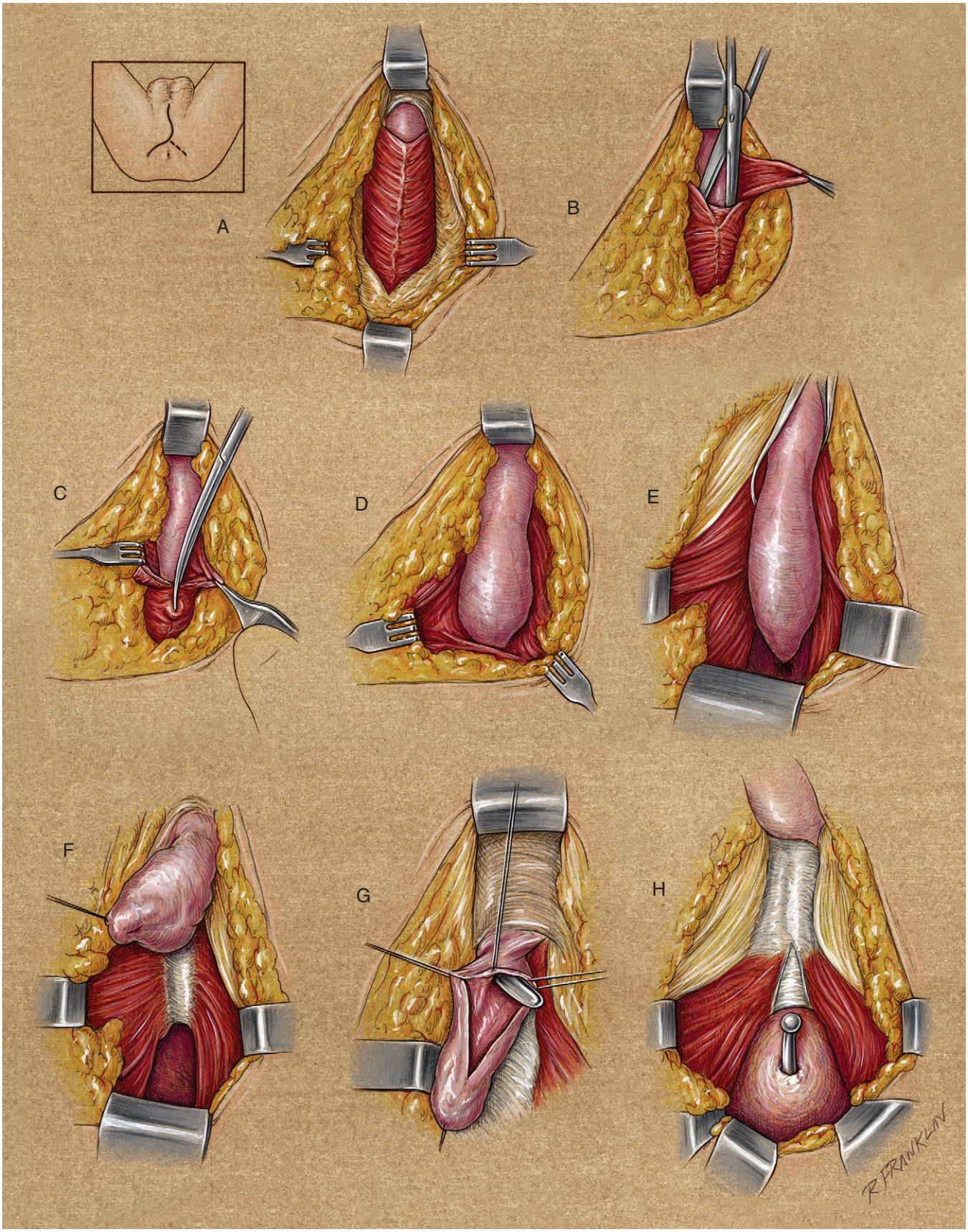


Figure 36–35. Diagram of a perineal repair of a membranous urethral stricture. A λ incision extends from the midline of the scrotum to the ischial tuberosities. **A,** Colles fascia has been opened to expose the midline fusion of the ischiocavernosus muscles and the tunica of the corpus spongiosum distal to the edge of the muscles. **B,** The scissors are introduced to develop the space between the muscle and the bulb of the urethra. **C,** An incision is made in the midline with the scissors, exposing the length of the bulb. **D,** The ischiocavernosus muscle is retracted to expose the full length of the bulb. **E,** The self-retaining retractor is placed to expose the inferior fascia of the genitourinary diaphragm. The bulb of the corpus spongiosum (bulbospongiosum) can now be mobilized to gain access to the fibrosed area of the urethra. **F,** The fibrosed urethra is incised, freeing the bulb. **G,** The anterior urethra is opened to make an adequate lumen. **H,** The Haygrove staff has been passed through the suprapubic cystostomy. Resection of the fibrotic distraction defect has allowed it to pass into the perineum.

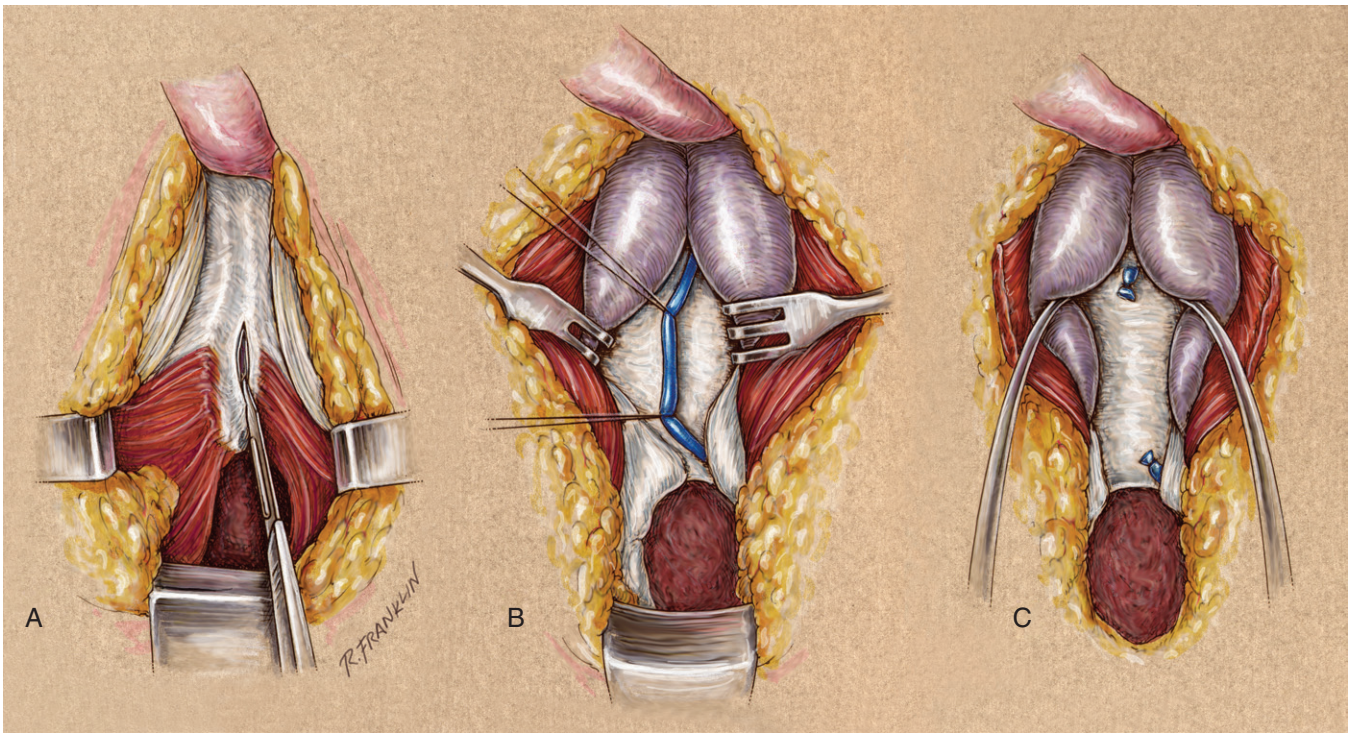


Figure 36–36. Division of the triangular ligament and development of the intracrural space. **A,** When the prostatic urethra is displaced, and the arc that the urethra must traverse needs to be shortened, that length can be shortened by incision of the triangular ligament. **B,** Incision and mobilization of the perichondrium and periosteum of the symphysis pubis to allow placement of retractors without trauma to the erectile bodies. Lateral displacement of the crura will expose the dorsal vein of the penis; after careful identification, the vein can be ligated and divided. **C,** Completion of the dissection affords additional exposure for resection of the fibrosis that surrounds the apex of the prostate and the proximal end of the disrupted urethra. (**A** to **C,** From Jordan GH. Reconstruction of the meatus–fossa navicularis using flap techniques. In: Schreiter F, editor. Plastic-reconstructive surgery in urology. Stuttgart: Georg Thieme; 1999. p. 338–44.)

corpus spongiosum—shortens the course that the corpus spongiosum must traverse and allows reconstruction without attendant chordee.

The proximal urethrotomy is spatulated so that it accepts at least a 32 French bougie à boule, and 10 to 12 anastomotic sutures are placed and tagged to allow identification of their position in the proximal anastomosis. We have used a combination of 3-0 Monocryl and 3-0 polydioxanone sutures for this purpose. No special needles are required for the placement of these sutures. However, a Heaney needle driver and a Ravitch needle driver can be useful in difficult cases. A lighted sucker is also beneficial at this point in the procedure. We recently have used a posterior retractor blade with integral light bundle and have found it very helpful with visualization.

After spatulation of the proximal urethrotomy and placement of the sutures, we spatulate the proximal portion of the anterior urethra. The spatulation is continued until the urethrotomy accepts a 30 to 32 French bougie à boule, and the anastomotic sutures are placed in their respective locations. Before seating the anastomosis, we introduce a soft silicone (Silastic) ribbed urethral stenting catheter through the anastomosis under direct vision. The wound is then copiously irrigated to reduce the clot around the area of the anastomosis, and the anastomosis is seated.

Next, we reattach the corpus spongiosum to the corpora cavernosa and the bulbospongiosum to the perineal body. We then place a small suction drain deep to the closure of the ischiocavernosus musculature and Colles fascia, and a second one superficial to that closure and beneath the subcutaneous closure.

In those cases in which the proximal urethra is significantly distracted in a rostral direction, the surgeon must be prepared to perform infrapubectomy (Fig. 36–37) or corporeal rerouting, or both (Fig. 36–38). The performance of the infrapubectomy, along with the development of the intercrural space, allows exposure of the apical prostatic urethra. When the prostatic urethra remains rostrally displaced, the impulse of the sound or instrument placed through the cystostomy tract into the bladder neck is often not readily apparent. In these situations, it is comforting to be able to palpate the bladder neck and the properly placed sound before embarking on a dissection beneath the pubis. In addition, if the rostral distraction is significant, the path of the anterior urethra over the hilum of the penis into the infrapubectomy often does not allow a tension-free anastomosis, and the infrapubectomy can be continued beneath one side of the corpora cavernosa, allowing rerouting of the corpus spongiosum (see Fig. 36–38).

Postoperative Management

We use a small soft silicone (Silastic) stenting catheter. Urine is diverted by way of the suprapubic cystostomy, and the urethral catheter is plugged and serves as a stent only. After the reconstruction, patients are initially kept at bed rest for 24 to 48 hours and then ambulated and discharged with the suprapubic catheter and stenting urethral catheter in place. They are also discharged on a regimen of oxybutynin and a suppressive antibiotic. The drains are removed as drainage allows.

A voiding trial with contrast material is performed between 21 and 28 days postoperatively. Patients are directed to stop taking oxybutynin 24 hours before the voiding trial. In anastomoses that are technically straightforward, the trial is performed at 21 days, and in those cases with more rostral distraction of the proximal

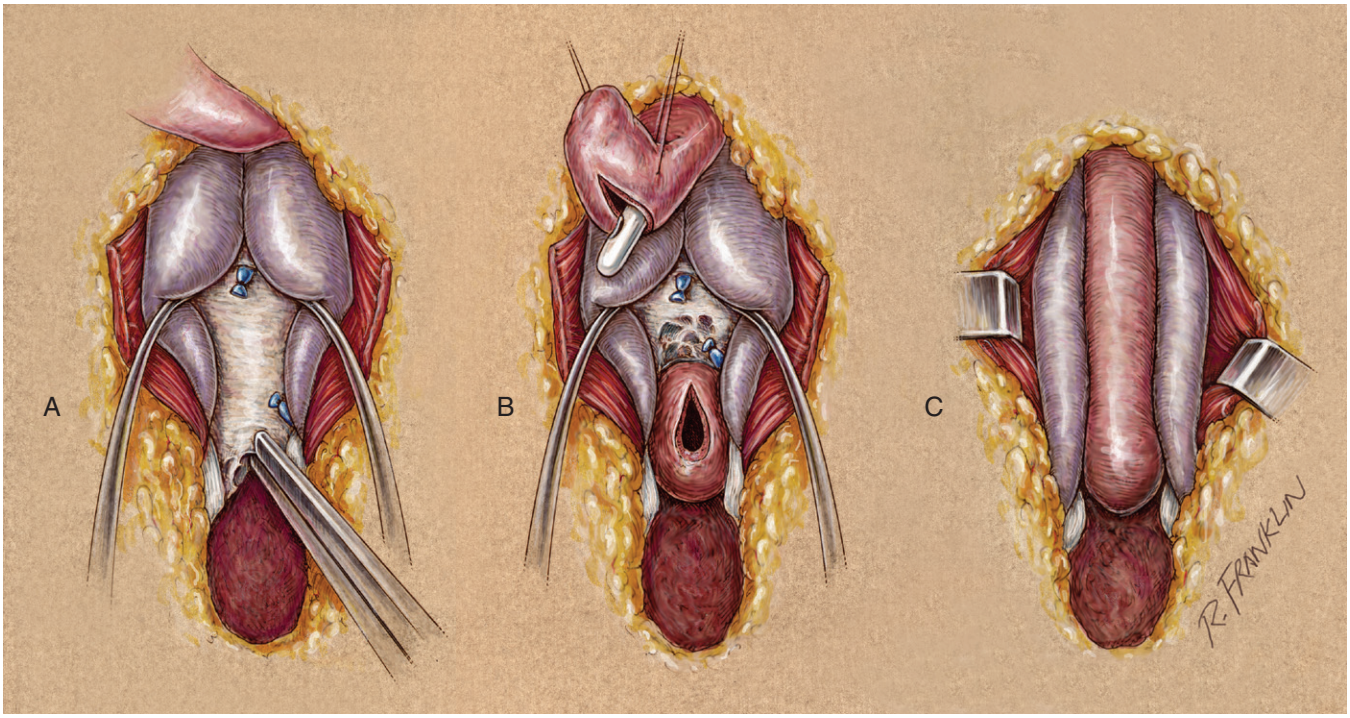


Figure 36–37. Infrapubectomy. If the prostate is elevated behind the symphysis pubis **(A)**, the inferior aspect of the symphysis is resected with a Kerrison rongeur. As much of the bone can be removed as necessary **(B)**, to afford a simple approximation of the ends of the urethra **(C)**.

urethra, the trial is delayed for 3 to 5 days longer. The trial involves removing the urethral catheter, filling the patient's bladder with contrast material, and instructing him to void. We do not use pericatheter retrograde urethrography for the evaluation of patients who have undergone urethral reconstruction. The voiding film is examined to ensure that there is not extravasation and that the reanastomosis appears widely patent. A urine culture specimen is also obtained, and the suprapubic catheter is plugged. The patient is allowed to void through the urethra for 5 to 7 days, and the suprapubic catheter is then removed. Patients remain on the suppressive antibiotic regimen until they are tube free, and a culture and a sensitivity test are performed. At that time, they are prescribed a short regimen of culture-specific antibiotic.

Approximately 6 months postoperatively, and again 1 year later, the patients are evaluated with flexible endoscopy. At that time, we consider the reconstruction to be mature, and it should be widely patent. Absent the reappearance of symptoms, we refer further follow-ups to the referring urologist.

We have almost completely replaced postoperative retrograde studies with flexible endoscopy. We have not found flow studies to be valuable in observing these patients and, in many cases (anterior urethral reconstruction), have found that retrograde urethrography is more confusing than helpful.

With the use of the techniques discussed or similar techniques, curative rates for reconstruction of posterior pelvic fracture urethral injuries are in the high 90% range. In large centers, failures are not due to technical problems (i.e., anastomotic restenosis). In general, failures are indicative of ischemia of the proximal corpus spongiosum with ensuing stenosis of the mobilized corpus spongiosum. This occurs because, with mobilization, the corpus spongiosum, in essence, becomes a flap with the vascular pedicle being the retrograde vascularity from the arborization of the dorsal arteries through the glans (Fig. 36–39).

We have studied this phenomenon in our trauma patients and have now arrived at conclusions that we believe allow us to predict the patients at risk for this ischemic atrophy phenomenon. Initially, we used pudendal angiography to study all our trauma patients who seemed to be at risk for bilateral deep internal pudendal artery injury at the time of trauma. These were patients who had evidence of injury to the dorsal penile nerves, patients in whom reconstruction had failed at other centers, patients with lateral impact pelvic fractures, and patients whose pelvic fractures were of the "windswept" variety (Brandes and Borrelli, 2001). We found that many patients had evidence of either unilateral or bilateral pudendal artery lesions but that most had evidence of vascular reconstitution. **Patients with an intact pudendal artery on one side often were potent and were reliably cured with reconstruction. Patients with only reconstituted vessels, either unilateral or bilateral, never were potent but were reliably reconstructed.** We found that these patients were optimal candidates for penile arterial revascularization to improve potency. Because we noted this relationship to potency, we began looking at our patients with duplex ultrasonography. We found that patients with normal pudendal arteries, either unilateral or bilateral, demonstrated normal arterial parameters on duplex evaluation. Those with only reconstituted arteries, either bilateral or unilateral, never had normal arterial parameters on duplex ultrasonography.

This now allows us to proceed to pudendal angiography only in those patients with abnormal arterial parameters on duplex ultrasonography; the patients with normal findings on ultrasonography predictably do well with reconstruction. Our data also show that patients do well with reconstruction if they have at least one side that is reconstituted, and those patients at risk for ischemic stenosis are only those with bilateral complete obstruction of the internal pudendal vessels. In such a patient, we now perform penile arterial

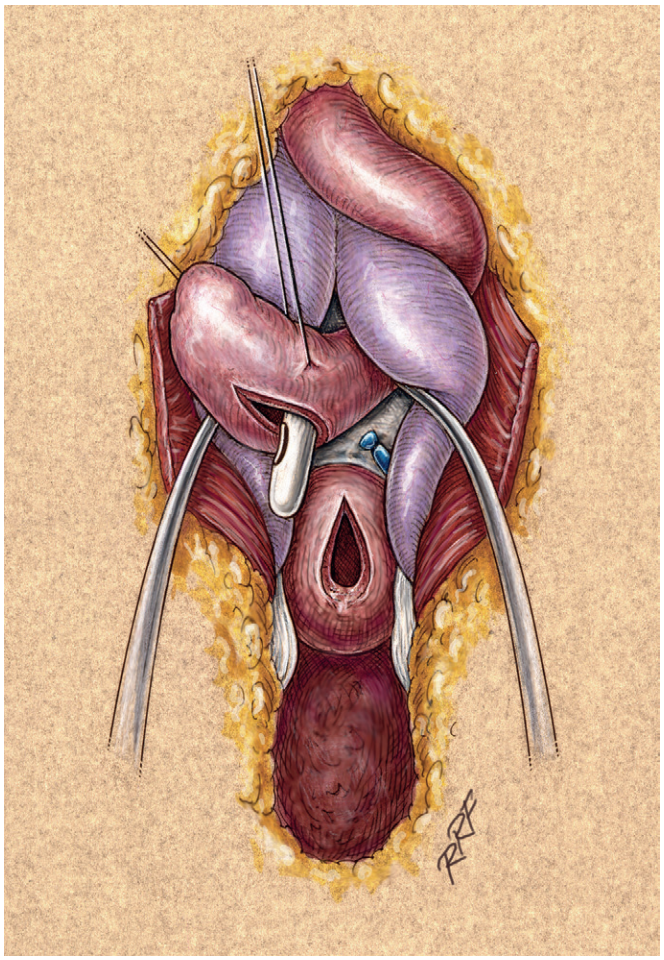


Figure 36–38. Resection of the pubis and rerouting of the urethra around the crus. When the prostate is markedly displaced, it may be necessary to expand the infrapubectomy. Sometimes, despite separation of the crura to the full extent possible, the two ends of the urethra do not meet when they are brought directly through the crus. It is necessary to bring the urethra lateral to one of the crura to make up this length.

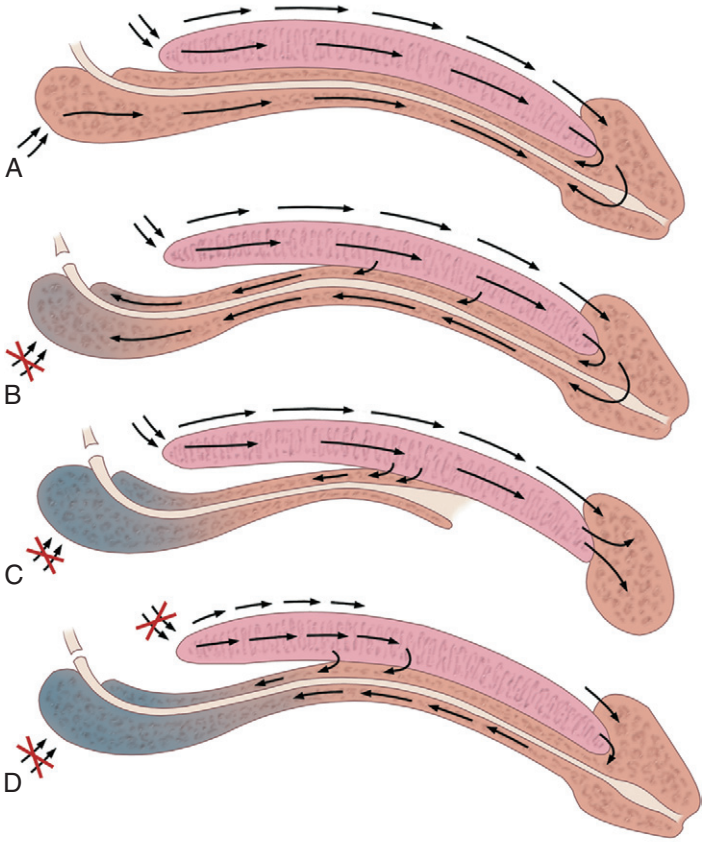


Figure 36–39. Diagrammatic representation of the deep vasculature of the penis. **A**, In the normal situation, through the common penile artery, flow is directed to the tip of the penis with arborization into the spongy erectile tissue of the glans penis. This provides retrograde flow into the corpus spongiosum. If the arteries of the bulb are intact, there is also antegrade arterial flow to the corpus spongiosum. **B**, With interruption of the arteries to the bulb and mobilization of the corpus spongiosum, all flow to the corpus spongiosum is retrograde through the common penile arterial system. **C**, In the case of hypospadias, in which the distal corpus spongiosum may have been interrupted, with proximal mobilization of the corpus spongiosum and therefore division of the arteries to the bulb. Even if the common penile circulation is intact to the tip of the penis, it may not adequately provide retrograde vascularity to the corpus spongiosum; hence, ischemic stenosis can ensue. **D**, In the case of injury to the common penile artery, with elevation of the proximal corpus spongiosum and division of the arteries to the bulb, blood flow to the proximal corpus spongiosum may not be adequate, leading to ischemic necrosis or ischemic stenosis.

revascularization to augment the vascularity and, with that accomplished, then proceed to urethral reconstruction (Jordan, 2005; Davies et al, 2009). We are currently evaluating new technology to see if we can get the same information regarding the deep vasculature without need for either duplex ultrasonography or angiography in many patients. The SPY Imaging System (Novadaq, Bonita Springs, FL) is a novel noninvasive technique of evaluating vasculature. It uses indocinen green (ICG) dye, which is a fluorescent compound injected intravenously. It binds to plasma proteins and consequently remains intravascular, making it ideal for imaging the arterial supply. A laser is used to excite the ICG dye and make it fluoresce. The filtered fluorescent images are captured by a charge-coupled device video camera demonstrating the vasculature. In many cases of pelvic fracture urethral distraction defects, erectile dysfunction is a consequence of the injury, although clearly in some patients, erectile dysfunction results from the reconstructive surgery. We think that the incidence of injury to the pudendal arteries is drastically underreported and underrecognized. Thus, we, along with others, believe that in many of these cases, the cause of erectile dysfunction is vascular (Brandes and Borrelli, 2001). However, others think that in most, the cause is neurologic (Shenfeld et al, 2003).

Summary

Using the maneuvers outlined, we have found that virtually all distraction injuries can be reconstructed through a perineal approach with an anastomotic technique. Although the above-and-below approach is used when concomitant bladder neck surgery is performed, the inability to accurately identify those patients has led us to perform bladder neck surgery at a second setting. We have therefore abandoned a transpubic approach as applied to posterior urethral distraction injuries.

Although we favor primary reconstruction of posterior urethral distraction injuries, others choose to manage these injuries endoscopically (Barry, 1989). We have found that the endoscopic management of pelvic fracture urethral injuries is not a simple procedure and must be undertaken only by a skilled and experienced surgeon. Many of these procedures can be categorized as a

"cut-for-light" procedure. Although there are surgeons who report success, the majority of cut-for-light procedures are not done with sufficient precision to allow adequate realignment of the urethra. We have seen many disasters that have resulted from these procedures and in most cases condemn the use of these modalities. In addition, no cut-for-light series compares favorably, with regard to long-term success rates, with series from large centers that use primary anastomotic techniques (Levine and Wessells, 2001).

In 1989, Marshall described his method of using stereotactic techniques for endoscopic alignment of the ends of the urethra. He emphasized the length of time it takes to obtain precise alignment before undertaking the endoscopic portion of the procedure. In his procedure, he passes a wire through the aligned ends of the urethra, minimally dilating the channel, and widening it with transurethral resection. The scar is stabilized by a period of self-catheterization. A communication with Marshall has determined that he has limited the applications of this procedure and does not advocate it as a primary modality. Patients whose medical condition, age, or concomitant orthopedic injury prevents them from being placed in the exaggerated lithotomy position, or reconstructed using a transpubic approach, may be managed with this technique.

In children, the goals of surgery are the same as in adults. In our experience, most children can be reconstructed by the same perineal exposure as in adults. Exposure is clearly more difficult, but nonetheless perineal anastomosis can be done (Hafez et al, 2005). However, the posterior, sagittal trans-sphincteric approach has been proposed as a better approach in children (Mathews et al, 1998; Peña and Hong, 2004). We agree that the posterior approach is an elegant method of exposure; however, our observation is that with this approach, surgeons tend to resort to techniques of substitution reconstruction where primary anastomosis could be done and, in our opinion, is superior. With our experience accumulating using the vessel-sparing approach to anterior urethral reconstruction—both primary anastomosis and augmented anastomosis—we have extended the technique to select patients with pelvic fracture urethral reconstruction and have found the approach feasible with good results in a small number of patients. The advantage however has not been proven.

Key Points: Distraction Injuries of the Urethra

- Urethral distraction injuries are the result of blunt pelvic trauma and accompany about 10% of pelvic fracture injuries. Many injuries appear to not totally distract the entire circumference of the urethra; instead, a strip of epithelium may be left behind.
- The use of aligning catheters acutely is somewhat controversial, but most would agree that the aligning catheter, at the very worst, facilitates subsequent reconstruction and, at best, often leaves the patient with an endoscopically manageable stenosis.
- As with any stricture, it is important to define the precise anatomy. The combination of contrast-enhanced studies with endoscopy and selective magnetic resonance imaging is useful. The appearance of the bladder neck on contrast-enhanced studies or on antegrade endoscopy is not predictive of ultimate function of the bladder neck. Hence, simultaneous reconstruction of the bladder neck and the posterior urethra is, for the most part, not currently undertaken.

VESICOURETHRAL DISTRACTION DEFECTS

Enthusiastic use of radical prostatectomy has unfortunately led to increasing experience with patients who have had total obliteration of their vesicourethral anastomosis. In some patients, there is distraction of the vesicourethral anastomosis with either a totally obliterating distraction defect or severe anastomotic stenosis. In addition, with the proposal that bladder tube interposition might enhance continence, a new entity, the stenotic or obliterated vesicourethral anastomosis due to ischemia of the bladder tube, is now encountered.

As with other defects, it is important to accurately determine the length of the defect. This can be accomplished by simultaneous cystography with retrograde urethrography, simultaneous retrograde urethrography and antegrade endoscopy through the suprapubic tube, or both.

There are a number of options for the management of these complex patients. Many have other medical problems, and it has been our observation that many have thick and small bladders, possibly contributing to the difficulty with the initial surgery. The ever-present issue of body habitus also must be considered and, in our opinion, contributes to problems with the initial anastomosis. An indwelling suprapubic tube must always be considered an option. In the individual who is significantly overweight, the results of aggressive reconstruction have not been good. The place for endoscopic techniques is covered later in this section; however, in the case of short-length distractions, we have had good success with aggressive incisions at the 3-o'clock and 9-o'clock positions followed in approximately 3 weeks with repeated incisions. Whether the holmium laser is better than the cold knife can be debated; the hot knife is not necessary. If one must "core through" to establish continuity, in our opinion endoscopic procedures have no place except as discussed later.

In some cases, a continent catheterizable bladder augmentation may indeed be a better operation than aggressive functional reconstruction; however, the very heavy patient makes construction of a functional catheter channel difficult. Diversion must also be entertained, and in patients in whom functional reconstruction is not an obvious choice, it then becomes a primary option.

If functional reconstruction is deemed possible, we think it is a reasonable choice and our technique is as follows. We place the patients in a low lithotomy position and use an abdominal-perineal combined approach. We make a lower midline incision, exposing the bladder and dissecting it from the lateral sidewall and further mobilizing the anterior bladder from beneath the pubis as aggressively as can be safely undertaken from above. We then open the peritoneum and develop the retrovesical space, again taking care to complete the dissection as safely as can be accomplished from above.

A second surgeon then begins the perineal dissection by a curvilinear perineal incision similar to that used for a radical perineal prostatectomy. The dissection is posterior to the transverse perinei musculature (posterior anal triangle) and carried along the anterior rectal wall to the area where fibrosis is encountered from the prior radical prostatectomy dissection. The impulse of the perineal surgeon's digits can usually be felt adjacent and lateral to the area of fibrosis and distraction at this point. In addition, the abdominal surgeon places a finger at the limits of the retrovesical dissection from above to provide another palpable landmark and to ensure a safe dissection anterior to the rectal wall and posterior to the

bladder and trigone. The perineal dissection is then joined to the abdominal dissection, and the rectal wall is completely peeled off the area of fibrosis associated with the distraction defect. We then place drains between the rectum and the distraction defect, encircling the area of fibrosis.

The dissection beneath the pubis is made easier by the excision of an ellipse of the rim of the superior pubic ramus. Total pubectomy is not required. The partial pubectomy can be performed with the reciprocating attachment of the Aesculap surgical drilling device (Aesculap, Tuttlingen, Germany); this makes placement of the sutures technically straightforward and improves the exposure for the dissection and resection of the distraction fibrosis.

At this point, the bladder is opened and the area of the bladder neck is determined. A sound is placed and advanced to the area of obliteration. This allows us to completely resect the well-defined area of fibrosis. The urethral stump is exposed and opened, and the site of the neobladder neck, having been identified, is opened. We marsupialize the bladder epithelium as described by Eggleston and Walsh (1985), place anastomotic sutures in the urethral stump, and pass a stenting catheter.

Before the vesicourethral anastomosis is seated, the omentum is mobilized and placed between the posterior wall of the anastomosis and the anterior rectal wall. We then seat the anastomosis and wrap the omentum around the area of anastomosis, tagging it into place. The lateral vesical spaces are drained with closed-suction drains, and a suprapubic tube is left in place when the vesicostomy is closed.

Postoperative care is the same as for a radical prostatectomy. The patients are discharged when their drainage and ambulation allow and their diet has been resumed. We evaluate the patients 4 to 6 weeks postoperatively, with the stenting urethral catheter removed and the bladder filled by way of the suprapubic tube.

Because one attempt has failed in these patients, we generally are conservative with the timing of a voiding trial. In some cases, voiding trials are being done at 2 to 3 weeks.

Our series continues to grow, and we continue to have excellent success in reconstruction. We have some patients who deem their continence adequate for their lifestyle; in the others, we have been successful with the placement of an artificial sphincter.

Others have proposed a different approach to these very difficult cases. In patients for whom multiple attempts at dilation or incision of these vesicourethral anastomotic stenoses have failed, Elliott and Boone (2001) proposed making an incision with placement of the UroLume endoprosthesis, followed at an interval by the placement of an artificial sphincter. They initially described nine men treated with this approach; seven of the men were satisfied with the results of their treatment at 17.5 months mean follow-up. Others (Mark et al, 1993; Kaplan, 2004; Anger et al, 2005) have proposed slight modifications of this approach and are also reporting adequate patency and continence in these patients. Additionally, there are centers accumulating experience with either a pure perineal or a pure abdominal approach with good success rates (Herschorn, 2007; Fisch, 2009).

COMPLEX FISTULAS OF THE POSTERIOR URETHRA

The increase in the performance of radical prostatectomy has also led to an increased incidence of vesicorectal or vesicourethrorectal fistulas. In most cases, these are small and managed by a transperineal, transanal–trans-sphincteric, or posterior approach. However, some cases are complex, with the fistulas associated with large granulated cavities. The problem is magnified when radiation (brachytherapy, external beam therapy, or both) is part of the equation. With radiation fistulas, a number of centers have gone to diversion with ileal conduit or bowel pouch as opposed to functional reconstruction. These cases have also been managed with the approach described earlier for vesicourethral distraction problems. The omentum, however, serves an even more important purpose in these cases. In addition, with the increasing application of "minimally invasive" modalities for carcinoma of the prostate (i.e., brachytherapy, combined brachytherapy with external beam irradiation, higher dose external beam irradiation, and cryotherapy), the magnitude of complexity of these problems of prostatic urethral fistulas, granulated cavities, and severe rectal injury continues to increase. We have tried to approach these problems aggressively, with preservation of function, where possible.

In many of these cases, salvage prostatectomy can be combined with rectosigmoid resection. In some cases, we have successfully reanastomosed the bladder to the membranous urethra. Preservation of continence has been mixed. Where vesicourethral anastomosis is not possible, a urachal-peritoneal flap combined with a rectus abdominis muscle flap is used to bolster the closed bladder neck and to keep the closed bladder neck from sticking to the back of the pubis. The bladder is augmented, and a continent catheterizable channel is developed. In some cases, the continuity of the colon cannot be reestablished, and a colostomy is performed as distally on the descending portion of the colon as possible. Whenever continuity of the colon can be reestablished, a J-pouch coloanal anastomosis is done. Omentum is used to envelop the rectal closure or to separate the rectal closure from the vesicourethral anastomosis. The combined abdominal-perineal approach that was previously described provides excellent safe exposure for management of these complex situations. The morbidity of this approach has been acceptable.

One must be careful in addressing the irradiated bowel. We had a patient who did well with his surgery for continent catheterizable augmentation and bowel closure, but when his colostomy was reversed, he developed an overwhelming colitis and a refistula, with an eventual septic death. Another patient had a breakdown of his bladder neck closure and to date remains with a large vesicoabdominal fistula. Thus it cannot be overemphasized that these cases must be individualized. When they go well, they go wonderfully well; when they do not, they become a disaster for the patient, the patient's family, and the surgeons involved.

Zinman recently reported a 10-year experience with the management of rectourethral fistula. That series had 33 patients who had fistulas and who had not been irradiated, and 33 more who had been irradiated. Mean follow-up for the entire series was about 20 months. The review was a retrospective review taken from office records and hospital records. All fistulas were repaired by an anterior transperineal approach using gracilis muscle interposition flaps, and in some cases with a buccal graft. In this series, 100% of the nonirradiated fistulas were successfully closed with a mean follow-up of 20 months, 85% of the irradiated fistulas were closed in a single stage, and 12% required an additional procedure, with an ultimate closure rate of about 97%. In the nonirradiated group, there were no urethral strictures noted with long-term follow-up; 5 recurrent strictures were noted in the irradiated group. In the nonirradiated group, 91% of the patients had their bowel undiverted. In the irradiated group, 39% had long-term bowel diversion. Zinman believes that the use of muscle interposition flaps are integral to achieving good results, and their use of buccal

mucosal grafts, where needed to augment the closure of the urinary tract, were also believed to be invaluable (Vanni et al, 2009). Clearly, both an estimation of ultimate urinary and bowel function are integral to the determination of the plan for reconstruction and/or diversion. Also, it must be recognized that the surgical approach chosen both facilitates and limits options (i.e., of the bowel, the urethra, and/or tissue interposition) (Lane et al, 2006).

Key Points: Vesicourethral Distraction Defects and Complex Fistulas of the Posterior Urethra

- Vesicourethral distraction defects are an unfortunate complication of radical prostatectomy.
- There are a number of options for management of these complex patients. An indwelling suprapubic tube must always be considered an option, long term. Likewise, in some cases, a continent catheterizable bladder augmentation may indeed be a better operation than aggressive functional reconstruction. If functional reconstruction is deemed reasonable, we have employed an above-and-below technique, in which laparotomy is combined with a posterior perineal triangle dissection.
- The interposition of omentum has been used both for distraction defects and for complex fistulas. This approach allows safe mobilization of the rectum from the area of the distraction scar or from the fistula site.
- When radiation is added to the equation, the complexity of reconstruction is magnified. The effects of radiation must be allowed to settle; tissue interposition is the rule, and in many cases functional reconstruction is not possible. Some think that diversion, in the case of the irradiated patient, is the safest and best option.
- Careful consideration of ultimate urinary and bowel function are integral to proper planning of surgery.

CURVATURES OF THE PENIS

Normal elasticity and compliance of all tissue layers of the penis are critical for erectile function, tumescence, and rigidity. Tissues must expand in all dimensions as the penis engorges with blood; eventually, the tissues of the tunica albuginea and the septal fibers of the corpora cavernosa are stretched to the limits of their compliance, and tumescence is converted to rigidity. In the normal penis, the tissues are symmetrically elastic and the erection is straight. In curvature of the penis, there is relative asymmetry of one aspect of the erect penis. In some cases, this arises from diminished compliance of one aspect of the tunica albuginea or outright foreshortening of one aspect of the erectile bodies.

The term *chordee* means curvature, but it is commonly used as if it refers to the tissues causing the curvature. This misuse of the term is seen in the statement "the chordee was resected"; properly phrased, "the chordee can be corrected by resecting the inelastic tissues that are causing the chordee."

Curvatures of the penis can be congenital or acquired. Some confusion also exists in common usage of the term *congenital curvature of the penis*. The terms *congenital curvature of the penis* and *chordee without hypospadias* have often been used interchangeably. We prefer to reserve the term *chordee without hypospadias* for those patients in whom the meatus is properly located on the tip of the glans penis, yet a ventral curvature is associated with abnormalities of the ventral fascial tissues or corpus spongiosum, or both. It has long been recognized that hypospadias is a condition that is associated in some males with either a diminutive penis or a micropenis. Although a small penis is not diagnostic of hypospadias, it is highly unusual for a patient with hypospadias to have an exceptionally large erect penis. In contrast, other congenital curvatures of the penis (ventral, lateral, or dorsal) are inevitably associated with the finding of a large erect penis. Because **the trauma that results in acquired curvature is virtually always associated with intercourse, the occurrence of acquired curvature is nil before the onset of puberty.** We have seen some patients in whom there was a history of trauma during vigorous masturbation, but these patients are the exception. Like congenital curvatures of the penis, acquired curvatures may be dorsal, lateral, ventral, or complex.

Types of Congenital Curvature of the Penis

The urethra begins as an epithelial groove in the midline of the ventral surface of the developing penis. As the groove extends, it deepens, with the edges eventually meeting to fuse into a tube. Fusion begins proximally and progresses distally. During normal development, the fusion of the urethral tube eventually reaches the tip of the glans penis. Proliferating mesenchyma surrounds the tube, separating it from the skin, and differentiates to form the corpus spongiosum, Buck fascia, dartos fascia, and overlying ventral skin of the penis. Fetal development of the penis is regulated by testosterone, produced by the fetal testis, which is converted by 5α-reductase to dihydrotestosterone. Dihydrotestosterone acts directly on cells with androgen receptors and on all layers of the male external genitalia. This embryologic process explains the development of the anterior urethra that is unique to males.

Maturation of these tissues into normal structures depends on the same growth factors that control the formation of the urethra. Even though urethral development has progressed normally, mesenchymal tissue development in the penis may be deficient or abnormal and result in dysgenetic and inelastic fascial layers. In unpublished data, Galloway and associates (El-Galley et al, 1997) have shown that at least in hypospadias, there is a deficiency of growth factors in the ventral penile skin. To our knowledge, to date there are no data that show the same growth factor deficiencies for the deeper tissues.

In 1973, Devine and Horton proposed a typing classification for the various congenital curvatures. In type I congenital curvature, the urethral meatus is at the tip of the glans. None of the surrounding layers are normally formed, however, and the epithelial urethra is associated with malfusion of the corpus spongiosum and all the tissues superficial to the urethra. Skin coverage of the epithelial tube is present. In type II, a dysgenetic band of fibrous tissue thought to be derived from the mesenchyma, which would have produced the Buck fascia and the dartos fascia, lies beneath and lateral to the urethra. However, the urethra is contained within a normally developed and fused corpus spongiosum.

In type III, the urethra, corpus spongiosum, and Buck fascia are all normally developed and ventrally fused. However, there is a short area of inelastic tissue in the dartos layer of the penis that causes a relatively sharp bend. Abnormal development of the dartos fascia is frequently associated with complex curvatures. With extensive involvement, the inelastic dartos can be sufficient

to restrain the penis and conceal the penile shaft. In many of these cases, there appears to be abnormal prominence of the mons fat pad. These stigmata are thought to be associated with an abnormality in the proper progression of virilization during fetal development.

In type IV, although the urethra, corpus spongiosum, and fascial layers are normally developed, there is relative shortness or inelasticity of one aspect of the tunica albuginea of the corpora cavernosa. Experience has shown that most patients whose congenital curvature is type IV seem to actually demonstrate evidence of a hypercompliance of the tunica albuginea. In these patients, the flaccid penis is normal in size and not necessarily impressively large, whereas the erect penis is large. The tunica albuginea of the corpora cavernosa is required to expand through a wide range, and if there is asymmetry in the compliance of the tunica, curvature occurs. It is not uncommon for patients with type IV curvature to have noticed curvature before puberty; but as they traverse puberty, an increase in the curvature is noted because of the penile hypertrophic growth spurt that occurs during this time.

Type V congenital curvature is also known as the congenital short urethra. This implies that there has been correct fusion of all elements of the penis (i.e., tunica albuginea, urethral epithelium, corpus spongiosum, Buck fascia, dartos fascia, and ventral skin). However, during erection, the correctly fused urethra and corpus spongiosum are not long or compliant enough to match the compliance of the other ventral tissue layers.

If type V congenital curvature exists at all, it occurs so rarely that when it is encountered, one should doubt the findings. Whereas discussion of the condition in the past has centered on the best location to "cut the urethra" during the repair, on the rare occasions when this condition is encountered, it is our belief that it should be diagnosed and treated only by the most experienced surgeons. In general, if the urethral meatus has developed to the tip of the glans, the urethra should not be divided to correct ventral curvature of the penis. Although there will obviously be extremely rare exceptions to this bold statement, if those exceptions are encountered, their existence should still be questioned.

The congenital curvature types I, II, and III represent forms of the hypospadias anomaly, and we prefer to refer to them collectively under the term *chordee without hypospadias*. This term implies that although the meatus is not improperly placed, curvature is due to inappropriate fetal development of the ventral penile structures. We prefer to refer to the type IV anomaly as congenital curvature of the penis. If a patient has findings of hypercompliance of the corpora cavernosa and a ventral curvature, the patient is diagnosed as having congenital ventral curvature of the penis; and if the hypercompliance causes a lateral curvature, it is referred to as congenital lateral curvature of the penis (left or right). Although, as mentioned, **the type V anomaly is so rarely encountered that it deserves its own diagnosis, we believe its correction is best discussed with types I, II, and III, under the category of chordee without hypospadias.**

Chordee without Hypospadias in Young Men

Patients with chordee without hypospadias usually present with either ventral curvature or ventral curvature associated with torsion (complex curvature). These young men do not typically have a greater than average stretched penile length (13.1 cm) (Schonfeld and Beebe, 1942) and will have noted curvature throughout life. If prepubescent, they have obvious curvature with erection; if postpubescent, they may offer a history of increasing curvature as they pass through puberty.

In many cases, there are abnormalities of the ventral penile skin. These might consist of either an element of hooded preputial skin or a high insertion of the penoscrotal junction. Although the patients have fusion of the preputial skin, there is also often a wrinkled appearance dorsally that we now recognize to be a form of the classic hooded preputial skin. In addition, in many cases, the tissues on the ventrum of the penis seem inelastic as the patient's penis is examined on stretch. This palpable inelasticity on the ventral penis consists of dysgenetic tissue, which can replace the Buck and dartos fascia layers; and in some cases, there is an element of inelasticity of the tunica itself.

During surgical exploration, Devine and Pepe obtained tissue from these patients for evaluation of 5α-reductase levels. Those data suggested a deficiency of the enzyme in the ventral dysgenetic tissue. The values were inconclusive at the time and the study was discontinued. El-Galley and colleagues (1997) also looked for growth factor deficiency in tissues of males with hypospadias and found a correlation. To our knowledge, however, a growth factor analysis has not been undertaken in patients with chordee without hypospadias.

An important part of the preoperative evaluation is the submission of instant or digital photographs of the erect penis, taken by the patient, documenting the curvature. The photographs are especially helpful in differentiating between the patients we refer to as having chordee without hypospadias and those with congenital curvatures of the penis. In a patient who has chordee without hypospadias, the photograph reveals an erect penis commensurate with the size of the detumesced penis, whereas in the congenital curvature patient, the erect penis is noticeably large. It is important to address the psychologic aspects of the condition as an integral part of the treatment, and many of our patients will see a psychologist preoperatively. Corrective surgery for chordee without hypospadias is highly successful, and, in almost all cases, an effective correction can be accomplished with a single operation (Devine et al, 1991). In some cases, the penis has been straightened by excision of all the dysgenetic tissues from the ventral side of the penis and wide mobilization of the corpus spongiosum from the glans penis into the perineum.

Even in patients with obvious abnormalities of the corpus spongiosum (i.e., poor ventral fusion or frank bifid corpus spongiosum), wide mobilization usually reveals that it is not the corpus spongiosum that remains as the ventral limiting factor. In most patients, the penis remains curved because of the inelasticity of the ventral aspect of the corpora cavernosa themselves. Furthermore, in an occasional patient, the corpus spongiosum becomes atretic distal on the shaft, and the urethra itself is only an epithelium-lined tube. Even in these patients, with wide mobilization of the epithelial distal portion and elevation of the proximal corpus spongiosum, it is unusual to find the corpus spongiosum or the epithelial tube limiting the ventral erection. If the epithelial tube has served as an adequate urethra (i.e., it is not stenotic), the morbidity of urethral division and subsequent need for urethral reconstruction must be considered before such a procedure is undertaken. Because the evolution of hypospadias repairs accomplished by wide mobilization of the corpus spongiosum and epithelial and corpus spongiosal elements distal to the meatus has allowed onlay procedures, the morbidities of urethral division must be strongly considered and, we believe, usually avoided.

In children, after mobilization and excision of the dysgenetic tissues, the residual chordee can usually be corrected by making a longitudinal incision, with a sharp blade, in the ventral midline of the corpora cavernosa while an artificial erection is maintained. The incision (midline ventral septotomy) can often be extended between the corporeal bodies for a significant distance, allowing the edges of the ventral tunica to move laterally. The penis will noticeably straighten with erection.

If this maneuver is not sufficient, the dorsal neurovascular structures can be mobilized in concert with Buck fascia, and a small ellipse or ellipses of dorsal tunica albuginea can be excised and closed with watertight plicating sutures. Caution is important, however, when the dorsal neurovascular structures are mobilized; with poor development of the ventral structures, which occurs in some patients, the arborization of the dorsal arteries provides the dominant vascularity to the glans.

Congenital Curvatures of the Penis

Patients with congenital curvature of the penis can have ventral, lateral (which is most often to the left), or, unusually, dorsal curvature. Photographs of the erect penis demonstrate a smooth curvature that generally involves the entire pendulous portion of the penile shaft.

Patients usually present as otherwise healthy young men between the ages of 18 and 30 years. Many of these patients have noticed curvature before passing through puberty but have presumed it to be normal. With puberty, however, they discover that the curvature is not normal, or they become sexually active and discover that the curvature impedes their efforts, or they notice increasing curvature as they pass through puberty, and this, in their minds, clearly would preclude sexual intercourse. On occasion, a patient waits until he is older than 30 years to deal with the anomaly, and, even less often, there is a younger adolescent, who is able to discuss his genitalia with his parents.

In circumcised patients, we make an incision through the circumcision scar, which in many cases is displaced well down on the penile shaft. Even with relatively significant displacement of the circumcision scar on the shaft of the penis, however, the reincision should be through the circumcision scar. The penis is then degloved by dissection of the layer immediately superficial to the superficial lamina of Buck fascia.

An artificial erection is obtained with normal saline while others use pharmacologic agents. We do not routinely recommend a tourniquet device, because constricting devices can conceal the proximal limits of the curvature. This is of most significance in cases of ventral curvatures, which frequently extend proximally. On occasion, some element of perineal pressure is initially required, but these are patients with normal erectile function, and their venous occlusive function is normal. The artificial erection demonstrates the character of the curvature and the location of maximal curvature. In patients with ventral curvature, there may be some illusion of thickening of the dartos and Buck fascia, and in those patients, the fibrous tissue is mobilized and completely excised. The corpus spongiosum is detached from the corpora cavernosa and mobilized from the glans to the penoscrotal junction.

After these tissues are excised, the artificial erection is repeated, and an occasional patient is found to have been completely straightened. Most patients, however, suffer from a differential elasticity between the dorsal and the ventral aspects of the corporeal bodies, and although the curvature may have been lessened, it persists unless further procedures are done to straighten the penis.

In the adult patient with persistent curvature, there are two options for surgical correction: (1) to lengthen the ventral aspect of the penis by making transverse incisions in the ventral tunica and placing an autologous tissue graft (we currently use the small intestinal submucosal graft at our institution), and (2) to shorten the dorsal aspect of the penis by elevating the neurovascular bundle, excising an ellipse or ellipses from the dorsum of the tunica albuginea, and closing the defects in watertight fashion (Nesbit [1965] procedure). **Because the size of the erect penis is usually not a problem in these cases of congenital curvature, we have chosen the second option and are strenuously against ventral grafting.** The recovery period after this procedure is much shorter, and the variabilities of graft take do not have to be considered. In addition, when a graft is used, there is always the possibility, although uncommon, of the development of graft-induced veno-occlusive dysfunction. **In a 2000 consensus conference sanctioned by the World Health Organization, the committee on Peyronie disease and congenital curvature of the penis agreed that the majority of, if not all, cases in men with the classic finding of congenital curvature of the penis were best managed with a plication or corporoplasty techniques but not grafting techniques** (Jardin et al, 2000; Lue, 2004). This consensus was reiterated at the next World Health Organization conference. It is therefore preferable to shorten the longer aspect of the penis in patients with congenital curvature. However, **if the patient falls into the category of chordee without hypospadias and shortness of the penis is an issue, we selectively use incisions with grafts to correct the curvature** (Devine and Horton, 1975).

After the decision has been made to proceed with excisions of ellipses of dorsal tunica, the Buck fascia can be elevated, in concert with the dorsal neurovascular structures, by beginning just lateral to the corpus spongiosum and carrying the dissection dorsally across the midline. Alternatively, the tunica can be exposed by excising the deep dorsal vein of the penis and opening the inner lamina of the Buck fascia. Elevation of the neurovascular structures is done by dissecting from the dorsal midline laterally around to the corpus spongiosum and from the coronal margin to the penopubic junction, thus limiting the effects of stretching the dorsal structures with exposure of the dorsum of the penis.

An artificial erection is obtained to plan the proposed ellipse excisions. We prefer to use several small ellipses rather than try to correct the curvature with one large ellipse. The first ellipse is usually positioned at the point of maximal concavity. The edges of the planned ellipse are then apposed with a Prolene suture. The artificial erection is repeated to assess the effects of that excision. If there is good straightening in that area of the shaft, the incisions are again well marked, the plicating sutures are removed, and the ellipses of tunica are made with a sharp scalpel blade. By dissection in the space of Smith and removal of only an ellipse of tunica, the ellipses are carefully excised to avoid damage to the underlying erectile tissue or can be merely closed under the reapproximated edge of the defect in the tunica albuginea. The edge of the ellipse is reapproximated with a combination of interrupted 4-0 polydioxanone sutures and a watertight running 4-0 polydioxanone suture.

After closure, we repeat the artificial erection to assess the results of the first ellipse with the others. A final artificial erection should demonstrate the penis to be perfectly straight. In cases of ventral curvature, or when complex curvatures are associated with an element of ventral curvature, a minimal degree of dorsal curvature after correction is acceptable. In most cases, as the sutures dissolve,

the penis either remains minimally dorsiflexed or becomes perfectly straight.

The Buck fascia is closed. Two small suction drains are placed superficial to the Buck fascia but deep to the dartos fascia. We then replace the skin sleeve, with its edges apposed with interrupted small Vicryl or Monocryl sutures. In all patients, we place a small Foley catheter, which is removed on the first postoperative day. The two small suction drains are also removed at 12 to 24 hours. Depending on the amount of edema and drainage, patients are discharged from the hospital on the evening of the first or early the second postoperative day.

A congenital lateral curvature of the penis is often associated with some complexity of curvature; patients frequently notice lateral curvature in association with a ventral or, less commonly, a dorsal curvature. However, some patients present with only lateral curvature, with the right side larger than the left, and curvature to the left.

In some cases, a repair of the lateral curvature can be approached through a small incision at the point of maximal curvature. Laterally placed incisions on the penile shaft are not cosmetically optimal. We prefer, however, a degloving incision after exposure of the deep penile structures; the point of maximal concavity is then marked. Prolene sutures are placed, and an artificial erection is again performed. The size of the ellipse is then assessed, and the ellipse is excised and closed as discussed earlier.

As mentioned, however, most cases of lateral curvature are associated with complex curvatures. In these patients, the correction of the curvature is similar to that described for patients with ventral curvature, by a circumcising incision with the skin reflected. In contrast to a ventral curvature, however, with a lateral curvature, the entire dorsal neurovascular bundle does not need to be reflected; therefore, it is seldom required, nor is it considered beneficial, to excise the deep dorsal vein in approaching the dorsum of the penis. The postoperative care is the same as described for a ventral curvature.

For the uncommon patient with a congenital dorsal curvature of the penis, the repair is best accomplished by mobilizing the lateral aspect of the corpus spongiosum to allow small ellipses lateral to the midline to be positioned on the ventrum of the penis, by the technique described before. Again, postoperative care is as described for a ventral curvature.

Although described as a method for plication for curvature associated with Peyronie disease, corporoplasty, the procedure described by Yachia (1993), is also useful for the correction of congenital curvatures. The procedure essentially consists of longitudinal incisions in the tunica albuginea with transverse closure. Thus the "long side" is plicated without the need for excision; however, the plication is durable in that the tunica is opened and closed with a resulting scar, rather than reliance only on the strength of sutures as originally described by Nesbit (1965). With this technique, closure is done with absorbable monofilament suture.

Acquired Curvatures of the Penis

Acquired curvatures of the penis inevitably follow trauma to the penis. Many of these cases are associated with Peyronie disease, also believed to be associated with trauma to the penis during intercourse (Bella et al, 2007). An occasional patient also presents who has had vigorous internal urethrotomy, with the incision extended outside the urethra and corpus spongiosum, and involving the tunica of the corporeal bodies, causing scarring that is significant enough to be associated with curvature.

Acquired Curvatures of the Penis That Are Not Peyronie Disease

When a young man presents with an acquired curvature of the penis, one must always consider Peyronie disease. However, many will not have true Peyronie disease. These patients, on close questioning, reveal a history of minimal lateral curvature of the penis and a clear memory of a lateral buckling injury that occurred during intercourse. In some cases, the patient remembers hearing a "snap" and notices immediate detumescence and significant ecchymosis of the penis. These patients are often referred with a diagnosis of Peyronie disease, but a diagnosis of curvature secondary to penile fracture is more accurate. Because of the noticeable events associated with fracture of the penis, many patients present acutely, and reconstruction can be accomplished at that time.

On occasion, however, a patient or his initial-care physician ignores the stigmata of the trauma (often described as "minimal" by patients), and the patient presents with a noticeable lateral scar that causes both indentation of the lateral aspect of the penis and, in some cases, curvature. Patients who had preexisting lateral curvature may actually notice that their penis has been straightened by the trauma, but they are disturbed by the concavity caused by the scar. In others, the small linear scar causes a significant lateral curvature.

Another group of patients presents after a similar buckling trauma to the penis but without associated detumescence or ecchymosis. These patients report noticing that their erections were painful for a period after the trauma, and then a nodule developed in the lateral aspect of the penis. Eventually, they present with a lateral linear scar that has led to curvature and indentation at the site. We refer to this injury as a subclinical fracture of the penis.

The lesion of a subclinical fracture of the penis is believed to be due to the disruption of the outer longitudinal layer of the tunica albuginea during the buckling trauma. The inner, circular layer is not disrupted, however, and maintains the blood-tight continuity of the corpus spongiosum. Another possible scenario is that both layers of the tunica albuginea are disrupted but the overlying Buck fascia maintains its integrity. There are also patients who notice a pop with intercourse and a period of pain with erections, followed by curvature of the penis—usually dorsal. These patients probably tear the septal insertion completely. These patients clearly behave more like Peyronie disease patients.

Patients usually have normal erectile function after subclinical or clinical fracture of the penis; there appears not to be an association with concomitant global cavernosal veno-occlusive dysfunction. However, the association of cavernosal veno-occlusive dysfunction and trauma of the penis continues to be seen, and some patients have significant problems with erectile dysfunction after fracture-type injuries of the penis. These injuries are not associated with shortening of the penis. In most cases, it is the lack of erectile dysfunction and penile shortening that help distinguish these patients from Peyronie disease patients. If a detailed history leads one to suspect blighted erectile function, an evaluation of erectile function should be accomplished before proceeding with surgery. At our institution, we evaluate these patients with duplex ultrasonography and selectively with dynamic infusion cavernosometry and cavernosography.

Although foreshortening of the penis is not a characteristic of either the injury itself or the resulting scar in either of these injuries, these patients are not thought to be best treated by approaching the opposite aspect of the scar and excising an ellipse of the tunica. This would result in bilateral scars, which would cause bilateral indentations of the penis, and although the penis would have been straightened by the correction, most patients are upset by the cosmetic and functional result of a near-circumferential indentation of the penis. Instead, we excise the scar and place a graft to replace the corporotomy defect caused by the scar excision. Because these scars are on the lateral aspect of the penis, minimal mobilization of Buck fascia, associated dorsal neurovascular structures, and corpus spongiosum is required at the site.

The results of the surgical correction described have been extremely effective. All such patients treated at the authors' institution have been successfully corrected with a single operation.

Key Points: Curvatures of the Penis

- Curvatures of the penis can be acquired or congenital. Congenital curvatures of the penis can be categorized as chordee without hypospadias or congenital curvature of the penis.
- In general, chordee without hypospadias is really a forme fruste of hypospadias. Although the meatus may not be abnormally placed, these patients usually have findings suggestive of hypospadias (i.e., malformation of the ventral structures of the penis). These patients are not characterized by large erect penises. In contrast, patients with congenital curvature of the penis seem to have exceptionally large erect penises.
- The entity of congenital curvature of the penis seems to be related to nonsymmetrical expansion of the erectile bodies, which must expand significantly during tumescence. In general, these patients are best reconstructed by excision with plicating closure or pure plication techniques. The use of grafts is not recommended because of the unusual but real occurrence of graft-induced veno-occlusive dysfunction in certain of these patients.

TOTAL PENILE RECONSTRUCTION

General

The principal techniques of penile reconstruction were originally developed for treatment of trauma patients, and, in many cases, these patients were victims of war injuries. In 1936, Bogaraz described a technique for phallic construction in a series of war-injured patients, and in 1944, Frumkin followed with a series from the Soviet Union. Aware of the work in the Soviet Union, Gillies and Harrison (1948) reported on a series of patients in whom they had accomplished penile reconstruction while stationed at a major hospital in the outskirts of London during World War II. In this series, there were a number of patients with a complete absence of the penis.

Initially, all procedures for phallic construction involved delayed formation and transfer of tubed abdominal flaps. These tubes were produced from random flaps of skin and because of their size were based on a tenuous blood supply. To allow new vascular patterns to become established in the transferred tissue, they were formed in stages, with a "delay" between the stages. In the "tube-within-a-tube" design, the inner tube allowed the placement of a baculum during intercourse, and the outer tube provided skin coverage. Patients voided through a proximal urethrostomy. This continued to be the "state-of-the-art" phallic construction and penile reconstruction until 1972, when Orticochea described total reconstruction of the penis using the gracilis musculocutaneous flap. In 1978, Puckett and Montie reported a series in which they constructed the penis with a tubed groin flap. In the early cases in this series, the flap was transferred in delayed fashion to the area of the penile stump. Later in the series, a microvascular free-transfer technique was employed.

In 1984, Chang and Hwang popularized the forearm flap, based on the radial artery, for phallic construction. Biemer (1988) reported a modification of the forearm flap, which was also based on the radial artery; and, in 1990, Farrow and colleagues reported their "cricket bat" modification of the radial forearm flap. **Today, forearm flaps are the most commonly employed method for total phallic construction and penile reconstruction.**

The forearm flap is usually harvested from the nondominant forearm. Preoperatively, the Allen test is used to screen patients carefully for arterial insufficiency. This test involves palpation of the radial and ulnar arteries in the wrist, with the patient making a tight fist to express blood from his hand. As he opens his hand, the fingers are pale, but if palmar circulation is normal and both arteries are patent, the fingers turn pink when one of the arteries is released. If, on the basis of either the Allen test or the patient's history, there is any doubt about the integrity of the radial and ulnar arteries or the palmar arch, upper extremity angiography is performed.

As described, the forearm flap is a fasciocutaneous flap vascularized by the radial artery; however, the ulnar artery also vascularizes the forearm fascia and most of the forearm skin. The radial artery arises as a continuation of the brachial artery and proximally lies beneath the belly of the brachioradialis muscle, becoming more superficial at the wrist. The ulnar artery is also a continuation of the brachial artery and vascularizes a similar area of skin and underlying adipose tissue. The vascularity of the overlying skin is achieved by way of the underlying (antebrachial) fascia, which is the superficial fascia investing the musculature of the forearm.

The forearm flap can be elevated and transferred on the superficial fascia. The lateral and medial antebrachial cutaneous nerves appear proximally beneath the fascia. The cephalic, basilic, and medial antebrachial veins are also included in the flap and constitute a portion of the venous drainage. In some patients, the vena comitans is the dominant venous drainage system. At the time of flap transfer, it is imperative to assess both the venous comitans and the superficial veins to determine which is the dominant system in the individual patient.

The various modifications of the forearm flap do not represent changes in the technique of flap elevation; rather, they are modifications in the design of the skin island and the relative position of the urethral paddle in relation to the skin that will eventually become shaft coverage. Each of these modifications has advantages in different situations.

In the forearm flap as described by Chang and Hwang (1984), the shaft is covered with the radial aspect of the skin paddle. A de-epithelialized strip is made, and a second skin island, on the ulnar aspect of the skin paddle, is tubed to form the urethra. The urethral tube is then rolled within the tube of skin to form a

tube-within-a-tube design. In the white population, this flap has demonstrated a tendency to lead to ischemic stenosis of the lateral paddle, where the urethra is constructed.

In the cricket bat modification, the urethral tube extends distally, closely overlying either the radial or the ulnar artery. We have experience with elevation of the cricket bat modification on both arteries. Proximal to the urethral strip, a broader portion of the skin paddle provides coverage of the shaft. The urethral portion is tubed and transposed by inverting it into the center of the shaft portion of the skin paddle. The advantage of this modification lies in centering the urethral portion over the respective artery, in contrast to the Chinese design, in which the ulnar aspect is far distal from the radial artery, with the potential for ischemic stenosis or loss of that portion. The cricket bat modification has been useful in trauma patients, particularly in those who have a significant stump of erectile bodies and urethra left after the injury.

The modification by Biemer (1988) also centers the urethral portion of the flap over the artery. As described by Biemer, the flap is elevated on the radial artery and includes a vascularized piece of the radial bone intended to provide rigidity to the new penis. The inclusion of cartilage and bone has not been universally successful, however, and rigidity in these flaps is obtainable by the use of either an externally applied or internally implanted prosthesis. If the bone is not elevated, the Biemer flap design can be elevated on either the radial or the ulnar artery. At our center, we most often elevate the flap on the ulnar artery, in a modification of the Biemer design.

Modifications of the Biemer design also include the glans construction technique that was originally described by Puckett and Montie (1978). In the original Biemer design, a central strip becomes the urethra, and lateral to that strip, two de-epithelialized portions and two lateral islands (lateral aspects of that skin paddle) are fused dorsally and ventrally to cover the shaft. With the modification of Puckett and colleagues (1982), a large island is left distally and flared back over the tip of the tubed flaps, creating the illusion of a glans penis. The Biemer design, especially when it is combined with Puckett's design for glanular construction, offers the best cosmetic results (Fig. 36–40).

There are several disadvantages to the use of a forearm flap for phallic construction. The major disadvantage of forearm flaps is the obvious donor site deformity. We have reconstructed the donor site with full-thickness skin grafts taken from the area of the inguinal crease, and the cosmetic result is far superior to that obtained when the donor site is reconstructed with split-thickness skin (even thick split-thickness skin). A second disadvantage lies in the **possibility of the development of cold intolerance in the hand of the donor side.** Early in our experience with the forearm flap, we reconstructed the radial artery with an interposition vein graft. We have since abandoned this procedure in the majority of our series and have not seen cold intolerance in our patients. Another disadvantage occurs in both male and virilized transgender patients **when the forearm skin is hirsute, because the hair can be problematic** if it is included in the portion of the flap used for urethral construction. In such patients, we try to identify the potential for the problem and refer them for epilation before surgery.

McRoberts and Sadove (2002) proposed the use of the fibular osteocutaneous flap for phallic construction. The fibula is elevated on the periosteal vessel along with the overlying skin paddle. As they described, urethral reconstruction is by tubed graft techniques, and their procedure had a 100% urethral complication rate. The center from Munich has proposed use of this flap with a prefabricated urethra. They place a tubed graft initially in the center of the paddle while it is still on the leg, then elevate the flap later and attach the urethra. We do not agree with the presumption that these tubed grafted urethras would behave differently; however, the surgeons in Munich propose the technique as a better one. For patients who only need vascularized tissue to cover the shaft of the penis, we have used the upper lateral arm flap. This is a fasciocutaneous flap, and its cutaneous vascular territory is centered on the radial collateral artery. The skin of the lateral upper arm is thin, with little subcutaneous adiposity. To mark the location of the lateral intramuscular septum and the course of the superior radial collateral artery, we draw a line joining the insertion of the deltoid with the lateral epicondyle. We begin the dissection posteriorly, elevating the superficial fascia until the posterior lateral portion of the intramuscular septum has been identified. A potential disadvantage of this flap lies in the fact that the entire venous drainage is dependent on the vena comitans, and although superficial veins do traverse the flap, none of them seems to provide significant venous drainage. Although this is disquieting, we have found the flap to be completely reliable thus far, with no losses due to venous insufficiency.

This flap has also been used for total phallic construction. For this purpose, the flap is expanded by tissue expander and elevated across the elbow, and the distal flap is elevated on the recurrent radial artery. As with the forearm flap, the donor site of an upper lateral arm flap can be disfiguring. However, because the scar is on the upper arm, it is more easily concealed beneath a shirtsleeve than a scar in the forearm. All the flaps described allow microneurosurgical coaptation of the flap cutaneous nerves with recipient nerves. With total phallic construction, the cutaneous nerves can be attached either to the dorsal nerves of the penis or to the dorsal nerves of the clitoris in the transsexual patient. When these nerves are not available, the nerves can be coapted to the pudendal nerve, which in most patients requires an interposition graft. These nerves are thought to provide the best restoration of erogenous cutaneous sensibility. We have also coapted the flap's cutaneous nerves to the ilioinguinal nerves, which provides sensation to the inner aspect of the thigh and the lateral aspect of the scrotum, and have achieved a reasonable degree of erogenous sensibility.

In most patients, the deep inferior epigastric vessels are the recipient vasculature for flap transfer. These vessels are medial branches of the iliac system and lie on the dorsal (deep) aspect of the rectus abdominis muscle. The artery usually remains deep to the muscle, although an early penetration of the artery into the muscle can be observed in some patients. The artery classically bifurcates at the level of the umbilicus and is generally accompanied by two or more venae comitantes. These vessels have been elevated by several methods, and Lund and colleagues (1995) described their elevation for penile revascularization with laparoscopic techniques. When the deep inferior epigastric vessels are used, it is often necessary to also include a saphenous vein for further venous runoff.

In some patients, however, these vessels are not available, and we have used a saphenous interposition graft to the superficial femoral artery. With use of this technique, we mobilize the saphenous vein well down the upper aspect of the thigh and then attach the vein to the femoral artery, making a temporary arteriovenous fistula. The fistula is divided, with the saphenous vein becoming the venous runoff and the interposition graft providing the arterial inflow. This system of recipient vessels is greatly inferior to a direct arterial anastomosis. Because of this, in a few patients we have divided the profunda femoris vessel and vigorously dissected it from its other branches. We have then done an end-to-end

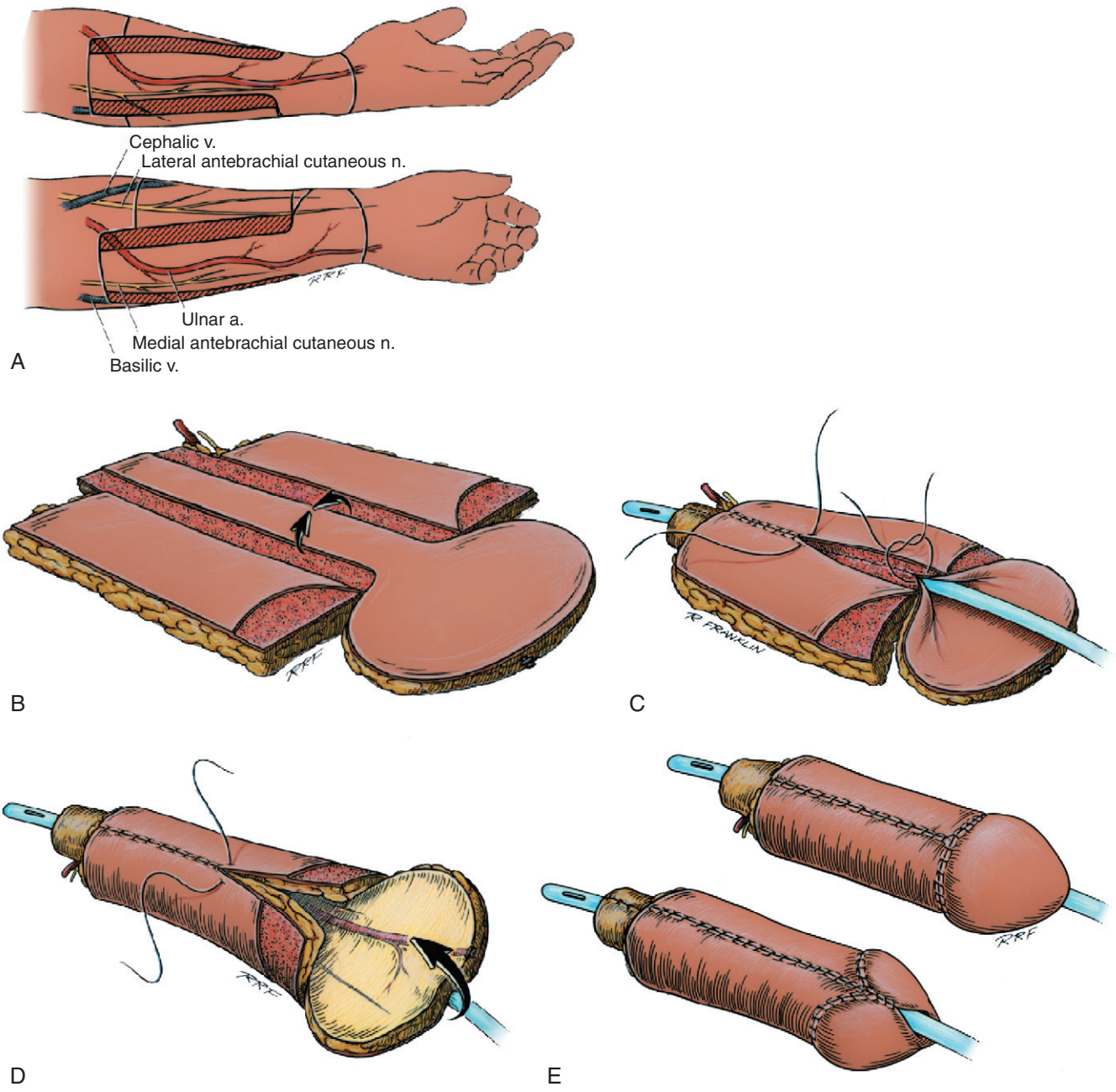


Figure 36–40. **A**, Schematic diagram of an ulnar forearm flap, modified Biemer design, on the patient's left (usually nondominant) forearm. **B**, Schematic of the elevated flap. Notice the flap has been divided into skin islands by de-epithelializing the strips. Laterally are the shaft skin islands, medially is the urethral skin island, and distally is the intergral glans, after the design of Puckett. **C**, Schematic of the configuration of the flap. Notice the urethral skin island has been tabularized to the level of the neomeatus. The lateral shaft skin islands are now in the process of being tabularized over the tabularized urethra. **D**, Schematic of the phallic flap as it is further configured, this view is of the dorsum. Notice the venral skin island has been closed over the urethra, the dorsal skin islands are being collected. The integral glans will then be reflected over the dorsum of the flap. **E,** The drawing of the appearance of the phallus after it is totally configured and transposed to the area of the "penis."

(artery-to-artery) anastomosis of the ulnar artery to the profunda femoris. However, the long-term consequences to the patient of dividing the profunda femoris are not clear. Immediate reconstruction of the profunda does not appear to be advantageous, as the dissection required to mobilize the profunda femoris to become a recipient vessel requires the division of a number of proximal branches, and these would not be reconstructed with an immediate reconstruction of the profunda femoris. Mention of this as a potential means of "creating" recipient vessels is not to recommend the procedure, because the procedure may yet have unacceptable long-term consequences. Another option in extreme cases is to use the superficial femoral, which could be reconstructed with a vein interposition. When the "classic" recipient vessels are not available, these other methods may be acceptable. However, we strenuously caution concerning their use, because the long-term consequences are not known. We currently believe

that division of the superficial femoral artery with immediate reconstruction is the better of these choices.

In the latter part of our series, we included the routine transfer of gracilis muscle to cover the area of the urethral anastomosis, increasing the vascularity to that area and significantly altering the incidence of anastomotic fistula and stricture formation. We have also elevated a bipedicled flap from the area of the penile shaft base, which is transposed beneath the phallic flap. This flap provides increased bulk and some modicum of scrotal construction, and when it is combined with the gracilis muscle, its thickness provides excellent coverage for the juncture of the flap with the base of the neoscrotum. Mobilization of a tunica dartos flap with tunica vaginalis pedicle, or a Martius flap in the transgender patient, may obviate the necessity to elevate and transpose a gracilis muscle flap.

During the phallic construction procedure, urine is diverted by means of a suprapubic cystostomy tube, and the urethra is stented with a No. 14 soft silicone (Silastic) catheter. A voiding study is usually performed between the third and fourth postoperative week.

Rigidity for intercourse in the patient with phallic construction is usually achieved by either an externally applied or a permanently implanted prosthesis. Prosthetic implantation is never undertaken until 1 year after phallic construction, because protective sensibility must be demonstrated in the flap. When the flap is transferred, it is, by definition, rendered insensate. At about 3 to 4 months after reconstruction, however, as nerve regeneration occurs, sensation becomes noticeable. In addition, before prosthetic implantation is undertaken, the urethra must be patent and proved to be durable.

At our center, we now have a large series of patients with internally implanted devices. We have implanted both hydraulic and articulated prostheses encased in Gore-Tex neocorpora. These devices are anchored to the ischial tuberosity and the pubis by anchoring the neocorpora to these bone structures. In most patients, we implant two cylinders or rods. Early in our series, we had problems with hematoma and seroma formation and subsequent infection. However, since modifying our antibiotic regimen and including the routine use of suction drains with the implant procedure, we have had excellent success with implantation. We currently place the antibiotic-coated (Inhibizone) AMS 700CXR.* The Titan prosthesis with hydrophilic coating and narrow base has also been used.

We also have implanted testicular prostheses in a number of patients. In patients in whom we have used a hydraulic device, we have implanted the pump in one neohemiscrotum and a testicular prosthesis in the opposite one.

Reconstruction after Trauma

In many ways, the problems of trauma patients are more challenging to solve than are those of patients who require total phallic construction. We have treated a large number of patients who have had devastating injuries to the penis after complicated prosthetic surgery or surgery to correct penile curvatures of Peyronie disease. The goal in these patients is to preserve the penile structures and function as much as possible, yet correct the deficiencies that are imposed on the patient by the trauma.

Acutely, urine must be diverted, necrotic tissue must be carefully debrided, and any foreign bodies that may have been implanted must be removed. Vigorous acute wound management stabilizes the wounds and allows active granulation to progress. In all trauma patients, an attempt should be made to save as many of the penile structures as possible.

Approximately 3 to 6 weeks after trauma, primary reconstruction can be undertaken, although we have elected to wait 4 to 6 months in some patients, depending on the situation. When significant adjacent tissue loss has occurred, the adjacent areas must be well reconstructed before proceeding with either phallic construction or penile reconstruction.

In the trauma patient, it is imperative that well-vascularized tissues be eventually transposed to the adjacent area, and reconstruction of these areas can be accomplished with a number of flaps. For groin reconstruction, the tensor fascia lata flap has been useful. The rectus femoris flap, characteristically long and large, can be transposed to the area of the lower abdomen and has been an extremely useful flap for inguinal and lower abdominal reconstruction. The gracilis muscle is an excellent flap for reconstruction of the perineum and the groin. Alternatively, the posterior thigh flap can be used for reconstruction of the groin and perineum and, in some cases, transposed to the lowermost portion of the lower abdomen. The rectus abdominis flap is a useful flap and can be elevated with a vertical or transverse skin paddle. In addition, the flap can be transposed to either the ipsilateral or contralateral side. Care must be taken in the patient who has had lower abdominal external beam irradiation.

Variations of the flap designs described for complete phallic construction have been successfully applied in select patients for penile reconstruction. An example is seen in one patient who suffered an injury to his penis from a shotgun blast. The blast injured a large portion of the patient's right corpus cavernosum, and the majority of the penile skin was either destroyed or used for urethral reconstruction. In this patient, a flap based on the Chinese design was elevated. However, because the urethral reconstruction was accomplished with a penile skin island, the ulnar portion of the flap was not needed for that purpose. Therefore the ulnar portion was de-epithelialized and tubularized to form bulk and a new right corporeal body. This patient is now sexually active, and the bulk of the tube's dermal section gives adequate support to his penis for intercourse.

Another patient required only distal urethral construction and glans reconstruction. For this patient, we based a flap on the Biemer design to construct a glans. The proximal portions of the flap were de-epithelialized, allowing fixation of the neoglans on the tips of the corporeal bodies, and an excellent functional and cosmetic result was achieved for this patient. The versatility of free-flap technology allows the solution of complex issues with reasonably acceptable functional and cosmetic results.

FEMALE-TO-MALE TRANSSEXUALISM

Female-to-male transsexual patients present a unique challenge, and no patient should be considered for definitive reassignment surgery without having undergone complex screening and evaluation by a team consisting of mental health professionals, as well as surgeons who are skilled in undertaking transgender surgery. It is imperative that an ongoing, stable, therapeutic relationship be established between the patient and a mental health professional at the time of definitive gender reassignment surgery. At our institution, the Harry Benjamin criteria (Ramsey, 1996) are strictly

*American Medical Systems, Inc., 10700 Bren Road West, Minnetonka, MN 55343; 952-930-6000.

adhered to, and surgery is accomplished by a team of urologists, plastic surgeons, and gynecologists.

In most patients, the first stage of female-to-male transsexual surgery consists of bilateral salpingo-oophorectomy, hysterectomy, vaginectomy, and urethral lengthening with colpocleisis. Even in the virginal patient, our surgeons have become skilled at accomplishing a hysterectomy and bilateral salpingo-oophorectomy by way of transvaginal surgery. We perform a vaginectomy at the same operation, leaving the anterior vaginal wall to be transposed as a random flap to lengthen the female urethra and allow colpocleisis. Lengthening of the female urethra brings the base of the native urethra up to what will be the base of the phallic flap; along with the transfer of gracilis muscle, it has significantly altered our surgical results with regard to urethral anastomotic fistula and stricture. Urine is diverted with a suprapubic tube, and a voiding trial is performed in approximately 21 days. Patients are generally in the hospital for 2 to 3 days and return 3 to 4 months later for phallic construction.

For phallic construction in the transsexual patient, we elevate a bipedicled flap of skin, as already described, from the area where the phallic structure will be implanted and transpose it to the undersurface of the neopenis. The patient is generally in the hospital for a period of 10 to 14 days after total phallic construction, and a voiding trial with contrast material is done at about 28 days postoperatively. After 1 year, when erogenous sensibility is demonstrated and the urethra is proved to be durable, prosthetic implantation is considered.

Key Points: Total Penile Reconstruction

- The principal techniques of penile reconstruction were originally developed for treatment of victims of war injuries. Initially, all of the procedures involved delayed tissue transfer. In 1978, Puckett and Montie reported a series of phallic reconstructions in which a groin flap was transferred by microvascular free-transfer techniques to the area of the penis. The phallus was insensible, but that represented the first free-flap reconstruction for phallic construction. In 1984, Chang and Hwang popularized use of the forearm flap. That flap has been modified by a number of individuals.
- Our preference is to use an ulnar forearm flap with a combined Puckett modification of the flap and Biemer modification of the glans. These flaps allow sensible phallic construction that lets the patient stand to void and permits eventual prosthetic implantation as the phallus has both protective and erogenous sensibility.
- The techniques employed in the transsexual patient are not different from those in the trauma patient. Often, the shapes of the skin paddles must be tailored to the individual patient.

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chapter 37

Surgery of the Scrotum and Seminal Vesicles

Parviz K. Kavoussi, MD ● Raymond A. Costabile, MD

Surgical Anatomy of the Scrotum
Preoperative Preparation
Surgery of the Scrotal Wall
Vasectomy
Spermatocelectomy/Surgery of the Epididymis
Hydrocelectomy
Surgical Treatment of Orchitis and Chronic Scrotal Pain
Surgery of the Seminal Vesicles

SURGICAL ANATOMY OF THE SCROTUM

The scrotum is a unique body component because the superficial anatomic location of the scrotum and scrotal contents facilitates physical examination, imaging, and surgical access. It is crucial to understand the blood supply to the organs within the scrotum when surgical intervention is indicated. This is summarized in Table 37–1.

The availability of multiple blood supplies to the testis allows continued testicular viability when one or two of the arteries are compromised by injury or ligation.

Scrotal anatomy allows easy access for surgical procedures, including surgery of the scrotal wall, vasectomy, spermatocelectomy, surgery of the epididymis, hydrocelectomy, and surgical treatment of orchitis.

Spread of Scrotal Infections and Postoperative Fluids Based on Scrotal Anatomy

There is a predictable pathway for the spread of scrotal infections and postoperative fluids based on scrotal anatomy. This defined anatomy for the spread of infection is demonstrated in patients with Fournier gangrene (necrotizing fasciitis of the scrotum). **Anatomic barriers to the spread of necrotizing fasciitis include the dartos fascia of the penis and scrotum, Colles fascia of the perineum, and Scarpa fascia of the anterior abdominal wall. The testes and epididymes tend to be spared from necrotizing fasciitis of the scrotum** (Figs. 37–1 and 37–2) (Gupta et al, 2007).

PREOPERATIVE PREPARATION

Anesthetic Technique for Scrotal Surgery

Effective anesthetic techniques for scrotal surgery range from local injection with or without sedation to spinal to general anesthesia. The use of a spermatic cord block with local infiltration of 0.5% xylocaine without epinephrine is a simple, cost-effective anesthetic technique that can be implemented by the surgeon for outpatient scrotal surgical procedures. Regional cord block can typically be performed without premedication with satisfactory patient analgesia (Magoha, 1998; Wakefield and Elewa, 1994). Spermatic cord block can be used in patients with large hydroceles for anesthesia by initially percutaneously draining the hydrocele, performing the block, followed by hydrocelectomy (Reale et al, 1998). Outpatient scrotal surgery performed with midazolam sedation and a local block, with sedation reversal at the end of the procedure has a very high patient satisfaction rate (Birch and Miller, 1994).

Preoperative Preparation and the Use of Antibiotics in Scrotal Surgery

The overall infection rate with scrotal surgery is relatively low, ranging from zero to ten percent. There is no difference in the incidence of postoperative wound infections or complications in patients undergoing hydrocelectomy or spermatocelectomy when comparing iodine-based versus chlorhexidine antiseptic preparations. Scrotal cases are considered as class II (clean-contaminated surgeries), which makes it reasonable to use preoperative antibiotics (Kiddoo et al, 2004). The American Urological Association (AUA) best practice policy statement on urologic surgery antimicrobial prophylaxis recommends a single dose of preoperative antibiotics if the patient has risk factors for infection, including advanced age, anatomic anomalies of the urinary tract, poor nutritional status, smoking, chronic corticosteroid use, immunodeficiency, externalized catheters, colonized endogenous/exogenous material, a distant coexistent infection, or prolonged hospitalization. The recommended antibiotic prophylaxis is a dose of a first generation cephalosporin, or clindamycin as an alternative antimicrobial (Wolf et al, 2008). **Patients who underwent preoperative clipping for hair removal the morning of surgery had a significantly lower wound infection rate**

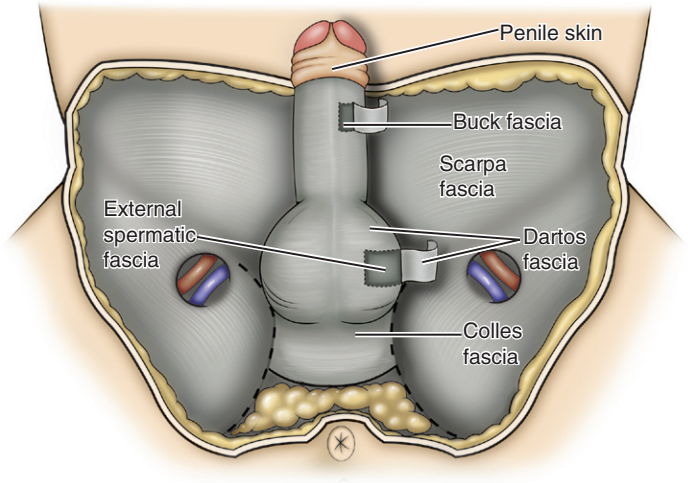


Figure 37–1. Anatomic barriers to the spread of infection. (Modified from Kavoussi PK, Costabile RA. Disorders of scrotal contents: orhcitis, epididymitis, testicular torsion, torsion of the appendages, and Fournier's gangrene. In: Chapple CR, Steers WD, editors. Practical urology: essential principles and practice. London: Springer-Verlag; 2011.)

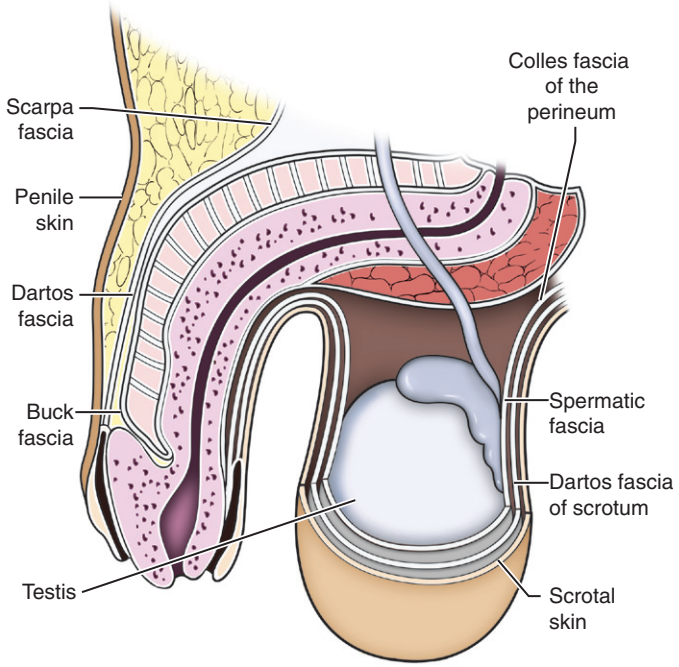


Figure 37–2. Sagittal view of anatomic barriers to the spread of infection. (Modified from Kavoussi PK, Costabile RA. Disorders of scrotal contents: orhcitis, epididymitis, testicular torsion, torsion of the appendages, and Fournier's gangrene. In: Chapple CR, Steers WD, editors. Practical urology: essential principles and practice. London: Springer-Verlag; 2011.)

Table 37–1.

Blood Supply to Testis, Epididymis, and Vas Deferens

TESTIS	EPIDIDYMIS	VAS DEFERENS
Testicular (internal spermatic) artery from aorta Deferential artery from internal iliac/superior vesicle artery Cremasteric (external spermatic) artery from inferior epigastric artery	Superior epididymal artery from testicular artery Inferior epididymal artery from deferential artery	Seminal vesicle region: deferential artery from internal iliac/superior vesicle artery Testicular region: deferential artery and inferior epididymal artery

than those who underwent shaving or clipping the night before surgery (Alexander et al, 1983).

SURGERY OF THE SCROTAL WALL

Cyst Excision

Patients with multiple scrotal cysts can be managed with surgical excision with excellent cosmetic results and low recurrence rates (Noël et al, 2006).

The classical management of scrotal sebaceous cysts is surgical excision with excellent outcomes and minimal morbidity with good cosmetic results. Less invasive techniques, such as Nd:YAG photocoagulation, have been performed successfully but are not considered standard management (Franco de Castro et al, 2002).

Partial/Total Scrotectomy

Partial scrotectomy is an uncommon procedure. Partial scrotectomy is most commonly performed with infectious processes such as Fournier gangrene. **Partial scrotectomy has been advocated after trans-scrotal exploration, orchiectomy, biopsy, or when aspiration has been performed for a scrotal mass and the pathology has revealed a nonseminomatous germ cell tumor of the testis.** Prompt and aggressive management has resulted in no local recurrences due to scrotal tumor contamination, even when a tumor was found in the scrotectomy specimen (Johnson and Babaian, 1980; Boileau and Steers, 1984; Leibovitch et al, 1995). In a small group that underwent aggressive local surgical resection and did not receive adjuvant chemotherapy, there was no increase in the local or distant recurrence (Giguere, 1988).

Total scrotectomy is less commonly performed than partial scrotectomy. Total scrotectomy is often necessary when there is extensive involvement of the scrotum with Fournier gangrene. Total scrotectomy has also been described for radical oncologic procedures, concomitantly with cystoprostatectomy, penectomy, or pelvic exenteration with aggressive cases of squamous cell carcinoma of the prostate (Sarma et al, 1991).

Debridement of the Scrotal Wall in Fournier Gangrene

Treatment of Fournier gangrene should include emergent radical surgical debridement and intravenous broad-spectrum antibiotics. When culture results are available the antibiotics can be tailored to the organisms based on sensitivities. Treatment should be performed expeditiously and aggressively, because Fournier gangrene is a life-threatening process. All nonviable and necrotic tissue must be aggressively excised (Fig. 37–3). **An empirical broad-spectrum antibiotic regimen for the initial treatment of Fournier gangrene includes a third-generation cephalosporin, an aminoglycoside (if the creatinine clearance is acceptable), and metronidazole.** Aggressive fluid resuscitation is required,



Figure 37–3. Aggressive debridement of Fournier gangrene. (From Kavoussi PK, Costabile RA. Disorders of scrotal contents: orhcitis, epididymitis, testicular torsion, torsion of the appendages, and Fournier's gangrene. In: Chapple CR, Steers WD, editors. Practical urology: essential principles and practice. London: Springer-Verlag; 2011.)

including the use of blood and blood products when needed. After debridement, adequate nutrition with early enteral feeding, when possible, is crucial for wound healing. Repeat debridement should be performed two days after the initial exploration to excise any remaining nonviable tissue. Multiple resections may be necessary. If the source of the infection is anorectal or the wound is contaminated, a colostomy may need to be performed to divert fecal flow (Ghnnam, 2008). Similarly, patients may require cystostomies for urinary diversion when there is a urinary source exacerbating the necrotizing fasciitis.

Once the patient has been initially treated and resuscitated and all necrotic tissue has been excised, most wounds can be closed secondarily. **Large wounds will often require skin grafts for coverage. Fasciocutaneous rotational thigh flaps may be used for coverage with good cosmetic results** (Bhatnagar et al, 2008). **Wound closure is performed as soon as there is no evidence of infection or remaining necrotic tissue, and there is a viable bed that will allow reapproximation or grafting** (Ghnnam, 2008). Patients with less than 50% scrotal skin loss can almost always be closed primarily without major difficulty. **The testes may be placed in thigh pouches until the time of definitive reconstruction in cases with major scrotal skin loss** (Gudaviciene and Milonas, 2008). **Vacuum-assisted closure devices (Wound V.A.C.) have been used to help these complex wounds heal after wide excision and debridement.** This technique has been shown to be as effective as conventional wound care in healing wounds. These patients require fewer dressing changes, have less pain, fewer skipped meals, and greater mobility (Ozturk et al, 2009). The use of a small intestinal submucosa graft and fibrin sealant is an option for closure of scrotal defects after excision for Fournier gangrene when standard grafting is not possible (Kavoussi and Bird, 2007).

A severity index has been created and validated to identify prognostic factors in patients suffering from Fournier gangrene. Parameters associated with mortality include abnormalities in heart rate, respiratory rate, serum creatinine, serum bicarbonate, serum lactate, and serum calcium. There is a 46% mortality rate in patients with a severity index score of nine or greater, and a 96% survival rate in patients with a severity index score of less than nine. Necrotizing fasciitis involving the abdominal wall or the lower extremities is associated with increased mortality (Corcoran et al, 2008).

VASECTOMY

Vasectomy is a highly effective and safe form of contraception (Schwingl and Guess, 2000). Vasectomy was first described by Sir Ashley Cooper in the United Kingdom when he did experiments to vasectomize dogs (Cooper, 1827). **Approximately 526,501 men undergo vasectomy annually in the United States, which makes vasectomy the most commonly performed urologic surgical procedure.** 0.01% of men between the ages of 25 and 49 undergo vasectomy annually (Barone et al, 2006). This comprises 11% of all married couples.

Anesthetic Techniques for Vasectomy

Vasectomy can be performed under sedation, spinal, or general anesthesia, although most surgeons perform vasectomy under local anesthesia because the majority of patients tolerate this method well and it minimizes anesthetic complications and morbidity.

The choice of local anesthetic is based on surgeon preference. Options for local anesthesia include the use of 1% or 2% lidocaine without epinephrine or a 50/50 mixture of lidocaine and bupivacaine. The vas deferens is isolated through the scrotal skin and grasped tightly between the thumb and the middle finger of the nondominant hand in a superficial position just beneath the scrotal skin. A 25-gauge needle is used to inject the local anesthetic subcutaneously to raise a small wheel over the vas deferens. Once superficial anesthesia is achieved, the needle is carefully advanced into the vasal sheath, and a small amount of anesthetic is injected. Great care should be taken to use as few punctures as possible and as little needle movement as possible to minimize the risk of hematoma formation.

EMLA (emulsion of lidocaine and prilocaine) cream applied as topical anesthesia on the scrotal skin one hour prior to injection of 1% lidocaine followed by vasectomy does not decrease the pain associated with vasectomy compared with the use of injectable anesthesia alone (Thomas et al, 2008).

The no-needle jet anesthetic technique has been described to eliminate the needle for anesthetic injection. This technique uses the MadaJet medical injector (MADA Medical Products, Carlstadt, NJ) to deliver lidocaine without epinephrine by means of a high-pressure injector through a tiny head to beneath the skin to diffuse a mist of anesthetic around the vas (Weiss and Li, 2005).

Conventional Technique

Vasectomy should be performed in a warm room with warm preparation solution to allow scrotal relaxation, regardless of the technique employed. Shaving should be

performed prior to the procedure to minimize the risk of infection. There is no difference in the rate of postvasectomy infection in men randomized to prophylactic antibiotics versus no antibiotics; therefore antibiotic prophylaxis is not recommended (Khan, 1978). In any chosen technique, the use of a single incision or bilateral scrotal incisions is based on surgeon preference. Many surgeons advocate bilateral scrotal incisions to minimize the risk of dividing the same side twice and to allow performing the vasectomy at a position in the midportion of the vas deferens. After induction of adequate local anesthesia, an incision is made over the isolated vas deferens, which is grasped tightly between the thumb and middle fingers. The vasal sheath is sharply divided down to the vas. The vas is delivered through the incision; the deferential artery, nerves, veins, and adjacent tissue are separated from the vas, and the vas is divided. Some surgeons remove a small segment of vas deferens, although most urologists who perform vasectomy reversals prefer not to, which allows easier future reversal. The AUA Policy Statement (American Urological Association, 2007) states that removal of a segment of vas deferens for histologic confirmation is not required or recommended. Most surgeons occlude both the testicular and abdominal ends of the vas with suture ligation, hemoclips, intraluminal fulguration with electrocautery, or fascial interposition. These techniques are further discussed below. The same procedure is repeated on the contralateral vas deferens.

"No-Scalpel" Technique

The no-scalpel vasectomy was initially described in China in 1974 (Li, 1976).

Routine antibiotic use is not needed for vasectomy patients undergoing no-scalpel vasectomy with sterile technique (Seenu and Hafiz, 2005). **The no-scalpel technique significantly decreases the rate of hematomas, infections, and pain during the procedure.** Patients who undergo the no-scalpel technique also resume sexual activity sooner after surgery and have a shorter operative time than occurs with the conventional technique (Sokal et al, 1999, Cook et al, 2007a).

There are several variations to the technique of the no-scalpel vasectomy. One technique involves firmly securing the vas through the skin with a ring-tipped vas deferens fixation clamp (Fig. 37–4) after local anesthesia has been administered as described above (Fig. 37–5). A modified, sharpened tipped curved hemostat (Fig. 37–6) is used to puncture the skin and the vas sheath, and the hemostat is spread to stretch the hole that is made. Then the vas deferens is lifted out, divided, the occlusion technique of choice is employed, inspection is done for hemostasis, and the vas deferens is replaced in the scrotum. The same procedure is performed

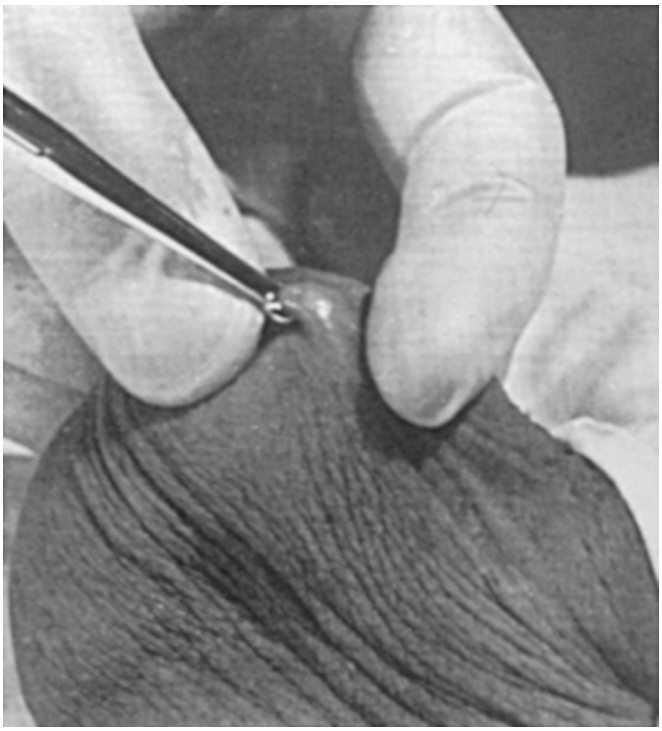


Figure 37–5. Vas fixed in the ring clamp. The scrotal skin is tightly stretched over the most prominent portion of the vas. (From Li S, Goldstein M, Zhu J, Huber D. The no-scalpel vasectomy. J Urol 1991;145:341–4.)

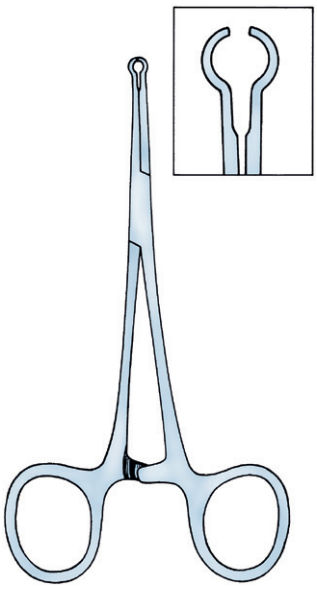


Figure 37–4. Ring-tipped vas deferens fixation clamp. Cantilevered design prevents injury. (From Li S, Goldstein M, Zhu J, Huber D. The no-scalpel vasectomy. J Urol 1991;145:341–4.)



Figure 37–6. Sharp, curved mosquito hemostat. (From Li S, Goldstein M, Zhu J, Huber D. The no-scalpel vasectomy. J Urol 1991;145:341–4.)

on the contralateral vas deferens (Huber, 1988). The perforation in the skin can be closed with an absorbable suture, but can also be left open, and will heal well without closure.

A variation of this technique employs local anesthesia; fixes the vas through the scrotal skin with the ring-tipped vas deferens fixation clamp; and pierces the scrotal skin, vas sheath, and vas deferens in the midline with a sharpened tipped curved hemostat held at 45 degrees from horizontal (Fig. 37–7). To prepare the vas deferens for division, the clamp is then rotated 180 degrees relative to the pierced vas deferens. The remainder of the procedure is performed in the same manner as described above, and this is done bilaterally (Schlegel and Goldstein, 1992).

Another technique for performing no-scalpel vasectomy is to isolate the vas deferens after induction of adequate local anesthesia, grasping it tightly between the thumb and middle finger, and puncture the skin overlying the vas deferens with a sharpened tipped curved hemostat. The curved hemostat is used to spread the skin to enlarge the vertical slit in the skin just large enough to allow the ring-tipped vas deferens fixation clamp to fit through to grasp the vas deferens. The vas deferens is grasped and brought up through the puncture, and the vasal fascia and vessels can be spread off the vas deferens to expose the bare vas deferens by spreading the sharp-tipped curved hemostat onto the vasal fascia to open the vasal fascia (Figs. 37–8 and 37–9). The remainder of the vasectomy is performed as described above for bilateral procedure (Li et al, 1991). **This modification of making the puncture prior to grasping the vas deferens with the ring-tipped vas deferens fixation clamp was found to significantly decrease the operative time and showed no difference in incision length, postoperative pain, or time to return to work in a randomized prospective evaluation** (Chen et al, 2005).

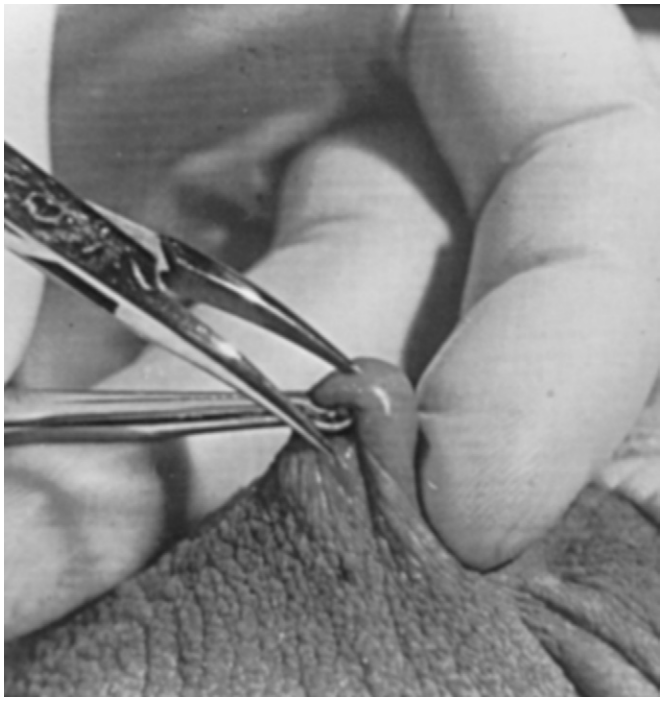


Figure 37–7. Puncture of the skin, vas sheath, and wall into the lumen. (From Li S, Goldstein M, Zhu J, Huber D. The no-scalpel vasectomy. J Urol 1991;145:341–4.)

Methods of Vasal Obstruction/Male Sterilization

There are a number of vasectomy occlusion techniques currently employed, including excision and ligation, thermal occlusion with intraluminal electrocautery, mechanical occlusion with hemoclips, fascial interposition, and chemical occlusion with percutaneous techniques.

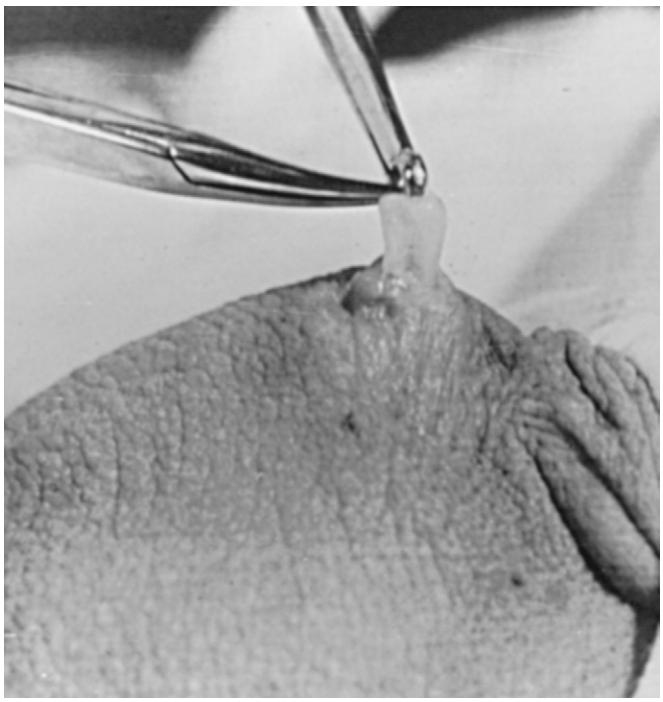


Figure 37–8. Delivery of the clean vas. (From Li S, Goldstein M, Zhu J, Huber D. The no-scalpel vasectomy. J Urol 1991;145: 341–4.)

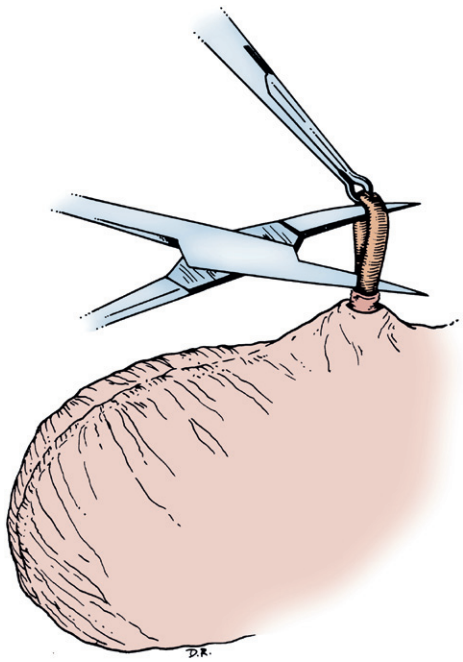


Figure 37–9. Segment cleaned. (From Li S, Goldstein M, Zhu J, Huber D. The no-scalpel vasectomy. J Urol 1991;145:341–4.)

There have been concerns about the risk of vasal necrosis and sloughing distal to the ligated end when suture ligation is performed, theoretically increasing the risk of recanalization. **Low-voltage thermal occlusion with intraluminal electrocautery in the abdominal and testicular ends of the divided vas deferens reduces recanalization rates to less than 0.5%** (Schmidt, 1987; Barone et al, 2004). **Vasectomy failure rates have been reported to be less than 1% when both the testicular and abdominal ends of the divided vas deferens are occluded with hemoclips** (Moss, 1974; Bennett, 1976). **Interposition of dartos fascia between the divided ends of the vas deferens is another technique for occlusion. This method has been reported to reduce the recanalization rate even further, nearly to zero** (Esho and Cass, 1978; Sokal et al, 2004).

Percutaneous vasectomy has been performed on over 500,000 men in China. This technique employs chemical occlusion by fixing the vas deferens up to the scrotal skin tightly, puncturing the lumen of the vas deferens with a 22-gauge needle, and then cannulating the lumen of the vas deferens with a 24-gauge blunt needle. For confirmation of vas deferens cannulation, Congo red is injected into the lumen of the abdominal end of the right vas deferens, and methylene blue is injected into the lumen of the left vas deferens prior to chemical occlusion by injection of 20 µl of two parts phenol to one part *N*-butyl-2-cyanoacrylate mixture. Following chemical occlusion the patient should void. If the urine is red, the left side was not cannulated, if it is blue, the right side was not cannulated, and if it is brown, that indicates bilateral successful cannulation (Ban, 1980; Li, 1980). Although these chemicals are not approved for use in the United States by the Food and Drug Administration, they appear to be safe by toxicologic testing and experience in China.

Fascial interposition is the technique that has been found to decrease vasectomy recanalization rates the most significantly. Randomized controlled trials examining the other techniques are not available. Several trials have been performed using irrigation of the abdominal ends of the vas deferens with saline, but there was no difference in time to azoospermia (Cook et al, 2007b).

Open-ended vasectomy, where the testicular portion of the vas deferens remains patent, is another technique that has been evaluated with the aim of decreasing epididymal pressure by performing intraluminal cautery or another method of occlusion on the abdominal end, while leaving the testicular end unoccluded. Ninety-seven percent of patients undergoing open-ended vasectomy develop sperm granulomas. This reduces pressure-induced damage to the epididymis, but increases the vasectomy failure rate to as high as 7% to 50% (Shapiro and Silber, 1979; Goldstein, 1983). **There is a significant decrease in the failure rate with open-ended vasectomy when fascial interposition is performed, decreasing the failure rate by approximately 7%** (Li et al, 1994).

Performing Vasectomy to Make Microscopic Vasectomy Reversal Easier

Technical aspects of performing vasectomy can affect the ease of microsurgical vasectomy reversal in the future if needed (Mammen et al, 2008). One procedural aspect is that excising a lengthy (>1 cm) segment of vas deferens is associated with the need for a higher scrotal incision, possibly up to the lower inguinal region, with the potential for anastomotic tension with microscopic vasectomy reversal. **Vasectomy reversal can be far more difficult when a lengthy portion of the vas deferens has been excised, with concomitant increases in operative time, length of incision, and postoperative pain** (Practice Committee of the American Society for Reproductive Medicine, 2006).

Another procedural aspect is the location along the length of the vas deferens where the vasectomy is performed. Experts in microsurgery agree that the anastomosis is least problematic when the lumen of the vas deferens is largest and most concentric, as opposed to the lumen in the epididymis or the convoluted vas (Mammen et al, 2008). Prospective studies show that the length of the testicular vas deferens present at the time of reversal has a direct correlation with the presence of seminal fluid containing intact sperm at the time of microscopic vasectomy reversal. A testicular length of vas deferens less than 2.7 cm correlates with seminal fluid without intact sperm 85% of the time, and testicular length over 2.7 cm is associated with intact sperm in seminal fluid 94% of the time. For each centimeter increase in testicular remnant length, the probability of whole sperm being present increases fourfold (Witt et al, 1994). **Division of the vas deferens should be performed approximately 3 cm distal to the cauda of the epididymis in the straight portion of the vas deferens at the time of vasectomy.**

The other technical aspect to consider is the occlusion technique employed. **All occlusive modalities for vasectomy carry a similarly high efficacy in terms of postprocedure azoospermia.** To date, no specific studies on occlusion technique as a predictor of reversal success have been performed. **Simple transection of the vas deferens followed by low-voltage intraluminal cautery occlusion followed by fascial interposition provides successful vasectomy and may result in minimal inflammatory reaction.** It would stand to reason that minimizing inflammation near the vas deferens would provide the optimum condition for microscopic vasectomy reversal in the future (Mammen et al, 2008).

Postoperative Care and Follow-up Semen Analysis

Routine postoperative care practices vary, but typically include the use of ice packs on the scrotum intermittently for the first 48 hours, limited heavy or strenuous activity for one week, and the use of nonsteroidal anti-inflammatory drugs, as needed, for pain, if the patient does not have any contraindications to these medications.

There is no vasectomy technique that is 100% effective, and a definitive standard to declare a patient sterile has not been agreed upon. Time to reach azoospermia is variable, although over 80% of patients achieve azoospermia by three months and after twenty ejaculations. Persistent nonmotile sperm are present in 1.4% of postvasectomy patients. **This data points to obtaining a semen analysis at three months and twenty ejaculations after vasectomy to reveal azoospermia.** If the semen analysis does not show azoospermia, periodic semen analyses can be obtained until azoospermia is achieved. Patients who have small numbers of persistent nonmotile sperm can be advised to cautiously discontinue contraception (Griffin et al, 2005). There is evidence that these men will ultimately reach azoospermia. **Vasectomy should be repeated if any motile sperm are found in the ejaculate three months after the initial vasectomy** (Aradhya et al, 2005).

An immunodiagnostic test, the SpermCheck Vasectomy (ContraVac, Charlottesville, VA), has been developed to allow patients to test themselves for severe oligospermia or azoospermia at home following vasectomy. This was developed to increase compliance with postvasectomy evaluation of semen parameters. The SpermCheck Vasectomy test was 96% accurate at predicting whether sperm counts were greater or less than a threshold of 250,000 sperm per milliliter (Klotz et al, 2008).

Complications: Local/Postoperative

Local complications of vasectomy include hematoma, infection, Fournier gangrene, chronic scrotal pain, and traumatic fistula/scrotal sinus (Awsare et al, 2005). **Surgeon volume and experience is the most important predictor of postoperative complications** (Kendrick et al, 1987).

Hematoma is the most common complication of vasectomy. The rate of hematoma formation after vasectomy ranges between 0.09% and 29%, with a mean incidence of 2% (Kendrick et al, 1987). The no-scalpel technique has decreased the hematoma rate to a 0.5% incidence (Pant et al, 2007).

The rate of infection from vasectomy with the conventional technique was reported between 12% and 38%, but decreased to 0.4% with the no-scalpel technique (Appell and Evans, 1980; Pant et al, 2007). Although it is an exceedingly rare complication, Fournier gangrene has been reported as a complication in men undergoing vasectomy (de Diego Rodríguez et al, 2000; Romero Pérez et al, 2004).

Up to 30% of men have short-term scrotal pain lasting a few weeks**. However, postvasectomy pain syndrome, or long-term scrotal pain after vasectomy, occurs in approximately one in 1000 vasectomies, although some report the incidence to be as high as 15%** (McConaghy et al, 1996; Awsare et al, 2005; Tandon and Sabanegh, 2008). Postvasectomy pain syndrome has no association with immediate postoperative complications such as hematoma or infection. There are several theories about the cause of postvasectomy pain syndrome. One is that dilation of the epididymal duct with obstruction of the testicular end of the vas deferens produces interstitial fibrosis. Another theory is that extravasation of spermatozoa, with epididymal duct rupture forming a sperm granuloma at the site where the vas deferens is transected, results in perineural fibrosis and inflammation, because sperm are highly antigenic (McMahon et al, 1992). This contradicts the previous belief that sperm granulomas are protective against postvasectomy pain syndrome by relieving pressure, although most sperm granulomas are asymptomatic (Tandon and Sebanegh, 2008). Interestingly, there are markedly increased pressures in the epididymis and the testicular end of the vas deferens after vasectomy, but these pressures were not found to be transmitted to the seminiferous tubules in human micropuncture studies (Johnson and Howards, 1975). It is unclear why some patients would develop long-term symptoms and others transient ones. Factors such as age, socioeconomic status, race, environmental, or vasectomy technique have not identified patients at risk for postvasectomy pain syndrome (Tandon and Sebanegh, 2008).

Conservative therapy should be the first line of therapy. This includes scrotal elevation and support, heat or ice (as needed for comfort), and nonsteroidal anti-inflammatory drugs. Empiric antibiotic therapy is not recommended without evidence of infection (Selikowitz and Schned, 1985). **Conservative therapy should be employed for at least three months for postvasectomy pain. Spermatic cord blocks should be considered after failure of conservative therapy.**

Surgical therapy might be considered if the above methods fail. **When pain is clearly localized to a sperm granuloma, excision of the granuloma and intraluminal cautery occlusion of the vas deferens may relieve the pain and prevent recurrence** (Schmidt, 1979). Epididymectomy has been performed in patients who had point tenderness to the epididymis, and epididymal dilation after vasectomy and failed conservative therapy. Predictors of poor outcomes with epididymectomy are atypical symptoms, concomitant erectile dysfunction, and a normal-appearing epididymis on scrotal ultrasound (West et al, 2000). **Up to 50% of patients who were properly selected for epididymectomy were cured of postvasectomy pain syndrome** (Chen and Ball, 1991). The patient must consider that vasectomy reversal will no longer be feasible after epididymectomy. **Vasectomy reversal rendered 69% of patients with postvasectomy pain syndrome pain free** (Nangia et al, 2000). **Although it has only been evaluated in a small number of patients, microscopic denervation of the spermatic cord in patients who had temporary relief with a spermatic cord block resulted in complete pain relief in 76% and improvement in pain in 9% of these men** (Levine and Matkov, 2001). The last resort consideration after failure of conservative and more invasive interventions have failed, is orchiectomy for severe intractable pain after vasectomy. **In this group, pain relief was reported in 73% of men who underwent inguinal orchiectomy versus 55% in those who underwent scrotal orchiectomy for postvasectomy pain syndrome** (Davis et al, 1990).

There is a report of 0.3% rate of scrotal sinus/vasocutaneous fistula after no-scalpel vasectomy (Pant et al, 2007).

Association of Vasectomy with Long-Term Systemic Disease

Previous studies found an increased risk of prostate cancer in men who underwent vasectomy (Giovannucci et al, 1993). Detection bias is thought to be the source of this association of prostate cancer with vasectomy (Millard, 1999). **Recent investigations have found that there is no association between vasectomy and prostate cancer** (Schuman et al, 1993; Holt et al, 2008). There is no association between vasectomy and prostate cancer in developing countries in which there are low incidences of prostate cancer in the general population as well (Schwingl et al, 2009). **Screening recommendations for prostate cancer should be no different in men who have undergone vasectomy than those who have not undergone vasectomy** (Healy, 1993).

Vasectomy does not place the patient at an increased long-term risk for cardiovascular disease or atherosclerosis (Coady et al, 2002; Goldacre et al, 2005).

Previous studies suggested that vasectomy may be a risk factor for patients with primary progressive aphasia, a dementia syndrome with aphasia as the presenting symptom (Weintraub et al, 2006). There are no longitudinal studies confirming this, and there have been many large, epidemiological studies comparing vasectomized and nonvasectomized men without any increased risk of dementia. There is no evidence that vasectomy adversely affects psychological health status (Thonneau and D'Isle, 1990).

Antisperm Antibodies

There is a disruption of the blood-testis barrier when vasectomy is performed. **Of men who undergo vasectomy, 60% to 80%**

of them have detectable levels of antisperm antibodies in the serum (Fuchs and Alexander, 1983). **After vasectomy, 50% to 60% of men develop sperm agglutinating antibodies, and 20% to 30% develop sperm immobilizing antibodies** (Kovacs and Frances, 1983). Although some studies suggest that antisperm antibodies persist, others suggest that they diminish in two or more years after vasectomy, but neither immune complex deposition nor circulation are increased in vasectomized men (Witkin et al, 1982).

Key Points: Vasectomy

- There is no vasectomy technique that is 100% effective, and a definitive standard for when to declare a patient sterile has not been agreed upon.
- The no-scalpel technique significantly decreases the rate of hematomas, infections, and pain during the procedure.
- Fascial interposition is the occlusion technique that has been found to decrease vasectomy failure rates the most significantly.
- Technical aspects of performing vasectomy can affect the ease of microsurgical vasectomy reversal in the future if needed.
- There is no association between vasectomy and prostate cancer or cardiovascular disease.

SPERMATOCELECTOMY/SURGERY OF THE EPIDIDYMIS

Surgical Indications

A spermatocele is a cystic dilation of an epididymal tubule, which is benign in nature. **Spermatoceles are very common, occurring incidentally in 30% of men on high-resolution ultrasound, and they are typically asymptomatic and do not cause epididymal obstruction, and therefore rarely require intervention.** Men typically seek surgical treatment when the spermatocele has reached the approximate size of the testis and is causing pain with point tenderness (Walsh et al, 2007).

Surgical treatment for chronic epididymitis is poorly studied in clinical trials with no level 1 evidence to support the use of a specific surgical procedure. In one study, ten patients with chronic epididymitis (defined as epididymal pain lasting greater than 3 months), underwent epididymectomy for intractable symptoms. Only one of these patients had significant improvement in pain (Davis et al, 1990). Other authors have reported much higher success rates, such as six out of seven patients (86%) having significant improvement in pain after epididymectomy (Chen and Ball, 1991). **Chronic or recurrent epididymitis and persistent epididymalgia with point tenderness to the epididymis may be reasonable indications for epididymectomy** (Padmore et al, 1996).

Surgical treatment for chronic epididymitis should only be considered after failure of extensive conservative therapy and after appropriate counseling, with the understanding that the symptoms may not improve after surgery, or may indeed worsen. A retrospective review of men who underwent epididymectomy for chronic epididymitis showed that outcomes were best when the patient had a palpable epididymal abnormality on physical examination. Men in this study without a palpable abnormality, but with sonographic changes, had slightly worse outcomes, and those with neither a palpable abnormality nor a demonstrable ultrasound abnormality did not improve with epididymectomy (Calleary et al, 2009).

Purulent epididymitis diagnosed by a combination of physical examination, ultrasound evaluation, and, occasionally, needle aspiration of the epididymis is an absolute indication for epididymectomy (Arbuliev et al, 2008). This is also the treatment of choice for epididymal abscesses and chronic infectious epididymitis that is unresponsive to antibiotic treatment**. Diagnostic epididymal puncture and aspiration should not be performed in men with interest in future fertility, because this will result in epididymal obstruction.**

Total epididymectomy may relieve chronic persistent pain localized to the epididymis after vasectomy.

Epididymal malignancies are extremely rare, and 73% of nontransilluminating, solid epididymal masses are benign adenomatoid tumors (Beccia et al, 1976). Surgical extirpation should be considered for adenomatoid tumors, especially if there is any suspicion for malignancy (Alvarez et al, 2009).

Partial/Total Epididymectomy

Any patient undergoing epididymal surgery should be extensively counseled that the surgery may impair his fertility, or even cause sterility if bilateral epididymal surgery is required, because the distal epididymis consists of a single tubule.

Partial/total epididymectomy can be approached scrotally through a median raphe or a unilateral transverse scrotal incision to deliver the testis. The vas deferens is identified, isolated, ligated, and divided. The testicular end of the vas deferens is then followed to the vasoepididymal junction. The tunica vaginalis is opened, and the plane of dissection between the epididymis and the testis is found in order to divide the epididymis from the testis. Great care should be taken to avoid injury to the spermatic cord and testicular artery. The efferent ducts superior to the testicular vasculature are ligated with an absorbable suture to complete the epididymectomy. The edges of the tunica vaginalis where the epididymis was excised are approximated with a running absorbable suture, which helps with hemostasis. The dartos fascia and skin are closed in layers with absorbable suture. In the case of partial epididymectomy, ligations are performed between the testis and epididymis with absorbable suture to excise the affected portion of the epididymis, while leaving the remainder attached to the testis with its vascular supply intact (Figs. 37–10 and 37–11).

Spermatocelectomy/Excision of Epididymal Cysts

Spermatocelectomy can be approached scrotally through a median raphe or a unilateral transverse scrotal incision to deliver the testis. The tunica vaginalis is opened, and the spermatocele is identified and dissected free from the epididymis. The epididymal–spermatocele attachment is ligated and divided to complete the spermatocelectomy. The tunica vaginalis is closed, and the dartos fascia and scrotal skin are reapproximated in layers.

Excision of Epididymal Tumors

As discussed above, the majority of epididymal nontransilluminating masses are benign adenomatoid tumors. Fine needle aspiration

of solid epididymal masses has been evaluated and found to be very accurate when compared with surgical pathology (Gupta et al, 2006). **When malignancy is suspected, an inguinal approach should be used with clamping of the spermatic cord and delivery of the testis.** The addition of testicular hypothermia by adding ice slush to the Chevassu maneuver (of clamping the vessels) was employed and found to salvage three out of five testicles with benign processes after clamping and parenchymal biopsy (Goldstein and Waterhouse, 1983). When malignancy is ruled out, the epididymal mass may be excised as for a spermatocelectomy.

Complications

Complications of epididymectomy, spermatocelectomy, and excision of epididymal masses are rare. Complications include bleeding, infection, damage to the testicular artery with resultant testicular atrophy, and recurrence in cases of spermatocelectomy (Kiddoo et al, 2004; Zahalsky et al, 2004). **Complications also include impairment of fertility with obstruction of the epididymal tubules and possible sterility in bilateral cases, necessitating counseling and recommending sperm cryopreservation in men who undergo bilateral procedures and have an interest in fertility.** Approximately 17% of patients undergoing spermatocelectomy will have resultant epididymal injury (Zahalsky et al, 2004). The overall complication rate has been reported to be as high as 20%, with the most common complications being persistent scrotal pain and infection. **Leaving a scrotal drain did not decrease complication rates** (Kiddoo et al, 2004).

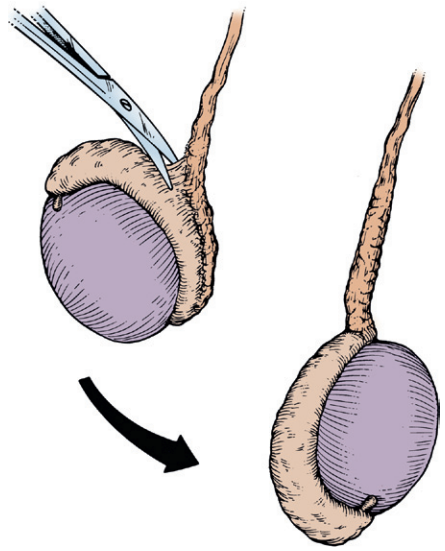


Figure 37–10. Convuluted vas dissected off the epididymal tunica.

HYDROCELECTOMY

The adult hydrocele is caused by excessive fluid secretion by the visceral tunica albuginea without adequate reabsorption of this fluid by the parietal peritoneum around the testis.

Inguinal Surgical Approach

Men diagnosed with hydroceles, where there is suspicion for concomitant malignancy, should undergo high-resolution scrotal ultrasound. If malignancy is suspected, an inguinal approach should be used to allow control of the spermatic cord in preparation for radical orchiectomy. If this approach is taken and no malignancy is encountered, the testis can be spared and the hydrocele can be repaired by one of the techniques described below.

Scrotal Surgical Approaches

When there is no evidence of malignancy on physical examination and high-resolution ultrasound, hydroceles may be approached scrotally through a median raphe or a transverse unilateral incision. In all techniques, the hydrocele is dissected and delivered intact to allow the easiest dissection. Once it is delivered, an opening in the sac is made away from the testis, epididymis, and cord structures, and the fluid is suctioned out. The hydrocele sac is then opened further to expose the sac for the elected repair. **The overall single-treatment success rates for surgical hydrocelectomy range between 90% and 100%** (Rodriquez et al, 1981).

Excisional techniques are the least likely to result in recurrence of a hydrocele. Excising the hydrocele is recommended for long-standing, thick-walled, loculated hydroceles. The hydrocele sac is opened, taking great care not to injure the spermatic cord, and the sac is simply excised, leaving room to oversew the edge of the excised sac without endangering

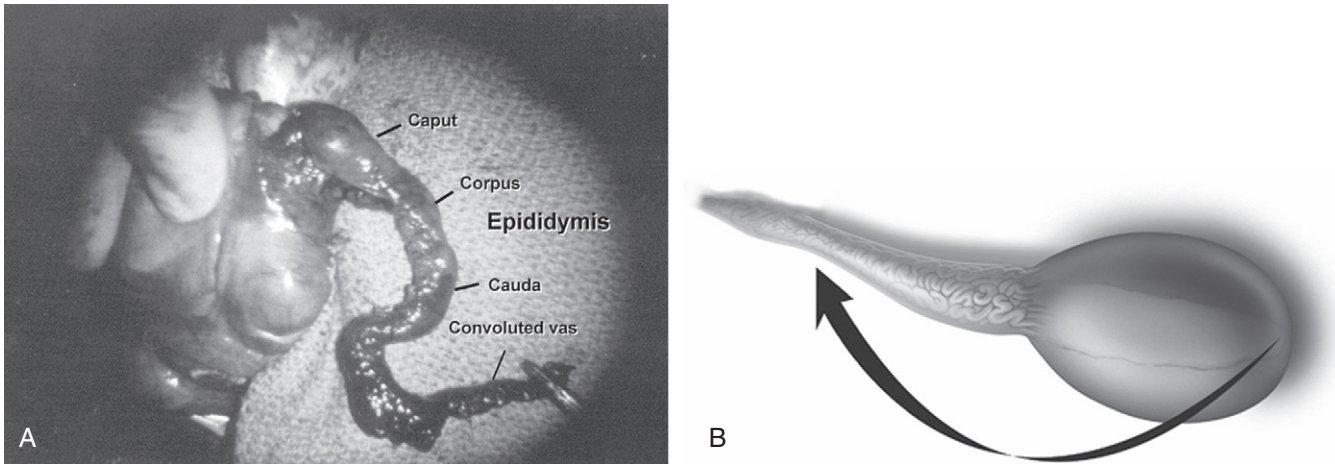


Figure 37–11. **A** and **B,** Entire vasoepididymal complex is dissected to the caput.

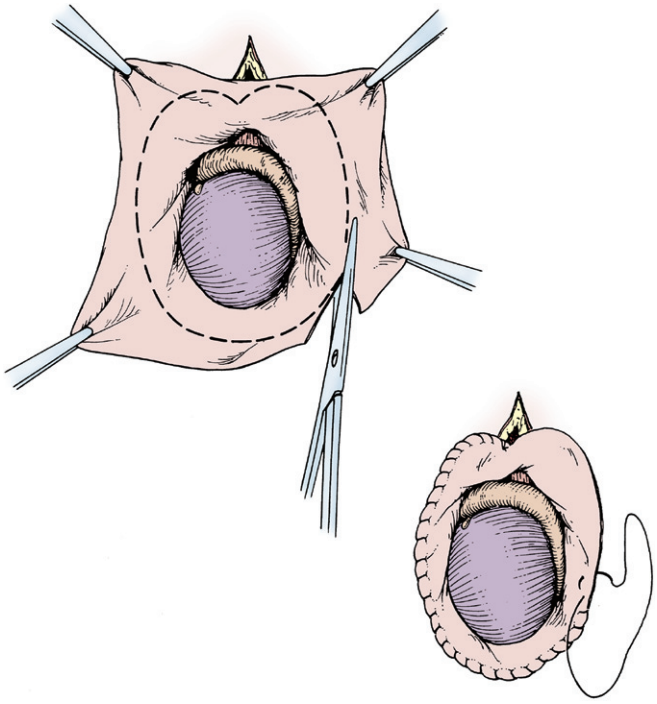


Figure 37–12. Simple excision of the thick-walled hydrocele sac and oversewn edges.

the cord or the epididymis. A 3-0 chromic suture can be used in a baseball stitch manner to oversew the edge of the sac (Fig. 37–12).

The Jaboulay bottleneck technique is a useful method for large, floppy, thin hydrocele sacs. This is performed by excising the sac as described above, but a larger margin of excision should be left between the edge of the sac and the testis and epididymis, to allow for sewing the edges of the sac together behind the cord, without compressing the cord (Fig. 37–13) (Jaboulay, 1902).

If there appears to be a risk for hematoma after excision and oversewing with either technique, a Penrose drain can be left in the dependent portion of the scrotum and fixed in place to the scrotum. The dartos fascia and skin are then closed in layers. Fluffs and a scrotal support are used for the dressing.

Plication techniques are suitable for thin-walled hydroceles but should not be used in large, long-standing, thick-walled, multiloculated hydroceles because this leaves a large bundle of plicated tissue in the scrotum. The Lord plication technique (1964) is performed by opening the hydrocele as described above, delivering the testis, cauterizing or oversewing the cut edges of the sac, and using interrupted, radially placed chromic sutures to plicate the sac. Closure is then performed as described above. Drains are not necessary with plications (Fig. 37–14).

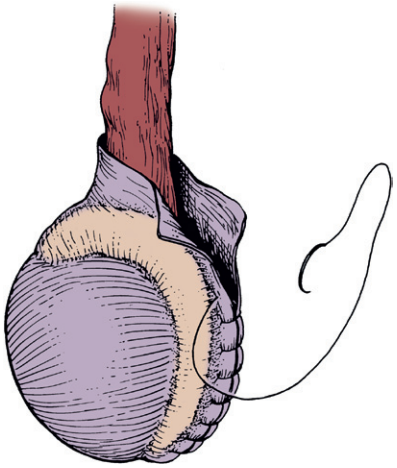


Figure 37–13. Jaboulay bottleneck technique for excision of thin, floppy sacs.

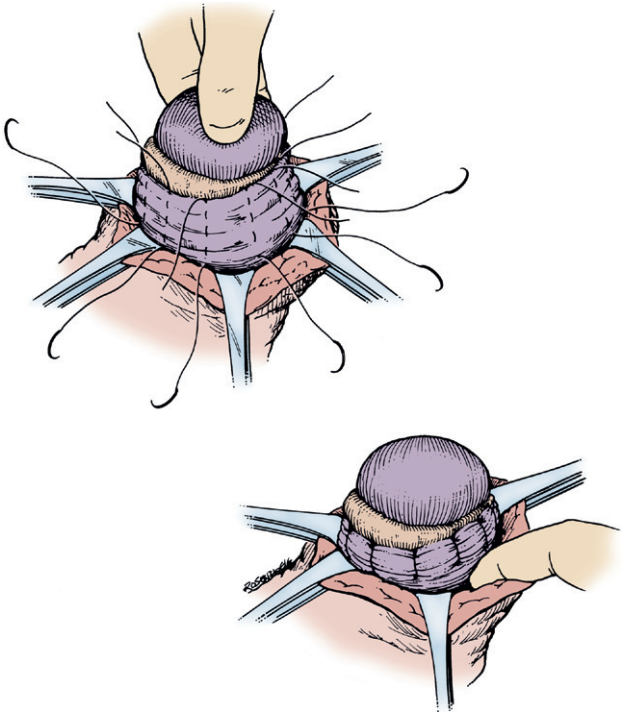


Figure 37–14. Lord placation technique.

Sclerotherapy

Sclerotherapy is another treatment option with a single-treatment success rate ranging from 33% to 75% (Levine and Dewolf, 1988). This may be a good choice for patients who cannot tolerate anesthesia or who refuse surgical treatment. **The common steps of the procedure include needle aspiration of the hydrocele fluid, followed by injection of local anesthesia, and ultimately instillation of the sclerosing agent.** The most commonly used sclerosing agent is tetracycline (500 mg), although 2.5% phenol solutions, 95% alcohol, and ethanolamine oleate have also been used effectively (Nash, 1984; Hellström et al, 1986; Miskowiak and Christensen, 1988). One study showed no statistically significant improvement in patients who underwent aspiration of hydrocele fluid alone versus aspiration plus instillation of tetracycline as a sclerosing agent, with a higher complication rate in the sclerotherapy group (Breda et al, 1992). When sclerotherapy was compared to hydrocelectomy, the success rate was higher in hydrocelectomy, although the hydrocelectomy group had a higher complication rate. Nonetheless, the patients who underwent hydrocelectomy had higher satisfaction rates (Beiko et al, 2003).

Table 37–2.
Hydrocelectomy Techniques and Risks

	RECURRENCE	HEMATOMA
Excision	Decreased	Increased
Plication	Increased	Decreased

Complications

The most common complication after hydrocelectomy is hematoma (Table 37–2). **The overall complication rate in hydrocelectomy is approximately 19%, including hematoma, infection, persistent swelling, recurrence, injury to spermatic vessels, and chronic pain.** Although the use of a drain in selected patients is recommended, it has not been proven to decrease complication rates thus far (Kiddoo et al, 2004). When repairing large hydroceles, great care must be taken to not injure the epididymis and spermatic vessels, because they may be splayed within the hydrocele layers. Injury to the epididymis or vas deferens can put the patient's future fertility at risk (Zahalsky et al, 2004).

Sclerotherapy complications include scrotal pain in 29% to 55% of patients (Rencken et al, 1990; Ovrebø and Vaage, 1991), recurrence, hematoma, and infection; febrile chemical epididymo-orchitis has also been reported with sclerotherapy (López Laur, 1989; Beiko et al, 2003). **Sclerotherapy can have an adverse effect on fertility and should be avoided in patients with interest in fertility potential** (Sigurdsson et al, 1994).

SURGICAL TREATMENT OF ORCHITIS AND CHRONIC SCROTAL PAIN

Orchitis is defined as inflammation of the testicle (Delavierre, 2003). The typical symptoms of orchitis include scrotal pain, swelling, tenderness, and skin fixation over the testicle. The Prehn sign has been described in orchitis and epididymitis when there is relief of pain with elevation of the testicle over the symphysis pubis (Noske et al, 1998). The Prehn sign is nonspecific and nondiagnostic and does not necessarily distinguish epididymo-orchitis from spermatic cord torsion. **Orchitis can cause an irreversible affect on spermatogenesis, impacting the quality and number of spermatozoa.** Lymphocytic infiltration and seminiferous tubule damage is seen on testicular biopsies of subfertile men with a history of chronic orchitis (Schuppe et al, 2008).

Chronic orchitis is defined as constant or intermittent scrotal pain lasting at least 3 months or longer, and of unclear cause (Costabile et al, 1991). **In patients with clinical orchitis, a scrotal ultrasonograph should be obtained because testicular malignancy has been reported to masquerade as orchitis** (Vaidyanathan et al, 2008). At least 10% of men with testicular malignancy will initially be incorrectly diagnosed as having an acute inflammatory process or spermatic cord torsion (Cook and Dewbury, 2000). High-frequency transducer sonography (7.5 to 10 MHz) is considered the best modality for evaluation of scrotal pathology including orchitis (Lee and Bhatt, 2008).

Although there is no level 1 evidence for the optimal treatment of chronic orchitis or epididymitis, local supportive therapy, including heat, nerve blocks, analgesics, tricyclic antidepressants, anticonvulsants (such as gabapentin), and anti-inflammatory drugs are common practice and may offer some relief (Davis and Noble, 1992). Other treatment options implemented for chronic epididymitis include phytotherapy, anxiolytics, narcotics, acupuncture, and steroid injection therapy (Nickel et al, 2002). Despite evidence that up to 75% of patients do not have an identifiable bacterial urinary tract infection concomitantly with their clinical epididymitis, antibiotics are routinely given. Empirical antibiotic administration in the absence of positive urine cultures has been steadily increasing, from 75% to 95% between the years of 1965 and 2005. **Antibiotic administration does not decrease the length of symptoms or the return to full activity in men without an identifiable bacterial pathogen** (Mittemeyer et al, 1966).

Orchiectomy

Surgical treatment for chronic orchitis is poorly studied in clinical trials, with no level 1 evidence to support the use of a specific surgical procedure. Fewer than 250 patients with chronic scrotal pain have been treated with differing surgical therapies in the available literature, despite the common nature of chronic scrotal pain. There is no level 1 evidence that orchiectomy is effective for the treatment of chronic orchalgia. If orchiectomy is recommended, the patient should previously have failed conservative therapy and must be apprised of the risks, benefits, and options of orchiectomy. Because many patients will continue to have pain or have pain recur after orchiectomy, the surgeon should be aware of the medical legal aspects of this action. **If orchiectomy is performed, it should be performed through an inguinal incision, because this approach has been shown to have a better outcome than the scrotal approach for orchalgia** (Davis and Noble, 1992).

Microsurgical Denervation of the Spermatic Cord

Some surgeons have attempted microsurgical denervation of the spermatic cord for symptomatic relief of chronic scrotal pain. **Microsurgical denervation of the spermatic cord was performed in 79 men on 95 testicular units for chronic orchalgia over a mean duration of 62 months. There was complete relief of pain in 71% of the patients, partial relief in 17%, and there was no change from the preoperative status in 12%, with no patients experiencing worsened postoperative pain.** The mean follow-up was 20.3 months (Strom and Levine, 2008). **Microscopic denervation should only be considered if the patient has temporary relief of orchalgia with a spermatic cord block with 10 ml of 0.5% bupivacaine** (Levine et al, 1996).

To mobilize the spermatic cord, microsurgical denervation is performed by the same approach as microscopic subinguinal ligation of the spermatic veins for varicocele repair. Microscopic transection of all branches of the genitofemoral nerve along the spermatic cord is performed while preserving the testicular artery, the vas deferens, the vasal vessels, and some of the lymphatics (Fig. 37–15). This procedure can also be performed laparoscopically (Cadeddu et al, 1999). If fertility is not an issue of concern, it is recommended to divide the vas deferens as well to eliminate the sympathetic innervation, which may contribute to orchalgia by a sympathetic dystrophy component (Levine et al, 1996).

Large, clinically palpable varicoceles can cause orchalgia. The pain typically improves with the patient in the supine position, as the varicocele decompresses. **In a small series of men who underwent microscopic varicocelectomy for clinically palpable varicoceles with concomitant orchalgia, just**

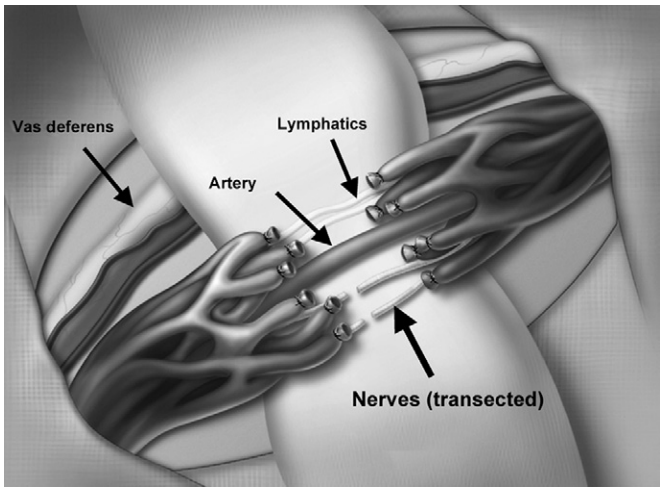


Figure 37–15. Microsurgical denervation. The goal is to transect all branches of the genitofemoral nerve while preserving the vas deferens, vasal vessels, testicular artery, and lymphatics.

over 50% had resolution of pain and 90% had improvement (Chawla et al, 2005). Higher success rates were reported in a previous, larger-powered, retrospective study (Peterson et al, 1998). Smaller, nonclinical varicoceles are unlikely to cause orchalgia and should be managed conservatively.

Retractile testes are another source of scrotal pain in the adult male. A careful history must be elicited to make this diagnosis, as the patient may not demonstrate a retractile testis on examination. The history is consistent with orchalgia only when the testis retracts up toward the external inguinal ring. This is typically seen in younger men with hyperactive cremasteric reflexes. Orchiopexy can be performed in these patients as it would in patients with intermittent torsion (Forte et al, 2003). **When orchiopexy is offered, it should be performed by a dartos pouch technique to prevent retraction, as is recommended for testicular torsion** (Redman and Barthold, 1995).

The other surgical treatment for orchalgia secondary to the retractile testis is to perform microscopic release of the cremasteric muscle. This is performed in a similar manner to microscopic subinguinal varicocelectomy. The spermatic cord is mobilized and isolated and the cremasteric muscle is divided circumferentially while preserving the vasculature of the spermatic cord and the vas deferens. This effectively releases the spermatic cord, thus not allowing retraction of the testis with hypercontraction of the cremasteric muscles.

Key Points: Surgery of the Scrotal Contents

- Patients undergoing epididymal surgery should be counseled that the surgery may impair their fertility, or even cause sterility if bilateral epididymal surgery is required.
- Sclerotherapy as treatment for a hydrocele can have an adverse effect on fertility and should be avoided in patients with an interest in fertility potential.
- Antibiotics should not be given for epididymitis or orchitis without evidence of infection.
- All patients with chronic orchalgia should undergo a scrotal ultrasound.
- When a clinically palpable varicocele is encountered in a patient with orchalgia, varicocelectomy will resolve the pain 50% of the time.

SURGERY OF THE SEMINAL VESICLES

In 1561, Gabriele Fallopius, a renowned Italian anatomist and physician, first described the seminal vesicles as paired male organs. He was considered an authority in the field of sexuality and advocated the use of condoms to decrease the transmission of syphilis. There was a great deal of interest in the seminal vesicles in the late 19th century due to their discovered involvement with inflammatory diseases (Brewster, 1985).

Seminal vesicle secretions contribute 50% to 80% of the volume of the ejaculate. The pH of the secreted fluid is neutral to slightly alkaline, and the mean volume is approximately 2.5 mL. The secreted fluid contains fructose and other carbohydrates necessary for sperm motility. It also contains a coagulation factor and prostaglandins A, B, E, and F (Tauber et al, 1975).

Primary disease processes of the seminal vesicles are very rare, although secondary processes are seen more commonly. Diagnosis of such entities has improved over the years with advanced imaging. Surgical access and management of seminal vesicle pathology can be difficult for the urologist due to the anatomic location.

Anatomy

The seminal vesicles are paired male organs with no equivalent in the female. It is useful to understand the developmental anatomy of the seminal vesicles to gain a full understanding of the anatomy in the adult patient. **The seminal vesicles begin as bilateral dorsolateral bulbous dilations of the distal mesonephric ducts between 12 and 12½ weeks of gestation.** By 13 weeks, these dilations have enlarged and the ejaculatory ducts are beginning to form in the developing prostate (Brewster, 1985). The seminal vesicle and the ampulla of the vas deferens join posterior and superior to the prostate to form the ejaculatory duct (Nguyen et al, 1996). By the early portion of the seventh month, the seminal vesicle has multiple outpouchings and a widened main central lumen (Fig. 37–16) (Brewster, 1985).

The adult seminal vesicle measures 5 to 6 cm in length and 3 to 5 cm in diameter with a volume capacity of 13 cm, although they decrease in size as men age (Redman, 1987). At the terminal portion of the vas deferens within the prostate, the major lumen of the seminal vesicle empties into the ejaculatory duct. The ejaculatory duct is in continuity with the seminal vesicle but does not share the thick muscular wall of the seminal vesicle (Fig. 37–17) (Nguyen et al, 1996). **The arterial supply to the seminal vesicle is from the vesiculodeferential artery, branching off from the umbilical artery** (Braithwaite, 1952). Venous drainage of the seminal vesicle follows the arterial supply draining through the vesiculodeferential veins and the inferior vesicle plexus. **Innervation of the seminal vesicles is by the hypogastric nerve (adrenergic and cholinergic) and the pelvic nerve. Lymphatic drainage of the seminal vesicles is through the internal iliac nodes** (Mawhinney and Tarry, 1991).

Congenital Anatomic Anomalies of the Seminal Vesicles

The incidence of unilateral seminal vesicle agenesis is 0.6% to 1%. **Unilateral seminal vesicle agenesis may be associated with ipsilateral renal anomalies and unilateral absence**

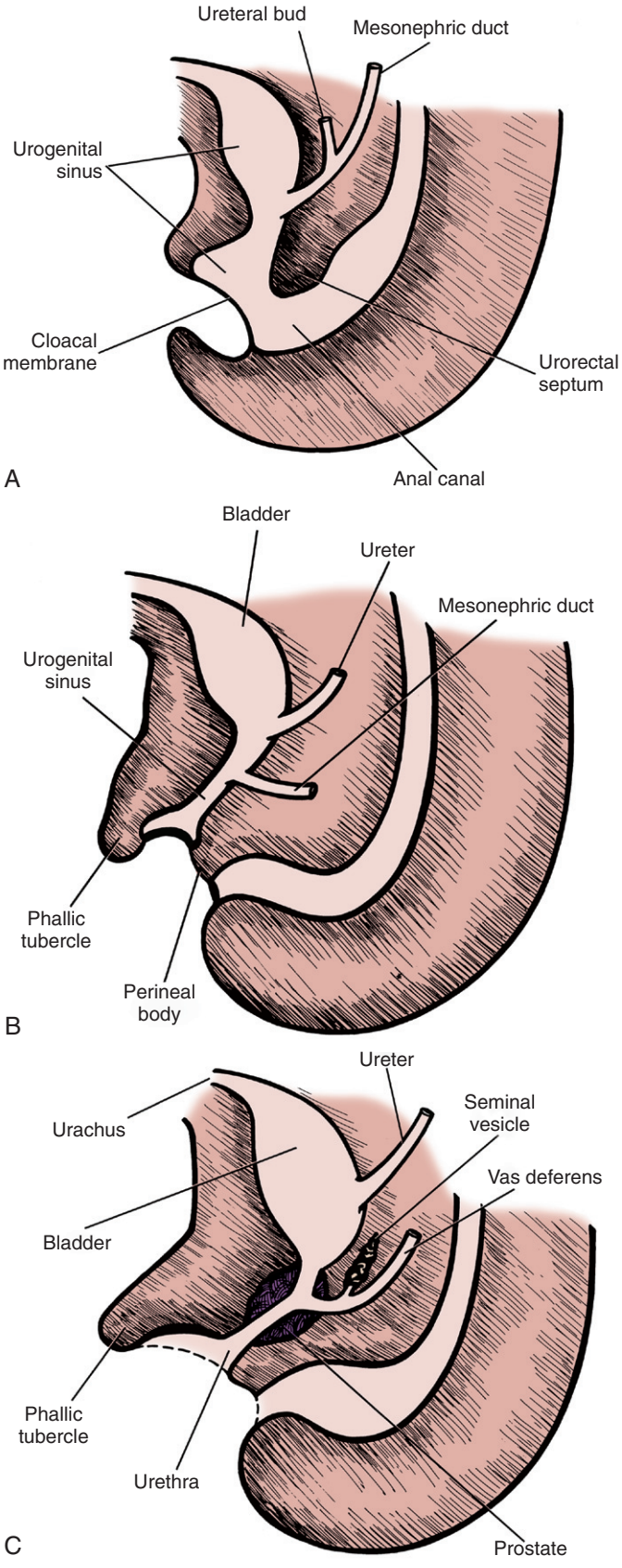


Figure 37–16. Intrauterine (fetal) development of the seminal vesicles. **A,** Fifth week. **B,** Eighth week. **C,** Thirteenth week. (Redrawn from Langman J. Medical embryology. 4th ed. Baltimore: Williams & Wilkins; 1981. p. 242–3.)

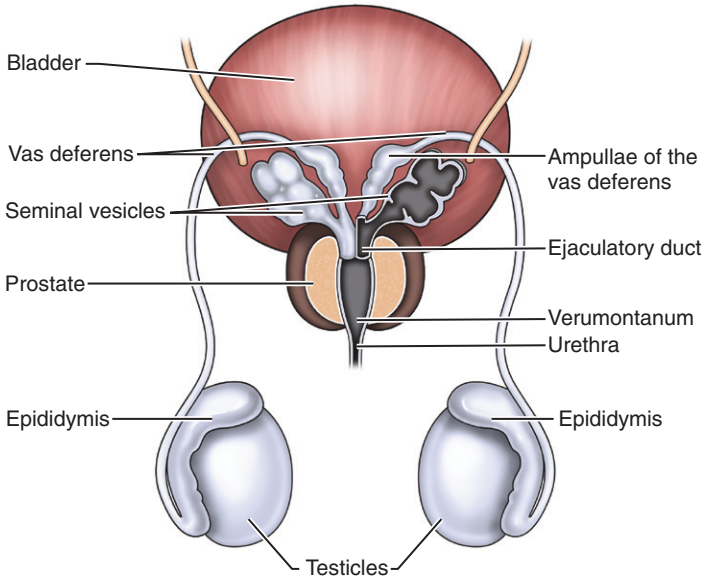


Figure 37–17. Posterior view of seminal vesicle anatomy in relation to the lower genitourinary tract (*bivalved areas in dark gray*).

of the vas deferens. This is thought to be secondary to an embryological insult at the seventh week of gestation prior to the separation of the ureteral bud from the mesonephric duct. If this insult occurs after the seventh week, it is unlikely that renal agenesis would be associated with the seminal vesicle agenesis (Hall and Oates, 1993). It is common to find bilateral absence of the seminal vesicles along with congenital bilateral absence of the vas deferens, which is typically associated with a cystic fibrosis transmembrane receptor mutation. Of these men, 70% to 80% carry the genetic mutation associated with cystic fibrosis (Anguiano et al, 1994; Chillon et al, 1995). Treatment is only necessary when fertility becomes an issue.

Infectious Processes of the Seminal Vesicles

Infection of the seminal vesicles is seen in underdeveloped countries more frequently than in the United States. The causative agents are *Mycobacterium tuberculosis* and *Schistosoma haematobium*. The diagnosis of bacterial seminal vesiculitis can be made by transrectal or perineal needle aspiration. Surgery is not usually indicated, and culture-specific systemic antibiotics are the treatment of choice (Gutierrez et al, 1994). Very rarely, seminal vesiculectomy is necessary to prevent recurrent bacteremia or to eliminate persistent symptoms (Indudhara et al, 1991). Seminal vesicle abscesses are rare, but have been associated with diabetes mellitus, chronic indwelling catheters, and endoscopic instrumentation (Gutierrez et al, 1994). Management of seminal vesicle abscesses is discussed below along with management of seminal vesicle cysts**. Infection, obstruction, or the combination of the two can result in calculi formation in the seminal vesicles.** Patients with seminal vesicle calculi present with hematospermia, perineal pain, painful ejaculation, and infertility. These stones can be managed through an open or laparoscopic vesiculectomy, or the stone can be retrieved endoscopically using a small-caliber ureteroscope (Ozgök et al, 2005; Cuda et al, 2006; Han et al, 2008).

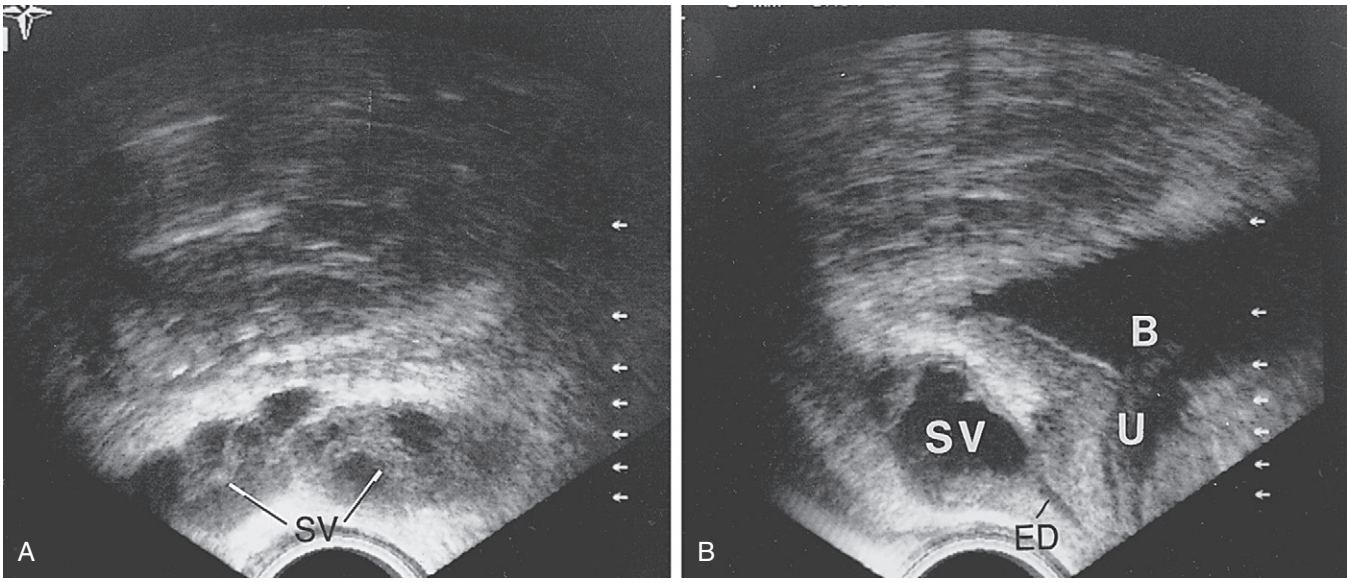


Figure 37–18. Transrectal ultrasound examination of normal seminal vesicles. **A,** Transverse view. **B,** Sagittal view. B, bladder; ED, ejaculatory duct; SV, seminal vesicle; U, urethra.

Evaluation of Abnormalities of the Seminal Vesicles

Normal seminal vesicles are not palpable on digital rectal examination. When a seminal vesicle cyst is present, the area immediately above the prostate may be compressible on digital rectal examination. This same area may feel firm or solid when a seminal vesicle tumor is present.

Semen analysis revealing a low seminal volume and a lack of liquefaction and fructose may indicate ejaculatory duct obstruction or absence of seminal vesicles (Goldstein and Schlossberg, 1988).

High-resolution transrectal ultrasonography (TRUS) has become the mainstay of imaging for the diagnostic evaluation of seminal vesicle pathology, because it is a reliable and inexpensive imaging modality. On TRUS, the seminal vesicles can be found just superior to the prostate, between the bladder and the rectum, and can be well visualized in the anteroposterior and sagittal views. The normal seminal vesicles should appear as flat, elongated, paired structures in the above described positions (Fig. 37–18). Along with the seminal vesicles, the ampullae of the vas deferens, the ejaculatory ducts within the prostate, and the verumontanum can be imaged and evaluated by TRUS. Abnormalities such as seminal vesicle obstruction, aplasia, atrophy, and cyst formation can be identified by TRUS (Carter et al, 1989).

Seminal vesicle obstruction may result in seminal vesicle dilation identifiable by TRUS with the following characteristics: anteroposterior diameter of greater than 15 mm, length greater than 35 mm, and large anechoic areas, which contain sperm when aspirated (Jarow, 1996; Colpi et al, 1997). Asymptomatic cystic dilation of the seminal vesicle was incidentally found in 5% of men undergoing TRUS for prostate cancer screening (Wessels et al, 1992).

TRUS revealing hyperechoic solid masses in the seminal vesicles (isoechoic to the prostate) are concerning for tumor. If there is a unilateral solid mass in the seminal vesicle, it is more likely to be a primary tumor, whereas if it is present in bilateral seminal vesicles, it is more likely to be a secondary tumor from a primary prostate, rectal, or bladder malignancy. TRUS-guided biopsy or aspiration is necessary to assist in the diagnosis.

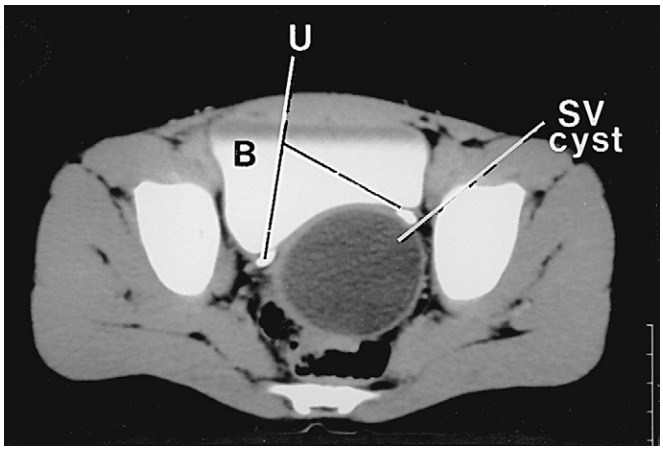


Figure 37–19. CT scan of seminal vesicle cyst (SV cyst). B, bladder; U, ureters.

Computed tomography (CT) has also been used to evaluate the seminal vesicles. **The normal appearance of the seminal vesicles on CT is that of paired structures just below the bladder with medium contrast similar to muscle** (Goldstein and Schlossberg, 1988)**.** A seminal vesicle cyst imaged by CT scan appears as a well-defined retrovesicular fluid density with the attenuation of water, from 0 to 10 Hounsfield units, cephalad to the prostate gland (Fig. 37–19). CT accurately images seminal vesicle anomalies, and is a good modality to allow for imaging of the ipsilateral kidney concomitantly (Arora et al, 2007).

In cases of primary seminal vesicle malignancy, CT scan may be useful to further characterize the lesion prior to intervention. A tumor within the seminal vesicle on CT has a higher attenuation than the normal seminal vesicle, but the tumor may appear cystic secondary to tumor necrosis (King et al, 1989). It is not possible to differentiate malignant tumors from benign ones on CT scan alone, although secondary tumors from the bladder, rectum, or prostate may have a more contiguous appearance (Sussman et al,

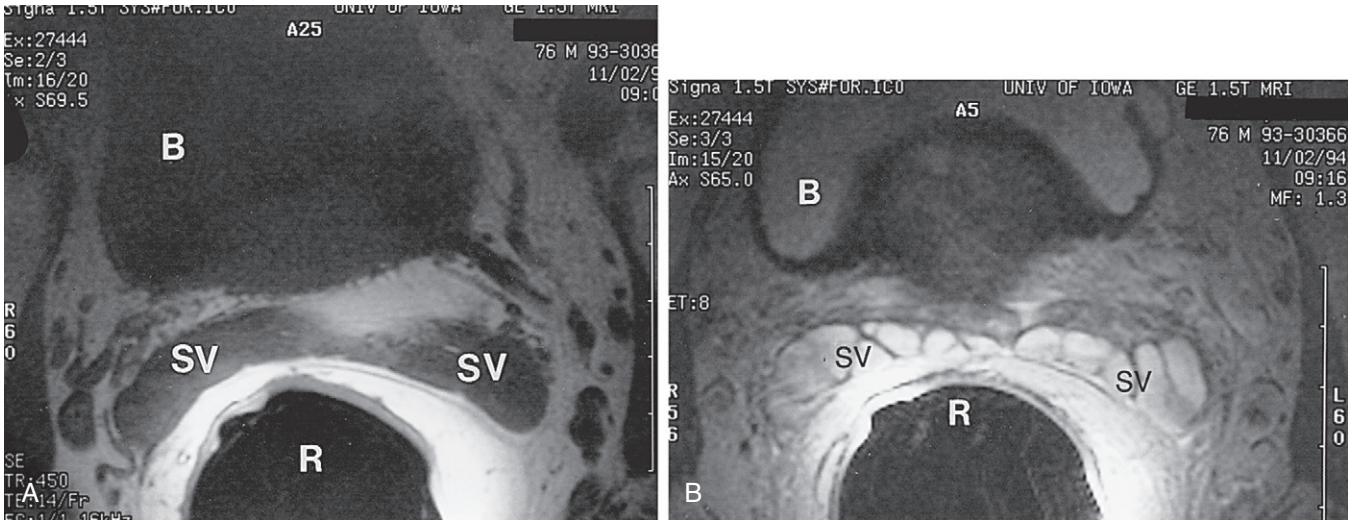


Figure 37–20. Transaxial MRI of normal seminal vesicles (SV) with endorectal coli. **A,** T1-weighted image. **B,** T2-weighted image. B, bladder; R, rectum.

1986). The CT findings of a leiomyosarcoma of the seminal vesicle are described as an irregular mass, resulting in enlargement of the seminal vesicle with displacement of the prostate gland (Upreti et al, 2003). CT, as well as magnetic resonance imaging (MRI), allows metastatic evaluation when seminal vesicle neoplasms are further characterized (Dahms et al, 1999).

MRI is another useful imaging modality for the seminal vesicles, which gives more anatomic detail than CT. On T2-weighted images, the ampulla of the vas deferens is visible approximately 71% of the time and exhibits low signal intensity. The seminal vesicles exhibit high signal intensity 79% of the time, low signal intensity 19% of the time, and a heterogeneous signal intensity 2% of the time on T2-weighted images (Roy et al, 1993). On T2-weighted images, the seminal vesicles generally have similar or higher intensity than fat in patients less than 70 years of age, and typically have signal intensity lower than that of fat in patients greater than 70 years of age. The convolutions of the seminal vesicles can be seen on T1-weighted imaging with contrast (Fig. 37–20) (Secaf et al, 1991).

On MRI, seminal vesicle agenesis is best exemplified on T1-weighted axial images (Fig. 37–21). Care must be taken to not mistake the vesicoprostatic venous plexus for small glands. Arteriovenous malformations appear as large ectatic vessels adjacent to the lateral edge of the seminal vesicle. After androgen ablation, seminal vesicles demonstrate low signal intensity on T2-weighted images and appear small in size (Secaf et al, 1991). The appearance of seminal vesicles after pelvic radiation reveals a decrease in size in a third of the patients. The seminal vesicles have a normal MRI appearance in 63% of the patients after pelvic radiation, 21% had normal signal intensity but had fewer tubules, 8% had diffuse loss of signal intensity appearing hypointense to fat, and 8% were hypointense to fat on T2-weighted images (Chan and Kressel, 1991). A seminal vesicle cyst may have variable signal intensities on T1-weighted images but typically demonstrates fluid signal intensities on T2-weighted images and does not enhance with the administration of intravenous gadolinium. Increased T1-weighted intensity represents increased proteinaceous concentration within the cyst or hemorrhage (Arora et al, 2007). Hemorrhagic seminal vesicle cysts have high signal intensity on T1- and T2-weighted images (Sue et al, 1989). A benign primary mass of the seminal vesicle appears as a sharply marginated mass arising from the seminal vesicle. The most common form of malignancy affecting

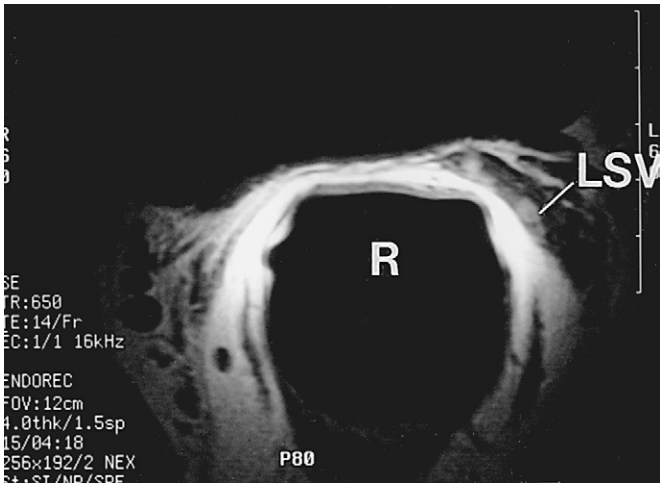


Figure 37–21. Transaxial T1-weighted endorectal magnetic resonance image of absent right seminal vesicle. LSV, left seminal vesicle; R, rectum.

the seminal vesicle is invasion of prostate cancer directly into the seminal vesicle. This can make the seminal vesicle appear large but does not always do so, and the seminal vesicle has low signal intensity on T2-weighted images (Secaf et al, 1991). **MRI is not necessary to make the diagnosis in cases with a seminal vesicle abnormality. If there is a palpable seminal vesicle abnormality, TRUS should be performed with biopsy if there is suspicion for malignancy. MRI is helpful with hemorrhagic lesions, and body imaging is useful for staging.**

Surgical Approaches to the Seminal Vesicles

The surgical approach to the seminal vesicles is mainly dependent on the expertise and comfort of the surgeon, although the characteristics of the lesion may impact the decision on the approach.

Preoperative preparation for seminal vesicle surgery should include a bowel preparation the evening before surgery, in case of

the uncommon occurrence of a bowel injury; GoLYTELY is recommended. A prophylactic systemic antibiotic is administered preoperatively, and two doses are given postoperatively. The use of intermittent compression stockings to prevent deep vein thrombosis during surgery is recommended.

Anterior Surgical Approaches to the Seminal Vesicles

The anterior surgical approach to the seminal vesicles has been well established and is a good open approach for patients with large benign masses or cysts, and for patients with an ectopic ureter draining into a seminal vesicle cyst, so the kidney, ureter, and seminal vesicle can all be approached concomitantly.

A popular open anterior approach is the transvesicle approach, which has been well described (Walker and Bowles, 1968; Politano et al, 1975). A lower midline infraumbilical incision is made sharply, and the rectus muscles are divided in the midline. The space of Retzius is developed. The anterior bladder is exposed, and a self-retaining retractor is placed. A longitudinal incision, about 7 to 10 cm long, is made in the anterior bladder wall, taking care to stay at least 3 to 4 cm proximal to the bladder neck. Moist sponges are placed in the bladder dome, and a bladder blade for the retractor is used to gently offer exposure. The ureteral orifices should be identified, and 8-Fr feeding tubes can be passed gently up the ureters to help with identification of the intramural ureters. A 5-cm longitudinal incision is made in the midline of the trigone with electrocautery on cutting current. Once the incision goes through the posterior bladder muscle, the ampullae of the vas deferens should be visible just below the bladder neck. The seminal vesicles should be identified just lateral to the ampullae of the vas deferens on the prostatic base. The seminal vesicles should be dissected free completely. Metal clips are placed on the vascular pedicle. A clip is placed on the proximal end of the vas deferens. A 2-0 chromic tie is used to ligate the end of the seminal vesicle at the prostate. The seminal vesicle is resected and removed. Care must be taken not dissect too deep through Denonvilliers fascia posteriorly, to not endanger the rectum. The posterior bladder wall is closed in two layers with a 2-0 absorbable suture in the muscle and a 4-0 absorbable suture in the mucosa. The sponges and ureteral catheters are removed, a 20-Fr urethral catheter is placed, and the anterior bladder wall is closed in the same fashion as the posterior bladder wall. A suction drain is placed in the perivesicle space, not overlying the suture line, and is brought out through a separate stab incision (Fig. 37–22). This drain can be removed when the output is less than 50 ml per day, typically in 2 to 3 days. The urethral catheter can be removed in 5 to 7 days. This approach has a lower rectal injury rate, although it places the ureters at a higher risk for injury and is more prone to blood loss.

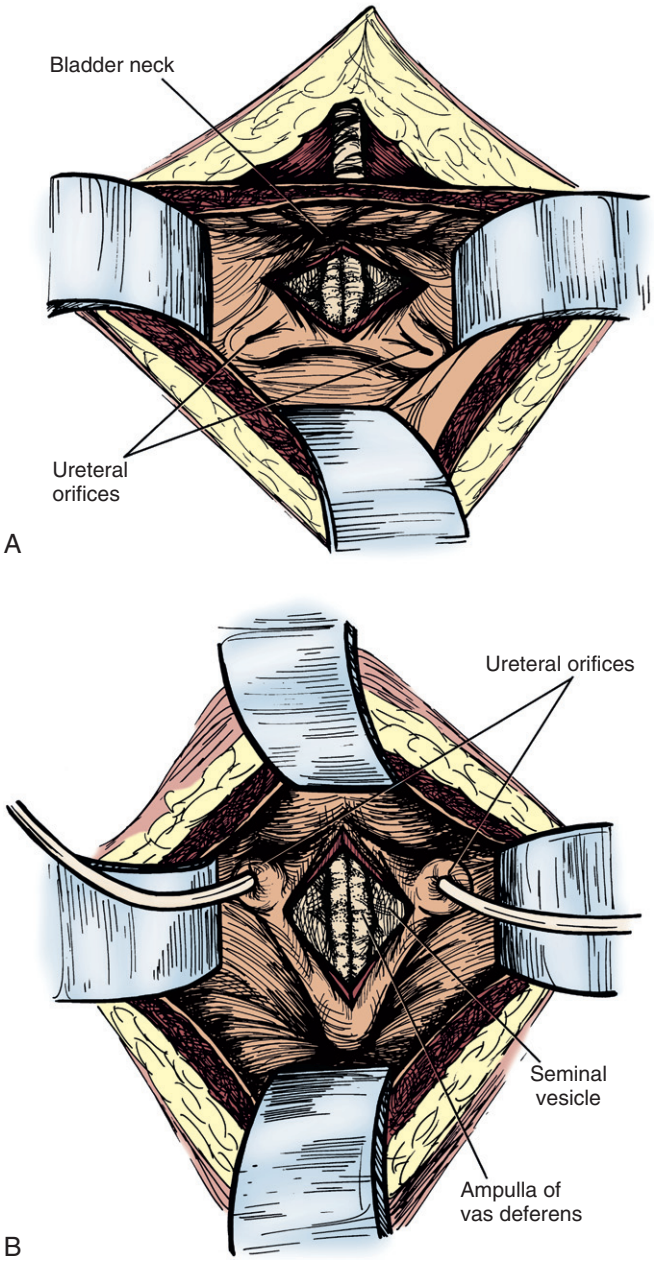


Figure 37–22. Transvesical approach to seminal vesiculectomy. **A,** Vertical incision between the ureteral orifices. **B,** Transverse incision 2 cm superior to the bladder neck below the ureteral orifices. (Redrawn from Hinman F Jr. Atlas of urologic surgery. Philadelphia: WB Saunders; 1989. p. 382.)

The perivesicle approach is useful in pediatric patients with a large seminal vesicle cyst, so that nephroureterectomy can be performed along with seminal vesiculectomy. A midline or Pfannenstiel incision will offer adequate exposure for this approach. Finger dissection is used to dissect the bladder from the lateral pelvic sidewall on the side with the cyst. The seminal vesicle cyst should be readily identifiable, the seminal vesicle should be dissected free in its entirety, and a 1-0 chromic can be placed through the cyst as a traction suture to assist with dissection. The ureter must be identified crossing the vas deferens to prevent ureteral injury. The superior, and possibly the inferior, vesicle arteries may be sacrificed to offer exposure to the base of the seminal vesicle. The cyst should be dissected away from the bladder, and any seminal vesicle vessels can be clipped and divided. When the base of the seminal vesicle is accessed at the prostate–seminal vesicle junction, it can be ligated with a 2-0 absorbable suture. Dissection of the proximal portion of the seminal vesicle must be done carefully by hugging the cyst, so not to injure the neurovascular bundle, which is directly lateral to the seminal vesicle. A clip is then placed just distal to the previously placed suture, and the seminal vesicle is resected. A suction drain is placed adjacent to the seminal vesicle bed and is brought out through a separate stab incision. The drain and urethral catheter may both be removed in 24 hours, as long as there is not excessive drainage through the drain.

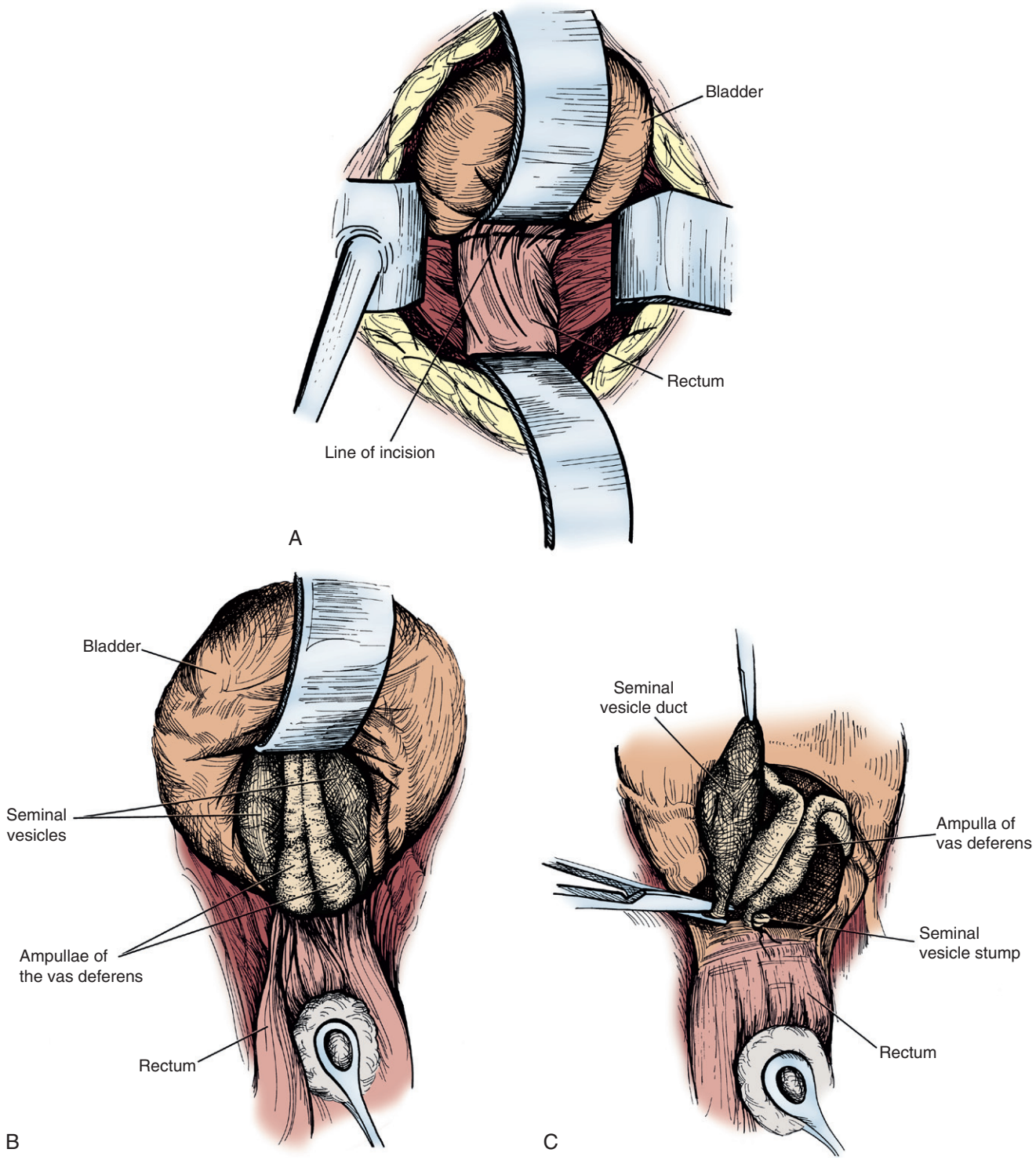


Figure 37–23. Retrovesical approach to seminal vesiculectomy. **A,** Incision line between base of bladder and peritoneal reflection over the rectum. **B,** Caudal dissection reveals the ampullae of the vas deferens on the midline and seminal vesicles immediately lateral to them. **C,** The duct of the seminal vesicle is ligated and transected. (Redrawn from Hinman F Jr. Atlas of urologic surgery. Philadelphia: WB Saunders; 1989. p. 379–80.)

A third anterior approach to the seminal vesicles is the retrovesicle approach and is useful for bilateral seminal vesiculectomies for bilateral small cysts or benign masses (de Assis, 1952). A urethral catheter should be placed, a midline incision is made, and the peritoneum is entered. A transverse incision is made in the peritoneal reflection over the rectum at the posterior bladder wall, taking great care to not enter the rectum. The posterior bladder is sharply dissected off the anterior rectal wall until the ampullae of the vas deferens and the tips of the seminal vesicles are visible. The seminal vesicles are dissected free to the base at the prostate–seminal vesicle junctions and are ligated and resected. A suction drain is placed at the posterior bladder and brought out through a separate stab incision. The incision is closed (Fig. 37–23).

Transperineal Surgical Approach to the Seminal Vesicles

The patient should be positioned as they would be for perineal prostatectomy. The same incision is made as would be for perineal prostatectomy, but the rectum needs to be dissected free high on the base of the prostate. A transverse incision is then made in Denonvilliers fascia above the base of the prostate–seminal vesicle junctions. This incision can be made longitudinally to allow better preservation of the neurovascular bundles for potency (Weldon and Tavel, 1988). A Lowsley retractor can be placed through the urethra into the bladder to elevate the prostate to provide traction to allow for easier dissection of the base of the seminal vesicle. Just below Denonvilliers fascia and above the prostate, the ampulla of the vas deferens can be dissected. If the surgery is being done for benign pathology, dissection can be carried laterally to the seminal vesicle. If it is being done for malignancy or recurrent infection, the ampulla of the vas deferens should be included in the specimen with a wider resection. The seminal vesicle should be dissected completely free, and the base should be ligated at the prostate–seminal vesicle junction with a 2-0 suture. A second tie or clip should be placed on the distal seminal vesicle, and the seminal vesicle should be divided. The divided end of the seminal vesicle is then grasped with an Allis clamp, and the Metzenbaum scissors are used in a spreading motion to free the rest of the seminal vesicle from surrounding tissue while using the Allis for traction. Metal clips are placed on the vascular pedicle and it is divided, typically within 1 cm of the distal tip of the seminal vesicle. The seminal vesicle is removed, a Penrose drain is left in the seminal vesicle bed, and the incision is closed in layers. The drain can be removed in 24 hours if there is minimal drainage. **The transperineal approach offers minimal blood loss, minimal pain, and early ambulation** (Fig. 37–24).

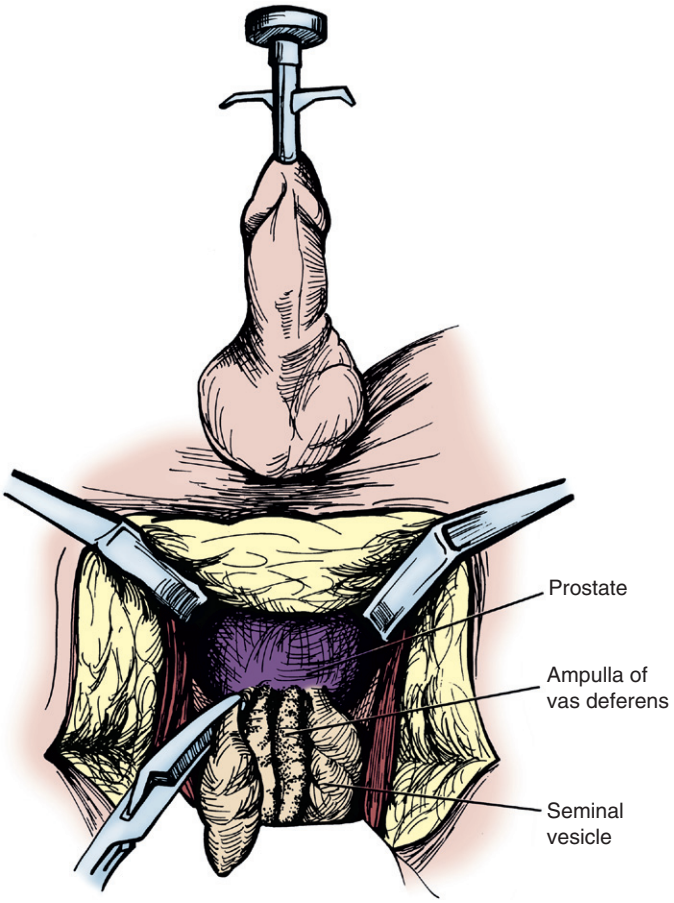


Figure 37–24. Transperineal approach to seminal vesiculectomy. (Redrawn from Hinman F Jr. Atlas of urologic surgery. Philadelphia: WB Saunders; 1989. p. 381.)

Posterior Surgical Approach to the Seminal Vesicles

Although the transcoccygeal approach is the least familiar to most urologists, it may be useful for patients who have had previous suprapubic or perineal surgeries. The patient is positioned in a prone, jackknife position (Kreager and Jordan, 1965). An L-shaped hockey stick incision is made from midway on the sacrum, 10 cm from the tip of the coccyx, and angled at the tip of the coccyx down the gluteal cleft stopping 3 cm from the anus. The lateral side of the coccyx is carefully divided free from the rectum and removed. The layers of the gluteus maximus are swept aside until the rectosigmoid is reached, and then it is carefully dissected from the underside of the sacrum. The lateral rectal wall is divided free medially from the levator ani muscle until the prostate is encountered on the side of the seminal vesicle pathology. Dissection is carried superior to the base of the prostate in the midline until the ampulla of the vas deferens is identified with the seminal vesicle just lateral to the ampulla. The seminal vesicle should be dissected and resected as previously described in the above approaches. A Penrose drain should be placed at the bed of the seminal vesicle and brought out through a separate stab incision from the closure. The drain can be removed in two to three days if there is no drainage (Fig. 37–25).

Laparoscopic/Robot-Assisted Surgical Approach to the Seminal Vesicles

Laparoscopic surgery on the seminal vesicles is most commonly performed concomitantly with prostate surgery. The technique for laparoscopic approach to the seminal vesicles was first described in 1993 (Kavoussi et al, 1993). Laparoscopy has also been applied to seminal vesiculectomy without prostatectomy and has been reported in a case of amyloid of the seminal vesicle (Vandwalle et al, 2007). Robot-assisted laparoscopy has also been used to excise seminal vesicle cysts (Moore et al, 2007; Selli et al, 2008). Patients are positioned in the supine position with careful padding of all pressure points, and the arms are tucked and padded. A split-leg table is necessary for the robot-assisted technique. Wide cloth tape is used across the chest and hips to secure the patient to the table, and the table is placed in steep Trendelenburg position. Prior to gaining access, a urethral catheter and an orogastric tube should be placed to decompress the bladder and stomach for subsequent trochar placement. To gain access, the Varess needle is placed periumbilically and a pneumoperitoneum is achieved, not exceeding pressures of 15 mm Hg. After an adequate pneumoperitoneum is achieved, the laparoscopic ports can be placed, placing the first one with an optical trocar for the camera port, and the following ones under direct laparoscopic visualization. The ports can be placed in either a horseshoe or a diamond

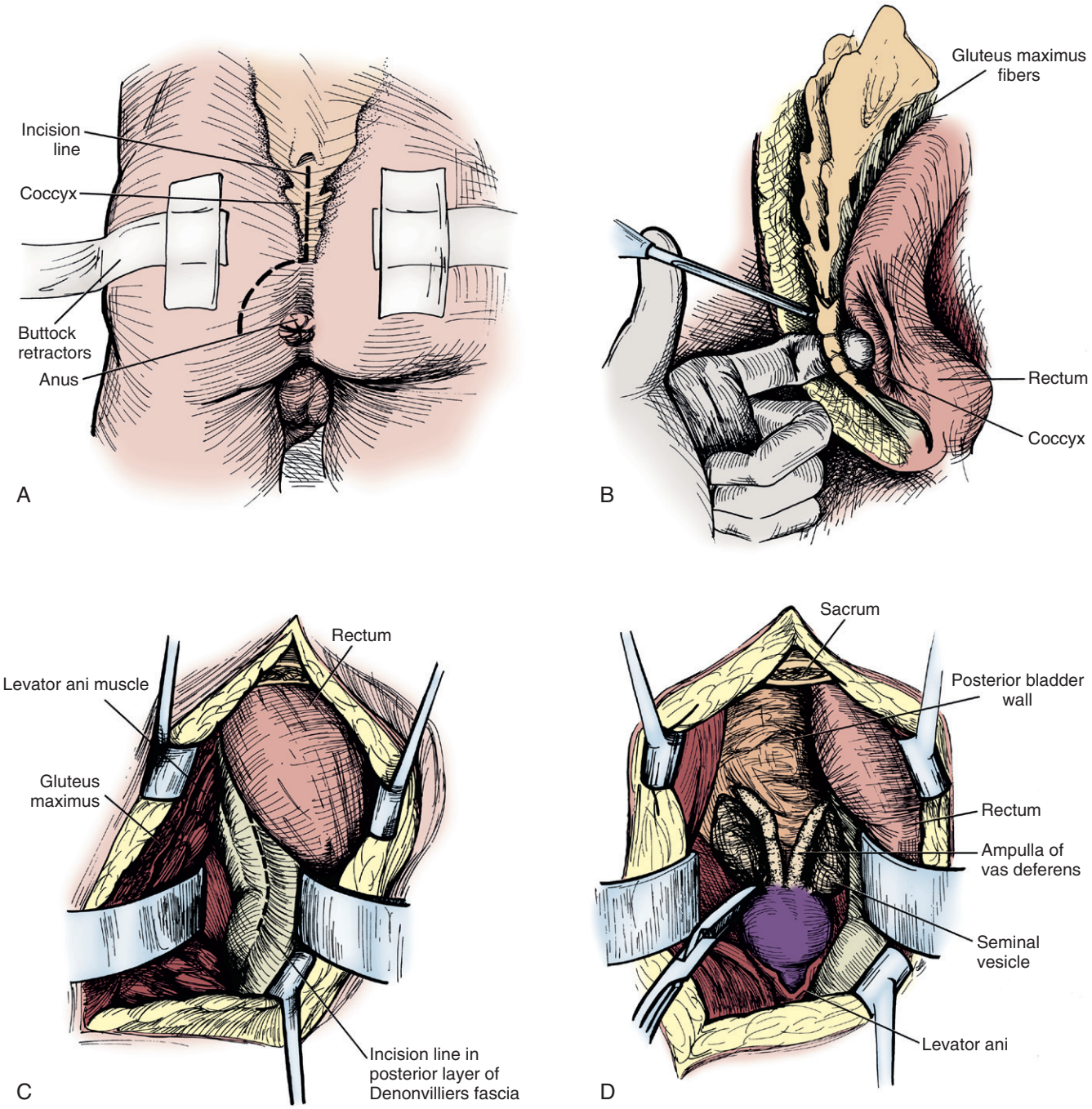


Figure 37–25. Transcoccygeal seminal vesiculectomy. **A,** Incision line over the lower sacrum on coccyx surrounding the anus. **B,** Dissection of the coccyx. **C,** Incision of Denonvilliers fascia after the rectum has been displaced. **D,** Exposure of the prostate and seminal vesicles. (Redrawn from Hinman F Jr. Atlas of urologic surgery. Philadelphia: WB Saunders; 1989. p. 381.)

arrangement for pure laparoscopy and can be placed in the same position as would be for prostatectomy for robot assistance (Fig. 37–26) (Menon et al, 2003; Lee et al, 2004). The peritoneum is then incised between the two obliterated umbilical ligaments just anterior to the rectum in the pouch of Douglas. The seminal vesicles can then be visualized and should be dissected carefully to avoid injury to the neurovascular bundles or the surrounding viscera. Monopolar energy should not be used in order to minimize injury to surrounding structures, and much of this dissection can safely be performed sharply. The seminal vesicle arterial pedicle can be managed with a clip or with bipolar cautery. The seminal vesicle should be dissected toward its junction with the ampulla of the vas deferens, and both can be clipped together at the base. The specimen can then be placed in an extraction bag and can be removed through one of the laparoscopic ports. The ports are then closed under visualization.

The extraperitoneal laparoscopic approach to the seminal vesicles was first described in 1997, and was performed concomitantly with radical prostatectomy (Raboy et al, 1997). In the following years, this approach gained more popularity (Bollens et al, 2001; Stolzenburg et al, 2003). A 1.5-cm periumbilical incision is made, and the preperitoneal space is entered. A balloon trocar is

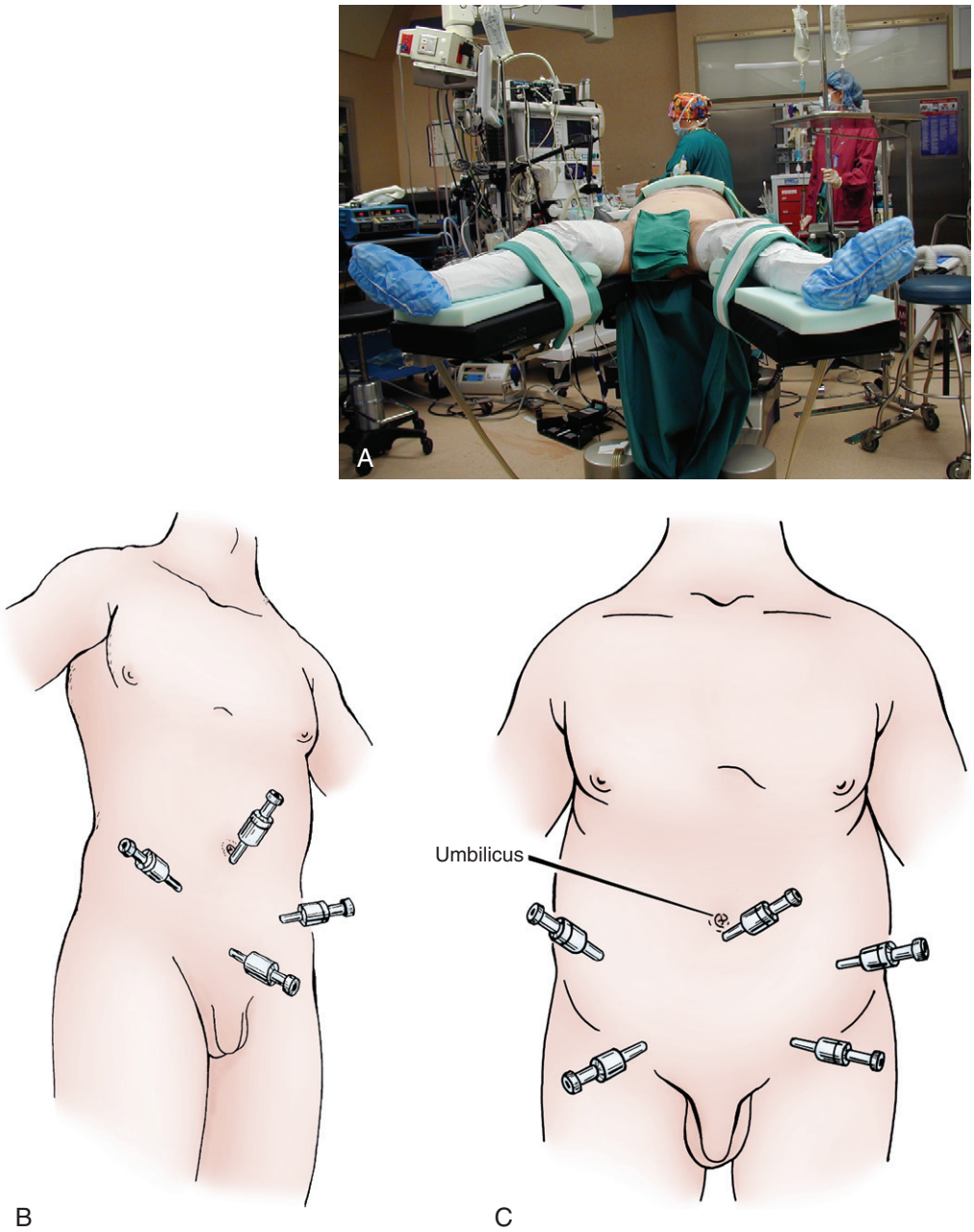


Figure 37–26. **A,** Positioning of the patient for laparoscopic seminal vesicle dissection. **B,** Diamond configuration of laparoscopic ports. **C,** Inverted U-shaped configuration of laparoscopic ports in obese patients. (From Winifield HN. Laparoscopic pelvic lymph node dissection for urological pelvic malignancies. Atlas Urol Clin North Am 1993;1:33–47.)

introduced into the preperitoneal space, and insufflation is performed under direct vision. The details of the technique are further described in detail in Chapter 103.

Surgical Treatment of Seminal Vesicle Cysts

Seminal vesicle cysts are thought to be secondary to ejaculatory duct obstruction and can be congenital or acquired (Heaney et al, 1987; King et al, 1991; Conn et al, 1992). **Seminal vesicle cysts are associated with ipsilateral renal agenesis or dysplasia in two thirds of patients; the cysts are secondary to maldevelopment of the distal mesonephric duct and are an error in ureteral budding** (Beeby, 1974). Seminal vesicle cysts have also been associated with polycystic kidney disease. In one report, seminal vesicle cysts were identified in 60% of patients with polycystic kidney disease, and some authors recommend that all patients with seminal vesicle cysts undergo renal imaging (Alpern et al, 1991; Hihara et al, 1993; Danaci et al, 1998). **Seminal vesicle cysts should only be treated if they are symptomatic or result in ejaculatory duct obstruction and affect fertility** (Surya et al, 1988).

Seminal vesicle cysts can be drained by a number of techniques. **TRUS-guided aspirations or transperineal aspirations**

can be performed on small seminal vesicle cysts that are symptomatic or obstructing the ejaculatory ducts. If the cyst reaccumulates fluid, resulting in recurrent symptoms or obstruction, it may be aspirated again with the injection of a sclerosing agent such as tetracycline. A small abscess in the seminal vesicle can be managed similarly with drainage (Frye and Loughlin, 1988; Shabsigh et al, 1989; Gutierrez et al, 1994). If the seminal vesicle cyst is proximal, adjacent to the prostate, transurethral resection can be performed to unroof the cyst at the 5-o'clock and 7-o'clock positions just distal to the bladder neck (Frye and Loughlin, 1988; de Lichtenberg and Hvidt, 1989). The same outcome has been reported by incising the seminal vesicle cyst to drain it cystoscopically with the use of a Collin knife (Gonzalez and Dalton, 1998). Seminal vesicle abscesses can be managed in a similar fashion. Some groups have reported using semirigid ureteroscopes to treat seminal vesicle cysts and abscesses (Razvi and Denstedt, 1995; Shimada and Yoshida, 1996; Okubo et al, 1998). If the above techniques for drainage of seminal vesicle cysts are unsuccessful, open or laparoscopic excision can be performed (Moudouni et al, 2006). Seminal vesiculectomy, along with nephroureterectomy should be performed in cases with an ectopic ureter. If the above techniques for seminal vesicle abscess fail, open drainage is required (Kore et al, 1994).

Surgical Treatment of Tumors of the Seminal Vesicles

Benign tumors of the seminal vesicle that occur more commonly than malignant ones include fibromas, leiomyomas, cystadenomas, schwannomas, and papillary adenomas (Mostofi and Price, 1973; Lundhus et al, 1984; Narayana, 1985; Mazur et al, 1987; Bullock, 1988; Gentile et al, 1994; Latchamsetty et al, 2002; Lee et al, 2006). Primary papillary adenomas and cystadenomas of the seminal vesicle typically occur in middle-aged men and are almost never bilateral, and they appear as simple cysts on imaging; therefore, the diagnosis is typically one made on final pathology after excision (Mazur et al, 1987). Amyloid localized to the seminal vesicles has also been reported (Jun et al, 2003). Twenty percent of men over the age of 76 have subepithelial deposits of amyloid in the seminal vesicles, and the reported incidence in male autopsies is 4% to 17% (Pitkanen et al, 1983; Ramchandani et al, 1993). Patients should only be treated if they are symptomatic and the diagnosis of amyloid of the seminal vesicle is made. Hydatid cysts of the seminal vesicle have also been reported (Kuyumcuoglu et al, 1991; Papathanasiou et al, 2006).

Seminal vesicle malignancies are extremely rare and are difficult to diagnose, because patients are typically asymptomatic until late in the course of the disease process. Primary malignancies of the seminal vesicles are extremely rare, and serum PSA and tissue biopsies can help differentiate primary malignancies from extension/metastasis of lymphoma, prostate, bladder, or rectal cancer. It is thought that the seminal vesicles low proliferative activity accounts for the low incidence of primary malignancies of the seminal vesicle (Meyer et al, 1982). **Primary adenocarcinoma of the seminal vesicle occurs in patients greater than 50 years old.** Serum PSA is normal and serum carcinoembryonic antigen is elevated (Mostofi and Price, 1973; Benson et al, 1984; Tanaka et al, 1987; Chinoy and Kulkarni, 1993; Thiel and Effert, 2002). **Primary sarcoma of the seminal vesicle is an extremely rare malignancy, which is diagnosed by biopsy, and is usually discovered late in the course of the disease process** (Benson et al, 1984; Chiou et al, 1985; Schned et al, 1986; Tanaka et al, 1987; Davis et al, 1988; Kawahara et al, 1988). All sarcoma types of the seminal vesicle, including leiomyosarcoma, rhabdomyosarcoma, angiosarcoma, and müllerian adenosarcoma-like tumor, behave very aggressively, and radical extirpation has varying outcomes (Amirkhan et al, 1994; Lamont et al, 1991; Laurila et al, 1992; Berger et al, 2002). Cystosarcoma phylloides and seminoma have also been reported as primary malignancies of the seminal vesicles (Fain et al, 1993; Adachi et al, 1991). Primary squamous cell carcinoma of the seminal vesicle has been reported and treated with surgical extirpation followed by adjuvant radiation therapy with success with short-term follow-up (Tabata et al, 2002).

Solid seminal vesicle masses that are benign on biopsy and show no evidence of local spread should be treated with seminal vesiculectomy only if they are symptomatic, which is a very rare occurrence. Solid masses of the seminal vesicles that are proven to be malignant by biopsy or with a high suspicion for malignancy should be surgically treated, although the optimal treatment is still debated because there have been so few primary seminal vesicle malignancies treated at any institution. Large primary malignancies of the seminal vesicles have been treated with radical pelvic surgery: cystoprostatectomy with pelvic lymphadenectomy or pelvic exenteration. Adjuvant therapy has not proven to be effective, although the only survivors in the literature underwent radical surgery followed by pelvic radiation and/or androgen ablation.

Complications of Seminal Vesicle Surgery

Complications of seminal vesicle surgery are minimized by the surgeon selecting the approach that he or she is most comfortable and facile performing. The surgeon must be aware of the following seminal vesiculectomy specific complications. Rectal injury can occur with the perineal approach to the seminal vesicles. If a preoperative bowel preparation was administered and there is no gross fecal contamination, a two-layer closure of the rectum may be performed closing the mucosal layer with a running 3-0 absorbable suture, and the submucosal layer with interrupted 4-0 silks. The anus should also be dilated prior to the end of the case. A temporary colostomy should be considered with a large rectal injury or gross fecal contamination. The bladder may also be injured during the perineal approach. The bladder should be closed in two layers, leaving a urethral catheter in place for 7 to 10 days postoperatively. During the perineal approach, the ureter may be injured. If this occurs, the injury should be repaired, or a double-J ureteral stent may be placed and left in place for 10 to 14 days postoperatively. Hemorrhage is least likely in the perineal approach, and the transvesicle approach is more prone to blood loss.

Complications of the laparoscopic approach include general laparoscopic complications, such as trocar injury to the bowel or great vessels, extraperitoneal insufflation, abdominal wall bleeding, and gas embolism. Bladder and rectal injuries may be repaired laparoscopically, as long as there is not gross fecal contamination with rectal injuries. The distal ureter is close to the tip of the seminal vesicle, and, if the ureter is injured it may be repaired laparoscopically, although a ureteral reimplant may be necessary, and performed open or laparoscopically, depending on the

experience of the surgeon. It is recommended that a ureteral stent and a pelvic drain be left in such cases. The neurovascular bundle runs just lateral to the tips of the seminal vesicles; therefore, injury to the neurovascular bundle can result in erectile dysfunction, regardless of the surgical approach. Potential complications of endoscopic management of the seminal vesicles include postvoid dribbling due to urinary reflux and infection (Goluboff et al, 1995).

Key Points: Surgery of the Seminal Vesicles

- Seminal vesicle secretions contribute 50% to 80% of the volume of the ejaculate.
- Unilateral seminal vesicle agenesis may be associated with ipsilateral renal anomalies and unilateral absence of the vas deferens.
- Normal seminal vesicles are not palpable on digital rectal examination.
- If there is a palpable seminal vesicle abnormality, TRUS should be performed with biopsy if there is suspicion for malignancy.
- The surgical approach to the seminal vesicles is mainly dependent on the expertise and comfort of the surgeon, although the characteristics of the lesion may impact the decision on the approach.
- Benign and malignant tumors of the seminal vesicles are very rare.

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chapter 38

Renal Physiology and Pathophysiology

Daniel A. Shoskes, MD, MSc, FRCSC • Alan W. McMahon, MD

Renal Physiology

Renal Pathophysiology

Renal physiology impacts the urological care of patients in numerous ways. These can include the pathophysiology of surgical disease (renal tubular acidosis, malignant paraneoplastic syndromes), the modification of surgical technique (ischemia reperfusion injury and intrarenal surgery), or iatrogenic complications of surgery (hyponatremia, metabolic complications of urinary diversions). The purpose of this chapter is not to turn urologists into nephrologists, but rather to provide a firm fundamental knowledge of renal physiology and pathophysiology to provide the foundation for urologic specific conditions and therapies.

RENAL PHYSIOLOGY

Vascular (Renal Blood Flow and Glomerular Flow Rate)

Renal Blood Flow (RBF)

RBF is regulated by changes in vascular resistance of all the arteries up to and including the efferent arteriole, which in turn is regulated by a variety of neurohormonal signals (see below).

Blood enters the kidney through the renal arteries and divides into progressively smaller arteries (interlobar, arcuate, and interlobular arteries) until it enters the glomerular capillary through the afferent arteriole. A portion of the plasma that enters the glomerulus is filtered across the glomerular membrane; this is called the *filtration fraction*. The rest of the blood exits the glomerular capillary through the efferent arteriole. In nephrons located in the renal cortex, these capillaries travel in close proximity to the tubules and modulate solute and water reabsorption. In juxtamedullary nephrons (located deeper in the medulla), the efferent arterioles branch out to form vasa recta, which participate in the countercurrent mechanism through which urine is highly concentrated and body water conserved (see later discussion).

Under normal resting conditions, RBF is 20% of total cardiac output. Total blood flow is different for men and women, averaging 982 ± 184 mL/min in women and 1209 ± 256 mL/min in men (Dworkin and Brenner, 2004). Renal plasma flow (RPF) is slightly less, averaging 592 mL/min in women and 659 mL/min in men, and varies with hematocrit (RPF = RBF × [1–Hct]). RBF is not evenly distributed to all parts of the kidney. Flow to the outer cortex is 2 to 3 times greater than that to the inner cortex, which in turn is two to four times greater than that to the medulla (Dworkin and Brenner, 2004).

Determinants of Glomerular Filtration

The most important function of the kidney is the process of glomerular filtration. Through the passive ultrafiltration of plasma across the glomerular membrane, the kidney is able to regulate total body salt and water content, electrolyte composition, and eliminate waste products of protein metabolism.

The process of filtration is analogous to fluid movement across any capillary wall, and is governed by Starling forces. The glomerular filtration rate (GFR) is thus determined by both hydraulic and oncotic pressure differences between the glomerular capillary and the Bowman space, as well as by the permeability of the glomerular membrane:

$$GFR = LpS \times (\Delta \text{hydrostatic pressure} - \Delta \text{oncotic pressure})$$

where Lp = glomerular permeability and S = glomerular surface area.

The rate at which filtration occurs within an individual nephron is termed the "single nephron GFR" (SN-GFR). A more relevant measurement is that of total GFR, which is the sum of all SN-GFR and is expressed in milliliters per minute. **GFR is thus a reflection of overall renal function.** Alterations in GFR can occur either with alterations in any aspect of Starling forces, or through a change in renal plasma flow (RPF).

1. *Transglomerular (hydraulic) pressure (TGP)*—the most significant determinant of GFR is the TGP. Although systemic arterial pressures impact on TGP, the glomerular capillary is unique in that it is interposed between two arterioles (the afferent and efferent arterioles) and thus can regulate intraglomerular capillary pressure (IGP) independent of systemic pressures through changes in afferent and efferent arteriolar tone. Under normal circumstances, the pressure within the Bowman space is essentially zero, and only in conditions of urinary obstruction does the pressure increase to clinically significant levels. Thus the TGP = IGP.
2. *Renal plasma flow*—increases in RPF lead to increases in GFR. Although the filtration fraction cannot exceed 20% under normal circumstances, an increase in RPF will lead to an increase in absolute GFR.
3. *Glomerular permeability*—generally, an increase in permeability does not lead to an increase in GFR, because the

glomerulus is already at maximal permeability for water and other relevant solutes. It may, however, lead to increased filtration of larger molecules not normally filtered, such as albumin. Reductions in permeability, or in glomerular surface area, can lead to reductions in GFR.

4. *Oncotic pressure*—the least relevant of all the variables. Under normal circumstances, plasma proteins are not filtered across the glomerular membrane and so oncotic pressure within the Bowman space is essentially zero.

Regulation of Glomerular Filtration Rate

Under normal circumstances, GFR is tightly maintained at a relatively constant level, despite large fluctuations in systemic arterial pressures and renal blood flow. This is accomplished through the processes of autoregulation and tubuloglomerular feedback.

1. *Autoregulation*—with increases in mean arterial pressure (MAP), afferent arteriolar tone increases to minimize increases in IGP. Similarly, with reductions in MAP, afferent arteriolar tone decreases to allow increased flow into the glomerulus to maintain IGP, thus maintaining GFR. Autoregulation of IGP is effective to a MAP of about 70 mm Hg; below that, reductions in MAP lead to similar reductions in GFR, and below a MAP of 40 mm Hg, filtration ceases. The mechanism(s) by which autoregulation is achieved is not well understood. It is likely mediated through myogenic stretch receptors in the afferent arteriole wall, possibly mediated by adenosine triphosphate (ATP) (Schnermann and Levine, 2003), but angiotensin II is also involved with more severe fluctuations.
2. *Tubuloglomerular feedback (TGF)*—tubular ultrafiltrate flow rates are monitored by cells in the macula densa. If SN-GFR increases, delivery of sodium cations (Na^+) and chloride anions (Cl^-) to the distal tubule also increases. This increased Cl^- delivery triggers a response by the macula densa, which ultimately leads to an increase in afferent arteriolar tone and subsequent decrease in RPF, thus returning SN-GFR (and tubular flow) back to baseline (Schnermann et al, 1998). Thus TGF can be thought of as a mechanism to minimize salt and water losses through regulation of GFR. The mediators of this response are not well understood, but it seems that angiotensin II plays a permissive role in TGF. Both adenosine and thromboxane can cause afferent arteriolar vasoconstriction and have been implicated in TGF. Nitric oxide (Schnermann and Levine, 2003) is also believed to be important, particularly in minimizing TGF in the setting of increased NaCl intake.

Under abnormal conditions however, neurohumoral responses become more important. With significant reductions in effective circulating volume (ECV), both norepinephrine and angiotensin II play an important role in maintaining GFR through arteriolar vasoconstriction, often at the expense of reduced RPF. Notably, renal prostaglandins (PGs) and nitric oxide offset afferent arteriolar vasoconstriction; so, arteriolar tone is a balance between the vasoconstrictive and vasodilatory effects of the above-mentioned hormones. Inhibition of PG synthesis (due to administration of nonsteroidal anti-inflammatory drugs), particularly in states of high angiotensin II production, can lead to severe vasoconstriction and acute reduction in GFR. In contrast, norepinephrine and angiotensin II levels are diminished in states of volume expansion, while dopamine and atrial natriuretic peptide levels are increased to facilitate an increase in RPF (dopamine) and natriuresis (atrial natriuretic peptide [ANP]), thus returning volume status back to normal.

Clinical Assessment of Glomerular Filtration Rate

Unfortunately, GFR cannot be measured directly. It can, however, be estimated by a variety of methods, some more accurate (but usually more cumbersome) than others.

Renal Clearance. **The best estimate of GFR can be obtained by measuring the rate of clearance of a given substance from the plasma.** However, in order to be accurate, the substance to be measured must meet certain criteria. It must:

- Be able to achieve a stable plasma concentration,
- Be freely filtered across the glomerulus,
- Not be secreted, reabsorbed, synthesized, or otherwise metabolized by the renal tubules, and
- Not be impacted by any other means of removal from the plasma.

If all these criteria are met, then:

$$\text{Filtered X} = \text{excreted X}$$

and since

$$\text{Filtered X} = \text{GFR} \times \text{plasma [X]}$$

and since

$$\text{Excreted X} = \text{urine [X]} \times \text{urine volume (in mL/unit time)}$$

we can now see that

$$\text{GFR} \times \text{P[X]} = \text{U[X]} \times \text{urine volume}$$

$$\text{GFR} = \text{U[X]} \times \text{urine volume/P[X]}$$

This is called the *clearance* of a substance and reflects the amount of plasma that is completely cleared of the substance per unit time. There are a number of substances that have been used clinically to estimate GFR.

1. *Inulin*—is a fructose polysaccharide that meets the necessary requirements, and inulin clearance is felt to be the best measure of GFR. However, it is not clinically useful because it is difficult to administer (requires an intravenous infusion of inulin), and difficult to measure.
2. *Radiolabelled compounds*—such as iothalamate or diethylenetriaminepentaacetic acid (DTPA). These clearances are also very accurate, but are again limited in clinical use by their cost and availability (Perrone et al, 1990).
3. *Creatinine*—**the most widely used estimate of GFR is the 24-hour creatinine clearance (CrCl)** (Levey, 1990). It uses endogenous creatinine, which is produced at a constant rate. The rate of production varies from individual to individual, but for a single individual daily variability is less than 10%. It has the advantage of being easy to perform (no intravenous [IV] infusion), is relatively cheap, and readily available. However, it is less accurate than inulin clearance, because some creatinine is cleared from plasma through proximal tubular secretion; thus a CrCl overestimates true GFR, on average, by 10% to 20%. This becomes even more important as GFR declines, because tubular secretion increases in response to increasing serum creatinine levels and may contribute up to 35% of all creatinine removal at GFR levels of 40 to 80 mL/min (Shemesh et al, 1985). **At best, then, the CrCl should be considered the "upper limit" of the true GFR.**

Plasma Markers. An even simpler method to estimate GFR is with the use of plasma levels of substances that can be used as surrogate markers of GFR. To be useful, the substance must fulfill the criteria outlined above. Three such substances have been used:

1. *Plasma creatinine (PCr)*—**the most widely used plasma marker of GFR.** While creatinine production is constant within an individual from day to day, there is marked variation in production rates between individuals. The absolute rate depends upon muscle mass, which in turn is influenced by age, sex, and body mass. Thus **there is no single "normal" PCr that reflects a "normal" GFR; it must be individualized for every person.** This can be accomplished through mathematical manipulation (see below). However, the relationship of PCr to GFR is relatively constant (Fig. 38–1), and thus changes in PCr can be used to predict corresponding changes in GFR. As a general rule of thumb, every 50% reduction in GFR results in a doubling of PCr. There are limitations to the use of the PCr that should be noted:
   - As GFR falls, tubular secretion of creatinine increases; so, PCr may not change noticeably until there has been a significant drop in GFR (Shemesh et al, 1985).
   - Creatinine production may increase in states of increased muscle breakdown (e.g., rhabdomyolysis) or with increased dietary protein intake or supplementation, leading to an underestimation of true GFR.
   - Creatinine production may decrease with liver cirrhosis, leading to an overestimation of true GFR.
2. *Plasma urea*—another widely used plasma marker. Urea production and excretion is highly variable, influenced, for instance by dehydration, high-protein diets, and increased tissue breakdown. As a result, it is a much less reliable marker of GFR than is the PCr and should not be used as the sole determinant.
3. *Plasma cystatin C*—is an endogenous protein found in all nucleated cells. It has a constant rate of production unaffected by diet, and clearance is not influenced by tubular functions (Filler et al, 2005). This test is not widely available at present, but likely will replace PCr as the standard test in GFR assessment.

Mathematical Correction. **There are a number of mathematical formulas that have been developed to improve the accuracy of the PCr estimation of GFR** (National Kidney Foundation, 2002). The two most widely used are the Cockcroft-Gault and "modification of diet in renal disease" (MDRD) formulas.

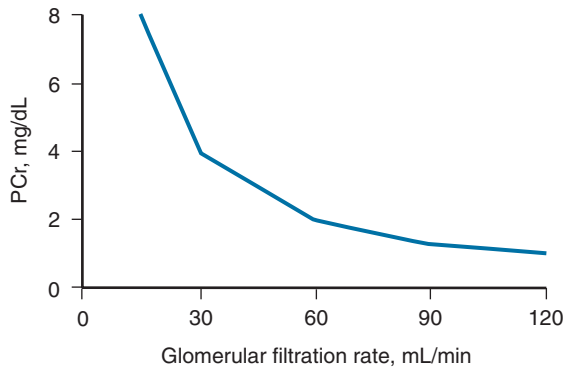


Figure 38–1. Relationship between serum creatinine and creatinine clearance. PCr, plasma creatinine.

1. *Cockcroft-Gault*—originally developed from data collected from individuals with normal renal function; it is a simple formula to estimate CrCl (not GFR) that corrects for age, sex, and body mass (Cockcroft and Gault, 1976). The formula is

$$\text{CrCl} = \frac{\{(140 - \text{age}) \times (\text{IBW in kg})}{[\text{PCr (mg/dL)} \times 72]\}} \times 0.85 \text{ (women)}$$

   It has the advantage of being very simple, but is not as accurate as other methods when renal function is impaired.
2. *MDRD formulas*—a series of formulas derived from data collected in patients with severe renal impairment; they are more complex but more accurate than the Cockcroft-Gault. The simplest estimate of GFR is the four-variable equation (PCr, age, sex, and ethnicity) (Manjunath et al, 2001):

$$\text{GFR (mL/min/1.73 m}^2) = 186 \times (\text{PCr [mg/dL]})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$$

In summary, the GFR is analogous to renal function. Total GFR is a summation of all SN-GFR, which in turn are determined primarily by TGP and glomerular permeability of the individual nephrons, and it is usually tightly regulated. **A GFR estimate should be obtained in all patients with renal impairment (rather than a PCr alone), and the recommended method is through the use of the four-variable MDRD formula or Cockcroft-Gault formula**.

Key Points: Renal Blood Flow and Glomerular Filtration Rate

- GFR reflects total renal function.
- GFR can be approximated by creatinine clearance.
- Formulas based on patient's age, weight, and serum creatinine can best estimate GFR.

Hormonal

Control of Renal Vascular Tone

Vascular tone of the renal vessels, the net balance of vasoconstrictive and vasodilatory forces, is crucial to the maintenance of renal blood flow, GFR, tubular renal function, and systemic blood pressure. **There is a complex network of hormones and vasoactive substances with both direct and indirect effects, resulting in a system that is pleiotropic and redundant.** Although much has been learned from animal models about the function of individual molecules, the complexity of the total system can lead to unexpected outcomes when individual pathways are manipulated pharmacologically. A summary of substances known to impact vascular tone is given in Table 38–1.

Vasoconstrictors

Angiotensin II. Angiotensin II is a potent vasoconstrictor. In the kidney, there is a more pronounced constrictive effect on the efferent than the afferent arteriole, due to inhibition of angiotensin II actions in the afferent arteriole by nitric oxide and prostaglandin (Arima, 2003). Elevated levels of angiotensin II are important for maintaining GFR in pathologic conditions that reduce RBF (e.g., renal artery stenosis, dietary sodium restriction). The classical effects of angiotensin II (vasoconstriction, aldosterone release, sodium retention) are mediated by the AT1 receptor (Kaschina and

Unger, 2003). The AT2 receptor, however, may cause intrarenal dilation and be protective against renal ischemic injury (Carey, 2005).

Norepinephrine. Norepinephrine vasoconstricts all the major vascular beds in the kidney, mediated through the α_1 receptor. In patients who receive norepinephrine as a pressor agent in the face of systemic vasodilation, renal function is preserved and may actually improve (Albanese et al, 2004).

Endothelin. **Endothelin is the most potent vasoconstrictor yet identified.** There are three isoforms, with ET-1 being the most fully described. An endothelin precursor (big ET-1; 39 amino acids) is cleaved to ET-1 (21 amino acids) by an endothelin converting enzyme found on the endothelial cell membrane. The endothelin receptors are subclassified into ET (A), which are purely vasoconstrictive, and ET (B). The ET (B) receptors may cause either vasodilation by stimulating the release of nitric oxide from endothelial cells, or vasoconstriction of vascular smooth muscle cells (Fellner and Arendshorst, 2004). ET-1 release is stimulated by angiotensin II, antidiuretic hormone, thrombin, cytokines, reactive oxygen species, and shearing forces acting on the vascular endothelium. ET-1 release is inhibited by nitric oxide, as well as by prostacyclin and atrial natriuretic peptide. Blockade of the ET (A) receptor can reduce renal vasoconstriction seen in such ischemic conditions as ureteral obstruction (Bhangdia et al, 2003).

ET-1 has a number of other actions besides vasoconstriction. ET-1 stimulates aldosterone secretion, produces positive inotropy and chronotropy in the heart, decreases renal blood flow and GFR, and releases atrial natriuretic peptide. **Despite reduction in RBF, sodium excretion is increased,** suggesting that ET may be responsible for maintaining sodium balance when the renin-angiotensin system is depressed (Perez del Villar et al, 2005). Medullary blood flow is preserved in the face of endothelin induced vasoconstriction, which may explain the relative stimulation of tubular functions (Evans et al, 2004).

Table 38–1.

Vasoactive Substances That Control Renal Artery Tone

Vasoconstriction
Angiotensin II
Norepinephrine
Vasopressin
Endothelin
Atrial natriuretic peptide
Vasodilation
Nitric oxide
Carbon monoxide
Prostaglandin E_2
Acetylcholine
Serotonin/bradykinin
Glucocorticoids

Vasopressin. Vasopressin acts directly on blood vessels through the vasopressin V1 receptor but does not directly change RBF at low doses (Malay et al, 2004). Vasopressin does potentiate the vasoconstrictive effects of norepinephrine (Segarra et al, 2002) and can induce renal ischemia at high doses**. At the low doses typically employed in the management of septic shock, renal function is preserved** (Holmes et al, 2001).

Atrial Natriuretic Peptide. Atrial natriuretic peptide (ANP) is a vasoactive hormone synthesized primarily by the atria in response to stretching, as occurs during physiologic levels of volume expansion (Fig. 38–2). **The primary actions of ANP on the kidney are increased GFR and natriuresis.** ANP can increase GFR without a change in renal blood flow (Sward et al, 2005) by the combination of afferent arteriolar vasodilatation and efferent arteriolar vasoconstriction. In addition, ANP dilates vessels that have been preconstricted by norepinephrine, angiotensin II, or vasopressin. ANP production increases during bilateral obstructive uropathy, which may be one mechanism of preserving GFR (Kim et al, 2002).

ANP increases natriuresis mainly through inhibition of sodium reabsorption in the medullary collecting duct (Zeidel et al, 1988); decreased renin and decreased aldosterone production may also play a role (Laragh, 1985). Clinically, however, infusion of low-dose ANP during surgery increases water and electrolyte excretion without measured systemic changes in cortisol, angiotensin II, or aldosterone (Koda et al, 2005). This approach has also been used to prevent ischemic renal damage in high-risk cardiac surgery (Sward et al, 2004).

Vasodilators

Nitric Oxide. Nitric oxide (NO) is a highly reactive gas that participates in multiple physiologic and pathophysiologic reactions in the body. **NO is synthesized from the reaction between arginine, reduced nicotinamide adenine dinucleotide phosphate (NADPH), and oxygen to produce citrulline, NADP, water, and NO.** This reaction is catalyzed by a family of enzymes called nitric oxide synthase (NOS).

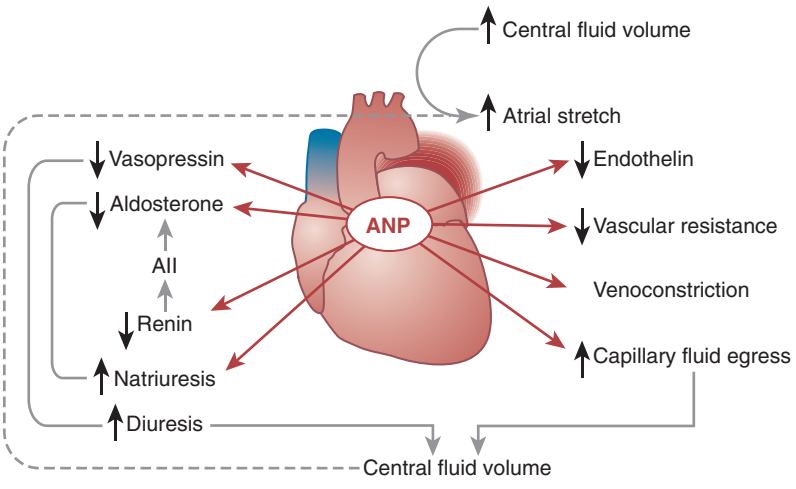


Figure 38–2. Schematic representation of the fundamental biologic processes of atrial natriuretic peptide (ANP). AII, angiotensin II.

Although all NOS enzymes catalyze the same reaction, they differ in distribution, expression, and stimuli. Neuronal (nNOS, NOS-1) and endothelial (eNOS, NOS-3) are constitutively expressed, and iNOS (NOS-2) is inducible. **eNOS is found in the vascular endothelium, and the NO produced there plays a key role in vasodilation and vascular remodeling** (Rudic et al, 1998). eNOS expression is stimulated by shear stress by activation of the tyrosine kinase c-SRC (Davis et al, 2004), by heat shock protein 90 (Harris et al, 2003), by oxidant stress (Cai et al, 2001), and by vascular mediators such as bradykinin, serotonin, adenosine, ADP/ATP, histamine, and thrombin (Arnal et al, 1999).

After its formation by vascular endothelial cells, NO diffuses to vascular smooth muscle cells where it activates soluble guanylyl cyclase (sGC), producing 3′,5′-cyclic guanosine monophosphate (cGMP). Subsequently, cGMP activates both cGMP- and 3′,5′-cyclic adenosine monophosphate (cAMP)-dependent protein kinases (PKG and PKA, respectively) leading to smooth muscle relaxation. eNOS blockade increases renal vascular resistance and decreases the glomerular ultrafiltration coefficient (Gabbai, 2001). NO also helps maintain vascular integrity, with increased expression being linked to decreased neointimal formation and medial thickening (Kawashima et al, 2001). Indeed, the degenerative changes seen in chronic allograft nephropathy related to cyclosporine use can be mitigated by increased nitric oxide expression (Chander et al, 2005). Increased eNOS activity is also associated with protection from renal ischemia-reperfusion injury (Shoskes et al, 1997).

Although raised local levels of NO from eNOS can be beneficial to renal function, induction of iNOS and overproduction of NO from inflammatory cells can be deleterious. In the face of free oxygen radicals at the site of inflammation, NO can interact with reactive oxygen species to form peroxynitrite, which induces protein damage by formation of nitrotyrosine. Increased iNOS has been related to damage from nitrotyrosine in glomerular disease (Trachtman, 2004), lupus nephritis (Takeda et al, 2004), and transplant rejection (Albrecht et al, 2002). Increased iNOS activity has direct renal effects as well, including upregulation of sodium and bicarbonate tubular transport (Wang, 2002).

Carbon Monoxide. Carbon monoxide (CO) gas is another reactive diffusible mediator with multiple effects throughout the body, especially in the kidney. **Heme oxygenase (HO), an essential enzyme in heme catabolism, catalyzes the rate-limiting step in heme degradation, resulting in the formation of iron, carbon monoxide, and biliverdin** (Hill-Kapturczak et al, 2002). Biliverdin is subsequently converted to bilirubin by biliverdin reductase. HO is expressed in two forms, constitutive HO-2 and inducible HO-1. Increased CO production produces vasodilation in the kidney and can counteract catecholamine induced vasoconstriction (Mustafa and Johns, 2001). In particular, both HO-1 and HO-2 are highly expressed in the medulla and help maintain renal medullary blood flow (Zou et al, 2000). In cirrhosis, decreased renal expression of HO-1 is linked to renal dysfunction (Miyazono et al, 2002). CO also regulates sodium transport in the loop of Henle, with HO-2 blockade inhibiting sodium excretion (Wang et al, 2003) and stimulation increasing natriuresis and diuresis (Rodriguez et al, 2003).

The other primary effect of CO in the kidney is renoprotection from oxidant injury. CO has documented anti-inflammatory, antioxidant, and cytoprotective actions (Sikorski et al, 2004). Indeed, a patient with a genetic HO-1 deficiency had significant tubular and vascular endothelial injury (Ohta et al, 2000). Increased CO is protective against ischemia-reperfusion injury in native and transplant kidneys (Nakao et al, 2005). Induction of HO-1 through agents such as bioflavonoids protects against tubular damage and improves renal transplant function (Shoskes et al, 2003).

Key Points: Hormonal

- Multiple chemical mediators act on renal vascular tone, which controls renal blood flow.
- Endothelin is the most potent vasoconstrictor.
- Nitric oxide and carbon monoxide are potent vasodilators.

Erythropoiesis

Red blood cell (RBC) production is a tightly regulated process. Basal RBC production is roughly 10 RBCs/hr, but this rate can be greatly increased during times of anemia or hypoxia. The kidney is the major organ involved in this process, and is responsible for monitoring RBC levels and increasing RBC output through the production of the hormone erythropoietin.

Erythroid Progenitor Cells. Mature RBCs are produced from a small pool of multipotent progenitor cells (Suda et al, 1984), which in turn are derived from the fetal liver. The earliest committed cell is the erythroid burst-forming unit (BFU-E), which, under appropriate stimulation, divides to produce erythroid colony-forming units (CFU-E). Further differentiation leads to the production of proerythroblasts, reticulocytes, and, ultimately (after extrusion of the nucleus), mature RBCs. The entire process requires about 2 weeks.

Erythropoietin. Maturation of the BFU-E and CFU-E depends on the appropriate growth factors. The most important of these factors is erythropoietin (EPO). The kidney is responsible for the majority of EPO production (90%), while the liver may contribute a smaller amount (10%). Kidney-derived EPO is produced by a subpopulation of interstitial fibroblasts, and possibly proximal tubular cells, in response to decreased O_2 tension.

EPO-deficient mice die in utero with a marked reduction in erythropoiesis (Munugalavadla and Kapur, 2005). Additional growth factors such as interleukin-3, GM-CSF, stem cell factor, activin, insulin-like growth factor (IGF-I), and, possibly, hepatic growth factor act synergistically with EPO to reduce apoptosis and thus promote proliferation of erythroid cells (Muta and Krantz, 1993).

EPO has also been shown to have effects outside of the bone marrow. EPO receptors have been demonstrated in kidney, brain, retina, heart, skeletal muscle, and endothelial cells (Juul et al, 1998). In the kidney, pretreatment with high-dose EPO has been shown to reduce ischemia-reperfusion injury in animal models, due to decreased apoptosis (Patel et al, 2004).

Regulation of EPO Production and Erythropoiesis. Production of EPO, and hence erythropoiesis, is closely associated with circulating O_2 tension. Under hypoxic conditions, the alpha subunit of the regulatory protein hypoxia-inducible factor-1 (HIF-1) is exposed (Wang et al, 1995). Binding of HIF-1 alpha with HIF-1 beta, hepatic nuclear factor-4 (HNF-4), and p300 turns on erythropoietin transcription (Arany et al, 1996). Once the hypoxia has been corrected, HIF-1 alpha is ubiquinated and rapidly degraded by proteosomes, thus shutting down erythropoietin production. There is also in-vitro evidence that hypoxia itself may directly increase erythropoiesis through HIF-1–mediated increases in autocrine motility factor (AMF) production and subsequent decrease in apoptosis (Mikami et al, 2005).

In states of chronic inflammation, erythropoiesis is decreased. Apoptosis of erythroid progenitor cells occurs in the presence of

the tumor-associated antigen RCAS1, which is also produced by macrophages under inflammatory conditions (Suehiro et al, 2005).

In certain malignancies, such as renal cell carcinoma, erythropoiesis is enhanced due to a mutation in the von Hippel-Lindau (VHL) gene. As a result, there are constitutively increased levels of HIF-1 and polycythemia (Wiesener et al, 2002).

Erythropoiesis is also decreased in most forms of chronic renal failure, and subsequently anemia is common in the later stages of the disease. This is due to decreased EPO levels as a result of a reduction in the number of functional EPO-producing cells within the kidney. Recombinant human erythropoietin (rHuEPO) has been shown to be an effective treatment for this type of anemia.

rHuEPO has also been used to treat anemia associated with malignancy but must be used with caution in these conditions because its use may be associated with an increased risk of venous thromboembolism and higher mortality (Bennett et al, 2008).

Bone Mineral Regulation

Normal regulation of bone mineralization, through maintenance of serum calcium and phosphorus levels, is achieved through the actions of vitamin D and parathyroid hormone (PTH). The actions of both hormones are exerted largely through the kidney (Fig. 38–3).

Vitamin D Regulation. **The kidney plays an important role in the regulation of vitamin D activity**. The major source of vitamin D is through dermal synthesis of the precursor compound cholecalciferol (vitamin D_3), or through dietary intake of vitamin D_3–fortified foods. Vitamin D_3 has minimal biological activity and requires two hydroxylations to become active. The first occurs in the liver through the action of 25-hydroxylase to form 25-hydroxycholecalciferol (calcidiol). The calcidiol molecule is bound to vitamin D binding protein and transported to the kidney, where it is filtered and reabsorbed by renal tubular cells. A second hydroxylation occurs within the tubular cell. Because these cells contain both 1α-hydroxylase and 24α-hydroxylase, hydroxylation will produce either inactive 24,25-dihydroxycholecalciferol or 1,25-dihydroxycholecalciferol (calcitriol), the biologically active form that is one hundred times more potent than calcidiol. Calcitriol production is regulated by calcidiol levels as well as the 1α-hydroxylase levels. These are, in turn, determined by PTH and plasma phosphate levels (increased enzyme activity) and serum calcitriol levels (decreased enzyme activity) (Portale et al, 1989). However, unregulated calcitriol synthesis can occur in macrophages in granulomatous conditions such as sarcoidosis and tuberculosis, and in prostate epithelial and cancer cells (Young et al, 2004).

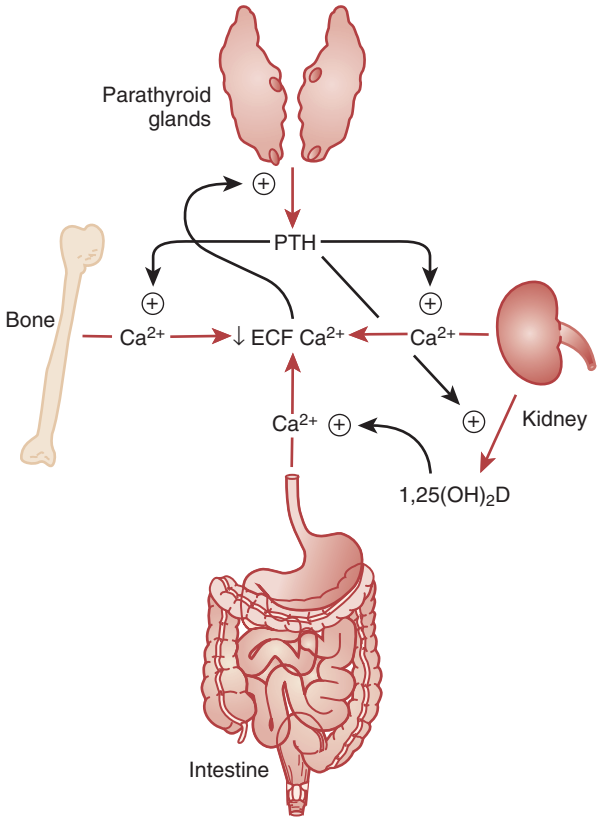


Figure 38–3. Effects of vitamin D and parathyroid hormone (PTH) on calcium homeostasis. ECF, extracellular fluid. (From Yu SLY. Renal transport of calcium, magnesium, and phosphate. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: WB Saunders; 2004. p. 536.)

Vitamin D Activity. Calcitriol functions through a single intracellular vitamin D receptor (VDR) to regulate gene transcription (Lowe et al, 1992). Its primary function is the maintenance of serum calcium and phosphorus levels. The four main target organs are the intestine (increases intestinal absorption of calcium, and to a lesser extent, phosphorus), the bones (regulates osteoblast activity, and in combination with PTH, allows for osteoclast activation and bone resorption), the kidney (increases reabsorption of calcium) and the parathyroid gland (suppresses PTH release). Recent evidence suggests that both calcidiol and calcitriol may also function as antiproliferative agents. Prostate epithelial and cancer cells demonstrate VDR, and vitamin D may suppress the growth of these cells, especially in combination with androgens (Tuohimaa et al, 2005).

In summary, vitamin D contributes to normal bone mineralization by maintaining normal serum calcium and phosphorus levels through increased intestinal absorption of calcium and phosphorus and increased renal reabsorption of calcium.

Parathyroid Hormone Regulation. Synthesis, secretion, and degradation of PTH are influenced directly by serum calcium levels through calcium sensing receptors located on parathyroid cells. During periods of hypocalcemia, PTH synthesis and secretion are increased while degradation is decreased. The opposite occurs during hypercalcemia. In addition, calcitriol has a suppressive effect on PTH synthesis and parathyroid cell proliferation, mediated through vitamin D receptors located on the surface of parathyroid cells. Hyperphosphatemia also directly stimulates PTH release, primarily in advanced renal insufficiency. Finally, other cations such as magnesium and aluminum have slight stimulatory effects, likely mediated through the calcium sensing receptors.

Parathyroid Hormone Activity. PTH exerts its activity through PTH/PTHrP receptors, which are localized primarily in the kidneys and bone.

Bone. Its effect on bone metabolism depends upon its administration; if given continuously, it stimulates bone resorption and increases serum calcium and phosphorus levels. Given intermittently, it leads to increased bone formation and mineral density.

Kidney. The renal effects of PTH are threefold. First, it increases active calcium reabsorption at the level of the distal tubule (Friedman and Gesek, 1993). Second, it decreases phosphate reabsorption in the proximal convoluted tubule (and the distal tubule, to a lesser degree) through its action on the sodium phosphorus cotransporter (Pfister et al, 1997). Third, it stimulates calcitriol production by increasing 1α-hydoxylase levels while decreasing 24α-hydroxylase levels (Broadus et al, 1980).

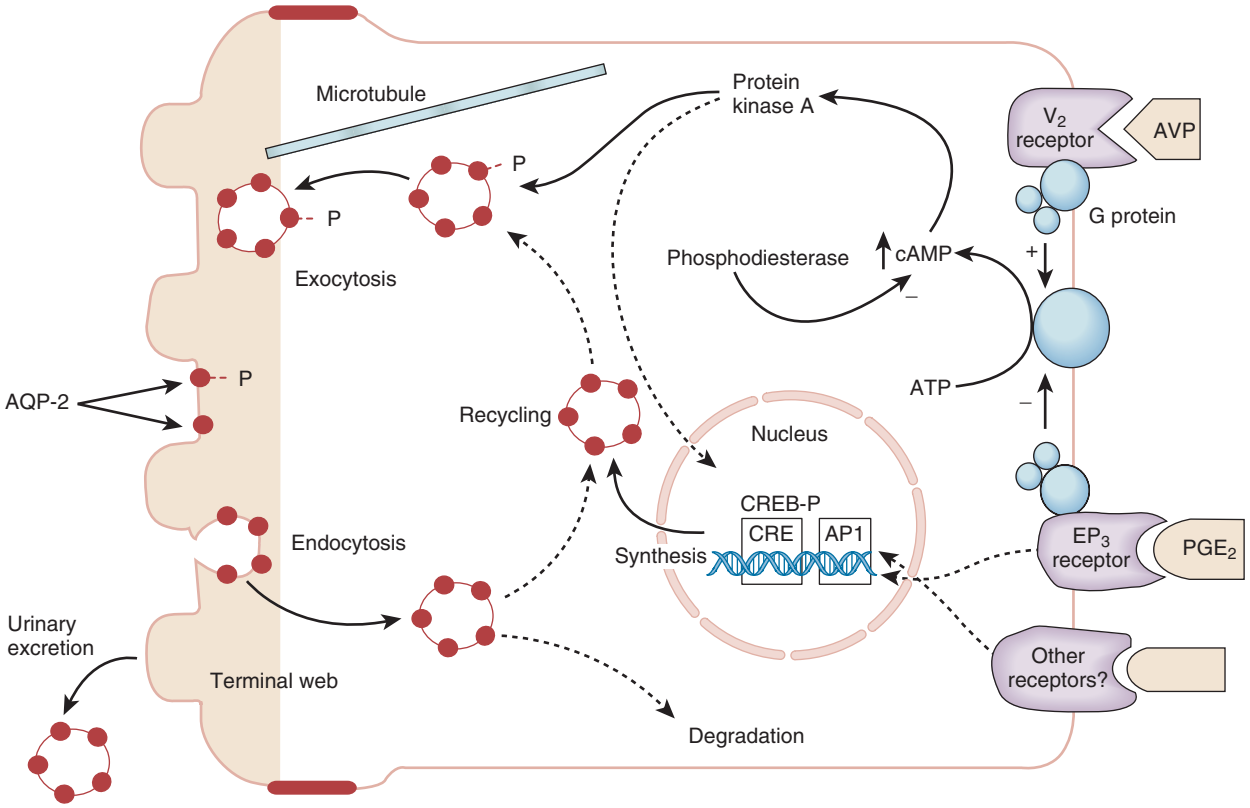


Figure 38–4. Action of antidiuretic hormone on aquaporin (AQP) transport. AC, adenylate cyclase; AP1, transcription factor; AVP, arginine vasopressin; cAMP, cyclic adenosine monophosphate; CRE, cAMP response element; CREB-P, CRE binding protein; EP_3, prostaglandin receptor; PGE_2, prostaglandin E_2. (From Brown D, Nielsen S. The cell biology of vasopressin action. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: WB Saunders; 2004. p. 574.)

In summary, PTH functions to maintain normal serum calcium and phosphorus levels by increasing bone resorption, increasing renal reabsorption of calcium and excretion of phosphorus, and stimulating production of calcitriol.

Antidiuretic Hormone

Antidiuretic hormone (ADH), or arginine vasopressin as it is called in humans, is a polypeptide secreted by the posterior pituitary gland. It functions to maintain serum osmolality and volume through the regulation of free-water excretion in the kidney.

ADH Actions. **ADH increases the passive reabsorption of water at the level of the collecting duct.** Through interaction with the V2 receptor, it facilitates the insertion of preformed water channels, known as aquaporin-2 (AQP-2), into the luminal membrane of the principal cells (Agre et al, 2002). This allows luminal water to enter the cell and then diffuse back into the systemic circulation through the basolateral membrane of the cell (Fig. 38–4). ADH increases urea reabsorption in the medullary collecting tubule through specific urea transporters, which helps maintain the high interstitial osmolality required for water reabsorption. ADH also increases systemic vascular resistance through interaction with the V1 receptor; this is of minor physiologic importance. Other effects of ADH include increased sodium reabsorption and potassium excretion, increased prostaglandin synthesis, increased ACTH secretion (through V3 receptors), and release of both factor VIII and von Willebrand factor from vascular endothelium.

Control of ADH Secretion. There are two major stimuli for ADH release, hyperosmolality and decreased effective circulating volume (ECV), as well as a number of less common factors (Table 38–2).

Table 38–2.
Physiologic and Pathologic Factors Affecting the Release of Antidiuretic Hormone

STIMULI	INHIBITORS
Hyperosmolality	Hypo-osmolality
Hypovolemia	Hypervolemia
Stress (e.g., pain)	Ethanol
Nausea	Phenytoin
Pregnancy	
Hypoglycemia	
Nicotine	
Morphine	
Other drugs	

Hyperosmolality. The major extracellular osmole is sodium; so, for practical purposes ADH release is governed by changes in serum sodium concentrations. Serum osmolality is monitored by osmoreceptors in the hypothalamus, and changes as little as one percent are enough to affect ADH release (Robertson, 1987).

Decreased ECV. Circulating volume is monitored by pressure (baro-) receptors in the carotid sinus, which stimulate ADH release in response to reductions in ECV. These receptors are much less sensitive than the osmoreceptors, and, as such, ADH release is not affected until there is a noticeable drop in mean arterial pressures (usually around 10% to 15% blood volume loss) and after other

vasoconstrictive hormones, such as renin and norepinephrine, have been activated.

Other Stimuli. There are a number of other factors that can increase ADH secretion (see Table 38–2). Nausea and pain are probably the most clinically relevant, and, as a result, postsurgical hyponatremia due to excessive ADH release is a potentially life-threatening problem.

When both decreased ECV and hyponatremia coexist, the pressure receptors usually override the osmoreceptors and prevent the inhibition of ADH secretion that is usually seen with hyponatremia (Baylis, 1987). This is clinically relevant in conditions of decreased ECV and hyponatremia, such as congestive heart failure where ADH secretion persists despite significant hyponatremia.

Renal Tubular Function

Basic Functions

The renal tubule has two basic functions: *reabsorption* (transport of substances from lumen to blood) and *secretion* (transport of substances from blood to lumen). Transport can involve one of two pathways: either *transcellular* (across the luminal and basolateral membrane) or *paracellular* (between cells) (Fig. 38–5). **Each section of the tubule** (Fig. 38–6) **is specialized to facilitate absorption and secretion of certain substances through a variety of transport mechanisms.**

Proximal Convoluted Tubule (PCT)

The PCT is responsible for reabsorption of 60% of the glomerular filtrate. Under normal circumstances it reabsorbs 65% of the filtered sodium, potassium, and calcium; 80% of filtered phosphate, water, and bicarbonate; and 100% of the filtered glucose and amino acids (Moe et al, 2004). The PCT is able to increase or decrease reabsorption in response to changes in GFR to maintain constant reabsorptive fractions through the process of *glomerulotubular balance*. This is accomplished mainly by the early (S1 and S2) segments of the PCT. The later (S3) segment is responsible for secretion of numerous drugs and toxins that are too large, or protein bound, to be filtered. As well, the PCT is responsible for the generation of ammonia from glutamine, which is necessary for urinary acidification.

Sodium. The majority of sodium reabsorption occurs in the PCT, and occurs through both secondary active and passive mechanisms (Fig. 38–7).

1. *Secondary active reabsorption*—luminal Na^+ moves passively into tubular cells; this movement, though, is driven by osmotic and electrochemical gradients between the luminal and intracellular environments established by the energy-requiring Na-K ATPase located in the basolateral cell membrane. There is an active exchange of three intracellular Na^+ for two extracellular K^+ ions, which keeps the intracellular sodium concentration low and the cell interior negative with respect to the lumen. This is called *secondary passive reabsorption*. Na^+ then enters the cell through coupled transport with other solutes (see below) or in exchange for H^+ through a Na^+/H^+ antiporter. The activity of this transporter is under neurohormonal regulation, and can be influenced by angiotensin II, norepinephrine, and dopamine to either increase or decrease Na^+ reabsorption in response to changes in effective circulating volume.

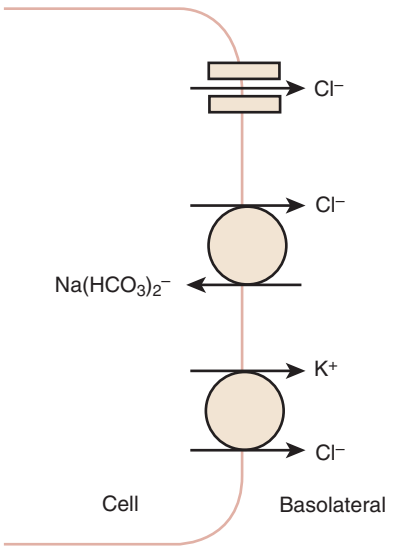


Figure 38–5. Example of transcellular transport between the tubule cell and the basolateral membrane. (From Moe OW, Baum M, Berry CA, Rector FC Jr. Renal transport of glucose, amino acids, sodium, chloride, and water. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: WB Saunders; 2004. p. 425.)

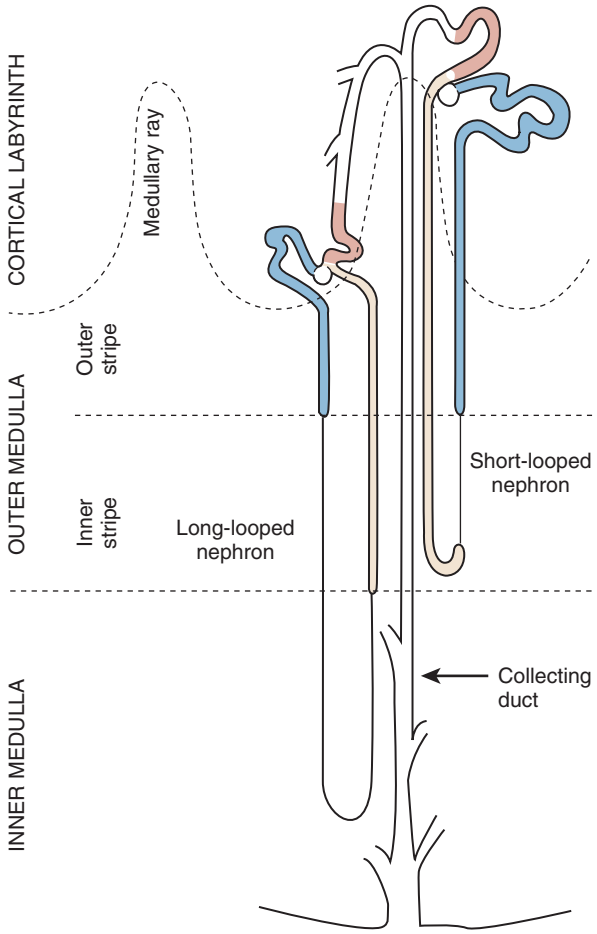


Figure 38–6. Organization of the renal tubule. (From Knepper MA, Gamba F. Urine concentration and dilution. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: WB Saunders; 2004. p. 601.)

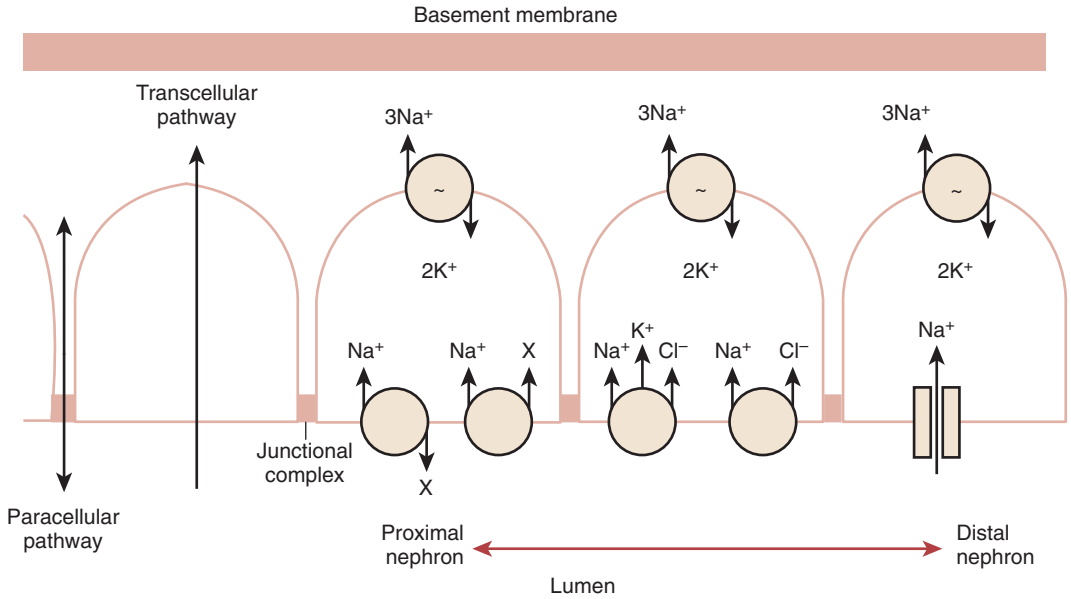


Figure 38–7. Mechanisms of sodium reabsorption in the proximal tubule. (From Moe OW, Baum M, Berry CA, Rector FC Jr. Renal transport of glucose, amino acids, sodium, chloride, and water. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: WB Saunders; 2004. p. 414.)

2. *Passive reabsorption*—this occurs when Na^+ moves paracellularly into the intercellular space. It is meditated through Cl^- transport across the paracellular pathway, which creates an electrochemical gradient favoring Na^+ movement out of the lumen into the intercellular space.

In summary then, sodium is the most significant solute for the PCT for three reasons:

- It is the only solute that is actively reabsorbed (through the basolaterally located Na-K ATPase pump).
- All other solutes are passively reabsorbed through Na^+ coupled transport.
- Early reabsorption of Na^+ (as well as other solutes) creates an osmotic gradient that facilitate passive reabsorption of water.

Potassium. The majority of potassium reabsorption occurs by the paracellular route. It is largely dependent on sodium and fluid movement, as potassium reabsorption parallels that of water and sodium.

Bicarbonate. **The majority of filtered bicarbonate (90%) is reclaimed in the PCT.** There is no upper limit to bicarbonate reabsorption; in states of volume depletion and increased proximal reabsorption of Na^+, bicarbonate reabsorption continues even in the presence of significant alkalemia (Moe et al, 2004). Bicarbonate is not transported across PCT cells; its reabsorption is dependent upon H^+ secretion by the Na^+/H^+ antiporter. Within the lumen, bicarbonate combines with H^+ to form H_2O and CO_2, which can diffuse intracellularly and be converted back to H^+ and bicarbonate and subsequently secreted through the basolateral membrane by a Na^+-coupled transporter and returned to the circulation. Both these reactions are catalyzed by carbonic anhydrase (Fig. 38–8).

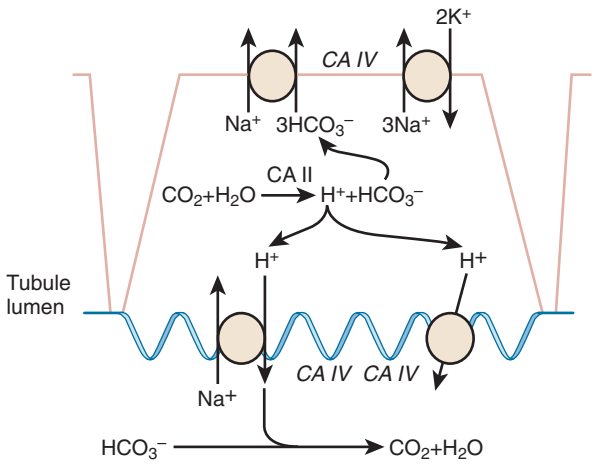


Figure 38–8. Reabsorption of bicarbonate in the renal tubule. CA, carbonic anhydrase. (From Hamm LL. Renal acidification mechanisms. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: WB Saunders; 2004. p. 500.)

Water. **Water reabsorption in the PCT is a passive process, driven by the reabsorption of other solutes and the subsequent osmotic gradient that develops between the lumen and intercellular space.** The majority of water reabsorption occurs in the late PCT. As with Na^+ movement, water can also move either transcellularly or paracellularly. Transcellular movement accounts for 80% of water reabsorption, and occurs through the specialized water channel aquaporin-1 (AQP-1) (Agre et al, 2002). Paracellular movement accounts for only 20% of water reabsorption and occurs across the tight junctions between cells.

Glucose. Glucose reabsorption is driven by passive Na^+ reabsorption. In the early (S1 and S2) PCT, this occurs through a high-capacity, low-affinity Na^+/glucose transporter called SGLT-2 (Moe et al, 2004). In the later (S3) segment of the PCT, reabsorption occurs through a low-capacity, high-affinity $2Na^+$/glucose transporter (also found in intestine) called SGLT-1. Intracellular glucose is then transported out of the cell through the basolateral membrane by the facilitative transporter GLUT-2. Under normal plasma glucose levels, all filtered glucose is reabsorbed. **However, if plasma levels exceed 200 mg%, then the filtered load will exceed the reabsorptive threshold and urinary glucose will be detected** (Fig. 38–9).

Proteins and Amino Acids. Amino acid transport is very complex. Generally, there are separate transporters for the basic, acidic, and neutral amino acids, and most are Na^+ dependent. There are a few amino acids that have specialized transporters, and some are Na independent. Larger proteins are usually catabolized by brush border peptidases and reabsorbed as amino acids; some, however, enter the cell through carrier-mediated endocytosis.

Phosphate. About 85% to 90% of filtered phosphate is reabsorbed, primarily in the PCT. Phosphate reabsorption occurs through a Na^+-phosphate cotransporter. The activity of this transporter is regulated by both plasma phosphate levels and parathyroid hormone levels (Fig. 38–10).

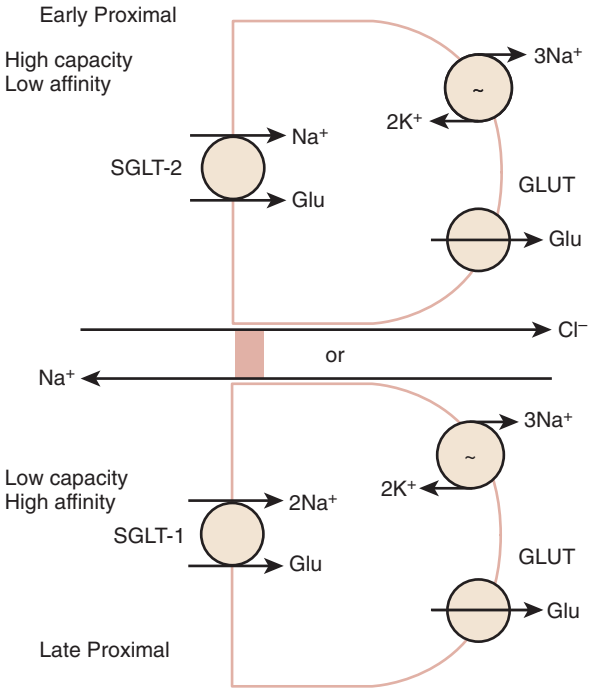


Figure 38–9. Absorption of glucose by the renal tubule. GLUT, glucose transporter; SGLT, sodium glucose-linked transporter. (From Moe OW, Baum M, Berry CA, Rector FC Jr. Renal transport of glucose, amino acids, sodium, chloride, and water. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: WB Saunders; 2004. p. 417.)

Calcium. Most calcium reabsorption occurs in the late S2 segment and early S3 segment of the PCT. It is a passive process, driven by the lumen (+) potential difference (PD). Calcium movement occurs by the paracellular route, through the specific calcium channel claudin-2 (Amasheh et al, 2002), located in the tight junctions. It is also possible that there is a small amount of active calcium reabsorption in the late S3 segment, but this is poorly characterized (Fig. 38–11).

Magnesium. About 15% of filtered magnesium is reabsorbed in the PCT, but the mechanism is poorly understood (Konrad et al, 2004).

Loop of Henle

The loop of Henle consists of four segments; the thin descending limb (DLH), the thin ascending limb (ALH), the medullary thick ascending limb (mTALH), and the cortical thick ascending limb (cTALH). It receives the 40% of ultrafiltrate not reabsorbed by the PCT. **Each segment of the loop of Henle has specific functions related to fluid, electrolyte, and acid-base balance, but the major function of the loop, as a whole, is to reabsorb 25% to 30% of the filtered Na^+ and to reabsorb**

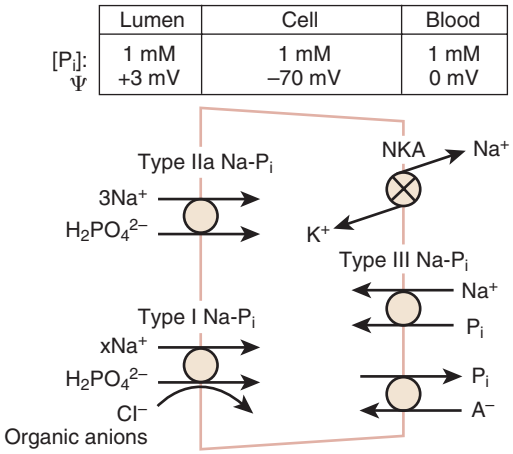


Figure 38–10. Absorption of phosphate by the renal tubule. (From Yu SLY. Renal transport of calcium, magnesium, and phosphate. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: WB Saunders; 2004. p. 555.)

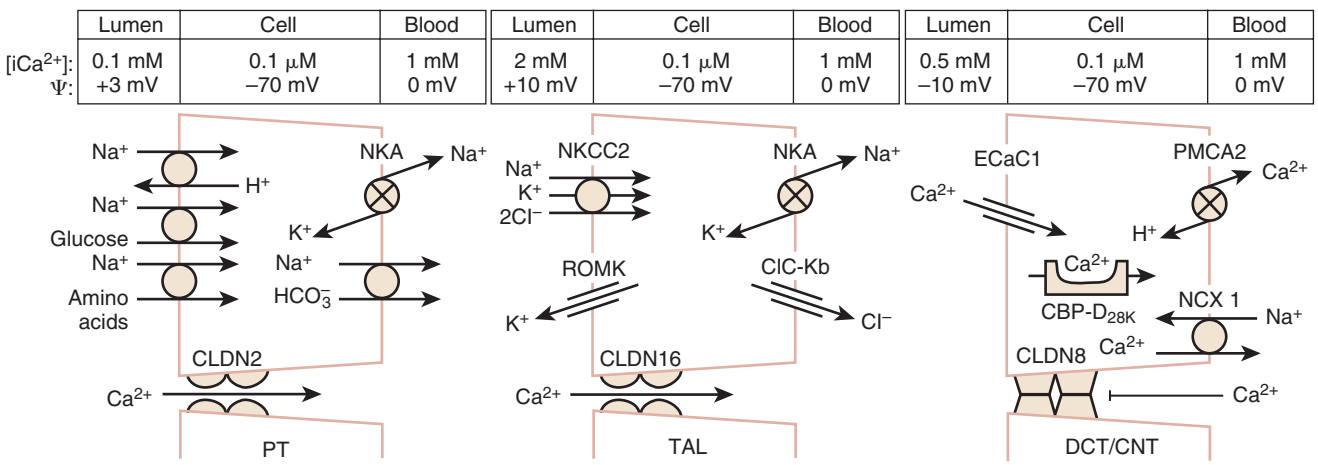


Figure 38–11. Absorption of calcium by the renal tubule. CNT, connecting tubule; DCT, distal convoluted tubule; PT, proximal tubule; TAL, thick ascending limb. (From Yu SLY. Renal transport of calcium, magnesium, and phosphate. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: WB Saunders; 2004. p. 538.)

NaCl in excess of water to establish an extremely concentrated medullary interstitium, which is necessary for the excretion of a concentrated final urine. The loop of Henle, like the PCT, is also controlled by glomerulotubular balance, which maintains a consistent ultrafiltrate delivered to the collecting ducts (Fig. 38–12).

Thin Descending Limb. The DLH consists of the segment of the nephron between the end of the PCT (S3 segment) and the bottom of the loop. Cortical nephrons, in general, have short DLH while juxtamedullary nephrons have longer DLH. There is very little active transport of any kind within the DLH, but it has very high water permeability due to abundant expression of AQP-1 (Agre et al, 2002).

Thin Ascending Limb. The ALH begins at the loop and continues up to the thick ascending limb. The AHL is of variable length; cortical nephrons may have very little ALH. Similar to the DLH, there is no active transport of solutes. However, unlike the DLH, the AHL is water impermeable. There is high permeability for NaCl as well as urea; so, reabsorption of these solutes occurs passively along an osmotic gradient, because the luminal concentrations of these solutes is quite high due to water removal during transit through the DLH.

Thick Ascending Limb. The TALH is far more active in terms of solute reabsorption than either thin limbs. Water reabsorption, however, is negligible because this segment of the loop is entirely impermeable to water due to the lack of aquaporins.

Sodium, Potassium, and Chloride. The TALH reabsorbs 25% to 30% of the sodium filtered across the glomerulus. This is primarily through the secondary active process driven by basolateral Na-K ATPase pumps that keep intracellular sodium concentration low. Na^+ is transported transcellularly by a $Na^+/K^+/2Cl^-$ (NKCC2) transporter located in the apical membrane. Once inside the cell, Cl^- is pumped out across the basolateral membrane by a Cl^-/K^+ cotransporter, which helps keep intracellular chloride concentration low. K^+, however, preferentially exits the cell back through the apical membrane K channel ROMK and reenters the tubular lumen, where it can interact once again with the NKCC2 transporter. **This K^+ recycling is important; without it, sodium reabsorption would be limited by the luminal potassium concentration, which is much lower than either sodium or chloride concentrations.** By recycling K^+, the tubule is able to reabsorb sodium independent of potassium. A secondary benefit of this process is to help establish a lumen (+) PD, which helps facilitate paracellular transport of a variety of cations, including sodium (Fig. 38–13).

The NKCC2 transporter is the site of action of loop diuretics. These drugs bind to the Cl^- receptor and interfere with normal transporter action, resulting in decreased NaCl reabsorption and subsequent diuresis.

Sodium reabsorption along the TAHL, in the absence of water reabsorption, is critical to the formation of the interstitial concentration gradient. This gradient is essential to subsequent urinary concentrating ability in the collecting duct. It also creates a progressively more hypotonic ultrafiltrate, which is important for water diuresis to occur (see below).

Calcium and Magnesium. About 15% of the filtered calcium is reabsorbed in the TALH. Reabsorption is passively driven by the lumen (+) PD by the paracellular route, facilitated by the calcium channel paracellin-1 (also known as claudin-16). Magnesium reabsorption (60% to 70%) also occurs in the TALH in a similar manner (Konrad et al, 2004). Inhibition of the NKCC2 transporter with loop diuretics induces renal calcium and magnesium wasting due to dissipation of the lumen (+) PD.

Bicarbonate. The TALH also reabsorbs 10% to 20% of the filtered bicarbonate, mainly through H^+ secretion by using the Na^+/H^+ exchanger. Water reabsorption occurring in the DLH increases bicarbonate reabsorption by increasing luminal bicarbonate concentrations.

Countercurrent Mechanism. A critical function of the kidney is the preservation of body water; this is accomplished through the osmotic reabsorption of solute-free water in the collecting tubule

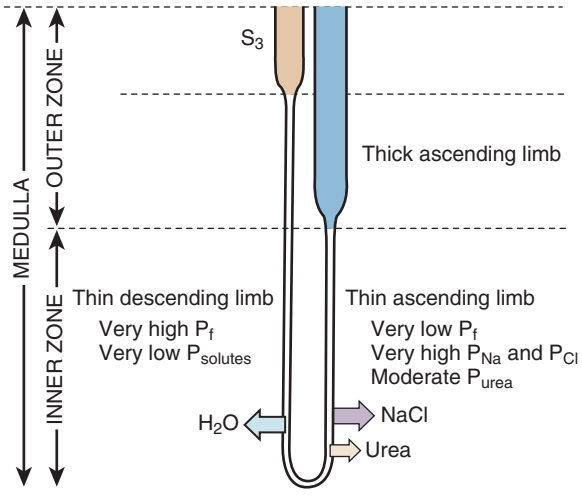


Figure 38–12. Anatomy of the loop of Henle. (From Moe OW, Baum M, Berry CA, Rector FC Jr. Renal transport of glucose, amino acids, sodium, chloride, and water. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: WB Saunders; 2004. p. 431.)

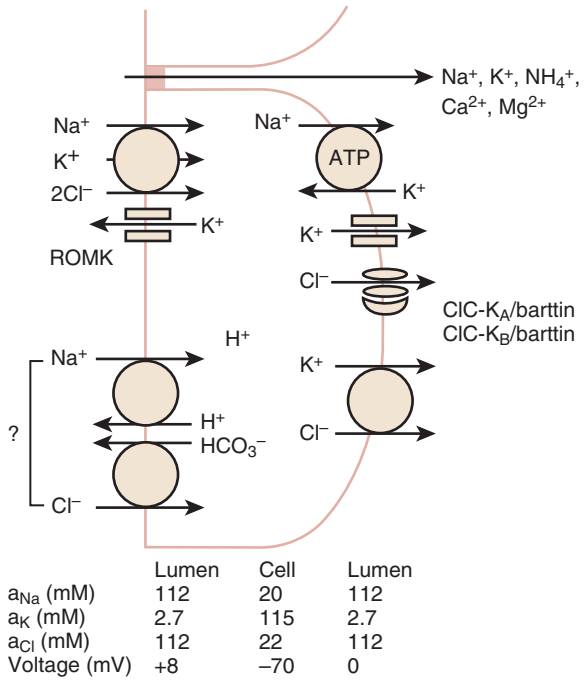


Figure 38–13. Paracellular transport of cations in the thick ascending limb. ROMK, renal outer medullary potassium channel. (From Moe OW, Baum M, Berry CA, Rector FC Jr. Renal transport of glucose, amino acids, sodium, chloride, and water. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: WB Saunders; 2004. p. 433.)

(see later) and the excretion of urine that is hyperosmolar with respect to plasma. Human kidneys can produce a urine concentration up to 1200 mOsm/kg. **To achieve this degree of urinary concentration, the kidney must be able to generate an interstitial osmotic gradient of similar degree.** Through the process of *countercurrent multiplication*, the loop of Henle is able to produce an interstitial osmotic gradient ranging from 285 mOsm/kg (isosmotic with plasma) in the outer medulla to 1200 mOsm/kg in the inner medulla. The basic steps of countercurrent multiplication are as follows:

1. Medullary interstitium is made hyperosmolar by the reabsorption of NaCl (in the absence of water reabsorption) in the ascending limbs of the loop of Henle.
2. Due to the hairpin (*countercurrent*) configuration of the loop, the concentration of the luminal fluid can be progressively increased *(multiplied)* to as much as 1200 mOsm/kg (Fig. 38–14). This allows the interstitial osmolarity to increase to similar levels.
3. In the presence of ADH, urea diffuses from the medullary collecting tubule into the interstitium, increasing the interstitial osmolarity even further (Yang and Bankir, 2005). This has a secondary benefit of increasing water reabsorption in the DLH, thus increasing luminal sodium and chloride concentrations in the ascending limbs and making step 1 even more efficient (Fig. 38–15).
4. Due to the high interstitial osmolality, water is passively reabsorbed in the medullary collecting tubule (in the presence of ADH). This could potentially lead to dilution of the interstitium. To minimize this effect, the volume of ultrafiltrate is minimized through water reabsorption in the cortical collecting tubule. Also, the vasa recta are arranged in a similar hairpin loop that allows water removal but minimizes removal of interstitial solutes (Pallone et al, 2003).

The osmotic gradient can be disturbed in certain clinical conditions. Increased medullary blood flow (as seen with osmotic diuresis) increases removal of interstitial solutes through the vasa recta and leads to a lower interstitial osmolality. As well, prolonged use of loop diuretics will prevent the transport of NaCl in the ascending limb of the loop of Henle, necessary for the ongoing maintenance of the interstitial hyperosmolality; hence, prolonged water diuresis may be seen after discontinuation of the drug, until the gradient can be reestablished.

Tamm-Horsfall Mucoprotein. The TALH is also the site of secretion of Tamm-Horsfall mucoprotein, or uromodulin. It is clinically important, because it forms the matrix of all urinary casts. Recently, it has been shown to be important in the prevention of urinary tract infections (Bates et al, 2004). It has also been implicated in the pathogenesis of cast nephropathy, medullary cystic renal disease, and familial juvenile hyperuricemic nephropathy.

Distal Tubule

The distal tubule is primarily involved in sodium and calcium reabsorption. There may be some capacity for H^+ and K^+ secretion, but the importance of this is unknown. The distal tubule can be subdivided into two sections, the distal convoluted tubule (DCT), and the connecting tubule (CNT).

Sodium and Chloride. The DCT reabsorbs another 5% to 10% of the sodium filtered through the glomerulus. As in the TAHL, it is a secondary active process, driven by basolateral Na-K ATPase pumps, that occurs in the absence of water reabsorption. Na^+ is reabsorbed electroneutrally with Cl^- by a Na^+/Cl^- (NCC) cotransporter that can be inhibited with the thiazide diuretics. Additionally, there may be some Na^+ reabsorption by the Na^+/H^+ exchange transporter in the luminal membrane. Notably, Na^+ reabsorption in the DCT is regulated by luminal sodium concentration but not by hormonal influences. **Hence, anything that increases delivery of Na^+ to the DCT will lead to increased Na^+ reabsorption in the section of the tubule.** One clinical example would be the use of loop diuretics. By inhibiting the NKCC2 transporter in the TAHL, Na^+ delivery increases to the DCT. In response, there is usually a marked increase in Na^+ reabsorption,

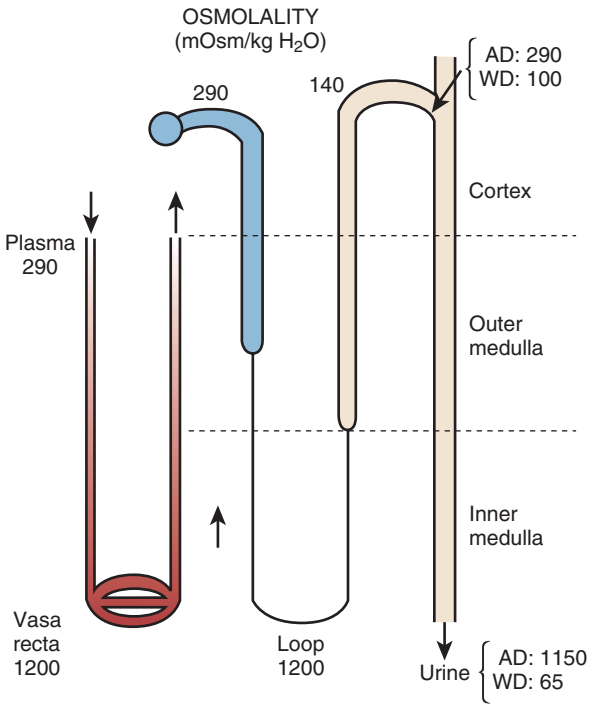


Figure 38–14. Countercurrent mechanism in the renal tubule. AD, antidiuresis; WD, water diuresis. (From Knepper MA, Gamba F. Urine concentration and dilution. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: WB Saunders; 2004. p. 604.)

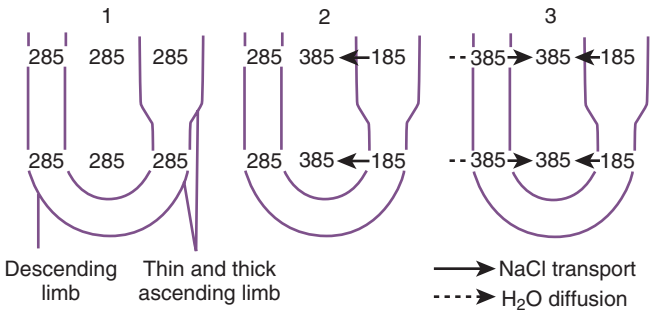


Figure 38–15. Role of active NaCl transport in initiating countercurrent multiplication. In step 1, at time zero, the fluid in the descending and ascending limbs and the interstitium is isosmotic to plasma. In step 2, NaCl is transported out of the ascending limb into the interstitium to a gradient of 200 mOsm/kg. In step 3, the fluid in the descending limb equilibrates osmotically with the hyperosmotic interstitium, primarily by water movement out of the tubule. Dilution of the interstitium by this water movement is prevented by continued NaCl transport out of the ascending limb. The result is the creation of an osmotic gradient between the ascending limb and the relatively hyperosmotic descending limb and interstitium.

which may significantly diminish the diuretic response achieved with the loop diuretic. Such a response may be minimized by concomitant use of a thiazide diuretic.

The connecting segment can also reabsorb sodium, but does so under the influence of aldosterone similar what occurs in the principal cells of the cortical collecting tubule.

Calcium. The DCT accounts for 10% to 15% of calcium reabsorption. Unlike either the PCT or loop of Henle, calcium reabsorption in the DCT is independent of Na^+ reabsorption. Calcium enters the cell through the luminal calcium channel $ECaC_1$ and binds to the intracellular binding protein calbindin D_{28} (Loffing, 2003). By doing so, free intracellular calcium concentration is kept low, thus facilitating inward movement of calcium. Extrusion from the cell occurs through the basolateral membrane using either a Ca^{2+}/H^+ (PMCA) or Na^+/Ca^{2+} (NCX) exchanger (Loffing and Kaissling, 2003). In contrast to the PCT or loop of Henle, movement of calcium by the paracellular route is inhibited due to the presence of the protein claudin-8, which markedly decreases calcium permeability through tight junctions.

Calcium reabsorption is regulated in this region by the actions of PTH and, to a lesser degree, calcitriol (vitamin D). PTH increases calcium reabsorption, possibly through alterations in intracellular voltage as a result of increased Cl^- flux through the basolateral membrane. Calcitriol is thought to increase the number of $ECaC_1$ channels and increase calbindin production, both of which would increase calcium reabsorption.

Magnesium. Five percent to 10% of filtered magnesium is actively reabsorbed in the DT by the transcellular route. This likely occurs through the luminal magnesium channel TRPM6 (Voets et al, 2004), and is driven by a basolateral Na-Mg pump that generates a Mg gradient favoring inward flow of Mg.

Collecting Tubule

The collecting tubule consists of two parts; the cortical collecting tubule (CCT) and the medullary collecting tubule (MCT). While the more proximal portions of the nephron are designed for bulk reabsorption of ultrafiltrate, the collecting tubules are responsible for the final qualitative changes in ultrafiltrate composition in response to dietary intake.

Cortical Collecting Tubule

The CCT consists of two distinct cell types, each with distinct functions. Principal cells (65%) are generally involved in NaCl reabsorption while intercalated cells (35%) are mostly involved with acid secretion. Both are also involved in K regulation.

Principal Cells

Sodium, Potassium, and Chloride. Sodium reabsorption occurs passively through the luminal Na channel $ENaC_1$ rather than through a cotransporter system (Loffing and Kaissling, 2003). Basolateral Na-K ATPase pumps keep intracellular sodium concentration low, facilitating inward movement of sodium. Movement of sodium intracellularly, without an accompanying anion, creates a lumen (–) PD that results in either passive paracellular movement of Cl out of the lumen, or secretion of intracellular K into the lumen to restore electroneutrality. Sodium reabsorption is regulated in the CCT primarily by aldosterone, which increases the number of open $ENaC_1$. Blockade of the Na channel by the diuretic amiloride leads to reduced Na reabsorption as well as K secretion, as the electrochemical gradient is eliminated, and thus the driving force for K secretion is abolished (Fig. 38–16). Prostaglandin E_2 also seems to inhibit Na reabsorption, and reduction of PGE_2 by nonsteroidal anti-inflammatory drugs leads to sodium retention.

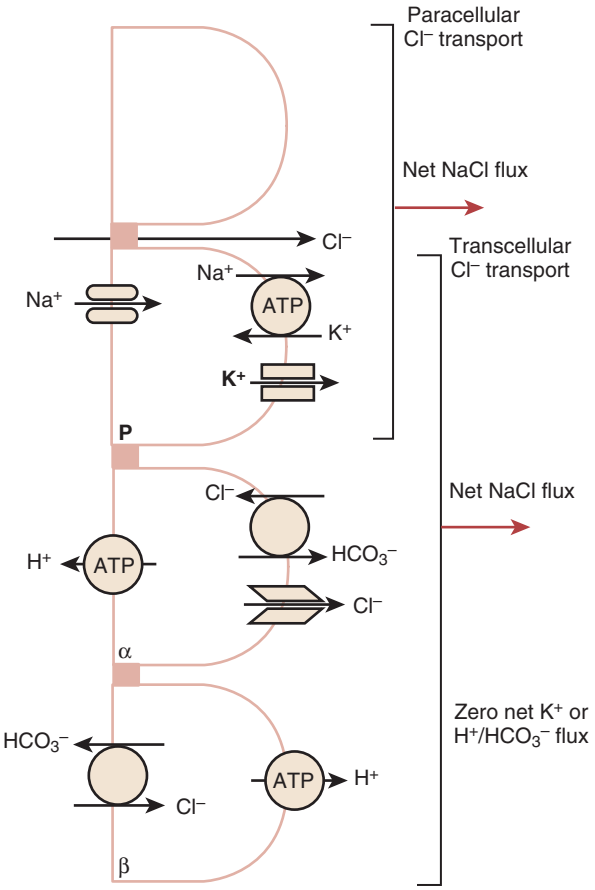


Figure 38–16. Effect of blockade of the Na channel by the diuretic amiloride. (From Moe OW, Baum M, Berry CA, Rector FC Jr. Renal transport of glucose, amino acids, sodium, chloride, and water. In: Brenner BM, editor. Brenner and Rector's the kidney. 7th ed. Philadelphia: WB Saunders; 2004. p. 439.)

K secretion in the CCT depends not only upon aldosterone sensitive inward Na movement, but also luminal flow rates. When flow decreases in the tubular lumen, local intraluminal potassium concentration increases and minimizes the favorable potassium gradient, thus minimizing secretion. This can be partially offset by the actions of ADH, which increase potassium secretion, possibly by the insertion of new K channels in the luminal membrane or by increased Na reabsorption (Wang, 1995). **Thus any condition that leads to decreased luminal flow rates, or increased aldosterone production, can lead to reduced potassium excretion.**

Water. The water permeability of the CCT is low in the basal state. However, it can be greatly increased in the presence of ADH. This is due to the insertion of preformed AQP-2 water channels into the luminal membrane (Agre et al, 2002), which allows water to be passively reabsorbed and equilibrate with the cortical interstitium through basolateral AQP-3 and AQP-4 channels. This is important for the development of highly concentrated final urine, because it decreases the volume of ultrafiltrate delivered to the MCT, where most of the final concentration of urine occurs (Knepper et al, 1994) (Fig. 38–17).

Intercalated Cells. There are two different types of intercalated cells, with different functions: type A intercalated cells, involved mostly with H^+ secretion; and type B intercalated cells, involved mostly with bicarbonate secretion.

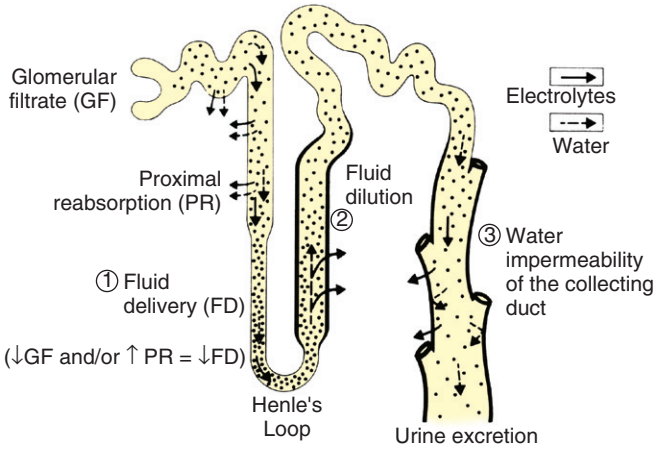


Figure 38–17. The components of the normal urine dilution mechanisms. (Redrawn from Berl T, Schrier RW. Water metabolism and the hypo-osmolar syndrome. In: Brenner BM, Stein JH, editors. Sodium and water homeostasis. New York: Churchill Livingstone; 1978. p. 1–23.)

Hydrogen and Bicarbonate. **In both cell types, intracellular H_2O, under the influence of carbonic anhydrase, is combined with CO_2 to produce H^+ and HCO_3^-.** As well, in both cell types, H^+ and HCO_3^- are secreted from the cell by similar transporters. However, what differs is the location of the transporters.

Type A intercalated cells have both H^+ ATPase and H^+-K^+ ATPase pumps located on the luminal membrane, which facilitate H^+ secretion into the tubular lumen. Bicarbonate is transported back to the systemic circulation by a HCO_3^-/Cl^- transporter on the basolateral side of the cell. The net effect is acidification of the urine and subsequent increase in extracellular pH. As expected, this process is stimulated under conditions of acidemia. Aldosterone seems to have a permissive effect on this, probably through actions on the H^+ ATPase pump, because increased urine H^+ loss and subsequent systemic alkalosis is seen in conditions of hyperaldosteronism.

Type B intercalated cells have similar transporters, but they have reversed polarity. That is, the H^+ATPase pumps are located on the basolateral side of the cell, while the HCO_3^-/Cl^- transporters are localized to the luminal membrane. The result is a net loss of bicarbonate and a decrease in systemic pH. This result is necessary in states of alkalemia and thus functions to lower systemic bicarbonate.

Potassium. Although there is normally a net secretion of potassium in the CCT, there is the potential for potassium reabsorption through the H^+-K^+ ATPase. This becomes more relevant in states of potassium depletion, when the activity of these pumps is increased. **Although this may serve to help correct systemic hypokalemia, it is often at the expense of increased H^+ secretion and resultant systemic alkalosis**.

Medullary Collecting Tubule

The MCT is divided into the outer MCT (oMCT) and inner MCT (iMCT). Both segments contain cells similar to the principal cells and intercalated cells found in the CCT; hence, the handling of sodium, potassium, hydrogen ion, and bicarbonate is very similar. The main functional difference lies with the MCT's water and urea permeabilities, and thus its ability to concentrate the urine to levels far greater than that of plasma.

Water and Urea. The MCT is relatively impermeable to water in the basal state, but under the influence of ADH, permeability increases in both the iMCT and oMCT by the insertion of AQP-2 water channels. This allows water to move out of the tubule into the hyperosmolar interstitium, and urine concentration occurs. Equally important to this process is urea. The oMCT is relatively impermeable to urea, both in the basal state and under ADH stimulation. In contrast, the iMCT has a high basal permeability for urea, due largely to specific urea transporters (UT-A1 and UT-A3) located on the basolateral cell membrane, and, also to a lesser extent, the luminal membrane. Short-term regulation is under the influence of ADH, which can increase urea permeability as much as fourfold through an increased number of urea transporters. Longer-term regulation can be affected by protein intake. **This allows a high concentration of urea to develop in the interstitium, thus sustaining the osmotic gradient that is responsible for water reabsorption and ultimately urinary concentration** (Yang and Bankir, 2005).

Key Points: Renal Tubular Function

- The nephron has different functional segments that control homeostasis.
- Most resorption of bicarbonate and ions occurs in the proximal tubule.
- The architecture of the loop of Henle allows a highly hypertonic interstitium to develop, which is crucial to maximal urinary concentration.

Sodium. As mentioned earlier, Na reabsorption in the MCT is similar to that occurring within principal cells in the CCT. However, it has been shown that Na reabsorption is diminished in the MCT under conditions of volume expansion. This is due, in part, to the actions of ANP, which decreases Na reabsorption in the iMCT but not the oMCT. This effect seems to be due to a reduction in the number of open Na channels in the luminal membrane.

RENAL PATHOPHYSIOLOGY

Sodium and Water Imbalances

Imbalances of sodium and water are often poorly managed and understood by clinicians, despite the mechanisms and appropriate therapy being quite well documented. **The most consistent clinical misconception is that sodium concentration reflects total body sodium content.** Because sodium is primarily extracellular, the serum concentration reflects water balance. Therefore hyponatremia can occur in the face of total body sodium excess, and hypernatremia can occur with sodium deficits. For an imbalance to occur, there has to be an imbalance between sodium and water not handled by the normal mechanisms of response. **Therefore the way to approach serum sodium abnormalities is to determine the water status of the patient and then to determine why the normal compensatory mechanisms have failed** (Fig. 38–18).

Hyponatremia

By definition, hyponatremia exists if there is a water excess relative to extracellular sodium that has not been handled by the normal compensatory mechanisms of thirst suppression and decreased

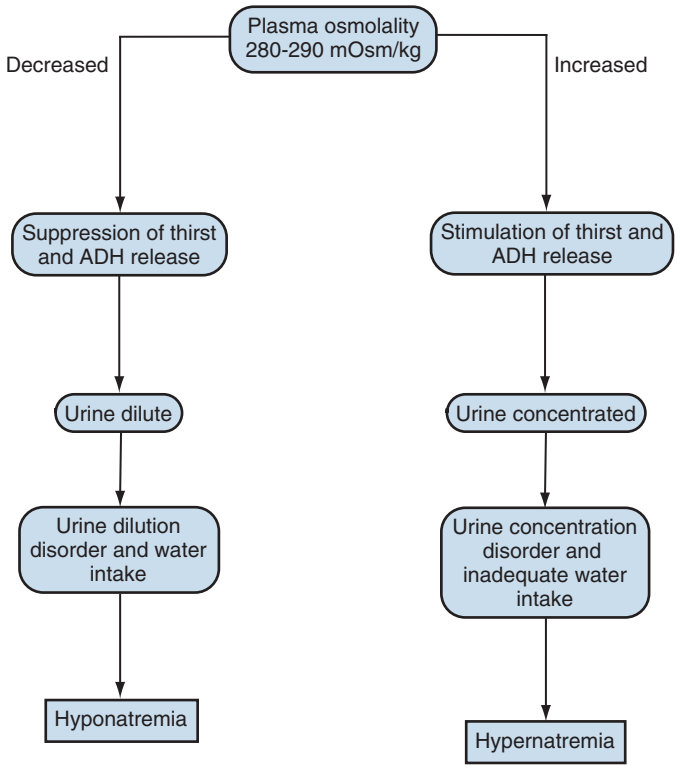


Figure 38–18. Flowchart illustrating the development of disorders of water metabolism. ADH, antidiuretic hormone.

Table 38–3.

Disorders Associated with the Syndrome of Inappropriate Antidiuretic Hormone Secretion

CARCINOMAS	PULMONARY DISORDERS	CENTRAL NERVOUS SYSTEM DISORDERS
Bronchogenic	Pneumonia (viral, bacterial)	Encephalitis (bacterial, viral)
Duodenum	Pulmonary abscess	Meningitis (viral, bacterial, tubercular, fungal)
Pancreas	Tuberculosis	Head trauma
Thymoma	Aspergillosis	Guillain-Barré syndrome
Ureter	Positive pressure breathing	Subarachnoid hemorrhage
Lymphomas	Asthma	Subdural hematoma
Ewing sarcoma	Pneumothorax	Cerebellar or cerebral atrophy
Mesothelioma	Cystic fibrosis	Cavernous sinus thrombosis
Bladder		Hydrocephalus
Prostatic		Shy-Drager syndrome
		Rocky Mountain spotted fever
		Delirium tremens
		Olfactory neuroblastoma
		Hypothalamic sarcoidosis
		Multiple sclerosis

Adapted from Levi M, Berl T. Water metabolism. In: Gonick HC, editor. Current nephrology (1983–1984), vol. 9. Chicago: Year Book Medical; 1986.

ADH release, leading to a serum sodium less than 135 mEq/L. Hyponatremia is seldom symptomatic unless severe (<120 mEq/L), but when severe and/or of sudden onset can produce seizures, altered mental state, coma and death. Most commonly hyponatremia occurs because the kidney is unable to excrete solute-free urine (Mallie et al, 1997). **To calculate the amount of water excreted or retained by the kidney, it is useful to consider that urine has two components: one that contains all of the solute in an isotonic solution (termed C_{osm}, or osmolar clearance) and another that contains only solute-free water (termed C_{H_2O} or free-water clearance).** The total urine volume (V) (e.g., liters per day) is the sum of C_{osm} and C_{H_2O}:

$$V = C_{osm} + C_{H_2O}$$

where P_{osm} = plasma osmolality and U_{osm} = urine osmolality.

When the urine is hypo-osmotic to plasma, C_{H_2O} is a positive value. **Hyponatremia occurs when one or more of these requirements are not fulfilled, such as when GFR is reduced, when diuretics impair NaCl reabsorption, or when vasopressin is in excess (e.g., SIADH).** If water intake exceeds the kidney's capacity to form solute-free water (>10 to 20 L/day), hyponatremia also occurs. This abnormality in solute-free water clearance in hyponatremic patients is reflected by the failure to excrete maximally dilute urine (U_{osm} = 100 mOsm/kg).

The diagnosis of hyponatremia is made by measurement of serum electrolytes. There are, however, several conditions in which a low serum sodium level is misleading. The reported lab value is usually in terms of sodium per volume of plasma, rather than water. If large molecules, such as lipids or protein, are present in large quantities, they decrease the amount of water in a given volume of plasma, but these molecules contribute little to plasma osmolality. **What is truly important is the amount of osmotically active solute per volume of water.** Pseudohyponatremia is most commonly seen with abnormal elevations of serum lipids or glucose. For every 1 g/dL increase in triglycerides, measured sodium is decreased by 2 mEq/L, and for every 100 mg/dL of glucose, measured sodium is decreased by 1.6 mEq/L.

Therefore the approach to a patient with true hyponatremia begins with an assessment of volume status (Fig. 38–19). Clinical features such as skin turgor, orthostatic hypotension, jugular venous distension, ascites, and respiratory crackles can all be helpful in this decision. Patients who are clinically hypovolemic by definition will have a sodium deficit greater than their water deficit. The appropriate renal response would be to excrete urine that is hypo-osmotic with a high C_{H_2O}. Therefore, if the urine is not hypo-osmotic, then the etiology is related to the kidney. Measuring the urinary sodium (U_{Na}) is a useful surrogate for urinary osmolality. Therefore a hypovolemic patient with an appropriately low U_{Na} (<20) has extrarenal sodium losses, such as from trauma, vomiting, diarrhea, burns, or third spacing. In a hypovolemic patient with an inappropriately high U_{Na} (>20), a renal source should be suspected, such as diuretic excess, osmotic diuresis, renal tubular acidosis, or mineralocorticoid deficiency. If the hyponatremic patient is hypervolemic, total body sodium can be low, normal, or high. A high U_{Na} of greater than 20 would point to renal failure. A low U_{Na} of less than 20 would suggest heart failure, cirrhosis, or nephrotic syndrome.

A patient who is euvolemic would have low or normal total body sodium. The differential diagnosis would include glucocorticoid deficiency, hypothyroidism, stress, and the syndrome of inappropriate antidiuretic hormone secretion (SIADH). **SIADH is a syndrome triggered by release of ADH by a mechanism other than low blood volume or high plasma osmolality, one associated with increased aquaporin expression in the kidney** (Kwon et al, 2001). The most common causes of SIADH are brain infections, surgery, neoplasm, and drug side effects (Table 38–3). Pharmacologic antagonists that can be used to treat patients with SIADH include lithium and demeclocycline.

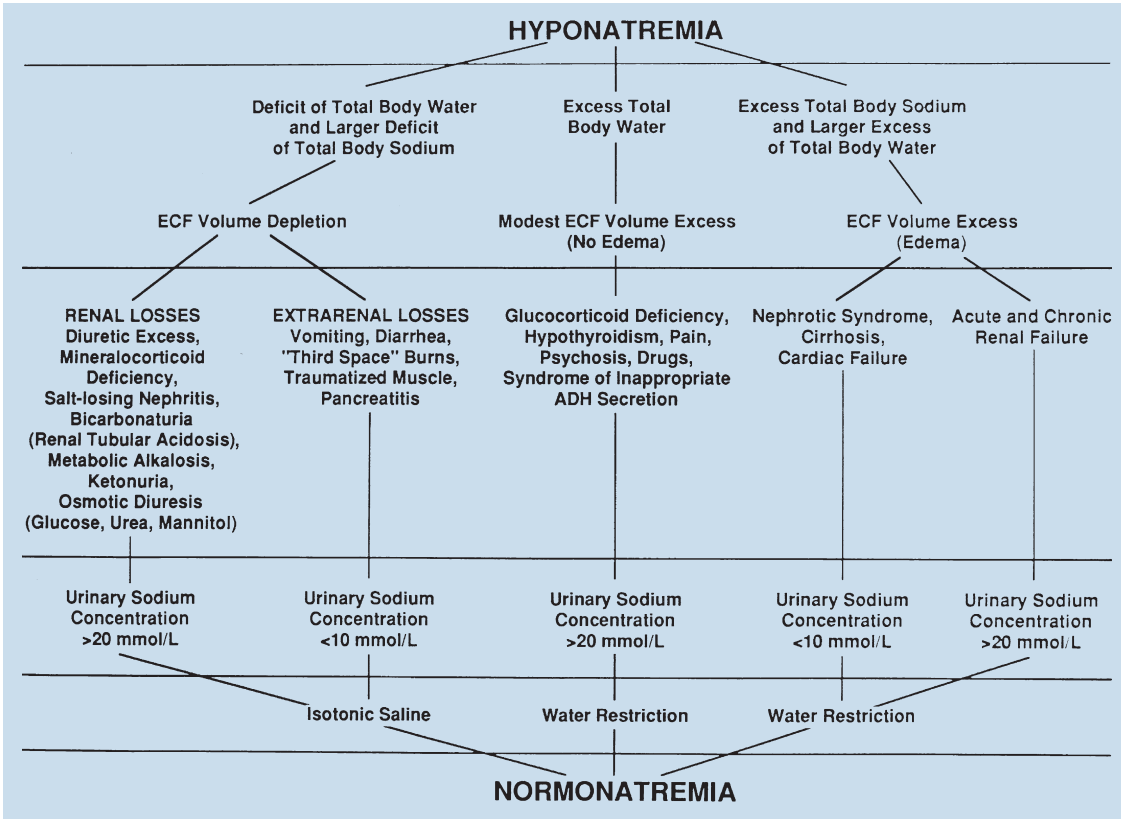


Figure 38–19. Clinical approach to patient with hyponatremia. ADH, antidiuretic hormone; ECF, extracellular fluid. (From Berl T, Anderson RJ, McDonald KM, Schrier RW: Clinical disorders of water metabolism. Kidney Int 1976;10:117–32.)

Lithium inhibits vasopressin action both proximal and distal to cAMP formation in the collecting duct (Miller, 1994). Demeclocycline, in doses ranging from 600 to 1200 mg/day, induces vasopressin-resistant diabetes insipidus that corrects the serum sodium within 1 to 2 weeks (Goh, 2004).

Therapy of hyponatremia is directed both at the cause of the condition and the water imbalance itself (Fig. 38–20). Patients with acute severe hyponatremia symptomatic with confusion, convulsions, or coma, should undergo fluid restriction plus administration of hypertonic (3%) saline (about 1 cc/kg/hr). Fluid overload is unlikely as long as fluid intake is restricted, but may be further reduced by simultaneous administration of a loop diuretic such as furosemide, which causes excretion of hypotonic fluid equivalent to half-normal saline. The serum sodium concentration should be raised to no more than 25 mEq/L in the first 48 hours, at a rate of no more than 2 mEq/L per hour, and the target goal should be 120 to 125 mEq/L. Total sodium deficit to reach this point can be calculated as

$$(\text{Volume of distribution}) \times \text{body weight (kg)} \times (125 - \text{plasma [Na]})$$

where volume of distribution is 0.5 for men and 0.6 for women. If the hyponatremia is severe but chronic, the rate of correction should not exceed 8 to 12 mmol/L/day, otherwise a cerebral demyelination syndrome may occur (Martin, 2004). Therefore the rate of correction should be slower (0.5 to 1 mEq/L/hr). During acute intervention for severe hyponatremia, frequent electrolyte measurements and patient reassessment are required. Aggressive therapy should be discontinued when the serum sodium concentration is raised 10% or symptoms subside. At that point, water restriction and reversal of underlying causes should suffice. This is also the best approach for therapy of asymptomatic hyponatremia. Obviously, patients with associated hypovolemia should have this corrected with the appropriate volume of normal saline.

Hypernatremia

The underlying problem of hypernatremia is a disorder of urine concentration with inadequate water intake (Adrogue and Madias, 2000). **Again, in hypernatremia it is the water balance that matters, and total body sodium can be high, normal, or even low.** Symptoms are nonspecific and overlap with those seen in hyponatremia, with the early occurrence of restlessness, nausea, and vomiting, which can progress to tremor, lethargy, and coma. Indeed, mortality is higher with hypernatremia than with most other electrolyte disorders. **Most patients with an intact thirst mechanism and free access to water can prevent hypernatremia** and, as such, the condition is more common at the extremes of age.

Again, the approach to a patient with hypernatremia begins with an assessment of fluid status (Fig. 38–21). Hypovolemia is common and may be due to renal conditions that fail to adequately concentrate the urine (loop diuretics, postobstructive diuresis), or to conditions of extrarenal water loss, such as seen with burns, diarrhea, or fistulas. Patients with hypervolemia will have a metabolic or iatrogenic reason for high sodium in excess of the elevated total body water. Causes include Cushing syndrome, primary hyperaldosteronism, and excessive exogenous sodium (orally or IV). Patients who are euvolemic may have renal or extrarenal losses and may be caused by diabetes insipidus, an impairment in renal concentrating ability due to lack of central production (neurogenic), or impaired renal response (nephrogenic).

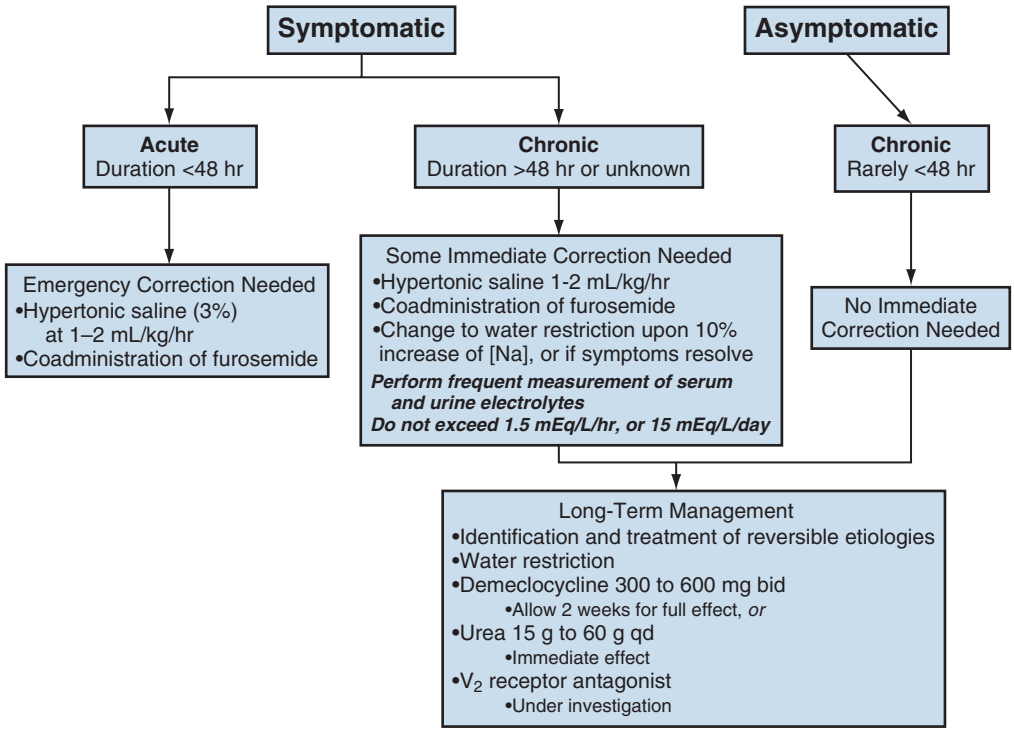


Figure 38–20. Therapy of hyponatremia. (From Halterman R, Berl T. Therapy of dysnatremic disorders. In: Brady H, Wilcox C, editors. Therapy in nephrology and hypertension. Philadelphia: WB Saunders; 1999. p. 261.)

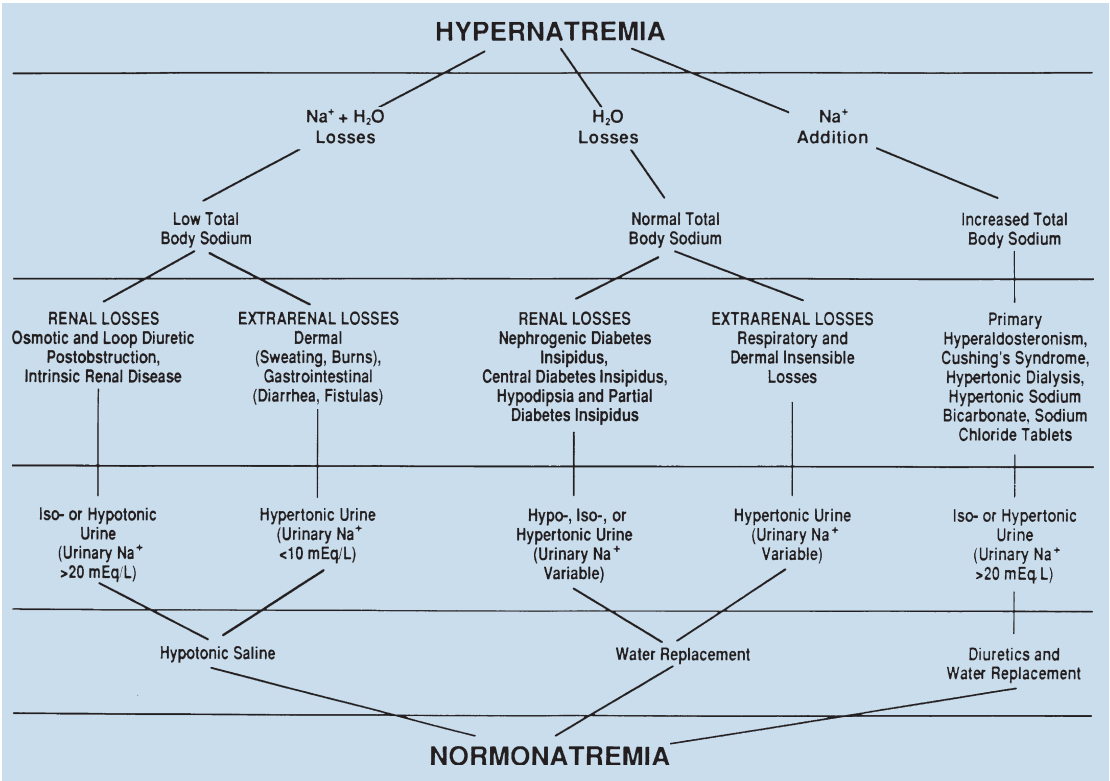


Figure 38–21. Clinical approach to patient with hypernatremia. (From Berl T, Anderson RJ, McDonald KM, Schrier RW. Clinical disorders of water metabolism. Kidney Int 1976;10:117–32.)

In neurogenic diabetes insipidus, vasopressin deficiency is most commonly caused by destruction of the neurohypophysis. To produce symptomatic polyuria, 80% to 90% of the neurosecretory neurons must be destroyed at or above the level of the infundibulum. Because of the reduced vasopressin level, the kidney excretes a high volume of dilute urine. This leads to a reduction in total body water, a rise in total-body osmolality, and thus hypernatremia. The related cellular dehydration stimulates thirst. Compensatory water intake decreases plasma osmolality (and Na^+ concentration) toward normal, but they stabilize at the threshold level for thirst, which is slightly above normal. **As in all forms of diabetes insipidus, the ability of the kidney to maximally concentrate the urine in response to vasopressin is also impaired in neurogenic diabetes insipidus. This abnormality occurs because the medullary osmotic gradient is reduced by the high urine flow.** In nephrogenic diabetes insipidus, secretion of vasopressin by the neurohypophysis is normal, but renal responsiveness to the hormone is attenuated or absent, and urinary concentrating ability is impaired (Sasaki, 2004). Several different mutations of the aquaporin gene have been identified, which contribute to the pathogenesis of this disorder (Leung et al, 2005).

Therapy of hypernatremia is directed at fluid deficit, water replacement, and reversal of underlying causes. Hypovolemia should be initially corrected with half-normal saline. If the patient is awake and not symptomatic, oral hydration with water is sufficient. Otherwise, intravenous (IV) therapy should be started with the goal of slowly lowering plasma osmolality to no more than 2 mOsm/L/hr to avoid cerebral edema. The water deficit can be calculated as

$$(\text{Volume of distribution}) \times \text{body weight (kg)} \times (\text{plasma [Na]}/140 - 1)$$

where, again, volume of distribution is 0.5 for men and 0.6 for women. For patients with central diabetes insipidus, desmopressin (a synthetic exogenous vasopressin) can be given intranasally. For nephrogenic diabetes insipidus, the underlying cause (lithium, hypercalcemia) should be treated. If polyuria persists while the kidney recovers, therapy includes modest sodium restriction, thiazide diuretics, and nonsteroidal anti-inflammatory drugs (Pattaragarn and Alon, 2003).

Key Points: Sodium and Water Imbalances

- Serum sodium represents sodium concentration, *not* total body sodium.
- The best tools to determine the cause of a sodium disorder are the history, volume status, and urinary sodium.
- Severe sodium deficit or excess must be corrected slowly.

Potassium Imbalances

Potassium is primarily an intracellular ion, and serum levels do not represent total body content in disease states. Because neuromuscular excitability is closely linked to serum potassium levels, extremes of low or high values can lead to cardiac arrhythmias and death. The body responds to changes in potassium intake and levels by controlling urinary excretion and by changing the balance between intra- and extracellular stores. **Urinary excretion can be increased in the kidney through increased aldosterone, a high sodium load in the distal tubule, and by acidosis. Potassium is driven into the cells by insulin, bicarbonate, and β-agonists.**

Hypokalemia

The most common causes of hypokalemia are increased losses through the gastrointestinal (GI) tract or urine, and increased intracellular shift of potassium in response to alkylosis (mnemonic: aLKylosis = low K^+). The most common iatrogenic causes are diuretics, laxatives, amphotericin, theophylline, and postobstructive diuresis. Metabolic causes include conditions associated with elevated aldosterone, such as adrenal adenoma, Cushing syndrome, and adrenal carcinoma. The patient may have no symptoms or present with signs and symptoms of their underlying condition (e.g., hypertension). Severe hypokalemia may produce tachycardia, heart block, and ST depression. Therapy is directed at correction of the underlying cause and oral or parenteral potassium supplementation. In general, intravenous potassium replacement should not exceed 40 mEq/hr.

Hyperkalemia

Hyperkalemia usually reflects decreased renal excretion of potassium or a shift out of cells into the extracellular space (usually by acidosis). A compromised excretory capacity can be further exacerbated by a GI bleed or hemolysis. The most common causes (Table 38–4) are renal failure, drugs (potassium-sparing diuretics, lithium, digoxin, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), chronic acidosis (e.g., renal tubular acidosis type 4), and hypoaldosteronism. Hemolysis of the drawn blood sample can falsely elevate serum potassium. Therefore when a patient has no symptoms, risk factors, or electrocardiogram (ECG) changes, but has an unexpectedly high value, the sample should be redrawn pending aggressive therapy. The classical ECG changes include a short QT interval, peaked T waves, and ultimately ventricular arrhythmias. Need for therapy is driven by the degree of elevation of potassium, the acuteness of elevation, and the presence of ECG changes. Mild hyperkalemia without ECG changes only requires dietary restriction and reversal of underlying causes. ECG changes require emergency therapy: intravenous calcium gluconate (to protect the heart) and a cocktail of drugs to drive the potassium into the cell, including sodium bicarbonate, insulin (given with glucose to avoid hypoglycemia), and nebulized albuterol (especially if there is a delay in gaining intravenous access). Therapy to increase intracellular potassium must be coupled with a therapy to remove potassium stores, or the hyperkalemia will recur once infusions stop. Potassium-binding exchange resins (kayexalate, calcium resonium) can be used for this purpose orally or by enema. Finally, hemodialysis can remove extracellular potassium the most quickly and completely.

Key Points: Potassium Imbalances

- Potassium is primarily intracellular.
- Serum potassium levels reflect total body potassium, as well as the equilibrium between intra- and extracellular potassium.
- Alkalosis produces low serum potassium.

Acid-Base Metabolism

Although the hydrogen ion (H^+) is present in miniscule concentrations in the extracellular fluid, compared with other common ions in the body, its primary importance is reflected by the multiple

Table 38–4.

Etiology of Hyperkalemia

Factitious
Laboratory error
Pseudohyperkalemia: in vitro hemolysis, thrombocytosis, leukocytosis
Increased Input
Exogenous: diet, salt substitutes
Endogenous: hemolysis, GI bleeding, catabolic states, crush injury, tumor lysis
Renal Failure
Acute: especially tubulointerstitial disease
Chronic: GFR < 15–20 mL/min
Impaired Renin-Aldosterone Axis
Addison disease
Congenital adrenal enzyme deficiencies (e.g., corticosterone methyl oxidase deficiency)
Drug induced: heparin, prostaglandin inhibitors, ACE inhibitors, pentamidine, β blockers
Hyporeninemic hypoaldosteronism
Primary hypoaldosteronism (normal renin)
Primary Renal Tubular Potassium Secretory Defect
Sickle-cell disease
Systemic lupus erythematosus
Postrenal transplantation
Obstructive uropathy
Tubulointerstitial renal disease
Pseudohypoaldosteronism
Hyperkalemic distal renal tubular acidosis
Inhibitors of Tubular Secretion
Diuretics: amiloride, spironolactone, triamterene
Cyclosporine
Lithium
Digitalis
Abnormal Potassium Distribution
Metabolic acidosis
Insulin deficiency
Hypertonicity (e.g., hyperglycemia)
Aldosterone deficiency
β-Adrenergic receptor blockade
α-Adrenergic receptor agonist
Exercise
Periodic paralysis
Digitalis
Succinylcholine

ACE, angiotensin-converting enzyme; GFR, glomerular filtration rate; GI, gastrointestinal.

Adapted from Rastegar A, DeFronzo RA. Disorders of potassium metabolism associated with renal disease. In: Schrier RW, Gottschalk CW, editors. Diseases of the kidney. 5th ed. Boston: Little, Brown; 1992. p. 1645–2661.

mechanisms that exist to control its concentration within a tight range. The reason is that small alterations in H^+ concentration has large effects on the relative concentrations of every other conjugate base and acid of all the weak electrolytes. At neutral body pH, most biologically active molecules are in their charged state and can more effectively be trapped within cells to perform their functions. Furthermore, pH determines the net charge of proteins, which influences protein conformation and enzyme binding characteristics. Outside normal blood pH (7.35 to 7.46), severe metabolic problems occur.

To maintain pH, the body has to deal with the daily production of acid. There is a large production of acid by the metabolism of carbohydrates and fats, largely in the form of carbon dioxide, at approximately 15,000 mmol per day. CO_2 is not an acid in the classical sense of the Brønsted-Lowry theory (Kildeberg, 1983), because it is not capable of donating a H^+ to a base. CO_2 can be considered a "volatile acid" because it is easily converted into H_2CO_3, carbonic acid:

$$H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons H_2O + CO_2$$

Each molecule of CO_2 excreted by the lungs results from the reaction of one molecule of bicarbonate with one molecule of H^+. The H^+ remains in the body as H_2O. The catabolism of ingested proteins to amino acids is another source of acid production, estimated at between 50 and 100 meq of H^+ per day (sulphate from the three sulphur-containing amino acids; phosphate from phosphoproteins). Because these acids cannot be excreted by the lungs, they are considered "fixed" and must be excreted by the kidneys.

Therefore the body has three primary mechanisms to handle physiologic and pathophysiologic acid loads: buffers in the blood, CO_2 excretion by the lungs, and H^+ excretion by HCO_3 metabolism in the kidneys (Vasuvattakul et al, 1992). The immediate response to an acid load is buffering. A buffer is simply a mixture of a weak acid and its conjugate base, or a weak base and its conjugate acid, that resists changes in pH when another acid or base is added. The key buffers in the blood are HCO_3 for metabolic acids and hemoglobin for CO_2. Within the cell, proteins and phosphates, which are found in higher concentrations than in the blood, become important as well. In the extracellular fluid, HCO_3 is responsible for about 80% of buffering. Changes in pH are governed by the Henderson-Hasselbach equation, which generally is

$$pH = pKa + \log \text{base/acid}$$

When specifically formulated for the bicarbonate system it becomes

$$pH = 6.1 + \log HCO_3^-/0.03 \times pCO_2$$

In general, optimal buffering occurs within 1.0 pH unit of the pKa. Therefore the pKa = 6.1 of bicarbonate buffer does not appear to be the most efficient for maintaining pH 7.4 that is required for normal homeostasis. **The bicarbonate buffer system is effective despite having a low pKa, because the body also controls pCO_2.**

Excretion of CO_2 by the lungs can occur rapidly and change both blood and intracellular pH. Elevated pCO_2 is detected by central and peripheral chemoreceptors that increase respiratory rate leading to increased alveolar ventilation. Respiratory compensation in response to a pure metabolic acidosis cannot reduce CO_2 to below 10 mm Hg and is therefore unable to maintain pH in the setting of a large acid load.

Although most of the daily acid production is volatile, and therefore excreted by the lungs, the kidneys must excrete the fixed acid, and, in doing so, also reabsorb most of the filtered bicarbonate so that efficient extracellular buffering can be maintained. A normal individual, with a GFR of 180 L/day and plasma [HCO_3^-] of 24 mEq/L, filters 4300 mEq of HCO_3^- daily from the glomerulus into the proximal tubule. Of this filtered load, less than 0.1% normally appears in the urine. **The bulk of the filtered bicarbonate is reclaimed in the proximal nephron, with approximately 80% of the filtered HCO_3^- reabsorbed within the proximal convoluted tubule.** In the tubular urine, H^+ and HCO_3^- are formed from CO_2 and H_2O in a reaction catalyzed by carbonic anhydrase (Kaunisto et al, 2002). The H^+ is returned to the tubular urine by two mechanisms: a Na^+-H^+ pump ("antiporter") and a direct H^+-ATPase proton pump. The net result

is the reabsorption of $NaHCO_3$ into the interstitial fluid and the secretion of H^+ into the proximal collecting duct urine. Note that the use of a carbonic anhydrase inhibitor, such as acetazolamide, reduces HCO_3 reabsorption and increases excretion of Na^+ and water, resulting in a weak diuretic effect (Puscas et al, 1999). The reabsorption of HCO_3 does not result in a net excretion of H^+ from the body; however, the proximal tubular reabsorption of HCO_3 is essential to preserving acid-base balance. The primary factors that increase HCO_3 reabsorption are arterial pCO_2, HCO_3 concentration in the lumen, luminal flow rate, and angiotensin II (de Mello-Aires and Malnic, 2002).

The remainder of the filtered bicarbonate is reabsorbed in the distal nephron by a mechanism independent of carbonic anhydrase. In the distal tubule, further H^+ is secreted through the production of "titratable acid," usually by buffering with phosphate. The term *titratable acidity* refers to the quantity of NaOH required to titrate urine back to a pH of 7.40, which is similar to that of blood. Other buffers, such as uric acid (pKa 5.75) and creatinine (pKa 4.97) contribute to the titratable acidity, but only to a minor extent. H^+ is also secreted through the production of ammonium ion (NH_4^+). NH_4 is produced from glutamine, primarily by proximal tubular cells (Michoudet et al, 1994). Because of its high pKa (about 9.2), it is present almost exclusively as the NH_4^+ ion. Ammonium excretion can increase significantly during systemic acidosis (Nagami, 2004), which is the key mechanism for secreting excess H^+, because at very low urinary pH, titratable acid cannot increase much (unless other ions, such as keto-anions, are being produced).

Regulation of H^+ secretion occurs through multiple biochemical and hormonal actions upon the above system. **Volume depletion** leads to Na retention and enhanced HCO_3 absorption, with a net loss of H^+. **Elevated pCO_2,** as seen in chronic respiratory acidosis (see below), will lead to a renal response of increased H^+ secretion. **Reduced GFR** will reduce the amount of filtered HCO_3, leading to increased H^+ excretion. **High aldosterone levels** indirectly increase H^+ excretion by increasing Na^+ absorption. **Low potassium and low chloride** increase HCO_3 reabsorption and can maintain chronic metabolic alkalosis.

Acid-Base Disorders

Those of us outside the fields of nephrology and anesthesia encounter acid-base disorders less commonly and are often intimidated by the process of working through the appropriate diagnosis. Nevertheless, once the terminology and basic equations are understood, the process is simple and, in many ways, mechanical (Corey, 2005). Common misconceptions begin with definition of terms. **The actual pH disturbance is an "emia," and the disease causing it is an "osis." Acidemia** refers strictly to a low arterial blood pH of less than 7.36. **Alkalemia** is a blood pH of greater than 7.44. **Acidosis** is an abnormal condition or process that would lower arterial pH if no other condition existed, and **alkalosis** is a condition that would raise pH. **The basic information required to diagnose an acid-base disturbance is a history, physical, serum electrolytes, and arterial blood gas.** If the acid-base disorder is caused by a respiratory problem, the pCO_2 will move in the opposite direction of the pH (Madias and Adrogue, 2003). If caused by a metabolic (renal) disorder, the HCO_3 will move in the same direction as the pH. In every disorder, there should be an attempt by the other acid-handling mechanism to compensate for the change. For instance, chronic loss of bicarbonate from the kidney causing a metabolic acidosis (low pH and low HCO_3) should lead to increased ventilation to try to excrete the excess acid by the lung, leading to a lower pCO_2 (respiratory compensation). In **simple** acid-base disorders, there is one mechanism causing the acid disturbance with an appropriate compensation. In **mixed** disorders, the clue to multiple mechanisms comes from significant under- or overcompensation. Although formulas have been developed to predict appropriate compensation for each disorder, visual nomograms are more practically used at the bedside.

Metabolic Acidosis

In metabolic acidosis, loss of bicarbonate leads to systemic acidemia, which produces a low arterial pH and low serum HCO_3. The appropriate compensation is increased respiration leading to a reduced pCO_2. In general, the expected degree of pCO_2 reduction is calculated as

$$\text{Expected } pCO_2 = 1.5 \times [HCO_3^-] + 8 \pm 2$$

This bicarbonate loss can be direct, or from secondary effects of other ions. The presence of active ions that are not measured in routine blood chemistry can be detected by the anion gap. The anion gap is defined as the difference between the levels of routinely measured cations (Na^+) and anions (Cl^- and CO_2) in blood:

$$\text{Anion gap} = Na^+ - (Cl^- + HCO_3^-) = 140 - (105 + 24) = 11$$

The normal range is 9 to 14 mEq/L. The predominant unmeasured anions include albumin, and phosphate. The major unmeasured cations include calcium, magnesium, and gamma globulins. If the anion gap is elevated in a patient with metabolic acidosis, the condition occurs because acids that do not contain chloride are present in the blood. The most common are ketones (diabetic ketoacidosis), lactate (lactic acidosis), and drug intoxication (methanol, aspirin) (Levraut and Grimaud, 2003).

Metabolic acidosis with a normal anion gap is caused by direct bicarbonate loss through the gut or kidney, or by the addition of exogenous acid that is buffered by bicarbonate (Table 38–5). The

Table 38–5.

Hyperchloremic Metabolic Acidosis (Normal Anion Gap)

Acid Loads
Ammonium chloride
Hyperalimentation
Ketoacidosis with renal ketone loss
Bicarbonate Losses
Diarrhea
Pancreatic, biliary, or small bowel drainage
Ureterosigmoidostomy
Drugs
Cholestyramine
Calcium chloride
Magnesium sulfate
Posthypocapnia
Defects in Renal Acidification
Proximal: decreased HCO_3^- reclamation
Distal: decreased net acid excretion
Primary mineralocorticoid deficiency
Hyper-reninemic hypoaldosteronism
Mineralocorticoid-resistant hyperkalemia
Dilutional

Adapted from Cogan MG, Rector FC Jr. Acid-base disorders. In: Brenner BM, Rector FC, editors. The kidney. 4th ed. Philadelphia: WB Saunders; 1991. p. 737–804.

patient history can give major clues to the diagnosis, either because of GI loss (vomiting, diarrhea, fistula), drug use (acetazolamide), or previous surgery (ileal conduit). Serum potassium can be a further clue to etiology. Low potassium is associated with loss through the GI tract or renal tubular acidosis because renin is stimulated from the volume contraction. In acidosis associated with severe renal dysfunction, potassium will often be elevated.

Renal Tubular Acidosis

Renal tubular acidosis (RTA) is a family of syndromes of metabolic acidosis from defects in tubular H secretion and urinary acidification. They are classified according to the mechanism of defect, and each type has different clinical manifestations.

RTA type I is the most common form and the most clinically significant to the urologist. It has also been called "classic" RTA and distal RTA. The old classification of RTA type III is now recognized as a type 1 variant. The underlying problem is failure of H^+ secretion in the distal nephron, which can be congenital or acquired. Associated disorders include autoimmune diseases (thyroiditis), toxic nephropathy, and chronic ureteral obstruction. **The hallmark is a hyperchloremic metabolic acidosis with a high urinary pH (>5.5) in the face of persistently low serum HCO_3.** If no metabolic acidosis is present but the condition is still suspected, then acid loading with ammonium chloride will drop the serum HCO_3 while maintaining a high urine pH. Volume contraction from sodium loss is common, which leads to secondary hyperaldosteronism and hypokalemia. These patients often develop recurrent renal stones, composed of calcium phosphate. The most likely contributing factor is low urinary citrate, coupled with a high urinary pH and hypercalciuria. Treatment with sodium bicarbonate can alkalinize the urine, correct the sodium defect, lower aldosterone and raise the potassium. Potassium citrate can augment the urinary citrate levels and inhibit stone formation (Domrongkitchaiporn et al, 2002).

Type II RTA, also called proximal, is caused by failure of bicarbonate reabsorption in the proximal tubule (Igarashi et al, 2002). The mechanisms of H^+ secretion in the distal tubular are overwhelmed, resulting in HCO_3 loss in the urine. The bicarbonate is replaced in the circulation by Cl^- resulting in hyperchloremia. Increased sodium delivery to the distal tubule increases aldosterone secretion resulting in hypokalemia. Ultimately, a new steady state is reached in which serum HCO_3^- is decreased, and hence, the filtered load, distal delivery, and urinary excretion of HCO_3^- are all reduced. **The acidosis is self-limited, because acid production and excretion are equivalent at this reduced pH; the plasma HCO_3^-** remains at 15 to 20 mEq/L. Because urinary citrate levels are not reduced, stone formation does not occur, despite increased urinary calcium. Because this condition is more common in children, it can lead to growth retardation and metabolic bone disease (Roth and Chan, 2001). Oral supplementation with $NaHCO_3$ can correct the condition but can lead to further hypokalemia, so potassium supplements may also be required. As an interesting aside (and possible memory aid), it was suggested that Dickens' character of Tiny Tim was based on a child with type II RTA (growth retardation, osteomalacia) that was reversed when Mr. Scrooge paid for his therapy (sodium bicarbonate).

Type IV RTA is due to impairment of cation exchange in the distal tubule, with reduced secretion of both H^+ and K^+. It is due to aldosterone deficiency or resistance. **The unique feature compared with other RTAs is hyperkalemia.** Patients often have associated azotemia and hypertension. The distal tubule H^+ pump functions normally, so patients are able to decrease urine pH to less than 5.5 in response to the acidosis. Urinary citrate may be normal or low, but renal dysfunction reduces secretion of calcium and uric acid, so stones do not form (Uribarri et al, 1994). Type IV RTA is occasionally seen in obstructive uropathy. Therapy is typically directed at controlling the hyperkalemia.

Metabolic Alkalosis

In metabolic alkalosis, the pH will be high (alkalemia) and the HCO_3 high (mirrors pH in primary metabolic disorder) (Khanna and Kurtzman, 2001). The appropriate respiratory compensation is reduced ventilation with increased pCO_2. The expected degree of respiratory compensation can be estimated by

$$\text{Expected } pCO_2 = 6 \text{ mm Hg per } 10 \text{ mEq/L increase in } HCO_3$$

An exogenous alkali load is usually rapidly excreted into the urine by the kidney, so other mechanisms are required to maintain the disorder. Maintenance of the alkalosis requires a process that greatly impairs the kidney's ability to excrete bicarbonate and prevent the return of the elevated plasma level to normal. Chloride deficiency leads to the kidney reabsorbing more bicarbonate anion than usual because there is not sufficient chloride anion present to maintain electroneutrality. This condition is reversed with fluid and chloride. Consequently, metabolic alkalosis is most conveniently classified as chloride responsive and chloride resistant.

The most common chloride responsive conditions are GI loss (vomiting, nasogastric drainage, laxative abuse) and kidney loss (diuretics). These make up over 90% of clinical cases of metabolic alkalosis (Table 38–6). Volume contraction in these conditions stimulates aldosterone production and distal secretion of H^+ and K^+. **Thus there may be a paradoxical aciduria, which will persist until volume is replaced.** Chloride-resistant metabolic alkalosis is associated with potassium loss from mineralocorticoid excess. They are associated with volume expansion and high urinary chloride levels, which can aid in the diagnosis. Common

Table 38–6.

Differential Diagnosis of Metabolic Alkalosis

MEASUREMENT	SALINE RESPONSIVE	NORMOTENSIVE: SALINE UNRESPONSIVE	HYPERTENSIVE: SALINE UNRESPONSIVE
Urinary [Cl^-]	<15 mEq/L	>15 mEq/L	>15 mEq/L
Blood pressure	Normal	Normal	Increased
Differential diagnosis	Vomiting Nasogastric suction	Diuretics Bartter magnesium deficiency	Primary mineralocorticoid excess

Adapted from Alpern RJ, Emmett M, Seldin DW. Metabolic alkalosis. In: Seldin DW, Giebisch G, editors. The kidney: physiology and pathophysiology. 2nd ed. New York: Raven; 1992. p. 2733–58.

causes are hyperaldosteronism (primary or secondary), Cushing syndrome, diuretics, and congenital conditions such as Bartter syndrome (hyperplasia of the juxtaglomerular apparatus).

Respiratory Acidosis

In respiratory acidosis, pH is low (acidemia) and pCO_2 is high, due to inadequate respiration (Epstein and Singh, 2001). The anticipated compensatory response is increased HCO_3:

Acute: Expected HCO_3 = 1 mEq/L for each 10 mm Hg pCO_2

Chronic: Expected HCO_3 = 3.5 mEq/L for each 10 mm Hg pCO_2

Elevated pCO_2 can be caused by increased production of CO_2, decreased ventilation, and increased CO_2 in the inspired air. Because increased production is usually handled quickly by increased respiration, and CO_2 does not vary except in ventilated patients, the most common cause is decreased ventilation. This can be due to central depression of respiration (e.g., opiates, trauma, cervical cord trauma), chest cavity problems (e.g., pneumothorax, pulmonary edema), upper airway obstruction, or iatrogenic causes (insufficient ventilation). Because CO_2 readily diffuses across all cellular membranes, marked elevation can severely interfere with intracellular metabolism. Clinical effects of elevated pCO_2, which are separate from acidosis per se, include elevated intracranial pressure, tachycardia, central depression, and eventually coma and death.

Respiratory Alkalosis

In respiratory alklalosis, pH is high (alkalemia) due to a low pCO_2. This is due to hyperventilation (Foster et al, 2001). The appropriate compensatory response is a lowering of HCO_3 by the following expected amounts:

Acute: Expected HCO_3 = 2 mEq/L for each 10 mm Hg pCO_2

Chronic: Expected HCO_3 = 5 mEq/L for each 10 mm Hg pCO_2

Common causes of hyperventilation that can lead to respiratory alkalosis are fever, pain, anxiety, septicemia, head trauma, pulmonary embolism, and iatrogenic (excessive mechanical ventilation). Neurological symptoms such as paresthesia and tetany may occur. Therapy is directed at improving oxygenation and ventilation.

Key Points: Acid-Base

- Physiologic chemical reactions require a narrow range of serum pH.
- Acid is excreted through the lungs and the kidney.
- Type 1 RTA (distal) is the only type associated with renal stones.
- In acid-base disorders, first determine whether the kidney (HCO_3) or lungs (pCO_2) are responsible for the primary disorder; then determine whether the compensatory response is appropriate.

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chapter 39

Renovascular Hypertension and Ischemic Nephropathy

Amr Fergany, MD, PhD ● Andrew C. Novick, MD

Historical Background
Definitions
Pathology and Natural History
Physiology of the Renin-Angiotensin-Aldosterone System
Pathophysiology of Renovascular Hypertension
Human Correlates of Experimental Renovascular Hypertension
Pathophysiology of Ischemic Nephropathy
Clinical Features of Renovascular Hypertension
Clinical Features of Ischemic Nephropathy
Diagnostic Evaluation
Cost-Effective Approach for Diagnosis
Renovascular Disease in Children
Management of Patients with Renal Artery Disease
Selection of Patients for Surgical or Endovascular Therapy
Surgical Revascularization
Percutaneous Transluminal Angioplasty
Endovascular Stenting
Other Renal Artery Diseases

HISTORICAL BACKGROUND

Richard Bright, Physician Extraordinary to the Queen of England, was the first to associate proteinuria, fullness and hardness of the pulse, and dropsy with "hardening of the kidneys" (Bright, 1827). In 1856, Traube, from an analysis of pulse tracings, suggested that the abnormality might be high blood pressure, and Mohomed (1874) demonstrated "high tension in the arterial system" in association with renal disease.

The critical experimental work was the discovery of renin by Tigerstedt and Bergemann (1898), who noted an increase in arterial blood pressure in rabbits injected with a saline renal extract. They reasoned that the renal extract contained a pressor substance and coined the term *renin*. However, the significance of their work was not recognized until the critical experiments by Goldblatt and colleagues (1934), who produced diastolic hypertension in dogs by clamping the main renal arteries and corrected the hypertension by clamp removal.

Soon thereafter, Butler (1937) reported the first reversal of hypertension after nephrectomy in a patient with a small "pyelonephritic kidney"; 1 year later, Leadbetter and Burkland (1938) reported another cure of hypertension in a child with pathologic signs of a renal arterial lesion.

These clinical observations were paralleled by laboratory investigation, and in 1940, Page and Helmer, and Braun-Menendez and associates, independently reported that renin itself was not a pressor substance but acted as an enzyme to release a pressor peptide, now called *angiotensin*, from a circulating plasma globulin. Goormaghtigh and Grimson (1939), who had previously described the juxtaglomerular cells, described increased granularity of these cells in both animals and humans with renal hypertension and postulated that these cells were secreting excessive amounts of renin.

There followed an aggressive but disappointing clinical experience with nephrectomy for cure of hypertension in patients with unilateral renal disease. This experience led to the search for a way of proving that a renal lesion was actually causing the hypertension. Smith (1948), reviewing the literature, reported relief of hypertension in only 19% of 200 patients whose elevated blood pressure was thought to result from unilateral renal disease. Thus it became apparent that even if pressor mechanisms did underlie some forms of renal hypertension, there were no ways to measure them.

This challenge led to studies of the effect of renal artery constriction on renal function. **In dogs, renal artery constriction resulted in a marked decrease in sodium and water excretion from the affected kidney** (Blake et al, 1950; Pitts and Duggan, 1950). In 1964, Howard and Connor used these observations to develop a differential renal function test based on bilateral ureteral catheterization to identify the "ischemic kidney." Another major advance was the development of translumbar aortography and the demonstration of its value in visualizing renal

arterial lesions (Smith et al, 1952). By 1957, the first large series of studies of patients with renal arterial lesions was reported (Poutasse and Dustan, 1957).

In addition, interest in what would become known as the *renin-angiotensin-aldosterone system* (RAAS) was also emerging as new discoveries were made. Accordingly, it was determined that there were two forms of angiotensin (Skeggs et al, 1954), and angiotensin was sequenced and synthesized (Bumpus et al, 1957). These critical advancements led to an accurate radioimmunoassay for angiotensin, the development of angiotensin analogues, and angiotensin-converting enzyme (ACE) inhibitors, all major tools now used to identify the patient with renovascular hypertension (RVH). More recently, the presence of a family of angiotensin receptors has been clarified (Kang et al, 1994; Goodfriend et al, 1996), and specific blockers of the angiotensin receptor have been used clinically for treatment of hypertension.

It is now recognized that the RAAS is a critical integrated system regulating not only blood pressure, sodium balance, and potassium balance but also regional blood flow and, in particular, the glomerular filtration rate (GFR) (Gunning et al, 1996; Laragh and Blumenfeld, 1996). Moreover, there is an expanding body of literature implicating angiotensin II in cell proliferation and interstitial fibrosis (Mai et al, 1993; Eng et al, 1994; Stoll et al, 1995; Egido, 1996; Gunning et al, 1996).

DEFINITIONS

Hypertension

As strange as it may seem, it has been difficult to establish a precise definition of *hypertension*. The problem was best stated by Sir George Pickering, who wrote that "there is no dividing line. The relationship between arterial blood pressure and mortality is quantitative; the higher the pressure the worse the prognosis" (Pickering and Pickering, 1995; Pickering et al, 1996). Indeed, cumulative data obtained from insurance companies have validated this point! **Untreated blood pressure in excess of 140/90 mm Hg is associated with excess mortality, and diastolic pressures below 70 mm Hg are optimal** (Lew, 1973). For operational purposes, the World Health Organization has defined hypertension in adults as a systolic pressure greater than 160 mm Hg or a diastolic pressure greater than 95 mm Hg or both. In addition, consistent elevation of blood pressure should be established with repeated readings before evaluation is instituted. In children, there is a rise in blood pressure with age; an upper normal limit of 130/80 mm Hg is reached by 12 to 15 years of age.

Renal Arterial Disease versus Renovascular Hypertension

The development of arteriography provided an accurate means of identifying renal arterial disease and heralded the advent of renal arterial vascular repair (Freeman et al, 1954), which renewed enthusiasm for surgical management of the disease. However, it soon became apparent that normotensive patients undergoing arteriography for other reasons often had renal arterial disease (Eyler et al, 1962), especially those with arteriosclerotic disease (Wilms et al, 1990), and autopsy figures supported the radiologic findings (Holley et al, 1964). Accordingly, **the finding of renal arterial disease alone is not sufficient justification to warrant correction in a hypertensive patient. The lesion must be functionally significant** (i.e., it must reduce blood flow by an amount sufficient to activate renin release, initiating RVH). Hence, **a practical definition of RVH is hypertension resulting from a renal arterial lesion that is relieved by correction of the offending lesion or removal of the kidney.**

PATHOLOGY AND NATURAL HISTORY

The two major pathologic entities that cause renal arterial disease are atherosclerosis obliterans (ASO) and fibrous dysplasia (FD). The Cleveland Clinic group has emphasized the importance of the various distinct histologic patterns, identifiable by angiographic techniques, that have predictable natural histories (Schreiber et al, 1984, 1989; Novick et al, 1994). Their classification is shown in Table 39–1.

Atherosclerosis

Approximately 70% of all renovascular lesions are caused by atherosclerosis (Novick et al, 1996). This disease may be limited to the renal artery but more commonly is a manifestation of generalized atherosclerosis, involving the abdominal aorta and coronary, cerebral, and lower extremity vessels. Atherosclerotic stenosis usually occurs in the proximal 2 cm of the renal artery, and distal arterial or branch involvement is distinctly uncommon. Owing to the proximal location of these lesions, oblique aortic views are often needed to adequately visualize the area of stenosis. The lesion involves the intima of the artery and, in two thirds of the cases, presents as an eccentric plaque (Fig. 39–1); in the

Table 39–1.

Classification and Natural History of Renovascular Disease

Atherosclerosis: Proximal intimal plaques. Seen predominantly in males and usually in older age groups. Progressive in about 40% of patients; may dissect or thrombose. May involve renal arteries only or may involve carotid and coronary arteries, aorta, and other vessels.

Intimal fibroplasia: Collagenous disease involving intima; seen in children and young adults. Progressive; may dissect. May involve other vessels.

True fibromuscular hyperplasia: Diffusely involves media. Seen in children and young adults. Progressive. Radiographically indistinguishable from intimal fibroplasia. Very rare.

Medial fibroplasia: Series of collagenous rings involving media of main renal artery, often extending into branches. Usually seen in women in their 30s and 40s. Produces typical "string of beads" pattern in angiography. Does not dissect, thrombose, or rupture, and seldom progresses after 40 years of age. May involve other vessels.

Perimedial (subadventitial) fibroplasia: Dense collagenous collar involving media, just beneath adventitia of vessel. Tightly stenotic, with extensive collateral circulation on angiography. Seen mostly in women ("girlie disease"). Progressive. Involves renal arteries only.

Miscellaneous: Renal artery aneurysms, middle aortic syndrome, periarterial fibrosis, and post-traumatic intimal or medial disease. Variable in location and obstruction; occurs in diverse clinical settings.

From Stewart BH, Dustan HP, Kiser WS, et al. Correlation of angiography and natural history in evaluation of patients with renovascular hypertension. J Urol 1970;104:231.

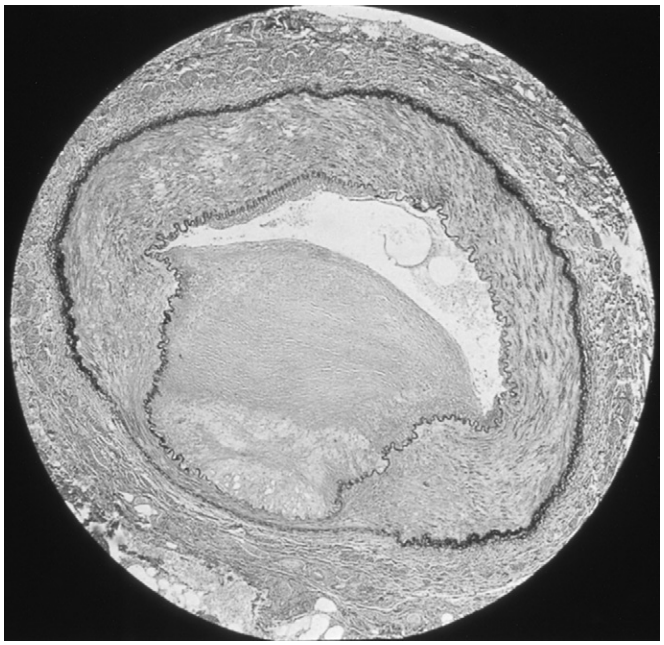


Figure 39–1. Histopathologic appearance of eccentric atherosclerotic plaque causing renal artery stenosis.

Table 39–2.

Natural History of Atherosclerotic Renal Artery Sclerosis

STUDY	PATIENTS (*N*)	PROGRESSION OF OBSTRUCTION (%)	COMPLETE OCCLUSION (%)
Wollenweber et al, 1968	30	63	NA
Stewart et al, 1970	39	36	8
Schreiber et al, 1984	85	44	16
Zucchelli et al, 1987	36	40	NA
Tollefson and Ernst, 1991	48	53	9
Zierler et al, 1994	80	42	11

NA, not available.

remainder, the vessel is circumferentially involved, with narrowing of the lumen and destruction of the intima. Dissecting hematomas frequently complicate this disease, sometimes resulting in thrombosis of the entire vessel.

The natural history of atherosclerotic renal artery disease (RAD) has been studied by obtaining sequential abdominal aortography or duplex ultrasound scanning in patients with documented renal artery lesions who have been treated medically (Table 39–2). The largest of these studies have shown that **progressive arterial obstruction occurs in 42% to 53% of patients with atherosclerotic renal artery disease, often within the first 2 years of radiographic follow-up. The incidence of progression to complete renal artery occlusion in these studies has ranged from 9% to 16%, and this has occurred more often in arteries that initially showed high degrees of stenosis.**

Schreiber and colleagues (1984) reviewed the natural history of atherosclerotic renal artery stenosis (ARAS) in 85 patients who were followed with sequential renal angiograms obtained 3 to 172 months after an initial diagnostic angiogram. Progressive obstruction of the renal artery due to atherosclerosis occurred in 37 patients (44%), including 14 (16%) in whom such progression eventuated in complete occlusion of the involved renal artery. In patients in whom progressive disease developed, it occurred primarily within the first 2 years of angiographic follow-up. The rate of progression of ARAS correlated directly with the degree of stenosis on the initial angiogram. The majority of renal arteries with mild (50%) or moderate (50% to 75%) stenosis on the initial angiogram were unchanged on follow-up angiograms. In contrast, 39% of renal arteries with more than 75% stenosis on the initial angiogram progressed to complete occlusion. Other studies have since validated this observation that **progression to 100% occlusion occurs more often and more rapidly in renal arteries that are initially involved with a high degree** (>75%) of stenosis (Tollefson and Ernst, 1991; Zierler et al, 1994).

Clinical follow-up of patients in the same study (Schreiber et al, 1984) also revealed that significantly more patients with progressive disease developed deterioration of overall renal function compared with patients with stable disease. Interestingly, **serial blood pressure control** was equivalent in these two groups, indicating that blood pressure is not a useful clinical marker for progressive ARAS.

These natural history data clearly show that **atherosclerotic renal artery disease progresses in many patients, and that loss of functioning renal parenchyma is a common sequela of such progression.** Such loss of renal function due to progressive atherosclerotic renal artery obstruction can result in end-stage renal disease (ESRD). In this setting, ESRD occurs in older patients with generalized atherosclerosis who are not suitable candidates for transplantation and whose prognosis on chronic dialysis is poor in terms of both the quality of life and longevity. An early study identified 25 patients in whom ESRD was clearly a consequence of advanced atherosclerotic renal artery disease (Novick, 1994b). Seventeen of these patients were maintained on chronic dialysis, and, of these, 13 died within 1 year (mean survival 8.7 months). The causes of death on dialysis were myocardial infarction (6), infection (2), gastrointestinal bleeding (1), ruptured aortic aneurysm (1), mesenteric infarct (1), cardiogenic shock (1), and cerebrovascular accident (1). In a subsequent study, Mailloux and colleagues (1988) analyzed the survival of patients started on dialysis from 1970 to 1985 according to the primary renal diagnosis. Patients with renovascular disease as the cause of ESRD had the poorest survival, with a 27-month median survival time and a 12% 5-year survival rate. In another study, in which 51 patients with bilateral ARAS were followed for 52 months, 12% of the patients progressed to ESRD, and an average rate of decline of GFR of 4 mL/min/yr was noted (Baboolal et al, 1998). A crude mortality rate of 45% was reported. These data further highlight that ESRD from atherosclerotic renal artery disease does not respond well to renal replacement therapy.

The exact incidence of ESRD caused by atherosclerotic renal artery disease in the United States is not known. Fatica and colleagues (2001) reported an increase in incidence of renal vascular disease (RVD) as a cause for ESRD in patients starting dialysis treatment. This increase was from 1.4% to 2.1%, with an annual increase of 12%. This information was derived from the recorded diagnosis of these patients in the U.S. Renal Data System database, and the disease was not specifically searched for. No increase in mortality on dialysis was found in these patients when compared with other etiologies of ESRD.

When investigating the use of CT angiography, van Ampting and coworkers (2003) reported a 27% incidence of significant renal artery stenosis (RAS) in 49 patients over 45 years of age starting dialysis.

Uzu and coworkers (2002) reported a higher (50%) incidence in 44 patients with ESRD who were studied by magnetic resonance angiography when additional vascular disease (cerebral, coronary, or peripheral) was also diagnosed.

In a report from England, Scoble and colleagues (1989) prospectively performed renal arteriography in all new patients with ESRD during an 18-month period. Atherosclerotic renal artery disease was the cause of ESRD in 6% of all patients, and in 14% of patients older than 50 years. Approximately 300,000 patients in the United States are currently being maintained on chronic dialysis. Their median age is older than 60 years, and a majority show evidence of generalized atherosclerosis obliterans. **Although the exact number of patients with ESRD caused by atherosclerotic renal artery disease is not known, based on the data previously described, there appear to be several thousand patients in this category**.

Fibrous (Fibromuscular) Dysplasia

Fibrous dysplasia (FD) is a nonatherosclerotic noninflammatory vascular disorder with multiple subtypes depending upon the portion of the vessel wall that is primarily involved. The vast majority of cases affect the media (medial fibroplasia); less common is perimedial fibroplasia, intimal fibroplasia, and fibromuscular hyperplasia.

Intimal Fibroplasia

Primary intimal fibroplasia occurs in children and in young adults and constitutes approximately 10% of the total number of fibrous lesions. This lesion is characterized by a circumferential accumulation of collagen inside the internal elastic lamina (Fig. 39–2). Disruption and duplication of the elastica interna occur more often in younger patients, with dissecting hematomas as a complication in many patients. The possibility of atherosclerosis as a cause of renal artery disease in this group can be excluded histologically by the absence of lipid demonstrable with special staining techniques. Intimal fibroplasia with complicating medial dissection is characterized pathologically by large dissecting channels in the outer half of the media. These lesions are thought to develop because of defects in the internal elastica with resultant medial dissection and aneurysmal dilatation.

Angiography in primary intimal fibroplasia reveals a smooth, fairly focal stenosis, usually involving the proximal or midportion of the vessel or its branches (Fig. 39–3). Dissecting hematomas may distort the area of the stenosis. With nonoperative management, progressive renal artery obstruction and ischemic atrophy of the involved kidney invariably occur. Severe intimal fibroplasia may subsequently develop de novo in the contralateral renal artery. Although primary intimal fibroplasia most commonly affects the renal arteries, it may also occur as a generalized disorder with concomitant involvement of carotid, upper and lower extremity, and mesenteric vessels.

Medial Fibroplasia

Medial fibroplasia is the most common of the fibrous lesions, constituting 75% to 80% of the total number. It tends to occur in women between the ages of 25 and 50 years and often involves both renal arteries. It may involve other vessels in the body, most notably the carotid, mesenteric, and iliac arteries. Microscopically, the internal elastic membrane is focally and variably thinned and lost. Within the alternating thickened areas, much of the muscle is replaced by collagen, hence the term *medial fibroplasia*. In other areas, thinning of the media occurs to the point of complete loss, and microaneurysms can be seen as saccules lined by only the external elastica. In extreme cases, giant aneurysms may be found in association with medial fibroplasia.

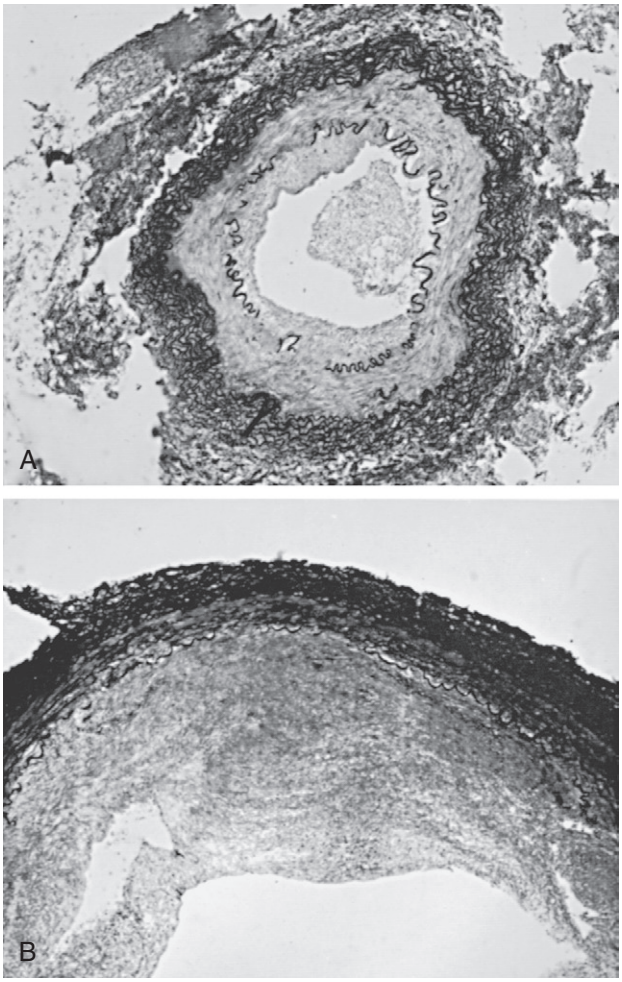


Figure 39–2. **A,** Photomicrograph of a cross section demonstrates intimal fibroplasia with focal fragmentation and partial absence of the elastica interna. **B,** Photomicrograph of cross section demonstrates severe renal arterial intimal fibroplasia with a dense cuff of intimal collagen apposed to the luminal surface of a partially disrupted elastica interna. A small recannulized channel is noted in the lower left. (From Novick AC. Renal vascular hypertension in children. In: Kelalis PP, King LR, Belman AB, editors. Clinical pediatric urology. Philadelphia: WB Saunders; 1984.)

Angiographically, medial fibroplasia demonstrates a typical "string of beads" appearance involving the distal two thirds of the main renal artery and branches (Fig. 39–4). The areas of stenosis are often overshadowed by contrast medium in the microaneurysms, making the degree of actual stenosis difficult to assess. The aneurysms themselves are greater in diameter than the normal renal artery proximal to the disease, and extreme collateral circulation is absent. These are important features in differentiating the lesion from perimedial fibroplasia.



Figure 39–3. Aortogram of a 6-year-old boy demonstrates proximal left renal artery stenosis *(arrow)* from intimal fibroplasia. (From Novick AC. Renal vascular hypertension in children. In: Kelalis PP, King LR, Belman AB, editors. Clinical pediatric urology. Philadelphia: WB Saunders; 1984.)

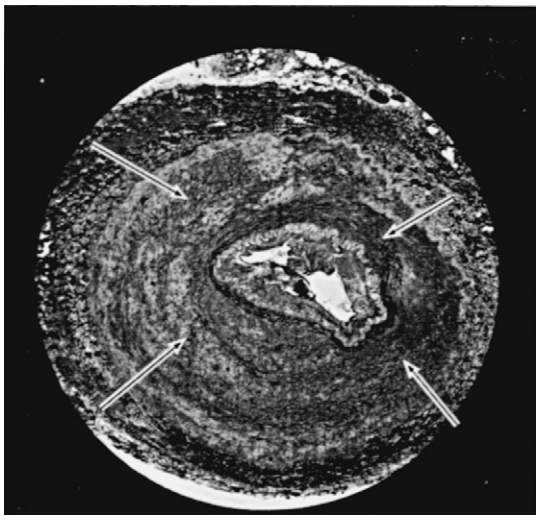


Figure 39–5. Cross section of the main renal artery in a girl with perimedial fibroplasia demonstrates a dense collagenous collar *(arrows)* involving the outer media of the vessel, which causes a severe progressive stenosis. (From Novick AC. Renal vascular hypertension in children. In: Kelalis PP, King LR, Belman AB, editors. Clinical pediatric urology. Philadelphia: WB Saunders; 1984.)

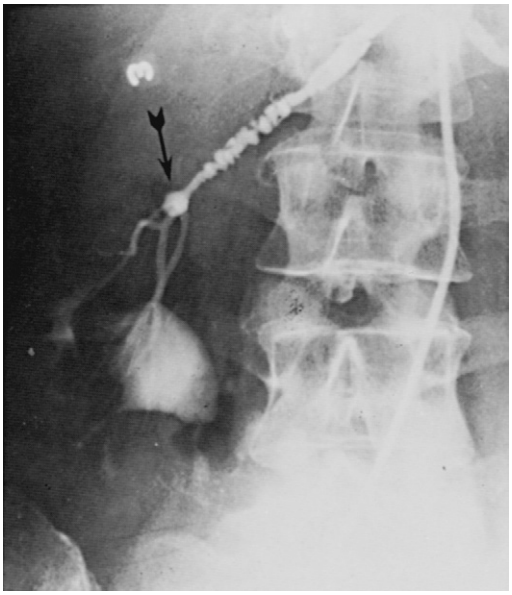


Figure 39–4. Selective right renal arteriogram reveals medial fibroplasia involving the main renal artery with typical "string of beads" appearance. (From Novick AC. Renal vascular hypertension in children. In: Kelalis PP, King LR, Belman AB, editors. Clinical pediatric urology. Philadelphia: WB Saunders; 1984.)

Schreiber and colleagues (1984) studied the natural history of renal artery disease due to medial fibroplasia in 66 patients who were followed with serial angiography. Progressive renal artery stenosis (RAS) occurred in 22 patients (33%), and, contrary to an earlier report, this occurrence was no different whether patients were older or younger than 40 years. Significantly, there were no cases of progression to total arterial occlusion in this group. Also, clinical follow-up revealed that serial decreases in either overall renal function or the size of the involved kidney seldom occurred in patients with progressive medial fibroplasia, suggesting that the risk of losing renal function is relatively small in patients with this disease who are managed medically.

Perimedial Fibroplasia

Perimedial fibroplasia occurs predominantly in young women between the ages of 15 and 30 years and has therefore been referred to, rather crudely, as *girlie disease*. It constitutes about 10% to 15% of the total number of fibrous lesions and occurs only in the renal artery. This is a tightly stenotic lesion that, pathologically, consists of a collar of dense collagen enveloping the renal artery for variable lengths and thicknesses. The collagen is deposited in the outer border of the media, usually replaces a considerable portion of the media, and may replace it completely in some areas (Fig. 39–5). Islands of smooth muscle are occasionally seen trapped within the collagenous ring. Special stains show that the lesion is confined within the external elastic lamina and contained in all cases by intact adventitial connective tissue. The arterial lumen may be further compromised by a process of secondary intimal fibroplasia. It has been suggested that this secondary thickening of the intima is related to slowing of blood flow through a narrowed arterial segment, with resultant platelet and fibrin deposition and subsequent fibrous organization.

The arteriogram in perimedial fibroplasia may give the appearance of arterial beading, but careful observation shows that the caliber of the normal segment of the vessel is not exceeded by the "bead" (Fig. 39–6). This fact, along with the frequent occurrence of extensive collateral circulation, differentiates this lesion angiographically from that of medial fibroplasia. Perimedial fibroplasia produces severe stenosis, and, although complicating thrombosis or dissection is relatively uncommon, progressive obstruction with ischemic renal atrophy occurs in almost all patients managed nonoperatively.

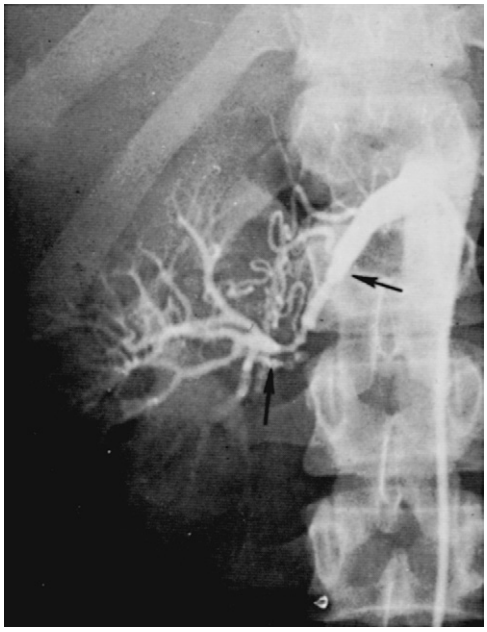


Figure 39–6. Renal arteriogram in a patient with perimedial fibroplasia shows slightly irregular, yet severe, stenosis of the midrenal artery *(arrows)* associated with extensive collateral circulation to the kidney. The small size of the arterial irregularities and the presence of collateral circulation distinguishes this lesion radiographically from medial fibroplasia. (From Novick AC. Renal vascular hypertension in children. In: Kelalis PP, King LR, Belman AB, editors. Clinical pediatric urology. Philadelphia: WB Saunders; 1984.)

Fibromuscular Hyperplasia

Fibromuscular hyperplasia is an extremely rare disease, constituting only 2% to 3% of fibrous lesions, and tends to occur in children and young adults. This is the only renal arterial disease in which true hyperplasia of the smooth muscle cells is present. The renal artery shows a concentric thickening of its wall with a mixture of proliferating smooth muscle and fibrous tissue in variable quantity. Angiographically, fibromuscular hyperplasia presents as a smooth stenosis of the renal artery or its branches and, from a radiographic standpoint, may be indistinguishable from intimal fibroplasia. Most patients with this disease have developed progressive vascular obstruction when followed with serial angiographic studies.

Key Points: Pathology of Renal Artery Stenosis

- The finding of anatomical stenosis does not denote arterial hypertension; renal artery stenosis has to be functionally significant to produce renovascular hypertension.
- The vast majority of cases of renovascular hypertension are caused by two entities: fibromuscular disease (generally younger patients) and atherosclerosis (generally older patients).
- Atherosclerosis of the renal artery is usually a component of generalized atherosclerosis, and can often be progressive, usually with associated loss of kidney function.
- Medial fibroplasia is the most common type of fibromuscular disease, and is rarely associated with progression to occlusion of the renal artery or renal function deterioration.

PHYSIOLOGY OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The RAAS plays a fundamental role in maintaining arterial blood pressure as well as extracellular volume. The system is composed of a series of proteins and peptides that react in a cascade, ultimately resulting in a widespread series of actions. Local renin-angiotensin systems are widely present in several organ systems and exert numerous local actions. **The main components of the system are angiotensinogen, renin, ACE, and various angiotensins, the most important being angiotensin II (AII). AII is a powerful vasoconstrictor that increases peripheral vascular resistance to raise blood pressure. In addition, AII stimulates sodium reabsorption directly and through stimulation of aldosterone synthesis. The primary role of the RAAS is to maintain tissue perfusion, especially in cases of hypovolemia.**

The basic cascade involves conversion of angiotensinogen to angiotensin I (AI) through the action of renin. This is the rate-limiting step for the entire system, and, accordingly, control of renin release regulates the activity of the whole system. ACE then acts on AI to produce AII, which exerts a wide variety of immediate and delayed actions on the vascular system and kidneys, as well as stimulates production of aldosterone from the adrenal cortex. In healthy subjects with normal dietary sodium intake, the RAAS probably plays a minor role in day-to-day blood pressure control. Several disease states, however, activate the RAAS. True hypovolemia or hypotension is the physiologic stimulus for AII secretion. Inappropriate activation of the RAAS occurs in cases of perceived hypovolemia, such as renal artery stenosis, congestive heart failure, or advanced hepatic disease, and leads to hypertension, inappropriate salt and fluid retention, or both.

Angiotensinogen

Angiotensinogen is a 452–amino acid protein and is the source of all angiotensins (Kageyama et al, 1984). It is formed as preangiotensinogen and loses the signal peptide as it becomes secreted from the cell as angiotensinogen. It functions as a serine protease inhibitor (serpin) similar to α_1-antitrypsin and antithrombin III, with which it shares some structural homology (Carrell et al, 1987). It is present in plasma in two forms, a smaller (52- to 60-kD) predominant molecule and a larger (450- to 500-kD) molecule that increases in pregnancy and after estrogen treatment (Tewksbury and Dart, 1982). The larger form is probably composed of the smaller molecule bound to other plasma proteins. Renin acts on the smaller form of angiotensinogen preferentially, cleaving AI off the larger molecule. Renin reacts with much less affinity with the larger form, also forming AI.

The liver is the primary site of synthesis of angiotensinogen, which is not stored but secreted directly after production. Angiotensinogen mRNA is widely present in several tissues that are regulated by local renin-angiotensin systems, including the central nervous system (CNS), kidney, adrenal, heart, and leukocytes (Dzau et al, 1987). Several hormones stimulate angiotensinogen synthesis by the liver, including estrogens and glucocorticoids. Stressful stimuli, such as infection or tissue injury, also increase plasma angiotensinogen levels (Hoj Nielsen and Knudsen, 1987). Feedback control through the RAAS is also present, with AII increasing and renin decreasing plasma levels of angiotensinogen.

Renin

Renin is a single–polypeptide chain aspartyl protease that is secreted from the juxtaglomerular cells of the afferent arteriole. **The kidney is the major site of renin production,** although renin mRNA is found in several other tissues where a local renin-angiotensin system functions. It is produced as pre-prorenin, and both active renin and prorenin are secreted (Atlas et al, 1980). The function of circulating prorenin is not clear, and it does not appear that prorenin is transformed to active renin in the circulation (Sealey et al, 1977). The action of renin is very specific, restricted to cleavage of a single bond, separating AI from angiotensinogen. Because renin controls the rate-limiting step of the RAAS, control of renin secretion regulates the activity of the RAAS. Several mechanisms affect the secretion of renin, as described in the following sections.

As the first and rate-limiting step for production of angiotensin II, targeting renin is an attractive option for inhibiting the RAAS. Recently a new class of orally effective medications targeting renin has been developed and approved for treatment of hypertension, direct renin inhibitors (DRI). The first of these medications is aliskiren, is a competitive analog and specific inhibitor of human renin, with therapeutic potential similar to other available antagonists of the RAAS (ACE inhibitors, angiotensin receptor blockers) (Nussberger et al, 2002).

Macula Densa Mechanism

The macula densa region of the thick ascending loop of Henle comes in close proximity to the juxtaglomerular cells and influences renin release. **Reduction of distal tubule salt delivery stimulates renin secretion, and vice versa.** Although sodium was initially thought to be responsible for this action, it now appears that the signal for macula densa–controlled renin release is the alteration of tubular chloride concentration (Lorenz et al, 1990).

Baroreceptor Mechanism

The juxtaglomerular cells of the afferent arteriole act as their own baroreceptors by responding directly to stretch of the afferent arteriole (Tobian et al, 1959). **Diminished cell stretch, as a result of renal hypoperfusion, hyperpolarizes the juxtaglomerular cells, resulting in decreased intracellular calcium and increased renin release.**

Neural Mechanism

The juxtaglomerular cells are richly innervated by β-adrenergic sympathetic nerve fibers. Stimulation of these β-adrenergic nerves leads to increased renin secretion (Keeton and Campbell, 1980). Dopamine is also stimulatory to renin release, although the limited number of dopaminergic nerve endings results in a much smaller role (Mizoguchi et al, 1983). Renal nerve stimulation is the mechanism through which renin release is increased as a result of exercise and tilting.

Endocrine and Paracrine Mechanisms

Several local and systemic hormones affect the rate of renin secretion. Foremost among these are prostaglandins. **Prostaglandin E_2** and **I_2** (prostacyclin), as well as exogenously administrated arachidonic acid, stimulate renin secretion (Franco-Saenz et al, 1980; Whorton et al, 1980). This prostaglandin effect is independent of the other mechanisms controlling renin release. AII inhibits renin release as a feedback mechanism. Other inhibitors of renin release include endothelin, vasopressin, and atrial natriuretic peptide.

Intracellular Mechanisms

Agents that increase adenylate cyclase activity increase the secretion of renin, including β-adrenergic agonists, prostaglandin E_2, prostaglandin I_2, dopamine, histamine, and parathyroid hormone. This is because cyclic adenosine monophosphate (cAMP) is an important second messenger in renin release. Intracellular calcium concentrations are also important in controlling renin release. AII, vasopressin, and adenosine increase intracellular calcium levels and inhibit renin secretion through their effect on intracellular calcium levels.

Angiotensin-Converting Enzyme

ACE is a zinc-containing single-chain glycoprotein enzyme. It is also known as *kininase II* and is a dipeptidyl carboxypeptidase (Ehlers and Riordan, 1989). It splits two amino acids off the carboxy terminus of AI to form AII and, at the same time, functions in the kallikrein-kinin system by inactivating bradykinin. ACE is found in a wide variety of organs, where it is primarily expressed on endothelial, epithelial, and neuroepithelial cells. A high concentration of ACE is found in the kidney, ileum, duodenum, and uterus (Lieberman and Sastre, 1983). **Although pulmonary endothelial ACE was presumed to be the major site of ACE activity for the systemic RAAS, it is now believed that peripheral sites might play an equal role.** The majority of circulating ACE originates from endothelial cells and macrophages.

ACE is expressed in several tissues where local renin-angiotensin systems function. Renal ACE is localized to the glomerular endothelial cells and the proximal tubule brush border, where it might play a role in cleaving filtered protein for reabsorption (Danilov et al, 1987). Within the CNS, ACE is found in several locations, where it functions in the local renin-angiotensin system. This local CNS renin-angiotensin system is thought to have dipsogenic and hypertensive effects as well as to stimulate vasopressin secretion (Strittmatter and Snyder, 1987). Adrenal ACE is found predominantly in the medulla, where it is thought to stimulate catecholamine secretion (Peach et al, 1971). ACE is found abundantly in the testes and prostate, in the Leydig cells, and also in cytoplasmic droplets in sperm (Pandey et al, 1984; Yotsumoto et al, 1984). In the female reproductive tract, ACE is found in follicular and fallopian tube oocytes (Brentjens et al, 1986). The precise role of ACE in the reproductive system has not been elucidated. Several hormones and disease states affect the level and activity of ACE. Corticosteroids, as well as thyroid hormones, stimulate ACE activity (Friedland et al, 1978; Smallridge et al, 1983). The serum ACE level is increased in silicosis, primary biliary cirrhosis, and sarcoidosis (Studdy et al, 1983). As mentioned previously, **ACE is not the rate-limiting step in the RAAS cascade; so, changes in serum ACE levels do not directly affect the activity of the systemic RAAS (circulating AII levels)**.

In addition to ACE, several angiotensinases act in the RAAS to lesser degrees. The physiologic contribution of these enzymes to the function of the RAAS is not clear. Most of these enzymes are present in body tissues such as the kidney. Among these are aminopeptidase A and angiotensinase A, B, and C. Nonspecific

angiotensinases hydrolyze AII and angiotensin III (AIII), inactivating them rapidly.

Angiotensin II

The role of the RAAS in the control of blood pressure and extracellular volume is carried out through the integration of a variety of actions performed by AII. Vasoconstriction and the release of aldosterone occur immediately and are of short duration, supporting the role of AII in maintaining tissue perfusion in hypovolemia. Other actions such as vascular growth and ventricular hypertrophy are slower in onset and longer in duration, lasting for several days or weeks.

Effect of Angiotensin II on Glomerular Circulation

One of the most important actions of AII is the autoregulation of the GFR in response to changes in renal perfusion. These are affected through changes in vascular resistance as well as mesangial cell tone. AII causes a marked increase in efferent arteriolar resistance in cases of renal hypoperfusion but does not affect afferent arteriolar resistance unless there is an increase in renal perfusion pressure. The result of this disproportionate increase in efferent over afferent resistance is an increase in capillary hydraulic pressure, and subsequently in filtration pressure, maintaining the GFR in the face of decreased renal perfusion (Hall et al, 1977). It is through inhibition of this action that ACE inhibitors result in a decrease in GFR in cases of renal artery stenosis. This effect of AII on the glomerular circulation is thought to be mediated through differential induction of vasodilatory prostaglandins from the afferent and efferent vessels (Hura and Kunau, 1988).

In addition to its effects on the glomerular vessels, AII directly results in mesangial cell contraction, leading to a decrease in the filtration coefficient of the glomerulus (Blantz et al, 1976).

Tubular Effects of Angiotensin II

AII-induced increases in the filtration fraction lead to an increase in the oncotic pressure in the postglomerular vessels. This leads to an increase in fluid reabsorption in the proximal tubules. AII receptors are also present on the proximal tubule brush border and basolateral sides, and AII is produced in large amounts locally within the proximal tubules. AII is present within the proximal renal tubule in much higher concentration than in the plasma (Seikaly et al, 1990). **The effect of AII on sodium reabsorption is bimodal; physiologic concentrations of AII stimulate sodium reabsorption in the proximal tubule, whereas higher concentrations inhibit sodium transport** (Harris and Young, 1977).

Medullary Effects

AII decreases medullary blood flow, leading to increased medullary hypertonicity and concentration of urine (Arendshorst and Finn, 1977).

Vascular Effects

AII raises blood pressure by increasing peripheral vascular resistance through a direct effect on vascular smooth muscle cells, causing them to contract. Medium-sized and small arteries are more responsive to AII than large vessels. Contraction occurs mainly in the vessels of the kidney, skin, mesentery, coronary arteries, and brain. Vessels of the lung and skeletal muscle are less responsive to AII. In addition to vasoconstriction, AII stimulates vascular smooth muscle cell growth, leading to a hypertrophic response (Geisterfer et al, 1988). Such smooth muscle proliferation results in left ventricular hypertrophy in cases of chronic stimulation of the RAS. AII is also involved in inflammatory processes including atherosclerosis. This cascade of cardiovascular events including hypertension, ventricular hypertophy, and atherosclerosis is felt to be central to the development of heart failure. With this mechanism in mind, interruption of the RAAS through multiple pharmacologic channels has become a major objective in lowering cardiac mortality associated with hypertension and heart failure.

Adrenal Effects

AII acts directly on the adrenal glomerulosa cells to stimulate aldosterone secretion. This is accomplished through increased desmolase activity and increased conversion of corticosterone to aldosterone (Aguilera, 1993). This augments the salt reabsorptive actions of AII to conserve sodium.

CNS Renin-Angiotensin-Aldosterone System

The CNS is affected mainly by the local renin-angiotensin system, but high circulating levels of AII may also affect CNS function. Central AII results in an increase in blood pressure as well as increased drinking and salt appetite (Sweet et al, 1971; Fitzsimons, 1980). Central AII also leads to increased secretion of corticotropin, prolactin, luteinizing hormone, oxytocin, and vasopressin (Unger et al, 1988).

Gonadal Renin-Angiotensin-Aldosterone System

Gonadal RAAS is present in both the testis and the ovary. The function of testicular RAAS is not clear; in the ovary, RAAS may play a role in oocyte maturation.

Angiotensin II Receptor Subtypes

Nonpeptide receptor antagonists have provided definite proof of at least two major angiotensin receptor subtypes, named AT1 and AT2. Both receptors are polypeptides containing 360 amino acids spanning the cell membrane several times. They are functionally distinct with a sequence homology of 30%. The gene for the AT1 receptor is located on chromosome 3, and the gene for the AT2 receptor is located on the X chromosome (Goodfriend et al, 1996). AT1 receptors are blocked by DuP 753 (losartan), and AT2 receptors are blocked by tetrahydroimidazopyridines such as PD 123177. AT1 receptors have a higher affinity for AII than AIII, but AT2 receptors bind both AII and AIII equally. AT1 receptors have been further subtyped into two isoforms, AT1A and AT1B, although the function of the subtypes is not clear.

The AT1A receptor is expressed in the liver, kidney, aorta, uterus, adrenals, ovary, spleen, and lung as well as in the hypothalamus.

The AT1B receptor is expressed in the pituitary, adrenals, kidney, uterus, and liver and is absent in the heart, brain, and spleen. In fetal life, the AT2 receptor is widely present in the adrenals, kidney, liver, skin, tongue, and brain. In the adult, this distribution becomes restricted to the adrenals, uterus, ovary, heart, and some nuclei in the brain.

In the kidneys, AT1 receptors are located predominantly in the glomeruli and tubulointerstitium, whereas AT2 receptors are located in the large cortical blood vessels (Goldfarb et al, 1994).

Almost all the vascular effects of AII, including vasoconstriction, aldosterone release, and β-adrenergic stimulation, are mediated by the AT1 receptor (Timmermans et al, 1992). The development of AT1 receptor antagonists (e.g., losartan) has produced a new class of drugs, as well as an effective tool for blocking the RAAS in a variety of disease states, including hypertension. Further, these new drugs modulate cardiac and renal injury responses to disease.

The function of the AT2 receptor has not been fully defined; however, it may act in a manner antagonistic to the AT1 receptor, especially in the cardiovascular system, where it exerts antiproliferative, antihypertrophic, and proapoptotic functions (Horiuchi et al, 1999). AT2 receptors are thus thought to mediate protective actions that counterbalance the potentially harmful actions mediated through the AT1 receptors. AT2 receptors are also believed to play a crucial role during gestational growth and development, mainly due to the widespread distribution of these receptors in most body tissues during fetal life. Reexpression of these receptors in adult life occurs as a response to vascular injury or inflammation (Horiuchi et al, 1999).

The signal transduction mechanism initiated by binding of AII to the AT1 receptor has been well described; however, the signal transduction mechanism for the AT2 receptor is not yet known. Binding of AII to the AT1 receptor leads to the dissociation of subunits of a guanine nucleotide–binding protein, which activates phospholipase C to generate diacylglycerol and inositol triphosphate. Inositol triphosphate releases calcium from the endoplasmic reticulum, and AII also increases calcium entry through the cell membrane. The intracellular calcium, as well as diacylglycerol, activates protein kinase C and other enzymes that phosphorylate protein and ultimately regulates the specific cellular function induced by AII (Goodfriend et al, 1996).

Other Angiotensins

The parent peptide of the angiotensin family is the decapeptide AI. Several other peptides are formed within the RAAS, some of which have weak activity compared with AII, and some of which have undetermined activity. As previously mentioned, AII (also called angiotensin 1-8) is the major active peptide in the system; it is an octapeptide formed by the removal of terminal histidine and leucine from the carboxy terminus of AI. AIII (or angiotensin 2-8) is similar to AII but lacks the aspartyl amino acid at the amino terminus of the polypeptide chain. It can be formed from AII or directly from AI. Angiotensin 1-7 lacks the three amino acids at the carboxy terminus of AI and has undetermined receptor activity. AIV is a hexapeptide lacking the two terminal amino acids at both ends of the AI polypeptide chain (Goodfriend et al, 1996).

The actions of angiotensin 1-7 have been defined. It appears to be formed from AI directly by a different enzyme than ACE, called neprilysin. ACE inhibitors thus increase the levels of circulating angiotensin 1-7. It acts in an opposing fashion to AII, producing vasodilatation and natriuresis, and also has antiproliferative effects on vascular smooth muscle (Chappell and Ferrario, 1999).

Key Points: Angiotensin II

- Angiotensin II is the major active component of the renin angiotensin aldosterone system; its main action is to raise blood pressure to maintain tissue perfusion.
- Angiotensin II directly stimulates aldosterone secretion from the adrenal gland.
- The kidney is the major site of renin production, which is the rate-limiting step in aldosterone II production. Renin production is stimulated by mainly by renal hypoperfusion.

PATHOPHYSIOLOGY OF RENOVASCULAR HYPERTENSION

The classic experiments on RVH were performed by Goldblatt and colleagues (1934), who demonstrated that hypertension could be produced by constricting the renal artery in the dog. Two models of experimental Goldblatt hypertension are described: the two-kidney, one-clip (2K,1C) model, in which one renal artery is clipped and the contralateral kidney is in place and normal; and the one-kidney, one-clip (1K,1C) model, in which one renal artery is clipped and the contralateral kidney is removed. RVH results in both models, but the evolution and the pathophysiologic mechanisms are different. These models provide the basis for understanding the mechanism and evolution of RVH in humans.

Two-Kidney, One-Clip Model

In the two-kidney, one-clip model, the renal artery to one kidney is clipped, resulting in ischemia of the clipped kidney. The RAAS is activated as a result of renal hypoperfusion, resulting in generalized vasoconstriction and systemic hypertension. The adrenal cortex is also stimulated, resulting in secondary hyperaldosteronism and promoting sodium retention by the stenotic kidney. This is the early phase of RVH and is totally mediated by high circulating levels of AII. The normal contralateral kidney is subjected to higher-than-normal perfusion pressure and reacts by suppression of renin secretion as well as "pressure" natriuresis, excreting higher-than-normal levels of sodium and water. Renal vein renin (RVR) from the normal kidney is equal to the arterial value, indicating no secretion by the kidney. In this manner, both kidneys work against each other, with the normal kidney preventing the systemic blood pressure and sodium content from reaching levels high enough to suppress renin release from the stenotic kidney.

Briefly, the two-kidney, one-clip model is characterized by the unilateral release of renin from the ischemic kidney accompanied by contralateral suppression of renin release from the normal kidney, sodium retention by the stenotic kidney, and excretion by the contralateral kidney; euvolemia; and hypertension dependent on AII-induced vasoconstriction. Accordingly, unclipping of the ischemic kidney, ACE inhibitors, or AII antagonists result in a marked decrease in blood pressure.

One-Kidney, One-Clip Model

In the one-kidney, one-clip model, one renal artery is clipped and the contralateral kidney is removed. The solitary ischemic kidney secretes renin, activating the RAAS and resulting in systemic

Table 39–3.
Phases of Experimental Renovascular Hypertension

Acute Phase
Renin dependency
Transitional Phase
Progressive volume and sodium retention
Gradual onset of secondary hyperaldosteronism
Thirst
Progressive suppression of renin secretion
Progressive decline of contralateral natriuresis
Chronic Phase
Volume expansion
Suppressed renin secretion
Systemic vasoconstriction
Increased sensitivity to angiotensin II
Increased vasopressin secretion
Increased sympathetic activity
Structural vessel wall changes
Development of contralateral nephrosclerosis

hypertension. Owing to the absence of the normal contralateral kidney, pressure natriuresis does not occur, and the stenotic kidney avidly conserves sodium and fluid, producing volume expansion. The elevation of blood pressure, sodium retention, and volume expansion gradually suppress renin release from the ischemic kidney. Accordingly, although the *generating* mechanism of hypertension is similar in both models, **hypertension in the one-kidney, one-clip model is largely *maintained*** by volume and sodium excess, in the face of normal circulating AII levels. ACE inhibitors or AII antagonists do not result in marked decrease of blood pressure. Under conditions of sodium depletion, hypertension once again becomes dependent on AII, with a marked response to ACE inhibition.

In addition, both models do not remain static but, rather, pass through an acute phase, a transitional phase, and then a final chronic phase (Table 39–3). In cases of two-kidney, one-clip hypertension, after several days or weeks a chronic phase is eventually reached in which unclipping of the stenotic kidney fails to normalize blood pressure. In this chronic phase, the elevated perfusion pressure, as well as high levels of AII, results in widespread arteriolar damage to the contralateral kidney. The excretory function (natriuresis) of the contralateral kidney declines, resulting in extracellular volume expansion, a decrease in circulating AII levels, and the gradual development of a "volume-dependent" type of hypertension. ACE inhibition or removal of the stenotic kidney fails to cure the hypertension in this phase of the disease unless sodium depletion is instituted. Systemic vasoconstriction continues to play a role in maintaining hypertension in the chronic phase, with increased sensitivity to AII, increased vasopressin secretion, and increased sympathetic nervous system activity.

HUMAN CORRELATES OF EXPERIMENTAL RENOVASCULAR HYPERTENSION

The situation in cases of human RVH is not as simple as the experimental models, but **in most cases human unilateral RAS resembles the two-kidney, one-clip model.** A similar sequence of events ensues, with activation of the RAAS resulting in hypertension and secondary hyperaldosteronism, sometimes resulting in hypokalemia. Relief of the stenotic lesion by revascularization or nephrectomy carries a higher chance of amelioration of hypertension if carried out before the development of a chronic phase in which parenchymal damage in the contralateral kidney maintains the blood pressure elevation.

Bilateral renal artery stenosis in humans does not clearly follow either experimental model but rather is a mixed picture with some characteristics of each. In this respect, a beneficial blood pressure response is seen with ACE inhibition, indicating overactivity of the RAAS, and there is also evidence of volume expansion with frequent pulmonary edema, as well as diuresis after revascularization. Different reasons for this mixed picture are possible, mainly owing to the asymmetrical development of renal artery stenosis, starting with unilateral disease and progressing to bilateral disease. Undetermined renal parenchymal damage may occur to the contralateral normal kidney before the onset of bilateral disease as well. Volume overload would then be exacerbated by the development of bilateral disease.

The one-kidney, one-clip model clinically resembles cases of stenosis to a solitary functioning kidney, unilateral renal artery stenosis with parenchymal damage to the contralateral kidney (nephrosclerosis or atheroembolism), and transplant renal artery stenosis.

PATHOPHYSIOLOGY OF ISCHEMIC NEPHROPATHY

In addition to RVH, a second, equally important phenomenon resulting from renal artery stenosis is deterioration of renal function, termed *ischemic nephropathy* (IN). This is a clinical syndrome that occurs through different pathophysiologic mechanisms, is distinct from RVH, and can occur in the absence of elevated blood pressure.

IN is the result of chronic hypoperfusion of the total functioning renal mass. This occurs in the setting of bilateral severe stenosis or stenosis to a functionally or anatomically solitary kidney. The pathophysiology of renal injury as a result of chronic ischemia is poorly understood. This injury is not simply cell death due to a lack of oxygen and nutrients, because the oxygen demand of the kidney never exceeds the supply. Experiments studying the effects of acute renal ischemia do not lend themselves to the explanation of chronic ischemic injury. For ischemic injury to occur, the reduction in renal blood flow needs to exceed the compensatory ability of the kidneys. Renal autoregulation fails to maintain the GFR when renal perfusion decreases below 70 to 80 mm Hg. This occurs when the luminal diameter of the renal artery is stenosed by more than 70% of the original size. At this point, the stenosis becomes hemodynamically significant, resulting in a gradual deterioration of the GFR with an accompanying rise in the serum creatinine level (Fig. 39–7).

Critical reduction of renal blood flow results in IN without affecting renal viability, because renal blood flow is severalfold higher than blood flow to other organs such as the liver or heart. This flow rate far exceeds the needs of the kidney for oxygenation but is necessary to drive glomerular filtration. It is estimated that the kidney needs only about 10% of its blood flow to maintain its oxygen requirement. Under conditions of chronic ischemia, collateral circulation to the kidney develops from the adrenal, lumbar, and ureteric vascular

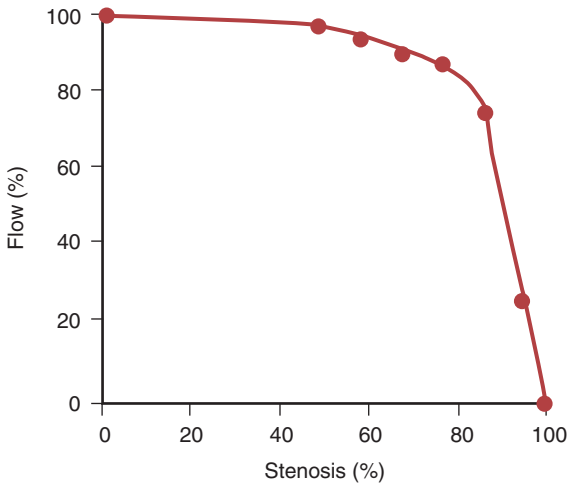


Figure 39–7. Relationship between renal artery stenosis and renal blood flow.

beds and can sustain renal viability even in cases of complete occlusion of the renal artery.

Reduction of renal blood flow activates the RAAS to produce angiotensin II, which maintains glomerular capillary hydrostatic pressure (and GFR) through efferent arteriolar vasoconstriction. Reduction of renal blood flow also leads to redistribution of blood within the kidney and diminished cortical blood flow to prevent medullary anoxia.

The cellular mechanisms by which a decrease in renal size and IN develop are not well understood. Several mechanisms play a role, including vascular mediators (endothelin, thromboxane, prostacyclin, and nitric oxide); calcium accumulation in or adenosine triphosphate (ATP) depletion of the ischemic cells; production of oxygen free radicals; or disruption of cellular membrane polarity (Textor, 1994). The exact role played by each of these mechanisms is not well defined. The action of repetitive cycles of hypoperfusion may allow renal injury to continue before repair is complete, whereas a disturbance in cellular repair processes may hinder recovery between these episodes (Textor, 1996). The point at (or mechanism through) which these changes become irreversible after relief of renal ischemia is even more poorly understood.

Although the exact mechanisms through which chronic ischemic injury of the kidneys occur are not clear, the resulting structural changes within the chronically ischemic kidney have been well identified. Tubular changes are usually most prominent, in the form of patchy tubular necrosis and atrophy. Glomeruli decrease in size, with wrinkling of the glomerular tuft and thickening of the Bowman capsule. Localized or global glomerular sclerosis is also seen. Hypercellularity of the juxtaglomerular apparatus is commonly seen. Blood vessels show the effects of comorbid conditions, such as essential hypertension, diabetes, and hyperlipidemia, with arteriolar thickening and hyalinosis.

Atheroembolism (Cholesterol Embolism)

Renal cholesterol embolism occurs most commonly in older hypertensive patients, with severe abdominal aortic ASO as the most common associated underlying cause, and contributes significantly to renal dysfunction in cases of IN (Vidt et al, 1989). Atheroembolism can occur spontaneously but more commonly follows manipulation of the atherosclerotic aorta by surgery, angiography, or the use of thrombolytic agents. In a review of 221 cases of cholesterol embolism, 69% were spontaneous, and an inciting event precipitated embolism in 31%. Renal manifestations were present in 50% of cases, and the mortality rate was 81% (Fine et al, 1987).

Atheromatous fragments lodged in blood vessels are highly thrombogenic, leading to occlusion of the vessels in which they lodge, and, at the same time, an inflammatory reaction and fibrosis are incited. Cholesterol crystals can remain histologically detectable in blood vessels for up to 9 months after the event. Diagnosis of atheroembolism is made by examination of biopsy samples from the affected tissue, most commonly skin, muscle, or kidney. Cholesterol microemboli are seen within the renal vasculature (needle-shaped cholesterol crystals, which appear birefringent on frozen section and are dissolved by the solvents used in permanent sections, leaving empty cholesterol clefts) and generally portend a poorer prognosis. In a study of 44 patients from the Cleveland Clinic, findings reflective of atheroembolism were identified on intraoperative biopsy of 16 patients (36%) at the time of open surgical renal revascularization. Patients with atheroembolism had a significantly decreased 5-year survival (54% versus 85%), compared with patients who did not exhibit histologic evidence of atheroembolism. Patients with atheroembolism had a significantly higher incidence of postoperative atherosclerotic complications as well as renal and renovascular complications (Krishnamurthi et al, 1999).

The organs most commonly affected by atheroembolism are the kidney, spleen, pancreas, and gastrointestinal tract. Virtually all organs can be affected, however, leading to multisystem organ disease. Cutaneous manifestations are the most common extrarenal manifestation, in the form of livedo reticularis (lacy bluish discoloration affecting the lower extremities), digital cyanosis or gangrene, ulceration, or subcutaneous nodules. Retinal emboli (Hollenhorst plaques) can occur, leading to visual symptoms, or can be silent.

Renal affection takes the form of deteriorating renal function, usually after a precipitating event. Decline of renal function can vary in severity from mild to rapid acute renal failure. Gradual improvement in renal function occurs after the event, but recurrent episodes lead to progressive loss of renal function with time (Siemons et al, 1987). Symptoms of renal involvement are usually absent, but new-onset hypertension or worsening of preexisting hypertension may occur.

A preventive approach to atheroembolism entails avoiding unnecessary or rough manipulation of atherosclerotic vessels, as well as avoiding prolonged anticoagulation in patients at risk for

Key Points: Ischemic Nephropathy

- Pathophysiologic aspects of renovascular hypertension differ according to the presence or absence of a normal contralateral kidney, from a euvolemic angiotensin II–dependent hypertension to a volume-expanded hypertension with a normal angiotensin II level.
- Ischemic nephropathy is the deterioration of kidney function secondary to renal artery stenosis, and follows separate and distinct pathophysiology from renovascular hypertension.
- Ischemic nephropathy occurs in the setting of bilateral significant renal artery stenosis or significant stenosis of the artery of a solitary kidney.

developing atheroemboli. **Management of cholesterol embolism is supportive, with removal of the inciting trauma if present, cessation of anticoagulation, control of hypertension, and institution of renal replacement therapy as needed.** Increased awareness of this condition has led to early diagnosis and institution of aggressive supportive care, resulting in a decline in mortality from the disease. A 1999 study of intensive multiorgan support for 67 patients reported a mortality rate of only 16%, with 32% of the survivors requiring long-term dialysis therapy (Belenfant et al, 1999).

CLINICAL FEATURES OF RENOVASCULAR HYPERTENSION

Although RVH is the most common correctable cause of secondary hypertension (with the exception of hypertension due to oral contraceptive use), the prevalence of RVH is probably less than 1% for patients with mild or moderate hypertension (Lewin et al, 1985). For this reason, before subjecting patients to numerous diagnostic procedures that are potentially invasive and costly, enough clinical suspicion needs to be generated to prevent unnecessary investigations of the patient with essential hypertension. Patients with RAS may also present with renal impairment (IN) in the presence or absence of RVH.

Clinical Clues

Symptoms suggestive of RVH are rare, with the exception of flank pain due to segmental infarction or arterial dissection, and generalized nonspecific symptoms in cases of Takayasu arteritis. The clinical course of hypertension, however, may be suggestive of a renovascular cause.

The age at presentation is a clue. The onset of hypertension before the age of 30 years or after the age of 55 years is more commonly associated with renovascular disease, typically FD in young patients and ASO in those older than 55 years. In the Cooperative Study for Renovascular Hypertension, the average age at the onset of essential hypertension was 35 years; for hypertension secondary to FD, the average age of onset was 33 years; and for atherosclerotic renal artery stenosis (ASO-RAS), the average age of onset was 46 years (Maxwell et al, 1972).

A family history of hypertension suggests essential hypertension, although there are reports of familial fibromuscular disease of the renal arteries, especially in females (Major et al, 1977; Pannier-Moreau et al, 1997).

Sudden onset and shorter duration of hypertension is usually associated with RVH; it may also be associated with a better chance of cure after treatment.

Hypertension that is difficult to control on two or three medications is more likely to be associated with renovascular disease. A sudden increase in severity or difficulty of control of previous mild or well-controlled hypertension is also suggestive of the development of RVH on top of preexisting essential hypertension.

Accelerated, malignant hypertension, or hypertensive crises are more frequently associated with RVH than essential hypertension (Simon et al, 1972).

Hypertension associated with episodes of pulmonary edema, evidence of generalized atherosclerotic disease, or gradual impairment of renal function is also suggestive of RVH.

Smoking is a risk factor for developing atherosclerotic disease. In a retrospective study comparing patients having documented RVH with patients having essential hypertension, 88% of patients with ASO-RAS were smokers, compared with 42% of patients with essential hypertension. Patients with FD also showed a higher incidence of smoking (71%) (Nicholson et al, 1983).

On physical examination, clues suggestive of RVH include severe hypertension, the presence of an upper abdominal or epigastric bruit (with both systolic and diastolic components), severe hypertensive retinopathy (grade III or IV), and evidence of generalized atherosclerosis.

Laboratory Investigations

The presence of mild *proteinuria* is not uncommon in RVH; however, nephrotic-range proteinuria has also been described with RVH (Kumar and Shapiro, 1980; Chen et al, 1995) and has been reversed by renal revascularization (Zimbler et al, 1987). Apart from renal artery disease, proteinuria may be the result of coexisting disease such as diabetes or glomerulosclerosis.

Azotemia in the presence of generalized atherosclerosis, with or without the presence of hypertension, is strongly suggestive of a renal arterial cause.

Hypokalemia (serum potassium level 3.4 mEq/L) especially in the absence of diuretic use is strongly suggestive of RVH resulting in secondary hyperaldosteronism. In the Cooperative Study for Renovascular Hypertension, 16% of patients with RVH were found to have hypokalemia (Maxwell et al, 1972).

CLINICAL FEATURES OF ISCHEMIC NEPHROPATHY

Epidemiologic Considerations

Epidemiologic studies indicate that atherosclerotic renal artery disease is quite common in patients with generalized atherosclerosis obliterans, regardless of whether or not RVH is present. These studies have involved renal angiography in patients with a documented abdominal aortic aneurysm, aorto-occlusive disease, or lower extremity occlusive disease. In such patients, the overall incidence of ARAS has ranged from 31% to 61%, with significant (>50%) ARAS present in 14% to 42% of patients (Table 39–4). In a detailed study by Olin and colleagues (1990), significant ARAS was present in 41 of 108 patients (38%) with an abdominal aortic aneurysm, 7 of 21 patients (33%) with

Table 39–4.

Prevalence of Atherosclerotic Renal Artery Stenosis (ARAS) in Patients with Peripheral Vascular Disease

STUDY	PATIENTS (*N*)	NO. WITH 50% ARAS	NO. WITH >50% ARAS
Choudhri et al, 1990	100	17 (17%)	42 (42%)
Wilms et al, 1990	100	NA	22 (22%)
Olin et al, 1990	318	71 (22%)	122 (38%)
Salmon and Brown, 1990	374	64 (17%)	52 (14%)
Swartbol et al, 1992	450	117 (26%)	104 (23%)
Valentine et al, 1993	98	36 (37%)	24 (24%)
Missouris et al, 1994	127	22 (17%)	35 (28%)

NA, not available.

aorto-occlusive disease, and 74 of 189 patients (39%) with lower-extremity occlusive disease.

Other studies have evaluated the prevalence of atherosclerotic renal artery disease in patients with coronary artery disease by obtaining abdominal aortography at the time of coronary angiography. Vetrovec and colleagues (1989) noted significant (>50%) ARAS in 22 of 76 patients (29%) with coronary artery disease. In a much larger study, Harding and colleagues (1992) found significant (>50%) ARAS in 164 of 817 patients (20%) with coronary artery disease. In the latter study, the prevalence of significant ARAS was greater in patients with more severe coronary artery disease; significant ARAS was present in 29% of patients with three-vessel disease and in 39% of patients with left-main disease. More recently, the Mayo Clinic group (Rihal et al, 2002) reported a 19% incidence of greater than 50% stenosis, 7% with greater than 70% stenosis, and 3.7% with bilateral stenosis in 297 hypertensive patients undergoing coronary angiography. Similar results are reported by Aqel and colleagues (2003) in a smaller group of 90 veterans with hypertension. A 16% incidence of severe stenosis and 6% incidence of bilateral disease were reported in this study. None of these studies reported an increase in complications related to the addition of abdominal angiography to coronary angiography. This would present a logical rationale for screening the renal arteries in patients with risk factors such as peripheral vascular disease, renal insufficiency, and hypertension.

In a large population-based study of nonselected subjects, Hansen and colleagues (2002) screened 870 patients for renal artery stenosis using duplex ultrasonography. An overall prevalence of 6.8% was noted, with 12% having bilateral disease, and stenosis was associated with hypertension, advancing age, and elevated LDL.

Another study has shown an increased prevalence of ARAS in patients with diabetes mellitus. Sawicki and colleagues (1991) evaluated 5194 consecutive autopsy protocols from patients who died between 1980 and 1988. Significant (>50%) ARAS was present in 4.3% of all patients but in 8.3% of all diabetic patients; all but one of the latter had type II diabetes mellitus. Bilateral ARAS was found in 30% of the nondiabetic patients with ARAS but in 43% of diabetic patients with ARAS. These data suggest that the presence of type II diabetes increases the risk of ARAS and that the latter is more likely to involve both kidneys.

These studies show that **ARAS is commonly present in patients with generalized atherosclerosis, particularly those with peripheral vascular disease or coronary artery disease. Although hypertension is also commonly present in such older patients with ARAS, it is far more likely to be idiopathic (essential) than renovascular in origin. Therefore, the prevalence of anatomic ARAS is much greater than that of atherosclerotic RVH.**

Screening and Diagnosis

The screening of patients for atherosclerotic renal artery disease is based, in part, on an early study by Gifford and associates (1965). These investigators found that in 53 of 75 older patients (71%) with unilateral renal atrophy, the renal atrophy was caused by stenosing atherosclerotic renal artery disease. Of equal importance was the finding that 22 of these 53 patients (42%) also had unsuspected atherosclerotic renal artery disease involving the opposite, normal-sized kidney. Subsequently, Lawrie and associates (1980) reviewed 40 patients with renal atrophy caused by total arterial occlusion and noted contralateral ARAS in 31 patients (78%). **These observations underscore the high incidence of renal artery disease, often bilateral, in patients with generalized atherosclerosis and diminished renal size. The additional finding of even mild azotemia in this setting further enhances the likelihood that underlying large vessel occlusive disease is present.**

Harding and associates (1992) evaluated clinical variables associated with ARAS in a study of 1235 patients undergoing simultaneous cardiac catheterization and abdominal aortography. **A multivariate logistic-regression analysis identified the following five risk factors as strongly predictive of significant ARAS: higher age, coronary artery disease, a history of congestive heart failure, female gender, and peripheral vascular disease. An elevated serum creatinine level was also predictive of ARAS** by univariate logistic-regression analysis. Hypertension was not helpful in identifying patients with ARAS.

Another important clinical clue to the presence of significant ARAS is the development of progressive azotemia after medical control of the blood pressure in patients with significant hypertension. This problem strongly suggests the presence of perfusion-dependent renal function due to significant underlying renal artery obstruction (Textor et al, 1983). In addition to reducing flow across a stenotic renal artery by lowering the systemic blood pressure, antihypertensive medications can impair renal function in such patients through other mechanisms as well. β-Adrenergic blockers produce a fall in cardiac output, which may occasionally diminish effective renal plasma flow and the GFR. ACE inhibitors can lead to deterioration of renal function through loss of efferent arteriolar vasoconstrictor tone in the kidney (Hricik et al, 1983).

Finally, **atherosclerotic renal artery disease should also be suspected in older patients with renal insufficiency and no obvious cause for the latter.** Corradi and associates (1993) obtained renal angiography in 51 consecutive patients with the following criteria: age older than 60 years, creatinine clearance less than 50 mL/min, no analgesic abuse, proteinuria less than 1 g/day, clinical signs of generalized atherosclerosis, and no biochemical or radiographic findings indicative of glomerulopathy, diabetic nephropathy, polycystic disease, obstructive nephropathy, or pyelonephritis. Angiographic studies revealed significant renal artery stenosis in 29 patients (56.8%); renal artery stenosis was present bilaterally in 10 patients (19.6%) and unilaterally in 19 patients (37.2%).

The studies described indicate that clinical screening for atherosclerotic renal artery disease is appropriate in older patients with most or all of the following features: (1) evidence of generalized atherosclerosis; (2) a decrease in the size of one or both kidneys; (3) renal insufficiency, even of a mild extent, particularly in patients with no obvious underlying cause; (4) the development of progressive azotemia after restoration of normotension with medical antihypertensive therapy; (5) coronary artery disease; (6) a history of congestive heart failure; and (7) peripheral vascular disease. It should be emphasized that **patients with atherosclerotic renal artery disease may or may not have significant hypertension, and this should not influence the decision to investigate the patient for this disease.**

DIAGNOSTIC EVALUATION

Several noninvasive studies are available to diagnose renal artery stenosis. Most of these studies are intended for hypertensive patients, aiming to identify those patients with a renovascular

cause of hypertension. Among these studies are rapid-sequence intravenous urography, ultrasonography, peripheral renin activity assays, captopril testing, and radionuclide renal scanning (with and without ACE inhibition). A variety of modern noninvasive tests have become available and have largely superseded the previously mentioned tests; these are duplex ultrasonography (DUS), magnetic resonance angiography (MRA), and CT angiography (CTA). These tests offer anatomic information only, with no functional information. **The definitive diagnosis of RAS, however, is documented by angiographic study of the aorta and renal vessels, which remains the "gold standard" against which all other diagnostic modalities are compared.**

Diagnostic evaluation for patients presenting with suspected RVH differs from that of patients presenting with suspected IN. **For patients with suspected RVH, a number of tests are available for functional diagnosis of RVH. These tests (plasma renin activity [PRA], captopril test, captopril renography, and RVR assays) diagnose hyperactivity of the RAAS but provide no anatomic information regarding the offending arterial lesion.** Captopril renography and RVR assays can localize the ischemic kidney as well. Anatomic delineation of the arterial lesion guides the treatment decisions and is obtained by intra-arterial angiography. A variety of noninvasive anatomic studies (DUS, MRA, and spiral CTA) can be used before angiography in cases in which clinical suspicion of RVH is not confirmed by functional tests.

The pathophysiology of RVH is different and distinct from that of IN. **The diagnostic evaluation of patients with suspected IN is hampered by the lack of functional tests** and the inability to determine conclusively that an anatomic lesion in the renal artery is responsible for impairment of renal function. Noninvasive anatomic testing is used to confirm a clinical suspicion of renal artery stenosis, which is definitively diagnosed by intra-arterial angiography. Stabilization or improvement of renal function after revascularization remains the final proof of the cause, provided that ischemic damage to the kidney has not become irreversible.

Intravenous Urogram

Until better methods were developed, a modification of the standard intravenous urogram, called the hypertensive, rapid-sequence, or minute-sequence urogram was used as a screening test for RVH. Several findings are suggestive of RVH, including a delayed appearance of contrast material in the calyces of the affected kidney (most important), disparity of renal size of more than 1.5 cm (most common finding), delayed hyperconcentration of contrast material within the affected collecting system, retention of contrast material in a nonobstructed collecting system, and notching of the pelvicalyceal system by collateral vessels.

The **poor sensitivity and specificity of the rapid-sequence urogram, as well as the development of multiple other more sensitive diagnostic tests, have led to the discontinuation of its use for diagnosing renovascular disease.**

Peripheral Plasma Renin Activity

Measurement of peripheral PRA is a functional test designed to diagnose overactivity of the RAAS. Originally intended as a screening test for RVH, it provides no anatomic information and has no value for diagnosing IN. In order to obtain meaningful results from this test, all antihypertensive medications should be discontinued for 2 weeks, and the PRA should be indexed to the sodium intake. Blood should be collected at noon after 4 hours of patient ambulation. When the test is standardized as mentioned, a sensitivity and specificity of 80% and 84%, respectively, can be expected (Pickering et al, 1984).

Important limitations to this test have restricted its general use. Sixteen percent of patients with essential hypertension have elevated PRA, whereas up to 20% of patients with RVH have normal PRA (Brunner et al, 1972). In addition, discontinuation of all antihypertensive medication in a population of patients with severe, sometimes life-threatening hypertension is not generally feasible.

Captopril Test

Measurement of peripheral PRA before and after an oral dose of captopril is called the *captopril test*. This is a functional test of RVH that does not provide anatomic information. The test is based on the observation that after the administration of ACE inhibitors, patients with RVH show a higher reactionary rise of PRA than patients with essential hypertension (Case and Laragh, 1979). Patients may continue to take β blockers, but all diuretics and ACE inhibitors need to be discontinued for at least 1 week before the test. A normal- or high-salt diet is needed. Blood should be drawn with the patient in the same position before and after captopril administration, after measurements of blood pressure are stable. An oral dose of 25 mg of captopril is used, and blood is drawn again 1 hour after the dose.

Criteria for a positive test are the presence of all the following: postcaptopril PRA greater than 12 ng/ml/hr, an absolute increase in PRA greater than 10 ng/ml/hr, and a 400% increase in baseline PRA (150% increase if the baseline PRA was more than 3 ng/ml/hr) (Muller et al, 1986). The test is generally safe, with the main risk being an excessive fall of blood pressure in hyper-reninemic patients who are also volume depleted. Overall sensitivity is about 74% and specificity is around 89% (Pickering et al, 1996). **The test is not reliable in patients who are azotemic, nor is it sufficiently accurate for use in children** (Gauthier et al, 1991).

The low sensitivity of the captopril test makes it unsuitable for use as a general screening test for RVH. The major strength of the captopril test is its accuracy in excluding RVH, especially in patients with low clinical suspicion. The high negative predictive value (approximately 95%) of captopril testing has been confirmed in several studies (Gosse et al, 1989; Svetkey et al, 1989; Frederickson et al, 1990).

Renal Vein Renins

The primary criterion for the functional diagnosis of RVH is hypersecretion of renin from the ischemic kidney combined with contralateral suppression of renin secretion. Calculation of net renin secretion from any kidney is performed by subtracting the renin value in the arterial blood to the kidney (inflow) from the renin value in the venous blood from the kidney (outflow). Because renin values in both the aorta and the inferior vena cava (IVC) are the same, IVC renin is used instead of aortic renin (Sealey et al, 1973). RVR assays are useful for localizing the ischemic kidney in unilateral renal artery stenosis, as well as the more ischemic kidney in bilateral cases. A moderate sodium intake should be maintained at the time of the sampling, which is usually performed with the patient in the

supine position. Blood samples from both renal veins as well as from the IVC are obtained.

Hypersecretion of renin from the ischemic kidney (>50% of PRA) confirms the diagnosis of RVH. Contralateral suppression of renin secretion (renal vein – IVC renin = 0) indicates an appropriate response of the normal contralateral kidney to the elevated blood pressure and predicts a cure of hypertension after revascularization. Increasing severity of stenosis reduces blood flow to the ischemic kidney, resulting in an increased RVR increment (after subtracting IVC renin) higher than 50% of the total peripheral PRA (Vaughan et al, 1973). In patients with high PRA and RVR failing to show an increment above 50% from both kidneys, sampling from segmental renal veins may be performed to localize the segment of kidney responsible for hypersecretion of renin (Schambelan et al, 1974). Administration of captopril results in accentuation of renin secretion from the ischemic kidney (similar to the captopril test), which increases accuracy in diagnosing RVH (Simon and Coleman, 1994). This is particularly useful when RVR values are equivocal, in cases of branch stenosis, and in cases of coexisting hypertension or renal disease.

Captopril Renography

Radionuclide renography without ACE inhibition has limited use for the functional or anatomic diagnosis of renovascular disease. The physiologic principle of captopril renography is the loss of preferential vasoconstriction of the efferent arteriole that is mediated by AII and maintains the glomerular pressure gradient in cases of RAS. This loss of postglomerular pressure results in a decreased GFR of the kidney distal to the stenosis, which is measured noninvasively by radionuclide renography.

The study is performed in well-hydrated patients on liberal salt intake. ACE inhibitors are discontinued for 3 to 5 days before the study, but other antihypertensives may be continued (Setaro et al, 1991). Oral hydration is continued on the day of the procedure. Oral captopril (25 to 50 mg) is usually used, although IV enalapril (0.04 mg/kg) can be used as well (Sfakianakis and Sfakianakis, 1988). The captopril renogram is obtained 1 hour after the captopril dose. The use of furosemide has also been suggested to improve the accuracy of ACE renography (Erbsloh-Moller et al, 1991).

Considerable debate continues around the optimal radionuclide agent to use for captopril renography. The most commonly used agents are technetium 99m (^{99m}Tc)–diethylenetriaminepentaacetic acid (DTPA) and iodine 131 (^{131}I)–orthoiodohippurate (OIH), with the recent addition of ^{99m}Tc-mercaptoacetyltriglycine (MAG3). The imaging characteristics of ^{99m}Tc compounds are better than that of ^{131}I compounds. On the other hand, OIH and MAG3 are excreted by both glomerular filtration and tubular secretion, whereas DTPA is excreted by glomerular filtration only, making it less optimal for patients with renal dysfunction. To date, ^{99m}Tc-MAG3 has shown the best results for captopril renography, especially in patients with impaired renal function (Dondi, 1991). Studies have shown that ^{99m}Tc-ethylenedicysteine (EC) can be used as an imaging agent for captopril renography to diagnose RVH and predict the outcome of revascularization (Ugur et al, 1999).

Captopril renographic diagnostic criteria have not been well standardized. The following are the criteria suggested by the Consensus Panel on Captopril Renography (Nally et al, 1991). Two categories of information are used: asymmetry of renal size and function as suggested by the scintigraphic images, and specific captopril-induced changes in the renogram. These changes on the postcaptopril renogram include a delayed time to maximal activity (>11 minutes), significant asymmetry of peak activity of each kidney, marked cortical retention of radionuclide, and a marked decrease in the GFR of the ipsilateral kidney. For radionuclides with tubular excretion (^{131}I-OIH and ^{99m}Tc-MAG3), the ratio of 20-minute counts to peak counts can also be used. Normally less than 0.3, a 0.15 change is considered significant. A small poorly functioning (30%) kidney that shows no change after ACE inhibition, as well as bilateral symmetrical change after ACE inhibition, is considered to be moderately indicative of RVH (Taylor et al, 1998).

The use of AT1 receptor antagonists for hypertension does not preclude the use of captopril renography as a diagnostic test. In a study comparing captopril renography in patients using AT1 receptor antagonists to hypertensive controls, Picciotto and colleagues (2003) found equally accurate results in both groups.

Overall, the sensitivity of captopril renography appears to be approximately 90% to 93%, and the specificity approximately 93% to 98% (if the test is used in patients with a strong clinical suspicion). More importantly, captopril renography is predictive of a cure or improvement in blood pressure after revascularization in 80% to 90% of cases (Nally, 1996). The presence of bilateral renal artery stenosis, renal artery stenosis to a solitary kidney, or impaired renal function (serum creatinine level > 2.5 to 3 mg/dL) decreases the accuracy of captopril renography.

Duplex Ultrasonography

DUS of the renal arteries is a noninvasive anatomic study that has shown an excellent ability to diagnose renal artery stenosis. It combines the use of real-time B-mode renal ultrasonography with color-coded pulsed Doppler to obtain blood flow velocities within the major abdominal vessels. Flow velocity at the renal hilum and inside the renal parenchyma can be measured as well. **The basis for diagnosing renal artery stenosis is the altered flow pattern distal to the stenosis, with a turbulent jet during systole and a decrease in diastolic flow**. Measurements are obtained at the proximal main renal artery using a standardized angle of incidence, and several indices as well as waveform analysis are used to diagnose stenosis. More than 180 cm/sec **peak systolic velocity (PSV) in the renal artery** is indicative of RAS (normal renal PSV averages 100 ± 25 cm/sec). PSV has been found to be the most important single indicator of RAS (Miralles et al, 1996). The ratio of the renal PSV to the aortic PSV (renal PSV/aortic PSV) is called the *renal aortic ratio* (RAR). A ratio of 3.5 or more indicates severe (>60%) stenosis. The use of the RAR is not possible in cases of aortic occlusive or aneurysmal disease because of the abnormal aortic flow patterns in these situations. Measurement of the flow patterns within the distal hilar renal artery branches, as well as within the parenchyma, can be analyzed to provide indices indicative of arterial stenosis or increased renovascular resistance (Nazzal et al, 1997; Riehl et al, 1997). These indices (acceleration time, acceleration index, resistive index) have not proved as universally reliable as the aforementioned (PSV, RAR) measurements. Intraluminal ultrasonography has also been used to measure flow rate directly within the renal artery (van der Hulst et al, 1996; Chavan et al, 1998), and this has been useful to evaluate the flow rate before and after angioplasty (Savader et al, 1998).

Diagnostic categories obtained by DUS include normal, mild stenosis (60%), severe stenosis (>60%), and technically unsatisfactory study (unable to visualize the renal arteries). Renal artery occlusion is indirectly diagnosed by the

findings of a small kidney and the inability to detect a renal artery flow pattern.

DUS offers significant advantages as a diagnostic tool for RAS. It is noninvasive, uses portable equipment that is relatively inexpensive and widely available, does not use iodinated contrast material, and has no effect on renal function. Azotemia does not affect the results of the study, and no discontinuation of antihypertensive medications is required. Repeated evaluations can be performed, which is particularly useful for postintervention and follow-up examinations.

The main disadvantage of DUS is its dependence on operator skill, with less reliable results obtained from less experienced vascular laboratories. In obese patients and patients with a lot of bowel gas, the renal arteries may be difficult to visualize. Accessory renal arteries are difficult to visualize, and occluded renal arteries cannot be diagnosed with certainty. Finally, DUS offers anatomic data with no indication of the functional significance of the lesion.

In a prospective study comparing DUS with angiography in 102 patients, DUS was found to have a sensitivity and specificity of 98%, correctly identifying the lesions in 182 of 187 arteries with different degrees of stenosis (Olin et al, 1995). In another prospective study in 41 patients, DUS (compared with angiography) revealed a sensitivity of 95% and a specificity of 90% (Strandness, 1994). In a more recent prospective study evaluating 53 patients with both DUS and angiography, a DUS sensitivity of only 75% was reported, with 103 (of 112) arteries and 12 (of 16) stenoses detected by DUS. Specificity for detecting RAS was 100% (Mollo et al, 1997).

In a study using slightly different diagnostic criteria (PSV > 210 cm/sec) and evaluating 46 patients, the sensitivity and specificity of DUS were 89.5% and 90.7%, respectively. Notably, in the same study, only 23 patients were hypertensive, and captopril renography was positive in only 5 cases (Miralles et al, 1993). The superior utility of DUS over captopril renography reported in this study was not validated in a more recent study prospectively comparing both DUS and captopril renography to angiography in 28 patients. After 11 (of 45) renal arteries were excluded from the study because no Doppler signal could be obtained, the accuracy of both diagnostic modalities was comparable, with a sensitivity and specificity for DUS and captopril renography of 78% and 81%, and 83% and 81%, respectively (Kaplan-Pavlovcic and Nadja, 1998).

Continuous developments in equipment and techniques of DUS are occurring and promise an increased accuracy and utility. Among these developments are the use of power Doppler imaging, three-dimensional imaging, harmonic imaging, and ultrasonic contrast agents. Power Doppler imaging is more sensitive, especially in the detection of low flow rates (Murphy et al, 1997). Three-dimensional imaging uses computer technology to produce a three-dimensional image of the region of interest. Harmonic imaging also improves the imaging of structures that might be moving, like the proximal renal arteries. The use of biodegradable microbubbles in the circulation increases the echogenicity and enhances the visualization of the renal vessels (Missouris et al, 1996).

Magnetic Resonance Angiography

MRA is a modern noninvasive anatomic diagnostic modality that has become available for diagnosing RAS. The techniques used for MRA are time of flight or phase contrast. Gadolinium DTPA enhances the blood signal, resulting in improved images of the aorta and the proximal renal arteries. **MRA has the advantage of being noninvasive, not using radiation, having a low technical failure rate, and not using iodinated contrast material, the latter factor making the technique suitable for use in patients with renal insufficiency** (Ghantous et al, 1999). Multiple projections can be obtained, and the morphology of the kidney can be evaluated as well. Functional information, including individual renal blood flow and GFR, can also be obtained (Grist, 1994).

The emergence of nephrogenic systemic fibrosis (NSF) with the use of gadolinium MRI contrast agents in patients with renal impairment has received much attention lately and has severely limited contrast MRI use in these patients. This is a rare but potentially life-threatening condition that results from dissociation of gadolinium from its parent compound and chelation with endogenous cations, thus liberating toxic free gadolinium. Affected patients develop multisystem fibrosis affecting primarily the skin, with devastating consequences. Most of the reported cases occurred in patients on dialysis; some studies report that the condition is more likely to occur in patients with acidosis (Broome et al, 2007).

MRA provides an image quality that is inferior compared with angiographic images. Only the proximal parts of the main renal arteries are visualized, without the ability to image the distal arterial tree. MRA is contraindicated in patients with magnetic implants and claustrophobia, and it uses sophisticated expensive equipment that might not be widely available.

MRA was compared with intra-arterial angiography in 103 patients, all of whom had both studies performed. When MRA was used, all main renal arteries and 31 of 33 accessory renal arteries were visualized, and 61 of 65 stenoses were diagnosed and graded correctly. The overall sensitivity was 93% and the specificity was 90% (Hany et al, 1998). Another study evaluated 62 patients with both MRA and angiography (Thornton et al, 1999). MRA had a sensitivity of 88% and a specificity of 98% and visualized 93% of all the arteries seen on angiography. The reproducibility of interpretation and interobserver variability of MRA were found to be comparable with those of conventional angiography in 54 patients who underwent both diagnostic procedures (Gilfeather et al, 1999).

A prospective study compared gadolinium-enhanced MRA to color DUS in 45 patients, and the results of both examinations were referenced to angiography in all cases (De Cobelli et al, 2000). Out of 13 accessory renal arteries detected by digital subtraction angiography (DSA), 12 were detected by MRA and only 3 were detected by DUS. The sensitivity and specificity of MRA were 94% and 91% for diagnosing all degrees of stenosis, whereas the sensitivity and specificity of DUS were 71% and 76%. For the detection of stenoses of more than 50%, the corresponding values were 93% and 95% for MRA, compared with 93% and 89% for DUS. Another group (Leung et al, 1999) compared the two modalities (and referenced results to DSA studies) and reported similar results, with slightly better sensitivity and specificity for MRA (90% and 86%) compared with DUS (81% and 87%). This study also confirmed the superior ability of MRA over DUS in detecting accessory renal arteries (96% vs. 5%). MRA was more sensitive in detecting RAS due to ASO than in detecting RAS due to FD, according to this study; this could be related to the more distal nature of most FD lesions. MRA can also diagnose renal artery aneurysms, and is useful for following the size of renal artery aneurysms over time, although aneurysms distal to the primary

branches of the renal artery are not well visualized on MRA (Browne et al, 2004).

Improved techniques and increased experience with MRA continue to increase its accuracy and utility. The use of time-resolved imaging to decrease artifacts, decrease venous overlap, and improve spatial resolution and contrast enhancement has been reported (Van Hoe et al, 2000). Gadolinium has been administered intra-arterially in vitro in an attempt to improve visualization of blood vessels (Omary et al, 1999). Multiecho gradient echo technique for three-dimensional MRA has been reported to produce high vessel-to-background contrast with decreased bowel-related artifact (Papachristopoulos et al, 1999). Although the recognition of nephrogenic systemic fibrosis (NSF), a serious complication of using gadolinium-based contrast agents for MRI in patients with renal insufficiency, has hampered the use of MRI in many patients with renal artery stenosis, several precautions have been recommended that may allow MRI contrast agents to be used with minimal risk. Cyclic gadolinium–based contrast agents have less chance of causing NSF if using smaller doses of contrast, and if avoiding gadolinium agents altogether in patients with estimated GFR of less than 30 mL/min or in patients with metabolic acidosis (Boyd et al, 2007; Othersen et al, 2007).

MRI has the potential to provide other important information, in addition to anatomical depiction of the arterial stenosis. Gadolinium clearance can be used to measure single-kidney glomerular filtration rate, and renal volume can be measured and followed to evaluate recovery after revascularization. Loss of corticomedullary differentiation and increased cortical-medullary transit time can also indicate renal ischemia, and reversal of these findings may indicate successful revascularization (Chrysochou et al, 2008).

Computed Tomography Angiography

The availability of spiral CT technology with rapid acquisition time has made possible imaging of the renal arteries. Scanning through the area of the renal arteries using thin (2-mm) slices during the arterial phase of contrast material injection is performed while the patient holds a single breath. Three-dimensional reconstruction of the axial image is then carried out, showing the abdominal aorta with its main branches. Atherosclerotic disease affecting the aorta and the renal arteries can be visualized, as well as renal morphology and parenchymal lesions. **Spiral CTA lacks the ability to define disease distal to the main stem renal artery, and a relatively large volume of intravenous (IV) iodinated contrast material is required to perform the study;** however, CTA might offer the advantages over MRA of cost, convenience, and widespread availability (Prokop et al, 1998).

Comparison between CTA and DSA in 82 patients revealed a sensitivity and specificity of 96% and 99%, respectively, for hemodynamically significant stenosis, with only 1 stenosis (of 34) missed on CTA. Thirty-three accessory renal arteries were visualized in this study, as well as 5 adrenal masses (Wittenberg et al, 1999). In another study evaluating 50 patients with suspected RAS, CTA showed a sensitivity of 90% and a specificity of 97% and demonstrated 27 of 28 accessory renal arteries (Kim et al, 1998). Modern CT technology can also be used to perform virtual endoscopy, which can be helpful for evaluating renal artery stenoses and positioning arterial stents (Neri et al, 2000). Multiple detector–row CT angiography is a new method of CT angiography that also promises more accurate depiction of the renal and other visceral arteries (Fleischmann, 2003; Pannu et al, 2002).

In order to clarify the various limitations of noninvasive imaging modalities in respect to accessory renal arteries as well as proximal branches of the renal artery, a study compared DUS, CTA, and MRA to angiography. The points of comparison were the ability to evaluate accessory renal arteries and proximal branches. Fifty-six patients underwent angiography; of those patients, 45 underwent DUS, 52 underwent CTA, and 28 underwent MRA. When angiography was used, 28 accessory renal arteries as well as 21 proximal (>2 cm from the aorta) renal artery branches were visualized. DUS depicted 21% of the accessory arteries and 0% of the proximal branches. MRA depicted 73% of the accessory arteries (and four additional arteries not seen on angiography), and 0% of the proximal branches. CTA depicted 92% of the accessory arteries and 76% of the proximal branches. Although experience with modalities differs among institutions, this study offers an interesting comparison of the limitations of these techniques (Halpern et al, 1999).

In a more recent study comparing MRA against CTA with intra-arterial DSA as the reference standard, there was no significant difference in the accuracy of both MRA and CTA, with sensitivity around 92% and specificity around 99% for both modalities. Patient acceptance was also measured, and estimated to be best for CTA, although the time consumed for reconstruction of the images was most in CTA (Willmann et al, 2003).

Contrast Arteriography

Intra-arterial angiography remains the gold standard for diagnosing renal artery disease, and it is the test against which the results of other tests are compared. The availability of modern interventional techniques (angioplasty and arterial stents) has allowed angiography to become a combined diagnostic and therapeutic procedure. However, for several reasons, angiography is not suitable for use as a preliminary screening tool for all patients suspected of having renal artery stenosis. It is an expensive test that cannot be done on an outpatient basis. It is also an invasive test using ionizing radiation and requiring arterial puncture, manipulation of arterial catheters, and injection of iodinated contrast material.

Complications of arterial puncture and manipulation include bleeding, hematoma, dissection, thrombosis, and distal embolization of atherosclerotic plaque, as well as cholesterol embolization. The use of iodinated contrast material carries the risk of allergic reaction and volume overload. The contrast load also leads to a transient impairment of renal function, especially in patients with preexisting renal insufficiency and in diabetic patients. Several advancements in the field of angiography have been directed at decreasing side effects from iodinated contrast material. These advancements include decreasing the contrast load through digital postprocessing, as well as the use of contrast agents with decreased nephrotoxicity, such as carbon dioxide or gadodiamide (Spinosa et al, 1999). The advent of digital subtraction angiography (DSA) has allowed reduction of the contrast load with a concomitant reduction in catheter size. Although the spatial resolution of DSA is lower than that of conventional angiography, the contrast resolution of DSA is superior. The ability to subtract bone and soft tissue with DSA is an important advantage, making conventional cut film angiography obsolete, and DSA the most commonly used technique today.

Early in the development of digital techniques, it was suggested that IV studies (IV-DSA) would be accurate and supersede the arterial approach (Wilms et al, 1986). The attraction of visualizing the renal arteries angiographically with an outpatient procedure was not realized, however. Several disadvantages led to the gradual abandonment of IV-DSA in favor of intra-arterial studies. These

disadvantages include the need for a large contrast material volume, the frequent need for central venous catheters to deliver this large volume, poor image quality owing to overlying visceral arteries, frequent uninterpretable studies, and poor opacification, especially in elderly patients or those with cardiac dysfunction (Buonocore et al, 1981; Smith et al, 1982).

Carbon dioxide has been introduced as a contrast agent for intra-arterial injection in an effort to reduce contrast nephrotoxicity from iodinated contrast material. An injected bolus of carbon dioxide displaces blood from the vessels to be imaged and provides sufficient contrast for adequate imaging using DSA technology and postprocessing enhancement. The injected carbon dioxide is cleared by the lungs without deleterious effects. Carbon dioxide has no effect on renal function, making it an ideal agent for use in patients with renal insufficiency. It is nonallergenic, cheap, and presents no problems with fluid overload. Smaller softer arterial catheters can be used for injection, minimizing trauma to the arterial walls. This technique can also provide information that is not visualized using standard iodinated contrast material, including small arteriovenous shunts, small tumor vessels, and minute amounts of arterial bleeding (Hawkins et al, 1994).

In a prospective study comparing carbon dioxide angiography with standard contrast arteriography in 100 patients, the overall accuracy of carbon dioxide DSA was 97% (Schreier et al, 1996). Carbon dioxide DSA was successfully used for guiding angioplasty and renal artery stenting in 17 patients in another study, with only one transient rise in the serum creatinine level (Caridi et al, 1999). Similarly, no cases of contrast nephropathy were reported in a study employing carbon dioxide DSA as the main imaging technique for patients with renal impairment (Fitridge et al, 1999). Carbon dioxide renal angiography has been used safely in children (Kriss et al, 1997). Although carbon dioxide is generally regarded as a benign contrast medium, a case of fatal complications (rhabdomyolysis and intestinal infarction) after carbon dioxide angiography has been reported (Rundback et al, 1997).

Ailawadi and colleagues (2003) evaluated the use of gadolinium as a contrast agent for intra-arterial angiography in patients with renal insufficiency and found it to be safe and adequate for imaging the renal arteries as well as first- and second-order branches. No comparison with conventional contrast angiography was performed, but this might be an option to decrease nephrotoxic side effects of angiography. Significant concern about NSF in patients with renal insufficiency will undoubtedly limit the use of gadolinium-based contrast agents in patients with renal impairment.

COST-EFFECTIVE APPROACH FOR DIAGNOSIS

The diagnostic approach for patients with renal artery stenosis should be tailored according to the predominant clinical picture, that is, patients with IN should be worked up differently from patients with hypertension as the presenting clinical problem. As mentioned previously, **patients with IN constitute the majority of patients presenting for treatment today, may not have hypertension as part of the clinical picture, and cannot be diagnosed by functional testing. In these patients, an anatomic diagnosis is pursued directly.** Patients with a strong suspicion of renal arterial disease should probably undergo intra-arterial angiography (iodinated contrast material or carbon dioxide) directly. Patients with mild or moderate suspicion of having renal artery stenosis should undergo a noninvasive anatomic test (DUS, MRA, or CTA). The choice of diagnostic procedure depends on patient's level of renal function (azotemic patients more suitable for DUS than CTA), as well as the experience with the various modalities at different centers. Positive findings on noninvasive testing should lead to definitive confirmation of the lesion and therapeutic planning through intra-arterial angiography. Negative findings on these tests should be interpreted with understanding of the limitations of each technique and should lead to further noninvasive testing if technical factors are suspected, or to no further testing if a technically perfect study is clearly negative in a patient with minimal clinical suspicion.

Patients with suspected RVH present a different diagnostic challenge. Functional evaluation of the RAAS is possible and is usually performed as a first step in the diagnosis before anatomic diagnosis. The steps used to screen and select patients for further study differ according to different centers and have changed over the last years, mainly owing to the introduction of reliable noninvasive anatomic imaging techniques.

Patients should be ranked according to the clinical findings suspicious for RVH into patients with low, moderate, and high suspicion. Like patients with IN, patients with a high suspicion for RVH are probably best served by performing angiography directly. Negative findings on other studies would not prevent these patients from progressing to angiography in any case. In bilateral cases, RVR assays can be used to localize the more ischemic side.

Patients with low or moderate suspicion of RVH are more problematic. In these cases, it is probably reasonable to perform captopril renography as a preliminary test. A positive test should be followed by further testing, preferably definitive diagnosis through angiography. Patients with low clinical suspicion and a technically satisfactory negative study should not be subjected to further testing. Technically unsatisfactory studies should probably be followed by a noninvasive test of a different type (e.g., DUS). These tests (DUS, MRA, or CTA) will provide no functional information or prediction of cure after intervention. To date, anatomic confirmation of the disease and treatment planning still require intra-arterial angiography.

The role of renin assays has decreased significantly since the 1980s. Few centers use the captopril test to exclude patients from having RVH, because of its consistently high negative predictive value. RVR assays are rarely used to diagnose RVH before a noninvasive test indicates the anatomic presence of stenosis; their role has focused on localizing the more ischemic kidney in bilateral cases.

Key Points: Diagnostic Evaluation

- In patients with clinical features of renovascular hypertension, the diagnosis is confirmed by contrast angiography.
- Noninvasive testing with CT angiography, MR angiography, and duplex ultrasonography is often used in suspicious cases before proceeding to contrast angiography.
- Except in rare circumstances, functional testing for renovascular hypertension has been largely superseded by anatomical testing for renal artery stenosis.
- There is no functional testing currently available to evaluate patients with ischemic nephropathy.

RENOVASCULAR DISEASE IN CHILDREN

Renovascular disease is estimated to cause 5% to 10% of childhood hypertension (Wyszyńska et al, 1992). The causes of renovascular hypertension in children are more variable than adults, and diagnosis is usually more difficult, particularly in young children and infants. Blood pressure measurement in children requires consideration of the child's age, sex and height. Inaccurate cuff size and positioning will result in inaccurate measurements, and blood pressure should be taken in a relaxed environment and in all four limbs. Causes of renovascular hypertension in children include fibromuscular dysplasia, vasculitis (Takayasu disease, Kawasaki disease, polyarteritis nodosa), syndromes such as neurofibromatosis, and extrinsic compression from tumors such as Wilms tumor or neuroblastoma. As in adults, intra-arterial digital subtraction angiography remains the definitive diagnostic procedure in children. In smaller children, general anesthesia will be required, and small-caliber coronary angiography catheters can be used. In general, life-long medical treatment is avoided in children with renovascular hypertension, and most children will be referred for surgical or endovascular revascularization. Medical management is useful in emergency control of blood pressure, optimization of blood pressure control in preparation for revascularization, and rare cases of widespread distal arterial disease not amenable to surgical or endovascular intervention.

MANAGEMENT OF PATIENTS WITH RENAL ARTERY DISEASE

Management options for patients with renal artery disease resulting in renovascular hypertension or ischemic nephropathy includes medical management, surgical revascularization (or nephrectomy), and endovascular treatment.

Medical Management

Medical treatment of renovascular hypertension is often the preferred treatment for patients with well-controlled mild hypertension in the absence of a threat to kidney function (from ischemic nephropathy or progressive arterial disease). Medical treatment is also reasonable in patients with advanced age and multiple comorbidities that place them at high risk for surgical or endovascular intervention. Some patients with ischemic nephropathy and hypertension who have poor potential for recovery of renal function (see later), are also managed medically. New classes of antihypertensive medications, including newer ACE inhibitors and angiotensin receptor antagonists (and potentially renin inhibitors), provide specific blockade of RAAS overactivity and adequate control of blood pressure.

Optimal medical therapy aims to reduce overall risk of cardiovascular disease in addition to lowering blood pressure, particularly in patients with atherosclerotic renal artery disease. This approach is important because patients with renal artery ASO usually have a large burden of systemic arterial disease and multiple risk factors for cardiovascular mortality. Strict blood pressure control is essential to a target blood pressure below 140/90, or below 130/80 in diabetics and patients with renal disease and proteinuria (Chobanian et al, 2003). Use of angiotensin receptor antagonists or ACE inhibitors as first-line therapy is attractive and usually effective in controlling blood pressure, although renal function has to be carefully monitored during use. Combination treatment with diuretics, calcium channel blockers, β or α blockers, and vasodilators is based on clinical results and patient comorbidities. In addition to blood pressure control, a complete treatment regimen includes treatment of dyslipidemia (to low-density lipoprotein cholesterol <100), strict management of diabetes (tight glucose control, medical nutrition, foot and eye care, physical activity), antiplatelet agents (aspirin, clopidogrel, or ticlopidine), smoking cessation, and management of complications of renal insufficiency (anemia, hyperparathyroidism, etc.), which are frequently present in patients with renal impairment.

SELECTION OF PATIENTS FOR SURGICAL OR ENDOVASCULAR THERAPY

Renovascular Hypertension

In patients with RVH secondary to FD, the decision for intervention (surgery or angioplasty) is guided by the specific type of disease as determined by angiographic findings and the associated natural history (Novick et al, 1996). **Medical management of hypertension is the preferred initial treatment for patients with medial fibroplasia, because loss of renal function from progressive obstruction is uncommon with this disease. Interventive treatment** in the latter category is reserved for patients whose blood pressure is difficult to control with multiple drugs. Conversely, renal artery stenosis secondary to intimal or perimedial fibroplasia generally progresses and often eventuates in ischemic renal atrophy. Furthermore, these lesions tend to occur in younger patients and to cause hypertension that is extremely difficult to control. Early interventional therapy in these patients is therefore indicated both to preserve renal function and to minimize the need for long-term antihypertensive medication.

In selecting patients with FD for surgical renal revascularization, the efficacy of percutaneous transluminal angioplasty (PTA) must also be considered. **The results of angioplasty for FD of the main renal artery have been excellent** and equal to those obtained with surgical revascularization; therefore, angioplasty is the initial treatment of choice in such cases. However, as many as 30% of patients with FD have branch renal arterial involvement, which increases the technical difficulty of, and often precludes, angioplasty. Therefore surgical renal revascularization is the primary interventional treatment in this category.

In patients with atherosclerotic RVH, more vigorous attempts at medical management are warranted, because these patients are older and often have extrarenal vascular disease. Therefore multiple-drug regimens that control the blood pressure are often the preferred approach. Indeed, the advent of new β-blocking agents and converting enzyme inhibitors has enhanced the efficacy of medical antihypertensive therapy. Intervention with surgery or endovascular therapy is best reserved for patients whose hypertension cannot be adequately controlled or when renal function is threatened by advanced vascular disease (Novick et al, 1996).

Ischemic Nephropathy

Anatomic Severity and Extent of Renal Artery Disease

After angiographic diagnosis of ARAS, and with knowledge of the natural history of this disease, one can identify those

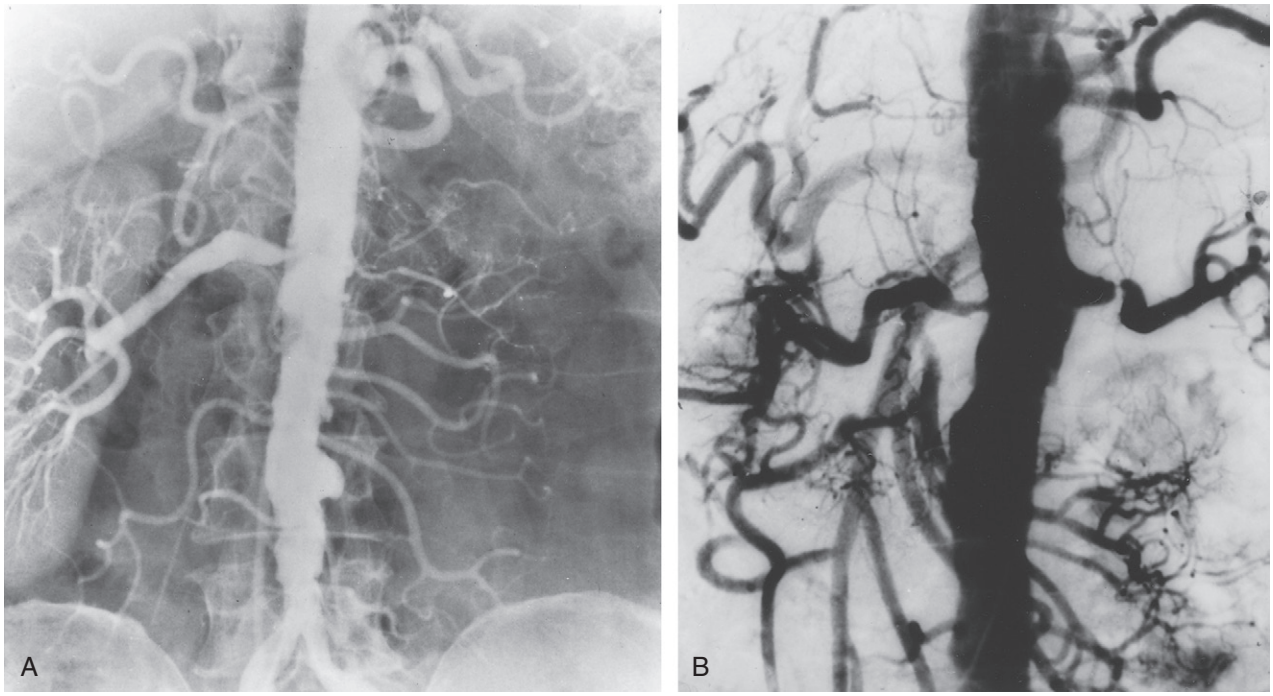


Figure 39–8. Atherosclerotic renal artery disease poses the greatest threat to overall renal function in patients with high-grade arterial stenosis to a solitary (right) kidney **(A),** and bilateral high-grade renal artery stenosis **(B),** as demonstrated on these abdominal aortograms.

patients in whom such disease poses a significant threat to overall renal function. This designation applies to patients with high-grade (>75%) arterial stenosis affecting their entire renal mass, namely, where such stenosis is present bilaterally or involves a solitary kidney (Fig. 39–8). In these patients, the risk of complete renal arterial occlusion is significant, and, if this occurs, the clinical outcome is a critical decrease in functioning renal mass with resulting renal failure. Intervention to restore normal renal arterial blood flow is indicated in such patients for the purpose of preserving renal function. In a study from the Cleveland Clinic (Novick et al, 1987), surgical revascularization for preservation of renal function was performed in 161 patients with ARAS bilaterally or in a solitary kidney. Postoperatively, renal function was improved in 93 patients (58%), stable in 50 patients (31%), and deteriorated in only 18 patients (11%).

The benefit of undertaking revascularization for the preservation of renal function in patients with unilateral ARAS and an unobstructed contralateral renal artery is not established. If the contralateral kidney is anatomically and functionally normal, revascularization for this purpose is clearly not warranted. If the opposite kidney is functioning but involved with some type of parenchymal disorder, revascularization of the ischemic kidney may benefit some patients, but specific indications for this approach are not well defined. Dean and associates (1991) reviewed the renal functional outcome after surgical revascularization in 53 patients with IN. The postoperative estimated GFR was improved significantly in 41 patients treated for bilateral ARAS but was unaltered in 12 patients with unilateral ARAS.

Complete occlusion of the renal artery most often eventuates in irreversible ischemic damage of the involved kidney. However, in some patients with gradual arterial occlusion, the viability of the kidney can be maintained through the development of collateral arterial supply (Morris, 1956; Zinman and Libertino, 1977; Schefft et al, 1980). Helpful clinical clues suggesting renal salvability in such cases include (1) angiographic demonstration of retrograde filling of the distal renal arterial tree by collateral vessels on the side of total arterial occlusion (Fig. 39–9), (2) a renal biopsy showing well-preserved glomeruli, (3) kidney size greater than 9 cm, and (4) function of the involved kidney on isotope renography or intravenous pyelography. When such criteria are present, restoration of normal renal arterial flow can lead to recovery of renal function.

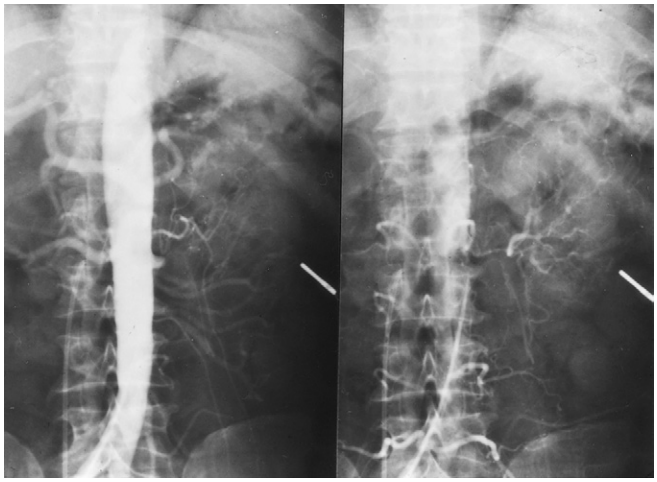


Figure 39–9. Abdominal aortograms reveal complete occlusion of the left renal artery *(left)* with filling of the distal renal artery branches from an extensive collateral supply on delayed film *(right)*.

Level of Renal Function

In general, revascularization to preserve renal function in patients with ARAS is most likely to be beneficial in those who have not yet sustained severe, permanent impairment of overall renal function. In a study from the

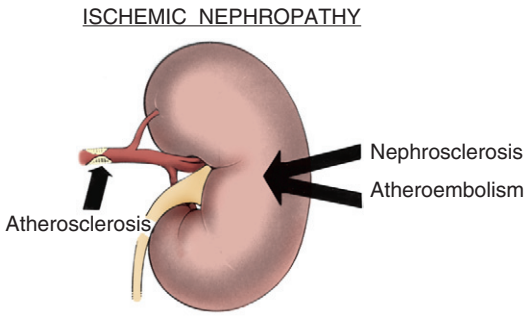


Figure 39–10. Patients with atherosclerotic renal artery disease often have renal parenchymal involvement with varied degrees of nephrosclerosis or atheroembolic disease.

Cleveland Clinic (Bedoya et al, 1989), we evaluated the effect of baseline renal function on the outcome of surgical revascularization in elderly patients with ARAS. The majority of these patients had preoperative serum creatinine levels of less than 3 mg/dL; postoperative renal function was stable or improved in 89% of patients in this category.

Revascularization to preserve renal function is generally not worthwhile in patients with severe azotemia (serum creatinine level >4 mg/dL), because advanced underlying renal parenchymal disease is inevitably present and obviates improvement in renal function with restored perfusion. This observation has been recorded by several groups including our own (Mercier et al, 1990; Chaikof et al, 1994). Severe nephrosclerosis is the most common form of renal parenchymal disease in such patients; however, renal cholesterol embolization may be an additional complicating feature (Fig. 39–10) (Vidt et al, 1989). In patients with atherosclerotic ischemic renal disease and a serum creatinine level greater than 4 mg/dL, our policy is to perform a renal biopsy to evaluate the severity of renal parenchymal involvement from one or both of these disorders.

Some patients present with severe impairment of overall renal function that has developed acutely after the initiation of medical antihypertensive therapy (Hricik et al, 1983; Textor and Novick, 1983). Such rapidly progressive renal insufficiency may be a manifestation of perfusion-dependent renal function due to underlying ARAS. If this problem is detected promptly, renal function often improves after discontinuation of the offending antihypertensive medications. Intervention to relieve renal arterial obstruction can prevent permanent renal damage in patients with this type of severe acute renal insufficiency.

In addition to the absolute level of renal function, the rate of decline in overall renal function is an important determinant of the outcome after intervention in atherosclerotic ischemic renal disease. In a study by Dean and associates (1991), patients with a rapid rate of deterioration in estimated GFR during the 6 months preceding surgical revascularization achieved the greatest benefit in terms of postoperative improvement of estimated GFR. Unfortunately, their data precluded definition of a critical rate of decline in estimated GFR that would predict retrieval of renal function by revascularization. Nevertheless, rapid deterioration of overall renal function in association with ARAS suggests a strong possibility of retrieval of function by intervention to restore normal renal arterial flow.

Occasional patients with ESRD from IN have had salvable renal function on revascularization (Wasser et al, 1981; Kaylor et al, 1989). The basis for this has been the presence of chronic bilateral total renal arterial occlusion in which, fortuitously, the viability of one or both kidneys has been maintained through collateral vascular supply. In such cases, revascularization can yield dramatic recovery of renal function (Fig. 39–11). Unfortunately, this clinical presentation is rare, and a less favorable outcome of bilateral arterial occlusion on renal viability is far more common.

We reported nine patients with ESRD, caused by atherosclerotic renal artery occlusion, who underwent surgical revascularization with subsequent recovery of renal function (Kaylor et al, 1989). The duration of dialysis preoperatively ranged from 1 to 13 months. In all cases, renal viability was being maintained by collateral vascular supply. Postoperatively, renal function improved immediately, and no patient required subsequent dialysis. Excellent overall rehabilitation was achieved in all patients. Six patients were alive at a mean interval of 4 years postoperatively and with satisfactory renal function (mean serum creatinine level of 2.7 mg/dL). Three patients died at a mean interval of 6.8 years postoperatively, and they all maintained satisfactory renal function (mean serum creatinine level of 3 mg/dL) until death. Although some patients with ESRD caused by atherosclerotic arterial occlusion can be salvaged in this manner, in most such cases irreversible loss of renal function has occurred. Therefore the most effective approach is to relieve arterial obstruction before ESRD develops.

Finally, it is important to emphasize that **patients with ESRD and ARAS without complete occlusion are not appropriate candidates for revascularization to restore function.** In such cases, main renal arterial blood flow is preserved, albeit at a reduced level, yet the supplied renal parenchyma is without function. The basis for this is the presence of severe unalterable parenchymal damage that precludes recovery of renal function with improved perfusion.

Renal Histopathology

Evaluation of renal histopathology can help to determine the presence of salvable renal function in selected patients with atherosclerotic renal ischemic disease. **In patients with ARAS and severe existing impairment of overall renal function (serum creatinine level >4 mg/dL),** renal biopsy findings can help to predict whether revascularization is likely to forestall further progressive renal insufficiency. In patients with atherosclerotic renal artery occlusion, renal biopsy findings can indicate whether the involved kidney is viable and functionally salvable on the basis of collateral vascular supply. The two predominant morphologic lesions in such patients are arteriolar nephrosclerosis and atheroembolic renal disease, with the former more often encountered. Both these diagnoses can be established on a frozen-section histopathologic examination, and, therefore the renal biopsy can be done at the same time as surgical revascularization, if the biopsy findings are favorable. In patients with arteriolar nephrosclerosis, the most important favorable criterion is histologic evidence that a majority of examined glomeruli are intact and viable (Zinman et al, 1977; Schefft et al, 1980). The presence of tubular atrophy, interstitial fibrosis, and arteriolar sclerosis are of lesser importance and do not necessarily preclude recovery of renal function; these findings may merely reflect the histologic changes of chronic reversible renal ischemia. However, the finding of widespread glomerular hyalinization indicates irreversible ischemic renal injury that obviates any benefit from relief of renal arterial obstruction (Fig. 39–12A). The finding of extensive atheroembolic disease would also preclude renal revascularization (Fig. 39–12B). Regarding the technique for renal biopsy in such patients, a more representative specimen of renal tissue is obtained with an open surgical (or laparoscopic) wedge biopsy than with a closed needle biopsy.

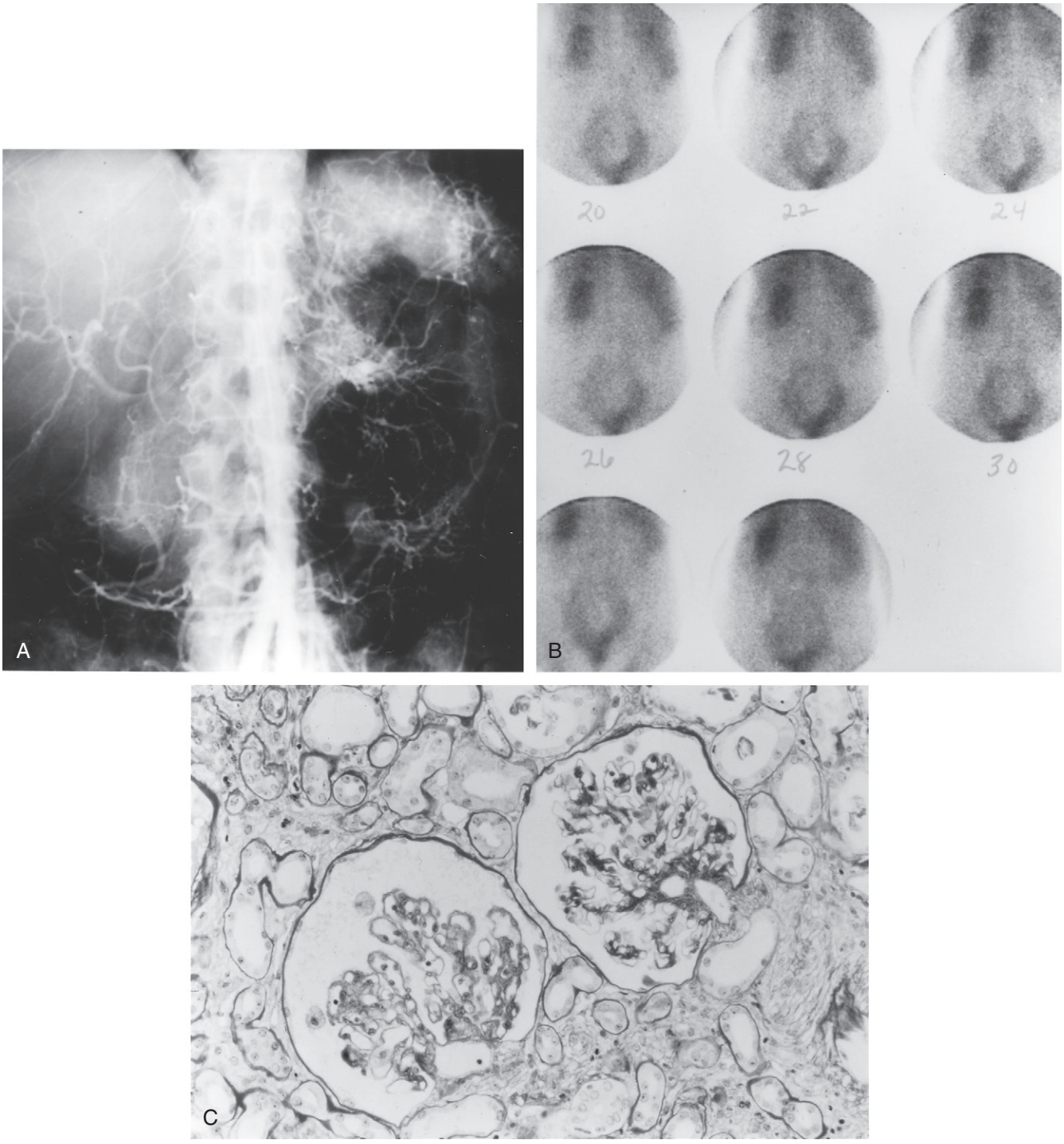


Figure 39–11. **A,** This abdominal aortogram was obtained in a 60-year-old woman who had been undergoing chronic dialysis for 9 months with no urine output. The aortogram shows complete bilateral renal artery occlusion with evidence of collateral vascular supply to the left kidney. **B,** Technetium renal scan confirms blood flow to the left kidney from collateral supply. **C,** Left renal biopsy shows hypoperfused but viable glomerular tissue, indicating a salvageable kidney. Left renal revascularization led to recovery of renal function and discontinuation of dialysis in this patient.

SURGICAL REVASCULARIZATION

Although repair of renal artery disease by revascularization is usually the main goal of surgical intervention, ablative surgery (nephrectomy) is occasionally more appropriate. The original surgery for renovascular hypertension, nephrectomy is a suitable alternative in hypertensive patients with a unilateral small kidney and markedly decreased ipsilateral function. Renal vein renin evaluation can confirm the kidney as the cause of hypertension, and laparoscopic nephrectomy can provide an attractive minimally invasive alternative to open nephrectomy in such cases (Fig. 39–13).

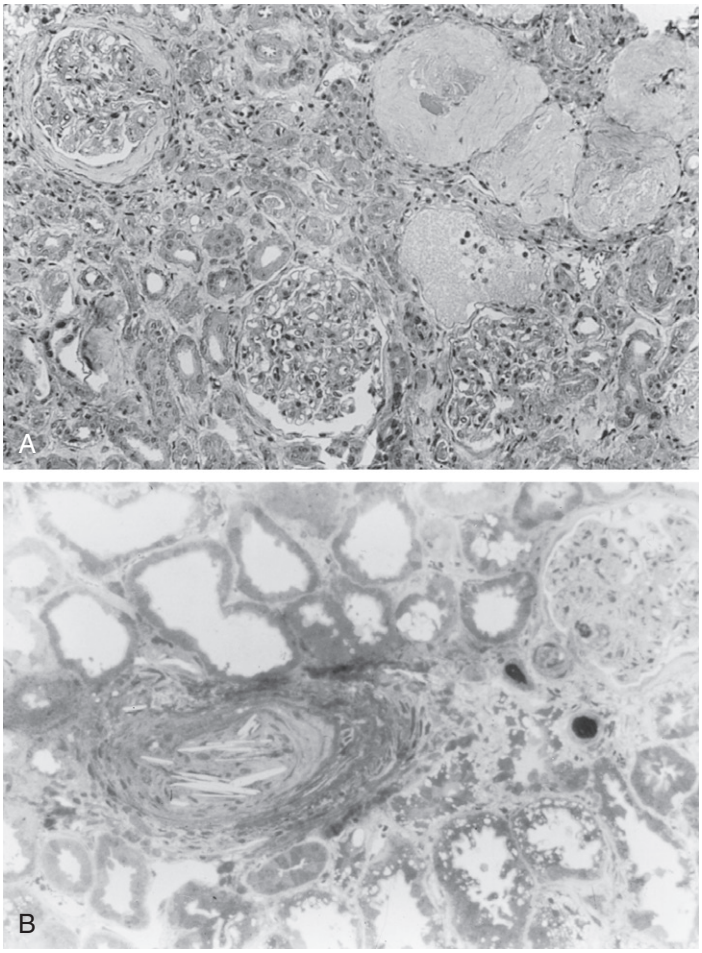


Figure 39–12. **A,** Light microscopic findings on biopsy of a kidney with total arterial occlusion demonstrate extensive glomerular hyalinization, which precludes any benefit from revascularization. **B,** Biopsy of a kidney in another patient demonstrates atheroembolic disease.

Preoperative Preparation

When surgical revascularization is indicated for renal artery disease, it is important to accurately define the general medical condition of the patient, because this will determine the risk of undertaking a major vascular operation. Most patients with renal arterial FD are young and otherwise healthy, and the operative risk is minimal in this group (Novick, 1994a). **In patients with atherosclerotic renovascular disease, the preoperative evaluation should include a thorough search for coronary artery disease, because this has been the leading cause of operative death after surgical revascularization.** In our program, in addition to a careful history, a physical examination, and an ECG, a thallium cardiac stress test is done on all operative candidates in this category. If any of these assessments suggest the presence of coronary artery disease, our policy is to perform coronary cineangiography and left-sided ventriculography. Myocardial revascularization is recommended for patients with significant correctable coronary artery disease before renal revascularization (Novick et al, 1981).

Cerebrovascular accident has also been a significant cause of death after renal revascularization in patients with atherosclerosis, albeit a less common complication than myocardial infarction. The approach to patients whose history or examination suggests extracranial cerebrovascular disease is analogous to that employed for patients with suspected coronary artery disease. In such patients, carotid arteriography is obtained preoperatively, and if significant occlusive disease is found, endarterectomy is recommended before renal revascularization (Novick et al, 1981).

In patients with generalized atherosclerosis and renal artery disease, cardiac function is often compromised to various degrees. In these patients, hypertension increases the workload on the left ventricle, which decreases cardiac reserve and renders the heart less efficient. In addition to having an impaired myocardium, these patients also often have a decreased intravascular volume because of prior treatment with diuretic agents. These patients can

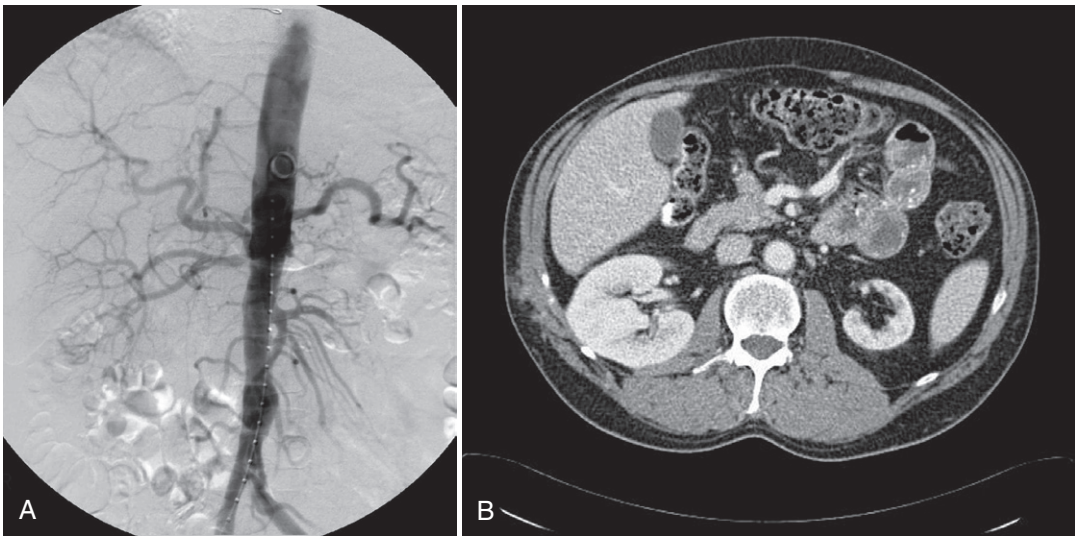


Figure 39–13. A 47-year-old male with poorly controlled hypertension (215/115) on four medications. CT scan shows a small left kidney **(A),** and angiography confirms an occluded left renal artery with minimal right renal artery stenosis **(B).** Renin evaluations from the infrarenal inferior vena cava, right and left renal veins were 15.4, 14.9, and 91.5 µg/L/hr, respectively. After laparoscopic left nephrectomy, blood pressure improved to 145/85 on one medication.

benefit from a careful hemodynamic assessment in an intensive care unit for 12 to 24 hours before surgical revascularization. In the intensive care unit, Swan-Ganz arterial and urethral catheters are placed for measurement of blood pressure, pulmonary capillary wedge pressure, pulmonary artery pressure, cardiac output, total peripheral resistance, and urinary output. While these parameters are being monitored, intravenous vasodilators can be administered to control the blood pressure and decrease the cardiac afterload, while the intravascular space is carefully expanded with isotonic fluid. Afterload reduction and fluid repletion, in this manner, optimize perioperative cardiac function by increasing cardiac output and decreasing cardiac work. This approach can enhance the safety of surgical renal revascularization in patients with generalized atherosclerosis.

Operative Techniques

Advances in both surgical renovascular reconstruction and medical antihypertensive therapy have limited the role of total or partial nephrectomy in the management of patients with renal artery disease. These operations are only occasionally indicated in patients with severe arteriolar nephrosclerosis, severe renal atrophy, uncorrectable renovascular lesions, and renal infarction.

A variety of surgical revascularization techniques are available for treating patients with significant renal artery disease. **Aortorenal bypass with a free graft of autogenous hypogastric artery or saphenous vein remains a popular method in patients with a healthy** abdominal aorta. Polytetrafluoroethylene aortorenal bypass grafts have been successfully employed by some authors, usually when an autogenous graft is not available. Renal endarterectomy also continues to be used occasionally to treat atherosclerotic renal artery disease. Patients with complex branch renal artery lesions are managed with extracorporeal microvascular reconstruction and autotransplantation.

In older patients, severe atherosclerosis of the abdominal aorta may render an aortorenal bypass or endarterectomy technically difficult and potentially hazardous to perform. In such cases, several authors prefer alternative surgical approaches that allow renal revascularization to be safely and effectively accomplished while avoiding operation on a badly diseased aorta. The most effective alternate bypass techniques have been a splenorenal bypass for left renal revascularization and a hepatorenal bypass for right renal revascularization. The absence of occlusive disease involving the origin of the celiac artery is an important prerequisite for these operations. A 1995 study indicated the presence of significant celiac artery stenosis in 50% or more of patients with ARAS (Fergany et al, 1995). This information underscores the importance of obtaining preoperative lateral aortography to evaluate the celiac artery origin in patients who are being considered for hepatorenal or splenorenal bypass.

Use of the supraceliac or lower thoracic aorta for renal revascularization is a more recent surgical alternative in patients with significant atherosclerosis of the abdominal aorta and its major visceral branches. The supraceliac aorta is often relatively disease-free in such patients and can be used to achieve renovascular reconstruction with an interposition saphenous vein graft. Simultaneous aortic replacement and renal revascularization have been associated with an increased risk of operative mortality, and this approach is best reserved for patients with a fixed indication for aortic replacement, such as a significant aortic aneurysm or symptomatic aortoiliac occlusive disease.

Results

Reports from several centers indicate that the techniques described previously for surgical renovascular reconstruction can be safely performed with a high technical success rate. **Patients with FD are usually otherwise healthy, and operative morbidity and mortality after revascularization in this group have been minimal** (Novick et al, 1987; Hansen et al, 1992). Operative mortality rates of 2.1% (Novick et al, 1987), 3.1% (Hansen et al, 1992), 3.4% (Bredenberg et al, 1992), and 6.1% (Libertino et al, 1992) have been reported after surgical revascularization in patients with atherosclerotic renal artery disease. An increased risk of operative mortality has been observed with bilateral simultaneous renal revascularization (Hallett et al, 1987), or when renal revascularization is performed in conjunction with another major vascular operation such as aortic replacement (Lawrie et al, 1989). Most studies have indicated a high technical success rate for surgical vascular reconstruction with postoperative thrombosis or stenosis rates of less than 10% (Novick et al, 1987; Van Bockel et al, 1987; Libertino et al, 1992).

In a retrospective study from the Cleveland Clinic, Tsoukas and colleagues (2001), evaluated the results of simultaneous aortic and renal revascularization and reported a 13% postoperative mortality rate for bilateral renal revascularization versus 7% for patients with unilateral renal revascularization, when both were performed simultaneously with aortic replacement. The 5-year survival rate for patients with preoperative serum creatinine more than 2 mg/dL was 53% compared with 85% for patients with lower creatinine. The authors recommend adjunctive use of endovascular techniques to decrease the magnitude of the surgical procedure for patients with concomitant aortic and bilateral renal artery atherosclerotic disease.

In evaluating the results of surgical revascularization for RVH, most studies have considered patients to be cured if the blood pressure is 140/90 mm Hg, or less, postoperatively. Patients have been considered to be improved if they have either shown a reduction in diastolic pressure of 10 to 15 mm Hg, or more, or become normotensive on medication. Failures have been those who have not qualified for either of the aforementioned categories. The results of surgical treatment for RVH vary according to the underlying pathologic diagnosis. In patients with FD, 50% to 60% are cured, 30% to 40% are improved, and the failure rate is less than 10% (Novick et al, 1987; Hansen et al, 1992). In patients undergoing revascularization for atherosclerotic RVH (Table 39–5), the failure rate is approximately the same; however, fewer patients are cured and more patients are improved postoperatively. The explanation for this is that RVH is often superimposed on existing essential hypertension in older patients. A study by Van Bockel and colleagues (1987) highlighted the excellent long-term results after reconstructive surgery for atherosclerotic RVH, with a mean

Table 39–5.

Results of Surgical Revascularization for Atherosclerotic Renovascular Hypertension

SERIES	PATIENTS (*N*)	NO. CURED	NO. IMPROVED	NO. FAILED
Van Bockel et al, 1987	105	19 (18%)	64 (61%)	22 (21%)
Novick et al, 1987	180	55 (31%)	110 (61%)	15 (8%)
Libertino et al, 1988	86	38 (44%)	44 (51%)	4 (5%)
Hansen et al, 1992	152	22 (15%)	116 (75%)	14 (10%)

Table 39–6.

Results of Surgical Revascularization for Atherosclerotic Ischemic Nephropathy

SERIES	PATIENTS (*N*)	NO. IMPROVED	NO. STABLE	NO. DETERIORATED
Novick et al, 1987	161	93 (58%)	50 (31%)	18 (11%)
Hallett et al, 1987	91	20 (22%)	48 (53%)	23 (25%)
Hansen et al, 1992	70	34 (49%)	25 (36%)	11 (15%)
Bredenberg et al, 1992	40	22 (55%)	10 (25%)	8 (20%)
Libertino et al, 1992	91	45 (49%)	31 (35%)	15 (16%)

follow-up of 8.9 years; postoperative hypertension was cured or improved in 83 of 105 patients (79%).

During the past 15 years, **more centers have been performing surgical revascularization to preserve renal function in patients with high-grade atherosclerotic arterial occlusive disease affecting both kidneys or a solitary kidney.** These are generally older patients with diffuse atherosclerosis, ostial renal artery lesions, and varied degrees of renal functional impairment. Studies from several centers (Table 39–6) have indicated improvement or stabilization of renal function postoperatively in 75% to 89% of patients. Considering the significant risks of progressive occlusive disease and renal failure that have been associated with medical management of such patients, these results demonstrate a favorable influence of revascularization on the natural history of untreated atherosclerotic renal artery disease.

We have reviewed the contemporary experience at the Cleveland Clinic, between 1980 and 1992, with surgical renal revascularization employing an extra-anatomic bypass operation (Fergany et al, 1995). A total of 175 operations were done, including hepatorenal bypass (n = 59), splenorenal bypass (n = 54), iliorenal bypass (n = 37), thoracic aortorenal bypass (n = 23), renal autotransplantation (n = 1), and superior mesenterorenal bypass (n = 1). There were five operative deaths (2.9%) and seven cases of postoperative graft thrombosis (4%). All patients with poorly controlled hypertension were cured or improved postoperatively. Among patients with IN, postoperative renal function improved in 35%, remained stable in 47%, and deteriorated in 18%. These extra-anatomic techniques have become an important component of the surgical armamentarium for ARAS.

In another study, we analyzed long-term clinical outcomes and survival after surgical revascularization for ARAS in 222 patients treated from 1974 to 1987 at the Cleveland Clinic (Steinbach et al, 1997). The indications for surgical revascularization were treatment of hypertension in 60 patients, preservation of renal function in 12 patients, and both control of hypertension and preservation of renal function in 148 patients. The mean postoperative follow-up interval was 7.4 years.

In this study, there were five operative deaths (2.2%), and postoperative thrombosis or stenosis of the repaired renal artery occurred in 16 patients (7.3%). Long-term improvement or stabilization of renal function was achieved in 71.3% of patients. Actuarial 5- and 10-year survival for the entire series from the time of revascularization was 81% and 53%, respectively. The expected 5- and 10-year survival for a comparable healthy population is 89% and 77%, respectively. Using a multivariate analysis, factors correlating with diminished long-term survival were age greater than 60 years (P = .002), coronary artery disease (P = .031), and previous vascular operations (P = .001). These data support the long-term therapeutic efficacy of surgical revascularization in patients with ARAS. The merits of newer forms of therapy, such as PTA and endovascular stenting, must ultimately be weighed against these results.

Cherr and colleagues (2002), reported on the results of surgical revascularization in 500 patients with atherosclerotic renal artery disease from 87 to 99. Unilateral surgery was performed in 40%, bilateral in 60%, and combined aortic and renal surgery in 41%. Mortality rate was 4.6% overall. Hypertension was cured, improved and unchanged in 12%, 73%, and 15%, respectively. Renal function was improved in 43%, unchanged in 47% and deteriorated in 10%.

The results of renal autotransplantation for renal artery stenosis due to various pathologies (fibromuscular disease [FMD], ASO, and Takayasu arteritis) were reported by Chiche and colleagues (2003). Results of surgery were better in the FMD patients with early or delayed nephrectomy performed in five of eight patients with ASO. Hypertension was cured or improved in 96% of patients with FMD, and 89% of patients with Takayasu disease.

Secondary Renal Revascularization

Relatively few reports have addressed the management of patients with recurrent renal artery stenosis after failed surgical revascularization or PTA. For patients in the latter category, repeat PTA may be attempted; however, ultimately, many of these patients will require surgical revascularization. **There has been controversy concerning whether the prior performance of PTA increases the technical difficulty or compromises the outcome of surgical renal revascularization.** A report by Dean and associates (1987) indicated that the task of arterial reconstruction may be rendered more complicated by a perivascular inflammatory response induced by PTA. Reports from McCann and colleagues (1988) and Martinez and coworkers (1990) found that surgical revascularization is not more technically difficult after PTA than when done primarily, and that the same satisfactory results can be achieved. The latter study comprised 53 patients treated surgically after failed PTA for renal artery stenosis. Three patients underwent nephrectomy because a nonviable kidney was found at operation. Successful surgical revascularization was achieved in all the remaining 50 patients. The authors noted no significant fibrosis or inflammation around the previously dilated renal artery. PTA necessitated performing a more complicated revascularization operation in only 1 patient. These data indicate that if the kidney is viable at operation, prior performance of PTA does not increase the technical difficulty of surgical renovascular reconstruction.

Recurrent renal artery stenosis after surgical revascularization is typically a late complication occurring weeks, months, or even years postoperatively. If the involved kidney is functionally salvable, then another attempt to restore normal renal arterial flow is indicated. There has been scant experience with PTA or stenting in this setting; however, this is an appropriate initial approach for focal stenotic lesions. Secondary surgical revascularization has constituted the predominant reported approach, and this may be technically

complicated (Stanley et al, 1985; Erturk et al, 1989). Reoperation often entails dissection in a surgical field obliterated by fibrous scar tissue, and it is most efficacious to employ a secondary reconstructive technique that avoids the site of previous surgery. In patients with recurrent renal artery stenosis after an abdominal aortorenal bypass, alternate approaches that may be used for secondary revascularization include hepatorenal bypass, splenorenal bypass, thoracic aortorenal bypass, iliorenal bypass, and renal autotransplantation.

PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY

Percutaneous dilatation of arterial stenoses (angioplasty) was originally introduced by Dotter and Judkins in 1964; however, their technique of using coaxial catheters of increasing diameter was limited to the femoral and popliteal arteries and did not gain wide acceptance. It was the development of the balloon catheter by Gruntzig and colleagues in 1978 that permitted the widespread use of angioplasty for dilatation of the renal, coronary, and almost all other visceral arteries. Numerous modifications have been made to the original technique since its introduction, and there are currently several approaches to performing renal PTA.

Technique

All angioplasty techniques require a high-quality angiogram before dilatation to accurately delineate the lesion and allow assessment of proper equipment needs and approach. A proper-sized balloon should be selected to correspond to the original diameter of the renal artery as measured on the angiogram. Because there is 15% to 20% magnification on the angiogram, the result is the intentional overdilatation of the renal artery by 1 mm. Progress of angioplasty is monitored as the balloon inflates, and a postdilatation angiogram is obtained to assess the results and diagnose complications. PTA should be performed only when a skilled vascular surgeon is immediately available in case inadvertent occlusion or disruption of the renal artery creates a surgical emergency.

The original Gruntzig coaxial technique uses an 8- or 9-Fr renal guiding catheter through which a 4.3- or 4.5-Fr balloon catheter is passed over a guidewire traversing the stenotic segment through a femoral arterial puncture. In selected circumstances, an axillary approach may be used. Modification of the original technique and balloon catheters have allowed the use of a 5-Fr femoral artery puncture through which a 5-Fr diagnostic catheter is passed to the renal artery using the Seldinger technique. After the lesion is negotiated with an appropriate guidewire, the diagnostic catheter is exchanged with a 5-Fr balloon catheter and the angioplasty is performed (Tegtmeyer et al, 1980).

Mechanism

The principal mechanism through which the increase in arterial diameter after PTA occurs in cases of ASO is fracture of the atherosclerotic plaque. Stretching of the arterial wall with tearing of the media and adventitia also occurs but contributes to a smaller degree in cases of ASO than in FD. This stretching effect probably occurs after the atherosclerotic plaque is fractured and becomes more pronounced with increasing plaque circumference and a decrease in the uninvolved area of the vessel wall.

Complications

Renal angioplasty is a complex and technically demanding procedure that should be performed only by skilled interventional radiologists to prevent the occurrence of potentially serious complications. The complications of PTA include those of standard angiography (complications related to arterial puncture and to the use of iodinated contrast material), as well as specific complications related to manipulation of the renal arteries. **Transient deterioration of renal function is the most frequently occurring complication and is related to the contrast load delivered during the procedure.** Adequate hydration, minimizing the volume of contrast material, separating the diagnostic procedure from the PTA (by several days), and possibly the use of carbon dioxide or non-nephrotoxic contrast agents may decrease the incidence of this complication.

Technical mishaps during PTA may lead to an intimal dissection or even thrombosis of the renal artery. A small intimal flap is usually inconsequential, healing without sequelae. A larger flap compromising blood flow is usually managed by placing an arterial stent across the dissection. Thrombosis of the renal artery can be managed by injecting a thrombolytic agent through the renal artery or by emergency surgery. Rupture of the renal artery, a rare complication, is also managed by emergency surgery after reinflation of the balloon catheter to control retroperitoneal hemorrhage. Overall, the complication rate can be expected to be 5% to 10%.

Fibrous Dysplasia

Several studies have reported the results of PTA on blood pressure in cases of FD. Cure of hypertension is usually defined as a diastolic blood pressure of 90 mm Hg, or less, with no antihypertensive medication. Improvement of hypertension is usually defined as either a decrease in diastolic pressure of 15 mm Hg or a diastolic pressure of 90, or less, with a decrease in the antihypertensive medication needed to maintain normal blood pressure. Standardization of the results of these studies is difficult for several reasons. Several definitions are not uniform, including *significant stenosis* (varying from >50% to >80% of the original lumen) and technical success (defined as no stenosis or insignificant residual stenosis). Measures of success are also variable, with most studies relying on clinical parameters (blood pressure response) as the measure of success. Follow-up angiographic studies are rarely available. In addition, most studies combine ASO and FD patients, and sometimes results or complication rates are not referred specifically to one of the disease groups. Further complicating the interpretation of results is the reporting of results per patient in some studies and per lesion in others. The results of these studies are summarized in Table 39–7. Data per patient are used, and represent primary procedures only.

Overall, PTA is usually performed in cases of FD without stent placement and has become the primary modality of treatment for these lesions. With the use of modern equipment and increasing experience with the technique, technical success has been more than 90% in most modern studies. A beneficial blood pressure response, that is, cure of hypertension or improvement in blood pressure control, can be expected in more than 80%, and up to 100% of cases (Fig. 39–14). The incidence of major complications (when reported for FD patients alone) was 6% or less. At short to moderate follow-up intervals, restenosis of the treated artery was reported in up to one third of cases; however, most of these cases have been successfully

Table 39–7.

Results of Angioplasty in Fibrous Dysplasia

STUDY	TECHNICAL SUCCESS	FOLLOW-UP	CURED	IMPROVED	FAILED	RE-STENOSIS	MAJOR COMPLICATIONS	MINOR COMPLICATIONS
Sos et al, 1983	87%	16 mo	52%	29%	19%		6%	0
Martin et al, 1985	82%	16 mo	25%	60%	15%		11%*	19%*
Greminger et al, 1989	88%	20 mo	41%	47%	12%	20%	6%	0
Klinge et al, 1989	90%		35%	50%	15%		12%*	23%*
Tegtmeyer et al, 1991	100%	39 mo	39%	59%	2%	10%	2%	14%
Plouin et al, 1993		9 mo				12%	0	10%
Losinno et al, 1994	95%	6 mo	57%	22%	21%			
Jensen et al, 1995	97%	12 mo	39%	47%	14%	7%	3%	12%
Bonelli et al, 1995	88.6%	43 mo	22%	63%	15%	5.7%	11.5%	10%
Klow et al, 1998	98%	12 mo	25%	63%	29%	33%	0	0
Lovaria et al, 1999				68%†	32%			
de Fraissinette et al, 2003	94	39 mo	14%	74%	12%	7%	2%	9%

*Combined results for ASO and FMD cases in the study.
†Combined cure and improvement.
ASO, atherosclerosis obliterans; FMD, fibromuscular disease.

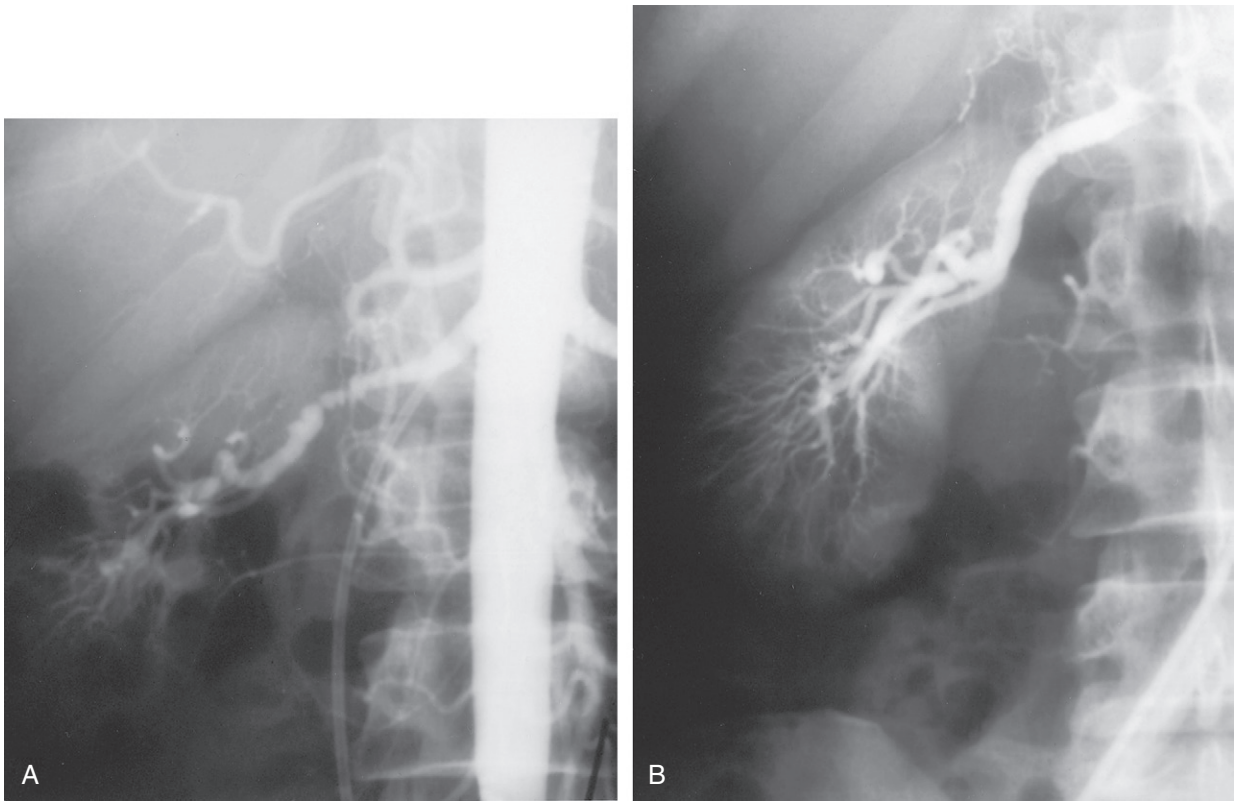


Figure 39–14. **A,** Right renal arteriogram shows medial fibroplasia causing stenosis of the main renal artery. **B,** After percutaneous transluminal angioplasty, the arteriogram shows relief of right renal artery stenosis.

redilated. Rare reports describe the use of renal artery stents for resistant fibrous lesions (Joffre et al, 1992; Imamura et al, 1998); however, these are usually not needed for this form of RAS.

Atherosclerotic Renal Artery Stenosis

The pattern of arterial disease in cases of ASO is different from that in FD. **Renal artery stenosis in cases of ASO is usually bilateral and ostial, or very proximal in the main renal artery. In most ostial cases, this represents encroachment of the atherosclerotic plaque in the abdominal aorta on the origin of the renal artery rather than primary renal artery disease.** The patients affected by atherosclerotic RAS are also different from patients with FD of the renal arteries. Patients with ASO are generally older and have a number of comorbid medical conditions, as well as generalized atherosclerosis affecting the coronary or carotid arteries or the peripheral vascular tree. Associated essential hypertension and nephrosclerosis are usually present. All the previously mentioned factors, as well as the propensity for atheroembolism in patients with generalized ASO, make PTA for ASO-RAS less successful and associated with higher morbidity (and some mortality) than in cases of FD.

Table 39–8.

Results of Angioplasty on Blood Pressure in Atherosclerosis Patients

STUDY	NO. OF PATIENTS	FOLLOW-UP	CU RED (%)	IMPROVED (%)	FAILED (%)
Sos et al, 1983	51	16 mo	17 (unilat)	30	53
			10 (bilat)	5	86
Tegtmeyer et al, 1991	75	24 mo	23	71	6
Martin et al, 1985	77	16 mo	15	50	35
Hayes et al, 1988	55	13 mo		26*	
Canzanello et al, 1989	100	22 mo	†	72 (unilat)	28
				45 (bilat)	55
Klinge et al, 1989	134		†	92	8
Plouin et al, 1993	59	9 mo			
Losinno et al, 1994	153		12	51	37
Eldrup-Jorgensen et al, 1995	52	16 mo	†	36	63
Jensen et al, 1995	107	12 mo	15	49	36
Bonelli et al, 1995	190	33 mo	8	62	30
Karagiannis et al, 1995	62	39 mo	15	40	45
Klow et al, 1998	295	61 mo	5	59	36

*Clinical benefit: cured or improved blood pressure or renal function.
†Combined with improved results as "benefit" result.
bilat, bilateral; unilat, unilateral.

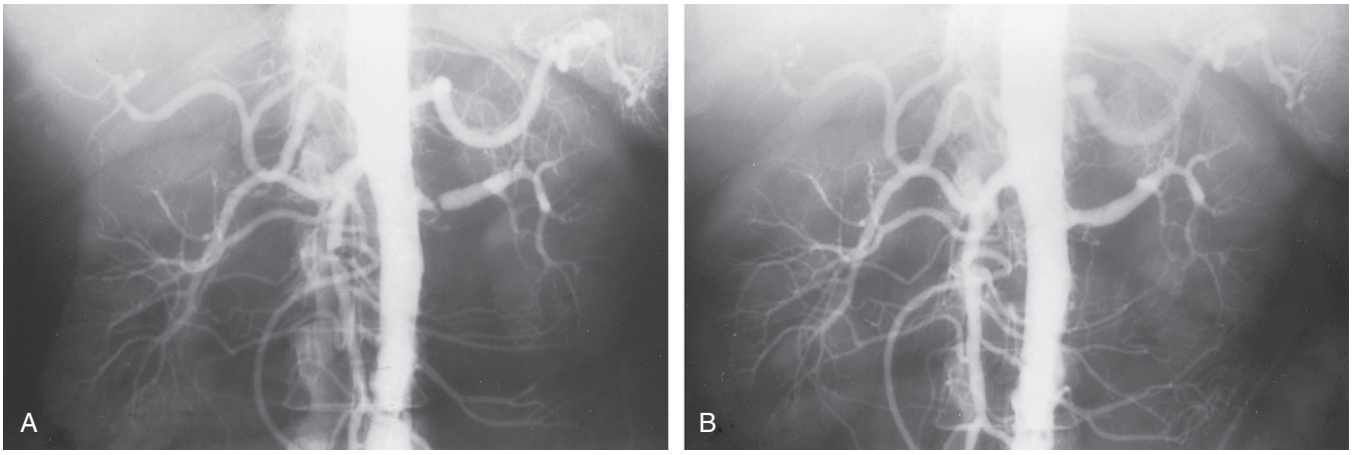


Figure 39–15. **A,** Aortography shows high-grade left renal artery stenosis from nonostial atherosclerotic plaque. **B,** After percutaneous transluminal angioplasty, aortography shows relief of left renal artery stenosis.

The presence of renal insufficiency or borderline renal function in a significant percentage of patients leads to an increased incidence of contrast nephrotoxicity as well.

The results of PTA on blood pressure in cases of RVH secondary to ASO are summarized in Table 39–8. Because of the previous factors, **the cure rate is lower than that for FD, commonly around 15%, and less in cases with bilateral PTA.** Failure to improve the blood pressure occurs in 15% to 85% in the reported series. Technical success at the time of angioplasty varies from 57% to 92% (Fig. 39–15), and is lower in cases in which separate results for ostial stenosis are reported (62% to 72%). Restenosis rates of 8% to 22%, and as high as 68% in some earlier series, are reported. Restenosis of ostial lesions is higher, reaching 35%, although more recent studies of ostial angioplasty show improved results (Eldrup-Jorgensen et al, 1995; Hoffman et al, 1998). Major complications requiring surgical intervention are reported in 5% to 24% of cases, and a mortality rate of 1% to 2% is also generally reported. More recent reports tend to show higher rates of technical success and lower complication rates (Martin et al, 1986), reflecting improved equipment and increasing expertise (Table 39–9); however, major complications and mortality rates reflect the fact that PTA is a serious procedure with significant attendant risks in this patient population. Renal artery stents are an adjunct to renal PTA that has been developed to improve the results obtained in ASO patients (see later).

With the advent of newer, more potent antihypertensive medications, as well as the increasing awareness of IN as a cause of renal failure, renal revascularization in patients with ASO is increasingly being performed with the intent of preserving or improving renal function, rather than the intent of curing RVH. **Several studies have reported the results of PTA on renal function in patients with ASO-RAS** (Table 39–10). Clinical benefit is defined as an improvement in renal function or a stabilization of renal function, in view of the steadily progressive decline in renal function associated with IN. With technically successful angioplasty, improvement can be expected in 15% to 43% of cases, and stabilization of renal function in 26% to 50% of cases. The remaining cases continue to suffer a decline in renal function. Although a mean follow-up of more than 100 months was achieved in one of these studies (Paulsen et al, 1999), follow-up for the rest of the studies is generally short to intermediate, ranging from 1 to 3 years. Percutaneous revascularization has also

Table 39–9.

Technical Success, Restenosis, and Complications of Angioplasty in Atherosclerosis Patients

STUDY	TECHNICAL SUCCESS	RESTENOSIS	MAJOR COMPLICATIONS*	MINOR COMPLICATIONS	MORTALITY
Sos et al, 1983	57%		10%	6%	0
Tegtmeyer et al, 1984	94%	15%†			
Martin et al, 1986	88%		11%†	19%†	0
Hayes et al, 1988	69%	68%	24%	7%	7%
Klinge et al, 1989	74%	22%	12%*	23%*	2%
Canzanello et al, 1989	73% 62% (ostial)	14%	7%	8%	2%
Greminger et al, 1989	88%		5%	3%	0
Weibull et al, 1993	83%	25%	17%	48%	0
Plouin et al, 1993		19% 35% (ostial)	0	7%	0
Losinno et al, 1994	95%		5%	5%	0
Bonelli et al, 1995	82%	8%	22.5%	15%	2.2%
Jensen et al, 1995	82% (nonostial) 72% (ostial)	15%	5%	3%	1%
Karagiannis et al, 1995	72%				
Eldrup-Jorgensen et al, 1995	92%	11%	5%		2%
Von Knorring et al, 1996	76%†	8%†		15%‡	
Hoffman et al, 1998	58% (ostial) only	27%	17%		4%
Klow et al, 1998	92%	43%	3%	4.2%	1%

*Includes emergency surgery and mortality.
†Combined results for atherosclerosis obliterans and fibromuscular disease groups in the study.
‡Combined major and minor complications.

Table 39–10.

Results of Angioplasty on Renal Function in Atherosclerosis Patients

STUDY	FOLLOW-UP	IMPROVED (%)	STABLE (%)	WORSE (%)
Martin et al, 1988*	16 mo	43		
Hayes et al, 1988	13 mo		26†	74
Jensen et al, 1995	12 mo		74‡	26
Karagiannis et al, 1995	39 mo	15	33	52
Zuccala et al, 1996	37 mo	40	50	10
Paulsen et al, 1999	104 mo	23	56	21

*Study population with impaired renal function (creatinine >1.7 mg/dL), no report of stable renal function.
†Clinical benefit: cured or improved blood pressure or renal function.
‡Combined with improved results as "benefit" result.

been reported to be successful in improving blood pressure control and renal function in a diabetic subset of ASO patients (Zuccala et al, 1998).

Inflammatory Renal Artery Stenosis

Takayasu arteritis is one of the causes of RAS in children and accounts for a majority of cases of RAS in South and East Asian countries. In the absence of active disease or inflammation, angioplasty has been performed to relieve RVH as well as to prevent renal loss. In a series of 24 patients aged 5 to 16 years, all with inactive disease, technically successful dilatation was achieved in 92%, with a restenosis rate of 20% after a mean of 33 months of follow-up, and these were successfully redilated. Half the children in this study were cured of hypertension, and the other half improved. No complications were specifically reported in this study (Sharma et al, 1996). In a slightly larger group of 31 children (age range 5 to 14 years) in which less importance was given to the presence of active disease, technical success was possible in 87% of cases, with a restenosis rate of 26% at a mean follow-up of 23 months. Thirty-one percent of the patients were cured, 61% improved, and 8% failed clinically. One acute occlusion of the renal artery was reported; it was successfully redilated (Tyagi et al, 1997).

These excellent results were not duplicated in a smaller Canadian study of six patients in which only one patient obtained clinical benefit and the remaining five patients proceeded to surgical autotransplantation (D'Souza et al, 1998). All these studies were in agreement that long stenoses starting at the ostium of the renal artery were much less likely to have a successful result with PTA.

Management of RAS secondary to Takayasu disease in adults with PTA has also been successful (Dong et al, 1987; Deyu et al, 1998; Sharma et al, 1998). Technical success was obtained in more than 80% of patients in these studies, with overall clinical benefit in the range of 85%.

Children

RAS in children is caused by a variety of arterial diseases, including FD, middle aortic syndrome, and neurofibromatosis. In Asian countries, a significant proportion of RAS in children is also caused by aortoarteritis (Takayasu disease). The main limitation to performing PTA in children was the lack of suitably small-sized equipment. With modern angiographic techniques and digital imaging, PTA has been reported in several studies and is becoming a primary mode of management for children with RVH. The largest series reporting on PTA for treatment of FD in children comprises 16 children, 12 of whom were

diagnosed with FD. Three patients required a secondary PTA. Overall, 9 patients were cured and 2 were improved; in 5 patients, the treatment failed, and 4 of these were treated surgically. The PTA failed in all 3 patients with multiple stenoses in this study (none had FD). There were no reports of complications in this study (Courtel et al, 1998).

Reports of smaller studies of PTA in children with FD also demonstrate the technical success and beneficial blood pressure response obtained with this treatment modality (Lund et al, 1984; Millan et al, 1985; Chevalier et al, 1987; Simunic et al, 1990). Angioplasty has been successfully used in very young children, with reports of 18-, 15-, and even 9-month-old children being treated using small coronary angioplasty equipment (Hofbeck et al, 1998; Lee et al, 1999; Liang et al, 1999).

ENDOVASCULAR STENTING

With increasing experience with PTA, limitations of the technique, especially in regard to atherosclerotic lesions, have become well recognized. These limitations involve mainly ostial lesions that represent engulfment of the renal ostium in aortic plaque. These cases represent a significant percentage of ASO-RAS cases, and elastic recoil of the plaque leads to poor initial results and frequent restenosis. **Renal artery stents are an adjunct to PTA that was introduced in an effort to oppose this recoil force and provide better results for angioplasty, especially in ostial lesions. Almost all renal artery stents in the literature have been placed to treat ASO of the renal arteries** (estimated at 97%), with many fewer stents placed in cases of FD, transplant renal arteries, and other miscellaneous renal arterial abnormalities (Rees, 1999).

Arterial stents are radiopaque, expandable metallic wire mesh tubes that have been widely used in the peripheral vascular system. Experience in other parts of the vascular as well as the biliary tree has led to the use of stents in the renal artery, although none are specifically approved by the U.S. Food and Drug Administration for use in the renal artery. Different stents are currently available and include the Palmaz, Strecker, Wallstent, and Nitinol stents. Stent expansion either is spontaneous on extrusion from a delivery catheter (self-expandable) or occurs on inflation of a balloon on which the stent is preloaded (balloon expandable).

Technique

Several techniques for stent placement in the renal artery have been developed. It is essential in all cases to obtain a high-quality angiographic study (immediately before stent placement at the same sitting or separately) in order to precisely delineate the lesion and assess balloon and stent length and diameter. The stent used should be long enough to traverse the entire lesion, taking into consideration shortening of the stent with expansion. Excessive length beyond the lesion is undesirable because the presence of the stent may excite an intimal hyperplastic reaction, placing healthy segments of the vessel at risk. This might also obstruct a site suitable for later bypass surgery. In cases of ostial lesions, the stent should be placed to protrude 1 to 2 mm into the aortic lumen to prevent restenosis due to recoil of the aortic plaque.

Indications

Current indications for stent placement are poor immediate results during PTA as well as restenosis after PTA. Stents are also used to treat angioplasty complications (artery dissection and intimal flaps) and thus have markedly reduced the incidence of emergency surgery for these complications. **"Primary" stent placement is becoming increasingly popular in cases of RAS in which PTA alone is unlikely to be successful (ostial lesions).**

Results

The results of several studies reporting on endovascular stent placement in the renal arteries are summarized in Tables 39–11 and 39–12. Most of the published experience in the renal arteries has been described using the Palmaz stent. With the exception of two of the earliest studies using Strecker and Wallstents, **the reported technical success for stent placement has consistently been above 95%**, and in most studies has been 99% or 100% (Fig. 39–16). With short to moderate follow-up intervals, restenosis of the renal artery after stent placement has ranged from 6% to 38%. A single early study (Wilms et al, 1991) reported a 71% restenosis rate; however, most larger contemporary series average a restenosis rate of 15% to 20%. Restenosis commonly

Table 39–11.

Renal Artery Stents: Blood Pressure Results

STUDY	CURED (%)	IMPROVED (%)	SAME (%)
Hennequin et al, 1994	14	86	0
Raynaud et al, 1994	6	45	49
Macleod et al, 1995	0	44	56
Van de Ven et al, 1995	0	75	25
Iannone et al, 1996	4	35	61
Henry et al, 1996	18	57	25
White et al, 1997		76*	24
Blum et al, 1997	16	62	22
Boisclair et al, 1997	6	61	33
Dorros et al, 1998	1	42	57
Tuttle et al, 1998	0	55	45
Fiala et al, 1998	0	53	47
Rodriguez-Lopez et al, 1999	13	55	32
Burket et al, 2000		71*	29
Sivamurthy et al, 2004		52*	48
Zeller et al, 2004		46*	54

*Combined "clinical benefit" rate.

Table 39–12.

Renal Artery Stents: Renal Function Results

STUDY	IMPROVED (%)	STABLE (%)	WORSE (%)
Rees and Snead, 1994	37	37	26
Iannone et al, 1996	36	46	18
White et al, 1997	20	75	5
Harden et al, 1997	34	34	32
Dorros et al, 1998		75*	25
Tuttle et al, 1998	13	76	11
Fiala et al, 1998	33	62	5
Rundback et al, 1998	29	71	0
Rodriguez-Lopez et al, 1999		95	5
Burket et al, 2000	43	24	33
Perkovic et al, 2001	8	57	35
Sivamurthy et al, 2004		87*	13
Zeller et al, 2004	34	39	27

*Combined "clinical benefit" rate.

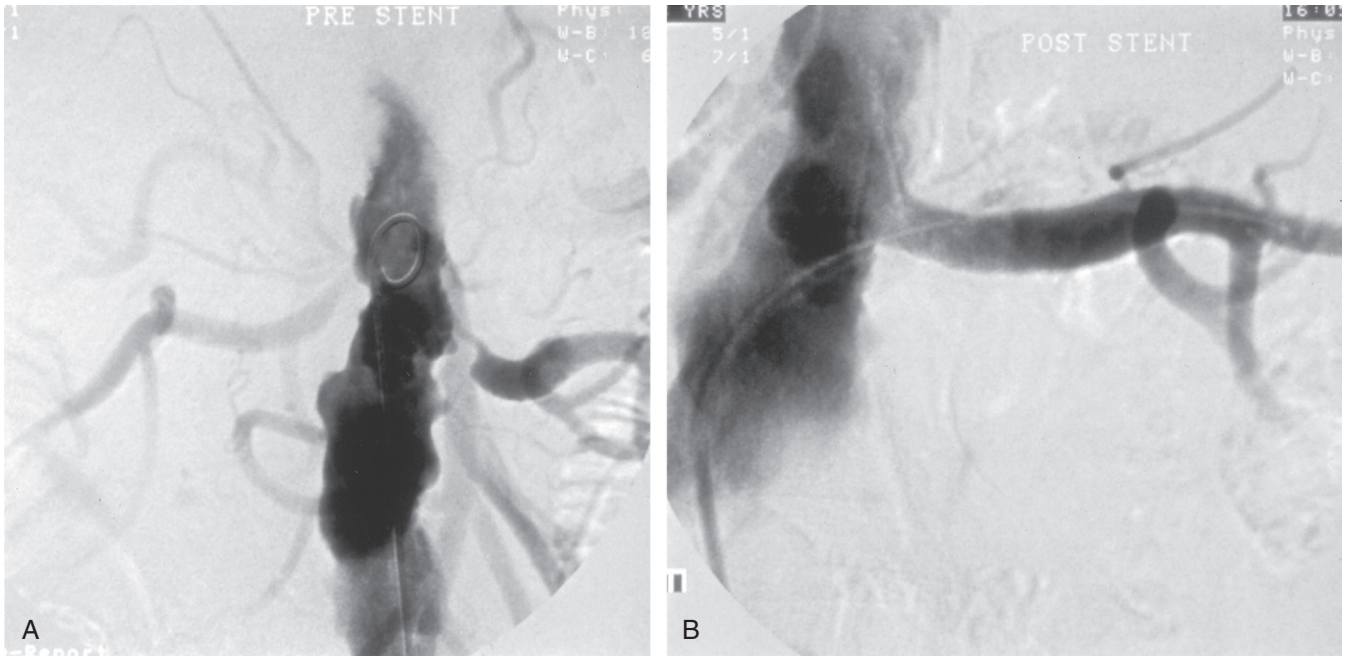


Figure 39–16. **A,** Aortography shows high-grade left renal artery stenosis from ostial atherosclerotic plaque. **B,** After endovascular stenting, aortography shows relief of left renal artery stenosis.

occurs within the stent owing to a hyperplastic intimal reaction. In other cases, an intimal lining about 1 mm thick covers the luminal surface of the stent. Renal arteries that are dilated and stented to a luminal diameter of less than 6 mm are more prone to develop restenosis.

The blood pressure response to renal revascularization by PTA and stenting is shown in Table 39–11. The low cure rates (31% at most) reflect the pathophysiologic nature of atherosclerotic renal artery disease in which anatomic stenosis is frequently associated with concomitant essential hypertension and renal parenchymal damage, precluding a simple pathologic explanation for hypertension. Revascularization for preservation of renal function has become the focus of intervention in cases of ASO-RAS. The result of renal artery stent placement (for renal function preservation or improvement) in various studies is shown in Table 39–12. Because of the progressive nature of renal dysfunction due to ASO, a clinical benefit is defined as improvement or stabilization (halt of decline) of renal function after revascularization. Improvement in renal function was achieved in 13% to 60% of cases, and stabilization was achieved in 24% to 75% of cases, with the remaining cases continuing to have progressive dysfunction.

Perhaps the clearest situation of IN is RAS to a solitary kidney, and it is on these patients that the effect of revascularization on renal function can be most clearly identified. In a study of 21 such patients, an improvement in the serum creatinine level was obtained after stent placement in 42% of cases, and stabilization in 29% of cases. Within the group of improved patients were 4 who were relieved of dialysis dependence. These results were associated with a major complication rate of 19% including a single early (and another late) procedure-related mortality (Shannon et al, 1998).

In the only prospective study comparing PTA alone versus PTA with stenting in ostial atherosclerosis, a total of 85 patients were randomized to either treatment group. Technical success was higher in the stented group (88% vs. 57%), and patency at 6 months was 75% for patients in the stent group versus 29% for PTA alone. In patients with successful primary procedures, restenosis occurred in 14% of the patients with stents and in 48% of patients with PTA alone. Stenting for immediate or late failure of PTA was required in 12 (of 42) patients in the PTA group. **This study reflects the overall higher success of PTA with stenting in treating ostial ASO when compared with PTA alone, and probably also justifies the increasing trend to perform primary stenting in these cases to avoid exposing patients to a secondary procedure** (Van de Ven et al, 1999).

Several studies addressed the factors affecting outcome after stenting and recommended selecting patients for interventional treatment based on their findings; Kennedy and colleagues (2003) and Zeller and colleagues (2003) both report that baseline renal insufficiency correlates with decreased survival and increased adverse events after renal artery stenting. In Zeller's study, the 5-year survival rate was 30% for patients with creatinine more than 2.5 mg/dL versus 95% in patients with creatinine less than 1.2 mg/dL. Major causes of death were cardiac events, cerebral events, and malignancy.

Perkovic and colleagues (2002) studied several parameters for patients undergoing renal artery stenting and reported baseline renal impairment, older age (>70), and diabetes as predictors of poor outcome. ACE inhibitor therapy after stenting appeared to improve outcome in this series.

Complications

Complications of renal artery stent placement are similar to those of renal PTA, with the added complications of stent delivery. The incidence of access site complications is higher because of the larger arterial puncture needed. The incidence of intimal injury and dissection is lower than that of PTA, because stent placement itself is a treatment for these complications. A higher incidence of contrast nephrotoxicity owing to a larger contrast load is noted, but the increasing use of carbon dioxide as a contrast agent may decrease the incidence of this

Table 39–13.
Complications of Renal Artery Stents

STUDY	MAJOR* (%)	MINOR (%)	MORTALITY† (%)
Macleod et al, 1995	10	31	3
Iannone et al, 1996	20	28	3
Henry et al, 1996	2	0	0
White et al, 1997	2	8	0
Blum et al, 1997	0	4	0
Boisclair et al, 1997	21	12	0
Harden et al, 1997	13	10	3
Dorros et al, 1998	1	14	1
Tuttle et al, 1998	4	19	0
Fiala et al, 1998	5	24	0
Rundback et al, 1998	9	0	4
Rodriguez-Lopez et al, 1999	3	7	3
Burket et al, 2000	1	4	
Perkovic et al, 2001	7	6	0.5
Sivamurthy et al, 2004	4	14	0.7

*Including mortality and emergency surgery.
†Procedure-related mortality only.

complication. The literature has rare reports of endovascular infection from renal artery stents, resolving after conservative therapy with IV antibiotics (Gordon et al, 1996), or progressing to form mycotic aneurysm of the aorta and renal artery necessitating major excision and vascular reconstructive surgery (Deitch et al, 1998).

Major complications (including death) are reported in 0% to 20% of cases (Table 39–13). Minor complications are reported in 0% to 40% of cases. Mortality directly related to the procedure is reported in almost all large series in the range of 3%. This attests to the fact that PTA with stent placement is not a benign procedure and is associated with definite risk. In a review of complications of stent placement in 50 patients, a complication rate of 20% was noted, 10% of patients suffered major complications, and a 10% rate of cholesterol embolism was reported (Beek et al, 1997).

In a meta-analysis of renal artery intervention studies earlier than 1998, including more than 1300 patients, initial technical success of stent placement was 98%, with major complications occurring in 11%. The overall cure rate for hypertension was 20%, whereas hypertension was improved in 49%. Renal function improved in 30% and stabilized in 38% of patients. The restenosis rate at follow-up of 6 to 29 months was 17%. Stent placement had a higher technical success rate and a lower restenosis rate than did renal PTA (98% versus 77% and 17% versus 26%, respectively; $P < .001$). The complication rate was not different between the two treatments (Leertouwer et al, 2000).

Proper patient selection for endovascular intervention in cases of ASO-RAD should be a careful process that takes into account the patient's chances of a successful outcome. This process should be as rigorous as patient selection for open surgery to minimize morbidity and poor outcomes from endovascular intervention. Recent studies have suggested that renal artery intervention (with or without stenting) may not improve overall patient outcomes compared with optimal medical treatment alone (van Jaarsveld et al, 2000), and a large prospective randomized multicenter study (CORAL [Cardiovascular Outcomes in Renal Atherosclerotic Lesions]) is currently underway attempting to provide informed clinical decisions regarding patient outcomes.

Complications of PTA with stenting were not found to be significantly different from those of PTA alone in a prospective study comparing both procedures. Specifically, bleeding-related complications were 19% in both groups; cholesterol embolism was 10% in both groups; and access site pseudoaneurysm and renal artery injury were slightly higher with stent placement (7% vs. 5%). Transient deterioration of renal function from contrast nephrotoxicity was noted in 24% of patients undergoing PTA and 21% of patients undergoing PTA with stent placement (Van de Ven et al, 1999).

Recent advances in renal artery intervention include the use of distal protection devices (DPD), and the use of drug-eluting stents (DES) to minimize restenosis. Distal protection devices include filters, baskets, nets, and balloons, most primarily intended for use in carotid artery stenting, and are intended to prevent distal embolization during manipulation of the renal artery. Although clinically apparent distal embolization is uncommon, such atheroemboli may be associated with decreased survival (Krishnamurthi et al, 1999). Experience with DPD has been promising but is still preliminary, with studies reporting retrieval of debris in 60% to 100% of cases (Holden et al 2006, Henry et al, 2001). Difficulty in deploying the devices in the distal renal artery due to early bifurcation or tortuosity may be encountered, resulting in successful use of such a device in three of five cases (Hagspiel et al, 2005). Future device innovations tailored to the renal artery and increasing experience with DPD will further clarify their role in renal artery interventions.

Drug-eluting stents have been used increasingly in coronary interventions, with the intention of decreasing in-stent restenosis, particularly of smaller vessels. Drug-eluting stents have been studied prospectively in the renal artery in 105 patients (Zähringer et al, 2007). Although both Sirolimus and Paclitaxel are used for stent coating, this study used Sirolimus-coated stents only. There was no significant difference in results between the bare stent group and the DES group after 2 years of follow-up, with clinical patency at 88.5% for the bare metal stent group and 98% for the DES group. Blood pressure–lowering effects did not differ significantly between the two groups either. Based on the results of this study, it may seem that DES do not offer an additional advantage in renal artery intervention over bare metal stents, but this may be due to the larger size of the renal arteries (about 6 to 7 mm) compared with the coronary arteries (5 mm or less), where restenosis may be more common. In the future, DES may prove useful in smaller renal arteries or branch disease.

OTHER RENAL ARTERY DISEASES

Renal Arterial Aneurysms

A renal arterial aneurysm is a localized dilatation of the main renal artery or its branches or both caused by weakening of the elastic tissue and media of the arterial wall. The estimated incidence of such lesions in the general population ranges from 0.09% to 0.3%. Renal arterial aneurysms may be clinically significant because of a causative relation to hypertension, associated local symptoms, or the risk of catastrophic rupture in certain situations (Novick, 1982). According to the classification of Poutasse (1975), there are four basic types of renal artery aneurysms: saccular, fusiform, dissecting, and intrarenal (Fig. 39–17).

Saccular aneurysms are the most common type and constitute about 75% of renal artery aneurysms. They generally occur at the bifurcation of the renal artery, perhaps owing to an inherent weakness in the wall of the artery at this point. Because of this

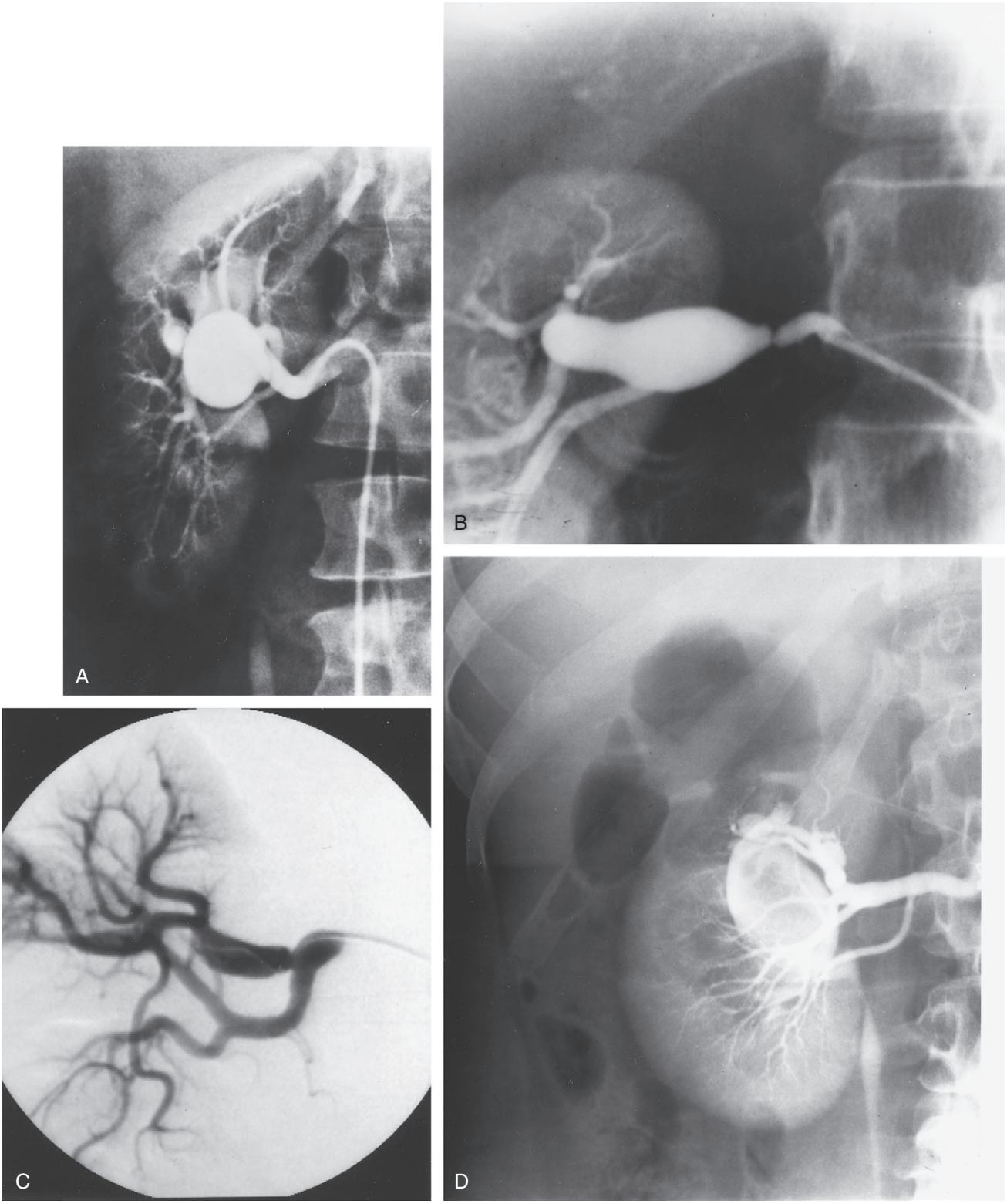


Figure 39–17. Selective renal arteriograms demonstrate the four types of renal artery aneurysms. **A,** Saccular aneurysm located at the bifurcation of the main renal artery. **B,** Fusiform aneurysm distal to a stenotic lesion of the main renal artery. **C,** Dissecting aneurysm involving a renal artery branch. **D,** Intrarenal aneurysm.

location, branch arterial involvement is common. The incidence of bilateral or multiple aneurysms or both is approximately 25%. These aneurysms may become involved with secondary atherosclerotic degeneration or intramural calcification or both. Incompletely calcified aneurysms may become soft, thin, and ulcerated between zones of calcification, thus predisposing to rupture. In addition to rupturing spontaneously, saccular aneurysms may erode into the renal vein or into the renal pelvis. Mural thrombus formation may also occur within saccular aneurysms, occasionally leading to peripheral renal embolization.

Fusiform aneurysms occur as a uniform dilatation of an entire segment of the renal artery to as much as three to four times its normal diameter. These aneurysms range in length from 1 to 3 cm and are generally not calcified. They are typically found in young hypertensive patients with stenosing fibrous renal arterial disease. The fusiform aneurysm is actually a poststenotic dilatation and can involve either the main renal artery or its branches. The major complication of this lesion is thrombosis of the involved arterial segment from progressive proximal stenosing vascular disease.

A dissecting aneurysm results from a tear in the internal elastic membrane of the renal artery, and as blood flows through the opening, the intima is separated from the remainder of the arterial wall. In some patients, the dissection may reenter the lumen distally to preserve renal function. In other cases, arterial thrombosis with renal infarction or rupture with hemorrhage may occur. Dissecting aneurysms are most often complications of renal arterial involvement with atherosclerosis, intimal fibroplasia, or perimedial fibroplasia. Less commonly, such an aneurysm may occur as an extension of a dissecting aortic aneurysm.

Intrarenal arterial aneurysms are of mixed origin and may be congenital, post-traumatic, iatrogenic, neoplastic, or associated with polyarteritis nodosa. They are usually saccular or fusiform and may or may not be calcified. Intrarenal aneurysms constitute approximately 17% of all renal arterial aneurysms, and they do have the propensity for rupture. Intrarenal aneurysms that occur after blunt trauma or closed renal biopsy occasionally resolve spontaneously with expectant management.

In general, the diagnosis of renal arterial aneurysm should be considered when ringlike calcification in or near the renal hilum is found on a plain abdominal radiograph. These calcifications occur in about 50% of cases. **The majority of renal arterial aneurysms are small and asymptomatic.** The most common clinical manifestations are hypertension, subcostal or flank pain, hematuria, an abdominal bruit, and, rarely, a palpable pulsating mass. RVH is reported to occur in 15% to 75% of patients and may be due to turbulent flow within an aneurysm, associated arterial stenosis, dissection, arteriovenous fistula formation, thromboembolism, or compression of adjacent arterial branches by a large aneurysm. Complications of renal arterial aneurysms include peripheral dissection, arterial thrombosis with renal infarction, emboli arising from mural thrombus within an aneurysm, obstructive uropathy, erosion into a vein with formation of an arteriovenous fistula, and spontaneous rupture with hemorrhage. Factors that appear to predispose to aneurysmal rupture include absent or incomplete calcification, aneurysmal size greater than 2 cm in diameter, coexisting hypertension, and pregnancy.

A small (2-cm) well-calcified renal arterial aneurysm in an asymptomatic normotensive patient does not require operative intervention. These aneurysms can be followed with serial plain abdominal radiographs to detect any change in size. Surgical removal is indicated for renal arterial aneurysms, regardless of size, in (1) aneurysm causing renal ischemia and hypertension, (2) dissecting aneurysm, (3) aneurysm associated with local symptoms such as flank pain or hematuria, (4) aneurysm occurring in a woman of child-bearing age who is likely to conceive, (5) aneurysm occurring with functionally significant renal arterial stenosis, (6) aneurysm with radiographic evidence of expansion on serial radiographs, or (7) aneurysm containing a thrombus detectable on angiography with evidence of distal embolization.

When none of these criteria are present, small (2-cm) asymptomatic noncalcified or incompletely calcified aneurysms can be managed nonoperatively. Such patients should be followed periodically with serial CT or MRI studies to document the size of the aneurysm. It is not possible to rigidly define indications for operative intervention in asymptomatic patients with aneurysms greater than 2 cm in diameter and with none of the previous criteria. The available data would seem to support surgical excision, if these aneurysms are not calcified throughout or are intrarenal because of the increased tendency to rupture in these settings.

In the largest series of renal artery surgery reported in the recent literature (Henke et al, 2001), a total of 121 patients underwent surgical repair. Eight unplanned nephrectomies were necessary resulting in the need for permanent dialysis in one patient, no perioperative mortality was encountered, and all but two reconstructions remained patent at follow-up.

In a retrospective review of surgical repair of renal artery aneurysms in 94 patients, Pfeiffer and colleagues (2003) encountered one postoperative mortality (in an emergency repair secondary to aneurysm rupture), overall morbidity of 17%, and a primary success rate of 97%.

English and colleagues (2004) reported their results of surgical repair of 72 renal artery aneurysms of varying etiology over a 16-year period. Only one aneurysm was deemed not reconstructable, and nephrectomy was performed. One operative mortality was encountered, and 12% of patients had significant perioperative morbidity, with 96% of repairs maintaining patency at 48 months.

A significant body of literature (almost all case reports) has accumulated over the last few years reporting successful endovascular management of renal artery aneurysms as well as dissection of the renal artery. In the case of renal artery aneurysms, two methods of endovascular treatment are reported. The first involves embolization of the aneurysm (usually with coils) to occlude it without disrupting the renal blood flow (Halloul et al, 2000; Karkos et al, 2000; Mounayer et al, 2000; Tshomba et al, 2002; Lupattelli et al, 2003). The second method involves placing an arterial stent in the renal artery or the branch where the aneurysm originates, thereby maintaining flow through the stent and effectively excluding the aneurysm (Tan et al, 2001; Bruce and Kuan, 2002; Pershad and Heuser, 2004). Stenting the renal artery across an aneurysm has also been described as a successful and rapid method of dealing with ruptured renal artery aneurysm (Schneidereit et al, 2003). Dissection of the renal artery also can be managed endovascularly by placing a renal artery stent through the area of dissection to keep the lumen patent and keep the dissected intima immobilized against the outer layers of the artery (Bilge et al, 2003).

Renal Arteriovenous Fistula

Renal arteriovenous fistulas are relatively uncommon lesions that are generally discovered during the course of angiographic evaluation for suspected renal or renovascular disease. There are three categories of renal arteriovenous fistulas: congenital, idiopathic, and acquired (Tynes et al, 1970; Novick, 1982).

Congenital fistulas have a cirsoid or angiomatous configuration with multiple communications between arteries and veins. They are usually supplied by a renal arterial branch of normal caliber. The angiographic appearance is one of multiple, small, interconnecting arterial and venous channels with impaired distal renal parenchymal vascularity and early filling of the renal vein. They constitute 22% to 25% of all renal arteriovenous fistulas, occur equally in both sexes, and generally do not become manifest until adult life.

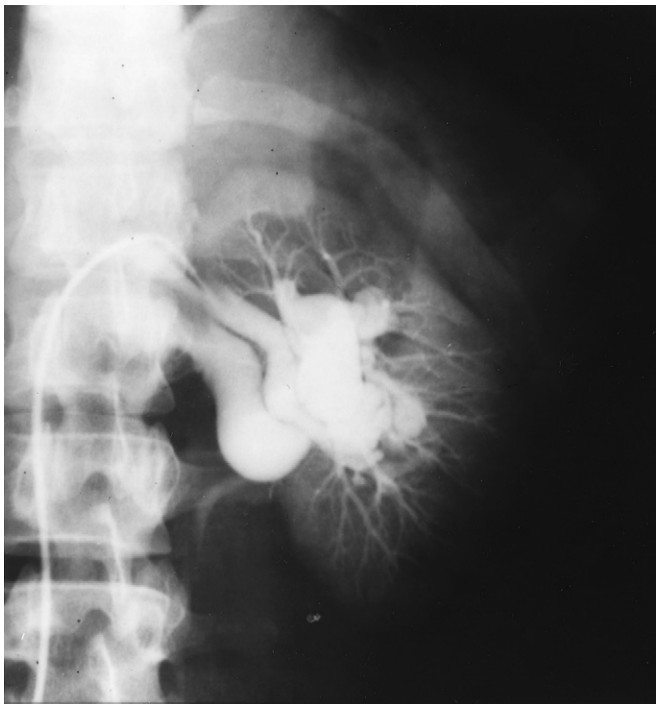


Figure 39–18. Left renal arteriogram shows renal arteriovenous fistula with early filling of the renal vein. This patient had previously undergone needle biopsy of the left kidney.

Table 39–14.

Causes of Renal Arterial Thrombosis and Embolism

Renal Artery Thrombosis
Blunt or penetrating trauma
Aortic or renal artery angiography
Atherosclerosis of aorta or renal artery
Fibrous dysplasia of renal artery
Polycythemia vera
Umbilical artery catheterization in neonates
Inflammation of renal artery
Syphilis
Polyarteritis
Thromboangiitis obliterans
Renal Artery Embolism
Bacterial endocarditis
Aseptic cardiac valvular vegetations
Open heart surgery
Atrial fibrillation
Saccular renal artery aneurysm
Cardiac tumor
Acute myocardial infarction
Ventricular aneurysm
"Paradoxical" embolism

Idiopathic fistulas are single, are not cirsoid, and have no apparent cause. They constitute only 3% to 5% of all renal arteriovenous fistulas. These lesions are called *idiopathic* because their angiographic appearance is similar to that of acquired arteriovenous fistulas, but their origin is unclear.

Acquired fistulas are the most common type, accounting for 70% to 75% of all renal arteriovenous fistulas. On angiography, they appear as solitary communications between an artery and a vein. By far the most common cause is iatrogenic trauma resulting from needle biopsy of the kidney (Fig. 39–18). Other causes include renal carcinoma, blunt or penetrating renal trauma, inflammation, and renal surgery such as nephrectomy, partial nephrectomy, or nephrolithotomy.

The clinical manifestations of a renal arteriovenous fistula depend on the size of the fistula. **Approximately 75% of patients have an abdominal bruit,** which is usually loud, high pitched, and continuous with systolic accentuation. Congestive heart failure, cardiomegaly, and diastolic hypertension are observed in 50% of patients. Hematuria is present in about one third of cases, tachycardia is occasionally found, and a palpable flank mass from spontaneous rupture is rarely encountered.

The management of a patient with a renal arteriovenous fistula depends on the cause of the fistula and the associated clinical manifestations. For patients with renal carcinoma, immediate nephrectomy is obviously indicated. **Approximately 70% of fistulas occurring after needle biopsy of the kidney close spontaneously within 18 months.** A smaller number of fistulas diagnosed immediately after renal trauma have also resolved spontaneously. Therefore in the absence of significant related symptoms, expectant management is appropriate initially in these cases.

Treatment of renal arteriovenous fistulas is indicated for patients who have hypertension, heart failure, severe hematuria, serial angiographic evidence of an expanding lesion, rupture, or progressive renal failure. When specific therapy of these lesions is indicated, renal-sparing procedures should be employed whenever possible.

Transcatheter angiographic occlusion is a nonsurgical therapeutic alternative that has been employed primarily in treating patients with postbiopsy fistulas, in which the arteriovenous connecting vessels are usually small. More recently, transcatheter occlusion of congenital or idiopathic fistulas with a stainless steel coil has also been performed.

Various operations have been employed in the surgical treatment of renal arteriovenous fistulas. **Most congenital or cirsoid fistulas have been managed with total or partial nephrectomy,** because of the difficulty of completely excising the many small communicating vessels. In patients with idiopathic or acquired fistulas, a single communication between the artery and the vein is characteristically present, and surgical obliteration of the fistula with preservation of the involved kidney is more often possible.

Renal Artery Thrombosis or Embolism

Thromboembolic disorders of the renal artery can present as fulminant clinical syndromes that threaten life or may be entirely asymptomatic and detected only at postmortem examination (Hoxie and Coggins, 1940; Schoenbaum et al, 1971). The various causes of acute renal artery thrombosis or embolism are listed in Table 39–14. The term *paradoxical embolism* refers to a clot originating in the venous circulation that gains entrance to the systemic arterial circulation through an intracardiac septal defect.

Renal arterial thrombosis commonly involves the proximal or middle third of the main renal artery, whereas renal arterial embolization generally involves peripheral arterial branches. Acute arterial occlusion is more common on the left side because of the more acute angle between the left renal artery and the aorta. Post-traumatic renal arterial occlusion is also more common on the left side, presumably because of the acute angulation of the shorter left

renal artery at its aortic junction, which predisposes to intimal disruption with deceleration of the mobile kidney.

The clinical symptomatology in these disorders is extremely varied. Bilateral acute renal arterial occlusion presents with rapidly progressing oliguric renal failure, whereas chronic occlusion of a single renal artery may be unnoticed because of the development of collateral circulation. The most common symptoms, when present, are dull, aching abdominal or flank pain often associated with nausea, vomiting, and fever. Other findings include hypertension, albuminuria, microscopic hematuria, leukocytosis, and elevation of serum lactate dehydrogenase levels.

Patients with unilateral renal arterial embolic occlusion generally have serious underlying extrarenal disease and are best managed nonoperatively with systemic anticoagulation or by percutaneous transcatheter thromboembolectomy (Millan et al, 1978; Hamilton, 1996). Patients with unilateral traumatic renal arterial thrombosis also often have severe associated injuries, and the results of vascular reconstruction are generally unsatisfactory unless this is undertaken within several hours of the time of injury. Surgical treatment in these cases is generally ill advised when a normal contralateral kidney is present. Percutaneous intra-arterial infusion of a fibrinolytic agent, such as streptokinase, now offers a nonoperative approach to the management of acute renal arterial thrombosis (Hamilton, 1996).

Renovascular reconstruction is generally indicated when renal artery thrombosis or embolism occurs bilaterally or in a solitary kidney. Alternatively, if angiographic and isotopic studies in such cases demonstrate an extensive collateral vascular supply maintaining renal viability, an initial therapeutic trial with one of the previously mentioned nonoperative approaches may be worthwhile.

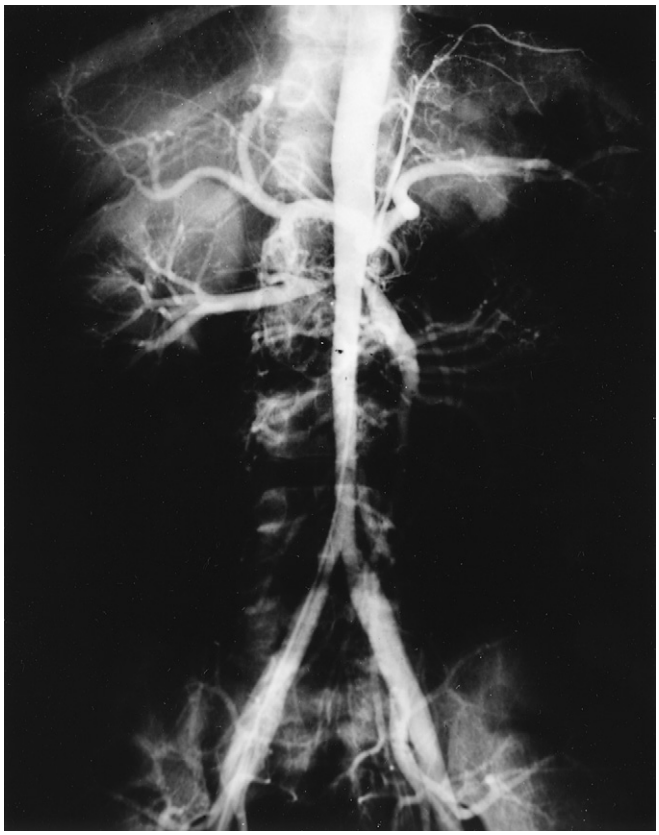


Figure 39–19. Aortography in a child with the middle aortic syndrome shows hypoplasia of the abdominal aorta and right renal artery stenosis.

Neurofibromatosis

Neurofibromatosis affecting the renal arteries is a congenital hereditary disorder characterized by café-au-lait cutaneous pigmentation, cutaneous neurofibromas, tumors of the CNS, skeletal disorders, and occasional gigantism (Grad and Rance, 1972; Tilford and Kelsch, 1973). Hypertension in patients with neurofibromatosis is most often due to renal artery stenosis; less commonly, this may be the result of an associated pheochromocytoma or aortic coarctation. Vascular abnormality occurs in the kidneys, heart, and gastrointestinal tract and consists of fibrosis and thickening of the intima, proliferation of neural tissue within the arterial wall, perivascular nodular proliferations, and occasional aneurysmal dilatation. In the kidney, arterial stenosis usually occurs at the origin or in the proximal third of the main renal artery, and the angiographic appearance may be indistinguishable from that of intimal fibroplasia. Considering the young age of these patients, renal revascularization is generally the treatment of choice for associated RVH.

Middle Aortic Syndrome

The middle aortic syndrome is a rare disorder, occurring in children or young adults, characterized by nonspecific stenosing arteritis affecting the aorta and its major branches, including the renal arteries (Fig. 39–19). This is thought to be a form of Takayasu disease, and an autoimmune pathogenesis is suspected (Kaufman, 1973). This disease can extensively involve the subdiaphragmatic aorta or, in some cases, may spare the aorta and involve primarily the renal or splanchnic vessels. The natural history is not well understood because most cases are diagnosed when the disease has already resulted in significant renal arterial stenosis in young good-risk patients, thus necessitating early revascularization. Because the inflammatory process generally does not extend to involve the iliac arteries, renal autotransplantation is the surgical treatment of choice.

Extrinsic Obstruction

Extrinsic obstruction of the renal artery has been observed but is extremely rare (Silver and Clements, 1976). Neural tissue, musculocutaneous fibers, and diaphragmatic crura have been suggested as etiologic factors contributing to this process. Other possible causes of extrinsic perivascular fibrosis include inflammation, trauma, tumor, or prior radiation.

The Page Kidney

In 1934, Page (1939) produced a renin-dependent model of hypertension by wrapping a dog kidney in cellophane. Hypertension could be reversed by removing the cellophane wrap or the kidney. **The clinical equivalent of this hypertensive model is the kidney compressed by a subcapsular or perirenal process causing renal ischemia, inducing unilateral hypersecretion of renin and contralateral suppression.** Causes of the perinephric process include blunt trauma, closed renal biopsy, anticoagulation, or hemorrhage from a tumor.

The diagnosis of the Page kidney depends on the presence of either a surrounding hematoma or an encasing fibrous

pseudocapsule. Imaging with ultrasonography, CT, or MRI localizes the hematoma or fibrous capsule.

The treatment of the Page kidney aims to preserve renal function and cure hypertension. Medical antihypertensive therapy plus observation, percutaneous evacuation of the perirenal hematoma, open drainage of the hematoma, and nephrectomy have all been used (Suffrin, 1975).

Some cases of the acute Page kidney with new-onset hypertension have spontaneously resolved. A hematoma may reabsorb, relieving the parenchymal compression without forming an adhesive fibrotic pseudocapsule. Treatment with medical antihypertensive therapy can control the blood pressure until the hematoma resolves. If the hematoma does not resolve, it may be drained percutaneously or surgically.

Renal Parenchymal Disease

Renin-mediated hypertension may be secondary to a variety of renal parenchymal diseases. The incidence of hypertension in patients with chronic pyelonephritis is approximately 5% to 10%. The mechanism of renin-mediated hypertension in such kidneys with segmental scars is ischemia of the relatively normal renal cortex in proximity to areas of interstitial fibrosis, within which are small vessels with intimal thickening. Other renal disorders that may cause hypertension include hydronephrosis, congenital hypoplasia or dysplasia, segmental hypoplasia (Ask-Upmark kidney), vesicoureteral reflux, renal cell carcinoma, benign cyst, Wilms tumor, radiation nephritis, or juxtaglomerular cell tumor.

Key Points: Management of Patients with Renal Artery Disease

- Medical management of renovascular hypertension is preferred in patients with mild hypertension or significant comorbidity.
- Medical therapy should aim to reduce overall risk of cardiovascular morbidity, not just lower blood pressure.
- Minimally invasive treatment by renal balloon angioplasty, with or without arterial stenting, has become the preferred method of treating patients with severe hypertension or ischemic nephropathy.
- Percutaneous angioplasty alone is usually successful for treating fibromuscular dysplasia; atherosclerotic disease generally requires arterial stenting in addition to angioplasty.
- Endovascular techniques have been successfully used to treat inflammatory diseases of the renal arteries, renal artery dissections, and renal artery aneurysm.
- Blood pressure results of revascularization (percutaneous or surgical) are significantly better in patients with fibromuscular disease due to the absence of intrinsic renal disease and less medical comorbidity.
- Selection of patients for endovascular or surgical revascularization should be carefully followed, to maximize chances of success and minimize patient morbidity.
- Surgical revascularization is currently employed in a minority of patients who have failed interventional treatment, or whose disease precludes interventional treatment.
- Surgical techniques that avoid operating on a badly diseased aorta (extra-anatomical bypass) can minimize patient morbidity, particularly when compared to combined aortic and renal revascularization.

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chapter 40

Pathophysiology of Urinary Tract Obstruction

Iqbal Singh, MCh (Urology), DNB (Genitourinary Surgery), MS, DNB ● Jack W. Strandhoy, PhD ● Dean G. Assimos, MD

Prevalence of the Problem
Global Renal Functional Changes
Pathologic Changes of Obstruction
General Issues in Management of Patients
Selected Extrinsic Causes of Ureteral Obstruction

Obstruction of the urinary tract can occur during fetal development, childhood, or adulthood. The point of obstruction can be as proximal as the calyces and as distal as the urethral meatus. The cause of obstruction may be congenital or acquired and benign or malignant. The impact of the obstruction is influenced by the extent or degree of obstruction (partial or compete, unilateral or bilateral), its chronicity (acute or chronic), the baseline condition of the kidneys, the potential for recovery, and the presence of other mitigating factors such as urinary infection. These may ultimately lead to permanent renal damage, which may result in limiting the excretion of metabolic wastes and altering water and electrolyte balance.

Certain terms used in this chapter as descriptors of this process need to be defined from the outset. *Hydronephrosis* is the dilation of the renal pelvis or calyces. It may be associated with obstruction but may be present in the absence of obstruction. *Obstructive uropathy* refers to the functional or anatomic obstruction of urinary flow at any level of the urinary tract. *Obstructive nephropathy* is present when the obstruction causes functional or anatomic renal damage.

PREVALENCE OF THE PROBLEM

The prevalence of urinary tract obstruction is best estimated from autopsy series. In a series of 59,064 autopsies performed on individuals ranging from neonates to geriatric subjects, hydronephrosis was reported in 3.1% (Bell, 1950). There were no gender differences in this series until the age of 20 years. However, hydronephrosis was more prevalent in women in the 20- to 60-year interval. The latter was attributed to pregnancy and development of gynecologic malignancies. It was more prevalent in males after age 60 years, because of prostatic diseases. Hydronephrosis has been reported to be present in 2% to 2.5% of children subjected to autopsy (Campbell, 1970; Tan et al, 1994). It is somewhat more prevalent in boys, and the majority of cases were in subjects younger than 1 year. The aforementioned prevalences are most likely an underestimate of obstructive events, because temporary bouts of obstruction such as those induced by prior pregnancy or stone episodes were not captured.

There are no new data regarding the prevalence and incidence of obstructive uropathy. However, there are new data on ureteropelvic junction obstruction and ureterocele that may permit certain inferences. Based on the United States published and coded data on ureteropelvic junction obstruction generated by the Healthcare Cost and Utilization Project (HCUP) and Kids' Inpatient Database (KID), the number of inpatient hospitalizations for ureteropelvic junction have decreased from 1.1 per 100,000 in 1994 to 0.8 per 100,000 in 2000. Although this may be influenced by a shift to more outpatient procedures or observational management, it could also be due to a decreasing incidence of this problem (Schulam et al, 2007). However, this has not been demonstrated for those afflicted with ureterocele where the rates have been stable over this interval (Pohl et al, 2007).

The pathophysiology of obstructive nephropathy is discussed in detail in the beginning of this chapter to provide a platform for understanding the clinical ramifications of this process, some of which are detailed in later sections that focus on unique causes of this problem. The mechanisms of obstructive nephropathy are unveiled at genetic, molecular, cellular, glomerular, renal tubular, whole kidney, and systemic levels. The impact of obstruction on the fetal and developing kidney is not emphasized because this is covered in other sections of this book. A list of possible causes of obstructive nephropathy is provided in Table 40–1.

GLOBAL RENAL FUNCTIONAL CHANGES

Glomerular Filtration, Renal Blood Flow, Collecting System Pressure

There are many functional changes in the kidney associated with obstructive nephropathy that affect renal hemodynamic variables and glomerular filtration. These are influenced by the extent and severity of obstruction, whether the obstruction is unilateral or bilateral, and whether the obstruction currently persists or has been relieved. A brief discussion of the determinants of glomerular filtration is in order to understand the interrelationships between changes in renal hemodynamics and alterations in the glomerular filtration rate (GFR) during and after obstruction. Factors influencing GFR are expressed in the following equation:

$$GFR = K_f(P_{GC} - P_T - \pi_{GC})$$

Table 40–1.
Possible Causes of Obstructive Nephropathy

Renal	
Congenital	Polycystic kidney
	Renal cyst
	Peripelvic cyst
	Ureteropelvic junction obstruction
Neoplastic	Wilms tumor
	Renal cell carcinoma
	Transitional cell carcinoma of the collecting system
	Multiple myeloma
Inflammatory	Tuberculosis
	Echinococcus infection
Metabolic	Calculi
Miscellaneous	Sloughed papillae
	Trauma
	Renal artery aneurysm
Ureter	
Congenital	Stricture
	Ureterocele
	Obstructing megaureter
	Retrocaval ureter
	Prune-belly syndrome
Neoplastic	Primary carcinoma of ureter
	Metastatic carcinoma
Inflammatory	Tuberculosis
	Amyloidosis
	Schistosomiasis
	Abscess
	Ureteritis cystica
	Endometriosis
Miscellaneous	Retroperitoneal fibrosis
	Pelvic lipomatosis
	Aortic aneurysm
	Radiation therapy
	Lymphocele
	Trauma
	Urinoma
	Pregnancy
	Radiofrequency ablation
Bladder and Urethra	
Congenital	Posterior urethral valve
	Phimosis
	Hydrocolpos
Neoplastic	Bladder carcinoma
	Prostate carcinoma
	Carcinoma of urethra
	Carcinoma of penis
Inflammatory	Prostatitis
	Paraurethral abscess
Miscellaneous	Benign prostatic hypertrophy
	Neurogenic bladder
	Urethral stricture

K_f is a glomerular ultrafiltration coefficient related to the surface area and permeability of the capillary membrane. P_{GC} is the glomerular capillary pressure, which is influenced by renal plasma flow and the resistances of the afferent and efferent arterioles. The hydraulic pressure driving fluid into Bowman space is resisted by the hydraulic pressure of fluid in the tubule (P_T), and also the increasing oncotic pressure (π) of the proteins remaining at higher concentrations in the late glomerular capillary and efferent arteriolar blood. Although filtered fluid is not completely free of small proteins, for practical purposes, its oncotic pressure is negligible. The net pressure determining glomerular filtration is referred to as the ultrafiltration pressure (P_{UF}) and is derived from ($P_{GC} - P_T - \pi_{GC}$). P_{GC} is also influenced by renal plasma flow (RPF). RPF depends upon the renal perfusion pressure and intrarenal resistance to flow, the latter primarily mediated by the resistances in the afferent and efferent arterioles. The aforementioned relationships are depicted in the following equation:

$$\text{RPF} = \frac{\text{aortic pressure} - \text{renal venous pressure}}{\text{renal vascular resistance}}$$

Thus constriction of the afferent or efferent arteriole or both would reduce RPF. Constriction of the afferent arteriole results in a decrease of P_{GC} and GFR, whereas an increase in efferent arteriolar resistance increases P_{GC}. Whole kidney GFR depends upon factors regulating perfusion of each glomerulus and also upon the percentage of glomeruli actually filtering. For each glomerulus, the single-nephron glomerular filtration rate (SNGFR) is determined by the previously mentioned GFR equation. Obstruction can transiently or permanently alter GFR and some or all of the determinants of GFR.

The results of animal experiments are used here to profile the hemodynamic, renal, and systemic responses of renal obstruction. The limitations of animal models including the potential for a species-specific response must be taken into consideration when making analogies or comparisons with humans.

Hemodynamic Changes with Unilateral Ureteral Occlusion

There are differences between unilateral ureteral obstruction (UUO) and bilateral obstruction (BUO) that have been characterized in animal models. These include hemodynamic patterns and other factors that influence GFR. Renal blood flow (RBF) was assessed in the classical studies characterizing hemodynamic differences. In some, RBF was measured directly with various types of flow probes, and in others it was determined indirectly by measuring RPF using secretory markers and indexing this to the hematocrit. A number of vasoactive substances are thought to play a role in the changes in RBF and GFR occurring with both models of obstruction. The timing of changes in intrarenal concentrations of vasoconstrictors and vasodilators during the course of obstruction and the release of obstruction is poorly understood. The varying hemodynamic patterns during the time course of obstruction may be due to a combination of vasoactive hormones synthesized and released at different rates, physical damage to glomerular and tubular units, and extrarenal compensatory mechanisms.

Animal experiments have demonstrated a triphasic pattern of RBF and ureteral pressure changes in UUO that differs from BUO or unilateral obstruction of a solitary kidney (Fig. 40–1). With UUO, RBF increases during the first 1 to 2 hours and is accompanied by a high P_T and collecting system pressure because of the obstruction. In a second phase lasting 3 to 4 hours, these pressure parameters remain elevated but RBF begins to decline. A third phase beginning about 5 hours after obstruction is characterized by a further decline in RBF, now paralleled by a decrease in P_T and collecting system pressure. These changes are explained by physical alterations in flow dynamics within the

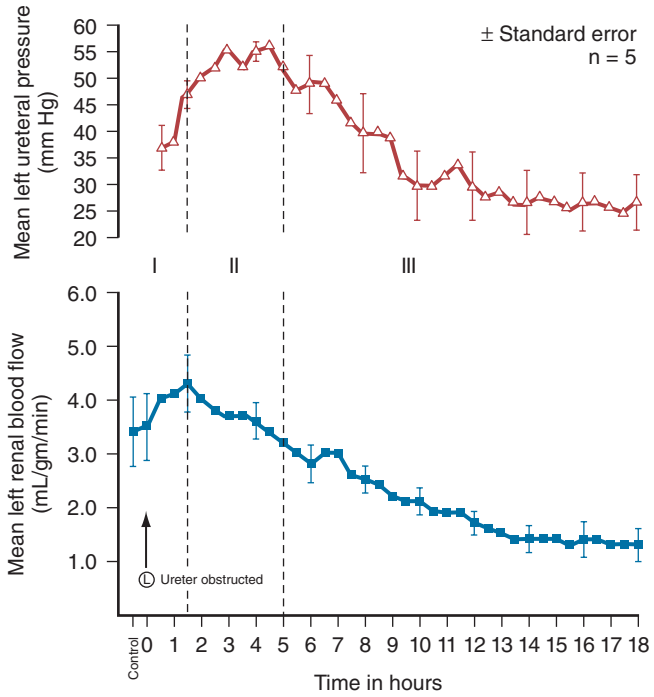


Figure 40–1. Triphasic relationship between ipsilateral renal blood flow and left ureteral pressure during 18 hours of left-sided occlusion. The three phases are designated by roman numerals and separated by vertical dashed lines. In phase I, renal blood flow and ureteral pressure rise together. In phase II, the left renal blood flow begins to decline and ureteral pressure remains elevated and, in fact, continues to rise. In phase III, the left renal blood flow and ureteral pressure decline together. (From Moody TE, Vaughn ED Jr, Gillenwater JY. Relationship between renal blood flow and ureteral pressure during 18 hours of total unilateral ureteral occlusion. Implications for changing sites of increased renal resistance. Invest Urol 1975;13:246–51.)

kidney and are modified by changes in the biochemical and hormonal milieu regulating renal resistance.

In the first phase of UUO, the increase in P_T would logically be expected to reduce GFR greatly. However, this is counterbalanced by an increase in RBF related to afferent arteriolar vasodilation (Vaughan et al, 1970), which limits the fall in GFR because P_{GC} rises. This hyperemic response has been attributed to stimulation of the tubuloglomerular feedback mechanism that relaxes the afferent arterioles as a consequence of decreased sodium delivery to the macula densa (Wright and Briggs, 1979), changes in interstitial pressure within the kidney (Vaughan et al, 1971; Francisco et al, 1980), or the release of vasodilators such as prostanoids like prostaglandin E_2 (PGE_2) (Allen et al, 1978). There are various lines of evidence supporting the role of prostaglandin involvement. Frøkiær and Sørensen (1995) demonstrated an increase in PGE_2 excretion in the urine from the contralateral kidney after UUO. In addition, studies have shown that the increase in PGE_2 and the vasodilation of the obstructed kidney could be blocked by indomethacin, a prostaglandin synthesis inhibitor (Allen et al, 1978; Blackshear and Wathen, 1978; Gaudio et al, 1980). Nitric oxide (NO) may also contribute to the early renal vasodilation in UUO. The kidney contains nitric oxide synthases (NOS) that are both constitutive (endothelial and neuronal isoforms) and inducible (iNOS). In obstructed kidneys from rabbits and rodents, iNOS increases (Salvemini et al, 1994; Miyajima et al, 2001). Furthermore, Lanzone and colleagues (1995) showed that administration of the NOS inhibitor N^G-monomethyl-L-arginine (L-NMMA) before UUO attenuated the early rise in RBF, and that the renal vasodilation returned when L-NMMA was discontinued. **Thus it is likely that both PGE_2 and NO contribute to the net renal vasodilation that occurs early following UUO.**

After this initial phase of several hours, GFR and RBF progressively decline in UUO (Jaenike, 1972; Harris and Yarger, 1974; Dal Canton et al, 1980). In contrast to the early rise in P_T in the initial phases of UUO, this parameter and RBF both decline 12 to 24 hours after obstruction. This is best explained by an increase in afferent arteriolar resistance (R_{aff}) that occurs. At this time, there are also shifts in regional blood flow in the kidney, with large portions of the cortical vascular bed not perfused or underperfused (Harris and Yarger, 1974; Gaudio et al, 1980). A shift in RBF from the outer cortex to more juxtamedullary regions was reported by Yarger and Griffith (1974) in dogs with UUO. **Thus reduced whole kidney GFR at this stage of obstruction is due not only to reduced perfusion of individual glomeruli, related to afferent vasoconstriction and reduced P_{GC}, but also to global reduction in filtration related to no perfusion or underperfusion of many glomeruli** (Arendshorst et al, 1974).

Vasoconstrictors appear to play a role in the reduction in RBF after UUO. There is evidence that the renin-angiotensin system is activated during UUO, that is, during the first phase of UUO renal vein renin levels increase (Moody et al, 1975; Yarger et al, 1980) even though there is a net renal vasodilation at this time**. Infusion of the angiotensin-converting enzyme (ACE) inhibitor captopril attenuates the declines in RBF and GFR in UUO, suggesting that angiotensin II is an important mediator of the preglomerular vasoconstriction occurring during the second and third phases of UUO** (Ichikawa et al, 1985).

Other vasoconstrictors also appear to be involved in the reduction of RBF with UUO. Thromboxane A_2 (TXA_2) is also thought to be an influential postobstructive vasoconstrictor that contributes to the continued reduction in GFR and RBF. Administration of TXA_2 synthesis inhibitors to the obstructed kidney limits the reduction in RBF and GFR (Klotman et al, 1986; Loo et al, 1987; Purkerson and Klahr, 1989). TXA_2 may be generated in the kidney itself, perhaps in glomeruli (Yanagisawa et al, 1990), but synthesis from macrophages migrating to the kidney during obstruction is another potential source of this vasoconstrictor (Schreiner et al, 1988; Harris et al, 1989).

Endothelin is another endogenous vasoconstrictor thought to participate in these events, although perhaps later in the established phase of UUO and after release of the obstruction. Administration of endothelin antagonists limits the reduction of RBF and GFR in rats during and after release of UUO (Bhangdia et al, 1998; Syed et al, 1998; Colon et al, 2000). Furthermore, endothelin excretion is increased in the targeted kidney after release of UUO in swine but not in the contralateral renal unit (Kelleher et al, 1992).

The kidney's response to the release of UUO depends on the duration and extent of obstruction and is also species specific. Many models of UUO use complete obstruction of the ureter for 24 hours before release. After release of 24-hour UUO, the GFR is initially 50% of normal in dogs and less than 25% of normal in rats, accompanied by greatly reduced RBF. There are also regional differences within the kidney. Harris and Yarger (1974) showed a

marked decrease in perfusion of the superficial cortex accompanied by an increase in juxtamedullary glomerular perfusion after release of 24 hours of UUO in rats. Tubuloglomerular feedback may play a role in these responses (Tanner, 1985). Some of the mediators of the hemodynamic changes in the kidney following release of the obstruction may be different from those involved in the earlier phases.

Hemodynamic Changes with Bilateral Ureteral Occlusion

The changes with BUO or obstruction of a solitary kidney are different. **In contrast to the early robust renal vasodilation with UUO, there is a modest increase in RBF with BUO that lasts approximately 90 minutes, followed by a prolonged and profound decrease in RBF that is greater than found with UUO** (Gulmi et al, 1995). Reyes and Klahr (1992) found that an NO synthesis antagonist caused a further decline in RBF and GFR compared with control values, suggesting that NO helps maintain renal hemodynamics in early BUO. Other potential vasodilators, such as platelet-activating factor (PAF), have been postulated to contribute to renal hemodynamic changes with BUO. Reyes and Klahr (1991) showed, in rats, that when vasoconstrictors such as TXA_2 were blocked, endogenous or exogenous intrarenal PAF-mediated vasodilation contributed to the preservation of RBF and GFR. The earlier and more profound decrease in RBF with BUO may be contributed to by increased renal nerve stimulation that initiates vasoconstriction related to increased renorenal reflex activity (Francisco et al, 1980; Ma et al, 2002). Endothelin may also contribute to these responses in BUO. The administration of an endothelin antibody to rats with BUO was reported to attenuate the decreases in GFR and RPF (Reyes and Klahr, 1992). Angiotensin II and TXA_2 are also probably involved in the changes occurring with BUO. The administration of inhibitors of either of these vasoconstrictors to rats, prior to BUO, resulted in improved postobstructive GFR and RPF compared with their administration at the time of release of obstruction (Purkerson and Klahr, 1989).

The intrarenal distribution of blood flow is quite different with BUO than with models of UUO. Jaenike (1972) used microspheres to show that 55% of the RBF perfused the cortical nephrons, while the innermost zones received only 14% of the flow in rats after BUO. Similarly, Solez and associates (1976) showed a 92% decrease in inner medullary plasma flow with 18 hours of BUO in rats**. Thus the shift seen with UUO of blood flow from outer to inner cortex is the opposite of that with BUO.**

Ureteral pressure is higher with BUO than with UUO. Although in both cases ureteral and tubular pressures are increased for the first 4 to 5 hours, the ureteral pressure remains elevated for at least 24 hours with BUO, whereas it begins to decline and approaches preocclusion pressures by 24 hours with UUO. The prolonged elevation in intratubular pressure contributes to the profound decrease in SNGFR and whole kidney GFR. Micropuncture studies (Yarger et al, 1972; Dal Canton et al, 1980) in which intratubular pressure is measured directly have demonstrated that it remains elevated in rats after 24 hours of BUO in comparison with pressure normalization in animals after 24 hours of UUO. Ureteral pressure remains high because BUO passes through a phase of preglomerular vasodilation and then a prolonged postglomerular vasoconstriction. This explains the persistent elevation in ureteral pressure in spite of a decrease in RBF and increase in renal resistance. In contrast, in UUO the initial preglomerular dilation and short-lived postglomerular vasoconstriction are followed by a more prolonged preglomerular vasoconstriction that tempers elevations in P_{GC} and hence in P_T. **This difference between the two pathophysiologic conditions has been hypothesized to be due to an accumulation of vasoactive substances in BUO that could contribute to preglomerular vasodilation and postglomerular vasoconstriction. Such substances would not accumulate in UUO because they would be excreted by the contralateral kidney. Atrial natriuretic peptide (ANP) appears to be one of these substances** (Purkerson et al, 1989). With excretory ability abrogated, BUO increases intravascular volume, as evidenced by an increase in pulmonary capillary wedge pressure and body weight, which serves as the stimulus for secretion of ANP. ANP increases afferent arteriolar dilation and efferent arteriolar vasoconstriction, thus increasing P_{GC}. It also decreases the sensitivity of tubuloglomerular feedback, inhibits release of renin, and increases K_f (Fried et al, 1987; Brenner et al, 1990; Cogan, 1990). In addition, changes within the renal unit may contribute to elevated pelvic pressure. In both rats and humans, ureteral obstruction increases COX-2 in the proximal dilated ureter but not in the distal nondilated ureter. When the obstruction was released, the urinary concentration of PGE_2 was elevated. Furthermore, a COX-2 selective inhibitor reduced pelvic pressure. Thus intrarenal PGE_2 acting on ureteral smooth muscle may contribute directly to increased pelvic pressure after obstruction (Nørregaard et al, 2006). Glomerular filtration and RBF remain depressed after release of BUO. This is due to persistent vasoconstriction of the afferent arteriole (Jaenike, 1972; Moody et al, 1977). The decrease in RBF in the renal medulla remains more prominent than in the cortex (Solez et al, 1976). Tubuloglomerular feedback does not appear to contribute to this response as it does with UUO (Tanner, 1985). Urine flow and sodium excretion are increased after release of BUO. ANP appears to play a prominent role in this response based on its natriuretic properties and those previously reviewed. It may also have a protective effect. Ryndin and associates (2005) reported that the administration of ANP or phosphoramidon, an inhibitor of ANP degradation, to rats with BUO resulted in improved GFR and a more brisk diuresis and natriuresis after release of obstruction.

In summary, both UUO and BUO involve increases in renal vascular resistances and increases in ureteral pressures. However, the timing and regulation of these changes differ (Fig. 40–2). With UUO, early renal vasodilation primarily mediated by prostaglandins and NO is followed by prolonged vasoconstriction and normalization of intratubular-ureteral pressure as the contralateral kidney contributes to fluid balance. With BUO, little early vasodilation is seen, and vasoconstriction is more profound. When the obstruction is released, the postobstructive diuresis is much greater with BUO because volume expansion, urea and other osmolytes, and secreted ANP contribute to a profound diuresis and natriuresis.

Partial Ureteral Occlusion

Although most models of urinary tract obstruction study complete obstruction over a fixed time interval, such as 24 hours, many clinical conditions involve partial obstruction over varying times. Partial obstruction models often involve perinatal obstruction where renal growth and differentiation may be affected, as well as hemodynamics and excretion. In many cases, the changes in renal hemodynamics and in tubular function are similar to those induced by more acute, complete models of obstruction but develop more slowly. In other cases, such as perinatal models of

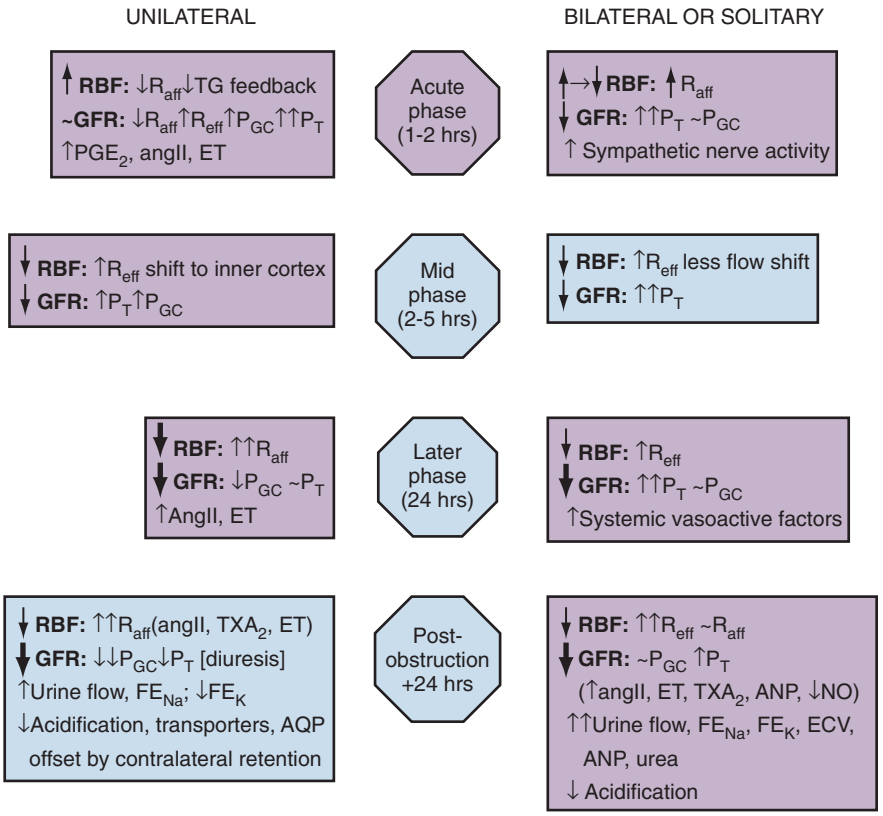


Figure 40–2. Summary of the functional changes during and following ureteral obstruction. Symbols and abbreviations indicate ↑↓, increases and decreases; ~, little change; angII, angiotensin II; ANP, atrial natriuretic peptide; AQP, aquaporin; ECV, extracellular volume; ET, endothelin; FE, fractional excretion; NO, nitric oxide; P_{GC}, glomerular capillary hydraulic pressure; P_T, proximal tubular hydraulic pressure; PGE_2, prostaglandin E_2; R_{aff}, afferent arteriolar resistance; R_{eff}, efferent arteriolar resistance; RBF, renal blood flow; TG feedback, tubuloglomerular feedback; TXA_2, thromboxane A_2.

obstruction either before or shortly after birth, an animal such as a rat is still in a period of nephrogenesis. **Consequently, formation of glomeruli and tubules may be compromised so that irreversible changes occur without total loss of kidney function.**

Recovery of renal function in adult animals with partial obstruction has been studied as a potential guideline for clinical treatment. Leahy and coworkers (1989) studied dogs in which partial UUO with stents was studied for up to 60 days. Reversibility of renal function was estimated by creatinine clearance. Renal function became normal in dogs partially obstructed for 14 days. Animals partially obstructed for 28 days recovered 31% of function, and those partially obstructed for 60 days recovered only 8% of function. Casts of the microvasculature showed arteriolar constriction, supporting the concept that postobstructive renal dysfunction is influenced by vascular responses.

Much less is known about the roles of vasoactive or inflammatory mediators in the partial ureteral obstruction model. As with acute occlusive models, administration of indomethacin or meclofenamate, both prostaglandin synthetase inhibitors, decreases GFR and increases arteriolar resistance (Ichikawa and Brenner, 1979) so that changes in eicosanoids are implicated in partial obstruction responses. Several investigators have shown that the renin-angiotensin-aldosterone axis is activated with partial obstruction, including studies in the fetus. Gobet and colleagues (1999) studied fetal sheep in utero and showed that partial obstruction of the bladder outlet increased renin messenger RNA (mRNA) after 2 weeks and increased the expression of renal AT2 receptors as well as the mRNA for transforming growth factor beta (TGF-β), a mediator of fibrosis.

One could hypothesize that changes in angiotensin II may be responsible for much of the hemodynamic, fibrotic, and apoptotic changes in neonatal animals with partial obstruction, as has been shown in more acute models. Beharrie and coworkers (2004) examined weanling male rats that had been subjected to a partial UUO. The partial obstruction led to proteinuria, hyperuricemia, and increased solute excretion primarily from the unaffected contralateral kidney. A parallel group of rats treated with the ACE inhibitor enalapril was protected from these changes. This suggests that angiotensin is involved with functional tubular changes as well. Eskild-Jensen and colleagues (2002) examined partial UUO for up to 24 weeks in young, postnatal pigs. The number of glomeruli was 28% less in the obstructed kidney, yet function was just transiently reduced by the occlusion. **Thus partial neonatal obstruction can impair nephrogenesis independently of renal functional decline, and these changes may depend upon species, stage of renal development, or degree of occlusion.** More work is needed to define the variables.

Various methods have been used to create partial obstruction. The models for preparing partial ureteral occlusions fall into three main categories. Intraluminal stents or catheters of varying sizes have been placed in the ureters of sheep (Abu-Zidan et al, 1999) and in dogs (Ryan and Fitzpatrick, 1987; Leahy et al, 1989) to restrict flow. In rats, or in growing animals, many investigators have used the technique of Ulm and Miller (1962), which involves splitting the psoas muscle longitudinally to form a groove into which the ureter is placed. This method has a potential advantage of increased constriction in proportion to the growth of the animal. Beharrie and colleagues (2004) used such a technique in young male weanling rats. A major problem with studies involving partial obstruction is the inability to determine reproducibly and accurately the degree of obstruction induced with these techniques. Thornhill and associates (2005) devised a method in neonatal rat pups of ligating a ureter along with a wire of a calibrated

diameter that was then removed to make a partial and graded constriction of one ureter. When ureteral diameter was reduced by 70% to 75%, renal growth and number of glomeruli were reduced and fibrosis and pelvic dilation were proportionately increased. GFR was reduced by 80% after 28 days of partial UUO. Such models may offer new opportunities to model the clinical condition reproducibly.

Egress of Urine from the Kidney

Although the normal flow of urine from the kidney through the urinary tract is compromised with obstruction, urine may still egress from the kidney. An example of this is extravasation at the calyceal fornix (pyelosinus) that occurs with acute obstruction, typically ureteral stones (Stenberg et al, 1988). Extravasation of urine into the venous (pyelovenous) and lymphatic system (pyelolymphatic) may also occur in this setting. In chronic obstruction, fluid is thought to exit into the renal venous system.

Effects of Obstruction on Tubular Function

Obstruction of one or both kidneys can have profound effects on sodium, potassium, and hydrogen excretion and mechanisms of urinary concentration and dilution. In the case of UUO, relatively normal function of the nonobstructed kidney partially offsets the reduced ability of the postobstructive kidney to reabsorb solutes and water. **Postobstructive diuresis, something that is commonly encountered after reversal of BUO, occurs uncommonly after release of UUO, probably as a consequence of the contralateral renal unit's functional capacities that are enhanced by an upregulation of ion transporters (Li et al, 2007).** The eventual correction of abnormal renal excretory function depends upon the degree and duration of obstruction.

Changes in tubule function after correction of UUO related to ureteropelvic junction or ureteral obstruction were characterized in 10 patients by Gillenwater and colleagues (1975). The mean period of obstruction in these cases was 12 months, and the range was from days to years. Functions of the normal and obstructed kidney were evaluated 1 week after relief of the obstruction. The GFR in the obstructed kidney was significantly less than that in the non-obstructed kidney (24 vs. 60 mL/min), and the urine osmolality and osmolar clearance were all significantly less in the postobstructed kidney. The similar osmolar clearances (volume of urine required to excrete urinary solute isosmotically) relative to GFR of the previously obstructed and unobstructed kidneys indicate that there is a true concentrating defect in the obstructed kidneys 1 week after relief of obstruction.

Urinary Concentrating Ability

Normal urine concentrating ability requires a hypertonic medullary interstitial gradient because of active salt reabsorption from the thick ascending limb of Henle, urea back flux from the inner medullary collecting duct, and water permeability of the collecting duct mediated by vasopressin and aquaporin water channels. Obstructive nephropathy can disrupt some or all of these mechanisms and lead to deficits in urinary concentration. A brief review of the normal concentrating mechanisms is provided to facilitate understanding the effects of obstruction.

In normal physiology, arginine vasopressin (AVP) is secreted into the bloodstream from the posterior pituitary gland in response to increased serum osmolality or a reduction in effective circulating volume. AVP binds to the V2 vasopressin receptor located on the basolateral surfaces of the collecting duct cells. This promotes G protein signaling, resulting in generation of cyclic adenosine monophosphate (cAMP). Generation of cAMP in turn activates protein kinase A, which stimulates the fusion of cytoplasmic vesicles containing aquaporin 2 (AQP2) with the apical membranes of the collecting duct cells. The fusion causes the normally watertight membrane to become water permeable. This promotes transcellular absorption of water through the AQP2 channels, which is transported through aquaporin 3 (AQP3) and aquaporin 4 (AQP4) channels located in the basolateral cell membrane into the interstitium. This sequence of events is driven by the osmotic gradient of sodium (Knoers, 2005). Another aquaporin, aquaporin 1 (AQP1), is abundant in renal proximal tubules, the thin descending limb of Henle, and the descending vasa recta in the kidney. It promotes urinary concentration through the countercurrent multiplier by facilitating water transport from the descending limb of Henle into the interstitium (King et al, 2001).

The onset of concentration defects may develop soon after obstruction. Jaenike and Bray (1960) demonstrated a concentrating defect in the unilaterally obstructed kidney after only 6 minutes of ureteral obstruction. Development of vasopressin resistance has been hypothesized as a mechanism of this occurrence. However, various studies have demonstrated conflicting results concerning whether vasopressin resistance is present. Vascular changes may play a role. Even after only 18 hours of UUO, Solez and colleagues (1976) found a decrease in inner medullary plasma flow that increased when the occlusion was released. Necrosis of both the inner and outer medullae was present, indicating that ischemia may contribute to the development of a concentrating defect.

Evidence from Li and coworkers (2001) demonstrated that the polyuria following the release of BUO correlates with a decreased expression of the aquaporin water channels AQP1, AQP2, and AQP3 in rats. Release of obstruction resulted in polyuria that gradually decreased over a 30-day period, even though urinary concentrating capacity remained significantly impaired. Expression of AQP2 and AQP3 became normal by 30 days after release, but the expression of AQP1 remained decreased.

Jensen and coworkers (2006) examined changes in water channels after bilateral ureteral obstruction in rats. As expected, postobstructive polyuria with reduced urine osmolality was accompanied by decreased expressions of AQP1, AQP2, and AQP3 compared with control rats. The AT1 antagonist candesartan attenuated reductions in GFR, urine output, and AQP suppression, as well as COX-2 induction in the inner medulla. These findings suggest that angiotensin II influences, directly or indirectly, the postobstructive diuresis of BUO.

Thus dysregulation of aquaporin water channels in the proximal tubule, thin descending loop, and collecting duct may contribute to the long-term polyuria and impaired concentrating capacity caused by obstructive nephropathy. Increases in angiotensin II may be a mediator of these changes.

Sodium Transport

A decrease in sodium transport in the nephron appears to play an additional prominent role in the decreased ability of the postobstructed kidney to concentrate urine. When UUO is released after an occlusion period of 24 hours, total urine excretion is normal

to modestly increased despite increased fractional excretion of sodium (FE_{Na}) in the previously obstructed kidney. This is attributed to the contralateral kidney compensating for the sodium losses of its mate. However, with BUO, sodium and water excretions may be quite robust after release of obstruction. The FE_{Na} may be increased to as much as 20 times normal in this setting (Zeidel and Pirtskhalaishvili, 2004). **Although ANP appears to play a role in sodium diuresis after release of BUO, it is unlikely to affect sodium transport defects associated with UUO.** The latter is most likely due to selective cell membrane changes in the nephron that reduce the number and effectiveness of sodium transporters. Such changes may also occur with BUO.

In spite of differential quantitative responses between UUO and BUO after release of the obstruction, the reabsorption defects in segmental nephron Na^+ transport are similar. Micropuncture studies of kidneys from animals have been undertaken to assess these responses. These studies demonstrate normal to modestly enhanced isotonic volume flux (J_v) in superficial proximal convoluted tubules after release of UUO or BUO. On the other hand, sodium delivery to the loop of Henle in juxtamedullary nephrons, and to the first accessible portion of the inner medullary collecting duct, is substantially increased after release of both UUO and BUO, indicative of reduced sodium transport. Sonnenberg and Wilson (1976) even found evidence for net influx of sodium throughout the medullary collecting duct, which further contributed to an increased FE_{Na}. However, this was more prominent with BUO in their rat model.

Studies in isolated perfused nephron segments have also provided knowledge about the impact of obstruction at the level of the nephron. They have shown normal isotonic reabsorption in the superficial proximal convoluted tubules from animals with either UUO or BUO, whereas J_v in proximal straight tubules from juxtamedullary nephrons was demonstrated to be impaired (Hanley and Davidson, 1982). Similarly, chloride reabsorption and transport-dependent oxygen consumption (QO_2) from the medullary thick ascending limb of the Henle loop (MTAL) were severely impaired (Hanley and Davidson, 1982; Hwang et al, 1993b).

Cell suspensions from nephron segments have been used to assess the effects of obstruction at a cellular level. Active transport of Na^+ across cell membranes requires apical entry through selective Na^+ transporters or channels and basolateral exit driven by sodium-potassium adenosine triphosphatase (Na^+,K^+-ATPase). Furthermore, adequate adenosine triphosphate (ATP) must be generated to drive these primary transport steps. Hwang and associates showed that the amount and activity of the apical Na^+,K^+,$2Cl^-$ cotransporter and bumetanide binding sites were reduced in cells isolated from the MTAL derived from obstructed rabbit kidneys. Basolateral transport is also affected in that ouabain-sensitive oxygen consumption, an index of Na^+,K^+-ATPase activity, has been shown to be reduced in cell suspensions from obstructed kidneys (Hwang et al, 1993a). A marked decrease in amiloride-sensitive oxygen consumption and Na^+ entry in isolated cells from the inner medullary collecting ducts of obstructed rabbit kidneys reflects reduced activity of the apical Na channel (ENaC). In addition, ouabain-sensitive transport as measured by oxygen consumption and ATPase activity was shown to be reduced in cells from this portion of the nephron harvested from obstructed kidneys (Hwang et al, 1993a). Because cell suspension studies indicate that ATP generation is not the rate-limiting step underlying sodium transport dysfunction in this setting, the evidence points to downregulation of sodium transporters. This may be due to translational factors (reduction in mRNA for transporter synthesis) or post-translational processing of receptor proteins (Hwang et al, 1993a).

The signals responsible for downregulation of transporter activity with obstruction have not been clearly defined, but a number have been hypothesized. Stasis of tubular fluid flow may be one of the signals. When urine flow is obstructed, upstream Na^+ delivery to apical cell membranes slows so that the transmembrane gradient is reduced. This could then serve as the signal for the downregulation of transporter activity or expression resulting in reduced active Na^+ transport across the basolateral cell membrane (Zeidel, 1993). Several studies indicate that this is a feasible mechanism. For example, ouabain-sensitive Na^+,K^+-ATPase activity is reduced in MTAL and collecting duct cells when mineralocorticoid activity is controlled and chronic furosemide or amiloride is given to reduce Na^+ entry into tubule cells (Petty et al, 1981; Grossman and Hebert, 1988). Additional studies have explored this concept in established cell lines. When A6 cells, an established line of collecting duct cells, are grown on a permeable substrate, Na^+ influx across the apical membrane through the ENaC Na^+ channel occurs. When Na^+ entry was blocked, this induced a decreased expression of β-subunit of the epithelial sodium channel in the apical membrane (Rokaw et al, 1996). Ischemia has also been proposed as a signal in this setting, where ischemia that accompanies the reduced perfusion of the kidney with obstruction can also be a mediator of reduced transporter expression. The reduction in major renal sodium transporters reported with ischemic models of renal failure supports this concept (Kwon et al, 2000). Other proposed downstream signals include changes in renal interstitial pressure and local generation of natriuretic substances. **Thus substrate delivery may be a regulatory step in the expression of sodium and possibly other transporters.**

Intrarenal and extrarenal substances and hormones can also modulate sodium transport. The milieu of influential hormones may be substantially different between UUO and BUO. A number of investigators have shown that obstruction markedly increases the endogenous production of PGE_2 in the renal medulla. Furthermore, supraphysiologic concentrations of PGE_2 are well known to produce natriuresis (Strandhoy et al, 1974), and studies in isolated tubules and cell suspensions show that PGE_2 inhibits Na reabsorption in the MTAL and throughout the collecting duct (CD). One mechanism of this natriuretic response may be that PGE_2 reduces the amount of Na^+,K^+-ATPase at the basolateral membrane (Marver and Bernabe, 1992). PGE_2 can also inhibit the tubular effects of vasopressin (Zook and Strandhoy, 1980), thereby contributing to the free water loss from the post-UUO kidney. The influence of other substances and hormones in the postobstructed UUO kidney is counterbalanced or minimized by the contralateral renal unit.

Li and coworkers (2007) found that BUO caused a persistent decrease in the alpha and beta subunits of the epithelial Na channel (ENaC) three days after relief of obstruction. Similar changes in ENaC occurred following UUO but only in the obstructed kidney. The contralateral control kidney showed no changes in ENaC expression. Furthermore, Jensen and coworkers (2006) showed in rats that at 2 days following BUO there was reduced expressions of the Na phosphate cotransporter (NaPi-2), the loop Na^+,K,$2Cl^-$ cotransporter (NKCC2) and the Na^+/H^+ exchanger (NHE3). These decreases in Na transporters were consistent with the postobstructive natriuresis. Candesartan partially reduced these changes and attenuated the natriuresis.

Extracellular fluid volume may be greatly expanded with BUO. When the BUO is relieved, both intrarenal and extrarenal factors greatly enhance salt and water excretion so that a postobstructive diuresis is often seen. The normal physiologic consequences

of extracellular fluid volume expansion ensue. These include a downregulation of sympathetic tone and the secretion of aldosterone and manifestation of the effects of ANP and probably other natriuretic factors. Levels of ANP are significantly elevated following BUO but not UUO (Purkerson and Klahr, 1989). The direct and indirect consequences of increased ANP levels include partial support of glomerular filtration, reduction of renin secretion and effects of angiotensin on transport, reduced aldosterone secretion, and direct inhibition of Na transport in the collecting duct (Brenner et al, 1990). Furthermore, BUO results in the accumulation of osmotic substances such as urea that can contribute to salt and water loss when the obstruction is relieved (Harris and Yarger, 1975, 1977). **The FE_{Na} following relief of BUO is typically greater than that after UUO because BUO causes retention of Na, water, urea nitrogen, and other osmolar substances and increased production of ANP, all of which stimulate a profound natriuresis. Although Na transporters are similarly downregulated in the affected kidney in UUO, the contralateral kidney adequately compensates to maintain Na balance.**

Potassium Transport

Obstruction has a complex impact on renal potassium handling, depending upon the type of obstruction. Harris and Yarger (1975) reported that there is a decrease in K^+ excretion, in proportion to the decrease in GFR, after release of a 24-hour period of UUO. This may be partially due to reduced delivery of Na^+ to the distal nephron and a low volume flow rate that would minimize the transmembrane gradient for K^+ secretion. Other investigations indicate that there is also an intrinsic defect in K^+ secretion after relief of UUO (Thirakomen et al, 1976). In contrast, K^+ excretion increases in parallel with Na^+ excretion with the relief of BUO. Micropuncture studies in rats showed that proximal reabsorption of K^+ remains unchanged, whereas secretion in the collecting duct is increased following release of BUO. This may be due to the massive increases in Na^+ and water delivery to the collecting duct acting as stimuli to secretion and also to the presence of high levels of ANP that can stimulate K^+ secretion in the distal nephron (Sonnenberg and Wilson, 1976).

Hydrogen Ion Transport and Urinary Acidification

Obstruction causes a deficit in urinary acidification that has been demonstrated in human subjects as well as animal models. The cumulative evidence indicates that the major acidification defect is in the distal nephron. Release of obstruction does not result in increased bicarbonate excretion, indicating that bicarbonate reclamation in the proximal tubule remains intact. In contrast, urinary pH does not decrease after an acid load, which is indicative of a distal nephron acidification defect, most likely related to defective H^+ transport in the collecting duct. A number of causes for the lack of acidification have been proposed, including defects in H^+-ATPase or H^+,K^+-ATPase, Cl^-/HCO_3^- exchange, a back leak of protons into the renal interstitium, or failure to generate a satisfactory transluminal electrical gradient. Obstruction has been demonstrated to decrease the expression of H^+-ATPase in the apical membrane of the intercalated cells of the collecting duct. However, the extent of this apical transporter decrease was too small to explain the significant acidification defects that develop. Therefore other mechanisms are also likely to play a role in the development of this acidification defect (Purcell et al, 1991). Valles and Manucha (2000) showed that the decrease in H^+-ATPase with UUO depends upon an increase in iNOS, which, in turn, appears to be regulated by angiotensin II. Thus recovery of H^+-ATPase activity in the inner medullary collecting duct of obstructed kidneys by losartan treatment may be related to a decrease in angiotensin-stimulated iNOS activity.

Wang and colleagues (2008b) showed that the urinary acidification defect and metabolic acidosis after release of BUO correlated with reduced expression of the Na^+/H^+ exchanger (NHE3) in the cortex, reduced electrogenic Na^+/HCO_3^- cotransporter (NBC1), the electroneutral Na^+/HCO_3^- cotransporter (NBCn1) and the anion exchanger, pendrin. These findings support alterations in both proton secretion and bicarbonate/anion transport in the acid-base defects found after the release of obstruction.

In the proximal tubule, glutamine uptake and oxidation and ammonia generation are diminished after release of obstruction. This has an impact on acid elimination in that a greater proportion of H^+ is buffered as titratable acid. Because phosphate excretion may be compromised, and binding of protons to phosphate has a limited capacity, the net result may be a lower urinary pH related to unbuffered protons, in spite of a net decrease in total H^+ secretion.

Effects of Obstruction on Anion and Other Cation Transport

The effects on phosphate reabsorption after the release of obstruction vary depending upon whether it was bilateral or unilateral. When BUO is released, accumulated phosphate is rapidly excreted in proportion to sodium (Beck, 1979). Conversely, a decrease in phosphate excretion and a net retention occur with release of UUO. Weinreb and colleagues (1982) showed that the decrease in the fractional excretion of phosphate following release of UUO in dogs produced no change in the transport of phosphate across brush border membrane vesicles. A reduced filtered load in the previously obstructed renal unit may stimulate increased phosphate reabsorption. Westenfelder and coauthors (1998) reported findings supporting the latter. They demonstrated that the increased reabsorption of phosphate after release of UUO in rats is due to a generalized increase in proximal tubular sodium reabsorption, a process linked to a reduction in GFR. They noted that this was linked to increased cotransport of phosphate and glucose with sodium.

Excretion of other cations is also induced by obstruction. **Magnesium excretion is markedly increased after the release of either UUO or BUO.** The increase most likely results from compromised transport in the thick limb of the Henle loop, which is related to ischemia. This causes decreased influx of Na^+, K^+, and Cl^- by the cotransporter and reduced back flux of K^+ across the apical membrane. It attenuates the positive luminal transepithelial voltage that normally drives the paracellular flux of both magnesium and calcium from lumen to basolateral membrane. The result is reduced passive reabsorption of Mg^{2+} and Ca^{2+} from the loop of Henle. However, calcium excretion may be increased or decreased, depending to a degree on the type of obstruction and the species. Although Mg^{2+} and Ca^{2+} are handled similarly in the thick limb of the Henle loop, calcium handling in the early distal tubule differs. Beaumont and coworkers (1989) demonstrated that the

thiazide-inhibitable sodium chloride cotransporter is rapidly downregulated during ischemia, such as may accompany ureteral occlusion. Blocking influx of Na^+ and Cl^- through this transporter hyperpolarizes the cells in the distal nephron, thereby increasing calcium reabsorption (Gesek and Friedman, 1992). Thus disruption of transport in areas of the nephron where Ca^{2+} and Mg^{2+} are differentially transported may account for varying effects of obstruction on their net transport and excretion.

Organic anions and cations are transported by the renal tubules as substrates of metabolism and as a mechanism of drug elimination. In rats, BUO decreases the renal clearance of *p*-aminohippurate (PAH), a prototypical substrate for the organic anion transporter 1 (OAT-1). Although secretion of PAH was reduced, the reduction did not correlate with a decrease in OAT-1 abundance or with cortical blood flow. It is postulated that decreased Na^+,K^+-ATPase activity, which provides the primary active transport to which OAT-1 is coupled, explains the decrease in PAH transport. In addition to the implications for drug transport and excretion with obstruction, this indicates that PAH clearance without measurement of extraction is an inaccurate index of RPF in postobstructed kidneys (Villar et al, 2004).

Effect of Obstruction on the Excretion of Peptides and Proteins

Some peptides and small proteins are normally filtered by the glomerulus and readily absorbed in the nephron. Some enzymes and proteins, such as Tamm-Horsfall protein and aquaporins, may normally be secreted into the tubular fluid. Obstruction can exaggerate or disrupt the excretion of these proteins and peptides. Some changes simply represent alterations in transport, whereas others are due to tubular damage and remodeling.

Monocyte chemoattractant protein 1 is a mediator of the inflammatory process accompanying obstruction in the kidney. Its excretion in the urine after UUO increases (Stephan et al, 2002) and has been considered an index of tubular damage. Conversely, epidermal growth factor (EGF) excretion, the renal cortical and outer medullary concentration of pre-pro-EGF, and excretion of Tamm-Horsfall protein (Storch et al, 1992) all decrease with obstruction. Urinary enzymes thought to be derived from the proximal tubule, such as alkaline phosphatase, γ-glutamyltransferase, *N*-acetyl-β-D-glucosaminidase, and leucine aminopeptidase have been reported to be elevated in patients with obstructed kidneys (Carr et al, 1994). However, such increases in enzymuria have been reported to be either biphasic, occurring only in the early stages of obstruction, or absent in animal models of partial or total ureteral obstruction (Everaert et al, 1998).

In summary, major changes occur with the ability of the kidney to concentrate the urine because of the downregulation of transporters and aquaporin water channels. These defects are enduring and correct slowly with time. Sodium excretion is greater after relief of BUO because extracellular volume is expanded and ANP directly affects transport and glomerular filtration. Potassium and phosphate excretions follow changes in sodium; they are decreased with UUO because of altered transporters and postobstructive retention and increased transiently with BUO in parallel with the massive natriuresis. Obstruction causes a deficit in urinary acidification that has been demonstrated both in humans and in animals. Magnesium excretion is increased in both models, but calcium handling is more complex. Changes in peptide excretion reflect mediators and markers of renal damage.

Metabolic Determinants of Ion Transport

An overview of the normal metabolic processes linked to ion transport provides a foundation for the understanding of changes that occur with obstruction. The myriad of transporters involved in maintaining cellular homeostasis and electrolyte balance is integrated longitudinally and vertically within the nephron. Families of ion-translocating ATPases mediate primary and secondary transport and are fueled by the availability and synthesis of ATP. In addition to providing energy for ion pumps, the adenine nucleotides can directly influence ATP-sensitive K^+ channels that link the activity of the sodium pump with the leak of potassium in some of the nephron segments, such as the thick ascending limb of the Henle loop and the collecting duct.

Although there is considerable variability between nephron segments, and even between species in the normal physiologic substrate for ATP generation in nephron segments, a few generalizations can be made. Aerobic glycolysis in several cell types, including renal tubules, links ATP generation to increased activity of Na^+,K^+-ATPase, QO_2, cAMP, and primary active transport of ions. In normal physiology, the renal cortex has a high rate of aerobic metabolism indicative of fatty acid oxidation and a low content of glycogen. Proximal tubules have relatively little glycolytic capacity and depend upon aerobic mitochondrial metabolism for ATP synthesis from substrates such as ketone bodies, fatty acids, glutamine, and lactate (Uchida and Endou, 1988; Ruegg and Mandel, 1990). Metabolism even varies along the length of the proximal tubule. For example, the proximal convoluted tubule cannot use glucose to support oxidative metabolism, but the proximal straight tubules can.

The medullary and cortical regions of the thick ascending limb of the Henle loop possess abundant mitochondria and high QO_2. Substantial energy reserves allow increased transport associated with glomerulotubular balance. This nephron segment and those downstream have the capability of aerobic and anaerobic glycolysis, which results in lactate accumulation and increased glycogen content (Abodeely and Lee, 1971; Cohen, 1979; Bagnasco et al, 1985). Compared with the proximal tubule, the medullary thick ascending loop of Henle has a greater capacity for anaerobic glycolysis but still requires ATP production from mitochondrial oxidative phosphorylation to maintain active Na^+ transport.

In addition to its role as a fuel for metabolism and transport, ATP and its metabolites can serve as regulators of solute transport, such as the ATP-sensitive K^+ channels previously mentioned, and activation of purinergic P_2 receptors within the kidney that modulate solute transport (Schwiebert and Kishore, 2001).

Although substrate availability for energy production related to transport is not generally rate limiting under physiologic conditions (Guder and Schmidt, 1976), some parts of the kidney, such as the thick ascending limb of the Henle loop, are located in areas where there is a tenuous balance between oxygen supply and demand. Consequently, these parts of the nephron are more susceptible to hypoxic injury and associated transport dysfunction. Therefore in addition to downregulation of the transport proteins themselves, with obstruction, the energy sources for transport function are at risk.

Renal obstruction provokes a number of changes in the metabolic cascade. There is a shift from oxidative metabolism to anaerobic respiration. This shift results in a reduction of renal ATP levels, an increase in amounts

of adenosine diphosphate (ADP) and adenosine monophosphate (AMP), and an increase in the renal lactate-to-pyruvate ratio (Stecker et al, 1971; Middleton et al, 1977; Nito et al, 1978; Klahr et al, 1986).

Cellular and Molecular Mechanisms Leading to Tubular Cell Death through Apoptosis

Renal obstruction produces tubular atrophy and cell death. The major mechanism by which tubular cells die is apoptosis, a process that is normally involved in postnatal development and tissue renewal in adults. The process can be triggered by both intrinsic and extrinsic factors and results in degradation and condensation of the nucleus. The cells are further degraded into apoptotic bodies, which are eventually phagocytized by healthy cells, usually without inducing inflammation. When rat kidneys are obstructed, renal tubular cell apoptosis begins in about 4 days and peaks after 15 days, with interstitial cell apoptosis continuing for the duration of obstruction (Choi et al, 2000). Glomerular cells appear to be resistant to obstruction-induced apoptosis. Pathological apoptosis of tubule cells from obstruction may secondarily trigger inflammatory responses from the release of cytokines and recruitment of leukocytes (Canbay et al, 2004).

Cysteinyl aspartate-specific proteinases (caspases) are known to mediate apoptotic cell death in obstructed kidneys (Hengartner, 2000; Truong et al, 2001). This family of 12 enzymes can be categorized into three main groups: initiators, effectors, and cytokine processors. Two distinct pathways of caspase activity are involved. One pathway involves activation of membrane death receptors by extrinsic binding of tumor necrosis factor alpha (TNF-α) to its receptor. A second pathway involves intrinsic stress signals that result in mitochondrial release of proapoptotic proteins such as cytochrome *c*. The two pathways converge to activate effector caspases, which cleave nuclear and cytoplasmic components, resulting in condensation of nuclear material and cell death. Truong and colleagues (2001) showed that all of the caspases increased with renal obstruction and that their levels paralleled renal cell apoptosis. Caspases 3 and 8 best correlated with renal cell apoptosis and appear to be central to this process (Choi et al, 2000; Truong et al, 2001).

In contrast to the defined role of angiotensin II in obstruction-induced renal fibrosis, its involvement in renal cell apoptosis is less clear. In mice with a knockout deletion of the AT2 receptor, there is a decreased degree of obstruction-induced apoptosis. However, these receptors are normally downregulated in the adult kidney, and their role in normal function and pathophysiologic responses is uncertain in the mature kidney. Angiotensin blockade or ACE inhibition has been shown by some investigators to reduce apoptosis in the early phases of renal obstruction (Truong et al, 1998; Eskild-Jensen et al, 2007), but others have reported conflicting results.

TNF-α can be a directly cytotoxic cytokine that can induce apoptosis in addition to its role in renal inflammation. When TNF-α binds to its receptor, TNFR1, an associated death domain (TRADD) binds to the TNFR1 and activates several signaling pathways. When coupled to a Fas-associated death domain, it triggers caspase 8 activation, which is pivotal to apoptosis. Alternatively, the TNFR1-TRADD complex can activate nuclear factor–κB (NFκB), which can have both pro- and antiapoptotic activity depending upon the cellular milieu. Increased amounts of TNF-α and its receptors have been demonstrated in rat models of obstruction (Tartaglia et al, 1991; Kaneto et al, 1996; Choi et al, 2000), along with other components of this cascade. These findings suggest an important role for TNF-α in apoptosis after obstruction.

Although the processes leading to renal apoptosis, inflammation, and fibrosis have many distinct pathways and mediators, they may also be intimately linked. Apoptosis is a primary cellular event leading to many toxic and ischemic insults. Although it is usually thought of as programmed cell death without inflammation, extensive damage to many cells may rupture and release cell contents and activate transcription factors, such as NFκB, to stimulate production of proinflammatory cytokines. Clearance of apoptotic debris through phagocytosis may directly stimulate fibrogenesis in many tissues, and fibrosis accompanying tissue injury may reciprocally induce pro-apoptotic gene expression such as the Fas/FasL pathway (Canbay et al, 2004).

Cellular and Molecular Changes Leading to Fibrosis

Urinary tract obstruction leads to progressive and, eventually, permanent changes in the structure of the kidney, including the development of tubulointerstitial fibrosis, tubular atrophy and apoptosis, and interstitial inflammation. A number of cytokines and growth factors have been shown to play roles in these events, among which the most prominent include transforming growth factor beta TGF-β, angiotensin II, NFκB, and TNF-α. Some are produced directly from the renal tubular and interstitial cells; others are generated from infiltrating macrophages.

Tubulointerstitial fibrosis develops as a consequence of extracellular matrix being synthesized and deposited at a greater rate than it is degraded, as well as to a relative increase in matrix due to collapse of parenchymal volume as nephrons are destroyed (Hewitson, 2009). A family of enzymes known as matrix metalloproteinases (MMPs), which includes collagenase, normally cleaves and degrades the collagenous and noncollagenous components of the extracellular matrix. **Obstruction increases the synthesis of tissue inhibitors of metalloproteinases (TIMPs) that reduce MMP activity, resulting in the accumulation of extracellular matrix.** Infiltrating macrophages stimulate TGF-β synthesis, and this growth factor increases TIMP production, thus reducing collagen turnover. Macrophages also produce other cytokines and growth factors, such as interleukin 2, interleukin 6, fibroblast growth factor, and platelet-derived growth factor (PDGF), that appear to contribute to this inflammatory and fibrotic process. Active TGF-β binds directly to its type 2 receptor, which subsequently activates and phosphorylates the type 1 TGF-β receptor. Both of these receptors have been shown to be upregulated in rats with UUO, in both the obstructed and contralateral renal units. This may be a factor in the hypertrophic response sometimes seen in the nonobstructed kidney (Sutaria et al, 1998). The activated type 1 TGF-β receptor subsequently phosphorylates SMAD (mobile transcription factors with a name derived from related genes in *Caenorhabditis elegans* [Sma] and *Drosophila* [Mad]) proteins. A heteromeric complex of SMAD proteins translocates to the nucleus, where it interacts with transcription factors to regulate gene transcription (Wamsley-Davis et al, 2004) and stimulates tubulointerstitial fibrosis (Fukasawa et al, 2004). Stimulation of TGF-β furthermore stimulates the JNK1 (c-JUN N-terminal protein kinase 1) pathway, which targets the activation of c-Jun and activates transcription factor 2, which are

critical components in activating fibronectin production. Increased mRNA expression of TGF-β is seen as early as 10 hours after obstruction and increases for 4 days (Walton et al, 1992; Diamond et al, 1994). The increase occurs primarily in medullary tubules and the interstitium and is less prominent in cortical tubules or glomeruli. Furthermore, TGF-β interacts with other profibrotic growth factors such as EGF and angiotensin II (Kaneto et al, 1993; Ishidoya et al, 1995; Chevalier et al, 1998).

Angiotensin II upregulates the expression of TGF-β1 in UUO, whereas ACE inhibitors or angiotensin receptor blockers diminish TGF-β1 expression and reduce tubulointerstitial fibrosis. This effect, and increases in TNF-α and NFκB promoted by activation of the renin-angiotensin axis, underscore the importance of this system in the obstructive process. Angiotensin II exerts its biologic effect through both AT1 and AT2 receptors, although in adult mammals, the AT1 receptors predominate and account for most of the known effects of the peptide. With UUO, a significant rise in both renal angiotensin II content and AT1 receptor expression is found (Misseri et al, 2004). Nephron angiotensin receptors are found in areas of the kidney where the peptide is known to have its greatest biologic effect: the proximal tubule, the thick ascending limb of the Henle loop, and the glomerulus (Sechi et al, 1992; Meister et al, 1993). The importance of this pathway has been shown in a murine AT1α receptor knockout model in which the mice have significantly less collagen expression and deposition, interstitial volume, and extent of obstruction-induced renal fibrosis (Morrissey and Klahr, 1998a). Angiotensin II stimulates cytosolic and mitochondrial oxidant production, which eventually leads to mitochondrial dysfunction. Activation of integrin signaling, release of TGF-β1 and transcription factor NFκB leads to a cell-type transition from epithelium to mesenchymal myofibroblasts that synthesize extracellular matrix (de Cavanagh et al, 2009). Angiotensin II activates the transcription factor NFκB, which, in turn, increases the expression of several chemokines and cytokines involved with the fibrotic process. The NFκB also upregulates the expression of the angiotensinogen gene and thereby provides a positive feedback for further angiotensin II production (Morrissey and Klahr, 1998b). The intimate link between angiotensin and NFκB was demonstrated in a study in which enalapril, an ACE inhibitor, reduced the levels of NFκB and fibrosis in a model of renal obstruction (Morrissey and Klahr, 1997).

The release of TNF-α, a potent inflammatory cytokine, is also stimulated by angiotensin, especially in the first few hours of renal obstruction. It can upregulate its own expression as well as that of other inflammatory mediators such as interleukin 1, PAF, NO, eicosanoids, and cell adhesion molecules. Although macrophages are a major source of TNF-α, renal tubular cells are also capable of producing it and become the predominant source of TNF-α after renal injury. Its role in renal inflammation and fibrosis is supported by studies in mice with knockout deletions of the two types of TNF receptors having less fibrosis.

Although the events leading to fibrosis are thought to be initiated by increased angiotensin II, other profibrotic factors appear to play a significant role because inhibition of angiotensin synthesis by ACE inhibitors or antagonism of the AT1 receptors blunts but does not completely abolish the fibrotic process (Kaneto et al, 1993; Ishidoya et al, 1995; Pimental et al, 1995).

In summary, obstruction of normal urine outflow results in biochemical, immunologic, hemodynamic, and functional changes. It stimulates a cascade in which elevated levels of angiotensin II, cytokines, and growth factors lead to tubular cell apoptosis and cellular inflammation, increased net matrix formation, and tubulointerstitial fibrosis. Many of the mediators are intrinsic to the renal tubular cells, whereas others are contributed by fibroblasts and by migrating macrophages (Fig. 40–3).

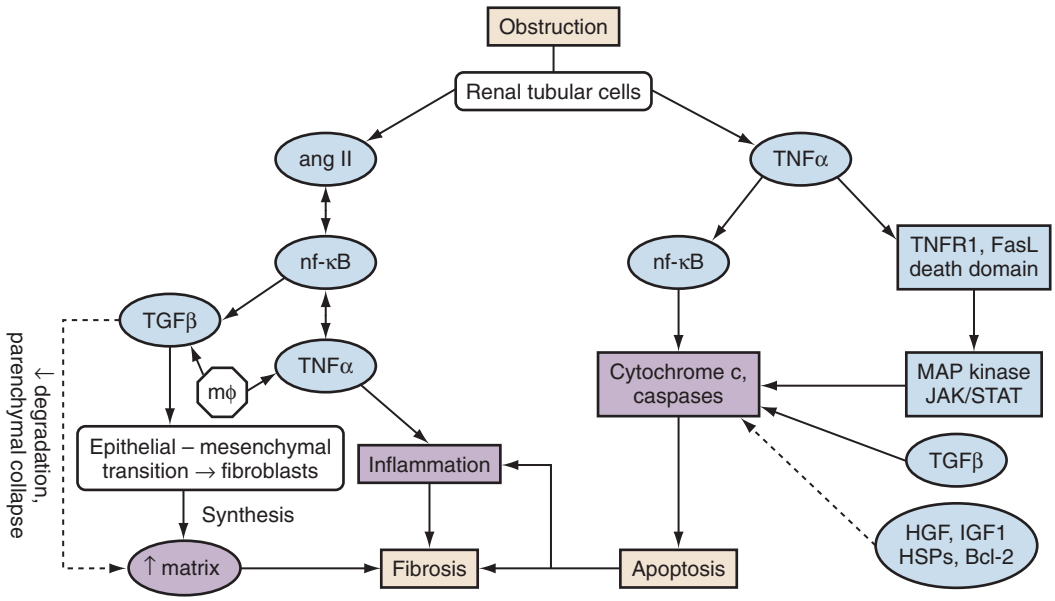


Figure 40–3. Summary of major pathways leading to tubulointerstitial fibrosis and tubular apoptosis as a consequence of ureteral obstruction. Membrane proteins and regulators are discussed in the text. ang II, angiotensin II; HGF, human growth factor; HSPs, heat shock proteins; IGF, insulin-like growth factor; JAK/STAT, Janus kinase/signal transducers and activators of transcription; mϕ, macrophages; MAP, mitogen-activated protein; NF-κB, nuclear factor κB; TGF, transforming growth factor; TNF, tumor necrosis factor; TNFR1, tumor necrosis factor receptor 1.

Experimental Treatment Approaches to Attenuate Renal Fibrosis and Functional Impairment

The aforementioned cascade of events points to many possible avenues to attenuate renal damage associated with obstruction. Experimental strategies to attenuate these noxious responses are reviewed.

Angiotensin antagonism is the best-studied therapeutic approach due to the clear link between angiotensin and renal injury and the clinical availability of ACE inhibitors and angiotensin receptor blockers (ARBs). Wamsley-Davis and colleagues (2004) administered the ACE inhibitor enalapril, the AT1 antagonists losartan or candesartan, or vehicle for up to 52 days to male rats with UUO. Candesartan inhibited the rise in JNK1 activity, losartan attenuated it, and enalapril did not affect it. Candesartan also reduced SMAD2 protein activation while attenuating the chronic tubulointerstitial fibrotic injury in obstructed kidneys and preserved renal mass. The apparent differences between candesartan, losartan, and enalapril may be dose- or delivery-related in that the AT1 antagonists were continuously infused by mini-pumps, whereas enalapril was added to the drinking water, and dose-response relationships were not examined. Manucha and colleagues (2005) showed, in rats, that losartan attenuated fibrosis in unilaterally obstructed kidneys by reducing oxidative stress as measured by lowered hydroxyl and oxygen radicals and increased superoxide dismutase and heat shock protein 70 levels.

In addition to the clear importance of angiotensin II in the processes leading to fibrosis and possibly apoptosis, other peptides in this family may be involved. Ureteral obstruction not only increases angiotensin-converting enzyme (ACE) and angiotensin II, but also decreases ACE-2, the enzyme most responsible for production of angiotensin-(1-7) (Bae et al, 2007). Angiotensin II stimulates many kinases probably involved in the profibrotic process, while angiotensin-(1-7) stimulates phosphatases that antagonize these effects (Gallagher et al, 2006). Inhibiting ACE shunts peptide production from angiotensin II towards more synthesis of angiotensin-(1-7). Thus the beneficial effects of ACE inhibitors and angiotensin receptor blockers may reside both in the synthesis and effect of less angiotensin II and the increased effect of angiotensin-(1-7). If so, the use of the latter as a drug could be explored, or there may be other means to modulate intrarenal kinases and phosphatases.

Manucha and colleagues (2004) showed that losartan prevented the development of renal fibrosis and kept interstitial volume and TGF-β mRNA expression to near control levels. Furthermore, these investigators implicated the well-known interactions between angiotensin II and activation of NOS isoforms and cyclooxygenase 2 (COX-2) in the inflammatory process. Whereas UUO increased iNOS in the obstructed renal medulla and increased neuronal NOS (nNOS) and endothelial NOS (eNOS) in the cortex, losartan treatment downregulated iNOS and nNOS with unchanged levels of eNOS. In addition, obstruction increased COX-2 expression in the obstructed renal cortex. It, too, was decreased by losartan treatment. **These studies suggest an important role of angiotensin-mediated profibrotic and apoptotic events occurring with renal obstruction that can be reduced with currently available inhibitors of angiotensin synthesis or receptor blockade.**

The known association of aldosterone and cardiac fibrosis prompted investigators to assess whether the administration of an aldosterone antagonist could attenuate the renal fibrosis generated with obstruction. Trachtman and coworkers (2004) examined this in a rat model of UUO. Whereas 1 week of obstruction produced minimal parenchymal damage, 2 weeks of obstruction produced renal fibrosis, which was significantly reduced by administration of the aldosterone antagonist spironolactone, without raising serum potassium or aldosterone concentrations.

Nitric oxide synthases are known to be double-edged swords in the processes of tissue perfusion and tissue inflammation. Obstruction increases inducible, neuronal, and endothelial NOS and high concentrations of NO can result in peroxynitrite production. Administration of L-arginine by infusion, or even by oral administration, prevents the upregulation of iNOS, blunts the increase in renal interstitial volume, and attenuates the infiltration of the renal parenchyma by macrophages in rats with obstructed kidneys (Ito et al, 2004c; Klahr and Morrissey, 2004). Gene therapy may be another approach. Ito and colleagues (2004b) showed that the gene for iNOS could be packaged in liposomes and delivered by intraureteral administration. Transfection and NO synthesis resulted in reduced fibrosis from ureteral obstruction.

Klahr and Morrissey (2003) showed that bone morphogenic protein (BMP) 7, a structural relative of TGF-β, was effective in preventing the tubulointerstitial changes and accelerating the return of renal function in a rat model of obstruction. They demonstrated that this agent inhibited apoptosis. This group also reported that the administration of hepatocyte growth factor has similar beneficial effects and proposed that it works by suppressing expression of TGF-β and PDGF. On the other hand, BMPs have been shown to also induce the epithelial-to-mesenchymal cell transition (Hu et al, 2009), which leads to fibrosis; so, the applicability of BMPs as drug candidates is not yet settled. Pirfenidone, a drug that purportedly inhibits collagen synthesis, downregulates production of multiple cytokines, and blocks fibroblast proliferation, may be another candidate to attenuate obstruction-induced renal injury and facilitate renal remodeling (Lasky, 2004).

The pathways of apoptosis, inflammation, and fibrosis all depend upon NFκB as a common mediator. Tamada and colleagues (2006) showed that kremezin, an oral adsorbant of indoxyl sulfate, lowers activation of NFκB and reduces inflammation and fibrosis. Curcumin, an ingredient of the spice turmeric, also appears to inhibit NFκB activity and interstitial inflammation and fibrosis (Kuwabara et al, 2006). This pathway appears important in drug-induced nephrotoxicity, as well as in obstructive nephropathy.

Heme oxygenase-1 (HO-1) exerts cytoprotection from a variety of kidney injuries. One of its endogenous products is carbon monoxide (CO). Wang and colleagues (2008c) found that low-dose CO protected against the fibrosis of UUO, probably by inhibiting TGF-β1 and other mediators of fibrosis. Similarly, Iwai and colleagues (2008) showed that induction of HO-1 with prophylactic cobalt protoporphyrin protected against renal fibrosis from UUO. Thus increasing HO-1 or its products may be a fruitful approach to treating obstructive nephropathy.

Although the results of the preliminary studies are encouraging, these agents should not be prescribed to patients for this purpose at this time. Their safety and efficacy first need to be established through carefully designed and controlled clinical studies.

Compensatory Renal Growth

Compensatory renal growth (CRG) of the unobstructed kidney was first described by Hinman (1943). This phenomenon has been subsequently demonstrated in a number of other animal models of UUO (Taki et al, 1983; Peters et al, 1993). There is evidence that

it occurs in the human fetus. An increase in contralateral renal volume has been detected ultrasonographically when contralateral hydronephrosis or unilateral renal agenesis is present (Mandell et al, 1993).

The mechanisms and nature of this growth are influenced by several factors including age, and degree and duration of obstruction. Both hyperplastic and hypertrophic CRG have been demonstrated (Dicker and Shirley, 1973; Castle and McDougal, 1984; Peters et al, 1993). CRG was demonstrated to decrease progressively with increasing age at which the obstruction occurred in animal models (Taki et al, 1983). **Studies of humans subjected to nephrectomy, a functional surrogate for obstruction, have demonstrated that a reduction in CRG occurs with increasing age** (Edgren et al, 1976). Animal experiments have also demonstrated that compensatory growth is directly proportional to the duration of obstruction (Chevalier et al, 1999). Compensatory growth is less prominent with partial than with total UUO (Chevalier and Kaiser, 1984; Eskild-Jensen et al, 2001). **While the kidney enlarges, an increase in the number of nephrons or glomeruli does not occur** (Peters et al, 1993). However, an increase in the length of the proximal tubule has been described, which may be due to an increase in cell size (Moller, 1988). In addition, there is augmented extracellular matrix synthesis and growth of mesangial cells (Kasinath et al, 2006; Sinuani et al, 2006). Insulin-like growth factor I (IGF-I), a mitogenic and anabolic peptide, may play a role in compensatory renal growth after obstruction. There is both animal and clinical evidence for its role. In rats, mean renal IGF-I is significantly elevated in the normal kidney compared with the contralateral 7-day obstructed kidney (Serel et al, 2000). Inferences can also be made from nephrectomy performed in animals and humans. Renal IGF-I mRNA levels are increased in immature rats previously subjected to nephrectomy (Mulroney et al, 1991). Significant increases in serum IGF-I have been demonstrated in humans after donor nephrectomy and peak 6 months after the procedure. Serum IGF-I was positively correlated with increases in renal volume demonstrated on serial postoperative imaging (Nam and Chang, 1999). It has also been demonstrated that the expression of IGF-I may be age dependent. Although renal IGF-I mRNA levels were found to be elevated after nephrectomy in immature rats, this did not occur in adult rats (Mulroney et al, 1991). Exogenous IGF-1 can attenuate renal injury from obstruction (Chevalier et al, 2000). Other growth factors, cytokines, and enzymes may be involved in regulating CRG, including IGF binding protein–3 (IGFBP-3), vascular endothelial growth factor (VEGF), matrix metalloproteinase–9 (MMP-9), interleukin-10 (IL-10), and TGF-β (Yildiz et al, 2008). Experimental studies suggest that CRG may be influenced by mitochondrial respiration (Tucci et al, 2008). The presence of compensatory growth in infants has been considered by some as an indicator that contralateral hydronephrosis is functionally significant (Koff and Peller, 1995). However, this approach has been challenged by others (Brandel et al, 1996). In addition, it was demonstrated that functional deterioration occurred in a rat model of partial UUO before compensatory growth developed in the contralateral renal unit. This implies that there may be a risk for functional renal loss if one uses only compensatory growth as an indication of correction of obstruction (Wen et al, 1999). Studies in children with unilateral renal tumors have shown that partial nephrectomy is associated with a greater degree of CRG versus nephrectomy, as assessed by ultrasonography (US) (Cozzi et al, 2007). The cause for this differential response is unknown but may be due the generation of more CRG factors in this setting.

Renal Recovery after Obstruction

The duration of obstruction has a significant influence on renal functional recovery. **When acute, complete ureteral obstruction is promptly relieved, full recovery of global GFR can occur.** In the rat model, after 3 days of UUO, GFR, and RBF were reduced to less than 10% of their baseline values. Both returned to their baseline within 14 days of relief of obstruction (Ito et al, 2004a). Bander and colleagues (1985) also noted complete return of GFR by 14 days after 24 hours of acute UUO, although they noted that the recovery was heterogeneous at the nephron level. Studying SNGFR, they found that approximately 15% of superficial and juxtamedullary nephrons were permanently lost, but hyperfiltration of the remaining nephrons allowed maintenance of whole kidney GFR. **Longer periods of complete ureteral obstruction are associated with diminished return of GFR.** Kerr (1954) reported that in dogs with complete UUO for 7 days, GFR 1 hour after relief of obstruction was 25% of the preligation GFR. GFR was then followed to assess the degree and time course of renal recovery. Maximal recovery was 58% of baseline, and this occurred within 57 days. Similar studies were conducted by Vaughan and Gillenwater (1971), who demonstrated that there was full functional renal recovery at 2 weeks after a 7-day period of UUO in dogs. This result declined to 70% recovery of GFR after 14 days of UUO, 30% after 4 weeks of UUO, and no recovery after 6 weeks of UUO.

The fate of the human kidney after prolonged periods of obstruction is less well defined and may be unpredictable. Functional recovery has been reported after a 150-day period of UUO (Shapiro and Bennett, 1976). Permanent reductions in GFR may occur after UUO or BUO in humans. However, there may be a differential pattern of recovery after BUO in adults. Jones and associates (1988) described two phases of functional improvement: an initial phase during the first 2 weeks after relief of obstruction, when tubular function improved, and a later phase occurring over the next 10 weeks, when GFR gradually improved. Patients with BUO or obstruction of a solitary kidney may also be at risk for unique sequelae such as chronic urinary acidification and concentrating defects (Berlyne, 1961).

Histopathological findings may predict recovery of renal function. The presence of increased collagen and elastin in renal parenchyma at the time of pyeloplasty has been shown to have a negative impact on recovery of renal function (Kim et al, 2005; Kiratli et al, 2008).

Renal parenchymal thickness based on computed tomography (CT) measurements has been used to estimate the renal function of chronically obstructed kidneys. One group compared renal surface areas in both kidneys calculated by multiplying the thickness (average of upper and lower pole values) by the renal length. They divided the surface area of one kidney by the sum of the surface areas of both and reported a strong correlation with differential renal function measured by nuclear medicine techniques (Feder et al, 2008). Another group measured the renal thickness at three discrete levels in the kidney and averaged these values. They reported that if the ratio of this measurement in the obstructed versus the unobstructed renal unit was less than 0.68, this correlated with a differential renal function of less than 20% (Kaplon et al, 2009). **Further studies are needed to corroborate these results before this approach is used in clinical practice.** Other factors influence functional return. Factors that have a positive influence on functional recovery include a smaller degree of obstruction, greater compliance of the collecting system, and presence of pyelolymphatic backflow (Shokeir et al, 2002).

Conversely, older age and decreased renal cortical thickness are predictors of diminished recovery of renal function (Lutaif et al, 2003).

Nuclear renography may help predict functional recovery. An assessment of functioning cortex with such imaging is the best predictor. For example, **dimercaptosuccinic acid (DMSA), a cortical agent, has been shown to be superior to tubular selective agents, such as diethylenetriaminepentaacetic acid (DTPA) or mercaptoacetyltriglycine (MAG3), for the prediction of renal recovery.** This was demonstrated in a prospective study in children undergoing pyeloplasty or ureteral reimplantation for ureterovesical junction obstruction (Thompson and Gough, 2001). It was postulated that DMSA better defines the functional cortex and is less affected by the dilated collecting system and dilution by undrained urine. Similarly, when the tubular agent *ortho*-iodohippurate was used, whole kidney activity was less predictive than the cortical phase (Kalika et al, 1981).

Renal recovery after relief of obstruction is affected by the duration of obstruction, degree of obstruction, patient's age, and baseline renal function. Cortical phase nuclear renograms may offer accurate prediction of the capacity of the kidney to recover after reversal of the obstruction.

PATHOLOGIC CHANGES OF OBSTRUCTION

Distinct gross and microscopic pathologic changes may occur with obstruction of the upper urinary tract. These may be affected by the presence of infection, duration of obstruction, and intra- versus extrarenal localization of the renal pelvis.

Gross Pathologic Findings

The gross pathologic changes occurring in the kidney have been characterized in animal models and parallel those in humans. Hodson (1969) and colleagues performed unilateral ureteral ligation in a porcine model and described pathologic changes in both kidneys over several time points. Dilation of the pelvis and ureter and blunting of the papillary tips were present in the obstructed kidney at 42 hours after obstruction, and the weight of this renal unit was heavier. Pelviureteric dilation and weight further increased and the parenchyma became edematous in the obstructed kidney at 7 days. The cortex remained slightly enlarged, and there was increased calyceal dilatation at 12 days in this renal unit; at 21 and 28 days, the external renal dimensions of both kidneys were similar. However, the cortex and medullary tissue in the obstructed kidney were diffusely thinned. Ladefoged and Djurhuus (1976) evaluated partial and complete obstruction in a porcine model. **They found that totally obstructed kidneys were enlarged, had a cystic appearance, and weighed less than the contralateral renal unit 6 weeks after obstruction. However, such gross differences in appearance were not present at this interval in the partially obstructed kidneys.**

Microscopic Pathologic Findings

Light microscopic changes reported in the aforementioned porcine model at 42 hours after obstruction included lymphatic dilation, interstitial edema, and tubular and glomerular preservation. Collecting duct and tubular dilatation was prominent by 7 days. In addition, further interstitial edema, widening of Bowman space, tubular basement membrane thickening, cell flattening, and cytoplasmic hyalinization were demonstrated. Papillary tip necrosis, regional tubular destruction, and inflammatory cell response were noted at 12 days (Hodson et al, 1969). Interstitial fibrosis and thickening of the tubular basement membranes were reported at 16 days after obstruction in a mouse model (Sharma et al, 1993). The inner cortex demonstrated severe tubular loss, proliferation of fibroblasts, and collagen deposition 3 weeks after obstruction in the porcine kidney. Cortical thinning and development of glomerular crescents were present at the 3- to 4-week interval in this model (Hodson et al, 1969). **Widespread glomerular collapse and tubular atrophy, interstitial fibrosis, and proliferation of connective tissue in the collecting system were reported at 5 to 6 weeks after obstruction in the porcine model** (Ladefoged and Djurhuus, 1976). Similar findings are noted in the chronically obstructed human kidney (Figs. 40–4 to 40–6).

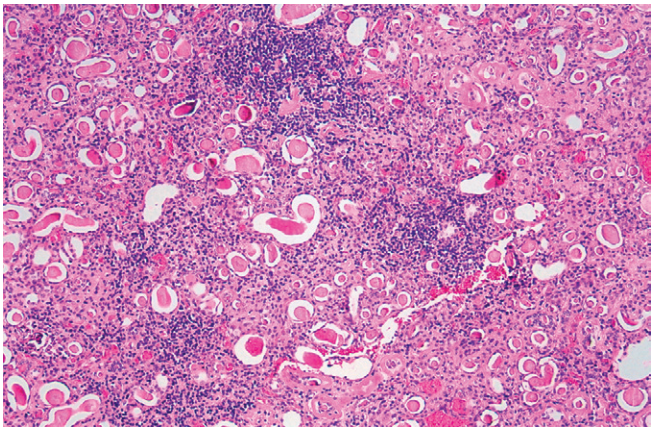


Figure 40–4. Sections of deep cortex and outer medulla from a patient with chronic obstructive uropathy. Tubules demonstrate thyroidization-type atrophy interspersed with mononuclear inflammatory infiltrate. Hematoxylin and eosin stain; original magnification, ×25. (Courtesy of Dr. Sami Iskandar.)

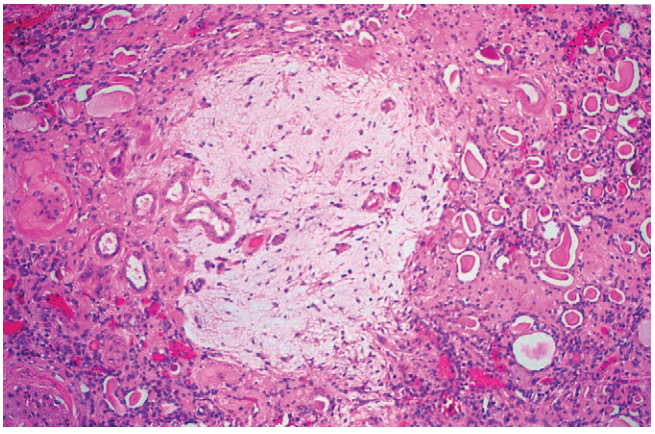


Figure 40–5. Sections of deep cortex and outer medulla from a patient with chronic obstructive uropathy. Obsolescent glomerulus *(left edge)* and pool of extravasated Tamm-Horsfall protein *(center)* are seen. Hematoxylin and eosin stain; original magnification, ×25. (Courtesy of Dr. Sami Iskandar.)

This is believed to be a result of interplay of several cellular and molecular mechanisms that collectively lead to the subtle development of tubular atrophy, macrophage infiltration/proliferation in the renal interstitial tissue, interstitial fibrosis and progressive loss of nephrons (Chevalier, 2006; Moon et al, 2006). These processes are also reviewed earlier in this chapter.

Electron Microscopic Pathologic Findings

Electron microscopic (EM) studies have confirmed the aforementioned light microscopic findings, including the presence of tubular atrophy, glomerular collapse, and renal pelvic smooth muscle atrophy at 5 to 6 weeks after obstruction (Fig. 40–7). Electron microscopic studies have also demonstrated other changes including the development of a cell-poor stroma composed of elastic and collagen fibers in the renal interstitium and obstructed portions of the collecting system (Ladefoged and Djurhuus, 1976). Collagen and elastin are normal components of the collecting system but are more prominent and have structural changes with obstruction (Gosling and Dixon, 1978; Murakumo et al, 1997).

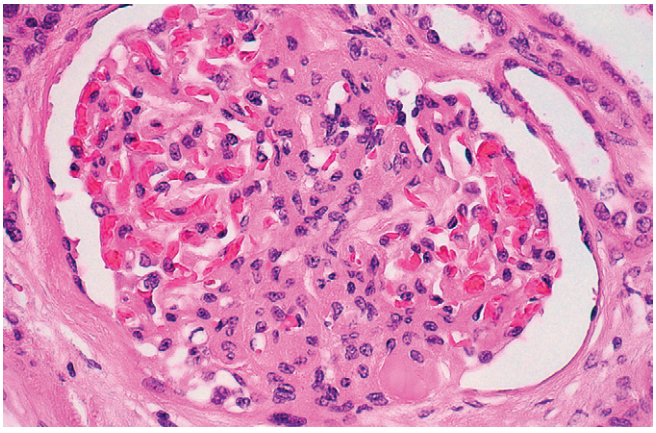


Figure 40–6. Sections of deep cortex and outer medulla from a patient with chronic obstructive uropathy. Glomerulus with segmental tuft sclerosis *(center)* and hyalinosis is seen. Hematoxylin and eosin stain; original magnification, ×100. (Courtesy of Dr. Sami Iskandar.)

GENERAL ISSUES IN MANAGEMENT OF PATIENTS

Diagnostic Imaging

As the clinical signs and symptoms of obstructive uropathy are so widely variable, prompt and accurate diagnosis is dependent upon appropriate imaging. The practicing urologist should be well versed in the diagnostic imaging modalities currently available, as well as their relative advantages, limitations, and appropriate modifications. An overview of current imaging techniques, with an emphasis on recent modifications, is presented here. Diagnostic tests used in the evaluation of upper urinary tract obstruction include ultrasonography, excretory urography (EXU), retrograde pyelography, antegrade pyelography, isotopic renography, computed tomography (helical), magnetic resonance imaging, and pressure flow study (Whitaker test).

Ultrasonography

Renal ultrasonography is a mainstay in the evaluation of suspected urinary tract obstruction. Although it is primarily an anatomic study, Doppler modifications may add a functional component. **There is no associated ionizing radiation, and it is thus considered safe in pediatric and pregnant patients. Because there is no need for iodinated contrast material, ultrasonography can be used in those with azotemia or contrast allergy.** Because it remains relatively inexpensive and widely available, ultrasonography is often a first-line investigational imaging modality to demonstrate dilatation, and it is also considered the best initial imaging modality for evaluating and following hydronephrosis (Watkin et al, 2007).

Renal parenchymal thickness can be measured readily, and cortical thinning may be indicative of chronic obstruction. The renal pelvis and calyces can be imaged, and dilatation is readily identifiable. **Caution in interpretation must be exercised, however, in that hydronephrosis is an anatomic as opposed to a functional diagnosis. Specifically, caliectasis and pelviectasis both may exist in an unobstructed system.** Functional inferences cannot be presumed from static images. For instance, the hydronephrosis of vesicoureteral reflux is not typically obstructive. In addition, renal sinus cysts can be misinterpreted as hydronephrosis. Conversely, early in acute obstruction, hydronephrosis may not be prominent, and the

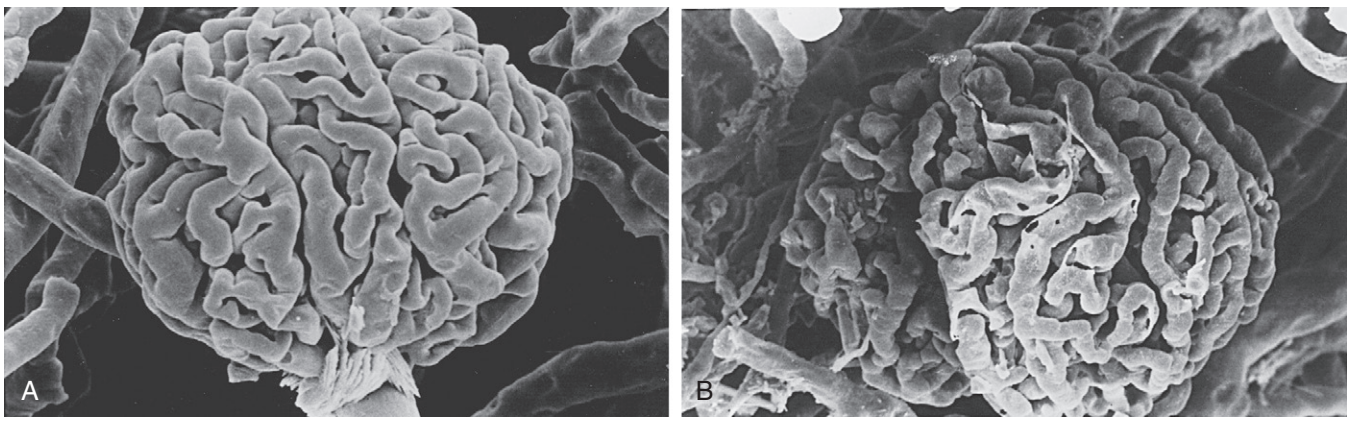


Figure 40–7. **A,** Scanning electron microscopic appearance of a normal glomerular cast (×390). **B,** Appearance of a glomerular microvascular cast after obstruction shows capillary collapse and irregularity (×390). (**A** and **B,** From Leahy AL, Ryan PC, McEntee GM, et al. Renal injury and recovery in partial ureteric obstruction. J Urol 1989;142:199–203.)

presence of an intrarenal collecting system or dehydration may lead to false-negative interpretations. **A prospective study of ultrasonography in obstruction by** Laing and colleagues (1985) **revealed a 35% false-negative rate in acute obstruction, underscoring the need to correlate the clinical picture carefully with the radiologic findings.**

Doppler ultrasonography allows measurement of the renal resistive index (RI), which has been used to assess for obstruction. The RI is defined as peak systolic velocity (PSV) minus the end-diastolic velocity (EDV) divided by the PSV. Several groups have assessed its ability to diagnose obstruction, but its utility has yet to be fully established. Platt and coworkers (1991) have suggested 0.7 as the upper limit of normal, with values greater than 0.7 reflecting elevated resistance to blood flow and thus suggesting obstructive uropathy. They subsequently reported their experience using this modality in 23 patients with acute unilateral obstruction. Three patients had false-negative studies, two of whom had pyelosinus extravasation and one of whom had been obstructed for less than 5 hours. They concluded that Doppler determination of RI was a valuable adjunct to routine sonographic evaluation of urinary tract obstruction (Platt et al, 1993). Conversely, others have found the sensitivity inadequate for the detection of obstruction. Tublin and associates (1994) reported that of 32 patients with colic, 12 of 19 patients with obstruction had normal RI, and 5 of 13 without obstruction had abnormal RIs.

One factor that may account for the dichotomy between such studies is the degree of obstruction. Chen and colleagues (1993) evaluated 27 patients with suspected obstruction by both Doppler ultrasonography and EXU. Overall, using an RI of 0.7 as the critical value, the sensitivity was only 52%. However, when correlated with degree of obstruction on EXU, RI was shown to differentiate the kidneys with mild obstruction from those with severe obstruction. In those with mild obstruction, the mean RI was only 0.64, whereas in those with severe obstruction the mean RI was 0.74, and the sensitivity of an RI greater than 0.70 for significant obstruction was 93.3%. Fung and coauthors (1994) also assessed this modality for evaluating obstruction. They measured RI in nine patients undergoing Whitaker testing for grade 3 or 4 hydronephrosis and reported that RI directly correlated with renal pelvic pressure. They determined that when renal perfusion pressures were normal, RI was less than 0.82. Major pitfalls in many of the studies assessing this modality have been the inconsistent definition of obstruction and degree of obstruction. **Although the presence of hydronephrosis associated with an abnormally elevated RI may be indicative of the severity of obstruction, it is important to recognize these limitations and use other clinical information and renal functional assessment for treatment planning.**

Crossing vessels are associated with ureteropelvic junction obstruction (UPJO), and their presence may influence treatment. Ultrasonographic techniques can be used to demonstrate their presence. Mearini and colleagues (2003), in a study of 21 patients with suspected UPJO, demonstrated the utility of color Doppler ultrasound scanning (CDUS) to correctly identify aberrant crossing vessels with an accuracy of 90.4%. Endoluminal sonography (EUS) is another useful means to evaluate a UPJO for a crossing aberrant vessel (Hendrikx et al, 2006). EUS uses a catheter-based sonographic probe, inserted under endoscopic and fluoroscopic control, that delivers a 360-degree cross-sectional view for assessing the ureter and periureteral structures. Recently, three-dimensional (3D) reconstruction of the two-dimensional (2D) endoluminal sonographic image has been shown to augment the diagnostic accuracy of this modality for comprehensive elucidation and assessment of the vascular morphology of the crossing vessel (Lin et al, 2008). Contrast-enhanced color Doppler imaging (CECDI) is another relatively new promising technique that is currently under evaluation. It has been compared with CT and magnetic resonance imaging (MRI) for the detection of crossing vessels in suspected ureteropelvic junction obstruction (UPJO). The CECDI technique uses galactose-based, echo-enhancing microbubble contrast agents that are administered intravenously, either as a single injection or as a fractionated, slow, continuous infusion. This is followed by color Doppler amplitude/frequency/pulsed-wave spectral imaging, which differentiates between arterial and venous flow signals. This permits identifying the presence of a crossing artery, vein, or both. Recently, Mitterberger and colleagues compared CECDI, MRI, and CT in correctly identifying the crossing vessels detected in patients with UPJO being subjected to laparoscopic pyeloplasty. The reported accuracies for CECDI, MRI, and CT were 100%, 100%, and 93%, respectively (Mitterberger et al, 2008).

Excretory Urography

Long considered the "gold standard" for the evaluation of the upper urinary tract, EXU has been supplanted by other modalities for many of its prior indications. Nevertheless, it provides both anatomic and functional information. **Acute urinary obstruction may be inferred from the *functional* abnormality of a delayed nephrogram and pyelogram on the affected side or sides. Delayed images may then ultimately reveal the *anatomic* level of obstruction and perhaps causation.** In addition, other signs may be present that may indicate chronicity of obstruction such as parenchymal thinning, extreme calyceal blunting, and ureteral tortuosity.

As the imaging is dependent upon glomerular filtration and renal concentration of the contrast medium, the utility of EXU is limited in those with renal insufficiency. Furthermore, the risk of contrast nephropathy increases with increasing serum creatinine. EXU, therefore, should not be performed in subjects with renal insufficiency, those who are at higher risk for developing contrast-induced nephropathy, or those with history of contrast allergy. Radiation exposure limits its utility in pregnancy, although abbreviated protocols have been established (Zagoria and Tung, 1997).

Retrograde Pyelography

Retrograde pyelography accurately defines ureteral and collecting system anatomy, including the location of an obstructive lesion and its extent. It should be considered in those who have renal insufficiency or have other risks for receiving intravenous iodinated contrast material. It may also be used in cases in which anatomy is not sufficiently defined with other imaging studies. In essence, a loopogram is another form of retrograde pyelography and may be useful in evaluating patients with cutaneous urinary diversion when obstruction is suspected.

Antegrade Pyelography

This technique may be helpful when other imaging studies do not adequately define collecting system or ureteral anatomy and when retrograde pyelography is not technically feasible.

Whitaker Test

First described by Whitaker in 1973**, this study involves measurement of renal pelvic pressure during infusion of**

either saline or contrast material into the collecting system through a percutaneous needle or nephrostomy at a fixed rate of 10 mL/min. A catheter is placed in the bladder to monitor intravesical pressure, which is subtracted from the measured collecting system pressures to calculate the "true pressure" within the pelvis. **A true intrapelvic pressure of less than 15 cm H_2O is considered normal, greater than 22 cm H_2O indicative of obstruction, and between 15 and 22 cm H_2O indeterminate.** Although its reliability to detect obstruction and differentiate degree of obstruction has been established in animal models (Ryan et al, 1989), the clinical utility of this test has been advocated by some and questioned by others. For example, one group reported that it was a valid test to confirm ureteral obstruction after renal transplantation (Kashi et al, 1993). However, others have reported a sensitivity and specificity of only 79% and 50% in this setting (Sperling et al, 2000).

Other concerns regarding potential shortcomings of the Whitaker test have been noted. Mortensen and colleagues (1983) reported wide variation in pelvic pressures in a normal porcine model, questioning the definition of a "normal" study. It has also been noted that a small, noncompliant obstructed system may give rise to a more rapid increase in pressure than a large, dilated obstructed system (Wahlin et al, 2001). Modifications have been suggested to overcome this pitfall. Individualized infusion rates based on maximum physiologic urine output have been advocated by some (Fung et al, 1995). Wahlin and colleagues (2001) proposed measuring flow as a function of pressure over a range of physiologic pressures. Resistance was then calculated and used to categorize responses as nonobstructed, indeterminate, or obstructed. They found that the major benefit of this modification was that it allowed identification of obstruction in some patients categorized as indeterminate with the standard Whitaker test. **These noted discordant results and the invasiveness of the study reflect the Whitaker test's limited applicability in contemporary clinical practice.**

Nuclear Renography

Nuclear renography is a useful, noninvasive test for evaluating patients with suspected obstruction. **It provides a functional assessment without exposure to iodinated contrast material.** Radiopharmaceuticals for renography are selected on the basis of the function to be studied. The glomerular agent technetium (Tc) 99m DTPA and the tubular agent ^{99m}Tc-MAG3 are most commonly used in the evaluation of obstruction. ^{99m}Tc-MAG3 has a high renal extraction rate, associated with rapid clearance, lower radiation dose, and tubular secretion. ^{99m}Tc-MAG3 has a 55% renal uptake in contrast with a 20% renal uptake associated with ^{99m}Tc-DTPA (Tremel et al, 1996). All radiopharmaceutical tracers are administered intravenously, and their uptake and subsequent clearance can then be evaluated and quantitated scintigraphically. From these data, relative renal function can be calculated. Obstruction can be assessed by measuring the clearance curves, either from a visual assessment of the pattern or from calculation of the half-time (time at which 50% of the radiopharmaceutical is eliminated from the collecting system). **By convention, a half-time less than 10 minutes is considered normal, greater than 20 minutes is considered obstructed, and between 10 and 20 minutes is equivocal.** Tracer clearance can be spuriously delayed because of renal insufficiency and the presence of vesicoureteral reflux, and some have suggested that renal immaturity in neonates may generate false-positive studies (Karam et al, 2003).

In order to detect obstruction, a high-flow state may be necessary. Therefore patients should be well hydrated to prevent misinterpretation related to low-flow states. Theoretically, bladder catheterization should be performed to maintain low intravesical pressure. However, in clinical practice this is used only in certain cases, such as suspected lower urinary tract obstruction, vesicoureteral reflux, neurogenic or noncompliant bladder, or low-lying, pelvic kidneys from which the renal signal may be obscured by intravesical radiopharmaceutical (Karam et al, 2003). The diuretic renogram is a modification designed to maximize flow and potentially distinguish truly obstructed collecting systems from those that are dilated but unobstructed. Because a given patient's response to the diuretic may be affected by the patient's baseline renal function, adjustments may need to be made on the basis of creatinine clearance (Upsdell et al, 1988).

In diuretic renography, as classically described, the diuretic, typically furosemide (F), is administered 20 minutes after the tracer to induce a brisk diuresis (F+20 study). Others have suggested alteration of diuretic timing to coincide with tracer administration (F+0) or precede it by 15 minutes (F–15). English and colleagues (1987) recognized that some patients with a partial obstruction may eliminate the tracer in the 20 minutes before the induction of diuresis using the standard F+20 sequence. To address this, they advocated administration of diuretic 15 minutes before injection of the radiopharmaceutical (F–15) so that initial tracer clearance could be studied during the period of maximal diuresis. Thirty-five renal units with hydronephrosis having equivocal or normal standard (F+20) diuretic renograms were evaluated by English and colleagues using the F–15 sequence. Using contralateral normal kidneys for comparison, they selected a clearance half-time of less than 5 minutes as normal, greater than 10 minutes as obstructed, and between 5 and 10 minutes as equivocal. With these criteria, 13 of the kidneys were demonstrated to be obstructed, and 18 were shown to be unobstructed. Only four kidneys remained in the equivocal range, underscoring the utility of this modified approach. This has also been confirmed in a crossover designed study demonstrating that **although an F+20 study is reliable when obstruction is demonstrated, both the F–15 and F+0 sequences can induce obstructed patterns in previously equivocal cases** (Turkolmez et al, 2004). A study by Tripathi and colleagues (2004), who evaluated the outcome of (F+0 renography) while investigating children with hydronephrosis, demonstrated that the sensitivity, specificity, and accuracy were 100%, 78%, and 83%, respectively. Liu and colleagues (2005) showed that the F+0 protocol had the advantage of a shorter time lag between the administration of furosemide and conclusion of the study, with earlier bladder filling than the F–15 protocol. **With the emergence of such techniques in isotopic renography, the differential renal function and drainage can be estimated with greater precision** (Frøkiaer et al, 2007).

Computed Tomography and Magnetic Resonance Imaging

Cross-sectional imaging, provided by CT and magnetic resonance urography (MRU), generates greater anatomic definition of abdominal and retroperitoneal anatomy than EXU or ultrasonography. **Both CT and MRU provide superior imaging of the obstructed upper urinary tract as compared to EXU** (Kemper et al, 2006). Unenhanced CT is the most sensitive method of detecting urinary tract stones and is currently the preferred imaging modality for evaluating most patients with suspected renal colic. Other advantages include its speed, reproducibility, and ability to detect other pathologic entities (Ulahannan et al, 2008). EXU currently has limited role, because noncontrast CT has

been shown to consistently outperform it for detecting renal/ureteral stones (Shine et al, 2008; Stacul et al, 2008).

Noncontrast CT directly demonstrates calculi classically considered radiolucent when evaluated by plain radiography, including uric acid, xanthine, dihydroxyadenine, and many drug-induced stones. Exceptions, however, are calculi composed of protease inhibitors, which are not visualized by noncontrast CT (Gentle et al, 1997). Secondary CT signs of obstruction such as ureteral dilatation, nephromegaly, decreased parenchymal density of the involved kidney as compared with the contralateral renal unit, perinephric stranding, or fluid can facilitate the diagnosis of acute obstruction. These signs have been reported to have a positive predictive value of 99% and negative predictive value of 95% for identification of acute ureteral obstruction (Smith et al, 1996). This is also an excellent technique for evaluating patients suspected of having chronic obstruction who have renal insufficiency or other contrast risks.

Contrast-enhanced CT has also been advocated for the evaluation of patients with chronic obstructive uropathy and normal serum creatinine. In addition to the aforementioned anatomic details afforded by noncontrast CT, functional evaluation including calculation of differential GFR is possible. Abou El-Ghar and colleagues (2004) compared contrast-enhanced CT with EXU and nuclear renography in 65 patients. **CT had significantly improved sensitivity for identification of the cause of obstruction compared with EXU.** Furthermore, they reported an excellent correlation between isotope and CT-estimated GFR. Multiphasic helical CT has also been shown to be useful in surgical planning for ureteropelvic junction obstruction, with sensitivity for detection of crossing vessel of 97%, specificity of 92%, and with an overall accuracy of 96% (El-Nahas et al, 2004).

A number of advances in MRI technology have facilitated the evaluation of patients with obstruction of the urinary tract. There are a number of different techniques used to generate MRI images. Comprehensive MRI includes static imaging (MRU), dynamic imaging (dy-MRI), and MR angiography (MRA). Magnetic resonance urography (MRU) can be executed essentially with two different imaging techniques: (1) static-fluid MRU that relies heavily on the T2-weighted turbo spin echo (TSE) sequences, and (2) gadolinium-enhanced excretory MRU, a dynamic sequence that relies on the administration of gadolinium with or without a diuretic. The image quality of an excretory gadolinium-enhanced MRU can be considerably improved by using intravenous hydration and diuretics (Ergen et al, 2007). Recent advances and emergence of newer techniques of MRU, such as fast spin echo (FSE) and postprocessing maximum-intensity projection (MIP), have advantages over the previously employed single-shot MRU approach. The accuracy of the former for identifying noncalculous obstruction was reported to be 93% as compared with 89% for the latter (Abou El-Ghar et al, 2008a). T2-weighted MRU is an excellent imaging modality for demonstrating an obstructed renal unit (Nolte-Ernsting et al, 2003). In this approach, gadolinium contrast (Gd-MRI), intravenous fluids, and furosemide are administered. MRU has been compared to EXU, and the former has been found to be superior in most cases. A prospective study compared it with EXU in patients with ureteral obstruction (Karabacakoglu et al, 2004). The accuracy of diuretic MRU for detection of obstruction was demonstrated to be 93% in those with obstructing stones and 100% in those with obstruction related to strictures or congenital anomalies, whereas the accuracy of EXU was 96% and 55%, respectively. A study by Khanna and colleagues (2005), comparing the diagnostic utility and accuracy of MRU versus EXU in 48 patients with obstructive uropathy, concluded that MRU was superior to EXU in patients with moderate to severe dilatation, staghorn and ureteral calculi, impaired renal function, extrinsic ureteric, and UPJ obstruction. However, they also found that EXU was better in depicting small calculi and mild hydronephrosis (Khanna et al, 2005) (Figs. 40–8 and 40–9).

MRU may be used to assess renal function. It has been demonstrated to have an excellent correlation with the renal isotope GFR



Figure 40–8. T2 magnetic resonance urography image showing right ureteral obstruction.

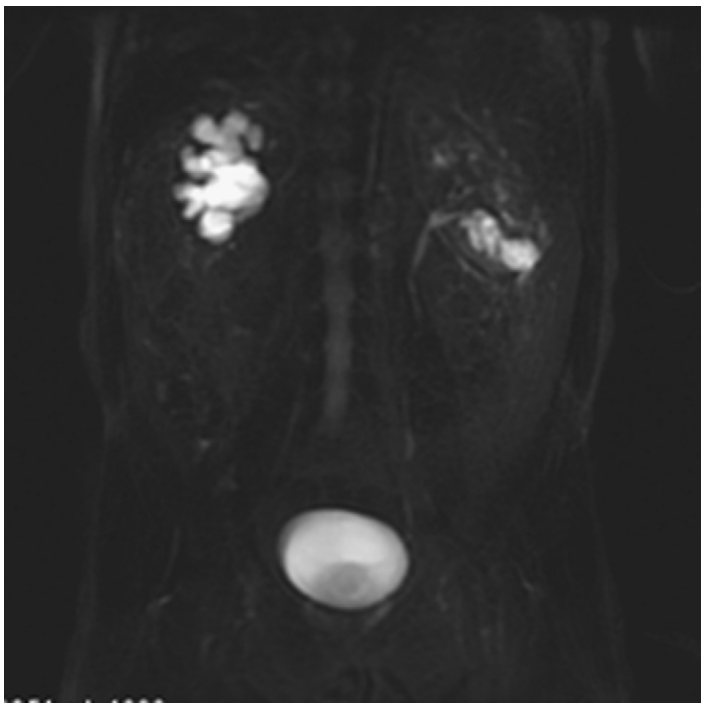


Figure 40–9. Magnetic resonance urography image showing right ureteropelvic junction obstruction.

in the adult (Abo El-Ghar et al, 2008b) and pediatric patients (Jones et al, 2008) with obstructed kidneys. The incorporation of intravenous administration of gadopentetate-DTPA has allowed a dynamic, functional assessment of the collecting system that correlates well with diuretic renal scintigraphy, yet provides far greater anatomic detail than nuclear studies. Differential GFR can be assessed with postimaging processing, and contrast washout can be measured to calculate renal clearance, differentiating dilated systems from obstructed systems (Rohrschneider et al, 2002; Chu et al, 2004). MRU with the contrast agent gadopenteate dimeglumine can be used to estimate renal function because it is filtered by glomeruli and is neither secreted nor reabsorbed by the renal tubules. Studies indicate the possibility of estimating single-kidney function with this technique (Hackstein et al, 2004; Krishnamurthi et al, 2005; O'Dell-Anderson et al, 2006).

Comprehensive MRI, including the incorporation of magnetic resonance angiography (MRA), is a useful modality for the evaluation of patients with UPJO. The sensitivity, specificity, and accuracy of this approach for identification of crossing vessels has been reported to be 95%, 94%, and 94%, respectively (El-Nahas et al, 2007). Cost, availability, time for acquisition of images, and need for sedation in pediatric patients have all been cited as possible limitations of this technique, but the superior anatomic detail, functional assessment, elimination of risk of contrast-induced nephropathy, and lack of ionizing radiation make this an attractive option. **The risk of nephrogenic systemic fibrosis associated with the use of some gadolinium agents (especially gadodiamide) in patients with renal insufficiency (GFR < 30 mL/min), limits the utility of using contrast MRI in such patients** (Broome et al, 2007; Frøkiaer and Zeidel, 2007; Sadowski et al, 2007; Abou El-Ghar et al, 2008b). **The absence of ionizing radiation has allowed its use in the assessment of children, women of child-bearing age, and pregnant patients** (Jorgensen et al, 2006) **with flank pain and hydronephrosis, which is further explored in the discussion of hydronephrosis of pregnancy later in this chapter. In children MRU has the potential to replace conventional uroradiological diagnostic tests in the near future. The present level of evidence does not suggest that MRI is clearly superior to combined ultrasonography (US) and CT imaging for the routine diagnosis and evaluation of obstructive uropathy.**

On the whole, both MRU and CT have critical roles in evaluating select patients with urinary tract obstruction. Although these studies can estimate renal function (He and Fischman, 2008), **nuclear renography remains the current gold standard.**

Hypertension

Hypertension can be precipitated by ureteral obstruction and is a well-recognized sequela of BUO or obstruction of a solitary kidney. Vaughan and Gillenwater (1973) noted hypertension in 17 of 22 patients with BUO, which resolved in 15 subjects upon relief of BUO. This response has also been demonstrated in pregnant patients with BUO (Satin et al, 1993). Patients with BUO are typically volume overloaded. Gulmi and colleagues (1989) measured ANP and plasma renin activity (PRA) in nine patients with BUO before and after relief of obstruction and compared them with those of age-matched control subjects. ANP was significantly increased in the BUO group prior to relief, and progressively returned to normal after drainage. Conversely, PRA was depressed prior to relief of BUO. These findings are suggestive of a volume-mediated mechanism for hypertension in BUO. Hypertension is significantly less common, however, with UUO (Vaughan and Sosa, 1995). In contrast to the BUO model, in UUO the contralateral, unobstructed kidney compensates and eliminates excess volume and solutes. Renin activation and resultant angiotensin II generation have been demonstrated in animal models of UUO and may be the mechanism by which new-onset hypertension occurs in this setting. Pain may be another contributing factor (el-Dahr et al, 1993). **In summary, there is a good chance of reversal of new-onset hypertension with relief of BUO, but this is less likely with UUO.**

Renal Drainage

Ureteral obstruction that is symptomatic, accompanied by fever, complicated by an undrained infection, or determined to be high grade, bilateral, or inducing renal failure warrants immediate drainage of the affected renal unit(s).

Minimally invasive endourologic and interventional radiologic techniques allow prompt drainage of the obstructed kidney. These measures may allow temporary drainage until a definitive procedure is performed or, in some circumstances, may be a permanent form of management. Urine specimens for urinalysis and culture should be obtained from the obstructed renal unit at the time of relief of obstruction when infection is suspected. Antibiotic therapy is started if these tests are indicative of infection or there are clinical signs and symptoms of infection.

The relative merits of indwelling ureteral stents and percutaneous nephrostomy tubes have been evaluated by several groups. Indwelling stents obviate the need for external collection devices but are associated with bothersome voiding symptoms. In spite of this, prospective studies have demonstrated that there is no statistically significant difference in health-related quality of life (Joshi et al, 2001; Mokhmalji et al, 2001). The choice of drainage ultimately depends on the clinical setting. If the patient has an uncorrectable coagulopathy or platelet abnormality, ureteral stenting is indicated. There does not appear to be a significant advantage of either approach in those requiring drainage for stone-related problems (Pearle et al, 1998; Mokhmalji et al, 2001). Compared with percutaneous nephrostomy placement, stent insertion may require greater x-ray exposure (Mokhmalji et al, 2001). This may be of concern in pregnant patients, particularly early in gestation when the fetus is most sensitive to radiation effects (McAleer and Loughlin, 2004). Ultrasound-guided ureteral stent placement is an option in this setting (Jarrard et al, 1993). Nephrostomy tube drainage is also an option for pregnant patients, and radiation exposure can be limited with the use of ultrasound guidance (Denstedt and Razvi, 1992; Agostini et al 2003). Percutaneous nephrostomy should be strongly considered if pyonephrosis is suspected. However, if it is not suspected and thick, purulent fluid is obtained from the kidney at ureteral stenting, placement of a large-diameter stent is recommended. If this does not provide satisfactory drainage, percutaneous nephrostomy should be performed. Percutaneous nephrostomy also allows estimation of differential renal function that can be used in making decisions regarding renal salvage (Al-Hunayan et al, 2008). Percutaneous nephrostomy is also a bailout procedure when retrograde stenting fails or is not feasible.

Ureteral stenting may not be as effective for treating patients with extrinsic ureteral obstruction. Docimo and Dewolf (1989) reported a mean 43% failure rate in ureteral stents placed for extrinsic ureteral obstruction, the majority related to malignancy. This was subsequently confirmed in a prospective

study evaluating success rates for retrograde ureteral stenting (Yossepowitch et al, 2001). Initial retrograde access failed in 27% of patients with extrinsic ureteral obstruction, compared with only 6% of those with intrinsic obstruction. At 3-month follow-up, 56.4% of stents placed for ureteral obstruction had failed. Of note, on multivariate analysis, stent diameter did not predict risk of stent failure. Chung and colleagues (2004) similarly identified an overall 42% rate of stent failure in patients with extrinsic obstruction of the ureter and additionally noted that 43% of those failures occurred within 6 days of the initial placement. **A diagnosis of cancer, metastatic disease requiring chemotherapy or radiation, and renal insufficiency were predictors of stent failure in this series.** Some have advocated the placement of two parallel ureteral stents to provide better drainage as an alternative to percutaneous nephrostomy (Liu and Hrebinko, 1998). **Closer monitoring for stent failure should thus be considered in patients with extrinsic ureteral obstruction** (Ku et al, 2004). Rosevear and colleagues (2007) reviewed their 9-year experience of managing extrinsic ureteral obstruction with retrograde stenting and found an overall success rate of 84%. They also found that a higher serum creatinine value was the only factor that was significantly associated with stent failure (Rosevear et al, 2007). The association of stent failure and poor renal function has also been reported by others (McCullough et al, 2008). The presence of extrinsic ureteral obstruction due to bladder or prostatic pathology, especially advanced malignancies, is another risk factor for stent failure (Danilovic et al, 2005). Encrustation is one of the causes of stent failure. This occurs commonly in pregnant patients, which may be due to increased calcium excretion during pregnancy (Goldfarb et al, 1989). Other reported risk factors for encrustation include urinary tract infection (UTI), stasis, dehydration, renal insufficiency, prolonged dwell time, and history of nephrolithiasis (Singh et al, 2001). A positive correlation between composition of the respective stones and stent encrustations has been reported (Rouprêt et al, 2005).

Choice of Surgical Intervention

After the acute obstruction has been addressed, definitive management is based upon the cause of the obstruction, the functional recovery of the affected kidney, and the condition of its counterpart, and the patient's age and medical status. Endoscopic, open, or laparoscopic ablative and reconstructive procedures may all be used. Indications and pertinent preoperative, intraoperative, and postoperative considerations are discussed elsewhere in this text. The decision to remove a kidney should be made only after the affected kidney has been adequately drained for a sufficient period of time, 6 to 8 weeks based on the results of animal experimentation (Kerr, 1954). Split renal function (SRF) can be assessed by measuring creatinine or inulin clearance (both surrogates of glomerular filtration) directly from bilateral nephrostomy tubes or a nephrostomy tube, and an indwelling urethral catheter when there is complete UUO and the other renal unit is not obstructed. However, nuclear imaging techniques are more commonly used to assess renal function in this setting.

A less-than-10% contribution to global renal function has been proposed as the threshold for nephrectomy, although others have used higher values (Thompson and Gough, 2001). Another criterion has been the ability of the affected renal unit to provide sufficient function to prevent dialysis dependence if the contralateral kidney were removed. These criteria were not generated by prospective study but by clinical inference from functional reconstructive outcomes. There is conflicting evidence in children regarding this threshold. One group reported that renal units with less-than-10% renogram-derived differential function in children have been shown to derive no benefit from reconstruction (Dhillon, 1998). Another group found that in children with moderate hydronephrosis (initial SRF <10%) significant improvement of SRF occurred one year following pyeloplasty (Wagner, 2008). In adults, a GFR of less than 10 mL/min/1.73 m^2 in the affected kidney successfully predicted renal function that did not stabilize or improve after surgical correction of obstruction (Khalaf et al, 2004). Another conflicting study showed that the renal function improvement following pyeloplasty in adult obstructed kidneys may not occur if the initial SRF was less than 30% (Ortapamuk et al, 2003). The decision to proceed with nephrectomy in a patient with significant global renal insufficiency, however, should not be based solely on the aforementioned criteria because this could hasten dialysis dependence and dramatically affect quality of life. The patient may prefer life with a stent or percutaneous nephrostomy, or an attempt at surgical reconstruction.

Pain Management

Five classes of drugs are used to treat pain associated with acute renal colic, namely, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotic analgesics, calcium channel blockers, corticosteroids, and α_1 blockers (Micali et al, 2006). NSAIDs and narcotic analgesics are now most commonly used (Davenport et al, 2005; Holdgate and Oh, 2005; Holdgate and Pollock, 2006). Cochrane meta-analysis studies have demonstrated the effectiveness of both agents but suggest that NSAIDs are preferred (Holdgate and Pollock, 2004, 2005; Das et al, 2006). Other investigators have demonstrated the superiority of NSAIDs (Lee et al, 2005; Engeler et al, 2008). **The present level of evidence supports the role of NSAIDs as first-line drugs for the management of renal colic presenting to the emergency department, with narcotics being reserved as second-line drugs.**

Both classes of medications may be administered parenterally, orally, or as a rectal suppository. NSAIDs are nonopioid analgesics that, unlike narcotics, target the inflammatory basis of pain. Prostaglandins, generated from arachidonic acid metabolism mediated by both *iso* forms of cyclooxygenase, potentiate pain receptors. Therefore inhibition of prostaglandin synthesis prevents this potentiation of nociceptors (Mense, 1983). Narcotic analgesics have a rapid onset but may promote nausea, emesis, constipation, urinary retention, hypotension, respiratory depression, excessive sedation and have a potential for addiction (Lasoye et al, 2004; Holdgate and Pollock, 2006).

Increases in collecting system pressure and ureteral wall tension are proposed mechanisms of renal colic (Holmlund, 1983). Primate models reveal that distention-mediated activation of renal pelvis mechanoreceptors results in spinothalamic (pain pathway) C fiber excitation. The mean threshold pressure to elicit this primate response was 32 mm Hg. This is similar to the 30-mm Hg proposed threshold for evoking pain in humans (Ammons, 1992). Interventions that reduce collecting system pressure should theoretically reduce pain.

NSAIDs have been demonstrated to reduce collecting system pressure. Pretreatment with indomethacin significantly blunted the rise in pelvic pressure and RBF in pigs with UUO (Frøkiaer et al, 1993). Indomethacin administered 30 minutes after UUO reduced an already elevated renal pelvic pressure by approximately 30% in rats (Sjodin et al, 1982). A study of four different NSAIDs in dogs with acute obstruction showed 25% to 58% reductions in renal pelvic pressure after administration of these drugs, which

were most pronounced after the first dose (Gasparich and Mayo, 1986). A concomitant reduction in RBF induced by NSAIDs is thought to be one of the mechanisms for decreasing collecting system pressure. This has been demonstrated in a canine model of UUO in which the administration of ketorolac, an NSAID, induced prompt reduction in both RBF and intrapelvic pressure (Perlmutter et al, 1993). A second potential mechanism involves regulation of aquaporin water channels. COX-2 expression is upregulated in the obstructed ureter (Nakada et al, 2002). There is also a downregulation of AQP2 water channels associated with this COX-2 induction, and this promotes diuresis after obstruction is relieved. Rats treated with a COX-2 inhibitor during obstruction had only a 28% reduction of AQP2, attenuating the diuresis occurring after release of UUO (Cheng et al, 2004).

The choice of pain management should be based on the patient's clinical profile. **NSAIDs should not be used in patients with renal insufficiency, because this could be exacerbated by the induced reduction in RBF.** COX-1 inhibitors should not be administered to patients at risk for gastrointestinal bleeding or when optimal platelet function is needed. Although COX-2 inhibitors are attractive on a pathophysiologic basis, the market withdrawal of some COX-2 inhibitors, related to increased risk of cardiac morbidity, underscores the need for prospective trials to assess their long-term safety in managing patients with renal colic.

The administration of α_1 blockers, calcium channel blockers, and corticosteroids have been used for medical expulsive therapy. Studies have demonstrated the utility of the first two medications to facilitate stone passage, while the benefit of the latter one is questioned. The use of α_1 blockers for this purpose has also been shown to reduce the requirement for analgesics (Micali et al, 2007; Singh et al, 2007; Sterrett et al, 2008; Wang et al, 2008a). Anticholinergic agents have been used in the setting of colic but their benefits have not been established (Holdgate and Oh, 2005; Prcić et al, 2006).

Patients may be fluid depleted as a result of anorexia and emesis, and therefore should receive intravenous hydration. However, there is no evidence that intravenous hydration facilitates stone passage (Springhart et al, 2006; Worster and Richards, 2005).

Postobstructive Diuresis

Mechanisms

Following the relief of urinary tract obstruction, postobstructive diuresis—a period of significant polyuria—may ensue. Urine outputs of 200 mL/hr or greater may be encountered. Although this occurs mainly after relief of BUO or obstruction of a solitary kidney, it can rarely occur when there is a normal, contralateral kidney (Schlossberg and Vaughan, 1984). The diuresis is typically a normal physiologic response to the volume expansion and solute accumulation occurring during obstruction. Sodium, urea, and free water are eliminated, and the diuresis subsides after solute and fluid homeostasis is achieved. With the return of homeostasis, the period of diuresis ends (Loo and Vaughan, 1985).

However, a "pathologic" postobstructive diuresis may ensue, characterized by inappropriate renal handling of water or solutes, or both. It is due to a number of mechanisms previously reviewed in this chapter, including a derangement of the medullary solute gradient and a number of altered signaling and transport pathways. Downregulation of sodium transporters with subsequent impaired sodium reabsorption in the thick ascending limb of the Henle loop prevents maintenance of the medullary interstitial solute gradient, promoting a continued diuresis (Rokaw et al, 1996). The increased endogenous production and altered regulation of ANP induce a saline diuresis (Kim et al, 2001b). In addition, other natriuretic peptides, such as the *Dendroaspis* natriuretic peptide, may play a role (Kim et al, 2002). Pathologic postobstructive diuresis is also marked by poor responsiveness of the collecting duct to antidiuretic hormone (ADH). This is thought to be due to a downregulation of aquaporin water channels in this segment of the nephron and perhaps in the proximal tubule, which has been demonstrated in experimental models of UUO and BUO (Nielsen and Agre, 1995; Frøkiaer et al, 1996; Kim et al, 2001a; Li et al, 2003).

Various reasons have been proposed for the rare occurrence of postobstructive diuresis with release of UUO and a normal contralateral kidney. GFR may be atypically preserved in the setting of distal tubular damage such that the kidney filters a normal volume but there is limited free water reabsorption. Alternatively, a pronounced aquaporin channel defect may be present, causing diminished free water absorption in this setting (Schlossberg and Vaughan, 1984; Li et al, 2003). An experimental study by Nørregaard and colleagues (2007) concluded that decreased Na^+,K^+,$2Cl^-$ cotransporter type 2, collapse of the inner medulla osmotic gradient, and suppressed phosphorylated renal aquaporins (AQP2) may be responsible for the impaired urine-concentrating capacity in the chronic postobstructive phase following release of ureteral obstruction. The rarity of this condition has been ascribed to compensatory retention of salt and water by the contralateral renal unit (Frøkiaer et al, 2007).

Clinical Management of Postobstructive Diuresis

The majority of patients do not demonstrate a clinically significant postobstructive diuresis following relief of urinary tract obstruction. Those who are susceptible to this phenomenon typically have signs of fluid overload including edema, congestive heart failure, or hypertension (Loo and Vaughan, 1985). The most common clinical setting is release of urinary retention. A catheter should be placed to drain the bladder rapidly in those with urinary retention. There is no role for gradual bladder decompression, because this has not been demonstrated to limit hematuria or the risk of postobstructive diuresis (Nyman et al, 1997).

Subjects in whom BUO or UUO in a solitary kidney is relieved should be monitored for a postobstructive diuresis. Serum electrolytes, magnesium, blood urea nitrogen (BUN), and creatinine should be checked. The intensity of monitoring depends on presence of risk factors for postobstructive diuresis and the subject's mental status, renal function, and electrolyte status. Those with normal renal function and electrolytes, no evidence of fluid overload, and who are mentally alert should have their vital signs and urine output monitored. They are allowed free access to oral fluids, and if they do not manifest signs of a postobstructive diuresis they can be discharged and return later for further urologic evaluation and care. If they show signs of a postobstructive diuresis but are alert, able to consume fluids, and have normal vital signs, observation is continued and the patients may consume fluids as desired. **This is a physiologic diuresis that, in the majority of cases, resolves when free water and excess solutes are eliminated.** Serum electrolytes, BUN, magnesium, and creatinine are checked daily until the diuresis resolves. If patients have signs of fluid overload, azotemia, or poor cognitive function, or if hypotension or other indicators of hypovolemia develop, more intense monitoring should be instituted. Vital signs and urine output are

checked more frequently. Electrolytes, BUN, magnesium, and creatinine are assessed every 12 hours, and more frequently if necessary. Urinary osmolarity should be checked in this setting. Hypo-osmolar urine is indicative of a primary water diuresis as opposed to a solute diuresis. Of note, an initial solute diuresis may convert to a pathologic water diuresis, underscoring the need for obtaining a baseline urine osmolarity and continued monitoring of this parameter.

The clinically stable patient with good cognitive function should be given free access to oral fluids. Intravenous fluids should probably not be administered, because this may prolong the period of diuresis. However, there may be a theoretical role for maintenance of volume expansion in this setting. Gulmi and associates (1995) demonstrated improved GFR in dogs undergoing volume expansion just prior to relief of BUO. This is linked to increased generation of ANP and the salutary effects of this peptide on RBF and GFR. A clinical trial is needed to determine whether this would facilitate recovery of GFR in humans.

Those with poor cognitive function should receive intravenous hydration, but below the normal maintenance amounts. The majority of these groups also have a self-limiting physiologic diuresis. On rare occasions, a pathologic diuresis develops and the patients can become hypovolemic because of excess water loss. They can develop electrolyte abnormalities as a result of this excess water loss, salt and potassium losses, or both. Massive polyuria with sodium, chloride, potassium, bicarbonate, phosphate, calcium, and magnesium wasting in this setting may promote electrolyte disturbances. These patients warrant the most intense monitoring and require careful electrolyte and fluid replacement, initially by an intravenous route. The urine is usually isosthenuric initially and intravenous fluid replacement with 0.45% saline administration at a rate lower than the urine output is recommended (Frøkiaer and Zeidel, 2007). Changes in the type and amount of intravenous fluid administration are based on the patient's clinical status, serum, and urinary electrolytes. Some patients have salt wasting associated with hyponatremia and hyperkalemia, mimicking adrenal insufficiency. This has been reported to occur mainly in children (Melzi et al, 1995). It is thought to be due to tubular resistance to aldosterone, and supporting evidence for this is the significantly increased serum aldosterone levels reported in these cases. The underlying cause may be a reduction in aldosterone receptors (Kuhnle et al, 1993).

Experimental Modulation of Postobstructive Diuresis

Animal and cell culture experiments demonstrate the potential of pharmacologically attenuating postobstructive diuresis. Ureteral obstruction induces expression of COX-2 in collecting duct cells (Guan et al, 1997). Evidence suggests that the downregulation of AQP2 receptors is mediated by COX-2. Administration of COX-2 inhibitors prevented the downregulation of AQP2 and significantly diminished postobstructive diuresis in rats with BUO (Cheng et al, 2004). In addition, with ureteral obstruction, there is blunted cAMP generation in response to vasopressin (Kim et al, 2001a). Vasopressin-induced, cAMP-mediated pathways induce phosphorylation and subsequent membrane insertion of AQP2 (Nishimoto et al, 1999; Van Balkom et al, 2002). A cAMP-independent, cyclic guanosine monophosphate (cGMP) pathway has been demonstrated in both in-vitro and in-vivo models to allow membrane insertion of AQP2 (Bouley et al, 2000). Acute exposure to the phosphodiesterase type 5 inhibitor sildenafil citrate elevated intracellular cGMP and has been shown to facilitate collecting duct accumulation of AQP2 (Bouley et al, 2005). **Although such data suggest that postobstructive diuresis can be manipulated pharmacologically, it is unclear whether such manipulation would be ultimately beneficial or harmful.**

SELECTED EXTRINSIC CAUSES OF URETERAL OBSTRUCTION

A plethora of intraperitoneal and extraperitoneal disease processes may ultimately result in ureteral obstruction. Hydronephrosis, either symptomatic or incidental, may thus be the initial presentation of these conditions. Herein, selected extrinsic causes of ureteral obstruction are reviewed.

Retroperitoneal Fibrosis

Retroperitoneal fibrosis is an uncommon condition in which a fibrotic and inflammatory mass envelops and potentially obstructs retroperitoneal structures, including either or both ureters. The initial report is now attributed to Albarran (1905), although idiopathic retroperitoneal fibrosis has had the eponym Ormond disease, after that author's description and definition of this clinical entity in 1948 (Albarran, 1905; Ormond, 1948). Of the two patients Ormond initially described, one had progressive renal deterioration and ultimately died of the disease, whereas the other underwent exploration and ureterolysis without subsequent signs or symptoms of recurrent ureteral obstruction during the ensuing 12 years, underscoring the need to recognize and address this process (Ormond, 1960).

Grossly, retroperitoneal fibrosis appears as a fibrous, whitish plaque that encases the aorta, inferior vena cava, and their major branches, and also the ureters, other retroperitoneal structures, and, at times, intraperitoneal structures including the gastrointestinal tract. Its longitudinal axis usually extends from the renal hilum to the pelvic brim, but it may extend into the pelvis, mediastinum, and even the optic orbit. Histologic features include a fibrous component and a chronic inflammatory infiltrate composed of lymphocytes, macrophages, plasma cells, and eosinophils. The infiltrate is both perivascular and diffuse. The fibrotic component consists of myofibroblasts and type-1 collagen (Corradi et al, 2007).

The etiology of retroperitoneal fibrosis is not well characterized. A number of mechanisms have been proposed. One is based on the development of vasculitis in the adventitial vessels of the aorta and perioaortic small vessels. This may lead to the release of antigens from atheromatous plaque such as ceroid, a complex lipoprotein, which induces an autoimmune antigenic response. The latter could induce local inflammation resulting in varying degrees of fibrosis (Baker, 2003). Antibodies for fibroblasts have been isolated in retroperitoneal fibrosis (Vaglio et al, 2006). In-vitro studies have demonstrated that such antibodies stimulate fibroblasts that could lead to the propagation of localized fibrosis (Chizzolini et al, 2002). Other immunologic events may play a role. Both CD3+ and CD20+ lymphocytes and IgG4-positive plasma cells have been identified (Corradi et al, 2007). The presence of clonal and oligoclonal B cells suggest that an errant B-cell disorder may play a role. Environmental toxins may play a role as suggested by the positive association between asbestos exposure and the development of retroperitoneal fibrosis (Uibu et al, 2004).

Limited information is available on its epidemiology. The incidence in Finland was reported to be 0.1 per 100,000 person-years

and the prevalence to be 1.38 per 100,000 inhabitants of this country (Uibu et al, 2004). The incidence has been estimated to be 1 in 200,000 in the Netherlands (Debruyne et al, 1982). It is more common in males, with a 2 to 3:1 male-to-female ratio. The mean age at onset is typically 50 to 60 years, but it may manifest in children as well as the elderly (Wu et al, 2002; Miller et al, 2003; Vaglio et al, 2006). Genetic influence is not thought to play a major role, because there have been no reports of familial clustering. Retroperitoneal fibrosis is associated with HLA-DRB1*03, an allele linked to a number of autoimmune diseases (Martorana et al, 2006).

Numerous medications have been associated with the development of retroperitoneal fibrosis and are listed in Table 40–2, along with other etiologies of this process. A definitive etiology of retroperitoneal fibrosis is found in only 30% of cases (Koep et al, 1977). The term "idiopathic retroperitoneal fibrosis" should be used only when an inciting etiology is not defined. **An underlying malignancy should always be considered, because one is reported to be present in 8% to 10% of such cases** (Amis, 1991). Unique infections can cause retroperitoneal fibrosis such as tuberculosis, histoplasmosis, and actinomycosis. It can occur after abdominal or pelvic surgery as well as abdominal trauma. Radiation and systemic chemotherapy have also been reported to induce it (Fassina et al, 2007; Vaglio et al, 2006).

Table 40–2.

Suspected Causes of Retroperitoneal Fibrosis

Drugs
Methysergide
Hydralazine
Reserpine
Haloperidol
LSD
Methyldopa
β Blockers
Ergotamine alkaloids
Phenacetin
Amphetamines
Pergolide
Bromocriptine
Chemicals
Avitene
Methyl methacrylate
Talcum powder
Retroperitoneal tumors
Inflammatory processes
Ascending lymphangitis
Chronic inflammatory bowel disease
Asbestosis
Amyloidosis
Erdheim-Chester disease
Sarcoidosis
Hemorrhage
Abdominal and pelvic surgery
Ruptured viscera
Henoch-Schönlein purpura with hemorrhage
Periarteritis
Aortic or iliac artery aneurysm
Inflammatory response to advanced atherosclerosis
Collagen vascular disease
Infection
Gonorrhea
Tuberculosis
Chronic urinary tract infection
Syphilis
Radiation injury
Other
Biliary tract disease
Endometriosis

A number of associations between retroperitoneal fibrosis and systemic diseases have been reported including autoimmune and inflammatory processes. These include autoimmune pancreatitis, autoimmune thyroid disease, small- and medium-sized vessel vasculitis, ankylosing spondylitis, rheumatoid arthritis, glomerulonephritis, sclerosing cholangitis, primary biliary cirrhosis, uveitis, psoriasis, and amyloidosis and Erdheim-Chester disease (Vaglio et al 2006; Loddenkemper et al, 2008).

Patients usually have nonspecific symptoms, which may include back, abdominal, or flank pain, weight loss, anorexia, and malaise. Signs can be similarly nonspecific and include hypertension (in 50%), fever, and lower extremity edema. Because of its insidious nature, many patients do not present until late in the disease course, manifesting with signs or symptoms attributable to ureteral or vascular obstruction (Amis, 1991). Reported laboratory abnormalities are nonspecific and include elevations in acute phase reactants, such as erythrocyte sedimentation rate and C-reactive protein (in 80% to 100%), elevated serum creatinine, hypergammaglobulinemia, and normochromic, normocytic anemia (Monev, 2002; Vaglio et al, 2006). Tests for autoimmune diseases may also be positive, such as those for antinuclear antibodies, rheumatoid factor, and antibodies against smooth muscle, double-stranded DNA, extractable nuclear antigen and neutrophil cytoplasm (Vaglio et al, 2006).

Before the advent of cross-sectional imaging, radiologic diagnosis relied upon imaging not the disease process itself but its secondary effects on the ureters. The classic radiologic findings included medial deviation of extrinsically compressed ureters with hydronephrosis. Medial deviation is a nonspecific finding, because it has been demonstrated in up to 18% of normal subjects (Saldino and Palubinskas, 1972). Hydronephrosis is typically demonstrated on ultrasonography, and there may also be a smooth, well-demarcated, hypoechoic or isoechoic mass anterior to the lumbar or sacral spine (Amis, 1991). Retrograde pyelography typically demonstrates hydronephrosis, with medially deviated and segmentally narrowed ureters without filling defects (Fig. 40–10). Currently, cross-sectional imaging with CT or MRI is the modality of choice for evaluating patients with suspected retroperitoneal fibrosis. Both modalities have been demonstrated to delineate accurately the extent of the disease when correlated with surgical exploration (Mulligan et al, 1989). **CT typically reveals a well-demarcated retroperitoneal mass, isodense with muscle on unenhanced studies** (Fig. 40–11) (Vivas et al, 2000). It typically surrounds the lower abdominal aorta, inferior vena cava, and iliac vessels—frequently enveloping the ureters. In contrast, masses secondary to malignancy usually displace the aorta anteriorly and the ureters laterally. Variable degrees of contrast enhancement may be seen, typically more pronounced earlier in the course of the disease when the presumably more-immature plaque has increased vascularity (Amis, 1991). Some have advocated noncontrast multidetector CT imaging combined with antegrade CT pyelography for evaluation, because it can define the fibrotic process and the level and degree of ureteral obstruction without administration of intravenous contrast material (Ghersin et al, 2004). However, the invasive nature of this diagnostic approach limits its applicability.

MRI offers cross-sectional and multiplanar evaluation of the retroperitoneal fibrosis plaque (Fig. 40–12). **Theoretically, MRI**

allows superior soft tissue discrimination and can more accurately distinguish the plaque from the great vessels than unenhanced CT. In addition, the disease can be followed without the radiation exposure of repeated CT (Burn et al, 2002). Fat saturation images are recommended to permit optimal discrimination from surrounding tissues (Elsayes et al, 2007; Cronin et al, 2008). Typically, T1-weighted images of the lesion reveal low to medium signal intensity (hypointense compared with muscle); T2-weighted imaging is variable. Low T2 signal intensity has been correlated with mature plaque (Mulligan et al, 1989). High signal intensity on T2-weighted images suggests increased water content and hypercellularity and may be due to inflammation associated with retroperitoneal fibrosis. However, the latter may be due to an underlying malignant process (Amis, 1991; Burn et al, 2002). A low intensity signal is present if the majority of the plaque is composed of fibrosis. With gadolinium administration, variable enhancement of the plaque may be seen, with a greater degree of enhancement in the more acute phases of the disease process. Enhancement ratios can be calculated with dynamic gadolinium enhancement, and investigators have used these ratios to assess disease activity and monitor treatment responses (Burn et al, 2002). ^{18}F-fluorodeoxyglucose positron emission tomography (F-18 FDG PET) is an imaging modality that detects hypermetabolic activity. It may depict the degree of inflammation in the plaque, which may predict response to immunosuppressive therapy as well as its therapeutic response (Vaglio et al, 2006; Young et al, 2008). The utility of F-18 FDG PET for management of retroperitoneal fibrosis is not yet defined; thus, further studies are warranted. Gallium-67 single photon emission–computed tomography (SPECT) scintigraphy has been used for evaluating responses to medical therapy of retroperitoneal fibrosis and for detection of recurrent disease. It demonstrates both the mass lesion and its inflammatory component (van Bommel et al, 2007).



Figure 40–10. Retrograde pyelogram performed in a patient with retroperitoneal fibrosis. Note evenly narrowed midureteral segment with proximal hydronephrosis. (Courtesy of Dr. Ronald Zagoria.)

If there is evidence of obstructive uropathy at presentation, therapy should be first directed at its correction. This may be accomplished with internalized ureteral stents, but percutaneous nephrostomy may be necessary if stenting is not possible or ineffective. **Biopsy to exclude malignancy should be performed next. This can be attempted percutaneously with CT, MRI, or ultrasound guidance.** Core tissue biopsy (histologic confirmation) is preferred over fine needle aspiration cytologic assessment. Although some have reported the latter to be an effective technique, others have noted pitfalls (Stein et al, 1997; Dash et al, 1999; Jogai, 2005). If this is not technically possible, or the tissue obtained is inadequate, an open surgical or laparoscopic biopsy is recommended with concomitant ureterolysis if malignancy is not suspected on frozen-section analysis. If the percutaneous biopsy demonstrates findings compatible with retroperitoneal fibrosis, possible inciting medications should be discontinued.

The potential morbidity of ureterolysis, accurate image-guided biopsy techniques, and more sensitive cross-sectional imaging studies for diagnosis and follow-up have made medical therapy the preferred approach in this setting. However, notably, there have

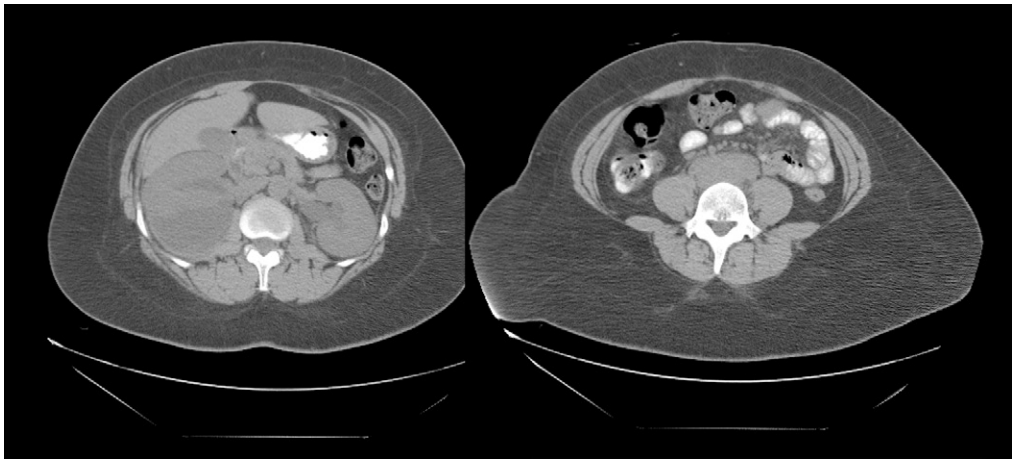


Figure 40–11. Unenhanced computed tomography performed in a patient with retroperitoneal fibrosis. Note hydronephrosis and soft tissue mass indistinguishable from the great vessels. (Courtesy of Dr. Ronald Zagoria.)

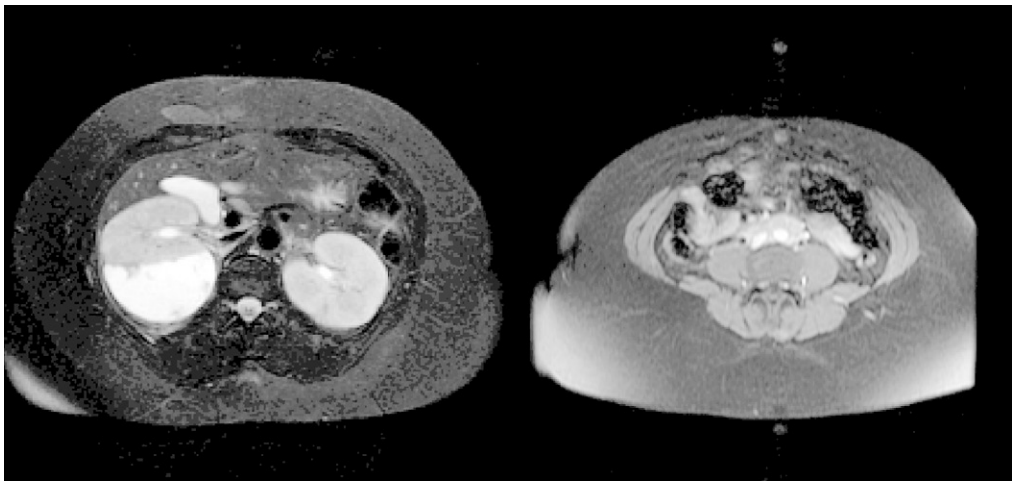


Figure 40–12. Unenhanced magnetic resonance imaging from the same patient as in Figure 40–9. (Courtesy of Dr. Ronald Zagoria.)

been no randomized prospective studies addressing the merits of initial medical therapy versus a surgical approach. Patients should be informed about the side effects of the proposed medical therapy and the risk of disease progression or undiagnosed malignancy. Medical therapy has been directed to address the presumed autoimmune and inflammatory components of retroperitoneal fibrosis.

The administration of corticosteroids has been used for primary therapy. Although many steroid regimens have been described, appropriate dosing schedules and duration of therapy have not been clearly established. The sequence suggested by Kardar and colleagues (2002) has been demonstrated to be effective after long-term follow-up. Their algorithm for adults consists of prednisolone administered at an oral dose of 60 mg on alternate days for 2 months, tapered to 5 mg daily over the next 2 months. The latter dose is continued for a total of 2 years. Of the 11 patients who completed this regimen, at a median follow-up of 63 months, 9 maintained a good response, 1 required ureterolysis, and 1 recurred but responded to reinitiation of therapy. van Bommel and associates (2007) treated 24 patients with prednisone for 1 year. They were initially treated with 60 mg per day for 6 weeks and tapered to 10 mg over the next 2 to 3 months, a dosage which was maintained for the remainder of the year. Six subjects (25%) had no response to the therapy, while 12 of 16 responders (67%) had relapses, with the majority responding to reinitiation of prednisone or alternative medical therapy at a median follow-up of 55 months. Fry and colleagues (2008) treated 27 patients with 30 to 40 mg of prednisolone per day for a mean of 34 months. Ureteral stents were typically removed at 12 months. Twenty-four (89%) initially responded, and 6 recurred at a mean of 15 months after steroid withdrawal.

Tamoxifen, a nonsteroidal antiestrogen, has also been used for primary treatment. It is thought to alter TGF-β, potentially limiting fibrosis. van Bommel and associates (2007) treated 19 patients with 20 mg of tamoxifen per day. The median duration of treatment was 8.5 months (range 5.5 to 15 months). Fourteen responded to therapy (74%) and 5 failed (26%). Successful combination therapy using a tapered steroid regimen and daily tamoxifen has also been described (Tziomalos et al, 2004).

Other treatments have been used as primary or salvage therapy for those afflicted with retroperitoneal fibrosis. Marcolongo and colleagues (2004) reported 26 patients who were treated with a 6-month course of prednisone, combined with either 6 months of cyclophosphamide or 1 year of azathioprine. Severe adverse effects in the cyclophosphamide group included death in one, sepsis in one, and severe leukopenia in two patients. In the azathioprine group, activation of hepatitis, pancreatitis, and oral candidiasis developed. All surviving patients had disease resolution, although seven required a second course of treatment. Swartz and associates (2008) treated 16 patients with idiopathic retroperitoneal fibrosis with a 3- to 6-month course of prednisone in conjunction with mycophenolate mofetil for approximately 2 years. One half of these patients were subjected to ureterolysis or ureteral reconstruction, while the others just underwent ureteral stenting. All had resolution or improvement of symptoms and were rendered stent free. Other groups have reported success with this regimen. Adler and colleagues (2008) treated 9 patients having histologically confirmed retroperitoneal fibrosis with these same two drugs for 6 months. All had radiographic regression of the retroperitoneal fibrosis, and 7 were rendered stent free. Scheel and associates reported on 7 patients receiving a similar regimen (Scheel et al, 2007). Six of 7 had radiographic regression, and 10 of 11 with obstructed renal units became stent free. Vega and colleagues (2008) administered colchicine and prednisone or deflazacort (steroid preparation) to 7 patients and reported that the majority experienced a regression in their disease. The coadministration of steroids in all of these series does not permit the determination of the efficacy of these various respective agents.

Ureterolysis is undertaken if medical therapy fails or if the patient is not a candidate for medical therapy. Traditionally, this has been done by an open surgical approach, but successful laparoscopic and robotic ureterolysis have been reported and may be feasible options (Duchene et al 2007; Stifelman et al, 2008). Bilateral ureterolysis is recommended, even in the setting of unilateral disease, as the disease typically progresses to involve the contralateral side. The ureteral dissection should begin in a region free of disease, and care must be taken to avoid devascularization of the ureter. A biopsy of the fibrotic area should be repeated to limit the risk of sampling error associated with percutaneous biopsy. Several strategies have been employed to prevent recurrent ureteral involvement in the fibrotic process. **The ureter may be displaced to a lateral position, brought to an intraperitoneal location by closing the peritoneum behind it, or wrapped within a sleeve of omentum. No single method has been definitively demonstrated to generate superior results** (Barbalias and Liatsikos, 1999). If it

is determined intraoperatively that ureterolysis is not technically possible, alternatives include ileal ureter replacement, autotransplantation, chronic ureteral stenting, or nephrostomy tube drainage.

Ureteral stents can generally be removed 6 to 8 weeks after ureterolysis (Varkarakis and Jarrett, 2005). Some have advocated postoperative medical therapy to expedite disease resolution or prevent recurrence (Varkarakis and Jarrett, 2005). Others have not found differences in outcomes for those who receive versus those who are not administered adjuvant therapy (Duchene et al, 2007).

Reported success rates for small series involving ureterolysis are 66% to 100%. The best success rate was reported by Elashry and colleagues (1996): 100% for seven laparoscopic and 100% in six open surgical procedures. Duchene and associates (2007) subjected 31 patients to laparoscopic or robotic ureterolysis and reported that this was successful in 38 of 46 obstructed renal units (83%). Alexopoulos and associates (1987), however, noted only 66% long-term success with ureterolysis combined with postoperative steroid administration in six patients. Of note, one of their patients failed 16 years after surgery and became dialysis dependent. **Long-term follow-up in those subjected to medical or surgical therapy is warranted.** Serial cross-sectional imaging should be obtained to assess for disease recurrence, progression, or findings suggestive of malignancy. Renal function should also be monitored.

Pelvic Lipomatosis

Pelvic lipomatosis is a rare, benign condition marked by exuberant pelvic overgrowth of nonmalignant but infiltrative adipose tissue, usually in the abdominal and pelvic cavities. The fat deposition generally occurs in the perivesical and perirectal spaces. Engels first described the condition in 1959, and it has been the subject of several reviews and many case reports in the interim. The largest review to date comprised 130 patients, whose mean age at presentation was 48 years. Racial and gender differences were noted, with 67% of the patients black and 33% white; there was an 18:1 male-to-female ratio (Heyns, 1991).

The etiology and incidence of this disorder are unknown. Obesity has been proposed to play a role, because radiographic improvement and worsening have been noted in response to weight loss and gain, respectively (Sacks et al, 1975). In addition, obesity has been noted in more than one half of the patients afflicted by pelvic lipomatosis (Heyns, 1991). However, if pelvic lipomatosis were simply a manifestation of obesity, its observed frequency should be far greater (Morretin and Wilson, 1971). The reported occurrence of pelvic lipomatosis in two brothers raises the possibility of an underlying genetic etiology (Tong et al, 2002). An abnormality in the chromatin-regulating high-mobility group A (HMGA) proteins has been implicated as a possible causative factor in pelvic lipomatosis, because transgenic mice with truncated HMGA developed pelvic lipomatosis (Fedele et al, 2001). Possible etiological genetic mutations have been traced to the HMGA2 gene located on the hypermobile cluster on chromosome 12 (Fedele et al, 2001). It is believed that pelvic lipomatosis may be a chronic inflammatory response triggered by urinary tract infection.

Approximately one half of patients present with lower urinary tract symptoms and one quarter with bowel symptoms, typically constipation. Suprapubic, back, flank, or perineal discomfort can also be an initial clinical manifestation. The nonspecific nature of these symptoms may result in a significant delay in diagnosis (Heyns, 1991). **Physical findings may include a suprapubic mass, a high-riding prostate, and an indistinct pelvic mass.** Hypertension has been reported in as many as one third of patients (Klein et al 1988; Heyns, 1991).

There are various radiologic signs of pelvic lipomatosis. On plain film, increased pelvic lucency may be noted (Fig. 40–13). **On excretory urography, the bladder characteristically assumes a pear or gourd shape, extrinsically compressed and elongated, and the bladder base is frequently elevated** (Fig. 40–14). At times, proliferation of the mature unencapsulated fat in the pelvis and retroperitoneum leads to **severe bilateral hydronephrosis.** In contrast to retroperitoneal fibrosis, which usually affects the proximal and midureters, pelvic lipomatosis causes significant displacement of the distal ureters medially (Lin et al, 2007). Hydroureteronephrosis may be seen (Heyns, 1991). CT is quite helpful in establishing the diagnosis, because it readily demonstrates pelvic fat (Fig. 40–15). Extrinsic compression of the rectum may also be demonstrated (Susmano and Dolin, 1979). CT may help in differentiating pelvic lipomatosis from other radiologically similar pelvic mass lesions such as lipomas, lipoplastic lymphadenopathy, and liposarcoma. Liposarcoma should be suspected if there is tissue heterogeneity, areas of positive attenuation coefficients, enhancement with contrast, and poor margination (Andac et al, 2003). MRI can also be used to make the diagnosis, because it permits characterization of fat deposits (Demas et al, 1988).

Evaluation should include cystoscopy, because some form of proliferative cystitis has been found in 75% of patients, including cystitis glandularis in up to 40% (Heyns, 1991). **However, the majority of patients with cystitis glandularis do not have pelvic lipomatosis** (Smith et al, 2008). The development of cystitis glandularis in this setting has been hypothesized to be due to accumulation of perivesical fat, causing compression of the bladder that leads to venous stasis, and the development of an edematous urothelium that subsequently sloughs off. As the urothelium regenerates, it may undergo



Figure 40–13. Plain radiograph of pelvis in a patient with pelvic lipomatosis. Note increased pelvic lucency. (Courtesy of Dr. Ronald Zagoria.)



Figure 40–14. Excretory urography of a patient with pelvic lipomatosis. Note classic pear-shaped bladder with increased surrounding pelvic lucency. (Courtesy of Dr. Ronald Zagoria.)

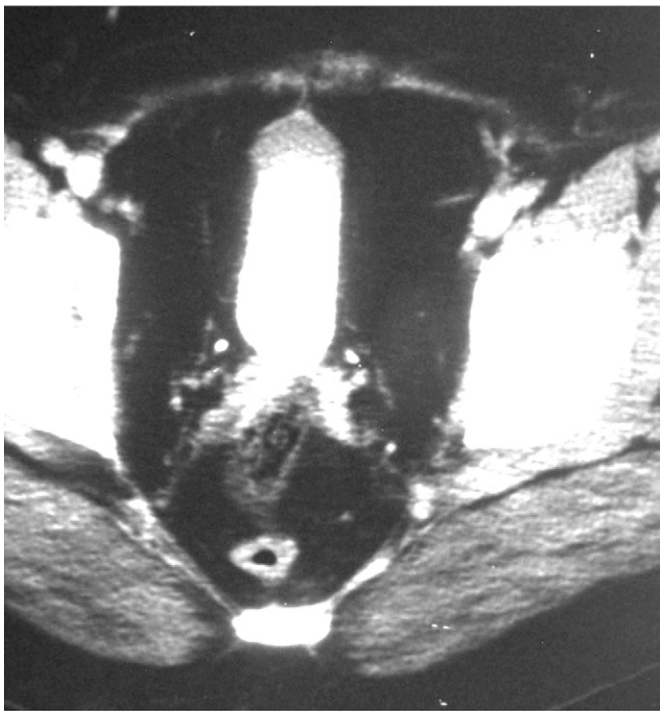


Figure 40–15. Computed tomography cystogram of a patient with pelvic lipomatosis. Note narrowed bladder and increased pelvic fat in perivesical and perirectal spaces. (Courtesy of Dr. Ronald Zagoria.)

a metaplastic change leading to development of cystitis glandularis. Continued cystoscopic surveillance is recommended in those with cystitis glandularis, because the development of bladder adenocarcinoma has been reported in this cohort (Sozen et al, 2004). **Elongation of the prostatic urethra, elevation of the bladder neck, and pelvic fixation may impair cystoscopic access to the bladder.** In Heyns' review (1991) of 72 patients in whom cystoscopy was attempted, evaluation of the bladder was difficult in 24% and impossible in 18%. Hence, flexible cystoscopy may be required if anatomic distortion precludes rigid cystoscopy.

The clinical signs and symptoms include lower urinary tract symptoms, hematuria, passage of debris in the urine, and problems with defecation. Klein and associates (1988) suggested that there are two clinically separate groups of patients. The first is composed of young, stocky men with irritative lower urinary tract symptoms, vague pelvic complaints, hypertension, and proliferative cystitis. This group may be more susceptible to developing progressive ureteral obstruction. Pelvic lipomatosis has been found to be associated with progressive uremia in up to 40% of patients observed for five years from the time of initial diagnosis (Sozen et al, 2004). The second group includes older men with incidentally discovered pelvic lipomatosis who are reported to have a more indolent course. Others have not found age to affect disease progression (Heyns, 1991). The accumulation of fatty pelvic tissue causes a mass effect that is known to compress both pelvic as well as intra-abdominal organs, causing obstruction of the ureters, rectum and sigmoid colon, the pelvic veins, and even the inferior vena cava. **Nevertheless, there is agreement that in light of the potential for progressive ureteral obstruction, long-term follow-up is mandated.** Overall, 39% of patients in Klein's series ultimately required operative intervention for upper tract obstruction.

Treatments with steroids, chemotherapy, radiotherapy, and chronic antibiotic therapy have not been reported to be successful. Surgical options in patients with obstructive uropathy secondary to pelvic lipomatosis include ureteral stenting, percutaneous nephrostomy, ureteral reimplantation, and urinary diversion with or without cystoprostatectomy (Sozen et al, 2004). Surgical intervention for removal of the pelvic lipomatous tissue is often limited, due to extensive deposits of fat, and their removal does not always lead to an improvement. Pelvic exploration should be approached cautiously, because there is obliteration of normal anatomic planes and increased vascularity within the fatty mass.

Obstetric and Gynecologic

Pregnancy

Hydronephrosis develops commonly during pregnancy, the reported occurrence varying between 43% and 100% (Faundes et al, 1998). This wide variability is due to the use of different definitions of hydronephrosis. The right kidney becomes hydronephrotic two to three times more commonly than the left (Cietak and Newton 1985; Faundes et al, 1998). Hydronephrosis may initially manifest in the first trimester, and it increasingly develops throughout pregnancy (Au et al, 1985; Loughlin, 1997). This progression was also reported in a large prospective study by Faundes and colleagues (1998), who found that hydronephrosis was present in 15%, 20%, and 50% of women during the first, second, and third trimesters, respectively. The degree of hydronephrosis also increased over time. Hydronephrosis has been demonstrated to be more common during a first-time pregnancy

(Erickson et al, 1979). The maximal calyceal diameters during pregnancy were measured over time by Faundes and associates (1998). These parameters are provided (Table 40–3), because they may be useful when evaluating patients with hydronephrosis during pregnancy. After delivery, hydronephrosis gradually resolves. **Approximately one third of patients may have persistent hydronephrosis during the first postpartum week, but it resolves in the majority within 6 weeks** (Cietak and Newton, 1985).

Two etiologies for hydronephrosis of pregnancy have been postulated, one hormonal and one mechanical. The 10% to 15% incidence of observed first-trimester ureteral dilatation, occurring before the uterus reaches the pelvic brim, supports a nonmechanical mechanism. Progesterone, a hormone in more abundance during pregnancy, has been hypothesized to promote ureteral dilatation and subsequent development of hydronephrosis (Faundes et al, 1988). The increased incidence and degree of hydronephrosis after the 20th week of gestation, a time when the uterus is large enough to compress the ureters extrinsically, supports a mechanical etiology. The significantly lower incidence of left-sided hydronephrosis also supports this hypothesis (Cietak and Newton, 1985). However, it is quite plausible that both mechanisms play a role.

Hydronephrosis of pregnancy is usually clinically silent. However, some with hydronephrosis of pregnancy may experience flank pain or develop pyelonephritis or renal failure. Renal ultrasonography should be undertaken in this setting. **The typical ultrasonographic findings of this entity are hydroureteronephrosis extending to the pelvic brim. When ureteral dilation extends below this, a different etiology of obstruction, such as a ureteral stone, should be considered.** If the latter is suspected, limited intravenous urography and low-energy CT are diagnostic options (White et al, 2007). However, MRI is now another consideration. **Magnetic resonance urography has been advocated by some as a noninvasive, nonradiating method of assessing those with hydronephrosis of pregnancy. The presence of hydroureter below the pelvic brim is readily apparent on high-resolution T2 sequences, and filling defects representing stones or soft tissue may be seen** (Spencer et al, 2004). In addition, MRI has proved useful in identifying other causes of acute abdominal pain in pregnancy, including appendicitis, ovarian torsion, and adrenal hemorrhage (Birchard et al, 2005). There is no current scientific evidence of definite adverse effects on the fetus or pregnancy due to the electromagnetic fields. MRI is currently viewed as a useful imaging technique for evaluating select pregnant patients with abdominal, flank, or pelvic pain (Fielding et al, 2006; Kanal et al, 2006). However, despite the lack of any proven adverse effects, the use of MRI is not advocated in the first trimester of pregnancy (Leyendecker et al, 2004). In addition, the administration of gadolinium contrast should be avoided in pregnant patients because it is known to cross the placental barrier (Shellock et al, 1999).

Table 40–3.

Observed and Adjusted Percentiles of Maximal Maternal Calyceal Diameter (mm) of Right and Left Kidneys According to Gestational Age

Gestational Age (wk)	Observed Percentiles				Adjusted Percentiles			
	RIGHT		LEFT		RIGHT		LEFT	
	50th	75th	90th	90th	50th	75th	90th	90th
4-6	0.0	3.0	5.0	2.1	1.4	2.4	3.4	0.1
7-8	0.0	0.0	5.0	0.0	0.3	3.2	4.5	2.2
9-10	0.0	0.0	4.0	0.0	1.2	4.0	5.7	3.5
11-12	0.0	5.0	7.0	6.0	2.0	4.9	7.0	4.5
13-14	0.0	5.8	8.0	6.9	2.7	5.7	8.4	5.3
15-16	0.0	1.0	8.9	4.9	3.0	6.7	9.8	6.0
17-18	5.0	9.5	12.0	8.8	3.7	7.6	11.2	6.6
19-20	0.0	8.0	11.0	7.7	4.2	8.6	2.6	7.1
21-22	5.0	9.0	13.8	6.8	4.6	9.6	13.9	7.1
23-24	8.0	12.0	15.0	8.2	4.9	10.5	15.1	7.9
25-26	7.0	13.0	16.7	8.0	5.3	11.4	16.2	8.2
27-28	7.0	13.0	21.0	9.0	5.6	12.2	17.2	8.4
29-30	7.0	11.0	16.0	9.0	5.9	13.0	18.0	8.6
31-32	8.0	15.5	19.4	8.2	6.1	13.7	18.7	8.7
33-34	4.5	13.0	20.5	8.5	6.4	14.3	19.3	8.8
35-36	6.0	15.0	19.0	8.0	6.6	14.8	19.7	8.9
37-38	5.0	14.0	20.4	8.0	6.8	15.2	19.8	8.9
39-42	7.0	14.0	17.0	9.2	7.1	15.5	19.8	8.7

The majority of patients with symptomatic hydronephrosis of pregnancy can be managed with conservative measures, such as intravenous hydration, analgesics, and antibiotic therapy when clinically indicated. However, placement of ureteral stents may be necessary when these measures are unsuccessful, especially with signs of sepsis or compromised renal function. **Rapid stent encrustation may be problematic, as urinary calcium excretion increases during pregnancy** (Goldfarb et al, 1989). This may necessitate more frequent stent changes. Percutaneous nephrostomy is an alternative if this occurs, and it is also a consideration if pyonephrosis is suspected.

Benign Pelvic Abnormalities

Tubo-ovarian Abscess. Pelvic inflammatory disease (PID) is a common problem, affecting 10% of women during their lifetime. **Tubo-ovarian abscess, occurring in approximately 15% of those afflicted with PID, may cause extrinsic ureteral obstruction,** which may even lead to anuria (Aral et al, 1991; Conde Santos et al, 2003). This process may be demonstrated with ultrasonography, CT, or MRI. Ureteral obstruction may resolve with antibiotic therapy or transvaginal drainage of the abscess. However, an open surgical or laparoscopic intervention may be required to drain or excise the involved ovary and fallopian tube if the aforementioned measures are unsuccessful. Placement of an internalized ureteral stent or percutaneous nephrostomy should be considered if high-grade renal obstruction or urosepsis is suspected. Stent or nephrostomy tube removal is undertaken after the inflammatory process has resolved. Follow-up renal imaging is recommended, because some patients have persistent obstruction.

Endometriosis. **Endometriosis is defined as the presence of functional endometrial tissue in an ectopic site.** Although endometriosis is usually confined to the ovaries, uterosacral ligaments, and cul-de-sac, it has been documented in almost every organ system in the body (Jubanyik and Comite, 1997). Endometriosis has the potential for malignant transformation (Takeuchi et al, 2006). It may affect 10% to 20% of women of reproductive age, with a peak incidence in the mid-20s (Eskenazi and Warner, 1997; Vigano et al, 2004; Berkley et al, 2005). Rarely, endometriosis of the urinary tract has been reported to occur in postmenopausal women (Maeda et al, 2009). There is no relationship of endometriosis with race or socioeconomic status.

Genitourinary endometriosis is a rare condition (Antonelli et al, 2006a, 2006b), with involvement of the urinary tract in 1% to 5% of those afflicted with this disorder. **Endometriosis of the**

urinary tract is predominantly found in the bladder, accounting for 70% to 80% of the cases. The ureter may be involved in 15% to 20% of the urinary tract cases (Williams, 1975; Giudice et al, 2004). Rarely, renal and urethral involvement may occur (Comiter, 2002; Giudice et al, 2004). Involvement may be either intrinsic or extrinsic. Intrinsic endometriosis is characterized by endometrial glands and stroma within the lamina propria, tunica muscularis, or ureteral lumen; extrinsic endometriosis is localized within periureteral tissue. Eighty percent of ureteral endometriosis is extrinsic and primarily involves the distal ureter (Klein and Cattolica, 1979). The left side is more often affected, and bilateral disease has been reported in up to 23% of cases (Antonelli et al, 2004). One theory for ureteral involvement is the occurrence of retrograde menstruation and implantation of endometrial cells. This is thought to occur more commonly on the left side due to relationships with the sigmoid colon and ipsilateral ovary and anatomic differences between the right and left side of the pelvis (Vercellini et al, 2000). Vesical endometriosis is usually solitary and typically involves the dome of the bladder (Schneider et al, 2006).

Classic symptoms and signs of urinary tract endometriosis include cyclical flank pain, dysuria, urgency, urinary tract infection, and hematuria (Jubanyik and Comite, 1997). Cyclical lower urinary tract symptoms, abdominal and pelvic pain are present in the majority of patients with bladder involvement. However, as many as one third are asymptomatic (Westney et al 2000; Schneider et al, 2006). Patients with intrinsic endometriosis experience these symptoms more than those with extrinsic disease. **Notably, a significant portion of patients with ureteral endometriosis do not have genitourinary symptoms.** For example, in one series, ureteral obstruction was silent in approximately 40% of those with severe ureteral endometriosis (Antonelli et al, 2004). Furthermore, silent loss of renal function has been reported in 25% to 43% of patients with ureteral endometriosis, which may result in total loss of function of the affected kidney (Watanabe et al, 2004). Historically, up to one third of kidneys affected by ureteral endometriosis were lost (Klein and Cattolica, 1979).

Because a large percentage of patients with ureteral endometriosis can have asymptomatic obstruction of the kidney with a loss of renal function, it has been recommended to image the upper urinary tract in all patients with pelvic endometriosis. An endoscopic endometriosis evaluation scale has been generated to quantitate the extent and depth of involvement. There is a positive correlation with this scale and genitourinary involvement (Giudice et al, 2004). Initial imaging may be done with ultrasonography as a noninvasive test to look for hydroureteronephrosis. An EXU may be a better test when the index of suspicion for ureteral involvement is high. Pyelographic findings of intrinsic disease include ureteral filling defects, whereas smooth strictured ureteral segments are seen with extrinsic disease (Stebbing and Notley, 1995). Retrograde ureteropyelography, CT, and MRI may help to ascertain the exact location and volume of the disease and may provide valuable information for planning treatment. On MRI the most frequent sign of ureteral endometriosis is the detection of a hypointense nodule along with hyperintense foci adjacent to the ureter on T2- and T1-weighted images (Balleyguier et al, 2004). MRI may be particularly useful for the detection of ureteric and/or bladder deep pelvic endometriosis (Kinkel et al, 2006; Marcelli et al, 2006). Cystoscopy and possible biopsy should be done in women with pelvic endometriosis, presenting with lower urinary tract symptoms, and in those with hematuria. Ureteroscopy and possible biopsy should be undertaken when upper urinary tract involvement is suspected (Comiter, 2002). Immunostaining of the biopsied tissue for ER, PR, CK7, CA125, and CD10 may help establish the diagnosis (Al-Khwaja et al, 2008).

Treatment has several goals: (1) preservation of renal function, with long-term relief of urinary obstruction, (2) management of the ongoing disease process by completely excising or ablating the endometriotic tissue with its reactive fibrotic component, (3) maintenance of the patient's fertility, and (4) relief of the patient's symptoms with the least invasive methods available. Treatment should be individualized according to age, reproductive desire, symptom severity, extent of lesion, and organ(s) involved (Pastor-Navarro et al, 2007).

If renal function is normal and there is minimal to mild hydronephrosis with no functional obstruction as determined by radionuclide renal scanning, hormone therapy may be prescribed. Ovarian hormonal ablation with gonadotropin-releasing hormone agonists has been used with success in some series. Rivlin and associates (1990) described three patients treated with leuprolide acetate for 6 to 9 months. One patient had BUO, and two had UUO. The obstruction resolved in the patient with BUO and in one of the patients with UUO. The failure occurred in the patient with intrinsic ureteral disease.

Hormonal therapy is generally not as effective for patients with extensive endometriosis, as reflected by its high treatment failure and recurrence rates (Lam et al, 1992). Postmenopausal patients may be reasonably controlled with luteinizing hormone–releasing hormone (LHRH) analogues.

Surgical intervention is the treatment of choice for most patients with significant hydroureteronephrosis and periureteral disease. If the patient does not desire future pregnancy, treatment is total abdominal hysterectomy and bilateral salpingo-oophorectomy. If pregnancy is desired, lesser extirpative procedures can be performed, such as unilateral oophorectomy. Ureterolysis may correct ureteral obstruction in those with extrinsic disease. If laparoscopic ureterolysis is undertaken, a transperitoneal approach is preferable in that it allows a superior assessment of endometrial implants on the peritoneum overlying the ureter (Watanabe et al, 2004; Frenna et al, 2007). Success rates of 85% have been reported for this approach (Ghezzi et al, 2006). If patients are suspected to have intraluminal ureteral involvement, ureteroscopic resection or ablation is a consideration (Ghezzi et al, 2007). However, if these procedures are unsuccessful or extensive disease is present, distal ureterectomy with reimplantation should be performed. This can be done by an open surgical, laparoscopic- or robotic-assisted approach. This typically results in excellent long-term results with regard to renal preservation (Antonelli et al, 2004; Antonelli et al, 2006a, 2006b). The surgical treatment of those afflicted with vesical endometriosis is dependent on the extent and depth of the disease. Those with superficial involvement can be treated with transurethral resection (Fedele et al, 2005; Sanchez et al, 2005). Transurethral resection is not an optimal treatment for deep vesical endometriosis, because it frequently recurs (Le Tohic et al, 2009). Patients with invasive disease are best treated with open surgical, robotic, or laparoscopic partial cystectomy (Sanchez et al, 2005; Fedele et al, 2005; Granese et al, 2008). A recent long-term follow-up study focusing on the laparoscopic management of vesical and ureteric endometriosis has demonstrated a significant reduction in preoperative symptoms without relapse (Seracchioli et al, 2010).

Ureteral stenting is indicated prior to pelvic dissection for posterior vesical endometriotic nodules and prior to partial cystectomy (Marcelli et al, 2006).

Surveillance with sonography is advisable to detect recurrent ureteral obstruction in patients with ureteral endometriosis treated by hormones, endourological ablation, or surgical extirpation (Generao et al, 2005).

Ovarian Remnants. **The ovarian remnant syndrome results from residual, viable ovarian tissue after bilateral salpingo-oophorectomy.** Although uncommon, it is a recognized complication of a technically difficult oophorectomy, most typically in those with endometriosis, PID, or prior abdominal and pelvic surgery (Lafferty et al, 1996; Nezhat et al, 2005). Ovarian remnants may be quite large, up to 10 cm, and may be present in the normal ovarian bed but may be located in other areas as a consequence of dissemination and implantation occurring during surgery (Lafferty et al, 1996). **Mass effect or a localized fibrosis may cause extrinsic ureteral obstruction.** This process may be demonstrated with ultrasonography, CT, or MRI (Klutke et al, 1993).

Treatment is usually surgical excision of the mass and ureterolysis. Preoperative ureteral stenting may be considered if there is high-grade obstruction or as an aid to intraoperative identification of the ureter, although the latter has not been reported to be necessary by some investigators (Lafferty et al, 1996). In a series of 64 patients with ovarian remnant syndrome managed surgically, the majority of the ovarian remnants were found to be attached to the ureter, bowel, pelvic side wall, bladder, and uterosacral ligaments (Nezhat et al, 2005).

Medical management of ureteral obstruction is an option for poor surgical candidates. Successful resolution of the mass and hydronephrosis have been reported with leuprolide acetate therapy. However, chronic medical therapy may be required to prevent recurrence (Koch et al, 1994).

Mass Lesions of the Uterus and Ovaries. Other benign lesions of the uterus and ovary may become large enough to cause extrinsic ureteral obstruction. These include uterine fibroids, ovarian cysts, and ovarian fibromas. **Uterine fibroids, the most common tumor of the upper female genital tract, are also the most common, benign gynecologic neoplasm causing ureteral obstruction** (Greenberg and Kazamel, 1995). The most common site of extrinsic ureteral obstruction is at the level of the pelvic brim. Surgical resection or ablation of the leiomyomas should be considered in this setting.

Vascular Causes of Ureteral Obstruction

The ureters course adjacent to vascular structures and, as a consequence, may be affected by various vascular disease processes and anomalies that may result in their obstruction. An overview of several of these entities is subsequently provided.

Arterial Causes of Obstruction

Abdominal Aortic Aneurysm. **Clinical signs and symptoms of ureteral obstruction may be the initial manifestation of an abdominal aortic aneurysm (AAA)** (Labardini and Ratliff, 1967). The obstruction may be due to a mass effect or localized inflammation (Pennell et al, 1985).

Currently, CT scanning is most frequently used to evaluate patients with an AAA that may demonstrate associated hydronephrosis (Fig. 40–16A and B). Ureteral findings associated with AAA vary. The ureters may be pushed laterally on both sides, or one side may deviate laterally while the opposite side is drawn medially within the perianeurysmal inflammation, or both may be medially deviated. Some have noted that lateral deviation of the ureter with AAA is usually not associated with obstruction (Labardini and Ratliff, 1967). **The medial deviation of the ureter associated with the desmoplastic reaction of inflammatory aneurysms (IAAA), however, carries a more significant risk of ureteral obstruction.** Although IAAA represents only between 4% and 15% of AAAs, the associated retroperitoneal desmoplastic reaction significantly increases the risk of ureteral obstruction, which has been reported in 21% of this cohort (Pennell et al, 1985; Arroyo et al, 2003).

At one time, ureterolysis was routinely performed during repair of IAAA associated with ureteral obstruction. However, this practice has generally been abandoned, because obstruction commonly resolves without ureterolysis. Placement of internalized ureteral stents is commonly undertaken prior to IAAA repair. Ureteral obstruction has been reported to resolve in 80% of patients managed with this approach (Arroyo et al, 2003). Some have advocated endovascular repair of the IAAA in this setting (Nevelsteen et al, 1999). Internalized ureteral stents are inserted prior to endovascular graft placement and are removed when it is thought that

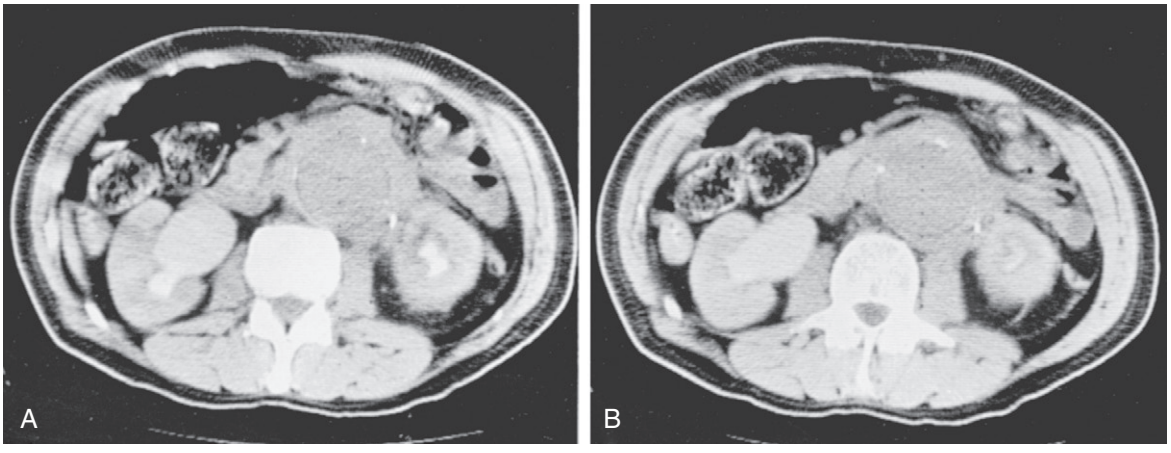


Figure 40–16. **A** and **B,** Computed tomography scans demonstrate extensive retroperitoneal fibrosis associated with aneurysm of the abdominal aorta.

the associated fibrosis has resolved. A 50% resolution of ureteral obstruction has been reported with this approach, while less favorable results have been demonstrated by others (Rehring et al, 2001; Deleersnijder et al, 2002; van Bommel et al, 2008). In a systematic review of endovascular repair of IAAA it was associated with persistent periaortic fibrosis leading to significant ureteral obstruction. Patients with IAAA treated with open surgery or an endovascular approach warrant close monitoring for development of recurrent or de novo ureteral obstruction, because delayed ureteral obstruction has been reported to occur (Simons et al, 2002; Jetty and Barber, 2004; Lambie et al, 2004).

Iliac Artery Aneurysms. Iliac artery aneurysms can cause ureteral obstruction, which may even lead to renal failure (Ochoa Urdangarain et al, 2006). Ureteral obstruction has been reported in 35% of those with common iliac artery aneurysms and 19% of those involving the internal iliac artery. **An iliac artery aneurysm should be suspected if a pulsatile mass is palpated on rectal examination** (Marino et al, 1987). The diagnosis can be made with various imaging studies including ultrasonography, MRI, and CT (Fig. 40–17A and B). Ureteral obstruction may be due to extrinsic compression or localized inflammation (Mineta et al, 2004).

Treatment options for common iliac artery aneurysms in the setting of ureteral obstruction include ureterolysis, aneurysm resection and graft placement, or endovascular graft placement. Options for obstructing internal iliac artery aneurysms include open surgical ligation and ureterolysis or initial endovascular occlusion and subsequent retrograde placement of an iliac artery endovascular graft. Internalized ureteral stents are typically placed before these procedures and are removed 6 to 8 weeks later. These patients need to be observed closely to determine whether ureteral obstruction resolves or recurs. If it recurs, management options include chronic internalized ureteral stenting, ureterolysis, or ureteral reconstruction (Marino et al, 1987).

An additional cause of ureteral obstruction is the retroiliac ureter (Corbus et al, 1960). Treatment of the ureteral obstruction involves transection of the ureter and transposition to the normal, anterior position. Other genitourinary abnormalities are associated with this condition, including renal hypoplasia, vesicoureteral reflux, ureteral ectopia, ectopic vas deferens, hypospadias, bifid scrotum, hypoplastic or duplex uterus, and hydrometrocolpos (Nguyen et al, 1989; Katz and Meirow, 1993). **Therefore a search for other genitourinary abnormalities should be undertaken in patients with retroiliac ureter.**

Ureteral Obstruction after Vascular Graft Placement. Hydronephrosis may occur in up to 10% to 20% of patients after aortic bypass graft surgery (Goldenberg et al, 1988; Schein and Saadia, 1991). There are several possible causes for this problem. Mechanical obstruction of the ureter may be due to graft placement anterior to the ureter, which is readily identified on axial imaging (Bouterie and Harbach, 1979). However, this is the cause in the minority of cases. Other possible etiologies include ureteral entrapment in perigraft fibrosis, ureteral devascularization, unidentified ureteral ligation, and ureteral compression from a postoperative pseudoaneurysm (Sant et al, 1983). Symptoms and signs of ureteral obstruction in this setting typically arise in the first postoperative year and include flank pain, anorexia, hypertension, anuria, and renal failure or insufficiency. A minority may remain asymptomatic or manifest delayed symptoms.

Management of this problem varies. If hydronephrosis is demonstrated early in the postoperative period and renal function is not compromised, close observation is initially indicated because hydronephrosis resolves spontaneously in the majority of cases (Goldenberg et al, 1988). Temporary internalized ureteral stent placement or percutaneous nephrostomy drainage may be required for those with renal impairment or severe symptoms while awaiting spontaneous resolution. If ureteral obstruction does not resolve spontaneously and the graft is placed anteriorly, transposition of the ureter and vascular graft should be a consideration. To reduce

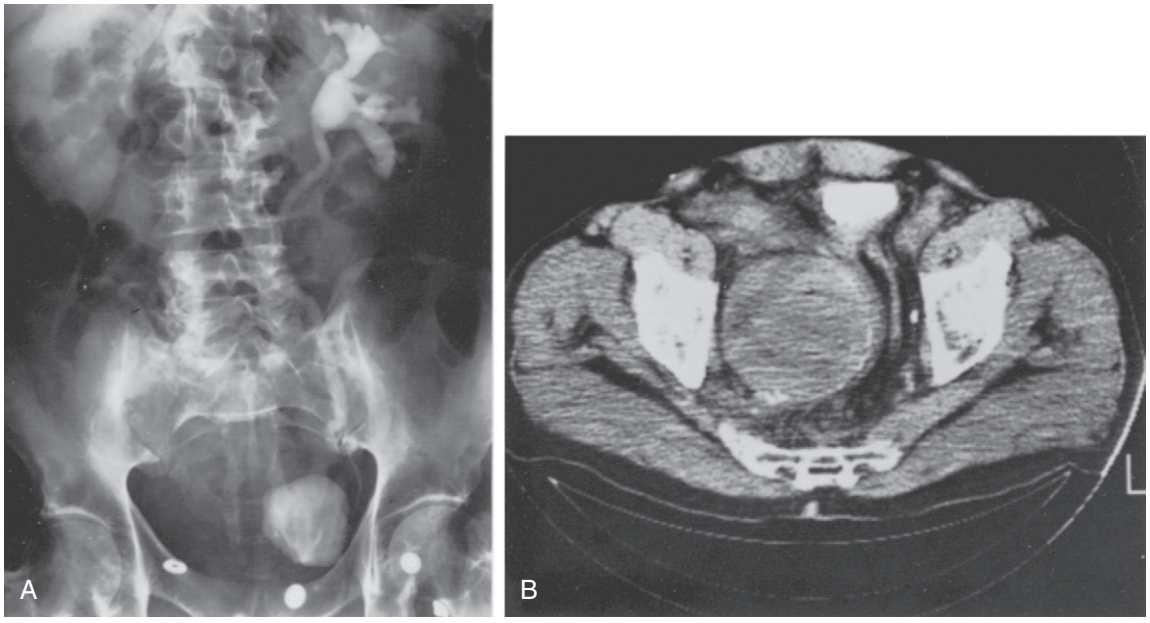


Figure 40–17. Right ureteral obstruction secondary to an aneurysm of the right hypogastric artery. **A,** Intravenous urogram demonstrates delayed visualization of the right kidney and marked deviation of the urinary bladder. **B,** Computed tomography scan demonstrates a large aneurysm. Note calcification of the wall.

the risk of graft infection, however, it has been suggested that the vascular graft, rather than the ureter, should be transected and repositioned (Bouterie and Harbach, 1979). A trial of steroid or tamoxifen therapy, similar to that employed for retroperitoneal fibrosis, may be considered if persistent ureteral obstruction is ascribed to perigraft fibrosis. Although success has been reported with such regimens, careful follow-up is mandatory because delayed treatment failure has been reported (Huben and Schellhammer, 1981; Baskerville and Browse, 1987; Jetty and Barber, 2004). Ureterolysis, and ileal ureter substitution, if the former is not feasible, are considerations if medical therapy is not successful. Chronic ureteral stenting may be required in those who are not candidates for the aforementioned procedures (Sant et al, 1983; Matlaga et al, 2003).

Uterine Artery Aneurysms/Pseudoaneurysms (UAA). UAA is a very uncommon problem that is typically associated with pregnancy. Symptomatic ureteral obstruction leading to hydronephrosis due to UAA has been reported (Leocadio et al, 2006). These conditions have been successfully managed by radiographic embolization or surgical ligation (Zimon et al, 1999).

Venous Causes of Obstruction

Puerperal Ovarian Vein Thrombophlebitis. Ureteral obstruction has been ascribed to a mechanical effect from a dilated ovarian vein, a condition called "ovarian vein syndrome." The clinical relevance of this entity has since been questioned (Dure-Smith, 1979). **However, ovarian vein pathology has been documented to be the cause of ureteral obstruction in the postpartum period. Puerperal ovarian vein thrombophlebitis, a rare but well-documented postpartum condition, has been reported to cause ureteral obstruction** due to perivenous phlegmon formation and resultant periureteritis (Dure-Smith, 1979; Johnson et al, 1998; Brown et al, 1999). Although more common on the right, it may occur in either or both ovarian veins. The associated signs and symptoms are often nonspecific but include abdominal or flank pain and fever, usually beginning 2 to 3 days after birth. On physical examination, abdominal tenderness and guarding may be elicited. A tender indurated adnexal mass may be discerned in 50% of patients (Toland et al, 1993). CT or MRI can detect this condition and the associated ureteral obstruction (Twicker et al, 1997).

The majority of patients respond to conservative measures, including antibiotic therapy (Brown et al, 1999). Internalized ureteral stent placement may also be required for management of ureteral obstruction and symptoms (Toland et al, 1993). Laparoscopic or open surgical ureterolysis and ovarian vein resection are undertaken if ureteral obstruction persists (Almeida et al, 2003; del Valle González et al, 2006).

Testicular Vein Thrombophlebitis. Thrombophlebitis of the left testicular vein causing extrinsic obstruction of the left ureter has been reported (Kretkowski and Shah, 1977). Although the patient presented with the clinical picture of UPJO, surgical exploration revealed a dilated and thrombosed left testicular vein impinging upon the proximal ureter. Ureterolysis and excision of the thrombosed vein eradicated the obstruction. A similar event could also occur on the right side (Meyer et al, 1992).

Circumcaval Ureter. Obstruction of the ureter has been described in association with an anomalous course posterior, medial, anterior, and finally lateral to the inferior vena cava (IVC) (Bateson and Atkinson, 1969). This course may lead to extrinsic obstruction of the ureter. Although commonly referred to as circumcaval or retrocaval ureter, a more appropriate term may be preureteral vena cava, because it is due to a congenital abnormality in development of the vena cava. The term retrocaval is now primarily used to describe ureters that simply course behind the IVC and reemerge laterally.

Formation of the infrahepatic vena cava is based upon the development and regression of three pairs of embryonic veins: the posterior cardinal, the supracardinal, and the subcardinal. It is postulated that the normally developed IVC results from persistence of the right subcardinal vein suprarenally and the right supracardinal infrarenally. The posterior cardinal veins persist as the common iliac veins (Bass et al, 2000). The anastomosis between the right subcardinal and supracardinal vein crosses anterior to the fetal ureter. In normal development, this connection regresses, and the supracardinal vein persists as the infrarenal IVC. The prevailing theory of the development of this anomaly is that the subcardinal vein persists as the infrarenal IVC, thus crossing anterior to the midportion of the ureter and resulting in its circumcaval course (Schulman, 1997). Others have suggested that the persistence of the posterior cardinal vein as the infrarenal cava is responsible for this anomaly. However, failure of the supracardinal vein to develop into the infrarenal IVC is common to both theories (Bass et al, 2000) (Fig. 40–18A to C).

The reported incidence of circumcaval ureter is approximately 1 in 1100. There is a 2.8-fold male predominance (Lutin et al, 1988). Symptomatic patients typically present in the third or fourth decade of life (Zhang et al, 1990). **This vascular anomaly is not always associated with ureteral obstruction** (Crosse et al, 1975). The majority involve the right ureter, although

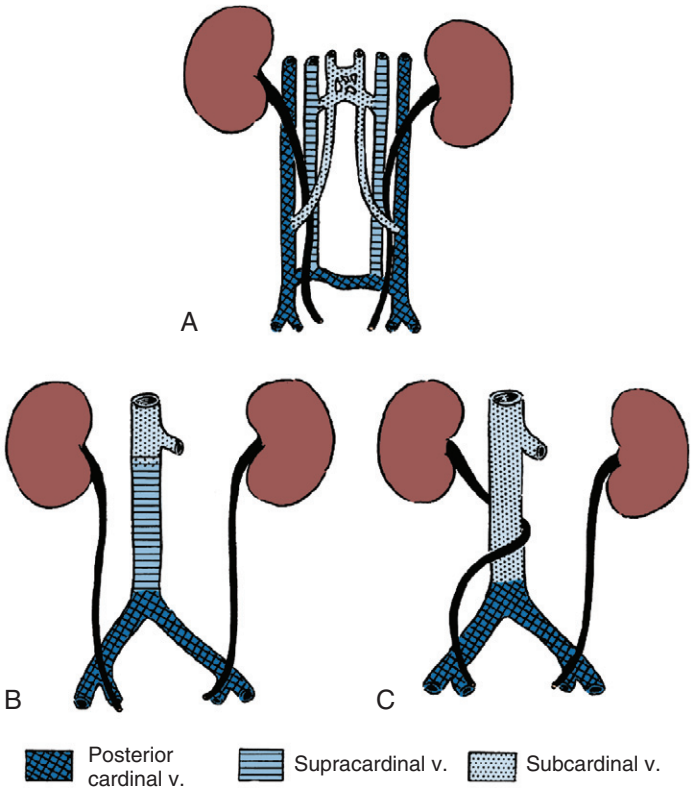


Figure 40–18. Relationship between the development of the infrarenal portion of the inferior vena cava and the retrocaval ureter. **A,** Primitive condition with the ureter winding among three cardinal veins. **B,** Usual method of formation of the vena cava from the right subcardinal vein (dorsal to ureter). **C,** Main portion of the vena cava formed from the subcardinal vein. (From Hollinshead WH. Anatomy for surgeons, vol. 2. 2nd ed. New York: Harper & Row; 1971.)

left-sided circumcaval ureter has been reported in association with a duplicated IVC and in association with situs inversus (Watanabe et al, 1991; Rubinstein et al, 1999). Other genitourinary anomalies may be present. Circumcaval right ureter with a retrocaval horseshoe isthmus has been reported (Knutson and Hawas, 2004).

Circumcaval ureter has been classified using different parameters based on intravenous urography or retrograde pyelographic findings. Bateson and Atkinson (1969) classified a ureter with an S-shaped, fish hook, or shepherd's crook appearance as type I (Fig. 40–19A). The ureter typically overlies or is medial to the lower lumbar vertebral processes and eventually crosses anterior to the iliac vessels, where it then assumes a normal distal course in this setting. A less-angulated "sickle-shaped" ureteral deformity is classified as type II (Fig. 40–19B). The point of maximal obstruction in type I is lateral to the lateral margin of the IVC and is associated with a greater degree of hydronephrosis than type II, in which the point of obstruction is at the lateral border of the IVC (Bateson and Atkinson, 1969). Another classification scheme is based on the level of obstruction; type I crosses at the level of the third lumbar vertebra, and type II crosses at the level of the ureteropelvic junction. The latter may be confused with ureteropelvic junction obstruction (Kenawi and Williams, 1976). The obstruction has been attributed to extrinsic compression of the ureter by the IVC, its lumbar or gonadal branches, or the psoas muscle. However, an intrinsic ureteral abnormality may be contributory as histologic studies of involved ureteral segments have demonstrated fibrotic changes (Kumar and Bhandar, 1985).

Abdominal and flank pain, recurrent urinary tract infection, and hypertension are some of the initial symptoms and signs. A number of cases are now discovered on imaging studies performed to evaluate patients with nonurologic problems (Belis and Milam, 1980; Sener, 1993). The diagnosis should be suspected when the aforementioned pyelographic findings are present (Fig. 40–20A to C). The diagnosis can be confirmed with CT and MRI (Fig. 40–21A

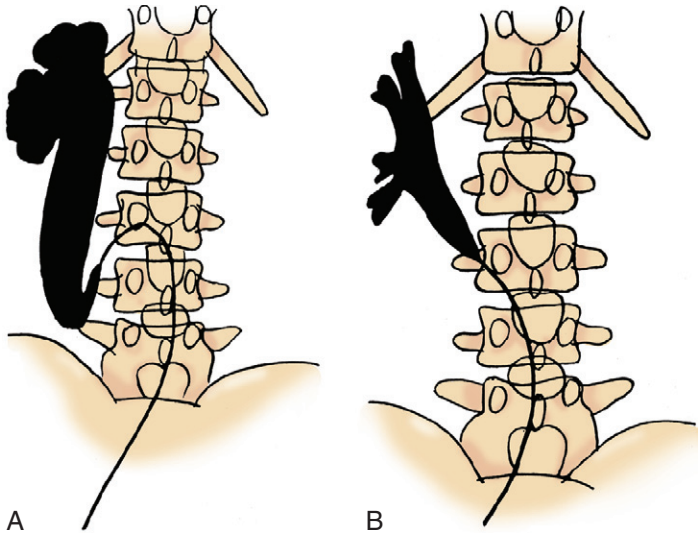


Figure 40–19. **A,** Diagram illustrating the radiologic features of the type 1 circumcaval ureter. **B,** Diagram illustrating the radiologic features of the type 2 circumcaval ureter. (**A** and **B,** From Bateson EM, Atkinson D. Circumcaval ureter: a new classification. Clin Radiol 1969;20:173–7.)

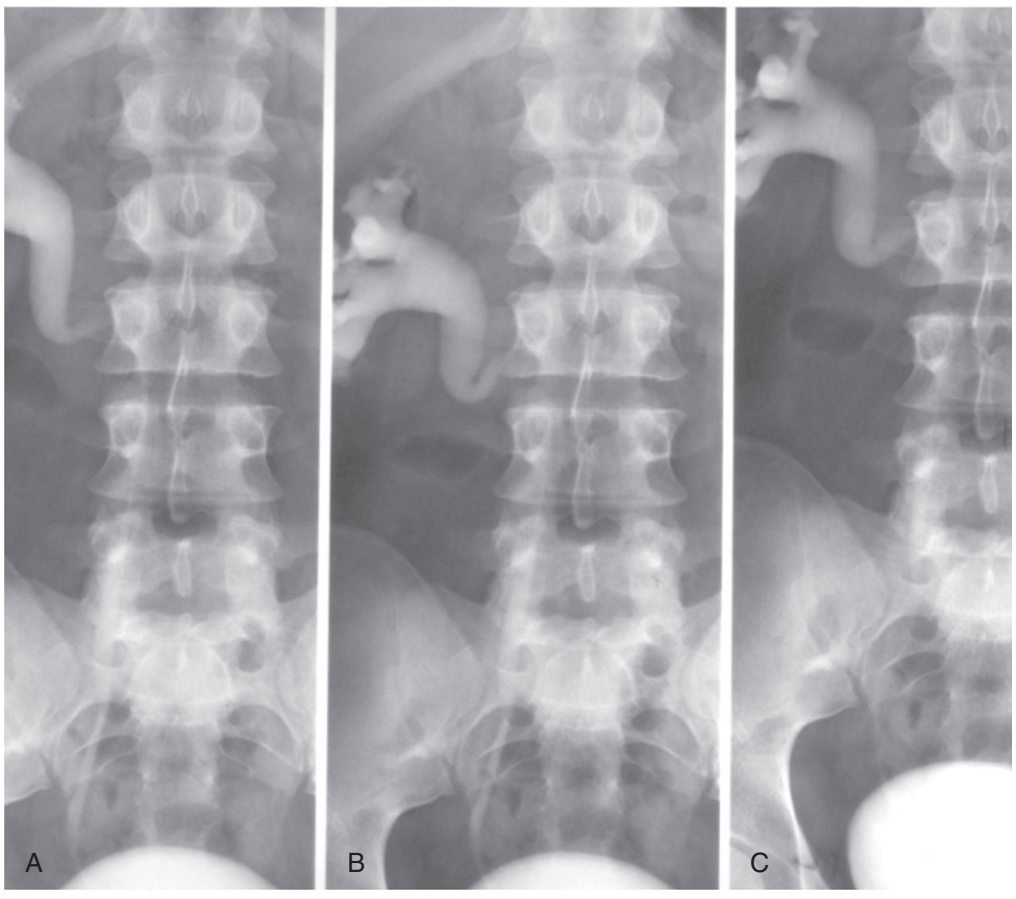


Figure 40–20. **A to C.** Excretory urography of a patient with type 1 circumcaval ureter. (Courtesy of Dr. Ronald Zagoria.)

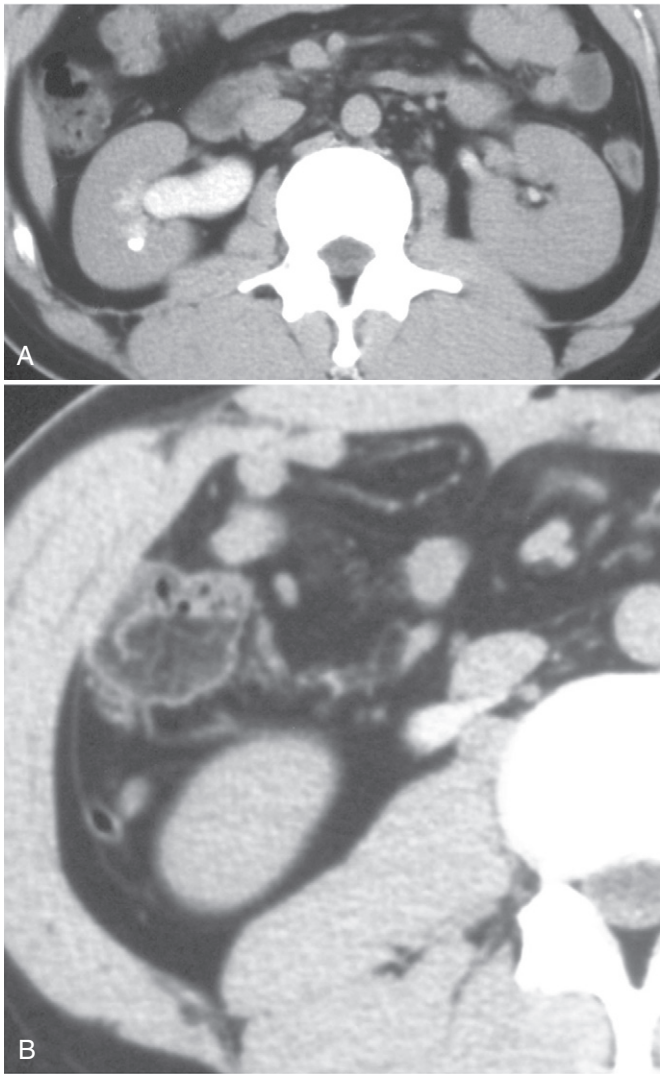


Figure 40–21. **A,** Contrast-enhanced computed tomography of a patient with circumcaval ureter. Note mild right-sided hydronephrosis. **B,** Lower section from same study and patient. Note ureter traversing posterior to inferior vena cava. (**A** and **B,** Courtesy of Dr. Ronald Zagoria.)

and B). Diuretic renography is used to confirm the presence and determine the functional impact of obstruction.

Treatment is undertaken only in the presence of obstruction. The ureter is divided proximally and at the distal point, from which it emerges lateral to the IVC. A spatulated ureteroureterostomy is performed. This has been performed by open, laparoscopic, and retroperitoneoscopic approaches and is best dictated by the surgeon's experience (Polascik and Chen, 1998; Gupta et al, 2001; Bagheri et al, 2009). Recently, pure robotic repair of retrocaval ureter has also been described successfully with its attendant ergonomic and technical benefits (Hemal et al, 2008). The most common complication associated with this procedure is ureteral stricture, reported to be 13% in one series (Hadzi-Djokic et al, 2009).

Key Points

- Ureteral obstruction leads to renal inflammation, increased extracellular matrix formation, tubulointerstitial fibrosis, and apoptosis of renal tubule cells.
- Unilateral and bilateral ureteral obstructions differ in the patterns of hemodynamic and ureteral pressure changes, and distribution of renal blood flow.
- Postobstructive diuresis occurs primarily with BUO and is usually self-limiting.
- Ureteral obstruction causes persistent decreases in concentrating ability, urinary acidification, and electrolyte transport.
- Key mediators of obstructive uropathy that are potentially amenable to current pharmacotherapy include angiotensin II, TGF-β, TNF-α, nitric oxide, thromboxane, and endothelin.
- Recovery of renal function after the correction of obstruction is adversely affected by increasing duration and degree of obstruction, increasing age of the patient, presence of infection, and decreased collecting system compliance.
- Nuclear renography provides the most reliable functional information. Other imaging modalities may provide an insight into the function of the affected renal unit(s).
- Cross-sectional imaging studies such as CT and MRI help determine the underlying cause(s) of obstructive uropathy.
- Drainage of the obstructed system is the first step in management in cases of threatened functional impairment or infection. Definitive management of the underlying pathology may then be considered as dictated by the disease process.
- Hydronephrosis of pregnancy is common, usually insignificant, and resolves postpartum.
- A tissue biopsy should be obtained in cases of suspected retroperitoneal fibrosis.

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chapter
41

Management of Upper Urinary Tract Obstruction

Stephen Y. Nakada, MD ● Thomas H.S. Hsu, MD

Ureteropelvic Junction Obstruction
Retrocaval Ureter
Ureteral Stricture Disease
Ureteroenteric Anastomotic Stricture
Retroperitoneal Fibrosis

Technologic advances have significantly improved both the diagnostic and therapeutic alternatives available in the contemporary management of upper urinary tract obstruction. The obstructive processes may be intrinsic, extrinsic, congenital, or iatrogenic, and in many cases the cause of obstruction may not be immediately evident. Furthermore, making an accurate diagnosis of obstruction can also be challenging.

The treatments for upper tract obstruction range from ureteral stent placement to complex procedures involving ileal interposition or autotransplantation. Myriad skills are required for total surgical management of upper urinary tract obstruction. Not surprisingly, endourology, laparoscopy, and robotics are more prominent in the surgical management of upper urinary tract obstruction. As a result of the wide array of available treatments, the practicing urologist must have an understanding of the indications and risks of all the options.

This chapter provides a contemporary, state-of-the-art presentation of the major surgical management strategies for patients with upper urinary tract obstruction. The chapter is organized by the anatomic location of obstruction. The etiology, diagnosis, indications for intervention, risks, and therapeutic options (including endoscopic, laparoscopic, robotic, and open approaches) are thoroughly reviewed.

URETEROPELVIC JUNCTION OBSTRUCTION

The diagnosis of "ureteropelvic junction obstruction" results in a functionally significant impairment of urinary transport from the renal pelvis to the ureter. Although most cases are congenital, the problem may not become clinically apparent until much later in life (Jacobs et al, 1979). Acquired conditions such as stone disease, postoperative or inflammatory stricture, or urothelial neoplasm may also present clinically with symptoms and signs of obstruction at the level of the ureteropelvic junction (UPJ). Similarly, extrinsic obstruction can occur at this level as well. This section focuses primarily on the diagnosis and treatment of "congenital" UPJ obstruction, although these techniques may be applied to the management of certain acquired conditions, in particular urinary stones.

Pathogenesis

Congenital UPJ obstruction typically results from intrinsic disease. A frequently found defect is the presence of an aperistaltic segment of the ureter, perhaps similar to that found in primary obstructive megaureter. In these cases, histopathologic studies reveal that the spiral musculature normally present has been replaced by abnormal longitudinal muscle bundles or fibrous tissue (Allen, 1970; Foote et al, 1970; Hanna et al, 1976; Gosling and Dixon, 1978) (Fig. 41–1). This results in failure to develop a normal peristaltic wave for propagation of urine from the renal pelvis to the ureter. Recognition that this type of segmental defect is often responsible for UPJ obstruction is of utmost importance clinically because such ureters may appear grossly normal at the time of surgery, and, in fact, may often be calibrated to 14 French or greater. Further investigations in the etiology of UPJ obstruction have shown decreased interstitial cells of Cajal at the UPJ in children (Solari et al, 2003). In addition, the cytokine produced in the urothelium has also been proposed to exacerbate UPJ obstruction (Chiou et al, 2005). Other experimental studies have implicated transforming growth factor-β, epidermal growth factor expression, nitric oxide, and neuropeptide Y in UPJ stenosis (Knerr et al, 2001; Yang et al, 2003). A less frequent intrinsic cause of congenital UPJ obstruction is true ureteral stricture. Such congenital ureteral strictures are most frequently found at the UPJ, although they may be located at sites anywhere along the lumbar ureter. Abnormalities of ureteral musculature have been implicated as electron microscopy has demonstrated excessive collagen deposition at the site of the stricture (Hanna et al, 1976).

Intrinsic obstruction at the UPJ may also result from kinks or valves produced by infoldings of the ureteral mucosa and musculature (Maizels and Stephens, 1980). In these cases, the obstruction may actually be at the level of the proximal ureter. This phenomenon appears to result from retention or exaggeration of congenital folds normally found in the ureter of developing fetuses. In some of these cases, the defects are bridged by ureteral adventitia. Grossly, this can manifest as external bands or adhesions that appear to be causing the obstruction. In fact, Johnston and colleagues, in 1977, reported that lysis of external adhesions can at times reestablish flow without pyeloplasty. In the majority of

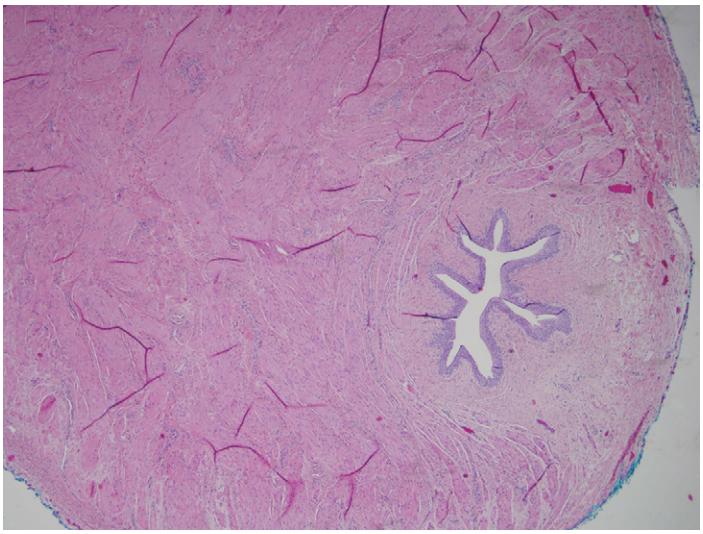


Figure 41–1. The microphotograph is taken through the ureteropelvic junction. There is marked attenuation of smooth muscles and smooth muscle in disarray and hypertrophy surrounding the urothelial lining.

cases, however, these bands or adhesions are likely to be a secondary phenomenon associated with intrinsic obstruction, so operative pyeloplasty would generally be most effective. The presence of these kinks, valves, bands, or adhesions may also produce angulation of the ureter at the lower margin of the renal pelvis in such a manner that, as the pelvis dilates anteriorly and inferiorly, the ureteral insertion is carried further proximally. In these cases, the most dependent portion of the pelvis is inadequately drained and the apparent "high insertion" of the ureteral ostium is actually a secondary phenomenon (Kelalis, 1976). In at least some cases, however, the high insertion itself is likely the primary obstructing lesion because this phenomenon is found more frequently in the presence of renal ectopia or fusion anomalies (Zincke et al, 1974; Das and Amar, 1984). As such, a high insertion can have implications in the subsequent surgical management, particularly endourologic approaches.

Controversy persists regarding the potential role of "aberrant" vessels in the etiology of UPJ obstruction. Significant crossing vessels have been noted in up to 63% of cases of UPJ obstruction but as little as 20% of cases of normal kidneys (Quillin et al, 1996; Zeltser et al, 2004; Richstone et al, 2009). Although these lower pole vessels have often been referred to as aberrant, these segmental vessels, which may be branches from the main renal artery or arise directly from the aorta, are usually normal variants (Stephens, 1982). In some patients, these lower pole vessels cross the ureter posteriorly and truly have an aberrant course. Historically, it has been believed that the associated vessel alone does not cause the primary obstruction (Hanna, 1978). In fact, the true etiology is an intrinsic lesion at the UPJ or proximal ureter that causes dilatation and ballooning of the renal pelvis over the polar or aberrant vessel. Recent studies using three-dimensional multidetector row computed tomography (CT) demonstrated that the precise location of crossing vessels did not correspond to the obstructive transition point in patients with UPJ obstruction (Lawler et al, 2005). In contrast, one group found improvement in patients undergoing only ligation of crossing vessels (Keeley, Jr. et al, 1996). Richstone and colleagues reviewed histopathology from 95 patients with UPJ obstruction and found that 43% of 65 patients with a crossing vessel had no intrinsic abnormality (Richstone, 2009). **Regardless, the presence of crossing vessels most certainly has a detrimental effect on the success rates of endopyelotomy** (Van Cangh et al, 1994; Nakada et al, 1998). UPJ obstruction with concominant anatomic anomalies such as horseshoe kidney and pelvic kidney also present further surgical challenges. Preoperative spiral CT angiographic studies are useful in these patients to identify crossing vessels and to aid in surgical planning (Pozniak et al, 1997). Notably, the current emphasis on laparoscopic and robotic pyeloplasty has quelled the interest in the relevance of preoperative assessment of crossing vessels because this can be addressed at the time of reconstruction.

UPJ obstruction may also result from acquired lesions. In children, vesicoureteral reflux can lead to upper tract dilatation with subsequent elongation, tortuosity, and kinking of the ureter. In some cases, these changes may only mimic the radiographic findings of true UPJ obstruction. However, true UPJ obstruction may definitely coexist with vesicoureteral reflux, although it may be difficult to determine whether the anomalies are merely coincident or whether the upper tract ureteral obstruction has resulted from the reflux (Lebowitz and Johan, 1982). Diuretic renography is first line for differentiating between UPJ obstruction and reflux.

Other acquired causes of obstruction at the UPJ include benign lesions such as fibroepithelial polyps (Berger et al, 1982; Macksood et al, 1985), urothelial malignancy, stone disease, and postinflammatory or postoperative scarring or ischemia. For these acquired diseases, the techniques discussed in this section may be useful adjuncts for management of the obstruction as long as the primary problem is also addressed where appropriate. For instance, fibroepithelial polyps can be managed using retrograde ureteroscopy and holmium laser excision (Lam et al, 2003a).

Patient Presentation and Diagnostic Studies

UPJ obstruction, although most often a congenital problem, can present clinically at any time of life. Historically, the most common presentation in neonates and infants was the finding of a palpable flank mass. However, **the current widespread use of maternal, prenatal ultrasonography has led to a dramatic increase in the number of asymptomatic newborns being diagnosed with hydronephrosis, many of whom are subsequently found to have UPJ obstruction** (Bernstein et al, 1988; Wolpert et al, 1989). A fraction of cases may also be found during evaluation of azotemia, which may result from bilateral obstruction in a functionally or anatomically solitary kidney. UPJ obstruction may also be incidentally found during studies performed to evaluate unrelated anomalies such as congenital heart disease (Roth and Gonzales, 1983). In older children or adults, intermittent abdominal or flank pain, at times associated with nausea or vomiting, is a frequent presenting symptom. Hematuria, either spontaneous or associated with otherwise relatively minor trauma, may also be an initial symptom. Laboratory findings of microhematuria, pyuria, or frank urinary tract infection might also bring an otherwise asymptomatic patient to the urologist. Rarely, hypertension may be a presenting finding (Riehle and Vaughan, 1981). **Radiographic studies should be performed with a goal of determining both the anatomic site and the functional significance of an apparent obstruction.** Although excretory urography remains a reasonable option for radiographic diagnosis, this study is less commonly used today. Classically, excretory urographic findings include delay in

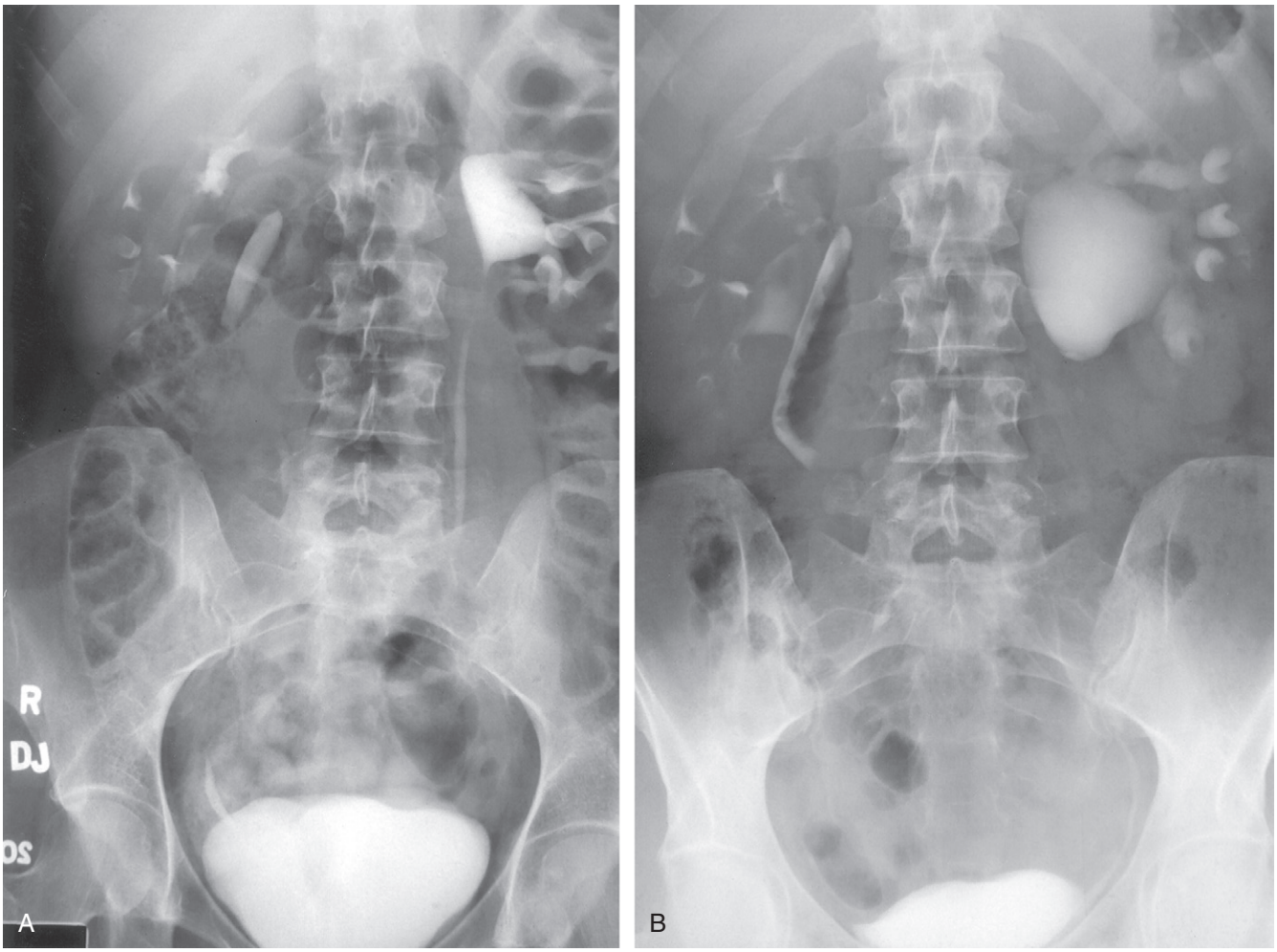


Figure 41–2. **A,** This patient with intermittent left flank pain underwent intravenous urography. The calyces are sharp bilaterally without evidence of obstruction. However, there is a "box-shaped" pelvis on the left side, which may be associated with intermittent obstruction. **B,** This intravenous urogram in the same patient was performed along with injection of intravenous furosemide, which brought out the obvious left-sided ureteropelvic junction obstruction. The patient's symptoms were subsequently relieved with a left pyeloplasty.

function associated with a dilated pelvicalyceal system. If the ureter is visualized, it should be of normal caliber. In some patients, symptoms may be intermittent and urography between painful episodes may be normal. In such cases the study should be repeated during an acute episode when the patient is symptomatic (Nesbit, 1956). Provocative testing with diuretic urography may allow accurate diagnosis in select cases. The patient should be well hydrated and the study then performed after injecting furosemide, 0.3 to 0.5 mg/kg (Malek, 1983) (Fig. 41–2).

CT scan is frequently obtained for any patient presenting with acute flank pain (Fielding et al, 1997; Dalrymple et al, 1998; Vieweg et al, 1998) (Fig. 41–3). **Moreover, CT scans provide detailed anatomic and functional information to aid in diagnosis of UPJ obstruction** (Fig. 41–4A-C). Both ultrasonography and CT scanning also have a role in differentiating acquired causes of obstruction such as radiolucent calculi or urothelial tumors. **In neonates and infants, the diagnosis of UPJ obstruction has generally been suggested either by routine performance of maternal ultrasonography or by the finding of a flank mass. In either setting, renal ultrasonography is usually the first radiographic study performed. Ideally, ultrasonography should be able to**



Figure 41–3. Noncontrast CT scan performed as the initial radiographic study in a patient presenting with left flank pain revealed hydronephrosis to the level of the ureteropelvic junction (UPJ). No calculus was visualized, and a presumed diagnosis of UPJ obstruction was considered. This proved correct on subsequent radiographic studies.

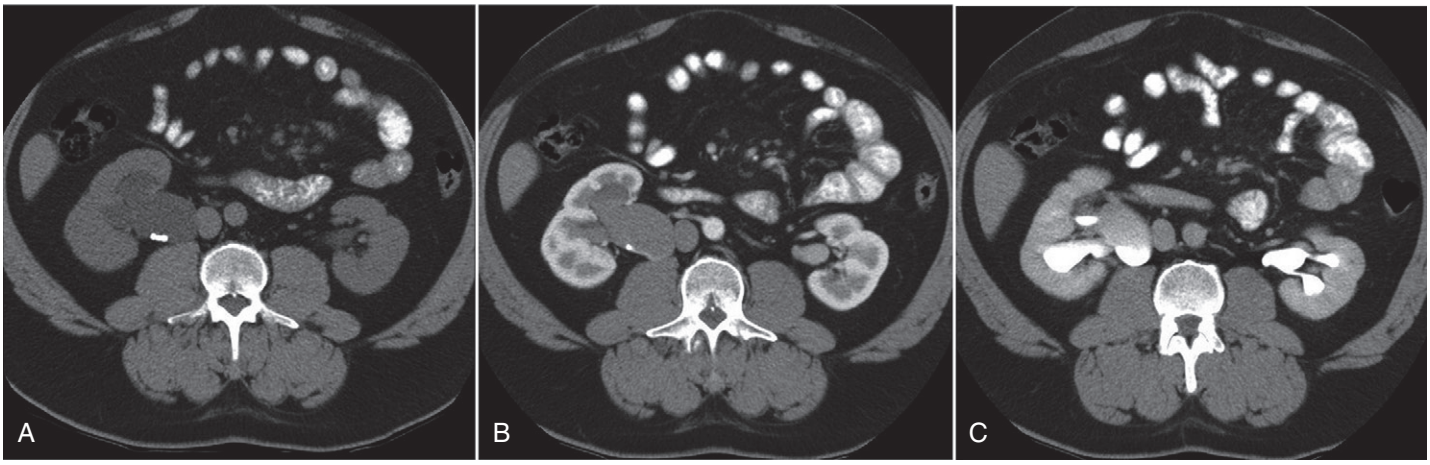


Figure 41–4. **A,** Contrast-enhanced CT scan identifies a classic ureteropelvic junction (UPJ) appearance in early-phase imaging. **B,** Early images reveal normal nephrogram and delayed filling of the obstructed, dilated UPJ. **C,** Delayed images demonstrate holdup of contrast drainage on the right compared with the normal left side.

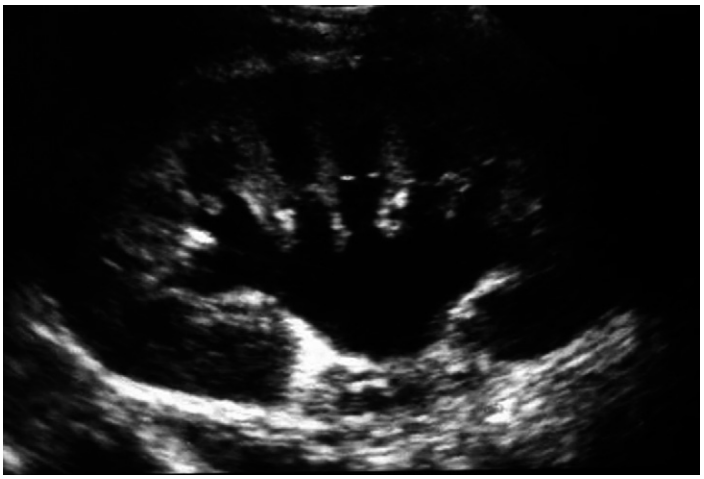


Figure 41–5. Classic ultrasound image of ureteropelvic junction obstruction, with dilated renal pelvis and infundibula and calyces. Note the ureter is not visualized in this image.

visualize dilatation of the collecting system to help differentiate UPJ obstruction from multicystic kidney and determine the level of obstruction. UPJ obstruction and multicystic kidneys are distinguishable in the majority of cases by ultrasound alone. With UPJ obstruction, the pelvis is visualized as a large, medial sonolucent area surrounded by smaller, rounded sonolucent structures representing dilated calyces. At times, dilated calyces will be seen connecting to the pelvis via dilated infundibula (Fig. 41–5).

Occasionally, a solid-appearing renal cortex can be seen surrounding the sonolucent areas or separating the dilated calyces. In contrast, the cysts of multicystic kidneys are visualized as various-sized sonolucent areas in random distribution. Although the cysts may be connected, this is rarely visualized sonographically. Furthermore, little solid tissue is seen and that which is present has a random distribution among the cysts. Rarely, a large, centrally located cyst may cause confusion in the diagnosis (King et al, 1984a). In this setting, nuclear renography should be performed. Specifically, a technetium Tc99m-diethylenetriamenepentacetic acid (^{99m}Tc-DTPA) scan allows differentiation of these two entities. Multicystic kidneys rarely reveal concentration of this isotope. When uptake is seen, the areas of functioning tissue are initially discrete and are usually medial to the bulk of the mass, which itself remains a "cold" area. In contrast, neonatal kidneys with UPJ obstruction generally exhibit good concentration of the isotope. Furthermore, even with severe obstruction in which only a cortical rim remains, uptake of the isotope will be seen peripherally in the cortex, again helping to differentiate this from multicystic kidney (King et al, 1984a).

Diuretic renography is effective in predicting recoverability of function in cases in which intravenous urography has revealed nonvisualization. Diuretic renography allows quantification of the degree of obstruction and can help differentiate the level of obstruction. Today, ^{99m}Tc-MAG3 is the preferred isotope because of favorable imaging and dosimetry considerations over ^{99m}Tc-DTPA or radioiodinated hippuran (Roarke, 1998). **Diuretic renography remains a commonly used study for diagnosing both UPJ and ureteral obstruction because it provides quantitative data regarding differential renal function and obstruction, even in hydronephrotic renal units.** Diuretic renography is noninvasive and readily available in most medical centers. Ideally diuretic renography can be used to follow patients for functional loss, most effectively when a standard protocol is used. The diuretic is given 20 minutes into the study to allow time for filling of the collecting system. One study found diuretic renography to be useful in children to rule out concomitant UPJ obstruction with associated high-grade reflux (Stauss et al, 2003). There is evidence that the diuretic renography using MAG-3 is a most accurate study for patients with UPJ obstruction following therapeutic intervention (Niemczyk et al, 1999) (Fig. 41–6).

The diagnosis of UPJ obstruction can generally be made with a high degree of certainty on the basis of the clinical presentation and the results of any one or more of the imaging studies already cited. It is preferable to have a combination of anatomic and functional studies, such as retrograde pyelogram and diuretic renography, in order to best plan therapy. Retrograde pyelography thus retains a role for confirmation of the diagnosis and for demonstration of the exact site and nature of obstruction before repair. In most cases, this study is performed at the time of the planned

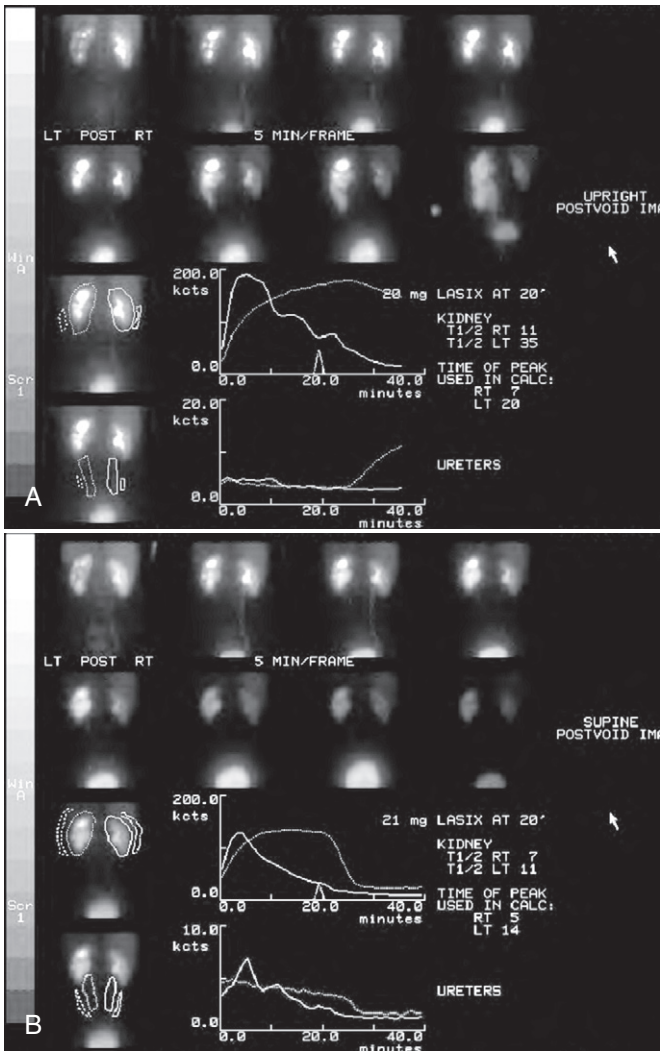


Figure 41–6. **A,** MAG-3 diuretic renography revealing functional ureteropelvic junction obstruction of the left kidney, with a $T_{1/2}$ greater than 35 minutes. **B,** Follow-up MAG-3 diuretic renography reveals normal drainage of the left kidney following successful laparoscopic pyeloplasty.

operative intervention in order to avoid the risk of introducing infection in the face of obstruction. However, retrograde pyelography is indicated emergently whenever the UPJ obstruction requires acute decompression, such as in the setting of infection or compromised renal function. **In cases in which cystoscopic retrograde manipulation has been unsuccessful or may be hazardous, particularly in neonates or infants, placement of a percutaneous nephrostomy is preferred. This allows the performance of antegrade studies that will help define the nature and exact anatomic site of obstruction.** It also allows decompression of the system in cases of associated infection or compromised renal function and allows assessment of recoverability of renal function after decompression. **When there remains some doubt as to the clinical significance of a dilated collecting system, placement of a percutaneous nephrostomy tube allows access for dynamic pressure perfusion studies.** First described by Whitaker in 1973, the renal pelvis is continuously perfused at 10 mL/min with normal saline solution or dilute radiographic contrast solution under fluoroscopic control. Renal pelvic pressure is monitored during the infusion, and the pressure gradient across the UPJ is determined. During the infusion, the bladder is continuously drained with an indwelling catheter to prevent transmission of intravesical pressures. Renal pelvic pressure ranging up to 12 to 15 cm H_2O during this infusion suggests a nonobstructed system. In contrast, pressures in excess of 15 to 22 cm H_2O are highly suggestive of a functional obstruction. Pressures between these extremes may be nondiagnostic (O'Reilly, 1986).

Although pressure perfusion studies can often provide valuable information regarding the functional significance of an apparent obstruction, these studies can at times be inaccurate. This inaccuracy may be a result of variations in renal pelvic anatomy and compliance (Koff et al, 1986) or positional variations (Ellis et al, 1995). As such, the urologist must be a diagnostician and collate the clinical presentation and results of all diagnostic studies performed in order to identify the best clinical intervention.

Indications and Options for Intervention

Contemporary indications for intervention for UPJ obstruction include the presence of symptoms associated with the obstruction, impairment of overall renal function or progressive impairment of ipsilateral function, development of stones or infection, or, rarely, causal hypertension. The primary goal of intervention is relief of symptoms and preservation or improvement of renal function. Traditionally, such intervention should be a reconstructive procedure aimed at restoring nonobstructed urinary flow. This is especially true for neonates, infants, or children in whom early repair is desirable because these patients will have the best chance for improvement in renal function after relief of obstruction (Bejjani and Belman, 1982; Roth and Gonzales, 1983; Wolpert et al, 1989). However, timing of the repair in neonates remains controversial (DiSandro and Kogan, 1998; Koff, 1998, 2000; Hanna, 2000; Shokeir and Nijman, 2000), mostly because of difficulty in defining those kidneys truly at risk for functional obstruction. In a prospective study of 104 neonates with primary unilateral hydronephrosis suspected of being caused by UPJ obstruction, after a mean follow-up of 21 months, only 7 (7%) required pyeloplasty for functional obstruction, defined as a progression of hydronephrosis or a 10% reduction in differential glomerular filtration rate on serial ultrasonography and diuretic renography (Koff and Campbell, 1994). All treated patients had a return of renal function to predetermination levels, supporting selective nonoperative management of neonatal hydronephrosis.

UPJ obstruction may not become apparent until middle age or later (Jacobs et al, 1979). Occasionally, if the patient is asymptomatic and the physiologic significance of the obstruction seems indeterminate, careful observation with serial follow-up studies may be appropriate, typically using diuretic renography. However, the majority of affected patients may ultimately benefit from reconstructive intervention (Jacobs et al, 1979; Clark and Malek, 1987; O'Reilly, 1989). **When intervention is indicated, the procedure of choice has historically been dismembered pyeloplasty. However, less invasive endourologic approaches have a role as an alternative in many centers** (Brannen et al, 1988; Motola et al, 1993a; Kletscher et al, 1995; Cohen et al, 1996; Nadler et al, 1996; Thomas et al, 1996; Tawfiek et al, 1998; Lechevallier et al, 1999; Gerber and Kim, 2000; Nakada, 2000; Conlin, 2002). **Most**

recently, laparoscopic and robotic pyeloplasty has gained acceptance as primary therapy at centers with appropriate skills and technology (DiMarco et al, 2006; Rassweiler et al, 2007).

Although success rates with most endourologic techniques have not proven to be comparable with those of open, laparoscopic, or robotic pyeloplasty, it has been suggested that the success rates may be significantly improved with careful patient selection. In an important prospective study, Van Cangh and colleagues (1994) achieved an overall success rate for endopyelotomy of 73%. However, these investigators found the presence of crossing vessels to be a major determinant of outcome (42% success rate in the setting of a crossing vessel vs. 86% success without a crossing vessel). Furthermore, when endopyelotomy was applied to patients with "a high degree of obstruction," the success rate was only 60% compared with an 81% success rate for those patients with "low-grade" obstruction. When patients with both a crossing vessel and a high degree of obstruction were excluded from analysis, the success rate improved to 95%, which is comparable with that of open pyeloplasty. However, other studies have suggested a less important role for these factors in regard to their impact on a successful outcome (Gupta et al, 1997; Danuser et al, 1998; Nakada et al, 1998).

Although the indications for intervention for UPJ obstruction are similar regardless of technique, it is critical to discuss the risks and benefits of all available options with patients. As such, each patient should be advised individually on the basis of all the anatomic and functional information available preoperatively. In this setting, many patients will opt for a minimally invasive approach, even with the understanding that success rates may be lower, or secondary intervention may become necessary. As a result of studies linking crossing vessels to hindered endourologic successes, there is increased interest in intraoperative management of the UPJ and crossing vessel by either an open or laparoscopic approach (Conlin, 2002). **Therefore for "secondary" UPJ obstruction, it remains reasonable to recommend an open or laparoscopic approach to any patient who has failed primary endourologic management and an endourologic approach to those who have failed open or laparoscopic repair.** The results of endourologic management in this setting remain generally excellent (Jabbour et al, 1998; Canes et al, 2008).

Rarely, nephrectomy may be the procedure of choice. Indications for nephrectomy as primary therapy include diminished function or nonfunction of the involved renal moiety and a normal contralateral kidney on the basis of radiographic and nuclear studies. These patients may be symptomatic with urinary tract infections or pain. In such cases, ultrasonography or CT scanning is generally performed and will reveal only a thin shell of parenchyma remaining. **Renography can provide quantitative measures of renal function, and generally kidneys with less than 15% differential function are nonsalvageable in adults.** If the potential for salvageability of function is still unclear, an internal stent or percutaneous nephrostomy may be placed for temporary relief of obstruction and renal function studies subsequently repeated. Nephrectomy may also be considered for patients in whom the obstruction has led to extensive stone disease with chronic infection and significant loss of function in the face of a normal contralateral kidney. Removal of the kidney may also be chosen over reconstruction for patients in whom repeated attempts at repair have already failed and in whom further intervention would therefore be extremely complicated. This option should be considered only when the contralateral kidney is essentially normal.

Options for Intervention

Endourologic Management

Operative intervention for UPJ obstruction has historically provided a widely patent, dependently positioned, well-funneled UPJ. In addition, the option to reduce the size of the renal pelvis is readily available with this approach. Although pyeloplasty has stood the test of time with a published success rate of 95%, several less invasive alternatives to standard operative reconstruction exist (Clark et al, 1987). **The advantages of endourologic approaches include reduced hospital stays and postoperative recovery. However, the success rate does not approach that of open, laparoscopic, or robotic pyeloplasty. Furthermore, whereas open, laparoscopic, or robotic pyeloplasty can be applied to almost any anatomic variation of UPJ obstruction, consideration of any of the less invasive alternatives require that the surgeon take into account the degree of hydronephrosis, ipsilateral renal function, concomitant calculi, and possibly the presence of crossing vessels.** Of note, Albani and colleagues (2004) reported contemporary long-term results with various endopyelotomy approaches to have a success rate of 67%, with the majority of failures in the first 32 months. More recently, DiMarco and colleagues (2006) reported long-term follow-up of more than 400 patients undergoing either percutaneous antegrade endopyelotomy or pyeloplasty. The 3-, 5-, and 10-year success rates were superior for pyeloplasty, 85% versus 63%, 80% versus 55%, and 75% versus 41%. Moreover, Rassweiler and colleagues (2007) compared retrograde laser endopyelotomy with laparoscopic retroperitoneal pyeloplasty in 256 patients in a 10-year single surgeon experience and found success rates were 73% for laser endopyelotomy compared with 94% for pyeloplasty.

Endourologic management of UPJ obstruction was introduced by Ramsay and colleagues in 1984 as a "percutaneous pyelolysis" and then popularized in the United States by Badlani and colleagues (1986), who coined the term "endopyelotomy." **Although various nuances in the technique have been described** (Korth et al, 1988; Van Cangh et al, 1989; Ono et al, 1992), **the basic concept of the endopyelotomy is a full-thickness lateral incision through the obstructing proximal ureter, from the ureteral lumen out to the peripelvic and periureteral fat.** A stent is placed across the incision and left to heal, in keeping with the original work of Davis in 1943, who performed an "intubated ureterotomy" to repair UPJ obstruction. Subsequently, alternative techniques using a retrograde approach to the UPJ were developed. The retrograde approach most used today is the ureteroscopic approach, typically using the holmium laser to incise the UPJ under direct visual control. Alternatively, a cautery wire balloon endopyelotomy, which incises the UPJ under fluoroscopic control, or percutaneous endopyeloplasty may be used (Gill et al, 2002). Recently, Vaarala and colleagues reported a small series of 64 patients who underwent either antegrade or retrograde cold knife or cautery wire balloon endopyelotomy. In this study, success rates ranged from 79% to 83%, without statistically significant differences among the three treatments (Vaarala et al, 2008). Of note, transplantation complications are particularly suited to endoscopic management, either antegrade or retrograde (Schumacher et al, 2006; Gdor et al, 2008a). **As far as efficacy is concerned, there is little evidence for significant differences between endopyelotomy techniques. The differences lie in technical considerations and complications.**

Percutaneous Antegrade Endopyelotomy

Indications and Contraindications. The indications to intervene for any patient with UPJ obstruction include the presence of symptoms, progressive or overall impairment of renal function, development of upper tract stones or infection, or, rarely, causal hypertension. Historically, a percutaneous approach for definitive management of UPJ obstruction was offered only to those patients undergoing percutaneous removal of associated stones or to those who had previously failed open pyeloplasty. However, encouraging results ultimately led many centers to offer percutaneous endopyelotomy as primary therapy for almost any patient with UPJ obstruction. **Even with the acceptance of laparoscopic pyeloplasty, percutaneous endopyelotomy is also appropriate for those patients with UPJ obstruction and concomitant pyelocalyceal stones, which can then be managed simultaneously. Contraindications to a percutaneous endopyelotomy are similar to the contraindications to any endourologic approach and include a long segment (>2 cm) of obstruction, active infection, or untreated coagulopathy.** Whereas the impact of crossing vessels is controversial, the mere presence of crossing vessels is not a contraindication to an endopyelotomy (Motola et al, 1993b; Nakada et al, 1998; Lam et al, 2003b). However, significant entanglement of the UPJ by crossing vessels can occasionally be identified and this may render any endourologic approach unsuccessful. When such entanglement is suggested by intravenous or retrograde pyelography (Fig. 41–7), it can be reliably verified using three-dimensional helical CT (Kumon et al, 1997).

Patient Preparation. Patients undergoing a percutaneous endopyelotomy undergo preoperative evaluation and preparation as if they were undergoing any percutaneous, laparoscopic, or open renal intervention. The evaluation includes an assessment for any comorbidity that may increase the risk of anesthesia. Sterile urine should be ensured at the time of definitive intervention. If upper tract infection cannot be cleared because of obstruction, temporization should be accomplished using internal stenting or percutaneous nephrostomy drainage alone. The patient should be counseled as to the risks and benefits of the procedure, and in particular the fact that the success rate of any endourologic approach, including percutaneous endopyelotomy, may be less than that of operative intervention. Patients should also be counseled of the risk of bleeding requiring transfusion, urinary leak, drainage-related complications, and hydropneumothorax, particularly if upper pole access is used.

Technique. **An endopyelotomy cannot be performed safely by any route until access across the UPJ is established.** This can be accomplished in a retrograde fashion cystoscopically or in an antegrade manner percutaneously. For retrograde access, the UPJ can almost always be traversed using a hydrophilic wire passed through an open-end catheter. Once the hydrophilic wire is successfully positioned in the pyelocalyceal system, the open-end catheter is advanced over it into the renal pelvis. The wire can then be withdrawn so that contrast material can be injected through the open-end catheter to guide subsequent percutaneous access.

With the patient in the prone position, the site for percutaneous access is chosen to allow straightforward access to the UPJ. Generally, a midposterior or superolateral calyx is chosen, although, occasionally, an inferolateral calyx may be used. Typically, the UPJ can be intubated in an antegrade fashion when the tract is initially

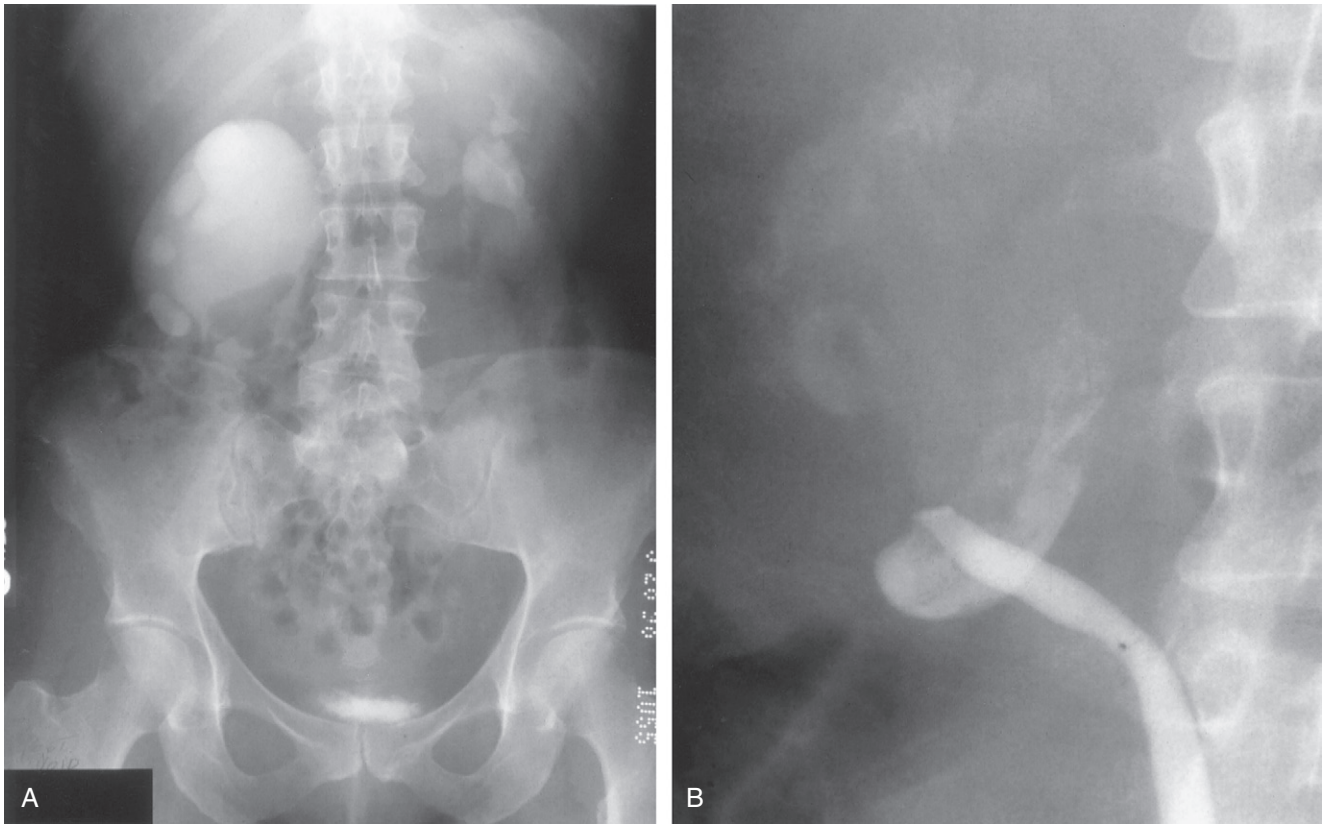


Figure 41–7. **A,** Intravenous pyelogram reveals apparent right ureteropelvic junction (UPJ) obstruction in this woman with right flank pain. **B,** Retrograde study suggests entanglement at the UPJ by crossing vessels. This was subsequently proved with three-dimensional CT angiography.

established with fluoroscopic control. Alternatively, once the tract is dilated and nephroscopy is performed, a wire can again be passed in a retrograde fashion through the open-end catheter and grasped from above so that through-and-through access is reestablished. In either case, as soon as access is obtained with one wire, an introducing catheter is used to pass a second wire as a "safety wire," so a working and a safety wire are now both in place. At this point, percutaneous access is complete and the endopyelotomy may be performed.

In the original descriptions of the technique both from the Institute of Urology in London (Ramsay et al, 1984) and from Long Island Jewish Hospital in New York (Badlani et al, 1986), the endopyelotomy was performed using a cold knife technique under direct vision. With one or two wires in place across the UPJ, a direct vision "endopyelotome" is used. This hook-shaped cold knife may be used to completely incise the UPJ in a full-thickness manner, from the ureteral lumen to periureteral and peripelvic fat (Fig. 41–8). **Rigorous anatomic studies have shown the incision should generally be made laterally because this is the location devoid of crossing vessels** (Sampaio, 1998). However, in cases of high insertion, the incision should instead "marsupialize" the proximal ureter into the renal pelvis, such that an anterior or posterior incision may be required (Fig. 41–9). When such incisions are done under direct vision, any crossing vessel can be directly visualized and avoided. In addition to the endopyelotome, the holmium laser or the cutting balloon catheter may also be used to perform an antegrade endopyelotomy.

Once the incision is complete, stenting is accomplished. There remains no consensus as to the optimal stent size or duration for endopyelotomy. A No. 14/7-Fr endopyelotomy stent may be used, passed in an antegrade fashion with the larger diameter end of the stent positioned across the UPJ. In some cases, especially when the patient has not been prestented, passage of this large-caliber stent may be difficult. In those instances, a No. 10/7-Fr endopyelotomy stent or even a standard No. 8-Fr internal stent may be used without compromising the ultimate outcome. Once proper positioning of the stent is determined fluoroscopically, any remaining safety wires are withdrawn. One group showed no difference between larger and standard stents in a porcine study of endopyelotomies (Moon et al, 1995). Alternatively, Danuser and colleagues (2001) demonstrated improved success rates using a modified 27-Fr stent following percutaneous endopyelotomy at nearly 2 years follow-up.

In the setting of a high insertion, the incision can often be extended to the dependent portion of the renal pelvis under direct vision, bridging the gap between the lateral wall of the ureter and the medial wall of the pelvis, across the periureteral and peripelvic fat. Once the incision is complete, the stent is already in place and nephrostomy drainage is instituted for 24 to 48 hours.

Postoperative Care. Avoidance of strenuous activity for 8 to 10 days after the procedure is recommended. The ideal stent size, duration of stent placement, and radiographic follow-up after endopyelotomy remains unclear (Canes et al, 2008). One study did report a benefit to larger stents in patients undergoing antegrade endopyelotomy (71% vs. 93%); however, a large-bore (27-Fr) catheter was used for the initial 3 weeks postoperatively (Danuser et al, 2001). On the other hand, Kletscher and colleagues (1995) reported no benefit to larger stents as did Hwang and colleagues (1996). Wolf and colleagues (1997) reported improved success using larger stents (12 Fr) in endoureterotomy patients in a retrospective review. Regarding stent duration, less is known. The original report and recommendation of 6 weeks by Davis (1943) is still often used, although Mandhani and colleagues (2003) identified no difference in results when comparing 57 patients stented for 2 weeks compared with 4 weeks. Although the need for prophylactic antibiotics while the stent is indwelling is not literature based, many use a daily suppressive dose.

Once the stent is removed, the patient returns 1 month later for clinical follow-up and radiographic evaluation. This generally includes a history, physical, urinalysis, and diuretic renography. If the patient remains asymptomatic and the diuretic renography reveals normal drainage (normal $T_{½}$), reevaluation is performed at 6 months and then at 12-month intervals. Most literature indicates that the majority of endopyelotomy failures occur within the first year of the procedure; however, longer-term studies demonstrate failures well beyond that timeframe (Nadler et al, 1996; Albani et al, 2004; DiMarco et al, 2006; Doo et al, 2007). For most adults, 2- and 3-year follow-up is justified because studies indicate even at 36 months some late failures are identified, but relatively few are identified at 60 months (Doo et al, 2007).

Results. The immediate and long-term results of percutaneous endopyelotomy are well established. Although percutaneous endopyelotomy compares favorably with open operative pyeloplasty in terms of postoperative pain, length of hospital stay, and return to prehospitalization activities (Brooks et al, 1995; Karlin et al, 1988), retrograde endopyelotomy and laparoscopy also offer favorable convalescence.

Gerber and Lyon, in 1994, reviewed the outcome of percutaneous endopyelotomy in 672 patients reported from 12 centers and found a success rate ranging from 57% to 100% (mean, 73.5%) at follow-up ranging from 2 to 96 months. Currently, success rates approaching 85% to 90% are being reported at experienced centers, with little difference in outcome noted in those patients undergoing the procedure for primary versus secondary UPJ obstruction (Motola et al, 1993a; Kletscher et al, 1995; Shalhav et al, 1998). Of note, Knudsen and colleagues (2004) reported long-term results in 80 patients using the cold knife and holmium laser for antegrade endopyelotomy, with 55-month follow-up. This series had a success rate of 67%, slightly lower than otherwise reported. Interestingly, DiMarco and colleagues (2006) reported on 182 antegrade endopyelotomies with a recurrence-free survival at a single center over 10 years as low as 41%. Of note, Schumacher and colleagues (2006) reported on three successful antegrade endopyelotomies in transplanted kidneys in 2006.

When percutaneous endopyelotomy does fail, several options exist including a retrograde endopyelotomy, repeat percutaneous endopyelotomy, or laparoscopic, robotic, or open operative intervention. There remains a role for spiral CT angiography in failed endopyelotomy, to rule out a crossing vessel. If a significant vessel is found, repeat endopyelotomy is generally not recommended (Nakada, 2000). **Alternatively, operative intervention is generally offered to any patient who has failed an endourologic approach. On the basis of available data, the results of laparoscopic pyeloplasty will not be compromised** (Motola et al, 1993b; Gupta et al, 1997; Conlin et al 2002).

Complications. **The complications associated with percutaneous endopyelotomy are analogous to those associated with percutaneous nephrolithotomy** (Badlani et al, 1988; Weiss et al, 1988; Cassis et al, 1991; Malden et al, 1992; Bellman, 1996), **and hemorrhage is a risk of any percutaneous upper tract procedure including endopyelotomy.** However, because in patients with UPJ obstruction the renal parenchyma is generally thinner than that associated with a normal kidney, and because the collecting system is dilated, this risk may be different than that in the general population of stone

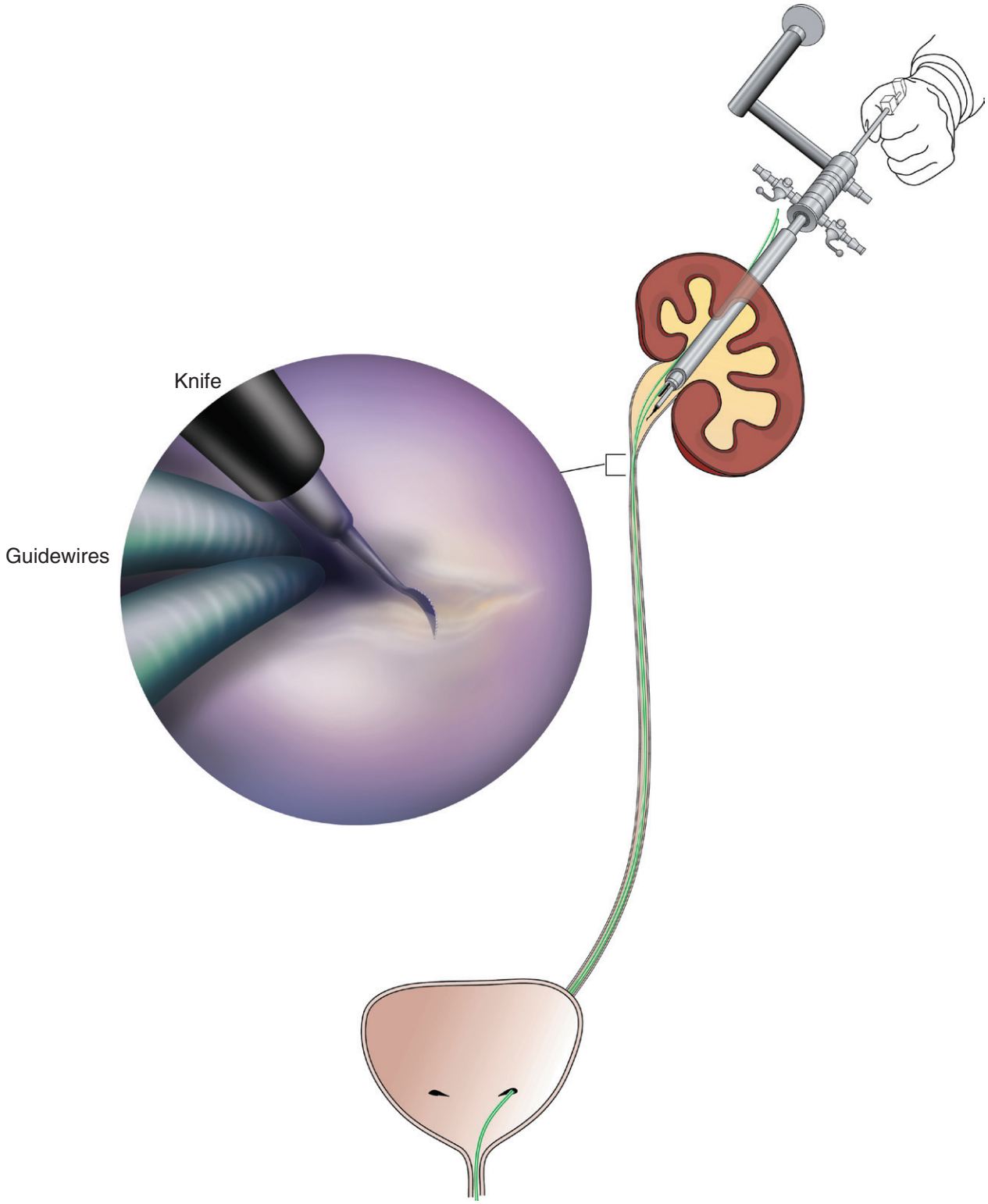


Figure 41–8. Percutaneous nephroscopic view of "cold knife" endopyelotomy *(inset)*. The line of incision is delineated by two guidewires, which have been passed across the ureteropelvic junction in an antegrade fashion through a superior calyx using a rigid nephroscope through a 30-Fr sheath. The lateral incision is performed under direct visual control.

patients undergoing percutaneous manipulation. Acute management in this setting is generally conservative to start: bed rest, hydration, and transfusion if necessary. The nephrostomy tube should not be irrigated acutely. Rather, it is preferable to allow the pyelocalyceal system to tamponade the bleeding. When continued bleeding does not respond to these conservative measures, the next step is selective angiographic embolization. **Generally, the urologist should have a low threshold to proceeding to angiography in order to minimize the need for transfusion and potential exploration.**

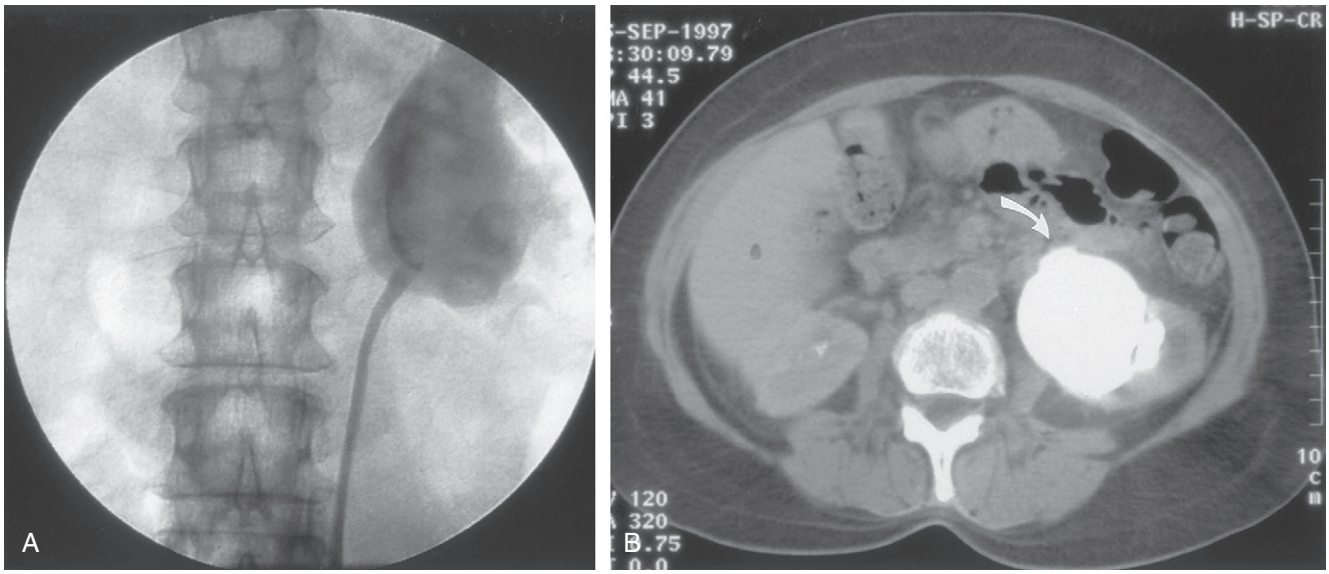


Figure 41–9. **A,** Retrograde study in this patient with left ureteropelvic junction obstruction reveals a "high insertion" of the left ureter. **B,** CT scan in this same patient reveals the ureter inserting on the anatomically anterior aspect of the renal pelvis. A marsupializing incision must be made in a true posterior direction from the ureter into the renal pelvis.

Successful angiographic embolization often obviates the need for operative "exploration" that can lead to nephrectomy.

Infection is a risk of any urinary tract manipulation including percutaneous endopyelotomy, and all attempts should be made to sterilize the urinary tract before the procedure. Whereas the role of prophylactic antibiotics at the outset of the procedure in the setting of a sterile urine is unproven, most urologists give a second-generation cephalosporin "on call" to the procedure. Consideration should be given to the use of prophylactic antibiotics while the endopyelotomy stent is indwelling for the month after the procedure, especially in women who are more prone to bacteruria.

Persistent obstruction is rare in the early postoperative period because of the internal stent. Occasionally, the stent can be obstructed from blood clots, and continued nephrostomy drainage for a few days typically allows the problem to resolve spontaneously.

Percutaneous Endopyeloplasty. Percutaneous endopyeloplasty is a hybrid technique described as an endoscopic Heineke Mikuliz repair performed through a percutaneous tract. In other words, endopyeloplasty combines percutaneous endopyelotomy and an endoscopic Fenger plasty. Initial and short-term reports by Gill and colleagues have been published demonstrating both feasibility and safety, and success rates have been similar to percutaneous endopyelotomy in limited comparative series (Gill et al, 2002; Canes et al, 2008). Latest reports include 55 patients with short-term follow-up with more than 90% success by these same authors (Stein et al, 2007). Early reports identified endopyeloplasty to be more effective in primary rather than secondary UPJ obstruction, most likely because tissue scarring may inhibit the endoscopic reconstruction.

Simultaneous Percutaneous Endopyelotomy and Nephrolithotomy. **Percutaneous endopyelotomy is particularly favorable when the UPJ obstruction is associated with upper tract stone disease because the stones can be managed concomitantly.** In such cases, percutaneous access is again established with a wire across the UPJ. The stone should be removed before the endopyelotomy so that stone fragments do not migrate into the peripyeloureteral tissue, as can happen if the endopyelotomy is performed first. Otherwise, localized obstruction may result from fibrosis or granuloma formation (Giddens et al, 2000; Streem, 2000). The urologist must take care to assure that the UPJ obstruction is not a result of edema from the concominant stone disease, in particular with stone disease in the renal pelvis. In this circumstance, initial management of the stone percutaneously and subsequent radiographic assessment of the UPJ once the stone has been removed are most prudent. In addition, if a nephrostomy tube is retained, a Whitaker test is straightforward and definitive to assess for persistent obstruction. Conversely, UPJ obstruction and solitary lower pole calculi do not represent a dilemma regarding UPJ edema, and combined percutaneous management remains most efficient. Alternatively, laparoscopic pyeloplasty and concominant stone removal is also effective for these patients.

Retrograde Ureteroscopic Endopyelotomy. A ureteroscopic approach to endopyelotomy was first suggested in 1985 when Bagley and colleagues reported a combined percutaneous and flexible ureteroscopic procedure approach for management of an "obliterated" UPJ. Subsequently, Inglis and Tolley (1986) reported a ureteroscopic "pyelolysis" for UPJ obstruction. Shortly thereafter, Clayman and colleagues (1990) reported an initial experience in a small number of patients performing ureteroscopic endopyelotomy with a No. 3- or 5-Fr cutting electrode passed under direct vision using large, rigid or flexible ureteroscopes. In that series, however, a No. 8-Fr nephrostomy tube was placed at the outset of the procedure and left indwelling for at least 48 hours. As such, that series still represented a "combined" endourologic approach to endopyelotomy. Stents were routinely left in place for 6 to 8 weeks, after which diagnostic studies were performed. With a mean follow-up approaching 1 year, a success rate of 81% was achieved in 16 patients. However, two patients developed distal ureteral strictures, probably resulting from the larger-diameter rigid instrumentation.

Thomas and colleagues (1996) subsequently reported their experience with ureteroscopic endopyelotomy. Again, only

relatively larger-diameter ureteroscopic instrumentation was available such that preoperative stent placement was routine, and some male patients required perineal urethrostomy. The endopyelotomy incision itself was performed with either cold knife or electrocautery attachments to the ureteroscope. The authors achieved a success rate of approximately 90%, although nephrectomy was ultimately performed in two patients, one of which was done urgently for bleeding. Cold knife ureteroscopic endopyelotomies are still being reported (e.g., Butani and Eschghi reported on a single surgeon experience with 135 cases from 1998-2004). Although three rigid ureteroscope and preprocedure stents were necessary, this group identified 96% success rates in primary procedures with an average 5-year follow-up (Butani and Eschghi, 2008). Notably, the complication rate was only 2.7%.

Advances in instrumentation and technique now allow a ureteroscopic approach to be performed reliably at a single setting (Conlin and Bagley, 1998), and this is now considered the standard. **The main advantage of a ureteroscopic approach is that it allows direct visualization of the UPJ and assurance of a properly situated, full-thickness endopyelotomy incision without the need for percutaneous access.** Another advantage of the ureteroscopic approach is a decrease in cost compared with the use of the cautery wire balloon, assuming ureteroscopic equipment and electroincision or holmium laser is already available. Moreover, the risks and morbidity of percutaneous access are avoided with the ureteroscopic procedure. Gettman and colleagues found that the retrograde ureteroscopic endopyelotomy was more cost effective than hot wire cutting balloon endopyelotomy, antegrade endopyelotomy, and pyeloplasty for treating UPJ obstruction when taking into account treatment failures (Gettman et al, 2003).

Indications and Contraindications. **The indications and contraindications to a ureteroscopic endopyelotomy include functionally significant obstruction, as defined earlier. Contraindications include relatively long areas of obstruction and upper tract stones, which are best managed simultaneously with alternative approaches, usually percutaneously or laparoscopically.** Another consideration is that in patients with significant hydronephrosis, the evidence indicates an antegrade endopyelotomy may be more efficacious (Lam et al, 2003b).

Technique. The instrument that allows the most straightforward retrograde access to the UPJ, as well as providing an effective working channel, is a small caliber (≤7-Fr) semirigid ureteroscope. In women, the UPJ can often be reached with a 6.9-Fr semirigid ureteroscope. In men, small-caliber (≤7.5-Fr) actively deflecting flexible ureteroscopes are typically used, and today with availability of improved ureteral access sheaths and improved flexible ureteroscopes, many retrograde endopyelotomies are done using the flexible ureteroscope.

General anesthesia is used in order to minimize patient movement during ureteroscopy and the subsequent incision of the UPJ. In preparation for the endopyelotomy, a retrograde pyelogram is performed under fluoroscopic control at the outset of the procedure. A hydrophilic guidewire is passed cystoscopically under fluoroscopic control and coiled in the pyelocalyceal system. The cystoscope is then withdrawn and exchanged for the semirigid ureteroscope. The ureteroscope is passed alongside the guidewire to the level of the UPJ. If the distal ureter is too narrow to allow easy passage of the ureteroscope, the intramural ureter can be dilated using a 5-mm balloon or a No. 9- or 10-Fr "introducing" catheter. If the ureter is still too narrow at any point to easily accommodate the ureteroscope, then an internal stent is placed and the procedure postponed for 5 to 10 days to allow "passive" ureteral dilatation. Alternatively, an actively deflecting flexible ureteroscope may be used, and in most cases a ureteral access sheath is quite useful. The sheath allows for rapid transfer of the ureteroscope for assessment of the UPJ. Once the flexible ureteroscope is passed to the UPJ, a 200-μm holmium fiber is placed through the working channel and the UPJ incised in the appropriate location, as suggested by the radiographic studies (Figs. 41–10 and 41–11).

Once the UPJ is reached with the ureteroscope, the renal pelvis is drained to assist movement across the UPJ during the incision. When using a semirigid ureteroscope, the 200- or 365-μm holmium laser fiber is inserted through the working channel as the ureteroscope is positioned at the proximal extent of the UPJ or in the renal pelvis itself. At a setting of 0.8 to 1.2 Joules and a frequency of 10 to 15 Hz, the UPJ is incised, usually in a posterolateral direction, while the ureteroscope is withdrawn back down across the UPJ. This procedure is repeated, and the incision gradually deepened to extend into the peripelvic and periureteral retroperitoneal space. Because this is done gradually and under direct vision, any visualized vessels, and thus potentially significant bleeding, are usually avoided.

The incision is carried caudally into normal ureteral tissue, until the UPJ is widely patent. Injection of contrast material through the ureteroscope can demonstrate extravasation and confirm an adequate depth of incision, although this is generally not necessary because the entire procedure has been performed under direct vision. Balloon dilation up to 24-Fr can also be performed to complete the incision. If any small bleeding points are visualized ureteroscopically, they can be treated by defocusing the holmium laser. Similarly, the balloon can be reinflated to allow tamponade for 10 minutes to see if the bleeding will subside. The ureteroscope is then withdrawn from the ureter while the safety wire is left in place in the renal pelvis for subsequent passage of a stent. Experimental studies have shown that 36-Fr balloon dilation alone can create linear incisions in the UPJ (Pearle et al, 1994). **Although retrograde balloon dilation alone has been reported for treatment of UPJ obstruction, long-term follow-up studies have shown a diminishing success rate over time, as low as 42%** (McClinton et al, 1993; Webber et al, 1997).

Once the ureteroscope has been removed, a stent is advanced over the remaining wire using fluoroscopic guidance. A Foley catheter is left indwelling, again to obviate the risk of reflux and extravasation at the site of the endopyelotomy incision and to rapidly identify any significant bleeding. Diuretic renography is performed 4 weeks after stent removal to assess results. Clinical and radiographic follow-up is then continued at 6- to 12-month intervals for 24 to 32 months.

Results. Biyani and colleagues (1997) described their initial experience with a ureteroscopic approach using holmium laser energy. With a mean follow-up of slightly more than 12 months, they achieved a success rate of 87.5% in a small group of patients. One patient developed a urinoma, which was managed conservatively. In 1998, Renner and colleagues reported a larger series of patients undergoing ureteroscopic laser endopyelotomy. Using a semirigid ureteroscope, the UPJ was incised at a posterolateral location unless vessels were visualized in that area, in which case a contralateral incision was made. Tawfiek and colleagues (1998) reported the Jefferson Medical College experience with ureteroscopic endopyelotomy. These investigators combined endoluminal ultrasound with their ureteroscopic approach in order to definitively identify crossing vessels or a ureteropelvic septum, which is present in patients with high-inserting ureters. The

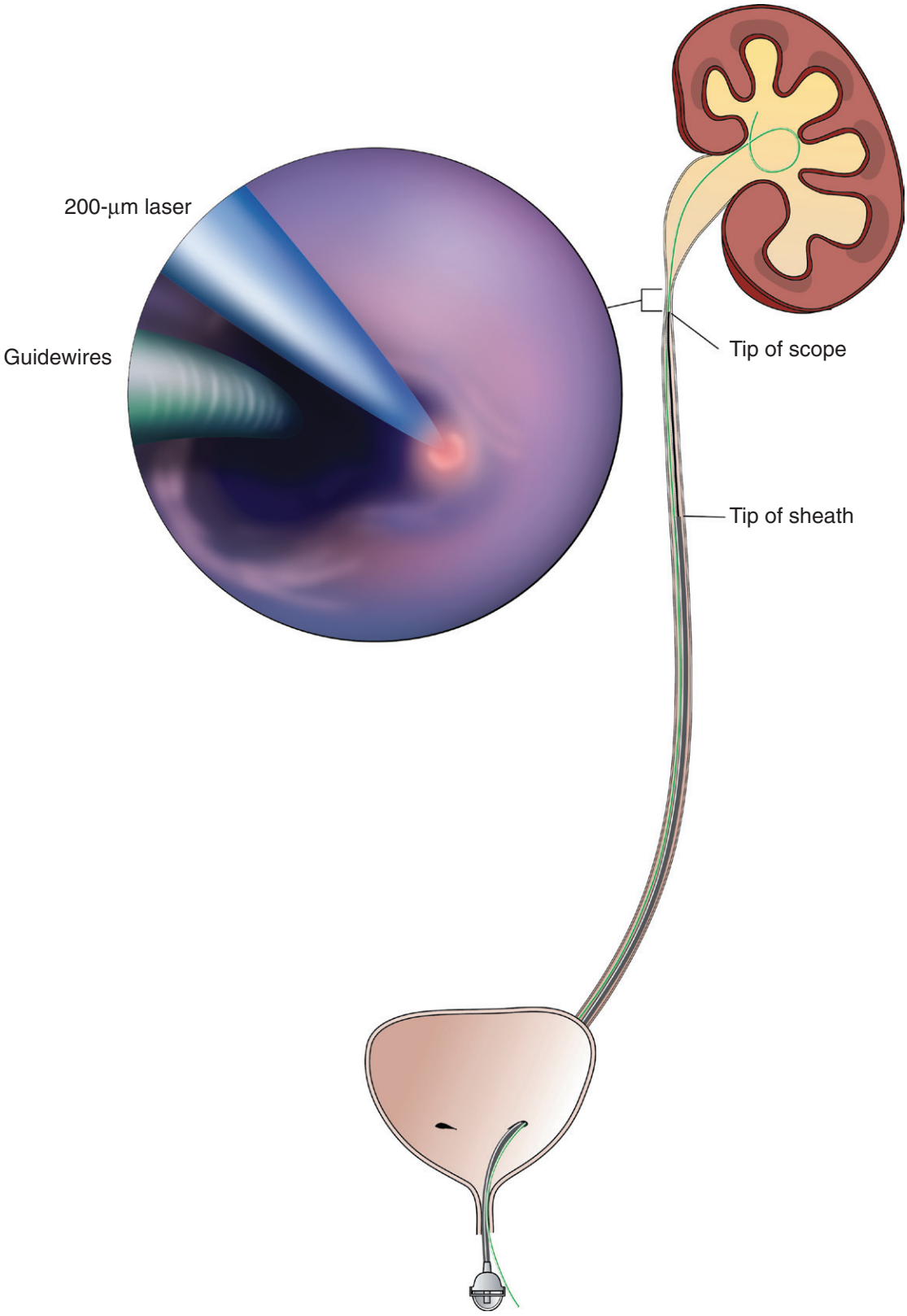


Figure 41–10. Flexible ureteroscopic endopyelotomy using holmium laser, demonstrating endoscopic view of the ureteropelvic junction *(inset)*. A safety wire is in place, and the ureteroscope is passed through a ureteral access sheath as a lateral incision is being made under endoscopic view, using holmium laser fiber. A properly sited, complete incision is straightforward with this direct visualization technique.

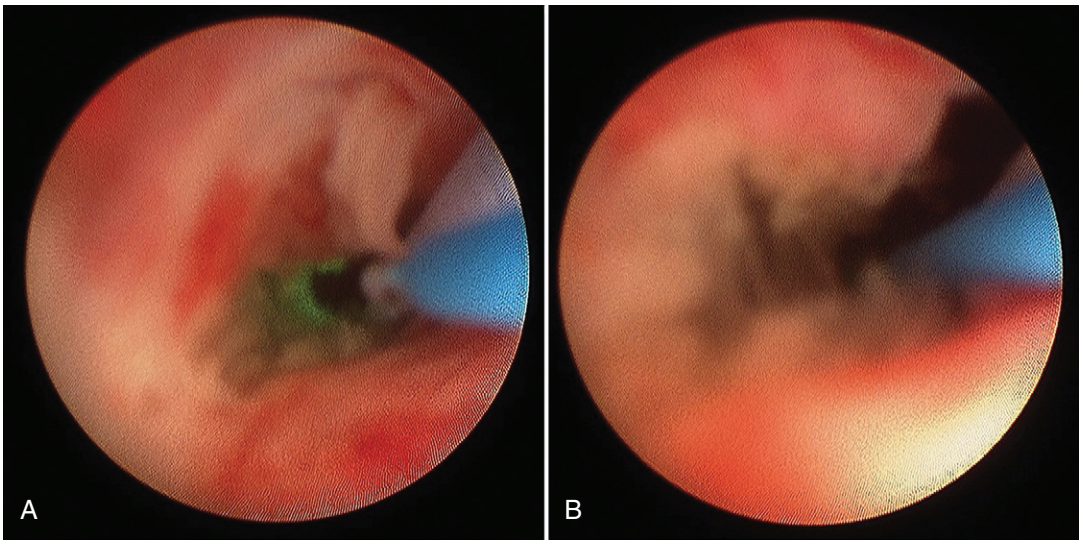


Figure 41–11. **A,** Endoscopic view of ureteropelvic junction (UPJ) stenosis with safety wire and laser fiber during incision. **B,** Following incision, note full-thickness incision and minimal bleeding with capacious UPJ.

authors believed this helped them definitively site their endopyelotomy incision. Different modalities were used for the endopyelotomy itself including electrocautery and holmium laser. An 87.5% success rate was achieved in 32 patients. There were no significant bleeding complications, and all patients were discharged within 24 hours of the procedure.

Gerber and colleagues and Matin and colleagues reported experiences with ureteroscopic holmium laser endopyelotomy, demonstrating success rates of 70% to 80% with follow-up out to 5 years (Gerber et al, 2000; Matin et al, 2003). **More recently, Yanke reported on 128 retrograde ureteroscopic endopyelotomies with a 60% success rate at 20 months while Rassweiler and colleagues reported 73% success in 113 patients at 63 months** (Rassweiler et al, 2007; Yanke et al, 2008). Improved results were reported by Conlin and associates (91% success rates) with retrograde endopyelotomy in patients when culling patients with crossing vessels greater than 4 mm using preoperative ultrasonography (Conlin, 2002). Giddens and colleagues also published excellent results when culling patients with anterior and posterior crossing vessels from retrograde endopyelotomy using endoluminal ultrasound (Giddens et al, 2000). **To date, the use of endoluminal ultrasound to identify crossing vessels has been controversial, and although it may play a role in preoperative decision making, similar data can be obtained using the less invasive spiral CT angiography. Regardless, the best endopyelotomy success rates still lag behind those of open or laparoscopic pyeloplasty.**

Complications. Complications of this approach have diminished in frequency and severity with the refinement of ureteroscopic instrumentation and the introduction of small-caliber holmium laser fibers. Postprocedural ureteral strictures are rare in contemporary series, and angiographic embolization and nephrectomy are rare using the retrograde approach. Most complications are minor and relate primarily to urinary leak, stent migration, and infection (Gerber and Kim, 2000; Tawfiek et al, 1998). Recently Castle and colleagues reported on ureteroarterial fistula 2 weeks following retrograde laser endopyelotomy, which could be fulgurated ureteroscopically (Castle et al, 2009).

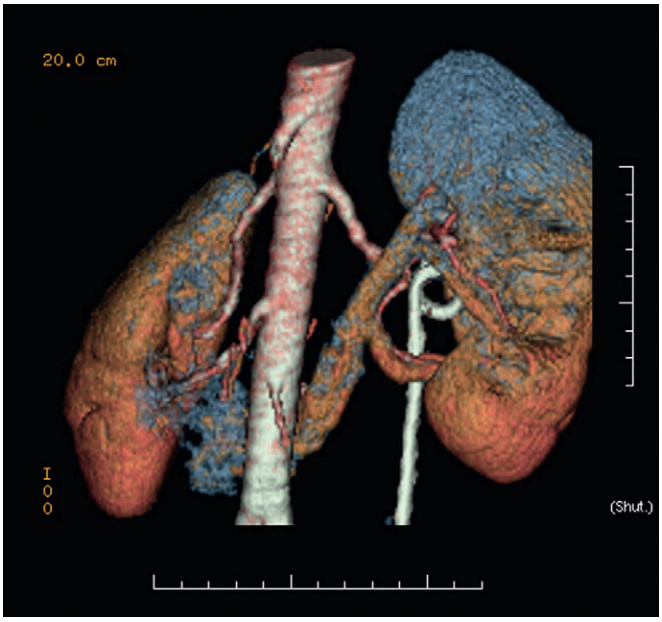


Figure 41–12. Spiral CT angiography with three-dimensional reconstruction clearly identifies an accessory lower pole crossing vessels at the level of the ureteropelvic junction (UPJ) in a patient with UPJ obstruction. This case was managed successfully with laparoscopic pyeloplasty.

Retrograde Cautery Wire Balloon Endopyelotomy. Use of a cautery wire balloon for management of UPJ obstruction was first reported in a clinical series by Chandhoke and colleagues in 1993. Use of this device gained initial acceptance by many clinicians because standard cystoscopic techniques and real-time fluoroscopy are all that is necessary for its use. Because the procedure is guided fluoroscopically, such vessels may increase the risk of hemorrhage after activation of the cautery wire balloon. Some authors recommended preoperative imaging for such vessels with relatively noninvasive techniques such as CT or three-dimensional CT angiography (Fig. 41–12) (Streem and Geisinger, 1995; Quillin et al,

1996; Nakada et al, 1998; Herts et al, 1999; Nakada, 2000). Nadler and colleagues (1996) reported on 28 patients 2 or more years after cautery wire balloon endopyelotomy. With a mean follow-up of 32.5 months, subjective improvement was noted in 61% of patients, and 81% had a patent UPJ on the basis of diuretic renography or Whitaker testing. More recent studies have demonstrated lower success rates than these initial series (32% to 63%) and perhaps that high-grade hydronephrosis has a negative impact on success (Albani et al, 2004; Sofras et al, 2004). El-Nahas and colleagues reported a small prospective randomized trial comparing retrograde ureteroscopic endopyelotomy to the hot-wire balloon endopyelotomy in 40 patients. Although not statistically significant, they found superior success rates (85% compared with 65%) and lower complication rates with the ureteroscopic endopyelotomy (El-Nahas et al, 2006). Ponsky and Streem reported on 64 patients undergoing either ureteroscopic endopyelotomy or hot wire balloon endopyelotomy and found equivalent success rates with both procedures yet higher major complication rates in the cautery wire balloon endopyelotomy, specifically transfusion and selective embolization (Ponsky and Streem, 2006). **The major complication associated with cautery wire balloon incision is hemorrhage. Although injury to crossing vessels has been reported using the cutting balloon catheter, strict adherence to lateral incision principles minimizes this risk** (Sampaio et al, 1993; Streem and Geisinger, 1995; Wagner et al, 1996). In addition, although some believe crossing vessels hinder success rates primarily, others believe hemorrhage is a real concern (Aslan et al, 1998). Currently, improved ureteroscopic instrumentation and the benefits of direct endoscopic visualization make ureteroscopic endopyelotomy the more pervasive retrograde approach.

Key Points: Endourologic Management of UPJ Obstruction

- Contemporary indications for intervention for UPJ obstruction include the presence of symptoms associated with the obstruction, impairment of overall renal function or progressive impairment of ipsilateral function, development of stones or infection, or, rarely, causal hypertension.
- The advantages of endourologic approaches include a significantly reduced hospital stay and postoperative recovery. However, the success rate does not approach that of standard open, laparoscopic, or robotic pyeloplasty.
- Whereas open, laparoscopic, or robotic operative intervention can be applied to almost any anatomic variation of UPJ obstruction, consideration of any of the less invasive alternatives requires that the surgeon take into account the degree of hydronephrosis, ipsilateral renal function, concomitant calculi, and, possibly, the presence of crossing vessels.
- Generally, the urologist should have a low threshold to proceeding to angiography in patients with bleeding following endopyelotomy in order to minimize the need for transfusion and potential exploration. Successful angiographic embolization often obviates the need for operative "exploration" that can lead to nephrectomy.

Laparoscopic and Robotic Intervention

Laparoscopic Pyeloplasty

Laparoscopic approach to pyeloplasty was first introduced in 1993 by Schuessler and colleagues (1993) and has been developed worldwide as a viable minimally invasive alternative to open pyeloplasty and endopyelotomy. Relative to both open pyeloplasty and endopyelotomy, laparoscopic pyeloplasty is associated with greater technical complexity and a steeper learning curve. **In the hands of the experienced laparoscopic surgeons, it has been shown to provide lower patient morbidity, shorter hospitalization, and faster convalescence, with the reported success rates matching those of open pyeloplasty (≥90%).** Following the similar surgical principles of anatomic dissection and repair used in open pyeloplasty, laparoscopic pyeloplasty has been shown to provide the success rates surpassing those of endopyelotomy by approximately 10% to 30%.

Indications and Contraindications. **The indications and contraindications for a laparoscopic repair are similar to those for either an endourologic or an open operative procedure. Indications to intervene include the presence of clinical symptoms of ureteropelvic junction obstruction, the progressive impairment of renal function, and the development of ipsilateral upper tract calculi or infection.** Cases requiring the transposition of crossing vessels obstructing ureteropelvic junction or the size reduction for massively dilated renal pelvis are suitable for the laparoscopic approach. **Absolute contraindications to intervene include the presence of uncorrected coagulopathy, the absence of adequate treatment of active urinary tract infection, and the presence of cardiopulmonary compromise unsuitable for surgery. The objective of the laparoscopic surgery is to provide a tension-free, water-tight repair with a funnel-shaped drainage product to relieve clinical symptoms and to preserve renal function.**

Techniques. Four laparoscopic techniques for pyeloplasty have been described in the literature including the standard transperitoneal approach, retroperitoneal approach, anterior extraperitoneal approach, and robotic-assisted approach. For each approach, a dismembered Andersen-Hynes pyeloplasty, which is preferred by most surgeons, or one of the nondismembered methods such as Y-V plasty and flap pyeloplasty (Culp) analogous to those described for the open pyeloplasty can be used.

Transperitoneal Laparoscopic Approach. The initial transperitoneal approach to laparoscopic pyeloplasty was first described by Schuessler and colleagues (1993) and Kavoussi and colleagues (1993), and **this approach has been the most widely used laparoscopic method due to its associated large working space and familiar anatomy.** Before the laparoscopic portion of the procedure, cystoscopy with retrograde pyelography is first performed to define the anatomy and confirm the diagnosis, followed by placement of a ureteral stent and a urethral Foley catheter. The patient is placed in a 45-degree lateral decubitus position, and access to the peritoneal cavity is obtained via either the Veress needle or the Hassan access technique. Three to five laparoscopic ports are placed after the creation of CO_2 pneumoperitoneum. Typically the umbilical port is for the laparoscope use. Colonic mobilization to expose the retropetioneal structures is the initial step of the laparoscopic procedure, although transmesenteric approach without bowel mobilization has been reported if renal pelvis or ureter can be readily recognized through the descending colonic mesentery (Romero et al, 2006). After medial mobilization

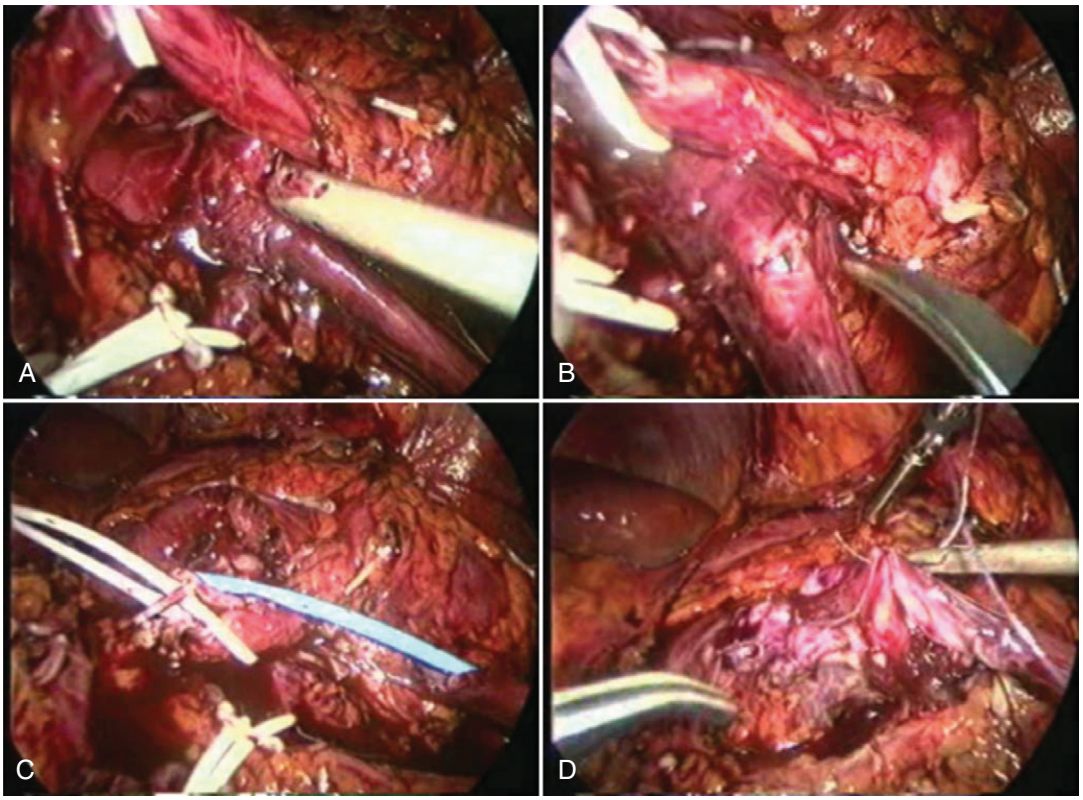


Figure 41–13. **A,** Transperitoneoscopic view of a patient with left pyelplasty. The patient's head is to the left. Note the proximal ureter is sandwiched between an anterior crossing lower pole renal artery (wrapped with white vessel loop and retracted upward) and a posterior crossing lower pole vessel (wrapped with white vessel loop). The suction-irrigator tip points at the left ureteropelvic junction. **B,** The left proximal ureter is being transected with laparoscopic scissors, revealing the preplaced ureteral stent within the ureteral lumen. **C,** The ureteral stent is transposed anterior to the anteriorly crossing vessel following circumferential transection of the proximal left ureter. **D,** Ureteropelvic anastomosis is completed with intracorporeal suturing techniques.

of the colon, the ureter is identified and dissected in the cephalad direction to achieve mobilization of the ipsilateral proximal ureter, ureteropelvic junction, and renal pelvis (Fig. 41–13A). Extensive dissection of the ureter and excessive electrocautery use in close proximity to the ureter should be avoided to minimize injury to its vascular supply. At this time, the anatomy of the proximal ureter, renal pelvis, and nearby vasculature are carefully examined to determine the etiology of the ureteropelvic junction obstruction and the appropriate type of surgical repair. The general methods and principles of various types of surgical repair for laparoscopic pyeloplasty are identical to those described for open pyelplasty. If dismembered pyeloplasty is to be performed, which is suitable for the presence of crossing vessels, the renal pelvis is first transected circumferentially above the ureteropelvic junction and the lateral aspect of the proximal ureter is spatulated (Fig. 41–13B). The renal pelvis and proximal ureter are then transposed to the opposite side of the crossing vessel, if such vessel is present, and the ureteropelvic anastomosis is then completed with intracorporeal suturing techniques (Fig. 41–13C-D). In the presence of redundant renal pelvis, reduction pelvioplasty may be performed by excising redundant renal pelvic tissue and closing the pyelotomy. The actual laparoscopic suturing maneuver can be accomplished either freehand or with a semiautomated device (EndoStitch, US Surgical, Newark, CT). Either continuous running or simple interrupted suturing method may be used in the dismembered laparoscopic pyeloplasty, typically with the 4-0 absorbable suture. A surgical drain is placed after the completion of the anastomosis, and one of the trocar sites is typically used as the drain exit site.

Retroperitoneal Laparoscopic Approach. The initial retroperitoneoscopic approach to pyeloplasty was first reported by Janetschek and colleagues (1996). Cystoscopy with retrograde pyelography and ureteral stent placement are first performed as described earlier. For the retroperitoneal approach, the patient is usually positioned in the flank position with the use of flexion and elevation of the kidney rest. Following Hassan access technique to enter the retroperitoneum, a retroperitoneal working space can be created with balloon dilation. Following CO_2 pneumoretroperitoneum, three to four laparoscopic ports are used to perform the laparoscopic pyeloplasty. The ureter is usually identified early in the procedure, and the dissection, mobilization, and ureteropelvic junction repair steps are identical to those described for the transperitoneal approach (Fig. 41–14).

Anterior Extraperitoneal Laparoscopic Approach. The anterior extraperitoneal laparoscopic approach to pyeloplasty was first described by Hsu and colleagues (2003). Cystoscopy with retrograde pyelography and ureteral stent placement are first performed as described earlier. For the anterior extraperitoneal approach, the patient is placed in a 45-degree lateral decubitus position. Access to the preperitoneal space is obtained using open surgical techniques via a 10-mm incision, after which a large preperitoneal space is created with balloon dilation. Following CO_2 insufflation and placement of four ports, the boundary between the retroperitoneal fat and peritoneal sac is identified and developed, allowing

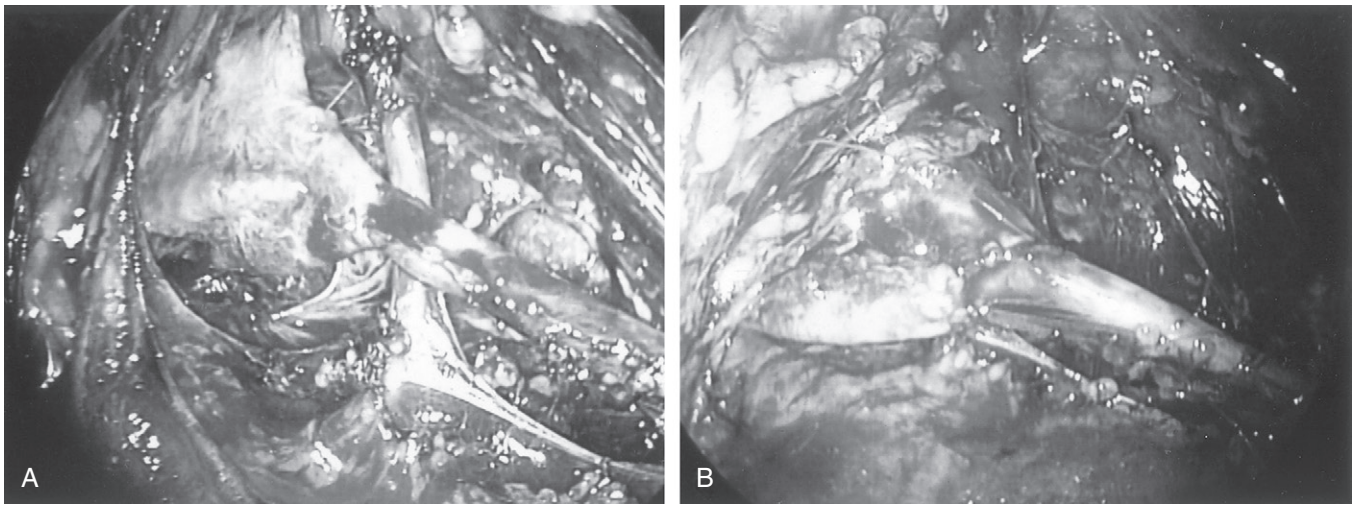


Figure 41–14. **A,** Retroperitoneal laparoscopic photograph of a case with right ureteropelvic junction (UPJ) obstruction. Note the presence of a lower pole crossing renal vessel anterior to the UPJ. **B,** Intraoperative view of completed ureteropelvic anastomosis after retroperitoneal laparoscopic dismembered pyeloplasty.

medial mobilization of the peritoneal sac containing the bowel contents en bloc. Subsequently, full exposure of the anterior aspects of the retroperitoneal structures including the ipsilateral ureter and kidney comes into view. The proximal ureter, ureteropelvic junction, and renal pelvis are identified, dissected, mobilized, and repaired as in the transperitoneal laparoscopic pyeloplasty. The entire procedure is completed in an extraperitoneal manner. A surgical drain is similarly placed at the end of the procedure.

Robotic-Assisted Laparoscopic Approach. The robotic-assisted laparoscopic pyeloplasty in the experimental setting was first reported by Sung and colleagues (1999). Its feasibility was subsequently confirmed with worldwide clinical application in recent years (Palese et al, 2005; Mufarrij et al, 2007; Schwentner et al, 2007; Yanke et al, 2008). The most widely used robotic system in the clinical setting today is the da Vinci Robot (Intuitive Surgical, Sunnyvale, CA), and the reported benefits of the robot include enhanced three-dimensional vision, motion scaling, tremor reduction, improved dexterity, and increased range of motion. Typically the procedure is performed in a transperitoneal manner providing a larger working space for the robotic arms, although the feasibility of retroperitoneal approach has been recently demonstrated in a small number of patients (Kaouk et al, 2008). Ureteral stent may be placed via a cystoscopic retrograde or laparoscopic antegrade manner. In both transperitoneal and retroperitoneal approaches, at least four different trocars are used in a robotic-assisted procedure including three for the robotic arms and one for the surgical assistant to perform suction, irrigation, retraction, and suture introduction. Following the initial laparoscopic access and trocar placement, the robotic system is placed in close proximity to the operating table and the robotic arms are attached to the laparoscope and specifically designed laparoscopic instruments. The surgeon at the console operates via the control of the robotic arms, while the assistant remains at the bedside and performs suction, retraction, exchange of laparoscopic instruments, suture needle introduction, and removal. The general surgical steps are identical to those described for non-robotic-assisted laparoscopic pyeloplasty.

Postoperative Care and Complications. Typically, a clear liquid diet is initiated on postoperative day 1 and advanced rapidly. Perioperative prophylactic antibiotic coverage is maintained. The Foley catheter is usually removed 24 to 36 hours postoperatively, and the surgical drain is removed before hospital discharge if the drain output remains negligible. If the drain output increases after the Foley catheter removal, the Foley catheter should be replaced for 7 days to eliminate urinary reflux along the stent in the treated ureter and decrease urinary extravasation at the ureteropelvic anastomosis. The ureteral stent is typically removed 4 to 6 weeks later in an outpatient setting, and follow-up including the use of imaging studies such as diuretic renal scan is performed as for any open pyeloplasty. Most of the complications of laparoscopic pyeloplasty are similar to those of general laparoscopic procedures including colonic injury, hemorrhage, ileus, pneumonia, congestive heart failure, thrombophlebitis, and urinoma formation. In the first 100 cases of laparoscopic pyeloplasty performed at Johns Hopkins (Jarrett et al, 2002), such complications occurred in 12% of the patients. Another large-scale review involving 189 cases of laparoscopic pyeloplasty identified approximately 2% to 2.3% intraoperative complication rate and 12.9% to 15.8% postoperative complication rate (Rassweiler et al, 2008). A typical postoperative appearance of a laparoscopic pyeloplasty patient is illustrated in Figure 41–15.

Results. Most of the published laparoscopic pyeloplasty reports have used the classic Andersen-Hynes dismembered technique because most laparoscopic surgeons attempt to duplicate the well-established principles of open surgery (Janetschek et al, 2000; Eden et al, 2001; Soulie et al, 2001; Jarrett et al, 2002; Turk et al, 2002; Inagaki et al, 2005; Bachmann et al, 2006; Rassweiler et al, 2008). The overwhelming majority of patients in these recent series had primary laparoscopic pyeloplasties, and the mean operative times are in the range of 119 to 252 minutes. In the experienced hands, the entire procedure can be consistently performed in less than 3.5 hours (Jarrett et al, 2002), reflecting greater confidence in intracorporeal suturing and knot tying. Perioperative complication rates are low, ranging from 2% to 15.8%, demonstrating the safety of the laparoscopic procedure. Open conversion rates are also low, in the range of 0% to 5.5%. Furthermore, blood transfusion risks are low, being limited to anecdotal reports. Postoperative analgesic use is generally minimal. Mean length of hospital stay ranges from 2.6 to 4.5 days, and such average has decreased to 3.8 days in the series reported since 2000. With mean follow-up times of 14 to 26 months, the rates of surgical success



Figure 41–15. Postoperative photograph of the abdomen of a patient with left-sided laparoscopic dismembered pyeloplasty. Note the four small scars from the laparoscopic procedure.

(defined as durable clinical and/or radiographic success) reach the range of 87% to 99%, with the majority of contemporary series reporting success rates of greater than 95%. The safety and efficacy of laparoscopic pyeloplasty have also been demonstrated in the pediatric population including patients younger than 1 year (Metzelder et al, 2006).

Recently the transmesenteric approach to laparoscopic pyeloplasty has been analyzed (Romero et al, 2006). In contrast to the traditional retrocolic approach involving transperitoneal bowel mobilization described previously, a longitudinal incision is made in the colonic mesentery overlying the ureteropelvic junction region, followed by dissection of the ureter and renal pelvis. The laparoscopic pyeloplasty is then completed in the standard transperitoneal fashion. Recognition of the renal pelvis and/or ureter through the colonic mesentery is necessary in a successful transmesenteric procedure, which is performed more commonly in cases involving renal malrotation, horseshoe kidneys, left ureteropelvic junction obstruction, and younger patients (who presumably tend to have less visceral fat allowing better transmesenteric visualization of renal pelvis/ureter). Compared with the conventional retrocolic approach, the transmesenteric approach has been found to provide shorter operative time (by a mean of 22.5%) without significant increase in complication or patency outcomes.

Most failures from laparoscopic pyeloplasty occur in the first 2 years, although up to 30% of failed cases may occur after 2 years postoperatively (Madi et al, 2008). **For the patients who fail laparoscopic pyeloplasty, open surgery has been used as a salvage procedure, with success rates of approximately 86%** (Thomas et al, 2005). **However, most cases can be well managed with endoscopic intervention such as endopyelotomy, with success rates of approximately 70%** (Varkarakis et al, 2004).

More data on robotic-assisted laparoscopic pyeloplasty have emerged recently (Palese et al, 2005; Mufarrij et al, 2007; Schwentner et al, 2007; Yanke et al, 2008). Like the conventional laparoscopic studies, the overwhelming majority of the patients in these recent series had primary robotic-assisted laparoscopic pyeloplasties. The mean operative times are in the range of 108 to 244.8 minutes. Perioperative complication rates are low (<10.3%). Open conversion rates are also relatively low (0% to 6.8%). Postoperative analgesic use is generally minimal. Mean length of hospital stay is in the range of 2.2 to 2.8 days. With mean follow-up times of 11 to 39.1 months, the rates of surgical success (defined as durable clinical and/or radiographic success) are in the range of 94.7% to 100%. These results were similar to those from the historic laparoscopic series in the literature. The feasibility of the robotic approach has also been demonstrated in the pediatric patients (Atug et al, 2005; Lee et al, 2006). The additional reported benefits provided by the robot include better three-dimensional magnification, increased range of motion, ease of dissection, and suturing. However, the value of the robot in the setting of clinical pyeloplasty remains controversial and has been addressed by one recent study (Link et al, 2006). In this study comparing robotic and laparoscopic pyeloplasty in a prospective manner, the mean operative time and total room time for robotic cases were found to be significantly longer than laparoscopic cases by 19.5 and 39 minutes, respectively. Robotic cases were also found to be more costly than laparoscopic cases (2.7 times) due to longer operative time, increased cosumables costs, and depreciation of the robot system. In the hands of experienced laparoscopic surgeons, the use of the robot does not seem to provide significant clinical or cost advantage compared with conventional laparoscopic approach. In additional to cost, additional concerns for the robotic-assisted laparoscopic pyeloplasty include limited instrumentation and need for experienced bedside laparoscopic assistance (Peschel et al, 2004).

No prospective randomized trial has been successfully completed to compare laparoscopic with open pyeloplasty to date. The unwillingness of the patients to undergo randomization due to the different levels of perceived invasiveness appears to be the most significant barrier to completing such studies. In a retrospective study, Bauer and colleagues (1999) compared 42 laparoscopic pyeloplasties and 35 open pyeloplasties. With a minimum follow-up of 12 months for each of the patients, the two groups were found to be equivalent in pain relief (90% vs. 91%, respectively) and relief of obstruction (98% vs. 94%, respectively). In another retrospective study, Soulie and colleagues examined 26 laparoscopic pyeloplasties and 28 open pyeloplasties (Soulie et al, 2001). The two groups were found to be equivalent in mean operating time (165 vs. 145 minutes, respectively); mean blood loss (92 mL vs. 84 mL, respectively); perioperative complication rate (11.5% vs. 14.3%, respectively); mean hospital stay (4.5 days vs. 5.5 days, respectively); and radiologic success (89% vs. 89%, respectively). However, more laparoscopic patients were found to have returned to normal activity by postoperative day 15 (90% vs. 70%, respectively). In a third retrospective study, Klingler and colleagues (2003) compared 40 laparoscopic pyeloplasties with 15 open pyeloplasties. In this series the laparoscopic group was found to have lower mean postoperative visual analogue scale score (day 1, 3.5 vs. 5.4; day 5, 0.9 vs. 3.1) and shorter mean hospital stay (5.9 vs. 13.4 days). In a fourth retrospective study, Simforoosh and colleagues (2004) compared 37 laparoscopic pyeloplasties and 32 open pyeloplasties and found equivalent clinical and radiologic success rates between the two approaches (89% and 83.8% for laparoscopic group and 96.5% and 87% for open group, respectively) with a mean follow-up of 16.5 months (laparoscopic group) and 11.4 months (open group). Finally, in a fifth retrospective

study, Calvert and colleagues (2008) examined the differences between 49 laparoscopic and 51 open pyeloplasty patients. Compared with open cases, laparoscopic cases were found to have significantly longer mean operating time (159 vs. 91 minutes) and significantly shorter mean time to normal diet (38 vs. 72 hours).

In the presence of the crossing vessel, dismembered pyeloplasty with transposition of the ureteropelvic junction anastomosis anterior to the crossing vessel has been the conventional teaching. Recently, an alternative approach has been reported to successfully manage ureteropelvic junction obstruction associated with the crossing vessel without the need for ureteral transection and reanastomosis. The technique involves laparoscopic mobilization of the entire ureteropelvic junction, proximal ureter, and renal pelvis from surrounding tissues without ureteral transection (Meng et al, 2003; Boylu et al, 2009). The crossing vessel, in addition, may be mobilized and transposed superiorly and fixed to the peripelvic tissues with metallic clips or sutures (Simforoosh et al, 2005; Gundeti et al, 2008; Masood et al, 2009). Such technique has been described to be most appropriate for the ureteropelvic junction obstruction cases involving normal-appearing ureter with peristalsis and unfavorable pelvic anatomy, in which ureteropelvic anasomosis cannot be achieved in a tension-free manner after ureteral transposition.

Primary ureteropelvic junction obstruction associated with renal anomalies such as horseshoe kidneys and pelvic kidneys have also been managed with laparoscopic pyeloplasty safely and successfully (Janetschek et al 1996; Hsu et al 2003; Bovie et al 2004). Furthermore, secondary ureteropelvic junction obstruction has similarly been managed with success. In a retrospective review, Sundaram and colleagues (2003) identified 36 cases of laparoscopic transperitoneal pyeloplasty for secondary ureteropelvic junction obstruction, mostly following failed retrograde or antegrade endopyelotomies. Mean operative time was 6.2 hours, longer than the reported times associated with primary ureteropelvic junction obstruction. Open conversion was necessary in one patient, and postoperative complication occurred in eight patients. With a mean follow-up of 21.8 months, the overall success rate of a greater than 50% decrease in pain, a patent ureteropelvic junction, and stable or improved function of the affected renal unit was 83% (30 of 36 patients). Shapiro and colleagues (2009) identified nine cases of laparoscopic transperitoneal pyeloplasty for secondary ureteropelvic junction obstruction after a failed open procedure. Mean operative time was 204 minutes. At a median follow-up of 66 months, 89% (eight of nine) patients had clinical and radiologic resolution of ureteropelvic junction obstruction, with stable renal function, pain-free status, and patent ureteropelvic junction.

Special Situations of Laparoscopic and Robotic-Assisted Laparoscopic Management of Ureteropelvic Junction Obstruction

Laparoscopic and Robotic-Assisted Laparoscopic Ureterocalicostomy

Ureterocalicostomy has been completed successfully via both laparoscopic and robotic-assisted laparoscopic approaches. Gill and colleagues (2004) performed laparoscopic ureterocalicostomy in two patients with ureteropelvic junction obstruction associated with small renal pelvis and dilated lower pole calix. In both patients a double-J ureteral stent was first placed into the ipsilateral ureter cystoscopically. With the patient in a 45- to 60-degree flank position, a transperitoneal approach using three or four ports was used to gain access to the ipsilateral renal unit laparoscopically. A circular rim of the tip of the thin lower pole renal parenchyma was identified and excised. The ureteropelvic junction was transected, followed by ligation of the renal pelvic opening. The ureter was spatulated laterally, and end-to-end ureterocaliceal anastomosis with mucosa-to-mucosa apposition over the preplaced double-J stent was performed with free-hand intracorporeal suturing and knot-tying techniques. The general reconstructive principles are identical to those of open ureterocalicostomy described previously including the need to achieve tension-free, water-tight, dependent drainage. Casale and colleagues (2008) reported successful robotic-assisted laparoscopic ureterocalicostomy in nine pediatric patients, following the identical reconstructive principles described earlier. Mean operative time was 168 minutes, and feasibility of the use of robot was well demonstrated. All patients were found to have no evidence of obstruction on diuretic radionuclide imaging at 12 months postoperatively.

Laparoscopic and Robotic-Assisted Pyeloplasty with Concomitant Pyelolithotomy

Presence of calculi in the setting of ureteropelvic junction obstruction can be managed laparoscopically with success. In a retrospective review, Ramakumar and colleagues (2002) reported 20 cases of laparoscopic pyeloplasty with concomitant extraction of renal stones through the pyelotomy site under laparoscopic guidance. In the series, extraction of the caliceal stones was assisted by the use of a flexible cystoscope introduced through a 10- to 12-mm port site. At a mean follow-up of 3 months, 90% of patients were stone free, and 90% patients had patent ureteropelvic junction radiographically. In another retrospective review, Stein and colleagues (2008) reported 15 cases of laparoscopic pyeloplasty with concomitant pyelolithotomy, involving the use of laparoscopic graspers, flexible cystoscopes, and/or laparoscopic irrigation. The overall stone-free rate was 80%. Robotic-assisted laparoscopic pyeloplasty with concomitant pyelolithotomy has also been demonstrated in eight patients recently, using the similar instruments including laparoscopic graspers (Atug et al, 2005). To complete the pyelolithotomy, one of the robotic arms was temporarily undocked to allow passage of a flexible nephroscope into the renal pelvis to gain visualization of the stones in the collecting system. In this small series, all patients were rendered stone free.

Laparoscopic Dismembered Tubularized Flap Pyeloplasty

Presence of a significant upper ureteral defect following the excision of ureteropelvic junction stricture may also be managed laparoscopically with success. Kaouk and colleagues (2002) described a case of laparoscopic pyeloplasty for secondary ureteropelvic junction obstruction, in which a 3-cm upper ureteral defect was found following excision of the long stricture. Using a four-port transperitoneal approach, a wide-base renal pelvic flap was created and tubularized to bridge the defect, using intracorporeal freehand suturing techniques. At a 2-month follow-up, excretory urography and diuretic renal scan confirmed a widely patent upper ureter.

Laparoscopic Calicovesicostomy

Presence of a large-capacity bladder in the setting of ureteropelvic junction obstruction associated with a low-lying obstructed renal unit can be managed successfully using an unconventional laparoscopic reconstructive strategy. Hsu and colleagues (2006)

described a case of laparoscopic management of ureteropelvic junction obstruction involving a horseshoe kidney with a unilateral hydronephrotic yet functioning lower pole moiety, ipsilateral ureteral duplication with high bifurcation, and complex anomalous renal vasculature. Rather than performing tedious anatomic dissection and complex ureteral reconstruction in such scenario as required in conventional laparoscopic pyeloplasty, a nephrotomy was created at the most dependent portion of the hydronephrotic lower pole moiety and then laparoscopically anastomosed to the bladder dome vesicostomy using intracorporeal freehand suturing and knot-tying techniques. At the 4-month follow-up, patent calicovesicostomy was confirmed endoscopically and clinically.

Key Points: Laparoscopic and Robotic Intervention

- Transperitoneal laparoscopic approach is the most widely used method due to its associated large working space and familiar anatomy.
- Retroperitoneal laparoscopic approach and anterior extraperitoneal approach rely on creation of a working space using manual or balloon dilation.
- Laparoscopic management of UPJ obstruction has been shown to provide low perioperative complication rate, short hospital stay, and success rates greater than 95% in the experienced hands.

Open Operative Intervention

General Surgical Principles

Several types of surgical incisions have been used for a pyeloplasty in the management of ureteropelvic junction (UPJ) obstruction. An anterior extraperitoneal approach is chosen by some because it allows surgical repair with minimal mobilization of the pelvis and proximal ureter. Alternatively, a posterior lumbotomy provides direct exposure to the UPJ and again allows repair with minimal mobilization of the surrounding structures. Like the anterior extraperitoneal approach, posterior lumbotomy is best suited to relatively thin patients without previous ipsilateral surgery. The authors' personal preference for most patients undergoing primary surgical repair of UPJ obstruction is an extraperitoneal flank approach. This incision may be subcostal but is usually performed through the bed of the 12th rib or carried anteriorly off its tip. The extraperitoneal flank approach is advantageous in that it is familiar to all urologists and provides excellent exposure without regard to body habitus. In the presence of other renal anomalies associated with the UPJ, such as horseshoe or pelvic kidney, anterior extraperitoneal approaches are often preferable, although laparoscopic management may be considered in this setting.

Before the definitive surgical management, drainage of a kidney with UPJ obstruction is recommended only in select circumstances including infection associated with the obstruction or azotemia resulting from obstruction in a solitary kidney or bilateral disease. Procedural drainage may be of value in the uncommon scenario of severe, unrelenting pain requiring emergent relief of obstruction. For any of these situations, such drainage can be achieved by placement of an internal ureteral stent or a percutaneous nephrostomy tube.

The clinical indications for placement of stents or nephrostomy tubes intraoperatively remain controversial and vary among the urologists. For adults, the authors' preference is for routine placement of a soft, inert, self-retaining internal ureteral stent, which is removed 4 to 6 weeks postoperatively. Such stents in adults can be easily removed in an outpatient office setting under local anesthesia. Routine use of internal ureteral stents offers several advantages, especially in the early postoperative period. Such practice appears to decrease the amount and length of time of urinary extravasation at the surgical repair site, thereby decreasing the risk of secondary fibrosis. Decreased urinary extravasation also allows earlier removal of external drains. For the uncomplicated pyeloplasty in adult patients, there appears to be no advantage to using both a nephrostomy tube and a stent because this may result in a prolonged hospital stay and an increased incidence of infection (Wollin et al, 1989). Instead, nephrostomy tubes may be reserved for complicated procedures such as those required for secondary UPJ obstruction or those associated with active inflammation. However, if a percutaneous nephrostomy tube had been placed preoperatively, it is generally left in place to allow proximal diversion and access for antegrade radiographic studies during the postoperative period.

Although the use of internal stents and nephrostomy tubes remains somewhat controversial, provision of external drainage from the site of surgical repair is absolutely necessary. Such external drainage may be achieved with a Penrose or closed suction drain placed near, but not on, the suture line and brought out through a separate stab incision. This practice helps to minimize the risk of urinoma formation leading to possible disruption of the suture line, scarring, or sepsis.

Historical Notes

The historical aspects of UPJ repair were previously examined by Kay in 1989 and by Schaeffer and Grayhack in 1986. The first reconstructive procedure was performed by Trendelenburg in 1886; however, the patient died of postoperative complications. In 1891 Kuster divided the ureter and reanastomosed it to the renal pelvis, thus apparently performing the first successful dismembered pyeloplasty. Kuster's technique, however, was prone to recurrent stricture. In 1892 Fenzer applied the Heineke-Mikulicz principle to UPJ repair. This surgical technique involves transverse closure of a longitudinal incision. However, this technique can cause shortening of the suture line on one side, thus resulting in buckling or kinking of the UPJ with recurrent obstruction. In 1916 Schwyzer introduced the Y-V-pyeloplasty, which was subsequently modified by Foley in 1937. However, this technique was best applied to high ureteral insertions and was essentially unsuitable when the UPJ itself was already in a dependent position. Later on, flap techniques were developed that were more universally applicable including the spiral flap of Culp and DeWeerd (1951) and the vertical flap of Scardino and Prince (1953). Thompson and colleagues (1969) reported the use of a renal capsular flap for complex cases in which an adequate amount of renal pelvis is not available for repair.

In 1949 Nesbit followed the principle of Kuster's dismembered procedure and further modified it by creating an elliptical anastomosis to decrease the likelihood of stricture formation at the site of repair. Also in 1949, Anderson and Hynes described their modifications of this dismembered technique that involved anastomosis of the spatulated ureter to a projection of the lower aspect of the pelvis after a redundant portion was excised. Use of healing by secondary intention was also investigated in the similar time period. The techniques of intubated ureterotomy were popularized by Davis in 1943, but they had been previously described by Fiori in 1905, Albarran in 1909, and Keyes in 1915.

Although a variety of techniques have been described for the management of UPJ obstruction, several basic principles must

always be applied to maximize the success of surgical repair. **For any procedure, the resultant anastomosis should be widely patent and completed in a watertight fashion without tension. In addition, the reconstructed UPJ should allow a funnel-shaped transition between the pelvis and the ureter that is in a position of dependent drainage.**

Dismembered Pyeloplasty

Indications. **At present, a dismembered pyeloplasty is preferred by most urologists in the surgical repair of UPJ obstruction because this procedure is almost universally applicable to the different clinical scenarios.** This approach can be used regardless of whether the ureteral insertion is high on the pelvis or already dependent. It also permits reduction of a redundant pelvis or straightening of a tortuous proximal ureter. Furthermore, **anterior or posterior transposition of the UPJ can be achieved when the obstruction is due to accessory or aberrant lower pole vessels.** In addition, unlike the flap techniques, **only a dismembered pyeloplasty allows complete excision of the anatomically or functionally abnormal UPJ itself.** It is important to note that a **dismembered pyeloplasty is not well suited to UPJ obstruction associated with lengthy or multiple proximal ureteral strictures or to patients in whom the UPJ obstruction is associated with a small, relatively inaccessible intrarenal pelvis.**

Technique. Surgical exposure to the UPJ is achieved by first identifying the proximal ureter in the retroperitoneum. The proximal ureter is then dissected cephalad to the renal pelvis, leaving a large amount of periureteral tissue to preserve the ureteral blood supply. A marking stitch of fine suture is then placed on the lateral aspect of the proximal ureter, below the level of the obstruction, to assist proper orientation for the subsequent repair. In a similar fashion, the medial and lateral aspects of the dependent portion of the renal pelvis are marked with traction sutures (Fig. 41–16A). The UPJ tissue is excised, and the proximal ureter is then spatulated on its lateral aspect. The apex of this lateral, spatulated aspect of the proximal ureter is brought to the inferior border of the renal pelvis, while the medial side of the ureter is brought to the superior aspect (Fig. 41–16B). The anastomosis is then performed with fine interrupted or running absorbable sutures, placed full thickness through the ureteral and renal pelvic walls, in a watertight manner (Fig. 41–16C). As discussed earlier, the authors' preference for adult patients is to routinely perform the anastomosis over an internal ureteral stent, which is left indwelling.

If the renal pelvis is exceptionally redundant, a "reduction" pyeloplasty can be performed by excising the redundant portion of the pelvis (Fig. 41–17A-C). The cephalad aspect of the pelvis is then closed with running absorbable sutures down to the dependent portion, which will subsequently be anastomosed to the ureter. In the event that aberrant or accessory lower pole vessels are found in association with the UPJ obstruction, a dismembered pyeloplasty allows transposition of the UPJ in relation to these vessels (Fig. 41–18).

Results. The overall success of open dismembered pyeloplasty has been favorable in the literature. In a retrospective review,

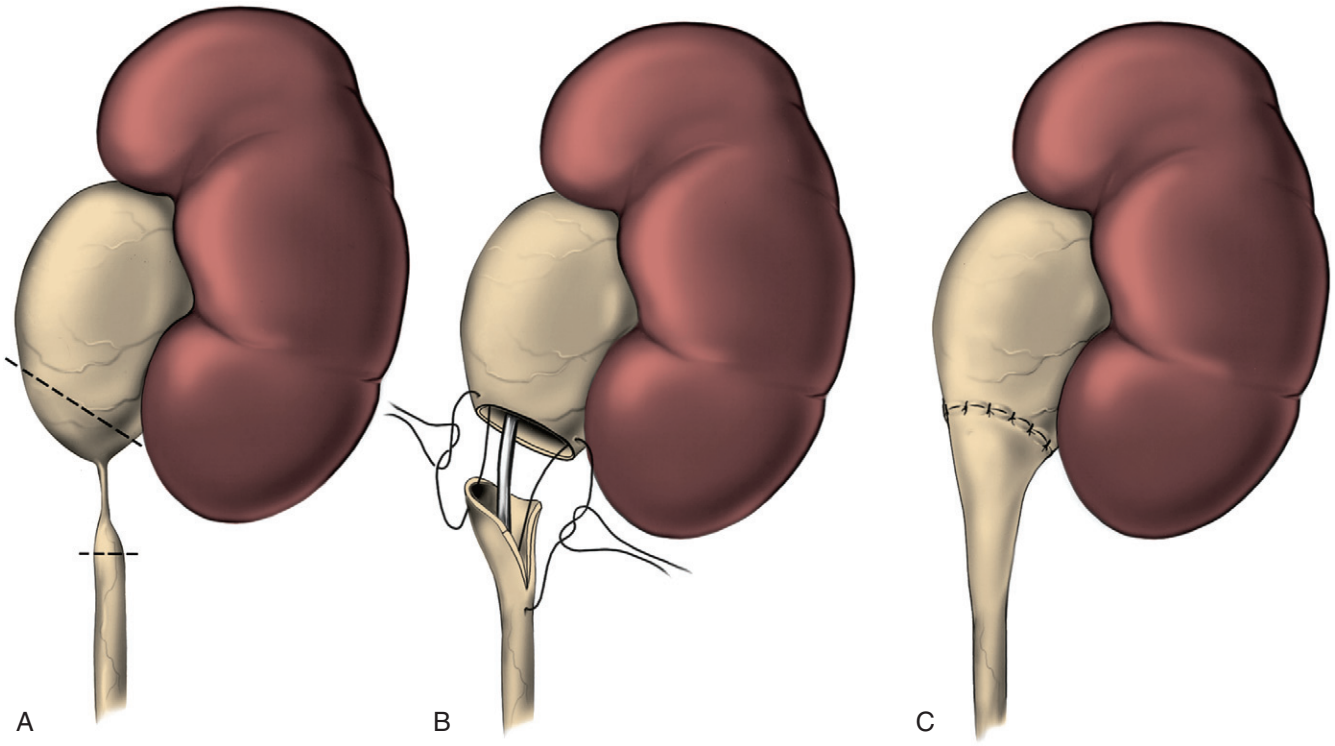


Figure 41–16. **A,** Traction sutures are placed on the medial and lateral aspects of the dependent portion of the renal pelvis in preparation for dismembered pyeloplasty. A traction suture is also placed on the lateral aspect of the proximal ureter, below the level of obstruction. This will help maintain proper orientation for the subsequent repair. **B,** Ureteropelvic junction is excised. The proximal ureter is spatulated on its lateral aspect. The apex of this lateral, spatulated aspect of the ureter is then brought to the inferior border of the pelvis while the medial side of the ureter is brought to the superior edge of the pelvis. **C,** Anastomosis is then performed with fine interrupted or running absorbable sutures placed full thickness through the ureteral and renal pelvis walls in a watertight fashion. In general, we prefer to leave an indwelling internal stent for adult patients. The stent is removed 4 to 6 weeks later.

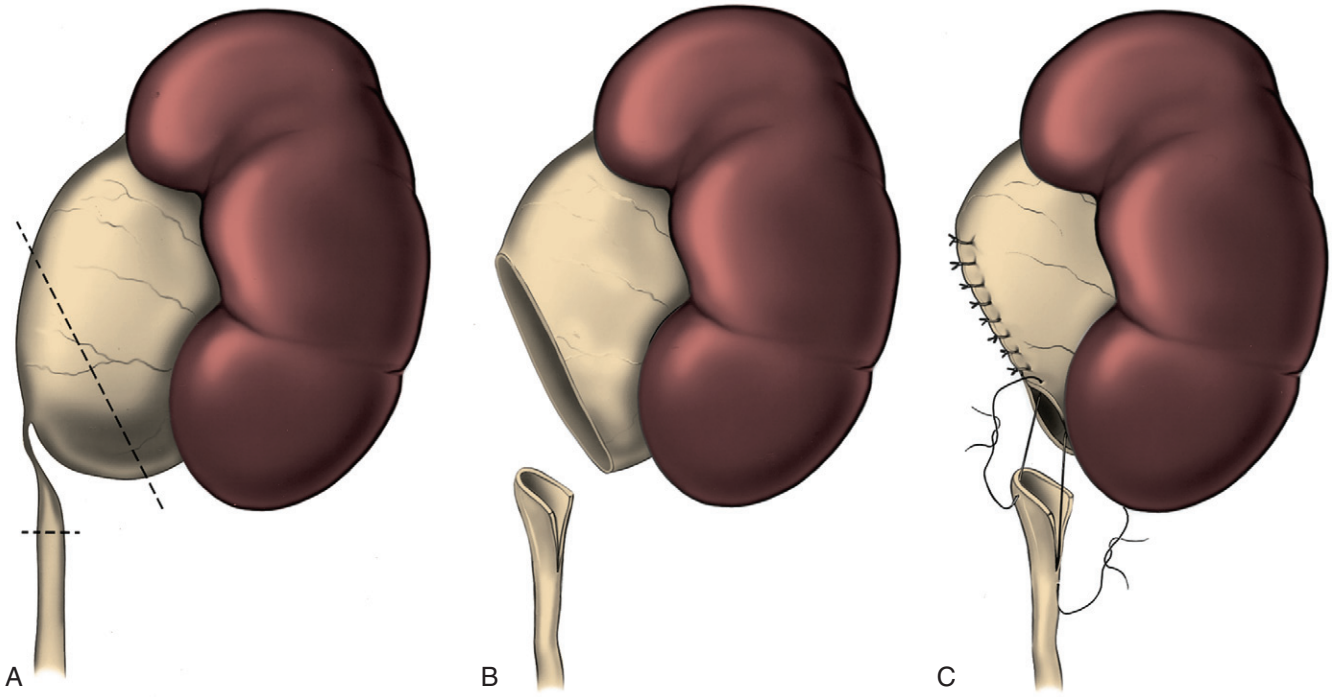


Figure 41–17. **A,** For large or redundant renal pelves, a reduction pyeloplasty is performed by excising the redundant portion between traction sutures. **B,** The cephalad aspect of the pelvis is then closed with running absorbable suture down to the dependent portion. **C,** The dependent aspect of the pelvis is then anastomosed to the proximal ureter.

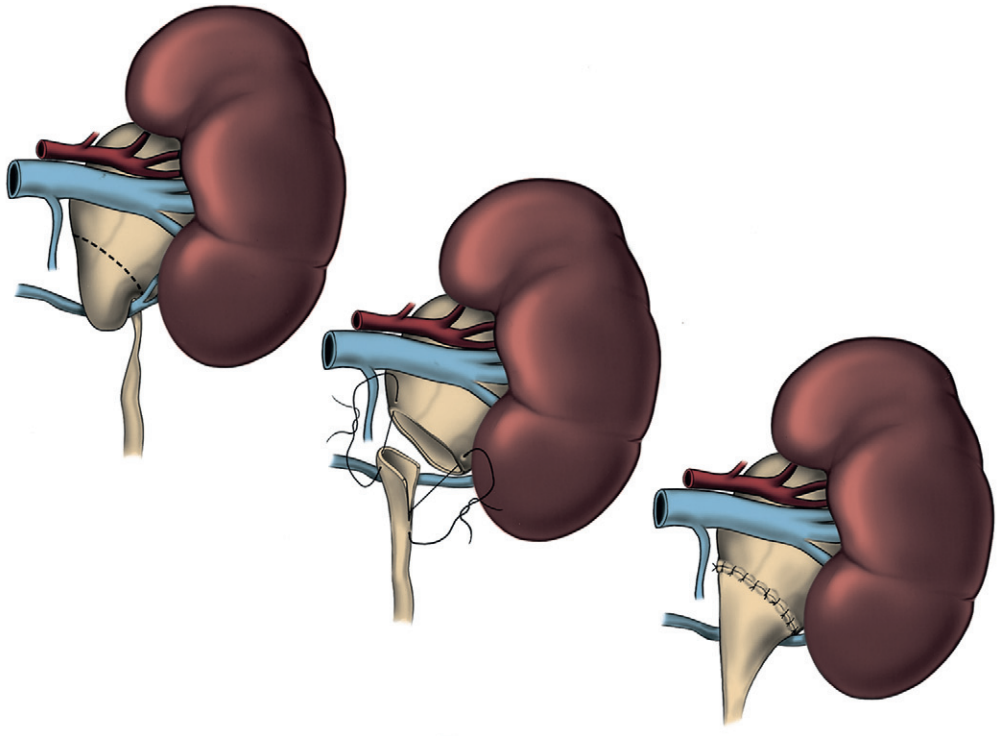


Figure 41–18. When aberrant or accessory lower pole vessels are found in association with the ureteropelvic junction (UPJ) obstruction, a dismembered pyeloplasty allows transposition of the UPJ in relation to the vessels.

Persky and colleagues (1977) noted that none of their 109 dismembered pyeloplasties for UPJ obstruction required subsequent nephrectomy. In another retrospective review involving 111 patients with UPJ obstruction undergoing open surgical repair over a 15-year-period, Clark and Malek (1987) found 95% success in resolution of clinical symptoms and 91% success in decompression of pelviocalyceal system on urography following one surgical repair. Of the 111 patients with open pyeloplasty, 95 (86%) patients underwent dismembered pyeloplasty. Examining the functional outcomes on the basis of split-function analysis from

preoperative and postoperative renal scans, O'Reilly (1989) found that open Anderson-Hynes dismembered pyeloplasty arrests functional deterioration in almost every case and improves function significantly in the majority in 26 consecutive patients with UPJ obstruction.

Flap Procedures

Foley Y-V-Plasty

Indications. **The Foley Y-V-plasty was originally designed for repair of a UPJ obstruction secondary to a high ureteral insertion.** Like other flap techniques, however, its use has generally been replaced by the more versatile dismembered pyeloplasty. Like other flap techniques, the Foley Y-V-plasty is specifically contraindicated when transposition of lower pole vessels is necessary. In situations requiring concomitant reduction of redundant renal pelvis, this technique is also of little value.

Technique. In Foley Y-V-plasty, the renal pelvis and proximal ureter are first exposed, and a widely based triangular or V-shaped flap is outlined with methylene blue or fine stay sutures. The base of the V is positioned on the dependent, medial aspect of the ipsilateral renal pelvis and the apex at the UPJ. The incision from the apex of the flap (the stem of the Y) will then be performed along the lateral aspect of the proximal ureter. The surgical incision in the ureter should be long enough to completely traverse the area of stenosis and extend for several millimeters into the normal-caliber ureter (Fig. 41–19A). The renal pelvic flap and ureterotomy are then created. A fine scalpel blade is used for the initial pelvic incision, after which a Potts or a fine Metzenbaum scissors is used to complete the flap and ureterotomy (Fig. 41–19B). An internal ureteral stent is now placed and the repair performed over it. First, the apex of the pelvic flap is approximated to the apex (inferior aspect) of the ureterotomy incision using fine absorbable suture. The posterior walls are then approximated using fine interrupted or running suture (Fig. 41–19C). Interrupted technique is likely to minimize pursing or buckling of the suture line, as well as local tissue ischemia. Anastomosis of the anterior walls is then performed, thereby completing the surgical repair (Fig. 41–19D).

Culp-DeWeerd Spiral Flap

Indications. **The Culp-DeWeerd spiral flap is generally best suited for large, readily accessible extrarenal pelves in which the ureteral insertion is already in a dependent, oblique position.** Although most of these patients are also good candidates for a standard or reduction dismembered pyeloplasty, the spiral flap may be of significant value when both UPJ obstruction and a relatively long segment of proximal ureteral narrowing or stricture occur in the same setting.

Technique. The spiral flap is first outlined with a broad base positioned obliquely on the dependent aspect of the renal pelvis. To maximize preservation of the flap blood supply, the base is placed in a position anatomically lateral to the UPJ, that is, between the ureteral insertion and the renal parenchyma. The pelvic flap itself may be spiraled posteriorly to anteriorly or vice versa. In either case, the anatomically medial line of incision (farthest from the parenchyma) is carried down the proximal ureter, completely traversing through the obstructed segment (Fig. 41–20A). Appropriate placement of the apex of the flap is determined by the length of flap needed. This, in turn, depends on the length of proximal ureter to be bridged. The longer the flap required, the farther away the apex will be from the base. However, to preserve vascular integrity of the flap, the ratio of flap length to width should not be greater than 3:1. In general, the outline of the flap should be made longer than what may initially be perceived as necessary because the flap will shrink once the pelvis is incised. If the flap is found to be too long, excess length can be reduced by trimming back the apex, thereby preserving its blood supply. Once the flap is created, the apex is rotated down to the most inferior aspect of the ureterotomy (Fig. 41–20B). The anastomosis with fine absorbable sutures is subsequently performed over an internal stent (Fig. 41–20C).

Scardino-Prince Vertical Flap

Indications. The Scardino-Prince vertical flap technique generally has limited clinical application. It may be appropriately used only when a dependent UPJ is situated at the medial margin of a large, square ("box-shaped") extrarenal pelvis (Fig. 41–21A). Its use in most instances has been replaced by a standard dismembered pyeloplasty, although the vertical flap may be preferable for relatively long areas of proximal ureteral narrowing. **It is important to note that the vertical flap technique generally cannot produce as long a flap as the spiral flap.**

Technique. The Scardino-Prince vertical flap is similar to the spiral flap technique except that the base of the flap is positioned

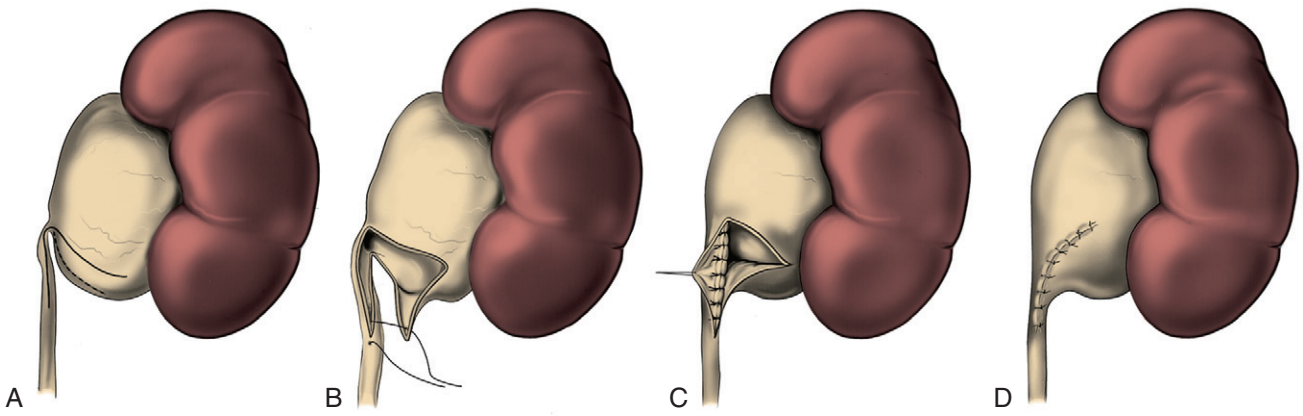


Figure 41–19. **A,** Foley Y-V-plasty is best applied to a ureteropelvic junction (UPJ) obstruction associated with a high insertion of the ureter. The flap is outlined with tissue marker or stay sutures. The base of the V is positioned on the dependent, medial aspect of the renal pelvis and the apex at the UPJ. The incision from the apex of the flap, which represents the stem of the Y, is then carried along the lateral aspect of the proximal ureter well into an area of normal caliber. **B,** The flap is developed with fine scissors. The apex of the pelvic flap is then brought to the most inferior aspect of the ureterotomy incision. **C,** The posterior walls are then approximated using interrupted or running fine absorbable suture. **D,** The anastomosis is completed with approximation of the anterior walls of the pelvic flap and ureterotomy.

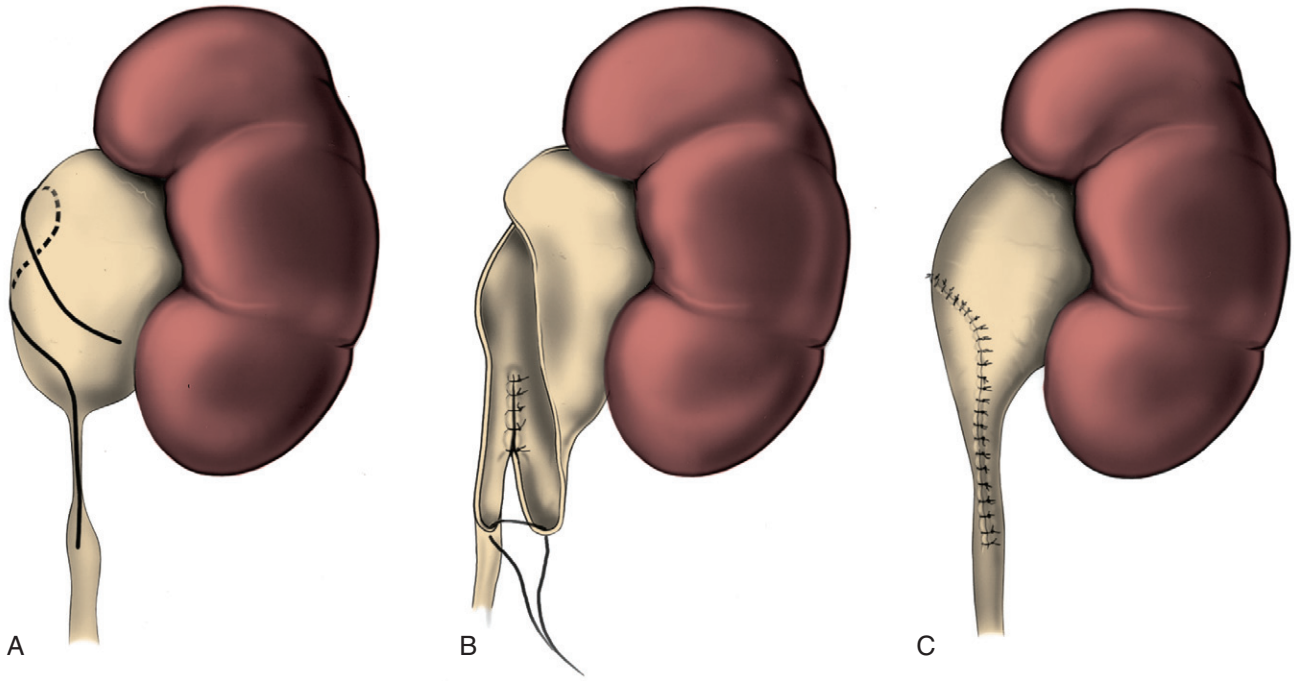


Figure 41–20. **A,** Spiral flap may be indicated for relatively long areas of proximal ureteral obstruction when the ureteropelvic junction (UPJ) is already in a dependent position. The spiral flap is outlined with the base situated obliquely on the dependent aspect of the renal pelvis. The base of the flap is positioned anatomically lateral to the UPJ, between the ureteral insertion and the renal parenchyma. The flap is spiraled posteriorly to anteriorly or vice versa. The anatomically medial line of incision is carried down completely through the obstructed proximal ureteral segment into normal-caliber ureter. The site of the apex for the flap is determined by the length of flap required to bridge the obstruction. The longer the segment of proximal ureteral obstruction, the farther away is the apex because this will make the flap longer. However, to preserve vascular integrity to the flap, the ratio of flap length-to-width should not exceed 3:1. **B,** Once the flap is developed, the apex is rotated down to the most inferior aspect of the ureterotomy. **C,** The anastomosis is then completed, usually over an internal stent, again using fine absorbable sutures.

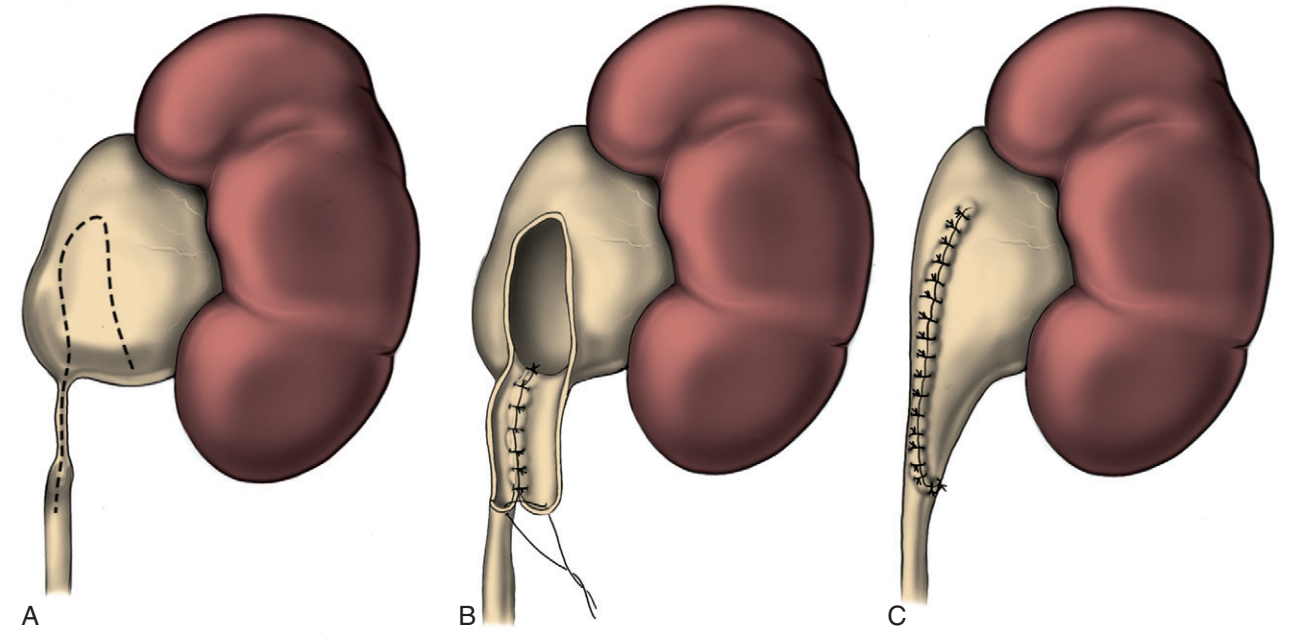


Figure 41–21. **A,** Vertical flap technique may be used when a dependent ureteropelvic junction (UPJ) is situated at the medial margin of a large, box-shaped extrarenal pelvis. In contrast to the spiral flap, the base of the vertical flap is situated more horizontally on the dependent aspect of the renal pelvis, between the UPJ and the renal parenchyma. The flap itself is formed by two straight incisions converging from the base vertically up to the apex on either the anterior or the posterior aspect of the renal pelvis. As for the spiral flap, the position of the apex determines the length of the flap, which should be a function of the length of proximal ureter to be bridged. The medial incision of the flap is carried down the proximal ureter completely through the strictured area into normal-caliber ureter. **B,** The apex of the flap is rotated down to the most inferior aspect of the ureterotomy. **C,** The flap is then closed by approximating the edges with interrupted or running fine absorbable sutures.

more horizontally on the dependent aspect of the renal pelvis, between the UPJ and the renal parenchyma. The flap itself is created by straight incisions converging from the base vertically to the apex on either the anterior or the posterior aspects of the renal pelvis. The site of the apex and the length of the flap are determined by the length of proximal ureter to be bridged. The medial incision is carried down the proximal ureter, completely traversing through the stenotic area and into normal-caliber ureter, using fine scissors (Fig. 41–21B). The apex of the flap is then rotated down and approximated to the most inferior aspect of the ureterotomy. Finally, the flap is closed with interrupted or running fine absorbable sutures (Fig. 41–21C).

Intubated Ureterotomy

Indications. The Davis intubated ureterotomy, which is rarely used today, was developed for surgical repair of lengthy or multiple ureteral strictures. If these strictures are found in association with UPJ obstruction, the intubated ureterotomy may be combined with any of the standard pyeloplasty procedures. However, in such situation, the intubated ureterotomy would be best combined with a spiral flap procedure. Compared with the vertical flap, the spiral flap can be made longer, which allows more of the strictured area to be bridged by a pelvic flap, thereby leaving a shorter area to rely on healing by "secondary intention." In fact, in this specific clinical setting, any flap technique would be preferable to a dismembered repair, at least in regard to blood supply preservation of and subsequent healing.

Technique. A flap is outlined as described previously, with the ureterotomy to be made completely through the long, strictured area (Fig. 41–22A). The flap is then created, with minimal dissection of the ureter in order to preserve its blood supply. Unlike the uncomplicated pyeloplasties, these cases require routine nephrostomy tube drainage to prevent postoperative urinoma formation. Nephrostomy drainage in these cases also allows access for subsequent antegrade radiographic studies during the postoperative period.

On the basis of the original description, the ureteral intubation is achieved with a stenting catheter that is placed across the stenotic area to the distal ureter or bladder. Proximally, it is brought out through the renal cortex alongside a nephrostomy tube. Currently, most urologists use a self-retaining, soft, inert, internal ureteral stent instead. The apex of the flap is brought over the stent as far down as possible on the ureterotomy, and the flap is closed with either interrupted or running absorbable suture (Fig. 41–22B). The distal aspect of the ureterotomy is then left open for secondary healing via ureteral regeneration (Fig. 41–22C).

An antegrade nephrostogram is usually obtained 6 weeks after the surgery. If there is no extravasation, the ureteral stent is removed cystoscopically and an antegrade radiographic study is repeated. When ureteral patency without extravasation is ensured with such study, the nephrostomy tube is clamped and subsequently removed.

Ureterocalycostomy

Indications. **Ureterocalycostomy may be used as a primary reconstructive procedure whenever a UPJ obstruction or proximal ureteral stricture is associated with a relatively small intrarenal pelvis** (Fig. 41–23A).

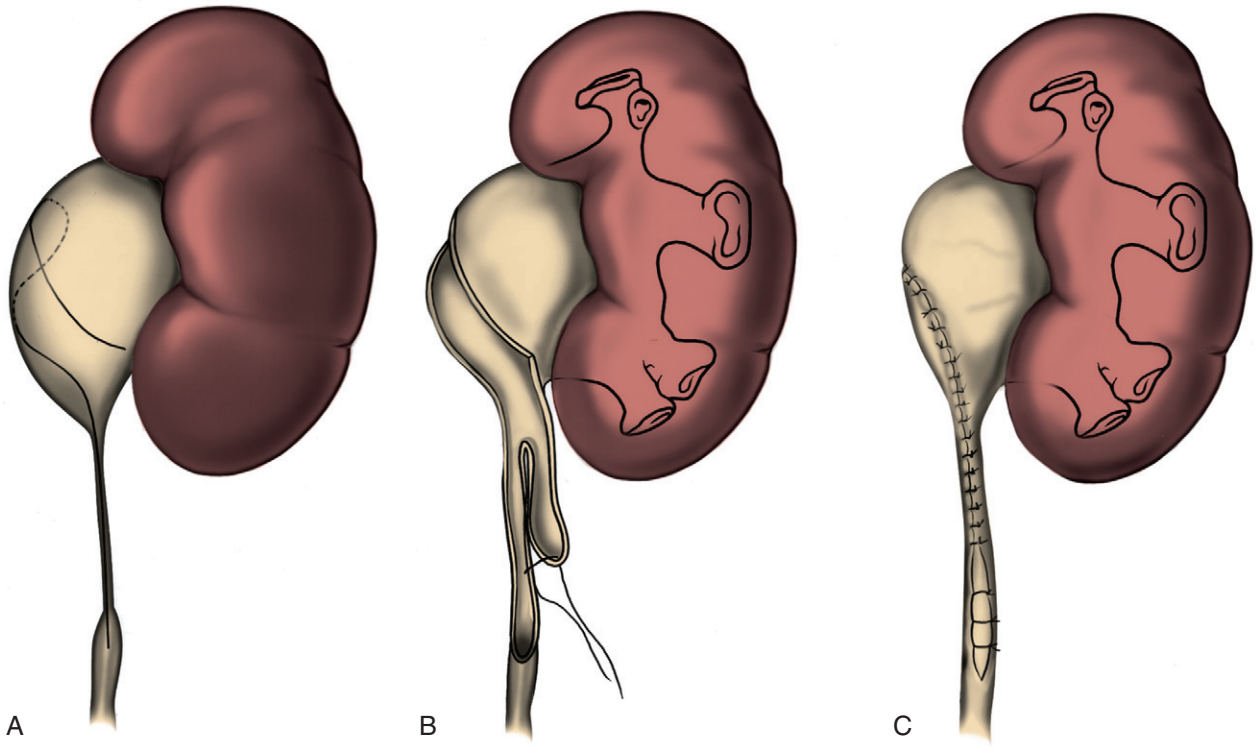


Figure 41–22. **A,** Intubated ureterotomy may be of value when a ureteropelvic junction obstruction is associated with extremely long or multiple ureteral strictures. A spiral flap is outlined and developed as described in Figure 41-20. The ureterotomy incision will be carried completely through the long strictured areas or through each of the multiple areas of stricture. **B,** The flap is developed, taking care to use minimal dissection of the ureter in order to preserve its blood supply. In contrast to uncomplicated repairs, nephrostomy tube drainage is used routinely. A self-retaining, soft, inert internal ureteral stent is then placed and positioned proximally in the renal pelvis or lower infundibulum and distally in the bladder. The apex of the flap is then brought as far down as possible over the stent on the ureterotomy, and the flap is closed with interrupted or running absorbable suture. **C,** The distal aspect of the ureterotomy is left open to heal secondarily by ureteral regeneration. A few fine absorbable sutures may be loosely placed to keep the sides of the ureter in apposition to the stent.

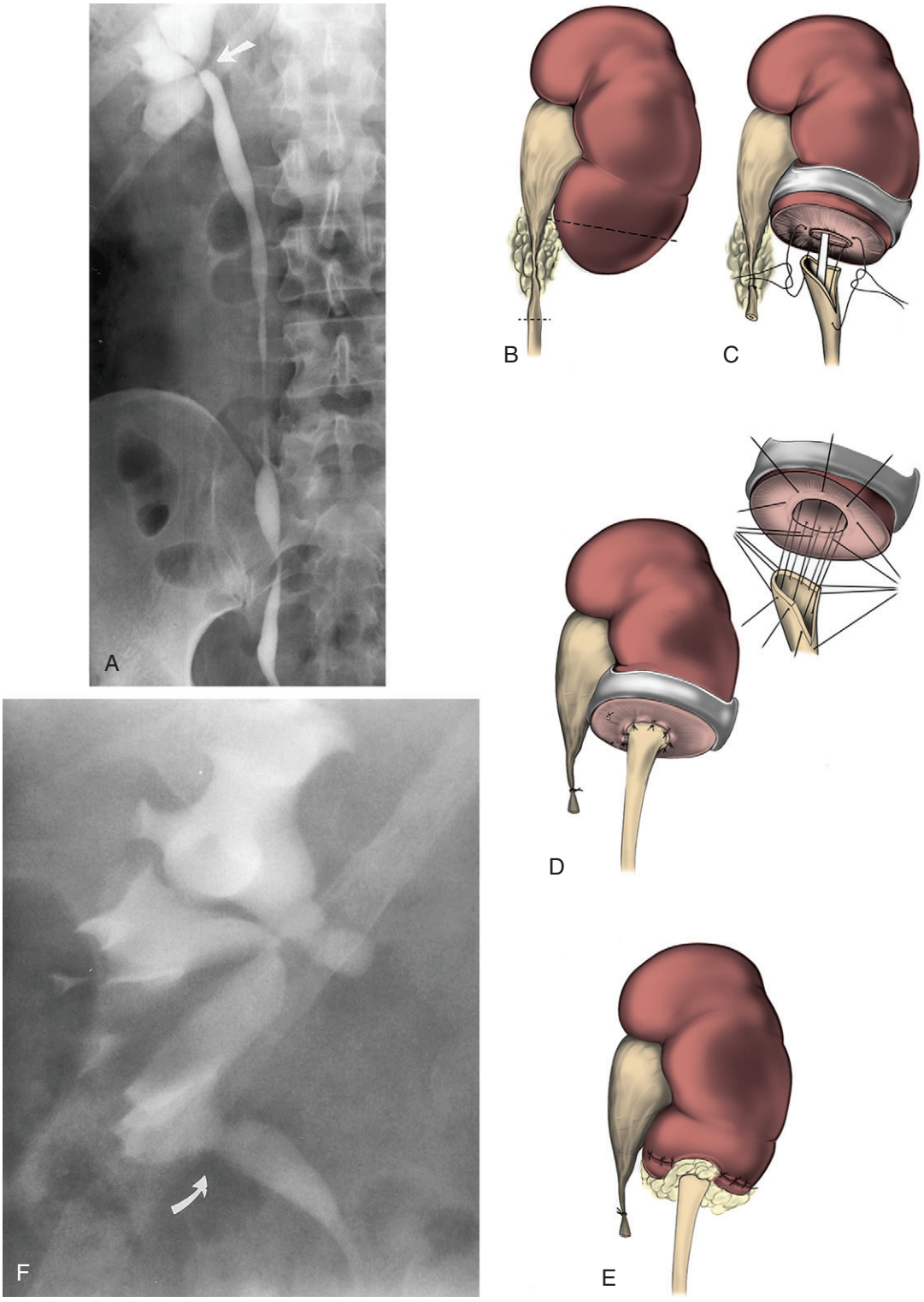


Figure 41–23. **A,** This patient complained of progressive right flank pain, and was found on this retrograde study to have a ureteropelvic junction obstruction *(arrow)* associated with a small intrarenal pelvis. This situation may be best managed with a ureterocalycostomy. **B,** The ureter is identified in the retroperitoneum and dissected proximally as far as possible. The kidney is mobilized as much as necessary to gain access to the lower pole and to subsequently perform the anastomosis without tension. A lower pole nephrectomy is performed, removing as much parenchyma as necessary to widely expose a dilated lower pole calyx. **C,** The proximal ureter is spatulated laterally. The anastomosis should subsequently be performed over an internal stent, and consideration should also be given to leaving a nephrostomy tube. The initial sutures are placed at the apex of the ureteral spatulation, and the lateral wall of the calyx with a second suture is placed 180 degrees from that. **D,** Anastomosis is then completed in an "open" fashion, placing each suture circumferentially (inset) but not securing them down until the anastomosis has been completed. **E,** Renal capsule is closed over the cut surface of the parenchyma whenever possible. However, the capsule should not be closed near the anastomosis itself because that may compromise the lumen by extrinsic compression. Instead, the anastomosis should be protected with a graft of perinephric fat or a peritoneal or omental flap. **F,** Intravenous urogram 2 months after right ureterocalycostomy reveals a widely patent ureterocalyceal anastomosis at the lower pole *(arrow)*.

When the UPJ is associated with rotational anomalies such as horseshoe kidney (Levitt et al, 1981), ureterocalycostomy may be useful to provide completely dependent drainage. **Furthermore, ureterocalycostomy is a well-accepted salvage technique for the failed pyeloplasty** (Ross et al, 1990).

Technique. The ureter is first identified in the retroperitoneum and dissected proximally with a generous amount of periureteral tissue. For secondary procedures, however, extensive scarring may preclude adequate identification and dissection of the renal pelvis itself (Fig. 41–23B). The kidney is then mobilized to gain access to the lower pole. An important technical point in ureterocalycostomy is that the parenchyma overlying the lower pole calyx must be resected rather than simply incised because a simple nephrotomy may lead to a secondary stricture (Couvelaire et al, 1964).

The proximal ureter is first spatulated laterally, and the ureterocalyceal anastomosis is completed over an internal stent. Leaving an indwelling nephrostomy tube should also be considered in these cases. The first suture is placed at the apex of the ureteral spatulation and lateral wall of the calyx, and the second suture is placed 180 degrees apart. The remainder of the anastomosis is then performed using an interrupted "open" suture technique. That is, each suture placed is left untied until the final one is in place (Fig. 41–23C). This method seems to provide a more accurate anastomosis under direct vision. When the full set of circumferential sutures has been placed, the sutures are secured down together (Fig. 41–23D). The renal capsule is closed over the cut surface of the parenchyma if possible. However, such closure should not be close enough to the anastomosis itself to cause extrinsic compression on the anastomosis. Instead, the anastomosis should be covered with perinephric fat or a peritoneal or omental flap (Fig. 41–23E). A follow-up urogram is generally obtained at 1 month following the ureteral stent extraction (Fig. 41–23F).

"Salvage" Procedures. Failed open pyeloplasty is a challenging problem that is usually best managed initially using an endourologic approach. In some cases, such approach may not be applicable. In these cases, successful reconstruction can at times be achieved using one of the flap or dismembered techniques already described. The secondary open operative reconstruction may be significantly aided by the placement of a ureteral catheter to aid intraoperative identification and dissection of the ureter and renal pelvis. In these situations, there is often a relatively long length of proximal ureteral stenosis to repair, and wide mobilization of the kidney and ureter is generally a necessity. This helps to bridge the area of stenosis and allows a tension-free secondary pyeloplasty.

Several other options are available for these secondary and often complex repairs. These surgical alternatives include those generally available for any extensive ureteral problem such as ileoureteral replacement and autotransplantation with a Boari flap pyelovesicostomy. For cases in which function of the involved kidney is already significantly compromised and the contralateral kidney is normal, nephrectomy can be considered.

Postoperative Care and Management of Complications. In general, external drains are removed 24 to 48 hours after cessation of urinary drainage, and internal ureteral stents, if placed, are removed on an outpatient basis approximately 4 to 6 weeks after the surgery. If a nephrostomy tube is used, a nephrostogram is obtained no sooner than 7 to 10 days postoperatively, or even later for particularly complicated repairs. If nephrostogram demonstrates a patent anastomosis without obstruction or extravasation, the tube is clamped for 12 to 24 hours and removed if there is no flank pain, fever, or leakage around the tube.

If urinary drainage persists after 7 to 10 days in cases without the use of internal ureteral stent or recurs after the removal of external drain, retrograde studies with an attempt to place an internal stent should be considered. This generally resolves the problem immediately, and the internal stent is removed 1 month later. If an attempt to place an internal stent is unsuccessful, a percutaneous nephrostomy should be placed. If drainage persists following nephrostomy tube placement, an internal or internal/external stent should be placed in an antegrade fashion. At times, despite the appropriate use of stents, drains, and nephrostomy tubes, urinary extravasation may result in urinoma formation, which is best managed with direct percutaneous drainage of the fluid collection, using ultrasound or CT guidance. Follow-up of the functional result is typically achieved with a urogram or renogram obtained approximately 4 weeks postoperatively or 4 weeks after removal of any stent or nephrostomy tube. Earlier studies are indicated if the patient develops symptoms.

Key Points: Open Operative Intervention

- Dismembered pyeloplasty can be applied to high ureteral insertion, redundant renal pelvis, and/or crossing vessels. It also allows excision of abnormal UPJ itself. It is the most versatile form of pyeloplasty. However, it is not well suited for lengthy or multiple proximal ureteral strictures or small, relatively inaccessible intrarenal pelvis.
- Flap procedures can be useful in situations involving relatively long segment of ureteral narrowing or stricture. Of the various flap procedures, a spiral flap can bridge a strictured or narrow area of longer length. The flap procedures are not appropriate in the setting of crossing vessels.
- Ureterocalycostomy may be used for UPJ obstruction or proximal ureteral stricture associated with a relatively small intrarenal pelvis. It may also be used as a salvage technique for the failed pyeloplasty.

RETROCAVAL URETER

Etiology and Diagnosis

Retrocaval ureter is a rare congenital urologic anomaly. It occurs as a consequence of the persistence of the posterior cardinal veins during embryologic development (Considine, 1966). Its presence should be suspected with the finding of a characteristic S-shaped deformity on intravenous or retrograde pyelography (Fig. 41–24A). Today, a definitive diagnosis can be made noninvasively using three-dimensional CT imaging (Fig. 41–24B) (Pienkny et al, 1999). Procedural intervention is indicated in the presence of functionally significant obstruction leading to pain or renal function deterioration.

Operative Intervention

Open Surgical Management

The standard repair of retrocaval ureter is open surgical pyelopyelostomy. In this procedure, the ureter, dilated renal pelvis, and inferior vena cava are identified and dissected using the standard open surgical techniques. The dilated renal pelvis is then transected, following which the ureter is transposed to its

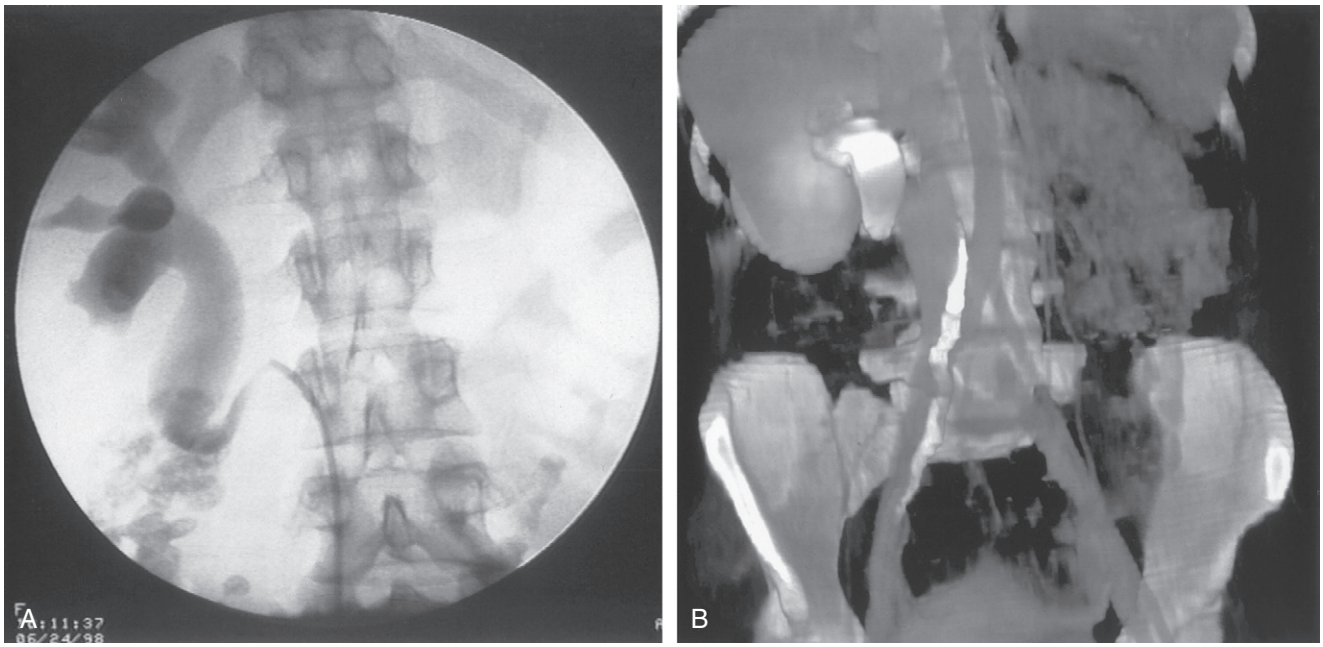


Figure 41–24. **A,** Retrograde pyelography in a patient with right-sided hydronephrosis. This study reveals a typical S-shaped deformity secondary to the ureter coursing laterally to medially posterior to the inferior vena cava. **B,** Three-dimensional spiral CT demonstrates the presence of a retrocaval ureter.

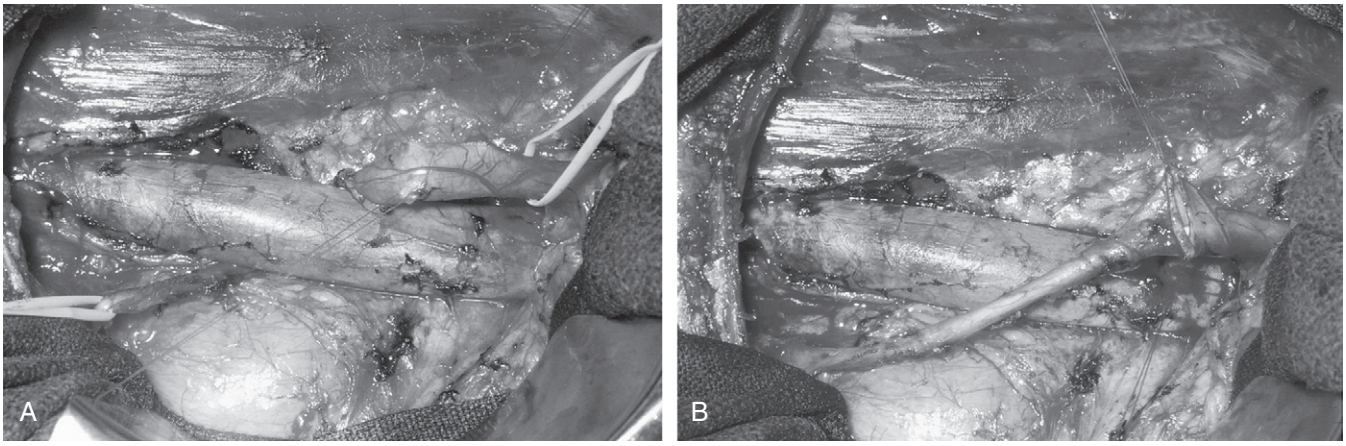


Figure 41–25. **A,** Intraoperative photograph of a patient with retrocaval ureter undergoing surgical repair via a retroperitoneal flank approach. Right side of the photo represents the cephalad direction. Note the dilated proximal right ureter passing behind the inferior vena cava. **B,** Right ureteropelvic anastomosis has been completed, following transection of the right renal pelvis and transposition of the ureter anterior to the inferior vena cava.

normal anatomic position anterior to the vena cava (Fig. 41–25). Pyelopyelostomy is then performed circumferentially with absorbable sutures in a tension-free, water-tight manner. Surgical drain and internal ureteral stent are typically used.

Laparoscopic Surgical Management

Retrocaval ureter has been managed successfully with the laparoscopic approach in the clinical setting as shown by a series of sporadic case reports in recent years (Baba et al, 1994; Matsuda et al, 1996; Polascik et al, 1998; Salomon et al, 1999; Gupta et al, 2001; Ramalingam et al, 2003). Either a transperitoneal or a retroperitoneal approach may be used laparoscopically. A double-J ureteral stent is first placed into the ipsilateral ureter cystoscopically. Following transperitoneal or retroperitoneal laparoscopic access, the ipsilateral ureter is identified and mobilized off the inferior vena cava. The ureter is then divided at the most distal segment of the dilated ureter. Redundant segment of dilated proximal ureter and stenotic segment of ureter are excised if present. The ureteral ends are positioned anterolateral to the vena cava, spatulated for 1.5 to 2 cm on opposite ends, and then anastomosed with absorbable sutures using intracorporeal suturing techniques over the stent. Tension-free, water-tight anastomosis is the objective. A surgical drain is then left in place before formal laparoscopic exit. The surgical drain is typically removed within a few days postoperatively, and the ureteral stent is typically removed 4 to 6 weeks postoperatively.

More recently, retrocaval ureter has been managed successfully with the robotic-assisted laparoscopic approach (Muffarrij et al, 2007; Hemal et al, 2008; Smith et al, 2009). A transperitoneal approach providing a large working space is typically used. The general principles of laparscopic ureteral dissection, division, transposition, and anastomosis are identical to those described in

conventional laparoscopic approach. At least four different ports are involved, including three for the robot and one for the surgical assistant providing suction, irrigation, suture introduction, and retraction.

The overall clinical results of the laparoscopic repair with or without the use of robots in the literature have been favorable, providing minimal postoperative patient morbidity, short convalescence, and anastomotic patency on short-term radiographic follow-up.

Key Points: Retrocaval Ureter

- Retrocaval ureter results from the persistence of the posterior cardinal veins.
- Retrocaval ureter can be diagnosed using intravenous or retrograde pyelography or 3-D CT.
- Procedural intervention is indicated in the presence of functionally significant obstruction, and both open and laparoscopic approaches can be successfully applied.

URETERAL STRICTURE DISEASE

Etiology

Common etiologies of ureteral stricture formation include ischemia, surgical and nonsurgical trauma, periureteral fibrosis, malignancy, or congenital (Table 41–1). **Proper evaluation and treatment of a ureteral stricture is essential to preserve renal function and rule out the presence of malignancy.** Although the classic radiographic presentation of a transitional cell carcinoma of the ureter is a radiolucent filling defect within the lumen with the characteristic goblet sign, it may appear as a benign stricture. In addition, metastatic tumors such as cervical, prostate, ovarian, breast, and colon cancer may appear as a ureteral stricture (Lau et al, 1998). Although the incidence of ureteral strictures in the general population is unknown, it is clear that the **presence of ureteral calculi and associated treatment of stones are risk factors.** Roberts and colleagues (1998) evaluated 21 patients with impacted ureteral stones and found that impaction for more than 2 months' duration was associated with a 24% incidence of stricture formation. Any ureteral instrumentation can lead to the development of a ureteral stricture. As advances in ureteroscopic technology have provided smaller, more flexible instruments with better optics, these endoscopic procedures have become less traumatic and are now associated with a long-term complication rate of less than 1% (Harmon et al, 1997). Other causes of benign ureteral strictures include radiation; abdominal aortic aneurysm; infections such as tuberculosis and schistosomiasis; endometriosis; and trauma including iatrogenic injury from previous abdominal or pelvic surgery or post–renal ablation injury (El Abd et al, 1996; Lacquet et al, 1997; Ramanathan et al, 1998; Oh et al, 2000; Johnson et al, 2004). Patients with presumed idiopathic ureteral strictures should be evaluated using CT scan to rule out the presence of an intrinsic ureteral malignancy or a lesion causing extrinsic compression.

Table 41–1.

Etiology of Ureteral Stricture

Malignancy (e.g., transitional cell carcinoma, cervical)
Ureteral calculus
Radiation
Ischemia/trauma due to surgical dissection
Periureteral fibrosis due to abdominal aortic aneurysm or endometriosis
Endoscopic instrumentation
Renal ablation injury
Infection (tuberculosis)
Idiopathic

Diagnostic Studies and Indications for Intervention

An intravenous pyelogram, retrograde pyelogram, or diagnostic ureteroscopy can define the location and length of the ureteral stricture reliably. CT can also delineate ureteral stricture disease, and CT urography can be used to help delineate the anatomy. Subsequent ureteroscopy with biopsy or barbotage should be performed in any patient for whom the etiology of the stricture is not certain. Diuretic renography will provide differential renal function and evaluate the renal unit for functional obstruction. **It is critical to assess the renal unit for function before starting treatment because endourologic therapies generally require 25% function of the ipsilateral moiety to have reasonable success rates** (Wolf et al, 1997). Once a ureteral stricture is diagnosed, indications for intervention include the need to rule out malignancy, compromised renal function, recurrent pyelonephritis, and pain associated with functional obstruction.

Endourologic Options for Intervention

Ureteral Stent Placement

Ureteral stent placement is effective acutely in treating most ureteral strictures, in particular intrinsic ureteral strictures. Wenzler and colleagues reported good success rates in treating intrinsic ureteral obstruction, with 88% success rates at 26 months (Wenzler et al, 2008). Although intrinsic ureteral strictures can be managed with endoscopic options, cases of extrinsic ureteral compression are better suited to percutaneous drainage or surgical management. In cases in which the patient is not a candidate for definitive repair, or has a poor prognosis, chronic stent placement with periodic stent changes may be considered. **The use of chronic stent placement must be guarded, particularly when treating ureteral obstruction from extrinsic compression because in many cases, adequate drainage is short-lived** (Chung et al, 2004; Docimo et al, 1989). Some urologists have placed two stents to maintain ureteral patency in cases in which a single stent did not provide adequate drainage (Yohannes et al, 2001). Recently Rosevear and colleagues (2007) reported 84% success rates in their series at 16 months using ureteral stents with 68% of the cases being for malignancy. The remainder included patients with retroperitoneal fibrosis and other benign extrinsic diseases. In 2006 Borin and colleagues reported the initial experience with a full-length metal stent for malignant, extrinsic ureteral obstruction (Borin, 2006). Liatsikos reported on 50 patients treated with the full metallic stent, and although concerns arose regarding stent exchange and encrustation, overall the study supported use of the stent at 12-month intervals (Liatsikos et al, 2010).

Retrograde Balloon Dilation

Retrograde dilatation of ureteral strictures has historically been part of the urologic armamentarium. The technique was rarely definitive and usually required repeated dilatations on a regular basis. In the early 1980s angiographic and vascular balloons were introduced into urologic practice, and the technique of balloon dilatation with temporary internal stenting became an accepted mode of treatment (Banner et al, 1983; Finnerty et al, 1984).

As for any patient with a ureteral stricture, the indications to intervene include functionally significant obstruction. Contraindications to this approach include active infection or a stricture longer than 2 cm because dilatation alone will rarely be successful in this setting. Moreover, any endoscopic technique is likely to fail with strictures greater than 2 cm (Fig. 41–26A-D).

A retrograde approach is indicated whenever access across the strictured area is easily accomplished using transurethral techniques. The procedure generally begins with a retrograde pyelogram performed under fluoroscopic control to precisely delineate the site and length of stricture. A floppy-tipped guidewire is passed in a retrograde fashion across the strictured area and coiled proximally in the pyelocalyceal system. This is most easily accomplished by passing an open-end catheter up to the level of the stricture to use as a guide for the hydrophilic or floppy-tipped wire. Passage of the open-end catheter through the strictured area over the wire will then aid subsequent passage of a balloon catheter. Techniques for bypassing difficult areas of obstruction have been described in detail (Mata et al, 1994).

At this point, the open-end catheter is withdrawn and replaced with a high-pressure, 4-cm-long, 5- to 8-mm balloon. Under fluoroscopic control, the balloon catheter is positioned across the strictured area with proper position ensured by visualization of radiopaque markers at the tips of the balloon. Balloon inflation is then begun, and a waist will be visualized at the strictured area, which will disappear with progressive balloon inflation (Fig. 41–27). After 10 minutes of tamponade, the balloon is deflated and withdrawn. A guidewire is still in place, and this is used to pass an internal stent, which is left indwelling for 2 to 4 weeks. Follow-up diuretic renography is generally performed approximately 1 month after stent extraction and at 6- to 12-month intervals thereafter.

Occasionally, access across the involved area cannot be obtained using fluoroscopic control alone. In such cases direct ureteroscopic

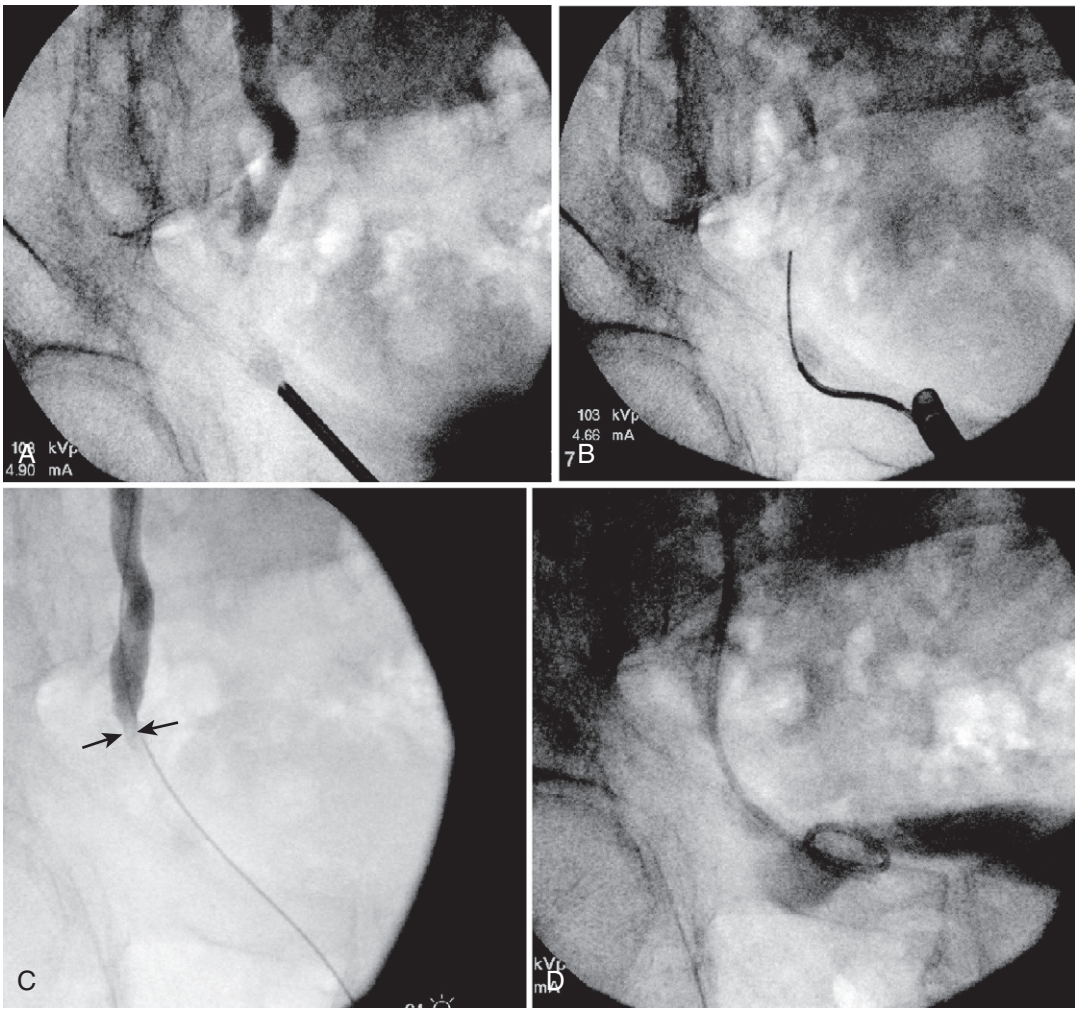


Figure 41–26. **A,** Antegrade and retrograde contrast demonstrating a distal ureteral stricture following prior traumatic ureteroscopic stone procedure. **B,** Image demonstrating complex guidewire access across this long and narrow stricture with retained proximal stones. **C,** The stricture is greater than 2 cm, and minimal contrast would pass through antegrade. **D,** Image following ureteral stent placement. This patient required ureteral reimplantation and stone removal.

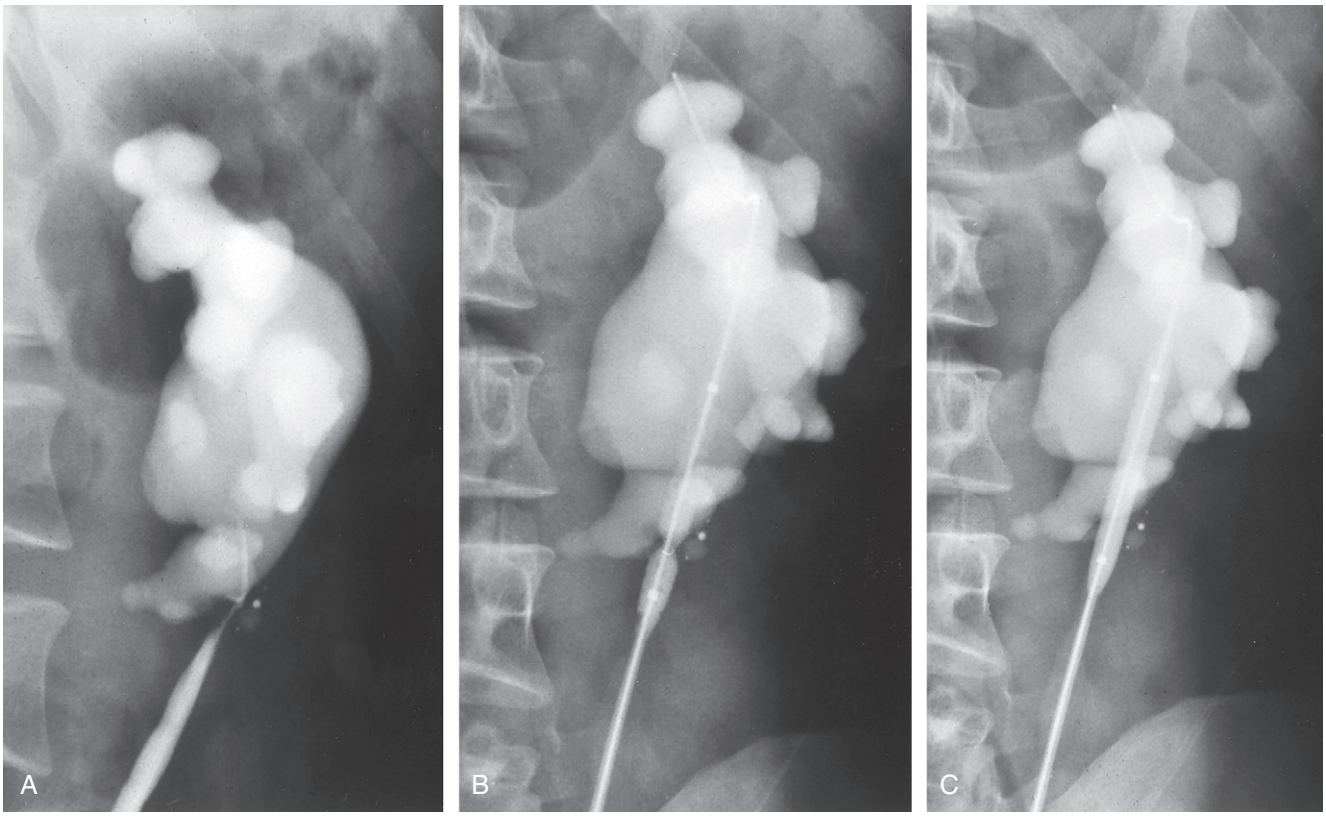


Figure 41–27. **A,** Retrograde study confirms a short stricture at the level of the ureteropelvic junction in this patient with a horseshoe kidney referred after failed ureteroscopic management of a ureteral calculus impacted at that level. **B,** The stricture has been traversed with a guidewire, over which a high-pressure balloon has been passed. A waist is evident at the level of the stricture during initial balloon inflation. **C,** Balloon inflation and stricture dilatation are complete with disappearance of the waist.

visualization can aid initial passage of the guidewire, and the procedure can be continued as described. Alternatively, a low-profile balloon can be passed through the ureteroscope and the stricture dilated under direct vision.

Antegrade Balloon Dilation

At times, retrograde access across a strictured area is impossible. In such cases, access can be obtained using an antegrade approach and fluoroscopic control (Mitty et al, 1983; Banner and Pollack, 1984), with or without direct antegrade ureteroscopic visualization (De Jonge et al, 1986). **Percutaneous nephrostomy drainage is established, and, in cases associated with infection or compromised renal function, percutaneous drainage alone is instituted to allow resolution of infection and return to baseline renal function.** Once that is accomplished, the percutaneous tract is used for access for a fluoroscopically or ureteroscopically guided approach. The procedure is then analogous to a retrograde approach. Under fluoroscopic guidance, an antegrade contrast agent study is used to definitively define the site and length of the stricture. A floppy-tipped guidewire or glidewire is passed antegrade across the level of obstruction, following which a balloon catheter is passed, and the balloon progressively inflated until the waist disappears. The balloon catheter is withdrawn over a wire and replaced with an internal stent, and a nephrostomy tube is also left indwelling. A follow-up nephrostogram is obtained within 24 to 48 hours to ensure proper positioning of a functional internal stent, and, at that time, the nephrostomy tube can be removed. Alternatively, access can be maintained by the use of an internal/external stent, which can be capped to allow internal drainage.

Results

Initial reports of retrograde and antegrade balloon dilatation of ureteral strictures suggested that results were better when the stricture was anastomotic and of relatively short duration and length (King et al, 1984b; Chang et al, 1987; Netto et al, 1990). Goldfischer and Gerber (1997) **reviewed the literature in regard to results of balloon dilatation of ureteral strictures and found reported success rates ranging from 50% to 76%. In that review, the best results were obtained in patients with iatrogenic, nonanastomotic strictures such as those following ureteroscopic instrumentation. In that setting, a success rate of 85% was achieved compared with a rate of 50% for anastomotic strictures.** Alternatively, Ravery and colleagues found a 40% success rate using retrograde balloon dilation in treating inflammatory ureteral strictures at 16 months' follow-up (Ravery et al, 1998). Richter and colleagues (2000) reviewed their results with balloon dilatation in 114 patients with a minimum 2-year follow-up. As in other series, balloon dilatation was more successful for patients with relatively short strictures. In addition, these authors noted the significance of an intact vascular supply on the success of this procedure. One series of transplant ureteral strictures demonstrated 79% success at 29 months using percutaneous balloon dilation in 14 transplant patients. Notably, these are short, anastomotic strictures in patients on immunosuppression (Voegeli et al, 1988). For longer ureteral strictures and those associated with compromised vascular supply, an incisional approach (endoureterotomy) was recommended as a more successful endourologic alternative to balloon dilatation. Of note, in experimental models, balloon dilation created

longitudinal incisions similar to endoureterotomy, possibly explaining some of the success seen using balloon dilation in ureteral strictures (Nakada et al, 1996).

Endoureterotomy

Endoluminal ureteral incision is a logical extension of balloon dilatation for "minimally invasive" management of ureteral strictures. As for balloon dilatation, access to and across the strictured area can be obtained in a retrograde or antegrade fashion, although a retrograde approach is preferable whenever possible because it is less invasive. The procedure is performed under direct vision using ureteroscopic control, or it can be guided fluoroscopically using the hot wire cutting balloon catheter. Generally, radiographic follow-up using diuretic renography is recommended for up to 3 years to detect most late failures (Wolf et al, 1997).

Retrograde Ureteroscopic Approach. A retrograde study is performed under fluoroscopic control at the outset of the procedure. Whenever possible, a floppy-tipped guidewire or hydrophilic glidewire is passed across the level of obstruction, as outlined earlier. If a wire cannot be passed across the strictured area using fluoroscopic control alone, the flexible ureteroscope is passed to the level of obstruction and the guidewire advanced through the ureteroscope across the involved area under direct vision. The ureteroscope is then withdrawn, but a safety wire is always left in place across the stricture. The ureteroscope is then reintroduced and passed alongside the guidewire to the level of obstruction.

The position for the endoureterotomy incision is chosen as a function of the level of the ureter involved. In general, lower ureteral strictures are incised in an anteromedial direction, taking care to stay away from the iliac vessels. In contrast, upper ureteral strictures are incised laterally or posterolaterally, again away from the great vessels (Meretyk et al, 1992) (Fig. 41–28).

The ureterotomy incision itself can be performed using a cold knife (Schneider et al, 1991; Yamada et al, 1995), a cutting electrode (Conlin et al, 1996), or a holmium laser (Fig. 41–29). Today, the availability of small-caliber laser fibers and actively deflecting flexible ureteroscopes make the holmium laser a common approach to endoscopic incision. In all cases, the incision is made from the ureteral lumen out to periureteral fat in a full-thickness fashion. Proximally and distally, the endoureterotomy should encompass 2 to 3 mm of normal ureteral tissue. In certain instances, the stricture must be balloon dilated to gain access across the stricture. Similarly, the strictures may be balloon dilated after endoincision, to enlarge the incision. Once the endoureterotomy incision is complete, the remaining guidewire is used to pass an internal stent. In general, the larger-diameter stents should be considered because larger stents (12-Fr) have been associated with improved results in some series (Hwang et al, 1996; Wolf et al, 1997). Similarly, Wolf and colleagues (1997) found benefit in the injection of triamcinolone ureteroscopically following endoureterotomy. Steroids and other biologic response modifiers may have a role in the future in managing select strictures.

Results. The success of holmium laser endoureterotomy ranges from 66% to 83% in series of greater than 10 patients with greater than 12 months' follow-up (Lane et al, 2006; Hibi et al, 2007; Gdor et al, 2008a). There is early evidence that strictures related to stone impaction and prior stone treatment may have lower success rates (56% in one series) than typical benign strictures (Gdor et al, 2008b). Of note, as the use of ureteroscopy and laser lithotripsy continues to grow, more strictures involving impacted stones may be encountered, and this may become a growing clinical problem. Gdor and colleagues also reported 67% success in treating transplant ureteral strictures using the holmium laser at 58 months' follow-up (Gdor et al, 2008a). **At this time the current available reports and the familiarity of ureteroscopy, coupled with relative availability of the holmium laser, make retrograde laser endoureterotomy an attractive initial management strategy for short ureteral strictures.**

Cautery Wire Balloon Incision. Cautery wire balloon incision has been used for ureteral strictures in the same manner as it has for UPJ obstruction. The procedure requires safety wire access across the strictured area and is performed under fluoroscopic control.

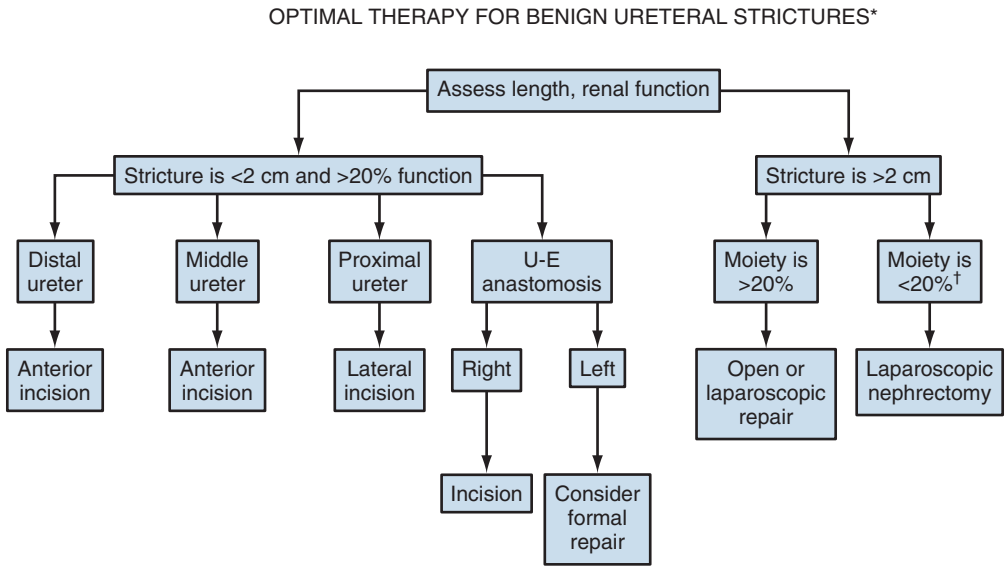


Figure 41–28. Algorithm for management of benign ureteral and ureteroenteric stricture disease.

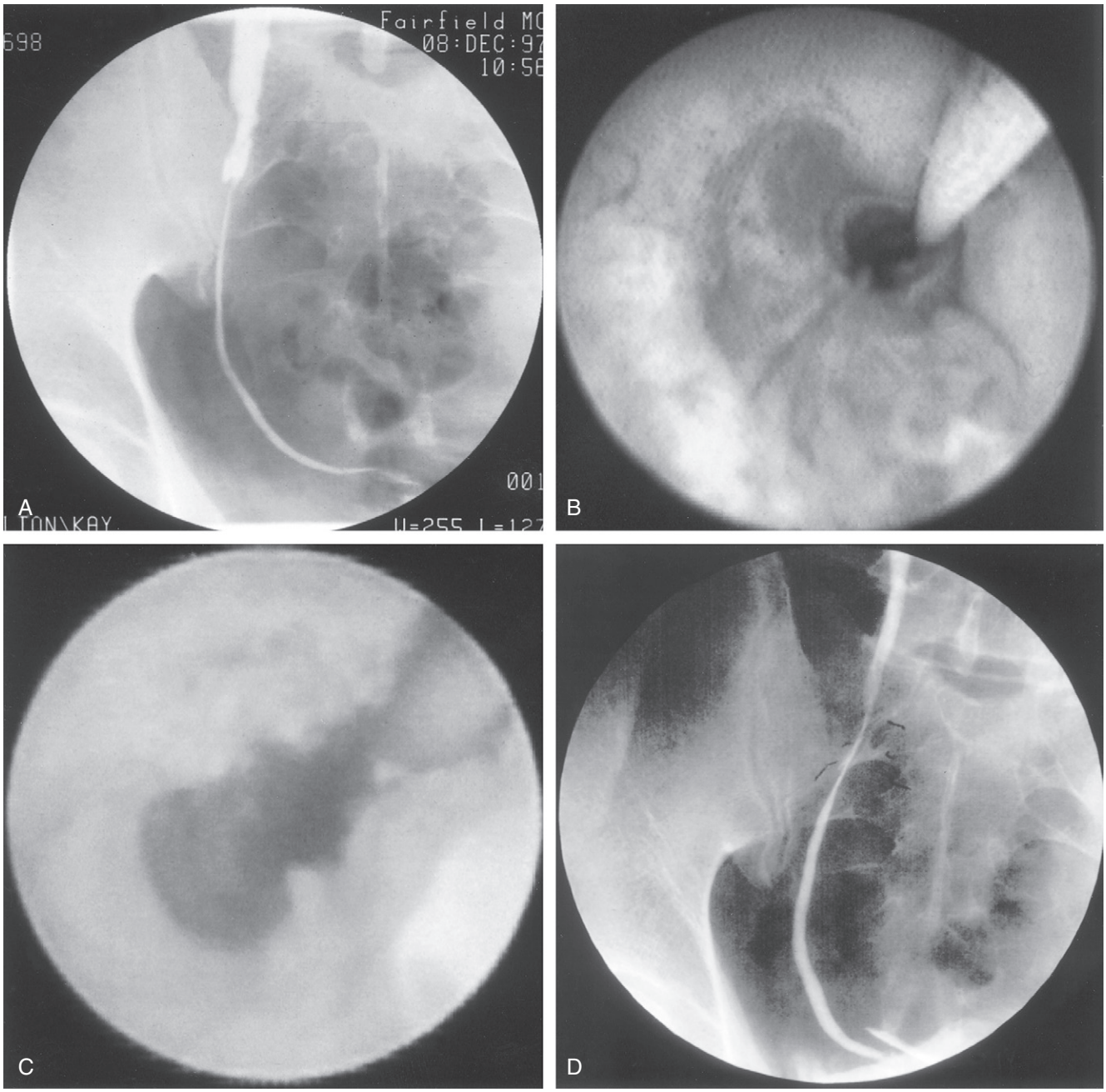


Figure 41–29. **A,** Antegrade study confirms hydronephrosis at the level of the iliac ureter in this patient referred for management after a complicated open ureterolithotomy. **B,** Ureteroscopic view confirms a tight ureteral stricture. **C,** Ureteral lumen is widely patent after holmium laser endoureterotomy. **D,** Follow-up ureterogram confirms resolution of the stricture.

The cautery wire balloon is passed in a retrograde or antegrade fashion and positioned across the stricture using radiopaque markers. In the proximal ureter, the incision should be posterolateral, whereas in the distal ureter, an anteromedial incision is used. **Fluoroscopically guided cautery wire balloon incision should not be used in close proximity to the great vessels such as at the iliac level of the ureter.** As for any form of endourologic management, success using this technique is dependent on the length and vascularity of the involved segment (Chandhoke et al, 1993b; Cohen et al, 1996; Wolf et al, 1997).

Antegrade Approach. When direct visual ureteroscopic access to the strictured area cannot be accomplished in a retrograde fashion, an antegrade approach may be used. Nephrostomy tube drainage is instituted, and any associated infection or compromised renal function is allowed to resolve before definitive incision. The percutaneous tract is dilated to a size large enough to allow a working sheath through which a flexible ureteroscope is passed. The procedure is then performed in a fashion analogous to a retrograde approach. A safety wire should be in place at all times alongside the ureteroscope, across the obstructed area and coiled distally in the bladder.

Combined Retrograde/Antegrade Approach. Rarely, a ureteral stricture is associated with an area of complete ureteral obliteration across which a wire cannot be passed to allow subsequent balloon dilatation or ureteroscopic endoureterotomy. In such cases a combined retrograde/antegrade approach has been

described (Cardella et al, 1985; Conlin et al, 1996; Beaghler et al, 1997; Knowles et al, 2001). The obstructed area is defined radiographically with a simultaneous antegrade and retrograde pyelogram. Ureteroscopes are passed simultaneously in both a retrograde and an antegrade manner, and the two opposing ureteral ends are localized under fluoroscopic guidance. A working guidewire is then passed from one end of the ureter, through and through to the other lumen, using a combination of fluoroscopic and direct visual control. For completely obliterated ureteral segments, this is most easily accomplished using the stiff end of a guidewire passed through a semirigid ureteroscope via the retrograde approach, although when a semirigid ureteroscope cannot be placed, a flexible ureteroscope or even an open-end ureteral catheter can be used to stabilize the wire from above or below. A "cut to the light" technique can be helpful in this setting. The ureteral segments are aligned as closely as possible under endoscopic and fluoroscopic guidance, and the light source to one of the ureteroscopes is turned off. The light from the opposite ureteroscope is then used to aid incisional restoration of urinary continuity. The strictured area is then recannulated using the stiff end of a guidewire, a small electrocautery electrode, or holmium laser. Once through-and-through control is obtained with a guidewire, a stent is passed and left in place for 8 to 10 weeks. As with other endourologic approaches to ureteral strictures, success rates are inversely related to the length of the strictured area. **Although success rates may be uncertain, internalization of urinary flow, even when dependent on long-term stent placement, can be a quality-of-life advantage for certain high-risk patients.** Knowles and colleagues reported a 90% patency rate in 10 patients treating obliterated distal ureteral segments using cautery wire balloon incision at 36 months' follow-up, 3 of whom required the combined approach (Knowles et al, 2001).

Key Points: Endourologic Management of Ureteral Strictures

- Proper evaluation and treatment of a ureteral stricture is essential to preserve renal function and rule out the presence of malignancy. It is critical to assess the renal unit for function before starting treatment because endourologic therapies generally require 25% function of the ipsilateral moiety to have reasonable success rates.
- The use of chronic stent placement for ureteral obstruction must be guarded, particularly when treating ureteral obstruction from malignant extrinsic compression because the drainage is often time limited.
- As for any patient with a ureteral stricture, the indications to intervene include functionally significant obstruction. Contraindications to this approach include active infection or a stricture longer than 2 cm.
- Current available reports and the familiarity of ureteroscopy, coupled with relative availability of the holmium laser, make retrograde laser endoureterotomy an attractive initial management strategy for short ureteral strictures.
- The position for the endoureterotomy incision is chosen as a function of the level of the ureter involved. In general, lower ureteral strictures are incised in an anteromedial direction, taking care to stay away from the iliac vessels. In contrast, upper ureteral strictures are incised laterally or posterolaterally, again away from the great vessels.

Table 41–2.

Bridging Various Ureteral Defect Lengths with Different Reconstructive Surgical Techniques

TECHNIQUE	URETERAL DEFECT LENGTH (cm)
Ureteroureterostomy	2-3
Ureteroneocystostomy	4-5
Psoas hitch	6-10
Boari flap	12-15
Renal descensus	5-8

Surgical Repair

Before any surgical repair, it is essential to conduct careful evaluation of the nature, location, and length of the ureteral stricture. Preoperative assessment typically includes an intravenous pyelogram (or antegrade nephrostogram) and a retrograde pyelogram if indicated. Other studies such as a nuclear medicine renogram to assess renal function and ureteroscopy, ureteral barbotage, or brushing to rule out carcinoma should be individualized. On the basis of such information, the appropriate surgical procedure can then be planned for the patient (Table 41–2).

Open Ureteroureterostomy

A short defect involving the upper ureter or midureter, either in the form of stricture or as a consequence of recent injury, is most appropriate for ureteroureterostomy. On the other hand, a lower ureteral stricture is usually best managed by ureteroneocystostomy with or without a psoas hitch or Boari flap. In the transplant setting, a donor ureteral stricture may be managed by a ureteroureterostomy to a healthy, native ureter. Because tension on the anastomosis almost always leads to stricture formation, only short defects should be managed by end-to-end ureteroureterostomy. Determination of whether or not enough ureteral mobility can be achieved to allow tension-free ureteroureterostomy usually cannot be made until the time of surgery.

The choice of surgical incision depends on the level of the ureteral stricture. A flank incision is appropriate for the upper ureter. A Gibson or a lower midline incision is suitable for the middle and lower ureter. If the patient has sustained an iatrogenic ureteral injury from a previous surgery performed through a Pfannenstiel incision, the same incision may be used for the ureteral reconstruction. In such situation, proximal ureteral dissection may be difficult through the Pfannenstiel incision, requiring cephalad extension of the lateral portion of the incision in a "hockey stick" fashion. Extraperitoneal dissection is usually performed except in cases of transperitoneal surgical ureteral injury.

Following surgical incision, the retroperitoneal space is developed as the peritoneum is mobilized and retracted medially. Frequently, the ureter can be easily identified as it crosses the iliac vessels. A Penrose drain or vessel loop may be placed around the ureter to assist its atraumatic handling. Direct handling of the ureter with forceps should be minimized. Care should be taken to preserve its adventitia, which loosely attaches the blood supply to the ureter.

During ureteral dissection and mobilization, enough mobility must be achieved to avoid tension after the excision of the diseased ureter. With a gunshot injury, devitalized tissue and an adjacent segment of normal-appearing ureter should be excised to eliminate late ischemia and stricture formation from the blast effect. Once both ends of the ureter have been adequately trimmed

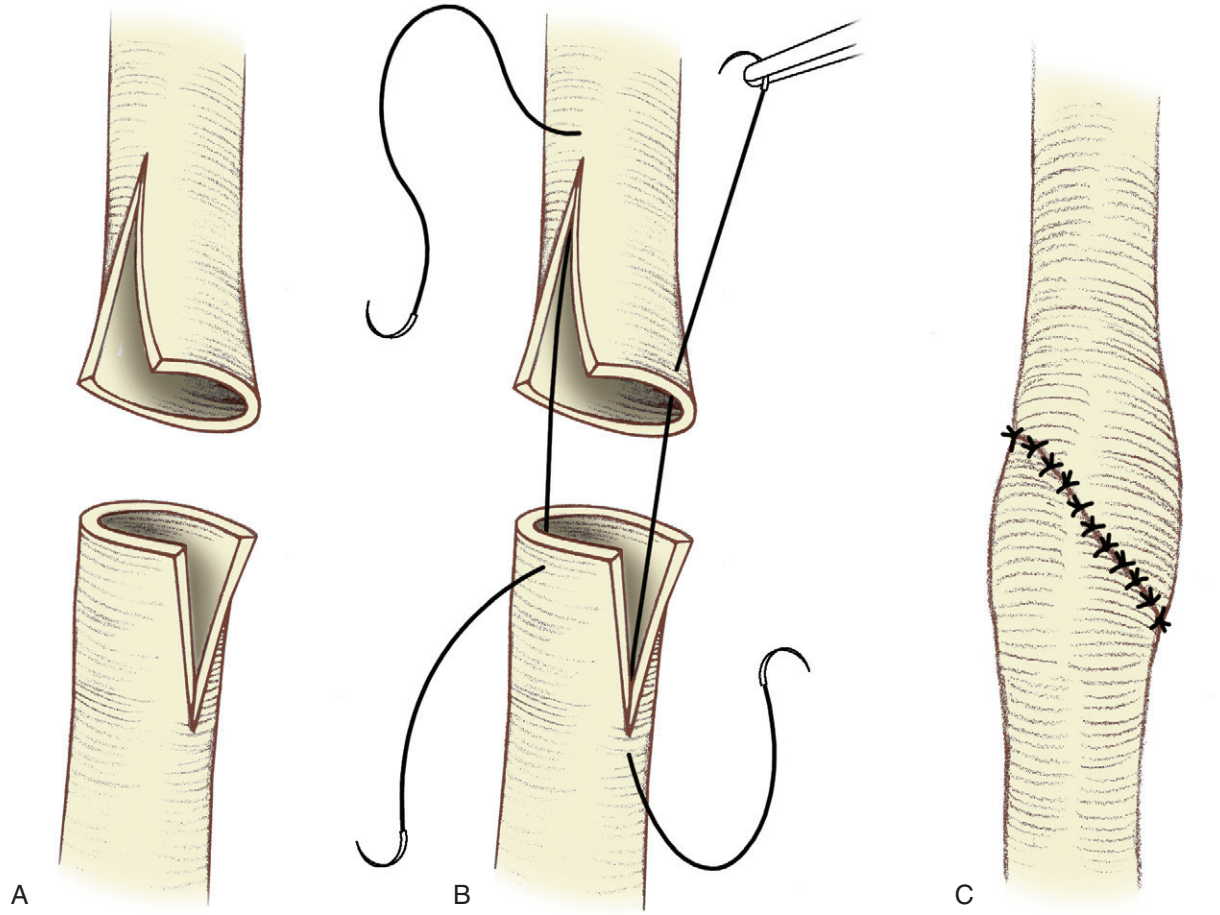


Figure 41–30. **A,** Spatulated ureteral ends. **B,** Placement of sutures. **C,** End-to-end ureteroureterostomy.

to healthy areas, mobilized, and correctly oriented, they are spatulated for approximately 5 to 6 mm. Spatulation is performed for both ureteral segments at 180 degrees apart. If a grossly dilated ureter is involved, it may be transected obliquely and not spatulated in order to match the circumference of the nondilated segment. A fine, absorbable suture is placed in the corner of one ureteral segment and the apex of the other, and the two ends of the suture are tied outside the ureteral lumen. The opposite corner and apex are similarly sutured and approximated. The anastomosis may then be completed by running these two sutures continuously and tying them to each other or in an interrupted fashion (Fig. 41–30). A double-J ureteral stent should be placed before completion of the anastomotic closure. Observation of reflux of methylene blue irrigant from the bladder to the ureterotomy can be used to verify the appropriate placement of the distal stent in the bladder. Retroperitoneal fat or omentum may be used to cover the anastomosis. A surgical drain is placed, and a Foley catheter is generally left indwelling for 1 to 2 days. The surgical drain may be removed if there is minimal output for 24 to 48 hours. If the surgical procedure is not performed entirely in a retroperitoneal manner, it is important to determine the nature of the fluid from the surgical drain, which can be achieved by checking the creatinine level of the fluid. If there is no urinary extravasation, the drain can then be removed. The double-J ureteral stent is removed endoscopically, usually 4 to 6 weeks postoperatively.

The success rate for a tension-free, watertight ureteroureterostomy is high—more than 90% (Carlton et al, 1969; Guiter et al, 1985). If a urinary fistula is suspected, a plain abdominal radiograph should first be obtained to verify the position of the double-J stent. The proximity of a drain to the anastomosis should also be checked because it may exacerbate a leak. Suction should be stopped if a suction drain device is used because straight drainage may assist closure of the ureteral leakage site. Reflux from voiding or bladder spasms may also contribute to prolonged urinary extravasation, a problem that can be managed by Foley catheter drainage and anticholinergics. Prolonged urinary leakage from the anastomosis may require the placement of a nephrostomy tube for proximal urinary diversion.

Laparoscopic Ureteroureterostomy

A laparoscopic approach may be offered to patients with ureteral stricture disease. Nezhat and colleagues (1992) first reported laparoscopic management of an obstructed ureter due to endometriosis. In this case, ureteroureterostomy was performed laparoscopically over a ureteral stent following resection of the obstructed ureteral site. In their more recent retrospective review involving eight laparoscopic ureteroureterostomy patients, seven were found to have patent anastomosis with relatively short follow-up, ranging from 2 to 6 months (Nezhat et al, 1998). More recently, the robotic-assisted approach has been applied to laparoscopic

ureteroureterostomy in a small number of patients (Mufarrij et al, 2007; Passerotti et al, 2008). The overall clinical experience in laparoscopic ureteroureterostomy is limited worldwide. However, in the hands of the experienced laparoscopic surgeons, it appears to be a viable minimally invasive approach applicable to almost any patient with a relatively short area of obstruction.

Open Ureteroneocystostomy

Ureteroneocystostomy to manage vesicoureteral reflux is covered elsewhere in the text. Ureteroneocystostomy without a psoas hitch or Boari flap in an adult is appropriate for injury or obstruction affecting the distal 3 to 4 cm of the ureter. A lower midline, Pfannenstiel, or Gibson incision may be used, and the extraperitoneal approach is generally more preferable. Following surgical incision, the ureter is usually identified as it crosses the iliac vessels, dissected distally, and transected at the level of the obstruction. Following adequate proximal ureteral mobilization, direct ureteroneocystostomy is performed only if a tension-free anastomosis is possible. Otherwise, a psoas hitch or Boari flap should be used as an adjunct. A direct, nontunneled anastomosis may be performed if postoperative reflux is acceptable. Otherwise, a submucosal tunnel is created for antireflux anastomosis. A double-J stent and surgical drain are used as described for ureteroureterostomy described earlier.

The issue of reluxing versus antirefluxing anastomosis in ureteroneocystostomy in adults has been examined previously. **In a retrospective review of adult patients with ureteroneocystostomy, no significant difference in the preservation of renal function or risk of stenosis was identified in the refluxing versus antirefluxing procedures** (Stefanovic et al, 1991). However, it is unclear if a nonrefluxing anastomosis decreases the risk of pyelonephritis in an adult patient.

Laparoscopic Ureteroneocystostomy

Successful laparoscopic application to ureteroneocystostomy has been reported by several investigators (Ehrlich et al, 1993; Reddy et al, 1994; Yohannes et al, 2001). Successful use of the robot in such clinical setting has also been reported (Mufarrij et al, 2007; Laungani et al, 2008; Williams et al, 2009). In the management of distal ureteral stricture, laparoscopic ureteroneocystostomy is usually performed transperitoneally incorporating intracorporeal suturing techniques. Large working space provided by the transperitoneal approach is especially advantageous in the setting of robotic involvement. Ureteral stenting is typically used postoperatively as in open surgery. The overall clinical experience for laparoscopic management of distal ureteral strictures is limited in the literature. However, the clinical outcomes have been reported to be favorable to and comparable with those of open surgical data while providing minimal postoperative morbidity, as in many other laparoscopic urologic procedures.

Open Psoas Hitch

The psoas hitch is an effective method to bridge a defect of the lower third of the ureter. However, a ureteral defect extending proximal to the pelvic brim usually requires more than a psoas hitch alone. Indications include distal ureteral stricture, injury, and failed ureteroneocystostomy (Prout and Koontz, 1970; Ehrlich et al, 1978; Rodo Salas et al, 1991). A psoas hitch may also be used in conjunction with other maneuvers such as a transureteroureterostomy (TUU) in more complicated urinary tract reconstruction. **Generally, a small, contracted bladder with limited mobility is considered as a contraindication.** In addition to the preoperative radiographic and endoscopic evaluation described previously, urodynamic studies may provide information regarding detrusor capacity and compliance before the surgery. Bladder outlet obstruction or neurogenic dysfunction, if present, needs to be treated preoperatively.

To gain access to the distal ureter, a Pfannenstiel or lower midline incision is usually used. Extraperitoneal approach is preferred, if possible. In such scenario, the space of Retzius is developed and the bladder mobilized by freeing its peritoneal attachments and dividing the vas deferens or round ligament. With traction, the ipsilateral dome of the bladder should be able to reach the level proximal to the iliac vessels. **Additional mobility can be achieved by dividing the contralateral superior vesical artery.** The ipsilateral ureter is identified as it crosses the iliac vessels, mobilized, and divided just above the diseased segment. An anterior cystotomy, generally created in a vertical or oblique fashion, is frequently made to assist manual displacement of the bladder toward the ipsilateral ureter. The ureter is delivered into the lumen of the bladder at the ipsilateral superolateral aspect of the dome, followed by the tension-free anastomosis with or without a submucosal tunnel. **The ipsilateral bladder dome is secured to the psoas minor tendon or the psoas major muscle using several absorbable sutures. Care should be taken to avoid injury to the genitofemoral nerve and the femoral nerve in the vicinity when placing these sutures.** Alternatively, psoas fixation may be performed before ureteroneocystostomy. A double-J stent is used usually, followed by closure of cystotomy with absorbable sutures (Fig. 41–31).

Relative to simple ureteroneocystostomy, psoas hitch can provide an additional 5 cm of length. Relative to Boari flap, the advantages of psoas hitch include increased technical simplicity and decreased risk for vascular compromise and voiding difficulties. The success rate of ureteroneocystostomy with a psoas hitch is greater than 85% in both adults and children on the basis of recent reports (Mathews and Marshall, 1997; Ahn and Loughlin, 2001). Complications occur uncommonly but have included urinary fistula, ureteral obstruction, bowel injury, iliac vein injury, and urosepsis (Fig. 41–32).

Laparoscopic Psoas Hitch

Ureteroneocystostomy with psoas hitch has been performed laparoscopically with success (Nezhat et al, 2004). Successful robotic-assisted application has also been reported (Mufarrij et al, 2007; Patil et al, 2008; Schimpf and Wagner, 2009). Preoperative ureteral stenting is generally performed, and the procedure is typically completed via the transperitoneal approach. Overall, the clinical experience with such procedure is quite limited in the literature. However, on the basis of short-term and intermediate-term follow-up data to date, the clinical outcomes appear to be satisfactory and equivalent in experienced hands.

Open Boari Flap

When the diseased ureteral segment is too long or when ureteral mobility is too limited to perform a tension-free ureteroureterostomy, a Boari flap may be a useful alternative. Boari first described the use of this technique in the canine model in 1894. **A Boari flap can be constructed to bridge a 10- to 15-cm ureteral defect, and a spiraled bladder flap can reach the renal pelvis in some circumstances, especially on the right side.** As in a psoas hitch, evaluation of bladder function should be performed preoperatively in addition to the ureteral evaluation. Bladder outlet obstruction and neurogenic dysfunction, if present, should be addressed preoperatively. **A small bladder**

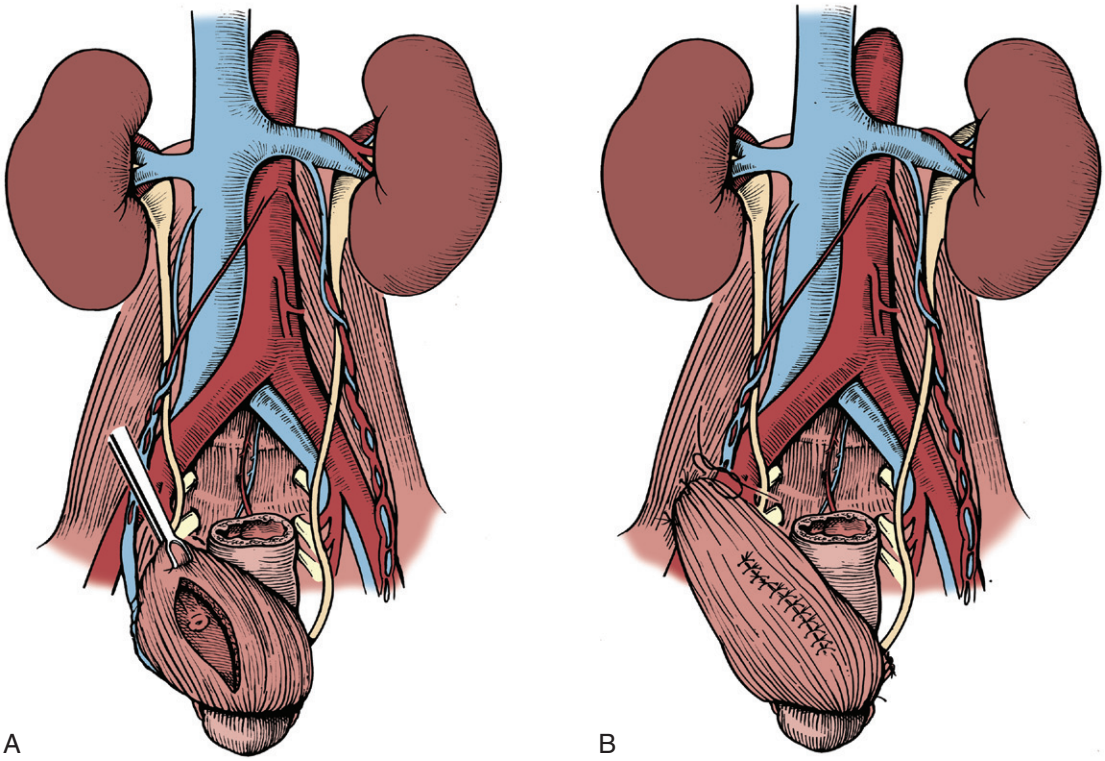


Figure 41–31. **A,** In psoas hitch, an anterior cystotomy is performed following bladder mobilization. **B,** The bladder dome is fixed to the ipsilateral psoas tendon, and the ureteral reimplantation is completed in a tension-free manner.

capacity is likely to be associated with difficult or inadequate Boari flap creation, warranting consideration of alternative methods in the preoperative surgical planning.

In Boari flap, a Pfannenstiel incision may be used at the time of surgery, although a midline incision is more preferable and allows easier access to the upper ureter. The bladder is mobilized from its peritoneal attachments, and the umbilical ligaments are divided. The contralateral bladder pedicle is divided and ligated, allowing greater mobility toward the ipsilateral ureter, and the ipsilateral bladder pedicle including the superior vesical artery is preserved. The affected ureter is carefully mobilized, with care being taken to preserve its blood supply. The diseased segment is then excised. Following the identification of the ipsilateral superior vesical artery or one of its branches, a posterolateral bladder flap is outlined on the basis of this vascular supply. The flap continues obliquely across the anterior bladder wall, with the base of the flap being at least 4 cm in width and the tip of the flap being at least 3 cm in width. The flap length should equal the estimated ureteral defect plus an addition of 3 to 4 cm if a nonrefluxing anastomosis is planned. Furthermore, the ratio of flap length to base width should not be greater than 3:1 to help minimize flap ischemia.

Following bladder flap creation, the distal end of the flap is pexed to the psoas minor tendon or psoas major muscle with several absorbable sutures. The ureter is delivered through a small opening created in the posterior flap, and a tension-free mucosa-to-mucosa refluxing anastomosis is performed after spatulation of the distal ureteral end. Alternatively, nonrefluxing tunneled anastomosis can be used. The flap is then tubularized anteriorly and closed using absorbable suture. Furthermore, the ureteral adventitia may be secured to the distal aspect of the flap, and the base of the flap may be secured to the psoas (Fig. 41–33).

The number of reported patients treated with a Boari flap is small, yet the results are good if a well-vascularized flap is used (Ockerblad, 1947; Scott, 1972; Thompson, 1974; Middleton, 1980; Benson et al, 1990; Motiwala et al, 1990) (Fig. 41–34). The most common complication is clearly recurrent stricture formation, resulting from either ischemia or excessive tension on the anastomosis. Rare pseudodiverticulum has also been reported (Berzeg et al, 2003).

Laparoscopic Boari Flap

Laparoscopic Boari flap has been uncommonly yet successfully performed in the clinical setting. Kavoussi and colleagues reported three successful cases for distal ureteral obstruction, in which a transperitoneal approach was used (Fugita et al, 2001). Following the same principles in open surgery, the bladder flap was created and anastomosed to the ureteral end over a stent in a tension-free, water-tight manner. Operative time ranged from 120 to 330 minutes, and blood loss ranged from 400 to 600 mL. Two patients were discharged home within 3 days postoperatively, while 1 patient was hospitalized for 13 days for *Clostridium difficile* colitis. With a follow-up of more than 6 months, there was radiographically demonstrated patency of the anastomosis. In this report, the information of the length of distal ureteral stricture was not available. However, in the clinical experience of one of the authors (TH), ureteral loss of 8 to 12 cm can be comfortably bridged with Boari flap in the laparoscopic setting, as in open surgery. More recently, laparoscopic boari flap assisted by the robot has been successfully performed (Schimpf and Wagner, 2009). Transperitoneal approach was used in all cases reported thus far.

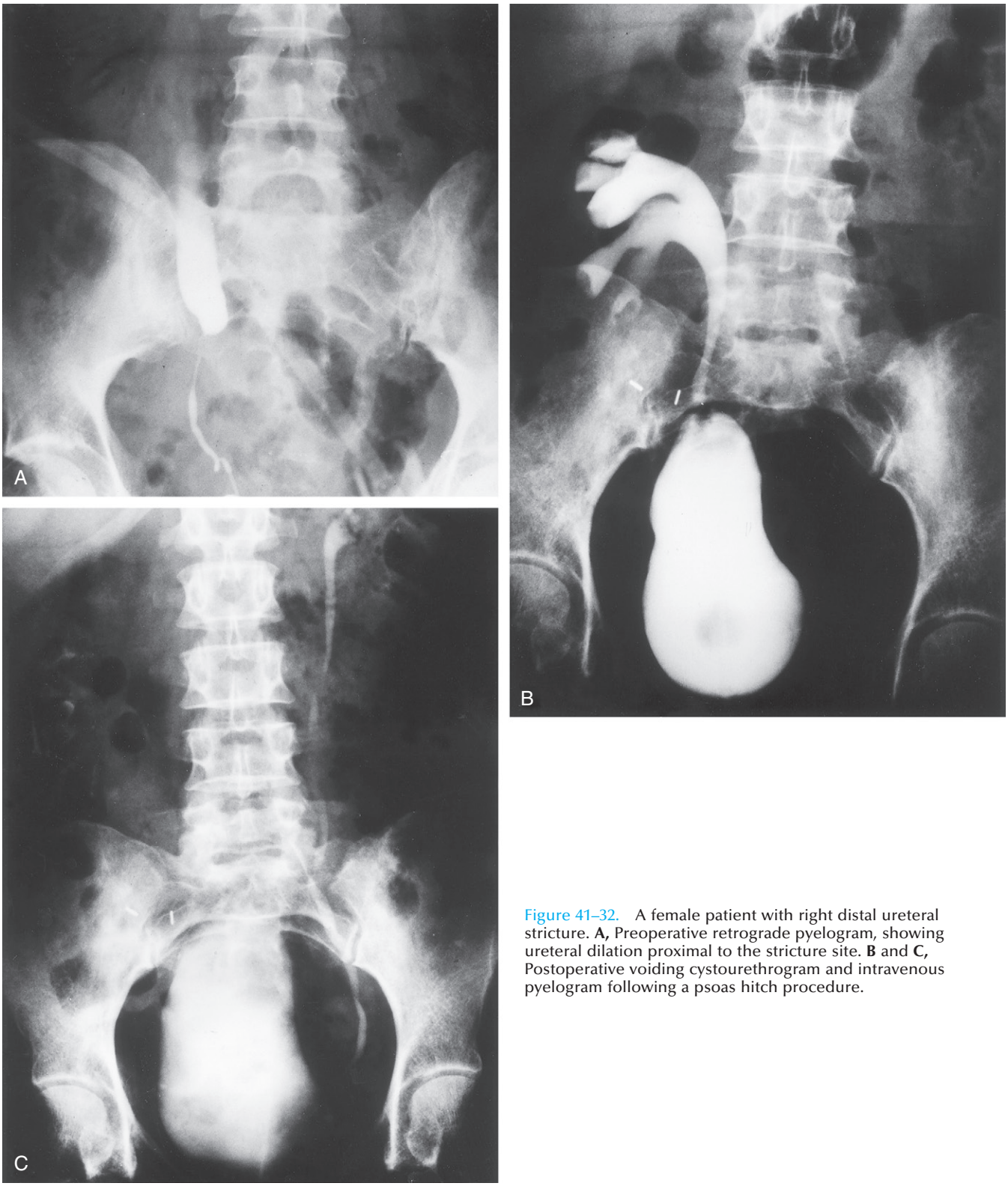


Figure 41–32. A female patient with right distal ureteral stricture. **A,** Preoperative retrograde pyelogram, showing ureteral dilation proximal to the stricture site. **B** and **C,** Postoperative voiding cystourethrogram and intravenous pyelogram following a psoas hitch procedure.

Renal Descensus

Renal mobilization, which was originally described by Popescu in 1964, can provide additional length to bridge a defect in the upper ureter or decrease tension on a ureteral repair (Harada et al, 1964; Passerini-Glazel et al, 1994). A transperitoneal, subcostal, midline, or paramedian incision may be used to gain access to the kidney and the appropriate level of the ureter. Following entry to the Gerota's fascia, the kidney is completely mobilized and rotated inferiorly and medially on its vascular pedicle. The lower pole of the kidney is then secured to the retroperitoneal muscle using several absorbable sutures. Up to 8 cm of additional length may be gained using this technique. In such cases the renal vessels—especially the renal vein—limit the extent to which the kidney

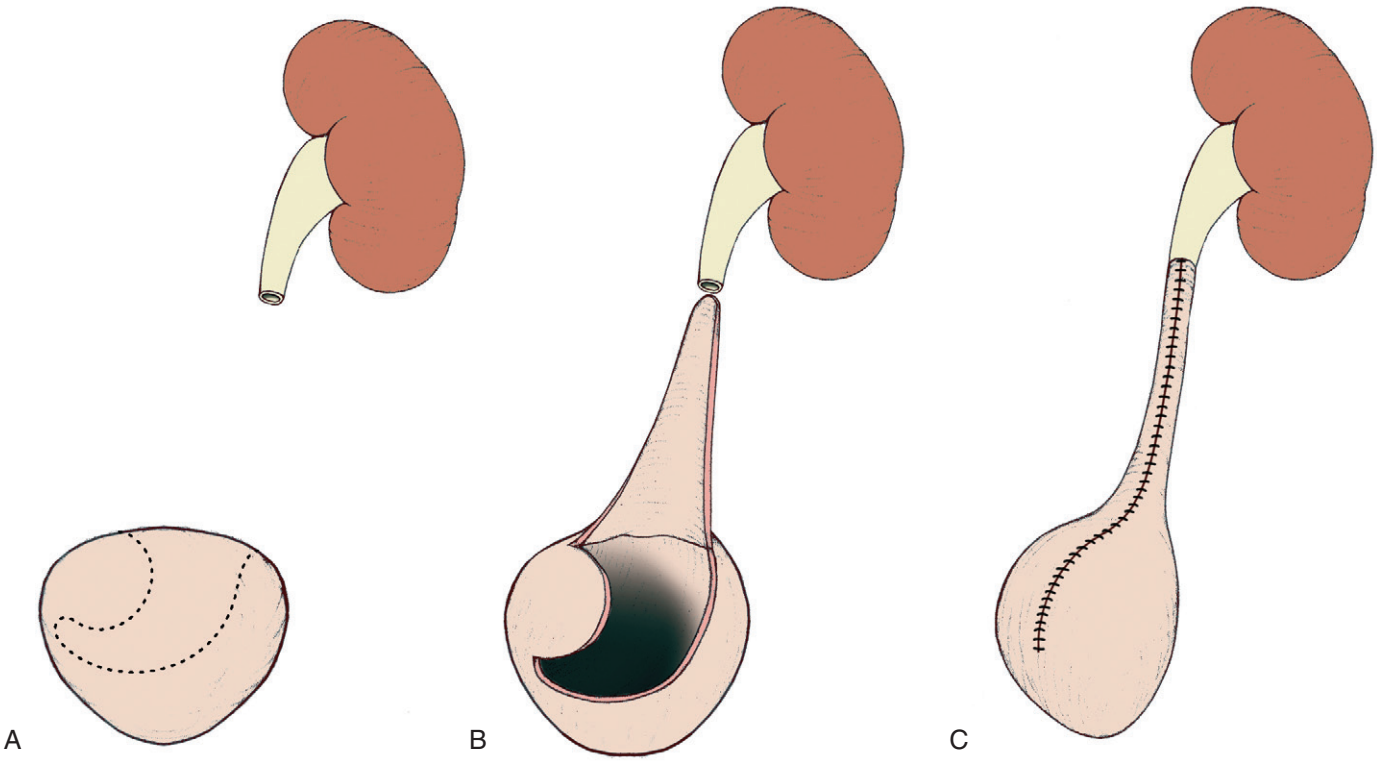


Figure 41–33. **A,** In Boari flap, the intended flap is first marked on the anterior and lateral aspects of the mobilized bladder. **B,** The flap is created, ensuring good vascular supply. **C,** Ureteroneocystostomy is completed, with the longitudinal bladder tube closure.

can be mobilized. As a solution, the technique for division of the renal vein with reanastomosis more inferiorly to the inferior vena cava may be performed but rarely applied clinically.

Intubated Ureterotomy

The Davis intubated ureterotomy has been described previously in this chapter. Because of the development of the more effective surgical treatment alternatives, this procedure is described primarily for historical interest. An intubated ureterotomy is generally used for a ureteral stricture too long for conventional ureteroureterostomy or ureteroneocystostomy and has been performed to treat stricture up to 10 to 12 cm in length. An innovative modification to this procedure has incorporated a buccal mucosal patch graft in a small number of patients with good results (Naude, 1999).

Open Transureteroureterostomy

The initial clinical application of TUU was described Higgins in 1934. In the management of ureteral stricture, a TUU may be used when ureteral length is insufficient for anastomosis to the bladder (Brannan, 1975). **The only absolute contraindication is insufficient length of the donor ureter to reach the contralateral recipient ureter in a tension-free manner. However, any disease process that may affect both ureters represents a relative contraindication. Absolute contraindications include the presence of a diseased recipient ureter or a donor ureter of inadequate length. Relative contraindications include history of nephrolithiasis, retroperitoneal fibrosis, urothelial malignancy, chronic pyelonephritis, and abdominopelvic radiation. Reflux to the recipient ureter, if present, needs to be identified and corrected simultaneously.** Therefore a voiding cystogram should be performed preoperatively, in addition to the other imaging and endoscopic studies previously described for thorough evaluation of both ureters.

In performing a TUU, a midline, transperitoneal approach is used to gain access to both ureters. Following medial colonic mobilization, the affected ureter is mobilized, preserving the adventitia with the ureteral blood supply, and divided just proximal to the level of obstruction. The contralateral colon is medially mobilized. Only the portion of recipient ureter needed for the anastomosis is exposed, which is generally 5 cm proximal to the level of division of the affected ureter. A tunnel under the sigmoid colon mesentery is created proximal to the inferior mesenteric artery to avoid ureteral tethering by this vessel, after which the donor ureter is then brought through the tunnel to the recipient side. Mobilization of the recipient ureter should be minimized to help preserve the integrity of its vascular supply. An anteromedial ureterotomy is made in the recipient ureter, which is then anastomosed to the spatulated donor ureteral end in a tension-free, watertight manner using either interrupted or running absorbable sutures. A double-J ureteral stent is usually passed from the donor renal pelvis, through the anastomosis and into the bladder. A second ureteral stent may also be placed throughout the length of the recipient ureter if the ureter is found to be adequately large in diameter.

The clinical success of TUU has been demonstrated by multiple investigators. Hendren and Hensle (1980) reported 75 cases of pediatric TUU without compromising a single recipient kidney. Hodges and colleagues (1980) reported a similar success in a large group of children and adults. However, two patients required revision due to ureteral kinking by the inferior mesenteric artery. The

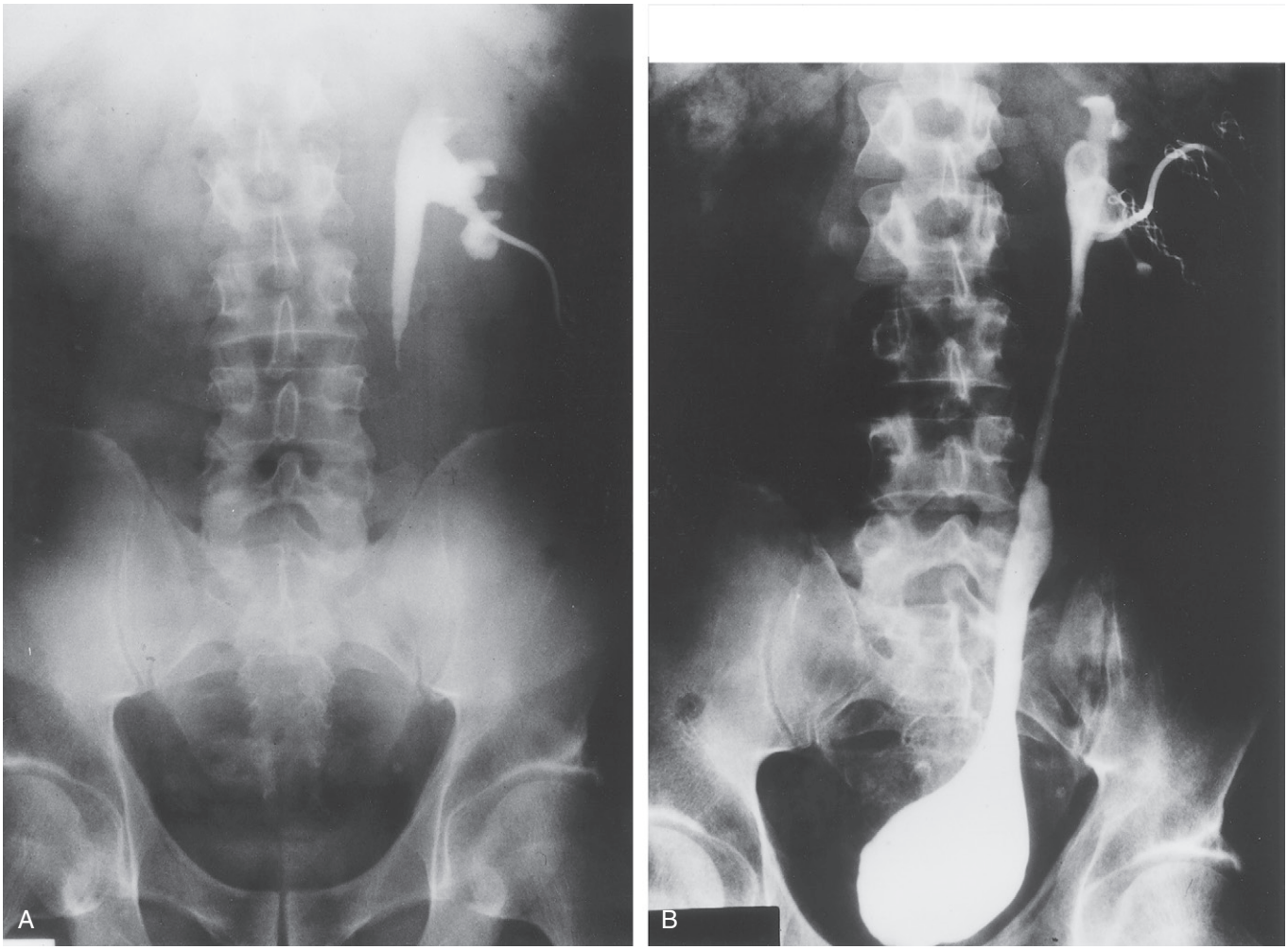


Figure 41–34. **A,** Preoperative nephrostogram of a patient with left proximal ureteral injury following aortobifemoral bypass surgery. **B,** Postoperative voiding cystourethrogram after a Boari flap procedure.

successful application of TUU was further confirmed more recently by Pesce and colleagues (Pesce et al, 2001). In two other recent studies, nephrectomy for ureteral stenosis was found to be rarely necessary (Mure et al, 2000; Sugarbaker et al, 2003).

Laparoscopic Transureteroureterostomy

Laparoscopic TUU is rarely performed and has been reported in three pediatric patients recently (Piaggio et al, 2007). The transperitoneal laparoscopic procedure was completed with the patient in the supine, Trendelenburg position. The general principles of donor and recipient ureteral dissection, donor ureteral ligation and transposition under the rectosigmoid mesentery, longitudinal ureterotomy at the medial aspect of the recipient ureter, and end-to-side anastomosis in a tension-free, water-tight manner are identical to those described for open surgery. Mean surgical time was 264 minutes (range: 200 to 313 minutes). Transient urine leak occurred in one of the three patients, with spontaneous resolution. There was normal renal function without complication at a mean follow-up of 6 months. Long-term clinical data to validate laparoscopic TUU are not yet available.

Open Ileal Ureteral Substitution

Surgical management of long length of ureteral defect or loss, especially the proximal ureter, is particularly challenging (Benson et al, 1990). Reconstruction of the ureter with tissue lined with urothelium is most preferable because urothelium is not absorptive and is resistant to the inflammatory and potentially carcinogenic effects of urine (Harzmann et al, 1986). Incorporation of other tissue in ureteral repair is, therefore, reserved for situations in which a defect cannot be bridged by other methods or the bladder is unsuitable for reconstruction. In this scenario, ileal interposition has been demonstrated to be a satisfactory option for complicated ureteral reconstruction. On the other hand, the appendix and fallopian tube have been found to be unreliable ureteral substitutes.

Shoemaker reported the first ileal ureter in a woman with tuberculous involvement of the urinary tract in 1909. Later, the metabolic and physiologic effects of the ileal ureter have been investigated in the canine model (Hinman and Oppenheimer, 1958; Martinez et al, 1965). When an isoperistaltic segment of ileum is directly anastomosed to the bladder, reflux and renal pelvic pressure increase are generally seen only during voiding. The retrograde transmission of intravesical pressure is dependent on the length of ileum segment used in interposition and the voiding pressure. In patients with ileal segments longer than 15 cm, Waldner and colleagues found no reflux into the renal pelvis in a report involving 19 cases of ileal ureter with refluxing ileo-vesical anastomosis (1999). Comparing dogs with tapered

versus nontapered ileal segments, Waters and colleagues (1981) found no difference in renal perfusion pressure or metabolic derangements.

A large clinical experience in ileal ureter involving 89 patients was reported by Boxer and colleagues (1979). Only 12% of patients with normal preoperative renal function developed significant metabolic problems postoperatively, and preoperative renal function was identified to be an important prognostic factor. In a separate study, nearly half of those with a serum creatinine of greater than 2 mg/dL developed hyperchloremic metabolic acidosis, requiring conversion to a conduit (Koch and McDougal, 1985). In the same study, patients with bladder dysfunction also experienced more complications. No sufficient clinical data exist to establish the superiority of a tapered segment, a nonrefluxing anastomosis, or a shorter, segmental replacement over a standard ileal substitution (Waters et al, 1981). **Therefore the general contraindications to an ileal ureteral substitution are baseline renal insufficiency with a serum creatinine of greater than 2 mg/dL, bladder dysfunction or outlet obstruction, inflammatory bowel disease, or radiation enteritis.**

Before the surgical procedure, a full mechanical and antibiotic bowel preparation is often used. A long midline incision is made. The ipsilateral colon is mobilized medially, and the affected ureter is dissected proximally to the level of healthy tissue. The proximal anastomosis may be performed at the level of the renal pelvis if the entire upper ureter is unhealthy. The length of the ureteral defect is measured, and an appropriate segment of distal ileum is chosen. The segment should be at least 15 cm away from the ileocecal valve, and adequate blood supply should be confirmed before harvesting. The mesentery is usually divided more extensively than with a standard ileal conduit to provide greater mobility. Occasionally, a segment of colon may be more accessible than ileum and is harvested using the similar surgical principles. **In the presence of a scarred or intrarenal pelvis, ileocalycostomy may be performed** (McQuitty et al, 1995). In this circumstance, excision of a piece of lower pole renal parenchymal tissue is helpful in preventing stenosis at the anastomosis, as in a typical ureterocalicostomy. Following bowel division, the distal end of the ileal segment is marked for orientation and bowel-to-bowel continuity is reestablished. A small window is made in the colonic mesentery, through which the segment of ileum is delivered laterally. Alternatively, the cecum and ascending colon can be reflected superiorly to avoid mesenteric window creation in performing right ureteral reconstruction. The orientation of the ileal segment is checked to ensure isoperistalsis, and the anastomoses are performed at the level of the renal pelvis or lower pole calyx and at the bladder (Fig. 41–35). Bilateral ileal ureteral substitution may be achieved by using a longer segment that travels intraperitoneally from one kidney to the other and then to the bladder. An alternative to such is to use two separate bowel segments.

Perioperative complications associated with ileal ureter include early urinary extravasation or urinoma formation and obstruction from edema, a mucus plug, or a kink in the segment. Ischemic necrosis of the ileal segment may occur and should be considered

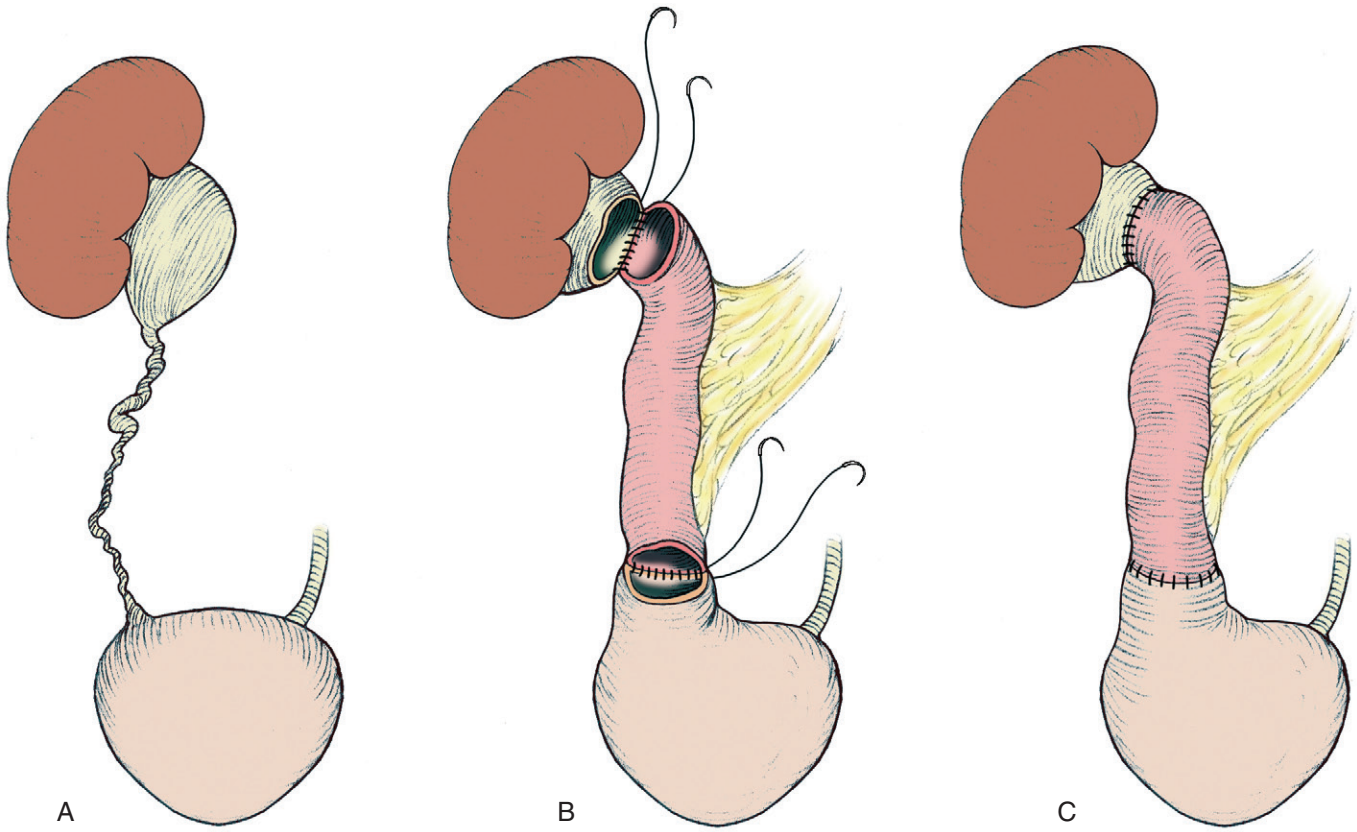


Figure 41–35. **A,** In ileal ureteral substitution, the affected ureter is first identified and dissected, which is followed by removal of the diseased portion. **B,** A piece of ileum is brought through the colonic mesentery to bridge the renal pelvis and the bladder. **C,** Both proximal and distal anastomoses are completed in full-thickness, water-tight, tension-free manner.

if signs of an acute abdomen are present. Significant electrolyte abnormalities and renal insufficiency are unusual if preoperative renal function is normal. **Patients with worsening metabolic abnormalities associated with a progressively dilating ileal ureter should be evaluated for vesicourethral dysfunction. Furthermore, malignancy arising from ileal ureter segment has been reported in four cases in the literature** (Austen et al, 2004), **and it is recommended that regular endoscopic examination should be performed starting at postoperative year 3 for early detection of such malignancy.** However, Matiaga and colleagues (2003) recently confirmed the safety and reliability of ileal ureter creation for complex ureteral stricture/loss in 18 patients with a mean follow-up of 18.6 months. This conclusion was further supported by Bonfig and colleagues (2004) in another contemporary series involving 43 patients with a mean follow-up of 40.8 months.

Laparoscopic Ileal Ureteral Substitution

The clinical experience in laparoscopic ileal ureteral substitution is limited worldwide, yet this procedure appears to hold significant promise. Gill and colleagues (2000a) reported successful laparoscopic ileal ureter replacement using a transperitoneal, three-port approach. The entire procedure including freehand suturing and knot tying was performed using the intracorporeal laparoscopic techniques. Although the operative procedure was relatively long at 8 hours, there was minimal postoperative morbidity and hospital stays were short (4 days), as in most other laparoscopic procedures. More recently, robotic-assisted laparoscopic ileal ureter was performed via a transperitoneal, four-port approach successfully (Wagner et al, 2008). Total operative time was 9 hours, with an acceptable hospital stay of 5 days. No complication was reported in either study.

Autotransplantation

In 1963 Hardy performed the first autotransplantation for a patient with proximal ureteral injury. Since then, clinical autotransplantation has been performed for a variety of problems including extensive ureteral loss or stricture (Hardy, 1963; Novick and Stewart, 1981; Chuang et al, 1999; Wotkowicz et al, 2004). Generally, autotransplant is considered when the contralateral kidney is absent or poorly functioning or when other methods for ureteral substitution or repair are not feasible. The kidney is harvested with maximal vessel length as in a typical live donor nephrectomy for allotransplantation, and the renal vessels are anastomosed to the iliac vessels to reestablish renal perfusion. A healthy segment of the proximal ureter is anastomosed to the bladder (Bodie et al, 1986). Alternatively, the ipsilateral renal pelvis may be anastomosed directly to the bladder (Kennelly et al, 1993).

Recently, laparoscopy has been successfully incorporated in autotransplantation for severe ureteral loss. Nephrectomy can be performed laparoscopically as in any typical laparoscopic donor nephrectomy, followed by renal graft retrieval, bench preparation, and autotransplantation in the ipsilateral iliac fossa via a Gibson incision using the standard open surgical techniques (Fabrizio et al, 2000; Meng et al, 2003; Blueblond-Langner et al, 2004). The use of laparoscopy in autotransplantation has been shown to provide reduced postoperative analgesic need and faster recovery because a large open upper abdominal or flank incision for renal harvest is avoided. Laparoscopic nephrectomy in autotransplantation is most commonly performed transperitoneally. However, retroperitoneal approach for such purpose has been applied successfully by Gill and colleagues (2000b).

Key Points: Surgical Repair of Ureteral Stricture

- Only short ureteral defects may be managed by end-to-end ureteroureterostomy.
- Distal ureteral stricture may be managed with ureteroneocystostomy with a psoas hitch or Boari flap.
- In psoas hitch, additional mobility can be achieved by dividing the contralateral superior vesical artery. Care should be taken to avoid injury to the genitofemoral nerve or femoral nerve.
- Boari flap may be used to bridge a 10- to 15-cm ureteral defect. Small bladder capacity is a contraindication to such flap creation. Care should be taken to ensure adequate vascular supply to the flap.
- Transureteroureterostomy is contraindicated in the presence of any disease process that may affect both ureters. It is also contraindicated if there is insufficient length of the donor ureter to reach the contralateral recipient ureter in a tension-free manner.
- Ileal ureter is useful in the presence of extensive ureteral loss. It is contraindicated in cases of baseline renal insufficiency with a serum creatinine of greater than 2 mg/dL, bladder dysfunction or outlet obstruction, inflammatory bowel disease, or radiation cystitis.
- Autotransplantation is considered when the contralateral kidney is absent or poorly functioning or when other methods for ureteral substitution or repair are not feasible.

URETEROENTERIC ANASTOMOTIC STRICTURE

Incidence and Etiology

Several factors determine the incidence of stricture formation at the anastomosis of the ureter and intestine at the time of urinary diversion. The longest follow-up data available are for urinary conduits, in which the stricture rate is between 4% and 8% and more common on the left (Schmidt et al, 1973; Skinner et al, 1980). Factors potentially influencing outcome in this population include the technique used for ureteral dissection, the segment of bowel used for the diversion, and the type of anastomosis performed. Because ureteral ischemia is central to the etiology of ureteroenteric strictures, careful attention to dissection is necessary to prevent complications. The ureteral blood supply runs parallel to the ureter in the adventitia. Although ureteral mobilization is necessary to approximate the ureter and bowel and prevent tension on the anastomosis, stripping the ureter of its surrounding adventitia can lead to distal ureteral ischemia and stricture formation. **When performing an ileal conduit, the left ureter is brought underneath the sigmoid mesentery just overlying the aorta. The additional length and dissection needed on the left and the possibility of angulation around the inferior mesenteric artery may lead to a higher incidence of stricture formation on the left** (Mansson et al, 1989).

Much controversy exists over the choice of bowel segment employed for conduit diversion. One theoretic advantage to the use of colon is the feasibility of performing a nonrefluxing

anastomosis. However, the reported incidence of renal deterioration with a nonrefluxing versus a refluxing ureterocolonic anastomosis has been mixed, and there does not appear to be a clear advantage with respect to renal function and colonization to a nonrefluxing anastomosis. The issues influencing stricture formation in continent urinary diversions become even more complex owing to the variety of bowel segments, reservoir configurations, and types of anastomoses available for reconstruction. **The reported rate of ureteroenteric anastomotic stricture after continent diversion is 3% to 25%, with the majority presenting within the first 2 years** (Lugagne et al, 1997; Weijerman et al, 1998; Kouba et al, 2007). Despite the paucity of randomized studies, there is a growing body of evidence in the literature that the risk of obstruction with a nonrefluxing anastomosis is significantly higher than that of a refluxing anastomosis. Pantuck and colleagues (2000) compared 60 nonrefluxing ureteroenteric anastomoses with 56 direct, refluxing anastomoses and found the long-term stricture rate to be 13% and 1.7%, respectively. With a mean follow-up of 41 months, there was no significant difference in the two groups with respect to hydronephrosis, pyelonephritis, nephrolithiasis, or renal insufficiency. Similarly, Roth and colleagues (1996) found a greater than fivefold increase in ureteral strictures in the group undergoing a nonrefluxing anastomosis. Their data also indicated that the risk of obstruction was unrelated to surgical expertise.

Studer and colleagues (1995) have reported a randomized study evaluating a nonrefluxing versus a refluxing anastomosis into an isoperistaltic afferent ileal limb. Thirteen percent of nonrefluxing anastomoses resulted in stricture formation, as compared with 3% of refluxing anastomoses. Although there is no clear evidence that reflux into an adult kidney is detrimental, it is clear that obstruction is quite harmful to renal function. These studies and others support the use of a refluxing anastomosis in low-pressure continent reservoirs.

Kouba and colleagues compared the Wallace and Bricker technique of ureteroileal anastomosis for continent and incontinent diversions and found low rates of stricture (0% to 3%) using both techniques in 186 patients with 34-month follow-up. Notably, using the Wallace technique (joined ureters) no strictures were identified compared with 3.7% in patients undergoing Bricker techniques (separate ureters). Of note, the group undergoing the Bricker anastomosis had a higher BMI than the Wallace group (Kouba et al, 2007).

Evaluation

A minimally invasive means of screening the upper tracts in patients who have undergone any type of urinary diversion is a renal ultrasound. In addition, patients with renal colic, recurrent urinary tract infection, or loss of renal function will require evaluation. In patients with hydronephrosis on ultrasound, an intravenous pyelogram and contrast study of the conduit or reservoir will provide information on the length and location of the stricture. If a stone or recurrent tumor is suggested, a CT scan or MRI may be helpful. Diuretic renography is indicated in patients with chronic hydronephrosis to assess differential renal function and confirm the presence of functional obstruction. If hydronephrosis is present but renal function is insufficient for intravenous urogram or renography, placement of a nephrostomy tube and performance of an antegrade nephrostogram is both diagnostic and therapeutic. This approach is also useful before endoscopic intervention and clarifies stricture length, which aids in surgical planning.

Indications for Intervention

Not all patients with urinary diversion and hydronephrosis require intervention. **Most patients with a long-term urinary conduit will have an element of chronic hydronephrosis that is not secondary to obstruction. In this population, a decrease in renal function or loss of reflux on a routine loop-o-gram should prompt diuretic renography to quantitatively assess for functional obstruction.** Indications for intervention in patients with diversions and hydronephrosis include pain, infection, and renal insufficiency associated with functional obstruction. Although recurrence of transitional cell carcinoma at the level of the anastomosis is uncommon, the radiographic picture of an irregular mass at the level of the stricture and the rapid progression of obstruction and loss of renal function should prompt further evaluation and intervention (Tsuji et al, 1996).

A particularly challenging subset of patients is those undergoing urinary diversion as part of a pelvic exenteration for gynecologic malignancy. Penalver and colleagues (1998) reported on 66 patients, 95% of who had undergone previous pelvic irradiation. Early and late complications at the ureteroenteric anastomosis were 22% and 10%, respectively. Eighty-five percent of their postoperative complications were managed successfully by conservative measures such as percutaneous nephrostomy.

Endourologic Management

Endourologic management of ureteroenteric strictures has evolved in a manner analogous to that for ureteral stricture disease. Although the initial procedures involved simple balloon dilatation and stent placement, unsatisfactory results led to incisional techniques using electrocautery and more recently the laser was applied using both fluoroscopic and direct endoscopic control. The current state-of-the-art incisional technique for endoureterotomy includes small-caliber flexible ureteroscopic instrumentation along with holmium laser incision (Siegel et al, 1982; Muench et al, 1987; Cornud et al, 1992; Delvecchio et al, 2000; Laven et al, 2001, 2003).

Endourologic management of ureteroenteric or ureterocolic strictures, unlike the management of ureteral strictures, still favors antegrade management. As such, endourologic procedures typically begin with antegrade percutaneous access. Simple percutaneous drainage is continued to allow relief of any associated infection or obstruction-related renal dysfunction. Once the patient is clinically stable, fluoroscopic control is used to pass a guidewire in an antegrade fashion across the anastomotic stricture, over which a balloon catheter can be positioned and inflated until the waist disappears. Stents are a routine part of endourologic management, and these are generally inserted in this same antegrade fashion. However, because of difficulty with mucus plugging of stents in this setting, many centers routinely use an internal/external stent, which can be easily flushed or changed over a wire. In addition, retrograde looposcopic access can be combined with percutaneous access and antegrade passage of a wire. With through-and-through control, the anastomosis can be visualized fluoroscopically or, preferably, with direct ureteroscopic, looposcopic, or trans-stomascopic visualization. Any number of procedures can then be used for the dilatation itself including balloon dilatation alone, electroincision with an electrode or hot wire cutting balloon, or holmium laser incision. In all cases, a stent is placed, usually for 4 to 8 weeks.

Balloon dilatation of ureteroenteric strictures was one of the first endourologic forms of management used, and fortunately long-term results are available. Notably, short-term reports using

high-pressure balloon dilation have demonstrated success rates as high as 61% (Ravery et al, 1998). Alternatively, Shapiro and colleagues (1998) reported balloon dilatation for 37 benign ureteroenteric strictures in 29 patients. Only 6 (16%) were considered to have a successful result at least 1 year after interventional treatment, and repeat dilatations were often required to maintain ureteral patency. Similarly, Kwak and colleagues (1995) achieved an overall success rate of less than 30% at 9 months for patients undergoing antegrade balloon dilatation of ureteroenteric strictures. More recently, DiMarco and colleagues (2001) reported a 5% 3-year success rate in 52 balloon dilations of ureteroenteric anastomotic strictures.

Metallic stents have also been used for ureteroenteric anastomotic strictures, with acceptable short-term results. Overall, of 30 patients in the published literature, the reported patency rate is greater than 80% with 6- to 22-month follow-up (Kurzer and Leveillee, 2005). **There is a higher incidence of encrustation and stone formation when using metallic stents for ureteroenteric anastomotic strictures, as well as the risk of tissue ingrowth and recurrent obstruction** (Kurzer and Leveillee, 2005). This may explain the limited published data using this approach. This author analyzed published success rates with endoureterotomy and balloon dilation and identified success rates in the literature of 18% and 63%, respectfully.

Cautery wire balloon incision has also been reported in patients treated for ureteroenteric strictures (Lin et al, 1999). For benign strictures, a stent-free long-term patency was achieved in only 30% of patients. Meretyk and colleagues reviewed the long-term results of endourologic management of ureteroenteric anastomotic strictures at Washington University. In that study, 15 patients with 19 ureteroenteric strictures were followed for an average of 2.5 years. An antegrade approach was used most frequently and was usually combined with electroincision. A 57% long-term stent-free patency rate was achieved, even with follow-up longer than 2 years (Meretyk et al, 1991). **Whereas long-term patency of most endoscopic procedures seems to be in the range of 50%, such approaches are still used preferentially as the initial intervention, reserving open operative management for those patients failing endourologic intervention** (Kramolowsky et al, 1987, 1988).

Cornud and associates (1996) reported their long-term results with percutaneous electroincision of ureterointestinal anastomotic strictures and specifically compared the results of fluoroscopic and endoscopic guidance. Twenty-seven patients were followed for longer than 1 year after stent removal, and an overall patency rate of 71% was reported. These investigators found better results when direct endoscopic control was combined with fluoroscopic guidance, compared with fluoroscopic guidance alone. In that report, right common iliac artery damage was reported during electroincision in one patient who had the procedure performed under fluoroscopic guidance alone. As a result, direct visual approaches have been favored for the management of ureteroenteric or ureterocolic anastomotic strictures, and the holmium laser has proven to be an excellent incisional tool. Endoureterotomy is typically performed antegrade, and success rates ranging from 50% to 80% have been reported (Singal et al, 1997; Laven et al, 2001; Watterson et al, 2002). These reports suggest the left side is more resistant to management because as the majority of the failures occurred on the left side in one series (Laven et al, 2003). **When considering endoscopic incision of a left ureteroenteric stricture, the risk of hemorrhage is a consideration because the sigmoid mesentery can be in close proximity. This, taken with the lower success rates of all endoscopic approaches on the left side, supports serious consideration to open repair when treating left ureteroenteric strictures.** In spite of this, Lovaco and colleagues reported good success treating 25 ureteroenteric strictures with endoureterotomy by an intraluminal invagination technique, with 80% success at more than 50 months' follow-up. Of note, this approach increases the distance between the incision site and surrounding vessels and viscera and does not favor left or right strictures (Lovaco et al, 2005).

Open Intervention

Open surgical management of ureterointestinal strictures is technically challenging and associated with a longer recovery than endoscopic options but is often necessary due to the low success rates of less invasive alternatives, in particular balloon dilatation (DiMarco et al, 2001). When undertaking open repair, it is optimal to sterilize the urine and prepare the bowel preoperatively. If a cutaneous stoma is present, it is prepared into the field and the conduit or reservoir drained with a Foley catheter during the procedure. Placement of a nephrostomy tube and ureteral stent is helpful. Through a midline incision, the conduit or reservoir is identified and preserved, the colon is reflected medially, and the proximal, dilated ureter is identified and traced down to the area of the previous anastomosis. Care is taken to preserve the adventitia and associated blood supply. If enough ureteral length is available, the ureter can be transected proximal to the stricture, spatulated, and anastomosed to a convenient area of the bowel. If the dissection is particularly difficult, there may be significant trauma to the conduit or reservoir, requiring major revision. In addition, insufficient ureteral length may require an additional segment of bowel to interpose between the ureter and the reservoir. The anastomosis is carried out over a 7-Fr stent, and a drain is left in situ. The stent remains for 4 to 6 weeks. **Satisfactory long-term success rates have been reported with open repair, as high as 80%** (Laven et al, 2003). **As expected, strictures longer than 1 cm were more likely to recur and the left side had lower success rates** (DiMarco et al, 2001; Laven et al, 2003). Major complications were encountered in 11% of cases in one series (DiMarco et al, 2001).

Key Points: Ureteroenteric Strictures

- Whereas long-term patency of most endourologic procedures for ureteroenteric strictures are in the range of 50%, such approaches are still used preferentially as the initial intervention, reserving open operative management for those patients failing endourologic intervention.
- When considering endoscopic incision of a left ureteroenteric stricture, the risk of hemorrhage is a consideration because the sigmoid mesentery can be in close proximity. This, taken with the lower success rates of all endoscopic approaches on the left side, supports serious consideration to open repair when treating left ureteroenteric strictures.
- Good long-term success rates have been reported with open repair, as high as 80%. As expected, strictures longer than 1 cm were more likely to recur and the left side had lower success rates.

RETROPERITONEAL FIBROSIS

Presentation and Etiology

Retroperitoneal fibrosis (RPF) is typically characterized by the presence of an inflammatory, fibrotic process in the retroperitoneum causing compression of the retroperitoneal structures including the ureters. RPF most commonly affects patients who are 40 to 60 years of age. However, more than 30 cases of RPF have been reported in patients younger than 18 years of age (Van Bommel, 2002). RPF cases have a male predominance, with a male-to-female ratio of 2 to 3:1. The true incidence is unknown but has been estimated to be 1:200,000 to 1:500,000 per year.

The retroperitoneal fibrotic mass generally centers around the distal aorta at L4-L5 and wraps around the ureters, leading to hydronephrosis via extrinsic compression on the ureters or interference with ureteral peristalsis (Lepor and Walsh, 1979; Koep and Zuidema, 1987). In most patients, the presenting symptom is pain in the lower back and/or flank. The pain, which is typically dull, noncolicky, and unchanged with posture, may radiate to the lower abdomen or groin. Furthermore, the pain is often relieved by aspirin rather than narcotics. Other symptoms include weight loss, anorexia, nausea, generalized malaise, fever, hypertension, and oliguria/anuria. The mass may compress the inferior vena cava, resulting in deep venous thrombosis and lower extremity edema (Rhee et al, 1994). The mass may extend proximally to the renal hilum and encase the renal vein, resulting in renal vein hypertension and subsequent gross hematuria (Powell et al, 2000). Aortic obstruction and involvement of the mediastinum, the biliary system, the mesentery, and the kidney itself are rare (Tripodi et al, 1998; Azuma et al, 1999; Dejaco et al, 1999; Klisnick et al, 1999). Distal extension to the bifurcation of the iliac vessels may occur, and extension to spermatic cord with scrotal involvement has been reported (Palmer and Rosenthal, 1999; Schulte-Baukloh et al, 1999). Duration of symptoms before diagnosis is usually 4 to 6 months, and approximately half of the patients present with fibrosis that has caused significant ureteral obstruction and symptoms secondary to uremia.

In approximately 70% of the cases, the disease is idiopathic. However, there is increasing evidence that idiopathic RPF may be an immune-mediated periaortitis. Ceroid, a complex polymer of oxidized lipids and protein found in atherosclerotic plaques, has been suggested as the antigen initiating the inflammatory response (Parums et al, 1991). Indeed, a higher incidence of aortic aneurysms has been identified in patients with RPF (Breems et al, 2000). RPF usually presents as an isolated disease entity, but it may present as part of multifocal fibrosclerosis, a rare syndrome characterized by fibrosis involving multiple organ systems. In such a scenario, the clinical presentation may include RPF, sclerosing mediastinitis, sclerosing cholangitis, orbital pseudotumor, and Riedel thyroiditis (Dehner and Coffin, 1998; Özgen and Cila, 2000). The pathogenesis of these disorders is unknown but appears to be autoimmune in nature.

Among the 30% of RPF patients that have an identifiable etiology, drugs such as methysergide (Sansert) and other ergot alkyloids are most commonly associated with RPF. β Blockers and phenacetin have also been implicated. The exact pathophysiology of drug-induced RPF remains unknown. Other causes of RPF include malignancies such as lymphoma, the most common malignancy in RPF cases, and multiple myeloma, carcinoid, pancreatic cancer, prostate cancer, and sarcoma (Webb and Dawson-Edwards, 1967; Usher et al, 1977). Radiotherapy for retroperitoneal malignancy is also known to produce a residual fibrotic mass leading to secondary ureteral obstruction. Abdominal aortic aneurysm may cause significant retroperitoneal inflammatory reaction, leading to fibrosis and ureteral obstruction. In addition, infectious etiologies such as tuberculosis, actinomyces, gonorrhea, or schistosomiasis have been suggested in the pathogenesis of RPF.

Association of retroperitoneal fibrosis with membranous glomerulonephritis has also been documented in the literature (Mercadal et al, 2000; Shirota et al, 2002). The exact etiology remains unclear, although the association has been speculated to be secondary to an unknown antigen triggering systemic immune response that leads to retroperitoneal fibrosis. Association of retroperitoneal fibrosis with ankylosing spondylitis and Wegner granulomatosis has also been reported, further suggesting an underlying immune etiology in some patients (Izzedine et al, 2002; LeBlanc et al, 2002).

Pathologically, the typical gross appearance of RPF is that of a smooth, flat, tan-colored, dense mass enveloping the surrounding retroperitoneal structures. It is also known to invade the ureter or psoas muscle. Histologically, the appearance of RPF is that of a nonspecific inflammatory process that varies with the stage of the disease. Early in the disease, affected tissue consists mainly of collagen bundles with capillary proliferation and inflammatory cells including lymphocytes, plasma cells, and fibroblasts. In the later stage, the mass becomes relatively acellular and avascular, consisting of sheets of hypocellular collagen. RPF secondary to malignancy is often histologically indistinguishable from idiopathic RPF, and it can be identified only on the basis of the demonstration of small islands of tumor cells within the fibrotic mass.

Evaluation

In most RPF patients, the clinical symptoms are generally nonspecific, and physical examination is usually unrevealing. Laboratory evaluation may reveal an elevated erythrocyte sedimentation rate, moderate leukocytosis, anemia, and variable renal insufficiency with associated electrolyte abnormalities. If the overall renal function is normal, an excretory urogram (EVU) or more commonly computed tomography (CT) with contrast may be performed. Typical EVU findings include hydronephrosis with medial deviation of the proximal ureter and midureter and a smoothly tapered ureter at the level of obstruction. Urinary obstruction is usually bilateral, but unilateral cases have been described. Uncommonly, there are patients with symptoms of urinary obstruction but little hydronephrosis on imaging. CT scan typically reveals hydronephrosis associated with a well-delineated retroperitoneal soft tissue mass enveloping the great vessels and the ureters (Fig. 41–36). If the patient has significant renal impairment, a retrograde pyelogram may be performed. In the radiographic evaluation of RPF, magnetic resonance imaging (MRI) can also be helpful because the mass itself has characteristic T1- and T2-weighted images. **Retroperitoneal fibrosis is characterized as a diffusely low signal intensity on T1-weighted imaging, although the T2 signal may vary considerably, with high signal intensity consistent with active disease** (Fig. 41–37A and B). With treatment, T2 signal often diminishes and thus provides a measure of therapeutic efficacy. Moreover, gadolinium enhancement may also prove valuable in assessing the response to treatment because associated decreases in gadolinium contrast enhancement should

also be expected following appropriate therapy (Cronin et al, 2008). If a kidney is suspected to be nonfunctioning, differential renography should be considered to determine renal function because it may affect surgical planning. Representative biopsies of the mass should be obtained percutaneously or at the time of open or laparoscopic ureterolysis to rule out malignancy and allow one to proceed with treatment for RPF.

Management

Initial Management

The initial management of RPF depends on the patient's clinical status. Patients with hydronephrosis and uremia should be emergently decompressed by either percutaneous nephrostomy or indwelling ureteral stents. The advantages to placing ureteral stents include the opportunity to perform retrograde pyelograms to evaluate the anatomy and the convenience of internal drainage. Interestingly, ureteral stent placement is usually not difficult to perform in the setting of ureteral obstruction due to RPF. In a critically ill patient with electrolyte abnormalities and little or no urine output, nephrostomy tube placement can be performed at the bedside with local anesthesia. **Following renal decompression, the patient needs to be monitored closely for postobstructive diuresis, renal function status, and appropriate replacement of fluids and electrolytes.**

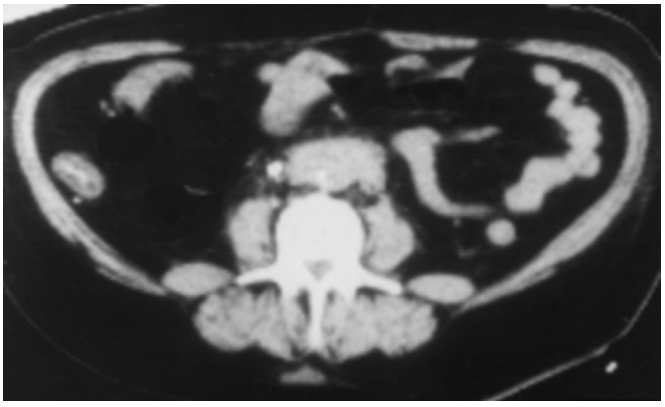


Figure 41–36. Typical CT findings of retroperitoneal fibrosis. The study demonstrates the presence of a homogeneous mass obliterating the outline of the great vessels at the lower lumbar area. Note the placement of a stent in the right ureter.

Following the initial management described earlier, an attempt to search for the etiology of RPF should be made. Methysergide or any other potentially inciting drug, if identified, should be discontinued. Although most patients with malignant RPF have a prior history of malignancy, a thorough evaluation for occult malignancy with careful application of imaging studies is necessary. Biopsy to rule out malignancy, performed percutaneously or at the time of ureterolysis to provide long-term relief of obstruction, needs to be considered. However, some believe that in patients with classic radiographic features on MRI or CT, no lymphadenopathy, and no history of prior malignancy, a biopsy is not essential before medical therapy.

Medical Management

Once the diagnosis of idiopathic RPF is made, the most common primary medical management has been steroid therapy. Although there has been no large clinical series because the disease entity is uncommon, there are approximately 170 cases of idiopathic RPF treated with steroids that resulted in about an 80% clinical response in the medical literature including having a decrease in size of the mass and improvement in ureteral obstruction or inferior vena cava compression (Kearney et al, 1976; Baker et al, 1987; Adam et al, 1998; Higgins et al, 1998; Van Bommel, 2002; Fry et al, 2008). The characteristic clinical response to steroid therapy includes resolution of pain and constitutional symptoms within days after treatment, a rapid fall of erythrocyte sedimentation rate, and diuresis. Dose and duration of steroid therapy varied considerably in the literature, but most therapies were of 6 months or greater in duration. Chronic steroid therapy up to 2 years has been shown to provide significant improvement in clinical symptoms and regression of retroperitoneal mass in 1 recent report involving 12 patients (Kardar et al, 2002). Although steroids do not reverse the established fibrosis, further inflammatory reaction and fibrosis with their associated symptomatology and sequaelae may be minimized. Therefore it appears that patients who have the evidence of active inflammation—manifested by increased erythrocyte sedimentation rate, leukocytosis, or active inflammation on a biopsy—are more likely to respond to steroid therapy.

In addition to steroids, other agents have been described to provide benefit in idiopathic RPF in isolated case reports including azathioprine, cyclophosphamide, cyclosporine, colchicine, and mycophenolate mofetil (Wagenknecht et al, 1981; McDougal et al, 1991; Grotz et al, 1998; Marzano et al, 2001; Vega et al, 2009). Medroxyprogesterone acetate, progesterone, and

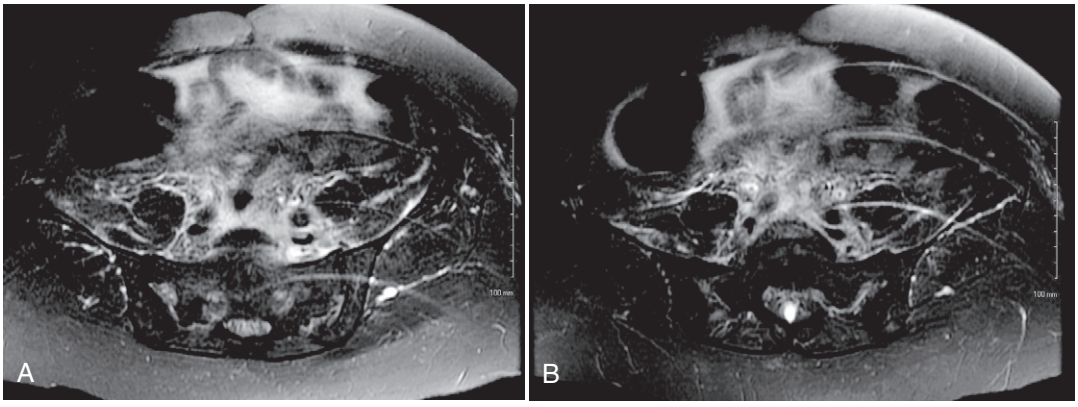


Figure 41–37. **A,** T2-weighted MR image of a symptomatic patient demonstrating retroperitoneal fibrosis with enhancement and thus active disease. **B,** Same patient after one month of medical therapy; note the decrease in enhancement on this corroborative T2-weighted image.

particularly tamoxifen, a nonsteroidal antiestrogen, have been found to be beneficial in idiopathic RPF in several case reports (Clark et al, 1991; Benson et al, 1993; Al-Musawi et al, 1998; Dedeoglu et al, 2000; Puce et al 2000). The exact mechanisms of action of these medications are unclear, but they are believed to inhibit fibroblastic proliferation leading to clinical response. Use of alternative or additional agents may decrease or eliminate steroid usage.

Surgical Management: Open Ureterolysis

Ureterolysis may be performed open surgically or laparoscopically, although open surgery has been considered the standard (Lindell and Lehtonen, 1988; Elashry et al, 1996). It is performed with concomitant biopsy of the mass in patients with an unclear diagnosis as the definitive initial treatment or in those who fail medical therapy. **When an open surgery is performed, a midline, transperitoneal abdominal incision is made to allow access to both ureters.** Placement of ureteral catheters or stents before the abdominal incision is advisable to assist identification and dissection of the ureters. **Although hydronephrosis may be unilateral on preoperative assessment, the process is generally bilateral requiring bilateral ureterolysis.** Following medial mobilization of the ascending and descending colon, deep biopsies of the mass should be obtained for frozen and permanent section to rule out malignancy. Dissection should begin at the distal, nondilated ureteral segment to avoid injury to the thin, dilated proximal segment. A right-angle clamp can be placed between the ureter and the retroperitoneal mass along the course of the ureter, and the fibrotic tissue is then incised above the clamp. This is repeated throughout the length of the entrapped ureter, using both blunt and sharp dissection techniques to free the affected ureter from its fibrous bed. The ureteral wall may become quite thin at times following the dissection. An inadvertent ureterotomy should be closed with absorbable suture. Ureteral excision with ureteroureterostomy is usually unnecessary.

Following bilateral ureterolysis, the ureters should be repositioned and protected from further fibrous entrapment. Several surgical options are available. One option is to retract the ureters laterally and secure the overlying peritoneum medially to the psoas muscle to maintain the ureters in this location. Another option is to close the peritoneum behind the ureters so that the ureters may be displaced anteriorly into the peritoneal cavity (Tresidder et al, 1972). It is important not to obstruct the ureter in the closure of the peritoneum at the ureteral hiatus. In a report on a group of patients with idiopathic RPF undergoing intraperitoneal placement of the ureters or lateral retroperitoneal placement of the ureters, no difference in the radiologic or clinical outcome was found (Barbalias and Liatsikos, 1999). In the setting of extensive RPF, a more definitive approach is to surround the ureters with omentum and reposition them within the peritoneal cavity (Carini et al, 1982). To perform the omental wrap, the omentum is first mobilized from its attachment to the transverse colon, followed by its division along its midline with ligation of the small omental vessels up to the gastric attachment. The short gastric vessels are then divided and ligated at the level of the stomach wall, after which the two halves of the omentum can be retracted laterally on the basis of the right and left gastroepiploic arteries. The entire length of the ureter can be surrounded by omental tissue, which is tacked in place with absorbable sutures (Fig. 41–38A and B). The omentum provides protection of the ureter against recurrent extrinsic compression and vascularity to a potentially ischemic ureter. Steroid therapy may be used postoperatively in an attempt to prevent recurrent upper tract and venous compression. If no ureterotomy occurs during ureterolysis, the previously placed stents may be removed shortly after surgery.

If ureterolysis is impossible to perform due to extensive periureteral fibrosis, renal autotransplantation may be performed if the ipsilateral renal unit demonstrates satisfactory function (Penalver et al, 2001). If no significant renal function can be recovered after an adequate time period of decompression in the presence of the satisfactory contralateral renal function, nephrectomy may be considered.

Surgical Management: Laparoscopic Ureterolysis

The first laparoscopic ureterolysis was reported by Kavoussi and Clayman in 1992. Subsequent success with such technique was confirmed by others (Puppo et al, 1994). A more recent report described an experience with laparoscopic ureterolysis in 13 patients including bilateral procedure in 7 and unilateral procedure in 6 (Fugita et al, 2001). Preoperative stent placement was performed in all cases before laparoscopy. For each ureter, the laparoscopic procedure was performed using a transperitoneal four-port approach. Following incision of the posterior peritoneum and mobilization of the colon, the affected ureter was dissected free from the retroperitoneal fibrotic tissue. Multiple frozen-section biopsies of the periureteral tissue were obtained to rule out malignancy. The edge of the posterior peritoneum was reapproximated to the sidewall underneath the ureter to intraperitonealize the ureter. Laparoscopic ureterolysis was completed successfully in 85% (11) of the cases, with 2 (15%) open conversions due to iliac vein injury (in one patient) and marked fibrosis (in one patient). Mean operative time was 381 minutes for bilateral procedures and 192 minutes for unilateral procedures. Mean use of parenteral analgesics was 59 mg of morphine sulfate equivalent. Mean hospital stay was 4 days. Postoperative complications

Key Points: Retroperitoneal Fibrosis

- The retroperitoneal fibrotic mass generally centers around the distal aorta at L4-L5 and wraps around the ureters, leading to hydronephrosis via extrinsic compression on the ureters or interference with ureteral peristalsis. In most cases the disease is idiopathic. Drugs such as methysergide and other ergot alkyloids are most commonly associated with RPF.
- RPF symptoms and signs are usually nonspecific. Laboratory evaluation may show an elevated erythrocyte sedimentation rate, moderate leukocytosis, anemia, and variable renal insufficiency associated with electrolyte abnormalities.
- Initial management of RPF in the presence of hydronephrosis and uremia includes emergent decompression by percutaneous nephrostomy or indwelling ureteral stents. Following decompression, the patient should be monitored closely for postobstructive diuresis.
- The most common primary medical management of idiopathic RPF has been steroid therapy, although other agents have been used.
- In surgical bilateral ureterolysis, the ureters need to be protected by intraperitonealization or omental wrapping. Both open and laparoscopic techniques may be applied successfully. If ureterolysis is impossible to perform, renal autotransplantation may be performed.

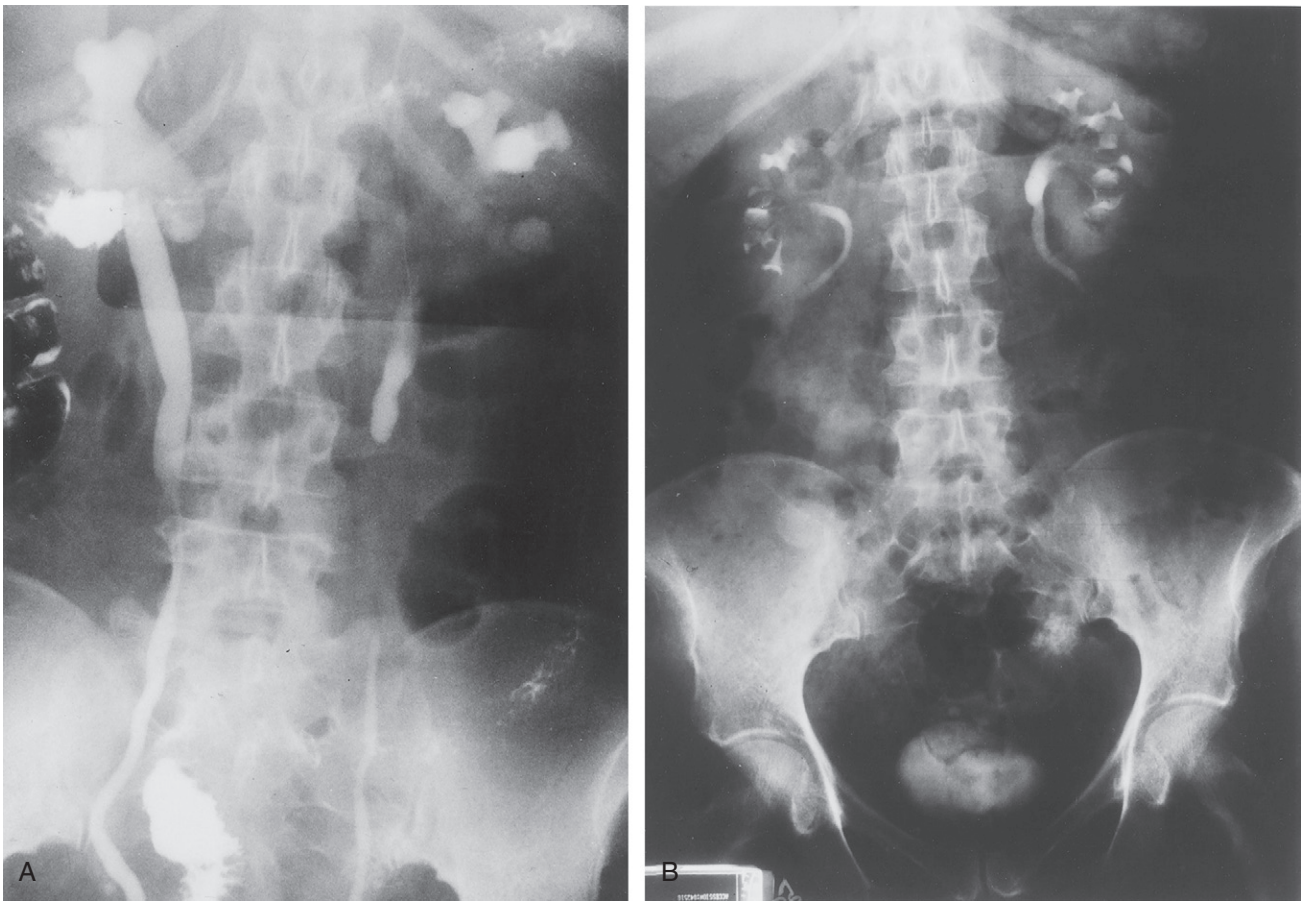


Figure 41–38. **A,** Preoperative intravenous pyelogram (IVP) of a patient with idiopathic retroperitoneal fibrosis, showing bilateral hydronephrosis with medial deviation of the ureters. **B,** Postoperative IVP of the same patient following surgical ureterolysis with intraperitoneal omental wrapping.

occurred in 30% (four) of the patients including epididymitis, umbilical port erythema, prolonged ileus, and urinary retention. Pathology showed fibrous tissue with lymphocytes, plasma cells, macrophages, and fibroblast proliferation in all cases. At a mean follow-up of 30 months, upper tract imaging such as intravenous urography or renal scan showed lack of obstruction in 92% (12) of the patients. A multi-institutional survey that included 17 academic centers identified that centers with a fellowship-trained laparoscopist performed laparoscopic ureterolysis, and in 59% of centers urologists performed the medical management. Notably in this survey the reported laparoscopic success rates were 83% (Duchene et al, 2007).

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter 42

Upper Urinary Tract Trauma

Richard A. Santucci, MD ● Leo R. Doumanian, MD

Renal Injuries

Ureteral Injuries

Traumatic injury is a leading national and international health problem. In the United States, 1 of every 14 deaths—more than 150,000 per year—results from trauma (Baker et al, 1992). Indeed, in young people, trauma results in more deaths between ages 1 and 37 years than any other cause. Violence alone claims 50,000 lives annually, and more than 2.2 million in the United States suffer injuries from assaults each year. With the development of trauma care systems and centers, death rates from major injuries have declined significantly over the past 20 years (Kivioj et al, 1990).

The initial evaluation and resuscitation of the injured patient are done by the emergency department physician and the trauma surgeon, but it is important that the involved urologist understand the mechanism of injury, its extent, the methods used in the initial resuscitation process, and their success rates. Individuals who survive the immediate impact of the initial trauma can often be resuscitated in the field. Immediate transport to a trauma center where complete evaluation and care can be provided is essential.

The first hour of care after a major injury is extremely important and requires rapid assessment of the injuries and resuscitation based on priorities established by the American College of Surgeons' Acute Trauma Life Support Program. The mnemonic "ABCDE" defines these priorities in order of importance: A, airway with cervical spine protection; B, breathing; C, circulation and control of external bleeding; D, disability or neurologic status; and E, exposure (undress) and environment (temperature control) (American College of Surgeons Committee on Trauma, 2004).

The best care provided to a polytrauma patient comes from a well-organized team of specialists, most often led by a surgeon experienced in trauma care. Because approximately 10% of injuries involve the genitourinary tract—with the kidney being the most commonly injured organ—the urologist is a valued team member because of the experienced care he or she can provide for these special types of injuries.

RENAL INJURIES

Presentation

The kidneys are the most common genitourinary organs injured from external trauma. The evaluation and management of renal injuries, occurring in up to 10% of abdominal trauma cases, has evolved over the past 2 decades. Advances in radiographic staging, improvements in hemodynamic monitoring, validated renal injury scoring systems, and essential details about the mechanisms of injury allow successful nonoperative management strategies for renal preservation. The majority of blunt and many penetrating injuries to the kidneys no longer require absolute surgical intervention despite association with other visceral injuries.

Motor vehicle accidents, falls from heights, and assaults contribute to the majority of blunt renal trauma. Direct transmission of kinetic energy and rapid deceleration forces places the kidneys at risk. **Perhaps the most important information to obtain in the history of the injury is the extent of deceleration involved in high-velocity impact trauma.** Major renovascular injuries, although exceedingly rare, occur at retroperitoneal points of fixation such as the renal hilum or ureteropelvic junction, resulting in renal artery thrombosis, renal vein disruption, and renal pedicle avulsion.

Penetrating renal injuries most often come from gunshot and stab wounds. Gunshot wounds comprise the great majority of penetrating trauma with stab wounds a distant second (86% vs. 14%). Injuries to the upper abdomen or lower chest should immediately alert the physician to potential renal injury. Often presenting with a more advanced grade of injury, penetrating mechanisms lead to higher rates of surgical exploration. Of all patients sustaining renal trauma in a large reported series, renal gunshot wounds occurred in approximately 4% (McAninch et al, 1993).

Initial assessment of gunshot wounds involves gathering important information regarding weapon characteristics including caliber and types. Bullet size and velocity has the greatest effect on soft tissue damage as predicted by the following equation:

$$KE = \frac{\text{mass} \times V^2}{2 \times G}$$

where KE = kinetic energy, V = velocity, and G = gravity.

Whether the preceding equation accurately reflects tissue destruction is controversial; however, the result of extensive soft tissue damage caused by high-velocity weapons requires debridement guided by individualized clinical observation (Santucci and Chang, 2004). The greater the bullet velocity, the larger the temporary cavity created, and the larger potential for soft tissue stretch and destruction (Hutton and Rich, 1996). Handguns are generally considered low-velocity firearms (<2000 ft/sec). Other factors to consider are bullet shape (i.e., blunt or narrow), type (i.e., hollow point, exploding, frangible), caliber, and velocity, which all may independently contribute to tissue disruption and injury.

Stab wounds from assault or self-inflicted injuries can cause both renovascular and parenchymal injuries. Common entry sites including the upper abdomen, flank, and lower chest should alert

the clinician to possible renal involvement. Should the weapon be recovered, its dimensions should be noted because the length and width give valuable information on its penetrating and destructive characteristics. In fact, trauma to the anterior axillary line is more prone to damage important renal structures like the renal hilum and pedicle, compared with the posterior axillary line more often resulting in parenchymal injury.

Physical examination of all body systems must be detailed and complete. In a conscious patient, a thorough history can be taken during the examination. Rapid resuscitation according to AAST guidelines should be followed for severe polytrauma. With a blunt mechanism, cervical spine immobilization is mandated until confirmed intact by radiography. Examination of the abdomen, chest, and back must be performed. The presence of a flank hematoma, abdominal or flank tenderness, rib fractures, and penetrating injuries to the low thorax or flank indicate possible renal injury.

Gunshot injuries can be misleading. Small entrance wounds often underestimate larger tissue destruction within the body. Exit wounds are frequently much larger. Soft tissue and bone can alter the bullet's trajectory; thus the projectile seldom takes a direct path from entrance to exit. Should the bullet fragment, secondary missiles are created, often resulting in multiple exit sites. When radiographs of the chest and abdomen are taken, it is useful to place a small metallic object such as a paper clip at entrance and exit sites to help define these locations on the films.

Hematuria

The best indicators of significant urinary system injury include the presence of microscopic (>5 red blood cells/high-power field [RBCs/HPF] or positive dipstick finding) or gross hematuria and hypotension (systolic blood pressure <90 mm Hg). The presence of microscopic hematuria is often characteristic. However, gross hematuria has been observed in minor renal contusions and microscopic hematuria has been associated with severe renal injuries. For example, hematuria was absent in 7% of 420 grade IV renal injuries in a recent analysis (Shariat et al, 2008a) and 36% of renal vascular injuries from blunt trauma demonstrated no blood in the urine (Cass, 1989). Also, approximately 50% of injuries to the ureteropelvic junction have no microscopic or gross hematuria. **Therefore the degree of hematuria and the severity of the renal injury do not consistently correlate.** In patients with blunt trauma, if shock is noted with microscopic hematuria, the incidence of significant renal injuries increases (Mee et al, 1989; Miller and McAninch, 1995; Nicolaisen et al, 1985). In addition, hematuria has been used as a general predictor of nonrenal intra-abdominal organ injury after blunt trauma (Knudson et al, 1992).

The authors use the first aliquot of urine obtained either by catheterization or by voiding to determine the presence of hematuria. Later urine samples are often diluted by diuresis from resuscitation fluids, resulting in an underestimation or absence of hematuria. Any degree of visible blood in the urine is regarded as gross hematuria. Microscopic hematuria can be detected by dipstick analysis or microanalysis. The dipstick method is rapid and has a sensitivity and specificity for detection of microhematuria of more than 97%, even though a poor correlation with actual urinalysis was noted in a study by Chandhoke and McAninch (1988). Although critical to the initial evaluation of traumatic urinary tract injury, the presence or absence of hematuria should not be the sole determinant in the assessment of a patient with suspected renal trauma. Because the significance of hematuria varies with blunt and penetrating mechanisms, the importance of proper staging of renal injuries cannot be underscored.

Classification

Numerous models have been proposed for staging and management of renal trauma according to the severity of the injury. The American Association for the Surgery of Trauma's Organ Injury Scaling Committee (Moore et al, 1989) developed the most widely used and accepted classification (Table 42–1; Fig. 42–1). On the basis of accurate grading made possible by contrast-enhanced computed tomography (CT), the AAST injury severity scale is a powerful and valid predictive tool for clinical outcomes in patients with renal trauma. Even with these minor variations in reporting, the classification system has established a common scale by which injuries can be identified at disparate centers according to the extent of damage, and it has worked well (Santucci et al, 2001). The widespread use and anatomic detail provided by CT imaging has now supplanted the much less sensitive and less specific excretory urography (intravenous pyelography [IVP]) for grading purposes.

Staging

Staging of renal trauma refers to the use of appropriate imaging studies to define the extent of injury. Assessment of clinical history and physical examination findings combined with imaging studies provides maximal guidance for treatment decisions. Proper staging is essential for nonoperative management of renal injuries.

Indications for Renal Imaging

The criteria for radiologic imaging include (1) all penetrating trauma patients with a likelihood of renal injury (abdomen, flank, or low chest) who are hemodynamically stable; (2) all blunt trauma with significant mechanism of injury, specifically rapid deceleration as would occur in a motor vehicle accident or a fall from heights; (3) all blunt trauma with gross hematuria; (4) all blunt trauma with hypotension defined as a systolic pressure of less than 90 mm Hg at any time during evaluation

Table 42–1.

American Association for the Surgery of Trauma Organ Injury Severity Scale for the Kidney

GRADE*	TYPE	DESCRIPTION
I	Contusion	Microscopic or gross hematuria, urologic studies normal
	Hematoma	Subcapsular, nonexpanding without parenchymal laceration
II	Hematoma	Nonexpanding perirenal hematoma confined to renal retroperitoneum
	Laceration	<1 cm parenchymal depth of renal cortex without urinary extravasation
III	Laceration	>1 cm parenchymal depth of renal cortex without collecting system rupture or urinary extravasation
IV	Laceration	Parenchymal laceration extending through renal cortex, medulla, and collecting system
	Vascular	Main renal artery or vein injury with contained hemorrhage
V	Laceration	Completely shattered kidney
	Vascular	Avulsion of renal hilum, devascularizing the kidney

*Advance one grade for bilateral injuries up to grade III.

Data from Moore EE, Shackford SR, Pachter HL, et al. Organ injury scaling: spleen, liver, and kidney. J Trauma 1989;29:1664–6.

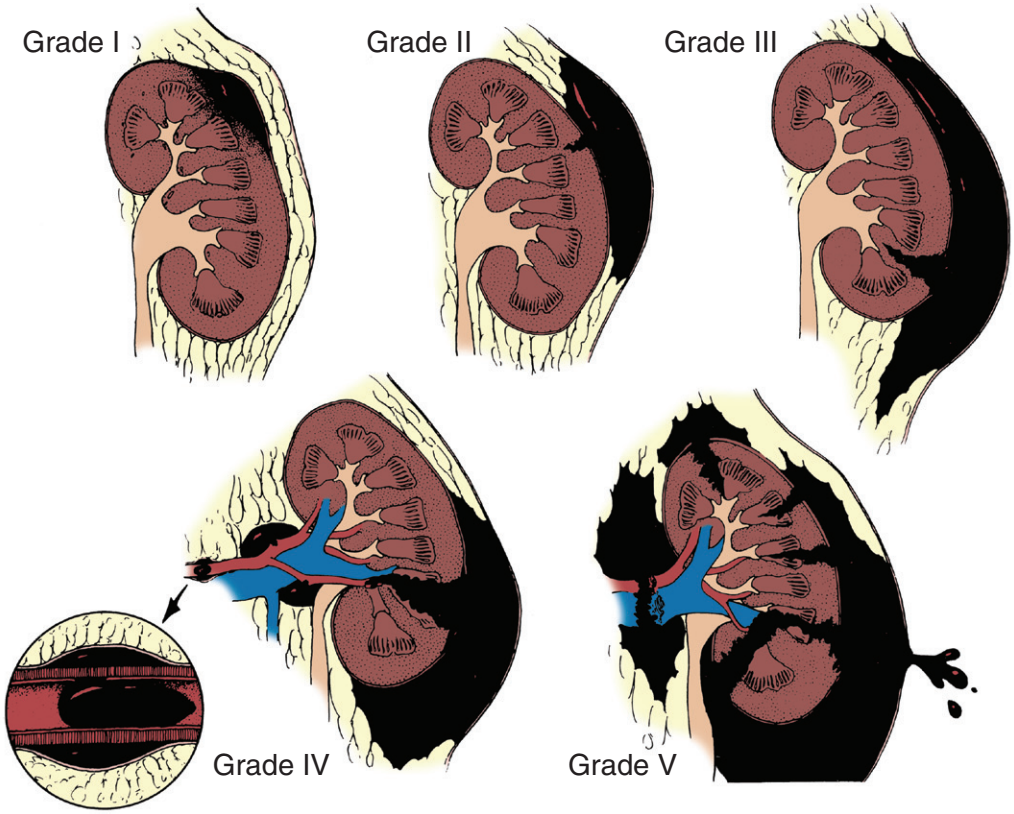


Figure 42–1. Classification of renal injuries by grade (based on the organ injury scale of the American Association for the Surgery of Trauma [based on Moore et al, 1989]).

and resuscitation; and (5) all pediatric patients with greater than 5 red blood cells (RBCs)/HPF. Patients who are hemodynamically unstable after initial resuscitation require surgical intervention.

The best indicator of renal injury is hematuria, defined as 5 RBCs/HPF by most authors. Historically, when used as the sole indication for renal imaging, IVP and other studies found a low incidence of renal abnormalities. An extensive prospective study based at San Francisco General Hospital evaluating indications for radiographic imaging has been ongoing for more than 25 years. The findings have been updated on three reports (Mee et al, 1989; Miller and McAninch, 1995; Nicolaisen et al, 1985). Figure 42–2 provides the results of the study for adult blunt renal trauma. On the basis of information from this study, all blunt trauma patients with gross hematuria and patients with microscopic hematuria and shock (systolic blood pressure <90 mm Hg any time during evaluation and resuscitation) should undergo renal imaging, usually with CT using intravenous contrast.

Patients with microscopic hematuria without shock can be observed clinically without imaging studies. As first noted by Miller and McAninch (1995), several studies confirm the findings that these patients rarely have a significant injury (<0.0016%). However, if possible renal injury is suspected on the basis of history or examination, imaging should be performed. For example, blunt rapid deceleration injuries such as high-speed motor vehicle accidents or falls from great heights are at risk for vascular injury. These can cause significant injury (usually ureteral avulsion or vessel injury) in the absence of microscopic hematuria.

Penetrating injuries with any degree of hematuria should be imaged. In a report by Carroll and McAninch (1985),

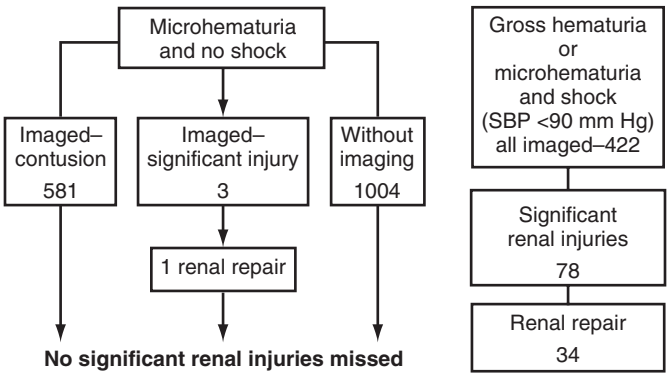


Figure 42–2. Algorithm demonstrating the results of the authors' study on radiographic assessment of renal injuries. In adults with blunt trauma, imaging studies may be performed selectively. SBP, systolic blood pressure. (From Miller KS, McAninch JW. Radiographic assessment of renal trauma. Our 15-year experience. J Urol 1995;154:352–5.)

27 of 50 patients with penetrating renal trauma had microscopic hematuria. Three of these patients had 0 to 3 RBCs/HPF, and one of the three had a renal pedicle injury. The presence of shock, degree of hematuria, location of the entry wound, and type of injury do not permit reliable discrimination among categories.

Pediatric patients (younger than 18 years) sustaining blunt renal trauma must be carefully evaluated. Children are known to be at a greater risk for renal trauma than adults after blunt abdominal injury (Brown and colleagues, 1998a). For pediatric patients, liberal use of imaging studies should be considered, especially in the setting of high-speed/high-energy deceleration injuries

(Buckley and McAninch, 2004). Children have a high catecholamine output after trauma, which maintains blood pressure until approximately 50% of blood volume has been lost. A recent review confirmed that the decision to image pediatric trauma cases on the basis of the adult criteria of gross hematuria, shock, and significant deceleration injury appropriately identified potential renal injuries just as they would in adult patients (Santucci et al, 2004).

Imaging Studies

Contrast-enhanced computed tomography (CT) is the gold standard for genitourinary imaging in renal trauma (Bretan et al, 1986; Federle et al, 1987). Highly sensitive and specific, CT provides the most definitive staging information: Parenchymal lacerations are clearly defined; extravasation of contrast-enhanced urine can easily be detected (Fig. 42–3); associated injuries to the bowel, pancreas, liver, spleen, and other organs can be identified; and the degree of retroperitoneal bleeding can be assessed by the size and dimensions of the retroperitoneal hematoma. Lack of uptake of contrast material in the parenchyma suggests arterial injury. **The added anatomic detail for diagnosis of renal contrast extravasation and parenchymal/vascular injuries has translated into improved confidence in our ability to nonoperatively manage major injuries.**

Currently, spiral CT is being used in many centers to evaluate renal injuries (Brown et al, 1998b). Arteriovenous scanning (typically 80 seconds after contrast administration) provides visualization of the kidneys in the nephrogenic phase of contrast excretion and is necessary to detect arterial extravasation. Injury to the renal collecting system may be missed; contrast material has not had time to be excreted into the parenchyma and collecting system adequately. Repeated/delayed scanning of the kidneys 10 minutes after injection of contrast identifies parenchymal lacerations and urinary extravasation accurately and reliably. Expert opinion holds that delayed films may be omitted when the kidneys are deemed normal, and no perinephric, retroperitoneal, pelvic, or perivesical fluid is present (Santucci et al, 2004). **Findings on CT that raise suspicion for major injury are (1) medial hematoma, suggesting vascular injury; (2) medial urinary extravasation, suggesting renal pelvis or ureteropelvic junction avulsion injury; and (3) lack of contrast enhancement of the parenchyma, suggesting arterial injury.**



Figure 42–3. Computed tomography scan of a right renal stab wound (grade IV), demonstrating extensive urinary extravasation and large retroperitoneal hematoma.

One major limitation of CT is the inability to define a renal venous injury adequately. With normal arterial perfusion, the parenchyma appears normal and the collecting system may contain contrast material. A medial hematoma accompanying the preceding findings strongly suggests a venous injury.

Historically, excretory urography was the most commonly used modality to evaluate genitourinary injuries. Largely replaced by CT, a limited role includes the intraoperative "single-shot" IVP. The indications are uncommon, but when the surgeon encounters an unexpected retroperitoneal hematoma surrounding a kidney during abdominal exploration, the study can provide essential information. The main purpose of the one-shot IVP is to assess the presence of a functioning contralateral kidney and to radiographically stage the injured side. The technique is key to gaining important information and minimizing the time involved: only a single film is taken 10 minutes after intravenous injection (IV push) of 2 mL/kg of contrast material. If findings are not normal or near normal, the kidney should be explored to complete the staging of the injury and reconstruct any abnormality found.

Morey and coworkers (1999) have reported their experience with single-shot intraoperative IVP for the immediate management of renal injuries; in 50 patients, the film quality was adequate to avoid renal exploration in 32%. This report supports the value of this intraoperative imaging technique when done properly.

Other imaging modalities have a limited role in the evaluation of genitourinary trauma. Sonography is being used with greater frequency in the immediate evaluation of injuries and can facilitate the rapid diagnosis of intraabdominal injuries (i.e., hemoperitoneum). However, the study cannot clearly delineate parenchymal lacerations, vascular disruptions, collecting system injuries, and urinary extravasation in the acute setting. If necessary, sonography can confirm the presence of two kidneys and can define a retroperitoneal hematoma. With the advent of power Doppler or other techniques such as ultrasound contrast, perhaps more functional information will be obtainable in the future from renal ultrasound in the trauma setting.

In select cases, renal arteriography can be considered an adjunct diagnostic imaging technique with possible therapeutic implications. Angiography is largely used to define arterial injuries suspected on CT or to localize and control arterial bleeding (Fig. 42–4). Renal embolization has proved useful in the primary setting with persistent bleeding in a hemodynamically stable patient. Case reports have shown that endovascular stenting can be used to treat traumatic renal artery dissection, but technical problems surrounding the need for postprocedure anticoagulation have not yet been solved. Pseudoaneurysms and arteriovenous fistula are treated by angiographic embolization to stop secondary hemorrhage. Superselective embolization therapy for renal trauma now provides an effective and minimally invasive technique to avoid unnecessary exploration that could otherwise result in a nephrectomy.

Nonoperative Management

Significant injuries (grades II to V) are found in only 5.4% of renal trauma cases (Miller and McAninch, 1995). Nonoperative management has become the standard of care in hemodynamically stable,

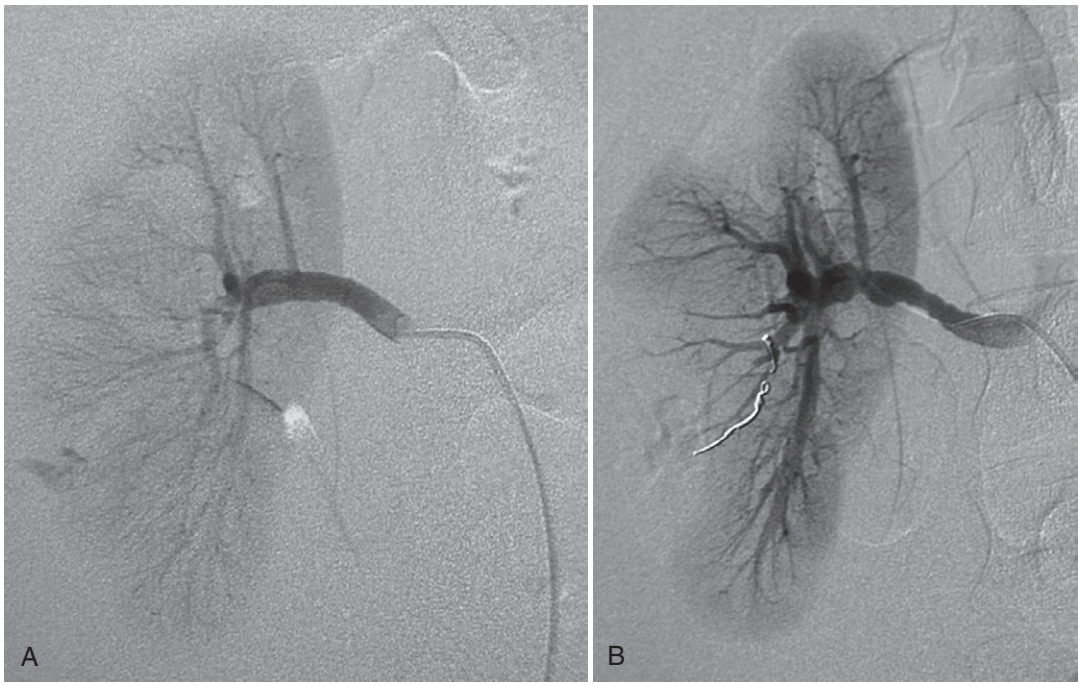


Figure 42–4. Angioembolization of renal laceration: **A,** Arteriography demonstrating active arterial bleeding. **B,** Coil embolization used to control bleeding. Note presence of coil and large, triangular area of infarct.

well-staged patients with American Association for the Surgery of Trauma (AAST) grade I to III renal injuries, regardless of mechanism (Santucci et al, 2004). Most experts agree that patients with grade IV and V injuries more often require surgical exploration, but even these high-grade injuries can be managed without renal operation if carefully staged and selected (Fig. 42–5) (Santucci and McAninch, 2000; Santucci et al, 2004).

A trial of expectant management has even been advocated for most adult blunt renal parenchymal injuries, many renal stab wounds, and selective renal gunshot wounds. Bluntly injured kidneys heal well when managed conservatively, even in the setting of urinary extravasation and nonviable tissue; 98% can be successfully managed without exploration (Broghammer et al, 2007). In fact, in a series of six hemodynamically stable, grade V blunt injuries, four (66%) kidneys demonstrated satisfactory function after conservative treatment (Altman, 2000).

Penetrating trauma from gunshot or stab wounds to the kidney can also be managed nonoperatively in stable patients. In one large series, 55% of renal stab wounds and 24% of gunshot wounds were appropriately managed nonoperatively in carefully selected patients with well-staged injuries (McAninch et al, 1991). Contrary to past experience, obligatory exploration is no longer mandated for renal gunshot wounds. Serafetinides (2004) treated 40 patients (54%) with low-velocity gunshots expectantly with few complications. Stab injuries have more evidence to support conservative management. Nonoperative management protocols resulted in no delayed nephrectomies in a cohort of 108 hemodynamically stable stab wound patients (Armenakas et al, 1999) Although blunt and penetrating trauma often requires exploration due to associated nonurologic injury, many authors argue for continued conservative approach intraoperatively, particularly in the presence of an injured kidney with a nonexpanding, nonpulsatile hematoma (Shariat et al, 2008b).

All patients with high-grade injuries (grades III to V) selected for nonoperative management should be closely observed with serial hematocrit readings. Strict bedrest is mandatory until gross hematuria resolves. Patients presenting with urinary extravasation or nonviable parenchyma may be considered for periodic inpatient imaging, although the authors are aware of no studies to prove it helps in the absence of worrisome symptoms (fever, flank

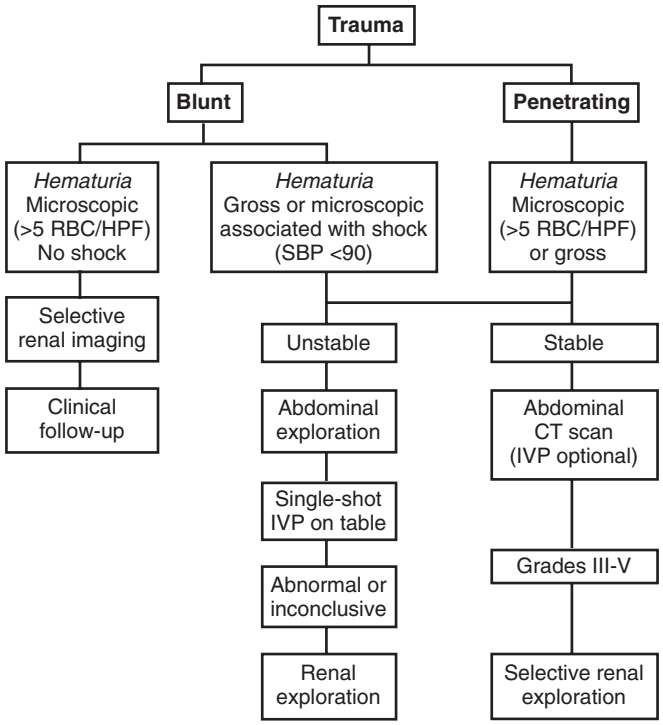


Figure 42–5. Flow chart for adult renal injuries to serve as a guide for decision making. CT, computed tomography; IVP, intravenous pyelography; RBC/HPF, red blood cells per high-power field; SBP, systolic blood pressure.

pain, dropping hematocrit). Although most grades II to IV injuries resolve uneventfully, delayed renal bleeding can occur in up to 25% (Wessells et al, 1997). Should bleeding persist or delayed bleeding occur, angiography with selective embolization of bleeding vessels can obviate surgical intervention.

Isolated Renal Injuries

The presence of concomitant injuries often influences the management of renal trauma; approximately 80% to 90% of renal injuries have major associated organ injury requiring surgical exploration. Although the majority of grade I to III renal injuries can be managed nonoperatively with excellent renal preservation, patients with grade V injuries, defined as hemodynamically unstable with major renovascular insults or multiple grade IV parenchymal lacerations, usually require immediate life-saving operative exploration. Thus a special subset of high-grade injuries, specifically an isolated grade IV insult without significant associated abdominal injuries, occurs more commonly from blunt trauma and in most circumstances can be managed nonoperatively.

Expectant management strategies of isolated kidney injuries allow for maximal renal preservation. Superselective embolization therapy for renal trauma provides an effective and minimally invasive means to stop active bleeding from parenchymal lacerations and even segmental arterial injury. Interventional radiology skills and techniques allow selective embolization of even the smallest parenchymal vessels with maximal preservation of functioning parenchyma. However, one must recognize that renal vessels are end arteries, and any selective vessel embolization results in tissue death peripheral to the embolized site.

The management of severe renal lacerations must balance two major issues: the increased incidence of nephrectomy in patients undergoing immediate as opposed to delayed renal exploration and the associated morbidity of patients managed expectantly. The experience with endovascular therapy for severe renal hemorrhage continues to grow. In a literature review of 10 case series, most renal traumas including most grade IV injuries were effectively managed with embolization therapy with a clinical success rate of 80% (Breyer, 2008). Indications for angiography with embolization therapy have included bleeding from a renal segmental artery with or without parenchymal laceration, unstable condition with grade III to IV injury, arteriovenous fistula or pseudoaneurysm, persistent gross hematuria, and/or blood loss exceeding 2 units in 24 hours. Future considerations to better define the criteria for angiography and embolization in patients with renal hemorrhage continue to be an area of research interest.

In special clinical circumstances, endovascular stents have been used with reported success during angiography in patients with renal artery thrombosis occurring from intimal flaps (Goodman et al, 1998). Longer-term follow-up and more cases are necessary to determine whether this will be a successful management approach, especially considering that most stents require anticoagulation after placement, which may not be possible in a trauma patient.

Those patients with grade IV parenchymal lacerations who have well-contained hematomas should be observed expectantly. An 88% renal salvage rate of isolated grade IV renal injuries managed conservatively has recently been documented (Buckley and McAninch, 2006). They should be closely monitored for bleeding, with vital signs, serial hematocrit readings, and pulse rates. If urinary extravasation is present, serial renal CT scanning can be considered. If significant urinary extravasation persists, placement of an internal ureteral stent for drainage often prevents prolongation of the extravasation and decreases the chance of perirenal urinoma formation. Experts recommend the use of broad-spectrum antibiotics to decrease the possibility of perinephric abscess, although the authors are aware of no convincing research that they decrease infection rates.

If nonoperative management is selected for a patient with gross hematuria whose injury has been well staged with appropriate imaging, hospital admission and bed rest are required. Once the gross hematuria clears, ambulation is allowed; should gross hematuria recur, bed rest is reinstated. Ambulation without any sequelae allows hospital discharge with close clinical follow-up. The patient should be watched for and warned about the possibility of renovascular hypertension and delayed bleeding.

Operative Management

Indications for renal exploration after trauma can be separated into absolute and relative (Voelzke and McAninch, 2008). **Absolute indications include (1) hemodynamic instability with shock; (2) expanding/pulsatile renal hematoma (usually indicating renal artery avulsion); (3) suspected renal pedicle avulsion (grade 5); and (4) ureteropelvic junction disruption. Relative indications are now rare: urinary extravasation together with nonviable tissue, renal injury together with colon/pancreatic injury, and a delayed diagnosis of arterial injury (which most likely will need delayed nephrectomy).** The management of the intraoperative presence of a nonexpanding retroperitoneal hematoma is controversial. Nonoperative therapy is recommended, regardless of mechanism.

Urinary extravasation alone from a grade IV parenchymal laceration or forniceal rupture can be managed nonoperatively with an expectation of spontaneous resolution of more than 90%. Should nonviable tissue constitute more than 25% in association with a parenchymal laceration or urinary extravasation or both, the potential for complications greatly increases and operative management is recommended (Alsikafi et al, 2006).

Segmental renal artery injury with an associated renal laceration results in a substantial amount of nonviable tissue (usually > 20%). Historically, it was believed that such injuries resolved more quickly with surgical reconstruction and tissue removal. Currently, nonoperative management is favored in hemodynamically stable patients, although concerns include delayed bleeding and urinoma formation. A recent series demonstrated excellent outcomes with only 1 of 18 (6%) patients requiring subsequent intervention during conservative management of segmental renal artery injuries (Elliott et al, 2007).

Incomplete staging is an important concern when determining whether renal exploration is necessary. When the patient's critical condition necessitates surgical intervention before appropriate imaging studies and renal injury is obvious (manifested by perirenal hematoma or hematuria), single-shot intraoperative IVP should be done (see earlier). If findings are not normal, renal exploration provides the opportunity to complete the staging process and reconstruct a significant injury. The authors' experience in exploring more than 200 renal units suggests that this approach is safe, without renal loss, and provides the opportunity to reconstruct high-grade injuries and prevent complications in the postoperative period.

Renal Exploration

Surgical exploration of the acutely injured kidney is best done by a transabdominal approach, which allows complete inspection of intra-abdominal organs and bowel.

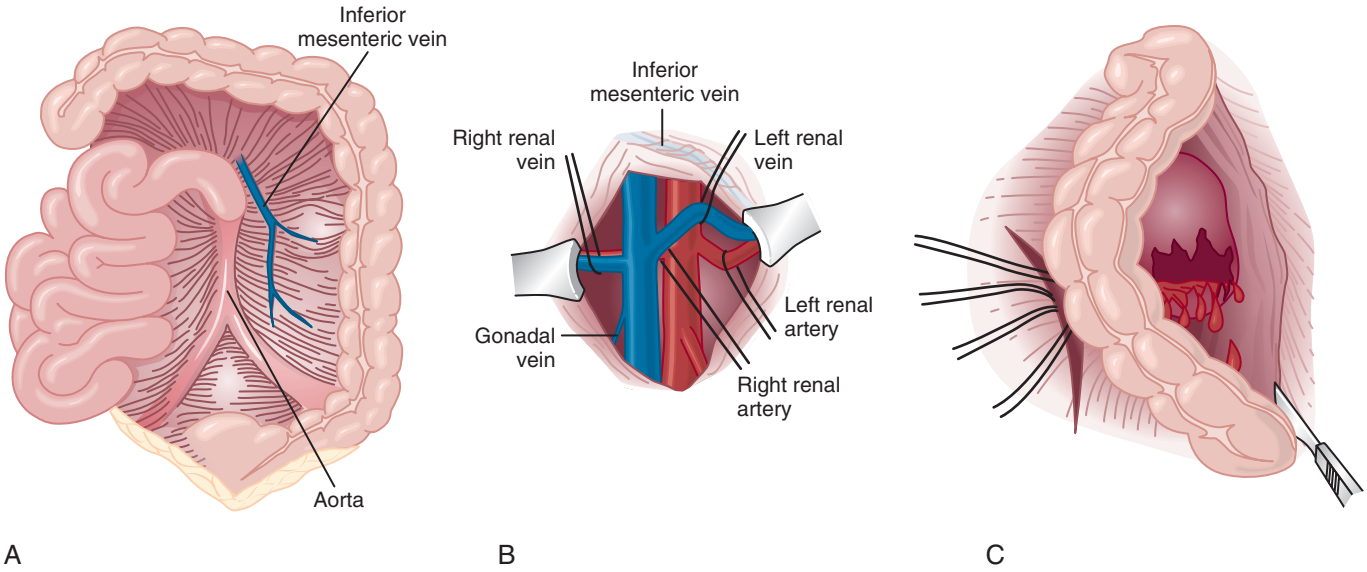


Figure 42–6. The surgical approach to the renal vessels and kidney. **A,** Retroperitoneal incision over the aorta medial to the inferior mesenteric vein. **B,** Anatomic relationships of the renal vessels. **C,** Retroperitoneal incision lateral to the colon, exposing the kidney.

In some reported series of penetrating injuries, associated organ injury has been noted to be as high as 94% (McAninch et al, 1993). Injuries to the great vessels, liver, spleen, pancreas, and bowel can be identified and stabilized if necessary before renal exploration.

The surgical approach to renal exploration is shown in Figure 42–6 (McAninch and Carroll, 1989). The renal vessels are isolated before exploration to provide the immediate capability to occlude them if massive bleeding should ensue when Gerota's fascia is opened (Scott and Selzman, 1966). The transverse colon is lifted superiorly onto the chest, and the small bowel is lifted superiorly and to the right. This exposes the midretroperitoneum. An incision is made over the aorta in the retroperitoneum just superior to the inferior mesenteric artery. The incision is extended superiorly to the ligament of Treitz. Exposure of the anterior surface of the aorta is accomplished and followed superiorly to the left renal vein, which crosses the aorta anteriorly. With a vessel loop controlling the vein, the anatomic relationships of the right and left renal arteries as they leave the aorta provide the ability to isolate and secure these structures with vessel loops. The right renal vein can be secured through this incision; if this proves difficult, reflecting the second portion of the duodenum provides excellent exposure to the vein.

Large hematomas may extend over the aorta and obscure the landmarks for the planned initial retroperitoneal incision. In such instances, the inferior mesenteric vein can be used as an anatomic guide for an appropriate incision. By making the retroperitoneal incision just medial to the inferior mesenteric vein and dissecting through the hematoma, the anterior surface of the aorta can be identified and followed superiorly to the crossing left renal vein.

The kidney is exposed by incising the peritoneum lateral to the colon, followed by mobilization off Gerota fascia. This maneuver often requires release of the splenic (left) or hepatic (right) attachments of the colon. Gerota fascia is then opened and the kidney with injury is completely dissected from the surrounding hematoma. Should troublesome bleeding develop, the previously isolated vessels can be temporarily occluded with a vascular clamp or a vessel loop tourniquet.

Is Early Vessel Isolation Necessary? Renal bleeding is a major cause of nephrectomy in renal trauma. **Obtaining early vascular control before opening Gerota fascia can decrease renal loss:** in a comparative series, the total nephrectomy rate was reduced from 56% to 18% (McAninch and Carroll, 1982). Carroll and coauthors (1989), evaluating the use of early vascular control, reported the need to occlude the vessels in 12% of renal explorations. In a series of 133 renal units in which early vessel isolation and control before opening Gerota fascia was achieved in all, McAninch and colleagues (1991) reported a renal salvage rate of 88.7%.

The need for early vascular control has been questioned. Corriere and colleagues (1991) reported a series of renal units in which vascular control was obtained only if needed after opening Gerota fascia. In this group, the total nephrectomy rate was 37.1%. Atala and colleagues (1991) reported a similar group of patients with a total nephrectomy rate of 36.2%. On the whole, the currently available data support an improved renal salvage rate with early vascular control because patients who require temporary vascular occlusion cannot be reliably identified before renal inspection.

Renal Reconstruction

The principles of renal reconstruction after trauma include complete renal exposure, measures for temporary vascular control, debridement of nonviable tissue, hemostasis by individual suture ligation of bleeding vessels, watertight closure of the collecting system if possible, coverage or reapproximation of the parenchymal defect, and judicious use of drains (Fig. 42–7).

Renorrhaphy is illustrated in Figure 42–8 and involves exposure of the kidney, debridement of nonviable tissue, hemostasis obtained with absorbable 4-0 chromic sutures on bleeding vessels (the addition of hemostatic agents such as Floseal [Baxter; Deerfield, IL] may also be helpful), closure of the collecting system, and approximation of the margins of the laceration (3-0 absorbable suture) with the use of renal capsule and an absorbable hemostatic agent bolster such as Gelfoam (Pfizer; New York, NY).

When polar injuries cannot be reconstructed, a partial nephrectomy should be done and all nonviable tissue removed, hemostasis obtained, and the collecting system closed. The open parenchyma should then be covered when possible by a pedicle flap of omentum (see Fig. 42–7). With its rich vascular and

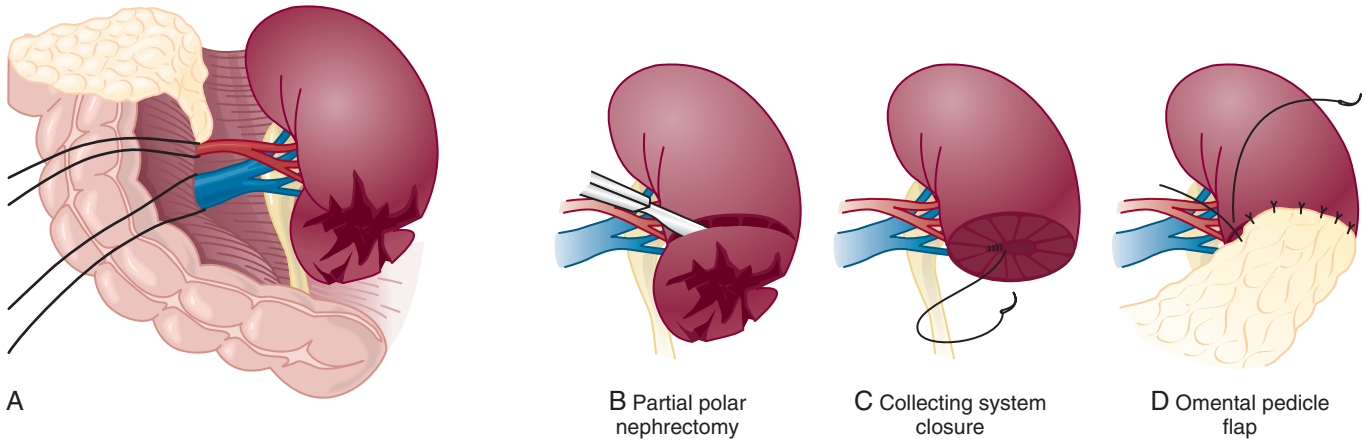


Figure 42–7. Technique for partial nephrectomy: **A,** total renal exposure; **B,** sharp removal of nonviable tissue; **C,** hemostasis obtained and collecting system closed; **D,** defect covered.

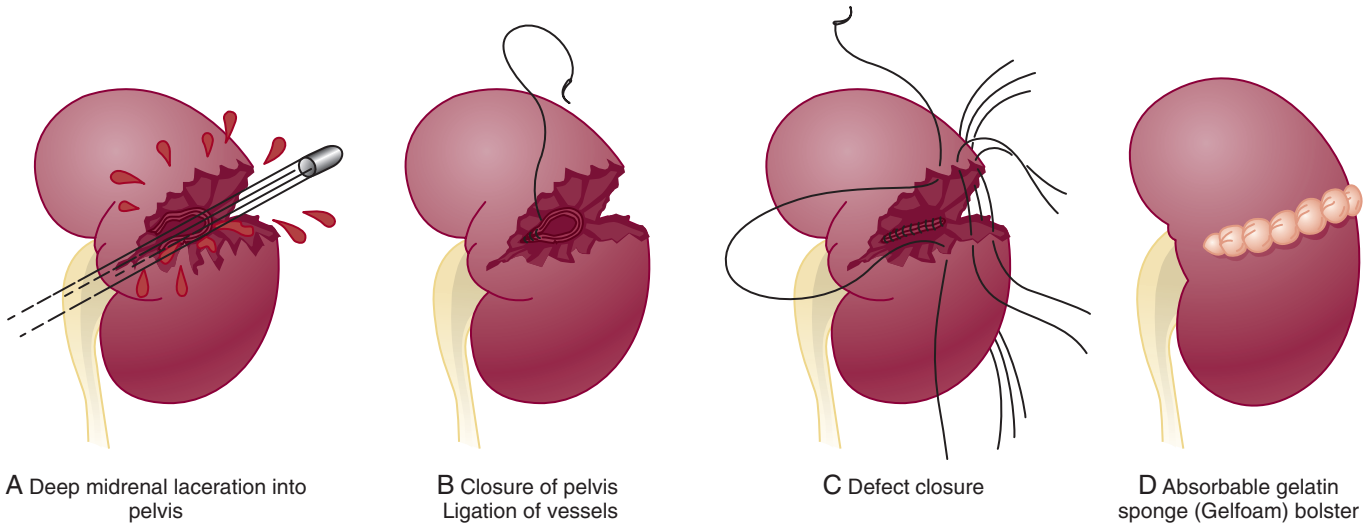


Figure 42–8. Technique for renorrhaphy: **A,** typical injury in midportion of kidney; **B,** debridement, hemostasis, and collecting system closure; **C,** approximation of parenchymal margins; **D,** sutures tied over gelatin sponge bolster.

lymphatic supply, omentum promotes wound healing and decreases the risk of delayed bleeding and urinary extravasation. Should it not be available, the use of absorbable mesh, peritoneal graft, or retroperitoneal fat has been successful (Master and McAninch, 2006).

Hemostatic agents such as Floseal are potent and have an increasing role in the management of genitourinary trauma (Evans and Morey, 2006). On the basis of experience from nephron-sparing surgery, gelatin matrix was applied to a porcine model of complex renal trauma and demonstrated less mean blood loss than conventional suture treatment (Hick et al, 2005; Pursifull et al, 2006).

In a high percentage of major renal injuries, intra-abdominal structures are also injured, the liver and spleen being the most common. Injuries to the colon, pancreas, and stomach also occur frequently, and in previous years total nephrectomy was suggested because of the high complication rate with attempted renal salvage. However, renal repair in these injuries has been successful with minimal complications (Rosen and McAninch, 1994; Wessells and McAninch, 1996). Drains should be used liberally in these repairs.

Renovascular Injuries. Renovascular injuries following trauma are uncommon and often have associated injuries requiring operative intervention. For major renovascular injuries, speedy nephrectomy is advocated. In rare instances where repair is possible, renal salvage rates are low, exemplified by a 33% renal salvage rate for main renal artery reconstruction even in the most expert of hands (Elliott et al, 2007). Vascular repair requires occlusion of the involved vessel with vascular clamps. The lacerated main renal vessels injured by penetrating trauma can be repaired with 5-0 nonabsorbable vascular suture (Fig. 42–9).

Main renal artery thrombosis from blunt trauma occurs secondary to deceleration injuries. The mobility of the kidney results in stretch on the renal artery, which in turn causes the arterial intima, low in elastic fibers, to disrupt. The consequent thrombus occludes the vessel, rendering the kidney ischemic (Fig. 42–10). Prompt diagnosis by CT or angiography may lead to immediate renal exploration in the appropriate candidate in an attempt to salvage the kidney, but outcomes for salvage remain dismally low and nephrectomy is almost always required.

Case reports of successful renal revascularization through the use of endovascular stents during angiography offer a new and perhaps promising approach to the problem of blunt trauma renal artery thrombosis caused by the intimal flap (Inoue et al, 2004). The great disadvantage of this approach has been the inability to effect anticoagulation in the polytrauma patient.

With delayed diagnosis (>8 hours), the kidney typically cannot be salvaged (Cass, 1989). With a 15-year

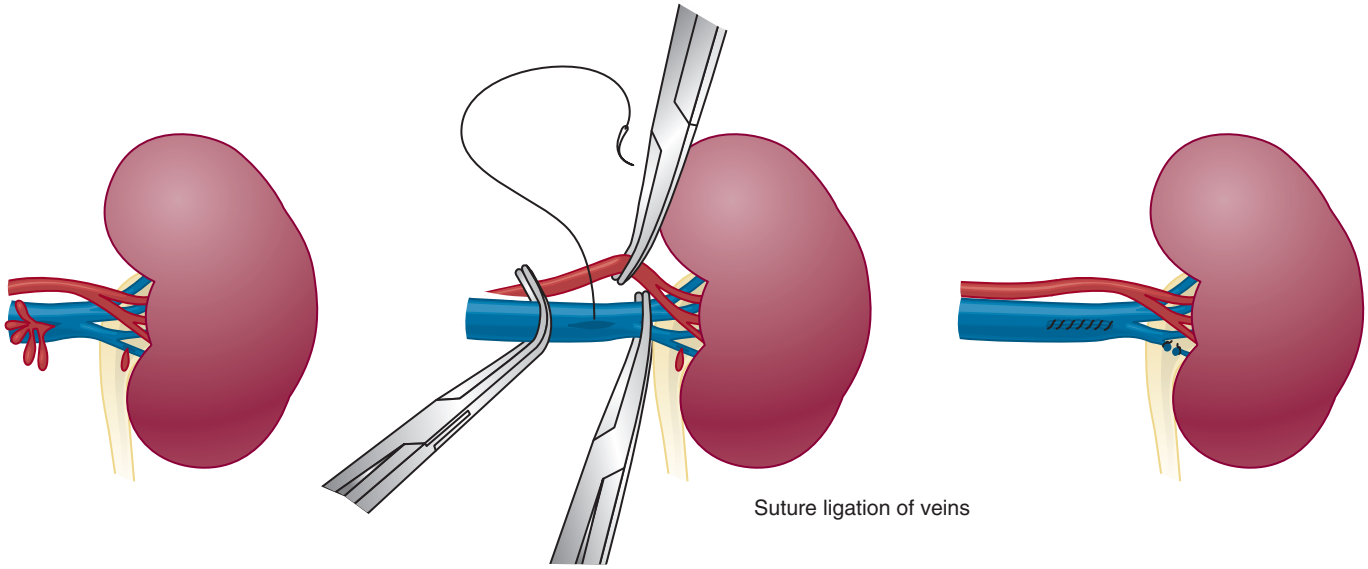
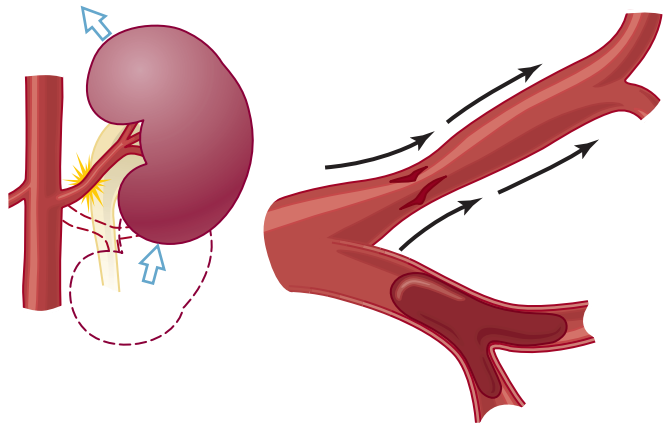
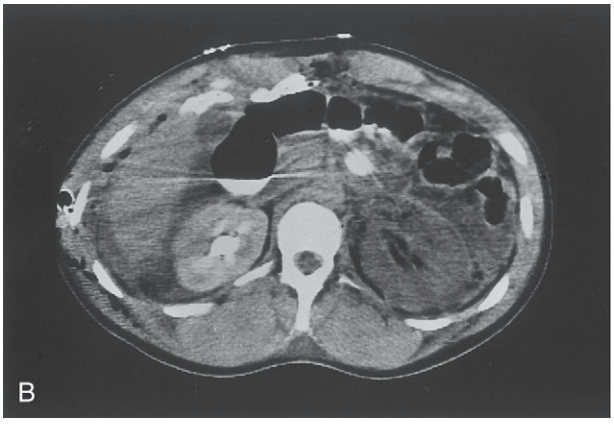


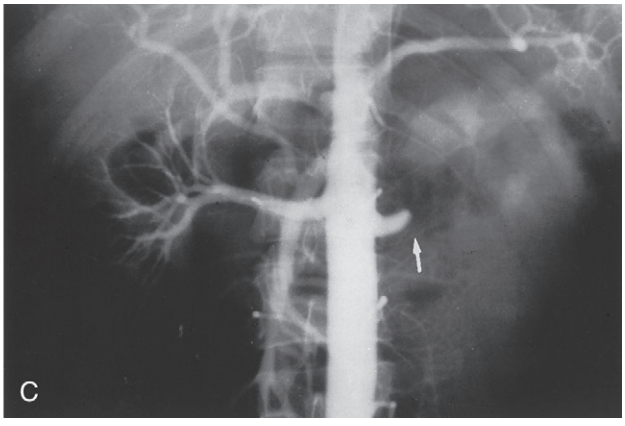
Figure 42–9. Vascular injuries. *Left,* Venous injuries may occur in the main renal vein or the segmental branches. *Middle,* Repair of main renal vein. *Right,* Ligation of segmental branch can be done safely.



A



B



C

Figure 42–10. **A,** Movement of the kidney from blunt trauma (deceleration injury) causes stretch on the renal artery, resulting in rupture of the arterial intima and formation of a thrombus. **B,** Computed tomography of a left kidney with renal artery thrombosis, demonstrating lack of contrast material perfusion to the kidney. **C,** Arteriography demonstrating complete occlusion of the left renal artery secondary to thrombus formation.

experience, Haas and colleagues (1998) have reported that surgical revascularization was seldom successful in renal artery thrombosis and at least 43% of their patients with repairs developed hypertension. Hypertension was also common in those observed nonoperatively. When repair is attempted in renal artery thrombosis, the area of injury (noted by a visible contusion on the vessel) should be excised and a replacement graft done, preferably with hypogastric or splenic artery. Many patients with renal vascular injury are critically injured, with numerous associated organ injuries; time constraints thus limit attempts at vascular repair and a nephrectomy must be done.

Segmental renal arterial injuries result in ischemic infarction to a segment of the kidney. These should be observed nonoperatively when diagnosed unless associated with a parenchymal laceration. Should the laceration with infarction be greater than 20% of the parenchyma, careful consideration should be given to endovascular embolization or surgical correction.

Injuries to the main renal vein require repair with fine vascular suture (5-0) (see Fig. 42–9). Partial occlusion of the vein is ideal for repair, but in some instances total occlusion with vascular clamps is necessary; if so, temporary occlusion of the renal artery is necessary.

Damage Control

Coburn (2002) has noted the benefit of damage control to improve renal salvage. The wound and area around the injured kidney are packed with laparotomy pads to control bleeding with a planned return in 24 hours to explore and evaluate the extent of injury. This approach is commonly used by trauma surgeons in patients with extensive injuries and has long been used by general surgeons. It may well be useful in managing complex renal injuries to avoid total nephrectomy.

Indications for Nephrectomy

The ability to reconstruct an injured kidney depends on numerous factors. The unstable patient, with low body temperature and poor coagulation, cannot risk an attempt at renal repair if a normal contralateral kidney is present (Davis et al, 2006). As noted earlier, damage control (packing the wound to control bleeding and attempting to correct metabolic and coagulation abnormalities) with a plan to return for corrective surgery within 24 hours provides an option in management. Total nephrectomy would be indicated immediately in extensive renal injuries when the patient's life would be threatened by attempted renal repair. When Nash and colleagues (1995) examined the reasons for nephrectomy in patients with renal injuries, 77% required removal because of the extent of parenchymal, vascular, or combined injury and the remaining 23% required nephrectomy in otherwise reconstructable kidneys because of hemodynamic instability.

Complications

Persistent urinary extravasation can result in urinoma, perinephric infection, and even renal loss. These patients are initially administered systemic antibiotics and carefully observed with appropriate antibiotics. In a high percentage, the extravasation resolves spontaneously (Matthews et al, 1997). Should it persist, placement of an internal ureteral stent often corrects the problem. A nonoperative approach with careful observation usually results in a functional renal unit.

Delayed renal bleeding can occur up to several weeks after injury but usually occurs within 21 days. The initial management is bed rest and hydration. Should the bleeding persist, angiography can often localize the bleeding vessel and embolization can often gain control.

Perinephric abscess rarely occurs after renal injury, but persistent urinary extravasation and urinoma are the typical precursors. Percutaneous drainage offers a good initial method of management, followed by surgical drainage if necessary.

Hypertension is seldom noted in the early postinjury period (Monstrey et al, 1989). The basic mechanisms for arterial hypertension as a complication of trauma are (1) renal vascular injury, leading to stenosis or occlusion of the main renal artery or one of its branches (Goldblatt kidney); (2) compression of the renal parenchyma with extravasated blood or urine (Page kidney); and (3) post-trauma arteriovenous fistula. In these instances, the renin-angiotensin axis is stimulated by partial renal ischemia, resulting in hypertension (Crosgrove et al, 1973; Goldblatt et al, 1934).

Key Points: Renal Trauma

Expectant management strategies of renal trauma allow for maximal renal preservation.

- The degree of hematuria and the severity of renal injury do not consistently correlate.
- Contrast-enhanced computed tomography (CT) is the gold standard for genitourinary imaging in renal trauma.
- Patients with microscopic hematuria without shock can be observed clinically without imaging studies.
- Hemodynamically stable, well-staged renal injuries should be conservatively managed (even with severe, high-grade injuries).
- Selective embolization provides an effective and minimally invasive means to stop active bleeding from parenchymal lacerations and segmental arterial injury.
- CT findings suspicious for major injury include (1) medial hematoma (vascular injury); (2) medial urinary extravasation (renal pelvis or ureteropelvic junction injury); and (3) lack of contrast enhancement of the parenchyma (arterial injury).
- Intraoperative "one-shot" IVP confirms the presence of a contralateral functioning kidney.
- Early vascular control before opening Gerota fascia can decrease renal loss.

URETERAL INJURIES

Etiology

Introduction

Acute ureteral injury results from external trauma, open surgery, laparoscopy, and endoscopic procedures. Although uncommon, intraoperative suture ligation, sharp incision and transection, avulsion, devascularization, and heat (e.g., microwave, electrocautery, or vibratory energy) or freezing (cryoablation) energies produce ureteral damage. Additionally, external violence from high-speed blunt mechanisms and penetrating stab and gunshot wounds contributes to the overall incidence. An unrecognized or mismanaged ureteral injury can lead to significant complications including urinoma, abscess, ureteral stricture, urinary fistula, and potential loss of an ipsilateral renal unit. Increased nephrectomy rates and a prolonged hospital stay are associated with a delayed or missed diagnosis from penetrating ureteral trauma (Kunkle

et al, 2006). Ureteral injuries are oftentimes subtle, and clinicians must maintain a high index of suspicion in order to prevent such comorbidity.

External Trauma

Ureteral injuries (Table 42–2) represent less than 1% of all genitourinary trauma. Damage to the ureter after external violence is quite rare, occurring in less than 4% of all penetrating and less than 1% of all cases of blunt trauma. During wartime in the past century, 3% to 15% of urologic injuries have ureteral involvement, with an average of 5% over reports from World War II up to modern conflicts (Busch et al, 1967; Marekovic et al, 1997; Selikowitz, 1977). In the nonmilitary setting, a similar incidence of 2% to 3% of ureteral injuries is caused by civilian gunshot wounds. Located in the retroperitoneum between the spinal vertebra and major muscle groups, the well-protected ureter is an unlikely target for injury. Great violence must be inflicted for ureteral damage to occur. **These patients often have significant concomitant injuries and a devastating degree of mortality that approaches one third** (Medina et al, 1998). Associated visceral injury is common, predominantly small (39% to 65%) and large (28% to 33%) bowel perforation (Campbell et al, 1992; Medina et al, 1998; Presti et al, 1989). A significant percentage (10% to 28%) (Medina et al, 1998; Presti et al, 1989) of patients with ureteral injuries also have associated renal injuries. A smaller percentage (5%) has associated bladder injuries (Medina et al, 1998).

The mechanism by which bullets injure the ureter is thought to be similar to the mechanism by which they injure analogous structures such as blood vessels; that is, not only by direct transection but by disruption of the delicate intramural blood supply and subsequent necrosis. In experimental models, such microvascular damage has been found as far away as 2 cm from the point of transection (Amato et al, 1970). Due to this "blast effect," the full extent of ureteral loss is sometimes underestimated on initial exploration. The ureter may appear entirely normal despite the cavitation injury. This finding provides experimental support for the technique of debriding the ureter back to a bleeding edge after bullet injury to remove tissue that may have invisible microvascular damage. Some authors have even advocated injection of intravenous fluorescein and examination of the ureter by a Wood lamp to ensure viability (Gill and McRoberts, 1992); however, the authors have not found published evidence to support this technique.

Whereas penetrating trauma imparts a large degree of energy over a small area (as in the course of a bullet), **blunt trauma patients with ureteral injuries are subject to extreme force applied over the entire body, like a fall from a height or a high-speed motor-vehicle accident. The great degree of energy imparted to the victim is associated with such uncommon injuries as fractured lumbar processes** (Evans and Smith, 1976) **and thoracolumbar spinal dislocation** (Campbell et al, 1992). These rapid deceleration injuries disrupt the ureter at fixed points along its course, namely the ureterovesical and, more commonly, the ureteropelvic junction. Therefore the presence of massive force injuries in the blunt trauma patient should always increase the level of suspicion for ureteral injury.

Penetrating trauma victims with any degree of hematuria or a wound pattern that suggests the possibility of genitourinary injury should be imaged. Blunt trauma patients with gross hematuria or microhematuria plus hypotension, a history of significant deceleration, or significant associated injuries should also be imaged (Mee and McAninch, 1989). Additional knowledge of the mechanism of injury and physical examination findings must be taken into account. For example, a history of rapid deceleration was found in 100% of patients with ureteropelvic junction (UPJ) injury in one small series (Boone et al, 1993); this finding is despite the fact that one third of these patients with UPJ injury have no evidence of hematuria (Presti et al, 1989).

The rare entity of UPJ disruption consequent to blunt trauma is often missed because the patients do not always exhibit hematuria, and the injury is difficult to palpate during intraoperative manual examination (Boone et al, 1993). Because of this, we recommend abdominal CT with contrast and delayed images whenever possible (Mulligan et al, 1998) or, if time does not permit, an intraoperative "one-shot" pyelogram (2 mL/kg intravenous contrast material given 10 minutes before flat plate abdomen radiograph). Typically, UPJ disruption is associated with an unusual pattern of either medial contrast extravasation (Kenney et al, 1987) (Fig. 42–11) or a "circumrenal" contrast extravasation (Kawashima et al, 1997).

Surgical Injury

Any difficult abdomino-pelvic surgical procedure, whether gynecologic, obstetric, general surgical, or urologic can potentially

Table 42–2.

American Association for the Surgery of Trauma Organ Injury Severity Scale for the Ureter

GRADE*	TYPE	DESCRIPTION
I	Hematoma	Contusion or hematoma without devascularization
II	Laceration	<50% transection
III	Laceration	≥50% transection
IV	Laceration	Complete transection with <2 cm devascularization
V	Laceration	Avulsion with >2 cm devascularization

*Advance one grade for bilateral up to grade III.

From Moore EE, Cogbill TH, Jurkovich GJ, et al. Organ injury scaling. III: chest wall, abdominal vascular, ureter, bladder, and urethra. J Trauma 1992;33:337–9.



Figure 42–11. Computed tomography showing right medial extravasation of contrast material in a patient with a renal pelvis laceration.

injure the ureter. The overall incidence of ureteral injury varies between 0.5% and 10% in most series (Al-Awadi et al, 2005). A review of 13 previously published studies concluded that **the following procedures contribute to iatrogenic ureteral injuries: hysterectomy (54%), colorectal surgery (14%), other pelvic procedures like ovarian tumor removal (8%), transabdominal urethropexy (8%), and abdominal vascular surgery (6%)** (St. Lezin and Stoller, 1991). One series reported that repeat cesarean section could also result in a large number of ureteral injuries, in this case up to 23% of the reported ureteral injuries at one hospital (Ghali et al, 1999). The total incidence of ureteral injury after gynecologic surgery is reported to be between 0.5% and 1.5%, and after abdominoperineal colon resection it ranges from 0.3% to 5.7% (St. Lezin and Stoller, 1991). Historically, open urologic procedures, because they often occur in proximity to the ureters, were also responsible for a significant number (21%) of reported ureteral injuries in one series (Selzman and Spirnak, 1996).

Intraoperative ureteral manipulation resulting in subsequent hydronephrosis is common after aortoiliac and aortofemoral bypass surgery (12% to 20%), but the course is benign in most (St. Lezin and Stoller, 1991). Surgical devascularization or inflammation can result in symptomatic ureteral stenosis, often delayed in presentation by months, occurring in 1% to 2% of these patients (St. Lezin and Stoller, 1991; Adams et al, 1992). This is in contrast to the experience of patients who suffer ureteral injury during pelvic surgery such as sigmoidectomy or hysterectomy: Without treatment, most of these patients are immediately symptomatic, suffer lasting complications, or require reconstructive surgery or nephrectomy (St. Lezin and Stoller, 1991).

In patients undergoing intra-abdominal vascular surgery, risk factors for surgical injury of the ureter include reoperation, placement of a vascular graft anterior to the ureter (Adams et al, 1992), and large dilated arterial aneurysms that cause retroperitoneal inflammation that can involve the ureter. The majority (up to 85%) of surgical injuries to the ureter after vascular procedures are not recognized immediately (Adams et al, 1992). When symptoms of ureteral injury are present, they include flank pain (36% to 90%), fever, ileus, abdominal distention, and urinary fistula (St. Lezin and Stoller, 1991; Adams et al, 1992).

Ureteroarterial fistulas deserve special mention. This rare and potentially catastrophic condition should be diagnosed and treated immediately due to life-threatening hematuria. The fistula (Fig. 42–12), mostly between the ureter and ipsilateral iliac artery, has been associated with previous pelvic surgery, radiation therapy, indwelling ureteral stents, infection, primary vascular disease, and pregnancy (Araki et al, 2008). The experience using endovascular stent grafts for the acute treatment of this devastating event has increased since Kerns and colleagues (1996) first reported their success.

Since the inception of laparoscopic surgery in the 1960s, ureteral injuries have resulted during these procedures, although they were not widely reported until the early 1970s (Grainger et al, 1990). At first, laparoscopy was developed and perfected only for gynecologic indications, but the explosion of laparoscopy into other surgical specialties has meant that the incidence of ureteral injury after minimally invasive surgery has likewise skyrocketed. At one center, the incidence of ureteral injuries from laparoscopy went from 0% of all reported ureteral injuries in the early 1980s to 25% of all the reported ureteral injuries only 5 years later (Assimos et al, 1994). Within 10 years, laparoscopic experience has grown, with a 0.8% rate of ureteral injuries on a review of 1300



Figure 42–12. Retrograde pyelography demonstrating ureteroiliac artery fistula.

laparoscopic urologic procedures (Vallancien et al, 2002). Currently, the reported rate of ureteral injury varies between 0.5% (experienced surgeons) and 14% (inexperienced surgeons) after laparoscopic hysterectomy (Harkki-Siren et al, 1999; Cosson et al, 2001; Leonard et al, 2007).

A large percentage of ureteral injuries after gynecologic laparoscopy occur during electrosurgical or laser-assisted lysis of endometriosis (Grainger et al, 1990). There are probably three reasons for this: (1) endometrioma can involve the ureter either extrinsically or intrinsically; (2) long-standing endometriosis can cause intraperitoneal adhesion, making ureteral visualization difficult (Ribeiro et al, 1999); and (3) the disease can deviate the ureters medially away from their normal anatomic position (Nackley and Yeko, 2000). A significant number of ureteral injuries also occur during tubal ligation, even when bipolar cautery is used (Grainger et al, 1990). In 1999 a series of 118 patients reported a 3.4% incidence of ureteral injury after laparoscopic hysterectomy severe enough to cause obstruction (Ribeiro et al, 1999); however, a recent combined six larger series with a much greater number of patients and presumably more experienced surgeons demonstrated a more reasonable 1% rate (Leonard et al, 2007). Although at least half of all ureteral injuries have no identifiable risk factors, injury to the urinary tract during hysterectomy is associated with malignancy, endometriosis, prior surgery, and surgery for prolapse (Vakili et al, 2005).

Technologic advances have allowed for thermoablative treatment of renal tumors that can result in ureteral damage. There may be a potentially higher risk of ureteral stricturing associated with ablation of medial or lower pole masses. In a porcine model, deliberate targeting of vital renal structures demonstrated an association of ureteropelviceal fistula and injury with radiofrequency ablation (RFA) (Brashears et al, 2005). With experience, the real clinical risks have decreased. A recent multi-institutional review

of 271 thermoablative procedures for small renal tumors reported only one ureteral injury (Johnson et al, 2004).

In contradistinction to open operation, where at least one third of ureteral injuries are recognized immediately (Rodriguez and Payne, 2001), **fewer injuries to the ureter are immediately identified after laparoscopy** (Grainger et al, 1990; Parpala-Sparman et al, 2008). **Therefore during laparoscopy, a high index of suspicion for ureteral injury is required.** The symptoms may develop acutely or insidiously, depending on the mechanism. Postoperatively, patients must be monitored for fever, peritonitis, and leukocytosis (Grainger et al, 1990; Parpala-Sparman et al, 2008), which herald the potential for missed ureteral injury. A smaller number of patients with missed ureteral injury present with hematuria or a pelvic mass representing urinoma (Grainger et al, 1990).

Avoidance of ureteral injury is predicated on intimate knowledge of its location, especially its relation to the uterine and ovarian arteries, if those structures are going to be ligated, as in a hysterectomy (Fig. 42–13). Visualization of the ureter in the area of the ureterosacral ligaments is thought to be especially difficult, and special care must be taken in this area (Grainger et al, 1990). It is axiomatic that ureteral injury is more likely in cases of uncontrolled bleeding, and adequate intraoperative hemostasis and surgical exposure should further decrease these injuries, even in high-risk cases. Intraoperative hydration or diuretic administration may enhance ureteral visualization and potentially further decrease the risk of injury. Preoperative ureteral stenting can be used to ease identification of the ureter in high-risk cases; however, published data in the gynecologic and colectomy population show that, although it may increase intraoperative recognition of ureteral injury, it may not actually decrease ureteral injuries (Leff et al, 1982; Bothwell et al, 1994; Kuno et al, 1998). Ureteral stents are not without complications: The rate of anuria after ureteral stent removal has been reported between 1% and 5% (Leff et al, 1982; Sheikh and Khubchandani, 1990; Kyzer and Gordon, 1994), and the rate of iatrogenic ureteral injury during stent placement has been reported as 1% (Bothwell et al, 1994). One study showed that stents might even increase rather than reduce the chance of intraoperative injury (Dowling et al, 1986). Ureteral stents cannot be placed on one side in 13% of cases, and total failure to place either catheter can occur in 2% (Bothwell et al, 1994). Fiberoptic catheters have been used with good effect (Ben-Hur and Phipps, 2000), although rare complications of ureteral edema and obstruction have been reported after their use (Chahin et al, 2002). Finally, some authors recommend injection of 5 to 10 mL of intravenous indigo carmine dye followed by cystoscopy to ensure patency of the ureters after laparoscopic hysterectomy. When this technique was used in 118 patients undergoing laparoscopic hysterectomy, 4 of 4 cases of ureteral occlusion were identified immediately (mostly caused by suture ligation) and repaired immediately without complications (Ribeiro et al, 1999).

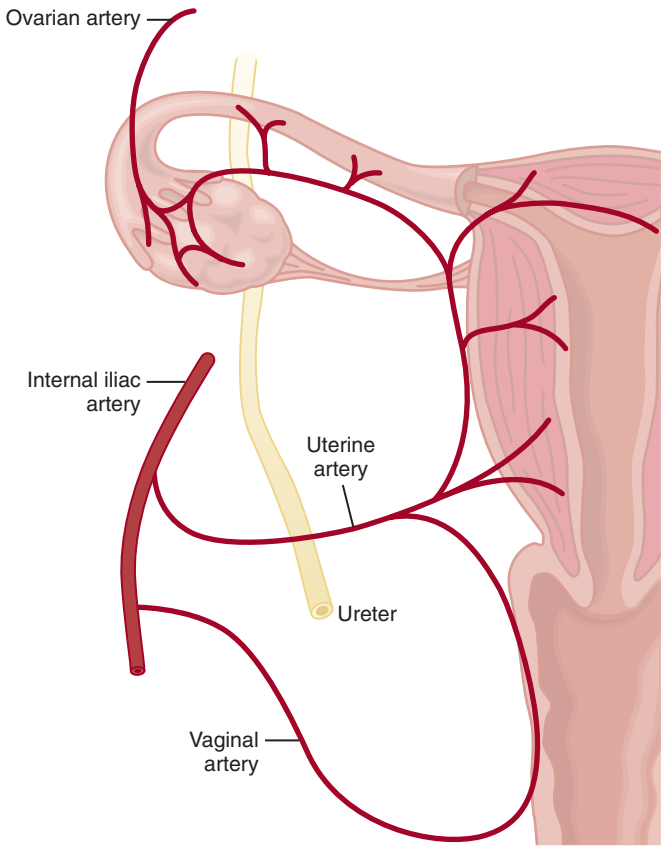


Figure 42–13. Ureteral anatomy showing relationship to fallopian tube and uterine artery.

Ureteroscopic Injury

Ever since Kaufman first reported ureteral injury after rigid ureteroscopy in 1984, countless ureteral misadventures have resulted from this procedure. In fact, ureteroscopic injury is the most common cause of iatrogenic ureteral trauma in modern series (Johnson et al, 2004). In the late 1980s, an explosion of ureteral injuries coincided with the widespread use of ureteroscopy as reported by Huffman (1989). Improvements in equipment and operator experience subsequently decreased the rate of ureteral perforation, to a stable average of 7% in the 1990s (range 0% to 28%) (Huffman, 1989). More recent expert series have a perforation rate of 1% to 5% (Schuster et al, 2001), of which 0.2% requires open surgery (Butler et al, 2004) with an additional 5% incidence of delayed stricture occurrence (Schuster et al, 2001).

One factor cited as a cause of ureteral injury during ureteroscopy was the persistence of stone basket attempts after recognition of a ureteral tear. Current recommendations are to stop the procedure and place a ureteral stent when ureteral perforations are identified (Chang and Marshall, 1987). The wide use of the holmium:yttrium-aluminum-garnet (Ho:YAG) laser to fragment larger stones before basket manipulation is attempted should further decrease the potential for this complication (Bagley et al, 2004). Extraureteric extrusion of calculi during laser fragmentation or basket retrieval has shown to be a minor complication and only rarely leads to stricture formation (Kriegmair and Schmeller 1995).

It is also recommended to perform ureteroscopy alongside or over a wire placed up into the renal pelvis (Chang and Marshall, 1987; Flam et al, 1988), although some experts no longer use a safety wire during routine flexible ureteroscopy (Bratslavsky and Moran, 2004). This wire assists not only safe ureteroscopy but also placement of a ureteral stent later in the case if necessary. **Factors associated with higher complication rates during ureteroscopy were longer surgery times, treatment of renal calculi, surgeon inexperience, and previous irradiation** (Huffman, 1989; Schuster et al, 2001). During stone fragmentation attempts, electrohydraulic lithotripsy is associated with the highest risk of ureteral injury (Fuganti et al, 2008), followed by the neodymium:YAG (Nd:YAG) laser and finally by the Ho:YAG laser (Johnson and Pearle, 2004). Factors that are thought to protect

against ureteral injury are smaller ureteroscopes (Flam et al, 1988; Huffman, 1989) and flexible ureteroscopes (Huffman, 1989).

Diagnosis

Gunshot and Stab Wounds

Incidence of Hematuria. Hematuria is a nonspecific indicator of urologic injury. Absence of hematuria in ureteral injury may result from an adynamic, partially transected ureter or a complete ureteral transection (Elliott and McAninch, 2006). Because many (25% to 45%) cases of ureteral injury after violence do not demonstrate even microscopic hematuria (Presti et al, 1989; Campbell et al, 1992; Brandes et al, 1994; Palmer et al, 1999), a high index of suspicion is required in cases of potential ureteral injury after penetrating trauma. With a 75% sensitivity for traumatic ureteral injury, wound location may be the only indicator for identifying ureteral injury in the acute setting (Elliott and McAninch, 2003). Attention to the course of the bullet or knife and wide use of imaging may decrease the rate of delayed appreciation of these wounds.

Intraoperative Recognition. In an analysis of previously published reports concerning ureteral injury from external violence, Armenakas (1999) noted that 93% of injuries were recognized promptly including 57% that were identified intraoperatively. The authors and others (Brandes et al, 1994; Medina et al, 1998) make every attempt to diagnose these injuries during exploration. Intraoperative detection requires a high degree of suspicion, but there is evidence that specific vigilance for ureteral injuries may decrease the incidence of missed injuries (McGinty and Mendez, 1977). The trajectory of the knife or missile must be carefully examined during laparotomy, and ureteral exploration should be undertaken in all cases of potential injury. Liberal use of preoperative diagnostic tools (urinalysis, IVP, CT), even if imperfect, is helpful.

Ultimately, intraoperative inspection of the retroperitoneum is the most important means of diagnosing ureteral injury due to penetrating trauma. Observation of ureteral peristalsis seen through the peritoneum and blind palpation do not reliably indicate a healthy ureter. Inadequate exploration or a low index of suspicion in the presence of multiple injuries is oftentimes responsible for missed ureteral injury. In the largest meta-analysis to date analyzing 16 busy trauma centers with 429 ureteral injuries with laparotomy, a collective 11% miss rate of ureteral injury was noted (Kunkle et al, 2006). From this review, it was further demonstrated that delayed diagnosis at exploration produces an association with prolonged hospital stay and statistically increased rates of nephrectomy.

Vigilance for delayed presentation of ureteral injuries also allows detection of injuries missed on presentation. Fever, leukocytosis, and local peritoneal irritation are the most common signs and symptoms of missed ureteral injury and should always prompt CT examination. In contrast to acute injuries, "missed" injuries that are discovered more than 48 hours after injury are best delineated with retrograde ureterography. Additionally, an unrecognized or mismanaged ureteral injury can lead to significant complications including urinoma, abscess, ureteral stricture, urinary fistula, and potential loss of an ipsilateral renal unit.

Methylene Blue. If a ureteral or renal pelvis injury is suspected intraoperatively, 1 to 2 mL of methylene blue dye can be directly injected into the renal pelvis with a 27-gauge needle to confirm the diagnosis. Care must be taken not to inject excessive dye because it can spill and stain local tissues, making determination of the source of leak impossible.

Imaging Studies

Excretory Urography. Ureteral injuries after external violence, unlike renal injuries, are difficult to detect with the usual array of diagnostic tools: preoperative urinalysis, CT scan, and intraoperative one-shot IVP. IVP is often unhelpful, proving nondiagnostic 33% to 100% of the time (Palmer et al, 1983; Presti et al, 1989; Campbell et al, 1992; Brandes et al, 1994; Azimuddin et al, 1998; Elliott and McAninch, 2003); however, in the absence of a better test, the authors still recommend intraoperative one-shot pyelography together with intraoperative inspection to detect ureteral injuries and assess the functional status of the contralateral system. When IVP abnormalities are found, obvious contrast extravasation can sometimes be seen (Fig. 42–14). However, IVP findings are often subtle and nonspecific, for example, delayed function, ureteral dilation, and ureteral deviation. Insensitivity of these usual diagnostic tools and high false-negative rates are some of the reasons why delay of detection occurs in a surprising 8% to 20% of cases (Presti et al, 1989; Brandes et al, 1994; Palmer et al, 1999).

Computed Tomography. CT is used increasingly in the evaluation of the trauma patient and, although it appears promising in detecting ureteral injuries (Kawashima et al, 2001), there are few



Figure 42–14. Excretory urography demonstrating extravasation in the upper right ureter consequent to stab wound. Note lack of contrast *(arrow)* in the ureter below the site of injury, indicating complete ureteral transection.

published data to assess its accuracy to date (Kenney et al, 1987; Townsend and DeFalco, 1995). Reports of the utility of CT in ureteral trauma are still limited to small numbers of cases.

Ureteral injuries can be difficult to diagnose on CT. If the urinary extravasation from the ureteral injury is contained by Gerota fascia, the extent of medial leakage can be small, obscuring the diagnosis (Kenney et al, 1987). It is also known that ureteral injuries often manifest with absence of contrast in the ureter on delayed images. This underscores the absolute necessity of tracing both ureters throughout their entire course on CT scans obtained to evaluate urogenital injuries (Townsend and DeFalco, 1995). In addition, because modern helical CT scanners can obtain images before intravenous contrast dye is excreted in the urine, delayed images must be obtained (5 to 20 minutes after contrast injection) to allow contrast material to extravasate from the injured collecting system, renal pelvis, or ureter (Brown et al, 1998; Mulligan et al, 1998; Kawashima et al, 2001). Because ureteral injuries are often detected late, periureteral urinoma seen on delayed CT scans may be diagnostic (Gayer et al, 2002).

In reported series, all patients with significant ureteropelvic laceration, for instance, had either medial extravasation of contrast material or nonopacification of the ipsilateral ureter on CT (Kenney et al, 1987; Kawashima et al, 2001). Such findings should always raise suspicion for ureteral injury.

Retrograde Ureterography. Retrograde ureterograms, the most sensitive radiographic test for ureteral injury, are used in some centers as a primary diagnostic technique to detect acute ureteral injuries (Campbell et al, 1992); however, the authors tend to use noninvasive methods such as one-shot IVP and CT scan or to make the diagnosis intraoperatively when feasible. Retrograde ureterography is used, however, to delineate the extent of ureteral injury seen on CT scan or IVP if further clinical information is necessary. Retrograde ureterography is most commonly used to diagnose missed ureteral injuries because it allows the simultaneous placement of a ureteral stent if possible.

Antegrade Ureterography. Anterograde ureterography is seldom used in the authors' practice. In cases in which ureteral injury is discovered, we most often plan retrograde ureterography and stent placement or open repair. If retrograde stent placement is not possible (usually secondary to a large gap in the two ends of the transected ureter), the authors use anterograde ureterography and stent placement at the time of percutaneous nephrostomy placement (Toporoff et al, 1992).

Management (Fig. 42–15)

External Trauma

Contusion

Ureteroureterostomy. Ureteral contusions, although the most "minor" of ureteral injuries, can heal with stricture or breakdown later if microvascular injury results in ureteral necrosis, with an incidence that is not currently known. **Severe or large areas of contusion should be treated with excision of the damaged area and ureteroureterostomy.**

Following certain general principles of ureteral surgery increases the success rate of this delicate surgery. Repair of the ureter must be meticulous (Fig. 42–16). Ureteral blood supply is tenuous, and a sequela of imperfect repair can be urine leakage that can result in patient debility, nephrectomy, and in rare cases even death. Principles of management of the injured ureter are as follows:

1. Mobilize the injured ureter carefully, sparing the adventitia widely, so as not to devascularize the ureter.

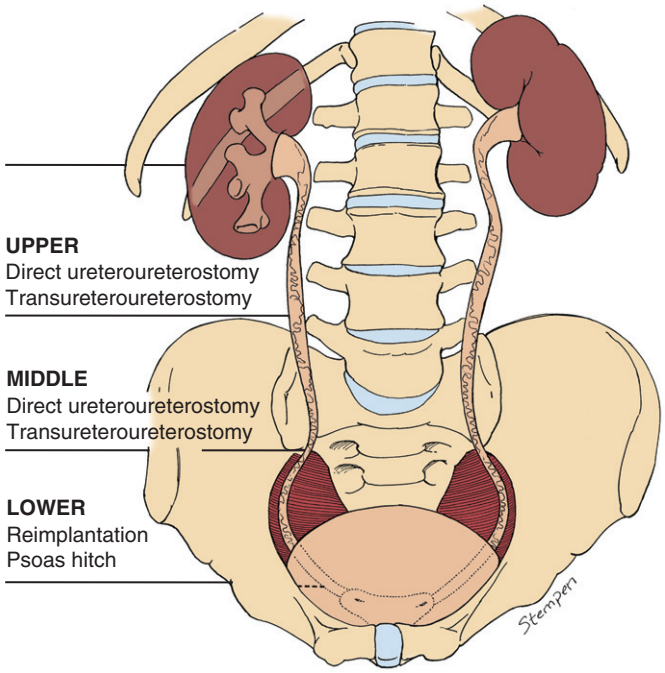


Figure 42–15. Suggested management options for ureteral injuries at different levels.

2. Debride the ureter liberally until the edges bleed, especially in high-velocity gunshot wounds.
3. Repair ureters with spatulated, tension-free, stented (Palmer et al, 1983), watertight anastomosis; using fine absorbable monofilament such as 5-0 polydioxanone; use optical magnification and retroperitoneal drainage afterward.
4. Retroperitonealize the ureteral repair by closing peritoneum over it.
5. With severely injured ureters, blast effect, concomitant vascular surgery, and other complex cases, consider omental interposition to isolate the repair when possible.

Ureteroureterostomy, or so-called end-to-end repair, is used in injuries to the upper two thirds of the ureter. It is required commonly, up to 32% of the time in large series (Presti et al, 1989; Elliott and McAninch, 2003), and has a reported success rate as high as 90% (Carlton et al, 1971). Complications after ureteroureterostomy, usually urine leakage, occur 10% to 24% of the time (Bright and Peters, 1977a; Pitts and Peterson, 1981; Presti et al, 1989; Campbell et al, 1992; Velmahos et al, 1996; Medina et al, 1998). Other acute complications include abscess and fistula. Chronic complications, usually comprising ureteral stenosis, are less common, involving approximately 5% (Palmer et al, 1999) to 12% (Velmahos et al, 1996) of patients. Interestingly, some authors report prolonged leakage of urine from the drain in patients with ureteral injury after external violence who underwent repair but otherwise did well. Steers and colleagues (1985) reported that most of their patients had persistent drainage (averaging 12 days) from the retroperitoneal Penrose drain after repair. This has not been our experience, but this observation might prompt watchful waiting in such patients who leak persistently after repair. Routine retroperitonealization of the repair may decrease the time or severity of postoperative urine leakage.

Management of dehiscence by percutaneous nephrostomy placement and ureteral catheter placement for at least 6 weeks has been reported in small studies, with a surprisingly good success

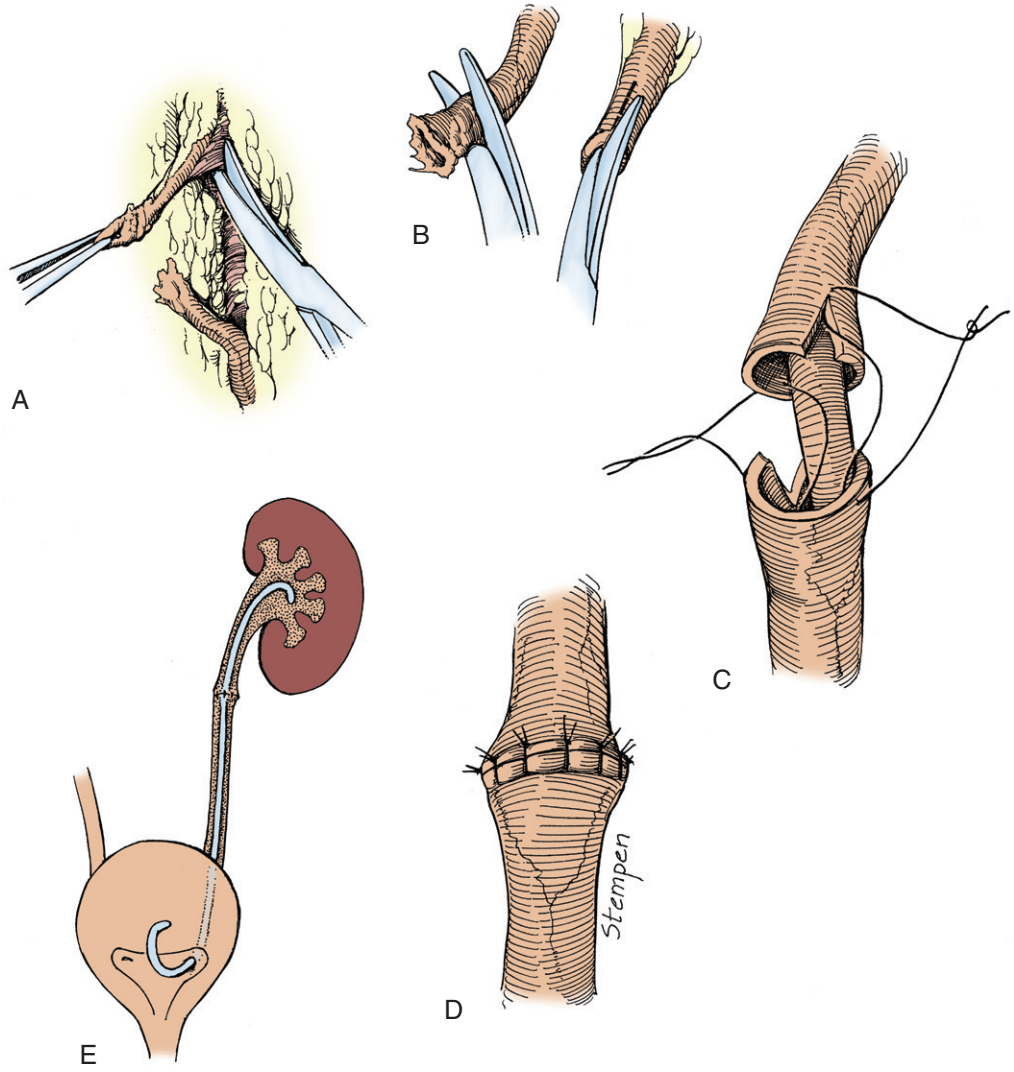


Figure 42–16. Technique of ureteroureterostomy after traumatic disruption: **A,** injury site definition by ureteral mobilization; **B,** debridement of margins and spatulation; **C,** stent placement; **D,** approximation with 5-0 absorbable suture; **E,** final result.

rate (83% [Toporoff et al, 1992] to 88% [Lang, 1984]). Other authors have recommended stenting for a longer period, up to 8 weeks (Steers et al, 1985).

Rarely, acute nephrectomy is required to treat ureteral injury after external violence. Reasons for nephrectomy include associated severe visceral injuries (although damage control without nephrectomy is probably preferable) or severe associated injury to the ipsilateral kidney when renal repair is not possible (McGinty and Mendez, 1977; Gill and McRoberts, 1992). Delayed nephrectomy may be required because of poor renal function (which can sometimes be seen after delayed recognition of an obstructing ureteral injury), severe panureteral injury when ileal ureter or other reconstruction is impossible, or persistent ureteral fistula (especially vascular fistula) despite previous intervention (Ghali et al, 1999).

Internal Stenting. Minor ureteral contusions can be treated with stent placement. Caution must be exercised, however, because minor-appearing ureteral contusions may stricture later or break down secondary to unappreciated microvascular damage to the ureter. When in doubt, the injured portion of the ureter should be debrided and ureteroureterostomy used to repair the injury.

Upper Ureteral Injuries

Ureteroureterostomy. Ureteral avulsion from the renal pelvis, or very proximal ureteral injury, can be managed by reimplantation of the ureter directly into the renal pelvis. The principles of repair include spatulation, lack of tension, stenting, postoperative drainage, and a watertight anastomosis with fine nonreactive absorbable suture. Although the majority of these injuries are treated by open surgery (especially when not discovered immediately), laparoscopic repair of ureteral injuries is increasingly common in the literature (Tulikangas et al, 2001; Ou et al, 2005). Laparoscopic pyeloplasty in the absence of trauma is now quite common (Eden et al, 2004; Yanke et al, 2008), and this procedure might mature into laparoscopic repair of traumatic UPJ avulsion in the future. Rarely, ureterocalycostomy, in which the ureteral stump is sewn end to side into an exposed renal calyx, can also be used where there is profound damage to the renal pelvis and UPJ (Matlaga et al, 2005). With technologic advances, robotics can also be successfully and safely used for a wide variety of delayed upper urinary tract reconstructions including dismembered pyeloplasty, ureteroureterostomy, and ureterocalicostomy (Mufarrij et al, 2007).

Autotransplantation. Autotransplantation of the kidney has been used after profound ureteral loss or after multiple attempts at ureteral repair have failed. This maneuver remains the final option before nephrectomy. Despite great efforts, renal units are sometimes lost after autotransplantation, occurring in 4 of 39 kidneys in two combined series (Bodie et al, 1986; Eisenberg et al, 2008). The nephrectomy portion of the autotransplantation can be performed with laparoscopic techniques (Fabrizio et al, 2000; Meng et al, 2003).

Bowel Interposition. Delayed ureteral repairs, especially when a long segment of ureter is destroyed, can also be performed by creation of a ureteral conduit out of ileum, much in the same way that an ileal conduit is constructed to drain the urine after cystectomy. Success rates for ileal replacement of the ureter have been reported to be 81% (Boxer et al, 1979; Verduyckt et al, 2002) to 100% (Matlaga et al, 2003; Bonfig et al, 2004). A recent review of long-term complications of 99 renal units reported a 3% anastomotic stricture and 6% fistula rate (Armatys et al, 2009). Some have used the Monti procedure, in which short segments of small or large bowel are formed into a long thin tube successfully in ureteral reconstruction (Ubrig et al, 2001; Ali-el-Dein and Ghoneim, 2003). Laparoscopic-assisted ureteral interposition by ileum has been described in two patients (Castillo et al, 2008). The use of appendix has also been reported by both open (Jang et al, 2002) and laparoscopic techniques (Reggio et al, 2008). Although most practitioners create a wide-open, refluxing, ileal replacement of the ureter, it appears that significant clinical reflux is not a problem (Waldner et al, 1999). The authors often prefer a standard ileal ureter technique instead of tapered bowel or appendix because patients place a premium on the reliability of the repair, and in the authors' experience the ileal ureter operation is reliable. Ileal interposition is not suggested for acute repair of ureteral injury but rather would be used in delayed or staged repairs.

Midureteral Injuries

Ureteroureterostomy: Transureteroureterostomy. A rarely used (Presti et al, 1989) but often (90% to 97%) successful (Rainwater et al, 1991; Sugarbaker et al, 2003) technique in adults is transureteroureterostomy (pediatric series show a lower success rate of 70% [Mure et al, 2000]). This form of repair involves bringing the injured ureter across the midline and anastomosing it end to side into the uninjured ureter and is most often performed as a secondary or delayed procedure. It might also be mandated in some cases of middle or distal ureteral injury, in which ureteroureterostomy or bladder flap/hitch repair is impossible (usually because of severe bladder scarring, a congenitally small bladder, or a long segment of missing ureter). Laparoscopic transureteroureterostomy has also been performed in the pediatric population (Piaggio and Gonzalez, 2007).

However, transureteroureterostomy leaves the patient and urologist with some vexing problems postoperatively. The injured ureter becomes difficult to intubate or image with ureteroscopy through the bladder—ureteral access needs to be provided by a nephrostomy placed on the injured side. Some authors believe this operation is contraindicated in patients with a history of urothelial cancer or calculi, although this information is seldom available to the operating trauma surgeon. Caution is required while performing this procedure because it involves surgery on the uninjured, contralateral ureter with the theoretic risk of converting unilateral ureteral injury into (iatrogenic) bilateral ureteral injury. Instead of transureteroureterostomy, the authors have preferred either ileal interposition or ureteroureterostomy with renal mobilization if necessary.

Lower Ureteral Injuries

Ureteroneocystostomy. Ureteroneocystostomy is used to repair distal ureteral injuries that occur so close to the bladder that the bladder does not need to be brought up to the ureteral stump with a psoas hitch or Boari procedure. Standard principles of ureteroneocystostomy include creation of a submucosal tunnel for a nonrefluxing ureteral repair—usually a tunnel that is at least three times longer than the ureter is wide. A new ureteral orifice is constructed with the use of interrupted 6-0 monofilament absorbable sutures in a watertight and nonobstructing fashion. The repair should be stented postoperatively.

In some cases, a refluxing nontunneled anastomosis can be considered if ureteral length is insufficient for tunneling or if tunneling is thought by the surgeon to increase the risk of ureteral stenosis. Refluxing uretero-neobladder (Minervini et al, 2005) and uretero–ileal loop (Wiesner and Thuroff, 2004) anastomoses show no increase in complications related to urine reflux, although these populations of patients are different from the average trauma population and reports do not address whether ureteral implantation into the native bladder is equally safe. Further study is necessary to resolve this issue, but the authors favor nontunneled anastomoses because they prefer the low risk of clinically significant reflux to the higher risk of possible ureteral obstruction using a tunneled approach.

Psoas Bladder Hitch. The psoas hitch procedure is a mainstay in the treatment of injuries to the lower third of the ureter and has a high success rate, from 95% to 100% (Middleton, 1980; Riedmiller et al, 1984; Ahn and Loughlin, 2001). Although it is preferred to ureteroureterostomy in this area because the tenuous independent blood supply might not survive transection, some authors believe that open end-to-end repair may still be considered a realistic treatment option in postoperatively detected iatrogenic lower ureteral injuries with distal stump preservation identified on retrograde pyelography (Paick et al, 2006).

Boari Flap. Injuries to the lower two thirds of the ureter with long ureteral defects (too long to be bridged by bringing the bladder up in the psoas hitch procedure) can be managed with a Boari flap or a transureteroureterostomy. In this case, a pedicle of bladder is swung cephalad and tubularized to bridge the gap to the injured ureter. The procedure is time consuming, however, and some have questioned its usefulness in the acute setting. The procedure is not commonly performed, but authors report a high success rate (Benson et al, 1990).

Minimally Invasive. More recently, laparoscopic and robotic repair of distal ureteral injuries has emerged as a viable alternative to open surgery. Laparoscopic direct ureteroneocystostomy, psoas bladder hitch, and Boari flap reconstructions have all been described (Fugita et al, 2001; Modi et al, 2008). A review of early results demonstrates laparoscopic ureteral reimplantation as effective as open techniques (Ogan et al, 2008). In a recent study of 45 patients receiving laparoscopic ureteroneocystostomy, overall success, defined as radiographic evidence of no residual obstruction, symptoms, renal deterioration, or need for subsequent procedures was 96% (Seideman et al, 2009). Robotics can now be successfully and safely used for a wide variety of delayed upper urinary tract reconstructions as well including dismembered pyeloplasty, ureteroureterostomy, and ureterocalicostomy (Mufarrij et al, 2007). Although limited data exist and longer-term outcomes are necessary, when performed in the delayed setting, many centers now use laparoscopic and even robotic management as primary treatment (Schimpf and Wagner, 2008). In the future, laparoscopic or robotic repair of ureteral injuries may indeed be the standard of care.

Partial Transection. Primary repair of a partial transection is used in the majority of ureteral injuries, up to 58% of the time in one large series (Presti et al, 1989). It must be limited to low-velocity gunshot wounds or stab wounds. Principles of primary repair involve spatulated, watertight closure under optical magnification, with interrupted or running 5-0 or 6-0 absorbable monofilament such as Maxon (polyglyconate) or Dexon (polyglycolic acid). The ureteral injury is closed by converting a longitudinal laceration into a transverse one so as not to narrow the ureteral lumen (Heineke-Mikulicz procedure). An internal stent and retroperitoneal drain are placed.

Damage Control. **In cases of ureteral injury after external violence, it is sometimes necessary to treat the injured ureter by deferring definitive treatment until later. This is usually because the patient is too unstable to tolerate the operative time required to complete the repair** (Cass, 1983). Some have suggested that in cases of severe hemorrhagic shock, uncontrollable intraoperative bleeding, or severe colon injury (especially those requiring colectomy), ureteral repair should be avoided in favor of nephrectomy or staged repair (Velmahos et al, 1996).

There are four options for damage control in ureteral injuries: (1) do nothing but plan a reoperation when the patient is more stable, usually within 24 hours; (2) place a ureteral stent and do nothing else; (3) exteriorize the ureter; or (4) tie off the ureter and plan percutaneous nephrostomy (Hirshberg et al, 1994). In most cases of planned staged repair, we tie off the damaged ureter, using long silk ties to aid the dissection of the ureteral stump during the second-stage repair. The kidney is then drained percutaneously. We advocate percutaneous placement of a nephrostomy tube, either by the surgeon just postoperatively or later by interventional radiology specialists. We have found that intraoperative open nephrostomy placement can be too time consuming in these unstable patients. Other authors have advocated placing an 8-Fr feeding tube into the ureter and exteriorizing it until definitive repair can be completed (Gill and McRoberts, 1992; Ball et al, 2005). If possible, appropriate planned ureteric reconstruction should be done after functional and anatomic imaging is performed.

Surgical Injury

Ligation. **Ligation of the ureter should be treated by removal of the ligature and observation of the ureter for viability. If viability is in question, ureteroureterostomy or ureteral reimplantation should be performed** (Assimos et al, 1994; Brandes et al, 2004). Placement of a ureteral stent, either by opening the bladder or by immediate cystoscopic placement, is highly advised.

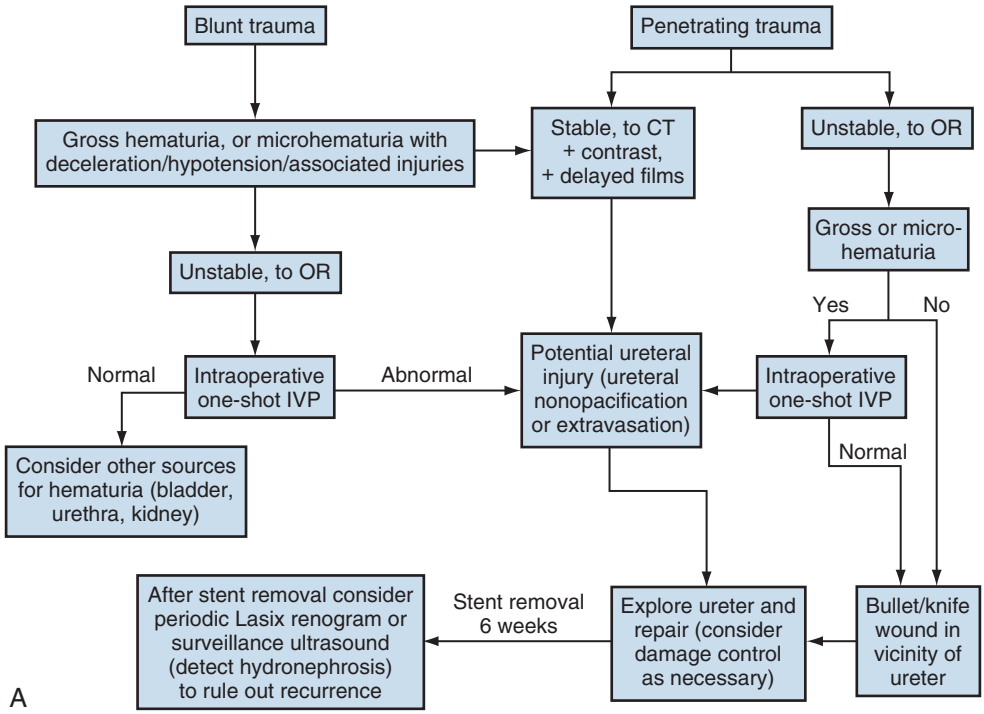
Transection

Immediate Recognition. Ureteral injuries that occur during vascular graft surgery are a special case. Intraoperative management of these injuries is debated and in the past recommendations has included nephrectomy (if the patient has an adequately functioning contralateral kidney) versus primary ureteroureterostomy with isolation of the repair with omentum (Adams et al, 1992). Nephrectomy in cases of ureteral injury is controversial and should be considered only in limited situations, usually involving prosthetic graft surgery. The argument for nephrectomy is that, although it is a radical solution, it avoids the potential for postoperative urine leakage around an aortic or iliac vascular graft, which can be potentially fatal (Schapira et al, 1981). Nephrectomy must be performed with caution, however, because the mortality rate from renal failure in routine aortic aneurysmectomy is 3% and climbs to 12% in patients with a ruptured aneurysm (Schapira et al, 1981). The argument for repair also cites the risk of postoperative renal insufficiency after nephrectomy in this population. Although an accurate assessment of the complication rate after repair of ureteral injuries that occur during vascular surgery is not available, the risk of breakdown of ureteral repair after other surgeries has been reported to be 8% (Ghali et al, 1999) to 40% (Spirnak et al, 1989). In one small reported series, breakdown resulted in nephrectomy in two of two patients (Spirnak et al, 1989). The authors recommend careful repair of the ureteral injury, reserving nephrectomy for patients who develop urine leakage postoperatively.

Immediately discovered injuries after nonaortic surgery are largely treated in the same way as ureteral injury after external violence. Most lacerations can be treated with ureteroureterostomy, although additional maneuvers such as retroperitonealization of the repair, omental wrapping of the repair, or placement of an ipsilateral nephrostomy tube have been advocated to decrease the potential for urine leakage or breakdown of the repair (Adams et al, 1992). With gained laparoscopic and robotic experience, several case reports demonstrate that these injuries are now being treated intraoperatively without the need for open conversion (Dinlenc et al, 2004; Ou et al, 2005). The technical principles and results are the same as delayed reconstruction. Ureteroscopic (Tsai et al, 2000) ureteroureterostomies for operative ureteral injuries have also been reported, although the authors have no direct experience with them.

Delayed Recognition. Intraoperative recognition of ureteral injuries occurs in as low as 34% of patients undergoing open operation (Ghali et al, 1999) and as low as 0% of those undergoing laparoscopy (Grainger et al, 1990). Delayed diagnosis of ureteral injury is most often (66% [Ghali et al, 1999] to 76% [Grainger et al, 1990]) achieved by CT pyelography, IVP, or retrograde ureterography (Grainger et al, 1990). Patients present with a variety of signs and symptoms: anuria (5 of 35 patients, most with bilateral injury), urogenital fistula (4 of 35 patients), persistent pain or fever (3 of 35 patients), urinary leakage from the wound (3 of 35 patients), hydronephrosis (1 of 35 patients), and hematuria (1 of 35 patients) (Ghali et al, 1999). Some authors have cited a triad of fever, leukocytosis, and generalized peritoneal signs as being most diagnostic for missed ureteral injury (Medina et al, 1998). Repair of these delayed-recognition injuries is controversial. Some advocate immediate attempt at placement of a double-J ureteral stent (Bright and Peters, 1977b), but this is possible in only 20% (Ghali et al, 1999; Oh et al, 2000) to 50% (Cormio et al, 1993). When stent placement is possible, some authors have reported an ultimate success rate as high as 73% without the need for open surgery (Dowling et al, 1986). Usually, failure to place a stent is due to complete obstruction of the ureter or too long a gap (Cormio et al, 1993). Some authors have suggested that stenting be avoided in patients who have had multiple pelvic operations, radiation therapy, or significant previous ureteral surgery because they suffer high rates of failure (Chang and Marshall, 1987). The time required for stenting has never been studied in a randomized, prospective, double-blind fashion, but some authors recommend at least 6 weeks (Selzman and Spirnak, 1996). Some authors had a 100% success rate in treating late ureteral complications with a ureteral stent for 3 months (Cormio et al, 1993). Other authors reported much less satisfactory results with stenting: in a series of ureteral injuries after laparoscopies that were recognized late (3 to 33 days after surgery), all ultimately required open repair (Oh et al, 2000).

Although some suggest stent placement as the first line of therapy for ureteral injuries with delayed recognition, others recommend that these injuries be repaired in an open fashion as soon



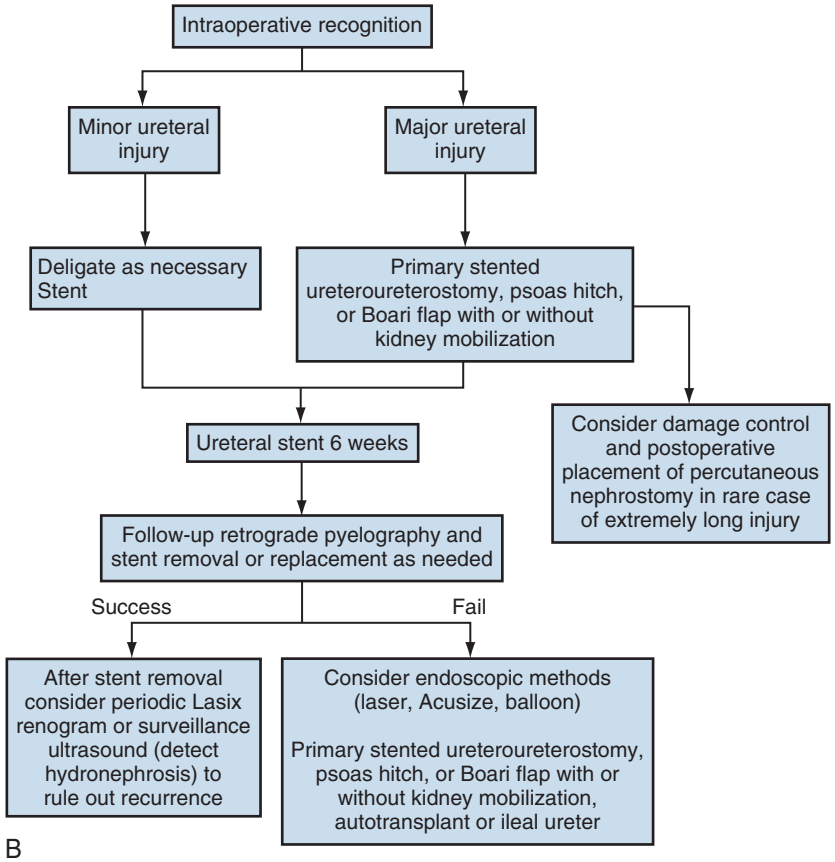


Figure 42–17. Algorithms for the diagnosis and treatment of ureteral injuries: **A,** from external violence; **B,** discovered intraoperatively.

Continued

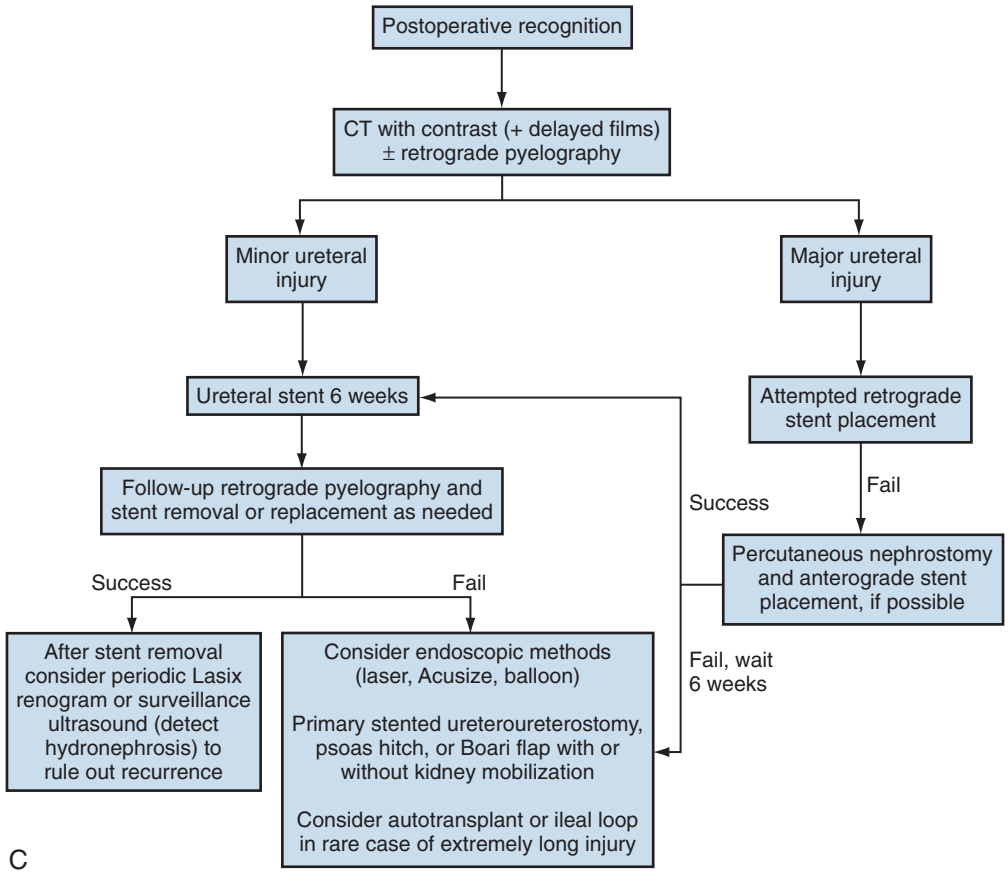


Figure 42–17, cont'd. **C,** discovered postoperatively. CT, computed tomography; IVP, intravenous pyelography; OR, operating room.

as possible. These authors cite low complication rates, which can be as low as in repair of injuries that are recognized immediately (Witters et al, 1986; Ghali et al, 1999). However, delayed diagnosis of ureteral injury itself increases the complication rate of the repair significantly (Selzman and Spirnak, 1996), from 10% to 40% in one series (Campbell et al, 1992), and some have advocated late repair (6 weeks) to allow maximal resolution of perioperative inflammation (Cangiano and deKernion, 1988).

The authors attempt retrograde placement of a ureteral stent in most cases of delayed recognition of ureteral injury. If stent placement is achieved, open repair is required only in patients with persistent leakage or ureteral stricture (Dowling et al, 1986; Cormio et al, 1993). In cases in which the authors cannot place a retrograde ureteral stent, they usually place a nephrostomy tube and make a gentle attempt at anterograde stenting of the injury. If this fails, the authors place a nephrostomy tube and wait 7 to 14 days to reattempt anterograde ureteral stenting. Ureteral balloon catheters, which stop urine from traveling down the ureter, may be required if simple stenting does not eliminate associated urine leakage or urinoma. If the ureter ultimately cannot be stented, the authors believe the safest approach is to allow at least 6 weeks for complete healing of the wounds and then attempt open repair. Some have reported the requirement for even longer ureteral drainage in some specialized cases, such as in the presence of ureteroenteric fistula (Bright and Peters, 1977b). The authors recognize that some experts in the field repair these injuries whenever they are discovered, with seemingly good results (Bright and Peters, 1977b; Flynn et al, 1979; Blandy et al, 1991; Oh et al, 2000).

Some authors have advocated treating postinjury ureteral stenosis endoscopically with either balloon dilation (Richter et al, 2000) or laser incision (Singal et al, 1997; Patel and Newman, 2004). Others have used endoluminal stents for ureteral obstruction after injury with good results in limited numbers of patients (Yohannes et al, 2001; Wenzler et al, 2008). The authors personally have had poor results after endoscopic dilation and incision techniques in the long, devascularized, postinjury or postoperative ureteral strictures that seem to dominate our practice, although they often try them in short strictures before open repair is contemplated. Metal endoluminal stents must be considered experimental until large series validate their use.

Ureteroscopy Injury

Avulsion. Ureteral avulsion during ureteroscopy is treated in the same manner as ureteral injuries after open or laparoscopic surgery, as detailed in the previous section.

Perforation. **Ureteral perforation can be treated by ureteral stenting, usually with no subsequent complications** (Flam et al, 1988; Huffman, 1989). The safest approach is to avoid injury by performing ureteroscopy over a ureteral guidewire. The next safest approach is to use a second ureteral "safety wire" that is always in place during ureteroscopy and assists ureteral stent placement in the presence of problems. The authors recognize that some expert centers do not use a ureteral guidewire during ureteroscopy and that some no longer use a safety wire (Bratslavsky and Moran, 2004), but we believe that a safety wire is most prudent for the majority of practitioners (Fig. 42–17).

Key Points: Ureteral Trauma

- Ureteral injuries must be carefully searched for or they will be missed.
- Intraoperatively, surgically expose and inspect the ureter when necessary: After penetrating injury, use CT scan and intraoperative one-shot IVP liberally. After penetrating injury, determine the course of the knife or bullet tract to ensure that the ureter is not at risk.
- If delayed recognition is suspected, use retrograde pyelography aggressively. Successful repair of ureteral injuries, whether from external violence or surgical misadventure, is predicated on the use of well-vascularized tissue.
- Ureteral viability must be ensured by interval removal of nonviable segment before ureteroureterostomy.
- Tenuously viable distal ureter is bypassed by sewing the bladder to the uninjured proximal ureteral stump.
- Upper ureteral injuries can be removed and the ureter reimplanted into the renal pelvis after renal mobilization. Avoidance of iatrogenic ureteral injury is of utmost importance.
- Safe ureteroscopy practices should be followed including using sound technique, limiting ureteroscopy times, using safety wires, scoping over guidewires, and halting ureteroscopy immediately in the face of any ureteral injury.
- Retroperitoneal surgery should be undertaken only with constant attention to the location of the ureter.

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chapter 43

Etiology, Pathogenesis, and Management of Renal Failure

David A. Goldfarb, MD ● Emilio D. Poggio, MD

Acute Kidney Injury
Acute Tubular Necrosis
Clinical Approach to the Differential Diagnosis of Acute Kidney Injury
Management of Acute Kidney Injury
Chronic Kidney Disease

Disorders of renal function are ubiquitous in the contemporary practice of medicine. Current estimates suggest that kidney disease affects approximately 10% to 13% of the adult American population (Coresh et al, 2007), and thus awareness of the diagnosis and management of this disease has been the focus of the National Kidney Foundation (NKF) and other health care organizations (www.kidney.org). In 2002 the NKF published the Kidney Disease Outcomes Quality Initiatives (K/DOQI) Guidelines setting up the framework for the definition, diagnosis, classification, and management of kidney disease. These guidelines broadly grouped kidney disease into two major categories: acute kidney injury (AKI) and chronic kidney disease (CKD). These conditions are common in clinical practice, so urologists are likely to encounter issues related to renal function and its aberration on a daily basis. This chapter is designed to give a contemporary insight into the nature of kidney disease and its treatment.

ACUTE KIDNEY INJURY

Definition

Acute kidney injury (AKI) is a common problem in the contemporary practice of medicine and urology. Prospective studies have demonstrated that 2% to 5% of all patients admitted to a general medical/surgical hospital unit will develop AKI (Nolan and Anderson, 1998). In selected patients in the intensive care unit following cardiovascular or abdominal vascular surgery, the incidence may exceed 20%. Epidemiologic studies continue to indicate that despite advances in the overall medical care of patients, the development of AKI is associated with significant increases in morbidity (which prolongs hospitalization and increases costs) and mortality (Dimick et al, 2003). The high occurrence and substantial morbidity and mortality of AKI demand a logical approach to its early recognition and prevention, as well as prompt diagnosis and management of its complications.

AKI is defined as a rapid reduction in renal function characterized by progressive azotemia (best measured clinically by serum creatinine [SCr]), which may or may not be accompanied by oliguria. This abrupt decline in renal function occurs over the course of hours to days and results in the failure to excrete nitrogenous wastes from the plasma or to maintain normal volume and electrolyte homeostasis. AKI can be diagnosed with certainty when the patient's prior renal function is known and the reduction in renal function is documented.

The cardinal feature of AKI is a decline in glomerular filtration rate (GFR). Although ideally determined by inulin or radio-isotopic clearance techniques, it is usually identified in routine clinical practice by a rise in serum blood urea nitrogen (BUN) or creatinine. **It is important to understand the limitations of these common clinical chemistries in order for them to be properly interpreted. The correlation among BUN, creatinine, and GFR assumes they are delivered into the serum at a constant rate. Therefore conditions such as hypercatabolic state and massive trauma, which may be seen in surgical patients, can affect renal function assessment. BUN may be disproportionately elevated in states of marked volume contraction, hypercatabolic states, and with marked increases in protein loads seen with gastrointestinal bleeding or total parenteral nutrition (TPN). SCr is produced at a constant rate by muscle and more accurately reflects GFR. When renal function deteriorates, tubular secretion represents an increasing proportion of creatinine excretion. Therefore creatinine clearance may overestimate GFR as renal function slowly declines when measured in the "steady state."** Both the creatinine clearance and the Cockcroft Gault calculation may be useful tools to estimate GFR because they take into account the patient's body size, age, and SCr. For example, the Cockcroft Gault formula states that creatinine clearance = (140 − age) × weight × (0.85, female) divided by 72 × plasma creatinine (Cockcroft and Gault, 1976). Both methodologies have their disadvantages. The urinary creatinine clearance method is cumbersome, and the Cockcroft Gault method may have a margin of error up to approximately 30% compared with GFR measured by formal I^{125} iothalamate techniques. Recently the Modification of Diet in Renal Disease (MDRD) calculations have been used as a way to estimate GFR. This equation has then been reformulated to account for various creatinine assay calibration biases across different laboratories (Levey et al, 2007). However, none of these techniques are suitable for estimating GFR in the AKI patient because such a "steady state" does not exist (Hoste et al, 2005). Use of "real-time" estimates of GFR using infused radio-isotopic

plasma disappearance techniques in the ICU patient with AKI has been advocated by some but has not achieved wide clinical acceptance. In clinical practice the experienced clinician infers from a rapidly rising SCr and clinical picture that the patient's true GFR is approaching zero.

Epidemiology and Classification of Acute Kidney Injury

Clinically, it is useful to separate the causes of AKI into three major categories: prerenal, intrarenal, and postrenal. Distinguishing among the three basic categories of AKI is a challenging clinical exercise. Assigning a patient to one of the three categories usually requires a combination of clinical and laboratory evaluations and may require invasive monitoring of central hemodynamics or imaging studies of the genitourinary tract. **The importance of differentiating the major causes of AKI must be stressed because the initial evaluation and management are tailored to the particular cause.** Because the greatest proportion of hospital-acquired AKI is secondary to acute tubular necrosis (ATN), this chapter places special emphasis on the diagnosis, pathophysiology, and management of ATN. For example, a report from Madrid evaluated 748 cases of AKI at 13 tertiary care hospital centers (Di Tullio et al, 1996). The causes of AKI were: 45% ATN, 21% prerenal, 13% acute or chronic renal failure, 10% urinary tract obstruction, 4% glomerulonephritis/vasculitis, 2% acute interstitial nephritis (AIN), and 1% atheroembolic renal disease. Earlier reports had documented that AKI occurs more commonly in the surgical/trauma ICU, medical ICU, and postoperative units. **A recent study of the American College of Surgeons National Surgical Quality Improvement Program has identified 11 independent preoperative predictors for the development of AKI including age 56 years or older, male sex, emergency surgery, intraperitoneal surgery, diabetes mellitus necessitating oral therapy, diabetes mellitus necessitating insulin therapy, active congestive heart failure, ascites, hypertension, mild preoperative renal insufficiency, and moderate preoperative renal insufficiency** (Kheterpal et al, 2009).

Prerenal Azotemia

Prerenal azotemia is caused by transient renal hypoperfusion that may induce a fall in GFR and produce urinary sodium avidity. The hallmark of prerenal azotemia is its reversibility with treatment of the underlying cause and the lack of structural damage to the kidney. The "gold standard" is the response to appropriate fluid repletion—return of renal function to the previous baseline within 24 to 72 hours is usually considered to represent prerenal disease.

Under normal circumstances, the kidney can maintain normal renal blood flow (RBF) and GFR down to perfusion pressures of approximately 60 mm Hg. The phenomena of autoregulation require a complex interaction of physiologic factors to maintain RBF and GFR. In some hospitalized patients with disordered autoregulation, a reduction in RBF and GFR may occur with modest or even no discernable fall in systemic blood pressure (BP). In the setting of decreased renal perfusion, angiotensin II (AII) and vasodilatory prostaglandins play an important role in maintaining glomerular hydrostatic pressure and GFR. The three major determinants of GFR are renal plasma flow, glomerular hydrostatic pressure, and glomerular permeability. **AII has selectively greater vasoconstrictor effects on the efferent than afferent arteriole, whereas vasodilatory prostaglandins can cause afferent arteriolar vasodilation. Drugs that selectively block AII synthesis, angiotensin-converting enzyme inhibitors (ACE inhibitors), and AII receptor blockers (angiotensin II receptor blockers or ARBs) or that inhibit vasodilatory prostaglandin synthesis such as nonsteroidal anti-inflammatory drugs (NSAIDs)** (Whelton, 1999) **may cause AKI. This is prone to occur in clinical settings when GFR is already compromised** (Toto et al, 1991; Whelton, 1999).

Table 43–1.

Prerenal Causes of Acute Kidney Injury

A. Volume depletion
   1. Surgical: hemorrhage, shock
   2. Gastrointestinal losses: vomiting, diarrhea, fistulae
   3. Renal: overdiuresis, salt-wasting disorders
B. Cardiac causes: Primary decrease in cardiac output
   1. Acute disorders: myocardial infarction, arrhythmias, malignant hypertension, tamponade, endocarditis
   2. Chronic disorders: valvular diseases, chronic cardiomyopathy (ischemic heart disease, hypertensive heart disease)
C. Redistribution of extracellular fluid
   1. Hypoalbuminemic states: nephrotic syndrome, advanced liver disease, malnutrition
   2. Physical causes: peritonitis, burns, crush injury
   3. Peripheral vasodilatation: sepsis, antihypertensive agents
   4. Renal artery stenosis (bilateral)

Prerenal azotemia may be encountered in both the volume-depleted and volume-overloaded patient (Table 43–1). True volume depletion may result from renal or extrarenal losses that result in systemic hypotension and renal hypoperfusion. In the volume-overloaded patient, with edematous states such as cirrhosis and congestive heart failure, prerenal azotemia may occur because the kidney perceives that the vascular tree is underfilled (i.e., "ineffective arterial blood volume"). This results in renal hypoperfusion. Prerenal azotemia may also occur owing to high-grade bilateral renal artery stenosis or in states of renal hypoperfusion due to redistribution of extracellular fluid with peripheral vasodilation as seen with sepsis. As noted earlier, ACE inhibitors/angiotensin II receptor blockers (ARBs) and NSAIDs may alter the vasoconstrictor effects of AII and the vasodilatory effects of prostaglandins to produce prerenal azotemia. This is especially the case in elderly patients with impaired GFR, subtle volume depletion, or occult renal artery stenosis.

The pathophysiology of prerenal azotemia relates to the reduction in renal blood flow. Renal hypoperfusion stimulates both the sympathetic nervous system and renin-angiotensin system to cause renal vasoconstriction and sodium avidity. Furthermore, hypotension is a powerful stimulus to the release of an antidiuretic hormone, which mediates water reabsorption. Hence urine production is characterized by low volume, decreased concentration of urinary sodium, increased urinary excretion of creatinine, and a high urine osmolality. Microscopy of the urinary sediment is usually bland. In essence, "prerenal azotemia is a good kidney looking at a bad world."

Therapy for prerenal azotemia is directed at optimizing volume status with isotonic fluids. In patients with the edematous disorders who have prerenal azotemia, special efforts are directed at

treating the underlying disease states (i.e., heart failure, cirrhosis) and optimizing systemic hemodynamics and renal perfusion.

The hepatorenal syndrome (HRS) represents a unique, severe form of prerenal azotemia. HRS refers to the development of AKI in the patient with advanced hepatic disease, often due to cirrhosis but also seen with metastatic tumor or alcoholic hepatitis. The reduction in renal perfusion appears to relate to relative splanchnic vasodilatation, which may be mediated via nitric oxide, the endothelium-derived relaxing factor (Martin et al, 1998; Gines and Arroyo, 1999). HRS is characterized by oliguria, a benign urinalysis, urinary sodium avidity, and a progressive rise in SCr (Cardenas, 2005). HRS is a prerenal disease because the kidneys are normal histologically and have been successfully used in renal transplantation (Koppel et al, 1969). The diagnosis is one of exclusion, after ATN, acute glomerulonephritis, vasculitis, or correctable forms of reduced renal perfusion have been excluded. Thus the diagnosis of HRS requires a lack of improvement in renal function following discontinuation of potential nephrotoxins and a trial of fluid repletion. The best hope for reversal of HRS is improvement in hepatic function or successful liver transplantation (Gonwa et al, 1991; Cardenas, 2005); however, not all cases of HRS will resolve with this approach (Pham et al, 2005). The utilization of simultaneous liver-kidney transplantation is evolving. It is difficult to predict which cases of HRS will regain renal function spontaneously with liver transplant alone versus those that have irreversible renal injury and would benefit from a kidney transplant. Protracted HRS may lead to irreversible loss of kidney function. There has recently been a consensus conference that has defined criteria to proceed with kidney transplantation in the setting of HRS (Eason et al, 2008). Results of medical interventions have been disappointing. Therapy with ACE inhibitors has been complicated by systemic hypotension and reductions in GFR (Gentilini et al, 1993). The ADH analog ornipressin, which should decrease splanchnic dilatation, may also induce renal ischemia (Guevara et al, 1998; Gulberg et al, 1999). Treatment with a prostaglandin analog, misoprostol, has yielded conflicting results, but preliminary evidence with *N*-acetylcysteine suggested improvement in splanchnic dilatation and nitric oxide production in a small series of HRS patients (Holt et al, 1999). Similarly, combination therapy with midodrine (a selective α_1-adrenergic agonist) and octreotide (a somatostatin analogue) has yielded preliminary information that it may be safe and effective as compared with renal-dose dopamine in a small series of HRS patients (Angeli et al, 1999). Terlipressin, a vasopressin analog available in Europe, is also showing promising results in small studies that need to be confirmed in larger multicenter trials (Fabrizi et al, 2006; Alessandria et al, 2007; Martin-Llahi et al, 2008; Sanyal et al, 2008; Karwa and Woodis, 2009; Skagen et al, 2009). Nevertheless, overall the impact of medical therapy for HRS has been minimal and the outlook for HRS without orthotopic liver transplantation appears bleak. The role of hemodialysis support appears to be limited to those HRS patients awaiting liver transplantation or resolution of their primary hepatic disease because survival is generally limited by the severity of liver failure. Hemodialysis is often difficult in HRS because of hemodynamic instability.

Postrenal Azotemia

Obstruction of the urinary tract may cause AKI. To be the cause of AKI, urinary tract obstruction must involve the outflow tract of both kidneys, unless preexisting renal dysfunction is present, in which case the obstruction may involve only a single kidney. Patients with acute urinary tract obstruction may present with hematuria, flank or abdominal pain, or signs of uremia. A high index of suspicion for urinary tract obstruction should exist for patients with prior abdominal or pelvic surgery, neoplasia, or radiation therapy. Although oligoanuria suggests complete obstruction, partial obstruction may exist in the presence of adequate urinary output. Oligoanuria is a powerful diagnostic clue that suggests a differential diagnosis of urinary tract obstruction, severe ATN with cortical necrosis, or bilateral vascular occlusion. Lesions that may cause obstruction can be either intrinsic or extrinsic to the genitourinary tract. If urinary tract obstruction is a diagnostic consideration, the renal ultrasound is sensitive and specific (90% to 95%) in confirming the diagnosis of hydronephrosis. This test may be operator dependent, so the experience of the radiologist is crucial. False-negative tests may be seen with periureteral metastatic disease or retroperitoneal fibrosis (Somerville et al, 1992). Renal radionuclide studies or retrograde pyelography may be helpful in this circumstance. If urinary tract obstruction is a diagnostic consideration, renal ultrasound should be performed because obstruction represents a potentially reversible cause of AKI.

Although urologists are familiar with the various primary pathologies responsible for obstruction, iatrogenic causes should additionally be considered. Any drainage device such as a urethral catheter or ureteral stent should be assessed for patency. Hemorrhage and lymphocele are uncommon sequelae of retroperitoneal surgery, but they can result in AKI by causing extrinsic compression. **Urinary extravasation or fistula formation is a complication of urinary tract reconstruction. This can cause a rise in the BUN and SCr because of reabsorption but preservation of actual kidney function.** Diagnosis of urinary extravasation requires analysis of fluid from the area near the reconstructed site. The drain creatinine is compared with the SCr. Ratios of 10:1 are virtually diagnostic for extravasation; however, smaller ratios may be observed when the urine has been diluted by other serous fluids. Other ways to confirm urinary extravasation are by intravenous administration of a vital dye excreted by the kidneys (such as indigo carmine or methylene blue) or radiographic demonstration of a fistula (isotope renography, retrograde pyelogram, cystogram, computed tomography [CT]). This type of AKI resolves with drainage of the urinoma and definitive treatment of the urinary fistula. The reader is referred to other chapters in this text for more in-depth review of obstructive uropathy.

Intrinsic Renal Disease

The major causes of AKI due to intrinsic renal disease include acute glomerulonephritis (AGN), AIN, and ATN. Because ATN is the most common cause of AKI in the hospitalized patient, special emphasis will be given to ATN.

Acute Glomerulonephritis

The presence of proteinuria, hematuria, and red blood cell casts is pathognomonic of glomerulonephritis. The importance of the urinalysis in the evaluation of patients with AKI cannot be overemphasized, and the physician must develop skill and expertise in interpreting the microscopic findings. Such skills are critical in the recognition of AGN as the cause of AKI because the diagnosis of AGN has a tremendous impact on disease management.

The combination of AGN (based on urinalysis findings) and a rapid loss of kidney function defines the clinical syndrome of rapidly progressive glomerulonephritis (RPGN). The differential diagnosis and management of RPGN are beyond the scope of this chapter (Lee et al, 2004). A simplified differential diagnosis of

Table 43–2.

Differential Diagnosis of Rapidly Progressive Glomerulonephritis

Multisystem Diseases

Systemic lupus erythematosus
Goodpasture disease
Henoch-Schönlein
Necrotizing vasculitis (including Wegener granulomatosis)
Cryoglobulinemia (hepatitis B or C related)
Neoplasia (colon, lung)
Relapsing polychondritis
Behçet disease

Superimposed on Primary Glomerular Disease

Membranoproliferative glomerulonephritis (type I, II)
Membranous glomerulonephritis
IgA nephropathy

Infectious Diseases

Poststreptococcal glomerulonephritis
Infectious endocarditis
Visceral sepsis
Hepatitis B or hepatitis C infection

Drugs and Toxic Agents

Allopurinol
D-Penicillamine
Hydralazine
Rifampin

Idiopathic

Type I: antiglomerular basement membrane antibody disease
Type II: immune complex–mediated disease
Type III: pauci-immune (antineutrophil cytoplasmic autoantibody positive)

Table 43–3.

Drugs That Most Commonly Cause Acute Interstitial Nephritis

Nonsteroidal anti-inflammatory drugs (particularly fenoprofen)
Penicillins and cephalosporins
Rifampin
Sulfonamides (furosemide, bumetanide, thiazide-type diuretics and trimethoprim-sulfamethoxazole)
Cimetidine, omeprazole
Allopurinol
Ciprofloxacin and perhaps other quinolones
5-aminosalicylates

RPGN is summarized in Table 43–2. It is crucial to appreciate the impact that urinary microscopic findings of AGN have on the aggressive evaluation and management of patient with this type of AKI. This usually includes a renal biopsy and detailed serologic evaluation for the presence of systemic vasculitis, collagen vascular disease, and an infectious process. RPGN comprises a group of glomerulonephritides that progress to renal failure in a matter of days to months in the presence of extensive extracapillary proliferation (i.e., crescent formation in a large percent of glomeruli). Patients with RPGN have been divided into three patterns defined by their immunologic pathogenesis: (1) type I: antiglomerular basement membrane (anti-GBM) (e.g., Goodpasture); (2) type II: immune complex deposition disease (e.g., systemic lupus erythematosus, poststreptococcal glomerulonephritis); and (3) type III: pauci-immune (e.g., antineutrophil cytoplasmic autoantibody [ANCA]–positive disease such as Wegener granulomatosis). Patients are categorized on the basis of the results of the immunofluorescence of the renal biopsies and results of serologic testing for anti-GBM titer, ANCA, lupus serologies, and so on. Specific therapies (including parenteral steroids, cyclophosphamide or other cytotoxics, and possibly plasma exchange) tailored to the disease entity diagnosed may be lifesaving. Hence early recognition of RPGN based on urinalysis findings is critical.

Acute Interstitial Nephritis

The diagnosis of AKI secondary to AIN may be suggested by the urinalysis findings of sterile pyuria, white blood cell casts, and eosinophiluria (using Hansel stain) (Michel and Kelly, 1998). **AIN is most often induced by drug therapy, although sarcoidosis, streptococcal, viral, or *Legionella* infections may also be responsible. The list of offending drugs associated with AIN is extensive, but the most common causes of AIN include those identified in** Table 43–3. The major histologic changes are interstitial edema and marked interstitial infiltrate of T lymphocytes and monocytes (Laberke and Bohle, 1980). Eosinophilic plasma cells and polymorphonuclear cells may also be detected. Granulomata formation, once thought particular to the renal disease of sarcoidosis, can occur in any form of AIN.

The clinical presentation, although variable, usually involves an abnormal urine sediment (described earlier), fever, and a rising SCr associated with the administration of the offending drug (Nolan et al, 1986). Skin rash is seen in about 25% of cases. Eosinophilia and eosinophiluria is present in more than 75% of cases, with the exception of AIN due to NSAIDs, where fever, rash, and eosinophilia are typically absent. Proteinuria with most drugs is usually modest with less than 0.5 to 1 g/day. Proteinuria in the nephrotic range has been frequently seen with AIN of NSAIDs (especially fenoprofen) and in selected cases with ampicillin, rifampin, ranitidine, and interferon. It is speculated that increased glomerular capillary permeability is related to cytokine release of the infiltrating T cells (Neilson, 1989). The development of AIN is not dose dependent, and recurrence can occur with second exposures to the same or related drug. The onset of AIN may occur from 3 to 5 days (especially second exposures) to several weeks after drug therapy.

The diagnosis is usually suspected in the AKI patient with characteristic urinary sediment abnormalities and a history of an offending drug therapy. Although the clinical picture may be highly suggestive of AIN, the diagnosis is confirmed only by renal biopsy. Most clinicians will observe the response to withdrawing the offending agent (Kida et al, 1984). No further evaluation or therapy is required if renal function begins to improve in several days. Lack of response, severe AKI, or uncertainty of diagnosis may be indications for definitive diagnosis with renal biopsy. Initial therapy consists of discontinuing the offending drug with the expectation that renal function will begin to improve in 3 to 7 days (Baker and Pusey, 2004). There are no controlled trials evaluating the efficacy of immunosuppressive therapy in the small number of patients reported with biopsy-proven AIN who did not respond to expectant management. There is some experimental and suggestive clinical evidence that steroid and/or cytotoxic therapy may be beneficial to hasten recovery of renal function and reduce interstitial fibrosis.

ACUTE TUBULAR NECROSIS

Incidence and Etiology

Overall, AKI may affect 2% to 7% of patients in a tertiary care hospital, and the incidence of AKI in the surgical or medical ICU may exceed 25% to 35% (Palevsky et al, 2008). **The majority of all hospital-acquired AKI is secondary to ATN** (Myers and Moran, 1986; Uchino et al, 2005). **Renal hypoperfusion and renal ischemia are the most common causes of ATN, although nephrotoxic insults from various agents are being recognized with increasing frequency. A detailed listing of both exogenous and endogenous nephrotoxic compounds is summarized in** Tables 43–4 **and** 43–5**.**

Pigment nephropathy may be suspected in the appropriate clinical situation (post-traumatic or atraumatic after intoxications) where there is discrepancy between the finding of hematuria by dipstick and the absence of red blood cells on urinary microscopy. In urology, two clinical circumstances have been identified in association with rhabdomyolysis. This includes protracted extended lithotomy positioning (as seen in urethral stricture cases) (Anema et al, 2000) **and after laparoscopic donor nephrectomy** (Kuang et al, 2002; Troppmann and Perez, 2003; Reisiger et al, 2005). **The combination of renal hypoperfusion and the nephrotoxic insult of myoglobin or hemoglobin within the proximal tubule can result in ATN. Early recognition of this disorder is crucial because a forced alkaline diuresis is indicated to minimize**

Table 43–4.

Causes of Exogenous Toxic Acute Kidney Injury

Antibiotics
Aminoglycosides
Cephalosporins
Sulfonamide, co-trimoxazol
Tetracyclines
Amphotericin B
Polymyxin, colistin
Bacitracin
Pentamidine
Vancomycin
Acyclovir
Foscarnet

Anesthetic Agents
Methoxyflurane
Enflurane

Contrast Media
Diatrizoate
Iothalamate
Bunamiodyl
Iopanoic acid

Antiulcer Regimens
Cimetidine
Excess of milk-alkali

Diuretics
Mercurials
Ticrynafen

Chemotherapeutic and Immunosuppressive Agents
Cisplatinum
Carboplatin
Ifosfamide
Methotrexate
Nitrosourea
Plicamycin
Cyclosporine A
Tacrolimus
D-penicillamine
Recombinant IL-2
Interferon

Analgesics
Nonsteroidal anti-inflammatory drugs

HIV Protease Inhibitors
Indinavir
Ritonavir

Organic Solvents
Glycols (ethylene glycol, diethylene glycol)
Halogenated hydrocarbons (CCl_4, tetra and trichloroethylene)
Aromatic hydrocarbons (Toluene)
Aliphatic-aromatic hydrocarbons
5-azacytidine (Vaseline, kerosene, turpentine, paraphenylene diamine)

Heavy Metals and Poisons
Insecticides (chlordane)
Herbicides (paraquat, diquat)
Rodenticide (elemental phosphorus)
Mushroom
Snake bites*
Stings*
Bacterial toxins*

Chemicals*
Aniline
Hexol
Cresol
Chlorates
Potassium bromate

Recreational Drugs†
Heroin
Amphetamine

Miscellaneous
Dextrans
Ethylenediaminetetraacetic acid
Radiation
Silicone
Epsilon-amino caproic acid*
Angiotensin-converting enzyme inhibitors

*Direct toxicity or indirect systemic effects (shock, intravascular hemolysis, or coagulation).
†Slow onset of renal failure unless associated with rhabdomyolysis.
From Nally JV. Acute renal failure. In: Stoller JK, Ahmed M, Longworth DL, editors. The Cleveland Clinic intensive review of internal medicine. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 568.

Table 43–5.

Acute Kidney Injury Related to Endogenous Nephrotoxic Products

Pigment Nephropathy
Myoglobin
Hemoglobin*
Methemoglobin*
Intrarenal Crystal Deposition
Uric acid
Calcium
Oxalate
Tumor-Specific Syndromes
Tumor lysis syndrome
Plasma cell dyscrasias (e.g., myeloma kidney)

*Questionable direct nephrotoxic effect.

From Nally JV. Acute renal failure. In Stoller JK, Ahmed M, Longworth DL, editors. The Cleveland Clinic intensive review of internal medicine. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 567.

nephrotoxicity. Similarly, the tumor lysis syndrome may be suspected in the appropriate clinical setting, when marked hyperuricemia/hyperuricosuria and crystalluria are recognized. A forced alkaline diuresis may limit nephrotoxicity and is usually recommended prophylactically before an aggressive chemotherapy regimen.

The list of potential exogenous nephrotoxic agents is exhaustive (see Table 43–4). Simply stated, a patient who develops ATN while receiving medications should have each medication reviewed for the possibility of nephrotoxicity. The most commonly seen nephrotoxins in the hospitalized patient include radiographic contrast material, antibiotics (especially aminoglycosides and amphotericin B), chemotherapeutic agents, NSAIDs, and ACE-inhibitor drugs.

In the contemporary practice of hospital-based medicine, recognition of AKI in HIV patients deserves special comments. Patients with HIV-infection may develop AKI due to the same causes as uninfected patients (Cohen et al, 2008), but protease inhibitors have been associated with the development of AKI. Ritonavir and indinavir (as well as acyclovir, foscarnet, and sulfadiazine) have been associated with reversible AKI thought secondary to crystalluria and intrarenal obstruction (Olyaei et al, 2000). In addition, patients treated with indinavir may present with renal colic because indinavir renal stones can be associated with urinary tract obstruction (Kohan et al, 1999). Newer antiretroviral agents may be toxic to the kidney, and newer forms of AKI related to AIN have recently been described (Cohen et al, 2008).

Natural History

The oliguric phase usually begins less than 24 hours after the inciting incident and may last for 1 to 3 weeks. Urine volume averages 150 to 300 mL/day. The oliguric phase may be prolonged in the elderly. During this phase, the clinician must be alert for the expected complications, with special emphasis on metabolic consequences, gastrointestinal bleeding, and infection.

The diuretic phase is characterized by a progressive increase in urine volume, a harbinger of renal recovery. However, the SCr may continue to rise for another 24 to 48 hours before it reaches a plateau and falls. Severe polyuria during this phase is seen less frequently now. Careful management during this phase is crucial because up to 25% of deaths with AKI may occur in this phase, usually related to fluid and electrolyte abnormalities, as well as infection. Finally, the recovery phase ensues. Renal function returns to near baseline, but abnormalities of urinary concentration and dilution may persist for weeks or months.

Pathophysiology

Knowledge of the basic processes involved in the development of ATN is a prerequisite to understanding contemporary therapies directed at limiting renal damage and promoting more rapid renal recovery (Fig. 43–1). In hospital practice, ischemic ATN is the most commonly encountered form of the disease. Therefore the following discussion focuses on ischemic renal injury.

A variety of biochemical changes occur during ischemia and reperfusion that are responsible for the cell dysfunction observed in ATN (Myers et al, 1984; Myers and Moran, 1986). **The sentinel biochemical event in renal ischemia is the depletion of adenosine triphosphate (ATP), which is the major energy currency for cellular work.** ATP is metabolized to adenosine monophosphate (AMP). During prolonged oxygen deprivation, AMP is further metabolized to the nucleosides adenosine, inosine, and hypoxanthine. These compounds diffuse from the cell, resulting in the loss of the substrate reservoir for ATP synthesis after reperfusion (Brady et al, 1996). Furthermore, hypoxanthine becomes an important substrate in the development of oxygen free radicals during the reperfusion period. Provision of exogenous adenine and inosine decreases cellular injury in experimental renal ischemia (Siegel et al, 1980).

ATP depletion results in impaired function of the plasma membrane and intracellular ATPases that are vital to normal cell function. As a consequence of impairment of the Na^+/K^+ ATPase, cytosolic concentrations of Na^+ and K^+ are altered and cell swelling results (Alejandro et al, 1995). **Dysfunction of the plasma membrane Na^+/Ca^{2+}-ATPase and intracellular Ca^{2+}-ATPase leads to high intracellular levels of Ca^{2+}. The increase in intracellular Ca^{2+} has been associated with multiple aspects of renal cell injury including disruption of the cytoskeleton, activation of Ca^{2+}-dependent phospholipases, acceleration of the conversion of xanthine dehydrogenase to xanthine oxidase (potentiating reperfusion injury), and uncoupling oxidative phosphorylation** (Brady et al, 1996). The activation of phospholipases results in damage to the lipid bilayer, which is critical to the normal function of the plasma membrane and intracellular organelles such as mitochondria. Phospholipase activation leads to an accumulation of free fatty acids and lysophospholipids, which are detrimental to vital cellular function, although the mechanism of such action is not clear.

Oxidative stress during reperfusion after ischemia is associated with cellular damage (Fig. 43–2). Recall that ATP is metabolized to hypoxanthine. High levels of intracellular Ca^{2+} activate a calmodulin-dependent protease that converts xanthine dehydrogenase to xanthine oxidase (Brady et al, 1996). The conversion of hypoxanthine to xanthine during reperfusion is the major source of superoxide. This is ultimately metabolized to OH^-, which causes cell damage. Finally, the protease calpain is activated and contributes to ischemic renal injury (Edelstein et al, 1997). Calpain regulates membrane channels, kinase activation, and interactions between cytoskeletal proteins.

As the name suggests, ischemic ATN is characterized by renal tubular cell injury. This may be sublethal or lethal. Because obvious necrosis is not a cardinal histopathologic finding in ATN (Racusen et al, 1991), sublethal injury is important. **During normal**

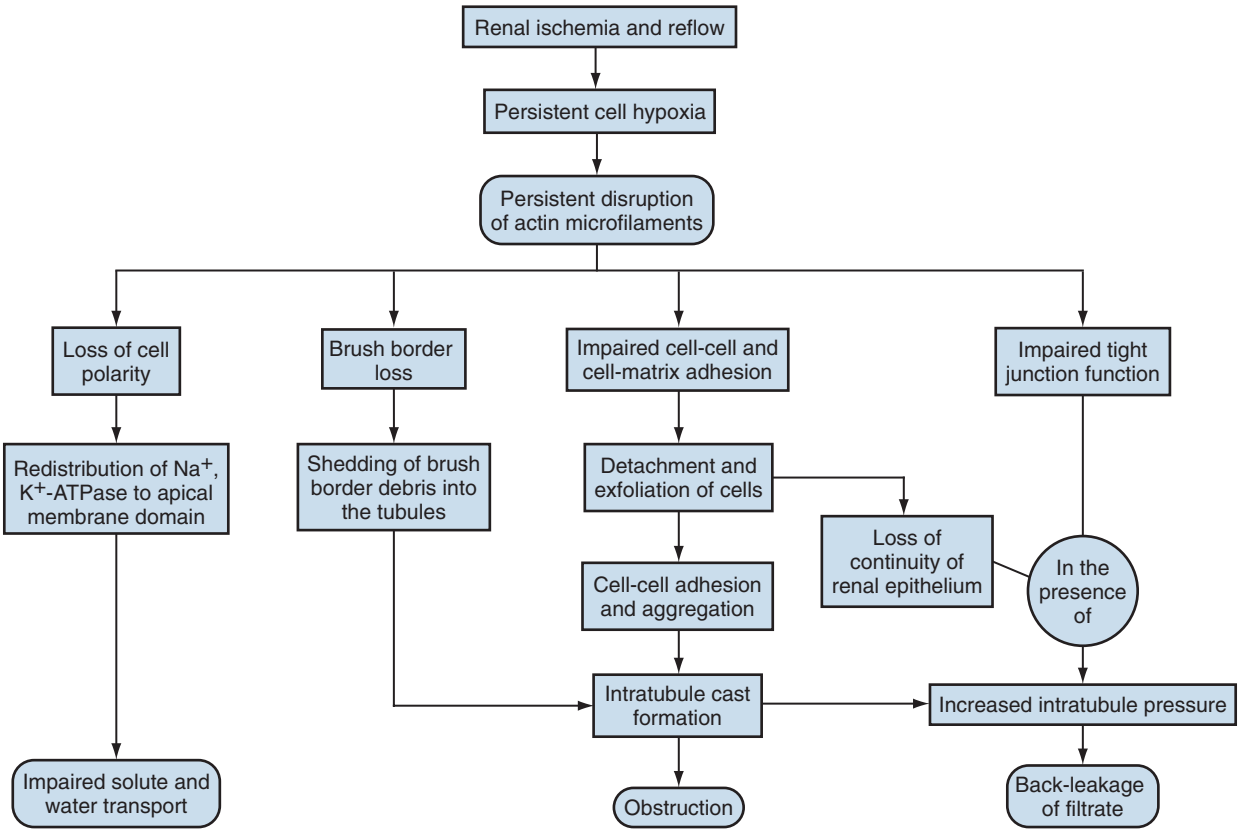


Figure 43–1. Pathophysiology of ischemic acute renal failure. The profound reduction in glomerular filtration rate associated with renal ischemia is due to a combination of intrarenal hemodynamic alterations and tubular epithelial injury leading to tubular obstruction and back-leakage of glomerular ultrafiltrate filtrate. (From Brady HR, Brenner BM, Lieberthal W. Acute renal failure. In: Brenner BM, editor. Brenner & Rector's the kidney. Philadelphia: WB Saunders; 1996. p. 1200–52.)

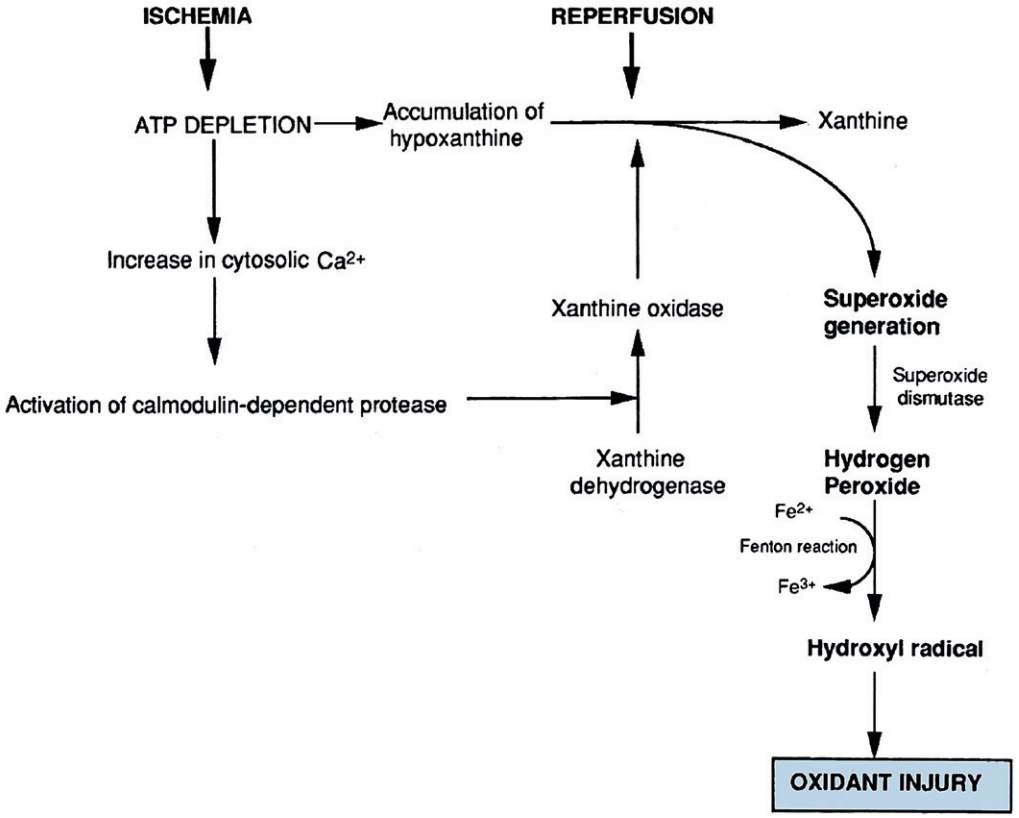


Figure 43–2. The pathophysiology of reperfusion injury. The generation of reactive oxygen species. See text for details. (From Brady HR, Brenner BM, Lieberthal W. Acute renal failure. In: Brenner BM, editor. Brenner & Rector's the kidney. Philadelphia: WB Saunders; 1996. p. 1200–52.)

function of the kidney, the medulla operates at the brink of hypoxia due to the countercurrent diffusion of oxygen from the descending to ascending vasa rectae. During prolonged ischemia, medullary hypoxia intensifies and the high metabolic requirement of the nephron structures located in the outer medulla is most sensitive to injury. The S3 portion of the proximal tubule sustains the most severe injury (Witzgall et al, 1994). **Other structures that sustain injury in this region include the medullary thick ascending limb (mTAL), which is metabolically active and rich in the energy requiring Na^+/K^+-ATPase.**

Sublethal injury to tubular cells leads to aberrations in the cytoskeletal organization of the tubule cells (Molitoris, 1991) (Fig. 43–3). This is manifest as a loss in the cell polarity. The brush border disappears, and there is redistribution of the basolateral Na^+/K^+-ATPase and integrins (Lieberthal, 1997). As a result, the normal unidirectional transport of salt and water across tubular cells is disrupted and the ability of the renal epithelium to act as a barrier to the free movement of solute and water is lost. The loss of the tight junctions permits backleak of glomerular filtrate, which has been one of the well-established pathophysiologic features of ATN (see Fig. 43–1). In addition to the loss of tight junctions, there is a loss in cell-matrix adhesion (Gailit and Clark, 1993). The redistribution of the integrins disrupts the normal cell adherence to the tubular basement membrane. As a result, abnormal cell–cell adherence develops and contributes to tubular obstruction. The validation of this concept is provided by research demonstrating that an excess of a matrix protein sequence (RGD peptides), which is a critical ligand for the β1 integrin, can ameliorate the reduction in GFR in experimental ATN (Noiri et al, 1994). Conceptually this works because the integrin receptors are saturated by the supplemented matrix protein sequence ligand, making them unavailable for abnormal cell–cell adhesion. This can reduce tubular obstruction and backleak of glomerular filtrate.

Following sublethal injury, the kidney has a remarkable capacity for repair of normal structure and function. The study of renal recovery from ATN is a relatively new concept with great potential for clinical application. Increased mitotic activity and epithelial regeneration are notable features of ATN (Thadhani et al, 1996). Certain aspects of renal recovery duplicate events in renal development (Witzgall et al, 1994). A number of growth factors play a role in recovery. Epidermal growth factor, insulin growth factor 1, and

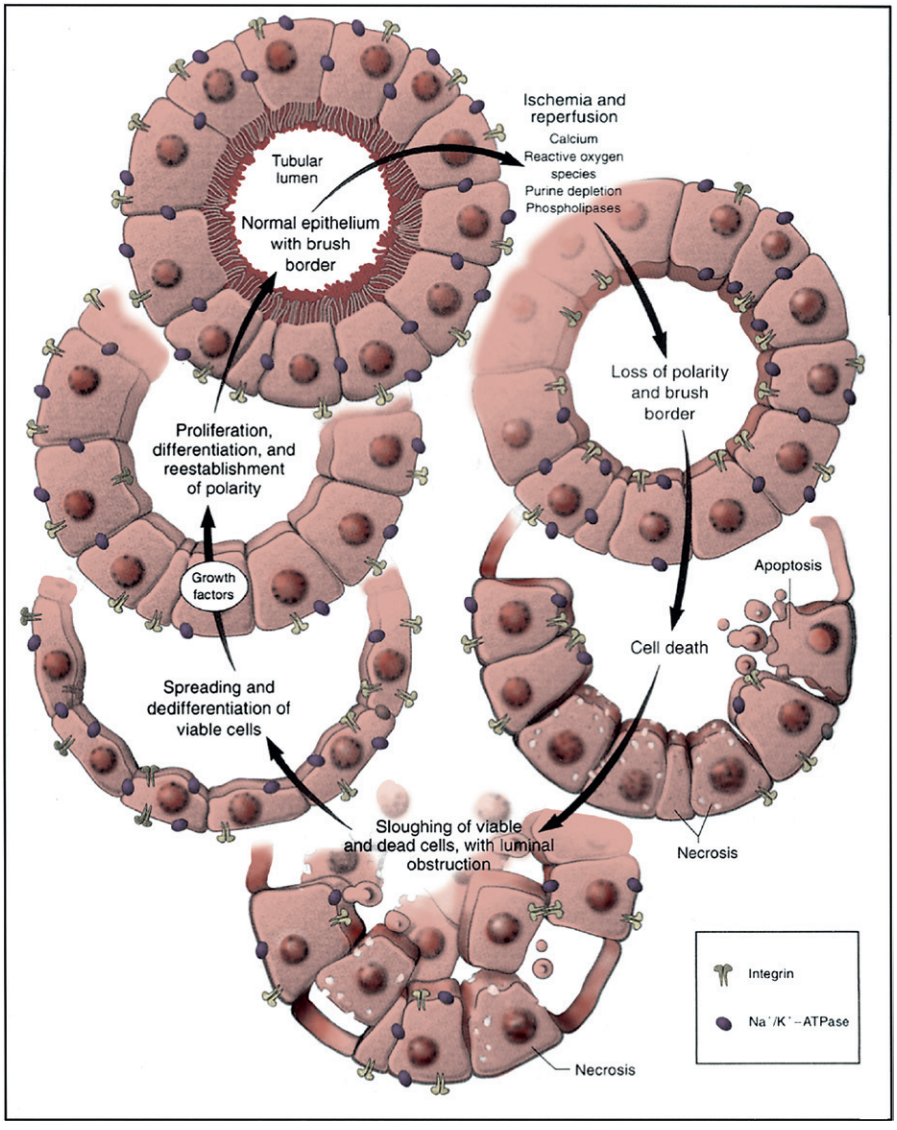


Figure 43–3. Tubular-cell injury and repair in ischemic acute kidney injury. After ischemia and reperfusion, morphologic changes occur in the proximal tubules. This includes loss of the brush border, loss of cell polarity, and redistribution of integrins and Na^+/K^+-ATPase to the apical surface. There is sloughing of viable and nonviable cells into the tubular lumen, resulting in the formation of casts and luminal obstruction. The damaged kidney can restore its structure and function. Spreading and dedifferentiation of viable cells occurs during recovery, which duplicates aspects of normal renal development. A variety of growth factors contribute to the restoration of normal renal architecture. (From Thadhani R, Pascual M, Bonventre JV. Acute renal failure. N Engl J Med 1996;334:1448–60. Copyright 1996, Massachusetts Medical Society. All rights reserved.)

hepatocyte growth factor have been demonstrated to limit renal injury and accelerate renal recovery in experimental ischemic ATN (Thadhani et al, 1996).

RBF is reduced by 50% or more in ischemic ATN, and the perfusion defect is most marked in the outer medulla. The two predominant reasons for this include vasoconstriction and congestion of the medullary vasculature by leukocytes, red cells, and platelets. Ischemic renal injury is marked by intrarenal vasoconstriction as a result of endothelial cell injury. Vasoconstriction results from the imbalance between endothelin (ET) and endothelial-derived nitric oxide (EDNO) (Lieberthal, 1997). Endothelin receptor blockers have been shown to ameliorate ischemic renal damage and improve renal function (Lieberthal, 1997). The endothelial injury sustained in ATN also leads to decreased production of EDNO by constitutive nitric oxide synthase. The decreased EDNO leads directly to vasoconstriction but also permits increased ET production (Lieberthal, 1998).

The persistent hemodynamic abnormalities in ATN are also maintained by congestion of the medullary vasculature. **Current evidence suggests that ischemic injury results in the release of inflammatory mediators that activate adhesion molecules on leukocytes and upregulates their receptors on the endothelium** (Kinsey et al, 2008). Antibodies directed at leukocyte adhesion molecules or their endothelial ligands (i.e., ICAM-1) ameliorate ischemic renal injury (Kelly et al, 1996; Dragun and Haller, 1999). **Neutrophils play an important part in the injury cascade. In models where the effects of neutrophils are eliminated by delivering antibodies to certain chemokines, injury is ameliorated** (Miura et al, 2001). **Interestingly, the tubular epithelium plays an active role in this inflammatory response by generating chemokines that potentiate recruitment of inflammatory cells** (Bonventre and Zuk, 2004). These include monocyte chemoattractant protein-1 (MCP-1), interleukin 8 (IL-8), regulated-on activation, normal T cells expressed and secreted (RANTES), and epithelial neutrophil-activating protein 78 (ENA-78). In addition to the role of neutrophils there is evolving evidence that lymphocytes are important in the ischemia/reperfusion injury paradigm. Knockout mice lacking CD4+/CD8+ cell adhesion receptors on T lymphocytes are protected from ischemic injury (Rabb et al, 2000). Also, costimulatory blockade can ameliorate ischemic injury (Takada et al, 1997). Newer agents are being developed to deal with the early inflammatory events in renal ischemia, which may bear practical application, particularly in the setting of renal transplantation.

CLINICAL APPROACH TO THE DIFFERENTIAL DIAGNOSIS OF ACUTE KIDNEY INJURY

General

Distinguishing among prerenal, intrinsic renal, and postrenal causes of AKI may prove to be a challenging clinical exercise (Fig. 43–4). **A thorough history and physical examination to assess volume status, cardiovascular**

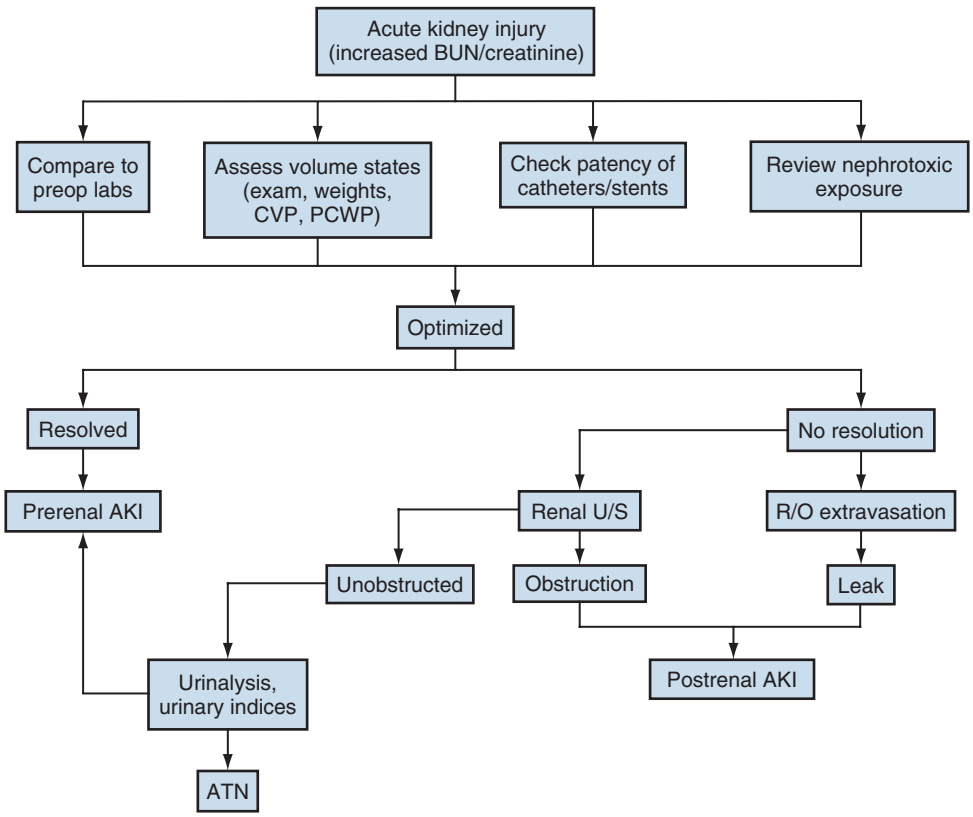


Figure 43–4. Algorithm for the differential diagnosis of acute renal failure. See text for details. AKI, acute kidney injury; ATN, acute tubular necrosis; BUN, blood urea nitrogen; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; R/O, rule out; U/S, ultrasound. (Modified from Goldfarb DA, O'Hara JF. Etiology, pathogenesis, and management of peri-operative acute renal failure. American Urological Association Update Series, Lesson 4, vol XX, 2001.)

hemodynamics, potential nephrotoxic insults, and evidence of systemic disease should be undertaken in AKI patients. All interventions and drug therapies surrounding an AKI event should be outlined against the timeline of changes in renal function. Therefore it is critical to know the level of preexisting renal function. One should identify the presence of risk factors known to be associated with AKI such as advanced age; comorbid conditions (heart failure, liver failure, renal insufficiency, diabetes); radiocontrast exposure; therapy with aminoglycoside antibiotics, NSAIDs, or ACE inhibitors; and atheroembolism. In perioperative AKI, critical intraoperative issues to identify include the nature and magnitude of the procedure (open vs. endoscopic), blood loss, hemodynamic stability, integrity of the urinary tract, and intraoperative drug treatment.

On examination, the vital signs and hemodynamic parameters should be critically assessed. Hypotension, particularly orthostatic hypotension, suggests volume depletion and prerenal AKI. Hypertension with advanced renal insufficiency can be an indicator of volume overload, suggesting the need for diuretics or dialysis. A patient's weight is helpful information, and its daily measurement is important in the diagnosis and management of AKI. An acute decrease in weight over days may indicate volume depletion and prerenal AKI. In contrast, increasing weight in association with a rising creatinine level occurs in ATN with volume overload. After major urologic procedures (e.g., cystectomy, nephrectomy, transplantation), measurement of the central venous pressure or pulmonary artery wedge pressure is the most accurate method to assess volume status. Other clinical parameters that correlate with volume status include neck vein distention, lung rales, and peripheral edema (pretibial or presacral).

The urine output may be a clue to the diagnosis of AKI. The presence of marked oligoanuria suggests urinary tract obstruction, renovascular occlusion, or cortical necrosis. In contrast, nonoliguric AKI is being recognized with increased frequency, and careful monitoring of SCr levels in patients at risk is of paramount importance.

Examination of the urinalysis results is fundamental to the evaluation of the patient with AKI (Perazella and Parikh, 2009). **The simple urinalysis may distinguish the cause of AKI among the various possibilities.** Table 43–6 **highlights the various urinary abnormalities associated with the clinical diagnoses.** For example, proteinuria, hematuria, and red blood cell casts are pathognomonic of glomerulonephritis. The classic sediment of ATN includes pigmented (muddy brown) granular casts and renal tubular epithelial cells, which may be seen in nearly 80% of cases of oliguric AKI.

Determination of urinary chemistry may be helpful in determining the cause of the AKI. The urine sodium, creatinine, and osmolality should be measured. The fractional excretion of sodium or the renal failure index should be calculated (Fig. 43–5). Note that a low fractional excretion of sodium (or renal failure index) may be associated with either prerenal azotemia or AGN (Table 43–7). These entities can be separated clinically by examination of the urinalysis results. Conditions associated with prerenal azotemia have bland urinalysis results, whereas proteinuria, red blood cells, and red blood cell casts are seen with AGN. Other causes of AKI associated with a low fractional excretion of sodium include hepatorenal syndrome and selected types of ATN such as that due to iodinated contrast material, rhabdomyolysis, sepsis, and multisystem organ failure. Both ATN and obstruction may have an increased fractional excretion of sodium or renal failure index. Here again, the urinalysis is crucial in sorting out the differential diagnosis. ATN has a classic sediment with pigmented coarsely granular casts, but the urinalysis results seen in obstruction are often bland with and without microhematuria.

The urine output may be a clue to the diagnosis of AKI. The presence of marked oligoanuria suggests urinary tract obstruction, renovascular occlusion, or cortical necrosis. In contrast, nonoliguric AKI is being recognized with increased frequency, and careful monitoring of SCr in patients at risk is of paramount importance.

Imaging

A variety of imaging modalities have clinical utility in the evaluation of AKI. The most widely used is renal ultrasonography. This noninvasive and readily available study is fairly sensitive for the identification of hydronephrosis, as discussed earlier in the section Postrenal Azotemia. Duplex ultrasonography of the renal artery is useful for the identification of renal artery stenosis (RAS) or thrombosis (Carman et al, 2001). The absence of a Doppler signal from the artery is a noninvasive sign to confirm renal artery thrombosis.

Another common imaging study in AKI is the abdominal plain radiograph to identify the presence or location of renal calculi or both. Additionally, the abdominal plain radiograph is particularly helpful to discern the proper position of the stents and drains. **The radionuclide renal scan is a useful imaging study in selected clinical circumstances. Tc^{99}-MAG^3 is a more useful imaging agent in renal insufficiency than Tc^{99}-DTPA and is able to evaluate both renal flow and**

$$\text{Fractional Excretion of Sodium } (FE_{Na}) = \left(\frac{U_{Na} \times V}{U_{creat} \times V} \right) \times P_{creat} \times \text{PNa} \times 100\%$$

$$\text{Renal Failure Index (RFI)} = \frac{U_{Na} \times P_{creat}}{U_{creat}}$$

Figure 43–5. Urinary indices.

Table 43–6.

Urine Sediment in Acute Kidney Injury

SEDIMENT FINDINGS	DIAGNOSIS
Normal	Prerenal/obstruction
RBC casts, RBCs	AGN/vasculitis
Eosinophils	AIN
Pigmented granular casts	ATN

AGN, acute glomerulonephritis; AIN, acute interstitial nephritis; ATN, acute tubular necrosis; RBCs, red blood cells.

Table 43–7.

Patterns of Urinary Indices in Acute Kidney Injury

	PRERENAL/AGN	ATN/OBSTRUCTION
Urinary [Na^+] mEq/L	<20	>40
Urine: plasma creatinine	>30	<20
Renal failure index	<1	>1
FENa	<1	>1
Urinary osmolality	>500	<400

AGN, acute glomerulonephritis; ATN, acute tubular necrosis.

function (Taylor, 1999). **The renal scan is a simple way to evaluate for renal flow in situations where renal artery thrombosis is a serious consideration such as after partial nephrectomy or renal transplantation.** It is especially useful when there is renal insufficiency that prohibits the use of iodinated contrast (Jafri et al, 1988). Urinary extravasation can also be assessed by isotope renography.

Radiocontrast studies (IVP, CT, angiography) are of limited value during AKI because of their ability to worsen renal insufficiency. Angiography is used to confirm renal artery thrombosis, stenosis, or dissection. Studies such as an IVP yield poor-quality images in azotemic patients because of the inability to adequately excrete contrast. Notwithstanding, radiocontrast studies are frequently performed just proximal to surgery and may contribute in this manner to perioperative AKI.

MANAGEMENT OF ACUTE KIDNEY INJURY

Management of AKI is based on its cause (Alkhunaizi and Schrier, 1996; DuBose et al, 1997). **When AKI is identified as prerenal, correction of the precipitating factors and restoration of renal perfusion usually leads to its resolution. Nephrotoxic drugs should be eliminated when clinically appropriate. Maintaining normal volume status is essential. In the postoperative setting, this implies judicious replacement of crystalloid, colloid, and blood with close monitoring of the central venous pressure. The management of postrenal AKI will depend on its etiology. Any obstruction needs appropriate drainage, and urinary extravasation needs to be controlled.**

The management of ATN focuses on the prevention of complications and providing an environment that is conducive to renal recovery (Table 43–8). Early consultation with a nephrologist improves the outcome of patients with AKI. Mehta and colleagues (2002) showed that nephrology consultation was delayed in 28% of ICU patients with AKI. Delay in consultation was associated with higher mortality, longer ICU length of stay, and increased number of systems failing at the time of consultation. During the initial evaluation, it is imperative to search for reversible causes such as volume depletion, obstruction, and vascular occlusion. During the initial stages, a trial of parenteral hydration with isotonic fluids may correct AKI secondary to prerenal causes. Thereafter, fluid status should be monitored vigilantly to maintain euvolemia. In a patient with oliguria, special attention must be given to avoiding excessive hydration and volume overload, which might precipitate the need for dialysis. Consideration may be given to using pharmacologic intervention to convert the patient from an oliguric to nonoliguric state. In general, increases in urinary volume make it easier to address problems of volume overload, hyperkalemia, and metabolic acidosis. Increases in urine volume may also provide room for supplemental TPN in the critically ill patient. Historically the morbidity, need for dialysis, and mortality was considered lower in the de novo nonoliguric form of ATN; however, more recent data challenge this notion (Liangos et al, 2005).

Table 43–8.
Complications of Acute Kidney Injury

Fluid Overload
Hypertension
Edema
Acute pulmonary edema
Electrolyte Disturbances
Hyponatremia
Hyperkalemia
Hypermagnesemia
Hyperphosphatemia
Hypocalcemia
Hypercalcemia (postrhabdomyolysis)
Hyperuricemia
Metabolic acidosis
Uremic Signs and Symptoms
Gastrointestinal
Nausea
Vomiting
Upper gastrointestinal bleeding
Neurologic
Mental status changes
Encephalopathy
Coma
Seizures
Peripheral neuropathy
Cardiac
Pericarditis
Uremic cardiomyopathy
Pulmonary
Pleuritis
Uremic cardiomyopathy
Hematologic
Bleeding
Anemia
Immunologic
Impaired granulocyte function
Impaired lymphocyte function

Pharmacologic Intervention

Pharmacologic intervention to convert oliguric ATN to nonoliguric ATN is a salutary goal for the reasons noted earlier (Townsend and Bagshaw, 2008). Experimental studies on the use of diuretics, dopamine, atrial natriuretic peptide (ANP), and calcium channel blockers (CCBs) that attempt to convert oliguria to nonoliguric AKI have been performed. The applicability of these experimental studies to patients with AKI remains unproved. **Uncontrolled studies suggest that patients who respond to mannitol, furosemide, or dopamine with an increased urine output have better outcomes than nonresponders** (Cosentino, 1995). The responders may simply have had less severe disease from the outset. Although de novo nonoliguric AKI has been associated with a lower mortality rate, there is little evidence that conversion from an oliguric to a nonoliguric state decreased mortality rate. **For the patients with established ATN, therapy with loop diuretics may increase urine output but has little effect on the severity or duration of the AKI** (Cosentino et al, 1994). Results of clinical trials involving diuretics, dopamine, ANP, and CCBs for established ATN are reviewed here.

Both loop diuretics and mannitol administration have been proved to minimize the degree of renal injury if given at the time of the ischemic insult (Hanley and Davidson, 1981; Schrier et al, 1984; Cosentino, 1995). **Both diuretics are capable of inducing a diuresis to wash out**

obstructive debris and casts. Loop diuretics (e.g., ethacrynic acid, furosemide, and bumetanide) exert their pharmacologic effect in the loop of Henle, causing a large solute diuresis. Additionally, they decrease active NaCl transport in the thick ascending limb of Henle and thereby limit energy requirements in the metabolically active segment, which often bears significant ischemic insult. There are several theoretical reasons why loop diuretics may be of benefit in AKI. Loop diuretics may protect cells of the ascending limb of Henle from hypoxic damage, increase tubular flow to prevent intratubular obstruction, inhibit tubuloglomerular feedback to maintain a favorable GFR, and increase RBF by decreasing renal vascular resistance. **The available clinical data do not support an improved outcome in patients who respond to loop diuretics** (Shilliday and Allison, 1994). **A prospective, randomized placebo-controlled study examining the effect of loop diuretics on renal recovery, dialysis, and death in patients with AKI found no effect** (Shilliday et al, 1997). Observational data suggested that diuretic use in critically ill patients with AKI is associated with an increased mortality rate using multivariate analysis and propensity scores (Mehta et al, 2002). A more recent prospective, multicenter, epidemiologic study found that the use of loop diuretics was not associated with higher mortality (Uchino et al, 2004). Therefore it is reasonable to give a trial of a loop diuretic in escalating doses, and if the patient does not respond, the drug should not be readministered because large doses of loop diuretics may be ototoxic and the large infusion volume may cause pulmonary edema.

Mannitol, an osmotic diuretic, theoretically ameliorates AKI by flushing intratubular casts, increasing RBF, increasing urine flow, reducing hypoxic cell swelling, protecting mitochondrial function, and scavenging free radicals. Mannitol use continues to be promoted prophylactically in certain high-risk patient groups because of its demonstrated benefit in animal models of AKI (Burke et al, 1983; Shilliday and Allison, 1994). **Mannitol has shown some benefit in the clinical setting of AKI** (Novick et al, 1983; Weimar et al, 1983; Simmons et al, 2008), **particularly when administered prophylactically or within a short time after an ischemic or nephrotoxic insult.** The best clinical example of this is its administration before renal artery clamping during partial nephrectomy. However, other studies in humans failed to demonstrate the effectiveness of mannitol in prevention or treatment of ischemic or toxic AKI (Shilliday and Allison, 1994; Baker and Pusey, 2004).

Dopamine has selective renal vasodilator properties that cause natriuresis and increased urine output. Low-dose "renal-dose" dopamine (0.4 to 2.0 μg/kg/min) activates dopamine-1 receptors, which induce renal vasodilation and increased RBF. **Objective review of controlled studies demonstrates that these benefits remain speculative** (Denton et al, 1996; Lassnigg et al, 2000). Bellomo and colleagues (2000) **reported on 328 critically ill patients with AKI who were randomly assigned to continuous infusion of placebo or low-dose dopamine (2 μg/kg/min). Peak SCr concentration, requirement for dialysis, length of hospital stay, and mortality rate did not differ between the two groups. Also, prophylactic use of low-dose dopamine in patients undergoing coronary artery bypass surgery has not been shown to be effective in preventing the development of renal impairment in these patients** (Woo et al, 2002). Lauschke and colleagues (2006) **recently reported on the effects of renal-dose dopamine on renal perfusion as measured by resistive indices obtained by ultrasonography. Although renal perfusion indeed increased in subjects with no AKI, renal vascular resistance actually increased in those with AKI, a finding that was more marked in older patients** (Lauschke et al, 2006). It is also important to note that the use of dopamine has been associated with serious cardiac, vascular, and metabolic complications in the critically ill and therefore should be used with caution (Polascik et al, 1999). Other than dopamine, the literature provides little guidance on the effects of other vasoactive agents on the kidney and thus a need for large randomized, controlled studies to clarify this issue (Baker and Pusey, 2004).

Fenoldopam is a selective dopamine receptor-1 agonist (DA-1) that causes DA-1 receptor-mediated vasodilation and does not stimulate DA-2 or α- or β-adrenergic receptors (Baker and Pusey, 2004). **Fenoldopam reduces renal vascular resistance and increases RBF and fractional excretion of sodium and free water clearance in studies in normal volunteers and hypertensive patients** (Mathur et al, 1999). A few studies in animal models (Singer and Epstein, 1998; Halpenny et al, 2001) are consistent with the notion that DA-1 agonists may be useful in preventing or treating AKI. Some clinical studies have been encouraging in the treatment (Stone et al, 2003) and prevention (Kini et al, 2002) of contrast-induced nephropathy and when used perioperatively in cardiovascular surgery (Halpenny et al, 2001). A recent multicenter trial, however, did not find any protective benefit of the selective dopamine-1 agonist (fenoldopam mesylate) in the prevention of contrast-induced renal dysfunction in an at-risk population (Landoni, 2007). One study showed when fenoldopam was used prophylactically in patients undergoing aortic surgery, its use was associated with improvement in renal function, reductions in dialysis requirements, length of hospital stay, and mortality (Gilbert et al, 2001). A meta-analysis of all randomized controlled trials using fenoldopam to prevent AKI, which included 1290 patients from 16 different studies, suggests that the use of this drug may be beneficial in reducing the need for renal replacement therapy, shortening ICU stay, and perhaps improving mortality (Landoni et al, 2007); however, because these studies were small, defining fenoldopam's role in clinical situations is difficult without a large-scale randomized controlled trial.

In some animal studies the effects of ischemic AKI could be reversed with the use of an intrarenal arterial infusion of ANP (Nakamoto et al, 1987; Shaw et al, 1987), **but other experimental studies have been contradictory. The proposed mechanism by which this occurs is the vasodilatory action of ANP.** In experimental models of established ATN, the combination of ANP with dopamine to prevent systemic hypotension resulted in a rise in GFR induced by arteriolar vasodilatation. The treated animals also exhibited less tubular necrosis and fewer casts, suggesting tubular recovery was promoted. **The efficacy of ANP in established ATN in humans has been evaluated in two trials** (Rahman et al, 1994). **First was a small, randomized trial suggesting a benefit of ANP therapy. More recently, a prospective, multicenter, randomized study with ANP in patients with ATN (oliguric and nonoliguric) has been reported. Overall, there was no established benefit on morbidity and mortality with ANP. However, in a subset of patients with oliguric ATN, clinical improvement was seen with ANP infusion.** Further studies in such a select population did not demonstrate benefit

(Lewis et al, 2000). ANP is still considered an investigational drug, and its role in the management of patients with ATN remains uncertain.

Experimental studies suggest the possibility of accelerating the rate of tubular regeneration in ATN by administration of growth factors such as insulin-like growth factor-1 (IGF-1) (Miller et al, 1992) and epidermal growth factor (EGF) (Hammerman, 1999). The recovery process involves both tubular cell regeneration and differentiation into mature functioning cells. The applicability of these observations to human disease remains to be determined. A report of a randomized trial of AKI patients of less than 7 days' duration found no benefit in patients treated with IGF-1 (Hirschberg et al, 1999). In a large, randomized, double-blind, placebo-controlled trial in intensive care units in 20 teaching hospitals involving 72 patients, it was shown that IGF-1 does not accelerate the recovery of renal function in AKI patients with substantial comorbidities (Hirschberg et al, 1999). Similarly, there is no role for thyroxine in modifying the course and outcome in AKI; in fact, it could have a negative effect on outcome through prolonged suppression of TSH (Acker et al, 2000). **Therefore on the basis of current evidence, there is no role for the use of growth factors to treat AKI.**

Calcium channel blockers inhibit voltage-gated calcium entry into cells and are reported to reverse vascular constriction, increase GFR, and improve renal plasma flow (Epstein, 1993). A few limited animal studies in experimental AKI generally support a protective benefit of calcium channel blockers. **The clinical benefit of calcium channel blockers most widely studied has been the effect on graft function in renal transplant recipients** (Alkhunaizi and Schrier, 1996).

In summary, review of the data regarding pharmacologic intervention for established ATN supports a trial of isotonic fluid repletion. Judicious use of intravenous loop diuretics may increase urine output, but their ability to have an impact on improved patient survival in AKI is still unproven. Similarly, the clinical data on "renal-dose" dopamine are scant and do not support its widespread use in established ATN. If a trial of dopamine is considered, it should be limited to a 24- to 48-hour infusion. Additional studies on the use of fenoldopam, ANP, dopamine, calcium channel blockers, and growth factors are warranted to examine their impact on the course of ischemic or nephrotoxic ATN.

Conservative Management

Once the clinical diagnosis of ATN is made, conservative medical management is in order (Table 43–9). **This would include attempts to minimize further renal parenchymal injury, ensure provision of nutrition, maintain the metabolic balance, and promote recovery of renal function.**

Optimizing the patient's volume status is imperative, particularly in patients with oliguric AKI (DiBona, 1994). If such patients are administered large volumes of IV fluid or allowed free access to oral fluids, they are at risk for developing fluid overload. In the oliguric patient, fluids should be restricted to total output plus insensible losses. If required, pharmacologic intervention with loop diuretics may promote increases in urinary volume.

Providing adequate nutrition is important for the recovery of the critically ill patient with AKI (Fiaccadori et al, 2008). **Preexisting or hospital-acquired malnutrition is an important factor contributing to high mortality seen in patients with AKI** (Druml, 1998; Kriz et al, 1998). AKI not only affects water, electrolyte, and acid-base metabolism but induces specific alterations in protein and amino acid, carbohydrate, and lipid metabolism (Druml, 1992). The metabolic alterations in AKI patients are determined not only by acute loss of renal function but also by the underlying disease process (i.e., sepsis, trauma, or multiple organ failure) and by the type and intensity of renal replacement therapy (RRT) (Druml, 1992, 2005).

The hallmark of metabolic alterations in AKI is activation of protein catabolism with excessive release of amino acids from skeletal muscle and sustained negative nitrogen balance (Druml, 1998; Price et al, 1998). Hepatic extraction of amino acids from the circulation, gluconeogenesis, and ureagenesis are all increased. Several additional catabolic factors (secretion of catabolic hormones, hyperparathyroidism, suppression and decreased sensitivities to growth factors, and release of inflammatory mediators) are operative in AKI. All of these factors mediate protein breakdown (Cianciaruso et al, 1991).

Frequently, AKI is associated with hyperglycemia caused by insulin resistance (Klouche and Beraud, 1998). When plasma insulin concentration is elevated, maximal insulin-stimulating glucose uptake by skeletal muscle is decreased by 50%. AKI is also associated with accelerated hepatic gluconeogenesis, mainly from conversion of amino acids released during protein catabolism, which cannot be suppressed by exogenous glucose infusions (Druml, 1992).

The triglyceride content of plasma lipoprotein is increased in AKI, whereas total cholesterol and high-density lipoprotein (HDL) cholesterol are decreased (Schneeweiss et al, 1990). The major cause of lipid abnormalities in AKI is impairment of lipolysis. RRTs themselves may have significant metabolic and nutritional consequences.

Table 43–9.

Conservative Medical Management of Acute Kidney Injury

Fluid Balance
Careful monitoring of intake/output and weights
Fluid restriction
Electrolytes and Acid-Base Balance
Prevent and treat hyperkalemia
Avoid hyponatremia
Keep serum bicarbonate >15 mEq/L
Minimize hyperphosphatemia
Treat hypocalcemia only if symptomatic or if intravenous bicarbonate is required
Uremia and Nutrition
Protein (1 to 1.8 g/kg/day) and maintain caloric intake; consider forms of nutritional support
Carbohydrate intake at least 100 g/day to minimize ketosis and endogenous protein
Catabolism
Drugs
Review all medications
Stop magnesium-containing medications
Adjust dosage for renal failure; readjust with improvement of glomerular filtration rate

Appropriate nutritional therapy in patients with AKI may be beneficial in promoting recovery (Fiaccadori et al, 2008). Caloric intake should be maintained, and carbohydrate intake should be at least 100 g/day to minimize ketosis and endogenous protein catabolism. A moderate protein intake of about 1 to 1.8 g/kg by weight per day may be required to maintain positive nitrogen balance. Higher protein intakes of up to 2.5 g/kg/day have been necessary to improve nitrogen balance in critically ill AKI patients on continuous dialysis, although no survival advantage was noted. **Hence it should be stressed that a low-protein intake (<0.5 g/kg/day) may be unnecessary and protein intake should not be severely restricted in AKI to limit the need for dialysis.** In terms of types of amino acids used, diet or solutions including both essential and nonessential amino acids in standard proportions are recommended**. Dietary phosphorus, potassium, and sodium chloride may be restricted. In the critically ill patient, nutritional support via TPN or enteral feedings should be considered. Prior studies demonstrate that provision of adequate nutrition to the AKI population may improve survival** (Chertow et al, 2000). Patients with AKI are candidates to develop significant electrolyte abnormalities such as hyperkalemia, metabolic acidosis, hyperphosphatemia, and hypocalcemia. These problems may be minimized by the prophylactic institution of a low-potassium diet accompanied by fluid restriction and oral phosphate binders.

Hyperkalemia is the most common and most dangerous electrolyte abnormality in the AKI setting. **If serum potassium exceeds 6 mEq/L, an electrocardiogram (ECG) should be performed with subsequent therapy based on the ECG findings. With hyperkalemia, the earliest changes demonstrate peaked T waves with subsequent broadening of the PR interval and eventual QRS broadening, which may mature into a sine wave form. The stages of therapy for acute hyperkalemia with ECG changes include (1) stabilizing the electrical membrane of the cardiac conduction system, (2) shifting potassium back intracellularly, and (3) eventual elimination of potassium from the body. Stabilizing the membrane of the cardiac conduction system may be accomplished with IV calcium salts, which have an immediate effect and a rather short duration of action. Shifting potassium into cells may be accomplished by a combination of IV glucose and insulin or IV sodium bicarbonate. Elimination of potassium from the body in a patient with AKI may be accomplished via the gastrointestinal tract with a cationic binding resin (Kayexalate). If severe hyperkalemia exists, dialysis may be required.**

Dialytic Interventions

General

Despite adequate medical therapy, dialysis may be required for patients with severe AKI. **The indications for the initiation of dialysis include volume overload, severe hyperkalemia, severe metabolic acidosis, pericarditis, selected poisonings, and uremic symptomatology.**

The initiation of dialysis for patients with AKI is usually precipitated by one or more of the specific indications. There is still debate on whether patient morbidity and mortality might be improved by early, more intensive dialysis to keep the BUN less than 80 to 100 mg/dL. A recent study from a multicenter trial suggested that in those patients who developed AKI requiring dialysis, patients with BUN levels lower than 76 mg/dL had a better prognosis than those with higher levels, suggesting that initiation of treatment at earlier time points may be beneficial (Liu et al, 2006). Nevertheless, **regardless of BUN levels, patients with AKI should begin dialysis on detection of severe fluid or electrolyte abnormalities or uremic symptomatology. A theoretic concern exists that the dialysis treatment itself may have a detrimental impact on the course of AKI from ATN. Three potential mechanisms have been postulated: a fall in urine volume, dialysis-induced hypotension, and complement activation resulting from the blood-dialysis membrane interaction.** Removal of excess volume and urea may both contribute to the fall in urine volume. Whether this reduction has an impact on clinical recovery of ATN is speculative. Hypotension is a common complication of hemodialysis in patients with AKI. Because autoregulation is impaired in ATN, such patients may be particularly sensitive to renal hypoperfusion, perhaps due to vascular injury of the endothelium and its vasodilatory products such as prostacyclin and nitric oxide. As a result, recurrent ischemic injury is more likely to occur and possibly delay the restoration of renal function. Complement activation during the blood-dialyzer interaction is a third possible mechanism for dialysis-induced renal injury. Animal models suggest that blood interaction with cuprophane membranes (but not more biocompatible membranes) can lead to neutrophilic infiltration into the kidney and prolong the course of AKI.

Dialysis Prescription and Modality

The contribution of the type of RRTs to clinical outcomes in AKI remains unresolved. Several factors operative during RRT for AKI may affect clinical outcome. These include dialysis modality, dialyzer membrane characteristics, and dosing strategies. Hemodialysis (HD) is the standard dialytic modality for hemodynamically stable patients with AKI. To perform acute hemodialysis, access to the circulation is required and usually involves placement of a venous catheter in the jugular, subclavian, or femoral vein. Blood is transported by a blood pump to the dialyzer, where it comes into close proximity with the dialysate solution across a semipermeable membrane. Contact of the blood with dialysate allows the removal of solutes by the process of diffusion, driven by a concentration gradient from blood to dialysate. Fluid may also be removed by the process of ultrafiltration driven by a pressure gradient across the dialyzer. HD treatments may be stressful hemodynamically and possibly complicated by hypotension, hypoxia, bleeding related to anticoagulant administered (usually heparin), and dialysis disequilibrium with its manifestations ranging from cramps and headaches to seizures and coma.

In the hemodynamically unstable patient, slow fluid and solute removal can be achieved with continuous renal replacement therapy (CRRT). In addition to being better tolerated hemodynamically, CRRT is also as efficient at removing solutes over the course of 24 to 48 hours as conventional hemodialysis. Although the clearance rates of some small solutes such as urea are slower, the rates are closer at 24 hours and more urea is removed over 48 hours with CRRT than with a single, intermittent run of standard hemodialysis.

Peritoneal dialysis permits the removal of solutes and fluid by using the peritoneal membrane as the dialyzer. This process does not require access to the circulation and is generally less stressful hemodynamically than standard hemodialysis. For this procedure, dialysate is instilled into the peritoneal space via a catheter that

is percutaneously placed. Fluid is allowed to dwell for a period of time and is then removed, taking with it uremic solutes by diffusion, as well as accomplishing ultrafiltration of fluid from an osmotic pressure gradient induced by high concentrations of glucose in the dialysate. Small randomized clinical trials suggest that peritoneal dialysis may be comparable with regard to efficacy and clinical outcomes to daily hemodialysis (Gabriel et al, 2008). Although it is not popular in the United States, this method remains an option in noncatabolic patients in which peritoneal dialysis use can maintain fluid and electrolyte homeostasis while preventing uremic symptomatology.

Nephrologists caring for AKI patients may select a continuous or intermittent method of dialysis. **An analysis of nine published studies comparing CRRT to intermittent HD (IHD) in patients with AKI showed no significant difference in clinical outcomes between the two groups** (Tonelli et al, 2002). **A more recent meta-analysis of 13 clinical trials, totaling 1400 patients, also observed no mortality difference between CRRT and IHD. However, after adjusting for severity of illness and study quality, mortality seemed to be lower in the CRRT group** (Kellum et al, 2002). Similarly, a recent well-designed study of 80 critically ill patients with AKI found no difference in survival or renal recovery between CVVHD and IHD groups (Augustine et al, 2004).

Dialysis membranes may be classified as cellulose-derived or non–cellulose-derived membranes. The non–cellulose-derived membranes are synthetic polymers and are generally more biocompatible but more expensive. **A meta-analysis of clinical trials comparing biocompatible versus nonbiocompatible membranes found no difference in mortality between groups** (Jaber et al, 2002). **Given the profound morbidity of patients with AKI, if a survival advantage attributable to biocompatible membranes exists, it is at best small.** Similarly, high-flux membranes have not demonstrated a survival benefit, recovery of renal function, or duration of dialysis (Ponikvar et al, 2001).

The dose of dialysis may be important in outcome. Several studies have attempted to link urea removal to clinical outcomes in patients with AKI. Earlier reports suggested that critically ill patients with AKI may benefit with adequate dialysis dosage. More recently, a trial of 172 patients with AKI who were randomized to either daily or alternate-day dialysis using biocompatible high-flux dialyzers was reported (Schiffl, 2002). Overall mortality was significantly improved in the daily dialysis group, which had a higher weekly dose of delivered dialysis. This was the first study to demonstrate that the amount of dialysis is an independent determinant of mortality in critically ill patients with AKI. However, a recent multicenter randomized clinical trial in which intensive renal replacement support (daily hemodialysis treatment) was prescribed to critically ill patients with AKI versus less-intensive treatment (every other day or low-dose dialysis treatment) did not decrease mortality, improve recovery of kidney function, or reduce the rate of nonrenal organ failure (Palevsky et al, 2008).

Prognosis of Acute Tubular Necrosis

The prognosis of ATN is dependent on the underlying primary disease that resulted in the AKI, as well as any complications that arise (e.g., infection, cardiovascular, gastrointestinal bleeding, central nervous system). The mortality rate for patients with ATN is consistently around 50% regardless of the study population (Biesenbach et al, 1992; Palevsky et al, 2008). This pessimistic outlook has changed little in the past 4 decades, despite the advent of effective dialysis (Lewers et al, 1970; Liano et al, 1993; Di Tullio et al, 1996; Uchino et al, 2005). Mortality rates remain high today despite effective control of uremia because of an older, sicker population with severe concomitant illnesses. Mortality rates have been quantified as high as 75% recently in several series in the ICU population. Higher mortality rates are seen in elderly patients, in patients with respiratory failure, multiorgan failure, preexisting chronic diseases, and systemic hypotension (Obialo et al, 1999). In a prospective multicenter study of mortality with critically ill patients with ATN, the factors predictive of early mortality were male gender, oliguria, mechanical ventilation, acute myocardial infarction, cerebrovascular accident/seizure, and chronic immunosuppression (Parker et al, 1998). Leading causes of death include bronchopulmonary infections, sepsis, cardiovascular disease, and bleeding disorders. Of patients who survive ATN, nearly half will have a complete recovery of renal function and a majority of the remainder has an incomplete recovery (Fig. 43–6) (Spurney et al, 1991). Only about 5% of all AKI patients require chronic maintenance dialysis.

A separate question is whether the development of AKI itself directly contributes to mortality. The answer appears to be a resounding "YES!" In a prospective study of 183 patients who developed AKI after IV contrast exposure, the in-hospital mortality rate was substantially higher in the AKI group (34% vs. 7%) than a matched control (Levy et al, 1996). This effect persisted after the adjustment of other comorbid diseases (relative risk = 5.5). The development of AKI is also known to increase morbidity of patients, prolong hospitalizations, and increase hospital costs.

Prevention of Acute Tubular Necrosis

Because the management of ATN is primarily one of conservative care and support, special attention should be focused on the prevention of AKI. Patients at high risk (i.e., patients with preexisting azotemia, the elderly, volume-depleted individuals, diabetics) warrant careful clinical consideration of the relative risks and benefits of diagnostic or therapeutic interventions that have potential for nephrotoxicity. This is especially true for patients at risk undergoing cardiac catheterization or other diagnostic studies requiring iodinated contrast material. Several studies deserve comment.

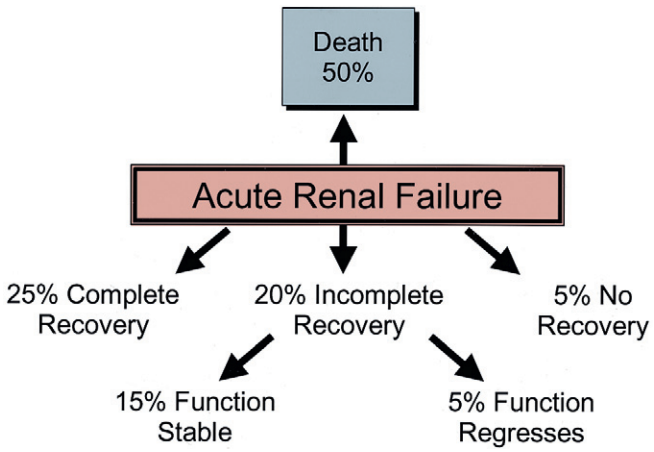


Figure 43–6. Prognosis of acute tubular necrosis.

A study by Solomon and colleagues (1994) confirmed that intravenous hydration with saline was critical in diminishing the nephrotoxic effects of coronary arteriography for patients with preexisting azotemia. The addition of either a loop diuretic or mannitol did not improve outcome. Rudnick and colleagues (1995) published a prospective, randomized trial of nearly 1200 well-hydrated patients undergoing cardiac catheterization to examine the effects of the newer nonionic contrast material. Patients were stratified for the presence or absence of azotemia (SCr ≥ 1.5 mg/dL) or diabetes mellitus. In patients without azotemia (with or without diabetes mellitus), the incidence of contrast-induced renal dysfunction was low (i.e., <1% to 2%) with either the ionic or nonionic contrast material. Those with preexisting azotemia had a 50% reduction in contrast-associated renal dysfunction with the nonionic material. These data suggest that in azotemic patients who require cardiac angiography, a protocol of intravenous hydration and use of a nonionic contrast material appear warranted. Moreover, a recent meta-analysis also demonstrated that the use of the newer iso-osmolar nonionic agents would be of benefit when compared with hypo-osmolar agents, especially in subjects with preexisting kidney disease and diabetes (McCullough et al, 2006).

In addition to these maneuvers in high-risk patients, pretreatment with *N*-acetylcysteine (600 mg orally twice daily for 48 hours) has been shown to reduce the incidence of radiocontrast-induced nephropathy (Tepel et al, 2000). A meta-analysis of randomized clinical trials using *N*-acetylcysteine in patients with reduced renal function clearly showed risk reduction for acute radiocontrast injury (Alonso et al, 2004). In contradistinction, a separately conducted meta-analysis of randomized controlled trials using *N*-acetylcysteine for the prevention of radiocontrast-induced nephropathy did not warrant a strong recommendation for its clinical use (Kshirsagar et al, 2004).

Recent trials compared the benefits of two hydration protocols in reducing radiocontrast-induced nephropathy. A trial involving 1620 patients undergoing coronary angioplasty demonstrated a benefit of isotonic hydration as superior to half-isotonic hydration in prevention of nephropathy (Mueller et al, 2002). **A smaller, single-center prospective randomized trial showed the benefit of IV hydration with sodium bicarbonate over sodium chloride given 1 hour before contrast exposure in the prophylaxis of contrast-induced renal dysfunction** (Merten et al, 2004). **The latter protocol has the advantage of timing because it was initiated 1 hour before the anticipated contrast study, rather than requiring 48 hours of pretreatment with *N*-acetylcysteine.** A recent multicenter trial did not find any protective benefit of the selective dopamine-1 agonist (fenoldopam mesylate) in the prevention of contrast-induced renal dysfunction in an at-risk population (Stone, 2003). Similarly, a meta-analysis did not find any compelling benefit for the use of theophylline, an adenosine antagonist, in the prevention of contrast-induced nephropathy (Bagshaw and Ghali, 2005). **In the aggregate, the aforementioned recommendations for the azotemic patients who require radiocontrast procedures warrant a protocol of IV hydration with isotonic fluids** (Weisbord and Palevsky, 2008) **and the use of nonionic contrast material in the lowest dose possible. The use of sodium bicarbonate as an isotonic fluid may be beneficial. Treatment with *N*-acetylcysteine for 48 hours before the procedure and/or special hydration with prestudy sodium bicarbonate are deserving of further study.**

Key Points: Acute Renal Failure

- Creatinine as an assessment of renal function needs to be interpreted in the context of clinical events that are occurring in the patient.
- Acute kidney injury is categorized on the basis of pathophysiology as prerenal, postrenal, or intrinsic renal. The etiology and pathogenesis determine management.
- Prerenal azotemia is transient renal hypoperfusion and responds well to isotonic fluid replacement.
- In considering postrenal causes of AKI, do not forget fistula as an iatrogenic cause.
- The inflammatory response is important in the pathogenesis of ATN and may become a future target for therapeutic intervention.
- Conservative management predominates for ATN. This entails dialysis support as needed with prevention of complications.
- Review of the data regarding pharmacologic intervention for established ATN supports a trial of isotonic fluid repletion. Judicious use of intravenous loop diuretics may increase urine output, but their ability to have an impact on improved patient survival in AKI is still unproven. Similarly, the clinical data on "renal-dose" dopamine are scant and do not support its widespread use in established ATN.
- Recommendations for the azotemic patients who require radiocontrast procedures warrant a protocol of IV hydration and the use of nonionic iso-osmolar contrast material in the lowest dose possible. Treatment with *N*-acetylcysteine for 48 hours before the procedure and/or special hydration with prestudy sodium bicarbonate are to be considered as well.

CHRONIC KIDNEY DISEASE

Approximately 20 to 25 million individuals in the United States have chronic kidney disease (CKD) (Coresh et al, 2007). The diagnosis of CKD implies a persistent abnormality in glomerular filtration rate (GFR) with a wide spectrum of causes. The Workgroup of the U.S. National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI) Advisory Board recommended that "chronic kidney disease" should be defined as sustained kidney injury greater than 3 months resulting in a GFR of less than 60 mL/min/1.73 m (Foundation, 2002). After an initial kidney insult, if the acute injury does not completely resolve, a continuing attrition of functional nephrons occurs over time. Figure 43–7 depicts the renal failure continuum consisting of several stages of functional deterioration associated with specific clinical and biochemical abnormalities. **Small changes in the SCr measurement correlate with significant alterations in the GFR when renal function is greater than 60 mL/min. This concept is illustrated by the SCr ordinate on the left side of** Figure 43–7, matched to the GFR line of identity crossing through the four different phases of progressive renal disease. However, the relationship between the SCr level and the GFR changes as the renal function deteriorates to less than 60 mL/min. **As noted on the right side of Figure 43–7, changes in the GFR (dashed, curved line) are represented by significantly larger increases in SCr level depicted on the right ordinate. This is especially true in CKD as the GFR decreases to levels below 30 mL/min.** Although an initial

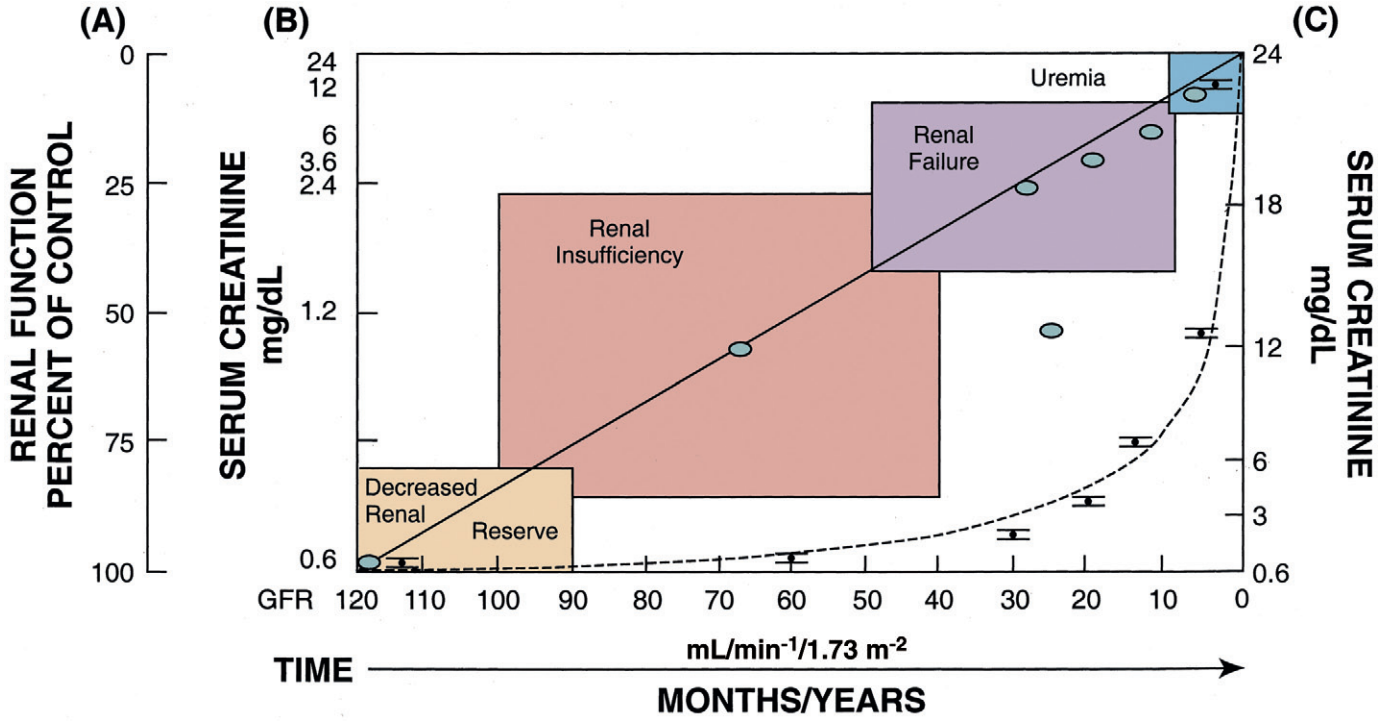


Figure 43–7. The course of progressive renal disease. The course of a patient who began with normal renal function corresponding to a serum creatinine concentration of 0.6 mg/dL and glomerular filtration rate (GFR) of 120 mL/min/1.73 m^2 is shown. *Y-axes:* The geometric serum creatinine ordinate at the left *(B)* applies to the solid line of identity *(open circles),* and the *rectangles* depict the various stages of progressive renal disease. The serum creatinine ordinate at the right side of the figure *(C)* should be used with the *dashed curve (ax-heads)* only. The ordinate at the extreme left *(A),* which describes the percentage of renal function remaining, applies generally. *Line of identity:* This line shows a decrease in function from 100% to 9% of normal corresponding to the diminution in GFR from 120 to 0 mL/min/1.73 m^2. The matching creatinine scale *(A)* is geometric. *Dashed curve:* Because GFR equals daily creatinine excretion/serum creatinine concentration and because the creatinine excretion is equal to daily production, which is constant, this equation is of the form $y = k/x$, which defines a hyperbola. This relationship remains valid over the course of chronic renal disease unless the creatinine production changes. The curve emphasizes that large changes in GFR may produce small and clinically imperceptible changes in serum creatinine concentration when overall renal function is near normal. Conversely, trivial changes in GFR produce large changes in serum creatinine concentration when the GFR is low. The rate of progression throughout the delineated stages depends on the nature of the underlying renal disease, host factors, treatment, and compliance with the medical regimen. (From Kimmel PL. Management of the patient with chronic renal disease. In: Greenberg A, editor. Primer on kidney disease. 2nd ed. San Diego (CA): Academic Press; 1998. p. 434.)

insult may decrease an individual's renal reserve, biochemical abnormalities are uncommon before the "renal-insufficiency" stage. Once severe "renal failure" occurs, clinical symptoms become more common.

The degree of adaptation taking place at each stage determines the extent of clinical and biochemical abnormalities. When kidney function is minimally impaired (≤60%), physiologic adaptation is complete. Because the GFR usually falls below 20% of normal, progressive anorexia with nausea, salt retention, acidosis, insomnia, anemia, muscle fatigue, and worsening BP control may occur. Structurally, after the GFR in humans falls below 50% of normal, a relentless progressive loss of function ensues even when the initial disease becomes inactive (Mitch et al, 1976). There is significant interest in those clinical and public health initiatives that can potentially identify and prevent progressive kidney failure. The National Kidney Foundation developed and published clinical practice guidelines for CKD in 2002 to more consistently diagnose and treat CKD and its comorbidities (Foundation, 2002; Patel et al, 2002; Eknoyan, 2003).

While the clinical course of progressive renal disease as illustrated in Figure 43–7 moves through several different phases, which include decreased renal reserve, renal insufficiency, renal failure, and frank uremia, the K/DOQI guidelines have developed a more uniform classification of the stages of CKD. These guidelines will have an impact on education between patients and providers, enhance the public's understanding of the different levels of kidney disease, and promote dissemination of specific research results for each stage. Because the GFR has been accepted as the best overall index of kidney function, the new staging schema (Table 43–10) is divided according to GFR levels. This classification represents a series of evidence-based clinical practice guidelines that describe specific recommendations for optimal CKD patient care (Patel et al, 2002).

Renal Mass Reduction and Chronic Kidney Disease

Recent evidence supports the view that deficits in nephron number predispose to progressive renal disease and hypertension (Chertow et al, 1996). Nephron number averages approximately 600,000 per kidney in the normal kidney with a standard deviation greater than 200,000 (Nyengaard and Bendtsen, 1992). Conceptually, partial ablation of renal mass through renal insult or surgical partial nephrectomy initiates a cycle of progressive glomerular injury in the remnant kidney. In this setting, the injury is associated with hyperfiltration, glomerular hypertrophy, and systemic hypertension (Brenner and Mackenzie,

Table 43–10.

Clinical Action Plan for Chronic Kidney Disease by GFR Levels

STAGE	DESCRIPTION	GFR (mL/min/1.73 m^2)	ACTION
	At increased risk	≥90 (with CKD risk factors)	Screening, CKD risk reduction
1	Kidney damage with normal or increased GFR	≥90	Diagnosis and treatment, treatment of comorbid conditions, slowing progression, CVD risk reduction
2	Kidney damage with mild decrease in GFR	60-89	Estimating progression
3	Moderate decrease in GFR	30-59	Evaluating and treating complications
4	Severe decrease in GFR	15-29	Evaluating and treating complications
5	Kidney failure	<15 (or dialysis)	Replacement (if uremia present)

Shaded area identifies patients who have chronic kidney disease; *unshaded area* designates individuals who are at increased risk for developing CKD. CKD is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage including abnormalities in blood or urine tests or imaging studies.

CKD, chronic kidney disease; CVD, cardiovascular; GFR, glomerular filtration rate.

From National Kidney Foundation: Clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 2002;39(2):S19.

1997). In human studies, Novick and colleagues (1991) demonstrated that with a greater than 50% reduction in total renal mass, the extent of proteinuria correlated directly with the duration of follow-up and inversely with the amount of renal tissue remaining. This discovery suggests that ongoing real injury occurs when a specific "set point" reduction in nephron number occurs. In certain population groups birth weight may be a risk factor for progressive renal failure if associated with intrauterine growth retardation. Low birth weight can lead to a 20% decrease in overall nephron number (Lopes and Port, 1995; Hughson et al, 2003; Keller et al, 2003). Glomerular size in African-Americans is larger than in whites, possibly reflecting smaller nephron number (Pesce, 1998) and perhaps attributable to lower birth weight (Garrett et al, 1994). Theoretically, the increased risk for African-Americans to develop "nephrosclerosis" could be linked to this low-birth-weight risk concept. Even allograft nephron number (donor kidney size compared with recipient body size) may be relevant in the development of chronic rejection and failure in human transplantation setting (Brenner and Mackenzie, 1997; Poggio et al, 2006). When the body mass of the donor is small, the functional demands on the allograft will be strained and may contribute to ongoing injury over time leading to allograft failure.

Interestingly, the age at loss of renal mass influences the kidney's response in humans. In patients undergoing unilateral nephrectomy for Wilms' tumors, renal growth was most marked in those individuals who had surgery at a younger age (Di Tullio et al, 1996). This finding can be applied to the contrasting observations comparing outcomes in congenital solitary kidney versus surgical unilateral nephrectomy. The volume of glomeruli in a congenital solitary kidney is five to six times that observed in a normal kidney (Bhathena et al, 1985). This increase in volume with decreased nephron number could explain the higher risk for ongoing parenchymal injury compared with surgical nephrectomy cases. Moreover, in former kidney donors postdonation GFR seems to stabilize after an initial decrease from predonation GFR due to the nephrectomy (Ibrahim et al, 2009). These reports support the concept that the true response to decreased renal mass in humans varies according to age at time of reduction, underlying conditions (causative agent, etiology), and the actual degree of reduction.

Mechanisms of Progression

Apoptosis (programmed cell death) triggered by ischemia, toxins, or endogenous mediators of damage can be the initial insult that causes renal damage. Apoptotic cell death is an active process under molecular control of regulatory proteins and is characterized by both morphologic and functional changes. These changes usually occur as a response to the cell and microenvironment in which the presence of certain "lethal factors" (e.g., tumor necrosis factor, Fas-ligand) or the absence of "survivor factors" (e.g., EGF, **IGF-1, IGF-2, basic fibroblast growth factor [bFGF]) promote apoptosis. Lethal factors can either activate specific cell death receptors or damage the cells in the absence of receptor activation** (Ortiz, 2000). **Although growth factors regulate hypertrophy and cell proliferation, they may also mediate apoptosis as a healing response. Understanding the role and regulation of apoptosis in renal disease will be a central theme in designing future therapeutic agents.**

A reduction in nephron mass follows cell death. Figure 43–8 illustrates the mosaic of events that occur with progressive nephron mass loss linking sympathetic nervous system activation, renal structural remodeling, altered gene expression/regulation, and several additional regulatory mechanisms for progression. Renal protective interventions are designed to counter those events that adversely affect the cortex and interstitium of the kidney. Both hemodynamic and nonhemodynamic factors are involved in the sustained renal injury after an initial insult. The hemodynamic events causing an increase in single nephron glomerular filtration rate (SNGFR) include increased glomerular plasma flow rates and capillary hydrostatic pressures in the remaining glomeruli. Elevated glomerular hydrostatic pressure is a major factor in renal injury after renal mass reduction (Meyer and Rennke, 1988). However, hyperfiltration alone in response to decreased nephron mass is not sufficient to induce pathologic glomerulosclerosis and interstitial fibrosis. Neurogenic factors and hypertension also play a significant role in ongoing renal injury. Increases in angiotensin II and nitric oxide (NO) activate the sympathetic nervous system (SNS), which plays a dominant role in the pathogenesis of hypertension in CKD (Myers et al, 1975). The rise in central SNS activity is generated by increased local expression of nitric oxide synthase (NOS)-mRNA and NO production coupled to an upregulation of NO production by interleukin-1 (IL-1) in the brain (Campese, 2000).

Nonhemodynamic mechanisms for renal injury involve a number of complex interactions for remodeling including structural changes (injury modeling), multiple

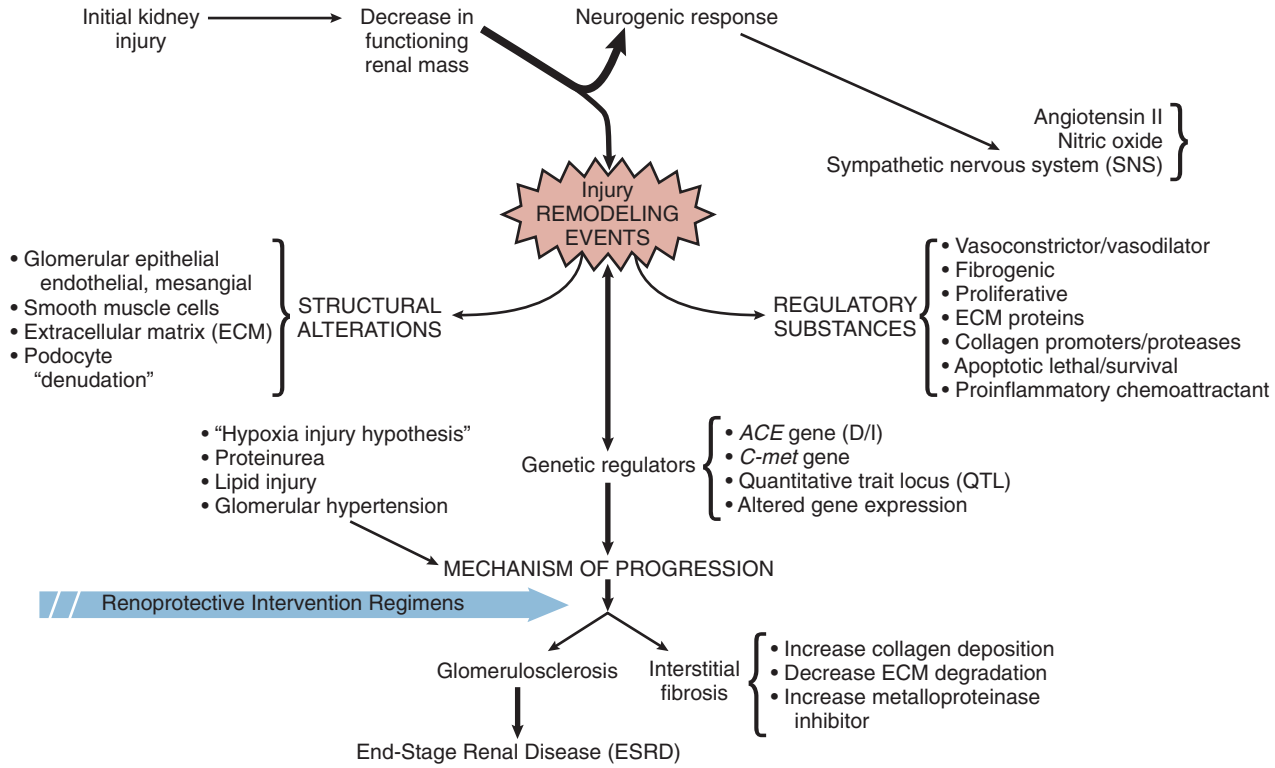


Figure 43–8. Kidney injury mosaic for progressive renal failure. *Fibrogenic factors:* Transforming growth factor-β (TGF-β), hepatocyte growth factor (HGF), matrix metalloproteinases (MMP-2 and MMP-9), nuclear factor-κβ (NF-κβ). *Vasoconstrictors:* Basic fibroblastic growth factor (bFGF), transforming growth factor-β, angiotensin II (ang II). *Vasodilators:* Prostaglandin E-1 (PGE-1), nitric oxide (NO). *Proliferative factor:* Vascular endothelial growth factors (VEGF), epidermal growth factor (EGF), growth factor (GF). *ECM expander:* Platelet-derived growth factor (PDGF), transforming growth factor-β. *Glomerular cell proliferation:* Angiotensin II (Ang II), basic fibroblastic growth factor (bFGF), PDGF, and EGF. *Collagen promoting:* PDGF, TGF-β, matrix metalloproteinases (MMP-2). *Chemoattractant:* Macrophage colony-stimulating factor (MCSF), chemoattractant protein-1. *Apoptotic lethal factors:* Fas-ligand (Fas-L). *Apoptotic survival factors:* EGF, bFGF, PDGF, insulin-like growth factor-1, insulin-like growth factor-2.

growth factors, and cytokines. Abnormal glomerular growth is associated with, and may be a marker for, the activation of these specific mechanisms leading to sclerosis during the remodeling phase after renal injury (Fogo, 2000). Injury remodeling involving both glomerular hyperplasia (increase in cell number) and glomerular hypertrophy (increase in cell size) can occur within 2 days of a significant decrease in overall renal mass (5/6 nephrectomy). Glomerular growth can occur because of increases in any of the cellular components. Structural changes in the glomeruli during remodeling include increased extracellular matrix (ECM) production; glomerular hypertrophy; glomerular proliferation (increase in cell number: epithelial, endothelial, mesangial cells); and glomerular basement (GBM) modification (Harris et al, 1992).

Foam cells are frequently located in segments of the glomerulus undergoing sclerosis and in the interstitium of diseased kidneys. Oxidized low-density lipoprotein (LDL) stimulates inflammation and fibrogenic cytokine production and can cause an increase in cell apoptosis and the production of endothelin and thromboxane. It also causes an increase in the release of renin from juxtaglomerular cells, thus enhancing vasoconstriction (Keane, 2000).

Many diseases have been associated with an imbalance of ECM synthesis and degradation. The glomerular mesangial cell responds to varied growth factors by proliferation and increased ECM production. An increase in collagen deposition and a decrease in the degradation of ECM components lead to interstitial fibrosis. The degree of tubular interstitial fibrosis has been closely correlated with the reduction in GFR in many different animal and human studies. Angiotensin II upregulates transforming growth factor-β1 (TGF)-β1, which is a potent fibrogenic factor playing a key role in the pathogenesis of interstitial fibrosis. The major physiologic regulators of ECM degradation in the glomerulus are matrix metalloproteinases (MMPs) (Lenz et al, 2000). MMPs are distinct, matrix-degrading enzymes such as stromelysins, gelatinases, elastases, and interstitial collagenases. Changes in MMP expression or activity can alter ECM turnover, which in turn may lead to glomerular scarring and a decline in renal function. MMPs may also indirectly affect regulation of certain growth factors that play a role in ECM turnover. Conceptually, progressive glomerular sclerosis may result from this shift in ECM turnover (attributable to MMP imbalance) toward increased matrix accumulation, a decreased filtration area, and progressive renal failure.

A wide range of conditions or substances can promote intrarenal growth and glomerular sclerosis in experimental models. These include a loss of renal mass, high-protein or high-salt diet, growth hormone, IGF-1, androgens, glucocorticoids, angiotensin, aldosterone, and endothelin. Aldosterone may promote fibrosis by several mechanisms including plasminogen activator inhibitor-1 expression with consequent alterations of vascular fibrinolysis through stimulation of TGF-β1 and reactive oxygen species. Although significant evidence has accumulated to implicate angiotensin II in mediating renal disease, aldosterone is also an important factor in causing progressive renal disease through both hemodynamic and direct cellular actions. Circulating aldosterone may mediate vascular fibrosis by a direct interaction with high-affinity, low-capacity corticoid receptors located in the cytosol of vascular fibroblasts (Epstein, 2001).

Angiotensin II upregulates the expression of multiple growth factors and cytokines. A number of cell-specific growth responses (glomerular cells, endothelial cells, glomerular visceral epithelial cells, mesangial cells) regulate glomerular growth. Endothelial cells inhibit smooth muscle cell migration and proliferation and produce vascular endothelial growth factors, nitric oxide, endothelin, and PDGF (Fogo, 1999). Vascular endothelial growth factors stimulate angiogenesis, whereas endothelin promotes hypertrophy and increased mesangial cell matrix.

In addition to regulatory substances, additional hypotheses have been developed to explain progression of different renal diseases. Fine and colleagues (Evanson et al, 1998) proposed a "chronic hypoxia hypothesis" suggesting that chronic oxygen deprivation to the tubular interstitial compartment can result in scarring. Within glomeruli, blood flow and oxygen delivery into the interstitial capillary network are reduced, resulting in lowered oxygen tension in the remaining vasodilated glomeruli with a high-flow tubular capillary system (hyperfiltration). Postglomerular capillaries exposed to the elevated pressure and increased flow develop endothelial swelling and functional changes that infringe on distal blood flow and oxygen delivery resulting in ischemia over time.

Genetic Factors

Family members of patients with kidney disease are disproportionately affected with progressive renal failure. The familial clustering of nephropathy has been reported in diabetes, hypertension, systemic lupus erythematosus and human immunodeficiency-associated nephropathy. Interestingly, **an individual's family history of end-stage renal disease (ESRD) is a better predictor of the future risk for renal failure than is BP or blood glucose** (Freedman et al, 1997; Satko and Freedman, 2004). A study sponsored by the National Kidney Foundation of Singapore, which screened more than 210,000 adults with renal disease, demonstrated a significant relationship between a family history and proteinuria with the potential for future renal failure (Ramirez et al, 2002).

Our understanding of those mechanisms involved in progression to sclerosis has expanded since the early 1990s. It is now clear that genetic traits may contribute to the structural and functional adaptations to a reduction in renal mass. In diabetes, genetic signaling in response to a metabolic injury may explain why only approximately 40% of those with type 1 diabetes develop diabetic nephropathy. In the Appropriate Blood Pressure Control and Diabetic (ABCD) study, the ACE DD genotype was the strongest predictor for the presence of nephropathy (14.2% of DD homozygotes have nephropathy vs. 7.8% of non-DD homozygotes) (Jeffers et al, 1997). The Genetique de la Nephropathie Diabetique study demonstrated a significant association between the D-allele frequency and progressive nephropathy in type 2 diabetics (Marre et al, 1997). Even in nondiabetic glomerular injury (IgA nephropathy) there was a greater reduction in GFR and worse biopsy in patients carrying the D-allele. Not only does the DD genotype impart increased risk of progression, but this genotype is also associated with an earlier need for dialysis.

It is hoped that large, collaborative genetic analysis will identify the genes underlying diabetic nephropathy and determine if the loci identified in prior smaller studies can be duplicated (Satko and Freedman, 2004, 2005). The National Kidney Foundation sponsored the Kidney Early Evaluation Program (KEEP) and the Southeastern Kidney Council/ESRD Network. These programs are screening high-risk American populations assessing the link between family history and kidney disease (Brown et al, 2003).

Studies in human renal disease have begun to map the loci of key growth factors. Zidek and colleagues (1998) uncovered a quantitative trait locus on chromosome 2 of a mouse model that is linked to genetic modulation of kidney compensatory growth. This quantitative trait locus is located close to the gene for ACE, growth hormone, and neurogrowth factor receptor (Schena et al, 1999), all of which influence renal growth. **Furthermore, altered gene expression in certain pathophysiologic settings that induce upregulation or inhibition of various growth factors may regulate the degree of response to an initial renal injury.** This may lead to hypertrophy, proliferation, or an increase in ECM. These growth factors include platelet-derived growth factor (PDGF), TGF-β, TGF-α, IGF-1, epidermal growth factors (EGFs), IL-1 and IL-6, tumor necrosis factor-α (TNF-α), angiotensin II, and endothelin. Angiotensin II, PDGF, and TGF-β play key roles in sclerosis and fibrosis. IGF-1, fibroblast growth factor (FGF), PDGF, and EGF may be altered in diabetes mellitus, leading to progressive renal injury and kidney failure in this patient cohort.

Therefore a more thorough understanding of susceptibility genes, regulatory genes for kidney disease progression, and treatment response genes may significantly improve our approach to CKD in the future.

Etiologies for Chronic Kidney Disease

The causes of progressive CKD parallel the most common causes of ESRD. Table 43–11 lists the incident causes of ESRD of varied causes by diagnosis from U.S. Renal Data System (Collins et al, 2009). **Diabetes mellitus and hypertension account for the largest percent of cases (71.2%) followed by glomerular diseases (7.2%). In patients younger than 40 years, CKD is most commonly caused by focal segmental glomerulosclerosis (FSGS), systemic lupus erythematosus (SLE), and then congenital abnormalities of the urinary tract or membranous glomerulonephritis.** Membranoproliferative glomerulonephritis (MPGN), scleroderma, and autosomal dominant polycystic kidney disease (ADPKD) account for the majority of cases of CKD developing in patients between the ages of 40 and 55 years. In the cohort of patients older than 55 years, atheroembolic disease; paraproteinemia (multiple myeloma, amyloid); nephrosclerosis; and analgesic nephropathy are the main causes of CKD. Those individuals older than the age of 70 developing CKD are growing exponentially.

Table 43–11.

Incidence of Reported End-Stage Renal Disease by Detailed Primary Renal Diagnosis

DIAGNOSIS	%
Diabetes mellitus	44.4
Hypertension	26.8
Glomerulonephritis	7.2
Cystic kidney disease	2.4
Urologic	1.5
All others	16.8
Missing	1.5

From Collins AJ, Foley RN, Herzog C, et al. United States Renal Data System 2008 Annual Data Report. Am J Kidney Dis 2009;53(1 Suppl.):S1–374.

The primary parenchymal renal diseases that have the greatest propensity to progress are FSGS, rapidly progressive glomerulonephritis (RPGN), chronic glomerulonephritis (GN), and MPGN. The development of CKD in patients with minimal change disease is rare in children and adults with a steroid-responsive clinical course. Patients at highest risk are those who do not respond to steroid therapy or who become late steroid nonresponders. The course of untreated FSGS is usually progressive to ESRD. Both children and adults usually develop ESRD 5 to 20 years from presentation. Malignant FSGS on biopsy exhibits a more rapid course to ESRD in 2 to 3 years. Those features associated with a more accelerated course are proteinuria greater than 10 to 15 g/day, SCr greater than 1.5 mg/dL at presentation, significant interstitial fibrosis, and glomerular sclerosis on biopsy.

Although MPGN type 1 is a slowly progressive disease, type 2 is more aggressive with a higher percentage of sclerotic glomeruli, crescent number, and greater degree of interstitial fibrosis. These features portend a poor outcome. Progressive renal insufficiency can occur in 20% to 25% of patients with MPGN progressing to ESRD over 20 years. At presentation, it is difficult to predict the renal outcome in most membranous patients compared with those with MPGN.

Forty percent of individuals with IgA nephropathy progress to ESRD after approximately 20 years of clinical disease. Markers of poor outcomes are persistent hypertension, proteinuria greater than 2 g/24 hr, initial abnormal SCr at time of biopsy, and severe sclerotic changes and interstitial fibrosis on biopsy.

A number of systemic diseases involve the kidney and can lead to progressive renal insufficiency (Table 43–12). **Progressive deterioration in renal function can occur in systemic vasculitis due to Goodpasture syndrome, Wegener granulomatosis, Henoch-Schönlein purpura, and cryoglobulinemia with or without hepatitis C.** Serologic tests (cryoglobulins, antineutrophil cytoplasmic autoantibody analysis, immune complex markers, antibodies to hepatitis B or C, antistreptolysin O, hemolytic complement levels CH50 and C3), and biopsy of temporal artery or kidney are useful in classifying the clinical presentation into the correct vasculitis category. A significant glomerular insult on biopsy coupled with a poor response to therapy signifies patients at risk for developing worsening renal dysfunction and eventual ESRD.

In type 1 diabetics, 50% of patients will reach ESRD between 7 and 10 years after the onset of proteinuria. In most patients with type 2 diabetes the time of onset is unknown, thus complicating the ability to predict the course of renal failure. Moreover, a significant percent have concomitant risk factors (smoking, hypertension, hyperlipidemia) along with the proteinuria (>3 g) and nephrosclerosis, which may accelerate time to ESRD.

Monoclonal immunoglobulins or light chains in both the serum and urine are observed in dysproteinemic states of light-chain nephropathy, amyloid, and cryoglobulinemia. Patients usually present with undiagnosed increases in SCr and proteinuria and are usually older than 40 years. Treatment of light-chain deposition disease (LCDD) is suboptimal with a significant percentage of patients progressing to ESRD if their presenting SCr values were greater than 4 mg/dL.

Malignancies of the gastrointestinal tract, breast, renal cell, prostate, skin, and so on can mediate an immune complex nephropathy potentially leading to CKD. Urologic, gynecologic, and lymphoproliferative malignancies can also result in renal injury and progressive chronic renal insufficiency. Non-Hodgkin lymphoma is associated with membranous glomerulonephritis, (MGN) and retroperitoneal tumors can cause ureteral obstruction and parenchymal infiltration or both.

Table 43–12.

Causes of Progressive Chronic Kidney Disease

Tubulointerstitial	
Hematopoietic:	Sickle cell disease, lymphoproliferative, dysproteinemia, neoplastic
Urologic:	Ureteral obstructions, reflux, prune-belly syndrome, prostatic hypertrophy
Vascular:	Radiation, hypertension, atheroemboli
Metabolic:	Cystinosis, oxalosis, uric acid nephropathy, hypercalcemia
Immunologic:	Renal allograft rejection, Sjögren syndrome
Toxic:	Analgesics, NSAIDs, chemotherapy
Immunosuppression:	Tacrolimus, cyclosporine
Heavy metals:	Lead, lithium
Hereditary	
Sickle cell disease	
Cystic disease:	ADPKD, medullary cystic disease
Alport syndrome	
Karyomegalic interstitial nephritis	
Primary Renal Disease	
Glomerular:	Idiopathic glomerulonephritis
Minimal change disease	
Focal segmental glomerulosclerosis	
Membranous glomerulonephritis	
IgA nephropathy	
Systemic Diseases	
Diabetes mellitus	
Infection-related glomerulonephritis	
SLE, HSP, systemic sclerosis	
Dysproteinemias/amyloid	
Thrombotic microangiopathies	
Vasculitis:	Crescentic glomerulonephritis, acute diffuse glomerulonephritis, ANCA glomerulonephritis (microscopic poly angiitis), Wegener granulomatosis, Churg-Strauss syndrome, Goodpasture syndrome, granular cell arteritis

ADPKD, autosomal dominant polycystic kidney disease; ANCA, antineutrophil cytoplasmic antibody; HSP, Henoch-Schönlein purpura; NSAIDs, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosis.

Certain hereditary diseases (sickle cell nephropathy, autosomal dominant polycystic kidney disease [ADPKD], medullary cystic, aplastic, dysplastic, or hypoplastic kidneys) can also lead to CKD. ADPKD is the most common hereditary renal disorder leading to ESRD. Gene linkage may be helpful in identifying the ADPKD gene loci on the short arm of chromosome 16. This test can be carried out in utero in children and in adults before cyst development. Only about 50% of ADPKD patients progress to renal failure. Risk factors for progression include male gender, African origin, early age of presentation,

ADPKD 1 gene, hypertension, and gross hematuria. Diverticular disease, cardiac valvular disease, and intracranial aneurysms are more common in ADPKD patients than in the general population and need to be considered in their care.

This should be differentiated from acquired renal cystic disease (ARCD). ARCD develops in the setting of CKD and end-stage kidney disease and is a consequence of renal disease rather than a cause. The important correlation associated with ARCD is the increased incidence of renal cell cancer (Denton et al, 2002).

Medullary cystic disease sometimes can be confused with the benign condition of medullary sponge kidney. Medullary cystic disease presents in childhood with tubular cystic lesions at the cortical medullary junction and can be most accurately detected by kidney biopsy. The kidneys are usually small, and the disease progresses to ESRD at a variable rate.

Tubular interstitial disease accounts for 3.8% of patients with CKD. Clinical manifestations depend on the degree of involvement, the tubular sites involved, and the level of compensation that the uninvolved areas provide. The diagnosis of chronic interstitial nephritis depends on the urinalysis and clinical history. The urine findings are variable, and white blood cells may be present. Obtaining an accurate medication history is essential, considering the broad range of etiologies. Three percent to 20% of patients treated with lithium over time develop CKD (Boton et al, 1987). Chronic lead nephropathy may demonstrate a protracted course that is gradually irreversible as evidenced by small contracted kidneys. Lead nephropathy can be associated with renal adenocarcinoma. Another form of chronic interstitial nephritis that progresses to ESRD is analgesic nephropathy. The course in analgesic nephropathy is variable depending on the number of pills consumed.

Obstructive uropathy involving the ureter, bladder, or urethra can lead to progressive renal insufficiency. Undetected ureteropelvic junction (UPJ) obstruction and posterior urethral valves are the most common types of congenital causes for progressive renal failure. Newer spiral CT methods may prove helpful in identification of the obstructing lesion. Regaining renal function postobstruction is dependent on both the degree and duration of obstruction (<2 weeks) and preservation of specific tubular acidifying abilities.

The percentage of ESRD population attributable to reflux nephropathy and nonreflux nephropathy has changed over time (Craig et al, 2000). In a study of pediatric renal failure trends in Australia and New Zealand, reflux represented a much larger proportion of the population in the 1970s than it did between 2002 and 2006 (Orr et al, 2009). Correspondingly, the incidence of hypoplasia/dysplasia increased during the same time period. There are debates regarding whether this may be attributed to changing disease categorization or more aggressive therapy of reflux. Finally, when stratified by age, reflux is more common in older children than hypoplasia/dysplasia, making it important for adult urologists to recognize. Women with reflux nephropathy demonstrate an increased risk of accelerated progression during pregnancy if the SCr is greater than or equal to 2.49 mg/dL. Vesicoureteral reflux may result in CKD from renal scarring. Vesicoureteral reflux may be either unilateral or bilateral, and progression to renal failure is related to the severity of reflux. Congenital reflux, particularly the higher grades, may be associated with renal dysmorphism where scarring is a nonpreventable consequence of maldevelopment. By contrast, acquired scarring is a consequence of pyelonephritis. It is this latter acquired group where aggressive management of reflux may prevent renal loss. Renal biopsy can be diagnostic, as well as prognostic, in obstructive neuropathy when relief of obstruction is not followed by restoration of renal function to baseline.

Over time, untreated urolithiasis can result in CKD. Gupta and colleagues reviewed the natural history of 33 urinary stone patients with a presenting SCr greater than 2.0 mg/dL before surgical intervention and after placement of ureteral stent or percutaneous nephrostomy tube (Gupta et al, 1994). The mean decrease in SCr with treatment was 1.2 mg/dL. There was no statistic difference in the rate of decrease between patients with pretreatment SCr levels of 2 to 2.9 mg/dL versus those with greater than 3 mg/dL. Furthermore, in a recent epidemiologic study by Rule and colleagues (2009), residents from Olmsted county with a history of a documented kidney stone ($n = 4774$) were more likely to develop CKD after the initial diagnosis than controls.

Renal artery stenosis (RAS) can result in progressive azotemia (Merten et al, 2004). "Flash" pulmonary edema with oliguria and azotemia may suggest the presence of bilateral RAS, warranting further evaluation. Usually, when the SCr is greater than 3 mg/dL, there is an underlying parenchymal abnormality contributing to kidney failure, in addition to the RAS. Dejani and colleagues (2000) have reported that only 25% of elderly patients with CKD (SCr > 2 mg/dL) and proximal RAS improved with renal revascularization. Renal artery stenting can improve the GFR of treated kidney, although the overall GFR may not change, perhaps reflecting the differential function of the contralateral kidney counterbalanced by the beneficial effect of the treated kidney (Grubb, 2000; Dharnidharka et al, 2002; Leertouwer et al, 2002).

Accurately monitoring the rate of decline in residual renal function (RRF) is important to determine whether the observed change in RRF is consistent with the natural history of the underlying disease or the result of an acute insult. If the RRF decline is inconsistent, an evaluation to uncover an alternate cause is warranted. Patients with CKD are at risk for acute renal failure from a broad range of causes. Nephrotoxic agents, infection, volume depletion, hypotension, progressive RAS, hypercalcemia, and hyperuricemia may all lead to worsening of underlying stable CKD as delineated in Table 43–13.

Clinical Assessment of CKD (Function, Proteinuria, Radiology, and Biopsy)

In practice, once the GFR decreases to less than 60 mL/min/1.73 m^2 for 3 months or more, patients are classified as having CKD. The adjusted relative risk from a population survey adjusted for age, proteinuria, hematuria, and hypertension found that changes in GFR occurred at a cutoff SCr value of 1.2 mg/dL (105 μm/L for women) and 1.4 mg/dL (125 μm/L for men) (Couchoud et al, 1999). However, in extrapolating SCr values to the actual GFR, the relationship may not be linear (see Fig. 43–7).

Other measurements that complement the SCr value may give a better index to the underlying predicted GFR. Creatinine clearance, creatinine clearance plus urea clearance divided by 2, GFR measurements (inulin iothalamate), and cystatin C all provide information on the level of renal dysfunction. Although the iothalamate GFR is the "gold standard" for measuring renal function, a dedicated staff and laboratory are mandatory to implement this test. The Cockcroft-Gault formula [creatinine clearance = (140 – age) × weight × (0.85 female) divided by 72 × plasma creatinine] is widely used throughout the world to estimate creatinine clearance (Cockcroft and Gault, 1976). Cystatin C, a 13-kilo-dalton nonglycosylated basic protein produced by all tissues, may have an advantage in detecting minor alterations in GFR and is a

Table 43–13.

Factors Associated with Acute Deteriorations in Chronic Kidney Disease

Nephrotoxic	**Parenchymal Injury**
Contrast-induced	Acute myocardial infarction
Pharmacologic agents	Valvular dysfunction
Aminoglycoside antibiotics	Superimposed "new" glomerulonephritis
NSAIDs	**Interstitial**
Cox 2 inhibitors	Hypercalcemia
Chemotherapeutic agents	Hyperuricosuria
Antirejection agents (cyclosporine, tacrolimus)	Atheroemboli
Anesthetic agents	**Drug-Induced**
Autoregulatory Dysfunction	Penicillin analogues
ACE inhibitors	Cephalosporins
Angiotensin receptor blocker	Sulfonamides
Anatomic/Structural	Rifampin
ADPKD and ACE inhibitors	Diuretics
Obstruction	Thiazide
Progressive renal artery stenosis	Furosemide
Renal vein thrombosis	**Miscellaneous**
Nephrolithiasis	Phenytoin
Hemodynamic/Perfusion Disorders	Allopurinol
Congestive heart failure	Cimetadine
Perioperative hypotension	
Volume depletion	
Gastrointestinal: bleeding, diarrhea, vomiting	
Excessive diuresis	
Sepsis with vasodilation	

ACE, angiotensin-converting enzyme; ADPKD, autosomal dominant polycystic kidney disease; COX-2, cyclooxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs.

potential candidate to complement SCr in the future, whereas SCr may be more accurate at lower levels of GFR (Grubb, 2000; Dharnidharka et al, 2002; Levey et al, 2007).

Most forms of CKD gradually and inevitably progress to ESRD over a 2- to 10-year time course, depending on the underlying renal lesion responsible for the CKD, combined with patient-specific factors. The K/DOQI staging and approach to treatment of CKD depends on the assessment of GFR (function assessment), level of proteinuria, and clinical comorbidities. **The National Institute of Health (NIH) Consensus Conference of 1993 recommended that patients with CKD be referred to a nephrologist when the SCr has increased to 1.5 mg/dL in females and 2 mg/dL in males** (Panel, 1994).

Renal Function Assessment

Although the SCr level is widely used as an index of renal function, SCr is affected by factors other than the GFR. At any given GFR the SCr concentration is significantly higher in men than in women, and in blacks than in whites. Total creatinine clearance (TCrCl) usually exceeds the GFR because of tubular secretion, whereas the urea clearance is usually lower than the GFR because of tubular reabsorption. The mean of the creatinine and the urea clearance is a more accurate estimate of the GFR than either is separately. Factors associated with creatinine excretion (age, gender, ethnicity, tubular creatinine secretion and inhibition) may affect the accuracy of standard SCr measurements. **The MDRD Study equation to predict the GFR incorporates SCr concentration and demographic characteristics (age, gender, and ethnicity). It is more accurate than other more widely used predictive equations or parameters (SCr level, 1/SCr, TCrCl+ Urea clearance/2, Cockcroft-Gault formula); however, it tends to underestimate GFR at higher GFR ranges** (Levey et al, 2006; Stevens et al, 2006). Although the MDRD Study equation has gained popularity, a new equation to estimate GFR has recently been published. This new model, the Chronic Kidney Disease Epidemiology Study equation or CKD-EPI equation, is expected to replace the MDRD study equation because it was developed using a combination of several studies in which kidney function was measured, including the MDRD Study. Although this equation retains the very good performance observed with the MDRD equation in subjects with estimated GFR below 60 mL/min/1.73 m^2, it further provides a lower bias in subjects with better preserved GFR levels (Levey et al, 2009).

Although these equations are better than other standard measures for GFR, they are still inaccurate for patients not in a steady state for creatinine balance or those with a medical condition interfering with creatinine excretion or creatinine assay or both (diabetic ketoacidosis or therapy with certain cephalosporins) (Coresh et al, 2007). These equations are still of doubtful application in subjects with no kidney disease and normal kidney function.

Most glomerular diseases that result in eventual ESRD progress slowly over 5 to 10 years. Patients presenting with RPGN, accelerated FSGS, Goodpasture syndrome, or Wegener granulomatosis can reach ESRD over a period of several months. In the MDRD study of 249 patients with a wide variety of nondiabetic renal disease, the GFR declined in 85% of patients whose initial GFR ranged from 13 to 55 mL/min (Hunsicker et al, 1997). The average rate of decline in nondiabetic renal disease was 4 mL/min/year in patients who progressed.

Considering the current K/DOQI staging of renal function linked to level of GFR, a number of medical centers and

commercial laboratories are using estimated GFR (eGFR) from SCr as a primary method of reporting kidney function because of inadequacies in SCr alone. The Modification of Diet in Renal Disease (MDRD) study equation is used most commonly to estimate GFR; however, it is expected that most laboratories eventually incorporate the CKD-EPI equation as the main method for estimating GFR. The estimation of GFR by any equation is not appropriate for patients who have rapidly changing kidney function, are at the extremes of age and body size, exhibit malnutrition or obesity, are paraplegic or quadriplegic, consume a vegetarian diet, or have diseases that have an impact on skeletal muscle status. Moreover, in sick, hospitalized patients with moderate-advanced renal failure, the Cockcroft-Gault, MDRD equations, and e-GFR perform poorly when estimating GFR and are not reliable measurements of residual renal function (RRF) (Poggio et al, 2005). In instances when the e-GFR may not be accurate, a 24-hour urine collection for creatinine plus urea clearance divided by 2 is recommended.

Proteinuria

Increased excretion of albumin is a sensitive marker for CKD attributable to diabetes mellitus, glomerular disease, interstitial disease, and hypertension. The American Diabetes Association and the National Kidney Foundation have recommended screening assessment using proteinuria measurement to detect CKD (Association, 2001; Levey et al, 1998). In adults albuminuria can be identified by the use of albumin dipstick, urinary albumin concentration (UAC), albumin/creatinine ratio (ACR) measured in a spot morning urine sample, or urinary albumin excretion (UAE) greater than or equal to 30 mg over 24 hours (Gansevoort et al, 2005). Traditionally the cutoff value indicating a UAE greater than 30 mg per 24 hours has been 3 mg/L (Brown et al, 2003). The standard urine protein dipstick is insensitive for low concentrations of albumin (<10 mg/dL) and for some immunoglobulin light chains. Dehydration, hematuria, exercise, infection, extremely alkaline urine (pH >8) can cause false-positive dipstick readings. Alternatively, a random urine protein-to-creatinine ratio can also be used for the assessment and management of patients with established CKD (Ginsberg et al, 1983; Schwab et al, 1987). This approach provides a comparable assessment of proteinuria to a 24-hour urine collection. Exceptions are in subjects with large variations in muscle mass (either low or high) in which the ratio could be distorted.

Radiographic Assessment

The radiographic assessment of CKD patients should take into account the impact of contrast on RRF. Imaging techniques in CKD are usually used for investigation of new AKI or for investigation of potential problems in nonrenal sites (e.g., cardiac catheterization, peripheral vascular concerns, abdominal investigations). Contrast material can induce worsening of underlying renal disease to the point of requiring renal replacement therapy (RRT). **All patients with abnormal SCr greater than 2 mg/dL should be considered for alternative diagnostic testing and prophylactic preventive strategies to avoid worsening renal function.** Specific measures may help lower the risk for AKI in patients with CKD undergoing radiographic assessment. These include volume expansion, hydration with IV administration of normal saline solution (sodium chloride 0.9%), one-half strength saline solution (sodium chloride 0.45%), sodium bicarbonate solution, infusion of mannitol, administration of atrial natriuretic peptide, loop diuretics, calcium antagonists, theophylline, dopamine, *N*-acetylcysteine, low-osmolar contrast, iso-osmolar contrast media, CO_2 angiography, hemodialysis shortly following contrast administration, and avoiding short intervals between contrast studies (Thomsen, 2003; Liss et al, 2005). See Prevention of Acute Tubular Necrosis earlier for recommendations. The use of gadolinium instead of iodinated contrast material should be considered for those subjects with more preserved kidney function, always keeping in mind the risk for nephrogenic systemic fibrosis (Bhave et al, 2008) (see later).

A number of reports have emphasized the value of normal saline solution hydration in patients with CKD and diabetes mellitus to generate a urine flow rate of 100 to 150 mL/hr, thus decreasing the risk for contrast-induced nephropathy (Solomon et al, 1994). Merely hydrating patients without ensuring effective urine flow is less valuable. Although no additional benefit to mannitol in the diabetic patient undergoing radio-contrast procedures has been shown, sodium bicarbonate solution infusion along with *N*-acetylcysteine may be of help. The antioxidant *N*-acetylcysteine (600 mg orally twice a day on the day before and on the day of administration of the contrast agent) along with hydration using a 0.45% saline solution intravenously may decrease the risk of AKI from radiographic contrast agents in this patient group (Tepel et al, 2000; Efrati et al, 2003).

Although not a cause of AKI or a trigger to progression of CKD, the use of gadolinium for imaging techniques like magnetic resonance imaging (MRI) has become a matter of significant concern in subjects with moderate to advance CKD. There are increasing reports confirming the strong association between the use of gadolinium-based agent contrast (GBCA) with a recently recognized condition termed *nephrogenic systemic fibrosis* or *NSF* (Bhave et al, 2008; Issa et al, 2008; Agarwal et al, 2009; Perazella, 2009). This is a systemic condition characterized by fibrosis of several tissues. Fibrosis of the skin has been universally described in subjects with advanced kidney disease or with end-stage renal disease who have received GBCA. Gadolinium is a nonionic, hyperosmolar contrast agent excreted unchanged by the kidney, so its half life (about 1 to 1.5 hours in subjects with normal kidney function) is prolonged with decreasing kidney function. Several types of gadolinium formulations are available, and NSF has been described with all of them, although the risk may vary depending on the formulation. In contrast to iodinated contrast agents, gadolinium does not seem to have a direct nephrotoxic effect, but its toxicity to other tissues when not renally excreted is of concern.

NSF is characterized by symmetric, bilateral fibrotic indurated plaques or subcutaneous nodules. The feet, ankles, shins, and hands are common initial sites of involvement followed by extension to more proximal areas of the extremities, trunk, and buttocks. Skin involvement occurs in all cases with systemic involvement being more variable. Connective tissues and muscles can be involved, which limits range of motion in these patients. Other visceral organs can also be involved. The diagnosis is clinical and histopathologic. The natural history of NSF is characterized as progressive, leading to a high mortality rate, though the disease may stabilize in a small percent of subjects.

Avoidance of gadolinium in patients with advanced kidney disease or on dialysis treatment is the main preventive strategy because no effective treatment exists once the disease has initiated. If use of GBCA is absolutely required, then hemodialysis treatment should immediately follow the administration of gadolinium in those patients already on dialysis. Peritoneal dialysis

seems not to be efficient in removing the agent, and thus a few hemodialysis sessions should be considered if gadolinium administration is unavoidable. Patients with moderate to advanced CKD (stages 3 and 4) that require imaging studies are at high risk for both iodinated contrast–induced nephropathy and for gadolinium-induced NSF. Selection of the imaging study should be based on the associated risks, and the patient should be clearly informed about them and the alternatives. When possible, two HD treatments (one immediately following gadolinium administration and the second one within 24 hours) following the administration of gadolinium should be strongly considered if vascular access already exists.

Urinalysis and Kidney Biopsy

The urine sediment examination is helpful in detection of CKD and the identification of the type of kidney disease. All patients with CKD should undergo a urinary sediment examination. Cells can originate from the kidney or from other sites within the urinary tract. The presence of a red blood cell (RBC) cast strongly suggests glomerulonephritis, especially if the RBCs are dysmorphic. Urinary eosinophils are usually associated with allergic tubular interstitial nephritis. If the urinalysis is negative, despite the patient's having apparent CKD, a second specimen should be examined at another time. The urine sediment should be examined because urinary dipsticks cannot detect tubular epithelial cells (that are casts in the urine), crystals, fungus, or parasites.

A renal biopsy is not usually performed to evaluate asymptomatic hematuria but is warranted if the GFR is less than 60 mL/min/1.73 m^2 and the urinalysis is abnormal. The approach to performing kidney biopsy, whether closed (CT-guided, ultrasound-guided) or open (standard or laparoscopic) depends on the overall clinical status, body habitus, patient's clotting parameters, and cumulative experience of the physician. The structural severity of glomerular injury and the immunopathologic category of disease are helpful in predicting renal outcome.

Renal Protective Strategies

Regardless of the nature of the initial insult, once a critical number of nephrons are destroyed, a steady decline in GFR occurs as the progressive loss in viable nephrons occurs. Strategies for delaying the relentless loss in nephron mass (Brenner, 2003) are inconsistently employed across a population with CKD. **Yet it is becoming increasingly clear that well-designed renal assessment and management programs are feasible and can be systematically applied to large numbers of CKD patients to decrease the rate of progression.**

A report of the International Society of Nephrology 2004 Consensus Workshop on Prevention of Progression of Renal Disease (Zandi-Nejad and Brenner, 2005) identified a number of therapeutic measures to prevent the progression of CKD including lifestyle modifications, BP control, glycemic control, reduction of proteinuria, protein restriction, lipid control, avoidance of nephrotoxic agents, early referral to a nephrologist, correction of anemia, optimization of calcium-phosphorus product, correction of acidosis, and maintenance of fluid balance.

Various pharmacologic trials comparing different medications have shown that patients with better BP control have significantly slower rates of deteriorating kidney function. Yet all agents have not been shown to slow progression on the basis of BP effect alone. Clinical trials have suggested that reducing mean arterial pressure to 82 mm Hg (125/75 mm Hg) provides more optimal renal function stability in patients with diabetes and proteinuria (>1.5 g/day), compared with more conventional mean arterial pressure targets of 107 mm Hg (140/90 mm Hg).

Conceptually, angiotensin II is critical in causing progressive renal disease by both hemodynamic and nonhemodynamic mechanisms. Blockade of the renin-angiotensin system contributes to preservation of renal function by decreasing glomerular pressure and proteinuria. Because proteinuria plays a sentinel role in renal scarring, a reduction in proteinuria correlates with slowing of disease progression (Acker et al, 2000). A recent meta-analysis of randomized clinical trials confirmed the predictive value of proteinuria and the renal protective effect of proteinuria reduction by ACE inhibitor therapy in large patient series (Chiurchiu et al, 2005). Clinical research findings support the view that preservation of renal function through angiotensin blockade can be achieved in patients with either diabetes mellitus or nondiabetic nephropathy (Kshirsagar et al, 2000). Reductions in proteinuria are greater with ACE inhibitors than with any other antihypertensive agent at the same level of BP control. Multiple ACE inhibitors have been evaluated in CKD. In the Microalbuminuria Cardiovascular and Renal Outcomes—Heart Outcome Prevention Evaluation (MICRO-HOPE) a subset of 35,077 patients with diabetes mellitus and microalbuminuria were treated with ramipril (Gerstein et al, 2000). Ramipril reduced the progression from microalbuminuria to overt nephropathy by 24% (P = .027). In the ACE Inhibitor in Progression of Renal Insufficiency (AIPRI) study, only part of the risk reduction in the ACE inhibitor group could be explained by the antihypertensive or antiproteinuric effect (Maschio et al, 1996). The AIPRI group performed a meta-analysis of 11 randomized clinical trials consisting of 17,060 patients with nondiabetic renal disease. This study concluded that antihypertensive regimens containing ACE inhibitors are more effective in slowing progression than regimens without ACE inhibitors. This same finding was observed in the Ramipril Efficacy in Nephropathy (REIN) Study (Allgren et al, 1997).

Jafar and colleagues (1999) proposed that ACE inhibitors act by mechanisms in addition to their BP lowering and antiproteinuric effect. ACE inhibitors also prevent the slow decline in PO_2 within the kidney. Considering the "hypoxia injury hypothesis," a potentially important renoprotective mechanism of ACE inhibition could stem from this improvement in interstitial capillary PO_2 levels, therefore decreasing renal sclerosis risk.

Angiotensin receptor blockers (ARBs) inhibit the type I angiotensin II receptor. Two large prospective, randomized trials have demonstrated that ARBs delay the progression of CKD in type 2 diabetic patients with overt nephropathy (Lewis et al, 2001; Parving et al, 2001). The Irbesartan Diabetic Nephropathy Trial (IDNT) examined the effect of ARBs (irbesartan) versus conventional therapy or the calcium channel blocker amlodipine in 1715 patients with type 2 diabetics. The doubling of SCr was 29% (P = .009) and 39% (P < .001) less than the risk in placebo and amlodipine-treated groups, respectively. Moreover, the Microalbuminuria Reduction with Valsartan (MARVEL) trial (Parving et al, 2001) supported the view that ARBs can potentially retard the progression of CKD in patients with type 2 diabetes.

Combining ACE inhibitors and ARBs has led to further reductions in CKD progression, along with BP, proteinuria, and microalbuminuria (Campbell et al, 2003; Segura et al, 2003). Some CKD patients on ACE inhibitors may experience an acute decrease in RRF with low renal perfusion states due to dehydration, congestive heart failure, and hypotension.

Individuals with bilateral RAS and ADPKD patients with cyst size larger than 10 cm may also experience a decrease in RRF while on ACE inhibitor therapy. A rise in SCr of more than 1 mg/dL after beginning ACE inhibitor therapy should prompt a clinical evaluation to explain the change in baseline function.

An intricate relationship exists between hemodynamic factors that regulate vascular tone and metabolic factors that govern circulating lipids. It is now apparent that the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors reduce production of molecules involved in fibrogenesis, reduce mesangial and smooth muscle cell proliferation, and decrease production of integrin adhesion molecules (Keane, 2000). Also, HMG-CoA reductase inhibition modulates small G-protein isoprenylation (involved in early gene product C-fos and C-jun transcription factors) and changes in cell cycle regulatory proteins (p21 ras). These are involved in intracellular cholesterol metabolism and cell damage at the membrane level. **In view of these findings, HMG-CoA reductase drugs should be part of the CKD treatment regimen.**

For more than 25 years it has been known that protein restriction can ameliorate many symptoms of renal insufficiency and prevent its progression. However, without regular dietary consultation, patients on a low-protein diet may experience a decrease in protein intake and deterioration of several nutritional parameters. A number of different diets have been used to help slow the progression of CKD. These dietary formulations include low-protein (0.6 g protein/kg ideal body weight) diets, very-low-protein diet (0.3 g protein/kg/day predominately vegetable protein) supplemented with essential amino acids, or very-low-protein diet supplemented with both essential amino acids and nitrogen-free analogues of amino acids (ketoacids). **The overall dietary requirement in CKD is approximately 0.6 g of protein/kg/day.** A recent in-depth analysis of the MDRD study results did note that each 0.2 g/kg/day reduction in protein intake was associated with a 29% slower rate of loss of GFR and a 51% prolongation in the time to dialysis for nondiabetic patients (Mitch, 2000). Two additional studies have demonstrated the beneficial effect of dietary protein restriction on retarding the progression of CKD in both diabetic and nondiabetic patients (Pedrini et al, 1996; Kasiske et al, 1998).

Table 43–14 summarizes a comprehensive strategy to achieve renal protection in patients with CKD (Jafar et al, 1999; Zandi-Nejad and Brenner, 2005). The comprehensive strategy illustrates specific interventions, treatment approaches, monitoring, and target benchmarks of treatment. Future therapies may mobilize progenitor cells for natural "renal repair" similar to those initiatives involving the heart and peripheral arterial disease (Kale et al, 2003; Zandi-Nejad and Brenner, 2005). The progenitor cells from the bone marrow may integrate after ischemic injury with potential for a functional improvement in the insulted organ remodeling. Progenitor cells may amplify biochemical signaling cascades (i.e., vascular and endothelial growth factor, IGF-1, stromal cell derived factor [SDF]) involved in rescue. Optimal organ targeting will require an ability to amplify the progenitor cell impact. Newer pharmacologic strategies of manipulating resident progenitor cells to treat ischemic renal disease, regenerate glomeruli or tubules, or address transplant vascular disease may offer hope for improved renal reserve in the future (Masuya et al, 2003; Regele and Bohmig, 2003). Preventing renal injury in at-risk settings may also be a direction of treatment for the future. Experimental data in an ischemia-reperfusion rat kidney model has shown that a single systemic dose of erythropoietin (EPO) preischemia or just before perfusion prevents injury (Sharples et al, 2004). These findings may have major implications in the prophylaxis against ischemic injury of tubules in humans.

Table 43–14.

Comprehensive Renoprotection Strategy

FOCUS AREA	GOAL	TREATMENT
Blood pressure control	<130/80 if proteinuria <1 g/day <125/75 if proteinuria >1 g/day	ACE inhibitor ARB Salt restriction Diuresis
Reduction in proteinuria	<0.5 g/day	ACE inhibitor ARB ? Aldosterone blockade
Glycemic control	HbA1C <7%	Oral hypoglycemic agents Diet Insulin
Dietary protein restriction	0.6 to 0. 8 g/kg/day*	Dietary consult
Lipid lowering	LDL ≤70 mg/dL†	Statin†‡ Triglyceride-lowering agent
Anemia management	Hemoglobin at 11-12 g/dL	Erythropoietin Iron
Lifestyle modifications	Ideal body weight* Smoking cessation Exercise 3 times per week Depression modification	Weight loss program (dietary counseling, surgery) Antidepressants
Calcium × phosphorous product	Ca × phosphorus product <55 Phosphorous <5.5 mg/dL Intact PTH 70-110 pg/mL (CKD stage 4) 30-70 pg/mL (CKD stage 3) 25(OH)vitamin D >30 ng/mL	Vitamin D supplementation Use dietary phosphorous restriction Phosphate binders

*Avoid malnutrition.
†Consider measuring nontraditional risk factors: homocysteine, LpA, C-reactive protein, fibrogen.
‡Treat hyperhomocysteinemia with folic acid.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; LDL, low-density lipoprotein; PTH, parathyroid hormone.

Preoperative Evaluation of CKD/ESRD

In CKD patients scheduled for an elective surgical procedure, a thorough preoperative assessment to define risk is warranted. Preoperative risk falls into three categories: patient-specific, procedure-specific, and anesthesia-specific risks (Bronson, 2000). CKD patients should be closely evaluated because they may have multiple comorbidities that would affect outcome. The risk of a specific procedure is proportional to the physiologic stress associated with the procedure. The American Society of Anesthesiologists physical status scale defines five classes, each with a specific 7-day mortality from 0.07% (no organic or psychiatric disease) to 33.58% (moribund with little chance of survival). However, this scale does not consider procedure-related risks. There is no set risk profile specific for CKD. In general, procedures associated with a higher level of risk include major joint replacement, craniotomy, cardiac procedures, large bowel procedure, and exploratory laparotomies. The anesthesia-specific risk takes into account the effects of anesthetic agents and physiologic responses to a host of possible operative events such

as hypotension, hypertension, blood loss, tachycardia, hypoxia, myocardial depression, and the acute worsening of renal function. In the CKD/ESRD population the major predictors of cardiac events are the presence of active ischemia, poor left ventricular function, and baseline ventricular arrhythmia.

Formal cardiac testing may be warranted preoperatively for patients with established ischemia, ventricular arrhythmias, and abnormal left ventricular ejection fraction. Although it is preferable to obtain an exercise imaging study rather than pharmacologic imaging study, a significant percent of CKD/ESRD patients will not achieve maximal predicted heart rate secondary to limited exercise capacity and medications. Pharmacologic testing with dobutamine stress echocardiography may be the best screening test for coronary disease in CKD (Marwick et al, 1998). A negative study had a low frequency of events over the short term (Chertow et al, 1997).

Hypertension also plays a role in determining operative risk. A BP of 180/110 mm Hg or more is associated with a greater risk for preoperative ischemic events. When possible, surgery should be delayed to bring BP down to an acceptable level in patients with hypertension and CKD.

CKD patients with chronic obstructive pulmonary disease (COPD), active asthma, or a current infection are at high risk for pulmonary complications. Upper abdominal and thoracic surgeries carry the greatest risk of compromising pulmonary function. If the forced expiratory volume vital capacity in 1 second (FEV_1) is greater than 2 L, the risk of a complication is low. An FEV_1 less than 1 L is associated with a significantly greater risk. Discontinuing smoking at least 3 months before surgery can significantly decrease the risk of pulmonary complications.

CKD patients with diabetes mellitus (DM) should achieve optimal control (<200 mg/dL) before surgery. The risk for infectious complications increases with blood sugars greater than 300 mg/dL. CKD patients with DM on oral hypoglycemic agents should be carefully monitored because hypoglycemia with sepsis and/or malnutrition can markedly increase morbidity and mortality.

Elective surgery should be avoided in CKD/ESRD patients in a malnourished state. Serum albumin less than 3.5 g/dL, prealbumin less than 30 mg/dL, protein-nitrogen appearance (PNA) or protein catabolic rate (PCR) less than 0.8 g/kg/day, and subjective global nutritional assessment score of less than 5 signify malnutrition. Nutritional (protein/calorie) supplements should be used preoperatively to improve the baseline nutritional status. In the setting of anorexia, all offending drugs should be eliminated and consideration given for using pharmacologic appetite stimulating agents (megestrol acetate).

Drug dosing in CKD/ESRD should be closely monitored to avoid both reversible and irreversible toxicities. Avoiding drugs that have the potential to accelerate loss of RRF is of paramount importance. The risk of adverse events may be linked to the patient's degree of residual renal dysfunction. Uremic toxins may modulate cytokine P450 enzyme activity, decrease glomerular filtration of drugs, and alter tubular secretion. High-risk therapies in the setting of CKD-ESRD include ACE inhibitors, radiographic contrast, volume depletion, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors, and aminoglycosides.

Conservative Management: Prevention of Uremic Complications

A comprehensive approach to achieving optimal renal care begins with the early detection of renal failure followed by the initiation of interventions that delay progression, prevent uremic complications, modify comorbidities, and when necessary prepare patients for RRT to optimize patient survival. The components of an optimal disease management program are depicted in Figure 43–9 (Pereira, 2000).

Decreased GFR is associated with complications in most organ systems. The most important complications include high BP, anemia, malnutrition, bone disease, neuropathy, and alterations in quality of life. As the patient moves from stage 2 to higher stages, he or she is more likely to develop additional comorbidities. The level of scrutiny and search for comorbidities increases as the stage of kidney disease advances. A number of factors increase cardiovascular risk. These include diabetes mellitus,

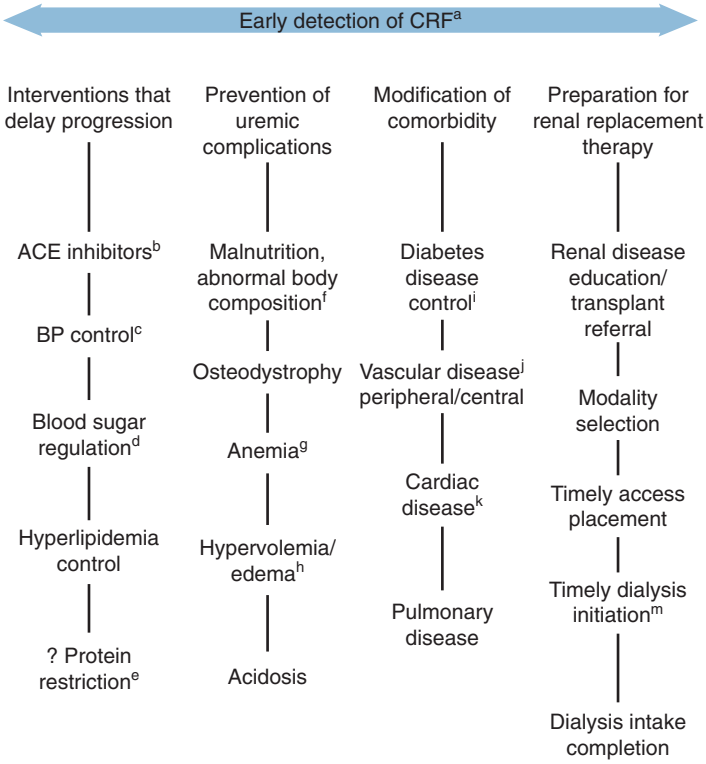


Figure 43–9. Optimization of kidney disease care. *a,* Screening high-risk patients; SCr >1.2 mg/dL. *b,* May require higher doses of angiotensin-converting enzyme (ACE) inhibitors (or ATI-receptor blockers) than required to lower blood pressure. *c,* Control blood pressure: target blood pressure (BP) level: mean arterial pressure ≤92 mm Hg. *d,* Blood sugar target HbA_{1C} <7%, AC glucose 80 to 120 mg/dL, HS glucose 100 to 140 mg/dL. *e,* Protein restriction, 0.67 g/kg/day with dietary consultation and objective measurements to avoid malnutrition. *f,* Parameters should include serum albumin plus subjective global assessment (SGA), anthropometrics, or measurements of lean body mass (fat-free mass). *g,* Pre–end-stage renal disease (ESRD) target Hct ≥30%, ESRD target Hct 30% to 36%. *h,* Effective volume equilibration is essential to avoid congestive heart failure, cellulitis/limb loss; increased admissions may require early initiation of dialysis. *i,* Avoid neuropathy, foot abnormalities, blindness. *j,* Peripheral vascular disease increases the risk for coronary artery disease; evaluate peripheral vascular flow. *k,* Cardiac echo to assess left ventricular hypertrophy; dobutamine stress echo for addressing ischemia; screening in high-risk individuals. *l,* Refer for education when CrCl <25 mL/min; referral to nephrology for screening evaluation including transplantation referral. *m,* Initiate dialysis K_rT/V <2.0 with signs of malnutrition. (Modified with permission from Pereira BJ. Optimization of pre-ESRD care: the key to improved dialysis outcomes. Kidney Int 2000;57:351–65.)

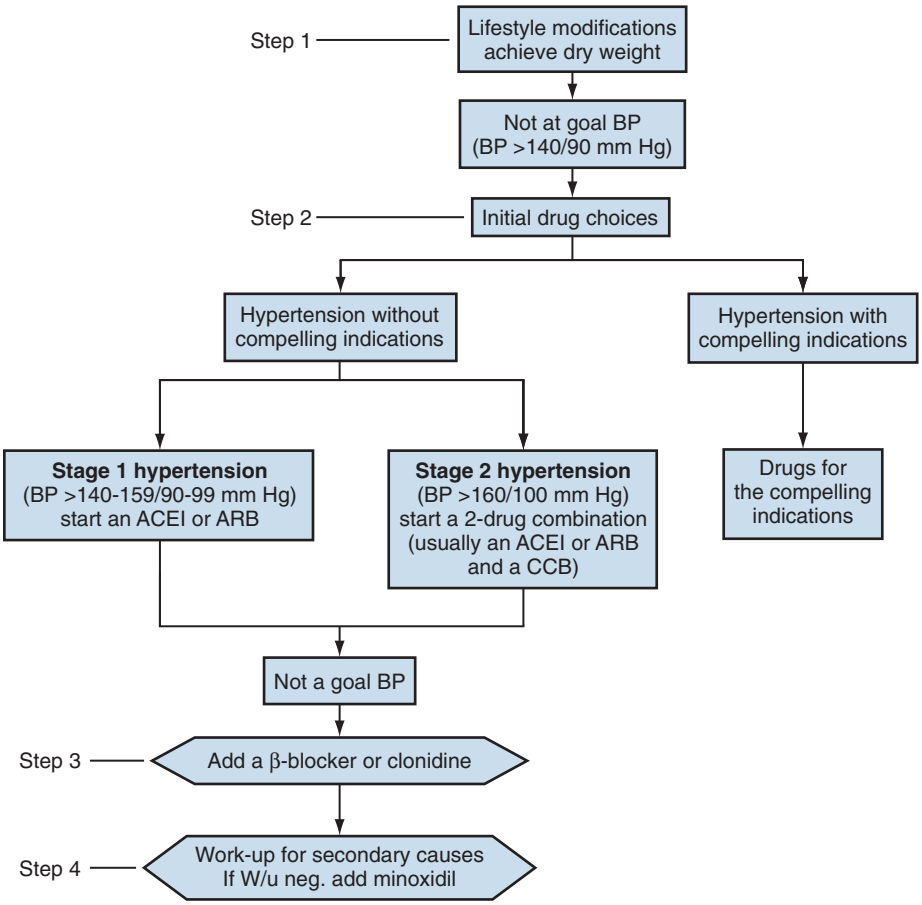


Figure 43–10. Algorithm for blood pressure management in chronic kidney disease. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; W/u, workup. (From National Kidney Foundation. Clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 2002;39[Suppl. 2]:1–266.)

hypertension, dyslipidemia, smoking, physical activity, psychologic factors, anemia, arterial stiffness, vascular/valvular calcifications, and calcium and metabolic bone disease status.

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) has defined hypertension in adults and the general population as systolic BP 140 to 159 mm Hg and diastolic BP 90 to 99 mm Hg. Normal BP is defined as less than 120/80 mm Hg. "Prehypertension" is defined as 120 to 139 mm Hg systolic and 80 to 89 mm Hg diastolic BP (Chobanian et al, 2003). In patients with CKD, particularly those with proteinuria greater than 1 g in 24 hours, the target BP goal (125/75 mm Hg) provides maximal protection against progression of renal disease (Klahr et al, 1994). Aggressive BP control should also be a goal for patients on dialysis (K/DOQI stage 5) as outlined in Figure 43–10.

Data have shown that mild renal failure (SCr ≥ to 1.4 but < 2.4 mg/dL) in high-risk patients had a 40% increase in the risk of cardiovascular death, myocardial infarction, or stroke compared with those patients with lower SCr levels (Gilbert et al, 2001). Because a large percentage of patients with CKD die of cardiovascular events before reaching dialysis (>60%), attention to risk factors is critical to extend survival. For optimal control of BP a combination regimen that includes a diuretic, ACE inhibitor, or ARB is essential not only to achieving BP control but to retarding the rate of progression of CKD. If the SCr is elevated (GFR <30 mL/min), a loop diuretic should be substituted for a standard thiazide.

Traditional atherosclerotic risk factors are frequently present in CKD. Low high-density lipoprotein (HLDL), elevated homocysteine, elevated LDL, and elevated LPA all define patients at high risk for cardiovascular events warranting lipid-lowering therapy and close cardiovascular screening. The Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) 2001 suggested that on the basis of results from the Heart Protection study and the PROVE-IT study, additional benefit may be achieved by reducing LDL cholesterol levels to substantially below 100 mg/L, especially in high-risk patients (Panel, 2001). Not only should medications be used by patients before stage 5 of CKD, but they should be maintained once the patient is transplanted. A meta-analysis comparing the efficacy of various antilipidemic therapies for peritoneal dialysis (PD), hemodialysis (HD), and transplant recipients demonstrated the effectiveness of HMG-CoA reductase inhibitors (Massy and Kasiske, 1996). Both statin and fibric acid derivatives have proven effective, although individual differences mandate periodic monitoring of fasting lipid levels and liver function tests. Updated information suggests statin treatment in established dialysis patients should be different. Two large multicenter randomized controlled trials in which two different statins were compared with placebo in hemodialysis patients showed no difference in preventing all-cause and cardiovascular mortality despite their efficacy in lowering LDL cholesterol (Wanner et al, 2005; Fellstrom et al, 2009). On the basis of these studies, the use of statins to prevent mortality in dialysis patients is not warranted.

Cigarette smoking is universally recognized as an independent risk factor for cardiovascular disease (CVD) and should be discouraged with this disease. There is a significant association between current smoking and cardiovascular outcomes, which further emphasizes the importance of smoking cessation.

Both vascular calcification and valvular calcifications have been found to be more common in CKD patients and impact on survival (Little and Pusey, 2004; Blacher et al, 1999). Although there are no randomized trials that have evaluated whether treatment of calcium phosphorous abnormalities or the use of calcium-based phosphate binders reduces the risk of CVD outcomes, the recommendation from K/DOQI clinical practice guidelines for bone metabolism and disease in CKD is that noncalcium-based binders be used if there is evidence of severe vascular calcification (Brown et al, 2003). The stage of CKD in which bone disease begins to develop has not been well documented, nor has a consensus been reached regarding the optimal screening methods for identifying early abnormalities of calcium/phosphorous metabolism and bone disease in CKD patients. Below a GFR of approximately 60 mL/min/1.73 m^2, there is a higher prevalence of abnormalities of bone metabolism.

Overweight and obesity are associated with increasing risks for a variety of cardiovascular complications and with higher all-cause mortality. Weight reduction is an important lifestyle modification for overweight patients. Although protein energy malnutrition (PEM) and wasting are common among CKD patients, no single nutritional marker is helpful in defining malnutrition. Changes in lean body mass over time in CKD may signal not only worsening uremia but also an increased risk for CVD. Specific methods for evaluating raising nutritional status include multifrequency bioimpedance (BIA), dual x-ray absorptiometry (DEXA), subjective global assessment (SGA), and hand-grip strength (HGS).

All patients with CKD should follow the American Diabetes Association's guidelines for blood glucose control. Recommendations have been based on evidence from the Diabetes Control and Complications Trial (DCCT) (Foundation, 1993; Craig et al, 2000). The target for diabetes control should be a hemoglobin A1C level of less than 7%, a preprandial glucose level of 80 to 100 mg/dL, and a bedtime glucose level of 100 to 140 mg/dL.

Observational studies have shown an association between anemia and adverse cardiovascular outcomes in CKD patients. It is unclear whether treatment of anemia prevents cardiovascular events in CKD patients. Recombinant human erythropoietin (rHu-EPO) is most likely to benefit the CKD patient who is symptomatic with a hematocrit value less than 30%. The treatment goal should be to achieve hemoglobin of greater than or equal to 12 g/dL. Hypertension can be more difficult to control as the hemoglobin is increased with EPO therapy. Hypertension worsens in approximately 23.5% of rHu-EPO-treated patients (Eschbach et al, 1987).

Cardiovascular disease begins early in the course of CKD. Among patients with creatinine clearance of less than 25 to 30 mL/min, left ventricular hypertrophy is present in 38% to 45% of patients compared with a prevalence rate of 16% to 31% among patients with higher levels of RRF.

Noninvasive testing of patients with kidney failure for cardiovascular disease is helpful, especially in high-risk patients. The diagnostic accuracy of perfusion imaging is lower than in patients not in renal failure. Dobutamine echocardiography has been reported to have a sensitivity of 96% and specificity of 86% and is the preferred screening instrument for coronary artery disease in CKD/ESRD patients.

Aggressively addressing comorbidities in CKD that may shorten survival is critical to extending life years for these patients.

Initiation of Renal Replacement Therapy

The K/DOQI guidelines recommend that dialysis be initiated when weekly renal K_rT/V_{Urea} (K_rT = kidney excretion over a 24-hour time period; V_{Urea} = urea distribution volume) decreases to less than 2, unless all three of the following criteria are met: (1) stable or increased edema-free body weight, (2) a random protein equivalent of total nitrogen appearance greater than 0.8 kg/day, and (3) an absence of clinical symptoms and signs attributable to uremia. The patient should begin some form of RRT if the K_rT/V_{Urea} value is less than 2 and greater than 6% involuntary reduction in edema-free weight exists, or if the patient is at less than 9% of standard body weight for National Health and Nutrition Examination III, or there is a reduction of serum albumin level by more than 0.3 g/dL. Despite these recommendations, a significant percentage of patients have RRF less than 10 mL/min/1.73 m^2 at the start of dialysis. Obrador and colleagues (1999) examined data on 90,897 patients who began dialysis in the United States from April 1995 to September 1997. The mean ± standard deviation SCr level at initiation was 8.5 ± 3.8 mg/dL. The mean predicted GFR was 7.1 ± 3.1 mL/min/1.73 m^2. Historically, mortality among late referrals is consistently higher than among those with more timely initiated RRT patterns. Holland and Lam (2000) identified independent predictors of delayed referral among a retrospective cohort of 362 predialysis patients, including age 65 years or older, female gender, and congestive heart failure.

The rationale for timely initiation of RRT is based on several different, independent lines of evidence. As renal function declines, spontaneous dietary protein restriction occurs. Declining renal function is associated with abnormal protein metabolism, malnutrition, and poor clinical outcomes. A lower serum albumin level correlates with an increased mortality risk for both HD and PD patients (Bruns et al, 1998).

End-Stage Renal Disease Demographics and Treatment Options

There is a steady growth of ESRD patients (stage 5) on renal replacement therapy (RRT) throughout the world (Collins et al, 2009). The incident rate in the United States is 360 new cases per million of population. The ESRD program in the United States comprises 506,256 patients: 354,754 on dialysis and 151,502 with a functioning transplant. In the United States the number of transplants continues to grow with 16,517 performed in 2008 (10,550 from deceased donors and 5967 from living donors). Transplants from living donors in the United States now constitute 36% of all transplants performed.

Critically important to all ESRD patients is a thorough understanding by the physician of dialysis practices that yield improved outcomes. The Dialysis Outcomes and Practice Patterns (DOPPS) study is a prospective, longitudinal study of hemodialysis practices from seven countries with large populations of dialysis patients (France, Germany, Italy, Japan, Spain, United Kingdom, and United States) (Gerstein et al, 2000). Linking the DOPPS scope of

work with the K/DOQI goals will help to develop continuous quality improvement programs and provide direct feedback to participating dialysis centers worldwide (Augustine et al, 2004). The DOPPS has collected information that will affect issues that relate to anemia management, modifiable hemodialysis practices to optimize outcome, vascular access, mortality and hospitalization, nutritional indicators, depression assessment, prescription utilization, acidosis, and vitamin prescriptions.

The mortality rate of RRT patients is strongly influenced by the percentage of enrolled diabetic patients, the dialysis dose, the type of hemodialytic membrane, erythropoietin therapy, and the nutritional status. Adjusted mortality rates of prevalent dialysis patients in the United States are now falling (www.USRDS.org).

Poor long-term survival of ESRD patients is illustrated by comparing the expected remaining lifetime on dialysis or transplant with the general U.S. population (2006, 2009). The expected remaining lifetime for Caucasian dialysis patients was only one-fourth to one-sixth those of the general population, with differences being highest among women age 40 to 65 years. By modality, the expected lifetimes for transplant patients are double those of dialysis patients among black males and more than three times as high for white males age 20 and older. Expected remaining lifetimes in transplant patients are still, however, only 52% to 69% of those of the general population. Compared with males, females have poorer outcomes in terms of more frequent hospitalizations, frequency of anemia, vascular access problems, malnutrition, poorer quality of life, and access to transplantation (Sehgal, 2000).

Multiple different RRTs are available for treatment of ESRD patients. The most commonly used RRTs are hemodialysis (HD), peritoneal dialysis (PD), and renal transplantation. Other treatment options include hemodiafiltration (combination of intermittent hemofiltration with simultaneous HD) and nocturnal home HD (slow-flow HD for an extended period overnight). **Outcome comparison suggests that renal transplantation is still the best overall treatment for ESRD patients, despite advances in dialytic options.** The time on dialysis may have an impact on the success of replacement therapy. Patients on HD for more than 10 years have a poorer outcome when transplanted compared with individuals receiving transplants with less time on dialysis. This finding is probably related to fixed vascular defects that occur in patients on chronic dialysis therapy. Reports confirm that longer waiting time on dialysis negatively affects post-transplant graft and patient survival (Meier-Kriesche et al, 2000). This effect was independent of age, race, donor characteristics, and original disease. Therefore patients who reach ESRD should undergo preemptive transplantation or transplantation as soon as possible, once on dialysis.

In comparing outcomes between different RRTs for nondiabetic patients, it is essential to consider the type of statistical model used to evaluate mortality (Cox proportional hazards regression vs. Poisson regression), the type of analysis employed (intent to treat vs. as treated), and the type of study patient (prevalent vs. incident) (Vonesh et al, 2000). Vonesh and colleagues (2004) reported that specific results are closely linked to stratification by age and modality. Appropriate patient selection is critical to optimizing the life years per patient with ESRD. PD has an early survival advantage compared with HD, whereas patients older than 45 with diabetes may have a survival advantage (in months) if started on HD.

Not all patients will benefit from RRT. Recommendations for withholding or withdrawing dialysis from suboptimal adult ESRD patients were recently published. These were based on feedback from the U.S. Renal Physicians Association (RPA) and American Society of Nephrology (ASN) in conjunction with broad representation from ESRD patients, family, and non-nephrologists (Galla, 2000).

Currently in the United States 93% of dialysis patients are treated with HD and 7% with PD. **The renal disease continuum** (Fig. 43–11) **demonstrates the critical junctures in renal disease care extending from the early diagnosis to management of the patient on dialysis. Processes of care for each stage should be developed from evidence-based recommendations and linked to auditing tools that can provide organizations and health care teams ongoing feedback for optimizing results. The concept of RRT assignment in an integrated fashion is a key to prolonging ESRD survival. An integrated approach combining HD, PD, and renal transplant over the life of an ESRD patient may provide the best approach to optimizing survival. An integrated care approach whereby patients are started on PD and transferred in a timely fashion to HD, when PD- or patient-related problems occur, demonstrates an increase in survival compared with those remaining on HD for their entire life span** (Van Biesen et al, 2000). Table 43–15 indicates transition points that may stimulate transfer from one modality to another. RRF is preserved longer on PD than on HD. BP is better controlled, and ventricular arrhythmias are observed less often on PD than on HD. Weight gain and inadequate dialysis after 3 years are more common on PD than with HD. Although vascular access problems and hemodynamic instability are the most common reasons for transfer to PD from HD, other reasons include infection (peritonitis, catheter, tunnel infections); inadequate dialysis; and catheter malfunction. K/DOQI has established specific guideline recommendations for both HD and PD. Quality guidelines are established for HD adequacy, PD adequacy, vascular access, anemia management, bone metabolism, and nutrition.

In 1997 the NKF's DOQI clinical guidelines on HD and PD were published. These are periodically updated and can be reviewed at www.kidney.org/professionals. For HD, DOQI recommended a single pool Kt/V of 1.3, urea reduction ratio (URR) more than 70%, allowing for errors or compliance problems in delivering the recommended dose of at least 1.2. Barriers to adequate HD include underprescription, inadequate vascular access, dialysis membrane, clotting, shortened treatment times, and "no show." The projected 2005 DOQI guidelines for PD will require a weekly KT/V of 1.7 or greater. Typically patients with high- to high-average transport characteristics are ideal candidates for automated peritoneal dialysis (APD), which uses an automated cycling device to perform dialysis exchanges at night. Low- to low-average transport characteristic patients seem to do best on the standard manual exchanges performed during the day. Several options are available to help PD patients meet adequacy targets combining standard manual exchanges with automated cycling devices.

Hospitalization Risk in CKD/ESRD

CKD patients are 10 times more likely to be hospitalized, and on average, hospitalization lasts 1 day longer compared with non–renal failure patients (Thamer et al, 1996). Hospital admissions for ESRD patients in the United States have remained relatively stable since 1993, and the number of hospital days has fallen 12% for HD patients, 16% for transplant, and 19% for PD patients. ESRD patients secondary to diabetes are admitted most frequently—2.3 times per year in 2002. Inpatient hospital care accounts for 41% of the total ESRD costs (Bruns et al, 1998).

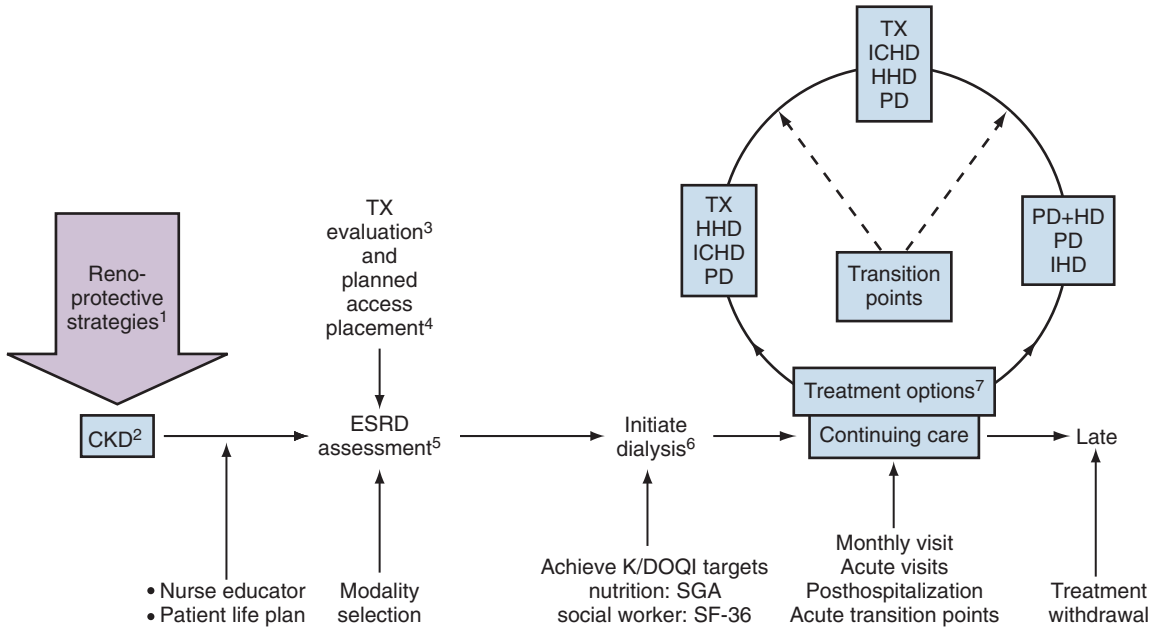


Figure 43–11. Kidney disease continuum. *1,* Population screening (serum creatinine >1.2 mg/dL), delay progression (stages 1 and 2). *2,* Preserve residual renal function, educate, and assess comorbidities (stages 3 and 4). *3,* Preemptive transplant. *4,* Peritoneal dialysis (PD)/hemodialysis modalities. *5,* Evaluate complication/risk; residual renal function 15 to 29 mL/min/1.73 m^2: prepare for renal replacement therapy. *6,* Initiate dialysis. KT/V (residual renal function) <2, avoid uremic complications, define physician problem-based care (stage 5: <15 mL/min/1.73 m^2). *7,* Integrate different therapies over time dependent on critical junctures to extend survival years and control comorbidities: malnutrition, uncontrolled blood pressure, inadequate solute/water removal, access failure, residual renal function preservation. CKD, chronic kidney disease; ESRD, end-stage renal disease; HHD, home hemodialysis; ICHD, in-center hemodialysis; IHD, intermittent hemodialysis; SGA, subjective global assessment; TX, treatment.

Table 43–15.

Transition Points for Modality Transfers

Peritoneal Dialysis Transfer to Hemodialysis
Recurrent infection
Catheter malfunction
Ultrafiltration failure
Adequacy (solute) failure
Psychologic burnout
"Peripheral vascular disease/stroke/myocardial infarction" activities of daily living failure
Hospitalization/surgery
Uncontrolled diabetes
Hypotension
Hemodialysis Transfer to Peritoneal Dialysis
Recurrent congestive heart failure
Access failure (steal, recurrent [3], lower extremity, option)
Hypercoagulability
Malnutrition
Intradialysis hypotension
Nursing home care

The total hospital discharges by general diagnostic related (DRG) charges from 1996-1998 for ESRD patients in the United States showed that the four most common causes for admission were circulatory (36.4%), renal system (15.6%), respiratory system (7.4%), and infection (5.7%) (Foley, 2007; Collins, 2009). Patients undergoing RRT are often hospitalized with general medical problems, most often stemming from comorbid conditions. The length of stay for HD patients differed by the medical service to which they were admitted. **Overall costs for hospitalization tended to be less on the nephrology service than on internal medicine service (6.3 days vs. 8.1 days)** (Kshirsagar et al, 2000). Total cost per admission was $2848 more for an HD admit to internal medicine service versus nephrology service, and yet the risk of readmission was not significantly higher.

Rocco and colleagues (1996) identified specific risk factors for hospital utilization in chronic dialysis patients from a cohort of 1572 patients in Network VI (North Carolina, South Carolina, and Georgia). **By using multiple regression analysis, the strongest predictors of the number of hospitalizations per year of patient risk included low serum albumin, decreased activity level, diabetes mellitus as a primary cause of ESRD, peripheral vascular disease, white race, increasing age, and congestive heart failure.** Both nutritional status (serum albumin, creatinine, transferrin, prealbumin, and lean body mass [bioelectrical impedance]) and inflammatory response (i.e., C-reactive protein [CRP]), are independent predictors of hospitalization in chronic HD patients (Ikizler et al, 1999).

Sarnak and colleagues (2000) demonstrated **that mortality rates secondary to sepsis are one to several hundredfold higher in dialysis patterns (HD and PD) compared with the general population.** Renal transplant recipients have sepsis-associated mortality rates approximately 20-fold higher than the general population but 15-fold lower than dialysis patients. Infection is the second-leading cause of death in patients with ESRD. Sepsis accounts for more than 75% of the infection deaths. Acquired immune deficiencies with uremia, advanced age, and a broad array of comorbid conditions contribute to the observed infection risk and admission rate for kidney disease patients.

Acute worsening of renal function may occur in hospitalized CKD patients. The proposed criteria for initiation of RRT in this setting are listed in Table 43–16 (Bellomo and Ronco, 1998). For ESRD patients undergoing high-risk surgery, sequential daily

dialysis for 3 days preoperatively should be entertained to optimize fluid and ensure stable serum potassium and solute levels.

In patients requiring RRT, aggressive volume and solute control are essential to achieving optimal postoperative recovery. Outpatient dialysis schedules may not meet the needs of in-hospital patients. Some individuals may require more intensive therapy either daily or continuously if hemodynamically unstable. A number of different therapies can be used to treat critically ill patients requiring RRT (Table 43–17). Ideally the BUN-to-albumin ratio should decrease less than 17 through aggressive dialysis. Patients with serum albumin less than 3 g/dL with correspondingly low prealbumin values less than 25 g/dL should undergo enteral feedings or aggressive oral supplementation. TPN may be used if the gastrointestinal tract is nonfunctional. Aggressive UF either alone or in conjunction with regular HD should be implemented to control edema and decrease the risk for intubation or reintubation, congestive heart failure, and infectious-related complications.

Table 43–16.

Proposed Criteria for Initiation of Renal Replacement Therapy

Oliguria (urine output <200 mL/12 hr)
Anuria or extreme oliguria (urine output <50 mL/12 hr)
Hyperkalemia ([K^+] >6.5 mmol/L)
Severe acidemia (pH <7.1)
Azotemia ([urea] >30 mmol/L)
Clinical significant organ (especially lung) edema
Uremic encephalopathy
Uremic pericarditis
Uremic neuropathy/myopathy
Severe dysnatremia ([Na] >160 or <115 mmol/L)
Drug overdose with dialyzable toxin

From Bellomo R, Ronco C. Indications and criteria for initiating renal replacement therapy in the intensive care unit. Kidney Int Suppl 1998;66:S106–9.

Pulmonary diffusion capacity and pulmonary capillary blood volume are compromised in diabetic CKD patients preoperatively. Low FIO_2 and high central venous pressures are indicators of pulmonary compromise. The alveolar oxygen (A-a PO_2) gradient and respiratory index are more abnormal postoperatively in diabetics versus nondiabetics at similar volume levels. Therefore smaller elevations in pulmonary capillary wedge pressure (PCWP) carry

Key Points: Chronic Renal Failure

- The National Kidney Foundation developed and published clinical practice guidelines for CKD in 2002 to more consistently diagnose and treat CKD and its comorbidities.
- At a set point (usually ≥50% reduction in GFR), a relentless progressive loss of renal function ensues even when the initial insult becomes inactive—the hyperfiltration hypothesis.
- Progression of renal insufficiency involves hemodynamic and nonhemodynamic mechanisms.
- ACE inhibitors are the most effective agents in slowing the progression of renal disease by both hemodynamic and no-hemodynamic mechanisms.
- The most common etiologies of CKD are diabetes and hypertension.
- Comorbidities associated with CKD need treatment to optimize survival and diminish morbidity. This includes managing hypertension, blood lipids, smoking cessation, target weight, anemia, and glycemic control.
- A newly recognized serious adverse advent, nephrogenic systemic fibrosis, has been linked to gadolinium-based contrast agents.
- Major surgical interventions mandate thorough medical evaluation, particularly cardiovascular health. The best cardiac noninvasive screening assessment is a dobutamine echocardiogram.

Table 43–17.

Defining Therapies for Acute Renal Failure in Patients with Chronic Kidney Disease

THERAPY	DEFINITION	INDICATION	MODALITY OPTION
HD	Convective-based process across semipermeable membrane	Solute/H_2O removal Hyperkalemia	IHD, DHD, CAVHD, CVVHD
Hemofiltration	Convective-based solute removal with plasma water filtered across highly permeable membrane	Volume control, acid-base disorders, azotemia, congestive heart failure, multiorgan failure	IH, CVVH, CAVH
Hemodiafiltration	Convective and diffusive process across semipermeable membrane, increased small and large molecule removal	Acidosis, possible multiorgan failure, ARDS, dialysis instability	IHDF, CAVHDF, CVVHDF
UF	Plasma water removal, 2-5 L/24 hr	Fluid removal, congestive heart failure, total body anasarca, intubation or reintubation risk	SCUF, CVVUF, IUF
Sustained low-efficiency dialysis	Slow, convective-based process across semipermeable membrane	IHD treatment failure due to hypotension or inadequate clearance	SLED
Peritoneal dialysis	Diffusive and convective transport across peritoneal membrane	Azotemia, volume control, hypotension, without access to continuous hemodialysis treatments	CAPD, CCPD (APD)

APD, automated peritoneal dialysis; ARDS, acute respiratory distress syndrome; ARF, acute renal failure; CAPD, continuous ambulatory peritoneal dialysis; CAVH, continuous arteriovenous hemofiltration; CAVHDF, continuous arteriovenous diafiltration; CCPD, continuous cyclic peritoneal dialysis; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; CVVUF, continuous venovenous ultrafiltration; DHD, daily hemodialysis; HD, hemodialysis; IHD, intermittent HD; IHDF, intermittent hemodiafiltration; IUF, intermittent ultrafiltration; SCUF, slow continuous ultrafiltration; SLED, sustained low-efficiency dialysis; UF, ultrafiltration.

more significant pulmonary morbidity in diabetics versus nondiabetics, warranting close attention to volume status. CKD patients have a poorly responsive ventilator control system that impedes timely ventilator weaning (Seki et al, 1993). Therefore reintubation has a significantly higher morbidity and mortality in CKD and should be avoided. Other preventive strategies involve vaccinations (Pneumovax influenza, hepatitis); hypertension control; identification of high-risk patients for congestive heart failure; early treatment of upper respiratory infection/bronchitis; and optimization of functional status (vision assessment, exercise, cognitive stability). Identifying patients with risk characteristics that lead to hospitalization and designing a management plan to modify risk are essential and deserving of further study.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter

44

Renal Transplantation

John Maynard Barry, MD ● Michael Joseph Conlin, MD, FACS

End-Stage Renal Disease
History of Human Renal Transplantation
Selection and Preparation of Kidney Transplant Recipients
Donor Selection, Preparation, and Surgery
Kidney Preservation
Recipient Selection for Deceased Kidney Transplants
Preoperative Assessment
Preparation of Kidney Graft
Recipient Operation
Postoperative Care
Renal Allograft Rejection
Problems
Conclusions

Kidney transplantation is the pioneer discipline in solid organ transplantation, and the relationship between transplant surgeon and nephrologist has served as a model for multidisciplinary team care. The Scientific Registry of Transplant Recipients (SRTR) provides a concept of national and center-specific outcomes data that can be applied to other disciplines in urology.

Each renal transplantation operation is a study of pelvic anatomy, each deceased donor nephrectomy is a study of intraperitoneal and retroperitoneal anatomy, and each living donor nephrectomy is a surgical procedure on a kidney, procedures that are decreasing in frequency because of the development of nonoperative methods of treating renal stones and obstruction. Nowhere in urology must the principles of urinary tract reconstruction and infection control be more rigorously applied than in the immunosuppressed kidney transplant recipient. Understanding the molecular mechanisms of antigen-lymphocyte interactions in transplantation should provide insights into other disease processes such as cancer and infection. Renal preservation principles are often applied to parenchyma-sparing renal operations and to complex renovascular reconstruction procedures. As more renal transplantations are performed, more of these patients are apt to present to the practicing urologist for evaluation and preparation of the urinary tract for transplantation, as well as the care of urologic problems after transplantation, which may or may not be related to the transplantation surgery or to the consequences of immunosuppression.

END-STAGE RENAL DISEASE

Incidence and Prevalence

The estimated number of patients starting renal replacement therapy each year for end-stage renal disease (ESRD) in the United States is about 360 per million population (U.S. Renal Data System [USRDS], 2010). The median age of these new ESRD patients is 64 years. Both the prevalence and the incidence of ESRD are more common in elderly than in young patients, in men than in women, and in African-Americans, Hispanics, and Native Americans than in Asians and whites. Diabetes mellitus is the most frequent cause of ESRD, followed in order by hypertension, glomerulonephritis, and renal cystic disease. Diabetes is especially common among Native Americans, and hypertension is disproportionately high among African-Americans. The incidence of ESRD is greater than that for any urologic malignancy except prostate cancer, and more patients die annually from ESRD than from any urologic malignancy (Heron et al, 2009; Jemal et al, 2009; USRDS, 2010).

Treatment Options

The purposes of renal replacement therapy are to prolong and maintain the quality of life. **The treatment or treatments that are chosen for an individual patient are those that will allow the longest extension of useful life.** Renal replacement therapy is now considered to be a right in the United States and most other developed countries. Permanent renal failure in adults is commonly defined as an irreversible glomerular filtration rate (GFR) of less than 10 mL/min or a serum creatinine level of greater than 8 mg/dL (Annual Report, 1994). About half of the patients who initiate renal replacement therapy have an estimated GFR less than or equal to 10 mL/min (USRDS, 2010). Patients with symptomatic uremia, especially children and diabetic adults, are considered on an individual basis as meeting criteria for permanent renal failure The generally accepted indications for dialysis initiation are pulmonary edema resistant to diuresis, severe uremic symptoms, hyperkalemia that fails to respond to medical therapy, metabolic acidosis unresponsive

to medical therapy, or uremic pericardial effusion. A reasonable goal for ESRD treatment programs is the transplantation of all patients in whom the risk is equal to or less than that of remaining on maintenance dialysis. Renal transplantation is the preferred method of therapy for most patients with ESRD because it is more cost effective and allows a return to a more normal lifestyle than maintenance dialysis does. A recent quality of life year (QALY) cost analysis strongly favored transplantation over dialysis (Mendeloff et al, 2004).

The number of patients listed for kidney transplantation continues to expand disproportionately to the number of kidney transplantations performed annually. There are currently more than 80,000 patients waiting for deceased donor kidney transplants, and with about 10,000 deceased donor kidney transplants performed annually, there are eight times as many ESRD patients waiting as there will be deceased donor kidneys available in the coming year. Despite this obvious disparity, the number of deceased donor kidney transplants has increased only 15% over the past 10 years, and this is mostly due to the increased use of kidneys from expanded-criteria donors (ECDs) and donation-after-cardiac-death donors (DCDs) (Scientific Registry of Transplant Recipients, 2009). The inadequate supply of deceased donor kidneys is one of the factors that has influenced the increase in the number of living donor kidney transplants in the past decade. The increase in living renal donation has been further facilitated by the widespread adoption of minimally invasive donor nephrectomy techniques; the increased use of living, biologically unrelated renal donors; and the development of protocols for transplantation across alloantibody barriers including ABO blood group incompatibility. Xenotransplantation and tissue engineering are fields of research for the continuing problem of inadequate supply of transplantable organs.

Hemodialysis is the predominant form of therapy for adults with ESRD. In the United States, it accounts for about two thirds of the treated ESRD patients (USRDS, 2010). Transplantation, however, is the predominant mode of care for patients younger than 20 years. About 10% of ESRD patients are treated with chronic peritoneal dialysis. A desire for self-care, a long distance from a hemodialysis unit, difficulties with hemodialysis therapy, serious cardiac disease, diabetes mellitus, and small stature are characteristics of patients especially suited for peritoneal dialysis. Unsuitable characteristics of patients for chronic peritoneal dialysis are considered to be obesity, hernias, poor hygiene, inflammatory bowel disease, and obliterated peritoneal space (Nicholson, 2001).

The advantages of living related donor renal transplantation compared with deceased donor renal transplantation are better probabilities of graft survivals, less recipient morbidity, specific planning of the operation to allow preemptive transplantation or limitation of the waiting time on dialysis, and partial alleviation of the insufficient supply of deceased donor kidneys. **The timing of preemptive renal transplantation must be such that the patient does not have months to years of usable function in the failing native kidneys.** Objections to transplantation before dialysis are that the procedure removes the experience of dialysis so that the advantages of transplantation are not appreciated and the concern that a preemptive deceased donor kidney transplantation means a patient has been unfairly advantaged over patients already on dialysis, some of whom have been waiting a long time for a kidney graft.

When compared with adults with ESRD, children are more likely to receive chronic peritoneal dialysis, and they are more likely to undergo renal transplantation (USRDS, 2010). There is a relatively greater availability of parental kidney donors, and children receive preferential points when they are listed for deceased kidney transplantation. **Special problems in children with ESRD include growth failure, poor nutrition, and psychiatric problems.** They often suffer from a cycle of depression, anxiety, and loss of self-esteem, and these problems can result in family stress and divorce (National Institutes of Health [NIH] Consensus Development Conference, 1993). The development of recombinant growth hormone has made possible the treatment of short stature in pediatric patients with chronic renal failure and after renal transplantation. Nutritional supplementation can be done by nasogastric feeding tube or button gastrostomy.

Results of Treatment

Data from the USRDS indicate that survival after renal transplantation is significantly better than that of patients treated with dialysis (USRDS, 2010). Although this may simply mean that healthier patients are more likely to be transplanted, more controlled analyses have indicated a significantly reduced mortality risk for renal transplant recipients when compared with acceptable transplantation candidates waiting on dialysis (Meier-Kriesche et al, 2001). Regardless of whether the treatment modality is dialysis or transplantation, the major causes of death are, in order, heart disease, sepsis, and stroke (USRDS, 2010).

The survival of kidney grafts has improved steadily over the past 3 decades but is now at a plateau. The results for the current era are quite remarkable (Table 44–1).

HISTORY OF HUMAN RENAL TRANSPLANTATION

The history of renal transplantation illustrates the successful combination of the fields of surgery, medicine, immunology, and government. Carrel established the modern method of vascular suturing at the turn of the 20th century, and he was awarded the Nobel Prize in 1912 for his work on organ grafting (Hamilton, 2001). In 1933 the first human renal allograft was performed by Voronoy in the Ukraine (Hamilton and Reid, 1984). The recipient was a 26-year-old woman who had attempted suicide by ingesting mercuric chloride. The donor was a 66-year-old man whose kidney was removed 6 hours after death. Under local anesthesia, the renal vessels were anastomosed to the femoral vessels and a cutaneous

Table 44–1.

Kidney Transplant Survival Rates for Primary Transplants: Current Era

DONOR	N	5-YR (%)	HALF-LIFE (yr)*
HLA-identical sibling	2189	87	29
One-haplotype sibling	3584	81	19
Spouse	2803	70	18
Other biologically unrelated	3094	78	18
Deceased	34,208	66	10
Standard criteria	28,440	70	11
Expanded criteria	5223	52	7

*Half-life is projected for those kidney transplants surviving the first year.
HLA, human leukocyte antigen.
Material from Cecka JM. The OPTN/UNOS renal transplant registry 2003. Clin Transpl 2003;1–12.

ureterostomy was performed. A small amount of blood-stained urine appeared, but the patient expired 48 hours after the procedure.

The first long-term success with human renal allografting, in which the patient survived for over a year, occurred in Boston in 1954, when a kidney from one twin was transplanted into the other, who had ESRD (Murray et al, 1955). In 1958 the first histocompatibility antigen was described. Radiation was used for immunosuppression in 1959, azathioprine became available for human use in 1951, and glucocorticoids became part of a standard immunosuppression regimen with azathioprine in 1962 (Goodwin et al, 1963). In the same year, the first use of tissue matching to select donor-recipient pairs was done. The direct crossmatch between donor lymphocytes and recipient serum was introduced in 1966, and heterologous antilymphocyte serum was used as an immunosuppressant in human renal transplantation.

In the late 1960s human renal preservation over 24 hours became possible with either pulsatile machine perfusion (Belzer et al, 1967) or simple cold storage after flushing with an ice-cold intracellular electrolyte solution (Collins et al, 1969). The beneficial effect of blood transfusions was described by Opelz and colleagues in 1973, and this led to immunologic conditioning with blood products for both deceased and living donor renal transplants. Donor-specific blood transfusions eventually became part of standardized pretransplantation immunologic conditioning protocols for living donor renal transplantation (Salvatierra et al, 1980). In the cyclosporin era, the beneficial effects of random blood transfusions and donor-specific blood transfusion protocols have been difficult to establish, and transfusion protocols have been associated with donor-specific sensitization and the transmission of viral illnesses. For these reasons, pretransplantation transfusion protocols are no longer routinely prescribed.

Medicare coinsurance for ESRD patients was passed into law in 1972 and instituted in 1973. This removed a significant impediment to renal transplantation in the United States. In the mid-1970s, brain-death laws were passed. This allowed organ retrieval from beating-heart deceased donors, reduced warm ischemia time, and improved the quality of deceased donor kidney grafts. The first clinical trials of cyclosporine were reported by Calne and colleagues in 1978, and 3 years later there were reports of the successful use of a monoclonal antibody for the treatment of renal allograft rejection in humans (Cosimi et al, 1981). In 1984 Congress passed the National Transplant Act, which authorized a national organ-sharing system and grants for organ procurement. The University of Wisconsin (UW) solution, introduced in the late 1980s, provided one solution for the preservation of all transplantable abdominal organs including kidneys (Belzer and Southard, 1988). Recombinant erythropoietin became available in 1989, and this significantly improved the quality of life for maintenance dialysis patients and reduced the need for blood transfusions (Carpenter, 1990). This has decreased the risk of virally transmitted infections and the risk of the development of anti-human leukocyte antigen (HLA) antibodies in potential kidney transplant recipients. Thirty-six years after the first long-term success of human-to-human kidney transplantation, Joseph E. Murray received the Nobel Prize in Medicine in 1990 for his pioneering work in renal transplantation.

Laparoscopic donor nephrectomy was introduced in 1995 to reduce disincentives for living donor nephrectomy (Schulam et al, 1996; Pradel et al, 2003).

The past decade has witnessed the development of novel immunosuppressive agents that may allow reduction and, in some cases, complete discontinuation of chronic immunosuppressive agents.

SELECTION AND PREPARATION OF KIDNEY TRANSPLANT RECIPIENTS

The pretransplantation evaluation is a multidisciplinary process that is performed well in advance of the renal transplantation operation and immunosuppression. **The purposes of the evaluation are generally considered to be to diagnose the primary renal disease and its risk of recurrence in the kidney graft and to rule out active invasive infection, a high probability of operative mortality, noncompliance, active malignancy, and unsuitable conditions for technical success** (Barry, 2001; Kasiske et al, 2001; Bunnapradist and Danovich, 2007).

Preliminary Screening

The process of evaluating the transplantation candidate is initiated by identifying the presence or absence of the risk factors at the top of the algorithm in Figure 44–1. Candidates with a history of substance abuse must have unannounced drug screens with negative results before continuing the process. Candidates with morbid obesity, defined as a body mass index of greater than 35, must demonstrate weight reduction before continuing the process because of the perioperative risks and earlier graft failures associated with renal transplantation in obese patients (Glanton et al, 2003; Meier-Kriesche et al, 2003). Bariatric surgery may be an option to prepare dialysis-dependent morbidly obese patients for transplantation (Alexander et al, 2004; Modanlou et al, 2009). Candidates considered to be at risk for noncompliance must demonstrate contract satisfaction. For example, a hemodialysis-dependent patient may be required to maintain his or her serum phosphorus level less than or equal to 6 mg/dL, predialysis serum potassium level less than or equal to 6 mmol/L, and interdialytic weight gain less than or equal to 5% of dry weight for a period of 3 months. It is recommended that patients older than 50 years or with a history of coronary artery disease, cardiac symptoms, or insulin-dependent diabetes mellitus undergo cardiac testing with further diagnosis and treatment of significant cardiac disease before proceeding with the rest of the algorithm (Lewis et al, 2002).

Kidney Disease Recurrence

Patients with focal segmental glomerulosclerosis, hemolytic-uremic syndrome, and primary oxalosis should be counseled about the significant probability of disease recurrence and the risk of secondary graft failure (Cameron, 1993; First and Peddi, 1999; Hariharan et al, 1999; Jamieson, 2005). Patients with a high risk of recurrent focal segmental glomerulosclerosis are those younger than 15 years of age, those who have a rapidly progressive course, and those with mesangial proliferation on biopsy of the native kidneys. If a first transplant has failed because of recurrent focal segmental glomerulosclerosis, the risk of recurrence in a second transplant approaches 80%. Hemolytic-uremic syndrome is a relatively common cause of ESRD in children, and recurrence has been associated with calcineurin inhibitor immunosuppression. Oxalosis can rapidly recur in a kidney graft, and this disease is probably best treated with combined liver and kidney transplantation to correct both the metabolic defect and the renal failure. The ESRD of renal amyloidosis, cystinosis, and Fabry disease are all potentially treatable with renal transplantation despite significant recurrence rates.

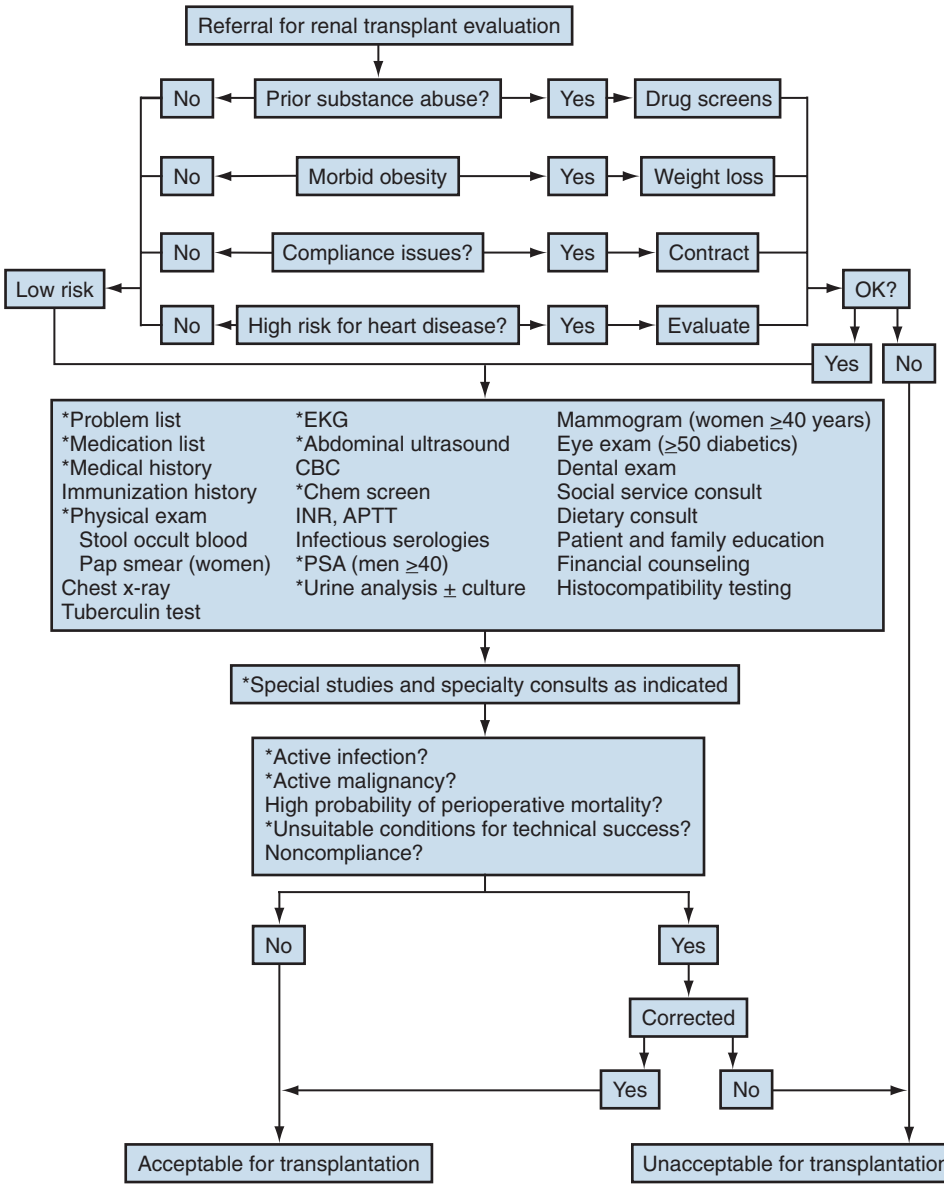


Figure 44–1. Algorithm for the evaluation of renal transplantation candidates. Circumstances may change the order in which data are obtained. APTT, activated partial thromboplastin time; CBC, complete blood cell count; EKG, electrocardiogram; INR, international normalized ratio; PSA, prostate-specific antigen; PT, prothrombin time. *Asterisks* indicate items of special significance for the urologist. (Modified from Barry JM. Current status of renal transplantation: patient evaluations and outcomes. Urol Clin North Am 2001;28:788.)

Diabetes mellitus and IgA nephropathy are examples of diseases that commonly recur in the transplanted kidney but rarely result in graft failure.

Autosomal dominant polycystic kidney disease, renal dysplasia, and Alport syndrome without antiglomerular basement membrane antibodies are examples of renal diseases that do not recur in the transplanted kidney.

Infection

Infections must be detected and treated before transplantation or prevented with immunizations.

Potential sources of dental sepsis must be treated. Dialysis access sites must be clear of infection. Pulmonary infections or tuberculin test conversions require treatment before immunosuppression. Reasonable indications for pretransplantation cholecystectomy are considered to be symptomatic cholecystitis and cholelithiasis with gallbladder wall thickening. Segmental colectomy is reasonable for patients with recurrent diverticulitis because of the morbidity and mortality of bowel perforation in the immunosuppressed kidney transplant recipient (Salem et al, 2004). Diabetic foot ulcers must be healed before transplantation, and urinary tract infection should be inactive at the time of engraftment.

Serologic testing for cytomegalovirus (CMV) is important because this disease is a major cause of morbidity in immunosuppressed patients. Patients who are seropositive for herpes simplex virus or who have a history of oral or genital herpes simplex or shingles need antiviral therapy during intense immunosuppression. Epstein-Barr virus titers are determined in children and, for the Epstein-Barr virus–seronegative child, a kidney from an Epstein-Barr virus–seronegative donor is preferred to reduce the risk of a post-transplantation lymphoproliferative disorder, the commonest new malignancy in pediatric organ transplant recipients. Recipient human immunodeficiency virus (HIV) infection

has been considered to be a contraindication to renal transplantation; however, successful outcomes have been reported in HIV-positive patients who have had low viral loads and sufficient CD4 T-cell counts. Chronic active hepatitis is a major cause of mortality in the late post-transplantation period. The treatment of chronic, active hepatitis B and C is evolving, and patients with active hepatitis C infection may benefit from antiviral therapy before transplantation (Mahmoud et al, 2005).

Corticosteroids enhance viral replication, and these infections should be inactive at the time of transplantation. Unless the patient is protected by antibody development after infection or prior immunizations, the following immunizations are given to transplantation candidates: hepatitis A, hepatitis B, pneumococcus, diphtheria, tetanus, pertussis, polio, varicella, measles, mumps, influenza, and rubella. Asplenic patients also receive HbCV vaccine, meningococcal polysaccharide vaccine, and pneumococcal vaccine.

Active Malignancy

To reduce the risk of cancer recurrence, a waiting time of 2 to 5 cancer-free years from the time of the last cancer treatment has been recommended for patients who have had invasive malignancies (Kasiske et al, 2001). Shorter intervals from cancer treatment to transplantation are generally accepted for patients who have had low-grade, noninvasive cancers. The calculation of expected remaining life times after transplantation (USRDS, 2010) and the application of cancer progression nomograms to recommend cancer-free intervals before transplantation may be helpful in individual cases (Secin et al, 2004). Cholecystectomy is recommended for transplantation candidates with gallbladder polyps greater than 1 cm in diameter because of the risk of malignancy (Boulton and Adams, 1997; Chattopadhyay et al, 2005).

High Probability of Perioperative Morbidity or Mortality

Heart disease is the predominant cause of death after renal transplantation (USRDS, 2010), and it is common for kidney transplantation candidates with a history of cardiac disease, cerebrovascular disease, or diabetes mellitus or who are older than 50 years to undergo a cardiac performance evaluation. Further testing and treatment are based on the results of a screening evaluation. Cerebrovascular disease, peptic ulcer disease, and significant pulmonary disease must be detected and treated. For example, patients with autosomal dominant polycystic kidney disease (ADPKD) and headaches or a family history of stroke should be screened for cerebral aneurysms (Pirson et al, 2002). Cigarette smoking increases the risks of surgery, post-transplantation malignancy, cardiovascular disease, and renal allograft loss (Sung et al, 2001). It must be stopped before transplantation in patients who already have clinical evidence of vasculopathy or cardiopulmonary disease.

Noncompliance

Compliance issues are extremely important in the long-term management of kidney transplant recipients. Transplantation candidates with chemical dependency need to have an objectively documented drug- or alcohol-free period of at least 6 months before transplantation (Kasiske et al, 2001). Financial and psychosocial consultations are necessary to identify and correct problems that could result in noncompliance, for example, the lack of funds to pay for maintenance immunosuppressants or a mental handicap that could prevent the recipient from following a post-transplantation treatment plan.

Unsuitable Conditions for Technical Success

Evaluations of the vascular system and the urinary tract are necessary to identify problems that need to be corrected before transplantation or addressed at the time of transplantation.

Patients with symptoms and signs of lower extremity arterial disease or a history of abdominal or pelvic vascular surgery need to undergo a diagnostic evaluation to be certain that revascularization of a kidney graft is possible. Vascular screening with Doppler flow studies is recommended for the indications listed in Table 44–2. If significant arteriosclerosis or venous disease is detected, it may be necessary to perform angiography on select alternative sites such as the aorta or splenic artery for renal revascularization or to plan corrective vascular surgery before renal transplantation.

Thrombosis is a significant cause of kidney transplant loss, especially in children (USRDS, 2010). Renal transplantation patients at risk for graft thrombosis are those with previous vascular access thrombosis, previous venous thrombosis, antiphospholipid antibodies, and previous large vein renal transplant thrombosis (DeLoughery, 2004). A hypercoagulable state can occur in the nephrotic syndrome with urinary loss of the natural anticoagulants antithrombin III, protein C, and protein S. Hyperhomocysteinemia is common in ESRD, and it has been associated

Table 44–2.

Recommendations for Doppler Flow Studies in Renal Transplant Candidates

	Areas Studied		
INDICATIONS	CAROTIDS	AORTA AND ILIAC ARTERIES, SPLENIC AND RENAL ARTERIES, LOWER EXTREMITY ARTERIES	PELVIC VEINS, INFERIOR VENA CAVA
Cerebrovascular symptoms or bruits	×		
Lower extremity claudication or bruits		×	
Extensive aortoiliac calcification or bruits		×	
Prior bilateral renal transplants		×	×
Prior abdominal vascular surgery		×	×
Prior abdominal radiation		×	×
Prior pelvic venous thrombosis			×

Modified from Barry JM. Current status of renal transplantation: patient evaluations and outcomes. Urol Clin North Am 2001;28:677.

with thrombophilia (Levey et al, 1998). Antiphospholipid antibodies are found in 30% to 50% of patients with systemic lupus erythematosus, a systemic cause of ESRD. Patients can be evaluated with the activated protein C resistance ratio (factor V Leiden mutation), protein C activity, protein S activity, antithrombin III activity, homocysteine level, prothrombin gene mutation, and antiphospholipid antibodies (DeLoughery, 2004; Irish, 2004). It is reasonable to screen for thrombophilia when a patient is admitted for renal transplantation, administer low-dose heparin intraoperatively to all recipients, and continue low-molecular-weight heparin therapy until the results of the thrombophilia panel are known. On the basis of the thrombophilia panel results, a decision can be made about intermediate or long-term anticoagulation.

The purposes of the urologic evaluation are to determine the suitability of the urinary bladder or its substitute for urinary tract reconstruction and to determine the necessity for removal of the native kidneys before or at the time of renal transplantation. The urologic evaluation includes a history for urologic disease and operations on the urinary tract; a physical examination including the location of scars, abdominal catheters, and stomas that may interfere with transplantation; urinalysis; urine or bladder wash culturing; and ultrasonography of the abdomen and pelvis to include a postvoid bladder image, the kidneys, and the gallbladder. Further study of the urinary tract is indicated for a history of urologic abnormalities, nonglomerular hematuria, single-organism bacteriuria, calculi, hydronephrosis, autosomal dominant polycystic kidney disease, significant bladder residual urine, or inconclusive preliminary imaging studies (Table 44–3). The anuric patient will need to be queried about bladder function that was present before urine production ceased. In chronic peritoneal dialysis patients, ultrasound examination of the bladder may overestimate residual urine.

An ESRD patient with upper urinary tract diversion may have a bladder that is acceptable for transplantation, especially if the original reason for diversion was vesicoureteral reflux. **A defunctionalized bladder usually regains normal volume within weeks of transplantation.** It is reasonable that transplantation candidates with small, contracted bladders who have had multiple lower urinary tract operations undergo bladder biopsy. If fibrosis is extensive on histologic examination and the bladder cannot be coaxed into becoming a low-pressure reservoir with bladder cycling, autoaugmentation or augmentation cystoplasty can be done before renal transplantation or afterward if satisfactory bladder function does not return within a few months (Barry, 2004). Functionalized augmentation is preferable to dry augmentation because it permits continence and bladder compliance to be documented before transplantation (Gonzales, 1997). A urothelium-lined augmentation is best because mucus does not have to be rinsed from the bladder on a regular basis. Advantages of gastrocystoplasty over enterocystoplasty are the lack of metabolic acidosis and significant mucus with the former. Disadvantages of gastrocystoplasty are the frequency-urgency syndrome due to acid from gastric mucosa and recalcitrant metabolic alkalosis. Patients with gastrocystoplasty who become anuric are at risk for bladder ulceration because acid produced by the gastric segment is not diluted with urine and washed out with voiding. Patients with augmented bladders usually require clean intermittent catheterization after transplantation, and the patient should be trained in this technique well in advance of the transplantation procedure. **Clean intermittent self-catheterization has been used successfully in transplant recipients for more than 2 decades for patients with neuropathic bladders or transient bladder outlet obstruction** (Schneidman et al, 1984).

Cyclophosphamide is commonly used to treat immune complex glomerulonephritis, and a bladder wash for cytologic examination is recommended for patients with prior cyclophosphamide therapy because of its reported association with transitional cell carcinoma (Radis et al, 1995).

Renal transplants into intestinal conduits or continent intestinal pouches have been successful. The pouches require frequent irrigations before transplantation to remove mucus and to maintain pouch volume.

Men with obstructing prostates whose voiding problems cannot be managed successfully with medical therapy are candidates for invasive prostatic therapies such as thermotherapy, prostatectomy, or transurethral incision of the bladder neck and prostate before or after transplantation. **Sometimes, it is possible to treat both hypertension and bladder outlet obstruction with one of the less specific α-adrenergic blocking agents such as doxazosin or prazosin.** It is preferable to avoid surgical treatment of bladder outlet obstruction in the oligo-anuric renal transplant candidate until after transplantation because of the risk of bladder neck contracture or prostatic fossa obliteration. If bladder outlet surgery is done pretransplant in the oligo-anuric patient, it is advisable to place a suprapubic cystostomy at the time of bladder outlet surgery to allow the patient to instill sterile water and void daily until the operative site has healed, usually 6 weeks, or to have the patient perform daily intermittent self-catheterization, fill the bladder, and then void.

The generally accepted recommendations for pretransplantation nephrectomy are outlined in Table 44–4. Renal calculi can be managed by minimally invasive techniques, and severe proteinuria and large polycystic kidneys without infection or solid tumor can be managed by renal infarction (Ubara et al, 2002). **The incidence of renal cell carcinoma is more common in patients with acquired renal cystic disease and in transplant recipients than in the general population,** and nephrectomy is indicated for solid renal tumors (MacDougall et al, 1990). If a polycystic kidney extends below the iliac crest, it is best

Table 44–3.

Recommendations for Additional Urologic Studies in Renal Transplant Candidates

STUDIES	INDICATIONS
Voiding cystourethrogram ± urodynamics	Voiding dysfunction, history of pyelonephritis or reflux, inconclusive ultrasonography
Cystoscopy	Suspected lower urinary tract cancer or planned invasive prostate therapy
Retrograde pyelography	Planned orthotopic renal transplantation or inconclusive ultrasonography
Renal CT scan	Inconclusive ultrasonography for stone or mass, autosomal dominant polycystic kidney disease to accurately size kidneys
Urine or bladder wash cytology	Prior cyclophosphamide therapy or significant irritative voiding symptoms
Bladder biopsy	Suspected bladder fibrosis or cancer
Retrograde loopogram	Intestinal conduit
Retrograde pouchogram	Intestinal or gastric reservoir

Modified from Barry JM. Current status of renal transplantation: patient evaluations and outcomes. Urol Clin North Am 2001;28:677.

Table 44–4.

Recommendations for Pretransplant Nephrectomy

Renal stones not cleared by minimally invasive techniques or lithotripsy
Solid renal tumors with or without acquired renal cystic disease
Polycystic kidneys that are symptomatic, extend below the iliac crest, have been infected, or have solid tumors
Persistent antiglomerular basement membrane antibody levels
Significant proteinuria not controlled with medical nephrectomy or angioablation
Recurrent pyelonephritis
Grade 4 or 5 hydronephrosis

removed to allow room for a kidney transplant. Pretransplantation nephrectomy is usually performed 6 weeks before transplantation or active wait-listing for deceased donor renal transplantation to allow wound healing and the detection and treatment of surgical complications. It is common to do kidney removal at the time of renal transplantation in children. It is common to do preliminary nephrectomies in adults, especially when the patient is to be listed for deceased donor renal transplantation, recurrent pyelonephritis has been noted, or when difficult nephrectomy with possible adjacent organ injury is anticipated. Bilateral nephrectomies for autosomal dominant polycystic kidney disease (ADPKD) at the time of renal transplantation have been reported (Glassman et al, 2000). The authors reserve this option for ADPKD patients who are undergoing living donor renal transplantation (Wagner et al, 2007). The use of synthetic erythropoietin has reduced the effects of anemia associated with nephrectomy while the patient awaits transplantation. Although laparoscopic or retroperitoneoscopic nephrectomies are becoming more commonly performed in these patients, bilateral vertical lumbotomies are quickly performed and well tolerated by patients with small kidneys undergoing nephrectomy (Freed, 1976). An open-flank approach is often used when a kidney is too large to be removed by a vertical lumbotomy or a laparoscopic technique. The open-abdominal approach is used when the kidneys are too large to remove with a minimally invasive technique or when additional procedures such as total ureterectomy, intestinal conduit removal, augmentation cystoplasty, the creation of a continent intestinal pouch, or the kidney transplantation are to be done at the same time.

Impotence is a significant problem in men with ESRD, and potency improves in a significant proportion of men after transplantation. Contributing factors to erectile dysfunction in ESRD are the accelerated arteriosclerosis associated with dialysis, hyperprolactinemia with secondary testosterone deficiency, side effects from antihypertensive drugs, and a poor self-image. **If penile prosthesis surgery is necessary before renal transplantation, a device that has no prevesical reservoir is recommended because a prevesical reservoir can interfere with urinary tract reconstruction and be mistaken for the urinary bladder until the reservoir has been accidentally incised.**

DONOR SELECTION, PREPARATION, AND SURGERY

The basic criteria for a renal donor are an absence of renal disease, an absence of active infection, and an absence of transmissible malignancy. Whether the kidney is removed from a living donor or a deceased donor, the surgical goals are to minimize warm ischemia time, preserve renal vessels, and preserve ureteral blood supply. In the deceased donor, it is also necessary to obtain histocompatibility specimens and sometimes necessary to remove iliac vessels for vascular reconstruction of the donor kidney.

Living Donor

On the basis of the preoperative evaluation, one must be able to assure the living donor of nearly normal renal function after unilateral nephrectomy. On evaluation, if one of the potential donor's kidneys is better than the other, the better kidney is left with the donor (Murray and Harrison, 1963). It is preferable to use the right kidney from women who may become pregnant because hydronephrosis of pregnancy and pyelonephritis of pregnancy occur predominantly in that kidney (Stevens, 1933; Monga, 1998). Although renal donation poses no great harm to pregnancy (Ibrahim et al, 2009a), it is recommended that pregnancy be delayed at least a year after nephrectomy (Nevis and Garg, 2009). An algorithm for the evaluation of a living renal donor is presented in Figure 44–2. Circumstances may change the order in which data are obtained. A living renal donor is considered to be unsuitable when one of the following is present: significant mental dysfunction, significant renal disease, high risk of perioperative mortality or morbidity, or significant transmissible disease. ABO incompatibility and a positive crossmatch between donor lymphocytes and recipient serum were usually considered to be contraindications to directed living renal donation, but immunosuppression protocols (Takahashi, 2007; Warren et al, 2004) and paired donation and altruistic chain transplant programs (Rees et al, 2009) are evolving to deal with those issues. Serologic testing is performed for HIV, human T-lymphoproliferative virus type 1 (HTLV 1), hepatitis, cytomegalovirus (CMV), and syphilis. Some programs also screen for Epstein-Barr virus, especially when the recipient is a child. Diabetes mellitus is excluded in the donor by determining that the casual or random plasma glucose level is less than 200 mg/dL, the fasting plasma glucose level is less than 125 mg/dL, or after a 75-g glucose load, the 2-hour plasma glucose level is less than 200 mg/dL (Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997). Abdominal ultrasonography can be performed to exclude donors with significant renal abnormalities and to detect incidental intra-abdominal abnormalities. Three-dimensional CT angiography without and with intravenous (IV) contrast material followed by a flat plate of the abdomen has been widely accepted because it satisfactorily excludes stone disease, demonstrates renal and vascular anatomy, and defines the urinary collecting system, all with minimal donor morbidity and at reasonable expense.

Hyperfiltration injury has not been a significant problem for living renal donors. Endogenous creatinine clearance rapidly approaches 70% to 80% of the preoperative level, and this has been shown to be sustained for more than 10 years (Najarian et al, 1992; Ibrahim et al, 2009b). The development of late hypertension is nearly the same as for the general population, and the development of proteinuria is negligible (Steckler et al, 1990; Kasiske et al, 1995). Older donor age and increased body mass index (BMI) have been associated with the development of hypertension and GFR under 60 mL/min/1.73 m^2 (Ibrahim et al, 2009b), and the authors disqualify potential living renal donors with BMIs over 33. The mortality of kidney donation has been estimated to be 0.02% (Matas et al, 2003), the risk of a potentially life-threatening or permanently debilitating complication has been

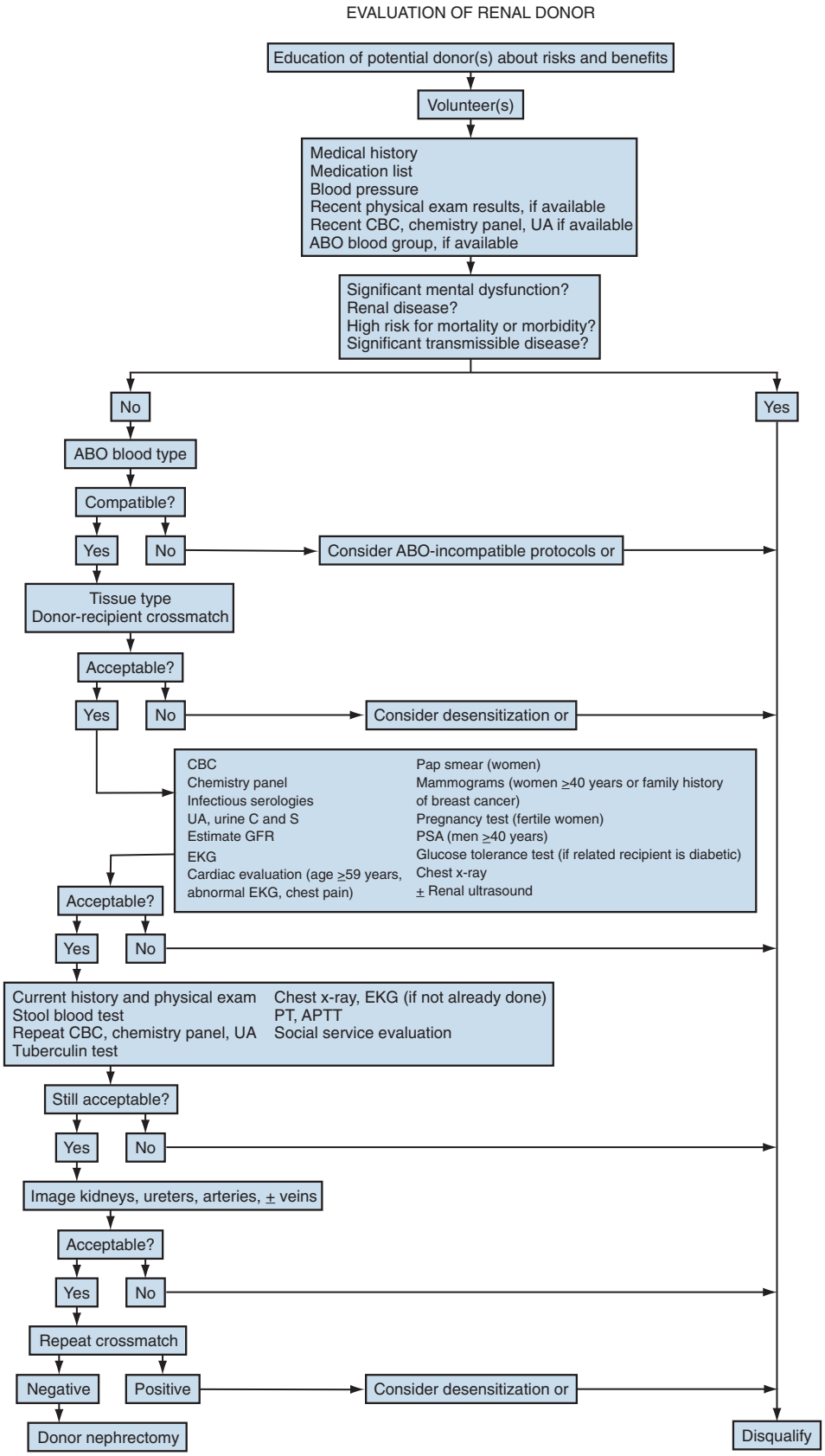


Figure 44–2. Algorithm for the evaluation of living renal donors. APTT, activated partial thromboplastin time; CBC, complete blood cell count; C&S, culture and sensitivity; EKG, electrocardiogram; GFR, glomerular filtration rate; PPD, tuberculin skin test; PSA, prostate specific antigen; PT, prothrombin time; UA, urinalysis.

estimated to be 0.23%, and there are isolated reports of ESRD developing in renal donors (Rosenblatt et al, 2008). **The short- and long-term risks of living donor nephrectomy are generally considered to be low enough, and the probability of successful graft outcome high enough, to make the risks acceptable for fully informed donors.**

Live donor nephrectomy can be performed either as an open or laparoscopically assisted procedure. Open live donor nephrectomy (ODN) can be performed through a flank incision with or without rib resection or by an anterior intraperitoneal or extraperitoneal incision. Laparoscopic donor nephrectomy (LDN) has become the preferred technique for live donor nephrectomy at most transplant centers in the United States (Ratner et al, 1999; Jacobs et al, 2004), and a retroperitoneoscopic approach for either kidney has been described (Yang et al, 2001). Regardless of the technique of living donor nephrectomy, diuresis is promoted by IV fluids, mannitol infusion, and loop of Henle diuretics. Overnight hydration of the living donor is unnecessary. It is common to prepare the LDN candidate with a clear liquid diet and a laxative the day before surgery. General anesthesia is used. Epidural analgesia for pain management is optional. Nitrous oxide inhalation is avoided to prevent bowel distension. IV fluids and mannitol are used to prevent oliguria associated with pneumoperitoneum.

Technique of Laparoscopic Live Donor Nephrectomy

The patient is placed in a modified right lateral decubitus position with the left side elevated approximately 45 degrees with a large gel roll. The table is partially flexed; it is unnecessary to raise the kidney rest. The patient is secured to the table with 2-inch cloth tape crossing just below the anterior superior iliac spines. This will permit rotation of the table during the procedure. Following the skin preparation and draping, the hand assist device is placed in a 7-cm periumbilical incision. The abdomen is insufflated to 15 mm Hg and inspected with a 10-mm, 30-degree telescope placed through a trocar in the hand assist device. Two 12-mm trocars are inserted under direct vision in the left lower quadrant and the subcostal regions, respectively (Fig. 44–3). These two trocars are generally all that are necessary. Occasionally, a third trocar (5 mm) is placed in the midaxillary line for lateral retraction.

Left laparoscopic donor nephrectomy is performed with the telescope in the most superior trocar, the left hand in the hand assist device, and the right hand using working instruments through the left lower quadrant trocar. First, the left colon is

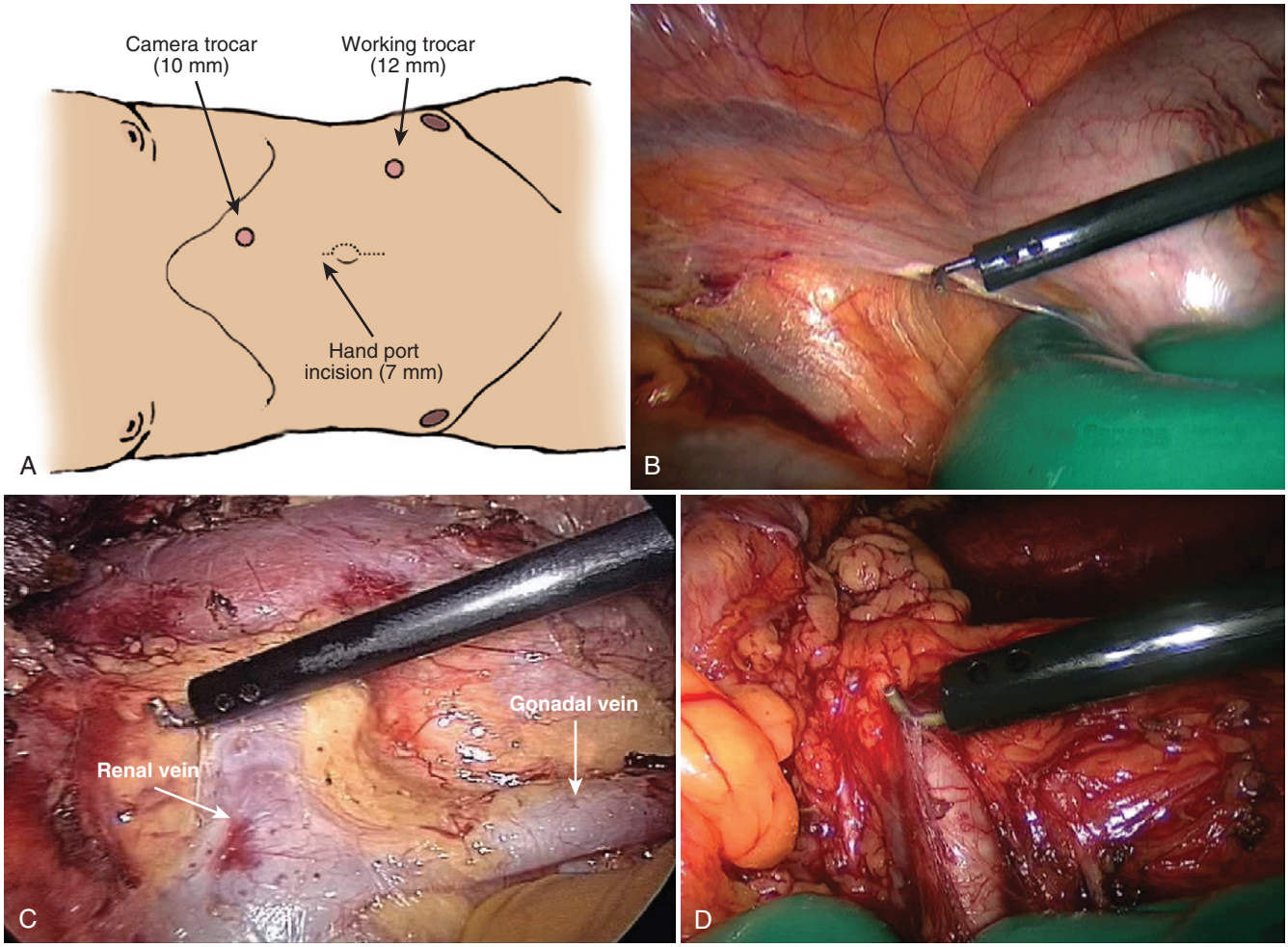


Figure 44–3. Hand-assisted laparoscopic left donor nephrectomy. **A,** Diagram showing location of the incision and trocar placement for left laparoscopic donor nephrectomy. **B,** Retraction and reflection of the colon. **C,** Exposure of gonadal and renal veins. **D,** Dissection of the posterior surface of the renal artery.

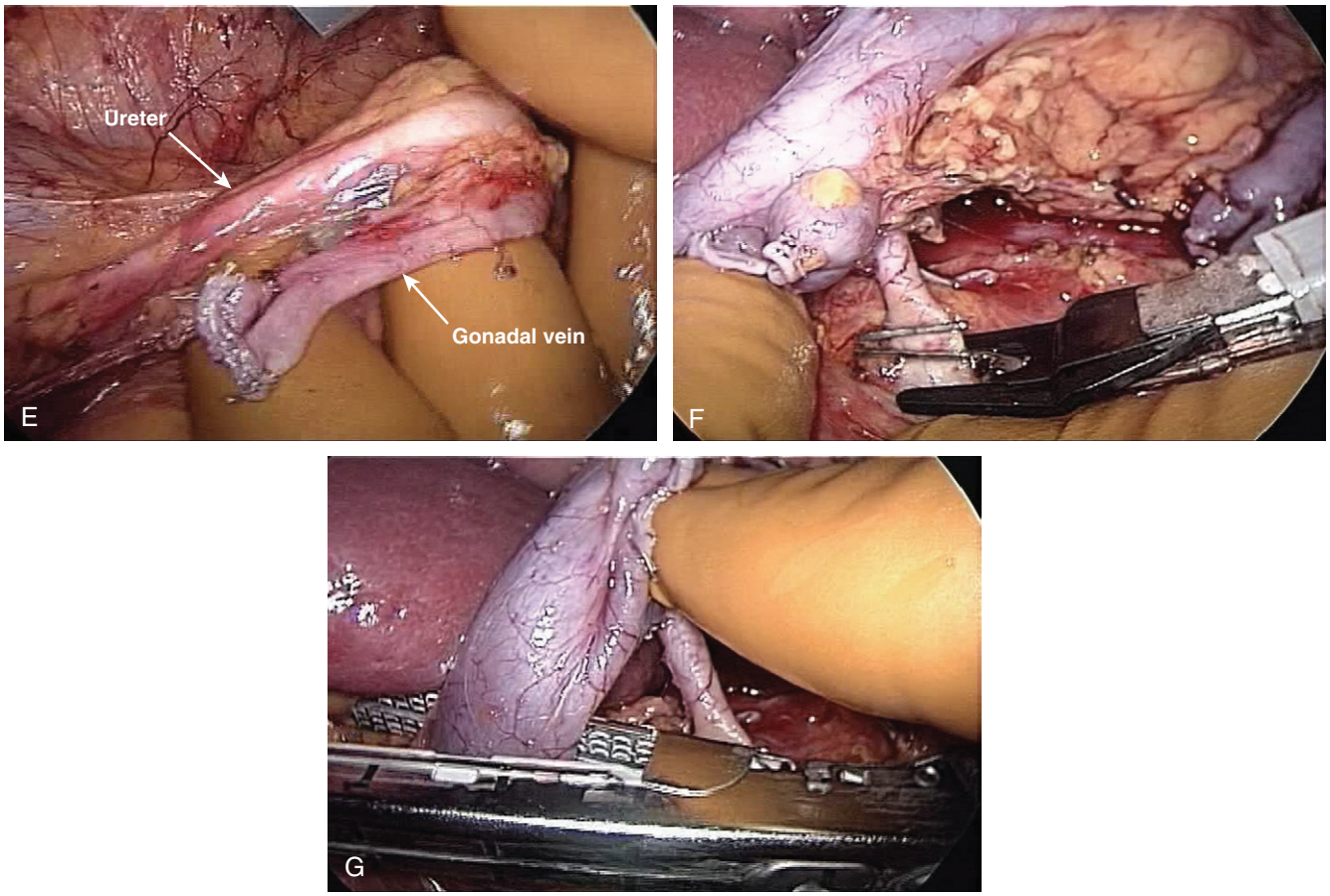


Figure 44–3, cont'd. **E,** Dissection of the ureter with preservation of periureteral tissue. **F,** Ligation of the renal artery with clips. **G,** Ligation of the renal vein with stapling device.

reflected from the level of the iliac vessels to above the spleen. Once the peritoneum is divided with scissors, ultrasonic cutting device, or hook electrocautery, the colon can often be reflected with blunt dissection. A combination hook, suction, and irrigation device is useful in this setting, enabling the surgeon to quickly switch between sharp dissection with hook cautery and blunt dissection with the suction probe. Anterior and medial retraction of the colon with the left hand will keep the tissue from being divided under tension and is critical to proper identification of the plane between the mesentery and Gerota fascia. The splenocolic ligament is left intact, and the plane of dissection is carried lateral to the spleen to allow the spleen to drop medially. The gonadal vein is generally visible after complete reflection of the left colon. Hook electrocautery is used to clean the surface of the gonadal vein to its insertion in the renal vein. The renal vein is dissected, and its branches (gonadal, lumbar, and adrenal veins) are freed in the process. The 10-mm laparoscopic right angle dissector is useful for dissection of these branches. The branches of the renal vein are divided with clips, vascular staples, or a feedback-controlled vessel bipolar sealing device. These bipolar devices will seal and divide vessels up to 7 mm in diameter. Avoiding the use of clips on the branches of the renal vein will diminish the chance of endoscopic vascular stapling device misfire due to a clip in the jaws of the stapling device.

After division of the lumbar vein, the renal artery is visible posterior to the renal vein. Be careful when dissecting in this area of the renal hilum because there is frequently more than one lumbar vein, and these are difficult to identify on preoperative CT scan because they do not reliably fill with contrast. The tissue surrounding the artery is divided with the hook electrocautery. Once the proper plane is entered immediately adjacent to the renal artery, the emancipated artery will spring free of the surrounding tissues.

The ureter is prepared by carefully dissecting it free of the surrounding tissue preserving sufficient periureteral tissue to protect the ureteral blood supply. The ureter is not divided until after the kidney and renal hilum have been completely dissected to prevent rotation of the kidney and torsion of the renal vessels. The kidney is completely freed laterally and flipped medially to allow exposure and dissection of the posterior surface of the renal vessels. When ready, the ureter is clipped distally with two large titanium clips and divided. Diuresis is visually confirmed and is necessary to prevent delayed graft function in the recipient. The back table to be used for renal perfusion is set up with slush in a pan, cold University of Wisconsin solution in a bag pressurized to 150 mm Hg, attached tubing with a vascular perfusion cannula, fine atraumatic forceps, and fine scissors. The division of the renal vessels is rehearsed with the surgical team to ensure all instruments are present, working, and the order of their use is familiar to all. The artery is ligated with three long titanium clips or with a vascular load (2.0- to 2.5-mm staples) of the endoscopic stapling device. Reticulating staplers are preferred. Care is taken to ensure that there are no clips within the jaws of the stapling device because this is the most common cause of misfire. The vein is also ligated and divided with a stapling device. The kidney is immediately delivered from the periumbilical incision, placed on slush, and

flushed through the artery with cold preservation solution. The kidney is then packaged sterilely and taken in an ice bath into the recipient's operating room or cold-stored until the time of transplantation if that procedure is delayed. The renal fossa, staple lines, and clips on vessels are inspected for bleeding; the colon is returned to its normal position; and the wounds are closed.

Right laparoscopic hand-assisted donor nephrectomy is slightly different from left donor nephrectomy. Positions of the monitor, surgical team and patient, incision, and trocar placements are the mirror images of those described for the left-sided procedure. However, the telescope is used through the right lower quadrant trocar, the left hand is placed through the hand assist device, and the upper trocar is used for working instruments operated with the surgeon's right hand. An additional 5-mm trocar is placed in the subxiphoid region through which a locking grasper can be placed for liver retraction. This grasper is used to lift the liver cranially and then clamped to the body wall. The remainder of the procedure is the same as for left nephrectomy, except for management of the renal vein. After clipping or stapling and dividing the renal artery, the renal vein is stapled with the stapling device placed through the upper trocar, across the renal vein, and flush with the inferior vena cava. The vein is incised with endoscopic scissors just beyond this staple line. Although it is not possible to obtain a small cuff of vena cava with this technique, the length of vein is usually adequate.

The advantages of LDN when compared with historical cases of ODN have been decreased analgesic requirement, decreased length of hospital stay, and an earlier return to work. The disadvantages have been reported to be increased operating time, donor surgeon preference for the left kidney, an increased need for special equipment, a longer warm ischemia time, and delayed graft function (Jacobs et al, 2004; Barry, 2005). Although initial renal transplant function may be somewhat slower to recover after LDN, single-center, longer-term results are not significantly different from those of ODN (Goel et al, 2004; Tooher et al, 2004). Earlier registry data indicated that 3-year kidney transplant survivals and projected half-lives of kidney transplants significantly favored the ODN flank approach over the LDN approach (Cecka, 2003). A difference in favor of ODN has been reported with the transplantation of adult kidneys into children (Troppman et al, 2005). As LDN teams become more experienced with the technique, these differences are expected to become insignificant, and emerging randomized trials of ODN versus LDN have reported equivalent renal transplant outcomes (Simforoosh et al, 2005).

Although LDN for right kidneys was initially associated with poorer results due to thrombosis of the shorter right renal vein, further experience with this technique yielded results equivalent to those reported for left LDN (Posselt et al, 2004). A single-port laparoscopic donor nephrectomy technique has been recently described (Gill et al, 2008).

Deceased Donor

The declaration of brain death is the responsibility of the potential deceased organ donor's physician.

The criteria for an ideal deceased kidney donor are normal renal function, no hypertension requiring treatment, no diabetes mellitus, no malignancy other than a primary brain tumor or treated superficial skin cancer, no generalized viral or bacterial infection, acceptable urinalysis, age between 6 and 50 years, and negative assays for syphilis, hepatitis, HIV, and human T-lymphoproliferative virus. Viral nucleic acid testing (NAT) is becoming more widely applied. It reduces infectious risk by shortening the period between infection and detectability (Kucirka et al, 2009). In an effort to expand the donor pool, the concepts of ECDs and DCDs have been adopted. ECDs are defined as donors older than 60 years old or donors 51 to 59 years old with any two of the following risk factors: cerebrovascular death, hypertension, and serum creatinine level greater than 1.5 mg/dL (Cecka, 2004). ECD kidney transplant survival rates, those from donors after cardiac death, and those from very young donors are significantly inferior to those from ideal deceased donor kidney transplants. The poorer graft survivals for kidneys from the very young are due to small anatomic parts and the risk of technical problems. There are, however, reports of successful kidney transplants from small deceased donors (Hudnall et al, 1989; Bretan et al, 1997). The transplantation of both kidneys from a deceased donor with abnormal renal function or abnormal biopsy findings has also been used with success as an option to expand the donor pool, but the long-term function of such kidneys is inferior (Light, 1999; Wolters et al, 2005). Table 44–5 shows biopsy guidelines that some have found useful for the selection of transplantable kidneys from expanded-criteria deceased kidney donors.

The initial goals of resuscitation of the brain-dead deceased donor are generally systolic blood pressure of 90 mm Hg or mean arterial pressure of 60 mm Hg and urinary output exceeding 0.5 mL/kg/hr. Monitoring of central venous pressure, capillary wedge pressure, or pulmonary artery pressure is helpful for managing fluid administration (Boyd et al, 1991; Soifer and Gelb, 1989; Wood et al, 2004). Serum electrolyte levels are checked every 2 to 4 hours. If the resuscitation goals cannot be met by fluid challenge and the central venous pressure is greater than 15 cm H_2O, dopamine or dobutamine at less than 10 μg/kg/min can be infused without causing renal vasospasm. Attempts are made to maintain a hematocrit greater than 24%, platelets greater than 10,000/microliter, international normalized ration (INR) less than 1.8, fibrinogen greater than 100 mg/dL, temperature 35° C to 38° C, and blood glucose 80 to 110 mg/dL. Blood is cultured if the donor has been hospitalized for more than 72 hours.

If bradycardia does not respond to atropine, dopamine, or low-dose epinephrine, a temporary pacemaker can be inserted. If intravascular volume expansion and vasopressors are unsuccessful in promoting a diuresis, furosemide with or without mannitol can

Table 44–5.

Biopsy Grading System for Expanded Criteria Deceased Donor Kidney Allografts

Biopsy Grading System				
FINDING	NONE	1%-20%	21%-50%	>50%
Glomerulosclerosis	0	1	2	3
Interstitial fibrosis	0	1	2	3
Tubular atrophy	0	1	2	3
Vascular narrowing	0	1	2	3

Biopsy Score Recommendations	
SCORE	RECOMMENDATION
0-3	Use as single allograft
4-6	Transplant both into one recipient
7-12	Do not use

Modified from Light JA. A 25-year history of kidney transplantation at the Washington Hospital Center. In: Cecka JM, Terasaki PI, editors. Clinical transplants 1998. Los Angeles: UCLA Tissue Typing Laboratory; 1999. p. 165.

be infused. If diabetes insipidus causes an unmanageable diuresis, aqueous vasopressin can be infused to reduce urinary output. Because hypothermia can cause cardiac irritability and coagulopathy, the head can be wrapped, IV fluids can be warmed, and the body can be placed on a warming blanket. Tissue typing and crossmatching can be performed on a peripheral blood sample or groin lymph nodes before organ retrieval. The deceased donor is maintained in the operating room by the anesthesiology team to ensure ventilation and circulatory support and to administer drugs such as diuretics, heparin, and α-blocking agents. Thyroid replacement therapy is controversial.

Most renal donors are now multiple organ donors, and the classic abdominal midline and cruciate incisions have been largely abandoned in favor of the total midline approach with median sternotomy, even when kidneys alone are retrieved. **The principles of deceased donor organ retrieval are adequate exposure, control of the vessels above and below the organs to be removed, initiation of preservation in situ, the removal of the organs, separation of the organs, completion of preservation, removal of histocompatibility specimens, removal of iliac vessels for vascular reconstruction of pancreas and liver grafts, and organ packaging.** The technical aspects of an en bloc method are illustrated in Figure 44–4 (Nakazato et al, 1992; Barry, 1996). Some retrieval teams prefer to do much more dissection in situ before organ removal. When that occurs, the kidneys are the last transplantable organs to be removed. To avoid renal warming in this situation, it is important to maintain surface cooling of the kidneys by surrounding them with ice slush during liver and pancreas recovery.

KIDNEY PRESERVATION

Cellular Injury

Warm ischemic injury is due to failure of oxidative phosphorylation and cell death due to adenosine triphosphate (ATP) depletion (Belzer and Southard, 1988). ATP is required for the cellular sodium-potassium pump to maintain a high intracellular concentration of potassium and a low internal concentration of sodium. **When the sodium-potassium pump is impaired, sodium chloride and water passively diffuse into the cells, resulting in cellular swelling and the "no-reflow" phenomenon after renal revascularization.** Cellular potassium and magnesium are lost, calcium is gained, anaerobic glycolysis and acidosis occur, and lysosomal enzymes are activated. This results in cell death. During reperfusion, hypoxanthine, a product of ATP degradation, is oxidized to xanthine with the formation of free radical scavengers that cause further cell damage.

Principles of Simple Cold Storage of Kidneys

Cellular energy requirements are significantly reduced by hypothermia. This is done by surface cooling, hypothermic pulsatile perfusion, or flushing with an ice cold solution followed by cold storage. Making the flush solution slightly hyperosmolar with impermeant solutes such as mannitol, lactobionate, raffinose, or hydroxyethyl starch helps prevent endothelial cell swelling and the "no-reflow" phenomenon. When the sodium-potassium pump is impaired, there is passive transfer of ions across the cell membrane, and if the electrolyte composition of the flush solution is nearly the same as that inside the cell, electrolyte balance will be maintained. ATP-$MgCl_2$ infusions have been evaluated as an energy source. Calcium channel blockers, xanthine oxidase inhibitors, free radical scavengers, vasoprotective agents, and lysosome stabilizers such as methylprednisolone have all been used to reduce ischemic injury (Marshall et al, 2001).

Clinical Kidney Transplant Preservation

The basic methods of kidney preservation are pulsatile machine perfusion with a protein-based solution (Belzer et al, 1967) and hypothermic flushing followed by simple cold storage (Collins et al, 1969). After demonstration that the two methods provided equivalent results with ideally harvested dog kidneys after 48 hours of preservation (Halasz and Collins, 1976), simple cold storage became more widely used for human kidney preservation. Machine perfusion has provided reliable human kidney preservation for up to 72 hours (Feduska et al, 1978), and it is becoming the preferred method of preserving kidneys from ECDs and DCDs.

The commonly used UW solution (Belzer and Southard, 1988) minimizes cellular swelling with the impermeant solutes lactobionate, raffinose, and hydroxyethyl starch. Phosphate is used for its hydrogen ion buffering qualities, adenosine is for ATP synthesis during reperfusion, glutathione is a free radical scavenger, allopurinol inhibits xanthine oxidase and the generation of free radicals, and magnesium and dexamethasone are membrane-stabilizing agents. A major advantage of this preservation solution has been its utility as a universal preservation solution for all intra-abdominal organs. Kidney graft survival rates have been significantly better for kidneys preserved with UW solution compared with Euro-Collins solution (Ploeg et al, 1992; Opelz and Wujciak, 1996) and with UW solution compared with histidine-tryptophan-ketoglutarate (HTK) solution (Stewart et al, 2009).

The detrimental effects of the events surrounding deceased donor kidney retrieval and preservation injury are shown by the 12% better 5-year graft survival for 5897 living biologically unrelated donor kidney transplants compared with 34,208 primary deceased kidney transplants (Cecka, 2004).

Expansion of the deceased kidney donor pool by the use of non-heart-beating donors and ECDs has resulted in renewed interest in pulsatile machine perfusion.

It has been clearly demonstrated in the laboratory to be superior to simple cold storage for kidneys subjected to significant warm ischemia time (Halasz and Collins, 1976) and to reduce delayed graft function in kidneys retrieved from standard criteria donors, as well as those retrieved from ECDs and DCDs (Moers et al, 2009).

RECIPIENT SELECTION FOR DECEASED KIDNEY TRANSPLANTS

A point system continues to evolve in the United States for the selection of deceased kidney transplant recipients. Initial screening consists of ABO blood group identity determination and negative microcytotoxicity lymphocyte crossmatches between donor and recipient. Patients whose serum reacts to a high proportion of lymphocytes on a random or selected panel have high panel reactive antibody (PRA) levels, and they receive additional points because the probability of obtaining a crossmatch-negative kidney for them is decreased compared with minimally sensitized transplant candidates. The time on the waiting list, histocompatibility between the donor and the recipient, prior

vital organ donation, and age younger than 18 years result in additional points. A score is developed for each of the potential recipients, and the candidates are placed in rank order by that score. The patient with the highest score is ranked first for that specific kidney. The kidney graft is then offered in turn to each of the potential recipients by the final rank. If there is no suitable recipient on a local list, the kidney graft is offered to those on a regional list and, if necessary, the national list.

Candidates for ECD kidney engraftment must agree to receive one of these kidneys before wait-listing. These kidney transplants are usually recommended for patients older than the age of 60 years, diabetic patients older than the age of 40 years, and patients

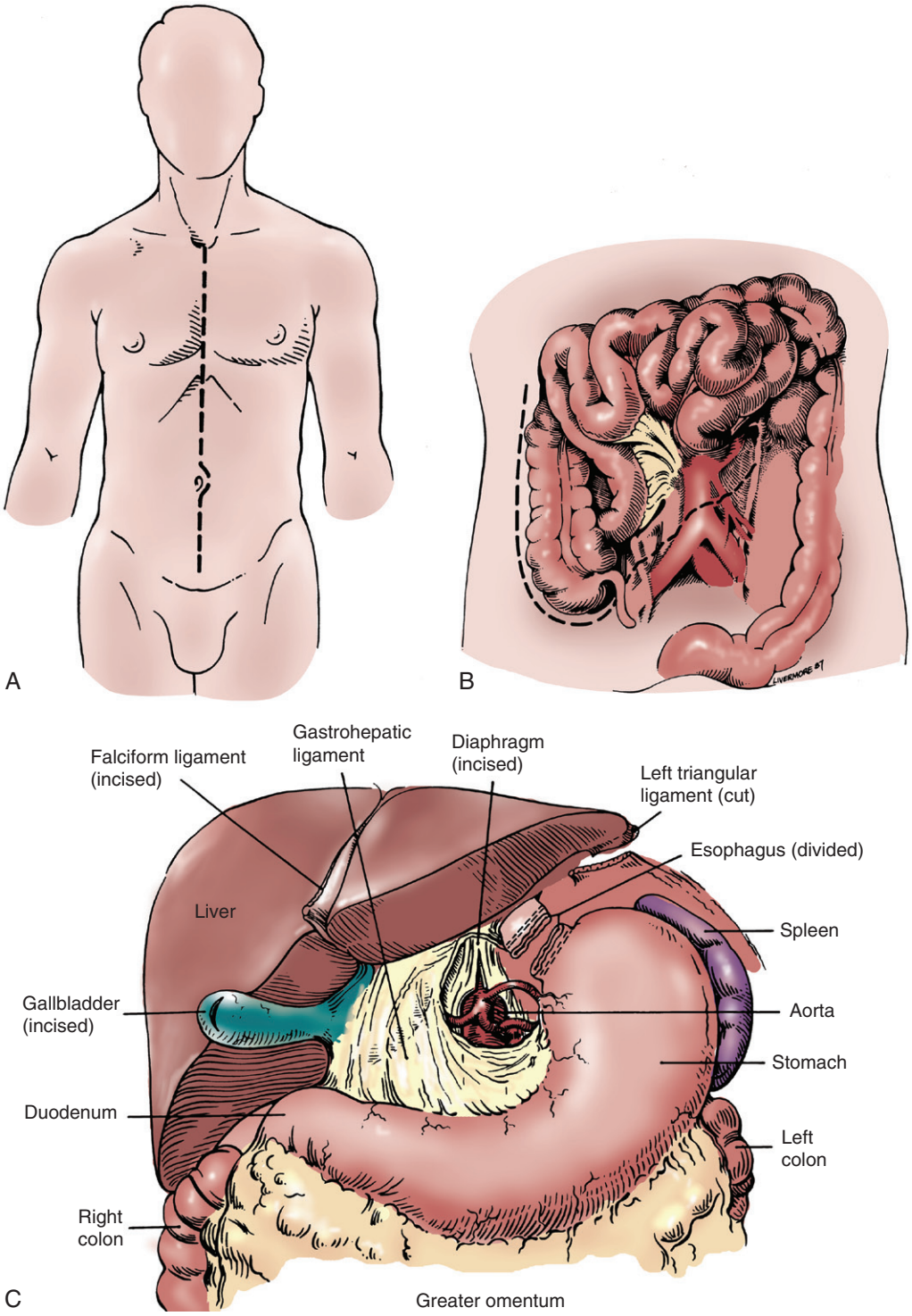


Figure 44–4. **A,** A total midline incision with splitting of sternum and diaphragm exposes all transplantable organs in the chest and abdomen. It also provides excellent exposure when retrieving only abdominal organs. **B,** The retroperitoneum is exposed as for a retroperitoneal lymphadenectomy. **C,** For multiple abdominal organ retrieval, the aorta is controlled above the celiac axis. The inferior vena cava (IVC) is controlled above the liver (not shown).

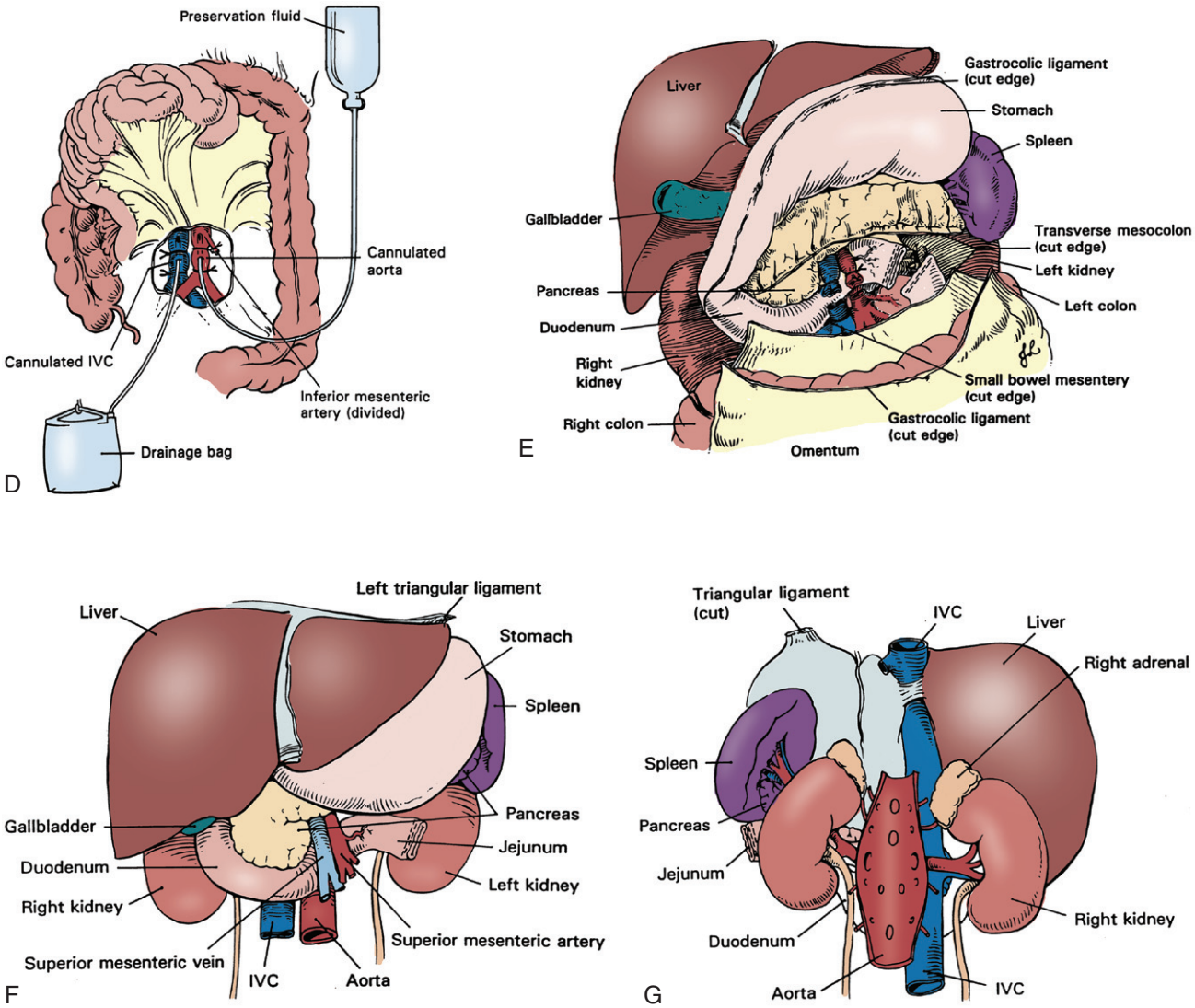


Figure 44–4, cont'd. **D,** The aorta and IVC are controlled below the renal vessels, heparin is administered to the donor, and the great vessels are cannulated. The proximal aorta is occluded, the IVC is vented into the chest or through the distal IVC cannula, and in situ flushing with an ice cold preservation solution is performed through the aortic cannula. **E,** The gastrocolic ligament is divided, the small bowel mesentery is divided along with the superior mesenteric artery and vein, and the small bowel is divided at the ligament of Treitz. **F,** The esophagus is divided, and, with further dissection, the en bloc specimen consisting of the liver, stomach, spleen, pancreas, both kidneys, aorta, and IVC is removed. **G,** The specimen is placed "face down" in a pan of slush and is separated, first, by splitting the aorta posteriorly between lumbar arteries to identify all renal arteries; second, by transecting the aorta between the superior mesenteric artery and the renal arteries; third, by splitting the anterior aortic wall between the renal arteries; fourth, by transecting the IVC just above the entrance of the renal veins; and fifth, by dividing the left renal vein where it enters the IVC. (**A** and **B,** From Barry JM. Cadaver donor nephrectomy. In: Novick AC, Streem SB, Pontes JL, editors. Stewart's operative urology. Baltimore: Williams & Wilkins; 1989. p. 294–300; **C-G,** from Barry JM. Donor nephrectomy. In: Marshall FF, editor. Textbook of operative urology. Philadelphia: WB Saunders; 1996. p. 235–47.)

who have significant dialysis access problems or who are unable to tolerate dialysis. The recipient age recommendation is lowered for those listed with an organ procurement agency with prolonged waiting times (Merion et al, 2005).

PREOPERATIVE ASSESSMENT

Just before kidney transplantation, the history, physical examination, and diagnostic studies of the recipient focus on a search for interval medical problems such as symptomatic cardiac disease, active infection, and the need for additional crossmatch testing because of recent blood transfusions or an out-of-date serum sample. Immunosuppression and infection prophylaxis protocols are assigned, a preliminary determination about the need for an intensive care unit bed is made, a final decision is made to perform the transplant operation, and the team queues up for the operating room. The quality of early renal function is directly correlated with cold ischemia time, and deceased donor kidney transplantation is done on an urgent basis.

PREPARATION OF KIDNEY GRAFT

A kidney graft removed from a living renal donor by an open technique requires little preparation by the kidney transplant recipient team because most of the preparation has been done in

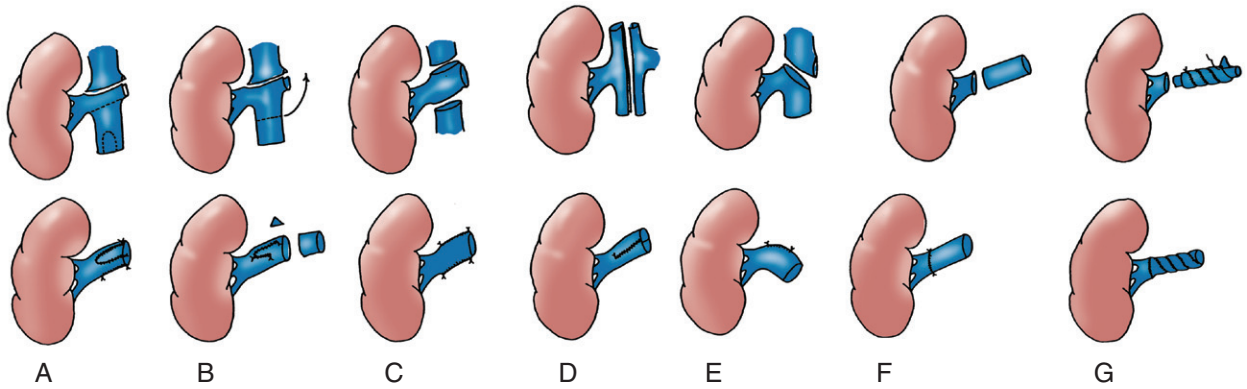


Figure 44–5. **A-G,** Methods of extending the right renal vein include modifications of the IVC and a free graft of donor external iliac vein. The first two methods are valuable when the cephalad portion of the right renal vein has been compromised by the separation of the liver graft from the kidney grafts. (**A** and **B,** From Barry JM, Lemmers MJ. Patch and flap techniques to repair right renal vein defects caused by cadaver liver retrieval for transplantation. J Urol 1995;153:1803; **C,** from Barry JM, Fuchs EF. Right renal vein extension in deceased kidney transplantation. Arch Surg 1978;113:300; **D** and **F,** from Barry JM, Hefty TR, Sasaki T. Clam-shell technique for right renal vein extension in cadaver kidney transplantation. J Urol 1988;140:1479; **E,** from Corry RJ, Kelley SE. Technic for lengthening the right renal vein of cadaver donor kidneys. Am J Surg 1978;135:867; **G,** from Nghiem DD. Spiral gonadal vein graft extension of right renal vein in living renal transplantation. J Urol 1989;142:1525.)

situ by the donor team. Because of the presence of significant amounts of perirenal fat, stapled vessels, and retraction of the renal vein into the renal hilum, significantly more bench work is required for kidneys removed laparoscopically. If not done by the LDN team, prompt identification of the renal artery and vein, removal of the staple lines, and rapid flushing of the kidney with ice cold preservation solution is the initial priority, followed by the final dissection.

For a deceased donor kidney, the short right renal vein can be extended with a variety of techniques that use the inferior vena cava or donor external iliac vein (Fig. 44–5). Before the use of donor inferior vena cava to provide extension of the right renal vein in deceased donor kidney transplants, the left kidney was preferred because of its longer renal vein. Techniques for the management of multiple renal arteries from deceased and living donors are shown in Figure 44–6.

RECIPIENT OPERATION

The usual responsibilities of the anesthesia and the surgical teams are described in Table 44–6.

A prophylactic antibiotic is administered just before surgery and continued postoperatively until the results of intraoperative cultures are known. If a nephrectomy or nephrectomies for autosomal dominant polycystic kidney disease are to be done at the same operation as the renal transplant, a fluoroquinolone antibiotic is often used instead of a cephalosporin because of better antibiotic penetration into renal cysts with the former (Elzinga et al, 1988). Immunosuppression is started just before or during surgery in the deceased kidney graft recipient and, in some programs, in the week before transplantation in the living donor kidney transplant recipient.

After the induction of anesthesia and the placement of a triple lumen central venous catheter, the genitalia and skin are prepared and a Foley catheter is placed in the bladder or bladder substitute. **It is helpful to have the catheter attached to a three-way drainage system that allows intraoperative filling and draining of the bladder, especially in a small recipient or in an individual who has a small, defunctionalized bladder or in a patient with perivesical scar tissue.** The bladder or bladder substitute is rinsed with a broad-spectrum antibiotic solution such as neomycin-polymyxin B and gravity filled. The catheter tubing is clamped until it is time to do the ureteroneocystostomy. A self-retaining ring retractor attached to the operating table that has been flexed and rotated toward the surgeon allows the operation to be performed by a surgeon and one assistant (Fig. 44–7). To prevent spinal injury, patients with significant back disease such as ankylosing spondylitis should be placed in a comfortable, padded position before anesthetic induction and table flexion avoided. Antibiotic irrigation is used liberally during the procedure. Central venous pressure is maintained between 5 and 15 cm H_2O with IV fluids. If fluid administration alone cannot maintain the mean arterial pressure at greater than 60 mm Hg and the systolic blood pressure greater than 90 mm Hg, respectively, a dopamine or dobutamine infusion is started.

Table 44–6.

Usual Responsibilities of Anesthesia and Surgical Teams during Renal Transplantation

ANESTHESIOLOGY	SURGERY
Anesthetic induction	Patient position
Central venous access	Bladder catheterization
Administration of antibiotics	Preliminary skin preparation
Administration of immunosuppressants	Surgical exposure of the operative site
Administration of heparin	Renal revascularization
Assurance of conditions of diuresis	Urinary tract reconstruction
	Wound closure

In adults and children who weigh more than 20 kg, a first kidney graft is usually placed extraperitoneally in the contralateral iliac fossa by way of a rectus-preserving Gibson or Rutherford Morison incision (Barry, 2007). This allows the renal pelvis and ureter to be the most medial structures in case subsequent urinary tract surgery is necessary on the kidney graft. Common exceptions to this principle are the obese recipient in whom it is easier to place a kidney graft in the right iliac fossa because of the more superficial iliac veins and the simultaneous pancreas and kidney transplant recipient in whom it is common to place the left kidney with its longer renal vein in the left iliac fossa. **If there is some doubt about whether or not there**

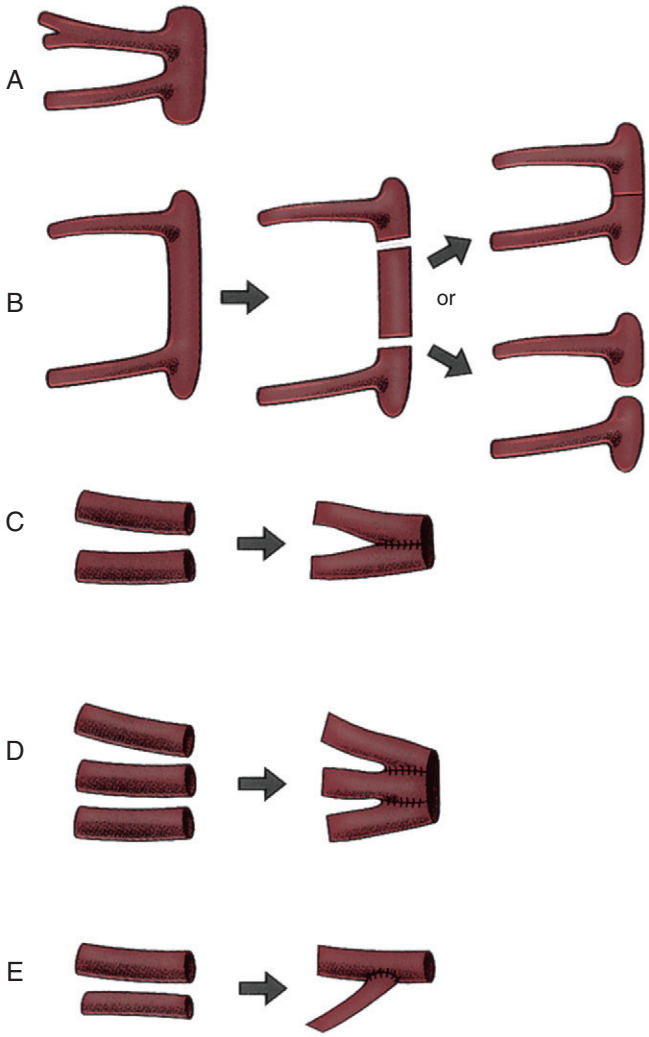


Figure 44–6. Preparation of the kidney transplant with multiple renal arteries. **A** and **B,** Use of aortic patches when the kidney is from a deceased donor. **C** and **D,** Pair of pants or three-legged pair of pants is used when an aortic patch is not available, such as when the kidney is from a living donor. **E,** Anastomosis of segmental renal artery to main renal artery. The segmental renal artery can also be anastomosed to the inferior epigastric artery using an end-to-end technique. (**A-E,** From Barry JM. Technical aspects of renal transplantation. In: Schrier RW, editor. Atlas of diseases of the kidney. Philadelphia: Current Medicine; 1998. p. 14.4.)

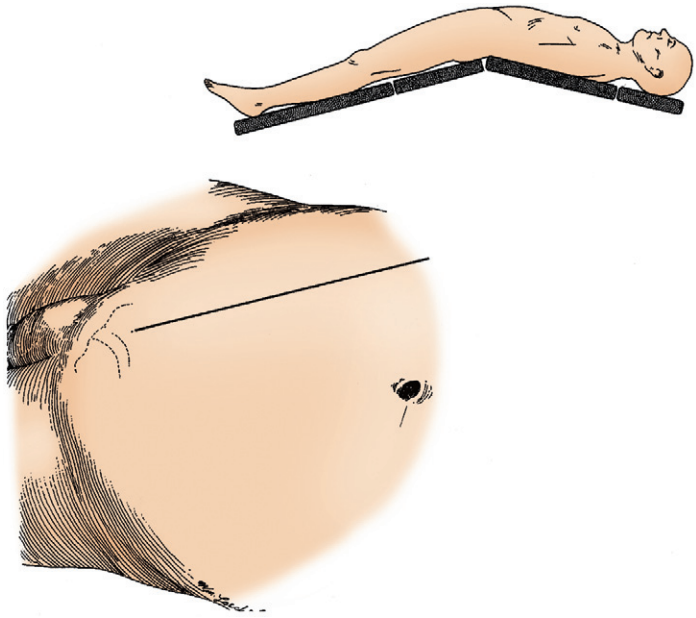


Figure 44–7. Patient position for kidney transplantation into right iliac fossa. Table flexion opens the iliac fossa and retropubic space, just as for radical cystectomy or open prostatectomy. Rotation of the table toward the surgeon, who stands on the patient's left side, assists in performance of the lateral aspects of the vascular anastomoses. (From Montie JE. Technique of radical cystectomy in the male. In: Marshall FF, editor. Textbook of operative urology. Philadelphia: WB Saunders; 1996. p. 399.)

will be enough room in the left pelvis of a small patient for a large kidney, placement of the kidney on the right side will allow access to a wider choice of arteries and veins for vascular reconstruction. In small children, this is accomplished by extension of the Gibson or Rutherford Morison incision to the right costal margin or by a midline abdominal incision. In men, the spermatic cord is preserved and retracted medially. In women, the round ligament is divided between ligatures. The recipient's target blood vessels are dissected. When the renal vein is short, it is helpful to completely mobilize the external and common iliac veins by dividing the gluteal and internal iliac veins between ligatures or large clips. These branches can be exposed by anterior retraction with a loop of heavy silk. Lymphatic vessels are divided between ligatures to prevent the development of postoperative lymphocele. **The surgeon must be careful not to mistake the genitofemoral nerve, which sometimes crosses the external iliac artery, for a lymphatic vessel.**

Before temporary vascular occlusion, heparin is commonly given intravenously to the recipient. During the vascular anastomosis, an infusion of mannitol is begun to act as a free radical scavenger and as an osmotic diuretic. Infusion of an electrolyte solution provides intraoperative volume expansion. The addition of an albumin infusion has been found to be helpful in promoting early renal function in the deceased donor kidney transplant (Dawidson et al, 1994). It is a common practice to keep the kidney transplant cool by wrapping it in a sponge containing crushed saline ice, dripping an ice-cold electrolyte solution on it, or placing it in a plastic bag or glove filled with slush. The renal artery is usually anastomosed to the end of the internal iliac artery or to the side of the external iliac artery (Fig. 44–8). Other possible locations for the arterial anastomosis are dictated by the clinical situation, and they include the common iliac artery, aorta, splenic artery, and native renal artery. Moderate arteriosclerosis of the internal iliac artery can be managed by endarterectomy. In the event of significant arteriosclerosis of that vessel, the renal artery is anastomosed end to side to the external iliac artery or to the common iliac artery. **A vascular punch is useful for creating a round hole in a rigid or arteriosclerotic vessel and in the common iliac artery or aorta of a child in order to prevent renal artery coaptation and thrombosis if hypotension occurs.**

When the pelvic vessels are unsuitable for renal revascularization, orthotopic renal transplantation with anastomosis of the renal artery to the splenic artery or native renal artery and venous reconstruction with the renal vein or inferior vena cava can be done (Gil-Vernet et al, 1989).

It is usually preferable to do the renal artery anastomosis first because it is the more critical of the two

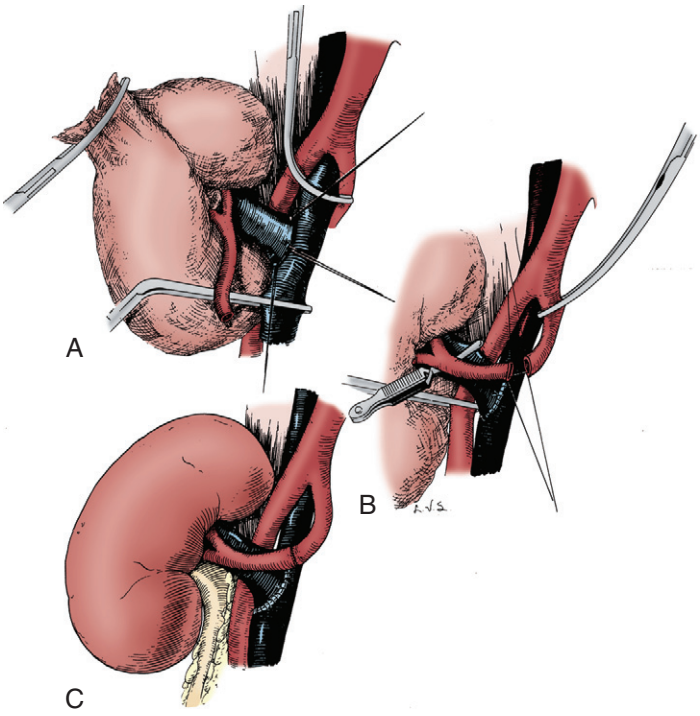


Figure 44–8. **A,** The renal vein is anastomosed to the external iliac vein, usually medial to the external iliac artery. When the recipient has a tortuous iliac artery, the venous anastomosis is best performed lateral to the bowed external iliac artery. **B,** In the absence of significant recipient arteriosclerosis, the renal artery is commonly anastomosed to the internal iliac artery with 5-0 or 6-0 monofilament, nonabsorbable sutures. Many prefer to perform the renal artery anastomosis before the venous anastomosis. If significant internal iliac arteriosclerosis is present or the contralateral renal artery has been used in a previous renal transplant in a man, the external or common iliac arteries become the target vessels for renal artery anastomosis. **C,** The completed venous and arterial anastomoses. (**A-C,** From Salvatierra O Jr. Renal transplantation. In: Glenn JF, editor. Urologic surgery. 4th ed. Philadelphia: JB Lippincott; 1991. p. 243–51.)

vascular anastomoses, the kidney is not tethered by the venous anastomosis, and venous occlusion can be delayed until after the renal artery anastomosis. This results in decreased iliac venous occlusion time and should reduce the risk of iliofemoral venous thrombosis. In cases where the renal vein is short and exposure is limited, it may be preferable to perform the venous anastomosis first. A man undergoing repeat renal transplantation with the prior transplant anastomosed to the contralateral internal iliac artery should not have the ipsilateral internal iliac artery used. This is to preserve blood supply to the corpora cavernosa and reduce the risk of iatrogenic impotence (Gittes and Waters, 1979). The renal vein, with or without an extension, is usually anastomosed end to side to the external iliac vein or to the junction of the external and common iliac veins. **When transplanting an adult kidney into the right retroperitoneum of a small child, the renal vein often has to be shortened to prevent redundancy with anastomosis to the inferior vena cava.**

Furosemide is commonly infused just before release of the vascular clamps. After renal revascularization, injection of verapamil, a calcium channel blocker, into the renal arterial circulation of the deceased donor kidney graft has been shown to protect the kidney from reperfusion injury (Dawidson et al, 1994).

Urinary tract reconstruction is usually by antireflux ureteroneocystostomy, of which there are several techniques (Stevens and Marshall, 1943; Politano and Leadbetter, 1958; MacKinnon et al, 1968; Konnak et al, 1975; Texter et al, 1976; Barry, 1983). **Most surgeons prefer an extravesical rather than the transvesical approach for ureteroneocystostomy because it is faster, a separate cystotomy is not required, and less ureteral length is necessary, thus ensuring a distal ureteral blood supply** (Figs. 44–9 and 44–10). Figure 44–9C demonstrates a rapid technique that can be used with or without a stent when the patient has a small bladder or the procedure must be quickly completed. **If a prior augmentation cystoplasty was done, the transplant surgeon will need to know the blood supply of the patch so as not to interfere with it at the time of transplantation.** Indications for ureteroureterostomy and pyeloureterostomy are short or ischemic allograft ureters, limited bladder capacity, or the surgeon's preference. Double-pigtail ureteral stents are used when there is concern about the ureteroneocystostomy technique or when ureteroureterostomy or pyeloureterostomy has been performed. The routine use of a ureteral stent for all cases has been shown to reduce the incidence of ureteral complications (Pleass et al, 1995; Mangus and Haag, 2004). Long-term results of renal transplantation into the valve bladder and other abnormalities of the lower urinary tract have been satisfactory (Luke et al, 2003; Mendizabel et al, 2005).

When a patient with an intestinal conduit undergoes renal transplantation (Surange et al, 2003), the kidney graft should be placed in such a way that it does not interfere with the flat surface at the stoma site and contribute to a poor fit of the urinary appliance and subsequent urinary leakage. The technique of ureteral implantation into an intestinal pouch is the same as that for ureteroneocystostomy. The pouch is irrigated free of mucus with an antibiotic solution, and the best site for the ureteral implantation is chosen with the pouch filled. Intraoperative identification of the conduit and subsequent ureteral anastomosis can be assisted by cannulation of the stoma with a 14-Fr Foley catheter and inflating the balloon with 3 to 4 mL of sterile water or staining the conduit with methylene blue. To avoid a kink in the allograft ureter, the kidney transplant can be placed upside down in the iliac fossa so that the ureter is pointing cephalad. The ureteral anastomosis is usually protected with a stent that is left in place for several weeks.

It is common practice to send swab culture specimens from the surface of the deceased donor kidney transplant and from the urinary bladder. It is unnecessary to do so from the surface of a living donor kidney unless there has been a break in sterile technique in the retrieval, perfusion, or transportation of the kidney.

When both kidneys from a deceased donor with marginal renal function are transplanted into the same recipient, one kidney can be transplanted into each iliac fossa by way of a vertical midline incision or by way of separate Gibson incisions, or both kidneys can be placed in the right retroperitoneum, one on top of the other (Masson and Hefty, 1998). This technique can also be used for simultaneous kidney and pancreas transplantation (Fridell et al, 2004). The first transplant can be anastomosed to the inferior vena cava and common iliac artery, and the second to the external iliac vein and external or internal iliac artery.

The transplantation of en bloc kidneys from a small child into an adult can be accomplished by (1) stapling the proximal donor aorta and IVC and anastomosing the distal stumps of these vessels to the recipient iliac vessels, (2) longitudinally splitting the donor aorta and IVC and anastomosing the vascular patches onto the recipient's iliac vessels, (3) excising a segment of external iliac artery and sewing the tube of donor aorta into the defect as an interposition graft, or (4) closing the cephalad IVC and inferior

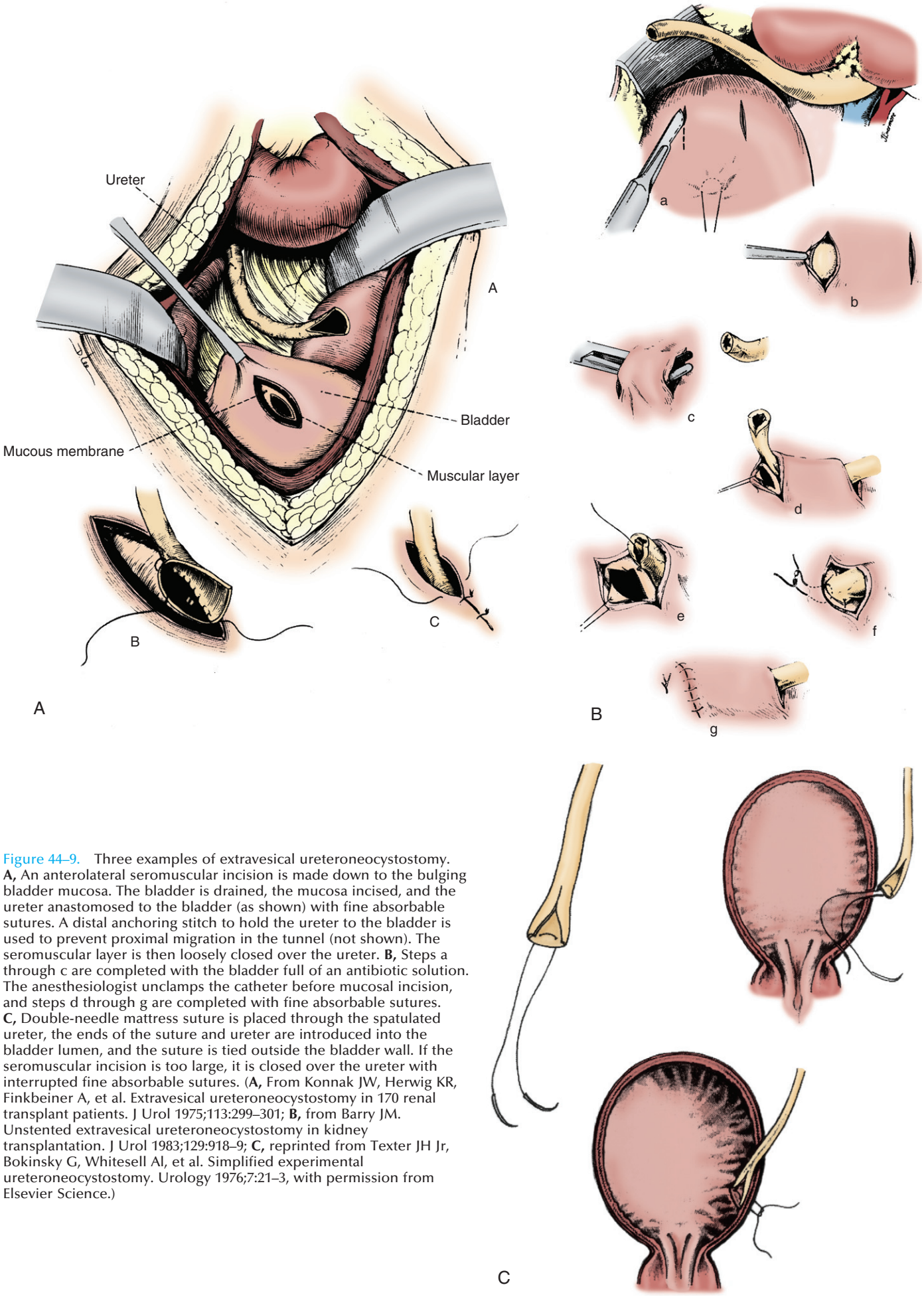


Figure 44–9. Three examples of extravesical ureteroneocystostomy. **A,** An anterolateral seromuscular incision is made down to the bulging bladder mucosa. The bladder is drained, the mucosa incised, and the ureter anastomosed to the bladder (as shown) with fine absorbable sutures. A distal anchoring stitch to hold the ureter to the bladder is used to prevent proximal migration in the tunnel (not shown). The seromuscular layer is then loosely closed over the ureter. **B,** Steps a through c are completed with the bladder full of an antibiotic solution. The anesthesiologist unclamps the catheter before mucosal incision, and steps d through g are completed with fine absorbable sutures. **C,** Double-needle mattress suture is placed through the spatulated ureter, the ends of the suture and ureter are introduced into the bladder lumen, and the suture is tied outside the bladder wall. If the seromuscular incision is too large, it is closed over the ureter with interrupted fine absorbable sutures. (**A,** From Konnak JW, Herwig KR, Finkbeiner A, et al. Extravesical ureteroneocystostomy in 170 renal transplant patients. J Urol 1975;113:299–301; **B,** from Barry JM. Unstented extravesical ureteroneocystostomy in kidney transplantation. J Urol 1983;129:918–9; **C,** reprinted from Texter JH Jr, Bokinsky G, Whitesell Al, et al. Simplified experimental ureteroneocystostomy. Urology 1976;7:21–3, with permission from Elsevier Science.)

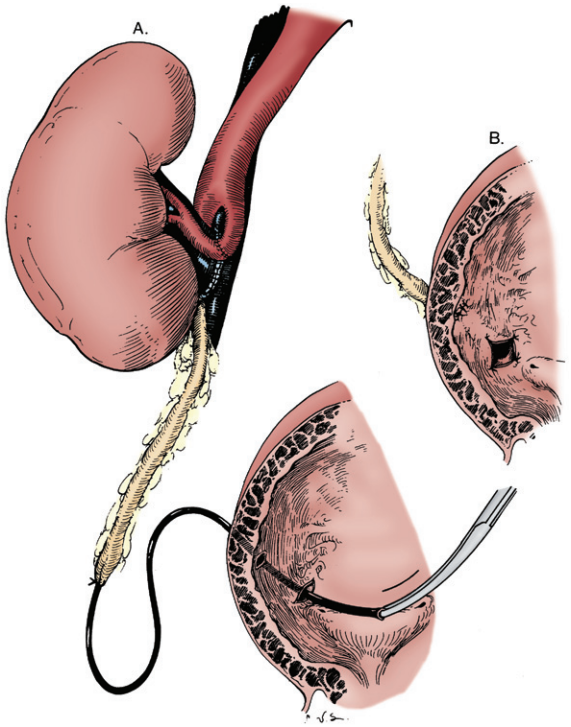


Figure 44–10. Transvesical ureteroneocystostomy. **A,** A No. 8-Fr catheter is passed through the submucosal tunnel and tied to the transplant ureter. **B,** The ureter is drawn through the tunnel, transected, and anastomosed to the bladder with fine absorbable sutures. The distal suture anchors the ureter to the bladder muscularis. Finally, the cystotomy is closed with one or two layers of absorbable sutures. (**A** and **B,** From Salvatierra O Jr. Renal transplantation. In Glenn JF, editor. Urologic surgery. 4th ed. Philadelphia: JB Lippincott; 1991. p. 243–51.)

aorta with lines of staples and anastomosing the distal donor IVC and proximal aorta to the recipient's common or external iliac artery and vein.

The uncomplicated renal transplantation can be closed by a variety of running or interrupted suture techniques with or without drains, although it is always easier to remove a drain than wish that one had been placed at operation. If the rectus-retracting approach has been used, it is not necessary to place any sutures in the rectus muscle; one simply closes the anterior rectus sheath after the external oblique, internal oblique, and transversus abdominis muscles and their fascial layers have been closed in the cephalad aspect of the wound. **A closed suction drain is recommended in the subcutaneous tissue of an obese patient.** A running absorbable subcuticular suture or the placement of absorbable dermal clips eliminates the need for subsequent suture or clip removal.

POSTOPERATIVE CARE

Fluid and Electrolyte Management

Postoperative fluid and electrolyte management are simple for patients with initial kidney graft function. IV fluid of 0.45% saline in 5% dextrose is given to replace estimated insensible losses, and 0.45% saline in 0% dextrose is given at a rate equal to the previous hour's urinary output. When the urinary output is high, this regimen reduces the probability of a glucose-driven diuresis. **An optional method of fluid management in the recipient of a living donor kidney transplant is a fixed-rate protocol of 125 to 200 mL/hr of 0.45 normal saline in 5% dextrose with an occasional fluid bolus if hypotension ensues** (Hatch et al, 1985). Serum electrolyte levels are monitored every 4 to 8 hours, and potassium is added to the IV solution when the serum potassium level declines to the middle of the normal range. When delayed graft function occurs, the previously described IV fluid is administered at a rate to maintain the central venous pressure at 10 to 15 cm H_2O for 2 to 3 hours, and furosemide is administered intravenously in an effort to induce a diuresis. The oliguric patient may require urgent treatment of hyperkalemia with IV calcium chloride, IV sodium bicarbonate, insulin and glucose, or dialysis.

If a diuresis has ensued and the next day's serum creatinine level is significantly reduced, a baseline radioisotope renogram is unnecessary. An ultrasonogram is indicated for delayed graft function, ipsilateral leg swelling, ipsilateral abdominal swelling, or a decreasing hematocrit. When oligoanuria occurs after renal transplantation, radioisotope renograms are commonly performed biweekly until the serum creatinine level begins to decrease without dialysis. If the radioisotope renogram deteriorates, a diagnostic renal biopsy is commonly done.

Management of Tubes and Drains

A urine culture is obtained just before catheter removal, and the patient is given a single dose of a broad-spectrum antibiotic at that time. If the urine culture is subsequently positive, culture-specific therapy is given for 10 to 14 days. The timing of catheter removal is variable, but most are removed within a week. A cystogram is optional. The closed suction drains are removed when the output is less than 50 mL/24 hr or in 3 weeks, whichever comes first. **If a ureteral stent was used to protect the urinary tract reconstruction, it is removed as an outpatient procedure a few weeks after the operation.** If the surgeon had attached the stent to the indwelling Foley catheter, it will come out as the Foley catheter is withdrawn.

Anticoagulation

Most patients undergoing renal transplantation meet the criteria for low-dose anticoagulation to prevent deep venous thrombosis. Patients with hypercoagulable states such as systemic lupus erythematosus, factor V Leiden mutation, prothrombin gene mutation, the anticardiolipin antibody syndrome, or deficiencies of protein C, protein S, or antithrombin III usually receive daily warfarin therapy after the discontinuance of heparin therapy.

RENAL ALLOGRAFT REJECTION

Histocompatibility

The histocompatibility systems of greatest importance in renal transplantation are the ABO blood group and the major histocompatibility complex (MHC) (Denton et al, 1999; Halloran, 2004). The donor and recipient must be ABO compatible because A and B substances are present on endothelial cells, and most individuals have antibodies to the red blood cell antigens they lack. A common exception is the transplantation of ABO blood group A_2 kidneys into blood group O and B recipients, who have low anti-A2 antibody levels (Alkhunaizi et al, 1999). A rare exception is the transplantation across major ABO

incompatibilities by recipient preparation with plasmapheresis to remove anti-A or anti-B antibodies, off-label use of the anti-CD 20 antibody rituximab with or without splenectomy to reduce antibody production, and intense induction immunosuppression (Takahashi, 2007; Warren et al, 2004).

The MHC antigens are glycoproteins on the cell membrane. They are encoded by MHC genes on the short arm of chromosome 6. Autosomal class I antigens are known as the HLA-A, HLA-B, and HLA-C antigens, and they are present on nearly all nucleated cells. They are detected by tissue typing T lymphocytes, usually with a DNA polymerase chain reaction amplification technique. HLA-DR, HLA-DQ, and HLA-DP antigens are class II antigens present on B lymphocytes, activated T lymphocytes, monocytes, macrophages, dendritic cells, and some endothelial cells. HLA-DR antigens are detected by tissue typing B lymphocytes. Testing for HLA-DQ and HLA-DP antigens is not routinely done. Recipient circulating cytotoxic antibodies against the MHC antigens of a specific donor are detected by pretransplantation crossmatching techniques, and a positive complement-dependent T-cell lymphocytotoxicity crossmatch is considered to be a contraindication to renal transplantation when the serum used is recently obtained from the transplantation candidate. **Protocols have been developed to use kidney transplants where the recipient has a positive crossmatch to the donor, and the crossmatch is rendered negative by plasmapheresis or immunoadsorption and immunoglobulin administration to permit an otherwise prohibited transplant to take place** (Jordan et al, 2004; Takahashi, 2007).

Because of inheritance patterns of the HLA antigens, each potential kidney graft recipient is a "half-match," or haploidentical, with her or his parents and children and has a 0.25 probability of HLA identity, a 0.50 probability of haploidentity, and a 0.25 probability of a total HLA mismatch with a sibling. Other than the cases of sibling HLA-identity, the influence of histocompatibility matching on graft survival has decreased because of more effective and less toxic immunosuppressive regimens (Halloran, 2004). Concern has been expressed about abandonment of the 0 HLA antigen mismatch allocation scheme for deceased donor kidney transplants that has been in effect for several years because of the significantly increased PRA levels after first kidney graft failure in recipients of HLA-mismatched kidneys. This is especially important in young recipients who have a high likelihood of needing a subsequent kidney transplant (Meier-Kriesche et al, 2009).

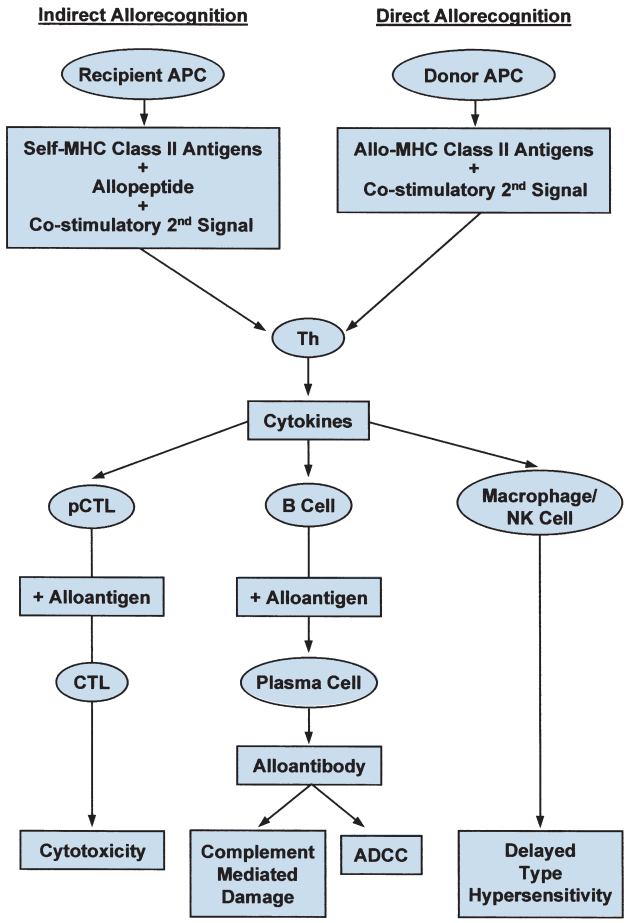


Figure 44–11. Cellular interactions in renal transplant rejection. CD4+ helper T cells (Th) are activated by antigen-presenting cells (APCs) that express incompatible major histocompatibility complex (MHC) class II antigens and provide a costimulatory second signal. The Th cells produce lymphokines that promote proliferation of B cells, maturation of CD8+ cytotoxic T lymphocytes (CTLs), activation of macrophages and natural killer (NK) cells, and induction of MHC class II antigens on renal cells. ADCC, antibody-dependent cell-mediated cytotoxicity; pCTL, precursor cytotoxic T cell.

Incompatibility with MHC antigens on donor tissue stimulates the immune response (Fig. 44–11). Class II antigens on donor dendritic cells can directly stimulate recipient CD4+ helper T cells and initiate the rejection process. These MHC antigens are also processed by recipient macrophages, which present these class II alloantigens to the CD4+ helper T cells. **A second, or costimulatory, signal must be provided by cognate ligands on the antigen-presenting cell to fully activate CD4+ helper T cells.**

These two signals cause the CD4+ helper T cells to secrete cytokines, most importantly, the T-cell growth factor interleukin-2 (IL-2), and to express anew cell surface IL-2 receptors. The cascade of events within the CD4+ helper T cell, after receiving the alloantigenic signal through the T-cell receptor and the costimulatory signal, is calcineurin activation; dephosphorylation of the nuclear factor of activated T cells, enabling it to enter the nucleus and bind to the IL-2 gene promoter; and the production of IL-2.

IL-2, the third signal, stimulates the IL-2 receptor, and this induces lymphocytes to proliferate. IL-2 is necessary for the maturation of CD8+ cytotoxic T-cell precursors into cytotoxic T cells. IL-2 also stimulates antigen-activated helper T cells to release other lymphokines such as IL-3, IL-4, IL-5, IL-6, and interferon-γ. IL-3 is a growth factor for bone marrow stem cells. IL-4, IL-5, and IL-6 enable alloantigen-activated B cells to mature into plasma cells, which produce cytotoxic antibodies against the MHC molecules of the graft. Interferon-γ activates the cytodestructive capabilities of macrophages, augments natural killer cell activity, and induces the expression of MHC class II antigens on kidney graft cells.

Classification of Rejection

Hyperacute rejection occurs immediately after renal revascularization. It is an irreversible process mediated by preformed circulating cytotoxic antibodies that develop after pregnancy, blood transfusions, or an earlier failed transplantation. Hyperacute rejection is rare when the microlymphocytotoxicity crossmatch between recipient serum and donor lymphocytes is negative.

Table 44–7.
Mechanisms of Action of Immunosuppressants

IMMUNOSUPPRESSANT	MECHANISM OF ACTION	INTERFERES WITH …
Glucocorticoids	Reduce transcription of cytokine genes	Intercellular signaling
Azathioprine	Inhibits purine synthesis	Lymphocyte proliferation
Mycophenolate mofetil	Inhibits purine synthesis	Lymphocyte proliferation
Sirolimus	Inhibits cell cycle progression	Lymphocyte proliferation
Tacrolimus	Inhibits calcineurin and IL-2 production	Intracellular signaling
Cyclosporine	Inhibits calcineurin and IL-2 production	Intracellular signaling
Monomurab CD3	Depletes T lymphocytes	Antigen recognition
Equine antithymocyte globulin	Depletes T lymphocytes	Antigen recognition
Rabbit antithymocyte globulin	Depletes T lymphocytes	Antigen recognition
Alemtuzumab (off label)	Depletes T and B lymphocytes	Antigen recognition and antibody production
Rituximab (off label)	Depletes B lymphocytes	Antibody production
Bortezomib (off label)	Depletes plasma cells	Antibody production
Basiliximab	Blocks IL-2 receptor	Intercellular signaling
Daclizumab	Blocks IL-2 receptor	Intercellular signaling

IL-2, interleukin-2.

Accelerated rejection is mediated by humoral and cellular components of the immune response. It occurs within days to weeks and often does not respond to antirejection therapy.

Acute rejection can occur any time after transplantation. **The symptoms of acute kidney transplant rejection are those of "the flu" accompanied by pain over an enlarged kidney graft, hypertension, decreased urinary output, fluid retention, increased serum creatinine levels, and radioisotope renography indicating decreased renal blood flow, glomerular filtration, and tubular function.** Acute pyelonephritis must be ruled out by urinalysis and subsequently negative urine culture. Needle biopsy of the kidney graft is the standard to confirm the diagnosis of acute rejection. The typical histologic findings of acute renal allograft rejection are mononuclear cellular infiltration, tubulitis, and vasculitis. The Banff classification, or some modification of it, is now accepted as the standard schema for diagnosing rejection (Solez et al, 2008). Biopsy samples are usually analyzed for C4d deposition. If it is present, a diagnosis of concurrent antibody-mediated rejection is made.

Chronic rejection is characterized by a gradual decline in renal function associated with interstitial fibrosis, vascular changes, and minimal mononuclear cell infiltration. A positive B-cell crossmatch or a positive flow crossmatch against donor B or T cells is considered to be predictive of chronic rejection and poorer long-term graft survivals (Ghasemian et al, 1997; Kimball et al, 1998; Haririan et al, 2009).

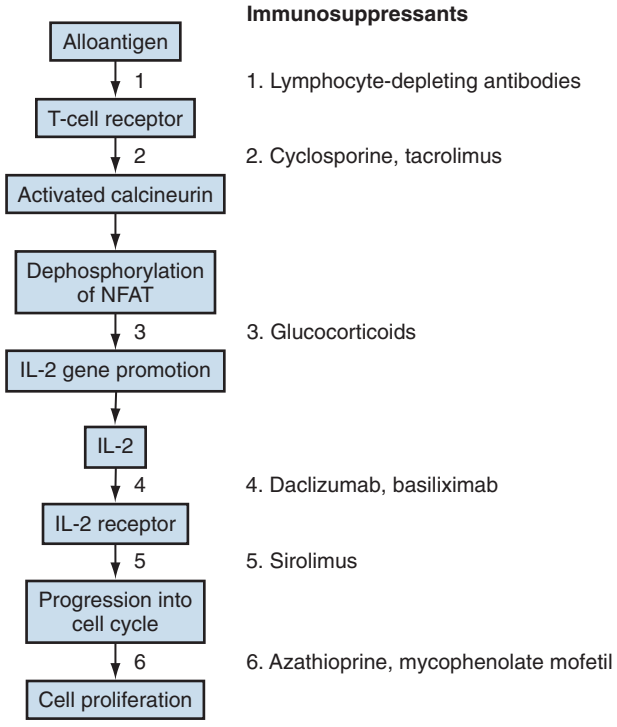


Figure 44–12. Sites of action of commonly used immunosuppressants. IL-2, interleukin-2; NFAT, nuclear factor of activated T cells.

Immunosuppression

Immunosuppressive drug regimens commonly include a glucocorticoid in combination with other drugs such as cyclosporine or tacrolimus (calcineurin inhibitors), azathioprine or mycophenolate mofetil (purine antagonists), and sometimes antilymphocyte antibody preparations. The most common maintenance immunosuppression is with a glucocorticoid, tacrolimus, and mycophenolate mofetil. Sirolimus inhibits cell cycle progression, and it is used in combination with glucocorticoids or with cyclosporine or tacrolimus in combination with glucocorticoids. The mechanisms and sites of action of clinically useful immunosuppressant medications are listed in Table 44–7 and illustrated in Figure 44–12. An example of an immunosuppression algorithm is presented in Figure 44–13. Antilymphocyte antibodies such as muromonab CD3, rabbit antithymocyte globulin, equine antithymocyte globulin, antibodies to the CD25 component of the IL-2 receptor such as daclizumab and basiliximab, or the off-label lymphocyte depleting antibody to CD52, alemtuzumab, are used by some as part of induction immunosuppressive regimens to allow the kidney graft to recover from preservation injury before the administration of the nephrotoxic calcineurin inhibitors cyclosporine or tacrolimus (Halloran, 2004).

Glucocorticoid therapy is usually started at high doses and then rapidly tapered, and sometimes discontinued, during the first few weeks after engraftment. Cyclosporine and tacrolimus have similar mechanisms of action, effectiveness, and cost but slightly different side effect profiles, and they are not used together. Both

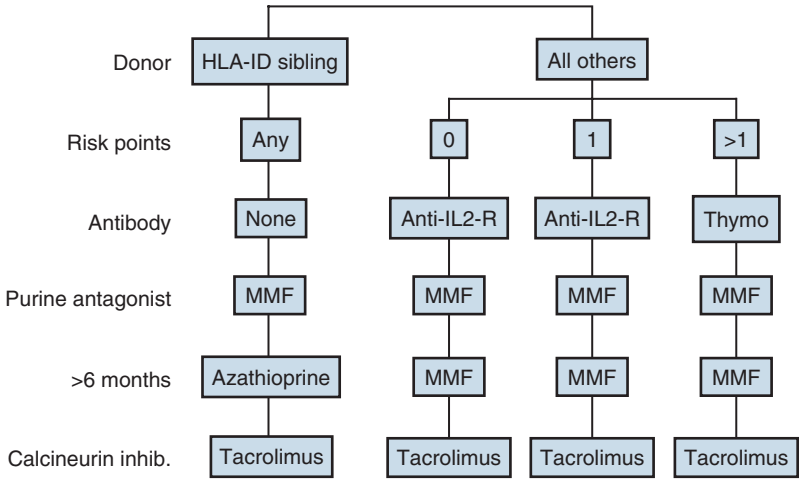


Figure 44–13. Example of kidney transplant immunosuppression protocol. This algorithm is based on donor and recipient histocompatibility, immunologic risk factors, and immunosuppressant mechanism of action. All patients receive glucocorticoids and undergo protocol biopsies beginning at 1 week if ABO incompatible. Assignment of immunologic risk points: 2 points each for greater than 50% panel reactive antibody, positive flow crossmatch; 1 point each for prior transplant, 6 HLA antigens mismatched, delayed graft function, African-American ethnicity, lupus nephropathy; subtract 1 point for age older than 60 years. Anti-IL2-R, interleukin-2 receptor antibody; HLA, human leukocyte antigen; Id, identical; Inhib; inhibitor; MMF, mycophenolate mofetil; Thymo, rabbit antilymphocyte antibody.

cyclosporine and tacrolimus are metabolized mainly by the cytochrome P-450 enzyme system. Substances that inhibit that system result in increased blood or plasma levels of these drugs (Table 44–8). Diltiazem and ketoconazole have been used to reduce calcineurin inhibitor dosing and cost while maintaining blood levels and the immunosuppressive effect (Patton et al, 1994). Drugs known to induce that enzyme system usually result in increased metabolism of cyclosporine and tacrolimus and decreased whole-blood or plasma levels and immunosuppressive effects. A determination of cyclosporine or tacrolimus blood levels is helpful when toxicity or insufficient immunosuppression is suspected. Drug interactions with sirolimus are similar to those with the calcineurin inhibitors. Higher and more frequent doses of cyclosporine and tacrolimus are usually necessary in children. Azathioprine and mycophenolate mofetil have similar mechanisms of action, but mycophenolate mofetil is more effective, more toxic, and more expensive. Table 44–9 lists the common organ system targets for toxicity of the drugs used for maintenance immunosuppression. Some programs taper patients off one or more of the maintenance immunosuppressants after many months of stable graft function, and others use lymphocyte-depleting antibody induction and calcineurin inhibitor monotherapy (Tan et al, 2009). The goals of such protocols are to decrease and possibly eliminate some maintenance immunosuppressants in order to reduce the long-term complications of malignancy, bone loss, infection, and post-transplant diabetes mellitus, as well as to reduce the costs of transplantation.

Conventional treatment for acute renal allograft rejection is high-dose pulses of glucocorticoids. Treatment of steroid-resistant rejection is with lymphocyte-depleting antibody preparations such as equine antithymocyte globulin, rabbit antithymocyte globulin, and alemtuzumab. In some cases, recalcitrant rejection and graft salvage can be achieved by conversion of one baseline immunosuppressive regimen to another, even in the presence of steroid-resistant rejection (Jordan et al, 1997).

Commonly used regimens to prevent infections and peptic ulcer disease are listed in Table 44–10. CMV disease is a significant problem after renal transplantation, and CMV-seronegative recipients have better outcomes than CMV-seropositive recipients, provided the kidney donor is also CMV seronegative. Prophylaxis against CMV disease is possible with ganciclovir, valganciclovir, or valacyclovir (Preiksaitis et al, 2005).

Future immunomodulation strategies in transplantation include blockade of T-cell costimulation, blockade of T-cell adhesion molecules, blockade of T-cell accessory molecules, peptide-mediated immunosuppression, gene therapy, and induction of tolerance (Starzl et al, 2003).

Table 44–8.

Potential Drug Interactions with Cyclosporine and Tacrolimus

Drugs That Affect Plasma or Whole Blood Concentrates		Drugs with Nephrotoxic Synergy
DECREASE	INCREASE	
Rifampin	Diltiazem	Gentamicin
Rifabutin	Verapamil	Tobramycin
Isoniazid	Nicardipine	Vancomycin
Phenobarbital	Erythromycin	Azapropazone
Phenytoin	Clarithromycin	Amphotericin B
Carbamazepine	Ketoconazole	Cisplatin
	Fluconazole	Melphalan
	Itraconazole	Cimetidine
	Clotrimazole	Ranitidine
	Bromocriptine	Diclofenac
	Danazol	
	Cimetidine	
	Methylprednisolone	
	Metoclopramide	

PROBLEMS

Early Graft Dysfunction

Early graft dysfunction can be due to infection, renal allograft rejection, urinary or vascular obstruction, cyclosporine or tacrolimus nephrotoxicity, hyperglycemia, or dehydration. The cause can usually be sorted out by following the suggestions in Table 44–11 and Table 44–12. Fever is common with infection and/or rejection. Physical examination for sinusitis, dental abscess, pneumonia, cholecystitis, appendicitis, diverticulitis, and kidney graft tenderness can be quickly performed. An ultrasound examination that includes a Doppler flow study can demonstrate renal allograft enlargement, the presence or absence of hydronephrosis, and blood flow in and out of the kidney graft. In addition, it can assess the gallbladder and native kidneys for stones and obstruction. Tremor can be a clue

Table 44–9.

Common Organ System Targets for Toxicities of Immunosuppressant Therapy

	PREDNISONE	CYCLOSPORINE	TACROLIMUS	SIROLIMUS	AZATHIOPRINE	MYCOPHENOLATE
Central nervous system	+	+	+	0	0	0
Gastrointestinal system	+	+	+	0	+	+
Kidney	0	+	+	0	0	0
Hematopoietic	0	0	0	+	+	+
Skin	+	+	0	0	0	0
Endocrine	+	+	+	+	0	0
Dyslipidemia	+	+	0	+	0	0
Wound healing	+	0	0	+	0	0

Table 44–10.

Postoperative Infection and Peptic Ulcer Prophylaxis

PROBLEM	COMMONLY USED DRUG PROPHYLAXIS	ALTERNATE(S)
Urinary tract infection	Trimethoprim-sulfamethoxazole × 3 mo	Nitrofurantoin
Pneumocystis pneumonia	Trimethoprim-sulfamethoxazole × 3 mo	Pentamidine inhalant
Oral candidiasis	Clotrimazole lozenges × 1-3 mo	Nystatin troches
Vaginal candidiasis	Clotrimazole vaginal inserts × 1-3 mo	Nystatin inserts
HSV	Acyclovir × 3 mo	Ganciclovir, valacyclovir, famciclovir
Primary CMV disease	Gancyclovir ± CMV immune globulin × 4 mo	Valacyclovir, acyclovir
Recurrent CMV disease	Ganciclovir × 3 mo or during antibiotic therapy	Valacyclovir, acyclovir
Peptic ulcer disease	H_2 receptor antagonist + antacid if symptomatic	

CMV, cytomegalovirus; HSV, herpes simplex virus.

Table 44–11.

Sorting Out Early Graft Dysfunction

CAUSE	PHYSICAL FINDING	INITIAL DIAGNOSTICS BASED ON SUSPICION
Infection	Fever, chills, normal or ↓ BP, ± pulmonary findings, ± native or kidney transplant tenderness	Chest radiograph, urinalysis, smears and cultures of sputum, urine, wound drainage, and blood; ultrasonogram of abdomen and kidney graft
Rejection	± Fever, normal or ↑ BP, normal or ↑ CVP, kidney transplant tenderness	Ultrasound of kidney graft, allograft biopsy
Obstruction	Vital signs normal unless infected, ± kidney transplant tenderness	Irrigate bladder catheter, ultrasound and Doppler flow study of kidney graft
Calcineurin inhibitor toxicity	Afebrile, normal or ↑ BP, normal CVP, ± tremor	Calcineurin inhibitor blood level
Hyperglycemia	Afebrile, ↓ BP, ↓ CVP	Blood sugar
Dehydration	Afebrile, ↓ BP, ↓ CVP	IV fluid bolus

BP, blood pressure; CVP, central venous pressure; IV, intravenous.

to calcineurin inhibitor toxicity that can be confirmed by determining the blood level of the calcineurin inhibitor. The pseudorejection of hyperglycemia can be quickly diagnosed with a bedside blood glucose determination. Dehydration can also be quickly diagnosed at the bedside and treated with a 5- to 10-mL/kg bolus of IV fluid.

Vascular Complications

Immediate vascular complications include kinking of the kidney graft's artery or vein, suture line stenosis, or thrombosis. Thrombosis of the kidney graft may occur because of hyperacute rejection or thrombophilia. Renal artery stenosis after renal transplantation is usually diagnosed because of hypertension that is progressively difficult to manage, with or without impaired renal function. Color Doppler sonography has a high sensitivity and specificity for detecting transplant renal artery stenosis (Radermacher et al, 2000). The causes are atheroma, faulty suture technique, clamp trauma, and immunologic mechanisms (Lacombe, 1988). The finding of a bruit over the kidney graft is unreliable because it is a common sign after renal transplantation with or without hypertension; however, the detection of a new bruit may

Table 44–12.

Differentiation of Calcineurin Inhibitor Toxicity from Acute Rejection

CHARACTERISTIC	TACROLIMUS OR CYCLOSPORINE TOXICITY	ACUTE REJECTION
Fever	No	Yes
Urinary output	Usually maintained	Decreased
Graft tenderness	No	Yes
Graft size	Stable	Increased
Serum creatinine level rise	Slow	Rapid
Cyclosporine/tacrolimus blood level	High	Normal or low
Graft biopsy	May be normal	Cellular infiltration, vasculitis, tubulitis

be significant. **Surgical intervention for transplant renal artery stenosis is difficult, with a significant risk of technical failure, and percutaneous transluminal angioplasty, with or without endoluminal stent placement, has become the initial treatment of choice** (Nicita et al, 1998).

Renal allograft rupture is rare and requires immediate operation. It is usually due to acute rejection or renal vein thrombosis. If it is due to the former, rejection crisis treatment and operative repair with bolstered mattress sutures, administration of topical thrombotic agents, and the use of synthetic glue and polyglactin mesh wrap can result in graft salvage (Chopin et al, 1989). If it is due to renal vein thrombosis, graft salvage with thrombectomy and repair of graft rupture is rare and allograft nephrectomy is usually necessary (Richardson et al, 1990).

Allograft Nephrectomy

The indications for allograft nephrectomy are to remove a symptomatic irreversibly rejected kidney transplant and, in the case of a chronically rejected asymptomatic graft, to withdraw immunosuppression and to prevent the development of anti-HLA antibodies that could delay or prevent a subsequent transplantation.

The usual approach is through the original incision. Within the first month after transplantation, allograft nephrectomy is a straightforward procedure and it is usually possible to remove all of the transplanted tissue. After 4 to 6 weeks, a dense fibrous reaction surrounds the kidney transplant and the procedure can be a formidable one. It is usually accomplished with the subcapsular technique and knowledge of the vascular reconstruction that was done at the time of transplantation. The surgeon must be prepared to occlude the vascular pedicle with a large vascular clamp, transect the vascular pedicle distal to the clamp, and either separately ligate the renal veins and arteries or oversew the stumps of the vessels with 4-0 or 5-0 vascular suture. The renal capsule and the intravesical ureteral stump are left behind. The wound is liberally irrigated with an antibiotic solution, a suction drain is commonly placed, and the wound is closed as described earlier in the section "Recipient Operation."

Perioperative antibiotic therapy is discontinued, changed, or continued on the basis of intraoperative culture results, and immunosuppression is discontinued within a few weeks. Cyclosporine or tacrolimus is withdrawn immediately; azathioprine, mycophenolate mofetil, or sirolimus is continued for 4 to 6 weeks because of residual allograft tissue, especially in the case of a subcapsular nephrectomy; and prednisone is gradually tapered and withdrawn with the following formula: 1 week of glucocorticoid taper for every month of immunosuppression for a maximum of 6 weeks.

Hematuria

Hematuria immediately after transplantation is usually due to catheter trauma or urinary tract reconstruction. If it cannot be controlled with catheter irrigation, endoscopy with clot evacuation and fulguration of the bleeding site or sites in the bladder is necessary. If those treatments fail, surgical exploration is indicated.

Late hematuria can be due to medical renal disease in the kidney graft, infection, calculus, or malignancy. If hematuria persists after treatment of a documented urinary tract infection, a standard hematuria work-up with microscopy for red blood cell casts or dysmorphic red blood cells should be done, followed, if necessary, by imaging of the native kidneys and kidney transplant, cystoscopy, a bladder wash for cytologic examination, and pertinent urothelial biopsies.

Fluid Collections

Most fluid collections after renal transplantation are incidental findings on baseline ultrasound examinations and require no treatment (Pollak et al, 1988). An algorithm for the evaluation and management of perigraft fluid collections is shown in Figure 44–14. When fluid collections are large or associated with dilatation of the collecting system, pain, fever, or an unexplained decline in renal function, an ultrasonically guided aspiration can be diagnostic. If the fluid is purulent, microscopic examination of the fluid for pus cells and organisms is done and antibiotic treatment is initiated. In the event of infection, cyclosporine or tacrolimus therapy is usually continued; azathioprine, mycophenolate mofetil, or sirolimus therapy is discontinued; and prednisone is reduced to less than 15 mg/day. Although percutaneously placed tube drainage can be effective, openly surgical drainage is often necessary for infected fluid collections. Lymph, urine, and blood can be differentiated from each other by creatinine and hematocrit determinations. Lymph has a creatinine concentration that is the same as that of serum, urine has a creatinine concentration higher than that of serum and approaching that of

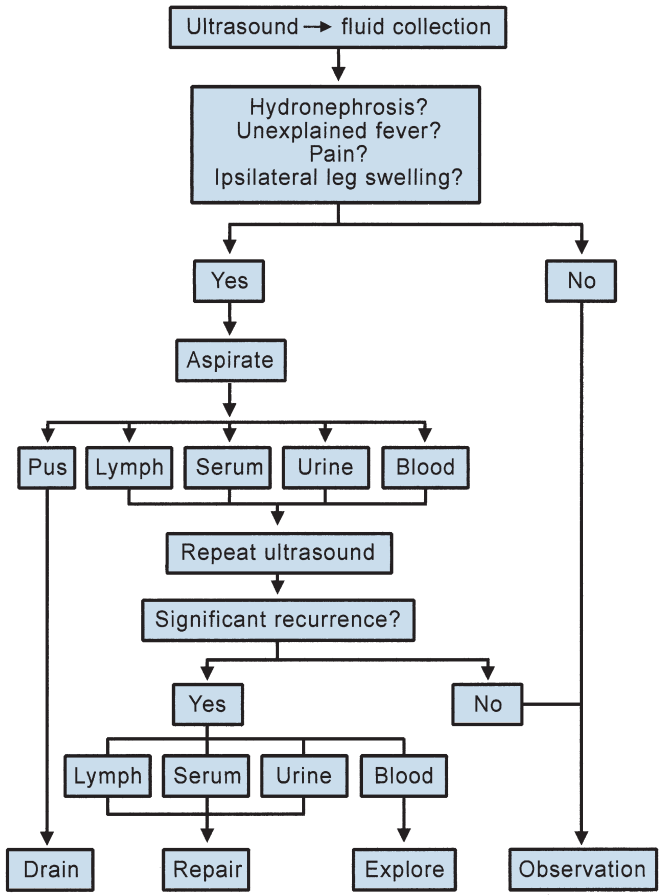


Figure 44–14. Algorithm for evaluation and treatment of perigraft fluid collection. (Modified from Barry JM. Renal transplantation. In: Krane RJ, Siroky MB, Fitzpatrick JM, editors. Clinical urology. Philadelphia: JB Lippincott; 1994. p. 325.)

bladder urine, and blood has a high hematocrit level when compared with the other two fluids.

If the symptoms or the urinary tract obstruction are relieved by aspiration and there is no recurrence of the fluid, no further treatment is necessary. If blood reaccumulates, exploration and control of bleeding are usually necessary.

If an uninfected lymphocele recurs, it is usually treated by unroofing it into the peritoneal cavity by either open or laparoscopic technique (Schweitzer et al, 1972; Gill et al, 1995). **Lymphoceles that are lateral to the kidney are difficult to access laparoscopically** (Gruessner et al, 1995). Success has been reported with percutaneous sclerosis (Rivera et al, 1996). If the lymphocele is infected, open drainage is often necessary.

Urinary extravasation often requires open surgical repair. A retrograde or CT cystogram will document leakage at the cystotomy or ureteroneocystostomy site. If a retrograde cystogram does not show extravasation, contrast CT may suggest, and percutaneous antegrade pyelography will confirm, a site of extravasation from the ureter or renal pelvis. Excretory urography may also be used but is often impractical in this setting because of inadequate renal function. Some urinary leaks at the ureteroneocystostomy site may be managed simply by bladder catheter drainage, with or without percutaneous nephrostomy; percutaneous or retrograde passage of a double-J ureteral stent; or performance of another ureteroneocystostomy. If open repair is necessary, retrograde pyelography and the passage of a ureteral catheter into the native ureter at the time of repair will facilitate the identification of that structure if it is necessary for ureteroureterostomy or ureteropyelostomy. Urinary tract repair is usually protected with a stent for 6 weeks and sometimes a small nephrostomy tube or an omental flap, or both. A suction drain is placed, and antibiotic therapy based on culture and sensitivity results is administered.

Obstruction and Stones

Figure 44–15 is an algorithm for evaluating hydronephrosis in the transplanted kidney. Ureteral obstruction in the immediate postoperative period is due to technical error, edema, a blood clot, unsuspected donor calculus, or perigraft fluid collection. Although endourologic techniques can be successful, a technical error is usually repaired with a stented ureteroneocystostomy. Edema usually resolves within a few days, and ureteral blood clots lyse with naturally produced urokinase.

The management of fluid collections was discussed previously.

Late causes of urinary tract obstruction are periureteral fibrosis, calculi, tumor, fungus ball, lymphocele, chronic ischemia of the distal ureter with stricture, and BK-related polyomavirus nephropathy. Ureteroneocystostomy meatal stenosis can be managed by endoscopic ureteral meatotomy, percutaneous ureteral dilatation followed by stent placement (Hobart et al, 2000), or open surgical repair. **There are reports of long-term success of the endourologic treatment of transplant ureteral stenosis** (Benoit et al, 1993; Streem et al, 1988). Failures are usually apparent within 1 year of treatment, and short, anastomotic strictures are the lesions most successfully treated with these techniques. If the stricture is distal and allograft ureteral length is sufficient, a repeat ureteroneocystostomy will do. For recurrent or long strictures, ureteropyelostomy and ureteroureterostomy as described earlier are reasonable options. Vesicopyelostomy, vesicocalycostomy, and interposition of a small bowel segment between the renal pelvis and the bladder (Orton and Middleton, 1982; Ehrlich et al, 1983; Del Pizzo et al, 1998) have all been used as surgical treatments for an obstructed allograft ureter.

Causes of urinary tract calculi after renal transplantation are considered to be persistent hyperparathyroidism, recurrent urinary

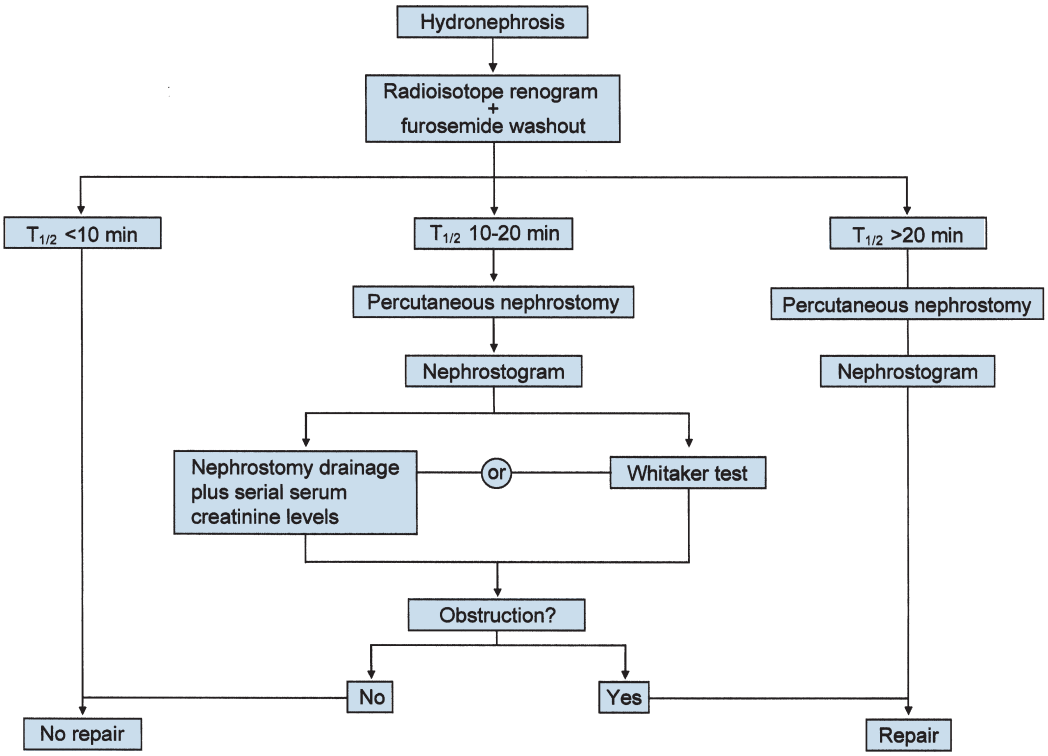


Figure 44–15. Algorithm for evaluation of renal transplant hydronephrosis.

tract infections, a foreign body such as a suture or staple, obstruction, a habitual decreased fluid intake, and distal renal tubular acidosis (Hefty, 1991). **Because the renal transplant is denervated, the patient will not experience typical renal colic and the diagnosis is suspected when renal function suddenly deteriorates or transplant pyelonephritis occurs.** Upper tract calculi are managed by the same techniques as calculi in the normal urinary tract; however, negotiation of the transplanted ureter may be difficult or impossible because of tortuosity, thus favoring percutaneous techniques. Extracorporeal shock wave lithotripsy has been used successfully with clever positioning of the patient in the shock wave path (Wheatley et al, 1991). Small bladder calculi are managed by transurethral extraction and irrigation with or without lithotripsy. If a cystolithotomy is selected as the procedure for a medium to large hard stone, the surgeon must take care not to damage the ureteroneocystostomy.

Urinary Tract Infection

Urinary tract infections after renal transplantation are present in up to 40% of patients and have been associated with increased mortality after transplantation (Chuang et al, 2005). In addition to immunosuppression and an indwelling bladder catheter, the following risk factors are often present: advanced recipient age, use of deceased donor kidney, female gender, diabetes mellitus, and preexisting urinary tract abnormalities. During the first 3 months after renal transplantation, prophylactic broad-spectrum antibiotics such as trimethoprim-sulfamethoxazole are usually prescribed. This drug combination also prevents pulmonary *Pneumocystis carinii* infection. Trimethoprim interferes with the tubular secretion of creatinine, and this can cause an increase in the serum creatinine levels. The urinary tract infections that occur months after transplantation are usually benign and respond readily to conventional antimicrobial therapy, guided by urine culture and sensitivity. **Patients with pyelonephritis should be screened with ultrasonography for obstruction or stone.** Graft dysfunction accompanied by fever can be due to either acute pyelonephritis or acute rejection, and it is important to differentiate between the two because increased immunosuppression during an episode of acute pyelonephritis can result in significant sepsis.

Candida cystitis often responds to foreign body removal and bladder irrigations with amphotericin B with or without oral fluconazole (Wise, 2002). Cyclosporine and tacrolimus doses usually have to be reduced when fluconazole is given because fluconazole interferes with the metabolism of both those immunosuppressants. Tissue-invasive infections often require IV fluconazole or amphotericin B.

Hemorrhagic cystitis can be due to adenovirus, cytomegalovirus, or BK polyomavirus (Paduch, 2007). Diagnosis is usually by real-time polymerase chain reaction (PCR).

BK polyomavirus infection can cause significant nephropathy in 6% of infected recipients (Trofe et al, 2004). It can be transmitted from the donor or be reactivated in the recipient by immunosuppression. Recognition and treatment can be challenging because the nephropathy often mimics a rejection crisis, and antirejection therapy can exacerbate the disease. It can also present as ureteral obstruction due to fibrosis. PCR of both blood and urine can identify the infection. Renal biopsy is often inconclusive. Treatment consists of reduction of immunosuppression and antiviral therapy such as cidofovir, which has significant nephrotoxicity (Williams et al, 2005).

Vesicoureteral Reflux

Although there is some controversy about the need for antireflux ureteroneocystostomy in kidney transplantation, common urologic thinking is that reflux of infected bladder urine or high-pressure reflux is damaging to a kidney. **The indications for antireflux surgery of the kidney transplant ureter are the same as those for nontransplanted patients** (Reinberg et al, 1990). If the reflux is due to high-pressure voiding, relief of the bladder outlet obstruction or augmentation cystoplasty with intermittent catheterization must be considered. Ureteral advancement techniques, ureteroureterostomy to a nonrefluxing native ureter, and submucosal injection techniques are all possible therapies.

Erectile Dysfunction

Erectile dysfunction after renal transplantation is common (Malavaud et al, 2000). **Factors unique to the transplant recipient are side effects from immunosuppression and a reduction of cavernosal blood supply by the renal arterial anastomosis** (Table 44–13). Sirolimus-treated men have been shown to have lower serum testosterone levels, higher follicle-stimulating hormone (FSH) and luteinizing hormone (LH) concentrations, and no difference in serum prolactin levels when compared with non–sirolimus-treated controls (Fritsche et al, 2004).

Treatment options for transplant recipients with erectile dysfunction are similar to those for the immunocompetent patient (Table 44–14). Sildenafil has been shown to improve GFRs in kidney transplant recipients (Rostaing et al, 2000) and not to alter blood levels of cyclosporine or tacrolimus (Cofan et al, 2002). Intracorporeal injections of vasoactive drugs and implantation of penile prostheses have successfully treated this problem (Lasaponara et al, 2004); however, the transplant recipient must be warned of the increased risk of infection when either of these invasive treatment options is used.

If a penile prosthesis is chosen as the most appropriate therapy, the following criteria are reasonable: stable graft function without a rejection crisis for at least 6 months; low doses of maintenance immunosuppressants; a low probability of device malfunction; no intra-abdominal components; minimal tissue dissection; no skin or urinary tract infections; prophylactic antibiotic therapy (parenteral, intraurethral, and wound irrigation); and postoperative oral antibiotics for 2 weeks. When a stress steroid protocol is used, 25 mg of prednisone (or its equivalent) are given with the preoperative medications and 12 and 24 hours later. Maintenance glucocorticoid therapy is resumed on the second postoperative day. The oral doses of cyclosporine or tacrolimus and azathioprine, mycophenolate mofetil, or rapamycin are not altered. The IV doses of cyclosporine and tacrolimus are one third the oral doses, and they are infused over 24 hours. The IV doses of azathioprine and mycophenolate mofetil are the same as the oral doses.

Pregnancy and Childbearing

After successful kidney transplantation, levels of FSH, LH, and testosterone usually become normal and spermatogenesis improves (Akbari et al, 2003; Kheradmand and Javadneia, 2003). **Among male recipients who have fathered children, there has**

Table 44–13.

Potential Causes of Erectile Dysfunction after Renal Transplantation

ANATOMIC LOCATION	EXAMPLES	MECHANISMS
Central		
Antihypertensives	Clonidine	α_2 Agonist
	Methyldopa	α_2 Agonist, ↑ prolactin
	Propranolol	β Antagonist
Peptides/amino acids	Prednisone	↓ ACTH
↓ Testosterone	Cimetidine	↑ Prolactin
	Cyclosporine	↑ Prolactin
	Sirolimus	Testis atrophy
Anxiety	Stress	↑ Norepinephrine
Autonomic/peripheral nerves	Diabetes mellitus	Axon injury
	Uremia	Axon injury
Cavernosal blood supply		
Internal iliac arterial tree	Renal artery anastomosis	↓ Penis blood flow
Accelerated arteriosclerosis	Prednisone, cyclosporine, propranolol, diabetes mellitus	↑ Cholesterol
Antihypertensives	Any	↓ Penis blood pressure and blood flow
Diuretics	Any	↓ Blood volume and penis blood flow
Cavernosal smooth muscle	Diabetes mellitus, ↑ cholesterol	Impair nitric oxide–mediated relaxation
	Cyclosporine, tacrolimus	↑ Thromboxane A_2
Tunica albuginea of penis	Propranolol	Peyronie disease

Modified from Barry JM. The evaluation and treatment of erectile dysfunction following organ transplantation. Semin Urol 1994;12:147.

Table 44–14.

Treatment Options for Transplant Recipients with Erectile Dysfunction

Psychotherapy/ counseling	Alternate sexual techniques
	Stop alcohol use
	Stop tobacco use
Medication changes	Treat hypertension with calcium antagonists, angiotensin-converting enzyme inhibitors, or α_1 blockers
	Change cimetidine to ranitidine, famotidine, or nizatidine
	Glucocorticoid withdrawal, if possible
Medication additions, if indicated by work-up	Testosterone replacement
	Thyroid replacement
	Bromocriptine
	Type 5 phosphodiesterase inhibitors
Vacuum erection devices	—
Intracavernous injections	Prostaglandin E_1
Vascular procedures	Angiodilation
	Revascularization
Penile prostheses	Malleable
	Mechanically jointed
	Inflatable without prevesical reservoir

Modified from Barry JM. The evaluation and treatment of erectile dysfunction following organ transplantation. Semin Urol 1994;12:147; and Barry JM. Male sexuality in renal transplant recipients. Transplant Immunol Lett 2000;16:7.

been no increase in congenital abnormalities in the offspring; however, it is recommended that impregnation be delayed for at least 1 year after transplantation (Armenti et al, 1998).

Successful renal transplantation usually restores fertility in premenopausal women. In a report based on thousands of pregnancies in renal transplant recipients, Davison and Milne (1997) reported the following: 94% of the conceptions that continued beyond the first trimester ended successfully; 50% of the deliveries were preterm; 30% of the women developed hypertension, preeclampsia, or both; intrauterine growth retardation occurred in about 20%; and rejection crises occurred in 10%. **There were no frequent or predominant abnormalities in the children, the transplanted kidney rarely caused dystocia, and the transplanted kidney was not injured during vaginal delivery.** A more recent observational study of 16,195 female kidney transplant recipients documented a markedly lower pregnancy rate and higher fetal loss rate than reported in the general U.S. population during the same time (Gill et al, 2009). Pregnancy safety information for immunosuppressive drugs is listed in Table 44–15. Guidelines for successful pregnancy are good general health for 2 years after transplantation, minimal proteinuria, no hypertension, no rejection, no urinary tract obstruction, nearly normal renal function, and low doses of maintenance immunosuppressants.

Pulmonary Infection

Pneumonia in the immunosuppressed kidney transplant recipient is usually due to common bacterial pathogens, but *Legionella, Nocardia,* mycobacteria, viruses, parasites *(Pneumocystis),* and fungi can all be etiologic agents.

Cancer

Kidney transplant recipients are more likely to develop cancer than age-matched subjects in the general population and patients wait-listed for deceased donor renal transplantation. Among 35,765 first-time recipients of deceased or living donor renal transplants, the rates for most malignancies were higher after kidney transplantation when compared with the general population and with 46,106 patients wait-listed for kidney transplantation. This was especially true for Kaposi sarcoma, non-Hodgkins lymphomas, nonmelanoma skin cancers, and kidney cancer (Kasiske et al, 2004.) A more recent registry report has

Table 44–15.

Pregnancy Safety and Immunosuppressants

	PREGNANCY CATEGORY
Glucocorticoids	C
Azathioprine	D
Mycophenolate mofetil	D
Sirolimus	C
Cyclosporine	C
Tacrolimus	C
Monomurab CD3	C
Antithymocyte globulin	C
Rituximab	C
Bortezomib	D
Alemtuzumab	C
Daclizumab	C
Basiliximab	C

B, no fetal risk in animals, no controlled studies; C, fetal risk cannot be ruled out; D, evidence of fetal risk.

Data from Physician's desk reference. 63rd ed. Montvale (NJ): Thomson PDR; 2009. p. 439, 625, 762, 1226, 2313, 2389, 2625, 3264; and U.S. Food and Drug Administration. <www.fda.gov> [accessed 03.09.09].

shown no increase in the incidence of prostate cancer after kidney transplantation (Webster et al, 2007).

Although Bacille Calmette-Guérin (BCG), a live, attenuated bacterium, has been used successfully to treat superficial bladder cancer in kidney transplant recipients (Palou et al, 2003), it should be used with caution, if at all, in immunocompromised transplant recipients because of the risk of systemic infection and the likelihood of diminished therapeutic response. Absorbed thiotepa may have an additive myelosuppressive effect if the patient is also taking azathioprine, mycophenolate mofetil, or sirolimus.

Enterocystoplasty has become recognized as a risk factor for carcinoma in the reconstructed bladder, and it is reasonable to begin bladder cancer surveillance 5 years after the augmentation procedure (Nahas et al, 1999).

Medical Vascular Complications

Nonsurgical hypertension after renal transplantation is common. Causes of this include medications (glucocorticoids, cyclosporine, and tacrolimus); intrinsic renal disease; and rejection.

In spite of aggressive preoperative assessment and treatment, myocardial infarction and stroke continue to be leading causes of death in these patients. Prednisone and cyclosporine increase cardiovascular risk because of the hyperlipidemia associated with these drugs, and post-transplant hyperlipidemia should be treated aggressively with dietary changes and, if necessary, antilipid medications.

New Diabetes Mellitus

New diabetes occurs in a significant percentage of kidney transplant recipients (Opelz and Dohler, 2009). **This is due to the diabetogenic effects of glucocorticoids and calcineurin inhibitors.** The incidence of insulin-dependent post-transplant diabetes mellitus is significantly higher in patients treated with tacrolimus than in those treated with cyclosporine.

CONCLUSIONS

Renal transplantation is the best therapy for most patients with ESRD. Morbidity and mortality have been significantly reduced by attention to pretransplantation evaluations, donor surgery, kidney preservation, recipient selection, recipient surgery, histocompatibility, immunosuppression, and the successful management of complications. **Organ shortage continues to be a significant problem.** The induction of tolerance and the successful use of xenografts remain elusive goals.

Key Points

- The incidence of end-stage renal disease (ESRD) is greater than any urologic malignancy except prostate cancer.
- More patients die annually of ESRD than of any urologic malignancy.
- The first long-term success with human kidney transplantation occurred in 1954.
- Medicare coinsurance has been one of the most significant advances for the treatment of patients with ESRD.
- Preliminary evaluation of ESRD patients for renal transplantation is important to prevent wastage of kidney grafts because of transplantation into unsuitable recipients.
- Protocols are evolved to deal with the issues of ABO incompatibility and positive crossmatches between donors and recipients.
- Laparoscopic-assisted donor nephrectomy has reduced disincentives for living renal donors.
- Urologists must be aware of the urologic problems that may prevent or impair renal transplant technical success.
- Urologists must be aware of the potential genitourinary problems of transplant recipients.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter 45

Urinary Lithiasis: Etiology, Epidemiology, and Pathogenesis

Margaret S. Pearle, MD, PhD ● Yair Lotan, MD

Epidemiology of Renal Calculi
Physicochemistry
Mineral Metabolism
Pathogenesis of Upper Urinary Tract Calculi

Although stone disease is one of the most common afflictions of modern society, it has been described since antiquity. With Westernization of global culture, however, the site of stone formation has migrated from the lower to the upper urinary tract and the disease once limited to men is increasingly gender blind. Revolutionary advances in the minimally invasive and noninvasive management of stone disease over the past 2 decades have greatly facilitated the ease with which stones are removed. However, surgical treatments, although they remove the offending stone, do little to alter the course of the disease. Indeed the overall estimated annual expenditure for individuals with insurance claims corresponding to a diagnosis of nephrolithiasis was nearly $2.1 billion in 2000, reflecting a 50% increase since 1994 (Pearle et al, 2005). Given the frequency with which stones recur, the development of a medical prophylactic program to prevent stone recurrences is desirable. To this end, a thorough understanding of the etiology, epidemiology, and pathogenesis of urinary tract stone disease is necessary.

EPIDEMIOLOGY OF RENAL CALCULI

The lifetime prevalence of kidney stone disease is estimated at 1% to 15%, with the probability of having a stone varying according to age, gender, race, and geographic location. **In the United States, the prevalence of stone disease has been estimated at 10% to 15%** (Norlin et al, 1976; Sierakowski et al, 1978; Johnson et al, 1979). Using data derived from the U.S. National Health and Nutrition Examination Survey dataset (NHANES II and III), Stamatelou and colleagues (2003) established a 5.2% prevalence of kidney stone disease from 1988 to 1994, which represents a 37% increase from 1976 to 1980, for which a 3.8% prevalence rate was determined. The finding of an increase in the prevalence of stone disease has been observed by others (Norlin et al, 1976; Yoshida and Okada, 1990; Serio et al, 1999; Trinchieri et al, 2000). In a unique dataset derived from a series of nationwide surveys conducted by the Japanese Society on Urolithiasis Research in cooperation with the Japanese Urological Association, the incidence of first-time stone episodes in the Japanese population has been determined over a 40-year time period (Yasui et al, 2008). The fifth such survey, reported in 2008, estimated the annual incidence of first-time stone events in 2005 and determined trends in stone prevalence using the previous surveys from 1965, 1975, 1985, and 1995. The authors found an increase in the age-adjusted annual incidence of first-time stone events, from 54.2 per 100,000 in 1965 to 114.3 per 100,000 in 2005. Although the incidence increased in all age groups and in both men and women, the age of peak incidence shifted in men from 20 to 49 years in 1965 to 30 to 69 years in 2005 and in women from 20 to 29 years in 1965 to 50 to 79 years in 2005.

Gender

Stone disease typically affects adult men more commonly than adult women. By a variety of indicators including inpatient admissions, outpatient office visits, and emergency department visits, men are affected two to three times more often than women (Hiatt et al, 1982; Soucie et al, 1994; Pearle et al, 2005). However, there is some evidence that the difference in incidence between men and women is narrowing. Using the National Inpatient Sample dataset representing hospital discharges, Scales and colleagues (2005) found that although overall population-adjusted discharges for a diagnosis of renal or ureteral calculus increased by only 1.6% from 1997 to 2002, discharges for women increased by 17%, whereas discharges for men decreased by 8.1%. This trend reflects a change in the ratio of male-to-female discharges from 1.7 in 1997 to 1.3 in 2002. Indeed, in 2002 hospital discharges were the same for men and women in this dataset. Whether trends in hospital discharges accurately reflect trends in the overall prevalence of the disease, however, is not clear. Stamatelou and colleagues (2003) also noted a slight decrease in the male-to-female ratio of stone disease, from 1.75 (between 1976 and 1980) to 1.54 (between 1988 and 1994) using the NHANES dataset.

Race/Ethnicity

Racial/ethnic differences in the incidence of stone disease have been observed. **Among U.S. men,** Soucie and colleagues (1994) **found the highest prevalence of stone disease in whites, followed by Hispanics, Asians, and African-Americans, who had prevalences of 70%, 63%, and 44% of whites, respectively.** Among U.S. women, the prevalence was highest among whites but lowest among Asian women (about half that of whites). Others found an even higher differential (threefold to

fourfold) between whites and African-Americans (Sarmina et al, 1987). Mente and colleagues (2007) attempted to identify genetic influences on stone disease by comparing stone prevalence among different ethnic groups residing in the same geographic region. Using Europeans (Caucasians) as the reference group, the relative risk of calcium stones was higher in individuals of Arabic (OR 3.8, 95% CI 2.7 to 5.2); West Indian (OR 2.5, 95% CI 1.8 to 3.4); West Asian (OR 2.4, 95% CI 1.7 to 3.4); and Latin American (OR 1.7, 95% CI 1.2 to 2.4) origin and significantly lower in those of East Asian (OR 0.4, 95% CI 0.3 to 0.5) and African (OR 0.7, 95% CI 0.5 to 0.9) descent. Interestingly, despite differences in prevalence of stone disease according to ethnicity, Maloney and colleagues (2005) observed a remarkably similar incidence of metabolic abnormalities between white and nonwhite stone formers from the same geographic region, although the distribution of abnormalities differed, suggesting that dietary and other environmental factors may outweigh the contribution of ethnicity in determining stone risk.

The gender distribution of stone disease varies according to race. Sarmina and colleagues (1987) **noted a male-to-female ratio among whites of 2.3 and among African-Americans of 0.65.** Michaels and colleagues (1994) also noted a reversal of the male predisposition to stone disease in Hispanics and African-Americans, reporting a male-to-female ratio of 1.8 among Asians, 1.6 among whites, 0.7 among Hispanics, and 0.5 among African-Americans, among a group of patients undergoing extracorporal shock wave lithotripsy. Soucie and associates (1994) observed a similar trend in the male-to-female ratio of the lifetime incidence of stone disease of 3.4 among Asians, 2.6 among whites, 2.1 among Hispanics, and 1.8 among African-Americans, although the actual ratios for each racial group differed in the two studies. Dall'era and colleagues (2005) reviewed emergency department records to identify patients presenting with symptomatic renal or ureteral calculi and found a male-to-female ratio of 1.17 among Hispanic patients compared with 2.05 for white patients.

Age

Stone occurrence is relatively uncommon before age 20 but peaks in incidence in the fourth to sixth decades of life (Marshall et al, 1975; Johnson et al, 1979; Hiatt et al, 1982). It has been observed that women show a bimodal distribution of stone disease, demonstrating a second peak in incidence in the sixth decade of life, corresponding to the onset of menopause (Marshall et al, 1975; Johnson et al, 1979). This finding and the lower incidence of stone disease in women compared with men have been attributed to the protective effect of estrogen against stone formation in premenopausal women, owing to enhanced renal calcium absorption and reduced bone resorption (McKane et al, 1995; Nordin et al, 1999). Indeed, Heller and colleagues (2002) identified lower urinary saturation of calcium oxalate and brushite in women compared with men. Moreover, urinary calcium was lower in women than in men until age 50, after which it reached equivalence in the two groups. Estrogen-treated postmenopausal women had lower urinary calcium and saturation of calcium oxalate than untreated women. However, others have observed a decreasing incidence of stone disease in women from a peak in the late 20s until age 50, after which it remained constant (Hiatt et al, 1982; Curhan et al, 1993). Yasui and colleagues (2008) observed a change in the peak incidence of stone disease in Japanese women from ages 20 to 29 in 1965 to ages 50 to 79 in 2005.

Alternatively, Fan and colleagues (1999) found that androgens increased and estrogens decreased urinary and serum oxalate in an experimental rat model, perhaps accounting for the reduced risk of stone formation in women. However, van Aswegen and colleagues (1989) found lower levels of urinary testosterone in stone formers compared with non–stone-forming control subjects, further confusing the issue.

Geography

The geographic distribution of stone disease tends to roughly follow environmental risk factors; **a higher prevalence of stone disease is found in hot, arid, or dry climates such as the mountains, desert, or tropical areas.** However, genetic factors and dietary influences may outweigh the effects of geography. Finlayson (1974) reviewed several worldwide geographic surveys and found that areas of high stone prevalence included the United States, British Isles, Scandinavian and Mediterranean countries, northern India and Pakistan, northern Australia, Central Europe, portions of the Malay peninsula, and China. Within the United States, **Mandel and Mandel** (1989a, 1989b) **identified the highest rates of hospital discharge for patients with calcium oxalate stones in the Southeast and for uric acid stones in the East, among the veteran patient population.** Soucie and colleagues (1994) **found increasing age-adjusted prevalence rates in both men and women going from north to south and west to east, with the highest prevalence observed in the Southeast** (Fig. 45–1). After controlling for other risk factors, the authors determined that ambient temperature and sunlight were independently associated with stone prevalence (Soucie et al, 1996).

Climate

Seasonal variation in stone disease is likely related to temperature by way of fluid losses from perspiration and perhaps by sunlight-induced increases in vitamin D. Prince and Scardino (1960) noted

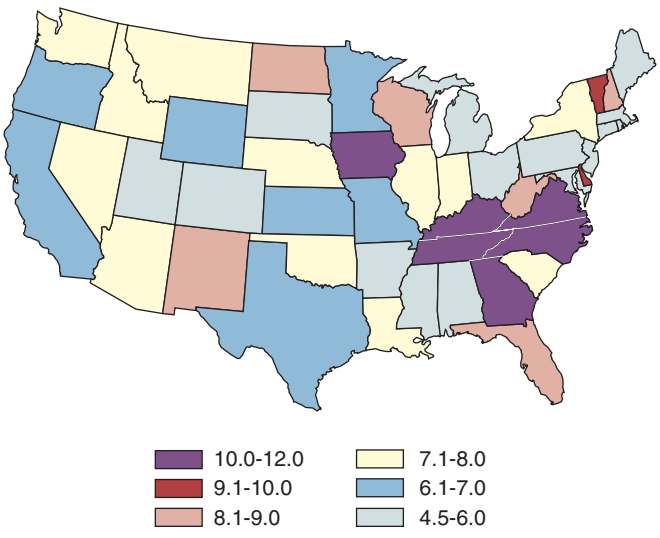


Figure 45–1. Geographic distribution of urinary tract stone disease in the U.S. veteran population from 1983 to 1986. Data are expressed as urinary tract stone patients per 1000 hospital discharges. (From Mandel NS, Mandel GS. Urinary tract stone disease in the United States veteran population: II. Geographical analysis of variations in composition. J Urol 1989;142:1516.)

the highest incidence of stone disease in the summer months, July through September, with the peak occurring within 1 to 2 months of maximal mean temperatures (Prince et al, 1956). Likewise, Bateson (1973) reported a peak incidence of stone disease between December and March in Australia, corresponding to the summer season. Using data obtained from the Taiwan National Health Insurance Research Database (1999-2003), Chen and colleagues analyzed monthly inpatient and outpatient medical benefit claims for a primary diagnosis of renal or ureteral calculi or renal colic and found that the peak incidence of stone-related claims occurred in July through September, with a sharp decline in claims in October (Chen et al, 2008). Ambient temperature, atmospheric pressure, and hours of sunshine all correlated with monthly stone-related claims, but after adjusting for seasonality, month, and trend, ambient temperature was found to be the most important determinant of stone-related events.

The study of military personnel translocated to desert locations has provided a unique opportunity to study the effect of climate on a defined population. Pierce and Bloom (1945) reported that American soldiers in an undisclosed desert location had an increase in symptomatic episodes of renal colic during the summer season. Another study of military personnel who developed symptomatic stones after arrival in Kuwait and Iraq disclosed a mean time interval to stone formation of 93 days (Evan et al, 2005). Finally, Parry and Lister (1975) measured urinary calcium and magnesium levels in soldiers before and 10 days after transfer to the Persian Gulf and noted increased urinary calcium levels from baseline in those soldiers transferred during the summer months but not among those transferred during the "cold season," which was attributed to sunlight-induced increased production of 1,25-dihydroxyvitamin D_3 ($1,25[OH]_2D_3$). Thus it is likely that climate and geography influence the prevalence of stone disease indirectly, through effects on temperature and possibly sunlight.

Brikowski and colleagues (2008) constructed two alternate models describing the temperature dependence of stone disease on the basis of reported regional stone prevalence rates and corresponding mean annual temperatures (MATs) in order to predict the anticipated change in stone prevalence due to global warming. Prevalence rates obtained from the Second Cancer Prevention Survey of 1982 (Soucie and Coates, 1996) were consistent with a nonlinear, or peaked, relationship between temperature and stone prevalence, while a dataset from the Veteran's Administration that was analyzed by the Urologic Diseases in America Project more closely approximated a linear fit (Pearle et al, 2005). Using a moderate-severity warming model to predict temperature change due to global warming in the United States, the authors estimated an increase of 1 to 1.5 million lifetime cases of climate-related nephrolithoiasis by 2050. According to the linear model of temperature dependence, the net effect of warming will be a northward expansion of the current-day "stone belt" (which occupies primarily the Southeast part of the United States) into the Midwest, such that by 2050 it will occupy the entire southeastern portion of the country and all of California. The nonlinear model predicts that the zone of elevated stone risk currently located in the Southeast will expand northward to include a band of states from Kansas to Virginia and Northern California, but with the increase in prevalence primarily concentrated south of the temperature threshold.

Occupation

Heat exposure and dehydration constitute occupational risk factors for stone disease as well. Cooks and engineering room personnel, both of whom are exposed to high temperatures, were found to have the highest rates of stone formation among personnel of the Royal Navy (Blacklock, 1969). Likewise, Atan and colleagues (2005) found a significantly higher incidence of stones among steel workers exposed to high temperatures (8%) compared with those working in normal temperatures (0.9%). Metabolic evaluation of these two groups of workers showed a higher incidence of low urine volume and hypocitruria among the workers in the hot area. Borghi and colleagues (1993) also noted differences in the incidence of stone disease and urinary stone risk factors between workers at a glass plant who were or were not chronically exposed to high temperatures causing massive perspiration. Those exposed to high temperatures exhibited lower urine volumes and pH, higher uric acid levels, and higher urine specific gravity, leading to higher urinary saturation of uric acid. Accordingly, those workers who formed stones had a remarkably high incidence of uric acid stones (38%).

Individuals with sedentary occupations such as those in managerial or professional positions have been found to carry an increased risk of stone formation for unclear reasons (Blacklock, 1969). This finding is consistent with the work of Robertson and colleagues (1980), who reported an increased risk of stone disease in affluent individuals, countries, and societies, which may be reflective of a more indulgent diet and lifestyle.

Body Mass Index and Weight

The association of body size and incidence of stone disease has been investigated. In two large prospective cohort studies of men and women, **the prevalence and incident risk of stone disease were directly correlated with weight and body mass index (BMI) in both sexes, although the magnitude of the association was greater in women than men** (Curhan et al, 1998; Taylor et al, 2005). Although these investigators identified a reduced risk of incident stone formation with high fluid (men and women) and low protein intake (men) (Curhan et al, 1993, 1997), they found that obesity and weight gain were independent risk factors for incident stone formation and could not be accounted for by diet alone (Taylor et al, 2005). Recent evidence linking obesity and insulin resistance with low urine pH and uric acid stones (Maalouf et al, 2004a, 2004b), as well as an association between hyperinsulinemia and hypercalciuria (Kerstetter et al, 1991; Shimamoto et al, 1995; Nowicki et al, 1998), could account for an increased risk of uric acid and/or calcium stones in obese patients. A study of stone-forming and non–stone-forming participants in the Health Professionals Follow-Up Study (599 stone-forming and 404 non–stone-forming men), Nurses' Health Study (888 stone-forming and 398 non–stone-forming older women), and Nurses' Health Study II (689 stone-forming and 295 non–stone-forming younger women) for whom 24-hour urine studies were collected correlated urinary stone risk profiles with BMI (Taylor et al, 2006). **Subjects with higher BMI excreted more urinary oxalate, uric acid, sodium, and phosphorus than those with lower BMI. Furthermore, similar to other studies, urinary supersaturation of uric acid increased with BMI.**

It has been suggested that the association of obesity with calcium oxalate stone formation is primarily due to increased excretion of promoters of stone formation (Siener et al, 2004; Negri et al, 2007). **In contrast, the association of obesity and uric acid stone formation is primarily influenced by urinary pH.**

Water

The beneficial effect of a high fluid intake on stone prevention has long been recognized. In two large observational studies, fluid intake was found to be inversely related to the risk of incident kidney stone formation (Curhan et al, 1993, 1997). Furthermore, in a prospective, randomized trial assessing the effect of fluid intake on stone recurrence among first-time idiopathic calcium stone formers, urine volume was significantly higher in the group assigned to a high fluid intake compared with the control group receiving no recommendations, and, accordingly, stone recurrence rates were significantly lower (12% vs. 27%, respectively) (Borghi et al, 1996).

Geographic differences in the incidence of stone disease have been ascribed in some cases to differences in the mineral and electrolyte content of water in different areas. Although several investigators reported a lower incidence of stone disease in geographic regions with a "hard" water supply compared with a "soft" water supply, where water "hardness" is determined by content of calcium carbonate (Churchill et al, 1978; Sierakowski et al, 1979), others found no difference. Schwartz and colleagues (2002) found no association between water hardness and incidence of stone episodes, although they did observe a correlation between water hardness and urinary magnesium, calcium, and citrate levels.

Key Points: Epidemiology

- Upper urinary tract stones occur more commonly in men than women, but there is evidence that the gender gap is narrrowing.
- Whites have the highest incidence of upper tract stones compared with Asians, Hispanics, and African-Americans.
- Prevalence of stone disease shows geographic variability, with the highest prevalence of stone disease in the Southeast.
- The risk of stone disease correlates with weight and body mass index.

PHYSICOCHEMISTRY

The physical process of stone formation is a complex cascade of events that occurs as the glomerular filtrate traverses the nephron. It begins with urine that becomes supersaturated with respect to stone-forming salts, such that dissolved ions or molecules precipitate out of solution and form crystals or nuclei. Once formed, crystals may flow out with the urine or become retained in the kidney at anchoring sites that promote growth and aggregation, ultimately leading to stone formation. The discussion that follows describes the process of stone formation from a physicochemical standpoint.

State of Saturation

A solution containing ions or molecules of a sparingly soluble salt is described by the *concentration product,* which is a mathematic expression of the product of the concentrations of the pure chemical components (ions or molecules) of the salt. For example, the concentration product (CP) expression for sodium chloride is CP = $[Na^+][Cl^-]$. A pure aqueous solution of a salt is considered *saturated* when it reaches the point at which no further added salt crystals will dissolve. The concentration product at the point of saturation is called the *thermodynamic solubility product,* K_{sp}, which is the point at which the dissolved and crystalline components are in equilibrium for a specific set of conditions. At this point, addition of further crystals to the saturated solution will cause the crystals to precipitate unless the conditions of the solution, such as pH or temperature, are changed.

In urine, despite concentration products of stone-forming salt components such as calcium oxalate that exceed the solubility product, crystallization does not necessarily occur because of the presence of inhibitors and other molecules that allow higher concentrations of calcium oxalate to be held in solution before precipitation or crystallization occurs. In this state of saturation, urine is considered to be *metastable* with respect to the salt. As concentrations of the salt increase further, the point at which it can no longer be held in solution is reached and crystals form. The concentration product at this point is called the *formation product,* K_f.

The solubility product and the formation product differentiate the three major states of saturation in urine: undersaturated, metastable, and unstable (Fig. 45–2). Below the solubility product, crystals will not form under any circumstances and dissolution of crystals is theoretically possible. At concentrations above the formation product, the solution is unstable and crystals will form. In the metastable range, between the solubility product and the formation product and in which the concentration products of most common stone components reside, spontaneous nucleation

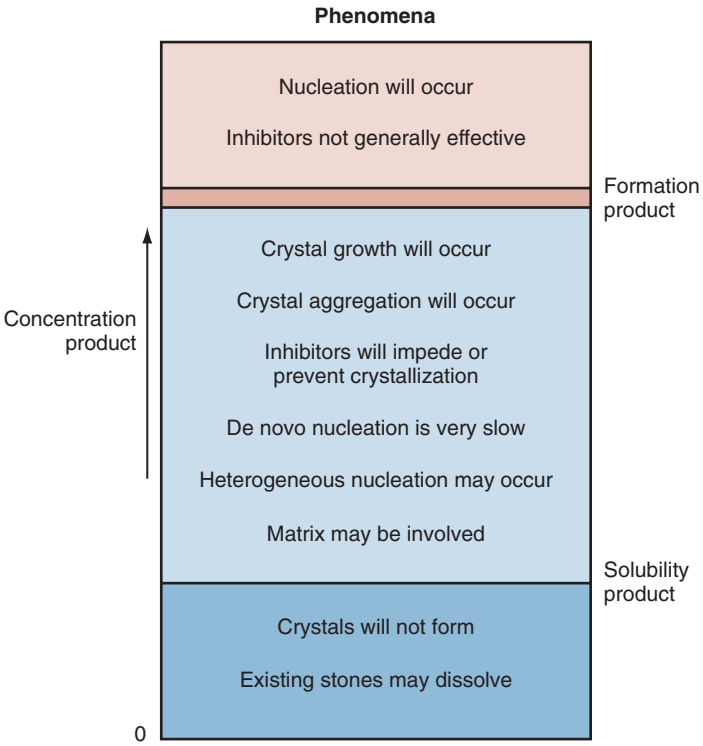


Figure 45–2. States of saturation. Listed are solid-solution phenomena that are likely to occur at a given range of concentration products. Three general situations are considered: (1) concentrations less than the solubility product (undersaturation), (2) concentrations that are metastable with respect to de novo precipitation (between the solubility product and the formation product), and (3) concentrations that are greater than the formation product (unstable). (From Meyer JL. Physicochemistry of stone formation. In: Resnick MI, Pak CYC, editors. Urolithiasis: a medical and surgical reference. Philadelphia: WB Saunders; 1990. p. 11–34.)

or precipitation does not occur despite urine that is supersaturated. It is in this area that modulation of factors controlling stone formation can take place and therapeutic intervention is directed.

In the metastable range of concentration products, although crystal growth can occur on existing crystals, de novo formation of crystals cannot occur in the length of time it normally takes for the filtered urine to reach the bladder. However, crystal formation can occur in this range under certain circumstances. First, in parts of the nephron local concentration products may exceed the formation product for long enough time periods to allow nucleation to occur. Second, local areas of obstruction or stasis in the upper urinary tract may prolong urinary transit time and allow crystal formation to occur in the metastable urine. Finally, microscopic impurities or other constituents in the urine can facilitate the nucleation process by adsorption of the crystal components in a geometric way that resembles the native crystal. The energy required for this "heterogeneous nucleation" process is much less than that required for "homogeneous nucleation."

To estimate the state of saturation for any given crystal system such as calcium oxalate or calcium phosphate, Pak and Chu (1973) developed a mathematic formula, the *activity product ratio,* that takes into account urine pH and the ionic activities of all major ion species directly involved in the stone-forming process or those that affect the overall ionic strength of the urine. Finlayson subsequently developed a computer program to measure the state of saturation, EQUIL 2, which is commonly used today (Werness et al, 1985). The *relative saturation ratio* or *concentration product ratio* is defined as the ratio of the concentration product of the urine to the solubility product of the specified stone-forming salt. A reduction in the numerator will lead to undersaturation of the urine with respect to the stone-forming salt and consequently reduce the likelihood of precipitation. This can be accomplished by reducing the urinary concentrations of the stone components (e.g., calcium or oxalate), by reducing the filtered load, or by increasing urinary reabsorption. In addition, complexation with substances such as citrate reduce available free ionic calcium and decrease the relative saturation ratio. On the other hand, manipulation of factors such as pH can significantly impact the concentration of ions such as phosphate, the generation of which is highly pH dependent. Manipulation of pH has little effect on oxalate concentration, however, because oxalic acid is a strong acid (pK = 4) and pH changes within the physiologic range will have little effect on oxalate concentration.

Rodgers and colleagues (2006) recently introduced a new computer program JESS (Joint Expert Speciation System) to calculate urinary saturation of stone-forming salts as an estimate of the propensity for stone formation, thereby challenging the accuracy of the widely accepted EQUIL 2 computer program. The JESS program recognizes several soluble complexes not taken into account by EQUIL 2 including dicalcium-dihydrogen phosphate and calcium phosphocitrate, whose formation depends on pH and citrate. Consequently, the fraction of ionized calcium, phosphate, and oxalate estimated by JESS will be lower than that estimated by EQUIL 2. In order to resolve the discrepancy between the two programs, the supersaturation index (SI) according to JESS and the relative saturation ratio (RSR) according to EQUIL 2 were compared with experimentally determined urinary saturation of brushite (Pak et al, 2009b) and calcium oxalate (Pak et al, 2009a). The experimentally determined method measures the concentration product ratio (CPR) without using computer-derived ionic activities. By determining the concentration product before and after incubation with a synthetic stone-forming salt, this method directly estimates saturation by measuring the extent of stone growth (in a supersaturated solution) or dissolution (in an undersaturated solution). No significant difference was found between experimentally determined CPR and JESS-derived SI, for either brushite or calcium oxalate. However, EQUIL 2–derived RSR was consistently and significantly higher than both CPR and SI, overestimating CPR by about 80% for brushite and 50% for calcium oxalate. **Because CPR is too labor intensive for routine use, saturation index according to JESS probably provides a more reliable estimation of urinary saturation than relative saturation ratio derived from EQUIL 2.**

Historically, urinary oxalate has been considered a more important contributor to calcium oxalate stone formation than urinary calcium (Nordin et al, 1972; Robertson and Peacock, 1980). This assumption is based on the findings of Nordin and colleagues (1972), who noted that a rise in urinary calcium concentration had less of an effect than a rise in oxalate concentration in increasing urinary saturation of calcium oxalate. They further showed that at high urinary calcium concentrations the saturation of calcium oxalate reached a plateau that did not exceed the theoretic formation product of calcium oxalate, whereas high oxalate concentrations did, thereby increasing the risk of calcium oxalate crystal formation. Pak and colleagues (2004), however, challenged the notion that urinary oxalate exerts a greater pathogenetic role than calcium in calcium oxalate stone formation. They demonstrated that the choice of stability constant used for calculating the relative saturation ratio determines the relative effects of urinary calcium and oxalate concentration. Using the commonly accepted stability constant of 2.746×10^3 (used in the EQUIL 2 program), the effect of urinary calcium and oxalate proved to be equivalent. Thus they concluded that **urinary calcium and oxalate are both important and equal contributors to calcium oxalate stone formation.** As such, reduction in both calcium and oxalate will be effective in reducing the relative saturation ratio, and intervention to prevent stone formation can be directed at either. When these studies were repeated using JESS, the same finding of an equivalent effect of calcium and oxalate on urinary SI of calcium oxalate was found, although the dependence of SI on calcium and oxalate was less marked than was demonstrated for RSR (Pak et al, 2009a).

Nucleation and Crystal Growth, Aggregation, and Retention

In normal human urine, the concentration of calcium oxalate is four times higher than its solubility in water. Urinary factors favoring stone formation including low volume and citrate and increased calcium, oxalate, phosphate, and uric acid all increase calcium oxalate supersaturation. Once the concentration product of calcium oxalate exceeds the solubility product, crystallization can potentially occur. However, in the presence of urinary inhibitors and other substances, calcium oxalate precipitation occurs only when supersaturation exceeds solubility by 7 to 11 times.

Homogeneous nucleation is the process by which nuclei form in pure solution. Nuclei are the earliest crystal structures that will not dissolve. Small nuclei are unstable; below a critical size threshold, dissolution of the crystal is favored over crystal growth. If the driving force (supersaturation level) and the stability of the nuclei are adequate and the lag time to nucleation is sufficiently short compared with the transit time of urine through the nephron, the nuclei will persist. Inhibitors, like citrate, destabilize nuclei, whereas promoters stabilize nuclei by providing a surface with a

binding site that accommodates the crystal structure of the nucleus. In urine, crystal nuclei usually form through heterogeneous nucleation by adsorption onto existing surfaces of epithelial cells (Umekawa et al, 2001), cell debris (Fasano et al, 2001), or other crystals (Kok, 1997).

Within the time frame of transit of urine through the nephron, estimated at 5 to 7 minutes, crystals cannot grow to reach a size sufficient to occlude the tubular lumen. However, if enough nuclei form and grow, aggregation of the crystals will form larger particles within minutes that can occlude the tubular lumen. Inhibitors can prevent the process of crystal growth or aggregation. Magnesium and citrate inhibit crystal aggregation. Nephrocalcin, an acidic glycoprotein made in the kidney, inhibits calcium oxalate nucleation, growth, and aggregation (Nakagawa et al, 1987; Asplin et al, 1991). Tamm-Horsfall mucoprotein, the most abundant protein in urine, inhibits aggregation (Hess et al, 1991), and uropontin inhibits crystal growth (Shiraga et al, 1992). Bikunin, the light chain of inter-α inhibitor, has been shown to be an efficient inhibitor of crystal nucleation and aggregation.

Opposing views regarding the formation and growth of crystal particles have led to controversy over the concept of free crystal particle growth versus fixed particle growth. Although it was initially concluded that free particle stone formation was impossible within the normal transit time through the nephron (Finlayson et al, 1978b), later recalculation using current nephron dimensions, supersaturation, and crystal growth rates determined that crystalline particles can be formed that are large enough to be retained during normal transit time through the kidney (Kok and Khan, 1994).

Fixed particle growth theory presupposes an anchoring site to which crystals bind, thereby prolonging the time the crystals are exposed to supersaturated urine and facilitating crystal growth and aggregation. A number of mechanisms have been proposed to account for crystal fixation. One favored theory proposes that oxalate-induced injury to renal tubular epithelial cells promotes adherence of calcium oxalate crystals (Miller et al, 2000). In animal models of stone formation in which administration of high oxalate loads leads to calcium oxalate crystal formation, elevated urinary levels of enzyme markers of cell injury including *N*-acetyl-β-glucosidase and alkaline phosphatase provide evidence of damage to renal tubular epithelial cells (Khan et al, 1992; Thamilselvan and Khan, 1998). Although the exact mechanism of oxalate-induced cell injury is not known, several studies have suggested that it is mediated by free radical formation (Thamilselvan and Khan, 1998, 1999). Not only are high concentrations of oxalate toxic to renal tubular cells, but calcium oxalate crystals themselves have also been shown to promote damage to cells (Khan et al, 1993, 1999; Thamilselvan and Khan, 1998; Thamilselvan et al, 1999). Despite these findings in animal models and in vitro systems, **evidence for oxalate-induced tubular damage in humans has been lacking.** Indeed, no increase in markers of oxidative stress or renal cell injury has been observed in normal individuals or stone formers after ingestion of a large oxalate load (Knight et al, 2007).

How oxalate-induced renal tubular cell damage potentially promotes crystal retention is not known. Randall (1937) first observed areas of damage associated with subepithelial plaques on the renal papillae. Later, structural analyses in hyperoxaluric rats demonstrated crystals attached to the injured epithelium lining the collecting ducts (Khan, 1991). In vitro studies confirmed increased binding of calcium oxalate crystals to injured renal epithelial cells in culture (Verkoelen et al, 1998). Whether the renal tubular cells or the interstitium constitutes the primary site of stone formation is unclear. Evidence of endocytosis of calcium oxalate crystals into renal tubular cells has been demonstrated in patients with disorders of oxalate metabolism (Saxon et al, 1974; Mandell et al, 1980; Lieske et al, 1992). Intracellular incorporation of these crystals could potentially lead to cell death and deposition of crystals in the interstitium, or transport of the crystals from the luminal to the basement membrane side could promote cell damage and subsequent erosion through to the papillary surface. Knoll and colleagues (2004) demonstrated in cell culture that oxalate-induced damage was more pronounced in renal nontubular compared with tubular cell lines and, further, that renal epithelial cells were more vulnerable to the toxic effects of oxalate on their basolateral side compared with their apical (luminal) side, implicating the interstitium as a possible site of primary stone formation.

In light of these recent findings, a number of investigators have revisited the role of Randall's plaques in the pathogenesis of stone formation. Low and Stoller (1997) mapped the papillae of patients undergoing endoscopic stone removal, as well as control subjects undergoing endoscopy for unrelated reasons, and found that papillary plaques occurred in 74% of stone formers compared with only 43% of control subjects. Stoller and colleagues (2004) hypothesized that the inciting event in the pathogenesis of stones may be vascular injury to the vasa recta near the renal papilla. Repair of damaged vessel walls could involve an atherosclerotic-like reaction that results in calcification of the endothelial wall, followed by erosion into the papillary interstitium and then into the collecting ducts, where it could serve as a nidus for stone formation.

Evan and colleagues (2003) presented an alternative view of the pathogenesis of stone formation on the basis of extensive analysis of papillary plaques derived from biopsies obtained during percutaneous nephrolithotomy in idiopathic calcium oxalate stone formers. **They localized the origin of the plaque to the basement membrane of the thin limbs of the loops of Henle and demonstrated that the plaque subsequently extends through the medullary interstitium to a subepithelial location** (Fig. 45–3). **Once the plaque erodes through the urothelium, it is thought to constitute a stable, anchored surface on which calcium oxalate crystals can nucleate and grow as attached stones.** Among idiopathic calcium oxalate stone formers, the volume of papillary surface covered by plaque was shown to correlate negatively with urine volume and positively with hypercalciuria (Kuo et al, 2003a, 2003b) and the number of stones formed (Kim et al, 2005a), providing further corroborating clinical evidence for this sequence of events. Furthermore, Matlaga and colleagues (2006) observed that in approximately half of a studied cohort of calcium oxalate stone formers the stones were observed to be attached to the renal papillae, suggesting that formation of attached stones is an early step in the process of stone formation.

Using high-resolution Fourier transform infrared microspectroscopy and electron diffraction, the crystal component of plaque was determined to be calcium apatite (Evan, 2003). Further analysis revealed that the deposits consisted of individual laminated particles with mineral and organic layers. All crystals were coated with organic material, and osteopontin was indentified on the outer surface of the crystal at the junction of the overlying organic molecular layer, potentially implicating osteopontin in plaque biology (Evan et al, 2005). Daudon and colleagues analyzed more than 5000 stones associated with Randall plaques and also found that carbapatite constituted the main component of the plaque in nearly all cases (Daudon et al, 2007).

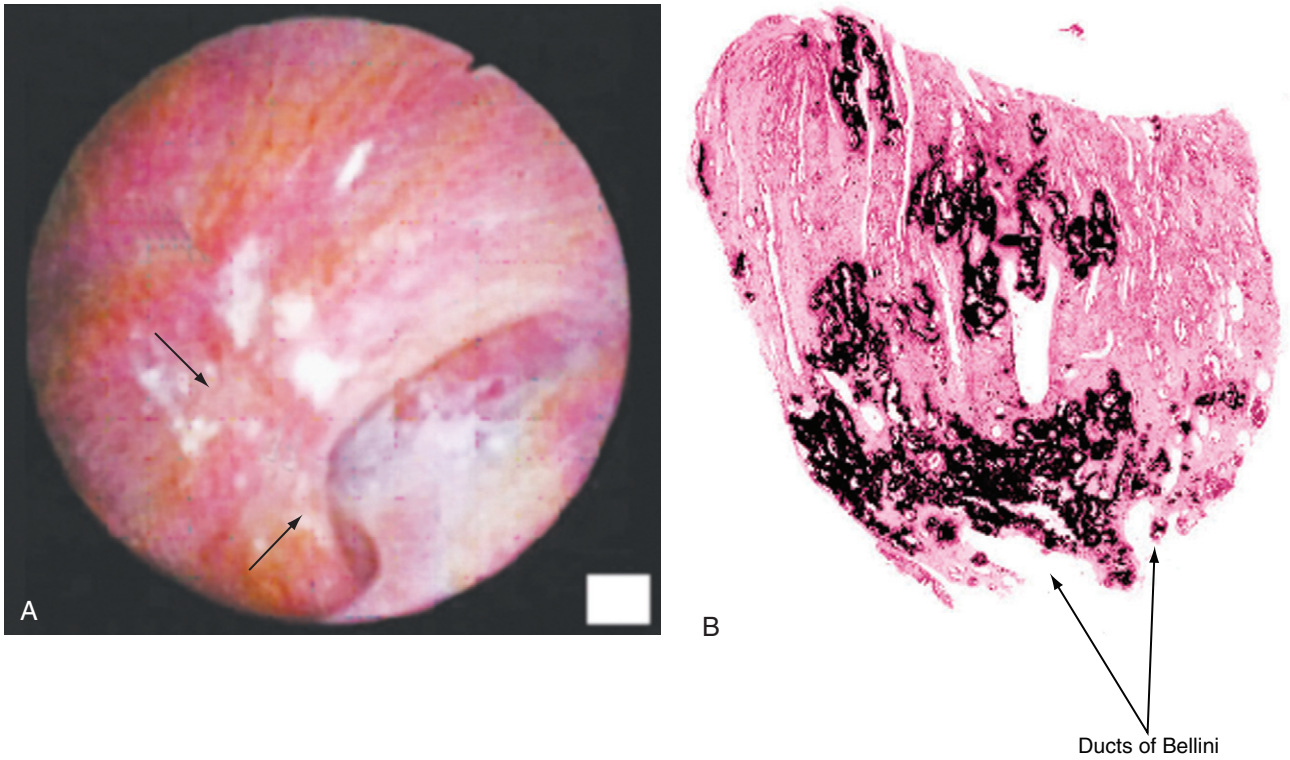


Figure 45–3. Endoscopic **(A)** and histologic **(B)** images of Randall plaques in calcium oxalate patients. In **A,** sites of Randall's plaques *(arrows)* appear as irregular white areas beneath the urothelium. In **B,** a low-magnification light-microscopic image of a papillary biopsy specimen is shown. Sites of calcium deposits were stained black by the Yasue metal substitution method for calcium histochemistry. (From Evan AP, Lingeman JE, Coe FL, et al. Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. J Clin Invest 2003;111:607–16.)

One intriguing but unproven hypothesis for the origin of the calcium phosphate particles described earlier involves nanobacteria, or calcifying nanoparticles (CNPs), which are self-propogating entities that precipitate calcium apatite on their exterior membrane but for which to date no genomic material has been identified (Kajander et al, 1998). Although the existence of these particles has been questioned (Cisar et al, 2000), several lines of evidence support a role of CNPs in stone formation (Kajander et al, 2001). CNPs have been detected in blood, blood products, and kidney stones, as well as in other pathologic calcifications (Ciftçioğlu et al, 1999, 2006). They have been shown to promote rapid precipitation of calcium phosphate from blood under physiologically unfavorable conditions (Kajander et al, 1998), and in an animal model intrarenal injection of CNP was shown to induce renal calcification (García et al, 2000). In a recent study in which renal papillary and blood samples were obtained from human patients undergoing nephrectomy, immunohistochemical staining using anti-CNP antibodies was positive in 8 of 11 papillary samples in which Randall plaques were visualized and in only one of those for which they were not (Ciftcioglu et al, 2008). In addition, 12 of 14 samples positive for CNP-like spheres on scanning electron microscopy demonstrated CNP growth in culture, compared with only one of three SEM-negative samples. Although not necessarily causative, these findings loosely suggest an association between CNP and Randall plaque.

The pathogenesis of stone formation in other calcium stone formers and in noncalcium stone formers may differ from that of typical idiopathic calcium oxalate stone formers. Indeed, distinct morphologic subtypes characterizing particular patient phenotypes have been found, consistent with divergent underlying pathophysiologic abnormalities. Unlike idiopathic calcium oxalate stone formers, **patients with enteric hyperoxaluria due to intestinal bypass for obesity demonstrate no plaque but instead show apatite crystal deposits plugging the inner medullary collecting duct lumens, along with associated epithelial cell damage with interstitial inflammation and fibrosis** (Fig. 45–4) (Evan et al, 2003). Interestingly, despite the acidic urine typically found in these patients, the crystal deposits are composed of apatite, which is generally unstable at low urine pH, suggesting discordance between local tubular pH and final urinary pH (Evan et al, 2006).

Brushite stone formers have been found to have pathology intermediate between idiopathic calcium oxalate stone formers and intestinal bypass patients, demonstrating interstitial apatite plaque *and* apatite plugging of the inner medullary and terminal collecting ducts, along with associated collecting duct injury and interstitial fibrosis (Fig. 45–5) (Evan et al, 2005). The pathogenesis of brushite stones has been postulated by Evan and colleagues (2005) to occur by way of crystallization of apatite in the collecting ducts leading to collecting duct injury, cell death, and enlargement of collecting ducts. Interstitial inflammation in response to the injured cells may lead finally to progressive involvement of adjacent renal tissue.

With distal renal tubular acidosis (RTA), patients typically exhibit extensive renal calcifications. In a subgroup of patients with distal RTA in whom most of the calcifications were surgically removable, endoscopic inspection of the renal papillae

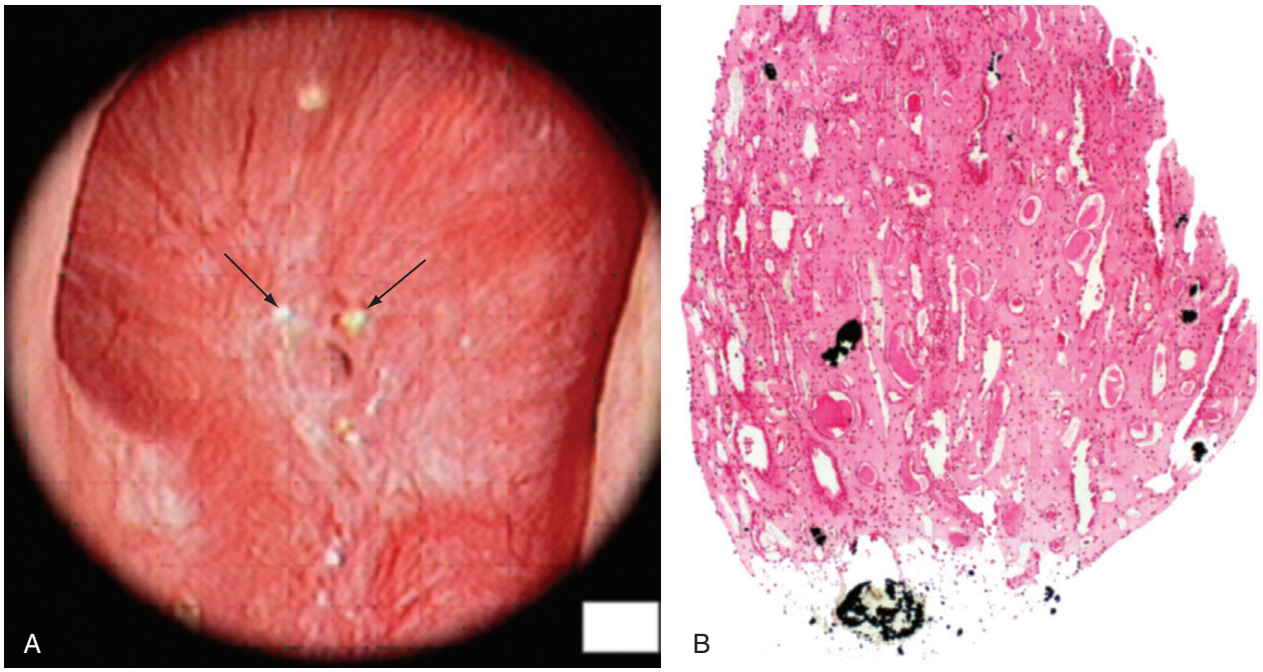


Figure 45–4. Endoscopic **(A)** and histologic **(B)** images of Randall plaques in intestinal bypass patients. In **A,** sites of Randall plaques *(arrows)* appear as irregular white areas beneath the urothelium. In **B,** a low-magnification light-microscopic image of a papillary biopsy specimen is shown. Sites of calcium deposits were stained black by the Yasue metal substitution method for calcium histochemistry. (From Evan AP, Lingeman JE, Coe FL, et al. Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. J Clin Invest 2003;111:607–16.)

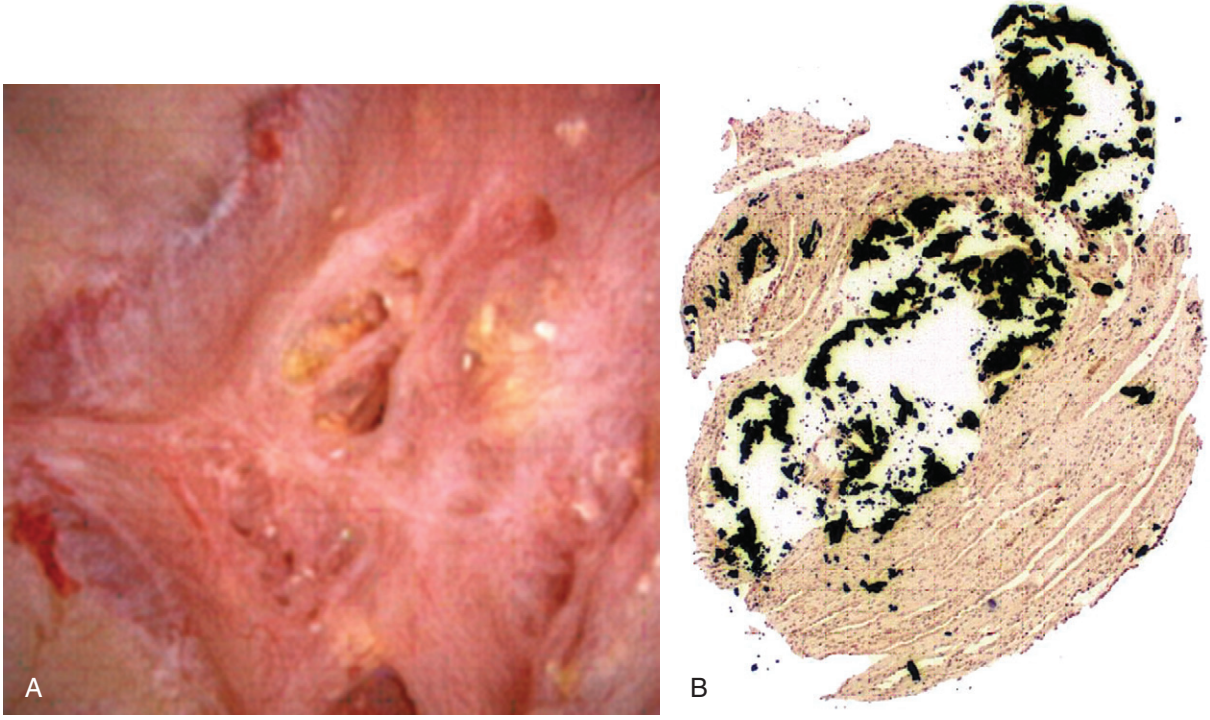


Figure 45–5. Endoscopic **(A)** and histologic **(B)** images of Randall plaques in brushite patients. In **A,** sites of Randall plaque appear as irregular white areas of crystalline deposit beneath the urothelium. In addition, a yellowish crystalline deposit is apparent at the opening of the ducts of Bellini. In **B,** a low-magnification light-microscopic image of a papillary biopsy specimen is shown. Sites of calcium deposits were stained black by the Yasue metal substitution method for calcium histochemistry. A large amount of Yasue-positive material is seen in the ducts of Bellini. (From Evan AP, Lingeman JE, Coe FL, et al. Crystal-associated nephropathy in patients with brushite nephrolithiasis. Kidney Int 2005;67:576–91.)

demonstrated a variety of findings (Evan et al, 2007). In some patients minimal papillary changes were observed, whereas in others the papilla were pitted and contained calcium phosphate plugs protruding from dilated collecting ducts with extensive surrounding fibrosis. Randall plaques were rarely encountered.

Finally, although patients with cystinuria were found to have plugging of the terminal collecting ducts of Bellini with masses of cystine crystals, surprisingly apatite deposits were also identified in the inner medullary collecting ducts and in the thin ascending limbs of the loops of Henle. It was speculated that perhaps the alkali load associated with treatment of cystine stone formers or obstruction of the inner medullary collecting ducts by the cystine plugs resulting in an acidification defect could promote apatite crystallization (Evan et al, 2006).

Whether tubular or interstitial calcifications are primarily responsible for renal stone formation is not entirely clear, and it is likely that both mechanisms play a role in particular clinical scenarios. Retention of crystals in the tubular lumen may lead to nephrocalcinosis, which may or may not be associated with renal stone formation. However, these crystals may lead to obstruction-induced tubulopathy and ultimately renal failure. Experimental evidence suggests that crystals bind preferentially to regenerating/redifferentiating renal tubular cells (Verkoelen et al, 2007). Crystal binding to the surface of these cells is thought to be mediated by a number of luminal membrane molecules including hyalurionic acid, osteopontin, annexin-II, and nucleolin-related protein. Clinical observation of nephrocalcinosis in 60% of preterm infants may be related to exposure of differentiating renal tubular epithelial cells to crystalluria caused by furosemide treatment (Ezzedeen et al, 1988; Downing et al, 1992). Indeed, the kidneys of these infants have been shown to strongly express hyaluronic acid and osteopontin at the luminal membrane (Verhulst et al, 2005).

Inhibitors and Promoters of Crystal Formation

At the concentrations that most stone-forming salt components are present in urine including calcium, oxalate, and phosphate, urine is supersaturated, thereby favoring crystal formation. However, **the presence of molecules that raise the supersaturation needed to initiate crystal nucleation or reduce the rate of crystal growth or aggregation prevents stone formation from occurring on a routine basis.** Although inhibitors have been identified for calcium oxalate and calcium phosphate, no specific inhibitors are known that affect uric acid crystallization.

Whole urine, when added to a solution of calcium phosphate, raises the supersaturation level required to initiate calcium phosphate crystallization (formation product) (Fleisch et al, 1962). Inorganic pyrophosphate was found to be responsible for 25% to 50% of the inhibitory activity of whole urine against calcium phosphate crystallization. Using different methodology, citrate, magnesium, and pyrophosphate together were noted to account for approximately 20% of the inhibitory activity of whole urine, with citrate comprising the most important factor of the three (Bisaz et al, 1978).

Citrate acts as an inhibitor of calcium oxalate and calcium phosphate stone formation by a variety of actions. First, it complexes with calcium, thereby reducing the availability of ionic calcium to interact with oxalate or phosphate (Meyer et al, 1975; Pak et al, 1982). Second, it directly inhibits the spontaneous precipitation of calcium oxalate (Nicar et al, 1987) and prevents the agglomeration of calcium oxalate crystals (Kok et al, 1986). Although it has limited inhibitory effect on calcium oxalate crystal growth, it has potent activity in reducing calcium phosphate growth (Meyer et al, 1975). Lastly, citrate prevents heterogeneous nucleation of calcium oxalate by monosodium urate (Pak and Peterson, 1986).

The inhibitory activity of magnesium is derived from its complexation with oxalate, which reduces ionic oxalate concentration and calcium oxalate supersaturation (Meyer et al, 1975). In addition, magnesium reduces the rate of calcium oxalate crystal growth in vitro (Desmars et al, 1973).

Polyanions including glycosaminoglycans, acid mucopolysaccharides, and RNA have been shown to inhibit crystal nucleation and growth. Among the glycosaminoglycans, heparin sulfate interacts most strongly with calcium oxalate monohydrate crystals (Yamaguchi et al, 1993).

Two urinary glycoproteins, nephrocalcin and Tamm-Horsfall glycoprotein, are potent inhibitors of calcium oxalate monohydrate crystal aggregation (Nakagawa et al, 1987). Nephrocalcin is an acidic glycoprotein containing predominantly acidic amino acids that is synthesized in the proximal renal tubules and the thick ascending limb. In simple solution, nephrocalcin strongly inhibits the growth of calcium oxalate monohydrate crystals (Nakagawa et al, 1987). Nephrocalcin has been identified in four isoforms: non–stone formers excrete greater quantities of two isoforms associated with the most inhibitory activity, whereas stone formers excrete urine enriched for the two isoforms lacking inhibitory activity (Nakagawa, 1997). The isoforms with inhibitory activity were found to contain γ-carboxyglutamic acid residues that were lacking in the isoforms isolated from stone formers.

Tamm-Horsfall protein is expressed by renal epithelial cells in the thick ascending limb and the distal convoluted tubule as a membrane-anchored protein that is released into the urine after cleavage of the anchoring site by phospholipases or proteases. **Tamm-Horsfall is the most abundant protein found in the urine and a potent inhibitor of calcium oxalate monohydrate crystal aggregation, but not growth.** The role of Tamm-Horsfall in stone formation is controversial and may depend on the state of the molecule itself, which can self-aggregate under certain conditions. A recent study using a Tamm-Horsfall (THP) knockout mouse model demonstrated spontaneous formation of calcium oxalate crystals in the kidneys of mice fed ethylene glycol and vitamin D, suggesting a protective role of Tamm-Horsfall protein against crystallization of calcium salts (Mo et al, 2004).

Osteopontin, or uropontin, is an acidic phosphorylated glycoprotein expressed in bone matrix and renal epithelial cells of the ascending limb of the loop of Henle and the distal tubule. **Osteopontin has been shown to inhibit nucleation, growth, and aggregation of calcium oxalate crystals, as well as to reduce binding of crystals to renal epithelial cells in vitro** (Asplin et al, 1998; Wesson et al, 1998). In an osteopontin knockout mouse model, intratubular calcium oxalate crystals can be induced in mice exposed to high levels of oxalate by ethylene glycol feeding (Wesson et al, 2003). Interestingly, in a THP knockout mouse model, mice fed ethylene glycol and vitamin D exhibited a dramatic increase in osteopontin levels over baseline but still formed calcium oxalate crystals (Mo et al, 2004). The authors concluded that osteopontin may constitute an inducible inhibitor of calcium oxalate crystallization that works in conjunction with constitutively expressed Tamm-Horsfall protein to prevent crystallization.

Lastly, inter-α-trypsin is a glycoprotein synthesized in the liver that is composed of three polypeptides (two heavy chains and one light chain), of which bikunin comprises the light chain. Bikunin is a strong inhibitor of calcium oxalate crystallization, aggregation, and growth in vitro (Hochstrasser et al, 1984; Atmani et al, 1999), and its expression has been shown to be upregulated in a rat model when exposed to oxalate.

Matrix

Renal calculi consist of both crystalline and noncrystalline components. The noncrystalline component is termed *matrix,* which typically accounts for about 2.5% of the weight of the stone (Boyce and Garvey, 1956). In some cases, matrix comprises the majority of the stone (up to 65%), usually in association with chronic urinary tract infection (Boyce and Garvey, 1956; Allen and Spence, 1966). The exact composition of matrix is difficult to ascertain because only 25% of it is soluble (Ryall, 1993); however, chemical analysis reveals a heterogeneous mixture consisting of 65% protein, 9% nonamino sugars, 5% glucosamine, 10% bound water, and 12% organic ash (Boyce, 1968). Among the proteins incorporated into the matrix substance are Tamm-Horsfall protein, nephrocalcin, a γ-carboxyglutamic acid–rich protein, renal lithostathine, albumin, glycosaminoglycans, free carbohydrates, and a mucoprotein called matrix substance A (Hess et al, 1996). Boyce and colleagues (1962) found that substance A is immunologically unique and present in the matrix component of all stone formers. Moore and Gowland (1975) determined that substance A is composed of three or four distinct antigens unique to stones that were detected in the urine of 85% of stone formers but in no normal individuals. A recent study using reversed-phase, high-performance liquid chromatography and tandem mass spectrometry to evaluate calcium oxalate stones identified 68 distinct proteins with 95% confidence including a significant number of inflammatory proteins (immunoglobulins, defensin-3, clusterin, complement C3a, kininogen, and fibrinogen (Canales et al, 2008). The exact role of matrix in stone formation, whether as a promoter, an inhibitor, or a passive bystander, has yet to be elucidated.

MINERAL METABOLISM

Calcium

Thirty to 40 percent of dietary calcium is absorbed from the intestine, with most being absorbed in the small intestine and only approximately 10% absorbed in the colon (Bronner et al, 1999). By a process of intestinal adaptation, absorption of calcium varies with calcium intake. At times of low calcium intake, fractional calcium absorption is enhanced; during high calcium intake, fractional calcium absorption is reduced. With a calcium-rich diet, a nonsaturable, paracellular pathway for calcium absorption predominates. A saturable, vitamin D–dependent transcellular pathway constitutes the major pathway for intestinal calcium absorption when calcium intake is limited; this pathway is downregulated by a diet replete in calcium (Buckley et al, 1980; Bronner et al, 1986). Because of the saturable component of calcium transport, a larger portion of calcium is absorbed when it is divided into several doses taken hours apart compared with a large single dose (Phang et al, 1968). A small amount of calcium is secreted into the lumen of the intestine, thereby reducing net calcium absorption, such that, overall, 100 to 300 mg of a total average calcium intake of 600 to 1200 mg daily will be absorbed.

Key Points: Physicochemistry

- Urine must be supersaturated for stones to form.
- Supersaturation alone is not sufficient for crystallization to occur in urine, owing to the presence of urinary inhibitors.
- Nephrocalcin, uropontin, and Tamm-Horsfall protein are important inhibitors of crystal nucleation, growth, or aggregation.
- Urinary calcium and oxalate are equal contributors to urinary saturation of calcium oxalate.
- Common calcium stones may originate from subepithelial plaques composed of calcium apatite that serve as an anchor on which calcium oxalate stones can grow.
- The noncrystalline component of stones is matrix, which is composed of a combination of mucoproteins, proteins, carbohydrates, and urinary inhibitors.

Calcium is absorbed in the ionic state, and incomplete calcium absorption is due in part to formation of soluble calcium complexes in the intestinal lumen. **As such, substances that complex calcium such as phosphate, citrate, oxalate, sulfate, and fatty acids reduce the availability of ionic calcium for absorption** (Allen, 1982). Calcium readily complexes with phosphate in the intestinal lumen, but because calcium phosphate formation is dependent on pH (pK = 6.1), high luminal pH favors calcium phosphate complexation, thereby reducing calcium availability. On the other hand, calcium oxalate complex formation displays less pH dependence and complex formation is less reversible. Consequently, an oxalate-rich diet reduces calcium absorption. Transcellular calcium absorption is mediated by $1,25(OH)_2D_3$ (calcitriol), which is reported to enhance calcium permeability at the brush border of the intestinal epithelial cells (Fontaine et al, 1981).

The active form of vitamin D, $1,25(OH)_2D_3$, is the most potent stimulator of intestinal calcium absorption. After conversion of 7-dehydrocholesterol in the skin to previtamin D_3 promoted by sunlight, previtamin D_3 is hydroxylated in the liver to 25-hydroxyvitamin D_3, which is further hydroxylated in the proximal renal tubule to $1,25(OH)_2D_3$. The conversion of 25-hydroxyvitamin D_3 to $1,25(OH)_2D_3$ is stimulated by parathyroid hormone (PTH) and by hypophosphatemia. **A decrease in serum calcium increases secretion of PTH, which in turn directly stimulates the enzyme 1α-hydroxylase, which is located in the mitochondria of the proximal renal tubule.** After transport via the bloodstream to the intestine, $1,25(OH)_2D_3$, binds to the vitamin D receptor in the brush border membrane epithelial cells to enhance calcium absorption.

Calcitriol also acts on the bone and kidney in addition to its action in increasing calcium absorption from the intestine. In the bone, $1,25(OH)_2D_3$, along with PTH, promotes the recruitment and differentiation of osteoclasts that subsequently mobilize calcium from the bone. Consequently, the filtered load of calcium and phosphate increases. However, PTH increases renal calcium reabsorption and enhances phosphate excretion, leading to a net increase in serum calcium, which ultimately suppresses further PTH secretion and synthesis of $1,25(OH)_2D_3$. Calcitriol modulates parathyroid function as well by inhibiting synthesis of PTH through enhanced vitamin D receptor and calcium-sensing receptor expression in the parathyroid glands (Dusso et al, 2005).

PTH is critical in maintaining normal calcium concentration in the extracellular fluid. PTH is an 84 amino acid protein that is the cleavage product of the precursor protein preproPTH. **Only mature PTH is secreted from the parathyroid gland, and the most potent stimulus for its secretion is a decrease in serum calcium** (Sherwood et al, 1968). In response to serum calcium levels, the G-protein-coupled extracellular calcium-sensing receptor (CaSR) regulates PTH secretion and renal tubular calcium reabsorption (Devuyst and Pirson, 2007). PTH stimulates mobilization of calcium from bone through the action of osteoclasts, further raising serum calcium and phosphorus. The action of PTH is mediated through changes in cyclic adenosine monophosphate (AMP) and phospholipase C (Dunlay et al, 1990; Muff et al, 1992). **At the kidney, PTH enhances renal calcium reabsorption and reduces renal tubular reabsorption of phosphate.** It also stimulates synthesis of $1,25(OH)_2D_3$, which leads to enhanced intestinal calcium and phosphate absorption. PTH has no direct effect on intestinal calcium absorption.

Phosphorus

Like calcium, inorganic phosphate absorption is dependent on both saturable, transcellular and nonsaturable, paracellular transport. At low phosphorus concentrations (1 to 3 mmol/L), saturable, absorptive transport occurs. At higher phosphorus levels, absorption increases without saturation (Walton et al, 1979). Approximately 60% of the phosphate in the diet is absorbed by the intestine. Active absorption of phosphate from the intestine involves a $1,25(OH)_2D_3$-regulated, sodium-dependent transport process (Danisi et al, 1980; Lee et al, 1986). Phosphate absorption is highly pH dependent; low luminal pH reduces phosphate transport, whereas high luminal pH enhances phosphate transport.

Approximately 65% of absorbed phosphate is excreted by the kidney and the remainder by the intestine. In normal healthy adults, 80% to 90% of the filtered load of phosphate is reabsorbed in the renal tubule and 10% to 20% is excreted in the urine. **Regulation of renal phosphate handling is primarily by way of PTH, which inhibits renal tubular reabsorption of filtered phosphate.**

Magnesium

Magnesium is absorbed from the intestine by passive diffusion or active transport, although passive diffusion accounts for most of the net magnesium absorption. Magnesium is absorbed in both the large and small intestine, with the majority absorbed from the distal small intestine. Hormonal regulation of magnesium is primarily through vitamin D.

Oxalate

Oxalate metabolism differs markedly from calcium metabolism. Although 30% to 40% of ingested calcium is absorbed from the intestine, only 6% to 14% of ingested oxalate is absorbed (Holmes et al, 1995; Hesse et al, 1999). Oxalate absorption occurs throughout the intestinal tract, with about half or more occurring in the small intestine and half in the colon (Holmes et al, 1995). Although oxalate absorption is difficult to measure directly, it has historically been estimated by urinary oxalate excretion, a relationship that is valid only if there is a linear relationship between ingested and excreted oxalate and if absorbed oxalate is not significantly taken up in the tissues, metabolized, or secreted back into the intestine. Holmes and colleagues (2001) in fact demonstrated that the relationship between ingested oxalate and absorbed oxalate is curvilinear, owing to higher absorption of oxalate at low intake compared with high intake. Moreover, they showed that oxalate absorption varies widely among individuals, ranging from 10% to 72% of ingested oxalate. A recent study suggested that hyperoxaluric stone formers absorb more oxalate in response to an oral oxalate load than stone formers with normal oxalate excretion (Krishnamurthy et al, 2003). Knight and colleagues (2007), however, found no difference between normal subjects and stone formers in intestinal absorption or renal handling of oxalate. In patients with small bowel disease or history of intestinal resection and an intact colon, oxalate absorption is markedly increased (Barilla et al, 1978a).

Oxalate transport occurs via both transcellular and paracellular pathways. Although transport by way of paracellular pathways and some nonmediated transcellular pathways is primarily passive, driven by electrochemical or concentration gradients, transcellular transport is largely actively mediated by membrane carriers. A putative anion exchange transporter, SLC26a6, that is expressed in the apical membrane of small intestinal and perhaps colonic epithelial cells has been implicated in intestinal oxalate transport (Hatch and Freel, 2005). Recent evidence suggests that oxalate may be secreted, as well as absorbed in the intestine (Jiang et al, 2006). In vitro flux studies using intestinal segments of mutant mice lacking SLC26a6 showed enhanced net absorption of oxalate due to defective oxalate secretion. Furthermore, in vivo *Slc26a6*-null mice were found to have elevated plasma and urinary oxalate levels, reduced fecal oxalate excretion, and a high incidence of calcium oxalate bladder stones compared with wild-type mice. These findings provide compelling evidence for a possible role of SLC26a6 in oxalate secretion and suggest a potential target for therapeutic agents that modify urinary oxalate absorption.

A number of other factors can influence oxalate absorption including the presence of oxalate-binding cations such as calcium or magnesium and oxalate-degrading bacteria. Coingestion of calcium and oxalate-containing foods leads to formation of a calcium oxalate complex, which limits the availability of free oxalate ion for absorption (Liebman and Chai, 1997; Hess et al, 1998). Oxalate-degrading bacteria, notably *Oxalobacter formigenes,* use oxalate as an energy source and consequently reduce intestinal oxalate absorption. The mechanism of action of *O. formigenes* in reducing urinary oxalate excretion may not be entirely accounted for by degradation of intestinal oxalate. A series of in vivo and ex vivo studies in rats colonized with *O. formigenes* demonstrated reduced urinary oxalate excretion and net colonic oxalate secretion, suggesting that *O. formigenes* may interact directly with intestinal mucosal epithelial cells to stimulate enteric secretion of endogenously derived oxalate (Hatch et al, 2006). The potential for therapeutic use of probiotics has been explored in several short-term clinical trials. In a small study of patients with primary hyperoxaluria and normal renal function or varying degrees of renal failure, administration of *O. formigenes* was associated with a reduction in serum and/or urinary oxalate (Hoppe et al, 2006). Although one uncontrolled study (Campieri et al, 2001) of calcium oxalate stone formers with mild hyperoxaluria showed a 24% to 40% reduction in urinary oxalate with the administration of a preparation of mixed lactic acid bacterium species, a randomized, controlled trial (Goldfarb et al, 2007) failed to demonstrate an effect of the same probiotic. At this time, the contribution of *O. formigenes* to the overall risk of stone formation is not fully understood.

Absorbed oxalate is nearly completely excreted in the urine (Hodgkinson et al, 1974; Prenan et al, 1982). Urinary oxalate is derived from both endogenous production in the liver (from ascorbic acid and glycine) and dietary sources. Historically, the contribution of dietary oxalate to urinary oxalate was presumed to be no greater than 20%. However, **recent evidence suggests that on average, half of urinary oxalate is derived from the diet, with the precise amount depending on the relative amount of ingested calcium and oxalate** (Holmes et al, 2001). It is estimated that greater than 98% of oxalate is ultrafilterable, and oxalate reabsorption is thought to be negligible. However, there is evidence from a number of animal models of a secretory pathway for oxalate that likely resides in the proximal renal tubule (Cattell et al, 1962; Williams et al, 1971; Knight et al, 1981; Tremaine et al, 1985).

Key Points: Mineral Metabolism

- Calcium absorption occurs primarily in the small intestine at a rate that is dependent on calcium intake.
- 1,25-Dihydroxyvitamin D_3 is the most potent stimulator of intestinal calcium absorption.
- PTH stimulates 1α-hydroxylase in the proximal tubule of the kidney to convert 25-dihydroxyvitamin D_3 to $1,25(OH)_2D_3$.
- PTH enhances proximal tubular reabsorption of calcium and renal phosphate excretion.
- Intestinal oxalate absorption is influenced by luminal calcium, magnesium, and oxalate-degrading bacteria.

PATHOGENESIS OF UPPER URINARY TRACT CALCULI

Classification of Nephrolithiasis

The most common component of urinary calculi is calcium, which is a major constituent of nearly 75% of stones. Calcium oxalate makes up about 60% of all stones; mixed calcium oxalate and hydroxyapatite, 20%; and brushite stones, 2%. Both uric acid and struvite (magnesium ammonium phosphate) stones occur approximately 10% of the time, whereas cystine stones are rare (1%) (Table 45–1) (Wilson, 1989). Stones associated with medications and their byproducts such as triamterene, adenosine, silica, indinavir, and ephedrine are uncommon and usually preventable.

Most classification systems for nephrolithiasis differentiate stones on the basis of the underlying metabolic or environmental abnormalities with which they are associated (Table 45–2). A number of pathophysiologic derangements contribute to calcium stone formation, either alone or in combination, including hypercalciuria (Zerwekh et al, 1988), hypocitraturia (Pak and Fuller, 1986; Pak, 1987; Coe et al, 1992; Bushinsky, 1998), hyperuricosuria, and hyperoxaluria. Uric acid, cystine, and struvite stones form in relatively unique settings: Uric acid stones form only in an acid urine (Halabe et al, 1994; Asplin, 1996), cystine stones are the result of impaired renal reabsorption of cystine (Marshall et al, 1976; Stephens, 1989; Joly et al, 1999; Nakagawa et al, 2000), and infection stones occur in an alkaline urine produced by urease-producing bacteria (Marshall et al, 1976). For some stones such as cystine, knowledge of the chemical composition of the stone may provide sufficient information to initiate appropriate therapy. However, due to the multiple causes associated with calcium-based stones, an understanding of the underlying metabolic disorders and environmental factors that predispose to stone formation is required in order to implement a rational treatment plan (Wall et al, 1988; Wall and Tiselius, 1990). Recent investigation into the molecular and genetic causes of stone formation may ultimately translate into newer treatment strategies (Frick et al, 2003; Langman, 2004).

Table 45–1.

Stone Composition and Relative Occurrence

STONE COMPOSITION	OCCURRENCE (%)
Calcium-Containing Stones	
Calcium oxalate	60
Hydroxyapatite	20
Brushite	2
Non–Calcium-Containing Stones	
Uric acid	7
Struvite	7
Cystine	1-3
Triamterene	<1
Silica	<1
2,8-Dihyroxyadenine	<1

From Pearle MS, Pak YC. Renal calculi: a practical approach to medical evaluation and management. In: Andreucci VE, Fine LG, editors. International yearbook of nephrology. New York: Oxford University Press; 1996. p. 69–80, Table 7–1, p. 69.

Calcium Stones

Hypercalciuria

Hypercalciuria is the most common abnormality identified in calcium stone formers (Pak et al, 1982; Coe et al, 1992; Bushinsky, 1998). However, the role of hypercalciuria in stone formation is controversial, owing to the overlap in urine calcium levels between stone formers and non–stone formers (Robertson and Morgan, 1972; Coe et al, 1992). There are several lines of evidence that support a pathogenetic role for hypercalciuria in stone formation. First, hypercalciuria is common in stone-forming patients, occurring in 35% to 65% of patients (Coe and Kavalach, 1974; Menon, 1986). Indeed, treatment strategies aimed at reducing urinary calcium levels are associated with a reduction in stone recurrence rates (Pearle et al, 1999), and medical therapy often fails in patients with persistent hypercalciuria (Strauss et al, 1982). Studies on genetic hypercalciuric stone-forming rats have suggested that hypercalciuria and subsequent calcium phosphate supersaturation play a critical role in stone formation (Bushinsky et al, 2000). Lastly, recent investigations of Randall plaques as potential precursors to calcium stone formation have shown that plaques occur more commonly in stone formers and their number is directly correlated with urine calcium levels and number of stone episodes (Kuo et al, 2003a; Kim et al, 2005b).

High urinary calcium concentrations lead to increased urinary saturation of calcium salts (Pak et al, 1976b) and reduced urinary inhibitory activity by way of complexation with negatively charged inhibitors such as citrate and chondroitin sulfate (Zerwekh et al, 1988). The normal kidney filters approximately 270 mmol of calcium daily and reabsorbs all but 4 mmol (Bushinsky, 1998). However, a variety of conditions lead to elevated urinary calcium levels and increased urinary saturation of calcium salts. Criteria

Table 45–2.

Diagnostic Classification of Nephrolithiasis

CONDITION	METABOLIC/ENVIRONMENTAL DEFECT	PREVALENCE (%)
Absorptive hypercalciuria		20-40
Type I	Increased gastrointestinal calcium absorption	
Type II	Increased gastrointestinal calcium absorption	
Renal phosphate leak	Impaired renal phosphorus absorption	
Renal hypercalciuria	Impaired renal calcium reabsorption	5-8
Resorptive hypercalciuria	Primary hyperparathyroidism	3-5
Hyperuricosuric calcium nephrolithiasis	Dietary purine excess, uric acid overproduction	10-40
Hypocitraturic calcium nephrolithiasis		10-50
Isolated	Idiopathic	
Chronic diarrheal syndrome	Gastrointestinal alkali loss	
Distal renal tubular acidosis	Impaired renal acid excretion	
Thiazide-induced	Hypokalemia	
Hyperoxaluric calcium nephrolithiasis		2-15
Primary hyperoxaluria	Oxalate overproduction	
Dietary hyperoxaluria	Increased dietary oxalate	
Enteric hyperoxaluria	Increased intestinal oxalate absorption	
Hypomagnesiuric calcium nephrolithiasis	Decreased intestinal magnesium absorption	5-10
Gouty diathesis	Low urinary pH	15-30
Cystinuria	Impaired renal cystine reabsorption	<1
Infection stones	Infection with urease-producing bacteria	1-5
Low urine volume	Inadequate fluid intake	10-50
Miscellaneous or no abnormality	NA	<3

From Pearle MS, Pak CY. Renal calculi: a practical approach to medical evaluation and management. In: Andreucci VE, Fine LG, editors. International yearbook of nephrology. New York: Oxford University Press; 1996. p. 69–80, Table 7–2, p. 70.

defining hypercalciuria are variable, but **the strictest definition classifies hypercalciuria as greater than 200 mg of urinary calcium/day after adherence to a 400-mg calcium, 100-mg sodium diet for 1 week** (Menon, 1986). Parks and Coe (1986) **defined hypercalciuria as excretion of greater than 4 mg/kg/day or greater than 7 mmol/day in men and 6 mmol/day in women.**

Historically, the term *idiopathic hypercalciuria* was applied to stone formers for whom classification of their metabolic abnormality was difficult. Calcium transport is regulated at three sites: intestine, bone, and kidney. Dysregulation at any of these sites can lead to hypercalciuria. Furthermore, calcium transport pathways may be interrelated; studies in genetic hypercalciuric rats have demonstrated that hypercalciuria may involve the dysregulation of multiple calcium transport systems (Frick et al, 2003). In 1974 Pak and colleagues divided hypercalciuria into three distinct subtypes on the basis of unique pathophysiologic abnormalities: absorptive hypercalciuria due to increased intestinal absorption of calcium, renal hypercalciuria due to primary renal leak of calcium, and resorptive hypercalciuria due to increased bone demineralization (Pak et al, 1974).

Although this classification system is still widely used due to its utility in simplifying the understanding and treatment of specific metabolic derangements, many have argued that hypercalciuria is associated with multiple, interrelated disturbances that cannot be readily separated into a specific organ system (Coe et al, 1992). Furthermore, studies into the molecular mechanisms of stone formation have identified gene mutations that can affect several organ systems, culminating in hypercalciuria (Frick et al, 2003; Langman, 2004). Improved understanding of the molecular and genetic causes of stone disease may well change the categorization and management of stones in the future.

Absorptive Hypercalciuria. Absorptive hypercalciuria (AH) is defined as increased urinary calcium excretion (>0.2 mg/mg creatinine) after an oral calcium load. Although fasting urinary calcium is usually normal in AH (<0.11 mg/dL glomerular filtration), severe forms of AH may occasionally be associated with fasting hypercalciuria as well. The underlying pathophysiologic abnormality in AH is increased intestinal absorption of calcium, which occurs in approximately 55% of stone formers (Menon, 1986). AH is classified as type I when urinary calcium remains high despite a low calcium diet (400 mg dietary calcium daily) and type II when urinary calcium normalizes with a restricted calcium intake. **The added systemic load of calcium due to intestinal calcium hyperabsorption results in a transient increase in serum calcium, which suppresses serum PTH and results in increased renal filtration of calcium, ultimately leading to hypercalciuria. Because the increase in intestinal absorption of calcium is matched by enhanced renal calcium excretion, serum calcium level remains normal.**

The cause of increased intestinal absorption of calcium has been variously ascribed to vitamin D–independent and dependent processes, as well as to upregulation of the vitamin D receptor (Breslau et al, 1992). However, no proposed mechanism completely accounts for all the findings associated with absorptive hypercalciuria, and there is no clear evidence that upregulation of intestinal calcium absorption is the primary cause. However, hypersensitivity to vitamin D has been shown to increase intestinal calcium absorption (Bushinsky and Monk, 1998). Moreover, several studies have linked hypercalciuria with the vitamin D receptor (VDR) gene. Jackman and colleagues (1999) identified a polymorphism in the VDR gene in 19 patients with a family history of nephrolithiasis and hypercalciuria, thereby establishing a potential link. Likewise, Scott and colleagues (1999) identified linkage between a microsatellite marker and the VDR locus on chromosome 12q12-14 in a cohort of 47 French Canadian pedigrees with idiopathic hypercalciuria and calcium nephrolithiasis.

Other studies, however, failed to confirm the association of VDR abnormalities with hypercalciuria (Zerwekh et al, 1995, 1998).

Indeed, other genetic loci have been identified in association with AH. Reed and colleagues (1999, 2002) mapped the locus for an inherited form of AH to chromosome 1q23.3-q24 and found a putative gene (subsequently shown by others to be homologous with the rat soluble adenylate cyclase gene) in this region in 12 unrelated white AH patients.

Another proposed etiology of AH is renal phosphate wasting leading to a subsequent increase in active vitamin D. Patients with hereditary hypophosphatemic rickets with hypercalciuria (HHRH) manifest this abnormality (Tieder et al, 1987). This disorder is characterized by decreased renal reabsorption of phosphate, hypophosphatemia and a subsequent compensatory increase in vitamin D levels, leading to enhanced absorption of calcium and phosphate from the intestine and hypercalciuria. The mutations associated with HHRH are thought to be inherited in an autosomal recessive pattern. Candidate genes for HHRH include *SLC34A1* and *SLC34A3,* which encode sodium-coupled phosphate transporters located in the apical membrane of the renal proximal tubule (NaPi-IIa and NaPi-IIc, respectively) (Devuyst and Pirson, 2007). Renal phosphate leak, however, is a rare cause of nephrolithiasis, affecting at best 2% to 4% of patients (Levy et al, 1995).

Renal Hypercalciuria. The kidney filters approximately 270 mmol of calcium and must reabsorb more than 98% of it to maintain calcium homeostasis (Bushinsky, 1998). Approximately 70% of calcium reabsorption occurs in the proximal tubule, with paracellular pathways predominating (Frick et al, 2003). In renal hypercalciuria, impaired renal tubular reabsorption of calcium results in elevated urinary calcium levels leading to secondary hyperparathyroidism (Coe et al, 1973). Serum calcium levels remains normal because the renal loss of calcium is compensated by enhanced intestinal absorption of calcium and bone resorption as a result of increased secretion of PTH and enhanced synthesis of $1,25(OH)_2D_3$. **High fasting urinary calcium levels (>0.11 mg/dL glomerular filtration) with normal serum calcium values are characteristic of renal hypercalciuria.** The elevated fasting urinary calcium and serum PTH levels differentiate renal from absorptive hypercalciuria.

Several lines of evidence support the existence of primary renal calcium leak. First, a subset of patients with fasting hypercalciuria and elevated PTH levels show no improvement in urinary calcium levels with ingestion of sodium cellulose phosphate (which binds intraluminal cations, including calcium) despite reduced intestinal calcium absorption (Pak and Galosy, 1979). Second, patients with renal hypercalciuria and secondary elevation in serum PTH have an exaggerated response to hydrochlorothiazide (HCTZ), implying a renal tubular defect in solute reabsorption (Sakhaee et al, 1985). In addition, calcium excretion was higher at baseline and the calciuric response to an oral glucose load (100 g) was significantly higher 3 hours after glucose ingestion in patients with renal hypercalciuria compared with AH patients and normal subjects (Barilla et al, 1978b).

The actual cause of renal calcium leak is not known, although various theories have been proposed involving renal injury, structural abnormalities, and functional defects (Sutton et al, 1980; Yendt et al, 1981). Excessive dietary sodium intake may lead to changes similar to those seen in patients with renal hypercalciuria (Breslau et al, 1982). However, Pak found that restricting sodium alone does not correct biochemical changes seen in patients with renal hypercalciuria (Pak, 1990).

Insights into the abnormalities associated with renal hypercalciuria have come from studies of several genetic disorders (Gambaro et al, 2004; Langman, 2004; Devuyst and Pirson, 2007). Dent disease (X-linked recessive nephrolithiasis), characterized by hypercalciuria, proteinuria, nephrolithiasis, and nephrocalcinosis, and X-linked hypophosphatemic rickets/osteomalacia (XLR) are linked to defects in the CIC-5 chloride channel. The gene for CIC-5 (*CLCN5*) is associated with nine known voltage-gated, transmembrane-spanning chloride channels found in renal tubule and bone cells that are associated with diverse cellular functions such as transepithelial transport, intravesicular acidification, volume regulation, and transmembrane potential homeostasis. Although the exact mechanism by which loss of CIC-5 chloride channels results in hypercalciuria is not understood, it may involve abnormal regulation of vitamin D and PTH.

Activating mutations in the gene encoding the calcium-sensing receptor (CaSR) have been associated with an autosomal dominant form of hypocalcemia by which low serum PTH levels lead to reduced renal calcium reabsorption and subsequent hypocalcemia and hypercalciuria (Devuyst and Pirson, 2007). A potent activating mutation in CaSR has been associated with a salt-losing nephropathy and secondary hyperaldosteronism likely related to dysfunction of the apical renal potassium channel ROMK as a result of constitutive activation of the abnormal CaSR. Other mutations in the genes for the Na^+-K^+-$2Cl^-$ co-transporter NKCC2 and the K^+ channel ROMK have been associated with autosomal recessive disorders characterized by fasting hypercalciuria and nephrocalcinosis. Bartter syndrome, an autosomal recessive syndrome characterized by hypokalemic metabolic alkalosis and secondary hyperaldosteronism, arises from defects in one of three genes involving transepithelial sodium chloride transport across the thick limb of the loop of Henle: the Na^+-K^+-$2Cl^-$ gene *SLC12A1,* the K^+ channel gene *KCNJ1,* or the chloride channel gene *CLCNKB* (Devuyst and Pirson, 2007). Mutations in each of these genes are associated with variable hypercalciuria and nephrolithiasis.

Resorptive Hypercalciuria. Resorptive hypercalciuria is an infrequent abnormality most commonly associated with primary hyperparathyroidism. Primary hyperparathyroidism is the cause of nephrolithiasis in about 5% of cases (Broadus, 1989). Excessive PTH secretion from a parathyroid adenoma leads to excessive bone resorption and increased renal synthesis of $1,25(OH)_2D_3$, which in turn enhances intestinal absorption of calcium. The net effect is elevated serum and urine calcium levels and reduced serum phosphorus levels. Although most patients with primary hyperparathyroidism demonstrate hypercalcemia and hypercalciuria, a normal serum calcium level in the presence of an inappropriately high serum PTH value may be seen in some cases, making the diagnosis more difficult. Administration of a thiazide diuretic will enhance renal calcium reabsorption and exacerbate the hypercalcemia, thereby facilitating the diagnosis ("thiazide challenge") (Coffey et al, 1977). When diagnosing primary hyperparathyroidism, other causes of hypercalcemia should be excluded.

Primary hyperparathyroidism is associated with nephrolithiasis in less than 5% of affected individuals (Heath et al, 1980; Parks et al, 1980). However, the diagnosis should be suspected in patients with nephrolithiasis and serum calcium levels greater than 10.1 mg/dL (Broadus et al, 1980; Menon, 1986). Serum calcium levels can vary by up to 5%, and patients with mild hyperparathyroidism may exhibit relatively small increases of serum calcium (Yendt and Gagne, 1968). As such, repeated measurements of serum calcium may be necessary to make the diagnosis. Measurement of serum ionized calcium may help in equivocal cases because it may be elevated in the setting of normal serum calcium (Yendt and Gagne, 1968). Urinary cyclic AMP levels have been used to diagnose primary hyperparathyroidism because PTH promotes release of cyclic AMP from the kidney, leading to increased

urinary cyclic AMP levels (Broadus et al, 1980). However, this test has been largely abandoned in favor of direct measurement of serum PTH. PTH also increases excretion of bicarbonate and phosphorus from the proximal renal tubule, resulting in phosphaturia and mild hyperchloremic acidosis. Aro and colleagues (1977) noted that a serum chloride–to-phosphate ratio greater than 33, along with a phosphate level below 2.5 mg/dL, should raise suspicion of hyperparathyroidism.

Sarcoid and Granulomatous Disease. Additional, rare causes of resorptive hypercalciuria include hypercalcemia of malignancy, sarcoidosis, thyrotoxicosis, and vitamin D toxicity. Many granulomatous diseases including tuberculosis, sarcoidosis, histoplasmosis, leprosy, and silicosis have been reported to produce hypercalcemia. Among these, sarcoidosis is most commonly associated with urolithiasis. **The hypercalcemia in sarcoidosis is due to the production of $1,25(OH)_2D_3$ from 1-α hydroxylase present in macrophages of the sarcoid granuloma, causing increased intestinal absorption of calcium, hypercalcemia, and hypercalciuria** (Hendrix, 1966; Bell et al, 1979). Pulmonary alveolar cells and lymph node homogenates in patients with sarcoidosis are capable of synthesizing vitamin D, a function usually limited to the kidney. Most patients with sarcoidosis have a suppressed level of PTH secondary to hypercalcemia (Cushard et al, 1972). Sarcoidosis can also be differentiated from other diagnoses by the rapid resolution of hypercalcemia with initiation of corticosteroid therapy (Breslau et al, 1982).

Malignancy-Associated Hypercalcemia. **Whereas primary hyperparathyroidism is the most common cause of hypercalcemia in an outpatient setting, malignancy is the main cause of hypercalcemia in hospitalized patients** (Rizzoli and Bonjour, 1992). An assay for intact PTH can help distinguish patients with hyperparathyroidism from those with other causes of hypercalcemia (Table 45–3) (Burtis et al, 1990). Tumors in patients with humoral hypercalcemia produce a PTH-related protein (PTHrP) whose production is regulated by calcium-sensing receptors on the cell surface (Chattopadhyay, 2006). Lung and breast cancers account for about 60% of malignancy-associated hypercalcemia, whereas renal cell (10% to 15%), head and neck (10%), and hematologic cancers such as lymphoma and myeloma (10%) account for the rest. Although direct mechanical destruction of bone constitutes one cause of hypercalcemia, many tumors secrete humoral factors including PTHrP, transforming growth factor-α, and cytokines such as interleukin-1 and tumor necrosis factor, which activate osteoclasts and result in bone lysis and hypercalcemia (Burtis et al, 1990; Mundy, 1990; Edelson et al, 1995).

Glucocorticoid-Induced Hypercalcemia. Glucocorticoids can significantly alter calcium metabolism through their actions on bone, intestine, and parathyroid glands. Their most potent effect is related to calcium metabolism in bones, where glucocorticoids promote bone resorption and reduce bone formation, ultimately leading to osteopenia with chronic use (Manelli and Giustina, 2000). Additionally, they stimulate release of PTH (Fucik et al, 1975). On the other hand, glucocorticoids inhibit intestinal absorption of calcium, which accounts for their effectiveness in preventing hypercalciuria induced by sarcoidosis (Manelli and Giustina, 2000). The net effect probably favors promotion of stone formation because nephrolithiasis is common in patients with Cushing syndrome (Faggiano et al, 2003). In one study, stones were found in 50% of patients with active Cushing syndrome, 27% of cured patients, and 6.5% of controls. Compared with controls, patients with active disease had a significantly higher prevalence of hypercalciuria, hypocitraturia, and hyperuricosuria, but these patients were also at greater risk of obesity and diabetes, which have been linked to stone formation (Faggiano et al, 2003).

Table 45–3.

Hypercalcemic States

CONDITION	PARATHYROID HORMONE	PHOSPHORUS	URINE CALCIUM	GLOMERULAR FILTRATION RATE	OTHER
Thiazide	N	N	L	N	Low K^+
Malignant tumors	NLH	L/N	H	N/L	Osteolytic or sclerotic bone lesions
Vitamin D excess	L	N/H	H	N/L	
Sarcoidosis	L	N	H	N/L	High $1,25(OH)_2D_3$
Coccidioidomycosis	L	N	H	N/L	High $1,25(OH)_2D_3$
Silicosis	L	N	H	N/L	High $1,25(OH)_2D_3$
Plasma cell granuloma	N	N	—	L	High $1,25(OH)_2D_3$
Leprosy	N	N	H	L	High $1,25(OH)_2D_3$
Hypothyroidism	N	N	H	N	High $1,25(OH)_2D_3$
Primary increase in $1,25(OH)_2D_3$	L	N	H	N	High $1,25(OH)_2D_3$
Pheochromocytoma	L/N	N	H	N	High $1,25(OH)_2D_3$
Hyperthyroidism	N	N	L/N	N	High calcitonin has been reported
Tuberculosis	L	H	H	L	
Addison disease	N	N	L/N	N	
Familial hypocalciuric hypercalcemia	H	N	N	N	
Lithium	N	—	—	—	Asymptomatic
Theophylline	L	N	H	N	
Paget disease	L	N	H	N	
Immobilization	L	L/N	—	—	
Acquired immunodeficiency syndrome					Usually only hypercalciuric Low $1,25(OH)_2D_3$

H, high; L, low; N, normal; $1,25(OH)_2D_3$, 1,25-dihydroxyvitamin D_3.

From Coe FL, Park JH, editors. Nephrolithiasis: pathogenesis and treatment. Chicago: Year Book Medical Publishers; 1988. p. 85.

Hyperoxaluria

Hyperoxaluria, defined as urinary oxalate greater than 40 mg/day, leads to increased urinary saturation of calcium oxalate and subsequent promotion of calcium oxalate stones. Additionally, oxalate has been implicated in crystal growth and retention by means of renal tubular cell injury mediated by lipid peroxidation and the generation of oxygen free radicals (Ravichandran and Selvam, 1990). Membrane injury facilitates the fixation of calcium oxalate crystals and subsequent crystal growth. Antioxidant therapy has been shown to prevent calcium oxalate precipitation in the rat kidney and to reduce oxalate excretion in stone patients (Selvam, 2002). Similarly, calcium oxalate crystal deposition on urothelium in vitro was prevented by free radical scavengers such as phytic acid and mannitol, purportedly by protecting the membrane from free radical–mediated damage (Thamilselvan and Selvam, 1997; Selvam, 2002). Recent human studies, however, failed to demonstrate increases in markers of oxidative stress or renal injury in normal subjects and stone formers ingesting large doses of oxalate (up to 8 mmol), thus calling into question the importance of oxalate-induced cell membrane damage in calcium oxalate stone formation (Knight et al, 2007).

Causes of hyperoxaluria include disorders in biosynthetic pathways (primary hyperoxaluria); intestinal malabsorptive states associated with inflammatory bowel disease, celiac sprue, or intestinal resection (enteric hyperoxaluria); and excessive dietary intake or high substrate levels (vitamin C) (dietary hyperoxaluria).

Primary Hyperoxaluria. Primary hyperoxaluria (PH) is the result of a rare autosomal recessive disorder in glyoxylate metabolism by which the normal conversion of glyoxylate to glycine is prevented, leading to preferential oxidative conversion of glyoxylate to oxalate, an end product of metabolism (Fig. 45–6). Consequently, markedly high levels of urinary oxalate ensue (>100 mg/day), leading to increased saturation of calcium oxalate and formation of calcium oxalate complexes and crystals in the renal tubular lumen. Some crystals attach to the surface of renal tubular epithelial cells and further aggregate into stones, whereas others are internalized into the tubular cells and then extruded into the renal interstitium, leading to marked nephrocalcinosis (Hoppe et al, 2009). Renal injury may be a consequence of direct cell toxicity from either high oxalate concentration or calcium oxalate crystals, mediated through reactive oxygen species. Renal impairment occurs from recurrent calcium oxalate stones and as a result of renal parencyhymal inflammation and interstitial fibrosis from severe nephrocalcinosis.

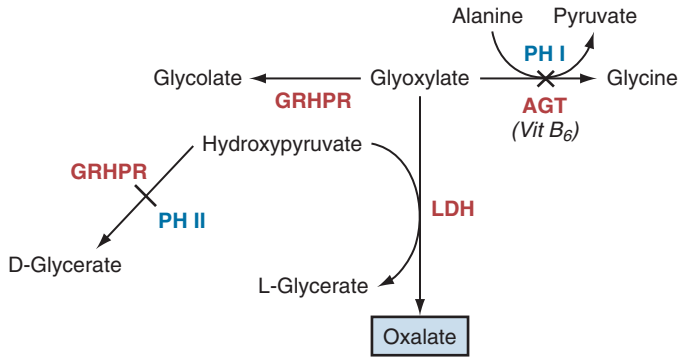


Figure 45–6. Pathway of oxalate metabolism in the liver. Defects in alanine:glyoxylate aminotranserase (AGT) are associated with primary hyperoxaluria type I (PH I), and defects in glyoxylate reductase/hydroxypyruvate reductase (GRHPR) are associated with primary hyperoxaluria type II (PH II). LDH, lactate dehydrogenase.

The primary enzyme catalyzing glyoxylate conversion to glycine is alanine/glyoxylate aminotransferase (AGT), which is synthesized in the liver. Mutations in this gene *(AGXT)* result in primary hyperoxaluria type 1, and patients with this disorder have elevated levels of oxalate and frequently glycolate. Elucidation of the crystal structure of AGT to 2.5A° has improved the understanding of mutations in the gene for this protein (Zhang et al, 2003). The most common mutation of the AGT gene *(AGXT)* results in a substitution of glycine by arginine at position 170, which results in failure of the enzyme to dimerize, thereby causing the enzyme to inappropriately target the liver mitochondria, where it is metabolically inactive, rather than the liver peroxisomes (Danpure et al, 2003). In vitro experiments have shown that by varying temperature in the presence of glycerol, the enzyme can be induced to dimerize correctly, thus becoming completely functional (Lumb et al, 2003). Other mutations result in accelerated AGT proteolysis, intraperoxisomal aggregation, and loss of catalytic activity (Langman, 2004). To date, more than 100 mutations have been identified in the *AGXT* gene.

Primary hyperoxaluria type 2 (PH2) is associated with a defect in glyoxylate reductase/hydroxypyruvate reductase (GRHPR) in the liver, resulting in hyperoxaluric nephrolithiasis, but with a less aggressive course with regard to renal failure than PH1 (Johnson et al, 2002). Patients with PH2 have elevated urinary levels of L-glyceric acid and oxalate because reduced GRHPR enzyme activity leads to increased hydroxypyruvate and glyoxylate, which are converted by lactate dehydrogenase to L-glyceric acid and oxalate. A third type of primary hyperoxalauria, non-I, non-II primary hyperoxaluria, accounts for 5% of patients with PH and is clinically indistinguishable from PHI or PHII, except these patients have normal AGT and GRHPR enzyme activities (Monico et al, 2002). The etiology of hyperoxaluria in non-I, non-II PH has yet to be identified.

If untreated, primary hyperoxaluria inevitably leads to end-stage renal failure, which occurs by age 15 in 50% of affected patients and is associated with an overall death rate of approximately 30% (Cochat et al, 1999). Because the liver is the only organ responsible for detoxification of glyoxylate, combined liver-kidney transplant is accepted treatment for most patients with severe primary hyperoxaluria. Reported 5-year patient and liver allograft survival after combined liver/kidney transplant are 80% and 72%, respectively (Jamieson et al, 2005). Furthermore, the renal function of survivors reportedly remains stable over time (Cochat et al, 1999; Hoppe and Langman, 2003).

Enteric Hyperoxaluria. The most common cause of acquired hyperoxaluria is enteric hyperoxaluria. This abnormality is associated with chronic diarrheal states, by which **fat malabsorption results in saponification of fatty acids with divalent cations such as calcium and magnesium, thereby reducing calcium oxalate complexation and increasing the pool of available oxalate for reabsorption** (Earnest et al, 1975). The poorly absorbed fatty acids and bile salts may increase colonic permeability to oxalate, further enhancing intestinal oxalate absorption (Dobbins et al, 1976). A strong relationship between fecal fat and urinary oxalate excretion has been demonstrated in patients with steatorrhea (Fig. 45–7) (Worcester et al, 1996). Dehydration, hypokalemia, hypomagnesuria, hypocitraturia, and low urine pH also increase the risk of calcium oxalate stone formation in patients with chronic diarrheal syndrome. Malabsorption of any cause can lead to increased intestinal absorption of oxalate. As such, small bowel resection (Smith et al, 1972),

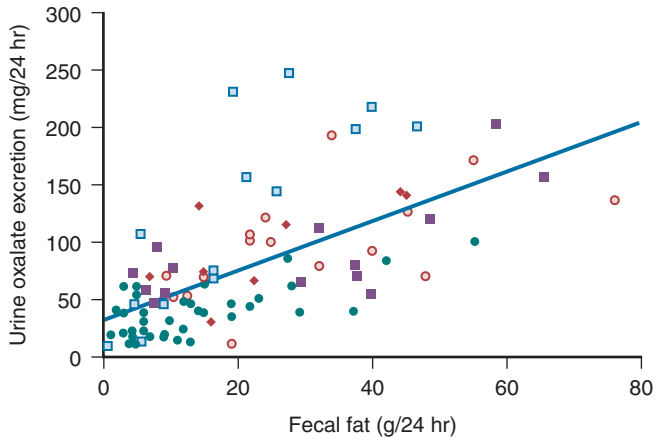


Figure 45–7. The relationship between fecal fat and urinary oxalate excretion in patients with steatorrhea. Diet oxalate was 300 to 500 mg/day in all but one study in which it was 55 to 90 mg/day. Diet calcium was 500 to 900 mg/day in all studies when reported. Normal urine citrate was less than 50 mg/day in all studies, except one in which it was less than 34 mg/day. Oxalate = 2.1 × fecal fat + 30.7 ($r^2 = 0.4$, $n = 96$, $P < .001$). (From Worcester EM. Stones due to bowel disease. In Coe F, Favus M, Pak C, et al, editors. Kidney stones: medical and surgical management. New York: Lippincott-Raven; 1996. p. 883–903.)

intrinsic disease, and jejunoileal bypass (Cryer et al, 1975) have all been associated with hyperoxaluria.

As the prevalence of obesity in the population has increased, bariatric surgery has become more popular and pervasive. In the past, jejunoileal (JI) bypass for obesity was discontinued in part due to renal failure and nephrolithiasis induced by severe hyperoxaluria. However, a recent retrospective review from the Mayo Clinic revealed 23 patients since 1985 diagnosed with enteric hyperoxaluria and calcium oxalate stones or oxalate nephropathy after Roux-en-Y gastric bypass surgery. Most concerning were the two patients with oxalate nephropathy and renal failure who required dialysis and/or renal transplant (Nelson et al, 2005). Mean urinary oxalate in this group was 0.92 mmol/day (normal < 0.46 mmol/day). Asplin and Coe (2007) compared 24-hour urine chemistries from 132 patients with nephrolithiasis who previously underwent modern bariatric surgery (gastric banding or gastric bypass) with 27 patients who underwent JI bypass, 2048 routine stone formers, and 168 normal subjects. Patients who underwent modern bariatric surgery had significantly higher adjusted mean urine oxalate excretion (83 mg/day) compared with routine stone formers (39 mg/day) and normal subjects (34 mg/day) ($P < 0.001$ for both comparisons), but not quite as high as JI bypass patients (102 mg/day, $P < 0.001$). Urinary saturation of calcium oxalate, the main driving force for calcium oxalate stone formation, was higher in bariatric surgery patients than in routine stone formers or normal subjects ($P < 0.001$ for both comparisons). A similar study in non–stone-forming adults who underwent laparoscopic Roux-en-Y or biliopancreatic diversion-duodenal switch procedures revealed that the bariatric group had a significantly higher mean urinary oxalate excretion than the controls and stone formers (67.2 vs. 34.1 and 37.0 mg per day, respectively, $P < 0.001$) (Patel et al, 2009). Sinha and colleagues (2007) determined that hyperoxaluria develops at least 6 months after undergoing Roux-en-Y gastric bypass surgery. In a prospective longitudinal study of 24 morbidly obese adults undergoing Roux-en-Y gastric bypass surgery who submitted a 24-hour urine before and 3 months after bypass surgery, urinary oxalate excretion increased by 32% after surgery from a mean of 31 mg/day preoperatively to a mean of 41 mg/day 3 months postoperatively ($P = 0.026$) (Duffey et al, 2008). Likewise, relative supersaturation of calcium oxalate rose significantly from 1.73 to 3.47 ($P = 0.0017$).

Dietary Hyperoxaluria. Overindulgence in oxalate-rich foods such as nuts, chocolate, brewed tea, spinach, broccoli, strawberries, and rhubarb can result in hyperoxaluria in otherwise normal individuals. Increased animal protein can also increase urinary levels of calcium and oxalate (Robertson et al, 1979). The contribution of dietary oxalate to urinary oxalate excretion can range from 24% to 42% (Holmes et al, 2001). In addition, severe calcium restriction may result in reduced intestinal binding of oxalate and increased intestinal oxalate absorption. Ascorbic acid supplementation has been shown to increase urinary oxalate levels by in vivo conversion to oxalate (Traxer et al, 2003), although increased clinical rates of stone formation have not been unequivocally linked to ascorbic acid use (Curhan et al, 1996, 1999).

Recent studies have also implicated *Oxalobacter formigenes,* an oxalate-degrading intestinal bacterium, as a potential modulator of intestinal oxalate levels (Duncan et al, 2002). Reduced levels or absent colonization of *O. formigenes* were found in stone formers compared with non–stone-forming control subjects, and individuals lacking the bacteria have been shown to have higher urinary oxalate levels (Sidhu et al, 1999; Mikami et al, 2003; Troxel et al, 2003). In a recent large case-control study of age- and gender-matched recurrent calcium oxalate stone formers ($n = 274$) and normal subjects ($n = 259$), 17% of stone formers and 38% of normal subjects tested positive for *O. formigenes* (Kaufman et al, 2008). Controlling for confounding factors, the odds ratio for colonization (case vs. control) was 0.3 (95% confidence interval 0.2 to 0.5). Interestingly, median urinary oxalate levels did not differ between those with or without *O. formigenes* colonization. **Cystic fibrosis patients, many of whom are exposed to prolonged antibiotic use, have also been shown to have absence of *O. formigenes* from the intestinal tract and corresponding elevated urinary oxalate levels** (Sidhu et al, 1998).

Idiopathic Hyperoxaluria. Several studies have suggested that mild hyperoxaluria is as important a factor as hypercalciuria in the pathogenesis of idiopathic calcium oxalate stones (Menon, 1986; Robertson et al, 1993). In some populations such as those inhabiting the Arabian Peninsula, the prevalence of calcium-containing stones is considerably higher than in the West despite the almost complete absence of hypercalciuria (Robertson and Hughes, 1993). Hyperoxaluria is implicated as the predominant risk factor in this population.

Abnormalities in the metabolism and transport of oxalate may contribute to calcium oxalate nephrolithiasis. Baggio and colleagues (1986) detected a higher rate of oxalate flux across the red blood cell membrane at steady state in 114 patients with a history of calcium oxalate kidney stones compared with control subjects. Treatment with oral HCTZ (50 mg/day), amiloride (5 mg/day), or both restored normal or nearly normal red blood cell oxalate exchange in all of the patients who initially demonstrated increased rates. Up to 50% of the time, however, the abnormality in red blood cell oxalate transport is not associated with hyperoxaluria. Furthermore, Motola and colleagues found high rates of oxalate flux in non–calcium oxalate stone formers as well, thus leading some to question the importance of this mechanism in calcium oxalate stone formation (Motola et al, 1992).

Hyperuricosuria

Hyperuricosuria is defined by urinary uric acid exceeding 600 mg/day. Up to 10% of calcium stone formers have high urinary uric

acid levels as the only abnormality (Menon, 1986). Hyperuricosuria increases urinary levels of monosodium urate, which in turn promotes calcium oxalate stone formation. At pH less than 5.5, the undissociated form of uric acid predominates, leading to uric acid and/or calcium oxalate stone formation. **At pH greater than 5.5, sodium urate formation promotes calcium oxalate stone formation through heterologous nucleation** (Grover et al, 1994). Uric acid may also reduce the effectiveness of naturally occurring inhibitors of crystallization (Robertson et al, 1976); **uric acid crystals can bind urinary glycosaminoglycans such as heparin that inhibit crystallization of calcium oxalate** (Finlayson et al, 1978a; Grover et al, 1994). Several studies have shown that patients with hyperuricosuria and calcium stones have higher rates of stone formation and more severe symptoms than stone formers with normouricosuria (Coe and Kavalach, 1974; Favus et al, 1980; Fellstrom et al, 1982).

The most common cause of hyperuricosuria is increased dietary purine intake. However, acquired and hereditary diseases may also be accompanied by hyperuricosuria including gout, myeloproliferative and lymphoproliferative disorders, multiple myeloma, secondary polycythemia, pernicious anemia, hemolytic disorders, hemoglobinopathies and thalassemia, complete or partial hypoxanthine-guanine phosphoribosyltransferase deficiency, overactivity of phosphoribosylpyrophosphate synthetase, and hereditary renal hypouricemia (Halabe and Sperling, 1994). The recent identification of a urate transporter in the proximal renal tubule, the anion exchanger URAT1, may provide new insight into the causes of hyperuricosuria (Enomoto et al, 2002; Ichida et al, 2004). Mutations in the gene encoding URAT1, *SLC22A12,* have been shown to cause hyperuricosuric hypouricemia (renal uric acid leak) along with exercise-induced acute renal failure and a high risk of kidney stones (Enomoto et al, 2002; Tanaka et al, 2003; Ichida et al, 2004; Iwai et al, 2004,).

Another potential gene abnormality, characterized by an increased prevalence of uric acid stones, has been identified in a small, isolated founder population in Sardinia. A susceptibility locus was identified on chromosome 10q21-q22 that codes for a protein with unknown function but that has a strong association with uric acid stones (Ombra et al, 2001; Gianfrancesco et al, 2003).

Hypocitraturia

Hypocitraturia is an important and correctable abnormality associated with nephrolithiasis that exists as an isolated abnormality in up to 10% of calcium stone formers and is associated with other abnormalities in 20% to 60% (Menon and Mahle, 1983; Pak and Fuller, 1986; Pak, 1994; Pak et al, 1985; Levy et al, 1995). Citrate is an important inhibitor that can reduce calcium stone formation by several mechanisms. First, citrate reduces urinary saturation of calcium salts by complexing with calcium (Pak et al, 1982). Second, citrate directly prevents spontaneous nucleation of calcium oxalate (Sakhaee et al, 1987). Third, citrate inhibits agglomeration and sedimentation of calcium oxalate crystals (Kok et al, 1986; Tiselius et al, 1993a, 1993b), as well as the growth of calcium oxalate and calcium phosphate crystals (Meyer and Smith, 1975). Finally, normal urinary citrate levels can enhance the inhibitory effect of Tamm-Horsfall glycoprotein (Hess et al, 1993).

Hypocitraturia is defined as a urinary citrate level less than 320 mg/day (Pak, 1987) or less than 0.6 mmol (men) or 1.03 mmol (women) daily (Menon and Mahle, 1983). **Acid-base state is the primary determinant of urinary citrate excretion. Metabolic acidosis reduces urinary citrate levels secondary to enhanced renal tubular reabsorption and decreased synthesis of citrate in peritubular cells** (Jenkins et al, 1985). A study comparing normal subjects and stone formers noted comparable mean serum citrate levels and filtered citrate loads in the two groups; however, 24-hour urinary citrate and the fasting citrate-to-creatinine ratio were significantly reduced and mean tubular reabsorption of citrate was significantly increased in the stone formers compared with control subjects (Minisola et al, 1989).

Indirect evidence for a primarily renal etiology of hypocitraturia comes from a study comparing intestinal absorption of citrate in idiopathic hypocitraturic stone formers and normal subjects (Fegan et al, 1992). Oral ingestion of citrate was followed by rapid and efficient absorption in both groups, with 96% to 98% absorbed within 3 hours. As such, hypocitraturia is unlikely to arise from impaired gastrointestinal absorption of citrate in stone formers without overt bowel disease.

Low urinary citrate results from a variety of pathologic states associated with acidosis. Distal renal tubular acidosis (RTA) is characterized by high urine pH (>6.8), high serum chloride, and low serum bicarbonate and potassium (Preminger et al, 1985). The inability to acidify urine in response to an oral acid (ammonium chloride) load confirms the diagnosis of RTA. Chronic diarrheal states cause intestinal alkali loss in the stool with subsequent systemic acidosis and hypocitraturia (Rudman et al, 1980). Excessive animal protein can provide an acid load, reducing citrate levels (Breslau et al, 1988). Indeed, a recent metabolic study evaluating the effect of a high-protein, low-carbohydrate diet demonstrated a significant reduction in urinary citrate and pH, likely as a result of low citrus and high animal protein intake (Reddy et al, 2002). Diuretics such as thiazides induce hypokalemia and intracellular acidosis (Nicar et al, 1984). Enalapril can cause hypocitraturia independently of systemic acidosis or hypokalemia, perhaps due to intracellular acidosis (Melnick et al, 1998). Finally, strenuous exercise may induce lactic acidosis (Sakhaee et al, 1987). However, hypocitraturia may also represent an isolated abnormality unrelated to an acidotic state.

Citrate levels in the urine increase in alkalotic states, as well as with elevated levels of PTH, estrogen, growth hormone, and vitamin D.

Low Urine pH

At low urine pH (<5.5), the undissociated form of uric acid predominates, leading to uric acid and/or calcium stone formation. Calcium oxalate stones form as a result of heterologous nucleation with uric acid crystals (Coe and Kavalach, 1974; Pak et al, 1976a). Any disorder leading to low urine pH may predispose to stone formation. Chronic metabolic acidosis can lead to low urine pH, hypercalciuria, and hypocitraturia. Acidosis increases bone resorption and produces renal calcium leak (Lemann, 1999; Lemann et al, 2003). "Gouty diathesis" refers to a stone-forming propensity characterized by low urine pH of unknown etiology with or without associated gouty arthritis (Levy et al, 1995).

Renal Tubular Acidosis

RTA is a clinical syndrome characterized by metabolic acidosis resulting from defects in renal tubular hydrogen ion secretion or bicarbonate reabsorption. There are three types of RTA: 1, 2, and 4. **Type 1 (distal) RTA is of particular significance to urologists not only because it is the most common form of RTA but also because it is the form of RTA most frequently associated with stone formation,** which occurs in up to 70% of affected individuals (Van

den Berg et al, 1983; Caruana et al, 1988). Indeed, symptoms associated with nephrolithiasis led to the initial diagnosis of RTA in upward of 50% of cases (Van den Berg et al, 1983).

Acid-base balance is maintained by the kidney through several mechanisms involving both the proximal and distal nephron. Because bicarbonate is freely filtered at the glomerulus, the **kidney must reabsorb or regenerate nearly all of the filtered bicarbonate each day** (≈4500 mmol) to maintain its buffering capacity (Pohlman et al, 1984). **Furthermore, the kidney must excrete excess acid,** which accumulates from the breakdown of carbohydrates, fats, and proteins and as a result of bicarbonate loss in the stool (Kinkead et al, 1995). A defect in either bicarbonate reabsorption or acid excretion will lead to metabolic acidosis.

Filtered bicarbonate (HCO_3^-) is almost completely reabsorbed in the proximal renal tubule through an indirect mechanism involving H^+ secretion (Laing et al, 2005). As sodium (Na^+) is pumped out of the proximal tubule cell by the Na^+/K^+-ATPase exchanger located in the basolateral membrane, intracellular sodium decreases, driving the Na^+/H^+ exchanger in the apical membrane. Additionally, an apical H^+-ATPase further secretes H^+ into the tubular lumen. Carbonic anhydrase in the tubular cells generates H^+ and HCO_3^-, thereby providing H^+ ions that are secreted into the tubular lumen. HCO_3^- is then transferred via a basolateral Na^+/HCO_3^- cotransporter to accomplish net transepithelial HCO_3^- absorption (Unwin et al, 2002). **The proximal nephron is a high-capacity, low-gradient transport system that allows reabsorption of filtered HCO_3^- without causing net H^+ secretion or significant changes in urinary pH** (Rocher and Tannen, 1986; Kinkead et al, 1995).

In the distal nephron, 5% to 10% of the filtered bicarbonate is reabsorbed in a manner similar to the proximal nephron. Net elimination of H^+ occurs through several mechanisms. **Hydrogen binds with urinary buffers such as phosphate and ammonia, allowing net elimination of hydrogen in the form of NH_4^+. Net H^+ excretion occurs through active secretion from α-intercalated cells.** These cells secrete H^+ using an H^+ ATPase and an H^+/K^+ ATPase exchanger (Laing et al, 2005). The intercalated cells also have a Cl^-/HCO_3^- anion exchanger that transports HCO_3^- into the blood and is homologous to the red cell anion exchanger known as "band 3 protein" (AE1) (Alper, 1991; Shayakul et al, 2004a, 2004b). **These active pumps generate a 1000:1 hydrogen ion gradient between the cell and the tubular lumen, allowing reduction of urine pH to as low as 4.5** (Kinkead et al, 1995). Another contributing factor is the lack of luminal carbonic anhydrase that prevents the rapid dissociation of carbonic acid catalyzed by the enzyme.

RTA occurs as a result of impairment of net excretion of acid into the urine (type 1) or of reabsorption of bicarbonate (type 2) (Kinkead et al, 1995). Distinction between these abnormalities provides the means for classification of RTA into proximal or distal, although both share the characteristic findings of hyperchloremic metabolic acidosis associated with inappropriately high urinary pH.

Type 1 (Distal) RTA. **Type 1 RTA comprises a syndrome of abnormal collecting duct function characterized by inability to acidify the urine in the presence of systemic acidosis.** The classic findings include hypokalemic, hyperchloremic, non–anion gap metabolic acidosis along with nephrolithiasis, nephrocalcinosis, and elevated urine pH (>6.0) (Pohlman et al, 1984). Patients with incomplete RTA also demonstrate defective renal acid excretion manifest as failure to lower urine pH below 5.5 after an acid load, but they do not manifest metabolic acidosis and consequently have normal serum electrolytes (Osther et al, 1989).

Patients with distal RTA commonly present as adults with symptoms of nephrolithiasis (Caruana et al, 1988). However, children comprise a third of affected individuals, and they often present with vomiting or diarrhea, failure to thrive, or growth retardation. The most common stone composition associated with distal RTA is calcium phosphate as a result of **hypercalciuria, hypocitraturia, and increased urinary pH** (Fig. 45–8) (Van den Berg et al, 1983; Pohlman et al, 1984). The metabolic acidosis promotes bone demineralization, which leads to secondary hyperparathyroidism and hypercalciuria. **Profound hypocitraturia, perhaps the most important factor in stone formation**

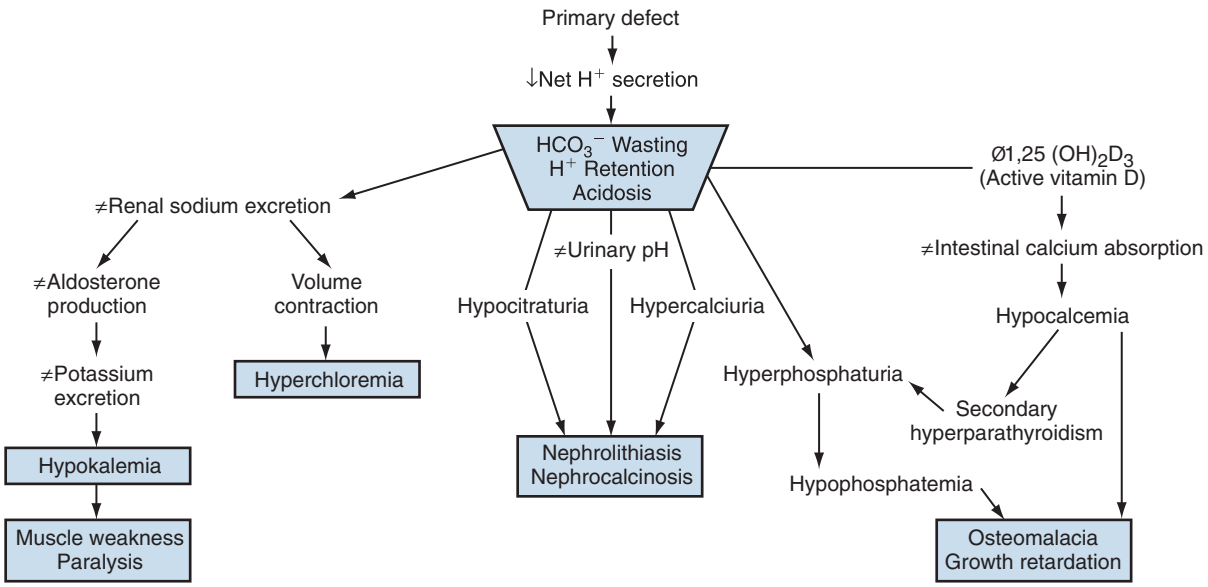


Figure 45–8. Pathophysiologic mechanisms accounting for clinical features of type 1 (distal) renal tubular acidosis. Primary defects in renal acid excretion lead directly and through hormonally mediated pathways to metabolic abnormalities that produce the clinical syndromes seen in renal tubular acidosis. (From Kinkead TM, Menon M. Renal tubular acidosis. AUA Update 1995;14:54.)

in this setting, is due to impaired citrate excretion as a result of metabolic acidosis but may also be related to abnormal renal tubular citrate transport or migration of citrate into the mitochondria due to intracellular acidosis (Osther et al, 1989; Kinkead et al, 1995).

Distal RTA occurs as a consequence of dysfunction of the α-type intercalated cells, which secrete protons into the urine via an apical H^+ ATPase that is coupled to an anion exchanger AE1 located at the basolateral membrane (Fig. 45–9) (Karet, 2002). Mutations in three genes in the α-type intercalated cells have been implicated in distal RTA; *SLC4A1* encodes the AE1 Cl^-/HCO_3^- anion exchanger, and *ATP6V1B1* and *ATP6V0A4* encode the B1 and A4 subunits, respectively, of the H^+ ATPase.

Distal RTA is a heterogeneous disorder that may be hereditary, idiopathic, or acquired (Laing et al, 2005). Although most cases of distal RTA are sporadic, both autosomal dominant and autosomal recessive patterns of inheritance have been identified. The inherited forms of distal RTA are both associated with growth retardation, nephrocalcinosis, renal calculi, and hypokalemic metabolic acidosis, but the phenotype is usually more severe in the autosomal recessive form of the disease. Autosomal recessive distal RTA also tends to occur earlier in life and is additionally associated with mental retardation and sensorineural hearing loss or deafness.

Mutations in the *SLC4A1* gene are most commonly associated with the autosomal dominant form of distal RTA, although an autosomal recessive form associated with a mutation in this gene is endemic in Southeast Asia, where it has been associated with sudden unexplained nocturnal death, hypokalemic periodic paralysis, and renal stones (Nimmannit et al, 1991, 1996; Sritippayawan et al, 2004).

Mutations in the *ATP6V1B1* and *ATP6V0A4* genes encoding the H^+ ATPase have been primarily associated with autosomal recessive distal RTA (Batlle et al, 2006). Although mutations in the *ATP6V1B1* gene have been implicated in RTA and severe childhood deafness, mutations in the *ATP6V0A4* gene have been associated with a milder form of hearing loss that occurs later, in early adulthood (Karet et al, 1999; Batlle et al, 2006).

Secondary distal RTA in sporadic cases is commonly associated with autoimmune diseases such as Sjögren syndrome and systemic lupus erythematosus, and it occurs more frequently in women than men (Buckalew, 1989). Secondary RTA is also associated with obstructive uropathy, pyelonephritis, acute tubular necrosis, hyperparathyroidism, and idiopathic hypercalciuria.

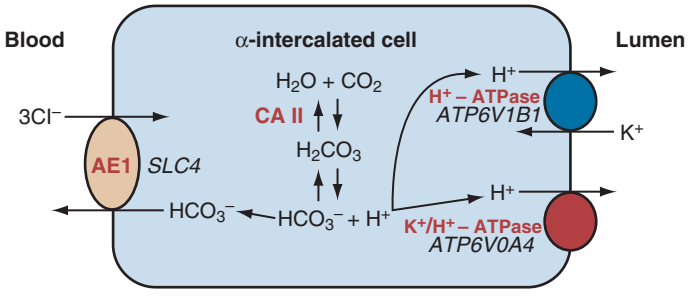


Figure 45–9. Mechanism of acidification in the collecting duct α-intercalated cell. Enzymes are shown in red and their corresponding genes in italics. The α-intercalcated cells secrete H^+ into the lumen of the distal tubule and collecting duct by way of an apical H^+ ATPase and possibly an H^+/K^+ ATPase exchanger. Bicarbonate is transported into the blood via a Cl^-/HCO_3^- anion exchanger on the basolateral membrane. Defects in the AE1 Cl^-/HCO_3^- anion exchanger or the H^+ ATPase result in failure to acidify the urine in distal renal tubular acidosis.

Type 2 (Proximal) RTA. **Proximal RTA is characterized by a defect in HCO_3^- reabsorption associated with initial high urine pH that normalizes as plasma HCO_3^- decreases and the amount of filtered HCO_3^- falls** (Laing et al, 2005). With reduced capacity of the proximal tubule to reclaim filtered HCO_3^-, more HCO_3^- is delivered to the distal tubule, which has a limited capacity for bicarbonate reabsorption. Consequently, bicarbonaturia ensues, resulting in reduced net acid excretion and metabolic acidosis. As the filtered HCO_3^- load declines with progressive metabolic acidosis, less bicarbonate reaches the distal tubule, until eventually the capacity of the distal tubule is sufficient to handle the load and no further bicarbonate is lost. At steady state, serum HCO_3^- is low (15 to 18 mEq/L) and urine pH is acid (<5.5).

This syndrome is usually associated with generalized defects in proximal tubule function similar to Fanconi syndrome, with loss of glycogen, protein, uric acid, and phosphate (Rocher and Tannen, 1986). **Nephrolithiasis is uncommon in this disorder owing to relatively normal urinary citrate excretion** (Laing et al, 2005). The clinical manifestations of proximal RTA include growth retardation and hypokalemia in children due to metabolic acidosis. Metabolic bone disease is seen more frequently with proximal RTA due to associated abnormalities in vitamin D metabolism and hypophosphatemia (Kinkead et al, 1995).

Most cases of proximal RTA are sporadic, but inherited diseases associated with proximal RTA have been described. In humans and terrestrial vertebrates, the kidneys control systemic pH in part by absorbing filtered HCO_3^- in the proximal tubule via an electrogenic Na^+/HCO_3^- cotransporter (NBCe1/SLC4A4). Homozygous point mutations in NBCe1 cause proximal renal tubular acidosis, glaucoma, and cataracts (Igarashi et al, 1999). Other mutations in this gene have been identified that cause voltage- and Na^+-dependent transport abnormalities, thereby causing both insufficient HCO_3^- reabsorption by the kidney (proximal RTA) and inappropriate anterior chamber fluid transport (glaucoma) (Dinour et al, 2004).

Carbonic anhydrase II catalyzes the hydration/dehydration of CO_2 and H_2CO_3 and is expressed in the renal proximal tubule, loop of Henle, and intercalating cells of the collecting duct, as well as in brain glial cells and bone osteoclasts (Laing et al, 2005). Deficiency of carbonic anhydrase II (carbonate hydrolyase, EC 4.2.1.1) is the primary defect in the syndrome of osteopetrosis, proximal renal tubular acidosis, and cerebral calcification. Fortunately, this is a rare abnormality (Sly et al, 1985; Roth et al, 1992).

Type 4 (Distal) RTA. **Type 4 RTA is associated with chronic renal damage, usually seen in patients with interstitial renal disease and diabetic nephropathy.** Reduction in glomerular filtration results in hyperkalemic, hyperchloremic metabolic acidosis due to loss of HCO_3^- in the urine and decreased excretion of ammonium (Pohlman et al, 1984). Aldosterone resistance is commonly associated with type 4 RTA (Davidman et al, 1988). Because aldosterone contributes to stimulation of distal acidification and H^+/K^+ exchange, aldosterone resistance results in decreased ammonia generation and further exacerbates hyperkalemia (Davidman et al, 1988). Patients with type 4 RTA can still generate acidic urine in response to an acid challenge.

Renal stone formation is uncommon in patients with type 4 RTA. A study comparing patients with type 4 RTA and matched subjects with a similar degree of renal impairment found that patients with type 4 RTA had significantly lower urinary pH and decreased urinary calcium excretion than controls (Uribarri et al, 1994). **The protection against renal stone formation in these patients may be attributed to reduced renal**

excretion of stone-forming substances such as calcium and uric acid owing to impaired renal function.

Hypomagnesuria

Hypomagnesuria is a rare cause of nephrolithiasis, affecting less than 1% of stone formers as an isolated abnormality, although it can be found in conjunction with other abnormalities in 6% to 11% of cases (Levy et al, 1995; Schwartz et al, 2001). **Magnesium complexes with oxalate and calcium salts, and therefore low magnesium levels result in reduced inhibitory activity. Low urinary magnesium is also associated with decreased urinary citrate levels, which may further contribute to stone formation** (Preminger et al, 1989; Schwartz et al, 2001). Whether low magnesium is the cause or effect of low citrate is not clear. Low magnesium levels occur with poor dietary intake (Pfab et al, 1985) or as a result of reduced intestinal absorption associated with intestinal abnormalities producing chronic diarrheal syndrome (Rudman et al, 1980).

Although a number of studies in rats have implicated hypomagnesuria as a factor in stone formation (Rushton and Spector, 1982), others (Faragalla et al, 1963; Borden et al, 1969; Rattan et al, 1993) have questioned the impact of magnesium (Su et al, 1991). Clinical studies regarding the role of magnesium are contradictory. Schwartz and colleagues (2001) found that hypomagnesiuric patients had higher stone recurrence rates than patients with normal urinary magnesium. However, other studies found no difference in magnesium excretion between stone patients and controls (Johansson et al, 1980; Esen et al, 1991). Of note, the lack of difference in mean magnesium levels may be a result of the small fraction of stone formers with low urinary magnesium levels.

Although magnesium has been shown to increase urinary pH, citrate, and magnesium and therefore to decrease urinary saturation of calcium oxalate in vitro (Khan et al, 1993) and in vivo (Curhan et al, 2001), two randomized trials comparing magnesium oxide with placebo or no treatment in stone formers have failed to demonstrate clinical benefit (Wilson et al, 1984; Ettinger et al, 1988).

Uric Acid Stones

Most mammals, except humans and Dalmatians, synthesize the hepatic enzyme uricase, which catalyzes the conversion of uric acid to allantoin, the end product of purine metabolism (Yu, 1981; Bannasch et al, 2004). Consequently, humans accumulate significantly higher levels of uric acid in their blood and urine (Watts, 1976; Yu, 1981). Because allantoin is 10 to 100 times more soluble in urine than uric acid, humans are prone to uric acid stone formation.

Uric acid is a weak acid with a pKa of 5.35 at 37° C. At that pH, half of the uric acid is present as the urate salt and half as free uric acid. Because sodium urate is approximately 20 times more soluble than the free acid, the relative proportion present as free uric acid strongly determines the risk of stone formation. **Urine pH is a critical factor in determining uric acid solubility;** at pH 5, even modest amounts of uric acid exceed uric acid solubility, whereas at pH 6.5, concentrations of uric acid exceeding 1200 mg/L remain soluble (see Fig. 45–10 on the Expert Consult website) (Asplin, 1996). Under normal conditions, the limit of uric acid solubility is approximately 96 mg/L, a level readily exceeded by normal daily uric acid excretion, which averages 500 to 600 mg/L. Consequently, urine may reach supersaturation, particularly at pH less than 6. Low urine pH increases concentrations of sparingly soluble undissociated uric acid, which leads to direct precipitation of uric acid. Of note, uric acid and sodium urate can also serve as a nidus for calcium oxalate stones through heterologous nucleation, and, thus, low urine pH is a risk factor for both uric acid and calcium oxalate stones (Coe and Kavalach, 1974; Levy et al, 1995).

The process of uric acid stone formation once uric acid crystals precipitate has not been fully elucidated. Although some investigators have suggested that uric acid crystal adhesion to kidney epithelial cells (Koka et al, 2000) and inhibitors such as glycosaminoglycans (Ombra et al, 2003) may play a role in uric acid stone formation, the involvement or importance of these factors in uric acid stone formation is unclear (Pak et al, 1976a).

The three main determinants of uric acid stone formation are low pH, low urine volume, and hyperuricosuria (Fig. 45–11). **The most important pathogenetic factor is low urine pH because most patients with uric acid stones have normal uric acid excretion but invariably demonstrate persistent low urine pH** (Pak et al, 1985, 2003a). Uric acid stones can develop as a result of congenital, acquired, or idiopathic causes. Congenital disorders associated with uric acid stones involve renal tubular urate transport or uric acid metabolism, leading to hyperuricosuria. Acquired causes of uric acid stones such as chronic diarrhea, volume depletion, myeloproliferative disorders, high animal protein intake, and uricosuric drugs may affect any of the three factors determining uric acid stone formation. Patients with "gouty diathesis" or idiopathic low urine pH typically demonstrate decreased fractional excretion of urate and do not have gout (Maalouf et al, 2004a). Patients with gouty diathesis differ from those with hyperuricosuric calcium nephrolithiasis in that the former generally have normal urinary uric acid levels and acidic urine, whereas the latter have hyperuricosuria and normal urine pH. Patients with hyperuricosuria frequently have high urinary sodium and calcium levels leading to increased

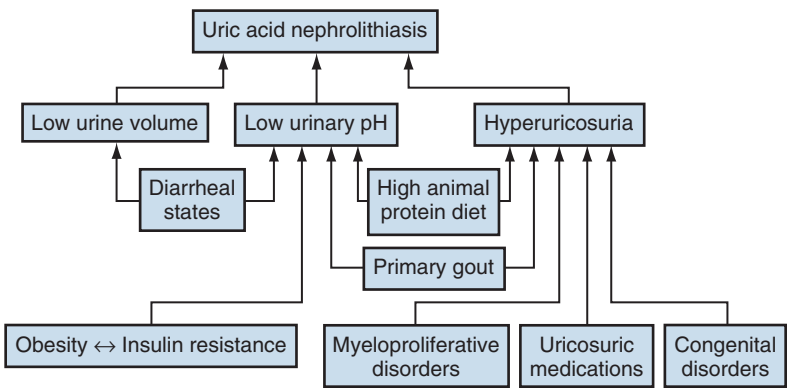


Figure 45–11. Pathophysiology and etiology of uric acid nephrolithiasis. The three major pathophysiologic mechanisms that contribute to uric acid nephrolithiasis are low urine volume, low urinary pH, and hyperuricosuria. Each of these mechanisms can result from diverse etiologies. The most important pathogenetic factor is low urinary pH. (From Maalouf NM, Cameron MA, Moe OW, Sakhaee K. Novel insights into the pathogenesis of uric acid nephrolithiasis. Curr Opin Nephrol Hypertens 2004;13:181–9.)

urinary saturation of sodium urate and calcium oxalate, placing them at risk for calcium oxalate stones (Sorensen and Chandhoke, 2002). Most patients with uric acid stones, however, have normal urinary uric acid levels and low urinary pH (Pak et al, 2003a).

Pathogenesis of Low Urine pH

Although the pathogenesis of low urine pH in idiopathic uric acid stone formers is not known with certainty and may be multifactorial, several potential mechanisms have been proposed. Sakhaee and colleagues (2002) first observed that normouricosuric individuals with pure uric acid stones were more likely to have diabetes mellitus or to demonstrate glucose intolerance than normal individuals or those with mixed uric acid/calcium oxalate or pure calcium oxalate stones. Furthermore, when a group of normouricosuric uric acid stone formers was placed on a controlled metabolic diet, the urinary pH was lower than that of either normal volunteers or other stone formers (mixed uric acid/calcium oxalate or calcium oxalate). Further investigation revealed that the uric acid stone formers excreted less acid into the urine as ammonium and proportionately more titratable acid and less citrate in order to maintain normal overall acid-base balance. **This apparent impairment in ammonium excretion in uric acid stone formers has been putatively linked to an insulin-resistant state**.

Supporting this hypothesis, Pak and colleagues (2003b) noted a higher prevalence of uric acid stones and low urinary pH among patients with non–insulin-dependent diabetes (34%) than among nondiabetic stone formers. Daudon and colleagues (Daudon et al, 2006) analyzed 2464 calculi and also found that uric acid stones comprised 36% of stones among 272 patients with type 2 diabetes mellitus but only 11% among 2192 patients without type 2 diabetes. Furthermore, uric acid stone formers have been found to share many of the characteristic features of the metabolic syndrome (a condition defined by insulin resistance and a high-risk atherosclerotic cardiovascular disease) including hypertriglyceridemia, hyperglycemia, obesity, and hypertension (Sakhaee et al, 2002; Pak et al, 2003b). In an elegant series of experiments, Abate and colleagues (2004) performed hyperinsulinemic euglycemic clamps to measure insulin sensitivity in a diverse group of non–stone-forming normal volunteers and a group of uric acid stone formers and determined that among normal subjects, low urine pH correlated with low rates of glucose disposal (indicating insulin resistance) and uric acid stone formers displayed the most severe levels of insulin resistance. This association of insulin resistance with low urinary pH was further corroborated by the finding of a strong inverse association of body weight (known to be associated with peripheral insulin resistance) and urinary pH, even after adjusting for urinary sulfate (a marker of animal protein intake) (Maalouf et al, 2004b).

The mechanism by which insulin resistance leads to low urine pH has not been completely elucidated. However, insulin has been shown in vitro to promote renal ammoniagenesis from the substrate glutamine (Chobanian et al, 1987; Nissim et al, 1995) and also to stimulate the Na^+/H^+ exchanger (NHE3) in the proximal tubule, which is responsible for either the direct transport or trapping of ammonium in the urine (Klisic et al, 2002). **Impaired ammonium production or excretion as a result of insulin resistance could leave hydrogen ions unbuffered in the urine, thereby leading to reduction in urine pH** (Fig. 45–12). Alternatively, free fatty acids, which are present in increased amounts in the blood in states of insulin resistance, could compete with α-ketoglutarate, the end product of glutamine metabolism, for entry into the Krebs cycle, thereby reducing ammonia production that normally occurs with glutamine deamination (Vinay et al, 1976).

Another potential mechanism for uric acid stone formation is loss of diurnal variation in urinary pH. In most individuals there is diurnal variation in both serum and urine pH, with alkalinization of the urine noted in the morning and after meals (Niv and Fraser, 2002). After consumption of a meal, secretion of gastric acid into the stomach lumen leads to compensatory base excretion by the parietal cells into the serum, resulting in transient alkalinization of the blood and urine, the so-called alkaline tide. Support for this hypothesis comes from the findings that vagotomy

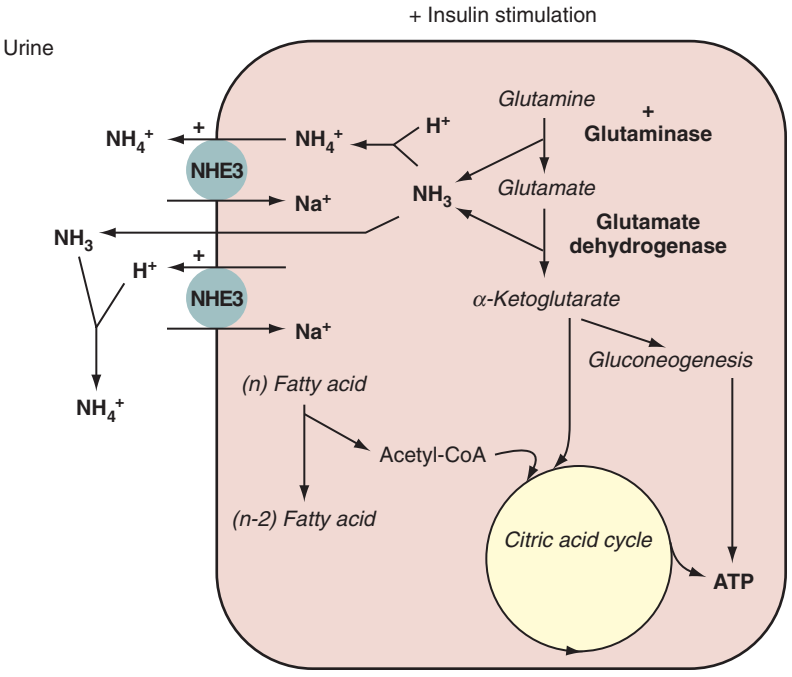


Figure 45–12. Potential effects of the insulin-resistant state on the generation and secretion of ammonium in the proximal tubule. The deamination of glutamine and glutamate provide ammonia. Insulin stimulates glutamine metabolism, as well as the sodium/hydrogen exchanger NHE3. NHE3 mediates ammonium transport by either directly carrying the ammonium ion or providing the luminal hydrogen ion to trap ammonia. The end product of glutamine metabolism is α-ketoglutarate, which can enter the Krebs cycle or gluconeogenesis to generate adenosine triphosphate (ATP). Alternatively, the metabolism of free fatty acids may generate acetyl-coenzymeA (CoA), which may compete with α-ketoglutarate to enter the Krebs cycle, thus providing energy to the cell but diminishing ammonia production. (n)-Fatty acid and (n-2)-Fatty acid represent fatty acids made of a skeleton of n and n-2 carbon atoms, respectively. (From Maalouf NM, Cameron MA, Moe OW, Sakhaee K. Novel insights into the pathogenesis of uric acid nephrolithiasis. Curr Opin Nephrol Hypertens 2004;13:181–9.)

prevents postprandial alkalinization of the urine (Gibaldi et al, 1975) and administration of antacids is associated with an increase in urine pH (Ahmad, 1986). Bilobrov and colleagues (1990) compared normal individuals and stone formers and found wide variations in urinary pH in normal individuals but persistently low urine pH among stone formers. Murayama and colleagues (1993, 2001) also found consistently low urinary pH (<6) in uric acid stone formers evaluated on both controlled metabolic and random diets and found absence of the postprandial and morning alkaline tides. In contrast, calcium oxalate stone formers maintained diurnal variation in urinary pH. Transient alkalinization of the urine may be sufficient to protect normal individuals from uric acid stone formation. The underlying cause of the absence of a urinary alkaline tide in uric acid stone formers is unknown but may be due to a renal defect rather than a gastric one (Maalouf et al, 2004a).

Acidic urine pH may also be promoted by increased endogenous acid production or by dietary influences. When idiopathic uric acid stone formers and normal subjects were maintained on a fixed, low acid-ash diet, net acid excretion (NAE) was higher in the former group compared with the latter, implicating higher endogenous acid production (Asplin, 1996). Furthermore, when controlled for urinary sulfate (a marker of acid intake), NAE was higher in uric acid stone formers and in non–stone formers with type 2 diabetes compared with normal controls (Cameron et al, 2006). These studies suggest that increased NAE in uric acid stone formers reflects not only dietary influences but also increased endogenous acid production, potentially as a result of obesity and/or insulin resistance.

Lipotoxicity, a process whereby fat is redistributed into nonadipocyte tissues such as the heart, liver, skeletal muscle, and pancreatic β cells, resulting in cellular injury, has been implicated in impaired insulin sensitivity, cardiac dysfunction, and hepatic steatohepatitis and has recently been postulated to play a potential role in the pathogenesis of chronic renal disease (Bagby 2004; Weinberg, 2006; Wahba and Mak, 2007). Whether or not lipotoxicity plays a role in impaired ammonium excretion or increased endogenous acid production leading to low urine pH in uric acid stone formers is unknown (Sakhaee, 2009).

Dietary content also plays a role in determining urine acidity. Breslau and colleagues (1988) evaluated 15 normal subjects in a three-way randomized, crossover study involving three, 12-day phases of study in which subjects were maintained on a controlled metabolic diet containing vegetable protein, vegetable and egg protein, or animal protein, with increasing sulfate content, respectively, in the three diets. As the fixed acid content of the diets increased, urinary calcium excretion increased from 103 mg/day on the vegetarian diet to 150 mg/day on the animal protein diet ($P < 0.02$). Moreover, the animal protein–rich diet was associated with the highest excretion of undissociated uric acid and lowest excretion of citrate due to the reduction in urinary pH. Urinary crystallization studies revealed that the animal protein diet, when matched for electrolyte composition and quantity of protein with the vegetarian diet, conferred an increased risk of uric acid stones but, because of opposing factors, not of calcium oxalate or calcium phosphate stones.

Hyperuricosuria

Hyperuricosuria is defined as urinary uric acid less than 600 mg/day (Menon, 1986). Hyperuricosuria predisposes to calcium oxalate or uric acid stone formation by causing supersaturation of the urine with respect to monosodium urate. Patients with gout and urinary uric acid levels less than 600 mg/day had significantly fewer stones than those with uric acid levels greater than 1000 mg/day (Hall et al, 1967; Yu and Gutman, 1967). The causes of hyperuricosuria have been discussed previously but include dietary factors, as well as acquired and hereditary diseases and defects in the urate transporter.

Low Urinary Volume

All conditions that contribute to low urinary volume increase the risk of uric acid supersaturation. Borghi and colleagues (1993) noted high uric acid relative supersaturation in workers exposed to hot temperatures compared with those working in normal temperatures. Likewise, high rates of uric acid stone formation have been found in populations living in warmer climates such as Israel (Shekarriz and Stoller, 2002).

Cystine Stones

Cystinuria is an inherited autosomal recessive disorder characterized by a defect in intestinal and renal tubular transport of dibasic amino acids, resulting in excessive urinary excretion of cystine (Ng and Streem, 1999, 2001). Although the defect also results in high urinary concentrations of lysine, ornithine, and arginine, the poor solubility of cystine leads to stone formation. Cystine is a dimer, composed of two cysteine molecules linked via a disulfide bond. Cystine is much less soluble than cysteine and is responsible for cystine stone formation. Cystine stones are rare, occurring in the United States and Europe with an incidence of only 1 in 1000 to 1 in 17,000 (Cabello-Tomas et al, 1999; Knoll et al, 2005). In children, cystinuria is the cause of up to 10% of all stones (Faerber, 2001; Erbagci et al, 2003; Knoll et al, 2005).

Under normal conditions amino acids are freely filtered by the glomerulus and almost completely reabsorbed in the renal proximal tubule. Cystine and the other dibasic amino acids are transported across the apical membrane of the renal proximal tubule by a sodium-independent heteromeric amino acid transporter in exchange for neutral amino acids. Cystine is reduced intracellularly to cysteine, thereby providing a favorable gradient for continued cystine reabsorption (Broer, 2008). In cystinuria, the defect in cystine transport results in high urinary levels. **Several factors determine the solubility of cystine including cystine concentration, pH, ionic strength, and urinary macromolecules.** The main contributor to cystine crystallization is supersaturation because there is no specific inhibitor of cystine crystallization in the urine (Pak and Fuller, 1983). Because of the poor solubility of cystine in urine, precipitation of cystine and subsequent stone formation occur at physiologic urine conditions (Joly et al, 1999). The solubility of cystine is highly pH dependent, with solubilities of 300 mg/L, 400 mg/L, and 1000 mg/L at pH levels of 5, 7, and 9, respectively (Dent et al, 1955). Ionic strength also influences solubility, and as much as 70 mg of additional cystine can be dissolved in each liter of solution as ionic strength increases from 0.005 to 0.3 (Pak and Fuller, 1983). Macromolecules such as colloid also increase cystine solubility, although the mechanism is unclear (Pak and Fuller, 1983). Therefore cystine is more soluble in urine than in synthetic solution (Fig. 45–13).

Other factors may contribute to stone formation in cystinuric patients as well. Sakhaee and colleagues evaluated 27 patients with documented cystine nephrolithiasis and identified hypercalciuria in 19%, hyperuricosuria in 22%, and hypocitraturia in 44% of patients, which could contribute to formation of not only cystine stones but also calcium or mixed calcium/cystine stones (Sakhaee et al, 1989).

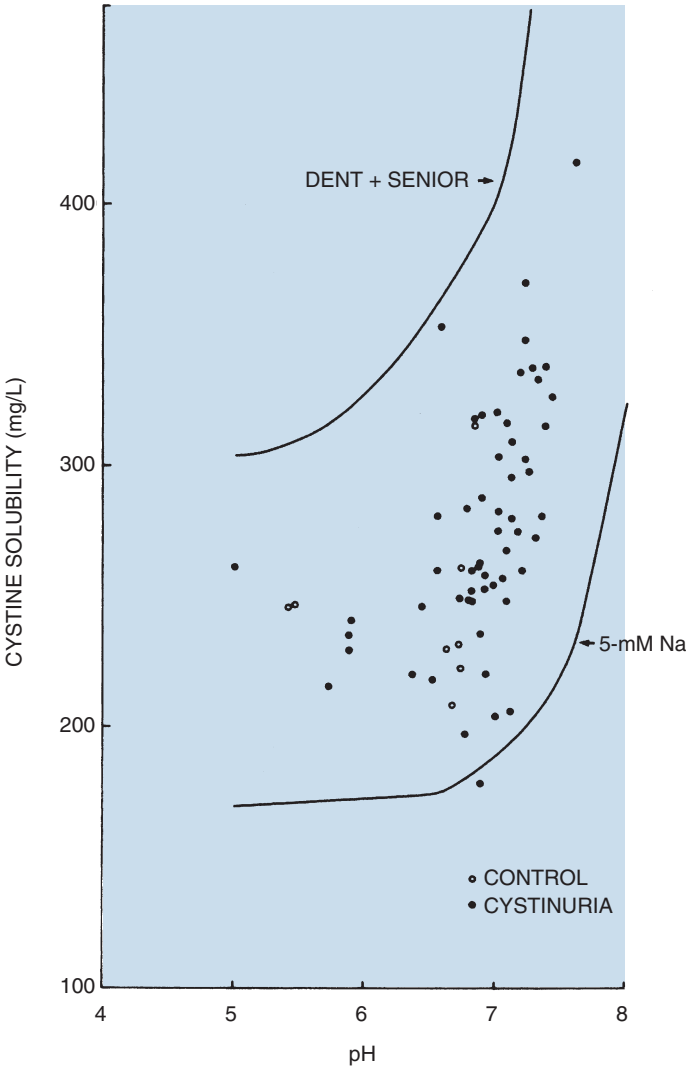


Figure 45–13. Cystine solubility in urine. Each point represents solubility of cystine determined in a separate urine sample by incubation with an excess of solid cystine. The solubility curve of Dent and Senior and that obtained in a 5-mM sodium cacodylate solution are plotted for comparison. (From Pak CY, Fuller CJ. Assessment of cystine solubility in urine and of heterogeneous nucleation. J Urol 1983;129:1066–70.)

The genetics of cystinuria have been studied extensively. Two genes involved in the disease have been identified, *SLC3A1* (Pras et al, 1994) and *SLC7A9* (Feliubadalo et al, 1999), which have been found to be associated with defects in the heavy and light subunits, respectively, of the cystine transporter. As of 2005, a total of 103 and 60 mutations had been reported in the *SLC3A1* gene and the *SLC7A9* gene, respectively (Font-Llitjos et al, 2005).

Historically, three types of cystinuria have been recognized in humans—type I, type II, and type III—on the basis of levels of urinary cystine in obligate heterozygotes of the proband (Rosenberg et al, 1966). However, this classification correlates poorly with molecular findings, and therefore it has recently been revised by the International Cystinuria Consortium (ICC) to take into account the chromosomal localization of the mutation: type A (chromosome 2), type B (chromosome 19), and type AB (both chromosomes) (Dello Strologo et al, 2002). Homozygotes with the condition exhibit urinary cystine levels as high as 2000 µmol/g of creatinine. Review by the ICC revealed that the average age at first stone diagnosis was 12.2 years, with a mean number of stone episodes of 0.42 and 0.21 per year occurring in men and women, respectively (Dello Strologo et al, 2002). Although mean urinary cystine levels are significantly higher in heterozygotes with type B abnormalities (475 µmol/g creatinine) compared with those with type A abnormalities (70 µmol/g creatinine), there is no difference in stone formation between the two groups, and, in fact, stone formation is uncommon (Dello Strologo et al, 2002).

Little information is available on the relative distribution of the types of cystinuria in specific populations. In 97 well-characterized families in the database of the ICC cohort of patients, which hail primarily from Italy, Spain, and Israel, 38%, 47%, and 14% transmitted type I, non–type I, and mixed cystinuria, respectively (Dello Strologo et al, 2002). In another study of 85 family members of 24 cystine stone formers, 24 additional family members were found to excrete excessive amounts of cystine, although only 5 of them (21%) had produced cystine calculi (Trinchieri et al, 2004).

Infection Stones

Infection stones (Bichler et al, 2002) are composed primarily of magnesium ammonium phosphate hexahydrate ($MgNH_4PO_4 \bullet 6H_2O$) but may in addition contain calcium phosphate in the form of carbonate apatite ($Ca_{10}[PO_4]_6 \bullet CO_3$). A Swedish geologist discovered magnesium ammonium phosphate in guano and named it "struvite" after his mentor, naturalist H.C.G. von Struve (Griffith and Osborne, 1987). Brown (1901) first theorized that bacteria split urea, thereby setting up the condition for stone formation, and indeed he later isolated *Proteus vulgaris* from a stone. Hager and Magath (1925) postulated that a bacterial enzyme hydrolyzed urea, and Sumner (1926) isolated urease from *Canavalia ensiformis*. It is now well established that struvite stones (magnesium ammonium phosphate) occur only in association with urinary infection by urea-splitting bacteria (Griffith and Musher, 1973).

Pathogenesis

The process of urealysis provides an alkaline urinary environment and sufficient concentrations of carbonate and ammonia to induce the formation of infection stones. Because urease is not present in sterile human urine, infection with urease-producing bacteria is a prerequisite for the formation of infection stones. A cascade of chemical reactions generates the conditions conducive to the formation of infection stones. Urinary urea, a constituent of normal urine, is first hydrolyzed to ammonia and carbon dioxide in the presence of bacterial urease:

$$(NH_2)_2CO + H_2O \rightarrow 2NH_3 + CO_2$$

The alkaline urine that results from this reaction (pH 7.2 to 8.0) favors the formation of ammonium:

$$NH_3 + H_2O \rightarrow NH_4^+ + OH^- \quad pK = 9.0$$

Under physiologic conditions, the alkaline urine would prevent further generation of ammonium. However, in the presence of urease, ammonia continues to be produced despite alkaline urine, further increasing urinary pH. The alkaline environment also promotes the hydration of carbon dioxide to carbonic acid, which then dissociates into HCO_3^- and H^+. Further dissociation of HCO_3^- yields carbonate and two hydrogen ions:

$$CO_2 + H_2O \rightarrow H_2CO_3 \quad pK = 4.5$$

$$H_2CO_3 \rightarrow H^+ + HCO_3^- \quad pK = 6.3$$

$$HCO_3^- \rightarrow H^+ + CO_3^{2-} \quad pK = 10.2$$

The dissociation of hydrogen phosphate under alkaline conditions provides phosphate, thereby completing the generation of constituent ions for infection stone formation:

$$H_2PO_4^- \rightarrow H^+ + HPO_4^{2-} \quad pK = 7.2$$

$$HPO_4^{2-} \rightarrow H^+ + PO_4^{3-} \quad pK = 12.4$$

This chemical cascade, along with physiologic concentrations of magnesium, provides the constituents necessary for precipitation of struvite. In addition, the concentrations of calcium, phosphate, and carbonate allow precipitation of carbonate apatite and hydroxyapatite, thereby comprising the components of infection stones (Fig. 45–14).

Although infection stones are a direct result of persistent or recurrent infection with urease-producing bacteria, they may also be associated with or exacerbated by urinary obstruction or stasis (Bichler et al, 2002). As such, growth of infection stones can progress at a rapid rate (Hinman, 1979).

Bacteriology

Although the family Enterobacteriaceae comprises the majority of urease-producing pathogens, a variety of gram-positive and gram-negative bacteria and some yeasts and *Mycoplasma* species have the capacity to synthesize urease (Table 45–4). **The most common urease-producing pathogens are *Proteus, Klebsiella, Pseudomonas,* and *Staphylococcus* species** (Griffith and Osborne, 1987), **with *Proteus mirabilis* the most common organism associated with infection stones** (Silverman and Stamey, 1983). Although *Escherichia coli* is a common cause of urinary tract infections, only rare species of *E. coli* produce urease (Bichler et al, 2002). Bacterial urease can be detected by the Urea-Rapid Test, a urea-indole medium from BioMerieux, Inc. (Durham, NC) (Bichler et al, 2002).

Bacteria may be involved in stone formation by damaging the mucosal layer of the urinary tract, resulting in both increased bacterial colonization and crystal adherence (Parsons et al, 1984; Grenabo et al, 1988). It has been proposed that ammonium, generated as a result of urealysis, may alter the glycosaminoglycan layer present on the surface of the transitional cell layer and significantly increase bacterial adherence to normal bladder mucosa, further exacerbating infection risk (Parsons et al, 1984). In addition, a study in rats found that injury to the bladder mucosa increased crystal adherence to the bladder wall, a process that was potentiated by the presence of common bacteria such as *Proteus*, *E. coli*, *Enterococcus,* and *Ureaplasma urealyticum* (Grenabo et al, 1988). Another potential mechanism for increased stone formation in the presence of bacteria is the finding that particular bacteria, such as *E. coli* and *Proteus,* may alter the activity of urokinase and sialidase, whereas organisms not typically associated

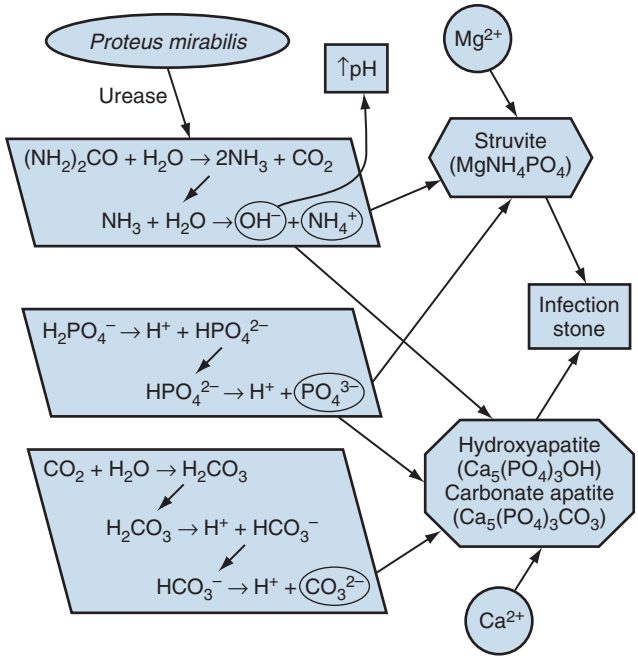


Figure 45–14. Schematic depicting concurrent events leading to struvite stone formation. (From Johnson DB, Pearle MS. Struvite stones. In Stoller ML, Meng MV. editors. Urinary stone disease: the practical guide to medical and surgical management. Totowa [NJ]: Humana Press; 2007.)

Table 45–4.

Organisms That May Produce Urease

ORGANISMS	USUALLY (>90% OF ISOLATES)	OCCASIONALLY (5%-30% OF ISOLATES)
Gram-negative	*Proteus rettgeri*	*Klebsiella pneumoniae*
	Proteus vulgaris	*Klebsiella oxytoca*
	Proteus mirabilis	*Serratia marcescens*
	Proteus morganii	*Haemophilus parainfluenzae*
	Providencia stuartii	*Bordetella bronchiseptica*
	Haemophilus influenzae	
	Bordetella pertussis	*Aeromonas hydrophila*
	Bacteroides corrodens	*Pseudomonas aeruginosa*
	Yersinia enterocolitica	*Pasteurella* species
	Brucella species	
Gram-positive	*Flavobacterium* species	*Staphylococcus epidermidis*
	Staphylococcus aureus	*Bacillus* species
	Micrococcus	*Corynebacterium murium*
	Corynebacterium ulcerans	*Corynebacterium equi*
	Corynebacterium renale	*Peptococcus asaccharolyticus*
	Corynebacterium ovis	*Clostridium tetani*
	Corynebacterium hofmannii	*Mycobacterium rhodochrous group*
Mycoplasma	T-strain *Mycoplasma*	
	Ureaplasma urealyticum	
Yeasts	*Cryptococcus*	
	Rhodotorula	
	Sporobolomyces	
	Candida humicola	
	Trichosporon cutaneum	

From Gleeson MJ, Griffith DP. Infection stones. In: Resnick MI, Pak CYC, editors. Urolithiasis: a medical and surgical reference. Philadelphia: WB Saunders; 1990. p. 115.

with infection stones do not (du Toit et al, 1992). This altered enzymatic activity may explain the frequent association of *E. coli* with stone formation despite lacking urease activity (Holmgren et al, 1989).

Epidemiology

Infection stones comprise 5% to 15% of all stones (Levy et al, 1995). However, struvite/carbonate apatite was the most common stone composition among a population of African-American stone formers in Ohio, accounting for a third of stones in males and nearly half the females in this population (Sarmina et al, 1987). **Because infection stones occur most commonly in those prone to frequent urinary tract infections, struvite stones occur more often in women than men by a ratio of 2:1** (Resnick, 1981). Other populations at risk of recurrent infection include the elderly (Kohri et al, 1991), premature infants or infants born with congenital urinary tract malformation, diabetics, and those with urinary stasis as a result of urinary tract obstruction, urinary diversion, or neurologic disorders. Spinal cord–injured patients are at particular risk for both infection and metabolic stones owing to neurogenic urinary tract dysfunction and hypercalciuria related to immobility. Patients with a functionally complete cord transection are at highest risk of developing a staghorn calculus (DeVivo et al, 1984).

Miscellaneous Stones

Xanthine and Dihydroxyadenine Stones

Xanthine stones comprise a rare stone type that is often confused with uric acid stones because both are radiolucent. They form as a result of an inherited disorder in the catabolic enzyme xanthine dehydrogenase (XDH) or xanthine oxidase, which catalyzes the conversion of xanthine to uric acid. Because xanthine is poorly soluble in urine, the high levels of xanthine that accumulate in XDH deficiency lead to xanthine stones (Seegmiller, 1968; de Vries et al, 1977; Cameron et al, 1993).

Allopurinol, which inhibits XDH and is consequently used to treat hyperuricemia and hyperuricosuria, can, at high levels, predispose to xanthine stones. This side effect is distinctly uncommon because the drug causes only partial inhibition of the enzyme and rarely reduces serum uric acid to levels lower than 3 mg/dL. Patients with Lesch-Nyhan syndrome who suffer from an inherited deficiency of the purine salvage enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT) are occasionally treated with high enough doses of allopurinol to place them at risk for xanthine stones (Cameron et al, 1993).

Children with inherited deficiencies of adenine phosphoribosyltransferase (APRT) can also present in infancy with renal complications and stones (Cameron et al, 1993). Children with APRT deficiency may be difficult to distinguish from those with HPRT deficiency because the insoluble product excreted, 2,8-dihydroxyadenine (2,8-DHA), is chemically similar to uric acid. Like xanthine stones, 2,8-DHA stones are extremely insoluble at any pH, but stone formation can be averted by the administration of allopurinol.

Ammonium Acid Urate Stones

Ammonium acid urate stones represent less than 1% of all stones (Herring, 1962; Klohn et al, 1986). In developing countries, however, endemic ammonium acid urate urolithiasis is still observed because it comprises bladder calculi in children (Minon Cifuentes and Pourmand, 1983; Vanwaeyenbergh et al, 1995). **Conditions associated with ammonium acid urate crystallization include laxative abuse, recurrent urinary tract infection, recurrent uric acid stone formation, and inflammatory bowel disease** (Borden and Dean, 1979; Klohn et al, 1986; Dick et al, 1990; Pichette et al, 1997; Soble et al, 1999). Soble and colleagues (1999) reviewed their experience with 44 patients identified as having stones composed of ammonium acid urate, although the ammonium acid urate contribution varied from 2% to 60%. Among these patients, 25% had a history of inflammatory bowel disease, 14% had a history of significant laxative abuse, 41% were morbidly obese, 36% had history of recurrent urinary tract infections, and 21% had a history of recurrent uric acid stones. The subgroup of patients with inflammatory bowel disease and ileostomy as the sole clinical risk factor had the highest mean ammonium acid urate content (39%), and ammonium acid urate constituted the predominant stone type in seven of eight such patients.

Patients with ileostomy after colectomy have markedly reduced urinary volume, pH, and sodium and are not prone to hyperoxaluria like other individuals with bowel disease because the colon is the main site of dietary oxalate absorption (Kennedy et al, 1982). As such, these patients are prone to ammonium acid urate and uric acid stones rather than calcium oxalate stones. **The underlying pathophysiologic mechanism of ammonium acid urate stone formation due to laxative abuse has been postulated to be the result of dehydration due to gastrointestinal fluid loss causing intracellular acidosis and enhanced ammonia excretion. Because urinary sodium is low in the setting of laxative use, urate complexes with abundant ammonia, thereby leading to urinary supersaturation of ammonium acid urate.**

Bowyer and colleagues (1979) demonstrated that ammonium acid urate precipitation is favored at pH 6.2 to 6.3. The association of recurrent uric acid stones with ammonium acid urate stones is likely related to the shared risk factors of low urine volume and pH. Soble and colleagues (1999) identified nine patients with stones of mixed composition, containing both uric acid and ammonium acid urate (mean ammonium acid urate content 27%), although eight of the nine patients had uric acid as the predominant constituent (range 40% to 95%). They theorized that transient fluctuations in urinary acidity and ammonium and sodium levels may shift the balance between uric acid and sodium- or ammonium-bound urate excretion.

Among the ammonium acid urate stone producers in Sobel and colleagues' study, obesity (body mass index >30) was the most prevalent characteristic in 41% of patients, after excluding patients with inflammatory bowel disease and ileostomy (none of whom was obese). Indeed, a statistically significant correlation was found between body mass index and ammonium acid urate content. This is consistent with recent evidence suggesting a correlation between stone risk and obesity (Powell et al, 2000) and between obesity and low urine pH (Maalouf et al, 2004b).

Matrix Stones

The association between urinary proteins and stone formation has long been recognized. Early experiments demonstrated that protein suspensions could promote calcium stone formation (Kimura et al, 1976). Both osteopontin and calprotectin have been shown to play a role in forming the matrix structure of urinary calcium stones (Tawada et al, 1999; Kleinman et al, 2004). However, stones composed predominantly of matrix are rare; these "stones" are typically radiolucent and may be mistaken for tumor or uric acid stones depending on the imaging study obtained

(Bani-Hani et al, 2005). The literature regarding matrix stones is sparse, consisting mostly of anecdotal case reports (Boyce and King, 1963; Allen and Spence, 1966; Bani-Hani et al, 2005). The matrix component of calcium-based stones comprises only 2.5% of the dry weight of the stone, whereas pure matrix stones may contain upwards of 65% protein (Allen and Spence, 1966). Boyce and Garvey (1956) determined that the composition of matrix stones was approximately two-thirds mucoprotein and one-third mucopolysaccharide by weight. Furthermore, they found that the matrix substance in crystalline calculi is closely related to the matrix substance found in matrix calculi. However, it is unclear why some matrix calculi fail to fully calcify. Although some have theorized that reduced urinary calcium levels may account for the preferential formation of matrix stones (Boyce and King, 1959; Allen and Spence, 1966), a recent metabolic evaluation of five patients with matrix stones revealed normal urinary calcium excretion (Bani-Hani et al, 2005). In renal failure patients undergoing dialysis, proteinuria may contribute to an increased risk of matrix stone formation. In these patients, matrix stones have been shown to include both microfibrillar protein (Bommer et al, 1979) and β_2-microglobulin (Linke et al, 1986).

Medication-Related Stones

Drug-induced stones form either directly due to precipitation and crystallization of a drug or its metabolite or indirectly by altering the urinary environment, making it favorable for metabolic stone formation (Daudon, 1999). Drugs such as loop diuretics (furosemide, bumetanide), acetazolamide, topiramate, and zonisamide contribute to calcium stone formation (Matlaga et al, 2003). Ephedrine (Powell et al, 1998; Assimos et al, 1999), triamterene (Ettinger et al, 1980; Carr et al, 1990), guaifenesin (Assimos et al, 1999), silicate (Farrer and Rajfer, 1984), indinavir (Bruce et al, 1997; Gentle et al, 1997), and ciprofloxacin (Matlaga et al, 2003) have all been associated with stones composed of the drug itself in patients who consumed excessive amounts.

Medications That Directly Promote Stone Formation

Indinavir Stones. Indinavir sulfate is a protease inhibitor that has been shown to be effective in increasing CD4+ cell counts and decreasing HIV-RNA titers in patients infected with human immunodeficiency virus (HIV) or who have the acquired immunodeficiency syndrome (Wu and Stoller, 2000). However, indinavir poses a risk for indinavir stone formation in treated patients, leading to an estimated incidence of 4% to 13% (Wu and Stoller, 2000). Indinavir is rapidly absorbed from the intestine, achieving peak plasma concentrations in less than 1 hour. The drug is metabolized in the liver and eliminated primarily in the stool, but about half of the ingested dose of indinavir is excreted essentially unchanged in the urine (Sutherland et al, 1997). In pure form, indinavir is relatively insoluble in aqueous solution, although the solubility is pH dependent. With a pKa of 5.5, indinavir has a solubility of 0.300 mg/mL at pH 5, 0.035 mg/mL at pH 6.0, and 0.020 mg/mL at pH 7.0 (Daudon et al, 1997; Hermieu et al, 1999). Although indinavir solubility increases significantly at pH levels below 5.5, the standard dose of indinavir in an individual with an average urine volume and pH would produce a urinary concentration of indinavir near the limit of solubility 3 hours after ingestion (Daudon et al, 1997). As such, **individuals taking indinavir on a regular basis are at high risk of producing indinavir stones due to the high urinary excretion and poor solubility of the drug at physiologic urinary pH.** Initiation of indinavir in 54 asymptomatic, indinavir-naïve, HIV-positive individuals led to indinavir crystalluria in 67% of subjects (Gagnon et al, 2000). After the first 2 weeks, indinavir crystalluria remained constant at a frequency of approximately 25% of urine sediments examined at each test point.

Triamterene Stones. Triamterene is a potassium-sparing diuretic commonly used for the treatment of hypertension. It is an uncommon stone composition, accounting for only 0.4% of 50,000 calculi in one report, with only one third of the stones composed largely or entirely of triamterene (Ettinger et al, 1980). An evaluation of triamterene stone formers revealed no significant differences between patients and matched control subjects with respect to total recovery of the drug, hourly excretion patterns, and urinary concentrations of triamterene and its sulfate metabolite (Ettinger, 1985). Approximately half of all subjects tested demonstrated urine concentrations of the sulfate metabolite that exceeded the observed solubility limit. One investigation determined that triamterene is more likely to become incorporated into existing stones or stone nidi than to promote stone formation independently (Werness et al, 1982). This may account for the rarity of this stone in non–stone formers, as well as the finding that hospitalization rates for urinary stones did not differ between patients prescribed triameterene and HCTZ (Jick et al, 1982).

Guaifenesin and Ephedrine. Consumption of large quantities of guaifenesin and ephedrine can lead to stones composed of their metabolites (Powell et al, 1998; Assimos et al, 1999). Most of the patients reported to have these stones are found to have consumed large quantities of over-the-counter preparations of cold medicine for the stimulatory properties of the ephedrine component, and a history of drug abuse is not uncommon (Assimos et al, 1999). Herbal ecstasy and Ma Huang are also popular ephedrine-containing preparations that are abused for stimulatory properties (Mack, 1997). Unfortunately, chronic ephedrine use leads to tachyphylaxis and prompts the use of increasing doses to achieve a comparable effect. Serious toxicity may result from ephedrine abuse including death, cardiomyopathy, stroke, hypertension, and seizures.

Silicate Stones. Silica is a common element seen in vegetables, whole grains, seafood, and even drinking water that is easily excreted in the urine (Matlaga et al, 2003). Silicate stones are extremely rare and have been associated with consumption of large amounts of silicate-containing antacids such as magnesium trisilicate (Haddad and Kouyoumdjian, 1986; Daudon, 1999).

Medications That Indirectly Promote Stone Formation. Other medications indirectly promote stone formation by increasing urinary stone risk factors. Corticosteroids, vitamin D, and phosphate-binding antacids can induce hypercalciuria. **Thiazides cause intracellular acidosis and subsequent hypocitraturia** (Nicar et al, 1984). Loop diuretics such as furosemide and bumetanide inhibit sodium and calcium resorption in the thick ascending loop of Henle, which in addition to a diuretic effect results in hypercalciuria (Matlaga et al, 2003). Renal calculi have been identified in up to 64% of low-birth-weight infants receiving furosemide therapy, and stones are consistently composed of calcium oxalate (Hufnagle et al, 1982; Shukla et al, 2001).

Carbonic anhydrase inhibitors such as acetazolamide block resorption of sodium bicarbonate at multiple segments in the nephron, thereby inducing a metabolic acidosis and leading to urinary alkalinization (Parfitt, 1969). **Chronic use results in hypocitraturia, hypercalciuria, and increased risk for calcium phosphate stones** (Matlaga et al, 2003). Topiramate is a widely used drug initially approved as an antiepileptic agent that is also used for the treatment of a variety of other neurologic disorders, as a migraine prophylactic agent, and for weight loss. Topiramate inhibits several isoenzymes of carbonic anhydrase with subsequent stone-potentiating effects (Vega et al, 2007).

Although the reported incidence of calcium stones with topiramate use is 1.5% (Shorvon, 1996), this number is thought to be an underestimate. A recent cross-sectional study comparing 32 topiramate-treated patients with 50 normal controls revealed systemic metabolic acidosis, increased fractional excretion of bicarbonate, higher urine pH, and lower urinary citrate excretion in the topiramate-treated group (Welch et al, 2006). Likewise, in a short-term longitudinal study of seven patients before and 3 months after initiation of topiramate, significant metabolic acidosis and increased urine pH, urinary bicarbonate excretion, and urinary saturation of calcium phosphate were seen with initiation of the drug (Welch et al, 2006). Zonisamide is a sulfonamide agent that also exerts an antiepileptic effect and has a weak carbonic anhydrase activity (Peters and Sorkin, 1993). Laxatives can lead to persistent diarrhea and increase the risk of ammonium acid urate stones. Patients abusing laxatives excrete large amounts of ammonia in the urine to eliminate excess acid, resulting in low urine pH. In the setting of low urine volume due to dehydration, the urine of these patients can be highly supersaturated with respect to ammonium urate (Matlaga et al, 2003). Lastly, cytotoxic agents promote a high cell turnover, resulting in urinary excretion of large amounts of uric acid.

Anatomic Predisposition to Stones

Patients with anatomic anomalies associated with urinary obstruction and/or stasis have been noted to have a high incidence of associated stones. It has long been debated whether the predisposition to stone disease is a result of urinary stasis and delayed transit time through the nephron, leading to higher likelihood of crystal formation and retention, or if these patients form stones as a result of the same or unique metabolic abnormalities associated with stone formation.

Ureteropelvic Junction Obstruction

The incidence of renal calculi in patients with ureteropelvic junction (UPJ) obstruction is nearly 20% (David and Lavengood, 1975; Lowe and Marshall, 1984; Clark and Malek, 1987). However, Husmann and colleagues (1995) **provided several lines of evidence to suggest that patients with UPJ obstruction and concurrent renal calculi carry the same metabolic risks as other stone formers in the general population.** First, among 111 adult patients with UPJ obstruction and stones for whom long-term follow-up was available, 62% developed recurrent stones after treatment of the UPJ obstruction and 43% of the recurrences occurred in the contralateral kidney. These findings suggest that a metabolic predisposition persisted despite correction of the obstruction. Second, 76% of 42 patients with noninfectious stones who underwent a metabolic evaluation demonstrated an underlying metabolic abnormality that could account for the stones, a rate comparable to that of other stone formers (Pak, 1982; Yagisawa et al, 1999). Finally, the type and distribution of metabolic abnormalities identified in these patients were similar to that of the general stone-forming population: hypercalciuria in 46% of patients, hyperuricosuria in 11%, hypocitraturia in 13%, primary hyperparathyroidism in 13%, and RTA in 3% (Pak et al, 1980). Treatment of patients with identifiable abnormalities significantly reduced their rate of recurrence, from 55% in patients managed conservatively to 17% in treated patients.

Matin and Streem also performed metabolic evaluations before definitive repair in 47 patients with UPJ obstruction with or without associated stones (Matin and Streem, 2000). An identifiable abnormality was found in 67% of the stone patients compared with only 33% of the control group; urinary calcium and the incidence of hypercalciuria and hyperuricosuria were significantly higher in the patients with stones compared with the controls, further underscoring the contribution of pathophysiologic background to stone-forming risk in patients with anatomic abnormalities.

Similar findings in two series of children with UPJ obstruction and concurrent renal calculi further support a metabolic contribution to stone formation in the presence of renal obstruction. Tekin and colleagues (2001) prospectively compared children with UPJ obstruction with and without stones to a control group of calcium stone formers without UPJ obstruction. Both groups of stone formers, those with and without UPJ obstruction, exhibited significantly higher urinary levels of citrate and lower levels of oxalate compared with the non–stone-forming children with UPJ obstruction. Husmann and colleagues (1996) reported a 70-fold increased risk of stone formation in the pediatric population with UPJ obstruction compared with normal children. Among 22 children who underwent treatment of their stones and UPJ obstruction, 68% of patients with nonstruvite stones developed a recurrence after surgical treatment and a metabolic abnormality was identified in 68%. Among the seven patients with nonstruvite renal calculi who did not experience a recurrence, only 29% had an identifiable metabolic abnormality. As such, correction of the UPJ obstruction did not prevent recurrent stones in most patients, further emphasizing the role of underlying metabolic abnormalities in the etiology of renal calculi in patients with UPJ obstruction.

Horseshoe Kidneys

Horseshoe kidneys occur with a prevalence of 0.25% but have an associated rate of renal calculi of 20% (Janetschek et al, 1988; Cussenot et al, 1992). Because of the high insertion of the ureter into the renal pelvis, there is a relative impairment of renal drainage, predisposing to UPJ obstruction. As such, the risk of stone formation has been attributed to urinary stasis rather than to metabolic derangements. Raj and colleagues (2004) reviewed 37 patients with horseshoe kidneys and stones and identified at least one metabolic abnormality in all 11 patients in whom 24-hour urine collections were available. Compared with a group of stone formers with normal renal anatomy, the patients with horseshoe kidneys exhibited a similar distribution of metabolic derangements, with the exception that hypocitraturia was overrepresented (55% in the patients with horseshoe kidneys vs. 31% in controls). It seems clear that **although urinary stasis likely contributes to a propensity toward stone formation in patients with horseshoe kidneys, an underlying metabolic abnormality is required for stone formation to occur.**

Caliceal Diverticula

Caliceal diverticula are associated with stones in up to 40% of patients (Middleton and Pfister, 1974). Like stones in horseshoe kidneys, it is unclear whether the stones are caused by local anatomic obstruction and urinary stasis or are due to underlying metabolic factors. Two groups of investigators have addressed this issue. Hsu and Streem (1998) identified metabolic abnormalities including hypercalciuria, hyperoxaluria and hyperuricosuria in 50% of 14 patients with stone-bearing caliceal diverticula. Notably, 64% of patients reported a history of synchronous or metachronous stones at a site distinct from the diverticulum, supporting the idea of underlying metabolic risk as a contributing cause of the stones. In contrast, Liatsikos and colleagues (2000) compared 49 patients with caliceal diverticula and stones with 44 stone

formers without diverticula and found a low rate of metabolic abnormalities in both groups (25% in patients with diverticula and 23% in the control patients). Of note, however, the metabolic evaluation in this study involved measurement of only urinary volume, creatinine, calcium, phosphorus, oxalate, and uric acid. Because low urinary pH and hypocitraturia are identified in approximately 10% and 28% of recurrent stone formers, respectively (Levy et al, 1995), the number of metabolic abnormalities reported in this series is likely underrepresented. Finally, a study by Matlaga and colleagues evaluated 29 patients who underwent percutaneous treatment of stone-bearing calyceal diverticuli and compared their 24-hour urine collections with those of 245 calcium oxalate stone-formers and 162 normal controls (Matlaga et al, 2007). The urinary stone risk parameters of the patients with calyceal diverticular stones were similar to calcium oxalate stone formers who demonstrated significantly greater hypercalciuria and higher calcium oxalate supersaturation compared with normal controls. Interestingly, urine aspirated directly from the diverticulum had lower calcium oxalate supersaturation than that of urine obtained from the ipsilateral and contralateral renal pelves. These findings imply that calyceal diverticular calculi arise from a combination of metabolic abnormalities and urinary stasis.

Stones formed in caliceal diverticula are mainly composed of calcium oxalate monohydrate, but they also contain struvite/carbonate apatite due to an infectious component. Concomitant urinary tract infection is found in up to 40% of cases with *Escherichia coli*, *Proteus,* and *Pseudomonas* being the most frequent pathogens (Monreal et al, 1998; Daudon et al, 2003).

Medullary Sponge Kidney

Medullary sponge kidney (MSK) is a disorder characterized by ectasia of the renal collecting ducts. Nephrocalcinosis and renal calculi are frequent complications of MSK (Lavan et al, 1971; Parks et al, 1982; Sage et al, 1982; Ginalski et al, 1990), but the exact risk factors for stone formation are not clearly understood. Although recurrent infection and urinary stasis within the ectatic tubules pose a risk for stone formation (Ginalski et al, 1990), renal tubular defects including hypercalciuria, impaired renal concentrating ability, and defective urinary acidification after an ammonium chloride load have been detected in some MSK patients (Granberg et al, 1971), further potentiating the risk of stone formation. Deck (1965) reported three cases of MSK associated with RTA, which led him to suggest that the acidification defect may constitute the primary event leading to MSK. Osther and colleagues (1988) performed ammonium chloride load tests in 13 patients with MSK and found renal acidification defects in 9 patients: 8 with distal RTA and 1 with proximal RTA. Likewise, Higashihara and colleagues (1984) reported renal acidification defects in 80% of patients (36% with distal RTA) and impaired concentrating ability in 90% of 11 MSK patients. The identification of mutations in the hydrogen proton pump genes *ATP6V1B1* and *ATP6V0A4* in two patients with MSK lends further support to an association between MSK and distal RTA (Carboni et al, 2009).

Despite these findings, three studies performed specifically on MSK patients with nephrolithiasis revealed no case of associated RTA (O'Neill et al, 1981; Parks et al, 1982; Yagisawa et al, 2001). O'Neill and colleagues (1981) identified hypercalciuria as the most common metabolic abnormality in 17 patients with MSK and nephrolithiasis, occurring in 88% of patients and attributed to absorptive hypercalciuria in most cases (59%). The spectrum of abnormalities in these patients was judged to be comparable with that of the general stone-forming population. Other investigators identified hypercalciuria less frequently, in only 9% to 44% of MSK patients with nephrolithiasis. In some cases, the cause of the hypercalciuria was attributed to renal calcium leak by which renal calcium reabsorption was presumed to be impaired by damaged renal tubules (Yendt, 1981; Parks et al, 1982; Yagisawa et al, 2001). Yagisawa identified hypocitraturia as the most common metabolic abnormality, occurring in 77% of 22 MSK patients (Yagisawa et al, 2001). Kinoshita (1990) likewise reported hypocitraturia in 58% of MSK patients. **Thus it appears that although renal acidification defects may be associated with MSK, hypercalciuria and hypocitraturia are likely contributing factors even in the absence of RTA.**

Stones in Pregnancy

Symptomatic stones during pregnancy occur at a rate of 1 in 250 (Lewis et al, 2003) to 1 in 3000 (Butler et al, 2000) pregnant women. Like stones in nonpregnant women, they occur more commonly in white than African-American women (Lewis et al, 2003). The majority of symptomatic stones occur in the second and third trimesters of pregnancy, heralded by symptoms of flank pain or hematuria (Stothers and Lee, 1992; Butler et al, 2000; Biyani et al, 2002; Lewis et al, 2003). The diagnosis can be difficult in this patient population; up to 28% of women are misdiagnosed with appendicitis, diverticulitis, or placental abruption (Stothers and Lee, 1992).

Although most stones pass spontaneously and complications are rare, one report identified an increased risk of premature rupture of the membranes in association with stone passage (Lewis et al, 2003). Although ultrasound constitutes the first-line imaging modality when renal colic is suspected, ultrasound has been reported to miss up to 40% of stones, and a limited, or one-shot intravenous urogram, was found to be more reliable (Butler et al, 2000).

A number of physiologic changes occur during pregnancy. Physiologic hydronephrosis occurs in up to 90% of pregnant women and persists up to 4 to 6 weeks postpartum (Swanson et al, 1995). Although hydronephrosis may be in part due to the effects of progesterone, compression of the ureters by the gravid uterus is at least a contributory, if not the primary, factor (Gorton and Whitfield, 1997; McAleer and Loughlin, 2004). Dilation is typically greater in the right ureter as a result of the engorged uterine vein and derotation of the enlarged uterus (Biyani et al, 2002). The physiologic dilatation may promote crystallization due to urinary stasis (Swanson et al, 1995), and the increased renal pelvic pressure has been suggested to increase the likelihood of stone movement and symptoms.

Important physiologic changes in the kidney occur during pregnancy and modulate urinary stone risk factors. Renal blood flow increases, leading to a 30% to 50% rise in glomerular filtration rate, which subsequently increases the filtered loads of calcium, sodium, and uric acid (McAleer and Loughlin, 2004). Hypercalciuria is further enhanced by placental production of $1,25(OH)_2D_3$, which increases intestinal calcium absorption and secondarily suppresses PTH (Gertner et al, 1986; Biyani et al, 2002). Hyperuricosuria has also been reported as a result of increased filtered load of uric acid (Swanson et al, 1995).

Despite increases in a number of stone-inducing analytes, pregnant women have been shown to excrete increased amounts of inhibitors such as citrate, magnesium, and glycoproteins (Maikranz et al, 1987; Smith et al, 2001). As such, the overall risk of stone formation has been reported to be similar in gravid and nongravid women (Coe et al,

1978; Drago et al, 1982). Although some studies found that the stone composition is similar between gravid and nongravid women, one multi-institutional study found that 74% of stones from pregnant women were composed predominantly of calcium phosphate and 26% were predominantly calcium oxalate (Coe et al, 1978; Drago et al, 1982; Ross et al, 2008).

Key Points: Pathogenesis

- Absorptive hypercalciuria is characterized by normal serum calcium, normal or suppressed PTH, normal fasting urinary calcium, and elevated urinary calcium.
- Renal hypercalciuria is due to impaired renal calcium reabsorption, which stimulates PTH secretion and leads to fasting hypercalciuria.
- Resorptive hypercalciuria is primarily due to primary hyperparathyroidism but may be seen with granulomatous diseases that elaborate $1,25(OH)_2D_3$.
- The most important determinant of uric acid stone formation is low urinary pH.
- Low urine pH seen in uric acid stone formers is likely due to impaired ammoniagenesis as a result of insulin resistance.
- In distal renal tubular acidosis, a defective H^+ ATPase accounts for excretion of excess acid into the distal tubule.
- Formation of infection stones requires alkaline urine that can be achieved only with infection with urease-producing bacteria.

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chapter 46

Evaluation and Medical Management of Urinary Lithiasis

Michael N. Ferrandino, MD ● Paul K. Pietrow, MD ● Glenn M. Preminger, MD

Diagnostic Evaluation of Nephrolithiasis
Use of Stone Analysis to Determine Metabolic Abnormalities
Role of Imaging in Determining Stone Composition
Economics of Metabolic Evaluation
Classification of Nephrolithiasis and Diagnostic Criteria
Conservative Medical Management
Selective Medical Therapy of Nephrolithiasis
Miscellaneous Scenarios
Summary

DIAGNOSTIC EVALUATION OF NEPHROLITHIASIS

Symptomatic urinary calculi are undoubtedly associated with significant patient discomfort. Despite the ability of many stones to pass spontaneously, the surgical treatments for calculi may themselves be morbid. Patients may suffer financial pain due to the expense of emergency department visits, office visits, surgical procedures, or time lost from work, in addition to the physical sequelae. Logically, most patients are interested in learning how to prevent a recurrence of such an episode. **Through even a rudimentary understanding of the physiologic causes of urinary calculus formation, physicians may offer a straightforward approach to elucidating the metabolic basis of nephrolithiasis for any given patient. This evaluation should be simple to perform, it must be economically viable, and it should provide information that can be applied toward a selective, rational therapy of stone disease** (Pak et al, 1980a).

Any evaluation should be able to identify associated metabolic disorders responsible for recurrent stone disease. These metabolic problems include distal renal tubular acidosis, primary hyperparathyroidism, enteric hyperoxaluria, cystinuria, and gouty diathesis. In many of these relatively uncommon conditions, it is generally agreed that selective medical therapy is indicated not only to prevent further stone formation but also to correct underlying physiologic disturbances that may lead to nonrenal complications (Pak et al, 2002a, 2003a).

Selection of Patients for Metabolic Evaluation

Debate continues regarding which patients require an extensive metabolic evaluation. First-time "stone formers" have often been estimated to have a 50% risk of recurrence within the subsequent 10 years (Uribarri et al, 1989). In two separate studies, Ljunghall and colleagues attempted to measure the incidence of a stone recurrence in a Northern European population. A retrospective review estimated the chance of recurrence as nearly 50% at 5 years, whereas a prospective evaluation noted a lower overall rate of 53% within 8 years (Ljunghall and Danielson, 1984; Ljunghall, 1987). Males had both a higher incidence of calculi overall, as well as a higher recurrence rate. Patients had a higher risk of repeat stones in the years immediately following their first episode. It is not completely apparent whether these were preexisting stones that passed later or whether they represent the formation of new calculi.

In fact, recent evidence suggests that the incidence of stone disease may be escalating, along with an increasingly higher percentage of female stone formers (Scales et al, 2007). In fact, the largest epidemiologic study to date suggests the once 3:1 male-to-female ratio of stone formers has now decreased to 1.3:1, not due to a decrease in male stone formation but a significant increase in female stone formation (Pearle et al, 2005). This finding is thought to be due to changes in diet and lifestyle.

First-Time Stone Formers

Considering that dietary and fluid manipulation alone can reduce rates of stone recurrence, some suggest that first-time stone formers should be provided empiric fluid and dietary recommendations until they suffer a recurrence (Borghi et al, 1996). Indeed, studies of "single stone formers" placed on a conservative program of high fluid intake alone or combined with avoidance of dietary excess revealed a low incidence of recurrent stone disease (Hosking et al, 1983). Calling this finding the "stone clinic effect," Hosking and colleagues noted metabolic inactivity in nearly 60% of all patients followed for more than 5 years.

In comparison, Pak has found that single stone formers have an equally high incidence of metabolic abnormalities as recurrent stone formers (Pak, 1982). Furthermore, these derangements are just as severe, leading the authors to conclude that single stone formers should undergo the same evaluation as recurrent stone formers. Similar findings were reported in a series of 182 patients, where half of the patients had hypercalciuria or hyperuricosuria, whereas roughly 20% had a systemic disorder that predisposed the patients to the formation of calculi (Strauss et al, 1982a). The remainder, 29.1%, had no metabolic disorder. Patients with single stones tended to be older when they passed their stones and required a greater rate of intervention to treat the calculus. The recurrence for both groups of patients was similar (≈10% at 3 years). Because the authors did not note substantial differences between solitary and recurrent stone disease, they recommended that first-time stone formers should be evaluated similar to patients with recurrent stone disease.

This approach has been partially refuted by Yagisawa and colleagues (1998), who noted that men with recurrent calculi had a higher rate of metabolic derangements than first-time stone formers. Although women had a trend toward the same pattern, this only achieved statistical significance with regards to decreased levels of urinary citrate (hypocitraturia) (Yagisawa et al, 1998). A more complete discussion of the economic aspects surrounding the decision to perform a metabolic evaluation is found later in this chapter.

Importantly, the formation of a first stone may be the harbinger of a more severe underlying systemic disorder such as renal tubular acidosis, bone disease, or hypercalcemia due to hyperparathyroidism. In such patients, metabolic evaluation is justified solely to make the correct diagnosis in order to prevent extrarenal complications. With the development of reliable parathyroid hormone assays, it is unacceptable to wait for bone loss before embarking on curative therapy. Although the clinical significance of normocalcemic hyperparathyroidism has been questioned and is frequently simply observed, current practice favors the treatment of those patients with at least 1 mg/dL above the upper limit of normal, marked hypercalciuria (urinary calcium excretion > 400 mg per day), reduced bone density, and an age of younger than 50 years (Bilezikian and Silverberg, 2004).

The decision to thoroughly investigate a first-time stone former should ideally be shared by the physician and the patient. Although some first-time stone formers will readily accept and follow conservative therapy, others may elect to undergo a thorough evaluation. It is quite reasonable to determine the extent of evaluation according to the estimation of potential/risk for recurrent stone formation (Smith, 1984). **Patients at higher risk for repeat episodes are those with a family history of stones, those with intestinal disease (particularly when causing chronic diarrheal states), pathologic skeletal fractures, osteoporosis, urinary tract infection or gout.** In these patients, an extensive evaluation is recommended. Any patients with stones composed of cystine, uric acid, or struvite should undergo a complete metabolic workup.

All children should be required to undergo a complete investigation because they have been found to have a significant risk of underlying metabolic disturbances (Polito et al, 2000; Tekin et al, 2001; Pietrow et al, 2002; Coward et al, 2003; Bartosh, 2004). Additionally, these young patients have more at stake because early, repeated episodes of urinary obstruction, urinary tract infection, and repeated radiographic imaging all have associated morbidities.

African-Americans have previously been observed to have a significantly lower incidence of nephrolithiasis than their Caucasian counterparts. Indeed, in a study by Sarmina and colleagues (1987), white patients had urinary calculi three to four times as often as black subjects. Notably, the male-to-female prevalence is not as drastic as it is for white subjects (1:1.55 compared with 2.3:1, respectively). This finding is taken one step further in a study by Michaels and colleagues (1994), in which the women made up roughly 60% of the African-American patients, thereby reversing the expected gender ratio. Sarmina found a higher incidence of infection calculi in the African-American population, whereas these stone types were excluded from analysis in the study by Michaels. Additional support for ethnic diversity is provided by Mente and colleagues (2007). Compared with Europeans, East Asian and African patients had a decreased relative risk of calcium nephrolithiasis, whereas Arabic, West Indian, West Asian, and Latin American patients had an increased relative risk. The authors found differing urinary profiles for a variety of the ethnicities reported when compared with Europeans. However, despite the decreased risk of calcium stone formation, patients of African ancestry demonstrated no significant differences in urinary metabolic derangements.

Following the assumption that a lower incidence of calculi might imply a significant risk of a metabolic or anatomic abnormality in those patients that still manage to make calculi, it seems reasonable to advocate for the performance of a metabolic evaluation for all patients of African-American descent. This suggestion is supported by recent studies that assessed the underlying metabolic abnormalities of non-Caucasian stone formers. **African-Americans, Asians, and Hispanics appear to have a surprisingly similar incidence of underlying metabolic disturbances when compared with Caucasian stone formers. These results suggest that dietary and environmental factors may be as important as ethnicity in the etiology of stone disease** (Beukes et al, 1987; Maloney et al, 2005).

Regardless of whether a particular, individual patient requires a full metabolic evaluation, it is prudent to perform at least a screening evaluation combined with a thorough history and physical examination to assess for underlying systemic syndromes that may cause recurrent calculi and extrarenal complications. This assessment should also screen for those patients at an increased risk of stone recurrence as outlined in the previous paragraphs (Table 46–1).

Table 46–1.

Indications for a Metabolic Stone Evaluation

Recurrent stone formers
Strong family history of stones
Intestinal disease (particularly chronic diarrhea)
Pathologic skeletal fractures
Osteoporosis
History of urinary tract infection with calculi
Personal history of gout
Infirm health (unable to tolerate repeat stone episodes)
Solitary kidney
Anatomic abnormalities
Renal insufficiency
Stones composed of cystine, uric acid, struvite

Key Points: Selection of Patients for Metabolic Evaluation

- The incidence of nephrolithiasis is increasing.
- The historic male predominance of stone formers is disappearing.
- Racial "protection" may be overcome by dietary indiscretions.
- Children are generally evaluated due to concerns about renal damage and long-term sequelae of stone recurrence.

Table 46–2.

Abbreviated Evaluation of Single Stone Formers

History
- Underlying predisposing conditions (per Table 46–1)
- Medications (calcium, vitamin C, vitamin D, acetazolamide, steroids)
- Dietary excesses, inadequate fluid intake or excessive fluid loss

Multichannel blood screen
- Basic metabolic panel (sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine)
- Calcium
- Intact parathyroid hormone
- Uric acid

Urine
- Urinalysis
  - pH > 7.5: infection lithiasis
  - pH < 5.5: uric acid lithiasis
  - Sediment for crystalluria
- Urine culture
  - Urea-splitting organisms: suggestive of infection lithiasis
- Qualitative cystine

Radiography
- Radiopaque stones: calcium oxalate, calcium phosphate, magnesium ammonium phosphate (struvite), cystine
- Radiolucent stones: uric acid, xanthine, triamterene

Intravenous pyelography: radiolucent stones, anatomic abnormalities

Stone analysis

Abbreviated Protocol for Low-Risk, Single Stone Formers

In single stone formers without increased risk for recurrence, the following abbreviated protocol may be applied (Table 46–2). A thorough medical history should be obtained for any underlying conditions that may have contributed to the stone disease. Due to the association between bowel disease and calcium oxalate nephrolithiasis (enteric hyperoxaluria), a careful history of bowel habits and bowel disease should be sought (Smith et al, 1972; Bohles et al, 1988; Lindsjö et al, 1989; McConnell et al, 2002; Worcester, 2002; Parks et al, 2003b). This includes questions regarding chronic diarrhea that could be caused by inflammatory bowel disease (Crohn, ulcerative colitis) or irritable bowel syndrome. A history of gout should be sought because this finding may predispose the patient to hyperuricosuria or gouty diathesis with either uric acid calculi or calcium oxalate stone formation (Grover and Ryall, 1994; Khatchadourian et al, 1995; Kramer and Curhan, 2002). As described by Pak and colleagues (2003c), patients with a history of diabetes mellitus may be at an increased risk of developing a gouty diathesis, with altered ammonium management, acidic urine, and a predisposition for a mixture of calcium oxalate and/or uric acid stones.

In addition, information should be obtained concerning the patient's dietary habits including fluid consumption and excessive intake of certain foods, as well as a list of all medications taken. A social history may provide obvious clues regarding a patient's hydration status. Do they have access to fluids on a regular basis or are they sequestered along an assembly line or in the operating suite? Does the patient perform daily tasks that would increase their insensible losses of fluids (manual labor, prolonged outdoor exposure, excessive exercise)? Some have suggested that a sedentary lifestyle may actually increase the risk of stone formation over those who perform manual labor. Indeed, patients on prolonged bedrest demonstrate alterations in urinary chemistry such that urinary calcium and phosphorous excretion increase significantly, leading to significant increases in urinary saturation of calcium phosphate, calcium oxalate, and monosodium urate (Hwang et al, 1988). A family history may reveal a genetic predisposition to urinary calculi if there is a history of close relatives affected by nephrolithiasis. Age of onset of the patient or of affected relatives may give clues regarding genetic disorders such as autosomal recessive cystinuria.

A multichannel blood screen is helpful in identifying certain systemic problems. These include primary hyperparathyroidism (high serum calcium and low serum phosphorus), renal phosphate leak (hypophosphatemia), uric acid lithiasis (hyperuricemia), and distal renal tubular acidosis (hypokalemia, decreased serum CO_2).

Voided urine specimens should be obtained for comprehensive urinalysis and culture. The urinalysis should include pH determination (preferably with an electrode) because a pH of greater than 7.0 is suggestive of infection lithiasis or of renal tubular acidosis, whereas a pH of less than 5.5 suggests uric acid lithiasis, secondary to gouty diathesis.

The urine sediment should be examined for crystalluria because particular crystal types may give a clue as to the composition of stones the patient is forming. Tetrahedral "envelopes" are seen in calcium oxalate lithiasis (Fig. 46–1), whereas rectangular, "coffin-lid" crystals are often seen in patients with struvite calculi (see Fig. 46–1). Hexagonal crystals confirm cystinuria (see Fig. 46–1), whereas uric acid crystals may be seen as amorphous fibers or irregular plates. The microscopic appearances of common calculi are summarized in Table 46–3.

Urine cultures are performed if there is a suspicion of infection-related calculi or if there are signs or symptoms of a urinary tract infection. A culture that is positive for urea-splitting organisms such as *Proteus, Pseudomonas,* and *Klebsiella* would help explain the formation of a struvite calculus. A positive culture will also warrant therapy with appropriate antibiotics before the initiation of any surgical procedure to remove the stone. The surgical management of a calculus during an active infection will place the patient in great risk of bacteremia or sepsis. **Unfortunately, many infected calculi will harbor bacteria even after treatment with broad-spectrum antibiotics.** Rocha and Santos demonstrated that bacteria can still be cultured from the interior of a calculus despite being soaked in iodine and alcohol for 6 hours (Rocha and Santos, 1969). Furthermore, McAleer and colleagues (2003) have shown that infection calculi contain large quantities of endotoxin after disintegration. In a comparison of infected versus noninfected calculi, infected stones contained 36 times more endotoxin. Half of the infected

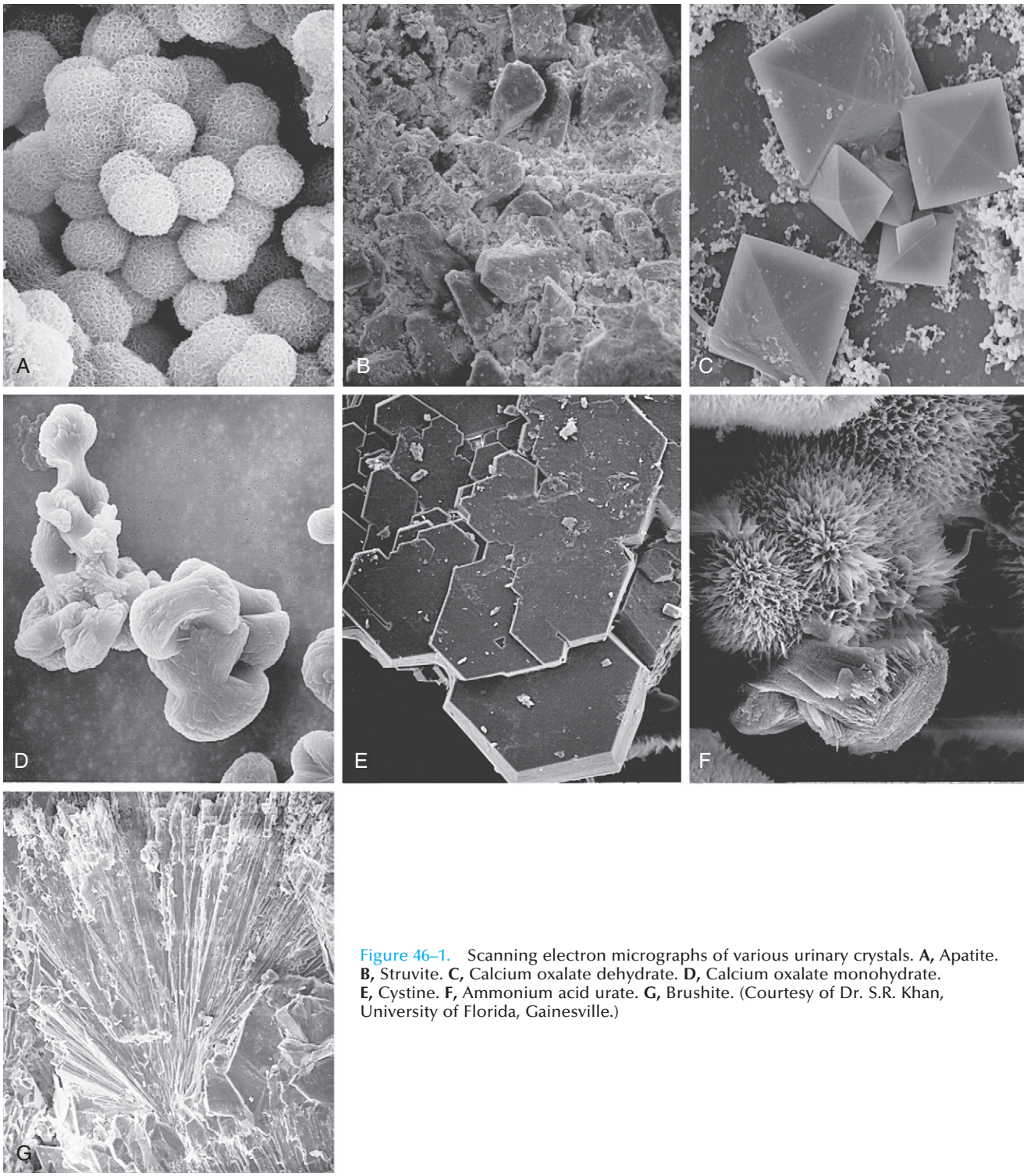


Figure 46–1. Scanning electron micrographs of various urinary crystals. **A,** Apatite. **B,** Struvite. **C,** Calcium oxalate dehydrate. **D,** Calcium oxalate monohydrate. **E,** Cystine. **F,** Ammonium acid urate. **G,** Brushite. (Courtesy of Dr. S.R. Khan, University of Florida, Gainesville.)

calculi grew bacterial cultures that were different from the preoperative urine specimens. The same investigators have described how endotoxin can cause a vascular collapse because it induces physiologic changes consistent with septic shock (McAleer et al, 2002).

Abdominal radiographs should be obtained to document the existence of any residual stones within the urinary tract. The radiopacity of any existing stones may suggest the type of stones that are present. Although magnesium ammonium phosphate and cystine stones are often radiopaque, they are not as dense as calcium oxalate or calcium phosphate stones. A plain abdominal film is also useful in identifying nephrocalcinosis (suggestive of renal tubular acidosis) and staghorn calculi (likely due to infection lithiasis). An intravenous pyelogram may be obtained to confirm the presence of radiolucent stones and also identify any anatomic abnormalities that may predispose the patient to stone formation. It is important to realize that the radiographic evaluation of a patient during a metabolic workup

Table 46–3.

Microscopic Appearance of Common Urinary Calculi

CHEMICAL TYPE	APPEARANCE
Calcium oxalate monohydrate	Hourglass
Calcium oxalate dihydrate	Envelope, tetrahedral
Calcium phosphate-apatite	Amorphous
Brushite	Needle shaped
Magnesium ammonium phosphate (struvite)	Rectangular, coffin-lid
Cystine	Hexagonal
Uric acid	Amorphous shards, plates

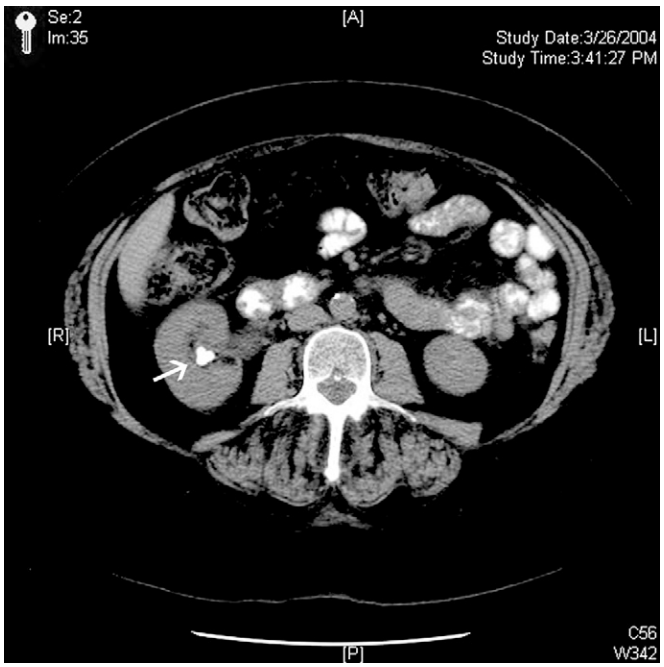


Figure 46–2. CT image of a urinary calculus. All stones (with the exception of some medication calculi) appear as dense, white objects within the urinary collecting system.

of the stone disease will differ from an approach taken during an episode of acute renal colic. In these instances, patients are frequently examined with multislice, noncontrasted computed tomography (CT), which is able to quickly image the entire collecting system in a rapid sequence (Fig. 46–2) (Smith et al, 1995; Sommer et al, 1995; Katz et al, 1996; Fielding et al, 1997).

Finally, available stones should be analyzed to determine their crystalline composition. The presence of uric acid or cystine would suggest the presence of gouty diathesis or cystinuria, respectively. The finding of struvite, carbonate apatite, and magnesium ammonium phosphate would suggest infection lithiasis. A predominance of a hydroxyapatite component suggests the presence of renal tubular acidosis or primary hyperparathyroidism and warrants an assessment of basic electrolytes. Stones composed of pure calcium oxalate or mixed calcium oxalate and hydroxyapatite are less useful diagnostically because they may occur in several entities including absorptive and renal hypercalciuria, hyperuricosuric calcium nephrolithiasis, enteric hyperoxaluria, hypocitraturic calcium nephrolithiasis, and low urine volume (Kourambas et al, 2001; Pak et al, 2004).

Key Points: Abbreviated Protocol for Low-Risk Single Stone Formers

- A complete medical history should be obtained from all stone formers.
- Patients should be screened for medical diseases that predispose to calculi.
- Serum metabolic panel and urinalysis are obtained.
- Urine microscopy for crystals may provide clues to diagnosis.
- Stone analysis may improve the accuracy of further evaluation.
- Basic radiography (plain films) screen for remaining calculi.

Extensive Diagnostic Evaluation

A more extensive evaluation, directed at the identification of underlying physiologic derangements, should be performed in patients with recurrent nephrolithiasis, as well as in stone formers at increased risk for further stone formation.

Pak initially described an extensive outpatient (ambulatory) evaluation in 1980 and subsequently made minor revisions to help simplify the process (Pak et al, 1980a; Levy et al, 1995). The basic strategy involves two outpatient visits, and most of the required laboratory analyses can be performed in a routine clinical laboratory with only a few of the specialized techniques being performed in a more sophisticated laboratory. **The entire schedule of visits and tests is outlined in** Table 46–4.

Before and throughout the period of evaluation, the patient is instructed to discontinue any medication that is known to interfere with the metabolism of calcium, uric acid, or oxalate. These medications include vitamin D, calcium supplements, antacids, diuretics, acetazolamide, and vitamin C. Any current medication for stone treatment (thiazides, phosphate, allopurinol, or magnesium) should be discontinued as well, to better understand the patient's baseline physiology (and pathophysiology). Three 24-hour urine samples are collected. The first two 24-hour specimens are obtained with the patient on a random diet, which is reflective of their usual dietary intake. It is important to stress to the patient that they are not to "perform" during their urine collections. An attempt on the patient's part to suddenly eat well or to increase fluid consumption for the sake of the test will only mask the underlying causes of their stone disease.

Most patients will require detailed instructions on the proper collection of a complete 24-hour urine specimen. The patient should choose a day when all voids can be completely captured and when the specimen will represent a "typical" day. The first morning void is discarded because this represents urine from the previous night and may not have had a predictable starting point. From that point on, all urine must be collected in the appropriate, laboratory-provided container. The canister may need to be kept on ice or preservatives should have been added according to the requirements of the specific laboratory. When the patient awakens the next morning, the first morning void is collected with the rest of the specimen, thereby completing a full 24 hours. Total urinary creatinine should be measured to provide an internal check. Males will be expected to have produced roughly 15 to 20 mg of creatinine for every kilogram of body weight during the 24-hour period. Females generally have less muscle mass and therefore will typically produce 10 to 15 mg

Table 46–4.

Outline of Extensive Ambulatory Protocol

	Blood				Urine							
	CBC	BMP	PTH	CALCIUM	URIC ACID	CREATININE	SODIUM	pH	TOTAL VOLUME	OXALATE	CITRATE	QUALITATIVE CYSTINE
Visit 1*	X	X		X	X	X	X	X	X	X	X	X
Visit 2†		X	X	X	X	X	X	X	X	X	X	
Fast				X		X			X			
Load				X		X		X				

*History and physical examination, diet history, radiologic evaluation, two 24-hour urines on random diet and dietary instruction for restricted diet.
†24-hour urine on restricted diet (400 mg calcium and 100 mEq sodium/day), fast and load test.
BMP, basic metabolic panel; CBC, complete blood count; PTH, parathyroid hormone.
Modified from Pak CY, Britton F, Peterson R, et al. Ambulatory evaluation of nephrolithiasis. Classification, clinical presentation and diagnostic criteria. Am J Med 1980;69(1):19–30.

of creatinine for every kilogram of body weight in 24 hours. Significant aberrations in total creatinine excretion from these estimated values imply incomplete collection, overcollection, greater than expected muscle mass, or less than expected muscle mass.

A third 24-hour sample may be collected after 1 week with the patient on a calcium-, sodium-, and oxalate-restricted diet. This dietary restriction is imposed to standardize the diagnostic tests, to better assess the etiology of hypercalciuria (i.e., AH I vs. AH II) and to prepare for the "fast and calcium load" test, which is performed on the second visit. Blood samples are obtained on both visits as outlined in Table 46–4.

Fast and Calcium Load Test

Due to the similar treatment of patients with absorptive hypercalciuria and renal leak, the performance of fast and calcium load testing is no longer performed by most clinicians. With little therapeutic distinction, there is not much of an incentive to discriminate between either type of hypercalciuria. **However, differentiation between absorptive and renal hypercalciuria is essential if one plans to place a patient with absorptive hypercalciuria on a calcium-binding resin** (see "Selective Medical Therapy of Nephrolithiasis" later in this chapter). A description of the "fast and calcium load" study is included here primarily for completeness and historical purposes.

A "fast and calcium load" study is performed on the morning of the second visit (Pak et al, 1975). **The purpose of this exercise is to help delineate between various causes of hypercalciuria.** As explained in Chapter 45 in greater detail, some patients are too efficient at absorbing calcium from the alimentary canal (absorptive hypercalciuria, types 1 and 2), whereas others suffer from a constant loss of calcium from the renal tubules (renal calcium leak). A third subset of patients has an overabundance of circulating parathyroid hormone, usually from a single parathyroid adenoma, and has a constant loss of calcium and phosphate (resorptive hypercalciuria or primary hyperthyroidism).

In order to differentiate among these three hypercalciuric subtypes, it is essential that the patients have adhered to the restricted diet for at least 7 days before this testing so as to eliminate the effects of absorbed calcium on fasting calcium excretion. To assure adequate hydration, distilled water (300 mL each) is taken 12 hours and 9 hours before the calcium loading. Other than water ingestion at these time periods, the patients are to be fasting. Two hours before the scheduled calcium loading, patients empty their bladder completely, discard this urine, and drink an additional 600 mL of distilled water. All urine produced over the next 2 hours is collected as a pooled sample before taking an oral calcium load (fasting urine). After the 2-hour fasting urine collection has been completed, a 1-g oral calcium load is administered using 250 mL of a liquid synthetic diet (Calcitest) as a carrier solution. This synthetic "meal" is prepared by adding 500 mL of water to a can of Calcitest. Because 250 mL of the synthetic meal contains only 100 mg of calcium, 39 mL of calcium glubionate (Neo-Calglucon) (900 mg of calcium) must be added to bring the total calcium up to 1 g. The final mixture should be taken slowly over a 5- to 10-minute period.

For the next 4 hours, urine is again collected as a pooled sample (postload urine). Both fasting and postload samples are then assayed for calcium and creatinine. Fasting urinary calcium is expressed as mg/dL glomerular filtrate (GF) because it is reflective of renal function. To obtain this unit of measurement, the urinary calcium in (milligrams per milligrams of creatinine) is multiplied by the serum creatinine concentration (in milligrams per deciliter). Normal fasting urinary calcium is less than 0.11 mg/dL GF. The postload urinary calcium is best expressed as milligrams per milligram of creatinine because it is a function of a fixed oral calcium load. The normal value for this measurement is less than 0.2 mg calcium/mg creatinine.

Key Points: Extensive Diagnostic Evaluation

- A complete metabolic evaluation may be obtained as an outpatient.
- Calcium fast/load tests can discriminate between the various forms of hypercalciuria.
- Routine performance of calcium fast/load tests is not required to complete a metabolic evaluation.

Simplified Metabolic Evaluation

The previously described extensive ambulatory protocol affords the physician a high diagnostic yield and is quite reliable. Unfortunately, many practicing physicians have found this protocol to be time consuming and difficult to perform due to the inability to find a reliable local laboratory or perceived complexities of the evaluation protocol. Indeed, the full evaluation does entail several office visits and requires strict adherence to fluid protocols during the calcium fast and load tests.

Several authors have suggested a more simplified approach that uses the same standard principles and procedures as the full outpatient evaluation. These simplified protocols do not include the calcium fast and loading tests and may not require adherence to a restricted diet, permitting them to be performed in a single office visit. Rivers and colleagues (2000) have recommended the collection of two separate 24-hour urine specimens. One is collected while on a restricted diet, whereas the other allows a random (typical) diet (Rivers et al, 2000). Such manipulation is well tolerated by the patient and may allow for identification of the various types of hypercalciuria with reasonable certainty.

Pak has also recognized the cumbersome nature of an extensive evaluation and has made similar recommendations (Pak, 1997). On the basis of the findings of a single 24-hour urine collection, patients are evaluated and treated without all steps of fasting and loading calcium challenges. Patients are separated into complicated and uncomplicated calcium stone disease on the basis of the presence or absence of normocalcemia, normouricemia, and calcium stones and the absence of urinary tract infection, bowel disease, or marked hyperoxaluria. Comprising the majority of all patients, uncomplicated calcium stone disease is further separated into a hypercalciuric group and a normocalciuric group. Medical therapy is then based on this distinction.

Lifshitz and colleagues (1999) have also advocated for a less complex approach. All patients undergo a basic metabolic screening, searching for systemic disorders that could pose a long-term health risk. They suggest that all patients should be advised about conservative nonspecific preventive measures. High-risk stone patients should have a more extensive metabolic evaluation based on two 24-hour urine samples.

The cornerstone of these simplified protocols has been the development of a urine preservation method that allows collection of urine without refrigeration. The patient is then able to submit an aliquot to a central laboratory for the analysis of various stone-forming substances (Nicar et al, 1987). The urinary constituents most commonly assayed include calcium, oxalate, citrate, total volume, sodium, magnesium, potassium, pH, uric acid, and sulfate. Although most of these parameters are self-evident, sulfate is added to the list to assess the volume of protein loading from animal meat. From such determinations, the urinary saturation with respect to stone-forming salts can be calculated.

At present, there are multiple private companies that offer laboratory services focused on simplified, accurate 24-hour urine assessment for stone-forming risk factors. A list of some of the more commonly used commercial laboratories is included in Table 46–5. The laboratories provide collection containers with chemical preservatives (obviating iced storage and transport) and extrapolate 24-hour cumulative data from the submission of a small aliquot of the entire collection. After the values of all urinary constituents and saturations have been determined, the physician receives a computerized printout that provides a numeric display of the test results (Fig. 46–3). A graphic display of this information may also be generated, highlighting the increased or reduced risk for each environmental, metabolic, or physicochemical factor (Fig. 46–4). These results should aid the physician in formulating a metabolic/physiologic diagnosis. It may be difficult to make a definitive diagnosis on a single 24-hour urinalysis; therefore repeated evaluation is often warranted. For example, it is desirable to confirm the presence of hypocitraturia or hyperuricosuria by repeat measurements.

There is controversy regarding the necessity of collecting two separate 24-hour urine specimens. As noted earlier, Rivers has advocated for the collection of two samples while on differing diets (random and restricted) (Rivers et al, 2000). Assuming that the patient complies, these data may be able to discern between type II absorptive hypercalciuria (AH II) and renal leak (hypercalciuria disappears while on the restricted diet in AH II). Researchers from Dallas have suggested that only one single 24-hour collection is required (Pak et al, 2001). Their study retrospectively reviewed and compared the results of two 24-hour urine samples that were collected on random diets. They noted no significant difference in the excretion of urinary calcium, oxalate, uric acid, citrate, pH, total volume, sodium, potassium, sulfate, or phosphorus. They concluded that the reproducibility of urinary stone risk factors was adequate in repeat samples, enough so that therapy would not have been altered.

Conversely, Parks and colleagues (2002) **have noted significant disparities between two separate collections.** More than 1000 patients were examined from both private practice and academic settings. They noted that within nearly 70% of the comparisons, there were large enough differences such that the standard deviation would contain clinically relevant disparities. The authors therefore conclude that relying on one specimen alone could easily lead to misdiagnosis and, consequently, mismanagement.

Finally, it is important to note that the "normal limits" cited on commercially available urine analysis packages may not be the same as the normal values quoted previously. Therefore one should pay close attention to those patients who may fall in the "gray zone" when using a commercially available urine analysis package.

Table 46–5.

Commercial Providers of 24-Hour Urinary Stone Risk Profiles

Dianon (Stratford CT)
LabCorp (Burlington NC)
LithoLink (Chicago IL)
ARUP Laboratories (Salt Lake City UT)
Quest Diagnostics (Madison NJ)
Mission Pharmacal (San Antonio TX)

Key Points: Simplified Metabolic Evaluation

- A simplified metabolic evaluation has been established.
- Commercial laboratories may facilitate the collection of 24-hour urine studies.
- There is no consensus regarding the need for one versus two 24-hour urine collections during an initial evaluation (although the authors prefer two collections).

USE OF STONE ANALYSIS TO DETERMINE METABOLIC ABNORMALITIES

Questions have arisen regarding the necessity of both chemical stone analysis and metabolic evaluation for patients with nephrolithiasis. **Although stone composition analysis is neither**

Litholink Laboratory Reporting System™

Patient Results Report

PATIENT	DATE OF BIRTH	PHYSICIAN
Sample, Patient	**06/03/1951**	**Sample, Physician**

Stone Risk Factors / Cystine Screening: Negative (12/03/04)

Values larger, bolder, and more toward red indicate increasing risk for kidney stone formation.

DATE	SAMPLE ID	Vol 24	SS CaOx	Ca 24	Ox 24	Cit 24	SS CaP	pH	SS UA	UA 24
12/04/04	089979	2.35	12.3	375	52	401	.95	6.04	0.6	0.85
12/03/04	089978	2.17	17.9	423	61	471	0.9	5.72	1.6	1.01

ABBR.	ANALYTE	NORMAL RANGE	TREATMENT RECOMMENDATION
Vol 24	Urine Volume	1/d: 0.5 - 4 L	*Raise vol at least 2L*
SS CaOx	Supersaturation CaOx	6-10	*Raise urine vol and cit, lower ox and ca.*
Ca 24	Urine Calcium	men <250, women <200	*IH, consider Hydrochlorothiazide 25 mg bid or chlorthalidone 25 mg qam, urine Na <100.*
Ox 24	Urine Oxalate	20-40	*usually dietary; if enteric, consider cholestyramine, oral calcium 1-2 gm with meals; if >80, may be primary hperoxauria.*
Cit 24	Urine Citrate	men >450, women >550	*consider K citrate 25 bid; if from RTA (urine pH > 6.5) also use K citrate*
SS CaP	Supersaturation CaP	0.5-2	*Urine usually pH > 6.5, IH common.*
pH	24 Hour Urine pH	5.8-6.2	*<5.8 consider K or Na citrate 25-30 mEq BID; 6.5, RTA if citrate is low; >8, urea splitting infection.*
SS UA	Supersaturation Uric Acid	0-1	*urine pH <6, creates UA stones. Treated with alkali*
UA 24	Urine Uric Acid	g/day: men <0.800, women <0.750	*dietary; if stones are severe and low protein diet fails try allopurinol 200 mg/d*

**Cystine Screening: positive result may be seen in patients with homozygous cystinuria and cystine stone disease, some individuals heterozygous for cystinuria without cystine stone disease, or in patients taking medications such as captopril or penicillamine.

Figure 46–3. Commercial 24-hour urine results are available and simplify the collection and reporting process. (Courtesy of Litholink, Inc.)

Table 46–6.

Mineralogic Names of Renal Calculi

Calcium oxalate monohydrate	Whewellite
Calcium oxalate dihydrate	Weddellite
Calcium hydrogen phosphate dihydrate	Brushite
Tricalcium phosphate	Whitlockite
Carbonate-apatite	Carbonate-apatite
Magnesium ammonium phosphate	Struvite
Cystine	None
Uric acid	None

always feasible nor desirable, there is helpful information from such an investigation that can aid with preventive therapy. Unfortunately, chemical and mineralogic names of common calculi are sometimes used interchangeably, causing significant confusion for the clinician. A list of these names is provided in Table 46–6.

Parks demonstrated that a given patient's supersaturation of urinary crystals coincides with the stones produced by said patient (Parks et al, 1997). Indeed, in their study, treatments that reduced stone rates also reduced the supersaturation values of the historical stone composition for that patient. If calculi develop due to prolonged supersaturation of various crystals (e.g., calcium oxalate, urate), then it is further reassuring that "snapshot," pooled urine supersaturation measurements accurately track stone admixtures and are a reliable index of long-term, "average" renal and urine supersaturations.

Assessment of stone composition, not just urinary crystal supersaturation, can be a helpful adjunct to a metabolic evaluation. **Because most stones are a mixture of more than one component, the relative ratios or predominance of any particular molecule may have predictive value.** In an analysis of almost 1400 patients who had both stone analysis and a complete metabolic evaluation, Pak noted that calcium apatite and mixed calcium oxalate-calcium apatite stones were associated with the diagnoses of renal tubular acidosis and primary hyperparathyroidism (odds ratios ≥ 2) but not with chronic diarrheal

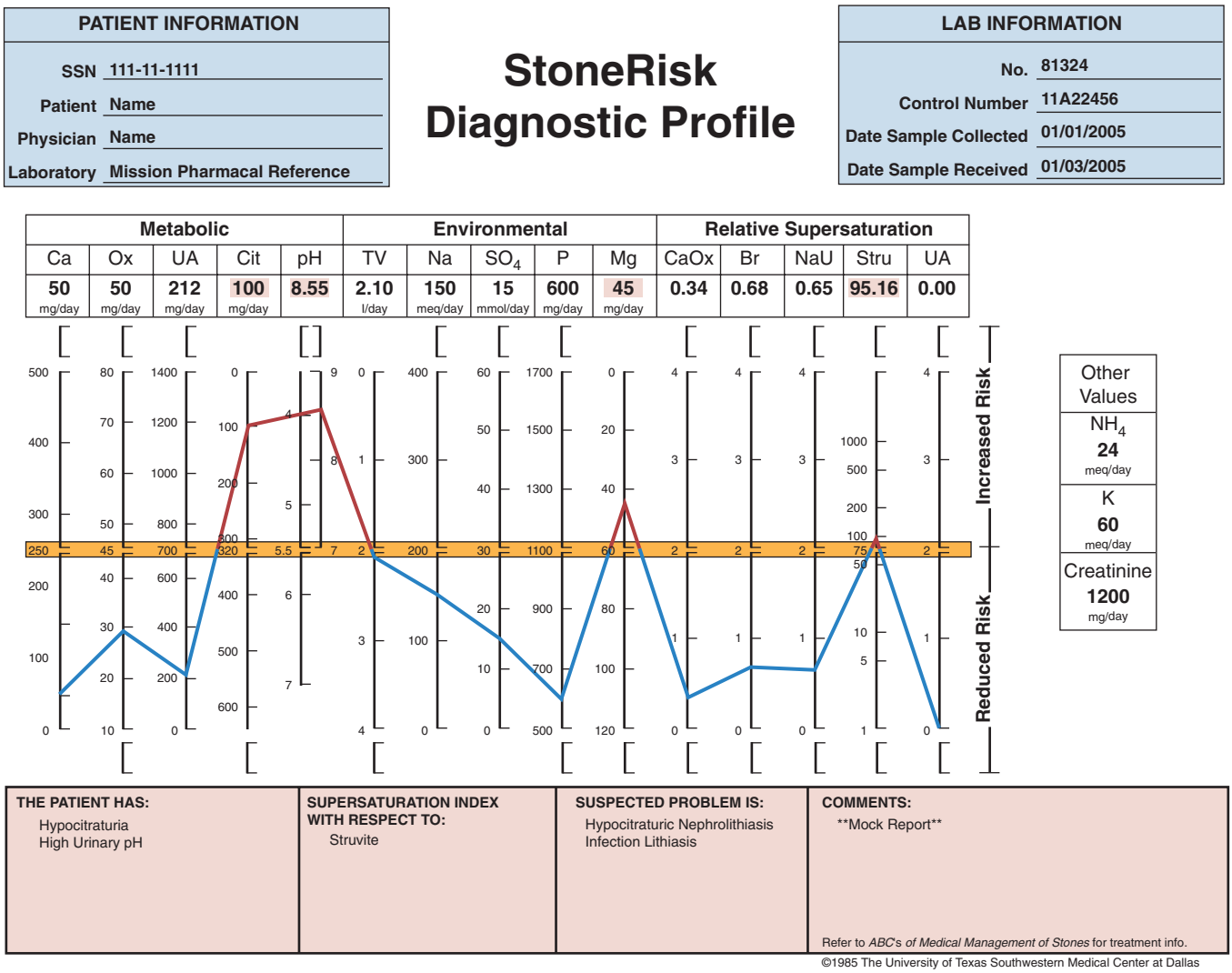


Figure 46–4. The 24-hour urine results may be presented graphically to assist with interpretation and planning. (Courtesy of Mission Pharmacal, Inc.)

syndromes (Pak et al, 2003b). As the phosphate content of the stone increased from calcium oxalate to mixed calcium oxalate-calcium apatite, and finally to calcium apatite, the percentage of patients with renal tubular acidosis increased from 5% to 39%, and those with primary hyperparathyroidism increased from 2% to 10%. Not surprisingly, pure and mixed uric acid stones were strongly associated with a gouty diathesis, whereas brushite stones were associated with renal tubular acidosis. As expected, there was a strong association between infection stones and infection and between cystine stones and cystinuria.

These findings were further supported by Kourambas and colleagues (Kourambas et al, 2001). Stone composition correlated with metabolic findings in a series of 100 consecutive patients. A significant risk of renal tubular acidosis (RTA) was documented in those patients producing predominantly calcium phosphate calculi. They maintain that the finding of a noncalcareous stone simplifies the evaluation by focusing the ensuing workup on the most obvious cause. Pure uric calculi are primarily a result of gouty diathesis, and patients may not require further testing.

Finally, Lingeman and colleagues noted that the finding of pure struvite/calcium apatite in a staghorn calculus predicted a low likelihood of finding other metabolic abnormalities during a workup. In their series, only 2 of 14 with pure infection stones had additional abnormalities compared with 7 of 7 patients with mixed chemical compositions. They therefore suggest that those patients with pure infection stones will not benefit from additional evaluation (Lingeman et al, 1995).

Key Points: Use of Stone Analysis to Determine Metabolic Abnormalities

- Stone analysis may obviate the need for a complete metabolic evaluation.
- Stone composition can direct metabolic investigation.

ROLE OF IMAGING IN DETERMINING STONE COMPOSITION

Radiologic imaging is priniciply used for determination of the presence or absence of calculi, renal anatomy, and associated findings (i.e., hydronephrosis). As such, diagnostic imaging plays a

crucial role in the surgical planning and follow-up of patients with nephrolithiasis. Aside from the inability to identify pure uric acid stones on plain radiography compared with CT, diagnostic imaging has not historically proven to be beneficial in the medical evaluation and management of stone disease.

Accompanying the ubiquity and increased utility of CT imaging, a number of authors have sought to identify characteristics wherein stone composition could be determined from this diagnostic modality (Mitcheson et al, 1983; Newhouse et al, 1984; Mostafavi et al, 1998; Nakada et al, 2000; Saw et al, 2000; Motley et al, 2001; Bellin et al, 2004; Deveci et al, 2004; Sheir et al, 2005). These investigations focused on Hounsfield unit (HU) measurements to determine stone composition. Both in vitro and in vivo work demonstrated significant differences in HU between pure uric acid stones and other stone types. However, it has been more difficult to differentiate pure struvite from cystine, calcium oxalate from brushite, and stones of mixed composition. Due to the significant variance in the readings obtained for different stone types, even with optimization of standard CT variables (collimation, pitch), this information has been of little clinical value.

More recently, the application of dual energy CT (DECT) technology is demonstrating the potential to better characterize stone type. In vitro studies using ratios of HU during DECT have been able to distinguish between uric acid, calcium phosphate, and calcium oxalate calculi (Matlaga et al, 2008). Further discrimination of stone composition has been reported by two other sets of investigators. Boll and colleagues (2009), using an alternative calculation method, showed graphical separation of relatively pure cystine, struvite, calcium oxalate and calcium phosphate, and brushite stones. This group's "DECTSlope" algorithm identified stone compositions unambiguously; however, separation of calcium oxalate and calcium phosphate calculi was not obtained. Finally, Grosjean and colleagues (2008) further characterized uric acid, cystine, struvite, calcium oxalate dihydrate, brushite, and calcium oxalate monohydrate into distinct groups with the use of DECT attenuation values. The ability to differentiate stone composition was noted to be lost when the image was subjected to respiratory motion artifact. Early work with DECT is promising but must be confirmed in vivo before incorporation into clinical decision making for the metabolic evaluation and medical management of nephrolithiasis.

ECONOMICS OF METABOLIC EVALUATION

Please see the Expert Consult website for this section.

CLASSIFICATION OF NEPHROLITHIASIS AND DIAGNOSTIC CRITERIA

Using an ambulatory protocol, the etiology of nephrolithiasis can be classified into 12 separate categories reflecting specific physiologic derangements. The details regarding the physiology and pathophysiology of these distinct entities are included in Chapter 45. These categories are listed in Table 46–7 along with the relative frequency of their occurrence as noted by Pak and colleagues at a dedicated Stone Clinic in an academic medical center (Levy et al, 1995). An argument can be made that these relative incidences may not be representative of the general population for two reasons. First, referral to an academic center may imply a more serious version of stone disease and may therefore represent a selection bias. Secondly, recognizing that there are at least some regional variations of stone incidence (Harvey et al, 1990), this particular patient population may be distinctly different from those in a different region of the United States or other regions of the world.

Table 46–7.
Classification of Nephrolithiasis

	Percentage	
	SOLE OCCURRENCE	COMBINED OCCURRENCE
Absorptive hypercalciuria	20	40
Type I		
Type II		
Renal hypercalciuria	5	8
Primary hyperparathyroidism	3	8
Unclassified calcium nephrolithiasis	15	25
Hyperoxaluric calcium nephrolithiasis	2	15
Enteric hyperoxaluria		
Primary hyperoxaluria		
Dietary hyperoxaluria		
Hypocitraturic calcium nephrolithiasis	10	50
Distal renal tubular acidosis		
Chronic diarrheal syndrome		
Thiazide-induced		
Idiopathic		
Hypomagnesiuric calcium nephrolithiasis	5	10
Gouty diathesis	15	30
Cystinuria	<1	
Infection stones	1	5
Low urine volume	10	50
No disturbance and miscellaneous	<3	

Modifed from Levy FL, Adams-Huet B, Pak CY. Ambulatory evaluation of nephrolithiasis: an update of a 1980 protocol. Am J Med 1995;98(1):50–9.

Calcium-Based Calculi

Hypercalciuria (>200 mg/day)

Absorptive Hypercalciuria. The classification of nephrolithiasis recognizes three broad categories of hypercalciuria. **Absorptive hypercalciuria (AH) involves an increase in the amount of calcium that is absorbed by the intestinal tract.** In AH type 1, this increased absorption will occur regardless of the amount of calcium in the patient's diet. Therefore these subjects will demonstrate an increased urinary excretion of calcium on both the fasting and loading specimens. In contrast, patients with AH type 2 absorptive hypercalciuria will have a normal amount of urinary calcium excretion during calcium restriction but will show elevations during their regular diet. Patients with both subtypes of absorptive hypercalciuria will have normal serum calcium and a normal level of circulating intact parathtyroid hormone (iPTH). In fact, **these patients often demonstrate a low iPTH due to suppression from a constant abundance of available serum calcium.**

Renal Hypercalciuria. **Renal hypercalciuria (RH) (also known as renal leak hypercalciuria) is thought to be due to a wasting of calcium by the functioning nephron.** The details of this process and various hypotheses are outlined in Chapter 45. As a result of constant loss of calcium from the distal tubules, these patients will demonstrate hypercalciuria during all phases of fasting, loading, or restriction of dietary calcium. **Most patients with RH will have normal serum calcium but may exhibit a mild elevation of iPTH as the regulatory systems attempt to "keep up" with the constant loss of calcium.**

Resorptive Hypercalciuria (Primary Hyperparathyroidism). **Patients with this disorder suffer from an overproduction of parathyroid hormone from either one dominant adenoma or from diffuse hyperplasia of all four glands.** The hallmark of this disorder is the persistence of increased urinary calcium during all parts of the dietary calcium manipulations. In addition, these patients frequently demonstrate hypercalcemia and elevations of the parathyroid hormone. The measurement of only the intact portion of the hormone (iPTH) has avoided confusion from the measurement of fragments of the same molecule (Kao et al, 1982; Nussbaum et al, 1987) and has greatly enhanced the ability to make this diagnosis.

Unfortunately, some patients may have normocalcemic hyperparathyroidism. These patients may be difficult to distinguish from those with renal leak hypercalciuria, during which serum calcium will be normal but a mild elevation of the iPTH can occur, creating a secondary hyperparathyroidism. In these instances the patients can be treated with a 2-week course of a thiazide diuretic such as chlorthaladone 25 mg daily. If the patient actually suffers from renal leak, than the calcium loss should be suppressed and the iPTH should return to normal (Aroldi et al, 1979; Barilla and Pak, 1979; Zechner et al, 1981). Those with true primary hyperparathyroidism will continue to circulate elevated levels of iPTH and may become mildly hypercalcemic, although this latter feature has been debated in the literature (Klimiuk et al, 1981; Farquhar et al, 1990; Strong et al, 1991).

Idiopathic Hypercalciuria. Idiopathic hypercalciuria can be found in both normal people and among stone formers (Coe et al, 1979). These patients may demonstrate elevated amounts of urine calcium in all phases of the dietary calcium manipulation but will not demonstrate serum abnormalities. **On a cautionary note, this term does not always enjoy a strict definition and is sometimes substituted to describe those patients with hypercalciuria who have not undergone further evaluation to discriminate between the various subcategories.** Although this diagnosis is not as "clean" as possible, it represents a more pragmatic approach to hypercalciuria because the treatment for absorptive and renal hypercalciuria is often the same (as outlined later in this chapter). Table 46–8 summarizes the laboratory parameters that help delineate the various types of hypercalciuria.

Key Points: Hypercalciuria

- Hypercalciuria can be divided into three causes: excessive gastrointestinal (GI) absorption, renal tubular leak, and hyperparathyroidism.
- Idiopathic hypercalciuria refers to unknown etiology or unevaluated etiology.

Table 46–8.
Differential Diagnosis of Hypercalciuria

	ABSORPTIVE	RENAL	RESORPTIVE
Serum calcium	Normal	Normal	Elevated
Parathyroid function	Suppressed	Stimulated (secondarily)	Stimulated (primarily)
Fasting urinary calcium	Normal	Elevated	Elevated
Intestinal calcium absorption	Elevated (primarily)	Elevated (secondarily)	Elevated (secondarily)

Hyperuricosuric Calcium Nephrolithiasis

Patients with hyperuricosuria may be prone to the formation of calcium oxalate calculi through a process called *heterogeneous nucleation* (also referred to as *epitaxy*) (Coe and Kavalach, 1974; Pak and Arnold, 1975; Coe, 1980). The details of this process are outlined in the previous chapter. These patients give a history of calcium oxalate nephrolithiasis and may have a history of hyperuricemia with symptomatic gout. During metabolic evaluation, these patients will demonstrate hyperuricosuria (>800 mg/day).

Hyperoxaluria (>40 mg/day)

Enteric Hyperoxaluria. **This entity is often one of the most striking findings during a metabolic evaluation because it involves multiple factors, all caused as a result of chronic diarrhea with its attendant dehydration and bicarbonate losses** (Worcester, 2002). The main hallmark is, of course, hyperoxaluria with values that can be quite high (i.e., >50 mg/day). As a result of intestinal fluid loss, patients will often exhibit low urine volumes. The bicarbonate loss (and the consumption of citrate as an acid/base buffer) can also cause a low urine pH and hypocitraturia (Rudman et al, 1980). Urine calcium excretion is often low due to the saponification of oral calcium with poorly absorbed fats in the intestinal tract.

Primary Hyperoxaluria. **This extremely rare disorder is caused by an inborn error of metabolism.** The more common variant, type 1, is due to a defect of the enzyme alanine-glyoxylate aminotransferase (AGT) via an autosomal recessive inheritance. Type 2 is a less common variant thought secondary to a defect in D-glycerate dehydrogenase, which has both glyoxylate/hydroxypyruvate reductase. Primary hyperoxaluria usually present during childhood with early stone formation, tissue deposition of oxalate (oxalosis), and renal failure due to nephrocalcinosis. Death often occurs before age 20 in untreated patients (Williams and Smith, 1968; Leumann and Hoppe, 1999). Metabolic evaluation will reveal high urine oxalate excretion, as well as high serum levels of this molecule.

Mild Metabolic Hyperoxaluria (Dietary). The importance of dietary oxalate and the possibility of an inheritable sensitivity to oral oxalate loads are debated and have already been discussed in the previous chapter. It appears increasingly evident that a deficiency of a bacterium found within intestinal flora *(Oxalobacter formigenes)* is a factor in the formation of calcium oxalate calculi (Allison et al, 1986; Sidhu et al, 1999; Troxel et al, 2003). Regardless of the underlying etiology, some patients without primary hyperoxaluria or without a history of bowel disorders will demonstrate an elevation of oxalate in their 24-hour urine collection. A review of the patient's dietary habits may reveal a predisposition

for those foods that are particularly high in oxalate. **Although this molecule is ubiquitous and cannot be avoided, certain foods can deliver substantial amounts of oxalate in one serving.** An abbreviated list of foods that are particularly high in oxalate are contained in Table 46–9 (Assimos and Holmes, 2000; Holmes and Assimos, 2004).

Hypocitraturic Calcium Nephrolithiasis (<550 mg, female; <450 mg, male)

There is some controversy regarding the definition of normal urinary citrate excretion. Women tend to have higher urinary citrate measurements than men, particularly before menopause (Pak, 1990). Menon and colleagues define hypocitraturia as citrate excretion of less than 110 mg for men and 200 mg for women (Menon and Mahle, 1983). Despite noting gender differences, Pak (1990) and colleagues define normal urine citrate as greater than 320 mg for both genders. In some of the earlier studies from Dallas, hypocitraturia was found in up to 50% of all patients evaluated, frequently in association with other abnormalities (Nicar, 1983). Park and Coe (1986) have also noted the importance of urinary citrate for the prevention of calcareous stones and have set the limits of normal at higher values with men being more than 450 mg and women at more than 550 mg daily. Nevertheless, hypocitraturia is considered one of the more common metabolic diagnoses, probably second only to hypercalciuria. The four causes of hypocitraturia follow.

Distal Renal Tubular Acidosis (Type 1). **Patients may have either an acquired or an inheritable version of renal tubular acidosis (RTA), with the incomplete version representing a less serious clinical pattern. Regardless of the actual cause, the laboratory hallmark of this disease is a low urine citrate (hypocitraturia) with an inappropriately high urine pH.** Often, the measured 24-hour urine citrate will be quite diminished with values less than 100 mg/day. The urine pH will be elevated to 6.5 or above. Hypokalemia is often evident on the serum studies, as is hyperchloremia. A nonanion gap acidosis may be present, as well with CO_2 values in the mid-teens (Preminger et al, 1985). First-void urines can be evaluated to assess the urine pH and screen for a renal tubular acidosis. Patients with RTA will be unable to acidify their urine overnight and should have a urine pH no lower than 5.5.

Distal RTA may present as an isolated entity or it may be the secondary manifestation of a variety of systemic and renal disorders. More than two thirds of patients with distal RTA are adults, but occasionally children will be identified with this disorder. Infants generally present with vomiting or diarrhea, failure to thrive, and growth retardation. Children often present with metabolic bone disease and renal stones, while adults frequently present with symptoms attributable to nephrolithiasis and nephrocalcinosis.

Up to 70% of adults with distal RTA have kidney stones (Caruana and Buckalew, 1988). Those patents with onset at an early age or with severe forms of the disorder may develop nephrocalcinosis and eventual renal insufficiency (Fig. 46–5A and B). RTA is more common in women, accounting for nearly 80% of all cases. It is important to note that secondary RTA can be induced by many common urologic disorders, which may also be sought following a diagnosis of acquired RTA. These include obstructive uropathy, pyelonephritis, acute tubular necrosis, renal transplantation, analgesic nephropathy, sarcoidosis, idiopathic hypercalciuria, and primary hyperparathyroidism (Buckalew, 1989) (Table 46–10).

Some patients will have an incomplete variant of the disease with less marked hypocitraturia and a more normal urine pH. Incomplete variants can be diagnosed with the use of an ammonium chloride loading challenge. In this evaluation, the fasting patient is given 0.1 g of ammonium chloride per kg body

Table 46–9.

High-Oxalate Foods

Tea (black)	Okra
Cocoa	Berries (some)
Spinach	Chocolate
Mustard greens	Nuts
Pokeweed	Wheat germ
Swiss chard	Soy crackers
Beets	Pepper
Rhubarb	

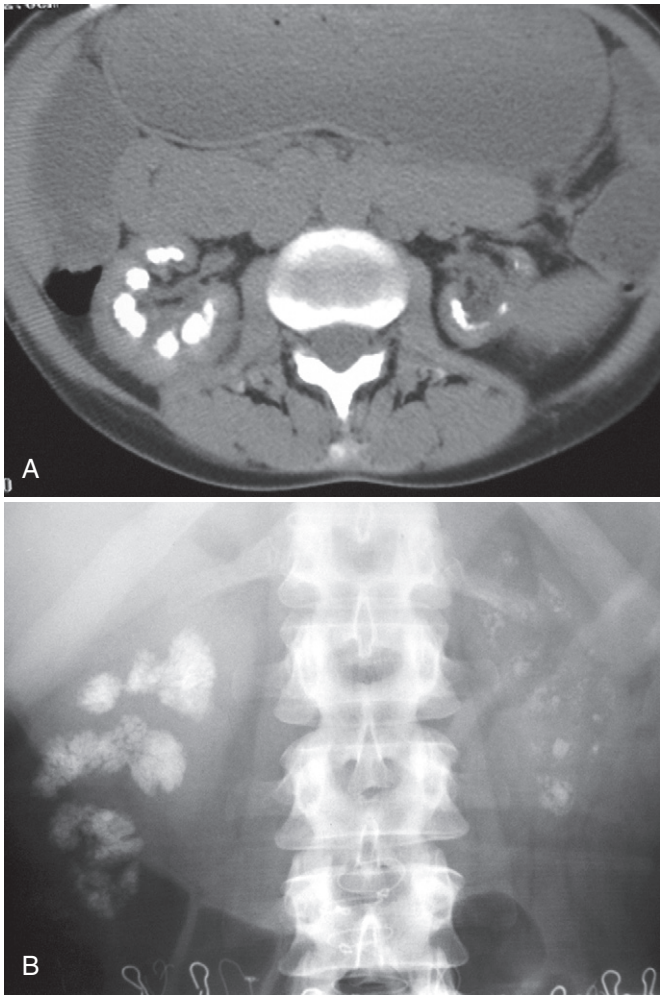


Figure 46–5. **A,** CT and **B,** plain film of a patient with renal tubular acidosis and renal failure. Both kidneys demonstrate severe calcification of the medullary pyramids consistent with nephrocalcinosis. Notice the atrophic left kidney on the CT image.

Table 46–10.

Causes of Acquired Renal Tubular Acidosis

Obstructive uropathy
Recurrent pyelonephritis
Acute tubular necrosis
Renal transplantation
Analgesic nephropathy
Sarcoidosis
Idiopathic hypercalciuria
Primary hyperparathyroidism

weight in crushed granules mixed with a soft drink. Subsequently, hourly measurements of urinary pH and bihourly measurements of serum pH or bicarbonate are taken over 4 to 6 hours (Pohlman et al, 1984). If the serum pH falls below 7.32 or the bicarbonate falls below 16 mmol/L but urinary pH remains at or above 5.5, the diagnosis of incomplete distal RTA is confirmed. If at any time the urinary pH falls below 5.5, the diagnosis of incomplete distal RTA is excluded (Preminger et al, 1985; Preminger, 1987; Preminger et al, 1988).

Chronic Diarrheal States. The laboratory findings in a patient with a chronic diarrheal disorder are similar to those patients described with enteric hyperoxaluria. However, these patients do not tend to suffer from bowel inflammation and subsequent heightened permeability to oxalate. Therefore urinary oxalate may be mildy elevated, but usually not to the extent as found in those patients with bowel resection or inflammatory disorders. These patients will likely demonstrate moderate decreases in urinary citrate excretion with associated low urine volumes (Fegan et al, 1992; Caudarella et al, 1993; Worcester, 2002; Parks et al, 2003b).

Thiazide-Induced Hypocitraturia. **One of the side effects of thiazide therapy is the development of hypocitraturia.** This defect is presumably secondary to the hypokalemia and resultant intracellular acidosis that may develop after prolonged therapy with thiazides (Pak et al, 1985a). Since thiazides are still widely utilized as a diuretic and for the management of hypertension, some patients may present with a stone episode after prolonged therapy with this medication. Stone patients who are treated with thiazides for the control of hypercalciuria should be screened for hypocitraturia (Pak et al, 1985b).

Idiopathic Hypocitraturia. Patients with idiopathic hypocitraturia include all those with 24-hour urine citrate less than 550 mg (males) or 450 mg (female) in the absence of any of the previously noted disease states. It is important to consider unrecognized incomplete RTA as a potential diagnosis because this disorder carries with it a significant risk of long-term morbidity. Additionally, a careful history should be taken to screen for bowel dysfunction.

Key Points: Hypocitraturia

- The definition of hypocitraturia may vary greatly.
- Severe hypocitraturia should immediately raise suspicions for renal tubular acidosis (RTA).
- Hypocitraturia frequently accompanies other diagnostic categories.

Hypomagnesiuric Calcium Nephrolithiasis (<80 mg)

Hypomagnesiuric calcium nephrolithiasis is characterized by low urinary magnesium, hypocitraturia, and low urine volume. It is frequently associated with chronic thiazide therapy (Ljunghall et al, 1981; Preminger et al, 1989). More commonly, inflammatory bowel disorders, particularly those that cause malabsorption, have been implicated in this process (Preminger, 1989). Excessive dependence on laxatives may also induce a pattern similar to chronic diarrheal states (Dick et al, 1990; Soble et al, 1999). The importance of this disorder has been questioned, however, with the suggestion that the stone-risk association of hypomagnesuria may actually be due to its effect on urinary citrate (Schwartz et al, 2001).

Uric Acid–Based Calculi

Gouty Diathesis

The pathophysiology of uric acid nephrolithiasis is explained in detail in the previous chapter but does deserve some mention in order to better understand its diagnosis. Because there are no known inhibitors of uric acid crystallization, undissociated uric acid will precipitate when the urine becomes supersaturated. The sigmoidal-shaped solubility curve will predict that at a pH of 6.5 more than 90% of all uric acid is ionized and therefore soluble. Fifty percent of uric acid will be soluble at a pH of roughly 5.5 (pK_a) (Gutman and Yu, 1968). By definition, patients with gouty diathesis have a urine pH of less than 5.5.

It follows, then, that patients with gouty diathesis and uric acid calculi will tend to have lower urine pH than normal subjects (Gutman and Yu, 1968). Twenty-four-hour measurements of this molecule will often be greater than 800 mg. Up to 20% of patients with gout will develop uric acid calculi, prompting examination of serum for hyperuricemia. Oftentimes, 24-hour urine collections can underestimate the total amount of uric acid if the specimen pH drops lower than 5.5. In this scenario, the uric acid forms precipitates and settles to the bottom of the collection container.

It should not be difficult to distinguish between those patients with hyperuricosuric calcium nephrolithiasis (HUCN), who form calcium oxalate stones and those with gouty diathesis, who can form either uric acid or calcium oxalate calculi. Patients with HUCN present with normal urinary pH and hyperuricosuria, accompanied sometimes by hypercalciuria. In contrast, those with gouty diathesis have a low fractional excretion of urate (that contributes to hyperuricemia) and low urinary pH (that leads to increased amount of undissociated uric acid) (Khatchadourian et al, 1995; Pak et al, 2003c). The varying biochemical and physicochemical presentations of the two conditions can be ascribed to overindulgence with purine-rich foods in those with HUCN and underlying primary gout in those with gouty diathesis (Pak et al, 2002b).

A dietary history should be obtained from all patients with uric acid calculi because they may tend to have purine gluttony (high intake of animal protein, specifically red meat). An astute clinician will at least give a brief consideration to the possibility of a neoplastic or myeloproliferative disorder. Patients with diabetes mellitus may also form uric acid calculi, as a result of disorders in ammonium handling with subsequent low urine pH (Pak et al, 2003c).

Uric acid calculi can be notoriously radiolucent. Tomography may overcome this difficulty (Fig. 46–6A and B), as can the acquisition of a noncontrasted renal CT. These stones frequently have an orange appearance, especially when viewed endoscopically. Uric acid stone formers can have a propensity to produce large volumes of small calculi that may cause obstruction as they pass down the ureter.

Key Points: Uric Acid–Based Calculi

- Hyperuricosuria may be associated with pure uric acid calculi or calcium oxalate calculi.
- Patients with gout may be predisposed to uric acid stones.
- Dietary indiscretion (purine gluttony) should always be suspected.

Cystinuria

Cystinuria is caused by an autosomal recessive error of transepithelial transport involving the intestine and the kidneys (Thier et al, 1965; Pak and Fuller, 1983). In this disease, patients are unable to reabsorb the dibasic amino acids: cystine, ornithine, lysine, and arginine (COLA). The resultant **accumulation of cystine causes crystallization when concentrations rise above the saturation point (roughly 250 mg cystine per liter of urine)** (Pak and Fuller, 1983).

Patients with this disorder may present at a young age and may have affected first-degree relatives. The stones are often yellow and waxy in appearance and are relatively faint on plain radiography. Staghorn calculi or multiple, filled calyces are common (Fig. 46–7).

Historically, a diagnosis of cystinuria was made with the use of a sodium nitroprusside spot test, which turned purple in the presence of cystine (Smith, 1977). Although this test is a helpful screening adjunct, quantitative measurements of cystine can be difficult to perform due to interference from other sulfhydryl-containing compounds (such as medications used to treat this disorder) or from significant variances with minor changes in urine pH or creatinine content (Pak and Fuller, 1983). Coe and colleagues have recently developed a more reliable method of cystine supersaturation measurement that may greatly aid in the diagnosis and especially the management of cystinuria (Nakagawa et al, 2000; Coe et al, 2001).

Cystinurics may also demonstrate additional metabolic anomalies on 24-hour urine studies (Sakhaee et al, 1989). In controlled dietary assessment of 27 patients with cystinuria, hypercalciuria was noted in 18.5% of patients, hyperuricosuria in 22.2%. Hypocitraturia was identified in 44.4% and was associated with defective renal acidification in 80% of the patients in whom it was tested. The authors noted that hypercalciuria, hyperuricosuria, and hypocitraturia frequently accompany cystinuria and speculated that these conditions might be renal in origin, rather than a result of dietary or environmental aberrations. They further concluded that these unrelated anomalies may contribute to the formation of calcium and uric acid stones, which sometimes complicate cystine nephrolithiasis.

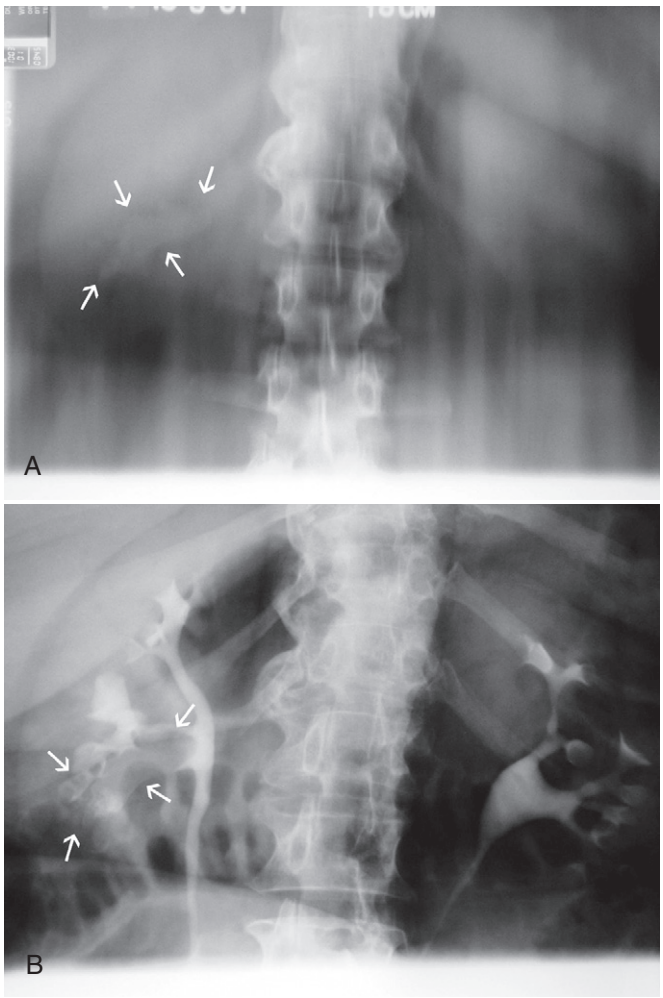


Figure 46–6. **A,** Plain film tomographic appearance of a lower pole partial staghorn uric acid calculus. **B,** The addition of intravenous contrast demonstrates the stone as a "filling defect" during the excretory portion of the intravenous pyelogram.

Key Points: Cystinuria

- Cystinuria manifests when concentrations exceed 250 mg/L.
- Cystinuria may be accompanied by other metabolic abnormalities.

Infection Calculi (Struvite)

Struvite calculi form in the presence of alkaline urine (pH above 7.2) and in an environment rich in ammonia (Nemoy and Staney, 1971). **The ammonia is thought to be produced via the splitting of urea by colonization with bacteria that produce urease.** The details of this process are presented in the preceding chapter. Many bacterial organisms are able to produce this enzyme (Table 46–11), the most notorious of which is *Proteus mirabilis*. Although *Escherichia coli* is unable to split urea, it may be associated with struvite calculi in up to 13% of infections (perhaps through a metachronous infection).

Patients with these calculi may present with the symptoms of acute pyelonephritis including fevers, chills, flank pain, dysuria, frequency, urgency, and malodorous, cloudy urine. Some patients may exhibit more chronic symptoms of malaise, fatigue, loss of appetite, and generalized weakness. Rarely, infections and obstruction have been long-standing enough to produce a

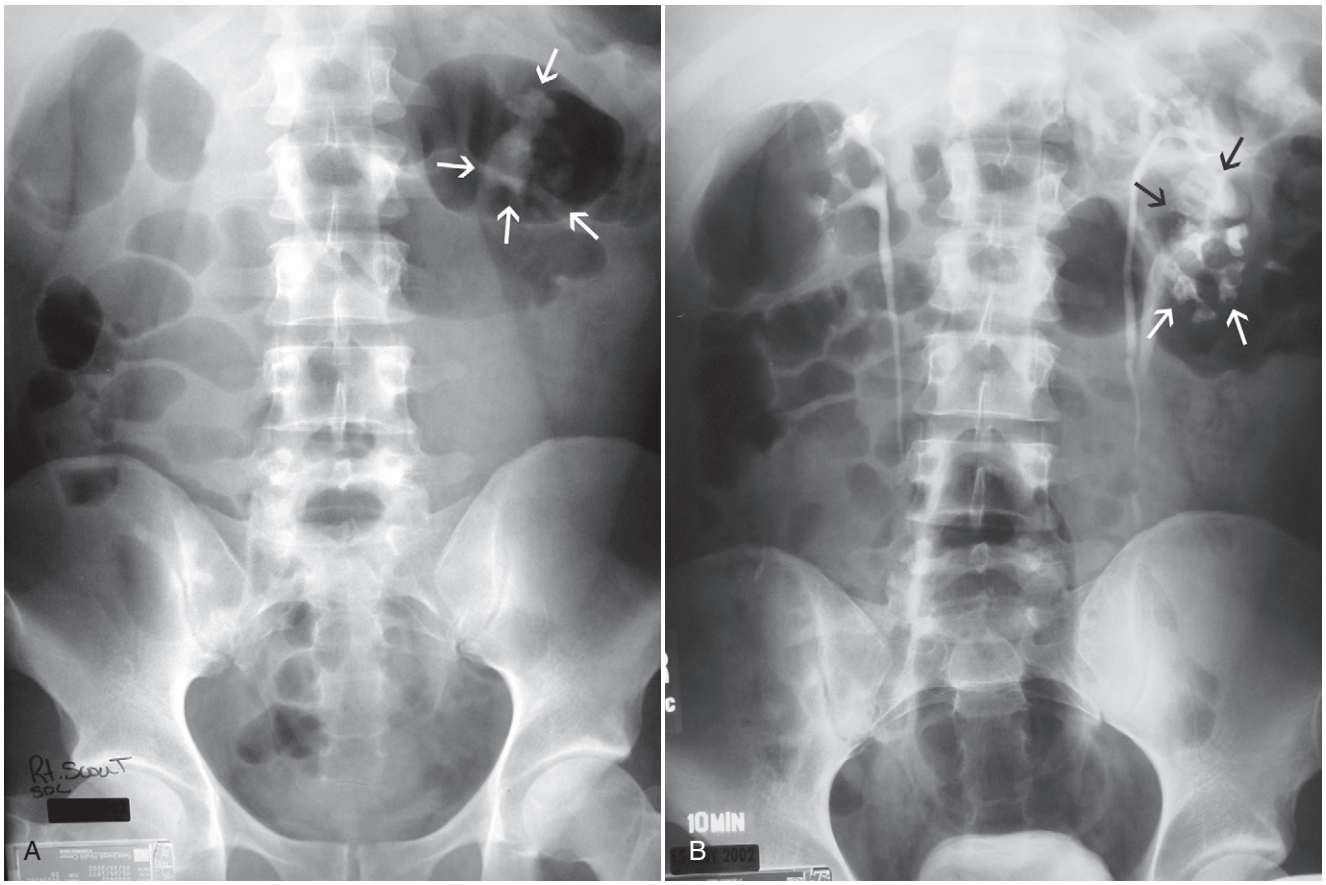


Figure 46–7. **A,** Cystine calculi are radiopaque on plain film but are less dense than other calcium-based calculi. Notice the stone within the lower pole of this duplicated system. Similar to uric acid stones, the cystine calculus is more clearly distinguished during the excretory phase of the intravenous pyelogram **(B).**

xanthogranulomatous pyelonephritis (XGP). XGP may cause the failure of an entire kidney or may just affect a portion. Spontaneous fistulae may develop to external surfaces or to peritoneal contents (Fig. 46–8).

Women are more often affected with struvite calculi than men, likely due to an increased susceptibility to urinary tract colonization. A history of a foreign body (e.g., forgotten stent, suture material, staple) or of a neurogenic bladder may be noted. Struvite calculi can be quite large and often fill multiple calyces or even the entire collecting system (Fig. 46–9). **This stone type accounts for the majority of all staghorn calculi.** Urine cultures will often reveal a bacterial pathogen, although, as noted previously, the presence of a sterile urine culture does not preclude the sequestration of bacteria within the calculus itself.

There is debate concerning the incidence of associated metabolic anomalies in patients with struvite calculi. Resnick has advocated the performance of a metabolic evaluation for all patients with infection calculi due to a high incidence of positive findings. Conversely, Lingeman studied 22 patients with infection calculi and noted that patients with pure struvite calculi were significantly less likely to have metabolic anomalies on 24-hour urine evaluation than those patients with mixed compositions of struvite and calcium oxalate (Resnick, 1981; Lingeman et al, 1995).

Key Points: Infection Calculi (Struvite)

- Women produce more infection calculi than men.
- The urine pH is usually greater than 6.5 and 7.0.
- Urea-splitting organisms are frequent.
- Infection calculi are the most likely to produce staghorn stones.

Low Urine Volumes (<2000 mL)

Some patients will exhibit few abnormalities on a complete evaluation other than low urine volumes. From a simplistic view, a low volume of urine output will concentrate the molecular components of crystal formation and raise the supersaturation risk. Intuitively, a patient with a relative state of dehydration will trend toward acidic urine, lowering the urine pH toward the pKa of uric acid (5.5) and potentially consuming titratable buffers such as citrate.

Many patients with low urine volumes work in professions that induce high insensible losses of fluid (manual labor, outdoor exposure) (Sakhaee et al, 1987; Borghi et al, 1990; Borghi et al, 1993a). Many work in environs that do not allow easy access to fluids and work breaks (assembly line, surgeons). A focused social history

Table 46–11.

Organisms That May Produce Urease

ORGANISMS	USUALLY (>90% OF ISOLATES)	OCCASIONALLY (5%-30% OF ISOLATES)
Gram positive	*Proteus rettgeri* *Proteus vulgaris* *Proteus mirabilis* *Proteus morganii* *Providencia stuartii* *Haemophilus influenzae* *Bordetella pertussis* *Bacteroides corrodens* *Yersinia enterocolitica* *Brucella* spp.	*Klebsiella pneumoniae* *Klebsiella oxytoca* *Serratia marcescens* *Haemophilus parainfluenzae* *Bordetella bronchiseptica* *Aeromonas hydrophila* *Pseudomonas aeruginosa* *Pasteurella* spp.
Gram positive	*Flavobacterium* spp. *Staphylococcus aureus* *Micrococcus* *Corynebacterium ulcerans* *Corynebacterium renale* *Corynebacterium ovis* *Corynebacterium hofmannii*	*Staphylococcus epidermidis* *Bacillus* spp. *Corynebacterium murium* *Corynebacterium equi* *Peptococcus asaccharolyticus* *Clostridium tetani* *Mycobacterium rhodochrous group*
Mycoplasma	T-strain *Mycoplasma* *Ureaplasma urealyticum*	
Yeasts	*Cryptococcus* *Rhodotorula* *Sporobolomyces* *Candida humicola* *Trichosporon cutaneum*	

From Gleeson MJ, Griffith DP. Infection stones. In: Resnick MI, Pak CYC, editors. Urolithiasis: a medical and surgical reference. Philadelphia: WB Saunders; 1990. p. 115.

should elucidate these factors and allow for proper identification and subsequent counseling.

No Disturbances

Pak has estimated that 3% of all patients undergoing a full metabolic evaluation will demonstrate no abnormalities (Pak et al, 1980a). **Although on the surface, these patients may present less of a diagnostic challenge, there is always a concern that the collections are not representative of the patient's true metabolic state** (Table 46–12). This could be secondary to an error in collection technique, failure to collect a full 24 hours worth of urine, changes in the patient's diet for the sake of the study, or intermittent indiscretions in diet. Furthermore, it is important to remember that a 24-hour urine collection represents a pooled sample. Heavy oxalate loading at one particular meal or bolus replacement of fluids at the end of a work day may produce average values that look normal but actually hide periods of extreme urine parameters that promote stone formation. Finally, most patients will collect their requested 24-hour specimens on days when they are home and able to stay close to the collection container. For most, this occurs on a weekend or nonworking day. It is possible (and quite likely) that collections on these days do not represent the patient's typical metabolic milieu that exists during the rest of the week (Rodgers et al, 1994; Rodgers et al, 1995; Norman, 1996; Hess et al, 1997).

Table 46–12.

Potential Causes of Erroneous 24-Hour Urine Collection

Error in collection technique (e.g., improper use of preservatives, ice)
Failure to collect a full 24 hours' worth of urine
Changes in the patient's diet for the sake of the study
Intermittent indiscretions in diet
Failure of specimen to accurately represent "typical" day
Bacterial contamination

The diagnostic criteria for the 12 principal classifications described in this section are summarized in Table 46–13**.**

CONSERVATIVE MEDICAL MANAGEMENT

Certain conservative recommendations should be made for all patients regardless of the underlying etiology of their stone disease. Unfortunately, it can be difficult to reach consensus regarding specific details from the available literature.

Fluid Recommendations

Volume

One mainstay of conservative management is the forced increase in fluid intake to achieve a daily urine output of 2 L (Borghi et al, 1999). Increased urine output may have two effects. First, the mechanical diuresis that ensues may prevent urinary stagnation and the formation of symptomatic calculi. More likely is that the creation of dilute urine alters the supersaturation of stone components. Indeed, Pak and colleagues (1980b) measured in vitro and in vivo effects of urinary dilution and discovered that both significantly reduced the urinary activity product ratio (state of saturation) of calcium phosphate, calcium oxalate, and monosodium urate. Moreover, the formation product ratio, which is the minimum supersaturation needed to elicit spontaneous nucleation, of calcium oxalate significantly increased.

Researchers at the University of Chicago have demonstrated that failure to increase urine output was one of three strong predictors of relapse for those patients followed in a dedicated stone clinic (Strauss et al, 1982b). The previously described "stone clinic effect" has been primarily attributed to increases in fluid intake and attendant increases in urinary output (Hosking et al, 1983).

However, while the concept of increased fluid intake is simple, it can be difficult to achieve patient compliance. Anecdotally, most physicians with an interest in kidney stone disease have seen that many patients are unable to maintain increased urinary output over the long term. This general impression has been borne out in an analysis of urine output changes from a large series of 2877 patients (Parks et al, 2003a). In this amalgam of university and private practice patients, the average increase in urinary volume was only 0.3 L per day. In addition, intermittent compliance may not be effective because small, early stones may develop during periods of intense dehydration. At least one author has

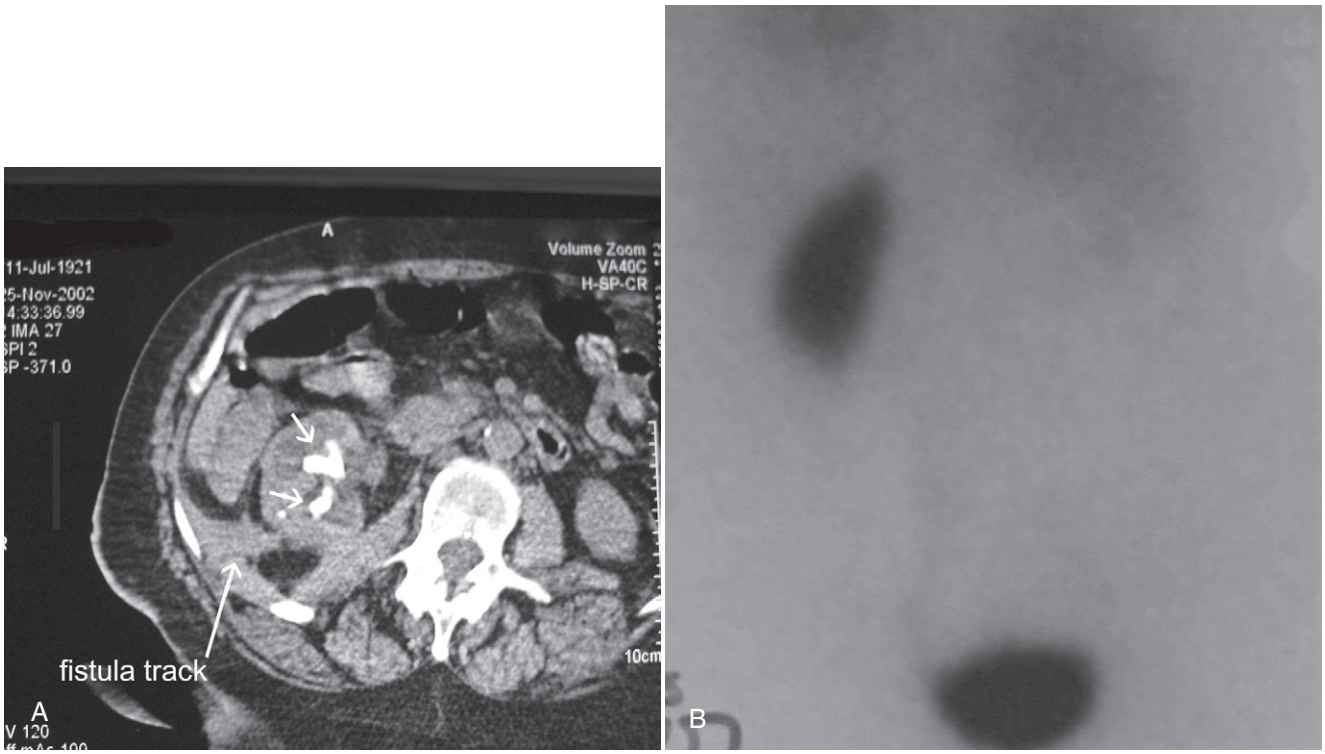


Figure 46–8. **A,** CT image of a staghorn calculus within the right kidney. *Arrow* points to a fistula that spontaneously eroded through Petit Triangle. This patient denied a history of recurrent urinary tract infections. **B,** Nuclear renogram of the same patient. Note the complete lack of function of the affected kidney. This organ was removed laparoscopically.

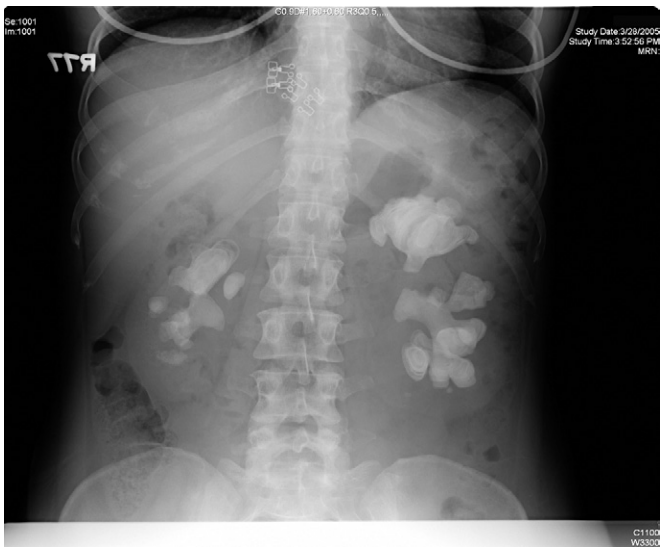


Figure 46–9. Plain film of a patient with bilateral staghorn calculi composed entirely of Struvite. This patient had a history of recurrent urinary tract infections dating back 15 years.

suggested that if a patient can voluntarily force fluid intake long enough to dilute renal concentrating abilities, then thirst mechanisms will take over and help maintain a high fluid intake and high urine output (Burns and Finlayson, 1981). Unfortunately, the more recent data from Parks and colleagues have not proved this finding to be reliable.

Water Hardness

If water intake is so important, is there a difference between water hardness that might ameliorate or augment its benefit? This concept has been the topic of conflicting articles within the general urologic and epidemiologic literature. In one study, patients with a known history of calcium nephrolithiasis were divided according to postal zip codes. Twenty-four-hour urine measurements were compared, as was the history of stone episodes (Schwartz et al, 2002). Although the 24-hour urine calcium, magnesium, and citrate levels increased directly with drinking water hardness, no significant change was found in urinary oxalate, uric acid, pH, or volume. Most importantly, the number of total lifetime stone episodes was similar between patients residing in areas with soft public water and hard public water. Patients consuming the softest water decile formed 3.4 lifetime stones and those who consumed the hardest water developed 3.0 lifetime stones. **The authors noted that although water hardness can alter urinary parameters, this ultimately appears to have little effect on clinical outcome.**

These findings are further supported by earlier work from Shuster and colleagues (Shuster et al, 1982). They examined 2295 patients from two regions: the Carolinas, which had soft water and high stone incidence, and the Rockies, which had hard water and low stone incidence. Home tap water samples from urinary stone patient hospitalizations were compared with controls. After adjusting for environmental factors, no significant difference between the two groups was obtained in tap water calcium, magnesium, and sodium concentrations. An incidental but potentially important finding was that those consuming water from a private well had an estimated relative risk of stone formation of 1.5 compared with those using public water. **They ultimately**

Table 46–13.

Diagnostic Criteria

	Serum			Urinary							
	Ca	P	PTH	Ca Fasting	Ca Load	Restricted	UA	Ox	Cit	pH	Mg
Absorptive hypercalciuria type 1	N	N	N	N	↑	↑	N	N	N	N	N
Absorptive hypercalciuria type 2	N	N	N	N	↑	N	N	N	N	N	N
Renal hypercalciuria	N	N	↑	↑	↑	↑	N	N	N	N	N
Primary hyperparathyroidism	↑	↓	↑	↑	↑	↑	N	N	N	N	N
Unclassified hypercalciuria	N	N/↓	N	↑	↑	↑	N	N	N	N	N
Hyperuricosuria	N	N	N	N	N	N	↑	N	N	N	N
Enteric hyperoxaluria	N/↓	N/↓	N/↓	↓	↓	↓	↓	↑	↓	N	N
Hypocitraturia	N	N	N	N	N	N	N	N	↓	N	N
Renal tubular acidosis	N	N	N/↑	↑	N	N/↑	N	N	↓	N/↑	N
Hypomagnesiuria	N	N	N	N	N	N	N/↓	N	↓	N	↓
Gouty diathesis	N	N	N	N	N	N	N/↑	N	N/↓	↓	N
Infection lithiasis	N	N	N	N	N	N	N	N	↓	↑	N

Fasting samples represent 2-hour collections obtained in morning following an overnight fast. Calcium load samples were obtained over a 4-hour period subsequent to oral ingestion of 1 g calcium.
↑ high; ↓ low; Cit, citrate; Mg, magnesium; N, normal; Ox, oxalate; PTH, immunoreactive parathyroid hormone; UA, uric acid.

concluded that water hardness should be a minor concern with respect to stone formation.

Unfortunately, this issue has not been completely put to rest because there is still evidence that hard water may confer some excess risk of stone formation. In a well-controlled study involving fixed diets and a cross-over design, 18 subjects with a history of calcium nephrolithiasis drank either hard water, soft water, or tap water (Bellizzi et al, 1999). The urinary levels of calcium demonstrated a significant 50% increase in the absence of changes of oxalate excretion. Although these changes are concerning, it is important to note that stone events were not used as a primary outcome.

Carbonated Beverages

A number of recent studies suggest that carbonated water offers increased protection against recurrent stone formation as compared with still water (Rodgers, 1997, 1998; Bren et al, 1998; Caudarella et al, 1998; Coen et al, 2001). It should be noted that these studies focused primarily on carbonated water, which has been demonstrated to increase urinary citrate levels.

Other types of carbonated beverages have also been examined. One study has demonstrated that increased intake of soda can confer an increased risk of subsequent stone recurrence (Shuster et al, 1992). The study sample consisted of 1009 male subjects, who reported consuming at least 160 mL per day of soft drinks. Half of the subjects were randomized to refrain from consuming soft drinks, while the remaining subjects served as controls. The intervention group had an observed 6.4% advantage in actuarial 3-year freedom from recurrence over the control group. One important secondary finding was that those who reported that their most consumed drink was acidified by phosphoric acid but not citric acid had a 15% higher 3-year recurrence-free rate than the controls. Meanwhile, those who consumed drinks acidified by citric acid had no increase in stone episodes when compared with controls. Recently, a comparison of self-selected diets to standardized diets combined with regulated fluid intake with still water or two sugar-free, caffeine-free carbonated beverages (one with high citrate content) documented no difference in urinary parameters among the standardized diets with regulated fluid intake but a significant increase in urinary volume, as well as a decrease in calcium oxalate saturation, when these were compared with the self-selected diets (Passman et al, 2009).

Additional epidemiologic studies have demonstrated the effects of particular fluids on the risk of stone recurrence (Curhan et al, 1996a, 1998b). For both men and women, there was a decrease in the risk of nephrolithiasis for those who consumed increased volumes of water, caffeinated or decaffeinated coffee, tea, beer, and wine. Conversely, daily servings of apple or grapefruit juice increased the risk of stone events. **Despite the epidemiologic evidence, the supersaturation risks associated with grapefruit juice have largely been discredited by subsequent evaluations** (Goldfarb and Asplin, 2001; Trinchieri et al, 2002; Honow et al, 2003).

In contrast to these epidemiologic findings, recent evidence suggests that caffeine intake may increase the risk of stone recurrence in calcium stone formers by increasing the excretion of calcium. Caffeine increased urinary Ca/Cr, magnesium/Cr, citrate/Cr, and sodium/Cr but not oxalate/Cr in stone formers and controls. Furthermore, supersaturation calculations increased, despite the noted increases in the inhibitors citrate and magnesium (Massey and Sutton, 2004).

Citrus Juices

Lemonade and orange juice have long been used as an adjunct to water in order to provide increased urinary volume and increased urinary citrate excretion. In a study of 12 hypocitraturic patients, lemonade made from reconstituted lemon juice provided enough citrate to correct the hypocitraturia in seven subjects (Seltzer et al, 1996). Urinary calcium excretion decreased an average of 39 mg daily, whereas oxalate excretion was unchanged. The lemonade mixture was well tolerated with only two patients complaining of mild indigestion that did not require cessation of therapy. Wabner and Pak (1993) have similarly evaluated the effects of orange juice on the urinary parameters of normal subjects and found that compared with potassium citrate, orange juice delivered an equivalent alkali load and caused a similar increase in urinary pH (6.48 vs. 6.75 from 5.71) and urinary citrate (952 vs. 944 from 571 mg per day). Therefore orange juice, like potassium citrate, decreased urinary undissociated uric acid levels and increased the inhibitor activity (formation product) of brushite (calcium phosphate). However, orange juice increased

urinary oxalate and did not alter calcium excretion, whereas potassium citrate decreased urinary calcium without altering urinary oxalate. They concluded that orange juice could be beneficial in the control of calcareous and uric acid nephrolithiasis. Further work evaluating the effects of distilled water, orange juice, and lemonade are provided by Odvina (2006). In a randomized, crossover study under controlled metabolic conditions 13 patients were evaluated. The author found that orange juice intake, not lemonade or water, led to a higher urinary pH and increased urinary citrate level. Urinary calcium was not different between the groups, but oxalate was elevated in the orange juice arm. Finally, the supersaturation of calcium oxalate and undissociated uric acid were lowest during the orange juice phase, but the brushite supersaturation was significantly higher during this phase.

In comparison, a recent evaluation of reconstituted lemonade (1 oz ReaLemon in ¾ cup of water) compared with 60 mEq of potassium citrate did not identify an increase in the urinary citrate excretion for the lemonade arm (Koff et al, 2007). Additionally, patients on lemonade therapy did not significantly alter their urinary pH, but a slight, though insignificant, increase in urinary volume was noted. However, 48% of the patients in this study did not demonstrate hypocitraturia before treatment, potentially confounding the results.

Using nuclear magnetic resonance spectroscopy, the citrate concentrations of a number of commercially available citrus and citrus-based beverages was assessed (Haleblian et al, 2008). This finding confirmed that natural juices are highest in citrate and potassium content with grapefruit juice containing the greatest amount of citrate (197.5 mEq/L) followed closely by lemon and orange juice (145.48 and 144.57 mEq/L, respectively). Of the commercially available citrus-based beverages, Crystal Light (Kraft Foods, Northfield, IL) exhibited the highest concentration of citrate (117.2 mEq/L). The clinical effects of citrus-based beverages in patients with hypocitraturia have yet to be studied but may offer alternatives to those patients who are not agreeable to citrus juices.

Overall, most evidence suggests that it is not the type of fluid ingested that is important for stone prevention but the absolute amount of fluid volume taken in per day. We therefore encourage all of our stone formers to drink at least 3000 mL per day to maintain a urine output greater than 2500 mL/24 hours.

Key Points: Fluid Recommendations

- Patients should be strongly encouraged to consume enough fluids to produce 2 L of urine per day.
- Water hardness is unlikely to play a significant role in recurrence risk.
- Carbonated water may confer some protective benefit.
- Soda flavored with phosphoric acid may increase stone risk, whereas those with citric acid may decrease risk.
- Citrus juices (particularly lemon and orange juices) may be a useful adjunct to stone prevention.

Dietary Recommendations

Although metabolic abnormalities probably contribute to the majority of risk factors for recurrent nephrolithiasis, increasing evidence suggests that dietary changes are having an important impact on renal stone disease. Indeed, recent studies have documented an increasing incidence of nephrolithiasis, along with a greater propensity of female stone disease, than previously reported. A more complete discussion of these trends can be found in the previous chapter on the epidemiology and pathophysiology of nephrolithiasis (Pak et al, 1997; Ramello et al, 2000; Trinchieri et al, 2000; Coward et al, 2003; Hesse et al, 2003; Stamatelou et al, 2003; Amato et al, 2004). Therefore alterations in diet and physical activity may significantly reduce the incidence of recurrent nephrolithiasis.

Protein Restriction

Epidemiologic studies from a number of countries have shown that the incidence of renal stones is higher in populations in which there is an increased animal protein intake. For example, in the northern and western regions of India animal protein intake is approximately 100% greater than in the southern and eastern regions, and the rate of kidney stones is four times greater. In the United Kingdom the frequency of upper tract stone disease correlates with the per capita expenditure on foodstuffs (Robertson et al, 1979, 1982). This effect may be partly because protein intake is higher in affluent people, and stone formation, for some reason, seems to be higher in the economically advantaged. When populations are matched for economic status, the intake of protein and other dietary constituents does not differ in recurrent-stone patients and controls. Even in subjects thus matched, however, stone patients secrete greater quantities of calcium in the urine than do controls for a given intake of protein (Wasserstein et al, 1987). Thus stone patients may be more sensitive to dietary protein loading than normal subjects.

Protein intake increases urinary calcium, oxalate, and uric acid excretion and the mathematically calculated probability of stone formation even in normal subjects. Indeed, according to Burns and Finlayson (1981), ingestion of protein is second only to ingestion of vitamin D in enhancing intestinal absorption of calcium. Early investigations of purine loading in controlled clinical laboratory settings confirmed the risk of hypercalciuria and hyperuricosuria with a diet high in animal protein (Pak et al, 1978; Fellstrom et al, 1983; Breslau et al, 1988). Stone patients also exhibit inappropriate hypercalciuria in response to carbohydrate, sodium, and oxalate intake. In one acute study, dietary protein restriction resulted in a decrease in calcium, phosphate, and oxalate (Liatsikos and Barbalias, 1999). In another study in hypercalciuric patients, protein restriction resulted in decreased urinary uric acid and increased urinary citrate as well (Giannini et al, 1999).

Borghi and colleagues (2002) have provided further support to the importance of dietary protein in stone formation. In a prospective fashion, patients were randomized to either a low-protein, low-salt, moderate-calcium diet or a low-calcium diet. Although acknowledging that it is difficult to separate the potential effects of the three facets of the first diet, there was a convincing 50% reduction in stone events compared with those patients on the low-calcium diet (Borghi et al, 2002). In another dietary study, the same group of investigators suggests that diets high in fruits and vegetables impart a significantly reduced risk of stone formation than do those diets high in animal protein (Meschi et al, 2004). Twelve normal subjects had fruits and vegetables eliminated from their diets, whereas 26 hypocitraturic calcium stone formers (with low fruit and vegetable intake) had their diet supplemented with low-oxalate-containing fruits and vegetables.

The normal subjects (without fruit and vegetable intake) demonstrated significant decreases in urinary potassium (–62%),

magnesium (–26%), citrate (–44%), and oxalate (–31%) while increasing their urinary excretion of calcium (+49%) and ammonium (+12%). In contrast, the hypocitraturic calcium stone formers (with increased fruit and vegetable intake) significantly increased their urinary volume (+64%), pH (5.84 → 6.19), potassium (+68%), magnesium (+23%), and citrate (+68%) while decreasing excretion of ammonium (–18%). Finally, the relative supersaturation of calcium oxalate and calcium phosphate rose significantly for the normal subjects without fruit and vegetable intake, whereas the supersaturation of calcium oxalate and uric acid fell in the stone formers with fruit and vegetable intake.

Not all investigators have noticed the relationship between intake of meat and hypercalciuria. Brockis and colleagues (1982) demonstrated that mean urinary excretion of calcium and oxalate were similar in matched groups of vegetarians and nonvegetarians. A large study at the University of Pennsylvania found that patients with recurrent nephrolithiasis consumed a diet similar in composition to that of case controls (Goldfarb, 1994). Most studies however, suggest that an increased intake of meat may exacerbate calcium oxalate stone disease.

Sodium Restriction

Sodium restriction has been widely recommended as an important element of dietary prevention of recurrent nephrolithiasis (Massey and Whiting, 1995). Indeed, the evidence implicating excess sodium ingestion as a cause of calcium stone disease comes from several authors in different countries. Ito and colleagues (1993) from Japan have noticed that calcium stone formers had increased levels of sodium ingestion compared with the daily recommended allowances for the Japanese nation. They also found that stone formers consumed larger amounts of animal protein. They did not comment on whether the increased sodium ingestion was caused by the protein excess or whether it acted as an independent risk factor.

Researchers in Dallas, Texas have confirmed the effects of salt-loading in a controlled cross-over study involving normal volunteers. In their study, 14 normal subjects participated in 2 phases of study of 10 days duration each, comprising a low-sodium phase (basal metabolic diet containing 50 mmol sodium per day) and a high-sodium phase (basal diet plus 250 mmol sodium chloride per day). The high sodium intake significantly increased urinary sodium (34 to 267 mmol per day), calcium (2.73 to 3.93 mmol per day), and pH (5.79 to 6.15) and significantly decreased urinary citrate (3.14 to 2.52 mmol per day). They noted that a high sodium intake not only increased calcium excretion but also increased urinary pH and decreased citrate excretion. **The net effect of a high-sodium diet was an increased propensity for the crystallization of calcium salts in urine** (Sakhaee et al, 1993).

The investigation by Borghi involving dietary manipulation included a low-salt diet, limited to 50 mmol of sodium chloride per day (Borghi et al, 2002). **When combined with animal protein restriction and moderate calcium ingestion, a reduced-sodium diet will decrease stone episodes by roughly 50%.** Further work from Italy has demonstrated that calcium stone formers who ingest large quantities of daily salt are more likely to suffer from decreased bone mineral density (Martini et al, 2000). In this study of 85 patients, all females were premenopausal, underscoring the risks of further osteopenia that they might suffer later in life. After adjustment for calcium and protein intakes, age, weight, body mass index, urinary calcium, citrate and uric acid excretion, and duration of stone disease, multiple-regression analysis showed that a high NaCl intake (≥16 g/day) was the single variable that was predictive of risk of low bone density in calcium stone–forming patients (odds ratio = 3.8).

Conversely, patients with hypocitraturic calcium oxalate stone formation may benefit from sodium supplementation (Stoller et al, 2009). Eight patients with isolated hypocitraturia, based on 24-hour urinalysis, were managed with regular diet and potassium citrate for 7 days followed by the addition of 3 g of daily sodium supplementation for 7 days. The cohort had significant increases in total urinary volume and sodium excretion /24 hours but did not demonstrate significant increases in calcium, oxalate, and uric acid, which led to significant decreases in the urinary supersaturation relative risk ratio for calcium oxalate stones.

Key Points: Dietary Recommendations

- Randomized studies have confirmed the advantage of a diet with reduced animal protein (meat) intake.
- A diet high in fruits and vegetables imparts a reduced risk of stone formation than do those diets high in animal protein.
- Randomized trials have demonstrated a benefit of dietary sodium restriction in both normal volunteers and stone formers.

Obesity

Obesity has been associated with impaired carbohydrate tolerance and an inappropriate calcium response to glucose ingestion. Thus the hypercalciuria seen in meat eaters may be a function of increased body weight (Menon and Krishnan, 1983). Trinchieri and colleagues found that daily urinary oxalate excretion was related to body mass index in a group of stone formers (Trinchieri et al, 1998b). The association between body size and risk of stone formation was studied formally by the Curhan group (Curhan et al, 1998a). In two large cohorts—the Health Professionals Follow-Up Study (HPFS) and the Nurses' Health Study (NHS)—the prevalence of stone disease history and the incidence of new stone formation were directly associated with weight and body mass index. The magnitude of the association was greater in women than in men. Subsequently, Curhan performed a subset analysis on the HPFS and NHS cohorts with evaluation of 24-hour urinalyses (Taylor and Curhan, 2006). Higher body mass index (BMI) was found to be associated with with increased urinary excretion of oxalate, sodium, uric acid, calcium, and phosphorous, as well as lower pH. It is noted, however, that calcium excretion was no longer associated with BMI once corrected for phosphorous and sodium excretion, thereby suggesting calcium excretion is a more closely related to composition of diet and not obesity.

These same cohorts of patients have been continuously followed, and the group from Boston has provided a recent update on the role of obesity and nephrolithiasis. **They demonstrated that increased BMI, larger waist size, and weight gain correlated with an increased risk of stone episodes. This increased stone risk was still more pronounced for women than men** (Taylor et al, 2005a).

In a review of a large national database, Powell and colleagues (2000) examined the serum and 24-hour urine parameters from nearly 6000 patients with a history of nephrolithiasis. Within this cohort, obese patients had increased urinary excretion of sodium, calcium, magnesium, citrate, sulfate, phosphate, oxalate, uric acid, and cystine combined with a decrease in urinary pH. Furthermore, obesity was associated with increased urinary volumes and urine

osmolality compared with the nonobese patients. Because sodium and sulfate excretion is related to daily intake of salt and protein, these findings support the theory that excessive food consumption is linked to risk of nephrolithiasis in obesity. Despite the global changes in urinary metabolites, only obese women (compared with nonobese women) had an increase in the stone episodes. Similar findings from Siener and colleagues (2004) support the association of obesity with the risk stone formation. In an analysis of urine chemistries from 527 calcium oxalate stone formers, the authors identified positive correlations among BMI and sodium, phosphorous, and uric acid excretion and negative correlations between BMI and urinary pH. Citrate and urinary volume and citrate did not correlate with BMI, unlike Powell's report.

One component of the American diet that appears to be related to obesity and metabolic syndrome is fructose. Fructose adds a caloric load to the American diet and may additionally directly affect the risk of stone formation. This simple sugar has been shown to increase urinary calcium excretion in both rats and humans in limited studies, as well as the production and excretion of uric acid in humans (Koh et al, 1989; Milne and Nielsen, 2000; Taylor and Curhan, 2008b). Taylor and Curhan's analysis of the HPFS and NHS (I and II) documented that increasing fructose intake correlated with an increasing relative risk of incident stone formation regardless of BMI, caloric intake, or other risk factors.

One study has specifically evaluated the metabolic disturbances of obese patients, defined as a BMI greater than 30 (Ekeruo et al, 2004). It was determined that the most common presenting metabolic abnormalities among obese patients included gouty diathesis (54%), hypocitraturia (54%), and hyperuricosuria (43%), which presented at levels that were significantly higher than those finding in nonobese stone formers. When present, chemical stone analysis showed a predominance of uric acid calculi, implicating excessively acidic urine in these subjects. Directed medical therapy and dietary recommendations were able to dramatically reduce stone episodes for these patients.

Metabolic Syndrome

The term *metabolic syndrome* consists of a cluster of disease states—glucose intolerance, elevated blood pressure, dylipidemia, and central obesity—that increase the risk of developing type 2 diabetes and coronary vascular disease. All of these issues are frequently found in the obese population. Assessment of the overall rise of type 2 diabetes, obesity, metabolic syndrome, and stone disease suggests potential correlation between these states. Three studies have identified an increased risk of stone disease in diabetics (Pak et al, 2003c; Taylor et al, 2005b; Lieske et al, 2006). Lieske's group identified an odds ratio of 1.22 for diabetes among stone formers, whereas Taylor's group found a relative risk of 1.31 to 1.38 of stone formation in diabetics depending on age and sex. These studies confirm the earlier work by Pak's group, wherein uric acid stones were identified in a statistically significant predominance for patients with diabetes, indicating innate metabolic abnormalities specific to patients with diabetes.

Recent studies suggest that the increased incidence of uric acid stone formation in obese stone formers may be secondary to the production of more acidic urine than nonobese patients. Combined data from the two largest stone centers in the United States found that urine pH appears to be directly correlated with body size (Maalouf et al, 2004). Furthermore, patients with type 2 diabetes have been found to have lower urinary pH than nondiabetics independent of the formation of uric acid stones (Cameron et al, 2006). When evaluating patients who form uric acid stones, Sakhaee and colleagues (2002) identified a much higher incidence of diabetes (both type 1 and 2) compared with other groups. Because diabetics have impaired ammonium excretion, these patients have been shown to have an increased incidence of uric acid stone formation (Pak et al, 2003c; Abate et al, 2004). Finally, low urine pH has been shown to directly correlate with the number of metabolic syndrome features (Maalouf et al, 2007). From evaluation of 24-hour urinalyses in 148 non–stone-forming patients, a statistically significant linear relationship was identified wherein with each additional characteristic of metabolic syndrome portended a decrease in urine pH. Additionally, the degree of insulin resistance was also inversely related to urinary pH.

Impact of Weight-Loss Diets

As the epidemic of obesity has increased in western society, so too has the popularity of weight-reducing diets. Current dietary fads include the use of low-carbohydrate, high-protein, high-fat diets (Atkins Diet, South Beach Diet, and Sugar Busters Diet). A number of studies have documented an increase in the urinary calcium load from increased protein intake (Licata et al, 1979; Breslau et al, 1988). In a study of the impact of a high-protein, low-carbohydrate diet (Atkins Diet), 10 healthy subjects engaged in a low-carbohydrate, high-protein diet for 6 weeks under the care of a clinical dietitian (Reddy et al, 2002). After 6 weeks, urine pH decreased from 6.09 to 5.67, net acid excretion increased by 51 mEq/day, and urinary citrate levels decreased from 763 mg/day to 449 mg/day. In addition, urinary saturation of undissociated uric acid increased more than twofold, urinary calcium levels increased from 160 mg/day to 248 mg/day, causing an estimated calcium balance decrease of 90 mg/day. **Therefore the consumption of a low-carbohydrate, high-protien diet delivers a marked acid load to the kidney, increases the risk for stone formation, and may increase the risk for bone loss.** Though changes in urinary parameters are recognized, there has yet to be a study investigating the incidence of stone disease in a population conforming to this diet. Potentially, addition of alkali therapy may reduce the acidosis and hypercalciuria, while normalizing citrate metabolism without increase in caloric intake.

Impact of Bariatric Surgery

Bariatric surgery continues to increase in popularity and administration as rates of obesity rise. Currently, the National Institutes of Health uses a guide of BMI greater than 40 kg/m^2 as a criterion for bariatric surgery, thereby making nearly 5% of the U.S. population operative candidates. Historically, the initial weight-loss operation was jejunoileal bypass. Due to the significant complications associated with this procedure—liver disease, malnutrition, bone disease, arthritis, kidney failure and renal calculi—the Food and Drug Administration banned its application in 1979 (Clayman et al, 1978).

At present, the most common bariatric procedure is Roux-en-Y gastric bypass (RYGB), accounting for 70% to 90% of weight-loss surgeries in the United States (Santry et al, 2005). Though initially thought to have a significantly lower risk of stone disease, a number of studies have reported a risk of oxalate nephropathy and nephrolithiasis in the RYGB population (Nelson et al, 2005; Asplin and Coe, 2007; Nasr et al, 2008). Nelson's group identified 14 of 23 patients with presenting with an incident stone event at a mean of 29 months. More sobering is that 2 patients in this study and 11 patients in a report from the Columbia group developed oxalate nephropathy and progressed to ESRD requiring dialysis. Twenty-four-hour urinary assessment in stone formers after RYGB

identified an elevated mean oxalate excretion (83 mg/day vs. 34 mg/day, $P < 0.001$) compared with normal non–stone formers. These studies evaluated patients with nephrolithiasis after RYGBs, so the incidence of new-onset stone formation and prevalence hyperoxaluria in this population cannot be determined.

Newer prospective data are emerging to evaluate this population prebariatric and postbariatric surgery (Sinha et al, 2007; Duffey et al, 2008). Urinary oxalate excretion was noted to increase significantly in both investigations, but with varying time courses. Duffey's group found an increase from 31 mg to 41 mg/day ($P < 0.05$) at 3 months following surgery, whereas Sinha's group identified a significant increase in urinary oxalate excretion at 12 months postoperatively. In an attempt to quantify the prevalence of hyperoxaluria, a multi-institutional study evaluated 58 non–stone-forming patients 6 months after bariatric surgery (RYGB and biliopancreatic diversion) (Patel et al, 2009). The authors found a 74% and 26% prevalance of hyperoxaluria (>45 mg/day) and profound hyperoxaluria (>100 mg/day) on a single 24-hour urine collection, which decreased to 52% and 9% when two 24-hour urinalyses were evaluated.

Currently, the pathophysiology of bariatric surgery–induced hyperoxaluria remains unclear. Potential causes include alteration in intestinal flora (i.e., *Oxalobacter forminges*), fat malabsorption, or a reduced amount of oxalate secretion. However, as the rate of bariatric surgery increases lockstep with the rising tide of obesity, identification of the mechanisms and treatment strategies will become increasingly important to minimize the risk of increased stone formation.

Key Points: Obesity

- Obesity is an independent risk factor for nephrolithiasis, particularly for women.
- Metabolic syndrome is associated with lower urinary pH.
- Obese patients have a higher propensity for uric acid calculi.
- High-protein, low-carbohydrate diets alter urinary parameters and may increase the risk of stone formation.
- Even modern bariatric surgery may significantly increase the overall risk of stone formation.

Role of Dietary Calcium

The preponderance of evidence now supports the maintenance of a moderate calcium intake in the face of calcareous nephrolithiasis (Curhan et al, 1993; Curhan, 1997; Takei et al, 1998; Trinchieri et al, 1998a; Martini and Wood, 2000; Lewandowski et al, 2001; North American Menopause Society, 2001; Borghi et al, 2002; Heller et al, 2003; Taylor et al, 2004). **Older recommendations to significantly restrict calcium intake likely led to an increase in available intestinal oxalate. As a result, this limitation in dietary calcium may subsequently increase oxalate absorption, thereby raising the supersaturation of calcium oxalate.** As noted earlier, a prospective, randomized study has shown that patients on a moderate calcium diet, combined with salt restriction and moderation of animal protein, had half as many stone episodes as those who attempted to follow a calcium-restricted diet (Borghi et al, 2002). Review of a large cohort of middle-aged nurses revealed that there was a decreased incidence of nephrolithiasis in those subjects who had increased levels of dietary calcium (Curhan, 1997; Curhan et al, 1997). Interestingly, this protection did not remain for those who received increased calcium intake from supplements instead of from dietary sources (i.e., dairy products).

There is further evidence to suggest that calcium supplementation can be safe if attention is paid to preparation and especially to timing. In a review of postmenopausal women, authors have demonstrated that initiation of calcium supplementation does not have deleterious effects on urinary calcium, oxalate, or citrate levels. Furthermore, calcium supplement with a meal or combined calcium supplement and estrogen therapy was not associated with a significant increased risk of calcium oxalate stone formation in the majority of postmenopausal osteoporotic patients (Domrongkitchaiporn et al, 2002b). Additional work from the same group has determined that the timing of calcium supplementation may have positive or negative effects (Domrongkitchaiporn et al, 2004). In a study of healthy male recruits, the authors compared the urinary effects of calcium carbonate supplementation taken with meals versus at bedtime. In both instances, urinary calcium excretion increased equal amounts. However, for those taking the calcium supplement with meals, this increase was offset by an equally significant decrease in urinary oxalate. As a result, there was no increase in urinary supersaturation of calcium oxalate when calcium supplementation was taken with meals, a protection that did not remain for the nighttime bolus ingestion.

Evidence also suggests that the type of calcium supplementation may have an impact on the potential of stone formation. Two long-term studies from researchers in Dallas document that supplementation with calcium citrate does not have a significant impact on stone formation. Calcium citrate is an over-the-counter calcium preparation that provides 950 mg of calcium citrate and 200 mg of elemental calcium in each tablet. As with other available calcium supplements, calcium citrate will significantly increase urinary calcium excretion. Yet this preparation offers the benefit of also increasing urinary citrate excretion. The concomitant increase in citraturia potentially offsets the lithogenic potential of calcium supplement–induced hypercalciuria and therefore provides a more "stone-friendly" calcium supplement (Sakhaee et al, 2004).

One clinical trial further studied the effects of long-term calcium citrate supplementation in premenopausal women. This investigation demonstrated that the urinary saturation of calcium oxalate and calcium phosphate (brushite) did not significantly change during calcium citrate therapy. It appears that the lack of calcium supplement–induced hypercalciuria was secondary to the downregulation of intestinal calcium absorption due to prolonged calcium supplementation and the inhibitory effects of citrate included in the calcium citrate preparation. The results of this long-term calcium citrate trial suggest that calcium supplementation using calcium citrate does not increase the propensity for crystallization of calcium salts within the urine. This protective

Key Points: Role of Dietary Calcium

- Dietary calcium restriction actually increases stone recurrence risk.
- Calcium supplementation is likely safest when taken with meals.
- Calcium citrate appears to be a more "stone-friendly" calcium supplement due to the additional inhibitor action of citrate.

effect is most likely due to an attenuated increase in urinary calcium excretion (from a decrease in fractional intestinal calcium absorption), a decrease in urinary phosphorus, and an increased citraturic response (Sakhaee et al, 1994).

Oxalate Avoidance

Because less than 10% to 15% of urinary oxalate is usually derived from dietary sources, it is unclear how helpful it is to promote the strict avoidance of oral oxalate loading. This factor is compounded by the fact that oxalate is ubiquitous and found in most vegetable matter. However, it does seem intuitive to avoid large portions of foodstuffs that are rich in oxalate such as spinach, beets, chocolate, nuts, and tea. Although general advice on a restricted oxalate intake might be given to patients with recurrent nephrolithiasis, a low-oxalate diet would be most useful in patients with enteric hyperoxaluria or those with underlying bowel abnormalities (Holmes and Assimos, 2004). A more extensive list of high-oxalate-containing foods may be found in Table 46–8. It is notable that recent work has illustrated similar relationships of dietary intake and urinary excretion of oxalate in a cross-sectional analysis of of HPFS and NHS (I and II) for both stone formers and non–stone formers, thereby further supporting the relatively small impact that dietary oxalate has on urinary oxalate excretion (Taylor and Curhan, 2008a).

There have been repeated concerns raised regarding the risk of vitamin C (ascorbic acid) ingestion and the possibility of its conversion to oxalate with subsequent urinary excretion. Unfortunately, conflicting evidence has been presented by multiple authors (Weaver, 1983; Trinchieri et al, 1991; Urivetzky et al, 1992; Curhan et al, 1996b, 1999; Trinchieri et al, 1998b; Baxmann et al, 2003; Traxer et al, 2003). In fact, conflicting conclusions have even been reported from the same group of authors, underscoring the need for close scrutiny of presented data. Some of the confusion stems from differences in study end points. Although the ingestion of large amounts of vitamin C may demonstrate increases in 24-hour oxalate excretion and therefore calcium oxalate supersaturation, this does not guarantee an eventual increase in the formation of symptomatic calculi.

In the end, it seems reasonable to avoid heavy dosing of vitamin C. Limiting one's intake to a maximum daily dose of less than 2 g is an easy recommendation to follow (Traxer et al, 2003).

Key Points: Oxalate Avoidance

- Avoidance of excess dietary oxalate loading is reasonable and intuitive.
- Vitamin C in large doses may increase the risk of stone recurrence. Doses should probably be limited to 2 g/day.

Conservative Management Summary

It is anticipated that with these conservative measures alone, a significant number of patients may be able to normalize their urinary risk factors for stone formation. Thus only these conservative measures may be necessary to keep their stone disease under control. After 3 to 4 months on conservative management, patients should be re-evaluated using either standard laboratory assays or a less comprehensive automated urinalysis package. If the patient's metabolic or environmental abnormalities have been corrected, the conservative therapy can be continued and the patient followed every 6 to 12 months with repeat 24-hour urine testing. It is believed that follow-up is essential not only to monitor the efficiency of treatment but also to encourage patient compliance. If, however, a metabolic defect persists, a more selective medical therapy may be instituted. For example, if significant hyperuricosuria (urinary uric acid > 800 mg/day) persists even after dietary restriction of meat products, medical therapy with allopurinol may be instituted.

SELECTIVE MEDICAL THERAPY OF NEPHROLITHIASIS

Improved elucidation of the pathophysiology and the formulation of diagnostic criteria for different causes of nephrolithiasis have made feasible the adoption of selective treatment programs (Pak et al, 1981; Preminger and Pak, 1985). Such programs should (1) reverse the underlying physicochemical and physiological derangements, (2) inhibit new stone formation, (3) overcome nonrenal complications of the disease process, and (4) be free of serious side effects. The rationale for the selection of certain treatment treatments are the assumptions that the particular physicochemical and physiological aberrations identified with the given disorder are etiologically important in the formation of renal stones (as previously discussed) and that the correction of these disturbances would prevent stone formation. Moreover, **it is assumed that such a selective treatment program would be more effective and safe than "random" therapy. Despite a lack of conclusive experimental verification, these hypotheses appear reasonable and logical.** Common medications used to treat urinary stone disease and their expected actions are summarized in Table 46–14. Medication dosages are noted in Table 46–15, and side effects are outlined in Table 46–16. A simplified treatment algorithm outlining basic evaluation and management is illustrated in Figure 46–10.

Efficacy Outside of an Academic Center

One potential criticism of the "selective" metabolic management of nephrolithiasis is that the collection of multiple urine and serum studies can be too time consuming to be feasible outside of an academic medical center with its dedicated research staff. **Although a commitment to follow-up can be tedious, it should be no worse for kidney stone patients than it is for those followed for cancer or voiding dysfunction.**

Indeed, Lingeman and colleagues (1998) compared the results of patient management from seven private practices to that achieved by a dedicated university clinic. Of note, the specialized stone management software and laboratory resources of the university clinic supported the private centers. They found that supersaturation values were effectively reduced in the network and stone clinic, and the reduction was proportional to the initial supersaturation value and increase in urine volume. The stone clinic achieved a greater supersaturation reduction, higher fraction of patient follow-up, and greater increase in urine volume, but the treatment effects in the network were, nevertheless, substantial and significant (Lingeman et al, 1998).

This finding is supported by a further study demonstrating the efficacy of medical prophylaxis when administered in a private practice setting (Mardis et al, 2004). When compared with conservative measures of dietary recommendations and fluid

Table 46–14.

Physicochemical and Physiologic Effects of Pharmacologic Therapy

	SODIUM CELLULOSE PHOSPHATE	ORTHOPHOSPHATE	THIAZIDE	ALLO-PURINOL	POTASSIUM CITRATE
Urinary calcium	Marked decrease	Mild decrease	Moderate decrease	No change	Mild decrease No change
Urinary phosphorus	Mild increase	Marked increase	Mild increase/no change	No change	No change
Urinary uric acid	No change	No change	Mild increase/no change	Marked decrease	No change
Urinary oxalate	Mild increase	Mild increase/no change	Mild increase/mild decrease	No change	No change
Urinary citrate	No change	Mild increase	Mild decrease	No change	Marked increase
Calcium oxalate saturation	Mild decrease/no change	Mild decrease	Mild decrease	No change	Moderate decrease
Brushite saturation	Moderate decrease	Mild increase	Mild decrease	No change	No change

Table 46–15.

Dosages of Common Medications Used to Prevent Urinary Calculi

Thiazide diuretics	
Hydrochlorothiazide	25 mg PO bid
Chlorthalidone	25-50 mg PO daily
Indapamide	2.5 mg PO daily
Sodium cellulose phosphate	10-15 g/day divided with meals
Orthophosphate	0.5 g PO tid
Potassium citrate	20 mEq PO bid-tid
Allopurinol	300 mg PO daily
Magnesium gluconate	0.5-1.0 g tid
Pyridoxine (B_6)	100 mg PO daily
D-Penicillamine	250 mg PO daily (titrated to effect)
α-Mercaptopropionylglycine	100 mg PO bid (titrated to effect)
Captopril	25 mg PO bid-tid
Acetohydroxamic acid	250 mg PO bid-tid

Table 46–16.

Potential Side Effects of Medications Used to Prevent Urinary Lithiasis

MEDICATION	SIDE EFFECT
Thiazide diuretics: hydrochlorothiazide, chlorthalidone, indapamide	Potassium wasting, muscle cramps, hyperuricosuria, intracellular acidosis, hypocitraturia
Sodium cellulose phosphate (SCP)	Gastrointestinal distress, hypomagnesemia, hyperoxaluria, parathyroid hormone stimulation
Orthophosphate	Similar to sodium cellulose phosphate, soft tissue calcification
Potassium citrate	Gastrointestinal upset, hyperkalemia
Allopurinol	Rash, myalgia
Magnesium gluconate	Diarrhea
Pyridoxine (B_6)	
D-Penicillamine	Nephrotic syndrome, dermatitis pancytopenia
α-Mercaptopropionylglycine	Rash, asthenia, rheumatologic complaints, gastrointestinal distress, mental status changes
Captopril	Rash, cough, hypotension
Acetohydroxamic acid	Thromboembolic phenomena, tremor, headache, palpitations, edema, gastrointestinal distress, loss of taste, rash, alopecia, anemia, abdominal pain

management, active pharmacologic treatment achieved a significantly greater reduction in stone episodes. These findings prompted the authors to conclude that medications validated in trials and guided by metabolic evaluation lower stone recurrence when used in a private practice setting, as they do in clinical trials from academic medical centers.

Absorptive Hypercalciuria

Thiazides

No treatment program is capable of correcting the basic abnormality of absorptive hypercalciuria type 1, and thiazide diuretics are not considered a selective therapy for absorptive hypercalciuria because they do not decrease intestinal calcium absorption in this condition (Pak, 1979). However, this class of medications has been widely used to treat absorptive hypercalciuria because of its hypocalciuric action and the high cost and inconvenience of alternative therapy (sodium cellulose phosphate). The use of thiazides was first described by Yendt and colleagues for the treatment of undifferentiated hypercalciuria (Yendt et al, 1966).

Thiazides directly stimulate calcium resorption in the distal nephron while promoting excretion of sodium. Long-term thiazide therapy results in volume depletion, extracellular volume contraction, and proximal tubular resorption of sodium and calcium. Thiazides may increase urinary excretion of magnesium and zinc, but these responses are not consistent. Potassium losses from thiazide therapy can cause hypocitraturia due to hypokalemia with intracellular acidosis.

Studies indicate that thiazide may have a limited long-term effectiveness in absorptive hypercalciuria type 1 (Zerwekh and Pak, 1980; Preminger and Pak, 1987). Despite an initial reduction in urinary excretion, the intestinal calcium absorption remains persistently elevated. These studies suggest that the retained calcium may be accreted in bone at least during the first few years of therapy. Bone density, determined in the distal third of the radius by photon absorptiometry, increases significantly during thiazide treatment in absorptive hypercalciuria, with an annual increment of 1.34%. With continued

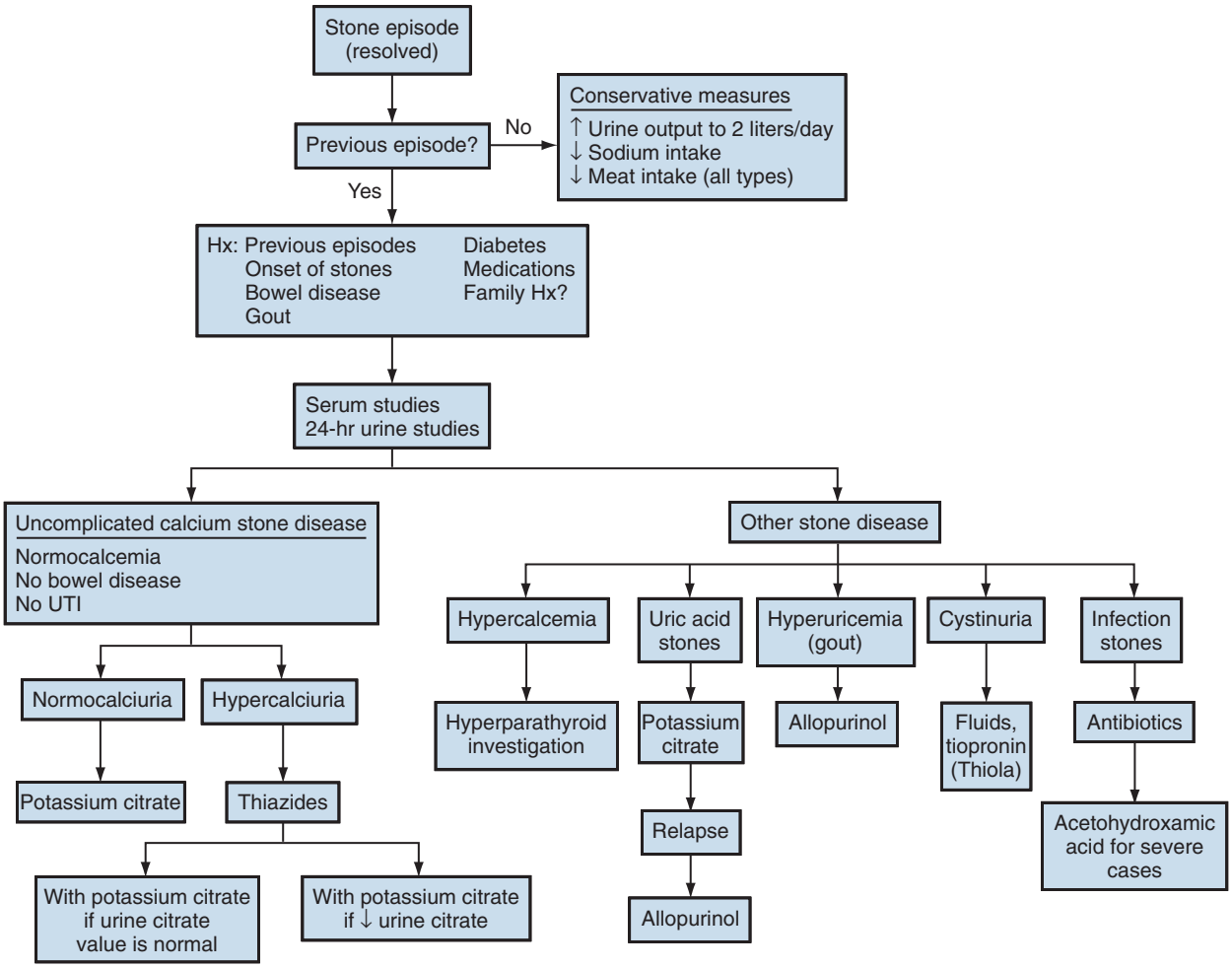


Figure 46–10. Simplified treatment algorithm for the evaluation and medical management of urinary lithiasis. Hx, history; UTI, urinary tract infection. (Modified from C.Y. Pak.)

treatment, however, the rise in bone density stabilizes and the hypocalciuric effect of thiazide becomes attenuated. These results suggest that thiazide treatment may cause a low turnover state of bone that interferes with a continued calcium accretion in the skeleton. The "rejected" calcium would then be excreted in urine. In contrast, bone density is not significantly altered in renal hypercalciuria, in which thiazide has been shown to cause a decline in intestinal calcium absorption commensurate with a reduction in urinary calcium.

Further work on this topic has been recently reported (Pak et al, 2003a). In this study, 28 patients with absorptive hypercalciuria type 1 were managed with thiazide (20) or indapamide (8) and potassium citrate for 1 to 11 years while maintained on diet low in calcium oxalate. Serum and urinary chemistry studies and bone mineral density were measured at baseline and at the end of treatment. During treatment, urinary calcium significantly decreased but urinary oxalate did not change. Urinary pH and citrate significantly increased, and urinary saturation of calcium oxalate significantly decreased by 46%. Stone formation rate decreased significantly from 2.94 to 0.05 per year. Notably, L2-L4 bone mineral density increased significantly by 5.7% compared with normal peak value, and by 7.1% compared with normal age- and gender-matched values. The authors concluded that **dietary restriction of calcium and oxalate, combined with thiazide and potassium citrate, satisfactorily controlled hypercalciuria but prevented complications commonly associated with sodium cellulose phosphate therapy.**

Although side effects are generally mild, they occur in about 30% to 35% of patients treated with thiazide. Side effects are usually seen on initiation of treatment but disappear with continued treatment. Lassitude and sleepiness are the most common symptoms and can occur in the absence of hypokalemia. **Potassium supplementation should always be considered, particularly in patients with evident potassium deficiency, patients on digitalis therapy, and those individuals who develop hypocitraturia.** Addition of potassium citrate has been documented to prevent occurrence of hypokalemia and hypochloremic metabolic acidosis in patients undergoing long-term thiazide therapy (Odvina et al, 2003). Occasionally, thiazides unmask primary hyperparathyroidism (i.e., "thiazide challenge"). Thiazides may also cause impaired carbohydrate tolerance and hyperuricemia. A more distressing complication is decreased libido or sexual dysfunction, which is seen in a small percentage of patients.

Sodium Cellulose Phosphate

Sodium cellulose phosphate (SCP), given orally, is a nonabsorbable ion exchange resin that binds calcium and inhibits calcium absorption (Blacklock and Macleod, 1974; Pak et al, 1974; Backman et al, 1980). **Unfortunately, despite early enthusiasm, the**

use of sodium cellulose phosphate has largely fallen out of favor and this medication is no longer available in the United States.

Guidelines for the Use of Thiazides in Absorptive Hypercalciuria

Thiazides do not correct the basic, underlying physiologic defect in absorptive hypercalciuria. Some guidelines are offered until more selective therapy can be developed.

In patients with absorptive hypercalciuria, type 1 thiazide is the first choice and should be combined with potassium citrate and dietary restrictions. If thiazides lose their hypocalciuric action (after long-term treatment), a drug holiday may be instituted and then thiazide therapy may be resumed. The authors recommend that potassium citrate and dietary alterations continue during this time period. Further research is warranted to identify a medication that will selectively reduce increased intestinal calcium absorption, thereby decreasing the calcium load available for urinary excretion and stone formation.

Other Hypocalciuric Agents

Other agents may be used in place of hydrochlorthiazide for the treatment of hypercalciuria. These medications include chlorthalidone (25 to 50 mg per day) or indapamide (2.5 mg per day). Indapamide is technically not a thiazide but does share a successful hypocalciuric effect with the other agents. Both agents have been shown to be equally efficacious yet may improve patient compliance with more convenient once-daily dosing (Jaeger et al, 1986; Lemieux, 1986; Coe et al, 1988; Ettinger et al, 1988; Ohkawa et al, 1992; Borghi et al, 1993b; Martins et al, 1996).

Amiloride in combination with thiazide (Moduretic) may be more effective than thiazide alone in reducing calcium excretion (Maschio et al, 1981; Leppla et al, 1983). However, this medication does not augment citrate excretion. Because amiloride is a potassium-sparing agent, potassium replacement is not necessary and could, in fact, be problematic**. It is not advisable to provide potassium supplementation to patients receiving a potassium-sparing diuretic.** Although the potassium-sparing effects of amiloride may be beneficial, the use of triamterene, another potassium-sparing agent, should be undertaken with caution because of reports of triamterene stone formation (Watson et al, 1981; Werness et al, 1982; Ettinger, 1985; Sorgel et al, 1985).

Absorptive Hypercalciuria Type 2

In absorptive hypercalciuria type 2 (AH2), no specific drug treatment may be necessary because the physiologic defect is not as severe as in absorptive hypercalciuria type 1. In addition, many patients show disdain for drinking fluids and therefore excrete concentrated urine. A moderate calcium intake (400 to 600 mg/day) and high fluid intake (sufficient to achieve a minimum urine output of >2 L/day) would seem ideally indicated because normocalciuria could be restored by dietary calcium restriction alone, and increased urine volume has been shown to reduce urinary saturation of calcium oxalate. Moreover, avoidance of excessive sodium intake might further decrease hypercalciuria and potential stone formation in patients with AH2.

Orthophosphate

Orthophosphate (neutral or alkaline salt of sodium and/or potassium, 0.5 g phosphorus three to four times/day) has been shown to inhibit 1,25-dihydroxyvitamin D synthesis (Van Den Berg et al, 1980; Insogna et al, 1989). **However, there is as yet no convincing evidence from randomized trials that this treatment restores normal intestinal calcium absorption.** Orthophosphate reduces urinary calcium probably by directly impairing the renal tubular reabsorption of calcium and by binding calcium in the intestinal tract. Urinary phosphorus is markedly increased during therapy, a finding reflecting the absorbability of soluble phosphate. Physicochemically, orthophosphate reduces the urinary saturation of calcium oxalate but increases that of brushite. Moreover, the urinary inhibitor activity is increased, probably owing to the stimulated renal excretion of pyrophosphate and citrate. Although contrary reports have appeared, this treatment program has been reported to cause soft tissue calcification and parathyroid stimulation (Dudley and Blackburn, 1970). It may be particularly indicated in absorptive hypercalciuria type 3. Orthophosphate is contraindicated in nephrolithiasis complicated by urinary tract infection because of the increased phosphorus load.

A formulation of low-release, neutral potassium phosphate has been developed to obviate the aforementioned problems with currently available orthophosphate preparations. This potassium phosphate preparation (UroPhos-K) is prepared in a wax matrix to provide slow release of the orthophosphate. This restricted release limits the amount of GI upset found with most current orthophosphate preparations. In addition, UroPhos-K contains phosphate salts of potassium and does not contain sodium. Therefore this preparation does not provide a sodium load, which could offset the hypocalciuric action of the orthophosphate. Finally, this medication is designed to yield a pH of 7.0 as compared with 7.3 for some available orthophosphate preparations. Therefore it is less likely that the crystallization of calcium phosphate may occur in the urine (Breslau et al, 1995).

A randomized, prospective, double-blind trial was performed in 21 patients with documented stone formation and absorptive hypercalciuria type 1. Patients received either UroPhos-K or placebo in a double-blinded fashion. No significant GI side effects were noted with the slow-release potassium phosphate preparation, nor was there a significant increase in fasting serum potassium or phosphorus. However, the UroPhos-K treatment did significantly reduce urinary calcium from 288 mg/day to 171 mg/day without altering oxalate excretion. Moreover, the urinary saturation of calcium oxalate was significantly reduced without altering brushite saturation. Also noted was a significant increase of inhibitor activity secondary to increased urinary citrate and pyrophosphate, thereby inhibiting the potential crystallization of calcium oxalate in the urine (Breslau et al, 1998; Heller et al, 1998). This medication is not yet approved for use in the United States.

Dietary Bran

Rice bran also binds intestinal calcium and increases urinary pyrophosphate (Ebisuno et al, 1991). In an uncontrolled long-term study, rice bran reduced stone recurrences. In another study, 73 patients with recurrent urinary stone formation were treated with 40 g of unprocessed bran daily. Hydrochlorothiazide was added during the summer months. Over a 2-year follow-up, three fourths of the patients were free of stones. The combination of thiazide and bran was superior to bran alone in preventing stone formation (Ala-Opas et al, 1987).

Renal Hypercalciuria

Thiazides are ideally indicated for the treatment of renal hypercalciuria. This diuretic has been shown to

Key Points: Absorptive Hypercalciuria

- Sodium cellulose phosphate (SCP) effectively decreases the absorption of intestinal calcium but has been abandoned due to GI intolerance and side effects.
- Thiazides do not treat the underlying cause of absorptive hypercalciuria but do reduce urinary calcium and manage its symptoms.
- Orthophosphates may have a role for the treatment of absorptive hypercalciuria when other methods are ineffective.

correct the renal leak of calcium by augmenting calcium reabsorption in the distal tubule and by causing extracellular volume depletion and stimulating proximal tubular reabsorption of calcium. The ensuing correction of secondary hyperparathyroidism restores normal serum 1,25-dihydroxyvitamin D concentration and intestinal calcium absorption. Thiazides have been shown to provide a sustained correction of hypercalciuria commensurate with a restoration of normal serum 1,25-dihydroxyvitamin D concentration and intestinal calcium absorption for up to 10 years of therapy (Preminger and Pak, 1987).

Physicochemically, the urinary environment becomes less saturated with respect to calcium oxalate and brushite during thiazide treatment, largely because of the reduced calcium excretion. Moreover, urinary inhibitor activity, as reflected in the limit of metastability, is increased by an unknown mechanism. These effects are shared by hydrochlorothiazide 25 mg twice/day, chlorthalidone 25 to 50 mg/day, or indapamide 2.5 mg/day. **Potassium citrate supplementation (40 to 60 mEq/day) is advised because this medication has been shown to be effective in averting hypokalemia and in increasing urinary citrate when administered to patients with calcium nephrolithiasis taking thiazide** (Nicar et al, 1984; Pak et al, 1985b).

A more complete discussion of the mechanism of action, efficacy, and side effects of thiazides for the treatment of hypercalciuria is presented in the preceding section. Furthermore, Table 46–17 provides a summary of the results of randomized trials involving the use of thiazides for the treatment of hypercalciuria. Of note, a recent meta-analysis of medical therapies for calculus prevention demonstrated that only thiazides have shown strong evidence for efficacy in randomized trials (Pearle et al, 1999).

Key Point: Renal Hypercalciuria

- Thiazides are first-line therapy for the treatment of renal leak hypercalciuria.

Primary Hyperparathyroidism

Parathyroidectomy is the optimum treatment for nephrolithiasis in patients with primary hyperparathyroidism (Parks et al, 1980; Fraker, 2000). This therapy may include the resection of a dominant adenoma or removal of all four hyperplastic glands. Following removal of abnormal parathyroid tissue, urinary calcium is expected to return to normal, commensurate with a decline in serum calcium and intestinal calcium absorption. However, these findings are not always dependable because some patients may suffer from changes in tubular and glomerular functions as a result of long-standing hypercalcemia/hypercalciuria (Farias et al, 1996).

There is no established medical treatment for the nephrolithiasis of primary hyperparathyroidism. Although orthophosphates have been recommended for the disease of mild-to-moderate severity, their safety or efficacy has not yet been proven. These medications should be used only when parathyroid surgery cannot be undertaken. Estrogen has been reported to be useful in reducing serum and urinary calcium in postmenopausal women with primary hyperparathyroidism (Ljunghall, 1983; Herbai and Ljunghall, 1983; Marcus et al, 1984; Coe et al, 1986; Selby and Peacock, 1986; Boucher et al, 1989; Diamond et al, 1996; Orr-Walker et al, 2000).

Key Point: Primary Hyperparathyroidism

- Hyperparathyroidism complicated by stone disease is best treated with surgical excision of the adenoma(s).

Hyperuricosuric Calcium Oxalate Nephrolithiasis

There are two pharmacologic approaches to the management of hyperuricosuric calcium nephrolithiasis. The first involves decreasing the production of uric acid. Allopurinol (300 mg per day) may be used to block the ability of xanthine oxidase to convert xanthine to uric acid (Coe, 1978). The resultant decrease in serum uric acid will ultimately lead to a decrease in urinary uric acid as well. **Allopurinol's use in hyperuricosuria associated with dietary purine overindulgence may also be reasonable if patients are unable or unwilling to comply with dietary purine restriction.** Physicochemical changes ensuing from restoration of normal urinary uric acid include an increase in the urinary limit of metastability of calcium oxalate (Pak et al, 1978). Thus the spontaneous nucleation of calcium oxalate is slowed by allopurinol treatment, probably via inhibition of monosodium urate–induced stimulation of calcium oxalate crystallization (Pak et al, 1979; Coe et al, 1980). Because of the potential exaggeration of monosodium urate–induced calcium oxalate crystallization, a moderate sodium restriction (150 mEq/day) is also advisable.

Few convincing randomized trials have demonstrated the efficacy of allopurinol for the treatment of hyperuricosuria. However, one study by Ettinger and colleagues (1986) stands out. In this double-blind, prospective, randomized trial, allopurinol was given to 60 patients with hyperuricosuria, normocalciuria, and recurrent calcium oxalate stones. A 6-month "grace period" was established, during which time any new calculus that was passed was not considered to represent failure of therapy. With a follow-up of up to 39 months, new stone events (stone growth or recurrence) occurred in 58% of the patients on placebo and in 31% of the patients on allopurinol. The placebo group had 63.4% less calculi, whereas the allopurinol group had 81.2% less calculi. The mean rate of calculus events was 0.26 per patient per year in the placebo group and 0.12 in the allopurinol group. The allopurinol group had a significantly longer time before the recurrence of stones.

Alternatively, management of hyperuricosuria may be approached by altering the urinary milieu such that uric acid remains in a dissolved state (Pak and Peterson, 1986). Central to this approach would be the obvious advantage of copious amounts of dilute urine to maintain uric acid at a low

Table 46–17.

Randomized Trials Using Thiazides for the Management of Nephrolithiasis

YEAR	AUTHOR	DIAGNOSIS	AGENT	NO. OF PATIENTS	NO. OF CONTROLS	EFFICACY	FOLLOW-UP	COMMENTS
1981	Brocks et al	Recurrent calcium stones	Bendroflumethiazide, 2.5 mg tid	29	33	83% remission in controls, 85% in treated: not significant	1.6 yr	Not all patients were hypercalciuric Only 16% of expected stones formed in controls, 24% in treated
1982	Scholz et al	Recurrent calcium stones	Hydrochlorothiazide, 25 mg bid	25	26	77% remission in controls, 76% in treated: not significant	1 yr	Fasting urinary calcium increased before treatment, decreased with thiazides, but not in controls Urine output increased in both groups, indicating that hydration was sufficient
1984	Laerum and Larsen	Recurrent stone formers	Hydrochlorothiazide, 25 mg bid	25	25	45% remission in controls, 75% in treated: significant difference Controls formed 21 stones, treated formed 230 stones: not significant	3 yr	General practice study 75% of patients did not have hypercalciuria Differences seen only after 18 mo
1988	Ettinger et al	Recurrent calcium stones	Chlorthalidone, 25 or 50 mg/day	42	31	55% remission in controls, 86% in treated: significant	3 yr	Only 15% of patients had hypercalciuria Compliance to diet not encouraged or assessed; to drugs, assessed Urine output not measured 16% dropout rate in controls, 35%-40% dropout rate with chlorthalidone
1984	Wilson et al	Recurrent calcium stone	Hydrochlorothiazide, 100 mg/day	21	23	65% remission in controls, 70% in treated: not significant 0.32 stone per yr in controls; 0.15 stone per yr in treated: significant	<3 yr	Not all patients hypercalciuric stones Other treatments— phosphates, magnesium, allopurinol—were ineffective
1992	Ohkawa et al	Idiopathic hypercalciuria	Trichlormethiazide, 4 mg/day	82	93	86% remission in controls, 92% in treated: not significant Stone formation rate significantly lowered in treated patients	3 yr	Multi-institutional study All patients had hypercalciuria Many were single stone formers
1993b	Borghi et al	Idiopathic hypercalciuria	Indapamide, 2.5 mg/day, or indapamide plus allopurinol, 300 mg/day	25	25	65% remission in controls, 95% in treated: significant		Urinary output did not rise in either group; thus hydration may not have been effective
TOTAL				249	256	73% remission in controls, 85% in treated patients		Beneficial effects with treatment seen only in trials with follow-up of ≥2 yr

concentration. Attempts to maintain the urine at a pH above the pKa may also be successful by promoting dissolution of this molecule (Pak et al, 1986b). This effect is usually achieved by the use of an alkalinizing agent such as potassium citrate (at a dose of 30 to 60 mEq/day in divided doses). In the study by Pak, the treatment produced a sustained rise in urinary pH by 0.55 to 0.85 to the high-normal range. Urinary citrate levels rose by 249 to 402 mg/day. Commensurate with these changes, urinary saturation of calcium oxalate (relative saturation ratio) and the amount of undissociated uric acid declined significantly. Stone formation declined from 1.55 per patient-year to 0.38 per patient-year during a mean treatment period of 2.35 years. Stones ceased to form in 16 of 19 patients during treatment.

There is some evidence that changes in urinary pH alone are inadequate for the management of hyperuricosuria (Pak et al, 2002b). If this is the case, the efficacy of citrate for the management of hyperuricosuria calcium nephrolithiasis may stem from the inhibitory activity of citrate with respect to calcium and oxalate crystallization.

Potassium citrate may be particularly useful in patients with mild-to-moderate hyperuricosuria (<800 mg/day), especially in whom hypocitraturia is also present.

Key Points: Hyperuricosuric Calcium Oxalate Nephrolithiasis

- Patients with hyperuricosuria should be instructed to decrease dietary purine intake.
- Allopurinol can decrease uric acid production and may be ideal for those patients with a history of gout.
- Potassium citrate can effectively alter the urinary milieu in patients with hyperuricosuria by decreasing the supersaturation of uric acid and calcium oxalate.

Enteric Hyperoxaluria

The management of patients with enteric hyperoxaluria usually involves directed therapy that addresses several abnormalities or abnormal physiology. Oral administration of over-the-counter calcium preparations (0.25 to 1 g four times/day) or magnesium has been recommended for the control of calcium nephrolithiasis of ileal disease (Worcester, 2002). Although urinary oxalate may decrease (probably from binding of oxalate by divalent cations), the concurrent rise in urinary calcium may obviate the beneficial effect of this therapy, at least in some patients (Barilla et al, 1978). Cholestyramine has also been suggested for the management of calculi in this disorder (Stauffer, 1977). This medication may be useful by binding bile salts in the bowel lumen, thereby decreasing the irritation of the colonic mucosa and the subsequent hyperabsorption of oxalate (Caspary et al, 1977). The replacement of dietary fat with medium chain triglycerides may be helpful in those patients who also have malabsorption.

Patients may exhibit hypomagnesiuria due to impaired intestinal absorption of magnesium. Because magnesium has been shown to complex oxalate, hypomagnesiuria may increase the urinary saturation of calcium oxalate (Caudarella et al, 1993). Although oral magnesium supplements may correct hypomagnesiuria, they may also provoke further diarrhea. Magnesium gluconate (0.5 to 1.0 g three times/day) appears to be better tolerated than magnesium oxide or hydroxide. **Treatment with potassium citrate (60 to 120 mEq/day) may correct the hypokalemia and metabolic acidosis in patients with enteric hyperoxaluria and, in some individuals, increase urinary citrate toward normal.** Consideration should be given to providing the liquid form of potassium citrate in patients with rapid GI-transit times because the liquid form of this medication may be better absorbed than the slow-release, wax matrix pills.

A high fluid intake is recommended to ensure adequate urine volume. Because excessive fluid loss may be present, an antidiarrheal agent may be necessary before sufficient urine output can be achieved. Calcium citrate may theoretically have a role in management of enteric hyperoxaluria. This treatment may lower urinary oxalate by binding oxalate in the intestinal tract. Calcium citrate may also raise the urinary citrate and pH by providing an alkali load (Harvey et al, 1985). Finally, calcium citrate may correct the malabsorption of calcium and adverse effects on the skeleton by providing an efficiently absorbed formulation of calcium.

Recently, the use of probiotics and the alteration of gut flora have been investigated (Hoppe et al, 2006; Lieske et al, 2005). The goal of these strategies is to increase the degradation of oxalate, thereby preventing intestinal absorption. The use of lactic acid bacteria and *O. formigenes* has preliminarily demonstrated reduction in urinary excretion of oxalate. Larger, long-term assessment is necessary, but further investigation into this relatively novel treatment approach is clearly warranted.

Key Points: Enteric Hyperoxaluria

- Fluid intake should be strongly encouraged to correct the relative state of dehydration.
- Dietary calcium may help bind intestinal oxalate and decrease its absorption.
- Slow release formulations of citrate should be avoided.

Hypocitraturic Calcium Oxalate Nephrolithiasis

In patients with hypocitraturic calcium oxalate nephrolithiasis, potassium citrate treatment is capable of restoring normal urinary citrate, lowering the urinary saturation and inhibiting crystallization of calcium salts. Because hypocitraturia is found in a number of different conditions, each is addressed individually.

Distal Renal Tubular Acidosis

Potassium citrate therapy can correct the metabolic acidosis and hypokalemia found in patients with distal renal tubular acidosis (Preminger et al, 1985). In addition, this medication is capable of restoring normal urinary citrate, although large doses (up to 120 mEq/day) may be required in severe acidotic states. With correction of the acidosis, urinary calcium should decline into the normal range. Because urinary pH is generally high to begin with in patients with renal tubular acidosis, the overall rise in urinary pH is small.

Potassium citrate therapy typically produces a sustained decline in the urinary saturation of calcium oxalate (from reduction in urinary calcium and in citrate complexation of calcium). The urinary saturation of calcium phosphate does not increase because the rise in phosphate dissociation is relatively small and

is adequately compensated by a decline in ionic calcium concentration. In addition, the inhibitory activity against the crystallization of calcium oxalate and calcium phosphate is augmented due to the direct action of citrate.

Investigators from Thailand have suggested that the target dose of potassium citrate for children with distal renal tubular acidosis should be from 3 to 4 mEq/kg/day in divided doses (Domrongkitchaiporn et al, 2002c; Tapaneya-Olarn et al, 2002).

Chronic Diarrheal States

The full management of enteric stone disease has been discussed previously in this chapter. Part of the entire management should involve the use of citrate to correct the acidosis that accompanies the chronic bicarbonate losses with diarrhea. The amount of potassium citrate will depend on the severity of hypocitraturia in these patients, with dosages ranging from 60 to 120 mEq in three to four divided doses.

It is recommended that a liquid preparation of potassium citrate be used rather than the slow-release tablet preparation because the slow-release medication may be poorly absorbed due to rapid intestinal transit time. In addition, frequent dose schedules (three to four times/day) for the liquid preparation are necessary because this form of the medication has a relatively short duration of biologic action.

Thiazide-Induced Hypocitraturia

Noted previously, thiazide therapy may cause hypocitraturia due to thiazide-induced hypokalemia with resultant intracellular acidosis (Nicar et al, 1984). Therefore it should be a common practice to administer potassium supplementation, preferably in the form of potassium citrate, to patients receiving thiazides for treatment of hypercalciuria. Potassium citrate has been shown to be equally effective as potassium chloride in correcting thiazide-induced hypokalemia. Moreover, the addition of potassium citrate not only prevents a fall in urinary citrate during thiazide therapy but may raise citrate excretion (Pak et al, 1985b).

Idiopathic Hypocitraturic Calcium Oxalate Nephrolithiasis

This entity includes hypocitraturia occurring alone, as well as in conjunction with other abnormalities (e.g., hypercalciuria or hyperuricosuria). Stones formed in this condition are predominantly composed of calcium oxalate. Potassium citrate therapy may produce a sustained increase in urinary citrate and a decline in the urinary saturation of calcium oxalate (Pak and Fuller, 1986). Two agents have been used for the treatment of hypocitraturia: sodium potassium citrate, commonly used in Europe, and potassium citrate—in liquid form or as a wax matrix tablet—used in the United States. The usual therapeutic dose is 30 to 60 mEq/day given in divided doses or as a single evening dose (Berg et al, 1992). Sodium citrate does not lower urinary calcium excretion, perhaps as a result of the increased sodium load associated with this therapy (Sakhaee et al, 1983; Preminger et al, 1988).

In general, citrate is well tolerated, although the potential for gastric upset is real. The current formulation of potassium citrate embedded within a wax matrix may help alleviate the risk of gastric irritation. Patients are strongly encouraged to take this medication with meals to act as a further buffer.

Long-term therapy with this medication has been shown to provide a favorable durable response in alteration of urinary parameters and stone formation rate (Robinson et al, 2009a). In a retrospective cohort of 503 patients on potassium citrate therapy for a mean of 41 months (range 6 to 168), urinary pH and citrate demonstrated significant increases (pH: 5.9 to 6.46; citrate 470 mg/day to 700 mg/day), with substantial improvement in urinary parameters in as little as 6 months of therapy. In addition potassium citrate decreased the stone formation rate from 1.89 stones per patient per year to 0.46.

Concern has been raised, however, regarding the overalkalinization of urine and an increase in the formation rate of calcium phosphate stones. Researchers analyzed a large stone database of more than 1200 patients and identified a threefold increase in calcium phosphate content of stones over the past 3 decades (Parks et al, 2004). As would be expected, rising urinary pH was directly associated with this finding, therefore raising the question of the role of potassium citrate in this finding of increasing calcium phosphate content. The same group of researchers then analyzed patients who transformed their stone content to increased calcium phosphate and found that those patients who transformed did receive more potassium citrate as compared with those who did not transform (Parks et al, 2009). The authors point out that the effect on urinary pH is possibly offset by the rise in urinary citrate.

Further work on this issue has shown that although the urinary pH does increase while patients are taking long-term potassium citrate, the stone formation rate in patients with a urine pH of greater than 6.5 is as significantly decreased as in those patients with a potassium citrate–treated pH of less than 6.5. Although stone composition was not evaluated in this particular study, the lack of difference in the stone formation rate in patients with a high urine pH strongly suggests that citrate administration does not increase the risk of calcium phosphate stone formation (Robinson et al, 2009b).

Key Points: Hypocitraturic Calcium Oxalate Nephrolithiasis

- Citrates are generally well tolerated with only a small risk of GI upset.
- Citrates are first-line therapy for the management of renal tubular acidosis (RTA), thiazide-induced hypocitraturia, and idiopathic hypocitraturia.
- There is conflicting evidence of an increased risk of calcium phosphate stone formation with the long-term use of potassium citrate therapy.

Hypomagnesiuric Calcium Nephrolithiasis

Hypomagnesiuric calcium nephrolithiasis is characterized by low urinary magnesium, hypocitraturia, and low urine volume. Therefore **management should include restoration of urinary magnesium levels with either magnesium oxide or magnesium hydroxide, as well as correction of the hypocitraturia with potassium citrate.** The administration of magnesium salts was first advocated on the theory that it reduced urinary excretion of oxalate. Some magnesium salts increase urinary magnesium excretion and thus produce a more favorable magnesium-to-calcium ratio in the urine, a condition that offers relative protection against stone formation. Magnesium decreases renal tubular citrate resorption through the chelation of citrate

and thus increases urinary citrate excretion. Melnick and colleagues (1971) found that stone recurrence dropped from 6 stones per year to 0.073 stone per year in a group of 149 recurrent calcium oxalate stone formers treated with magnesium oxide. Prien and Gershoff (1974) reported that about 70% of patients administered 300 mg of magnesium oxide and 100 mg of pyridoxine demonstrated complete cessation of stone formation. Johansson and colleagues (1980) treated 56 patients with 400 to 500 mg of magnesium hydroxide. Eighty percent of the treated patients were free of stones, in comparison to 50% who did not receive magnesium supplementation. The rate of stone formation dropped from 0.8 stone per year to 0.03 stone per year in the treated patients and from 0.5 stone per year to 0.22 stone per year in the control subjects. At least one randomized trial showed no difference in recurrence rates between treated and untreated patients (Ettinger et al, 1988).

Several magnesium salts have been used for the treatment of stone disease. Magnesium oxide and magnesium hydroxide are poorly absorbed and produce only a slight decrease in urinary oxalate and a modest increase in urinary magnesium (Barilla et al, 1978; Johansson et al, 1980). Urinary calcium levels are increased during magnesium oxide supplementation (Melnick et al, 1971; Fetner et al, 1978; Tiselius et al, 1980), and thus urinary saturation of calcium oxalate is not significantly lowered with magnesium oxide. Lindberg and colleagues (1990) found that either magnesium citrate or magnesium oxide induced only modest beneficial changes in urinary biochemistry when administered on an empty stomach. When the magnesium salts were provided with meals, however, they caused more prominent changes in urinary biochemistry and lowered the relative saturation of urine with calcium oxalate or brushite.

GI intolerance is the major side effect of magnesium therapy. At this time, magnesium supplementation is not widely used. Magnesium supplementation had been used in patients with sodium cellulose phosphate for the treatment of patients with absorptive hypercalciuria type 1 and may currently be used with potassium citrate in patients with chronic diarrheal syndromes.

A new magnesium preparation (potassium-magnesium citrate) has been developed but not yet approved for use. It provides both magnesium and citrate in the same tablet. This formulation of potassium-magnesium citrate has been shown to provide as much bioavailable potassium as other preparations (Koenig et al, 1991). In addition, magnesium excretion was significantly increased, as was the excretion of urinary citrate. The ability to deliver potassium has been further studied as it relates to thiazide-induced hypokalemia. This medication was demonstrated to provide just as much bioavailable potassium as other, standard agents (Wuermser et al, 2000).

Ettinger has reported on a randomized, double-blind trial of potassium-magnesium citrate versus placebo. In their study, new calculi formed in 63.6% of subjects receiving placebo and in 12.9% of subjects receiving potassium-magnesium citrate. When compared with placebo, the relative risk of treatment failure for potassium-magnesium citrate was 0.16. The authors concluded that potassium-magnesium citrate effectively prevents recurrent calcium oxalate stones and could be depended on to provide up to 85% protection over 3 years. Similar to work performed with potassium citrate, Odvina and colleagues (2006) have demonstrated the ability of potassium-magnesium citrate to prevent hypokalemia and hypomagnesemia in patients on thiazide therapy.

Key Points: Hypomagnesiuric Calcium Nephrolithiasis

- Magnesium supplementation can provide benefits in stone reduction.
- The use of magnesium has been limited by the risk of diarrhea.
- Potassium-magnesium may restore urinary magnesium and citrate levels with minimal GI side effects.

Gouty Diathesis

The major goal in the management of gouty diathesis is to increase the urinary pH above pH 5.5., preferably between 6.0 and 6.5 (Khatchadourian et al, 1995). In the past, urine alkalinization has been accomplished with either sodium bicarbonate or various combinations of sodium and potassium alkali therapy. Although sodium alkali may enhance dissociation of uric acid and inhibit uric stone acid formation by raising urinary pH, this medication may be complicated by the development of calcium-containing stones (calcium phosphate and/or calcium oxalate). Potassium citrate is advantageous not only as a good alkalinizing agent but also because it appears to be devoid of the complication of calcium stones. Potassium citrate should be given at dose sufficient to maintain urinary pH at approximately 6.5 (30 to 60 mEq/day in two to three divided doses). **Attempts at alkalinizing the urine to a pH of greater than 7.0 should be avoided. At a higher pH, there is a danger of increasing the risk of calcium phosphate stone formation.** If the urinary uric acid excretion is elevated or hyperuricemia exists, allopurinol (300 mg/day) should be added.

Cystinuria

The object of treatment for cystinuria is to reduce the urinary concentration of cystine to below its solubility limit (200 to 300 mg/L) (Pak and Fuller, 1983). The initial treatment program includes a high fluid intake to attempt to produce $2\frac{1}{2}$ to 3 L of urine per day. This amount of urine output will dramatically raise the denominator of the concentration fraction and help reduce the supersaturation of urine with respect to cystine. Others have recommended the oral administration of soluble alkali (potassium citrate) at a dose sufficient to raise the urinary pH to 6.5 to 7.0 (Chow and Streem, 1998; Joly et al, 1999). This treatment strategy attempts to increase the solubility of the filtered cystine to prevent crystal formation. Although alkali therapy may help, it is important to remember that the pKa of cystine is 8.3, which creates two problems. First, it is quite difficult to achieve a urine pH this high, making excessive alkalization an unrealistic target. Secondly, raising the urine pH to these levels will put the patient at risk for the formation of calcium phosphate calculi.

There is good evidence that excess dietary sodium can lead to increases in cystine excretion (Norman and Manette, 1990; Lindell et al, 1995; Rodriguez et al, 1995; Fjellstedt et al, 2001). Indeed, these authors have demonstrated that the restriction of dietary sodium should be an integral aspect of the global management of cystinuric patients. Fjellstedt has even shown that the use of sodium citrate rather than potassium citrate may diminish the efficacy of other medical interventions such as the

sulfhydryl-containing compound α-mercaptoprionylglycine (Thiola).

When this conservative program is ineffective, **the next line of therapy involves the use of agents that increase cystine solubility in urine via formation of a more soluble mixed-disulfide bond (i.e., cystine to drug, rather than cystine to cystine). These agents include α-mercaptopropionylglycine (Thiola, Tiopronin), D-penicillamine (Cuprimine), or Captopril.**

The first agent studied was D-penicillamine. Interestingly, little has been written specifically about this agent and its use in the treatment of cystinuria since the 1960s to 1970s (Crawhall and Thompson, 1965; McDonald and Henneman, 1965; Lotz et al, 1966; Combe et al, 1993). Although moderately effective, D-penicillamine quickly became associated with frequent side effects including nephrotic syndrome, dermatitis, and pancytopenia. One recent study from the Children's Hospital of Pennsylvania documented 9 of 11 patients without toxicity for an average of 109 months of follow-up following initial dose escalation (DeBerardinis et al, 2008). Typical doses start at 250 mg per day and are titrated to effect.

The next medication to be introduced for the treatment of cystinuria was α-mercaptopropionylglycine (Thiola, Tiopronin) (Remien et al, 1975; Hautmann et al, 1977; Johansen et al, 1980). This agent also contains a sulfhydryl group that forms a disulfide bond with cystine. Although this agent has been shown to be slightly less effective at capturing cystine molecules in vivo (Harbar et al, 1986), **α-mercaptopropionylglycine is better tolerated than D-penicillamine and therefore enjoys clinical superiority** (Pak et al, 1986a). However, side effects are still possible with Thiola. Indeed, Pak demonstrated that overall side effects to α-mercaptopropionylglycine were relatively common and occurred in 64.7% without a history of D-penicillamine treatment, compared with 83.7% who suffered toxicity to D-penicillamine. Moreover, serious adverse reactions requiring cessation of therapy were less common with α-mercaptopropionylglycine. Among the patients who took both drugs, 30.6% had to stop taking α-mercaptopropionylglycine, whereas 69.4% could not tolerate D-penicillamine. Common side effects include asthenia, GI distress, rash, joint aches, and mental status changes. Dosages start at 100 mg, taken orally two times per day, and are titrated to achieve urinary concentrations of cystine less than 250 mg/L urine. Pak has reported total daily doses as high as 1200 mg (Pak et al, 1986a).

As described earlier, Coe and colleagues (2001) have recently presented an assessment of cystine prophylaxis on the basis of the supersaturation of cystine in the presence of thiol-based medications. In essence, this assay measures how much "room" there is in the patient's urine for more cystine to be dissolved. Demonstration that the urine is not yet fully saturated implies a lower risk for spontaneous stone formation.

Finally, the angiotensin-converting enzyme inhibitor captopril has been used to treat cystinuria due to its available sulfhydryl group. Although this agent enjoyed early enthusiasm (Sloand and Izzo, 1987; Streem and Hall, 1989; Cohen et al, 1995), its popularity seems to have waned (Michelakakis et al, 1993). Side effects are less severe than the other agents and include fatigue, hypotension, and chronic cough. **Yet there have been no long-term clinical trials demonstrating the effectiveness of captopril in preventing recurrent cystine stone formation.**

The medical management of cystinuria can be quite challenging. Although the array of medication choices is not particularly complicated, it is often difficult to achieve patient compliance (Barbey et al, 2000). Indeed, due to the genetic nature of the disease process, these patients frequently begin their stone formation at a young age, thereby exposing their kidneys to the risk of chronic stone passage and potential parenchymal loss (Lindell et al, 1997) (Fig. 46–11 on the Expert Consult website). Assimos and colleagues (2002) have examined the clinical status of 40 cystinuric patients followed at two medical centers and compared their "kidney health" with 3964 calcium oxalate stone formers enrolled in a database. The mean serum creatinine for stone-forming cystinuric patients was significantly higher than that of the calcium oxalate cohort. Male gender, increasing number of open surgical stone-removing procedures, and nephrectomy were significant variables associated with an increased serum creatinine. An alarming number of cystinuric patients had undergone nephrectomy for any reason (14%) versus the patients in the calcium oxalate cohort (3%).

Unfortunately, despite the obvious consequences of poor medical compliance, a recent study suggests that few patients are able to achieve and maintain targeted goals of medical intervention (Pietrow et al, 2003). Of the 26 patients followed at a dedicated stone center, only 15% achieved and maintained therapeutic success, as defined by urine cystine concentration less than 300 mg/L. An additional 42% achieved therapeutic success but subsequently had failure at an average of 16 months (range 6 to 27). Of these patients, two thirds regained therapeutic success at an average of 9.4 months (range 4 to 20). Nineteen percent never achieved therapeutic success, whereas an additional 23% failed to present to follow-up appointments or provide subsequent 24-hour urine studies despite their having been referred to a tertiary care center. It is important to note that patient self-assessment of medical compliance was uniformly high regardless of physician perceptions or treatment results.

Key Points: Cystinuria

- The medical compliance of patients with cystinuria can be poor.
- Treatment consists of aggressive fluid intake, urinary alkalinization, salt avoidance, and the use of a cystine-binding agent.
- α-mercaptopropionylglycine (Thiola) is the most frequently used cystine binding agent.

Infection Lithiasis

The preferred management of struvite calculi involves aggressive surgical approaches. **The AUA Guidelines Committee has recently released updated guidelines that strongly recommend endoscopic-based therapy (i.e., percutaneous nephrolithotomy) as the first-line therapy for managing complex, renal staghorn calculi** (Preminger et al, 2005). **This report noted that complete elimination of all infected stone material is essential for the prevention of recurrent struvite stone formation.** A complete discussion of surgical therapy for large calculi is beyond the scope of this chapter and can be found elsewhere within this textbook.

The medical management of infection calculi centers on the prevention of recurrence, rather than medical dissolution. As such, long-standing effective control of infection with urea-splitting organisms should be

achieved if at all possible with improved bladder health, adequate urinary drainage, and suppressive antibiotics (Bichler et al, 2002; Hess, 1990). Unfortunately, such control is difficult to obtain in the face of residual calculi because stones often harbor organisms and endotoxin within their interstices (Rocha and Santos, 1969; McAleer et al, 2002, 2003). Antibiotics should be tailored to the predominant organism found on culture and sensitivity screening (Hugosson et al, 1990). Notably, cultures do not always correlate well between a patient's urine and a resuspension of stone material (Fowler, 1984). Therefore strong clinical suspicion is always indicated, and all patients undergoing removal of presumed struvite calculi should be covered with broad-spectrum antibiotics that account for local resistance patterns. Although cultures may become negative during treatment, it is important to remember that recurrence of colonization is likely if residual fragments remain within the collecting system.

Following surgical stone removal, residual fragments may be dissolved with hemiacidrin irrigation (Renacidin) under careful observation. Historically, use of this agent was associated with significant toxicity and even death. Closer scrutiny revealed that many, if not most, of these cases involved the use of irrigation in infected urine and/or sepsis. Therefore this agent should only be employed after urinary tract infection and/or colonization has been brought under control. The renal pelvis is first irrigated with sterile saline solution at a rate of 120 mL/hr for 24 to 48 hours, beginning on the fourth or fifth postoperative day. The height of irrigation is adjusted to the lowest level necessary to maintain the flow rate at 120 mL/hr. If there is leakage around a surgical drain or through the incision, irrigation is stopped until additional healing occurs. The patient is observed carefully for development of fever or any flank discomfort and for elevation of serum creatinine, magnesium, or phosphate levels (Dretler and Pfister, 1984). Occurrence of any of these conditions requires immediate cessation of irrigation.

If, after 48 hours, the patient's condition remains satisfactory and there is no infection, no leakage, and no fever or flank discomfort, irrigation is begun with an appropriate solution. Flow rate is continued at 120 mL/hr through the irrigation tube or catheter. Most authors (Jacobs and Gittes, 1976; Nemoy and Stamey, 1976; Palmer et al, 1987) instruct their patients to stop the irrigation themselves if there is evidence of flank pain at any time.

The progress of irrigation is followed by radiographic tomography of the calculi at intervals. Irrigation is continued for 24 to 48 hours after the last radiographically visible fragments have disappeared. In some instances, the rate of irrigation may be reduced to prevent irritation of the kidney or bladder, or sterile saline solutions may be alternated with irrigating solutions. Chemolysis with various agents is no longer routinely used for the management of struvite calculi.

Acetohydroxamic acid, a urease inhibitor, may reduce the urinary saturation of struvite and therefore retard stone formation (Griffith et al, 1978). **When given at a dose of 250 mg three times/day, acetohydroxamic acid has been shown to prevent recurrence of new stones and inhibit the growth of stones in patients with chronic urea-splitting infections.** At least two studies have demonstrated significant efficacy in randomized, placebo-controlled trials (Williams et al, 1984; Griffith et al, 1991). In these investigations, patients were treated with acetohydroxamic acid and antibiotics. Recurrence rates and subsequent stone growth were significantly less for patients treated with drug therapy compared with placebo. In addition, in a limited number of patients, this agent has caused dissolution of existing struvite calculi (Rodman et al, 1983). **However, a significant percentage of patients receiving chronic acetohydroxamic acid therapy experienced minor side effects and 15% developed deep venous thrombosis.** Indeed, Rodman and colleagues (1987) have demonstrated that patients receiving acetohydroxamic acid enter into a state of low-grade intravascular coagulation, requiring careful follow-up for signs of thrombosis.

Several authors have reported high rates of medication cessation due to intolerable side effects. In the previously noted randomized studies, 22% to 68% of treated patients had to stop therapy and withdraw from the investigation. Reported side effects have been varied and include thromboembolic phenomena, tremor, headache, palpitations, edema, GI distress, loss of taste, rash, alopecia, anemia, and abdominal pain. Due to these concerns, this agent is frequently reserved for those patients deemed too ill for surgical management. Other acidifying agents have been reported by Wall and Tiselius (1990) but do not appear to have been widely used. These include ammonium chloride, methenamine hippurate, and ascorbic acid.

Key Points: Infection Lithiasis

- Struvite calculi are best managed with surgical removal rather than chemical dissolution.
- Recurrent infections (and therefore recurrent calculi) may be avoided with the use of antibiotic prophylaxis.
- Acetohydraxamic acid (Lithostat) can effectively inhibit urease, but its widespread use is precluded by significant side effects.

Ammonium Acid Urate Stones

Ammonia acid urate calculi are infrequently seen in industrialized nations and are often associated with laxative abuse (Dick et al, 1990; Kato et al, 2004). The largest described series has been reported by Soble and colleagues (1999) from the Cleveland Clinic. In their series, 23 women and 21 men ranging in age from 20 to 81 years (mean 48.7) were treated for stones partly composed of ammonium acid urate. Stone composition ranged from 2% to 60% ammonium acid urate (mean 24.1) of the total stone mass. No patient had a pure ammonium acid urate stone, although 11 (25%) had stones with ammonium acid urate as the predominant crystal. The authors identified one or more potential risk factors for ammonium acid urate for most patients. Of the patients, 25% had a history of inflammatory bowel disease with 22.7% having undergone ileostomy diversion, 13.6% admitted to a history of significant laxative use or abuse, 40.9% were morbidly obese, 36.4% had a history of recurrent urinary tract infections, and 20.5% had a history of recurrent uric acid stones. On the basis of these findings, the authors suggested that laxative abuse should not be assumed for all patients with ammonia acid urate calculi, but rather, a metabolic evaluation or full history should be sought for each patient.

Medical treatment for these calculi is determined by the underlying cause of the stone. Those with laxative abuse are strongly encouraged to develop a healthier bowel regimen. Those with chronic infections are treated much like those with struvite calculi. Bowel disease is treated, if possible, while standard recommendations of fluid intake, oral calcium, alkalinization and oxalate reduction are made. Those with a history of uric acid calculi are

Table 46–18.

Medications Associated with Renal Calculus Formation

Calculi Formed from Drug
Indinavir
Ephedrine
Triamterene
Magnesium trisilicate antacids (silicates)
Sulfamethoxazole-trimethoprim
Calculi Provoked by Drug
Carbonic anhydrase inhibitors
Topirimate
Furosemide
Vitamin C (excess)
Vitamin D (excess)
Laxatives

also treated in a similar manner with increased fluid intake, protein and salt restriction, and possible utilization of citrates or allopurinol.

Miscellaneous and Drug-Induced Stones

Some stones are formed from supersaturation of medications themselves or may be due to the effects of a particular agent. Several medications have been associated with stone disease and are listed in Table 46–18.

Calculi formed from antiretroviral medications used to treat human immunodeficiency virus (HIV) have been described, particularly with Indinavir (Crixivan) (Bach and Godofsky, 1997; Hug et al, 1999; Sundaram and Saltzman, 1999; Saltel et al, 2000). These calculi can be quite soft and often dissipate rapidly during endoscopy or shockwave lithotripsy. **Difficulties may arise during diagnosis because indinivir stones may not be visible on plain film radiography and may even be undetectable on a stone protocol CT** (Gentle et al, 1997; Sundaram and Saltzman, 1999). Treatment entails aggressive hydration and endoscopy for those stones that do not pass spontaneously. The radiolucency of the calculi often precludes successful treatment with shock wave lithotripsy. In the short term, patients may be temporarily taken off of indinavir until an aggressive fluid habit can be established. Some patients require cessation of this antiretroviral and the initiation of a different agent.

As described earlier, triamterene, a potassium-sparing antihypertensive agent, may crystallize in the urinary tract, requiring cessation of this medication (Werness et al, 1982; Sorgel et al, 1985). For this reason, triamterene is not recommended as an adjunct to thiazides during the treatment of hypercalciuric states.

Carbonic anhydrase inhibitors may be associated with the formation of calcium-based calculi, particularly calcium phosphate (Kondo et al, 1968; Parfitt, 1969). In this scenario, the use of the medication creates a chronic intracellular acidosis. This effect, in turn, creates a urinary milieu reminiscent of a distal tubular acidosis with hyperchloremic acidosis, high urine pH, extremely low urinary citrate, and hypercalciuria. Treatment may be accomplished with potassium citrate replacement or, more logically, cessation of the medication.

Topiramate is a relatively new antiepileptic medication with significant promise for the treatment of refractory epilepsy. Unfortunately, it may mimic the effect of a carbonic anhydrase inhibitor and lead to the formation of urinary calculi (Kossoff et al, 2002; Kuo et al, 2002; Lamb et al, 2004). The incidence of such an effect has been reported to be approximately 5% (Kossoff et al, 2002).

Finally, **multiple authors have described calculi that have formed in patients taking over-the-counter supplements containing ephedrine** (Blau, 1998; Powell et al, 1998; Assimos et al, 1999; Hoffman et al, 2003; Bennett et al, 2004; Smith et al, 2004; Whelan and Schwartz, 2004). These calculi are likely radiolucent but have been reported to be "visible" on noncontrast CT. Ephedrine stones have been treated with a variety of methods including shock wave lithotripsy, endoscopy, and even alkalinization therapy. Because this supplement has a risk of abuse, it may be difficult to effectively interfere with the formation of future stone events.

MISCELLANEOUS SCENARIOS

Medical Management of Bladder Calculi

In the United States, bladder calculi usually occur in men older than 50 years and are usually associated with bladder outlet obstruction. The diagnosis of a bladder stone should result in a complete urologic evaluation for factors that cause urinary stasis such as urethral stricture, benign prostatic hyperplasia, bladder diverticulum, and/or a neurogenic bladder. Occasionally, bladder stones may result as a consequence of a retained foreign body.

In contrast to renal stones, **bladder stones are usually composed of uric acid (in noninfected urine) or struvite (in infected urine).** Reports from the United States revealed uric acid stones in nearly 50% of patients with bladder stones (Douenias et al, 1991). Such patients often have bladder outlet obstruction, causing them to decrease fluid intake with the resultant production of concentrated, acidic urine. The occurrence of calcium oxalate or cystine stones in the bladder suggests the presence of calculi in the kidney with subsequent ureteral passage and entrapment in the bladder.

Bladder calculi are usually solitary but may develop in large numbers in the presence of urinary stasis (Sarica et al, 1994). **The typical symptoms of a vesical stone are intermittent, painful voiding and terminal hematuria.** Discomfort may be dull, aching, or sharp suprapubic pain, which is aggravated by exercise and sudden movement. Severe pain usually occurs near the end of micturition, as the stone becomes impacted at the bladder neck. Relief may be afforded by assuming a recumbent position. The pain may be referred to the tip of the penis, scrotum, perineum, and occasionally the back or hip. **Besides pain, there may be an interruption of the urinary stream from impaction of the stone at the bladder neck or urethra.**

Bladder calculi are frequently missed on plain film due to a high component of uric acid and because of overlying prostatic tissue. Such stones form negative shadows in the cystogram phase of IVU. Ultrasonography is useful for detecting radiolucent calculi. Cystoscopic examination is the surest method for detecting vesical calculi.

The vast majority of bladder calculi can be removed via endoscopic techniques. Various lithotriptors have been used including ultrasonic handpieces, lasers, pneumatic devices, and electrohydraulic probes (Ikari et al, 1993; Razvi et al, 1996). Transurethral and percutaneous approaches have been described with good success. Stone dissolution is feasible with the use of

Suby G or M solution. This method is quite protracted and is now rarely employed. **Suby's solutions or Renacidin may prove beneficial in irrigating indwelling suprapubic or urethral catheters to decrease and prevent encrustation and occlusion** (Kennedy et al, 1992; Getliffe et al, 2000). Twice-daily or thrice-daily irrigation with 0.25% or 0.5% acetic acid solution also serve as beneficial prophylaxis against recurrent struvite calculi when catheters must be left indwelling for long periods. Uric acid calculi may be dissolved by irrigation with alkaline solutions.

The mainstay of therapy for the prevention of recurrent bladder calculi involves relief of the bladder outlet obstruction. This treatment may include the performance of a transurethral resection of the prostate or an open prostatectomy if the gland is quite large.

Medical Management of Pediatric Calculi

Children may develop urinary calculi due to several underlying etiologies as outlined in the previous chapter. Evaluation and management depend on the causative process.

Neoatal Nephrolithiasis

Neonates with furosemide-induced nephrolithiasis present with hematuria, worsening renal function, and calcific densities on ultrasonography or plain film radiography. Nephrocalcinosis is often present on imaging studies. This same process has been seen in other infants with severe low birth weight and/or prematurity and no history of loop diuretic usage.

Management of neonatal nephrolithiasis entails the obvious optimatization of the infant's overall health. **Cessation of furosemide diuresis is considered helpful and standard therapy. There was a previous suggestion that treatment with thiazide diuretics may actually promote the resolution of this process and reverse the likely parenchymal injury** (Noe et al, 1984). **This observation has not been supported by other investigators, however.** Pope and colleagues (1996) noted a 50% resolution rate of the nephrocalcinosis after cessation of loop diuretics, but this finding was unrelated to any other factor including the use of thiazides. Instead, a low calcium-to-creatinine ratio at the time of diagnosis was the best predictor of resolution. Further research by Knoll and Alon (2000) using an animal model of the disease did not demonstrate a therapeutic effect of the use of thiazides on furosemide-induced nephrocalcinosis.

At the least, this evidence suggests that neonates treated with loop diuretics should be screened for the development of nephrocalcinosis. **Although switching to a thiazide diuretic may not actively cause the dissolution of calculi, it at least removes the causative agent and allows the kidney an opportunity to heal and clear the calcium deposits.**

Children and Adolescents

As children reach physical maturity at a younger age, it is not surprising that the incidence of urinary calculi in adolescence appears to be increasing. Within the United States this finding is likely further related to the increasing prevalence of obesity within this same age group. **Nevertheless, the appearance of urinary calculi during childhood should raise the distinct possibility of an inherited genetic disorder such as cystinuria, distal renal tubular acidosis, or primary hyperoxaluria.**

The evaluation of pediatric nephrolithiasis has been hampered in the past by a lack of consensus regarding normal laboratory values during 24-hour urine collections in children. Clinicians have therefore relied on calculated ratios to correct for the wide variation in weight within this diverse patient population. The most important of these has been the urinary calcium-to-creatinine ratio. A calculated urinary calcium-to-creatinine ratio above 0.2 has been considered abnormal and frequently prompts intervention.

Several investigators have explored the use of urinary supersaturation calculations to assess for stone risk factors in children (Battino et al, 2002; Lande et al, 2005). These calculations may miss abnormalities otherwise overlooked by "traditional" cumulative measurements. At least one of these authors, however, notes that the importance of supersaturation wanes considerably in the face of low urine volumes (Lande et al, 2005).

Evidence strongly supports close and aggressive follow-up of pediatric stone formers. Pietrow and colleagues (2002) found that 50% of children 10 years or younger with urinary calculi have an identifiable metabolic derangement. Additionally, those with abnormal urinary metabolites are five times more likely to have recurrent stones. However, the identification of these abnormalities is more challenging in the pediatric population. Reference values for this population are not as well defined and may require adjustments on the basis of body weight and urinary creatinine to best delineate abnormalities (Borawski et al, 2008).

The medical management of nephrolithiasis and the prevention of subsequent recurrences in children do not differ that dramatically from the approaches undertaken for adults. All patients (and their parents) are counseled to improve fluid intake. Dietary recommendations are similar to those made for adults. It is important to emphasize that dietary calcium is not to be avoided in this age group. Rather, calcium should be sought through the ingestion of dairy and other natural sources rather than with the use of supplements. Such sources will also bind dietary oxalate during meals and may decrease calcium oxalate supersaturation in the urine.

Children with cystinuria or hyperoxaluria are managed as outlined in the previous section within this chapter. The exception to this would be a general reticence to begin sulphur-binding agents in cystinuric children, without first maximizing fluid intake and the use of citrates to alkalinize the urine.

Children with documented hypocitraturia and/or distal renal tubular acidosis are usually treated with citrates at a dose of 4 mg/kg/day (Domrongkitchaiporn et al, 2002a). Hypercalciuria may respond to increased fluid intake and decreased sodium (salt) ingestion, much like the adult population. Thiazides may be employed for recalcitrant hypercalciuria. The long-term efficacy and safety of thiazides in the pediatric population has not been well studied and established.

Medical Management of Calculi during Pregnancy

The management of calculi during pregnancy is currently undergoing a transformation. These changes, however, are developing mainly within the realm of surgical intervention, not medical therapy. As noted in the preceding chapter on the pathophysiology of calculi, **pregnant women create a unique urinary**

environment that is prone to stone formation. Although the amount of urinary calcium rises quite notably (Gertner et al, 1986)**, this effect is offset by an accompanying increase in urinary citrate. As a result, is is widely assumed that there is no net increase or decrease in the risk of calculi formation during pregnancy** (Coe et al, 1978; Maikranz et al, 1987). **Due to these temporary physiologic changes, a metabolic evaluation is not generally undertaken to determine the cause of the stone disease until after the woman has delivered and returned to her baseline state of health.**

The acute evaluation of a pregnant woman with suspected renal colic begins with a thorough history and physical examination. A urinalysis is obtained and examined for signs of active urinary tract infection. Patients may also present with vague abdominal pain, unexplained fevers, recurrent urinary tract infections, persistent bacteriuria, or microscopic hematuria. A previous history of nephrolithiasis should also be sought because the increased dilation of the ureters during pregnancy may increase the risk that a preformed stone will break loose and attempt to pass.

Radiation exposure to the fetus should be avidly avoided. Therefore ultrasonography has become the first-line imaging study to search for calculi during pregnancy. Although this modality provides adequate images of the kidneys, it can be difficult to fully discern the ureters and their contents. Additionally, hydronephrosis of pregnancy may be confused for hydronephrosis from an obstructing calculus. **A limited IVP consisting of one scout image followed by one plate taken approximately 30 minutes after the injection of contrast may be obtained. Each plain film exposes the fetus to 0.1 to 0.2 rads, well below the threshold of 1.2 rads, at which point the risk begins to increase.** Radiation exposure should be particularly avoided during the first trimester during the time of organogenesis and the greatest fetal risk.

In keeping with the concern of fetal radiation exposure, assessment of a low-dose CT protocol was performed (White et al, 2007). The average radiation exposure was 0.7 rads (0.2 to 1.3 rads). Of the 20 patients evaluated for flank pain, 13 were identified as having urinary stones ranging from 1 to 12 mm.

Approximately 66% to 85% of pregnant women with ureteric colic spontaneously pass the calculi when treated conservatively with hydration, analgesics, and, if infected, antibiotics (Jones et al, 1979; Stothers and Lee, 1992). The goal of therapy for the remaining patients is to do the least required to keep the kidney functioning, the patient free from symptoms, and the urine uninfected. **Stents should be placed cystoscopically with minimal radiographic or sonographic monitoring** (Loughlin and Bailey, 1986; Jarrard et al, 1993). Some studies have demonstrated an increased rate of encrustation, requiring frequent changes. In some instances the stents migrated down the ureter because of the physiologic dilation (Stothers and Lee, 1992). Stents are often exchanged every 4 to 6 weeks to avoid excessive encrustation and the risk of obstruction.

Because many expectant mothers take calcium supplementation, a more "stone-friendly" form of this mineral has been developed (Citracal Prenatal Rx, Mission Pharmacal, Inc., San Antonio, TX). In this formulation, calcium is bound to citrate, which delivers extra stone inhibitor into the urine, thereby offsetting the effects of worsening absorptive hypercalciuria. Iron and folate are also added to complete the elements commonly found in prenatal multivitamin supplements. Although there are no randomized data to support the use of this supplement in pregnant women, its use does make intuitive sense for patients at risk of recurrent calculi during pregnancy.

A full discussion of the surgical management of calculi during pregnancy is beyond the scope of this chapter**. There is growing evidence, though, that ureteroscopy, with holmium laser lithotripy, performed later during pregnancy is safe and free of increased risk to the fetus or mother** (Lifshitz and Lingeman, 2002; Watterson et al, 2002). Indeed, the definitive nature of one uncomplicated ureteroscopy likely represents less risk than the anesthesia associated with multiple stent changes, plus the infectious risk of an indwelling foreign body.

Key Points: Medical Management of Calculi

- Bladder calculi are best managed with endoscopic techniques. Subsequent recurrence is prevented by relief of the bladder outlet obstruction.
- Neonatal nephrocalcinosis is frequently caused by loop diuretics. Cessation of this medication is essential.
- Neonatal nephrocalcinosis may be reversed by the use of thiazides.
- The majority of ureteral calculi during pregnancy pass spontaneously.
- There is a growing trend toward endoscopic relief of symptomatic calculi during pregnancy.

SUMMARY

Selective medical therapy of nephrolithiasis is highly effective in preventing new stone formation. A remission rate of greater than 80% and overall reduction in individual stone formation rate of greater than 90% can be obtained in patients with nephrolithiasis. In patients with mild-to-moderate severity of stone disease, virtually total control of stone disease can be achieved with a remission rate of greater than 95%.

Selective pharmacologic therapy of nephrolithiasis also encompasses the advantages of overcoming nonrenal complications, as well as averting certain side effects that may be caused by nonselective medical therapy. Despite these advantages, it is clear that selective medical therapy cannot provide total control of stone disease. **A satisfactory response requires continued, dedicated compliance by patients to the recommended program and a commitment of the physician to provide long-term follow-up and care.**

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The complete reference list is available online at www.expertconsult.com.

chapter
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Percutaneous Approaches to the Upper Urinary Tract Collecting System

J. Stuart Wolf, Jr., MD, FACS

History and Introduction
Indications for Percutaneous Access
Anatomic Considerations
Obtaining Percutaneous Access
Postprocedural Nephrostomy Drainage
Training in Percutaneous Access and Procedures
Complications

HISTORY AND INTRODUCTION

Commonly ascribed to Goodwin and colleagues (1955), the first therapeutic percutaneous nephrostomy actually was performed by Thomas Hillier in 1865 (Bloom et al, 1989). Hillier, at the Hospital for Sick Children at Great Ormond Street, repeatedly aspirated the hydronephrotic kidney of a young boy for symptom relief over a 4-year period until his death at 8 years of age. Subsequently there were a few reports of diagnostic percutaneous renal aspirations, but it was not until Goodwin and colleagues published their landmark report in 1955 that therapeutic percutaneous nephrostomy was rediscovered. Even then, the utility of percutaneous access to the upper urinary tract collecting system was limited to drainage of obstructed kidneys until Fernström and Johansson (1976) reported the percutaneous removal of renal calculi, termed "percutaneous pyelolithotomy."

In the 30-plus years since that report, a number of procedures have been performed using the convenient and safe percutaneous route to accessing the upper urinary tract collecting system including drainage of an obstructed kidney, nephrolithotomy, endopyelotomy, and resection of urothelial tumors. More recently, percutaneous access to portions of the kidney other than the collecting system has expanded the diagnostic and therapeutic choices for patients with renal diseases. Other chapters in this book address these indications, including Chapters 49 and 56. This chapter addresses only percutaneous access to the upper urinary tract collecting system, focusing on the creation, maintenance, and postprocedure management of the percutaneous tract. The final section of the chapter reviews the general complications of percutaneous access to the upper urinary tract collecting system. Specific aspects of the procedures performed through the percutaneous access are covered in Chapters 7, 41, 48, and 53.

INDICATIONS FOR PERCUTANEOUS ACCESS

Simple Drainage or Access

Percutaneous drainage of the upper urinary tract collecting system can be for diagnostic or therapeutic indications. **The only remaining popular indication for diagnostic percutaneous nephrostomy is to perform a Whitaker test,** which requires placement of a small-caliber nephrostomy tube through which contrast material is instilled at specific flow rates while pressures are measured to assess for ureteral obstruction (see more detailed description in Chapter 41). In other cases, diagnostic nephrostography is performed as an adjunct to therapeutic percutaneous nephrostomy.

Therapeutic percutaneous nephrostomy tubes can be placed to drain the kidney (see Chapter 7) and access the upper urinary tract for direct instillation of therapeutic agents (see Chapter 53) or to perform a surgical procedure. **Percutaneous nephrostomy is indicated to drain the upper urinary tract collecting system in cases of obstruction at an intrarenal location, at the ureteropelvic junction, or anywhere in the ureter.** Obstruction of the lower urinary tract is best treated by drainage of the bladder rather than the kidney, unless secondary obstruction of the upper tract has developed that is refractory to vesical drainage. An alternative to percutaneous drainage is drainage through a ureteral catheter or stent placed in a retrograde fashion (cephalad from the bladder to the kidney, as opposed to antegrade, which is placement from the kidney toward the bladder). **The choice of antegrade or retrograde drainage of the upper urinary tract collecting system depends on the indication for the procedure, patient's medical condition,**

particular anatomy of the patient, and preferences of both the patient and the physician.

All things being equal, a retrograde route to drainage is preferred over the antegrade route. This includes most cases of acute and chronic ureteral obstruction without infection (Rosevear et al, 2007; Wenzler et al, 2008). **In the setting of upper urinary tract collecting system obstruction complicated by infection, however, drainage is an emergency and in many such cases percutaneous rather than retrograde drainage may be best** (Ng et al, 2002)**, unless retrograde drainage can be obtained expeditiously and assuredly. Percutaneous nephrostomy tubes and retrograde ureteral stents are generally equivalent in their capacity to resolve fever in patients with upper urinary tract obstruction and fever** (Pearle et al, 1998), **but in a given patient circumstances may dictate preference for one access over the other.** Retrograde placement of a ureteral stent generally requires regional or general anesthesia, whereas a percutaneous nephrostomy tube can be inserted under local anesthesia; this is an important consideration in an ill patient. Because the percutaneous route has a greater initial success rate than the retrograde one in cases in which the collecting system is dilated, it might be preferred in a patient who needs rapid intervention. This is especially true when the ureteral obstruction is long, severe, or involving the ureteral orifice—all of which can make retrograde stent placement more difficult. Conversely, untreated coagulopathy is a contraindication to percutaneous access, but internal ureteral stents can be placed safely in an anticoagulated patient. A final consideration is patient preference. Although the health-related quality of life for patients with percutaneous nephrostomy tubes and those with internal ureteral stents is similar, a given patient may prefer one route over the other (Joshi et al, 2001). For additional discussion of percutaneous nephrostomy versus internal ureteral stent for drainage of the upper urinary tract, see Chapter 7.

Percutaneous Surgery

Access into the upper urinary tract collecting system may be indicated to directly instill therapeutic agents. This includes chemolysis of urinary calculi and intracavitary topical therapy for urothelial carcinoma. In most cases, the access elected for the instillation will already be present after the preceding surgical procedure.

An important indication for percutaneous access into the upper urinary tract collecting system is for intrarenal or intraureteral surgery. This includes percutaneous endopyelotomy and endoureterotomy (see Chapter 41), **nephrolithotomy, treatment of calyceal diverticula and hydrocalyces, and antegrade ureteroscopic treatment of large ureteral stones** (see Chapter 48); **percutaneous resection of urothelial tumors** (see Chapter 53); **and less common procedures such as management of fungal bezoars.** For all of these procedures skillfully attaining access, properly managing postoperative drainage, and preventing and treating complications related to the percutaneous access are major components of the procedure. The remainder of this chapter centers on these topics.

ANATOMIC CONSIDERATIONS

Given that the visualization of the kidney and surrounding structures during standard percutaneous entry guided by fluoroscopy or ultrasonography is limited, understanding of the renal and perirenal anatomy is critical for obtaining access that is both effective and safe. Even armed with this knowledge, variations in anatomy can make access challenging for the experienced surgeon and prohibitive for the inexperienced one.

Perirenal Anatomy

The kidneys are well-protected organs, situated retroperitoneally and surrounded by adipose tissue. The mobility of the kidneys is limited by the short renal hilar vessels, although nephroptosis ("falling kidney") can occur, especially in thin women with a paucity of perirenal fat. In such cases the kidney not only descends but also rotates anteriorly. This can be troublesome during percutaneous punctures with the patient in a prone position.

The kidneys lie adjacent to the vertebral bodies, usually extending from the 11th or 12th thoracic to the 2nd or 3rd lumbar vertebrae (Fig. 47–1). The right kidney is displaced a few centimeters inferior to the left kidney. The longitudinal axis of the kidneys parallels the lateral edges of the psoas muscles, about 30 degrees from vertical, with the lower poles lateral to the upper poles. The kidneys are also tilted 30 degrees off the frontal plane, with the lower poles anterior to the upper poles. Finally, the kidneys are rotated out of the frontal plane as well, with the lateral aspect of the kidney posterior to the medial aspect, such that each kidney is rotated 30 degrees posteriorly from the renal hilum.

Immediately posterior to the kidneys are the quadratus lumborum and psoas muscles, except at the upper poles where the diaphragm is posterior (Fig. 47–2). **The pleura can be violated during percutaneous entry into the upper pole of the kidney. This risk is greater as the access to the kidney is moved cephalad.** The lung itself lies above the 11th rib, so direct lung injury is unlikely unless the 10th intercostal space (superior to the 11th rib) is used as the entry site. The ribs curve inferiorly from medial to lateral, such that more portions of the kidney can be approached subcostally with a medial as opposed to lateral access site.

The lateral, anterior, and medial perirenal relationships are more varied than the posterior ones (Fig. 47–3). On the right side, the liver is anterior to the upper pole of the kidney and can extend in some individuals to cover the entire anterior surface. On the left, the spleen covers less of the kidney anteriorly. Both the liver and spleen can extend lateral to the kidneys and are therefore at risk of injury with a lateral puncture into the kidney. **The ascending and descending colon can be lateral or even posterior to the right and left kidneys, respectively. The apposition of the colon to the kidney varies with location; it**

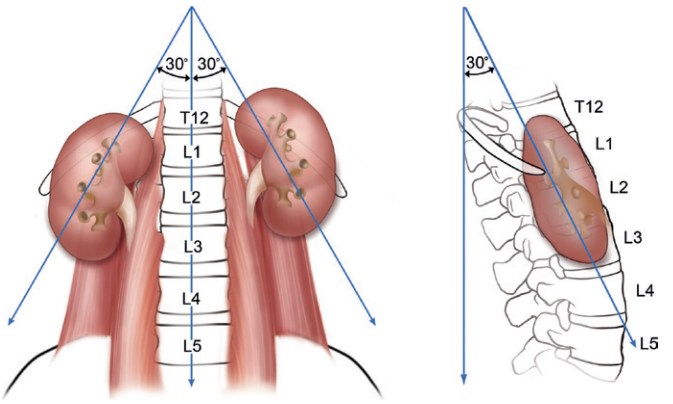


Figure 47–1. Location of kidneys in the retroperitoneum.

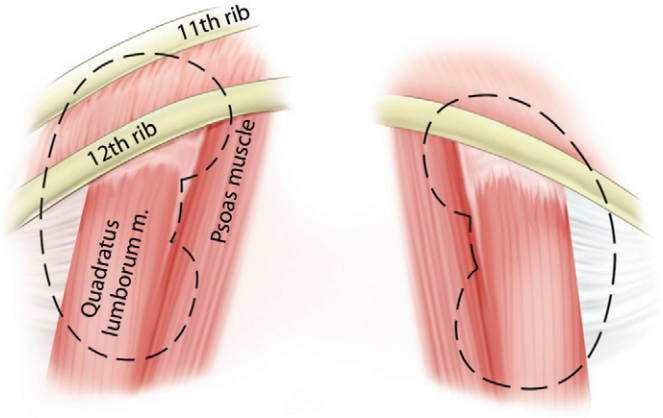


Figure 47–2. Muscles and ribs posterior to the kidneys.

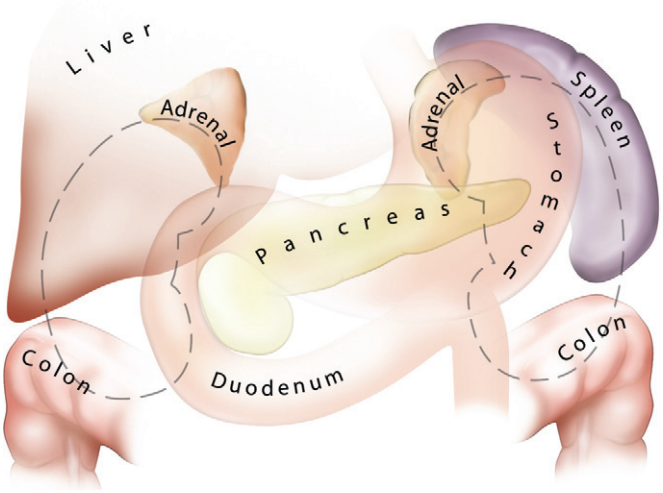


Figure 47–3. Viscera lateral, anterior, and medial to the kidneys.

is greatest on the left side and at the lower pole. In one study of computed tomograms the left colon was posterior in 16.1% of cases, and the right colon was posterior in 9% of cases at the level of the lower pole. At the midaspect of the kidney the colon was posterior in 5.2% and 2.8%, respectively, and at the upper pole 1.1% and 0.4%, respectively (Boon et al, 2001). Additional visceral relations to the kidney include the adrenal glands (medial to the upper pole of both kidneys), the duodenum and gallbladder (anterior and medial to the right kidney), and the tail of the pancreas (anterior and medial to the left kidney). These structures can be injured with a misdirected or excessively deep puncture.

Renal Parenchyma and Collecting System

The renal parenchyma is composed of cortical and medullary tissue. The renal cortex is the outermost layer. It contains the glomeruli and proximal and distal convoluted tubules. The more interior medulla contains the renal pyramids. These are inverted cones (the base of which is superficial and the apex is deep) that

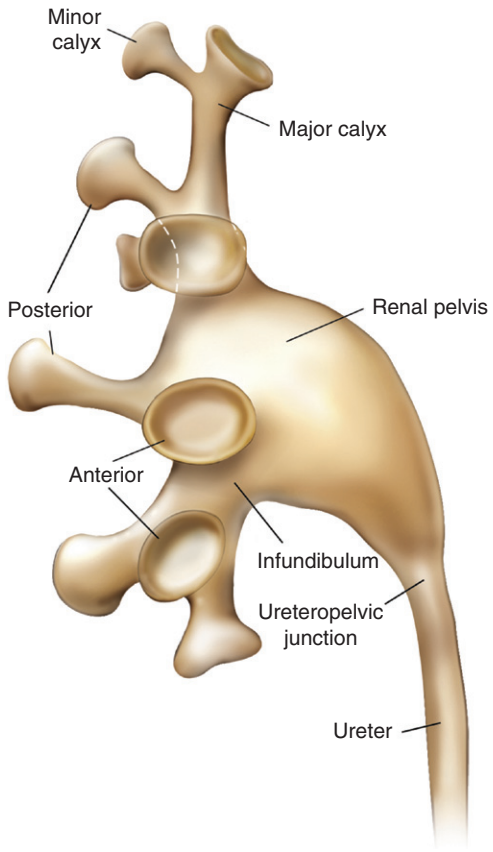


Figure 47–4. Upper urinary tract collecting system.

comprise the loops of Henle and the collecting ducts, which coalesce at the apex of the pyramid into papillary ducts that open on the surface of the renal papillae. There are approximately 20 papillary ducts draining into each papilla. The columns of Bertin are invaginations of cortical tissue that surround the renal pyramids except at their apices.

The renal papillae drain into the minor calyces, which are the most peripheral portions of the intrarenal collecting system. If only one papilla drains into a minor calyx, it is described as a simple calyx. When there are two or more papillae entering the calyx, it is termed a *compound calyx*. The outermost wall of the calyx, into which the papilla is set, is the calyceal fornix. **There are 5 to 14 minor calyces in each kidney (mean of 8, with 70% of kidneys having 7 to 9 minor calyces)** (Sampaio and Mandarim-de-Lacerda, 1988). **There are three drainage zones: the upper pole, the middle region, and the lower pole. Compound calyces are the rule in the upper pole, are common in the lower pole, and are rare among the middle calyces.** The minor calyces, either directly or after coalescing into major calyces, drain by infundibula into the renal pelvis (Fig. 47–4). Occasionally a minor calyx will open directly into the renal pelvis without an intervening infundibulum. Some infundibula are unusually narrow, even if they drain adequately, and can present an obstacle to endoscopy, especially with the relatively large rigid nephroscope.

The compound calyces of the poles of the kidney are oriented facing their respective poles. The simple calyces usually come in pairs, one facing anteriorly and one facing posteriorly (Fig. 47–5). The upper pole calyceal system almost always contains at least one compound calyx, and in some cases this is the only calyx in the

system. Drainage of the upper pole into the renal pelvis is by a single midline infundibulum in the majority of kidneys. The lower pole system often contains a compound calyx as well. The calyceal drainage from the lower pole is via a single infundibulum in about half of kidneys and through a series of paired anterior and posterior calyces in approximately half of kidneys. With compound calyces rare in the middle calyceal system, the middle calyces are typically arranged in a series of paired anterior and posterior calyces. In about two thirds of kidneys, there are two major calyceal systems—an upper and lower one—and the middle calyces drain into either or both systems. In the other third of kidneys, the middle calyceal system is distinct from the upper and lower systems, either coalescing into a middle major calyx before emptying into the renal pelvis or with drainage of the middle minor calyces directly into the renal pelvis through short infundibula.

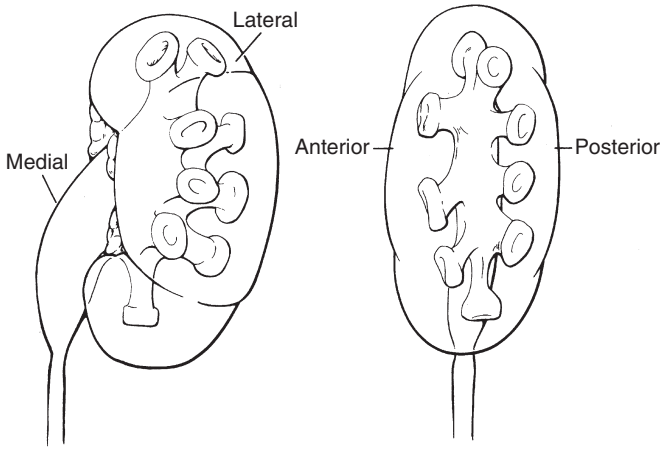


Figure 47–5. Calyceal orientation of polar and middle calyces. (From Smith AD, editor. Controversies in endourology. Philadelphia: WB Saunders; 1995.)

An important consideration for percutaneous renal surgery is determining the anterior-posterior orientation of the calyces because access (from the typical posterior or posterolateral approach) into a posterior calyx allows relatively straight entry into the rest of the kidney, whereas percutaneous puncture of an anterior calyx requires an acute angulation to enter the renal pelvis, which may not be possible with rigid instrumentation (Fig. 47–6). Efforts have been made to determine which calyces are likely to be anterior and which are likely to be posterior, solely on the basis of their medial-lateral position on anterior-posterior radiography. The distinction pertains to the middle and lower calyceal system, which contains (in almost all middle systems and approximately half of the lower system) paired anterior and posterior minor calyces. The upper pole system, with its almost uniformly compound calyceal system, is less problematic in this regard. Paired anterior and posterior calyces usually enter

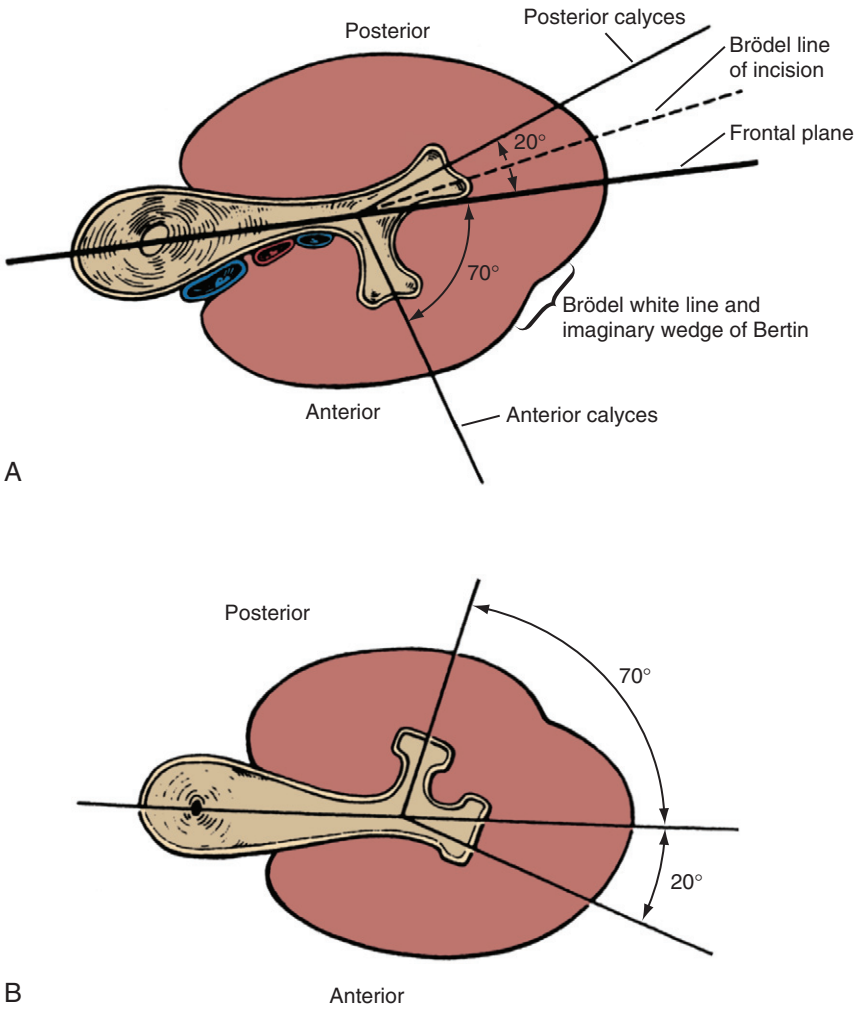


Figure 47–6. Relation of anterior and posterior calyces to renal parenchyma in Brödel-type kidney **(A)** and Hodson-type kidney **(B).** The optimal site of percutaneous entry from the posterior aspect of the kidney is into a posterior calyx because the path into the renal pelvis is fairly straight. If entry is into an anterior calyx (from the posterior aspect of the kidney) then an acute angulation must be made to enter the renal pelvis, which may not be possible with rigid instrumentation. (From Smith AD, editor. Controversies in endourology. Philadelphia: WB Saunders; 1995.)

about 90 degrees from each other. As such, the relative medial-lateral orientation (on anterior-posterior radiography) is determined by the relationship of this 90-degree unit to the frontal plane of the kidney. In a Brödel-type kidney this unit is rotated anteriorly, such that the posterior calyces are about 20 degrees behind the frontal plane and the anterior calyces are 70 degrees in front of the frontal plane. The posterior calyces are lateral, and the anterior calyces are medial in this case. The Hodson-type kidney is the opposite; the calyceal pairs are rotated posteriorly, with the posterior calyces 70 degrees behind the frontal plane and appearing medial and the anterior calyces 20 degrees in front of the frontal plane and appearing lateral (see Fig. 47–6). Most right kidneys have a Brödel-type orientation (posterior calyces are lateral), and most left kidneys have a Hodson-type orientation (posterior calyces are medial). **Because variation is considerable, the lateral-medial orientation of the calyces on antero-posterior radiography cannot be used to reliably determine the optimal calyx for entry and additional maneuvers are required to determine the exact calyceal anatomy.**

Intrarenal Vasculature

Although the renal arterial anatomy is variable, in general the main renal artery divides into an anterior and a posterior branch. The former then divides within or before the renal sinus into four anterior segmental arteries: the apical and lower segmental arteries (which supply the tip of the upper pole and the entire lower pole, respectively), and the upper and middle segmental arteries (which supply the remainder of the anterior half of the kidney). The posterior branch of the renal artery supplies the remainder of the posterior half of the kidney (Fig. 47–7). Once the anterior segmental arteries and the posterior branch of the renal artery enter the renal parenchyma, they divide into interlobar arteries, which are also called infundibular arteries owing to their course adjacent to the calyceal infundibula of the renal collecting system. At the cortico-medullary junction, near the base of the renal pyramids, each interlobar artery usually divides into two arcuate arteries that run along the renal pyramid. The next division is into the interlobular arteries, which run along the outer surface of the renal pyramids and are derived at right angles from the arcuate arteries. The final divisions, the afferent arterioles of the glomeruli, come off the interlobular arteries in the peripheral renal cortex. Each renal arteriole is an "end-artery," meaning that each cell in the kidney derives blood supply from one arteriole. For this reason renal arterial vascular injury must be avoided in order to prevent loss of renal function. The potential for arterial injury is least in Brödel's line, an avascular plane approximately at the lateral margin of the kidney, extending from the superior apex of the kidney (limited by the circulation of the apical anterior segmental artery) to the lower pole of the kidney (limited by the circulation of the lower anterior segmental artery). **Additionally, the safest place to percutaneously access the collecting system is directly into the calyceal fornix because this will avoid the interlobar (infundibular) arteries adjacent to the calyceal infundibula and the arcuate arteries that skirt the renal pyramid** (Sampaio et al, 1992).

The venous anatomy of the kidney does not have the same defined structure as the arteries. Moreover, there is free

Key Points: Anatomic Considerations

- Both the diaphragm and pleura can be violated during percutaneous entry into the upper pole of the kidney.
- The ascending and descending colon can be lateral or even posterior to the right and left kidneys, respectively. The apposition of the colon to the kidney varies with location; it is greatest on the left side and at the lower pole.
- An important consideration for percutaneous renal surgery is determining the anterior-posterior orientation of the calyces.
- The lateral-medial orientation of the calyces on antero-posterior radiography cannot be used to reliably determine the optimal calyx for entry.
- The safest place to percutaneously access the collecting system is directly into the calyceal fornix.

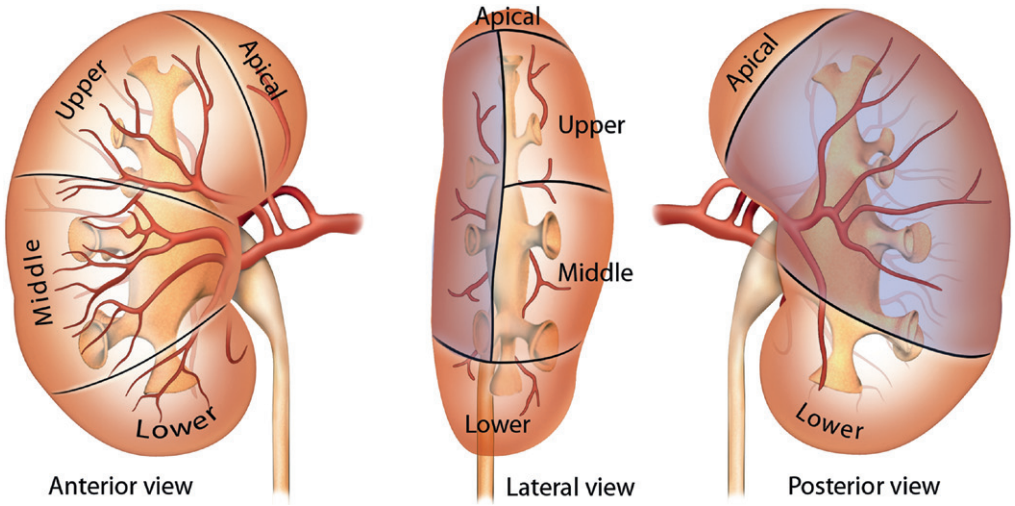


Figure 47–7. Arterial supply to the kidney. The kidney is supplied by the anterior and posterior branches of the main renal artery. The anterior branch supplies both the anterior half of the kidney and the polar regions via four segmental branches. The posterior branch of the renal artery supplies the posterior aspect of the kidney (represented by the shaded region). An avascular plane, known as Brödel line, separates the anterior and posterior circulations.

cross-circulation among the intrarenal veins via arcades. This enhances vascular outflow from the kidneys, reduces the risk of venous congestion, and makes renal venous injury less damaging to renal function than arterial injury.

OBTAINING PERCUTANEOUS ACCESS

Adequate percutaneous access to the upper urinary tract collecting system is a critical part of the percutaneous procedure. Over time more urologists are being trained to attain percutaneous access, but only a minority of urologists maintains this skill in practice (Bird et al, 2003; Lee et al, 2004a). Although there is some controversy regarding the success and complications associated with percutaneous access attained by urologists versus radiologists (Watterson et al, 2006; El-Assmy et al, 2007), the critical distinction in ensuring effective access for a subsequent percutaneous procedure is not who obtains access but rather that the access for urologic surgery is directed by a urologist. **The optimal situation is for the urologist to be present at the time access is attained, either performing the access procedure or actively directing the radiologist as to which calyx to enter and at what angle.** If that is not possible, then the urologist should discuss beforehand with the radiologist attaining access the pertinent considerations in that particular patient.

Periprocedural Antimicrobials

Prevention of infectious complications is a major consideration when considering percutaneous access into the upper urinary tract collecting system. **In an elective setting, confirmation that urine is sterile is optimal. In cases of anatomic abnormality, recent hospitalization, distant coexistent infection, recent catheterization, or other situations that suggest increased likelihood of bacteriuria, a urine culture is recommended. In the setting of an externalized catheter or staghorn renal calculus, bacteriuria is likely and a preoperative urine culture should be considered standard practice. In other cases a screening urinalysis may be adequate, with subsequent culture if the urinalysis is suspicious for infection.** When there is bacteriuria, a therapeutic course of culture-directed antimicrobials should be administered to sterilize the urine. Optimally, a repeat urine culture should be obtained to confirm urine sterility, although this might not be practical. In cases with colonized exogenous material such as an externalized urinary catheter or an infected calculus, it may not be possible to eradicate the infection before the percutaneous procedure. The goal then is to suppress the bacterial count before intervention.

The American Urological Association recommends periprocedural antimicrobial prophylaxis for all cases of percutaneous renal surgery (Wolf et al, 2008). Although there are no randomized, controlled trials to support this recommendation, nonrandomized data suggest a postprocedure urinary infection rate of 35% to 40% if antimicrobial prophylaxis is not used compared with 0% to 17% if prophylaxis is used (Charton et al, 1986; Darenkov et al, 1994). The need for antimicrobial coverage for simple percutaneous drainage of the upper urinary tract collecting system is not certain.

Antimicrobial coverage should include organisms common to the urinary tract (*Escherichia coli, Proteus* sp., *Klebsiella* sp., *Enterococcus* sp.) and the skin (*Staphylococcus aureus, coagulase-negative Staphylococcus* sp., group A *Streptococcus* sp.). Recommended agents include first- and second-generation cephalosporins; aminoglycosides (or aztreonam in patients with renal insufficiency) plus either metronidazole or clindamycin; ampicillin/sulbactam; or a fluoroquinolone. When the antimicrobial is being administered only for prophylaxis (i.e., not treatment of known or presumed infection), the duration of treatment should be for 24 hours or less. A short (≤24 hours) course of antimicrobials at the time of nephrostomy tube removal also can be considered (Wolf et al, 2008).

Patient Positioning

The prone position was described by Goodwin and colleagues (1955) for percutaneous access to the upper urinary tract collecting system, and over time this position became standard. It has the advantage of presenting a large surface area (the patient's back) that provides many choices of access sites and a stable horizontal working surface. The posterior or posterolateral approach is the most direct one to the desirable posterior calyces and comes closest to approaching the kidney through Brödel's avascular line. Prone positioning does have some disadvantages, however. It is associated with a decrease in cardiac index (Hatada et al, 1991), and in cases where inadequate padding is provided it is associated with decreased pulmonary capacity, although if enough padded support ensures free abdominal and chest wall movement, then pulmonary capacity is greater in the prone compared with the supine position (Edgcombe et al, 2008). The anesthesiologist has poor access to the airway with the patient in the prone position. Prone positioning might not be possible in patients with morbid obesity and/or spinal concavity, and the prone position can be associated with neuromusculoskeletal complications such as nerve compression or stretch injury, ocular or facial injury, and rhabdomyolysis. Finally, the prone position requires that the surgeon stand, often holding instruments at a distance using outstretched arms, which leads to surgeon fatigue. To address these deficiencies, urologists have introduced supine and lateral decubitus positioning for percutaneous renal surgery.

Valdivia Uria and colleagues (1987) first reported the supine approach to percutaneous nephrostolithotomy, culminating in their 1998 review of 557 patients with percutaneous nephrostolithotomy performed in this position (Valdivia Uria et al, 1998). They reported few complications including no hydrothoraces or pneumothoraces, no colon injuries, and only a 0.5% rate of major hemorrhage (see later for further discussion of complications). Variations of this position include completely supine, supine with the ipsilateral side elevated, and supine combined with ipsilateral flank elevation and asymmetric lithotomy position (Falahatkar et al, 2008; Papatsoris et al, 2008; Scoffone et al, 2008; Zhou et al, 2008). In the prone position, with a posterior or posterolateral skin entry, the posterior calyces are the best to enter because they allow access to the renal pelvis and the rest of the kidney. In the supine position, the skin entry site is lateral or anterolateral so the best calyces to enter are often the anterior ones. The angle of the access sheath when doing a procedure such as percutaneous nephrostolithotomy in the supine position is angled toward horizontal (compared with vertical during percutaneous nephrostolithotomy in the prone position), which reduces the pressure in the collecting system and facilitates stone fragments washing out through the sheath. Supine positioning does not require repositioning after induction of anesthesia, and the urethra is more easily accessed than in the prone position. The supine position is a safer position with regard to neuromusculoskeletal complications. Finally, because the percutaneous entry is more lateral than during a prone

procedure, the instruments are closer to the surgeon, resulting in less physical strain on the surgeon and the opportunity to sit during the procedure.

There are some disadvantages to the supine position for percutaneous renal surgery, however. First, it is not familiar to most urologists because the prone position is used in most training programs. Second, the reduced pressure in the collecting system results in a lower volume and thus less room for visualization and manipulation. Third, upper pole calyceal access is more difficult in the supine compared with prone position. Finally, with optimal placement of pads and bolsters, the prone position may provide better ventilation than the supine position (Edgcombe et al, 2008).

A systematic review including literature through 2008, which included 9 studies of supine and 25 for prone percutaneous nephrolithotomy, found that for cases involving obese patients or staghorn calculi, prone percutaneous nephrolithotomy was associated with decreased operative time, similar rate of hemorrhage, and improved stone-free rate (de la Rosette et al, 2008b). In the only randomized study, however, operative time favored the supine position without differences in other parameters (Falahatkar et al, 2008).

Less commonly used for percutaneous renal surgery is the flank (lateral decubitus) position, which was first described by Kerbl and colleagues (1994). This position allows simultaneous access to the anterior and posterior aspects of the kidney and appears to be particularly useful for morbidly obese patients or those with spinal deformities in whom both supine and prone positioning are difficult (Gofrit et al, 2002; Basiri et al, 2008b; Karami et al, 2009).

Although the supine and flank positions offer some potential benefits, overall experience is limited and the only North American report is a single case (Kerbl et al, 1994). As such, the remainder of this chapter concerns access into a posterior calyx from a posterior or posterolateral direction with the patient in the prone position, which remains the standard.

The initial step in a percutaneous procedure is often cystoscopic retrograde placement of a ureteral catheter. This can be performed with the patient in prone position (using a flexible cystoscope) or in lithotomy with subsequent prone repositioning. In the "upside-down" bladder the bubble of air from initial introduction of the cystoscope often approximates the location of the ureteral orifices. Prone cystoscopy can be performed on a standard operating or fluoroscopy table but is simplified by the use of "spreader bars" on the foot of the table (also called a "split-leg table"). The legs are spread by abducting the legs with the knees straight. This provides better access to the external urethral meatus.

Careful placement of padding is important in the prone position (Fig. 47–8). Support the head with padding in a neutral position that allows access to the mouth. Make sure there is not undue pressure on the facial bones, nose, and ears. Place the ipsilateral arm above the head to get it out of the operative field, with the shoulder and elbow at right angles with the use of generous padding. Position the contralateral arm the same way, or leave it straight and tucked at the side. Rest the lateral aspects of the chest on rolled blankets or other bulky foam or gel bolsters to allow for chest and abdominal wall expansion. Alternatively, purpose-made pads and supports provide more assured patient positioning (Papatsoris et al, 2009). Provide support under the ankles to take pressure off the feet, and pad the knees and feet. Prepare the perineum and ipsilateral flank sterilely, and cover unsterile areas with drapes. Cover the flank with an adherent drape that incorporates a fluid collection pouch.

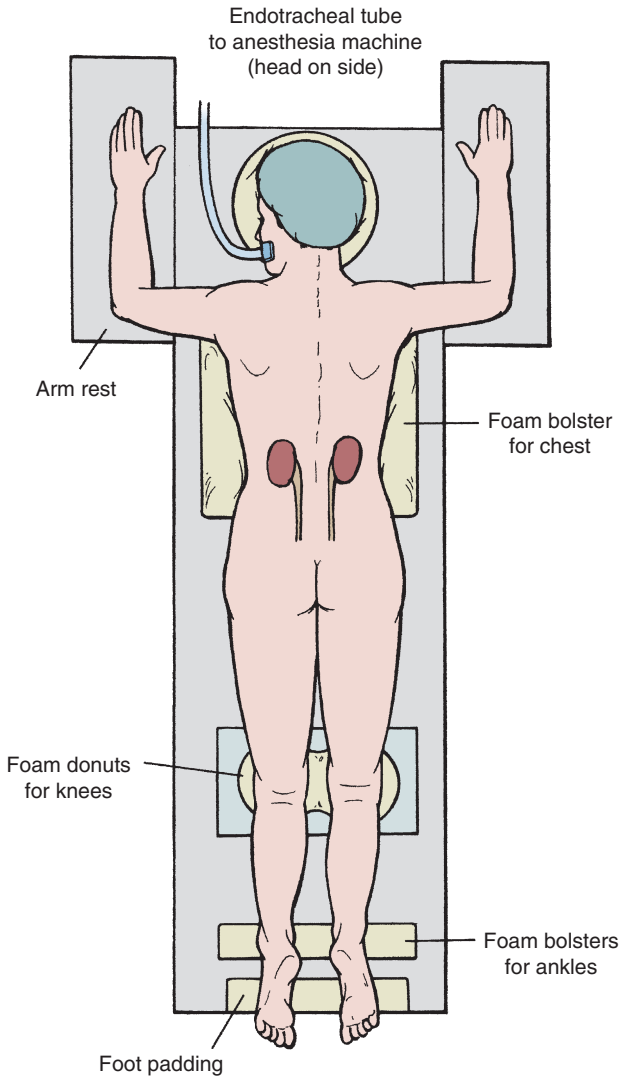


Figure 47–8. Padding for prone positioning.

Choice of Access Site to the Collecting System

The access site into the upper urinary tract collecting system is a critical determinant of the success of the subsequent procedure. **In the prone position, the preferred calyces are the posterior ones (or the posterior aspect of compound calyces), which allow better access to the remainder of the collecting system.** Usually, the anterior calyces can be approached through a posterior calyx. In cases that involve a calyceal diverticulum, narrow infundibulum, or pathology in an eccentric anterior calyx, direct puncture into an anterior location might be required. The ability to access the rest of the collecting system is limited with such access. **Percutaneous access should never be directly into an infundibulum or the renal pelvis, which greatly increases the risk of vascular injury** (Sampaio et al, 1992). The state of the renal parenchyma overlying the intended calyx of entry also must be considered because if it is thin, the tract into the collecting system may not close well after nephrostomy tube removal.

An upper pole calyx is generally the most versatile site through which to enter the upper urinary tract collecting system. The renal pelvis, lower pole calyces, and ureter usually can be entered with a rigid nephroscope from a well-placed upper pole access. Because of the posterior tilt of the upper pole of the kidney, the lower pole does not offer assured access to the upper pole. Access to the middle calyces will usually require a separate access or use of flexible instrumentation. Often, a middle calyx will offer adequate access to the ureteropelvic junction, as needed in cases such as endopyelotomy. In other cases, the calyx of entry should be selected on the basis of the distribution of the pathology to be treated. Efforts should be made to select a calyx that will allow treatment through a single site with rigid instrumentation. If this is impossible, then the site that will allow the largest portion of the pathology to be treated should be selected. The remaining pathology can be addressed with a second (and rarely a third or more) access or with flexible instrumentation through the initial access site.

Subcostal access is the safest route to the kidney because pleural injuries are rare with entry below the 12th rib. Nonetheless, if entry directly above the 12th rib (11th intercostal space) provides the best access to the optimal calyx, then the benefit generally exceeds the risk (Fig. 47–9). Entry above the 11th rib, however, has a greater potential for pleural and even lung injury, so when the best access calls for a direct puncture above the 11th rib, additional maneuvers should be considered to make access safer. A subcostal access sheath placed into a lower calyx can be tilted cephalad, displacing the kidney caudally to allow access to an upper pole calyx at a lower intercostal level (Karlin and Smith, 1989). Another alternative is to angle the access tract cephalad from a subcostal entry site (Liatsikos et al, 2005; Rehman et al, 2008). This approach provides limited access to the rest of the kidney. These alternatives can result in damage if the kidney is moved caudally with excessive force. Access above the 10th rib is associated with a high incidence of pleural violation and lung injury and should be avoided unless absolutely necessary. Thoracoscopically guided access superior to the 10th rib can be performed to reduce the risk of lung injury (Finelli and Honey, 2001).

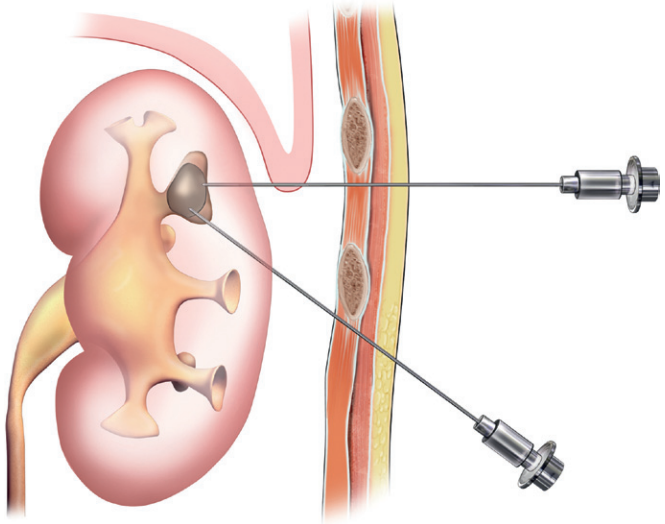


Figure 47–9. Subcostal and supracostal percutaneous access to an upper pole calyx. The supracostal approach provides more direct access and provides a better angle for endoscopy of the rest of the kidney.

Although standard preoperative ultrasonography or intravenous urography is sufficient in most cases for treatment planning, in complex cases cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) might be helpful. CT is a standard at many centers. For more accurate representation of the renal collecting system, three-dimensional imaging reconstructions are useful (Hubert et al, 1997; Buchholz, 2000; Ng et al, 2005; Thiruchelvam et al, 2005; Patel et al, 2009).

Retrograde Assistance for Access into the Collecting System

One of the advantages of urologist participation in obtaining the initial percutaneous access is the opportunity to provide retrograde transurethral assistance. This assistance can take many forms, from placing a ureteral catheter, to inserting a flexible ureteroscope, to obtaining the percutaneous access using a retrograde inserted device.

The simplest form of retrograde transurethral assistance is to place a 5- or 6-Fr straight ureteral catheter up into the renal pelvis (Fig. 47–10 on the Expert Consult website). Air and/or contrast material can be injected to delineate and dilate the intrarenal collecting system anatomy (Fig. 47–11 on the Expert Consult website), and a guidewire can be passed from below and grasped by the nephroscope to establish through-and-through access from the external urethral meatus to the percutaneous entry site. A dual-lumen catheter can be placed as well. The small caliber of either catheter, however, does not provide much outflow from the kidney and may not prevent stone or tumor fragments from passing into the ureter along the catheter. A ureteral occlusion balloon catheter, which incorporates an approximately 15-Fr spherical balloon on the distal tip, more consistently prevents material from migrating down the ureter. The balloon should be carefully inflated in the renal pelvis, making sure the balloon is not in the ureter—which could lead to ureteral rupture—and then gently pull down to occlude the ureteropelvic junction (Fig. 47–12). Another alternative is to place a ureteral access sheath (usually 11 to 15 Fr) over a retrograde-inserted guidewire (Landman et al, 2003). The large outer diameter of the sheath effectively prevents particles from passing around the sheath into the ureter, and the large inner diameter affords excellent outflow of small stone particles. The disadvantages of employing a ureteral access sheath include the potential ureteral trauma from passing such a large device into the ureter and clogging of the catheter lumen by oversized stone fragments.

A ureteroscope passed retrograde can greatly facilitate percutaneous entry into the intrarenal collecting system (Grasso et al, 1995; Kidd and Conlin, 2003; Patel et al, 2008) by allowing the surgeon to observe and correct the percutaneous placement of a needle. A basket can then be passed through the ureteroscope to grasp the end of the percutaneous guidewire; pulling this out the urethra provides through-and-through access (Fig. 47–13). Even if the pathology being addressed is so large that direct visualization of the percutaneous needle is obscured (e.g., complete staghorn calculus), the ureteroscope can still be used to rapidly attain through-and-through access. Moreover, the ureteroscope may have better access to some sites in the kidney than the nephroscope and can be used to assist in the procedure (e.g., fragment or relocate stones, fulgurate small tumors).

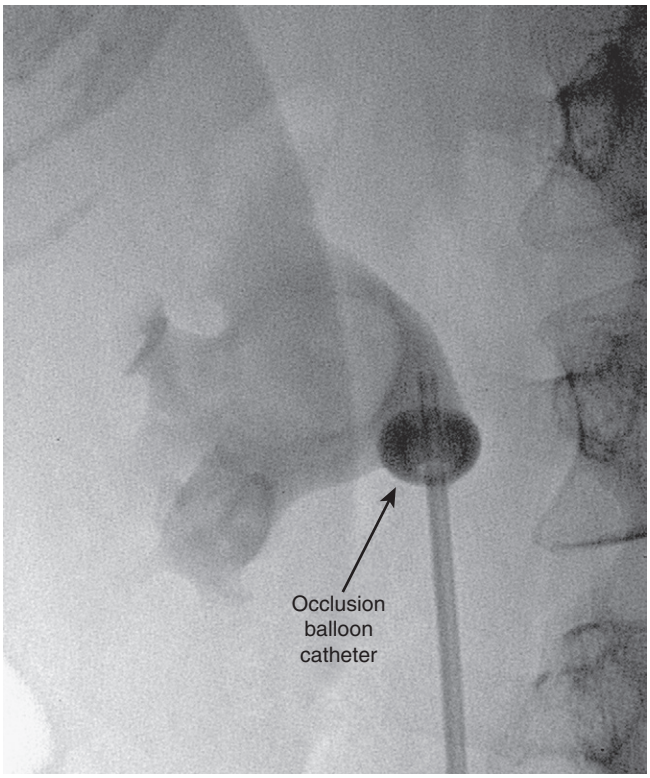


Figure 47–12. Occlusion balloon inflated and snugged down at ureteropelvic junction of contrast-filled upper tract collecting system.

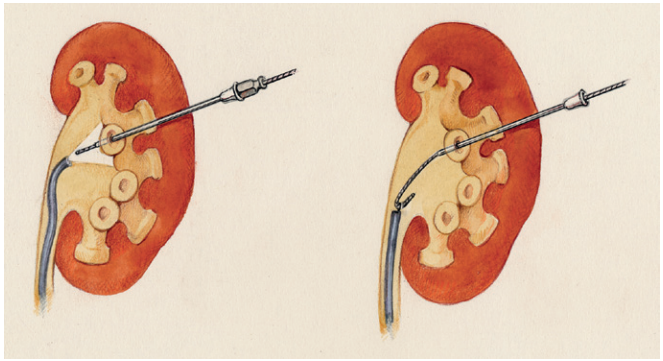


Figure 47–13. Ureteroscope retrograde assistance. The needle can be directly visualized entering the calyx, and a wire can be grasped and pulled down the ureter and out the urethra.

The "ultimate" retrograde assistance to percutaneous access into the upper urinary tract collecting system is the retrograde approach to percutaneous access. Although the antegrade approach is much more commonly performed, a retrograde approach may be selected when the surgeon has limited experience with antegrade percutaneous renal puncture or in situations in which there might be a technical advantage to the retrograde approach such as morbid obesity or a hypermobile or abnormally situated kidney (Mokulis and Peretsman, 1997). The Lawson Retrograde Nephrostomy Wire Puncture Set (Cook Urological; Spencer, IN) is the device commercially available for this use. After retrograde placement of a guidewire into the renal pelvis, pass the 7-Fr Torcon catheter—which is actively deflectable from 0 to 140 degrees (Fig. 47–14A)—over the guidewire and into the desired calyx. Insert the 3-Fr

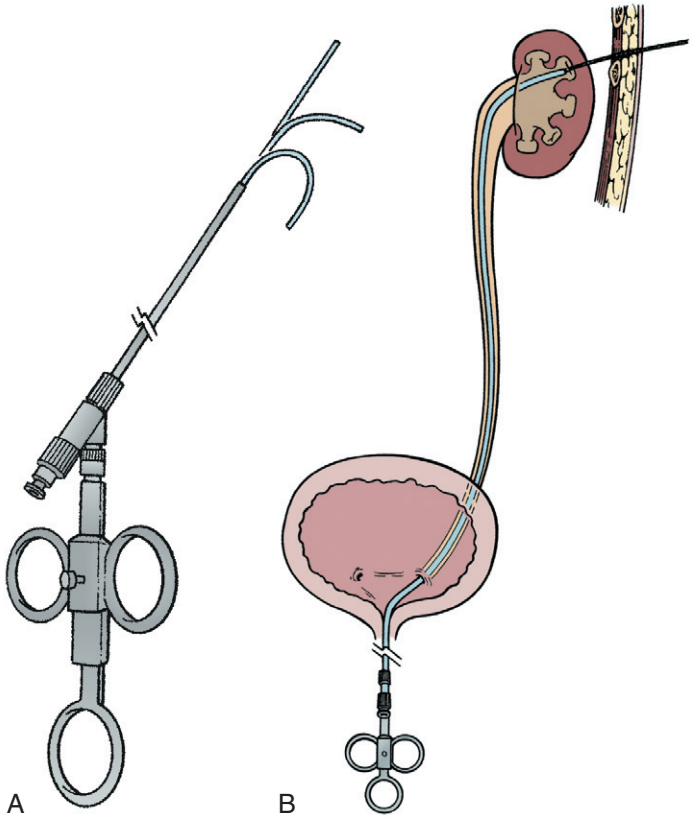


Figure 47–14. Retrograde percutaneous access. **A,** Torcon deflectable catheter. **B,** Assembled unit passing puncture needle out through the abdominal wall and skin.

polytetrafluoroethylene (PTFE) sheath containing the 0.017-inch stainless steel puncture wire through the Torcon catheter. Advance the puncture wire through the kidney and body wall under fluoroscopic control, withdrawing and repositioning it if any obstacles such as a rib are encountered (Fig. 47–14B). Make a small skin incision and grasp the wire externally. Use the fascial dilators in an antegrade fashion until the Torcon catheter can be advanced through the tract. Once the end of the catheter exits the skin, exchange the puncture wire for a standard 0.035 inch guidewire, thus attaining through-and-through access.

Antegrade Approach to Access into the Collecting System: Needles and Guidewires

The antegrade approach to percutaneous access into the upper urinary tract collecting system is the standard. It affords the most control of the skin entry site and can be guided by ureteroscopy or a variety of imaging modalities.

The general scheme of antegrade access is to place a needle through the skin into the upper urinary tract collecting system. Through the needle a guidewire is placed and then over the guidewire are placed catheters and other devices, eventually enlarging the tract until the desired lumen is reached for the purpose of the procedure. This is the Seldinger technique, described (for vascular access) by Sven-Ivar Seldinger (1953). The standard choices for the needle are a 21-gauge needle through which is passed a 0.018-inch

guidewire or an 18-gauge needle through which is passed a standard 0.035-inch guidewire. Both needles have a blunt sheath and a sharp obturator (Fig. 47–15). The 21-gauge needle has the advantage of causing relatively minor injury as it is passed through tissue. Multiple passes can generally be made with little risk of hemorrhage from the needle itself; the option to place and replace the needle multiple times is advantageous because getting the tip of the needle into the right spot in the kidney is the most difficult aspect of percutaneous access into the upper urinary tract collecting system. The 18-gauge needle is more traumatic, and multiple passes should be avoided. The advantage of the 18-gauge needle is that it is stiffer. In a number of circumstances the 21-gauge needle does not maintain trajectory adequately (e.g., scarred kidney, obese patient) and the 18-gauge needle is more effective. In addition, the 0.018-inch guidewire that passes through the 21-gauge needle (Fig. 47–16) must be exchanged for a standard 0.035-inch guidewire for subsequent tract dilation or catheter placement. This requires an extra step, which adds to the complexity of the procedure and increases the risk of loss of access.

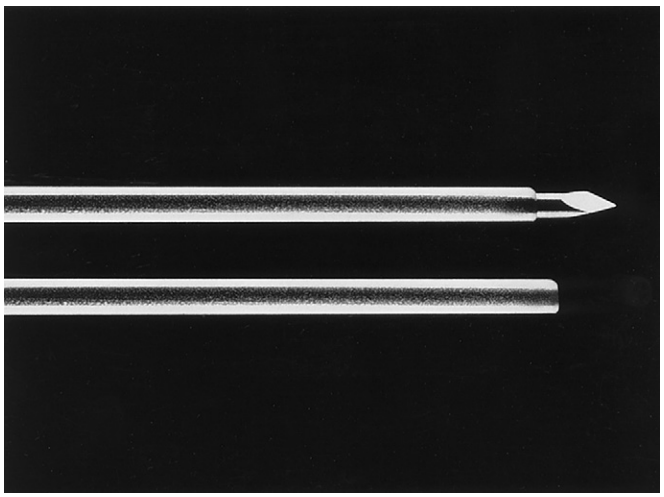


Figure 47–15. Percutaneous access needle, with a blunt sheath and a sharp obturator.

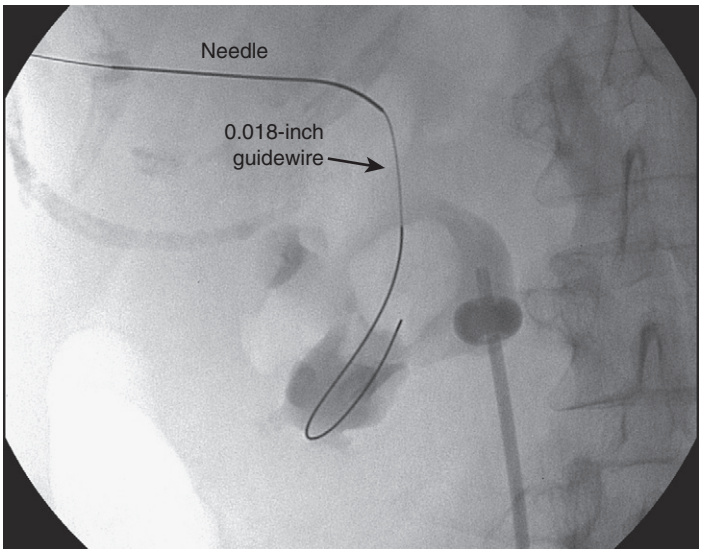


Figure 47–16. 0.018-inch guidewire passed through percutaneous needle. This wire is exchanged for a 0.035-inch guidewire for subsequent manipulation.

Balancing the reduced efficacy of the 21-gauge needle and its increased potential for loss of access, versus the increased risk of trauma with the 18-gauge needle, it is recommend that the 21-gauge needle be used when the operator is less experienced or if minimizing trauma is paramount. The 18-gauge needle should be used when an experienced operator is confident that the tip of the needle can be placed within the desired calyx with just a few attempts.

Two methods can be used to exchange the 0.018-inch for a 0.035-inch guidewire. A coaxial introducer incorporates a small catheter within a slightly larger catheter. After inserting the 0.018-inch guidewire and removing the needle, the coaxial introducer is advanced over the guidewire until the end is within the renal collecting system. The surgeon should remove the inner catheter and 0.018-inch guidewire and then advance a 0.035-inch guidewire through the outer catheter into the collecting system. The second method is the use of a graduated introducer, which fits over the 0.018-inch guidewire at its tip but then enlarges to a lumen that will accept the 0.035-inch guidewire. A few centimeters back from the tip there is a hole through which the 0.035-inch guidewire can pass. After inserting the 0.018-inch guidewire and removing the needle, pass the graduated introducer over the guidewire until it is a few centimeters inside the kidney, such that the side hole is within the renal collecting system. Remove the 0.018-inch guidewire and then insert an angled or J-tipped 0.035-inch guidewire through the introducer until the end of the wire exits the catheter within the collecting system. With either the coaxial or graduated introducer, a stiffener can be used to assist in passing the device over the relatively insecure 0.018-inch guidewire.

The safest initial 0.035-inch guidewire to use for upper urinary tract percutaneous access is a PTFE-coated J-wire. The "J" tip makes the guidewire unlikely to perforate out of the collecting system. This guidewire will not easily pass down the ureter, however, which is more easily done with a floppy tip PTFE-coated guidewire or a hydrophilic guidewire with a straight or angled tip.

Antegrade Approach to Access into the Collecting System: Technique of Initial Access

The initial percutaneous access to the upper urinary tract collecting system described by Goodwin and colleagues (1955) was "blind." In 1974 Pedersen first reported ultrasonographic guidance (Pedersen, 1974). Although "blind" access is still occasionally reported and in expert hands can be successful, in most cases the initial antegrade percutaneous access into the upper urinary tract collecting system is obtained with real-time imaging guidance. Ultrasonography and fluoroscopy are most commonly employed, with the choice based on patient characteristics and physician preference (Basiri et al, 2008a).

Ultrasonographic Guidance

Ultrasonography has the advantages of portability (the mobile ultrasound machine is easier to maneuver than a C-arm fluoroscopy unit and does not require a radiolucent operating table), the ability to rapidly evaluate different aspects of the kidney, and no delivery of ionizing radiation. In addition, retrograde injection of contrast material or air is not necessary because the collecting system can readily be distinguished within the kidney on the basis of ultrasonographic appearance alone. **The disadvantages of**

ultrasonography include less clear visualization of the percutaneous needle (although etched needles made for enhanced sonographic appearance are available), a limited field of view compared with fluoroscopy, and difficulty monitoring the subsequent steps of the procedure. Ultrasonography is the first choice in imaging when retrograde access cannot be attained or is difficult to attain, such as in kidneys above urinary diversions, transplanted kidneys, kidneys above a completely obstructed ureter, or when radiation exposure is a concern. Additionally, when percutaneous access is necessary for simple drainage of the kidney, such that the exact site of access is not critical as long as puncture into the renal pelvis or an infundibulum is avoided, ultrasonography is more expedient and convenient than fluoroscopy.

Using a hand-held 3.5- or 5-MHz ultrasound transducer, inspect the kidney and select a calyx for percutaneous entry. Needle guides can be placed on the transducer to direct the needle in the plane of visualization of the probe. Some prefer to place the needle freehand instead, moving the transducer around to gain different views of the kidney and needle. Observe the needle as it is advanced until it appears that the tip is within the collecting system (Fig. 47–17). Removing the obturator and aspirating urine confirms entry.

Fluoroscopic Guidance

Fluoroscopic guidance is more commonly employed for gaining antegrade access to the upper urinary tract collecting system for percutaneous renal surgery. **Although retrograde instillation of air and/or contrast material is not absolutely essential** (Tabibi et al, 2007), **most urologists find that it enhances fluoroscopically guided percutaneous access** (Fig. 47–18). **Fluoroscopy provides excellent delineation of the intrarenal collecting system anatomy and pathology, a wide field of view (that can be collimated down to reduce radiation exposure), and the ability to monitor all steps of the procedure. In some cases combining the techniques is an excellent approach, using ultrasonography to guide the initial needle placement and then using fluoroscopy (after injection of air and contrast through the sonographically guided needle) to confirm that the desired calyx has been accessed and to monitor the subsequent steps of the procedure** (Osman et al, 2005). If the entry site is incorrect, then fluoroscopy of the air-and-contrast filled collecting system can be used to guide another needle into the desired calyx. With this combination, retrograde assistance is not necessary. This technique is especially useful in accessing nondilated systems without retrograde assistance (Patel and Hussain, 2004).

There are two well-described methods of fluoroscopic guidance for antegrade percutaneous access into the upper urinary tract collecting system: the "eye-of-the-needle" technique and the "triangulation" technique (Miller et al, 2007). Both have their proponents, and there is no clear advantage of one over the other. Through the retrograde device, inject contrast material to delineate the collecting system after first taking note of any radiopaque pathology for later reference. Comparing a spot film of the unopacified collecting system with the opacified view is useful in this regard. Once the options for the calyces of entry are identified, inject air to define which calyces are posterior. In the prone position, air rises up the posterior calyces. The "double-contrast" pyelogram (both contrast material and air) provides the best determination of the pertinent intrarenal anatomy.

To perform the "eye-of-the-needle" technique, first inspect the kidney with the fluoroscopy unit directly above the patient (directed vertically) and select the desired calyx. Next, rotate the top of the fluoroscopic unit 30 degrees toward the operator, which brings the fluoroscopic view more or less end-on with the posterior calyces. The unit can be additionally rotated slightly cephalad or caudad to line it up more exactly with the axis of the calyx. Place the tip of a hemostat on the skin and move it until it is directly over the desired calyx. Mark this site and make an incision large enough to accept the needle and initial dilators. Place the tip of the access needle into this incision, and then move the shaft of the needle while keeping the tip in place until the needle is directly in line with the axis of the fluoroscopy unit; doing so gives the appearance of a "bull's eye" with the hub of the needle

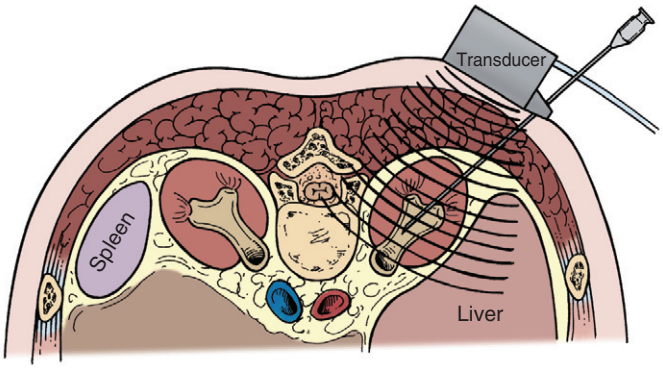


Figure 47–17. Ultrasonographic guidance of puncture needle.

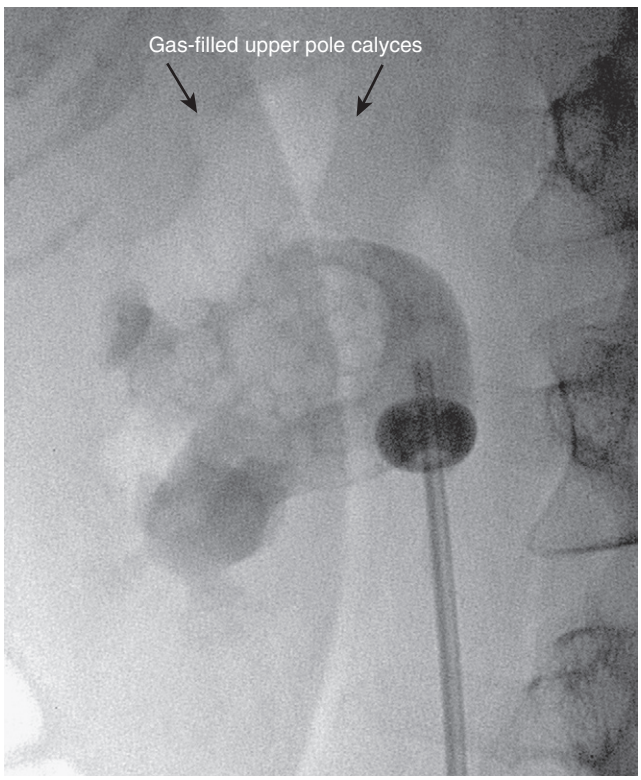


Figure 47–18. Injection of air into contrast-filled upper tract collecting system reveals posterior calyces, in this case most clearly the upper pole calyces. Compare with Figure 47–12, before injection of air.

(appearing as a circle) around the shaft (which appears as a dot). The fluoroscopic view is as if the operator is looking down the shaft of the needle at the targeted calyx—thus the term "eye of the needle" (Fig. 47–19A). Advance the needle straight in, while checking with fluoroscopy and adjusting the angle of the needle as needed to maintain the "bull's-eye" appearance. If the needle is more than a few centimeters deep and readjustment is necessary, the needle may have to be withdrawn before a new trajectory can be followed. The 21-gauge needle can be difficult to control during this step. If this occurs, substitute the more easily passed 18-gauge needle. Once the needle's axis is fixed and it is thought that the needle is approaching or is in the kidney (typically a "pop" can be felt when the renal capsule is punctured), then rotate the fluoroscopy unit away from the operator, back to vertical or even 10 to 15 degrees beyond vertical. Now the needle appears "in profile" as a straight line. With the cephalo-caudad and medial-lateral axes of the needle now fixed, advance or withdraw the needle to change its anterior-posterior position (depth) to get the tip of the needle into the desired calyx (Fig. 47–19B). Aspiration of urine or air after removing the obturator confirms entry. Instillation of contrast material can be used to confirm entry as well, but if the needle is misplaced, the extravasated contrast material can obscure subsequent fluoroscopic visualization. If a gently passed guidewire stays within the contours of the collecting system, then this confirms proper entry with risking troublesome extravasation of contrast material.

It should be remembered that the ionizing radiation presents a small but real risk. When the operator must grasp the access needle within the fluoroscopy field, it is best to hold the needle with a hemostat, sponge forceps, or purpose-built needle holder to reduce

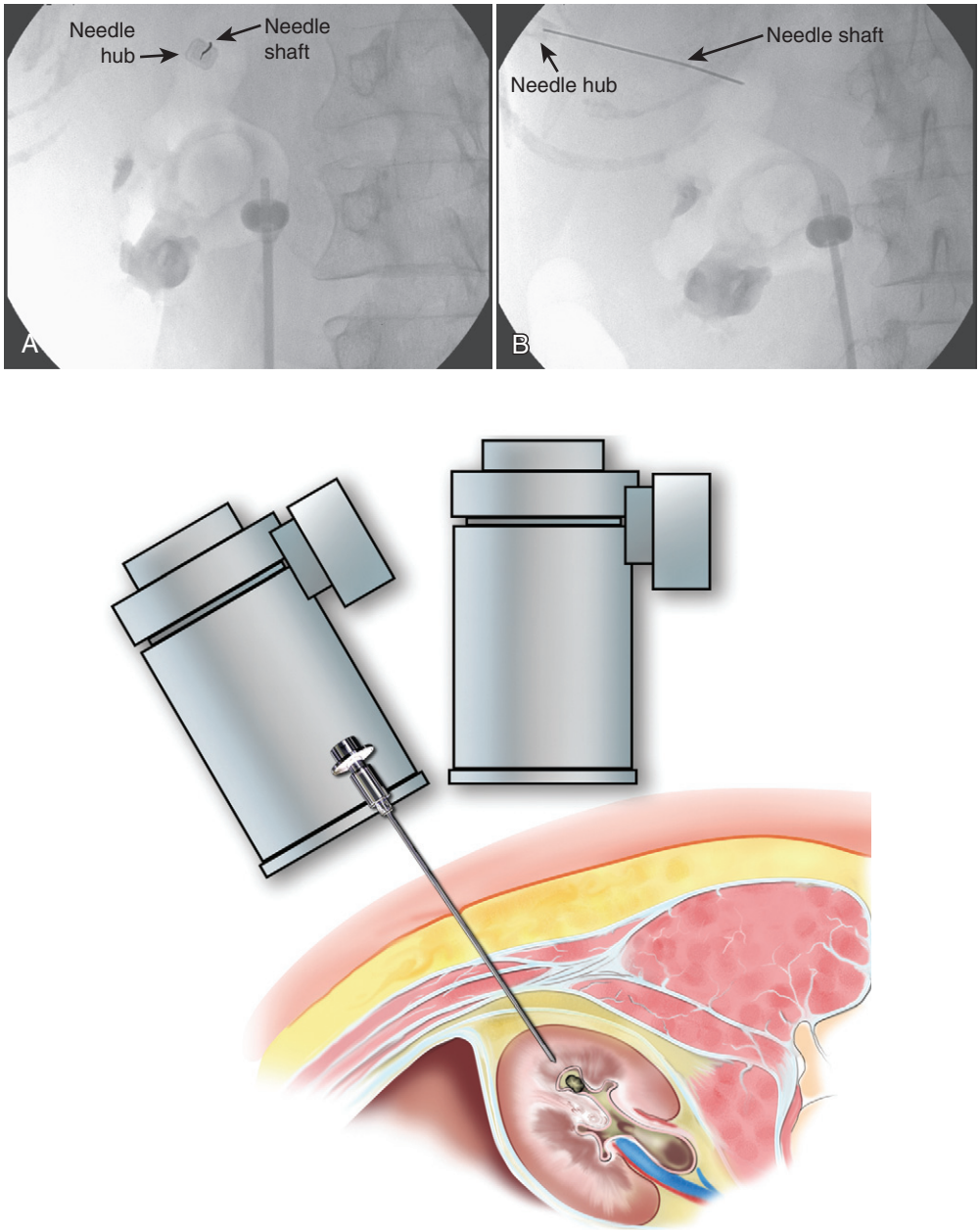


Figure 47–19. "Eye-of-the-needle" fluoroscopic guidance. **A,** With the top of the fluoroscopic unit rotated 30 degrees toward the operator, the needle is lined up directly over the intended calyx of entry. **B,** With the fluoroscopy unit rotated away from the operator, the needle is now seen in profile, and in the figure has already been advanced under fluoroscopic control to achieve collecting system entry.

radiation exposure to the operator's hand. Collimating the field down as much as possible while still maintaining an adequate field of view reduces radiation exposure to the patient and all personnel in the room. Moving a collimated field around to maintain the object of interest in the field is preferable to maintaining a wide field that includes the operator's hands and unnecessary body parts of the patient. For additional information about radiation safety, see Chapter 4.

To use the "triangulation" technique, inspect the kidney with the fluoroscopy unit directly above the patient to select the desired calyx and hold the needle in the approximate position of the desired angle of entry. Rotate the top of the fluoroscopy unit cephalad and lateral, and widen the field of view with the collimator such that medial-lateral (left-right) movements of the needle are apparent. Move the shaft of the needle while keeping its tip in place until the needle is aimed toward the desired calyx (Fig. 47–20A). Then rotate the top of the fluoroscopy unit medially 45 degrees. While keeping the medial-lateral orientation of the needle constant, move the needle in the cephalo-caudad (up-down) plane until the needle is again aimed toward the desired calyx (Fig. 47–20B). Resting the forearm on the patient's back will help stabilize the needle in one plane while moving in the other. Move the fluoroscopy unit back and forth between these two positions until the needle remains aimed at the desired calyx on both views. Advance the needle under fluoroscopic guidance while monitoring the anterior-posterior direction (depth) of the needle tip. If the needle position in the medial-lateral and cephalo-caudad planes is maintained, the needle should enter the targeted calyx.

With the "eye-of-the-needle" technique, the proper cephalo-caudad and medial-lateral axes of the needle are verified and maintained on a single fluoroscopic view and the confirmatory view is necessary only to confirm the depth of the needle tip. For the "triangulation" technique, one fluoroscopic view is used to assess the medial-lateral axis and another is used to assess the cephalo-caudad axis, with the depth of the needle tip being assessed on both views (Miller et al, 2007). The advantage of the triangulation technique over the "eye-of-the-needle" technique is that the needle cannot be passed too deeply because the depth of advancement is monitored continuously. The disadvantage of the "triangulation" technique is that maintaining both the medial-lateral and cephalo-caudad planes is difficult because both are not being monitored at the same time as in the "eye-of-the-needle" technique. Use of the 18-gauge rather than a 21-gauge needle is recommended with the "triangulation" technique to help maintain angle of entry.

Advanced Guidance

In some complex cases, percutaneous access into the kidney guided by CT or MRI might be considered. The initial access is obtained into the desired calyx with the patient on the CT or MRI table, similar to the techniques used for needle biopsy (Barbaric et al, 1997; Hagspiel et al, 1998; Thanos et al, 2006). Bowel and other viscera can be imaged to protect against their injury, and this approach is especially useful in cases of anatomic abnormalities (LeMaitre et al, 2000; Matlaga et al, 2003) and for nondilated collecting systems (Merkle et al, 1999; Egilmez et al, 2007).

Three-dimensional fluoroscopy has the potential to provide images with a level of quality equivalent to CT. This modality has proven useful in other disciplines such as orthopedic surgery (Kendoff et al, 2009). In a study of this technology applied to percutaneous access of porcine kidneys, it appeared to be effective (Soria et al, 2009), although simultaneous retrograde access and injection of contrast material was still helpful. Clinical application of three-dimensional fluoroscopy to percutaneous renal collecting system access has not yet been reported.

Three-dimensional ultrasonography accurately represents the renal collecting system (Ghani et al, 2008) and appears useful for renal imaging (Kim et al, 2008) and for teaching percutaneous access into an in vitro renal model (John et al, 2009). Given that three-dimensional ultrasonography has been applied to other therapeutic urologic applications (such as percutaneous drainage of prostatic abscesses) (Varkarakis et al, 2004), investigation of its use for clinical percutaneous access of the collecting system is anticipated.

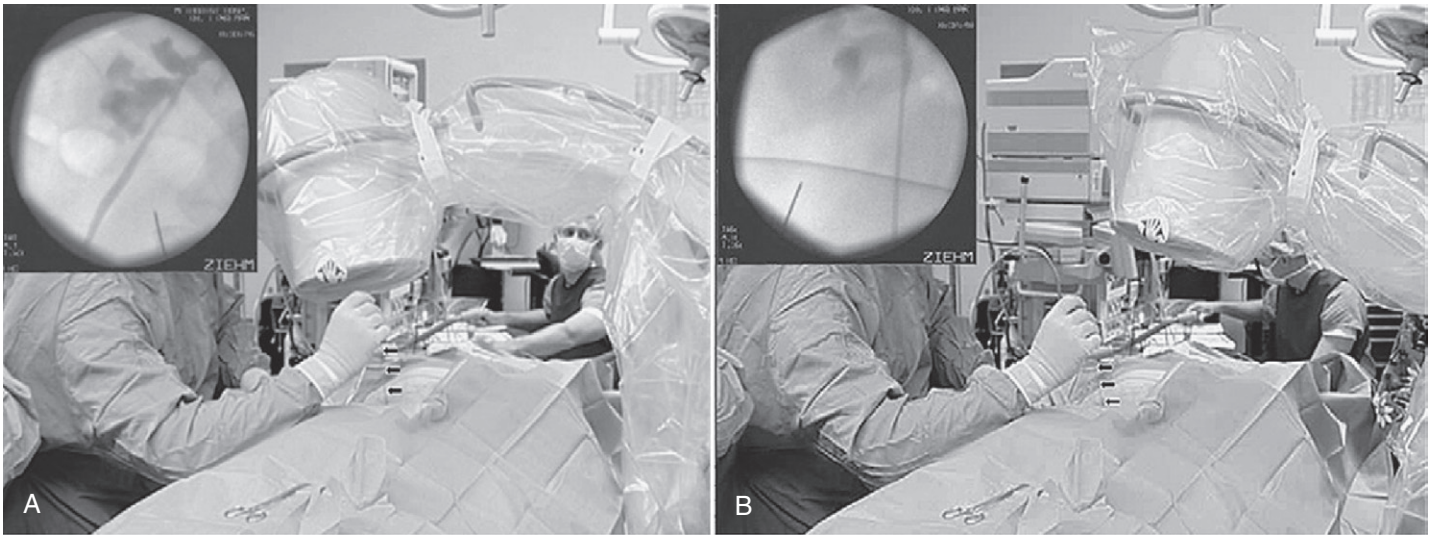


Figure 47–20. Triangulation fluoroscopic guidance. **A,** With the top of the fluoroscopy unit rotated laterally and cephalad, adjust the access needle *(arrows)* medial-lateral orientation of the needle. **B,** After rotating top of the fluoroscopy unit rotated medially, and while keeping medial-lateral orientation of the needle constant, move the needle in the cephalo-caudad plane until the needle is again aimed toward the desired calyx. (From Miller NL, Matlaga BR, Lingeman JE. Techniques for fluoroscopic percutaneous renal access. J Urol 2007;178:15–23.)

There has been one report of a novel image localization system that projects the ultrasonographic puncture tract onto the fluoroscopy screen, which incorporates some of the advantages of both modalities (Mozer et al, 2007).

In addition to advanced image guidance of percutaneous access to the intrarenal collecting system, technologic enhancements have been applied to the initial needle puncture. The Urorobotics Laboratory at Johns Hopkins University has developed the robotic percutaneous access to the kidney with remote center of motion device (PAKY-RCM) (Cadeddu et al, 1997b). This is a robotic arm with 7 degrees of freedom that places a needle into the intrarenal collecting system as directed by the control device that pivots the tip of the needle about a fixed point on the skin. In a nonrandomized clinical trial, the PAKY-RCM system was equivalent to an expert physician in gaining access to the collecting system in terms of time and accuracy (Su et al, 2002). In a randomized trial in an in vitro kidney model, the PAKY-RCM took slightly more time but was more accurate than manual needle insertion (Challacombe et al, 2005b). This device can also be controlled at distance with telepresence technology (Bove et al, 2003; Netto et al, 2003). A percutaneous access needle with an impedance-based sensing system to detect entry into the collecting system has also been developed, but clinical use has not been reported (Hernandez et al, 2001; Roberts et al, 2002).

"Blind" Access

The upper urinary tract collecting system can also be accessed "blindly," without any imaging guidance (Chien and Bellman, 2002). The only situation in which this should be considered is if sonography is not available and there is complete ureteral obstruction (precluding retrograde instillation of contrast material or opacification of the collecting system with intravenous contrast). The lumbar notch, also known as the *superior lumbar triangle* or *Grynfeltt lumbar triangle,* has been reported to be a reliable landmark for blind percutaneous renal access (Fig. 47–21). The lumbar notch is an area of muscular insufficiency through which hernias can occur. It is located posteriorly below the 12th rib. The superior border is the 12th rib and latissimus dorsi muscle, the lateral border is the transversus abdominis and external oblique muscles, the medial border is the quadratus lumborum and sacrospinalis muscles, and the inferior border is the internal oblique muscle. Insert a needle 3 to 4 cm deep into the notch at a 30-degree cephalad angle to enter the collecting system. Another blind approach to the collecting system is to insert a needle directly perpendicular to the body surface 1 to 1.5 cm lateral to the L1 vertebral body, which will lead directly to the renal pelvis if anatomy is normal. If fluoroscopy is available, then air and contrast material can be injected through a blindly placed needle to fluoroscopically assess its position and guide another needle if needed. In the only randomized clinical trial comparing "blind" access to image-guided access, entry into the collecting system was successful in 50% and 90% of cases, respectively (Basiri et al, 2007). Use of the technique is not recommended in most settings.

Working Access

Once good access to the collecting system is attained, exchange the initial guidewire through a catheter for a different one as needed. Dilate the tract over the guidewire with stiff plastic dilators or a metal fascial cutter to enlarge the tract to 8 to 12 Fr. If the goal of the procedure is simple drainage, then a small-caliber nephrostomy tube can be placed over the single guidewire to complete the procedure.

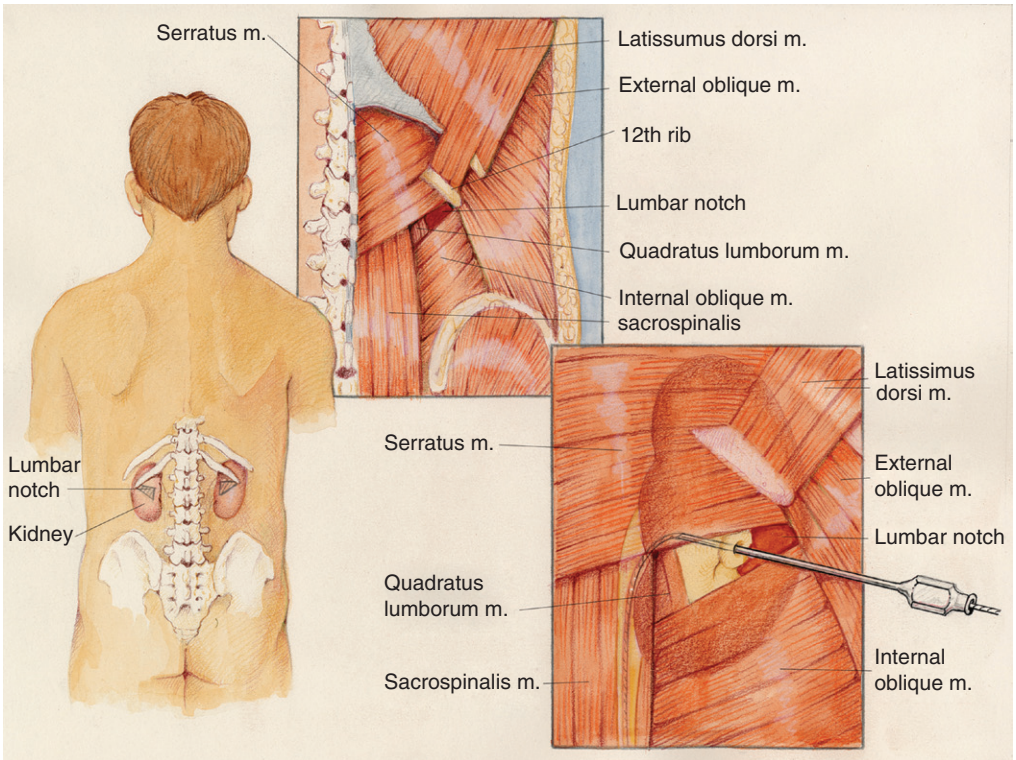


Figure 47–21. The lumbar notch is a useful anatomic landmark for blind percutaneous access to the renal collecting system. It is bounded superiorly by the latissimus dorsi muscle and the 12th rib, medially by the sacrospinalis and quadratus lumborum muscles, laterally by the transversus abdominis and external oblique muscles, and inferiorly by the internal oblique muscle.

Safety Wire

If ureteroscopic assistance is used, the first guidewire inserted into the kidney can be grasped with the ureteroscope and pulled down the ureter and out the external urethral meatus. With this through-and-through access, the guidewire cannot be lost. **In all other situations, the goal for a therapeutic percutaneous procedure is to get two guidewires down the ureter into the bladder, generally a super-stiff (working) guidewire and a floppy tip or J-tipped PTFE-coated (safety) guidewire.** One important exception is in cases in which a dependent lower pole has been accessed percutaneously. If there is extreme angulation to get from the lower pole calyx to the ureteropelvic junction and down the ureter, placing a super-stiff guidewire down the ureter may put undue force on the kidney and risk tearing parenchyma. In such cases, the flexible safety guidewire should still be directed down the ureter if possible, but the stiff working wire over which the dilation is performed can simply be directed toward the upper pole. Additionally, in some cases the pathology (e.g., calyceal obstruction, impacted ureteral stone, large staghorn stone) prevents the surgeon from getting a guidewire down the ureter or even into the remainder of the intrarenal collecting system. In such cases attempts should be made to get as much guidewire as possible into the upper urinary tract collecting system. A guidewire with a moveable core is useful in this setting because it can be coiled more tightly.

There are several techniques for getting a guidewire down the ureter. The safest maneuver is to place a stiff angled-tip hydrophilic guidewire adjacent to the initial stiff angled-tip hydrophilic guidewire using a coaxial or dual-lumen catheter. Remove the coaxial or dual-lumen catheter and place an angled tip catheter (Kumpe, Cobra, or coudé tip) over the angled-tip hydrophilic guidewire to help direct it down the ureter. Once the stiff angled-tip hydrophilic guidewire is down the ureter, optimally all the way into the bladder, use the coaxial or dual-lumen catheter to place a second guidewire down the ureter. In cases of secure access, the initial wire can be exchanged for a stiff angled-tip hydrophilic guidewire through an angled tip catheter to get down the ureter right away (Fig. 47–22); alternatively, the surgeon can use a stiff angled-tip hydrophilic guidewire as the initial wire.

Dilation of Tract

Once there is adequate wire access into the upper urinary tract collecting system, dilate the tract to allow insertion of working instruments. In most cases the goal of dilation for percutaneous renal surgery is to place a 30-Fr inner-diameter/34-Fr outer-diameter plastic access sheath. In some cases a smaller sheath, with an inner diameter measuring 12- to 24-Fr, is adequate. Renal access sheaths generally have a beveled tip, such that one side of the sheath extends farther than the other part. This bevel is used to maintain access into part of the collecting system on one side of the sheath while allowing extra mobility on the other side. Sheath repositioning is facilitated by the bevel. In cases of pathology at the edge of the collecting system, however, the bevel is a disadvantage because the entire tip of the sheath cannot be placed into the collecting system. Both opaque and clear sheaths are available; some prefer the clear sheaths because structures next to the sheath can be visualized.

In the early years of therapeutic percutaneous renal procedures, the tract was dilated gradually over the course of many days by placing sequentially larger tubes. Acute dilation of the tract was first reported by Castañeda-Zúñiga and associates in 1982 (Castañeda-Zúñiga et al, 1982). There are several dilator systems available. **Regardless of the method used, is it imperative that the dilator does not pass too far into the collecting system.** If this occurs, an infundibulum, the renal pelvis, or the ureteropelvic junction can be torn or perforated, either directly by the dilator or indirectly by a stone pushed aside by the dilator. The dilator should be passed just into the calyx. It is better to dilate a bit "short" of the targeted calyx than to dilate too far and create trauma. The initial inspection with the nephroscope confirms entry of the sheath into the calyx. If the sheath is not deep enough, then simply replace the dilating device and redilate after advancing the device. The dilators should not be used to dilate the skin; the skin should be incised to allow entry of the final sheath without pressure on the skin edges.

Rigid metal dilators, introduced by Alken (1985), are a series of progressively enlarging coaxial stainless steel rods that pass over an 8-Fr guide rod. The first step in tract dilation is to pass the 8-Fr guide rod over a 0.035-inch guidewire. The end of the guide rod

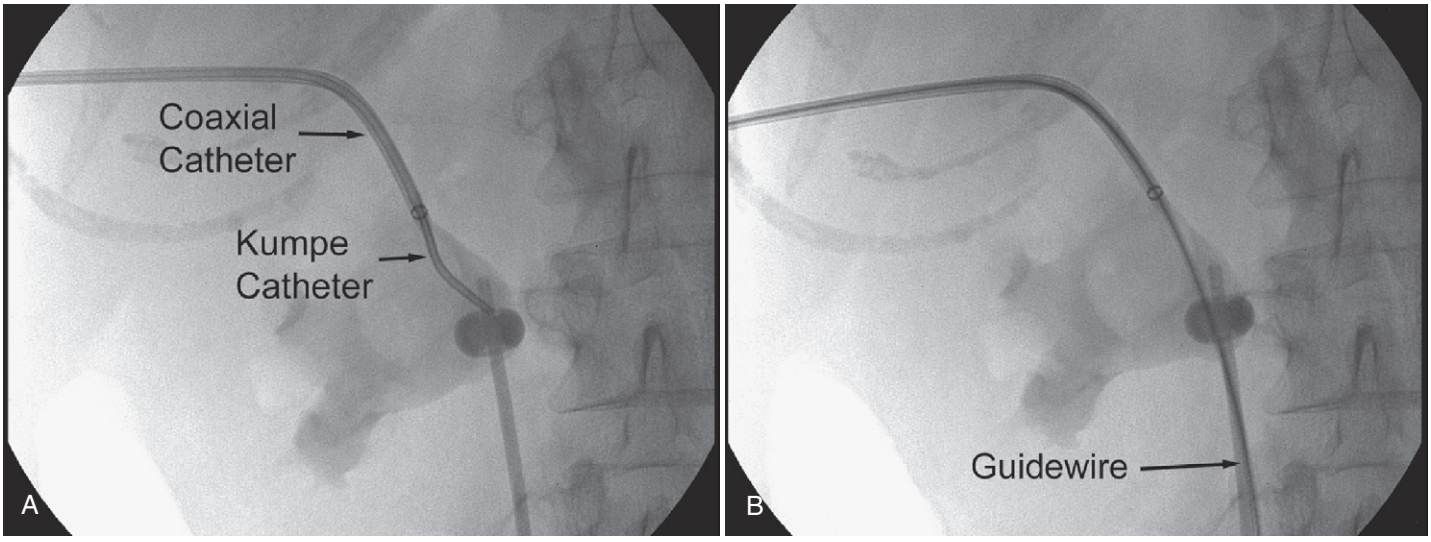


Figure 47–22. **A,** Kumpe catheter placed through the outer sheath of a coaxial catheter and manipulated toward the ureteropelvic junction helps direct a guidewire **(B)** down the ureter.

has a ball that prevents advancement of the first dilating rod beyond the tip. The ball is positioned at the intended depth of the dilation (Fig. 47–23). After passing the first rod, each successive metal rod is passed sequentially over the former until the desired tract is achieved, up to a 30-Fr rod over which is passed a 30/34-Fr plastic sheath. **The advantages of the rigid metal dilator system are that it is the most effective dilator, able to dilate even when there is dense perirenal scarring from prior procedures, and that is it inexpensive on a per-case basis because it is reusable. The disadvantage is that, for the same reason they are so effective, the rigid metal dilators can do considerable damage.** The depth of the dilation can be hard to maintain accurately, especially when pushing hard against tough scar tissue. One group has modified the rigid metal rods, tapering the ends and adding centimeter markings (Shen et al, 2007).

Semirigid plastic dilation sets (often referred to as "Amplatz" dilators, after Kurt Amplatz, the senior author in the initial publication [Rusnak et al, 1982]) consist of progressively larger firm plastic (polyurethane) dilators that are passed over an 8-Fr PTFE guiding catheter that fits over a 0.035-inch guidewire (Fig. 47–24). The dilators are passed one after the other, not coaxially like the rigid metal dilators but progressively, advancing one dilator, removing it, advancing the next largest dilator, and so on until the final tract diameter is achieved. The working sheath is passed over the final dilator and then the dilator and 8-Fr catheter are removed, leaving the working wire and sheath in place. The dilators are made in increments of 2 Fr, but if the tissue being dilated is soft, then not every dilator needs to be used. **The advantages of the semirigid plastic dilation system are that trauma to the collecting system is theoretically less likely than with the rigid metal dilators (although experienced urologists have found no difference between the two systems in terms of safety), but the disadvantage is that hemorrhage can occur each time a dilator is withdrawn.** Current semirigid plastic dilators are sold as disposable devices, so they are more expensive on a per-case basis than rigid metal dilators.

Balloon dilators (Fig. 47–25) were developed to obviate the repetitive dilations of the rigid metal and semirigid plastic dilation systems, which are both time consuming and potentially dangerous. This is the most common dilation method for percutaneous renal surgery today (Benway and Nakada, 2008). The appropriate working sheath is back-loaded onto the balloon dilation catheter, which is passed over the working wire until the radiopaque marker is at the intended depth of dilation (Fig. 47–26). The dilating balloon is inflated with a pressure syringe. A "waist" appears at the site(s) of greatest resistance, usually the abdominal wall fascia and the renal capsule (Fig. 47–26B). Once the balloon is fully expanded (Fig. 47–26C), the working sheath is passed over the balloon (Fig. 47–26D) (Fig. 47–27 on the Expert Consult website). The balloon catheter has a "shoulder," which is the portion between the end of the balloon and the point at which the maximal diameter is achieved. The sheath should not be passed beyond the maximal diameter of the balloon because this can cause significant injury. **Balloon dilators, which are expensive one-time use devices, are less effective than rigid metal and semirigid plastic dilation systems in densely scarred tissue but are more effective when the kidney is hypermobile** (Kumar and Keeley, 2008). **Most** (Heggagi et al, 1991; Davidoff and Bellman, 1997; Safak et al, 2003; Kukreja et al, 2004), **but not all** (Gonen et al, 2008a), **studies have**

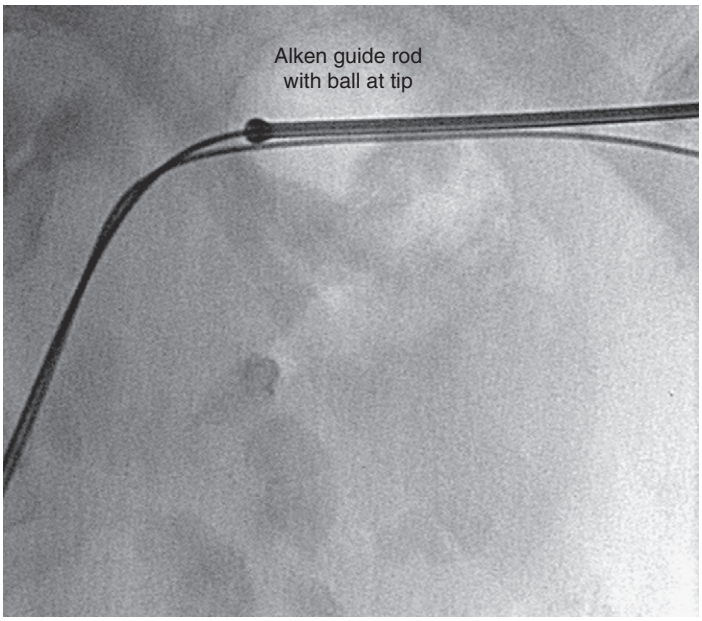


Figure 47–23. Alken guide rod is positioned with the ball at the tip of the rod positioned at the intended depth of the dilation.

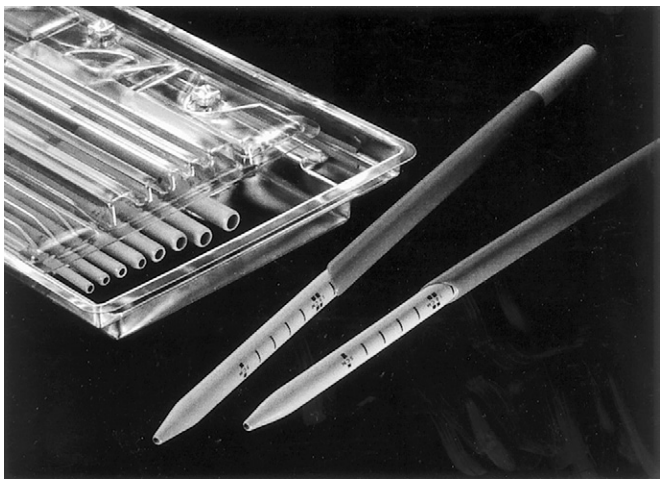


Figure 47–24. Amplatz dilators with sheaths.

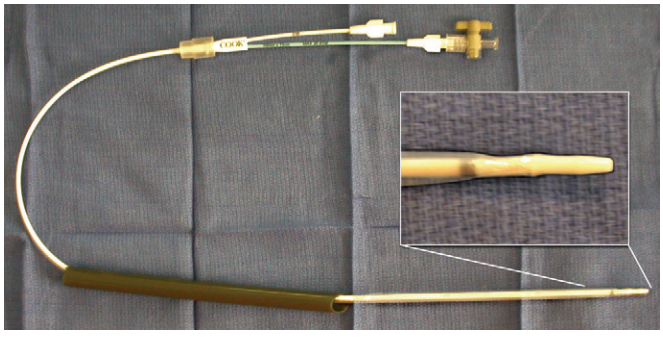


Figure 47–25. Balloon dilation catheter with preloaded sheath.

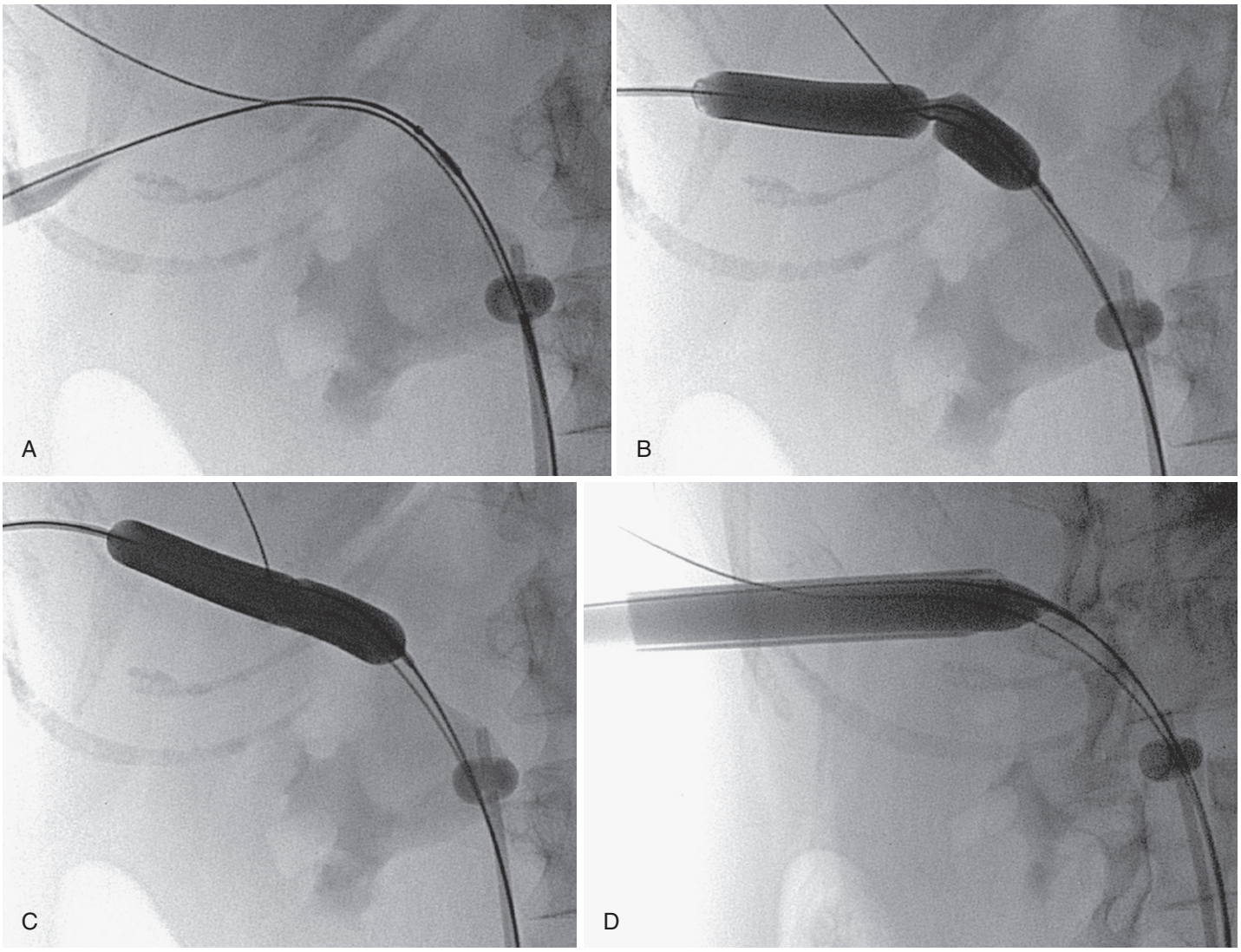


Figure 47–26. Balloon dilation of tract and placement of working sheath. **A,** Balloon catheter is inserted over wire, with distal radiopaque marker is at the intended depth of dilation. **B,** "Waist" appears as balloon is inflated. **C,** Balloon is fully expanded. **D,** Sheath is passed over balloon, taking care not to advance it beyond the point of maximal diameter of the balloon.

suggested that hemorrhage and transfusion rates are less with the balloon dilators compared with rigid metal and semirigid plastic dilators.

In an effort to further simplify dilation of the renal access tract, a number of single-step techniques have been described. The simplest is passage of the final semirigid plastic dilator without prior dilation by the smaller dilators (Frattini et al, 2001). This technique is reported to work well in comparison with other methods, even in patients with prior renal surgery, but the forward force that needs to be applied is appreciable (Ziaee et al, 2007; Amjadi et al, 2008; Falahatkar et al, 2009). Devices designed specifically for single-step dilation include a balloon dilator with an expandable sheath (Pathak and Bellman, 2005; Baldwin et al, 2006; Maynes et al, 2008) and a rigid dilator with an expandable sheath (Goharderakhshan et al, 2001). Preliminary results with these devices appear favorable.

The most common cause of difficult tract dilation is prior renal surgery (Joel et al, 2005). Densely scarred kidneys present a challenge. If even semirigid plastic or rigid metal dilators fail, novel uses of devices such as Collings knives and atherotomy cutting balloons can be employed (Davis et al, 1991; Williams et al, 2008).

Modifications in Special Situations

In cases of anomalous kidneys (malrotated, ptotic, ectopic, horseshoe, and other fused kidneys), alteration of the percutaneous approach to the upper urinary tract collecting system may be necessary. As noted earlier, in some situations real-time guidance of the needle puncture with CT or MRI might be considered, but in most cases preoperative CT or magnetic resonance suffices. Because the orientation of some organs might change with patient position, imaging in the intended position of surgery might be useful. **Preoperative cross-sectional imaging of anomalous kidneys helps plan patient position, choice of calyx, and orientation of the tract, taking into account**

distance of the kidney from the skin, calyceal orientation, vasculature, and the relative orientation of adjacent organs.

Horseshoe kidneys frequently require percutaneous intervention. Although antegrade access into horseshoe kidneys is somewhat different than into normal kidneys, standard techniques can generally still be used. CT or MRI should be considered for preoperative assessment of horseshoe kidneys, both to assess for the possibility of retro-renal colon (Skoog et al, 1985) and to assess the vasculature and relationship of the calyces to the anticipated puncture site. In a series of 12 patients undergoing percutaneous nephrolithotomy in horseshoe kidneys, 5 had bowel posterior to the kidney on CT (Al-Otaibi and Hosking, 1999). Horseshoe kidneys often have extra and eccentric calyces that can be hard to access. In other ways, however, percutaneous access to a horseshoe kidney is more favorable than in normal kidneys. The antero-postero tilt of the kidney is prominent, which makes the upper pole the most superficial and posterior aspect of the horseshoe kidney. In addition, the upper pole is usually inferior to the ribs. **Upper pole access is useful in horseshoe kidneys because this is the easiest calyx to enter, the puncture rarely needs to be supra-costal, and it provides excellent access to most of the kidney and the ureter owing to the alignment of long axis of the moiety** (Fig. 47–28). The initial entry into a horseshoe kidney is more medial than in normal kidneys and can pass through the paraspinous musculature. The distance to the lower pole and ureter can be great in an obese or muscular patient, such that extra-long rigid nephroscopes or flexible nephroscopy may be necessary. In some cases, middle calyceal access is preferred because the upper pole is so far away from the pathology, but lower pole calyces are usually not safely accessible with direct percutaneous puncture. The vasculature of horseshoe kidneys is aberrant, but vessels enter and exit the kidney in an antero-medial location (except for some at the isthmus), so direct vessel injury is rare with well-planned access (Janetschek and Kunzel, 1988). Overall, among a total of 256 percutaneous procedures (primarily nephrolithotomy) recently reported in horseshoe kidneys, there were 11 (4.3%) major hemorrhagic complications and only 1 (<0.4%) colon injury (Al-Otaibi and Hosking, 1999; Shokeir et al, 2004; Lojanapiwat, 2005; Darabi Mahboub et al, 2007; Mosavi-Bahar et al, 2007; Viola et al, 2007; Majidpour and Yousefinejad, 2008; Miller et al, 2008; Symons et al, 2008; Gupta et al, 2009).

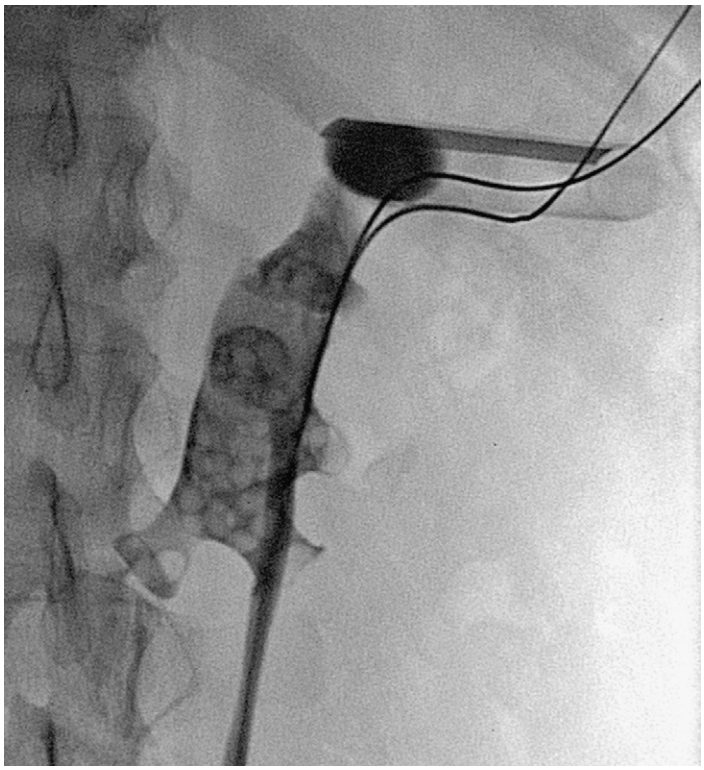


Figure 47–28. Percutaneous access sheath (radiolucent except for a radiopaque stripe) in upper pole of horseshoe kidney. Note medially directed lower pole calyx. Although not apparent from this radiograph, the access site is subcostal.

Another way to access anomalous kidneys is with an anterior approach using laparoscopic assistance. This is most applicable to pelvic ectopic kidneys because a posterior approach is often blocked by the bony pelvis, although laparoscopic assistance has been used for percutaneous nephrolithotomy of a large calculus in an anteriorly directed calyx in the isthmus of a horseshoe kidney (Maheshwari et al, 2004b) and a large calculus in an anterior diverticulum of a horseshoe kidney (Wong and Zimmerman, 2005). The bowels can be mobilized off of the surface of the kidney laparoscopically, and the access needle is passed through the anterior abdominal wall into the kidney under vision from the laparoscope. Retrograde assistance is still desirable because opacifying the collecting system assists in simultaneous fluoroscopic confirmation of calyceal entry and wire passage. Dilation and sheath insertion can be assessed both laparoscopically and fluoroscopically. In 10 series of laparoscopically directed antegrade percutaneous nephrolithotomy into pelvic kidneys published since 2001 that described a total of 33 patients, all procedures were reported to be successful and without complications (Troxel et al, 2002; Maheshwari et al, 2004a; Santos et al, 2004; Aron et al, 2005b; Aquil et al, 2006; Goel et al, 2006; Matlaga et al, 2006; El-Kappany et al, 2007; Mousavi-Bahar et al, 2008; Gupta et al, 2009). As a simpler alternative to laparoscopic assistance, anterior percutaneous access into pelvic kidneys using a supine oblique position with a pad under the ipsilateral hemipelvis, as well as using ultrasonography to assess for intervening bowel, has been reported to be a safe technique in selected patients (Desai and Jasani, 2000; Mosavi-Bahar et al, 2007). If bone does not intervene between the appropriate calyx and the skin, then a posterior approach can be used just above the iliac bone (Atmaca et al, 2007) or through the greater sciatic foramen (Watterson et al, 2001).

Transplanted kidneys also mandate changes in the approach to percutaneous access of the upper urinary tract. The transplanted kidney, typically positioned extraperitoneally in the iliac fossa, has variable angles of the calyces depending on the placement of the kidney by the transplant surgeon. The usual approach is from the antero-lateral direction, with the patient in the supine position. **Percutaneous nephrostomy is the preferred approach to obstruction and for endoscopy of the collecting system in the transplant kidney** (Mostafa et al, 2008). Ultrasonography is most convenient for initial access to the collecting system because retrograde assistance for fluoroscopy is difficult owing to the site and angle of the reimplanted ureter. Fluoroscopy can then be used as needed to facilitate subsequent steps. The dense fibrosis that often surrounds a transplant kidney can make dilation of the tract difficult, and semirigid plastic or rigid metal dilators may be necessary if balloon dilation fails. Of 42 percutaneous procedures in transplant kidneys reported in six recent series, using

Key Points: Obtaining Percutaneous Access

- Optimally, the urologist is present at the time percutaneous access is attained, either performing the procedure or actively directing the radiologist.
- If there is increased likelihood of bacteriuria, preprocedure urine culture is recommended. Periprocedural antimicrobial prophylaxis is recommended in all cases.
- Preoperative cross-sectional imaging of complex cases, especially anomalous kidneys, helps plan patient position, choice of calyx, and orientation of the tract.
- In the prone position, the preferred calyces are the posterior ones. Percutaneous access should never be directly into an infundibulum or the renal pelvis.
- An upper pole calyx is generally the most versatile site through which to enter the upper urinary tract collecting system.
- Subcostal access is the safest route to the kidney, but if entry directly above the 12th rib provides the best access to the optimal calyx, then the benefit generally exceeds the risk.
- Retrograde assistance facilitates antegrade access to the upper urinary tract collecting system.
- Ultrasonography and fluoroscopy are both commonly used to guide percutaneous access to the intrarenal collecting system. A useful combination is ultrasonography to guide the initial needle placement followed by fluoroscopy to confirm that the desired calyx has been accessed and to direct and monitor the subsequent steps of the procedure.

ultrasonographically directed percutaneous access with or without adjunctive fluoroscopy, all but one were technically successful and there were no complications (Francesca et al, 2002; Klingler et al, 2002; Challacombe et al, 2005a; He et al, 2007; Krambeck et al, 2008a; Rifaioglu et al, 2008).

POSTPROCEDURAL NEPHROSTOMY DRAINAGE

The final surgical consideration after percutaneous renal surgery is which drain(s), if any, to insert into the upper urinary tract collecting system. Options include an externalized nephrostomy tube or nephroureteral stent, an internal or externalized ureteral stent, or no drainage tube at all. Additional discussion of these options can be found in Chapter 7.

Nephrostomy Tube

For years the standard drainage after percutaneous surgery of the upper urinary tract collecting system has been an externalized nephrostomy tube. There are a variety of choices for postoperative nephrostomy tubes.

Balloon Catheters

The Foley and Councill catheters used for transurethral drainage can be used as nephrostomy tubes as well (Fig. 47–29). These tubes come in a range of diameters; typically 16- to 24-Fr catheters are used for postoperative nephrostomy drainage. **The 5-mL retention balloon might be too large for some collecting systems and does not need to be completely inflated.** The balloon can cause calyceal obstruction if it is pulled into an infundibulum. **Saline or water should be used to inflate the balloon because viscous contrast material might hinder emptying of the balloon when removal is attempted.** An advantage of the Councill catheter is the ability to pass a small-caliber catheter through the end hole and down the ureter, providing more secure access to the upper urinary tract collecting system and maintaining ureteral patency. **All nephrostomy tubes, even ones with robust internal retention devices, should be fixed to the skin externally with a suture or other mechanism.** External fixation of a tube, however, does not necessarily prevent internal dislodgement of the tube. Especially in a large patient, the distance from the skin to the upper urinary tract collecting system can change with patient movement, and the tube (fixed at the skin) can pull out of the kidney. **The potential for tube dislodgement is one of the best arguments in favor of nephrostomy tubes that have some extension down the ureter to maintain a conduit to the upper urinary tract collecting system even if the renal pelvic portion of the tube is pulled out of the kidney.**

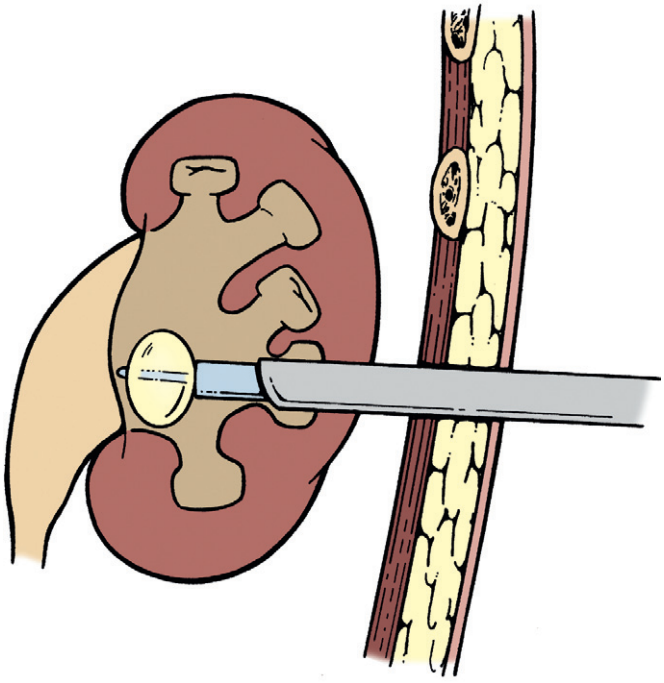


Figure 47–29. Councill catheter.

Malecot Catheter

The wings of the Malecot catheter expand when the catheter is at rest, providing a modest but atraumatic and nonobstructive retention mechanism (Fig. 47–30A). When the catheter is being placed or removed, a stiffener is inserted through it to push on the distal end of the Malecot tip and straighten the wings. During removal this stiffener can misalign with the Malecot tip if the tube is not straight; pulling the catheter back until the tube is straight helps the stiffener line up properly. **The Malecot catheter is also available with an extension that is directed down the ureter. This modification is called a "re-entry" catheter because it simplifies placing a guidewire through the Malecot catheter and down the ureter into the bladder** (see Fig. 47–30A). The extension is long enough (18 cm) so that in most patients the Malecot tube can be withdrawn until the

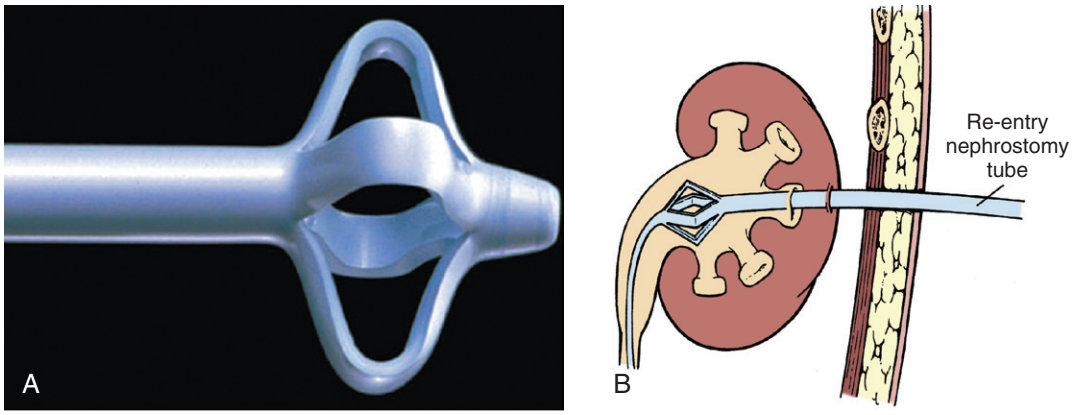


Figure 47–30. **A,** Malecot catheter. **B,** Malecot catheter with ureteral extension ("re-entry" catheter).

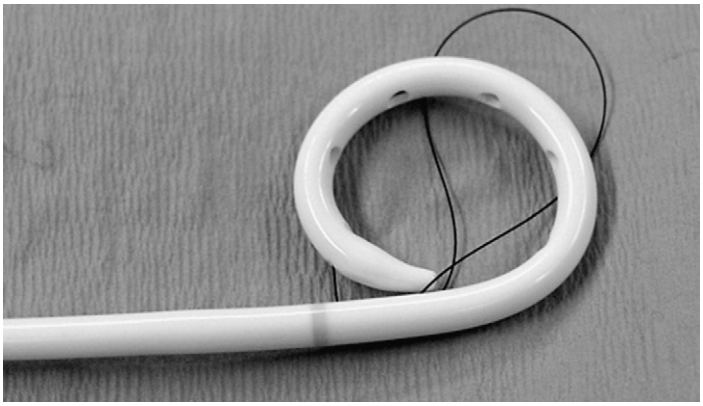


Figure 47–31. Cope catheter, with the retention string loosened for demonstration.

wings are externalized and a guidewire can be placed into the ureter. Malecot catheters for renal use are large-bore catheters, ranging from 16 to 30 Fr, although Malecot catheters as small as 8 Fr are available.

Cope Catheter

A more secure retention mechanism is provided by Cope nephrostomy tubes. **A string exits the catheter a few centimeters from the distal tip and then re-enters the catheter near the tip** (Fig. 47–31). **Pulling on the string forms a secure coil that is not easily dislodged from the renal pelvis.** The string is fixed at the external end of the tube with a locking mechanism or by wrapping it around the tube and fixing it in place with a rubber cuff. Cope catheters employ the same coil shape used in pigtail ureteral stents. The active reinforcement of the coil strength by the string provides more secure retention than the passive coil of a pigtail, and as such Cope catheters have replaced pigtail catheters for most percutaneous uses. Cope nephrostomy tubes, ranging from 6 to 14 Fr in diameter, can be used for simple upper urinary tract drainage and instillation procedures, as well as after percutaneous surgery.

Nephroureteral Stent

The Cope retention mechanism is also used in nephroureteral stents. A nephroureteral stent has a renal coil like that of a Cope nephrostomy tube, but the tube continues on to a ureteral extension that travels down the ureter to end in a passive pigtail that rests in the bladder (Fig. 47–32). The ureteral portion can be the same diameter as the nephrostomy portion, or it can be narrower. A nephroureteral stent is passed percutaneously over a wire that ends in the bladder. Once the end is coiled generously in the bladder, careful inspection of the fluoroscopy image reveals the location of the side holes in the renal coil. By moving the catheter in and out while pulling on the string and rotating the external portion of the tube clockwise, the Cope retention coil is formed in the renal pelvis (Figs. 47–33 and 47–34 on the Expert Consult website) **A nephroureteral stent offers excellent control of the entire upper urinary tract, from renal pelvis to bladder, and is unlikely to become dislodged.** Nephroureteral stents are available in diameters of 8.5 or 10.2 Fr, and the standard lengths (from renal to bladder coil) are 20 to 28 cm.

Circle Catheter

A final type of nephrostomy tube is the circle nephrostomy tube (Fig. 47–35), **which is secure, easily exchanged, causes little trauma, rarely occludes, and provides excellent drainage and avenue for irrigation of the renal pelvis.** The circle nephrostomy tube requires two percutaneous access sites to the kidney, and this tube is most useful when maintenance of two tracts is desired, such as for irrigation of the renal pelvis or if more than one access is necessary for second-look nephroscopy (Kim et al, 2005). After obtaining access at two distant calyces, a flexible nephroscope or flexible ureteroscope passed over one wire is used to grasp the wire coming from the other site. When the endoscope is withdrawn, the wire is now in position to guide placement of the circle nephrostomy tube. Radiopaque markers on the tube delineate the location of the drainage holes, which should be maintained within the intrarenal collecting system. External drainage of the circle nephrostomy tube requires a Y-connector.

General Considerations

The advantages of a postoperative nephrostomy tube include good drainage and control of the upper urinary tract, and maintenance of percutaneous access for additional procedures. It was initially thought that a postoperative nephrostomy served to tamponade the nephrostomy tract and reduce hemorrhage, but subsequent studies have suggested that is not the case. When hemorrhage does occur, however, the larger caliber of a nephrostomy tube provides better drainage of the upper urinary tract collecting system than an internal ureteral stent. In addition, if a large perforation has occurred during the procedure, the additional diversion of urine away from the site might be

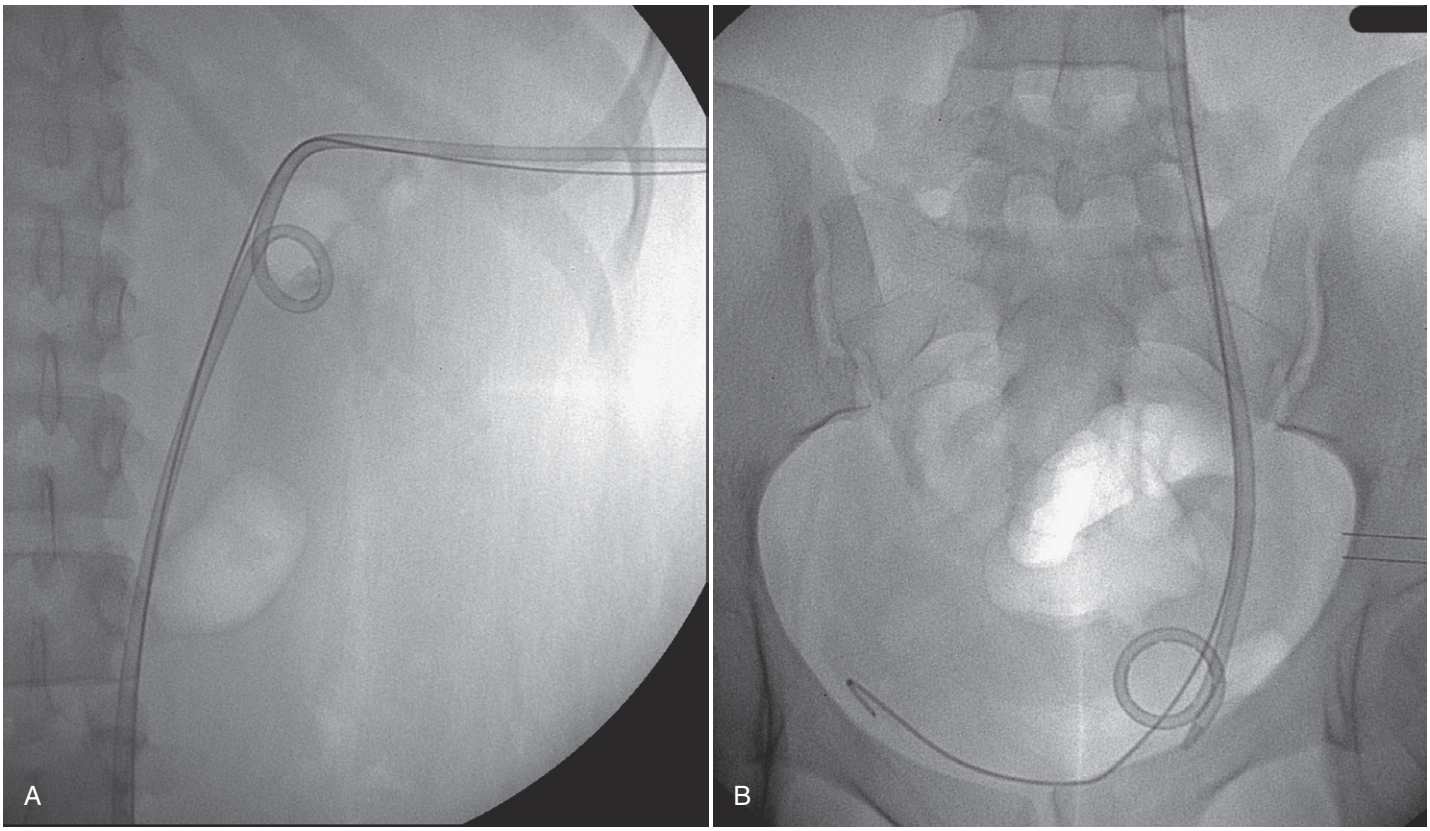


Figure 47–32. Nephroureteral stent. **A,** Renal coil. **B,** Bladder coil.

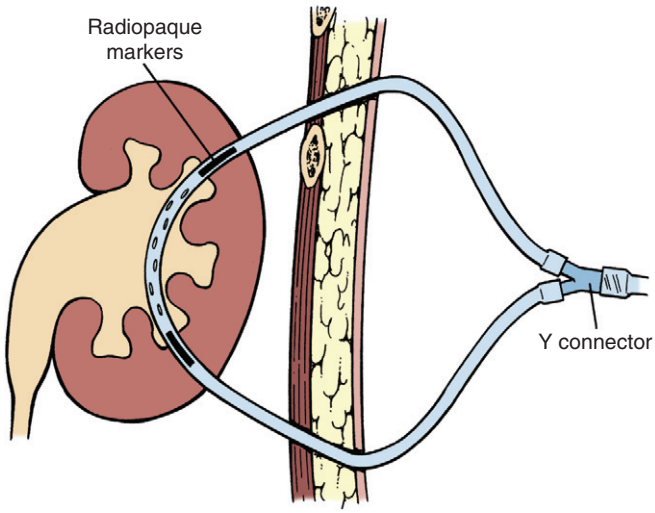


Figure 47–35. Circle nephrostomy tube.

advantageous. When a nephrostomy tube is left in place following percutaneous renal surgery, it is usually in the dilated access site. At least one group has attempted to reduce the discomfort associated with supracostal percutaneous renal surgery by placing a small-caliber postoperative nephrostomy tube in a new subcostal site and leaving the dilated supracostal access site without a nephrostomy tube (although there was no control cohort for comparison) (Kim et al, 2006).

Including along with the nephrostomy a tube that goes down the ureter provides the greatest control and assurance of drainage. Because entry of a tube into the bladder is associated with additional symptoms, though, such a tube should only be used when needed. Considerations include the size of the patient (which determines to a large extent the risk of tube dislodgement), the importance of maintaining drainage, and the desire for ureteral intubation (e.g., ureteral obstruction that might resolve if intubated, ureteral injury that should be bypassed). Aside from the choice of retention mechanism, the main remaining consideration is the diameter of the nephrostomy tube.

A number of studies have compared the impact of nephrostomy tube diameter after percutaneous renal surgery including one prospective trial with alternating assignment to 28-Fr versus 9-Fr nephrostomy tubes (Maheshwari et al, 2000) and four randomized controlled trials comparing large-caliber tubes (20 to 24 Fr) to small-caliber tubes (8 to 18 Fr) (Liatsikos et al, 2002; Pietrow et al, 2003; Desai et al, 2004; Marcovich et al, 2004). **Among the five studies, comprising a total of 170 patients with nephrostomy tubes, four revealed less pain and two reported less urinary leakage in the patients with smaller tubes. Bleeding was not increased in the groups with smaller tubes in any of the studies.** Only one study found no benefit to the smaller tube (Marcovich et al, 2004). Although tube diameter is not related to bleeding overall, the removal of larger tubes occasionally can be followed by immediate hemorrhage; this is rare with smaller tubes. As such, large-caliber nephrostomy tubes

should be removed in a radiology suite where there is the opportunity for immediate replacement of the tube. Small-caliber tubes can be removed safely at the bedside after a period of clamping to assess clinically for distal ureteral obstruction.

"Tubeless" with Ureteral Stent

A "tubeless" percutaneous procedure—one that omits the postoperative nephrostomy tube—was initially proposed by Wickham and colleagues (1984). This practice never met with widespread acceptance, especially after Winfield and colleagues (1986) reported disastrous outcomes with this technique. The concept was revived in 1997 by Bellman and colleagues (1997), with the addition of an internal ureteral stent left in place for a week or two. Since then, many studies have evaluated the practice of omitting the nephrostomy tube after percutaneous renal surgery. Although this technique is called "tubeless," most series employ a ureteral stent for at least a short period postoperatively.

Options for ureteral stenting without a nephrostomy tube after percutaneous renal surgery include an internal ureteral stent that is removed cystoscopically, an internal ureteral stent with an attached string that exits out the flank to allow removal of the ureteral stent without cystoscopy, and an externalized (out the urethra) ureteral stent that is removed along with the urethral catheter to which it is attached. The potential advantages of omitting the nephrostomy tube after percutaneous renal surgery include decreased pain and analgesic use, avoidance of an external drainage device, abbreviated hospital stay, and decreased health care costs (secondary to shortening the duration of hospitalization). The seminal report of Bellman and colleagues (1997) described placing an internal ureteral stent antegrade, looking at the tract through the nephroscope as the sheath is withdrawn, and leaving a percutaneous guidewire in place for a few hours in the recovery room before removing it if there is no hemorrhage. Among 50 patients undergoing tubeless percutaneous renal procedures, compared with a cohort of patients with a nephrostomy tube placed after surgery, hospitalization was briefer, narcotic use was less, return to normal activities was sooner, and costs were less. Since then, many studies including several randomized controlled trials have evaluated omission of nephrostomy tube postoperatively with placement of an internal ureteral stent (Table 47–1). It is important to note that none of these studies included patients with significant bleeding or perforation, or in whom secondary nephroscopy was intended.

Of the six trials in Table 47–1 (Feng et al, 2001; Desai et al, 2004; Marcovich et al, 2004; Sofikerim et al, 2007; Agrawal et al, 2008; Singh et al, 2008b) **that compared postoperative drainage with a large-caliber percutaneous nephrostomy tube (16 to 24 Fr) to drainage with an internal ureteral stent and no nephrostomy tube, five revealed a benefit to omission of the nephrostomy tube in terms of reduced narcotic use and decreased length of hospitalization.** Both studies that evaluated return to normal activity found a benefit to omitting the nephrostomy tube, and in one study (Feng et al, 2001) omission of the nephrostomy tube was associated with decreased cost. **Among the four studies** (Desai et al, 2004; Marcovich et al, 2004; Choi et al, 2006; Shah et al, 2008) **that compared postoperative drainage with a small-caliber percutaneous nephrostomy tube (8 to 9 Fr) with drainage with an internal ureteral stent and no nephrostomy tube, the benefit of omitting the nephrostomy tube was less apparent, with only one study suggesting a decrease in narcotic use, two indicating a reduced hospital stay, and one finding a more rapid return to normal activity. In none of these comparisons in** Table 47–1**, however, did there seem to be any danger to nephrostomy tube omission; technical success rates and complications appeared similar between the groups.**

There are some disadvantages to using an internal ureteral stent as an alternative to a nephrostomy tube, however, including loss of the percutaneous tract for a secondary procedure and the cost, inconvenience, and discomfort associated with an internal ureteral stent that requires cystoscopic removal at a later date. In

Table 47–1.

Randomized Controlled Trials of PCN versus Internal Ureteral Stent after Percutaneous Renal Surgery

Reference		Feng et al, 2001	Desai et al, 2004	Marcovich et al, 2004	Choi et al, 2006	Sofikerim et al, 2007	Agrawal et al, 2008	Shah et al, 2008	Singh et al, 2008b
No. Patients (size PCN)	Large PCN	19 (22 Fr)	24 (18 Fr)	30 (22 Fr)	101 (16 Fr)	10 (20 Fr)	20 (24 Fr)		
	Small PCN					10 (9 Fr)	20 (8 Fr)	12 (8.2 Fr)	32 (8 Fr)
	Internal stent	8	24	30	101	10	20	12	33
MSO4 Equiv. (mg, mean)†	Large PCN	37.7	26.3	56.8	12.7	21.8*	22.1		
	Small PCN					14	22.1	10.7	24.6
	Internal stent	5.3*	12*	41.5*	8.2*	8.8	24.6	9.1	15.0*
Complications (%)	Large PCN	11%	25%	10%	11%	—	10%		
	Small PCN					—	5%	17%	22%
	Internal stent	0%	17%	13%	5.0%	—	10%	33%	18%
Stone Free (%)	Large PCN	49%	83%	90%	100%	—	85%		
	Small PCN					—	85%	—	88%
	Internal stent	79%	79%	93%	100%	—	90%		88%
Hospitalization (days, mean)	Large PCN	3.7	3.1	4	2.3	4.4	3.3		
	Small PCN					4.3	3.7	1.6	1.8
	Internal stent	1.9*	1.6*	2.1*	0.9*	3.4*	3	1.6	1.4*
Recovery (days, mean)	Large PCN	—	—	7.2	9.1	—	—		
	Small PCN					—	—	7	—
	Internal stent	—	—	4.2*	5.6*	—	—	4.2*	—

PCN, percutaneous nephrostomy tube.
*Statistically different from other values ($P < 0.05$).
†If reported as meperidine or diclofenac, then divided by 10.

order to obviate the problems associated with the ureteral stent, several groups have offered alternatives including insertion of an externalized ureteral stent or insertion of an internal stent with an attached string that exits out the flank. In both cases the stent can then be removed before hospital discharge without an additional procedure. Goh and Wolf (1999) first reported in 1999 the use of an externalized ureteral stent (single pigtail) as an alternative to a postoperative nephrostomy tube. Since then there have been a number of reports of this option (Lojanapiwat et al, 2001; Abou-Elela et al, 2007; Karami et al, 2007; Rana and Mithani, 2007; Al-Ba'adani et al, 2008) including two randomized controlled trials, one comparing an externalized ureteral stent to a large-caliber nephrostomy tube, which suggested a benefit in terms of reduced narcotic use and length of hospital stay (Tefekli et al, 2007), and one comparing internal and external ureteral stents, which revealed no difference between the two techniques except for a lack of outpatient stent-related symptoms in the external stent group (Gonen et al, 2009). Shpall and colleagues (2007) described the modification of leaving the attached string on the stent and placing the stent "upside down" so that the string can exit the flank. They described removing the stent as an outpatient 3 and 12 days postoperatively, but since then others have reported removing the stent at the bedside on the first postoperative day (Berkman et al, 2008). Use of a Polaris Loop stent (Boston Scientific, Natick, MA) placed "upside down" offers less resistance at the time of removal (Fig. 47–36).

These modifications of nephrostomy tube omission avoid many of the disadvantages of an internal ureteral stent but still leave the problem of loss of access in case a secondary procedure is required. With improved endoscopes, better ancillary tools, and growing experience with percutaneous surgery, the need for secondary procedures is declining. In properly selected patients including those who do not for some other reason need external drainage (e.g., pyonephrosis, significant bleeding, significant collecting system injury) and those who are unlikely to need a secondary procedure, omission of the postoperative nephrostomy tube appears to be safe and effective.

No Drainage Tube

Recently, some authors have reintroduced the idea of a "totally tubeless" percutaneous renal surgery, omitting both the nephrostomy tube and ureteral catheter. The procedure is done in selected patients, with low-volume stones, atraumatic single access, and no hemorrhage, perforation, or obstruction (Aghamir et al, 2004; Karami and Gholamrezaie, 2004; Gupta et al, 2005; Mandhani et al, 2007; Crook et al, 2008b; Mouracade et al, 2008). In light of the findings of studies comparing internal stents with nephrostomy tubes, it is not surprising that the three randomized controlled trials of "totally tubeless" percutaneous renal surgery summarized in Table 47–2 (Aghamir et al, 2008; Crook et al, 2008a; Istanbulluoglu et al, 2009) also found reduced duration and intensity of convalescence in the groups without nephrostomy tubes. The more important comparison would be "totally tubeless" versus internal stent without nephrostomy tube, which to date has not been reported.

Adjuncts to Drainage without Nephrostomy Tubes

One of the concerns with any approach that omits the nephrostomy tube after percutaneous renal surgery is that of hemorrhage

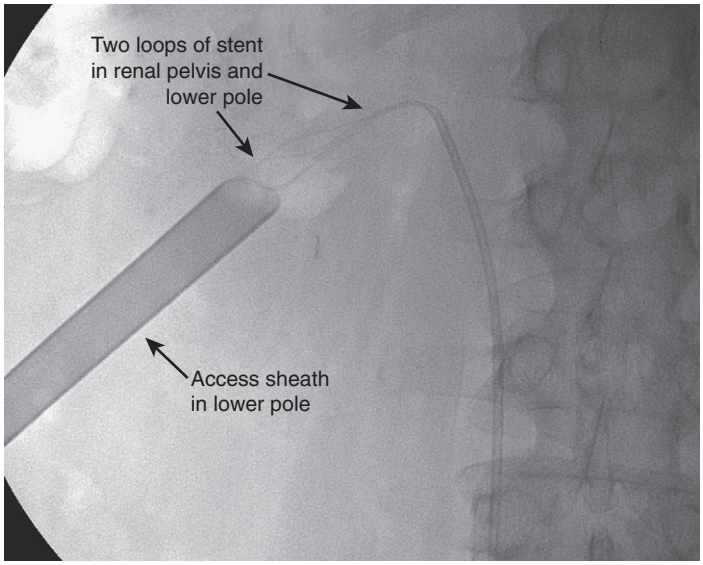


Figure 47–36. Use of a Polaris Loop stent (Boston Scientific, Natick, MA) placed "upside down." An attached string is left exiting the flank, which allows removal of the stent without an additional procedure.

Table 47–2.

Randomized Controlled Trials of "Totally Tubeless" Percutaneous Renal Surgery

Reference		Aghamir et al, 2008	Crook et al, 2008a	Istanbulluoglu et al, 2009
No. Patients (size tube)	Tube	25 (26-Fr PCN)	30 (PCN + stent)	45 (14 Fr. PCN)
	No tube	25	30	45
MSO4 Equiv. (mg, mean)	Tube	23.6	10.4	Required by 100%
	No tube	10	4.5*	Required by 11%*
Complications (%)	Tube	24%	10%	13%
	No tube	12%	6.7%	4.4%*
Stone Free (%)	Tube	—	87%	—
	No tube	—	83%	—
Hospitalization (days, mean)	Tube	3.4	2.6	3.5
	No tube	2.3*	1.3*	2.1*
Recovery (days, mean)	Tube	—	15.5	—
	No tube	—	10*	—

PCN, percutaneous nephrostomy tube.
*Statistically different from other value ($P < 0.05$).

from the tract. **Although the evidence from randomized controlled trials suggests that the size or presence of the nephrostomy tube does not affect the degree of postoperative bleeding, there is still a potential for dramatic bleeding after any percutaneous procedure—and such bleeding would be more problematic without a nephrostomy tube in place.** Several groups have described adjuncts intended to enhance hemostasis of the percutaneous tract including direct monopolar cauterization of the tract (Mouracade et al, 2008), cryotreatment of the tract (Okeke et al, 2009), and insertion/instillation of hemostatic agents into the tract including oxidized cellulose (Aghamir et al, 2006), gelatin sponge (Singh et al, 2008a), gelatin granules plus thrombin (Lee et al, 2004b; Nagele et al, 2006), and fibrin glue (Noller et al, 2004). One nonrandomized comparison of percutaneous nephrolithotomy with and without electrode cauterization of the tract reported a lower blood transfusion rate in the first group (1.2% vs. 6.5%, respectively) (Jou et al, 2004). A nonrandomized comparison of tract cryotherapy without a nephrostomy tube in 30 patients versus a 24-Fr nephrostomy tube without tract cryotherapy in 30 patients suggested that there was shorter hospitalization and less hemorrhage and urine leakage in the patients treated with cryotherapy. The high rate of postoperative hemorrhage requiring angio-embolization in the control group, 13%, confounds the analysis (Okeke et al, 2009). There have been three randomized controlled trials of hemostatic adjuncts for percutaneous renal surgery without nephrostomy tubes, comparing patients managed without hemostatic adjuncts with those managed with gelatin sponge (Singh et al, 2008a), oxidized cellulose (Aghamir et al, 2006), and fibrin glue (Shah et al, 2006). None of the three studies found an impact of the adjunct on measures of hemostasis (postoperative hematocrit, hemorrhage, and/or blood transfusions). Narcotic use was reduced in both studies in which it was evaluated. Hospital stay and urinary leakage were each assessed in two studies, and each was improved in one study. Some nonrandomized studies also have suggested a shortened hospitalization and/or reduced narcotic use after tract hemostatic maneuvers, but because improvements in hemostasis and urinary leakage are not consistently found, the mechanism for improvement in these secondary outcomes is not clear (Mikhail et al, 2003; Aron et al, 2004; Borin et al, 2005). **Overall, the utility of any of adjuncts for tract hemostasis is not certain and further study is necessary.**

Key Points: Postprocedural Nephrostomy Drainage

- The advantages of a postoperative nephrostomy tube include good drainage and control of the upper urinary tract, as well as maintenance of percutaneous access for additional procedures. Inclusion of an extension down the ureter provides the greatest control and assurance of drainage.
- Small-caliber nephrostomy tubes are associated with less pain than large-caliber nephrostomy tubes and are not associated with any increased hemorrhage.
- Use of a ureteral stent instead of a large-caliber nephrostomy tube is associated with reduced narcotic use and decreased length of hospitalization. The benefit of nephrostomy omission is less when compared with a small-caliber nephrostomy. In properly selected patients, use of a ureteral stent instead of a nephrostomy tube does not affect stone-free or complication rates.
- Options for ureteral stenting without a nephrostomy tube after include an internal ureteral stent that is removed cystoscopically, an internal ureteral stent removed by string exiting out the flank, and an externalized ureteral stent that is removed along with the urethral catheter to which it is taped.
- Following straightforward procedures with atraumatic single access and no hemorrhage, perforation, or obstruction, some patients can be managed without a nephrostomy tube or a ureteral stent.
- The utility of adjuncts for tract hemostasis is uncertain.

TRAINING IN PERCUTANEOUS ACCESS AND PROCEDURES

Efforts to enhance training for percutaneous surgery of the upper urinary tract have focused on obtaining percutaneous access. Summarizing their own experience and other reports (Allen et al, 2005; Tanriverdi et al, 2007), de la Rosette and colleagues (de la Rosette et al, 2008a) estimated that a trainee must perform approximately 24 percutaneous nephrolithotomies to attain proficiency, whereas competence is not achieved until the experience includes 60 cases and excellence is not obtained until more than 100 cases have been performed. The American College of Radiology's "Practice Guideline for the Performance of Percutaneous Nephrostomy" recommends that a physician must have performed at least 15 percutaneous nephrostomies as primary operator, with acceptable outcomes, in order to be considered qualified as a supervising physician (ACR, 2007). Training during residency is the most effective way to develop the skills, but maintenance of skills requires ongoing experience. In a survey of urologists who completed a single residency program, those trained in percutaneous access were more likely to perform percutaneous surgical procedures than those not trained in percutaneous access (92% vs. 33%). Of those who performed percutaneous surgery, urologists with training did more procedures than those without training (14.0 vs. 3.3 procedures annually). However, only about a third of respondents in both groups continued to attain their own percutaneous access (27% vs. 11%) (Lee et al, 2004a).

Nonhuman models can also assist training (Laguna et al, 2002). An inanimate trainer is marketed by Limbs and Things, Ltd (Bristol, UK). Several biologic models using ex-vivo porcine kidneys incorporate a body wall simulator composed of a chicken carcass (Hammond et al, 2004; Hacker et al, 2007), full-thickness porcine skin including subcutaneous tissue and muscle (Zhang et al, 2008), or silicon (Strohmaier and Giese, 2005). The most advanced trainer is the PERC Mentor (Simbionix Ltd, Lod, Israel), a computer-assisted simulator for percutaneous access procedures guided by fluoroscopy (Fig. 47–37). Some of the biologic models can be used to teach steps in the subsequent procedure (e.g., nephrolithotomy, endopyelotomy), but the main focus is on attaining percutaneous access. The PERC Mentor has undergone preclinical validation, confirming that training on the PERC Mentor improves performance on the PERC Mentor (Knudsen et al, 2006), and that trained individuals more proficiently attain percutaneous renal access in a porcine in-vivo model (Margulis et al, 2005), but validation of the impact on performance in the human operating room is lacking (Stern et al, 2007). At the least, these trainers can serve as an introduction for the trainee by orienting them to the necessary anatomic considerations and familiarizing them with the physical movements of the procedure. It is unknown if these or other devices can be used to validate the skills of trainees and practitioners.



Figure 47–37. PERC Mentor (Simbionix Ltd, Lod, Israel).

Taking simulation even farther, Bruyère and colleagues (2008) used computer-assisted design and rapid prototyping based on CT images to create a silicon model of a patient's kidney, complete with artificial flank and respiratory motion. After practicing percutaneous nephrolithotomy on the model several times, the percutaneous nephrolithotomy on the patient went smoothly using the practiced technique. Creating a specific renal model for each patient is too expensive and laborious for routine application currently, but with anticipated technical improvements, this iteration of "personalized medicine" might play a role in training and treatment planning.

COMPLICATIONS

Given enough time and access sites to the upper urinary tract collecting system, in most cases the primary goal of the percutaneous procedure can be achieved. The challenge with percutaneous surgery, then, is to do so while also avoiding complications. If complications do occur, then prompt recognition and management will usually avoid major morbidity. Some complications of percutaneous renal surgery are specific to the procedure including migration of stone outside the kidney, retained foreign bodies such as tips of wires and probes, and tumor seeding of the percutaneous tract. In this section the general complications of percutaneous renal surgery are discussed.

Acute Hemorrhage

Acute hemorrhage is the most common significant complication of percutaneous access into the upper urinary tract collecting system. **Percutaneous nephrostomy alone results in hemorrhage requiring transfusion in 0.5% to 4% of procedures** (Radecka and Magnusson, 2004; Wah et al, 2004; ACR, 2007; Rana et al, 2007)**. With the addition of percutaneous nephrolithotomy, likely owing to the larger caliber of the percutaneous tract and increased intrarenal manipulation, the incidence of hemorrhage to the point of transfusion rises to 6% to 20%** (Kukreja et al, 2004; Netto et al, 2005; Preminger et al, 2005; Muslumanoglu et al, 2006; Chew et al, 2009). This wide variation in transfusion rate, which likely is more variable than the rate of significant hemorrhage, reflects differences in the complexity of the procedure, patient factors, and physician triggers for use of blood products. **Factors associated with hemorrhage during percutaneous surgery include patient characteristics, multiple access sites, supracostal access, increasing tract size, tract dilation with methods other than balloon dilation, prolonged operative time, and renal pelvic perforation** (Stoller et al, 1994; Martin et al, 1999; Kukreja et al, 2004; Netto et al, 2005; Hegarty and Desai, 2006; Chew et al, 2009).

Technical errors predispose to hemorrhage as well. Infundibular entry risks injury to interlobar (infundibular) arteries. Access into an anterior calyx or any calyx that does not afford direct access to the pathology invites overly aggressive torquing of the sheath and rigid endoscope, which also can lead to hemorrhage. If direct access cannot be obtained, then flexible instrumentation should be considered. Additionally, misuse of any tool—lithotrites (ultrasonic, pneumatic, electro-hydraulic, or laser), resectoscopes, wires, sheaths, graspers, baskets, and so on—can cause hemorrhage.

Most hemorrhage occurs from the renal parenchyma, and in most cases this hemorrhage is not significant. Small arteries and veins are always injured to some degree by percutaneous entry into the kidney. Parenchymal bleeding is minimized by proper entry and dilation and by careful manipulation of the sheath, but it still can occur. **The access sheath provides intraoperative tamponade of parenchymal bleeding. Postoperatively, hemostasis is achieved by collapse of the parenchyma onto itself.** Unless the postoperative nephrostomy tube is as large as or larger than the sheath used during the procedure, it likely does not contribute to hemostasis. There is no difference in measures of postoperative bleeding between small (8- to 18-Fr) and large (20- to 28-Fr) tubes (Maheshwari et al, 2000; Liatsikos et al, 2002; Pietrow et al, 2003; Desai et al, 2004; Marcovich et al, 2004), and randomized controlled trials suggest that hemorrhage is no greater when the nephrostomy tube is omitted altogether (Feng et al, 2001; Desai et al, 2004; Marcovich et al, 2004; Choi et al, 2006; Sofikerim et al, 2007; Tefekli et al, 2007; Aghamir et al, 2008; Agrawal et al, 2008; Crook et al, 2008a; Shah et al, 2008; Singh et al, 2008b; Gonen et al, 2009; Istanbulluoglu et al, 2009). **If there is noticeable bleeding from the tract after sheath removal following an otherwise unremarkable procedure, this suggests bleeding from intraparenchymal vessels.** Hemostatic maneuvers such as cauterization or placement of hemostatic material can be considered**, but in general the best management is to insert and occlude a nephrostomy tube, apply pressure to the incision, and let the collecting system clot off.** A tubeless approach is not advised in such cases because maintenance of percutaneous access to the upper tract might facilitate management. Nephrostomy tubes should not be irrigated the day or evening of the procedure if they are not draining; it is best to let the collecting system remain occluded to tamponade bleeding. By the next morning, it is safe to gently irrigate the tube because hemostasis is more certain.

If the procedure was not complicated by bleeding, but severe hemorrhage occurs following sheath removal and is refractory to the hemostatic measures described earlier, then use of a Kaye Nephrostomy Tamponade Balloon (Cook Urological, Spencer, IN) should be considered. This is a nephrostomy tube surrounded by a balloon (Fig. 47–38) (Kaye and Clayman, 1986), which is inflated up to 36 Fr to tamponade the parenchymal bleeding just as the sheath did intraoperatively. This device should be removed under fluoroscopic guidance with guidewire access down the ureter in case tube reinsertion is required for recurrent bleeding.

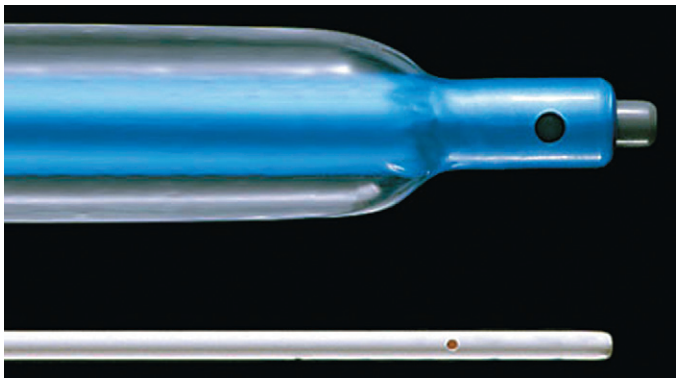
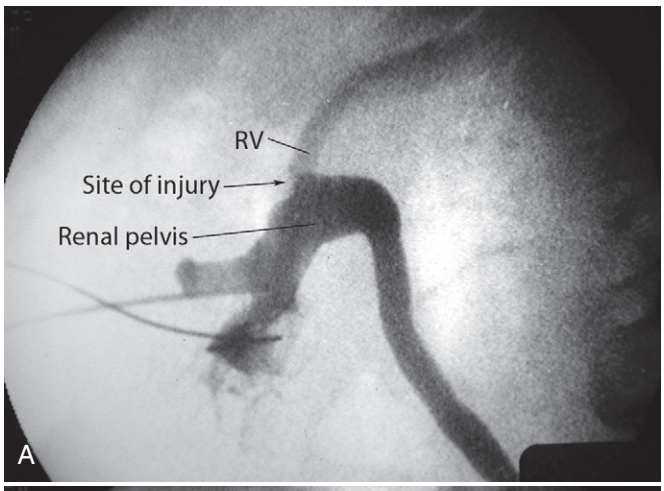


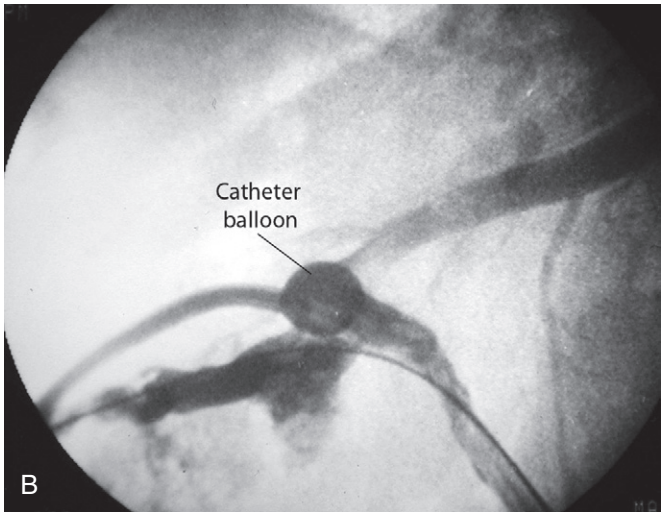
Figure 47–38. Kaye Nephrostomy Tamponade Balloon.

Intraoperative hemorrhage from an injured vein or artery within the collecting system mandates cessation of the procedure if vision is lost. In most cases, especially if the injury appears to be venous, then placing a nephrostomy tube and letting the collecting system clot off is effective. If this is not effective, then Gupta and colleagues (1997) have described inserting a Councill catheter as a nephrostomy tube, with the balloon inflated slowly at the site where contrast material enters into the venous system until repeated nephrostography reveals no more extravasation of contrast material (Fig. 47–39). A hole should be cut into the tube proximal to the balloon to provide drainage of calyces obstructed by the balloon (Fig. 47–40). An additional alternative, described in one case of a large venous injury, is to place a large-bore catheter through the injury site into the main renal vein and then back it out several days later (Shaw et al, 2005). A small arterial injury can sometimes be addressed with fulguration under direct vision, but if this is not successful and bleeding does not cease with pressure, or in cases of significant arterial hemorrhage, then selective angioembolization will likely be required (see later).

Delayed Hemorrhage

Postoperative hemorrhage can occur with the nephrostomy tube in place, at time of tube removal, or after discharge from the hospital. **Approximately 1% of major percutaneous**





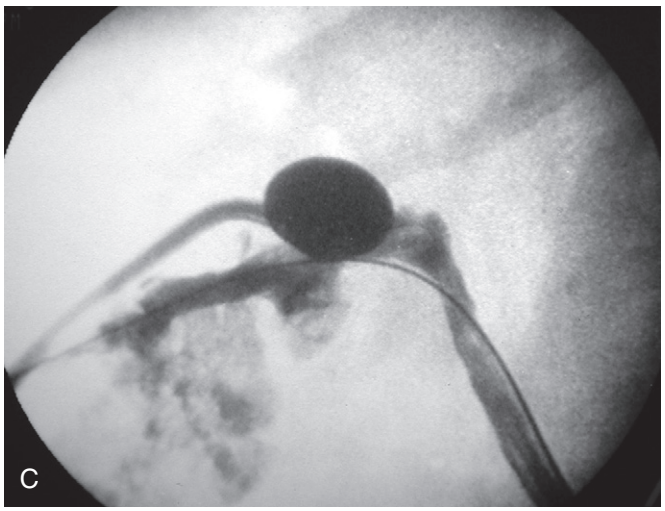


Figure 47–39. **A,** Nephrostogram reveals contrast material entering the renal vein (RV) indicating a large venous injury. **B,** The balloon of a Council catheter nephrostomy tube is inflated at the site of injury **(C)** until contrast material no longer enters the renal vein.

procedures are complicated by delayed hemorrhage requiring treatment (Kessaris et al, 1995; Martin et al, 2000; Richstone et al, 2008). In one large series, the incidence was greatest following percutaneous resection of upper tract urothelial carcinoma (3.2%) and least following percutaneous endopyelotomy (0.8%) (Richstone et al, 2008). **Delayed hemorrhage is usually due to arteriovenous fistulas or arterial pseudoaneurysms, with the latter being more common.** Arteriovenous fistulas occur when a paired set of artery and vein are injured, and arterial blood enters directly into vein (Fig. 47–41). The weak vein wall cannot sustain the high arterial pressure and ruptures. Bleeding is most commonly noted into the collecting system but can be outside the kidney as well. The latter should be suspected if the hematocrit falls but the urine remains relatively clear. It can be confirmed with CT or ultrasonography. An arterial pseudoaneurysm occurs when an artery is injured, clots off, and then intermittently ruptures, often clotting off again at variable intervals (Fig. 47–42A). Continuous bleeding suggests an arteriovenous fistula, and intermittent bleeding suggests arterial pseudoaneurysm, but the distinction is not critical because treatment is the same. In a large series of Kessaris and colleagues (1995), of the 0.8% of 2200 patients requiring treatment for delayed hemorrhage after percutaneous renal surgery, 24% of the hemorrhages occurred within 24 hours of surgery, 41% between 2 and 7 days after surgery, and 35% more than 7 days later. **Any report of bright red blood in the urine after percutaneous renal surgery should prompt hospital admission and consideration of angiography, which is diagnostic in more than 90% of cases** (Richstone et al, 2008). **The standard treatment of renal arteriovenous fistulae and arterial**

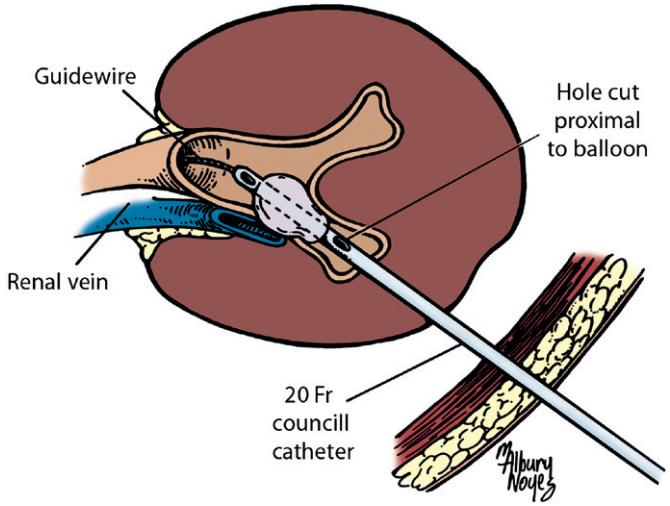


Figure 47–40. An extra hole created proximal to the balloon of the Councill catheter allows for drainage of calyces obstructed by the balloon.

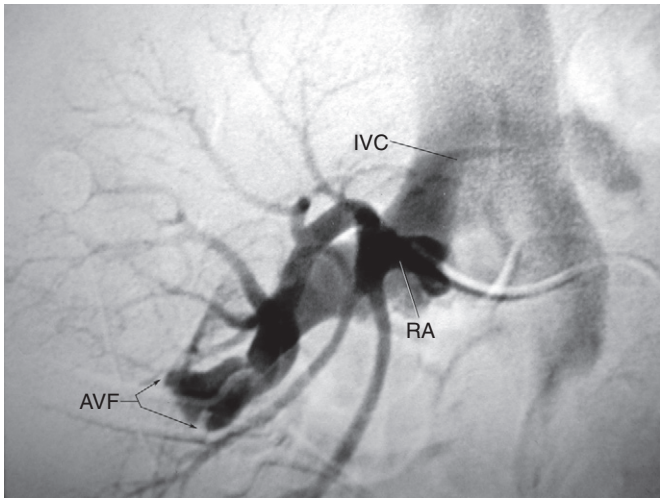


Figure 47–41. Angiography of the renal artery (RA) is followed promptly by contrast material appearing in the inferior vena cava (IVC), suggesting the presence of an arteriovenous fistula (AVF).

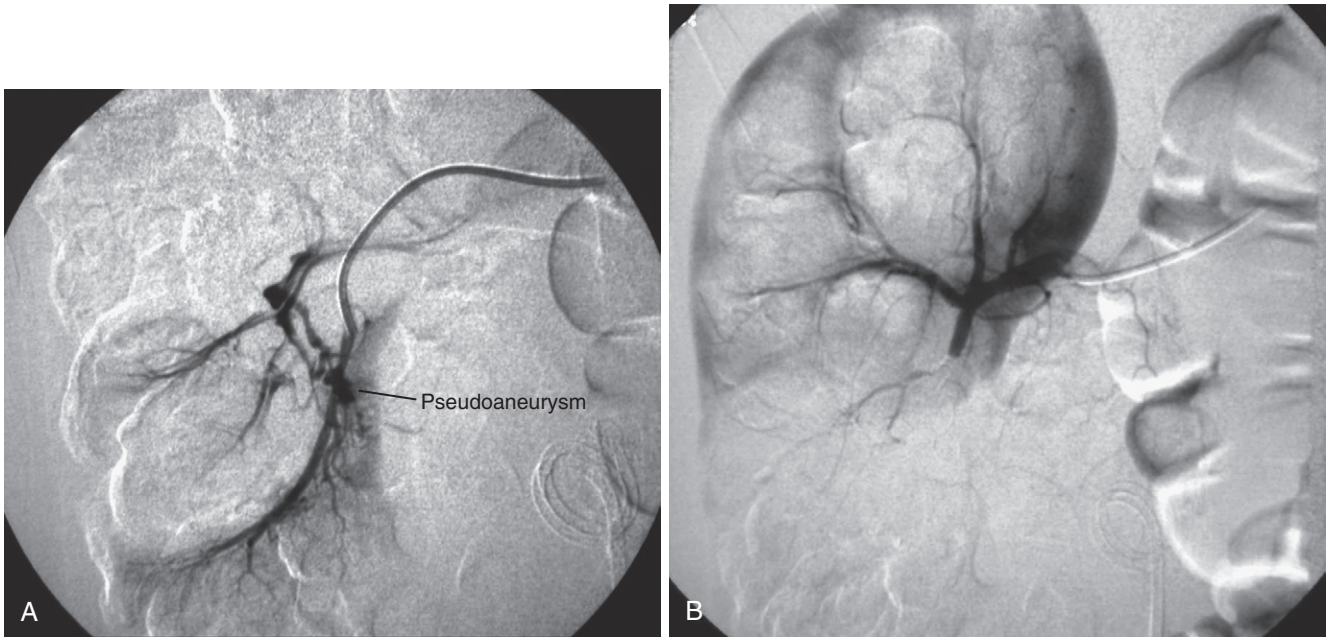


Figure 47–42. **A,** Angiography demonstrates a pseudoaneurysm in the lower pole of the right kidney. **B,** Angio-embolization was successful at occluding the pseudoaneurysm but also devascularized a large portion of the lower pole.

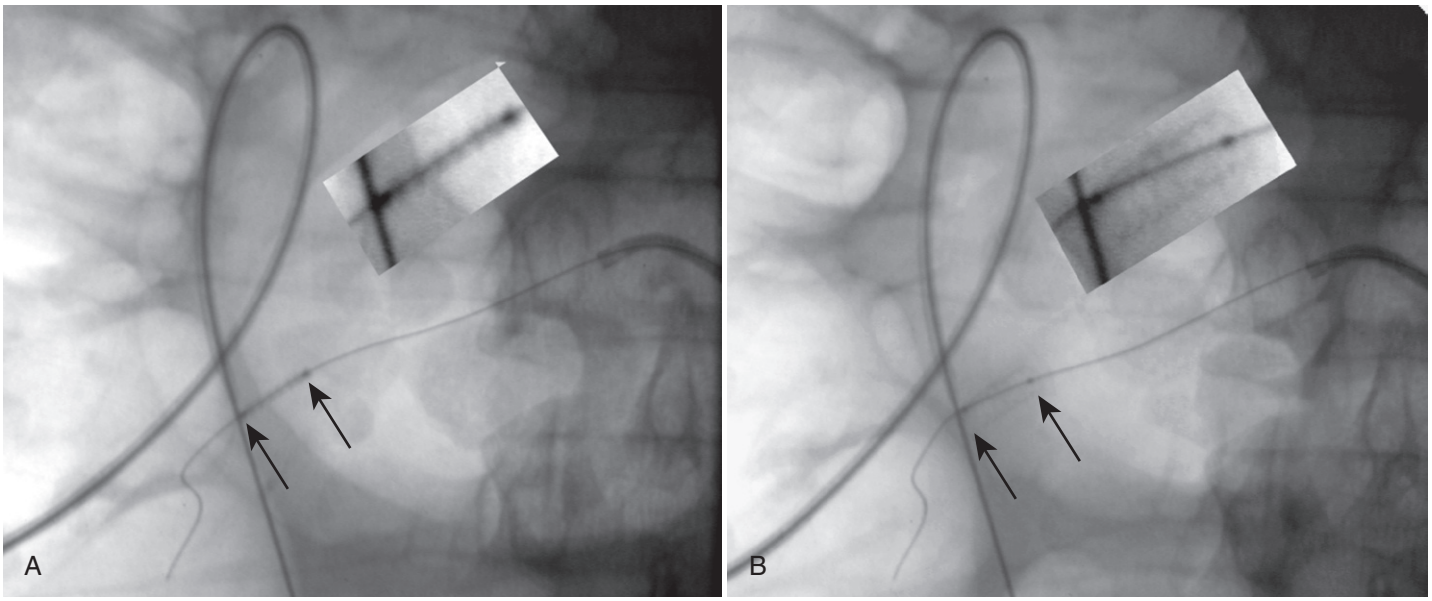


Figure 47–43. Covered arterial stent placed in branch of renal artery injured during endopyelotomy. **A,** Stent before balloon expansion. **B,** Stent after balloon expansion. Inset in each figure is a 2× enlargement of stent (indicated by *arrows*).

pseudoaneurysms is selective angio-embolization, which is highly effective; among three series reporting 72 patients undergoing selective angio-embolization after percutaneous renal surgery, success was noted in 68 (94%) (Patterson et al, 1985; Martin et al, 2000; Richstone et al, 2008). Nephrectomy may be required if selective angio-embolization fails, and partial or total renal loss may occur if angio-embolization is not selective enough (Fig. 47–42B). Additionally, the embolization coils can migrate to unwanted locations, immediately or delayed.

A recently introduced alternative to angio-embolization is endovascular placement of a covered stent to occlude the site of arterial injury (Sprouse and Hamilton, 2002; Areste et al, 2005). This treatment maintains patency of the feeding artery, thereby preserving renal parenchyma, and obviates the risk of migration of embolization coils (Fig. 47–43). Another alternative is ultrasonographically guided percutaneous puncture of an arterial pseudoaneurysm, with injection of thrombin or fibrin tissue adhesive (Benjaminov and Atri, 2002; Lagana et al, 2006).

Untreated coagulopathy is an absolute contraindication to percutaneous renal surgery. Percutaneous access can be safely obtained if coagulopathy is reversed or anticoagulant medications are stopped. Anticoagulants can be restarted once the urine clears, preferably after nephrostomy tube removal, but the patient should be closely monitored.

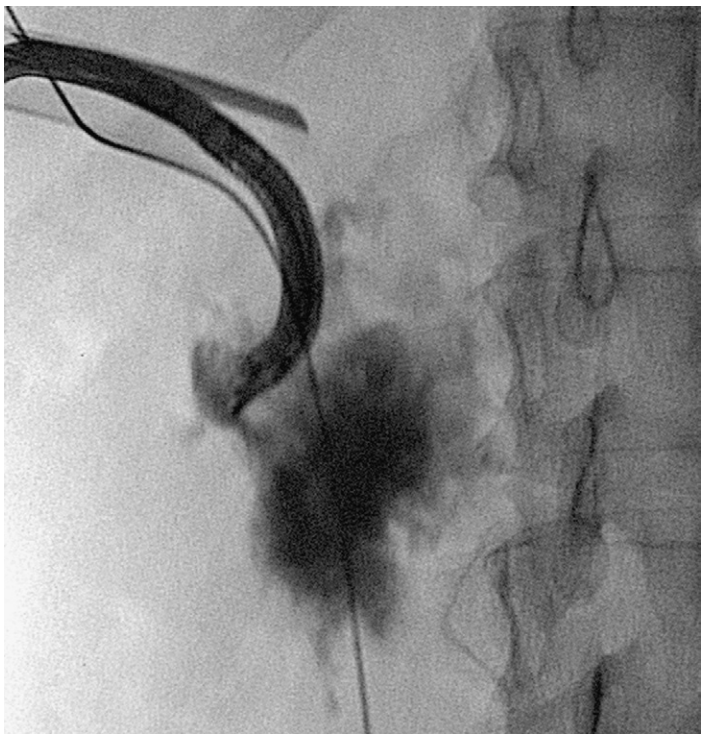


Figure 47–44. Renal pelvic perforation confirmed with injection of contrast material through flexible nephroscope.

Collecting System Injury

Tears in the infundibulum are not uncommon during percutaneous surgery of the upper urinary tract collecting system. They generally do not cause problems intraoperatively as long as there is no hemorrhage. Ureteral injuries are rare but can occur as a result of inflating the ureteral balloon occlusion catheter in the ureter or during other ureteral manipulation. These injuries generally will heal over a ureteral stent. Renal pelvic perforation can occur during initial access or during dilation. Pushing on a renal pelvic stone too hard during lithotripsy or misusing a lithotripter or resectoscope can also perforate the renal pelvis. **Renal pelvic perforation is usually recognized intraoperatively** (Fig. 47–44). **Collapse of a previously distended renal pelvis is a usual sign if the perforation is not visualized directly at first.** A perforation that has not been recognized intraoperatively might be heralded by postoperative abdominal distention, ileus, and/or fever. **If noted intraoperatively, abort the procedure unless it is near completion, in which case the task can be completed at lower irrigation pressure if the patient is doing well clinically. At the completion of a**

case in which renal pelvic perforation has been noted, insert a nephroureteral stent or a nephrostomy tube plus an internal ureteral stent to optimize drainage and then wait 2 to 7 days before nephrostography and tube removal, depending on the severity of the injury. If renal pelvic perforation is detected postprocedure, despite adequate drainage of the collecting system, then placement of a percutaneous drain into the urinoma might be required. There have been reports of massive intra-abdominal collection of extravasated fluid after percutaneous renal surgery (Peterson et al, 1985; Pugach et al, 1999; Ghai et al, 2003).

Visceral Injury

Any abdominal organ close to the kidney can be injured during percutaneous renal surgery including the colon, duodenum, jejunum, spleen, liver, and biliary system.

Colon injury occurs during percutaneous renal surgery in the prone position at a rate of less than 1% (Segura et al, 1985; Lee et al, 1987; Gerspach et al, 1997; El-Nahas et al, 2006; Michel et al, 2007). **As would be expected on the basis of the anatomy, with the apposition of the colon to the kidney being greatest on the left side and at the lower pole, the left colon is injured twice as often as the right colon and the majority of colon injuries involve access to the lower pole** (El-Nahas et al, 2006). Additional risk factors include advanced patient age, dilated colon, prior colon surgery or disease, thin body habitus, and the presence of a horseshoe kidney (Goswami et al, 2001; El-Nahas et al, 2006; Michel et al, 2007; Korkes et al, 2009). Injury might be less likely with the patient in the supine position; one study reported a retrorenal colon on CT in 1.9% of patients in the supine position versus 10% in prone patients (Hopper et al, 1987). The clinical incidence of colon injury, however, is much lower than this figure would suggest.

Intraoperative detection of colonic injury confers easier management. If not determined intraoperatively, colon injury should be considered postoperatively if a patient develops unexplained fever, prolonged ileus, unexplained leukocytosis, rectal bleeding, evidence of peritoneal inflammation, or fecaluria or pneumouria. Clinically apparent nephrocolonic fistula may be the presenting sign, or the injury may not be noted until the time of postoperative nephrostogram. **Most colon injuries are extraperitoneal and can be managed conservatively** (Gerspach et al, 1997; El-Nahas et al, 2006; Korkes et al, 2009). **The main principle of care is prompt and separate drainage of the colon and urinary collecting system.** Back out the offending nephrostomy tube into the colon to serve as a colostomy tube, considering exchanging it for a larger tube to enhance colonic drainage, and obtain separate access to the upper urinary tract with either a new percutaneous access that does not traverse the colon or a retrograde-placed ureteral stent. Administer broad-spectrum antibiotics. Give nothing by mouth for a few days, and then start clear liquids. If there is no increase of colostomy output, then administer high-calorie protein supplementation and eventually a regular diet. Parenteral feeding is usually not required. Confirm lack of communication between the colon and collecting system with contrast injection of the tubes before removing them. If the injury is intraperitoneal, or if the patient develops peritonitis or sepsis, then open surgical repair may be required.

Duodenal and jejunal injuries are even less common than colonic injury, described in only a few cases reports (Culkin et al, 1985; Morris et al, 1991; Kumar et al, 1994; Ahmed and Reeve, 1995; Santiago et al, 1998; Lopes-Neto et al, 2000; Al-Assiri et al, 2005; Ricciardi et al, 2007). Detection is by clinical signs and symptoms of peritonitis or by noting a nephroenteric fistula during postoperative nephrostography. Although open surgery may be required, conservative management using percutaneous intraduodenal catheterization or simple nasogastric or nasoduodenal drainage, combined with drainage of the upper urinary tract, fasting, and parenteral feeding, has been successful.

Studies based on CT and MRI have suggested that splenic and hepatic injuries should be unlikely unless the kidney is accessed above the 10th rib, although access above the 11th or 12th rib might traverse these organs in rare cases (Hopper and Yakes, 1990; Robert et al, 1999). If splenomegaly or hepatomegaly is present, these relationships change and access guided by CT is recommended. Splenic or hepatic injuries to orthotopic and normal-sized organs occur almost exclusively with supracostal upper pole renal access. Splenic injury might require laparotomy and potentially splenectomy owing to hemorrhage (Kondas et al, 1994; Shah et al, 2007), but conservative management has been successful as well (Goldberg et al, 1989; Santiago et al, 1998; Carey et al, 2006; Schaeffer et al, 2008). Liver injury is less likely to be associated with significant hemorrhage—indeed the liver can be traversed percutaneously to obtain biliary access (Nadler et al, 2002), and purposeful transhepatic percutaneous renal surgery has been reported (Matlaga et al, 2006). As such, liver injuries during percutaneous renal surgery can be managed conservatively (El-Nahas et al, 2008).

There have been a few reported cases of biliary peritonitis due to injury of the gallbladder or biliary tree, which require laparotomy owing to the high mortality rate of bile peritonitis (Martin et al, 1996; Saxby, 1996; Kontothanassis and Bissas, 1997; Ricciardi et al, 2007). Postoperative pancreatitis, without evidence of direct pancreatic injury, has been described as well (Chitale et al, 2005).

Pleural Injury

Hydrothorax, and occasionally pneumothorax, is a risk of percutaneous access to the upper urinary tract collecting system. Access below the 12th rib rarely results in hydrothorax or pneumothorax (<0.5%) (Munver et al, 2001; Radecka et al, 2003; Lojanapiwat and Prasopsuk, 2006). The incidence of pleural complications with punctures above the 12th rib (the 11th intercostal space) is generally considered an acceptable risk if that approach provides optimal access to the upper urinary tract. Access above the 11th rib or higher carries a much greater risk of pleural injury. **Among 16 reports that distinguished between access above the 12th rib and access above the 11th rib, reporting a total of 1384 supracostal percutaneous accesses, the incidence of hydro/pneumothorax that required intervention varied from 0% to 18% for access superior to the 12th rib (weighted mean of 4.6%) and from 0% to 100% for access superior to the 11th rib (weighted mean of 24.6%)** (Young et al, 1985; Picus et al, 1986; Narasimham et al, 1991; Golijanin et al, 1998; Kekre et al, 2001; Munver et al, 2001; Gupta et al, 2002; Wong and Leveillee, 2002; Muzrakchi et al, 2003; Radecka et al, 2003; Aron et al, 2005c; Lojanapiwat and Prasopsuk, 2006; Yadav et al, 2006; Shaban et al, 2008; Sukumar et al, 2008; Yadav et al, 2008).

Nephropleural fistula (urinothorax) is a direct and persistent communication between the intrarenal collecting system and the intrathoracic cavity (Ray et al, 2003; Shleyfer et al, 2006; Handa

et al, 2007). It can follow percutaneous renal access of the upper urinary tract in the setting of pleural transgression. Some degree of distal ureteral obstruction usually contributes to the problem. Most commonly, nephropleural fistula is diagnosed after the percutaneous tube is removed, but it can occur in the setting of a recognized hydrothorax when the persistent communication is documented on nephrostography at the time of intended tube removal. Lallas and colleagues (2004) reported that nephropleural fistula never occurred in association with subcostal access but did complicate 2.3% of punctures superior to the 12th rib and 6.3% of punctures superior to the 11th rib.

Pleural complications of supracostal percutaneous access can often be detected with chest fluoroscopy during or at the conclusion of the procedure. Fluid can be seen tracking along the lateral borders of the chest cavity and compressing the ipsilateral lung. Although postoperative chest radiography is more sensitive than intraoperative fluoroscopy, in the series by Ogan and colleagues (2003), thoracostomy was never required on the basis of postoperative chest radiography when intraoperative chest fluoroscopy was negative. **Nonetheless, formal chest radiography is recommended following all cases of supracostal percutaneous renal access.**

Thoracostomy is not necessary for all patients with hydrothorax. If hydrothorax is noted intraoperatively, then insert a small-caliber (8-Fr to 12-Fr) Cope nephrostomy tube as the thoracostomy (Fig. 47–45), using fluoroscopic guidance and the same general techniques as for antegrade percutaneous renal access (Ogan and Pearle, 2002). A Heimlich valve, rather than water seal drainage, is all that is necessary in the absence of lung injury. If a hydrothorax is noted on the postoperative chest radiograph, then place a small-caliber tube only if the effusion is large or there is evidence of respiratory compromise or hemodynamic instability. A large-bore thoracostomy tube as for lung injury is rarely required.



Figure 47–45. A 12-Fr Cope catheter placed into the chest when a large hydrothorax was noted intraoperatively on fluoroscopy.

Metabolic and Physiologic Complications

Normal saline should be the irrigant for percutaneous renal surgery, with the exception of glycine or similar nonelectrolytic isotonic fluids when monopolar electrocautery is used. Irrigation with water during percutaneous renal surgery risks intravascular hemolysis, which can be fatal. At least one death associated with water irrigation during percutaneous nephrolithotomy has been described (Bennett et al, 1984), and the author is aware of an unreported case. Intravascular or extravascular extravasation of nonelectrolytic isotonic fluid from continued irrigation in the setting of a large venous injury or collecting system perforation, respectively, can result in hyponatremia and other electrolyte abnormalities, renal or hepatic dysfunction, and mental status changes. When normal saline is used in uncomplicated cases, the amount of fluid absorption is generally clinically insignificant (Kukreja et al, 2002; Koroglu et al, 2003), although in one study 28% of patients absorbed more than a liter (Malhotra et al, 2001). A large amount of saline extravasation can lead to clinically significant respiratory distress or cardiac failure due to volume overload.

Venous gas embolism is a rare but potentially fatal complication of percutaneous renal surgery. The gas (in this case, air) enters the venous system and passes through the right heart into the pulmonary circulation, blocking the output of the right heart, which results in hypoxemia, hypercapnia, and depressed cardiac output. Gas can also pass through a patent foramen ovale to enter the arterial system, which can result in neurologic deficits. Among six reported cases of venous gas embolism in association with percutaneous renal surgery, three were associated with air pyelography in combination with percutaneous access of the kidney (Miller et al, 1984; Cadeddu et al, 1997a; Droghetti et al, 2002), one involved percutaneous surgery without air pyelography (Turillazzi et al, 2009) and two occurred after retrograde injection of air into the renal pelvis but before percutaneous puncture (Varkarakis et al, 2003; Song et al, 2007). Venous gas embolism is indicated by hypoxemia, evidence of pulmonary edema, increased airway pressure, hypotension, jugular venous distention, facial plethora, dysrhythmias, and auscultation of a mill-wheel cardiac murmur and/or the appearance of a widened QRS complex with right heart strain patterns on electrocardiography. The most sensitive measure is a sudden decrease in capnometry reading of the P(end-tidal) CO_2. Swift response is required and includes rapid ventilation with 100% oxygen, positioning the patient head down with the right side up, and general resuscitative maneuvers.

Postoperative Fever and Sepsis

After percutaneous nephrolithotomy, 15% to 30% of patients have a fever. Risk factors for fever after percutaneous nephrolithotomy include infectious stones, preoperative urinary tract infection, hydronephrosis, and indwelling ureteral stent or nephrostomy tube (Charton et al, 1986; Troxel and Low, 2002; Aghdas et al, 2006). **Most patients with fever after percutaneous nephrolithotomy, assuming appropriate antimicrobial prophylaxis, do not have infection** (Cadeddu et al, 1998). **Sepsis occurs in 1% to 2% of patients after**

percutaneous nephrolithotomy (Dogan et al, 2007; Gonen et al, 2008b). Sepsis implies an infection, which is not always present; "systemic inflammatory response syndrome" is a more accurate description. Preoperative urine cultures should be treated. Even if bacteriologic cure is not possible (e.g., infectious stone, indwelling nephrostomy tube), bacterial counts should be suppressed as much as possible to reduce the risk of infectious complications. Nonetheless, a negative urine culture does not guarantee against sepsis because the voided urine culture may not reflect the intrarenal urine (Rao et al, 1991). **Because the febrile patient who will progress to sepsis cannot be predicted, careful observation, appropriate diagnostic evaluation, and initiation of antimicrobial therapy and other supportive care is indicated if a postoperative fever does not resolve promptly.**

If pus is aspirated upon initial percutaneous to the upper urinary tract, the safest measure is to abort the procedure and leave a nephrostomy tube for drainage. Aron and associates (2005a), on the basis of their experience in 19 patients with purulent fluid from the kidney at initial puncture for percutaneous nephrolithotomy, suggested that aborting the procedure might not always be necessary. They continued the procedure in 12 patients and delayed it in 7. Of the 12 patients in whom the procedure was continued, two (17%) had postprocedure sepsis. Among the seven patients in whom the procedure was delayed (for 3 to 7 days), two (29%) had sepsis after the second procedure (both of whom had additional portions of the kidney containing undrained pus that were discovered at the time of the delayed percutaneous nephrolithotomy). An important difference was in the quality of the aspirated material. One patient in whom percutaneous nephrolithotomy was continued and two in whom the procedure was delayed had "frank pus" as opposed to "purulent fluid" in the other cases. All three of these patients with frank pus were among the four who developed sepsis. The authors recommend that if frank pus is aspirated, then the procedure should be aborted. If the aspirate is a cloudy nonviscous liquid, it might be safe to proceed. This approach has not yet been validated in additional studies. This report also suggests that not all patients with "purulent fluid" are infected. Of the 19 patients, the culture of the aspirate revealed bacteria in only 6. This suggests that infection may have been sterilized by previous antibiotic usage. The turbid fluid may indicate a sterile inflammatory response to the stone, or the fluid may consist of debris related to the renal calculus. Another important point is that a single nephrostomy tube may not drain all areas of infection in the kidney, especially if there is intrarenal obstruction.

Neuromusculoskeletal Complications

Prone positioning for percutaneous renal surgery has the potential for a number of neuromusculoskeletal injuries (Shermak et al, 2006; Edgcombe et al, 2008). **Excessive pressure on neural and vascular structures, whether directly from the operative table or indirectly through the positioning of limbs, may lead to short- or long-term disability.** Most reported injuries associated with prone positioning are related to the head and neck region including ocular injury resulting in visual loss, facial nerve injury or necrosis over facial bones or the tip of the nose, and cerebrovascular accident due to carotid or vertebrobasilar artery dissection. Careful padding of the head, in a neutral and nonextended position, is important. Malpositioning of the extremities can lead to peripheral nerve injury (Winfree and Kline, 2005). The shoulder and elbow should not be abducted more than 90 degrees, so as to prevent brachial plexopathy, and generous padding at the elbow and forearm reduces the risk of nerve compression. Knees need to be padded. Ankles should be elevated to reduce pressure on the dorsum of the foot.

Venous Thromboembolism

The incidence of venous thromboembolism with percutaneous renal surgery is low (<3% in older series of percutaneous nephrolithotomy) (Segura et al, 1985; Lee et al, 1987), but there are no recent data. **The American Urological Association's Best Practice Statement for the prevention of deep vein thrombosis in patients undergoing urologic surgery does not include percutaneous renal surgery among procedures for which prophylaxis against venous thromboembolism is recommended** (Forrest et al, 2009). Early ambulation is the best measure to reduce the already low risk of venous thromboembolism.

Tube Dislodgement

Whether the percutaneous nephrostomy tube is intended to be short or long term, inadvertent tube dislodgement risks poor patient outcomes. The tube does not need to fall out of the patient completely; especially in a patient with a large subcutaneous layer, the tube can remain attached at the skin but pull out from within the kidney when the distance between the skin and kidney increases with patient movement. Nonetheless, **all tubes should be secured at the skin to reduce the risk of at least one mechanism of tube removal.** Tubes vary in their inherent ability to resist removal. **Malecot tubes are the easiest to pull out, and circle nephrostomy tubes are the hardest. The Cope retention mechanism is more secure than Malecot wings but does not retain as well as a balloon** (Canales et al, 2005). For long-term indwelling, circle nephrostomy tubes and Cope nephrostomy tubes are most commonly used. Ironically, the Malecot tube is also the one most likely to become entrapped; tissue can grow over the wings, making removal difficult and traumatic (Sardina et al, 1995; Tasca and Cacciola, 2004).

If a nephrostomy tube has been in for only a short time, then complete dislodgement often leads to complete loss of percutaneous access. Using a nephrostomy tube with a ureteral extension, whether it is only partially down the ureter as in the Malecot re-entry tube or all the way into the bladder as in a nephroureteral stent, will increase the chance of having some access back into the kidney even if the renal retention device pulls out of the kidney. For tubes that have been in place more than a few weeks, the tract is usually mature enough that carefully probing with an angled hydrophilic wire and judicious use of contrast material to outline the tract can allow restoration of the percutaneous access. Tube malposition can usually be corrected under fluoroscopic control, but guidance by CT might be helpful as well (Jones and McGahan, 1999).

Collecting System Obstruction

Transient ureteral obstruction owing to ureteral edema or blood clot occurs commonly. To assess for this, nephrostomy tubes should be removed after nephrostography or after a period of clamping to assess clinically for distal ureteral obstruction. Much more uncommon is stricture formation, which can occur in the ureter, at the ureteropelvic junction, or in an infundibulum. If the stricture occurs early in the postprocedure course, then a

nephrocutaneous fistula will develop. If it develops late, then hydronephrosis or hydrocalyx will occur. **In one large series there was a 2% rate of infundibular stenosis after percutaneous nephrolithotomy** (Parsons et al, 2002). The obstructions developed in the areas that had been accessed percutaneously. Predisposing factors in this and other smaller reports (Ballanger et al, 1987; Weir and Honey, 1999; Buchholz, 2001) include large stone burden requiring multiple or long procedures and prolonged nephrostomy tube drainage, previous open stone surgery, diabetes mellitus, and obesity. The ureter (Culkin et al, 1987; Lopes-Neto et al, 2008) and the ureteropelvic junction (Green et al, 1987; Ben Slama et al, 2005) are smaller in caliber than the intrarenal collecting system and are therefore also susceptible to trauma.

Obstruction after percutaneous renal surgery should respond to endoscopic treatment in most cases, but open surgical reconstruction or excision with partial nephrectomy or total nephrectomy may be required.

Key Points: Complications

- Hemorrhage during percutaneous surgery is associated with inappropriate access site, multiple access sites, supracostal access, increasing tract size, tract dilation with methods other than balloon dilation, prolonged operative time, and renal pelvic perforation or other intraoperative technical errors.
- In most cases of hemorrhage during percutaneous surgery or at the time of sheath removal, placing a nephrostomy tube and letting the collecting system clot off is effective. If bleeding is more severe, additional measures may be required.
- Delayed hemorrhage is usually due to arteriovenous fistulas or arterial pseudoaneurysms. Bright red blood in the urine after percutaneous renal surgery should prompt hospital admission and consideration of angiography. Selective angio-embolization is highly successful in treatment.
- If renal pelvic perforation is noted intraoperatively, abort the procedure unless it is near completion. Insert a nephroureteral stent or a nephrostomy tube plus a ureteral stent to optimize drainage.
- Most colon injuries from percutaneous renal surgery are extraperitoneal and can be managed conservatively by draining the colon and urinary collecting system separately.
- Hydrothorax or pneumothorax requiring intervention is related to the level of percutaneous access. Incidence estimates are less than 0.5% below the 12th rib, 4.6% above the 12th rib, and 24.6% above the 11th rib. Pleural complications can often be detected with chest fluoroscopically during the procedure, but a chest radiograph should also be obtained following all cases of supracostal percutaneous renal access.
- Normal saline should be the fluid used for irrigation during percutaneous renal surgery, with the exception of glycine or a similar nonconductive solution when monopolar electrocautery is used.
- If pus is aspirated on initial percutaneous to the upper urinary tract, the safest measure is to abort the procedure and leave a nephrostomy tube for drainage.

Loss of Renal Function

Despite the direct puncture of renal parenchyma and enlargement of sometimes multiple tracts to up to 34 Fr, the kidney suffers little permanent damage after uncomplicated percutaneous renal surgery. On the basis of several different techniques of study, a kidney loses negligible function after percutaneous renal surgery (Ekelund et al, 1986; Chen et al, 1992; Saxby, 1997; Kilic et al, 2006), and in one study there appeared to be less damage to the kidney after percutaneous nephrolithotomy than after shock wave lithotripsy (LeChevallier et al, 1993). In the setting of impaired function, especially due to obstructing calculi, percutaneous surgery will often improve renal function (Chandhoke et al, 1992; Chatham et al, 2002; Bilen et al, 2008). Percutaneous renal surgery also causes no significant change in function of solitary kidneys (Jones et al, 1991; Liou and Streem, 2001; Canes et al, 2009). In one study of patients surveyed a mean of 19 years after treatment, there was no difference between shock wave lithotripsy and percutaneous nephrolithotomy in the development of renal insufficiency or hypertension (Krambeck et al, 2008b).

When there is renal loss following percutaneous renal surgery, it usually owes to disastrous vascular injury or the angio-embolization used to treat hemorrhage. In the original American Urological Association guideline on staghorn calculi (Segura et al, 1994), renal loss after percutaneous nephrolithotomy was estimated at 1.6%; data were insufficient to calculate a new figure in the 2005 update of the guidelines (Preminger et al, 2005).

Death

Death after percutaneous renal surgery is extremely rare, and when it occurs it is usually due to underlying cardiovascular conditions. In the current American Urological Association guideline on management of staghorn calculi, the median death estimate for percutaneous nephrolithotomy was zero, which reflects the paucity of data on the subject (Preminger et al, 2005).

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter
48

Surgical Management of Upper Urinary Tract Calculi

Brian R. Matlaga, MD, MPH • James E. Lingeman, MD

Historical Overview
Renal Calculi
Ureteral Calculi
Urinary Calculi during Pregnancy
Stone Removal: Surgical Techniques and Technology

HISTORICAL OVERVIEW

Kidney Calculi

Although calculi in the kidney were rare before the Industrial Revolution (Shah and Whitfield, 2002), the existence of nephrolithiasis was known to Hippocrates, who described the symptoms of renal colic: "An acute pain is felt in the kidney, the loins, the flank and the testis of the affected side; the patient passes urine frequently; gradually the urine is suppressed. With the urine, sand is passed." It is not certain whether Hippocrates actually performed surgery on patients with renal calculi, but he did describe the following operations: the drainage of tuberculous and nontuberculous pyelonephritic abscesses, the incision of swelling in the loin due to renal tumefaction resulting from stone, and the drainage of kidneys presenting with acute congestion caused by pyelonephritis (Wershub, 1970). In the centuries that followed Hippocrates there was little scientific progress in the surgical therapy for patients with renal calculi. The alleged first account of a surgical attempt to remove a stone from a patient's kidney is the case of the French archer of Bagnolet. Little is known of the authenticity of this tale of a condemned man afflicted with a renal calculus who agreed to allow surgery on the affected kidney with the condition that if he survived he would be freed. According to the anecdote the man survived the open surgical stone removal and was freed in 1474 (Herman, 1973). Unfortunately there are no first-hand records of this event so the veracity of this claim is uncertain. The first verifiable account of renal stone surgery was in 1550, when Cardan of Milan opened a lumbar abscess on a young girl and removed 18 calculi (Desnos, 1972). For the following 2 centuries most surgeons were in agreement that the only indication for open renal surgery was the infected calculous kidney, distended by the accumulation of purulent matter, or those kidneys in which the calculus could be palpated in the organ itself.

In 1734 Lafite incised a swelling in a patient's loin and drained considerable purulence. Twenty-two days later the pus reaccumulated; he probed the incision and found a stone in the region of the kidney. Lafite widened the prior incision and removed two calculi; the patient recovered well. Four years later Lafite again removed stones from a man who had undergone drainage of a lumbar swelling 11 years before and who had a persistent urinary fistula. Lafite concluded that it was possible to remove the stones at the time of the first surgical intervention rather than subject the patient to multiple procedures (Ballenger et al, 1933). In 1872, William Ingalls of Boston City Hospital removed a large calculus from the right kidney of a 31-year-old woman with a persistent pyelocutaneous fistula (Spirnak and Resnick, 1983). Ingalls incised the sinus tract of the fistula and extracted the stone with forceps, thus performing the first recorded nephrolithotomy in America. In 1880, Henry Morris of England was the first to remove a stone from an otherwise healthy kidney by nephrolithotomy, extracting a 31-g mulberry calculus from the kidney of a young woman (Dudley, 1973).

As the surgical techniques of nephrolithotomy evolved, renal parenchymal incisions were made in a variety of different ways in an effort to reduce hemorrhagic morbidity. Heineke, in 1879, first described a pyelotomy incision for the extraction of calculi. The operation rapidly found favor and was employed by many surgeons, although it was not possible to extend the incision to permit extraction of large renal calculi without damaging the retropelvic renal artery (Wershub, 1970). Josef Hyrtl, in 1882, and Max Brödel, in 1902, described a relatively avascular plane near the midline (5 mm posterior) of the convex border of the kidney through which the collecting system of the kidney could be entered. In continental Europe, credit for the plane was given to Hyrtl; but in England and the United States it was called the Brödel bloodless line or the Brödel white line (Schultheiss et al, 2000). Although the existence of this avascular plane was an important discovery, surgeons continued to find that bleeding during nephrolithotomy was a considerable problem. Zuckerkandl described an inferior pyelonephrolithotomy in which a pyelotomy incision was extended into the lower pole of the kidney. Partner recommended a V-shaped incision with two limbs radiating toward the poles of the kidney. Other attempts were made to control the persistent problem of bleeding, including compression of the hilar vessels and various methods of suturing. In 1887, Czerny was the first to approximate the cut edges of the incised kidney with suture to control hemorrhage and to prevent fistula formation. In the same year, Guyon reported that nephrectomy, although efficacious in curing patients suffering from calculous pyonephrosis, was more dangerous than nephrolithotomy because lithiasis was

often bilateral (Wershub, 1970). In 1889 Kümmell was the first surgeon to perform a partial nephrectomy for calculous pyonephrosis (Redman, 1983). Lower, in 1913, revived interest in pyelolithotomy when he suggested that this technique may be a safer and easier method of removing renal calculi than nephrolithotomy. Although several small series of cases indicated that there might be a higher incidence of stone recurrence after pyelolithotomy, other studies showed that recurrence was no more common than it was after nephrolithotomy (Murphy, 1972). These findings, in conjunction with rapid advancements in the field of radiography, brought about a decided preference for pyelolithotomy (Gil-Vernet and Culla, 1981). In 1943 Dees and Fox reported the first use of coagulum to remove small stones and stone fragments from the renal pelvis and calyces (Marshall, 1983). Fibrinogen and thrombin were used to make a coagulum that was injected into the renal pelvis and produced a flexible cast of the pelvis and calyces. The use of this technique was limited initially owing to the scarcity of materials and the risk of blood-borne disease transmission. However, interest in coagulum pyelolithotomy was renewed when cryoprecipitate was found to be a safe and readily available source of concentrated fibrinogen (Fischer et al, 1980).

An important advance in the open surgical approach to the kidney was the intrasinusally extended pyelolithotomy, pioneered by Gil-Vernet in 1965. Because of its wide applicability and minimal morbidity this approach to the renal collecting system became the procedure of choice for treatment of the majority of renal pelvic calculi. Patients harboring large or complex calculi could be effectively treated with extended pyelolithotomy combined with multiple radial nephrotomies (Wickham et al, 1974). In 1968 **Smith and Boyce described anatrophic nephrolithotomy, a procedure that derived its name from the technique of incising the renal parenchyma along the avascular plane between the anterior and posterior vascular distributions. Because an incision in this plane does not interrupt the blood supply to the renal parenchyma it does not result in atrophy, hence the term *anatrophic*.** This procedure permits a relatively bloodless operation that encompasses stone removal, reconstruction of the calyceal system, and closure of the renal capsule with preservation of renal function. **Although stone-free rates of these modern surgical techniques were excellent, morbidity was significant, and the search for new techniques and technologies continued.**

Ureteral Calculi

Ambroise Paré is credited with the first account of a ureteral calculus, when, in 1564, he described "the cruel pain [that] tormented the patient in that place where the stone lodged." Paré also stated that death was the consequence of having calculi impacted in both ureters (Murphy, 1972). Morris recounted that surgical intervention was an option in the treatment of ureteral stones when he reported in 1898 that "operations on the ureter are an advance of the last few years, but not many have been recorded up to the present time" (Ballenger et al, 1933). Thomas Emmet, of New York, published an account in 1879 of three female patients with stones impacted at the distal aspect of the ureter. In one patient Emmet opened the bladder and removed the stone with forceps; in a second patient he removed a stone by cutting down on it through the vaginal wall. These procedures were the first records of a surgeon making a definite diagnosis of ureteral calculus and deliberately and successfully performing a ureterolithotomy. In the years that followed, intraperitoneal, perineal, sacral, transrectal, and transvaginal approaches were used. In 1910 **Gibson, of New York, described an incision parallel to and just above the Poupart ligament, wholly extraperitoneal, by which the lower ureter, even down to its entrance into the bladder, could be readily exposed.** This safe and comparatively easy approach to the ureter gave open ureterolithotomy a solid basis for success.

The Rise of Endourology

Before the development of endoscopy attempts to blindly extract calculi were not uncommon. In 1889, Gustav Kolisher performed the first successful stone manipulation, reporting that he "located the stone with a metal-tipped catheter several inches above the ureteric orifice and through it injected 30 cc of sterile oil," displacing the stone (Murphy, 1972).

The development of minimally invasive surgical techniques for the treatment of patients suffering from urinary lithiasis has been greatly dependent on technologic advances in the fields of **fiberoptics, radiographic imaging, and lithotripsy (shockwave, ultrasonic, electrohydraulic, and laser).** These advancements have accelerated the evolution of modern techniques of calculus removal, including **ureteroscopy, percutaneous nephrolithotomy (PNL), and extracorporeal shockwave lithotripsy (SWL). In 1979 Arthur Smith defined the term *endourology* as closed controlled manipulation within the genitourinary tract** (Smith et al, 1979).

Ureteroscopy

The practice of ureteroscopy began by happenstance when, in 1912, Hugh Hampton Young introduced a pediatric cystoscope into the massively dilated ureter of a child with posterior urethral valves (Young and McKay, 1929). Aided by the child's secondary ureteral dilation, Young was able to advance the cystoscope to the level of the renal pelvis, thus becoming the first urologist to view the intrarenal collecting system endoscopically. Unfortunately the following 3 decades held few significant advances in ureteroscopic technology until knowledge of fiberoptics could be put to clinical use. By 1957 Curtiss and Hirschowitz combined a large number of glass fibers into a coherent bundle and fused the fibers at their ends to allow them to move individually along their length, thus creating the first flexible endoscope (Hirschowitz et al, 1957). In 1964 Marshall reported the first urologic use of this new type of flexible endoscope when he passed the scope through an open ureterotomy to the level of the renal pelvis, thereby performing the first flexible ureteroscopy. Subsequently, two of his associates, McGovern and Walzak, performed the first transurethral flexible ureteroscopy when they passed the same 9-Fr flexible endoscope to inspect a ureteral calculus. Since then, developments in optics and mechanics have greatly improved the design of flexible ureteroscopes.

Currently available ureteroscopes range from 54 to 70 cm in length and have a tapered shaft diameter that increases proximally. As the tip of the ureteroscope is inserted into the ureter and passed retrograde, the ureter is slowly dilated. Initial ureteroscopes had neither a working nor an irrigating channel. Most modern ureteroscopes have a single working channel, and some have a second irrigation channel that serves to distend the ureter and maintain visualization.

Early flexible ureteroscopes were passive, and the subsequent incorporation of active tip deflection has greatly increased their utility. Active deflection refers to deflection of the tip of the

endoscope, which is controlled by the surgeon through a lever mechanism on the handle of the endoscope. Flexible ureteroscopes have been introduced with two segments of active deflection, with the active primary site of deflection providing 170 to 180 degrees of up and down movement; the secondary active deflection, located several centimeters proximal to the primary deflection, is a 130-degree one-way downward deflection. This design greatly facilitates entry into the lower pole infundibulum. Other manufacturers have designed flexible ureteroscopes with 270 degrees of deflection, which also facilitates entry into the lower pole infundibulum.

More recently, efforts have been devoted to advancing the imaging capability of the flexible ureteroscope. Digital endoscopes, which incorporate an optical chip [complementary metal oxide semiconductor [CMOS] or charge-coupled device [CCD]) at the tip have been introduced. Although the initial generation of these chips were quite large, further refinements have reduced their size so that they can be applied to flexible ureteroscopes. Advantages associated with this technology include improved optical characteristics, obviating focus and white-balancing issues, and decreased surgeon fatigue, because cumbersome proximal camera and light cord attachments are not required. Image processing software permits digital zoom capability as well. In comparing digital flexible ureteroscopy to conventional fiberoptic flexible ureteroscopy, investigators have noted that the digital devices are associated with superior imaging characteristics (Humphreys et al, 2008). Several disadvantages of the digital device must be recognized, however: digital ureteroscopes are larger in diameter compared with their fiberoptic counterparts, and the technology also is more costly.

Interestingly, the first reports of rigid ureteroscopy trailed those of flexible ureteroscopy by almost 10 years. In 1977 Goodman reported on three cases in which a pediatric cystoscope was used to treat patients with ureteral maladies. These initial rigid ureteroscopes employed a rod-lens system that was large (10 to 13 Fr) and inflexible. Most rigid ureteroscope designs have replaced this rod-lens system of image transmission with fiberoptics, which allows significant reduction in the size of the endoscope. In addition, the flexibility of the fiberoptic bundles allows the shaft of the endoscope to become somewhat bendable along its vertical axis, hence the term *semirigid ureteroscope*.

Parallel to improvements in rigid and flexible ureteroscopes were advances in intracorporeal lithotripters, including ultrasonic, electrohydraulic, pneumatic, and laser probes, allowing efficient stone fragmentation through the miniaturized modern ureteroscopic equipment. Many new stone retrieval devices, designed to pass through the working channel of a ureteroscope, have been introduced with the capability for manipulation and deflection.

Percutaneous Stone Removal

The first description of percutaneous stone removal was that of Rupel and Brown (1941) of Indianapolis, who removed a stone through a previously established surgical nephrostomy. It was not until 1955, however, that Goodwin and associates described the first placement of a percutaneous nephrostomy tube to drain a grossly hydronephrotic kidney. These researchers did not have the benefit of radiographic guidance, and so the drainage tube was placed without imaging. In 1976, Fernstrom and Johannson first reported the establishment of percutaneous access with the specific intention of removing a renal stone. Subsequent advances in endoscopes, imaging equipment, and intracorporeal lithotripters allowed urologists and radiologists to refine these percutaneous techniques through the late 1970s and early 1980s into well-established methods for removal of upper urinary tract calculi.

Extracorporeal Shockwave Lithotripsy

The phenomenon that sound waves can be focused has been known since antiquity. The ancient Greeks, as taught by Dionysius, used this knowledge to construct vaults that allowed them to overhear the conversations of their imprisoned enemies. In the 18th and 19th centuries, cabinets constructed with echo or sound mirrors were capable of transmitting the ticking of a pocket watch over a distance exceeding 60 feet.

High-energy shockwaves, too, have been recognized for many years. Examples of high-energy shockwaves include the blast effect associated with explosions, as well as the potentially window-shattering sonic boom created when aircraft pass beyond the speed of sound. Engineers at Dornier Medical Systems in what was then West Germany, during research on the effects of shockwaves on military hardware, demonstrated that these shockwaves are reflectable and therefore focusable. The possibility of applying shockwave energy to human tissue was discovered when, by chance, a test engineer touched a target body at the very moment of impact of a high-velocity projectile. The engineer felt a sensation similar to an electric shock, although the contact point at the skin showed no damage at all (Hepp, 1984). This observation and its potential military applications led Dornier to pursue a method of generating a reproducible shockwave.

Beginning in 1969 and funded by the German Ministry of Defense, Dornier began a study of the effects of shockwaves on tissue. Specifically, the study was to determine if the shockwaves generated by a projectile striking the wall of a military tank would damage the lungs of a crew member leaning against the same wall. During the study, Dornier engineers developed techniques to reproducibly generate shockwaves. In the course of this effort the engineers discovered that shockwaves generated in water could pass through living tissue (except for the lung) without discernible damage to the tissue but that brittle materials in the path of the shockwaves would be fragmented.

At some point a possible medical application of shockwaves became apparent: if shockwaves could safely pass through tissue but fragment brittle materials, perhaps they could be used to break up kidney stones. Dornier engineers found that lower-energy shockwaves, which would be appropriate for medical applications, could be generated in a predictable and reproducible manner by an underwater electrical spark discharge.

In 1972, on the basis of preliminary studies performed by Dornier Medical Systems, an agreement was reached with Egbert Schmiedt, director of the urologic clinic at the University of Munich, to proceed with further investigation of the therapeutic potential of this technology (Chaussy and Fuchs, 1986). This research was supported by the West German Federal Ministry of Research and Technology, and the development of the Dornier lithotripter progressed through several prototypes, ultimately culminating in February 1980 with the first treatment of a human by SWL. The production and distribution of the Dornier HM3 lithotripter began in late 1983, and SWL was approved by the U.S. Food and Drug Administration in 1984. Since Dornier's pioneering work, numerous other companies have demonstrated that shockwaves capable of stone fragmentation may be generated by electromagnetic induction, microexplosions, focused lasers, and piezoelectric crystals. To date, more than 3000 lithotripters of all types have been placed worldwide, and more than 1 million patients are treated annually with SWL.

RENAL CALCULI

The primary goal of surgical stone management is to achieve maximal stone clearance with minimal morbidity to the patient. The introduction of SWL as well as continuing advancements in the field of endourology have allowed most patients with renal stones to be treated in a minimally invasive fashion. However, as the armamentarium of treatment modalities available to the urologist has increased, new controversies regarding the indications for these therapies have developed. Currently, urologists face the challenge of selecting the optimal treatment modality on the basis of the patient's and the stone's characteristics. Four minimally invasive treatment modalities are available for the treatment of patients with kidney stones and are discussed in this chapter: SWL, PNL, ureteroscopy, and laparoscopic stone surgery. SWL has also been used in combination with PNL ("sandwich technique") as well as with ureteroscopic lithotripsy. Advances in endoscopic technology and surgical technique have dramatically reduced the need for open surgical procedures to treat patients with renal and ureteral calculi.

Most patients harboring "simple" renal calculi can be treated satisfactorily with SWL. However, there are other patients who are unlikely to achieve a successful outcome with SWL; factors associated with poor stone clearance rates after SWL include **large renal calculi, stones within dependent or obstructed portions of the collecting system, stones of certain composition (cystine, calcium oxalate monohydrate, and brushite), and obesity or a body habitus that inhibits imaging and targeting of the stone.** For patients with these clinical characteristics, alternative treatment modalities, such as ureteroscopy or PNL, should be considered. The urologist, then, when treating a patient with a renal calculus, must ask: **Is the patient an appropriate candidate for SWL, or should other treatment modalities be used?**

Stone-related factors (size, number, location, composition), renal anatomy, and clinical factors of the patient (Table 48–1) as well as the morbidity inherent in each treatment modality and the availability of the requisite equipment should all be considered before selecting the optimal therapy. Although treatment decisions are ultimately the result of an integrated analysis of a multiplicity of factors, for the sake of simplicity these factors and considerations in management of kidney calculi are reviewed separately (Fig. 48–1).

Preoperative Evaluation

The evaluation of patients with urolithiasis in the current era of minimally invasive therapies has not changed substantially from that of the previous era of open stone surgery. Although standard imaging of urinary tract calculi has historically relied on plain abdominal radiography and intravenous urography, recent evidence suggests that unenhanced helical computed tomography (CT) has gained widespread acceptance (Heidenreich et al, 2002). Nephrotomography, radionuclide studies, and retrograde or contrast-enhanced studies are only occasionally necessary to obtain more detailed anatomic and functional information.

Bacteriologic evaluation of the urine is mandatory for all patients. The composition of any previous stone material passed or removed from the patient is extremely important. If previous stones have contained significant amounts of calcium oxalate monohydrate (whewellite) or brushite, fragmentation with SWL may be expected to be more difficult. If a stone of such composition is of a large size, the patient may achieve a better outcome with a percutaneous or ureteroscopic procedure rather than with SWL. Cystinuria may be revealed by previous stone analysis or by the characteristic cystine crystals on urinalysis. Any patient whose stone or stones have radiographic features suggestive of cystine (low radiodensity, ground-glass appearance, smooth edges, bilateral stones) should be screened for cystinuria before treatment because these stones are often not well fragmented by SWL. Many stones may harbor bacteria even though bacteriuria is only intermittently present. This is particularly true in the patient who has received antibiotics in the past. Mariappan and associates (2005) have reported that **the best predictor of post-PNL urosepsis is stone culture or renal pelvic urine culture results rather than bladder urine culture results. The fragmentation of stones, despite sterile urine, may release preformed bacterial endotoxins and viable bacteria that place the patient at risk for septic complications** (Scherz

Table 48–1.

Factors Affecting Management of Renal Stones

STONE FACTORS	RENAL ANATOMIC FACTORS	CLINICAL (PATIENT) FACTORS
Size	Obstruction or stasis	Infection
Number	Hydronephrosis	Obesity
Composition	Ureteropelvic junction obstruction	Body habitus deformity
	Calyceal diverticulum	Coagulopathy
	Horseshoe kidney	Juvenile
	Renal ectopia or fusion	Elderly
	Lower pole	Hypertension
		Renal failure

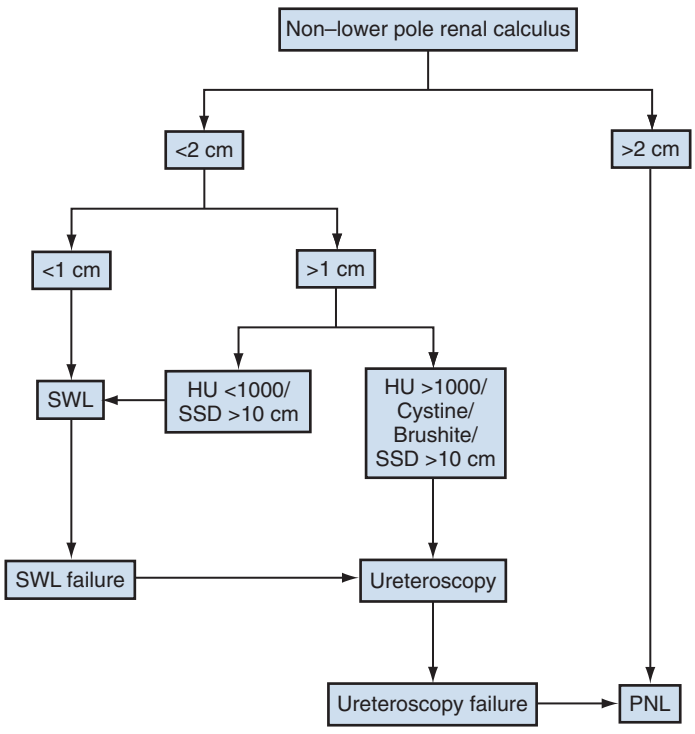


Figure 48–1. Treatment algorithm. HU, Hounsfield unit; PNL, percutaneous nephrolithotomy; SSD, skin-to-stone distance: SWL, shockwave lithotripsy. (Adapted from Wen CC, Nakada SI. Treatment selection and outcomes: renal calculi. Urol Clin North Am 2007;34[3]:409–19.)

and Parsons, 1987; McAleer et al, 2002, 2003; Paterson et al, 2003). In a review of a large series of patients undergoing PNL, de la Rosette and coworkers (2008) also confirmed that a positive preoperative urine culture was a significant predictor of postoperative morbidity. Therefore, patients who have radiographic or clinical features suggestive of struvite or in whom infection is suspected should receive a regimen of broad-spectrum antibiotics before surgery to reduce the risk of sepsis. Parenteral antibiotics should be administered perioperatively in any patient in whom urinary infection is suspected.

Natural History

Calyceal Stones

Before the introduction of minimally invasive therapies, urologists were often reluctant to remove incidentally found, asymptomatic, or minimally symptomatic calyceal stones because of the high morbidity associated with open surgery. Although the traditional indications for the treatment of a renal calculus, including pain, infection, and obstruction, have not changed, the introduction of minimally invasive procedures has allowed patients with mild or even no symptoms to consider these less morbid treatments. However, the decision for intervention should be based on a thorough understanding of the natural history of calyceal stones.

Hubner and Porpaczy (1990) reviewed the natural history of calyceal stones followed for an average of 7.4 years. During the observation period, 45% of the stones increased in size, 68% of the patients experienced symptoms of infection, and 51% of the patients experienced pain. Inci and associates (2007) also found that for patients with asymptomatic lower pole calculi, one third of the stones progressed in size and 11% ultimately required surgical intervention. Thus, **most calyceal stones, in the absence of intervention, are likely to increase in size and cause symptoms of pain or infection.** Furthermore, as time progresses and stone size increases the likelihood of spontaneous stone passage becomes further reduced. Burgher and associates (2004) reported a series of 300 patients initially presenting with asymptomatic renal calculi who were observed for a mean of 3.26 years. **Seventy-seven percent of patients experienced progression of calculi, with 26% requiring surgical intervention. Those patients who initially presented with calculi larger than 4 mm were more likely to fail observation than were patients with smaller solitary calculi.** Keeley and colleagues (2001) reported the results of a randomized prospective trial of SWL versus observation for 200 patients with small asymptomatic calyceal calculi. Although the authors found little difference in the number of patients in each group requiring additional treatment, the **interventions in the observation group were more invasive. Patients in the SWL group required no invasive treatment** on follow-up and could be adequately managed with analgesia or antibiotics. However, there was no evidence of a difference in stone-specific symptoms, quality of life, or renal function tests between the two groups at study's end. The authors concluded that SWL does not appear to improve the clinical outcome of patients with small, asymptomatic renal calculi. **Considering the entirety of the literature to the present time, the necessity of treating patients with small (<5 mm), nonobstructive, asymptomatic stones in a prophylactic fashion remains undetermined.** However, **should asymptomatic stones not be treated, patients must be advised about the need for regular follow-up; a significant proportion of these calculi will eventually become symptomatic and require intervention.** Treatment decisions in these situations should be based on the individual patient's risk factors and the patient's preference. In several groups of patients, including pediatric patients, patients with a solitary kidney, patients in high-risk professions (e.g., pilots), and women considering pregnancy, treatment of asymptomatic calyceal stones may be indicated. Importantly, if asymptomatic stones are to be managed expectantly, a metabolic evaluation should be performed, to direct a regimen that will prevent stone growth and thereby reduce the need for future surgery (Galvin and Pearle, 2006).

Historically, simple calyceal stones documented to be immobile and not causing obstruction have been thought to be unlikely causes of flank pain. However, it has been reported that **the pain induced by nonobstructive calyceal stones is characterized by a dull, deep ache, different from the classic pain of renal colic** (Coury et al, 1988). It has been reported that endoscopic treatment of calyceal calcifications is associated with improved pain relief for many patients (Taub et al, 2006). Therefore, **a patient who is thought to be symptomatic from a calyceal stone should be treated.**

Staghorn Calculi

Staghorn calculi are those stones that fill the major part of the renal collecting system. Typically, they occupy the renal pelvis and branch into most of the calyces, mimicking the horns of a deer or stag (Fig. 48–2). Most staghorn stones are composed of struvite (Segura et al, 1994). Until the early 1970s some physicians believed that patients harboring staghorn calculi should not be treated (Segura, 1997). However, a better understanding of the natural history of staghorn stones has evolved. It is now generally accepted that, if left untreated, a staghorn calculus is associated with progressive deterioration of renal function. Additionally, morbidities associated with an untreated staghorn stone include pain, recurrent urinary tract infection, and sepsis events. Furthermore,

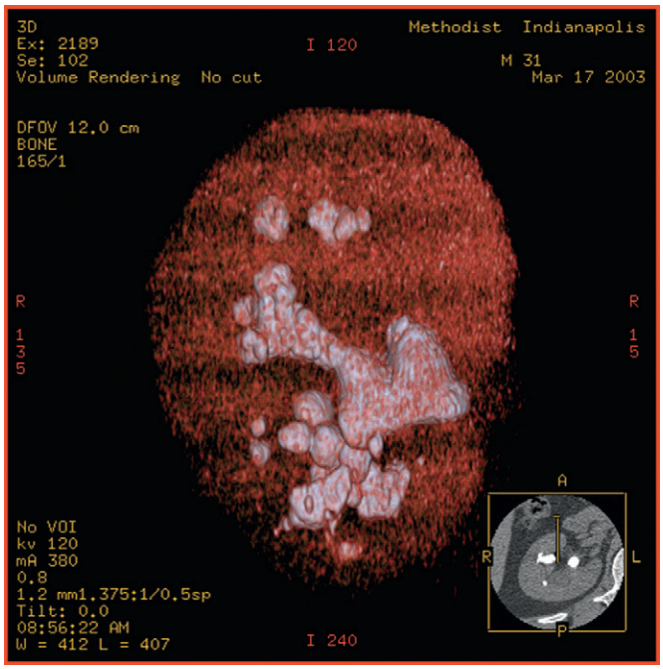


Figure 48–2. Three-dimensional CT reconstructed image of a staghorn calculus.

patients with untreated staghorn calculi face an increased risk of death.

Thus, **untreated struvite staghorn calculi eventually destroy the kidney and pose a significant risk to the patient's life.** The American Urological Association (AUA) Nephrolithiasis Clinical Guidelines, released in 2005, recommended that in otherwise healthy individuals, **newly diagnosed struvite staghorn calculi should be treated surgically** (Preminger et al, 2005). Moreover, **struvite stones must be removed completely to minimize the risk of continued urea-splitting bacteriuria.**

Stone Factors

Stone factors to be considered in the treatment of patients with kidney calculi include **stone burden (size and number), stone composition, and stone location.** Because a significant issue in renal stone location is the treatment of a lower pole stone and the influence of renal anatomy on the treatment results of such calculi, further discussion of this topic is included in the section on renal anatomic factors.

Treatment Decisions by Stone Burden

Stone burden (size and number) is perhaps the single most important factor in determining the appropriate treatment modality for a patient with renal calculi. However, cutoff points for stone size that would categorize those who should be treated by SWL and those who should undergo other treatment modalities have not been definitively determined. For now, kidney calculi are generally divided into the categories of nonstaghorn and staghorn stones. Most controversy related to surgical treatment focuses on the subject of nonstaghorn stones.

Nonstaghorn Calculi. In examining the efficacy of SWL in the treatment of patients with renal calculi, passage of stone debris rather than fragmentation of the stone is the primary limiting factor (Renner et al, 1999). There is general agreement that stone free is the most rigorous definition of successful outcome of any stone removal procedure and that complete stone clearance should be the preferred goal of any intervention (Psihramis et al, 1992). However, because SWL outcome is dependent on spontaneous stone clearance, treatment results are often reported in terms of "success rates," which may be defined as patients who are either stone free or who have asymptomatic, small, residual fragments. Various cutoff points between 2 and 5 mm are used in the literature to define the size of these fragments, making study comparisons difficult. In many cases, failure of SWL is not due to a failure of stone fragmentation but rather a failure to clear the resulting stone fragments. Failure to clear stone fragments is a concern, because it results in a higher re-treatment rate as well as a higher number of ancillary procedures. Clayman and associates (1989) suggested that in comparing the results of SWL and PNL or in comparing different lithotripters, the parameters of stone-free rate, re-treatment rate, and number of auxiliary procedures should be combined into an effectiveness quotient that may better express treatment results and allow one to compare different treatment modalities:

$$\frac{\%\ \text{stone free}}{100\% + \text{re-treatment} + \%\ \text{auxiliary procedures}} \times 100$$

For example, Netto and associates (1991), in a study comparing PNL and SWL for patients with lower pole calculi, reported overall stone-free rates of 93.6% and 79.2% for PNL and SWL, respectively; these values were not significantly different. However, the effectiveness quotients of 93.7% and 55.9% for PNL and SWL did differ significantly because this calculation incorporated the 41% re-treatment rate for the SWL group.

The negative effect of an increasing stone burden (size and number) on the results of SWL has been described by a number of groups, dating from the initial reports of SWL to the present generation of lithotripters (Drach et al, 1986; Lingeman et al, 1986a; El-Assmy et al, 2006a; Tan et al, 2006). A now-axiomatic principle of SWL is that **as stone burden increases, the stone-free rate declines and the need for ancillary procedures and re-treatment rises.** Importantly, stone burden is not defined solely on the basis of the largest stone present in the kidney but also it takes into account the overall number of stones present. Furthermore, larger stone burdens are associated with a higher rate of residual stones, a point of particular concern in the treatment of patients with struvite calculi (Preminger et al, 2005).

Figure 48–3 illustrates the effect of the size of solitary renal stones on the results of SWL. PNL, although more invasive and

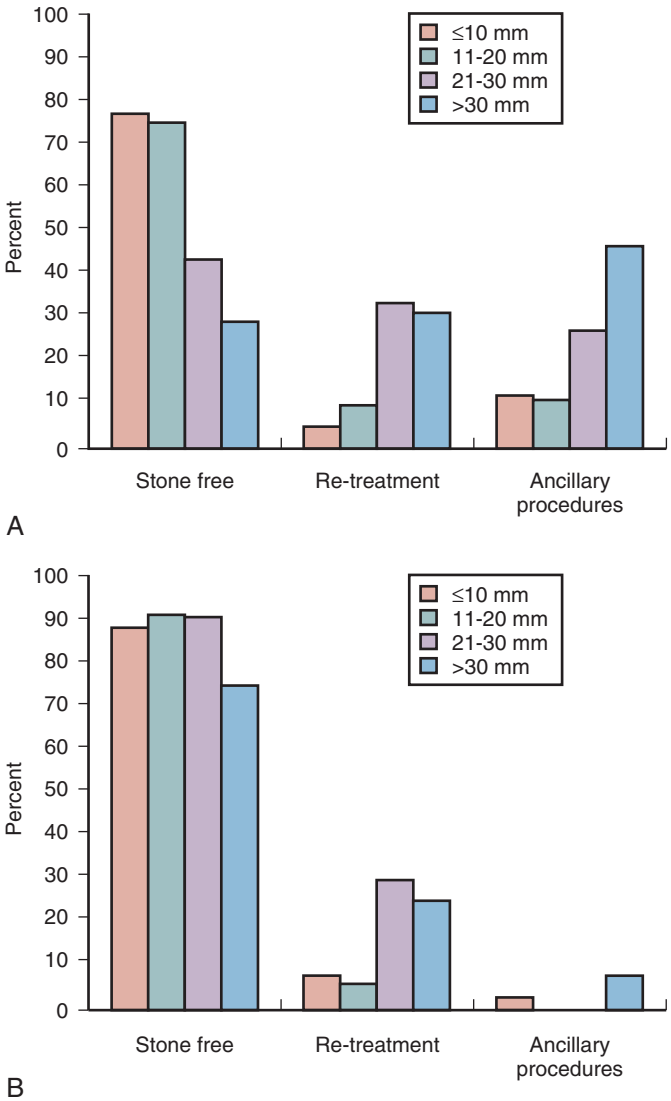


Figure 48–3. **A**, Solitary nonstaghorn calculi treated by shockwave lithotripsy, stratified by size. **B**, Solitary nonstaghorn calculi treated by percutaneous nephrolithotomy, stratified by size.

often associated with higher morbidity, achieves better stone-free rates than does SWL and is not affected by stone size (Lingeman et al, 1987a). Ureteroscopy, an alternative treatment for patients with renal calculi, is also negatively affected by increasing stone burden, although to a lesser degree than is SWL, because stone fragments are often removed or vaporized. Thus, as stone burden increases, PNL becomes more efficient than either SWL or ureteroscopy.

Importantly, **50% to 60% of all solitary renal calculi are less than 10 mm in diameter** (Cass, 1995; Renner and Rassweiler, 1999; Logarakis et al, 2000). **Treatment results of SWL for this substantial group of patients are generally satisfactory** and independent of stone location or composition. Although better results can be achieved with PNL or ureteroscopy for patients with stones smaller than 10 mm, these procedures are more invasive, are associated with greater morbidity, and may be reserved for special circumstances (e.g., anatomic malformation causing obstruction, SWL failure).

Patients with calculi between 10 and 20 mm are often treated with SWL as first-line management. However, stone location and composition can meaningfully affect the results of SWL for patients with calculi in this size range and should be carefully considered. For example, SWL results for patients with 10- to 20-mm stones in the lower pole are inferior (55%) to SWL results for patients with stones in the upper and middle pole calyces (71.8% and 76.5%, respectively) (Saw and Lingeman, 1999). A prospective, randomized controlled trial compared SWL and PNL for patients with lower pole renal calculi; the stone-free rate for PNL was 95%, versus 37% for SWL (Albala et al, 2001). Stone composition merits consideration when evaluating treatment alternatives for patients with stones larger than 10 mm, as cystine calculi and brushite calculi both respond poorly to SWL treatment. This effect is particularly pronounced for stones larger than 15 to 20 mm. Therefore, patients with renal stones of 10 to 20 mm and factors predicting poor treatment outcomes with SWL should be advised about alternative therapeutic modalities. Both PNL and ureteroscopy are less affected by stone location and composition, and good results may be attained with these modalities for patients with 10- to 20-mm renal stones.

Patients with renal calculi greater than 2 cm who are treated with SWL monotherapy commonly experience poor treatment outcomes, a fact that was first recognized over two decades ago in an NIH Consensus Conference. Interestingly, the 2 cm threshold for SWL first noted in that conference document is still valid in the present day (Consensus Conference, 1988). Murray and coworkers (1995) reported that SWL monotherapy for renal calculi greater than 3 cm yielded an overall success rate of 27% at 3 months follow-up. The best stone-free rate (60%) was obtained for stones smaller than 500 mm^2 that were located primarily within the renal pelvis; the stone-free rate for stones with surface areas larger than 1000 mm^2 was a dismal 8%. Notably, steinstrasse occurred in 23% of patients. El-Assmy and colleagues (2006a) reported on patients with large-volume renal calculi treated with SWL monotherapy. Long-term follow-up demonstrated a stone-free rate of 59%; significant complications occurred in 13%, and unplanned secondary procedures were required in 18.4% of cases.

As an alternative to SWL for large-volume calculi, ureteroscopy emerged in the 1990s as a viable treatment option. Grasso and associates (1998) provided one of the earliest series of patients with large (>2 cm) upper urinary tract stones treated by ureteroscopy. One third of patients with renal stones required a second-look endoscopy; and in three patients with renal calculi, conversion to PNL was necessary. The overall success rate, defined as pulverization of the stone to dust or fragments smaller than 2 mm, after the second ureteroscopy procedure was 91%, which is comparable to PNL results. However, the 6-month follow-up data, which were available for 25 patients, demonstrated that only 60% of patients were stone free, whereas 24% had small lower pole debris and 16% had new stone growth. As surgical techniques and technology have evolved, ureteroscopy has been applied to patients with progressively larger stone burdens with acceptable results and morbidity (Mariani, 2007; Ricchiuti et al, 2007; Breda et al, 2008). In general, these treatment approaches have relied on a staged approach to achieve a successful outcome.

In summary, for patients harboring nonstaghorn stones smaller than 10 mm, SWL is usually the primary approach. For patients with stones between 10 and 20 mm, SWL can still be considered a first-line treatment unless factors of stone composition, location, or renal anatomy suggest that a more optimal outcome may be achieved with a more invasive treatment modality (PNL or ureteroscopy). Patients with stones larger than 20 mm should primarily be treated by PNL unless specific indications for ureteroscopy are present (e.g., bleeding diathesis, obesity).

Staghorn Calculi. Patients suffering from staghorn calculi remain a challenging problem for the practicing urologist. **Most staghorn stones are composed of struvite,** and factors that predispose to urinary tract infection and retained urine increase the likelihood of struvite stone formation (Gettman and Segura, 1999). However, other crystals, including cystine, calcium oxalate monohydrate, and uric acid, can assume a staghorn configuration.

The conservative treatment of patients with staghorn calculi exposes the patient to an increased risk of renal loss as well as a mortality rate of up to 30% (Blandy and Singh, 1976; Rous and Turner, 1977; Koga et al, 1991). Therefore the ideal management of patients with staghorn calculi is composed of three stages. First, complete surgical removal of the entire stone burden is essential. **If all of the infected stone debris is not evacuated, urea-splitting bacteriuria may persist, which can ultimately lead to eventual stone regrowth.** The urologist should select the procedure or combination of procedures most likely to render the patient free of stone material while minimizing the risk of morbidity and mortality. Second, any metabolic abnormalities must be identified and appropriately treated. It has been reported that metabolic abnormalities are not uncommon in patients with infected stones (Segura et al, 1981). However, others have found that stone recurrence after complete elimination of calculi is uncommon (Silverman and Stamey, 1983). Different definitions of the term *infection stone,* and in particular the inclusion of mixed struvite and calcium oxalate stones in studies, probably explain these contradictory reports. In a group of patients with infection stones, those with pure struvite stones were significantly less likely to have metabolic abnormalities than were patients who had stones composed of a mixture of struvite and calcium oxalate (Lingeman, 1995; Lingeman et al, 1995c). Finally, anatomic abnormalities that may contribute to stasis within the urinary tract should be addressed.

Classification of Staghorn Calculi. The traditional definition of staghorn calculus is a renal pelvic stone with extension into the renal calyces. Historically, staghorn calculi were classified as partial or complete. Partial staghorn calculi were defined as renal pelvic calculi extending into two calyceal groups, and complete staghorn stones were defined as renal pelvic calculi extending into all major calyceal groups, filling at least 80% of the collecting system. At

the time this definition was popularized there was only one treatment option for patients with these calculi: open surgery. With the introduction of newer and less invasive treatment modalities that are highly sensitive to stone burden there is a greater need to classify staghorn calculi according to reproducible, quantitative criteria that allow clinicians to better evaluate treatment outcomes.

The morphologic classification into partial and complete staghorn calculi is inadequate, as demonstrated by Lam and colleagues (1992c), who reported considerable overlap in stone burdens of calculi grouped as partial or complete staghorn stones. When stone burden was assessed by stone surface area as measured on a kidney-ureter-bladder (KUB) radiographic image, for stones between 501 and 1500 mm^2 an overlap between partial and complete staghorn calculi commonly occurs. To remedy this limitation several groups have proposed new classification schemes to better define staghorn calculi (Rocco et al, 1984; Griffith and Valiquette, 1987; Ackermann et al, 1989; Di Silverio et al, 1990). However, the cumbersome and subjective nature of these classification approaches has resulted in limited clinical use.

Therefore, at present, the most accurate method to estimate the volume of a staghorn calculus is CT with three-dimensional reconstruction. This technique permits highly accurate determination of stone volume as well as the three linear dimensions of renal calculi and correlates well with the actual volume of the stone, as measured by water displacement (Lam et al, 1992c). Thiruchelvam and coworkers (2005) reported that an added benefit of three-dimensional image reconstruction is in planning for subsequent percutaneous stone removal. However, three-dimensional CT reconstructions are costly, time consuming, and not widely available, thus limiting the utility of this technology. Nadler and associates (2004) have reported the use of coronal reconstructions of axial CT images to calculate the craniocaudal length of stones, which can facilitate more economical stone volume calculations.

Surgical Management of Staghorn Calculi. Historically, patients with staghorn calculi were subjected to open surgical stone removal procedures. Overall, the stone-free rate after open surgery for patients with struvite staghorn stones was reported to be about 85%, with a 30% stone recurrence rate (Griffith et al, 1978). With the rise of endourology, however, minimally invasive procedures proved competitive with open surgery. In a comparison of PNL and anatrophic nephrolithotomy, Lingeman and associates (1987a) demonstrated that the stone-free rates of the two interventions were similar. Additionally, the convalescence, hospital stay, and blood transfusions were less for PNL. More recently, Al-Kohlani (2005) performed a randomized controlled trial comparing PNL and open surgery. Similar to the previous work of Lingeman they found that the morbidity, hospital stay, and operating room time all favored PNL, and the patients treated with PNL all returned to work sooner.

For patients with staghorn calculi, SWL monotherapy has a limited role in the management of this type of stone burden. A number of groups have reported that SWL monotherapy for staghorn calculi is associated with poor stone-free rates. Furthermore, patients treated with SWL require a greater number of secondary procedures. Postoperative complications are more common and include morbidities such as steinstrasse, renal colic, sepsis, and perinephric hematoma. The success rate of PNL as initial therapy for staghorn renal calculi is independent of stone composition and superior to SWL for all types of stone material. When treating struvite stones, SWL monotherapy may be particularly problematic because residual, "clinically insignificant" fragments can prevent the sterilization of urine, increasing the risk of stone regrowth.

The use of multiple endourologic techniques for the treatment of patients with staghorn stones is referred to as combination therapy or "sandwich therapy." The most frequently used multimodal regimen was described by Streem and colleagues (1997) and consisted of a primary percutaneous stone debulking followed by SWL of any inaccessible, residual infundibulocalyceal stone extensions or fragments. After SWL a secondary percutaneous procedure was performed. These various stages are usually separated by 1 or 2 days. Stone-free rates for combined therapy are similar to those obtained by PNL alone or by open surgery (Lam et al, 1992b). **The management of patients with staghorn stones by a combined approach must be viewed as primarily percutaneous in nature, with SWL being used only as an adjunct to minimize the number of access points required.** Improved PNL techniques, incorporating the increasing use of flexible nephroscopy and providing complete or nearly complete clearance of stone material at the time of the primary procedure, may have decreased or eliminated the need for additional SWL treatment (Preminger et al, 2005).

The 2005 AUA Nephrolithiasis Committee has published recommendations for the management of patients with staghorn calculi based on a meta-analysis of outcome data from published, peer-reviewed articles. According to the committee, all treatment options (SWL, PNL, combined PNL and SWL, open surgery) must be discussed with the patient (Preminger et al, 2005). As a guideline, however, **PNL, followed by either SWL or repeated PNL, should be used for most patients with struvite staghorn calculi, with PNL being the initial element of the combination therapy.** SWL and open surgery should not be used for most of these patients as a first-line treatment. PNL and SWL are equally effective in treating patients with small-volume staghorn stones when the renal anatomy is normal or nearly normal. Open surgery may be an option in unusual situations in which a staghorn stone is not expected to be removed by a reasonable number of PNL or SWL procedures. Nephrectomy is an option for the patient with a poorly functioning kidney harboring a staghorn stone. Although there are limited data for the treatment of pediatric patients with staghorn calculi, PNL is a safe and effective therapy. Pediatric patients often experience better stone-free rates than do adults with treatment by SWL. The stone-free rate with SWL monotherapy, reported by studies including only pediatric patients, is 78%; although more than one procedure is generally required to achieve this outcome; fortunately, complications are infrequent (Preminger et al, 2005). However, the developing kidney may be more susceptible to the bioeffects of SWL (Connors et al, 2006).

Treatment Decisions by Stone Composition

Dretler (1988) first introduced the concept that stone fragility, defined as the readiness with which a stone is fragmented by SWL, is variable among stones of different composition. Saw and Lingeman (1999) subsequently reported that, when adjusted for size, cystine and brushite calculi are the most resistant to SWL, followed by calcium oxalate monohydrate; following, in descending order of resistance to fragmentation, are struvite, calcium oxalate dihydrate, and uric acid stones (Pittomvils et al, 1994; Saw and Lingeman, 1999). Stone composition affects not just resistance to fragmentation but also the type of fragments produced. Cystine and calcium oxalate monohydrate, in addition to being difficult to fragment, tend to produce relatively large pieces that may be difficult to clear from the collecting system (Pittomvils et al, 1994;

Rutchik and Resnick, 1998). In general, **patients with such stones (i.e., brushite, cystine, calcium oxalate monohydrate) should be treated by SWL only when the stone burden is small** (i.e., <1.5 cm). Those patients with larger stones should preferentially be treated with PNL or ureteroscopy. Interestingly, the outcome of intracorporeal lithotripsy is also affected by stone composition. Teichman and colleagues (1998c) reported that the holmium laser was the most effective lithotrite for fragmenting struvite stones and the least effective lithotrite for fragmenting calcium oxalate monohydrate stones. These results are consistent with the known thermal threshold for each stone composition.

Patients suffering from cystinuria present a unique challenge to the urologist. Assimos and associates (2002) reported that **cystinuric patients have higher serum creatinine levels compared with a cohort of calcium oxalate stone formers.** Importantly, they also reported that **cystinuric patients are at greater risk for renal loss than are calcium oxalate stone formers** and that open stone surgery for these patients is associated with higher serum creatinine concentration and potential renal loss. Furthermore, patients with cystinuria have been reported to be poorly compliant with medical therapy, increasing the likelihood of recurrent stone events (Pietrow et al, 2003a). Chow and Streem (1998) analyzed 31 cystinuric patients who underwent selected intervention for 61 stone events and reported that the probability of stone recurrence at 1 and 5 years was 27% and 73%, respectively. Achieving stone-free status prolonged the time to stone recurrence compared with patients left with residual fragments, a finding confirmed by Knoll and associates (1988). The high likelihood of repeated procedures underlines the need to select not just the least invasive treatment modality but also the most effective treatment modality. Treatment efficacy is of particular importance, as Barbey and associates (2000) reported that decreased renal function was more pronounced in cystinuric patients subjected to more stone removal procedures. Evan and associates (2006) have also reported that patients with cystinuria demonstrate anatomic findings, such as collecting tubule crystal plugging, as well as glomerular changes consistent with medical renal disease. These findings were more severe in subjects with extensive stone-forming histories, confirming the unique nature of this population.

Therefore, when stone removal is required, a minimally invasive approach is preferred. SWL, when it is used unselectively to treat patients with cystine stones, yields poor results. Hockley and colleagues (1989) found that stone-free rates when applying SWL to calculi less than 20 mm or 20 mm or greater were 70.5% and 41%, respectively, whereas the stone-free rates for those who underwent PNL were 100% and 92%, respectively. Kachel and associates (1991) suggested the following treatment algorithm for patients with cystine stones: SWL monotherapy for cystine renal calculi 15 mm or smaller and PNL for stones larger than 15 mm in diameter. Rudnick and colleagues (1999) reported success with retrograde ureterorenoscopic fragmentation in patients with 1.5- to 3.0-cm renal calculi. This approach is especially appealing because it has an inherently low morbidity. Both Ahmed and associates (2008) and Trinchieri and associates (2007) have confirmed that endourologic approaches to patients with cystine calculi yield superior results, with minimal morbidity.

Brushite calculi have a resistance to fragmentation that is surpassed only by that of cystine calculi (Dretler, 1988). Klee and associates (1991) described 30 patients with a total of 46 brushite stones. The overall success rate for patients treated by SWL monotherapy was 65% (with success defined as fragments < 4 mm), with a mean of 1.5 SWL sessions required per stone. However, only 11% of patients became stone free. PNL and ureteroscopy achieved 100% success rates and stone-free rates of 100% and 66%, respectively. Of 20 kidneys with residual fragments smaller than 4 mm, 12 had rapid regrowth to significant size within 3 to 12 months. Parks and associates (2004) found that SWL use was more frequent among brushite stone formers than among a similar cohort of calcium oxalate stone formers. Therefore, **when brushite calculi are suspected or confirmed, a surgical treatment algorithm similar to that for cystine stones should be applied.**

Although resistance to SWL is generally common for very hard stones, it also characterizes the rare and very soft **matrix** calculi that are composed of as much as 65% organic matter (compared with 2% to 3% organic matter in most noninfected urinary calculi). Matrix stones are radiolucent and are often associated with urea-splitting bacteriuria. SWL is not an effective treatment modality for patients with these stones. These situations are usually best treated with PNL (O'Connor et al, 1990). SWL is usually ineffective because of the stone's gelatinous nature, and ureteroscopy may be compromised by the large volume of stone material present (Bani-Hani et al, 2005).

Another soft radiolucent stone is composed of **indinavir,** a protease inhibitor commonly used in the treatment of human immunodeficiency virus infection (Daudon et al, 1997). A significant number of patients who receive this drug develop symptoms or signs of indinavir nephrolithiasis (Saltel et al, 2000; Nadler et al, 2003). Reiter and coworkers (1999) reported an incidence of symptomatic stone episodes in 12.4% of 105 patients treated with indinavir. The mean time from the initiation of indinavir therapy until the acute stone episode was 21.5 weeks. Twelve of 16 stones were passed spontaneously. Kohan and colleagues (1999) described 13 symptomatic patients with indinavir stones; conservative therapy was successful in 11 patients, and 2 patients were treated by stent placement. Pure indinavir stones are not detectable with standard radiography or CT. However, some patients form indinavir stones that contain a calcium component, which may be radiographically visible (Sundaram and Saltzman, 1999). Hydration and analgesic therapy are recommended for the initial treatment of patients with indinavir stones. Indinavir therapy may need to be temporarily or permanently discontinued, in which case another protease inhibitor may be substituted. Invasive intervention may be necessary for patients with prolonged renal obstruction, signs of sepsis, or unremitting symptoms.

The ability to predict stone composition and, consequently, the number of shockwaves required for complete stone fragmentation would be of great benefit in selecting appropriate treatment of patients with stone disease. If a stone is of a type not amenable to treatment by SWL, other modes of treatment could be pursued. However, except for cystinuric patients and patients who have had previous stone analysis, accurate prediction of stone composition based on imaging and the patient's history is difficult. The ability of plain radiography to differentiate subtypes of calcium oxalate stones and possible relationships to stone fragility was first suggested by Dretler (Dretler, 1988; Dretler and Polykoff, 1996). A number of investigators subsequently examined the utility of x-ray patterns to predict stone fragility. In general, smooth edged stones with a uniform and homogenous structure require more shockwaves to fragment than do reticulated, spiculated stones with an irregular margin or structure. Additionally, stones that were more dense than bone (using either the 12th rib or a transverse process as a reference point) responded more poorly to SWL.

Non–contrast-enhanced helical CT, which is presently the most commonly utilized method of evaluating patients with suspected renal colic, may be useful when trying to identify stone composition. Several in-vitro investigations of this technology have been reported. Mostafavi and associates (1998) first performed an in-vitro study that used the attenuation levels acquired by CT to accurately predict the chemical composition of pure urinary calculi. Similarly, Saw and associates (2000) found that, in an in-vitro investigation, CT was able to differentiate between stone groups (each containing at least 60% of one stone constituent) on the basis of absolute attenuation values.

Joseph and associates (2002) have provided an in-vivo corollary when they reported that SWL success rates were significantly lower for those calculi with attenuation values greater than 1000 Hounsfield units (HU) than for those calculi with attenuation values less than 1000 HU. Gupta and associates (2005) have confirmed that there is a linear relationship between Hounsfield unit measurement of a stone and the likelihood of that stone fragmenting in a single SWL session. Other investigators have further advanced knowledge in this area, performing prospective studies to evaluate the utility of Hounsfield unit measurement in predicting stone fragmentation. Wang and associates (2005) confirmed that stone density greater than 900 HU (along with stone burden greater than 700 mm^3 and irregular stone shape) is a predictor of a poor SWL outcome. El-Nahas and coworkers (2007), too, found that a stone density greater than 1000 HU predicted failure.

Although CT attenuation values can distinguish some stone types in vivo, such as uric acid from calcium stones, the use of attenuation values alone results in considerable overlap; the range of values for calcium oxalate monohydrate and struvite stones does not allow these types to be confidently distinguished. Furthermore, it is not certain that the ease with which a stone is fragmented by SWL can be predicted by knowing only the major mineral composition of the stone. For example, cystine stones, which are considered difficult to break, have been shown in certain cases to break easily (Bhatta et al, 1989). Williams and associates (2003), too, reported that **the variability in stone fragility to shockwaves is large, even within groups defined by mineral composition. It is likely that this variability in fragility could be due to variation in stone composition or structure,** including variable amounts of secondary mineral in the stone, variation in the spatial arrangement of the secondary mineral within the stone, and variation in the layer structures of the primary and secondary minerals within a stone. Williams and associates (2002) also reported that displaying the data acquired by helical CT with use of bone windows can reveal remarkable internal structural detail of kidney calculi (Fig. 48–4 on the Expert Consult website). It is clear that CT provides a wealth of information about stone characteristics. However, additional work is needed to determine the utility of this powerful imaging tool in determining the susceptibility of a given stone to SWL.

Dual-source CT is a recent innovation in CT technology; it incorporates two unique x-ray sources, rather than a single x-ray source as in conventional CT. In addition to improved temporal resolution, dual-source CT scanners have the ability to operate the two x-ray sources simultaneously, which has the potential to differentiate materials on the basis of their unique energy-dependent profiles. Dual-source CT technology has been reported to reliably differentiate calcium stones from uric acid stones (Flohr et al, 2006) as well as calcium phosphate stones from calcium oxalate stones (Matlaga et al, 2008; Boll et al, 2009).

Renal Anatomic Factors

There are certain anatomic factors, either congenital or acquired, that can hinder stone clearance after SWL. Congenital anomalies manifest not uncommonly in the upper urinary tract, and almost all that affect the drainage of the kidney are associated with an increased incidence of calculous disease. Such abnormalities include ureteropelvic junction (UPJ) obstruction, horseshoe kidney, and other ectopic or fusion anomalies as well as calyceal diverticula. Hydronephrosis, too, is associated with a failure to clear stone fragments after SWL. Although not, strictly speaking, an anatomic abnormality, the dependent position of lower pole calyces may also affect stone clearance after SWL. In addition, stone-free rates after SWL for patients with hydronephrosis or obstruction are poor. Any patient with obstruction distal to the targeted stone should not undergo SWL treatment. If both obstruction and infection are present, SWL may result in life-threatening urosepsis. Furthermore, the patient is unlikely to clear stone fragments unless the concomitant obstruction is alleviated.

Ureteropelvic Junction Obstruction

UPJ obstruction in adults is commonly associated with urinary calculi. Furthermore, a stone at the UPJ can exacerbate the degree of preexisting obstruction and further compromise the renal unit (Rutchik and Resnick, 1998). The role of anatomic obstruction and associated urinary stasis in stone formation is not clearly established. Husmann and colleagues (1995) reviewed the records of patients with simultaneous UPJ obstruction and renal calculi and found that 71% of patients with nonstruvite stones had significant metabolic abnormalities. Matin and Streem (2000) have also reported that patients with UPJ obstruction are at increased risk for lithogenic factors associated with metabolic stone disease. Thus, **in addition to anatomic obstruction, underlying metabolic abnormalities are commonly present in patients with UPJ obstruction.**

Although patients with stones and concomitant UPJ obstruction have traditionally been treated by open pyeloplasty and stone extraction, PNL with concomitant endopyelotomy can achieve good results with less morbidity. Endopyelotomy, defined as incision of the UPJ obstruction intraluminally, has an overall success rate between 67% and 88% (Ramsay et al, 1984; Van Cangh et al, 1989, 1994; Motola et al, 1993; Kletscher et al, 1995; Nadler et al, 1996; Albani et al, 2004; Knudsen et al, 2004). Percutaneous endopyelotomy can be combined with PNL, which permits efficient stone removal as well as careful endoscopic inspection of the UPJ. Success rates for combined PNL and endopyelotomy are comparable to endopyelotomy alone; a large, long-term review of endopyelotomy from the Mayo Clinic found that the presence of a stone did not adversely affect treatment outcome (Dimarco et al, 2006). Although retrograde endopyelotomy is another technique for the treatment of UPJ obstruction, the antegrade approach is preferable when renal calculi are present because it simplifies the stone removal aspect of the procedure.

Laparoscopic pyeloplasty has emerged as a commonly applied treatment for patients requiring surgical repair of UPJ obstruction. Because stones are commonly present in such situations there has been interest in laparoscopic stone removal at the time of laparoscopic pyeloplasty. Ramakumar and colleagues (2002) initially reported the feasibility of laparoscopic pyeloplasty with concomitant pyelolithotomy. Ball and associates (2004) subsequently noted, however, that laparoscopic pyeloplasty with concomitant pyelolithotomy is most efficacious when it is applied to patients

with limited stone burdens. As surgical instrumentation had advanced, Stein and associates (2008) have subsequently reported that increasing stone burdens can be efficiently treated, using laparoscopic, rather than endoscopic, instrumentation. Atug and associates (2005) have also reported the application of robotic technology, specifically robotic graspers, to accomplish pyelolithotomy at the time of a robotic pyeloplasty; this technique, too, permits the efficient removal of a stone burden.

Calyceal Diverticula

Calyceal diverticula are congenitally derived, nonsecretory, urothelium-lined eventrations of the renal collecting system that are filled with urine. A narrow neck communicating with the collecting system is typically present, which permits the diverticulum to fill passively with urine. Calyceal diverticula are uncommon, having been reported as incidental findings in 0.2% to 0.6% of individuals undergoing renal imaging (Middleton and Pfister, 1974; Timmons et al, 1975; Wulfsohn, 1980; Michel et al, 1985). Stones have been reported to form in 9.5% to 50% of these cavities and can cause pain and hematuria or harbor bacteria (Yow and Bunts, 1955; Williams et al, 1969; Middleton and Pfister, 1974). The role of metabolic factors versus urinary stasis in the pathogenesis of stone formation in calyceal diverticula is controversial. Burns and coworkers (1984) suggested that particle retention time, especially in the setting of a diverticulum, could be the cause of stone formation. However, several studies examining metabolic data have drawn conflicting conclusions. Although Hsu and Streem (1998) have reported metabolic abnormalities in 50% of 14 patients with calyceal diverticular calculi, Liatsikos and associates (2000) found a low incidence of metabolic abnormalities in 49 patients with calyceal diverticular stones. Matlaga and associates (2007) reported that it is likely a combination of both urinary stasis and metabolic factors that incite stone formation in these structures.

Historically, patients with calyceal diverticula were treated by open surgical nephrotomy with closure of the infundibulum, marsupialization and fulguration of the diverticular cavity, or partial nephrectomy. However, with the development of minimally invasive surgical therapies, including PNL, ureteroscopy, SWL, and laparoscopic surgery, open surgical treatments are now uncommon. The use of SWL for the treatment of patients with diverticular calculi is controversial. Most investigators agree that **to prevent stone recurrence, eradication of the diverticulum should accompany stone removal,** a goal that is not achieved with SWL (Cohen and Preminger, 1997). Furthermore, **the stone-free rate for patients with calculi within calyceal diverticula who are treated by SWL averages only 21%** (range, 4% to 58%) (Renner and Rassweiler, 1999). However, an average of 60% (range, 36% to 86%) of patients will become symptom free after SWL. The follow-up in series showing the highest symptom-free rates is relatively short (3 to 6 months); on extended follow-up, Jones and associates (1991b) demonstrated that some of the patients initially rendered symptom free will subsequently become symptomatic and require re-treatment. The highest success rate with SWL was reported by Streem and Yost (1992), who treated a series of 19 patients harboring calyceal diverticular calculi smaller than 1.5 cm and a functionally patent diverticular neck. An initial stone-free rate of 58% and a symptom-free rate of 86% were achieved, probably as a result of careful selection of patients; all of the diverticula filled with contrast material on preoperative intravenous pyelography, and the ostia were well visualized. In addition, the aggregate stone size was smaller than 1.5 cm. However, recurrent stone growth was demonstrated in 1 patient during the follow-up period, and 6 of 9 patients with infection presumed to be secondary to the diverticulum developed recurrent infections.

The percutaneous approach for the management of subjects with diverticular stones provides the patient with the best chance of becoming stone and symptom free (Al-Basam et al, 2000; Monga et al, 2000; Auge et al, 2002b). Furthermore, there is an excellent chance of ablating the diverticular cavity by this approach. **A direct percutaneous approach to the calyceal diverticulum is preferable because it allows use of a rigid nephroscope for stone extraction, dilation and incision of the diverticular neck (if desired), and fulguration of the diverticular epithelium.** Kim and associates (2005a) reported a novel, single-stage procedure that does not require ureteral catheter placement or entrance into the renal collecting system. Percutaneous access is directed onto the diverticular cavity harboring stone, two movable core J wires are coiled in the diverticular cavity, and the track is balloon dilated. Once the stone material is removed, the cavity is fulgurated.

Retrograde ureteroscopic management is a reasonable option for certain patients with diverticula in the upper and middle portions of the kidney when the stone burden is less than 2 cm and the diverticular neck is short and accessible (Grasso et al, 1995b). Ureteroscopy may avoid some of the morbidity of a percutaneous approach, while being more effective than SWL. With the ureteroscope the surgeon may use a laser fiber to incise the stenotic infundibulum, fragment the stone, and ablate the diverticular lining. Fuchs and David (1989) reported a stone-free rate of 73% and a symptom-free rate of 86% with this approach, and Batter and Dretler (1997) reported that of 18 patients in whom they could access the diverticulum, all were symptom free at a mean follow-up of 39 months. It should be noted, however, that many subjects in these reports required multiple procedures to achieve a successful outcome; the price for the minimally invasive nature of ureteroscopy may be an increased acceptance of a staged treatment approach. Auge and associates (2002b), however, reported a symptom-free rate of 35% and stone-free rate of 19% for this technique, leading them to conclude that a percutaneous approach should be considered the primary treatment modality for calyceal diverticula. Turna and associates (2007) have also reported the results of a long-term study, finding that PNL is associated with superior stone-free rates relative to ureteroscopy when applied to calyceal diverticula.

Laparoscopic management of patients with symptomatic calyceal diverticula has been described in several small series and case reports (Gluckman et al, 1993; Ruckle and Segura, 1994; Harewood et al, 1996; Hoznek et al, 1998; Curran et al, 1999). Miller and associates (2002) reported a series of five patients with symptomatic, stone-bearing calyceal diverticula who underwent retroperitoneoscopic surgical therapy. The authors concluded that the optimal candidates for this approach are those with a symptomatic calyceal diverticulum with thin overlying renal parenchyma, those with a large stone burden, and those with an anterior lesion inaccessible to or unsuccessfully managed by other approaches. Wyler and associates (2005) and Terai and associates (2004) have both reported the treatment of calyceal diverticula from a retroperitoneoscopic approach as well. It should be noted, however, that the laparoscopic approach is more invasive than PNL and therefore is usually limited to treatment of diverticula in anterior calyces, which are otherwise difficult to access with a percutaneous

approach. Surgeons undertaking a laparoscopic approach should be facile with intraoperative laparoscopic ultrasound and laparoscopic suturing techniques.

Horseshoe Kidney and Renal Ectopia

Horseshoe kidney is the most common congenital renal anomaly, and patients with this condition are often affected by urolithiasis (Evans and Resnick, 1981). A horseshoe kidney is considered the result of a median fusion of metanephric tissue during early gestation. Subsequent entrapment of the fused lower pole isthmus by the inferior mesenteric artery results in an incomplete cephalad migration and an associated malrotation of the kidney (Hohenfellner et al, 1992). In many cases, the UPJ is anomalous because of a high ureteral insertion into an elongated renal pelvis. This can cause impaired urine drainage, a likely reason that up to two thirds of such patients are found on evaluation to have hydronephrosis, infection, or urolithiasis (Lampel et al, 1996). Although SWL can be used to treat patients with calyceal stones in a horseshoe kidney, the anomalous orientation of the kidney makes localization of the calculi more difficult, especially for stones in the anteromedial calyces. Placement of the patient in a prone position may facilitate localization of the stone (Jenkins and Gillenwater, 1988). Alternatively, a "blast path" technique, which uses the observation that sufficient acoustic pressure for stone fragmentation exists beyond F2 along the axis of the shockwave in many lithotripters, may be employed (Locke et al, 1990). Reported results of SWL treatment of patients with horseshoe kidney stones are variable; stone-free rates between 28% and 78% have been reported (Esuvaranathan et al, 1991; Vandeursen and Baert, 1992; Theiss et al, 1993; Kirkali et al, 1996; Lampel et al, 1996; Kupeli et al, 1999). Much of the wide range of results can be explained by variability in stone size and location among the different studies. Theiss and colleagues (1993) stratified stones by location and found, as expected, that the clearance rate for lower calyceal stones was inferior to that of middle and upper calyceal stones (a stone-free rate of 53.8% vs. 100%). Kirkali and associates (1996) studied a series of 18 patients with calculi larger than 10 mm and found a stone-free rate of 28%. Patients with renal calculi in horseshoe kidneys treated by SWL required a higher number of shockwaves per treatment and also experienced a higher re-treatment rate (30% vs. 10%) than did patients with similar stones in orthotopic renal units (Chaussy and Schmiedt, 1984; Drach et al, 1986; Lingeman et al, 1986a). Lampel and associates (1996) reported a recurrence rate of 86% for patients harboring persistent fragments after SWL compared with a 14% recurrence rate for patients who were stone free. Although stone-free rates, in aggregate, are low for patients with horseshoe kidneys, with proper selection these rates can be improved. Favorable factors for SWL of horseshoe kidneys include **a stone burden smaller than 1.5 cm and nonobstructed collecting system drainage.**

Several groups have applied ureteroscopic techniques to the treatment of calculi residing in horseshoe kidneys. Andreoni and associates (2000) treated three patients in this manner, with successful outcomes. Weizer and colleagues (2005), too, reported a similar experience. In both series, ureteral access sheaths, holmium laser energy, and nitinol grasping devices were used. Symons and colleagues (2008) also reported successful ureteroscopic treatment of stone burdens within horseshoe kidneys, although a majority of the patients required a staged approach with more than one treatment session. However, taken all together, these studies confirm that ureteroscopy may be an effective treatment modality for a stone burden less than 1.5 cm in horseshoe kidneys; flexible ureteroscopes, and devices such as the holmium laser, nitinol graspers, and ureteral access sheaths should be available when this approach is selected. Because spontaneous expulsion of stone fragments may be variable in these situations, meticulous attention should be given to the extraction of stone material.

For patients with larger calculi or for those who demonstrate evidence of poor urine drainage, PNL should be the primary approach. **The results of PNL for patients with calculi in a horseshoe kidney are generally superior to those achieved with SWL, with an average stone-free rate of 84%** (range, 75% to 100%) (Esuvaranathan et al, 1991; Jones et al, 1991a; Al-Otaibi and Hosking, 1999; Raj et al, 2003; Shokeir et al, 2004). **The optimal point of entry for these kidneys is through a posterior calyx, which is typically more medial than in the normal kidney** because of the altered renal axis and rotation associated with the midline fusion (Fig. 48–5). Except in the isthmus of the horseshoe kidney, where the vascular supply can vary, **vessels tend to enter the kidney anteriorly. An upper pole collecting system puncture is often appealing because the entire kidney is usually subcostal.** In most cases the lower pole calyces are anterior and inaccessible percutaneously. During PNL the flexible nephroscope often aids in accessing stones within anteromedial calyces, which may be difficult to reach with a rigid nephroscope.

An ectopic kidney can be found in a pelvic, iliac, abdominal, thoracic, or crossed position. The most common site of ectopia is the pelvis, and the incidence of pelvic kidney is estimated to be 1 in 2200 to 1 in 3000 patients. Although the ectopic location of the kidney can cause positioning problems during SWL treatment, calculi in these kidneys can often be approached with SWL. Although stone-free rates have been reported to be in the range of 66% to 71%, in some cases multiple treatment sessions may be



Figure 48–5. Antegrade nephrostogram performed after percutaneous nephrolithotomy of a horseshoe kidney via an upper pole access. Note the subcostal nature of the access and the unique calyceal orientation inherent in a horseshoe kidney.

necessary (Sheir et al, 2003; Tunc et al, 2004). Certain maneuvers may be required to adequately target the stone. If the bony pelvis shields the stone from the shockwave of the lithotripter, a prone position may be necessary. In general, stone clearance rates may be maximized by minimizing the stone burden treated.

Overall, stone-free rates for PNL of ectopic kidneys are better than those achieved with SWL. Likely, these superior success rates are due to the use of flexible nephroscopy and nitinol grasping devices. Percutaneous access for ectopic renal units is generally obtained with the patient in the supine position. Although Desai (2009) and others have reported using only ultrasound to guide the access portion of the procedure, such an imaging modality may increase the risk for bowel injury. Alternatively, laparoscopic assistance can be used to guide access and minimize the likelihood of bowel injury (Fig. 48–6). Holman and Toth (1998) and Maheshwari and associates (2004) have described laparoscopy-assisted PNL, reporting good results and no major complications. Matlaga and associates (2006) have also described unique cases that required transhepatic and transiliac access, maneuvers that highlight the need to tailor the intervention to the patient's clinical situation. Alternatively, CT guidance can permit percutaneous access into the ectopic renal collecting system without injury to adjacent organs (Matlaga et al, 2003). Flexible ureteroscopy can also be an attractive alternative for this unusual problem if the stone burden is not large. Weizer and associates (2005) reported a series of patients with renal calculi in an ectopic kidney who were treated successfully with ureteroscopy.

Lower Pole Calculi

Although SWL is the preferred method for treatment of most patients with symptomatic upper tract calculi, there is considerable controversy concerning the management of patients with lower pole renal calculi (Tolley and Downey, 1999). The limitations of SWL for treatment of patients with lower pole stones were first noted in a meta-analytic study by Lingeman and associates (1994). These investigators reported that the stone-free results achieved with PNL were superior to those of SWL: **the overall stone-free rate for SWL applied to lower pole calculi was 60% compared with 90% for PNL.** Stratified according to stone size, patients with stones smaller than 10 mm had stone-free rates of 74% when they were treated by SWL compared with 100% by PNL. Among patients with stones of 10 to 20 mm, stone-free rates were 56% for the SWL group compared with 89% for the PNL group. A regression analysis demonstrated that increasing stone burden was associated with progressively less successful stone-free outcomes for patients treated with SWL, whereas for PNL-treated patients stone-free rates were not different across categories of stone size. This study has prompted a number of groups to assess the impact of lower calyceal anatomy (Table 48–2). Furthermore, since the mid 1980s, a significant change in renal stone distribution has been noted, with an increase in the percentage of SWL treatments for patients with renal calculi being performed for lower calyceal stones (2% in 1984 to 48% in 1991) (Lingeman et al, 1994). This change in stone distribution may be explained by the tendency of small, radiographically undetectable fragments to gravitate to more dependent calyces after SWL therapy and to act as a nidus for new stone growth (Carr et al, 1996).

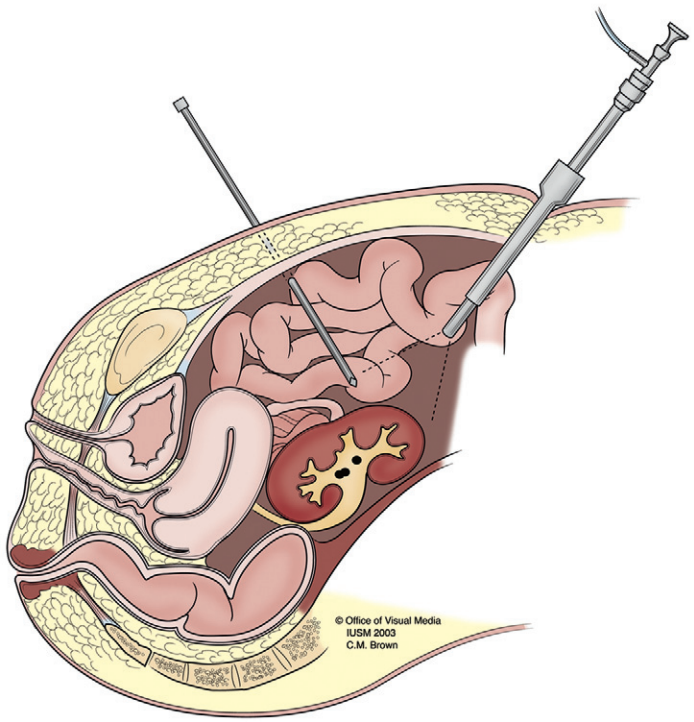


Figure 48–6. Laparoscopy-assisted percutaneous nephrolithotomy technique in which the bowel is reflected off the ectopic kidney before radiographically and laparoscopically guided percutaneous access. (© 2003, Indiana University Medical Illustration Department.)

The reasons for poor clearance of fragments from the lower pole after SWL are unclear. Intuitively, the gravity-dependent position of the lower pole calyx may impede the passage of stone fragments (Elbahnasy et al, 1998b). However, several investigators have proposed that in addition to the gravity-dependent positioning of the lower pole calyces, anatomic features may play an important role in the evacuation of stone fragments from this location. Anatomic factors were first suggested by Sampaio and Aragao (1992, 1994), who described the anatomy of the lower pole by use of polyester resin endocasts of the intrarenal collecting system obtained from adult cadavers (Fig. 48–7). The authors hypothesized that a lower pole with multiple infundibula might have poor drainage and consequently less possibility of eliminating stone fragments than would an inferior pole drained by a single infundibulum receiving fused calyces. They also hypothesized that a small diameter of the lower pole infundibulum might hinder passage of stone fragments. Finally, the authors examined the angle formed between the lower infundibulum and the renal pelvis and hypothesized that an angle greater than 90 degrees should facilitate drainage of fragments from the lower pole. Other investigators have analyzed the impact of lower pole anatomy on SWL stone clearance and have come to divergent conclusions (Albala et al, 2001). Although many have reported that certain anatomic factors alone, or in combination, may promote stone clearance, others have found no effect on lower pole anatomy in predicting treatment outcome.

One of the confounding issues in examining lower pole outcomes is the reproducibility of lower pole anatomic measurements. Pace and colleagues (2000) reported that there is wide variability in lower calyceal infundibular width between different intravenous pyelography phases. They found that the width was greatest on the compression film and smallest on the postvoid film, which prompted them to suggest the use of standardized timing when infundibular width is measured from an intravenous pyelogram. Although some of the disparity regarding the lower pole anatomic influences on stone-free status may be due to the techniques in which the parameters were measured, other sources of variability may be due to the type of lithotripter employed. In addition, stone composition, an important variable,

Table 48–2.

Treatment Outcomes for Lower Pole Calculi

STUDY	STONE-FREE RATE (%)		
	Shockwave Lithotripsy	Ureteroscopy	Percutaneous Nephrolithotomy
Lower Pole Calculi <1 cm			
Lingeman et al, 1994	74		100
Elashry et al, 1996		87	
Elbahnasy et al, 1998b	52	62	
Grasso and Ficazzola, 1999		82	
Gupta et al, 2000	72		
Kourambas et al, 2000		85	
Albala et al, 2001	63		100
Hollenbeck et al, 2001		82	
Schuster et al, 2002		79	
Sorensen et al, 2002	74		
Pareek et al, 2005	47		
Pearle et al, 2005*	35	50	
Lower Pole Calculi 1 to 2 cm			
Lingeman et al, 1994	56		89
Grasso and Ficazzola, 1999		71	
Saw and Lingeman, 1999	55		
Gupta et al, 2000	51		
Albala et al, 2001	23		93
Hollenbeck et al, 2001		63	
Madbouly et al, 2001	57		
Schuster et al, 2002		64	
Sorensen et al, 2002	41		
Sumino et al, 2002	51		
Kuo et al, 2003a*		31	76
Lower Pole Calculi >2 cm			
Lingeman et al, 1994	33		94
Grasso and Ficazzola, 1999		65	
Grasso et al, 1998		76	
Albala et al, 2001	14		86
El-Anany et al, 2001		60	

*CT measured outcome.

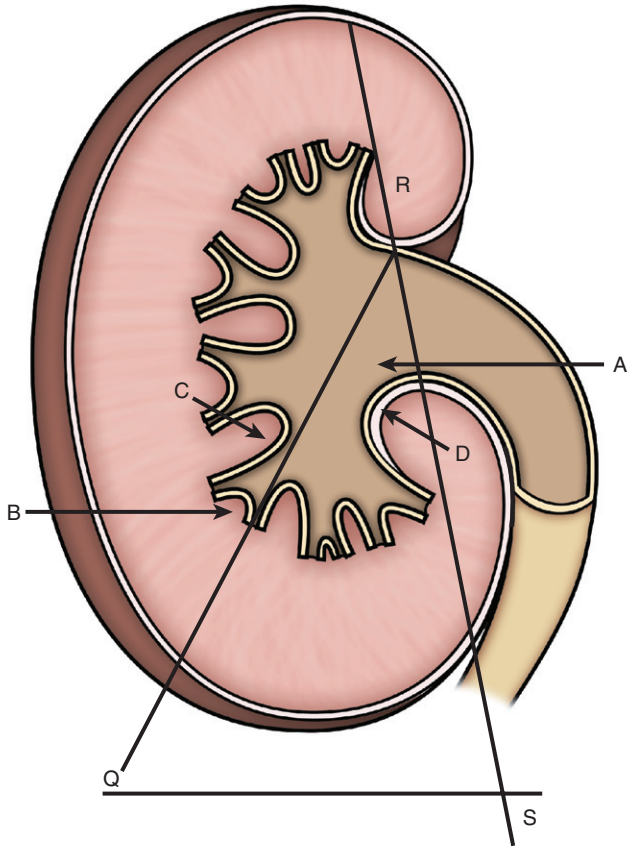


Figure 48–7. Measurement scheme for lower pole anatomy. LPIL (lower pole infundibular length): measure A to B; LPIW (lower pole infundibular width): measure C to D; LPIP (lower pole infundibulopelvic) angle: measure QRS angle. (Reprinted with permission from Albala DM, Assimos DG, Clayman RV, et al. Lower pole I: a prospective randomized trial of extracorporeal shock wave lithotripsy and percutaneous nephrostolithotomy for lower pole nephrolithiasis—initial results. J Urol 2001;166:2072–80.)

is often neglected in these studies. However, it is likely that an obtuse versus an acute lower pole infundibulopelvic angle is important in fragment clearance after SWL. The most appropriate method for measuring lower pole infundibulopelvic angle and its relevant cutoff values as well as the significance of other lower pole anatomic features as predictive factors of stone clearance are yet to be determined. It may be that, in the future, computer modeling may be of benefit in these cases. Poulakis and associates (2003) developed an artificial neural network, incorporating both anatomic factors and dynamic measurements, and were able to accurately predict a successful outcome for patients undergoing SWL in over 90% of cases.

Despite the lower stone-free rates achieved with SWL therapy, a number of clinicians advocate this modality for the treatment of patients with lower pole calculi. In fact, a survey performed by Gerber (2003) found that 65% of urologists would use SWL for lower pole stones 1 to 2 cm in size and 2% would treat stones greater than 2 cm with SWL. Interestingly, however, success rates for SWL of lower pole calculi are generally poor. In trials comparing SWL to PNL, such as those performed by Elbahnasy and associates (1998a) and Cass (1996), the stone-free rate for PNL is superior. Similarly, in series just addressing patients treated with SWL, stone-free rates for lower pole calculi greater than 2 cm are less than 50% (Obek et al, 2001; Chen and Streem, 1996).

The poor stone clearance rates for patients with lower pole calculi treated by SWL have prompted investigators to examine techniques to facilitate fragment passage. McCullough (1989) anecdotally reported that postural drainage may assist in the elimination of retained fragments from dependent calyces. Brownlee and associates (1990) subsequently treated patients with residual lower pole fragments with controlled inversion therapy, using intravenous hydration, inversion, and percussion. D'a Honey and associates (2000) reported a pilot study to determine whether

mechanical percussion with inversion therapy and furosemide-induced diuresis can move stone fragments out of the lower pole of the kidney. At a mean time of 63 days after SWL, this group reported an 83% stone passage rate. In a subsequent study, Pace and associates (2001) compared the effectiveness of mechanical percussion, inversion, and furosemide-induced diuresis with observation for elimination of lower calyceal fragments after SWL. They reported that 40% of patients with residual lower pole fragments treated with this regimen became stone free compared with 3% in the observation group; the observation group was then treated with this regimen as part of a crossover design, and 43% were rendered stone free. Other authors have reported lower pole irrigation techniques as adjuncts to SWL (Nicely et al, 1992; Graham and Nelson, 1994). More recently, pharmacotherapy with potassium citrate and thiazide diuretics has been described (Soygur et al, 2002; Arrabal-Martin et al, 2006). However, at this point in time none of these techniques has gained widespread acceptance.

As previously described, retrospective studies have indicated **the results of SWL of lower pole calculi are inferior to those of PNL and depend on stone size.** Albala and associates (2001) performed a multicenter, randomized, prospective study (Lower Pole I) that compared the treatment outcomes for patients with lower pole calculi after either PNL or SWL. The stone-free rate at 3 months after treatment, as measured by nephrotomograms, was 95% for those undergoing PNL and 37% for those undergoing SWL. Of note, **stone clearance from the lower pole after SWL was especially poor as stone size increased above 10 mm.** For patients with stones smaller than 10 mm, 20 of 20 (100%) patients treated with PNL were stone free whereas 12 of 19 (63%) treated with SWL were stone free. For those patients with calculi of 11 to 20 mm, 26 of 28 (93%) treated with PNL were stone free, whereas 6 of 26 (23%) treated with SWL were stone free. Finally, for patients with calculi of 21 to 30 mm, 6 of 7 (86%) treated with PNL were stone free whereas 1 of 7 (14%) treated with SWL was stone free. The main advantage of SWL was the lower associated morbidity.

In the decade since Grasso and Ficazzola (1999) first reported on a series of patients with lower pole calculi who underwent ureteroscopic treatment, the field of endourology has witnessed a number of advancements in instrumentation, technique, and technology. Consequently, ureteroscopy is now routinely applied to stones in the lower pole calyces, and a number of groups have reported success with this approach. Hollenbeck and associates (2001) reviewed 61 patients who underwent 68 ureteroscopic procedures for the treatment of lower pole calculi. Laser lithotripsy was performed in situ, without displacement of the stone from the lower pole. After a single procedure, 62% were stone free, and after a second procedure, 69% were stone free. Stratified by size, 71% of patients with stones smaller than 10 mm and 75% of patients with calculi of 10 to 20 mm were stone free.

There are certain maneuvers that may facilitate ureteroscopy for lower pole stones. Any device passed through the working channel of a flexible ureteroscope will have an adverse effect on the scope's deflectability, potentially hindering access to the lower pole. However, nitinol baskets and flexible grasping devices have less of a deleterious effect than do laser fibers and may be used to displace a lower pole stone to a mid or upper calyceal location. Kourambas and associates (2000) found that the stone-free rate of patients who were treated with stone displacement before fragmentation was 90% compared with a stone-free rate of 83% for those patients who underwent in-situ fragmentation. Schuster and associates (2002) similarly reported a 77% stone-free rate for patients with lower pole calculi smaller than 1 cm treated in situ versus an 89% stone-free rate for those treated with displacement first. For patients with calculi larger than 1 cm, 100% of those undergoing displacement first were treated successfully compared with 29% of those treated in situ. The ureteral access sheath also may improve stone-free rates for this clinical scenario. Portis and associates (2006) performed a prospective study of patients with intrarenal calculi between 5 and 15 mm and found that with an access sheath and stone displacement a stone-free outcome, by strict CT criteria, was achieved in 59%.

Recognizing the technologic advances in ureteroscopy, **the Lower Pole Stone Study Group compared ureteroscopy and PNL for patients with 10- to 25-mm lower pole stones** (Kuo et al, 2003a). **The primary outcome was a stone-free state, as measured by CT. The results of the study favored PNL, with a 71% stone-free rate, compared with a 37% rate for ureteroscopy. Although the length of hospitalization was shorter for the ureteroscopy cohort, interestingly the convalescence was not different, possibly owing to the morbidity of the ureteral stent among those undergoing ureteroscopy.** The definition of stone free was strict and based on CT; if the definition is broadened to include fragments smaller than 4 mm, the stone-free rate improved to 80% for the ureteroscopy cohort and to 100% for the PNL cohort (Kuo et al, 2003a). Thus, ureteroscopy for patients with a large renal stone burden is probably inferior to PNL and should be used only for those patients who are poor candidates for PNL. The Lower Pole Stone Study Group also performed a prospective, randomized study of SWL and ureteroscopy for lower pole stones smaller than 10 mm. Although there was a 15% difference in stone-free rates between SWL (35%) and ureteroscopy (50%), the difference was not statistically significant. The recovery time, however, was shorter for SWL, and more SWL patients would prefer to be re-treated by that modality (Pearle et al, 2005).

The optimal approach for management of patients with lower pole stones continues to evolve (Fig. 48–8). **SWL is a consideration for individuals with lower pole stones of 1 cm or less in aggregate size, because there is a reasonable chance of achieving a stone-free state with minimal attendant morbidity. Patients with lower pole stones of 2 cm or more are still best served with PNL because this offers them the best chance of being rendered stone free with one procedure. Much of the controversy regarding treatment of lower pole stones is limited to stones of 10 to 20 mm in diameter. PNL, ureteroscopy, and SWL are all acceptable options. Stone composition and lower pole anatomy should be considered in recommending a treatment modality for these patients. Patients with an acute lower pole infundibulopelvic angle (with or without other unfavorable anatomic features), patients whose SWL treatment has failed, and patients known to have stones resistant to SWL should be treated with PNL or ureteroscopy.** In the future it may be possible to predict which patients among this group will have good results with the different treatment modalities.

Clinical Factors

The treatment of urinary tract calculi must be viewed in the context of the patient as a whole. Any coexisting clinical factors that may affect the safety and the efficacy of the selected treatment must be considered.

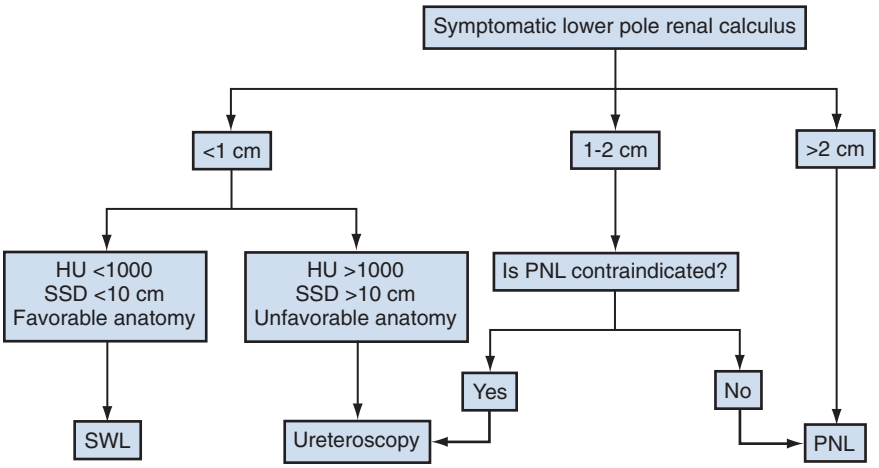


Figure 48–8. Treatment algorithm. HU, Hounsfield unit; PNL, percutaneous nephrolithotomy; SSD, skin-to-stone distance; SWL, shockwave lithotripsy. (Adapted from Galvin DJ, Pearle MS. The contemporary management of renal and ureteric calculi. BJU Int 2006;98:1283–8.)

Table 48–3.

Guidelines for Antimicrobial Prophylaxis for Endourologic and Shockwave Lithotripsy Procedures

PROCEDURE	ORGANISMS	PROPHYLAXIS INDICATED	ANTIMICROBIAL OF CHOICE	ALTERNATIVE ANTIMICROBIAL	DURATION OF THERAPY
Shockwave lithotripsy	GU tract	All	Fluoroquinolone TMP-SMX	Aminoglycoside (Aztreonam) ± ampicillin First- or second-generation cephalosporin Amoxicillin/clavulanate	<24 hr
Percutaneous nephrolithotomy	GU tract and skin	All	First- or second-generation cephalosporin Aminoglycoside (Aztreonam) ± metronidazole or clindamycin	Ampicillin/sulbactam Fluoroquinolone	<24 hr
Ureteroscopy	GU tract	All	Fluoroquinolone TMP-SMX	Aminoglycoside (Aztreonam) ± ampicillin First- or second-generation cephalosporin Amoxicillin/clavulanate	<24 hr

GU, genitourinary; TMP-SMX, trimethoprim-sulfamethoxazole.

Urinary Tract Infection

Urinary tract infection, in the presence of renal calculi, can be difficult to eradicate unless the offending stones are completely removed. For these patients, then, PNL or ureteroscopy, both of which permit the complete removal of stone fragments, may be preferable to SWL. The reported incidence of sepsis after SWL is less than 1%, although a staghorn calculus increases this rate substantially to 2.7% to 56% (Lam et al, 1992a; Meretyk et al, 1997). The risk of sepsis increases if the urine culture demonstrates bacterial growth before SWL (Zink, 1988). Furthermore, the risk of sepsis is also greater in the presence of obstruction (Meretyk et al, 1992). Therefore, **SWL should be performed only if the urine is sterile and there is no distal obstruction.** The American Urological Association guideline for antibiotic therapy (Wolf et al, 2008) has provided specific recommendations for endourologic procedures (Table 48–3).

Morbid Obesity

Morbid obesity, which may be defined as more than 100 pounds overweight, greater than 200% of ideal body weight, or a body mass index (BMI) greater than 40, poses a number of physiologic and technical challenges to the successful treatment of kidney stones (Giblin et al, 1995; Freedman et al, 2002). The respiratory and cardiovascular morbidities inherent in a morbidly obese state can significantly increase the perioperative risk associated with even a minimally invasive procedure. Morbid obesity may make SWL impractical or technically impossible because of weight limitations on the lithotripter table or gantry, of the inability to target the stone radiographically, or the distance of the stone to the skin exceeds the maximum allowable focal distance of the lithotripter. When the increased distance from the skin surface to the stone renders positioning of the stone at the focus of the shockwave impossible, a blast path technique that relies on high pressures produced at a point located coaxially beyond F2 may be required (Whelan et al, 1988; Locke et al, 1990). Although the successful treatment of obese patients with SWL has been reported, high-energy settings of the lithotripter may be required. Should the urologist treating a morbidly obese patient have a choice among different SWL machines, the machine with the greatest focal length and highest peak pressure should be selected.

Despite these potential maneuvers, the morbidly obese may still achieve a suboptimal outcome after SWL. Several groups have acknowledged that BMI is a significant negative predictor of a stone free outcome after SWL (Ackermann et al, 1994; Portis et al, 2003). Because many patients undergo preoperative CT, the concept of a skin-to-stone distance (SSD), quantified on CT, has been popularized. More recently, this concept has been evaluated

by the SSD metric, defined on preoperative axial imaging. Perks and associates (2008) reported that success rates were 79% versus 57% for SSD less than or greater than 9 cm, respectively. Pareek and associates (2005) similarly found that only 20% of stone-free patients had an SSD greater than 10 cm, whereas 85% of patients with residual stone patients had an SSD of 10 cm or greater; the SSD was a stronger predictor of treatment failure than the BMI.

Although obesity may have an adverse effect on SWL outcome, endoscopic interventions may be less sensitive to this parameter. In many cases PNL is the only effective treatment option for the morbidly obese patient with a complex renal calculus. The judicious use of an extralong working sheath, along with extralong rigid nephroscopes, flexible nephroscopes, and longer instruments, can overcome the increased SSD in these patients. Pearle and associates (1998) described 57 obese patients (BMI > 30) who underwent PNL. The overall stone-free rate (88.3%) and the complication and transfusion rates (12.8% and 5%, respectively) were comparable to the results of PNL in an unselected population of patients. Koo and associates (2004) similarly reported that **the outcome of PNL is independent of the patient's BMI.**

Significant alterations in technique are not required when a ureteroscopic approach is selected for the morbidly obese patient with a renal calculus. **For morbidly obese patients who do not harbor an excessively large stone burden the ureteroscopic approach may be preferable** (Dash et al, 2002; Natalin et al, 2009). In fact, when compared with subjects of normal weight, ureteroscopy of morbidly obese confers no additional morbidity (Preminger et al, 2007).

Spinal Deformity or Limb Contractures

Patients with spinal deformity or limb contractures may also be difficult to position within the lithotripter. Alternative treatment modalities, including PNL and ureteroscopy with flexible instruments, may be preferable in these patients (Rubenstein et al, 2004). Ureteral access sheaths may facilitate repeated re-entry of the renal collecting systems in these situations as well. Owing to the unusual anatomy that is often present **a preoperative CT scan can help in planning percutaneous access.** In certain cases CT guidance may be necessary to safely obtain percutaneous access into the renal collecting system (Matlaga et al, 2003).

Uncorrected Coagulopathy

Although **SWL or PNL treatment of patients with uncorrected coagulopathy can result in life-threatening hemorrhage,** such patients can be safely treated once the bleeding diathesis has been corrected (Streem and Yost, 1990). However, **if the patient's coagulopathy is the result of a pharmacologic therapy that cannot be safely discontinued, ureteroscopy with holmium:yttrium-aluminum-garnet (holmium:YAG) laser lithotripsy is the preferable approach.** Since Grasso and Chalik (1998) first reported that this was a safe and effective treatment method for patients with uncorrected coagulopathies, several other investigators have published similar findings. Watterson and associates (2002) as well as Turna and associates (2008) have reported safely managing patients with this approach.

Other Groups

The management of renal calculi in children is discussed in Chapter 135. However, when children as well as the elderly, the hypertensive, and those with impaired renal function are treated with SWL any adverse effects of the shockwaves may be enhanced. Care should be taken to limit the number and energy of shockwaves applied in such circumstances (Janetschek et al, 1997; Evan et al, 1998; Lifshitz et al, 1998).

Assessment and Fate of Residual Fragments

In the era of open stone surgery residual fragments of any size suggested a failed procedure. However, the increasing popularity of SWL as the treatment of choice for most patients with upper tract urinary calculi has changed the definition of a successful outcome and introduced the concept of **clinically insignificant residual fragments** (Newman et al, 1988). Newer definitions of treatment success were required after the observation that **although many patients had successful stone fragmentation with SWL not all patients completely and spontaneously passed all of the stone fragments.** Furthermore, the clearance of stone fragments produced by shockwaves is not immediate; as many as 85% of patients have radiologic evidence of residual fragments in the kidney several days after SWL (Drach et al, 1986). Although most fragments will pass spontaneously during the first 3 months after SWL, continued clearance of fragments can occur for more than 24 months after treatment (Chaussy and Schmiedt, 1984; Graff et al, 1988; Kohrmann et al, 1993). Therefore, since the introduction of SWL, treatment outcomes for patients with renal calculi have been reported by two different terms: *stone-free rate* and *success rate*. The stone-free rate is self-explanatory, but the success rate includes patients who are stone free as well as those with clinically insignificant residual fragments. These different methods of reporting treatment results, the lack of consensus regarding the definition of clinically insignificant residual fragments, and the various modalities used for assessing postprocedural stone-free status (KUB radiography, nephrotomography, ultrasonography, CT) make the comparison of endourologic stone removal procedures with SWL difficult.

Clinically insignificant residual fragments were initially defined as residual fragments 4 mm or smaller in diameter associated with sterile urine in an otherwise asymptomatic patient (Newman et al, 1988). However, **small residual stones often become clinically symptomatic** (Streem et al, 1996; Zanetti et al, 1997; Candau et al, 2000). Streem and colleagues (1996) first reported on the prospective, long-term follow-up study of post-SWL residual fragments; in a series of 160 patients with small, residual, asymptomatic calcium oxalate or calcium phosphate stones (≤4 mm), 43% had suffered a significant symptomatic episode at a mean follow-up of 23 months.

Residual fragments not only may become symptomatic but also can act as a nidus for new stone growth. Complete stone removal will decrease the risk of stone recurrence and regrowth (Singh et al, 1975; Patterson et al, 1987; Newman et al, 1988). Stone recurrence rates of 6% to 15% have been reported for patients who were rendered stone free after SWL, compared with rates of 17% to 80% when residual fragments were present (Graff et al, 1988; Newman et al, 1988; Nijman et al, 1989; Beck and Riehle, 1991; Fuchs et al, 1991; Zanetti et al, 1991; Nakamoto et al, 1993). In the long-term prospective study of Streem and associates (1997), residual fragments (<4 mm) after SWL were found to pass spontaneously in 24% of patients, although 18% of patients experienced stone growth. Similarly, a retrospective study of 83 patients with residual fragments (<4 mm) after SWL found complete stone clearance occurred in 33% of subjects but 37% of

subjects developed increased stone burden (Candau et al, 2000). In this study the size of the residual fragment influenced the likelihood of its becoming symptomatic.

Many investigators have noted that, **after SWL, residual fragments are commonly localized to lower pole calyces no matter where the stone was treated in the kidney** (Drach et al, 1986; Graff et al, 1988; Liedle et al, 1988; Zanetti et al, 1991; Kohrmann et al, 1993). As well, the incidence of stone recurrence is greater in the lower pole calyces after SWL (Zanetti et al, 1991; Kohrmann et al, 1993; Carr et al, 1996) as opposed to PNL. Furthermore, at 1-year follow-up there is a significantly greater rate of new stone formation in those treated with SWL and the recurrent stones are more likely to be in the lower calyces. A plausible explanation for these results is that fine debris, undetectable by KUB radiography, persists after SWL and, because of gravity, tends to settle in the most dependent calyces, serving as a nidus for new stone formation.

In patients with infection-related calculi, the consequence of residual fragments is particularly harmful. Residual fragments may harbor the offending bacteria and thus perpetuate postoperative bacteriuria and persistent infection. Furthermore, stone regrowth has been reported in up to 75% of such patients after SWL, compared with 10% of patients who experienced complete stone removal (Beck and Riehle, 1991; Zanetti et al, 1991).

For patients with metabolic stone disease (e.g., those with cystinuria), complete stone removal does not prevent stone recurrence but it does prolong treatment intervals (Chow and Streem, 1998). Thus, residual stones, including small stones, may not have an immediate clinical relevance but are likely to affect the patient's well-being in the long term. In these situations it is important to select a treatment approach that is most likely to render the patient stone free.

The sensitivity of the method used to detect residual stones after a stone removal procedure has important effects on the reported incidence and size of residual fragments. In early studies investigating stone clearance after SWL, plain radiography was commonly used to determine stone-free status. A plain radiograph can detect an opaque stone fragment as small as 2 mm (Thornbury and Parker, 1982). However, Denstedt and coworkers (1991) reported that for patients with large renal calculi treated by a combination of PNL and SWL, plain radiography overestimated stone-free rates by 35% and 17%, respectively, compared with flexible nephroscopy. Several groups have reported that nephrotomography is superior to plain radiography in evaluating stone-free status; additional residual stone fragments are detected in 12% to 47% of patients (Hjollund Madsen, 1972; Schwartz et al, 1984; Goldwasser et al, 1989). Ultrasonography is inferior to plain radiography and is particularly inadequate in detecting ureteral stones, although this modality is very effective in diagnosing hydronephrosis (Yilmaz et al, 1998; Older and Jenkins, 2000). In fact, ultrasonography should be considered after all ureteroscopic procedures because silent obstruction has been reported to occur in certain, albeit rare, instances (Weizer et al, 2002). A prospective study comparing the relative efficacy of abdominal radiography and renal ultrasonography with excretory urography for the evaluation of asymptomatic patients 1 month after SWL treatment demonstrated that the combination of ultrasonography and abdominal radiography was as good as or better than intravenous urography in identifying residual stone fragments and renal abnormalities, including hydronephrosis (Coughlin et al, 1989). The authors suggested that **routine radiologic evaluation of asymptomatic patients after SWL could be limited to abdominal radiography and ultrasonography.**

Although flexible nephroscopy may be considered the "gold standard" for assessment of residual stones after PNL, its routine use has been challenged by studies showing the high sensitivity of CT in detecting residual stones after PNL. Pearle and coworkers (1999) noted that CT had 100% sensitivity for detecting residual stones after PNL in 36 patients evaluated with both CT and flexible nephroscopy. Selective use of flexible nephroscopy based on positive CT findings would have avoided an unnecessary procedure in 20% of patients. In a retrospective study of 121 patients who underwent CT after PNL (including 59% stone-free patients and 16% patients with fragments of 1 to 3 mm), Waldmann and associates (1999) reported that routine nephroscopy would not have been required in 75% of cases. Given its wide availability and high sensitivity, non–contrast-enhanced CT has become the primary method for evaluation of patients after PNL.

Adjunctive Medical Treatment

Any patient who requires surgical stone removal should be offered a metabolic evaluation and stone analysis. **Appropriate medical therapy can decrease the risk of stone recurrence and stone regrowth** (Lifshitz et al, 1999a). Mardis and associates (2004) emphasized the importance of the administration of validated medical therapies, guided by metabolic evaluation, in reducing stone recurrence rates after treatment. Others (Lee et al, 1999; Cicerello et al, 1994) have reported similar experiences, describing reduced stone recurrence rates after a metabolic evaluation and medical management. Although recurrence rates are lower in a stone-free state, medical management is also effective in the presence of residual fragments (Fine et al, 1995). Kang and associates (2007) and Raman and associates (2009) have both reported that, after PNL, appropriate medical therapy will reduce the risk of stone recurrence or progression of any residual fragments. Any postprocedural medical management should not supercede the choice of a treatment approach that gives the patient the best chance to achieve a stone-free status with minimal morbidity. However, it is reasonable to begin a metabolic work-up, such as

Key Points: Renal Calculi

- The majority of patients with renal calculi have a normal kidney and a small stone burden and can be managed best with SWL. Patients with lower pole calculi larger than 10 mm will experience significantly better stone-free rates after PNL than after SWL.
- The procedure of choice for patients with staghorn calculi is PNL. When they are left untreated, staghorn calculi are associated with the loss of renal function and increased mortality.
- Patients harboring stones that are resistant to fragmentation (cystine, brushite, calcium oxalate monohydrate) should undergo SWL only when the stone burden is small.
- The percutaneous approach to patients with calculi in calyceal diverticula provides the best chance for a stone- and symptom-free outcome.
- The outcome of PNL is independent of the patient's body mass index, and therefore PNL is a good treatment option for the morbidly obese with a large stone burden. For the morbidly obese with a small stone burden, ureteroscopy is the optimal approach.

24-hour urinalysis, while the patient is waiting to undergo a scheduled procedure. In this way the time from diagnosis of a stone to the treatment of a metabolic abnormality may be minimized and medical therapy may be begun expeditiously.

URETERAL CALCULI

The goal of the surgical treatment of patients suffering from ureteral calculi is to achieve complete stone clearance with minimal attendant morbidity. Improvements in surgical technology, such as SWL, rigid and flexible ureteroscopes, the holmium:YAG laser, and basket devices, have greatly augmented the urologist's ability to efficiently treat such patients, regardless of the size or location of the ureteral calculus. Although the treatment options available to the urologist are greater now than they have ever been, most patients with ureteral calculi do not require intervention. Ureteral calculi 4 mm or smaller will usually pass spontaneously, although in some cases with discomfort and expense to the patient. Ureteral calculi of any size may be associated with renal obstruction, and care must be taken to prevent irreversible damage to the kidney, whether the patient selects expectant or active treatment.

Perhaps the greatest dilemma facing the urologist today is "to blast or not to blast" (i.e., to choose between the two most frequently used modalities in ureteral stone treatment—SWL and ureteroscopy). PNL is a less commonly used treatment option and is usually reserved for a limited group of patients with large, proximal ureteral stones. Open ureterolithotomy is rarely indicated, although it may be an option as a salvage procedure. Laparoscopic ureterolithotomy has been described both as a salvage procedure in lieu of an open ureterolithotomy as well as a first-line therapy. The ultimate role of this procedure in the urologic armamentarium is yet to be determined, although it is effective for a select group of patients.

The factors that the urologist must consider when recommending treatment to patients with ureteral calculi may be grouped into three broad categories: stone-related factors (location, size, composition, duration of presence, and degree of obstruction), clinical factors (the patient's tolerance of symptomatic events, the patient's expectations regarding treatment outcome, associated urinary tract infection, solitary kidney, and abnormal ureteral anatomy), and technical factors (equipment available for treatment, costs) (Table 48–4). These factors may be thought of as treatment modifiers; the presence or absence of one or more of these factors may shift the balance toward certain treatment modalities or away from other treatment modalities.

Natural History

The indications for intervention in the management of patients with ureteral calculi have clearly been affected by the increased efficiency and reduced morbidity of minimally invasive treatment modalities. Although the traditional indications for intervention (intolerable or intractable symptoms, infection, obstruction, and a stone that is unlikely to pass spontaneously) have not changed, the array of technologies currently available allows almost any symptomatic patient to be considered a candidate for stone removal. An early cost analysis in the era of minimally invasive surgery (Lingeman et al, 1986b) reported that when a patient requires hospitalization it is less costly to remove the patient's stone with either SWL or ureteroscopy than to attempt to control the patient's symptoms with pharmacotherapy only. However, many patients will pass their stone spontaneously, making a surgical intervention unnecessary. A thorough knowledge, then, of the natural history of ureteral stones permits a well-informed judgment of when conservative measures (e.g., observation), rather than intervention, are indicated. Furthermore, such data help the patient consider the spectrum of options and decide whether to try to endure further symptoms or to elect immediate stone removal.

In the absence of external ureteral compression or internal narrowing, **the width of the stone is the most significant measurement affecting the likelihood of stone passage** (Ueno et al, 1977). The 5-mm reference size has emerged as a breakpoint; when evaluating for passage, ureteral stones are generally categorized as greater than or less than 5 mm in greatest diameter (Table 48–5). There have been four studies, including 197 patients, that have evaluated the likelihood of a 5-mm stone passing spontaneously. A meta-analysis of the studies' data found that the likelihood of a stone less than 5 mm passing spontaneously was 77%. Three studies, including 104 patients, have evaluated the likelihood of stones greater than 5 mm passing spontaneously. A similarly performed meta-analysis found that the likelihood of stones greater than 5 mm passing spontaneously was 46%. Morse and Resnick (1991) reported that **the rate of spontaneous passage is greater for distal ureteral stones (71%) than for proximal ureteral stones (22%).** Hubner and associates (1993) also reported that the likelihood of spontaneous stone passage was directly related to stone location at the time of presentation, because the rate of spontaneous passage for stones in the distal ureter was 45%, compared with 12% for the

Table 48–4.

Factors Affecting Management of Ureteral Stones

STONE FACTORS	CLINICAL FACTORS	TECHNICAL FACTORS
Location	Symptom severity	Available equipment
Size	Patient's expectations	Cost
Composition	Associated infection	
Degree of obstruction	Solitary kidney	
	Abnormal ureteral anatomy	

Table 48–5.

Likelihood of Spontaneous Stone Passage

STUDY	NO. OF PATIENTS	NO. REQUIRING INTERVENTION (%)	NO. PASSING STONE (%)
		Stone Size <5 mm	
Miller and Kane, 1999	59	4 (7)	55 (93)
Hussain et al, 2001	9	0 (0)	9 (100)
Coll et al, 2002	114	29 (25)	85 (75)
Kupeli et al, 2004	15	12 (80)	3 (20)
Weighted average	**197**	**23**	**77**
		Stone Size > 5 mm	
Miller and Kane, 1999	16	8 (50)	8 (50)
Hussain et al, 2001	15	6 (40)	9 (60)
Coll et al, 2002	73	42 (58)	31 (42)
Weighted average	**104**	**54**	**46**

proximal ureter. These rates have been affirmed by a more recent review of CT of ureteral calculi (Coll et al, 2002). **For patients with stones of 5 mm or less, conservative management should be considered,** whereas the chance of spontaneous passage for larger stones and more proximal stones diminishes considerably and thus intervention should be more readily contemplated.

Miller and Kane (1999) analyzed the interval from presentation to passage to develop a time course for counseling patients. They found that the interval to stone passage was highly variable and dependent on both stone size and location: for 95% of stones to pass, 31 days were required for stones 2 mm or less, and about 40 days were required for stones 2 to 6 mm. Furthermore, only 4.8% of patients with stones smaller than 2 mm required intervention compared with 50% of patients with stones 4 to 6 mm. Cummings and coworkers (2000) trained an artificial neural network to predict outcome in patients with ureteral stones with 76% accuracy. The duration of symptoms before initial presentation was the most influential factor, followed by degree of hydronephrosis. The importance of symptom duration was reported by several other authors, who concluded that if significant progress has not occurred after 1 month of observation, intervention is usually required (Ibrahim et al, 1991; Hubner et al, 1993; Singal and Denstedt, 1997).

A number of investigators have reported on the use of pharmacologic means to promote ureteral stone passage, a practice that has been termed *medical expulsive therapy.* Both calcium-channel blockers and α-adrenergic blockers have demonstrated effects on ureteral smooth muscle, making them the logical target for clinical evaluations. Borghi and associates (1994) first reported a randomized, double-blind, placebo-controlled study that compared the effectiveness of nifedipine plus methylprednisolone with the effectiveness of the corticosteroid alone in hastening stone passage. They found that the calcium-channel blocker plus corticosteroid group experienced a greater rate of passage than the group treated with the corticosteroid alone. Since this report there have been other publications detailing varied combinations of medical treatments, including corticosteroid, nonsteroidal anti-inflammatory drug, calcium-channel blocker, and α-adrenergic blocker medications. These studies are difficult to interpret in aggregate because there is no uniformity in the medication studied, duration of treatment, adjunctive therapy, and inclusion criteria. The common theme across these studies, however, was that medical treatment with either α-adrenergic blockers or calcium-channel blockers increased the likelihood of spontaneous stone passage. The benefit of corticosteroids is small, however. Hollingsworth and associates (2006) performed a meta-analysis of these pharmacologic therapies, defining their efficacy in promoting the spontaneous stone passage. They found that there was a significant benefit for both calcium-channel blockers and α-adrenergic blockers in improving stone passage rates. However, the question of an optimum medical regimen was not definitively answered. **A subsequent meta-analysis, performed by the AUA/European Association of Urology (EAU) Ureteral Stones Guidelines Panel, found that α-adrenergic blockers were superior to nifedipine and may be the preferred agent for medical expulsive therapy** (Preminger et al, 2007). Importantly, if medical expulsive therapy is to be selected by the patient and physician, the patient must be reasonably comfortable with the therapeutic approach and counseled on the attendant risks, including drug side effects and that the drug is being administered for an "off label" use.

Stone Factors

Location

The location at which the passage of a ureteral stone is arrested is an important factor in assessing the likelihood of spontaneous passage as well as in determining the optimal treatment options and their relative successes. The statistical **probability of spontaneous ureteral stone passage is directly related to the distance of the ureter to be traversed and inversely related to stone size.**

Ureteral stones usually become impacted at three distinct sites where the caliber of the ureter narrows: the UPJ, the iliac vessels, and the ureterovesical junction. Historically the ureter was divided into thirds: the proximal ureter, from the UPJ to the upper edge of the sacrum; the middle ureter, from the superior to the inferior margin of the sacroiliac joint; and the distal ureter, from the inferior margin of the sacrum to the ureterovesical junction. This three-part division was based on the different open surgical approaches to stones in the ureter. However, with the development of minimally invasive techniques, open surgery is rarely indicated and the ureter is more often now divided into two segments, proximal and distal; the point of division is the narrow part of the ureter where it crosses the iliac vessels, reflecting a technical impediment for rigid ureteroscopy (Segura et al, 1997). Although in the early experience with endourology this impediment was reflected in inferior treatment outcomes for proximal ureteral calculi, as skill and equipment have evolved this effect has lessened (Tables 48–6 and 48–7).

Historically SWL was the preferred treatment for patients with proximal ureteral calculi. The 1997 AUA Nephrolithiasis Guideline Panel documented an 83% stone-free rate for SWL of proximal ureteral stones, a result that required 1.4 procedures per patient to achieve. In the distal ureter the results of SWL were 85%,

Table 48–6.

Ureteroscopic Treatment Outcomes for Distal Ureteral Calculi

STUDY	NO. OF PATIENTS	MEAN STONE SIZE (MM)	STONE-FREE RATE (%)
Pearle et al, 2001	32	6.4	91
Sofer et al, 2002	348	10.3	99
Zeng et al, 2002	180	6-20	93
Aghamir et al, 2003	247	<10	96
Sozen et al, 2003	464	8.8	95

Table 48–7.

Ureteroscopic Treatment Outcomes for Proximal Ureteral Calculi

STUDY	NO. OF PATIENTS	MEAN STONE SIZE (MM)	STONE-FREE RATE (%)
Lam et al, 2002	31	8.2	97
Sofer et al, 2002	194	12.0	97
Aghamir et al, 2003	115	>10	75
Sozen et al, 2003	36	7.4	83
Fong et al, 2004	51	9.0	90
Wu et al, 2005	39	15.1	92
Lee et al, 2006	20	18.5	35

requiring 1.3 treatments per patient. The updated guidelines of 2007 reported that SWL resulted in a stone-free outcome for 82% of patients treated for a proximal ureteral stone and 74% of patients treated for a distal ureteral stone. Interestingly, a statistical comparison of the two analyses confirms that the decline in efficacy for SWL of distal ureteral stones was statistically significant. There is no clear explanation for this change over the intervening decade. For those patients with proximal ureteral stones there was no difference in outcome if SWL was performed in situ or using a pushback technique.

With the increased dissemination of flexible ureteroscopy, the anatomic location of the targeted stone has had progressively less effect on treatment outcome. In 1997 the Guideline Panel recommended SWL for small stones in the proximal ureter and either SWL or ureteroscopy for large proximal ureteral stones. However, in the 2007 document, ureteroscopy is now deemed appropriate for stones of any size in the ureter. The stone-free rate for proximal ureteral stones was 81%, and for distal ureteral stones the stone-free rate was 91%. Stone-free rates were better for ureteroscopy than for SWL when treating distal ureteral stones of any size, as well as for proximal ureteral stones greater than 10 mm. The results for ureteroscopy with a flexible ureteroscope for proximal ureteral stones were better than those achieved with a rigid device, although this difference was not statistically significant.

In select cases with impacted stones in the upper ureter, which have failed treatment with SWL or ureteroscopy, percutaneous stone removal is a reasonable option (Maheshwari et al, 1999). In this way, rather than standard retrograde access, percutaneous antegrade access to the stone is established for subsequent endoscopic removal. Other cases in which a percutaneous approach for an upper ureteral stone may be appropriate would be in combination with renal stone removal and in cases of ureteral stones that occur after urinary diversion.

Stone Burden

The stone burden, in terms of both size and number, may affect what form of therapy will be the most efficient and confer the highest stone-free rate. The likelihood of a successful outcome with SWL is known to be adversely affected by an increasing stone burden for not just renal calculi but also ureteral calculi. In the 2007 AUA/EAU guideline, ureteral stones were classified as either less than or greater than 10 mm. At all locations in the ureter the treatment outcome for stones less than 10 mm was superior to that for stones greater than 10 mm. Specifically, for stones in the distal ureter the stone-free rate for stones less than 10 mm treated by SWL was 86%, compared with a 74% stone-free rate for those greater than 10 mm. For proximal ureteral stones, the trend held true, as 90% of patients with stones less than 10 mm achieved a stone-free outcome, compared with 68% with stones greater than 10 mm. Ureteroscopy is also affected by stone burden, but perhaps to a lesser extent. For distal ureteral stones treated with ureteroscopy, stone-free outcomes occurred in 97% of cases when the burden was less than 10 mm and in 93% of cases when the burden was greater than 10 mm. For stones in the proximal ureter the outcomes stratified by stone size were almost identical: 80% of patients were stone free for stones less than 10 mm and 79% were stone free for stones greater than 10 mm.

Stone Composition

Stone composition, if it is known, is useful information to help discern which treatment strategy may be favored (e.g., SWL for fragile calcium oxalate dihydrate stones or ureteroscopy and intracorporeal lithotripsy for cystine or brushite stones that are relatively resistant to SWL). In general, most ureteral stones are resistant to medical dissolution therapy. However, in the moderately symptomatic or asymptomatic patient with an incomplete obstruction caused by a uric acid stone, urine pH manipulation may be attempted as part of a conservative treatment approach. Urine pH manipulation should also be considered for the patient who does not desire or cannot medically tolerate anesthesia for SWL or ureteroscopy and who is thought to harbor a uric acid stone.

Duration of Stone Presence

The management of patients with ureteral stones may be affected by the duration of a stone's presence or the patient's symptoms. The length of time a stone has been in the ureter is significant because of the potential for irreversible loss of renal function. However, even with complete ureteral obstruction, irreversible loss of renal function does not occur before 2 weeks, although it can progress to total renal unit loss at up to 6 weeks (Vaughan and Gillenwater, 1971).

Andren-Sandberg (1983) reported that in 358 patients with ureteral stones, nuclear renography detected impaired renal function in 27% of patients who were asymptomatic. Furthermore, 7% of these patients had persistent renal impairment up to 17 months after stone passage. Holm-Nielsen and associates (1981) reported that of 134 patients with unilateral ureteral stones, one third of the patients with obstruction lasting more than 4 weeks suffered irreversible renal damage. Similarly, Kelleher and associates (1991) found that sequential renal scintigraphy performed on 76 patients with obstructive ureteral calculi demonstrated an 18% incidence of reduced renal function (defined as a decrease in relative function greater than 7%). Two of the 14 patients had persistent loss of renal function after treatment. These two patients had undergone previous unsuccessful attempts at stone removal, emphasizing the importance of achieving stone-free status at the time of the initial procedure. Irving and associates (2000) studied 54 patients with ureteral calculi and reported that 28% of patients had silent loss of renal function at presentation. Interestingly, small calculi were as likely to be associated with diminished renal function as were larger stones, and patients who underwent early intervention (before 7 days) for diminished renal function had a better outcome than did patients with delayed intervention. **Because the patient's symptoms and stone size do not predict loss of renal function, and because there is no clear time threshold for irreversible damage, intervention should be considered in any patient with ureteral obstruction unless the ability to closely monitor renal function is available.**

Clinical Factors

Pain

Pain (renal or ureteral colic) is the primary presenting symptom of most patients with ureteral obstruction and is the source of considerable morbidity. The pain of ureteral colic is mediated by prostaglandins released by the ureter in response to obstruction. Prostaglandins act to increase ureteral peristalsis to aid in stone passage and also to sensitize nociceptors to stimuli such as bradykinins that induce pain and visceral responses (nausea, vomiting) (Selmy et al, 1994). For these reasons, prostaglandin inhibitors such as indomethacin and ketorolac are particularly effective in

relieving the pain and nausea of ureteral obstruction and are commonly used for this purpose in the emergency department setting (Brown, 2006). However, **prostaglandin inhibitors must be used with caution or avoided entirely in patients with compromised renal function; infusion of ketorolac in an acute unilateral ureteral obstruction model decreased ipsilateral renal blood flow by 35%** (Perlmutter et al, 1993).

Management of ureteral obstruction on the basis of symptoms should be tailored to the amount of time the symptoms have persisted. Patients presenting with early symptoms of renal colic may be managed expectantly for stone passage as long as their symptoms are controllable with oral medical therapy. Patients with symptoms of longer duration may be more appropriately managed by relieving the ureteral obstruction through either the placement of a ureteral stent or definitive stone treatment. Patients with ureteral stones causing severe symptoms refractory to conservative and medical therapy require prompt treatment.

Infection

Infection associated with ureteral stones, or obstructed pyelonephritis, is a not uncommon and potentially life-threatening urologic emergency. Such patients are typically febrile and may present with signs of septic shock, such as hypotension. Urgent drainage of the obstructed portion of the urinary tract by either ureteral catheter or percutaneous nephrostomy is essential. A urine culture specimen from the obstructed segment will aid in directing antibiotic therapy. Definitive stone therapy should be delayed until urine cultures are negative and the patient has recovered completely.

The Patient's Expectations

The patient's expectations must be considered in recommending different treatment modalities. For ureteral stones with low probability of spontaneous passage the patient must be informed of the available treatments, including the relative benefits and risks associated with each. Although ureteroscopy is more invasive than SWL, the patient may achieve immediate or nearly immediate stone-free status with a single procedure. Although SWL is less invasive, a patient may be reluctant to select this modality because it entails an often lengthy follow-up until fragment clearance as well as the risk of unplanned additional invasive procedures and re-treatments. Conversely, patients may select SWL as a consequence of apprehension of the anesthesia associated with ureteroscopy or the possibility of a temporary ureteral stent.

Solitary Kidney

Patients with ureteral stones in either surgically or functionally solitary kidneys require a modification of standard treatment algorithms. **A ureteral stone obstructing a solitary kidney demands prompt attention,** usually with internal drainage and definitive stone treatment (SWL or ureteroscopy).

Aberrant Anatomy

Ureteral stones in patients with abnormal anatomy (ureteral ectopia, ureteroceles, megaureters) may have impaired egress because of obstructive or functional factors (Kajikawa et al, 1985; Diamond et al, 1994; Dretler, 1995). These patients may not respond to therapies such as SWL with the same level of success as do those with normal ureteral anatomy. The anatomic abnormality may need to be corrected or circumvented to permit successful treatment of ureteral stones. For example, patients with recurrent stones that become lodged and obstruct the ureter in a ureterocele should have the ureterocele treated (by either endoscopic incision or open excision with reimplantation) simultaneously with ureteral stone removal. Ureteroscopy, with modern endoscopes and implements, has been reported to be a successful technique with which to treat patients with unusual renal or ureteral anatomy (Weizer et al, 2005). One anatomic situation in which retrograde ureteroscopic treatment is likely not to be successful is that of the patient who has previously undergone a cross-trigonal ureteral reimplant. Krambeck and associates (2007) reported on a series of patients who had previously undergone ureteral reimplantation, finding that a cross trigonal reimplant was associated with a need for more invasive stone removal procedures and that ureteroscopy often failed in this population, because the kidney could not be accessed in a retrograde fashion.

Technical Factors

The treatment of patients with ureteral calculi depends on multiple surgical technologies, and the availability of certain equipment will affect the possible options for treatment. Few operating environments will have all possible lithotripters, ureteroscopes, lithotrites, or stone retrieval devices immediately available. In addition, the surgeon's preference and technical expertise will also affect the technique chosen. The majority of urologists and patients with stone disease in the United States do not have direct access to a fixed lithotripter on an unlimited basis. Therefore, treatment decisions may need to be modified according to lithotripter availability. Patients with symptomatic ureteral stones and no immediate lithotripter access have several options: they may be clinically observed with pain and emetic control; they can undergo placement of an internal ureteral stent to relieve the symptoms of renal colic (but then may suffer stent-related morbidities); or they may have primary ureteroscopic removal of the stone, provided the requisite endoscopic equipment is available.

Because of recent pressures to decrease resource use there is increasing emphasis in the modern medical environment on the reduction of cost. Such economic pressures have promoted the movement toward less invasive, more cost-effective therapy for patients with ureteral stones. Most studies performed in the United States have found that ureteroscopy is a more cost-effective intervention than SWL, a differential that is likely due to the higher re-treatment rate associated with SWL. Grasso and colleagues (1995a) analyzed the cost of ureteroscopy and SWL for patients with ureteral calculi. When they compared outpatient ureteroscopic lithotripsy with SWL monotherapy, treatment costs were similar. However, the addition of re-treatments and auxiliary procedures after SWL more than doubled the costs and weighed heavily against this modality's cost-effectiveness. Kapoor and associates (1992) compared the treatment costs of SWL and ureteroscopy: as a consequence of the significantly higher success rates (97% vs. 75%), ureteroscopy was the more cost-effective treatment approach. Parker and associates (2004) studied the cost associated with treating proximal ureteral stones and found that ureteroscopy was less costly, again as a consequence of its superior initial treatment success. Several investigators have approached the question of cost-effectiveness treatment for ureteral calculi by constructing decision analysis models. Wolf and associates (1995) used a literature-based probability decision tree to determine the more effective and cost-efficient therapy for patients with distal ureteral calculi and found that although initial SWL was only slightly more expensive than ureteroscopy the cost differential increased when additional complications and re-treatments were calculated. Lotan and associates (2002) also constructed a decision analysis model to determine the most cost-effective treatment for

ureteral stones. Although observation was the least costly intervention, ureteroscopy was a less costly intervention than SWL for the treatment of stones at all locations in the ureter. Thus taken all together, **ureteroscopy is the most cost-effective treatment strategy for ureteral stones at all locations, after observation fails.**

Laparoscopic Ureterolithotomy

Laparoscopy should be considered whenever one contemplates the open surgical removal of a ureteral calculus. Although the indications for this surgery are not common there are certain patients for whom this may be an acceptable approach, such as those with concomitant upper tract abnormalities (e.g., ureteral stricture, UPJ obstruction) requiring surgical repair.

Both transperitoneal and retroperitoneal approaches have been described for laparoscopic ureterolithotomy (Wuernschimmel and Lipsky, 1993; Gaur et al, 1994). Keeley and associates (1999a) utilized laparoscopic ureterolithotomy in only 1.1% of patients treated in a 5-year period, with successful results in all cases. The indications for a laparoscopic procedure included stones that could not be accessed ureteroscopically, stones that did not fragment with other treatment modalities, and large (>1.5 cm) proximal ureteral stones. Confirming the superior morbidity of the procedure, Goel and Hemal (2001) reported the results of a prospective comparison of laparoscopic and open ureterolithotomy. A number of other centers have reported their successful experiences with the application of this technique (Turk et al, 1998; Gaur et al, 2002; El-Feel et al, 2007; El-Moula et al, 2008). Among these groups the techniques were varied; some describe suturing and stenting the ureter, whereas others leave the ureter unsutured and unstented. Further advancing laparoscopic stone surgery, Rane and associates (2008) reported the successful case of a single-port laparoscopic ureterolithotomy. Although many of the aforementioned authors suggest that laparoscopic ureterolithotomy may be used as a primary procedure, it is more likely that this operation will be reserved for those patients who require a salvage procedure after failed ureteroscopy or SWL or who have another indication for a laparoscopic procedure.

Key Points: Ureteral Calculi

- Conservative management for a patient with a ureteral stone smaller than 5 mm is appropriate because there is a high likelihood of stone passage. Ureteral stones larger than 5 mm are unlikely to pass spontaneously.
- Obstructed pyelonephritis due to a ureteral calculus is a not uncommon and potentially life-threatening emergency that is best treated by urgent decompression of the urinary tract.
- Both SWL and ureteroscopy are highly effective for patients with ureteral calculi.
- Medical expulsive therapies with agents such as tamsulosin may promote spontaneous stone passage.

URINARY CALCULI DURING PREGNANCY

Incidence

Urolithiasis is an infrequent complication of pregnancy. However, pain from renal colic is the most common nonobstetric reason for hospital admission during pregnancy (Rodriguez and Klein, 1988). Furthermore, the occurrence of urinary calculi during pregnancy presents danger not only to the mother but also to the fetus because renal colic, infection, and obstruction are all associated with premature labor (Maikranz et al, 1987; Hendricks et al, 1991). The reported incidence of symptomatic urinary calculi during pregnancy ranges from 1 in 200 to 1 in 2500 pregnancies; the wide variation in reported incidence may be due to the small numbers of patients in these studies (Gorton and Whitfield, 1997). However, **the incidence of symptomatic urinary calculi has been calculated to be the same for pregnant women as for nonpregnant women of childbearing age** (Coe et al, 1978; Hendricks et al, 1991). Multiparous women have been reported to be affected more often than primiparous women, in some cases by a ratio of about 3:1 (Horowitz and Schmidt, 1985; Rodriguez and Klein, 1988). However, when it is adjusted for age, the incidence for multiparous women is no greater than that for primiparous women (Swanson et al, 1995). Calculi present with equal frequency on the left and right sides, although ureteral calculi occur almost twice as frequently as renal calculi (Stothers and Lee, 1992; Parulkar et al, 1998). The majority of patients with symptomatic calculi present during the second or third trimesters but rarely during the first trimester (Denstedt and Razvi, 1992; Stothers and Lee, 1992; Swanson et al, 1995).

Although symptomatic urolithiasis may be an uncommon complication of pregnancy, renal colic during pregnancy is a serious concern, because such an event may be dangerous to both the mother as well as the fetus. Swartz and associates (2007) analyzed the hospital discharge data from 1987 through 2003 in the state of Washington and found that women admitted for nephrolithiasis had a significantly greater (adjusted odds ratio 1.8) risk of preterm delivery compared with women without stones. Lewis and associates (2003) also reviewed a large database comprised of over 21,000 deliveries and found that of the 86 patients diagnosed with a stone during pregnancy there was an increased risk of preterm premature rupture of membranes (2.9% in non-stone patients vs. 7% in stone patients). Preterm premature rupture of membranes, as the authors note, carries with it an increased risk of morbidity and mortality to the newborn.

Etiology

Pregnancy induces significant physiologic alterations, some of which affect the urinary system. The most remarkable anatomic change is the dilation of the renal calyces, pelvis, and ureters, which is usually evident by the first 6 to 10 weeks of gestation. Pregnancy-induced hydronephrosis is the most common cause of dilation of the urinary tract in pregnancy and may cause flank discomfort or even mimic renal colic. **Upper tract dilation is seen in up to 90% of pregnant women by the third trimester** and may persist for as long as 12 weeks postpartum (Boridy et al, 1996). The **right ureter tends to be more dilated than the left,** and the dilation rarely is observed distal to the pelvic brim (Schulman and Herlinger, 1975). Rarely, spontaneous rupture of the kidney may occur, and if it does, it more commonly happens on the right side (MacNeily et al, 1991; Loughlin, 1994). Both **humoral as well as mechanical factors have been implicated in the etiology of hydronephrosis in pregnant women.** Circulating progesterone, a humoral factor that is increased in pregnancy, causes relaxation of ureteral smooth muscle, reducing ureteral peristalsis. Paller and Ferris (1996) have reported that dilation of the urinary collecting system can be reproduced in an animal model by the administration of

estrogen and progesterone. However, recent evidence suggests that mechanical factors, in particular the gravid uterus directly compressing the ureters, are likely to be primary in the pathogenesis of this condition; women with an altered upper urinary tract in whom the ureter does not cross the pelvic brim, such as those with ileal conduit or renal ectopia, do not experience hydronephrosis during pregnancy (Rasmussen and Nielsen, 1988; Dafnis and Sabatini, 1992; Swanson et al, 1995). Although the exact etiology of hydronephrosis of pregnancy is not yet well defined, most would agree that both mechanical and humoral factors play a role in the pathogenesis of this condition.

Other important physiologic changes in pregnancy include an increase in renal plasma flow, which induces a 30% to 50% increase in glomerular filtration rate. As a result of this physiologic alteration **the normal ranges of serum creatinine and blood urea nitrogen are approximately 25% lower for the pregnant patient.** Importantly then, a serum creatinine value that is in the normal range for the nonpregnant population may actually represent a decrease in renal function for the pregnant patient (Paller and Ferris, 1996). **The increase in renal plasma flow and glomerular filtration rate also increases the filtered loads of sodium, calcium, and uric acid, causing a state of hypercalciuria and hyperuricosuria** (Boyle et al, 1966; Howarth et al, 1977; Gertner et al, 1986). Hypercalciuria is further exacerbated by the suppression of parathyroid hormone and the increase in circulating 1,25-dihydroxycholecalciferol produced by the placenta, which increases intestinal absorption of calcium. Twenty-four-hour urine chemistries performed among pregnant women have also demonstrated that urinary pH is elevated in the course of pregnancy, most dramatically during the second trimester (Resim et al, 2006). However, **these potentially lithogenic physiologic changes are offset by an increase in the excretion of urinary inhibitors, such as citrate and magnesium, as well as an increase in urine output** (Biyani and Joyce, 2002). It has been postulated that metabolic alterations in the urine may contribute to the accelerated encrustation of ureteral stents during pregnancy (Denstedt and Razvi, 1992; Loughlin, 1994). Ross and associates (2008) have reported that stones that occur during pregnancy are most commonly calcium phosphate in composition, a finding that may be explained by the relatively elevated urinary pH and hypercalciuria that occur in the pregnant state.

Evaluation

Although renal colic is the most common nonobstetric cause of abdominal pain in hospitalized pregnant women, the diagnosis of urolithiasis in the pregnant patient can be challenging; many of the usual presenting signs and symptoms may be masked by the patient's gravid status. As gestation progresses, the perception and localization of pain may be altered. Stothers and Lee (1992) reported that 28% of pregnant patients ultimately diagnosed with an obstructing stone were initially, and incorrectly, diagnosed with appendicitis, diverticulitis, or placental abruption. For most patients, however, **the most common presenting symptom is flank pain, usually accompanied by either macroscopic or microscopic hematuria** and, in some cases, urinary tract infection (Stothers and Lee, 1992). Hematuria can occasionally occur in the normal course of pregnancy; however, hematuria without discomfort is unusual in a patient with stone disease (Swanson et al, 1995). It is particularly important to obtain a urine specimen for culture from these patients because pyuria may commonly be seen in the urinalysis of a pregnant patient, which diminishes the sensitivity of this test in detecting urinary tract infection (Hendricks et al, 1991; Houshiar and Ercole, 1996; Parulkar et al, 1998). A diagnosis of urinary calculi should be considered in evaluation of a pregnant patient who suffers from persistent urinary tract infection or infection with a urea-splitting organism. Other symptoms that may indicate urolithiasis include irritative voiding symptoms, chills, nausea, and vomiting. However, these symptoms may also occur with other intra-abdominal conditions so the urologist must maintain a high index of suspicion when examining these patients.

An important factor in the radiographic evaluation of pregnant patients suffering from stone disease is the risk of ionizing radiation exposure to the fetus. The principal effects of irradiation on the fetus include teratogenesis, carcinogenesis, and mutagenesis. However, the risk associated with radiation depends critically on the gestational age and the amount of radiation delivered (Biyani and Joyce, 2002). **During the first trimester, the period of early organogenesis and rapid cell division, the embryo is sensitive to the effects of radiation** (Swartz and Reichling, 1978). Although the fetus has diminished sensitivity to the teratogenic effects of radiation in the second and third trimesters, such exposure may increase the risk for development of childhood malignant neoplasia (Harvey et al, 1985).

Because the radiation dose below which no deleterious effects on the fetus may occur has not been defined with certainty, it may be presumed that exposure to any level of radiation will carry some degree of risk. For this reason **ultrasonography has become the standard initial study in evaluation of the pregnant patient thought to be experiencing renal colic.** Unfortunately, it can be difficult to adequately visualize the ureter with ultrasound examination as well as to distinguish dilation of the ureter that may be associated with a normal pregnancy from ureteral obstruction due to calculus. Stothers and Lee (1992) reported that renal ultrasonography for the detection of calculi had a sensitivity of 34% and a specificity of 86%. Butler and associates (2000) similarly reported that ultrasonography diagnosed 60% of 35 women who were later proven to have nephrolithiasis. Several techniques have been recommended to improve the diagnostic capability of this technology. Color Doppler imaging allows the sonographer to differentiate the iliac artery and vein from the dilated ureter. MacNeily and associates (1991) reported that the use of this technique can distinguish a dilated infrailiac ureter, which was strongly correlated with ureteral obstruction. Color Doppler imaging can also demonstrate jets of urine expelled from the ureter into the bladder. Deyoe and associates (1995) reported that if there are no ureteral jets on the suspected side of obstruction, ureteral obstruction can be diagnosed with a sensitivity of 100% and a specificity of 91%. However, Burke and Washowich (1998) reported that there is variation in ureteral jet symmetry in later pregnancy and recommended the use of this technique with caution. Renal vascular resistance increases in the presence of acute obstruction, and duplex ultrasonography allows the quantification of this alteration by calculating the kidney's resistive index (Ulrich et al, 1995). Shokeir and Abdulmaaboud (1999) prospectively evaluated 117 nonpregnant patients with ultrasonography; they reported that resistive index measurements had 77% sensitivity and 83% specificity in diagnosis of ureteral calculi and that change in resistive index had 88% sensitivity and 98% specificity. Horrigan and associates (1996) reported that **renal resistive index remains unchanged from the nonpregnant state throughout the course of pregnancy and also is unaffected by the physiologic hydronephrosis of pregnancy, which suggests that this imaging modality may**

be useful in detecting acute obstruction in this population. Shokeir and associates (2000) evaluated pregnant women in a manner similar to their initial study and found that resistive index had a sensitivity of 45% and a specificity of 91% in detecting an obstructing ureteral calculus; change in resistive index had a sensitivity of 95% and a specificity of 100%. If an obstructing calculus cannot be visualized by conventional renal sonography, **transvaginal ultrasonography can provide imaging of the distal ureter.** In a series of 13 women, 6 of whom were pregnant, Laing and associates (1994) identified distal ureteral stones in all 13 patients with transvaginal ultrasonography and in only 2 by transabdominal ultrasonography.

If the clinician determines that ultrasound evaluation is inadequate, other imaging studies may be considered. **If intravenous pyelography is required, a limited study is recommended.** Stothers and Lee (1992) were able to visualize calculi in 16 of 17 pregnant patients with a three-film study, obtaining scout, 30-second, and 20-minute films. Nuclear renography is a technique that can provide a functional assessment of pregnant patients with suspected ureteral obstruction while exposing them to a limited amount of radiation. However, the radioisotope is excreted in the urine, and the bladder reservoir can provide a significant source of radiation exposure to the fetus, necessitating high fluid intake and frequent voiding for these patients (Biyani and Joyce, 2002). This radiographic technique unfortunately does not provide good anatomic detail or visualization of calculi. Magnetic resonance imaging (MRI) does not rely on ionizing radiation or contrast medium, making it a potentially attractive tool to evaluate pregnant patients. Because MRI does not visualize calcium, stones are seen as filling defects overlying the high signal intensity of urine (Fig. 48–9). The visualization of smaller stones with this technique is difficult (Hattery and King, 1995; Roy et al, 1995). Spencer and associates (2004) reported on the use of MRI to evaluate pregnant women with hydronephrosis and flank pain and found that this technique enabled the accurate distinguishing of physiologic hydronephrosis of pregnancy from hydronephrosis due to an obstructing ureteral calculus. White and associates (2007) have reported on a technique of low-dose radiation exposure CT for the evaluation of pregnant women; however, at present the reliability of low-dose CT in the diagnosis of urinary calculi is unresolved. **Conventional CT should be avoided during pregnancy because the radiation dose is particularly high.**



Figure 48–9. Magnetic resonance urogram from a pregnant woman with right renal colic, demonstrating a right ureteropelvic junction stone as a filling defect in the bright, T2-weighted urinary collecting system.

Treatment

Fifty to 80 percent of pregnant patients with symptomatic calculi will pass their stones spontaneously when treated conservatively with hydration and analgesia (Denstedt and Razvi, 1992; Stothers and Lee, 1992; Gorton and Whitfield, 1997; Parulkar et al, 1998). Intervention is required in approximately one third of patients, usually for pain uncontrolled by analgesia or signs of persistent obstruction and infection. When treatment is selected, it should be recognized that there is some controversy regarding the most appropriate method of intervention. Some have maintained that ureteral stents are the optimal treatment of such patients. Although ureteral stents do effectively drain an obstructed collecting system, they are by no means the perfect solution to this problem. The changes in urinary chemistry that occur during pregnancy, in particular the hypercalciuria and hyperuricosuria, have been implicated in the accelerated encrustation of ureteral stents that is encountered in this population. As a consequence of this phenomenon it has been recommended that ureteral stents placed in pregnant women be exchanged every 4 to 6 weeks. Ostensibly, then, for a woman in an early gestational stage, multiple stent changes will be required over the course of the pregnancy. An indwelling stent places these women at an increased risk for bacteriuria, urinary tract infection, as well as stent migration, all of which are serious morbidities that may have an adverse effect on the pregnancy. Ureteral stents themselves are associated with pain, which can have a negative impact on a patient's quality of life.

Percutaneous nephrostomy drains are an alternative treatment option for pregnant women with obstructing renal calculi. Just as with ureteral stents, nephrostomy tubes will effectively drain an obstructed collecting system. However, many of the same limitations that apply to ureteral stents also apply to nephrostomy drains. Khoo and associates reported that of 29 pregnant women managed with nephrostomy drainage, over half required tube exchanges, replacements, or flushings that were required due to either dislodgement or obstruction. Kavoussi and associates (1992) also reported that the majority of pregnant patients managed with nephrostomy drainage will require exchange of the tube due to occlusion from debris. One third of the patients in the Kavoussi and associates' series ultimately required nephrostomy removal due to recurrent drain obstruction, fever, or pain.

Both ureteral stent placement and nephrostomy drain placement are temporizing procedures that do not remove the obstructing symptomatic calculus. Therefore, both of these interventions imply that in the postpartum period the mother will require a definitive procedure to remove the calculus. It may be hypothesized that one of the advantages of both ureteral stent and nephrostomy drain placement is that neither of these procedures requires a general anesthetic. However, many of the reports of ureteroscopy in pregnancy have described local anesthesia, regional anesthesia, or sedoanalgesia, all approaches that obviate the need for general anesthesia. It is likely that recent improvements in surgical technology may be responsible for the increased

utilization of ureteroscopy in the treatment of pregnant women. In recent years there have been great advances in both semirigid and flexible ureteroscopes. As recently as a decade ago, standard ureteroscope diameter ranged up to 11 Fr, in contrast to modern endoscopes that typically have a diameter of 6 to 8 Fr. Consequently, accessing all aspects of the renal collecting system in a safe and expedient manner is now a straightforward endeavor that generally does not require ureteral dilatation or other extraordinary maneuvers. The widespread utilization of intracorporeal lithotrites such as the holmium laser permits the safe and atraumatic fragmentation of calculi at any location. Improvements in flexible grasping devices have enhanced the efficiency of stone extraction.

Overall, complications in pregnant women undergoing ureteroscopy are uncommon. Semins and associates (2009) performed a meta-analysis of all reports of ureteroscopy of pregnant women to define the rate of complications in this population. They then compared the complication rate to the AUA/EAU Ureteral Stones Guidelines and found that there was no difference in the complication rates among pregnant and nonpregnant women undergoing ureteroscopy. Other treatment modalities that are effective in the nonpregnant patient are not appropriate for this population. Although there have been reports of the inadvertent treatment of pregnant patients with SWL, with no adverse sequelae to the fetus, pregnancy remains a contraindication to this treatment modality (Chaussy and Fuchs, 1989; Frankenschmidt and Sommerkamp, 1998). PNL should be deferred until after birth because this procedure often requires prolonged anesthesia and radiation exposure.

Key Points: Urinary Calculi during Pregnancy

- Ultrasonography is the standard initial imaging study in evaluation of a pregnant patient.
- Improvements in ureteroscopy technology now permit ureteroscopic access to and treatment of stones at any location in the collecting system of the pregnant patient.
- It is important to minimize ionizing radiation exposure to the pregnant patient during ureteroscopy by use of a below-table x-ray source and to shield the fetus with a lead apron placed below the patient.

STONE REMOVAL: SURGICAL TECHNIQUES AND TECHNOLOGY

Intracorporeal Lithotripters

Ureteroscopy and PNL occupy an essential place in the treatment of urinary calculi as increasing technologic advancements allow easier access to stones in all parts of the kidney and ureter. In particular, improvements in ureteroscopic equipment emphasize the need for appropriate and effective miniaturized intracorporeal lithotripsy devices. Smaller ureteral stones can be extracted intact with endoscopic baskets or grasping devices after ureteral dilation, if necessary. However, larger ureteral stones require lithotripsy to permit the safe extraction of calculus fragments. The fragmentation of renal stones during PNL requires an approach different from that applied to ureteral intracorporeal lithotripsy. Although small and flexible endoscopic lithotrites are essential for the occasional difficult-to-approach kidney stone, renal stones can be visualized with a rigid nephroscope in most cases. In these situations, with a large kidney stone burden, the efficiency of the lithotrite is the most important requirement and size and flexibility are of secondary importance. The urologist who treats patients suffering from urolithiasis thus requires an armamentarium of intracorporeal lithotripsy devices, each maximizing a different quality (e.g., size, flexibility, efficiency).

Four techniques are available for intracorporeal lithotripsy: electrohydraulic lithotripsy (EHL), laser lithotripsy, ultrasonic lithotripsy, and ballistic lithotripsy. These techniques can be divided into those lithotrites that are flexible (laser lithotripsy and EHL) and those that are rigid (ultrasonic and ballistic lithotripsy). Here the mechanisms, advantages, disadvantages, and surgical techniques of the various flexible and rigid intracorporeal lithotripters are reviewed.

Flexible Lithotripters

Electrohydraulic Lithotripsy. EHL was invented in 1955 by Yutkin, an engineer at the University of Kiev, and was the first technique developed for intracorporeal lithotripsy (Grocela and Dretler, 1997). The first reported use of EHL outside the Eastern bloc was in 1960, when a modified version of Yutkin's invention, the Urat-1, was used to fragment bladder calculi (Rouvalis, 1970). EHL was first applied to renal calculi during an open surgical lithotomy in 1975 (Raney and Handler, 1975). In 1985, Lytton reported the first experience treating patients with ureteral stones with a rigid ureteroscope and a 5-Fr EHL probe; no immediate or long-term complications were encountered (Green and Lytton, 1985). The use of smaller EHL probes through a flexible ureteroscope was first reported in 1988 (Begun et al, 1988).

The EHL probe is essentially an underwater spark plug composed of two concentric electrodes of different voltage polarities separated by insulation. When a current sufficient to overcome the insulative gap is applied, a spark is produced. The spark discharge causes the explosive formation of a plasma channel and vaporization of the water surrounding the electrode. The rapidly expanding plasma causes a hydraulic shockwave followed by formation of a cavitation bubble (Fig. 48–10). Depending on the proximity of the probe to the stone surface, the collapse of the cavitation bubble may be symmetrical (at a distance of about 1 mm from the stone), resulting in a strong secondary shockwave, or asymmetrical (at a distance equivalent to a maximum bubble

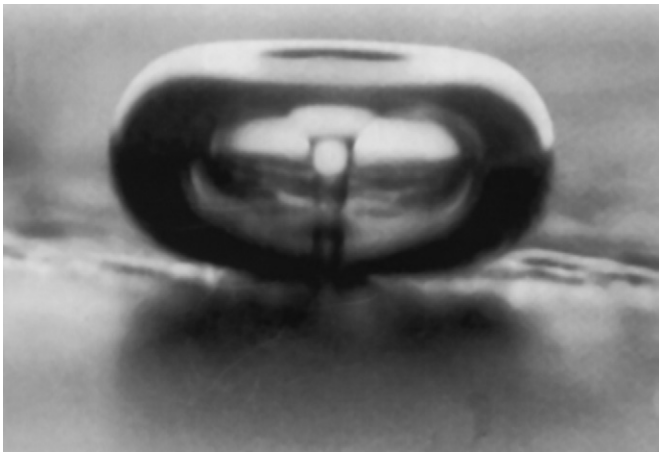


Figure 48–10. Photograph of liquid microjet produced by an asymmetrically collapsing cavitation bubble. (Courtesy of Dr. Larry Crum.)

radius of about 3 mm), leading to the formation of high-speed microjets (Vorreuther et al, 1995; Zhong et al, 1997). **Unlike in SWL the shockwave is not focused, so the stone must be placed where the shockwave is generated.** The first EHL probes developed were of larger diameters (9 Fr), which, because of their size, had a narrow margin of safety. Later improvements in technology allowed the development of smaller probes, from 1.6 to 5 Fr, that were safer and had the ability to be passed through small-diameter, flexible ureteroscopes without occluding the irrigation or working channel. There is little difference in fragmentation ability among the different-sized probes, but the larger probes tended to be more durable (Segura, 1999). Subsequent improvements in the EHL generator allowed the surgeon more control over energy discharge, pulse, and duration. Although it was originally hypothesized to function optimally in a ⅙ to ⅐ normal saline solution, Denstedt and Clayman (1990) demonstrated that EHL works equally well in a normal saline solution, eliminating the hazard of irrigating the upper urinary tract with a hypotonic solution.

Advantages and Disadvantages. **The major disadvantage of EHL is its propensity to damage the ureteral mucosa and its association with ureteral perforation.** Raney (1978) reported that with a 9-Fr probe, 90% of ureteral stones could be successfully fragmented, but there was a 40% incidence of ureteral extravasation. Ureteral perforation remained an issue of concern with EHL in the ureter despite advancements in technology and technique. Hofbauer and coworkers (1995), in a prospective study of 72 patients, reported a perforation rate of 17.6% with EHL versus 2.6% with pneumatic lithotripsy. However, others have reported a lower rate of perforation, with a mean incidence of 8.5% recorded. Vorreuther and associates (1995) suggested that the mechanism of damage is the expansion of the cavitation bubble, and thus injury may occur even when the probe is not in direct contact with the mucosa. The diameter of the cavitation bubble depends on the energy used and can expand to more than 1.5 cm when energies greater than 1300 mJ are employed. Therefore **the risk of perforation is greater with higher energies, such as in treatment of a hard stone.** Even with smaller probes and lower energy settings, perforation may occur if repeated pulses are applied close to the mucosa. Santa-Cruz and colleagues (1998), in a comparative in-vitro study, reported that the holmium laser and EHL were associated with a higher risk of perforation compared with the coumarin pulsed-dye laser and pneumatic lithotripter. When the authors placed a 3-Fr probe 0.5 mm from the ureteral wall, perforation was induced with an average of 24 pulses. **The risk of perforation may be higher for impacted stones** associated with significant mucosal edema or if vision is impaired by the minor hemorrhage that commonly occurs during EHL (Hofbauer et al, 1995).

As with most lithotrites, **retrograde propulsion of calculi and fragments can occur during EHL and is more pronounced than with holmium:YAG lithotripsy** (Teichman et al, 1997). In a series of 43 patients treated for proximal ureteral calculi, 14% required subsequent SWL for stones that migrated into the kidney (Yang and Hong, 1996). Placement of a basket or other retention device above the stone may prevent stone retropulsion. However, care should be taken not to activate the EHL device directly on the basket wires or the guidewire. Another disadvantage of EHL compared with holmium:YAG lithotripsy is the larger number and size of fragments produced, especially for stones larger than 15 mm. The repeated passage of the ureteroscope to extract the multiple stone fragments produced during EHL may exacerbate mucosal irritation (Teichman et al, 1997).

EHL will successfully fragment 90% of stones. However, treatment failures may be due to a variety of stone compositions. Stone surface characteristics may also play a role in fragmentation efficiency; rough calculi have been reported to fragment more readily than smooth calculi (Basar et al, 1997). Although EHL successfully fragments most ureteral stones, the average 3-month stone-free rate is only 84% because some of the fragments created during lithotripsy and not removed may be retained in the ureter. Stone-free rates decrease with ureteral stones larger than 15 mm and are significantly lower than those reported for holmium:YAG lithotripsy (67% vs. 100%) (Teichman et al, 1997).

The advantages of EHL include probe flexibility, especially the smaller probes such as the 1.9 Fr, which allows intracorporeal lithotripsy throughout the entire upper urinary tract through rigid or flexible ureteroscopes. Only the holmium:YAG laser, configured with the 200-µm fiber, offers comparable size and flexibility advantages (Elashry et al, 1996). The 1.6-Fr EHL probe may be even more flexible than the 200-µm laser fiber (Poon et al, 1997).

EHL is also the least costly intracorporeal device, requiring the purchase of a comparatively inexpensive generator and probes. An average of 1 to 1.3 probes are used per case, except in instances of harder stones (e.g., calcium oxalate monohydrate stones), when two or more EHL probes may be needed (Elashry et al, 1996; Huang et al, 1998).

Technique. For intraureteral lithotripsy, the smaller 1.6- and 1.9-Fr probes should be used. **The EHL fiber tip should be positioned 2 to 5 mm distal to the end of the ureteroscope** to protect the lens system from being damaged when the probe is discharged. Before the EHL generator is activated the stone must be clearly visible. **The probe is placed about 1 mm from the stone surface,** a distance allowing maximum shockwave emission (Zhong et al, 1997). Initially, low voltage (50 to 60 V) and short intermittent or single pulses are used to enhance safety. The generator output is increased as needed to fragment the stone. However, it is recommended that the treating physician limit the maximum output used in treating ureteral stones to minimize the risk of perforation. The goal of the treatment is to create fragments that can be removed with grasping forceps or a basket device or fragments that are likely to pass spontaneously. Attempts to reduce the stone to fragments smaller than 2 mm are not recommended because damage to the urothelium may occur (Denstedt and Clayman, 1990). After 50 to 60 seconds of firing, the insulation at the tip of the probe may peel away and at this time a new probe should be used (Segura, 1999).

Laser Lithotripsy. *Laser* is an acronym for *l*ight *a*mplification by *s*timulated *e*mission of *r*adiation, which is a concise description of how a laser works. Laser energy is produced when an atom is stimulated by an external energy source, which creates a population of electrons in an excited state. These excited or higher-energy electrons can release their excess energy in the form of photons or light energy. Laser light differs from natural light in that it is coherent (all photons are in phase with one another), collimated (photons travel parallel to each other), and monochromatic (all photons have the same wavelength (Floratos and de la Rosette, 1999). These unique features of laser light allow considerable energy to be transmitted in a highly concentrated manner. Lasers are named after the medium that generates their specific wavelength of light; for example, the laser was developed in 1960 and the first medium used was the ruby. In 1968, Mulvaney and Beck reported that although the ruby laser could effectively fragment urinary calculi it generated excessive heat and was not appropriate for clinical use. This continuous-wave laser simply heats the stone until vaporization occurs, which requires the laser

to generate heat greater than the melting point of the stone. A solution for this problem came with the development of pulsed lasers: the application of pulsed energy results in high-power density at the stone's surface but little heat dissipation. The first widely available laser lithotrite was the pulsed-dye laser, which employed a coumarin green dye as the liquid laser medium. Although the coumarin pulsed-dye laser represented a major advancement in intracorporeal lithotripsy there were a number of significant drawbacks to this technology: stones of certain composition (calcium oxalate monohydrate, cystine) would not fragment well or even at all, coumarin dye is a toxic agent and required cumbersome disposal procedures, and the required eye protection made visualization of the stone and fiber difficult.

Continued technologic advancements eventually led to the development of the holmium:YAG laser. The holmium laser is a solid-state laser system that operates at a wavelength of 2140 nm in the pulsed mode. Pulse duration of the holmium laser ranges from 250 to 350 μsec and is substantially longer than the pulse duration in pulsed-dye lasers. The holmium laser is highly absorbed by water; and because tissues are composed mainly of water the majority of the holmium laser energy is absorbed superficially, which results in superficial cutting or ablation. **The zone of thermal injury associated with laser ablation ranges from 0.5 to 1.0 mm** (Wollin and Denstedt, 1998). The mechanism of stone fragmentation of the holmium:YAG laser is different from that of the pulsed-dye lasers. **The long holmium:YAG pulse duration produces an elongated cavitation bubble that generates only a weak shockwave,** in contradistinction to the strong shockwave produced by short-pulse lasers. Vassar and associates (1999) demonstrated that during holmium lithotripsy, stone fragmentation began before bubble collapse and shockwave production. Furthermore, no stone fragmentation occurred when the fiber was discharged at an incident angle of 90 degrees. Lithotripsy was more efficient for dry stones in air, indicating that the holmium laser requires direct absorption of laser energy. These data as well as the presence of thermal products after holmium irradiation, such as glowing hot stone fragments, indicate that **holmium laser lithotripsy occurs primarily through a photothermal mechanism that causes stone vaporization** (Dushinski and Lingeman, 1998; Wollin and Denstedt, 1998; Vassar et al, 1999).

Advantages and Disadvantages. The holmium:YAG laser can transmit its energy through a flexible fiber, which facilitates intracorporeal lithotripsy throughout the entire collecting system. However, compared with EHL, the holmium:YAG laser is safer and more efficient. Whereas EHL may cause injury to the ureter even when the probe is activated several millimeters away from the ureteral wall, the holmium laser may be safely activated at a distance of 0.5 to 1 mm from the ureteral wall (Santa-Cruz et al, 1998). **The ability of the holmium laser to fragment all stones regardless of composition is a clear advantage** over the coumarin pulsed-dye laser. Successful fragmentation of ureteral stones of all compositions has been reported, and mean perforation and stricture rates are generally in the range of 1% to 2%. During PNL the holmium laser is most helpful in clearing smaller stones (<2 cm) when the use of flexible instruments is required for access to stones in a calyx remote from the nephrostomy site (Wollin and Denstedt, 1998). The **holmium laser is one of the safest, most effective, and most versatile intracorporeal lithotripters.** Further advantages of the holmium laser include its production of significantly smaller fragments as compared with other lithotrites. These small fragments are easily irrigated out of the collecting system, which reduces the need for extraction of the fragments with basket or grasping devices (Teichman et al, 1998b). **The holmium laser produces a weak shockwave, which reduces the likelihood of retropulsion of the stone** or stone fragments compared with EHL or pneumatic lithotrites (Teichman et al, 1998b; Vassar et al, 1999; Sofer and Denstedt, 2000). However, the 365- and 550-μm laser fibers will cause significantly more retropulsion than the 200-μm fibers (White et al, 1998). Of note, Kang and associates (2006) have demonstrated that not just the laser fiber size, but also laser settings, such as the pulse duration, will also affect stone retropulsion. The authors found that stone retropulsion could be significantly reduced by increasing the laser pulse duration.

The holmium laser has several distinct operating advantages compared with the coumarin pulsed-dye laser. The required eye protection for the holmium laser does not compromise the ureteroscopic view of the stone or the fiber (Segura, 1999). In fact, the holmium laser properties are such that with use of energy levels applied for stone disease (i.e., less than 15 watts) the operator's cornea would be damaged only if it were positioned at a distance of 10 cm or less from the fiber (Scarpa et al, 1999). The holmium laser is more compact than the coumarin laser, requires minimal maintenance, and is ready for use 1 minute after it is turned on.

The major disadvantage of the holmium laser is the initial high cost of the device and the cost of the laser fibers. Elashry and coworkers (1996) noted an advantage of EHL over holmium laser lithotripsy in capital and service contract cost and lithotripter cost per case. However, **the holmium laser has multiple soft tissue applications and can be used to treat patients with benign prostatic hyperplasia, strictures, and urothelial tumors.** In addition, the laser fibers are reusable, so that the effective cost of the holmium laser device and reusable fibers may be lower than that of EHL (Teichman et al, 1998b). The most significant improvement in holmium laser lithotripsy will likely come from improved delivery fibers. At present, the smallest fiber in widespread use, the 200-μm fiber, impedes deflection of a flexible ureteroscope by up to 20 degrees. As smaller laser fibers, such as those of 150-μm diameter and smaller, are produced, it is likely that this effect on endoscope deflection will be further reduced. The fracture of a laser fiber inside of an endoscope can result in a catastrophic failure of the scope, as when this occurs the fiberoptic bundles that transmit images and light are generally destroyed. Future efforts toward maximizing fiber durability may reduce these events.

A potential side effect of holmium laser lithotripsy is the production of cyanide when uric acid stones are treated, which has been reported in vitro. However, a **review of clinical experience suggests no significant cyanide toxicity from holmium laser lithotripsy** (Teichman et al, 1998a).

Technique. The technique of holmium laser lithotripsy is relatively straightforward and involves placement of the fiber on the stone surface before the laser is activated (Table 48–8). Clear vision is essential at all times to avoid mucosal perforation. After initiation of holmium laser lithotripsy, a short pause is often required because of the "snowstorm effect" created by the scattering of minute stone fragments, which can be cleared by endoscopic irrigation (Scarpa et al, 1999). Caution must be exercised in operating the holmium laser near a guidewire or a basket because **the holmium laser is capable of cutting through metal** (Freiha et al, 1997; Lane et al, 2005). Furthermore, the laser fiber should extend at least 2 mm beyond the tip of the endoscope to avoid destroying the lens system or the working channel of the endoscope. Baskets used to stabilize calculi during laser lithotripsy

Table 48–8.

Holmium Laser Lithotripsy: Points of Technique

Do

Keep the fiber tip in view at all times.
Start at low settings and increase only as necessary.
Work from the inside of the stone outward.
Keep the fiber tip at least 2 mm from the urothelium.

Don't

Have one person controlling the fiber and another the foot pedal.
Discharge the laser fiber inside the working channel or on guidewires and baskets.
Pass the fiber tip through the back wall of stones.
Get impatient—holmium:YAG laser lithotripsy is not necessarily fast.

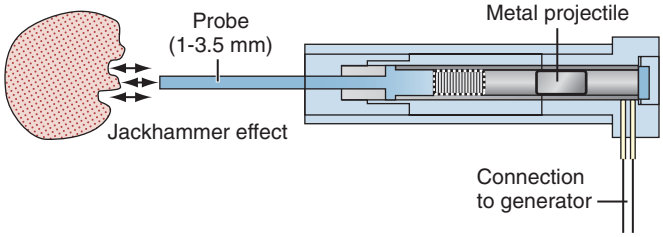


Figure 48–11. Schematic illustration of the LithoClast (Electromedical Systems, Kaufering, Germany) handpiece mechanism. An oscillating pellet provides ballistic energy to the probe, resulting in a jackhammer-like effect on calculi. (Courtesy of Dr. John Denstedt.)

should be the preformed type and not the type manufactured by bending of the wire, so if they are inadvertently transected by the holmium laser they will retain the basket shape and will not cause a sharp barbed effect (Grasso and Chalik, 1998).

Holmium laser fibers are available in 200-, 365-, 550-, and 1000-µm diameters as well as end- or side-firing fibers. However, only the 200- and 365-µm fibers are used for flexible intracorporeal lithotripsy. Teichman and colleagues (1998c) reported that the 550-µm side-firing fiber is more effective than the end-firing fiber during PNL, suggesting that the more nearly normal (perpendicular) laser-to-calculus incident angle provided by the side-firing fiber enhances lithotripsy. However, in treatment of ureteral stones, the end-firing fiber may produce a better angle of attack. **Lithotripsy with the holmium laser depends on the pulse energy output and the diameter of the optical delivery fiber, suggesting that lithotripsy efficiency correlates with energy density** (Vassar et al, 1998). Energy density increases with decreasing fiber diameter, although Calvano and associates (1999) demonstrated, in vitro, that peak lithotripsy occurred with 365- and 550-µm fibers, whereas the 200-µm fiber can act as a fine drill, which is less effective. Compared with some of the soft tissue applications of the holmium laser, the power used for stone fragmentation is considerably lower. In general, pulse energies of 0.6 to 1.2 J and pulse rates of 5 to 15 Hz are used (Wollin and Denstedt, 1998; Spore et al, 1999). Because high-pulse energy narrows the safety margin and may increase stone retropulsion as well as fiber damage, **it is recommended that treatment be begun with low-pulse energy (e.g., 0.6 J) with a pulse rate of 6 Hz and that pulse frequency be increased (in preference to increasing pulse energy) as needed to speed fragmentation** (Spore et al, 1999). To maximize lithotripsy efficiency, the treating physician should move the laser fiber over the stone surface in a "painting" fashion, vaporizing the stone rather than fragmenting it, and avoid drilling into the stone, fracturing the fiber tip, or drilling past the stone, damaging the urothelium. The laser fiber should be kept at least 1 mm from the urothelium, and lithotripsy should proceed until the stone fragments are small enough to be passed spontaneously or can be safely retrieved with a basket or grasping device.

Rigid Lithotripters

Ballistic Lithotripsy. Ballistic lithotripsy relies on energy generated by the movement of a projectile (Fig. 48–11). The initial movement of the projectile can be induced by a variety of stimuli, but once the projectile is in contact with another object the ballistic energy is transferred to the object. Flexible objects preserve the momentum of the energy, but inflexible objects, such as a stone, fragment on impact (a "jackhammer" effect).

Several manufactures have introduced ballistic lithotrites. The Swiss LithoClast, introduced in the early 1990s, was the first ballistic lithotrite. The metal projectile in the handpiece of the LithoClast is propelled by measured bursts of compressed air against the head of a metal probe at a frequency of 12 cycles per second. The probe tip is placed against the stone, and the LithoClast is activated by a foot pedal (Denstedt et al, 1992). Following the introduction of the LithoClast, the electrokinetic lithotripter was introduced in the mid 1990s (Menezes et al, 2000). The electrokinetic lithotripter consists of a rheostat and a handset containing an electric coil that generates an electromagnetic field, which then vibrates the probe at 15 to 30 cycles/sec. Whereas the LithoClast is connected to the hospital central air supply or to a compressed air tank, the electrokinetic lithotripter requires electrical power. In both instruments the discharged probe is brought back into its former position by a rubber bushing around the base of the probe (Vorreuther et al, 1998). Studies comparing the LithoClast and the electrokinetic lithotripter, using the same stone fragmentation mechanism, showed no significant difference in stone fragmentation, proximal stone migration, and safety margin. However, the handpiece of the electrokinetic lithotripter is significantly heavier than that of the LithoClast (Vorreuther et al, 1998; Menezes et al, 2000). Rane and associates (2008) first reported on a novel, handheld ballistic lithotripter, the StoneBreaker. This portable device utilizes a small cylinder-based air supply, rather than hospital air, simplifying its ergonomic profile.

Advantages and Disadvantages. **The ballistic lithotrites provide an effective means for stone fragmentation in the entire urinary tract, with a wide margin of safety.** Successful fragmentation of ureteral stones of all compositions has been reported in 73% to 100% of cases, a success rate similar to that of EHL. The lower success rate of 73.7% reported by Knispel and associates (1998) suggests reduced efficiency of the LithoClast when it is applied through the deflected working channel (30 degrees) of the 6.9-Fr semirigid ureteroscope. As well, a significant decrease in the maximum tip displacement and velocity of the LithoClast 0.89-mm flexible probe occurs when it is used through a flexible ureteroscope deflected more than 24 degrees (Zhu et al, 2000). Grocela and Dretler (1997) also reported that for the current ballistic devices, bowing of the probe during lithotripsy results in significant power loss. Ballistic devices may be especially advantageous when large or hard stones are encountered during PNL or endoscopic lithotripsy of bladder calculi. In contrast to ureteral stones, kidney stones are easily "pinned down" against the urothelium during ballistic lithotripsy, allowing a rapid and more

efficient fragmentation method than ultrasonic lithotripsy. Once the bulk of the calculus is fragmented, lithotripsy can be completed with the ultrasonic lithotripter, which can also aspirate minute stone fragments (Denstedt, 1993; Teh et al, 1998; Yavascaoglu et al, 1999). Compared with EHL, ultrasonic lithotripsy, and laser lithotripsy, ballistic devices have a significantly lower risk of ureteral perforation (Piergiovanni et al, 1994). In an animal model, despite 6 minutes of activation in direct contact with the ureteral wall, a ballistic lithotripter was unable to cause perforation (Santa-Cruz et al, 1998). Furthermore, because no heat is produced during lithotripsy, the risk of thermal injury to the urothelium is eliminated.

One of the advantages of ballistic lithotrites is their relatively low cost and low maintenance. Although the devices are more expensive than EHL, in terms of capital equipment purchasing, there are no disposable costs and the probes have an extremely long life span (Hofbauer et al, 1995).

Disadvantages of ballistic devices include the rigid nature of the technology, which requires ureteroscopes or nephroscopes with straight working channels. In addition, **ballistic lithotripsy is associated with a relatively high rate of stone retropulsion,** reported in 2% to 17% of ureteral stone treatments. Often, failure to fragment a stone is related to an inability to trap a ureteral stone in a capacious ureter (Denstedt et al, 1992). The migration rate depends on the initial stone location; there is a higher chance of stone migration for proximal ureteral stones compared with distal ureteral stones (Knispel et al, 1998). Limited data are available on the beneficial effects of suction devices, such as the LithoVac, in limiting stone migration. Delvecchio and colleagues (2003) reported the use of the 0.8-mm pneumatic lithotripsy probe placed through a 4.8-Fr hollow LithoVac suction probe in 21 patients with ureteral stones. Overall stone-free rate at 3 months was 95%, and the suction device reportedly facilitated lithotripsy by preventing stone migration and maintaining a clear endoscopic view.

Teichman and associates (1998b) reported that fragments larger than 4 mm are produced by all types of endoscopic lithotrites, with the exception of the holmium:YAG laser. Fragmenting a stone into pieces smaller than 4 mm with a ballistic lithotripter can be challenging, especially a hard stone in a dilated ureter. Fragments larger than 4 mm are associated with a higher rate of repeated ureteroscopy and therefore should be removed with baskets or stone graspers during the initial procedure (Keeley et al, 1999b).

Technique. Like other lithotrites, the ballistic lithotripter should be activated only when there is a clear view of the stone and the probe position can be identified. Fixation of the stone is rarely difficult in the kidney or the bladder but may be a problem in the ureter. Fixation of ureteral stones with a basket or proximal placement of a ureteral occlusion balloon is sometimes necessary. The goal of ballistic lithotripsy in the ureter is to generate fragments that are small enough to permit spontaneous passage (<2 mm). However, more often, larger fragments have to be removed with a basket or grasping device. The relatively atraumatic nature of ballistic lithotripsy may allow the avoidance of stent placement after ureteroscopy. Tan and colleagues (1998) reported the use of a stent in only 9 of 68 patients undergoing ballistic lithotripsy. In this series, difficult ureteral access and severe edema and trauma at the site of stone impaction were indications for stent placement.

Ultrasonic Lithotripsy. Mulvaney first reported the use of ultrasound vibrations to break renal calculi in 1953. Since then, ultrasonic lithotripsy has become a commonly used modality for the treatment of renal calculi during PNL as well as for the fragmentation of bladder and ureteral stones. The ultrasound probe works by applying electrical energy to excite a piezoceramic plate in the ultrasound transducer (Fig. 48–12). The plate resonates at a specific frequency and generates ultrasonic waves at a frequency of 23,000 to 25,000 Hz. At operating frequencies there is no audible sound, although 98 dB of ultrasonic inaudible noise levels have been measured (Segura and LeRoy, 1984).

Ultrasound energy is transformed into longitudinal and transverse vibrations of the hollow steel probe, which then transmits the energy to the calculus. The probe tip causes the stone to resonate at high frequency and to break; but when the probe is placed on compliant tissue, such as urothelium, damage is minimal because the tissue does not resonate with the vibrational energy (Grocela and Dretler, 1997). Although some heat may develop at the end of the probe during lithotripsy, with an irrigation rate of 30 mL/min the temperature increase at the tip of the probe can be reduced to a maximum of 1.4° C (Marberger, 1983). Because irrigation may be limited during ureteroscopy, **ultrasonic lithotripsy is more efficient during PNL, owing to the greater flow of irrigant through the larger diameter ultrasonic probes that can be used.** The ultrasonic lithotripter system is connected to suction so that debris from the stone is removed continuously with the irrigating fluid during lithotripsy. In addition, the flow of fluid through the hollow probe serves to cool the instrument. Heating of the ultrasound transducer should alert the surgeon to possible occlusion in the probe lumen, an occurrence more commonly encountered with small-diameter probes that are used in the ureter. Although many manufacturers provide an integrated power and suction foot switch for the ultrasonic unit, wall suction with intermittent clamping of the suction tubing by an assistant is a simple and inexpensive alternative. In general, suction is applied only when the ultrasonic lithotripter is

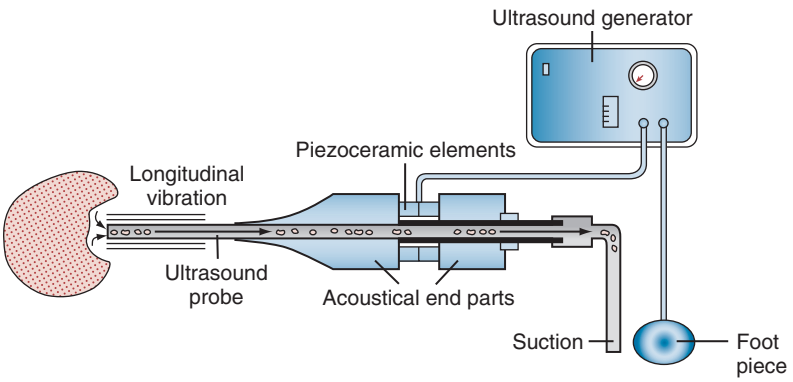


Figure 48–12. Ultrasound lithotripsy generator and handpiece.

activated, and suction pressures in the range of 60 to 80 cm H_2O are sufficient to maintain adequate flow of irrigant during lithotripsy. Higher suction pressures tend to draw air bubbles into the system, impeding vision. Ultrasonic probes are available at sizes ranging from 2.5 to 12 Fr. The 2.5-Fr probe is solid and contains no hollow center for suction. Therefore, when it is used in the ureter, heat dissipation is slow. Bending the probe results in energy loss at the convexity of the bend, with the energy being transformed to heat (Marberger, 1983).

Stones vary in their susceptibility to destruction with ultrasound. Although the chemical composition of the stone influences the time required for complete disintegration (cystine, calcium oxalate monohydrate, and uric acid being the most resistant to fragmentation), the size, density, and surface structure of the calculus appear to be more important. Smaller stones are more rapidly destroyed, as are rough stones. Smooth-surfaced large stones may be more difficult to fragment (Marberger, 1983; Segura and LeRoy, 1984).

Auge and associates (2002a) have reported on a new combination intracorporeal lithotripter that incorporates ballistic lithotripsy and ultrasonic lithotripsy modalities (LithoClast Ultra). In their in-vitro study of this device it was found to more efficiently fragment and clear phantom stones compared with a standard ultrasonic or ballistic device. These findings were confirmed in a subsequent in-vitro study by Kuo and associates (2004).

Advantages and Disadvantages. The major advantage of ultrasonic lithotripsy is the efficient combination of stone fragmentation and simultaneous fragment removal. Fragments smaller than 2 mm are aspirated through the hollow lithotrite along with the irrigation fluid. Larger fragments may be removed with forceps or baskets. The efficiency of this technique coupled with the minimal risk of serious tissue damage has made this technology popular. Ultrasonic lithotripsy is often the first modality used for stone fragmentation during PNL.

However, the rigid nature of ultrasonic probes and their small diameter limit the appeal of this technology in treatment of ureteral stones. A ureteroscope with a straight working channel is required. Furthermore, a relatively large 5-Fr working channel is needed to accommodate the 4.5-Fr hollow probe. However, success rates between 69% and 100% have been reported (Denstedt, 1996; Gur et al, 2004). The technology may be particularly useful for patients with large ureteral stones as well as for those suffering from steinstrasse because removal of stone debris is facilitated. Excellent results have also been reported for distal ureteral stones easily accessible to the rigid ureteroscope (Grocela and Dretler, 1997; Segura, 1999). Chaussy and colleagues (1987) reported a 96.6% complete fragmentation rate in 118 patients with a 2.5-Fr solid probe that can be used with smaller ureteroscopes, and Fuchs (1988) has reported similar results. However, in a later report, Murthy and associates (1997) compared a group of 25 patients treated by a rigid ureteroscope and the 3-Fr ultrasonic solid probe with a group of 122 patients treated by the LithoClast ballistic device, and the overall success rate was significantly higher for the LithoClast group than for the ultrasonic group (97.3% vs. 84%, respectively).

Technique. When ultrasonic lithotripsy is applied during PNL the stone should first be trapped between the probe and the urothelium. The application of gentle pressure to the stone enhances fragmentation, but the temptation to push too hard should be avoided because calculi can easily be pushed through the urothelium. The risk of perforation increases with smaller or more ruggedly surfaced stones as the force applied to the stone is transferred to a smaller surface area of the urothelium. The risk of perforation is particularly high in the thin-walled renal pelvis or ureter rather than in a calyx that is backed by renal parenchyma.

When ureteral stones are treated the ureter may need to be dilated to allow passage of the offset rigid ureteroscope. The ultrasonic probe is passed through the working channel and placed directly on the stone. If necessary, the stone can be engaged in a stone basket to prevent proximal migration. As with other intracorporeal lithotripsy devices the goal of treatment is either to fragment the stone completely or to generate fragments that are small enough to be extracted or passed spontaneously.

Combination Ballistic and Ultrasonic Devices

Several manufacturers have introduced combined ultrasonic and pneumatic devices that aim to combine the superior fragmentation ability of the pneumatic component with the ability of the ultrasonic modality to simultaneously evacuate stone fragments. The first combination device brought to the clinical market was the Lithoclast Ultra (Boston Scientific, Natick, MA), which relied on a combination handpiece (actually, two separate handpieces connected together) to join the ultrasonic and pneumatic components. The first portion of the combination handpiece was a traditionally designed pneumatic handle, with a smaller-diameter solid probe. The ultrasonic handle, driven by a standard piezoelectric mechanism, was modified to allow the coaxial insertion of the pneumatic probe. Each modality can be activated separately or in unison; when operated in unison, the ballistic fragmentation of the stone is accomplished with the pneumatic component and the ultrasonic component then removes the resulting debris.

Given the varied types of rigid intracorporeal devices (standalone ballistic and ultrasonic as well as combination ballistic and ultrasonic), a rigorous and impartial evaluation of intracorporeal lithotripters is a subject of importance to urologists. Each device may have certain unique properties that make it more suitable for particular applications, and manufacturer's claims may contain elements of bias that make it difficult for the urologist to ascertain which device may be most suitable to purchase. Therefore, a number of investigators have devised testing methods to compare intracorporeal lithotrites. Liatsikos and associates (2001) first reported an in-vitro testing system designed to measure the efficiency of ultrasonic lithotrites in which stone phantoms were fragmented in a nephroscope-guided manner. The inherent weakness in this study design was that stone fragmentation was directed by hand, which could introduce significant operator bias. Haupt and Haupt (2003) subsequently reported an in-vitro system that relied on an elaborate weight and fulcrum to bring a stone phantom into contact with the probe tip at a constant force. Although operator bias was no longer present, this system was complex and cumbersome, making replication challenging. Kuo and associates (2003b) have presented a novel and simple hands-free testing system in which the ultrasonic handpieces were secured upright and the stone phantom placed into contact with the probe by a weight mechanism (Fig. 48–13). This design system was first utilized to test the efficiency of pure ultrasonic lithotrites and measured the time it took for the probe to penetrate the stone phantom. In this study the Olympus LUS-2 (Olympus, Melville, NY) produced the fastest overall stone penetration time.

Following the introduction of the combination ultrasonic and pneumatic devices, the same testing apparatus previously used by Kuo and associates (2004) to evaluate the ultrasonic devices was used to evaluate the LithoClast Ultra. Because of the wide variety of ultrasonic power and pneumatic frequency settings available the testing apparatus was used to assess the efficiency of various setting combinations. The end point was stone penetration time,

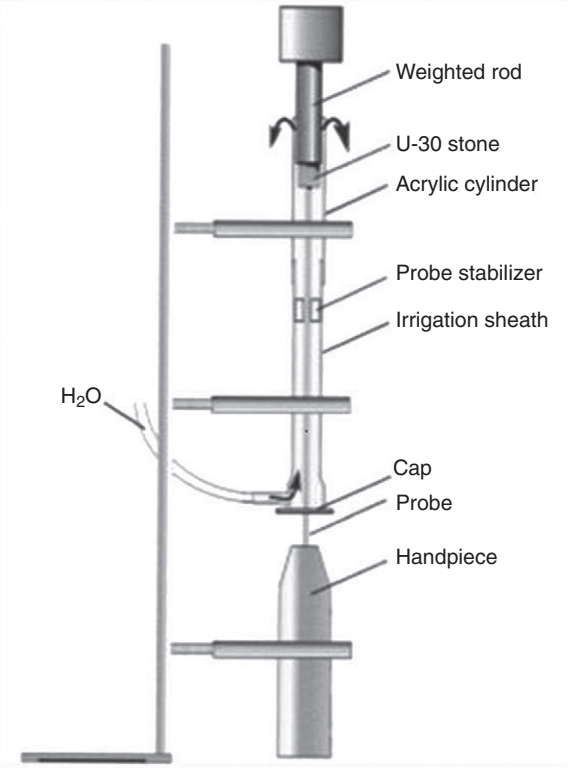


Figure 48–13. In-vitro testing apparatus for a "hands free" testing approach to the evaluation of intracorporeal lithotrites.

and the fastest stone penetration times were achieved at settings of 100% ultrasonic power and 12-Hz pneumatic frequency. Pietrow and associates (2003b) have evaluated the efficiency of the Lithoclast Ultra combination device in a clinical setting, performing a prospective, randomized trial comparing the combination device with standard ultrasonic lithotrites in patients undergoing PNL. The stone clearance times were significantly better for the combination device than for the conventional ultrasonic lithotripters.

The Cyberwand (Gyrus ACMI, Southborough, MA) is an intracorporeal lithotripter that relies on a dual ultrasonic probe design that incorporates coaxial high-frequency and low-frequency probes. The dual probe design creates a synergistic effect, which enables efficient stone fragmentation while still allowing the suction evacuation of small fragments just as other ultrasonic devices do. Kim and associates (2007) used the aforementioned hands-free testing design previously described by Kuo and associates to find that the stone penetration time for the Cyberwand was almost twice as rapid as it was for the Lithoclast Ultra.

Conclusion

The current technology of intracorporeal lithotripsy provides the urologist with several effective options for stone fragmentation, depending on the type of endoscope used (rigid or flexible) and the location and accessibility of the stone. **The holmium laser has become the mainstay of ureterorenoscopic lithotripsy by virtue of its ability to fragment all stones. As well, the use of small-diameter fibers allows access to all areas of the ureter and intrarenal collecting system. However, for patients with complex, large-volume calculi undergoing PNL, the combination devices will permit more efficient fragmentation of the stone.** When selecting a lithotripter for purchase, the institution must take into account the number and nature of stone-related procedures performed to maximize the utility and cost-effectiveness of the device.

Extracorporeal Shockwave Lithotripsy

Methods and Physical Principles

In extracorporeal SWL a source external to the patient's body generates a shockwave. Specifically, the energy source rapidly deposits pulses of energy into a fluid environment, which results in the generation of a shockwave. **Shockwaves are surfaces that divide material ahead, not yet affected by the disturbance, from that behind, which has been compressed as a consequence of energy input at the source** (Sturtevant, 1996). These waves move faster than the speed of sound, and the stronger the initial shock, the faster the shockwave moves. Their behavior is characteristic of the propagation of nonlinear waves. Although the shockwaves in lithotripters generate large pressures, they are relatively weak in that they induce only slight compression and deformation of a material. **The uniqueness of the shockwave lithotripter is in its exploitation of shockwave focusing. Relatively weak, nonintrusive waves are generated externally and transmitted through the body. The shockwaves build to sufficient strength only at the target, where they generate enough force to fragment a stone.**

Generator Type. **There are three primary types of shockwave generators: electrohydraulic (spark gap), electromagnetic, and piezoelectric.**

Electrohydraulic (Spark Gap) Generator. **In the electrohydraulic shockwave lithotripter, a spherically expanding shockwave is generated by an underwater spark discharge** (Cleveland et al, 2000). High voltage is applied to two opposing electrodes positioned about 1 mm apart. The high-voltage spark discharge causes the explosive vaporization of water at the electrode tip. **For the spherically expanding shockwave to be focused onto a calculus the electrode is placed at one focus (termed F1) of an ellipsoid, and the target (the kidney stone) is placed at the other focus (termed F2).** Figure 48–14 (on the Expert Consult website) shows a hemiellipsoid reflector and a spark gap typical of those used in the older electrohydraulic machines. This arrangement allows the projection of the majority of the original shockwave energy from the electrode tip to the stone, provided the electrode tip is precisely at F1. The body of the electrode varies in orientation among machines in that it is positioned within the ellipsoid to provide an easy means of replacement as it deteriorates.

The clear advantage of this generator is its effectiveness in breaking kidney stones (Lingeman, 1997). **Disadvantages are the substantial pressure fluctuations from shock to shock and a relatively short electrode life.** New longer life electrodes (like the NewTrode by HMT) have been developed to overcome these drawbacks. Another issue to consider is that as the electrode deteriorates, it wears down, and a 1-mm displacement of the electrode tip off of F1 can shift F2 up to 1 cm off of the initial target.

Electromagnetic Generator. Whereas the electrohydraulic lithotripter produces focused shockwaves by bouncing spherically expanding shocks off of an ellipsoid reflector, **the electromagnetic generators produce either plane or cylindrical shockwaves.** The plane waves are focused by an acoustic lens (Fig. 48–15); the cylindrical waves are reflected by a parabolic reflector (Fig. 48–16) and transformed into a spherical wave. The

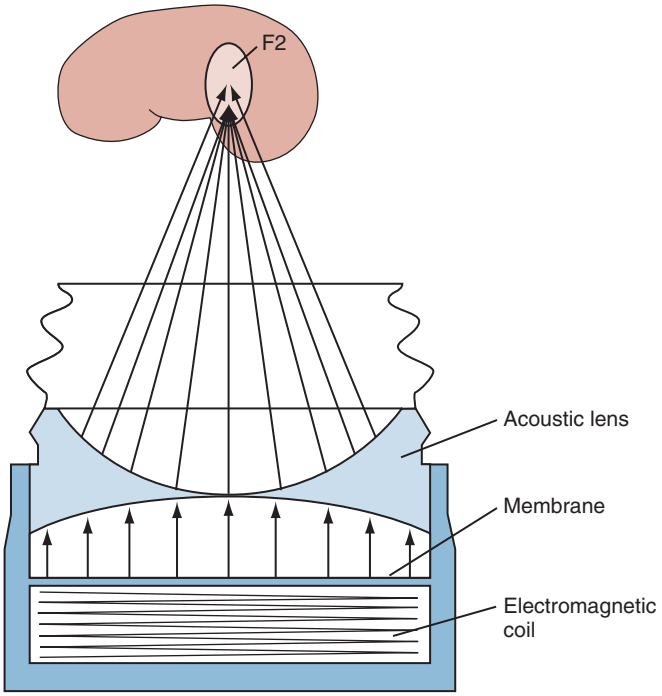


Figure 48–15. Schematic view of an electromagnetic shockwave generator that uses an acoustic lens to focus the shockwave. An electromagnetic coil is used to generate the shockwave.

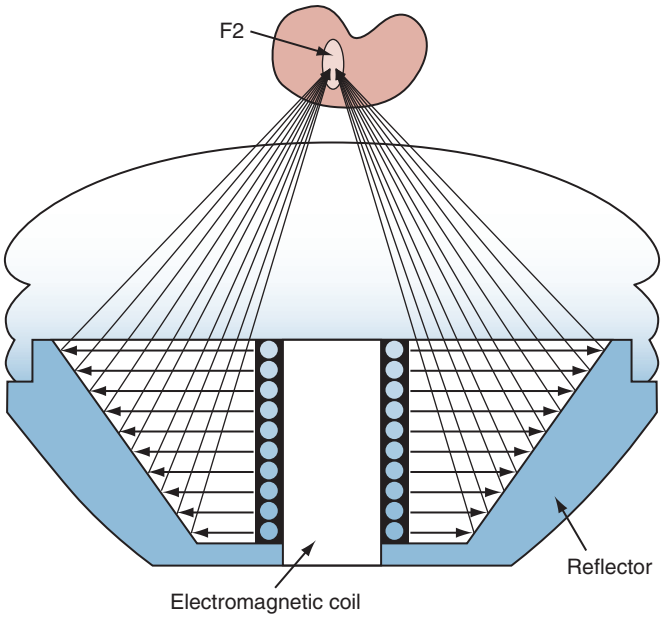


Figure 48–16. Schematic view of an electromagnetic shockwave generator that uses a parabolic reflector to focus the shockwave. An electromagnetic coil is used to generate the shockwave.

basic design of an electromagnetic generator is simple. Figure 48–15 shows a system that uses a water-filled shock tube containing two conducting cylindrical plates separated by a thin insulating sheet. When an electrical current is sent through one or both of the conductors, a strong magnetic field is produced between the conductors, moving the plate against the water and thereby generating a pressure wave. The electromagnetic force that is generated, termed *magnetic pressure,* causes a corresponding pressure (shockwave) in the water. The shock front produced is a plane wave that is of the same diameter as the current-carrying plates. **The energy in the shockwave is concentrated onto the target by focusing it with an acoustic lens.** The electromagnetic system that uses a cylindrical source (see Fig. 48–16) also has a cylindrical coil surrounded by a cylindrical membrane that is pushed away from the coil by the induction of a magnetic field between the two components. In both systems the pressure pulse has only one focal point (F2) that is positioned on the target.

Electromagnetic generators are more controllable and reproducible than electrohydraulic generators because they do not incorporate a variable in their design such as the underwater spark discharge. Other advantages include the introduction of energy into the patient's body over a large skin area, which may cause less pain. In addition, a small focal point can be achieved with high-energy densities, which may increase its effectiveness in breaking stones. This generator will deliver several hundred thousand shockwaves before servicing, thereby eliminating the need for frequent electrode replacement, which is required with most electrohydraulic machines. A disadvantage of this design may be that the small focal region of high energy results in an increased rate of subcapsular hematoma formation. The rate of subcapsular hematoma formation for the Storz Modulith has been suggested to be 3.1% to 3.7% (Dhar et al, 2004). Piper and associates (2001) suggested that perinephric hematomas may occur in up to 12% of patients treated with a DoLi S lithotripter. In contrast, perinephric hematomas were reported to occur in approximately 0.6% of patients undergoing SWL with the unmodified Dornier HM3 machine (Chaussy and Schmiedt, 1984; Knapp et al, 1987).

Piezoelectric Generator. **The piezoelectric lithotripter also produces plane shockwaves with directly converging shockfronts.** These generators are made of a mosaic of small, polarized, polycrystalline, ceramic elements (barium titanate), each of which can be induced to rapidly expand by the application of a high-voltage pulse (Fig. 48–17). Owing to the limited power of a single piezoelectric element, 300 to 3000 crystals are necessary for the generation of a sufficiently large shock pressure. The piezoelectric elements are usually placed on the inside of a spherical dish to permit convergence of the shockfront. The focus of the system is at the geometric center of the spherical dish.

The advantages of this generator include the focusing accuracy, a long service life, and the possibility of an anesthetic-free treatment because of the relatively low-energy density at the skin entry point of the shockwave. For this reason, piezoelectric lithotripters in general tend to produce less discomfort than do lithotripters with other energy sources. **A major disadvantage of this system is the insufficient power it delivers, which hampers its ability to effectively break renal stones.** The piezoelectric energy sources produce some of the highest peak pressures of any lithotripter, but the actual energy delivered to the stone per shockwave pulse is several orders of magnitude lower than that delivered by an electrohydraulic machine because of the extremely tiny volume of F2.

Other Generators. Microexplosive generators have also been produced but have not gained widespread acceptance. The explosion of tiny lead azide pellets within a parabolic reflector generates the device's shockwave (Kuwahara et al, 1987). Despite the effectiveness of this type of generator in producing shockwaves, this technology has not met with commercial success because of concerns about the storage and handling of the volatile lead azide pellets. Still other methods of shockwave generation use a laser

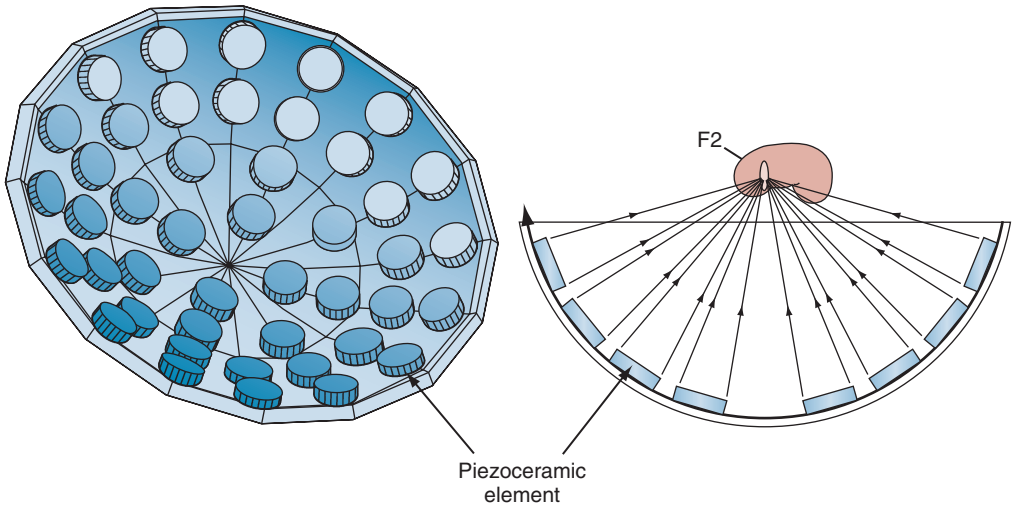


Figure 48–17. Schematic view of a piezoelectric shockwave generator. Numerous polarized polycrystalline ceramic elements are positioned on the inside of a spherical dish.

beam or a multistage light gas gun, but these too have not been well received commercially.

Imaging Systems. There are three basic designs used by lithotripter manufacturers for stone localization. They are fluoroscopy alone, ultrasonography alone, and the combination of ultrasonography and fluoroscopy.

Fluoroscopy Alone. The original Dornier HM3 lithotripter used two x-ray converters arranged at oblique angles to the patient and 90 degrees from each other to localize the stone effectively at F2. To reduce the cost of lithotripters, an adjustable C-arm has been subsequently introduced on many devices. There is presently a remarkable similarity in the fluoroscopic systems used among manufacturers. This appears to be primarily the result of a common theme in the industry to develop multifunctional tables around these machines. The fluoroscopic system typically consists of a high-quality digitized x-ray imaging system mounted on a rotatable C-arm with an isocentrically integrated shockwave source. Because the shockwave head can be rotated out of the field of the fluoroscopic system, the table can be used for routine urologic fluoroscopic applications.

The primary advantages of fluoroscopy still include its familiarity to most urologists, the ability to visualize radiopaque calculi throughout the urinary tract, the ability to use iodinated contrast agents to aid in stone localization, and the ability to display anatomic detail. The disadvantages include the exposure of the staff and patient to ionizing radiation, the high maintenance demands of the equipment, and the inability to visualize radiolucent calculi without the use of radiographic contrast agents.

Ultrasonography Alone. Ultrasonic localization was initially designed to aid multifunctional lithotripters for treatment of both urinary and biliary stones. It is presently used in several low-cost machines because it is inexpensive to manufacture and to maintain compared with fluoroscopic systems. Another major advantage of this technology is in the treatment of children and infants when one is concerned about the dose of ionizing radiation. In addition, ultrasonography can localize slightly opaque or nonopaque calculi.

Despite its advantages there are a number of significant disadvantages of ultrasound imaging. Sonographic localization of a kidney stone requires a highly trained operator. To complicate the issue of stone detection is the fact that it is almost impossible to view a kidney stone in areas such as the middle third of the ureter or when there is an indwelling ureteral catheter. Once a stone is fragmented, it is difficult to identify each individual stone piece. Unfortunately, these disadvantages tend to overshadow the advantages of ultrasound imaging.

Combination of Ultrasonography and Fluoroscopy. As the demand for interdisciplinary lithotripters has increased, the lithotripsy industry has responded, in some cases combining ultrasonography and fluoroscopy for stone localization. There are clearly advantages to these setups, but each system has a drawback that limits one of the functions of the system.

Anesthesia. The approach to anesthesia for lithotripsy has changed considerably since clinical SWL began in 1980. At that time, regional or general anesthesia was used in all instances because the unmodified HM3 device (15.6-cm ellipsoid; 80-nF generator) produced a powerful shockwave and treatment at recommended energy levels caused intolerable pain. Subsequently, urologists and lithotripter manufacturers recognized that the HM3 is considerably more powerful at the recommended energy setting than is necessary for the fragmentation of most renal calculi, an observation that spawned interest in less powerful lithotripters with lessened anesthesia requirements (Marberger et al, 1988; Wilbert et al, 1987). Several researchers have noted that the original HM3 lithotripter without modification produces excellent clinical results when it is used at lower energy settings (Pettersson et al, 1989; Tiselius, 1991; Tolley et al, 1991). In addition, such settings create a smaller lesion at F2 in experimental animals (Connors et al, 2000).

The discomfort experienced during SWL is related directly to the energy density of the shockwave as it passes through the skin as well as the size of the focal point. In the past decade several new and useful anesthetic techniques adaptable to SWL have been produced that were not available at the time SWL was introduced and include short-acting parenteral sedative-narcotics and topical agents.

Short-acting agents, such as the narcotic alfentanil and the sedative-hypnotics midazolam and propofol, have been used in various combinations to allow most SWL treatments with any lithotripter (including the unmodified Dornier HM3) to be accomplished comfortably for the patient without the need for general

or regional anesthesia, if the patient so desires. Monk and associates (1991) compared two sedative-analgesic techniques (midazolam-alfentanil vs. fentanyl-propofol) and found that both techniques provided adequate anesthesia for SWL with use of an unmodified Dornier HM3 lithotripter. Anesthesia and recovery times were significantly shorter than those recorded for epidural anesthesia techniques. These findings have been confirmed by others (Nelson et al, 2001; Burmeister et al, 2002; Ozcan et al, 2002).

Another approach to minimize anesthesia requirements during SWL has been the use of topical agents. EMLA cream, a eutectic mixture of lidocaine and prilocaine, has been shown significantly to reduce anesthesia requirements during SWL (Basar et al, 2003). A topical agent, EMLA cream should be applied at least 45 minutes before SWL. The combination of topical agents and short-acting intravenous agents is likely to minimize the amount of these agents required and to shorten recovery times.

Not all patients are well served by treatment with a low-energy SWL technique, and therefore a variety of factors need to be considered in choosing the preferred approach for SWL. Calculi composed of cystine, calcium oxalate monohydrate, or brushite are known to be resistant to fragmentation; if their presence is anticipated, delivery of higher levels of shockwave energy with attendant increased anesthesia requirements should be expected (Dretler, 1988; Klee et al, 1991). Thin patients have more pain during SWL because the converging shockwave is more concentrated at the point of skin penetration. Children and extremely anxious individuals may be served best by general anesthesia. If a lengthy treatment session is anticipated (i.e., bilateral SWL or treatment of ureteral and renal stones), the larger amount of topical and intravenous agents required lessens their appeal.

One important observation regarding the issue of general anesthesia versus intravenous sedation was reported by Sorensen and colleagues (2002) and Eichel and colleagues (2001). In a comparison of patients treated with the DoLi 50 lithotripter, those patients who received general anesthesia experienced a significantly greater stone-free rate than did those patients who underwent intravenous sedation. One possible explanation for this finding is the more controlled respiratory excursion that is conferred by the general anesthetic.

Lithotripter Comparisons

Shockwave lithotripters are considered by the U.S. Food and Drug Administration to be Class II devices. As such, for a lithotripter to be brought to market simply requires documentation that the device has the same intended use and the same technologic characteristics as a predicate device that has already been approved and brought to market. Specific testing that evaluates, in a proscribed manner, the lithotripter's treatment efficacy and safety is not required. Largely as a consequence of this practice, few, if any, appropriately designed comparative trials of lithotripters exist in the published literature. In addition, **there are no validated standards within the lithotripsy industry regarding a method of quantification of the power and efficiency of lithotripters, a problem further compounded by a lack of knowledge of the number of shockwaves that can be safely administered to a kidney during any single SWL session with any lithotripter.** Although there is general consensus that re-treatment rates are an appropriate indicator of lithotripter effectiveness, the lack of clinical agreement about the appropriate outcome of lithotripsy (i.e., stone free vs. residual fragments of various size) further hampers comparisons of lithotripters.

Only a small part of the literature published to date on the outcomes of SWL presents data that are stratified sufficiently to permit a meaningful comparative analysis. Surprisingly, despite the proliferation of lithotripters and the variety of solutions devised for stone targeting and shockwave delivery, no other lithotripter system has convincingly equaled or surpassed the results produced by the unmodified Dornier HM3 device. That the most effective lithotripter was invented first is a remarkable achievement for Dornier. In general, the less powerful lithotripters with smaller focal points result in lower stone-free rates or higher re-treatment rates. Additionally, **it is now recognized that SWL inflicts a trauma similar to a renal contusion, which occasionally can result in adverse clinical sequelae.** Potential concerns about the long-term effects of lithotripsy with the unmodified Dornier HM3 device may have been one motivating factor in the trend within the lithotripsy industry toward, at first, lower power but eventually higher power lithotripters with smaller focal points, with the goal that the efficacy of lithotripsy could be maintained while producing fewer deleterious effects on renal tissue (Figs. 48–18 [on the Expert Consult website] and 48–19). Unfortunately, **the newer lithotripters are less efficacious than the original Dornier device, and no published information is available to suggest that newer lithotripters produce fewer adverse effects for equivalent degrees of efficacy.**

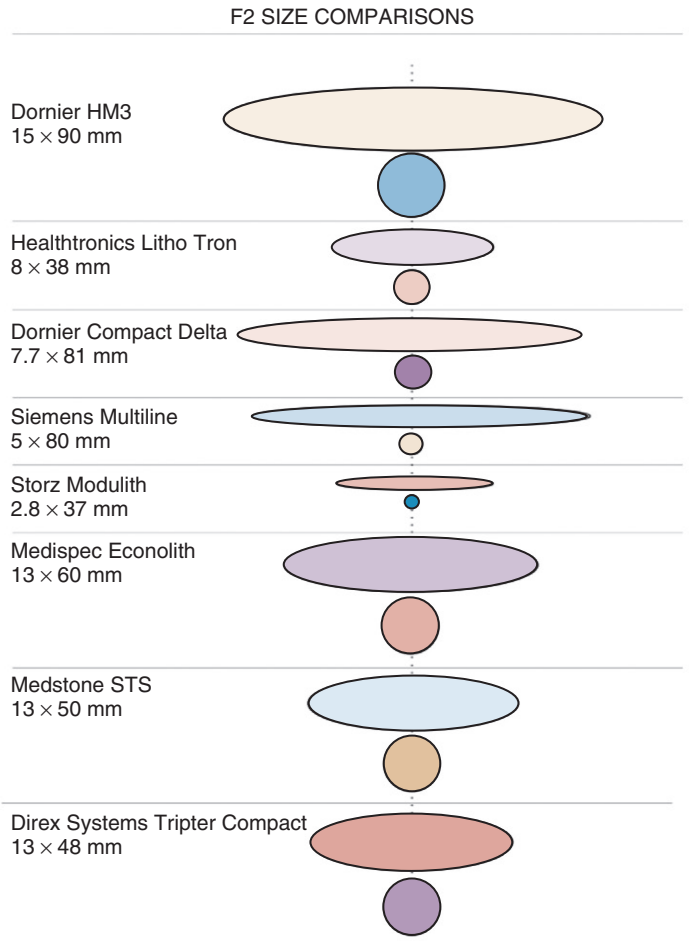


Figure 48–19. Comparison of the focal zones of selected clinical lithotripters showing their dimensions along the axis of the lithotripter *(ellipses)* and in the focal plane at the focus *(circles)*.

Mechanisms of Stone Comminution

Present knowledge in the field of SWL suggests that comminution of a renal stone in a lithotripter field is the consequence of failure of the stone material due to the mechanical stresses produced either directly by the incident shockwave or indirectly by the collapse of cavitation bubbles. These events could be occurring simultaneously or separately at the surface of the stone or within the interior of the stone (Fig. 48–20). Several potential mechanisms for SWL stone breakage have been described: spall fracture, squeezing, shear stress, superfocusing, acoustic cavitation, and dynamic fatigue.

Before each of these mechanisms is discussed, consideration of the typical shockwave profile is required. A typical pressure pulse generated by an electrohydraulic shockwave lithotripter is shown in Figure 48–21. It involves **an initial short and steep compressive front with pressures of about 40 MPa that is followed by a longer, lower-amplitude negative (tensile) pressure of 10 MPa, with the entire pulse lasting for a duration of 4 μsec.** Note that the ratio of the positive to negative peak pressures is approximately 5:1. Pressure measurements near the focal region of a Dornier unmodified HM3 indicate a 6-dB beam, of a width of approximately 15 mm. Because kidney stones are also generally of this dimension, the wavefront incident on the stone can be considered a plane wave (Muller, 1990; Cleveland et al, 2000).

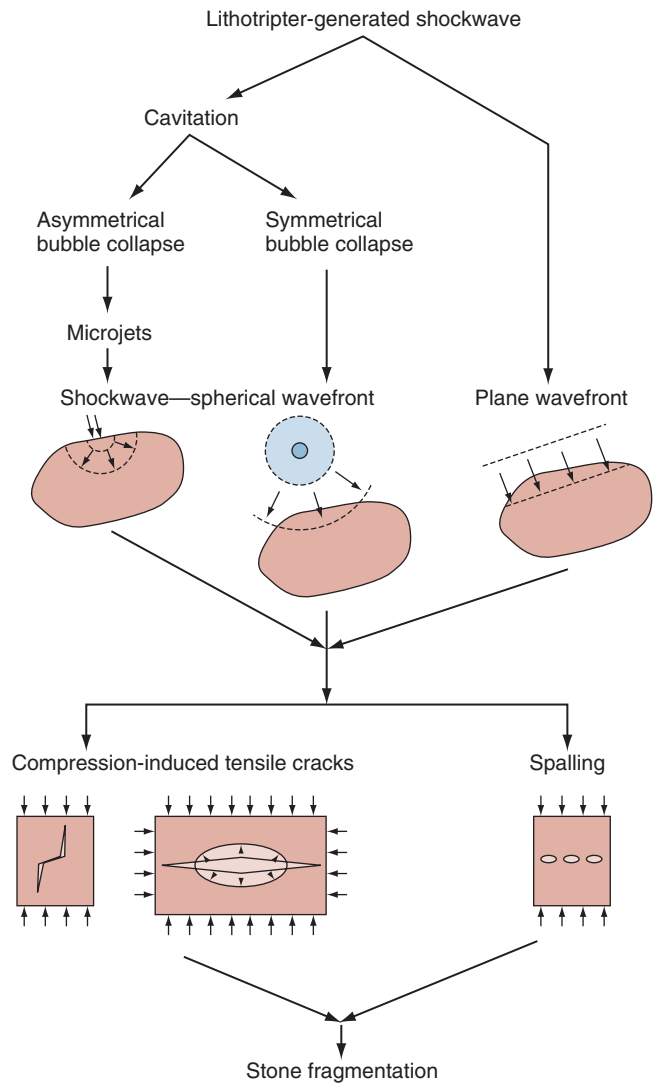


Figure 48–20. Summary of how the various mechanical forces generated by a lithotripsy shockwave might cause a kidney stone to fracture. (Reproduced with permission of Dr. Bradley Sturtevant.)

The first mechanism by which a stone might break is through spall fracture. Once the shockwave enters the stone it will be reflected at sites of impedance mismatch. One such location is at the distal surface of the stone at the stone-fluid (urine) interface (although there could be other internal sites, such as cavities in the stone and interfaces of crystalline and matrix materials). As the shockwave is reflected, it is inverted in phase to a tensile (negative) wave. If the tensile wave exceeds the tensile strength of the stone, there is an induction of nucleation and growth of microcracks that eventually coalesce, resulting in stone fragmentation, which is termed *spallation.* The failure plane is located perpendicular to the applied tensile stress. This mechanism is thought to be of considerable importance in that kidney stones, like most brittle materials, will be much more likely to fail under tension rather than compression (Johrde and Cocks, 1985). Lokhandwalla and Sturtevant (2000) have suggested that the trailing negative pressure of the lithotripter pulse also exerts tensile stresses of an order of magnitude similar to that of the spall mechanism. Contributing factors to the effectiveness of spallation in generating stone breakage appear to be the size and the shape of the stone as well as its physical properties (i.e., fracture toughness, acoustic speed, density, and void dimensions). More spherically shaped stones may focus the tensile wave after reflection and thus further increase the tensile stress. Stones with larger diameters may allow sufficient tensile stress to be generated so that the tensile strength of the stone can more easily be exceeded. If these factors are important, then smaller, irregularly shaped stones may not fracture by spallation.

Eisenmenger (1998) first suggested that **the second mechanism for stone breakage, termed *squeezing-splitting* or**

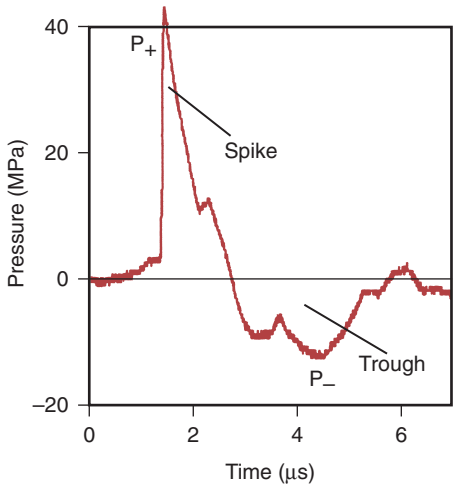


Figure 48–21. A typical pressure pulse at the lithotripter focus (F2) as measured by a polyvinylidene difluoride membrane hydrophone. First, there is a steep positive pressure front of about 40 MPa, which is followed by a negative pressure of 10 MPa, with the entire pulse lasting for a duration of 4 μsec. (From Coleman AJ, Saunders JE, Preston RC, et al. Pressure waveforms generated by a Dornier extracorporeal shockwave lithotriptor. Ultrasound Med Biol 1987;13:651–7.)

***circumferential compression,* occurs because of the difference in sound speed between the stone and the surrounding fluid.** The shockwave inside the stone advances faster through the stone than the shockwave propagating in the fluid outside the stone. The shockwave that propagates in the fluid outside the stone thus produces a circumferential force on the stone, resulting in a tensile stress in the stone that is at its maximum at the proximal and distal ends of the stone. The resulting squeezing force could split the stone either in a plane parallel to the shockwave propagation direction or, depending on the elastic properties of the stone, possibly in a plane parallel to the shockwave front. It has been theorized that squeezing should be enhanced when the entire stone falls within the diameter of the focal zone. Thus, current third-generation lithotripters that have very small focal zones will not make use of this mechanism, as the stone size is typically greater than the focal zone, whereas the original Dornier HM3 machine would.

The third mechanism is shear stress. Shear stress will be generated by shear waves (also termed *transverse waves*) that develop as the shockwave passes into the stone. The shear waves propagate through the stone and will result in regions of high shear stress inside the stone. In contrast to compression waves, which move the molecules in the direction of propagation, a shear wave results in translation of molecules transverse to the direction of propagation, and therefore the molecules are not compressed but are shifted sideways by the wave. Many materials are weak in shear, particularly if they consist of layers, because the bonding strength of the matrix between layers often has a low ultimate shear stress. Calcium oxalate stones commonly possess alternating layers of mineral and matrix, and the shear stress induced by the transverse wave could cause such stones to fail. Theoretical work by Sapozhnikov and colleagues (2003) suggests that the shear wave mechanism will lead to a tensile strain in cylindrical stones that is 5 to 10 times larger than that induced by spall. They also suggest that cracks will be initiated in the center of the stone and grow in a direction perpendicular to the axis of the stone.

The fourth mechanism for stone breakage, superfocusing, is the amplification of stresses inside the stone due to the geometry of that stone. The shockwave that is reflected at the distal surface of the stone can be focused either by refraction or by diffraction from the corners of the stone. Several groups have demonstrated that these reflected waves can be focused to regions of high stress in the interior of the stone and that this can lead to failure (Gracewski et al, 1993; Xi and Zhong, 2001). The regions of high stress (both tensile and shear) are dependent on the geometry of the stone as well as its elastic properties.

The fifth potential mechanism for SWL stone breakage is cavitation (Coleman et al, 1987; Crum, 1988; Vakil and Everbach, 1993; Zhong and Chuong, 1993; Zhong et al, 1993). *Cavitation* is defined as the formation and subsequent dynamic behavior of bubbles. The lithotripter-generated pressure field has been found to induce cavitation in both in vitro and in vivo studies. The negative pressure in the trailing part of the pulse causes bubbles to grow at nucleation sites. A nucleation site is an inhomogeneity in the fluid, which leads to preferential formation of free gas under stress. During the negative pressure wave, the pressure inside the bubble falls below the vapor pressure of the fluid, and the bubble fills with vapor and grows rapidly in size (almost three orders of magnitude). As these bubbles grow, they oscillate in size for about 200 μsec and then collapse violently, giving rise to high pressures and temperatures. In the absence of any boundaries, a cavitation bubble remains spherical during collapse, releasing energy primarily by sound radiation, the majority of which is in the form of a shockwave (see Fig. 48–21). This shockwave generates a positive and negative wave and therefore can induce all of the fragmentation mechanisms described in the preceding. However, in the presence of a boundary, a liquid jet, also termed a *cavitation microjet,* forms inside the bubble during the collapse (Crum, 1979, 1988). This jet can accelerate to extremely large speeds because it converts most of its kinetic energy from the collapse of the cavity interface to the jet itself. The typical bubble radii found in SWL vary from 1 μm to 1 mm, and bubble jet velocities range from 22 m/sec to 800 m/sec. In actual jet-impact cases the duration of the pressure pulse is only a few microseconds, and in most instances, the peak pressure lasts for only about 1 μsec. If the liquid jet is near the surface of a stone, it creates a locally compressive stress field in the stone, which propagates spherically into the stone interior.

Numerous investigators have exposed either aluminum foil or brass plates to the focused shockwave generated by a Dornier HM3 machine and observed significant microjet damage (pitting) on the surfaces of these metals. If this event occurs at the surface of a kidney stone, erosion of this surface would be expected; Averkiou and Crum (1996) reported this event for SWL-treated plaster of Paris target stones. To determine if cavitation is the primary mechanism of stone fragmentation, investigators have developed in-vitro systems that would eliminate or dampen cavitational events. Such systems have included a viscous medium that possesses a much lower number of nucleation sites and a chamber that allows one to increase the ambient pressure that surrounds the growing cavitation bubbles (Vakil et al, 1991; Delius, 1997; Stonehill et al, 1998). These in-vitro systems have shown reduced stone damage along with a reduction in cavitation activity. Work by Bailey and associates (1998, 1999), in which the positive and negative waves were inverted with a pressure release reflector, also showed a reduction in stone comminution. All of these studies suggest that cavitation plays a significant role in damaging brittle objects.

The final mechanism of stone fragmentation to be considered defines stone breakage in terms of a dynamic fracture process, in which the damage induced by SWL accumulates during the course of the treatment, leading to the eventual destruction of the stone. Essential to this process is nucleation, growth, and coalescence of flaws within the stone caused by a tensile or shear stress (Fig. 48–22). Because renal calculi are not homogeneous but rather have either a lamellar crystalline structure bonded by an organic matrix material or an agglomeration of crystalline and noncrystalline material there are numerous sites of preexisting flaws (microcracks). All of the fracture mechanisms described have the potential to generate progressive damage to the interior of the stone. By use of the cohesive-zone model, a mathematical approach of predicting the qualitative features of transient microcrack damage accumulation, Lokhandwalla and Sturtevant (2000) were able to calculate the number of shockwaves required for a spall-like failure to occur in a typical calcium oxalate monohydrate calculus. The values they determined had a range of two orders of magnitude (30 to 3000 shocks), which is well within the clinical dose presently used to treat patients. These investigators further suggested that mechanisms other than spall are also likely to inflict damage to stones, and spall may be a factor only in a small portion of the stone.

Bioeffects: Clinical Studies

Acute Extrarenal Damage. SWL induces acute injury in a variety of extrarenal tissues (Evan et al, 1991, 1998). SWL has been associated with trauma to organs such as the liver and

skeletal muscle, as evidenced by elevated levels of bilirubin, lactate dehydrogenase, serum aspartate transaminase, and creatine phosphokinase within 24 hours of treatment (Lingeman et al, 1986a; Ruiz Marcellan and Ibarz Servio, 1986; Parr et al, 1988). These parameters begin to fall within 3 to 7 days of SWL treatment and are normal at 3 months. Other findings of damage outside the kidney have included reports of visceral injuries, such as perforation of the colon, hepatic hematoma, splenic rupture, pancreatitis, and abdominal wall abscess. Extrarenal vascular complications have been reported to occur as well, such as rupture of the hepatic artery, rupture of the abdominal aorta, and iliac vein thrombosis. Thoracic events, such as pneumothorax and urinothorax, have even been described. Fortunately, these events are all exceedingly rare, and have generally been presented as isolated incidents.

In addition, early clinical studies noted that shockwaves could induce cardiac arrhythmia, an observation that led to electrocardiographic synchronization with R-wave triggering on the Dornier HM3 device (Chaussy and Schmiedt, 1984). However, later clinical studies with non–water bath lithotripters have concluded that treating ungated to cardiac rhythm is safe.

Although the lithotripter is characterized by the spatial distribution of its acoustic output (the focal zone, or F2), it is known that high acoustic pressure does extend beyond this zone (Fig. 48–23). Therefore, it is reasonable to expect that organs other than the kidney are exposed to stresses sufficient to cause injury. One such organ is the pancreas; a retrospective follow-up study from the Mayo Clinic suggested that patients who underwent SWL for the treatment of kidney stones in 1985 were at increased risk for developing diabetes mellitus compared with controls (Krambeck et al, 2005). The development of diabetes was related to the total number of shockwaves and the power level of the lithotripter. Although these data are provocative, there were a number of limitations of the study, including that the stone disease of the SWL cohort was more severe than the control cohort, a family history of diabetes was not ascertained for either group, and the data for the SWL group were collected by self-report questionnaire whereas the control group was examined by chart review. Several other groups have subsequently investigated this subject, however; and these findings have not been confirmed by any other study (Sato et al, 2008; Makhlouf et al, 2009). At present, then, there have yet to be any corroborative analyses confirming a relationship between diabetes and SWL.

Acute Renal Injury: Structural and Functional Changes. Virtually all patients who undergo SWL for renal stones demonstrate hematuria after approximately 200 shockwaves. Hematuria is so common that it may be considered an incidental finding, and its severity is rarely of concern. Although hematuria was initially considered to be a consequence of irritation of the urothelium as stones were fragmented by shockwaves, it is now known that such is not the case. Detailed morphologic studies have demonstrated that shockwaves rupture blood vessels and can damage surrounding renal tubules (Fig. 48–24). SWL is now known to induce such structural changes in the treated kidney in the majority, if not all, SWL patients, regardless of the type of lithotripter employed (Table 48–9).

In porcine subjects, the preferred animal model for studying acute renal injury, SWL traumatizes vessels ranging in size from the glomerular and cortical capillaries and vasa recta, to the larger arcuate and intralobular vessels. The resulting hemorrhagic lesion generally extends from cortex to medulla and comprises torn blood vessels with platelet aggregation and red blood cells in the interstitial space (Figs. 48–25 and 48–26 on the Expert Consult website). Affected renal corpuscles typically show breaks in the Bowman capsule, blood in the urinary space, and damage to the

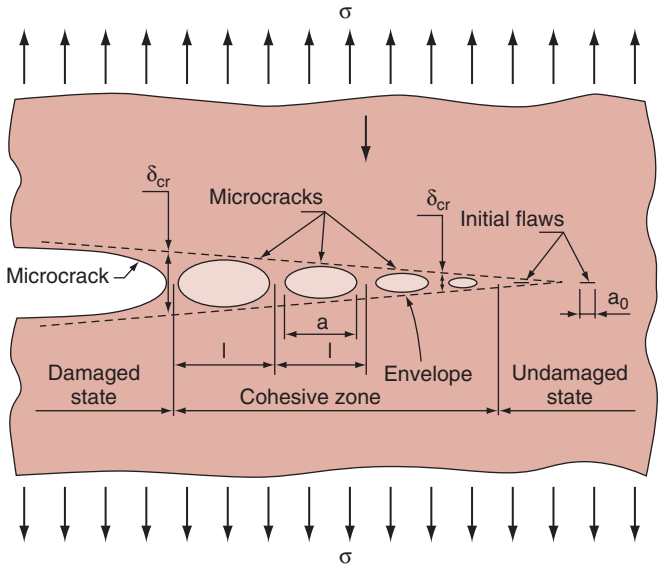


Figure 48–22. Coalescence of microcracks with a main crack. The undamaged stone has some initial flaws or microcracks of known length. These flaws occur in renal calculi either at a lamellar crystalline structure bonded by an organic matrix material or at an agglomerate of crystalline and noncrystalline material. When stressed, these microcracks grow until they coalesce with the main crack; and because this event is repeated throughout the stone, it eventually fragments. (Reproduced with permission of Dr. Bradley Sturtevant.)

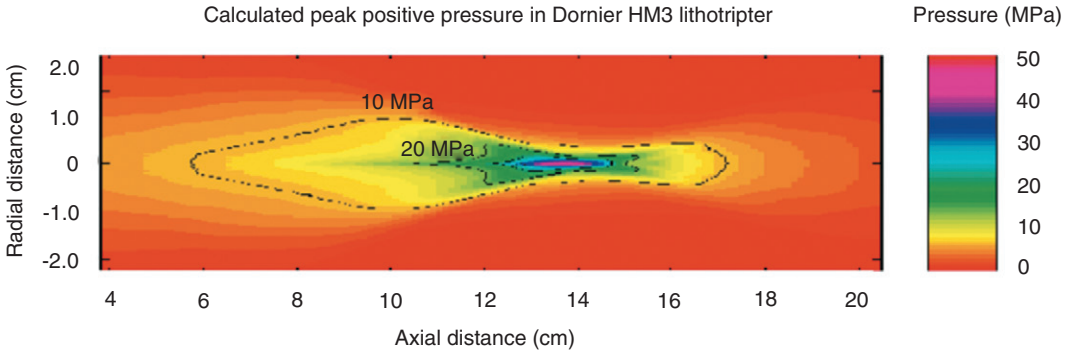


Figure 48–23. Predicted peak positive pressure in a Dornier HM3 lithotripter. The pressure is not focused to a point but extends over a finite volume.

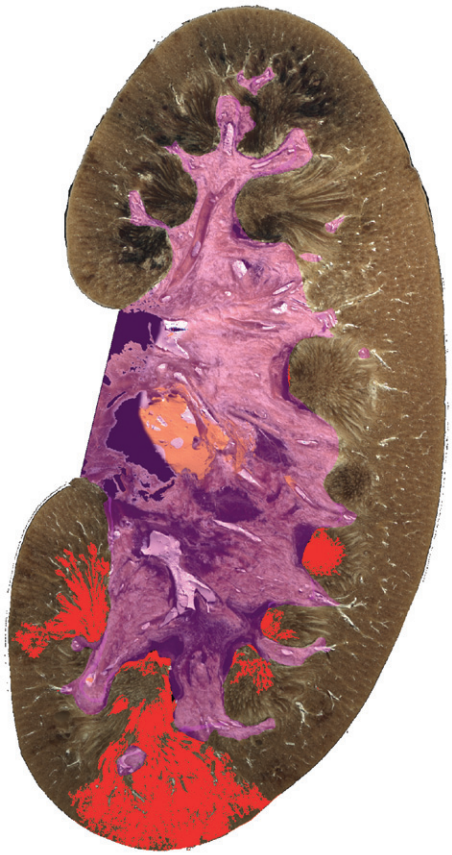


Figure 48–24. Macroscopic photomicrograph of a coronal section through the kidney of a juvenile pig (about 6 weeks old) treated with 2000 shocks at 24 kV by an unmodified Dornier HM3 lithotripter and examined 4 hours after treatment. The region of intraparenchymal hemorrhage has been colored red by an automated computer color recognition program. Note that the lesion involves multiple papillae and in some regions extends through the cortex to the renal capsule, where a subcapsular hematoma may develop.

Table 48–9.

Renal Side Effects of Shockwave Lithotripsy in Experimental Animal Models (Canine and Porcine)

Acute Histologic Changes
Venous thrombi
Cellular disruption and necrosis
Mild tubular necrosis (ischemic changes)
Intraparenchymal hemorrhage
Tubular dilation and cast formation
Damage and rupture of veins and small arteries
Rupture of glomerular and peritubular capillaries
Chronic Histologic Changes
Nephron loss
Dilated veins
Streaky fibrosis
Diffuse interstitial fibrosis
Calcium and hemosiderin deposits
Hyalinized and acellular scars from cortex to medulla

podocytes and mesangial cells (Fig. 48–27 on the Expert Consult website). Renal tubules often contain blood cell casts, and the tubular cells may show ischemic changes. In the setting of a more severe injury, complete necrosis of the endothelium and vascular smooth muscle may result. A typical clinical dose of 2000 shockwaves with the Dornier HM3 lithotripter, operated at 24 kV with shockwaves delivered at 2 Hz produces a lesion measuring 5% to 6% of the functional renal volume (Fig. 48–28).

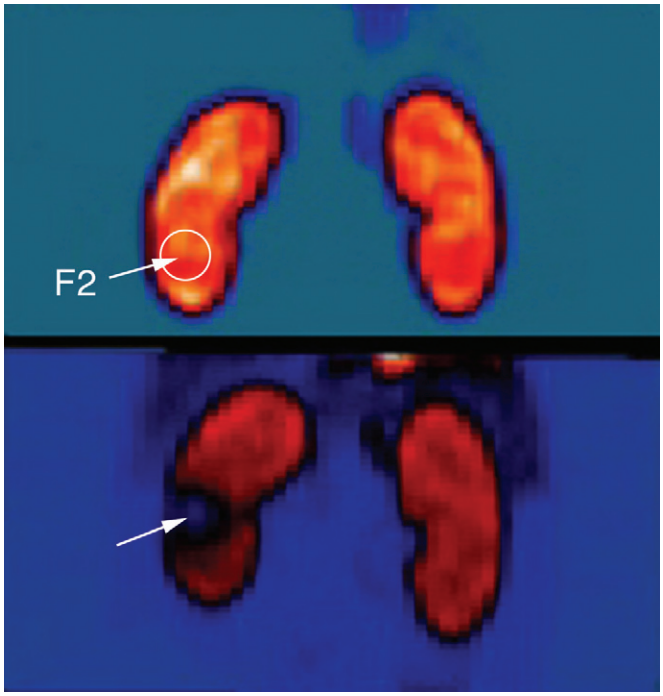


Figure 48–28. Shockwave lithotripsy–treated and control kidneys imaged by positron emission tomographic scanning before and immediately after treatment with 3500 shockwaves to the lower pole, at level six, with a DoLi 50 device. The site of F2 (lower pole) on the shocked kidney shows a 50% reduction of renal blood flow *(arrow)*.

Table 48–10.

Acute Renal Side Effects: Risk Factors for Shockwave Lithotripsy

Age
Obesity
Coagulopathies
Thrombocytopenia
Diabetes mellitus
Coronary heart disease
Preexisting hypertension

There have been reports of moderate to severe renal injury occurring after SWL, generally manifesting as a hemorrhagic event. Hematoma rates range from less than 1% up to as high as 20%, depending on the type of lithotripter used and the treatment parameters employed, as well as the radiographic modality and timing of imaging follow-up. In addition, the later generation lithotripters that have small focal areas and extremely high peak positive pressures are reported to produce higher clinically significant hematoma rates (3% to 12%), a trend that is worrisome (Thuroff et al, 1988; Ueda et al, 1993; Kohrmann et al, 1995; Piper et al, 2001). Several risk factors for the development of a post-SWL hematoma have been identified (Table 48–10). Dhar and associates (2004) reported that the probability of a subcapsular hematoma increased 2.2 times for every 10-year increase in the patient's age. Knapp and associates (1988) found patients with existing hypertension to be at increased risk for the development of perinephric hematomas as a consequence of SWL. In particular, those patients

having unsatisfactory control of their hypertension at the time of SWL had the highest incidence of hematoma formation. Additional risk factors for hemorrhage were diabetes mellitus, coronary artery disease, and obesity, all of which suggest a link to a vascular disorder. The appearance of renal hematomas can range in severity from a mild contusion localized within the renal parenchyma to a large hematoma (Fig. 48–29) associated with severe bleeding, possibly necessitating blood transfusion or rarely even angiographic embolization. Although some hematomas may persist for many months to years, it has been reported that most resolve within weeks and without long-term sequelae.

Chronic Renal Injury: Structural and Functional Changes. At present there is a paucity of information on the chronic injury induced by SWL, due in great part to the lack of experimental animal studies. Nonetheless, it is well accepted that shockwaves damage blood vessels, and the resulting hemorrhage initiates an inflammatory response that ultimately leads to scar formation.

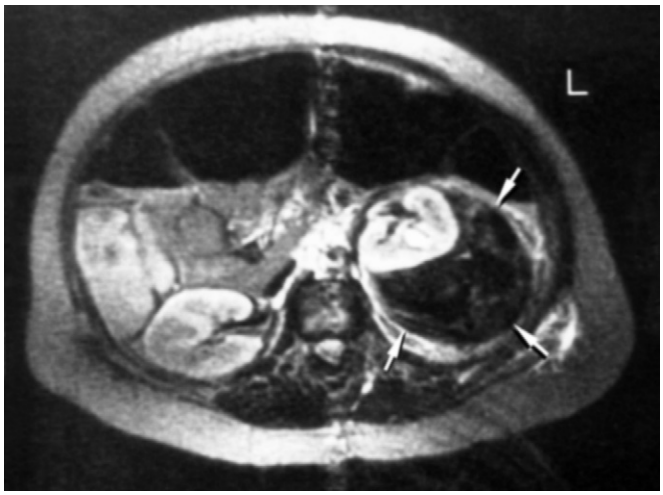


Figure 48–29. MR image taken 24 hours after shockwave lithotripsy with 1200 shocks at 22 kV (by an unmodified Dornier HM3 lithotripter) shows a large subcapsular hematoma *(arrows)* in the treated (left) kidney.

Parenchymal fibrosis, a precursor to renal scarring, is seen as early as 1 month after SWL, and scar formation has also been reported to be a dose-dependent phenomenon. Clinically there are **four potential chronic renal changes that may be associated with SWL treatment. They are an accelerated rise in systemic blood pressure, a decrease in renal function, an increase in the rate of stone recurrence, and the induction of brushite stone disease. All four effects appear to be linked to the observation that the acute renal injury at F2 progresses to scar formation.**

The possibility that SWL might be associated with significant changes in systemic blood pressure was first suggested by Peterson and Finlayson (1986) and has been investigated by others (Table 48–11). Lingeman and coworkers (1987b) reported that 8.2% of 243 patients who were normotensive at the time of SWL developed blood pressure changes requiring antihypertensive medication. Mean follow-up in this group of patients was 1.5 years, giving an annualized incidence of hypertension of 5.5%. Similar data have been reported by Williams and Thomas (1989). After these reports suggesting that hypertension could be a long-term complication of SWL, a large study involving almost 1000 patients was undertaken at the Methodist Hospital of Indiana (Lingeman et al, 1990). This study found a small but statistically significant change in diastolic blood pressure associated with SWL therapy. The observed effect of SWL on diastolic pressure change persisted even after controlling statistically for other variables that might be associated with variation in blood pressure, such as age, sex, pretreatment baseline blood pressure, and number of treatment sessions. Janetschek and colleagues (1997) performed a prospective study that demonstrated age was a significant risk factor for post-SWL hypertension, with an increase in intrarenal resistive index observed in patients 60 years of age and older. The mechanism of hypertension after SWL is not well elucidated. Although subcapsular hematomas can induce hypertension, such changes are generally transient. There has been a report, however, of mesangial proliferation in porcine models after SWL that could induce hypertensive changes.

The possibility that SWL treatment might be associated with a long-term reduction in renal function has been suggested by several investigators. Williams and associates (1988) found a

Table 48–11.

Blood Pressure Changes in Shockwave Lithotripsy–Treated Patients

STUDY	LENGTH OF STUDY (MO)	NO. OF SHOCKS		CHANGE IN INCIDENCE OF HYPERTENSION	CHANGE IN DIASTOLIC BLOOD PRESSURE
		Range	Mean		
Liedle et al, 1988	40	Not recorded	1043	No change	Not recorded
Williams et al, 1988	21	800-2000	1400	Increased	Increased
Puppo et al, 1988	12	1100-1900	1380	No change	No change
Montgomery et al, 1989	29	110-3300	1429	Increased	No change
Lingeman et al, 1990		Not recorded	1289	No change	Increased
Yokoyama et al, 1992	19	1500-3000	Not recorded	Not recorded	Increased
Janetschek et al, 1997	26	2600-3000	2735	Increased (60-80 year age group)	Increased (60-80 year age group)
Jewett et al, 1998	24	Not recorded	4411	No change	No change
Strohmaier et al, 2000	24			Increased	Increased
Elves et al, 2000	26.4	Not recorded	5,281	No change*	No change*
Eterovic et al, 2005	3	1800-3200	Not recorded	No change	No change
Krambeck et al, 2006a	228	500-4500	1125	Increased	Not recorded
Eassa et al, 2008	43.6	Not recorded	Not recorded	Increased	No change
Sato et al, 2008	204	400-2300	928	No change	Not recorded

significant decrease in the percentage of effective renal plasma flow 17 to 21 months after SWL for patients with two kidneys. Orestano and colleagues (1989) noted that patients receiving more than 2500 shocks had a reduction in creatinine clearance and a prolongation of ^{131}I-Hippuran transit time 30 days after SWL in the treated kidney; in some cases, similar findings were noted in the contralateral kidney. Lingeman and associates have reported that patients with a solitary kidney demonstrated elevated serum creatinine levels 5 years after SWL (Brito et al, 1990). These observations stand in contrast to the early reports by Chaussy and Fuchs (1986), which suggested a significant increase in renal function 3 months to 1 year after SWL. In addition, a longer follow-up study of patients treated in Munich has failed to confirm this increase in renal function (Liedle et al, 1988).

An additional concern is that **stone recurrence rates may be higher after SWL because of residual stone debris** (Pearle et al, 1999). A study by Carr and associates (1996) documented new stone formation in 298 consecutive patients who initially were determined to be stone free after SWL and compared those findings with those of 62 patients treated by PNL. Their data showed a significant increase in the rate of new stone formation within 1 year of SWL treatment compared with PNL. The authors suggested that fine sand debris generated from SWL treatment remained in the kidney and gravity acted to position it as a nidus in the calyceal system.

There has been reported to be a significant increase in the number of calcium phosphate stone formers during the past 3 decades (Mandel et al, 2003; Parks et al, 2004). An intriguing finding in Parks and colleagues' work was that when all kidney stone formers were analyzed for the number of SWL procedures, the **calcium phosphate stone formers had received a significantly higher number of procedures than did the idiopathic calcium oxalate stone formers when rates were adjusted for number of stones and duration of stone disease.** Furthermore, the brushite stone formers had received a significantly greater number of SWL treatments than had the apatite stone formers. The histopathologic examination of the brushite stone formers revealed advanced levels of tissue changes in the renal cortex and papilla that included interstitial fibrosis, tubular atrophy, glomerular obsolescence, and deposition of large amounts of biologic hydroxyapatite in the lumens of inner medullary collection ducts (Evan et al, 2005). Although these data do not establish a cause-and-effect relationship, clearly there is an association between brushite stone disease and high levels of SWL treatment sessions. Because apatite stone disease is likely to be related to higher urine pH levels in these patients, animal studies that showed the initial site of SWL injury to be localized to the microvessels and collecting duct of the renal papilla may explain the loss of control over normal urinary fluid pH.

Mechanism for Tissue Injury

The mechanism for the traumatic effects of SWL is not known, although Delius and colleagues (1988) have speculated that the violent collapse of cavitation bubbles generated by the shockwaves is primarily responsible for the cellular changes (Table 48–12). This concept is based on data showing that cavitation bubbles are present during shockwave application and that lithotripter shockwaves can cavitate water and blood in vitro (Coleman et al, 1987). Crum (1988) documented that SWL does produce acoustic cavitation, possibly as the result of the high intensity of the shockwave amplitude, and noted that the cavitation microjets are sufficiently forceful to pit or deform metal test foils. Zhong and coworkers (2001) suggested that it is expansion of the bubbles in a vessel that will lead to rupture of the wall of that blood vessel, testing this in an in-vitro setting.

Table 48–12.

Reversible and Irreversible Injury

Reversible Changes
Mild tubular necrosis
Casts and red blood cells in tubular lumen
Vacuolar changes of tubular lumen
Mild interstitial edema and hemorrhage
Irreversible Changes Resulting in Loss of Renal Tissue
Disruption of nephrons
Extensive interstitial edema
Large hematomas of cortex and medulla
Rupture and occlusion of veins and arteries
Fracture of glomerular and peritubular capillaries

No group had been able to positively detect and validate acoustic cavitation within the kidney during SWL treatment until Bailey and associates (2005) created a passive cavitation detection system using two confocal spherical bowl PZT transducers. This device was used for coincidence detection of cavitation bubble emissions within a 2 × 2 × 2-mm sampling volume centered on F2 of a Dornier HM3 lithotripter. An ultrasound scan head targeted at this spot was used to image echogenicity in and around the sample volume. Signal (passive cavitation detection, hyperechoic spots) was intense in the urinary space during SWL treatment, and a signal was also seen in the renal cortex after only 1000 shocks. At that time a small fluid space was noted at the site of the parenchymal signal. These data suggest that **once blood vessels have been ruptured and blood has collected in pools there is a greater potential for cavitation to occur. The pooling of blood provides a large fluid-filled space for cavitation bubbles to grow and collapse.** In this model the accuracy of tissue targeting was confirmed by inducing a lesion with high-intensity focused ultrasound. Further evidence that cavitation plays a role in tissue injury comes from a study by Evan and associates (2002) in which the degree of tissue injury was compared between a standard rigid reflector and a pressure release reflector. The pressure release reflector generates a shockwave in which the negative tail precedes the positive peak, resulting in a suppression of cavitation activity. No injury was detected in the kidneys treated with the pressure release reflector; the standard rigid reflector induced the expected lesion.

Techniques to Optimize SWL Outcome

For all lithotripters the urologist has the ability to control a number of device parameters that may affect the ultimate treatment outcome (Table 48–13). These parameters include the acoustic output and focal volume that are employed, optimal coupling, the number of shockwaves administered, the rate at which they are dispensed, and the power or voltage that is used. In addition, other intraoperative factors that may affect stone breakage can be controlled, such as anesthetic technique.

Although all lithotripters generate waveforms that are fundamentally similar, lithotripters may be distinguished from one another by the peak pressure and spatial extent of their acoustic field. The physics of acoustics dictate that the pressure field of a lithotripter is focused not at a particular point in space but rather is distributed over a volume of space. Most commonly, that focal zone is a cigar-shaped region, although the volume of that zone may differ greatly among devices. Recent in-vitro studies suggest

Table 48–13.

Factors That Induce the Degree of Renal Trauma Associated with Shockwave Lithotripsy

Aggravating Factors

Number of shocks
Period of shockwave administration—shorter period increases damage
Accelerating voltage—higher voltage increases damage
Type of shockwave generator—first- vs. second/third-generation devices
Kidney size—juvenile vs. adult
Preexisting renal impairment

Mitigating Factors

Pretreatment with 100 to 500 shocks at low energy level to reduce lesion size
Treatment at a slow rate of shockwave delivery (60 shocks/min or less)

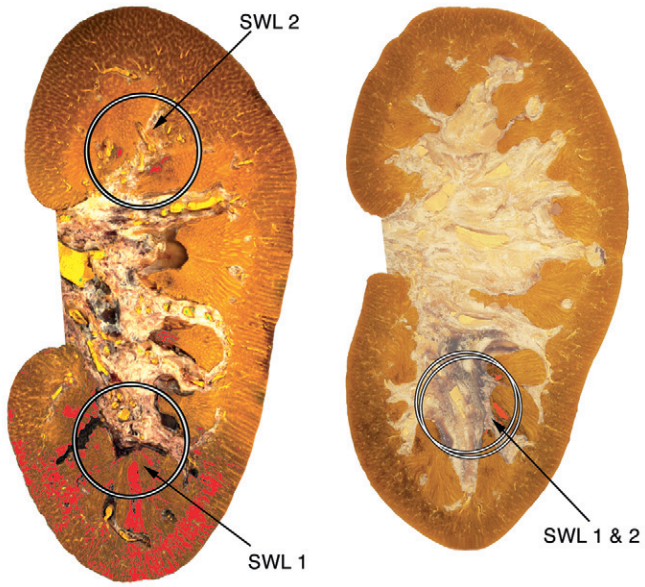


Figure 48–30. On the left is a coronal section of a kidney from an animal treated with 2000 shocks at 24 kV first to the lower pole (shockwave lithotripsy [SWL] 1) and then an additional 2000 shocks at 24 kV to the upper pole (SWL 2) of the same kidney. The typical lesion *(in red)* is seen at the lower pole; however, a greatly reduced lesion is seen on the upper pole. These data suggested that a pretreatment protocol might reduce the lesion induced by a clinical dose of shockwaves. At right, lesion size is shown in an animal first treated at the lower pole with 500 shocks at 12 kV (SWL 1) and then treated again at the lower pole with 2000 shocks at 24 kV (SWL 2). A greatly reduced lesion is also noted for this protocol.

that the focal width generated by a lithotripter affects stone breakage; a wider focal width has been reported to increase the likelihood of stone breakage (Sapozhnikov et al, 2007). Because the kidney tends to move, as a consequence of respiratory motion, the stone may move in and out of a narrow focal zone. Another potential drawback of a narrow focal zone is that less energy may be deposited into the stone. When the focal zone is narrower than the stone being treated, the tensile stress inside of a stone is reduced; for the stone to be subjected to the full force of shear stress, the outer surface of the stone must be subjected to high-pressure shockwave energy.

The first generation lithotripter was a water bath design that was a large, stationary machine. The present generation of lithotripters have dry treatment heads, which make them smaller and more easily transportable. However, they require a coupling medium, such as gel or oil, to join the patient to the device. Optimal coupling permits the efficient transfer of energy from the lithotripter to the patient; poor coupling will reduce stone breakage. Most commonly, energy transfer through a coupling medium is attenuated by air pockets in the coupling interface itself. Decoupling and recoupling, which may occur during repositioning of a patient during SWL, can generate large volume air pockets in the coupling medium. Such air pockets can have a dramatic effect on treatment efficacy: air pockets of just 2% of the coupling interface reduce breakage by 20% to 40% (Pishchalnikov et al, 2006; Neucks et al, 2008). Although there is no way to monitor coupling during treatment, simple steps can minimize the likelihood of air pockets developing. Dispensing gel from a squirt bottle and rubbing the gel by had to cover the treatment head and skin degrades the coupling interface. Improved coupling can be achieved by delivering a large volume of gel as a mound dispensed from the stock jug and allowing the gel to spread upon contact between the treatment head and the skin.

During an SWL treatment session the urologist can directly control the rate at which shockwaves are delivered and the number of shockwaves dispensed. In a recent literature review and meta-analysis of randomized control trials evaluating different shockwave delivery rates, a rate of 60 shocks per minute was found to break stones more effectively than 120 shocks per minute (Semins et al, 2008). Cavitation is thought to play a role in this effect, because the dynamic bubbles are given a longer time interval to dissipate with a slower rate and therefore have less of a shielding effect and energy draw from subsequent shocks. The disadvantage of a slow rate is, of course, a longer treatment time, particularly if the number of shockwaves being delivered is predetermined. However, slowing the rate has also been shown to be protective of kidney vasculature (Evan et al, 2007). The lowest number of shockwaves possible should be used to reduce renal injury, but this number is generally predetermined and many patients are likely to be overtreated. Risks and benefits need to be weighed regarding possible overtreatment versus need for further procedures when deciding on shockwave number.

Another parameter urologists adjust is the energy setting on the machine. Increasing the power setting on most electromagnetic lithotripters actually narrows the focal zone, which, as discussed earlier, decreases stone breakage and may also increase the risk of renal injury and renal hematoma (Connors et al, 2000). In the past several years, studies have shown that "ramping up" the energy of the lithotripter can be protective of renal injury (Fig. 48–30). Lesion size is decreased after pretreatment with low-energy shockwaves (100 to 2000 at 12 kV followed by 24 kV) (Willis et al, 2006). Interestingly, Connors and coworkers (2009) showed in a pig model that the voltage that is initiated is less important than the actual ramping up, as pretreatment groups with 100 shockwaves at 18 kV or 24 kV both had significantly smaller lesions than just treating with 2000 shockwaves at 24 kV without pretreatment. The reduction in renal injury is thought to be secondary to vasoconstriction because the same beneficial effect was blocked when dopamine was administered (Willis et al, 2006). In addition, ramping up the voltage has been shown to result in better stone breakage when using the same total shockwave energy (Zhou et al, 2004). With regard to voltage parameters, the technique of ramping up appears to both improve stone breakage and reduce tissue injury.

The original lithotripter, the Dornier HM3, required a general anesthetic for treatment. However, later generations of lithotripters were developed for treatment to be performed without anesthesia. To minimize treatment discomfort the lithotripters were designed with wider aperture, which will spread the acoustic field across a broader area of the patient's skin, reducing skin surface pain. However, this wider aperture resulted in a narrow focal zone, which had a deleterious effect on stone breakage. Interestingly, the higher pressures used with these newer machines result in higher adverse event rates as well. The effect of respiratory motion, as described previously, further hampers stone targeting and acts to reduce stone breakage rates.

To reduce stone motion, urologists can perform SWL with general anesthesia, which will control the patient's respiratory rate and volume. Two clinical studies compared the outcome of SWL performed with intravenous sedation and SWL performed with general endotracheal anesthesia. General anesthesia yielded significantly better outcomes: 78% to 87% stone-free rates versus 51% to 55% with intravenous sedation (Eichel et al, 2001; Sorensen et al, 2002). Because general anesthesia is associated with superior outcomes this may be the anesthesia of choice for SWL, unless contraindicated for medical reasons.

Key Points: Shockwave Lithotripsy

- Most patients with uncomplicated kidney stones can be successfully treated with SWL.
- Shockwaves break stones via multiple different mechanisms, including both compressive and tensile forces.
- SWL is associated with both anatomic and functional injuries to the kidney.
- The effectiveness of SWL can be enhanced by ensuring optimal coupling of the patient to the lithotripter, treating at a slower rate (60 shocks/min), and treating with general anesthesia.
- The adverse effects of SWL may be reduced by initiating treatment at low power settings and slowly ramping up the power to standard treatment energy.

Percutaneous Nephrolithotomy

Fernstrom and Johansson first reported the technique of creating a percutaneous track specifically to remove a stone in 1976. Subsequent reports have established PNL as a routinely used technique to treat patients with large or otherwise complex calculi (Alken et al, 1981; Wickham and Kellett, 1981; Segura et al, 1982; Clayman et al, 1984). Advances in surgical technique and technology have enabled the continuous evolution of PNL, allowing the urologist to remove calculi percutaneously with increasing efficiency. Because the percutaneous approach to stone removal is superior to the open approach in terms of morbidity, convalescence, and cost, PNL has replaced open surgical removal of large or complex calculi at most institutions (Matlaga and Assimos, 2002). Here the specific aspects of percutaneous techniques as they relate to stone removal are delineated.

Preparation of the Patient

The initial evaluation of the patient who is being considered for PNL should be a complete history and physical examination. A complete medical history will **identify those patients with an absolute contraindication to PNL, such as uncorrected coagulopathy, as well as those with an active, untreated urinary tract infection.** The placement of a percutaneous nephrostomy drain, without manipulation of the calculus, may be an appropriate therapy if the stone is associated with obstruction of the renal unit and sepsis. If it is medically feasible, **aspirin and other antiplatelet medications should be discontinued 7 days before the date of surgery** (Mak and Amoroso, 2003).

Preoperative laboratory evaluation of patients scheduled for PNL should include a complete blood cell count as well as serum electrolyte determinations and renal function tests. Martin and colleagues (2000) have reported that it is unnecessary to obtain screening coagulation studies before PNL for an otherwise healthy patient. **Urine culture is mandatory for all patients who undergo PNL;** perioperative antibiotics can be appropriately tailored to culture-specific organisms. Typing and screening of the patient's blood should be performed, although preoperative cross-matching is usually not necessary.

Historically, it has been viewed as mandatory to evaluate the patient's collecting system by either intravenous urography or retrograde pyelography. Recently, as more patients are initially evaluated with helical CT, it is no longer mandatory to have these studies at the preoperative evaluation (Park and Pearle, 2006). **In most cases, the decision to perform PNL may be based on the stone burden displayed on the CT images.** The main advantage of CT is the ability to assess the spatial relationship of the kidney relative to the stone and that of the kidney in relation to adjacent peritoneal and retroperitoneal structures. Retrorenal colon has been reported to be present in less than 1% of all patients, but its incidence may be higher in those who have undergone jejunoileal bypass, those in a nursing home, or those with spinal cord injury (Sherman et al, 1985). These patients may benefit from initial CT. Patients with ectopic kidneys, both congenital and iatrogenic (e.g., due to renal allograft, autotransplantation), as well as patients with dysmorphic body habitus due to congenital malformations such as spinal dysraphism may also benefit from cross-sectional imaging before PNL; intra-abdominal structures, such as the bowel, may be located between the skin and the renal access point. A KUB radiograph may be obtained immediately before the procedure to verify stone location. Retrograde pyelography can be performed at the time of the surgical procedure, acquiring information about calyceal anatomy that may aid in selecting the targeted puncture site. However, for certain patients, such as **those with calyceal diverticula, for whom the surgical approach is affected by the diverticulum's relationship to the collecting system, intravenous or retrograde pyelography may be required at the time of initial evaluation.** Radionuclide scanning may be necessary in select patients, particularly those harboring staghorn calculi, to evaluate differential renal function.

Antibiotics. Although there are no prospective, randomized controlled trials confirming the need for antibiotic prophylaxis during PNL, it is generally accepted that antibiotic prophylaxis will reduce infectious complications. The antimicrobial of choice is a first- or second-generation cephalosporin or an aminoglycoside with metronidazole or clindamycin; ampicillin/sulbactam or a fluoroquinolone is recommended as an alternative. Mariappan and associates (2005) have reported a prospective controlled study that also found that oral ciprofloxacin 1 week before PNL significantly reduced the risk of postoperative urosepsis. Importantly, **urinary calculi may harbor bacteria even though bacteriuria is only intermittently present.** This is particularly true

in the patient who has been taking antibiotics in the past. For those patients who do have preoperative bacteriuria, stone cultures produced bacteria in 77% of cases in a series reported by Larsen and associates (1986). The most frequently identified organisms were *Proteus mirabilis, Escherichia coli, Klebsiella* species, *Pseudomonas* species, *Enterococcus* species, and *Enterobacter* species. However, sterile urine does not preclude postoperative bacteriuria, because Charton and colleagues (1986) reported a 35% incidence of bacteriuria after PNL among patients with sterile preoperative urine culture specimens in whom prophylactic antibiotic therapy was not used. Mariappan and associates (2005) have also reported that the best correlate with post-PNL sepsis is stone culture or renal pelvic urine culture, not bladder urine culture. **The fragmentation of stones, despite sterile urine, may release preformed bacterial endotoxins and viable bacteria that place the patient at risk for septic complications** (Scherz and Parsons, 1987; McAleer et al, 2002, 2003; Paterson et al, 2003). Therefore, patients who have radiographic or clinical features suggestive of struvite or in whom infection is suspected should receive broad-spectrum antibiotics before surgery to reduce the risk of sepsis. Antibiotic treatment may also reduce bleeding secondary to inflammation and friability of renal parenchyma. Approximately one third of patients with an indwelling ureteral stent will, despite sterile urine on a preoperative analysis, be colonized with bacteria; *Enterococcus* and *Staphylococcus epidermidis* are the most frequent offending organisms (Reid et al, 1992; Lifshitz et al, 1999b). For patients with indwelling stents, then, a course of antibiotic prophylaxis, particularly for gram-positive organisms, may be beneficial before instrumentation.

Anesthesia. PNL can be performed after the administration of general, epidural, or local anesthesia. Local anesthesia, usually in combination with intravenous sedatives and analgesics, has been reported in a number of centers (Clayman et al, 1983; Hulbert et al, 1986; Preminger et al, 1986; Ohlsen and Kinn, 1993). Local anesthesia may be an option when general anesthesia is contraindicated. A local anesthetic, such as lidocaine, can be delivered into the access tract by use of an 8.3-Fr anesthetic injection catheter with multiple side holes or with a dual-lumen ureteral access catheter (Dalela et al, 2004). Regional anesthesia (e.g., epidural, spinal) can be used for percutaneous procedures, but several problems may be associated with these regional anesthetic techniques. First, a relatively high block is necessary to eliminate all renal pain. Second, distention of the renal pelvis during PNL may cause a vasovagal reaction that is not always prevented by regional anesthesia (Grasso and Taylor, 1997). General anesthesia is usually preferred when a more lengthy procedure is planned because it is the best means of protecting the airway when patients are in a prone position. **In cases in which upper pole puncture is contemplated, general anesthesia should be used because it permits control of respiratory movements,** which is essential to minimize the risk of pulmonary complications. **A close relationship between the surgeon and the anesthesia team is essential to optimize the outcome of a PNL procedure.** The anesthesiologist should be aware that pulmonary injuries, including hydrothorax and pneumothorax, can occur during PNL; to that end, the anesthesiologist should monitor airway pressures, end-tidal carbon dioxide levels, and oxygen saturation and should auscultate the lungs frequently. Acute anemia due to blood loss or dilution may also occur, emphasizing the need for frequent hemodynamic assessments. Because of the large amounts of fluids administered to the patient during nephroscopy there is a potential risk for hypothermia, a disorder associated with an increased risk of morbid cardiac events. Warming of irrigation fluids as well as patient warming devices may attenuate this risk.

The fundamental techniques of gaining and maintaining are reviewed in Chapter 47.

Stone Removal. After the nephrostomy access has been appropriately dilated and the Amplatz sheath positioned the urologist can proceed with stone removal by endoscopic techniques. In the early days of PNL several authors reported the successful extraction of renal calculi with Randall forceps (modified to allow passage over a guide wire) or stone baskets under only fluoroscopic, not visual, guidance (Castaneda-Zuniga et al, 1982; Pollack and Banner, 1984). However, fluoroscopically guided stone removal is no longer recommended because it is not as safe or as efficient as the removal of calculi under direct vision.

Physiologic solutions should be used for irrigation during PNL to minimize the risk of dilutional hyponatremia in the event of large-volume extravasation (Carson, 1986). The height of the irrigant should be maintained at 80 cm or less above the patient to minimize intrapelvic pressure and to prevent fluid absorption through pyelovenous backflow (Miller and Whitfield, 1985). The use of an Amplatz working sheath also prevents elevated intrapelvic pressures. Rigid nephroscopy is performed initially, and stones up to 1 cm in diameter can be grasped with rigid graspers or stone baskets and extracted intact through the 30-Fr Amplatz sheath. Stones larger than 1 cm require fragmentation before extraction. Several intracorporeal lithotripsy techniques are available.

Rigid nephroscopy is the preferred method for stone removal; however, only the simplest intrarenal collecting systems can be completely inspected with a rigid nephroscope through a single access. Therefore, **flexible nephroscopy should be used during every PNL to survey the entire intrarenal collecting system for residual stone fragments.** Pressurization of irrigation fluid (to 300 mm Hg) during flexible nephroscopy is necessary to adequately distend the collecting system and to improve visualization (the use of an Amplatz sheath is mandatory when pressurized irrigation is used). The entire collecting system should be examined systematically, including the proximal ureter. Injection of contrast material through the flexible nephroscope is helpful in maintaining orientation and verifying that each calyx has been inspected. Small stone fragments can be removed with a stone basket passed through the flexible instrument, and larger stones can be fragmented with laser or EHL. Alternatively, fragments may be flushed or manipulated into the renal pelvis with a combination of high-pressure irrigant and a floppy-tipped J wire, where they may be retrieved more easily with rigid instruments. The goal of PNL is complete or nearly complete clearance of stone material at the time of the primary procedure, which greatly simplifies secondary procedures, if necessary. Furosemide is administered intravenously when the nephrostomy tube is placed at the conclusion of PNL to promote and to maintain diuresis.

Special Situations

Calyceal Diverticula. Calyceal diverticula are nonsecretory, transitional cell epithelium-lined cystic cavities within the renal parenchyma. A narrow communication with the pelvicalyceal system almost always exists. The incidence of calyceal diverticula diagnosed on routine intravenous pyelography ranges from 0.21% to 0.45% (Hulbert et al, 1986). Calculi have been reported in 9.5% to 50% of calyceal diverticula (Jones et al, 1991b). Percutaneous access into stone-bearing diverticula poses several unique

problems. Direct puncture is often difficult because of the small size of the cavity and the frequent occurrence of calyceal diverticula in the upper pole of the kidney. After successful puncture is achieved, negotiation of a guide wire into the renal pelvis is often not possible. A similar situation can occur when a stone fills a calyx so completely that a guide wire cannot be passed through the infundibulum into the renal pelvis or in the rare case of infundibular stenosis. To overcome these difficulties, a special access technique is required.

Contrast media can be instilled through a ureteral catheter to localize the diverticulum. However, if the stones are visible on fluoroscopy it is often preferred to puncture directly onto the stone (Ohlsen and Kinn, 1993). **Direct puncture into the diverticulum allows use of rigid instruments that provide superior visualization compared with flexible instruments that are used in an indirect approach.** Optimal visualization is essential in trying to identify the communication between the diverticulum and the renal collecting system. Direct access is also beneficial because fulguration of the urothelium can easily be achieved by a resectoscope equipped with a roller-ball electrode. Jones and colleagues (1991b) reported that direct percutaneous access into the diverticulum could be established in all but 2 of 24 patients. Likewise, Shalhav and associates (1998) reported that in a group of 30 patients with calyceal diverticula, direct access was performed in 28 patients. When direct puncture fails, a neighboring calyx can be punctured and the diverticulum entered indirectly by perforating the wall of the diverticulum or by entering in a retrograde fashion through the diverticular neck (Hedelin et al, 1988). However, the results with an indirect approach are inferior (Jarrett and Smith, 1986).

Kim and associates (2005a) have described a single-stage technique for the treatment of patients with calculi residing in a calyceal diverticulum (Fig. 48–31). Once the diverticulum is punctured, a 0.035-inch movable core J wire is coiled within the diverticulum. It is important to ensure that not only the floppy tip of the wire but also the solid core is coiled within the diverticulum, so that sufficient stabilization is provided for proper placement of coaxial dilators. A second 0.035-inch movable core J wire serving as a safety wire is then passed through the 10-Fr sheath of the coaxial dilator. With two guide wires coiled within the diverticular lumen, balloon dilation of the track can be performed safely. Care should be taken to avoid perforation of the back wall of the diverticulum. Once the balloon dilator is inflated, the working sheath is passed over the balloon as close as possible to the diverticulum without advancing the balloon. In small diverticula, this results in the placement of the sheath outside the diverticulum. An 11-Fr alligator forceps is passed through the rigid nephroscope and used to follow the wire and gently spread renal parenchyma to allow entry into the calyceal diverticulum under direct vision. Stone material is extracted with grasping forceps or ultrasonic lithotripsy. Careful inspection of the urothelium with the rigid nephroscope is performed in an effort to identify a flattened renal papilla, which suggests an obstructed calyx rather than a diverticulum. The neck of the diverticulum is often difficult to identify because it can be diminutive. Methylene blue injected through the ureteral catheter can facilitate visualization of the ostium. Once a guidewire is passed into the renal pelvis, the neck of the diverticulum can be balloon dilated or incised.

Because calyceal diverticula are lined by a nonsecretory endothelium, most authors advocate fulguration at the time of PNL because this will ablate 76% to 100% of diverticula (Monga et al, 2000; Kim et al, 2005b). Auge and associates (2002b) and Turna and associates (2007) have also reported the results of long-term studies in which they found that PNL accompanied by ablation of the diverticulum is associated with superior stone-free rates. Alternatively, Hulbert and coworkers (1986) reported treating 10 patients with calyceal diverticula and suggested that trauma to the wall of the diverticulum caused by the dilation process is sufficient to ablate the diverticular lumen. In this series, a nephrostomy tube was left in place for 2 weeks. However, Donnellan and colleagues

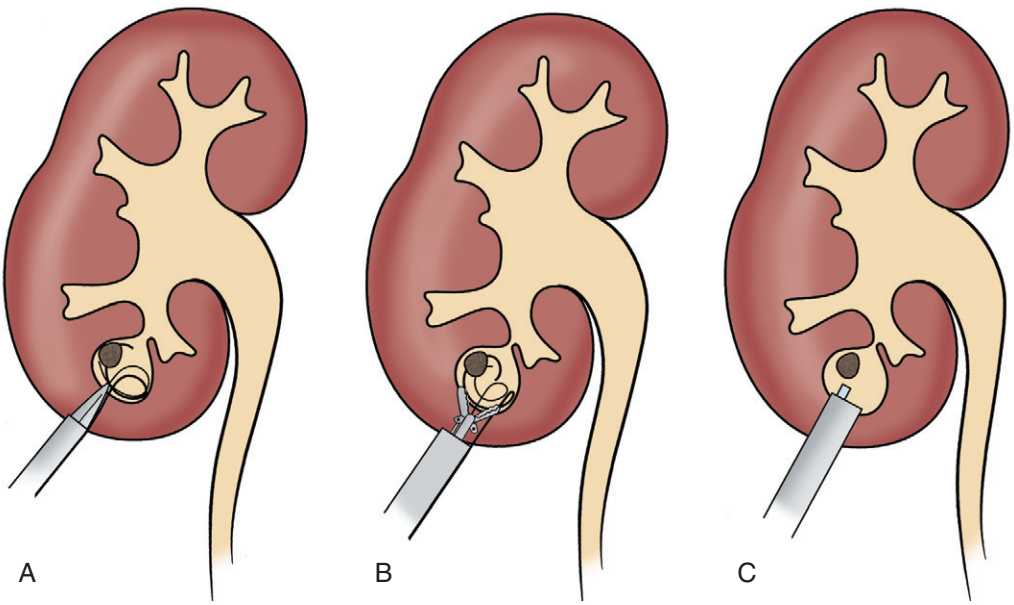


Figure 48–31. Access into small diverticula. **A,** Balloon dilator is advanced as far as possible without perforating the back wall of the diverticulum. The working sheath is placed just outside the diverticulum. **B,** Alligator forceps spread the parenchyma and allow advancement of the nephroscope under vision into the diverticulum. The working sheath is then advanced over the nephroscope and into the diverticulum **(C).**

(1999) reported that treatment of 20 patients with calyceal diverticula by dilation or incision of the diverticular neck without fulguration resulted in complete ablation of the diverticulum in only 30% of patients, leading the authors to conclude that fulguration should be performed routinely to ensure diverticular ablation. Typically, after ablation of the diverticulum, a nephrostomy tube is placed for 48 to 72 hours.

Horseshoe Kidney. Horseshoe kidney is the most common congenital renal anomaly, with an estimated incidence of 1 in 400 and a male-to-female ratio of 2:1 (Jones et al, 1991a). The unique location and orientation of the horseshoe kidney are due to the incomplete cephalad migration and malrotation of the kidney, a consequence of the entrapment of the isthmus under the inferior mesenteric artery (Hohenfellner et al, 1992). The UPJ is commonly deformed owing to the high insertion of the ureter into a typically elongated renal pelvis. The course of the proximal ureter is similarly aberrant; it drapes ventrally over the renal symphysis, where it may be compressed by vessels supplying the lower pole and isthmus. Ureteral obstruction that may result from these anomalies can give rise to hydronephrosis, urinary stasis, sepsis, and calculi formation in up to 70% of patients (Jones et al, 1991a; Lampel et al, 1996).

In considering PNL in a horseshoe kidney, the characteristic lower and centrally oriented position of the kidney, the orientation of the collecting system, and the abnormal blood supply should be taken into account. Janetschek and Kunzel (1988) performed postmortem examinations of six horseshoe kidneys, in situ, and found normal renal arteries in all specimens. However, accessory arteries entering the renal hilum, aberrant polar and isthmus arteries originating from the aorta, and hypogastric and common iliac arteries were noted as well; all blood vessels, except a select few supplying the isthmus, entered the kidney from its ventromedial aspect. Therefore, **a puncture of the dorsal or dorsolateral aspect of the kidney will be well away from major renal vessels.**

Skoog and associates (1985) have reported an association between horseshoe kidney and retrorenal colon. A preoperative CT can be of assistance in determining the presence of a retrorenal colon as well as in defining the stone-bearing calyces. **The lower pole calyces lie within a coronal plane, angled medially, and are seldom suitable for direct puncture** (Al-Otaibi and Hosking, 1999). However, **the upper pole calyces are more posterior and lateral and are often subcostal, providing a convenient and relatively safe route for PNL access.** The standard site for PNL (inside the posterior axillary line just caudad to the 12th rib) is punctured, but the angle of the puncture is caudad rather than cephalad. Because most of the calyces of horseshoe kidneys point either dorsomedially or dorsolaterally, they are more favorably positioned for puncture than are normal renal units (Janetschek and Kunzel, 1988). Because of the malrotation of the kidney, the renal pelvis may be more anteriorly located and the length of the nephrostomy track may exceed the length of the rigid nephroscope, necessitating the use of flexible nephroscopy or multiple accesses. Flexible nephroscopy may also be required to gain access to the lower medial calyces, where stones are often found.

Raj and associates (2003) reported a multicenter analysis of 24 patients with calculi in a horseshoe kidney who underwent PNL. The overall stone-free rate was greater than 90%, most accesses were upper pole, and flexible nephroscopy was performed in almost all patients. The authors noted that the rigid nephroscope was rarely sufficient to remove the whole stone burden. Miller and associates (2008) have reported a similar series of patients undergoing PNL of horseshoe kidneys; upper pole access was used in all cases, as was flexible nephroscopy.

Transplantation and Pelvic Kidneys. Urolithiasis is uncommon in patients who have undergone renal transplantation, with a reported incidence of 0.5% to 3% (Harper et al, 1994; Shoskes et al, 1995; Del Pizzo and Sklar, 1999). Factors that may predispose transplant recipients to form calculi include metabolic abnormalities, foreign bodies (nonabsorbable suture material, forgotten stents), recurrent infection, and papillary necrosis. On occasion, calculi may have been present in the donor kidney (Pardalidis et al, 1994). Typical renal colic does not occur because the transplantation kidney and ureter are denervated; the presentation may instead resemble acute rejection or acute tubular necrosis (Harper et al, 1994; Rhee et al, 1999). Benoit and colleagues (1996) reported that in a series of 1500 transplantation patients, 12 (0.8%) were diagnosed with urinary calculi. Three patients presented with obstructive anuria, one patient presented with abdominal pain, and eight patients were asymptomatic and diagnosed by ultrasonography.

Renal allografts present a unique anatomic situation for PNL. The most common surgical anatomy is for the donor left kidney to be placed extraperitoneally into the recipient's right iliac fossa; alternatively, the right kidney is transplanted in the left iliac fossa. In either case, the renal pelvis is located medially, requiring that the kidney be rotated 180 degrees on its axis. Thus, the posterior calyces point anteriorly and, consequently, an anterior approach to the kidney is similar to a posterior approach to native kidneys. In the usual percutaneous approach to a transplanted kidney the patient is placed in the lithotomy position, which allows simultaneous cystoscopic access to the bladder. A ureteral catheter is inserted for instillation of contrast material. Access is most safely established (i.e., avoiding intraperitoneal contents) into the lower pole with the skin puncture as caudal as possible. Percutaneous access to transplanted kidneys is actually facilitated by their superficial location. However, scar formation around the graft may make the initial needle puncture and tract dilation more difficult (Rhee et al, 1999). Once access is established, PNL can be performed by standard methods (Pardalidis et al, 1994). Del Pizzo and Sklar (1999) have reported the use of a mini-perc technique in 14 transplantation patients in whom access was established with the aid of intraoperative ultrasonography with a 16-Fr suprapubic peel-away introducer and sheath. No data are available to show an advantage of the mini-perc technique compared with the larger diameter working sheaths. Although delayed closure of the access site after catheter removal in immunosuppressed transplantation patients is a concern, most authors report that even nephrostomy tracts dilated to 30 French closed normally (Caldwell and Burns, 1988; Gedroyc et al, 1989; Del Pizzo and Sklar, 1999). Rifaioglu and associates (2008) have described that not all patients will require tract dilation to 30 French, and in some cases acceptable outcomes may be achieved with percutaneous flexible nephroscopy alone.

Patients with ectopic pelvic kidneys necessitate a different and more complicated approach for PNL as a result of their unique anatomy. The incidence of pelvic kidney has been estimated to range from 1 in 2200 to 1 in 3000 in autopsy series (Zafar and Lingeman, 1996). The pelvic kidney is retroperitoneal, posterior to the peritoneum and anterior to the sacrum. Interposing bowel loops between the kidney and the anterior abdominal wall prevent a direct puncture through the anterior abdominal wall. Eshghi and colleagues (1985) first described a laparoscopically assisted PNL technique for pelvic kidneys, a technique that has been further characterized by others (Zafar and Lingeman, 1996; Holman and



Figure 48–32. CT-guided percutaneous access of a renal transplant for subsequent percutaneous nephrolithotomy procedure.

Toth, 1998; Matlaga et al, 2006). Desai and associates (2007) have reported on PNL in pelvic ectopic kidneys using only ultrasound guidance. Although the stone-free rate was 100%, a bowel injury did occur in one patient. Consequently, if laparoscopy will not be used to assist guidance and reflect intervening organs away from the anticipated course of percutaneous access, percutaneous access could be obtained utilizing CT guidance (Fig. 48–32), as described by Matlaga and associates (2003).

Morbid Obesity. Patients suffering from morbid obesity present technical as well as anesthetic challenges during any surgical intervention (Freedman et al, 2002). Often, one or more comorbid factors complicate management of these patients. General anesthesia may be a special concern for patients in the prone position because of restricted respiratory capacity that may require higher ventilation pressures intraoperatively. Some studies suggest an increased postoperative morbidity in morbidly obese patients, mostly because of the higher incidence of wound infection and thromboembolic events. Pearle and coworkers (1998) first examined the issue of PNL among the obese when they evaluated a group of obese patients undergoing PNL. They found that performing PNL, with standard, prone techniques, was not associated with an increased risk of morbidity; in fact, complication and transfusion rates as well as the length of hospitalization was no different. Koo and colleagues (2004) have subsequently reported that the outcome of PNL is independent of the patient's BMI. El-Assmy and colleagues (2006b) also reported that the stone-free outcome of PNL is also unrelated to BMI.

Positioning the morbidly obese patient for PNL can be difficult; and in particular for large patients, two surgical tables may need to be secured together (Hofmann and Stoller, 1992). Patient positioning should be closely inspected, and pressure points should be identified and padded. Hofmann and Stoller (1992) described a morbidly obese patient who developed acute rhabdomyolysis secondary to crush injuries from placement in the lateral approach, so if this technique is used care must be taken to minimize muscle crush injury. The major difficulty in performing PNL in the morbidly obese patient is the long distance from the skin to the collecting system, which may exceed the length of the working sheath or the length of the rigid nephroscope. **Extralong Amplatz working sheaths (≥20 cm) and extralong rigid nephroscopes are now available that can overcome this challenge.** Alternatively, the Amplatz sheath can be secured by a suture, allowing easy retrieval even when it migrates under the skin. On occasion, when the long Amplatz sheath is not sufficient to reach the kidney, an incision can be made through the subcutaneous tissue to the muscles of the flank, and the PNL track is created from the level of the muscle sheath (Curtis et al, 1997). Alternative instrumentation can also be employed: Giblin and colleagues (1995) described the successful use of a 30-Fr gynecologic laparoscope (with a working length of 27 cm) in patients in whom the SSD precluded the use of standard access sheaths and nephroscopes. Another possibility is to dilate the tract and place a nephrostomy tube for 1 week to let the tract mature. In some cases, maturation of the track allows the kidney to fall back posteriorly closer to the skin, allowing the use of standard nephroscopic instrumentation. Flexible nephroscopy can also be performed through the mature tract, reducing the necessity of rigid nephroscopy (Hofmann and Stoller, 1992). Liberal use of flexible nephroscopy in obese patients improves the stone-free rate and decreases the need for additional access (Pearle et al, 1998).

After stone removal, consideration should be given to the type of nephrostomy tube used. **Tube displacement tends to occur more often in morbidly obese patients,** so balloon-type catheters or reentry Malecot catheters may be preferable (Carson et al, 1988). Alternatively, if a Cope loop catheter is used, placement of a ureteral catheter should be considered to ensure that access to the kidney is not lost should the nephrostomy tube become displaced.

Bilateral Simultaneous Percutaneous Nephrolithotomy

Patients with large, bilateral stone burdens present a formidable challenge to the urologist; rendering these patients stone free can require separate staged procedures and multiple anesthetics. In 1987, Colon-Perez and associates (1987) first reported simultaneous bilateral PNL in a series of three patients. Since that time the procedure has evolved and several dictums have been established. It is recommended that either the side that is more symptomatic or the side that is more difficult be treated first. Patients may be positioned prone or with the treated side elevated.

Later series have expanded on this initial report. Most groups have reported that there is a marked advantage in terms of hospitalization and convalescence, suggesting that a simultaneous bilateral PNL provides the patient a less morbid, more rapid method of stone resolution than does staged PNL or a sandwich technique (Dushinski and Lingeman, 1997; Nadler et al, 1998; Holman et al, 2002). Silverstein and associates (2004) also reported that stone-free rates, blood loss per operation, and transfusion rates for simultaneous and staged bilateral PNL were similar. Furthermore, the reduced total operative time, hospital stay, and total blood loss along with the requirement for only one anesthesia session makes simultaneous bilateral PNL an attractive option for select patients. Desai and associates (2007) have issued a caveat that patients with exceptionally large stone burdens or complex intrarenal collecting system anatomy should not be selected for a simultaneous bilateral PNL. Bagrodia and associates (2009) performed an outcome cost analysis of simultaneous bilateral PNL, confirming the superior morbidity and convalescence of this approach.

Taking all of the evidence together, should a simultaneous bilateral approach be selected the second side should be pursued only

if no significant bleeding is encountered on the first side, the first side did not take an undue amount of time, the patient is clinically stable, and the anesthesia team is agreeable.

Complications

Even for the most experienced urologist, major complications can still occur in up to 7% of patients undergoing PNL, and minor complications may be encountered in up to 25% of patients (Preminger et al, 2005). **Hemorrhage is the most significant complication of PNL, with transfusion rates reported to be from less than 1% to 10%.** Bleeding from an arteriovenous fistula or pseudoaneurysm that requires angiographic embolization occurs in less than 0.5% of patients. Other potential complications include sepsis (postoperative temperature above 38.5° C (101.3° F) is found in almost one fourth of patients undergoing PNL), adjacent organ injury (bowel, spleen), failed access, and perforation of renal pelvis and ureter. The need for open surgery is rare and mostly reported as part of early experience in various studies. The mortality rate of PNL is between 0.046% and 0.8% (Lang, 1987; Lee et al, 1987; Henriksson et al, 1989; Jones et al, 1991a; Lam et al, 1992b; Segura et al, 1994; Dyer et al, 1997; Matlaga et al, 2004). When supracostal puncture is performed, the risk of pneumothorax or pleural effusion requiring drainage may be higher (see Table 48–14). Finally, failure of equipment is an often ignored but significant potential complication. During initial experiences with PNL, concern was expressed about the extent of renal damage caused by the creation and dilation of the transparenchymal nephrostomy tract. However, although some scarring does occur along the percutaneous tract, there is little or no significant effect on renal function (Eshghi et al, 1989).

Because the kidney is an extremely vascular organ, some degree of bleeding occurs during every PNL. Significant bleeding usually requires cessation of the procedure because of impaired visualization. In most cases the source of hemorrhage is venous and placement of a nephrostomy tube is usually sufficient to control the bleeding. If bleeding persists despite the placement of a nephrostomy tube, clamping the tube for a time may facilitate the tamponade of any bleeding points. If these measures do not control the hemorrhage, a Kaye nephrostomy tamponade balloon catheter should be placed. The Kaye nephrostomy tube incorporates a low-pressure 12-mm balloon that may be left inflated for prolonged periods to tamponade bleeding from the nephrostomy tract (Kaye and Clayman, 1986). If bleeding persists despite placement of a Kaye catheter, immediate angiography should be performed to identify a possible arteriovenous fistula or false aneurysm. Angiography is both diagnostic and therapeutic, because arteriovenous fistulas and false aneurysms are best managed by embolization. In the rare event that bleeding cannot be controlled with angiography, partial nephrectomy may be required.

PNL can lead to some absorption of irrigation fluid; therefore, the use of physiologic irrigating solutions is mandatory. The amount of absorbed fluid depends mostly on the irrigant pressure and the length of the procedure. Larger amounts of fluid absorption may occur with extravasation of fluid due to collecting system perforation. Extravasation usually occurs into the retroperitoneal tissue and may be noted by medial displacement of the kidney during fluoroscopy. Minor perforations are common during PNL; premature termination of the procedure is usually not necessary if a low-pressure system (i.e., Amplatz sheath) is being used. However, with more significant perforations, termination of the procedure and nephrostomy drainage are advisable. Intraperitoneal extravasation is a less common but potentially more serious complication than retroperitoneal extravasation. Because the patient is prone, abdominal distention may be difficult to recognize, although the anesthesiologist will usually note a gradual rise in the patient's diastolic blood pressure with consequent narrowing of the pulse pressure and increase in central venous pressure; in advanced cases, ventilation may become difficult because of increased abdominal pressure. Early recognition of major extravasation is crucial. Some authors have suggested that irrigant input and output should be monitored during PNL; and if a discrepancy of more than 500 mL is encountered, cessation of the procedure should be considered (Lee et al, 1986; Segura, 1993). However, a strict accounting of irrigating fluid balance is often not possible during PNL and should not be considered mandatory. Intraperitoneal extravasation may be treated by vigorous diuresis; alternatively, peritoneal drainage has been reported (Carson and Nesbitt, 1985).

When a supracostal puncture is performed, extravasation of irrigant into the pleural cavity may occur. The use of a working sheath tends to minimize extravasation into this space because intrarenal pressure remains low. The chest should be examined at the end of PNL procedures in which a supracostal puncture is used. Fluoroscopy with use of the C-arm is usually sufficient to examine for pneumothorax or hydrothorax (Ogan et al, 2003). If the surgeon has a high index of suspicion for a thoracic complication, a chest radiograph may be obtained postoperatively. If a greater than 10% pneumothorax or hydrothorax occurs, aspiration is generally sufficient because lung injury is extremely rare. Should the pneumothorax recur, a chest tube should be placed. Ogan and Pearle (2002) have described placement of a chest tube under fluoroscopic guidance at the time of the PNL.

Table 48–14.

Open Stone Surgery in the Modern Era

	ASSIMOS ET AL, 1989	KANE ET AL, 1995	PAIK ET AL, 1998	MATLAGA AND ASSIMOS, 2002
No. of open stone surgery cases (% of total stone removal procedures)	37 (4.1)	25 (3.13)	42 (5.4)	7 (0.7)
Stone-free rate (%)	100	71	93	100
Indications (%)				
Complex stone burden	3 (8.1)	3 (12)	23 (55)	0
Endoscopic treatment failure	18 (49)	51 (20)	12 (29)	1 (14)
Anatomic abnormality or concomitant open surgery	13 (35)	8 (32)	11 (46)	6 (86)
Body habitus	5 (14)	5 (19)	4 (10)	0
Other	2 (5)	6 (24)	4 (10)	0

Colonic injury is an unusual complication and is often diagnosed on postoperative nephrostogram, although passage of gas or feculent material through the nephrostomy track, intraoperative diarrhea, and hematochezia or peritonitis are all signs of a possible colonic perforation. Typically, the injury is retroperitoneal; thus, signs and symptoms of peritonitis are infrequent. If the perforation is extraperitoneal, management may be expectant, with placement of a ureteral catheter or double-J stent to decompress the collecting system and withdrawal of the nephrostomy tube from an intrarenal position to an intracolonic position to serve as a colostomy tube (Gerspach et al, 1997). The colostomy tube is left in place for a minimum of 7 days and is removed after a nephrostogram or a retrograde pyelogram shows no communication between the colon and the kidney (LeRoy et al, 1985; Wolf, 1998).

Ureteroscopic Management of Ureteral Stones

Basic ureteroscopic techniques and intracorporeal lithotripsy techniques have been reviewed elsewhere. Herein, issues of anesthesia and specific points of technique and complications of ureteral stone management are reviewed.

The increasing miniaturization of and improvements in the technology of ureteroscopy have greatly altered the anesthetic considerations associated with this procedure. Ureteroscopy was initially performed exclusively under general or regional anesthesia as a consequence of the large-caliber ureteroscopes that were available. However, as ureteroscopes have become more diminutive, intravenous sedation, or sedoanalgesia, has provided another practical anesthetic option for patients harboring ureteral stones. The short duration of modern sedoanalgesic agents allows rapid relief of pain, efficient titration of analgesia, and rapid recovery after the procedure. Ureteroscopy can be safely and efficiently performed under local or intravenous sedation, with success rates equivalent to those of patients undergoing general or regional anesthesia (Cybulski et al, 2004). Because most ureteral orifices will accommodate a 6- to 7-Fr device, immediate access to ureteral calculi with a 7-Fr flexible ureteroscope is possible. Furthermore, the small-diameter fibers of the holmium:YAG laser allow the immediate treatment of ureteral calculi.

The ability to fragment and remove calculi with a ureteroscope has dramatically advanced the urologist's ability to render patients stone free with a single procedure. Early stone-free results with flexible ureteroscopy did not exceed those of in-situ SWL (Drach et al, 1986; Bagley, 1990; Frang et al, 1992; Mogensen and Andersen, 1994). However, as smaller ureteroscopes were introduced and the holmium:YAG laser became available, success rates for ureteroscopy have increased (Preminger et al, 2007). Although it is a more invasive technique than SWL, ureteroscopy with small, rigid or flexible endoscopes is the most efficient technique for treatment and removal of ureteral stones. Patients desiring a single procedure with maximal efficacy should be counseled on the advantages of a ureteroscopic approach.

When the ureteral orifice is too narrow to accommodate a ureteroscope, dilation may be accomplished with serial dilators, balloons, or even the ureteroscope itself. The anatomy of male patients may not allow a rigid ureteroscope to be easily passed above the iliac vessels, but a flexible ureteroscope can usually be advanced over a guidewire. The entire ureter can be more easily accessed with a rigid ureteroscope in female patients. Once the stone is visualized, fragmentation with the lithotrite of choice is performed. Complete fragmentation to a size less than that of the safety wire (0.035 inch) should allow passage of all fragments without sequelae. Alternatively, fragmentation to a size sufficient for extraction by a stone retrieval device achieves a stone-free state for the patient at the end of the procedure.

If significant ureteral edema or manipulation occurs, a post-ureteroscopy stent should be placed to prevent colic and obstruction. There have been two unique meta-analyses addressing this subject (Makarov et al, 2008; Nabi et al, 2007); both have found that for uncomplicated ureteroscopy, a ureteral stent may be safely omitted. If the clinical situation does not allow primary ureteroscopy (sepsis, inability to advance the ureteroscope, ureteral injury, equipment failure), a ureteral stent is placed and the problem corrected. Secondary or post-stent ureteroscopy has the advantage of working through a dilated ureter, often allowing the use of larger rigid ureteroscopes.

Steinstrasse

Steinstrasse, literally "street of stones," describes the accumulation of stone fragments in the ureter obstructing the collecting system after SWL. This complication has been reported in 2% to 10% of SWL cases and directly correlates with increasing stone burden (Coptcoat et al, 1987; Weinerth et al, 1989; Sulaiman et al, 1999; Madbouly et al, 2002). Large stone burden, staghorn calculi, bilateral SWL, and preexisting ureteral obstruction are all known to be risk factors for steinstrasse (Weinerth et al, 1989). Steinstrasse may occur in as many as 41% of patients undergoing SWL monotherapy for staghorn calculi, although with the increasing use of PNL in the treatment of patients with large stones the incidence of steinstrasse has lessened (Coptcoat et al, 1987; Wirth et al, 1992).

The spectrum of presentation of patients suffering from steinstrasse is variable. Some patients may be entirely asymptomatic; others will present with the typical symptoms of renal colic, urinary tract infection, and renal insufficiency, with a time to presentation ranging from hours to months after SWL. More than 70% of steinstrasse occurs in the distal ureter (Coptcoat et al, 1987; Fedullo et al, 1988; Al-Awadi et al, 1999; Sulaiman et al, 1999).

The placement of a ureteral stent before SWL therapy may decrease the risk of steinstrasse. However, even when a ureteral stent is placed, steinstrasse may still occur. The management of patients suffering from steinstrasse depends on their clinical presentation. Patients with steinstrasse who are asymptomatic can often be observed initially; spontaneous stone clearance occurs in up to 60% to 80% of cases (Fedullo et al, 1988; Preminger et al, 1989; Kim et al, 1991). However, patients with bilateral obstruction, obstruction of a solitary kidney, severe refractory pain, or infected hydronephrosis should be managed with prompt urinary tract decompression by internal ureteral stenting, nephrostomy tube drainage, or ureteroscopic management. Large leading fragments unlikely to pass spontaneously and failure of expectant management are additional indications for intervention (Coptcoat et al, 1987; Weinerth et al, 1989).

When intervention is required, a minimally invasive approach is often successful. Coptcoat and associates (1988b) reported that percutaneous nephrostomy alone permitted passage of all stone fragments in 75% of cases. Dretler (1994) also recommended placement of a percutaneous nephrostomy tube for patients with pain or sepsis, reserving endoscopic intervention for afebrile patients with large leading fragments or after at least 4 weeks of observation. However, Weinerth and colleagues (1989) found that seven of nine patients initially treated with percutaneous

nephrostomy eventually required ureteroscopic basket extraction or lithotripsy. The use of prophylactic antibiotics in expectantly managed cases is recommended, as are frequent radiologic and ultrasound examinations. Failure of steinstrasse to resolve within 3 to 4 weeks may necessitate intervention (Coptcoat et al, 1987).

Should patients require a ureteroscopic intervention, success rates have been reported to be good (Coptcoat et al, 1988a; Weinerth et al, 1989). However, caution is warranted in undertaking the retrograde endoscopic treatment of a patient with steinstrasse; the complication rate of ureteroscopy may be increased over that of percutaneous nephrostomy or SWL (Al-Awadi et al, 1999). Alternatively, SWL of the lead fragment of steinstrasse also has a high reported success rate and has been associated with a low rate of complications (Kim et al, 1991; Sulaiman et al, 1999). Finally, PNL, with or without concomitant ureteroscopy, can also be used to treat patients suffering from steinstrasse (Coptcoat et al, 1988b). PNL is particularly appealing if significant stone burden remains in the kidney, as is commonly the case. Open ureterolithotomy has been reported by multiple authors as a salvage procedure for steinstrasse but is rarely required in the modern endoscopic era (Kim et al, 1991; Al-Awadi et al, 1999; Sulaiman et al, 1999).

In summary, steinstrasse is a well-known complication of SWL, with most cases resolving spontaneously. When intervention is required, percutaneous nephrostomy alone has a success rate of more than 70%. Ureteroscopic intervention is definitive and predictable, with an immediate success rate approaching 100%. Additional SWL may be successful, but the results are less predictable than with ureteroscopy. PNL may be used as a salvage procedure, with open ureterolithotomy reserved for failure or for complications of less invasive modalities.

Complications

As modern ureteroscopes have become smaller and less traumatic, as safer intracorporeal lithotripters have become widely available, and as a better understanding of the technical principles of ureteroscopy has been developed, the number of complications arising from the management of ureteral stones has been steadily decreasing.

Fortunately, most of the complications caused by ureteral stones and their management respond favorably to simple drainage of urine with ureteral catheters or stents.

Perforation. As is true with most ureteroscopic complications, the incidence of ureteral perforation has decreased over time, as technology and technique continue to improve. In a series of ureteroscopic procedures reported in 1992, ureteral perforation was reported in approximately 15% of cases. More recent series report a perforation rate of 0% to 4%. **A number of actions may result in a ureteral perforation; some of the more commonly encountered scenarios include the splitting of a ureter after balloon dilation or a traumatic injury due to forceful and misdirected manipulation of a stone.** In some cases an intracorporeal device such as a lithotrite or electrocautery can cause full-thickness damage to the ureter. The incidence of ureteral perforation varies among the different intracorporeal lithotrites, with the highest incidence of ureteral perforation occurring with electrohydraulic lithotripsy. Baskets and grasping devices may also cause injury, because in the process of grasping a stone or lesion it is possible to inadvertently snare part of the ureter, which may result in a perforation. In addition, the pressurized irrigation can cause perforation or calyceal rupture.

Adherence to the tenets of safe ureteroscopy will minimize the likelihood of a ureteral perforation. Nonetheless, such a complication may still occur and it is important for the urologist to be familiar with the treatment of this event. **When a ureteral perforation is recognized the ureteroscopic procedure should be terminated and a stent should be placed across the injury.** The risk of perforation underscores the importance of using saline as an irrigant, to prevent electrolyte derangements due to fluid extravasation. In cases of a severe injury, with significant extravasation of fluid, a percutaneous nephrostomy drain may also be necessary. Urinoma can result from perforation as well and may need to be drained. Antibiotics should be given because of the risk of infected urine and abscess formation. In general, a stent should be left in place for approximately 4 weeks after injury. Subsequent imaging after ureteral stent removal is mandatory, to evaluate for a proper healing and adequate drainage.

Schuster and associates (2002) found a significant association of ureteral perforation with increased operative time. This suggests that if the procedure is difficult and not progressing it is wise for the urologist to stop, place a stent, and plan for a staged procedure. The best prevention strategies are similar to the principles discussed earlier, including controlled maneuvers without force, knowing the margin of safety of the equipment being used, and always using both a working and safety guidewire.

Stricture. The development of a postoperative ureteral stricture is one of the more serious complications that may occur after ureteroscopy. Approximately 2 decades ago, the reported incidence of ureteral stricture after ureteroscopy was as high as 10%. More recently, however, the incidence of a postoperative stricture is reported to be much lower at 0.5% to 4%. It is likely that the improvements in surgical technology and technique are responsible for this dramatic reduction.

Although the cause of a ureteral stricture is likely multifactorial, certain factors have been reported to increase the patient's risk for stricture development. Roberts and coworkers (1998) reported a 24% stricture rate for stones that had been impacted an average of 11 months. Impacted stones are defined by the inability to pass a wire or catheter beyond the stone or stones that have been present and not moved for 2 months or more. Meng and coworkers (2003) have reported that a ureteral perforation may also increase the risk of stricture formation, finding that strictures occurred in 5.9% of patients who suffered a ureteral perforation during ureteroscopy. It may be that an inflammatory response that results in devascularization and ischemia promote this process, because such local changes can result in a cicatrization of the ureter. Patients with a history of ureteral surgery, pelvic radiation, and impacted stones are also at greater risk secondary to altered blood flow and poor healing. Devascularization injury can also result in ureteral necrosis, which necessitates open or laparoscopic repair. However, some patients develop a ureteral stricture in the presence of no intraoperative misadventures, suggesting that there is much about this process that remains to be elucidated.

To reduce the risk of stricture, care should be taken during all parts of the procedure, because the traumas that may increase the risk of this event are many and varied. **Overly aggressive manipulation of a ureteroscope across a narrow segment of ureter, as well as trauma or perforation from injudicious manipulation of intracorporeal devices or lithotrites may all increase the risk of stricture. Because of the reported occurrence of a postoperative ureteral stricture even after an uncomplicated ureteroscopy, it is recommended that all patients undergo postoperative imaging after ureteroscopic instrumentation to ensure that such a complication is recognized.** Although most patients with a stricture will be symptomatic, some will not be, so

imaging is necessary in all patients to exclude such cases of silent obstruction because there is a risk of renal loss if it is not identified. In one study 23% of those with postoperative obstruction, 2.9% of the total cohort, had silent obstruction (Weizer et al, 2002).

The management of a postureteroscopic ureteral stricture will depend primarily on its length and location, although other factors such as the time elapsed since injury, nature of trauma, and patient-specific parameters merit consideration. For many short strictures, endoscopic management may be appropriate, and incision and dilation may yield a good result. For longer strictures, however, ureteral reconstruction can be more complex, requiring either open or laparoscopic repair. The types of reconstruction available are essentially the same as those for ureteral avulsion. If a stricture is short but has failed endoureterotomy, a ureteroureterostomy may be possible after the affected portion has been resected.

Submucosal Stone/Lost Stone. The submucosal stone and the lost stone represent two points on a continuum of iatrogenic displacement of a ureteral calculus into the wall of the ureter. Extrusion of a urinary calculus may occur in up to 2% of ureteroscopic procedures. When the stone only migrates to the submucosa, a problematic complication can develop, because removal of such stones is difficult. If submucosal stones are encountered, laser excision followed by ureteral stent placement is recommended. Submucosal stones are of concern, because they can increase the risk of ureteral stricture formation.

Complete extrusion of a calculus, also known as a "lost stone," can occur in the setting of a ureteral perforation. In most cases, if the fragment is completely outside the collecting system it can be left in place. Attempts to retrieve the stone may exacerbate the injury as well as increase the risk of significant irrigant extravasation. When an extruded stone is recognized, the procedure should be terminated and a ureteral stent placed. Antibiotics should be administered to prevent the theoretical risk of abscess formation, although such a complication would be rare. One of the most serious sequelae of such an event is the later development of a ureteral stricture; for this reason patients who suffer this complication should undergo postoperative imaging. Additionally, patients with an extruded stone should also undergo imaging to confirm the location of the stone and they should be informed of this finding. It is possible that, in the future, the "lost" stone could be confused for a ureteral stone, and it is important for the patient to be aware that such a situation exists.

Avulsion. Perhaps the most catastrophic complication that can occur during a ureteroscopic procedure is avulsion of the ureter. Fortunately, such a complication is a rare occurrence, reported in less than 1% of all cases; in fact, a recent review of over 1000 patients undergoing ureteroscopy reported no episodes at all of ureteral avulsion (Krambeck et al, 2006b). **Ureteral avulsion generally occurs as a consequence of overly forceful manipulation of a large or impacted calculus.** It has been reported that the proximal one third of the ureter may be at greatest risk for avulsion, because it is the portion of the ureter that has the least muscular tissue support. A ureteral avulsion is usually diagnosed when a portion of the ureter is withdrawn from the patient, along with the stone and basket or grasper.

There are a number of maneuvers the urologist can undertake to avoid a ureteral avulsion. Blind basketing, the removal of a ureteral calculus without the aid of endoscopy, may increase the risk of ureteral avulsion and should never be considered an appropriate method of stone extraction. In fact, even endoscopically guided basketing should be reserved for small stones only. In general, a safe ureteroscopic procedure relies on the placement of both safety and working guidewires. **Before engaging a stone in a basket or grasping device, it should be endoscopically evaluated, to determine if it is of a size that would be likely to be extracted out of the ureter. When the stone is engaged in the basket or grasper, the stone and device should both be kept under direct vision as they are extracted, so that the size of the stone can be continually compared with the size of the ureteral lumen.** If the stone appears to be too large to be removed intact, it should be fragmented into smaller pieces that may either pass spontaneously or be extracted. If a stone too large to pass through the ureter is inadvertently engaged with a basket or grasping device, it should be released or replaced more proximally. Should it not be possible to release the stone the basket should be disassembled and the ureteroscope passed alongside of the basket and the entrapped stone fragmented in situ. The use of a grasping device, rather than a basket, may simplify the release of an entrapped stone. The great benefit of having a safety wire in place is that should a stone become entrapped in the ureter a ureteral stent may be placed that will passively dilate the upper urinary tract and perhaps permit a more straightforward procedure at a later date.

Should a ureteral avulsion occur, a reasoned and considered approach to the management of the affected patient is advisable. Although it may be tempting to perform an immediate primary repair at the time of injury, in general a delayed repair is recommended. The patient should undergo immediate diversion of the renal unit with the placement of a percutaneous nephrostomy drain. In some cases, a urinoma may develop as a consequence of urinary extravasation; these collections are generally amenable to percutaneous drainage. Subsequent ureteral reconstruction techniques depend on the location of the injury and the amount of viable ureter that remains. For extensive injuries the treatment options are generally limited to ileal interposition (ileal ureter) or renal autotransplantation. Although a transureteroureterostomy may be a replacement option for some patients who suffer a ureteral injury, this repair technique is contraindicated in stone formers. For a more distal ureteral injury, a ureteral reimplantation with either a psoas hitch or Boari flap may also be successful. Nephrectomy has been reported to be an option for these patients as well; however, given the recurrent nature of stone disease and the fact that stone formers may be at increased risk for hypertension and diabetes, this approach is controversial.

Ureteroscopic Management of Intrarenal Calculi

Huffman and associates (1983) first described the removal of large renal pelvic calculi with a rigid rod-lens ureteroscope and an ultrasonic lithotripter. However, rigid ureteroscopy is generally limited to stones in ureteral locations, because it is usually impossible to negotiate a rigid ureteroscope into the renal collecting system. In the decades since this initial report of ureteroscopic treatment of renal calculi, the therapeutic potential of ureteroscopy has been greatly advanced, primarily owing to the popularization of flexible, fiberoptic ureteroscopy. Over the previous 2 decades, advances in fiberoptic technology have facilitated the development of practical flexible ureteroscopes; concomitant improvements in flexible intracorporeal lithotripters as well as intracorporeal grasping devices have promoted the use of flexible ureteroscopes for the treatment of renal calculi with a high degree of success.

Fuchs and Fuchs (1990) reported the first large series of patients with renal calculi who were treated by flexible ureteroscopy. In all cases, flexible ureteroscopy was performed following a 1- to 2-week period of ureteral stent placement. The overall stone-free rate was 87%, and the only complications reported were two cases of sepsis. The subsequent introduction of more miniaturized, flexible, actively deflectable ureteroscopes (7.5 Fr) has permitted the majority of ureteroscopic procedures to be performed without routine ureteral dilation. In a large series of patients with renal stones who underwent treatment with holmium laser lithotripsy, ureteral dilation was necessary in only 185 (31%) (Sofer and Denstedt, 2000). Numerous baskets and graspers now allow full deflection of flexible ureteroscopes, facilitating treatment of often difficult-to-access lower pole stones (Lukasewycz et al, 2004; Pearle et al, 2005).

As ureteroscopic technology has advanced, and as surgeons have gained increasing comfort with this technique, this intervention has become an increasingly common treatment for patients with renal calculi. Single session success rates, generally defined as successful fragmentation with complete stone clearance or the presence of "clinically insignificant" residual fragments, are reported to be in the 70% to 80% range (Mariani, 2007; Ricchiuti et al, 2007; Breda et al, 2008). Even greater success rates may be achieved after a secondary procedure. Complication rates are low, with fever and urinary tract infection being the most commonly encountered adverse events. Even the treatment of staghorn calculi has been described, although this is not a widely used technique (Mariani, 2007)

Technique

Proximal ureteral and intrarenal calculi can be accessed with actively deflectable, flexible ureteroscopes. Although, historically, a ureteral stent was left indwelling before ureterorenoscopy, this maneuver is currently necessary only when difficulty is encountered introducing the flexible ureteroscope into the ureter. If necessary, the stent is left for 2 to 4 weeks before the procedure (Erhard et al, 1996). The use of small-diameter ureteroscopes minimizes the necessity of ureteral dilation for stone access and may decrease associated morbidity. In cases of multiple stones or large stone burden requiring multiple passages of a basket, a ureteral access sheath may facilitate stone removal. A comparative study of ureteroscopic lithotripsy with or without access sheath showed that operative time was significantly reduced by use of the access sheath, despite a greater mean stone burden in the access sheath group (Kourambas et al, 2001).

When a retrograde ureteroscopic approach is used to treat patients with intrarenal calculi, two wires are placed initially. The flexible ureteroscope is passed over one working wire in a monorail fashion. Saline is used for irrigation. When an implement is present within the working channel, simple gravity irrigation is inadequate and pressurized irrigation is required. The holmium:YAG laser lithotripter is used in almost all cases, and the laser energy required usually does not exceed 1 J and 15 Hz. Stones in lower pole calyces can be treated in situ or moved, with flexible graspers or a basket, into a position that allows better visualization. A head-down patient position with the ipsilateral flank elevated may help with stone and fragment visualization because fragments tend to migrate superiorly and are thus more easily localized during treatment. When access into the lower pole is difficult, prone positioning of the patient with the head down 20 degrees has been shown to provide the broadest angle of entry to the lower pole infundibulum (Bercowsky et al, 1999). The goal of holmium laser lithotripsy is to reduce the stone to fine dust and to small fragments 2 mm or less in diameter. If the stone is large, the collecting system may often become lined with fine dust and debris, which can obscure residual stones. Furthermore, poor visualization may lead to perforation. In such cases, either the irrigant in the intrarenal collecting system may be aspirated through the ureteroscope or a ureteral stent can be placed and the situation approached in a staged fashion.

Fragmentation of stones in situ in the lower pole can be challenging. If the lower pole infundibulum is accommodating, the most straightforward way to treat the stone is to engage it in a nitinol basket and displace it to the renal pelvis or an upper pole calyx. In this way it is generally a straight passage of the scope, with minimal deflection of the tip, which will simplify ureteroscopic laser lithotripsy. Residual fragments also should be more likely to evacuate spontaneously from the kidney.

Ureteral Access Sheath

The utilization of a ureteral access sheath as an adjunct to ureteroscopy was first reported by Takayasu and Aso in 1974 as a means to simplify access to the intrarenal collecting system. It was not until more than 2 decades later that the ureteral access sheath was rediscovered and refined, simplifying the deployment and safety of these devices. The present generation of ureteral access sheaths consists of a hydrophilic outer coating, as well as a tapered transition from obturator to sheath, which facilitates their retrograde placement. The walls of the sheaths are designed not only for a slim profile but also for strength and often are reinforced so as to resist kinking.

Kourambas and associates (2001) have reported that the ureteral access sheath can be successfully deployed in over 90% of attempted placements. In this randomized, controlled study these authors also found that the use of an access sheath decreased operating room time, simplified reentry of the ureter, and, likely as a consequence of these two points, was associated with decreased operating room costs. In a larger, retrospective study from the same institution, L'Esperance and associates (2005) reported on a series of 173 patients undergoing ureteroscopy with an access sheath and compared these outcomes to those of 83 patients undergoing ureteroscopy without an access sheath. They found that the stone-free rate was significantly higher when the access sheath was employed (79% vs. 67%; $P = .042$). Portis and associates (2006) also reported on a prospective series of patients undergoing ureteroscopy with a ureteral access sheath and commented that the sheath facilitated the active extraction of all stone fragments. Finally, ureteral access sheaths may have an added benefit when treating infection-related calculi, because the use of a sheath has been reported to maintain low intrapelvic pressures during ureteroscopy (Rehman et al, 2003). Additionally, as irrigating fluid drains through the access sheath external to the patient, the need for periodic emptying of the patient's bladder during a prolonged procedure is eliminated.

Open Stone Surgery

Historically, most patients with symptomatic upper urinary tract calculi underwent open surgical lithotomy. Those patients with a small to moderate stone burden typically underwent pyelolithotomy, radial nephrolithotomy, or ureterolithotomy. For those patients harboring staghorn calculi, more extensive procedures were required, including anatrophic nephrolithotomy, extended pyelolithotomy combined with radial lithotomies, and bench surgery with autotransplantation. However, the introduction of SWL and the development of endourologic techniques for stone

removal have dramatically diminished the role of open stone surgery, especially for stone removal procedures, and open surgery is now one of the least common treatments of patients harboring upper urinary tract calculi. Matlaga and Assimos (2002) reported that of 986 surgical procedures for stone removal performed at their institution between 1998 and 2001, 0.7% were open surgical procedures. Others have reported similar findings (Table 48–14), with an incidence of open stone surgery ranging from 0.3% to 5.4% (Assimos et al, 1989; Segura, 1990; Kane et al, 1995; Paik et al, 1998).

Renal Calculi

Minimally invasive techniques have clear advantages over open surgical techniques for patients harboring small to moderate burdens in otherwise normal kidneys. In 1985, Brannen and associates retrospectively compared PNL and open surgery for the treatment of patients with renal and proximal ureteral stones. Although the overall stone-free rate was similar, those patients treated by PNL experienced a shorter hospital stay, a lower narcotic requirement, and a shorter recovery period. Preminger and associates (1985) compared 88 patients undergoing PNL with 41 patients undergoing open stone surgery and found that PNL was associated with lower postoperative morbidity, more rapid convalescence, greater satisfaction of the patient, and reduced hospital costs for stones smaller than 2.5 cm. Brown and associates (1986) have also demonstrated that PNL is more cost effective than open stone surgery because of its reduced morbidity.

A more controversial issue has been the treatment of patients harboring staghorn calculi, a condition that carries a significant risk of mortality if it is untreated. Boyce and Elkins (1974) established anatrophic nephrolithotomy as a standard treatment of patients with staghorn stones in the United States. Overall, the reported stone-free rate after open surgery for struvite calculi is about 85%, with a 30% stone recurrence rate during 6 years (Griffith, 1978). In comparing results for a combination of PNL and SWL with reported results of anatrophic nephrolithotomy, Kahnoski and associates (1986) reported stone-free rates (85%) similar to those for the open surgical procedures, although convalescence and hospital stay for PNL were shorter and blood loss was less.

Snyder and Smith (1986) compared PNL with anatrophic nephrolithotomy for patients with staghorn calculi. They reported that although the retained stone fragment rate was higher for PNL than for anatrophic nephrolithotomy (13% vs. 0%), shorter procedure times, reduced need for blood transfusions and narcotics, and far more rapid return to work were achieved with PNL.

A meta-analysis undertaken by the AUA documented stone-free rates of 81.6% for open stone surgery, 80.8% for combined PNL and SWL, 73.3% for PNL, and only 50% for SWL monotherapy (Segura et al, 1994; Preminger et al, 2005). The more invasive the procedure, the greater the stone-free rate; however, morbidity was higher as well. Although SWL carried the lowest morbidity, a greater number of unplanned post-treatment interventions were necessary. The AUA concluded that for most patients, neither SWL monotherapy nor open stone surgery should be the first-line treatment of staghorn stones. As a guideline, PNL, followed by SWL or repeated PNL procedures as warranted, should be used for most patients with struvite staghorn calculi.

There are no strict guidelines that define which patient should undergo an open surgical procedure for stone removal. Some indications, such as a stone burden too large for PNL, clearly rely on the surgeon's judgment and experience and the availability of equipment. Also, those patients harboring calculi that may require multiple PNL or SWL treatments may be good candidates for an open procedure. Although a single open surgical procedure may seem to be the optimal procedure in the short term, the inevitable scar tissue that develops will compromise any future stone removal procedures. A small group of patients whose conditions are refractory to PNL, SWL, and ureteroscopy may require an open surgical procedure as a salvage technique.

Nephrectomy remains an option for patients with nonfunctioning kidneys or stone disease with a normal contralateral kidney. Partial nephrectomy is also an option for a stone in a localized area of irrevocably poor function. In addition, patients with an associated anatomic abnormality requiring open operative intervention, such as UPJ obstruction and infundibular stenosis, may be candidates for an open surgical approach. Some patients requiring open surgery unrelated to their urologic problem may also benefit from a simultaneously performed open procedure.

Ureteral Calculi

Although ureterolithotomy has been a time-honored technique for many decades it is seldom performed in the modern, endourologic era. A meta-analysis undertaken by Segura and associates (1997) for the AUA demonstrated median stone-free rates of 87% and 90% for stones in the distal ureter treated by open surgical removal and ureteroscopy, respectively. In the proximal ureter, the stone-free rate for ureterolithotomy was 97% compared with 83% and 72% for SWL and ureteroscopy, respectively. Although the results of open surgery in the proximal ureter were somewhat better than those of minimally invasive techniques, the greater morbidity and longer hospitalization associated with open surgery favored a primary endourologic solution for ureteral stones. Further miniaturization of ureteroscopes, combined with the now widespread availability of the holmium:YAG laser, has increased the success rate for a ureteroscopic approach to proximal ureteral calculi. Grasso and Bagley (1998) have reported a large series of patients undergoing ureteroscopy for proximal ureteral calculi, finding a 97% stone-free rate. Open surgery for patients with ureteral stones is now indicated only as a salvage procedure, when a planned abdominal operation coincides with a symptomatic ureteral stone episode, or when another ureteral abnormality requires open surgical repair.

Laparoscopic Renal Stone Removal

Laparoscopic ureterolithotomy has been previously discussed; the focus of the following section is on laparoscopic treatment of renal calculi. The advent of laparoscopic renal stone removal procedures has provided the urologist with another means to circumvent open stone surgery. Every type of "lithotomy" procedure has been reported by use of a laparoscopic approach (Raboy et al, 1992; Winfield et al, 1993; Ruckle and Segura, 1994; Van Cangh et al, 1995; Harmon et al, 1996; Deger et al, 2004). However, a laparoscopic approach to stone removal should be considered only if the results with SWL or endoscopic approaches are expected to be poor.

There are certain cases in which a laparoscopic lithotomy may be considered a reasonable therapy. Situations that may benefit from a laparoscopic approach include the following: pyeloplasty with pyelolithotomy; patients harboring stones in poorly functioning polar areas or with nonfunctioning kidneys; pelvic kidneys containing a large stone volume, in which laparoscopic techniques can be used to reflect overlying bowel, allowing pyelolithotomy or percutaneous stone removal; and ureterolithotomy for the extremely rare endoscopic failure. In present practice, however,

the utilization of laparoscopy in the treatment of renal calculi has been reported to be limited; Desai and Assimos (2008) reported that only 1% of patients require such an approach. In this series, the most common indication for a laparoscopic approach was renal stones with a concomitant UPJ obstruction.

Key Points: Stone Removal: Surgical Techniques and Technology

- The holmium:YAG laser is one of the safest, most versatile, and most effective intracorporeal lithotripters and has become the standard lithotrite for the ureteroscopic approach.
- For patients undergoing PNL, a rigid lithotripter, such as a combination ultrasonic/ballistic device, will provide for more efficient stone removal than will a flexible lithotripter.
- For PNL, the preferred point of entry into the collecting system is along the axis of the calyx, through the papilla.
- The goal in selecting access for PNL is to remove the greatest stone burden with the rigid nephroscope, thereby maximizing the efficiency of the procedure.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter 49

Malignant Renal Tumors

Steven C. Campbell, MD, PhD • Brian R. Lane, MD, PhD

Historical Considerations
Classification
Radiographic Evaluation of Renal Masses
Renal Cell Carcinoma
Treatment of Localized Renal Cell Carcinoma
Treatment of Locally Advanced Renal Cell Carcinoma
Other Malignant Renal Tumors

HISTORICAL CONSIDERATIONS

The introduction of nephrectomy and other subsequent surgical interventions for renal diseases provided the clinical information and histopathologic insight that form the basis of current concepts regarding renal tumors. The first documented nephrectomy was accomplished in 1861 by Wolcott, who operated with the mistaken assumption that the tumor mass was a hepatoma. In 1867, Spiegelberg removed a kidney incidentally in the course of excising an echinococcus cyst. The first planned nephrectomy was performed by Simon in 1869 for persistent ureteral fistula, and this patient survived with cure of the fistula. One year later (1870), the first planned nephrectomy in the United States was successfully accomplished by Gilmore in Mobile, Alabama, for treatment of atrophic pyelonephritis and persistent urinary tract infection (Glenn, 1980; Herr, 2008). Harris (1882) subsequently reported on 100 surgical extirpations of the kidney, a sufficient number to permit analysis of clinical, surgical, and pathologic features of renal disorders that require surgery.

With surgical intervention, tissue became available to pathologists for histologic interpretation. Unfortunately, such interpretation was not always accurate, and there were often serious professional differences of opinion. According to Carson (1928), the first accurate gross description of kidney tumors dates to 1826, with Konig's observations. In 1855, Robin examined solid tumors apparently arising in the kidney and concluded that renal carcinoma arose from renal tubular epithelium. This interpretation was confirmed by Waldeyer in 1867. Unfortunately, theoretical and practical considerations of renal tumors were confused by Grawitz (1883), who contended that such apparent renal tumors arose from adrenal rests within the kidney. He introduced the terminology *struma lipomatodes aberrata renis* as descriptive nomenclature for the tumors of clear cells that he believed were derived from the adrenal glands. He based his conclusions not only on the fatty content of the tumors, analogous to that seen in the adrenal glands, but also on the location of the tumors beneath the renal capsule, the approximation to the adrenal glands, the lack of similarity of the cells to uriniferous tubules, and the demonstration of amyloid similar to that seen with adrenal degeneration.

This histogenetic concept was adopted by subsequent investigators, and pathologists of the era readily embraced the idea that renal tumors truly arose from the adrenal glands. In 1894, Lubarch endorsed the idea of a suprarenal origin of renal tumors, and the term *hypernephroid tumors,* indicating origin above the kidneys, was advocated by Birch-Hirschfeld (Birch-Hirschfeld and Doederlein, 1894). This semantic and conceptual mistake led to the introduction of the term *hypernephroma,* which predominated in the literature describing parenchymal tumors of primary renal origin. Some clarification of the histopathology of renal tumors was derived from the work of Albarran and Imbert (1903), and the four-volume contribution of Wolff (1883), written between 1883 and 1928, added further historical significance to the understanding of renal tumors (Glenn, 1980).

The modern era has brought an appreciation that renal cell carcinoma (RCC) includes a number of distinct subtypes derived from the various parts of the nephron, each with a unique genetic basis and tumor biology (Linehan et al, 2003, Cohen and McGovern, 2005; Novick, 2007; Rini et al, 2009). **Other major advances in the past several decades have included the introduction of radical nephrectomy followed by a trend toward nephron-sparing surgery and, more recently, a variety of minimally invasive approaches** (Robson, 1963; Uzzo and Novick, 2001; Abreu and Gill, 2003; Herr, 2005, 2008; Novick, 2007). **One common theme that has persisted is that RCC remains primarily a surgical disease—it is still considered the paradigm of the chemorefractory tumor;** and although immune-based and targeted molecular approaches have shown promise, overall response rates remain low (Négrier et al, 2002; Milowsky and Nanus, 2003; Escudier et al, 2007; Motzer et al, 2007; Rini et al, 2009). Unfortunately, the incidence of RCC is gradually increasing; and despite a trend toward earlier detection, mortality rates remain high.

CLASSIFICATION

Renal masses can be malignant, benign, or inflammatory as classified by Barbaric (1994) (Table 49–1), **or they can be classified based on radiographic appearance (simple cystic, complex cystic, fatty tumors, and others)** (Table 49–2). These classification schemes have been updated taking into account current knowledge about the distinct subtypes of RCC and recent advances in our understanding of the various benign and malignant tumors of the kidney (Eble et al, 2004; Cohen and McGovern, 2005; Rini et al, 2009). This approach is practical and should assist in the differential diagnosis of renal masses.

Table 49–1.

Renal Masses Classified by Pathologic Features

MALIGNANT	BENIGN	INFLAMMATORY
Renal cell carcinoma	Simple cyst	Abscess
Clear cell	Angiomyolipoma	Focal pyelonephritis
Papillary	Oncocytoma	Xanthogranulomatous pyelonephritis
Chromophobe	Renal adenoma	Infected renal cyst
Collecting duct	Metanephric adenoma	Tuberculosis
Urothelium based	Cystic nephroma	Rheumatic granuloma
Transitional cell carcinoma	Mixed epithelial/stromal tumor	
Squamous cell carcinoma	Reninoma (JG cell tumor)	
Adenocarcinoma	Leiomyoma	
Sarcoma	Fibroma	
Leiomyosarcoma	Hemangioma	
Liposarcoma	Vascular	
Angiosarcoma	Renal artery aneurysm	
Hemangiopericytoma	Arteriovenous malformation	
Malignant fibrous histiocytoma	Pseudotumor	
Synovial sarcoma		
Osteogenic sarcoma		
Clear cell sarcoma		
Rhabdomyosarcoma		
Wilms tumor		
Primitive neuroectodermal tumor		
Carcinoid		
Lymphoma		
Leukemia		
Metastasis		
Invasion by adjacent neoplasm		

Malignant renal tumors include RCC, urothelial-based lesions (addressed elsewhere), sarcomas, embryonic or pediatric tumors, and lymphomas and metastases. Benign renal tumors are diverse and present unique diagnostic challenges (see Chapter 51). Inflammatory and vascular lesions must also be considered in the differential diagnosis.

RADIOGRAPHIC EVALUATION OF RENAL MASSES

Several radiographic modalities are currently available for detection and evaluation of renal masses, each with relative strengths and limitations (Davidson et al, 1997; Zagoria, 2000; Israel and Bosniak, 2003a; Zhang et al, 2007a; Herts, 2009). A systematic approach is necessary to ensure diligent evaluation of suspected renal masses, given the large differential diagnosis and considerable overlap between benign and malignant renal lesions (Fig. 49–1; see Table 49–2) (Ananthakrishnan et al, 2007; Simmons et al, 2007).

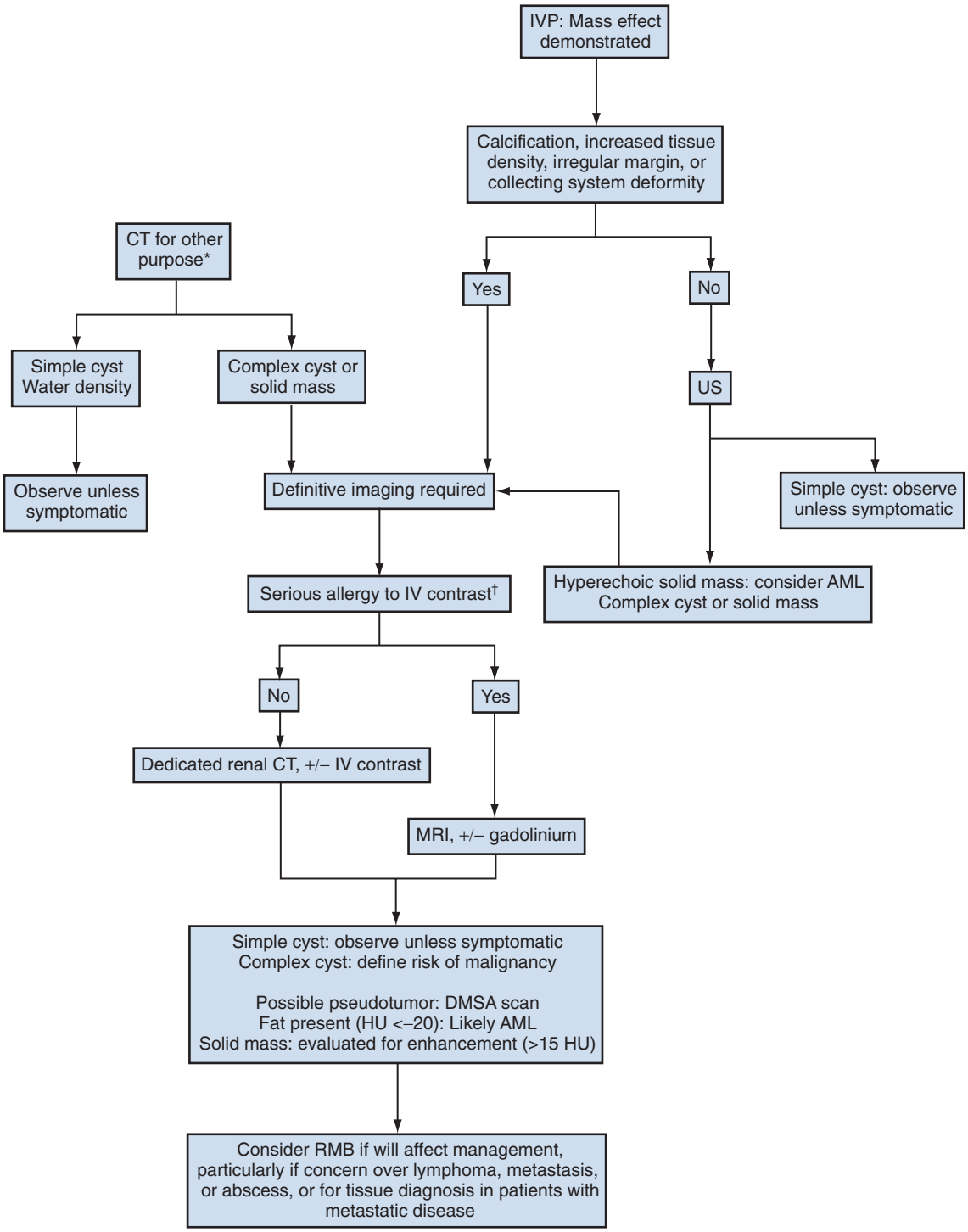
Although **intravenous pyelography** was often the first test that indicated a renal mass in the past, it is now only occasionally used for the evaluation of hematuria. **The lack of sensitivity and specificity of intravenous pyelography for the detection of parenchyma tumors is well documented.** In particular, intravenous pyelography may miss small anterior or posterior lesions that do not distort the collecting system or the contour of the kidney. **Features suggestive of malignancy on intravenous pyelography include calcification within the mass, increased tissue density, irregularity of the margin, and distortion of the collecting system** (Zagoria, 2000).

When a renal mass is identified by intravenous pyelography, unless the mass has features suggestive of malignancy, ultrasonography should be the next study

Table 49–2.

Renal Masses Classified by Radiographic Appearance

SIMPLE CYSTIC	COMPLEX CYSTIC	FATTY TUMORS	ALL OTHERS
Cyst	Cystic nephroma	Angiomyolipoma	Renal cell carcinoma
Multiple cysts	Cystic renal cell carcinoma	Lipoma	Sarcomas
Peripelvic cysts	Hemorrhagic cyst	Liposarcoma	Lymphoma, leukemia
Calyceal diverticulum	Infected cyst		Metastases
Hydronephrosis	Renal abscess		Lobar nephronia
	Septated cyst		Abscess
	Hydrocalyx		Tuberculosis
	Cystic Wilms tumor		Xanthogranulomatous pyelonephritis
	Mixed epithelial/stromal tumor		Urothelium-based tumors
	Vascular		Transitional cell carcinoma
	Renal artery aneurysm		Squamous cell carcinoma
	Arteriovenous malformation		Adenocarcinoma
	Tuberculosis		Wilms tumor
			Oncocytoma
			Renal adenoma
			Metanephric adenoma
			Reninoma (JG cell tumor)
			Leiomyoma
			Fibroma
			Hemangioma
			Carcinoid
			Primitive neuroectodermal tumor



*In this era, most renal masses are initially identified with CT obtained for other purposes, and in this setting a dedicated CT of the kidneys should be considered.
†In the presence of chronic kidney disease, the risks of contrast nephropathy must also be weighed against those of nephrogenic systemic fibrosis associated with MRI.

Figure 49–1. Algorithm for radiographic evaluation of renal masses. IVP, intravenous pyelography; US, ultrasonography; AML, angiomyolipoma; CT, computed tomography; DMSA, dimercaptosuccinic acid; MRI, magnetic resonance imaging; RMB, renal mass biopsy.

performed because it is noninvasive, accurate, and relatively inexpensive (Davidson et al, 1997; Paspulati and Bhatt, 2006). Ultrasonography is reliable for differentiation of solid tissue from fluid and can establish the diagnosis of a simple renal cyst. **Strict ultrasonographic criteria for simple cysts have been defined and include a smooth cyst wall, a round or oval shape without internal echoes, and through-transmission with strong acoustic shadows posteriorly.** If these criteria are met, observation is sufficient in an asymptomatic patient.

In evaluating complicated renal cysts, important ultrasonographic features include thickness and contour of the cyst wall, number and thickness of any septa, presence of any calcifications, density of the renal cyst fluid, and presence of solid components. ultrasonography is helpful in suggesting the fat content of an angiomyolipoma (AML) by its characteristic increased echogenicity (Nelson and Sanda, 2002). **A renal mass that is not clearly a simple cyst by strict ultrasound criteria should be evaluated further with computed tomography (CT).**

A dedicated (thin-slice) renal CT scan remains the single most important radiographic test for delineating the nature of a renal mass. CT, with and without the administration of contrast material, is necessary to take full advantage of the contrast enhancement characteristics of highly vascular renal parenchymal tumors (Davidson et al, 1997; Zagoria, 2000, Prasad et al, 2008; Ng et al, 2008; Zhang et al, 2007a). **In general, any renal mass that enhances with intravenous administration of contrast material on CT by more than 15 Hounsfield units (HU) should be considered an RCC until proved otherwise** (Fig. 49–2) (Hartman et al, 2004). **Solid masses that also have substantial areas of negative CT attenuation numbers (below –20 HU) indicative of fat are diagnostic of AMLs** (Nelson and Sanda, 2002). In 10% to 20% of solid renal masses CT findings are indeterminate, and additional testing or surgical exploration is needed to establish a definitive diagnosis. **On occasion, CT demonstrates an enhancing renal segment that is isodense with the remainder of the kidney, suggestive of a renal pseudotumor.** Renal pseudotumors may be due to a hypertrophied column of Bertin, renal dysmorphism, or an unusually shaped kidney (Bhatt et al, 2007). In this situation, the **diagnosis of a pseudotumor can be confirmed by isotope renography with technetium-labeled dimercaptosuccinic acid or glucoheptonate** (Fig. 49–3). These isotope studies demonstrate an area of increased density if the mass is a pseudotumor and an area of decreased density if the mass is a cyst or solid tumor (Israel and Bosniak, 2003a).

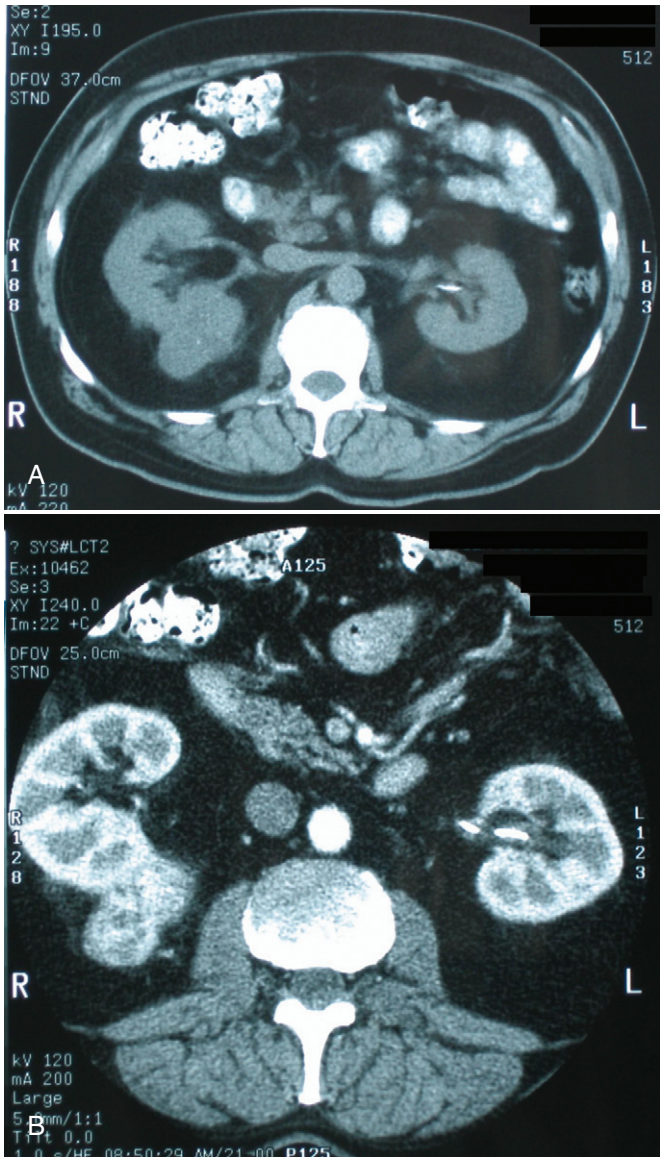


Figure 49–2. **A,** Unenhanced CT scan shows solid, right posterior renal mass. **B,** After administration of the contrast agent, CT scan shows that the mass enhances more than 20 HU and is thus highly suggestive of RCC. This mass was excised and confirmed to be a clear cell renal cell carcinoma. (Courtesy of Dr. Terrence Demos, Maywood, IL.)

Magnetic resonance imaging (MRI) is the alternate standard imaging modality for the characterization of a renal mass (Pretorius et al, 2000; Zhang et al, 2004; Bassignani, 2006). **A basic consideration in the evaluation of a renal mass is that for such a mass to be considered malignant it must enhance with the intravenous administration of contrast material. Such enhancement can now be determined equally well by magnetic resonance angiography with intravenous gadolinium-labeled diethylenetriaminepentaacetic acid, although the assessment is qualitative rather than quantitative.** On T1-weighted scans before and after administration of gadolinium, enhancement (vascularity) of the mass is detected (Fig. 49–4). This technique is most helpful in patients for whom iodinated contrast medium is contraindicated because of severe allergy. **One concern with MRI with gadolinium is the uncommon but potentially serious complication of nephrogenic systemic fibrosis (NSF), which is more common in patients with renal insufficiency** (Bach and Zhang, 2008). Current recommendations are to avoid MRI, particularly serial studies, in this population whenever possible, and to dialyze patients after the study if severe chronic kidney disease (CKD) is present. MRI was previously the imaging procedure of choice in patients with CKD and a renal mass. Now many radiologists prefer CT with intravenous contrast and careful periprocedural hydration, but decision making must be individualized. Contrast-enhanced ultrasonography using microbubbles has also shown promise for the safe characterization and assessment of enhancement of renal masses and may play an important role in patients with CKD in the future (Simmons et al, 2007).

Renal arteriography has a limited role in the diagnostic evaluation of renal masses and is primarily reserved for patients with concomitant renal artery disease. In equivocal cases, the presence or absence of neovascularity may help establish the diagnosis of RCC. However, 20% to 25% of RCCs are angiographically indistinct, even though most of these tumors are not truly avascular and demonstrate contrast enhancement by 10 to 25 HU on CT.

Renal mass biopsy is now being revisited for the evaluation of renal masses (Wunderlich et al, 2005; Lane et al, 2007b; Maturen et al, 2007; Volpe et al, 2007; Lebret et al, 2007; Strope and Wolf, 2008; Wang et al, 2009). Historically the

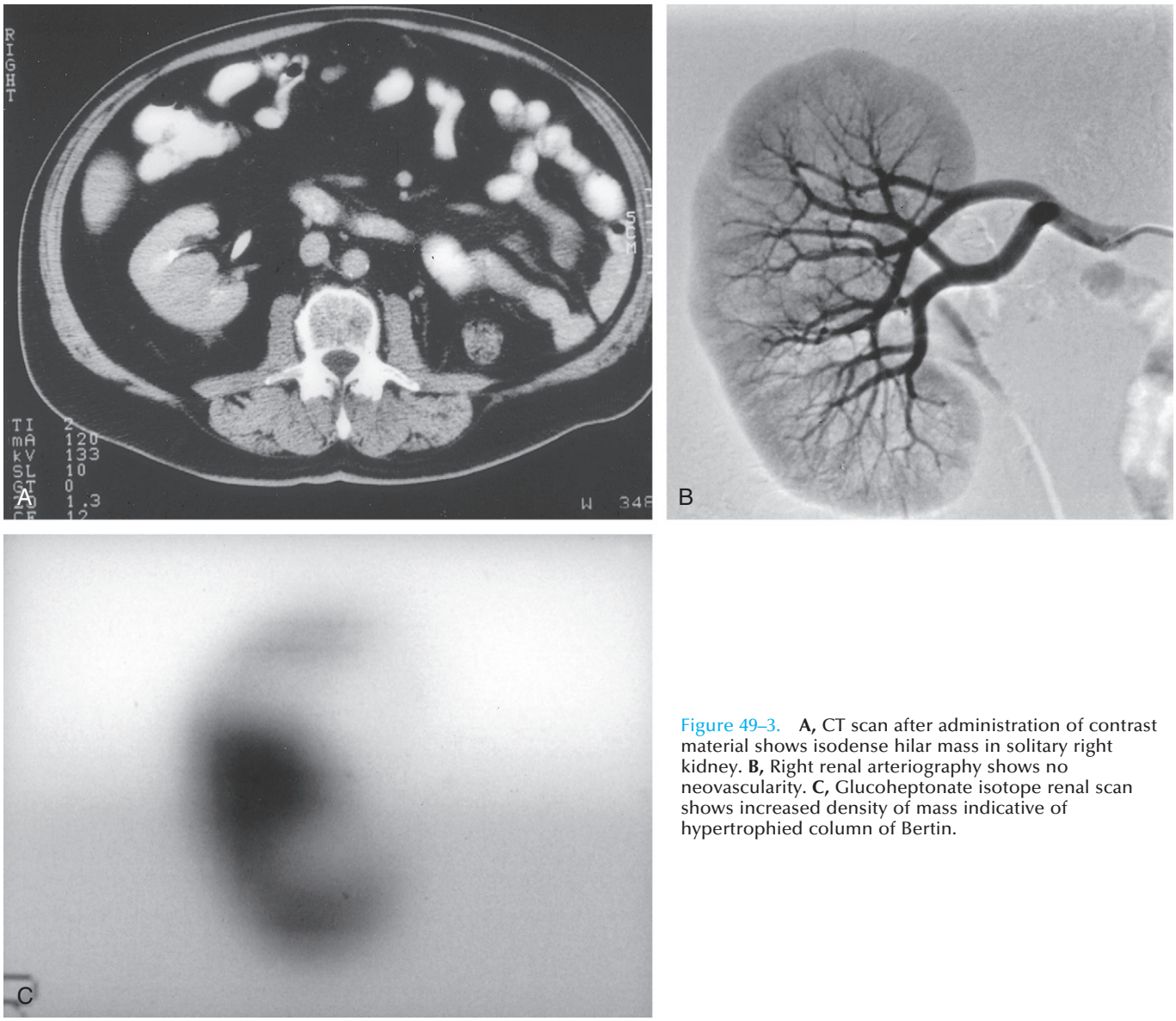


Figure 49–3. **A,** CT scan after administration of contrast material shows isodense hilar mass in solitary right kidney. **B,** Right renal arteriography shows no neovascularity. **C,** Glucoheptonate isotope renal scan shows increased density of mass indicative of hypertrophied column of Bertin.

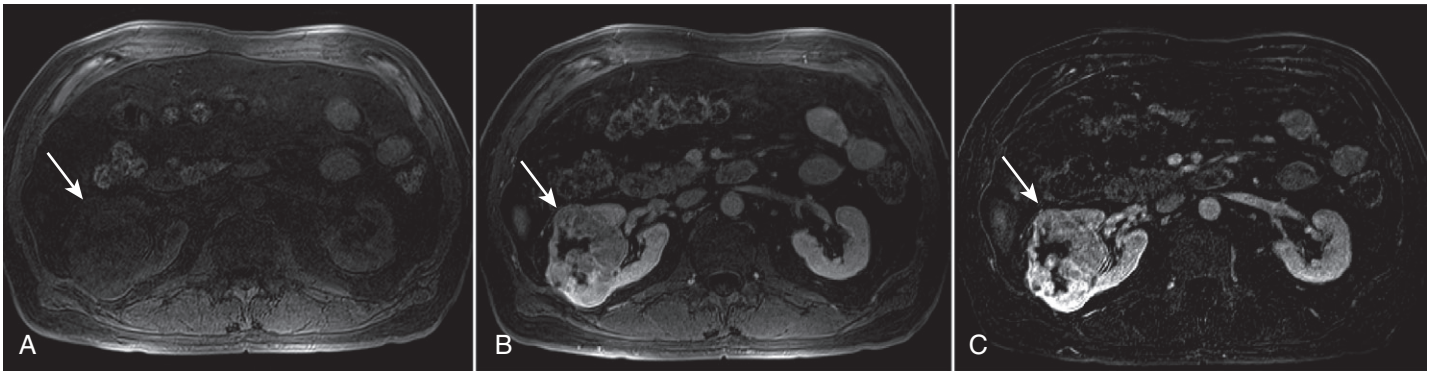


Figure 49–4. Unenhanced and contrast-enhanced MR images of renal cell carcinoma *(arrows)*. **A,** Unenhanced fat-saturated T1-weighted volume-interpolated breath-hold examination (VIBE) image. **B,** Contrast-enhanced VIBE image. **C,** Subtraction image generated by electronically subtracting image A from image B shows a large enhancing mass in the lateral anterior right kidney that is partially exophytic and extends to the central sinus. Although a subjective assessment of enhancement is often possible after contrast administration **(B),** any signal intensity remaining on the subtraction image **(C)** represents enhancement after contrast administration. (Courtesy of Dr. Brian Herts, Cleveland, OH.)

false-negative rate of renal mass biopsy was thought to be 18%, too high to justify routine use. However, most of these "false negatives" were in reality instances in which the mass could not be adequately targeted or the material obtained was insufficient for the pathologist to make a definitive determination. Review of this literature has shown that, although about 15% of renal mass biopsy specimens are nondiagnostic, the real false-negative rate was only 4% in studies prior to 2001 and less than 1% since then (Lane et al, 2007b). Overall accuracy is greater than 80%. Assessment of tumor grade and histologic type, which reflects tumor aggressiveness, is also accurate in the majority of cases (Barocas et al, 2006; Schmidbauer et al, 2008). The risks of clinically significant perinephric bleeding and pneumothorax also appear to be low (<1%), and needle tract seeding is exceedingly rare when centrally located, infiltrative renal masses are excluded. Poorly differentiated transitional cell carcinoma is much higher risk for needle tract seeding than RCC. Given the great heterogeneity in the tumor biology of enhancing clinical T1 renal masses, with 20% benign, 60% indolent RCC, and 20% potentially aggressive RCC, **renal mass biopsy is now being considered more frequently, particularly in patients who are potential candidates for a wide variety of treatment options ranging from observation to surgical excision.** Younger, healthy patients who are unwilling to accept the uncertainty associated with renal mass biopsy are still typically managed primarily based on radiographic and clinical considerations. **More traditional indications for renal mass biopsy include suspicion of renal abscess or when RCC must be differentiated from metastatic malignant disease or renal lymphoma** (Herts and Remer, 2000; Anderson et al, 2006; Vasudevan et al, 2006; Beland et al, 2007; Kummerlin et al, 2008a; Somani et al, 2007; Shannon et al, 2008; Volpe et al, 2008).

The differentiation between a benign renal cyst and a cystic RCC remains one of the more common and difficult problems in renal imaging (Balci et al, 1999; Harada et al, 2002; Kausik et al, 2002; Israel and Bosniak, 2005; Warren and McFarlane, 2005). When a complex renal cyst is identified, determination of its benign or malignant nature is based on evaluation of the wall of the lesion; its thickness and contour; the number, contour, and thickness of any septa; the amount, character, and location of any calcifications; the density of fluid in the lesion; the margination of the lesion; and the presence of solid components. **Bosniak developed a useful classification scheme primarily based on CT imaging criteria that divides renal cystic lesions into categories that are distinct from one another in terms of the likelihood of malignancy** (Bosniak, 1997; Israel and Bosniak, 2005). **Category I lesions are uncomplicated, simple, benign cysts** of the kidney that are straightforward to diagnose on ultrasonography, CT, or MRI. These are by far the most common renal cystic lesions, and **in the absence of associated symptoms, no treatment is necessary.**

Category II lesions are minimally complex cysts that are generally benign but have some radiologic findings that cause concern (Fig. 49–5). **These lesions include septated cysts, cysts with calcium in the wall or septum, infected cysts, and hyperdense (high-density) cysts** (Bosniak, 1997; Israel and Bosniak, 2005). Hyperdense cysts are benign lesions that contain old, degenerated, or clotted blood; therefore, the CT attenuation of their contents is increased (>20 HU). Classic hyperdense renal cysts are small (<3 cm), round, and sharply marginated and do not enhance after the administration of contrast material (Fig. 49–6). **This category has now been subdivided to differentiate category II lesions that do not require surveillance from category IIF lesions that mandate surveillance. The nuances involved in this classification are highlighted in** Table 49–3. High-quality imaging, preferably CT, and considerable radiologic expertise are required to optimize the characterization of complex renal cystic lesions. The risk of malignancy for category IIF renal cysts is 5% to 10%, and these lesions should be observed with periodic renal imaging (Kausik, 2002; Israel and Bosniak, 2003b, 2005).

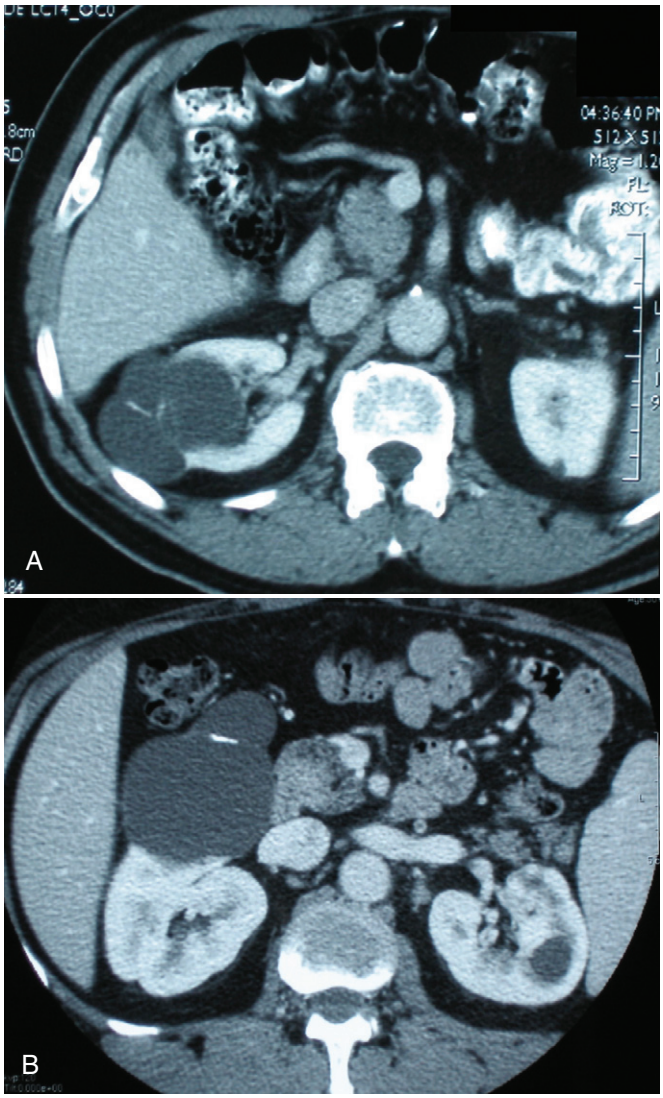


Figure 49–5. Bosniak class II renal cysts. **A,** CT scan shows right renal cyst with thin internal septation. **B,** CT scan in another patient shows relatively thin, curvilinear calcification in the septa of the wall of right renal cyst. (Courtesy of Dr. Terrence Demos, Maywood, IL.)

Category III lesions are more complex renal cysts that cannot be confidently distinguished from malignant neoplasms (Kausik, 2002; Israel and Bosniak, 2005). **The radiographic features include thickened irregular or smooth walls or septa in which measurable enhancement can be observed** (Fig. 49–7). In the absence of a mitigating factor such as renal trauma or infection, surgical exploration is usually indicated in healthy patients. About 50% of these lesions are malignant; the remainder prove to be benign multiloculated, hemorrhagic, or densely calcified cysts (see Table 49–2). Fine-needle aspiration of complex cysts is rarely performed because of concern about sampling error and tumor cell spillage.

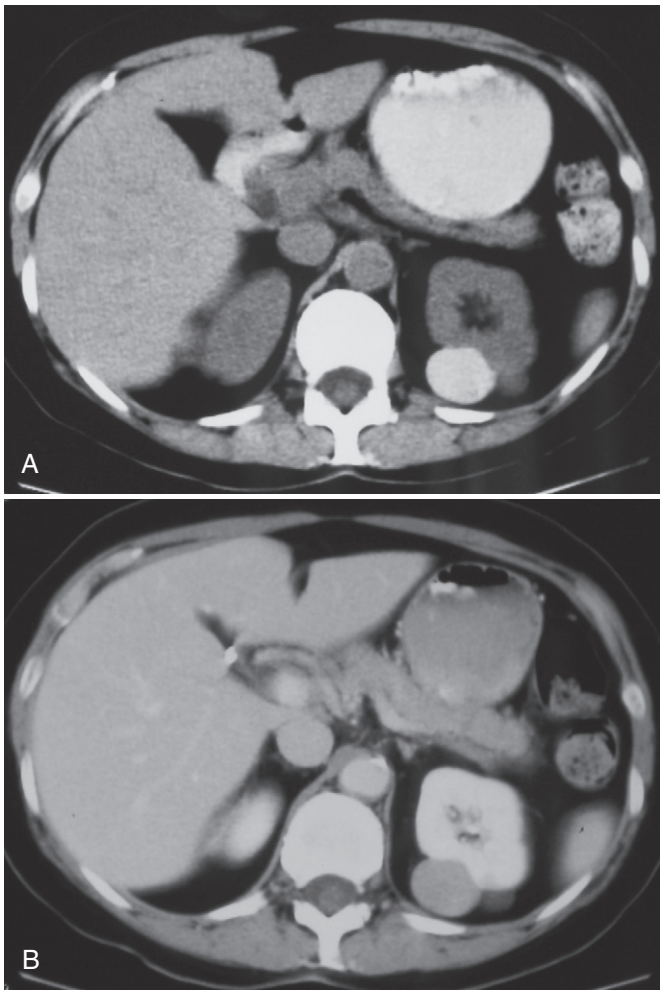


Figure 49–6. Bosniak class II hyperdense cyst. **A,** Unenhanced CT scan shows small, smooth-walled, high-density left renal cyst. **B,** CT scan after administration of contrast material shows no enhancement of the cyst. This is an extreme example of a hyperdense cyst. (Courtesy of Dr. Terrence Demos, Maywood, IL.)

Category IV lesions have large cystic components; irregular, shaggy margins; and, most important, solid enhancing portions that provide a definitive diagnosis of malignancy (Fig. 49–8) (Bosniak, 1997; Israel and Bosniak, 2003c, 2005). Category IV lesions are almost invariably cystic RCCs that, if localized, require surgical treatment.

For radiographically detected solid renal masses, the differential diagnosis is extensive and includes conditions such as RCC, oncocytoma, AML, transitional cell carcinoma, metastatic tumor, abscess, infarct, vascular malformation, and renal pseudotumor (see Table 49–2). The diagnosis of most of these lesions can be established on the basis of the clinical presentation and the characteristic radiographic features (Table 49–4), occasionally combined with endourologic studies or needle biopsy of the mass (Simmons et al, 2007; Dyer et al, 2008). **However, it is not possible to reliably distinguish RCC from benign renal neoplasms, including oncocytoma and fat-poor AML, with current diagnostic techniques. Ten to 20 percent of small, solid, CT-enhancing renal masses with features suggestive of RCC prove to be benign after surgical excision** (Silver et al, 1997). Although oncocytoma is a benign tumor (see Chapter 51), it can be multifocal and is occasionally associated with RCC in the same or the opposite kidney (Licht, 1995; Dechet, 1999).

RENAL CELL CARCINOMA

Incidence

RCC, which accounts for 2% to 3% of all adult malignant neoplasms, is the most lethal of the common urologic cancers. Traditionally, 30% to 40% of patients with RCC have died of their cancer, in contrast to the 20% mortality rates associated with prostate and bladder carcinomas (Landis et al, 1999; Pantuck et al, 2001b). Approximately 54,000 new diagnoses of RCC are made each year in the United States, and 13,000 patients die of disease (Russo et al, 2008, Carrizosa and Godley, 2009; Jemal et al, 2009). **Overall, approximately 12 new cases are diagnosed per**

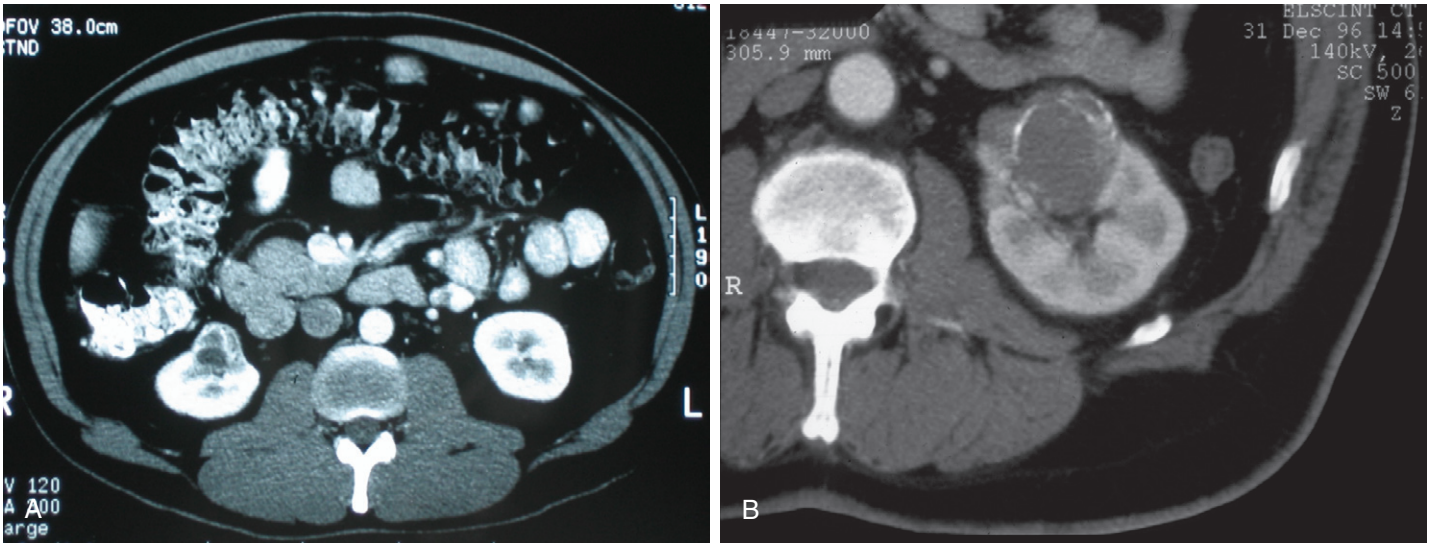


Figure 49–7. Bosniak class III cysts. **A,** CT scan shows complex right renal cyst with thick and irregular septa and inhomogeneous character. **B,** CT scan shows somewhat thick-walled, complex left renal cyst also exhibiting irregular calcification and moderate heterogeneity. (Courtesy of Dr. Terrence Demos, Maywood, IL.)

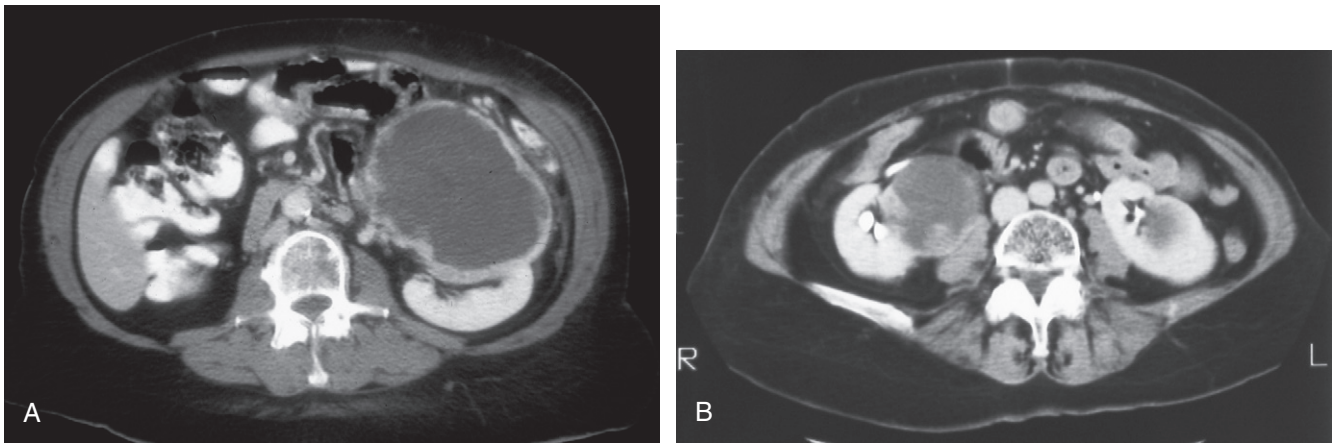


Figure 49–8. Bosniak class IV cysts. **A,** CT scan shows complex left renal cystic lesion with thick, enhancing walls. **B,** CT scan shows complex right cystic lesion with enhancing nodular areas and inhomogeneity. Both lesions proved to be renal cell carcinoma.

Table 49–3.

Classification of Complex Renal Cysts

BOSNIAK CLASSIFICATION	RADIOGRAPHIC FEATURES	RISK OF MALIGNANCY	MANAGEMENT
I	Water density Homogeneous, hairline thin wall No septa No calcification No enhancement	None	Surveillance not necessary
II	Few hairline thin septa in which "perceived" enhancement may be present Fine calcification or short segment of slightly thickened calcification in wall or septa No unequivocal enhancement	Minimal	Surveillance not necessary
IIF	Hyperdense lesion (≤3 cm), well marginated, with no unequivocal enhancement Multiple hairline thin septa Minimal smooth wall thickening "Perceived" enhancement of wall or septae may be present Calcification may be thick and nodular but must be without enhancement Generally well marginated No unequivocal enhancement	Minimal 3%-5%	Periodic surveillance
	Hyperdense lesion >3 cm or totally intrarenal, with no enhancement	5%-10%	Periodic surveillance
III	"Indeterminate," thickened irregular or smooth walls or septa in which measurable enhancement is present	50%	Surgical excision
IV	Clearly malignant lesions that can have all the criteria of category III but also contain enhancing soft tissue components	75%-90%	Surgical excision

100,000 population per year, with a male-to-female predominance of 3:2 (Landis et al, 1999; Wallen et al, 2007; DeCastro and McKiernon, 2008; Woldrich et al, 2008; Carrizosa and Godley, 2009). **This is primarily a disease of the elderly patient, with typical presentation in the sixth and seventh decades of life** (Pantuck et al, 2001b; Wallen et al, 2007). Incidence rates are 10% to 20% higher in African Americans for unknown reasons (Chow et al, 1999, Lipworth et al, 2006; Stafford et al, 2008). **The majority of cases of RCC are believed to be sporadic; only 2% to 3% are familial** (Lipworth et al, 2006).

The incidence of RCC has increased since the 1970s by an average of 3% per year for whites and 4% per year for African-Americans, largely related to the more prevalent use of ultrasonography and CT for the evaluation of a variety of abdominal complaints (Chow et al, 1999; DeCastro and McKiernon, 2008; Kummerlin et al, 2008b). This trend has correlated with an increased proportion of incidentally discovered and localized tumors and with improved 5-year survival rates for patients with this stage of disease (Konnak and Grossman, 1985; Thompson and Peek, 1988; Kessler et al, 1994; Pantuck et al, 2001b; Parsons et al, 2001, Kane et al, 2008). However, other factors must also be at play because Chow and colleagues (1999) have documented a steadily increasing mortality rate from RCC per unit population since the 1980s, and this was observed in all ethnic and both sex groups. They reported that the incidence of advanced tumors per unit population has also increased; and although the proportion of advanced tumors has decreased, the mortality rate per unit population has still been negatively affected (Chow et al, 1999; Hock et al, 2002; Wallen et al, 2007; DeCastro and McKiernon, 2008). This suggests that a deleterious change in tumor biology may have occurred during the past several decades, perhaps related to tobacco use, dietary factors, or exposure to other carcinogens (Chow et al, 1999; Pantuck et al, 2001b; Hock et al, 2002; Parsons et al, 2002; Kane et al, 2008).

Table 49–4.

Radiologic and Pathologic Correlates for Renal Masses

SIMPLE CYSTIC	COMPLEX CYSTIC	FAT-CONTAINING MASS	CALCIFIED MASS	STRONGLY ENHANCING SOLID MASS	MODERATELY ENHANCING SOLID MASS	INFILTRATIVE MASS	MULTIFOCAL/ BILATERAL MASSES
Benign cyst	Cystic RCC	AML		Clear cell RCC	Papillary RCC	Lymphoma	Familial RCC
Peripelvic cyst	Hemorrhagic cyst	Liposarcoma	RCC	AML	Chromophobe RCC	High-grade TCC	Metastases
Hydronephrosis	Hyperdense cyst	Lipoma	TCC	Occasional papillary RCC	Oncocytoma	Sarcomatoid RCC	Sporadic, multifocal RCC
Caliceal diverticulum	Benign complex cysts		Benign complex cyst	Occasional chromophobe RCC	Other benign tumors	Collecting duct RCC	AML (TS)
	Cystic nephroma MESTK		XGP	Occasional oncocytoma	Fat-poor AML	Medullary cell RCC	Lymphoma
	Cystic Wilms tumor		Renal artery aneurysm		Adenoma	XGP	Cystic tumors (ADPKD)
	Infected cyst/ abscess		Concomitant nephrolithiasis		Metanephric adenoma	Occasional metastases	
	Hydrocalix				Unifocal lymphoma		
	Arteriovenous malformation				Sarcoma		
	Renal artery aneurysm				Lobar nephronia		
					Infarct		

ADPKD, autosomal dominant polycystic kidney disease; AML, angiomyolipoma; MESTK, mixed epithelial/stromal tumor of the kidney; RCC, renal cell carcinoma; TCC, transitional cell carcinoma; TS, tuberous sclerosis; XGP, xanthogranulomatous pyelonephritis.

Adapted from Simmons MN, Herts BR, Campbell SC. Image based approaches to the diagnosis and treatment of renal masses [lesson 39]. AUA Update Series 2007;26:382–91.

RCC in childhood is uncommon, representing only 2.3% to 6.6% of all renal tumors in children (Castellanos et al, 1974; Chan et al, 1983; Freedman et al, 1996; Asanuma et al, 1999; Broecker, 2000). Mean age at presentation in children is 8 to 9 years, and the incidence is similar in boys and in girls. **Although Wilms tumor is much more common in younger children, RCC is as common as Wilms tumor during the second decade of life.** RCC in children and young adults is more likely to be symptomatic and to exhibit papillary histology, and a predilection for locally advanced, high-grade disease, and unfavorable histologic subtypes has also been reported (Freedman et al, 1996; Renshaw et al, 1999; Sánchez-Ortiz et al, 2004b; Cook et al, 2006; Estrada et al, 2005). TFE3 protein overexpression, which correlates with the presence of *ASPL-TFE3* and *PRCC-TFE3* gene translocation events involving the X and first chromosomes, is relatively common in children and young adults with RCC and is unique to this population (Heimann et al, 2001; Geller et al, 2008). The clinical significance of TFE3 protein overexpression is not well defined, although preliminary data suggest that these tumors may show differential sensitivity to certain chemotherapeutic agents (Argani et al, 2002; Heimann et al, 2001; Perot et al, 2003; Bruder et al, 2004). **Most studies suggest that stage for stage, children and young adults with RCC may respond better to surgical therapy,** and a number of long-term survivors have been reported after radical nephrectomy and lymphadenectomy for lymph node–positive disease (Freedman et al, 1996; Asanuma et al, 1999; Abou El Fettouh et al, 2002; Geller et al, 2008; Sánchez-Ortiz et al, 2004b; Geller et al, 2008). **An aggressive surgical approach with formal lymphadenectomy has thus been recommended at the time of radical nephrectomy when RCC is suspected in children or young adults** (Freedman et al, 1996; Asanuma et al, 1999; Geller et al, 2008; Selle et al, 2006; Bosquet et al, 2008).

Table 49–5.

Etiology and Environmental Factors of Malignant Renal Tumors

Established

Tobacco exposure
Obesity
Hypertension

Putative

Lead compounds
Various chemicals (e.g., aromatic hydrocarbons)
Trichloroethylene exposure
Occupational exposure (metal, chemical, rubber, and printing industries)
Asbestos or cadmium exposure
Radiation therapy
Dietary (high fat/protein and low fruits/vegetables)

Etiology

RCCs were traditionally thought to arise primarily from the proximal convoluted tubules, and this is probably true for the clear cell and papillary variants. However, it is now established that other histologic subtypes of RCC, such as chromophobe and collecting duct RCC, are derived from the more distal components of the nephron (Störkel, 1996; Oyasu, 1998; Pantuck et al, 2001a).

The most generally accepted environmental risk factor for RCC is tobacco exposure, although the relative associated risks have been modest, ranging from 1.4 to 2.5 compared with controls (Table 49–5). All forms of tobacco use have been implicated, and risk increases with cumulative dose or

pack-years (Kantor, 1977; La Vecchia et al, 1990; McLaughlin et al, 1995; McLaughlin and Lipworth, 2000; Moyad, 2001; Dhote et al, 2004; Lindblad, 2004; Lipworth et al, 2006; Carrizosa and Godley, 2009). Relative risk is directly related to duration of smoking and begins to fall after cessation, further supporting a cause-and-effect relationship (La Vecchia et al, 1990; McLaughlin et al, 1995; Parker et al, 2003b). Tobacco use accounts for 20% to 30% of cases of RCC in men and 10% to 20% in women (McLaughlin et al, 1995; McLaughlin and Lipworth, 2000).

Obesity is now accepted as another major risk factor for RCC with an increased relative risk of 1.07 for each unit of rising body mass index (Chow et al, 2000; Bergstrom et al, 2001; Bjorge et al, 2004; Calle and Kaaks, 2004; Reeves et al, 2007). The increased prevalence of obesity likely contributes to the increased incidence of RCC in Western countries, and it has been estimated that more than 40% of cases of RCC in the United States may be causally linked to obesity (Calle and Kaaks, 2004). Potential mechanisms linking obesity to RCC include lipid peroxidation leading to DNA adducts, increased insulin-like growth factor-1 expression, increased circulating estrogen levels, and increased arterionephrosclerosis and local inflammation (Kasiske et al, 1992; Huang et al, 1998; Gago-Dominguez et al, 2002; Calle and Kaaks, 2004).

Hypertension appears to be the third major etiologic factor for RCC. Diuretics and other antihypertensive medications have also been implicated, but the weight of the epidemiologic evidence suggests that it is the underlying disorder, hypertension, rather than the treatment, that increases the risk of RCC (McLaughlin et al, 1995; Yuan et al, 1998; McLaughlin and Lipworth, 2000; Lipworth et al, 2006). The proposed mechanisms are hypertension-induced renal injury and inflammation or metabolic or functional changes in the renal tubules that may increase susceptibility to carcinogens (Lipworth et al, 2006).

Although a number of other potential etiologic factors have been identified in animal models, including viruses, lead compounds, and more than 100 chemicals such as aromatic hydrocarbons, no specific agent has been definitively established as causative in human RCC (Bennington and Beckwith, 1947; Kantor, 1977). The potential role of trichloroethylene exposure has been actively investigated; some studies showed relative risks ranging from twofold to sixfold, but others have argued that inherent biases likely account for these results (Vamvakas et al, 2000; Mandel, 2001; Moyad, 2001; Bruning et al, 2003, Lipworth et al, 2006; Lock and Reed, 2006). However, Brauch and colleagues (1999) reported an increased incidence and unique pattern of von Hippel-Lindau gene (*VHL*) mutations in this population, which would argue in favor of a potential causative role for this compound. Slightly increased relative risks for RCC have been reported for workers in the metal, chemical, rubber, and printing industries and those exposed to asbestos or cadmium, but the data are not particularly convincing (Kolonel, 1976; Pesch et al, 2000; Moyad, 2001; Hu et al, 2002; Dhote et al, 2004; Lindblad, 2004; Lipworth et al, 2006; Carrizosa and Godley, 2009).

Case-control studies have shown that RCC is more common among individuals with low socioeconomic status and urban background, although the causative factors have not been defined (Kantor, 1977; Goodman et al, 1986; Muscat et al, 1995; Yuan et al, 1998). The typical modern Western diet (high in fat and protein and low in fruits and vegetables), increased intake of dairy products, and increased consumption of coffee or tea have been associated with RCC, but the relative risks have been modest, and conflicting data are available in most instances (Yu et al, 1986; Lindblad et al, 1997; Moyad, 2001; Handa and Kreiger, 2002; Dhote et al, 2004; Lindblad, 2004; Murai and Oya, 2004, Lipworth et al, 2006; Wolk et al, 2006; Carrizosa and Godley, 2009). A family history of RCC may also be a factor; one study showed a relative risk of 2.9 for individuals with a first- or second-degree relative with RCC (Gago-Dominguez et al, 2001).

Other potential iatrogenic causes include Thorotrast (which was used as a contrast agent in the past), and radiation therapy, but, again, the relative risks are low (Wenz, 1967; Romanenko et al, 2000). Vogelzang and colleagues (1998) reported four cases of RCC developing in a previously irradiated field, and a slightly increased incidence of RCC has been reported in men who received retroperitoneal irradiation for the treatment of testicular cancer. Survivors of childhood Wilms tumor also appear to be at increased risk for RCC, possibly related to prior radiation therapy or chemotherapy (Cherullo et al, 2001). An increased incidence of RCC is also observed in patients with end-stage renal failure and certain familial syndromes such as tuberous sclerosis, as discussed later (Ishikawa et al, 1990; Bjornsson et al, 1996; Neumann and Zbar, 1997).

Familial Renal Cell Carcinoma and Molecular Genetics

Since the early 1990s, significant advances have been made in our understanding of the molecular genetics of RCC. Novel familial syndromes of RCC have been identified, and the tumor suppressor genes and oncogenes contributing to the development of both sporadic and familial forms of this malignancy have been characterized (Table 49–6) (Linehan et al, 1995; Zbar et al, 1995; Schmidt et al, 1997; Weirich et al, 1998; Choyke et al, 2003; Linehan et al, 2003; Pavlovich et al, 2003; Zimmer and Iliopoulos, 2003;

Table 49–6.
Familial Renal Cell Carcinoma (RCC) Syndromes

SYNDROME	GENETIC ELEMENT	MAJOR CLINICAL MANIFESTATIONS
von Hippel-Lindau	*VHL* gene (chromosome 3p25-26)	Clear cell RCC Hemangioblastomas of the central nervous system Retinal angiomas Pheochromocytoma
Hereditary papillary RCC	c-*MET* proto-oncogene (chromosome 7q31)	Type 1 papillary RCC
Familial leiomyomatosis and RCC	Fumarate hydratase (chromosome 1q42)	Type 2 papillary RCC Cutaneous leiomyomas Uterine leiomyomas
Birt-Hogg-Dubé	*BHD1* gene (chromosome 17p12q11)	Chromophobe RCC Oncocytoma Transitional tumors* Occasional clear cell RCC Cutaneous fibrofolliculomas Lung cysts Spontaneous pneumothorax

*Also known as hybrid oncocytic tumors and containing features of both chromophobe RCC and oncocytoma.

Data from Linehan, 2002; Choyke et al, 2003; Linehan et al, 2003; Maranchie and Linehan, 2003; Pavlovich et al, 2003; Pavlovich and Schmidt, 2004; Sudarshan and Linehan, 2006; Coleman, 2008; Pfaffenroth and Linehan, 2008; Hansel and Rini, 2008; and Nathanson and Stephenson, 2009.

Pavlovich and Schmidt, 2004; Klatte and Pantuck, 2008; Nathanson and Stephenson, 2009). The impact of this new information should not be underestimated because it has fundamentally changed our perceptions about RCC. **We now, more than ever, recognize the distinct nature of the various histologic subtypes of RCC, and advances in molecular genetics have contributed to a major revision in the histologic classification of this malignant neoplasm** (Oyasu, 1998; Linehan et al, 2003; Young et al, 2008; Roma and Zhou, 2007; Pfaffenroth and Linehan, 2008; Zhou, 2009). **A direct and beneficial impact on management of patients has also been achieved, with molecular targeted agents now extending survival for patients with advanced RCC** (Linehan, 2002; Vira et al, 2007; Hudes et al, 2007, Motzer et al, 2007; Lane et al, 2007c; Kroog and Motzer, 2008; Clark and Cookson, 2008).

Knudson and Strong recognized that familial forms of cancer might hold the key to the identification of important regulatory elements known as tumor suppressor genes (Knudson, 1971; Knudson and Strong, 1972). **Their observations about the childhood tumor retinoblastoma, in which familial cases tend to be multifocal and early onset, led them to propose a two-hit theory of carcinogenesis. They hypothesized that a gene product that could suppress tumor development must be involved and that both alleles of this "tumor suppressor gene" must be mutated or inactivated for tumorigenesis to occur.** Furthermore, Knudson postulated that patients with the familial form of the cancer are born with one mutant allele and that all cells in that organ or tissue are at risk, accounting for the early onset and multifocal nature of the disease. In contrast, sporadic tumors develop only if a mutation occurs in both alleles within the same cell; and because each event occurs with low frequency, most tumors develop late in life and in a unifocal manner (Knudson, 1971; Knudson and Strong, 1972). Knudson's hypothesis has proved true for retinoblastoma and a number of other tumor types, including RCC (Choyke et al, 2003; Linehan et al, 2003; Pavlovich et al, 2003; Zimmer and Iliopoulos, 2003; Pavlovich and Schmidt, 2004; Sudarshan and Linehan, 2006). Identification of familial cases of RCC was particularly important because it allowed linkage analysis between affected family members.

von Hippel-Lindau Disease, *VHL* Gene, and Genetics of Clear Cell Renal Cell Carcinoma

The familial form of clear cell RCC is von Hippel-Lindau disease. This is a relatively rare autosomal dominant disorder that occurs with a frequency of 1 per 36,000 population. **Major manifestations include the development of RCC, pheochromocytoma, retinal angiomas, and hemangioblastomas of the brainstem, cerebellum, or spinal cord** (Table 49–7) (Horton et al, 1976; Go et al, 1984; Green, 1986; Jennings et al, 1988; Lamiell et al, 1989; Maher et al, 1990; Neumann and Zbar, 1997; Hansel and Rini, 2008; Nathanson and Stephenson, 2009). All of these tumor types are highly vascular and can lead to substantial morbidity, much of which can be avoided with prompt recognition and careful, skilled management. In particular, central nervous system lesions can lead to paralysis or death and the retinal lesions to blindness if they are not identified and managed in an expedient manner. **Other common or important manifestations of von Hippel-Lindau disease include renal and pancreatic cysts, inner ear tumors, and papillary cystadenomas of the epididymis** (Neumann and Zbar, 1997). **An increased incidence of neuroendocrine tumors of the pancreas has also been reported** in von Hippel-Lindau disease (Zbar et al, 1999; Coleman, 2008). Penetrance for all of these traits is far from complete, and some, such as pheochromocytomas, tend to be clustered only in certain families (Table 49–8) (Neumann and Zbar, 1997, Coleman, 2008; Nathanson and Stephenson, 2009). **RCC develops in about 50% of patients with von Hippel-Lindau disease and is distinctive for its early age at onset (often in the third, fourth, or fifth decade of life) and for its bilateral and multifocal involvement** (Horton et al, 1976; Go et al, 1984; Green, 1986; Jennings et al, 1988; Lamiell et al, 1989; Maher et al, 1990; Neumann and Zbar, 1997; Vira et al, 2007; Nathanson and Stephenson, 2009). With improved management of the central nervous system manifestations of the disease, RCC has now become the most common

Table 49–7.
Manifestations of the von Hippel-Lindau Syndrome

ORGAN SYSTEM	LESION	INCIDENCE (%)
Eye	Benign retinal angiomas	49-59
Central nervous system	Benign hemangioblastomas	42-72
Kidney	Clear cell renal cell carcinoma	24-70
	Renal cysts	22-59
Adrenal gland	Pheochromocytoma	18
Pancreas	Islet cell tumors	12
	Malignant islet cell tumor	2
	Pancreatic cysts	21-72
Epididymis	Cystadenoma	10-26
Ear	Endolymphatic sac tumor	10

Data from Horton et al, 1976; Green, 1986; Lamiell et al, 1989; Maher et al, 1990; Neumann and Zbar, 1997; Friedrich, 1999; Choyke et al, 2003; Linehan et al, 2003; Maranchie and Linehan, 2003; Pavlovich et al, 2003; Sudarshan and Linehan, 2006; Coleman, 2008; Hansel and Rini, 2008; and Nathanson and Stephenson, 2009.

Table 49–8.
Incidence of Major Manifestations of von Hippel-Lindau Disease by Mutation Status

DISEASE TYPE	HEMANGIOBLASTOMA	RENAL CELL CARCINOMA	PHEOCHROMOCYTOMA	GERMLINE MUTATION TYPES
1	High	High	Low	Full gene deletions, partial gene deletions, nonsense mutations, and splice acceptor mutations
2A	High	Low	High	Missense mutations in specific areas
2B	High	High	High	Partial gene deletions, nonsense mutations, and missense mutations
2C	No	No	High	Missense mutations in other specific areas

Adapted from Nathanson and Stephenson, 2009; data from Sudarshan and Linehan, 2006; Kaelin, 2007; and Coleman, 2008.

cause of mortality in patients with von Hippel-Lindau disease (Maher et al, 1990; Neumann and Zbar, 1997). Screening for von Hippel-Lindau disease and important considerations for the management of RCC in von Hippel-Lindau disease are reviewed later in this chapter.

Early clues to the genetic elements involved in the development of RCC came from cytogenetics. These studies demonstrated a common loss of chromosome 3 in kidney cancer, particularly the clear cell variant, and led to intensive efforts to find a tumor suppressor gene in this region (Zbar et al, 1987; Seizinger et al, 1988; Hosoe et al, 1990; Lerman et al, 1991). Reports by Kovacs and colleagues (1989) and Cohen and associates (1979) of translocations involving chromosome 3 further implicated this chromosome as an important regulatory element. Southern blot testing and analysis for restriction fragment length polymorphisms with a wide variety of genetic markers subsequently demonstrated loss of heterozygosity in distinct regions on the short arm of chromosome 3 (reviewed by Jennings et al, 1995). **Sophisticated molecular genetic linkage studies in patients with von Hippel-Lindau disease eventually led to the identification of the *VHL* tumor suppressor gene** (Latif et al, 1993). **This gene, which is located at chromosome 3p25-26, has now been completely sequenced, and its role as a tumor suppressor gene for both the sporadic and the familial forms of clear cell RCC has been confirmed** (Gnarra et al, 1994; Linehan et al, 1995; Zbar, 1995; Furge and Teh, 2009; Nathanson and Stephenson, 2009). The *VHL* gene consists of three exons, and it encodes a protein of 213 amino acids. A large number of common mutations or "hot spots" in the gene have been identified, and a direct correlation between genotype and phenotype has been established in some cases (Gnarra et al, 1994; Linehan et al, 1995; Zbar, 1995; Brauch et al, 2000; Pavlovich and Schmidt, 2004; Kaelin, 2007). For instance, missense mutations (type 2 mutations) that result in a full-length but nonfunctional protein are commonly found in families with von Hippel-Lindau disease that develop pheochromocytomas, whereas deletions leading to a truncated protein (type 1 mutations) are typically found in families that do not develop pheochromocytomas (see Table 49–8) (Crossey et al, 1994; Linehan et al, 1995; Maher and Kaelin, 1997; Neumann and Zbar, 1997; Walther et al, 1999c; Hes et al, 2000; Friedrich, 2001; Pavlovich and Schmidt, 2004; Sudarshan and Linehan, 2006; Coleman, 2008). The identification of this tumor suppressor gene represented a major advance in the field and required close collaboration between clinical urologic-oncologists and molecular geneticists. The important historical steps in solving this challenging puzzle were reviewed by Linehan and colleagues (1995) and Zbar (1995), who spearheaded this important effort.

As with most tumor suppressor genes, both alleles of the *VHL* gene must be mutated or inactivated for development of the disease; the observed inheritance patterns have conformed to Knudson's hypotheses. As expected, almost all patients with von Hippel-Lindau disease were found to have germline mutations of one allele of the *VHL* tumor suppressor gene, and autosomal dominant inheritance from the affected parent was confirmed (Gnarra et al, 1994; Linehan et al, 1995, 2003). The second allele is commonly lost by gene or chromosome deletion (Zbar, 1995). Also, as predicted, most sporadic clear cell RCCs were found to harbor mutations or other genetic mechanisms, such as hypermethylation, that inactivated both alleles of the *VHL* gene (Zbar, 1995; Linehan et al, 2003; Nathanson and Stephenson, 2009). However, they differ in that both mutations must be acquired after birth, accounting for the late onset and the unifocal nature of the sporadic form of the disease.

Subsequent work has focused on the function of the VHL protein and its potential mechanisms of action. The VHL protein is known to bind to elongins B and C, CUL-2, and RBX1 to form an E3 ubiquitin ligase complex and thereby modulates the degradation of important regulatory proteins (Gorospe et al, 1999; Lisztwan et al, 1999; Zbar et al, 1999; Wiesener et al, 2001; George and Kaelin, 2003; Linehan et al, 2003; Pavlovich and Schmidt, 2004; Sudarshan and Linehan, 2006; Vira et al, 2007). **A critically important function of the VHL protein complex is to target the hypoxia-inducible factors 1 and 2 (HIF-1 and HIF-2) for ubiquitin-mediated degradation, keeping the levels of HIFs low under normal conditions. The HIFs are intracellular proteins that play an important role in regulating cellular responses to hypoxia, starvation, and other stresses. Inactivation or mutation of the *VHL* gene leads to dysregulated expression of the HIFs** (Maxwell et al, 1999; Yu et al, 2001), **and they begin to accumulate in the cell. This, in turn, leads to a severalfold upregulation of the expression of vascular endothelial growth factor (VEGF), the primary angiogenic growth factor in RCC, contributing to the pronounced neovascularity associated with clear cell RCC** (Gnarra et al, 1996; Iliopoulos et al, 1996; Gunningham et al, 2001; Igarashi et al, 2002; Linehan et al, 2003; Sudarshan and Linehan, 2006; Vira et al, 2007). HIFs also upregulate the expression of tumor growth factor-α, platelet-derived growth factor (PDGF), glucose transporter (Glut 1), erythropoietin, and carbonic anhydrase IX (CA-IX), a tumor-associated antigen with specificity for clear cell RCC (Fig. 49–9) (Zbar et al, 1999; Wykoff et al, 2000; Turner et al, 2002; Wiesener et al, 2002; Linehan et al, 2003; Grabmaier et al, 2004; Sudarshan and Linehan, 2006; Vira et al, 2007). In addition, the VHL protein appears to influence the cell cycle, cellular differentiation, and intracellular processing of important matrix molecules such as fibronectin, and it may impact the metastatic process by upregulating the chemokine receptor CXCR4. All of these functions may contribute to the pathogenesis and distinctive character of this disease (Lieubeau-Teillet et al, 1998; Kamada et al, 2001; Bindra et al, 2002; Hergovich et al, 2003; Linehan et al, 2003; Na et al, 2003; Pavlovich and Schmidt, 2004; Klatte and Pantuck, 2008).

Other genetic elements potentially involved in the development of sporadic clear cell RCC include additional loci on the short arm of chromosome 3 and the *TP53* and *PTEN* tumor suppressor genes. Sophisticated molecular analyses, including complete gene sequencing and assessment for inactivation of the promoter by hypermethylation, has failed to reveal *VHL* gene abnormalities in a small proportion of sporadic clear cell RCCs, and the search for additional regulatory elements has continued (Clifford et al, 1998b; Hamano et al, 2002; Banks et al, 2006). Loss of heterozygosity has also been observed at 3p12-p14 and 3p21.2-p21.3 and is particularly common in tumors with wild-type VHL status (Shridhar et al, 1997; van den Berg and Buys, 1997; Clifford et al, 1998a; Lott et al, 1998; Velickovic et al, 2001; Bodmer et al, 2002). The functional importance of these loci is suggested by experiments showing that the transfer of fragments of chromosome 3 containing only these genetic elements can suppress tumorigenesis in RCC cell lines (Van den Berg and Buys, 1997; Lovell et al, 1999; Bodmer et al, 2002). A candidate tumor suppressor gene at 3p12 has been described and may contribute to a *VHL*-independent pathway to RCC (Lovell et al, 1999). Increased immunostaining for TP53 has been reported in 6% to 40% of RCCs, with some studies suggesting a correlation with tumor grade and stage (Reiter et al, 1993; Uhlman et al, 1994; Haitel et al,

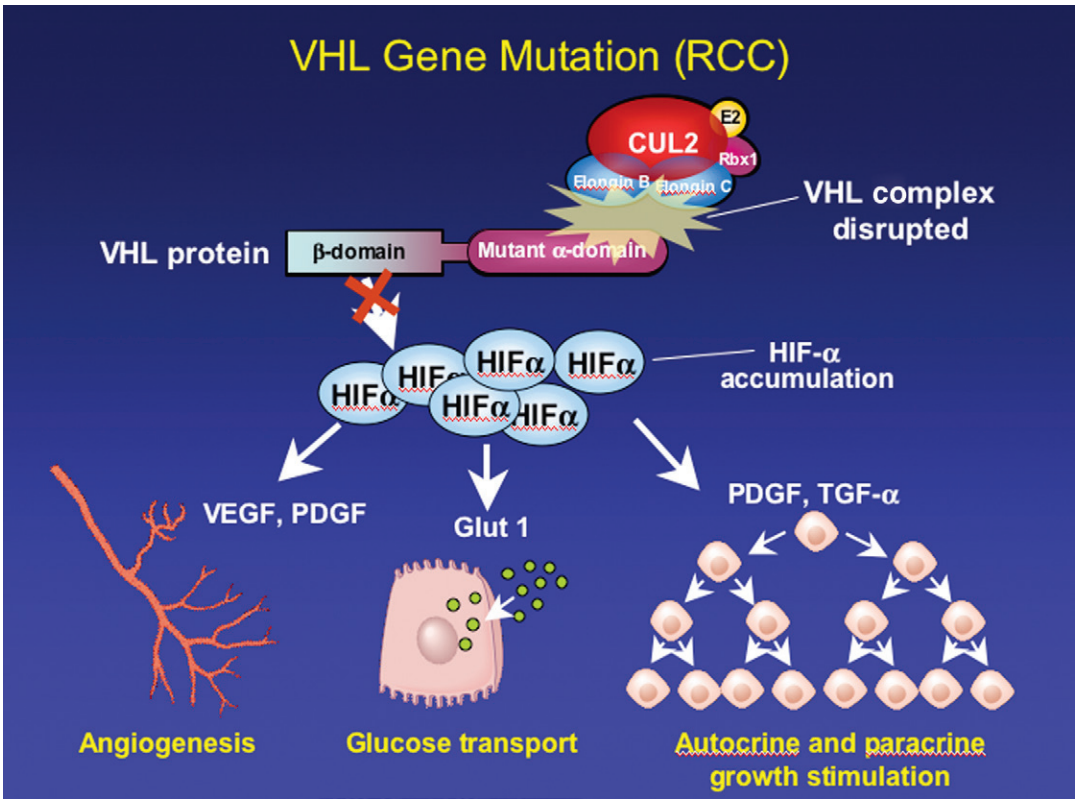


Figure 49–9. Biologic functions of the von Hippel-Lindau (VHL) protein. The wild-type VHL protein targets hypoxia-inducible factor-α (HIF-α) for degradation. Mutation of the *VHL* gene allows HIF-α to accumulate, leading to increased expression of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), Glut 1, and transforming growth factor-α (TGF-α). This, in turn, has important implications with respect to tumor angiogenesis, metabolic activity, and autocrine and paracrine stimulation. RCC, renal cell carcinoma. (From Linehan WM, Walther MM, Zbar B. The genetic basis of cancer of the kidney. J Urol 2003;170:2163–72.)

1999). However, the data regarding *TP53* in RCC have been controversial, and no clear consensus is available at this time. Of more relevance is the *PTEN* tumor suppressor gene, which is downregulated in a subset of RCC tumors (Alimov et al, 1999; Kondo et al, 2001; Brenner et al, 2002; Velickovic et al, 2002; Horiguchi et al, 2003; Shin et al, 2003; Hara et al, 2004; Robb et al, 2007; Hager et al, 2007; Pantuck et al, 2007; Klatte and Pantuck, 2008). The PTEN protein inhibits phosphatidylinositol-3-kinase–dependent activation of protein kinase B (Akt), a key intermediary in the mammalian target of rapamycin (mTOR) pathway (Kim et al, 2009). **Loss of PTEN leads to constitutive activation of mTOR, which promotes tumorigenesis, and this pathway has proven to be fertile ground for pharmacologic intervention** (see Tumor Biology and Clinical Implications and Chapter 50) (Hudes et al, 2007; Klatte and Pantuck, 2008; Kim et al, 2009; Hudes, 2009b).

Oncogenes, such as c-*MYC*, c-*ERBB1*, c-*Ha-RAS*, c-*FOS*, and *RAF-1*, have also been studied in clear cell RCC, but the available data suggest limited involvement (Slamon et al, 1984). Downregulation of DNA mismatch repair genes may contribute to genetic instability in RCC and allow accumulation of multiple genetic defects (Deguchi et al, 2003).

Familial Papillary Renal Cell Carcinoma and Genetics of Papillary Renal Cell Carcinoma

Several studies have documented distinct cytogenetic findings in non–clear cell histiotypes of RCC; chromosome 3 and *VHL* gene abnormalities are uncommon in these variants (Störkel et al, 1997; Oyasu, 1998; Sudarshan and Linehan, 2006; Vira et al, 2007). **These observations suggested a distinct genetic basis for non–clear cell RCC. Papillary RCC, the second most common histologic subtype of RCC, is characterized by trisomy for chromosomes 7 and 17 as well as abnormalities on chromosomes 1, 12, 16, 20, and Y** (Störkel et al, 1997; Oyasu, 1998; Pavlovich et al, 2003). In 1995, Zbar and colleagues at the National Cancer Institute reported a **second familial syndrome of RCC—hereditary papillary RCC (HPRCC).** This followed a number of isolated case reports that suggested clustering of papillary RCCs within certain families (Zbar et al, 1994). In Zbar and colleagues' series (1995) there were 10 families with 41 affected members (29 men and 12 women). Median age at diagnosis was 45 years, and most patients developed multifocal and bilateral papillary RCC. **Type 1 papillary RCC is typically found in this syndrome rather than type 2, which is commonly seen in the hereditary leiomyomatosis and RCC syndrome.** Unlike von Hippel-Lindau disease, most patients with HPRCC do not develop tumors in other organ systems (Czene and Hemminki, 2003; Pfaffenroth and Linehan, 2008; Nathanson and Stephenson, 2009). Mean survival in affected individuals was only 52 years in Zbar and colleagues' series, although the number of patients dying of RCC was not defined. The development of CKD due to a combination of malignant replacement of the renal mass and loss of functioning nephrons secondary to various interventions is a potential contributor to morbidity and mortality in this syndrome (Ornstein et al, 2000). CT is the preferred imaging modality for patients with HPRCC because it has the greatest sensitivity for detecting the small, hypovascular lesions that are common in this syndrome (Sudarshan and Linehan, 2006; Pfaffenroth and Linehan, 2008; Nathanson and Stephenson, 2009).

Studies of families with HPRCC demonstrate an autosomal dominant mode of transmission, similar to all of the familial RCC syndromes, and provide insight into the molecular genetics of HPRCC as well as a subset of patients with sporadic papillary RCC (Zbar et al, 1995; Schmidt et al, 1997; Linehan et al, 2003, Vira et al, 2007). Again, molecular linkage analysis in affected families played a key role in the discovery of this gene, which was localized to chromosome 7q31. However, in this case, the inciting event is activation of a proto-oncogene, rather than inactivation of a tumor suppressor gene. **Missense mutations of the c-*MET* proto-oncogene at 7q31 were found to segregate with the disease, implicating it as the relevant genetic locus** (Schmidt et al, 1997; Pavlovich et al, 2003). The protein product of this gene is the receptor tyrosine kinase for the hepatocyte growth factor (also known as scatter factor), and its activation leads to cellular proliferation and other potentially tumorigenic effects (Vira et al, 2007). **Most of the mutations in HPRCC have been found in the tyrosine kinase domain of c-*MET* and apparently lead to constitutive activation** (Schmidt et al, 1997; Pavlovich et al, 2003; Sudarshan and Linehan, 2006). The mutated MET protein can transform NIH 3T3 murine fibroblasts and is tumorigenic in immunodeficient murine models. Trisomy for chromosome 7, which is commonly found in HPRCC, develops primarily through duplication of the chromosome harboring the mutant allele of the c-*MET* proto-oncogene and effectively increases the dosage of the activated receptor (Zhuang et al, 1998; Sudarshan and Linehan, 2006; Hansel and Rini, 2008). Relatively early onset and multifocality in HPRCC are due to inheritance of the mutated *c-MET* gene, which places all the cells in the kidney at risk from birth, but the incomplete penetrance and variable clinical courses associated with this syndrome suggest that additional genetic loci or epigenetic phenomena may modulate the phenotype (Choyke et al, 2003; Linehan et al, 2003; Pavlovich et al, 2003; Pavlovich and Schmidt, 2004; Schmidt at al, 2004; Vira et al, 2007). Schmidt and colleagues (2004) have described three more families with HPRCC and have shown age-dependent penetrance and a variable clinical course according to the site of mutation and family involved. **Whereas tumors in HPRCC tend to be less aggressive than their sporadic counterparts, it is clear that some can metastasize and become lethal** (Schmidt et al, 2004; Vira et al, 2007). **Schmidt and colleagues report *c-MET* mutations in 13% of patients with sporadic papillary RCC, suggesting that this molecular defect also contributes to a subset of this disease population** (Schmidt et al, 1999; Sudarshan and Linehan, 2006; Vira et al, 2007). Small molecule inhibitors of the c-*MET* receptor are currently in development and may prove useful for the management of HPRCC and the subset of patients with sporadic RCC who harbor this mutation (Bellon et al, 2008; Hansel and Rini, 2008; Pfaffenroth et al, 2008).

Hereditary Leiomyomatosis and Renal Cell Carcinoma

In 2001, Launonen and colleagues described a new familial renal cancer syndrome in which patients commonly develop cutaneous and uterine leiomyomas and type 2 papillary RCC (Choyke et al, 2003; Kiuru and Launonen, 2004; Pavlovich and Schmidt, 2004; Sudarshan and Linehan, 2006; Sudarshan et al, 2007). Mean age at diagnosis is in the early 40s (Hansel and Rini, 2008; Nathanson and Stephenson, 2009). **Renal tumors in this syndrome are unusual for familial RCC in that they are often solitary and unilateral, and they are more likely to be aggressive than other forms of familial RCC** (Linehan et al, 2003; Maranchie and Linehan, 2003; Pavlovich and Schmidt, 2004; Sudarshan and Linehan, 2006; Grubb et al, 2007; Hansel and Rini, 2008). Collecting duct RCC, another highly malignant variant of RCC, has also been observed in this syndrome, which was named **hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome** (Linehan et al, 2003; Grubb et al, 2007; Nathanson and Stephenson, 2009). The histologic hallmark of these tumors is large, prominent eosinophilic nuclei and nucleoli with perinucleolar clearing (Grubb et al, 2007; Merino et al, 2007).

The HLRCC locus was mapped to a region on 1q42-44, and this was later shown to be the site of the fumarate hydratase gene (Tomlinson et al, 2002; Linehan et al, 2003; Toro et al, 2003; Pavlovich and Schmidt, 2004; Alam et al, 2005). Fumarate hydratase is an essential enzyme in the Krebs cycle of oxidative metabolism. Again, **autosomal dominant inheritance** was observed, and this appears to be a tumor suppressor gene rather than an oncogene (Linehan et al, 2003; Pavlovich and Schmidt, 2004). The mechanistic link between a metabolic enzyme located in the mitochondria and tumorigenesis is still an enigma and remains an active area of investigation (Pollard et al, 2003; Pavlovich and Schmidt, 2004). One hypothesis is that fumarate accumulation may stabilize HIF-1 by preventing its hydroxylation, which targets it for degradation (Isaacs et al, 2005; Sudarshan and Linehan, 2006; Ratcliffe, 2007; Coleman, 2008; Hansel and Rini, 2008; Pfaffenroth and Linehan, 2008).

Penetrance for RCC in HLRCC is lower than for the cutaneous and uterine manifestations, with only a minority (20%) of patients developing RCC (Choyke et al, 2003; Sudarshan and Linehan, 2006; Pfaffenroth and Linehan, 2008; Nathanson and Stephenson, 2009). In contrast, almost all individuals with this syndrome will develop cutaneous leiomyomas and uterine fibroids (if female), usually manifesting at the age of 20 to 35 years (Sudarshan and Linehan, 2006; Vira et al, 2007). A high proportion of women have had a hysterectomy for fibroids before formal diagnosis of HLRCC (Coleman, 2008). Leiomyosarcomas of the uterus have been reported in HLRCC, although they appear to be uncommon (Sudarshan and Linehan, 2006; Pfaffenroth and Linehan, 2008; Nathanson and Stephenson, 2009). **Prompt surgical management of the renal tumors is recommended in this syndrome, given their tendency toward invasive and aggressive behavior** (Linehan et al, 2003; Grubb et al, 2005b, 2007; Sudarshan and Linehan, 2006; Vira et al, 2007; Coleman, 2008). **This is in contrast to other familial syndromes of RCC, for which management tends to be more conservative,** as discussed later (Grubb et al, 2007; Vira et al, 2007; Pfaffenroth and Linehan, 2008).

Birt-Hogg-Dubé Syndrome

Birt-Hogg-Dubé syndrome, in which patients develop cutaneous fibrofolliculomas, lung cysts, spontaneous pneumothoraces, and a variety of renal tumors primarily derived from the distal nephron, is named after three Canadian physicians who first described the cutaneous lesions in 1977 (Toro et al, 1999; Linehan et al, 2003; Pavlovich et al, 2003, 2005; Pavlovich and Schmidt, 2004; Adley et al, 2006; Hansel and Rini, 2008). **The renal tumors typically include chromophobe RCC, oncocytomas, and hybrid or transitional tumors that exhibit features of both of these entities.** However, other forms of RCC, including a substantial proportion of clear cell RCC, have been observed in this syndrome (Pavlovich et al, 2002; Adley et al, 2006). **Overall penetrance for renal tumors is 20% to 40%, but when they occur**

they are often bilateral and multifocal (Choyke et al, 2003; Pavlovich et al, 2002; Linehan et al, 2003; Pavlovich and Schmidt, 2004: Pfaffenroth and Linehan, 2008; Toro et al, 2008). Average age at renal tumor diagnosis is approximately 50 years (Pavlovich et al, 2005). Most renal tumors in Birt-Hogg-Dubé syndrome have limited biologic aggressiveness, although metastatic behavior and lethality have been reported (Pavlovich et al, 2005)

The *BHD* gene responsible for this syndrome has been mapped to chromosome 17p12q11.2 and is now fully sequenced (Khoo et al, 2001). **Recent studies have shown that the gene product is folliculin,** which appears to be a tumor suppressor gene, although its function with respect to this syndrome is still under investigation (Adley et al, 2006; Vira et al, 2007; Toro et al, 2008). One hypothesis is that folliculin may interface with the mTOR pathway (Toro et al, 2008; Nathanson and Stephenson, 2009). Germline mutations in this gene have been found in 88% of kindreds (Toro et al, 2008). As with all of the other well-characterized familial RCC syndromes, an **autosomal dominant pattern of inheritance** is observed and genetic testing is now available (see Table 49–6) (Choyke et al, 2003; Maranchie and Linehan, 2003; Pavlovich et al, 2005; Adley et al, 2006; Toro et al, 2008).

Tumor Biology and Clinical Implications

Resistance to Cytotoxic Therapy

RCC is a prototype of the chemorefractory tumor because it has only demonstrated limited or modest responses to traditional chemotherapeutics (Motzer and Russo, 2000; Rini et al, 2009). **Study of the tumor biology of RCC provides insight into its refractory nature and, through elucidation of the VEGF and mTOR pathways, is beginning to yield agents with clinical benefit for advanced disease** (Table 49–9) (Rini et al, 2009).

Table 49–9.

Tumor Biology and Clinical Implications

BIOLOGIC CHARACTERISTIC	CLINICAL IMPLICATIONS
Expression of multidrug resistance	Contributes to chemorefractory nature of RCC
Immunogenic	10%-20% response rate with interferon or IL-2 3%-5% complete response rate with high-dose IL-2
Angiogenic	Vascular invasion can lead to venous tumor thrombus 20%-40% response rates with agents targeting VEGF (bevacizumab) or the VEGF receptor (sunitinib, sorafenib, etc.) Prolonged recurrence-free survival and overall survival with some antiangiogenic agents
Dependence on mTOR pathway	Agents targeting mTOR prolong survival in patients with poor-risk RCC (temsirolimus) and demonstrate responses in patients failing prior targeted molecular therapies (everolimus)

IL-2, interleukin-2; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor.

Expression of multidrug resistance (MDR) proteins, such as MDR-1 (also known as P-glycoprotein) and MDR-related proteins, which act as energy-dependent efflux pumps for a wide variety of hydrophobic compounds, contribute to the chemorefractory nature of advanced RCC (Mickisch, 1994; Chapman and Goldstein, 1995). However, the resistance of RCC to cisplatin and other agents that are not handled by MDR proteins, and the downregulation of MDR-1 in high-grade tumors and metastases (Tobe et al, 1995), suggests redundancy in resistance mechanisms. The ancillary benefit of this refractoriness has been an impetus for clinical investigations of immunomodulators and targeted-molecular therapies, which have markedly altered our paradigms for the management of patients with advanced RCC (see Chapter 50).

Immunobiology and Immune Tolerance

Several lines of evidence demonstrate that RCC is immunogenic, and this knowledge has stimulated intensive efforts to harness the immune system to improve outcomes for patients with advanced disease. Tumor-infiltrating immune cells can be readily isolated from RCC, including (1) cytotoxic T cells with specificity for antigens on tumor cells and (2) dendritic cells and helper T cells, which express interleukin (IL)-1 and IL-2 and function as antigen-presenting cells (Finke et al, 1992; Gaudin et al, 1995; Elsasser-Beile et al, 1999; Schwaab et al, 1999). **Of the tumor-associated antigens for RCC, carbonic anhydrase IX (CA-IX or MN-9) has demonstrated the most specificity** (Liao et al, 1997; McKiernan et al, 1997; Shuch et al, 2008). **This antigen, which is recognized by the G250 monoclonal antibody, is expressed almost ubiquitously by clear cell RCC and only rarely by other RCC subtypes.** Immunohistochemical analysis of CA-IX expression has been investigated as a diagnostic and a prognostic marker for clear cell RCC (Bui et al, 2003; Divgi et al, 2007; Leibovich et al, 2007). In normal tissues, the expression of CA-IX is restricted to the gastric mucosa, large bile ducts, and pancreas, and its expression in normal renal epithelial cells is suppressed by wild-type VHL protein (McKiernan et al, 1997; Ivanov et al, 1998; Vissers et al, 1999). CA-IX has also been investigated for reverse transcriptase-polymerase chain reaction detection of circulating RCC cells in the peripheral blood (McKiernan et al, 1999; De la Taille et al, 2000; Ohlmann et al, 2006), and CA-IX based tumor vaccine protocols have been developed (Hernandez et al, 2002; Lamers et al, 2006; Kim et al, 2007). Radioactively labeled G250 has shown promise for the detection of RCC metastases by radionuclide scanning (Brouwers et al, 2003), and more recently by positron emission tomography (Divgi et al, 2007). All these potential applications of CA-IX are, at present, promising but experimental.

A second class of factors that may modulate immunotherapeutic responses in kidney cancer is the B7 family of cell surface glycoproteins, which are expressed on various immune and nonimmune cells (Thompson et al, 2007b). B7-H1 is a T-cell coregulatory molecule that is normally expressed by macrophage lineage cells, can be induced on activated T lymphocytes, and is aberrantly expressed by RCC (Thompson et al, 2007b). Tumor-associated B7-H1 impairs antigen-specific T-cell function, and blockade of B7-H1 has been shown to potentiate antitumoral responses in preclinical models (Thompson et al, 2004). Consequently, blockade of tumor-associated B7-H1 has garnered much attention in the recent literature as a potential means to boost antitumoral immune responses. Thompson and associates (2006) have shown that B7-H1 expression by clear cell RCC tumors correlates with aggressive pathologic features and is

associated with an increased risk of disease progression, even after multivariate adjustment. Consequently, abrogation of B7-H1 signaling is being investigated as a means to facilitate the response of RCC to various immunotherapeutics (Thompson et al, 2007b).

Clinical observations such as validated responses to immunotherapy, prolonged disease stabilization, and occasional spontaneous tumor regression also support the immunogenicity of RCC. The response of RCC to immunomodulators, such as interleukin (IL)-2, interferon-alfa, and tumor-infiltrating lymphocytes, argues in favor of an important role for the immune system in the tumor biology of RCC (Rosenberg et al, 1998; Motzer and Russo, 2000; Coppin et al, 2005). **Indeed, high-dose IL-2 remains the only treatment with curative potential for patients with metastatic RCC, with durable and complete regression of disease accomplished in a finite proportion (3%-5%) of patients** (Coppin et al, 2008). **The estimated incidence of spontaneous regression of RCC has ranged from 0.3% to as high as 7%, although most experienced clinicians believe that the lower figure is more accurate** (Oliver et al, 1989; Vogelzang et al, 1992). **Most spontaneous regressions have been noted in patients with pulmonary metastases and have occurred after cytoreductive nephrectomy,** but regression of primary RCC has also been reported in the absence of any form of treatment (Vogelzang et al, 1992). **Remission can be durable, and this phenomenon, although rare, is thought to be real and has been assumed to be due to immune surveillance,** although other possibilities cannot be excluded (Papac, 1998; Young, 1998; Coppin et al, 2008).

Unfortunately, response rates of immunotherapy for RCC have been disappointing, typically ranging from 15% to 20%, despite a variety of creative treatment strategies, suggesting immune tolerance (Motzer and Russo, 2000; Ng et al, 2002; Coppin et al, 2008). **A number of observations support impaired immune surveillance in RCC, and a variety of mechanisms affecting virtually all levels of regulation of the immune system have been proposed.** Defects in transcriptional regulation via nuclear factor-kappaB (NF-κB) are present in the tumor-infiltrating lymphocytes and dendritic cells of 60% of RCCs (Finke et al, 2001; Thornton et al, 2004). Defective NF-κB signaling impairs lymphocyte function, predisposes lymphocytes to apoptosis, and leads to deficient recruitment and activation of dendritic cells (Alexander et al, 1993; Kolenko et al, 1997; Troy et al, 1998; Ling et al, 1998; Uzzo et al, 1999a; Kallfelz et al, 1999). Improved understanding of the mechanisms contributing to immunotolerance in RCC should suggest novel and rational strategies for improving outcomes for patients with advanced disease. For example, in addition to its antiangiogenic activity, sunitinib also appears to stimulate antitumor immunity by reversing myeloid-derived suppressor cell-mediated immunosuppression (Ko et al, 2009). Although the current targeted therapies appear to have significant impact on other aspects of RCC pathogenesis, such as angiogenesis, it remains to be seen whether augmentation of the antitumoral immune responses seen with some agents contributes to their clinical activity.

Angiogenesis and Targeted Pathways

RCC has long been recognized as one of the most vascular of cancers as reflected by the distinctive neovascular pattern exhibited on renal angiography (Fig. 49–10). Dependence on angiogenesis is also suggested by preclinical

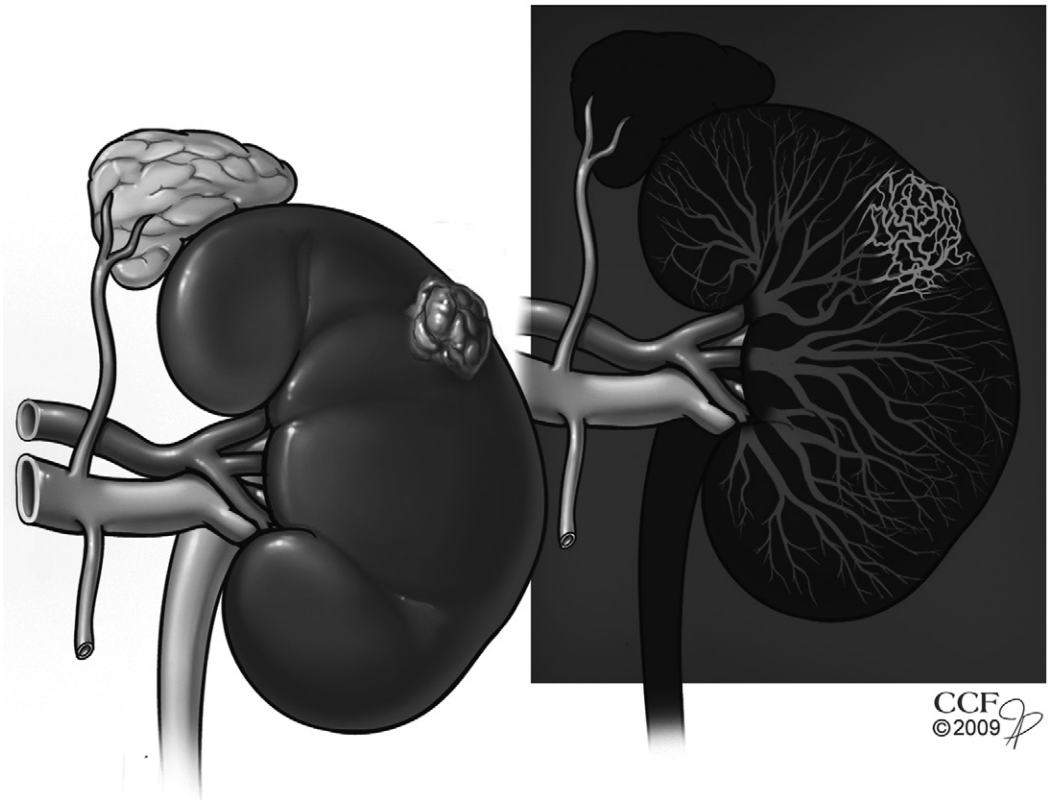


Figure 49–10. Neovascularity associated with renal cell carcinoma. Renal angiogram shows left renal mass exhibiting markedly increased neovascularity within renal tumor. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2007-2009. All Rights Reserved.)

studies demonstrating blockade of the growth and metastasis of RCC by several well-established antiangiogenic agents (Fujioka et al, 1996; Tan et al, 1996; Dhanabal et al, 1999; Drevs et al, 2000). **The primary angiogenesis inducer in clear cell RCC appears to be VEGF, which is suppressed by the wild-type VHL protein under normal conditions and is dramatically upregulated during tumor development** (Gnarra et al, 1996; Iliopoulos et al, 1996; Tomisawa et al, 1999; Gunningham et al, 2001; Igarashi et al, 2002; Linehan et al, 2003; Sudarshan and Linehan, 2006; Vira et al, 2007; Lane et al, 2007d). Increased levels of VEGF have been found in the serum and urine of patients with RCC, and a correlation with stage and grade has been reported (Tsuchiya et al, 1998; Chang et al, 2001; Horstmann et al, 2005). Elevated serum levels of basic fibroblast growth factor and other putative angiogenesis inducers for this malignant neoplasm have also been reported in RCC patients compared with normal control subjects (Campbell, 1997; Slaton et al, 2001; Currie et al, 2002; Yagasaki et al, 2003). Functional relevance of VEGF has been demonstrated by studies showing increased levels of VEGF transcript in most hypervascular tumors, whereas the less common hypovascular counterparts exhibit reduced expression of VEGF (Takahashi et al, 1994).

VEGF is actually a family consisting of several subtypes, most of which are regulated by HIFs and VHL (also see earlier under Familial Renal Cell Carcinoma and Molecular Genetics) **and bind to one or more of the corresponding VEGF receptor family members** (Lane et al, 2007d). VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1) are receptor tyrosine kinases that are the target of several multi–tyrosine kinase inhibitors with activity against RCC (Carmeliet, 2005; Hicklin and Ellis, 2005). Upon binding of ligand (VEGF), key tyrosine residues along the intracellular portion of the VEGFR are phosphorylated, which leads to the binding of specific intracellular factors and activation of corresponding pathways. Pathways known to be activated by phosphorylation of VEGFRs include the Raf-MEK-Erk and phosphatidylinositol-3-kinase/Akt/mTOR pathways that promote endothelial cell survival and proliferation (Carmeliet, 2005; Hicklin and Ellis, 2005). However, the promiscuity of the interactions between the various ligands, receptors, and downstream effectors leads to a host of effects that may be difficult to predict in the absence of analyses investigating the complete microenvironment of the cancer or endothelial cell. This promiscuity is likely a major reason that two therapeutic agents that have the "same" mode of action are found to have disparate clinical or off-target effects. **In contrast, bevacizumab is a monoclonal antibody that binds to VEGF and sequesters the ligand so that it cannot interact with VEGFR; its clinical activity is therefore almost certainly directly related to this activity.**

Given the dependence of RCC on angiogenesis and the absence of generally effective forms of systemic therapies, it is not surprising that RCC has been targeted for antiangiogenic approaches. Initial clinical trials identified several antiangiogenic compounds such as TNP-470, roquinimex, and thalidomide with limited activity in patients with advanced RCC (de Wit et al, 1997; Stadler et al, 1998). Thalidomide, for example, has shown only rare responses despite its potent antiangiogenic effects, and toxicity can be substantial, including thrombotic events and neurologic morbidity (Daliani et al, 2002; Escudier et al, 2002b; Nathan et al, 2002; Fanelli et al, 2003; Matthews and McCoy, 2003). More promising initial results were reported for bevacizumab, a humanized anti-VEGF antibody, which was associated with a significant delay in time to progression for patients with metastatic RCC compared with placebo (Yang et al, 2003a). Bevacizumab therapy commonly leads to shrinkage in the total tumor burden, although in this initial experience objective partial responses were uncommon and there were no complete responses, consistent with a tumoristatic rather than a tumoricidal mechanism of action. **A number of other multiple kinase inhibitors that target the VEGF pathway were subsequently tested in clinical trials and found to have substantial activity in patients with advanced RCC, culminating in approval of two agents, sunitinib (Sutent) and sorafenib (Nexavar), for this indication by the U.S. Food and Drug Administration (FDA) in December 2005 and January 2006** (Motzer et al, 2005, 2006). These agents are now commonly used for front-line and treatment-refractory metastatic RCC (see further details in Chapter 50). Several other antiangiogenic compounds are currently in clinical trials investigating these and other potential applications for the treatment of advanced RCC.

In general, antiangiogenic agents offer a number of potential advantages in that they are not genotoxic and target stable endothelial cells rather than genetically unstable tumor cells. They are thus unlikely to induce secondary cancers or tumor resistance. In addition, many antiangiogenic agents have proved to be synergistic with one another and with cytotoxic therapies, and their side effects should not overlap those of conventional forms of therapy (Campbell, 1997; Lane et al, 2007d).

Signal Transduction, Cell Cycle Regulation, and Other Targeted Molecular Pathways

Aberrant activation of additional signal transduction pathways in RCC may also contribute to altered cell cycle kinetics and represent excellent targets for therapeutic intervention. One such regulatory pathway in RCC is the mammalian target of rapamycin (mTOR) pathway, which interfaces with Akt (protein kinase B) and the *PTEN* tumor suppressor gene (Brenner et al, 2002; Velickovic et al, 2002; Horiguchi et al, 2003; Shin et al, 2003; Hara et al, 2004; Robb et al, 2007; Pantuck et al, 2007; Klatte and Pantuck, 2008). Expression of mTOR is upregulated by various growth factors or by mutation or loss of *PTEN* (Kim et al, 2009). Through complex pathways involving a variety of intermediaries, the mTOR pathway leads to increased expression of HIF-1 and other growth-promoting and potentially tumorigenic sequelae (Klatte and Pantuck, 2008; Kim et al, 2009). **Inhibition of mTOR with temsirolimus (Torisel), now also FDA approved, has yielded prolonged survival in patients with poor-risk, metastatic RCC, confirming the clinical relevance of this pathway** (Hudes et al, 2007; Hudes, 2009b).

Other important growth regulatory elements in RCC include the insulin-like growth factor axis (Takahashi et al, 2005), **telomerase, and BCL2.** Insulin-like growth factor receptor expression has been documented in RCC, and Parker and colleagues (2003a) have correlated this with decreased survival. Increased telomerase activity, which has been found in 56% to 93% of RCCs, may also affect the cell cycle by maintaining telomere length (Mehle et al, 1996; Yoshida et al, 1998; Orlando et al, 2001). Progressive telomere loss occurs each time a normal cell divides and eventually leads to growth inhibition and cellular senescence. Increased expression of BCL2, which protects against programmed cell death, has also been reported in RCC and may contribute to tumor viability and treatment failure (Huang et al, 1999; Gobe et al, 2002).

Proliferative index, as defined by proliferating cell nuclear antigen (PCNA) or Ki-67 staining, has correlated with pathologic parameters and clinical outcomes in RCC, suggesting that regulation of the cell cycle plays an important role in the tumor biology of RCC (deRiese et al, 1993; Delahunt et al, 1995; Tannapfel et al, 1996; Bui et al, 2004; Tollefson et al, 2007). **Increased expression of tumor growth factor-α and its receptor tyrosine kinase, the epidermal growth factor receptor (EGFR), have been reported in RCC** and may contribute to tumorigenesis by promoting cell proliferation or transformation through an autocrine mechanism (Gomella et al, 1989; Mydlo et al, 1989; Sargent et al, 1989; Lager et al, 1994; Moch et al, 1997; Ramp et al, 1997). The functional relevance of EGFR in the development of RCC has also been suggested by preclinical studies testing the efficacy of the C225 monoclonal antibody, which neutralizes EGFR and blocks tumor growth and metastasis (Prewett et al, 1998; Brouwers et al, 2004). Unfortunately, phase II clinical trials using agents that target EGFR, including erlotinib (Tarceva), gefitinib (Iressa), and ABX-EGF, demonstrated a lack of substantial activity in patients with advanced RCC (Rini et al, 2008). Based on these disappointing results, agents targeting the EGFR pathway have fallen out of favor, although there may be a role for their use in patients with cancers that express high levels of EGFR (Ravaud et al, 2008).

The hepatocyte growth factor and its receptor, the c-*MET* proto-oncogene, may also contribute to the pathogenesis of RCC (Sweeney et al, 2002a). The role of activating mutations of the c-*MET* proto-oncogene in the etiology of hereditary papillary RCC has already been discussed, but data suggest that upregulated expression of this ligand may occur in most of the histologic subtypes of RCC (Natali et al, 1996; Pisters et al, 1997; Schmidt et al, 1997; Clifford et al, 1998a; Horie et al, 1999). Hepatocyte growth factor is expressed by proximal tubular cells in the normal kidney, where it is involved in the branching tubulogenesis of the developing kidney and regeneration after renal injury. In vitro, hepatocyte growth factor has mitogenic and morphogenic effects on renal epithelial cells (Clifford et al, 1998a). Increased serum levels of hepatocyte growth factor have also been reported in most patients with RCC, independent of histologic subtype, and activation of this factor by phosphorylation at two sites is associated with cancer progression (Petri et al, 1997; Miyata et al, 2006). Taken together, these data suggest that hepatocyte growth factor and its receptor may play an important role in the tumor biology of RCC, although constitutive activation of the receptor, which may be the most potent mechanism, appears to be primarily limited to familial papillary RCC.

Proteases, Adhesion, and the Extracellular Matrix

Interactions among cancer cells, adjacent cells, and the surrounding matrix can strongly influence their pathogenic potential. Altered intracellular processing and secretion of fibronectin and other matrix proteins is found in RCC, representing one consequence of *VHL* gene mutation (Lieubeau-Teillet et al, 1998; Ohh et al, 1998). This fundamental defect most likely has important effects on tumor biology, given the important role of the matrix in regulating cellular differentiation and tumor invasiveness and metastasis. Increased expression of proteases, such as plasmin and the matrix metalloproteinases, has correlated with reduced survival in RCC and may also contribute to the aggressive behavior of RCC (Walther et al, 1997a; Kugler et al, 1998). Downregulation of E-cadherin and cadherin-6, which mediate adhesion between cancer cells, is well documented in RCC and has correlated with poor outcomes in most studies (Morton et al, 1995; Paul et al, 2004). Aberrant regulation of α-catenins, the cytoplasmic proteins that bind cadherins and mediate their effects on the cytoskeleton, has also been observed in RCC, and a correlation with compromised survival has been reported (Shimazui et al, 1996; Paul et al, 1997).

Other studies have defined the adhesion molecules that facilitate interactions between tumor cells and endothelial cells in RCC. Steinbach and colleagues (1996) have shown that sialyl-Lewis^x/endothelial leukocyte adhesion molecule-1 and VLA-4/vascular cell adhesion molecule-1 interactions regulate this process, which presumably influences the ability of tumor cells to move into or out of the vascular system during the metastatic cascade.

Pathology

Most RCCs are round to ovoid and circumscribed by a pseudocapsule of compressed parenchyma and fibrous tissue rather than a true histologic capsule. Unlike upper tract transitional cell carcinomas, most RCCs are not grossly infiltrative, with the notable exception of collecting duct RCC and some sarcomatoid variants (Farrow, 1997). Tumor size has averaged between 4 and 8 cm in most series but can vary from a few millimeters to large enough to fill the entire abdomen. Tumors smaller than 3 cm were previously classified as benign adenomas, but some small tumors have been associated with metastases (Nguyen and Gill, 2009), and **most pathologists agree that with the exception of oncocytomas and some small (<1 cm) low-grade papillary adenomas there are no reliable histologic or ultrastructural criteria to differentiate benign from malignant renal epithelial tumors** (Farrow, 1997; Eble et al, 2004) (see Chapter 51). When they are bivalved, RCCs consist of yellow, tan, or brown tumor interspersed with fibrotic, necrotic, or hemorrhagic areas; few are uniform in gross appearance. Cystic degeneration is found in 10% to 25% of RCCs and appears to be associated with a better prognosis compared with purely solid RCC (Corica et al, 1999; Koga et al, 2000; Onishi et al, 2001; Nassir et al, 2002; Imura et al, 2004; Webster et al, 2007). Calcification can be stippled or plaque-like and is found in 10% to 20% of RCCs.

Nuclear features can be highly variable. Grading has been based primarily on nuclear size and shape and the presence or absence of prominent nucleoli. Fuhrman's system (Table 49–10) **has been most generally adopted and is now recognized as an independent prognostic factor for RCC generally and for clear cell RCC in particular** (Fuhrman et al, 1982; Pantuck et al, 2001a; Lang et al, 2005; Lohse et al, 2005; Zhou, 2009).

Table 49–10.
Fuhrman's Classification System for Nuclear Grade in Renal Cell Carcinoma

GRADE	NUCLEAR SIZE	NUCLEAR OUTLINE	NUCLEOLI
1	10 mm	Round, uniform	Absent or inconspicuous
2	15 mm	Irregular	Small (visible at 400× magnification)
3	20 mm	Irregular	Prominent
4	≥20 mm	Bizarre, often multilobed	Prominent, heavy chromatin clumps present

Aggressive local behavior is not uncommon with RCC and can be expressed in a variety of ways. **Frank invasion and perforation of the renal capsule, renal sinus, or collecting system are found in approximately 20% of cases, although displacement of these structures is a more common finding.** Further spread to involve adjacent organs or the abdominal wall is often precluded by the Gerota fascia, although some high-grade RCCs are able to overcome this natural barrier. **One unique feature of RCC is its predilection for involvement of the venous system, which is found in 10% of RCCs,** more often than in any other tumor type (Skinner et al, 1972; Schefft et al, 1978). This is most commonly manifested in the form of a contiguous tumor thrombus that can extend into the inferior vena cava (IVC) as high as the right atrium (Blute et al, 2007). Many such tumor thrombi are highly vascularized by arterial blood flow (Novick et al, 1990), and some directly invade the wall of the renal vein or vena cava, which correlates with compromised prognosis (Zini et al, 2008).

M**ost sporadic RCCs are unilateral and unifocal. Bilateral involvement can be synchronous or asynchronous and is found in 2% to 4% of sporadic RCCs, although it is considerably more common in patients with familial forms of RCC, such as von Hippel-Lindau disease** (Farrow, 1997; Linehan et al, 2003). **Multicentricity, which is found in 10% to 20% of cases, is more common in association with papillary histology and familial RCC** (Mukamel et al, 1988; Cheng et al, 1991; Whang et al, 1995; Campbell et al, 1997a; Richstone et al, 2004; Krambeck et al, 2008). Satellite lesions are often small and difficult to identify by preoperative imaging, intraoperative ultrasonography, or visual inspection; they appear to be the main factor contributing to local recurrence after partial nephrectomy (Campbell et al, 1996a; Richstone et al, 2004). **Microsatellite analysis suggests a clonal origin for most multifocal RCC within the same kidney** (Junker et al, 2002), **but tumor in the contralateral kidney is likely to be an independent growth if it is synchronous or a metastasis if it is asynchronous** (Kito et al, 2002). Molecular analyses, such as gene expression profiling, may help to determine whether an asynchronous tumor is a second primary tumor or a metastasis (Lane et al, 2009).

All RCCs are, by definition, adenocarcinomas, derived from renal tubular epithelial cells (Zambrano et al, 1999; Pantuck et al, 2001a; Renshaw, 2002; Zhou, 2009). **Most RCCs share ultrastructural features, such as surface microvilli and complex intracellular junctions, with normal proximal tubular cells, and are believed to be derived from this region of the nephron** (reviewed in Farrow, 1997). Similarly, immunohistochemistry for lectins and other cell surface antigens has supported derivation from the proximal convoluted tubule (Kim and Kim, 2002). **However, more recent data suggest that this information applies primarily to the more common clear cell and papillary variants of RCC** (Table 49–11), **whereas most other histologic subtypes of RCC appear to be derived from more distal elements of the nephron** (Störkel et al, 1997; Zambrano et al, 1999; Pantuck et al, 2001a; Renshaw, 2002; Linehan et al, 2003; Pavlovich and Schmidt, 2004).

Since the early 1990s the histologic classification of RCC has undergone several major revisions (Zambrano et al, 1999; Renshaw, 2002; Linehan et al, 2003; Eble et al, 2004; Zhou, 2009). Traditionally, RCC was divided into four histologic subtypes: clear cell, granular cell, tubulopapillary, and sarcomatoid. On the basis of advances in the molecular genetics of RCC and a more discerning interpretation of histologic and ultrastructural features, a newer classification scheme was proposed by Kovacs (1993). This classification system was approved by an international consensus workshop of clinicians and researchers in the field (Weiss et al, 1995; Störkel et al, 1997; Zambrano et al, 1999; Pantuck et al, 2001a; Renshaw, 2002; Linehan et al, 2003; Pavlovich and Schmidt, 2004). In this system, granular cell tumors were reclassified into other categories based on distinct histopathologic features, chromophobe RCC was recognized as a new RCC subtype, and sarcomatoid features were categorized as variants of other histologic subtypes rather than a distinct tumor type (Weiss et al, 1995; Störkel et al, 1997; Oyasu, 1998; Zambrano et al, 1999; Renshaw, 2002; Linehan et al, 2003; Pavlovich and Schmidt, 2004). **Current practice is to identify the primary histologic subtype and comment on the presence and extent of sarcomatoid differentiation rather than to separate these tumors into a distinct category, although the prognostic implications have not changed** (Mian et al, 2002; Cheville et al, 2004; Eble et al, 2004; Zhou, 2009). Depending on well-defined histologic and ultrastructural criteria, granular cell tumors were reclassified as papillary RCC, eosinophilic variants of chromophobe RCC, or combined with clear cell RCC (Weiss et al, 1995; Kovacs et al, 1997; Störkel et al, 1997; Oyasu, 1998; Zambrano et al, 1999; Renshaw, 2002; Zhou, 2009). Another important development was the identification of renal medullary carcinoma that is common in young African-Americans with sickle cell trait (Davis et al, 1995b; Störkel et al, 1997; Hakimi et al, 2007). With additional advances in ancillary pathologic studies, including electron microscopy, immunohistochemistry, molecular genetics and cytogenetics, several additional unique subtypes of RCC have been identified since the implementation of the 1993 classification system. Based on these findings, an updated classification of malignant epithelial tumors of the kidney was presented by the World Health Organization in 2004 (see Table 49–11; Eble et al, 2004).

The 2004 World Health Organization classification reflects current understanding of RCC not as a single malignant neoplasm but rather a group comprising several different tumor subtypes, each with a distinct genetic basis and unique clinical features (see Table 49–11). Important changes include the addition of several RCC subtypes with distinct pathologic and clinical features that were previously grouped within "conventional" or unclassified RCC, such as RCC associated with XP11.2 translocations/*TFE3* gene fusions, which has microscopic features of both clear cell and papillary RCC and occurs primarily in children and young adults (Argani et al, 2001; Camparo et al, 2008; Geller et al, 2008), and the indolent mucinous tubular and spindle cell carcinoma (Hes et al, 2002; Ferlicot et al 2005; Fine et al, 2006). Sophisticated gene expression profiling and proteomic analyses support the individuality of each of these tumor subtypes and hold great promise for differentiating additional subtypes in the future (Takahashi et al, 2003, 2004; Amy-Bazille et al, 2004; Furge et al, 2004; Sugimura et al, 2004; Yang et al, 2004, 2006; Young et al, 2008). This is clearly a field in evolution, with changes stimulated by basic science advances and astute clinical observation.

Clear Cell Renal Cell Carcinoma

Clear cell RCC accounts for 70% to 80% of all RCCs, representing the garden variety of RCC formerly known as "conventional" RCC (Störkel et al, 1997; Eble et al, 2004; Rini et al, 2009). **These tumors are typically yellow when they are bivalved and are highly vascular,** containing a network

Table 49–11.

Pathologic Subtypes of RCC

HISTOLOGY*	FAMILIAL FORM AND GENETIC FACTORS	GROSS CHARACTERISTICS	MICROSCOPIC PATHOLOGIC CHARACTERISTICS	OTHER CHARACTERISTICS
Clear cell RCC (70%-80%)	von Hippel-Lindau disease *VHL* gene (3p25-26) mutation or hypermethylation Chromosome 3p deletions Also, loss of chromosome 8p, 9p, 14q; gain of chromosome 5q	Well-circumscribed, lobulated, golden yellow tumor Necrosis and hemorrhage common Venous involvement also common Cystic degeneration	Hypervascular tumor Nests or sheets of clear cells with delicate vascular network IHC†: low MWCKs,‡ vimentin, EMA, CA-IX	Originate from proximal tubule Aggressive behavior more common Tumor shrinkage common with targeted molecular therapy May respond to immunotherapy
Multilocular cystic clear cell RCC (uncommon)	Identical to clear cell RCC	Well-circumscribed mass of small and large cysts	Cysts lined by single layer of grade 1 clear cells No expansive nodules of tumor cells	Almost uniformly benign clinical behavior
Papillary RCC (10%-15%)	Type 1: HPRCC Type 2: HLRCC Activation of c-*MET* oncogene (7q31-34) by mutation common in HPRCC but uncommon (~10%) in sporadic cases Trisomy of chromosome 7 and 17; loss of Y	Fleshy tumor with fibrous pseudocapsule Necrosis and hemorrhage are common	Hypovascular tumor Papillary structures with single layer of cells around fibrovascular cores Type 1: basophilic cells with low-grade nuclei Type 2: eosinophilic cells with high-grade nuclei IHC: LMWCKs, CK7 (type 1 > type 2), AMACR	Originate from proximal tubule Commonly multicentric Common in ARCD Type 1: good prognosis Type 2: worse prognosis
Chromophobe RCC (3%-5%)	Birt-Hogg-Dubé syndrome Fumarate hydratase gene (1q42-43) mutation Loss of multiple chromosomes (1, 2, 6, 10, 13, 17, 21)	Well-circumscribed, homogeneous Tan or light brown cut surface	"Plant cells" with pale cytoplasm, perinuclear clearing or "halo," nuclear "raisins," and prominent cell borders Positive Hale colloidal iron staining IHC: diffuse CK7	Originate from intercalated cells of collecting duct Generally good prognosis, although sarcomatoid variant associated with poor prognosis
Collecting duct carcinoma (<1%)	Unknown Multiple chromosomal losses	Firm, centrally located tumor with infiltrative borders Light gray to tan-white	Complex, highly infiltrative cords within inflamed (desmoplastic) stroma High-grade nuclei, mitoses	Originate from collecting duct Poor prognosis May respond to chemotherapy
Renal medullary carcinoma (rare)	Associated with sickle cell trait	Infiltrative, gray-white Extensive hemorrhage and necrosis	Poorly differentiated cells with lacelike appearance Inflammatory infiltrate	Originate from collecting duct Dismal prognosis
Unclassified RCC (1%-3%)	Unknown	Varied	Varied	Origin not defined Generally poor prognosis
RCC associated with Xp11.2 translocations/*TFE3* gene fusions (rare)	Various mutations involving chromosome Xp11.2 resulting in *TFE3* gene fusion	Well-circumscribed, tan-yellow tumor	Variable; often clear cells with papillary architecture IHC: nuclear *TFE3*	Occur in children and young adults; 40% of pediatric RCC t(X;17) present with advanced stage and follow indolent course t(X;1) can recur with late lymph node metastases
Post-neuroblastoma RCC (rare)	Unknown	Well circumscribed	Oncocytic or clear cells with solid and papillary architecture	Occurs exclusively in children with prior neuroblastoma
Mucinous tubular and spindle cell carcinoma (rare)	Unknown	Well-circumscribed, tan-white-pink tumors centered in medulla	Mixture of tubules and spindle-shaped epithelial cells; mucin background	Favorable prognosis

*Sarcomatoid variants of all of these subtypes have been described and are associated with compromised prognosis.
†Immunohistochemistry using these markers can help to differentiate between RCC subtypes.
‡Cytokeratin (CK): low (or high)-molecular-weight cytokeratins (MWCKs).
ARCD, acquired renal cystic disease; HLRCC, hereditary leiomyomatosis and RCC syndrome; HPRCC, hereditary papillary RCC syndrome; IHC, immunohistochemistry; RCC, renal cell carcinoma.
From Eble JN, Sauter G, Epstein JI, et al. Pathology and genetics of tumours of the urinary system and male genital organs. Lyon (France): IARC Press; 2004; data from Storkel, 1997; Renshaw, 2002; Zambrano et al, 1999; Pantuck et al, 2001; Linehan et al, 2003; Pavlovich and Schmidt, 2004; Klatte et al, 2008; and Zhou, 2009.

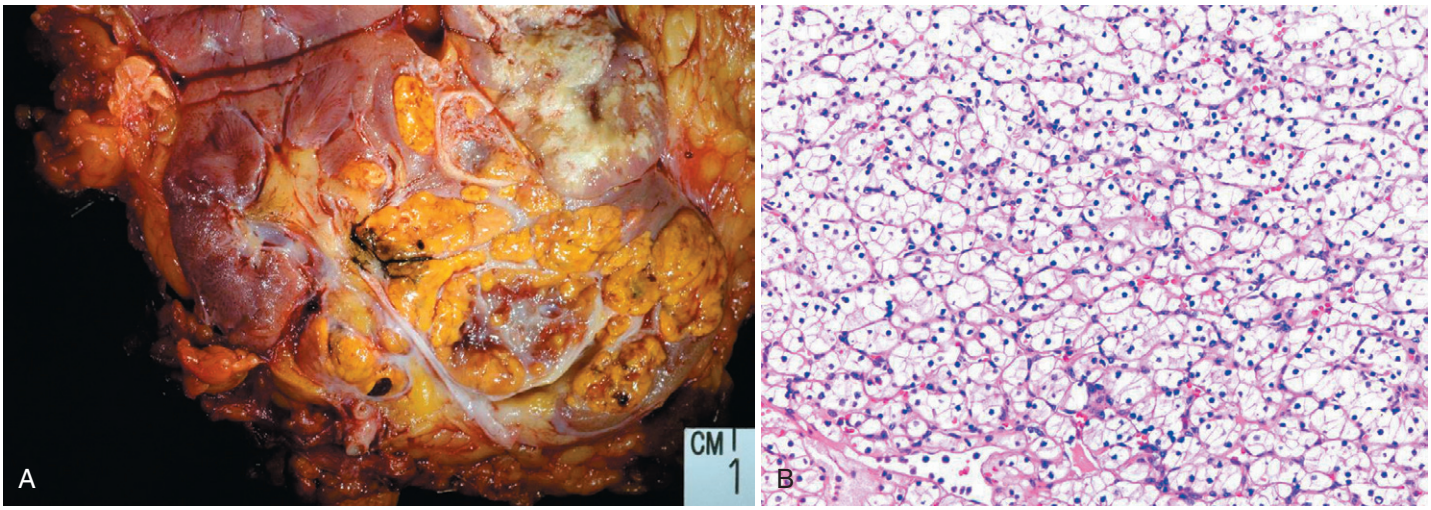


Figure 49–11. **A,** Clear cell renal cell carcinoma (RCC) with typical golden yellow color. **B,** Low-power view of typical microscopic appearance of a low-grade clear cell RCC demonstrating a delicate vascular network interspersed within homogeneous nests of cells with clear cytoplasm. (Courtesy of Dr. Ming Zhou, Cleveland, OH.)

of delicate vascular sinusoids interspersed between sheets or acini of tumor cells (Fig. 49–11). **On microscopic examination, clear cell RCC can include clear cell, granular cell, or mixed types.** Clear cells are typically round or polygonal with abundant cytoplasm containing glycogen, cholesterol, cholesterol esters, and phospholipids, all of which are readily extracted by the solvents used in routine histologic preparations, contributing to the clear appearance of the tumor cells (Farrow, 1997). However, granular cells, which have eosinophilic cytoplasm and abundant mitochondria, can predominate. Two to 5 percent of clear cell RCC demonstrate sarcomatoid features, and clear cell RCC is more likely to exhibit venous tumor extension than any other subtype of RCC (Rabbani et al, 2004). **In general, patients with clear cell RCC have a worse prognosis compared with papillary or chromophobe RCC, even after stratification for stage and grade** (Lau et al, 2002; Cheville et al, 2003; Beck et al, 2004). **However, most responders in immunotherapy protocols have had clear cell RCC, and these protocols are now being reserved primarily for this population** (Childs et al, 2000; Drachenberg and Childs, 2003). **Chromosome 3 alterations and *VHL* mutations are common in clear cell RCC, and mutation or inactivation of this gene has been found in a majority of sporadic cases** (Clifford et al, 1998b; Zambrano et al, 1999; Renshaw, 2002; Linehan et al, 2003). The familial form of clear cell RCC, the von Hippel-Lindau syndrome, has already been reviewed.

Papillary Renal Cell Carcinoma

Papillary RCC, which has also been designated chromophilic RCC in previous classification schemes, is the second most common histologic subtype (Störkel et al, 1997; Eble et al, 2004; Pignot et al, 2007; Gontero et al, 2008). **It represents 10% to 15% of all RCCs,** although it is **more commonly found in patients with end-stage renal failure and acquired renal cystic disease** (Ishikawa and Kovacs, 1993; Störkel et al, 1997). On microscopic examination, most tumors in this category consist of basophilic or eosinophilic cells arranged in papillary or tubular configuration; previously, more than 50% or 75% of the tumor had to exhibit such architectural features to qualify as a papillary RCC (Fig. 49–12). **One unique feature of papillary RCC is its tendency toward multicentricity, which approaches 40% in many series** (Renshaw and Corless, 1995; Amin et al, 1997a; Campbell et al, 1997b; Chow et al, 2001; Zhou, 2009).

Two distinct variants of papillary RCC have been described by characteristic cytogenetics, immunostaining profiles and gene expression profiling (see Fig. 49–12) (Renshaw et al, 1997; Störkel et al, 1997; Oyasu, 1998; Delahunt et al, 2001; Eble et al, 2004; Yang et al, 2005). **Type 1 papillary RCC, the more common form, consists of basophilic cells with scant cytoplasm; type 2 papillary RCC include potentially more aggressive variants with eosinophilic cells and abundant granular cytoplasm** (Delahunt et al, 2001; Amsellem-Ouazana et al, 2002; Leroy et al, 2002; Renshaw, 2002; Choyke et al, 2003; Gunawan et al, 2003; Pignot et al, 2007). **The two subtypes of papillary RCC correspond with two familial RCC syndromes: hereditary papillary RCC syndrome (type 1) and hereditary leiomyomatosis and RCC syndrome (type 2)** (Rosner et al, 2009). Although mounting molecular and genetic evidence indicate that these 2 subtypes appear to represent distinct entities, subclassification of papillary RCC into type 1 and type 2 is not routinely practiced within the community of genitourinary pathologists at present (Eble et al, 2004; Yang et al, 2005; Pignot et al, 2007). First, although patients with hereditary leiomyomatosis and RCC syndrome have compromised survival relative to those with hereditary papillary RCC syndrome, oncologic outcomes in patients with sporadic forms of these entities are not well defined (Pignot et al, 2007; Gontero et al, 2008). Moreover, evolving definitions of these entities and corresponding differences in interpretation and classification may contribute to the current lack of consensus about this issue (Pignot et al, 2007; Gontero et al, 2008).

The cytogenetic abnormalities associated with papillary RCC are characteristic and include trisomy of chromosomes 7 and 17 and loss of the Y chromosome (Kovacs et al, 1989). Other common findings include gain of chromosomes 12, 16, and 20 and loss of heterozygosity on chromosome 14 (Oyasu, 1998; Brunelli et al, 2003b; Kuroda et al, 2003a; Pavlovich and Schmidt, 2004; Zhou, 2009). *VHL* mutations are rare in papillary RCC, confirming distinct genetic pathways to tumorigenesis (Kenck et al, 1996; Zambrano et al, 1999; Linehan et al, 2003; Rosner et al, 2009). Papillary RCC is more likely to be

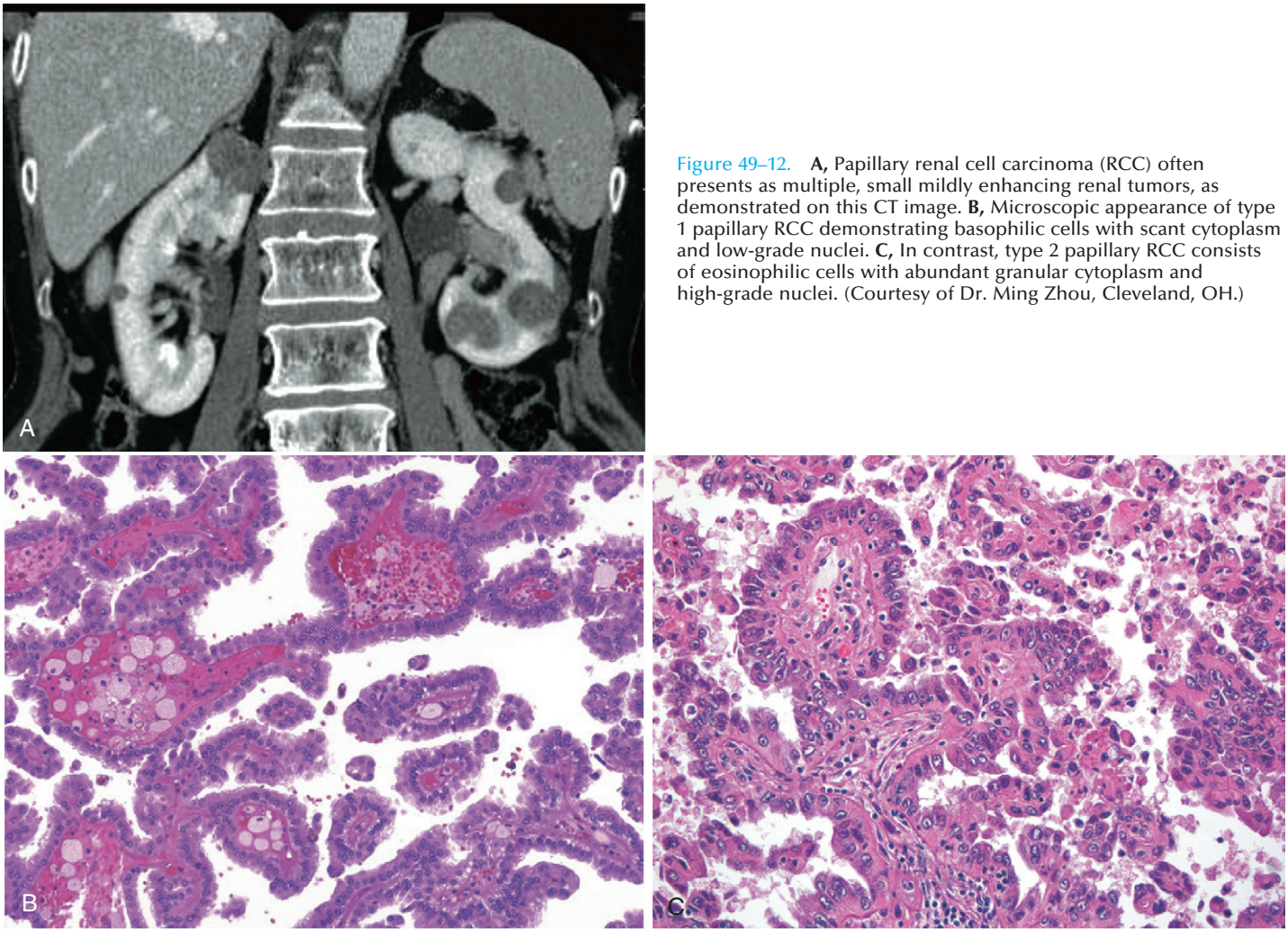


Figure 49–12. **A,** Papillary renal cell carcinoma (RCC) often presents as multiple, small mildly enhancing renal tumors, as demonstrated on this CT image. **B,** Microscopic appearance of type 1 papillary RCC demonstrating basophilic cells with scant cytoplasm and low-grade nuclei. **C,** In contrast, type 2 papillary RCC consists of eosinophilic cells with abundant granular cytoplasm and high-grade nuclei. (Courtesy of Dr. Ming Zhou, Cleveland, OH.)

hypovascular, perhaps owing to the lack of *VHL* mutations that regulate VEGF, the primary proangiogenic molecule in RCC (Blath et al, 1976; Herts et al, 2002; Kim JK et al, 2002). As discussed earlier, activating mutations of the c-*MET* proto-oncogene located on chromosome 7, which encodes the receptor for hepatocyte growth factor, appear to be common and pathogenic in inherited papillary RCC (Schmidt et al, 1997; Pavlovich and Schmidt, 2004). Indeed, this genetic defect is now being targeted for novel treatment approaches with use of small molecule inhibitors (Schmidt et al, 1997; Linehan et al, 2003; Rosner et al, 2009). Interestingly, these mutations have been detected in only about 10% of sporadic papillary RCCs, suggesting divergent molecular pathways (Schmidt et al, 1999).

The prognosis associated with papillary RCC remains controversial. Many older studies suggested a tendency toward low-grade disease, and one literature review indicated that 80% of papillary RCCs are confined to the kidney, which has obvious prognostic implications (Blath et al, 1976; Mancilla-Jimenez et al, 1976; Boczko et al, 1979; Mydlo and Bard, 1987; Farrow, 1997; Chow et al, 2001). On the other hand, more recent studies contain a somewhat increased proportion of high-grade and advanced tumors, often leading to the patient's demise due in part to the ineffectiveness of current systemic therapies against papillary RCC (Lager et al, 1995; Amin et al, 1997a; Renshaw, 2002; Margulis et al, 2008). One recent study indicates that although venous tumor thrombus was less common with papillary RCC than clear cell RCC, outcomes in this subgroup of patients were compromised (Margulis et al, 2008). Conversely, although lymph node involvement was more common with papillary RCC than clear cell RCC in the same study, patients with lymphatic involvement with papillary RCC had higher cancer-specific survival at 5 years (65% vs. 19%, $P = .03$). **At present, most authors believe that papillary RCC, and type 1 papillary RCC in particular, carry a better prognosis than clear cell RCC when compared grade for grade and stage for stage** (Moch et al, 2000; Lau et al, 2002; Amin et al, 2002; Beck et al, 2004; Zhou, 2009).

Papillary adenomas are small (≤5 mm) tumors that resemble papillary RCC under the microscope, are often well encapsulated and low grade, and are commonly found at autopsy (Farrow, 1997; Renshaw, 2002). These lesions, which possess many of the same genetic alterations found in larger papillary RCCs, are benign neoplasms (see Chapter 51).

Chromophobe Renal Cell Carcinoma

Chromophobe RCC, first described by Theones and colleagues in 1985, is a distinctive histologic subtype of RCC that appears to be derived from the cortical portion of the collecting duct (Störkel et al, 1997). **It represents 3% to 5% of all RCCs** (Oyasu, 1998; Eble et al, 2004; Klatte et al, 2008a). The tumor cells typically exhibit a relatively transparent cytoplasm with a fine reticular pattern that has been described as a "plant cell" appearance (Fig. 49–13). The chromophobic nature

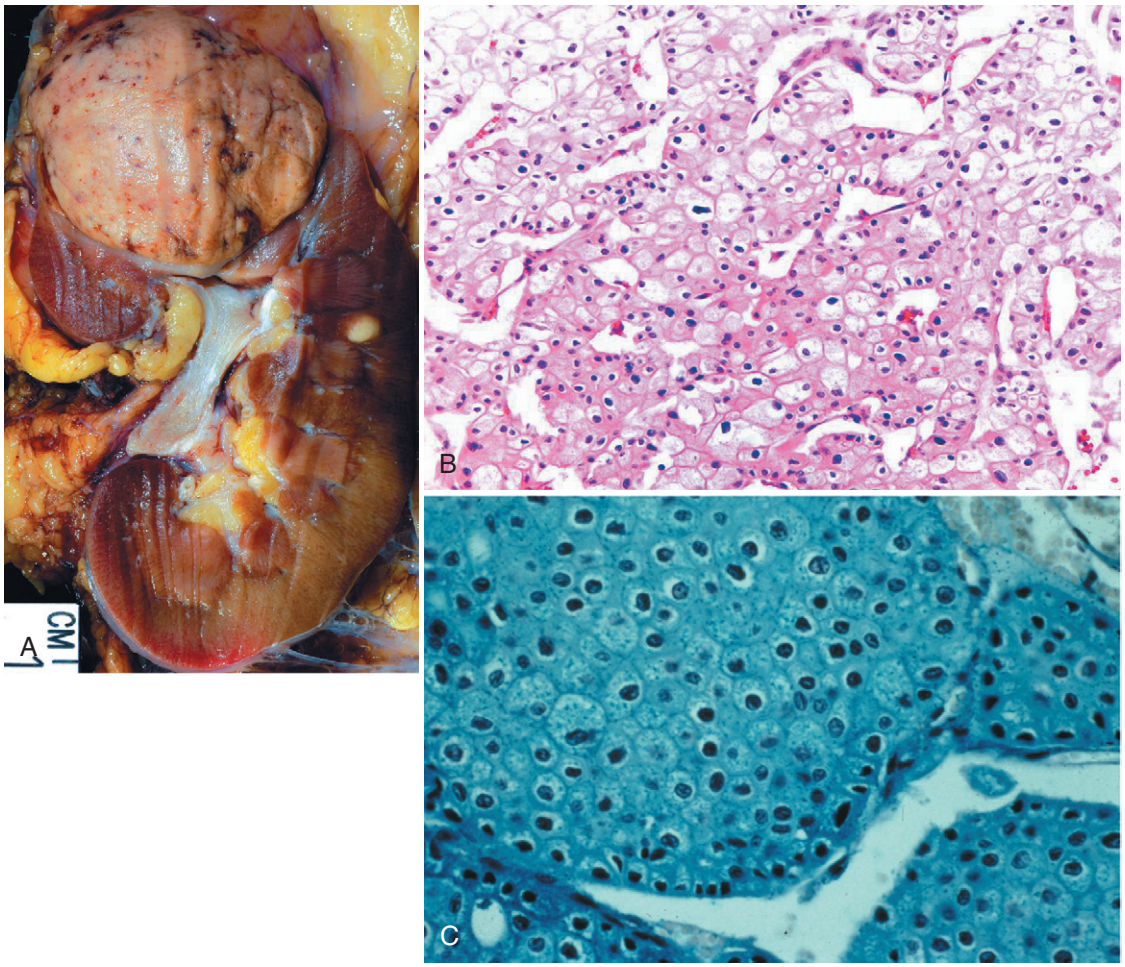


Figure 49–13. **A,** Chromophobe renal cell carcinoma (RCC) typically appears as a well-circumscribed, homogeneous, tan tumor. **B,** Chromophobe RCC with admixture of classic (chromophobic) and eosinophilic cells. Characteristic features include distinct cytoplasmic borders, perinuclear halos, and nuclear "raisins." The classic variant is notable for its "plant cell" appearance. **C,** Chromophobe RCC stains positive for Hale colloidal iron and demonstrates multiple microvesicles on analysis by electron microscopy. (Courtesy of Dr. Ming Zhou, Cleveland, OH.)

of this classic variant is responsible for the name of this histologic subtype (Nagashima, 2000; Kuroda et al, 2003a). However, eosinophilic variants of chromophobic RCC have also been described and constitute about 30% of cases (Theones et al, 1988; Störkel et al, 1997; Latham et al, 1999; Kuroda et al, 2003a). In either case, **a perinuclear clearing or "halo" is typically found and electron microscopic findings consist of numerous 150- to 300-nm microvesicles, which are the single most distinctive and defining feature of chromophobe cell carcinoma** (Nagashima, 2000; Krishnan and Truong, 2002). **These microvesicles characteristically stain positive for Hale colloidal iron, indicating the presence of a mucopolysaccharide unique to chromophobe RCC** (see Fig. 49–13) (Theones et al, 1988). Most chromophobe RCCs also stain positive for various cytokeratins and most are negative for vimentin (Cochand-Priollet et al, 1997). **Genetic analysis has revealed multiple chromosomal losses, most frequently the whole chromosomes 1, 2, 6, 10, 13, 17, and 21, and flow cytometric analysis has demonstrated hypodiploid DNA content in most cases** (Schwerdtle et al, 1996; Bugert et al, 1997; Iqbal et al, 2000; Polascik et al, 2002). Some studies have reported an increased incidence of *TP53* mutations in this histologic subtype and upregulated expression of the c-*KIT* oncogene has also been reported (Contractor et al, 1997; Yamazaki et al, 2003; Pan et al, 2004; Petit et al, 2004; Huo et al, 2005). Chromophobe RCC is commonly seen in the Birt-Hogg-Dubé syndrome, but most cases are sporadic (Pavlovich et al, 2002).

Most studies of the clinical behavior of chromophobe RCC suggest a better prognosis for localized chromophobe RCC than for clear cell RCC but a poor outcome in the subset of patients with sarcomatoid features or metastatic disease (Polascik et al, 2002; Lau et al, 2002; Cindolo et al, 2005a; Cheville et al, 2003; Peyromaure et al, 2003; Beck et al, 2004; Klatte et al, 2008a). Most early reports suggested a tendency to remain localized despite growth to large size, as well as a predominance of low-grade disease (Theones et al, 1988). Subsequent reports have verified that chromophobe RCC generally presents at an earlier stage, with more than 90% of patients remaining cancer free for 5 or more years after treatment (Crotty et al, 1995; Campbell et al, 1996b; Peyromaure et al, 2003; Cindolo et al, 2005a; Klatte et al, 2008a). However, a more adverse prognosis has been reported for high-grade tumors, including those with sarcomatoid differentiation (Campbell et al, 1996b; Renshaw et al, 1999; Kuroda et al, 2003a; Klatte et al, 2008a). Lymph node and distant metastases are commonly seen with such variants, and systemic disease is poorly responsive to IL-2 (Renshaw et al, 1999; Motzer et al, 2002; Klatte et al, 2008a). Initial data with the mTOR inhibitor temsirolimus indicate that this agent may have some

activity for metastatic chromophobe RCC; among 18 patients receiving treatment, 16 had stable disease and 1 had a partial response (Stadler et al, 2007). Clearly, further clinical evaluation will be required to identify the most effective therapeutic agents for patients with metastatic, non–clear cell RCC.

Collecting Duct Carcinoma

Carcinoma of the collecting ducts of Bellini is a relatively rare subtype of RCC, accounting for less than 1% of all RCCs (Kennedy et al, 1990; Rumpelt et al, 1991; Carter et al, 1992; Störkel et al, 1997; Srigley and Eble, 1998; Swartz et al, 2002). Many reported cases have occurred in younger patients, often in the third, fourth, or fifth decades of life (Carter et al, 1992). Most patients are symptomatic at presentation, and up to 50% have metastatic disease at the time of detection (Tokuda et al, 2006). *Ulex europaeus* agglutinin 1 reactivity and positivity for E-cadherin and c-KIT help to distinguish this entity from aggressive papillary RCC, but this staining profile can also be present in urothelial carcinoma and differential diagnosis often requires careful examination of multiple sections (Rumpelt et al, 1991; Oyasu, 1998; Polascik et al, 2002; Kobayashi et al, 2008). Expression of high-molecular-weight cytokeratin was initially believed to support a collecting duct origin, but more recent studies suggest that this is not a reliable marker for collecting duct carcinoma (Rumpelt et al, 1991; Oyasu, 1998; Polascik et al, 2002; Kobayashi et al, 2008). Small collecting duct carcinomas can arise in a medullary pyramid, but most are large, infiltrative masses and extension into the cortex is common (Pickhardt et al, 2001; Kobayashi et al, 2008). On microscopic examination, these tumors consist of an admixture of dilated tubules and papillary structures typically lined by a single layer of cuboidal cells, often creating a cobblestone appearance. Deletions on chromosome 1q and monosomy of chromosomes 6, 8, 11, 18, 21, and Y have been reported, but the number of tumors analyzed thus far has been limited (Fuzesi et al, 1992; Steiner et al, 1996; Polascik et al, 2002). **Most reported cases of collecting duct carcinoma have been high grade, advanced stage, and unresponsive to conventional therapies** (Carter et al, 1992; Chao et al, 2002b; Polascik et al, 2002; Mejean et al, 2003; Tokuda et al, 2006; Kobayashi et al, 2008). Reflecting the fact that collecting duct RCC may share features in common with transitional cell carcinoma, some patients with advanced collecting duct RCC have responded to cisplatin- or gemcitabine-based chemotherapy (Milowsky et al, 2002; Peyromaure et al, 2003; Kobayashi et al, 2008).

Renal Medullary Carcinoma

Renal medullary carcinoma is a subtype of RCC that occurs almost exclusively in association with the sickle cell trait. It is typically diagnosed in young African-Americans, often in the third decade of life, and many cases are both locally-advanced and metastatic at the time of diagnosis (Davis et al, 1995b; Polascik et al, 2002; Swartz et al, 2002; Zhou, 2009). Most patients do not respond to therapy and succumb to their disease in a few to several months (Davis et al, 1995b; Herring et al, 1997; Figenshau et al, 1998; Polascik et al, 2002). Mean survival in Davis and coworkers' series (1995b), which consisted of 34 patients, was only 15 weeks. **This tumor shares many histologic features with collecting duct carcinoma, and some consider it a subtype of collecting duct carcinoma or at least a closely related tumor** (Störkel et al, 1997; Polascik et al, 2002; Swartz et al, 2002). Renal medullary carcinoma is thought to arise from the calyceal epithelium near the renal papillae but is often highly infiltrative (Davidson et al, 1995; Davis et al, 1995b). The site of origin (renal papillae) and association with sickle cell trait suggest that a relatively hypoxic environment may contribute to tumorigenesis.

Sarcomatoid Differentiation

Sarcomatoid differentiation is found in 1% to 5% of RCCs, most commonly in association with clear cell RCC or chromophobe RCC, but variants of most other subtypes of RCC have been described (Weiss et al, 1995; Störkel et al, 1997; Oyasu, 1998; Delahunt, 1999; dePeralta-Venturina et al, 2001; Kuroda et al, 2003e; Cheville et al, 2004; Zhou, 2009). Most authors now believe that sarcomatoid lesions represent poorly differentiated regions of other histologic subtypes of RCC rather than independently derived tumors (DeLong et al, 1993; Oyasu, 1998; Delahunt, 1999; Eble et al, 2004). A thorough search for epithelial-derived malignant components is almost always fruitful; it is rare to find a truly pure sarcomatoid renal mass (Delahunt, 1999). **For this reason, this entity is no longer recognized as a distinct histologic subtype of RCC** (Eble et al, 2004). **Sarcomatoid differentiation is characterized by spindle cell histology, positive staining for vimentin, infiltrative growth pattern, aggressive local and metastatic behavior, and poor prognosis** (Fig. 49–14) (Ro et al, 1987; DeLong et al, 1993; Cangiano et al, 1999; Eble et al, 2004). Invasion of adjacent organs is common, and median survival has been less than 1 year in most series (Ro et al, 1987; Cangiano et al, 1999; Escudier et al, 2002a; Mian et al, 2002; Nanus et al, 2004; Dall'Oglio et al, 2005; Zhou, 2009). Multimodal approaches should be considered if performance status allows based on the extremely poor prognosis with surgery alone and selected reports demonstrating modestly improved response rates in patients receiving IL-2–based immunotherapy, chemotherapy, or targeted molecular therapy after surgery (Cangiano et al, 1999; Bangalore et al, 2001; Fujiwara et al, 2008; Rini et al, 2009).

Unclassified Renal Cell Carcinoma

Unclassified RCC represents a small minority of cases (<3%) of presumed RCC with features that remain indeterminate even after careful analysis (Zisman et al, 2002a). **Most are poorly differentiated and are associated with a highly aggressive biologic behavior and a particularly poor prognosis** (Zisman et al, 2002a; Karakiewicz et al, 2007). Included within this "catch-all" category are RCCs with extensive sarcomatoid differentiation and no discernible epithelial component. Advances in molecular diagnostics, such as gene expression profiling, may enable further classification of unusual tumors that previously would have fallen into this category and identify candidate pathways for targeted molecular therapeutics (Yang et al, 2006; Young et al, 2008).

Clinical Presentation

Because of the sequestered location of the kidney within the retroperitoneum, many renal masses remain asymptomatic and nonpalpable until they are advanced. With the more pervasive use of noninvasive imaging for the evaluation of a variety of nonspecific symptom complexes, more than 50% of RCCs are now detected incidentally (Pantuck et al, 2000). Several studies have shown that such tumors are more likely to be confined to the kidney, and a positive impact on survival has been reported, although the potential contributions of lead and length time biases have not been defined (Konnak and Grossman, 1985; Thompson and Peek, 1988; Kessler

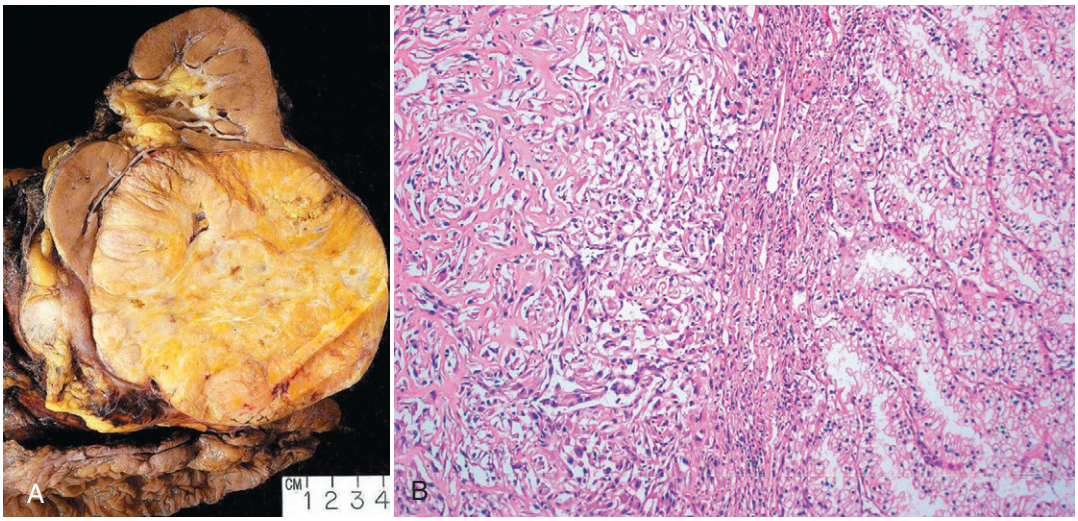


Figure 49–14. **A,** Clear cell renal cell carcinoma (RCC) with sarcomatoid differentiation demonstrating extension into the perinephric fat. **B,** High-grade RCC with typical spindle-cell appearance on the left indicating a component of sarcomatoid differentiation. (Courtesy of Dr. Ming Zhou, Cleveland, OH.)

Table 49–12.

Clinical Presentation of Renal Cell Carcinoma

Incidental
Local Tumor Growth
Hematuria
Flank pain
Abdominal mass
Perirenal hematoma
Metastases
Persistent cough
Bone pain
Cervical lymphadenopathy
Constitutional symptoms
Weight loss/fever/malaise
Obstruction of the Inferior Vena Cava
Bilateral lower extremity edema
Nonreducing or right-sided varicocele
Paraneoplastic Syndromes
Hypercalcemia
Hypertension
Polycythemia
Stauffer's syndrome

Table 49–13.

Incidence of Systemic Syndromes Associated with Renal Cell Carcinoma

SYNDROME	%
Elevated erythrocyte sedimentation rate	55.6
Hypertension	37.5
Anemia	36.3
Cachexia, weight loss	34.5
Pyrexia	17.2
Abnormal liver function	14.4
Hypercalcemia	4.9
Polycythemia	3.5
Neuromyopathy	3.2
Amyloidosis	2.0

From Gold PJ, Fefer A, Thompson JA. Paraneoplastic manifestations of renal cell carcinoma. Semin Urol Oncol 1996;14:216–22.

et al, 1994; Tsui et al, 2000b; Parsons et al, 2001; Lee et al, 2002; Leslie et al, 2003; Nguyen et al, 2006; DeCastro and McKiernan, 2008; Kane et al, 2008).

Symptoms associated with RCC can be due to local tumor growth, hemorrhage, paraneoplastic syndromes, or metastatic disease (Table 49–12). Flank pain is usually due to hemorrhage and clot obstruction, although it can also occur with locally advanced or invasive disease. **The classic triad of flank pain, gross hematuria, and palpable abdominal mass is now rarely found** (Jayson and Sanders, 1994). This is fortunate because this constellation of findings almost always denotes advanced disease, and some refer to it as the "too late triad." Before the advent of ultrasonography and CT, most patients with RCC presented with one or more of these signs or symptoms, and many were incurable. Other indicators of advanced disease include constitutional symptoms, such as weight loss, fever, and night sweats, and physical examination findings such as palpable cervical lymphadenopathy, nonreducing varicocele, and bilateral lower extremity edema due to venous involvement. A minority of patients present with symptoms directly related to metastatic disease, such as bone pain or persistent cough. **A less common but important presentation of RCC is that of spontaneous perirenal hemorrhage, although the underlying mass is often obscured by the blood.** Zhang and colleagues (2002) **have shown that more than 50% of patients with perirenal hematoma of unclear etiology have an occult renal tumor, most often AML or RCC.** Repeat CT a few months later will often provide a definitive diagnosis.

Paraneoplastic syndromes are found in 20% of patients with RCC, and few tumors are associated with the diversity of such syndromes (Table 49–13). In fact, **RCC was previously referred to as the internist's tumor because of the predominance of systemic rather than local manifestations** (Sufrin et al, 1989; Gold et al, 1996; Moein and Dehghani, 2000; DeLuca et al, 2002; Kamra et al, 2002; Hagel et al, 2005; Costanzi et al, 2008). Now, a more appropriate name would be the radiologist's tumor, given the frequency of incidental detection (Parsons et al, 2001; DeCastro and McKiernan, 2008; Kane et al, 2008). Nevertheless, it is still important to evaluate for paraneoplastic phenomena because they can be a source of major morbidity and

can affect clinical decision making. Under normal circumstances, the kidney produces 1,25-dihydroxycholecalciferol, renin, erythropoietin, and various prostaglandins, all of which are tightly regulated to maintain homeostasis. RCC may produce these substances in pathologic amounts, and it may also elaborate a variety of other physiologically important factors, such as parathyroid hormone–like peptides, lupus-type anticoagulant, human chorionic gonadotropin, insulin, and various cytokines and inflammatory mediators (Sufrin et al, 1989; Gold et al, 1996; Ather et al, 2002; Elias, 2005). These substances are believed to be responsible for the development of constitutional symptoms such as weight loss, fever, and anemia as well as some of the distinct paraneoplastic syndromes observed with this malignancy (Altundag et al, 2005; Elias, 2005).

Hypercalcemia has been reported in up to 13% of patients with RCC and can be due to either paraneoplastic phenomena or osteolytic metastatic involvement of the bone (Sufrin et al, 1989; Gold et al, 1996; Magera et al, 2004; Klatte et al, 2007d; Pepper et al, 2007; Schwarzberg and Michaelson, 2009). The production of parathyroid hormone–like peptides is the most common paraneoplastic etiology, although tumor-derived 1,25-dihydroxycholecalciferol and prostaglandins may contribute in a minority of cases (Goldberg et al, 1964; Mangin et al, 1988; Sufrin et al, 1989; Gold et al, 1996; Walther et al, 1997b; Magera et al, 2004; Massfelder et al, 2004; Klatte et al, 2007d; Pepper et al, 2007). Recent data suggest that the expression of parathyroid hormone–like peptides is suppressed by the wild-type VHL protein, and these peptides may act as potent growth factors for RCC (Massfelder et al, 2004). This may account in part for the observation that patients with RCC who present with hypercalcemia have a compromised prognosis, with a relative risk of death from cancer progression of 1.78 compared with patients with normal serum calcium levels (Magera et al, 2004). **The signs and symptoms of hypercalcemia are often nonspecific and include nausea, anorexia, fatigue, and decreased deep tendon reflexes. Medical management predominates and includes vigorous hydration followed by diuresis with furosemide and the selective use of bisphosphonates, corticosteroids, or calcitonin** (reviewed in Gold et al, 1996; Coleman, 2004; Pepper et al, 2007; Schwarzberg and Michaelson, 2009). **Bisphosphonate therapy is now established as standard of care for patients with hypercalcemia of malignancy, as long as renal function is adequate** (Schwarzberg and Michaelson, 2009). Zoledronic acid, 4 mg intravenously every 4 weeks, appears to be particularly effective in patients with RCC but must be withheld in the presence of renal insufficiency (Lipton et al, 2003, 2004; Coleman et al, 2004; Schwarzberg and Michaelson, 2009). Indomethacin has also proved useful in a minority of cases (Gold et al, 1996; Walther et al, 1997b). More definite management includes nephrectomy and occasional metastasectomy, depending on the clinical circumstances. Systemic therapy to reduce the burden of disease is also desirable but difficult to achieve in patients with RCC (Goldberg et al, 1980). Hypercalcemia related to extensive osteolytic metastases is much more difficult to palliate because it is not amenable to surgical approaches, but many such patients may respond to bisphosphonate therapy (Lipton et al, 2003, 2004; Coleman et al, 2004). Some patients with hypercalcemia related to osteolytic metastases may also benefit from focused radiation therapy if limited sites of involvement can be identified (Gold et al, 1996).

Hypertension and polycythemia are other important paraneoplastic syndromes commonly found in patients with RCC (Moein and Dehghani, 2000). Hypertension associated with RCC can be secondary to increased production of renin directly by the tumor; compression or encasement of the renal artery or its branches, effectively leading to renal artery stenosis; or arteriovenous fistula within the tumor (Robertson et al, 1967; Sufrin et al, 1989). Less common causes include polycythemia, hypercalcemia, ureteral obstruction, and increased intracranial pressure associated with cerebral metastases (Sufrin et al, 1989). Polycythemia associated with RCC can be due to increased production of erythropoietin, either directly by the tumor or by the adjacent parenchyma in response to hypoxia induced by tumor growth (Gross et al, 1994; Wiesener et al, 2007).

One of the more fascinating paraneoplastic syndromes associated with RCC is nonmetastatic hepatic dysfunction, or Stauffer syndrome, which has been reported in 3% to 20% of cases (Stauffer, 1961; Rosenblum, 1987; Giannakos et al, 2005; Moria et al, 2006; Young et al, 2008). Almost all patients with Stauffer syndrome have an elevated serum alkaline phosphatase level, 67% have elevated prothrombin time or hypoalbuminemia, and 20% to 30% have elevated serum bilirubin or transaminase levels (Sufrin et al, 1989). Other common findings include thrombocytopenia and neutropenia, and typical symptoms include fever and weight loss, which is not surprising given that many patients are found to harbor discrete regions of hepatic necrosis (Sufrin et al, 1989; Gold et al, 1996). Hepatic metastases must be excluded. Biopsy, when indicated, often demonstrates nonspecific hepatitis associated with a prominent lymphocytic infiltrate (Hanash, 1982). Elevated serum levels of IL-6 have been found in patients with Stauffer syndrome, and it is believed that this and other cytokines may play a pathogenic role (Blay et al, 1997). Hepatic function normalizes after nephrectomy in 60% to 70% of cases. Persistence or recurrence of hepatic dysfunction is almost always indicative of the presence of viable tumor and thus represents a poor prognostic finding (reviewed in Sufrin, 1989).

A variety of other less common but distinct paraneoplastic syndromes associated with RCC have been reviewed by Sufrin and colleagues (1989), including Cushing syndrome, hyperglycemia, galactorrhea, neuromyopathy, clotting disorders, and cerebellar ataxia (Ather et al, 2002; Kamra et al, 2002; Hagel et al, 2005; Mohammed et al, 2006; Ammar et al, 2008).

In general, treatment of paraneoplastic syndromes associated with RCC has required surgical excision or systemic therapy and, except for hypercalcemia, medical therapies have not proved helpful.

Screening and Clinical Associations

A number of factors make screening for RCC appealing (Cohn and Campbell, 2000; Herts, 2005; Carrizosa and Godley, 2009). **Most important, RCC remains primarily a surgical disease requiring early diagnosis to optimize the opportunity for cure.** Unfortunately, our ability to salvage patients with advanced disease remains limited. Consistent with these observations, several studies have demonstrated an apparent advantage to early or incidental diagnosis of RCC (Konnak and Grossman, 1985; Thompson and Peek, 1988; Kessler et al, 1994; Cohn and Campbell, 2000; Tsui et al, 2000b; Parsons et al, 2001; Lee et al, 2002; Leslie et al, 2003).

The primary factor that limits the widespread implementation of screening for RCC is the relatively low incidence of RCC in the general population (approximately 12 cases per 100,000 population/year) (Wallen et al, 2007; DeCastro and McKiernon, 2008; Woldrich et al, 2008; Carrizosa and Godley, 2009). In this setting a screening test must be almost

100% specific to avoid an unacceptably high false-positive rate, which would lead to unnecessary, expensive, and potentially harmful diagnostic or therapeutic procedures. In addition, even if the test were 100% sensitive and specific, the yield from screening would be so low that it would not be considered cost effective (Cohn and Campbell, 2000; Carrizosa and Godley, 2009). Even when one considers populations with established risk factors for RCC, such as male sex, increased age, and heavy tobacco use, generalized screening would be difficult to justify because the increase in relative risk associated with each of these factors is at best twofold to threefold (Paganini-Hill et al, 1988; Cohn and Campbell, 2000; Carrizosa and Godley, 2009). Another confounding factor is the prevalence of clinically insignificant tumors such as renal adenomas, which are found at autopsy in 10% to 20% of individuals, and other benign or slow-growing tumors (Xipell, 1971; Bosniak et al, 1995; Cohn and Campbell, 2000; Pantuck et al, 2000; Parsons et al, 2001). There is clearly a risk that such clinically insignificant lesions could be detected, leading to unnecessary evaluation and treatment (Pantuck et al, 2000; Parsons et al, 2001). **All these factors recommend against generalized screening efforts for the detection of RCC.**

Review of the literature describing the use of dipstick analysis for hematuria and ultrasonography or CT for screening for RCC supports these conclusions (Cohn and Campbell, 2000; Herst, 2005; Carrizosa and Godley, 2009). Urinalysis is simple and inexpensive, but the yield of RCC in several screening studies has been exceedingly low (Mohr et al, 1986; Thompson, 1987; Mariani et al, 1989; Murakami et al, 1990). In part, this may be because small RCCs are often not associated with hematuria (gross or microscopic) because this is a parenchymal rather than an urothelium-based malignant neoplasm (Tosaka et al, 1990). The incidence of RCC in ultrasound or CT screening studies has ranged from 23 to 300 per 100,000 population, and an apparent advantage of screening has been debated because an increased proportion of organ-confined tumors has been found in screened populations compared with historical controls (Sohma et al, 1989; Tosaka et al, 1990; Spouge et al, 1996; Tsuboi et al, 2000; Filipas et al, 2003; Fenton and Weiss, 2004; Herts, 2005; Malaeb et al, 2005; Turney et al, 2006; Carrizosa and Godley, 2009). However, although the yield of RCC has been higher than expected, it is still relatively low; and it is unlikely that such efforts would be considered cost effective (Cohn and Campbell, 2000; Herts, 2005). Overall, the yield of RCC in such studies is an order of magnitude lower than the yield from prostate-specific antigen–based screening for prostate cancer, and many of the same controversies about lead and length time biases that have plagued the debate about screening for prostate cancer also apply to RCC (Cohn and Campbell, 2000; Pantuck et al, 2000; Parsons et al, 2001; Fenton and Weiss, 2004; Herts, 2005; Carrizosa and Godley, 2009). Because of these considerations, it is difficult to justify generalized screening efforts for RCC given the currently available technology.

Several investigators are now reporting novel molecular assays to detect RCC-related biomarkers in the urine or serum that may substantially alter our perspective about screening for RCC. These assays can detect microsatellite alterations in the DNA, *VHL* gene mutations or hypermethylation, expression of RCC-specific proteins such as CA-9, or upregulation of angiogenic factors, including VEGF (Eisenberger et al, 1999; De la Taille et al, 2000; Chang et al, 2001; Ashida et al, 2003; Battagli et al, 2003; Chen and Getzenberg, 2004; Hoque et al, 2004; Uzzo et al, 2004). Proteomic profiling of the urine to detect RCC-specific markers also holds much promise for the future (Rogers et al, 2003).

For now, however, the focus of screening for RCC must be on well-defined target populations, such as patients with end-stage renal disease and acquired renal cystic disease, tuberous sclerosis, and familial RCC (Table 49–14). Eighty percent of patients with end-stage renal disease eventually develop acquired renal cystic disease, and 1% to 2% of this subgroup develops RCC (Ishikawa et al, 1980, 1990; Matson and Cohen, 1990; Levine et al, 1991; Cheuk et al, 2002; Brown, 2004). **Overall, the relative risk of RCC in patients with end-stage renal disease has been estimated to be 5- to 20-fold higher than that in the general population** (Ishikawa et al, 1990, 1991, 2004; Matson and Cohen, 1990; Levine et al, 1991; Levine, 1992; Cowie, 2002; Denton et al, 2002; Brown, 2004; Farivar-Mohseni et al, 2006). Fifteen percent of patients with RCC in the setting of end-stage renal disease have metastases at the time of presentation, and many such patients die of malignant progression (Levine et al, 1991; Brown, 2004; Ishikawa, 2004). Given these considerations, screening for RCC is recommended in this population, which is substantial, representing almost 300,000 patients in the United States alone. There are, however, a number of problems associated with screening this population of patients. These include concerns about short life expectancy, increased incidence of adenomas (20% to 40% vs. 10% to 20% in the general population), complexity of imaging given the altered architecture associated with acquired renal cystic disease, and inevitable cost-related issues (Mindell, 1989; Levine et al, 1991, 1997; Sarasin et al, 1995; Cowie, 2002). **A reasonable compromise for patients with end-stage renal disease is to target those without other major comorbidities, to delay screening until the third year on dialysis, and to take into account the sex and type of renal replacement therapy, although data about the last factors are admittedly controversial**

Table 49–14.

Screening for Renal Cell Carcinoma: Target Populations

Patients with End-Stage Renal Disease
Screen only patients with long life expectancy and minimal major comorbidities.
Perform periodic ultrasound examination or CT scan beginning during third year on dialysis.
Patients with Known von Hippel-Lindau Syndrome
Obtain biannual abdominal CT or ultrasound study beginning at age 15 to 20 years.
Perform periodic clinical and radiographic screening for nonrenal manifestations.
Relatives of Patients with von Hippel-Lindau Syndrome
Obtain genetic analysis.
If positive, follow screening recommendations for patients with known von Hippel-Lindau syndrome.
If negative, less stringent follow-up is required.
Relatives of Patients with Other Familial Forms of Renal Cell Carcinoma
Obtain periodic ultrasound or CT study and consider genetic analysis.
Patients with Tuberous Sclerosis
Perform periodic screening with ultrasound examination or CT scan.
Patients with Autosomal-Dominant Polycystic Kidney Disease
Routine screening is not justified.

(Brown, 2004; Carrizosa and Godley, 2009). Ishizuka and colleagues (2000) have demonstrated elevated serum levels of VEGF in dialysis patients with RCC, suggesting a potential role for biomarkers for screening this population in the future. Interestingly, recent data suggest that renal transplant recipients remain at high risk for RCC in the native kidneys, and Neuzillet and colleagues (2005) have recommended continued periodic radiologic screening even after transplantation (Ianhez et al, 2007).

An increased incidence of RCC has also been debated in tuberous sclerosis, an autosomal dominant disorder in which patients can develop adenoma sebaceum (a distinctive skin lesion), epilepsy, mental retardation, and renal cysts and AMLs (Shapiro et al, 1984; Bernstein et al, 1986; Washecka and Hanna, 1991; Aoyama et al, 1996; Bjornsson et al, 1996; Robertson et al, 1996; Sampson, 1996; Tello et al, 1998; Choyke et al, 2003; Lendvay and Marshall, 2003; Narayanan, 2003; Cohen and Zhou, 2005; Radkowski et al, 2006). Many cases of RCC in this syndrome have been characterized by early onset and multifocality, suggesting a genetic predisposition (Washecka and Hanna, 1991; Lendvay and Marshall, 2003). In addition, the Eker rat, which is mutant for the rodent homologue of the *TSC2* gene responsible for the development of tuberous sclerosis in humans, develops RCC at high frequency, as do *TSC2*-deficient knockout mice (Yeung et al, 1994; Kobayashi et al, 1997, 1999; Hino et al, 1999; Lendvay and Marshall, 2003; McDorman and Wolf, 2002). Furthermore, an increased incidence of *TSC2* mutations has been found in human RCC (Duffy et al, 2002; Lendvay and Marshall, 2003), and Liu and colleagues (2003) have shown that loss of this tumor suppressor gene leads to upregulated expression of VEGF through an mTOR and HIF-2α–mediated mechanism, analogous to the role of the VHL protein. **Such biologic and clinical observations argue in favor of an increased predisposition for RCC in this syndrome, which is consistent with most, although admittedly not all, relevant demographic data** (Shapiro et al, 1984; Bernstein et al, 1986; Washecka and Hanna, 1991; Aoyama et al, 1996; Bjornsson et al, 1996; Robertson et al, 1996; Sampson, 1996; Tello et al, 1998; Lendvay and Marshall, 2003; Martignoni et al, 2003; Cohen and Zhou, 2005; Rakowski et al, 2006; Nathanson and Stephenson, 2009). **A reasonable conclusion is that periodic renal imaging should be pursued in patients with tuberous sclerosis; such a policy will also facilitate follow-up for the development and progression of AML.**

Screening for RCC in autosomal dominant polycystic kidney disease (ADPKD) was previously recommended, but several factors have prompted a reassessment of this policy. **More recent studies suggest no significantly increased risk of RCC in ADPKD,** and imaging is extremely difficult in this population related to the altered intrarenal architecture (Torres et al, 1985; Gregoire et al, 1987; Keith et al, 1994; Sessa et al, 1997; Soderdahl et al, 1997; Cohn and Campbell, 2000; Gupta et al, 2000; Mosetti et al, 2003). The increased incidence of adenomas in ADPKD would also mitigate against a potential benefit of screening (Torres et al, 1985; Gregoire et al, 1987). **Taken together, these considerations suggest that screening for RCC in patients with ADPKD should not be pursued.**

Special consideration should also be given to von Hippel-Lindau disease in any discussion of the value of screening for RCC. This syndrome should be considered in any patient with early-onset or multifocal RCC or RCC in combination with any of the following: a history of visual or neurologic disorders; a family history of blindness, central nervous system tumors, or renal cancer; or coexistent pancreatic cysts, epididymal lesions, or inner ear tumors (Neumann and Zbar, 1997; Choyke et al, 2003; Linehan et al, 2003; Pavlovich and Schmidt, 2004; Vira et al, 2007; Pfaffenroth and Linehan, 2008; Coleman, 2008; Hansel and Rini, 2008; Nathanson and Stephenson, 2009). **Patients suspected of having von Hippel-Lindau disease, or the appropriate relatives of those with documented disease, should strongly consider genetic evaluation.** The entire *VHL* gene has now been sequenced and sophisticated molecular analysis is readily available and offers a number of important advantages (Zbar et al, 1999; Linehan et al, 2003; Vira et al, 2007; Pfaffenroth and Linehan, 2008). **Patients with germline mutations can be identified and offered clinical and radiographic screening that can identify the major manifestations of von Hippel-Lindau disease at a presymptomatic phase, allowing potential amelioration of the considerable morbidity associated with this syndrome** (Glenn et al, 1992; Maranchie and Linehan, 2003; Vira et al, 2007; Pfaffenroth and Linehan, 2008). Investigators at the National Institutes of Health have recommended that such patients be evaluated with (1) annual physical examination and ophthalmologic evaluation beginning in infancy; (2) estimation of urinary catecholamines at the age of 2 years and every 1 to 2 years thereafter; (3) MRI of the central nervous system biannually beginning at the age of 11 years; (4) ultrasound examination of the abdomen and pelvis annually beginning at the age of 11 years, followed by CT every 6 months if cysts or tumors develop; and (5) periodic auditory examinations (Choyke et al, 1995; Friedrich, 1999; Maranchie and Linehan, 2003). Less intensive protocols have also been advocated, although all relevant organ systems should be addressed (Fraser et al, 2007; Foulkes and Hodgson, 1998). Individuals who are found to be wild type for both alleles of *VHL* also benefit because they can be spared much of the expense and anxiety associated with such intensive surveillance protocols.

Molecular screening is also available for patients suspected of having hereditary papillary RCC and other familial forms of RCC and should be discussed with appropriate family members (Schmidt et al, 1997; Linehan et al, 2003; Zbar et al, 2007; Vira et al, 2007; Pfaffenroth and Linehan, 2008; Coleman, 2008; Hansel and Rini, 2009, Nathanson and Stephenson, 2009). Again, individuals at risk, as defined by the presence of mutations of the c-*MET* proto-oncogene or other relevant genetic alterations, and those with suggestive clinical or family histories should be evaluated with abdominal ultrasonography or CT at periodic intervals. Further testing may be indicated according to the syndrome involved.

Staging

Until the 1990s the most commonly used staging system for RCC was Robson's modification of the system of Flocks and Kadesky, and this schema is still embedded in the mindset of many urologists (Fig. 49–15) (Robson, 1963; Robson et al, 1969). In retrospect, the limitations of this classification scheme are readily evident. The primary problem can be found in stage III, where tumors with lymphatic metastases, a very poor prognostic finding, were combined with those with venous involvement, many of which can be treated and potentially cured with an aggressive surgical approach (Gettman and Blute, 2002; Leibovich et al, 2003c; Nguyen and Campbell, 2006). Further imprecision resulted from the fact that the extent of venous involvement was not delineated in this system, and tumor size, an important prognostic parameter, was not incorporated. The net effect was that the prognostic significance of the various stages

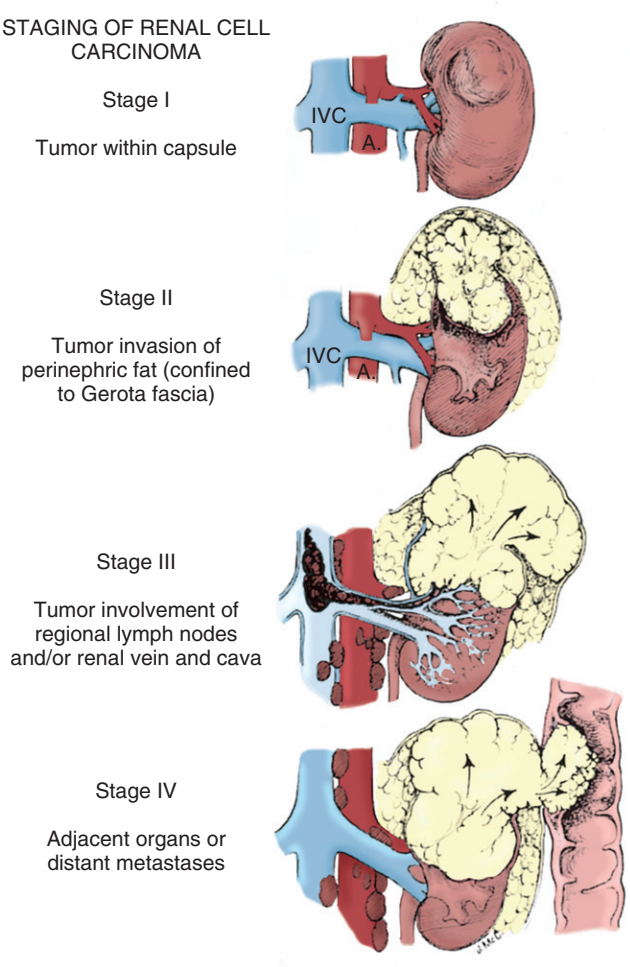


Figure 49–15. Staging of renal cell carcinoma as proposed by Holland, in accordance with classification systems developed by Robson, Murphy, and Flocks and Kadesky. A, aorta; IVC, inferior vena cava. (From Holland JM. Cancer of the kidney: natural history and staging. Cancer 1973;32:1030. Copyright © 1973 American Cancer Society.)

Table 49–15.

International TNM Staging System for Renal Cell Carcinoma

T: Primary Tumor			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor ≤7.0 cm and confined to the kidney		
T1a	Tumor ≤4.0 cm and confined to the kidney		
T1b	Tumor >4.0 cm and ≤7.0 cm and confined to the kidney		
T2	Tumor >7.0 cm and confined to the kidney		
T2a	Tumor >7.0 cm and ≤10.0 cm and confined to the kidney		
T2b	Tumor >10.0 cm and confined to the kidney		
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond the Gerota fascia		
T3a	Tumor grossly extends into the renal vein or its segmental (muscle containing) branches or tumor invades perirenal and/or renal sinus fat but not beyond the Gerota fascia		
T3b	Tumor grossly extends into the vena cava below the diaphragm		
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava		
T4	Tumor invades beyond the Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)		
N: Regional Lymph Nodes			
NX:	Regional lymph nodes cannot be assessed		
N0:	No regional lymph nodes metastasis		
N1:	Metastasis in regional lymph node(s)		
M: Distant Metastases			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis present		
Stage Grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 or T2	N1	M0
	T3	Any N	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

Modified from Edge SB, Byrd DR, Compton CC, et al, editors. AJCC cancer staging manual. 7th ed. New York: Springer; 2010.

was blunted, with some studies reporting equivalent survival for patients with stage II and stage III tumors (Skinner et al, 1971).

The tumor, nodes, and metastasis (TNM) system proposed by the Union International Contre le Cancer (UICC) represented a major improvement because it separated tumors with venous involvement from those with lymphatic invasion and defined the anatomic extent of disease more explicitly (Beahrs et al, 1988; Leibovich et al, 2003b; Nguyen and Campbell, 2006; DeCastro and McKiernon, 2008). Another advantage of the TNM system is that it has facilitated comparison of clinical and pathologic data from various centers across the globe (Leung and Ghavamian, 2002; Leibovich et al, 2003b; Nguyen and Campbell, 2006).

In 2009 the American Joint Committee on Cancer (AJCC) proposed a revision of the TNM system that is now the recommended staging system for RCC (Table 49–15) (Edge et al, 2010). The TNM classification for RCC has undergone several modifications in the past 3 decades in an effort to more accurately reflect tumor biology and prognosis and to guide clinical management. It is important to be cognizant of these changes when comparing studies from different eras (Nguyen and Campbell, 2006). **In 1997 the previous division of stages T1 and T2 at tumor size of 2.5 cm was abandoned because several studies showed no prognostic significance at this level. Analysis of the Surveillance, Epidemiology, and End Results (SEER) program database demonstrated survival differences associated with 5-, 7.5-, and 10-cm cut points, and the 7-cm cut point between stages T1 and T2 was adopted because it reflected the mean tumor size in the database** (Guinan et al, 1995a; Gettman et al, 2001b; Ficcarra et al, 2006; Salama et al, 2005). **In the 2002 version stage T1 was subdivided: T1a represents tumor size of 4 cm or less, and T1b represents tumor size between 4 and 7 cm, reflecting data in the literature demonstrating excellent outcomes for patients with small (≤4 cm), unilateral, confined tumors managed by either partial or radical nephrectomy** (Butler et al, 1994; Lerner et al, 1996; Hafez et al, 1999; Igarashi et al, 2001; Frank et al, 2004a, 2005b, Nguyen and

Campbell, 2006). **The most recent change for organ-confined tumors is a subdivision of T2 tumors: T2a tumor represents tumors between 7 and 10 cm, and T2b represents tumors greater than 10 cm** (see Table 49–15), supported by a number of studies demonstrating prognostic relevance at this breakpoint (Frank et al, 2005b; Klatte et al, 2007c).

Other major revisions in 2009 included a reclassification of tumors with adrenal metastasis, venous thrombi, and lymphatic involvement, representing a substantial departure from previous staging paradigms for RCC (Table 49–16) (Edge et al, 2010). **Contiguous extension of tumor into the ipsilateral adrenal gland is now classified as T4 and metastatic involvement of either adrenal as M1, reflecting likely patterns of dissemination.** The poor prognosis of adrenal involvement from RCC is well documented and supported this important change (Sagalowsky et al, 1994; Sandock et al, 1997; Paul et al, 2001a; Von Knobloch et al, 2004; Lam et al, 2005a; Shvarts et al, 2005a; Siemer et al, 2005; Thompson et al, 2005a; Nguyen and Campbell, 2006; Kirkali et al, 2007). **The favorable prognosis of isolated renal venous thrombi prompted a downgrading from stage T3b to stage T3a in the 2009 version** (Moinzadeh and Libertino, 2004; DeKernion, 2005; Leibovich et al, 2005; Shvarts et al, 2005a; Thompson et al, 2005a; Ficarra and Artibani, 2006; Gofrit et al, 2007; Ficarra et al, 2007b; Margulis et al, 2007c). **Finally, lymphatic extension, which previously was subdivided based on the number of involved nodes, has now been compressed to simplify this aspect of the staging process, because prognostic relevance of the previous version was not observed** (Edge et al, 2010).

TNM staging classically is defined by the most advanced feature demonstrated by the tumor, yet important prognostic information can be lost in the process. Many tumors exhibit multiple adverse findings, such as high-level tumor thrombus along with ipsilateral adrenal involvement. Ideally all of the relevant anatomic staging information would be captured, at least parenthetically (e.g., pT4 [ipsilateral adrenal involvement; also exhibiting IVC thrombus above the diaphragm]). Future staging systems will ideally capture all of this information, because a number of investigators have demonstrated strong prognostic relevance to such combinations of parameters (Liebovich et al, 2005; Shvarts et al, 2005a; Thompson et al, 2005a; Fujita et al, 2007; Ficarra et al, 2007a, 2007b; Klatte et al, 2007c; Terrone et al, 2008).

The clinical staging of renal malignant disease begins with a thorough history, physical examination, and judicious use of laboratory tests (Nguyen and Campbell, 2006; DeCastro and McKiernon, 2008). **Presentation with systemic symptoms such as significant weight loss (>10% of body weight), cachexia, or poor performance status all suggest advanced disease, as do physical examination findings of a palpable mass or lymphadenopathy.** A nonreducing varicocele and lower extremity edema suggest venous involvement. Abnormal liver function test results, elevated serum alkaline phosphatase or lactate dehydrogenase level or sedimentation rate, hypercalcemia, and significant anemia point to the probability of advanced disease (Gelb, 1997; Srigley et al, 1997; Nguyen and Campbell, 2006; Lane and Kattan, 2008).

The radiographic staging of RCC can be accomplished in most cases with a high-quality abdominal CT scan and a routine chest radiograph, with selective use of MRI and other studies as indicated (reviewed in Bechtold and Zagoria, 1997; Choyke et al, 2001; Griffin et al, 2007, Zhang et al, 2007a; Ng et al, 2008; Herts, 2009). MRI can be reserved primarily for patients with locally advanced malignant disease, equivocal venous involvement, or allergy to intravenous contrast material (Choyke, 1997; Pretorius et al, 2000; Choyke et al, 2001; Zhang et al, 2007a; Herts, 2009). CT findings suggestive of extension into the perinephric fat include perinephric stranding (Fig. 49–16), which is a nonspecific finding, or a distinct soft tissue density within the perinephric space, which is a more definitive but uncommon finding (Bechtold and Zagoria, 1997; Herts, 2009). Overall, the accuracy of CT or MRI for detection of involvement of the perinephric fat is low, reflecting the fact that extracapsular spread often occurs microscopically (Pretorius et al, 2000; Choyke et al, 2001; Leung and Ghavamian, 2002; Kamel et al, 2004; Zhang et al, 2007a). Many of these potentially locally advanced cases are managed with radical nephrectomy, so the clinical relevance of this imprecision in staging is blunted. Ipsilateral adrenal involvement can be assessed with reasonable accuracy through a

Table 49–16.

2010 Revision of AJCC Staging for Kidney Cancer (7th Edition): Summary of Substantial Changes

Division of T2: organ confined
T2a: 7-10 cm
T2b: >10 cm
Upgrading of adrenal involvement
T4 if contiguous extension into ipsilateral adrenal
M1 otherwise
Downgrading of isolated renal venous thrombus
Previously T3b, now T3a
Compression of nodal involvement
Any nodal involvement now N1
Recommendation that all potentially adverse features be captured at least parenthetically
For example, T3b (tumor with inferior vena cava thrombus below level of diaphragm, also exhibiting extension into the perinephric fat)

Data from Edge SB, Byrd DR, Compton CC, et al, editors. AJCC cancer staging manual. 7th ed. New York: Springer; 2010. p. 479–89.

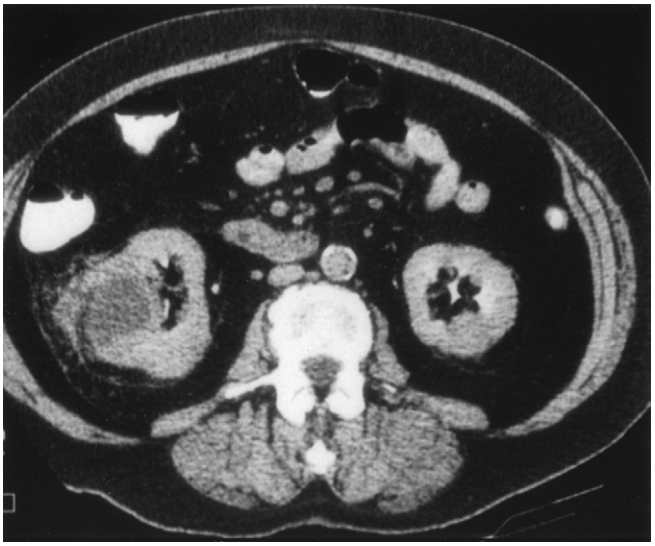


Figure 49–16. Contrast-enhanced CT scan shows right renal tumor with perinephric stranding suggesting invasion of the perinephric fat.

combination of preoperative CT and intraoperative inspection. **Patients with an enlarged or indistinct adrenal gland on CT, extensive malignant replacement of the kidney, or palpably abnormal adrenal gland are at risk for ipsilateral adrenal involvement and should be managed accordingly** (Sagalowsky et al, 1994; Sandock et al, 1997; Paul et al, 2001a; Sawai et al, 2002; Kobayashi et al, 2003; Zhang et al, 2007a; Ng et al, 2008; Lane et al, 2009). **Enlarged hilar or retroperitoneal lymph nodes 2 cm or more in diameter on CT almost always harbor malignant change, but this should be confirmed by surgical exploration or percutaneous biopsy if the patient is not a surgical candidate. Many smaller nodes prove to be inflammatory rather than neoplastic and should not preclude surgical therapy** (Studer et al, 1990; Choyke et al, 2001; Israel and Bosniak, 2003a; Zhang et al, 2007a; Bach and Zhang, 2008; Ng et al, 2008; Herts, 2009). MRI can add specificity to the evaluation of retroperitoneal nodes by distinguishing vascular structures from lymphatic ones (Bechtold and Zagoria, 1997; Bassignani, 2006). **MRI is still the premier study for evaluation of invasion of tumor into adjacent structures and for surgical planning in these challenging cases** (Bechtold and Zagoria, 1997; Choyke, 1997; Pretorius et al, 2000; Choyke et al, 2001; Bassignani, 2006; Bach and Zhang, 2008; Herts, 2009). Obliteration of the fat plane between the tumor and adjacent organs (e.g., the liver) can be a misleading finding on CT and should prompt further imaging with MRI. In reality, surgical exploration is often required to make an absolute differentiation.

The sensitivities of CT for detection of renal venous tumor thrombus and IVC involvement are 78% and 96%, respectively (Bechtold and Zagoria, 1997; Zhang et al, 2007a; Ng et al, 2008; Herts, 2009). CT findings suggestive of venous involvement include venous enlargement, abrupt change in the caliber of the vein, and intraluminal areas of decreased density or filling defects. The diagnosis is strengthened by the demonstration of collateral vessels. Most false-negative findings occur in patients with right-sided tumors in whom the short length of the vein and the mass effect from the tumor combine to make detection of the tumor thrombus difficult (Bechtold and Zagoria, 1997; Herts, 2009). Fortunately, most such cases are readily identified and dealt with intraoperatively. **MRI is well established as the premier study for the evaluation and staging of IVC tumor thrombus, although recent data suggest that multiplanar CT is likely equivalent** (Choyke et al, 1987; Goldfarb et al, 1990; Kallman et al, 1992; Bechtold and Zagoria, 1997; Choyke, 1997; Oto et al, 1998; Sun et al, 1999; Pretorius et al, 2000; Sohaib et al, 2002; Israel and Bosniak, 2003a; Ergen et al, 2004; Hallscheidt et al, 2005; Zhang et al, 2007a; Ng et al, 2008). MRI and multiplanar CT are noninvasive methods that provide reliable information about both the cephalad and caudal extent of the thrombus and can often distinguish bland from tumor thrombus (Pretorius et al, 2000; Choyke et al, 2001, Bassignani, 2006; Bach and Zhang, 2008; Herts, 2009). **Venacavography is now best reserved for patients with equivocal MRI or CT findings or for patients who cannot tolerate or have other contraindications to cross-sectional imaging.** Transesophageal echocardiography also appears to be accurate for establishing the cephalad extent of the tumor thrombus, but it is invasive and provides no distinct advantages over MRI or CT in the preoperative setting (Glazer and Novick, 1997). Doppler ultrasonography is operator dependent and does not provide the anatomic resolution available with MRI or multiplanar CT (Habboub et al, 1997).

Metastatic evaluation in all cases should include a routine chest radiograph, careful and systematic review of the abdominal and pelvic CT or MRI findings, and liver function tests (Choyke et al, 1987; Griffin et al, 2007; Zhang et al, 2007a; Ng et al, 2008; Herts, 2009). **Most investigators agree that a bone scintiscan can be reserved for patients with elevated serum alkaline phosphatase or bone pain and that a chest CT scan can be reserved for patients with pulmonary symptoms or an abnormal chest radiograph** (Lim and Carter, 1993; Seaman et al, 1996; Choyke et al, 2001). **However, patients with locally advanced disease, enlarged retroperitoneal lymph nodes, or significant comorbid disease may mandate more thorough imaging to rule out metastatic disease and to aid in treatment planning** (Choyke et al, 2001; Griffin et al, 2007). As always, evaluation and management must be individualized on the basis of the clinical circumstances. Shvarts and colleagues (2004) have shown that performance status is a powerful predictor of bone metastasis. In their analysis, patients with good performance status (Eastern Cooperative Oncology Group performance status score of 0), no evidence of extraosseous metastases, and no bone pain were at extremely low risk and did not benefit from bone scintigraphy. They recommended a bone scintiscan for all other patients, and the incidence of bone metastasis in this group was above 15%.

Positron emission tomography (PET) has also been investigated for patients with high risk of metastatic RCC, with most studies showing good specificity but suboptimal sensitivity. At present its best role is for patients with equivocal findings on conventional imaging. In this setting an abnormal PET scan may indicate metastatic disease and could strongly influence further evaluation and management (Hoh et al, 1998; Ramdave et al, 2001; Nimeh et al, 2002; Jadvar et al, 2003; Kang et al, 2004; Lawrentschuk et al, 2006; Griffin et al, 2007; Powles et al, 2007; Bouchelouche et al, 2008; Nieh, 2009). PET/CT combined with radiolabeled monoclonal antibody to CA-9 is also being explored in this population for molecular imaging of clear cell RCC (Brouwers et al, 2002; Divgi et al, 2007; Zhang, 2008). Biopsy of the primary tumor and/or potential metastatic sites is also selectively required as part of the staging process.

Prognosis

Important prognostic factors for cancer-specific survival in patients with localized RCC include specific clinical signs or symptoms, tumor-related factors, and various laboratory findings (Table 49–17) (Lane and Kattan, 2008). **Overall, tumor-related factors such as pathologic stage, tumor size, nuclear grade, and histologic subtype have the greatest utility on an independent basis. However, an integrative approach, combining a variety of factors that have proved to have independent value on multivariate analysis, appears to be most powerful** (Kattan et al, 2001; Zisman et al, 2001b; Frank et al, 2002; Sorbellini et al, 2005; Lane and Kattan, 2008; Parker et al, 2009; Isbarn and Karakiewicz, 2009). Patient-related factors, such as age, CKD, and co-morbidity, have a significant impact on overall survival in some patients and should be a primary consideration during treatment planning for patients with localized RCC (Hollingsworth et al, 2006; Berger et al, 2009; Pettus et al, 2008).

Clinical findings suggestive of a compromised prognosis in patients with presumed localized RCC include symptomatic presentation, weight loss of more than 10% of body weight, and

Table 49–17.

Prognostic Factors for Renal Cell Carcinoma

ANATOMIC	CLINICAL	HISTOLOGIC	MOLECULAR
Tumor size	Performance status (Karnofsky, ECOG)	Nuclear grade	Hypoxia-inducible factors: CA-IX, IGF-1, VEGF, VEGFRs, CA-XII, CXCR3, CXCR4, HIF
Venous involvement	Systemic symptoms (cachexia, loss of >10% of body weight)	Histologic subtype	Costimulatory molecules: B7-H1, B7-H3 (tumor cell/vascular), B7-H4, PD-1
Extension into contiguous organs	Symptomatic vs. incidental presentation	Presence of sarcomatoid features	Cell cycle regulators: PTEN, TP53, Bcl2, Cyclin A, CDKN1B, Skp2
Adrenal involvement (direct or metastatic)	Anemia	Presence of histologic necrosis	Adhesion molecules: EpCAM, EMA, E-Cad, α-catenin, Cad-6
Lymph node metastases	Hypercalcemia	Vascular invasion	Other factors: Ki-67, XIAP, Survivin, EphA2, Smac/DIABLO, PCNA, Caveolin-1, AR, CD44, Annexin II, Gelsolin, Vimentin, CA-125), aberrant DNA methylation, Na^+,K^+-ATPase α_1 subunit, vitamin D receptor, retinoid X receptor
Distant metastases	Elevated lactate dehydrogenase	Invasion of perinephric or renal sinus fat	
Metastatic burden of disease	Elevated erythrocyte sedimentation rate	Collecting system invasion	
	Elevated C-reactive protein	Surgical margin status	
	Thrombocytosis		
	Elevated alkaline phosphatase		

Modified from Lane BR, Kattan MW. Prognostic models and algorithms in renal cell carcinoma. Urol Clin North Am 2008;35:613–25.

Table 49–18.

TNM Stage and 5-Year Survival for Renal Cell Carcinoma

FINDINGS	ROBSON STAGE	TNM (2002)	TNM (2009)	5-YEAR SURVIVAL (%)
Organ confined (overall)	I	T1-2N0M0	T1-2N0M0	70-90
≤4.0 cm	I	T1aN0M0	T1aN0M0	90-100
>4.0 cm to 7.0 cm	I	T1bN0M0	T1bN0M0	80-90
>7.0 to 10.0 cm	I	T2N0M0	T2aN0M0	65-80
>10.0 cm	I	T2N0M0	T2bN0M0	50-70
Invasion of perinephric or renal sinus fat	II	T3aN0M0	T3aN0M0	50-70
Invasion of renal vein or branches	IIIA	T3bN0M0	T3aN0M0	40-60
Invasion of IVC below diaphragm	IIIA	T3cN0M0	T3bN0M0	30-50
Invasion of IVC above diaphragm or invasion of IC wall	IIIA	T3cN0M0	T3cN0M0	20-40
Direct adrenal involvement	II	T3aN0M0	T4N0M0	0-30
Locally advanced (invasion beyond Gerota fascia)	IVA	T4N0M0	T4N0M0	0-20
Lymphatic involvement	IIIB	(Any)TN1-2M0	(Any)TN1M0	0-20
Systemic metastases	IVB	(Any)T(Any)NM1	(Any)T(Any)NM1	0-10

IVC, inferior vena cava.

Data from Butler et al, 1994; Sagalowsky et al, 1994; Targonski et al, 1994; Guinan et al, 1995; Lerner et al, 1996; Sandock et al, 1997; Hafez et al, 1999; Motzer et al, 1999; Igarashi et al, 2001; Paul et al, 2001a; Vasselli et al, 2001; Pantuck et al, 2002a; Kontak and Campbell, 2003; von Knobloch et al, 2004; Patard et al, 2004; Phillips and Taneja, 2004; Leibovich et al, 2005b; Siemer et al, 2005; Thompson et al, 2005a; Margulis et al, 2007b; Lane and Kattan, 2008; Wotkowicz et al, 2008; Bedke et al, 2009; Bertini et al, 2009; Campbell et al, 2009; Choueiri, 2009; Kanao et al, 2009; and Shuch et al, 2009.

poor performance status (Gelb, 1997; Srigley et al, 1997; Kattan et al, 2001; Zisman et al, 2001b; Kim HL et al, 2003; Kontak and Campbell, 2003; Schips et al, 2003; Patard et al, 2004a). Anemia, thrombocytosis, hypercalcemia, albuminuria, elevated serum alkaline phosphatase, C-reactive protein, lactate dehydrogenase, or erythrocyte sedimentation rate, and other paraneoplastic signs or symptoms have also correlated with poor outcomes for patients with RCC (Gelb, 1997; Srigley et al, 1997; Symbas et al, 2000; Jacobsen et al, 2000; O'Keefe et al, 2002; Kim HL et al, 2003; Kontak and Campbell, 2003; Vaglio et al, 2003; Patard et al, 2004a; Karakiewicz et al, 2007; Magera et al, 2008). Although abnormal values are more common in patients with advanced RCC, some of these abnormalities, including hypercalcemia, anemia, and elevated erythrocyte sedimentation rate, were independent predictors of cancer-specific mortality in patients with localized clear cell RCC after accounting for other major prognostic factors (Magera et al, 2008).

Pathologic stage has proved to be the single most important prognostic factor for RCC (Thrasher and Paulson, 1993; Delahunt, 1998; Kontak and Campbell, 2003; Leibovich et al, 2005a; Lane and Kattan, 2008; Kanao et al, 2009). The RCC TNM staging system clearly distinguishes between patient groups with different predicted cancer-specific outcomes (Table 49–18), confirming that the extent of locoregional or systemic disease at diagnosis is the primary determinant of outcome for this disease (Bassil et al, 1985; Hermanek and Schrott, 1990; Kontak and Campbell, 2003; Lane and Kattan, 2008). Previous studies confirmed that the 2002 modification of the TNM system provided better prognostic ability than its predecessors (Ficarra et al, 2005; Frank et al, 2005a), and it is anticipated that the 2010 TNM staging system will impart further improvements (Frank et al, 2005a; Leibovich et al, 2005a; Thompson et al, 2005a).

Several studies demonstrate 5-year survival rates of 70% to 90% for organ-confined disease and document a 15% to 20% reduction in survival associated with invasion of the perinephric fat (Kontak and Campbell, 2003; Leibovich et al, 2005a; Lane and Kattan, 2008). **Renal sinus involvement is classified along with perinephric fat**

invasion as T3a, and several studies suggest that these patients may be at even higher risk for metastasis related to increased access to the venous system (Bonsib et al, 2000; Uzzo et al, 2002; Thompson et al, 2005a; Margulis et al, 2007b; Bedke et al, 2009; Bertini et al, 2009). **Collecting system invasion has also been shown to confer poorer prognosis in otherwise organ-confined RCC** (Uzzo et al, 2002; Klatte et al, 2007a). **Several reports have shown that most patients with direct or metastatic ipsilateral adrenal involvement, which is found in 1% to 2% of cases, eventually succumb to systemic disease progression,** suggesting a hematogenous route of dissemination or a highly invasive phenotype (Sagalowsky et al, 1994; Sandock et al, 1997; Paul et al, 2001b; Von Knobloch et al, 2004; Siemer et al, 2005; Thompson et al, 2005a). The most recent staging system now reclassifies tumor as T4 if there is direct invasion of the adrenal gland or otherwise as M1, to reflect this poor prognosis (Guinan et al, 1997; Thompson et al, 2005a).

Venous involvement was once thought to be a very poor prognostic finding for RCC, but several reports demonstrate that many patients with tumor thrombi can be salvaged with an aggressive surgical approach. These studies document 45% to 69% 5-year survival rates for patients with venous tumor thrombi as long as the tumor is otherwise confined to the kidney (Novick et al, 1990; Thrasher and Paulson, 1993; Staehler and Brkovic, 2000; Quek et al, 2001; Zisman et al, 2003; Leibovich et al, 2005b; Blute et al, 2007; Haferkamp et al, 2007; Klatte et al, 2007b; Wotkowicz et al, 2008; Subramanian et al, 2009). At one extreme, Golimbu and associates (1986) reported 84% 5-year survival in the best of circumstances—tumor thrombus limited to the main renal vein and tumor otherwise confined to the kidney. **Patients with venous tumor thrombi and concomitant lymph node or systemic metastases have markedly decreased survival, and those with tumor extending into the perinephric fat have intermediate survival** (Montie et al, 1991; Glazer and Novick, 1996; Gettman et al, 1999; Naitoh et al, 1999; Sweeney et al, 2002b; Bissada et al, 2003; Kim HL et al, 2004c; Moinzadeh and Libertino, 2004; Leibovich et al, 2005b; Klatte et al, 2007b; Wotkowicz et al, 2008). The most recent version of the TNM system advocates capturing all such adverse features during the staging process.

The prognostic significance of the cephalad extent of tumor thrombus has been controversial, and it is difficult to compare various series because of selection biases and related covariables (Leibovich et al, 2005b; Wotkowicz et al, 2008). In several series the incidence of advanced locoregional or systemic disease increased with the cephalad extent of the tumor thrombus, accounting for the reduced survival associated with tumor thrombus extending into or above the level of the hepatic veins (Sosa et al, 1984; Thrasher and Paulson, 1993; Kim HL et al, 2004a; Wotkowicz et al, 2008). However, other data suggest that the cephalad extent of tumor thrombus is not of prognostic significance as long as the tumor is otherwise confined (Libertino et al, 1987; Glazer and Novick, 1996; Staehler and Brkovic, 2000; Blute et al, 2007). **Direct invasion of the wall of the vein appears to be a more important prognostic factor than level of tumor thrombus and is now classified as pT3c independent of the level of tumor thrombus** (Hatcher et al, 1991; Zini et al, 2008).

The major drop in prognosis comes in patients whose tumor extends beyond the Gerota fascia to involve contiguous organs (stage T4), which is rarely associated with 5-year survival, and in patients with lymph node or systemic metastases (Thrasher and Paulson, 1993; Thompson et al, 2005a). **Lymph node involvement has long been recognized as a dire prognostic sign because it is associated with 5- and 10-year survival rates of 5% to 30% and 0% to 5%, respectively** (Bassil et al, 1985; Phillips and Taneja, 2004). **Systemic metastases also portend a particularly poor prognosis for RCC, traditionally with 1-year survival of less than 50%, 5-year survival of 5% to 30%, and 10-year survival of 0% to 5%, although these numbers have improved modestly in the era of targeted treatments** (Motzer et al, 1999; Motzer and Russo, 2000; Négrier et al, 2002; Sella et al, 2003; Rini et al, 2009). **Patients presenting with synchronous metastases fare worse,** with many patients dying of disease progression within a year (Motzer et al, 1999, 2004; Mekhail et al, 2005; Leibovich et al, 2005b; Rini et al, 2009). **For patients with asynchronous metastases the metastasis-free interval has proved to be a useful prognosticator because it reflects the tempo of disease progression** (Maldazys and deKernion, 1986; Négrier et al, 2002; Motzer et al, 2004; Mekhail et al, 2005; Rini et al, 2009). **Other important prognostic factors for patients with systemic metastases include performance status, number and sites of metastases, anemia, hypercalcemia, elevated alkaline phosphatase or lactate dehydrogenase levels, thrombocytosis, and sarcomatoid histology** (Maldazys and deKernion, 1986; Motzer et al, 1999; Motzer and Russo, 2000; Négrier et al, 2002; Leibovich et al, 2003b; Motzer et al, 2004; Mekhail et al, 2005; Escudier et al, 2007; Choueiri et al, 2007; Lane and Kattan, 2008). **The presence of bone, brain, and/or liver metastases, and multiple metastatic sites have been associated with further compromise in prognosis** (Négrier et al, 2002; Leibovich et al, 2005b; Mekhail et al, 2005; Escudier et al, 2007). These factors have been used to effectively categorize patients with metastatic RCC as low, intermediate, and poor risk, with corresponding differences in median survival (Table 49–19) (Motzer et al, 1999; Boumerhi et al, 2003; Motzer et al, 2004; Mekhail et al, 2005; Choueiri et al, 2007; Escudier et al, 2007). These risk groups provide important information for determining the likelihood of benefit a patient may expect to receive after cytoreductive nephrectomy and/or resection of other metastatic disease.

Another significant prognostic factor for RCC is tumor size, which has proved to be an independent prognostic factor for both organ-confined and invasive RCC (Kattan et al, 2001; Kontak and Campbell, 2003; Lane and Kattan, 2008). Giuliani and colleagues (1990) reported 5-year survival rates of 84% for patients with tumor diameter less than 5 cm, 50% for tumors between 5 and 10 cm, and 0% for tumors more than 10 cm in diameter. To a large extent, this is due to a strong correlation between tumor size and pathologic tumor stage, but several studies have subsequently demonstrated that tumor size can function as an independent prognostic factor (Guinan et al, 1995b; Kattan et al, 2001; Sorbellini et al, 2005; Crispen et al, 2008b; Nguyen and Gill, 2009). Larger tumors are more likely to exhibit clear cell histology and high nuclear grade, and both of these factors correlate with a compromised prognosis (Frank et al, 2003b; Lane et al, 2007a; Thompson et al, 2009). A review of 1771 patients with organ-confined RCC showed 10-year cancer-specific survival rates of 90% to 95%, 80% to 85%, and 75% for patients with pT1a, pT1b, and pT2 tumor, respectively (Patard et al, 2004a). Many other studies have also shown a particularly favorable prognosis for the unilateral pT1a tumors that are now being discovered with increased frequency. In series from the Cleveland

Table 49–19.

Integrated Predictive Tools for Renal Cell Carcinoma

INSTITUTION, STUDY	SETTING	TUMOR SUBTYPE	PROGNOSTIC INDICATORS	PROGNOSTIC INFORMATION	FORMAT
Preoperative					
Cleveland Clinic, Lane et al (2008)	Localized, amenable to PN	All	Tumor size, symptoms, gender, age, smoking	Histology	Nomogram
MSKCC/Mayo Clinic, Raj et al (2008)	Localized	All	Tumor size, symptoms, gender, lymphadenopathy, necrosis on imaging	Recurrence	Nomogram
Keio (Japan), Kanao et al (2009)	Localized, metastatic	All	TNM stage	Survival	Nomogram
Postoperative					
MSKCC, Kattan et al (2001)	Localized	All	TNM stage, tumor size, histology, symptoms	Recurrence	Nomogram
UCLA, Zisman et al (2001b)	Localized	All	TNM stage, nuclear grade, performance status	Survival	Algorithm, decision boxes
UCLA, Zisman et al (2002c)	Localized, metastatic	All	TNM stage, nuclear grade, performance status, metastasis (UISS)	Survival	Algorithm, decision boxes
Mayo Clinic, Frank et al (2002)	Localized, metastatic	Clear cell	TNM stage, tumor size, nuclear grade, histologic necrosis (SSIGN)	Survival	Algorithm
Mayo Clinic, Leibovich et al (2003a)	Localized	Clear cell	TN stage, tumor size, nuclear grade, histologic necrosis	Recurrence	Algorithm
UCLA, HL Kim et al (2004b)	Localized, metastatic	All	TNM stage, performance status, metastasis, expression of TP53, vimentin, CA-IX in patients with metastatic disease	Survival	Nomogram
MSKCC, Sorbellini et al (2005)	Localized	Clear cell	TNM stage, tumor size, nuclear grade, histologic necrosis, microvascular invasion, symptoms	Recurrence	Nomogram
Multi-institutional, Karakiewicz et al (2007)	Localized	All	TNM stage, tumor size, nuclear grade, histologic subtype, local symptoms, age, gender	Survival	Nomogram
Mayo Clinic, Parker et al (2009)	Localized	Clear cell	Expression of B7-H1, survivin, Ki-67 (BioScore)	Survival	Algorithm
UCLA, Klatte et al (2009)	Localized	Clear cell	Expression of Ki-67, TP53, endothelial VEGFR-1, epithelial VEGFR-1, epithelial VEGF-D	Survival	Nomogram
Metastatic					
MSKCC, Motzer et al (1999)	Untreated	All	No prior nephrectomy (metastasis within 1-2 yr of presentation), anemia, abnormal corrected calcium, elevated LDH, low performance status	Survival	Algorithm
Cleveland Clinic, Mekhail et al (2005)	Untreated	All	Metastasis at or within 12 mo of nephrectomy, anemia, abnormal corrected calcium level, elevated LDH, number of metastatic sites, prior radiotherapy	Survival	Algorithm
Mayo Clinic, Leibovich et al (2005a)	After nephrectomy	Clear cell	Metastasis at or within 2 yr of nephrectomy, symptoms, location, number of sites and complete resection of metastases, tumor thrombus, nuclear grade, histologic tumor necrosis	Survival	Algorithm
UCLA, Leibovich et al (2003b)	Immunotherapy	All	Lymph node status, constitutional symptoms, metastasis location, sarcomatoid features, TSH level	Survival	Algorithm
MSKCC, Motzer et al (2004)	Immunotherapy	All	Anemia, abnormal corrected calcium level, reduced performance status	Survival	Algorithm
Multi-institutional, Escudier et al (2007)	Immunotherapy	All	Metastasis at or within 2 yr of nephrectomy, anemia, abnormal corrected calcium level, elevated LDH, number of metastatic sites, prior radiotherapy	Survival	Algorithm
Cleveland Clinic, Choueiri et al (2007)	VEGF-targeted therapy	Clear cell	Metastasis at or within 2 yr of nephrectomy, abnormal corrected calcium level, reduced performance status, high platelet count, high neutrophil count	Survival	Algorithm
Multi-institutional, Motzer et al (2008)	Sunitinib treated	Clear cell	Metastasis at or within 12 mo of nephrectomy, anemia, abnormal corrected calcium level, elevated LDH, number of metastatic sites, elevated alkaline phosphatase, thrombocytosis, low performance status	Progression	Nomogram

Keio, Keio University School of Medicine, Tokyo, Japan; LDH, lactate dehydrogenase; MSKCC, Memorial Sloan-Kettering Cancer Center; SSIGN, Mayo Clinic Stage, Size, Grade and Necrosis Score; TSH, thyroid-stimulating hormone; UCLA, University of California, Los Angeles; UISS, UCLA Integrated Staging System; VEGF(R), vascular endothelial growth factor (receptor).

Clinic and the Mayo Clinic, such tumors were associated with greater than 95% 5-year cancer-specific survival rates, whether they were managed with nephron-sparing surgery or radical nephrectomy (Butler et al, 1994; Lerner et al, 1996; Cheville et al, 2001; Gill et al, 2007; Lane and Gill, 2007; Crispen et al, 2008b).

Other important prognostic factors for RCC include nuclear grade, histologic subtype and symptomatic presentation. Several grading systems for RCC have been proposed on the basis of nuclear size and morphology and presence or absence of nucleoli. Unfortunately, interobserver variability is common in the assignment of nuclear grade; there is no ideal classification system that can overcome the subjectivity of this exercise. Nevertheless, almost all the proposed grading systems have provided prognostic information for RCC, and nuclear grade has proved in most cases to be an independent prognostic factor when subjected to multivariate analysis (Goldstein, 1997; Ficarra et al, 2001; Kattan et al, 2001; Zisman et al, 2001b; Lohse et al, 2002, 2005; True, 2002; Kontak and Campbell, 2003; Patard et al, 2004c; Lang et al, 2005; Lane and Kattan, 2008; Ficarra et al, 2009).

Fuhrman's classification system has been the most generally adopted grading system for RCC. In Fuhrman and colleagues' original report (1982) **the 5-year survival rates for grades 1 to 4 were 64%, 34%, 31%, and 10%, respectively, and nuclear grade proved to be the most significant prognostic factor for organ-confined tumors in this series.** Subsequent reports have demonstrated correlations between Fuhrman's nuclear grade and tumor stage, tumor size, venous tumor thrombi, and lymph node and systemic metastases (Bretheau et al, 1995; Lang et al, 2005; Lohse et al, 2005; Ficarra et al, 2009). Significant differences have been consistently observed between low-grade (grades 1/2) and high-grade (grade 3/4) tumors with some difficulty distinguishing the intermediate grades. Based on these studies, some have recommended changing to a three-tiered system, but this remains a matter of investigation (Medeiros et al, 1997; Lang et al, 2005; Lane and Kattan, 2008; Zhou 2009). In addition, although significant differences according to nuclear grade have been reported in series that have included patients with all types of RCC or clear cell RCC alone, the relevance of the Fuhrman classification system to evaluation of other subtypes of RCC is not entirely clear. Papillary RCC may be better subgrouped into type 1 and type 2, and oncocytic neoplasms may be better classified as chromophobe RCC, hybrid oncolytic tumors, and oncocytomas, although whether these provide better prognostic information about cancer recurrence has not been determined (see Pathology).

Histologic subtype also carries prognostic significance, although, again, primarily at the ends of the spectrum. The presence of sarcomatoid differentiation or collecting duct, renal medullary, or unclassified histologic subtype denotes a poor prognosis (Carter et al, 1992; Davis et al, 1995b; Chao et al, 2002b; Escudier et al, 2002a; Mian et al, 2002; Polascik et al, 2002; Mejean et al, 2003; Cheville et al, 2004; Nanus et al, 2004; Tokuda et al, 2006; Kobayashi et al, 2008; Zhou 2009). Several studies now suggest that clear cell RCC may have a worse prognosis on average compared with papillary or chromophobe RCC, although there are clearly poorly differentiated tumors in each of these subcategories that can be lethal (Moch et al, 2000; Amin et al, 2002; Lau et al, 2002; Cheville et al, 2003; Krejci et al, 2003; Beck et al, 2004; Patard et al, 2005; Lane and Kattan, 2008; Crispen et al, 2008b; Dall'Oglio et al, 2008; Lam et al, 2008; Margulis et al, 2008; Klatte et al, 2008b; Rothman et al, 2009). Finally, several subtypes of RCC are predictably indolent, including multiloculated cystic clear cell RCC and mucinous tubular and spindle cell carcinoma.

For patients with clinically localized disease, mode of presentation (incidental vs. symptomatic) can be combined with other predictive elements to better stratify patients after primary surgical management (Kattan et al, 2001; Patard et al, 2004a; Sorbellini et al, 2005; Karakiewicz et al, 2007; Lane and Kattan, 2008). In addition, patients with systemic symptoms suggestive of metastatic spread have significantly poorer outcomes than those with only local symptoms, such as hematuria or flank pain (Kattan et al, 2001; Sorbellini et al, 2005).

Dozens of genes that may have prognostic or therapeutic significance for patients with RCC have been identified using high-throughput technologies (Takahashi et al, 2003; Zhao et al, 2006; Lane et al, 2008b). Gene expression profiling (cDNA microarrays) can quantify the levels of thousands of individual messenger RNA transcripts within an individual tumor sample. Alterations in gene expression can then be correlated with the amount and location of specific gene products (proteins) using immunohistochemical staining of cancer specimens (Kim HL et al, 2004a; Liu et al, 2004; Parker et al, 2009). Construction of tissue microarrays can facilitate the screening of hundreds of tumors, but interpretation of results can be challenging due to tumor heterogeneity and the selection of only a small amount of tissue for analysis (Kim HL et al, 2004a; Liu et al, 2004; Leibovich et al, 2007). Furthermore, when evaluating the potential value of a new marker, it is important to consider its contribution after accounting for other known prognostic factors (George and Bukowski, 2007; Tunuguntia and Jorda, 2008).

Several molecular markers appear to serve as independent prognostic factors for RCC and have provided important insights into tumor biology (see Tumor Biology) (Bui et al, 2001; Han et al, 2003; Crispen et al, 2008b; Nogueira and Kim, 2008; Parker et al, 2009). One such factor is CA-IX, which is regulated by the *VHL* gene and overexpressed in most clear cell RCCs (Bui et al, 2003, 2004; Leibovich et al, 2007). Although initial studies indicated that decreased expression of CA-IX is independently associated with poorer survival in patients with metastatic RCC (Bui et al, 2003; Kim et al, 2005), this association does not appear to apply for patients with localized disease (Kim et al, 2005; Leibovich et al, 2007). CA-IX also may serve as a marker for response to systemic therapy, making CA-IX immunostaining of particular value for patients with advanced disease (Bui et al, 2004; Atkins et al, 2005; Cho et al, 2007). B7-H1 is a T-cell coregulatory molecule that is a strong independent predictor of disease progression for RCC (Thompson et al, 2006; Parker et al, 2009). This association holds even after accounting for other molecular factors and the major clinical and pathologic predictors (Krambeck et al, 2007; Parker et al, 2009). Increased proliferative index as assessed by Ki-67 has also been correlated with reduced survival in clear cell RCC (Bui et al, 2004; Klatte et al, 2009; Parker et al, 2009). Although initial data indicated that Ki-67 expression was a surrogate for histologic necrosis, more recent studies have found Ki-67 to be an independent predictor and have incorporated it into predictive algorithms (Tollefson et al, 2007; Klatte et al, 2009; Parker et al, 2009). Other factors that appear to be useful include cell cycle regulators, such as the tumor suppressor *TP53* (Kim HL et al, 2004a; Shvarts et al, 2005b; Klatte et al, 2009); various growth factors and their receptors, including members of the VEGF family (Jacobsen et al, 2000; Rivet et al, 2008; Phyoc

et al, 2008; Klatte et al, 2009); adhesion molecules; and other factors, such as survivin (Parker et al, 2006, 2009; Byun et al, 2007; Krambeck et al, 2007).

Several investigators have now developed tools that combine various prognostic factors, and this has greatly improved our predictive capacity for patients with RCC (see Table 49–19) (Kattan et al, 2001; Zisman et al, 2001b; Frank et al, 2002; Sorbellini et al, 2005; Lane and Kattan, 2008). For instance, Kattan and colleagues (2001) have combined manner of presentation (incidental vs. local or systemic symptoms), tumor histology, tumor size, and pathologic stage to develop a nomogram that predicts cancer-free survival after nephrectomy. Tumor grade was not included in this analysis because its role for non–clear cell RCC has not been clearly defined. A subsequent analysis from this same group focused only on patients with clear cell RCC and incorporated tumor grade, assessment of tumor necrosis, and vascular invasion to further improve prognostication (Fig. 49–17) (Sorbellini et al, 2005). Such nomograms provide an individual assessment of risk that clinicians can use during patient counseling (www.nomograms.org). Although several predictive algorithms incorporate histologic necrosis (Frank et al, 2002; Sorbellini et al, 2005), the utility of this predictor has been called into question in some recent studies because its assessment has not been standardized and it is not routinely reported at many centers (Isbarn and Karakiewicz, 2009).

Pantuck and colleagues (2001a) **have also performed an integrated analysis of prognostic factors for patients with all stages of RCC with encouraging results. A sophisticated multivariate analysis revealed three independent prognostic factors that were most robust for predicting outcomes, namely, TNM stage, performance status, and tumor grade** (Zisman et al, 2001b). The UCLA integrated staging system (UISS) was subsequently modified to identify patients with localized or metastatic disease at low, intermediate, and high risk of disease progression and has been validated internally and externally (Zisman et al, 2002b; Patard et al, 2004c; Cindolo et al, 2006, 2008; Parker et al, 2009). Molecular factors such as *TP53*, Ki-67, VEGF family members, and CA-IX have also been incorporated into UISS-based algorithms to predict outcomes for patients with localized or metastatic RCC (Kim et al, 2005; Klatte et al, 2009).

Another predominant model that provides individualized information for patients with clear cell RCC is the SSIGN score, which incorporates 1997 TNM stage, tumor size, nuclear grade, and presence of tumor necrosis to predict recurrence and survival after radical nephrectomy (Frank et al, 2002). Estimated cancer-specific survival according to the SSIGN score was based on data from more than 1800 patients and has subsequently been validated in several other datasets (Ficarra et al, 2006, 2009; Fujii et al, 2008; Zigeuner et al, 2010). Thompson and colleagues (2007d) have also developed a dynamic outcome prediction model that provides patients with cancer-specific survival rates that improve as the disease-free interval following surgery increases. Most recently, the group at Mayo Clinic has developed a sequential approach in which the predicted outcomes for patients at various risk of recurrence according to clinical and pathologic factors can be further stratified based on molecular data incorporated into a BioScore (Parker et al, 2009). The expression of B7-H1, survivin and Ki-67 each added independent predictive ability after accounting for either the UISS or SSIGN score, especially for patients at intermediate or high risk of recurrence (Parker et al, 2009).

TNM staging systems and prognostic algorithms have different purposes. The TNM staging system is used to provide a universal

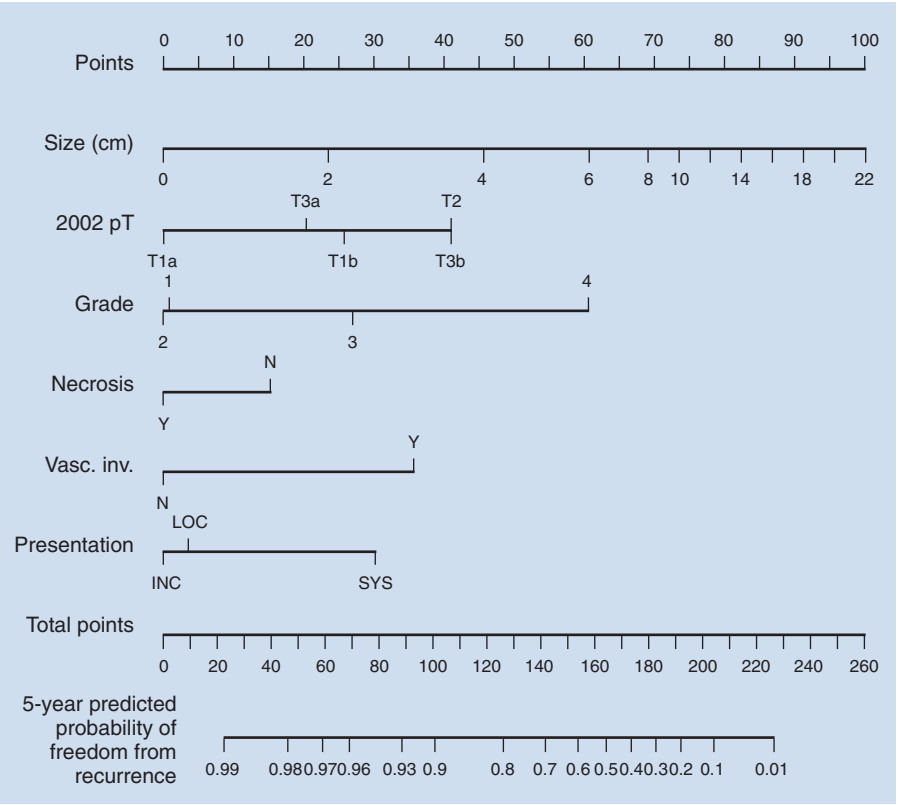


Figure 49–17. Postoperative nomogram predicting recurrence of clear cell renal cell carcinoma after nephrectomy. Locate the tumor size on the size axis. Draw a line upward to the points axis to determine how many points toward recurrence the patient receives for this parameter. Repeat this process for the other axes, each time drawing straight upward to the points axis. Sum the points achieved for each predictor and locate the sum on the total points axis. Draw a straight line down to find the probability that the patient will remain free of recurrence for 5 years, assuming the patient does not die of another cause first. (Adapted from Sorbellini M, Kattan MW, Snyder ME, et al. A postoperative prognostic nomogram predicting recurrence for patients with conventional clear cell renal cell carcinoma. J Urol 2005;173:48–51.)

language for communication between clinicians and patients and is based solely on the anatomic extent of cancer dissemination. **A wealth of literature now supports the notion that algorithms that incorporate multiple predictive elements, such as nomograms and artificial neural networks, outperform risk assessment based on expert opinion or simpler models, such as classic staging systems** (Dawes et al, 1989; Ross et al, 2002; Isbarn and Karakiewicz, 2009; Shariat et al, 2009). **The development and use of these predictive tools can help guide counseling and follow-up of patients with RCC and identify patients more likely to benefit from specific interventions.**

TREATMENT OF LOCALIZED RENAL CELL CARCINOMA

Localized renal masses, clinical stages T1 and T2, have increased in incidence owing to more widespread use of cross-sectional imaging and now represent a relatively common clinical scenario (Lipworth et al, 2006; Jemal et al, 2009). Our perspectives about clinical T1 renal masses have changed substantially in the past 2 decades. Previously, all were presumed to be malignant and managed aggressively, most often with radical nephrectomy. **We now recognize great heterogeneity in the tumor biology of these lesions and multiple management strategies are now available, including radical nephrectomy (RN), partial nephrectomy (PN), thermal ablation (TA), and active surveillance (AS)** (Kunkle et al; 2008; Campbell et al, 2009) (Fig. 49–18). Concepts that were once controversial, such as elective PN, are now accepted as standards of care (Kunkle et al, 2008; Campbell et al, 2009). A greater understanding of the tumor biology and appreciation of the deleterious functional consequences of RN has stimulated a reassessment of this field (Nguyen et al, 2008a; Russo and Huang, 2008; Campbell et al, 2009).

Overall, about 20% of solid, enhancing, clinical T1 renal masses are benign, most often oncocytomas or atypical AMLs, although the incidence of benign pathology can vary greatly in different subpopulations (Frank et al, 2003b; Remzi et al, 2006; Snyder et al, 2006; Pahernik et al, 2007; Kutikov et al, 2008a; Russo and Huang, 2008; Campbell et al, 2009). Young to middle-aged women, in particular, are more likely to have benign pathology, as high as 40% in some series (Eggener et al, 2004; Lane et al, 2007a). One potential explanation is that some benign renal masses, such as cystic nephroma and atypical AML, may be influenced by the hormonal milieu and are thus more common in this patient population. In contrast, the proportion of benign tumors appears to increase gradually in males as they age (Lane et al, 2007a). An even more important determinant of benign pathology is tumor size, with multiple studies confirming this (Lane et al, 2007a; Campbell et al, 2009). Frank and colleagues (2003b) have demonstrated a direct relationship between tumor size and the incidence of malignancy. In their series 30% of tumors less than 2 cm were benign, compared with 22% of tumors between 2 and 3 cm and with 20% between 3 and 4 cm. Only 9.5% of clinical T1b tumors were benign. Algorithms to predict benign versus malignant pathology for patients with clinical T1 renal masses are available and have demonstrated modest accuracy (Lane et al, 2007a; Campbell et al, 2009).

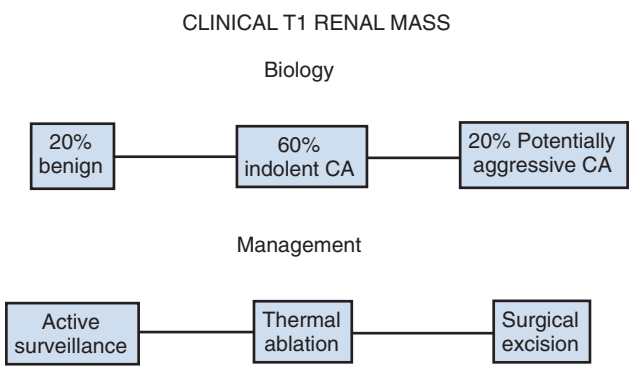


Figure 49–18. Clinical T1 renal masses are heterogeneous, with 20% benign and only about 20% exhibiting potentially aggressive features. Management options have expanded greatly, ranging from radical nephrectomy, the previous standard, to active surveillance. CA, cryoablation.

Tumor size has also correlated with biologic aggressiveness for clinical T1 renal masses, as reflected by high tumor grade, locally invasive phenotype, or adverse histologic subtype. In the study by Frank and colleagues (2003b), such adverse findings were uncommon in tumors less than 4 cm diameter. In this subset only 1.7% demonstrated invasion of the perinephric fat, 0.7% had venous involvement, 0.6% had lymph node involvement, and only 15% were high grade. Such features were more commonly observed in clinical T1b tumors in this series. Other studies suggest a cut point at 3 cm, with tumors larger than this much more likely to exhibit potentially aggressive histopathologic features (Remzi et al, 2006; Pahernik et al, 2007). Surveillance studies confirm a slow growth rate and low risk of metastasis for many small renal tumors (Bosniak et al, 1995; Kassouf et al, 2004; Kato et al, 2004; Chawla et al, 2006; Kouba et al, 2007; Kunkle et al, 2007a, 2008; Lamb et al, 2004; Sowery and Siemens, 2004; Volpe et al, 2004; Wehle et al, 2004; Abouassaly et al, 2008; Crispen et al, 2009). Other clinical factors such as patient age and sex, symptomatic presentation, and smoking history have also been studied, although none of these factors can provide substantial predictive value with respect to tumor aggressiveness (Lane et al, 2007a). **Current algorithms incorporating clinical and radiographic factors to predict tumor aggressiveness are very limited in their accuracy, with concordance indices less than 0.60, and not much better than a coin flip** (Lane et al, 2007a). **Conventional renal mass biopsy can substantially improve on this, having demonstrated reasonable accuracy for assessment of tumor grade and histology and should be considered in patients who are candidates for a wide range of management strategies** (Herts and Baker, 1995; Campbell et al, 1997a; Brierly et al, 2000; Dechet et al, 2003; Volpe et al, 2004, 2007; Lebret et al, 2007; Somani et al, 2007; Kummerlin et al, 2008a; Lane et al, 2008b; Schmidbauer et al, 2008). Younger, healthy patients who are unwilling to accept the uncertainty associated with renal mass biopsy and older, frail patients who will be managed conservatively independent of biopsy results should be managed without a biopsy.

Radical Nephrectomy

Notwithstanding advances in our understanding of the genetics and biology of RCC, surgery remains the mainstay for curative treatment of this disease. The objective of surgical therapy is to excise all tumor with an adequate surgical margin. Simple nephrectomy was practiced for many decades but was supplanted by RN when Robson and colleagues (1969) established this procedure as the "gold standard" curative operation for

localized RCC with their report of 66% and 64% overall survival for stage I and II tumors, respectively. These results demonstrated improved survival rates compared with those of patients treated by pericapsular nephrectomy. RN is still a preferred option for many patients with localized RCC, such as those with very large tumors (most clinical T2 tumors) or the relatively limited subgroup of patients with clinical T1 tumors that are not amenable to nephron-sparing approaches (Nguyen et al, 2008a). **RN has more recently fallen out of favor for small renal tumors due to concerns about CKD, and should only be performed when necessary** (Nakada, 2005; Russo and Huang, 2008; Nguyen et al, 2008a; Campbell et al, 2009).

The main concern with RN is that it predisposes to CKD, which in turn is associated with morbid cardiovascular events and increased mortality rates. Several studies have shown an increased risk of CKD on longitudinal follow-up after RN, including a landmark study from Memorial Sloan-Kettering Cancer Center that looked at 662 patients with a small solitary tumor, a normal opposite kidney, and a "normal" serum creatinine level—essentially patients who would be considered for elective PN (Huang et al, 2006; Russo and Huang, 2008). The first major finding was that 26% of this patient population had preexisting grade 3 CKD (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2), demonstrating that this patient population is substantially different than the kidney transplant donor population that is often considered analogous. In reality, the donor population is not comparable because it is carefully screened to exclude CKD and related comorbidities. The second major finding was that the incidence of grade 3 CKD (eGFR < 60 mL/min/1.73 m^2) was much more common after RN than PN, 65% versus 20%, respectively (P < .001). More severe CKD (eGFR < 45 mL/min/1.73 m^2) was also much more common after RN than PN, 36% versus 5%, respectively (P < .001).

Several studies illustrate the negative implications of CKD, including a population-based study that followed more than a million patients for 2.8 years and reported increased rates of cardiovascular events and death as the degree of CKD worsened even after controlling for hypertension, diabetes, and other potential confounding factors (Go et al, 2004). The relative risks of cardiovascular events were 1.4, 2.0, 2.8, and 3.4 for eGFR (mL/min/1.73 m^2) of 45 to 60, 30 to 45, 15 to 30, and less than 15, respectively. Relative death rates were 1.2, 1.8, 3.2, and 5.9 for these same subgroups, respectively. **These data highlight the need to optimize renal function and underscore nephron-sparing procedures as an overriding principle in the management of clinical T1 renal masses; RN should only be performed when necessary** (Miller et al, 2008; Russo and Huang, 2008; Thompson et al, 2008; Campbell et al, 2009; Huang et al, 2009; Lane et al, 2009).

The prototypical concept of RN encompasses the basic principles of early ligation of the renal artery and vein, removal of the kidney with primary dissection external to the Gerota fascia, excision of the ipsilateral adrenal gland, and performance of a complete regional lymphadenectomy from the crus of the diaphragm to the aortic bifurcation (O'Malley et al, 2009a). **Controversy has arisen regarding the need for many of these practices on a routine basis** (Lam et al, 2004b; O'Malley et al, 2009a). **Performance of a perifascial nephrectomy is of undoubted importance** during RN for preventing postoperative local tumor recurrence because approximately 25% of clinical T2 RCCs manifest perinephric fat involvement (Lam et al, 2007; Thompson et al, 2007a). **Preliminary renal arterial ligation remains an accepted practice; however, in large tumors with abundant collateral vascular supply, it is not always possible to achieve complete preliminary control of the arterial circulation** (O'Malley et al, 2009a). It has been well demonstrated that **removal of the ipsilateral adrenal gland is not routinely necessary in the absence of radiographic adrenal enlargement unless the malignant lesion extensively involves the kidney, is locally advanced, or is located in the upper portion of the kidney immediately adjacent to the adrenal gland** (Sagalowsky et al, 1994; Leibovich et al, 1995; Kletscher et al, 1996; Kozak et al, 1996; Sandock et al, 1997; Tsui et al, 2000a; Paul et al, 2001a; Lam et al, 2004b; Siemer et al, 2004; O'Malley et al, 2009a; Lane et al, 2009).

The need for a complete regional lymphadenectomy in all patients undergoing RN also remains controversial, and a randomized study of lymphadenectomy versus controls at the time of renal surgery failed to show a distinct advantage (Blom et al, 1999; Schafhauser et al, 1999; Terrone et al, 2003; Blute et al, 2004a; Phillips and Taneja, 2004; Patard, 2005; Blom et al, 2008; Leibovich and Blute, 2008; O'Malley et al, 2009b). There are several factors that may mitigate against a benefit of routine lymphadenectomy (Leibovich and Blute, 2008; O'Malley et al, 2009a). First, RCC metastasizes through the bloodstream and the lymphatic system with equal frequency. Consequently, most patients with positive lymph nodes eventually develop blood-borne metastases despite undergoing lymphadenectomy, and many patients with RCC will develop disseminated metastases without ever having lymphatic involvement. In addition, the lymphatic drainage of the kidney is variable and even an extensive retroperitoneal dissection may not remove all possible sites of metastasis. Many believe that only a relatively small percentage of patients (<2% to 3%) are likely to benefit from routine lymphadenectomy, namely, the subset of patients with micrometastatic disease (Golimbu et al, 1986; Giuliani et al, 1990; Herrlinger et al, 1991; Leibovich and Blute, 2008; O'Malley et al, 2009a). In all likelihood, the involved lymph nodes in many of these patients would be removed by conventional RN, which incorporates the renal hilar and immediately adjacent paracaval or para-aortic lymph nodes.

At present, the need for routine performance of an extended lymphadenectomy in all cases of RN is not well defined and most urologists perform this selectively (Blom et al, 1999; Blute et al, 2004a; Daneshmand et al, 2005; Phillips and Taneja, 2004; Leibovich and Blute, 2008). Blute and colleagues (2004a) have reported risk factors for lymphatic involvement with RCC, including high tumor grade, sarcomatoid component, histologic tumor necrosis, tumor size larger than 10 cm, and tumor stage pT3 or pT4. The incidence of lymph node involvement in their series was 10% if two or more of these factors were present and only 0.6% if fewer than two were present. Most of these factors can be assessed preoperatively or with intraoperative frozen-section analysis, and this could be used to guide decision making with respect to lymphadenectomy. With this approach only the hilar and regional lymph nodes would be removed for low-risk patients (Leibovich and Blute, 2008).

Open surgical techniques for RN are described in detail in Chapter 54. **The surgical approach for RN is determined by the size and location of the tumor as well as by the body habitus of the patient** (Diblasio et al, 2006; Russo, 2006). The operation is usually performed through a transperitoneal incision to allow abdominal exploration for metastatic disease and early access to the renal vessels with minimal manipulation of the tumor. The authors prefer an extended subcostal for most

patients undergoing open RN. The thoracoabdominal approach is employed only occasionally, when RN is performed in patients with very large and potentially invasive tumors involving the upper portion of the kidney. An extraperitoneal flank incision may be appropriate in elderly patients or patients of poor surgical risk, but exposure can be limiting, particularly in patients with large tumors or those with contentious hilar anatomy (Diblasio et al, 2006; Russo, 2006). In reality, most of these patients are now managed with a laparoscopic approach in this era.

Laparoscopic RN has emerged as a less morbid alternative to open surgery in the management of low- to moderate-volume (10 to 12 cm or smaller), localized RCCs with no local invasion, limited or no renal vein involvement, and manageable lymphadenopathy. Laparoscopic RN is associated with diminished postoperative discomfort and shortened recovery, and costs compare favorably with the open approach (Meraney and Gill, 2002; Hemal et al, 2007b). Available outcome data suggest that cancer-specific survival after laparoscopic RN is comparable to that after open RN (Cadeddu et al, 1998; Dunn et al, 2000; Meraney et al, 2000; Chan et al, 2001; Gill et al, 2001; Portis et al, 2002; Saika et al, 2003; Wille et al, 2004; Permpongkosol et al, 2005b; Yoshino et al, 2005; Breda et al, 2007b; Burgess et al, 2007; Hemal et al, 2007a; Columbo et al, 2008). In an early multi-institutional report of 157 patients undergoing laparoscopic RN for clinical stage I (T1-2) RCC, the 5-year actuarial disease-free rate for all patients was 91% (Cadeddu et al, 1998). Only 5 patients developed retroperitoneal or metastatic tumor recurrence, and there were no port site recurrences. Current laparoscopic techniques allow replication of the important tenets of RN, and outcome data reflect this at several centers (Cadeddu et al, 1998; Dunn et al, 2000; Meraney et al, 2000; Chan et al, 2001; Gill et al, 2001; Kim FJ et al, 2003; Portis et al, 2002; Saika et al, 2003; Simon et al, 2004; Wille et al, 2004; Permpongkosol et al, 2005b ; Burgess et al, 2007; Hemal et al, 2007b; Columbo et al, 2008). A variety of approaches including transperitoneal, retroperitoneal, and hand-assisted laparoscopic RN have been popularized and are described elsewhere in this text (see Chapter 55) (Cadeddu et al, 1998; Gill et al, 2001; Matin et al, 2002; Nelson and Wolf, 2002; Makhoul et al, 2004; Desai et al, 2005; Nadler et al, 2006; Chung et al, 2007; Kawauchi et al, 2007; Miyake et al, 2007). The current data suggest that elderly and morbidly obese patients, those with a history of previous abdominal surgery, and those with large tumor size may also be considered for laparoscopic renal surgery, although selection of patients must be judicious and surgical expertise and experience should also be taken into account (Fazeli-Matin et al, 1999; Parsons et al, 2002; Matin et al, 2003; Cobb et al, 2004; Fugita et al, 2004; Steinberg et al, 2004; Viterbo et al, 2005; Feder et al, 2008; Gabr et al, 2008).

Laparoscopic approaches are now accepted as standard in the field for RN in appropriately selected patients, providing equivalent oncologic outcomes to the open counterpart with the advantages of more rapid recovery (Desai et al, 2003b; Meraney et al, 2003; Steinberg et al, 2003; Abreu et al, 2004; Fenn and Gill, 2004; Finelli et al, 2004b, 2005; Johnston et al, 2005; Permpongkosol et al, 2005; Hollingsworth et al, 2006; Burgess et al, 2007; Hemal et al, 2007b; Columbo et al, 2008). **One concern is that laparoscopic RN has become particularly appealing to patients and physicians due to these considerations, and this has likely been a major driver in the overutilization of RN over the past several years** (Fig. 49–19). Even in the current era, most patients with small renal masses are still managed with RN, despite convincing outcomes data in favor of nephron-sparing approaches such as PN (Hollenbeck et al, 2006; Miller et al, 2006; Porter and Lin, 2007).

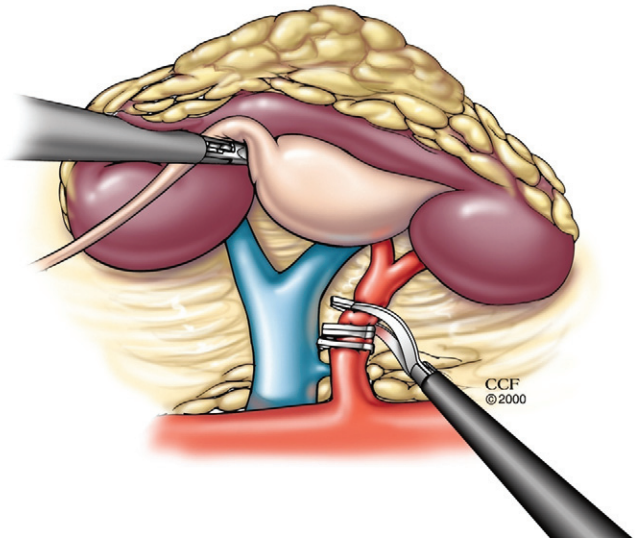


Figure 49–19. Laparoscopic radical nephrectomy (a retroperitoneal approach is illustrated) provides excellent oncologic outcomes and rapid recovery but predisposes patients to chronic kidney disease and attendant cardiovascular risks and increased mortality rates. Nephron-sparing approaches should be prioritized whenever possible. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2007-2009. All Rights Reserved.)

Several studies on outcomes after RN for localized RCC have now demonstrated that the risk for postoperative recurrent malignant disease is stage dependent, and surveillance protocols should reflect this (Sandock et al, 1995; Levy et al, 1998; Eggener et al, 2001; Janzen et al, 2003; Stephenson et al, 2004a; Theodorescu et al, 2004; Sorbellini et al, 2005; Skolarikos et al, 2007). For instance, in a study from M. D. Anderson Cancer Center (Levy et al, 1998), 68 of 286 patients (23.8%) developed metastatic RCC after RN and the incidence was 7.1% for stage T1N0M0, 26.5% for T2N0M0, and 39.4% for T3N0M0. The risk for developing recurrent malignant disease was greatest during the first 3 postoperative years. Stephenson and colleagues (2004a) also reported substantially increased risk of recurrence in patients with stage pT3a and pT3b compared with pT1 and pT2, and recurrences were diagnosed earlier in the former, with a median of 12 versus 26 months. **These data indicate that surveillance for recurrent malignant disease after RN for RCC can be tailored according to the initial pathologic tumor stage.** The recommended surveillance scheme is depicted in Table 49–20. Postoperative bone scintiscans and head CT scans are necessary only in the presence of related symptoms. This surveillance scheme is cost effective and enables early detection of most cases of recurrent RCC after RN for localized disease. Other important prognostic factors for RCC, such as tumor size, grade, and histologic subtype, can also influence the risk and pattern of recurrence and are now integrated into predictive algorithms that will be useful for more individualized surveillance in the near future (Kattan et al, 2001; Pantuck et al, 2001a; Zisman et al, 2002c; Frank et al, 2003a, 2005e; Lam et al, 2005b; Sorbellini et al, 2005; Antonelli et al, 2007). **Surveillance for CKD is also of paramount importance along with timely referral for nephrologic consultation** (Lane et al, 2009). Close nephrologic surveillance and skilled management can delay the progression of CKD and mitigate against the negative effects of associated

conditions, including cardiovascular disease, poor bone health, anemia, and sexual dysfunction (Lane et al, 2009).

Partial Nephrectomy

Nephron-sparing surgery for the treatment of a renal tumor was first described by Czerny in 1890 (reviewed in Herr, 2005). However, high morbidity limited its application. In 1950, Vermooten suggested that peripheral encapsulated renal neoplasms could be excised locally while leaving a margin of normal parenchyma around the tumor. **Interest in PN for RCC has been stimulated by advances in renal imaging, experience with renal vascular surgery for other conditions, improved methods of preventing ischemic renal damage, growing numbers of incidentally discovered low-stage RCCs, greater appreciation of the deleterious effects of CKD, and good long-term survival in patients undergoing this form of treatment** (Uzzo and Novick, 2001; Russo et al, 2008; Campbell et al, 2009; Lane et al, 2009; Novick, 2009). Nephron-sparing surgery entails complete local resection of the renal tumor while leaving the largest possible amount of normal functioning parenchyma in the involved kidney (Fig. 49–20).

Table 49–20.

Postoperative Surveillance after Radical Nephrectomy for Localized Renal Cell Carcinoma

PATHOLOGIC TUMOR STAGE	HISTORY, EXAMINATION, AND BLOOD TESTS*	CHEST RADIOGRAPH	ABDOMINAL CT SCAN
pT1aN0M0	Yearly	—	—
pT1b-2bN0M0	Yearly	Yearly	—
pT3-4N0M0	Every 6 mo	Every 6 mo for 3 yr, then yearly	At 1 yr, then every 2 yr
pTxN1M0	Every 6 mo for 3 yr, then yearly	Every 4 mo for 2 yr, then every 6 mo	Every 6 mo for 1 yr, then yearly

*Blood tests should include serum creatinine, blood urea nitrogen, electrolytes, serum calcium, alkaline phosphatase, and a liver function panel.

Accepted indications for PN traditionally included situations in which RN would render the patient anephric or at high risk for ultimate need of dialysis (Licht et al, 1994; Ghavamian and Zincke, 2001; Uzzo and Novick, 2001; Nguyen et al, 2008a; Russo et al, 2008; Campbell et al, 2009; Lane et al, 2009). This encompassed patients with bilateral RCC or RCC involving a solitary functioning kidney. A solitary functioning kidney may be the result of unilateral renal agenesis, prior removal of the contralateral kidney, or irreversible impairment of contralateral renal function by a benign disorder. Another traditional relative indication for PN was represented by patients with unilateral carcinoma and a functioning opposite kidney affected by a condition that might threaten its future function, such as renal artery stenosis (Campbell et al, 1993; Hafez et al, 2000), hydronephrosis, chronic pyelonephritis, ureteral reflux, calculus disease, or systemic diseases such as diabetes and nephrosclerosis (Uzzo and Novick, 2001; Gilbert et al, 2003; Nguyen et al, 2008a; Russo et al, 2008; Campbell et al, 2009; Lane et al, 2009; Novick, 2009).

In patients with bilateral synchronous RCC, the general approach has been to preserve as much functioning renal tissue as possible. This entails performing bilateral PNs when feasible, usually as staged procedures if the tumors are relatively large. When a locally extensive tumor on one side precludes nephron-sparing surgery, an RN is performed on the more involved side along with a contralateral PN (Booth et al, 2008; Nguyen et al, 2008a; Rothman et al, 2008). **Margin width appears to be immaterial as long as the final margins are negative; this is particularly relevant when the tumor is located within the hilum and preservation of renal function is at a premium** (Castilla et al, 2002; Sutherland et al, 2002; Li et al, 2008; Yossepowitch et al, 2008; Campbell et al, 2009).

Patients with RCC involving a functionally or anatomically solitary kidney must be advised about the

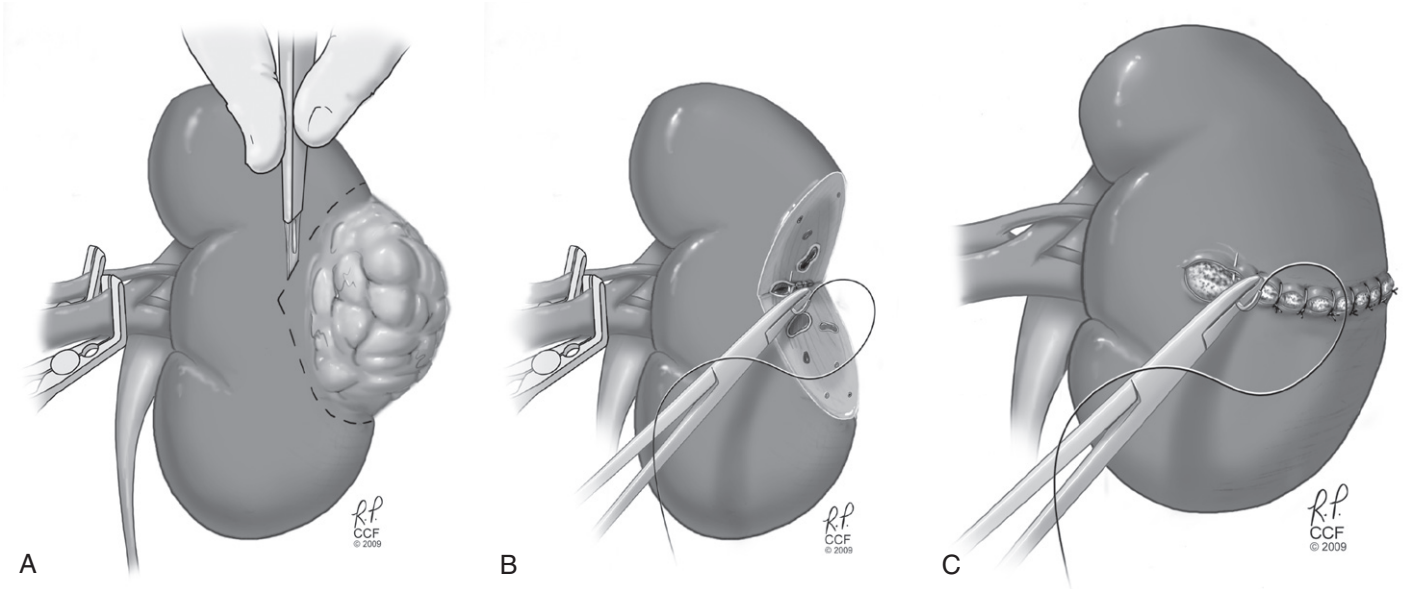


Figure 49–20. Essential steps in partial nephrectomy. **A,** Temporary occlusion of the vascular pedicle and excision of the tumor with a rim of normal parenchyma. **B,** Closure of the collecting system and ligation of transected vessels. **C,** Capsular reconstruction. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2007-2009. All Rights Reserved.)

potential need for temporary or permanent dialysis postoperatively, which, according to the authors' experience, occurs in 3.5% and 0.5% of cases, respectively (Fergany et al, 2006). In this series, 18 of 400 patients (4.5%) with a solitary kidney managed with PN eventually progressed to end-stage renal failure at a mean of 3.6 years after surgery. Many of these patients also had preexisting CKD before surgery, and in some instances only a small remnant kidney could be preserved owing to tumor size and anatomic considerations. Similarly, Ghavamian and colleagues (2002) reported a 12.7% incidence of acute renal failure when operating on a solitary kidney, with 15.9% developing proteinuria and 12.7% experiencing severe CKD on a long-term basis. **A functioning renal remnant of at least 20% of one kidney is necessary to avoid end-stage renal failure, although this presumes good functional status of the remaining parenchyma** (Uzzo and Novick, 2001). **Overall preservation of renal function is thus achieved in the great majority of patients with PN, even in patients with traditional imperative indications** (Uzzo and Novick, 2001; Nguyen et al, 2008a; Novick, 2009). **Local recurrence after PN for imperative indications has ranged from 3% to 5%,** because many of these cases are particularly challenging owing to hilar tumor location, the need to minimize the amount of excised functional parenchyma, tumor multifocality, or other complexities (Uzzo and Novick, 2001; Nguyen et al, 2008a).

PN is now standard of care for the management of clinical T1 renal masses in the presence of a normal contralateral kidney, presuming that the mass is amenable to this approach (Nguyen et al, 2008a; Russo et al, 2008; Russo and Huang, 2008; Huang et al, 2009; Campbell et al, 2009; Lane et al, 2009; Novick, 2009). This indication was previously considered "elective," but recent data demonstrating the importance of optimizing renal function after surgery for clinical T1 renal masses has persuasively altered this perspective. A robust literature now demonstrates equivalent oncologic outcomes with PN when compared with RN in appropriately selected patients, and the renal functional outcomes tilt the balance in favor of nephron-sparing approaches whenever feasible (Lau et al, 2000; Lee et al, 2000; McKiernan et al, 2002b; Becker et al, 2006b; Mitchell et al, 2006; van Poppel et al, 2007; Rabets and Novick, 2006; Russo et al, 2008; Thompson et al, 2008; Campbell et al, 2009; Huang et al, 2009; Lane et al, 2009). **Prior experience with "elective" PN for T1a RCC demonstrated local recurrence rates of 1% to 2%, and overall cancer-free survival well over 90%** (Uzzo and Novick, 2001; Campbell et al, 2009). The morbidity of PN has also decreased substantially in recent years in experienced hands (Thompson et al, 2005d; Diblasio et al, 2006; Joudi et al, 2007; Patard et al, 2007). **Extension of this approach to clinical T1b tumors has yielded similar encouraging results** (Becker et al, 2006a; Carini et al, 2006; Dash et al, 2006; Campbell and Novick, 2006; Crispen et al, 2008a; Nguyen et al, 2008a; Pahernik et al, 2008; Campbell et al, 2009; Peycelon et al, 2009). **The majority of local recurrences observed after PN are most likely a manifestation of undetected microscopic multifocal RCC in the renal remnant—most are found distant from the previous tumor bed. Concern about local recurrence after PN is counterbalanced by a 1% to 2% incidence of contralateral RCC on longitudinal surveillance,** in which case RN would have left the patient with tumor in a solitary kidney (Nguyen et al, 2008a; Russo et al, 2008). Interestingly, Clark and colleagues (2001) have shown that quality of life and psychological adaptation may be better after PN compared with RN, and costs appear to be comparable whether RN is performed open or laparoscopically (Uzzo et al, 1999c; McKiernan et al, 2002a; Shekarriz et al, 2002; Poulakis et al, 2003; Stephenson et al, 2004b).

Evaluation of patients with RCC for PN should include preoperative testing to exclude locally extensive or metastatic disease and additional specific renal imaging to delineate the relationship of the tumor to the intrarenal vascular supply and collecting system. For centrally located tumors, this information has traditionally been obtained with a combination of studies including CT, renal arteriography, and, occasionally, renal venography. Three-dimensional volume-rendered CT (or MRI) is now established as a noninvasive imaging modality that can accurately depict the renal parenchymal and vascular anatomy in a format familiar to urologic surgeons (Coll et al, 1999; Uzzo et al, 2000a; Berman et al, 2001; Vanderbrink et al, 2004; Nguyen et al, 2008a; Simmons et al, 2007; Novick, 2009). This study integrates essential information from arteriography, venography, excretory urography, and conventional two-dimensional CT into a single imaging modality and obviates the need for more invasive renal imaging (Derweesh et al, 2004; Simmons et al, 2008). The surgical techniques for performing nephron-sparing surgery in patients with RCC are reviewed in Chapters 54 and 55.

One of the largest reported studies of nephron-sparing surgery is from the Cleveland Clinic and reviewed the results of PN for the treatment of localized, sporadic RCC in 485 patients (Hafez et al, 1999). The mean postoperative follow-up was 4 years, and overall and cancer-specific 5-year survival rates for patients in this series were 81% and 92%, respectively. Recurrent RCC developed postoperatively in 44 patients (9%), including 16 (3.2%) with local recurrence in the remnant kidney and 28 (5.8%) with metastatic disease. In another study from the Cleveland Clinic, long-term results of nephron-sparing surgery were reviewed in 107 patients with localized sporadic RCC treated before 1988 who were followed for a minimum of 10 years or until death (Fergany et al, 2000). Cancer-specific survival was 88% at 5 years and 73% at 10 years. Long-term renal function was preserved in 100 patients (93%). These results are particularly impressive given the patient population in that era, almost all of whom underwent PN for imperative indications. Ten-year follow-up was also provided by Herr (1999), who reported that 97% of patients remained cancer free after PN in the setting of a normal contralateral kidney, a more select population of patients. These data confirm that **nephron-sparing surgery provides effective long-term therapy for patients with localized RCC and can preserve renal function in the overwhelming majority** (Saad et al, 2005; Nguyen et al, 2008a; Novick, 2009).

A more recent trend has been to perform PN by minimally invasive approaches, which is a considerable challenge given concern about margin status when visualization can be compromised by suboptimal hemostasis and in the absence of tactile input. Nevertheless, several series have now reported encouraging results, and this field is evolving rapidly (Gill et al, 2002, 2003b, 2006, 2007, 2008; Hu et al, 2002; Guillonneau et al, 2003; Simon et al, 2003; Allaf et al, 2004; Finelli et al, 2004a; Kane et al, 2004; Mabjeesh et al, 2004; Frank et al, 2006; Porpiglia et al, 2008; Turna et al, 2008; Nadu et al, 2009). Many groups have now developed techniques that essentially duplicate the open surgical technique, including occlusion of the renal vasculature, excision of the tumor with a rim of normal parenchyma, and intracorporeal suturing to close the collecting system and repair the capsular defect (Desai

et al, 2003a; Gill et al, 2007; Gill et al, 2008). Hemostasis remains the primary challenge given the great blood flow associated with the kidneys, and a variety of adjuvant approaches have been explored to accomplish this, including the use of tissue sealants, hemostatic dissecting devices, and robotic technology (Gettman et al, 2001b; Yoshimura et al, 2001; Richter et al, 2003; Hasan et al, 2004a, 2004b; Herrel et al, 2004; Urena et al, 2004; Finley et al, 2005; Gill et al, 2008; Porpiglia et al, 2008; Turna et al, 2008). **Margin status and intermediate oncologic outcomes associated with laparoscopic PN appear to be equivalent to open PN in experienced hands, presuming sensible patient selection** (Lane and Gill, 2007).

A recent study from three centers of excellence provides important information about outcomes with open and laparoscopic PN, albeit somewhat in the developmental phase of the latter (Gill et al, 2007) (Table 49–21). This study evaluated 1029 open PN (OPN) and 771 laparoscopic PN (LPN), with analysis focused on patient and tumor characteristics in addition to perioperative outcomes. Strong selection bias is evident, as expected for any new technique, because the LPN group was found to have favorable characteristics in terms of better general health, smaller tumor size, and more asymptomatic presentation and less likely to have central tumor location, preexisting CKD, or a solitary kidney. LPN was associated with shorter operative times and less blood loss, although warm ischemic times were longer and the risk of urologic complications was higher. Warm ischemic time is particularly important in this era because it is now established as the major modifiable determinant of postoperative renal function (Thompson et al, 2007c; Lane et al, 2008a). In addition, urologic complications, such as postoperative hemorrhage and urinary leak, and the need for subsequent procedures, were substantially increased in the LPN group on a comparative basis (Gill et al, 2007). **Recent advances in the technique of LPN, such as the early unclamping maneuver in which the vascular pedicle clamp is removed immediately after running a deep parenchyma suture across the defect, hold great promise for improving on these outcomes** (Baumert et al, 2007; Bollens et al, 2007; Breda et al, 2007b; Simmons et al, 2007). Nguyen and Gill (2008) have reported substantially reduced warm ischemic times with this approach, and postoperative bleeding rates have also fallen, presumably because potential bleeders can be identified intraoperatively and prospectively addressed prior to closing the capsule. Please refer to Chapter 55 for further technical details regarding LPN.

Clinical guidelines for long-term surveillance after PN for sporadic localized RCC have been developed (Eggener et al, 2001; Frank et al, 2003a; Janzen et al, 2003; Theodorescu et al, 2004; Lam et al, 2005b; Sorbellini et al, 2005; Antonelli et al, 2007; Skolarikos et al, 2007; Klatte et al, 2008b), originally based on a detailed analysis of tumor recurrence patterns in 327 patients treated at the Cleveland Clinic (Hafez et al, 1997). In this series, recurrent RCC developed after nephron-sparing surgery in 38 patients (11.6%), including 13 patients (4%) who developed local recurrence and 25 patients (7.6%) who developed metastatic disease (Hafez et al, 1997). The incidence of postoperative local recurrence and metastatic disease varied according to the initial pathologic tumor stage as follows: 0% and 4.4% for T1N0M0 tumors, 2% and 5.3% for T2N0M0 tumors, 8.2% and 11.5% for T3aN0M0 tumors, and 10.6% and 14.9% for T3bN0M0 tumors. The peak postoperative intervals for development of local recurrence were 6 to 24 months (in T3 tumors) and more than 48 months (in T2 tumors). T1 tumor stage in this series represented tumor size of less than 2.5 cm, based on a previous TNM classification system. **These data indicate that surveillance for recurrent malignant disease after PN for sporadic RCC can be tailored according to the initial pathologic tumor stage and tumor size or an algorithm based on these and other clinicopathologic factors predictive of recurrence** (Frank et al, 2003a; Klatte et al, 2008b). A relatively straightforward surveillance scheme recommended by the authors is depicted in Table 49–22. This protocol minimizes costs, radiographic exposure, and patient inconvenience while still allowing for detection of most clinically relevant recurrences.

Patients who undergo nephron-sparing surgery for RCC may be left with a relatively small amount of renal tissue and are at risk for development of long-term renal functional impairment from hyperfiltration renal injury (Modlin and Novick, 2001; Abdi et al, 2003; Lane et al, 2009; Novick, 2009). In a study of 14 patients observed for up to 17 years after PN in a solitary kidney, patients with more than 50%

Table 49–21.

Comparison of Open vs. Laparoscopic Partial Nephrectomy

PATIENT AND TUMOR CHARACTERISTICS	TYPE OF NEPHRECTOMY		*P* VALUE
	Open	Laparoscopic	
Total number of patients	1029	771	
ASA score ≥3	75.8%	45.9%	<.0001
ECOG PS ≥1	14.7%	1.4%	<.0001
Symptomatic tumor	33.5%	8.8%	<.0001
Solitary kidney	21.6%	4.2%	<.0001
Serum creatinine level >2.0 mg/dL	6.4%	1.6%	<.0001
Tumor >4.0 cm	31.4%	8.8%	<.0001
Central tumor location	53.3%	34.4%	<.0001
Perioperative Outcomes			
Operative time (min)	258	200	<.0001
Blood loss (mL)	376	300	<.0001
Ischemia time (min)	20	31	<.0001
Urologic complications	5.0%	9.2%	.006
Subsequent procedures	3.5%	7.0%	<.0001
Hemorrhage	1.6%	4.2%	.0002

From Gill IS, Kavoussi LR, Lane BR, et al. Comparison of 1,800 laparoscopic and open partial nephrectomies for single renal tumors. J Urol 2007;178:41-6.

Table 49–22.

Postoperative Surveillance after Partial Nephrectomy for Localized Renal Cell Carcinoma

PATHOLOGIC TUMOR STAGE	HISTORY, EXAMINATION, AND BLOOD TESTS*	CHEST RADIOGRAPH	ABDOMINAL CT SCAN
pT1aN0M0	Yearly	—	—
pT1b-2bN0M0	Yearly	Yearly	Every 2 yr
pT3N0M0	Every 6 mo for 3 yr, then yearly	Every 6 mo for 3 yr, then yearly	Every 6 mo for 3 yr, then every 2 yr

*Blood tests should include serum creatinine, blood urea nitrogen, electrolytes, serum calcium, alkaline phosphatase, and a liver function panel.

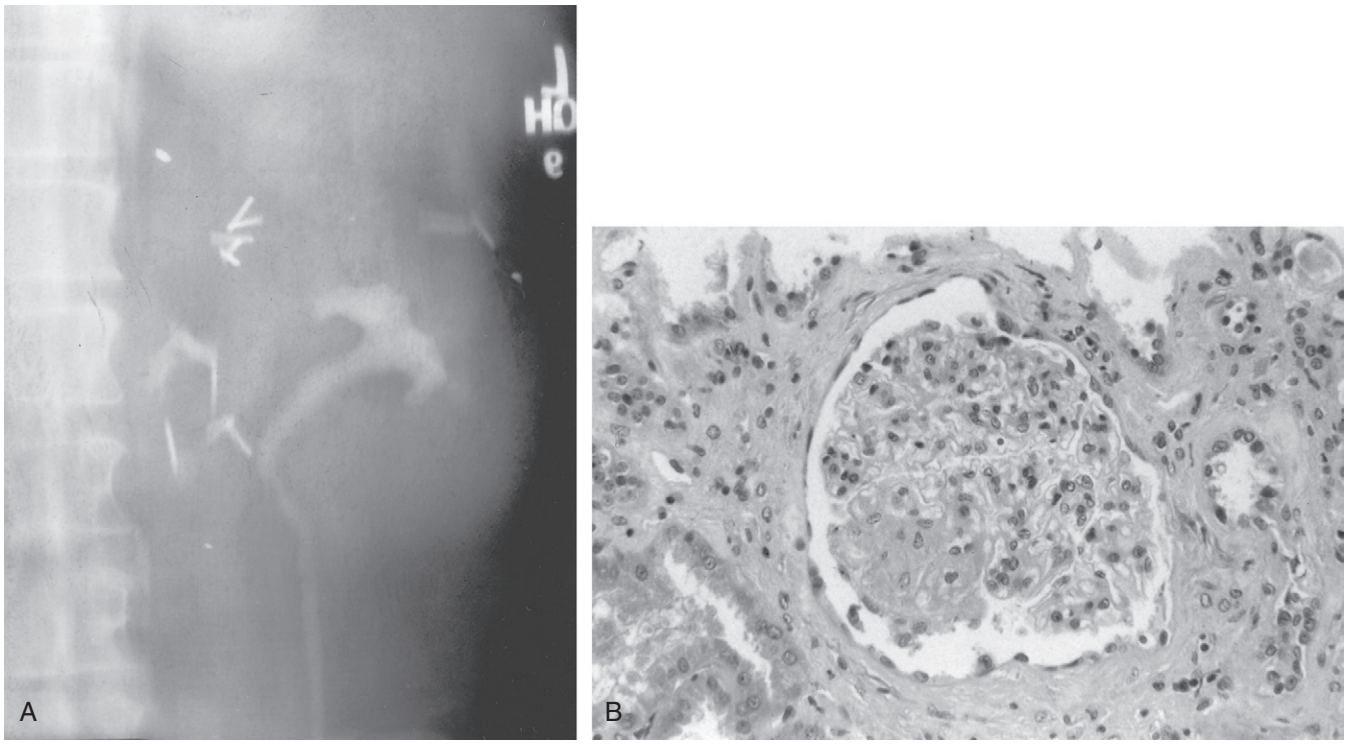


Figure 49–21. **A,** Ten years after partial nephrectomy for large tumor in solitary left kidney, intravenous pyelogram shows function of small renal remnant. The patient had developed nephrotic syndrome at this time. **B,** Renal biopsy specimen shows focal segmental glomerulosclerosis indicative of hyperfiltration nephropathy.

reduction in overall renal mass were found to be at increased risk for development of proteinuria, focal segmental glomerulosclerosis, and progressive renal failure (Novick et al, 1990). The development of proteinuria correlated directly with the length of follow-up and inversely with the amount of remaining renal tissue. Renal biopsy revealed focal segmental glomerulosclerosis in several patients with severe proteinuria (Fig. 49–21). These findings mirror those observed in experimental animal models of partial renal ablation (Brenner, 1983). **Because proteinuria is the initial manifestation of this phenomenon, a 24-hour urinary protein measurement should be obtained yearly in patients with a solitary remnant kidney to screen for hyperfiltration nephropathy.**

Efforts to prevent or to ameliorate the damaging effects of renal hyperfiltration have primarily focused on dietary and pharmacologic intervention (Modlin and Novick, 2001; Lane et al, 2009). Animal studies have suggested that angiotensin-converting enzyme inhibitor (ACEI) agents and dietary restriction of protein may mitigate this type of glomerulopathy (Meyer et al, 1985). Preliminary clinical data appear to support this concept. Novick and Schreiber (1995) studied five patients who had developed proteinuria with stable renal function after PN in a solitary kidney. Four of these patients had documented focal segmental glomerulosclerosis on renal biopsy during follow-up, although all five patients had normal renal morphologic features at the time of surgery. Treatment with ACEI therapy and a low-protein diet decreased the level of proteinuria in four patients. Data from other studies have also suggested that ACEI therapy can significantly diminish proteinuria in patients with established renal disease (Goldfarb, 1995). **This information suggests that ACEI therapy and a low-protein diet may improve the long-term renal functional outcome for patients with a remnant kidney after PN.** The optimal time for initiating the regimen is not clear, and it may be best to implement this therapy as early as possible to obviate the maladaptive responses that can lead to progressive sclerosis and renal failure in this setting.

There is experimental evidence that nonhemodynamic processes may also contribute to progression of sclerosis in the remnant kidney (Goldfarb, 1995). This raises other therapeutic possibilities, such as thromboxane inhibitors, anticoagulants, lipid-lowering agents, and other pharmacologic agents. Future clinical trials, it is hoped, will clarify the potential value of these treatment approaches.

Thermal Ablative Therapies

Thermal ablative (TA) therapies, including renal cryosurgery and radiofrequency ablation (RFA), have emerged as alternative nephron-sparing treatments for patients with localized RCC (Marshall, 1999; Murphy and Gill, 2001; Lowry and Nakada, 2003; Hinshaw and Lee, 2004; Mabjeesh et al, 2004; Ost and Kavoussi, 2007; Sterrett et al, 2008; Matin and Ahrar, 2009). **Both can be administered percutaneously or through laparoscopic exposure and thus offer the potential for reduced morbidity and more rapid recovery** (Johnson et al, 2004; Sterrett et al, 2008). **However, long-term efficacy is not as established as with surgical excision and preliminary data suggest that the local recurrence rates may be somewhat higher than that reported for traditional surgical approaches** (Campbell et al, 2009; Kunkle et al, 2008; Matin and Ahrar, 2009). Another concern has been the lack of accurate histologic and pathologic staging associated with these modalities, because the treated lesion is left in situ.

The ideal candidates for TA procedures may be patients with advanced age or significant comorbidities who prefer a proactive approach but are not optimal candidates for conventional surgery, patients with local recurrence after previous nephron-sparing surgery, and patients with hereditary renal cancer who present with multifocal lesions for which multiple PNs might be cumbersome if not impossible (Kunkle et al, 2008). Patient preference must also be considered, and some patients not fitting these criteria may also select TA, a decision that can be supported as long as balanced counseling about the current status of these modalities has been provided (Ost and Kavoussi, 2007; Sterrett et al, 2008; Matin and Ahrar, 2009). Finally, tumor size is also an important factor in patient selection because the current technology does not allow for reliable treatment of lesions larger than 4.0 cm in diameter (Zagoria et al, 2007; Matin and Ahrar, 2009).

Experience with renal cryosurgery predates that of RFA and has been more extensive (Sterrett et al, 2008; Matin and Ahrar, 2009). **The kidney may be an anatomically favored organ for cryosurgery,** particularly compared with the prostate, another target organ for cryoablation. Unlike the prostate, which is in intimate, fixed contact with the rectum and the sphincteric mechanism, the kidney can be laparoscopically mobilized, thereby minimizing the risk of injury to adjacent vital structures. Furthermore, while the prostate often harbors multifocal, infiltrative carcinoma, the kidney usually presents with unifocal, well-circumscribed malignancy. Because the renal tumor and "ice ball" that forms during treatment can be readily visualized with ultrasonography, the ice ball can be confirmed to completely and circumferentially obliterate the tumor margins, including a surrounding margin of healthy tissue, with increased precision and confidence. An extensive body of experimental work is available to guide and support clinical cryoablation (Hinshaw and Lee, 2004; Sterrett et al, 2008).

Established prerequisites for successful cryosurgery include rapid freezing, gradual thawing, and a repetition of the freeze-thaw cycle. The mechanism underlying tissue cryodestruction is thought to involve immediate cellular damage and delayed microcirculatory failure (Gill and Novick, 1999; Baust and Gage, 2005; Ost and Kavoussi, 2007; Stein and Kaouk, 2007; Sterrett et al, 2008; Matin and Ahrar, 2009). Ice formation occurs initially in the extracellular space, causing the extracellular fluid to become hyperosmotic. To equilibrate chemical osmolality, water permeates from the intracellular compartment into the extracellular compartment. Osmolality of the intracellular fluid is thus increased, leading to intracellular solute concentration and dehydration, which cause desiccation trauma—the first step of chemical cellular injury. Continued rapid supercooling leads to the second step of cellular damage—intracellular ice formation. Intracellular ice irreversibly disrupts cell organelles and the cell membrane, a lethal event. Delayed microcirculatory failure occurs during the slow thaw phase of the freeze-thaw cycle, leading to circulation arrest and cellular anoxia. Progressive disruption of the microcirculation occurs along a cascade of events: vasoconstriction, endothelial cell destruction causing vessel walls to become porous, interstitial edema, platelet aggregation, microthrombi, and, ultimately, vascular congestion and obliteration. Cells that survive the initial cryogenic assault are destroyed by this secondary insult of ischemia. Repetition of the rapid freeze–slow thaw cycle potentiates the damage. The cryoablation area is thus rendered ischemic, leading ultimately to a circumscribed necrosis (Hinshaw and Lee, 2004; Ost and Kavoussi, 2007; Sterrett et al, 2008; Matin and Ahrar, 2009).

Further work defined treatment parameters required to bring this treatment into the clinical domain. Chosy and colleagues (1996) demonstrated that complete necrosis of in-vivo porcine renal parenchyma could be consistently achieved only at temperatures of –19.4° C or lower; necrosis was incomplete at temperatures above this threshold. Campbell and coworkers (1998) **confirmed that the target lethal temperature of –20° C was achieved at a distance of 3.1 mm inside the leading edge of the ice ball as visualized by real-time ultrasonography.** Thus, to ensure complete cell kill, the ice ball must extend well beyond the visible margins of the targeted tumor. In practice, we routinely extend the ice ball approximately 1 cm beyond the edge of the tumor, as determined by both laparoscopic and real-time ultrasonographic imaging (Gill et al, 1998). The availability of sophisticated and reliable ultrasonography and the introduction of finer cryoprobes that allow more accurate and less traumatic probe placement have contributed to even greater interest in visceral cryosurgery (Onik et al, 1993; Pantuck et al, 2002b; Ost and Kavoussi, 2007; Stein and Kaouk, 2007; Sterrett et al, 2008; Matin and Ahrar, 2009).

Clinical experience and follow-up of patients after renal cryoablative therapy suggests successful local control in 90% to 95% of patients, although many studies provide limited, and often incomplete, follow-up (Gervais et al, 2005; Gill et al, 2005; Davol et al, 2006; Matin et al, 2006; Ost and Kavoussi, 2007; Stein and Kaouk, 2007; Atwell et al, 2008; Sterrett et al, 2008; Matin and Ahrar, 2009). Diagnosis of local recurrence after thermal ablative treatments can be challenging because evolving fibrosis within the tumor bed can be difficult to differentiate from residual cancer. **In general, central or nodular enhancement within the tumor bed on extended follow-up has been considered diagnostic of local recurrence, and the general clinical experience with cryoablation has thus far supported this** (Bolte et al, 2006; Weight et al, 2008). However, the number of studies that have incorporated routine post-therapy biopsies to provide histologic confirmation are in the minority (Gill et al, 2000a; Weight et al, 2008; Matin and Ahrar, 2009). Weight and colleagues (2008) demonstrated that none of the 60 patients with absence of enhancement after cryoablation had residual cancer on follow-up biopsy while peripheral and central enhancement were associated with cancer in 8% and 63% of patients, respectively.

Reported rates of local recurrence in some of the ablation series may represent underestimates because about 20% of small renal masses are benign rather than RCC, and a pretreatment biopsy, although strongly advocated in the field, has not been routinely performed in many series (Silver et al, 1997; Young et al, 2002; Heilbrun et al, 2007; Sterrett et al, 2008). In addition, patients may have a recurrence at other sites in the kidney, and this should also be considered local recurrence although the mechanism is different (novel tumor occurrence due to multifocality rather than treatment failure). Hasan and colleagues (2004a) reported two such ipsilateral occurrences when their patients were observed for a minimum of 48 months, so the true incidence of local recurrence in this series was 10%, not the reported 5%, higher than would be expected for conventional PN for an analogous population of patients with small renal tumors. Indeed, recurrence in the tumor bed after conventional PN is uncommon; most local recurrences are distant from the original tumor site. This cumulative experience suggests that local control after cryoablative therapy approaches, but may not reach, that attained by conventional surgical excision (Kunkle et al, 2008; Matin and Ahrar, 2009).

Other concerns with cryoablation, and TA in general, relate to surgical salvage and long-term outcomes. Most local recurrences can be salvaged with repeat ablation, although some patients with progressive disease eventually require conventional surgery. Nguyen and colleagues (2008b) **have shown that PN and minimally invasive approaches are often not possible in this setting due to the extensive fibrotic reaction induced by the previous treatment.** This reaction appears to be more significant after cryoablation than after RFA or PN, although the precise reasons for this are unclear at present. Long-term outcomes after TA are limited, and the few that are available suggest suboptimal outcomes in a finite proportion of patients (Kunkle et al, 2008; Campbell et al, 2009). In the most robust and mature single institution experience with cryoablation, 5- and 10-year disease-free survival rates were 78% and 51%, respectively, much less than would be expected for PN for an analogous population of patients with small renal tumors (Aron et al, 2007). Complications associated with cryoablation can include renal fracture, hemorrhage, adjacent organ injury, ileus, and wound infection, although major morbidity is decidedly uncommon (Lane et al, 2005; Ost and Kavoussi, 2007; Finley et al, 2008; Sterrett et al, 2008; Matin and Ahrar, 2009).

The experience with RFA is more limited—this technology is at an earlier state of development than cryoablation (Corwin et al, 2001; Murphy and Gill, 2001; Rendon et al, 2001; Zelkovic and Resnick, 2003; Mabjeesh et al, 2004; Hegarty et al, 2006; Aron et al, 2007; Ost and Kavoussi, 2007; Sterrett et al, 2008; Matin and Ahrar, 2009). Mechanistically, heat above 45° C leads to irreversible cellular damage, and temperatures higher than 55° C to 60° C result in immediate cell death. Application of high-frequency electrical current by RFA induces excitation of ions, frictional forces, and heat, which in turn cause denaturation of intracellular proteins and melting of cellular membranes, a lethal sequence of events. These effects are observed at tissue temperatures above 41° C but increase directly with increasing temperature and duration of treatment (Mabjeesh et al, 2004; Sterrett et al, 2008; Matin and Ahrar, 2009). Temperatures in excess of 100° C are typically obtained at the tips of the probes, and thermosensors near the tips can be used to monitor progress during active treatment. Temperature dissipates at points more distant from the probe tip, and multiple probes are typically required to achieve adequate heating of the entire region of interest (Murphy and Gill, 2001). **One disadvantage of RFA is that the treatment effect is more difficult to monitor in real time—there is no true "ice ball" equivalent** (Zelkovic and Resnick, 2003). **Rather, treatment is typically based on empirical results from previous probe alignments, and this allows a fairly predictable target zone of up to 4.0 cm to be treated in most cases.** Maximal tumor size that can be adequately treated would of necessity be smaller than this, given the need to extend the treatment zone beyond all edges of the tumor. Novel approaches to extend these boundaries are being explored (Matin and Ahrar, 2009).

Local control after RFA is difficult to determine owing to a number of complexities, although most estimate that this will be 80% to 90% on a longitudinal basis using strict definitions of local recurrence (Matin et al, 2006; Ost and Kavoussi, 2007; Kunkle et al, 2008; Levinson et al, 2008; Campbell et al, 2009; Matin and Ahrar, 2009). Loss of enhancement on cross-sectional imaging within the lesion has generally been accepted as an indicator of successful treatment after TA (Raman et al, 2008), although a report by Weight and colleagues (2008) has challenged this. This group described 6 patients with no enhancement on MRI performed 6 months after RFA who were found to have apparently viable cancer cells on biopsy of the tumor bed, indicating that 24% of lesions with no radiographic suspicion for tumor persistence may have been incompletely treated (Weight et al, 2008). The technology for RFA continues to improve, and most contemporary series report low rates of local recurrence, although some patients have required repeat treatments to achieve local control, which is an infrequent event with cryoablation and rarely required with conventional surgical treatments for localized RCC (Anderson et al, 2005; Coleman et al, 2005; Schenk et al, 2005; Ost and Kavoussi, 2007; Sterrett et al, 2008; Matin and Ahrar, 2009). Complications are uncommon but have included acute renal failure, stricture of the ureteropelvic junction, necrotizing pancreatitis, and lumbar radiculopathy, so careful and judicious selection of patients is essential (Ogan et al, 2002; Coskun et al, 2003; Elias et al, 2004; Schenk et al, 2005; Weizer et al, 2005a, 2005b; Ost and Kavoussi, 2007; Sterrett et al, 2008; Matin and Ahrar, 2009). Direct comparison with cryoablation is inevitable but perhaps unfair because RFA is earlier in its development and recent advances suggest great promise (Anderson et al, 2005; Coleman et al, 2005; Schenk et al, 2005; Ost and Kavoussi, 2007; Sterrett et al, 2008; Matin and Ahrar, 2009). Nevertheless, with the development of protocols to administer cryoablation percutaneously, many centers are offering cryoablation to patients who otherwise might have been treated with RFA in the past (Shingleton and Sewell, 2001, 2002; Bassignani et al, 2004; Silverman et al, 2005; Tuncali et al, 2006; Atwell et al, 2007, 2008; Georgiades et al, 2008; Hinshaw et al, 2008).

Other exciting new technologies, such as high-intensity focused ultrasound (HIFU) and frameless, image-guided radiosurgical treatments (CyberKnife), are also under development and may allow extracorporeal treatment of small renal tumors in the future (Kohrmann et al, 2002; Ponsky et al, 2003; Wu et al, 2003; Roberts et al, 2006; Svedman et al, 2006; Clark et al, 2007; Marberger, 2007; Ponsky et al, 2007; Klinger et al, 2008; Liang et al, 2008; Matin and Ahrar, 2009). However, at present cell kill with these modalities is not sufficiently reliable and they are best considered developmental (Matin and Ahrar, 2009).

Active Surveillance

There was once relatively little information about the growth rate of RCC because almost all renal tumors were excised shortly after detection based on prior paradigms of management (Chawla et al, 2006; Crispen and Uzzo, 2006; Jewett and Zuniga, 2008; Chen et al, 2009). **The incidental discovery of many small RCCs in asymptomatic elderly patients or those of poor surgical risk has provided the opportunity to observe the growth rate of these tumors in patients who are unable or unwilling to undergo surgery** (Derweesh and Novick, 2003; Chawla et al, 2006; Crispen and Uzzo, 2006; Rendon and Jewett, 2006; Kouba et al, 2007; Abou Youssif et al, 2007; Abouassaly et al, 2008; Jewett and Zuniga, 2008; Klatte et al, 2008b; Campbell et al, 2009; Chen et al, 2009). Bosniak and associates (1996) reported one of the first and largest series of active surveillance (AS) that included 72 small (<3.5 cm) renal tumors in 68 patients who were observed with serial imaging studies for intervals ranging from 2 to 10 years (mean, 3.3 years). On CT these were well-marginated, homogeneous, solid, enhancing tumors consistent with RCC. **During the period of observation these tumors grew at slow and variable rates of up to 1.1 cm per year, with a median growth rate of 0.36 cm**

per year. In 32 patients whose tumors grew to larger than 3 cm, surgical excision was performed; all the excised tumors proved to be stage pT1a RCCs, and the majority were grade 1 tumors. Significantly, none of the patients developed metastasis during the period of surveillance.

Subsequent series from several institutions have confirmed that many small renal masses will grow relatively slowly (median growth rate 0.28 cm/yr), and there have been only 4 patients with metastasis in these series (1.2%), suggesting that this may be a reasonable management strategy in carefully selected patients who are not candidates for conventional surgery or thermal ablative approaches (Chawla et al, 2005, 2006; Crispen and Uzzo, 2006; Rendon and Jewett, 2006; Jewett and Zuniga, 2008; Campbell et al, 2009). However, a critical review of this literature is required to recognize the limitations of this series of studies (Campbell et al, 2009). First, they represent a highly select population; most AS series have included only relatively small, well-marginated, and homogeneous renal masses, a substantial proportion (20% or more) of which may have been benign (Frank et al, 2003b; Crispen and Uzzo, 2006; Lane et al, 2007a). In addition, follow-up in most series is limited to 2 to 3 years and in some cases the growth rate was calculated backward by obtaining old films for which the lesion of interest was either previously missed or dismissed, introducing a strong selection bias (Bosniak et al, 1996; Crispen and Uzzo, 2006; Jewett and Zuniga, 2008). Finally, in most of these series, there is a subpopulation of patients with rapidly growing tumors that appear to have more aggressive characteristics. For instance, in the series from Volpe and colleagues (2004), 25% of the masses doubled in volume in 12 months and 22% reached a diameter of 4 cm, triggering surgical intervention. Similarly, Sowery and colleagues (2004) reported 9 tumors with mean growth rate of 1.43 cm per year, representing a substantial proportion of their patients. Salvage of patients with metastatic RCC is unlikely, and in some patients the window of opportunity for nephron-sparing surgery may be lost. As additional retrospective series are analyzed and prospective datasets compiled, the validity of these concerns will be more rigorously evaluated. All of these concerns would argue in favor of a proactive treatment plan for most patients with masses suspicious for RCC (Crispen and Uzzo, 2006).

Nevertheless, these studies suggest that patients with small, solid, enhancing, well-marginated, homogeneous renal lesions, who are elderly or poor surgical risks, can safely be managed with observation and serial renal imaging at 6-month or 1-year intervals (Chawla et al, 2005; Viterbo et al, 2005; Crispen and Uzzo, 2006; Jewett and Zuniga, 2008; Campbell et al, 2009; Chen et al, 2009). In this population, the risk of competing noncancer causes of death and the risk of intervention will most often outweigh the risk of RCC progression (Hollingsworth et al, 2007). In fact, recent data indicate that active treatment of small renal masses in elderly patients (>75 years of age) may not confer a measurable survival benefit over AS, further supporting a conservative approach in many of these patients (Lane et al, 2009). **AS is not appropriate for patients with larger (>3 to 4 cm), poorly marginated, or nonhomogeneous solid renal lesions** (Remzi et al, 2006; Kunkle et al, 2007a). **AS is also not advisable in younger, otherwise healthy patients with small, solid tumors that have radiographic characteristics consistent with RCC** (Campbell et al, 2009). Even if these lesions are smaller than 3 cm, the current data indicate that most will grow and eventually reach a size at which metastasis becomes a possibility. Unfortunately, growth rates on observation do not allow differentiation of benign versus malignant histology (Siu et al, 2007; Crispen et al, 2008d). Therefore, in this setting, it is more appropriate to consider treating the tumor by surgical excision or thermal ablation when it is small, clearly localized, and still amenable to nephron-sparing approaches (Van Poppel et al, 2007; Campbell et al, 2009; Chen et al, 2009).

Clinical T1 Renal Mass: Algorithm for Management

Acknowledging substantial controversy with respect to the management of small renal masses, with some current practices discordant with what the literature supports, the AUA Practice Guidelines Committee organized a panel to review this topic, with the final document published in 2009 (Campbell et al, 2009). This process included a systematic meta-analysis of the literature, and the final document was vetted through an extensive peer review process. As expected, the database for open surgical techniques was most substantial and mature (Table 49–23). In contrast, follow-up for many of the other modalities was rather limited. **Review of the data demonstrates strong selection biases, with RN procedures used to treat larger tumors, and AS and TA primarily applied to an older population of patients.** There were almost no comparative studies; the overwhelming majority was retrospective and primarily observational. Other limitations of the data are detailed in the final document. The analysis revealed a small number of statistically significant comparisons of consequence for which confounding factors were unlikely to account for differences (Campbell et al, 2009).

Table 49–23.

Patient Demographics and Study Information

	AS	RFA	Cryo	LPN	OPN	LRN	ORN
Median Patient Age, years (No. studies; No. patients*)	68 (12; 390)	70 (19; 745)	66 (15; 644)	60 (26; 2245)	60 (28; 6418)	61 (17; 1581)	63 (16; 6235)
Median Tumor Size, cm (No. studies; No. patients*)	2.2 (12; 390)	2.7 (19; 745)	2.6 (15; 644)	2.6 (26; 2245)	3.0 (25; 5596)	5.1 (15; 1391)	5.4 (14; 584)
Median Follow-Up, months (No. studies; No. patients*)	29 (12; 390)	19 (10; 528)	17 (10; 463)	15 (17; 1639)	47 (22; 5057)	18 (8; 795)	58 (13; 5294)

*Numbers of studies and patients differ across variables because some studies did not report all information.

AS, active surveillance; cryo, cryoablation; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radical nephrectomy; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RFA, radiofrequency ablation.

Adapted from Campbell SC, Novick AC, Belldegrun A, et al. Guideline for management of the clinical T1 renal mass. J Urol 2009;182:1971–9.

One such finding pertained to urologic complications, such as postoperative hemorrhage or urine leak, with PN procedures (laparoscopic and open) associated with the highest rates, likely reflecting the substantial technical challenges associated with these procedures (Table 49–24). This was thought to be a valid finding because PN procedures tended to be applied to younger patients and smaller tumors—patients who would be less likely to have such complications unless the complications were associated with procedural characteristics. **A second significant result related to local recurrence, which was defined as any persistent or recurrent disease present in the treated kidney or ipsilateral renal fossa after initial treatment.** This definition was adopted from the working group of Image-Guided Tumor Ablation (Goldberg et al, 2005; Campbell et al, 2009). **TA procedures had significantly higher rates of local recurrence when compared with all other treatment modalities** (Table 49–25). This was also judged to be a valid finding, because these modalities were used to treat relatively small tumors and had short follow-up durations. In reality, it has been estimated that when confounding factors such as length of follow-up are taken into consideration, the local recurrence rates for cryoablation and RFA will be substantially higher than for surgical excision (Kunkle et al, 2008). Many such recurrences can be salvaged with repeat ablation, but when this is not possible, surgical salvage can be very challenging (Kunkle et al, 2008; Nguyen et al, 2008b). Other ongoing concerns with TA were reviewed previously. **Analyses of other survival end points, such as metastasis-free, cancer-specific, and overall survival indicated that all such survival rates were relatively high across treatments, reflecting the limited biologic aggressiveness of most clinical T1 renal tumors.** Given strong selection biases and highly variable follow-up differences across treatments, comparisons related to these outcomes were not informative (Campbell et al, 2009).

Consensus statements regarding all of the current treatment modalities are provided in Table 49–26**. Final management recommendations were framed in terms of each treatment modality's utility in the context of four index patients defined by tumor size (T1a vs. T1b) and general health** (Fig. 49–22). Index patient 1, a healthy patient with a clinical T1a renal mass, is the most commonly encountered scenario. PN is a standard for this patient, with RN an alternate standard that should be applied only when PN is not feasible. One of the main concepts that is emphasized by this guideline document relates to the status of **nephron-sparing approaches as an overriding principle for the management of this patient population, presuming that adequate oncologic control can be achieved** (Campbell et al, 2009). TA and AS are both options for index patient 1, although there are substantial concerns about these management strategies in this healthy patient. Given the complexity of counseling with such divergent options for management, the panel believed strongly that a urologist should be involved in this process. The panel also strongly advocates research priority for renal mass biopsy with molecular profiling to improve the estimation of tumor aggressiveness and facilitate more rational patient selection in this field (Fig. 49–23).

Table 49–24.

Major Urologic Complications

STUDY TYPE	NO. OF STUDIES	COMPLICATION RATE* (95% CI†)	MEDIAN PATIENT AGE (yr)	MEDIAN TUMOR SIZE (cm)
RFA	20	6.0 (4.4-8.2)	70	2.7
Cryo	15	4.9 (3.3-7.4)	67	2.6
LPN	22	9.0 (7.7-10.6)	60	2.6
OPN	15	6.3 (4.5-8.7)	59	3.0
LRN	13	3.4 (2.0-5.5)	61	5.1
ORN	6	1.3 (0.6-2.8)	62	5.2

*Statistically significant differences ($P < .05$): ORN rates are significantly lower than all other interventions; LPN rates are significantly higher than Cryo, RFA, LRN, and ORN rates; OPN rates are significantly higher than LRN and ORN rates; Cryo, RFA, and LRN rates are significantly higher than ORN rates; LPN and OPN rates are statistically indistinguishable; OPN, Cryo, and RFA rates are statistically indistinguishable; Cryo, RFA, and LRN rates are statistically indistinguishable.

†Confidence interval calculated using a random effects model.

LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radical nephrectomy; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RFA, radiofrequency ablation.

Adapted from Campbell SC, Novick AC, Belldegrun A, et al. Guideline for management of the clinical T1 renal mass. J Urol 2009;182:1971–9.

Nephron-Sparing Surgery in von Hippel-Lindau Disease and Other Forms of Familial Renal Cell Carcinoma

RCC in von Hippel-Lindau disease differs from its sporadic counterpart in that the diagnosis is made at a young age and there are usually multiple bilateral renal tumors (Maher and Kaelin, 1997;

Table 49–25.

Local Recurrence-Free Survival

STUDY TYPE	NO. OF STUDIES	SURVIVAL RATE* (95% CI†)	MEDIAN PATIENT AGE (yr)	MEDIAN TUMOR SIZE (cm)	MEDIAN FOLLOW-UP (mo)
RFA	10	87.0 (83.2-90.0)	70	2.7	19
Cryo	10	90.6 (83.8-94.7)	67	2.6	18
LPN	17	98.4 (97.1-99.1)	61	2.6	15
OPN	21	98.0 (97.4-98.5)	60	3.1	47
LRN	8	99.2 (98.2-99.7)	61	4.6	18
ORN	10	98.1 (97.3-98.6)	63	4.8	58

*Statistically significant differences ($P < .05$): LPN, OPN, LRN, and ORN rates are statistically indistinguishable and are all significantly higher than Cryo and RFA rates; Cryo and RFA rates are statistically indistinguishable.

†Confidence interval calculated using a random effects model.

LPN, laparoscopic partial nephrectomy; LRN, laparoscopic partial nephrectomy; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RFA, radiofrequency ablation.

Adapted from Campbell SC, Novick AC, Belldegrun A, et al. Guideline for management of the clinical T1 renal mass. J Urol 2009;182:1971–9.

Table 49–26.

Management of the Clinical T1 Renal Mass: AUA Guidelines Consensus Statements

TREATMENT MODALITY	CONSENSUS STATEMENT
Radical nephrectomy (RN)	RN, particularly laparoscopic RN, is very appealing to patients and physicians but is greatly overutilized. Nephron-sparing approaches should be considered in all patients with a clinical T1 renal mass as an overriding principle, presuming adequate oncologic control can be achieved, based on compelling data demonstrating an increased risk of chronic kidney disease (CKD) associated with RN and a direct correlation between CKD and morbid cardiovascular events and mortality on a longitudinal basis. RN is still a viable option when necessary based on tumor size, location, or radiographic appearance if the surgeon judges that nephron-sparing surgery is not feasible or advisable. A laparoscopic approach to RN is now an established standard and should be considered if this procedure is required because it is associated with a more rapid recovery.
Active surveillance (AS)	AS is a reasonable option for the management of localized renal masses that should be discussed with all patients and should be a primary consideration for patients with decreased life expectancy or extensive comorbidities that would make them at high risk for intervention. For patients who are candidates for intervention, counseling about AS should include a balanced discussion of the small but real risk of cancer progression, lack of curative salvage therapies if metastases develop, possible loss of window of opportunity for NSS and substantial limitations of the current AS literature. Larger tumors (>3 to 4 cm) and those with aggressive appearance, such as infiltrative growth pattern, may be associated with increased risk and should be managed in a proactive manner.
Thermal ablation (TA)	TA (cryoablation or radiofrequency ablation), either percutaneous or laparoscopic, is an available treatment option for the patient at high surgical risk who wants active treatment and accepts the need for long-term radiographic surveillance after treatment. Tumor biopsy (core biopsy is recommended for better diagnostic accuracy) should always be performed prior to treatment to define histology and should also be considered after treatment, particularly if there is any suspicion of recurrence. Counseling about thermal ablation should include a balanced discussion of the increased risk of local recurrence when compared to surgical excision, potential need for reintervention, lack of well-proven radiographic parameters for success, particularly after RFA, potential for difficult surgical salvage if tumor progression is found and the substantial limitations of the current thermal ablation literature. Larger tumors (>3.5 cm) and those with irregular shape or infiltrative appearance may be associated with increased risk of recurrence when managed with thermal ablation.
Partial nephrectomy (PN)	Surgical excision by PN is a reference standard for the management of clinical T1 renal masses, whether for imperative or elective indications, given the importance of preservation of renal parenchyma and avoidance of CKD. This treatment modality is greatly underutilized. PN has well established longitudinal oncologic outcomes data comparable to RN. Adequate expertise and careful patient selection are important. A laparoscopic approach can provide more rapid convalescence but has been associated with an increased risk of major urologic complications and longer warm ischemia times when compared with traditional open partial nephrectomy (OPN). In general, OPN is preferred for complex cases such as tumor in the renal hilum, tumor in a solitary kidney, or multiple tumors.

Adapted from Campbell SC, Novick AC, Belldegrun A, et al. Guideline for management of the clinical T1 renal mass. J Urol 2009;182:1271–9.

Uzzo and Novick, 1999; Zbar et al, 1999; Grubb et al, 2005a; Nathanson and Stephenson, 2009). Although these are generally low-stage tumors, they are capable of progression to metastasis and represent a frequent cause of death in patients with von Hippel-Lindau disease. RCC in these patients is characterized histopathologically by both solid tumors and renal cysts that contain either frank carcinoma or a lining of hyperplastic clear cells representing incipient carcinoma (Fig. 49–24) (Christenson et al, 1982; Walther et al, 1995; Nathanson and Stephenson, 2008). **Therefore, adequate surgical treatment of localized RCC in von Hippel-Lindau disease requires excision and/or ablation of all solid and cystic renal lesions whenever feasible** (Grubb et al, 2005a; Nathanson and Stephenson, 2008). Choyke and colleagues (2001) have shown that intraoperative ultrasonography may be a valuable adjunct for this population of patients. In their series this study identified additional tumors in 25% of patients with hereditary renal cancer undergoing renal exploration.

The surgical options in patients with bilateral RCC and von Hippel-Lindau disease are bilateral nephrectomy and renal replacement therapy or nephron-sparing approaches such as PN or TA to avoid end-stage renal disease (Herring et al, 2001; Roupret et al, 2003; Drachenberg et al, 2004; Nathanson and Stephenson, 2008). **The general philosophy has been to pursue nephron-sparing strategies whenever possible, given the multifocal nature of the disease, even for centrally located tumors** (Drachenberg et al, 2004; Grubb et al, 2005a; Nathanson and Stephenson, 2008). Although early results of PN were promising, subsequent studies suggested a high incidence of postoperative tumor recurrence in the remaining portion of the kidney (Novick and Streem, 1992; Grubb et al, 2005a). It is likely that most of these local recurrences were a manifestation of residual microscopic RCC that was not removed at the time of the original PN (Walther et al, 1995; Grubb et al, 2005a).

One multicenter study delineated the long-term outcomes after surgical treatment of localized RCC in 65 patients with von Hippel-Lindau disease managed at eight medical centers in the United States (Steinbach et al, 1995). RCC was present bilaterally and unilaterally in 54 and 11 patients, respectively. RN and PN were performed in 16 and 49 patients, respectively. The mean postoperative follow-up interval was 68 months. The 5-year and 10-year cancer-specific survival rates for all patients were 95% and 77%, respectively. The corresponding rates for patients treated with PN were 100% and 81%, respectively. In the latter group, 25 patients (51%) developed postoperative local recurrence; however, only 2 of these patients had concomitant metastatic disease. Survival free of local recurrence was 71% at 5 years but only 15% at

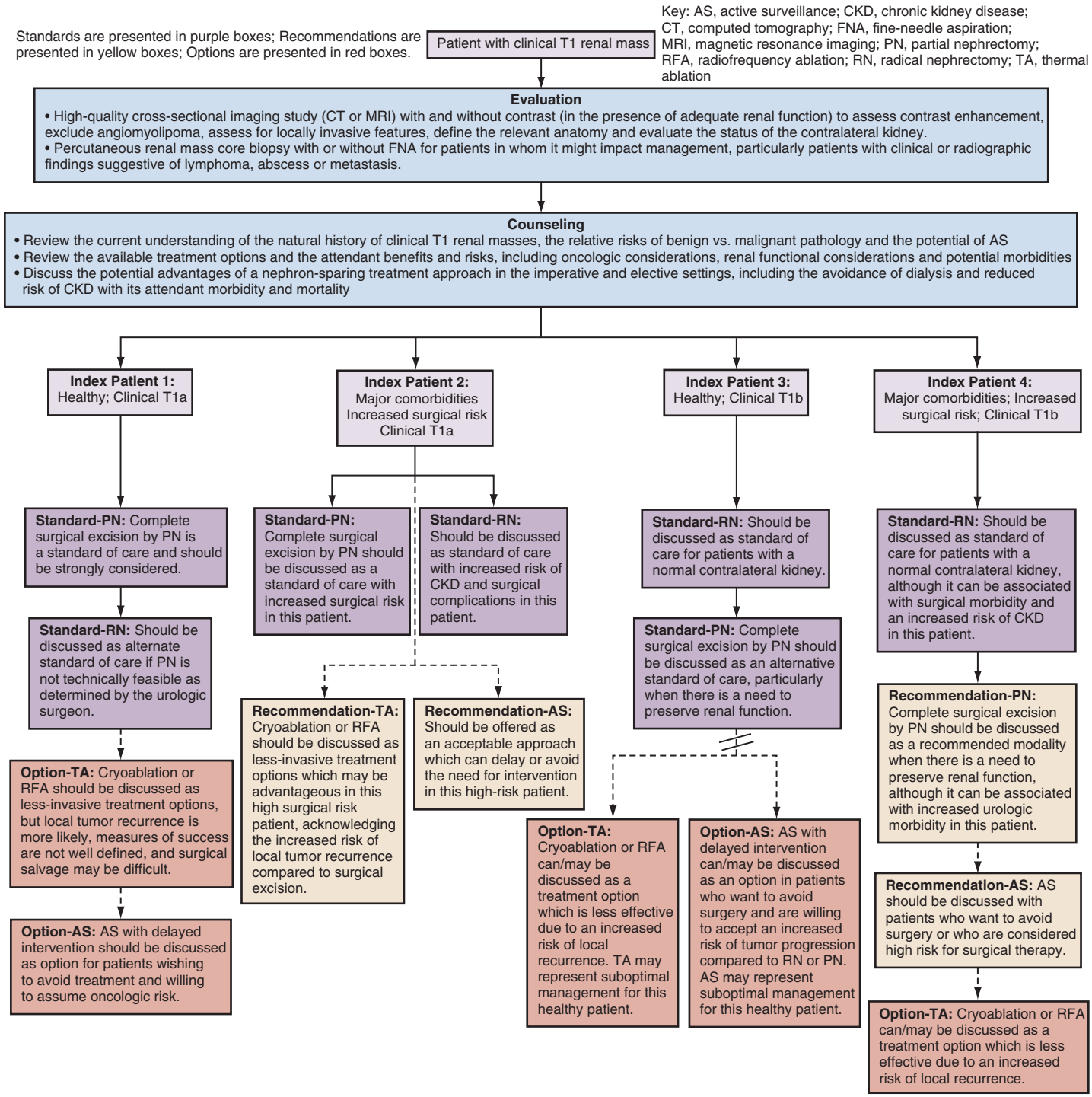


Figure 49–22. Algorithm for the evaluation, counseling, and management of the patient with a clinical T1 renal mass. (Adapted from Novick AC et al. Guideline for management of the clinical stage 1 renal mass. ⟨http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/renalmass09.pdf⟩; 2009 [accessed 06.01.11].)

10 years. **Similarly,** Roupret and colleagues (2003) **reported a 27.4% incidence of local recurrence at mean follow-up of 55.9 months after PN for patients with von Hippel-Lindau disease, confirming that these patients are at much higher risk for local recurrence than are patients with sporadic RCC.**

Duffy and colleagues (2004) **at the National Cancer Institute have defined a 3-cm threshold for intervention in patients with von Hippel-Lindau disease.** In their series, a total of 108 patients with von Hippel-Lindau disease and solid renal tumors smaller than 3 cm were observed a mean of 58 months and none developed metastatic disease. In contrast, metastases developed in 20 of 73 patients (27.4%) with tumors larger than 3 cm and the frequency of metastases increased with increasing tumor size. A 3-cm cut point has thus been proposed to reduce the number of surgical interventions, to optimize renal function, and to minimize the risk of metastatic disease. **The authors have emphasized that this recommendation also**

applies to patients with hereditary papillary RCC and Birt-Hogg-Dubé syndromes (Walther et al, 1999a; Herring et al, 2001; Duffey et al, 2004; Grubb et al, 2005b; Nathanson and Stephenson, 2008). **Hereditary leiomyomatosis is an exception in that tumors in this syndrome are more aggressive and should be managed accordingly, even when less than 3 cm** (Nathanson and Stephenson, 2008).

Taken together, these studies suggest that PN can provide effective initial treatment of patients with RCC and von Hippel-Lindau disease but should be withheld until tumor size reaches or eclipses 3.0 cm. In recent years, TA has been used more frequently in this patient population as an alternative nephron-sparing approach (Grubb et al, 2005b; Matin et al, 2008; Nathanson and Stephenson, 2008). **After initial management, patients with von Hippel-Lindau disease must be observed closely because most will eventually develop locally recurrent RCC with the concomitant need for repeat renal intervention** (Campbell and Novick, 1995; Grubb et al, 2005a; Ploussard et al, 2007). In this setting, repeat PN can be challenging because of postoperative fibrosis, and TA may be preferred to reclaim local control (Shingleton and Sewell, 2002; Hwang et al, 2004; Mabjeesh et al, 2004; Matin et al, 2008; Nathanson and Stephenson, 2008; Nguyen et al, 2008b). Targeted agents are now being investigated in an effort to slow disease progression in patients with this syndrome (Grubb et al, 2005a). When removal of all renal tissue is necessary to achieve control of malignant disease, renal transplantation can provide satisfactory replacement therapy for end-stage renal disease and appears to be safe despite the tumor diathesis (Goldfarb et al, 1997).

Comprehensive management of patients suspected of having familial RCC should also include genetic counseling and screening for other manifestations of the disease process (see earlier section on familial RCC and molecular genetics) (Nathanson and Stephenson, 2008). For patients with von Hippel-Lindau disease, identification of pheochromocytoma or central nervous system hemangioblastoma is particularly important before surgical intervention for RCC (Leung et al, 2008; Nathanson and Stephenson, 2008).

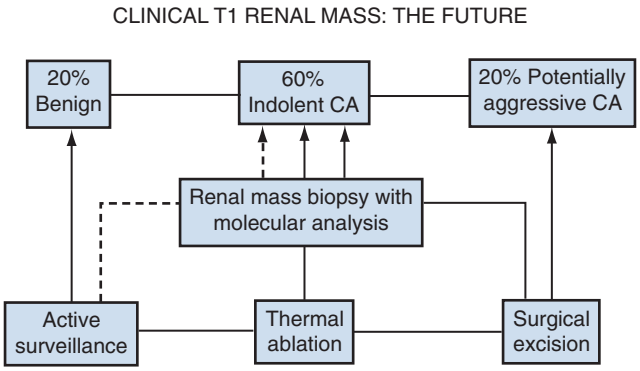


Figure 49–23. The AUA guideline panel for the management of the clinical T1 renal mass strongly advocates research priority for renal mass biopsy with molecular profiling to facilitate more rational management of this patient population. CA, cryoablation.

TREATMENT OF LOCALLY ADVANCED RENAL CELL CARCINOMA

Inferior Vena Caval Involvement

One of the unique features of RCC is its frequent pattern of growth intraluminally into the renal venous circulation, also known as venous tumor thrombus. In extreme cases this growth may extend into the IVC with cephalad migration as far as the right atrium or beyond (Fig. 49–25). The absence of metastases in many patients with vena caval extension is an intriguing aspect of this cancer's behavior (Gettman and Blute, 2002; Wotkowicz et al, 2008). **Forty-five to 70 percent of patients with RCC and IVC thrombus can be cured with an aggressive surgical approach including radical nephrectomy and IVC thrombectomy** (see Key Points box). In general, patients with tumor that is otherwise confined to the kidney and nonadherent thrombi have the best prognosis; those with tumor extending into the perinephric fat, lymph node involvement, or direct invasion of the wall of the IVC are at much

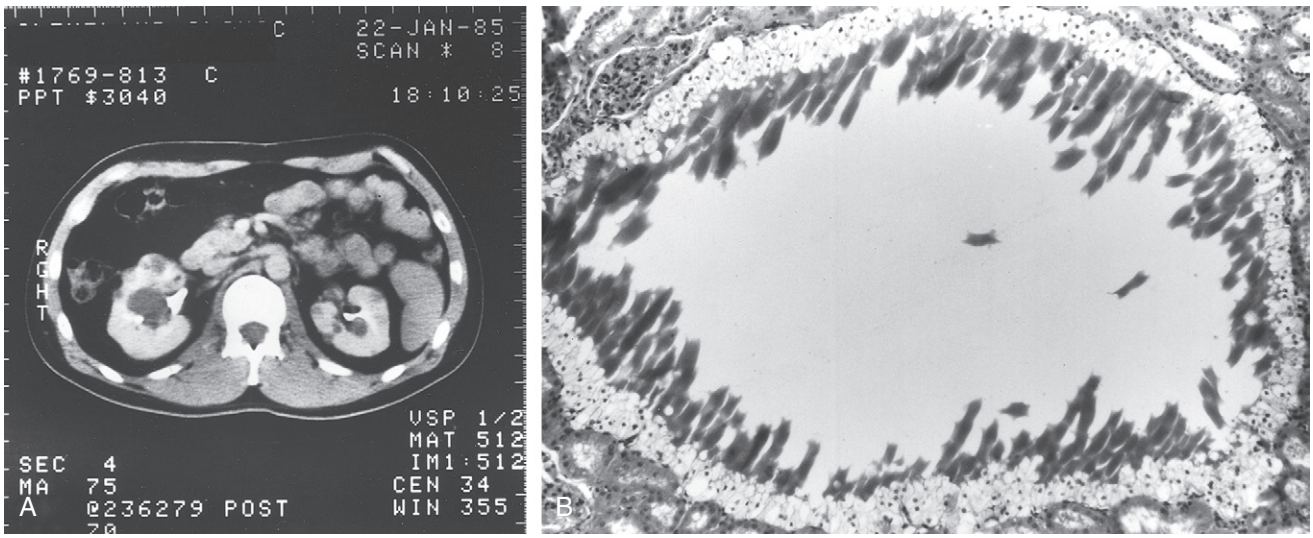


Figure 49–24. **A,** CT scan after administration of contrast agent shows bilateral solid and cystic renal masses in patient with von Hippel-Lindau disease. **B,** Histopathologic section of one of the renal cysts shows lining of clear cells representing incipient carcinoma.

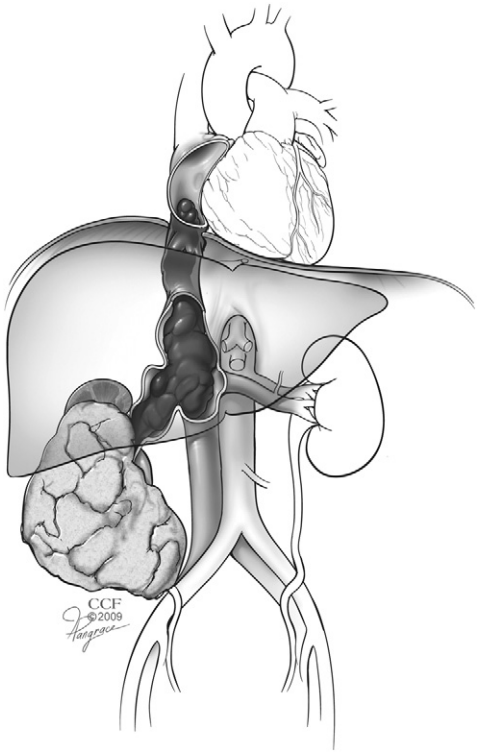


Figure 49–25. Schematic illustrating renal cell carcinoma in the right kidney with tumor thrombus extending through renal vein into the inferior vena cava and terminating in the right atrium. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2007-2009. All Rights Reserved.)

Key Points: Treatment of Locally Advanced RCC

- Involvement of the venous system occurs in 4% to 10% of patients with RCC.
- Forty-five to 70 percent of patients with venous tumor thrombus can be cured with nephrectomy and thrombectomy.
- Thrombus extending into the IVC below the level of the main hepatic veins can be readily managed with isolation of the involved vasculature and removal of tumor thrombus.
- Thrombus extending above the main hepatic veins requires more extensive dissection, venovenous bypass, or cardiopulmonary bypass and circulatory arrest.
- For large tumors with radiographic suspicion of invasion into adjacent structures or organs (cT4), complete excision with en-bloc resection of the involved structures provides the only chance of cure.
- Bulky lymphadenopathy carries a poor prognosis similar to metastatic disease, although surgical resection should be considered if feasible and if appropriate given careful assessment of disease location/burden and patient age/comorbidities.
- High-quality preoperative imaging (CT or MRI) should be obtained close to the anticipated surgery to plan for and achieve intraoperative success.
- Although locally advanced RCC is still primarily a surgical disease, adjuvant systemic therapy trials should be encouraged and, in select patients, neoadjuvant approaches may be considered.

higher risk for recurrence (Hatcher et al, 1991; Montie et al, 1991; Glazer and Novick, 1996; Gettman et al, 1999; Naitoh et al, 1999; Sweeney et al, 2002b; Bissada et al, 2003; Kim et al, 2004a; Moinzadeh and Libertino, 2004; Leibovich et al, 2005b; Haferkamp et al, 2007; Zini et al, 2008).

Overall, involvement of the venous system with RCC occurs in 4% to 10% of patients. Venous tumor thrombus should be suspected in patients with a renal tumor who also have lower extremity edema, isolated right-sided varicocele or one that does not collapse with recumbency, dilated superficial abdominal veins, proteinuria, pulmonary embolism, right atrial mass, or nonfunction of the involved kidney. Staging of the level of IVC thrombus is as follows: I, adjacent to the ostium of renal vein; II, extending up to the lower aspect of the liver; III, involving the intrahepatic portion of the IVC but below the diaphragm; and IV, extending above the diaphragm. The prognostic significance of IVC thrombus level has been controversial. Most studies suggest that the incidence of locoregional or systemic progression is higher in patients with level III-IV IVC thrombus, and this probably accounts for the reduced survival reported in this subgroup in some series (Sosa et al, 1984; Quek et al, 2001; Zisman et al, 2003; Kim et al, 2004a; Leibovich et al, 2005b). Others series have shown that any IVC involvement is worse than renal vein involvement without distinction with regard to IVC level; in these series, other factors, such as nodal or metastatic involvement and tumor grade, have more impact on overall survival (Blute et al, 2004b; Terakawa et al, 2007). However, other reports confirm that many patients with level IV IVC thrombi can be cured of disease with surgical resection, as long as the tumor is otherwise confined and other adverse features are absent (Libertino et al, 1987; Glazer and Novick, 1996; Sweeney et al, 2002b; Ciancio et al, 2007; Granberg et al, 2008). The seventh edition of the TNM staging system distinguishes tumors with thrombi above the diaphragm (stage T3c) from those with IVC thrombi below the diaphragm (stage T3b) and those with thrombi only within the renal vein or its branches (stage T3a) (Edge et al, 2010).

MRI is a noninvasive and accurate modality for demonstrating both the presence and the cephalad extent of vena caval involvement and has been the preferred diagnostic study at most centers for the past few decades (Goldfarb et al, 1990; Kallman et al, 1992; Bechtod and Zagoria, 1997; Choyke, 1997; Oto et al, 1998; Sun et al, 1999). Administration of gadolinium during the study often allows tumor thrombi to be differentiated from bland thrombus, because the latter does not demonstrate enhancement. **More recent evidence suggests that multiplanar CT can provide essentially equivalent information, including delineation of the cephalad and caudal extent of the thrombus** (Fig. 49–26) (Pretorius et al, 2000; Choyke et al, 2001; Bassignani, 2006; Zhang et al, 2007a; Bach and Zhang, 2008; Ng et al, 2008; Herts, 2009). **The importance of high-quality preoperative imaging cannot be overemphasized and should be obtained as close as possible to the date of surgery because progression of the tumor thrombus may mandate important changes in intraoperative management** (Blute et al, 2004b; Wotkowicz et al, 2008).

Invasive contrast-enhanced imaging is reserved for patients in whom MRI and CT findings are equivocal or for whom MRI and CT are contraindicated. Although inferior venacavography using antegrade and/or retrograde contrast injection remains an accurate diagnostic study for assessment of

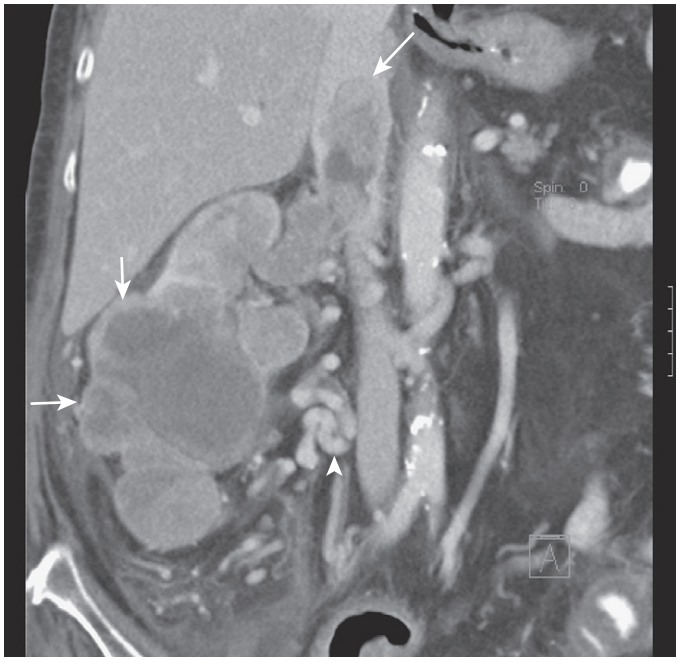


Figure 49–26. CT scan demonstrating lower pole right renal cell carcinoma *(small arrows)* with level III inferior vena cava (IVC) thrombus. The *large arrow* indicates the upper extent of the tumor thrombus within the intrahepatic portion of the IVC. The *arrowhead* indicates extensive retroperitoneal venous collateral vessels associated with restricted flow within the IVC.

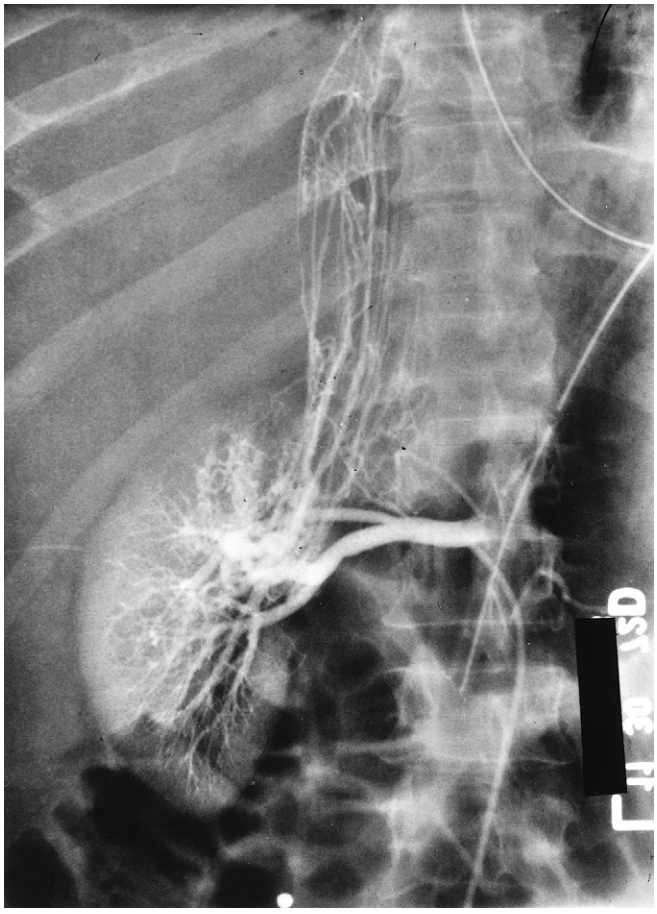


Figure 49–27. Right renal arteriogram shows arterialization of a supradiaphragmatic vena caval thrombus.

IVC involvement, this invasive technique is generally unnecessary in the modern imaging era. Some have also advocated the use of renal arteriography as an adjunctive preoperative study in patients with RCC involving the IVC, with distinct vascularization of tumor thrombus observed in 35% to 40% of cases (Fig. 49–27) (Novick et al, 1990; Wotkowicz et al, 2008). When this finding is present, preoperative embolization of the renal artery can be performed in an attempt to shrink the thrombus and facilitate the surgical procedure. However, Subramanian and colleagues (2009) have demonstrated that preoperative renal artery embolization does not provide any measurable benefit in reducing blood loss or complications of nephrectomy with tumor thrombectomy. In their series of 225 patients with IVC thrombi, embolization was associated with a higher risk of perioperative death and a trend toward increasing blood transfusions in multivariable analysis. In patients with extensive supradiaphragmatic vena caval thrombi, when adjunctive cardiopulmonary bypass with deep hypothermic circulatory arrest is considered, coronary angiography can also be performed preoperatively (Novick et al, 1990). If significant obstructing coronary lesions are found, these can be repaired simultaneously during cardiopulmonary bypass. Transesophageal echocardiography is an invasive study that is unnecessary before surgery but can be an important intraoperative diagnostic modality for monitoring the supradiaphragmatic portion of the thrombus if needed (Glazer and Novick, 1997; Wotkowicz et al, 2008).

Although involvement of the IVC with RCC renders the task of complete surgical excision more complicated, this approach offers the only realistic hope for cure for most patients (Quek et al, 2001; Blute et al, 2004b). After mobilization of the kidney and ligation and transection of the arterial blood supply, vascular control of the involved portion of the IVC is then obtained. In general, level I thrombi are isolated by a Satinsky clamp and are thus readily removed (Fig. 49–28A). Level II thrombi require sequential clamping of the caudal IVC, contralateral renal vasculature, and cephalad IVC along with mobilization of the relevant segment of the IVC and occlusion of lumbar veins. The renal ostium is then opened and the thrombus is removed, all in a bloodless field (see Fig. 49–28B). When tumor thrombus invades the wall of the vena cava, aggressive resection of the involved vena cava and attainment of negative surgical margins are required to minimize the risk of recurrence (Hatcher et al, 1991; Blute et al, 2007; Wotkowicz et al, 2008). IVC grafting or reconstitution is required in some instances, but patients with a completely occluded IVC do not require this because of collateral blood flow (Sarkar et al, 1998; Blute et al, 2007). Distal bland thrombus within the IVC or iliac vessels may be left in situ, although the IVC should be ligated or clipped cephalad to this level to prevent pulmonary embolism.

Vascular control for level III and level IV IVC thrombi requires more extensive dissection, venovenous bypass, or cardiopulmonary bypass and hypothermic circulatory arrest. For level III thrombi, mobilization of the liver and exposure of the intrahepatic IVC will often allow the thrombus to be mobilized caudad to the hepatic veins, and venous isolation can then proceed as for a level II thrombus (see Fig. 49–28C) (Gallucci et al, 2004; Ciancio et al, 2007). If this is not possible, the IVC should be clamped above the liver and a Pringle maneuver can be performed whereby the portal triad is temporarily occluded (Burt, 1991; Ciancio and Soloway, 2001, 2002; Vaidya et al, 2003; Jibiki et al, 2004; Ciancio et al, 2007). Venovenous bypass is commonly used in these cases but may not be required if adequate collateral flow is present (Ciancio et al, 2002). Level IV IVC thrombi have

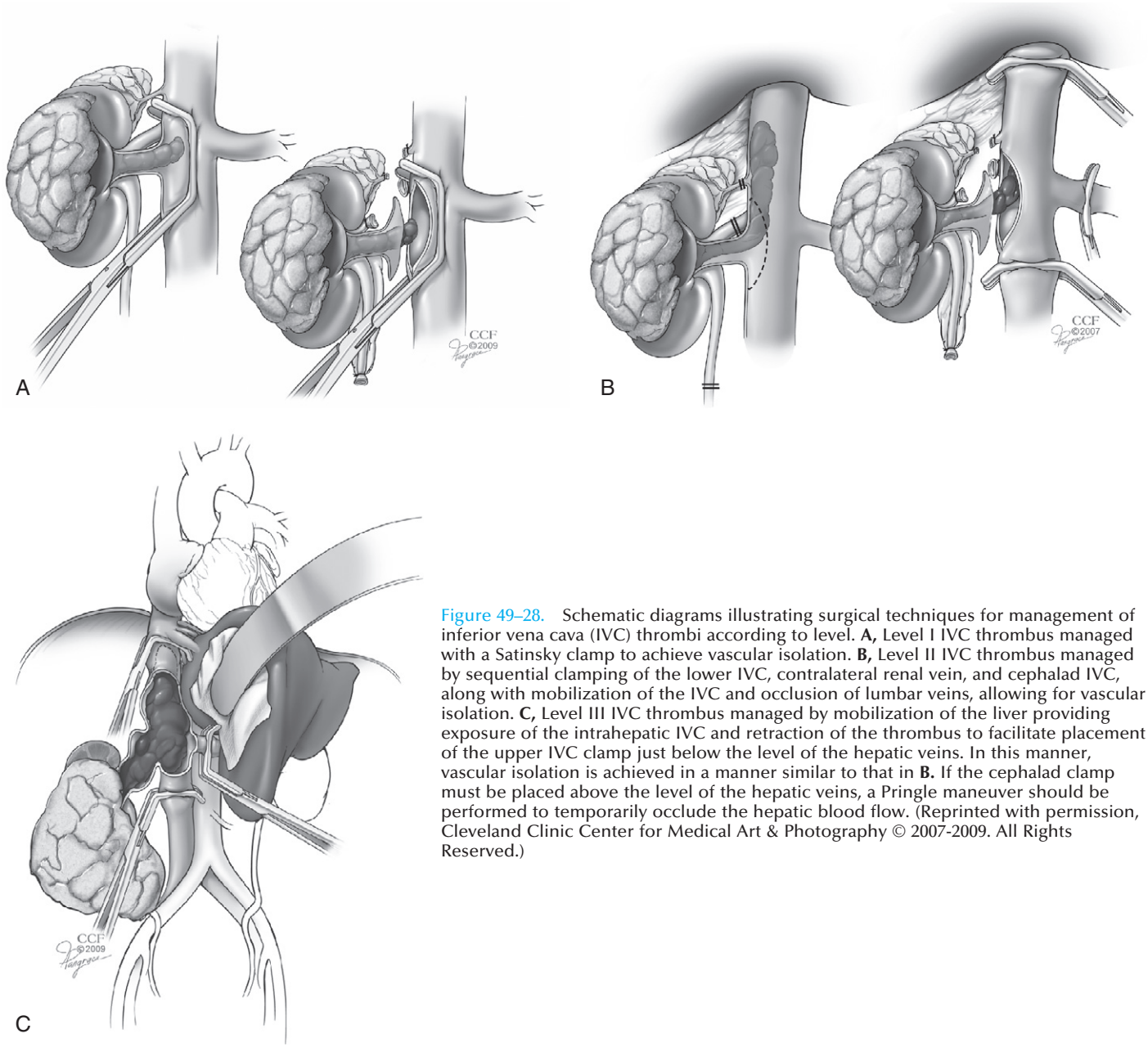


Figure 49–28. Schematic diagrams illustrating surgical techniques for management of inferior vena cava (IVC) thrombi according to level. **A,** Level I IVC thrombus managed with a Satinsky clamp to achieve vascular isolation. **B,** Level II IVC thrombus managed by sequential clamping of the lower IVC, contralateral renal vein, and cephalad IVC, along with mobilization of the IVC and occlusion of lumbar veins, allowing for vascular isolation. **C,** Level III IVC thrombus managed by mobilization of the liver providing exposure of the intrahepatic IVC and retraction of the thrombus to facilitate placement of the upper IVC clamp just below the level of the hepatic veins. In this manner, vascular isolation is achieved in a manner similar to that in **B.** If the cephalad clamp must be placed above the level of the hepatic veins, a Pringle maneuver should be performed to temporarily occlude the hepatic blood flow. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2007-2009. All Rights Reserved.)

traditionally been managed with cardiopulmonary bypass and hypothermic circulatory arrest, and this is still the preferred approach in complex cases (Blute et al, 2007; Wotkowicz et al, 2008). However, many centers are now trying to avoid hypothermic circulatory arrest and the associated hypocoagulable state that ensues after coming off the pump and the increased risk of cerebrovascular accident and myocardial infarction that accompanies this procedure (Shinghal et al, 2003; Ciancio et al, 2007; Subramanian et al, 2009). In this case the thrombus is mobilized below the atrium, allowing sequential vascular control to be achieved without opening the heart. Further detail about these procedures can be found in Chapter 54.

The risk of morbidity can be substantial for thrombi extending above the diaphragm and mortality rates associated with radical nephrectomy and IVC thrombectomy have been reported to be as high as 5% to 10% in some series, depending on the patient's comorbidities and tumor characteristics (Staehler and Brkovic, 2000; Blute et al, 2004b). Therefore patient selection and surgical planning are of paramount importance (Gettman et al, 2003), and this procedure has for the most part been reserved for patients with good performance status in whom preoperative studies show no substantial lymphadenopathy or systemic metastasis. However, there may be a palliative role for surgery in some patients with metastasis who experience severe disability from intractable edema, ascites, cardiac dysfunction, or associated local symptoms such as abdominal pain and hematuria (Slaton et al, 1997). In addition, nephrectomy and IVC thrombectomy can also be considered in patients with metastatic disease who may be expected to experience a more prolonged disease course after cytoreduction, particularly those with level I or II or readily managed level III IVC thrombi (Zisman et al, 2002b, 2003). Using predictive algorithms to identify patients with poor-risk metastatic RCC, and in

consultation with colleagues in medical oncology, the significant morbidity of aggressive surgery should be avoided in those with limited life expectancy.

Locally Invasive Renal Cell Carcinoma

The sequestered location and propensity for aggressive behavior of RCC results in occasional patients presenting with large primary tumors that invade adjacent structures. Patients with pathologic stage T4 disease represent less than 2% of surgical series, but this proportion may increase somewhat with the reclassification of RCC invading directly into the adrenal gland into this category (Thompson et al, 2005a; Karellas et al, 2009). **Patients with locally advanced RCC usually present with pain, generally from invasion of the posterior abdominal wall, nerve roots, or paraspinous muscles.** Liver extension is uncommon, and intrahepatic metastases occur more often than local extension. The capsules of large tumors may indent and compress adjacent liver parenchyma but seldom actually grow by direct extension into the liver. Margulis and colleagues (2007a) reported that invasion of adjacent organs was confirmed pathologically in only 40% of the patients in whom it was suspected based on preoperative imaging. If tumor extension into the liver is identified intraoperatively, en-bloc partial hepatectomy is rarely curative but may occasionally be worthwhile. Duodenal and pancreatic invasion is uncommon and a poor prognostic sign. The propensity for RCC to parasitize vessels may account for extension into the colon and its mesentery. **In evaluation of patients with large, invasive upper quadrant abdominal masses, a broad differential diagnosis should be considered, including adrenocortical carcinoma, infiltrative transitional cell carcinoma, sarcoma, and lymphoma, in addition to locally invasive RCC.**

Because surgical therapy is the only potentially curative management for RCC, extended operations with en-bloc resection of adjacent organs are occasionally indicated (see Key Points box). **Complete excision of the tumor, including resection of the involved bowel, spleen, or abdominal wall muscles, is the aim of therapy.** Margulis and colleagues (2007a) report that even with aggressive surgical management, 10 of 12 patients with pathologic T4 disease experienced disease recurrence at a median of 2 months after surgery. Similarly, although negative surgical margins were achieved in 63% of patients, 34 of 38 patients (90%) in another series ultimately died of disease at a median of 12 months after surgery (Karellas et al, 2009). Important perioperative concerns for patients with locally advanced RCC include a full and proper preoperative consent, including the increased morbidity and mortality of such an approach and the likelihood of concomitant organ resection, a full bowel preparation and consideration for preoperative embolization of the renal arterial blood supply, which may reduce bleeding in cases in which it may be difficult to obtain renal arterial control as one of the initial surgical maneuvers. Vaccination against *Streptococcus pneumoniae, Haemophilus influenzae* type B, and *Neisseria meningitides* should be performed preoperatively when splenectomy is likely during nephrectomy (Shatz, 2005; Habermalz et al, 2008). If not already immunized, splenectomized patients should receive these vaccines in the postsurgical setting to prevent sepsis due to one of these encapsulated organisms (Shatz, 2005; Habermalz et al, 2009).

Incomplete excision of a large primary tumor, or debulking, is rarely indicated. In one study, only 12% of patients who underwent incomplete excision of locally extensive tumor were alive at 1 year (DeKernion et al, 1978). Karellas and colleagues (2009) reported similarly poor results in patients with positive margins at the time of nephrectomy for stage pT4 RCC. The same concern holds true during resection of recurrent RCC, in which complete excision is of paramount importance (Eggener et al, 2008; Margulis et al, 2009). **Most reports suggest that less than 5% of patients with extension into adjacent viscera (stage pT4) survive 5 years after surgery.** Most randomized studies evaluating the role of cytoreductive nephrectomy, including those using immunotherapy (Flanigan et al, 2004) and, more recently, targeted molecular agents, did not include a substantial number of patients with this subcategory of disease, and their conclusions should not be extrapolated to this population of patients. Resection of locally advanced disease can be a major undertaking, and its primary indications should be for curative or palliative intent.

The role of radiation therapy in the treatment of locally extensive RCC is controversial. Several early studies suggested that preoperative radiotherapy could improve survival (Richie, 1966; Cox et al, 1970). A subsequent study by van der Werf-Messing (1973), however, compared results for preoperative therapy with controls and found no survival difference at 5 years. Routine postoperative radiotherapy has not been shown to influence overall survival and can be hazardous because of proximity of small bowel, which is highly radiosensitive. When tumor is known to have been left behind in the renal fossa or adjacent structures, postoperative radiotherapy may occasionally retard progression of the tumor mass (Kao et al, 1994). This approach is rarely used today and has largely been replaced by the use of systemic agents for residual or locally recurrent disease.

Local Recurrence after Radical Nephrectomy or Nephron-Sparing Surgery

Local recurrence of RCC after radical nephrectomy, which includes recurrence in the renal fossa, ipsilateral adrenal gland, or ipsilateral retroperitoneal lymph nodes, is an uncommon event, occurring in 2% to 4% of cases (see Key Points box) (Uson, 1982; Sandock et al, 1995; Levy et al, 1998; Ljungberg et al, 1999; Itano et al, 2000; Schrodter et al, 2002; DiMarco et al, 2004; Stephenson et al, 2004a; Master et al, 2005; Margulis et al, 2009). **Risk factors include locally advanced or node-positive disease and adverse histopathologic features** (Esrig et al, 1992; Sandock et al, 1995; Levy et al, 1998). In contrast, local recurrence after radical nephrectomy is rare in patients with low-stage pT1-2N0M0 RCC. **Only about 40% of local recurrences are isolated; the majority of patients with local recurrence also have systemic disease, and a thorough metastatic evaluation should be pursued** (Uson, 1982; Phillips and Messing, 1993; Sandock et al, 1995; Itano et al, 2000; Schrodter et al, 2002; Eggener et al, 2008).

Surgical resection of isolated local recurrence of RCC after radical nephrectomy should be considered, because it can provide long-term cancer-free status for 30% to 40% of patients (Esrig et al, 1992; Tanguay et al, 1996; Itano et al, 2000; Schrodter et al, 2002; Wiesner et al, 2002; Gogus et al, 2003; Master et al, 2005; Bandi et al, 2008; Margulis et al, 2009). An algorithm incorporating risk factors that predicts survival in patients with systemic metastases (Motzer criteria) can predict survival in this group of patients; 2-year overall survival rates for low-, intermediate-, and high-risk patients are 88%, 51%, and

11%, respectively (Eggener et al, 2008). Importantly, feasibility of resection proved to be another independent favorable prognostic parameter in this patient population (Eggener et al, 2008). **Complete resection of abdominal recurrences is often a formidable task because the natural tissue barriers are no longer present and invasion of contiguous organs is common. En-bloc resection of adjacent organs is often required, and the risk of morbidity can be substantial** (Esrig et al, 1992; Tanguay et al, 1996; Itano et al, 2000; Wiesner et al, 2002; Gogus et al, 2003; Eggener et al, 2008; Margulis et al, 2009). Margulis and colleagues (2009) have reported on 54 patients with local recurrence after nephrectomy managed by surgical resection, 69% of whom also received adjunctive systemic therapy. Risk factors associated with an increased risk of cancer-specific death after resection included recurrent tumor size, sarcomatoid features in the recurrence specimen, positive surgical margin, abnormal alkaline phosphatase, and increased lactate dehydrogenase. Patients with 0, 1, and greater than 1 adverse risk features demonstrated cancer-specific survival times of 111, 40, and 8 months, respectively. Cancer-specific survival after resection of isolated retroperitoneal lymph node recurrence after nephrectomy is longer than after nephrectomy for node-positive disease, reflecting the aggressive biology of RCC with synchronous nodal metastases (Boorjian et al, 2008). Intraoperative radiation was not found to be of oncologic benefit (Master et al, 2005), but radiation therapy may be of value for palliation of symptomatic local recurrence in patients who are not operative candidates.

Local recurrence in the remnant kidney after PN for RCC has been reported in 1.4% to 10% of patients, and the main risk factor is advanced T stage (Campbell and Novick, 1994; Lane and Gill, 2007; Krambeck et al, 2008). **Most of these local recurrences are distant from the tumor bed and are thus probably a result of unrecognized tumor multicentricity or de novo occurrence rather than true treatment failure** (Campbell and Novick, 1994; Lane and Gill, 2007; Krambeck et al, 2008). Recent data confirm that local recurrence after PN is uncommon, even with a positive surgical margin (Permpongkosol et al, 2006; Kwon et al, 2007; Kutikov et al, 2008b; Yossepowitch et al, 2008). **Patients with isolated local recurrence after PN can be considered for repeat PN, completion nephrectomy, TA, or AS** (Bratslavsky et al, 2008; Johnson et al, 2008; Magera et al, 2008; Berger et al, 2009). TA is now being used more frequently in this setting because of concern about fibrosis within the renal fossa, but conventional PN can and should be performed when anatomy and tumor characteristics are amenable (Gittes and Blute, 1982; Moll et al, 1993; Campbell and Novick, 1994; Frank et al, 2005a). Regardless, the histopathologic features of the resected tumor and the disease-free interval since initial surgery should be considered along with the presence of CKD and other comorbidities during this decision process, because preservation of renal function may have greater impact on survival than cancer extirpation in certain patients. For this reason, biopsy of the recurrent tumor may be of value when nonextirpative options are being considered.

Local recurrence after thermal ablation often represents treatment failure; many local recurrences develop within the previous tumor bed (McDougal et al, 2005; Matin et al, 2006; Levinson et al, 2008; Nguyen et al, 2008b; Berger et al, 2009). Reported incidences range between 3% and 10% for cryoablation and between 5% and 20% for radiofrequency ablation (McDougal et al, 2005; Gill et al, 2006; Matin et al, 2006; Weight et al, 2008; Levinson et al, 2008; Kunkle and Uzzo, 2008; Kunkle et al, 2008; Berger et al, 2009). Diagnosis of local recurrence in this setting is established by the demonstration of persistent central enhancement within the tumor bed or an enhancing lesion at any other site within the ipsilateral kidney (Weight et al, 2007; Berger et al, 2009). A biopsy can provide more definitive information. Importantly, the true incidence of local recurrence in this population is not well defined because radiographic factors predictive of recurrence have been challenged, particularly for RFA, most studies have not incorporated routine biopsy of the tumor bed during surveillance, and length of follow-up in many series is limited (Weight et al, 2007; Stein et al, 2007). Most of these recurrences can be managed with repeat ablation, but this is not always feasible. Beyond this, management options are similar to those for recurrence after PN, with the caveat that salvage surgery in this setting is often challenging owing to the dense inflammatory reaction induced by thermal ablation (Kowalczyk et al, 2008; Nguyen et al, 2008b).

Adjuvant Therapy for Renal Cell Carcinoma

Unfortunately, recurrence develops in a significant proportion of patients thought to be rendered disease free after surgical resection, primarily due to occult micrometastatic disease. Although postsurgical recurrence is not common in patients with low-stage, organ-confined disease, locally advanced RCC and RCC with other adverse histopathologic features carry a significant risk of recurrence. Various predictive tools can assist in the assessment of the risk in individual patients (Zisman et al, 2002c; Leibovich et al, 2003a), although on the whole, **distant metastases develop in 20% to 35% and local recurrence in 2% to 5% of patients** (Rabinovitch et al, 1994; Lane and Kattan, 2008). In view of these findings, **a strong rationale for systemic postoperative adjuvant therapy exists in high-risk patients. However, almost all adjuvant studies in this field have been negative thus far, with a few highly controversial exceptions, and the standard in this field remains observation if the patient will not consider an adjuvant trial** (see Key Points box).

Key Points: Treatment of Local Recurrence and Adjuvant Therapy for Renal Cell Carcinoma

- Isolated local recurrence after radical nephrectomy occurs in 2% to 4% of patients and a thorough metastatic evaluation should be pursued if resection is under consideration.
- Local recurrence after partial nephrectomy is more common at sites distant from the tumor bed and can be managed by repeat partial nephrectomy, completion nephrectomy, ablation, or surveillance.
- Local recurrence after tumor ablation often reflects incomplete tumor eradication; management options include repeat ablation, surveillance, or salvage surgery.
- Despite a significant likelihood of recurrence of RCC with poor-risk features, there is no established evidence of a benefit for adjuvant therapy in patients without evidence of disease after surgical resection.
- Ongoing adjuvant clinical trials investigating targeted molecular agents and other novel systemic approaches should be supported in an effort to identify an efficacious adjuvant strategy.

Clinical end points used in adjuvant trials include recurrence-free survival, time to recurrence, and overall survival. Ideal trial design incorporates placebo-controlled and blinded protocols and preferably independent radiographic review to confirm that all entered patients are truly disease free at study entry and to confirm and accurately time all recurrences. Intent to treat analysis is another strong expectation in this field. **Until recently, many adjuvant trials performed in patients with RCC have been underpowered to detect small differences in survival and primary end points related to tumor recurrence have been difficult to assess in view of flaws in study design.** A variety of adjuvant approaches have been investigated, including hormonal manipulation, radiotherapy, immunotherapeutics, vaccines, and, most recently, targeted molecular agents. Early adjuvant trials tested postoperative medroxyprogesterone acetate (Pizzocaro et al, 1987) or perioperative radiotherapy (van der Werf-Messing, 1973; Kjaer et al, 1987) with negative results.

Despite demonstrable antitumor effects in patients with metastatic disease, IL-2 and interferon alfa did not prove to be beneficial in the adjuvant setting. Four randomized studies were performed, three with interferon alfa and one with IL-2 (Porzolt et al, 1992; Pizzocaro et al, 2001; Messing et al, 2003; Clark et al, 2003). The studies investigating interferon used various doses, preparations (L-interferon, interferon alfa-2a, interferon alfa-2b), and duration of therapy (6 to 12 months); none demonstrated a benefit when compared with controls. Clark and colleagues (2003) randomized patients to observation versus high-dose IL-2 (600,000 units/kg every 8 hours on days 1 to 5 and 15 to 19). A total of 69 patients were registered, 44 with locally advanced and/or nodal disease and 25 with completely resected metastatic disease. An interim analysis prompted closure of the trial primarily because of the toxicity of high-dose IL-2; there was no clinically meaningful benefit for the population as a whole or in either subgroup. Given the limited usage of immunotherapy in patients with metastatic disease at present, it seems unlikely that further adjuvant trials of immunotherapy will be conducted in the near future.

A variety of autologous tumor vaccine–based approaches have been used to immunize RCC patients in the postoperative setting, with largely negative results (Table 49–27). The most controversial results came from a prospective trial in which 553 patients were apparently randomized to observation or intradermal treatment with an autologous vaccine (Jocham et al, 2004). The final report included 202 patients on observation and 177 on active treatment, and this cohort of 379 patients was referred to as the intent-to-treat group by the investigators, although biases may have played a role in this determination. At 5 years, the recurrence-free survival rates were significantly improved for the vaccine-treated group (P = .0204). However, in addition to concern about the legitimacy of its intent to treat analysis, this trial was not blinded, did not include a placebo control, and did not undergo external review of data; therefore, this finding has been viewed by experts in the field with some degree of skepticism.

The largest adjuvant clinical trial for patients with high-risk localized RCC, the Oncophage trial, has recently been completed, reporting no benefit with an autologous tumor vaccine (Wood et al, 2008). Patients with clear cell histology meeting entry criteria after nephrectomy were randomized to undergo observation versus intradermal injections of autologous heat-shock protein HSPPC-96 (Vitespan/Oncophage). HSPPC-96 binds peptide fragments derived from the patient's own tumor and can act as a chaperone for antigen presentation; a dose of 25 mg was administered weekly for 4 weeks, then once every 4 weeks until vaccine depletion (Wood et al, 2004). More than 2000 patients were evaluated, and 728 were analyzed by intention-to-treat (Wood et al, 2008). No patient experienced grade 3 or 4 treatment-related toxicity. A placebo arm was not incorporated, but an independent review was performed and determined time to progression. Unfortunately, it appears that HSPPC-96 tumor vaccine does not influence the natural history of RCC in the adjuvant setting.

Current trials using targeted molecular agents with activity in patients with metastatic RCC, such as sunitinib and sorafenib, have enrolled a large number of patients with surgically resected RCC who are at high risk for recurrence (Table 49–28) (Jonasch and Tannir, 2008). These agents are orally administered and thus their use is appealing in an adjuvant setting, although there are many uncertainties regarding optimal choice and dose and duration of therapy. In addition, the toxicities of these agents may limit their usefulness in the absence of demonstrable metastatic disease because patients taking a potentially preventive treatment tend to have a much lower threshold for toxicities. Please refer to Chapter 50 for a more detailed discussion of these tyrosine kinase inhibitors and their rationale for patients with advanced RCC.

Table 49–27.

Randomized Adjuvant Trials with Autologous Tumor Cell Preparations

STUDY	PATIENTS ELIGIBLE	TREATMENT GROUPS	NO. OF PATIENTS	5-YR RFS	5-YR OS
Galligioni et al (1996)	T1N0-1M0	Control	60	72%	78%
		Vaccine + BCG	60	63%	69%
Jocham et al (2004)	T2-3bN0-3M0	Control	202	67.8%	Not stated
		Vaccine	177	77.4%	Not stated
Wood et al (2008)	T2N0M0 (grade 3, 4) or T3a-cN0-1M0 or T4N1-2M0	Control	367	57%*	82%*
		HSPPC-96†	361	60%*	82%*

*Estimate at 3 yr; hazard ratio for recurrence was 0.923 (95% CI: 0.729-1.169 , P = 0.5) and for overall survival was 0.978 (95% CI: 0.702-1.364, P = 0.9).
†Heat shock protein–based vaccine derived from patient's own tumor.
BCG, bacille Calmette-Guérin; OS, overall survival; RFS, recurrence-free survival.

Table 49–28.

Current Clinical Trials of Adjuvant Treatment for Renal Cell Carcinoma (RCC)

TRIAL	STUDY GROUPS	ROUTE	TREATMENT DURATION	INCLUSION CRITERIA
Adjuvant Rencarex Immunotherapy Phase III Trial to Study Efficacy in Nonmetastatic Renal Cell Carcinoma (ARISER)	Rencarex (G250 mAb) vs. placebo	IV	24 wk	No evidence of residual disease No evidence of metastatic disease (M0) Clear cell RCC Meets one of the following stage criteria: Stage T3a, T3b, T3c, or T4 with N0 or Nx Stage T1b or T2 with microscopic vascular invasion and grade 3 or 4 Any T stage with N+ M0
Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Cell Carcinoma (ASSURE)	Sunitinib vs. sorafenib vs. placebo for 1 yr	PO	1 yr	No evidence of residual or recurrent disease No evidence of metastatic disease (M0) Clear cell and non–clear cell RCC eligible Stage T2-T4 or stage T1b with grade 3 or 4 N1/N2 if complete dissection performed
Sorafenib for Patients with Resected Primary Renal Cell Carcinoma (SORCE)	Sorafenib (for 1 or 3 yr) vs. placebo	PO	3 yr	No evidence of residual macroscopic disease after resection No evidence of metastatic disease (M0) Clear cell and non–clear cell RCC eligible Intermediate- or high-risk disease according to UISS
Sunitinib Trial in Adjuvant Renal Cancer (STAR)	Sunitinib vs. placebo for 1 yr	PO	1 yr	No evidence of metastatic disease (M0) Clear cell and non–clear cell RCC eligible High-risk RCC according to UISS No prior systemic therapy

UISS, UCLA Integrated Staging System (Zisman et al, 2002c).

OTHER MALIGNANT RENAL TUMORS

Sarcomas of the Kidney

Sarcomas represent 1% to 2% of all malignant renal tumors in adults, with a peak incidence in the fifth decade of life (Srinivas et al, 1984; Russo, 1991; Spellman et al, 1995; Frank et al, 2000). Renal sarcoma is less common but more lethal than sarcoma of any other genitourinary site, including the prostate, bladder, and paratesticular region (Russo, 1991; Russo et al, 1992). **Differentiation of renal sarcoma from sarcomatoid RCC is often difficult on the basis of clinical presentation, radiographic findings, and, in some cases, pathologic analysis.** Identification of any features of the various subtypes of RCC excludes the diagnosis of primary renal sarcoma. The common signs and symptoms associated with renal sarcoma in adults include palpable mass, abdominal or flank pain, and hematuria and are similar to those seen with large, rapidly growing RCCs (Economou et al, 1987). Abdominal CT typically demonstrates a large soft tissue mass involving or derived from the kidney, a finding that is again similar to that associated with many sarcomatoid RCCs (Farrow et al, 1968; Shirkhoda and Lewis, 1987; Russo, 1991). Specific findings suggestive of sarcoma rather than of RCC include apparent origin from the capsule or perisinuous region, growth to large size in the absence of lymphadenopathy, presence of fat or bone suggestive of liposarcoma or osteosarcoma, and hypovascular pattern on angiography, although one notable exception is the hemangiopericytoma, which is highly vascular (Smullens et al, 1982; Shirkhoda and Lewis, 1987). Renal sarcoma should be suspected in any of these circumstances or in any patient with a very large or rapidly growing renal mass (Table 49–29).

Sarcomas of the kidney, like sarcomas of any other site, share in common a distinct tumor biology that has important implications with respect to management (reviewed in Russo, 1991). **These tumors are derived from mesenchymal components and are thus free of many of the natural barriers to dissemination that confine other tumor types. They are typically surrounded by a pseudocapsule that is readily identifiable but that cannot be relied on for surgical dissection because it is often infiltrated with cancer cells,** which can extend for some distance into the surrounding tissues. In many cases this cannot be recognized macroscopically, although it is often manifested in the form of local recurrences, which are common after surgical extirpation, even when a wide excision has been performed. **High-grade sarcomas often metastasize, with the lungs being a primary site of spread, and prognosis is poor; many patients die of disease progression in a matter of months. Low-grade sarcomas tend to pursue a more indolent course,** although local recurrences often require repeat resection to prolong survival and minimize morbidity.

In general, the most important prognostic factors for sarcomas are margin status and tumor grade. The initial resection is the key event because, for many patients, this is their best chance for a long-term cure. For renal sarcomas this often mandates radical nephrectomy along with en bloc excision of adjacent organs (Srinivas et al, 1984; Brescia et al, 2008). MRI can be useful for preoperative planning by defining tissue planes and proximity to vital structures. This is primarily a surgical disease, and wide excision is the goal with intraoperative monitoring of margin status. Chemotherapeutic agents that have demonstrated activity against metastatic sarcomas include doxycycline and ifosfamide, but even in the best of circumstances response rates are disappointing (Antman et al, 1993). The combination of radiation therapy and chemotherapy, which has proved effective in an adjuvant setting for the management of sarcomas of the extremity, has not provided much benefit for renal or retroperitoneal sarcomas (Russo, 1991). At present, the role of such adjuvant approaches for the management of renal sarcomas is not well defined, although a multimodal

Table 49–29.

Characteristics of Other Malignant Renal Tumors

TUMOR TYPE	CHARACTERISTICS	MANAGEMENT
Sarcomas	Leiomyosarcoma most common Typically hypovascular Often rapidly growing and occasionally appear to be derived from the renal capsule	Wide local excision with confirmation of negative margins
Renal lymphoma and leukemia	Multiple radiographic patterns described Typically hypovascular Suspect in patients with massive retroperitoneal lymphadenopathy or lymphadenopathy in other regions of the body or atypical locations	Biopsy should be considered. Extirpative surgery should be avoided. Typically managed with chemotherapy and/or radiation therapy
Metastatic tumors	Most common sources include lung, breast, and gastrointestinal cancers, malignant melanoma, and hematologic malignancies. Typically hypovascular and multifocal	Biopsy should be strongly considered. Typically managed with systemic therapy or palliative care
Carcinoid	Typically hypovascular May present as carcinoid syndrome Derived from neuroendocrine cells	Surgical excision
Small cell carcinoma of the kidney	Neuroendocrine derivation Typically hypovascular Most locally advanced or metastatic	Multimodal therapy with surgery and platinum-based chemotherapy
Primitive neuroectodermal tumor	Derived from primitive neural crest cells Hypovascular pattern typical Poor prognosis	Multimodal therapy
Wilms tumor	Heterogeneous solid renal mass on CT	Multimodal therapy analogous to treatment protocols for pediatric Wilms tumor

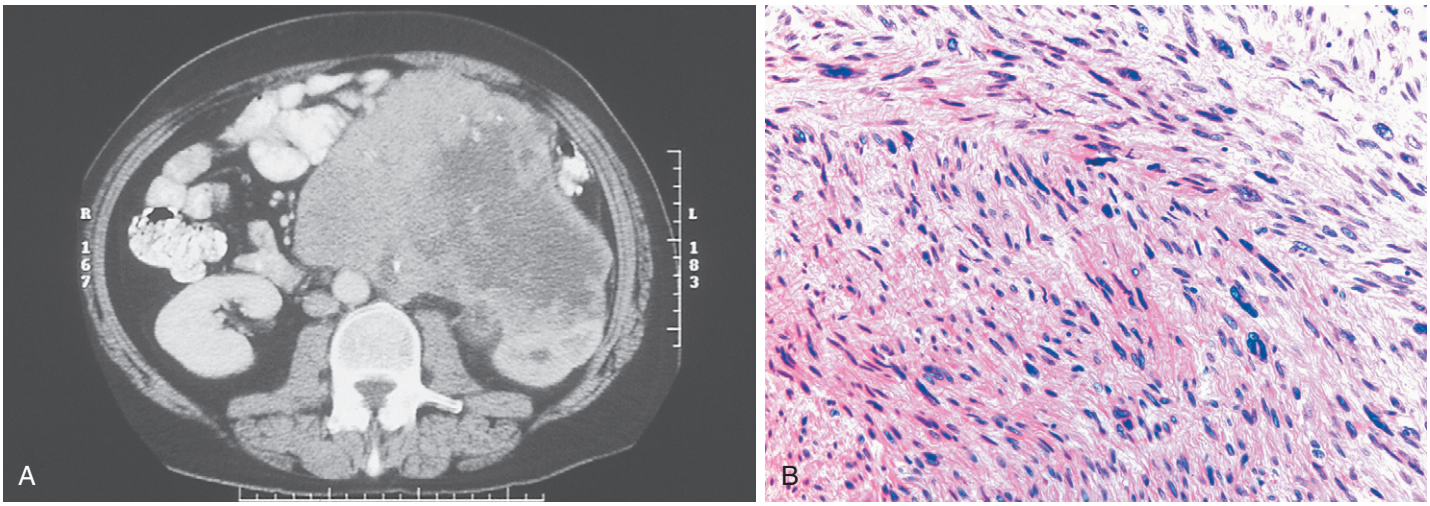


Figure 49–29. **A,** CT scan demonstrates a large leiomyosarcoma of the left kidney. **B,** Microscopic features of leiomyosarcoma include spindle cells, blunt-ended nuclei, and eosinophilic cytoplasm. (Courtesy of Dr. Michael McGuire, Evanston, IL, and Dr. Ming Zhou, Cleveland, OH.)

approach is often pursued if performance status allows, given the poor prognosis.

The largest single-institution series of renal sarcomas include only 15 to 26 cases and represent a composite experience extending for a period of several years (Farrow et al, 1968; Srinivas et al, 1984; Shirkhoda and Lewis, 1987). In all such series leiomyosarcoma has been the most common histologic subtype, and in many series liposarcoma has been the second most common. In contrast, for retroperitoneal sarcomas, the order is reversed, with liposarcoma being the most common histologic subtype (Karakousis et al, 1995). All such series report a poor prognosis; the experience of Srinivas and colleagues (1984) at Memorial Sloan-Kettering Cancer Center is representative. In this series of 16 patients with renal sarcomas, 15 underwent nephrectomy, often with en-bloc excision of adjacent organs; 5 received adjuvant radiation therapy and chemotherapy without apparent benefit; and 13 died within 6 months after surgery. Vogelzang and associates (1993) reported a more encouraging experience with 21 patients with primary renal sarcomas; there were six long-term survivors after surgery alone. A predominance of low-grade disease may account for these favorable outcomes. However, even in this series, the majority of patients died of progressive disease within a few to several months after diagnosis. Saitoh and colleagues (1982) defined the common sites of metastases of renal sarcomas: lung first and foremost but also lymph nodes and liver.

Leiomyosarcoma is the most common histologic subtype of renal sarcoma, accounting for 50% to 60% of such tumors (Fig. 49–29). **The cell of origin is the smooth muscle cell of the capsule or other perinephric structures** (Moudouni et al, 2001; Deyrup et al, 2004). Niceta and associates

(1974) identified 66 cases of renal leiomyosarcoma in the literature and reported a female predominance; most patients presented in the fourth through sixth decades of life. Renal leiomyosarcoma, like other renal sarcomas, tends to displace rather than invade the parenchyma, and is characterized by rapid growth rate, frequent metastasis, and high local and systemic recurrence rates (Pollack et al, 1987; Deyrup et al, 2004). In the cases reviewed by Niceta, most patients were treated primarily with radical nephrectomy and died within 2 years. In the Mayo Clinic series, 14 of 15 patients with renal leiomyosarcoma died of disease progression within 4 months to 5.5 years after surgery (Farrow et al, 1968).

Other than leiomyosarcoma, a wide variety of histologic subtypes have been described because almost every conceivable type of sarcoma has been found in the kidney. **Liposarcoma** is readily distinguished from RCC because of the presence of adipose tissue, but it is often confused with AMLs or with large, benign renal lipomas (Frank et al, 2000). Renal liposarcoma typically develops in the fifth and sixth decades of life and often grows to extremely large size (Economou et al, 1987). Response to radiation therapy and cisplatin-based chemotherapy in an adjuvant setting has been reported by Belldegrun and deKernion (1987) and should be considered in patients with high-grade disease or positive margins. **Osteogenic sarcoma** is a rare but distinctive form of renal sarcoma that contains calcium and is often rock hard (Micolonghi et al, 1984; Leventis et al, 1997). Extensive calcification in a large, hypovascular tumor should suggest the diagnosis. The appearance on plain films can mimic a staghorn calculus, but the readily evident mass effect should suggest xanthogranulomatous disease or, more rarely, osteogenic sarcoma. Again, prognosis is poor; most patients die of disease progression within a few years after diagnosis. **Less common histologic subtypes include rhabdomyosarcoma, fibrosarcoma, carcinosarcoma, malignant fibrous histiocytoma, synovial sarcoma, schwannoma, angiosarcoma, and malignant hemangiopericytoma** (Raghavaiah et al, 1979; Weiss et al, 1984; Mordkin et al, 1997; Tsuda et al, 1997; Cerilli et al, 1998; Merchant et al, 1998; Chieng et al, 1999; Koyama et al, 2001; Bella et al, 2002; Chen et al, 2003; Shannon et al, 2005; Khan et al, 2006; Leggio et al, 2006; Hung et al, 2008; Mirza et al, 2008). **Malignant hemangiopericytomas** present at a mean age of 40.3 years, which is younger than most other renal sarcomas, and are notable for their extensive vascularity (Argyropoulos et al, 2005; Chaudhary et al, 2007; Brescia et al, 2008). Preoperative angioembolization has been described and may simplify surgical excision (Smullens et al, 1982).

Renal Lymphoma and Leukemia

Renal involvement with hematologic malignant neoplasms, which include the lymphomas and leukemias, is common—found at autopsy in approximately 34% of patients dying of progressive lymphoma or leukemia. However, these processes are uncommonly seen in clinical practice because they are often silent and generally occur only as a late manifestation of systemic disease (Richmond et al, 1962; Pollack et al, 1987; McVary, 1991). The role of the urologist in the evaluation of renal lymphoma or leukemia is critically important and can include differentiation from other renal malignant neoplasms, timely provision of a pathologic diagnosis, and preservation of renal function (reviewed in McVary, 1991). Renal involvement is more common with non-Hodgkin's lymphoma than with Hodgkin's disease, and, as with most other forms of extranodal non-Hodgkin's lymphoma, histologically diffuse forms predominate over nodular forms (Richmond et al, 1962; Pollack et al, 1987; Yasunaga et al, 1997; O'Riordan et al, 2001). Primary renal lymphoma is rare, with only a few well-documented case reports in the literature (Kandel et al, 1987; Pollack et al, 1987; Arranz-Arija et al, 1994; Dimopoulos et al, 1996; Yasunaga et al, 1997; Tuzel et al, 2003; Zomas et al, 2004; Ahmad et al, 2005; Garcia et al, 2007). This is not surprising given the relative paucity of lymphoid tissue in the normal renal parenchyma. Hematogenous dissemination of lymphoma to the kidney is most common and is thought to occur in 90% of cases; direct extension from retroperitoneal lymph nodes accounts for the remainder. Hartman and colleagues (1982) have correlated pathologic and radiographic patterns and have shown that the most common pattern of renal involvement consists of multiple small renal nodules that tend to develop between the individual nephrons. Eventually, these nodules become confluent, forming radiographically detectable masses. At the extreme, they can replace the entire parenchyma of the kidney, leading to renal failure.

The CT scan is the radiographic modality of choice for the diagnosis of renal lymphoma and for monitoring response to therapy (Jafri et al, 1982; Pollack et al, 1987; Sheeran and Sussman, 1998; Urban and Fishman, 2000). The common radiographic patterns associated with renal lymphoma have been defined by Heiken and associates (1991) and confirmed by a number of other investigators (Table 49–30). Renal lymphoma can present as multiple distinct renal masses; as a solitary renal mass, which can be difficult to differentiate from RCC; as diffuse renal infiltration; or as direct invasion of the kidney from enlarged retroperitoneal nodes (Cohan et al, 1990; Heiken et al, 1991; Eisenberg et al, 1994; Sheeran and Sussman, 1998; Sheth et al, 2006). A hypovascular pattern on angiography is typical for renal lymphoma (Pollack et al, 1987). **Renal lymphoma should be suspected in patients with massive retroperitoneal lymphadenopathy, splenomegaly, or lymphadenopathy in other regions of the body or atypical regions within the retroperitoneum** (Jafri et al, 1982; Dimopoulos et al, 1996). Relative to this, the main landing zones for RCC should be kept in mind—the interaortocaval region for right RCC and para-aortic region for left RCC—and lymphadenopathy centered outside of these areas should raise suspicion for lymphoma. Any patient with a prior history of lymphoma and a renal mass should also be evaluated for renal recurrence rather than for RCC. In general, lymphomas are more common in patients with iatrogenic immune suppression, acquired immunodeficiency syndrome (AIDS), autoimmune diseases, or graft-versus-host disease and in patients with a history of radiation therapy (McVary, 1991). These clinical associations may also increase the index of suspicion about a diagnosis of systemic lymphoma.

Table 49–30.

CT Findings Associated with Lymphoma

FINDING	INCIDENCE (%)
Multiple renal masses	45
Solitary renal mass	15
Renal invasion from enlarged retroperitoneal lymph nodes	25
Diffuse renal involvement	10
Predominantly perinephric involvement	5

Data from Pollack HM, Banner MP, Amendola MA. Other malignant neoplasms of the renal parenchyma. Semin Roentgenol 1987;22:260–74; and Heiken JP, Gold RP, Schnur MJ. Computed tomography of renal lymphoma with ultrasound correlation. J Comput Assist Tomogr 1991;1:245–50.

Renal involvement related to leukemia is more common in children, paralleling the demographics of the disease, and is more commonly due to lymphocytic leukemia than the myelogenous forms (Araki, 1982; Pollack et al, 1987). Leukemia typically involves the kidney in a diffusely infiltrative pattern and most often represents a late manifestation of systemic disease. However, as for renal lymphoma, a variety of other radiographic patterns have been observed, as reviewed by Pollack and colleagues (1987).

If lymphoma or leukemic renal involvement is suspected, consideration should be given to percutaneous biopsy to obtain a pathologic diagnosis; and if exploratory surgery is necessary, intraoperative biopsy and frozen-section analysis should take priority. If lymphoma or leukemia is confirmed, the kidney should be spared and complete staging of the neoplasm should be performed to preclude the need for a secondary procedure (McVary, 1991). Truong and colleagues (2001) have demonstrated the utility of fine-needle aspiration in the diagnosis of renal lymphoma, although additional tissue may be required in many cases to classify the lymphoma accurately and to guide further therapy (Hunter et al, 2006). **Extirpative surgery should be avoided if renal lymphoma and leukemia are suspected because the treatment of these processes is generally systemic chemotherapy with or without radiation therapy.** The classic chemotherapy regimen for non-Hodgkin's lymphoma is the CHOP protocol, which includes cyclophosphamide, doxorubicin, vincristine, and prednisolone (Colevas et al, 2000). Nephrectomy is seldom indicated except in patients with severe symptoms, such as uncontrollable hemorrhage. The other notable exception is the extremely rare patient with primary renal lymphoma in whom a combination of nephrectomy and systemic chemotherapy may represent optimal therapy (Okuno et al, 1995; Garcia et al, 2007). Fourteen cases of marginal zone B-cell lymphoma (MALT) localized to the kidney have been described with some apparently cured by surgery alone (Garcia et al, 2007).

Both renal lymphoma and leukemia are commonly silent but can be associated with hematuria, flank pain, or progressive renal failure. Fever, weight loss, and fatigue, the so-called B symptoms of lymphoma, are much more common (Yasunaga et al, 1997; Zomas et al, 2004). Renal failure can be due to extensive replacement of the functioning parenchyma or bilateral ureteral obstruction associated with enlarged retroperitoneal lymph nodes (more common with lymphoma) (reviewed in McVary, 1991). In reality, renal failure in such patients is more often related to medical causes, such as hypercalcemia or urate nephropathy, that can develop during systemic treatment of advanced disease. The diagnosis of renal failure related to parenchymal replacement by lymphoma or leukemia requires exclusion of other related causes of renal failure and demonstration of improvement in renal function after administration of systemic chemotherapy or radiation therapy (Choi et al, 1997; O'Riordan et al, 2001).

Metastatic Tumors

Metastatic tumors are the most common malignant neoplasms in the kidney, outnumbering primary renal tumors by a wide margin. Autopsy studies have shown that 12% of patients dying of cancer have renal metastases, making the kidney one of the most common sites for metastatic dissemination (Pollack et al, 1987). **The profuse vascularity of the kidney makes it a fertile soil for the deposition and growth of cancer cells.** Almost all renal metastases develop through a hematogenous route of spread; only a small minority are caused by direct invasion of tumors derived from adjacent organs such as the pancreas, colon, and adrenal gland. **The most common sources of renal metastases include lung, breast, and gastrointestinal cancers; malignant melanoma; and the hematologic malignant neoplasms,** which are reviewed in the preceding section (Klinger, 1951; Choyke et al, 1987; Pollack et al, 1987; Aron et al, 2004; Martino et al, 2004; Sánchez-Ortiz et al, 2004b; Stage et al, 2005). Of the solid malignant neoplasms, lung cancer is most commonly associated with renal metastases. Olsson and colleagues (1971) found that 20% of patients dying of lung cancer had renal metastases, 60% of which were bilateral. Klinger (1951) reviewed 5000 autopsies and found 17 cases of renal metastases from lung cancer, 11 from gastric cancer, 9 from breast cancer, 7 from pancreatic cancer, 4 from esophageal cancer, 6 from other gastrointestinal primary cancers, and 1 from malignant melanoma. In a series of 27 renal metastases reviewed by Choyke and associates (1987), 7 patients had primary lung cancer, 7 had gastrointestinal malignant neoplasms, 4 had malignant melanoma, 2 had breast cancer, and 2 had endometrial carcinoma. Most renal metastases are multifocal, and almost all are associated with widespread nonrenal metastases (Choyke et al, 1987; Pollack et al, 1987). Choyke and associates (1987) reported that renal metastases from lung, breast, and colon carcinomas are notable because they are occasionally large and solitary, making them difficult to differentiate from RCC.

The typical pattern of renal metastases consists of multiple small nodules that are often clinically silent, although they can lead to hematuria or flank pain in exceptional circumstances (Walther et al, 1979; Pollack et al, 1987). **CT is the primary diagnostic modality for renal metastases and typically demonstrates isodense masses that enhance only moderately (5 to 30 HU)** after administration of intravenous contrast material (Pollack et al, 1987; Ferrozzi et al, 1997).

Renal metastases should be suspected in any patient with multiple renal lesions and widespread systemic metastases or a history of nonrenal primary cancer. If there is any uncertainty about the diagnosis, a CT- or ultrasound-guided percutaneous renal biopsy usually provides pathologic confirmation (Gattuso et al, 1999; Sánchez-Ortiz, 2004a). Most patients with renal metastases are managed with systemic therapy or placed on a palliative care pathway, depending on the clinical circumstances. Nephrectomy is almost never required except in extenuating circumstances, such as uncontrollable renal hemorrhage. Patients with a solitary, strongly enhancing renal lesion and a history of organ-confined, nonrenal malignant disease are more likely to have RCC, particularly if the interval between the two diagnoses is substantial. In one study involving 100 consecutive patients with a renal mass and a history of nonrenal malignancy, none of the 54 patients without other evidence of disease progression had a renal metastasis (Rybicki et al, 2003; Sánchez-Ortiz, 2004a). However, even in this circumstance, a renal mass biopsy or aspiration should be considered because it may preclude the need for surgical intervention.

Other Malignant Tumors of the Kidney

Other malignant tumors of the kidney include adult Wilms tumor and neuroendocrine tumors including renal carcinoid, small cell carcinoma, and primitive neuroectodermal tumor (PNET). All are relatively uncommon, but each has distinct tumor biology.

Carcinoid tumors arise from neuroendocrine cells, which are not normally present in the kidney (Romero et al, 2006). This is thus a rare renal malignant neoplasm with fewer than 60 cases reported in the English literature (Kawajiri et al, 2004; Mufarrij et al, 2005; Romero et al, 2006; Hansel et al, 2007; Lane et al, 2007b; Canacci et al, 2008). Primitive stem cells within the kidney or retained neural crest tissue may give rise to these tumors (Krishnan et al, 1997; Begin et al, 1998). A correlation with horseshoe kidneys has been reported, with previous studies showing an increased relative risk of 82-fold compared with normal kidneys (Begin et al, 1998; Romero et al, 2006). Carcinoid tumors stain positive for markers of neuroendocrine tissue such as neuron-specific enolase and chromogranin (Kulke and Mayer, 1999; Lane et al, 2007b). **Measurement of urinary or plasma serotonin or its metabolites can be diagnostic** (Kulke and Mayer, 1999). **Only a minority of patients will present with the carcinoid syndrome—episodic flushing, wheezing, and diarrhea** (Jensen and Doherty, 2001; Romero et al, 2006; Lane et al, 2007b). Median age at diagnosis is 49 years (Romero et al, 2006). CT findings are nonspecific, and many renal carcinoids are small and nonaggressive. However, in a recent review of renal carcinoids, metastases were found in 46% of patients at diagnosis (Romero et al, 2006). Surgical excision is the mainstay of treatment (Kawajiri et al, 2004). Nephron-sparing surgery is preferred if the diagnosis is suspected preoperatively. Prognosis is good, particularly when associated with a horseshoe kidney (Krishnan et al, 1997; Begin et al, 1998; Lowrance et al, 2006). Significant adverse prognostic factors include age older than 40 years, tumor size greater than 4 cm, high mitotic rate, purely solid gross morphology, metastasis at initial diagnosis, and tumor extending through the renal capsule (Romero et al, 2006).

Other neuroendocrine tumors including small cell carcinoma and large cell neuroendocrine carcinoma can occur in the kidney but are even less common than renal carcinoids (Gonzales-Lois et al, 2001; Majhail et al, 2003; Lane et al, 2007b). **Approximately 30 cases of small cell carcinoma of the kidney have been reported for which another primary site could not be identified** (Mackey et al, 1998; Gonzalez-Lois et al, 2001; Akkaya et al, 2003; Majhail et al, 2003; Mirza et al, 2007). **On pathologic examination, small cell carcinoma has features of neuroendocrine and epithelial neoplasms and must be differentiated from Wilms tumor, PNET, lymphoma, and metastasis from pulmonary small cell carcinoma** (Gonzalez-Lois et al, 2001; Akkaya et al, 2003). **Positive staining for neuron-specific enolase, chromogranin, and synaptophysin is characteristic** (Akkaya et al, 2003). Preoperative differentiation from RCC is difficult, although a relatively hypovascular pattern may be an indication. Many small cell carcinomas of the kidney are locally advanced or metastatic at presentation, and flank pain or hematuria is common (Majhail et al, 2003; Mirza et al, 2007). Multimodal therapy with nephrectomy or tumor debulking combined with platinum-based chemotherapy regimens is advocated for extrapulmonary small cell carcinoma in general and may also be useful for the renal manifestation of this malignant neoplasm (Majhail et al, 2003; Mirza et al, 2007). Long-term survivors are described but rare, and new treatment regimens are needed.

PNET is related to the Ewing sarcoma family of tumors that are more common in the pediatric population, typically manifesting in the bone or soft tissues of the extremities, trunk, and head and neck and only rarely in the viscera or kidneys (Jimenez et al, 2002; Maly et al, 2004). However, a person of any age may be affected and several cases of PNET have been reported in the kidneys of adults (Rodriquez-Galindo et al, 1997; Karnes et al, 2000; Doerfler et al, 2001; Parham et al, 2001; Thomas et al, 2002; Pomara et al, 2004; Thyavihally et al, 2008). The majority of renal PNET are seen in patients aged 10 to 39 years (Ellinger et al, 2006). These tumors are derived from primitive neural crest cells, and positive staining for CD99 in addition to vimentin, cytokeratin, and neuron-specific enolase strongly supports the diagnosis (Gonlusen et al, 2001; Parham et al, 2001; Ginsberg et al, 2002; Maly et al, 2004; Ellinger et al, 2006). On microscopic examination, renal PNET typically shows small round cells that may form characteristic Homer-Wright rosettes (Marley et al, 1997; Pomara et al, 2004; Thyavihally et al, 2008). A characteristic t(11;22)(q24;q12) translocation is highly specific for PNET and can help differentiate it from neuroblastoma or adult Wilms tumor (Marley et al, 1997; Quezado et al, 1997; Parham et al, 2001; Jimenez et al, 2002). Clinical symptoms are nonspecific, and CT often demonstrates a heterogeneous ill-defined mass with areas of necrosis (Doerfler et al, 2001). Again, equivocal enhancement with contrast medium is typical and differentiation from RCC is often difficult. Renal PNET appears to behave more aggressively than similar tumors at other sites and may represent a distinct clinical entity (Rodriquez-Galindo et al, 1997; Parham et al, 2001; Jimenez et al, 2002; Pomara et al, 2004; Thyavihally et al, 2008). A strong propensity for local recurrence and early metastasis to lymph nodes, lung, liver, and bone has been described (Rodriquez-Galindo, 1997; Quezado et al, 1997; Gonlusen et al, 2001; Ellinger et al, 2006). **Multimodal treatment protocols combining tumor debulking, chemotherapy targeted to round cell or Ewing's family of tumors, and radiotherapy to the renal bed are often employed, but prognosis is poor with overall 5-year disease-free survival of 45% to 55%** (Casella et al, 2001; Ellinger et al, 2006; Thyavihally et al, 2008).

Wilms tumor is the most common abdominal malignant neoplasm in children, but 3% of Wilms tumors are seen in adults. Of these, 20% are found between the ages of 15 and 20 years and the remaining 80% are distributed between the third and seventh decades of life (Winter et al, 1996). Adult and pediatric Wilms tumors are histologically similar with a distinctive triphasic pattern consisting of varying amounts of blastema, epithelium, and stroma (Orditura et al, 1997). **Pathologic staging is the same as for pediatric Wilms tumor, and most authors recommend treating adult patients with the same therapeutic protocols that have been tested and proven in children** (Firoozi and Kogan, 2003). Adult Wilms tumor typically presents as a heterogeneous intrarenal mass on CT with a relatively hypovascular pattern, but differentiation from RCC can be difficult if not impossible in many cases (Winter et al, 1996; Orditura et al, 1997; Reinhard et al, 2004). Clinical presentation of adult Wilms tumor is also similar to that of RCC, and this tends to be an unsuspected pathologic diagnosis in most cases. **Multimodal therapy should be considered analogous to the treatment protocols for pediatric Wilms tumor** (Bozeman et al, 1995; Green, 1997; Neville and Ritchey, 2000; Terenziani et al, 2004). Prognosis is worse for adults with Wilms tumor than for children with this malignant neoplasm because adults are more likely to present with advanced disease and a sudden drop in performance status (Winter et al, 1996; Akmansu et al, 1998).

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chapter 50

Treatment of Advanced Renal Cell Carcinoma

Ramaprasad Srinivasan, MD, PhD • W. Marston Linehan, MD

Prognostic Factors

Surgical Management of Metastatic Renal Cell Carcinoma

Immunologic Approaches in the Management of Advanced Clear Cell Renal Cell Carcinoma

Molecular Basis for Targeted Approaches in Clear Cell Renal Cell Carcinoma

Targeted Molecular Agents in Clear Cell Renal Cell Carcinoma

Systemic Therapy for Non–Clear Cell Variants of Renal Cell Carcinoma

Renal cell carcinoma **(RCC) is a term that includes a variety of cancers arising in the kidney and comprises several histologically, biologically, and clinically distinct entities** (Linehan et al, 2007, 2009). An estimated 58,240 new cases of cancer arising in the kidney or renal pelvis were diagnosed in 2010 in the United States (Jemal et al, 2010). **Approximately one third of all newly diagnosed RCC patients present with synchronous metastatic disease and an additional 20% to 40% of patients with clinically localized disease at diagnosis will eventually develop metastases** (Skinner et al, 1971; Rabinovitch et al, 1994; Bukowski, 1997). Metastatic RCC is almost always fatal, with 10-year survival rates of less than 5% (Bukowski, 1997; Motzer et al, 1999, 2000; Motzer and Russo, 2000; Négrier et al, 2002); patients with metastatic disease account for the majority of deaths (approximately 13,000 a year in the United States) related to RCC (Jemal et al, 2010).

Advances in our understanding of the genetic and molecular defects underlying the individual subtypes of RCC have led to the development of novel agents designed to reverse or modulate aberrant pathways contributing to renal oncogenesis. These "targeted" therapeutic strategies have largely supplanted other treatment modalities in the initial management of metastatic clear cell kidney cancer; however, surgery, irradiation, and cytokine therapy remain appropriate choices in the management of selected patients with advanced clear cell RCC. Although agents effective in clear cell RCC are often used in patients with other subtypes of RCC there is scant evidence from prospective studies demonstrating benefit in non–clear cell RCC variants. More recently, elucidation of aberrant oncogenic pathways in papillary, chromophobe, and other variants of RCC has paved the way for evaluation of targeted therapeutic approaches in these histologic subtypes (Linehan et al, 2009).

PROGNOSTIC FACTORS

Patients with metastatic RCC generally have a poor prognosis, with the majority succumbing to their disease. Ten-year survival in patients diagnosed with metastatic disease was estimated to be less than 5% in the era of cytokine therapy and is unlikely to change significantly with the advent of targeted therapy. However, **several clinical features such as a long time interval between initial diagnosis and appearance of metastatic disease and presence of fewer sites of metastatic disease have been observed to be associated with better outcome. Conversely, poor performance status and the presence of lymph node and/or liver metastases are some factors associated with shorter survival.** Investigators at the Memorial Sloan-Kettering Cancer Center evaluated a variety of clinical and laboratory parameters in 670 patients enrolled on various clinical trials of chemotherapy or immunotherapy in an effort to identify those pretreatment factors that were able to best predict outcome (Motzer et al, 1999). **In a multivariate analysis, a poor performance status (Karnofsky score <80), an elevated serum lactate dehydrogenase (LDH) level (>1.5 times upper limit of normal), a low hemoglobin (less than the lower limit of normal), an elevated corrected calcium concentration (>10 g/dL), and lack of prior nephrectomy were independent predictors of a poor outcome** (Table 50–1). **Patients could be stratified into three distinct prognostic groups based on these five poor prognostic factors** (Table 50–2). **The overall survival (OS) times in patients with no adverse factors (favorable-risk group), one to two risk factors (intermediate-risk group), and more than three risk factors (poor-risk group) were 20 months, 10 months, and 4 months, respectively** (Fig. 50–1) (Motzer et al, 1999). Subsequently, the same group

Table 50–1.

Adverse Prognostic Factors in 670 Patients Treated with Chemotherapy or Immunotherapy at the Memorial Sloan-Kettering Cancer Center

Karnofsky performance score <80%
Elevated lactate dehydrogenase (>1.5 times upper limit of normal)
Low hemoglobin (<lower limit of normal)
Elevated corrected calcium (>10 mg/dL)
Absence of prior nephrectomy

Data from Motzer RJ, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 1999;17:2530–40.

Table 50–2.

Risk Stratification Based on Adverse Prognostic Factors in 670 Patients Treated with Chemotherapy or Immunotherapy at the Memorial Sloan-Kettering Cancer Center

RISK GROUP	NO. OF ADVERSE PROGNOSTIC FACTORS	MEDIAN OVERALL SURVIVAL
Good	0	20 months
Intermediate	1-2	10 months
Poor	3-5	4 months

Data from Motzer RJ, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 1999;17:2530–40.

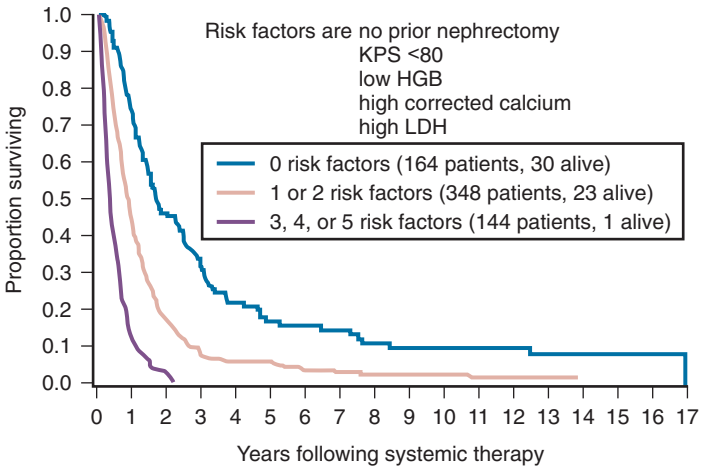


Figure 50–1. Survival analysis stratified according to risk group in 670 patients treated with chemotherapy or immunotherapy at the Memorial Sloan-Kettering Cancer Center (n = 656; 14 patients missing one or more of the five risk factors were excluded). KPS, Karnofsky performance score; HGB, hemoglobin; LDH, lactate dehydrogenase. (From Motzer RJ, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 1999;17:2530–40.)

identified poor performance status, high calcium level, low hemoglobin value, elevated LDH level, and short time interval from initial diagnosis to treatment as factors that could best predict a poor outcome in 463 patients receiving interferon-based therapy in the first-line setting (Motzer et al, 2002). This prognostic model was found to be predictive of survival in an independent data set derived from patients treated at the Cleveland Clinic and provides independent, external validation of the proposed model (Mekhail et al, 2005). Similar prognostic schemes have also been proposed by the Groupe Français d'Immunotherapie and by investigators from the University of California, Los Angeles (Tsui et al, 2000). **Validated prognostic models are used in clinical practice to help make appropriate management decisions as well as in the design and interpretation of clinical trials.** Modifications of these prognostic schemes as well as identification of reliable molecular markers are under investigation as suitable predictors of response to and survival after therapy with newer targeted agents against vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathway components (Choueiri et al, 2007, 2008b; Motzer et al, 2008a).

SURGICAL MANAGEMENT OF METASTATIC RENAL CELL CARCINOMA

Debulking or Cytoreductive Nephrectomy in Patients with Metastatic RCC

The role of cytoreductive nephrectomy preceding systemic therapy has been extensively studied in the era of cytokine therapy. The impetus for exploring this approach in metastatic RCC was provided both by the perception that bulky tumors might inhibit key components of the immune system critical for combating cancer and by observations suggesting that removal of large primary tumors may provide clinical benefit. To support this practice early proponents of cytoreductive nephrectomy had cited (1) the rare but well-described occurrence of spontaneous regression of metastatic lesions after nephrectomy (Bloom, 1973; Middleton, 1980; Snow and Schellhammer, 1982; Marcus et al, 1993); (2) preclinical data suggesting that large primary tumors may inhibit T-cell function (Kudoh et al, 1997; Bukowski et al, 1998; Ling et al, 1998; Uzzo et al, 1999a, 1999b); and (3) the inability of systemic agents, particularly cytokines, to induce meaningful responses in primary renal tumors in most patients (Sella et al, 1993; Rackley et al, 1994; Wagner et al, 1999). However, the risk of perioperative morbidity and mortality and the inability of a significant proportion of patients undergoing nephrectomy to subsequently receive systemic therapy clearly underlined the need for unequivocal evidence of clinical benefit as well the ability to identify patients likely to benefit from this approach.

Nephrectomy as the sole therapeutic intervention in the context of metastatic disease is unlikely to alter outcome, as suggested by small retrospective analyses (DeKernion et al, 1978). However, several retrospective studies have demonstrated the feasibility of a combined modality approach in which nephrectomy is followed by cytokine therapy, with some suggesting that this approach may favorably impact response and survival. Investigators from the National Cancer Institute (NCI) reported their experience in 195 patients undergoing nephrectomy followed by high-dose interleukin-2 (IL-2) therapy between the years 1985 and 1996 (Walther et al, 1997b). An overall response rate of 18% (including a complete response rate of 4%) after IL-2 therapy was observed in this study. A notable finding that emerged from this study was that although the majority of patients underwent successful resection of the primary tumor only 107/195 (55%) went on to receive IL-2 therapy. Rapid postoperative disease progression and perioperative surgical and medical morbidity were the most common factors preventing delivery of systemic therapy, suggesting that careful patient selection may play an important

role in the successful application of this combined modality approach. The impact of patient and/or disease characteristics on outcome is further highlighted by a retrospective study. In Bennett and associates' (1995) series of 30 patients, which included several patients with unfavorable performance status (Eastern Cooperative Oncology Group [ECOG] 2) and multiple metastatic sites including patients with brain or liver metastases, only 7 (23%) were able to proceed with IL-2 after nephrectomy. Conversely, in a series that included only patients with favorable clinical/prognostic factors (e.g., good performance status, minimal comorbidity, no liver or brain metastases), the majority of patients were able to proceed to systemic therapy after nephrectomy, with high response rates (35% to 40%) and OS (median 20 to 22 months) after cytokine-based treatment (Fallick et al, 1997; Figlin et al, 1997). **Although these retrospective analyses and small single-arm prospective studies confirmed the feasibility of a tandem surgical/cytokine therapeutic approach, their major contribution was in laying the foundation for controlled, prospective studies to determine if outcomes with cytokine therapy could be improved by prior nephrectomy.**

The most compelling evidence in support of cytoreductive nephrectomy is provided by two randomized phase III studies conducted by the Southwest Oncology Group (SWOG) and the European Organization for Research and Treatment of Cancer (EORTC). The larger of the two studies, SWOG trial 8949, randomized 241 patients with metastatic RCC to receive interferon-α-2b either as initial therapy or after cytoreductive nephrectomy (Flanigan et al, 2001). Salient eligibility criteria included a histologic diagnosis of kidney cancer (all histologic subtypes were allowed); good performance status (ECOG 0 or 1); presence of a resectable primary renal tumor; no prior chemotherapy, irradiation, or immunotherapy; and adequate organ function. **Although there were no significant differences in the response rates to interferon observed in the two study arms, OS was improved in the surgery plus interferon arm (median 11.1 vs. 8.1 months for interferon alone, *P* = .05)** (Fig. 50–2). These data were similar to those from a smaller EORTC trial (a total of 85 patients randomized to interferon alone or interferon after nephrectomy) that used a similar design and reported a survival advantage favoring the surgery plus interferon arm (median OS 17 vs. 7 months, $P = .03$) (Mickisch et al, 2001). A combined analysis of both trials revealed data that were consistent with those reported in the individual trials (Flanigan et al, 2004). **These data support the use of cytoreductive nephrectomy in carefully selected patients with metastatic RCC who are likely candidates for subsequent cytokine therapy** (data summarized in Table 50–3).

The impact of cytoreductive nephrectomy on outcome in patients receiving VEGF or mTOR pathway inhibitors remains to be determined and is the subject of ongoing trials. Similarly, although some patients with non–clear cell histologic subtypes of RCC were included in the aforementioned trials, the role of nephrectomy before systemic therapy in these patients is unclear.

Resection of Metastases

Most patients with metastatic RCC will not achieve a cure or long-term disease remission with currently available systemic agents.

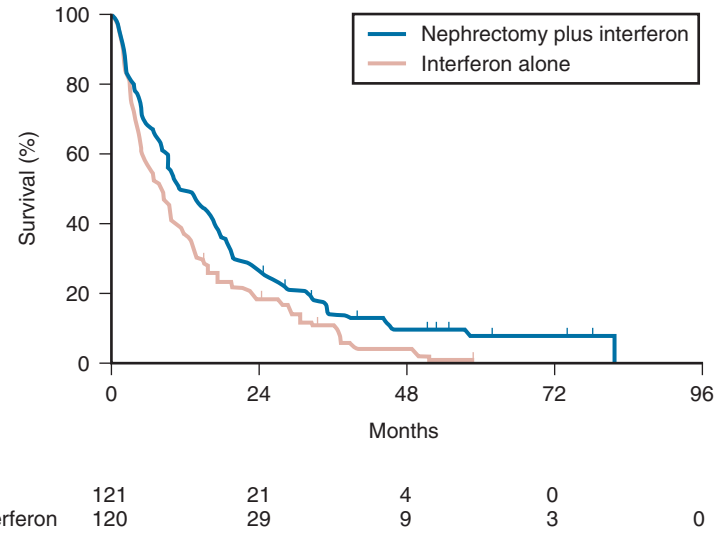


Figure 50–2. Actuarial survival among 241 patients with metastatic renal cell carcinoma randomized to either interferon-α alone or interferon-α after cytoreductive nephrectomy. (From Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med 2001;345:1655–59.)

Table 50–3.

Summary of Outcome in Randomized Studies of Interferon-α Alone or Interferon-α after Cytoreductive Nephrectomy in Patients with Metastatic Kidney Cancer

	NO. OF ELIGIBLE PATIENTS			RESPONSE RATE AFTER IFN (%)			MEDIAN OVERALL SURVIVAL (MO)		
STUDY	Total	IFN	Nx Plus IFN	IFN	Nx Plus IFN	*P*	IFN	Nx Plus IFN	*P*
Flanigan et al, 2001	241	121	120	3.6	3.3	NS	8.1	11.1	.05
Mickisch et al, 2001	83	42	41	12	19	.38	7	17	.03
Flanigan et al, 2004	331	163	161	5.7	6.9	.60	7.8	13.6	.002

IFN, interferon-α; Nx, cytoreductive nephrectomy.

However, resection of limited metastatic disease has been reported by several groups to be associated with long disease-free intervals and OS. It should be emphasized that metastasectomy has not been evaluated systematically in a prospective, randomized fashion and that the favorable outcome ascribed to resection of solitary metastatic disease may reflect patient selection bias, inherent differences in tumor biology, and natural history or other confounding factors.

Most studies detailing outcome after metastasectomy are retrospective series. In most series, isolated pulmonary metastases were the lesions most commonly amenable to resection with curative intent. The OS of patients undergoing complete resection of limited metastatic disease is quite impressive, with reported median 5-year survival rates of 35% to 50% in many series (Middleton, 1967; Skinner et al, 1971; Tolia and Whitmore, 1975; O'Dea et al, 1978; Pogrebniak et al, 1992; Kierney et al, 1994; Friedel et al, 1999; Murthy et al, 2005; Russo et al, 2007). The larger of these studies have also attempted to identify patients most likely to benefit from this approach. In a series of 278 patients with recurrent RCC treated at the Memorial Sloan-Kettering Cancer Center, 211 were reported to have undergone either complete (141 patients) or incomplete (70 patients) resection of recurrent tumor from a variety of metastatic sites (Kavolius et al, 1998). **In this series, complete or "curative" resection was associated with a longer OS (44% 5-year survival vs. 14% in patients undergoing incomplete resection); multivariate analysis also identified the presence of a solitary metastatic lesion, age younger than 60 years, and a disease-free interval of more than 1 year as favorable prognostic indicators. In addition, some studies have suggested that pulmonary metastases, smaller tumor size (<4 cm in one series), and metachronous lesions are predictors of better outcome after metastasectomy** (Friedel et al, 1999; Piltz et al, 2002; Murthy et al, 2005). Although not supported by convincing evidence of survival benefit from prospective studies, resection of isolated metastatic lesions is a reasonable and widely employed practice in selected RCC patients.

Palliative Surgery

Cytoreductive nephrectomy can be performed with palliative intent in patients with intractable pain, hematuria, constitutional symptoms, or a variety of paraneoplastic manifestations such as hypercalcemia, erythrocytosis, secondary thrombocytosis, or hypertension. Symptoms such as pain and laboratory abnormalities including hypercalcemia can often be effectively managed medically, whereas symptoms such as hematuria may be amenable to alternative treatment approaches (e.g., angioembolization). Furthermore, **resection of the primary renal tumor does not always result in clinical benefit;** for instance, in one series, only a little over half the patients (7/12) with hypercalcemia experienced clinically meaningful reductions in serum calcium levels (Walther et al, 1997a). **Cytoreductive nephrectomy with palliative intent is therefore performed relatively infrequently but is appropriate in some patients.**

Resection of metastases to alleviate pain or to forestall potentially life-threatening or debilitating complications is often indicated in a variety of situations. Patients who may benefit from noncurative resection of metastatic lesions include those with solitary brain metastases, metastatic lesions in weight-bearing bones or joints, or vertebral metastatic lesions with impending spinal cord or radicular compromise (Sundaresan et al, 1986; Kollender et al, 2000; Sheehan et al, 2003). Surgical resection is often combined with radiation and/or systemic therapy in many of the aforementioned situations.

Key Points: Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma

- Two randomized studies have demonstrated improved survival in carefully selected metastatic RCC patients undergoing cytoreductive nephrectomy followed by cytokine therapy (interferon-α) compared with those receiving cytokine therapy alone.
- Several patient and/or disease characteristics appear to influence outcome; patients with poor performance status, comorbid medical conditions, rapidly progressive disease, presence of brain metastases, and so on, are unlikely to benefit from this approach.
- The role of cytoreductive nephrectomy as a prelude to systemic therapy with currently available novel targeted agents is unclear and is the subject of ongoing clinical trials.

Key Points: Metastasectomy

- Resection of isolated metastatic lesions is appropriate in selected patients.
- Several retrospective studies have suggested that patients undergoing complete resection of isolated metastatic foci may experience long disease-free intervals, with median overall survival rates of 35% to 50% in some reports.
- Several factors are associated with an improved outcome after metastasectomy, including complete resection, presence of solitary metastatic lesions, age younger than 60 years, smaller tumor size, presence of pulmonary metastases, and development of metachronous metastatic disease.
- There are no prospective, randomized studies demonstrating a favorable outcome with metastasectomy. It is therefore possible that the favorable outcome after resection of limited metastatic disease may be a reflection of patient selection bias, differences in tumor biology and natural history, or other confounding factors not related to resection.

Key Points: Palliative Surgery in Advanced Renal Cell Carcinoma

- In some patients with advanced RCC, cytoreductive nephrectomy may help alleviate symptoms related to the primary tumor (e.g., intractable pain, hematuria) or paraneoplastic manifestations.
- However, nonsurgical options are often effective in palliating symptoms associated with RCC; cytoreductive nephrectomy is hence infrequently performed with purely palliative intent.
- Resection of metastatic lesions (often in combination with radiation or systemic therapy) is sometimes performed for relief of symptoms or to prevent life-threatening or disabling sequelae.

IMMUNOLOGIC APPROACHES IN THE MANAGEMENT OF ADVANCED CLEAR CELL RENAL CELL CARCINOMA

The host immune system has long been believed to play an important role in the causation and control of renal cell cancer. A report detailing spontaneous regression of metastatic lesions after radical nephrectomy provides perhaps the earliest evidence implicating the immune system in the regulation of kidney cancer. The phenomenon of spontaneous regression, thought to represent T- or B-cell mediated antitumor immunity, has sparked great enthusiasm over the years and generated several reports describing this phenomenon (Braren et al, 1974; Silber et al, 1975; Middleton, 1980; Robson, 1982; Snow and Schellhammer, 1982; Kavoussi et al, 1986; Marcus et al, 1993; Edwards et al, 1996). Although rare **(it is estimated that the true incidence of spontaneous regression is less than 1%)** and often transient, the presumed immunologic mechanisms underlying this event have nonetheless played an important part in the development of immunotherapeutic approaches in kidney cancer. The presence of immune cells, notably cytotoxic T lymphocytes, in resected tumors and the identification of tumor-associated antigens that can serve as human leukocyte antigen (HLA)-restricted targets on tumor cells for T cell—mediated cytotoxicity have also kindled interest in immune-based strategies in renal cell cancer (Finke et al, 1994; Boon et al, 1997; Ada, 1999; Rosenberg, 1999). Early clinical studies explored the efficacy of agents believed to act as nonspecific stimulators of the host immune system components, such as cytokines, with or without adoptive cellular therapy. More recently, investigators have evaluated a variety of novel approaches including allogeneic immunotherapy, vaccines, and modulators of T-cell function. Most immunotherapy strategies have been directed at clear cell RCC, and the utility of these approaches in non–clear cell variants remains to be explored.

Interferons

The interferons are a group of proteins with diverse biologic functions, including immunomodulatory properties. Interferon-α was one of the earliest cytokines to be evaluated for activity in RCC. Initial trials with interferon utilized leukocyte-derived interferon. The subsequent availability of recombinant interferon-α in the early to mid 1980s allowed investigators to evaluate higher doses of this cytokine in a series of phase 2 trials. **Initial trials demonstrated overall response rates of 16% to 26% in patients treated with interferon-α, and several subsequent trials have confirmed the activity of this agent, with response rates generally in the 10% to 15% range** (deKernion et al, 1983; Quesada et al 1983, 1985, 1989; Umeda and Niijima, 1986; Muss et al, 1987; Rosenberg et al, 1987; Figlin et al, 1988; Minasian et al, 1993; Motzer et al, 2002). **The limited long-term survival data available suggest that durable complete responses with this agent are relatively rare (<2%).** A variety of dosing schedules and routes have been evaluated to determine the optimal interferon regimen; no single mode of administration or dosing schedule has so far demonstrated superiority over others (Kirkwood et al, 1985; Umeda and Niijima, 1986; Muss et al, 1987; Minasian et al, 1993). Similarly, the addition of chemotherapy or other cytokines to interferon-α has failed to improve the outcomes seen with single-agent therapy (Rosenberg et al, 1989b; Sella et al, 1992; Ravaud et al, 1994, 1998; Ellerhorst et al, 1997; Tourani et al, 1998, 2003; Dorval et al, 1999; Négrier et al, 2000a, 2000b).

Several prospective, randomized trials evaluating the efficacy of interferon-α have demonstrated a modest but statistically significant improvement in outcome after treatment with this agent. A randomized phase III study that assigned 335 patients to receive either interferon-α or medroxyprogesterone demonstrated a higher response rate (14% vs. 2%) and OS (median 8.5 vs. 6 months, hazard ratio 0.72, $P = .017$) favoring the interferon arm of the study (Medical Research Council Renal Cancer Collaborators, 1999). A second study randomized 160 patients with metastatic RCC to receive vinblastine alone or in combination with interferon-α; a higher response rate (16% vs. 2.5%) and improved OS (median 16 vs. 9 months, $P = .0049$) with the addition of interferon was observed in this study (Table 50–4) (Pyrhonen et al, 1999). Two additional randomized studies suggested that vinblastine is unlikely to have contributed significantly to the activity of this combination by showing that survival was not improved with the addition of vinblastine to interferon-α (Neidhart et al, 1991; Fossa et al, 1992). Lastly, a meta-analysis of randomized trials of interferon against a variety of agents suggested that interferon-based therapy conferred a survival advantage (Coppin et al, 2005). **Despite its relatively modest activity, based on the just described data and relative ease of administration compared with IL-2, interferon was commonly the agent of choice in the initial treatment of metastatic RCC until the advent of VEGF pathway antagonists.**

Interleukin-2

Clinical trials in the early 1980s initially identified IL-2 as an active agent in RCC, with some IL-2–based regimens leading to objective response rates in excess of 30% (Rosenberg et al, 1989a, 1993). In a subsequent report detailing 255 patients treated on a series of

Table 50–4.
Summary of Results from Selected Randomized Trials of Interferon-α in Metastatic Renal Cell Carcinoma

STUDY	AGENT(S)	PHASE	NO. OF PATIENTS TOTAL (RANDOMIZED)	OVERALL RESPONSE RATE (%)	OVERALL SURVIVAL	
					Median (mo)	*P*
Medical Research Council, 1999	IFN vs. MPA	3	335 (167 vs. 168)	13 vs. 7	8.5 vs. 6.0	<.01
Pyrhonen et al, 1999	IFN + vinblastine vs. vinblastine	3	160 (79 vs. 81)	16 vs. 2.5	15.8 vs. 8.8	<.01
Neidhart et al, 1991	IFN vs. IFN + vinblastine	3	165 (82 vs. 83)	13 vs. 13	NA	NS
Fossa et al, 1992	IFN vs. IFN + vinblastine	3	178 (87 vs. 91)	11 vs. 24	12 vs. 12	NS

IFN, interferon; MPA, medroxyprogesterone acetate; NA, not available; NS, not significant.

phase 2 trials at the NCI, a more modest overall response rate of 15% (37/255 patients) was noted (Fyfe et al, 1996). **Several trials conducted by the NCI and the Cytokine Working Group as well as meta-analyses of published data have consistently demonstrated response rates in the range of 15% to 20%** (Lotze et al, 1986; Rosenberg et al, 1987, 1989a, 1993; Fisher et al, 1988; Dutcher et al, 1997a). **More importantly, 7% to 9% of patients receiving high-dose IL-2 are reported to have achieved complete regression of all metastatic tumor, with the majority of complete responders (>60%) demonstrating no evidence of disease recurrence on long-term follow-up** (Fisher et al, 1997, 2000; Rosenberg et al, 1998). There have also been reports of long-term disease-free remission in partial responders whose limited disease burden after IL-2 therapy rendered them amenable to resection of localized metastases. **High-dose IL-2 was approved by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic kidney cancer in 1992, based largely on its ability to induce durable complete responses in some patients.**

The initial studies with IL-2 were conducted using an intravenous bolus regimen with doses of 600,000 or 720,000 IU/kg administered every 8 hours as tolerated to a maximum of 15 doses. A major limitation of this dosing regimen is the considerable associated toxicity that has limited its widespread use. Vascular leak syndrome, and the resulting hypotension, third-space fluid retention, respiratory compromise, and multiorgan damage are some of the more problematic concomitants of IL-2 therapy and led to an unacceptably high treatment-related mortality rate (2% to 5%) in early studies with this agent (Rosenberg et al, 1987; Kammula et al, 1998). Subsequently, careful patient selection, intensive monitoring schemes, and early interventions with IV fluids, vasopressors, and antibiotics have served to significantly reduce mortality associated with IL-2 (Kammula et al, 1998). However, the significant morbidity and expense associated with delivering bolus high-dose IL-2 have led several investigators to explore alternative regimens aimed at reducing toxicity without compromising efficacy. Numerous single-arm phase 2 studies have evaluated a variety of alternative regimens, including daily subcutaneous administration and continuous intravenous infusion (Escudier et al, 1994a, 1994b, 1995; Atkins et al, 2001; Négrier et al, 2000b, 2005, 2008). Many of these studies have reported overall response rates of 10% to 30%, suggesting comparable efficacy to high-dose bolus administration based on data from historical controls. However, two randomized studies have demonstrated that, although well tolerated, lower-dose regimens are associated with lower overall response rates, as well with fewer durable, complete responses (Table 50–5) (Yang et al, 2003b; McDermott et al, 2005).

Attempts to enhance the efficacy of IL-2 therapy have led investigators to explore combination therapy with other cytokines, cytotoxic chemotherapy, and adoptive cellular immunotherapy. Early experience with combination cytokine therapy was promising, with one study reporting a 31% overall response rate in patients treated with high-dose bolus IL-2 and interferon (Rosenberg et al, 1989b). However, subsequent studies have indicated that this combination is more toxic and no more effective than IL-2 alone (Ravaud et al, 1994; Bukowski et al, 1997; Dutcher et al, 1997b; Tourani et al, 1998, 2003). A multicenter, randomized phase III study compared the efficacy of intermediate-dose IL-2 administered by continuous intravenous infusion with interferon-α or the combination in 425 patients with metastatic clear cell RCC (Négrier et al, 1998). **Although the combination of IL-2 and interferon resulted in a higher response rate (18.6%) and 1-year event-free survival (EFS 20%) compared with IL-2 (overall response rate 6.5%, 1-year EFS 15%) or interferon (overall response rate 7.5%, 1-year EFS 12%) alone, there was no significant difference in survival between the groups** (Fig. 50–3). Combination therapy also resulted in higher toxicity than either agent given alone. Regimens combining IL-2 and cytotoxic chemotherapy (particularly 5-fluorouracil [5-FU]) have been the subject of numerous studies. Unfortunately, reports of high response rates in initial studies (49% in a study using IL-2, interferon, and 5-FU) could not be reproduced in later studies (Atzpodien et al, 1993; Ellerhorst et al, 1997; Dutcher et al, 2000; Négrier et al, 2000a). Similarly, despite the promise of preclinical and early clinical studies, the addition of ex-vivo expanded tumor-infiltrating lymphocytes or lymphokine-activated killer cells to high-dose IL-2 has not reliably demonstrated improved clinical benefit and these approaches have been largely abandoned (Rosenberg et al, 1993; Law et al, 1995; Figlin et al, 1999).

Given the considerable toxicity associated with high dose IL-2 and the relatively small proportion of patients who derive benefit from this therapy, identification of predictors of response and

Table 50–5.

Summary of Results from Selected Randomized Trials of Interleukin-2 in Metastatic Renal Cell Carcinoma

STUDY	TREATMENT ARMS	NO. OF PATIENTS	DOSE, ROUTE, AND SCHEDULE	RESPONSE		OVERALL SURVIVAL	
				ORR	*P*	Median (mo)	*P*
Négrier et al, 1998	IL-2	138	18×10^6 IU/m^2/d × 5 days, CIV	6.5		12	
	IFN	147	18×10^6 IU three times a week, SC	7.5		13	.55
	IL-2 + IFN	140	18×10^6 IU/m^2/d × 5 days, CIV +6×10^6 IU three times a week, SC	18.6	.01	17	
Yang et al, 2003b	IL-2	156	720,000 U/kg every 8 hours × 5 days, IV bolus	21		NA	
	IL-2	150	72,000 U/kg every 8 hours × 5 days, IV bolus	13	.048	NA	.41
	IL-2	94	250,000 U/day × 5 days, SC, week 1 125,000 U/day × 5 days, SC, weeks 2 to 6	10	.033	NA	.38
McDermott et al, 2005	IL-2	96	600,000 U/kg every 8 hours × 5 days, IV bolus	23		17	
	IL-2+ IFN	96	5×10^6 IU/m^2 every 8 hours × 3, then 5×10^6 IU/m^2/day × 5 days/week, SC+ 5×10^6 IU three times a week, SC	10	.018	13	.21

CIV, continuous intravenous infusion; IFN, interferon-α; IL-2, interleukin-2; IV, intravenous; NA, not available; ORR, overall response rate; SC, subcutaneous.

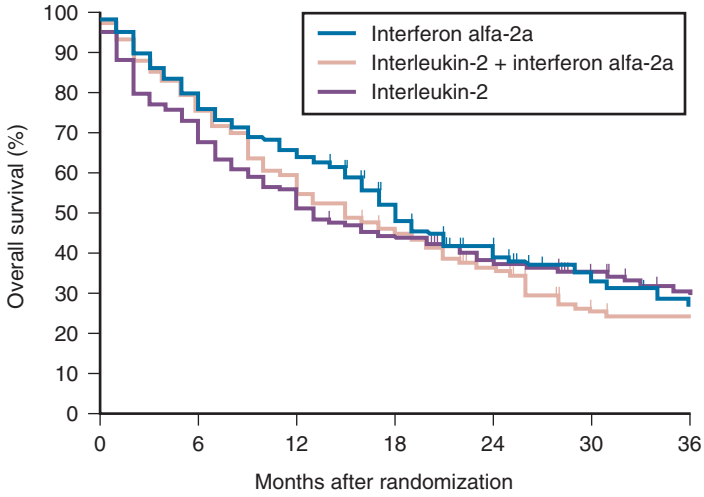


Figure 50–3. Kaplan-Meier curves for overall survival among 425 patients randomized to receive interleukin-2 alone, interferon-α alone, or both. (From Négrier S, Escudier B, Lasset C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. Groupe Français d'Immunotherapie. N Engl J Med 1998;338:1272–78.)

long-term outcome has received considerable attention. The predictive value of a variety of histologic, clinical, laboratory, and molecular parameters has been studied. **Patients with clear cell RCC appear most likely to benefit from IL-2 therapy,** although the exceedingly small number of patients with non–clear cell histologies typically enrolled in studies of IL-2 makes it difficult to draw definitive conclusions about efficacy in this subgroup of patients. **Patient performance status, number of metastatic sites, site of metastases, prior nephrectomy, and time from nephrectomy to systemic therapy are some of the factors that may impact outcome.** In one study, patients with more than one site of metastasis, those with metastatic disease within 1 year of diagnosis, and those with liver metastases had the worst outcome, with a median survival of 6 months (Négrier et al, 2002). Overexpression of carbonic anhydrase IX (CAIX or G250) has been observed in a retrospective analysis to be associated with a higher probability of response to IL-2 (Atkins et al, 2005). When combined with histologic features, CAIX expression was found to be predictive of IL-2 responsiveness and OS. The expression of CAIX is regulated by hypoxia-inducible factor (HIF), and both HIF and CAIX are upregulated in tumors with VHL loss; it is therefore unclear if CAIX expression influences the behavior of these tumors or is merely a surrogate for VHL dysfunction. Although intriguing, these data should be validated in prospective trials before CAIX and/or histologic parameters can be reliably used to select patients most likely to benefit from cytokine therapy.

The role of cytokine therapy in the current management of kidney cancer has changed with the availability of novel inhibitors of VEGF and mTOR pathways with activity in clear cell RCC. Single-agent interferon, the previous standard in many institutions, is no longer used in the first-line treatment of clear cell RCC. However, given the inability of newer targeted agents to induce durable responses, high-dose intravenous IL-2 remains a reasonable option in the initial therapy of carefully selected patients with metastatic clear cell RCC.

Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic hematopoietic stem cell transplantation allows the replacement of host or recipient immune and hematopoietic systems with those of a healthy, HLA-compatible donor. The therapeutic potential of hematopoietic stem cell transplantation lies largely in the ability of the transplanted donor graft to generate an allogeneic antitumor immune response known as the graft-versus-tumor effect. This approach has been used successfully with curative intent in a variety of hematologic malignancies (Thomas et al, 1977; Weiden et al, 1979, 1981). The ability of a variety of immune-based approaches to induce remissions in patients with RCC and evidence suggesting that the host immune system in these patients may be compromised and/or tolerant to tumor cells have led several investigators to evaluate allogeneic hematopoietic stem cell transplantation in kidney cancer.

The approach was initially studied by investigators at the National Heart, Lung and Blood Institute exploring the efficacy of reduced intensity hematopoietic stem cell transplantation in patients with treatment-refractory metastatic RCC. Eligible patients underwent reduced intensity conditioning with cyclophosphamide (120 mg/kg) and fludarabine (125 mg/m^2) followed by infusion of a granulocyte colony-stimulating factor–mobilized peripheral blood stem cell graft from a 5/6 or 6/6 HLA-matched sibling donor. The initial experience with hematopoietic stem cell transplantation in metastatic RCC was published by Childs and colleagues (2000). Ten of the first 19 patients treated with this transplant approach had tumor shrinkage, including 3 who had a complete response and 7 who had a partial response. As more recently reported, 74 patients have undergone hematopoietic stem cell transplantation for RCC at the National Institutes of Health. Of these, 73 patients have demonstrated durable engraftment, achieving 100% donor T-cell chimerism by day 100 posttransplant. Twenty-nine of 74 (39%) patients have had a disease response, including 7 complete (9%) and 22 partial responders (30%) (Takahashi et al, 2008). **Preliminary data suggest that disease response after hematopoietic stem cell transplantation is a clinically meaningful phenomenon because regression of metastatic RCC appears to be associated with a trend toward improved survival. Survival in nonresponders has been less than 6 months, in contrast to those achieving a partial response who survived a median 2.5 years posttransplant. Several durable responses have been noted, and the first patient who underwent a transplant remains in complete remission more than 10 years after the procedure.** Hematopoietic stem cell transplantation is associated with a variety of adverse events typically associated with conditioning chemotherapy (e.g., pancytopenia), a variety of opportunistic infections, and graft-versus-host disease (GVHD). Eight patients in the just-mentioned series died of transplant-related causes (transplant-related mortality of 11%), most due to GVHD and its attendant infectious complications. Several other trials have since confirmed the efficacy of this approach in RCC (Table 50–6) (Rini et al, 2001, 2002; Bregni et al, 2002; Artz et al, 2005; Barkholt et al, 2006). However, a Cancer and Leukemia Group B (CALGB) intergroup trial evaluating the feasibility of performing hematopoietic stem cell transplantation for metastatic RCC in a multi-institutional setting in the United States reported no responses in 22 patients undergoing hematopoietic stem cell transplantation from an HLA-matched sibling donor after cyclophosphamide/fludarabine–based conditioning (Rini et al,

Table 50–6.

Summary of Results from Selected Trials of Allogeneic Hematopoietic Stem Cell Transplantation in Metastatic Renal Cell Carcinoma

STUDIES	CONDITIONING AGENTS	GVHD PROPHYLAXIS	AGVHD (II-IV)	CGVHD	TRM	RESPONSE (PR OR CR)
Childs et al, 2000; Takahashi et al, 2008	Cy + Flu	CSP (First 25 patients) CSP + MMF (subsequent patients)	55%	21%	11%	39%
Artz et al, 2005; Rini et al, 2001, 2002	Cy + Flu	Tacro + MMF	22%	39%	14%	22%
Bregni et al, 2002	Cy + Flu + Thiotepa	CSP + MTX	86%	71%	0%	57%
Barkholt et al, 2006	Multiple fludarabine-based regimens	CSP ± MMF or MTX	40%	33%	16%	32%
Rini et al, 2006	Flu + Cy	Tacro + MTX	32%	23%	9%	0%

aGVHD, acute graft-versus-host disease; ATG, antithymocyte globulin; cGVHD, chronic graft-versus-host disease; CR, complete response; CSP, cyclosporine; Cy, cyclophosphamide; MMF, mycophenolate mofetil; MTX, methotrexate; PR, partial response; Tacro, tacrolimus; TRM, treatment-related mortality.

2006). Median OS was only 5.5 months, with most patients dying of disease progression (median time to progression of 3 months). Inclusion of a number of patients with multiple adverse prognostic factors, sparing use of donor lymphocyte infusions (only 2/22 patients received donor lymphocyte infusions despite disease progression in the majority), and inclusion of patients with non–clear cell histology are some of the factors that may account for the poor outcome observed in this trial. This trial clearly highlights the importance of appropriate patient selection and the need for identifying prognostic factors likely to predict for a favorable outcome. In a European multicenter study of 106 patients undergoing transplantation, chronic GVHD, good performance status (Karnofsky score = 80), administration of donor lymphocyte infusions, and fewer than three sites of metastatic disease were identified as factors favorably impacting survival (Barkholt et al, 2006). Given the high morbidity and mortality with this approach, careful patient selection is of great importance. **Hematopoietic stem cell transplantation remains an experimental approach in the management of RCC;** strategies for minimizing the toxicity associated with this procedure and maximizing antitumor effects are being explored and are required to render this approach more widely applicable.

MOLECULAR BASIS FOR TARGETED APPROACHES IN CLEAR CELL RENAL CELL CARCINOMA

The development of antagonists of the VEGF pathway in the treatment of clear cell RCC is an often-cited paradigm in the evolution of rational targeted therapeutic strategies and represents a logical progression from identification of a defective cellular pathway to rational drug design and structured clinical evaluation. The earliest clues to the central role played by VEGF in renal oncogenesis came from studies attempting to identify the genetic basis of the von Hippel-Lindau familial kidney cancer syndrome. **In the early 1990s, investigators at the National Cancer Institute studying families with von-Hippel-Lindau disease used genetic linkage analysis to identify germline mutations or deletions in the *VHL* gene as the basis for this disease** (Latif et al, 1993). Individuals carrying germline *VHL* mutations are at increased risk for developing tumors in multiple organs, including bilateral, multifocal clear cell kidney cancer. **The *VHL* gene is a classic tumor suppressor gene, with inactivation of the normal *VHL* allele in affected tissues by a somatic "second hit" required for tumor formation.**

The *VHL* gene resides on the short arm of chromosome 3 and encodes the VHL protein, which can be synthesized as two alternatively spliced variants (Latif et al, 1993; Gnarra et al, 1996; Iliopoulos et al, 1998; Linehan, 2003). One of the better-understood functions of the VHL protein is its association with elongins B and C and CUL2 to form a protein complex that serves to tag certain cellular proteins for delivery to and degradation by the ubiquitin system (Duan et al, 1995; Pause et al, 1997; Stebbins et al, 1999; Linehan, 2003; Kaelin, 2004). Proteins targeted for ubiquitin-mediated degradation include the α subunits of a group of transcriptionally active proteins known as hypoxia-inducible factors (HIFs) (Iliopoulos et al, 1996; Pause et al, 1997; Maxwell et al, 1999; Cockman et al, 2000; Ohh et al, 2000; Ivan et al, 2001; Jaakkola et al, 2001). In cells with intact VHL function, HIF levels are primarily controlled by ambient oxygen tension. In normoxic conditions, hydroxylation of key proline residues on HIF promotes its association with the VHL/elongin/CUL complex and subsequent degradation; conversely, hypoxia impedes prolyl hydroxylation of HIF and its subsequent degradation, leading to intracellular accumulation of HIF α subunits. **Mutations in *VHL* interfere with its binding to either HIF or elongin/CUL 2 and promote HIF accumulation even under normoxia. HIF accumulation, in turn, leads to the upregulation of a variety of proangiogenic and growth factors, including VEGF, platelet-derived growth factor (PDGF), transforming growth factor-α, Glut-1, and erythropoietin, which are believed to play critical roles in the development and progression of clear cell RCC** (Fig. 50–4) (Duan et al, 1995; Iliopoulos et al, 1996; Kaelin, 2004; Linehan et al, 2007). **Although originally identified as a germline defect in von Hippel-Lindau families, evidence of somatic *VHL* inactivation by mutation or promoter hypermethylation has been observed in a high proportion of sporadic clear cell tumors (91% in a recent series)** (Herman et al, 1994; Gnarra et al, 1996; Zhuang et al, 1996a, 1996b; Nickerson et al, 2008). The recognition of VHL loss as a central event in renal oncogenesis has paved the way for the development of novel agents targeting components of this pathway in the management of metastatic clear cell RCC.

TARGETED MOLECULAR AGENTS IN CLEAR CELL RENAL CELL CARCINOMA

Antagonists of the Vascular Endothelial Growth Factor Pathway

Bevacizumab

Bevacizumab, a humanized monoclonal antibody against VEGF-A, was the first VEGF pathway antagonist used in clinical trials to test the hypothesis that modulation of aberrantly expressed components of the VHL pathway would be associated with clinical activity in clear cell RCC. In a three-arm phase 2 study, patients with metastatic clear cell RCC whose disease had progressed after prior cytokine therapy were randomized to receive either one of two dose levels of bevacizumab (10 mg/kg or 3 mg/kg administered every 2 weeks intravenously) or placebo (Table 50–7) (Yang et al, 2003a). **An interim efficacy analysis performed after 116 patients (of a planned 240 patients) were enrolled in the study demonstrated a significantly longer progression-free survival (PFS) in patients assigned to 10 mg/kg bevacizumab compared with those receiving placebo (4.8 vs 2.5 months, *P* < .001)** (Fig. 50–5). There was no corresponding improvement in OS, although the crossover design used in this trial (patients progressing on placebo were allowed to cross over to the bevacizumab arm) may have influenced this outcome. The overall response rate in patients receiving bevacizumab was modest (objective response rate of 10%, all in patients assigned to the 10 mg/kg dose). The agent was well tolerated, with bleeding, hypertension, fatigue, and proteinuria being some of the more common adverse events reported. Single-agent bevacizumab has not been compared with either cytokines (often used in first-line treatment before the advent of VEGF pathway antagonists) or other VEGF pathway antagonists such as sunitinib in prospective trials.

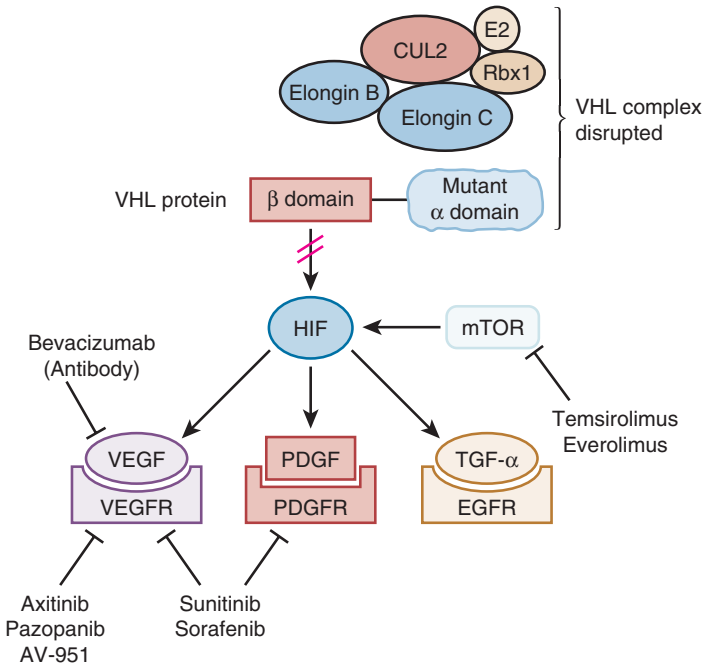


Figure 50–4. Targeting the VHL pathway in clear cell renal cell carcinoma. Loss of VHL activity leads to accumulation of HIF and several proangiogenic and growth factors that can serve as targets for anticancer drugs. HIF can also be upregulated by mTOR, which promotes HIF translation. (Adapted from Linehan WM, Bratslavsky G, Pinto PA, et al. Molecular diagnosis and therapy of kidney cancer. Annu Rev Med 2010;61:329–43.)

Several strategies for improving the efficacy of bevacizumab have been explored, including combination with cytokines (interferon-α) and other targeted agents (e.g., erlotinib, a small molecule inhibitor of epidermal growth factor receptor tyrosine kinase activity). A single-arm phase 2 study of bevacizumab plus erlotinib showed promising activity with an overall response rate of 25% (higher than would be expected with bevacizumab alone based on historical data) and median PFS of 11 months (Hainsworth et al, 2005). However, a subsequent randomized phase 2 study failed to demonstrate the superiority of this combination (median PFS 9.9 months) over bevacizumab alone (median PFS 8.5 months, *P* = .58) (Bukowski et al, 2007). Two large randomized phase 3 studies have compared the combination of bevacizumab and interferon-α to interferon-α alone (Table 50–8). **In a Cancer and Leukemia Group B study (CALGB 90206) of 752 patients with previously untreated metastatic clear cell RCC randomized to one of two treatment arms, a higher response rate (25.5% vs. 13.1%, *P* < .0001) and PFS (8.5 months vs. 5.2 months, *P* < .0001) were observed in**

Table 50–7.

Summary of Selected Studies of Bevacizumab-Based Regimens in Metastatic Renal Cell Carcinoma

STUDY	AGENT(S)	PHASE	STUDY POPULATION	NO. OF PATIENTS	OVERALL RESPONSE RATE (RECIST)*	MEDIAN PFS (MO)*	MEDIAN OS (MO)*
Yang et al, 2003a	Bev (10 mg/kg) vs. Bev (3 mg/kg) vs. placebo	Randomized, 3-arm phase 2	Cytokine-refractory clear cell	116	10% vs. 0% vs. 0%	**4.8 vs. 3.0 vs. 2.5**	
Escudier et al, 2007b	Bev + IFN-α vs. IFN-α	Randomized phase 3	Previously untreated clear cell	649	**31% vs. 13%**	**10.2. vs. 5.4**	NR vs. 19.8
Rini et al, 2008a	Bev + IFN-α vs. IFN-α	Randomized phase 3	Previously untreated clear cell	732	**26% vs. 13%**	**8.5. vs. 5.2**	NA
Bukowski et al, 2007	Bev + Erlotinib vs Bev	Randomized phase 2	Previously untreated clear cell	104	14% vs. 13%	9.9 vs. 8.5	20 vs. NR

*Statistically significant differences indicated in bold.
Bev, bevacizumab; IFN-α; interferon-α; NA, not available; NR, not reached; OS, overall survival; PFS, progression-free survival.

patients assigned to bevacizumab plus interferon-α compared with those receiving interferon-α alone (Rini et al, 2008a). **A multicenter European trial (AVOREN) with a similar design also reported similar results with PFS (10.2 vs. 5.4 months, *P* = .0001) and objective response rate (31% vs. 13%) favoring the combination arm** (Fig. 50–6) (Escudier et al, 2007b). Updated survival data from both trials were recently reported, demonstrating no improvement in overall survival associated with the addition of bevacizumab to interferon (Escudier et al, 2010; Rini et al, 2010). While neither study permitted crossover of patients assigned to interferon-α at progression, a significant number of patients (>60%) subsequently received anticancer therapy off protocol, potentially confounding overall survival analysis. Both trials reported a higher incidence of some grade 3 adverse events such as hypertension, fatigue, anorexia, and asthenia in patients receiving combination therapy. Both the CALGB and Avoren trials were large, well-designed, and well-conducted multicenter studies that suggest that the addition of bevacizumab to interferon may be associated with clinical benefit (i.e., improvement in PFS). However, these trials did not include an arm with bevacizumab alone (owing to insufficient evidence of single-agent activity at the time these trials were designed to justify a bevacizumab-only arm), making it difficult to determine if inclusion of interferon in this regimen, with its attendant toxicities, adds meaningful clinical benefit. Interestingly, the median PFS observed in the combination arm of the CALGB trial (8.5 months) is similar to that observed with bevacizumab alone in a phase 2 trial of previously untreated patients with clear cell RCC (Bukowski et al, 2007). Lastly, bevacizumab (either alone or in combination with interferon) has not been compared prospectively with VEGF receptor (VEGFR) antagonists such as sunitinib, arguably the current standard of care for most newly diagnosed patients with metastatic clear cell RCC. **Bevacizumab is not widely used as a single agent in the initial therapy for metastatic clear cell RCC but may have a role in patients who have failed standard therapy with first-line VEGFR antagonists, either alone or in combination with other agents, particularly interferon. Ongoing and future trials may help determine the best use of this agent in the overall management of patients with clear cell RCC.**

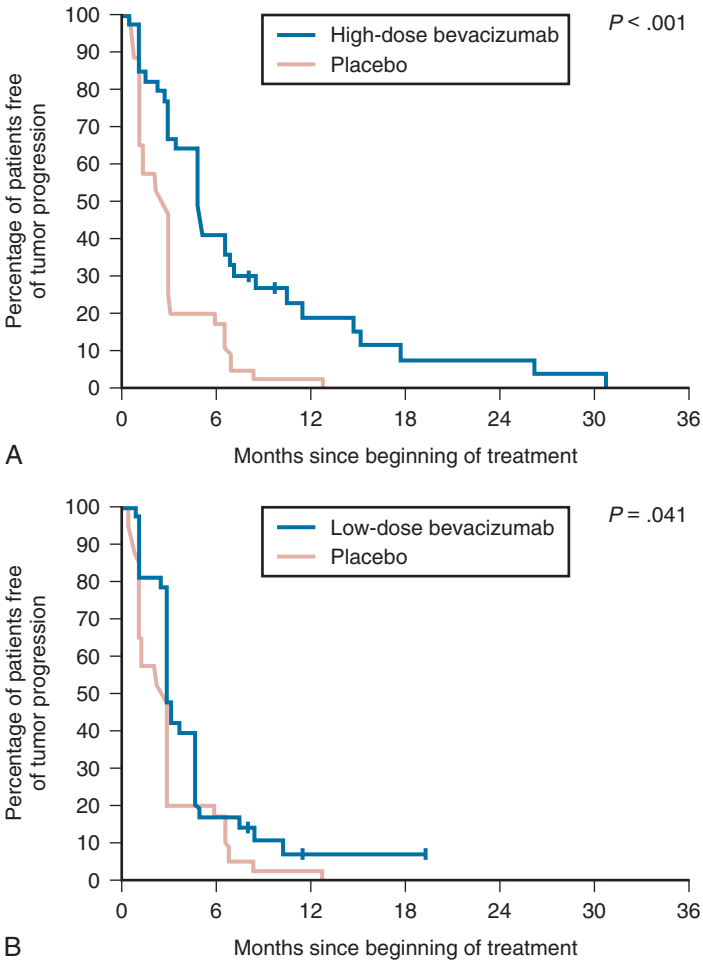


Figure 50–5. Kaplan-Meier analysis of 39 patients assigned to high-dose bevacizumab (10 mg/kg, **A**) and of 37 patients assigned to low-dose bevacizumab (3 mg/kg, **B**) compared with 40 patients assigned to receive placebo. (From Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med 2003a;349:427–34.)

Sorafenib

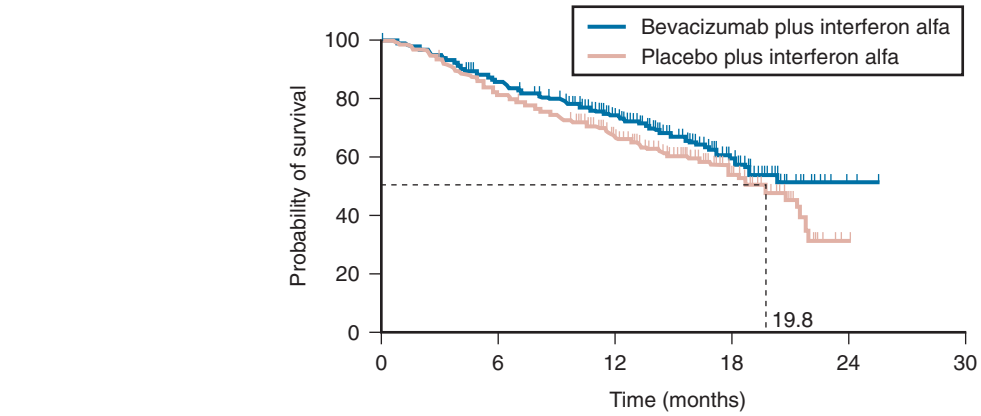
Sorafenib is an oral receptor kinase inhibitor with activity against VEGFR2, PDGF receptor-β, and raf-1. A phase 2 trial using a randomized discontinuation design provided initial evidence that sorafenib is active in RCC (see Table 50–8) (Ratain et al, 2006). Two hundred and two patients were enrolled on this trial, and all of them received 400 mg of sorafenib twice daily for the first 12 weeks. Sixty-five patients who demonstrated stable disease at the end of this period (defined in this trial as within ± 25% of baseline) were then randomized to either continued treatment with sorafenib or to placebo. Patients randomized to sorafenib had a superior PFS (24 weeks) versus

Table 50–8.

Summary of Selected Studies of Sorafenib in Metastatic Renal Cell Carcinoma

STUDIES	AGENT(S)	PHASE	STUDY POPULATION	NO. OF PATIENTS	OVERALL RESPONSE RATE (RECIST)*	MEDIAN PFS (MO)*	MEDIAN OS (MO)*
Ratain et al, 2006	Sorafenib vs. placebo	Phase 2 randomized discontinuation	Treatment-refractory, all histologic subtypes	202		**6 vs. 1.5**	NA
Escudier et al, 2007a, 2009a	Sorafenib vs. placebo	Randomized phase 3	Cytokine-refractory clear cell	903	10% vs. 2%	**5.5 vs. 2.8**	17.8 vs. 15.2
Escudier et al, 2009b	Sorafenib vs. IFN-α	Randomized phase 2	Previously untreated clear cell	189	5% vs. 9%	5.7 vs. 5.6	NA

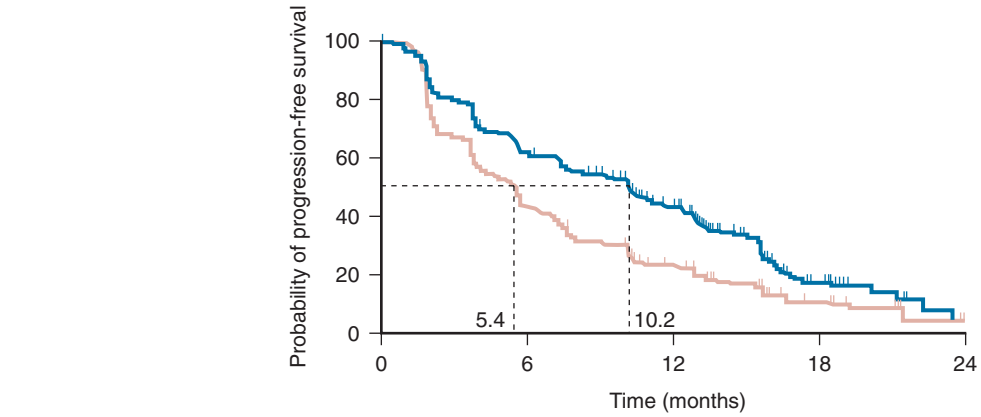
*Statistically significant differences indicated in bold.
IFN-α, interferon-α; NA, not available; NR: not reached; OS: overall survival; PFS: progression-free survival.



Number of patients at risk

Placebo plus interferon alfa	322	262	176	53	1	0
Bevacizumab plus interferon alfa	327	275	19t7	60	2	0

A



Number of patients at risk

Placebo plus interferon alfa	322	137	59	15	0
Bevacizumab plus interferon alfa	327	196	107	18	0

B

Figure 50–6. Kaplan-Meier analysis of **(A)** overall survival and **(B)** progression-free survival in 649 patients assigned to receive interferon-α alone or in combination with bevacizumab. (From Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 2007b;370:2103–11.)

those receiving placebo (6 weeks, $P = .0087$). A global, multicenter, placebo-controlled randomized phase 3 trial with 903 patients (the TARGET study) was subsequently undertaken to evaluate the efficacy of sorafenib in patients with metastatic RCC who had previously received cytokine therapy (Fig. 50–7) (Escudier et al, 2007a). **This trial echoed the results seen in the phase 2 trial, with patients randomized to receive sorafenib experiencing a longer PFS (median 5.5 months) versus those receiving placebo (2.8 months, $P < .01$) at a planned interim analysis.** After this interim analysis patients progressing on placebo were allowed to cross over to receive sorafenib. **Mature survival data from this trial were recently presented and demonstrated no significant difference in OS between the two groups (17.8 months for sorafenib vs. 15.3 months with placebo, $P = .146$) in an intent-to-treat analysis** (see Fig. 50–7) (Escudier et al, 2009a). However, if patients who crossed over from placebo to sorafenib were censored, the survival data demonstrated a statistically significant advantage favoring sorafenib (median OS 17.8 vs. 14.3 months, $P = .029$). Results from this exploratory "pre-crossover" survival analysis suggest that the survival end point may have been influenced by the crossover design. Overall response rate to sorafenib in this trial was relatively low, with 10% of patients experiencing a partial response; however, more than 70% of patients receiving sorafenib had some degree of tumor regression. **The side effect profile of sorafenib is comparable to that of other agents in this class and includes hypertension, fatigue, rash, hand-foot syndrome, and diarrhea. The efficacy of sorafenib in the first-line setting was investigated in a randomized phase 2 study that assigned 189 previously untreated patients with metastatic clear cell RCC to receive either sorafenib or interferon-α** (Escudier et al, 2009b). **Although patients receiving sorafenib had a higher likelihood of achieving tumor regression (68% vs. 39%), PFS in the two groups was nearly identical (median 5.7 months for sorafenib vs. 5.6 months for interferon, P = NS)** (Table 50–9). **Although sorafenib is FDA-approved for the treatment of advanced kidney cancer, its precise role in the management of these patients remains to be determined in view of the plethora of VEGFR antagonists currently available or under investigation.** Dose-intensive regimens of sorafenib (up to 800 mg twice daily) are being explored in an attempt to enhance

the efficacy of this agent, but to date there is no convincing evidence that higher doses offer additional clinical benefit. **Currently, sorafenib is infrequently used in the first-line setting.** Anecdotal evidence and small case series suggest that patients whose disease has progressed on other VEGFR inhibitors may respond favorably to sorafenib, and the agent is commonly used in patients whose disease has progressed on sunitinib or similar agents.

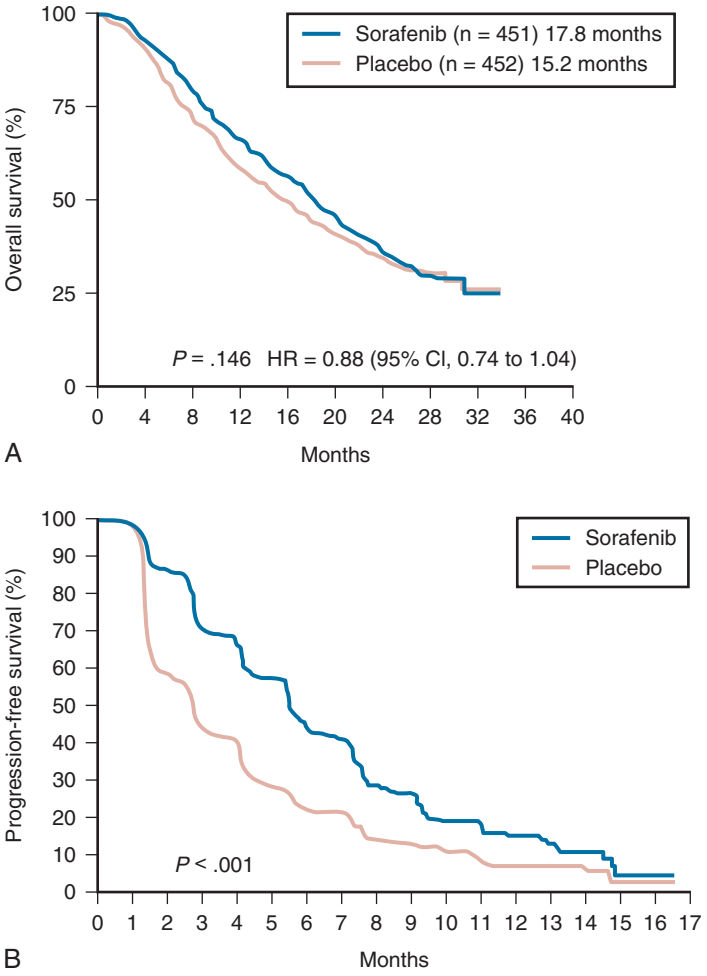


Figure 50–7. Kaplan-Meier analysis of overall survival (**A**) and progression-free survival (**B**) in 903 metastatic renal cell carcinoma patients randomized to sorafenib or placebo. (From Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol 2009a;27:3312–18; and Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007a;356:125–34.)

Sunitinib

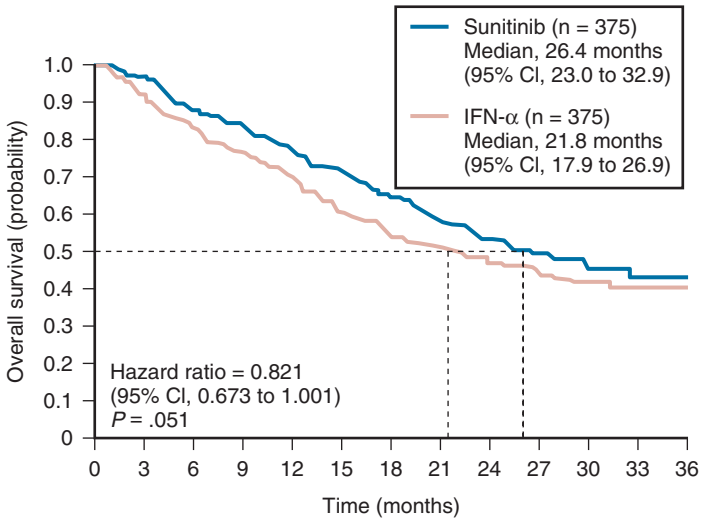
Sunitinib is currently the most widely used oral VEGFR kinase inhibitor in the initial treatment of metastatic clear cell RCC. It is a potent inhibitor of VEGFR2, PDGFR-β, c-*KIT*, and fms-like tyrosine kinase-3. As with sorafenib, simultaneous targeting of VEGF and PDGF pathways by this agent is likely to act synergistically in inhibiting tumor angiogenesis, by directly disrupting VEGF-mediated vascular endothelial development and proliferation and by interfering with vascular pericyte function, which is dependent on the integrity of PDGF signaling. Initial evaluation of sunitinib was undertaken with two single-arm open-label phase 2 trials in patients with metastatic RCC, most of whom had previously received cytokine therapy (Motzer et al, 2006a, 2006b). Sunitinib was administered orally at a dose of 50 mg/day during the first 4 weeks of a 6-week cycle on both trials (see Table 50–9). Remarkably high overall response rates (30% to 40%) with a median PFS of more than 8.5 months were observed in these trials, leading to the approval of this agent for treatment of advanced RCC by the FDA. A landmark phase 3 randomized trial comparing sunitinib with interferon-α as first-line therapy in patients with metastatic clear cell RCC further demonstrated the activity of sunitinib in this patient population (Motzer et al, 2007). In this study, 750 patients were randomized to receive either sunitinib or interferon-α. **An interim analysis based on independent, third-party radiologic assessment demonstrated a significantly superior PFS (median 11 months vs, 5 months, *P* = .001) and overall response rate (31% vs. 6%, *P* = .001) favoring the sunitinib arm** (Fig. 50–8). **Gastrointestinal events, particularly diarrhea, dermatologic manifestations such as rash and hand-foot syndrome, constitutional symptoms such as fatigue and asthenia, and hypertension were the most commonly adverse events associated with sunitinib, whereas bone marrow suppression, decline in left ventricular ejection fraction, and hypothyroidism were other notable side effects. Sunitinib also performed better than interferon in a quality of life assessment conducted as part of the study. Mature survival data from this study were recently reported and demonstrated superior OS in the sunitinib study arm based on an intent-to-treat analysis (median OS 26.4 vs. 21.8 months, *P* = .051)** (Motzer et al, 2009). **Based on these data,**

Table 50–9.

Summary of Selected Studies of Sunitinib in Metastatic Renal Cell Carcinoma

STUDIES	AGENT(S)	PHASE	STUDY POPULATION	NO. OF PATIENTS	OVERALL RESPONSE RATE (RECIST)*	MEDIAN PFS (MO)*	MEDIAN OS (MO)*
Motzer et al, 2007, 2009	Sunitinib vs. IFN-α	Randomized phase 3	Previously untreated clear cell	750	**31% vs. 6%**	**11 vs. 5**	**26.4 vs. 21.08**
Motzer et al, 2006a	Sunitinib	Single-arm phase 2	Cytokine-refractory clear cell	63	40%	8.7	NA
Motzer et al, 2006b	Sunitinib	Single-arm phase 2	Cytokine-refractory clear cell	106	44%	8.1	NA

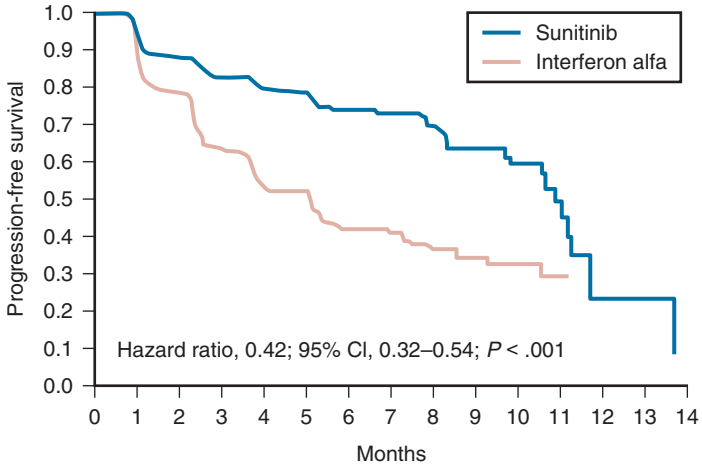
*Statistically significant differences indicated in bold.
NA, not available; OS, overall survival; PFS, progression-free survival.



No. of deaths/
No. at risk

Sunitinib	0/375	44/326	38/283	48/229	42/180	14/61	4/2
IFN-α	0/375	61/295	46/242	52/187	25/149	15/53	1/1

A



No. at risk

Sunitinib	375	235	90	32	2
Interferon alfa	375	152	42	18	0

B

Figure 50–8. Kaplan-Meier analysis of overall survival **(A)** and progression-free survival **(B)** in 750 previously untreated patients with metastatic renal cell carcinoma receiving either sunitinib or interferon-α. (From Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27:3584–90; and Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115–24.)

sunitinib has become the most widely used agent in the initial management of metastatic clear cell RCC patients in the United States.

Other VEGF Pathway Antagonists

Agents such as sunitinib and sorafenib have activity against a wide array of target molecules, some of which may not be relevant in clear cell RCC. Although these agents are relatively well tolerated when compared with conventional cytotoxic chemotherapy, dose reductions and termination of treatment due to toxicity are not infrequently warranted in patients receiving these drugs. **A variety of newer agents with selective activity against the VEGFR family have recently gained attention as a possible means of diminishing the side effects associated with therapy without compromising efficacy** (Table 50–10). **Axitinib** is an oral small molecule tyrosine kinase inhibitor of VEGFR1, VEGFR2, and VEGFR3. In a phase 2 trial of axitinib in 52 patients with advanced kidney cancer, an overall response of 44%, including two complete responses (4%), and a median time to progression of 15.7 months were reported (Rixe et al, 2007). Most patients treated on this study displayed some degree of tumor shrinkage, and many had been pretreated with either IL-2 or interferon. Diarrhea, fatigue, and hypertension were the most commonly encountered grade 3 and 4 events and were amenable to medical management in most patients. Several other agents with selective activity against the VEGFR family are also under investigation. One agent in this class, **pazopanib,** was the subject of a recent randomized, double-blind, placebo-controlled phase 3 trial in patients with metastatic clear cell RCC who had received no or one prior cytokine-based therapy (Sternberg et al, 2010). In the 405 patients randomized (2:1) to receive either pazopanib or placebo, PFS (median 9.4 months vs. 4.2 months, *P*

Table 50–10.

Summary of Selected Studies of Selective VEGFR Receptor Antagonists in Metastatic Renal Cell Carcinoma

STUDY	AGENT(S)	PHASE	STUDY POPULATION	NO. OF PATIENTS	OVERALL RESPONSE RATE (RECIST)*	MEDIAN PFS (MO)*	MEDIAN OS (MO)*
Sternberg et al, 2010	Pazopanib vs. placebo	Randomized phase 3	Metastatic clear cell RCC patients with 0-1 prior cytokine therapy	435	**30% vs 3%**	**9.2 vs 4.2**	NA
Bhargava et al, 2009	AV-951 vs. placebo	Phase 2 randomized discontinuation	Previously untreated metastatic RCC of all histologies	272	28%	NA	NA
Rixe et al, 2007	Axitinib	Single arm phase 2	Previously untreated clear cell RCC	52	44%	15.7	29.9

*Statistically significant differences indicated in bold.
NA, not available; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma.

Table 50–11.

Summary of Selected Studies of mTOR Inhibitors in Metastatic Renal Cell Carcinoma (RCC)

STUDY	AGENT(S)	PHASE	STUDY POPULATION	NO. OF PATIENTS	OVERALL RESPONSE RATE (RECIST)*	MEDIAN PFS (MO)*	MEDIAN OS (MO)*
Hudes et al, 2007	Tem vs. IFN-α vs. tem/IFN-α	Randomized phase 3	Poor prognosis, previously untreated, all histologic subtypes	626	8.6% vs. 4.8% vs. 8.1%	**5.5 vs. 3.1 vs. 4.7**	**10.9 vs. 7.3** vs. 8.4
Motzer et al, 2008b	Everolimus vs. placebo	Randomized phase 3	Clear cell RCC refractory to VEGF-targeted therapy	410	1% vs. 0%	**4.0 vs. 1.9**	NR vs. 8.8

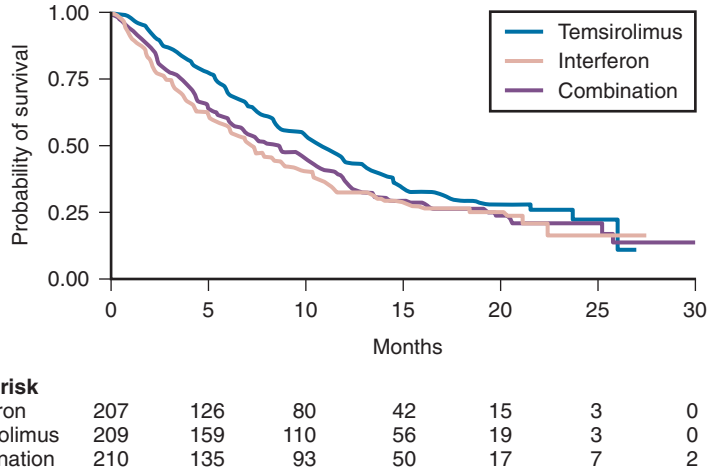
*Statistically significant differences indicated in bold.
IFN-α, interferon-α; NR, not reached; OS, overall survival; PFS, progression-free survival; tem, temsirolimus.

= .0000001) and response rates (30% vs. 3%) clearly favored the pazopanib study arm. Furthermore, reported toxicities were mild, with very few grade 3 and 4 adverse events encountered. **Tivozanib (AV-951),** yet another inhibitor of VEGFR1 to VEGRF3, has been evaluated in a phase 2 randomized discontinuation trial with demonstration of activity in RCC as well as an appealing adverse event profile (Bhargava et al, 2009). **The approach directed at a single type of growth factor receptor has the potential to provide a strategy for precisely targeting a component of the VHL pathway in clear cell kidney cancer while avoiding the toxicity of multiple kinase inhibitors. Prospective randomized trials of selective VEGFR inhibitors are required to determine if these agents offer tangible advantages over currently FDA-approved agents.**

Inhibitors of the Mammalian Target of Rapamycin

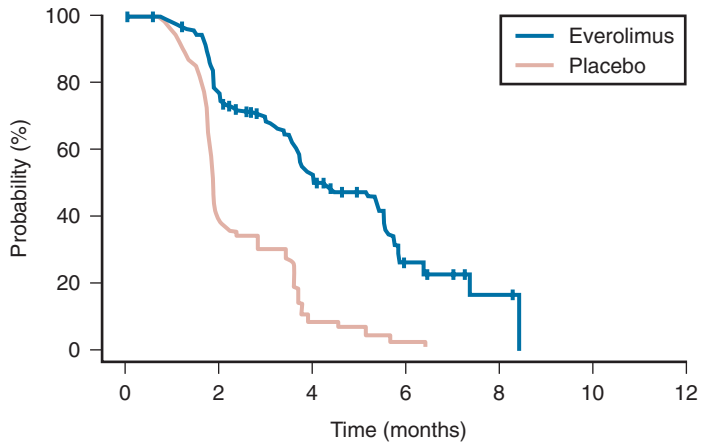
mTOR is a key intracellular protein that is a component of several signaling cascades including those mediating the effects of some growth factors. **It appears to play a role in regulating translation and stability of HIF-1α, and preclinical models have suggested that growth inhibition occurring in response to mTOR inhibitors correlates with a block in HIF-1α translation** (Hudson et al, 2002; Thomas et al, 2006). Two analogues of sirolimus, **temsirolimus** and **everolimus,** have been clinically evaluated with demonstrable activity in RCC.

A phase 2 trial of **temsirolimus** evaluated three different doses (25 mg, 75 mg, and 250 mg per week administered intravenously) in 111 patients assigned randomly to one of the dose levels (Table 50–11). The overall response rate observed on this trial was modest (7%, including one patient with a complete response), and the median PFS was 15 months (Atkins et al, 2004). Responses and PFS appeared to be independent of temsirolimus dose. An exploratory subgroup analysis based on stratification of patients according to MSKCC risk groups revealed that patients in the poor-risk group had a longer median OS compared with historical controls receiving interferon-α (8.2 vs. 4.9 months). Based on this observation, a three-arm randomized phase 3 trial of 626 patients with three or more predefined poor risk features was undertaken (Hudes et al, 2007). Patients with previously untreated metastatic kidney cancer of all histologic subtypes were eligible and randomized to receive temsirolimus alone (25 mg intravenously every week), interferon-α alone (up to 18 million units subcutaneously three times a week) or temsirolimus (15 mg intravenously every week) plus interferon-α (6 million units subcutaneously three times a week). PFS was superior in both temsirolimus-containing arms compared with interferon alone (median 3.8 months vs. 1.9 months). **Importantly, the trial also demonstrated a significantly higher OS in the temsirolimus arm compared with the interferon-only arm (median OS 10.9 vs. 7.3 months, *P* = .008), while the addition of temsirolimus did not appear to significantly alter OS compared with interferon alone (median OS 8.4 vs. 7.3 months, *P* = .70)** (Fig. 50–9). Temsirolimus was fairly well tolerated, and most



No. at risk							
Interferon	207	126	80	42	15	3	0
Temsirolimus	209	159	110	56	19	3	0
Combination	210	135	93	50	17	7	2

Figure 50–9. Kaplan-Meier estimates of overall survival in 626 metastatic renal cell carcinoma patients with adverse prognostic features randomized to receive temsirolimus alone, interferon-α alone, or combination therapy. (From Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271–81.)



Number at risk							
Everolimus	272	132	47	8	2	0	0
Placebo	138	32	4	1	0	0	0

Figure 50–10. Kaplan-Meier estimates of progression-free survival in 410 patients with metastatic renal cell carcinoma randomized to everolimus or placebo. (From Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008b;372:449–56.)

common adverse events such as mucositis, fatigue, rash, hyperglycemia, hypophosphatemia, hypercholesterolemia, and pulmonary complications were amenable to medical and/or supportive measures. **Based on these data, temsirolimus was approved by the U.S. FDA for the treatment of patients with metastatic RCC, and the agent is a reasonable front-line choice in patients presenting with poor-risk features.**

Everolimus is an orally bioavailable inhibitor of mTOR. It was the subject of a phase 3 trial in patients with metastatic clear cell RCC whose disease had progressed after therapy with sunitinib, sorafenib, or both (Motzer et al, 2008b). Patients were randomized to receive either everolimus, 10 mg once daily (n = 272), or placebo (n = 138) (see Table 50–11). **The trial was stopped after an interim analysis demonstrated superior PFS in the everolimus arm (median 4 months) compared with the placebo arm (median 1.9 months)** (Fig. 50–10). At the time of this analysis, median survival had not been reached in the everolimus group and was 8.8 months for the placebo group; OS was not significantly different in the two groups. **Although the agent offers only a modest improvement in PFS in patients progressing on first-line VEGFR antagonists, it is nonetheless a reasonable therapeutic option and has been approved by the U.S. FDA for this indication.**

Combination and Sequential Therapy with Agents Targeting the VHL Pathway

Combinations of two or more classes of agents with activity centered on different components of the VHL pathway provides an attractive strategy that might serve to increase efficacy as well as eliminating potential mechanisms of resistance. **A major limitation of this approach is the overlapping toxicity profile of several drugs, necessitating significant dose reductions of individual drugs** (Feldman et al, 2009; Patel et al, 2009). Ongoing trials will determine if the synergy engendered by combination therapy can adequately offset the effects of dose reduction.

Given the profusion of agents with single-agent activity in RCC, identifying the optimal sequencing of these agents is a question of considerable importance. A randomized study has demonstrated that everolimus can prolong PFS compared with placebo in patients who have progressed on first-line VEGFR antagonists (Motzer et al, 2008b). Smaller retrospective analyses have suggested that a proportion of patients who have progressed on one VEGF pathway inhibitor may benefit from a second agent targeting the same pathway (Rini et al, 2008b; Tamaskar et al, 2008). Carefully designed clinical trials are required to identify the most

effective strategies for sequencing multiple agents, as well as to categorize patients most likely to benefit from a given sequence based on molecular characterization of their tumors.

Other Treatment Options in Patients with Clear Cell Renal Cell Carcinoma

Chemotherapy

Conventional cytotoxic chemotherapy has been largely ineffective in the management of clear cell RCC. Numerous chemotherapeutic agents including 5-FU, platinum compounds, gemcitabine, vinblastine, and bleomycin have been evaluated as single agents in this disease but have failed to demonstrate clinically meaningful activity; a wide array of combination chemotherapy regimens have fared little better (Haas et al, 1976; Hahn et al, 1977; Zaniboni et al, 1989; Mertens et al, 1993, 1994; Amato, 2000; Rini et al, 2000, 2005; Stadler et al, 2006). **Comprehensive meta-analyses of chemotherapy trials in RCC indicate the overall response rate is 5.5% to 6.0%** (Yagoda et al, 1995). Although the mechanisms underlying this profound chemoresistance have not been fully elucidated, overexpression of the multidrug resistance gene *(MDR)* has been proposed as one possible culprit (Fojo et al, 1987). However, the addition of MDR inhibitors such as toremefine, cyclosporine, and verapamil to conventional chemotherapeutic agents has failed to improve their efficacy, suggesting that other, as yet unrecognized, factors may be at play (Braybrooke et al, 2000). **Cytotoxic chemotherapy has no role in the current management of most patients with clear cell RCC.** One situation in which chemotherapy may bear further investigation is in patients whose tumors demonstrate a sarcomatoid component; a small case series has suggested promising activity for gemcitabine-based chemotherapy in this setting, prompting further study of this approach (Nanus et al, 2004).

Hormonal Therapy

Hormonal therapy had been the subject of trials in RCC in the 1970s and 1980s, preceding the advent of cytokines. These studies were prompted by both the lack of effective therapies for kidney cancer and by the belief that a male preponderance (kidney cancer occurs approximately twice as frequently in males) implied a hormonal basis for this malignancy. Hormonal agents such as medroxyprogesterone have been noted to induce tumor regressions in a small minority of patients, but overall response rates are too low (approximately 2%) to have meaningful clinical impact in most patients (Schomburg et al, 1993; Harris, 1983; Medical Research Council Renal Cancer Collaborators, 1999; Braybrooke et al, 2000). **Progestational and other hormonal agents have no role in the current management of renal cell cancer.**

SYSTEMIC THERAPY FOR NON–CLEAR CELL VARIANTS OF RENAL CELL CARCINOMA

Non–clear cell subtypes of kidney cancer are relatively rare (constituting approximately 15% of all kidney cancer) and have been the subject of few prospective studies. Given the unavailability of agents of proven efficacy in papillary, chromophobe, and other rare histologic subtypes, patients with non–clear cell renal tumors often receive agents with activity in clear cell RCC.

Recent advances in our understanding of some subtypes of RCC are bound to lead to a more rational approach to their management. As with clear cell RCC, hereditary forms of papillary and chromophobe RCC may hold the key to the identification of critical molecular events leading to these tumors both in familial and sporadic settings (Linehan, 2003; Linehan et al, 2009). Hereditary papillary renal cancer (HPRC) is a familial condition characterized by the predisposition of affected individuals to develop bilateral, multifocal papillary type I RCC. **HPRC is characterized by the presence of activating germline mutations in the tyrosine kinase domain of the proto-oncogene c-*MET*, which is located on chromosome 7; this is usually accompanied by nonrandom duplication of the chromosome containing the mutated allele** (Schmidt et al, 1997, 1998, 1999, 2004; Zhuang et al, 1998; Linehan, 2003; Linehan et al, 2009). c-MET is a cell surface receptor that is normally activated on binding its ligand, hepatocyte growth factor (HGF) but is rendered constitutionally active in the presence of mutations in the kinase domain of this protein (Bottaro et al, 1991; Dharmawardana et al, 2004; Peruzzi and Bottaro, 2006; Giubellino et al, 2009). The HGF/c-MET pathway is involved in regulating a variety of biologic functions, including cell growth, proliferation, and motility (Fig. 50–11) (Jeffers et al, 1998; Giubellino et al, 2009). Somatic c-MET alterations have been noted in a proportion of patients with sporadic papillary RCC, with activating mutations identified in approximately 13% of papillary tumors in one series. Trisomy 7 (both *HGF* and c-MET are located on chromosome 7) has been described in more than two thirds of papillary tumors and may represent an alternative mechanism contributing to activation of the c-MET pathway (Kovacs et al, 1991; Henke and Erbersdobler, 2002).

VEGFR inhibitors active in clear cell RCC do not seem to be effective in papillary RCC. Sorafenib and sunitinib were shown to have minimal activity in retrospective studies of papillary RCC patients (Choueiri et al, 2008a). Prospective phase 2 trials with sunitinib have demonstrated that this agent is associated with low response rates (5% to 10%) in papillary RCC. The Southwest Oncology Group reported an 11% overall response rate with erlotinib, an oral EGFR inhibitor, in 52 patients with metastatic papillary RCC with a 6-month PFS of only 29%. More recently, the realization that c-MET activation may play an important role in some forms of papillary RCC has led to the evaluation of foretinib (formerly known as XL880 and GSK1363089), a novel tyrosine kinase inhibitor with activity against c-*MET* and VEGFR2 in this RCC subtype. A multicenter, open-label phase 2 trial studied two dosing regimens (an intermittent regimen in which the drug was administered orally at a dose of 240 mg/day for the first 5 days of every 14-day cycle and a continuous or daily dosing regimen at a dose of 80 mg/day) in patients with metastatic papillary RCC and those with bilateral multifocal disease (Srinivasan et al, 2009). A recent interim analysis in the first 53 patients enrolled on trial (including seven HPRC patients with germline c-*MET* mutations and bilateral multifocal tumors) has been reported in abstract form. Of 44 evaluable patients in both dosing regimens, 6 had a confirmed partial response (objective response rate 14%) and an additional 34 (77%) had stable disease as their best response. Striking responses were seen in some patients, including regression of renal tumors in patients with bilateral multifocal disease. The adverse event profile associated with this drug is similar to that observed with other VEGFR antagonists. Patients on this trial will be retrospectively stratified based on the presence or absence of c-MET pathway activation (germline or somatic c-*MET* mutation or trisomy 7 or 7q31 amplification in

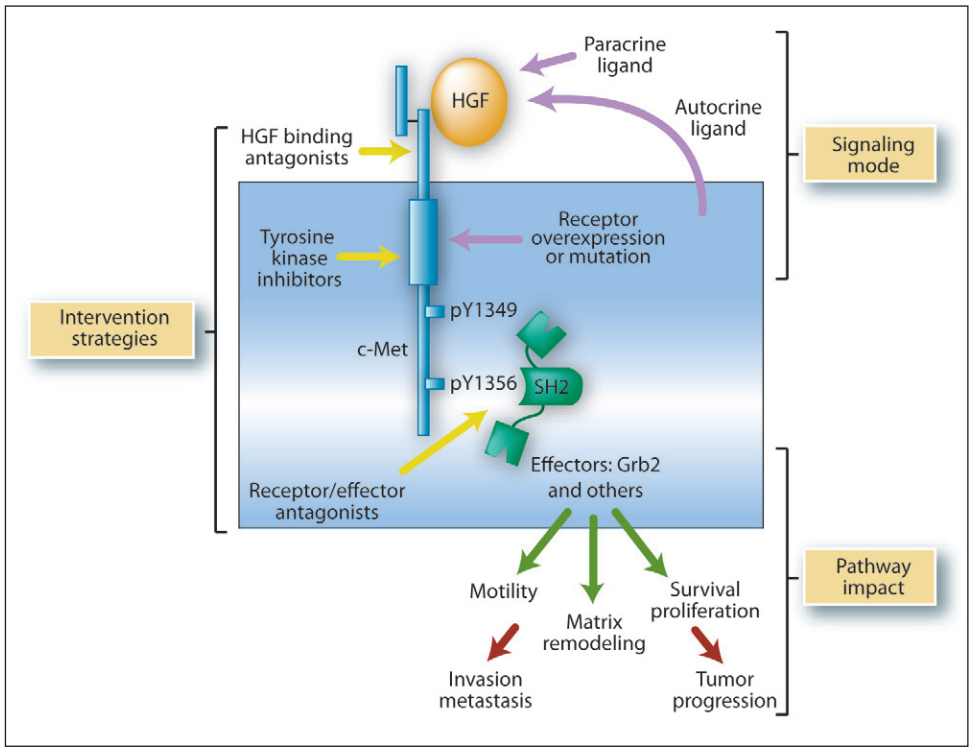


Figure 50–11. c-MET oncogenic signaling pathway. Important downstream biochemical and biologic consequences of c-MET activation (by HGF binding or by constitutive activation of the receptor tyrosine kinase activity by mutation) are represented. The c-MET ligand (HGF), c-MET tyrosine kinase activity, and downstream effectors (such as Grb-2) are potential targets for drugs in tumors with aberrant pathway activation. (From Peruzzi B, Bottaro DP. Targeting the c-Met signaling pathway in cancer. Clin Cancer Res 2006;12:3657–60.)

tumor tissue) to help explore the correlation between c-MET activation and response to foretinib. Foretinib and other agents targeting the c-MET pathway warrant further evaluation in patients with papillary RCC.

An exploratory subgroup analysis of patients enrolled in large randomized phase 3 study evaluating the efficacy of temsirolimus versus interferon in "poor prognosis" patients suggests that mTOR inhibitors may have activity in some non–clear cell variants. Approximately 20% of the patients enrolled in this trial had non–clear cell histologies (predominantly papillary RCC). The outcome of 37 patients with non–clear cell RCC treated with temsirolimus (both OS and PFS) was found to be better than that of 36 patients receiving interferon in this subgroup analysis. Although these data suggest that temsirolimus may have activity in some non–clear cell variants, these conclusions are limited by the fact that this is a subgroup analysis (Dutcher et al, 2009). Prospective studies evaluating the efficacy of mTOR inhibitors are required to clarify the role of these agents in different subsets of RCC.

Cytotoxic chemotherapy has been used with modest success in collecting duct carcinoma, a rare kidney cancer variant with similarities to urothelial malignancies. In a series of 23 patients with metastatic collecting duct carcinoma, a response rate of 26% (including one complete response) was reported with a regimen comprising gemcitabine and carboplatin. Median PFS (7.1 months) and OS (10.5 months) were modest (Oudard et al, 2007). **In summary there is no standard approach of proven efficacy for most patients with non–clear cell RCC, although some promising approaches are being evaluated. Enrollment in suitable trials should be considered for all patients with non–clear cell RCC.**

SUGGESTED READINGS

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chapter
51

Benign Renal Tumors

Vitaly Margulis, MD ● Surena F. Matin, MD ● Christopher G. Wood, MD

Renal Cysts
Renal Cortical Adenoma
Metanephric Adenoma
Oncocytoma
Angiomyolipoma
Cystic Nephroma and Mixed Epithelial/Stromal Tumor
Leiomyoma
Other Benign Renal Tumors

Benign renal neoplasms constitute a rather large and heterogeneous group of renal lesions that can be found in the kidney. These include the simple renal cyst, selected complex renal cysts, cortical and metanephric adenomas, angiomyolipoma, oncocytoma, the rarer cystic nephroma, mixed epithelial/stromal tumor, and leiomyoma, as well as other, even more esoteric tumor types. Management approaches to these lesions can vary widely, from no management for the simple renal cyst to selective embolization for larger angiomyolipomas and surgical extirpation for solid renal masses when the differential diagnosis includes renal cell carcinoma (RCC). With the increased use of cross-sectional abdominal imaging for renal-specific as well as other nonspecific complaints, it is expected that the identification of both benign and malignant renal tumors will continue to increase in the coming years (Patard, 2009). Moreover, with the increase use of, and refinements to, renal mass biopsy, the management of both benign and malignant renal neoplasms is still evolving in a way that the indications for intervention, and the type of intervention, may change significantly in the coming years (Lane et al, 2008; Campbell et al, 2009). Now, with advanced multidimensional imaging techniques, as well as minimally invasive, nephron-sparing surgical approaches, percutaneous ablative approaches, and the concept of active surveillance in the armamentarium of the practicing urologist, management of all renal lesions, including those that are presumptively benign in etiology, continues to evolve (Raj et al, 2007; Benway and Bhayani, 2009; Murphy et al, 2009).

At present, however, the urologist is left primarily with imaging studies such as ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) to assess whether a renal lesion is benign or malignant before therapeutic decisions are made. And unless the mass has clear radiographic features that suggest a benign etiology, such as clear evidence of fat seen with most angiomyolipomas or the smooth walls and lack of enhancement of a simple or minimally complex cyst, the vast majority of benign renal lesions are diagnosed only after definitive therapy such as surgical intervention has been implemented. There are several clinical features that have been linked to an increased likelihood of a renal mass having a benign etiology, including smaller size, female sex, and older age, but none of these factors can be relied on to avoid intervention if a specific pretherapy diagnosis cannot be made (Kutikov et al, 2006; Snyder et al, 2006; Glassman et al, 2007; Lane et al, 2007; Beisland et al, 2009; Murphy et al, 2009).

In this chapter the most common benign renal neoplasms that occur in the kidney are identified. The discussion is then focused on the etiology and natural history, clinical presentation, imaging characteristics, and treatment options, when treatment is indicated.

RENAL CYSTS

In much the same way as the molecular biology of RCC was elucidated through the study of familial genetic syndromes such as von Hippel-Lindau disease, the molecular basis for cyst formation has been further elucidated through the genetic analysis of familial renal cystic syndromes, such as autosomal dominant polycystic kidney disease (ADPKD). **Through these studies researchers have identified that loss of specific genes, such as *PKD1* and/or *PKD2* (polycystins) lead to cyst formation in patients with ADPKD. Polycystin-1 and polycystin-2 form a complex that represents a critical ion channel in the kidney, the loss of which results in cyst formation through the loss of intracellular calcium dysregulation and dysfunction of the primary renal cilia, a poorly understood organelle that is in part responsible for normal renal development** (Pei, 2003; Weimbs, 2007; Ibraghimov-Beskrovnaya and Bukanov, 2008). Whether these genetic changes are common to sporadic forming "benign" renal cystic disease remains to be proven, but many of the phenotypic and genetic changes noted in the kidneys of patients with familial cystic disease syndromes have been identified in sporadic cystic disease (Qian et al, 1996; Pei, 2001).

Perhaps the best description of the natural history of sporadic renal cysts can be found in the recently updated study by Terada and associates (2008). In this study of 61 patients with simple renal cysts and a mean of 10 years of follow-up, the authors noted that the cysts increased in both size and number over time. The average increase in size of the cysts was 1.9 mm per year, but the authors also noted that the rate of size increase decreased with age. Interestingly, two cysts developed renal neoplasms during the course of the study and no differences were noted in the clinical characteristics of the cysts that developed neoplasms from those

that did not. **Regarding the risk factors for the development of cysts, increasing age, male gender, presence of hypertension, and the presence of renal insufficiency were all associated with the development of sporadic renal cysts** (Terada et al, 2004). **Renal cysts remain the most common benign renal lesions, representing more than 70% of asymptomatic renal masses.** They can be solitary or multiple and unilateral or bilateral (Terada et al, 2002).

In addition to sporadic cystic disease of the kidney, and the cysts that occur with familial syndromes such as ADPKD and autosomal recessive polycystic disease, cysts are also known to occur in association with end-stage renal disease in patients on dialysis (Bisceglia et al, 2006). **There appears to be a higher incidence of RCC associated with the development of acquired renal cystic disease, much like that seen with von Hippel-Lindau disease and tuberous sclerosis, such that the pathogenesis of these cystic lesions may be quite different from that seen with sporadic simple or minimally complex cysts** (Truong et al, 2003).

Renal cystic lesions can be imaged through a variety of radiographic techniques, including ultrasonography, CT, as well as MRI. On ultrasonography, simple renal cysts have a smooth wall, are fluid filled with no internal echoes, and have evidence of posterior wall enhancement. Evidence of internal echoes, calcifications or nodularity in the wall, or internal septa on ultrasonography suggest a more complex cyst that might be worthy of further imaging that includes intravenous administration of a contrast agent (Quaia et al, 2008; Eknoyan, 2009).

The Bosniak classification for renal cystic lesions, as reviewed in Table 51–1, is perhaps the most useful and widely employed method for characterizing renal cystic lesions and for assessing the likelihood of the presence of a concomitant malignancy within the cyst (Israel and Bosniak, 2005; Warren and McFarlane, 2005). In general, Bosniak class I, II, and IIF cysts are likely to represent benign lesions, thus requiring either no therapy or just continued radiographic follow-up, in the case of class IIF lesions (Fig. 51–1). These recommendations are based on a number of series published in the

Table 51–1.
Bosniak Classification of Renal Cysts

BOSNIAK CLASSIFICATION	IMAGING CHARACTERISTICS	INCIDENCE OF MALIGNANCY	THERAPY
I	Simple cyst with a hairline thin wall that does not contain septa, calcifications, or solid components. It measures water density in Hounsfield units and does not enhance with intravenous administration of a contrast agent.	1.7%	No therapy or follow-up required
II	Cyst may contain a few hairline thin septa and fine calcifications, or a short segment of slightly thickened calcification may be present in the wall or septa. Uniformly high-attenuation lesions <3 cm (so-called high-density cysts) are well marginated and do not enhance with intravenous administration of a contrast agent.	18.5%	No therapy or follow-up required
IIF	Cysts may contain multiple hairline thin septa or minimal smooth thickening of their wall or septa. Their wall or septa may contain calcifications that may be thick and nodular, but no measurable contrast enhancement is present. These lesions are generally well marginated. Totally intrarenal nonenhancing high-attenuation renal lesions ≥3 cm are also included in this category.	18.5%	Repeat imaging to assess stability of size and radiographic characteristics
III	"Indeterminate" cystic masses have thickened irregular or smooth walls or septa in which measurable contrast enhancement is present.	33%	Excision or ablation
IV	Clearly malignant cystic masses can have all the criteria of category III but also contain enhancing soft tissue components.	92.5%	Excision or ablation

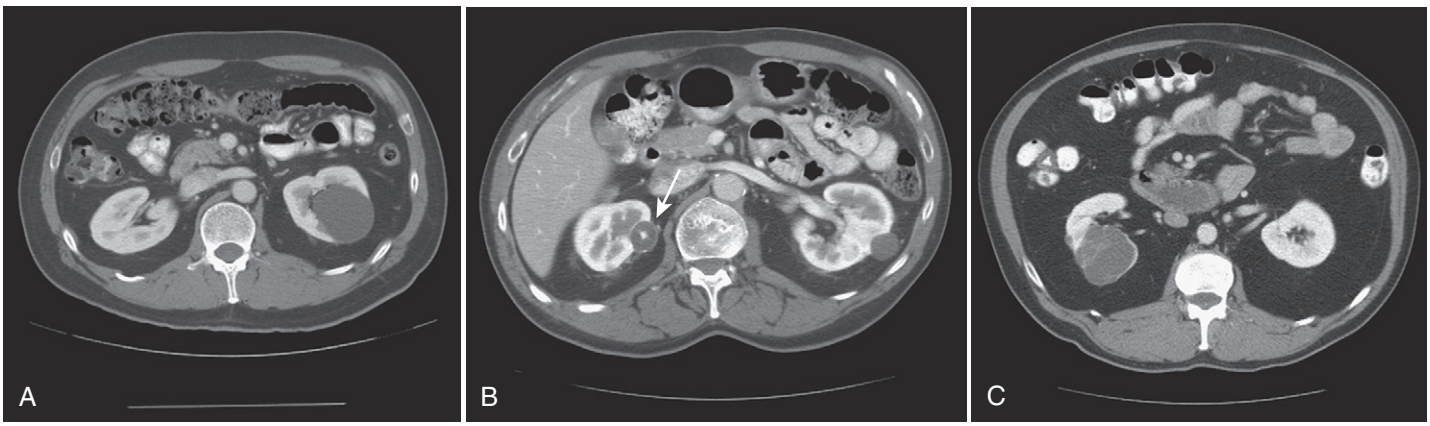


Figure 51–1. **A,** CT scan of a Bosniak I renal cyst. **B,** CT scan of a Bosniak II renal cyst. Note internal calcification. **C,** CT scan of a Bosniak IIF renal cyst. Several thin irregular septations are present within the cyst. (Copyright 2009, C.G. Wood.)

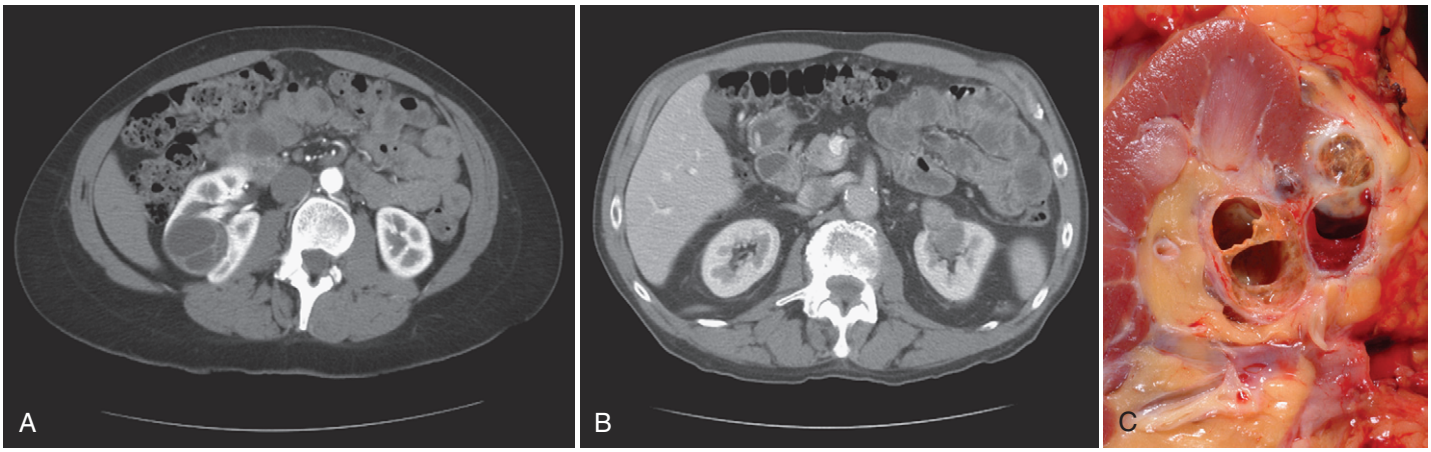


Figure 51–2. **A,** CT scan of a Bosniak III renal cyst. Thick, irregular septations are present within the cyst. **B,** CT scan of a Bosniak IV renal cyst, with a solid enhancing nodule. **C,** Bivalved Bosniak IV renal cyst demonstrating a solid component that proved to be conventional renal cell carcinoma. (Copyright 2009, C.G. Wood.)

literature by Bosniak and others that include both radiographic as well as pathologic follow-up (Warren and McFarlane, 2005).

Because of the higher risk of malignancy associated with Bosniak class III and IV lesions, therapy is recommended (Fig. 51–2). The definitive therapy would be surgical excision, although ablative therapies such as cryotherapy or radiofrequency ablation of cystic masses have been reported (Raman et al, 2009) (see Chapter 49).

The overwhelming majority of simple or minimally complex cysts require no further follow-up or therapy once diagnosed (Eknoyan, 2009). Rarely, benign cystic lesions of the kidney can grow to such a large size that they can cause pain or other symptomatology, including hypertension (Porpiglia et al, 2009; Zerem et al, 2009). Symptoms can also occur as a consequence of hemorrhage within the cyst or spontaneous/traumatic cyst rupture (Hughes et al, 1995; Rainio et al, 2006; Ishikawa et al, 2008; Vaidyanathan et al, 2008).

A variety of therapeutic interventions have been described for benign symptomatic cystic lesions of the kidney. These include aspiration, surgical resection, cyst decortications, as well as sclerotherapy with a variety of different agents (Cho et al, 2008; Ham et al, 2008; Baysal and Soylu, 2009; Canguven et al, 2009; Choi et al, 2009; Porpiglia et al, 2009). Although none of these approaches seems to be better than the others described, it is noted that with aspiration and sclerotherapy there is a higher incidence of cyst recurrence and multiple treatments may be needed to satisfactorily ablate the cystic lesion. A word of caution is warranted regarding the treatment of peripelvic cysts: given their proximity to the vital structures of the kidney, including the renal vessels and collecting system, laparoscopic, rather than percutaneous, approaches may be associated with a higher safety margin and better efficacy (Okumura et al, 2003; Camargo et al, 2005).

Key Points: Renal Cysts

- Renal cysts remain the most common of benign renal lesions, representing more than 70% of asymptomatic renal masses.
- The overwhelming majority of simple or minimally complex cysts require no further follow-up or therapy once diagnosed.
- The Bosniak classification for renal cystic lesions is perhaps the most useful and widely employed method for characterizing renal cystic lesions and assessing the likelihood of the presence of a concomitant malignancy within the cyst.

RENAL CORTICAL ADENOMA

The designation and management of purportedly benign renal cortical adenomas remains a subject of controversy in the urologic literature. These lesions are small, solid cortical renal lesions that are thought to have a benign course (Renshaw, 2002). **Histologically, renal adenomas appear as small, well-circumscribed lesions characterized by uniform basophilic or eosinophilic cells with benign-appearing nuclear and cellular features, arranged as tubulopapillary or purely papillary growth. The incidence of renal adenomas increases with age and male sex, and these tumors also have been associated with acquired renal cystic disease that results in end-stage renal failure** (Leroy et al, 2001; Denton et al, 2002; Snyder et al, 2006; Ferda et al, 2007). The incidence of renal adenomas in autopsy series ranges from 7% to 23%, although antemortem pathologic diagnosis of renal adenoma is much less common, in part owing to the pathologist's concern that there are no reliable histopathologic, ultrastructural, or immunohistochemical criteria to distinguish benign from malignant lesions of the kidney (Licht, 1995). **In fact, in a more recent study in which immunohistochemical analyses were used to further characterize renal adenomas, it was suggested that these lesions may be linked to the development of papillary RCC and represent a biologic link and continuum as a premalignant precursor** (Wang et al, 2007). In this study, researchers examined 542 nephrectomy specimens obtained over 8 years. Seven percent of these demonstrated evidence of renal adenoma; and of these, 47% were associated with a concomitant papillary RCC. Adenomas that arose in the setting of papillary RCC tended to be multiple (61%). Eighty-two percent of adenomas found in the study had a similar immunohistochemistry staining profile as papillary RCC, staining positive for α-methyl-coenzyme A racemase. In other studies, renal adenomas shared similar cytogenetic profiles to papillary RCC, such as trisomy of chromosomes 7 and 17, thus suggesting a biologic link between the two neoplasms (Brunelli et al, 2003a, 2003b).

The overwhelming majority of renal adenomas remain asymptomatic, are undetectable radiographically due to their small size (<1 cm), and require no further therapy. Size of the neoplasm has historically been utilized to differentiate renal adenoma from more malignant neoplasms of the kidney. Thoenes and colleagues (1986) provided a reassessment of the histologic classification of renal tumors and defined renal adenoma as a tumor with nuclear grade I and a diameter of at least 1 cm. For many years, a "3-cm rule" was pervasive in the urologic literature, dating back to the original autopsy studies by Bell (1938) when he noted that only 1 of 38 renal cortical tumors had associated metastases whereas 70 of 106 tumors larger than 3 cm were associated with metastases.

The diagnosis of renal adenoma remains controversial; many believe that all solid renal epithelium-derived masses are potentially malignant and therefore should undergo treatment (Renshaw, 2002).

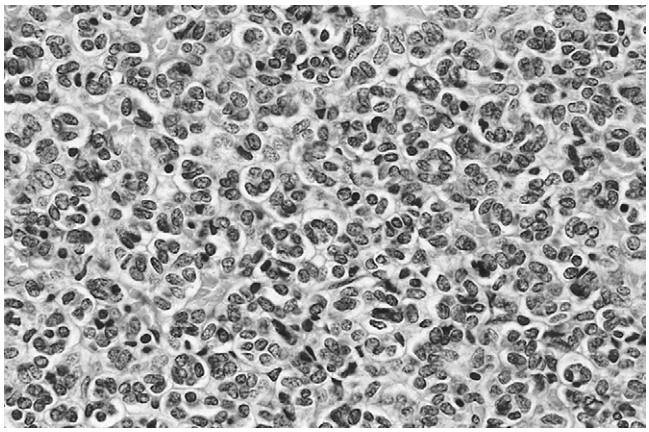


Figure 51–3. Classic metanephric adenoma with small, intensely basophilic cells arranged in an acinar pattern.

Key Points: Renal Cortical Adenoma

- The diagnosis of renal adenoma remains controversial; many believe that all solid renal epithelium-derived masses are potentially malignant and therefore should undergo treatment.
- Renal adenomas may be linked to the development of papillary RCC and represent a biologic link and continuum as a premalignant precursor.
- The incidence of renal adenomas increases with age and male sex, and these tumors also have been associated with acquired renal cystic disease resulting in end-stage renal failure.

METANEPHRIC ADENOMA

In 1995 Davis and colleagues reported 50 cases of an unusual and novel renal mass lesion with distinctive histologic features and a benign clinical course despite occasional symptomatic presentation and large tumor size. In this series, mean tumor size was 5.5 cm (up to 15 cm) and nearly half of the patients presented with flank pain, gross hematuria, or a palpable mass. Six additional patients presented with polycythemia, and hypercalcemia has also been reported in association with this tumor type, which was designated *metanephric adenoma (*Davis et al, 1995; Mahoney et al, 1997; Kuroda et al, 2003b). Metanephric adenoma was officially accepted as a primary benign renal tumor based on consensus from the Heidelberg classification (Kovacs et al, 1997). A higher male-to-female ratio was initially reported in the series of Davis and colleagues (1995), but it is likely that **there is actually a female predominance as has been reported in other series** (Jones et al, 1995; Snyder et al, 2006; Bastide et al, 2009). Incidental presentation is most common, and peak incidence is in the fifth decade of life (Renshaw, 2002). Polycythemia can be seen in 10% of patients and appears to be due to the production of erythropoietin and other cytokines by the tumor (Yoshioka et al, 2007; Bastide et al, 2009). Radiographically these tumors can have peripheral or central calcifications and may be hypovascular on contrast-enhanced CT and hyperechoic on ultrasonography (Bastide et al, 2009).

On microscopic examination these tumors consist of very small, often highly basophilic epithelial cells that form small acini and occasionally tubular or papillary structures within a predominantly acellular stroma (Fig. 51–3). Davis and colleagues (Renshaw, 2002) argued that metanephric adenoma might be histologically related to epithelial Wilms tumor because they believed that it exhibited histologic similarities to the metanephric, hamartomatous elements of nephroblastomatosis. Along these lines, it is interesting to note that many of these tumors exhibit evidence of regression in the form of scarring or calcification. In addition, Muir and colleagues (2001) have shown positive staining for the Wilms tumor protein WT1 and an immunohistochemical staining profile that suggests a histogenetic relationship to Wilms tumor. An alternative theory for the origin of metanephric adenoma was proposed by Brown and associates (1997), who found gain of chromosomes 7 and 17 by fluorescent in-situ hybridization in 8 of 11 of these tumors. These findings suggest a clonal neoplastic disorder potentially related to papillary RCC, but others have argued that this series may have been contaminated by inclusion of some cases of papillary RCC, which can be difficult to differentiate from metanephric adenoma (Brunelli et al, 2003a). Arroyo and colleagues (2001) showed that metanephric adenomas are part of a spectrum of related tumors, bridging metanephric stromal tumors, metanephric adenofibromas, and Wilms tumor. Pesti and colleagues (2001) have described a putative tumor suppressor gene for metanephric adenoma at chromosome 2p13. Various histologic stains have been evaluated to help distinguish metanephric adenoma from other renal neoplasms. **The Wilms tumor marker WT1 is frequently expressed in metanephric adenoma** (Muir et al, 2001; Bosco et al, 2007). **α-Methylacyl-CoA racemase (AMACR) is poorly expressed in metanephric adenoma but highly expressed in papillary RCC** (Olgac et al, 2006), **whereas S-100 protein expression is very high in metanephric adenoma, weak in Wilms tumor, and absent in papillary RCC** (Azabdaftari et al, 2008). Skinnider and colleagues (2005) demonstrated the potential utility of an expression panel to help differentiate papillary RCC and metanephric adenoma using a panel of cytokeratins 7, 8, 18, and 19 and vimentin. **Using these various markers appears to have improved the diagnostic yield of percutaneous biopsy and fine-needle aspiration** (Bosco et al, 2007; Patel et al, 2009), **but the index of initial suspicion needs to be high for biopsy to be considered.**

Only one case of metastasis has been described in association with classic metanephric adenoma into a regional lymph node,

and death related to this entity has not been reported (Renshaw, 2002). However, Picken and colleagues (2001) have described malignant stromal elements associated with a metanephric neoplasm of the kidney in a 21-year-old woman who died of progressive cancer, and they have proposed that there may be a spectrum of metanephric tumors that includes rare, aggressive variants. Atypical histologic features and multifocality in childhood have also been reported (Jain et al, 2007; Kohashi et al, 2009). **Given the rarity of this tumor and the lack of highly predictive clinical or radiographic criteria, metanephric adenoma remains primarily a pathologic diagnosis. If radiographic findings raise the index of suspicion, then percutaneous core biopsy with fine-needle aspiration may prove helpful in establishing a diagnosis for nephron-sparing treatment or observation, but most patients will require surgical excision because of concern for malignancy** (Fig. 51–4).

Key Points: Metanephric Adenoma

- Metanephric adenoma is a recently described, rare benign mass that radiographically may be indistinguishable from RCC.
- It is typically found incidentally, has a female predominance, and has a peak incidence in the fifth decade of life.
- The diagnosis is often made after surgical excision and can be confirmed with immunostain panels for cytokeratins, WT1, S-100, and AMACR.

ONCOCYTOMA

Renal oncocytoma is the most common benign tumor that appears as an enhancing renal mass on cross-sectional imaging and is presumed to be RCC until surgical excision, representing one of the ultimate challenges in preoperative diagnosis for the urologist. It accounts for 3% to 7% of kidney tumors (Morra and Das, 1993). Oncocytoma initially became accepted as a distinct entity after a report of 13 cases in 1976 by Klein and Valensi. Multiple additional reports since that time, including more recent genotyping studies, confirm it to be a benign histology with a distinct cell of origin and genetic abnormalities (Lieber et al, 1987; Davis et al, 1991; Licht et al, 1993; Perez-Ordonez et al, 1997; Amin et al, 1997; Dechet et al, 1999; Chao et al, 2002; Kuroda et al, 2003a). Cases of metastatic disease have been reported, yet these are considered exceptionally rare and may represent cases of malignant degeneration or pseudometastases (Paner et al, 2005; Oxley et al, 2007).

Grossly these tumors are mahogany or tan, homogeneous, and well circumscribed with a pseudocapsule and typically a central stellate scar (Fig. 51–5). Microscopically the cells are round or polygonal and arranged in a nested growth pattern. **The cells are uniform and highly eosinophilic, owing to an abundance of mitochondria** (Renshaw, 2002). In up to one third of cases, hemorrhage, extension into perinephric fat, cellular atypia, prominent nucleoli, and pleomorphism may be seen, yet the clinical behavior in these cases is within what is expected with a benign course (Amin et al, 1997; Perez-Ordonez et al, 1997). The most common genetic abnormality is loss of chromosome 1p (Lindgren et al, 2004; Paner et al, 2007). Other common cytogenetic findings include loss of the Y chromosome and chromosome 14q and rearrangements of 11q13 (Schwerdtle et al, 1997; Chao et al, 2002; Polascik et al, 2002; Lindgren et al, 2004). **The chromosomal abnormalities typically seen in RCC are not seen in renal oncocytomas, further reinforcing the**



Figure 51–4. CT scan showing a metanephric adenoma in a middle-aged woman. (Copyright 2009, S.F. Matin.)

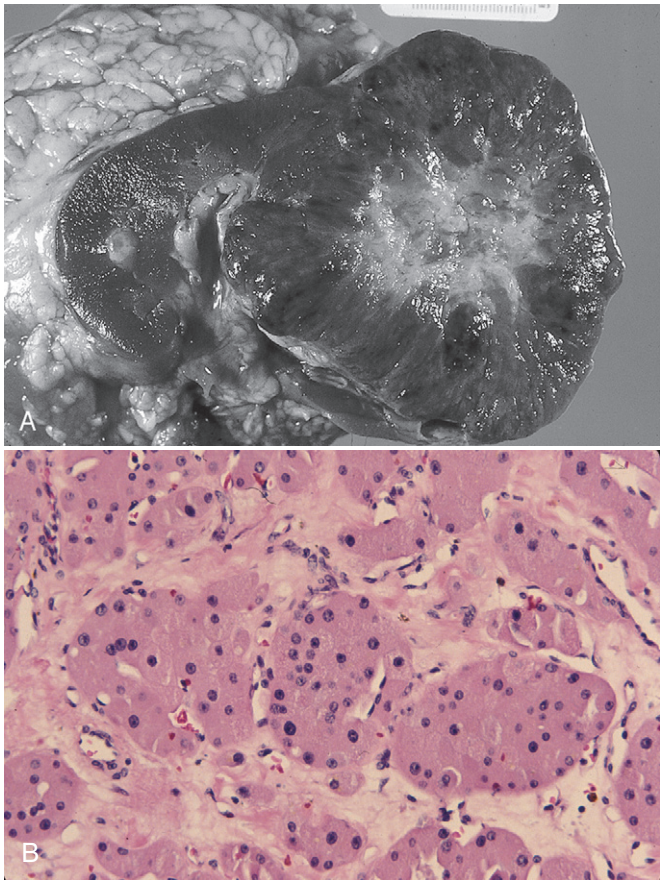


Figure 51–5. **A,** Bivalved renal oncocytoma demonstrating central scar. **B,** Oncocytoma with large eosinophilic cells arranged in distinct nests.

concept that these tumors are genotypically distinct from RCC (Minor et al, 2003). **However, histologically, the greatest dilemma arises from distinguishing chromophobe and clear cell RCC with eosinophilic characteristics from oncocytoma.** Hale colloidal iron staining is the classic differentiating marker for oncocytoma, but it can have nonspecific staining and be difficult to interpret (Leroy et al, 2000). Cytokeratin profiles are helpful in distinguishing these histologic findings (Skinnider et al, 2005; Adley et al, 2006). Expression of cytokeratin-7 is seen in 66% of chromophobe RCC and only 5% of oncocytomas, and parvalbumin is expressed in 100% of chromophobe RCC and 47% of oncocytomas (Leroy et al, 2000; Adley et al, 2006). A variety of other markers have been recently described to differentiate oncocytoma from RCC, particularly chromophobe RCC, but the clinical utility for most of these has not yet been fully developed. These include Pax-2, expressed in metanephric tissues and vital for renal tubule development; pattern of claudin-7 and 8 expression, tight junction proteins expressed in distal nephron epithelium; a vimentin expression pattern; c-*KIT* expression; and S-100 (Pan et al, 2004; Lin et al, 2006; Hes et al, 2007; Rocca et al, 2007; Lechpammer et al, 2008; Gupta et al, 2009; Osunkoya et al, 2009). An "optimal" panel for distinguishing between chromophobe and clear cell RCC and oncocytoma was recommended by Liu and colleagues in 2007, consisting of a combination of three markers (vimentin, glutathione-S-transferase-α, and epithelial cell adhesion molecule). These investigators achieved 100% sensitivity and 100% specificity for the differential diagnosis of chromophobe carcinoma, oncocytoma, and clear cell carcinoma (Liu et al, 2007). The feasibility of molecular signatures and gene profiling is being evaluated as potentially useful tests for the accurate diagnosis of tumors such as oncocytoma (Schuetz et al, 2005; Yang et al, 2006), but such studies are not yet a clinical reality.

As noted previously there are several distinct similarities to chromophobe RCC, which also is derived from the distal renal tubules. **Chromophobe RCC, particularly the eosinophilic variant, and oncocytoma are histologically similar and their distinction often requires additional pathologic testing** (Weiss et al, 1995; Renshaw, 2002). The commonality of these two tumors is further evidenced in patients with Birt-Hogg-Dubé syndrome, in whom both oncocytomas and chromophobe RCC develop, in addition to cutaneous fibrofolliculomas and spontaneous pneumothoraces (Pavlovich et al, 2005; Toro et al, 2008). Some of the renal tumors display a histology between these two tumors, prompting some to speculate that chromophobe RCC and oncocytoma represent points in a spectrum of neoplasia (Chao et al, 2002; Linehan, 2003; Pavlovich et al, 2005; Toro et al, 2008).

The greatest clinical dilemma remains the inability to confidently differentiate between renal oncocytoma and RCC on clinical or radiographic testing. Both have a similar age at presentation, have a male-to-female predominance, and are similarly sized at presentation. Although oncocytomas were more likely to be asymptomatic at presentation, most RCC are also diagnosed incidentally in the current era, eliminating this clinical scenario as a differentiator (Davis et al, 1991; Licht et al, 1993; Lieber, 1993; Amin et al, 1997; Perez-Ordonez et al, 1997; Dechet et al, 1999). **The typical spoke-wheel pattern seen on angiography or the stellate scar on cross-sectional imaging may bring up the question of a renal oncocytoma, but these findings have a poor predictive value by themselves** (Davidson et al, 1993; Licht et al, 1993; Licht, 1995). On MRI, oncocytomas may have distinct T1 and T2 signal patterns that can be suggestive but these are not definitive findings (Harmon et al, 1996). T2-weighted images on MRI do not differentiate oncocytoma from RCC (Dann et al, 2006). For lesions undergoing surveillance, the growth rates of RCC and oncocytoma are similar, so growth kinetics also do not help differentiate these tumors either (Chawla et al, 2006; Crispen and Uzzo, 2007; Siu et al, 2007). In 4% to 13% of cases, tumors are multicentric, are bilateral, or have a metachronous presentation (Lieber et al, 1987; Davis et al, 1991; Licht et al, 1993; Amin et al, 1997; Perez-Ordonez et al, 1997; Dechet et al, 1999; Tickoo et al, 1999; Minor et al, 2003). Familial renal oncocytomatosis was initially described (Weirich et al, 1998) in five families in which it presented at a young age as multicentric, bilateral and recurrent oncocytomas. Nonfamilial forms of bilateral multifocal oncocytomas resembling oncocytomatosis can also occur (Fig. 51–6). A recent cytogenetic evaluation of a patient with apparently sporadic oncocytomatosis and hybrid tumors showed different chromosomal losses than the Birt-Hogg-Dubé syndrome (Al-Saleem et al, 2004).

Recent clinical studies highlight the differing incidence of oncocytoma based on age and gender. Cao and colleagues (2005) **and** Skolarus and colleagues (2008) **showed an increasing incidence of oncocytoma in older patients presenting with a small incidentally discovered renal mass. Two different reports highlight that younger females are nearly twice as likely as their male**



Figure 51–6. CT scan of a patient with multiple bilateral oncocytomas. (Copyright 2009, S.F. Matin.)

counterparts to have a benign tumor, which includes oncocytoma and angiomyolipoma but is probably largely driven by the higher rates of angiomyolipoma in women (Cao et al, 2005; Snyder et al, 2006).

Historically fine-needle aspiration or core biopsy was compromised by high false-negative or nondiagnostic specimens, given the difficulty in differentiating oncocytoma with RCC subtypes (Weiss et al, 1995; Campbell et al, 1997). **However, the diagnostic accuracy of percutaneous biopsy has markedly improved, particularly when a core biopsy is done in addition to a fine-needle aspiration and bolstered with the use of immunostains** (Liu and Fanning, 2001; Barocas et al, 2006; Lebret et al, 2007; Volpe et al, 2007; Kummerlin et al, 2008; Schmidbauer et al, 2008), **prompting some investigators to revisit the role of the biopsy in the management of some patients with an incidental renal tumor** (Shah et al, 2005; Lebret et al, 2007; Volpe et al, 2007). When multiple tumors are present, one must consider the possibility of RCC coexisting with oncocytoma, which in some series has been shown to be as high as 32% (Davis et al, 1991; Licht et al, 1993; Licht, 1995; Gudbjartsson et al, 2005). Consideration of biopsy in these cases must be thoughtfully considered to provide a sampling of all sites of disease that are of concern.

Treatment options for a known oncocytoma range from observation to thermal ablation, laparoscopic or open partial nephrectomy, and even radical nephrectomy depending on the clinical scenario and uncertainty regarding the diagnosis (Licht, 1995; Romis et al, 2004; Gudbjartsson et al, 2005; Crispen and Uzzo, 2007). **If oncocytoma is highly suspected and surgery is indicated, a nephron-sparing approach is preferred given the benign nature of these lesions and the very low probability of recurrence** (Licht, 1995; Romis et al, 2004; Gudbjartsson et al, 2005). **Frozen section analysis is usually not sensitive enough to differentiate the eosinophilic appearance of oncocytomas with eosinophilic RCCs and should not be used to guide surgical strategy.** Thermal ablation, although sometimes reported as a treatment option, commits the patient to long-term radiographic surveillance, given the lower success rates of these procedures and the unknown long-term outcomes, tests that would be considered unnecessary should surgical excision be performed. In most cases the treatment options are isolated to observation, particularly for the older or sicker patient, and surgical resection, particularly for the younger healthier patient.

Key Points: Oncocytoma

- Renal oncocytoma is a common benign renal tumor that is clinically and radiographically indistinguishable from RCC.
- There may be a higher incidence of oncocytoma in older patients with a small renal mass as opposed to younger patients.
- Oncocytomas are derived from the distal renal tubules, similar to chromophobe RCC, and may represent a spectrum of neoplasia as evidenced in the Birt-Hogg-Dubé genetic syndrome. However, there is no evidence that oncocytomas undergo malignant transformation in sporadic cases.
- If oncocytoma is suspected preoperatively, a percutaneous core biopsy in addition to fine-needle aspiration may reliably provide a diagnosis when core tissue is available for additional immunostain panels.
- Recent advancements in immunostain panels have greatly improved the diagnostic accuracy of pathologic diagnosis from pathologic specimens and even core biopsy specimens.
- Frozen section analysis at the time of surgery may not reliably distinguish oncocytoma from RCC and should not be used to guide surgical strategy.

ANGIOMYOLIPOMA

Angiomyolipoma accounts for less than 10% of renal tumors, with autopsy series and ultrasound-screened populations showing a 0.3% and 0.13% incidence in the general population (Eble, 1998). It is a benign neoplasm consisting of thick-walled aneurysmal vessels, smooth muscle, and varying levels of mature adipose tissue (Tamboli et al, 2000; Nelson et al, 2002; Bissler et al, 2004). Initially considered to be a form of hamartoma or choristoma, recent evidence suggests a neoplastic origin with evidence of a monoclonal, rather than polyclonal, source (Green et al, 1996; Sepp et al, 1996; Kattar et al, 1999). Angiomyolipoma is now considered to be of neural crest origin, possibly derived from perivascular epithelioid cells (PEC). Originally described in 1911 by Fischer, its current name was given by Morgan in 1951 (Eble, 1998). The tumor strongly expresses estrogen receptor-β as well as androgen receptor, is predominantly found in females, and is rare before puberty, suggesting a potential hormonal influence (Boorjian et al, 2008).

The typical sporadic presentation is of a middle-aged woman with a single asymptomatic tumor. Sporadic angiomyolipomas appear to have a slow growth rate and are usually detected incidentally (Seyam et al, 2008). **Angiomyolipoma is the most common renal neoplasm associated with spontaneous perirenal hemorrhage, closely followed by RCC** (Zhang et al, 2003). Skolarus and colleagues (2008) suggested that there may be a decreased incidence of sporadic angiomyolipoma with increasing age. These tumors are most often sporadic but can also be associated with the autosomal dominant tuberous sclerosis complex (TSC). **Twenty to 30 percent of angiomyolipomas are in patients with TSC, and approximately 50% of patients with TSC develop angiomyolipomas** (Eble, 1998; Neumann et al, 1998; Tamboli et al, 2000; Lendvay et al, 2003; Minor et al, 2003). TSC-associated angiomyolipomas typically present at a younger age (mean age 30 years); there is less female-to-male predominance (2:1) with multiple, bilateral, and symptomatic tumors (Eble, 1998; Neumann et al, 1998; Lendvay et al, 2003). Because of the variable penetrance of the *TSC* mutation, the classic triad of seizures, adenoma sebaceum, and mental retardation may not be present because this mutation is seen in a minority of patients (Steiner et al, 1993). Patients with TSC also develop renal cysts and may be at higher risk of developing RCC. Lymphangioleiomyomatosis is also significantly associated with renal involvement in TSC (Rakowski et al, 2006).

Similar to RCC, most angiomyolipomas are now diagnosed incidentally during workup of unrelated complaints (Lemaitre et al, 1997; Seyam et al, 2008). The literature correlating tumor size and symptoms, however, is derived prior to this era, when most angiomyolipomas were diagnosed after the development of symptoms. The Wunderlich syndrome, or massive retroperitoneal hemorrhage, representing the most significant complication of renal angiomyolipoma, was reported in up to 10% of patients and could be associated with significant morbidity and potential mortality if not promptly treated (Oesterling et al, 1986; Steiner et al, 1993;

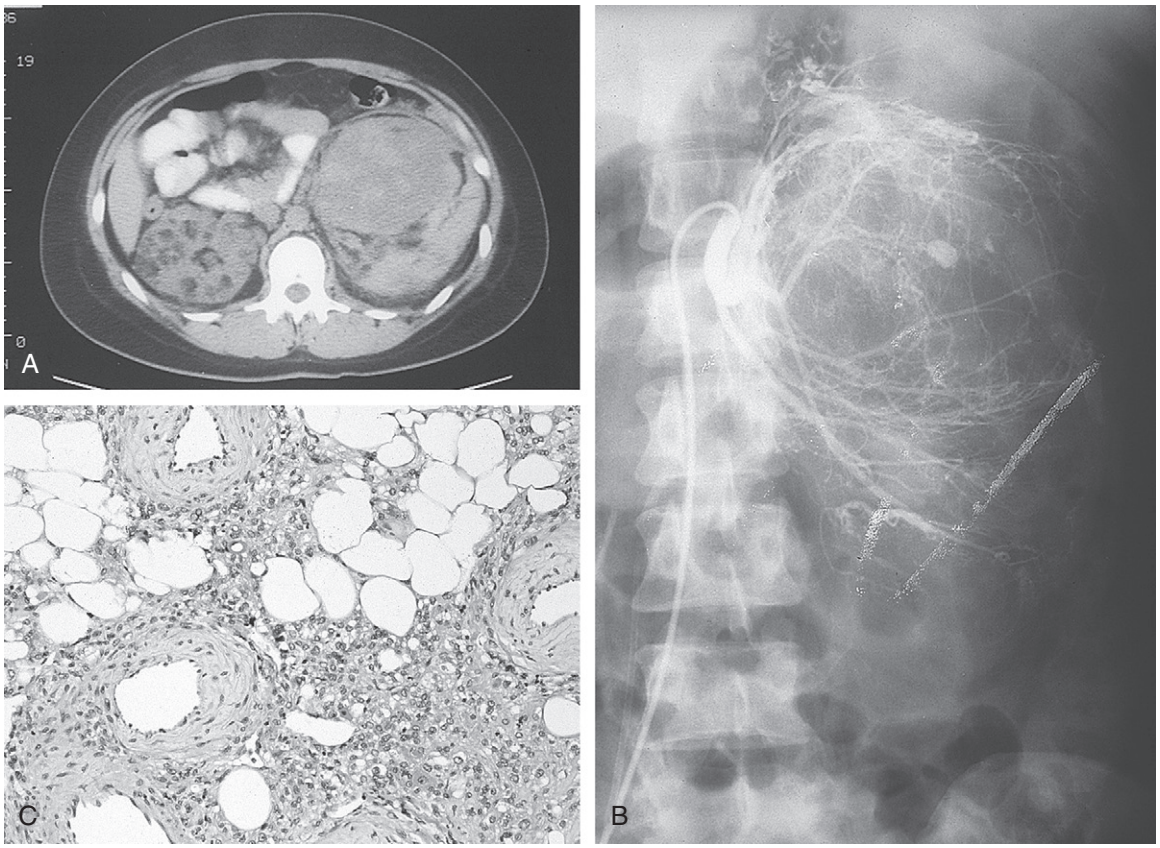


Figure 51–7. **A,** CT scan demonstrating large bilateral renal angiomyolipomas in a patient with tuberous sclerosis. **B,** Renal angiogram shows increased vascularity and aneurysmal dilation characteristic of angiomyolipoma. **C,** Typical microscopic appearance of angiomyolipoma with admixture of mature adipose tissue, smooth muscle, and thick-walled blood vessels.

Eble, 1998). The most common cause of spontaneous retroperitoneal hemorrhage is angiomyolipoma, followed by RCC (Zhang et al, 2003). Pregnancy appears to increase the risk of hemorrhage from angiomyolipoma, a factor that can influence clinical decision making (Eble, 1998).

Angiomyolipoma is the only benign renal tumor that is confidently diagnosed on cross-sectional imaging (Fig. 51–7). **The presence of fat (confirmed on nonenhanced thin-cut CT by a value of –20 Hounsfield Units [HU] or less) within a renal lesion is considered the diagnostic hallmark** (Jinzaki et al, 1997; Lemaitre et al, 1997; Bosniak et al, 1998; Simpfendorfer et al, 2009). **Findings of more than 20 pixels with attenuation less than –20 HU and of more than 5 pixels with attenuation less than –30 HU have been shown to have a positive predictive value of 100%** (Simpfendorfer et al, 2009). Ultrasonography shows a well-circumscribed, highly echogenic lesion with shadowing (Siegel et al, 1996; Lemaitre et al, 1997). On angiography (or CT-angiography) aneurysmal dilation is found in 50% of angiomyolipomas (Lemaitre et al, 1997). The size of the aneurysms has been reported to correlate with the risk of rupture (Yamakado et al, 2002). MRI can be used in difficult cases or in lieu of CT, with findings on fat-suppressed images being highly suggestive of the diagnosis.

Despite the radiographic hallmarks of angiomyolipoma the diagnosis can be confused in the three following situations: confusion with liposarcoma, possibility of fat-containing RCC, and possibility of a fat-poor angiomyolipoma resembling an RCC. Large angiomyolipomas can be confused with retroperitoneal liposarcomas, which are very rare. A good quality, high-resolution CT however will invariably show several features that are characteristic of angiomyolipoma, the primary one being a small indentation of the renal parenchyma even when the tumor envelops the kidney (Fig. 51–8), whereas liposarcomas will compress or only extrinsically push the

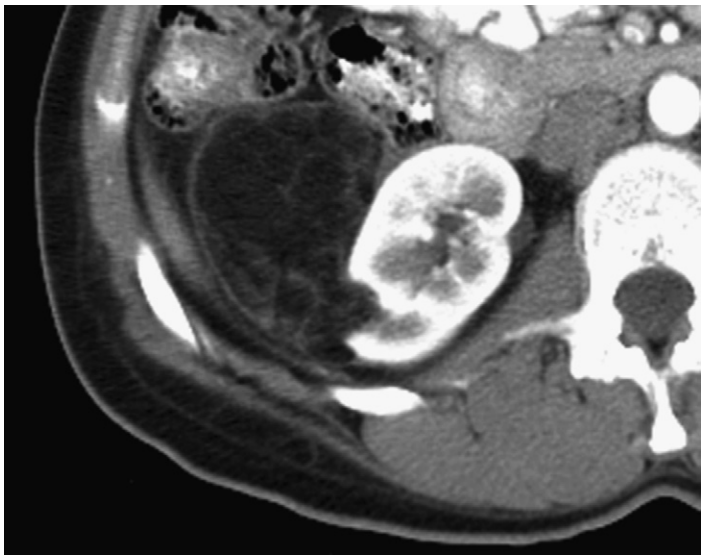


Figure 51–8. CT scan of angiomyolipoma with parenchymal indentation. (Copyright 2009, S.F. Matin.)

renal parenchyma (Clark and Novick, 2001; Wang et al, 2002). Although RCC containing fat density has also been reported, these extremely rare cases also contained calcifications, a finding usually almost never seen with angiomyolipoma (Henderson et al, 1997; Lemaitre et al, 1997; Roy et al, 1998). Most recently a report of two cases of RCC with very small amounts of intratumoral fat but without calcification was reported, adding to two other reported cases in the literature (Hayn et al, 2009). Fat-poor angiomyolipoma, seen in 14% of cases or more, is much more difficult to diagnose, owing to the paucity of mature adipose tissue (Lemaitre et al, 1997; Kim et al, 2004; Milner et al, 2006). Lane and colleagues (2008) showed that fat-poor angiomyolipoma was more commonly single, smaller, and found in older patients. Various imaging modalities have attempted to accurately identify these lesions preoperatively and differentiate them from RCC, with mixed success. On CT many appear to have hyperattenuation on noncontrast imaging and have a homogeneous and prolonged enhancement pattern (Jinzaki et al, 1997; Kim et al, 2004; Hafron et al, 2005; Milner et al, 2006; Silverman et al, 2007). **Detailed pixel distribution analysis cannot differentiate between fat-poor angiomyolipoma and RCC** (Catalano et al, 2008). Ultrasonography can show a hyperechoic or isoechoic lesion, suggesting a fat-poor angiomyolipoma (Jinzaki et al, 1997). **Because of the nonspecific nature of these findings most patients are often treated as having a presumed RCC. However, these radiographic findings may prompt the attentive urologist to consider a percutaneous biopsy if the suspicion is raised by imaging. Percutaneous biopsy can play an important role in diagnosis in these cases, because a core biopsy should be eminently accurate in the diagnosis of angiomyolipoma** (Lebret et al, 2007; Silverman et al, 2007).

Although an invariably benign nature of angiomyolipoma is well accepted, extrarenal occurrences are occasionally seen and have been reported in the hilar lymph nodes, retroperitoneum, and liver, with direct extension into the venous system (Eble, 1998; Türker Köksal et al, 2000; Gögüs et al, 2001; Nelson and Sanda, 2002; Lin et al, 2003; Bissler and Kingswood, 2004; Akcali et al, 2006; Haritharan et al, 2006; Blick et al, 2008; Schade et al, 2008). Even in these cases a benign clinical course follows, indicating multicentric origin rather than malignancy with metastasis. Many angiomyolipomas exhibit regions of cellular atypia, and the pathologic differential diagnosis can include a number of subtypes of sarcoma, including fibrosarcoma, leiomyosarcoma, and liposarcoma, depending on the relative amounts of adipose, vascular, or smooth muscle tissue present (Wang et al, 2002). **Positive immunoreactivity for HMB-45, a monoclonal antibody raised against a melanoma-associated antigen, is characteristic for angiomyolipoma and can be used to differentiate this tumor from sarcoma and other tumors** (Eble, 1998). There have been two reports of high-grade and eventually lethal leiomyosarcoma arising within an angiomyolipoma. Christiano and colleagues (1999) have described a highly pleomorphic angiomyolipoma that was associated with the development of multiple pulmonary nodules, the majority of which stained positive for HMB-45 (Ferry et al, 1991). They believed that this case represented a malignant transformation of angiomyolipoma, which, if it does occur, must be exceedingly rare. **However, these cases may also have represented the more recently described entity of epithelioid angiomyolipoma. In 1997, Eble and colleagues published their experience of five patients who had angiomyolipoma with a predominant epithelioid component; and more recently this malignant epithelioid variant of angiomyolipoma that can metastasize has been further described in patients with and without TSC, many of whom succumbed to the disease** (Pea et al, 1998; L'Hostis et al, 1999; Martignoni et al, 2000; Cibas et al, 2001; Menè et al, 2001; Nelson and Sanda, 2002; Saito et al, 2002; Bissler and Kingswood, 2004; Huang et al, 2007; Limaiem et al, 2008; Matsuyama et al, 2008; Moudouni et al, 2008; Zanelli et al, 2008; Kato et al, 2009). This phenotype is characterized by epithelioid cells that are cytokeratin negative and HMB-45 positive. Whether this extremely rare variant represents malignant degeneration of a preexistent angiomyolipoma or a de-novo tumor without a benign precursor remains unknown.

For optimal management of angiomyolipoma, treatment must be individualized. **The management should take into account the size of the tumor, presence of symptoms, and patient factors.** In particular, the risk of hemorrhage must be weighed during the evaluation. In general, most symptomatic angiomyolipomas have been relatively large and most studies in the literature have focused on a 4-cm cut point (Steiner et al, 1993; Nelson and Sanda, 2002). On the basis of an extensive literature review, Oesterling and coworkers (1986) reported that 82% of patients with angiomyolipomas larger than 4 cm in diameter were symptomatic, with 9% in hemorrhagic shock at the time of presentation; in contrast, patients with smaller tumors were symptomatic 23% of the time. Echoing these findings, Dickinson and colleagues (1998) reported that all 18 patients with angiomyolipomas smaller than 4 cm in their series were asymptomatic, whereas 7 of 13 patients with angiomyolipomas of 4 to 8 cm and 5 of 6 patients with tumors larger than 8 cm required intervention, primarily related to pain or bleeding. These observations have been confirmed and extended by a number of investigators (Blute et al, 1988; Steiner et al, 1993; Lemaitre et al, 1995; De Luca et al, 1999; Seyam et al, 2008). Steiner and colleagues (1993) reported that patients with angiomyolipomas larger than 4 cm were symptomatic 52% of the time, with 30% requiring surgical intervention, whereas patients with smaller tumors never required surgery and were asymptomatic 76% of the time. Although it was primarily retrospective, limited follow-up with a mean of 4 years was available for 24 patients with 28 tumors in this series. Interval growth was documented in 6 of 13 tumors with diameter of more than 4 cm and in 4 of 15 tumors smaller than 4 cm. A slower growth rate and a low risk of hemorrhage for smaller tumors was also supported by Kennelly and colleagues (1994), who observed 17 angiomyolipomas with tumor size of less than 4 cm for a mean of 3.8 years. Similarly, De Luca and colleagues (1999) studied 32 incidentally discovered angiomyolipomas smaller than 5 cm in diameter and found that 92% remained asymptomatic and unchanged in size. **Even so, occasional larger angiomyolipomas undergoing observation, some for up to 18 years, can remain asymptomatic** (Kennelly et al, 1994; Hadley et al, 2006; Danforth et al, 2007), **reinforcing the concept that size represents a continuum of risk, not an absolute phenomenon, and highlighting the need for individualized tailoring of treatment recommendations.** Multicentric angiomyolipomas and those in patients with tuberous sclerosis represent a special group that has demonstrated increased growth rates of approximately 20% per year, in contrast to a mean growth rate of 5% per year for solitary, sporadic angiomyolipomas (Steiner et al, 1993; Nelson and Sanda, 2002; Harabayashi et al, 2004; Seyam et al, 2008).

Although no large prospective studies evaluating the long-term outcomes of angiomyolipomas have been performed, the information reviewed here allows one to propose general guidelines for

management. Asymptomatic, smaller tumors, which by convention have been those with a diameter less than 4 cm, can be observed expectantly, with repeat initial imaging at 6 to 12 months to define the growth rate and clinical significance. Repeat imaging can be lengthened once stability is established, with follow-up performed only annually or biannually for smaller tumors (Oesterling et al, 1986; De Luca et al, 1999; Matin et al, 2008). **Intervention should be considered for larger tumors, particularly if the patient is symptomatic, taking into account the patient's age, comorbidities, and other related factors. Women of childbearing age and patients with limited access to surveillance or to emergency care should also consider a proactive approach** (Nelson and Sanda, 2002). **A nephron-sparing approach, by either selective embolization or open or laparoscopic/robotic partial nephrectomy, is clearly preferred in patients with angiomyolipomas requiring intervention. Preservation of renal tissue remains a priority in those with TSC or multicentric angiomyolipoma and particularly in patients with underlying renal insufficiency.** The feasibility and efficacy of partial nephrectomy by either wedge resection or enucleation in patients with angiomyolipoma is well established, with preservation of renal function achieved even in patients with large lesions in a solitary kidney (Fazeli-Matin and Novick, 1998; Boorjian et al, 2007; Minervini et al, 2007). Selective embolization is reported by some to be the preferred modality, and data from 76 patients in six series have documented long-term success in most cases (Nelson and Sanda, 2002; Harabayashi et al, 2004). However, a substantial proportion of patients experienced persistent or recurrence of symptoms or hemorrhage and most of these required repeated procedures, including embolization or surgery (Hamlin et al, 1997; Han et al, 1997; Kehagias et al, 1998; Mourikis et al, 1999; Nelson and Sanda, 2002; Lenton et al, 2008). The overall complication rate with embolization in these series was 10%, similar to rates of partial nephrectomy (Boorjian et al, 2007), and included hemorrhage, abscess formation, or sterile liquefaction of the tumor requiring percutaneous drainage or surgical intervention. **These data highlight the need for extended follow-up after selective embolization, which would not be required after partial nephrectomy** (Nelson and Sanda, 2002). **Selective embolization should be considered as first-line therapy in patients with acute or potentially life-threatening hemorrhage, because surgical exploration in this setting is often associated with total nephrectomy** (Pappas et al, 2006; Chang et al, 2007). Ablative therapies such as radiofrequency ablation (Prevoo et al, 2008) and cryoablation (Bachmann et al, 2005; Byrd et al, 2006; Littrup et al, 2007; Caviezel et al, 2008) have also been utilized for the treatment of angiomyolipoma, but follow-up remains short, the evaluation of success remains poorly defined, and the duration for continued radiographic surveillance is unknown, thus committing the patient to multiple, long-term imaging. Ablative therapies may have their best role for the treatment of patients with TSC who have multicentric angiomyolipomas or older patients with comorbidities who require treatment and are not candidates for embolization.

Key Points: Angiomyolipoma

- Angiomyolipoma is the only benign renal tumor confidently diagnosed on cross-sectional imaging by the presence of fat on nonenhanced thin-cut CT. Fat-poor angiomyolipoma may still be confused with RCC but if it is suspected preoperatively then percutaneous biopsy is eminently capable of providing the diagnosis, with positivity for HMB-45 typically seen with angiomyolipoma.
- Angiomyolipoma is the most common renal tumor associated with spontaneous hemorrhage, followed by RCC.
- Treatment must be individualized, based on the presentation, pregnancy status, tumor size, and renal function.
- The treatment of choice in cases of acute hemorrhage is selective renal angioembolization.
- Treatment options for elective management of larger angiomyolipomas include selective renal angioembolization and open or minimally invasive partial nephrectomy. Embolization is associated with a high rate of secondary procedures.

CYSTIC NEPHROMA AND MIXED EPITHELIAL/STROMAL TUMOR

Although considered separate entities by the 2004 World Health Organization classification of renal neoplasms, cystic nephroma and mixed epithelial/stromal tumors of the kidney (MEST) are rare benign renal neoplasms that have overlapping clinical, morphologic, and immunohistochemical characteristics (Lopez-Beltran et al, 2006; Turbiner et al, 2007; Lane et al, 2008; Montironi et al, 2008). Recent demonstration of striking similarities between global gene expression profiles in cystic nephroma and MEST further strengthens the notion that these two entities represent opposite ends of the spectrum of the same biologic process (Zhou et al, 2009). **Female predilection and history hormonal ablation therapy in male patients, combined with the frequent expression of estrogen and progesterone receptors, suggest that the sex-steroid hormones might play a role in the pathogenesis of these rare lesions** (Turbiner et al, 2007; Lane et al, 2008; Montironi et al, 2008; Stamatiou et al. 2008).

Cystic Nephroma

Cystic nephroma is a characteristic renal lesion with a bimodal age distribution and a benign clinical course (Tamboli et al, 2000). Diagnostic peaks occur primarily in the first 2 to 3 years of life, predominantly in males, and again in the fourth and fifth decades with a significant (8:1) female prevalence (Madewell et al, 1983; Upadhyay and Neely, 1989; Castillo et al, 1991; Stamatiou et al, 2008; Kuzgunbay et al, 2009). As with other renal lesions, presenting signs can include abdominal mass, pain, and hematuria, but the majority of cystic nephromas are incidental findings (Madewell et al, 1983; Kuzgunbay et al, 2009). Several familial cases have been reported in the literature, and there have been anecdotal reports of sarcoma and clear cell carcinoma arising from cystic nephroma (Bal et al, 2005; Omar et al, 2006; Raj et al, 2006; Ashley and Reinberg, 2007).

Radiologically, most cystic nephromas are solitary, centrally located, and widely variable in size (mean 9 cm) and commonly demonstrate curvilinear calcifications, herniation into the renal collecting system, and septal enhancement (Fig. 51–9A, B) (Madewell et al, 1983; Turbiner et al, 2007). **Consequently, reliable radiologic differentiation between cystic nephroma and cystic RCC in adults or Wilms tumor in children is not possible** (Vujanic et al, 2000).

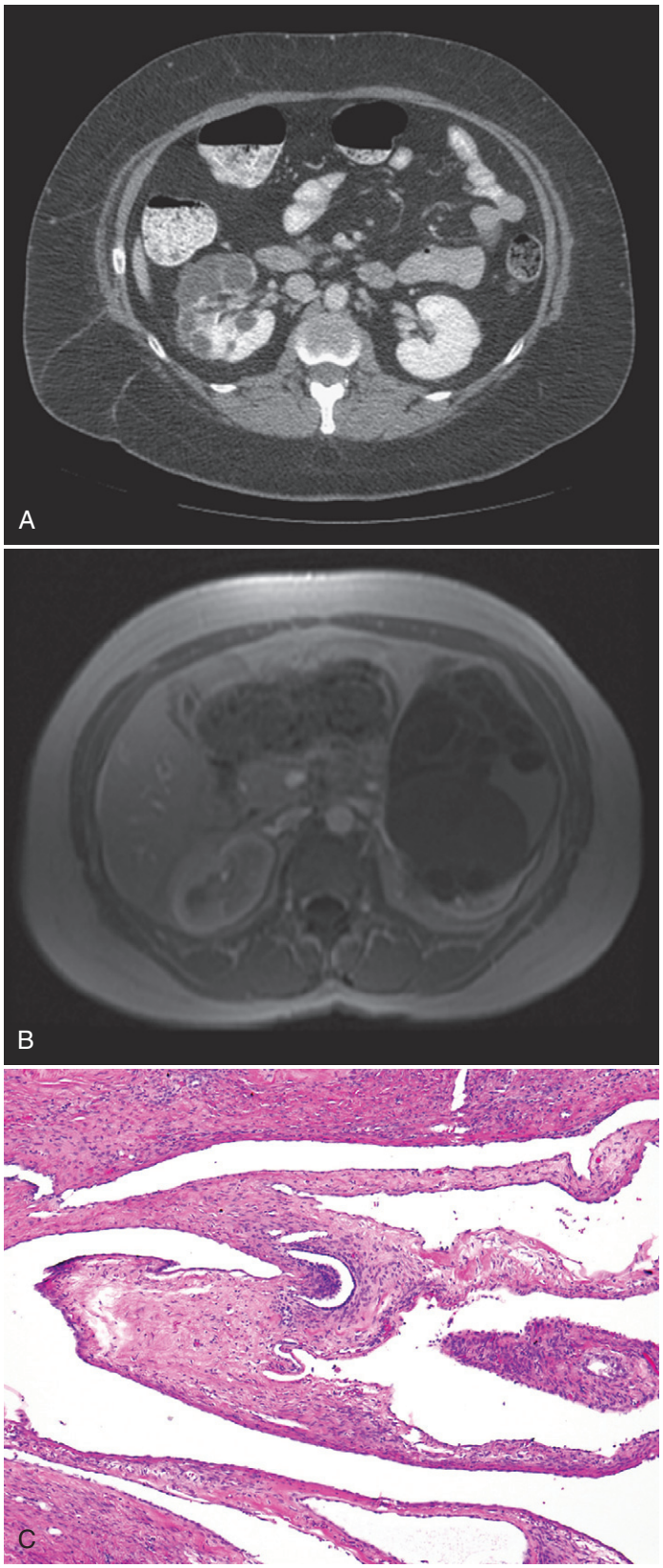


Figure 51–9. Cystic nephroma. CT **(A)** and MR **(B)** images do not allow reliable distinction from cystic renal cell carcinoma or cystic Wilms tumor. **C,** The variably sized cystic spaces are lined by flattened epithelium (low magnification). (Copyright 2009, V. Margulis.)

Histologically, cystic nephromas are well encapsulated by a thick fibrous pseudocapsule and are composed of cysts lined by flattened, cuboidal, or hobnail epithelium (see Fig. 51–9C). The stromal component can range from dense paucicellular collagen to markedly cellular fascicles of spindle cells, closely resembling ovarian stroma (Tamboli et al, 2000). Immunohistochemical studies reveal affinity of the epithelial component for cytokeratins, whereas stromal components frequently stain positive for CD10, calretinin, inhibin, estrogen, and progesterone receptors (Turbiner et al, 2007; Montironi et al, 2008).

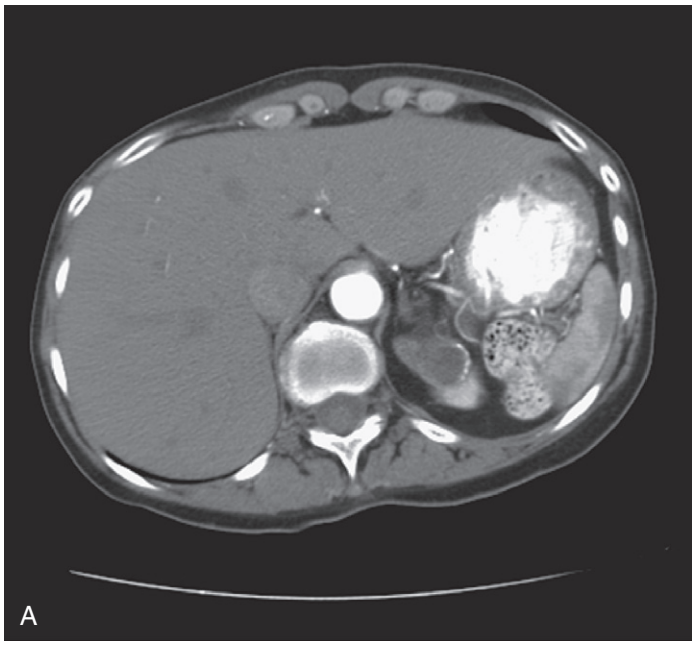
Because of concern for cystic Wilms tumor, most children with cystic nephromas continue to be managed by radical nephrectomy, whereas a nephron-sparing approach with partial nephrectomy, if feasible, is an attractive option in adults.

Mixed Epithelial/Stromal Tumor

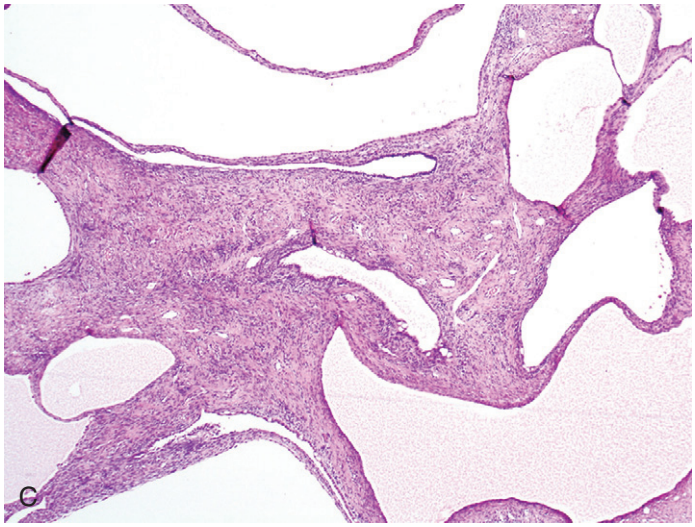
MEST is a rare benign adult renal neoplasm with a variable admixture of epithelial and mesenchymal components (Adsay et al, 2000). Previously these tumors have been described as congenital mesoblastic nephroma, leiomyomatous renal hamartoma, solid and cystic biphasic tumor, cystic hamartoma, solitary multilocular cyst, and adult metanephric stromal tumor (Adsay et al, 2000; Pierson et al, 2001; Mai et al, 2007). **Similar to cystic nephromas, MEST exhibits striking female predominance with a diagnostic peak in the fourth decade. The majority of women diagnosed with MEST had a history of receiving estrogen replacement therapy, and the only male patient in the largest MEST series had a long history of androgen deprivation therapy for prostate cancer** (Adsay et al, 2000). Presenting signs and symptoms of MEST are similar to those of cystic nephroma with the majority detected incidentally (Adsay et al, 2000; Turbiner et al, 2007; Montironi et al, 2008).

Radiologic appearance of MEST is of a complex cystic renal mass, typically classifying these tumors as Bosniak class III to IV lesions, indistinguishable from cystic RCC (Fig. 51–10A) (Adsay et al, 2000). A typical MEST has a benign clinical course, but recently a case of malignant transformation to a sarcomatoid carcinoma and several cases of local recurrence of a malignant stromal component with a dismal clinical course have been described (Adsay et al, 2000; Nakagawa et al, 2004).

Grossly, MEST appears encapsulated and ranges from 2 to 24 cm (mean 6 cm) (Adsay et al, 2000; Mai et al, 2007). Involvement of renal hilum and compression of the pelvicalyceal system is common, but gross infiltration of adjacent renal parenchyma is not seen (see Fig. 51–10B). The mesenchymal component is characterized by spindle cells showing variable degrees of smooth muscle, fibroblastic, or myofibroblastic differentiation with interspersed collagen bundles. The epithelial components vary from regular tubules to complex tubulopapillary structures with or without cystic dilatation, lined by cuboidal to flattened epithelium that may show clear cell changes and have a characteristic hobnail appearance (see Fig. 51–10C) (Adsay et al, 2000; Antic et al, 2006; Turbiner et al, 2007; Montironi et al, 2008). As in cystic nephroma, the epithelial components stain positive for cytokeratins whereas estrogen and progesterone receptor staining has been observed in the majority of the mesenchymal elements of MEST (Adsay et al, 2000).







A preoperative diagnosis of MEST should be considered in perimenopausal women receiving hormone therapy; however, because radiologic differentiation from RCC is not reliable, surgical intervention, preferably with a nephron-sparing approach should be offered to appropriately selected patients.

Key Points: Cystic Nephroma and Mixed Epithelial/Stromal Tumor

- These tumors are at opposite ends of the spectrum of the same biologic process with overlapping clinical, morphologic, and immunohistochemical characteristics.
- There is a female predilection, and a history of hormonal ablation therapy is noted in male patients.
- Frequent expression of estrogen and progesterone receptors in tumor tissue is reported.
- Clinical distinction from RCC or cystic Wilms tumor is not possible.
- If feasible, a nephron-sparing approach with partial nephrectomy is the preferred management strategy.

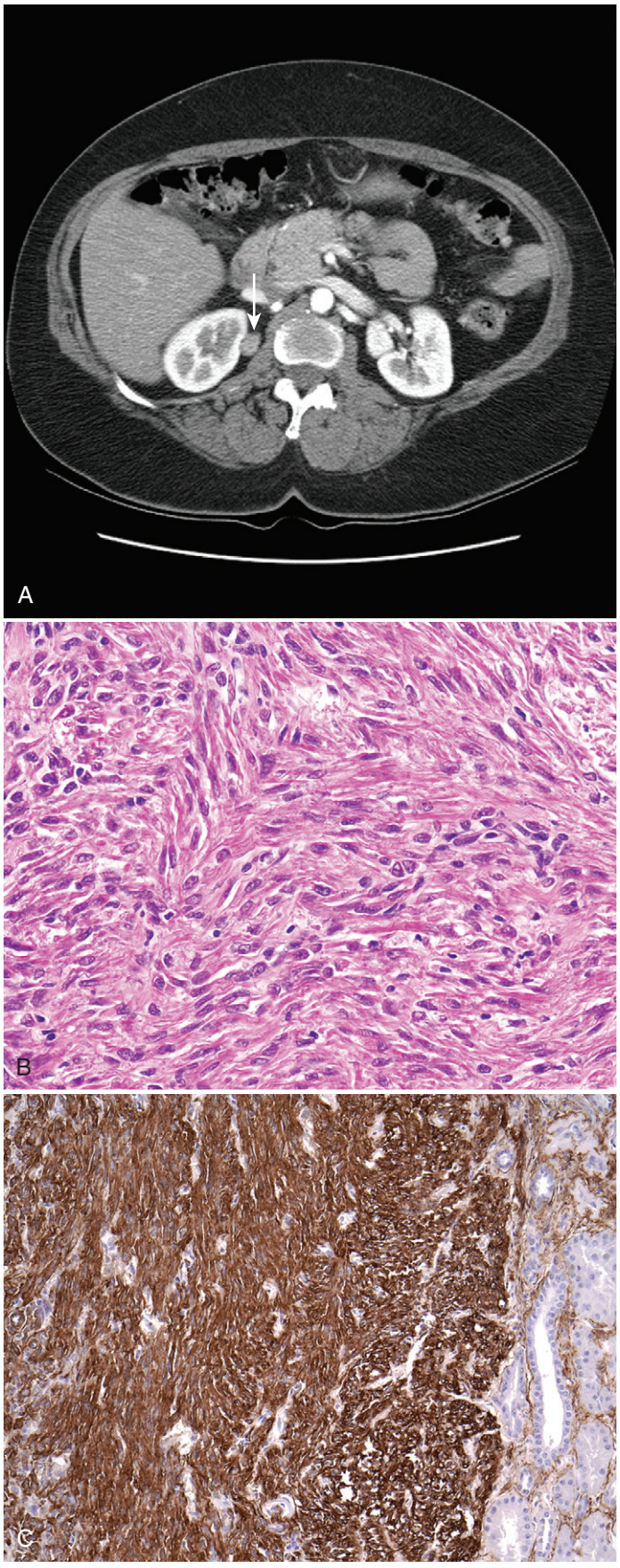
LEIOMYOMA

Leiomyomas are rare, benign tumors that may arise from smooth muscle cells anywhere along the genitourinary tract (Tamboli et al, 2000). In the kidney these tumors most commonly arise from the renal capsule, but renal pelvis and renal vein sites of origin have been reported (Wells et al, 1981; Steiner et al, 1990; O'Brien et al, 1992; Rao et al, 2001). **Leiomyomas are found at autopsy with a frequency of 4.2% to 5.2%, but only a minority are discovered clinically, representing approximately 1.5% of all benign renal tumors treated surgically** (Romero et al, 2005). As with other renal lesions, in the age of widespread utilization of computerized tomographic abdominal imaging, the vast majority of leiomyomas are found incidentally (Romero et al, 2005; Derchi et al, 2008).

Renal leiomyomas have a characteristic appearance of a small exophytic renal mass with or without enhancement arising from renal capsule, but conclusive radiologic differentiation from RCC is not possible (Fig. 51–11A) (Steiner et al, 1990; Derchi et al, 2008).

Grossly, leiomyomas are well encapsulated and range from purely cystic to mixed solid/cystic or solid in appearance. Histologic examination reveals intersecting fascicles of smooth muscle with no evidence of hypercellularity, pleomorphism, mitotic activity, or necrosis (see Fig. 51–11B) (Steiner et al, 1990; Tamboli et al, 2000). Immunohistochemical stains confirm the smooth muscle nature of the tumor with strong diffuse positive staining for smooth muscle markers desmin and caldesmon (see Fig. 51–11C) (Romero et al, 2005). **Large lesions have traditionally been**

Figure 51–10. Mixed epithelial and stromal tumor. **A,** CT scan characteristics are not distinguishable from renal cell carcinoma. **B,** Gross photograph of a partial nephrectomy specimen demonstrating a well-circumscribed mass composed of variably sized cysts separated by thick white septa. **C,** Medium-power magnification shows cysts lined by hobnailed cells and spindle cell stroma. (Copyright 2009, V. Margulis.)



managed with radical nephrectomy, but nephron-sparing approaches should be considered for peripherally located small lesions.

Key Points: Leiomyoma

- The characteristic appearance is of a small solid renal mass arising from the renal capsule.
- Radiologic differentiation from RCC is not possible.
- Nephron-sparing approaches are preferred when technically possible.

OTHER BENIGN RENAL TUMORS

A multitude of rare benign tumors derived from the various mesenchymal components of the kidney have been described and include multiple histiotypes, such as fibromas, lipomas, lymphangiomas, and hemangiomas (Ligato et al, 1999; Tamboli et al, 2000). Current radiologic methods do not allow for conclusive differentiation of these benign tumors from malignant renal lesions, and surgical excision is often needed for pathologic confirmation.

Among these, noteworthy is reninoma, which is a benign tumor of the renal juxtaglomerular cell apparatus (Wong et al, 2008). With fewer than 100 cases reported in the literature, females in the third and fourth decade are most commonly affected (Martin et al, 2001; Rubenstein et al, 2002; Wong et al, 2008). **Clinical presentation is dominated by hypersecretion of renin and includes hypertension and hypokalemia and associated symptoms such as polydipsia, polyuria, myalgia, and headaches** (Schonfeld et al, 1991; Rubenstein et al, 2002). The radiologic appearance is that of a small (<3 cm) solid hypovascular renal mass; and surgical excision, preferably sparing the remaining renal parenchyma, results in rapid decline of plasma rennin levels, normalization of blood pressure, and resolution of the associated symptoms (Dunnick et al, 1983; Schonfeld et al, 1991; Tanabe et al, 2001). Histologic examination reveals sheets of polygonal to spindle-shaped cells with indistinct cell borders, abundant eosinophilic cytoplasm, and minimal atypia (Martin et al, 2001). Strong immunostaining for factor VIII and factor VIII–related antigens is characteristic and confirms derivation from endothelial cell lineage (Sanfilippo et al, 1982). Although a benign clinical course is expected, one case of malignant reninoma has been documented in the literature (Duan et al, 2004).

Figure 51–11. Renal leiomyoma. **A,** CT scan with characteristic appearance of a small renal mass arising from the renal capsule. **B,** Medium-power magnification shows uniform spindle cells with thin cigar-shaped nuclei, without any pleomorphism. **C,** Strong positive immunohistochemical staining with smooth muscle actin in the leiomyoma. Note lack of smooth-muscle actin staining in the normal renal tubules on the right. (Copyright 2009, V. Margulis.)

Key Points: Other Benign Renal Tumors

- Numerous rare benign tumors derived from the various mesenchymal components of the kidney have been described.
- Radiologic differentiation from renal malignancy is not possible.
- Reninoma, a benign tumor of the renal juxtaglomerular cell apparatus, is an important but rare cause of secondary hypertension and hypokalemia.

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chapter 52

Retroperitoneal Tumors

Stanley Bruce Malkowicz, MD

Incidence and Etiology
Pathology
Benign Lesions
Malignant Lesions
Diagnosis
Staging
Management
Metastatic Disease

Retroperitoneal tumors are relatively rare lesions yet of interest to the urologist because they present in a key anatomic location and often involve urologic organs. Because of their location these lesions usually demonstrate indolent growth and present as relatively large lesions. Although some lesions are benign the majority are malignant and are best treated by surgical extirpation when possible. This often requires the excision of involved organs, most often the kidney. Beyond the obvious effort to obtain negative surgical margins during removal, optimal treatment strategies are difficult to systematize owing to the inability to accrue sufficient prospective evidenced-based data. Additionally, much of the available data is intertwined with surveys and treatment approaches to sarcomas of extremities.

The clinical approach to these lesions from the perspective of assessment and surgery is fairly standard. Anthracycline chemotherapy is the basis of treatment, and the advantages and limitations of this approach have been further defined by recent treatment series. The exact role and efficacy for radiation therapy in these lesions continues to be explored. The role for targeted therapy is being investigated.

INCIDENCE AND ETIOLOGY

Retroperitoneal sarcomas are relatively rare lesions that comprise nearly 15% of the soft tissue sarcomas that occur annually and thus account for approximately 2000 cases per year (Jemal, 2009). Surveillance, Epidemiology, and End Results (SEER) data from the U.S. National Cancer Institute have identified 2.7 cases per 100,000 individuals at a steady rate over the past 30 years (Porter, 2006). Actually, fewer than half of all retroperitoneal tumors are sarcomas. Fifteen to 20 percent are benign lesions such as lipomas, and the remainder consist of primary lymphoma or primary urologic tumors such as germ cell lesions (Jemal et al, 2002). Presentation is usually in the sixth decade of life, but the age range is broad (Gronchi et al, 2009). There is a slight male predominance, and two thirds of patients have high-grade malignancy. Approximately 10% will present with metastatic disease, with lung and liver the most common sites of spread (Lewis, 1998).

Although histologic types may span any age range, rhabdomyosarcoma tends to cluster in younger patients, even excluding the pediatric population, whereas malignant fibrous histiocytoma is seen in older patients. Gastrointestinal stromal tumor has been more thoroughly recognized recently, and appropriate characterization is key because targeted therapeutic approaches are available for this lesion.

The etiology of retroperitoneal sarcoma is poorly understood. The etiology of sarcoma has been attributed to prior radiation exposure and toxins, yet it is difficult to account for this in the majority of cases. Approximately 0.1% of patients who receive radiation therapy may develop a sarcoma at the treatment site. The most common lesion associated with radiation is malignant fibrous histiocytoma. Some association exists between dioxin exposure and the development of sarcoma, but prolonged periods of exposure and significant latency were also noted (Hardell and Sandstom, 1979).

PATHOLOGY

Retroperitoneal sarcomas arise primarily from soft tissues of fibrous and adipose origin as well as muscle, nerve, and lymphatic tissue. These tissues are derived from primitive mesenchyme from the mesoderm with some contribution from neuroectoderm (Economou, 1987). Their location allows for a rather long indolent preclinical course during which time the tumor can grow to significant proportions. This growth may result in local areas of necrosis or liquefaction as the tumor outstrips its vascular supply.

In classic reviews of these lesions the common tissue distribution in descending order is liposarcoma, leiomyosarcoma, and fibrosarcoma, followed by other histologies (McGrath et al, 1984; Karakousis et al, 1985, Jacques et al, 1990; Storm and Mahvi, 1991; Rossi et al, 1993). Malignant fibrous histiocytoma is expressed more prominently in contemporary series; however, owing to intensive pathologic interest in defining this disorder, many tumors previously described as variants of fibrosarcoma or liposarcoma have been reclassified as malignant fibrous histiocytoma (Rööser et al, 1991; Pezzi et al, 1992). Therefore fibrosarcoma has been replaced in frequency order by this condition.

Additionally, several previously characterized leiomyosarcomas are now correctly identified as gastrointestinal stromal tumors. By various histologic and immunohistochemical stratification it became apparent that these tumors were less like smooth muscle and more similar to cells of the myenteric nervous system. It is now believed that these tumors probably originate from stem cells

Table 52–1.
Tumors of the Retroperitoneum

Benign	Malignant
Lipoma	Liposarcoma
Pelvic lipomatosis	Leiomyosarcoma
Myelolipoma	Malignant fibrous histiocytoma
Leiomyoma	Rhabdomyosarcoma
Hemangiopericytoma	Fibrosarcoma
	Gastrointestinal stromal tumor
	Synovial sarcoma

Table 52–2.
Genetic Alterations in Retroperitoneal Tumors

TUMOR	ABERRATION	GENE(S) INVOLVED
Alveolar rhabdomyosarcoma	t(2;13) ($q^{35};q^{14}$)	*PAX3-FKHR*
	t(1;13) ($p^{36};q^{14}$)	*PAX7-FKHR*
Myxoid/round cell liposarcoma	t(12;16) ($q^{13};p^{11}$)	*TLS-CHOP*
Atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLPS)	Supernumerary ring chromosomes; giant marker chromosomes	Amplification of region 12q14-15, Including *MDM2, CDK4, HMGA2, SAS, GL1*
Dedifferentiated liposarcoma	Same as for ALT/WDLPS	Same as for *ALT/WDLPS*
Sporadic gastrointestinal stromal tumor	Activating kinase mutations	*KIT* or *PDGFRA*

that differentiate toward an interstitial cell of Cajal phenotype (Table 52–1) (Quek and George, 2009).

The molecular pathology of sarcomas is complex, and many lesions demonstrate the theme of specific chromosomal translocations creating a fusion chimeric transcription factor. A sophisticated understanding of these changes has been further developed in lesions less commonly seen in the adult retroperitoneum. A partial list of these alterations is presented in Table 52–2. These factors interact with the upstream regulatory component of a gene and can significantly affect the expression of that gene at the messenger RNA level. The nucleic acid binding domain of the chimeric transcription factor confers target specificity within the tissue genome while the transcription factor portion of this novel protein determines the transactivation potential and expression level of the target gene (Crozat et al, 1993; Ladanyi, 1995; Panagopoulos et al, 1996; Tschoep et al, 2007; Torsten and West, 2010). The description of this pathologic mechanism predated a similar finding recently described in prostate cancer.

Additionally, the development of extra abnormal chromosomes (ring chromosomes and giant rods) involving chromosome 12 can result in the amplification of certain gene products such as *MDM2* and *SAS*. *MDM2* can be involved in TP53 inactivation, which can contribute to carcinogenesis (Berner et al, 1996; Elkahloun et al, 1996). Series of investigations regarding soft tissue leiomyosarcoma have revealed exceptionally complex, multiple gene alterations that are not easily categorized. These molecular insights into the pathology of sarcoma have not translated into therapeutic targets as readily as the gastrointestinal stromal tumors histology but may provide approaches for future therapeutic strategies directed at these lesions (Van Roggen and Hogendoorn, 2000; Nielson and West, 2010).

Gastrointestinal stromal tumors demonstrate activated c-*KIT* mutations in 8% to 88% of lesions. Additionally, analogous gain of function mutations were demonstrated in platelet-derived growth factor receptor-α (PDGFR-α). These mutations suggested a role for targeted therapy in these lesions (Heinrich et al, 2003; Corless et al, 2004).

Gene expression profiling has also been explored in sarcomas, which allows the identification of some putative biomarkers in the study of these lesions and has suggested that malignant fibrous histiocytoma, rather than a separate entity, may represent a common end point of several different sarcomas (Tschoep, 2010).

BENIGN LESIONS

Lipomas

Lipomas consist almost entirely of mature fat and are uncommonly found in the retroperitoneum. They are probably the most common soft tissue tumor in humans. Most of these lesions occur superficially, but they may occur in other areas, such as the retroperitoneum. Deep lipomas within the retroperitoneum are usually not as well circumscribed as their superficial counterparts and can conform to irregular spaces in this body space (DeWeerd and Dockerty, 1952; Mowat and Clark, 1961). The adipocytes are normal or slightly larger in appearance and have a well-developed vascular network. There is very little in the way of nuclear irregularity. Differing levels of fibrous connective tissue can be found in these lesions. The rim of the lipocyte is reactive for S-100 protein. Although the majority of these masses are idiopathic, they can occasionally be a manifestation of steroid lipomatosis.

Pelvic lipomatosis, although not a distinct tumor per se, was first described in 1959 as an overgrowth of fat in the perivesical and perirectal area. It is a hyperplastic rather a neoplastic entity that can create a space-occupying lesion. Approximately two thirds of patients are African-American, and women are rarely affected (Heyns, 1991). The growth is diffuse rather than nodular, and often it is difficult to distinguish it from normal adipose tissue. The condition may be associated with cystitis glandularis (Yalla et al, 1975). The general clinical course is slowly progressive and may result in the need for urinary diversion (Klein et al, 1988). Occasionally, fat necrosis in these lesions can be mistaken for sarcomatous degeneration (Andac et al, 2003).

Myelolipoma

Myelolipoma is a tumor-like growth of mature fat and bone marrow elements. Although it usually occurs in the adrenal gland it can be seen as an isolated pelvic lesion (Chen et al, 1982; Sanders et al, 1995). It is distinct from extramedullary hematopoietic tumors, which are usually multiple and generally associated with mild proliferative diseases and skeletal disorders. These generally occur in patients older than age 40 years and are rarely greater than 5 cm (Fowler et al, 1992; Mukherjee et al, 2010). They are usually noted as incidental findings on imaging. The adrenal gland can create inferior renal displacement due to a radiolucent mass. Pathologically it may display the features of a lipoma or have a darker appearance if myeloid elements predominate. Adrenal myolipoma development may be secondary to prolonged stress and excessive stimulation with adrenocorticotropic hormone.

Leiomyoma

These generally rare lesions are seen in a distribution that represents smooth muscle tissue in the body. They are overwhelmingly found in the female genital tract but have also been reported in the urinary bladder. There are occasional reports of these tumors in the retroperitoneum, where they can grow asymptomatically to a considerable size. Leiomyomas stain positive for desmin, which separates them from their malignant counterpart. Extension of these lesions from the uterus into the vascular system can create tumor thrombi not unlike those seen with renal lesions (Clement, 1988).

MALIGNANT LESIONS

Liposarcoma

Liposarcomas are among the most common of primary retroperitoneal tumors and are distinguished by their often large dimensions and range of subtypes. These lesions have their peak incidence between ages 40 and 60 (Kindblom et al, 1975). They account for 10% to 15% of sarcomas, and approximately 20% of these lesions arise in the retroperitoneum. One unfortunate clinical feature of these lesions is their usual tendency to recur, often within the first 6 months after surgery. The principal tissue type is usually recapitulated at the time of recurrence. The rate of metastasis depends on the degree of tumor differentiation, with nearly 90% of poorly differentiated tumors metastasizing (Enterline et al, 1960; Spittle et al, 1971; Weiss and Rao, 1992).

Significant advances in cytogenetics have allowed the reclassification of these lesions on a molecular basis. Well-differentiated and dedifferentiated lesions are a continuum of lesions based on the genetic abnormality of giant and ring chromosomes usually involving chromosome 12. Gene amplification, particularly of *MDM2,* drives their pathology (Pilotti et al, 1998; Forus et al, 2001). Myxoid and round cell lesions (poorly differentiated myxoid) are another continuum that have fusion transcripts caused by translocations in chromosomes 16 and 12 as their principal pathologic feature. Pleomorphic liposarcomas are rare and poorly understood (Dal Cin et al, 1997).

Unlike benign lipomas, liposarcomas may bear little resemblance to classic fat-filled structures. The gross lesion is usually described as having a "fish flesh" appearance and, although generally encapsulated, it can often display invasive characteristics. Besides the retroperitoneum, these lesions arise in the deep soft tissues of the proximal extremities. They generally present as very large lesions when originating from the retroperitoneum.

Myxoid liposarcomas are the most common type and usually occur in the lower extremity. They account for 50% of sarcomas and represent a large proportion of retroperitoneal lesions. The peak presentation is in the fifth decade. These tumors display a background of stellate mesenchymal cells and a prominent capillary pattern often described as a "chicken wire" appearance. The distinct cell is the lipoblast, which is similar to the fetal adipocyte. These cells are noted by a lipid vacuole that scallops the nucleus. This creates the lipoma-like appearance of these lesions, which can demonstrate fusion proteins (TLS-CHOP) on molecular analysis. Higher-grade lesions tend to demonstrate a higher number of *TP53* mutations (Deitos et al, 1997). The round cell subtype is also referred to as a lipoblastic variant and is distinguished by sheets of round cells with lipoblastic differentiation. These lesions are considered the most aggressive part of the spectrum of myxoid lesions.

Well-differentiated liposarcomas most resemble lipomas and are usually designated as low grade. They are a common sarcoma of later life. Subvariants include the lipoma-like, inflammatory, sclerosing, and differentiated types. The first three variants are often confused with benign processes such as scarring or inflammation, whereas the differentiated subtype is often noted in long-standing retroperitoneal lesions and considered higher grade. Generally these lesions are now considered as a group with dedifferentiated lesions because they share genetic similarities.

Pleomorphic liposarcomas comprise 10% to 15% of liposarcomas and are defined as high-grade malignant variants with very bizarre nuclei and huge lipoblasts.

Leiomyosarcoma

Leiomyosarcomas account for less than 10% of all soft tissue sarcomas yet a significant percentage of retroperitoneal sarcomas because almost half of them appear in this region. They have a 2:1 female-to-male presentation and generally occur in middle age (mean age 60 years). The molecular pathology of these lesions has not been reduced to any common pathway and demonstrates a tremendous amount of variation on cytogenetic and molecular analysis. The tumors are usually categorized by site of origin (soft tissue, vascular, or superficial), although many of the soft tissue lesions are believed to originate from smaller blood vessels. On imaging examinations, however, they appear to have moderate to low vascularization.

Grossly, low-grade leiomyosarcomas can be difficult to distinguish from leiomyomas but higher-grade lesions display a more infiltrative fleshlike appearance (Shmookler and Lauer, 1983). Low-grade lesions are often distinguished from leiomyomas by their chromatin pattern and the number of mitoses (more than five mitoses per high-power field) present in the specimen.

Again, a continuum exists in the pathologic progression of these smooth muscle lesions; therefore the cut point between benign, moderate, and high grade may sometimes be arbitrary. There is little evidence of sarcomatous degeneration from benign leiomyomas. The characteristic pathologic finding of a leiomyosarcoma is malignant spindle cells with "cigar"-shaped nuclei. The muscle fascicles interweave. These tumors immunohistochemically stain for smooth muscle myosin, vimentin, and actin and less often for desmin. They stain negative for S-100. Ultrastructural features include bundles of thin cytofilaments, which can help distinguish leiomyosarcomas from other lesions.

A rare retroperitoneal variant of these tumors are leiomyosarcomas that originate from the great vessels (Demers et al, 1992). These occur predominantly in women. Tumors of the iliac vessels usually present as lower extremity edema, whereas those of the inferior vena cava can display findings consistent with Budd-Chiari syndrome (Cardell et al, 1971). Resection of these lesions is recommended when anatomically feasible. Survival, however, is usually less than 2 years, and many inferior vena caval tumors are unresectable because of the intrahepatic location of many of these lesions.

Malignant Fibrous Histiocytoma

Malignant fibrous histiocytoma was originally described in 1963 and has come to be the predominant histologic diagnosis for currently reported soft tissue sarcomas (Ozello et al, 1963). It was first defined as a sarcoma of primary histiocytic origin, but it is now believed that it is a lesion derived from fibroblast differentiation. Many pleomorphic variants of fibrosarcoma, liposarcoma, and

rhabdomyosarcoma have been reclassified into this category. With the thorough evaluation of a tumor specimen, distinct regions of leiomyosarcoma, liposarcoma, and other soft tissue sarcomas may be identified. In such cases the tumor may be defined by those findings and the mention of an associated malignant fibrous histiocytoma pattern (Weiss, 1982). These lesions are most often seen on the extremities and are less common in the retroperitoneum. Their molecular pathology is unclear. An analysis of these lesions in the retroperitoneum suggests that many of these could be reclassified as a dedifferentiated liposarcoma and that they may represent a common end point for several tissue types (Coindre et al, 2003; Tschoep et al, 2007). Storiform-pleomorphic, myxoid, giant cell, and inflammatory subtypes of malignant fibrous histiocytoma may coexist in a particular lesion.

The storiform-pleomorphic variant has a distinct but not pathognomonic pinwheel pattern caused by the collagen pattern of curling fascicles of cells. It is the most common variant, usually comprising 40% to 60% of most series. Although this pattern may predominate, it may not be present throughout the lesion in question. Areas of collagen or foamy cells may also be encountered. The nuclei tend to be irregular and large with discernible mitosis. The constellation of tissue histology and nuclear irregularities in addition to the inflammatory components differentiate this lesion from benign entities.

Myxoid malignant fibrous histiocytoma comprises 25% of this overall tumor type. It is often difficult to distinguish it from liposarcoma; however, the myxoid subtype has little neutral fat but is rich in mucopolysaccharide residing in intracytoplasmic vacuoles.

Malignant fibrous histiocytoma, giant cell type, is distinguished by large benign-appearing osteoclasts. Multinucleated giant cells and the stroma comprise the malignant components of this lesion. If cartilage or osteoid is detected, these lesions are classified as a soft tissue osteosarcoma, which usually has a poorer prognosis than malignant fibrous histiocytoma.

Fibrosarcoma

Fibrosarcomas are malignant tumors of fibroblast origin. They have a range of gradation and grossly display a classic "fish flesh" pattern with hemorrhage and necrosis. Low-grade lesions can display a herringbone/spindle-shaped histologic pattern. On retrospective review these lesions are often reclassified as malignant fibrous histiocytoma or as a desmoid lesion (aggressive fibromatosis). Therefore these lesions represent a smaller proportion of primary retroperitoneal tumors than previously reported. There is a greater incidence of blood-borne metastases from this tumor to the lung and bones (Bizer, 1971).

Rhabdomyosarcoma

Rhabdomyosarcoma comprises a minor percentage of reported retroperitoneal sarcomas yet is a significant lesion in pediatric oncology as well as pediatric tumors associated with the genitourinary system. These lesions are generally classified as embryonal, botryoid, alveolar, or pleomorphic, with a spindle cell subtype more recently described within the embryonal type (Horn and Enterline, 1958; Cavazzana et al, 1992). The pathology of these lesions is associated with chromosomal abnormalities and the fusion transcripts associated with these translocations.

Embryonal rhabdomyosarcoma comprises more than half of all rhabdomyosarcomas and has a large array of anatomic locations, including the genitourinary tract and retroperitoneum. It can range from very well to poorly differentiated lesions and can express the multiple stages of muscle development. Botryoid lesions are an anatomic variant of the embryonal type and generally found in hollow viscera. The spindle cell subtype is noted for its favorable clinical behavior.

Alveolar rhabdomyosarcoma accounts for approximately 20% of all rhabdomyosarcomas and tends to occur more frequently in the extremities. The tumor is arranged in aggregates of round or oval cells that create irregular spaces reminiscent of alveoli. They can be classified into subtypes based on fusion gene transcripts *(PAX-FKHR)*. These tissues may be surrounded by fibrous septa, and areas of necrosis are not uncommon.

Pleomorphic rhabdomyosarcoma comprises 5% of adult rhabdomyosarcomas and generally occurs in older patients. It usually is found in the extremities and is not unlike malignant fibrous histiocytoma in its appearance. The absence of cross striations makes diagnosis difficult. With all rhabdomyosarcomas, immunostaining for desmin, myoglobin, and muscle-specific actin is useful.

Malignant Hemangiopericytoma

These rare lesions originate from pericytes, which are unique cells that arborize about small vessels and capillaries. Their contractile properties allow them to control microvascular flow and permeability. Fewer than 200 of these lesions have been described, yet 25% of them have occurred in the retroperitoneum or pelvis. They are usually well circumscribed and, if possible, complete surgical excision is warranted. Hemangiopericytomas display a rich vascular pattern and stain positive for factor VIIIa. They are negative for desmin and actin. The clinical behavior of these lesions is difficult to predict, but metastases may develop in 20% to 50% of cases. Those lesions with more than four mitoses per 10 high-power field have a worse prognosis (Enzinger and Smith, 1976; Zirkin 1977).

DIAGNOSIS

Because of their slow growth and anatomic location, retroperitoneal tumors (usually sarcomas) tend to grow to a large size before they are detected. In one series of soft tissue sarcomas the average size at diagnosis for extremity lesions was 5 cm, whereas retroperitoneal lesions were 16.5 cm (Hueman et al, 2008); thus such lesions can often be enormous by usual pathologic standards. Although the age at presentation is distributed across a large spectrum, the majority of patients are diagnosed with retroperitoneal tumors in the sixth decade of life. Because the progression of symptoms is slow there is usually a lag time of 5 months from initial symptoms to diagnosis. The principal clinical finding is an abdominal mass and abdominal pain (60% to 80%) (McGrath, 1984). Many patients also experience nausea and vomiting and weight loss (20% to 30%). Neurologic findings are noted in 30% of patients (Cohan et al, 1988). Lower extremity edema is seen in 17% to 20% of patients whereas urinary symptoms are surprisingly rare, occurring in 3% to 5% of patients in most series.

Physical examination will generally demonstrate a protuberant abdomen that may be accompanied by an appearance of extremity wasting. Lymphadenopathy is not usually associated with retroperitoneal sarcomas (<5%) (Fong et al, 1993). Lower extremity edema and/or increased abdominal wall venous markings suggest the presence of vena cava compression or obstruction.

Diagnostic imaging is imperative to delineate the anatomic limits of the lesion and assess the integrity and function of

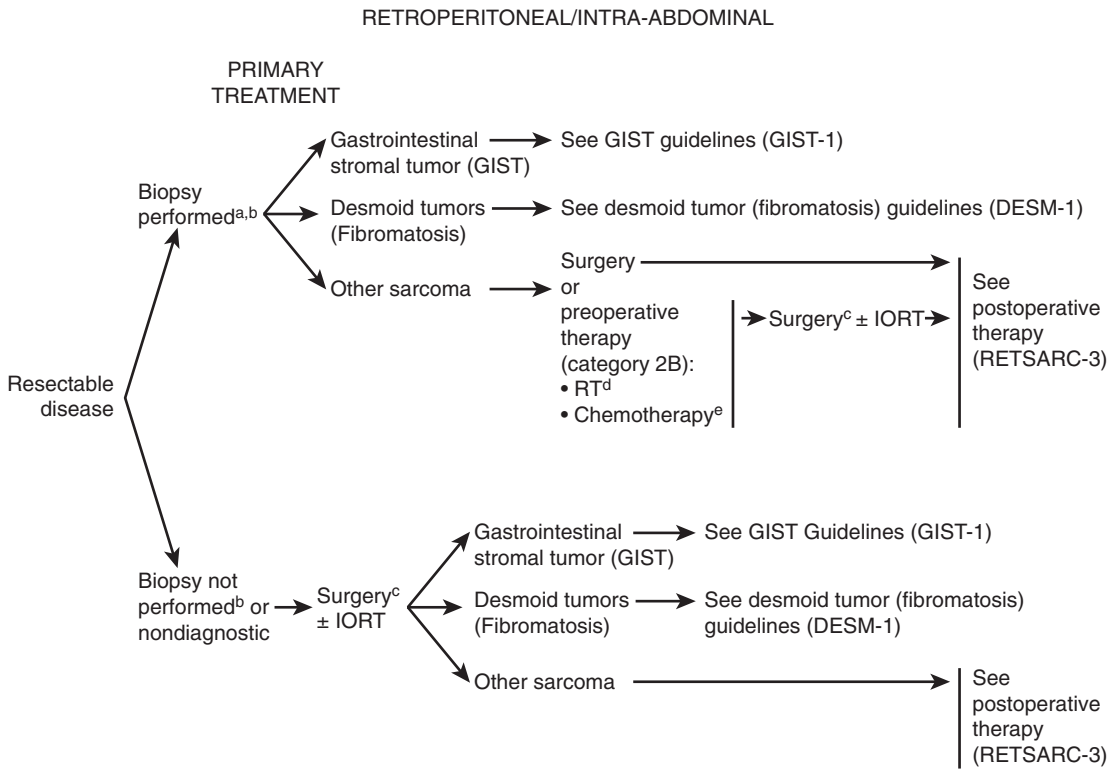
adjacent organs. This is most appropriately demonstrated with cross-sectional imaging (Neifeld et al, 1982; Chang et al, 1987). Important issues to address with this modality are bilateral renal function, the presence or absence of visceral metastases, and lymphadenopathy. Attention should also be given to the axial skeleton. Tumor involvement of neural foramina suggest unresectability of the lesion. Germ cell tumors, which should be suspected in young men and diagnosed through a thorough physical examination and testicular ultrasound examination, are usually distinguished on computed tomography (CT) from other primary retroperitoneal lesions. This is also generally true for lymphomas. CT, however, is not particularly diagnostic for the multiple tumor histologies of primary retroperitoneal tumors except for a liposarcoma with high fat content.

Cross-sectional imaging has largely supplanted a multiple-study approach to staging, and the application of magnetic resonance arteriography allows for the delineation of vascular involvement by these uncommon lesions. From a practical standpoint, CT and magnetic resonance imaging are complementary rather than redundant and should be employed as needed (Bland et al, 1987). The majority of information necessary for appropriate staging should be obtainable through a CT scan with and without contrast enhancement and chest imaging.

The role for preoperative biopsy is controversial. In some cases imaging will not provide a reasonable diagnosis, in which case a biopsy prior to definitive resection may be required (Barth et al, 1992). Most surgeons agree that surgical exploration is the next most appropriate step for a mass suspected of being a sarcoma and that a preoperative biopsy should be reserved for cases in which a diagnosis will change therapy, such as the need for neoadjuvant imatinib mesylate for gastrointestinal stromal tumors or protocols of neoadjuvant chemotherapy for germ cell tumors or lymphomas (Windham and Pisters, 2005). When a biopsy is performed, a CT-guided core biopsy is the preferred approach. In the case of gastrointestinal stromal tumors a biopsy may be made endoscopically, which is preferable because these lesions are vascular and tend to fragment (Fig. 52–1) (Rabin et al, 2009).

STAGING

The principal staging system used for soft tissue sarcoma is the American Joint Committee on Cancer (AJCC) system (Table 52–3). Alternate systems are the French Federation of Cancer Centers Sarcoma Group system and the National Cancer Institute system. Staging is driven in large part by tumor grade, which in the revised AJCC system is three tier. Tumor grading is determined by several factors, including atypical mitosis, cytoplasmic and nuclear pleomorphism, and necrosis (Leyvraz and Costa, 1988; Kulander et al, 1989). Grade 1 lesions are denoted by few mitoses, acellularity, minimal alterations of the nucleus, and absent or few nucleoli. Scoring often takes into consideration other factors such as tumor size and patient age. Grade 2 lesions display small- to moderate-sized nucleoli, moderate nuclear pleomorphism, irregular chromatin distribution, and a moderate amount of mitoses. Areas of



[a]See Principles of Patholigic Assessment of Sarcoma Specimens (SARC-A).
[b]Biopsy required of considering preoperative therapy, including endoscopic biopsy for suspected GIST lesions.
[c]See Principles of Surgery (SARC-C).
[d]See Guidelines for Radiation Therapy (SARC-D).
[e]See Principles of Systemic Therapy (SARC-E).

Figure 52–1. National Comprehensive Cancer Network treatment algorithm for retroperitoneal sarcoma.

Table 52–3.

Classification and Staging of Retroperitoneal Tumors

Primary Tumor (T)		Anatomic Stage/Prognostic Groups				
		Stage	T2b	N0	M0	G1,GX
TX	Primary tumor cannot be assessed	IIA	T1a	N0	M0	G2, G3
T0	No evidence of primary tumor		T1b	N0	M0	G2, G3
T1	Tumor ≤5 cm in greatest dimension*					
T1a	Superficial tumor	IIB	T2a	N0	M0	G2
T1b	Deep tumor†		T2b	N0	M0	G2
T2	Tumor >5 cm in greatest dimension†					
T2a	Superficial tumor	III	T2a, T2b	N0	M0	G3
T2b	Deep tumor		Any T	N1	M0	Any G
Regional Lymph Nodes (N)						
NX	Regional lymph nodes cannot be assessed	IV	Any T	Any N	M1	Any G
N0	No regional lymph node metastasis					
N1	Regional lymph node metastasis					
Distant Metastases (M)						
M0	No distant metastasis					
M1	Distant metastasis					
Histologic Grade						
GX	Grade cannot be assessed					
G1	Grade 1					
G2	Grade 2					

*Superficial tumor is located exclusively above the superficial fascia.
†Invasion of the fascia; deep tumor is located exclusively beneath the superficial fascia, superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia.

necrosis may be noted in the microscopic field. Grade 3 lesions are characterized by numerous mitoses, gross chromatin clumping, moderate or considerable necrosis, and variation in nuclear morphology. The distinction between T1 and T2 lesions is made at 5 cm, but for matters of retroperitoneal lesions all are considered deep.

MANAGEMENT

Surgery

Extirpative surgery is the principal and most effective form of therapy for primary retroperitoneal tumors. Preoperative planning to assess the extent of the disease is essential because successful surgery is defined by complete excision of the mass with adequate margins of normal tissue. A complete resection rate between 38% and 78% (average 55%) is reported in many large series (Sindelar et al, 1993; Karakousis and Velez, 1996; Lewis et al, 1998; Stoeckle et al, 2001; Gronchi et al, 2004). In several large series of retroperitoneal sarcomas, univariate and multivariate analysis of independent treatment variables has been reported. In more than 280 patients completeness of resection was the single most important positive predictive feature (Bevilacqua et al, 1991; Catton et al, 1994; Singer et al, 1995; Anaya et al, 2009, Bonvalot et al, 2009). Intermediate or high tumor grade is a strong negative feature (Bevilacqua et al, 1991; Anaya et al, 2009). In most reported series, intermediate- and high-grade lesions comprise 55% to 70% of the tumors described. Tumor histology, tumor size, or patient age were not significant factors in survival in multiple-variable analysis (Wurl et al, 2000; Ferrario and Karakousis, 2003). Therefore carefully planned and skillfully executed surgical therapy is critical for any chance at long-term success (Malerba et al, 1999; Bautista et al, 2000).

Operative Technique

The classic approach for surgery on these lesions is described through long midline or chevron incisions. The tumors are usually right sided or left sided; however, a few actually rise from the midline. A full flank position such as that employed for renal stone surgery is discouraged because it can limit exposure to the full retroperitoneum or abdomen (Storm and Mahvi, 1991; McGrath, 1984). Because these lesions are not compartmentalized by the retroperitoneum they can cross many anatomic boundaries. It is important, therefore, to determine the potential for resectability, beyond that presupposed through imaging. This is first accomplished by developing a subadventitial plane along the lateral borders of the great vessels extending dorsally between the spine and psoas and quadratus muscles. In this manner one can determine if the tumor has spread along a spinal nerve route and into the spinal foramina or even farther into the spinal cord. If this is the case, the tumor is generally considered unresectable. It has also been suggested that the lateral incision of the peritoneum into the deep body wall is important to explore on a level posterior to the spinous processes. If the operator's fingers can bimanually palpate the tumor, this sarcoma is considered resectable.

It is imperative in the preoperative period that both the patient and the surgeon realize the potential need for en-bloc resection of affected organs. This can include vascular structures as well as the kidney and a portion of the diaphragm, liver, stomach, gallbladder, spleen, pancreas, and gut. In a review of several series, up to 68% of operations required resection of an adjacent organ to ensure adequate negative margins. The most frequently resected organs are listed in decreasing order in Table 52–4. In one review (Russo et al, 1997) it was reported that 20% of patients undergoing surgery for a retroperitoneal sarcoma required nephrectomy. The majority of them (72%) underwent this during their initial

Table 52–4.

Frequency of Resection of Specific Organs in Surgery for Retroperitoneal Tumors

ORGAN	FREQUENCY OF RESECTION (%)
Kidney	32-46
Colon	25
Adrenal gland	18
Pancreas	15
Spleen	10

Table 52–5.

Comparison of Surgical Outcomes in Selected Series of Tumors of the Retroperitoneum

SERIES	NO. OF PATIENTS	RESECTION (%)		MEAN SURVIVAL (mo)	
		Complete	Partial	Complete	Partial
Karakousis et al, 1996	68	40	10	84	48
Kilkenny et al, 1996	63	78	16	41	9
McGrath et al, 1984	47	74	16	120	24
Dalton et al, 1989	116	54	21	72	13

resection. The usual reason for nephrectomy was total encasement of the organ, followed by dense adherence to the kidney and less often by direct invasion of the renal unit. Although a Dacron graft can be employed to replace a portion of resected aorta there is debate among surgeons with regard to the need for venous reconstruction. Many believe that the venous collateral vessels that develop secondary to vena caval compression are adequate to allow for appropriate drainage from otherwise vascular-compromised organs. There has been a greater trend toward major blood vessel reconstruction in an attempt to achieve complete resection of retroperitoneal lesions, but this must be done with careful preoperative planning (Song et al, 2009). In such cases, vascular patency was maintained in approximately 80% of patients, with the majority of thromboses occurring within the first month postoperatively.

A special case is the presence of a leiomyosarcoma of a major vessel such as the inferior vena cava. This has been addressed by inferior vena caval ligation, primary or patch repair, or tube grafting (Hollenbeck et al, 2003). A local recurrence occurred in 33% of patients, and distant disease was noted in 48%. The 3- and 5-year disease-specific survival rates were 76% and 33%. When bowel viability is questionable that segment should be resected if possible. An area of caution is in the resection of the femoral nerve, which may be considered in cases of deep involvement of the psoas (Jones et al, 2009). In one series, 6 of 10 patients developed fractures during long-term follow-up as a result of falls related to absent active knee extensors. Although many visceral organs can be resected, unresectability is usually denoted by sarcomatosis, nerve root involvement, pelvic side wall involvement, malignant ascites, or the presence of distant metastasis (McGrath 1984; Storm and Mahvi, 1991; Karakousis and Velez, 1996).

When defining the operative field it is often necessary to release multiple intra-abdominal adhesions. This must be performed meticulously because an enterotomy and subsequent fistula formation can cause major morbidity. Tactile as well as visual perceptions aid in avoiding violation of the bowel. In addition, the use of sharp, curved Mayo scissors rather than Metzenbaum scissors may aid in avoiding this complication. During the dissection of a large tumor mass it is often necessary to shift the location of the dissection when one particular area becomes difficult owing to concerns of a clear margin or the potential for vascular damage. A centripetal dissection allows one to dissect those areas that are amenable to dissection and that in turn may free up a previously more constrained area of the operative field (Fernandez-Trigo and Sugarbaker, 1993). Morbidity and mortality rates for contemporary surgical series are acceptable. An operative mortality of 2% to 7% with morbidity rates of 6% to 25% is the norm. Hemorrhage, intra-abdominal abscess, and enterocutaneous fistula are the most commonly described complications.

Another surgical technique is the modified thoracoabdominal approach, which has been developed and popularized by Skinner (1977). Those familiar with the technique believe that it allows maximum exposure to the posterior retroperitoneum, which is often a difficult area to assess through a midline incision. Additionally, it provides access and control to the ipsilateral great vessels above the diaphragm. Whether a left- or right-sided procedure is performed, excellent exposure can be developed in the contralateral retroperitoneal region without difficulty.

Several recent studies have also suggested the potential value of aggressive surgery in retroperitoneal soft tissue sarcoma, which includes the resection of clinically normal-appearing organs such as the ipsilateral renal unit (Gronchi et al, 2009; Bonvalot et al, 2010). Although it was demonstrated that this could be done with a reasonable margin of safety and lower local recurrence rates (28% vs. 48%), there was no difference in overall survival rates between aggressive and less aggressive surgery. Furthermore, as one might expect, an increase in overall morbidity was noted as more normal organs were resected. Widespread adoption of such an approach has not been recommended until prospective studies demonstrate an advantage.

Surgical Outcome

The classic overall survival for patients presenting with retroperitoneal sarcomas is poor. In a multi-institutional review the 2-, 5-, and 10-year mean survival rates for patients with this disease were 56%, 34%, and 18%, respectively (Storm and Mahvi, 1991). Recent series suggest 2-year survivals of more than 70% and 5-year survivals of 50% to 60% in patients without metastases (Lewis et al, 1998; Stoeckle et al, 2001). The effective surgical management of retroperitoneal tumors has been limited by their size at presentation, which often results in secondary organ involvement. This has a poor impact on the ability to achieve negative surgical margins even with the resection of adjacent organs. Historically, a complete surgical resection with negative margins was achieved in 50% to 60% of patients. The more recent series demonstrate complete resection rates in the 60% to 80% range, which may be due to improvements in imaging, preoperative planning, and surgical technique.

Those patients who achieve a complete resection display superior survival to those patients with incomplete resection of their tumors (Table 52–5). This is also supported in a laboratory model (Tsivian et al, 2002). In an analysis of microscopic margins, however, positive margins at this level of pathologic resolution had little impact on recurrence-free survival (Stojadinovic et al, 2002; Anaya et al, 2009).

On average the 5-year survival of patients with completely resected tumors is 54% compared with 17% for incomplete resections; at 10 years this difference is 45% to 17%. Thus a nearly 40% survival advantage is seen at 5 to 10 years in those patients with complete surgical resection of their lesion. Tumor recurrence after complete surgical resection, however, is significant. There is a 72% chance of local recurrence at 5 years and a 90% chance of recurrence at 10 years in most series. These data imply fairly poor survival at 15 years (Storm and Mahvi, 1991; Thomas et al, 2009).

Reoperative surgery for the treatment of recurrent retroperitoneal sarcoma can be of value. Over 60% of patients may experience a complete resection (Lewis et al, 1998). In one series, 30 patients with a previous complete resection of the primary lesion experienced local tumor recurrence at a mean interval of 23 months, and 60% of these patients were rendered free of disease after reoperative surgery. To accomplish this, 33% of these patients required the resection of adjacent viscera. Those patients who achieved a complete resection with a second operation had a 33-month median survival compared with a 14-month median survival in those patients who did not experience a second complete resection (Wang et al, 1994). In a recent series, 79% of patients achieved palliation of tumor-related symptoms on first resection of a recurrence and survival was improved with a complete or incomplete resection compared with biopsy only (Grobmyer et al, 2009). Second or third recurrences occurred over shorter intervals and were less likely to be completely resectable. Tumor grade was the most important determinant of long-term survival.

The role of subtotal resection has never been clearly established, yet some data suggest that this may have some positive value compared with palliative or debulking surgery. The argument for the possible value of incomplete resection has been made in the management of liposarcomas. In a series of 55 patients, 75% received symptom relief from their surgery and partial resection compared with biopsy or exploration alone, which had a significant impact on increased survival (26 vs. 4 months) (Shibata et al, 2001). In another report, 22 patients with complete resection of tumor displayed a similar median survival to 15 patients with subtotal resection (median survival > 120 months), compared with those only having a partial palliative resection or exploration (12 to 20 months) (Shiloni et al, 1993). An aggressive surgical approach in cases in which near-complete resection can be obtained has also been advocated by others (Karakousis and Velez, 1996). In general, partial debulking does not confer a survival advantage for retroperitoneal sarcoma except perhaps in the case of lower-grade liposarcoma (Anaya et al, 2009).

Palliative surgery for unresectable disease has to be determined on a case-to-case basis. The usual consideration is gastrointestinal obstruction or pain. In one large series of palliative attempts, perioperative mortality was 9% and complications occurred in 29% of patients (Yeh et al, 2005). Alternate options include radiation therapy, chemotherapy, and supportive care.

Considering the relative rarity of retroperitoneal sarcomas it is reasonable to consider if such lesions should be exclusively treated at high-volume centers. In a review of 260 soft tissue sarcomas treated over a 3-year period, 86 were treated at one center while the remainder were managed at 38 other centers (Bhangu et al, 2004; Bonvalot et al, 2010). The rate of local recurrence was 19% at the specialty center and 39% in aggregate at the other hospitals. Survival was significantly different between groups for larger (>5 cm) and high-grade lesions. Similarly, in a registration study of over 4000 soft tissue sarcomas treated at more than 200 centers in Florida, 68.1% were treated at low-volume centers and the remainder at seven other sites (Gutierrez et al, 2007). There were significant differences in 30- and 90-day mortality and improved survival for high-grade lesions, lesions larger than 10 cm, and retroperitoneal sarcomas (39 vs. 31 months, $P = .011$). On multivariate analysis, center effect was a significant independent predictor of improved survival (odds ratio = 1.292, $P = .047$).

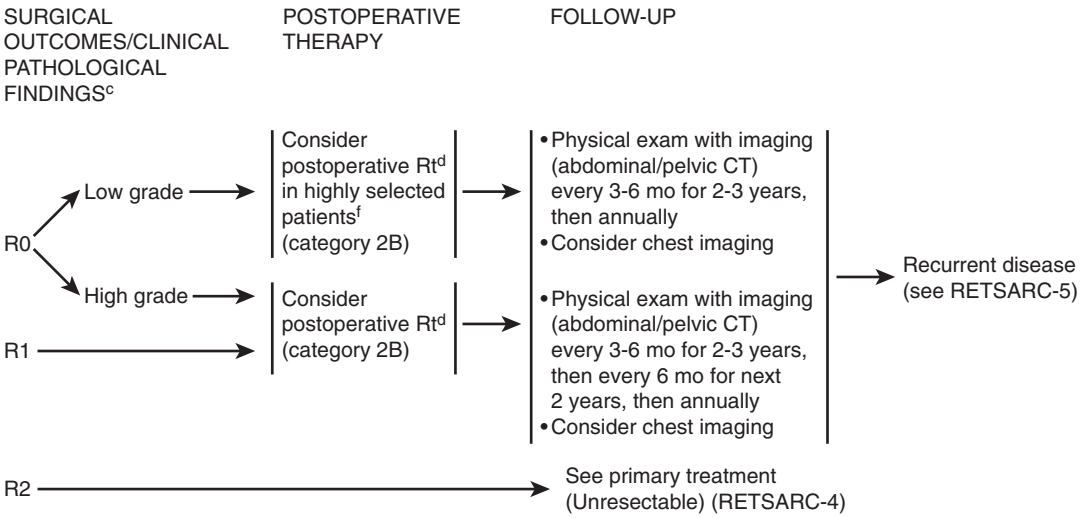
Postoperative monitoring of patients with primary retroperitoneal sarcoma has been established by authority opinion based on the rapidity of recurrence, the advantage of re-resection, and the lethality of this condition. It would be appropriate to perform abdominal and pelvic CT, chest imaging, and biochemistry profile with a complete blood cell count every 3 to 6 months for 2 to 3 years. A lengthening of this follow-up interval may be considered only after 3 years. Data support the concept that close follow-up allows for early detection and less bulky recurrences that allow for more successful salvage surgery (Fig. 52–2) (Gupta et al, 2000).

The effect of tumor grade on patient survival cannot be underestimated. Low-grade lesions display a 50% survival advantage over intermediate- and high-grade lesions at 5 years (74% to 24%) and a 30% survival at 10 years (42% to 11%). This is demonstrated even in the presence of total surgical resection. Although staging systems generally demonstrate three or four tumor grades, outcomes generally dichotomize into high grade and low grade. In an attempt to better stratify outcomes an effort has been made to establish prognosis in retroperitoneal sarcoma by histology (Anaya et al, 2009, 2010). More than 300 patients treated over a decade were categorized as having atypical lipomatous tumor, nontypical lipomatous tumor (liposarcoma), and other tumors. This provided outcome stratification for all three groups and applied to primary and recurrent lesions. On multivariable analysis, liposarcoma and "other" histologic processes were independent predictors of survival. The concordance ratio was approximately 0.74. This analysis has been incorporated into a retroperitoneal sarcoma–specific postoperative nomogram in which age, tumor size (>15 cm), type of presentation, multifocality, completeness of resection, and histology are independent predictors of overall survival, with a concordance index of 0.73 (Fig. 52–3) (Anaya et al, 2010; Ardoino et al, 2010).

Although aggressive surgical resection of retroperitoneal sarcoma serves as the foundation of therapy for this condition, the high local recurrence rate and eventual mortality from this disease has prompted the exploration of adjuvant therapeutic modalities.

Radiation Therapy

Radiation therapy has been used successfully in extremity sarcoma, and therefore it is reasonable to consider it for local control in retroperitoneal sarcoma. Unfortunately, the total dose is often limited by radiosensitive structures in the tumor bed. Radiation therapy may be delivered in the neoadjuvant, intraoperative, and adjuvant settings. It may be administered as external-beam therapy or brachytherapy. A preoperative approach is attractive because the viscera are often displaced by the tumor volume and a lack of surgical adhesions further reduces dose to the bowel. Additionally, the effective radiation dose is lower in the preoperative setting. The feasibility of administering radiation in the neoadjuvant setting has been demonstrated in several small series (Gieschen et al, 2001; Jones et al, 2002; Petersen et al, 2002). Unfortunately, many series will combine this with brachytherapy or intraoperative radiation and therefore not give a meaningful sense of the toxicity of neoadjuvant therapy alone. In a series of 40 patients



[c]See Principles of Surgery (SARC-C)
[d]See Guidelines for Radiation Therapy (SARC-D)
[f]For example, patients with an extremely large tumor, critical anatomic surface where recurrence would cause morbidity, or close margins.

Figure 52–2. National Comprehensive Cancer Network follow-up recommendations for retroperitoneal sarcoma.

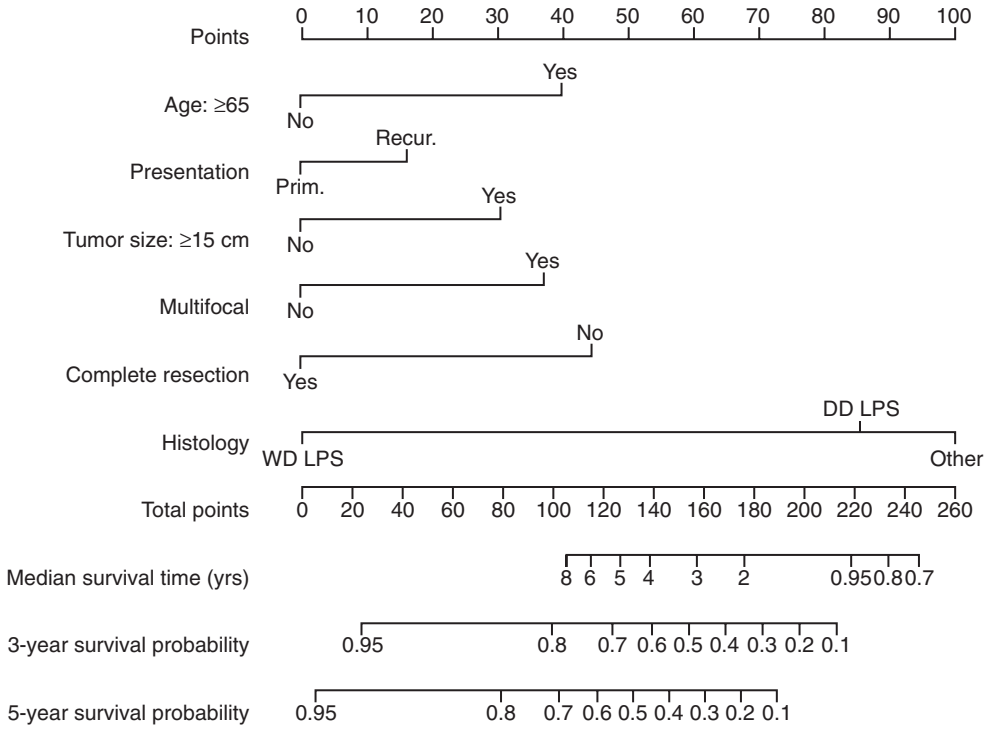


Figure 52–3. Postoperative nomogram for median, 3-, and 4-year overall survival in patients with nonmetastatic resectable disease. (From Anaya DA, Lahat G, Wang X, et al. Postoperative nomogram for survival of patients with retroperitoneal sarcoma treated with curative intent. Ann Oncol 2010;21[2]:397–402.)

receiving preoperative or postoperative therapy, significantly more complications were noted in the postoperative cohort (Zlotecki et al, 2005). In another review of 72 patients who received preoperative therapy, 46% had a 5-year disease-specific survival and those who completed therapy and had a macroscopically complete resection demonstrated a 60% disease-specific survival (Pawlik et al, 2006). Attempts at phase 3 trials have been limited by poor accrual (Kane, 2006).

Some small studies have evaluated combination neoadjuvant radiation with chemotherapy usually doxorubicin-based treatment. In one study of 23 patients, 26% of patients demonstrated a clinical and pathologic complete response. In another investigation, 90% of patients who underwent a laparotomy after irradiation and chemotherapy had an R0 or R1 resection (Pisters et al, 2003). The feasibility of this approach has been demonstrated, yet phase 2 trials are needed.

Intraoperative radiation therapy is feasible and has the advantages of administering a dose in a single large fraction. The largest series using this technique are somewhat confounded by the use of external-beam irradiation as well (Sindelar et al, 1993; Gieschen et al, 2001). In both studies, local control rate was significantly higher in the intraoperative radiation therapy group. At 8 years, the phase 3 trial demonstrated a significant difference (20% vs. 80%) in local control but toxicity was significantly higher in the cohort receiving intraoperative radiation therapy.

Chemotherapy

Multimodal therapy for extremity sarcoma has provided an inference for the role of chemotherapy in retroperitoneal lesions. The majority of large-scale chemotherapy trials, however, comprise patients with extremity disease, so these findings may not be directly applicable. Overall, the argument for adjuvant therapy seems reasonable because the potential for distant recurrence is significant with retroperitoneal lesions. The data in this regard have been somewhat contradictory, yet a meta-analysis of these studies suggests a slight advantage of 4% overall survival for the use of adjuvant doxorubicin therapy to decrease the risk of death and recurrence in patients with high-grade lesions (Gilbeau et al, 2002; Pervaiz et al, 2008). Such therapy is associated with toxicity, however, and has mixed acceptance for retroperitoneal lesions (Zalupski et al, 1993).

The association of c-*KIT* mutations and alterations in PDGFR-α suggest a role for tyrosine kinase inhibitors and other targeted therapy in gastrointestinal stromal tumors. One trial of adjuvant imatinib therapy for high-risk, completely resected gastrointestinal stromal tumors demonstrated a significant 1-year relapse-free survival advantage (97% vs. 83%), and other trials are in progress (Gold et al, 2006).

METASTATIC DISEASE

Approximately 20% of patients with soft tissue retroperitoneal sarcoma will present with metastatic disease. Those patients who experience recurrence after treatment for localized disease generally do so by 60 months. Recurrence is demonstrated at multiple sites (47%), or it is local (30%). Isolated pulmonary lesions occur in approximately 20% of patients. Three-year survival in patients undergoing complete excision of lung-only lesions is 38%.

Doxorubicin is the foundation for chemotherapy in advanced sarcoma (Gottlieb et al, 1975; Borden et al, 1987). The general response rate is 20% to 25%, but sustained complete responses are uncommon. Median survival is 7.7 to 12 months (Santoro et al, 1995). Other classic agents demonstrating activity include dacarbazine, ifosfamide, methotrexate, and cyclophosphamide. In several phase 3 studies, however, combination treatments were not superior to single-agent doxorubicin (Yap et al, 1980; Antman et al, 1993; Edmonson et al, 1993). Other phase 3 studies have not demonstrated superior response yet do show significant increased toxicity (myelosuppression and cardiac) with the addition of other agents (Santoro et al, 1995). Another combination regimen of mesna, doxorubicin (Adriamycin), ifosfamide, and dacarbazine (MAID) has been successful in neoadjuvant programs for sarcomas of the extremities compared with historical controls, yet less data are available with regard to other soft tissue sites. In general, salvage therapy for patients has been associated with poor responses and little in the way of advantages in quality of life (O'Sullivan and Bell, 2003; O'Sullivan et al, 2003).

More recently, gemcitabine has been investigated as an initial agent in advanced disease and for salvage therapy. As a single agent the results have been disappointing, with response rates below 5% in either setting (Okuno et al, 2003; Svancarova et al, 2002). The combination of gemcitabine and docetaxel in patients with unresectable leiomyosarcoma, however, demonstrated a 10% complete response and an overall response of 53%. It was believed to be a tolerable and active combination in treated and untreated patients (Hensley et al, 2002).

Disseminated intraperitoneal spread of disease is very difficult to treat. A novel approach is the application of photodynamic therapy (Bauer et al, 2001). In a preliminary report, patients underwent surgical debulking and were treated with porfirmer sodium (Photofrin) and laser light. Of an initial 11 patients, 5 demonstrated no evidence of disease over a range of 2 to 17 months. The advancement of such technologies and the implementation of small molecule therapy may provide improved outcomes for such patients in the future.

In advanced gastrointestinal stromal tumors the response to classic combination chemotherapy is negligible (Edmonson et al, 2002). Imatinib demonstrated an overall objective response rate of 53.7% and stable disease in 27.9% of patients (Demetri et al, 2002). Follow-up has demonstrated a median time to progression of 24 months and median overall survival of 57 months (Blanke et al, 2008). Sunitinib, another small-molecule tyrosine kinase inhibitor that affects multiple kinases, has demonstrated activity in imatinib-refractory/intolerant patients (Demetri et al, 2009). The success of targeted therapy in this lesion has encouraged further research using novel targeted therapy in other forms of metastatic retroperitoneal disease.

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The complete reference list is available online at www.expertconsult.com.

chapter
53

Urothelial Tumors of the Upper Urinary Tract and Ureter

Arthur I. Sagalowsky, MD ● Thomas W. Jarrett, MD ● Robert C. Flanigan, MD

Basic and Clinical Biology
Epidemiology and Etiology
Natural History
Pathology
Prognostic Factors
Diagnosis
Staging
Treatment

BASIC AND CLINICAL BIOLOGY

An upper urinary tract tumor can be defined as any neoplastic growth that affects the lining of the urinary tract from the calyces to the distal ureter. These tumors display behaviors that are similar to those of tumors arising in bladder, but they also have many characteristics that separate them from those tumors. For example, unlike bladder urothelial cancers, upper urinary tract cancers are relatively less common and are associated with several familial syndromes. They are more difficult to visualize directly and to reach with topical therapies; and, given the anatomic difference between the upper and lower urinary tracts in terms of muscle thickness and other factors, they may have different prognoses.

EPIDEMIOLOGY AND ETIOLOGY

Incidence and Mortality Rates

The etiology, natural history, pathology, detection, and staging of urothelial tumors are presented in Chapters 80, 81, and 82. Only the features that differentiate upper tract tumors from bladder tumors and that are pertinent to treatment are revisited here.

Upper urinary tract urothelial tumors involving the renal pelvis or ureter are relatively uncommon, accounting for 5% to 7% of all renal tumors and about 5% of all urothelial tumors (Fraley, 1978; Melamed and Reuter, 1993; Jemal et al, 2004). Because renal pelvic tumors generally are not reported separately, worldwide statistics vary substantially between nations and are not accurate. However, the highest incidence appears to occur in Balkan countries, where urothelial cancers represent 40% of all renal cancers.

The frequency of urothelial tumors of the upper tract is increasing, even though the tumors represent only a small percentage of all urothelial neoplasms (McCarron et al, 1982; Richie, 1988; Williams, 1991; Herr, 1998; Messing and Catalona, 1998; Munoz and Ellison, 2000; David et al, 2009). The peak incidence of upper tract tumors is 10 per 100,000 per year, occurring in the age range of 75 to 79 years. Fortunately, synchronous bilateral urothelial upper urinary tract tumors are very rare (Holmang and Johansson, 2004). In one series from Sweden the percentage of upper tract tumors that were bilateral was 1.6%, preceded in 80% of cases by a bladder cancer diagnosis. There may be a decreasing incidence of bilaterality secondary to the prohibition of phenacetin-containing analgesics in the 1960s. An evaluation of data from 1973 to 1996 with use of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database showed 9057 cases, 5379 of the renal pelvis and 3678 of the ureter. In comparison of age-adjusted annual incidence rates, an increase in ureteral neoplasms from 0.69 to 0.73 per 100,000 person-years was found but no change in the incidence of renal pelvic tumors was apparent. In addition, the rate of in-situ neoplasm increased from 7.2% to 23.1%. **The incidence of ureteral and renal pelvis tumors in the United States from 1985 to 1994 was 0.73 and 1.0 each per 100,000 person-years, respectively, based on the SEER database** (Munoz and Ellison, 2000). **The 5-year disease-specific survival was 75% overall and 95%, 88.9%, 62.5%, and 16.5% for in-situ, localized, regional, and distant disease, respectively.** Several factors account for this increase in survival for patients with upper tract tumors. Survival of patients with the more prevalent transitional cell carcinoma (TCC) of the bladder is improved owing to more effective diagnosis and treatment. This produces a length-time bias of longer time at risk for development of upper tract tumors. The National Cancer Data Base (NCDB) for the United States for the years 1993 to 2005 identified a total of 334,480 bladder cancers, 15,105 renal pelvis cancers, and 10,128 ureteral cancers (David et al, 2009). There was a significant increase in high-grade tumors in each of the sites during those years. The percentage of early stage tumors increased for both the renal pelvis and the ureter. However, overall, there was no change in survival during those years. Upper tract urothelial tumors are rarely diagnosed at autopsy but rather present clinically during the patient's lifetime (Resseguie et al, 1978). It also appears that the true incidence of upper tract tumors is increasing as the population ages. Patients with upper tract cancer are generally older than patients with bladder tumors (Melamed and Reuter, 1993). Upper tract tumors rarely present before the age of 40 years, and the mean age at presentation is 65 years (Anderstrom et al, 1989). **In conclusion there appears to be a slight increase in the U.S. national**

incidence of ureteral cancers during the past 2 decades. Fortunately, this has been associated with a slight improvement in the overall and disease-specific survival of patients with upper tract malignant neoplasms.

Key Point: Upper Tract Urothelial Tumors

- The frequency of urothelial tumors of the upper tract is increasing.

Variations by Sex and Race

Men are about twice as likely to develop upper urinary tract tumors as are women (Greenlee et al, 2000). In addition, whites are about twice as likely as African-Americans to develop upper tract tumors (Greenlee et al, 2000). On the other hand, SEER data suggest that disease-specific annual mortality is greater in black men than in white men (7.4% vs. 4.9%) and greater in women than in men (6.1% vs. 4.4%) (Munoz and Ellison, 2000). As is the case with bladder cancer, women who develop upper urinary tract cancer are 25% more likely than men to die of their disease (Greenlee et al, 2000). Accurate data regarding racial differences in mortality are not available.

Upper Urinary Tract Tumors after Known Bladder Cancer

On the basis of SEER data from the period 1973 to 1996, Rabbani and colleagues (2001) reported that upper urinary tract cancers developed in 657 of 91,245 cases of bladder cancer with adequate follow-up (median 4.1 years). The relative risk for upper urinary tract tumors for white men and women was 64.2% and 75.4% at or before 2 years, 44.3% and 40.5% at 2 to 5 years, 50.8% and 42.1% at 5 to 10 years, and 43.2% and 22.2% at more than 10 years, respectively. These authors concluded that the incidence of upper tract cancers is stable on long-term follow-up and that upper tract surveillance must remain rigorous for an extended period. **The incidence of upper tract recurrence has been shown to be higher in patients with carcinoma in situ than in patients with noninvasive papillary TCCs and in patients treated with cystectomy for carcinoma in situ rather than for invasive cancer** (Solsona et al, 1997; Premoli et al, 2006; Slaton et al, 1999). **Upper urinary tract recurrence is also more likely to occur with high-grade bladder cancer (hazard ratio [HR] 2.16), in T1 versus Ta disease (HR 1.16), and in patients with trigonal or periureteral presentation (HR 1.76)** (Wright et al, 2009). On pathologic evaluation, recurrence is most likely to be superficial (Ta, T1, Tis) and to occur in the distal ureter only (47%). However, this finding has not been reported in all series. For example, in patients with Ta, T1, and Tis bladder cancers treated with bacille Calmette-Guérin (BCG), Herr and colleagues (1996) reported a 21% upper tract recurrence rate after a median interval of 7.3 years; the majority of tumors were invasive, and 38.8% of patients with recurrence died of their upper urinary tract disease.

Etiology and Risk Factors

Balkan Nephropathy. Balkan nephropathy is characterized by a degenerative interstitial nephropathy occurring in Balkan countries. Afflicted families display a much higher incidence of upper urinary tract TCC, in some areas 100 to 200 times greater than in nonaffected individuals (Petkovic, 1975). Curiously, bladder cancer incidence is not affected. Tumors are generally of low grade and are more frequently multiple and bilateral than are upper tract TCCs due to other causes (Radovanovic et al, 1985). Balkan nephropathy is familial but not obviously inherited, suggesting an environmental etiology that has yet to be identified. **Recent studies suggest that dietary exposure to aristolochic acid may be responsible** (Grollman et al, 2007). Interestingly, family members who leave home early in life may not be affected (Radovanovic et al, 1985). **Overall, the incidence of this syndrome may be declining** (Stefanovic et al, 2008). **However, poorer outcomes are still seen in women (HR 2.2), with tumor size larger than 3 cm (HR 2.8), and with stage T3 or T4 disease (HR 3.1)** (Dragicevic et al, 2007).

Smoking. Cigarette smoking appears to be the most important of the modifiable risk factors for upper urinary tract cancer, producing an incidence three times that seen in nonsmokers. It appears that this risk is dose related, with a rate as high as 7.2 times normal for long-term (>45 years) smokers (McLaughlin et al, 1992). Former smokers also have a twofold increased risk compared with age-matched persons with no smoking history. This risk declines only partially after smoking ceases. In addition, the risk from smoking seems more often to lead to ureteral rather than to renal pelvic tumors.

Coffee Consumption. A relative risk of 1.8 times normal has been described in individuals who consumed more than seven cups of coffee per day (Ross et al, 1989). However, after controlling for cigarette smoking, this risk decreased to 1.3.

Analgesics. Analgesic abuse is a well-documented risk factor associated with the development of upper urinary tract cancers (Johansson et al, 1974; Morrison, 1984; McCredie et al, 1986). In one study, 22% of patients with renal pelvic tumors and 11% of patients with ureteral tumors reported a history of analgesic abuse with a latency period of approximately 2 years (Steffens and Nagel, 1988). Renal papillary necrosis and phenacetin consumption also appear to be independent but synergistic risk factors. Each alone resulted in relative risk factors of 6.9 and 3.6, respectively, but together increased risk 20 times (McCredie et al, 1986). Although phenacetin is the most well-described causative agent in analgesic nephropathy, most patients have reported taking combination preparations that included caffeine, codeine, acetaminophen, and aspirin or other salicylates (De Broe and Elseviers, 1998). Histologic findings associated with analgesic abuse include thickening of the basement membrane (pathognomonic) and papillary scarring. Thickening of the basement membrane has been demonstrated in 15% of patients with upper urinary tract tumors and should alert the physician to the presence of analgesic abuse and the subsequent risk of contralateral involvement (Palvio et al, 1987). The degree of papillary scarring also appears to be closely related to tumor grade, although not with the development of squamous metaplasia or squamous cancer (Stewart et al, 1999).

Arsenic. Excess inorganic arsenic in drinking water from artesian wells is a major health hazard in certain parts of the world and is associated with an increased risk of upper tract urothelial tumors in addition to other diseases (Tan et al, 2008). Chronic exposure to arsenic in southwestern Taiwan has long been associated with a form of peripheral vascular disease known as blackfoot disease that causes dry gangrene of the extremities. Throughout all regions of Taiwan an increased rate of upper tract urothelial tumors has been noted. These tumors behave in a similar fashion to other upper urinary tract tumors of similar grade and stage. However, there is a distinct female predominance of the upper

tract tumors seen in Taiwan in contrast to the male predominance seen in all other areas of the world. Some have postulated that the women may be exposed to arsenic fumes during cooking by steam heat over boiling water. If this is correct it implies an inhaled risk as well as the risk of ingestion from drinking water with high arsenic content.

Occupation. A significantly increased risk for upper urinary tract tumors has been reported for persons employed in chemical, petroleum, and plastic industries (relative risk of 4); patients with exposure to coal or coke (relative risk of 4); and patients with exposure to asphalt or tar (relative risk of 5.5) (Jensen et al, 1988). Aniline dyes, β-naphthylamine, and benzidine have been implicated as causative agents, and tumors can occur at long intervals (up to 15 years or more) after exposure.

Chronic Inflammation, Infection, or Exposure to Chemotherapeutic Agents. The development of squamous cell cancer (and less commonly adenocarcinoma) has been shown to be related to chronic bacterial infection associated with urinary stones and obstruction (Godec and Murrah, 1985; Spires et al, 1993). In addition, exposure to cyclophosphamide, an alkylating agent, also appears to confer an increased risk (Brenner and Schellhammer, 1987).

Heredity. Several familial syndromes have been associated with the development of upper tract TCC (Frischer et al, 1985; Orphali et al, 1986; Lynch et al, 1990). Lynch syndrome II, for example, is characterized by the early development of colonic tumors (without polyposis) and extracolonic neoplasms, including upper tract urothelial tumors. Unlike with nonhereditary cancers, these patients are typically younger (mean, 55 years) and are more likely to be female (Lynch et al, 1990).

NATURAL HISTORY

Location and Distribution of Tumors

Ureteral tumors occur more commonly in the lower than in the upper ureter. Overall, about 70% of ureteral tumors occur in the distal ureter, 25% in the midureter, and 5% in the proximal ureter (Anderstrom et al, 1989; Messing and Catalona, 1998). This phenomenon may be a reflection of downstream implantation. One area of consensus is that removal of the entire ureter is mandatory when upper urinary tract cancers are removed by nephroureterectomy. Bilateral involvement (either synchronous or metachronous) occurs in 1.6% to 6.0% of sporadic upper tract TCCs (Babaian et al, 1980; Murphy et al, 1981; Kang et al, 2003).

Patients with upper urinary tract tumors are at risk for development of bladder cancer, with an estimated incidence that varies in multiple reports from 15% to 75% within 5 years of the development of the upper tract cancer (Kakizoe et al, 1980; Huben et al, 1988; Anderstrom et al, 1989; Hisataki et al, 2000; Miyake et al, 2000; Kang et al, 2003). **This high incidence of metachronous bladder involvement suggests that routine bladder surveillance should be performed.** Why are upper tract cancers followed by bladder cancers more often than bladder cancers are followed by upper tract cancers? Theories include downstream seeding, longer exposure time to carcinogens in the bladder, and greater number of urothelial cells in the bladder that are subject to random carcinogenic events. Studies have suggested that in high-grade cancers (with associated *TP53* gene mutations), which also tend to be more rapidly recurrent, specific gene mutations noted in upper tract cancers are also demonstrated in subsequent bladder cancers (Harris and Neal, 1992; Lunec et al, 1992; Habuchi et al, 1993). In contrast, microsatellite studies in low-grade upper tract cancers, which tend to recur less rapidly in the bladder, have suggested genetic discordance between these upper tract tumors and subsequent bladder cancers in 46% of cases (Takahashi et al, 2000).

Upper tract cancers have traditionally been reported to develop in 2% to 4% of patients with bladder cancer, with a mean interval to recurrence of 17 to 170 months (Oldbring et al, 1989; Solsona et al, 1997; Rabbani et al, 2001). **Risk factors that have been reported to predict a higher likelihood of the development of upper tract cancers after bladder cancer treatment include stage, grade, multiplicity of tumors in the bladder, presence of ureteral reflux, presence of recurrent carcinoma in situ in the bladder after BCG treatment, multifocal carcinoma in situ in the bladder at the time of cystectomy, and presence of bladder cancers arising close to a ureteral orifice** (Zincke et al, 1984; Herr et al, 1992; Hudson and Herr, 1995). Two long-term follow-up series have reported that upper tract recurrence after bladder cancer diagnosis may be much higher than previously thought, occurring in approximately 25% of cases. This phenomenon may be the result of selection of patients, with more high-grade and dysplastic tumors reported in these series (Herr et al, 1996; Solsona et al, 1997).

Delayed recurrence is more common in the ureter than in the renal pelvis and appears to occur earlier (at 40 vs. 67 months). In patients treated with BCG for carcinoma in situ of the bladder, upper urinary tract cancer is even more common (about 30% of cases) and appears to occur distally (in the distal, juxtavesical, and intramural portions of the ureter), especially in those patients subjected to cystectomy whose disease is refractory to BCG. Therefore, in cases of high-risk bladder cancer (high-grade T1 disease or carcinoma in situ), imaging of the upper urinary tract should probably be performed annually as part of routine follow-up (Herr et al, 1996).

Upper tract urothelial cancers are often associated with a poor prognosis. Up to 19% of patients with upper tract TCC have been reported to present initially with metastatic disease (Akaza et al, 1970). **However, one recent study based on a four-institution review suggested that although upper tract urothelial cancers were more often invasive and more often poorly differentiated than bladder cancers, in pathologically matched cohorts recurrence with less aggressive disease, progression to more advanced disease, and death occurred with equal frequency among patients with upper tract and lower tract (bladder) urothelial cancers** (Catto et al, 2007). **Several studies have suggested that renal pelvic tumors have a better overall prognosis and 5-year disease-specific and recurrence-free survival than do ureteral tumors** (Park et al, 2004). **However, overall prognosis of upper tract tumors seems to be principally related to tumor stage and to a lesser degree to tumor grade.** In one series, 5-year survival was 100% for Ta and Tis, 91.7% for T1, 72.6% for T2, and 40.5% for T3 tumors. Multivariate analysis in this series showed that tumor stage ($P = .0001$) and age of the patient ($P = .042$) were the only statistically significant predictors of survival (Hall et al, 1998a).

Progression to Muscle Invasion and Metastases

The thin muscle layer of the renal pelvis and ureter probably allows earlier penetration of invasive upper tract tumors through the thinned muscle layer than is seen in bladder cancers (Cummings, 1980; Richie, 1988). In a recent report, 164 patients with

upper tract tumors were compared with 2197 patients with bladder cancer. High-grade and deeply invasive TCC occurred in 28.2% of bladder cancers compared with 39.5% of upper tract tumors (Stewart et al, 2005). The renal parenchyma itself may be a barrier to the spread of stage T3 cancers, whereas periureteral tumor extension is a risk factor for early tumor dissemination (Batata and Grabstald, 1976; Guinan et al, 1992a). This anatomic phenomenon may be at least part of the explanation as to why renal pelvic tumors appear to have a better prognosis than ureteral tumors. In one large series of 611 patients treated at 97 hospitals, the 5-year survival rates of patients with stage T3 tumors of the renal pelvis and ureter were 54% and 24%, respectively (Guinan et al, 1992a).

Patterns of Spread

TCCs of the upper urinary tract may spread in several different ways, including direct invasion into the renal parenchyma or surrounding structures, lymphatic or vascular invasion, and epithelial spread by seeding or direct extension. It is clear that high-grade tumors demonstrate a greater propensity to invade and that renal parenchymal invasion is the most significant predictor of the development of metastases (95%), followed by vascular invasion (83%) and lymphatic invasion (77%) (Davis et al, 1987).

Epithelial. To describe the clonal nature of urothelial tumors of the bladder and upper tract, two theories of the nature of this phenomenon have been proposed. The monoclonality theory describes the multiple tumors as the descendants of a single genetically transformed cell that populates the urothelium. In contrast, the field theory assumes a diffuse "cancerization" that is the result of exposure to a carcinogen and results in the independent development of nonrelated tumors at different sites. Although the majority of the evidence supports the monoclonality theory, most of this evidence has resulted from the study of advanced invasive cancers. It seems that a small but significant proportion of multifocal cancers are, in fact, derived from different clones (Hafner et al, 2002).

Epithelial spreading may occur in both antegrade (most common) and retrograde manners. Antegrade seeding is thought to be the most likely explanation for the high incidence of recurrence in patients in whom a ureteral stump is left in situ after nephrectomy and incomplete ureterectomy (Johnson and Babaian, 1979).

Lymphatic. Lymphatic spread from the upper urinary tract extends to the para-aortic, paracaval, and ipsilateral common iliac and pelvic lymph nodes (Batata and Grabstald, 1976). This extension, of course, depends on the location of the primary tumor and is directly related to the depth of invasion of the primary tumor. Whether lymphadenectomy should be performed routinely and the extent of lymphadenectomy remain controversial (Nakazono and Muraki, 1993; Komatsu et al, 1997). In a series of nephroureterectomy and lymph node dissection, Secin and associates (2005) reported positive lymph nodes in 20% of cases (mean number of lymph nodes sampled, 7.3; range, 1 to 17). Death from disease was 25% for patients with N0 tumors compared with 66.7% in the N1-2 group ($P < .001$). In this series the presence of suspicious lymph nodes on preoperative imaging studies was the only preoperative predictor of lymph node metastasis on multivariate analysis ($P = .02$).

Hematogenous. The most common sites of hematogenous metastases from upper tract tumors are the liver, lung, and bone (Batata et al, 1975). Although it is very rare, direct extension into the renal veins and vena cava may occur in renal pelvic tumors (Jitsukawa et al, 1985; Geiger et al, 1986).

PATHOLOGY

The majority of upper tract tumors are urothelial cancers. Of these, the majority are transitional cell in origin; squamous cell cancers and adenocarcinomas represent a small minority (Bennington et al, 1975; Vincente et al, 1995; Flanigan and Kim, 2004).

Normal Upper Tract Urothelium

The urothelial lining of the upper urinary tract closely approximates that of the bladder except for the markedly reduced thickness of the muscle layer and the abutting of the urothelium to the renal parenchyma proximally. The epithelial layer is continuous from the level of the calyces to the distal ureter. It has been postulated that the urothelial layer may even "extend" into the collecting ducts, raising the possibility that collecting duct renal cancers may be closely related to urothelial cancers and perhaps better treated by agents used for urothelial cancers (Orsola et al, 2005). This observation needs further confirmation.

Renal Pelvis and Calyces. The walls of the calyces and the pelvis contain fibrous connective tissue and two layers of smooth muscle and are lined on their inner surfaces by transitional epithelium (Dixon and Gosling, 1982) (Figs. 53–1 and 53–2). Thin muscle layers originate in the minor calyces and form a spiral, helical arrangement (Fig. 53–3).

Ureter. The ureter demonstrates two continuous thin muscle layers with a loosely spiraled internal layer and a more tightly



Figure 53–1. Low-magnification view of a section through the kidney. The renal medulla ends in the pointed renal papilla. Urine empties into the Y-shaped space made up of the renal calyces (the arms of the Y) and the pelvis (the base of the Y).

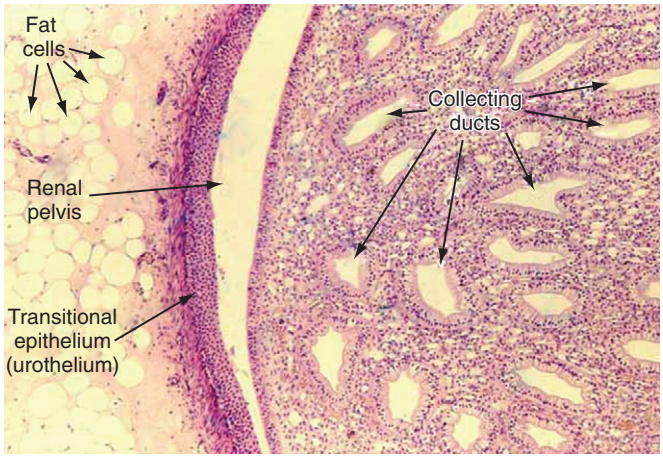


Figure 53–2. This image shows several large collecting ducts near the end of a medullary pyramid (i.e., close to their opening into the pelvis). The transitional epithelium of the renal pelvis is continuous with that of the ureters and bladder.

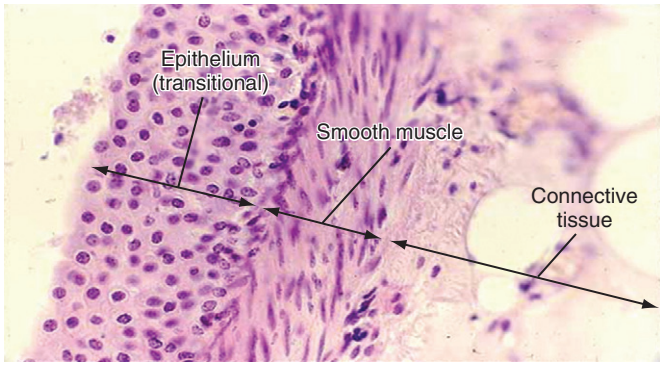


Figure 53–3. In this specimen from the renal pelvis the connective tissue immediately beneath the epithelium is inconspicuous, obscured by a layer of smooth muscle (note elongated nuclei). Beneath the smooth muscle is loose connective tissue, including conspicuous adipocytes.

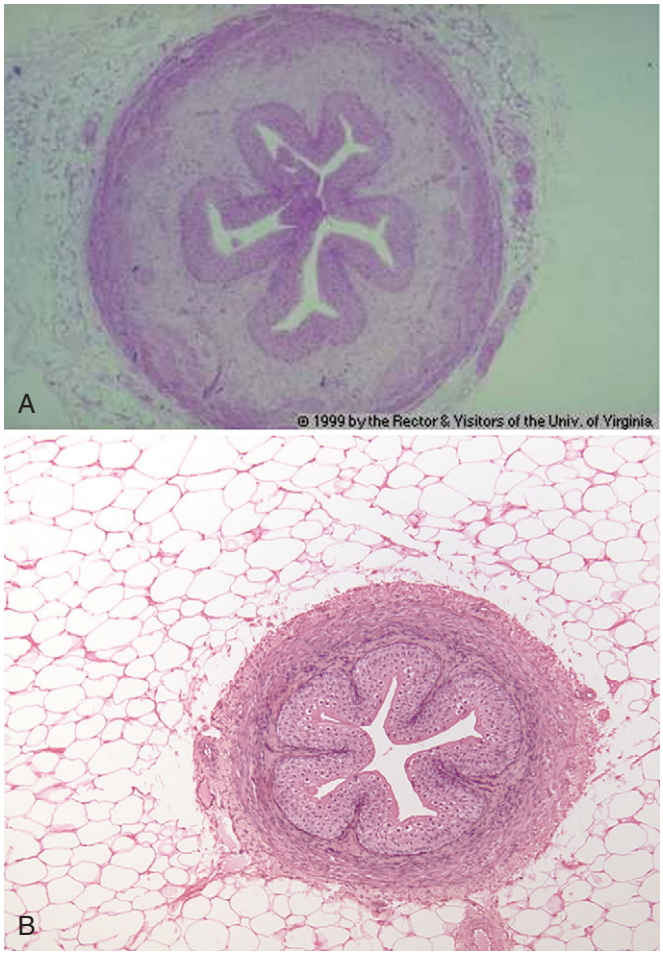


Figure 53–4. **A** and **B,** Cross section of ureter. The ureter has an irregular lumen, which is lined by transitional epithelium. Under the epithelium is a connective tissue layer and, beneath that, three layers of smooth muscle: inner longitudinal, middle circular, and outer longitudinal. (**A,** © 1999, Rector & Visitors of the University of Virginia.)

spiraled external layer. In the lower third of the ureter, a third outer longitudinal layer is present. All three layers merge with the three layers (inner longitudinal, middle circular, and outer longitudinal) of the bladder wall, which run longitudinally, transversely, and obliquely. Beneath the outer muscle coat is the serosa, made up of loose connective tissue and containing blood vessels and lymphatics (Hanna et al, 1976; Notley, 1978) (Figs. 53–4 and 53–5).

Abnormal Urothelium

Metaplasia and Dysplasia. **Several studies have suggested that upper tract urothelial cancers progress through histologic changes from hyperplasia to dysplasia to frank carcinoma in situ in a significant proportion of patients** (Heney et al, 1981; McCarron et al, 1982). Carcinoma in situ may be patchy and may extend proximally to the collecting ducts of the kidney (Mahadevia et al, 1983). More severe urothelial dysplastic changes are associated with a greater risk for tumor recurrence in the distal ureter and bladder and a reduced prognosis.

Benign Lesions: Inverted Papillomas and von Brunn Nests. Inverted papillomas, although generally considered benign lesions, often have been shown to be associated with either synchronous or

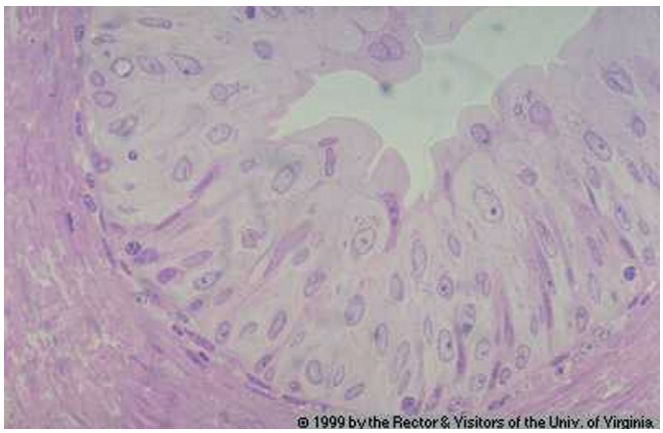


Figure 53–5. Transitional epithelium and loose connective tissue that compose the mucosa of the urinary tract. Transitional epithelium superficially resembles nonkeratinized stratified squamous epithelium, but note that the epithelial cells nearest to the apical (outer) surface are not flattened but cuboidal. Transitional epithelium is a stratified epithelium characterized by the fact that the most apical cells are the roundest and largest in diameter. It is designed to be able to increase its surface area as the lumen is dilated by urine. (© 1999, Rector & Visitors of the University of Virginia.)

metachronous upper tract urothelial tumors (Renfer et al, 1988; Stower et al, 1990; Chan et al, 1996; Cheville et al, 2000). One series demonstrated an 18% incidence of malignancy associated with inverted papilloma of the ureter (Grainger et al, 1990). Other studies have suggested that there are two types of urinary inverted papilloma. The lesions of type 1 behave in a benign fashion, whereas those of type 2 may have a malignant potential. Because there is currently no way to distinguish between these two types, it has been advised that follow-up for all cases of inverted papilloma be continued for at least 2 years after initial diagnosis (Asano et al, 2003). Similarly, these findings suggest close surveillance of the upper tracts for malignancy is warranted when inverted papilloma is diagnosed.

Transitional Cell Carcinoma. TCC makes up more than 90% of upper urinary tract tumors, may present as papillary or sessile lesions, and may be unifocal or multifocal. On histologic examination these lesions are similar to TCCs of the bladder, but the relative thinness of the muscle layer of the renal pelvis and ureter makes invasion through the muscle coat an earlier event. Carcinoma in situ, as in the bladder, can be particularly difficult to identify and can vary in appearance from a whitish plaque to epithelial hyperplasia or a velvety red patch due to increased submucosal vascularity (Melamed and Reuter, 1993). Progression to muscle invasion or invasion into the renal parenchyma or adventitial tissues may occur and is more likely, given the relative thinness of the muscle coat of the upper tracts.

Non–Transitional Cell Carcinoma. Non-TCCs of the upper tracts represent a wide spectrum of lesions, from benign to highly malignant. The most common of these are squamous cell cancers and adenocarcinomas.

Squamous Cell Cancers. Squamous cell cancers make up 0.7% to 7.0% of upper urinary tract cancers (Babaian and Johnson, 1980; Blacker et al, 1985). They are frequently associated with a condition of chronic inflammation or infection or with analgesic abuse (Stewart et al, 1999). These tumors occur six times more frequently in the renal pelvis than in the ureter and are generally moderately to poorly differentiated and more likely to be invasive at the time of presentation.

Adenocarcinomas. Adenocarcinomas account for less than 1% of all renal pelvic tumors and are typically associated with long-term obstruction, inflammation, or urinary calculi (Stein et al, 1988; Spires et al, 1993). These tumors typically present at advanced stage and display a poor prognosis.

Micropapillary Variant. A micropapillary variant of TCC in the bladder is associated with aggressive behavior and poor outcome. This histologic subtype is very rare in the upper urinary tract. Holmang and associates (2006) described 26 patients with this entity in the upper urinary tract. Twenty-two patients had stage T3 disease at presentation, and carcinoma in situ or lymphovascular invasion was noted in 64% and 81% of cases, respectively. Five-year survival was only 26.9%, and overall the disease-specific mortality was 77%.

Other Miscellaneous Tumors. Fibroepithelial polyps (benign) (Musselman and Kay, 1986; Blank et al, 1987) and neurofibromas (benign) (Varela-Duran, 1987) are uncommon lesions that are typically treated by simple excision.

Multiple types of sarcomas have also been reported to involve the upper urinary tracts, including leiomyosarcomas (Madgar et al, 1988), plasmacytomas (Igel et al, 1991), and angiosarcomas (Coup, 1988). Because of the rare nature of these tumors they are typically treated by excision with adjuvant therapy that is based on the experience with tumors of similar histology occurring elsewhere in the body.

PROGNOSTIC FACTORS

Stage. **Stage is currently the most important predictor of survival in patients with upper tract urothelial tumors** (Png et al, 2008). The most commonly used staging system is the TNM system (see later section on staging). Upper tract cancers can spread by direct invasion, mucosal seeding, and hematologic and lymphatic routes. Prognosis decreases as stage increases; the most significant decrease in survival is observed in T3 tumors that have penetrated into the perirenal or periureteral fat (Grabstald et al, 1971).

Grade. The traditional grading system used for bladder cancer is also applicable to upper urinary tract tumors. Broder's original system, modified by Ash, grades tumors from grade 1 to grade 4: grade 1 tumors are primarily papillomas, and grade 4 tumors are highly anaplastic and poorly differentiated tumors (Melamed and Reuter, 1993). The World Health Organization's system, proposed by Mostofi, eliminates papillomas and grades tumors from grade 1 to grade 3. Recently, tumor grading has been divided into low grade and high grade (Epstein, 1998). Papillomas and papillary urothelial neoplasms of low malignant potential are also described. **Certainly, tumors of high grade are more likely to invade into the underlying connective tissue, muscle, and surrounding tissues. Tumors of high grade are also more likely to be associated with concomitant carcinoma in situ.**

Location. There remains disagreement as to whether the location of an upper tract tumor affects prognosis. Several studies have suggested that renal pelvic tumors have a better prognosis than ureteral cancers (Park et al, 2004). In contrast, others have argued that when renal pelvic and ureteral tumors are matched for stage there is no significant difference in prognosis (Hall et al, 1998b).

Associated Carcinoma in Situ. **As in bladder cancer, carcinoma in situ of the upper tract is associated with a poor prognosis and a likelihood of future development of invasive urothelial cancers.** Carcinoma in situ of the distal ureter is most common in patients with bladder carcinoma in situ treated with BCG (30% likelihood).

Lymphovascular Invasion. **Lymphovascular invasion has been suggested to be an independent prognostic factor for disease-specific survival in upper tract TCC.** In a Japanese study, 173 consecutive patients undergoing surgical treatment of upper tract TCC had lymphovascular invasion determined (Kikuchi et al, 2005). Lymphovascular invasion was found in 30% of cases and was more frequent in advanced pathologic stage. Overall 5- and 10-year survival rates were 84.9% and 80.4%, respectively, in the absence of lymphovascular invasion compared with 40.2% and 21.1% with lymphovascular invasion. In three recent single-center and two multicenter series including a total of 1841 patients with upper tract tumors, the prevalence of lymphovascular invasion varied from 23.7% to 37.8%. Lymphovascular invasion correlated with increasing tumor stage and grade and with disease recurrence and disease-specific survival (Akao et al, 2008; Bolenz et al, 2008; Lin et al, 2008; Chung et al, 2009). In multivariate analysis, lymphovascular invasion was an independent and stronger predictor of recurrence and survival than were tumor stage or grade. Kikuchi and colleagues (2009) reported on a large international, 13-center collaborative series of 1453 patients who underwent radical nephroureterectomy for upper tract urothelial tumors. The overall prevalence of lymphovascular invasion was 24%. Lymphovascular invasion correlated with tumor grade stage, lymph node status, and tumor necrosis. In multivariate analysis, lymphovascular invasion was an independent predictor

of disease recurrence and survival for patients with either negative lymph nodes or unknown nodal status. However, lymphovascular invasion was not an independent predictor of outcome for patients with positive lymph nodes. Further prospective, large-scale studies are needed to confirm these observations. As with bladder and other solid organ cancers, lymphovascular invasion is the presumed mechanism that leads to regional lymph node and to systemic hematogenous metastases.

Molecular Biology (Chromosome Abnormalities) and Markers. The molecular and genetic basis of upper tract TCCs appears to be similar to that of TCCs of the bladder. These events have been better described in bladder cancers and are reported in detail in Chapter 80. Briefly, the genetic events leading to the development of upper tract tumors seem to be associated with the overexpression of tumor suppressor genes, including *TP53* (on chromosome 17p), the retinoblastoma gene (*RB*) on chromosome 13q, and several gene foci on chromosome 9 (including the genes for CDKN2C [formerly p18] and CDKN2A [formerly p16] proteins located at 9p21 and 9p32-33). It is generally thought that chromosome 9 abnormalities occur early in the development of these cancers but are not typically associated with high-grade and dysplastic changes, whereas *TP53* is more often associated with increased grade and dysplasia. It would also seem, however, that by the time the tumor has been able to invade into the lamina propria both genetic events are likely to have occurred (Spruck et al, 1994). Zigeuner and associates (2004) reported that decreased TP53 immunoreactivity and TP53 overexpression in upper tract tumors were associated with advanced tumor stage and poor prognosis. However, the findings were not independent of stage and grade in multivariate analysis. Eltz and associates (2008) provided a comprehensive review of molecular markers in upper tract urothelial tumors.

TP53. The TP53 nuclear protein staining of cytology specimens obtained ureteroscopically appears to correlate well with the presence of upper tract TCC. In one study, of 36 TP53-positive specimens 28 had simultaneous evidence of upper tract TCC; 80% of the remaining patients who were evaluated serially also had confirmed TCC. All 14 TP53-negative studies occurred in patients with no sign of concurrent malignant disease on ureteroscopy (Keeley et al, 1997b).

c-MET. Recently the roles of c-*MET* and *RON,* members of the *MET* proto-oncogene family of tyrosine kinases, have been studied in upper urinary tract tumors (Compérat et al, 2008). c-*MET* overexpression correlated with vascular invasion and a worse clinical outcome, whereas that of *RON* did not correlate with outcome.

COX-2. Abnormal expression of cyclooxygenase-2 (COX-2) has been reported in many forms of human cancer, including bladder urothelial cancer. Kang and coworkers (2008) reported abnormal expression of COX-2 in stromal cells of upper urinary tract cancers correlated with high tumor stage and grade and poor prognosis.

CDKN1B. CDKN1B (formerly p27), a cyclin-dependent kinase inhibitor, has also been shown to predict the prognosis of upper tract tumors. In one study, low levels of CDKN1B staining were indicative of a worse disease-specific survival (Kamai et al, 2000).

Loss of Heterozygosity. Loss of heterozygosity at 9p21 has been observed in bladder cancer and now in upper tract TCC by microsatellite instability analysis. It has been shown that TCC can occur in patients with hereditary nonpolyposis colorectal cancer (HNPCC) syndrome. Patients with this syndrome show genomic lesions in DNA mismatch repair genes (Amira et al, 2003). Furthermore, an inverted growth pattern of cancer has also been associated with microsatellite instability, with a sensitivity and specificity of 0.82 in one study. This finding suggests that microsatellite instability may serve as a marker for inverted growth in upper urinary tract cancers (Hartmann et al, 2003). Ho and coworkers (2008) have reported that a urine-based assay testing for a total panel of 77 markers for microsatellite instability in 30 patients detected 83.3% of cases of an upper urinary tract tumor.

Ploidy-Flow Cytometry. Tumor ploidy has been shown to correlate with survival in upper tract tumors. In one study, tumor aneuploidy was associated with poor 5- and 10-year survival rates of 25% and 0%, respectively (Blute et al, 1988).

Overexpression of Hypoxia-Inducible Factor-1α (HIF-1α). **HIF-1α is a transcription factor that plays an important role in cellular hypoxia adaptation. In a series of patients with upper tract urothelial cancer, positive HIF-1α expression was found in two thirds of cases (was absent in normal urothelium). HIF-1α was significantly associated with high T stage, nodal stage, and grade as well as cancer-specific survival (HR 2.23, *P* = .004)** (Ke et al, 2008).

Other Markers. Rapid urine tests for urothelial malignant neoplasms have been studied extensively for the purpose of identifying lower urinary tract tumors. Less is known about their value in upper tract cancers. Urinary levels of NMP22, a nuclear matrix protein–based marker, have been found to be elevated in patients with upper tract cancer (Carpinito et al, 1996). Although the sensitivity of this test for determining the presence of low-grade tumors is probably higher than that of cytology, the specificity is low. Recently, urine fluorescence in-situ hybridization (FISH) was reported to have a sensitivity of 87.5% and a specificity of 80% for detection of upper tract tumors in a small series (Akkad et al, 2007).

In one series, an analysis of fibrinogen-fibrin degradation products (AuraTek FDP) was compared with the bladder tumor antigen (BTA) test and urine cytology. In this study, the accuracy of the FDP test was 83% compared with 62% for BTA and 59% for cytology (Siemens et al, 2003). Telomerase activity has been shown to be present in most (>95%) upper tract urothelial cancers. It can be detected in exfoliated urinary specimens in a high percentage of patients and thus may prove to be a potentially useful marker (in addition to conventional cytology) to identify upper tract cancers (Wu et al, 2000).

DIAGNOSIS

Symptoms and Signs

The most common presenting symptom of upper tract urothelial tumors is hematuria, either gross or microscopic. This occurs in 56% to 98% of patients (Murphy et al, 1981; Guinan et al, 1992a; Raabe et al, 1992). Flank pain is the second most common symptom, occurring in 30% of tumors. This pain is typically dull and believed to be secondary to a gradual onset of obstruction and hydronephrotic distention. In some cases, pain can be acute and mimic renal colic, typically ascribed to the passage of clots that acutely obstruct the collecting system. These common symptoms of localized disease (hematuria, dysuria) and of advanced upper tract tumors (weight loss, fatigue, anemia, bone pain) are similar in type and frequency to those of bladder cancer. However, flank pain due to obstruction by tumor or clot is more prevalent in upper tract tumors, having been reported in 10% to 40% of cases (Babaian and Johnson, 1980; McCarron et al, 1983; Richie, 1988; Williams, 1991; Melamed and Reuter, 1993). Flank pain in patients with upper tract tumors does not correlate with either locally advanced tumor stage or worse prognosis, as is

the case with bladder cancer. About 15% of patients are asymptomatic at presentation and are diagnosed when an incidental lesion is found on radiologic evaluation. Patients may also present with symptoms of advanced disease, including flank or abdominal mass, weight loss, anorexia, and bone pain. Nearly all upper tract tumors are diagnosed during the patient's life, and therefore upper tract urothelial cancer represents a rare autopsy finding (Ressequie et al, 1978).

Radiologic Evaluation

Although intravenous pyelography has been the traditional means for diagnosis of upper tract lesions, computed tomographic (CT) urography is increasingly performed today. CT is easier to perform and less labor intensive than intravenous pyelography. It also has a higher degree of accuracy in determining the presence of renal parenchymal lesions. On the other hand, small urinary filling defects (<5 mm) may be missed between the "cuts" of the traditional CT scan. More recently, CT urography has been performed to obtain a three-dimensional image of the upper tracts. This technique appears to be equal to intravenous pyelography in imaging the ureters and renal pelvis (McTavish et al, 2002). With CT urography, the sensitivity for detecting upper tract malignant disease has been reported to approach 100%, with a specificity of 60% and a negative predictive value of 100% (Caoili et al, 2002). CT urography does, however, expose the patient to higher doses of radiation.

Radiolucent filling defects, obstruction or incomplete filling of a part of the upper tract, and nonvisualization of the collecting system are the typical findings suggestive of an upper urinary tract tumor. Filling defects, which account for 50% to 75% of cases, typically require the intravenous administration of contrast material to be identified (Murphy et al, 1981; Fein and McClennan, 1986). The differential diagnosis of these defects includes blood clot, stones, overlying bowel gas, external compression, sloughed papilla, and fungus ball. Stones can be ruled out most easily by confirmation of calcification by renal ultrasonography or CT. TCCs have an average density of 46 Hounsfield units (HU) and a range of 10 to 70 HU (Lantz and Hattery, 1984). This is in contrast to an average of 100 HU seen in radiolucent uric acid stones (range, 80 to 250 HU). Thus CT can be useful in distinguishing between these two common causes of radiolucent filling defect on excretory urography or retrograde ureterography. The impact of hydronephrosis and nonvisualization for renal pelvis tumors versus ureteral tumors as indicators of a higher stage is uncertain. Nonvisualization is reported in 20% of renal pelvis tumors, only 33% of which are invasive (McCarron et al, 1983). Nonvisualization is reported in 37% to 45% of ureteral tumors and carried a 60% risk of invasion in one series (McCarron et al, 1983). In other reports there is no correlation of nonvisualization and stage (Batata and Grabstald, 1976; Anderstrom et al, 1989). Hydronephrosis with or without an associated filling defect is linked with invasion in 80% of ureteral tumors (McCarron et al, 1983; Cho et al, 2007).

Radiolucent, noncalcified lesions may require additional evaluation by retrograde urography or ureteroscopy, with or without biopsy and cytology. Overall, retrograde urography has an accuracy of 75% in diagnosis of an upper tract malignant neoplasm (Murphy et al, 1981). An incompletely filled or obstructed renal infundibulum or calyx, occurring in 10% to 30% of cases, again typically requires retrograde urography or ureteroscopy to confirm the diagnosis. Obstruction of the urinary tract is a poor prognostic sign for tumor invasion (Babaian and Johnson, 1980).

Evaluation of the contralateral kidney is important not only because of possible bilaterality of the disease but also because it allows a determination of the functionality of the contralateral kidney. This is an extremely important part of the management process. At times, a split-function renal scan may be helpful in determining the contribution of both the "diseased" and the presumed "normal" kidney to the patient's overall renal function.

Some have suggested that ultrasonography has sensitivity equal to that of urography in evaluating patients with painless gross hematuria for upper tract malignant disease (Yip et al, 1999; Data et al, 2002). For staging purposes, CT or magnetic resonance imaging (MRI) is most useful in determining the extent of invasion, an associated mass lesion outside the collecting system, and the presence of lymph node or distant metastases (Milestone et al, 1990). CT is also more sensitive than conventional radiography in determining minimally radiopaque substances, making it useful in identifying urine excreted by poorly functioning areas of kidney (as in obstructed areas) (Kenney and Stanley, 1987). The greatest downside of CT or MRI is in the detection of small lesions that may be lost in volume averaging. In one series, CT predicted TNM stage in 60% of patients; it understaged 16% and overstaged 24% (Scolieri et al, 2000).

Cystoscopy

Because upper urinary tract tumors are often associated with bladder cancers, cystoscopy is mandatory in the evaluation to exclude coexistent bladder lesions.

Ureteroscopic Evaluation and Biopsy

The technical advances achieved in the realm of endoscopic equipment have made the flexible and rigid ureteroscope a key part of the evaluation (and treatment) of upper urinary tract tumors. **Diagnostic accuracy can be improved from approximately 75% with excretory or retrograde urography alone to 85% to 90% when it is combined with ureteroscopy** (Streem et al, 1986; Blute et al, 1989). Although pyelovenous and pyelolymphatic migration has been reported with ureteroscopy, this phenomenon appears to be uncommon and should not preclude its use (Lim et al, 1993).

As with bladder tumors, 55% to 75% of ureteral tumors are low grade and low stage (Cummings, 1980; Richie, 1988; Williams, 1991). **Also, like bladder cancers, approximately 85% of renal pelvic tumors are papillary and the remainder sessile.** Invasion of the lamina propria or muscle (stage T1 or T2) occurs in 50% of papillary and in more than 80% of sessile tumors. Overall, therefore, 50% to 60% of renal pelvic tumors are invasive into either the lamina propria or muscle. In ureteral tumors, invasion is also more common than in bladder tumors (Anderstrom et al, 1989; Williams, 1991).

In addition to visualization of the tumor, ureteroscopy allows more accurate biopsy of suspected areas, with either biopsy forceps or brushing. Good histologic correlation (78% to 92%) between the ureteroscopic biopsy specimen and the final pathologic specimen has been established (Keeley et al, 1997c; Guarnizo et al, 2000). It appears that fresh samples obtained ureteroscopically provide the best chance of predicting eventual pathologic findings. In one study, a cell block from biopsy specimens was prepared when a visible tumor was present, and grades of ureteroscopic biopsy specimens were compared with grades and stages of surgical specimens in 42 cases. Of 30 low- or moderate-grade

specimens, 29 (90%) proved to be low- or moderate-grade TCC; 11 of 12 high-grade specimens (92%) proved to be high-grade TCC, and 8 (67%) were invasive (T2 or T3) (Keeley et al, 1997c). In contrast, the urologist's impression of the tumor grade based on ureteroscopic appearance is likely to be correct in only 70% of cases, suggesting that biopsy is also needed to further define this important aspect of staging (El-Hakim et al, 2004).

Because of the small size of ureteroscopic biopsy specimens, a precise correlation with eventual tumor *stage* is difficult. Therefore, in predicting the tumor stage, a combination of the radiographic studies, the visualized appearance of the tumor, and the tumor grade provides the surgeon with the best estimation of eventual tumor stage. Although, as stated earlier, grading of the tumors may be fairly accurate, staging is much more problematic. Of 40 urothelial tumors staged in one series (40% in the renal pelvis, 20% in the proximal ureter, and 40% in the distal ureter), ureteroscopic grade matched surgical grade in 78% of cases and was less than surgical grade in the remaining 22%. Lamina propria was present in 68% of biopsy specimens (62% of cup biopsies and 100% of loop biopsies), but tumors thought to be Ta were upstaged to T1 to T3 in 45% of cases at the time of complete resection of the lesion (Guarnizo et al, 2000). Therefore, accurate tumor grading on ureteroscopic biopsy is critical in estimating tumor stage. In one series, a biopsy specimen showing grade 3 tumor accurately predicted tumor stage in more than 90% of cases (Skolarikos et al, 2003).

Is ureteroscopy (with or without biopsy) necessary in all cases of suspected upper tract tumors? No. In fact, ureteroscopy should probably be reserved for situations in which the diagnosis remains in question after conventional radiographic studies and for those patients in whom the treatment plan may be modified on the basis of the ureteroscopic findings, for example, endoscopic resection. Although there is no evidence that ureteroscopy diminishes the prognosis of a patient destined to proceed to nephroureterectomy, and although the risks of tumor seeding, extravasations, and dissemination are low in experienced hands, these risks are real and should preclude ureteroscopy when it is unnecessary (Hendin et al, 1999).

Antegrade Endoscopy

In some cases of upper tract tumors, percutaneous access to the renal pelvis may be required for diagnosis or treatment. In such cases, antegrade urography and uroscopy may be useful for tumor resection, biopsy, or simple visualization. Larger-caliber scopes that can be passed into the renal pelvis in this manner may be particularly helpful in resecting or debulking larger volumes of tumor in this area (Streem et al, 1986; Blute et al, 1989). One must remember, however, that tumor cell implantation in the retroperitoneum and along the nephrostomy tube tract has been reported after these procedures (Tomera et al, 1982; Huang et al, 1995).

Role of Cytology and Other Tumor Markers

Urine cytology is a specific tool that is useful in the diagnosis of upper tract carcinomas. On the other hand, the sensitivity of cytology remains an issue. In general, the sensitivity of voided urine (or bladder wash) cytology is directly related to tumor grade. Overall accuracy estimates of the sensitivity of cytology have ranged from about 20% for grade 1 tumors to 45% and 75% for grade 2 and grade 3 tumors, respectively (Murphy and Soloway, 1982; Konety and Getzenberg, 2001).

Even if a voided cytology specimen is abnormal in a patient with an upper tract filling defect, one must be cautious in determining the site of origin of the malignant cells. Ureteral catheterization for collection of urine or washings may provide more accurate cytologic results. However, even in this setting, a substantial false-negative or false-positive result (22% to 35%) can be expected (Zincke et al, 1976). It would appear that saline washing provides a better cell yield and improves cytologic results secondary to the release by hydroscopic forces of loosely adherent cells from the urothelium. Still better accuracy can be achieved by brush biopsy through a retrograde catheter or ureteroscope. Sensitivity in the 90% range with specificity approaching 90% may be possible with these techniques (Streem et al, 1986; Blute et al, 1989). Brush biopsies have, however, also been reported to result in severe complications, including massive hemorrhage and perforation of the urinary tract with extravasation (Blute et al, 1981).

It appears that the exposure of urothelial cells to ionic, high-osmolar contrast agents as in retrograde pyelography may worsen cytologic abnormalities. Thus, it is probably prudent to obtain cytologic specimens before the use of these agents (Terris, 2004).

Early results suggest that FISH also may be useful in the diagnosis of upper tract urothelial tumors. In a study of 21 consecutive upper urinary tract urothelial cancer patients and 10 healthy controls using FISH probes for chromosomes 3, 7, 17, and the *CDKN2A* (9p21) gene, overall sensitivity of FISH was significantly higher than that of cytology while specificity for both was 100% (Luo et al, 2009).

STAGING

The staging of upper urinary tract tumors parallels the staging of bladder tumors and is presented in Chapter 80.

TNM Staging System

The TNM classification and staging system is the most commonly used. A comparison of the American Joint Committee on Cancer (AJCC) staging system and the TNM system is presented in Table 53–1.

The histologic characteristics and biology of upper tract tumors still affect treatment decisions, technologic improvements notwithstanding. The entity of benign papilloma, which responds favorably regardless of the extent of treatment, is well described in older series of upper tract tumors (Bloom et al, 1970; Batata and Grabstald, 1976). The existence of similar low-grade papillomas of low-grade malignant potential in the bladder remains controversial (Cheng et al, 1999; Cheng and Bostwick, 2000; Oyasu, 2000). It is unclear whether the differences between upper tract papillomas and bladder papillomas are biologic or semantic. **Approximately 85% of renal pelvis tumors are papillary;** the remainder are sessile. This distribution is similar to that of bladder tumors. However, the stage of upper tract tumors is T1 or T2 in approximately 50% of papillary and 80% of sessile lesions, respectively (Cummings, 1980; Richie, 1988; Williams, 1991). Thus, 50% to 60% of renal pelvis tumors are invasive, in contrast to most bladder tumors, which are noninvasive; 55% to 75% of ureteral tumors are low grade and low stage, but invasion is still more common than among bladder tumors (Anderstrom et al, 1989; Williams, 1991). Patients with upper urinary tract tumors present most often in the sixth or seventh decade of life and thus are

Table 53–1.

AJCC and TNM Staging and Classification Systems for Upper Urinary Tract Tumors

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Papillary noninvasive carcinoma
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue.
T2	Tumor invades the muscularis.
T3	Tumor invades periureteral fat (for renal pelvis only). Tumor invades beyond muscularis into perinephric fat or the renal parenchyma.
T4	Tumor invades adjacent organ or through the kidney into the perinephric fat.
Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastases
N1	Metastasis to a single lymph node, 2 cm or less in greatest dimension
N2	Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node, more than 5 cm in greatest dimension
Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

AJCC Staging System	TNM Classification System
0	T0
I	Ta, Tis, T1, N0, M0
II	T2, N0, M0
III	T3, N0, M0
IV	T4 or any T, N+, M+

AJCC, American Joint Committee on Cancer.

generally older than patients with bladder tumors (Melamed and Reuter, 1993).

Tumors of the renal pelvis are slightly more common than ureteral tumors (Batata and Grabstald, 1976; Richie, 1988; Maulard-Durdux et al, 1996). Ureteral tumors occur in the distal, middle, and proximal segments in 70%, 25%, and 5% of cases, respectively (Babaian and Johnson, 1980; Anderstrom et al, 1989; Williams, 1991; Messing and Catalona, 1998). **After conservative treatment, ipsilateral upper tract tumor recurrence is common in a proximal to distal direction and is seen in 33% to 55% of cases** (Mazeman, 1976; Johnson and Babaian, 1979; Babaian and Johnson, 1980; Cummings, 1980; McCarron et al, 1983). Recurrence proximal to the original lesion is rare.

Key Point: Upper Tract Tumor Recurrence

- Multiple upper tract recurrences are common in a proximal to distal direction.

This high rate of ipsilateral recurrence is due in part to a multifocal field change, which is even more pronounced than in bladder cancer. Areas of atypia, dysplasia, or carcinoma in situ are reported in 60% to 95% of specimens after nephroureterectomy for renal pelvis tumor (Johansson et al, 1976; Kakizoe et al, 1980; Heney et al, 1981; Nocks et al, 1982; McCarron et al, 1983; Melamed and Reuter, 1993). Molecular techniques demonstrate that downward seeding of tumor accounts for some recurrences (Harris and Neal, 1992). Tumor multifocality does not lessen survival of patients independent of stage (Messing and Catalona, 1998).

Metachronous bilateral upper tract tumors are rare. In a review of all 768 cases of upper tract tumor reported in western Sweden from 1971 to 1998, the rate of metachronous bilateral tumors was 3.1% and was associated with increased age and short survival time after the event (Holmang and Johansson, 2006).

The occurrence of bladder tumors after upper tract tumors, and vice versa, is another expression of the field change, multifocal risk that affects initial treatment decisions. Carcinoma in situ is present in the distal ureter at the time of cystectomy in 7% to 25% of cases (Melamed and Reuter, 1993; Solsona et al, 1997; Herr, 1998); 15% to 50% of all cases of upper tract tumor occur in patients with a history of bladder tumor (Batata and Grabstald, 1976; Babaian and Johnson, 1980). The incidence of upper tract tumor after bladder tumor is 2% to 4% with a mean time to occurrence of 70 months (Shinka et al, 1988; Oldbring et al, 1989; Melamed and Reuter, 1993; Herr et al, 1996). Upper tract tumors are reported in 3% to 9% of patients after cystectomy for bladder cancer in older series (Zincke and Neves, 1984; Mufti et al, 1988).

Particular insight into the contemporary risk for upper tract tumor after treatment of bladder cancer is provided in several large series (Solsona et al, 1997; Herr, 1998; Rabbani et al, 2001; Mullerad et al, 2004; Sved et al, 2004; Canales et al, 2006; Tran et al, 2008; Wright et al, 2009). Herr (1998) found that among 307 patients with bladder tumor observed for a median of 12 years there was an overall incidence of upper tract tumors of 23%. The cumulative risks for upper tract tumors were 10%, 26%, and 34% at 5 years, 5 to 10 years, and 15 years, respectively. Upper tract tumors occurred in 26% of another subgroup of 87 patients with bladder tumor observed for more than 15 years. Delayed upper tract tumors were more common in the ureter than in the renal pelvis and appeared at a median follow-up of 56 months. Median time to delayed ureteral versus renal pelvis tumors was 40 months versus 67 months, respectively. Ureteral tumors occurred in 29% of 66 patients who were successfully treated with intravesical BCG for carcinoma in situ. In a subset of 105 patients who underwent cystectomy for BCG-refractory carcinoma in situ, ureteral carcinoma in situ was present in the distal, juxtavesical, and intramural portions of the ureter in 35%, 68%, and 81% of cases, respectively. In a retrospective study from the same center, treatment outcome in patients with upper tract tumor was worse in patients with a prior history of bladder cancer (superficial or invasive) independent of upper tumor stage (Mullerad et al, 2004). Similarly, Sved and colleagues (2004) reported upper tract tumors in 2% of patients (5 of 235) observed for a mean of 42 months after radical cystectomy for bladder cancer. Upper tract tumor was diagnosed at a mean follow-up of 39.6 months, because of hematuria in four cases, and on routine intravenous urography in the remaining case. Presence of tumor in the prostatic urethra of the cystectomy specimen was the only initial tumor feature that was associated with a higher risk of subsequent upper tract tumor. This may be a predictor of a higher risk of multifocal tumor in such cases. Outcome was poor with disease-related mortality in four of the cases. In contrast, in a review of 91,245 patients with bladder

cancer from the SEER database for 1973 to 1996, upper tract tumor occurred in 657 patients (0.7%) at a median follow-up of 4.1 years (Rabbani et al, 2001). These patients had lower tumor stage and improved disease-specific survival than did patients with primary upper tract tumors. Canales and coworkers (2006) found that patients with two or more stage Ta bladder cancer recurrences within 12 months were at increased risk for upper tract tumors and that surveillance of the upper tracts is indicated. In an update on the earlier study by Herr and associates (1996), Tran and associates (2008) found that the risk for upper tract recurrence after cystectomy for bladder cancer was 4% and 7% at 3 years and 5 years, respectively. Patients who had any tumor in the ureter at the time of cystectomy, including only carcinoma in situ, were at greatest risk for upper tract recurrence. Wright and colleagues (2009) reviewed 99,338 patients with bladder cancer in the SEER registry from 1988 to 2003. Upper tract tumors occurred in 0.8% of patients, at a median time of 33 months. Seventy-one percent of these were seen within 5 years, and only 6% of the total occurred after 10 years. On multivariate analysis high-grade and non–muscle-invasive bladder tumors correlated with a higher risk for subsequent upper tract tumors. The latter point likely relates to a lower mortality rate from the original bladder cancer and thus a greater competing risk for upper tract disease.

Solsona and colleagues (1997) reported that carcinoma in situ was present in the distal ureter in 25% of 138 cystectomies performed for bladder carcinoma in situ, compared with only 2.3% and 2.9% among 786 and 179 cases of stage Ta to T1 versus stage T2 disease, respectively. This may indicate that bladder carcinoma in situ carries a higher risk of multifocal disease than do other forms of bladder tumor.

The incidence of bladder tumor after treatment of upper tract tumor is 20% to 75% (Batata and Grabstald, 1976; Kakizoe et al, 1980; Nocks et al, 1982; Huben et al, 1988; Anderstrom et al, 1989; Sakamoto et al, 1991; Williams, 1991; Melamed and Reuter, 1993; Hisataki et al, 2000; Kang et al, 2003; Matsui et al, 2005). Bladder tumor after upper tract tumor occurs earlier than the reverse, at a median of 21 months versus 86 months afterward, respectively. Both bladder tumor and contralateral upper tract tumor after initial unilateral upper tract tumor are examples of the multifocal nature of urothelial tumor. In one study, subsequent bladder tumors appeared earlier than did contralateral upper tract tumors (Kang et al, 2003). Renal insufficiency was associated with a higher risk of contralateral upper tract tumor.

The occurrence of bladder tumor after treatment of upper tract tumor may be due to a field effect, distal tumor seeding, or both. Association of a higher bladder tumor incidence after upper tract tumor multifocality supports a role of distal seeding (Matsui et al, 2005). However, reports of distinct tumor clones by microsatellite analysis support a field effect (Takahashi et al, 2001). The paradoxical finding that the risk of subsequent bladder tumor is inversely related to upper tract tumor size and stage may reflect a higher and earlier risk of death from the primary tumor in these cases. In the reports by Hisataki and coworkers (2000), Matsui and associates (2005), and Terakawa and colleagues (2008), increased upper tract tumor stage at the time of nephroureterectomy correlated with a higher risk for subsequent bladder tumor. In a recent European multicenter study reported by Novara and coworkers (2008) prior bladder tumor before upper tract tumor was the only independent risk factor for bladder tumor after nephroureterectomy in multivariant analysis. Raman and associates (2007) reported that the grade, but not the stage, of the prior upper tract tumors correlated with the pathologic findings of the subsequent bladder tumors.

Three particular forms of upper tract urothelial tumors, those seen in Balkan nephropathy, those associated with analgesic abuse, as well as those seen in arsenic-endemic regions of Taiwan, each have an even higher tendency to multiple and bilateral recurrences than do sporadic tumors (Markovic, 1972; Petkovic, 1975; Mahoney et al, 1977; Johansson and Wahlquist, 1979; Melamed and Reuter, 1993; Stewart et al, 1999; Tan et al, 2008). The typically low-grade nature of the tumors and the frequent renal insufficiency seen in Balkan nephropathy underscore the importance of conservative treatment when possible. The degree of scarring of renal papillae seen in phenacetin abuse correlates in a dose-dependent manner with the risk of high tumor grade and progression. Calcification of renal papillae after analgesic abuse is associated with development of squamous carcinoma of the renal pelvis (Stewart et al, 1999).

There is a strong correlation of grade and stage for upper tract tumors. **The single most important determinant of outcome is tumor stage** (Tables 53–2 and 53–3) (Bloom et al, 1970; Grabstald et al, 1971; Batata et al, 1975; Wagle et al, 1975; Babaian and Johnson, 1980; Cummings, 1980; McCarron et al, 1983; Huben et al, 1988; Anderstrom et al, 1989; Guinan et al, 1992b; Terrell et al, 1995; Messing and Catalona, 1998).

Key Points: Staging of Upper Tract Tumors

- Staging of upper tract tumors parallels that of bladder cancer.
- Stage is the most important determinant of outcome.

Table 53–2.

Correlation of Tumor Stage and Grade for Upper Tract Urothelial Tumors

LOCATION AND STAGE	HIGH GRADE (%)
Pelvis	
Low	5
High	91
Ureter	
Low	26
High	64

Data from McCarron JP Jr, Mills C, Vaughn ED Jr. Tumors of the renal pelvis and ureter: current concepts and management. Semin Urol 1983;1:75–81.

Table 53–3.

Literature Review of Overall Survival of Patients with Upper Tract Urothelial Tumors (Renal Pelvis or Ureter) by Stage and Grade

	5-YEAR SURVIVAL (%)
Tumor Grade	
1-2	40-87
3-4	0-33
TNM Stage	
Ta, T1, Tcis	60-90
T2	43-75
T3	16-33
T4	0-5
N+	0-4
M+	0

The primary tumor characteristics that suggest invasion, the high incidence of ipsilateral multifocal abnormality, and the risk of recurrence distal to the primary lesion are all offered in support of radical excision of large, proximal, and likely invasive tumors of the upper tract. Conversely, the same risks of multiple recurrence and the fact that tumor stage is the main determinant of outcome support conservative nephron-sparing surgery in many cases.

Upper tract tumors spread in the same ways as bladder tumors do, through lymphatic and hematogenous routes and by direct extension into contiguous structures. Thus, **the common metastatic sites are the lungs, liver, bones, and regional lymph nodes.** Preoperative evaluation for the extent of disease includes chest radiography, abdominal CT, liver function tests, and occasional bone scintigraphy. The thin muscle layer of the renal pelvis and ureter may allow earlier penetration of invasive upper tract tumors than is seen in bladder neoplasms (Cummings, 1980; Richie, 1988). However, this is not a valid reason for radical versus conservative treatment if a lesion is either noninvasive or invasive and organ confined (stage T2) (Gittes, 1980). The renal parenchyma may be a barrier, slowing distant spread of stage T3 renal pelvis tumors. In contrast, periureteral tumor extension carries a high risk of early tumor dissemination along the periureteral vascular and lymphatic supply. Improved survival of patients with stage T3 renal pelvis tumors versus ureteral tumors has been reported by several investigators (Batata and Grabstald, 1976; Guinan et al, 1992a; Park et al, 2004). Guinan and colleagues confirmed this observation among 611 patients treated at 97 hospitals and in a collection of 250 cases reported in the literature (Guinan et al, 1992a). The 5-year survival rates for patients with stage T3 tumors of the renal pelvis and ureter were 54% and 24%, respectively. In a multivariate analysis, patients with ureteral tumors had a higher local and distant failure rate than did those with renal pelvis tumors of the same stage and grade (Park et al, 2004). Renal pelvis and upper ureteral tumors spread initially to para-aortic and paracaval nodes, whereas distal ureteral tumors spread to pelvic nodes (Batata et al, 1975; Heney et al, 1981; Nocks et al, 1982; Mahadevia et al, 1983; McCarron et al, 1983; Jitsukawa et al, 1985; Geiger et al, 1986).

TREATMENT

The treatment of upper tract urothelial tumors has undergone significant changes. **The relatively low frequency of these lesions and the lack of prospective randomized trials do not permit absolute conclusions about treatment impact on outcomes.** In the past, treatment recommendations were based, at least in part, on practical limitations in follow-up and detection of local disease recurrence. Technologic improvements in imaging and, most important, direct endoscopic visualization of all levels of the urinary tract allow earlier and more accurate initial diagnosis and treatment and improved follow-up. Treatment may be based primarily on the risk the tumor poses and on the efficacy of a specific treatment rather than on other considerations. The specific indications and techniques for each form of treatment (open vs. laparoscopic radical nephroureterectomy; open vs. retrograde endoscopic vs. percutaneous renal-sparing tumor ablation) are addressed later in this chapter. However, the following introductory considerations apply.

The least invasive and least ablative treatment necessary for safe control of the tumor is preferred. Most upper tract urothelial tumors are not large or bulky. Thus, laparoscopic surgery is ideal, at least for the renal portion of radical nephroureterectomy when the tumor warrants removal of the entire renal unit (see later). A variety of approaches with various combinations of laparoscopic and open techniques are employed for distal ureterectomy. Low-grade noninvasive upper tract tumors are managed initially by ablative renal-sparing surgery. Retrograde ureteroscopy and ureteropyeloscopy are preferred when tumor size, number, and access allow complete tumor ablation. Percutaneous antegrade tumor ablation is chosen when the anatomy and the tumor do not allow complete ablation through a retrograde approach.

Open Nephron-Sparing Surgery for Renal Pelvis Tumors: Pyelotomy and Tumor Ablation and Partial Nephrectomy

Indications

Open conservative surgery may be applied in selected cases when nephron sparing for preservation of renal function is required (Gittes, 1966, 1980; Petkovic, 1972a, 1972b; Mazeman, 1976; Johnson and Babaian, 1979; Babaian and Johnson, 1980; Cummings, 1980; Wallace et al, 1981; Tomera et al, 1982; McCarron et al, 1983; Zincke and Neves, 1984; Bazeed et al, 1986; Ziegelbaum et al, 1987; Messing and Catalona, 1998). Tumor in a solitary kidney, synchronous bilateral tumors, and predisposition to form multiple recurrences, as in endemic Balkan nephropathy, are all reasons to consider nephron sparing (Fig. 53–6). Pyeloscopy as an initial diagnostic component to open conservative surgery has been supplanted by retrograde or



Figure 53–6. Patient with an invasive tumor of the upper calyx of a solitary kidney. The patient elected an upper pole partial nephrectomy.

percutaneous antegrade renal endoscopy (Huffman et al, 1985). Direct endoscopic visualization of the lesion and biopsy with cup forceps or brush establish a definitive diagnosis and tumor grade (Gill et al, 1973). The brush biopsy has renewed value because tissue obtained by small cup biopsy forceps used through narrow-caliber flexible endoscopes is limited. Preoperative determination of the stage of renal pelvis tumors remains difficult. Large size, broad base, and nonpapillary pattern favor tumor invasiveness. These improvements in initial diagnosis and assessment of tumor stage and grade allow more specific treatment, including conservative surgery when it is indicated.

The documented risk of wound implantation by tumor is low after open conservative surgery if simple precautions are followed to minimize spillage (Gittes, 1980; Tomera et al, 1982; McCarron et al, 1983). Modern percutaneous antegrade renal surgery allows resection of virtually any lesion formerly treated by open pyeloscopy, and the risk of tumor spillage is even lower (see following discussion).

Technique

Preoperative arteriography is not routinely obtained. However, it may be helpful before partial nephrectomy of rare hypervascular renal pelvis tumors. The affected segmental renal artery may be embolized or more easily identified at the time of surgery on the basis of the arteriogram.

The patient is placed in either a full flank or a torque position, as shown in Chapter 54. The full flank position provides optimal exposure to the renal pelvis for pyelotomy and excision of a large noninvasive tumor. The torque position allows both anterior and posterior exposure to the renal pedicle for partial nephrectomy. An extrapleural, extraperitoneal flank, or thoracoabdominal incision is made. Removal of a portion of the 11th or 12th rib provides maximal exposure to the kidney and aids in mobilization of the upper pole and in gaining access to the renal vessels. Removal of a rib is especially helpful in obese patients or in those with a high kidney. An incision off the tip of the 12th rib suffices in thin patients with a low kidney and is accompanied by less potential wound discomfort or morbidity. After the incision is completed, the Gerota fascia is opened posteriorly and the entire kidney is mobilized. The renal vessels and the ureter are each isolated with a vessel loop.

The wound is packed with dry sponges to isolate the kidney before any intrarenal incisions are made. For pyelotomy and tumor excision the renal pelvis and the major calyceal infundibula are exposed by dissecting the hilar and renal sinus fat as for an extended pyelolithotomy. A gentle curvilinear incision is made in the renal pelvis, and the tumor is excised; the base is cauterized with electrocautery, laser, or argon beam coagulator. Finally, the pelvis is closed with 4-0 chromic catgut or other absorbable suture.

The techniques of partial nephrectomy for renal pelvis tumors are essentially the same as those described in Chapter 54, with the added proviso of taking care to minimize the risk of tumor spillage. The involved segment of the intrarenal collecting system is clamped before removal of the tumor-bearing portion of the kidney is begun. The collecting system of the renal remnant is closed with absorbable 4-0 suture. Identified individual bleeding points are oversewn with 4-0 vascular Prolene or polydioxanone suture. Additional hemostasis is provided by use of electrocautery and the argon beam coagulator on the raw parenchymal surface. The edges of the renal defect and the adjoining renal capsule are approximated over Surgicel bolsters with 2-0 chromic catgut suture.

A suction drain is placed in the renal bed in all cases. A temporary urinary diversion stent is not used routinely unless difficulty is encountered in closing the collecting system.

Results

The reported overall risk of tumor recurrence in the ipsilateral renal pelvis after initial pyelotomy or partial nephrectomy varies from 7% to 60% (Mazeman, 1976; Murphy et al, 1980, 1981; Wallace et al, 1981; McCarron et al, 1983; Zincke and Neves, 1984; Ziegelbaum et al, 1987; Messing and Catalona, 1998). The risk of recurrence after conservative surgery increases with tumor stage from less than 10% for grade 1 to 28% to 60% for grades 2 and 3. The moderate to high risk of recurrence primarily reflects the inherent multifocal atypia and field change of the renal pelvis (Heney et al, 1981; Nocks et al, 1982; Mahadevia et al, 1983; McCarron et al, 1983). The possibility of incomplete initial treatment of the primary tumor cannot be totally excluded.

Estimates of overall and cancer-specific survival after conservative surgery of renal pelvis tumors are hampered by the lack of prospective, controlled, randomized trials and the small numbers of affected patients. The inherent bias introduced by selection of patients for conservative treatment based on medical comorbidities is another variable. Murphy and associates (1980) reported 5-year survival of 75% and 2-year survival of 46% after conservative surgery in patients with grade 1 and grade 2 renal pelvis tumors, respectively. McCarron and associates reported rates of cures, cancer-related deaths, and deaths due to unrelated causes of 33% each in nine patients who underwent conservative surgery (McCarron et al, 1983). **Radical nephroureterectomy and dialysis still offer the best chance of cure and survival in patients with a large, invasive, high-grade, organ-confined renal pelvis tumor (T2N0M0) in a solitary kidney** (Gittes, 1980; McCarron et al, 1983).

Open Radical Nephroureterectomy

Indications

Radical nephroureterectomy with excision of a bladder cuff is recommended for large, high-grade, invasive tumors of the renal pelvis and proximal ureter (Batata and Grabstald, 1976; Skinner, 1978; Babaian and Johnson, 1980; Cummings, 1980; Murphy et al, 1981; Nocks et al, 1982; McCarron et al, 1983; Richie, 1988; Williams, 1991; Messing and Catalona, 1998). Radical surgery also retains a role in treatment of medium-grade, noninvasive tumors of the renal pelvis and upper ureter when they are large, multifocal, or rapidly recurring despite maximal efforts at conservative surgery.

Key Point: Indications for Radical Nephroureterectomy

- The treatment of large, invasive tumors of the renal pelvis and proximal ureter is radical nephroureterectomy with removal of a bladder cuff.

Technique

Choice of Incision. Radical nephroureterectomy may be performed through a variety of approaches. The choice of incision is largely one of the surgeon's preference and is based on the

surgeon's experience, the patient's body habitus and medical comorbidities, and the size of the kidney. The operation may be performed through one incision with the patient placed in a flank torque position, as shown in Chapter 54 and as described in the section on open nephron-sparing surgery (Fig. 53–7). In male patients the genitalia are included in the surgical field so that the bladder catheter may be accessed during the procedure. An extrapleural, extraperitoneal, thoracoabdominal incision is begun over the 11th or 12th rib or off the tip of the 12th rib, as described earlier. In contrast to the incision for partial nephrectomy, for which adequate exposure to the kidney is the primary concern, the lower ureter and the bladder must also be exposed for nephroureterectomy. Thus, the middle and anterior portions of the skin incision angle down toward the pelvis rather than in a subcostal direction (see Fig. 53–7). The peritoneum may be opened at any time to increase exposure as necessary. The thoracoabdominal approach offers the best exposure to the kidney but may cause a greater degree of postoperative atelectasis than the anterior subcostal approach. This may be an important consideration in patients with chronic lung disease.

The operation may also be performed through a single long midline incision and intraperitoneal exposure. However, exposure to the kidney is limited from this approach, particularly for left-sided tumors.

Alternatively, the patient may be positioned supine with a small roll placed behind the rib cage on the affected side. The nephroureterectomy is performed through an upper anterior subcostal incision and a lower quadrant Gibson incision as for renal transplantation. A lower midline or Pfannenstiel incision may be substituted (Fig. 53–8). A lower midline incision avoids dividing muscles, is fast, and provides direct exposure to the prevesical space. However, a Gibson incision provides easier exposure to the distal ureter. Nephrectomy may be difficult from an anterior subcostal approach in obese patients.

Radical Nephrectomy. The entire kidney, along with all the perinephric fat and the Gerota fascia, is fully mobilized (Figs. 53–9 and 53–10). The renal vessels are dissected and individually secured and divided in a standard manner. The authors prefer at least one 0 silk tie and 4-0 vascular Prolene suture ligature on an RB needle for each renal artery and renal vein. Combinations of ties plus large hemoclips may be substituted for the suture ligature. The adrenal is a not-infrequent site of metastasis for urothelial tumor. Traditionally, the ipsilateral adrenal gland has been included with the specimen. However, as in the case of renal cell

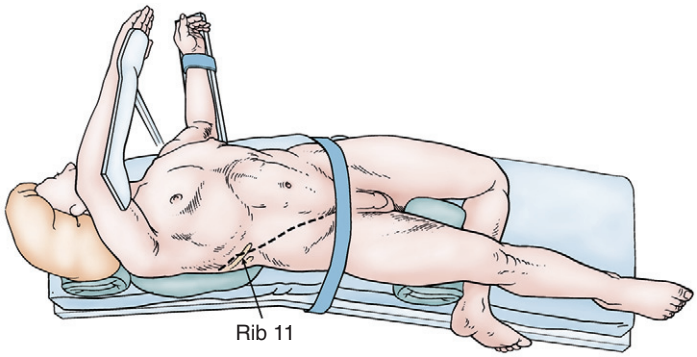


Figure 53–7. Patient in torque flank position for radical nephroureterectomy through a single thoracoabdominal incision. The shoulder girdle is rotated into a full flank position. The pelvic girdle is rolled back nearly to a supine position. All potential pressure points are carefully padded.



Figure 53–8. Radical nephroureterectomy may be performed through a long midline incision or through a subcostal plus Gibson, lower midline, or Pfannenstiel incision. The patient is supine, and the table is mildly flexed. Placement of a small roll under the edge of the rib cage is helpful. (From Sagalowsky AI. Renal transplantation and autotransplantation. In: Marshall F, editor. The textbook of operative urology. Philadelphia: WB Saunders; 1996:320–30.)

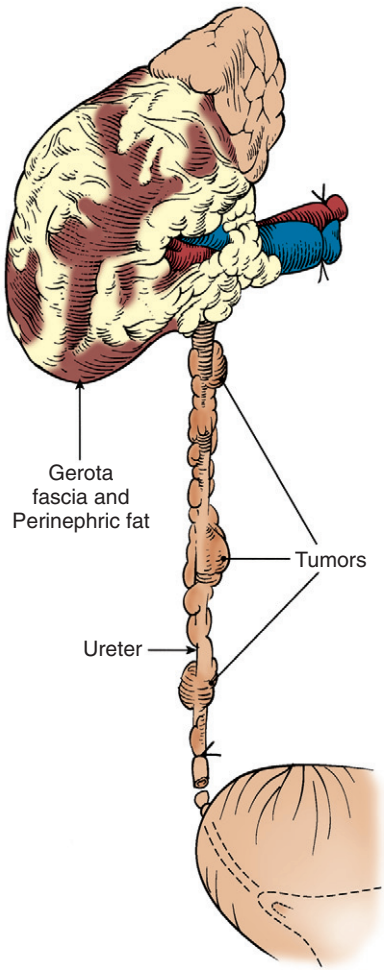


Figure 53–9. Radical nephroureterectomy specimen including the kidney, Gerota fascia, and perinephric fat, with or without the ipsilateral adrenal gland. Note that the ureter is divided distally in the pelvis between ties for a separate distal ureterectomy.

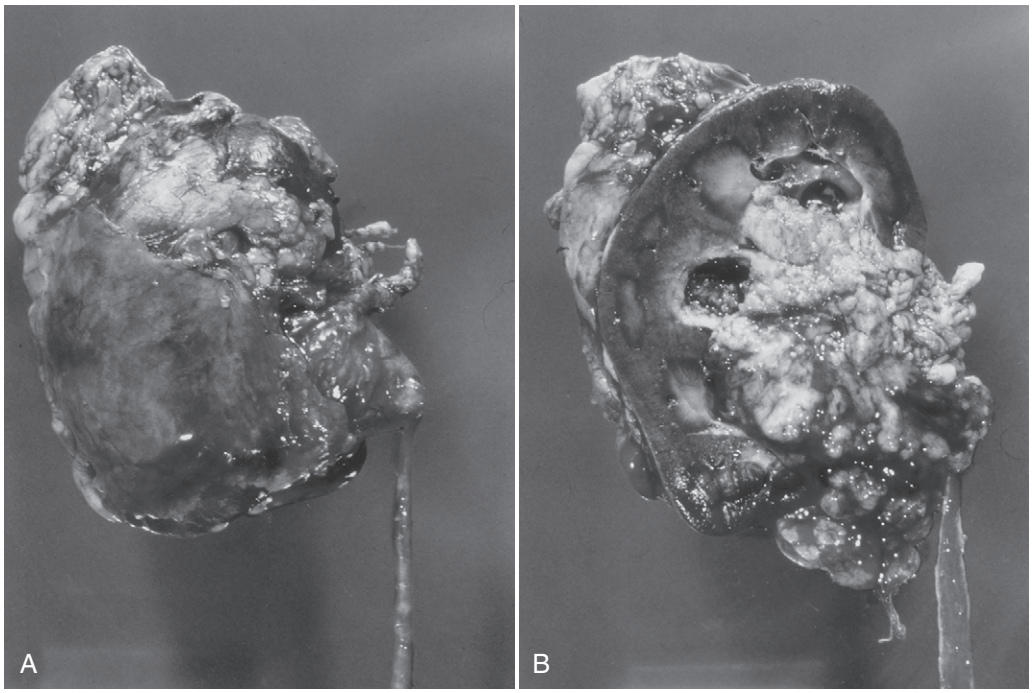


Figure 53–10. **A,** Intact nephroureterectomy specimen for a large renal pelvis tumor. **B,** Bivalved specimen reveals the tumor.

carcinoma, **adrenalectomy adds little to the cure for upper tract tumors.** One may omit adrenalectomy if the gland appears normal on preoperative imaging studies and is grossly normal at the time of surgery and if the disease seems localized within the renal pelvis. However, adrenalectomy is prudent for maximal control if locally advanced disease is discovered.

Management of Distal Ureter and Bladder Cuff

Complete distal ureterectomy with a bladder cuff is necessary with nephroureterectomy and represents a distinct portion of the case, whether an open or laparoscopic approach to the kidney is used. General principles include intact complete ureteral excision with controlled occlusion of the ureteral orifice. **The entire distal ureter, including the intramural portion and the ureteral orifice, is removed.** Failure to completely remove the entire distal ureter and ureteral orifice is associated with a high rate of tumor recurrence. The ureter may be kept in continuity with the kidney to obviate the risk of tumor spillage from the lumen. However, the attached kidney is cumbersome, and this technique is not necessary as long as the distal ureter is divided between ties or clips at a location that is free of gross abnormality. Following are the options available for management of the distal ureter, whether an open or laparoscopic approach is used. If a laparoscopic approach is chosen, the incision can be placed to facilitate both intact specimen extraction and dissection of the distal ureter. One should keep in mind that TCC is a tumor that has the potential to seed nonurothelial surfaces and that maintenance of a "closed system" is important, especially with high-grade tumors.

Traditional Open Distal Ureterectomy

This operation can be done through Gibson, low midline, and Pfannenstiel incisions, depending on the patient's anatomy and the extent of proximal ureteral dissection required. Transvesical, extravesical, and combined approaches have been described. The transvesical approach is the most reliable approach for ensuring complete ureteral excision. An anterior cystotomy may be made and intravesical and extravesical dissection performed as for ureteral neocystostomy (Fig. 53–11); 1 cm of bladder mucosa is included circumferentially around the ureteral orifice. The defect in the bladder wall at the ureteral hiatus is closed in two layers from within the bladder with interrupted 2-0 or 3-0 absorbable suture on the muscle and 4-0 suture on the mucosa. The anterior cystotomy is closed carefully in two layers with running 3-0 absorbable suture. The urethral catheter is maintained for 5 to 7 days; a suprapubic catheter is not routinely used. A flat suction drain is left in the perivesical space.

Complete distal ureterectomy may be performed entirely by extravesical (Fig. 53–12) dissection of the distal ureter and the intramural portion within the bladder wall all the way to the ureteral orifice. The need for a cystotomy is avoided with this approach. The ureter is tented up, and the bladder mucosa is divided between clamps. The defect in the bladder wall is closed in layers, as described previously. Care must be taken to ensure a complete dissection of the intramural portion of the ureter and to avoid contralateral injury from excessive traction.

Transurethral Resection of the Ureteral Orifice

This approach, also referred to as the pluck technique, should be reserved for proximal, low-grade tumors (Abercrombie et al, 1988; Palou et al, 1995). The patient is placed in the lithotomy position, and the ureteral orifice and intramural ureter are aggressively resected to the extravesical space (Fig. 53–13). The patient is then positioned for the nephrectomy portion of the procedure, in which dissection must extend down to the perivesical space. The advantage is avoidance of a second incision in performing an open nephroureterectomy. Walton and coworkers (2009) showed equivalent oncologic outcomes in a long-term retrospective study comparing this to traditional bladder cuff techniques. The advantages are less apparent with laparoscopic nephrectomy, in which an incision is necessary for specimen extraction, and this can be used

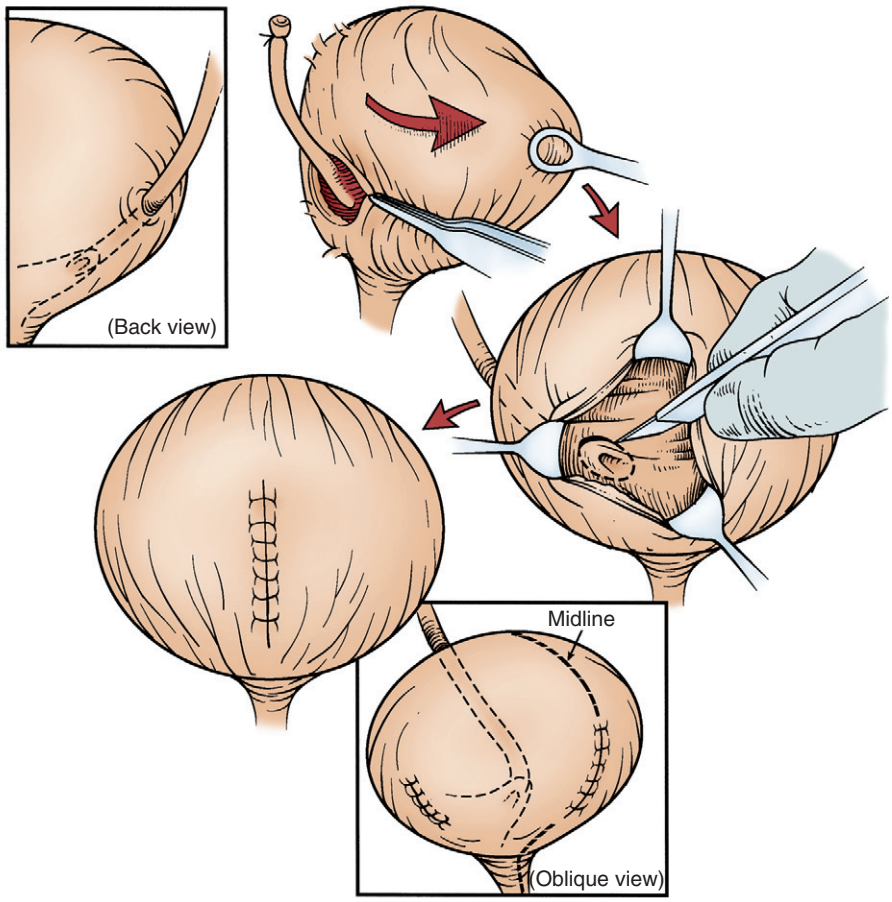


Figure 53–11. Complete distal ureterectomy with bladder cuff is performed by combined extravesical and transvesical dissection.

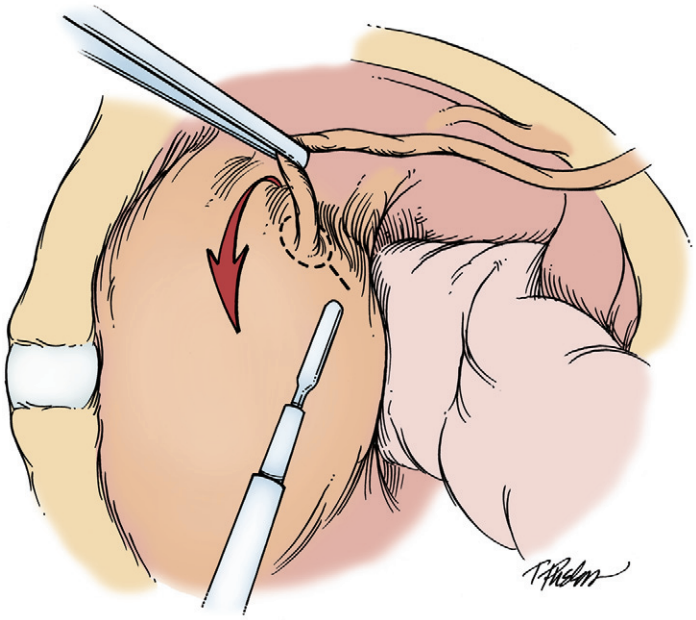


Figure 53–12. Complete distal ureterectomy by extravesical approach. Traction is placed, everting the orifice outside the bladder. Care must be taken to ensure complete removal and to avoid injury to the contralateral ureteral orifice.

for dissection of the distal ureter. In addition there is exposure of nonurothelial surfaces, which may predispose to local recurrence, especially with more dysplastic tumor (Jones and Moisey, 1993; Arango et al, 1997).

Intussusception (Stripping) Technique

Several variations of this procedure have been described (McDonald, 1953; Clayman et al, 1983; Roth et al, 1996; Angulo et al, 1998). Basically, a ureteral catheter is placed in the ipsilateral ureter at the beginning of the procedure. The nephrectomy portion of the procedure is carried out, and the ureter is dissected as far distally as possible. The ureter is then ligated and transected with the ureteral catheter secured to the proximal end of the distal ureter (Fig. 53–14). After nephrectomy, the patient is moved to the lithotomy position; the ureter is intussuscepted by traction into the bladder, and a resectoscope is used to excise the bladder cuff and free the ureter from the bladder. Concerns with this technique are presented by Giovansili and associates (2004), who described a failure rate of 18.7% in which there may have been disruption of the ureter and the need for an additional surgical incision.

Transvesical Ligation and Detachment Technique

This technique most closely mimics the open technique. Before the nephrectomy portion of the procedure, the patient is placed in the low lithotomy position, a ureteral catheter is placed, and two suprapubic 3-mm trocars (Fig. 53–15) are placed transvesically. The ureter is tented up, and a loop ligature is placed around the catheter and the orifice, creating a "closed" system. A Collins knife circumscribes the ureteral orifice, and further dissection is facilitated by the grasper, which provides traction until the extravesical

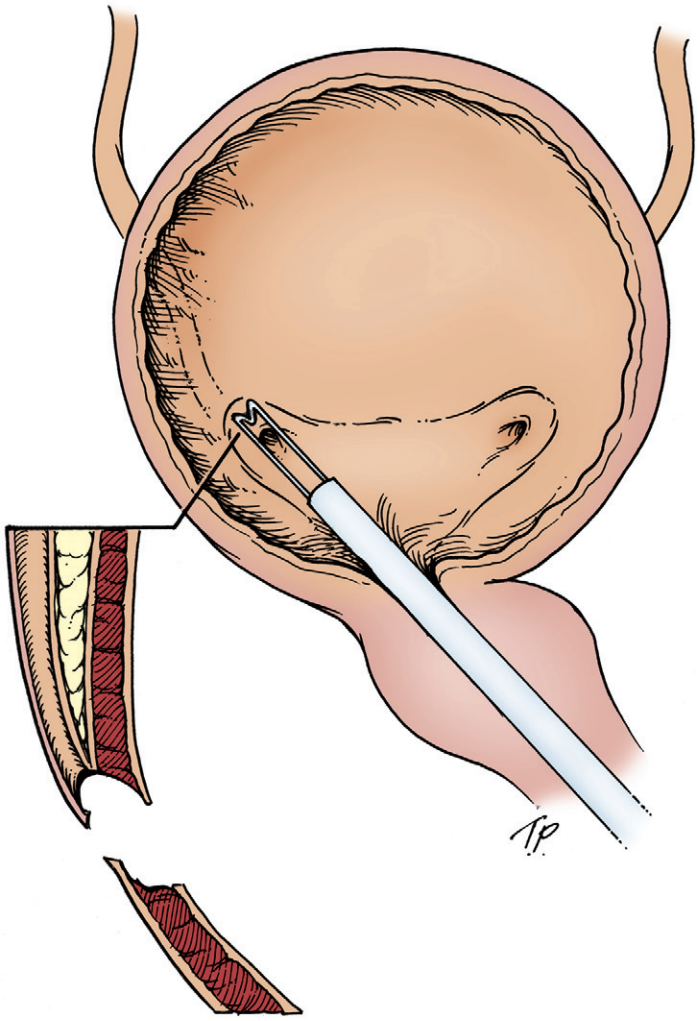


Figure 53–13. The entire orifice and intramural ureter are resected transurethrally until the extravesical fat is seen. This portion is usually done at the beginning but can be done at the end of the procedure.

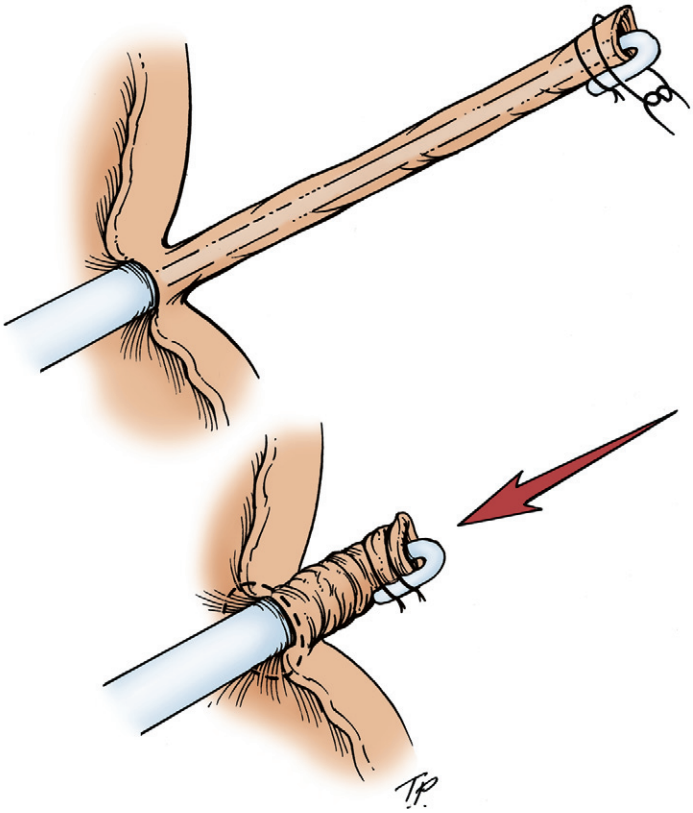


Figure 53–14. With the intussusception technique, a ureteral catheter is placed at the beginning of the case. After nephrectomy the ureter is divided and the catheter is secured to the distal portion of the ureter. The patient is moved to the lithotomy position, and the ureter is intussuscepted into the bladder with retrograde traction. A resectoscope is used to excise the attached orifice.

space is reached. There has been excellent clinical success reported with this technique (Gill et al, 1999), but it can be technically difficult. Agarwal and associates (2008) described a technique that appears similar but dissects the ureter only to the extravesical space.

Total Laparoscopic Technique

Flexible cystoscopy is performed before the laparoscopic portion of the case, and a Bugbee electrode is used to cauterize the orifice and intramural ureter completely. Cauterization of the intramural portion of the ureter is important for identification of the distal limits of the dissection during the laparoscopic portion of the procedure. A 20- or 22-Fr Foley catheter is placed before proceeding to the laparoscopic portion. The nephrectomy and ureteral dissection are carried down to the detrusor muscle. Antegrade traction is placed on the ureter, everting the orifice out of the bladder, and an endovascular stapling device is placed as distally as possible (Fig. 53–16). A flexible cystoscope can be placed at this time if there is any question of the adequacy of the specimen or concern of disturbance of the contralateral ureteral orifice. The endovascular stapling device is then deployed, laying two rows of staples on the bladder and specimen sides. This allows a closed system after division of the ureter.

Management of Distal Ureter—Considerations

Much controversy surrounds the management of the distal ureteral cuff during nephroureterectomy. No study has shown a clear advantage of any single technique (Macejko et al, 2008). However, it is universally accepted that the ureter must be removed in its entirety. Failure to do so places the patient at an unacceptable risk for distal recurrence, especially with high-grade tumors. Because of the rarity of the disease and other factors it is unlikely that a study will be designed to resolve this issue. There is some concern of the use of techniques that violate the closed system, especially with high-grade/stage and lower ureteral tumors. In addition, total laparoscopic techniques appear to be associated with a higher local recurrence rate, possibly due to retained ureter in the bladder (Romero et al, 2007). When considering an approach, the surgeon should take into account tumor location, potential for seeding, patient factors, and personal experience.

Lymphadenectomy

Regional lymphadenectomy is included with radical nephroureterectomy. For renal pelvis and proximal or middle ureteral tumors the ipsilateral renal hilar nodes and the adjacent para-aortic or paracaval nodes are resected. This dissection adds little time or morbidity to the surgery. On occasion, lymphadenectomy is more hazardous in patients with severe atherosclerosis of the aorta or grossly positive and fixed nodes. Node dissection is limited or omitted in these cases.

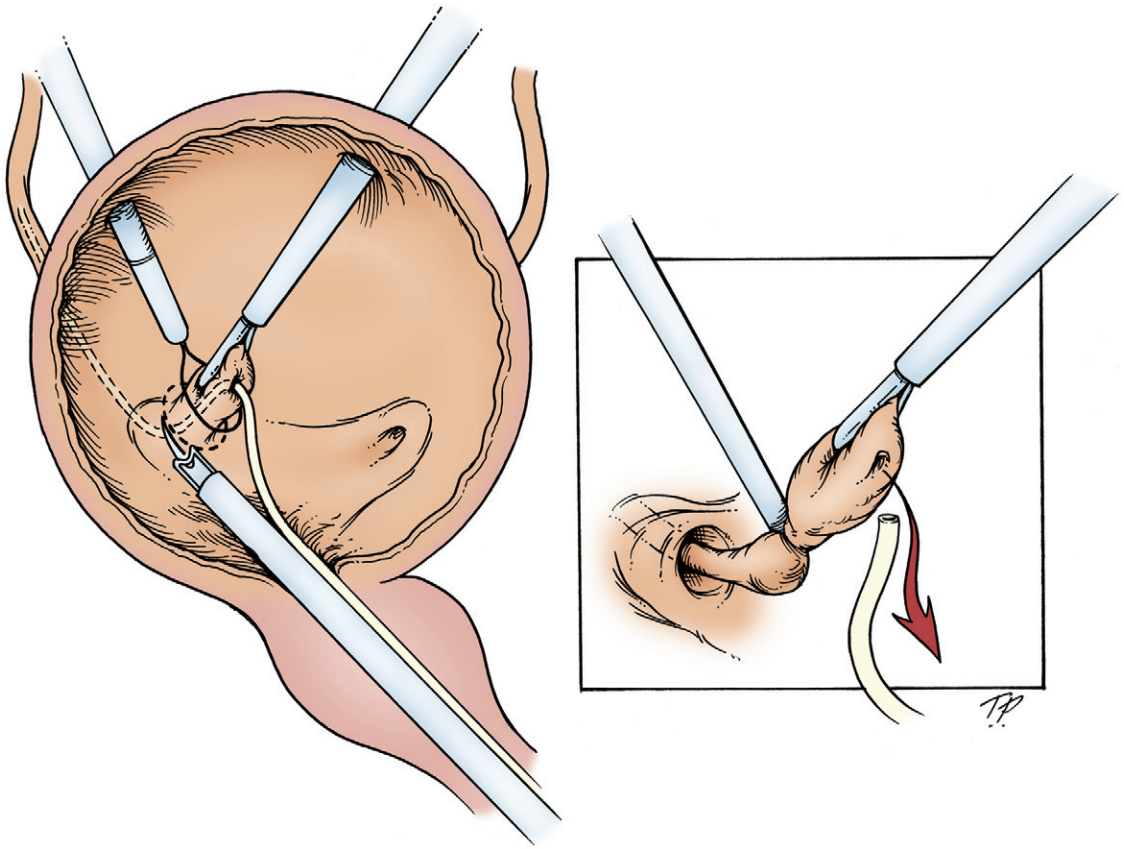


Figure 53–15. A ureteral catheter is placed, and two laparoscopic ports are placed transvesically. The ureteral orifice is tented up; a loop is placed around the orifice to occlude the opening and to place traction on the ureter. A Collins knife then facilitates the dissection to the extravesical space.

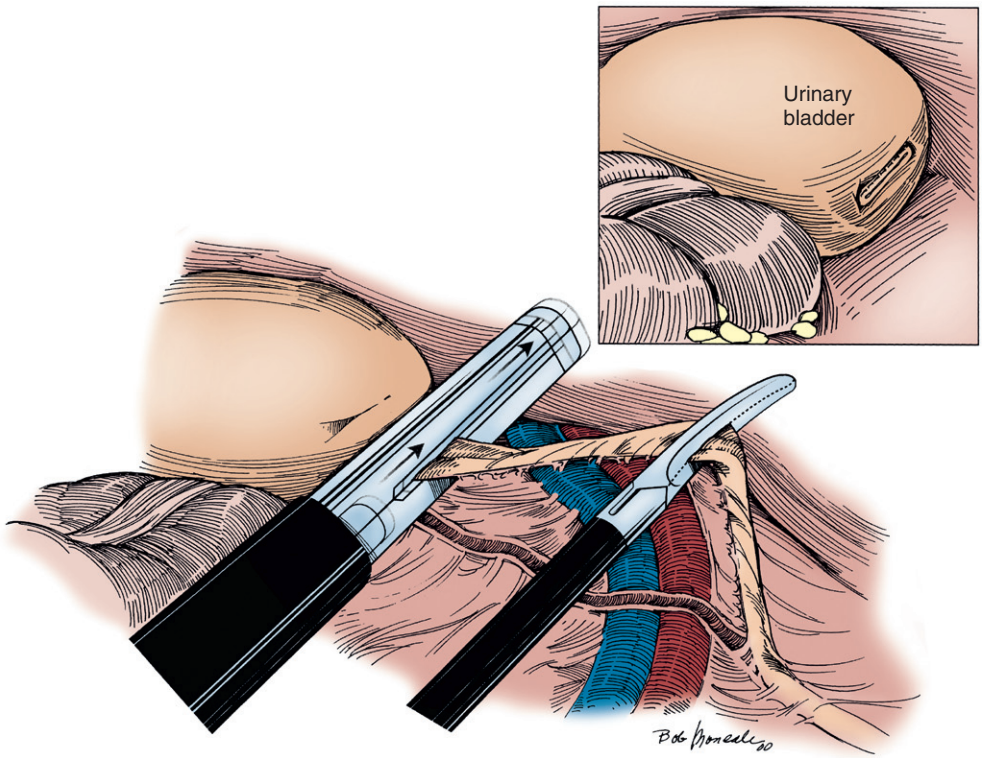


Figure 53–16. The ureter is dissected extravesically to the ureteral orifice. Lateral traction is placed on the ureter, everting the orifice, and the endovascular stapling device is placed at the distal margin, providing simultaneous ligation and division of the distal ureter at the level of the bladder. A cystoscope can be placed to ensure that the entire ureter is removed.

Key Point: Lymphadenectomy with Radical Nephroureterectomy

- Regional lymphadenectomy is included with radical nephroureterectomy.

Results

The outcome strongly correlates with tumor stage and grade as summarized in Tables 53–2 and 53–3, compiled from numerous series. The role of complete distal ureterectomy with excision of a bladder cuff in radical nephroureterectomy for upper tract tumors is well established. The risk of tumor recurrence in a remaining ureteral stump is 30% to 75% (Bloom et al, 1970; Strong et al, 1976; Johansson and Wahlquist, 1979; Babaian and Johnson, 1980; Kakizoe et al, 1980; Mullen and Kovacs, 1980; McCarron et al, 1983). This risk is likely to remain or even to increase as the use of radical nephroureterectomy becomes more selective for patients, mainly those with higher risk tumors. All patients who underwent an extravesical dissection and tenting up of the ureter in the series by Strong and associates (1976) retained a portion of the ureter and the ureteral orifice; this demonstrates that the transvesical dissection of the ureter must be thorough to avoid such an error. Complete ureterectomy with a bowel cuff should accompany nephroureterectomy of a renal unit draining into a urinary diversion. Mufti and coworkers (1988) reported a tumor recurrence rate of 37.5% when the ureteroenteric anastomosis was not removed.

The need or benefit of radical nephroureterectomy versus simple nephrectomy or conservative nephron-sparing surgery is less well defined. Radical nephroureterectomy is recommended as providing optimal chance for survival in numerous series (Batata et al, 1975; Johansson and Wahlquist, 1979; Murphy et al, 1980; McCarron et al, 1983; Zungri et al, 1990). Batata and colleagues (1975) reported that radical nephroureterectomy provided a 5-year survival rate of 23% among patients with locally advanced disease (stage T3 to T4, N1 to N2). Johansson and Wahlquist (1979) reported survival advantage at 5 years for radical versus simple nephrectomy of 84% versus 51%, respectively, and of 74% versus 37%, respectively, for patients with high-stage tumors only. McCarron and associates (1983) reported that the subgroup of patients with large, high-grade, but organ-confined disease obtained the most benefit from radical versus conservative surgery. The death rate due to tumor was 29% versus 89% for the radical and conservative surgery groups, respectively. In the series reported by Murphy and associates (1980), radical surgery conferred a survival advantage over conservative surgery at 5 years of 88% versus 75% for grade 1 tumors and of 90% versus 46% for grade 2 tumors. The retrospective, uncontrolled nature of all these series limits the conclusions that may be drawn. In summary, radical nephroureterectomy is warranted for patients with high-grade invasive disease that is organ confined (stage T1 to T2, N0) or is only locally advanced (stage T3 to T4, N0 to N2, M0). Tumor-free survival rates are high after radical nephroureterectomy for organ-confined disease and are guarded to poor for locally advanced disease. Treatment decisions in patients with compromised renal function must balance the potential beneficial effect of radical surgery on control of the tumor versus the morbidity, mortality, and quality of life risks associated with dialysis.

Regional lymphadenectomy is a recommended accompaniment of radical nephroureterectomy for upper tract tumors in multiple reports (Grabstald et al, 1971; Batata et al, 1975; Batata and Grabstald, 1976; Skinner, 1978; Johansson and Wahlquist, 1979; Babaian and Johnson, 1980; Cummings, 1980; Heney et al, 1981; McCarron et al, 1983; Richie, 1988; Williams, 1991; Messing and Catalona, 1998; Brausi et al, 2007; Kondo et al, 2007; Abe et al, 2008). However, the authors in nearly every one of these series find little therapeutic value from lymphadenectomy, and almost every patient with node-positive disease develops early distant metastases. In the series by Batata and Grabstald (1976), 5-year survival was seen in 23% of patients with completely resected stage T3 to T4, N1 to N2 disease. One of the limitations in assessing the role of lymph node dissection for radical nephroureterectomy is that, as with the treatment of renal cell carcinoma, the lymphatic drainage for renal pelvis tumors is not precise and thus the boundaries of lymphadenectomy are unclear. Investigators in recent series have readdressed these issues. Kondo and colleagues (2007) compared outcomes after radical nephroureterectomy for 45, 36, and 88 patients who underwent complete regional, incomplete regional, or no lymphadenectomy, respectively. Overall cancer-specific survival did not correlate with more extensive lymphadenectomy. However, with multivariate analysis a statistically significant benefit was seen with complete lymphadenectomy and higher lymph node counts for patients with stage pT3-4 disease. In a recent retrospective, uncontrolled series Brausi and associates (2007) compared outcomes in 82 patients with stage pT2-4 upper tract tumors who underwent lymphadenectomy with removal of more than five nodes at the time of radical nephroureterectomy or no lymphadenectomy in 44 and 42 cases, respectively. In both univariate and Cox proportional hazard analysis the T stage and performance of lymph node dissection correlated with disease recurrence and disease-specific survival. In a larger contemporary series, Abe and associates (2008) compared outcomes in 166 patients and 146 patients who did or did not undergo lymphadenectomy, respectively, at the time of renal surgery for upper urinary tract tumor. In multivariate analysis, pathologic lymph node status, as well as grade and stage, correlated with cause-specific survival. Among the group who underwent lymphadenectomy survival was similar for those with fewer than six and more than six nodes removed. Survival for patients with resected negative nodes was higher than for those who did not undergo lymphadenectomy (stage pNx). **The rationale for continuing regional lymphadenectomy is that it adds little time or morbidity to the surgery, is important for prognosis, and may occasionally have therapeutic value.** Earlier diagnosis in contemporary experience may identify more patients with limited nodal metastases who might benefit from radical surgery. Patients with proven nodal disease are obvious candidates for more careful follow-up and for trials exploring the role of adjuvant therapy.

Laparoscopic Radical Nephroureterectomy

The indications for laparoscopic nephroureterectomy are the same as those for open nephroureterectomy. Laparoscopic nephroureterectomy can be performed by transperitoneal, retroperitoneal (Hattori et al, 2005), and hand-assisted approaches (Landman et al, 2002; Stifleman et al, 2000). All show a significant decrease in morbidity compared with an open surgical approach for appropriately selected patients. All laparoscopic techniques involve two distinct portions of the procedure: nephrectomy and excision of the distal ureter with intact specimen extraction for accurate staging. Management of the distal ureter is described previously in the chapter. One should bear in mind several factors with

laparoscopic nephroureterectomy, including the risk of tumor seeding from both the ureter and the bladder. For these reasons, removal of an intact specimen is desirable. The incision should be strategically placed for both extraction of the specimen and dissection of the distal ureter. Because an incision is necessary regardless of the approach chosen, some techniques for avoidance of a second incision for the distal ureter described previously have less utility.

Technique

Transperitoneal Laparoscopic Nephroureterectomy

Laparoscopic Removal of Kidney Down to Midureter. The patient is placed supine with the ipsilateral hip and shoulder rotated approximately 20 degrees (Fig. 53–17). The patient is secured to the table and can be easily moved from the flank position (nephrectomy portion) to the modified supine position (open portion) by rotating the operative table. The ipsilateral flank and urethra are prepared and draped, and a Foley catheter is placed before insufflation of the abdomen.

The abdomen is insufflated, and three or four trocars are placed as outlined in Figure 53–18, with the first usually being the lateral trocar. Subsequent trocars are placed under direct vision. With this configuration, the camera is kept at the umbilicus for the entire procedure. The upper midline and lateral trocars are used by the surgeon for the dissection of the kidney and the proximal half of the ureter. The lower midline and lateral trocars are used for the dissection of the distal ureter. A 3-mm trocar just below the xiphoid can be helpful in retracting the spleen and liver for left- and right-sided lesions, respectively. The exception is with obese patients, when shifting of the trocars may be necessary to provide optimal visualization (Fig. 53–19). If a hand-assist approach is chosen, the hand port site should be placed so that it can be used for the dissection of the distal ureter and open bladder cuff as indicated.

The table is rotated so the patient is in the flank position. The peritoneum is incised along the white line of Toldt from the level of the iliac vessels to the hepatic flexure on the right and to the splenic flexure on the left. The colon is moved medially by releasing the renocolic ligaments while leaving the lateral attachments of the Gerota fascia in place to prevent the kidney from "flopping" medially. The colon mesentery should be mobilized medial to the great vessels to facilitate dissection of the ureter, renal hilum, and local lymph nodes as needed.

Proximal Ureteronephrectomy. The proximal ureter is identified, just medial to the lower pole of the kidney, and dissected toward the renal pelvis. If an invasive ureteral lesion is suspected, the dissection should include a wide margin of tissue. The renal hilum is identified, and its vessels are exposed with a combination of blunt and sharp dissection. The artery is ligated and divided by use of a gastrointestinal stapling device with a vascular load or multiple clips. The renal vein is then divided in a similar fashion (Fig. 53–20). With vascular control ensured, the kidney is dissected free, either inside or outside the Gerota fascia, depending on the tumor location and stage. For upper pole lesions thought to invade the parenchyma, the ipsilateral adrenal should be removed.

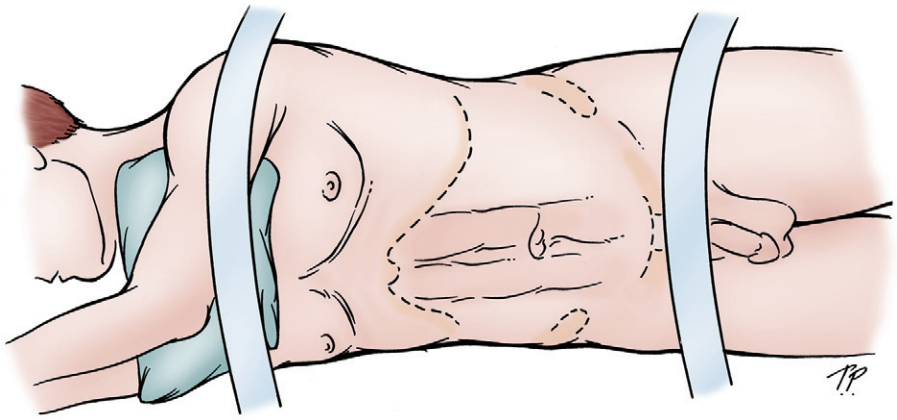


Figure 53–17. The patient is positioned on the table in a modified lateral decubitus position with the ipsilateral flank rotated up 15 degrees. The patient is secured to the table at the chest, waist, and lower extremity. This setup allows the patient to be moved to the full flank or supine position with simple rotation of the operating table. (From Jarrett TW. Laparoscopic nephroureterectomy. In: Bishoff JT, Kavoussi LR, editors. Atlas of laparoscopic retroperitoneal surgery. Philadelphia: WB Saunders; 2000. p. 105.)

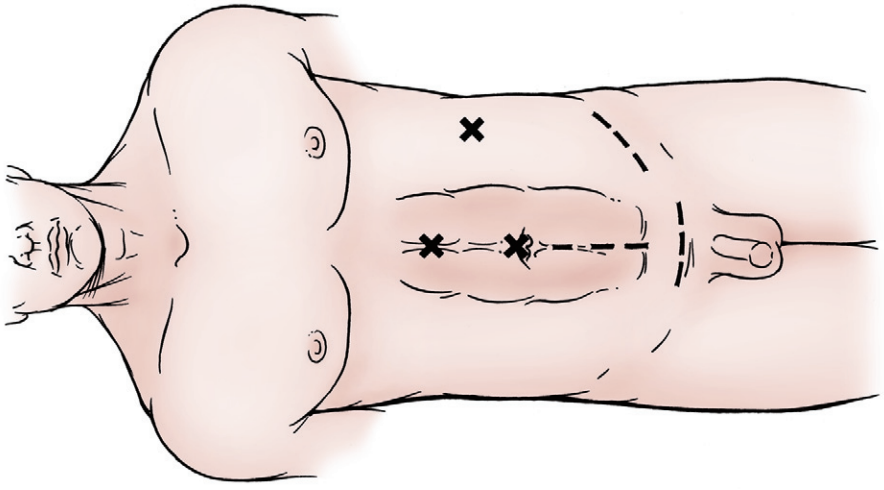


Figure 53–18. Port configuration for laparoscopic-assisted nephroureterectomy. Three ports are generally used for the kidney and upper ureteral dissection. A fourth midline port between the umbilicus and symphysis can be placed, if needed, for further ureteral dissection. The incision is then strategically placed to allow the distal ureteral dissection and specimen removal. The choice of incision largely depends on patient factors and level of dissection reached during the laparoscopic portion of the procedure. A low abdominal (midline or Pfannenstiel) incision is favored if the dissection is below the iliac vessels. A Gibson-type incision will give exposure of the more proximal ureter, if necessary.

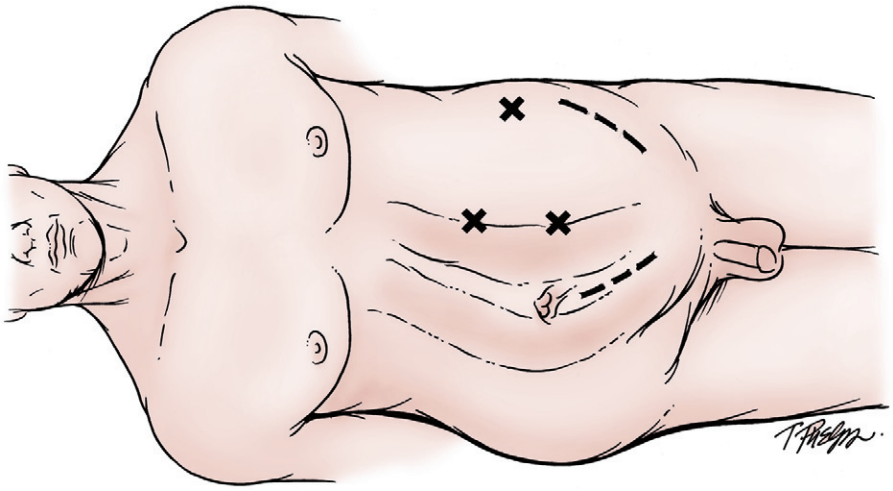


Figure 53–19. For obese patients undergoing laparoscopic-assisted nephroureterectomy the trocars are shifted laterally to accommodate the increased distance from the kidney.

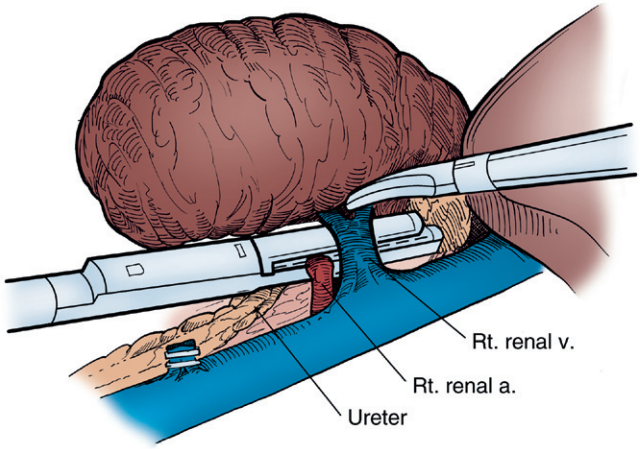


Figure 53–20. The vessels of the renal hilum are carefully dissected, and the endovascular stapling device, with a vascular load, is used to simultaneously ligate and divide the vessels in a controlled environment. (From Jarrett TW. Laparoscopic nephroureterectomy. In: Bishoff JT, Kavoussi LR, editors. Atlas of laparoscopic retroperitoneal surgery. Philadelphia: WB Saunders; 2000. p. 112.)

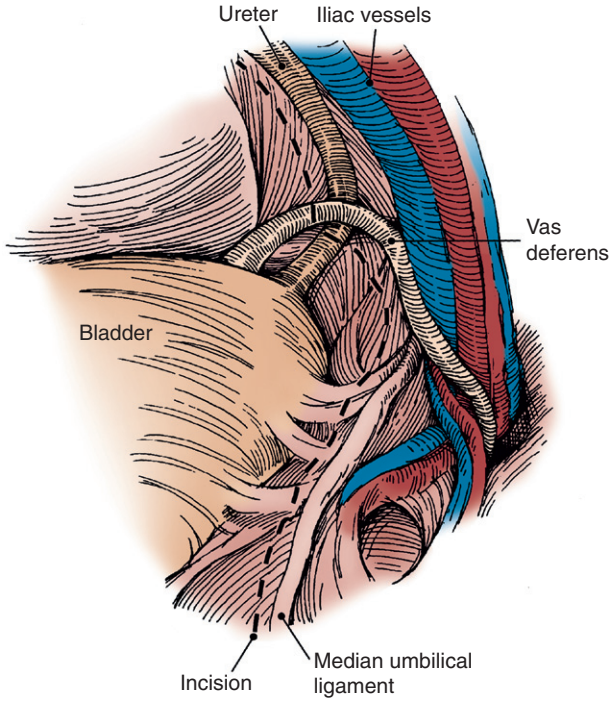


Figure 53–21. The peritoneal incision is continued below the iliac vessels medial to the median umbilical ligament and lateral to the bladder. The vas deferens is divided between clips in the male patient. In the female patient the round ligament is divided, giving full exposure of the distal ureter to the bladder.

The ureteral dissection is continued distally, keeping in mind that the ureteral blood supply is generally anteromedially located in the proximal third, medially located in the middle third, and laterally located in the distal third. Dissection of the lower half may require placement of the fourth trocar. In the area of primary disease, surrounding tissue should be left to provide an adequate tumor margin. The ureteral dissection is continued as far as is technically feasible. If the distal limits of the dissection are below the level of the iliac vessels, the remainder of the procedure can easily be completed through a lower abdominal incision. The specimen is placed in the pelvis, and the renal bed is inspected meticulously for bleeding. At this time, the 10-mm port sites are closed before proceeding to the open portion of the case.

Open Distal Ureterectomy with Excision of Bladder Cuff. The patient is now moved to the supine position, which can usually be done without re-preparation, and a low midline Pfannenstiel or Gibson incision is made (see Fig. 53–18). The choice of incision largely depends on the tumor location, the body habitus of the patient, and the most caudal level of ureteral dissection attained during the laparoscopic portion. The Gibson incision is preferable when the distal ureter cannot be freed laparoscopically to the level of the iliac vessels. The open distal ureterectomy is described in the section on open techniques.

Dissection of the Distal Ureter. If one is to consider a total laparoscopic procedure or to minimize the open distal portion, the ureteral dissection needs to continue to the level of the bladder. The patient is placed in the Trendelenburg position to move the bowel contents out of the pelvis. The peritoneal incision is extended from the level of the iliac vessels into the pelvis lateral to the bladder and medial to the medial umbilical ligament (Fig. 53–21). The vas deferens in male patients and the round ligament in female patients is clipped and divided. The ureter can now be traced between the bladder and the medial umbilical ligament down to its origin at the bladder. The bladder cuff may be dissected extravesically, freeing the ureter from the surrounding detrusor

muscle. Flexible cystoscopy at this point may be helpful in confirming complete ureterectomy and patency of the contralateral ureteral orifice.

Results

The first laparoscopic nephroureterectomy was performed in 1991 by Clayman and associates. Since that time the technical aspects and safety of laparoscopic procedures have been well established. There are multiple published series of laparoscopic nephroureterectomy with varying techniques (Chung et al, 1996; Keeley and Tolley, 1998; Salomon et al, 1999; Shalhav et al, 2000; Jarrett et al, 2001; Stifleman et al, 2001; Bariol et al, 2004; Hsueh et al, 2004; Matin and Gill, 2005; Wolf et al, 2005). Each varies with regard to approach (transperitoneal vs. retroperitoneal), management of the distal ureter by open removal, transurethral resection, and total laparoscopic management. As with other laparoscopic renal procedures there is no clear-cut benefit of any one approach with regard to morbidity, cosmesis, or return to activity. All, however, show a benefit with regard to morbidity compared with open surgery.

The efficacy of laparoscopic nephroureterectomy is being established for cancer control. With intermediate and long-term follow-up, cancer-related outcomes appear comparable to those of the open counterpart (McNeill et al, 2000). El Fettouh and colleagues (2002), in a multi-institutional study with 116 patients, showed the local and bladder recurrence rates to be 2% and 24%, respectively. The rate of distant metastasis was 9%, and positive margins were seen in 4.5% of cases. More recently, Berger and associates (2008) showed a 5-year cancer-specific survival of 80%, 70%, 68%, 60% and 0% for stage Ta/Tis, T1, T2, T3, and T4 lesions, respectively. Schatteman and associates (2007) similarly showed cancer-specific survival rates of 100%, 86%, 100%, 77%, and 0% for stage Ta, T1, Tis, T3, and T4 lesions. In both studies there was a worsening prognosis with increasing tumor stage. Long-term data are available from Muntener and associates (2007a), who studied 37 patients with follow-up of 60 to 148 months. In this study, 11 patients had disease progression and died of TCC 7 to 59 months after the operation. Tumor stage was the only factor significantly associated with disease recurrence. Waldert and coworkers (2009) compared open to laparoscopic outcomes and showed no significant difference in cancer outcomes and the advantage of lower morbidity for well-selected patients.

Local recurrence and port-site seeding are major concerns. There have been five reported instances of port-site seeding involving TCC of the upper urinary tract. Two of these cases were discovered after simple nephrectomy for presumed benign disease in which the principles of surgical oncology were inadvertently not followed (Ahmed et al, 1998; Otani et al, 1999). Three instances were for intended nephroureterectomy for high-grade disease (Ong et al, 2003; Matsui et al, 2004; Barrett, verbal communication, September 1998). Muntener and associates (2007b) reported a single case of local recurrence among 166 cases. In this instance there was obvious violation of the ipsilateral urinary tract, noted perioperatively. Although the potential for seeding exists, it does not appear any higher than that for the open surgical counterpart as long as good surgical principles are followed.

In summary there does not appear to be a significant difference between laparoscopic and open nephroureterectomy when the principles of surgical oncology are followed. Management of the bladder cuff still has shown variability and a tendency toward higher recurrences with minimally invasive approaches. Lymphadenectomy can be performed laparoscopically and should be utilized based on the clinical situation.

Open Segmental Ureterectomy

Ureteroureterostomy

Indications. **Segmental ureterectomy and ureteroureterostomy are indicated for noninvasive grade 1 and grade 2 tumors of the proximal ureter or midureter that are too large for complete endoscopic ablation and for grade 3 or invasive tumors when nephron sparing for preservation of renal function is a goal.**

Technique. The patient is placed in a modified flank position for lesions of the proximal ureter or in a supine position with a roll under the ipsilateral lumbar space for midureteral tumors. An angular extraperitoneal incision from the tip of the 12th rib toward the pelvis provides good exposure to the midureter. The ureter is identified, mobilized, and secured with vessel loops proximally and distally. The approximate location of the lesion is known from preoperative imaging and ureteroscopy. The tumor is palpated, and the ureter is ligated 1 to 2 cm proximal and distal to the tumor (Fig. 53–22A). The involved ureteral segment is excised and sent for frozen-section analysis to confirm the diagnosis, grade, and stage and to verify that both ends of the ureter are tumor free. A regional lymphadenectomy is performed. The ureter is repaired by mobilizing both ends to allow a tension-free anastomosis. A defect of up to 4 cm is amenable to ureteroureterostomy in most cases. The entire kidney may be mobilized downward to provide additional length to the proximal ureter when necessary. The periureteral blood supply is preserved as the ureter is mobilized. The ureteral ends are spatulated and anastomosed with interrupted absorbable 4-0 sutures (see Fig. 53–22B and C). A ureteral stent is placed as the anastomosis is in progress, and a closed-suction drain is placed in the retroperitoneal space near but not touching the repair (see Fig. 53–22D).

Distal Ureterectomy and Direct Neocystostomy or Ureteroneocystostomy with a Bladder Psoas Muscle Hitch or a Boari Flap

Indications. **Complete distal ureterectomy is recommended for tumors in the distal ureter that cannot be removed completely by endoscopic means** (Bloom et al, 1970; Johnson and Babaian, 1979; Babaian and Johnson, 1980; Pagano, 1984; Johnson et al, 1988; Anderstrom et al, 1989; Williams, 1991; Messing and Catalona, 1998). Larger, high-grade, organ-confined, invasive lesions comprise the majority of these tumors.

Technique. The patient is placed in the supine position. It is desirable to include the genitalia in the surgical field so that a bladder catheter may be placed and accessible during the procedure. A Gibson, Pfannenstiel, or lower midline incision provides good exposure to the distal ureter and bladder for the ureteral excision and the repair. The distal ureterectomy is performed as described in the section on radical nephroureterectomy. Extra care is warranted to avoid spillage of known tumor in the distal ureteral segment.

The choice of a nonrefluxing or refluxing anastomosis is controversial (Pagano, 1984). The nonrefluxing anastomosis may limit infections as well as seeding of the upper tract with tumors from the bladder. The refluxing anastomosis may facilitate follow-up surveillance of the upper tract with imaging studies and ureteroscopy.

Direct ureteroneocystostomy may be possible if only a short segment of the juxtavesical and intramural ureter is removed. Additional techniques are required when the entire distal ureter

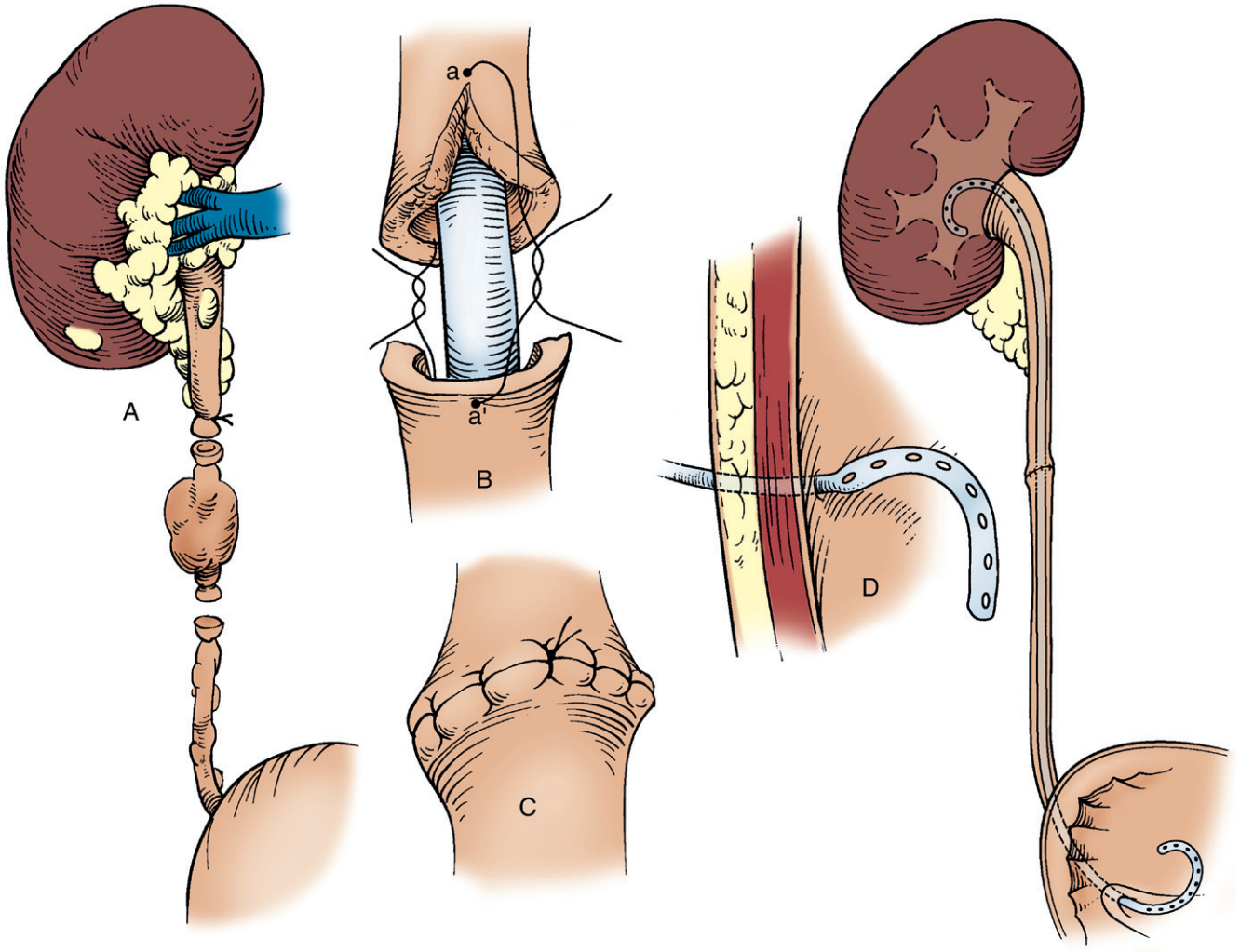


Figure 53–22. **A,** Segmental ureterectomy between ties for a large, invasive tumor of the midureter. **B** and **C,** Ureteroureterostomy of spatulated ends of the ureter. The repair is performed over an internal stent. **D,** Completed repair with closed-suction drain in retroperitoneal space.

is removed. The first choice is a bladder psoas muscle hitch. The superior vesical attachments on the opposite side of the bladder are freed. An anterior cystotomy is made, and the bladder is mobilized upward over the iliac vessels to the psoas muscle at the level of the iliac crest (Fig. 53–23A and B). The bladder is secured to the psoas muscle and tendon with a row of interrupted 2-0 chromic sutures. Entrapment of the genitofemoral nerve is avoided. The ureteral end is spatulated and brought through an opening in the uppermost portion of the bladder. Angulation must be avoided at the ureteral hiatus. A nonrefluxing anastomosis is performed by placing the ureter in a mucosal trough or tunnel if there is sufficient ureteral length (see Fig. 53–23C). The anastomosis is completed with interrupted 4-0 chromic sutures. A ureteral stent, a urethral catheter, and a closed-suction drain in the perivesical space are placed in all cases (see Fig. 53–23D). The anterior cystotomy is closed in two layers with 3-0 absorbable suture. Insertion of a suprapubic catheter is optional.

The bladder psoas muscle hitch provides considerable length if the bladder is of normal size and compliance. However, if an even greater gap must be bridged, a Boari flap from the anterior bladder wall combined with a psoas muscle hitch will reach the proximal ureter (Figs. 53–24 and 53–25). If the need for a Boari flap is anticipated, the incisions for the flap should be marked before making the cystotomy and psoas hitch. The spatulated end of the ureter is anastomosed to the cephalad end of the bladder flap, as described previously. The bladder tube is folded and closed in two layers with running 3-0 absorbable suture.

Subtotal Ureterectomy

Indications. Some tumors may require removal of long segments of the ureter by virtue of multifocality and number. However, the tumor grade and stage may not warrant nephroureterectomy. In addition, nephron sparing may be necessary because of compromised function of the contralateral kidney.

Technique. Complete ileal ureteral substitution may be performed as described in Chapter 85. The proximal ileal segment is anastomosed to the renal pelvis, and the distal ileum is connected to the bladder. Ileal interposition may be performed to repair a long midureteral defect when neither ureteroureterostomy nor bladder mobilization is feasible. A suitable length of ileum to bridge the gap is selected. The ileum is narrowed over a 14-Fr catheter held along the mesenteric edge of the bowel to approximate the diameter of the ureter. Discarding excess bowel from the antimesenteric edge decreases problems with mucus plugging, preserves intestinal blood supply, and allows more efficient peristalsis of urine across the ileal segment. The vermiform appendix has also

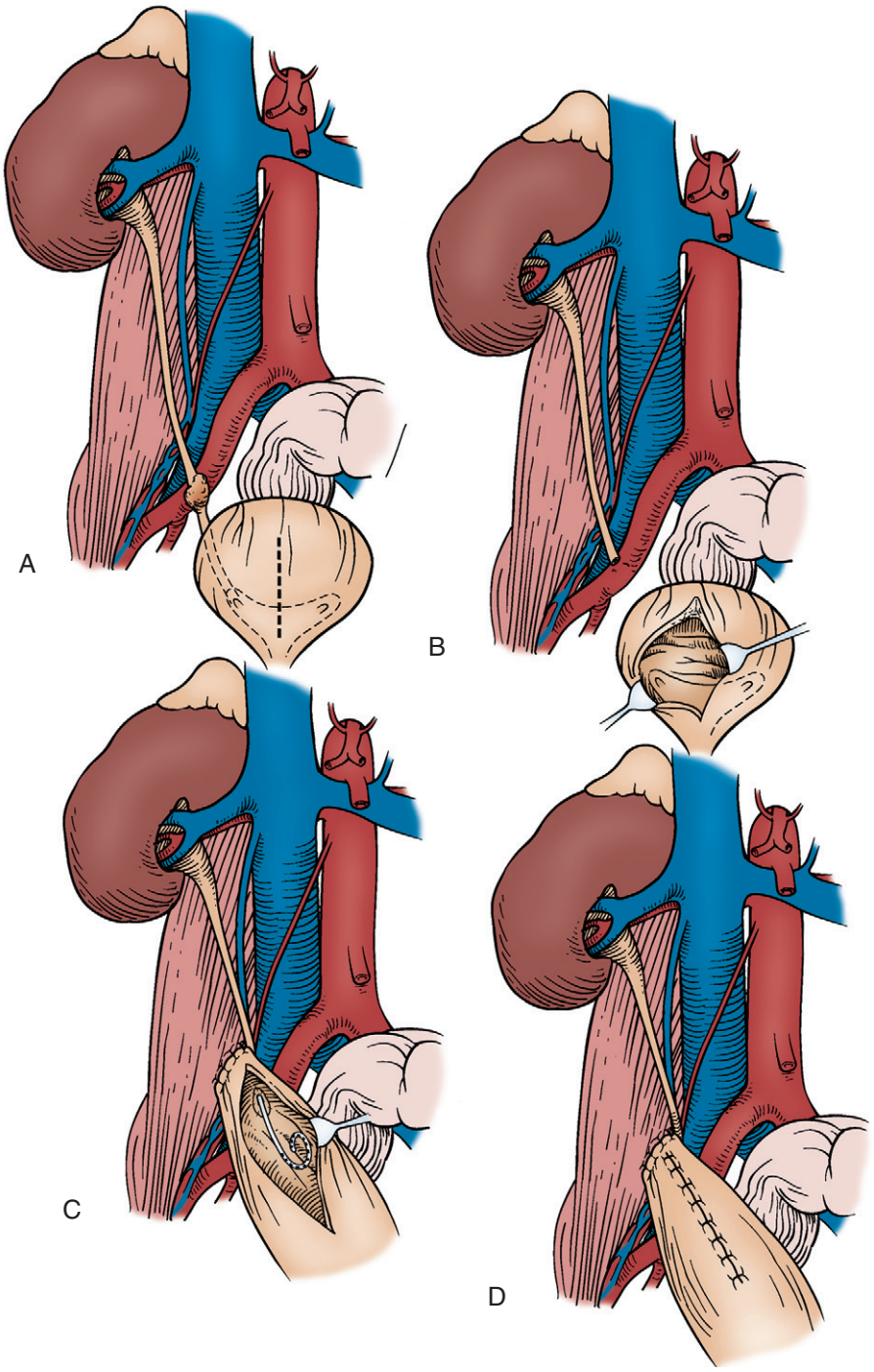


Figure 53–23. **A** and **B,** Distal ureterectomy for invasive tumor of the distal ureter. **C,** The bladder is advanced and secured to the psoas muscle. The ureter is anastomosed to the posterior upper aspect of the bladder hitch. **D,** The anterior cystotomy is closed. A closed-suction drain, ureteral stent, and bladder catheter are placed *(not shown)*.

been used for segmental ureteral substitution (Goldwasser et al, 1994). A preoperative bowel preparation is indicated when possible use of intestine is anticipated.

Finally, total ureterectomy, renal autotransplantation to the iliac fossa, and pyelocystostomy are options when the entire ureter is involved with multiple tumors (Pettersson et al, 1984). However, modern endoscopic techniques provide less invasive means of tumor control with lower morbidity in most cases.

Results

In the past, some authors recommended radical nephroureterectomy for all patients with upper tract urothelial tumors (Skinner, 1978). Others suggested segmental ureterectomy only for patients with low-grade, noninvasive tumors of the distal ureter (Babaian and Johnson, 1980). The cumulative results from the series in Tables 53–2 and 53–3 for patients with upper tract tumors of the renal pelvis or ureter reveal that **outcome strongly correlates with tumor stage and grade. Moreover, the results are similar for radical or nephron-sparing surgery.** The outcomes for only ureteral tumors are shown in Tables 53–4 and 53–5. Again, overall survival strongly correlates with stage and grade regardless of the extent of surgical treatment. Overall 5-year survival is excellent for patients with grade 1 and grade 2 noninvasive ureteral tumors. Five-year survival remains approximately 50% for patients with stage T2 disease but falls dramatically for stage T3. McCarron and associates (1983) reported 5-year survival of 64%

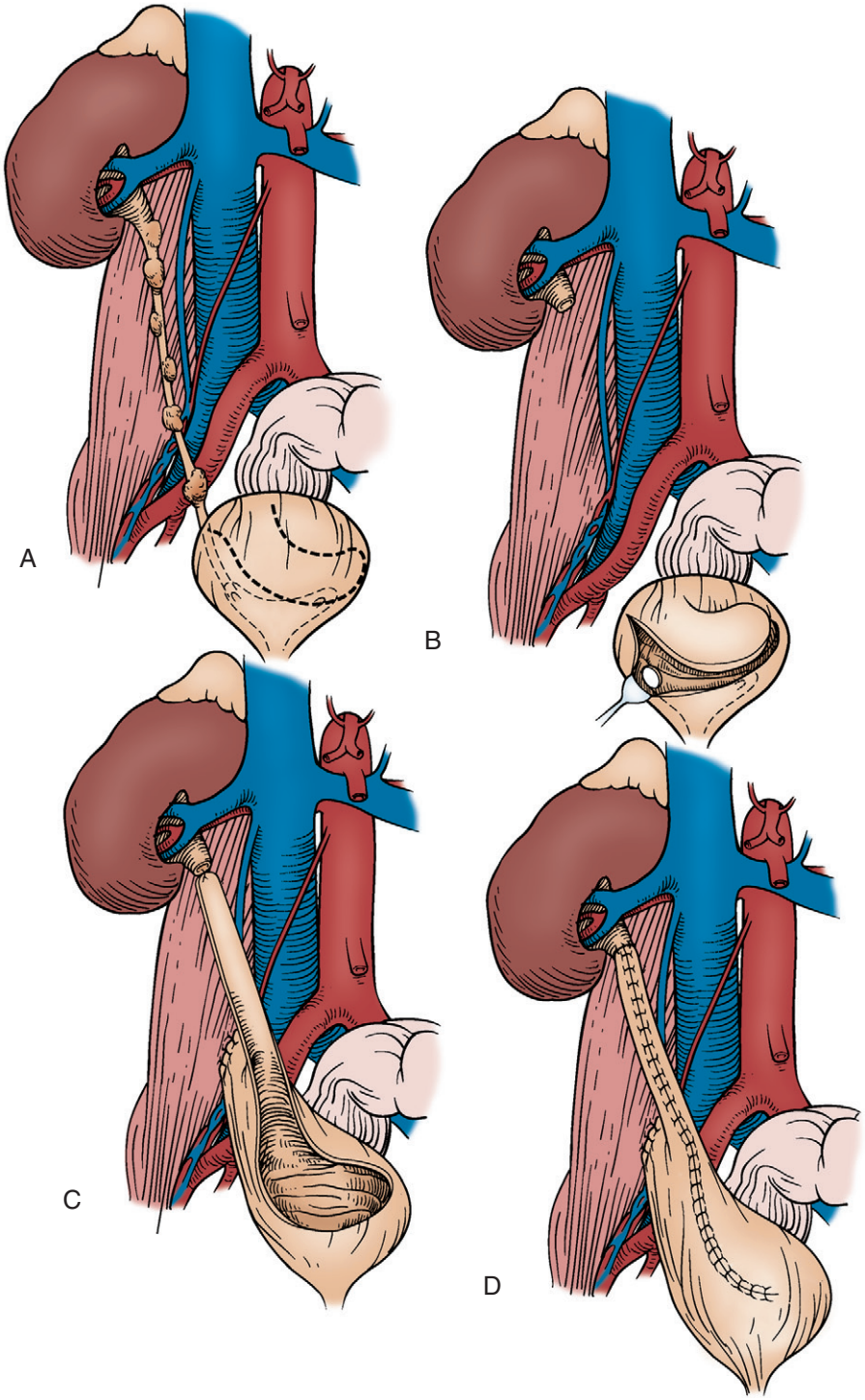


Figure 53–24. **A,** Subtotal ureterectomy required for nephron sparing in a patient with multiple diffuse ureteral tumors. **B,** A spiral flap is fashioned from the anterior bladder wall. **C,** The psoas hitch plus Boari flap reaches the remaining proximal ureter. **D,** Completed anastomosis and bladder closure. The ureteral stent, bladder catheter, and closed-suction drain are not shown.

for patients with stage Ta tumors treated by either segmental ureterectomy or endoscopic tumor ablation. In the same series, 5-year tumor-free survival was 66% and 50% for stage T1 and T2 tumors, respectively, treated with segmental or distal ureterectomy. Anderstrom and colleagues (1989) reported no tumor-related deaths and only one recurrence among 21 patients treated with segmental ureterectomy for low-grade, noninvasive ureteral tumors who were observed for a median of 83 months.

Booth and associates (1980) reported 5-year survival of 72% versus 31% among 144 patients with ureteral tumors having either superficial or deep ureteral muscle invasion, respectively. This observation has not been duplicated in other series. The concept is of doubtful validity owing to the thin nature of the ureteral wall.

One of the few reports of 5-year cancer-specific survival by stage for patients with ureteral tumors comes from Grabstald and coworkers (1971). Disease-specific survival was 64% and 100% for stage Ta to T1 and stage T2 disease, respectively. All deaths were due to unrelated causes. In contrast, for patients with stage T3 disease, cancer-specific survival was only 7% and the death rate due to tumor was 87%.

The risk of ipsilateral recurrence after conservative treatment of ureteral tumors is 33% to 55% (Mazeman,

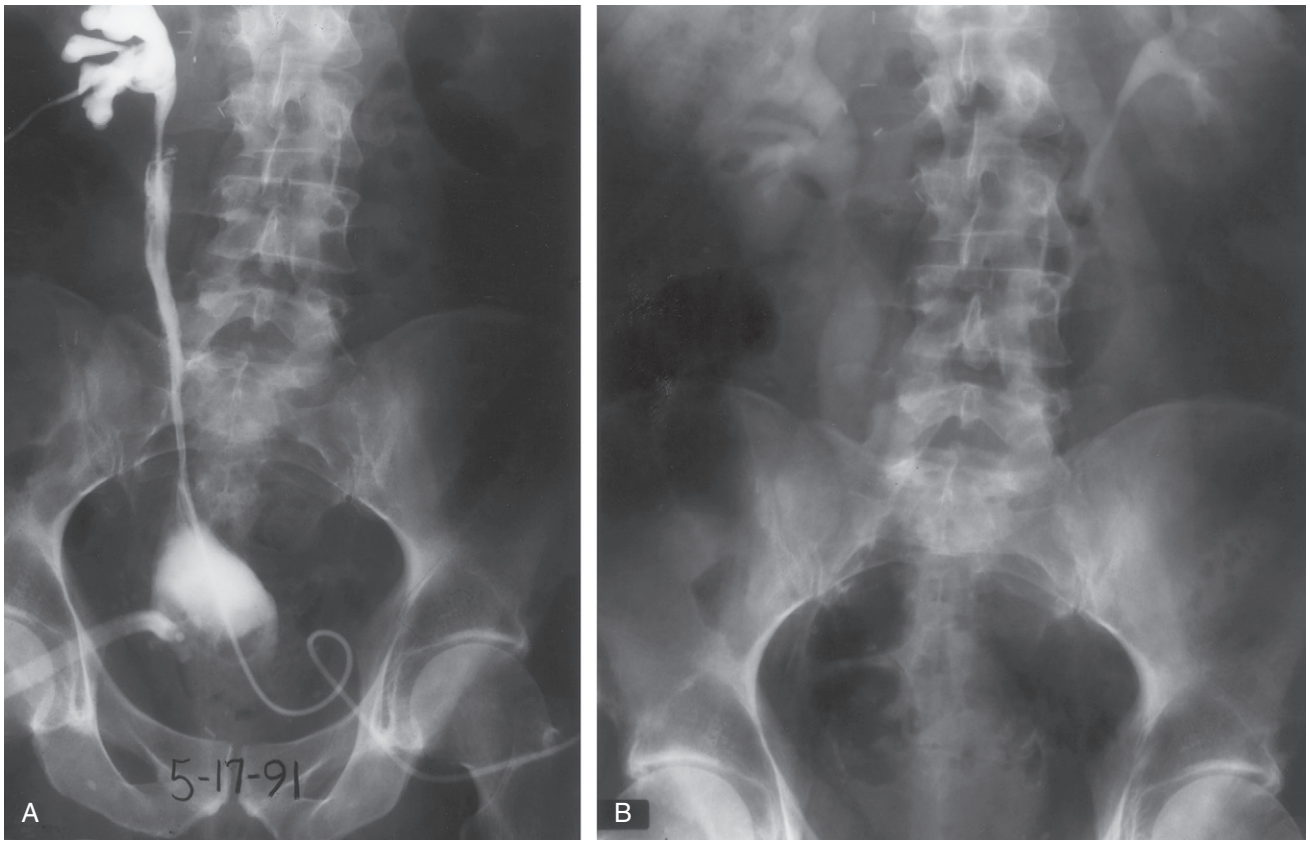


Figure 53–25. Patient with subtotal ureterectomy and repair by psoas hitch and Boari flap. **A,** Early postoperative intravenous urogram with external stent in place. **B,** Intravenous urogram: 10-minute film 2 years postoperatively shows good renal function and drainage across ureteral repair.

Table 53–4.

5-Year Survival (%) for Patients with Ureteral Tumors by Stage and Grade

	BLOOM ET AL, 1970 (N = 102)	BATATA AND GRABSTALD, 1976 (N = 77)	MCCARRON ET AL, 1983
Tumor Grade			
1-2	56-83	50-80	60-87
3-4	16	0-20	15
TNM Stage			
Ta, T1, Tcis	62	60-90	64-81
T2	50	43	46
T3	33	16	22
T4	—	—	—
N+	0	0	4
M+	0	0	—

Table 53–5.

Results of Segmental Resection for Localized Ureteral Tumors

STUDY	NO. OF PATIENTS	LOCAL RECURRENCE (%)	FOLLOW-UP (mo)
Johnson and Babaian, 1979	6	16.6	44
Zungri et al, 1990	35	8.5	86
Maier et al, 1990	17	17.6	41.4
Wallace et al, 1981	7	14.3	93.6
Anderstrom et al, 1989	21	4.7	83

1976; Johnson and Babaian, 1979; Babaian and Johnson, 1980; McCarron et al, 1983; Williams, 1991). Most recurrences are distal to the original lesion, but proximal recurrences are also seen (Strong et al, 1976). The risk for recurrence and the need for follow-up are lifelong (Herr, 1998). Grossman (1978) reported a stage T2 local recurrence in a patient 16 years after segmental ureterectomy and ureteroureterostomy for a grade 1, stage Ta, midureteral tumor. The authors have seen a recurrence of a grade 2, stage Ta tumor in the distal ureter 18 years after segmental ureterectomy of a grade 1, stage Ta tumor of the proximal ureter (Sagalowsky, unpublished data, 1999).

The following are general recommendations for treatment of ureteral tumors in patients with good contralateral renal function. **Segmental ureterectomy is offered for grade 1 to grade 2, stage Ta to stage T1 tumors of the proximal ureter or midureter that are not amenable to complete ablation by endoscopic means because of size or multiplicity. Segmental excision also is offered for grade 1 to grade 2, stage T2 tumors of the proximal ureter or midureter. Distal ureterectomy and neocystostomy are offered for low-grade, low-stage tumors that are not controlled by endoscopic means. Ureteral excision may also be suitable for some high-grade, locally invasive tumors of the distal ureter.**

Laparoscopic Distal Ureterectomy and Reimplant

Various laparoscopic techniques for distal ureterectomy and reimplant have been reported (Rouprêt et al, 2007). **The indications are the same as those for the open counterpart and reserved for low-risk distal tumors. The distal ureter is dissected down to the ureteral orifice and the proximal end anastomosed to the bladder using standard techniques. The early reports are encouraging, but strict adherence to oncologic principles must be followed.**

Endoscopic Treatment

Basic Attributes

Hugh Hampton Young described the first endoscopic evaluation of the upper urinary tract in 1912. Subsequent advances in technology allow us to reach all parts of the urinary tract with minimal morbidity through antegrade and retrograde approaches. Diagnosis and treatment of upper tract TCC have become possible with these improvements because tumor biopsy and ablation by various energy sources are possible even through the smallest instruments. In addition, miniaturization has made follow-up surveillance of the upper tract more practical with the use of smaller ureteroscopes, which usually do not require previous stenting, or with active dilation of the distal ureter.

Tumors of the upper urinary tract can be approached in a retrograde or antegrade fashion. The approach chosen depends largely on the tumor location and size. In general, a retrograde ureteroscopic approach is used for low-volume ureteral and renal tumors. An antegrade percutaneous approach is preferred for larger tumors of the upper ureter or kidney and for those that cannot be adequately manipulated in a retrograde approach because of location (e.g., lower pole calyx) or previous urinary diversion. In cases with multifocal involvement, combined antegrade and retrograde approaches can be considered (Figs. 53–26 and 53–27).

The basic principles for treatment of TCC of the upper urinary tract are similar to those for the bladder counterpart (Fig. 53–28). The tumor is sampled and ablated by electrocautery or laser energy sources. A staged procedure should be considered for high-volume disease or disease that is thought to represent high pathologic grade or stage. In such cases, when subsequent nephroureterectomy most likely will be necessary for cure, only biopsy and partial ablation are performed to minimize the risks of perforation or major complications. Endoscopic management is completed only after the pathologic examination shows that the patient is an acceptable candidate for continued minimally invasive endoscopic management. If the pathologic process is unresectable, of high grade, or invasive, the patient should proceed immediately to nephroureterectomy, provided he or she is medically fit. Patients who undergo renal-sparing therapy must be committed to a lifetime of follow-up with radiographs and endoscopy.

Ureteroscopy and Ureteropyeloscopy

The ureteroscopic approach to tumors was first described by Goodman in 1984 and is generally favored for ureteral and smaller renal tumors. With the advent of small-diameter rigid and flexible ureteroscopes, tumor location is less of a limiting factor than it used to be. **The advantage of a ureteroscopic approach is lower morbidity than that of the percutaneous and open surgical counterparts, with the maintenance of a closed system. With a closed system, nonurothelial surfaces are not exposed to the possibility of tumor seeding.**



Figure 53–26. Retrograde pyelogram of a patient with a solitary kidney and multifocal low-grade tumors, which required both antegrade and retrograde approaches.

The major disadvantages of a retrograde approach are related to the smaller instruments required. Smaller endoscopes have a smaller field of view and working channel. This limits the size of tumor that can be approached in a retrograde fashion. In addition, some portions of the upper urinary tract, such as the lower pole calyces, cannot be reliably reached with working instruments. Smaller instruments limit the ability to remove large tumors and to obtain deep specimens for reliable staging. Retrograde ureteroscopy is difficult in patients with prior urinary diversion.

Key Point: Ureteroscopy

- Ureteroscopy offers lower morbidity and a closed-system approach to the tumor.

Technique and Instrumentation. A wide variety of ureteroscopic instruments are available, each with its own distinct advantages and disadvantages. In general, rigid ureteroscopes are used primarily for the distal ureter and midureter. Access to the upper ureter and kidney with rigid endoscopy is unreliable, especially in the male patient. Larger, rigid ureteroscopes provide better visualization because of their larger field of view and better irrigation. Smaller rigid ureteroscopes (8 Fr) generally do not require active dilation of the ureteral orifice (Fig. 53–29A).

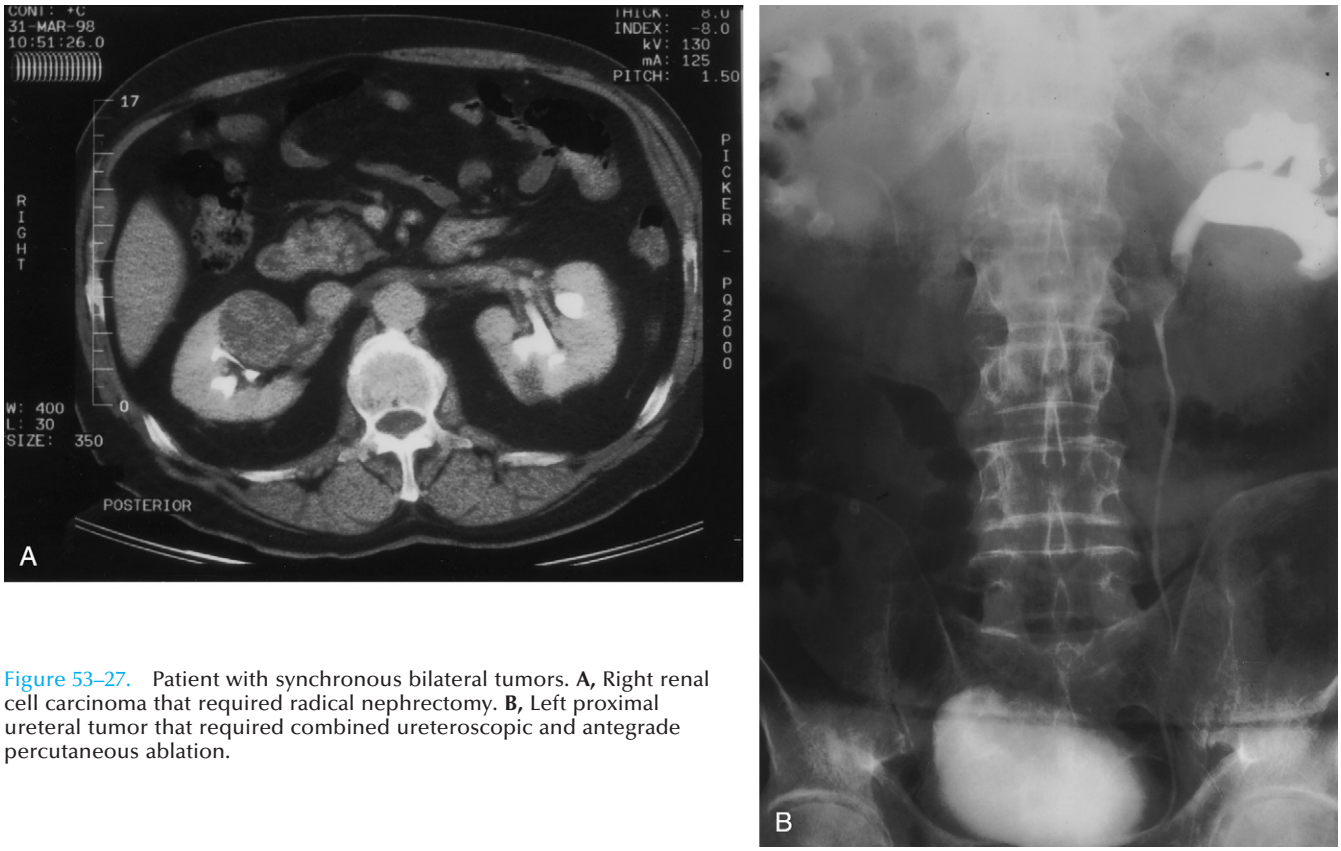


Figure 53–27. Patient with synchronous bilateral tumors. **A,** Right renal cell carcinoma that required radical nephrectomy. **B,** Left proximal ureteral tumor that required combined ureteroscopic and antegrade percutaneous ablation.

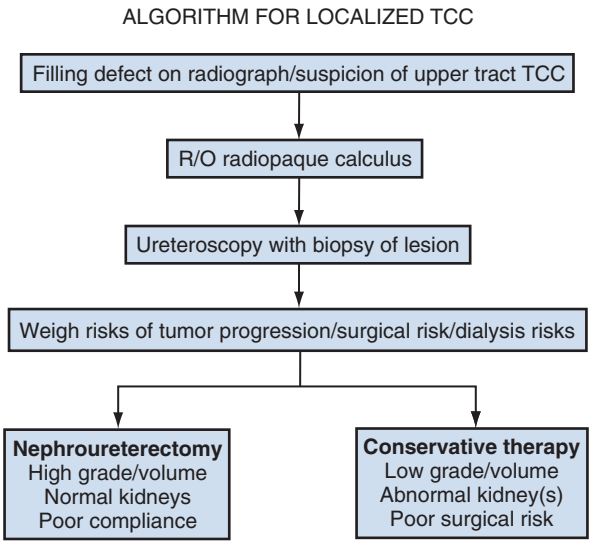


Figure 53–28. Algorithm for endoscopic approach to upper tract transitional cell carcinoma (TCC).

Newer-generation, flexible ureteropyeloscopes are available in sizes smaller than 8 Fr to allow simple and reliable passage to most portions of the urinary tract (Abdel-Razzak and Bagley, 1993; Grasso and Bagley, 1994; Chen and Bagley, 2000; Chen et al, 2000). These are generally preferred in the upper ureter and kidney, where the rigid ureteroscope cannot be reliably passed. **Flexible ureteroscopes, however, have technical limitations, such as a small working channel, that limit irrigant flow and the diameter of working instruments. Further limitations of flexible ureteroscopy include reduced access to certain areas of the kidney, such as the lower pole, where the infundibulopelvic angle may limit passage of the scope, and prior urinary diversion** (Fig. 53–29B).

Endoscopic Evaluation and Collection of Urine Cytology Specimen. Cystoscopy is performed and the bladder inspected for concomitant bladder disease. The ureteral orifice is identified and inspected for lateralizing hematuria. A small-diameter (6.9 or 7.5 Fr) ureteroscope is passed directly into the ureteral orifice, and the distal ureter is inspected for any trauma from a previously placed guide wire or dilation. A guide wire is then placed through the ureteroscope and up the ureter to the level of the renal pelvis under fluoroscopic guidance. The flexible ureteroscope is used to visualize the remaining urothelium. **When a lesion or suspicious area is seen, a normal saline washing of the area is performed before biopsy or intervention** (Bian et al, 1995). If the ureter does not accept the smaller ureteroscope, active dilation of the ureter is necessary.

Special circumstances include prior urinary diversion and tumor confined to the intramural ureter. With cases of prior urinary diversion, identification of the ureteroenteric anastomosis is difficult and may require antegrade percutaneous passage of a guide wire down the ureter before endoscopy. The wire can be retrieved from the diversion, and the ureteroscope can be passed in a retrograde fashion. The nephrostomy tract does not need to be fully dilated in this setting. Wagner and associates (2008) described their experience with endoscopic monitoring of patients with ureteral carcinoma in situ after radical cystectomy. A second type of case is tumor in the intramural ureter. When a tumor protrudes from the ureteral orifice, complete ureteroscopic

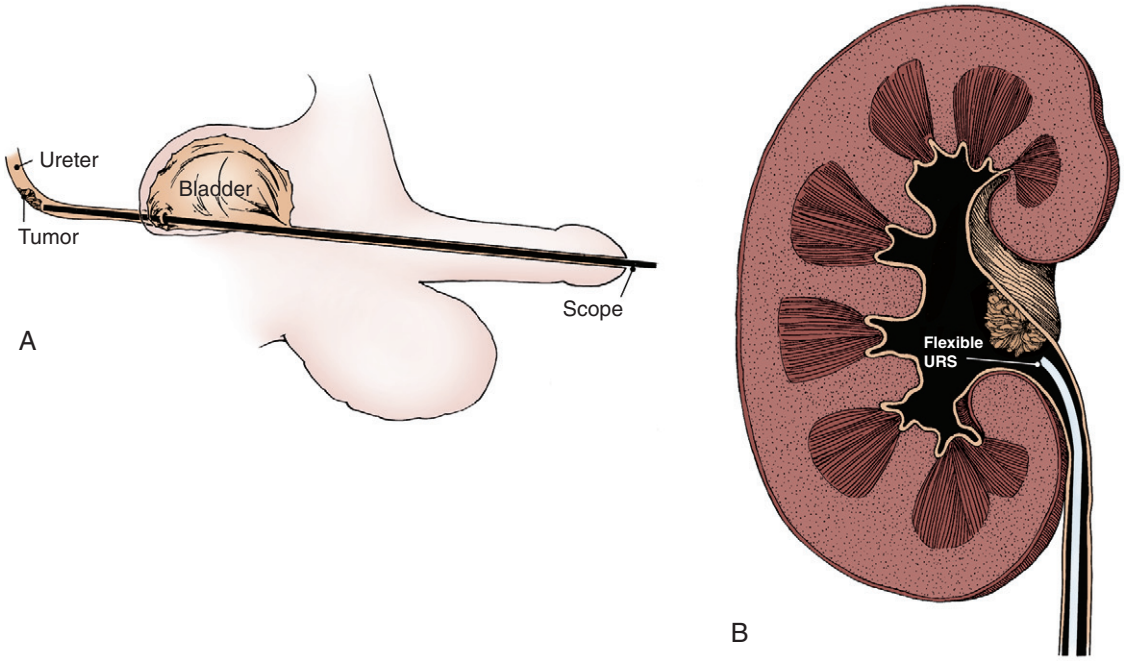


Figure 53–29. **A,** Rigid ureteroscopic approach. **B,** Flexible ureteroscopic approach. URS, ureteroscope.

ablation of the tumor or aggressive transurethral resection of the entire most distal ureter can be done with acceptable results (Palou et al, 2000).

Biopsy and Definitive Treatment. Three general approaches can be used for tumor ablation: bulk excision with ablation of the base, resection of the tumor to its base, and diagnostic biopsy followed by ablation with electrocautery or laser energy sources. Regardless of technique used, special attention to biopsy specimens is necessary. Specimens are frequently minute and should be placed in fixative at once and specially labeled for either histologic or cytologic evaluation (Tawfiek et al, 1997).

Ureteroscopic Techniques. The tumor is debulked by use of either grasping forceps or a flat wire basket engaged adjacent to the tumor (Fig. 53–30A). Next, the tumor base is treated with either electrocautery or laser energy sources. This technique is especially useful for low-grade papillary tumor on a narrow stalk. The specimen is sent for pathologic evaluation.

A ureteroscopic resectoscope is used to remove the tumor (Fig. 53–30B). Only the intraluminal tumor is resected, and no attempt is made to resect deep (beyond the lamina propria). Extra care is necessary in the midureter and upper ureter, where the wall is thin and prone to perforation. Ureteral resectoscopes are approximately 12 Fr and require more extensive dilation of the ureteral orifice. With larger volume disease of the distal ureter, Jarrett and associates (1995a) described extensive dilation of the ureter followed by resection with a long standard resectoscope. **The tumor is adequately sampled with forceps and sent to the pathology laboratory for diagnostic evaluation. The tumor bulk is then ablated to its base with laser or electrosurgical energy** (Fig. 53–30C and D). Multiple biopsy specimens are often required when small, flexible 3-Fr biopsy forceps are used. Electrocautery delivered through a small Bugbee electrode (2 or 3 Fr) can be used to fulgurate tumors. However, the variable depth of penetration can make its use in the ureter dangerous, and circumferential fulguration should be avoided because of the high risk of stricture formation. More recently, laser energy with either neodymium:yttrium-aluminum-garnet (Nd:YAG) (Smith et al, 1984; Schilling et al, 1986; Schmeller and Hofstetter, 1989; Carson, 1991) or holmium:YAG (Bagley and Erhard, 1995; Razvi et al, 1995; Matsuoka et al, 2003; Suoka et al, 2003) sources has been popular. Each has characteristic advantages (Fig. 53–31) and can be delivered through small, flexible fibers (200 or 365 μm) that fit through small, flexible ureteroscopes without significant alteration of irrigant flow or scope deflection.

Key Point: Biopsy and Ablation

- The lesion is sampled first for cytology and for histopathologic staging, if possible; then it is ablated.

The holmium:YAG laser is well suited for use in the ureter. The tissue penetration is less than 0.5 mm, which allows tumor ablation with excellent hemostasis and minimal risk of full-thickness injury to the ureter. Its shallow penetration may, however, make its use cumbersome with larger tumors, especially in the renal pelvis. Settings most commonly used for the holmium:YAG laser are energy of 0.6 to 1 J with frequency of 10 Hz. The Nd:YAG laser has a tissue penetration of up to 5 to 6 mm, depending on laser settings and duration of treatment. In contrast to the holmium:YAG laser, which ablates tumor, the Nd:YAG laser works by coagulative necrosis with subsequent sloughing of the necrotic tumor. The safety margin is significantly lower and can limit its use in the ureter, where the ureteral wall is thin. Settings most commonly used for the Nd:YAG laser are 15 W for 2 seconds for ablation of tumor and 5 to 10 W for 2 seconds for coagulation.

A ureteral stent is placed for a variable duration to aid with the healing process. Large tumors usually require multiple treatment sessions during several months.

Results. Multiple series have shown the safety and efficacy of ureteroscopic treatment of upper tract TCC (Elliott et al, 1996;

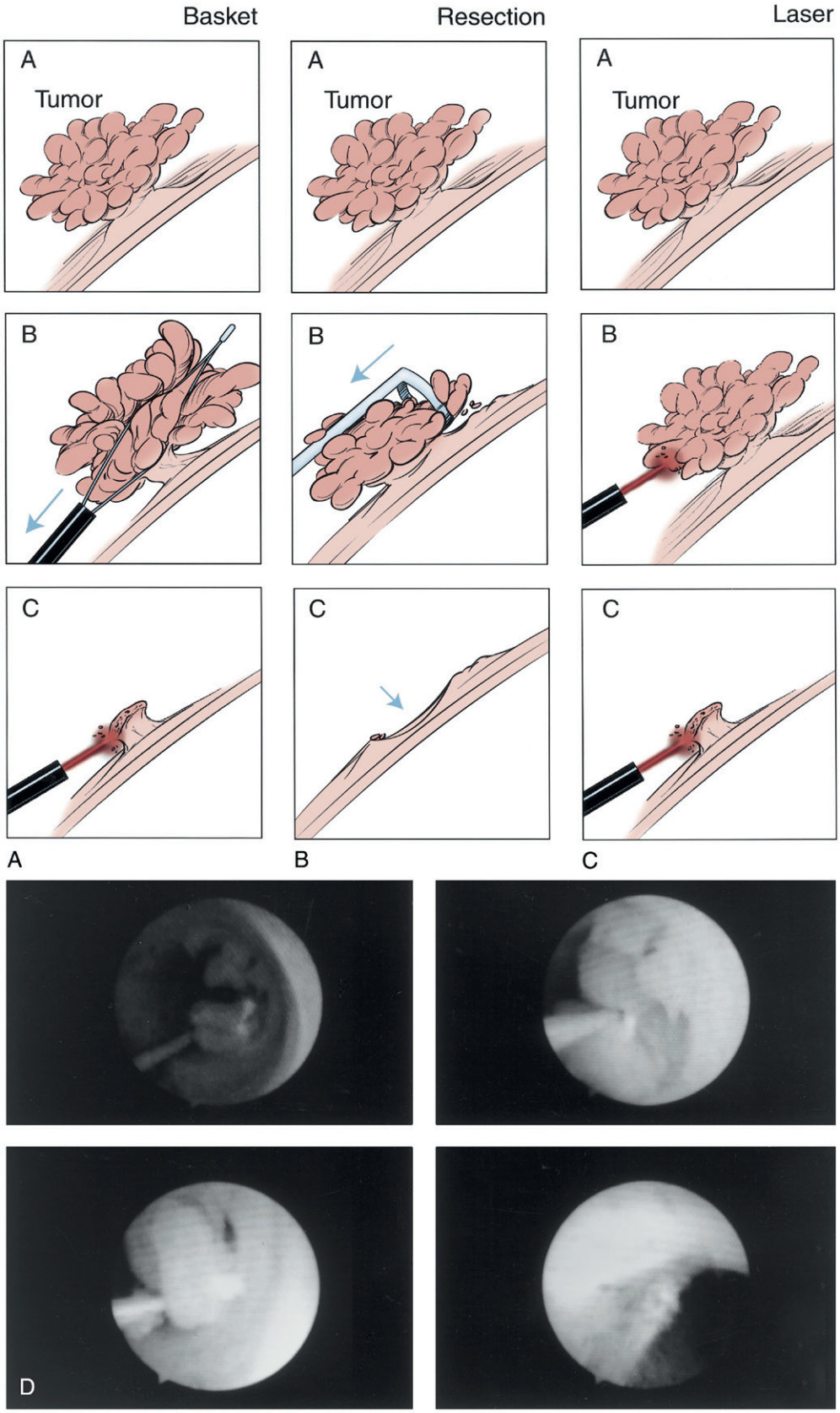


Figure 53–30. Techniques for ureteroscopic treatment of ureteral and renal tumors. **A,** The tumor is identified and removed piecemeal by grasping forceps to its base. **B,** Alternatively, a flat wire basket can be deployed alongside the tumor. The tumor is engaged and removed, with care taken not to avulse the adjacent ureter. With either of these technique, the base is treated with electrocautery or a laser energy source. **C,** The tumor is identified and removed by a ureteroscopic resectoscope. The technique differs from the technique for bladder tumors in that only intraluminal tumor is resected. No attempt is made to resect deep, as with a bladder tumor. The scope is not arching deep into the tissue. **D,** The tumor is sampled for diagnostic purposes. The bulk of the tumor is then ablated with electrosurgical or laser energy. Laser energy is generally preferred because it has more reliable delivery of energy and depth of penetration. The two most commonly used energy sources are holmium:yttrium-aluminum-garnet and neodymium:yttrium-aluminum-garnet.

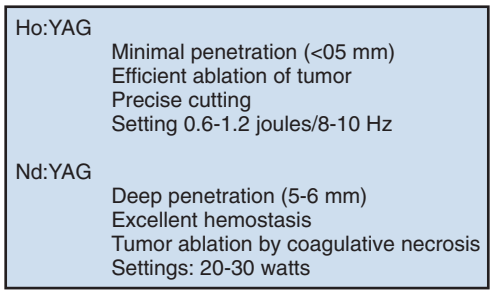


Figure 53–31. Characteristics of holmium (Ho):YAG and neodymium (Nd):YAG laser energy sources. YAG, yttrium-aluminum-garnet.

Table 53–6.

Results of Ureteroscopic Approach to Upper Tract Transitional Cell Carcinoma

STUDY	NO. OF PATIENTS	RECURRENCE (%)	NXUX (%)	FOLLOW-UP (mo)
Keeley et al, 1997	41	8(19)	20	3-116
Elliott et al, 1996	37	17(46)	16	3-132
Martinez-Pineiro et al, 1996	28	8(29)	11	2-119
Daneshmand et al, 2003	30	27(90)	10	4-106
Sowter et al, 2007	37	27(74)	30	5-115

NXUX, nephroureterectomy.

Englemeyer and Belis, 1996; Martinez-Pineiro et al, 1996; Keeley et al, 1997a, 1997b; Iborra et al, 2003). In a literature review of 205 patients (Tawfiek and Bagley, 1997), the overall recurrence rates for ureteral and renal pelvic lesions were 33% and 31.2%, respectively, and the risk of bladder recurrence was 43%. In the largest series (Keeley et al, 1997a) there was a single cancer death directly attributed to recurrent upper tract disease. As with any TCC, the most important prognostic indicator for tumor recurrence was grade. Keeley and associates (1997c) showed a recurrence rate of 26% for grade 1 tumors and 44% for grade 2 tumors, which roughly correlated with previously established recurrence rates for open conservative surgery.

More recent literature shows the long-term feasibility of the ureteroscopic approach, but concerns over the high rate of ipsilateral recurrences remain (Table 53–6). Daneshmand and colleagues (2003) reported a large number of recurrences with an overall ipsilateral recurrence rate of 90% with three to four recurrences per patient. Sowter and associates (2007) showed an ipsilateral recurrence rate of 74%. Thompson and colleagues (2008) studied 83 patients who underwent endoscopic management of tumors, 76 of which were ureteroscopic. The overall recurrence rate was 55%. Nephroureterectomy eventually was performed in 33%. This is important in considering patients with a normal contralateral kidney. Patients must be counseled in the need for lifetime follow-up and possible treatment of ipsilateral recurrence.

Complications were uncommon and usually related to the patient's comorbidities. Complications specific to ureteroscopic therapy included ureteral perforation, which can be managed with indwelling ureteral stent, and ureteral stricture. Stricture formation rate ranged from 5% to 13% (Elliott et al, 1996; Martinez-Pineiro et al, 1996; Keeley et al, 1997a). The complication rates have dropped in more contemporary series, most likely related to smaller endoscopes, improved laser energy sources, and refinements in endoscopic techniques.

Two major concerns of the ureteroscopic approach are the accuracy of ureteroscopic biopsies and the limitations of biopsies, especially with regard to staging (Huffman, 1988). Retrospective reviews of patients who underwent ureteroscopic biopsy followed by nephroureterectomy found the accuracy of ureteroscopic diagnosis to be 89% to 94% and the pathologic grading to match the open surgical technique in 78% to 92% (Keeley et al, 1997a; Guarnizo et al, 2000). From prior studies, we know that there is an excellent correlation between grade of lesion and stage (Chasko et al, 1981; Heney et al, 1981). This holds true for the ureteroscopic approach (Keeley et al, 1997c) because 87% of patients with grade 1 or grade 2 tumors had noninvasive disease (stage Ta or T1) whereas 67% of patients with grade 3 tumors had invasive disease (stage T2 or T3). This information supports the notion that tumor grade is the most important prognostic factor; and although stage cannot be directly assessed, noninvasive disease can be expected in most cases of low-grade tumor.

A final concern is whether ureteroscopy promotes progression or spread of disease to other urothelial surfaces or metastatic sites. There have been reports of increased tumor appearance in refluxing ureters of patients with bladder tumors (de Torres Mateos et al, 1987) and in the ipsilateral urinary tract and bladder of patients after ureteroscopic treatment. However, Kulp and Bagley (1994) reported on 13 patients who underwent multiple ureteroscopic treatments followed by nephroureterectomy; they found no unusual propagation of TCC in the specimens. Concerns that ureteroscopy may promote metastatic spread were raised by Lim and associates (1993), who found tumor cells in renal lymphatics after ureteroscopy. However, Hendin and colleagues (1999) reported no increased risk of metastatic disease in a group of patients who underwent ureteroscopy before nephroureterectomy compared with a group undergoing nephroureterectomy alone.

Percutaneous Approach

The percutaneous approach was first described by Tomera and coworkers in 1982 and is generally favored for larger tumors located proximally in the renal pelvis or proximal ureter. **The main advantage of the percutaneous approach is the ability to use larger instruments that can remove a large volume of tumor** in any portion of the renal collecting system. Because deeper biopsy specimens are obtained, tumor staging as well as grading is usually possible. In addition, a percutaneous approach may avoid the limitations of flexible ureteroscopy, especially in complicated calyceal systems or areas difficult to access, such as the lower pole calyx or the upper urinary tract of patients with urinary diversion. With a percutaneous approach, the established nephrostomy tract can be maintained for immediate postoperative nephroscopy and administration of topical adjuvant therapy.

The main disadvantages are the increased morbidity compared with ureteroscopy and the potential for tumor seeding outside the urinary tract. Establishment of the nephrostomy tract has inherent risks, and the procedure usually requires inpatient admission. Distinct risks related to a percutaneous approach are loss of urothelial integrity and exposure of nonurothelial surfaces to tumor cells. This open system provides the possibility of tumor implantation in the nephrostomy tract.

Technique and Instrumentation

Establishment of the Nephrostomy Tract. Cystoscopy is performed, and an open-ended ureteral catheter is positioned in the pelvis. Contrast material is injected to define the calyceal anatomy,

and a percutaneous nephrostomy tract is established through the desired calyx (Fig. 53–32). Tumors in peripheral calyces are best approached with direct puncture distal to the tumor (Fig. 53–33). Disease in the renal pelvis and upper ureter is best approached through an upper or middle pole access to allow scope maneuvering through the collecting system and down the ureteropelvic junction. The tract is dilated by either sequential (Amplatz) or balloon dilation to accommodate a 30-Fr sheath. Correct positioning of the nephrostomy tract is crucial to the success of the procedure and should be done by the urologist or by the radiologist after direct consultation with the operating surgeon.

A nephroscope is inserted, and the ureteral catheter is grasped, brought out the tract, and exchanged for a stiff guide wire, thus providing both antegrade and retrograde control. Complete nephroscopy is performed with rigid and flexible endoscopes when necessary. Any suspicion of upper ureteral involvement warrants antegrade ureteroscopy.

Biopsy and Definitive Therapy. **After identification, the tumors are removed by one of the following four techniques** (Fig. 53–34). In the first technique, which uses a cold-cup biopsy forceps through a standard nephroscope, the bulk of the tumor is grasped by forceps and removed in piecemeal fashion until the base is reached (see Fig. 53–34A). A separate biopsy of the base is performed for staging purposes, and the base is cauterized with a Bugbee electrode and cautery. Low-grade papillary lesions on a thin stalk are easily treated in this manner with minimal bleeding.

Alternatively, a cutting loop from a standard resectoscope is used to remove the tumor to its base (see Fig. 53–34B). Once again, the base should be resected and sent separately for staging purposes. This approach is more effective for larger, broad-based tumors for which simple debulking to a stalk is not possible.

For the third technique, which uses flexible or rigid endoscopes, the tumor is sampled and treated with holmium:YAG or Nd:YAG

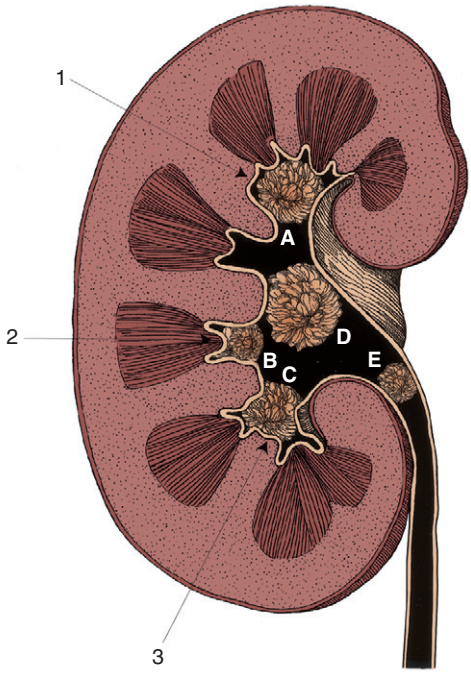


Figure 53–32. Nephrostomy tract puncture site. Position of the nephrostomy is imperative for successful percutaneous resection of transitional cell carcinoma of the renal collecting system and upper ureter and requires careful preoperative evaluation of radiographs for tumor location. Tumors in peripheral calyces (A to C) are best approached by direct puncture as far distally in the calyx as possible. Tumors in the renal pelvis (D) and upper ureter (E) are best approached by puncture to an upper (1) or middle (2) calyx, which allows the scope to be maneuvered in the renal pelvis and down the ureter. Tumors in the lower calyx are approached by lower calyx puncture (3).

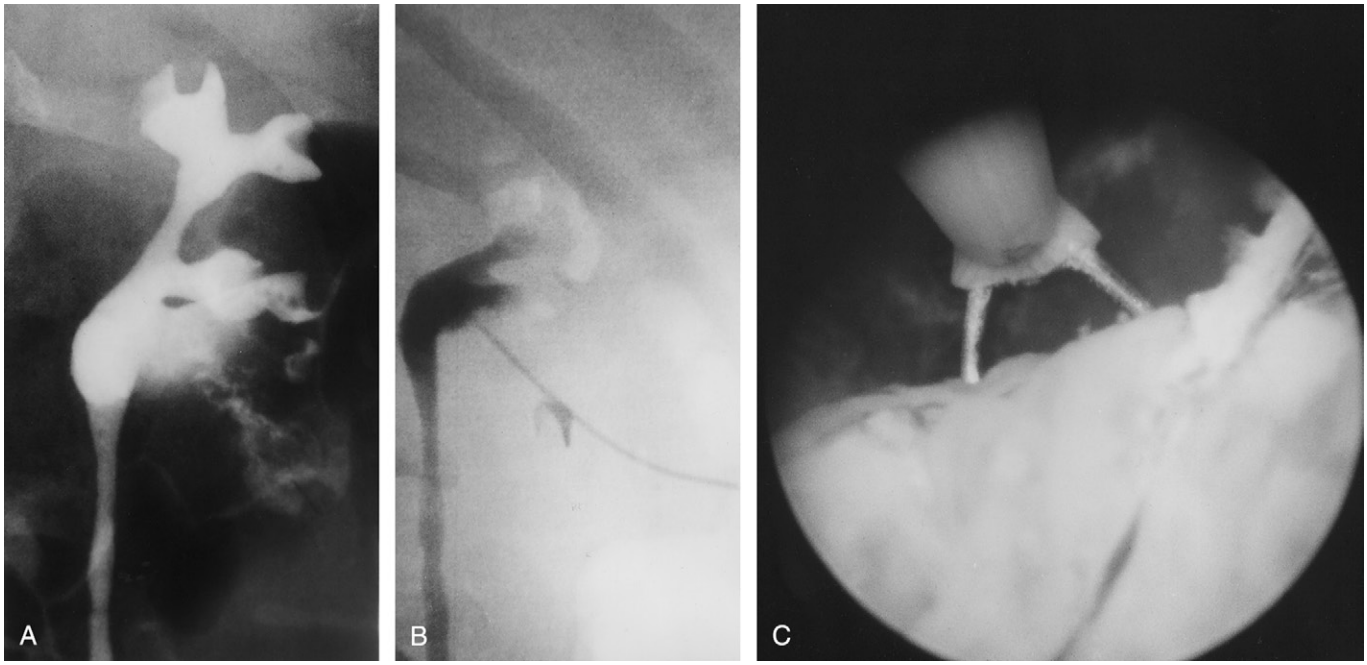


Figure 53–33. **A,** Retrograde pyelogram of a man with transitional cell carcinoma of the lower calyx in a solitary kidney. **B,** Access distal in the calyx allows a clear view of the tumor. **C,** Subsequent resection.

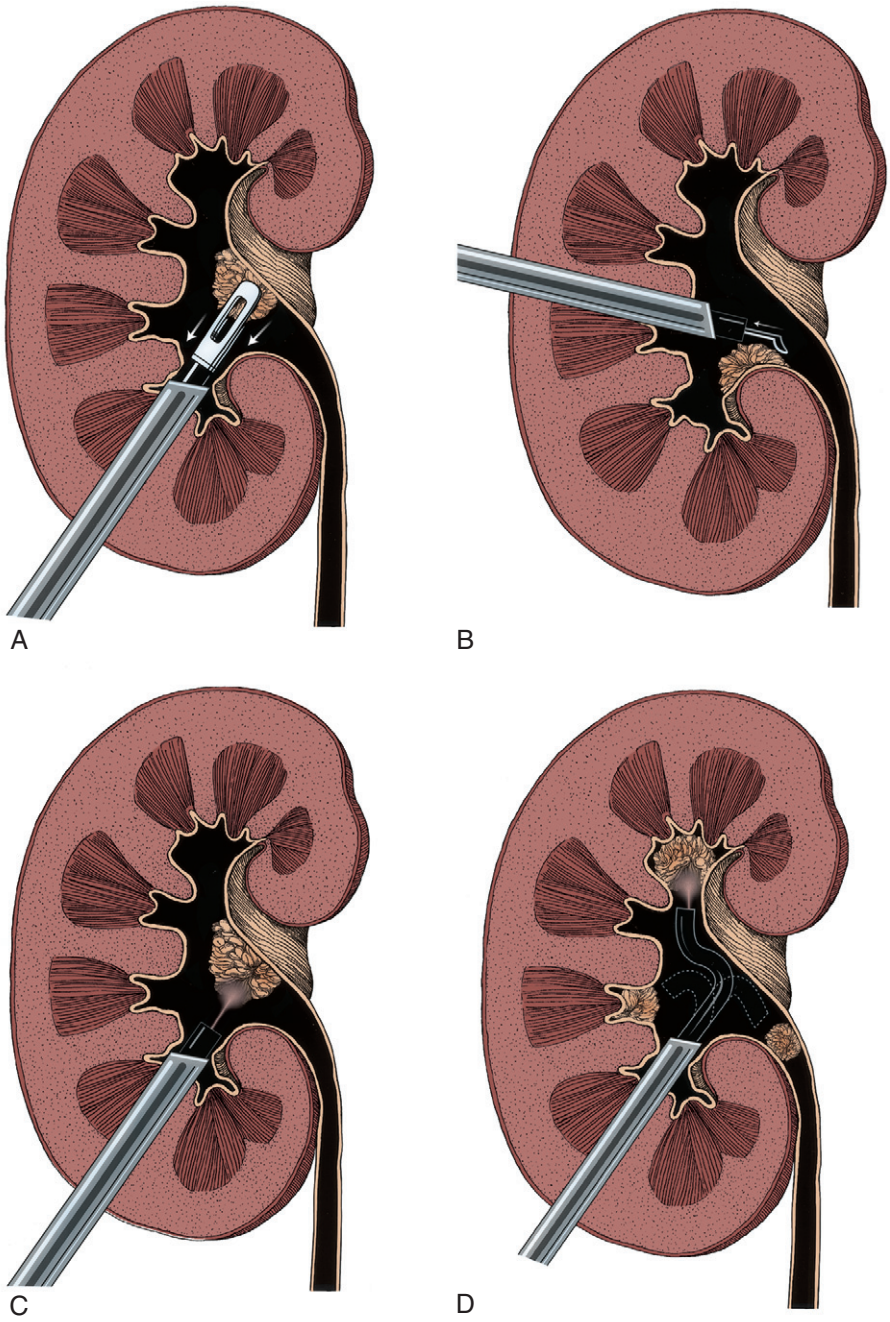


Figure 53–34. Techniques for percutaneous removal of transitional cell carcinoma of the renal collecting system. **A,** The tumor is identified and debulked by forceps to its base. The base is sampled and sent separately for evaluation. This technique works well for papillary tumors on a narrow stalk. Broad-based tumors may cause excessive bleeding and are best approached with resection or laser therapy. **B,** With use of a standard resectoscope the tumor is identified and resected to its base. Special care should be taken to avoid resection into major renal vasculature. The tumor is identified, sampled for diagnostic purposes, and treated by holmium or neodymium laser sources. This can be done through a standard nephroscope **(C)** or with a flexible cystoscope **(D).**

laser at 25 to 30 W (see Fig. 53–34C and D). Tissue may also be obtained with a small snare used for gastrointestinal polyps.

Regardless of approach, a nephrostomy tube is left in place. This access can be used for second-look follow-up nephroscopy to ensure complete tumor removal (Fig. 53–35). Nephroureterectomy is indicated if the pathologic examination shows high-grade or invasive disease.

Second-Look Nephroscopy. Follow-up nephroscopy is performed 4 to 14 days later to allow adequate healing. The tumor resection site is identified, and any residual tumor is removed. If no tumor is identified, the base should be sampled and treated by cautery or the Nd:YAG laser (15 to 20 W and 3-second exposures). The nephrostomy tube can be removed several days later if all tumors have been removed. If the patient is being considered for adjuvant topical therapy, a small, 8-Fr nephrostomy tube is left to provide access for instillations. Some authors advocate third-look nephroscopy before removal of the nephrostomy tube (Jarrett et al, 1995b).

Results. Because of the rarity of the disease there are limited retrospective series (Table 53–7) with adequate numbers and follow-up from which to draw reasonable conclusions (Jarrett et al, 1995b; Patel et al, 1996; Clark et al, 1999; Goel et al, 2003; Palou et al, 2004; Rouprêt et al, 2006). In a literature review of 84 patients, Okada and colleagues (1997) found an overall recurrence rate of 27%. Tumor grade strongly predicted outcomes; Jarrett and associates (1995b) showed the recurrence rate for grades 1, 2, and 3 lesions to be 18%, 33%, and 50%, respectively. The only cancer-related mortalities in this series were in patients with high-grade disease. Lee and colleagues (1999) reviewed their 13-year experience with percutaneous management, comparing 50 patients who underwent percutaneous management with 60 patients who

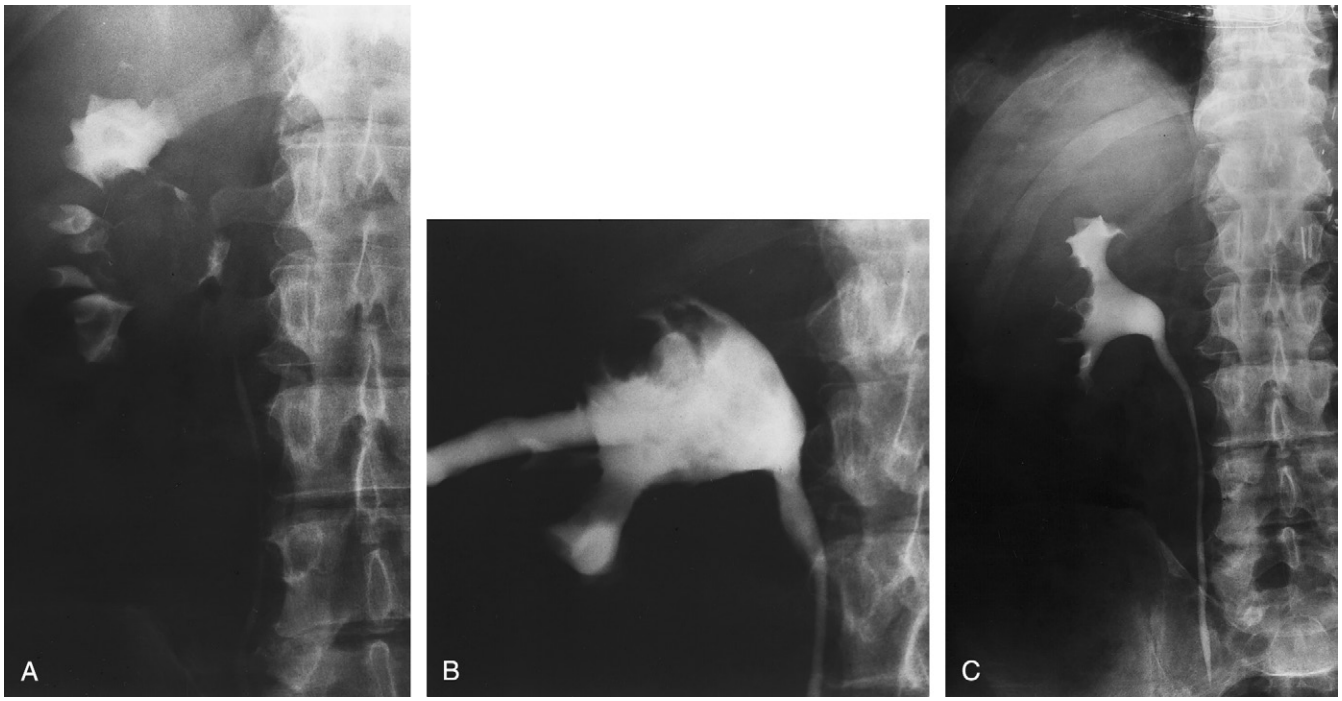


Figure 53–35. **A,** A 65-year-old man presented with a solitary kidney and a 5-cm renal pelvis tumor. **B,** Nephrostogram after patient underwent staged resection. **C,** Three-month follow-up retrograde pyelogram after completed resection. The patient showed grade 1 transitional cell carcinoma without invasion to submucosa.

Table 53–7.

Results of the Percutaneous Approach to Upper Tract Transitional Cell Carcinoma

STUDY	NO. OF PATIENTS	RECURRENCE (%)	NXNU (%)	FOLLOW-UP (mo)
Jarrett et al, 1995	36	10 (28)	42	9-111
Patel et al, 1996	28	6 (23)	23	12-108
Clark et al, 1999	18	3 (33)	11	2-76
Palou et al, 2004	34	14 (41)	15	3-131
Rouprêt et al, 2007	24	8 (32)	20	18-188

NXUX, nephroureterectomy.

underwent nephroureterectomy, and found no significant difference in overall survival. As expected, patients with low-grade disease did well regardless of modality and patients with high-grade disease did poorly regardless of treatment option.

Most would agree from the literature that percutaneous management is acceptable in patients with low-grade (grade 1) disease regardless of the status of the contralateral kidney, provided the patient is committed to lifelong endoscopic follow-up. Patients with grade 3 disease do poorly regardless of modality chosen but should probably undergo nephroureterectomy to maximize cancer therapy (provided they are medically fit). The largest area of controversy surrounds the use of percutaneous management for patients with grade 2 disease and a normal contralateral kidney. Jabbour and associates (2000) retrospectively evaluated 24 patients and found a disease-specific survival of 95% overall and 100% and 80% for stage Ta and stage T1 lesions, respectively. This study shows an acceptable result with conservative treatment of noninvasive grade 2 disease. With more invasive lesions, the potential for disease progression and metastatic disease is significant and nephroureterectomy should be considered.

Complications from percutaneous management of tumors are similar to those for benign renal processes and include bleeding, perforation of the collecting system, and secondary ureteropelvic junction obstruction. Complications increase in number and severity with higher tumor grade (Jarrett et al, 1995b). This finding is probably due to the more extensive pathologic process and treatments necessary to eradicate the tumor. Unlike ureteroscopic resection, the percutaneous method can stage tumors and, as expected, stage increases with tumor grade.

A major concern of the percutaneous approach is the potential seeding of nonurothelial surfaces with tumor cells. Although there have been multiple reported cases of nephrostomy tract infiltration with high-grade tumors (Tomera et al, 1982; Slywotzky and Maya, 1994; Huang et al, 1995; Oefelein and MacLennan, 2003; Treuthardt et al, 2004), there were no reported occurrences in the three largest series (Jarrett et al, 1995b; Patel et al, 1996; Clark et al, 1999). Tract seeding is a possibility but appears to be an uncommon event.

Isolated Upper Tract Cytologic Abnormality or Urinary Marker

On occasion, one is faced with a patient who has an isolated abnormal cytologic finding or other urinary marker from the upper urinary tract. **By definition, the patient should have normal intravenous urography and retrograde pyelography, normal cystoscopy, and normal biopsy findings from the bladder and urethra.** Radical nephroureterectomy was performed in the past for a unilateral cytologic abnormality of the upper tract to eliminate presumed carcinoma in situ. This practice is not recommended (Gittes, 1980; McCarron et al, 1983;

Williams, 1991; Messing and Catalona, 1998). Upper tract cytology suffers from the same limitations in specificity as does bladder cytology. Furthermore, properly collected upper tract samples are of limited volume and cell count compared with bladder washings. Any source of inflammation, such as urinary infection or calculus, may produce a false-positive result. A subsequent cytologic abnormality from the contralateral side during follow-up is not rare in cases of true-positive results from early carcinoma in situ (Murphy et al, 1974; Khan et al, 1979). A variety of urinary markers are being studied to aid in detection of urothelial tumor recurrence. At this time, both urine FISH and urine nuclear matrix protein show particular promise.

Ureteropyeloscopy is indicated in such cases because the yield for direct visualization of small lesions is superior to that of retrograde pyelography. An attempt to perform biopsy and confirm the diagnosis is indicated before treatment is considered. A consistently abnormal finding on upper tract cytology may signify carcinoma in situ. Current treatment options are limited. Instillation of topical immunotherapy or chemotherapy may be performed through ureteral catheters or a small percutaneous nephrostomy. However, the contact time of the agent with the urothelium is minimal. Reports of efficacy are uncontrolled and anecdotal. Frequent-interval reevaluation with urinalysis, bladder cytology, cystoscopy every 3 months and retrograde pyelography or ureteropyeloscopy every 6 months is indicated for 1 to 2 years. However, one must avoid overtreatment and excessive evaluation and instrumentation of a patient who may have had a single false-positive result.

Adjuvant Therapy

After Organ-Sparing Therapy

Any procedure short of nephroureterectomy has a higher local recurrence due to the established risk of ipsilateral recurrence. Several approaches are available to minimize these risks. They fall into two basic categories: instillation of immunotherapeutic or chemotherapeutic agents and brachytherapy of the nephrostomy tract.

Instillation Therapy. Instillation therapy can be accomplished in several ways. Accepted techniques include antegrade instillation through a nephrostomy tube (Fig. 53–36) and retrograde instillation directly into a ureteral catheter or by reflux in a patient with an indwelling ureteral stent or iatrogenically created vesicoureteral reflux. Patel and Fuchs (1998) described a convenient technique of outpatient instillation through a ureteral catheter placed suprapubically. Regardless of the technique chosen, administration to the upper urinary tract should be done under low pressure and in the absence of active infection to minimize the risk of bacterial sepsis or systemic absorption of the agent.

Results. **The same agents used to treat urothelial carcinoma of the bladder are used to treat tumors of the upper urinary tract. Many studies have described small, retrospective, uncontrolled series of patients undergoing therapy with thiotepa** (Elliott et al, 1996; Patel et al, 1996), **mitomycin** (Eastham and Huffman, 1993; Weston et al, 1993; Martinez-Pineiro et al, 1996; Keeley et al, 1997a; See, 2000), **and BCG** (Table 53–8) (Smith et al, 1987; Studer et al, 1989; Eastham and Huffman, 1993; Sharpe et al, 1993; Jarrett et al, 1995b; Hayashida, 2004; Rastinehad et al, 2009). Although the cumulative experience appears encouraging, no individual study has shown statistical improvement with relation to survival and recurrence rates. Possible reasons for this include (1) insufficient numbers to show clinical significance because of the relative rarity of the disease; (2) tumors of the upper urinary tract, which have a tumor biology different from that of their bladder counterparts; and (3) an inadequate delivery system that, unlike in the bladder, does not allow uniform delivery of the agent with adequate dwell time to enable a clinical response. Furthermore, in the report by Hayashida and colleagues (2004) with intrarenal perfusion of BCG, despite initial return of cytology results to normal, 50% of patients (5 of 10) developed disease recurrence after a mean follow-up of 50.9 months, and all of these suffered cancer-specific mortality. There is no doubt that more studies are required to settle this issue. The attempt to decrease multiple recurrences in the upper tract is reasonable in well-selected patients.

The most common complication of instillation therapy is bacterial sepsis. To minimize this problem, patients must be evaluated for active infection before each treatment and only a low-pressure delivery system should be used. Agent-specific complications of

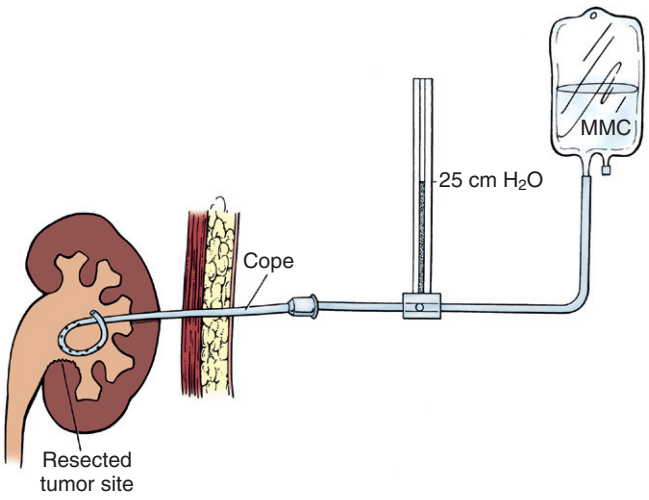


Figure 53–36. Setup for administration of topical immunotherapy or chemotherapy to the upper urinary tract through a previously placed nephrostomy tube. Therapy is instilled by gravity with a mechanism that prevents excessive intrarenal pressures. High pressures have been linked to complications of systemic absorption and bacterial sepsis. MMC, mitomycin C.

Table 53–8.

Percutaneous BCG Instillation for Prevention of Recurrence of Upper Tract Urothelial Tumors

AUTHOR	NO. OF PATIENTS	NO. OF RENAL UNITS	RECURRENCE (%)	DOD (%)	MEAN FOLLOW-UP (mo)
Rastinehad et al, 2009	125	133	33	—	61
Thalmann et al, 2002	37	41	49	38	42
Clark et al, 1999	17	18	35	35	20.5
Jarrett et al, 1995	19	19	33	10	55

BCG, bacille Calmette-Guérin; DOD, dead of disease.

the various therapies include ramification of systemic absorption of the agent. Bellman and colleagues (1994) described upper urinary tract complications of percutaneous BCG instillation. Granulomatous involvement of the kidney in the absence of systemic signs of BCG infection was most commonly seen. Mukamel and associates (1991) saw an inordinate decrease in renal function for patients receiving BCG who had vesicoureteral reflux.

Brachytherapy. Brachytherapy to the nephrostomy tract through iridium wire or delivery system was described by Patel and coworkers (1996) and Nurse and colleagues (1989). There were no instances of tract recurrences in this series, although the authors acknowledged the rarity of the event. The only major complication attributed to the brachytherapy was cutaneous fistula formation requiring nephroureterectomy.

After Complete Excision

Radiation Therapy. The rationale for focal radiation therapy is to decrease the risk of local relapse after radical surgery for locally advanced non–organ-confined disease (stage T3 to T4, N+). Most series concluding that postoperative irradiation is beneficial are small or even anecdotal, uncontrolled, and retrospective (Holtz, 1962; Brady et al, 1968; Leiber and Lupu, 1978). In one series with 41 patients, postoperative radiation therapy decreased local recurrence but had no effect on distant relapse or survival (Brookland and Richter, 1985). Maulard-Durdux and associates (1996) retrospectively reviewed 26 patients who received 46 Gy to the wound bed after radical surgery for upper tract tumors. Tumors were grade 2 in 40% and grade 3 in 60% of cases. Tumor stage was T2, T3, and N+ in 42%, 58%, and 35% of cases, respectively. Five-year survival is shown in Table 53–9. Overall 5-year survival was 49%, with 30% remaining disease free. All patients with local relapse also had distant relapse, leading the authors to conclude that adjuvant radiation therapy is not beneficial.

The largest experience addressing this issue is that reported by Hall and associates (1998b). A retrospective review of 252 patients with upper tract tumors who were observed for a median of 64 months was performed. Radical nephroureterectomy was performed in 77% of cases. Initial tumor stage was T3 in 19% and T4 in 10% of cases; 50% and 52%, respectively, of patients with stage T3 and stage T4 tumors received 40 Gy to the wound bed postoperatively. Disease-specific and overall 5-year survival was 41% and 28%, respectively, for patients with stage T3 disease. Actuarial 5-year disease-specific survival for stage T3 with or without adjuvant radiation therapy was 45% and 40%, respectively. Median survival was 6 months for stage T4 disease. There were no long-term survivors in this group. Local relapse occurred in only 9% of the entire series and was seen only in patients with stage T3 and stage T4 disease. Among the patients who received adjuvant radiation, isolated local relapse without distant metastases occurred in only 10% and 4% of stage T3 and stage T4 cases, respectively. Thus **radical nephroureterectomy alone provides a high rate of local control. Adjuvant radiation for high-stage disease does not decrease local relapse or protect against a high rate of distant failure.**

Table 53–9.

5-Year Survival after Postoperative Adjuvant Radiation Therapy for Upper Tract Urothelial Tumors

	5-YEAR SURVIVAL (%)
Tumor Grade	
2	90
3	0 ($P < .01$)
TNM Stage	
2	60
3	19
N0	49 ($P = .04$)
N+	15

Data from Maulard-Durdux C, Dufour B, Hennequin C, et al. Postoperative radiation therapy in 29 patients with invasive transitional cell carcinoma of the upper urinary tract: no impact on survival? J Urol 1996;155:115–7.

Systemic Chemotherapy. **The major limitation to long-term survival for patients with locally advanced upper tract tumors is distant relapse with metastatic disease. Both induction (neoadjuvant) and adjuvant systemic therapy with agents used for proven metastatic disease** (see following discussion) **are reasonable. However, there are no controlled trials that establish the efficacy of either induction or adjuvant chemotherapy in this setting.** The small number of cases treated with adjuvant chemotherapy are anecdotal and preclude definitive conclusions of efficacy.

Key Point: Metastatic Disease

- Distant relapse with metastatic disease is the main limitation in survival of patients, not local recurrence.

Follow-Up

Issues in Assessing for Recurrence

The propensity of upper tract tumors for multifocal recurrence and metastatic spread with more dysplastic lesions makes follow-up complicated. Postoperative evaluation must routinely include evaluation of the bladder, the ipsilateral (if organ-sparing therapy was chosen) and contralateral urinary tracts, and the extraurinary sites for local and metastatic spread. A follow-up regimen is thus dependent on the time from surgery, the approach chosen (organ sparing vs. radical), and the potential for metastatic spread. General recommendations for time intervals are listed in Figure 53–37.

General Procedures

All patients should be assessed at 3-month intervals the first year after they are rendered tumor free by endoscopic or open surgical approaches (Keeley et al, 1997a). This schedule is largely based on work with bladder TCC that shows that most tumor recurrences after bladder resection develop in the first year (Varkarakis et al, 1974; Loening et al, 1980). The upper urinary tract is more difficult to monitor, and delayed recognition of upper tract tumor recurrence may lead to disease progression and poor results (Mazeman, 1976). Evaluation should include history, physical examination, urinalysis, and office cystoscopy because of the high risk of bladder recurrences in patients treated both conservatively and with nephroureterectomy (Mazeman, 1976). If the patient requires endoscopic evaluation of the upper urinary tract, cystoscopy can be done in conjunction with that procedure.

Urine cytology may be helpful in assessing for upper tract recurrence, especially for high-grade tumors (Murphy et al, 1981). The utility, however, is decreased with less dysplastic tumors (Grace et al, 1967; Sarnacki et al, 1971; Zincke et al, 1976). The same tumor markers under study for bladder TCC

- Physical examination, urine cytology (only for high-grade lesions) and cystoscopy
  - Every 3 months–first year
  - Every 6 months thereafter–years 2 through 3
  - Yearly–thereafter
- Contralateral imaging (IVU or retrograde pyelography)–yearly
- Ipsilateral endoscopy (patients undergoing organ-sparing therapy)–
  - Every 6 months–first several years
  - Yearly–thereafter
- Metastatic evaluation–necessary in all patients with significant risk of disease progression (i.e., high grade or invasive disease)
  - Physical examination, chest x-ray, comprehensive metabolic panel with liver enzymes
    - Every 3 months–first year
    - Every 6 months–years 2 through 3
    - Yearly–years 4 and 5
    - After 5 years–evaluation of urothelium only
  - Computed tomography or MRI of abdomen and pelvis–
    - Every 6 months–years 1 and 2
    - Yearly–years 3 through 5
  - Bone scan–only for elevated alkaline phosphatase level or symptoms of bone pain

Figure 53–37. Follow-up begins after open surgery or when the patient is rendered tumor free by endoscopic management. The commencement of follow-up may be altered according to the potential for disease progression.

are promising for upper urinary tract TCC (Brown, 2000). One marker that may be preferentially more involved in upper tract TCC than in bladder TCC is the DNA mismatch repair gene *MSH2* (Leach et al, 2000).

Specific Procedures

Bilateral disease, either synchronous or metachronous, is seen in 1% to 4% of patients (Petkovic, 1975; Babaian and Johnson, 1980; Murphy et al, 1981), and thus imaging of the contralateral kidney is required on a regular basis. Yearly intravenous urography is usually sufficient. However, retrograde pyelography may be necessary if the patient is not a candidate for injection of contrast medium or if intravenous urography is not diagnostic. CT or ultrasonography is helpful in distinguishing stones from soft tissue densities. Further evaluation of filling defects on imaging studies usually requires ureteroscopic evaluation.

If an organ-sparing approach is chosen, the ipsilateral urinary tract must be assessed as well as the remainder of the urinary tract. The frequency and duration of the follow-up assessments depend largely on the grade and stage of the lesion, but they are usually every 6 months for several years and annually thereafter. Radiographic evaluation of the upper tracts alone is not adequate because Keeley and colleagues (1997a) showed that 75% of early tumor recurrences were visible endoscopically and not radiographically. With tumors approached in a percutaneous fashion, immediate follow-up nephroscopy can be performed through the established nephrostomy tract.

In the past, the burden of repeated endoscopic evaluation of the upper urinary tracts was a major deterrent to conservative therapy. The use of smaller, 7.5-Fr flexible ureteroscopes has greatly eased the burden of follow-up because ureteroscopes can be reliably passed up the ureter without the need for dilation of the ureteral orifice or prior stenting. Others have advocated resection of the ureteral orifice to facilitate subsequent surveillance ureteroscopy in the office setting (Kerbl and Clayman, 1993). Even though technology has somewhat facilitated follow-up, both physician and patient must be committed to nephron-sparing treatment.

Metastatic Restaging

Metastatic restaging is required in all patients at significant risk for disease progression to local or distant sites. This group includes those with high-grade or high-stage disease. Metastatic restaging is generally not necessary for low-grade disease when the risks of invasive and subsequent metastatic disease are negligible. Included in metastatic restaging is imaging of the ipsilateral renal bed for recurrence with cross-sectional imaging. Follow-up restaging includes chest radiograph, liver function tests, cross-sectional body imaging, and selective use of bone scintigraphy based on an understanding of natural disease history and metastatic pathways (Korman et al, 1996).

Treatment of Metastatic Disease

Outcomes are poor in patients with metastatic urothelial tumors of the upper urinary tract. **The systemic chemotherapy regimens offered for treatment are the same as those used for TCC of the bladder.** These regimens are discussed in Chapter 82. Only limited data on response rates of advanced upper tract tumors to chemotherapy are available because of the rarity of these lesions. Prospective randomized trials comparing chemotherapeutic regimens for upper tract tumors are not feasible for this reason. Patients with advanced upper tract tumors are excluded from most trials on treatment of advanced bladder cancer. Therefore, one must extrapolate likely chemotherapy response rates for upper tract disease from observations in bladder cancer trials. However, the need for effective use of perioperative chemotherapy for patients with locally advanced and metastatic upper tract tumors remains great. In a study of 184 patients accrued over three consecutive time intervals from 1986 to 2004 at M. D. Anderson Cancer Center, the median recurrence-free survival was 2.4 years and did not improve over time (Brown et al, 2006). The decline in renal function after nephroureterectomy in these mostly elderly patients may compromise the ability to administer effective postoperative chemotherapy and is yet another reason to consider neoadjuvant chemotherapy for patients with upper tract tumors and evidence of regional lymph node metastases.

The MVAC (methotrexate/vinblastine/doxorubicin [Adriamycin]/cisplatin) regimen continues to have the highest response rate (Sternberg et al, 1989). However, complete responses are rare, and the duration of response is limited, with overall survival of 12 to 24 months. Toxicity is high and dose limited in some patients. For all these reasons there is considerable ongoing investigation with newer agents, including paclitaxel, ifosfamide, carboplatin, and gemcitabine, used in various combinations and sequences (Roth et al, 1994; Bajorin et al, 1998; Redman et al, 1998; Vaughn et al, 1998; Kaufman et al, 2000; Lorusso et al, 2000). Many of these show initial overall response rates similar to the response rate to the MVAC regimen and lower toxicity. Occasional major responses are seen (Fig. 53–38). However, thus far, complete responses are rare, and neither durability of response nor survival is better than that seen with the MVAC regimen. In summary, upper tract

Key Points: Chemotherapy

- The chemotherapy for advanced upper tract TCC is the same as for bladder cancer.
- Controlled trials limited to upper tract tumors are not practical because of the low prevalence of disease.

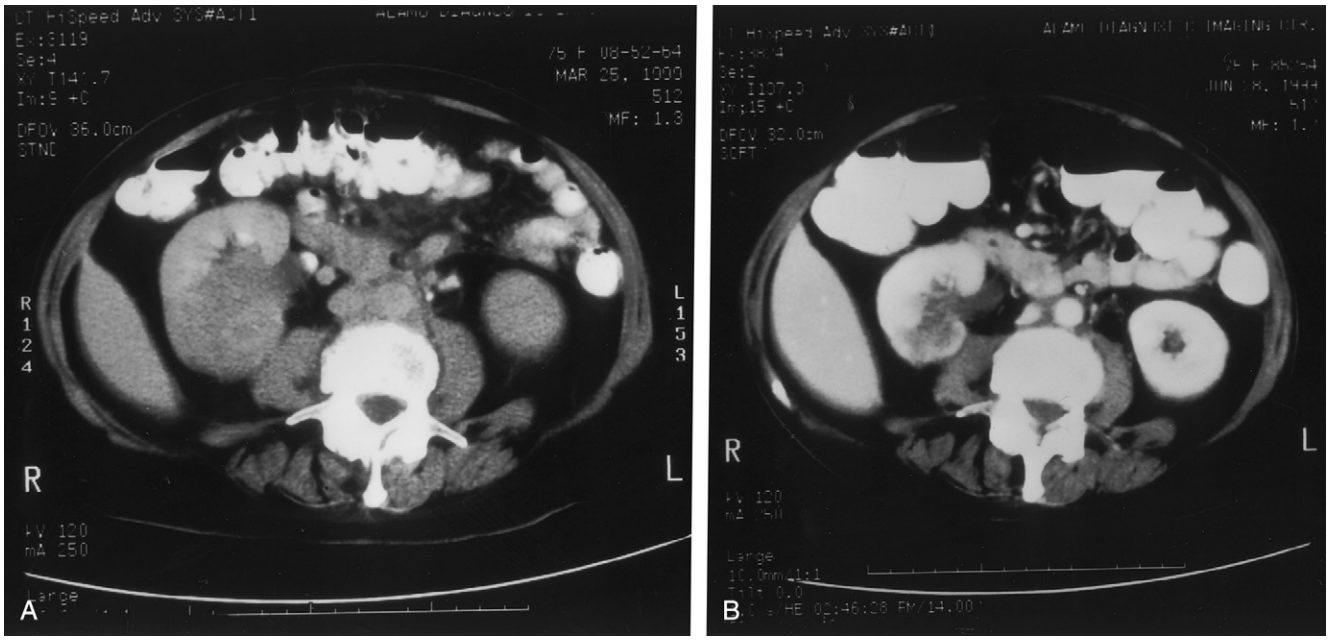


Figure 53–38. A patient presented with a large, biopsy-proven transitional cell carcinoma of the kidney as well as lung and axillary metastases. **A,** Initial appearance of the renal tumor. **B,** Marked shrinkage of the tumor after four courses of paclitaxel-gemcitabine chemotherapy. The lung and axillary metastases disappeared, and nephroureterectomy was performed. During the next year, the patient developed a brain metastasis. (Courtesy of Dr. Randall Singleton.)

urothelial cancer, like bladder cancer, is chemosensitive. It is to be hoped that additional improvements in treatment efficacy and safety are forthcoming, with further experience with new chemotherapeutic regimens. Alternative strategies, such as biologic response modifiers and gene therapy, also should be explored.

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chapter
54

Contemporary Open Surgery of the Kidney

Patrick A. Kenney, MD ● Chad Wotkowicz, MD ● John A. Libertino, MD

History
Surgical Anatomy
Preoperative Evaluation and Preparation
Surgical Approaches
Surgery for Benign Disease
Surgery for Malignancy
Complications of Open Renal Surgery

HISTORY

The history of open renal surgery is characterized by the spirit of innovation, investigation, and excellence that distinguishes modern urology (Table 54–1). Despite progress in minimally invasive techniques and other alternatives, open renal surgery remains a vital field that continues to benefit from refinement and research. Open surgery is an essential component of the contemporary, cutting-edge surgical armamentarium.

SURGICAL ANATOMY

General

Knowledge of regional anatomy is vital to safe and efficient renal surgery (Figs. 54–1 to 54–4 on the Expert Consult website). The renal capsule, perinephric fat, Gerota fascia (renal fascia), and paranephric fat are important landmarks in staging and surgery of renal malignancy (see Fig. 1–27).

Renal Vasculature

Arterial

The origin of the right renal artery is beneath the left renal vein and it typically passes posterior to the inferior vena cava (IVC) (Fig. 54–5; see also Fig. 1–33). **During transabdominal left radical nephrectomy, knowledge of this anatomic relationship may prevent inadvertent ligation of the right renal artery** (Fig. 54–6; see Fig. 54–7 on the Expert Consult website). The inferior adrenal artery and a branch that supplies the renal pelvis and ureter arise from the renal artery. In the majority of cases the renal artery branches in the distal third of the vessel or the renal sinus.

The kidney is divided into four segments (superior, anterior, posterior, inferior) that are supplied by one or more segmental renal arteries, which are end arteries (Fig. 54–8 on the Expert Consult website). **Ligation or occlusion of a segmental artery, or any of its branches, leads to devitalization of renal tissue.** Intraoperatively, one can administer methylene blue dye and occlude the segmental arteries to define the borders of the vascular segments. Despite variation in the origin of the branches supplying the renal segments, the anatomic pattern of the segments is constant (Graves, 1954). Three planes between the vascular segments can be demonstrated (see Fig. 54–8 on the Expert Consult website) and are important for intrarenal surgery. In theory, incision in the plane between the anterior and posterior segments affords reduced blood loss (Brodel, 1900) and has been described for anatrophic nephrolithotomy (Smith and Boyce, 1968). This plane, located on the posterior surface of the kidney, is not to be confused with the "Brodel white line," a whitish linear depression on the lateral aspect of the anterior surface of some kidneys formed by fusion of anterior and posterior columns of Bertin, which demarcates a highly vascular area (Brodel, 1900) (Fig. 54–9).

Typically, the first division of the renal artery creates the anterior and posterior segmental branches (see Fig. 1–30A and B). The posterior segmental branch of the main renal artery arises proximal to the hilum, passes posterior to the renal pelvis, and supplies the posterior renal segment. Classically, a crossing vessel responsible for ureteropelvic junction (UPJ) obstruction is an aberrant posterior segmental artery passing anterior to the UPJ. The anterior segmental branch of the main renal artery divides into four divisions: the apical (superior) segmental artery, the anterior superior segmental artery, the anterior inferior segmental artery, and the basilar (inferior) segmental artery. These are also referred to as the apical, upper, middle, and lower anterior segmental arteries, respectively. These segmental arteries then divide further into lobar arteries (associated with each renal pyramid) and further into two or three interlobar arteries (Fig. 54–10). The interlobar arteries travel through the renal medulla alongside either side of the pyramids. They divide at the corticomedullary junction into arcuate arteries that give rise to the interlobular arteries that travel radially to the capsule. They give off numerous side branches en route, including the afferent arterioles.

Venous

In parallel to the renal arterial system, the renal venous system progresses from the interlobular veins to the arcuate, interlobar, lobar, and segmental veins (see Fig. 1–32). The segmental veins

Table 54–1.

Important Advances in Open Renal Surgery

YEAR	INNOVATION
1869	Gustav Simon performed the first nephrectomy in a human to treat a ureterovaginal fistula, after first demonstrating that dogs are able to survive with a solitary kidney (Simon, 1870).
1878	Kocher and Langham use a midline incision to accomplish an anterior transperitoneal nephrectomy (Kocher and Langham, 1878).
1881	Morris performed the first nephrolithotomy (Morris, 1881).
1884	Wells performed an inadvertent partial nephrectomy while removing a perirenal fibrolipoma (Wells, 1884).
1887	Czerny carried out the first planned partial nephrectomy to treat a renal tumor (Herr, 2008).
1891	Kuster completed the first successful dismembered pyeloplasty (Kuster, 1896–1902).
1903	Grégoire performed the first procedure resembling a radical nephrectomy, described as an en-bloc resection of a kidney, perirenal fat, adrenal gland, and lymphatic tissue for cancer (Grégoire, 1903).
1913	Berg employed a transverse abdominal incision and mobilization of the colon to safely control the renal pedicle. He also obtained control of the renal veins and made a cavotomy to extirpate caval tumor thrombi (Berg, 1913).
1922	Rehn performed caval resection with reimplantation of the contralateral renal vein (Rehn, 1922).
1932	Rosenstein performed a palliative partial nephrectomy for renal cancer in a patient with contralateral renal insufficiency, defining an indication for nephron-sparing surgery (Rosenstein, 1921).
1959, 1960	Kerr and Klotz described renal hypothermia to minimize ischemic damage while prolonging available operative time for partial nephrectomy (Kerr et al, 1960; Herr, 2008).
1973	Libertino and Zinman described revascularization of the totally occluded renal artery (Zinman and Libertino, 1973).
1998	Libertino described use of a minimally invasive approach for cardiopulmonary bypass for vena cava thrombectomy (Fitzgerald et al, 1998).

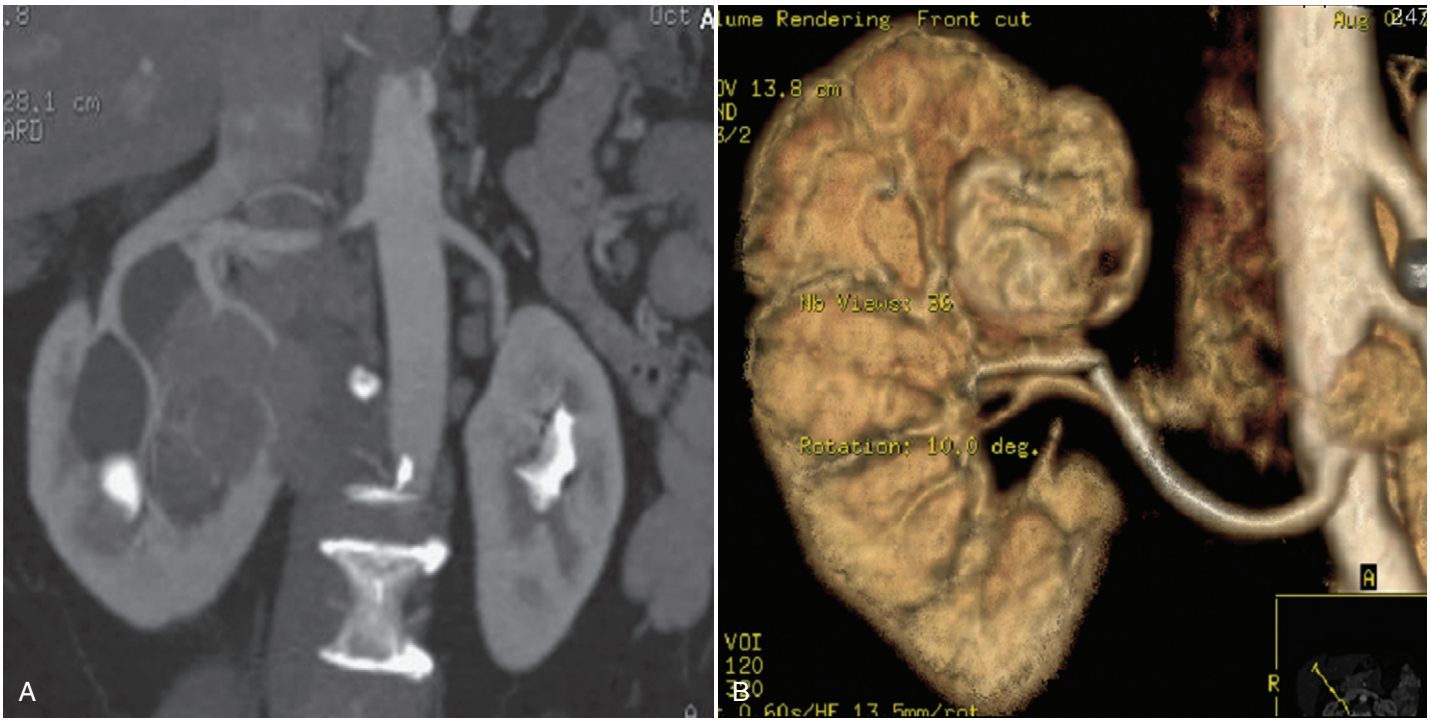


Figure 54–5. Arterial anatomy can be well defined using CT **(A)** and three-dimensional reconstruction **(B)**.

combine to form three to five venous tributaries, the confluence of which forms the main renal vein near the hilum. Each kidney is typically drained by a single renal vein that courses anterior to the renal artery and joins the lateral aspect of the vena cava. The left renal vein is longer than the right, making the left kidney attractive for donor nephrectomy. The left renal vein typically passes anterior to the aorta.

Unlike the arterial structure of the kidney, the renal venous system is characterized by a rich anastomotic network between the various renal segments. One may ligate and divide segmental veins without compromising drainage. The right renal vein does not receive significant branches. Tributaries draining into the main left renal vein include the gonadal vein, the left adrenal vein, and one or two large lumbar veins, all of which can be injured during mobilization of the left renal vein. Because of these collateral vessels, one is at liberty to ligate the left renal vein at the caval junction without eliminating venous return.

Anomalies of Renal Vasculature

Frequent anatomic variation in the renal vasculature contributes to the complexity of open renal surgery. Multiple renal arteries, which typically arise from the

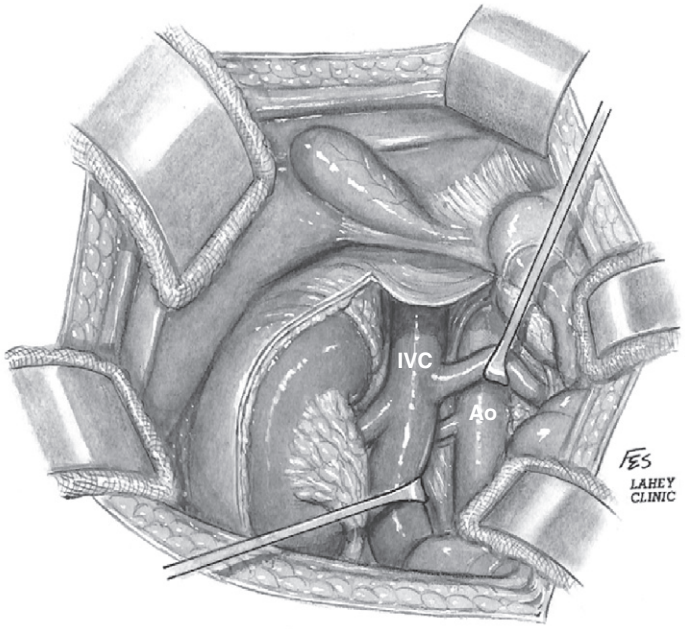


Figure 54–6. Relationship of right kidney to great vessels. IVC, inferior vena cava; Ao, aorta. (© The Lahey Clinic.)

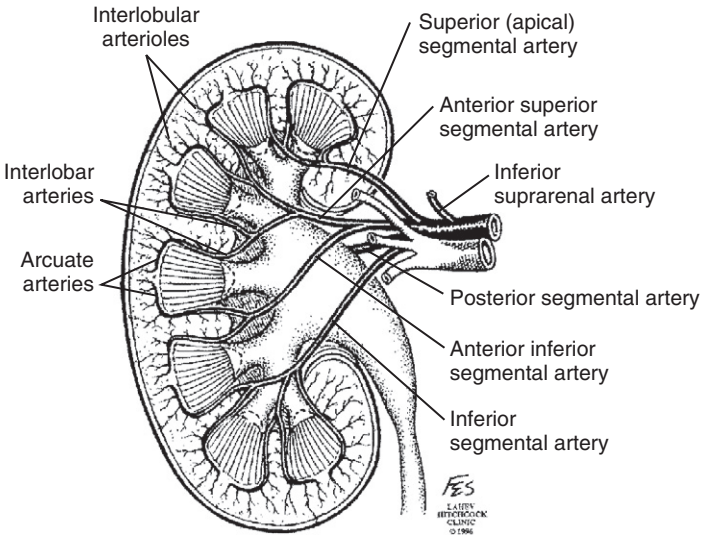


Figure 54–10. Anatomic relationship of cascading intrarenal vessels. (© The Lahey Clinic.)

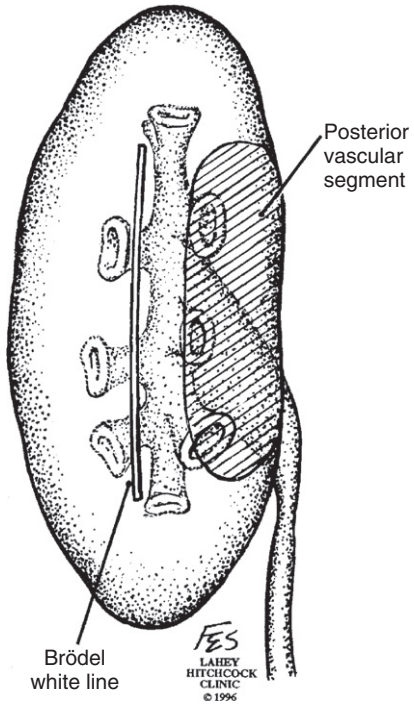


Figure 54–9. Brödel white line and posterior vascular segment. (© The Lahey Clinic.)



Figure 54–11. Horseshoe kidney with multiple arterial branches well defined with three-dimensional imaging.

aorta or iliac arteries, are the most common variation, occurring in 25% to 30% of the population (Merklin and Michels, 1958; Boijsen, 1959; April, 1997). Supernumerary hilar renal arteries originate at the aorta adjacent to the renal artery and traverse the renal hilum, whereas polar renal arteries originate at a greater distance from the main renal artery and enter the renal parenchyma directly. Ectopic and horseshoe kidneys more frequently have supernumerary renal arteries (Fig. 54–11).

Venous anomalies occur less frequently. Supernumerary renal veins occur less commonly on the left than right (Merklin and Michels, 1958). The most common variation is duplication of a renal vein (6%) (April, 1997). Retroaortic left renal veins occur in approximately 2% of patients. Circumaortic renal veins are present in 1.6% to 6.0% of the population (Kottra and Castellino, 1970).

One must be vigilant to identify these infrequent anomalies during preoperative evaluation or intraoperative dissection.

Lymphatics

Lymphatics parallel the arterial system from the renal cortex into the sinus and then empty into hilar nodes associated with the renal vein (see Figs. 1–34 [on the Expert Consult website] and 1-35). There is communication between parenchymal lymphatics and those of the renal capsule and perinephric fat. From the first description of renal lymphatic drainage in 1935 to modern day lymphatic dissections the complexity of renal lymphatic drainage beyond the hilum has been apparent (Parker, 1935; Assouad et al, 2006). For the surgeon, the most important characteristic of renal lymphatics is variability in drainage. More so than in malignancies of the penis, testis, bladder, and prostate, the role of regional lymphadenectomy in kidney cancer remains controversial.

Key Points: Surgical Anatomy

- The origin of the right renal artery is beneath the left renal vein. It typically passes posterior to the IVC. During transabdominal left radical nephrectomy, knowledge of this anatomic relationship may prevent inadvertent ligation of the right renal artery.
- The kidney is divided into four segments (superior, anterior, posterior, inferior) that are supplied by one or more segmental renal arteries, which are end arteries. Ligation or occlusion of a segmental artery, or any of its branches, leads to devitalization of renal tissue.
- The renal venous system is characterized by a rich anastomotic network between the various renal segments. One may ligate and divide segmental veins without compromising drainage.
- The right renal vein does not receive significant branches. Tributaries draining into the main left renal vein include the gonadal vein, the left adrenal vein, and one or two large lumbar veins, all of which can be injured during mobilization of the left renal vein. Because of these collateral vessels, one is at liberty to ligate the left renal vein at the caval junction without eliminating venous return.
- Frequent anatomic variation in the renal vasculature contributes to the complexity of open renal surgery. Multiple renal arteries, which typically arise from the aorta or iliac arteries, are the most common variation, occurring in 25% to 30% of the population.

PREOPERATIVE EVALUATION AND PREPARATION

A thorough preoperative evaluation is essential to safe open renal surgery. The preoperative evaluation is directed at patient selection, staging of disease, identification and optimization of medical comorbidities, imaging, preoperative procedures such as renal artery embolization, and prevention of surgical morbidity. Patient selection and clinical staging of renal disease are covered in other chapters of this text.

Table 54–2.

Preoperative Workup: Basic Components

Complete blood cell count
Chemistry panel (including electrolytes, creatinine, glucose)
Coagulation profile
Blood type and screen
Urinalysis and culture
Chest radiograph*
Electrocardiogram*
Pulmonary function testing*
Arterial blood gas analysis*

*If deemed necessary after assessment of cardiac and pulmonary risk factors.

Identification and Optimization of Cardiovascular and Pulmonary Comorbidities

Open renal surgery often requires prolonged nonphysiologic positioning with attendant impingement of cardiovascular and pulmonary function. The flank position may impede ventilatory capacity as well as decrease venous return to the heart, with resultant reduction in cardiac output. Patients may have significant bleeding, fluid shifts, or increased oxygen demand, which can result in imbalance in oxygen supply and demand. Preoperative evaluation including laboratory and imaging studies, along with judicious specialist consultation is essential (Table 54–2).

Cardiovascular

Some patients will benefit from referral to a consulting cardiologist for consideration of resting 12-lead electrocardiogram, noninvasive evaluation of left ventricular function, noninvasive stress testing, medication adjustments, or preoperative coronary revascularization (coronary artery bypass graft or percutaneous coronary intervention). **Patients with unstable coronary syndromes, decompensated heart failure, significant arrhythmias, or severe valvular disease should be evaluated and treated by a cardiologist before noncardiac surgery** (Fleisher et al, 2007). It is incumbent on the urologist to identify these patients and others who are at risk of cardiovascular complications and to refer them for evaluation by a specialist.

In addition, patients with known coronary artery disease or signs or symptoms suggestive of new coronary artery disease should receive a preoperative cardiac assessment (Fleisher et al, 2007). **In asymptomatic patients, referral should be made based on a history and physical examination** (Lee et al, 1999; Fleisher et al, 2007). The history should elucidate symptoms of cardiovascular disease, risk factors for cardiac disease, and pertinent medications (Table 54–3). The Revised Cardiac Risk Index (RCRI), a simple validated index to predict cardiovascular complications, was developed at a tertiary care facility for prediction of cardiac risk of major noncardiac surgery in patients 50 years of age or older (Lee et al, 1999). The RCRI, which is composed of six independent predictors of cardiac complications, identifies patients at risk of cardiac complications (Table 54–4) and may be helpful for preoperative risk stratification.

Pulmonary

In noncardiothoracic surgery, risk factors for postoperative pulmonary complications include chronic

Table 54–3.

Pertinent Cardiovascular History

Shortness of breath, dyspnea on exertion, or paroxysmal nocturnal dyspnea
Angina
Orthostatic intolerance
Bleeding diathesis
Coronary artery disease, including previous myocardial infarction
Heart failure
Carotid disease
Peripheral arterial disease
Cerebrovascular disease
Arrhythmias
Valvular disease
Pacemaker or implantable cardioverter-defibrillator
Chronic obstructive pulmonary disease (e.g., emphysema)
Pulmonary hypertension
Diabetes mellitus
Renal impairment
Nutritional status
Tobacco, alcohol, and illicit drug use
Assessment of functional capacity
Medications (e.g., herbs, supplements, antiplatelet agents, anticoagulants)

Table 54–4.

Revised Cardiac Risk Index

Independent Predictors
High-risk surgery
History of ischemic heart disease
History of congestive heart failure
History of cerebrovascular disease
Preoperative treatment with insulin
Preoperative serum creatinine level >2.0 mg/dL

NO. OF RISK FACTORS	RATE OF MAJOR CARDIAC COMPLICATION
0	0.4%
1	0.9%
2	7%
3 or more	11%

From Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100(10):1043–9.

obstructive pulmonary disease, age older than 60 years, inhaled tobacco use, American Society of Anesthesiologists (ASA) class II or higher, functional dependence (i.e., inability to perform activities of daily living or need for equipment and assistance for some activities of daily living), congestive heart failure, pulmonary hypertension, and hypoalbuminemia (Qaseem et al, 2006; Bapoje et al, 2007). The urologist should screen for these risk factors and refer the patient for preoperative pulmonary evaluation and risk reduction.

Even in the absence of baseline risk factors, open renal surgery itself may disturb a patient's pulmonary equilibrium and render him or her at risk for postoperative pulmonary complications. For instance, transection of upper abdominal and flank muscles, removal of ribs, impairment of diaphragm function through nerve or muscular injury, pneumothorax, hemothorax, and pleuritic pain may all contribute to pulmonary difficulties. **Prolonged surgery (>3 hours) is an independent predictor of pulmonary complications, as is either thoracic or upper abdominal surgery** (Qaseem et al, 2006).

Pulmonology consultation, preoperative pulmonary function testing, chest radiography, or arterial blood gas analysis may benefit patients who are at risk of pulmonary complications. Preoperative interventions such as smoking cessation 6 to 8 weeks before surgery and inspiratory muscle training may reduce the risk of pulmonary complications (Bapoje et al, 2007). In patients with significant pulmonary risk factors or impairment an anterior surgical approach in the supine position might be preferable to the flank approach (Novick, 2007). Risk can be ameliorated after surgery by deep breathing exercises or incentive spirometry and by selective rather than routine use of nasogastric drainage (Qaseem et al, 2006; Bapoje et al, 2007).

Renal Evaluation

Although a definitive discussion of renal impairment and its impact on surgical decision making is beyond the scope of this chapter, assessment of renal function is mandatory before open renal surgery. As discussed later in the section on partial nephrectomy, preservation of renal function is a vitally important aspect of contemporary renal surgery. Knowledge of preoperative renal dysfunction is essential.

Initial renal evaluation should include urinalysis and measurement of serum creatinine concentration. **The serum creatinine value is the most widely used surrogate marker of glomerular filtration rate (GFR) but is not ideal.** Changes in the serum creatinine level can reflect a change in GFR but may also represent a change in production of creatinine or tubular secretion of creatinine. A better estimate of GFR is provided by 24-hour creatinine clearance (CrCl), which reflects the volume of plasma that is cleared of creatinine per minute. Because creatinine is also cleared by tubular secretion in addition to filtration, the 24-hour CrCl tends to overestimate GFR. GFR can also be estimated by renal radionuclide imaging. For instance, renal scan with technetium-99 diethylenetriaminepentaacetic acid (DTPA) can provide an estimate of GFR but its use is limited in patients with renal insufficiency. **A commonly used method, which is favored by the senior author, is to estimate GFR using the Modification of Diet in Renal Disease (MDRD) Study equation** (Levey et al, 1999):

$$\text{GFR (mL/min/1.73 m}^2) = 186 \times (S_{Cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African-American})$$

If extirpative renal surgery is anticipated to render the patient at high-risk of dialysis dependence, preoperative nephrology referral and placement of hemodialysis access, such as a Tesio catheter (Medical Components, Harleysville, PA), are advisable. Patients must be made aware that the risks of open renal surgery include chronic kidney disease, dialysis dependence, and the systemic consequences of renal insufficiency.

Imaging

Modern imaging permits a thorough anatomic evaluation of the urinary tract before open renal surgery. It is essential to identify anatomic variants before surgery such as supernumerary renal arteries, retroaortic left renal vein, circumaortic renal vein, duplicated collecting system, and renal ectopia. A variety of imaging

modalities are available, including intravenous pyelography, retrograde pyelography, ureteroscopy, computed tomography (CT), ultrasonography, magnetic resonance imaging (MRI), renal arteriography, and renal venography.

Three-dimensional (3D) volume-rendered CT is a valuable tool in the evaluation of patients undergoing renal surgery (Coll et al, 1999; Derweesh et al, 2003). **CT can demonstrate vital information including the anatomy of the renal vasculature, orientation of the kidney, and characteristics of renal tumors, including location, depth of penetration into the kidney, relationship with collecting system, and segmental arterial supply to the tumor** (Coll et al, 1999) (Figs. 54–12 to 54–14). CT is also able to characterize other surgically relevant processes, including renal arterial disease, nephrolithiasis, and hydroureteronephrosis (Herts, 2005).

The importance of imaging to open renal surgery is likely to increase with time. Future possibilities include image-guided open surgery, the objective of which is to provide surgeons enhanced visualization of the surgical field by merging data from preoperative images with an intraoperative view (Benincasa et al, 2008). In addition, simulation of complex nephron-sparing surgery based on 3D imaging may be possible (Wunderlich et al, 2000).

Angioembolization

Since its introduction in the early 1970s, renal artery embolization (RAE) has been employed for palliation of inoperable renal tumors, to control bleeding, and as part of multimodal treatment of hypervascular metastatic disease (Almgard et al, 1973). In addition, RAE is used as a preoperative adjunct to resection of locally advanced renal tumors, with or without metastases (Paster et al, 1975) (Fig. 54–15).

Proposed benefits of preoperative RAE include shrinkage of an arterialized tumor thrombus to ease surgical removal, reduced blood loss, facilitation of dissection due to tissue plane edema, ability to ligate the renal vein before the renal artery at time of nephrectomy, and modulation of the immune response (Klimberg et al, 1985; Bakal et al, 1993; Kalman and Varenhorst, 1999; Schwartz et al, 2007; Wotkowicz and Libertino, 2007; Wszolek et al, 2008). Ligation of the renal vein before the renal artery is useful in the setting of hilar tumors, tumors with significant medial extension, or considerable perihilar adenopathy (Schwartz et al, 2007; Wotkowicz and Libertino, 2007; Wszolek et al, 2008). Before ligating the renal vein, one should characterize the completeness of embolization to prevent unnecessary blood loss in cases of incomplete embolization. In the senior author's experience this assessment can be made by evaluating renal venous return during surgery. In addition, angioembolization can also be useful for renal tumors associated with large arteriovenous malformations that are having a deleterious hemodynamic impact (Figs. 54–16 and 54–17).

There may be a survival benefit to preoperative RAE. In a case-control study, preoperative RAE and nephrectomy was associated with a survival benefit when compared with nephrectomy alone (Zielinski et al, 2000). In comparison to matched controls, preoperative RAE was associated with improved overall survival at 5 years (62% vs. 35%, $P = .01$) and 10 years (47% vs. 23%, $P = .01$). This possible survival benefit has not been demonstrated in a prospective trial.

Although there is no conclusive evidence that RAE has any immunotherapeutic benefit it is plausible that angioinfarction may augment the immune response to the renal tumor (Kalman and Varenhorst, 1999). There are reports of regression of metastases from renal cell carcinoma after RAE and nephrectomy (Mohr and Whitesel, 1979; Swanson et al, 1983). The postinfarction syndrome that is nearly universal may be cytokine mediated. Several studies have shown that RAE is immunomodulatory, with

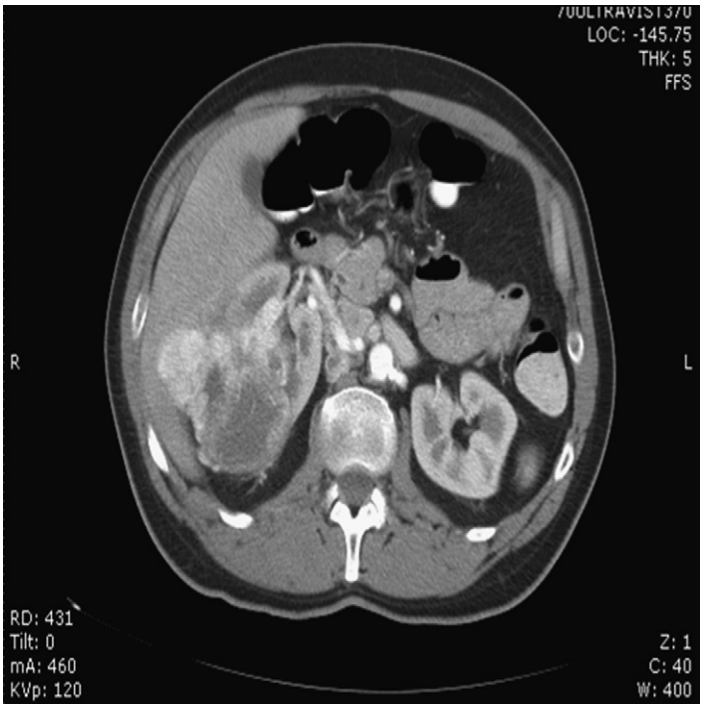


Figure 54–12. Contrast-enhanced CT axial reconstruction demonstrating large right hypervascular mass suggestive of renal cell carcinoma.

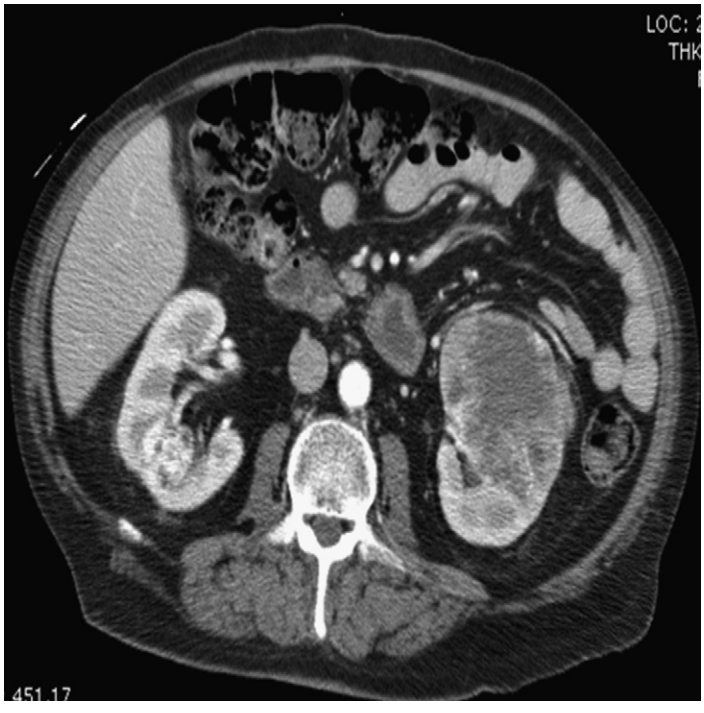


Figure 54–13. CT scan demonstrating two incidentalomas in an elderly man undergoing imaging to rule out appendicitis. A left partial nephrectomy was performed first followed by a right radical nephrectomy in 3 to 4 months.

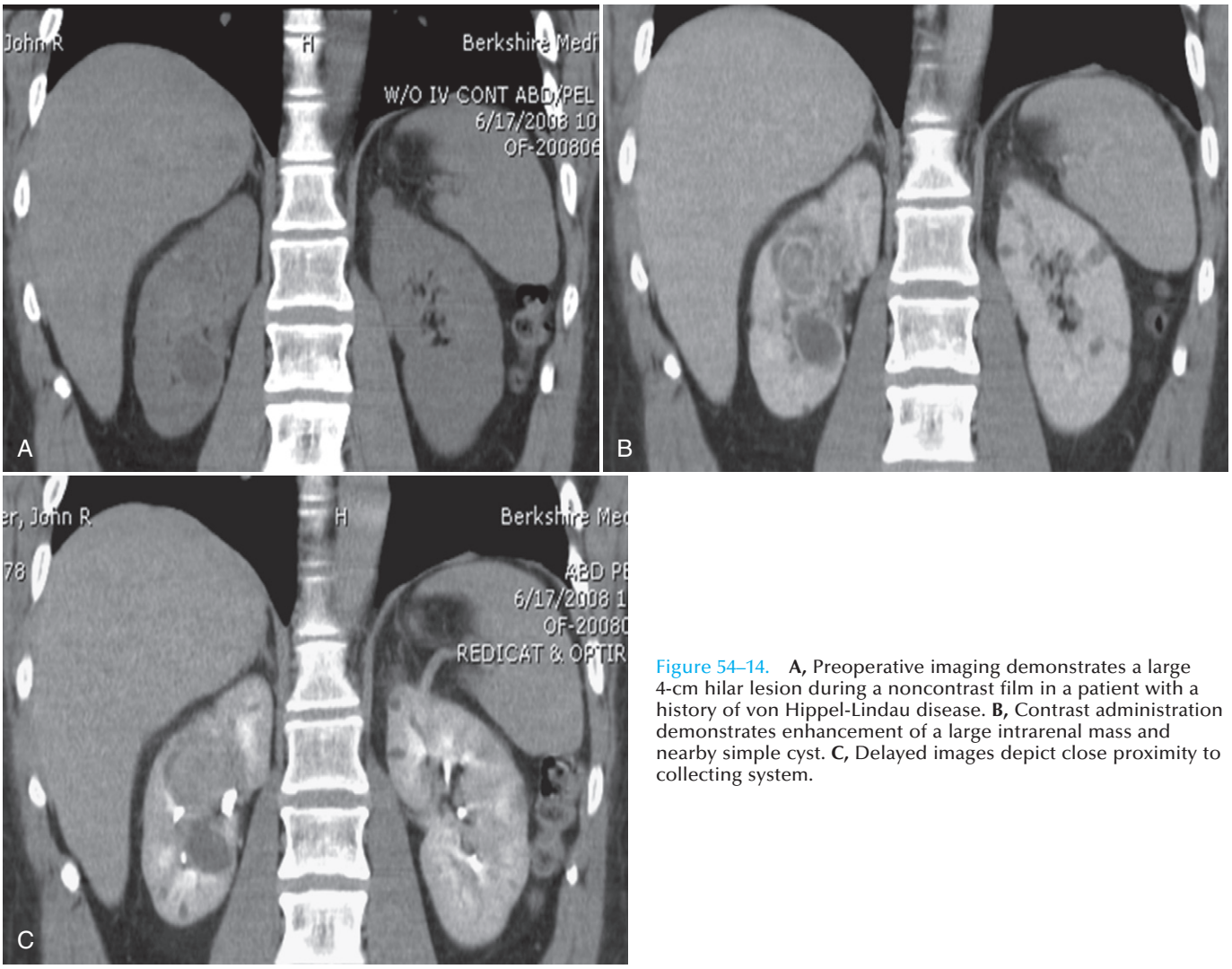


Figure 54–14. **A,** Preoperative imaging demonstrates a large 4-cm hilar lesion during a noncontrast film in a patient with a history of von Hippel-Lindau disease. **B,** Contrast administration demonstrates enhancement of a large intrarenal mass and nearby simple cyst. **C,** Delayed images depict close proximity to collecting system.

documented changes in natural killer cell activity (Bakke et al, 1982), increased cell-mediated cytotoxicity (Johnson and Kalland, 1984), and alteration in lymphocyte proliferation (Nakano et al, 1983). There are no modern molecular data to support these findings.

The postinfarction syndrome, which is characterized by flank pain, nausea, and fever, occurs in approximately three fourths of patients and is the most frequently cited complication of RAE (Schwartz et al, 2007). Other complications, including incomplete embolization, coil migration, and groin hematoma, occurred in fewer than 5% of patients (Schwartz et al, 2007). Rarely cited complications include hyponatremia (Huang et al, 2003), paraplegia due to occlusion of spinal arteries, or inadvertent angioinfarction of other organs such as the colon (Roy et al, 1999).

The data regarding preoperative RAE are limited, without any randomized trials evaluating the technique. As a result, in some institutions, surgeons rarely employ preoperative RAE (Boorjian et al, 2007). It is the practice of the senior author to perform preoperative RAE for large renal tumors with hypervascular characteristics or IVC tumor thrombus (Wotkowicz and Libertino, 2007). The ideal timing of nephrectomy after embolization is unclear (Craven et al, 1991; Weckermann et al, 1992; Kalman and Varenhorst, 1999; Schwartz et al, 2007). At the Lahey Clinic, surgery usually is timed 4 weeks after angioinfarction. An imaging study to assess the cranial limit of tumor thrombus is repeated shortly before the operation. Although prospective trials are needed to evaluate the role of preoperative RAE in the treatment of renal cell carcinoma, the senior author has found it a useful preoperative adjunct in the management of locally advanced RCC.

Surgical Site Infection Prophylaxis

A preoperative urinalysis and culture should be obtained for all patients undergoing open renal surgery. Patients with urinary tract infection or bacteriuria should be treated with culture-guided antibiotics before surgery, with the goal of sterilizing the urine or reducing the bacterial count if the urine cannot be sterilized (Wolf et al, 2008).

In the absence of active infection or bacteriuria, judicious antimicrobial prophylaxis may reduce the risk of surgical site infection and systemic sepsis. In cases in which the urinary tract is not entered, such as radical nephrectomy, antibiotics should be targeted to skin flora (e.g., a first-generation cephalosporin or clindamycin). The American Urological Association (AUA) advises that in these clean cases the use of antibiotics should be limited to

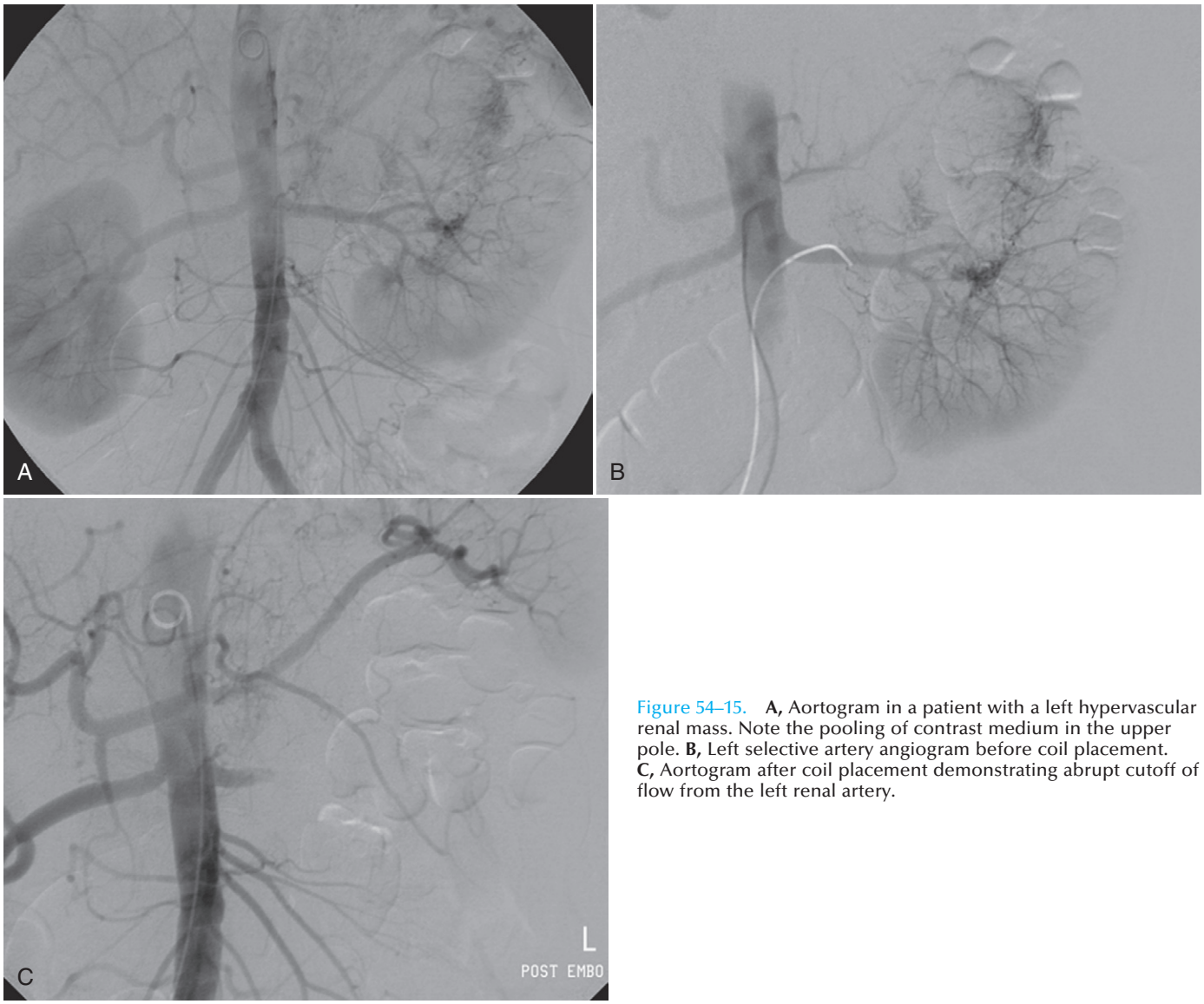


Figure 54–15. **A,** Aortogram in a patient with a left hypervascular renal mass. Note the pooling of contrast medium in the upper pole. **B,** Left selective artery angiogram before coil placement. **C,** Aortogram after coil placement demonstrating abrupt cutoff of flow from the left renal artery.

patients with risk factors (Table 54–5) (Wolf et al, 2008). In renal surgery in which the urinary tract is entered both skin and genitourinary flora should be covered (with a first- or second-generation cephalosporin or aminoglycoside with metronidazole or clindamycin, or ampicillin/sulbactam, or fluoroquinolone) (Wolf et al, 2008).

Open renal surgery is often complex and time consuming. Antibiotics should be readministered during surgery after one to two half-lives to ensure adequate drug levels are maintained until wound closure (Bratzler and Houck, 2005). Antibiotic prophylaxis should not continue beyond 24 hours (Bratzler and Houck, 2005).

In addition to antibiotics, sterile technique is employed to reduce the rate of surgical site infection. Although there is no conclusive evidence to support hair removal as a method of reducing surgical site infection, the authors recommend clipping hair at the incision site before sterile preparation of the field (Tanner et al, 2006). It is the practice of the senior author to use povidone-iodine scrub and paint, although one study has found paint alone to be equivalent to scrub and paint for abdominal surgery (Ellenhorn et al, 2005). One should avoid alcohol-containing products because of flammability (Armstrong et al, 2001). Finally, proper surgical technique with regard to tissue handling, hemostasis, avoidance of unnecessary hypothermia, and excision of devitalized tissues is an essential component of infection prevention (Mangram et al, 1999).

Venous Thromboembolism Prophylaxis

There is a paucity of date to guide prophylaxis for venous thromboembolism (VTE) in open renal surgery. Although both the AUA and American College of Chest Physicians (ACCP) guidelines recommend pharmacologic VTE prophylaxis in open renal surgery, the data supporting these recommendations are imperfect (Geerts et al, 2008; Forrest et al, 2009). The ACCP recommends routine VTE prophylaxis in all open urologic procedures, although this recommendation is largely based on data from other surgical specialties and radical retropubic prostatectomy. The ACCP recommends preoperative use of graduated compression stockings along with intermittent pneumatic compression devices, pharmacologic prophylaxis after surgery (low-dose unfractionated heparin, low-molecular-weight heparin, or fondaparinux), or both. In patients at high risk of bleeding, the ACCP advises pharmacologic

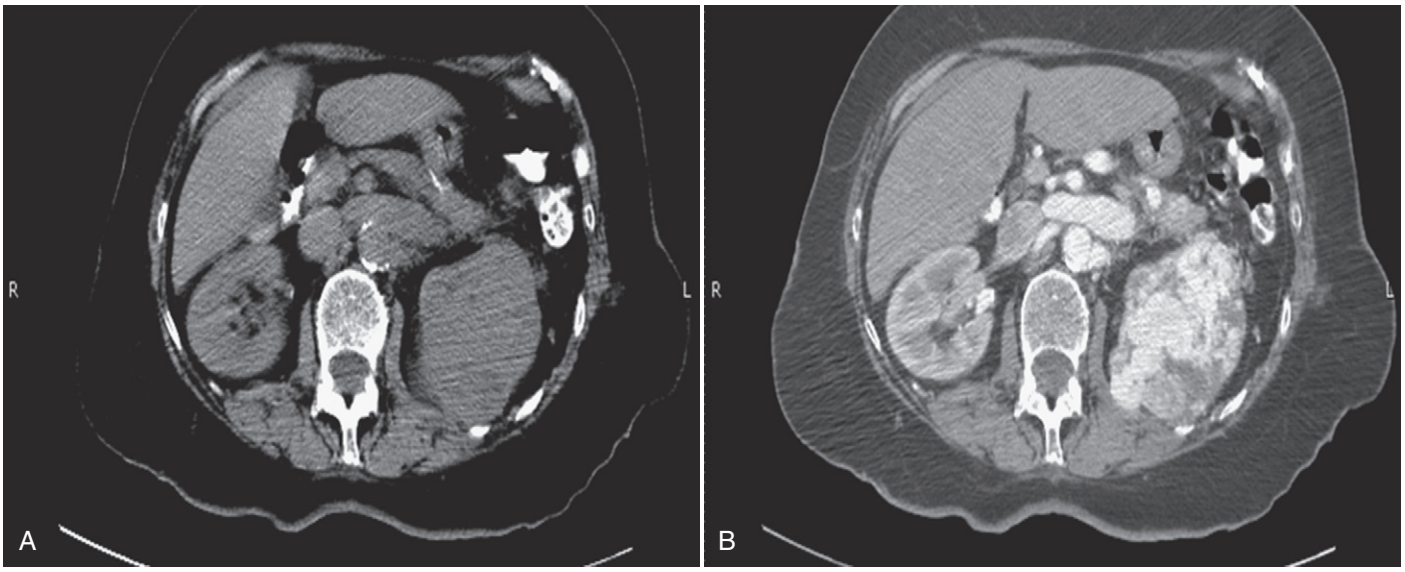


Figure 54–16. Noncontrast **(A)** and contrast-enhanced **(B)** CT images of a patient with high output cardiac failure secondary to arteriovenous malformation associated with left renal cell carcinoma. Notice the equal contrast intensity of the aorta, left renal artery, and left renal vein.

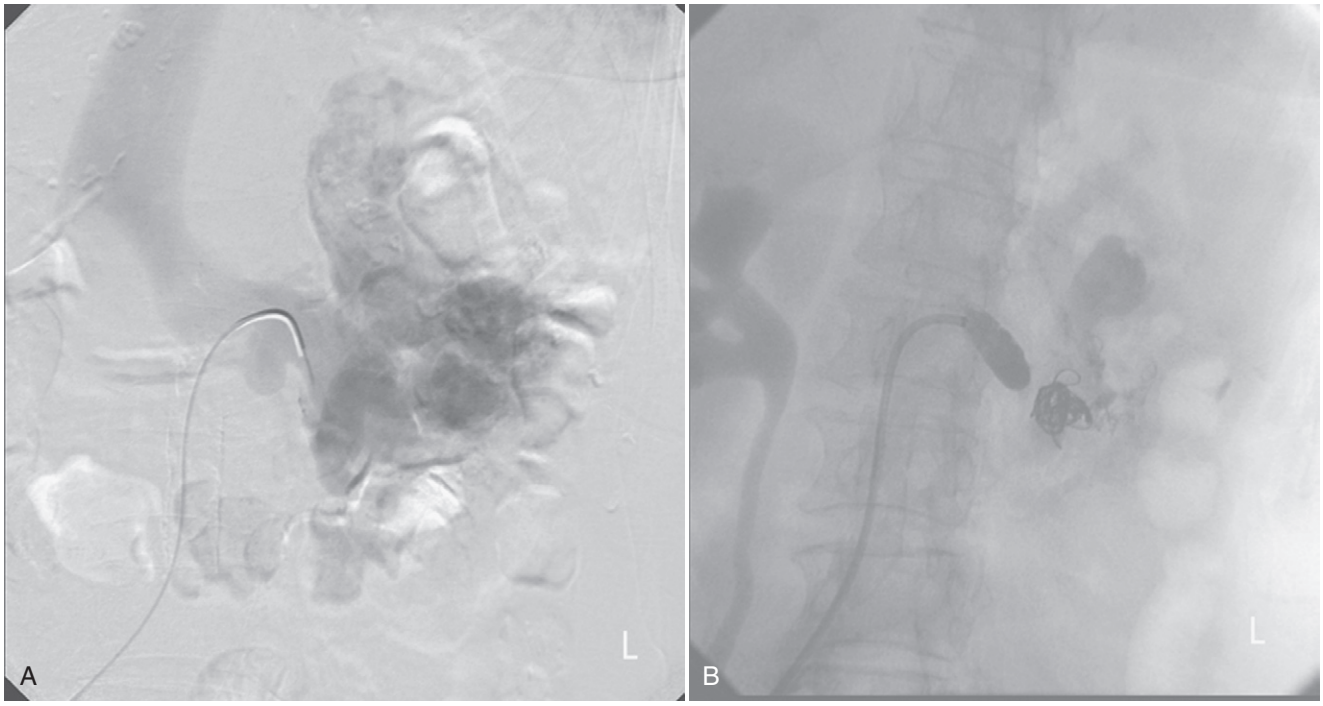


Figure 54–17. **A,** Left selective renal angiogram demonstrates immediate filling of the renal vein and inferior vena cava. **B,** Angiogram after placement of coils demonstrates complete angioinfarction. Contrast medium in the contralateral renal pelvis confirms contralateral renal function.

therapy once the bleeding risk has diminished. **The AUA recommends use of mechanical prophylaxis in all patients undergoing open surgery and consideration of pharmacologic prophylaxis in patients with elevated risk for VTE** (Tables 54–6 and 54–7).

It is the authors' practice to apply intermittent pneumatic compression devices before open renal surgery for all patients. In the opinion of the senior author there is not sufficient evidence to support routine use of pharmacologic VTE prophylaxis given the associated risk of hemorrhage. At the Lahey Clinic addition of pharmacologic prophylaxis is determined on a case-by-case basis by subjectively assessing an individual's risk of VTE (see Tables 54–6 and 54–7). In partial nephrectomy, a procedure with significant risk of hemorrhage, pharmacologic prophylaxis is avoided in the vast majority of cases at the Lahey Clinic. This practice is supported by a retrospective review from Memorial Sloan-Kettering Cancer Center that describes a low prevalence (1.5%) of clinically apparent VTE after radical or partial nephrectomy (Pettus et al, 2006). This is an order of magnitude lower than the estimated 15% to 40% rate of asymptomatic VTE (i.e., found on screening) on which the current ACCP recommendations are based (Geerts et al, 2008). The clinical significance of asymptomatic VTE is unclear.

Table 54–5.

Risk Factors for Surgical Site Infection

Alteration in Host Defense
Advanced age
Anatomic anomalies of the urinary tract
Poor nutritional status
Smoking
Chronic corticosteroid use
Immunodeficiency
Alteration in Pathogen
Externalized catheters
Colonized endogenous/exogenous material
Distant coexistent infection
Prolonged hospitalization

From Wolf JS Jr, Bennett CJ, Dmochowski RR, et al. Best practice policy statement on urologic surgery antimicrobial prophylaxis. J Urol 2008;179(4):1379–90.

Table 54–6.

Venous Thromboembolism: Risk Stratification

Low Risk
Minor surgery in patients younger than age 40 years with no additional risk factors
Moderate Risk
Minor surgery in patients with additional risk factors
Surgery in patients age 40 to 60 years with no additional risk factors
High Risk
Surgery in patients older than age 60 years
Surgery in patients age 40 to 60 years with additional risk factors
Highest Risk
Surgery in patients with multiple risk factors

Data from Geerts and colleagues (2008) and Forrest and colleagues (2009).

Table 54–7.

Venous Thromboembolism: Risk Factors

Surgery
Trauma (major or lower extremity)
Immobility, paresis
Malignancy
Cancer therapy (hormonal therapy, chemotherapy, or radiotherapy)
Venous compression (tumor, hematoma, arterial abnormality)
Previous venous thromboembolism
Increasing age
Pregnancy and the postpartum period
Estrogen-containing oral contraception or hormone replacement therapy
Selective estrogen receptor modulators
Erythropoiesis-stimulating agents
Acute medical illness
Heart or respiratory failure
Inflammatory bowel disease
Nephrotic syndrome
Myeloproliferative disorders
Paroxysmal nocturnal hemoglobinuria
Obesity
Smoking
Varicose veins
Central venous catheterization
Inherited or acquired thrombophilia

Data from Geerts and colleagues (2008) and Forrest and colleagues (2009).

Key Points: Preoperative Evaluation and Preparation

- Patients with unstable coronary syndromes, decompensated heart failure, significant arrhythmias, or severe valvular disease should be evaluated and treated by a cardiologist before noncardiac surgery.
- Patients with known coronary artery disease or signs or symptoms suggestive of new coronary artery disease should receive a preoperative cardiac assessment. In asymptomatic patients, referral should be made based on a history and physical examination (e.g., Revised Cardiac Risk Index).
- In noncardiothoracic surgery, risk factors for postoperative pulmonary complications include chronic obstructive pulmonary disease, age older than 60 years, inhaled tobacco use, ASA class II or higher, functional dependence, congestive heart failure, pulmonary hypertension, and hypoalbuminemia.
- Prolonged surgery (>3 hours) is an independent predictor of pulmonary complications, as is thoracic and upper abdominal surgery.
- Pulmonology consultation, preoperative pulmonary function testing, chest radiography or arterial blood gas analysis, smoking cessation, and inspiratory muscle training may be of benefit.
- Measurement of serum creatinine concentration is the most widely used surrogate marker of GFR but is not ideal. The method favored by the senior author is to estimate GFR using the MDRD Study equation.
- CT can demonstrate vital information, including the anatomy of the renal vasculature, orientation of the kidney, and characteristics of renal tumors, including location, depth of penetration into the kidney, relationship with collecting system, and segmental arterial supply to the tumor.
- Proposed benefits of preoperative RAE include shrinkage of an arterialized tumor thrombus to ease surgical removal, reduced blood loss, facilitation of dissection due to tissue plane edema, ability to ligate the renal vein before the renal artery at the time of nephrectomy, and modulation of the immune response.
- The postinfarction syndrome, which is characterized by flank pain, nausea, and fever, occurs in approximately three fourths of patients and is the most frequently cited complication of RAE.
- A preoperative urinalysis and culture should be obtained for all patients undergoing open renal surgery.
- The AUA recommends use of mechanical prophylaxis in all patients undergoing open surgery and consideration of pharmacologic prophylaxis in patients with elevated risk for VTE. This is controversial.

SURGICAL APPROACHES

Safe, effective open renal surgery is predicated on good functional exposure of the kidney. The kidney is a retroperitoneal structure in close proximity to the great vessels, pancreas, spleen, liver, colon, and duodenum. These neighbors serve as landmarks to guide dissection, as well as potential sources of complications and impediment to adequate exposure. An incision that is too small or inappropriately placed will increase the difficulty of open renal surgery and may adversely impact patient outcomes.

Good functional exposure permits the surgeon to perform the planned procedure, diminishes the risk of injury to surrounding structures, and permits definitive treatment of an intraoperative complication, such as injury to a great vessel (Libertino, 1998). Proper exposure limits the amount of required retraction, which can be a source of injury to surrounding structures such as the liver or spleen (Cooper et al, 1996).

One must balance numerous variables when selecting a surgical approach to the kidney. **The ideal surgical approach is one that is tailored not only to the operation being performed but also to the anatomy as defined on preoperative imaging, previous surgical history, body habitus, and presence of limiting factors such as kyphoscoliosis or pulmonary disease** (Libertino, 1998).

The primary approaches to the kidney are the subcostal, supracostal, and transcostal flank incisions, the thoracoabdominal approach, the dorsal lumbotomy, as well as the midline, paramedian, and subcostal anterior approaches (Table 54–8).

Flank Approaches

The flank approaches are undertaken with the patient in lateral decubitus position with flexion of the table. Flexion tightens the skin and muscles of the flank and improves exposure by increasing the distance between the iliac crest and costal margin. Positioning for the flank approaches can impede pulmonary function and venous return to the heart, with resultant deficits in ventilation and cardiac output (Longnecker, 2007). When the table is flexed with the kidney bar elevated, ischemic injury to a previously operated on contralateral kidney may result (Matin and Novick, 2001). Flank approaches may not be ideal in patients with preexisting cardiopulmonary deficits or kyphoscoliosis. Each of the flank approaches can result in injury to the intercostal nerves with denervation and paresis of the flank musculature, leading to chronic postoperative pain or flank bulge in 3% to 49% of patients (Ward et al, 1974; Chatterjee et al, 2004). Gravity will tend to move the abdominal panniculus of an obese patient away from the operative field, a distinct advantage of the flank approaches.

Table 54–8.

Approaches to the Kidney: Salient Features

APPROACH		APPLICATIONS AND ADVANTAGES	DISADVANTAGES AND POTENTIAL COMPLICATIONS
Flank	Subcostal	Useful for surgery on lower renal pole, ureteropelvic junction, and upper ureter, as well as simple nephrectomy, nephrostomy tube insertion, and drainage of perinephric abscess Extraperitoneal approach prevents peritoneal contamination Abdominal panniculus falls away from incision	Poor option for radical or partial nephrectomy and in patients with significant scoliosis or who will not tolerate flank position (e.g., severe pulmonary comorbidity) Provides poor access to renal hilum and renal vasculature Exposure possibly hindered by the iliac crest and subcostal nerve Risks chronic flank pain and bulge and ischemic injury to a postoperative contralateral kidney
	Supracostal	Useful for radical nephrectomy for modest-sized tumor and partial nephrectomy Extraperitoneal, extrapleural approach Good renal, suprarenal, and retroperitoneal exposure Permits pivoting of the 11th or 12th rib on a single articulating surface posteriorly without removal of a rib Abdominal panniculus falls away from incision	Poor option for patients with significant scoliosis or who will not tolerate flank position (e.g., severe pulmonary comorbidity) Longer operative time Risks chronic flank pain and bulge and ischemic injury to a postoperative contralateral kidney
	Transcostal	Same as supracostal	Same as supracostal Morbidity due to rib resection
Thoracoabdominal		Useful for radical nephrectomy and partial nephrectomy of large renal masses, especially those of the upper pole Valuable for right-sided tumors in which the liver and hepatic veins would reduce exposure and make vascular control difficult using a different approach (Chute et al, 1949; Clarke et al, 1958; Khoury, 1966; Middleton and Presto, 1973; Libertino, 1998) Useful for radical nephrectomy for renal tumors with venous extension and those involving adjacent structures (e.g., liver, spleen, or pancreas) as well as for excision of suprarenal masses (Libertino, 1998) Provides maximal suprarenal exposure Permits synchronous biopsy or resection of pulmonary lesions	Longer operative time Greater potential pulmonary morbidity (Novick, 2007) Damage to phrenic nerve (Novick, 2007)

Table 54–8.

Approaches to the Kidney: Salient Features—cont'd

APPROACH		APPLICATIONS AND ADVANTAGES	DISADVANTAGES AND POTENTIAL COMPLICATIONS
Dorsal lumbotomy		Useful for simple nephrectomy for small atrophic kidney, simultaneous bilateral simple nephrectomies in end-stage renal disease, pyeloplasty, pyelolithotomy and upper ureterolithotomy, and open renal biopsy Rapid Affords fresh tissue planes in patients with numerous prior abdominal or flank procedures No muscles are transected; only posterior fascial layers are incised, leading to strong wound closure and less incisional pain With detachment of the costovertebral ligament the 12th rib can be retracted widely, rendering resection of the rib unnecessary (Gardiner et al, 1979; Novick, 2007)	Poor option for radical or partial nephrectomy, for large or superiorly displaced kidneys, and for procedures requiring extensive ureteral mobilization (e.g., long stricture) Morbid obesity and musculoskeletal irregularity may limit access between the iliac crest and 12th rib (Novick, 2007) Previous retroperitoneal surgery may cause obliteration of the normal planes of dissection rendering the approach less favorable Poor control of the renal vessels
Anterior	Subcostal (extraperitoneal or transperitoneal)	Useful for open renal biopsy, nephrectomy and renovascular surgery Favorable approach for upper pole tumors and in patients with a wide subcostal angle (Chute et al, 1967) Provides good access to the superior and lateral aspect of kidney; the transperitoneal approach permits good access to the renal hilum The extraperitoneal approach diminishes risk of ileus and intra-abdominal injury	The extraperitoneal approach provides limited access, especially to the pedicle The transperitoneal approach may risk ileus, adhesions and bowel obstruction The left transperitoneal anterior subcostal approach has been associated with splenic injury (Mejean et al, 1999)
	Chevron	Useful for renovascular surgery and renal tumors extending into the vena cava Useful in obese patients and in those with a wide subcostal angle Provides outstanding access to both kidneys, renal pedicles, and the great vessels	Ileus, adhesions, and possible bowel obstruction Transection of the abdominal wall muscles may lead to pain and morbidity
	Midline transperitoneal	Useful for trauma, renovascular surgery, reconstructive procedures (e.g., ileal ureter), and bilateral procedures Rapid Provides good access to renal pedicle Practical in patients with a narrow subcostal angle	Ileus, adhesions, and possible bowel obstruction
	Paramedian (extraperitoneal or transperitoneal)	Same as midline Provides added strength with two-layer fascial closure	Ileus, adhesions, and possible bowel obstruction (transperitoneal) Limited exposure of the kidney (extraperitoneal)

It is imperative to understand the anatomy of the flank before employing these approaches (see Figs. 1–3, 1–4, 1–5, and 1–8). There are three principal flank approaches: subcostal, supracostal, and through the bed of a resected rib.

Subcostal Flank Approach

This approach offers good exposure of the renal parenchyma and upper ureter. It is an advantageous approach for surgery on the lower renal pole, UPJ, and upper ureter (e.g., ureterocalicostomy, pyeloplasty, and stone surgery). Simple nephrectomy, insertion of a nephrostomy tube, and drainage of a perinephric abscess may all be accomplished through a subcostal flank incision. Because the approach is extraperitoneal, contamination of the peritoneal cavity is avoided. Access to the renal hilum and vascular pedicle is poor, which is the most salient disadvantage of this approach. The subcostal flank approach is not appropriate for radical or partial nephrectomy (Libertino, 1998). The incision may be caudal to the kidney, hampering access to the upper pole, renal pelvis, and hilum (Novick, 2007). Exposure may be further hindered by the iliac crest and subcostal nerve, the anterior division of the 12th thoracic nerve.

After induction of anesthesia, insertion of an endotracheal tube, and introduction of a Foley catheter into the urinary bladder to monitor urine output, the patient is placed in the lateral position. The head is supported to maintain proper alignment of the cervical spine. The tip of the 12th rib should be positioned over the kidney bar (Fig. 54–18). The patient's back should be nearly flush with the edge of the table to ensure unfettered access by the surgeon. To preserve stability and prevent forward roll, the dependent leg is flexed at the hip and knee and the top leg is kept straight. A pillow is placed between the knees. An axillary roll is deployed just caudal to the axilla to prevent compression or injury of the axillary neurovascular bundle. Other pressure points, including the upper foot, are padded with foam. The

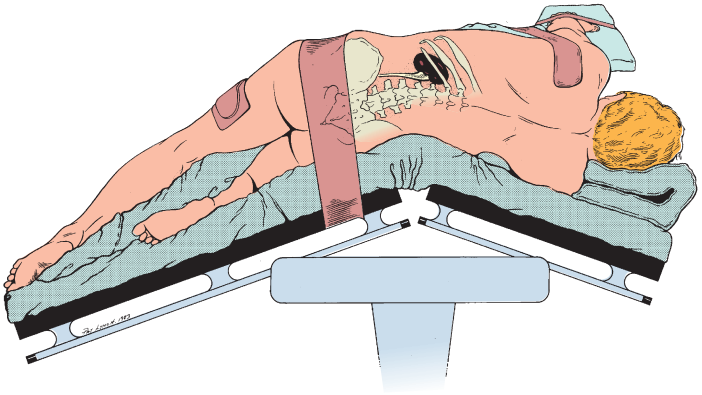


Figure 54–18. Position of the patient for the flank approach. Note the axillary pad. The kidney rest may be elevated if further lateral extension is needed.

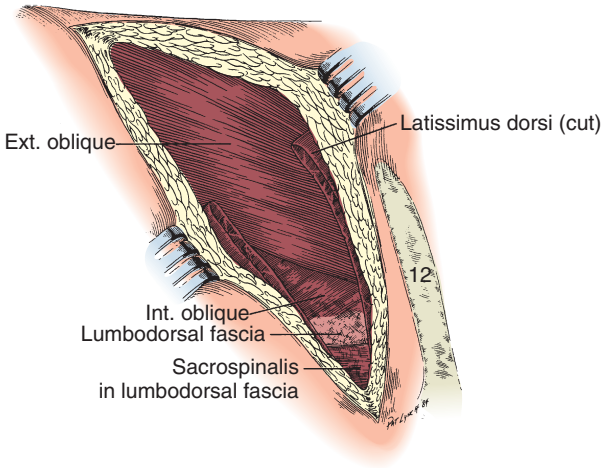


Figure 54–20. Left subcostal incision. The latissimus dorsi muscle has been divided to expose the lumbodorsal fascia and the posterior aspects of the abdominal muscles.

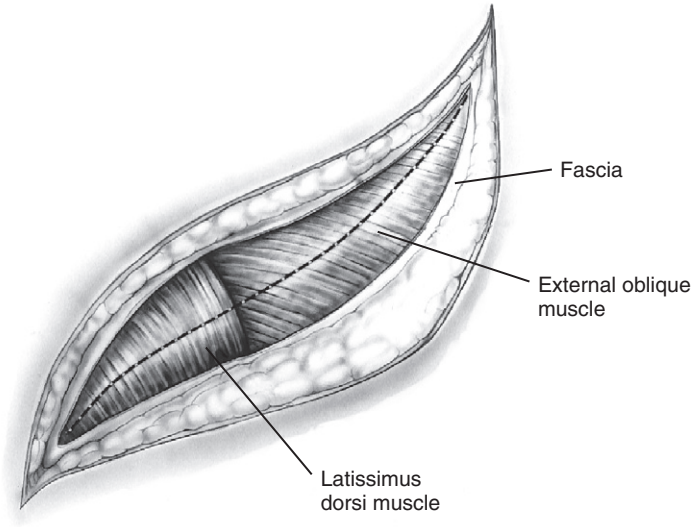


Figure 54–19. Superficial incision through flank. (From Libertino JA. Reconstructive urologic surgery. 3rd ed. Philadelphia: Mosby; 1997.)

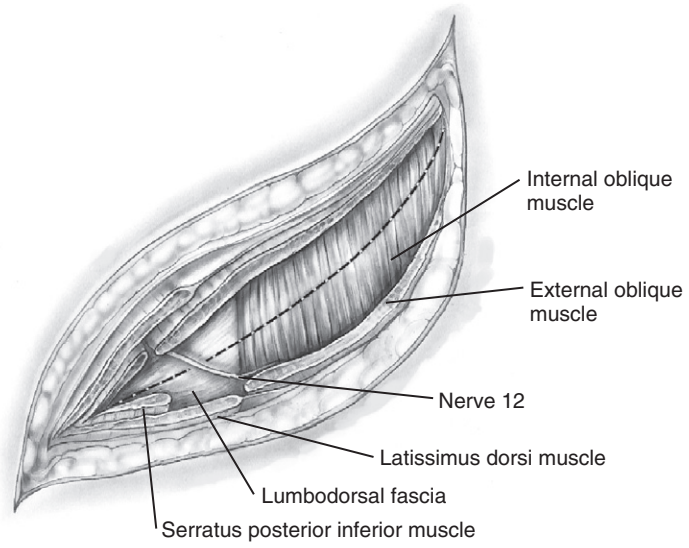


Figure 54–21. Dissection through flank muscles. (From Libertino JA. Reconstructive urologic surgery. 3rd ed. Philadelphia: Mosby; 1997.)

nondependent arm should be placed on a padded Mayo stand so that the arm is horizontal with slight forward rotation at the shoulder. The bed is flexed until the flank muscles are under stretch. A kidney bar can be employed if necessary. The bed is placed in Trendelenburg position so that the flank is rendered parallel to the floor. The patient is secured to the mobile part of operating table with 2-inch wide adhesive tape, which fixes the patient in place while allowing adjustment of flexion.

After sterile preparation and draping, the skin incision begins at the costovertebral angle, approximately at the lateral border of the sacrospinalis muscle just inferior to the 12th rib. The incision is made a fingerbreadth below and parallel to the 12th rib and is carried onto the anterior abdominal wall. In an attempt to avoid the subcostal nerve, the incision can be curved gently downward at the midaxillary line. If needed, the incision can be extended caudally or medially to the lateral border of the rectus abdominis.

The incision is carried sharply through the subcutaneous tissue, exposing the fascia of the latissimus dorsi and external oblique muscles (Fig. 54–19). Electrocautery is used to incise the muscles in the line of the incision (Fig. 54–20), starting with the latissimus dorsi posteriorly. The serratus posterior inferior muscles, which insert into the lower four ribs, are also encountered in the posterior portion of the wound and transected. In the anterior aspect of the wound the external oblique muscle is divided. These maneuvers expose the fused lumbodorsal fascia, which gives rise to the internal oblique and transversus abdominis muscles. The lumbodorsal fascia and internal oblique muscle are divided (Fig. 54–21). By using two fingers inserted into an opening created in the lumbodorsal fascia at the tip of the 12th rib, the peritoneum is swept medially as the transversus abdominis is split digitally. The subcostal nerve should be identified between the internal oblique and transversus abdominis muscles and spared (Figs. 54–22 and 54–23).

To maximize exposure in the posterior aspect of the incision, one may incise the posterior angle of the lumbodorsal fascia, exposing the sacrospinalis and quadratus lumborum muscles. Dividing the costovertebral ligament permits superior retraction of the 12th rib if enhanced exposure is deemed necessary. A

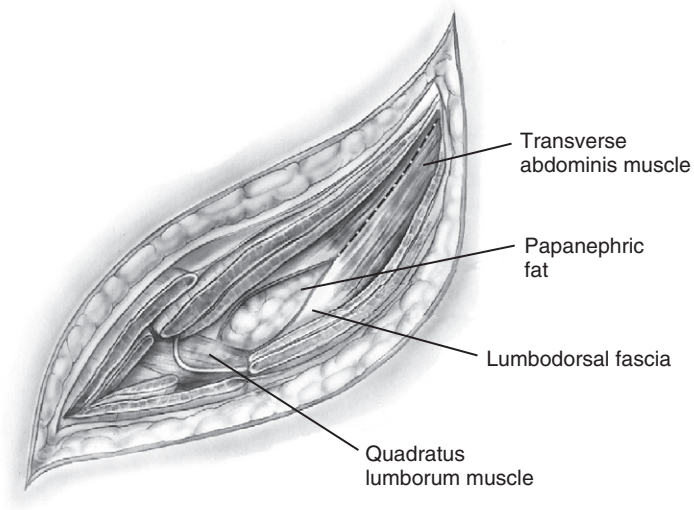


Figure 54–22. Opening lumbodorsal fascia to gain entrance to retroperitoneum. (From Libertino JA. Reconstructive urologic surgery. 3rd ed. Philadelphia: Mosby; 1997.)

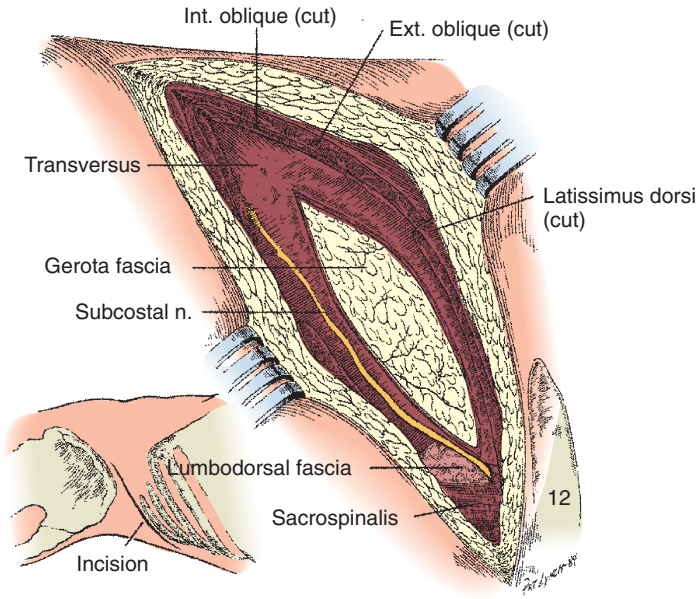


Figure 54–23. The lumbodorsal fascia and transverse muscles have been divided to expose the Gerota fascia. The subcostal nerve and vessels pierce the lumbodorsal fascia posteriorly and course forward on the transverse muscle.

Bookwalter (Codman & Shurtleff, Raynham, MA) flank retractor is used for exposure.

To facilitate wound closure, the kidney bar is lowered and the table is partially taken out of flexion. The wound is closed in layers using No. 2 Nylon. The transversus abdominis and internal oblique muscles are closed in one layer. The lumbodorsal fascia is reapproximated, followed by the external oblique, serratus posterior inferior, and latissimus dorsi muscles. The skin edges are reapproximated with staples or subcuticular 2-0 polyglactin (Vicryl). A closed drainage system or Penrose drain should be externalized through a small counterincision below the wound. After applying a sterile dressing to the wound, the authors place the Penrose drain into a collection bag designed for urinary stomas, which is secured

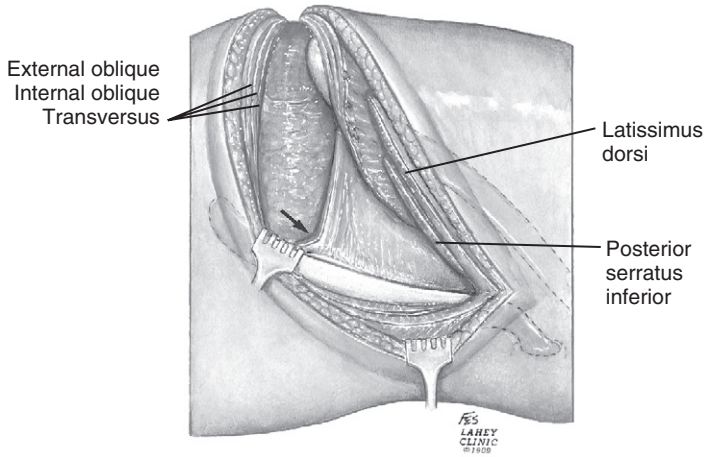


Figure 54–24. Relationship of flank musculature to supracostal area. (© The Lahey Clinic.)

to the abdominal wall. This allows drainage to be easily recorded and protects the skin from the drain output.

Supracostal Flank Approach

The supracostal flank incision is favored at the Lahey Clinic for most modest-sized renal tumors and most partial nephrectomies (Fig. 54–24). When properly executed it affords an extraperitoneal, extrapleural approach to the kidney with excellent exposure of the renal and suprarenal areas. In addition, this approach permits the 11th or 12th rib to pivot posteriorly without removing a rib. Turner-Warwick (1965), who popularized the approach, believed that the supracostal approach provides maximal posterior exposure, simplifies wound closure, and is less morbid than a transcostal incision requiring rib resection. More recently, an 8-cm modified mini-flank supra-11th rib incision has been described as a safe, effective approach to radical or partial nephrectomy for renal cortical tumors (Diblasio et al, 2006).

The level of the incision is determined by the patient's anatomy, location of the lesion, and the operation planned. For partial nephrectomy the level of incision is determined by the position of the kidney in relation to the ribs as seen on preoperative radiographic studies and by the location and size of the tumor.

The patient is positioned as described for the subcostal flank incision. A skin incision at the superior aspect of the 12th or 11th rib is made, beginning at the lateral border of the sacrospinalis muscle and continuing until the lateral border of the ipsilateral rectus abdominis muscle. The incision is carried sharply through the subcutaneous tissue. The latissimus dorsi and serratus posterior inferior muscles are transected in the posterior aspect of the wound, revealing the intercostal muscles.

The external and internal oblique muscles are divided. The lumbodorsal fascia is opened at the tip of the rib to avoid both peritoneum and pleura. Moving medially, the transversus abdominis muscle is divided carefully while sweeping the peritoneum medially and inferiorly. The diaphragm is exposed by transection of the transversalis muscle. The pleura is identified between the divided transverses abdominis muscle and the diaphragm and can be mobilized superiorly.

The lateral aspect of the sacrospinalis is identified and is either incised or retracted to permit access to the neck of the rib and its attachments. Division of the intercostal muscles should start at the most distal aspect of the rib and proceed toward the spine.

The corresponding intercostal nerve is identified and spared. To avoid the neurovascular bundle the intercostal muscles are divided in close proximity to the superior aspect of the rib. The plane between the chest wall and pleura is developed by entering the investing fascia surrounding the intercostal nerve, which allows an extrapleural dissection (Fig. 54–25). The slips of the diaphragm attached to the inferior ribs are transected. Proceeding posteriorly, the intercostal or transverse costal ligament is divided, which permits free movement of the 12th rib (supra 12th) or the 11th and 12th rib (supra 11th).

Proper closure restores separation between the thoracic and abdominal cavities. At time of closure, local anesthetic can be used to perform an intercostal nerve block under direct vision. As described by Turner-Warwick (1965), the detached diaphragm is externalized through the intercostal space and sutured to the free edge of the intercostal muscles and to the inferior cut edge of the serratus posterior inferior muscle. The edges of the transected latissimus dorsi muscle are reapproximated while incorporating the upper margin of the serratus posterior inferior muscle. A drain is externalized through a separate stab incision.

Over time, the senior author has modified the closure of the supracostal incision. The diaphragm is closed primarily and not externalized. A rib punch is used to create a hole in the rib above and below the incision. A No. 2 Nylon suture, which is passed through the ribs and the diaphragm, is used to restore integrity of the chest wall. The latissimus dorsi, serratus posterior inferior, and intercostal muscles are closed in a single layer.

Transcostal Flank Approach

The classic flank approach involves resection of the 11th or 12th rib and entrance into the retroperitoneum through the bed of the resected rib (Hess, 1939; Hughes, 1949; Bodner and Briskin, 1950). It provides similar exposure to the supracostal incision but is a more complicated and more morbid incision. This transcostal approach fell out of favor at the Lahey Clinic decades ago with the advent of the supracostal approach.

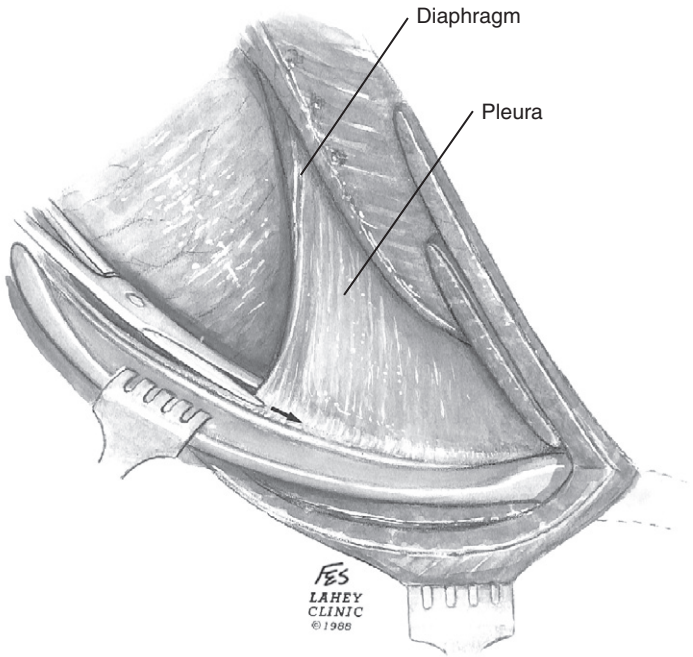


Figure 54–25. Following the intercostal nerve to remain extrapleural back to the intercostal ligament. (© The Lahey Clinic.)

The site of incision is determined by the position of the kidney and the location of disease. Typically, for a lower pole tumor a supra-12th rib incision is adequate. For mid and upper pole tumors, a supra-11th incision is often satisfactory. On a urogram a horizontal line that traverses the hilum of the kidney will intersect with the rib that should be resected. In cases requiring upper pole access the surgeon should approach the kidney through the rib above the one indicated by the horizontal line transversing the hilum.

The patient is placed in the flank position. A trans-12th rib approach will be described. The skin is incised directly over the 12th rib from the lateral border of the sacrospinalis muscle and continuing until the lateral border of the ipsilateral rectus abdominis muscle. The latissimus dorsi, serratus posterior inferior, and external oblique muscles are divided with electrocautery over the center of the 12th rib, exposing the periosteum. The periosteum is incised with a knife. A periosteal elevator is employed to separate the rib from its periosteum. One must be vigilant to preserve the neurovascular bundle.

The exposed rib is resected with a rib cutter as posterior as possible. Rongeurs help remove additional rib and sharp fragments. Bone wax is used to obtain hemostasis and a smooth surface. The anterior attachments of the rib are divided, permitting the rib to be excised.

One enters the retroperitoneum by incising the posterior layer of periosteum at the tip of the rib. As the incision is extended laterally along the length of the rib bed, a finger is used to sweep away the pleura and peritoneum. The internal oblique is divided with cautery. Proceeding anteriorly, the transversus abdominis is then split with fingers. As in other flank approaches, effort should be made to preserve the 12th nerve coursing between the internal oblique and transverse muscles. The pleura is sharply separated from the fascia under the 11th rib above. The diaphragmatic attachments to the thoracoabdominal wall are divided. With sharp dissection the peritoneum is released from the transverse fascia to improve exposure.

In cases of 11th rib resection, the pleural reflection will be in the posterior aspect of the wound atop the diaphragm. One can mobilize the pleura superiorly by dividing its attachments to the diaphragm, or the two can be mobilized together by dividing the diaphragm.

To close the wound, the kidney rest is lowered and flexion is partially reduced. The incision is closed in layers. If an inadvertent pleural tear was created, an 8-Fr "dart" chest drain (Arrow International, Reading, PA) is placed and the pleural defect is closed using 2-0 silk. Infiltration of local anesthetic into the fascia around the intercostal nerves is helpful for analgesia. Drains are brought out through a separate stab incision.

Thoracoabdominal Approach

The thoracoabdominal approach (Fig. 54–26) is used for the management of large renal masses, suprarenal or upper pole masses, renal tumors with venous extension, as well as tumors involving adjacent structures (Mortensen, 1948; Chute et al, 1949; Cooper et al, 2002). The incision provides maximal suprarenal exposure. It is particularly useful on the right side, where the liver and hepatic veins impede exposure and make control of the renal pedicle difficult. This transpleural incision may be associated with additional pulmonary morbidity compared with the other flank or anterior approaches (Novick, 2007), but the incision permits

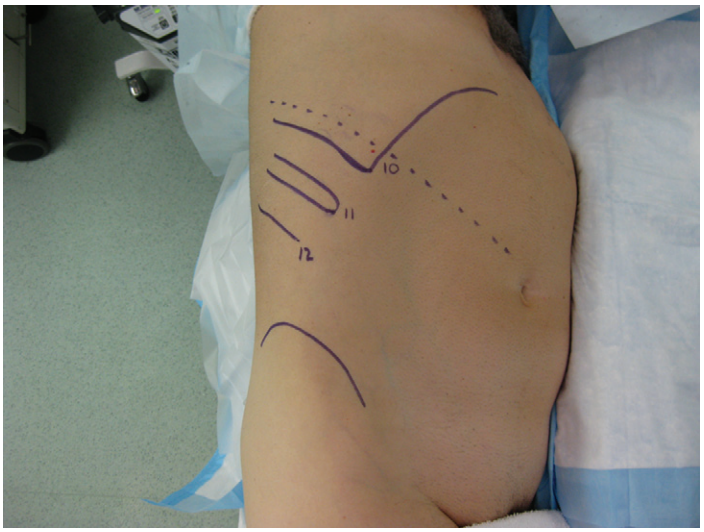


Figure 54–26. Thoracoabdominal incision at the supra-tenth border with patient in lateral decubitus position.

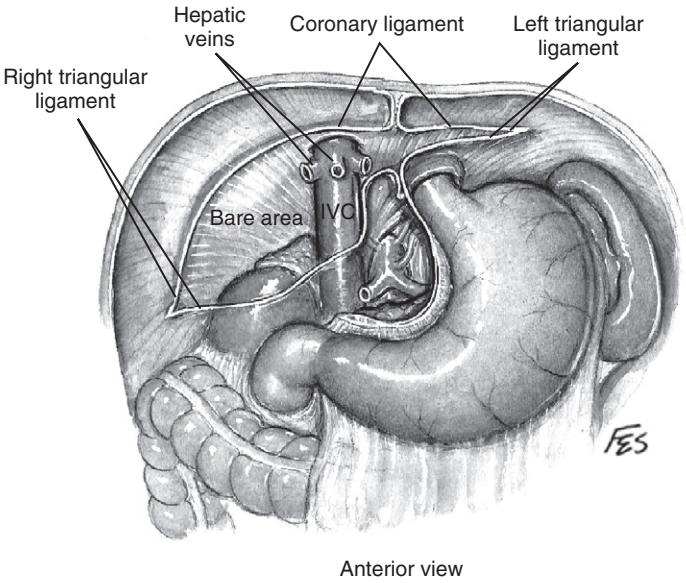


Figure 54–27. Relationship of liver and triangular and coronary ligaments to vena cava. IVC, inferior vena cava. (© The Lahey Clinic.)

resection of very large tumors, including those that involve adjacent structures (Buse et al, 2006). The phrenic nerve may be injured in this approach, compromising diaphragmatic function.

For this approach the flank position is modified to permit access to the anterior abdominal wall. The patient is positioned in a semi-oblique manner with a rolled blanket or beanbag supporting the flank. The legs are positioned similar to the traditional flank position. The pelvis is rotated in a more horizontal position than in the flank incisions, at an angle of approximately 75 degrees rather than 90 degrees from level.

The level of the incision is determined by the nature of the tumor, including size and relationship to surrounding structures such as the liver. In the experience of the senior author, approaching through the 9th or 10th interspace provides sufficient exposure in the majority of cases. For particularly large tumors or those involving the liver, an incision through the 8th interspace may be required. Dividing the intercostal ligament is an essential maneuver to obtain good exposure.

The skin incision begins at the lateral aspect of the sacrospinalis muscle over the 10th or 11th rib and travels obliquely across the anterior abdominal wall to the midpoint of the contralateral rectus abdominis muscle above the umbilicus. Alternatively, the incision can be carried caudally toward the symphysis pubis. The subcutaneous tissues are divided with cautery.

In patients with involvement of the IVC the abdominal portion of the wound should be opened first to permit exploration for evidence of metastatic disease. Otherwise, the chest and abdomen can be opened in the order of preference of the surgeon. The rectus abdominis, external oblique, latissimus dorsi, and serratus inferior posterior muscles are divided. The internal oblique and transversus abdominis muscles are transected. The underlying peritoneum is opened, and the peritoneal cavity is explored.

The chest is entered. The costal cartilage is transected. While staying close to the superior border of the rib, the intercostal muscles are divided. This exposes the underlying pleura and diaphragm. The pleura is opened sharply, taking care to avoid the lung. The costovertebral ligament is divided. The diaphragm is opened from its thoracic surface. Starting anteriorly and proceeding posteriorly, the diaphragm is opened in a curvilinear fashion staying about two fingerbreadths from the chest wall to avoid injuring the more central phrenic nerve.

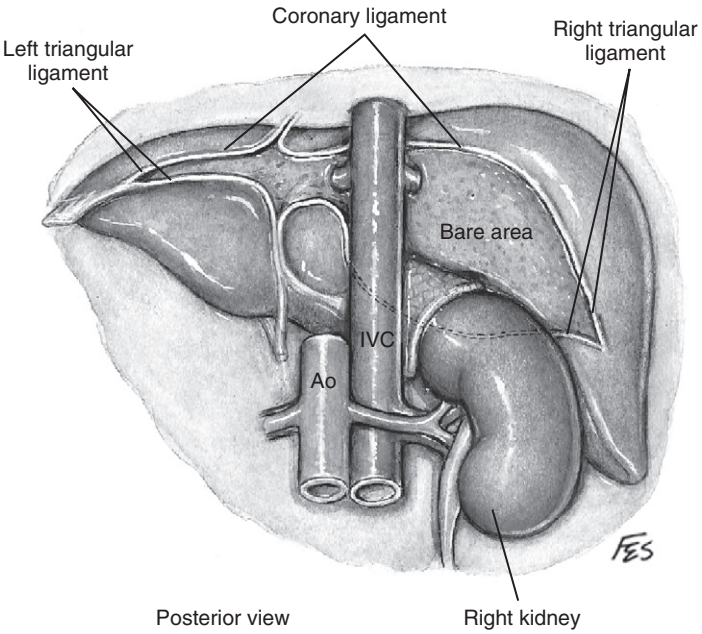


Figure 54–28. Posterior view of relationship of liver and triangular and coronary ligaments to vena cava. IVC, inferior vena cava; Ao, aorta. (© The Lahey Clinic.)

The liver or spleen is gently retracted upward. Additional hepatic mobility can be obtained by dividing the coronary ligament and the right triangular ligament of the liver (Figs. 54–27 and 54–28). For right-sided tumors, the kidney and great vessels are approached by mobilizing the colon medially and kocherizing the duodenum (Fig. 54–29). For tumors on the left, the colon and the tail of the pancreas are mobilized, providing excellent exposure of the renal pedicle.

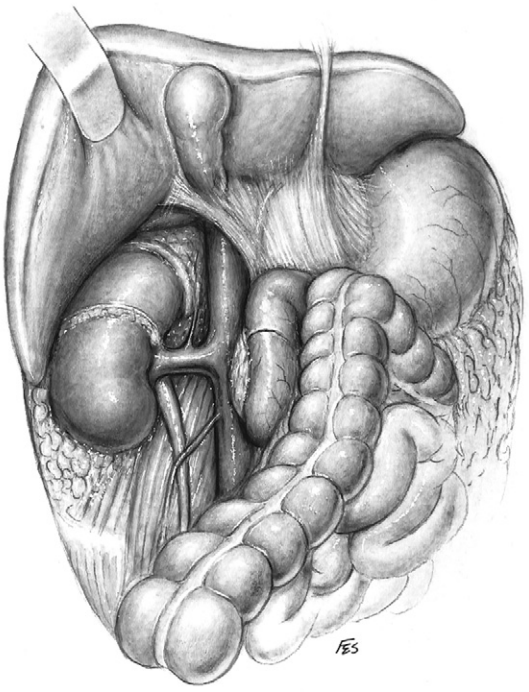


Figure 54–29. Access to vena cava by Langenbeck maneuver. (© The Lahey Clinic.)

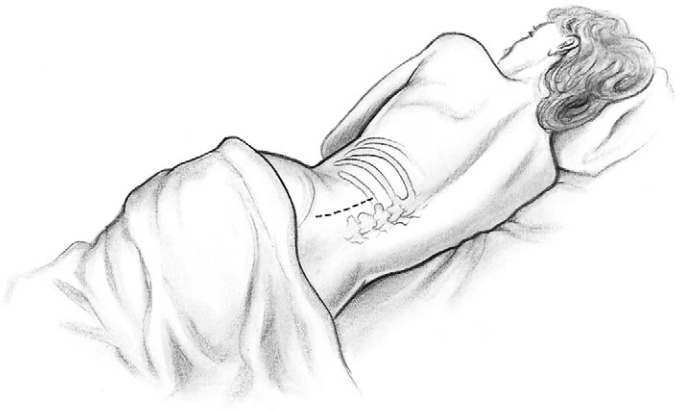


Figure 54–32. Lateral decubitus position for lumbodorsal approach. (© The Lahey Clinic.)

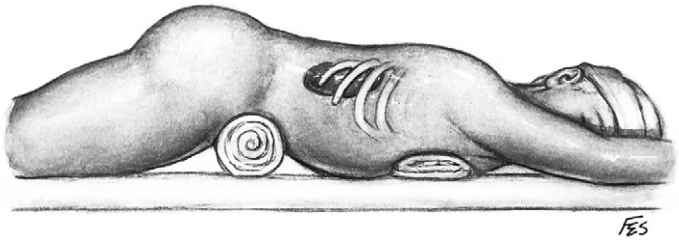


Figure 54–33. Prone position for lumbodorsal approach. (© The Lahey Clinic.)

After the procedure the posterior peritoneum is closed with running 2-0 polyglactin. The continuity of the diaphragm is restored with 2-0 silk, with the knots tied on the abdominal surface. When necessary the diaphragm can be repaired with a polytetrafluoroethylene (PTFE) patch (W. L. Gore and Associates, Medical Products Division, Flagstaff, AZ). The integrity of the rib cage is restored by reapproximating the costal arch with No. 2 Nylon. An 8-Fr "dart" chest drain is placed and attached to a Pleur-Evac drainage system (Teleflex, Research Triangle Park, NC). The pleura and intercostal muscles are reapproximated using 2-0 polyglactin, taking care to incorporate the diaphragm toward the medial surface. The anterior peritoneum is closed with 2-0 polyglactin. The abdominal wall muscles and rectus sheaths are reapproximated with 1-0 polydioxanone (PDS). The subcutaneous tissue is brought together with 3-0 plain suture. Staples are used to close the skin. A Penrose drain is externalized through a separate stab incision.

Dorsal Lumbotomy

The lumbodorsal approach is useful for simple nephrectomy for a small atrophic kidney, simultaneous bilateral simple nephrectomies, renal biopsy, pyeloplasty, pyelolithotomy and upper ureterolithotomy, and other procedures on the renal pelvis or upper ureter (Andaloro and Lilien, 1975; Gardiner et al, 1979; Novick, 1980) (see Figs. 54–30 and 54–31 on the Expert Consult website). The incision is particularly advantageous in patients with extensive prior abdominal or flank operations because it avoids dissection in scarred or adhesed planes. Because muscles are retracted rather than transected, patients benefit from less pain and a strong closure (Gil-Vernet, 1964; Gardiner et al, 1979). Postoperative flank bulges are less common than with the flank approaches. Rib resection is not necessary because exposure is adequate with division of the costovertebral ligament and rib retraction (Gardiner et al, 1979; Novick, 2007). The lumbodorsal approach is appropriate neither for large kidneys nor for those that are superiorly displaced. The incision provides limited exposure of the ureter and is thus not ideal for operations requiring dissection beyond the upper ureter. The lumbodorsal approach allows marginal access to the renal hilum that may adversely impact control of the renal vasculature. This is the most significant shortcoming of the approach.

For a unilateral procedure the patient is placed in the lateral decubitus position with the table minimally flexed (Fig. 54–32). In the case of a bilateral procedure the patient is placed prone with the table partially flexed to broaden the distance between the iliac crest and 12th rib (Fig. 54–33). Supports under the sternum and pubis permit movement of the anterior abdominal wall with respiration.

The dorsal lumbotomy is an anatomic approach to the kidney, with incision of fascial planes rather than muscle (see Fig. 54–3). A vertical skin incision is made from the inferior border of the 12th rib to the iliac crest, in line with the lateral border of the sacrospinalis muscle. The subcutaneous tissues are divided, exposing the latissimus dorsi muscle. The aponeurosis of the latissimus dorsi is separated from the posterior layer of the lumbodorsal fascia where it overlies the sacrospinalis muscle. The posterior layer of the lumbodorsal fascia, a strong fascial covering, is incised, which allows the sacrospinalis muscle to be retracted medially. The costovertebral ligament is divided, which permits superolateral retraction of the 12th rib, which improves access superiorly. The fused middle and anterior layers of the lumbodorsal fascia are divided, permitting the quadratus lumborum muscle to be

retracted medially (Fig. 54–34). The ilioinguinal nerve should be identified and spared. Entry into the paranephric space is achieved by incising the transversalis fascia. Division of the perinephric fascia reveals the kidney.

The incision is closed by returning the muscles to anatomic position and by reapproximating the lumbodorsal fascia. Some advocate closure of the lumbodorsal fascia in two layers, although reapproximation of the fascia overlying the sacrospinalis muscle as a single layer may be adequate (Menon, 1998). A drain should be externalized.

Anterior Approaches

The anterior incisions can be used for either transperitoneal or extraperitoneal access to the kidney (Fig. 54–35). The transperitoneal anterior approaches offer good access to the renal pedicle at the expense of a longer postoperative ileus and risk of future small bowel obstruction due to intra-abdominal adhesions. Seprafilm (Genzyme Corporation, Cambridge, MA), a sodium hyaluronate and carboxymethylcellulose membrane, can be used to decrease the risk of adhesions. The extraperitoneal anterior approaches provide inferior exposure and are of limited utility.

Anterior Midline

An anterior midline incision is the incision of choice for management of renal trauma because it permits exploration for associated intraperitoneal injuries. It can also be employed for renovascular surgery, reconstructive procedures including ileal ureteral replacement, and bilateral renal procedures.

With the patient in the supine position, a midline skin incision is made from the xiphoid process to the symphysis pubis, curving around the umbilicus. After dividing the subcutaneous tissues with electrocautery, the linea alba is sharply incised to expose the underlying preperitoneal fat and peritoneum. The peritoneum is grasped with two smooth forceps and elevated to reduce risk of bowel injury. The peritoneum is sharply opened between the two forceps. A finger is inserted into the peritoneal cavity and is used to tent the peritoneum away from bowel as the incision is extended with scissors. The ligamentum teres should be divided and suture ligated.

Control of the renal pedicle can be obtained directly through the posterior parietal peritoneum or by medial reflection of the colon. On the left, the approach involves a vertical incision in the posterior peritoneum below the ligament of Treitz. This space contains the anterior surface of the aorta, the crossing left renal vein, and often the inferior mesenteric vein and gonadal vessels. The superior mesenteric artery should be on the anterior surface of the aorta and is usually 1 to 2 cm cephalad to the left renal vein. Gentle dissection along the hilum at this level provides good vascular control. A second approach to the left renal hilum is through the lesser sac. In this approach, the gastrocolic omentum is divided and entered. The transverse colon can then be retracted inferiorly. The peritoneum below the pancreas can be incised. The vessels are identified (Fig. 54–36). It is the authors' preference to incise the colon along the white line of Toldt and reflect the colon anteromedially. This permits access to the renal pedicle both anteriorly and posteriorly. The artery can be isolated posteriorly and the venous system identified and controlled anteriorly.

Similarly, the right kidney can be reached directly by incision of the hepatic flexure and a Kocher maneuver to free the duodenum and reflect it medially. Further incision along the white line of Toldt frees the colon, permitting exposure of the anterior Gerota fascia. After the duodenum is reflected, the anterior surface of the vena cava is exposed. Care is taken not to injure the pancreas, gonadal vein, adrenal vein, or accessory renal vessels. The main renal vein is mobilized. Posterior to the renal vein along its superior margin lies the renal artery (Fig. 54–37), which normally runs a retrocaval course. The renal artery can be isolated here or between the vena cava and aorta when greater length is required.

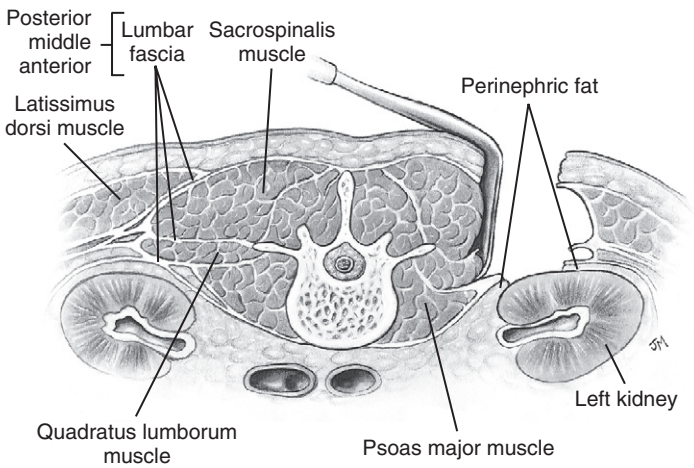


Figure 54–34. Cross-sectional view of Gil-Vernet approach. (From Libertino JA. Reconstructive urologic surgery. 3rd ed. Philadelphia: Mosby; 1997.)

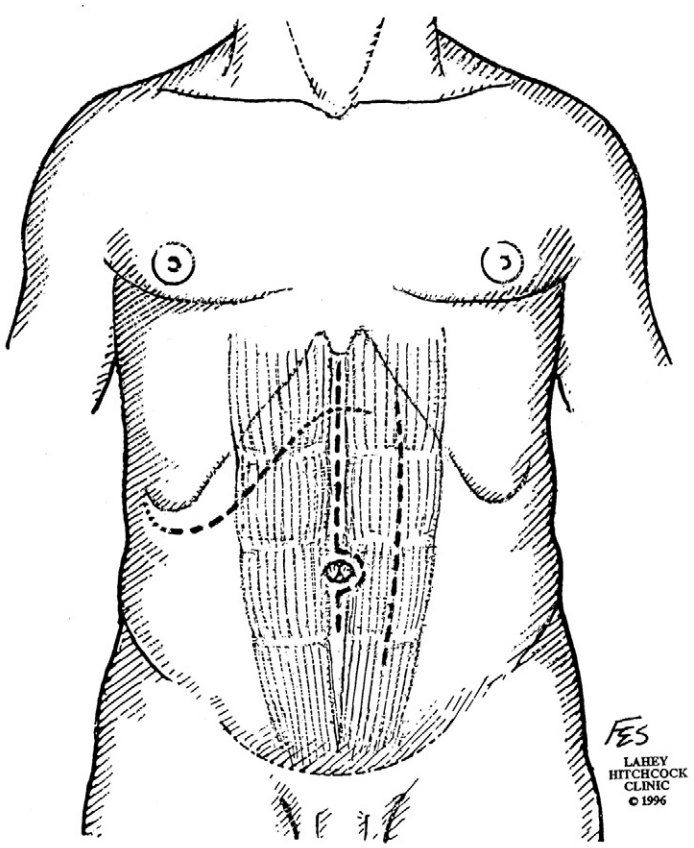


Figure 54–35. Three anterior approaches to renal surgery. (© The Lahey Clinic.)

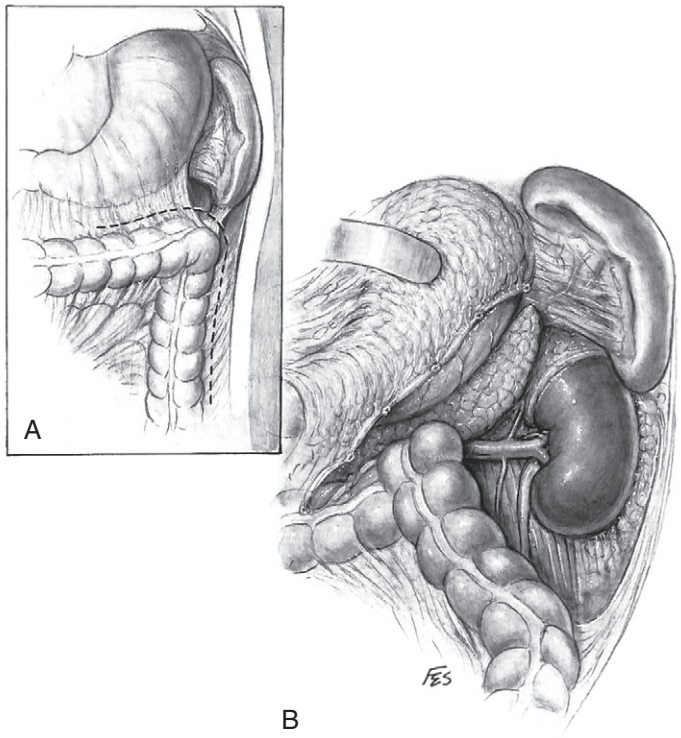


Figure 54–36. **A,** Left gastrocolic, phrenocolic, and lateral peritoneal attachments are divided. **B,** Stomach, pancreas, and spleen are gently retracted upward without mobilizing kidney. (© The Lahey Clinic.)

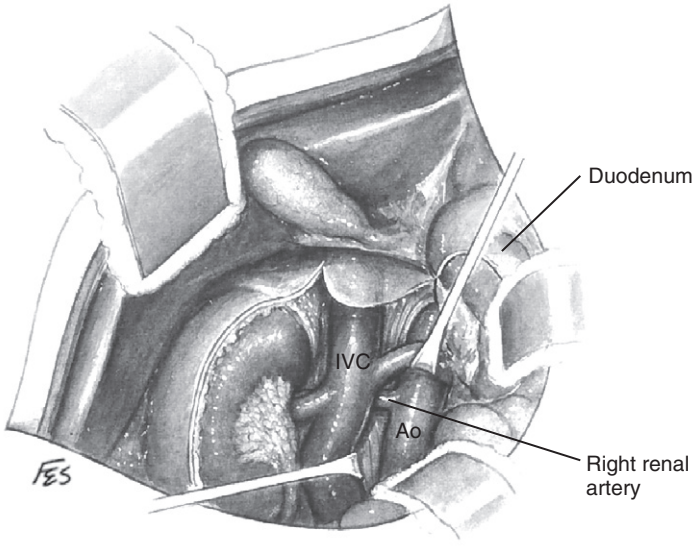


Figure 54–37. Exposure of right renal artery behind overlying left renal vein. IVC, inferior vena cava; Ao, aorta. (© The Lahey Clinic.)

After the procedure is complete, the peritoneum is closed with 2-0 polyglactin. The fascia is closed with polypropylene (Prolene) or polydioxanone. After bringing the subcutaneous tissues together with 3-0 plain sutures, the skin edges are reapproximated with staples or subcuticular 2-0 polyglactin. A Penrose drain is externalized through a separate stab incision.

Anterior Paramedian

The paramedian approach, which is a straightforward incision with a strong closure, is occasionally employed but provides limited exposure to the kidney. A paramedian skin incision is made approximately 3 cm lateral to the midline. The subcutaneous tissues are divided with electrocautery. The anterior rectus sheath is divided. By sharply transecting the transverse tendinous intersections, one is able to reflect the belly of the muscle medially. The posterior rectus sheath and transversalis fascia are then divided in the line of the incision.

By developing the plane between the peritoneum and transversalis fascia from diaphragm to iliac crest, one can make an extraperitoneal approach to the kidney, although this offers marginal renal access (Tessler et al, 1975). Alternatively, the peritoneum is opened and the kidney is approached as described earlier.

The peritoneum is closed with 2-0 polyglactin. The fascia is closed with polypropylene or polydioxanone. After bringing the subcutaneous tissues together with 3-0 plain sutures, the skin edges are reapproximated with staples or subcuticular 2-0 polyglactin. A Penrose drain is externalized through a separate stab incision.

Anterior Subcostal

The transperitoneal anterior subcostal incision can be employed for both radical and partial nephrectomy, especially for upper pole tumors. With extension of the incision to the lateral border of the contralateral rectus abdominis muscle, the transperitoneal anterior subcostal approach can be used for renovascular surgery. The extraperitoneal subcostal incision has limited utility in adults owing to marginal access to the renal pedicle. It is rarely employed.

The patient is placed in the supine position. The skin is incised from the tip of the 11th rib to the contralateral rectus abdominis muscle, starting two fingerbreadths below the costal margin. The subcutaneous tissues are divided with electrocautery, exposing the external oblique muscle laterally and the rectus sheath medially. After dividing fibers of the latissimus dorsi muscle in the lateral aspect of the wound, the external oblique muscle is transected. The anterior rectus sheath is opened, and the rectus abdominis muscle is retracted medially or divided. The internal oblique muscle, transversus abdominis muscle, posterior layer of the rectus sheath, and the transversalis fascia are divided. This exposes the underlying peritoneum.

For the extraperitoneal approach the peritoneum is reflected from the transversalis fascia using blunt dissection. The retroperitoneal space is entered laterally while retracting the peritoneum and its contents medially. In the more commonly employed transperitoneal approach the peritoneum is opened. The ligamentum teres is encountered in the midline, divided, and suture ligated. The kidneys are approached as described earlier.

The peritoneum is closed with 2-0 polyglactin. The fascia is closed with 1-0 polydioxanone. After bringing the subcutaneous tissues together with 3-0 plain sutures, the skin edges are reapproximated with staples or subcuticular 2-0 polyglactin. A Penrose drain is externalized through a separate stab incision.

Chevron Incision (Bilateral Subcostal Approach)

The chevron incision, essentially a bilateral anterior subcostal approach, is advantageous for renovascular surgery and radical nephrectomy with IVC tumor thrombectomy. Exposure of the renal pedicles and great vessels is outstanding. The incision starts at the tip of the 11th rib, extends approximately two fingerbreadths below and parallel to the costal margin, curves superiorly

in the midline, travels parallel to the contralateral costal margin, and terminates at the tip of the contralateral 11th rib.

After dividing the subcutaneous tissues with electrocautery, the latissimus dorsi muscle, external oblique muscle, anterior rectus sheath, rectus abdominis muscle, internal oblique muscle, transversus abdominis muscle, posterior rectus sheath, and transversalis fascia are divided. The peritoneum is opened, dividing the ligamentum teres as described previously.

The peritoneum is closed with 2-0 polyglactin. The fascia is closed with 1-0 polydioxanone or 2-0 nylon. After bringing the subcutaneous tissues together with 3-0 plain sutures, the skin edges are reapproximated with staples or subcuticular 2-0 polyglactin. A Penrose drain is externalized through a separate stab incision.

Key Points: Surgical Approaches

- Good functional exposure permits the surgeon to perform the planned procedure, diminishes risk of injury to surrounding structures, and permits definitive treatment of an intraoperative complication, such as injury to a great vessel.
- The ideal surgical approach is one that is tailored not only to the operation being performed but also to the anatomy as defined on preoperative imaging, previous surgical history, body habitus, and presence of limiting factors such as kyphoscoliosis or pulmonary disease.
- The salient features of the surgical approaches to the kidney are summarized in Table 54–8.

SURGERY FOR BENIGN DISEASE

Simple Nephrectomy

Indications

Simple nephrectomy, removal of the kidney within the Gerota fascia, is employed to manage nonmalignant diseases of the kidney. Indications for simple nephrectomy include durable nonfunction or poor function of a kidney due to obstruction, infection, trauma, stones, nephrosclerosis, vesicoureteral reflux, polycystic kidney, or congenital dysplasia. Nephrectomy is undertaken when reconstructive procedures have failed or are contraindicated due to poor function of the renal unit, advanced age, or significant comorbidity. Simple nephrectomy of a functional kidney may be employed to relieve intractable symptoms or associated problems, such as bleeding, pain, hypertension, or persistent infection. Simple nephrectomy is an accepted treatment for renovascular hypertension that is refractory to other organ-sparing therapies.

Preoperative Evaluation and Preparation

In addition to a genitourinary history, one must ascertain the patient's full medical history, with a special focus on cardiovascular, pulmonary, and surgical history. Factors influencing choice of incision should be elucidated on history and examination, including body habitus and sites of prior abdominal or flank operations. One must be cognizant of a patient's renal status and the anticipated function that will remain after surgery. Estimation of global renal function as previously described is essential. Determination of differential renal function by radionuclide scan is advisable, particularly if renal dysfunction or abnormal split function is suspected.

Techniques

Simple nephrectomy can be performed through the flank and anterior abdominal approaches as described earlier. The approach can be either extraperitoneal or transperitoneal. Removal of atrophic kidneys with end-stage disease can also be accomplished through a dorsal lumbotomy incision (Andaloro and Lilien, 1975; Novick, 1980). **For all approaches the key steps of a simple nephrectomy are the approach, mobilization of the kidney, division of the artery followed by the vein, division of the ureter, removal of the kidney, and closure.**

Standard Flank Approach. A flank approach (Fig. 54–38) is preferable in patients with multiple prior anterior abdominal operations and in obese patients. An extraperitoneal approach is preferred in patients with an infected renal unit or numerous prior transperitoneal procedures. The kidney can be approached extraperitoneally through the subcostal route, although consideration should be given to a supracostal approach depending on the patient's anatomy.

The perinephric space is entered. To avoid inadvertent entry into the peritoneum a vertical incision is made in Gerota fascia on the lateral aspect of the kidney, revealing the underlying perinephric fat. The kidney is mobilized sharply by developing a plane between the renal capsule and the perinephric fat. If there have been numerous episodes of pyelonephritis or prior renal operations, developing this plane can be challenging. Inadvertent entrance into the renal capsule should be avoided. When developing the plane at the lower pole the ureter is identified but not yet ligated. Downward traction on the kidney permits the upper pole to be mobilized. The adrenal gland is left in position.

With the use of lateral traction on the kidney to expose the hilum, the vascular pedicle is dissected free from surrounding fat and lymphatics. The renal hilum can be approached either anteriorly or posteriorly. In the anterior approach, gonadal, adrenal, and lumbar branches draining into the left renal vein are ligated and divided. The mobilized renal vein is retracted to reveal the renal artery located posteriorly (see Figs. 54–8 and 54–39). The left renal artery should be differentiated from the superior mesenteric artery by ensuring that the renal artery emanates from the lateral aspect of the aorta and by palpating the superior mesenteric artery before ligating the renal artery. The renal artery is ligated away from the hilum using two medium vascular Hem-o-Lok clips on the stump side and a 2-0 silk tie on the specimen side. The artery is divided proximal to the silk tie. The arterial stump is then suture ligated with 2-0 silk. After division of the renal artery, the renal vein is similarly ligated and divided. In the posterior approach the artery is encountered before the renal vein and is ligated and divided before mobilization of the vein. The ureter is doubly clamped and divided. The specimen is removed. The distal aspect of the transected ureter is suture ligated with 2-0 polyglactin.

Ideally, the renal artery and vein are ligated individually as described previously, because taking the vessels en bloc may increase risk of arteriovenous fistula (Lacombe, 1985; Okamoto et al, 2001). In cases complicated by severe fibrosis and scarring, one may not be able to safely control the vessels individually, in which case en-bloc ligation and division may be necessary. A drain is brought out through a separate stab incision.

Subcapsular. In patients with a history of significant renal infection or prior renal surgery, severe inflammation and scarring may obliterate the usual tissue planes within the Gerota fascia, rendering mobilization of the kidney unsafe and inefficient. In these

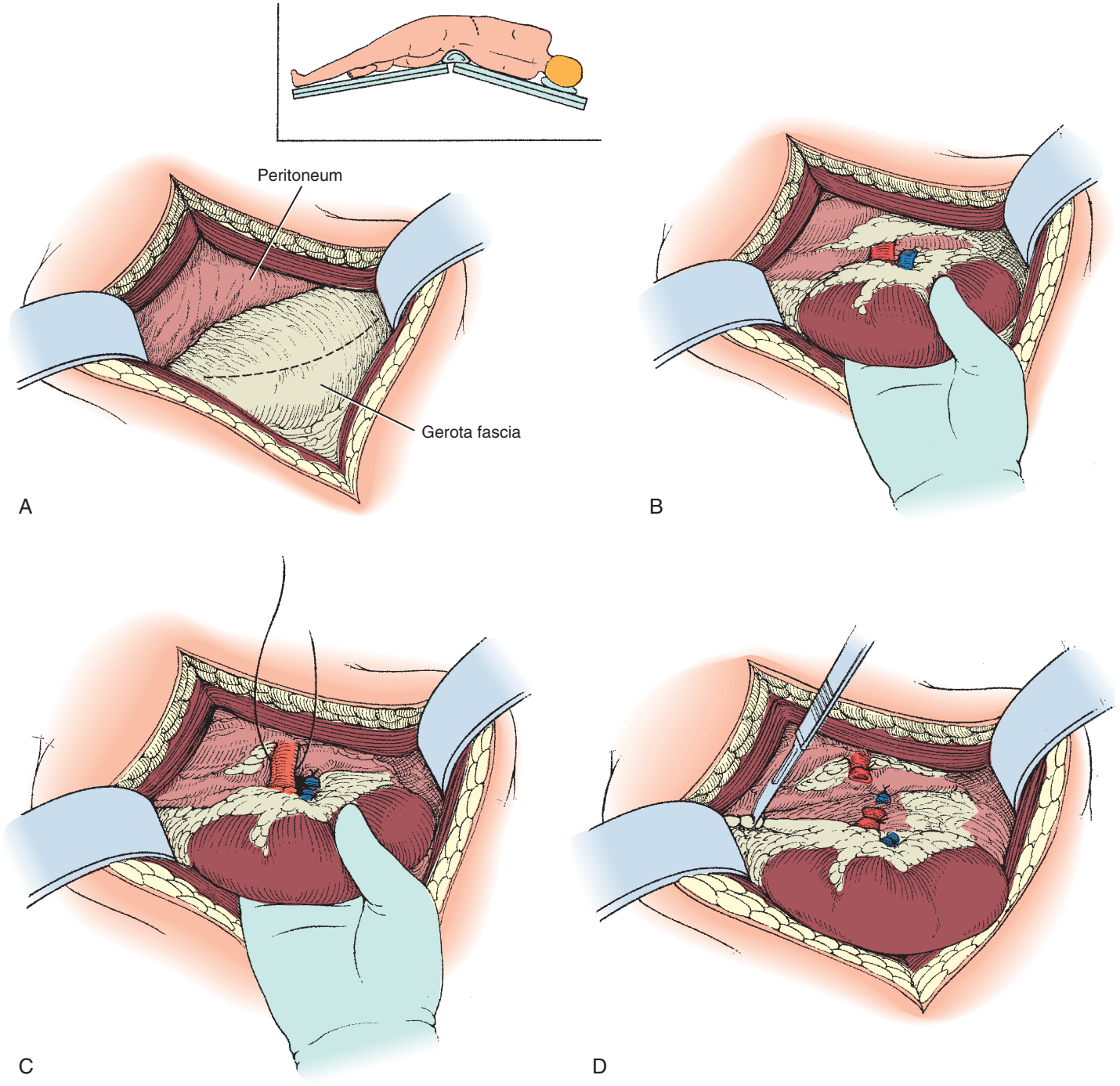


Figure 54–38. **A** to **D,** Technique of simple left nephrectomy through an extraperitoneal flank incision.

cases a subcapsular nephrectomy is indicated (Kimbrough and Morse, 1953; Kittredge and Fridge, 1958) (Fig. 54–40).

Subcapsular nephrectomy can be an arduous procedure. In patients who had prior renal surgery, care should be taken in entering the retroperitoneal space because the perirenal fat may be attenuated and the parenchyma can be unintentionally incised when opening the transversalis fascia. After entry into retroperitoneal space and determination that scarring precludes traditional simple nephrectomy, the renal capsule is incised longitudinally over the convex surface of the kidney.

Holding sutures of 2-0 polyglactin or Allis clamps are placed on the anterior aspect of the renal capsule for traction. While gently pulling on the anterior edge of the renal capsule and proceeding toward the hilum, sharp dissection is used to free the capsule from the underlying parenchyma. When the capsular flap has been raised adequately to expose the hilum, the parenchyma of the kidney is retracted laterally to expose the renal vessels. The artery and vein are ligated and divided in succession. The ureter is ligated and divided. The kidney is removed. Any devascularized perirenal tissue is excised. A drain is essential.

Transperitoneal Anterior Abdominal Approach. A transperitoneal anterior abdominal approach is used to perform simple nephrectomy in patients with renal trauma, flank scarring from prior operations, for bilateral nephrectomies, and in patients who are

unable to tolerate the flank position. After making a transperitoneal midline incision or anterior subcostal incision, the Gerota fascia and the renal hilum are approached as described earlier. A Bookwalter retractor is employed. The Gerota fascia is entered medially and the hilum secured before mobilizing the kidney. On the left, retraction of the left renal vein inferiorly exposes the left renal artery, which is then ligated with 2-0 silk (see Fig. 54–39). For right nephrectomy, the right renal artery is ligated between the aorta and IVC (see Fig. 54–8). After securing the artery the renal vein is ligated and divided. After ligating the renal artery a second time, it is divided. The kidney is then mobilized within the Gerota fascia, the ureter is ligated and divided, and the specimen is removed. A drain is brought out through a separate stab incision.

Key Points: Simple Nephrectomy

- Simple nephrectomy, removal of the kidney within the Gerota fascia, is employed to manage nonmalignant diseases of the kidney.
- For all approaches the key steps of a simple nephrectomy are the approach, mobilization of the kidney, division of the artery followed by the vein, division of the ureter, removal of the kidney, and closure.

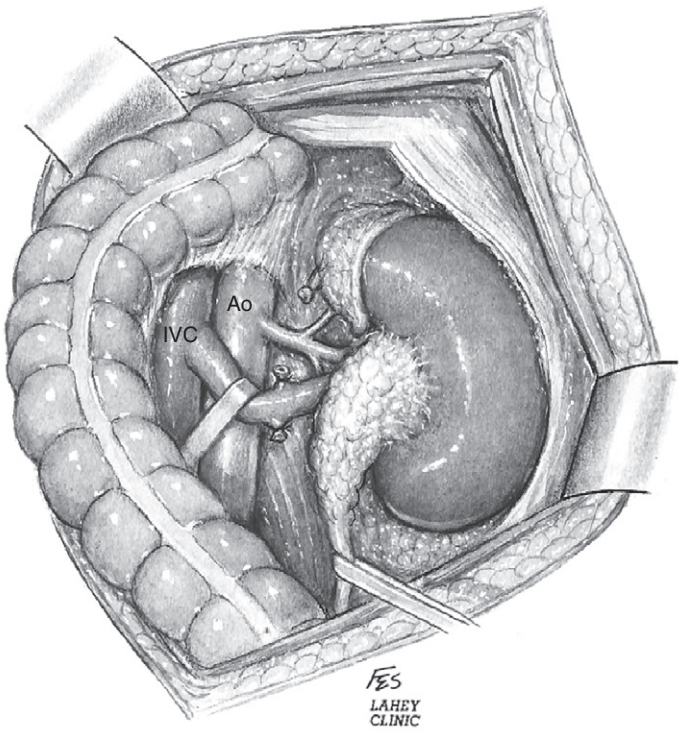


Figure 54–39. Ligation of adrenal and gonadal vessels and retraction of renal vein exposing main renal artery. IVC, inferior vena cava; Ao, aorta. (© The Lahey Clinic.)

Renovascular Surgery

Background

Renal artery surgery was first described in 1949 by Dos Santos for atherosclerotic disease utilizing a dedicated renal endarterectomy to treat an occlusive plaque. By restoring flow to the affected renal unit it became apparent that patency could be accomplished by removal of the intima and media of the arterial system. The drawbacks to this approach stemmed from the weakness of the native adventitia and the incidence of intimal flaps leading to postoperative aneurysms and restenosis. To maximize the repair surgeons soon came to recognize the benefits of vein patch renal angioplasty, thereby limiting narrowing and dilation. Transaortic endarterectomy was explored as an alternative option, allowing simultaneous repair; however, the high rates of recurrent stenotic disease precluded it becoming a mainstay in therapy (Libertino, 1992).

Renal endarterectomy and repair with saphenous vein or synthetic graft can be a suitable option for short well-defined segments of mural dysplasia. Recurrent stenosis is often attributed to residual microscopic mural disease not appreciated at the time of surgery. The authors prefer to treat renal stenotic lesions using aortorenal bypass procedures. If the saphenous vein is unavailable, cephalic vein or PTFE is recommended. In some instances the aorta is too diseased for reimplantation and alternate arterial conduits are chosen, as described later.

Etiology

The primary disease entities necessitating revascularization include atherosclerosis (75%) and fibrous dysplasia

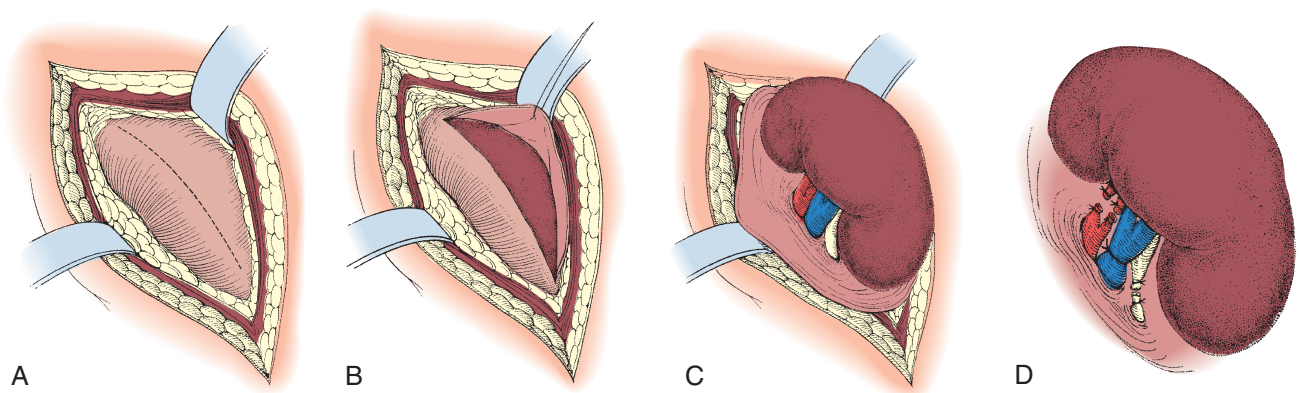


Figure 54–40. **A** to **D,** Technique of subcapsular nephrectomy.

(25%). Patients can present with hypertension and renal insufficiency when the lesion is chronic. Less than 3% of the hypertensive population has a renovascular etiology versus an estimated 18% to 20% in patients undergoing cardiac angiography and 35% to 50% of patients with aortic occlusive disease (Olin et al, 1990; Anderson et al, 1994; Rihal et al, 2002). Hypertension is a direct result of activation of the renin-angiotensin-aldosterone system, whereas renal impairment (ischemic nephropathy) is secondary to reduced perfusion pressure and loss of glomerular filtration capacity.

Atherosclerosis. In general, atherosclerosis affects patients in the sixth to seventh decades of life. The diagnosis of renovascular hypertension caused by atherosclerosis is being discovered in younger patients, which may be attributable to increased imaging studies. Atherosclerosis may be limited to the renal artery in 15% to 25% of patients but tends to be part of a generalized process affecting the major arterial branches of the aorta. Bilateral disease is present in up to 40% of patients (Fig. 54–41). Unilateral disease is more common in the left renal artery with contralateral disease present in 40% at the 4-year mark (Libertino et al, 1988). Although renal arteries are end arteries by anatomic definition, the slow onset of atherosclerosis permits development of collateral vessels, resulting in minimal clinical symptoms.

Mural Dysplasia. Fibrous dysplasia is progressive and more common in children and young adults. Segmental stenotic sections develop secondary to hyperplasia of smooth muscle and the associated layers of the arterial wall. Various categories exist under the broad definition of fibrous dysplasia.

Primary intimal fibroplasia accounts for 10% of lesions and occurs in children and young adults. The process can develop in contralateral kidneys or other vessels in a progressive nature. Angiographically the disease has smooth, focal stenosis involving the proximal or middle portion of renal vessels or branches (Fig. 54–42).

Medial fibroplasia accounts for 75% to 80% of fibrous lesions primarily in women between 25 and 50 years of age. With angiography, arteries demonstrate a "string of beads" in the distal two thirds of the main renal artery and its branches (Fig. 54–43). Multiple microaneurysms can also be appreciated. An estimated 33% demonstrate progression, whereas complete occlusion is rare.

Perimedial (subadventitial) fibroplasia accounts for 10% to 15% of fibrous lesions and is limited to the renal arteries. Angiographically the appearance is similar to that of medial fibroplasia but there are no microaneurysms and extensive collateral circulation is present (Fig. 54–44). Without intervention this entity leads to severe stenosis and progressive obstruction with ischemic nephropathy. The disease often afflicts young females.

Fibromuscular hyperplasia is an extremely rare lesion, accounting for less than 5% of mural dysplasia in children and young adults. These lesions progress over time. Although most of these

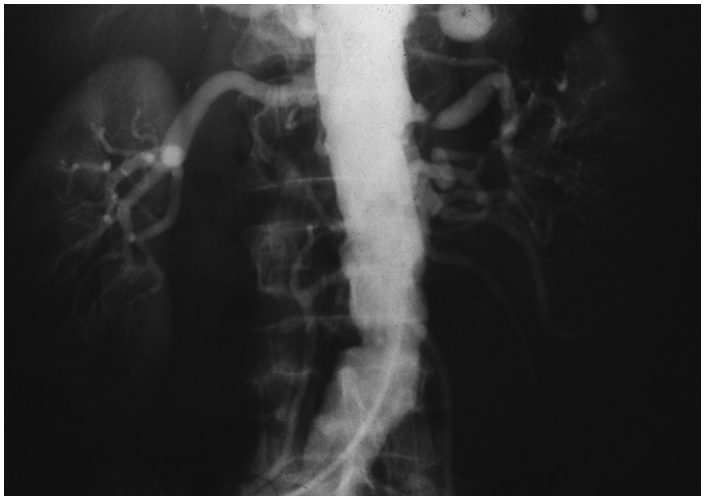


Figure 54–41. Left renal artery stenosis secondary to atherosclerotic disease of the aorta.

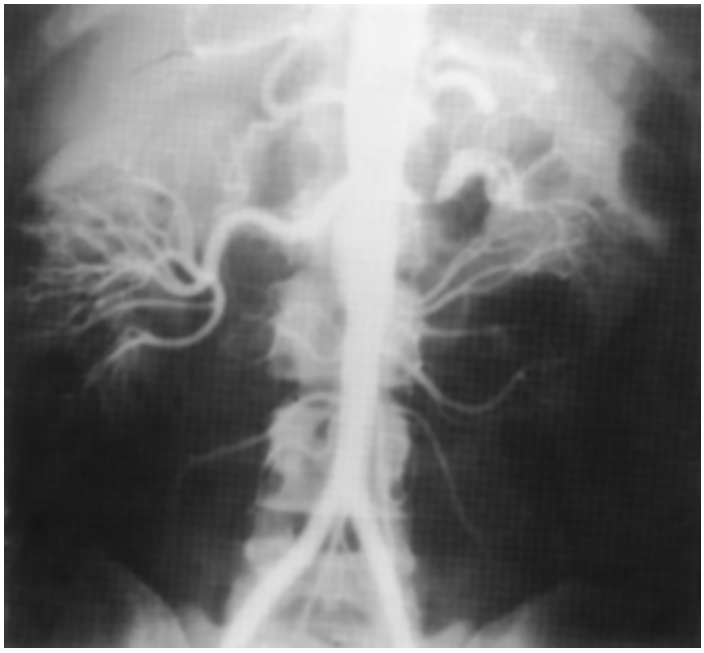


Figure 54–42. Intimal fibroplasia. (From Libertino JA. Reconstructive urologic surgery. 3rd ed. Philadelphia: Mosby; 1997.)

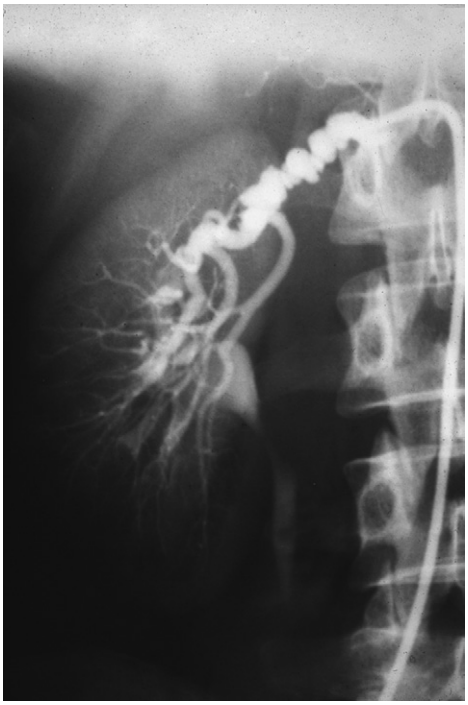


Figure 54–43. Selective right renal angiogram demonstrating medial fibroplasia "beads on a string" in a solitary right kidney.

lesions can mimic one another the final diagnosis should be made after histologic examination when possible.

Renal Aneurysms. Aneurysmal disease can lead to progressive renal damage and hypertension. By definition these lesions may be true (congenital or acquired) or false from trauma. Angiographically they can be divided into saccular, dissecting, fusiform, and intrarenal. Saccular forms occur in the main renal artery or at the anterior-posterior branch point and are the most common (Fig. 54–45). Dissecting aneurysms result from a disruption of the internal elastic membrane in certain populations (e.g., atherosclerosis, intimal fibrodysplasia, and perimedial fibrodysplasia). Fusiform aneurysms are noncalcified and common in younger hypertensive patients with fibromuscular dysplasia (Fig. 54–46).

Intrarenal aneurysms are considered congenital and account for one fifth of aneurysmal disease affecting the kidney (Fig. 54–47). In some instances they may develop secondary to atherosclerosis, mural dysplasia, trauma, inflammation (arteritis), or needle biopsy. Intervention is warranted for lesions larger than 2 cm or those associated with hypertension. Lesions can rupture and dissect leading to ischemia or may contribute to thrombus formation and warrant intervention (revascularization or coil placement). Women in childbearing age with evidence of aneurysms are urged to undergo repair secondary to risk of rupture and associated high rates of maternal and fetal mortality (Figs. 54–48 and 54–49) (Yang and Hye, 1996; Centenera et al, 1998).

Embolic Disease. Embolic disease affecting the arterial tree is often secondary to migration of cardiac thrombus from underlying atrial fibrillation, acute myocardial infarction, ventricular aneurysms, subacute bacterial endocarditis, mitral valve disease, prosthetic valves, and cardiac tumors (myxomas). Paradoxical emboli can arise from VTE via patent foramen ovale. Iatrogenic emboli can arise during manipulation of atherosclerotic vessels during aortic surgery or angiographic procedures. Emboli commonly migrate to the left renal artery because of its acute angle from the aorta.

Management of emboli is often time dependent in terms of renal salvage, and patients are best treated with thrombolysis or percutaneous transcatheter embolectomy. Emboli affecting

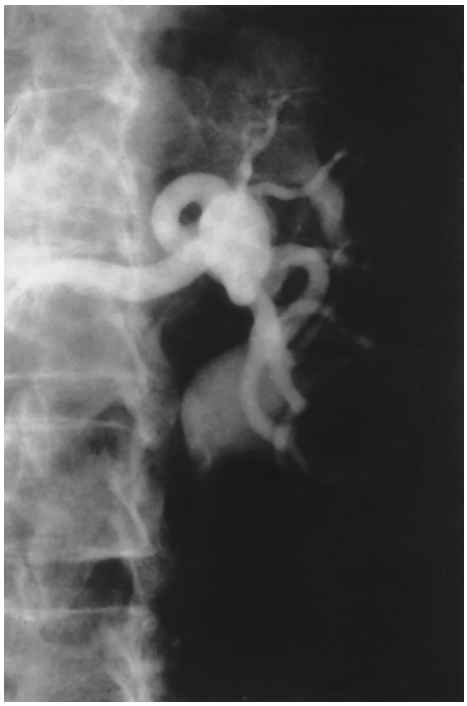


Figure 54–45. Saccular aneurysm in left renal artery (atherosclerosis). (From Libertino JA. Reconstructive urologic surgery. 3rd ed. Philadelphia: Mosby; 1997.)

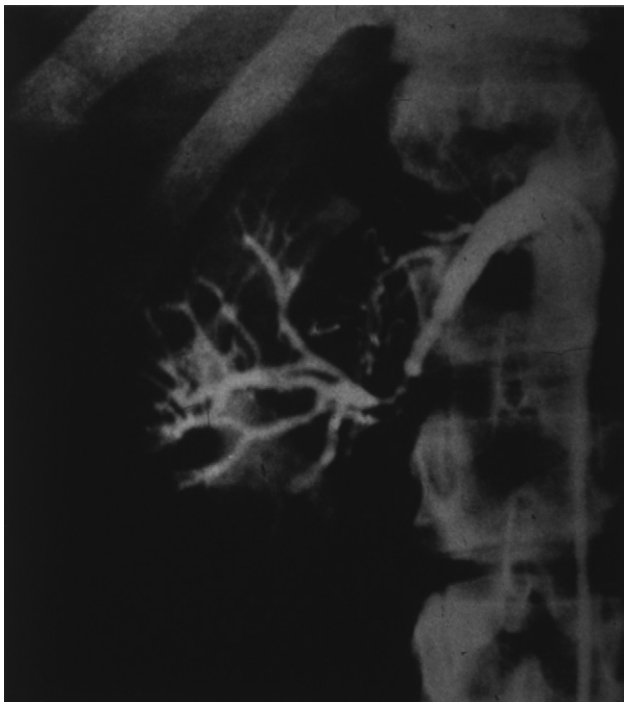


Figure 54–44. Selective right renal angiogram demonstrating perimedial (subadventitial) fibroplasia with decent collateral vasculature.



Figure 54–46. Fusiform aneurysms in right renal artery. (From Libertino JA. Reconstructive urologic surgery. 3rd ed. Philadelphia: Mosby; 1997.)

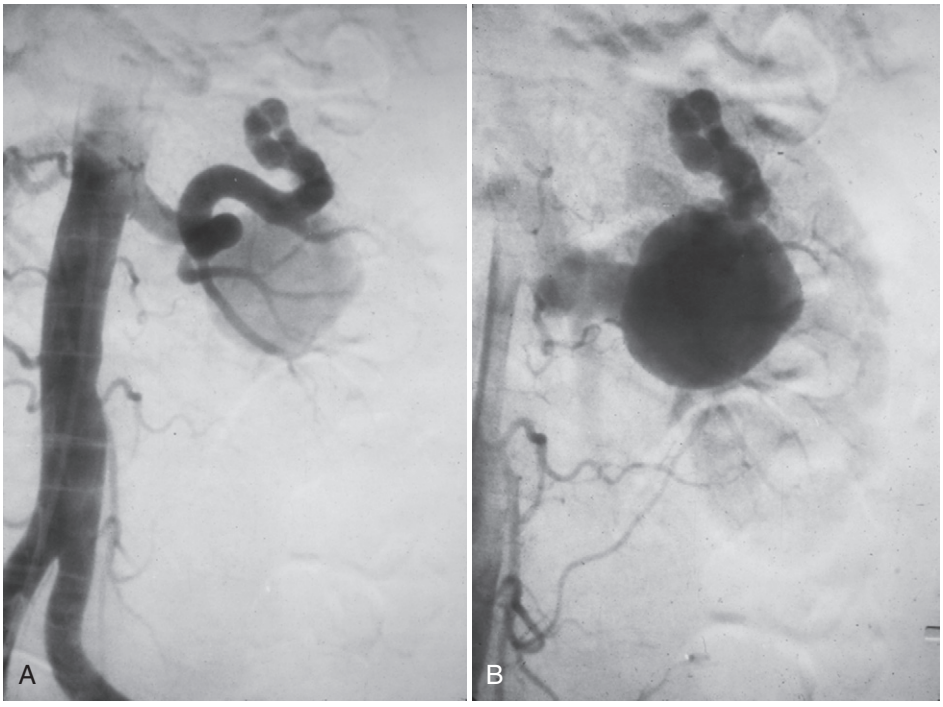


Figure 54–47. **A,** Large left congenital renal aneurysm and arteriovenous malformation. **B,** Note early filling of the renal vein and inferior vena cava.

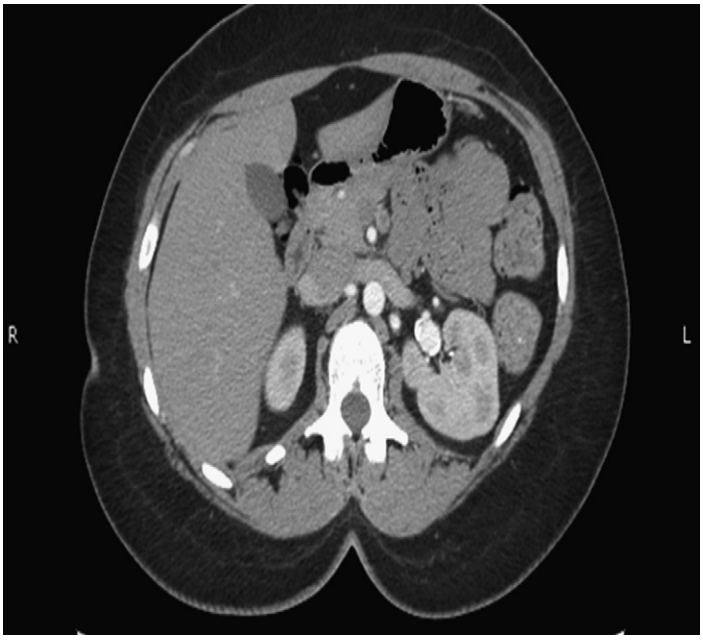


Figure 54–48. CT showing a 16-mm left renal artery aneurysm in a 26-year-old woman that was discovered during workup for abdominal pain to rule out appendicitis.

solitary kidneys or both kidneys need to be treated by thrombolysis (e.g., streptokinase) and catheter embolectomy. Surgical intervention is based on clinical response to conservative measures and the complexity of the case.

Trauma. Blunt or penetrating renal trauma, iatrogenic in some cases, can rarely cause acute renal artery thrombosis. Blunt trauma more frequently involves the left renal artery. Isolated injury is infrequent, and most of these patients have other associated injuries (extremity or rib fractures with pneumothorax or hemothorax or hepatic and splenic lacerations or contusions). Because of its rigidity the intima is torn, resulting in hemorrhage and propagation of thrombus. The adventitia and media, which are more elastic, will stretch. In general, patients with traumatic renal artery thrombosis only should undergo an attempt at surgical repair in the presence of a solitary kidney or bilateral occlusion. Unfortunately, therapy for traumatic renal artery thrombosis is often unsuccessful even when performed within a short time after the injury.

Arteriovenous Malformations. Arteriovenous malformations may be congenital or acquired with a wide range of symptoms. High-output cardiac failure from arteriovenous malformations in renal cell carcinomas have been described (Crawford et al, 1979). In cases of renal tumors, preoperative angioembolization may help restore cardiac integrity before nephrectomy (see Figs. 54–16 and 54–17). Iatrogenic causes include renal artery biopsy, partial nephrectomy, radiofrequency ablation, and cryotherapy. Percutaneous approaches are highly successful for treating these lesions. Open surgery is rarely required for these renovascular lesions and when indicated is often in the form of a nephrectomy.

Takayasu Disease. Takayasu inflammatory disease is characterized by localized periarteritis with mononuclear infiltration, multinucleated giant cells, and disruption of elastic arterial wall fibers. Although the disease has been primarily associated with patients of Asian descent, it is now known to coexist in the Western world. Takayasu arteritis typically affects young women (80% of affected patients are younger than 35 years old). Takayasu disease was initially described for its ocular findings. Clinicians later discovered that its arterial lesions were more widespread than initially thought. For diagnostic and surgical reasons it has been classified angiographically into four categories based on the location of the lesions: (1) aortic arch and its great vessels, (2) descending thoracic and upper abdominal aorta, (3) simultaneous involvement of categories 1 and 2 (65% of all cases), and (4) pulmonary artery with or without categories 1 through 3. Of the cases reported in the literature, 50% are associated with hypertension. Renal artery disease is most common, followed by proximal hypertension caused by coarctation of the aorta and loss of arterial elasticity (Fig. 54–50) (Ishikawa, 1978).

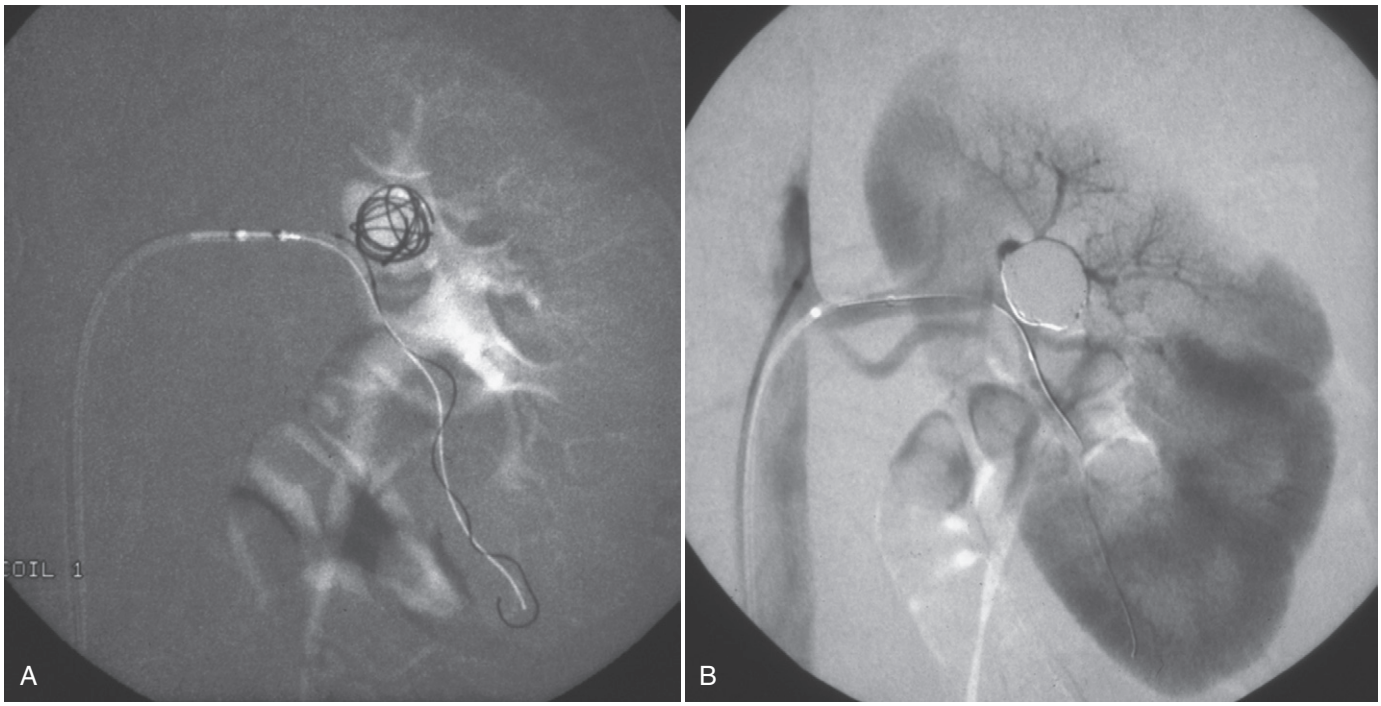


Figure 54–49. **A,** Selective angiography and coiling of aneurysm. **B,** Repeat angiogram demonstrating no flow to aneurysm.

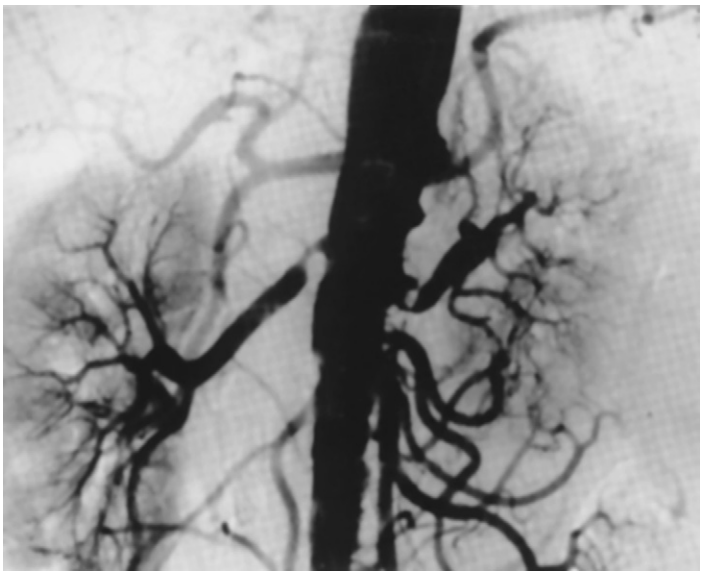


Figure 54–50. Bilateral renal artery stenosis caused by Takayasu disease. (From Libertino JA. Reconstructive urologic surgery. 3rd ed. Philadelphia: Mosby; 1997.)

Neurofibromatosis. Neurofibromatosis is a hereditary disease characterized by café-au-lait spots, cutaneous fibromas, and neurofibromas. Hypertension associated with neurofibromatosis is usually caused by pheochromocytoma or, more rarely, by coarctation of the aorta. Arterial lesions associated with neurofibromatosis have been reported occasionally since the first published report in 1905. Renovascular hypertension associated with neurofibromatosis has been described in 20 cases, 18 of which were in children. The vascular lesions are characterized by intimal endothelial nodules in the vessel wall. The aorta is frequently involved, and the renal arteries may demonstrate long areas of stenosis, which are probably best treated by revascularization procedures rather than by angioplasty.

Management Options

The gradual decline in renal revascularization procedures is a testament to improved medical management and appropriate population based on imaging screening protocols. Advances in percutaneous transluminal angioplasty and renal artery stent development have lessened the need for open renal bypass surgery, respectively.

Medical Therapy. By the time of referral most patients have been on multiple drug therapy (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers and β-adrenergic blockers) targeted at the renin-angiotensin and aldosterone cascades. ACE inhibitors manage hypertension and provide a means to predict who will benefit from surgery (e.g., ACE inhibitor test, captopril-furosemide renogram). Medical management is best targeted at lesions least likely to progress to complete occlusion and ischemic nephropathy, such as medial fibroplasia.

It is important to reiterate that although ACE inhibitors can improve hypertension there is little evidence to support their role in delaying progression of occlusive disease process. An inadvertent consequence of ACE inhibitors is a reduction in GFR by eliminating angiotensin II–induced efferent arteriolar constriction. In patients with bilateral disease or solitary kidneys there will be a paradoxical increase in blood pressure secondary to increased renin secretion and azotemia.

Interventions. Indications for surgical or percutaneous (angioplasty or stenting) intervention are listed in Table 54–9**. In general, patients who have elevated creatinine levels, poor functional studies, or unfavorable histology are unlikely to benefit from revascularization.**

Patients with high significant risk factors are better suited with endovascular repair. Percutaneous approaches (angioplasty and

Table 54–9.

Indications for Surgical or Percutaneous Intervention

Hypertension not responsive to multimodal medical therapy
ACE-I or ARB induced GFR reduction or elevation of creatinine concentration
Congestive heart failure (recurrent and difficult to manage)
Favorable renal biopsy (salvageable glomeruli)
Creatinine concentration less than 4.0 mg/dL
Evidence of collateral circulation and renal size >7 cm
Positive nuclear function study
Doppler resistive index <0.80
Lateralization of renin on renal vein sampling
Progressive occlusion

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate.

stenting) are ideal approaches for short, nonostial, nonoccluded lesions in the proximal or mid main renal artery often found in fibromuscular dysplasia. As a general rule, stents can be used for bilateral atherosclerotic disease or solitary kidneys in patients unable to tolerate open surgery. Open repair is indicated in failed endovascular repairs or when concomitant aortic repair is undertaken.

Preoperative Evaluation. In general, renovascular candidates can be divided into two groups: atherosclerosis and mural dysplasia. The former population is older with multiple comorbidities. The high incidence of concomitant carotid and coronary artery disease warrants evaluation with angiography or 3D CT angiograms. Preoperative revascularization via percutaneous stenting is preferable to limit morbidity associated with recovery. Simultaneous procedures are ill advised and performed under the rarest of circumstances. Percutaneous procedures have a 1% to 3% incidence of dissection requiring open repair, and the authors therefore recommend full workup in case conversion is necessary. Recommended noninvasive options for evaluation include duplex Doppler ultrasonography, captopril-enhanced renal scans, and magnetic resonance angiography. Although angiography remains the gold standard the nephrotoxic risk may be too high.

Endovascular Procedures. Percutaneous transluminal angioplasty was first performed in 1964 by Dotter and Judkins for peripheral vascular disease and expanded to the renal arterial system by Gruntzing and Hopff 10 years later (Dotter and Judkins, 1964; Gruntzig and Hopff, 1974). Technical advances and an aging population have resulted in aortic and renal open revascularization rates decreasing 73% from 1998 to 2001 while percutaneous procedures increased by 173% (Knipp et al, 2004).

Percutaneous transluminal angioplasty is now a widely used technique for treatment of patients with renal artery disease. Little controversy exists about its role in the treatment of patients with fibromuscular dysplasia. The results reported are excellent and are comparable to those obtained by surgical revascularization. In up to 30% of patients, mural dysplasia involves the arterial branch points, which increases the technical difficulties of balloon dilation and often renders it impossible to perform.

Several factors influence the success of transluminal angioplasty in patients with atherosclerotic renal artery stenosis. In this population, the success rate associated with nonostial lesions is 80% to 85%. For unilateral ostial lesions and lesions that originate within the aorta, patency rates average only 30% to 35%. Patients with total renal artery occlusion, bilateral involvement, and renal artery aneurysms are not considered candidates for percutaneous transluminal renal angioplasty (PTRA) because of historically poor response rates (Novick, 1994).

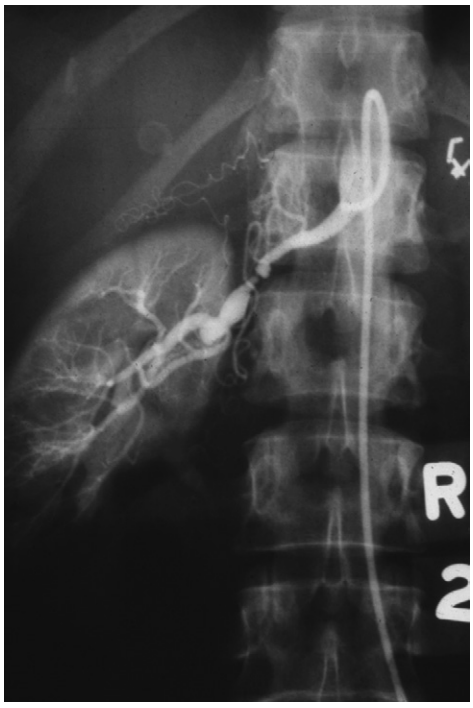


Figure 54–52. Right renal angiogram demonstrating significant mid renal artery stenosis from subadventitial disease. Note extensive adrenal collateral and distal reconstitution.

Complications associated with PTRA were reported in 10% of patients. The most frequently reported complications are main renal artery dissection, thrombosis and occlusion, segmental artery infarction, and hematoma (Eklof et al, 2009). Pseudoaneurysms are also a recognized risk. Thus, although the procedure is performed under local anesthesia, all patients must be considered as preoperative for open repair. With this in mind, patients require a comprehensive preoperative evaluation and postoperative observation. In addition, it is the authors' practice to have an operating room available and urology and anesthesiology teams aware of the procedure in the event open repair is required.

Open Surgical Repair.

AORTORENAL BYPASS. The widespread popularity of the aortorenal bypass graft for renal artery disease stems from its technical ease of insertion and favorable short-term and long-term patency rates (see Fig. 54–51 on the Expert Consult website). The procedure eliminates the hazardous dissection of the juxtarenal aorta required with endarterectomy, and overall patency rates range from 94% to 99% (Libertino et al, 1980). **Almost all disease processes affecting renal artery patency, particularly the fibrodysplasias, may be bypassed with an aortorenal graft** (Figs. 54–52 and 54–53). One notable exception is severe atherosclerotic disease that renders the aorta an unsafe vessel from which to obtain blood flow. In this instance, alternative bypass procedures are indicated (Libertino and Selman, 1982).

The autogenous saphenous vein has emerged as the preferred graft in adults and is the most common graft material used for restoration of renal blood flow at the Lahey Clinic. Saphenous vein is readily available and closely approximates the size of the renal artery. The intima is less thrombogenic than prosthetic material and accommodates the creation of a precisely contoured anastomosis with a delicate thin-walled

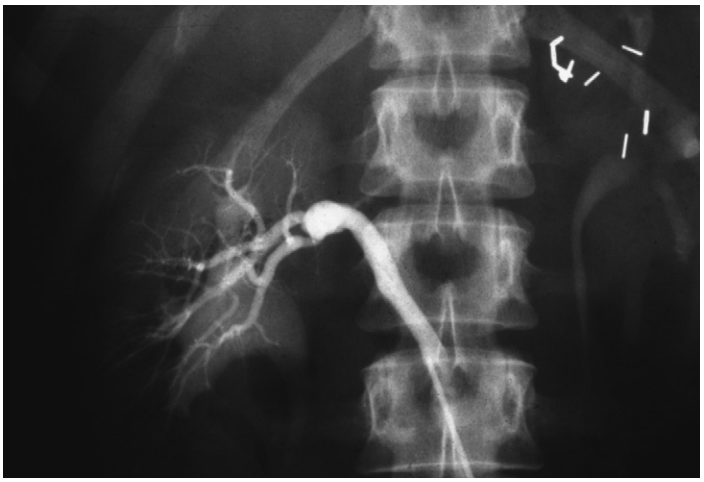


Figure 54–53. Postoperative angiogram demonstrating patent right renal artery after end-to-end saphenous vein aortorenal bypass.

distal renal artery. Patent anastomoses can be achieved with 2- to 3-mm lumen branches beyond the major bifurcation. When saphenous vein is not available, the authors' prefer to use cephalic vein or PTFE graft (Libertino and Zinman, 1980).

In children, autogenous hypogastric artery is the most favorable graft material with which to revascularize the renal artery. Its size approximates that of the renal artery, and its intima is free of fibromuscular disease. The saphenous vein should never be used in this population because it is too small and readily undergoes aneurysmal dilation. Conversely, the hypogastric artery in older adults is usually heavily involved with atheroma and thus is not a suitable graft material.

PROCUREMENT OF SAPHENOUS VEIN

The procurement of an adequate segment of the greater saphenous vein is critical to the success of the bypass procedure. Meticulous technique in exposure and excision of the vein is essential to prevent mural trauma and ischemia and associated stenosis and dilatation in the long term. The contralateral vein is harvested, allowing two surgical teams to work simultaneously. The vein is mobilized through a single long incision in the upper thigh beginning parallel and caudal to the groin crease (Fig. 54–54). When the femoral artery is palpable, the incision is made directly over the pulsation; otherwise, the incision is 2 to 3 cm lateral and caudal to the ipsilateral pubic tubercle. After the junction of the saphenous and femoral veins has been exposed the incision is extended toward the knee directly over the vein. Finger dissection between the vein and the overlying skin is helpful to ensure accurate placement of the incision, to prevent the development of potentially necrotizing skin flaps. The ideal graft is 20 cm long with an outside diameter of 4 to 6 mm. Excess vein should always be available for revision of any intraoperative technical problems that may occur during anastomosis. The areolar tissue is not dissected from the specimen, and the adventitia is left undisturbed. To decrease transmural ischemia the vein graft remains in situ until the renal vessels are mobilized and it is ready to be used. If the graft is removed prematurely, it is placed in cold lactated Ringer solution or autologous blood, even if only for a short time. The caudal end of the vein is cannulated with a Marks needle secured with a fine silk. The vein is flushed with dilute heparinized saline solution, and the cephalic end is secured with a microvascular Schwartz clamp (Fig. 54–55). The vein is distended to a

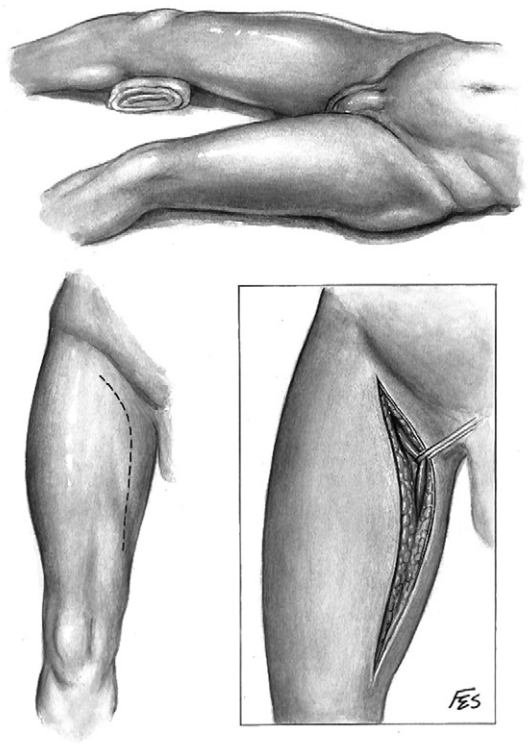


Figure 54–54. Procurement of saphenous vein. (© The Lahey Clinic.)

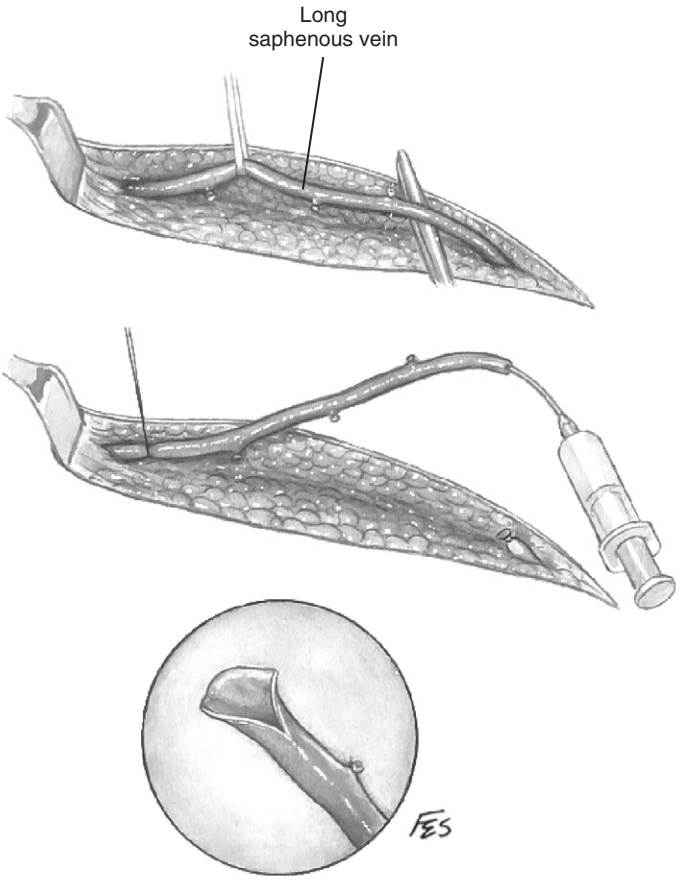


Figure 54–55. Harvesting of saphenous vein. (© The Lahey Clinic.)

minimal diameter of 5 to 6 mm and transected with Potts scissors. The in-situ vein remnant is secured with a silk suture ligature. The thigh incision is not closed until the bypass procedure is completed to ensure that any delayed bleeding resulting from heparinization is identified and controlled.

TECHNIQUE FOR INSERTION OF SAPHENOUS VEIN GRAFT

Systemic heparin is administered about 30 minutes before clamping the arteries. The saphenous vein graft should be oriented properly to avoid misalignment during implantation. The proximal end with Marks needle is transected with Potts scissors. Either an end-to-end or end-to side anastomosis may be performed distally, depending on the anatomy encountered. For aortorenal bypass the proximal anastomosis is obviously always end to side. A distal end-to-end anastomosis is preferred because it permits the best laminar flow.

The aorta, having been exposed widely from the level of the renal arteries to the inferior mesenteric artery, is gently palpated to locate a suitable soft location for the anastomosis. A medium-sized side-biting vascular clamp is placed on the anterolateral portion of the infrarenal aorta in a tangential manner. A vertical 13- to 16-mm aortotomy is made without excising the aortic wall or attempting to perform localized endarterectomy. The former is unnecessary because intraluminal aortic pressure will spread the edges of the linear aortotomy to the appropriate dimensions when the clamp is released. The vein graft is anastomosed to the aorta with two continuous sutures of 5-0 polypropylene after it has been spatulated (Fig. 54–56). A microvascular clamp is placed on the end of the saphenous vein graft, and the aortic clamp is released. The graft is permitted to lie anterior to the vena cava on the right side or anterior to the renal vein on the left side. Although it is preferable to leave the vein too long rather than too short, it should not be so long as to bend into an acute angle at any point. The renal artery is secured distally with a smooth-jawed microvascular clamp(s) placed on either the main artery or a segmental branch. The proper site for the arterial anastomosis is selected. An end-to-end anastomosis is performed using continuous or interrupted sutures of 6-0 polypropylene (see Fig. 54–51 on the Expert Consult website). When the recipient vessel is 3 mm or less in diameter, interrupted sutures are used exclusively. Likewise, an interrupted suture line is used in children to prevent "purse-string stenosis" as their vessels grow. Although the authors usually perform an interrupted anastomosis even in adults, continuous suture lines may be run between interrupted sutures at four quadrants without the danger of "purse-string stenosis." Bleeding from needle holes at the anastomosis can usually be controlled with thrombogenic mesh such as Surgicel (Ethicon, Somerville, NJ). Multiple grafts can be employed when disease affects kidneys with more than one renal artery (Fig. 54–57; see Figs. 54–51 and 54–58 on the Expert Consult website).

Native saphenous vein and arterial autografts have been shown in many clinical studies to preserve glomerular function, and patency has been confirmed with postoperative angiography. PTFE grafts have been shown to be a feasible option in renal revascularization with concomitant aortic replacement. Customized grafts can compensate for discrepancies in anastomotic sizes. Seven-year patency rates of over 95% have been reported by Paty and associates (2001) in more than 400 revascularization procedures.

ALTERNATIVES TO AORTORENAL BYPASS

HYPOGASTRIC AUTOGRAFTS

The authors often make use of the internal iliac artery to repair lesions of the segmental renal arteries. Extensive collateral flow to the pelvis enables one to use this arterial conduit. An anterior subcostal with modified Gibson incision is the senior author's preferred approach. Alternatively, an anterior midline incision may by used for both renal artery mobilization and harvesting of the internal iliac artery. Evidence of atherosclerosis in the graft is a contraindication. Vessel loops are placed at proximal and distal branch point locations (Fig. 54–59). The artery is harvested by a second team as the primary team is nearing completion of their bench component. The hypogastric artery and branches are tailored to accommodate the branch points of the disease segments, and end-to end anastomoses are performed using 6-0 and 7-0 polypropylene suture (Fig. 54–60). The kidney is then autotransplanted into the groin as described in later sections.

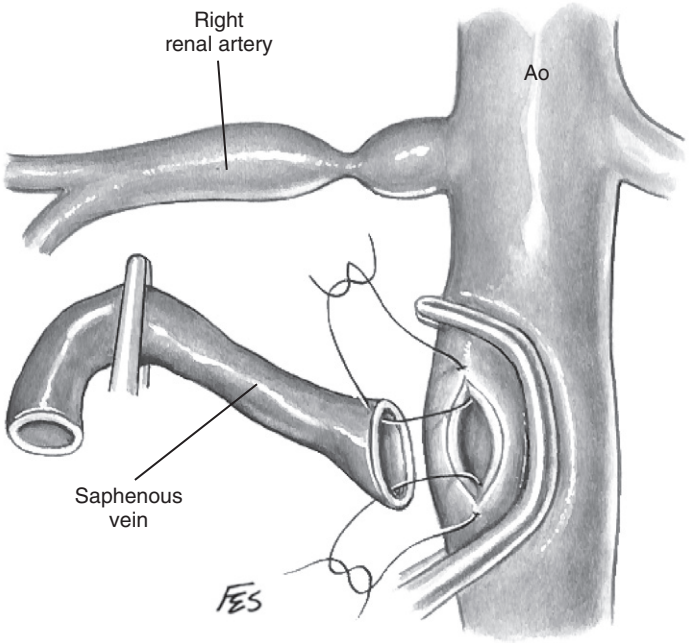


Figure 54–56. Aortic-to-graft anastomosis is carried out before graft-to-renal artery anastomosis when an end-to-end anastomosis is desired. Ao, aorta. (© The Lahey Clinic.)

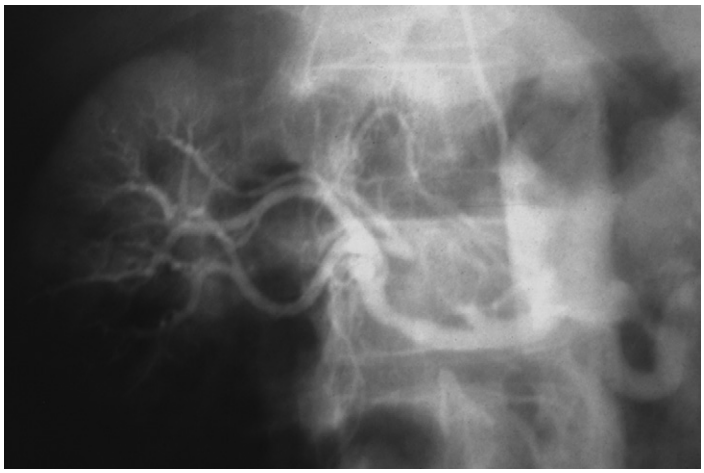
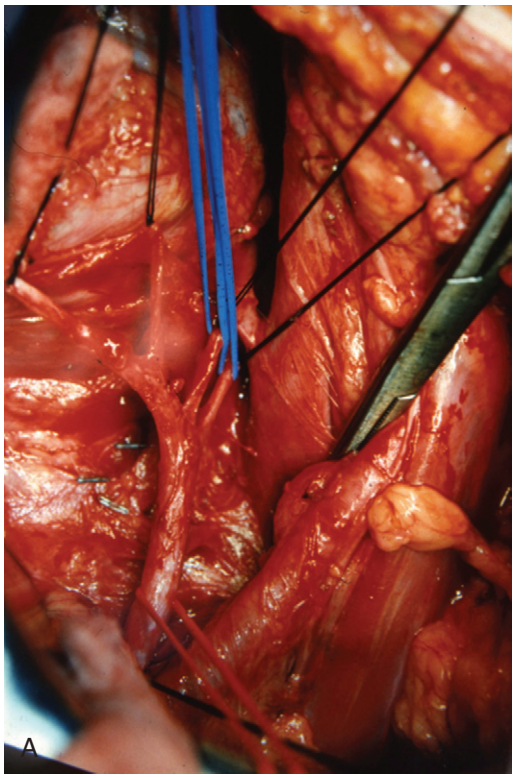


Figure 54–57. Aortogram demonstrating right upper pole renal artery occlusion and lower pole aneurysm at the bifurcation. The patient was treated with dual saphenous vein aortorenal bypass grafts.



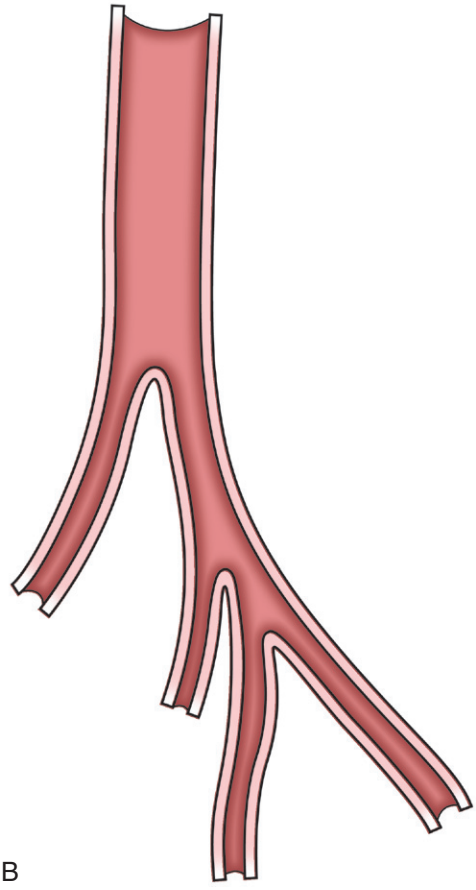


Figure 54–59. **A,** Exposure of the internal iliac (hypogastric) artery and associated branching vessels. **B,** Hypogastric graft with four branches to accommodate multiple repair anastomoses.

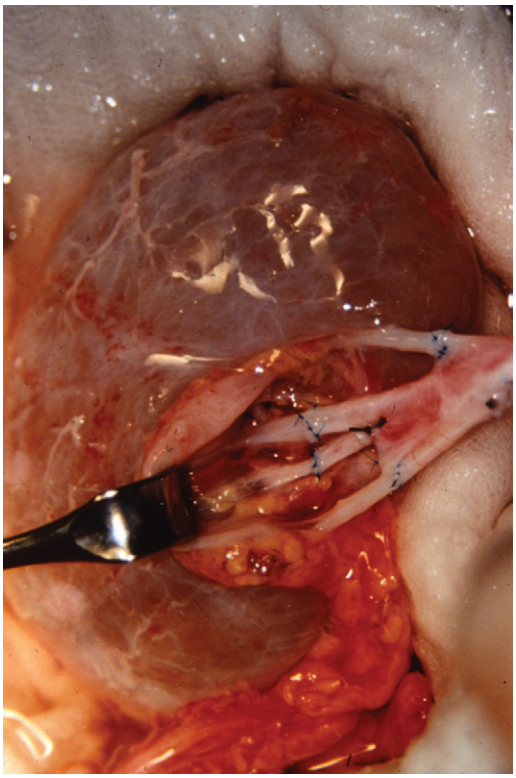


Figure 54–60. Distal anastomoses using 6-0 and 7-0 polypropylene suture followed by renal autotransplantation.

SPLENORENAL ARTERIAL BYPASS

Patients with diffuse atherosclerosis, significant aortic disease or prior aortic surgery, and left renal arterial disease are candidates for a splenorenal artery bypass. Preoperative lateral and oblique angiography should confirm the absence of disease of the celiac axis. CT reconstructions in combination with MRI have replaced angiography in some cases. Calcification of the distal splenic artery is a rare finding that would obviously preclude its use for repairs. The native state of the splenic artery provides an ideal location for bypass requiring only one anastomosis. Intraoperative use of ultrasound is suggested to establish blood flow rates, and at least 125 mL per minute is recommended.

The initial exposure is through a supracostal 11th incision. This incision permits a retroperitoneal approach without entry into the pleural cavity. The planes between the adrenal and kidney (within Gerota fascia) posterosuperiorly and between the kidney and pancreas anteromedially are entered with sharp dissection using tenotomy scissors. Manipulation of the pancreas should be avoided when identifying the splenic artery at its superior border. The artery is next mobilized from the splenic hilum to the celiac plexus without violating the peritoneal space (Fig. 54–61). Branches to the pancreas are ligated using 4-0 silk suture, and a Schwartz clamp is placed at the origin of the splenic artery. One may increase the caliber of the lumen using a Fogarty balloon, Gruntzig balloon catheter, or coronary artery dilators. The artery is next divided in close proximity to the hilar bifurcation point. Collateral blood flow from the short gastric eliminates the need for a splenectomy.

The left kidney is mobilized within the retroperitoneum. The authors recommend isolating the arterial supply via the posterior approach to avoid the superior mesenteric artery. Once adequate length is obtained the vessels are anastomosed in an end-to-end

fashion with interrupted or continuous 6-0 polypropylene sutures (Fig. 54–62). After completion of the anastomoses, Surgicel may be placed to promote hemostasis around needle entry points. Saphenous vein interposition grafts can be employed to eliminate tension between the splenic and left renal artery if necessary (Fig. 54–63).

Postoperatively, patients are maintained on heparin. Postoperative Doppler studies or a ^{99m}Tc-mercaptoacetyltriglycine (MAG3) renogram may be used to evaluate renal perfusion. Complications include thrombosis and graft failure. Pancreatitis and associated pancreatic pseudocysts have occurred in a small subset of over 175 splenorenal bypass patients treated at the Lahey Clinic.

HEPATORENAL AND GASTRODUODENAL ARTERY BYPASS

The indications for alternatives to aortorenal bypass for right-sided lesions are similar to those for the contralateral side and can be managed with hepatorenal or gastroduodenal saphenous bypass grafts as have been described by the authors' group (Libertino and Lagneau, 1983, Libertino et al, 1976). The common hepatic artery arises from the celiac plexus coursing laterally above the head of the pancreas until the confluence of the portal vein complex before branching into ascending and descending limbs. The ascending portion lies medial to the biliary tree and in front of the portal vein before branching into the right and left proper hepatic arteries. The descending limb becomes the gastroduodenal artery and can also be used in certain situations.

Variation within the hepatic arterial tree is almost twice that in the renal system, with an estimated 48% of living liver donors having aberrant vasculature (Hiatt et al, 1994). In addition to a sound understanding of the anatomy the surgeon must be patient during dissection of the porta hepatis, making every effort to spare all arterial components. Accessory arteries will hypertrophy in response to the loss of the common hepatic artery.

Unlike on the left side, the transabdominal approach is necessary for right-sided repairs. The right renal artery is identified and dissected under the IVC as close to the aorta as possible. The common and proper hepatic arteries are isolated and clamps placed before dividing the gastroduodenal artery. A 10- to 12-mm arteriotomy is made in the inferior wall of the hepatic artery at the ostium of the gastroduodenal artery. A reversed autogenous saphenous vein graft is sewn between this and the renal artery using interrupted or continuous 6-0 polypropylene (Fig. 54–64; see Fig. 54–65 on the Expert Consult website).

ILEORENAL BYPASS

In rare instances a patient requiring open surgical revascularization may not be able to undergo aortorenal, splenorenal, or hepatorenal bypass surgery and an alternative such as the ileorenal bypass may be needed (Fig. 54–66). Unfortunately most patients with significant atherosclerosis of the renal aorta have equivalent disease at the level of the common iliac arteries. Progression of iliac atherosclerosis may lead to chronic ischemia of kidneys undergoing this form of revascularization. A midline incision is made, and a saphenous vein graft harvest performed. The

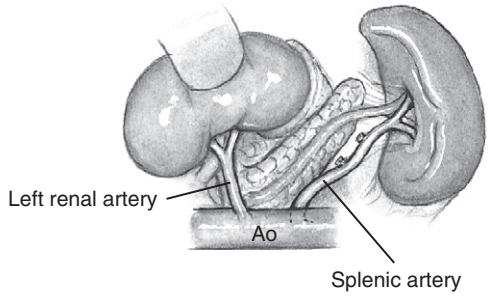


Figure 54–61. Mobilization of splenic and left renal arteries. Ao, aorta. (© The Lahey Clinic.)

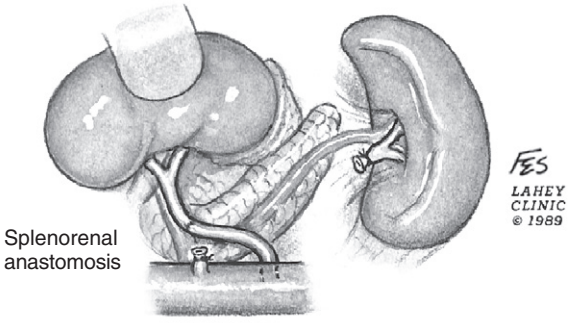


Figure 54–62. Splenorenal anastomosis. (© The Lahey Clinic.)

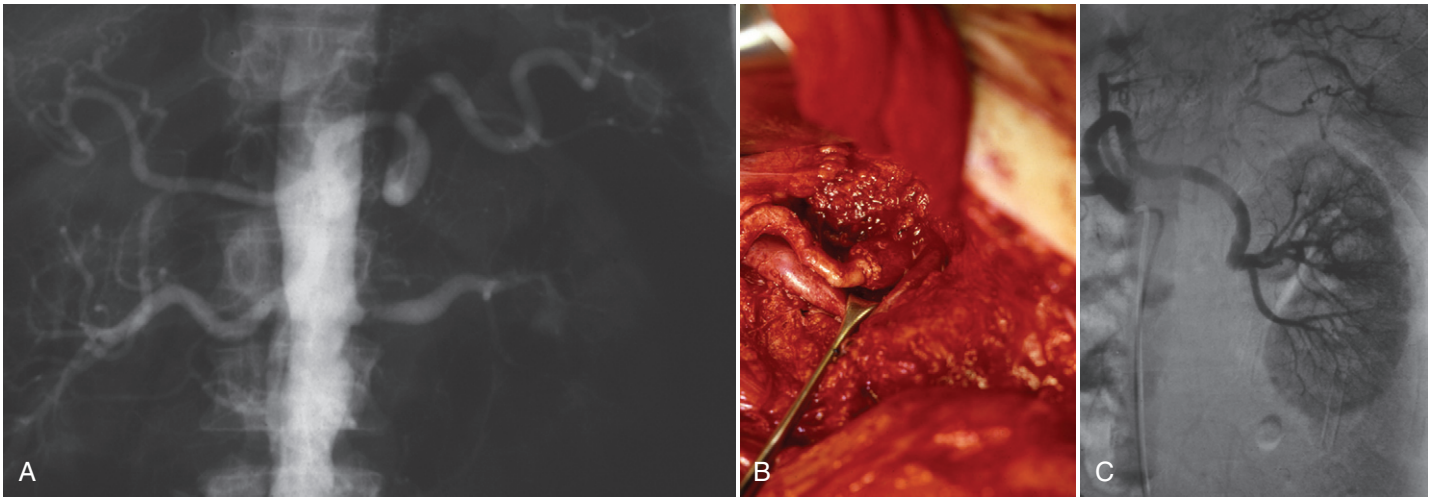


Figure 54–63. **A,** Aortogram demonstrating left renal artery stenosis, diseased aorta, and patent splenic artery. **B,** Splenorenal bypass using saphenous vein interposition graft. **C,** Postoperative selective aortogram.

corresponding colon is mobilized along the line of Toldt from the splenic or hepatic flexure to the iliac vessels. Utilization of the contralateral iliac artery is an option if significant ipsilateral disease is present. Vessel loops and vascular clamps are used in standard fashion to perform an end-to-side anastomosis at the iliac vessel and end-to-end technique at the renal artery using 6-0 polypropylene suture (Figs. 54–67 and 54–68; see Fig. 54–69 on the Expert Consult website).

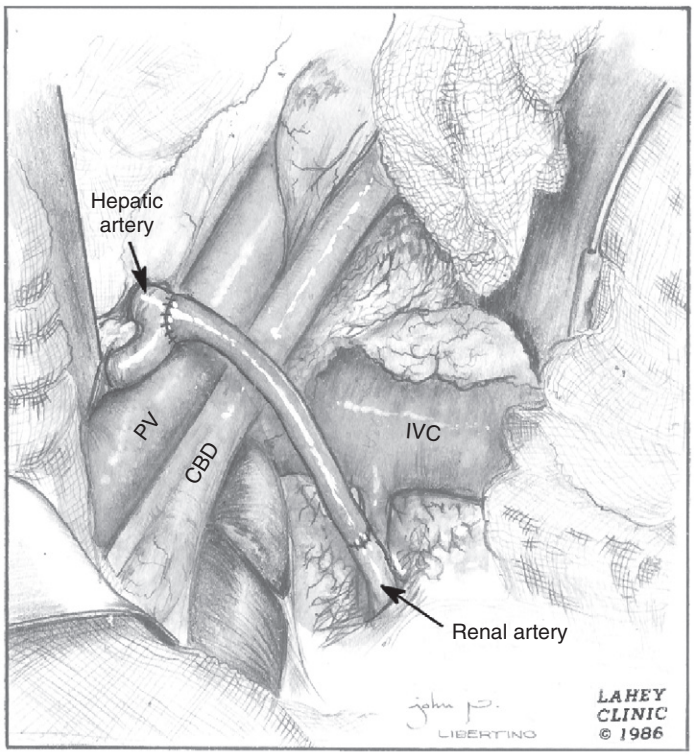


Figure 54–64. Diagram of hepatic artery to right renal artery end-to-end anastomosis using a saphenous vein graft that overlies the porta hepatis. CBD, common bile duct; IVC, inferior vena cava; PV, portal vein. (© The Lahey Clinic.)

THORACIC AORTORENAL BYPASS

If the splenic artery is heavily atherosclerotic, a thoracic aortorenal bypass is an option. The subdiaphragmatic supraceliac and descending thoracic aorta is often free of atherosclerosis and can serve as an alternative for renal vascular reconstruction using a saphenous vein graft. Preoperative angiography to rule out disease at this level is essential. Novick (2007) describes using a supra–9th rib incision extending across the midline for left-sided lesions. The cephalad extent of the incision provides great exposure of the thoracic aorta and left renal artery. The left colon is reflected

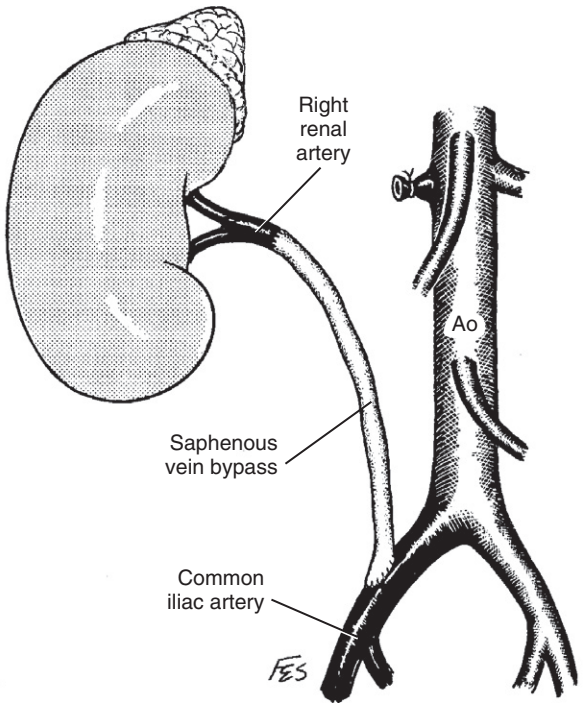


Figure 54–66. Iliac artery to renal artery saphenous vein bypass graft—an alternative to autotransplantation. Ao, aorta. (© The Lahey Clinic.)

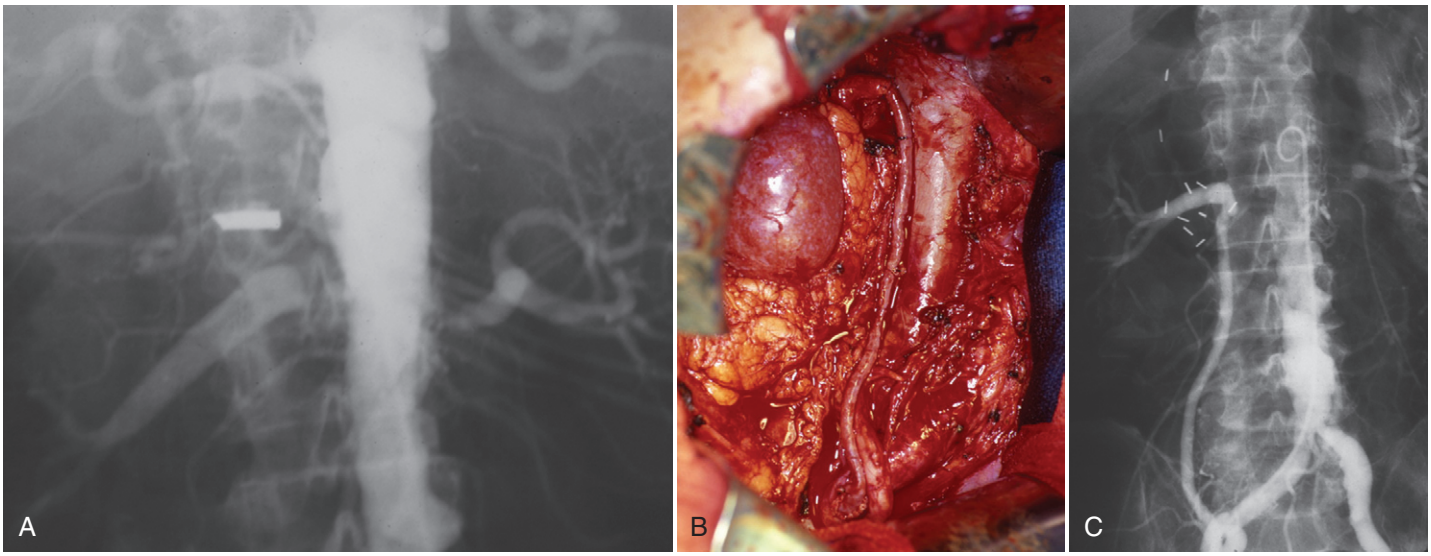


Figure 54–67. **A,** Preoperative angiogram. **B,** Right ileorenal bypass using sequential saphenous vein grafts. **C,** Postoperative angiogram with restored flow to the right kidney.

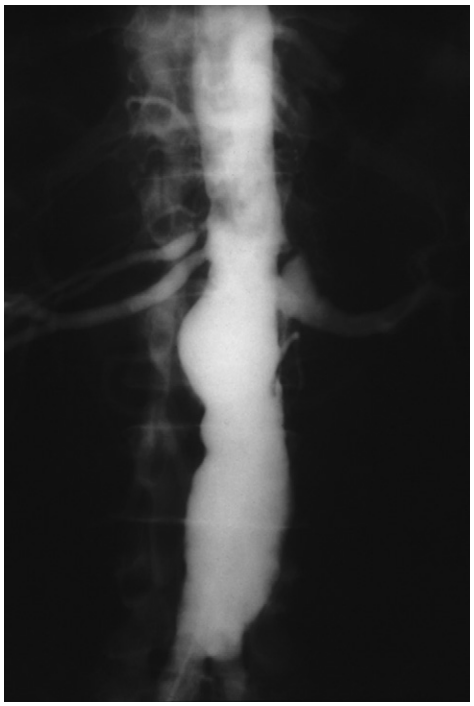


Figure 54–68. Preoperative aortogram demonstrating multiple right renal arteries with stenosis at the aortorenal junction.

medially in standard fashion to expose the renal artery in the retroperitoneum. After exposure of the thoracic aorta a DeBakey clamp is used to partially occlude a lateral segment before making a small aortotomy. A reversed autogenous saphenous vein graft is then sewn in an end-to-side fashion. Systemic heparinization is not employed because the aortic flow is preserved (Fig. 54–70). The hiatus in the diaphragm is extended by 2 cm laterally, permitting passage of the saphenous vein behind the pancreas into the retroperitoneal space. An end-to-end anastomosis is performed to the left renal artery. For right-sided lesions the subdiaphragmatic supraceliac and lower thoracic aorta can be accessed via an anterior bilateral incision. The steps are repeated in a similar fashion to the left-sided approaches.

Thoracic inlet revascularization of the renal system has several advantages. The high flow thoracic aorta in conjunction with the relatively acute angle of the proximal graft is hemodynamically advantageous and decreases the thrombogenicity that would be associated with sluggish arterial flow. The ability to perform the anastomosis without complete aortic cross clamping avoids systemic heparinization and spinal cord ischemia. Renal ischemia is limited to the time necessary to perform the distal vein-to-renal artery anastomosis, which rarely exceeds 25 minutes. Autogenous graft material limits the immune response associated with synthetic material.

Novick (2007) reports resolution or improvement of hypertension in 86% of his surgical population with preservation or enhanced renal function in 95% within the same group of 23 patients. All patients demonstrated extensive atherosclerosis of the abdominal aorta and celiac artery stenosis precluding hepatic and splenic bypass.

MESENTERORENAL BYPASS

The superior mesenteric artery has been utilized in conjunction with a saphenous vein interposition graft leaving the marginal artery of Drummond responsible for collateral circulation between

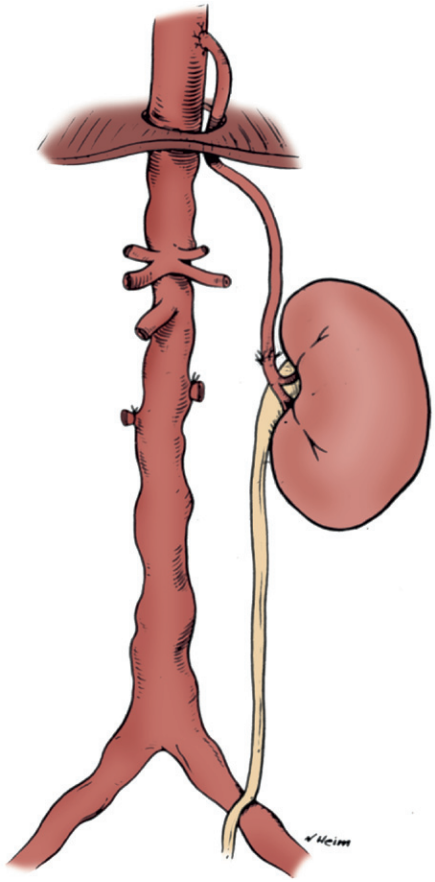


Figure 54–70. Technique of left thoracic aortorenal revascularization.

the celiac and inferior mesenteric artery. Novick (2007) describes significantly enlarged superior mesenteric arteries associated with complete infrarenal aortic occlusion in which extensive collateral circulation provided insurance against bowel ischemia. Midline incisions provide excellent exposure for both right and left renal arteries. Exposure of the suprarenal aorta is obtained by cephalad retraction of the pancreas and first portion of the jejunum and medial refection of the mesocolon. The superior mesenteric artery can be palpated 2 to 3 cm above the renal arteries. This artery is mobilized 2 to 3 cm beyond the takeoff of the aorta. A reversed saphenous vein interposition graft is anastomosed end to side along the lateral aspect of the superior mesenteric artery. An end-to-end anastomoses is performed from the graft to the right or left renal artery (Fig. 54–71).

RENOVASCULAR SALVAGE SURGERY. Despite the successful patency rates that have been achieved with endovascular approaches, occasional patients remain who will need an open salvage procedure in the setting of postoperative complications or recurrent disease (Lacombe and Ricco, 2006). Surgical dissection is complicated by inflammatory changes. Renal artery stents preclude thromboembolectomy. Wide resection with interposition vein patch angioplasty is the primary choice with alternate bypass as a reserve option. Fibromuscular revisions fare better than atherosclerotic ones owing to less inflammatory reaction and a generally healthier population.

REVASCULARIZATION OF AN OCCLUDED RENAL ARTERY

Predictors of functional return after revascularization of an ischemic renal unit have been elucidated. **The kidney with a**

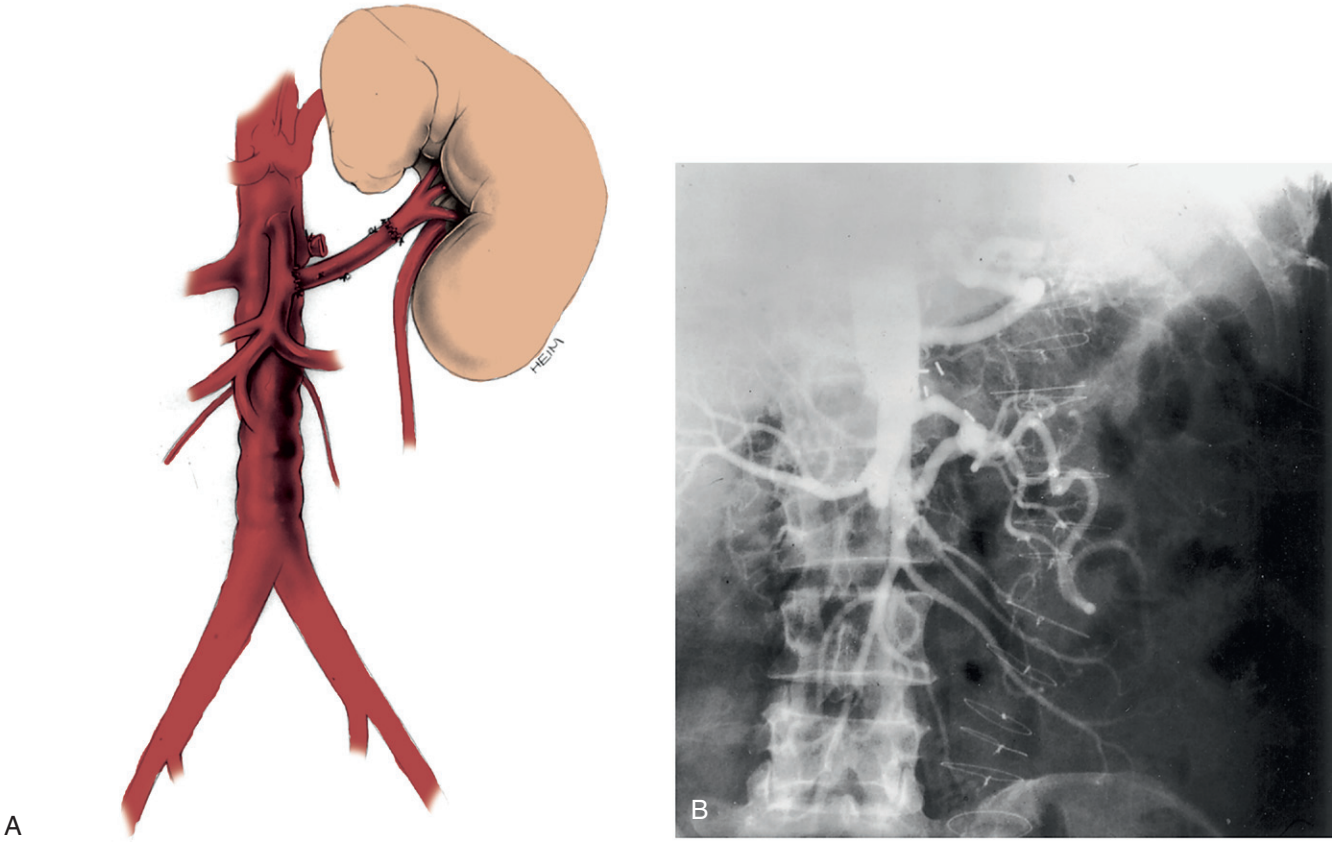


Figure 54–71. **A,** Technique of superior mesenterorenal bypass to the left kidney with a saphenous vein graft. **B,** Aortogram in a patient who underwent left mesenterorenal saphenous vein bypass shows excellent flow to the left kidney.

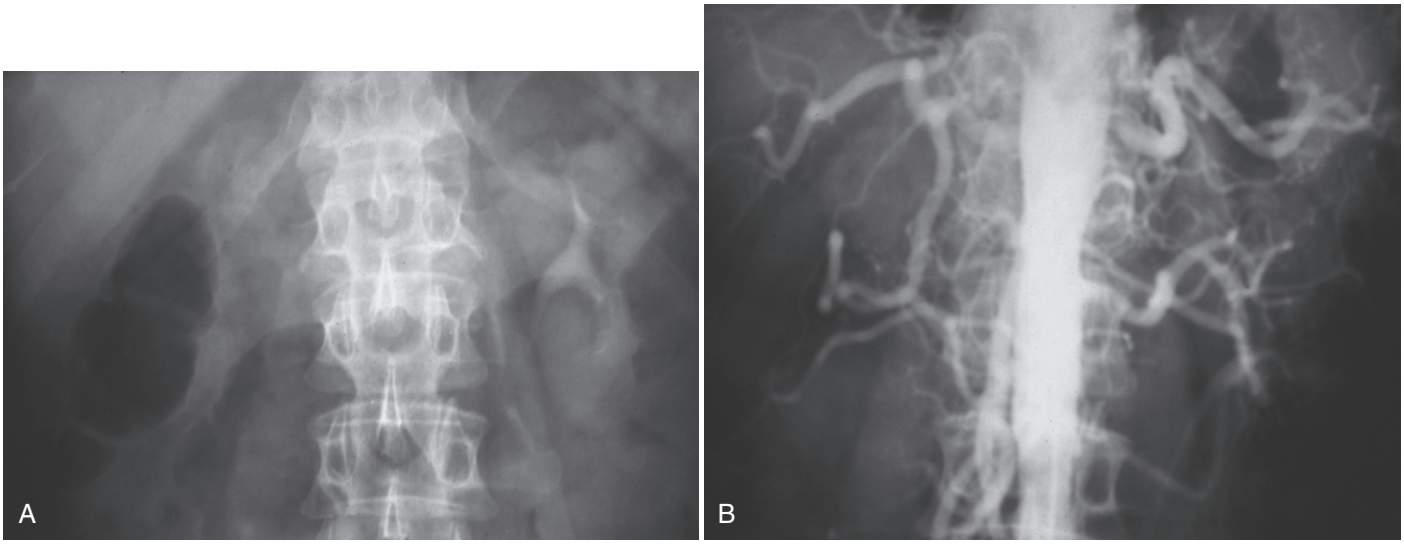


Figure 54–72. **A,** Preoperative intravenous pyelogram demonstrating functional left system with no contrast medium in the right system. **B,** Preoperative angiogram demonstrating complete occlusion of the right renal artery with extensive collateral vessels.

totally occluded renal artery may be revascularized when the following criteria are fulfilled: angiographic demonstration of a nephrogram, proximal occlusion with retrograde filling of distal circulation by perihilar collateral vessels, intraoperative back-bleeding from a renal arteriotomy distal to the occlusion, and demonstration on intraoperative frozen section or preoperative biopsy of an intact glomerular architecture (Zinman and Libertino, 1973, 1977; Libertino et al, 1980) (Figs. 54–72 and 54–73).

OUTCOMES AND COMPLICATIONS. Although open renovascular surgery has seen a significant decline in numbers, the success rates justify the role it continues to play in the treatment of renovascular hypertension. In more than 300 procedures performed at the

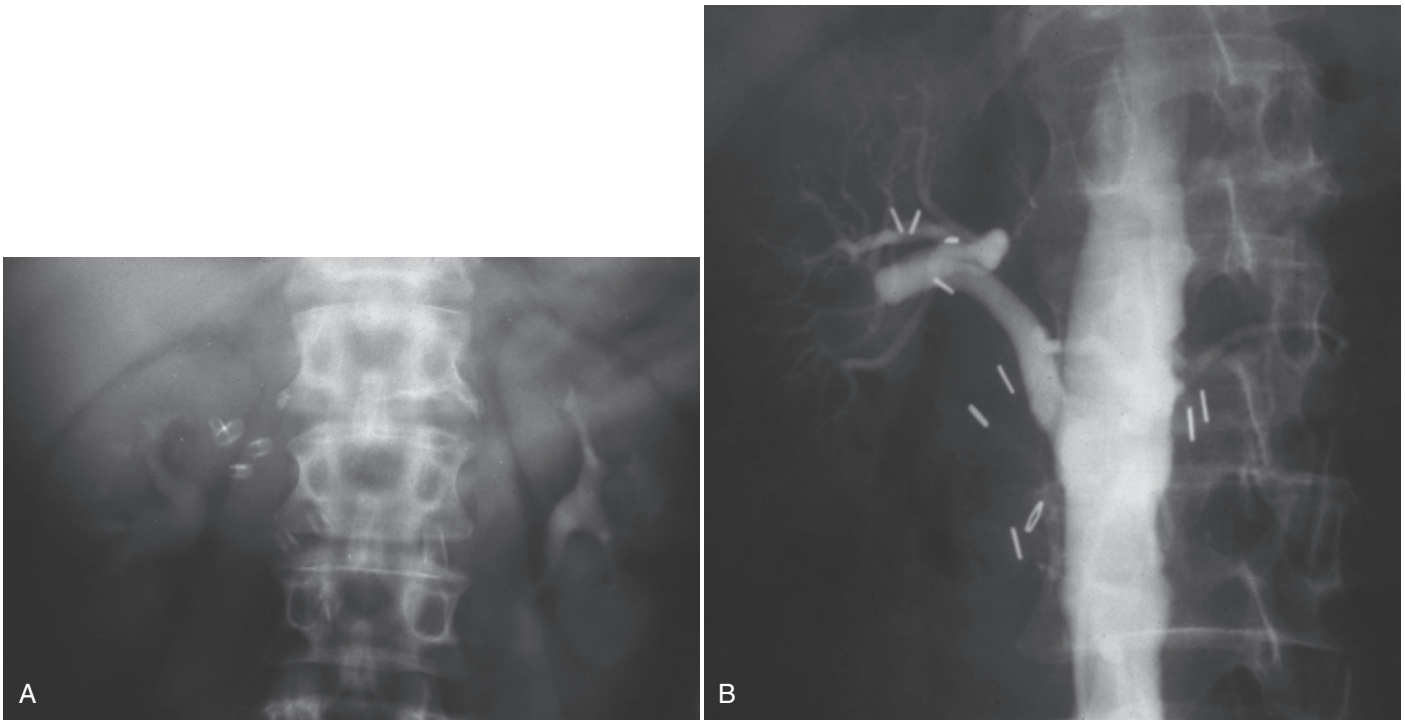


Figure 54–73. **A,** Postoperative intravenous pyelogram with contrast enhancement in the right collecting system. **B,** Postoperative angiogram with restoration of flow to the right kidney.

Lahey Clinic the overall success rate is 85%, and other contemporary series produce similar results (Lawrie et al, 1989; Libertino et al, 1992). The surgeon who performs open renovascular surgery is now confronted with a greater number of failed percutaneous approaches, which tend to have lower revascularization success rates. These procedures can be technically demanding and should be performed by persons with a strong background in vascular surgery.

Early complications include hemorrhage, thrombosis, subintimal dissection, false aneurysm, and distal branch vessel embolization. Postoperative bleeding is often attributable to surgical technique or overzealous anticoagulation. Covering the anastomoses with thrombogenic material such as Surgicel can limit bleeding. Perihilar vasculature is often collateralized and deserves attention during mobilization. False aneurysm formation can lead to delayed bleeding, as can infected suture lines. Postoperative thrombosis if recognized early enough is best treated with anastomotic revision.

Intimal dissection can occur in significantly atherosclerotic vessels during suture placement. Sutures that pass from intima to adventitia in theory have a lower chance of disrupting plaque. Atheroemboli can travel after clamping or unclamping a diseased aorta, resulting in a pulseless extremity requiring thromboembolectomy.

Extirpative Surgery. Reconstructive surgery is preferable to nephrectomy, considering that the kidney is fundamentally healthy and both atheromatous and mural diseases are potentially bilateral entities. The major determinant in favor of nephrectomy is poor viability or nonviability of the affected renal unit. In the presence of failed medical therapy and significant medical comorbidity a nephrectomy should be the primary therapy. Patients with complete occlusion of previous placed grafts may undergo a trial of streptokinase or tissue plasminogen activator if the occlusion is discovered early enough (<6 hours). Nephrectomy may be the treatment of choice for restenosis after reconstruction when the occlusion is unresponsive to tissue plasminogen activator and there is marginal function. Nephrectomy is also a suitable option for those with extensive unilateral arterial disease at the segmental level (multiple branch-point lesions) in the setting of normal contralateral renal function.

Partial nephrectomy in this situation is based on the premise that the disease process is localized and that preservation of normal remaining nephrons is worth the increased operative time and surgical risk. Patients with branch lesions that produce segmental ischemia and localized overproduction of renin may be treated by arterial bypass when the segmental branch is large enough; by arteriotomy and dilation, especially in pediatric patients; or by partial nephrectomy with an upper, lower, or midsegmental renal resection. Knowledge of the segmental blood supply to the kidney is essential for proper performance of partial nephrectomy.

Midpolar partial nephrectomy may be useful in patients with segmental lesions that affect the superior or inferior branches of the anterior segmental renal artery (Fig. 54–74). Selective arteriography is essential to understand the arrangement and distribution of the anterior and posterior arterial branches. Venography and segmental venous renin assays are obtained from the venous branches draining the affected tissue. These tests are helpful when main renal vein renin levels do not lateralize.

Extracorporeal Renal Surgery and Autotransplantation

Background

The first successful renal autotransplant was recorded by J. D. Hardy in 1963 for ureteral disease. Since that time the indications for "renal bench" surgery have broadened and have resulted in

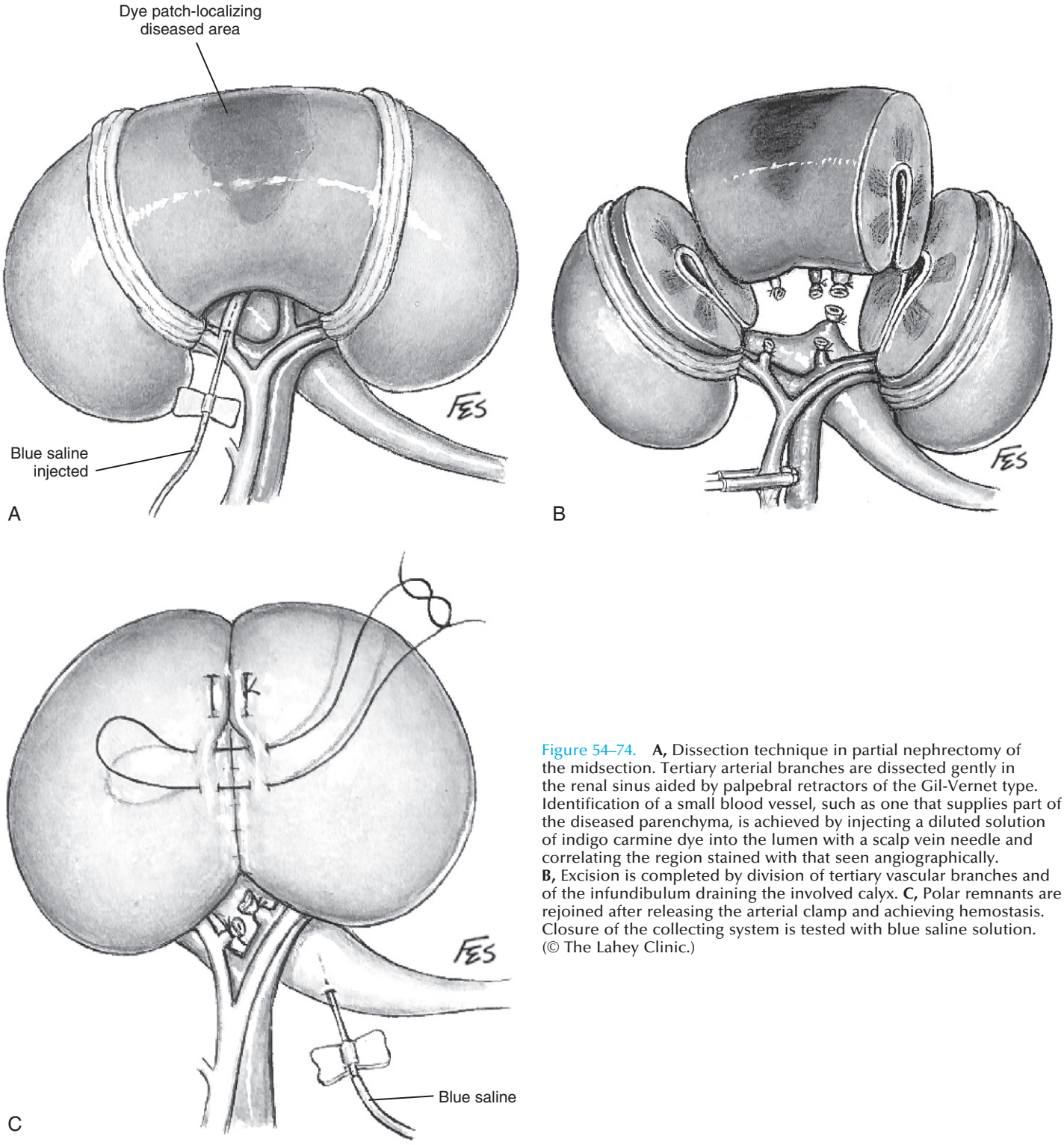


Figure 54–74. **A,** Dissection technique in partial nephrectomy of the midsection. Tertiary arterial branches are dissected gently in the renal sinus aided by palpebral retractors of the Gil-Vernet type. Identification of a small blood vessel, such as one that supplies part of the diseased parenchyma, is achieved by injecting a diluted solution of indigo carmine dye into the lumen with a scalp vein needle and correlating the region stained with that seen angiographically. **B,** Excision is completed by division of tertiary vascular branches and of the infundibulum draining the involved calyx. **C,** Polar remnants are rejoined after releasing the arterial clamp and achieving hemostasis. Closure of the collecting system is tested with blue saline solution. (© The Lahey Clinic.)

improved clinical outcomes (Ota et al, 1967; Husberg et al, 1975; Putnam et al, 1975; Wotkowicz and Libertino, 2004). Complex renovascular disease, renal tumors, and staghorn calculi have been the mainstay of the authors' experience. Extracorporeal partial nephrectomy was described more than 30 years ago for renal cell tumors and provides an alternative to dialysis in select patients. Laparoscopy has also been added to the field to help limit morbidity and speed recovery (Fabrizio et al, 2000; Meng et al, 2003).

Many of the initial feasibility studies were performed in canine models and gradually expanded to the human population (Belzer et al, 1970). Vascular repair of complex intrarenal disease is performed using native veins of saphenous, splenic, and iliac origin or hypogastric arterial grafts. The last is often best suited to pediatric or young adult populations with limited size discrepancy and a lack of atherosclerotic disease. Technical advances with respect to surgical magnification have expanded the indications. **Overall**

Key Points: Renovascular Surgery

- The primary disease entities necessitating revascularization include atherosclerosis (75%) and fibrous dysplasia (25%).
- Patients can present with hypertension and renal insufficiency when the lesion is chronic. Less than 3% of the hypertensive population has a renovascular etiology versus an estimated 18% to 20% of patients undergoing cardiac angiography and 35% to 50% of patients with aortic occlusive disease.
- Causes include atherosclerosis, mural dysplasia, renal aneurysms, embolic disease, trauma, arteriovenous malformations, Takayasu disease, and neurofibromatosis.
- Indications for surgical or percutaneous (angioplasty or stenting) intervention are listed in Table 54–9.
- In general, patients who have an elevated creatinine concentration, poor functional studies, or unfavorable histology are unlikely to benefit from revascularization.
- Almost all disease processes affecting renal artery patency, particularly the fibrodysplasias, may be bypassed with an aortorenal graft. Other options include hypogastric autografts, splenorenal arterial bypass, hepatorenal and gastroduodenal artery bypass, ileorenal bypass, thoracic aortorenal bypass, and mesenterorenal bypass.
- The autogenous saphenous vein has emerged as the preferred graft in adults.
- The kidney with a totally occluded renal artery may be revascularized when the following criteria are fulfilled: angiographic demonstration of a nephrogram, proximal occlusion with retrograde filling of distal circulation by perihilar collateral vessels, intraoperative back-bleeding from a renal arteriotomy distal to the occlusion, and demonstration on intraoperative frozen section or preoperative biopsy of an intact glomerular architecture.
- The major determinant in favor of nephrectomy is poor viability or nonviability of the affected renal unit.

renal insult associated with these complex procedures has been limited with advances in hypothermic perfusates commonly used in transplantation, which provide an isotonic external milieu (Belzer et al, 1992). **In limiting membrane transport the metabolic requirements decrease while maintaining cellular integrity. In addition the cold solution shrinks parenchyma, leading to better vascular and collecting system exposure** (Novick et al, 1979).

Indications

Most arterial disease requiring bench approaches have extension at and beyond the anterior and posterior division branch points (Fig. 54–75). Stenotic lesions and aneurysms may be resected and repaired with interposition saphenous vein grafts. Multiple branch lesions may be amenable to hypogastric artery interposition utilizing the branches of the internal iliac artery when atherosclerosis is absent. Renal tumors have also been removed utilizing an ex-vivo approach in select patient populations (solitary kidneys), with limited small volume series in the literature (Fig. 54–76) (van der Velden et al, 1992). The ureter can be affected by the numerous processes (trauma, iatrogenic, and inflammatory) that lead to urinary obstruction or extravasation. Left untreated, these patients develop chronic infections and eventual renal failure. Recurrent nephrolithiasis can lead to ureteral stenosis secondary to repeat trauma from ureteroscopy and scarring from percutaneous approaches. **Indications for autotransplantation include tumors in solitary kidneys, recurrent staghorn calculus and concomitant renovascular disease, sterile urine and recurrent nephrolithiasis causing damage to a ureter, calculi associated with congenital abnormalities, or extensive ureteral stricture. Transitional cell carcinoma of the renal pelvis or ureter in solitary kidneys can be managed with this approach.**

Although an ileal segment interposition graft can obviate the need for ureteroscopy, the long-term metabolic sequelae are not

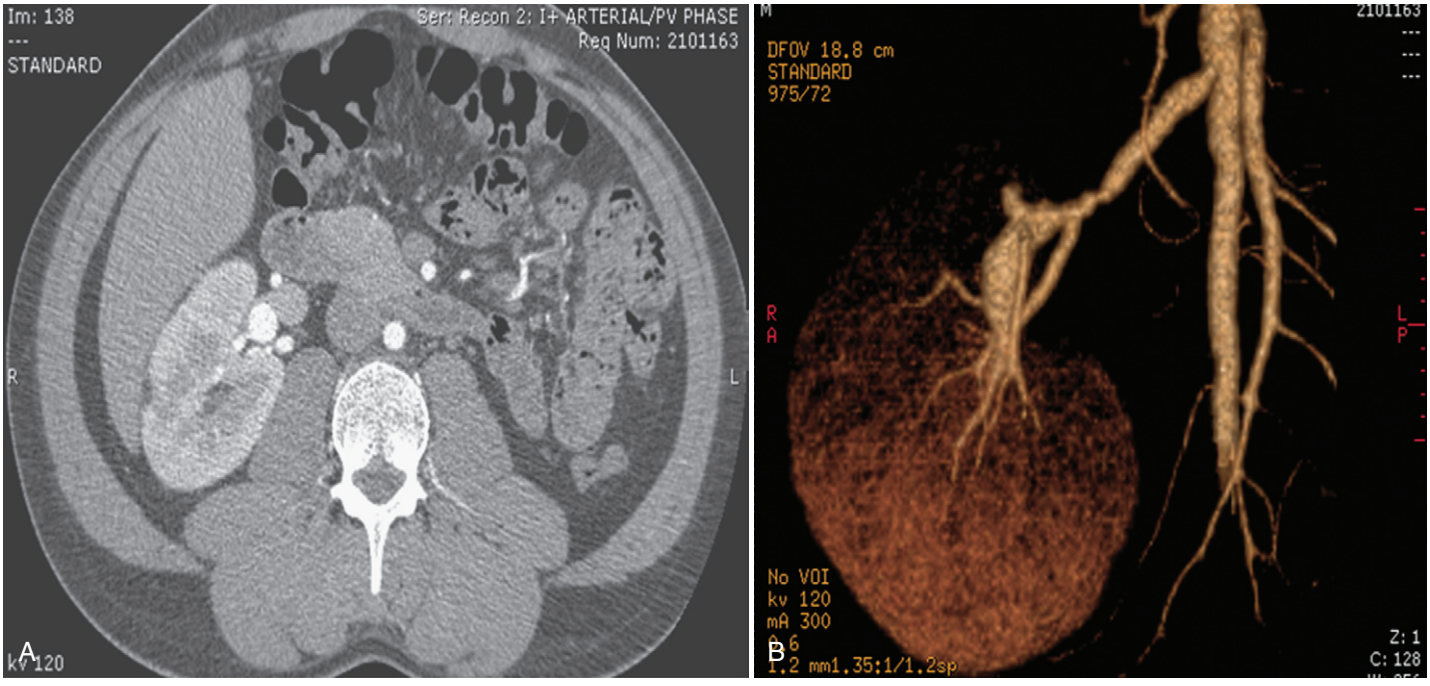


Figure 54–75. **A,** CT scan in a 33-year-old man with an atrophic left kidney and fibromuscular dysplasia and a 2.4-cm aneurysm in the right kidney and uncontrolled hypertension. **B,** Three-dimensional reconstruction demonstrates location of renal artery aneurysm.

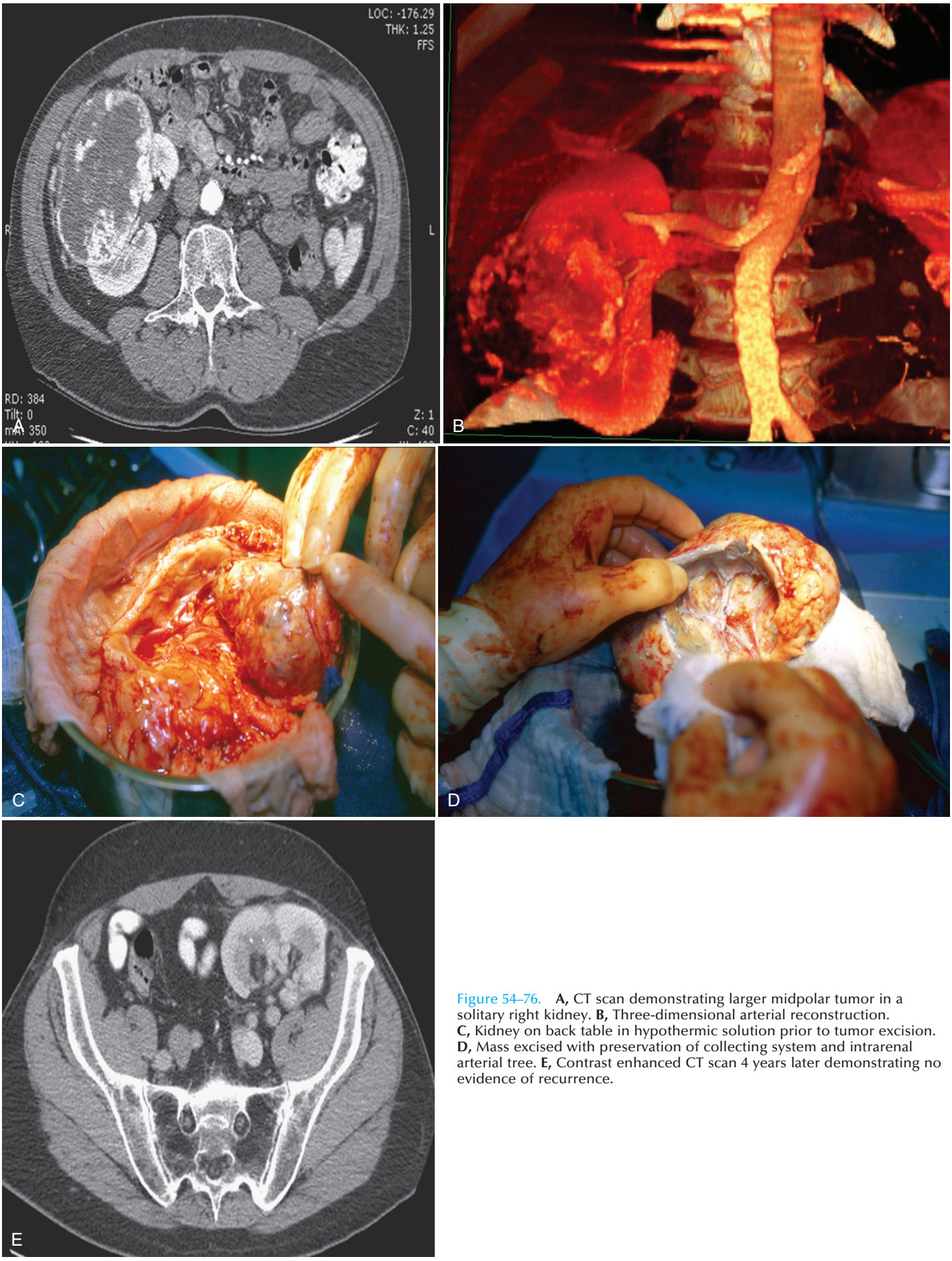


Figure 54–76. **A,** CT scan demonstrating larger midpolar tumor in a solitary right kidney. **B,** Three-dimensional arterial reconstruction. **C,** Kidney on back table in hypothermic solution prior to tumor excision. **D,** Mass excised with preservation of collecting system and intrarenal arterial tree. **E,** Contrast enhanced CT scan 4 years later demonstrating no evidence of recurrence.

insignificant (Chung et al, 2006). Autotransplantation, pyelovesicostomy, and a Boari flap can minimize reflux and allow passage of stones (Olsson and Idelson, 1980).

Autotransplantation is an acceptable option for complicated tumors in solitary kidneys and bilateral malignancies. A pyelovesicostomy is recommended to facilitate easy surveillance. Patients with traumatic arterial injuries can also be treated with autotransplantation.

Preoperative Evaluation and Preparation

In addition to preoperative screening, renal and pelvic anatomy are evaluated with dedicated 3D CT angiography, paying specific attention to the iliac vessels. The hypogastric artery and associated branches are ideal conduits for complex multiple-vessel repairs given their size, which is similar to the native renal artery branches. Renal functional scans (e.g., MAG3) should document at least 15% to 25% of the global renal function before surgery. Kidneys with extensive small vessel disease and compromised parenchyma are limited by poor flow dynamics and decreased filtration capabilities and are not candidates for renal autotransplantation. Patients with chronic renal insufficiency or solitary kidneys must consent for placement of vascular dialysis catheters before surgery, and the authors' nephrology colleagues are made aware of this procedure.

Surgical Procedure

The advantages of renal bench surgery include a bloodless field and optimal exposure of the vascular tree and collecting systems. The ideal length of cold ischemic time should be no greater than 5 to 6 hours. Ex-vivo repair also allows the integrity of the anastomosis to be tested before reimplantation. The technical aspects of bench surgery are demanding and should be performed in high-volume centers with surgeons experienced in vascular and transplantation surgery. The authors prefer a flank approach for an adrenal-sparing donor nephrectomy with preservation of the proximal one third of the ureter. The kidney is completely mobilized and vessel loops passed around the main renal artery and vein. Renal vessels and ureter are dissected to provide maximum length (Fig. 54–77). Mannitol may be given before ligation and division of the vasculature to promote diuresis. Hypothermic University of Wisconsin solution is the authors' choice for perfusate on removal and initiation of extracorporeal surgery (Belzer et al, 1992). Once the feasibility of the extracorporeal repair has been determined a second team can reposition the patient supine and expose the ipsilateral fossa for reimplantation via a Gibson incision. A single midline incision is another approach that allows access to both operative sites and keeps the ureter in continuity. After the vessels are taken the abdominal wall serves as a bench for microvascular repair or removal of tumor.

Once the renal vessels have been ligated the kidney is flushed with hypothermic solution and placed in an ice-slush solution to minimize ischemia. For vascular anastomosis 5-0 and 6-0 polypropylene is preferred; however, finer suture can be used with surgical magnification. Both native and graft vessels are intermittently flushed with heparinized saline to minimize clot formation. Arterial spasm can be alleviated with papaverine flushes. The integrity of the anastomosis is evaluated with flushing of hypothermic solution (see Figs. 54–78 [on the Expert Consult website] and 54–79).

For flank approaches a standard curvilinear Gibson incision provides access to the iliac fossa and vessels. Cautious dissection and ligation of surrounding lymphatics is imperative to prevent postoperative lymphocele formation and to minimize the risk of suture line infections. The external vein is mobilized cephalad to the junction where the internal iliac artery crosses over. The venous anastomosis between the renal vein and external iliac vein is completed with continuous or running 5-0 polypropylene in an end-to-side fashion. A disease-free internal iliac artery is anastomosed with continuous or interrupted 6-0 polypropylene to the renal artery end to end. If there is evidence of disease not detected with preoperative imaging then an end-to-side approach is advisable to limit stenosis, recognizing that perfusion pressures may be lower secondary to flow turbulence. Intraoperative ultrasonography can be performed to assess inflow. Surgicel may be wrapped around the anastomosis to ensure hemostasis at needle sites, which tend to ooze once systemic anticoagulation is initiated after surgery. The ureter is reimplanted using an extravesical Grégoire-Lich anastomosis or a Leadbetter-Politano tunneled reimplant using absorbable suture (Figs. 54–80 and 54–81). A psoas hitch and/or Boari flap may be required for extremely short ureters. A 6-Fr transplant double-J stent is next placed across the anastomosis. A Penrose drain or 7-Fr Jackson-Pratt drain is left for 24 to 48 hours.

Postoperative Care and Complications

Elevated lactate dehydrogenase levels can also indicate the presence of a renal infarct. A MAG3 scan can be obtained to evaluate uptake and excretion, but the majority of kidneys repaired ex vivo show immediate and somewhat prolonged periods of acute tubular necrosis. Patients will need to be on systemic heparin therapy during the immediate postoperative period, which increases the risk of hemorrhage and anastomosis rupture. Vascular leaks or thrombosis occur in 1% to 2% of transplants and need urgent surgical revision. Peritransplant fluid collections are of concern and need to be evaluated and treated. Collections discovered between weeks 1 and 3 are usually urinomas and occur in 4% to 5% of transplanted kidneys. Depending on severity they can be managed with revision of the ureteroneocystotomy or stent placement. Fluid collections presenting at 3 to 6 months represent lymphocele formations and occur in 5% to 10% of patients. Presenting symptoms include ureteral obstruction with rising creatinine concentration and iliac vein compression with lower extremity edema. Small lymphoceles can be managed conservatively whereas larger ones require more invasive procedures, such as percutaneous drainage or sclerosing agents. When percutaneous approaches fail, a peritoneal window can be created laparoscopically to facilitate permanent drainage. Patients with infected urine and extravasation can progress to abscess formation, suture line infection, and graft loss.

Outcomes

Numerous investigators have reported acceptable outcomes with extracorporeal surgery and renal autotransplantation. The authors' success rate is 90% in more than 25 autotransplants, primarily for renovascular disease. Other contemporary series demonstrated similar results with resolution of hypertension in over 90% of patients with preserved or improved renal function, respectively (Jordan et al, 1985; Novick et al, 1990a; Wotkowicz and Libertino, 2004).

These outcomes support the role of autotransplantation for renovascular disease. Numerous case reports and small series demonstrate the feasibility of the procedure for additional indications as listed previously.

Partial Nephrectomy for Benign Disease

In addition to treating malignant disease, which is discussed later in the chapter, partial nephrectomy can also be used for localized

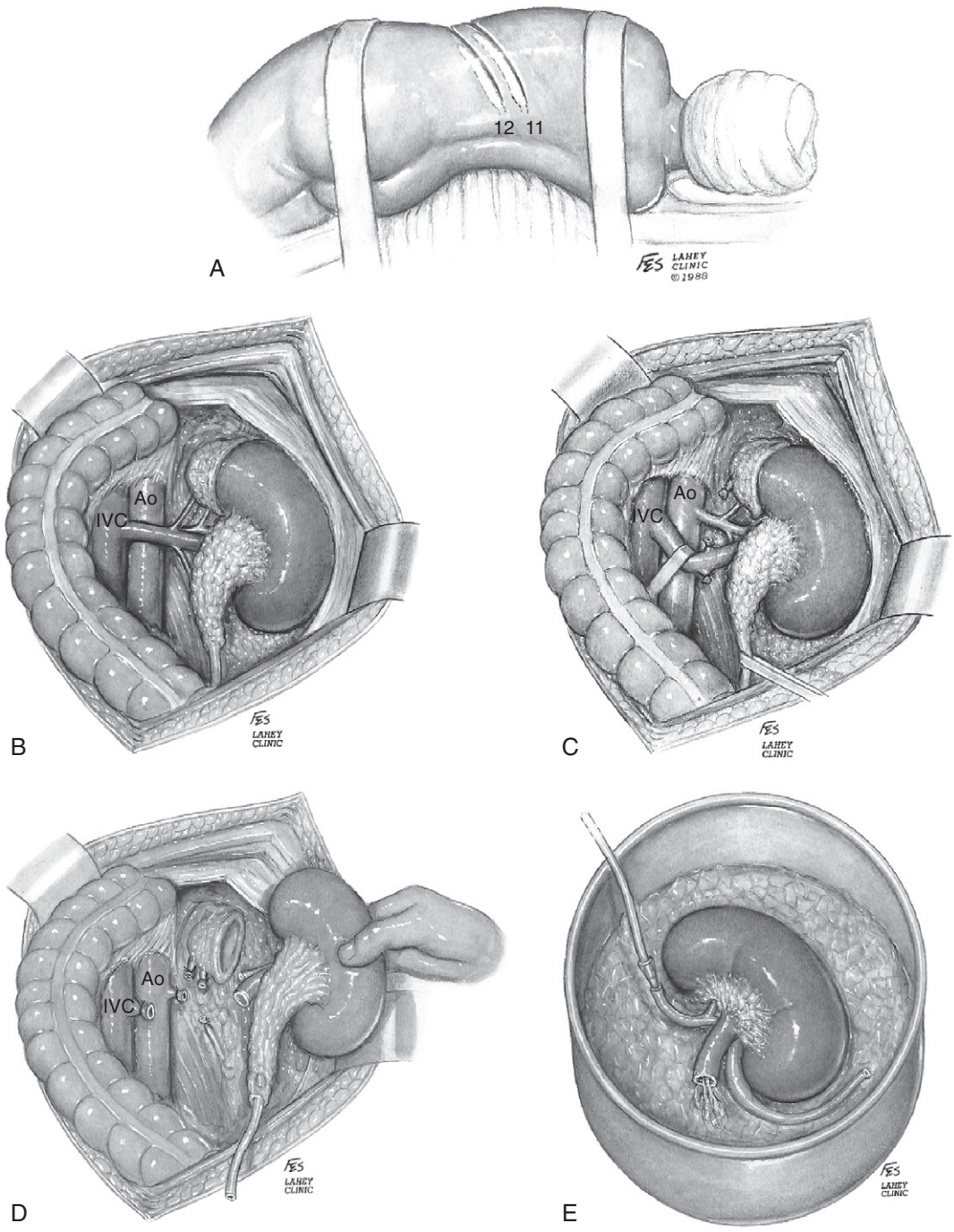


Figure 54–77. Nephrectomy for autotransplant is shown. **A,** Patient is placed in the flank position. An 11th rib supracostal incision maximizes renal exposure. **B,** Dissection of the left kidney demonstrates exposure of the renal vein to its origin at the vena cava (IVC). **C,** After ligation of the adrenal and gonadal vessels, the renal vein is mobilized to expose the renal artery. **D,** Division of the renal vessels is at the origin of the aorta (Ao) and vena cava. The ureter is transected below the pelvic brim. Care is taken not to maintain adventitial tissue or ureter. **E,** Chilled preservation solution (heparinized lactated Ringer solution) is perfused through the renal artery. (© The Lahey Clinic.)

benign disease of the kidney (Leach and Lieber, 1980). The indications include hydronephrosis with parenchymal atrophy or atrophic pyelonephritis in a duplicated renal segment; calyceal diverticulum complicated by infection, stones, or both; calculus disease with obstruction of the lower pole calyx or segmental parenchyma disease with impaired drainage (Papathanassiadis and Swinney, 1966; Bates et al, 1981); renovascular hypertension due to segmental parenchymal damage or noncorrectable branch renal artery disease (Aoi et al, 1981; Parrott et al, 1984); traumatic renal injury with irreversible damage to a portion of the kidney (Gibson et al, 1982); and removal of a benign renal tumor, such as an angiomyolipoma or oncocytoma (Maatman et al, 1984).

In a partial nephrectomy for suspected malignancy the renal capsule is excised along with the specimen. **In benign disorders a flap of renal capsule can be reflected off the diseased parenchyma and used in renorrhaphy** (Figs. 54–82 and

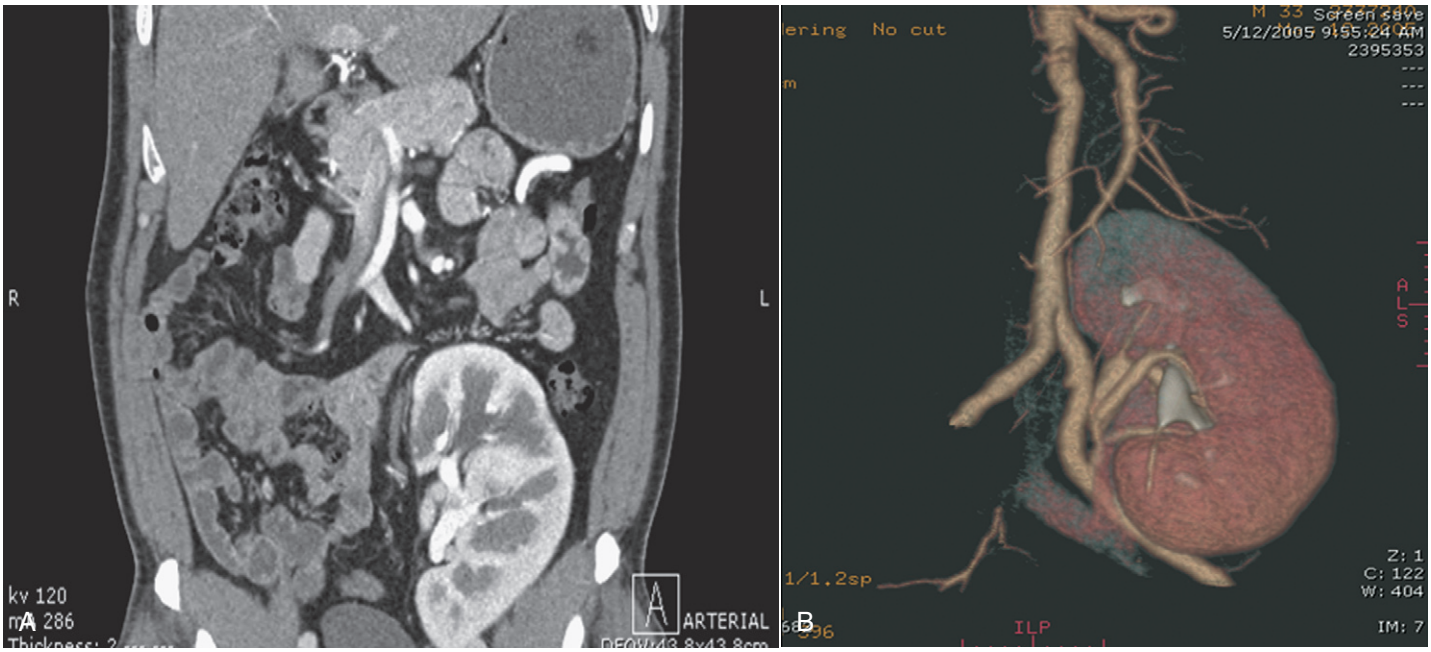


Figure 54–79. **A,** Follow-up CT scan 3 years after operation demonstrates good renal function and lack of aneurysm. The patient takes no antihypertensive medication. **B,** Three-dimensional reconstructions demonstrate no aneurysmal dilation.

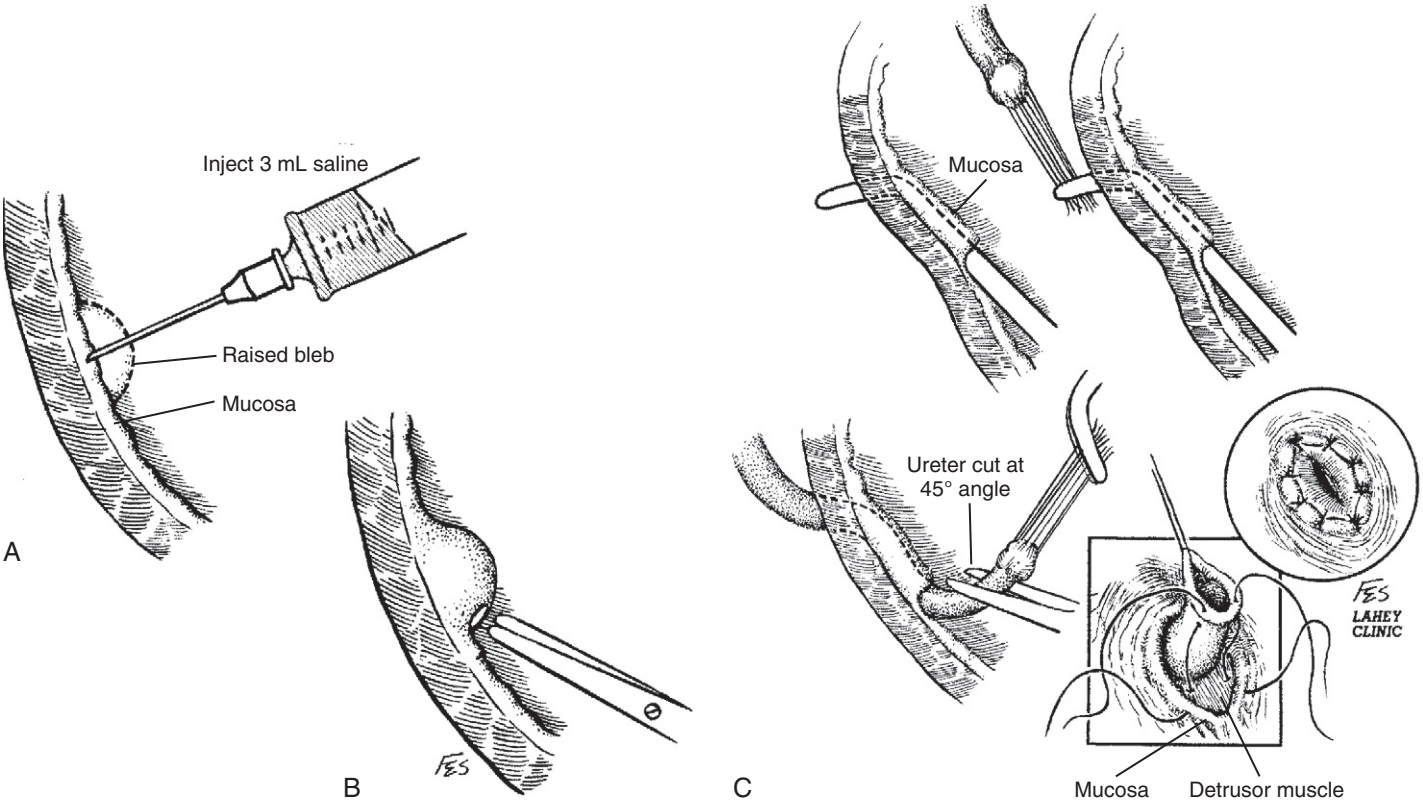


Figure 54–80. Modification of the Politano-Leadbetter technique is shown. **A** and **B,** The submucosal tunnel is created. Injection of 3 mL of saline raises the mucosal layer and permits earlier dissection. **C,** Right-angle clamp is placed along the mucosal tunnel. (© The Lahey Clinic.)

54–83). The remaining techniques are the same as those described for malignant disease.

Heminephrectomy can be carried out in a duplicated collecting system. The division between the specimen and what will be remnant parenchyma is evident from atrophy of the diseased segment or can be delineated by pyelotubular backflow after distending the affected collecting system with blue dye. Segmental arterial and venous branches to the diseased portion of the kidney are ligated and divided. Clamping of the artery supplying the nondiseased segment is usually unnecessary. Renorrhaphy

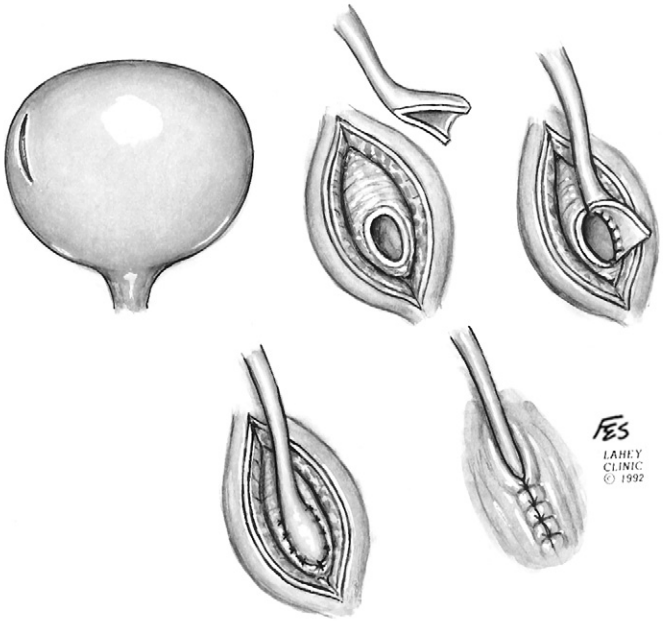


Figure 54–81. The Grégoire-Lich technique of extravesical ureteroneocystostomy is shown. (© The Lahey Clinic.)

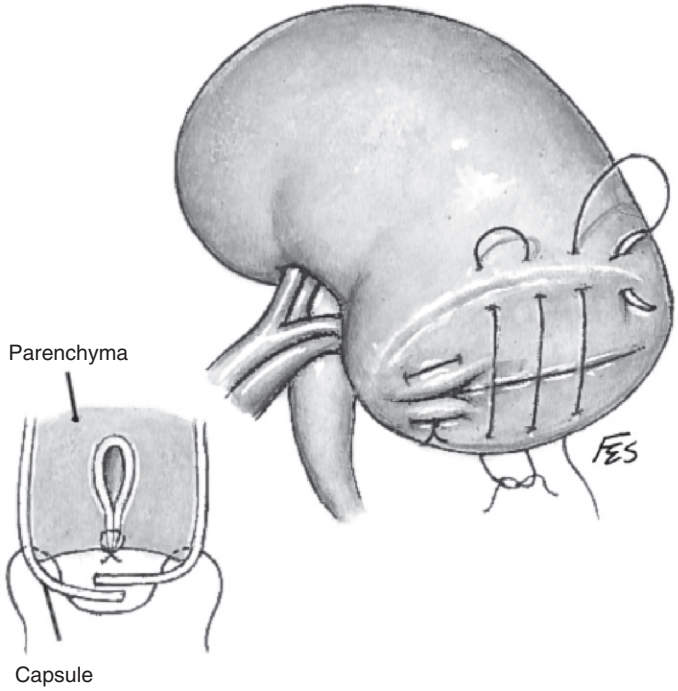


Figure 54–82. Closure of capsular layer over cut edge of renal parenchyma. Horizontal mattress sutures of 3-0 catgut catch free edges of capsule. View after arterial hemostasis has been completed and after the collecting system has been closed. (© The Lahey Clinic.)

proceeds as described for malignancy, although the remnant collecting system in a duplex system will not have been violated and therefore will not require repair.

Stone Surgery

Open surgery for nephrolithiasis is rare, making up less than 2% of stone procedures in contemporary practice (Kerbl et al, 2002; Matlaga and Assimos, 2002). Appropriate candidates for open stone surgery have failed less invasive techniques such as extracorporeal shockwave lithotripsy or endoscopic treatment, have anatomic abnormalities precluding less invasive treatment, or have an exceedingly complex stone array.

Pyelolithotomy

Pyelolithotomy can be effective in removing a small stone burden. This is rarely performed as a solitary procedure because efficacious minimally invasive techniques are more commonly employed. The kidney is approached through a flank or extraperitoneal anterior subcostal incision. The Gerota fascia is opened. The kidney is mobilized within the Gerota fascia and reflected medially to expose the posterior surface. The ureter is located inferiorly and tracked superiorly past the UPJ to the hilum. A U-shaped incision is made on the pelvis, avoiding the UPJ. A forceps is passed through the pyelotomy and is used to remove the stones. A nephroscope also can be employed to inspect the collecting system. A ureteral catheter is passed in an antegrade fashion to ensure that the ureter is free of stone debris. The pelvis is closed with a 4-0 absorbable suture, a Penrose drain is externalized, and the wound is closed in layers.

Extended Pyelolithotomy and Radial Nephrolithotomy

For larger stones and staghorn calculi, a pyelolithotomy can be extended into the sinus after dissecting intrasinus fat away from the pelvis and infundibula. The U-shaped incision will start at the base of an inferior calyx and end at the base of a superior calyx. The stone is separated from the urothelium and removed with forceps. One can dilate an infundibulum to remove a large calyceal component of the stone. In cases in which a calyceal stone is too large to remove through the infundibulum, a radial nephrotomy can be done to extract the stone. The stone is localized by palpation through the capsule, and a radial capsulotomy is sharply made over the stone. The parenchyma is bluntly opened, and the stone is extracted with forceps. The nephrotomy is closed with 2-0 polyglactin suture and Surgicel bolster.

Anatrophic Nephrolithotomy

Knowledge of the segmental renal arterial circulation is fundamental to anatrophic nephrolithotomy. The parenchyma is divided at the border between anterior and posterior vascular segments, permitting removal of complex staghorn calculi.

A supracostal approach is advantageous. The Gerota fascia is opened and the kidney is mobilized. The hilum is sharply dissected, exposing the main renal artery and posterior segmental artery. The renal pelvis and ureter do not need to be mobilized. The arterial branch to the posterior segment is clamped. As the posterior segment whitens, administration of methylene blue permits identification of the border between the anterior and posterior segments, which marks a relatively avascular plane. The line is scored with cautery.

The main renal artery is occluded. The kidney is placed in an ice slush bath and allowed to cool. The capsule is sharply incised

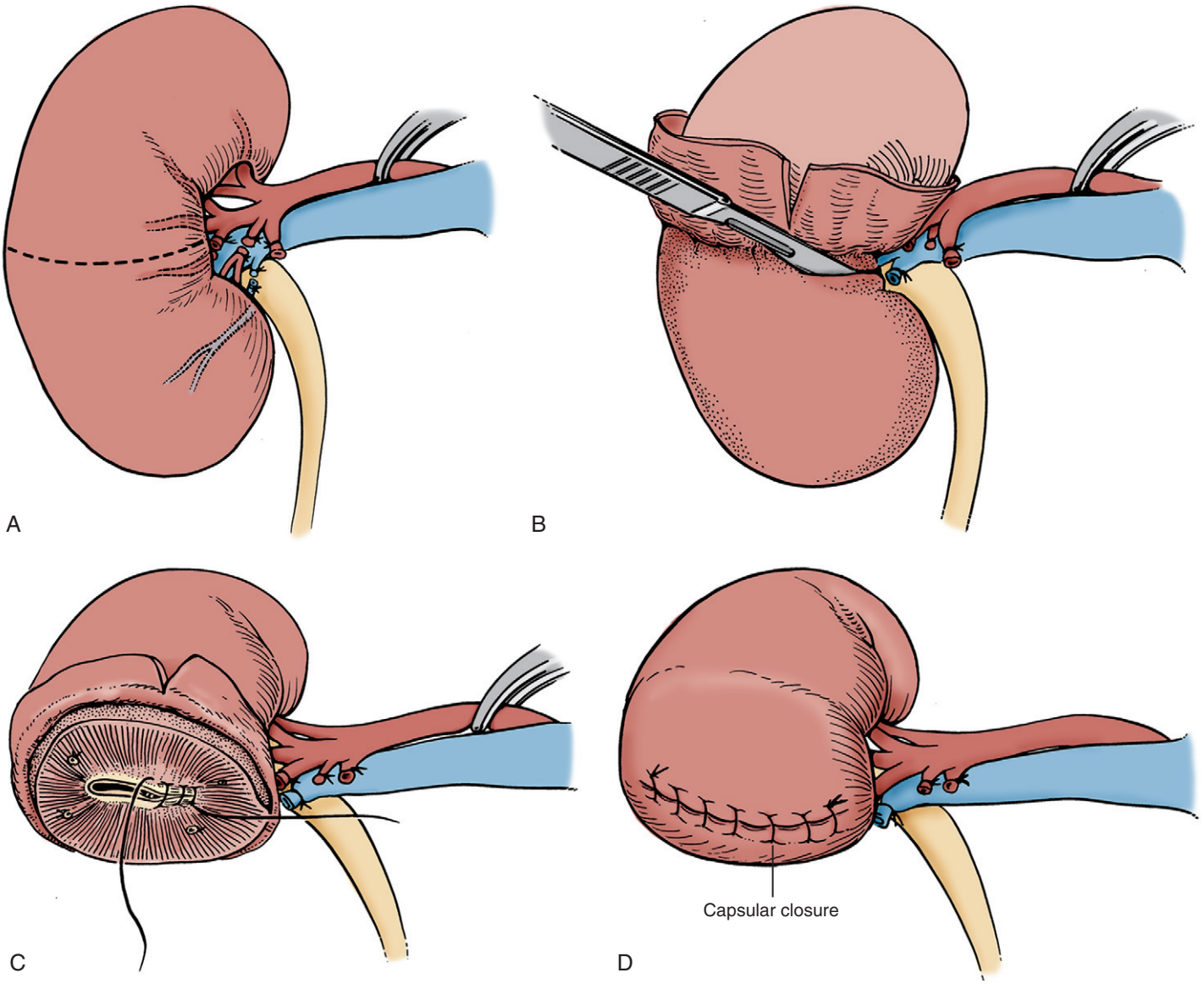


Figure 54–83. **A** to **D,** Technique of transverse renal resection for a benign disorder. The renal capsule from the diseased parenchyma is preserved and used to cover the transected renal surface.

along the border between the anterior and posterior segments, being careful to avoid the poles, which have a separate blood supply. The parenchyma is separated bluntly between the anterior and posterior segments. The renal pelvis and calyces are sharply incised, and the stone is removed. Intraoperative ultrasonography, fluoroscopy, and nephroscopy can be employed to ensure stone clearance.

A ureteral stent is placed in an antegrade fashion. The renal pelvis is reapproximated with a running 3-0 monocryl suture. Blood flow is restored to the kidney. Any bleeding vessels are sutured with 2-0 or 3-0 polyglactin. The renal capsule is closed with a running, locking 2-0 polyglactin suture. A Surgicel bolster can be employed. A Penrose drain is externalized through a separate stab excision.

Excision of Simple Renal Cysts

Simple renal cysts are characterized radiographically by thin walls; lack of septation, calcifications, or solid components; and lack of enhancement (Israel and Bosniak, 2005). Asymptomatic cysts are a common incidental radiographic finding. Mass effect from large cysts can cause symptoms or obstruction. Surgical excision of the cyst may be required and is usually handled laparoscopically (Fig. 54–84).

In the unusual circumstance that open surgery is required the kidney is approached through an extraperitoneal flank, dorsal lumbotomy, or anterior approach. The best approach is determined by the size and location of the cyst. After the Gerota fascia is opened, the perirenal fat surrounding the cyst and nearby parenchyma is mobilized. The field is packed to protect surrounding tissues in the event of spillage. A needle is used to aspirate the contents of the cyst, which are sent for cytologic evaluation and culture. The cyst is entered sharply with scissors. The wall of the cyst is excised near normal parenchyma, leaving a few millimeters of cyst wall to be oversewn. Biopsy of the cyst base is performed if there is intraoperative suspicion for malignancy. If frozen section is consistent with malignancy, partial nephrectomy is performed. Otherwise, the cut edges are oversewn with 2-0 polyglactin suture

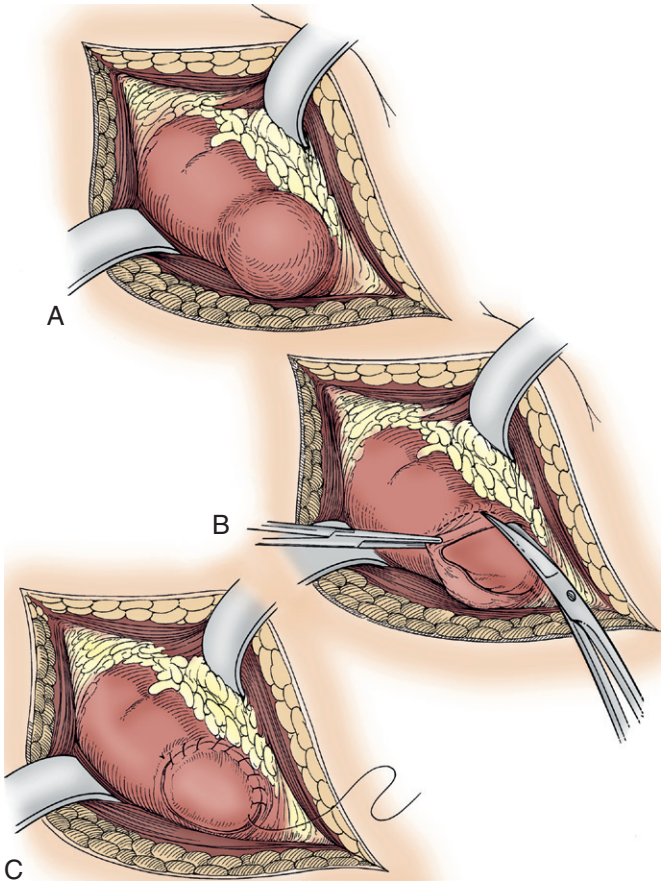


Figure 54–84. **A** to **C,** Technique of excision of renal cyst.

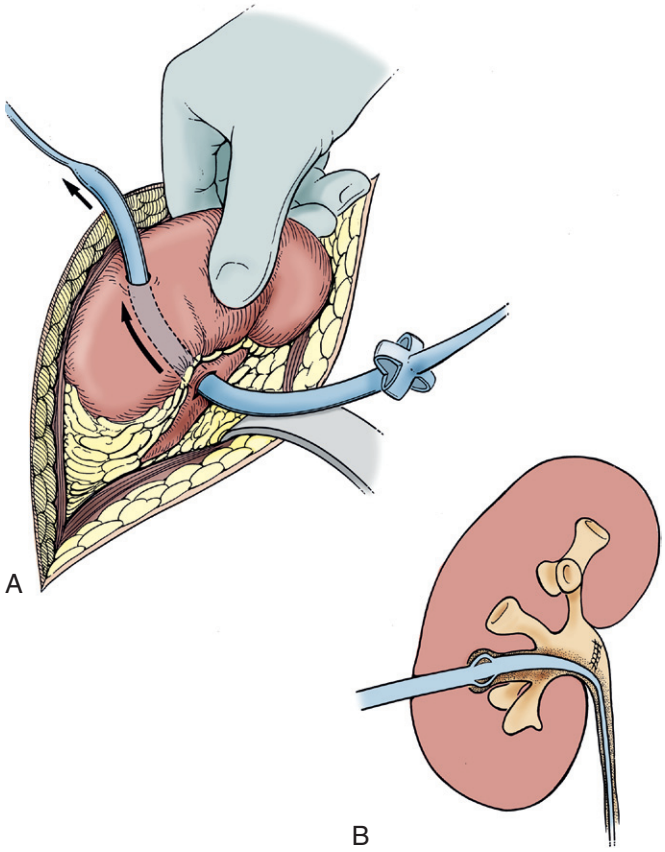


Figure 54–85. **A** and **B,** Technique of open nephrostomy tube insertion.

for hemostasis. Cautery is employed as needed and can be used in the spray mode to cauterize the lining of the cyst. For infected cysts, a drain is externalized.

Open Nephrostomy

With the widespread adoption of percutaneous nephrostomy drainage and endoscopic placement of ureteral stents, open insertion of a nephrostomy tube has become rare. **When endoscopic and percutaneous approaches have failed, open nephrostomy can be lifesaving** (Fig. 54–85). A nephrostomy tube may also be inserted as an adjunct to an open reconstructive procedure such as pyeloplasty or ureterocalicostomy (Willscher and Conway, 1987).

The kidney is approached through a retroperitoneal flank incision. The Gerota fascia is opened laterally. The kidney is mobilized within the Gerota fascia and reflected medially to expose the posterior surface. The ureter is located inferiorly. Dissection proceeds superiorly along the ureter to the renal pelvis. Two 2-0 polyglactin stay sutures are placed in the renal pelvis a safe distance away from the UPJ. With a hooked scalpel, a 2-cm incision is made parallel to the long axis of the kidney between the holding sutures, avoiding the UPJ.

A silk suture is passed through the tip of a Malecot catheter. A Randall stone forceps is passed through the pyelotomy into a lower pole calyx. The tip of the forceps is aimed at the convex border of the kidney, because a nephrostomy on the anterior or posterior surface of the kidney has a higher risk of hemorrhage from damage to intrarenal vessels. While pressure is applied with the forceps, the tip of the forceps is palpated at the convex border of the kidney. A radial capsulotomy is made over the tip of the forceps. The tract through the parenchyma is widened slightly by opening the forceps, which is then used to grasp the silk suture. The forceps is gently withdrawn back through the pyelotomy, while reducing the wings of the Malecot catheter by pulling on the distal aspect of the tube. The tube is thus drawn through the tract, placing the tip in the lower calyx. The silk suture is removed. Rather than using a curved clamp and a Malecot catheter, one can use a Willscher nephrostomy tube, which is equipped with a stylet to puncture the parenchyma.

The tube is sutured to the renal capsule using a 3-0 absorbable purse-string or figure-of-eight suture. The tube is externalized through a separate anterior flank stab incision, ensuring that the tube does not kink. It should not exit beneath a supine patient.

The pyelotomy is closed with a running 4-0 monocryl suture, and the holding sutures are removed. The nephrostomy tube is secured to the skin using a heavy silk suture. A Penrose drain is placed in the region of the repaired pyelotomy and externalized through an additional stab incision. The wound is closed in layers.

Postoperative care of the tube is directed at prevention and treatment of obstructed drainage. The tube should be gently irrigated if it is not draining appropriately. If irrigation does not restore flow or if irrigant exits around the catheter insertion site, antegrade nephrostography should be performed to assess tube position. It is essential to adequately secure the tube at the skin level to prevent dislodgement. The tube should be replaced under fluoroscopic guidance every 6 to 8 weeks, or more frequently if the patient is prone to stone encrustation.

Renal Biopsy

Since the first description of percutaneous renal biopsy nearly 60 years ago (Iversen and Brun, 1951), the role of open renal biopsy has gradually diminished. Generally, open renal biopsy is indicated when a percutaneous biopsy might be associated with excessive risk, such as in patients with a solitary kidney or uncorrected coagulopathy. Open surgery enables hemostasis and provides more tissue for evaluation than percutaneous biopsy. Laparoscopy also permits hemostasis and should be considered before open surgery. The authors have not performed an open renal biopsy at the Lahey Clinic since 1975.

The kidney is approached through a dorsal lumbotomy or subcostal flank incision. The right kidney, which is more inferior, more readily lends itself to biopsy and is preferred. After the Gerota fascia is entered the perirenal fat surrounding the lower pole is mobilized. Two fine absorbable stay sutures are placed in the renal capsule. A third stay suture is placed between them into the parenchyma. An elliptical incision is made in the renal capsule around the third suture, measuring 0.5 to 1.0 cm by 1.0 to 2.0 cm. A wedge biopsy is then performed by deepening the elliptical incision on an angle toward the center of the specimen. The biopsy should include renal cortex and medulla, although deep biopsies risk entry into the collecting system and should be avoided. The capsule is closed primarily using the stay sutures. A Surgicel bolster can be employed. Excellent hemostasis should be assured before the wound is closed in layers.

SURGERY FOR MALIGNANCY

Radical Nephrectomy

Indications and Evaluation

Radical nephrectomy involves the en-bloc removal of the kidney outside the Gerota fascia together with the ipsilateral adrenal gland as well as complete regional lymphadenectomy from the crus of the diaphragm to the aortic bifurcation (Robson et al, 1969; Skinner et al, 1971). **Whereas partial nephrectomy is the treatment of choice for T1 tumors when feasible, radical nephrectomy remains the definitive therapy for T2 or larger tumors.**

Clinical staging of renal cell carcinoma involves radiologic evaluation of tumor size, extension beyond the Gerota fascia and into adjacent structures, venous involvement, and evaluation for nodal and metastatic disease. Renal cell carcinoma is staged with the 2010 American Joint Committee on Cancer (AJCC) TNM staging classification (Tables 54–10 and 54–11). Preoperative radiographic studies such as ultrasonography, CT, and MRI are important. Through preoperative imaging, one is able to determine the clinical stage of the tumor, define the anatomy of the affected kidney, and assess the structure or function of the contralateral kidney. All patients should undergo a metastatic evaluation including a chest radiograph and an abdominal CT scan. A bone scintiscan is indicated in patients with bone pain or elevated serum levels of alkaline phosphatase. Preoperative renal, cardiac, and pulmonary evaluations are essential, as described earlier.

Tumor thrombus involving the IVC should be suspected in patients with lower extremity edema, varicocele, dilated superficial abdominal veins, proteinuria, pulmonary embolism, right atrial mass, or nonfunction of the involved kidney. MR venography is the authors' preferred study for evaluating the presence and the distal extent of involvement of the IVC (Pritchett et al, 1987; Goldfarb et al, 1990) (Fig. 54–86). The use of invasive inferior vena cavography is limited to those patients with a nondiagnostic MR venogram or ultrasound evaluation, in those in whom MRI is contraindicated, and in patients who underwent preoperative angioinfarction with coils that would produce scatter leading to poor quality MR images (Fig. 54–87). Transesophageal echocardiography (Treiger et al, 1991; Glazer and Novick, 1997) and transabdominal Doppler ultrasonography (McGahan et al, 1993) are also useful. **In patients with known IVC tumor thrombus the authors perform intraoperative transesophageal**

Table 54–10.

TNM Staging of Renal Cancer

Primary Tumor (T)	
TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor
T1	Tumor ≤7 cm in greatest dimension, limited to the kidney
T1a	Tumor ≤4 cm in greatest dimension, limited to the kidney
T1b	Tumor >4 cm but not >7 cm in greatest dimension limited to the kidney
T2	Tumor >7 cm in greatest dimension, limited to the kidney
T2a	Tumor >7 cm but ≤10 cm in greatest dimension, limited to the kidney
T2b	Tumor >10 cm, limited to the kidney
T3	Tumor extends into the major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond the Gerota fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches or invades perirenal and/or renal sinus fat but not beyond the Gerota fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond the Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

From the AJCC cancer staging manual. 7th ed. New York: Springer-Verlag; 2010. p. 482. Used with permission of the American Joint Committee on Cancer, Chicago, Illinois.

Table 54–11.

AJCC/UICC Staging of Renal Cell Carcinoma

STAGE	TNM CLASSIFICATION		
I	T1	N0	M0
II	T2	N0	M0
III	T1 or T2	N1	M0
	T3	N0 or N1	M0
IV	T4	Any N	M0
	Any T	Any N	M1

AJCC, American Joint Committee on Cancer; UICC, Union Intemationale Contre le Cancer.

From the AJCC cancer staging manual. 7th ed. New York: Springer-Verlag; 2010. p. 485. Used with permission of the American Joint Committee on Cancer, Chicago, Illinois.

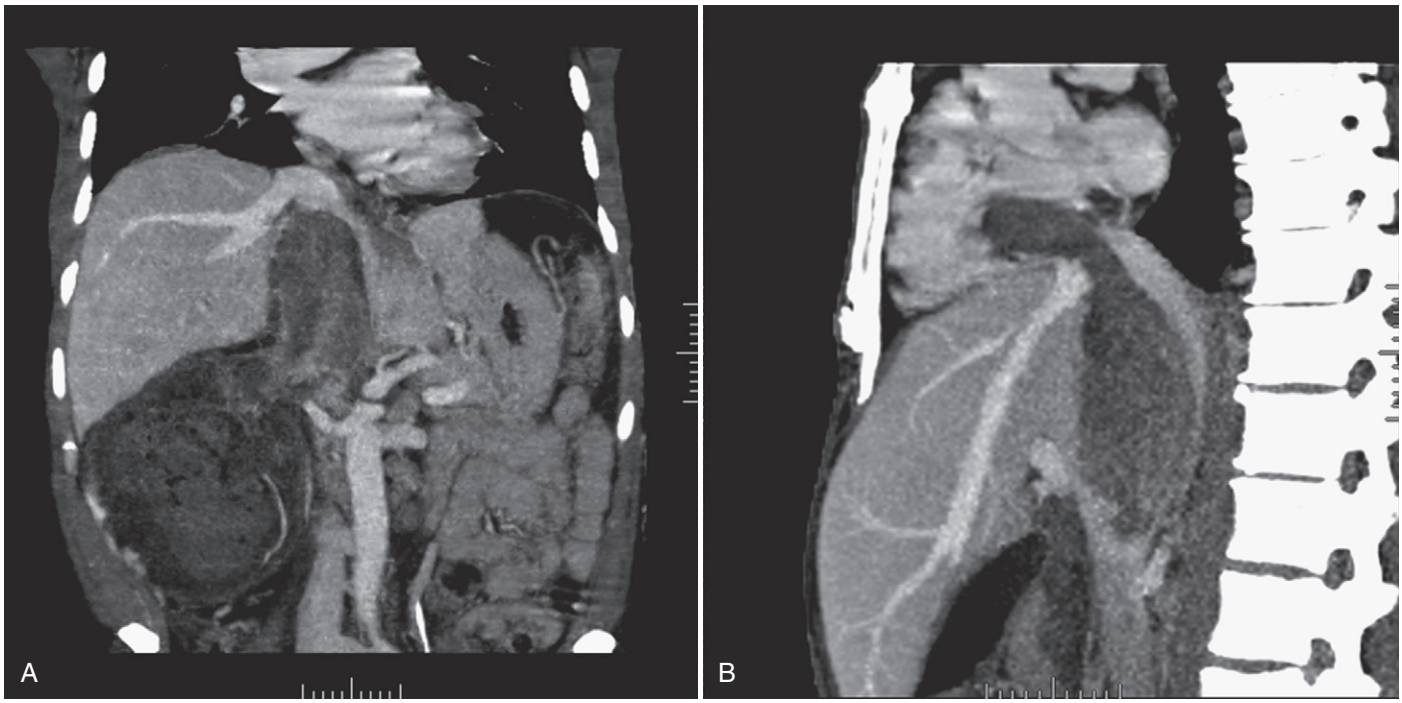


Figure 54–86. **A,** Coronal MR image demonstrates tumor extending to the level of the diaphragm. **B,** Sagittal MR reconstruction demonstrates thrombus that extends farther into the right atrium. The patient would eventually require cardiopulmonary bypass and deep hypothermic circulatory arrest.

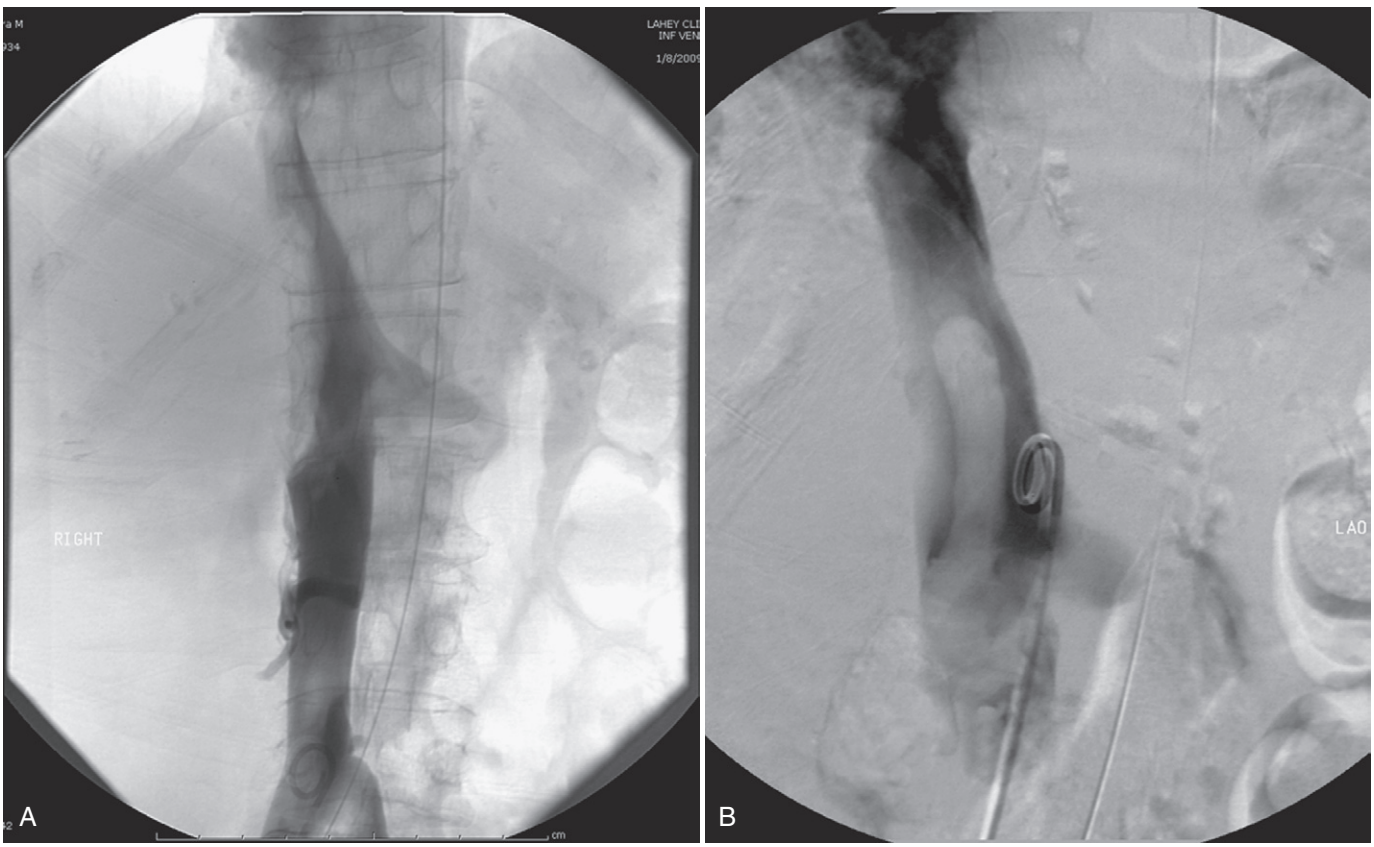


Figure 54–87. **A** and **B,** Preoperative cavogram demonstrating filling defect at the T10 level consistent with tumor thrombus in a patient with a large right renal mass. The patient required cardiopulmonary bypass and deep hypothermic circulatory arrest.

echocardiography to evaluate the distal extent of the tumor thrombus before making the incision.

As discussed earlier, the senior author favors preoperative angioinfarction for large renal tumors with hypervascular characteristics or IVC tumor thrombus (Wotkowicz and Libertino, 2007). Proposed benefits of preoperative RAE include shrinkage of an arterialized tumor thrombus to ease surgical removal and reduce blood loss. **When cardiopulmonary bypass (CPB) with deep hypothermic circulatory arrest is anticipated, surgeons at some institutions will also perform preoperative coronary angiography** (Belis et al, 1989; Novick et al, 1990b). **Coronary lesions can be repaired concurrently during CPB.**

Technique

The key elements of radical nephrectomy include the surgical approach, early ligation of the renal artery and vein, removal of the kidney outside the Gerota fascia, removal of the ipsilateral adrenal gland, and a complete regional lymphadenectomy extending from the crus of the diaphragm to the aortic bifurcation.

Surgical approaches are determined by tumor location and size, body habitus, prior surgical history, and surgeon preference. Although simple nephrectomy is often accomplished through an extraperitoneal approach, radical nephrectomy is best performed through a transperitoneal incision. This permits abdominal exploration for metastatic disease and access to the pedicle before significant manipulation of the tumor. The senior author prefers either an anterior or a thoracoabdominal approach.

Anterior Approach. A transperitoneal anterior midline, anterior subcostal, or chevron incision is made. The abdomen is systematically examined for metastatic disease. The approach for left and right tumors is described.

Right. The right kidney is approached by taking down the hepatic flexure and incising the peritoneal reflection along the right paracolic gutter. This permits the colon to be reflected medially in a plane anterior to the Gerota fascia. A Kocher maneuver, in which the lateral peritoneal reflection of the duodenum is incised and the duodenum reflected medially, is used subsequently to expose the underlying IVC and pararenal aorta (see Fig. 54–90). These maneuvers typically provide adequate access to the right renal pedicle and great vessels.

The right renal vein, which is relatively short and does not typically receive large tributaries, is mobilized. The gonadal vein enters the IVC and is ligated before the dissection of the right renal vein to avoid troublesome bleeding. The right renal artery lies posterior to the renal vein along its superior margin and normally runs a retrocaval course (see Fig. 54–37). The renal artery can be isolated to the right of the vena cava. Alternatively, in cases of a large medial tumor or significant nodal disease in the hilum, the renal artery can be controlled between the vena cava and aorta (Fig. 54–88).

Left. On the left side the white line of Toldt is incised and the colon is reflected medially to expose the great vessels. Division of the splenocolic ligaments reduces traction on and injury to the spleen. This approach permits access to the renal pedicle both anteriorly and posteriorly, which is the authors' preference. The left renal artery can be isolated posteriorly and the venous system identified and controlled anteriorly.

The left renal vein passes anterior to the aorta and is longer than the right renal vein. Unlike the right side it receives gonadal, adrenal, and lumbar tributaries, which are ligated and divided. **Identifying the left renal artery from the posterior approach is recommended to avoid inadvertent ligation**

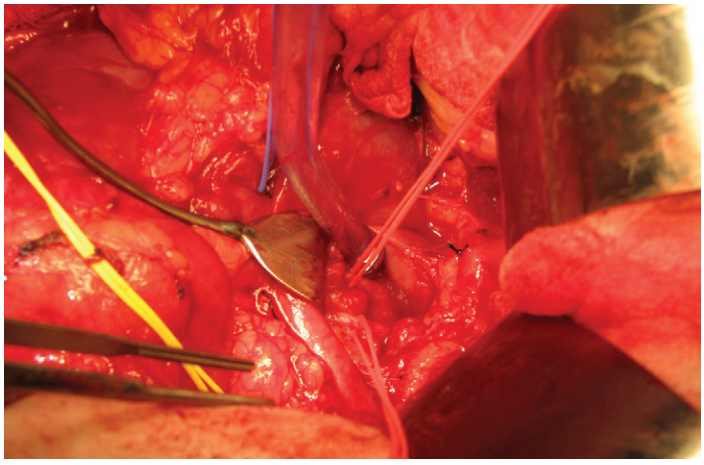


Figure 54–88. Two right renal arteries are isolated with red vessel loops at the interaortocaval junction. The vein retractor is retracting the inferior vena cava, and the Yankauer suction is displacing the left renal vein cephalad.

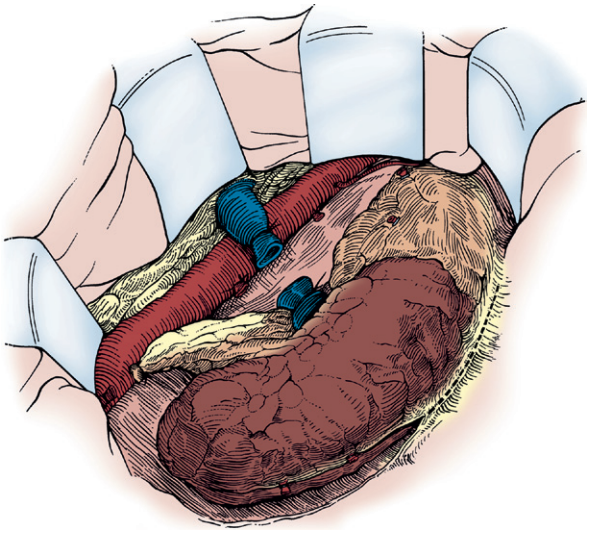


Figure 54–90. After the pedicle is secured and the ureter divided, the kidney is mobilized outside the Gerota fascia. (Reproduced with permission from Novick AC, Streem SB, Pontes E, editors. Stewart's operative urology. 2nd ed. Baltimore: Williams & Wilkins; 1989.)

of the superior mesenteric artery, which is on the anterior surface of the aorta 1 to 2 cm cephalad to the left renal vein. Alternatively, the artery can be isolated from an anterior approach by retracting the mobilized vein. The artery is mobilized toward the aorta, ligated, and divided. Two large Hemo-Lok clips and a 0 silk suture ligature are used to secure the main renal artery with a silk tie on the specimen side, followed by the vein (see Fig. 54–89 [on the Expert Consult website] and Figs. 54–90 and 54–91). Preoperative arterial embolization permits venous ligation to be performed first, which is occasionally necessary in complex dissections.

Mobilization of Kidney and Completion of the Case. After dividing the renal pedicle, the kidney is mobilized outside the Gerota fascia with blunt and sharp dissection. Any remaining vascular attachments are ligated with nonabsorbable sutures and divided. The ureter is ligated and divided. The kidney and adrenal gland are removed. A Penrose drain is placed in the empty renal fossa and

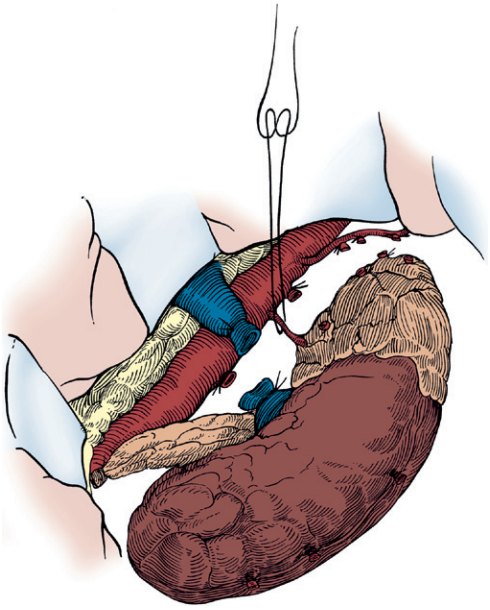


Figure 54–91. Remaining medial vascular attachments are secured and divided to complete the nephrectomy. (Reproduced with permission from Novick AC, Streem SB, Pontes E, editors. Stewart's operative urology. 2nd ed. Baltimore: Williams & Wilkins; 1989.)

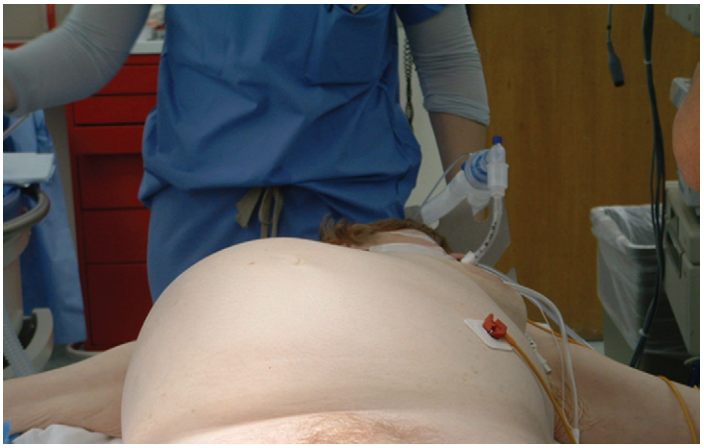


Figure 54–92. Patient with right flank mass positioned supine.

externalized through a separate stab incision. The abdomen is closed in layers as previously described.

Thoracoabdominal Approach. **For large renal tumors, especially those of the upper pole, the thoracoabdominal approach is preferable to an anterior approach** (Fig. 54–92; see Fig. 54–93 on the Expert Consult website). On the right side the liver is retracted cephalad. The hepatic flexure of the colon and the duodenum are reflected medially, exposing the IVC, the renal pedicle, and the anterior surface of the kidney (Figs. 54–94 to 54–96). The renal artery and vein are handled as described for the anterior approach. The ureter and right gonadal vein are ligated and divided. The kidney is mobilized outside the Gerota fascia down to the psoas fascia. The additional vascular attachments to the upper pole tumor and adrenal gland are exposed by medial retraction of the IVC along with caudal and lateral retraction of the kidney. They are ligated and divided. A curved-shaped clamp is passed along the superior portion of the adrenal gland to

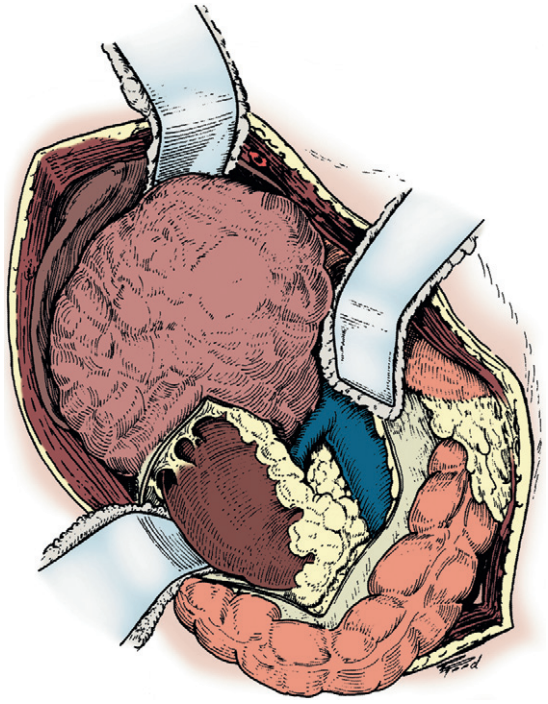


Figure 54–94. Exposure of large right upper pole tumor through a thoracoabdominal incision. (Reproduced with permission from Novick AC, Streem SB, Pontes E, editors. Stewart's operative urology. 2nd ed. Baltimore: Williams & Wilkins; 1989.)

gain control of the phrenic vessels using a 0 silk suture ligature. The specimen is mobilized fully away from the liver and removed en bloc.

On the left side the splenic flexure and the descending colon are mobilized. After the left renal pedicle is secured the kidney is mobilized outside the Gerota fascia. The upper border is dissected from the spleen, and the medial border is dissected from the tail of the pancreas. The ureter is ligated, and the specimen is removed.

Ipsilateral Adrenalectomy

Ipsilateral adrenalectomy may be associated with increased morbidity, adrenal insufficiency, and longer operative times. In 511 patients, Tsui and colleagues failed to demonstrate a correlation between tumor size and adrenal involvement, although presence of the tumor in the upper pole was a prognostic factor for adrenal involvement. Mordhorst and associates suggested that an adrenal-sparing approach should be taken in patients with tumors of less than 8 cm and no evidence of lymph node or organ metastasis. **Contrary to the classic description of radical nephrectomy, removal of the ipsilateral adrenal gland is not routinely necessary unless the tumor either extensively involves the kidney or is located in the upper portion of the kidney** (Sagalowsky et al, 1994).

Regional Lymphadenectomy

Complete regional lymphadenectomy, a traditional component of radical nephrectomy, encompasses removal of lymphatic tissue from the crus of the diaphragm to the aortic bifurcation. The lymph nodes can be removed en bloc with the kidney and adrenal gland or separately after completing the nephrectomy.

One enters and proceeds along a plane close to the adventitia of the aorta, which permits removal of all periaortic lymph tissue. One must be vigilant to avoid injury to the celiac trunk and

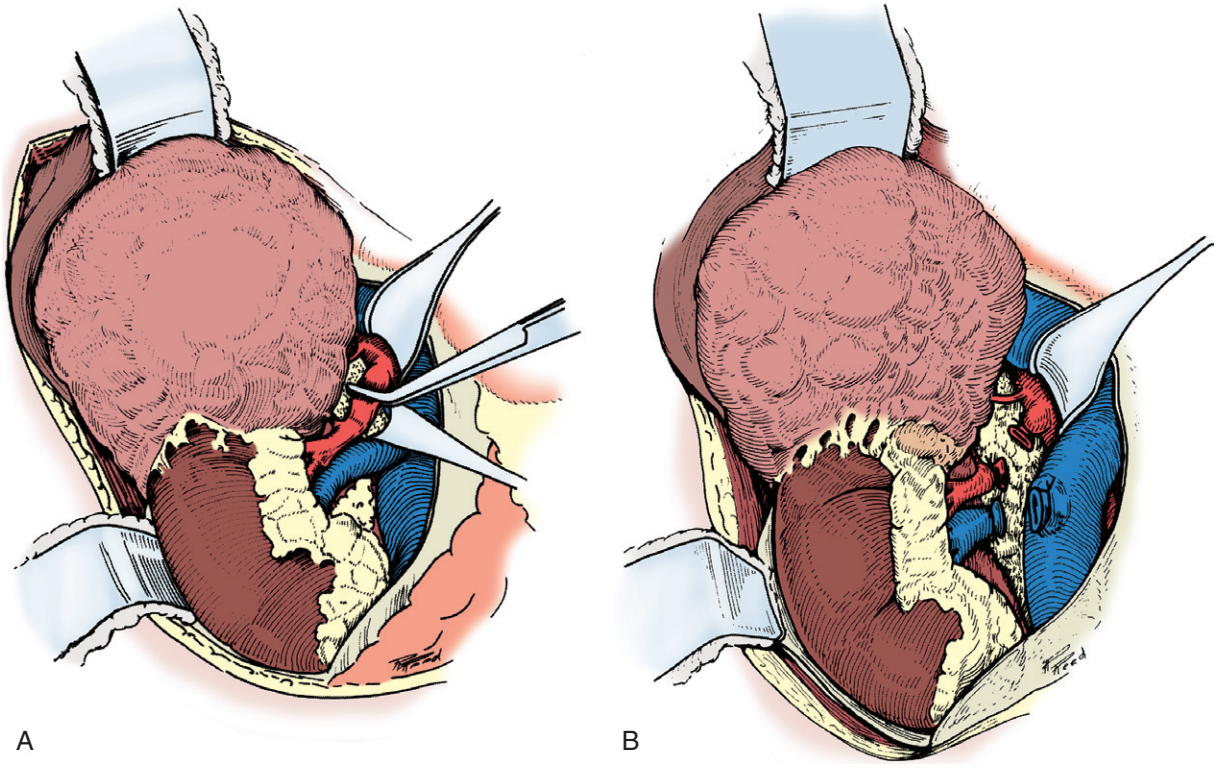


Figure 54–95. **A** and **B,** The renal artery and vein are secured and divided. (Reproduced with permission from Novick AC, Streem SB, Pontes E, editors. Stewart's operative urology. 2nd ed. Baltimore: Williams & Wilkins; 1989.)

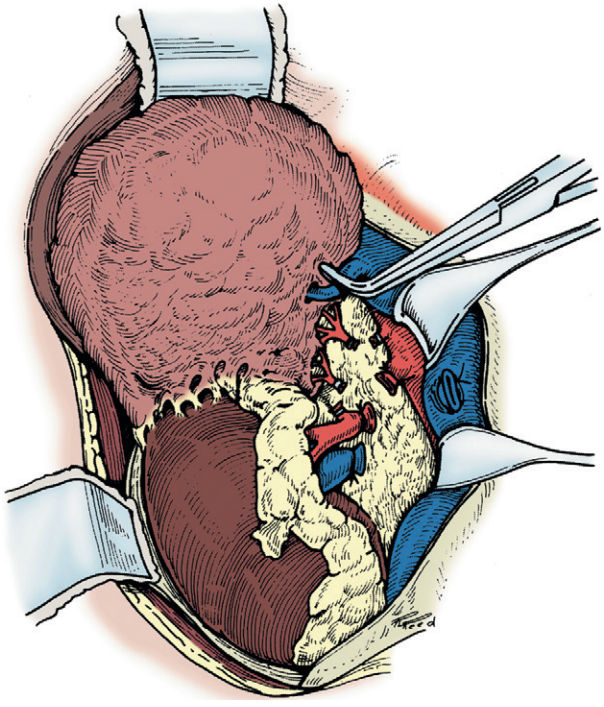


Figure 54–96. The vena cava is retracted medially to expose the remaining superior vascular attachments, which are secured and divided. (Reproduced with permission from Novick AC, Streem SB, Pontes E, editors. Stewart's operative urology. 2nd ed. Baltimore: Williams & Wilkins; 1989.)

superior mesenteric artery, which emanate from the anterior aorta. Proceeding downward to the origin of the inferior mesenteric artery, the sympathetic ganglia and nerves are removed together with the lymphatic tissue. The cisterna chyli, which is located medial to the right crus, is secured along with entering lymphatic vessels. After lymphadenectomy, the surgical field is copiously irrigated with sterile water. The argon laser beam can be helpful for hemostasis in extensive lymphadenectomies. Penrose drains are left for at least 48 hours.

Although lymphadenectomy is a recognized component of pathologic staging, the impact of lymphadenectomy on progression-free and overall survival is controversial. The European Organization for Research and Treatment of Cancer (EORTC) trial 30881, a randomized trial comparing radical nephrectomy with lymphadenectomy to radical nephrectomy alone in patients with clinical N0M0 renal cell carcinoma, did not demonstrate a survival benefit (Blom et al, 2009). The role of lymph node dissection in patients with locally advanced disease, clinical suspicion of nodal disease, or metastatic disease is unclear. There may be a subset of patients with micrometastatic lymph node involvement who can benefit from lymphadenectomy (Giuliani et al, 1990). Prospective trials of patients at higher risk of lymph node metastasis are needed.

Venous Extension and Tumor Thrombectomy

Renal cell carcinoma is associated with venous tumor thrombus in 4% to 10% of cases (Schefft et al, 1978). **In the absence of metastases, an aggressive surgical approach with curative intent is justified.** Five-year survival rates of 40% to 68% have been reported after radical nephrectomy and tumor thrombectomy (Libertino et al, 1987; Neves and Zincke, 1987; Skinner et al, 1989; Novick et al, 1990b). Although the level

Key Points: Radical Nephrectomy

- Although partial nephrectomy is the treatment of choice for T1 tumors when feasible, radical nephrectomy remains the definitive therapy for T2 or larger tumors.
- The key elements of radical nephrectomy include the surgical approach, early ligation of the renal artery and vein, removal of the kidney outside the Gerota fascia, removal of the ipsilateral adrenal gland, and a complete regional lymphadenectomy extending from the crus of the diaphragm to the aortic bifurcation.
- Identifying the left renal artery from the posterior approach is recommended to avoid inadvertent ligation of the superior mesenteric artery, which is on the anterior surface of the aorta 1 to 2 cm cephalad to the left renal vein.
- For large renal tumors, especially those of the upper pole, the thoracoabdominal approach is preferable to an anterior approach.
- Removal of the ipsilateral adrenal gland is not routinely necessary unless the tumor either extensively involves the kidney or is located in the upper portion of the kidney.
- The impact of lymphadenectomy on progression-free and overall survival is controversial.

of IVC involvement is not predictive of survival, tumor thrombus limited to the renal vein is associated with improved survival compared with thrombus in the IVC (Moinzadeh and Libertino, 2004). The most favorable outcomes are achieved when the tumor does not involve the perinephric fat or regional lymph nodes (Cherrie et al, 1982). Although there are several systems for categorizing venous tumor thrombi based on the distal extent of the thrombus, a rational and commonly employed scheme that is preferred by the senior author is shown in Figure 54–97 and Table 54–12.

Renal Vein Tumor Thrombus (Level I). Tumor thrombus in the renal vein often can be approached using the techniques of a standard radical nephrectomy. The kidney, great vessels, and renal pedicle are exposed, mobilized, and controlled through a thoracoabdominal incision. After ligation of the renal artery the tumor thrombus is gently palpated to ensure that no further extension into the vena cava is present. Preoperative angioinfarction permits ligation of the venous system before taking the artery, which can occasionally be helpful.

The kidney is dissected free, leaving the renal vein as the only attachment point (see Figs. 54–98 and 54–99 on the Expert Consult website). Two Satinsky or carotid clamps are placed in close apposition to each other at the junction of the renal vein and IVC, sparing any lumbar tributaries (see Fig. 54–100 on the Expert Consult website). With a scalpel, the IVC is transected proximal to both clamps, leaving them on the IVC. The proximal clamp is removed, which leaves a margin of caval wall for reconstruction with the distal clamp still in place. The caval defect is closed with running 4-0 polypropylene suture, with caution taken to minimize reduction of the IVC diameter (see Fig. 54–101 on the Expert Consult website). Surgicel may be placed over the repair for additional hemostasis.

Perirenal or Infrahepatic Tumor Thrombus (Level II). Transesophageal echocardiography is performed before making the incision to evaluate the cephalad extent of tumor thrombus (Fig. 54–102). Radical nephrectomy with removal of a perirenal or infrahepatic IVC thrombus is best approached through a chevron incision. For very large tumors involving the upper pole of the kidney a thoracoabdominal incision may be used instead. Most often these lesions are resected without CPB.

The colon is reflected medially, and a Kocher maneuver is employed to mobilize the duodenum. A Bookwalter retractor is used for exposure. The caudate lobe of the liver can be exposed and a sweetheart retractor placed under it, taking caution to identify and safeguard the porta hepatis. Control of the IVC is obtained with limited manipulation to prevent embolization of tumor thrombus. Rummel tourniquets are placed above and below the thrombus and around the contralateral renal vein (see Figs. 54–103 and 54–104 on the Expert Consult website). The renal artery, associated lumbar and minor hepatic veins, as well as the contralateral renal vein are isolated and circumferentially dissected. One can sacrifice perforating veins to the caudate lobe of the liver, which permits the IVC to be separated from the caudate lobe and exposes several more centimeters of IVC (Novick, 2007).

The renal artery and the ureter are ligated and divided. The specimen is mobilized outside the Gerota fascia, leaving the renal vein as the sole attachment. Preoperative renal angioinfarction may produce an inflammatory response that precludes safe early mobilization of the renal artery. In this instance the authors defer ligation of the renal artery until the tumor thrombectomy has been completed.

Venous occlusion is obtained with the previously placed Rummel tourniquets. An alternative is to use a Satinsky clamp on the IVC and a bulldog vascular clamp on the contralateral renal vein (Novick, 2007). A longitudinal anterior cavotomy is made, and the thrombus is freed from the caval wall to the level of the renal vein ostium using a spatula and gentle manipulation. In most cases the thrombus is not attached to the wall of the cava. The IVC is gently flushed with heparinized saline and evaluated for residual fragments. The infrarenal clamp is released transiently to purge the system of debris and limit the risk of embolus. Alternatively the suprarenal clamp can be released while applying positive pulmonary pressure to flush the cava free of fragments. The cavotomy is closed with a continuous 4-0 polypropylene suture (Figs. 54–105 and 54–106 on the Expert Consult website). Radical nephrectomy is carried out after closure of the vena cava has been completed.

Whereas the senior author prefers to incise the anterior wall of the cava, an alternative is to open the anterior surface of the renal vein over the thrombus and extend the venotomy posteriorly with scissors (Fig. 54–107). With gentle downward traction the tumor thrombus is extracted from the cava through the venotomy, which is repaired as described previously.

Occasionally the tumor thrombus invades the wall of the IVC necessitating caval wall resection. The lumen can be safely narrowed by half and closed primarily. To maintain the lumen in larger resections the cava can be reconstructed with PTFE or a pericardial graft in cases in which the chest is opened (Sarkar et al, 1998) (Fig. 54–108). When necessary, a segment of IVC can be excised without reconstruction. Resection of the infrarenal vena cava is usually safe and relies on the extensive venous collateral network that develops in the setting of tumor thrombus, particularly through the lumbar drainage system. **In right radical nephrectomy with tumor thrombectomy the suprarenal vena cava can be resected, but only if the left renal vein has been ligated distal to its venous tributaries (i.e., gonadal, lumbar, and adrenal veins). These veins then provide venous drainage from the left kidney. Given the lack of venous tributaries on the right side the**

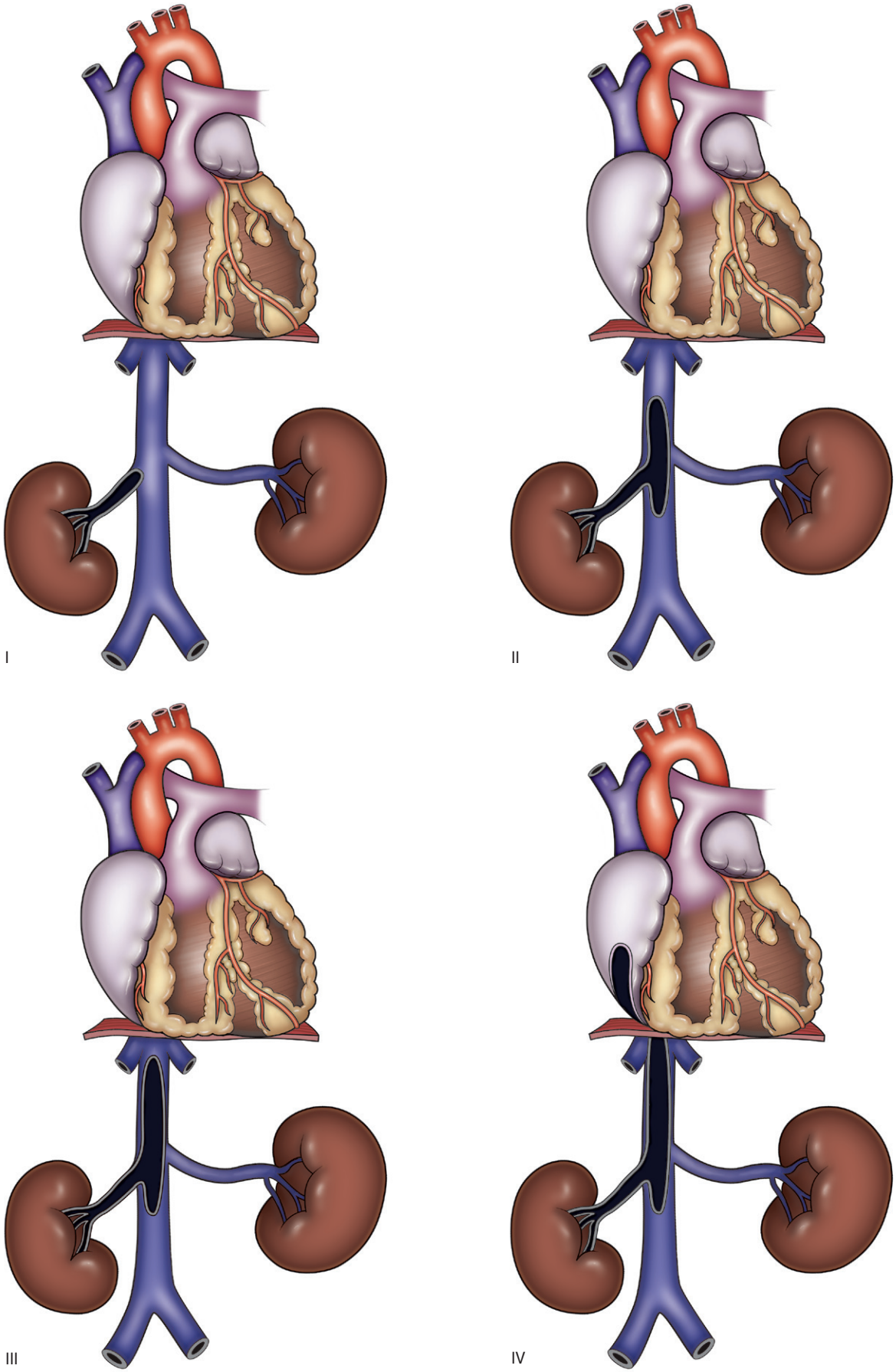


Figure 54–97. Classification of venous tumor thrombus extension. (From Wang GJ, Carpenter JP, Fairman RM, et al. Single-center experience of caval thrombectomy in patients with renal cell carcinoma with tumor thrombus extension into the inferior vena cava. Vasc Endovasc Surg 2008;42[4]:335–40.)

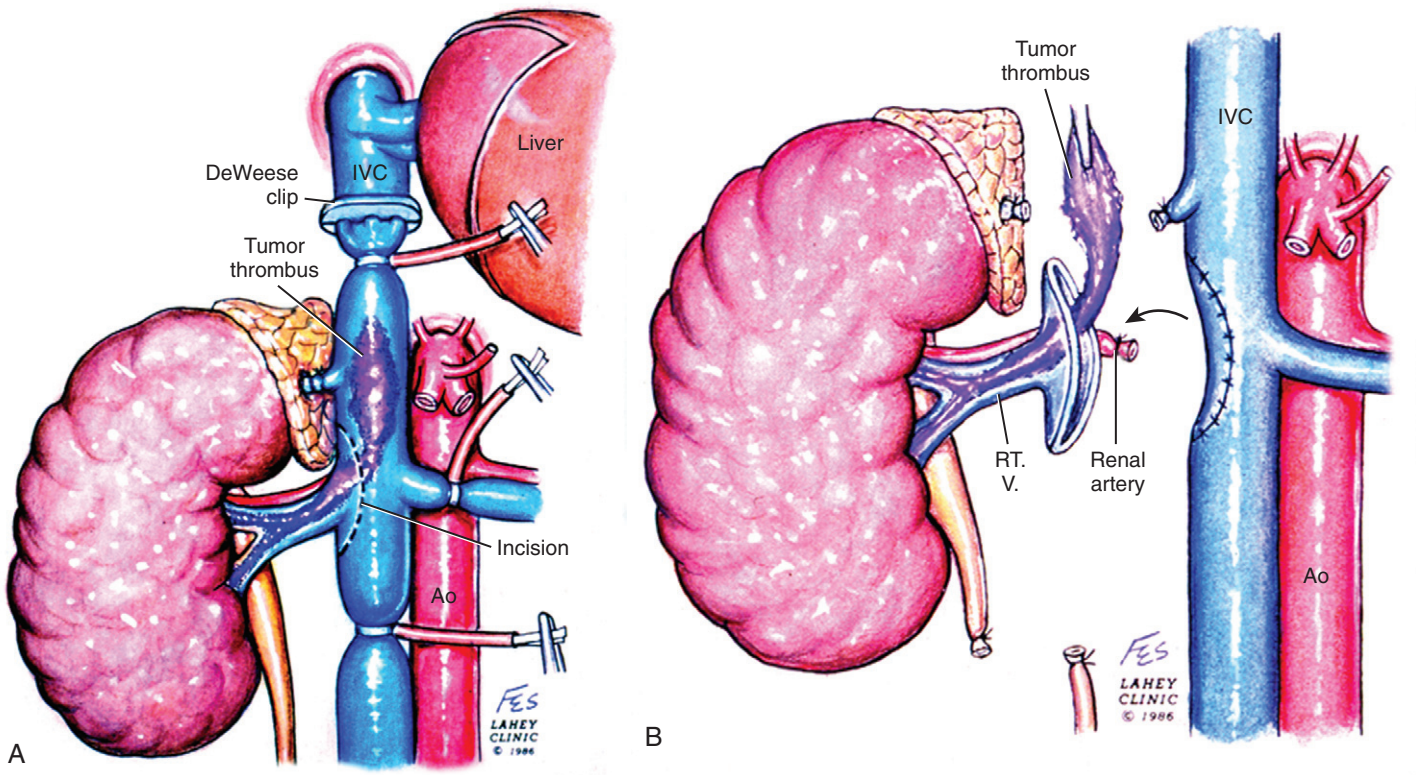


Figure 54–102. **A** and **B,** Technique for removing infrahepatic tumor thrombus with assistance of Rummel tourniquets avoiding cardiopulmonary bypass. Ao, aorta; IVC, inferior vena cava; RT. V, right vein. (© The Lahey Clinic.)

Table 54–12.
Classification of Venous Tumor Thrombus Extension

LEVEL	DISTAL EXTENT OF THROMBUS
I	Limited to renal vein
II	Infrahepatic inferior vena cava
III	Retrohepatic inferior vena cava in proximity to renal veins
IV	Supradiaphragmatic inferior vena cava or right atrium

suprarenal vena cava should not be resected for a left-sided tumor unless one provides alternative venous drainage for the right kidney with autotransplantation or a saphenous vein graft to the splenic, portal, or inferior mesenteric vein.

Bland tumor thrombus completely occluding the cava can be managed with staple interruption to limit the risk of pulmonary embolism. Resection or ligation of the IVC should be prefaced by efforts to preserve the integrity of the lumbar drainage system.

Intrahepatic and Suprahepatic Tumor Thrombus (Levels III and IV). The literature supports extirpative surgery for these tumors provided patients have a decent Eastern Cooperative Oncology Group (ECOG) performance status score and that there is not extensive locoregional invasion or metastatic disease (Staehler and Brkovic, 2000; Ficarra et al, 2001; Parekh et al, 2005; Blute et al, 2007; Klatte et al, 2007; Terakawa et al, 2007). **Radical nephrectomy with excision of an intrahepatic or suprahepatic IVC thrombus is a challenging procedure requiring special techniques including CPB owing to the difficulty of obtaining vascular control above the tumor thrombus.** Using traditional or minimally invasive bypass, which was pioneered at the Lahey Clinic, safe resection with excellent oncologic outcome is possible (Cummings et al, 1979; Foster et al, 1988; Skinner et al, 1989; Novick et al, 1990b; Burt, 1991; Fitzgerald et al, 1998; Ciancio et al, 2002; Wotkowicz et al, 2006).

Conventional Circulatory Bypass. Transesophageal echocardiography is performed after induction of anesthesia to assess the distal extent of the thrombus. **In general, the authors recommend CPB with deep hypothermic circulatory arrest for a thrombus within 2 cm of the hepatic veins and cephalad** (Shahian et al, 1990). After a chevron incision is made the abdomen is evaluated for evidence of metastatic disease. Once respectability has been confirmed a median sternotomy is made (Fig. 54–109). The duodenum is kocherized. A Langenbeck maneuver, in which the right triangular and coronary ligaments of the liver are divided, is performed. This permits the right lobe of the liver to be rotated medially and cephalad, which exposes the retrohepatic IVC up to the diaphragm (Figs. 54–110 to 54–112).

The kidney is completely mobilized outside the Gerota fascia, with minimal traction to prevent embolism of the tumor thrombus. The gonadal vein and ureter are taken with Hem-o-Lok clips or 0 silk ties. The superior pole and adrenal are mobilized in a routine fashion along with the associated phrenic vessels. The last portion of dissection is the hilum. As stated earlier, isolating the

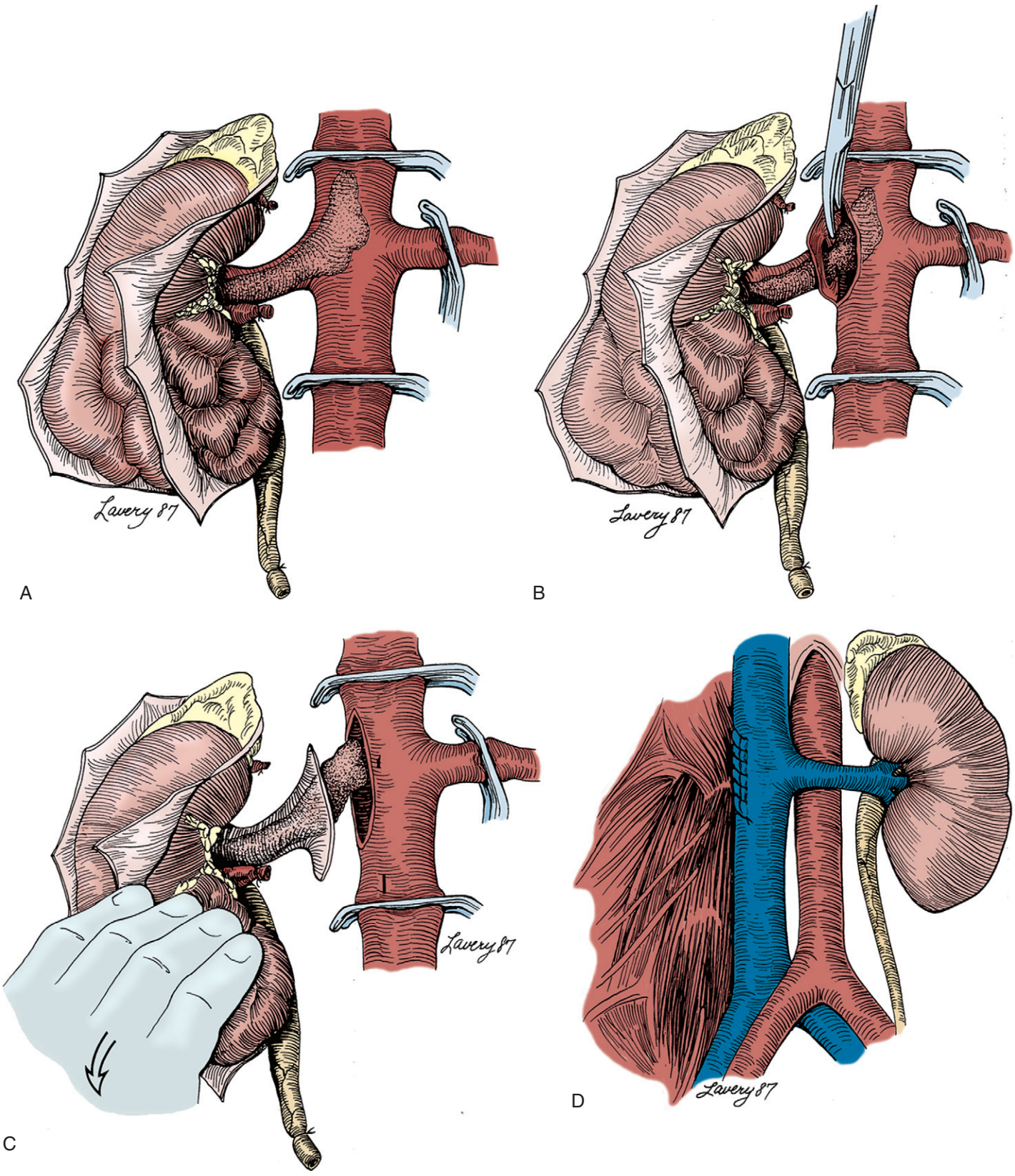


Figure 54–107. **A** to **D,** Technique of radical nephrectomy and venal caval tumor thrombectomy with infrahepatic tumor thrombus. The anterior surface of the renal vein is incised over the tumor thrombus, and the incision is continued posteriorly with scissors, passing just beneath the thrombus. (Reproduced with permission from Novick AC, Streem SB, Pontes E, editors. Stewart's operative urology. 2nd ed. Baltimore: Williams & Wilkins; 1989.)

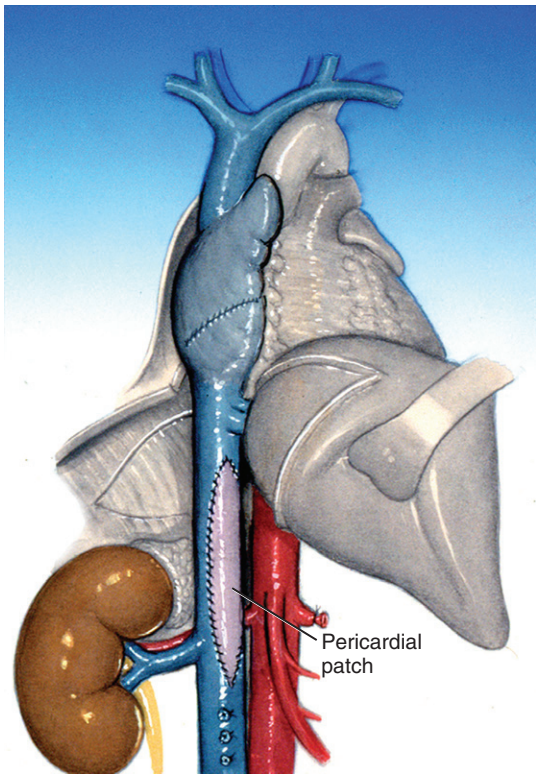


Figure 54–108. Vena cava reconstruction using pericardial patch graft.

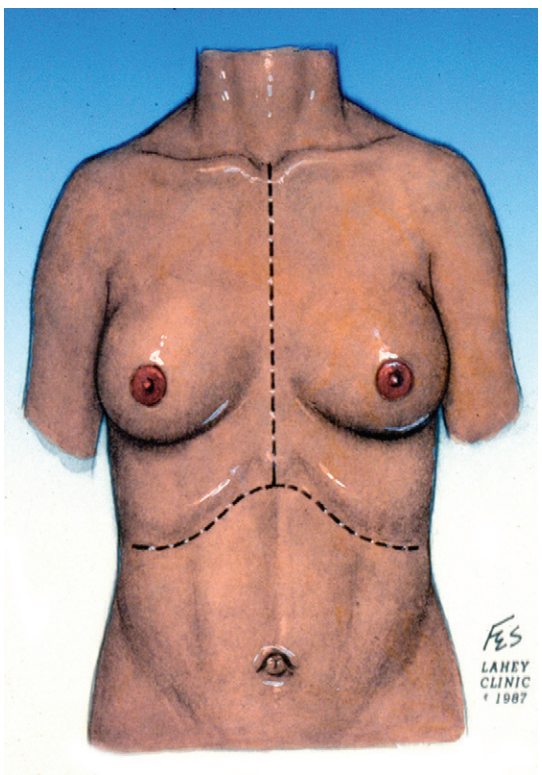


Figure 54–109. Traditional median sternotomy and chevron incisions for cardiopulmonary bypass and circulatory arrest. (© The Lahey Clinic.)

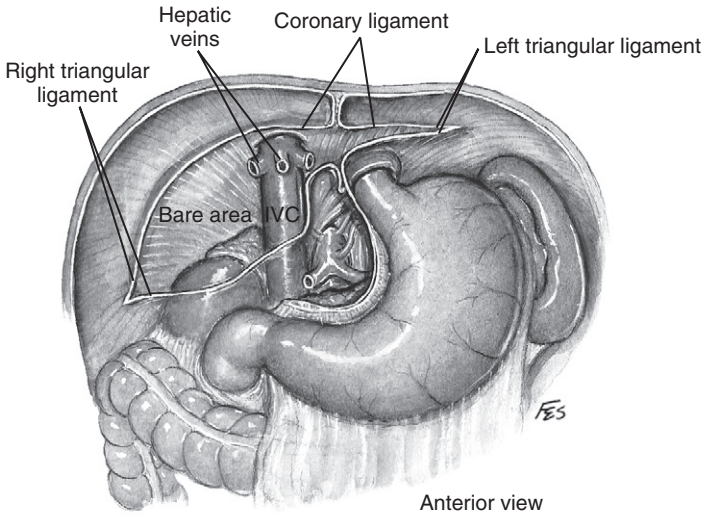


Figure 54–110. Relationship of liver and triangular and coronary ligaments to the vena cava. IVC, inferior vena cava. (© The Lahey Clinic.)

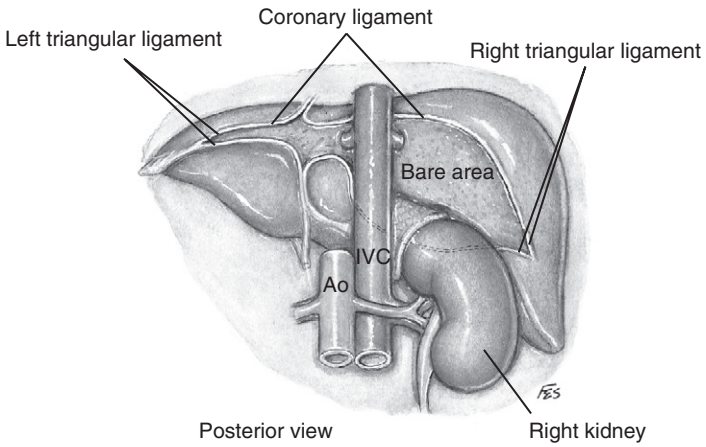


Figure 54–111. Posterior view of relationship of liver and coronary ligaments to the vena cava. Ao, aorta; IVC, inferior vena cava. (© The Lahey Clinic.)

renal artery from the posterior approach is recommended especially for left-sided tumors, given the risk of injury to the superior mesenteric artery. The main renal artery should be palpated in patients who had preoperative angioinfarction. If a pulse is present, the artery should be treated as unoccluded. The renal artery is taken with two large Hem-o-Lok clips and 0 silk suture ligatures, leaving the renal vein as the sole attachment (see Fig. 54–113 on the Expert Consult website). Few cases proceed in as straightforward a manner as described, because inflammation may make anatomic planes challenging to discern and the venous collateral vessels may be daunting.

The infrarenal vena cava and contralateral renal vein are exposed. The dissection is extended inferiorly to the bifurcation

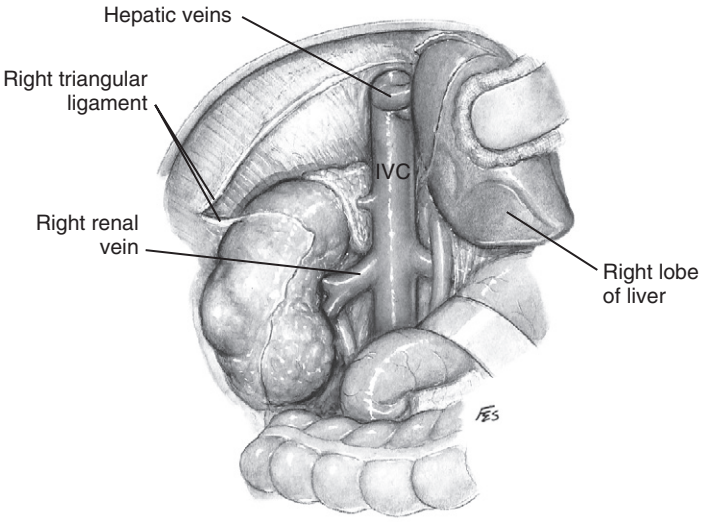


Figure 54–112. Access to vena cava by the Langenbeck maneuver. IVC, inferior vena cava. (© The Lahey Clinic.)

of the common iliac veins when bland or tumor thrombus extends there. Meticulous hemostasis is obtained before heparinization and initiation of CPB.

The patient is heparinized. The aortic arch and superior vena cava are cannulated. CPB is initiated (Fig. 54–114). A right atriotomy provides distal control of the tumor thrombus, which minimizes the risk of embolization. When the heart fibrillates, the aorta is clamped and crystalloid cardioplegic solution is infused. Inflow blood temperature is reduced as low as 10° C, resulting in deep hypothermia. The head and abdomen are packed in ice. After 15 to 30 minutes, a core temperature of 18° C to 20° C is achieved. Flow through the perfusion machine is stopped. Approximately 95% of the blood volume is drained into the pump, leaving no flow to any organ. Hypothermic circulatory arrest can be maintained for at least 40 minutes without incurring a cerebral ischemic event (Svensson et al, 1993). This interval can be extended by maintenance of "trickle" blood flow at a rate of 5 to 10 mL/kg/min (Mault et al, 1993) or by adjunctive retrograde cerebral perfusion (Pagano et al, 1995).

An anterior cavotomy is made using Potts forward and reverse scissors. The cavotomy should circumscribe the ostium of the renal vein and extend to the minor hepatic veins above the caudate lobe of the liver. The field will be nearly bloodless. For tumor extending into the right atrium the atrium is also opened (Fig. 54–115). The thrombus is extracted with the patient in Trendelenburg position and using positive-pressure respiration. If possible, the tumor thrombus is removed intact along with the kidney, although the thrombus may need to be removed in pieces if it is friable or adherent to the caval wall (Fig. 54–116). When necessary, a Fogarty catheter is passed from the atrium into the hepatic veins to retrieve portions of tumor thrombus. The authors ensure that tumor thrombus removal is complete by performing venacavoscopy with a flexible cystoscope. The cavotomy is closed with a double-armed 4-0 polypropylene running suture. The atriotomy is closed. Radical nephrectomy is carried out while rewarming to 37° C and coming off bypass. The patient is decannulated. Protamine is administered to reverse the heparin. Any leaking areas on the IVC are repaired with interrupted 4-0 polypropylene sutures. The abdomen is drained, and chest tubes are placed. Fresh frozen plasma, platelets, and desmopressin are used if needed to treat coagulopathy.

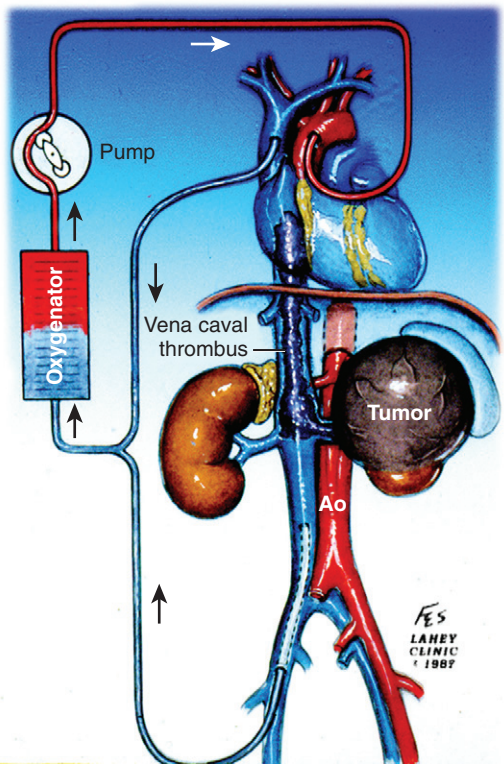


Figure 54–114. Traditional median sternotomy approach with cannulation of the aortic arch, superior vena cava, and right femoral vein for cardiopulmonary bypass. Ao, aorta. (© The Lahey Clinic.)

Minimally Invasive Cardiopulmonary Bypass. Since 1998, the authors have used a minimally invasive approach to CPB originally developed for aortic valve replacement (Fig. 54–117; see Figs. 54–118 to 54–126 on the Expert Consult website) (Cosgrove and Sabik, 1996; Fitzgerald et al, 1998). Unlike the traditional approach the kidney is not mobilized as extensively before heparinization and bypass. A chevron incision is used. The colon is mobilized, and the IVC is exposed using the Kocher and Langenbeck maneuvers.

The right subclavian artery is mobilized via an infraclavicular incision followed by a 2-inch right parasternal incision at the heads of the third and fourth ribs with resection of the rib cartilage and ligation of the right internal thoracic artery. Periosteum, muscles, and pleura are preserved for closure. The right pericardium is opened, exposing the superior vena cava and right atrium, and a Finochietto retractor is placed. Systemic heparinization is initiated as an 8-mm synthetic graft is sewn to the right subclavian artery for arterial return, while a two-stage venous cannula is positioned into the right atrium for venous outflow. CPB and circulatory arrest are initiated, and the patient is cooled. A right atriotomy is made to gain distal control of the thrombus and prevent passage into the pulmonary circulation. Tumor thrombus is removed from the cava, and a gauze pad is passed through the cava to the cardiothoracic team for removal of any loose debris (see Fig. 54–125 on the Expert Consult website). The remainder of the operation proceeds as described previously for a traditional median sternotomy.

Alternatives to Cardiopulmonary Bypass

VENOVENOUS BYPASS. **Patients with nonadherent supradiaphragmatic tumor thrombi that do not extend into**

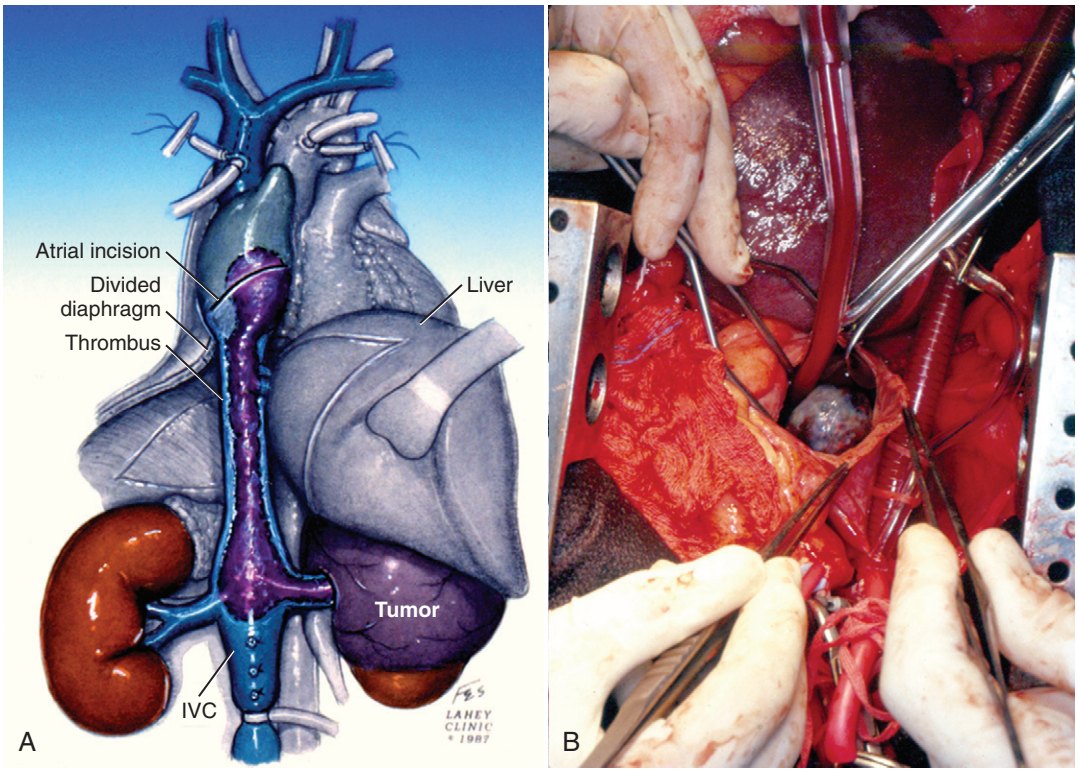


Figure 54–115. **A** and **B,** Tumor thrombus extension into right atrium removed using traditional median sternotomy approach and an atriotomy for retrieval of thrombus. IVC, inferior vena cava. (**A,** © The Lahey Clinic. **B,** From Wotkowicz C, Libertino JA, Sorcini A, Mourtzinos A. Management of renal cell carcinoma with vena cava and atrial thrombus: minimal access vs. median sternotomy with circulatory arrest. BJU Int 2006;98:289–97.)

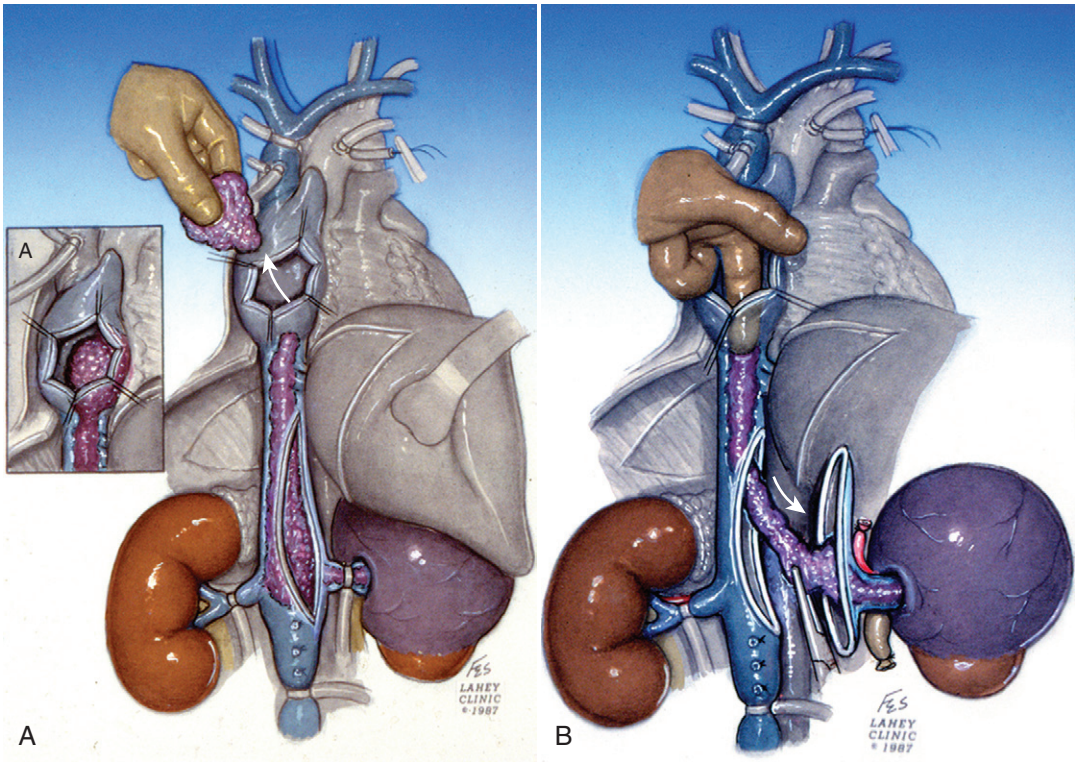


Figure 54–116. **A** and **B,** Tumor thrombus finger fracture and removal after formal atriotomy with retraction sutures *(inset A)*. Manual displacement from atrium through diaphragm and removal through anterior cavotomy. (© The Lahey Clinic.)

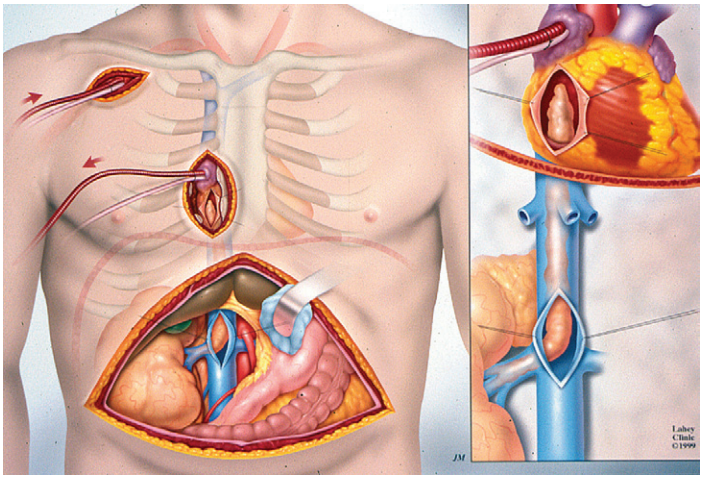


Figure 54–117. Minimal access technique utilizing a synthetic graft to the subclavian artery for arterial return and a two-stage venous cannula into the right atrium for venous return. (© The Lahey Clinic.)

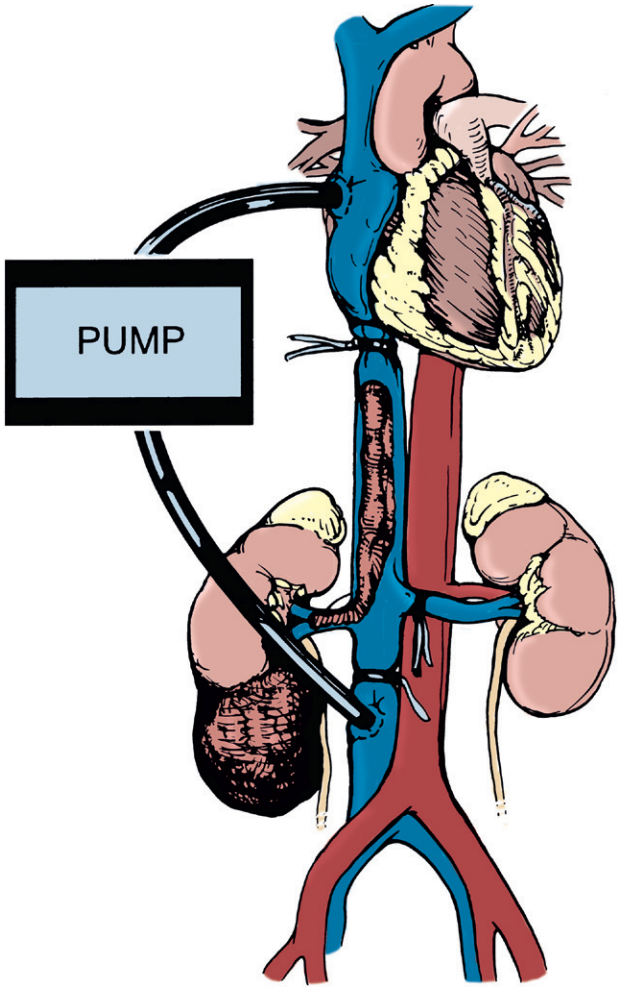


Figure 54–127. Technique of venovenous bypass for removal of supradiaphragmatic vena caval tumor thrombus.

the right atrium can be managed with venovenous bypass using a caval-atrial shunt (Foster et al, 1988; Burt, 1991). The intrapericardial vena cava, infrarenal vena cava, and contralateral renal vein are temporarily occluded. Cannulae are inserted into the right atrium or axillary vein and the femoral veins or infrarenal vena cava. Bypass is initiated using a primed pump to maintain flow to the right side of the heart (Fig. 54–127). This avoids the decline in cardiac output due to the reduced preload associated with occlusion of the intrapericardial and infrarenal vena cava. The cavotomy is made and the thrombectomy performed. **Bleeding from the hepatic venous system, which can be brisk, is managed with a Pringle maneuver, cross clamping the hepatic veins, or both.** Bleeding from the lumbar veins, which originates from the uncontrolled azygous and hemiazygous systems, is difficult to control and is a major downside of this technique. The cava is repaired and the nephrectomy performed as previously described. This technique helps to avoid some of the complexities of CPB with deep hypothermic circulatory arrest, albeit at the risk of hepatic venous bleeding.

EXTENSIVE LIVER MOBILIZATION AND OTHER TECHNIQUES. Extensive liver mobilization, employed for decades at the Lahey Clinic, is another approach to avoid CPB (see Fig. 54–128 on the Expert Consult website) (Libertino, 1987; Ciancio et al, 2007). The liver is mobilized to the left after the division of the ligamentum teres, falciform ligament, triangular ligament, and superior coronary ligament of the liver. This provides excellent access to the retrohepatic portion of the vena cava, leaving on the major hepatic veins in continuity after a Pringle maneuver is performed. The surgeon palpates and milks the tumor thrombus caudally to the level of the hepatic veins, and a standard cavotomy is performed.

D'Ancona and associates (2005) describe the removal of a suprarenal tumor thrombus using extracorporeal circulation and deep hypothermic arrest without violation of the thoracic cavity. After exposure of the vena cava the liver is retracted inferiorly to expose the pericardium at the level of the diaphragm. A pericardial window permits cardiac defibrillation. Extracorporeal circulation is established via the right femoral artery, right femoral vein, and subclavian vein. Core hypothermia to 20° C is achieved before circulatory arrest is begun. Infrahepatic and suprahepatic longitudinal incisions provide access for thrombus removal.

Chowdhury and associates (2007) discuss another alternative for intra-atrial tumor thrombus utilizing CPB, mild hypothermia, and an intermittent cross clamping of the supraceliac aorta to avoid the risks associated with circulatory arrest.

Outcomes. The incidence of complications in treating tumors of this magnitude has decreased with refinements in surgical techniques, intraoperative monitoring, and postoperative critical care (Boorjian et al, 2007; Wotkowicz and Libertino, 2007). Prolonged pulmonary support and renal replacement therapy may be necessary. The authors' minimal access technique, used in more than 30 patients, avoids median sternotomy with equivalent oncology outcomes. Eliminating the median sternotomy reduces the dose of postoperative analgesics, avoids reoperative sternotomy in patients with a prior coronary artery bypass, and results in a shorter operative time, shorter hospital stays, and decreased transfusion and mechanical ventilatory support (Wotkowicz et al, 2006).

Cytoreductive Nephrectomy and Metastasectomy

Palliative nephrectomy is often performed for tumors that are very large with significant extrarenal disease in an effort to decrease

Key Points: Venous Extension and Tumor Thrombectomy

- Renal cell carcinoma is associated with venous tumor thrombus in 4% to 10% of cases. In the absence of metastases an aggressive surgical approach with curative intent is justified.
- In patients with known IVC tumor thrombus, intraoperative transesophageal echocardiography can be done to evaluate the distal extent of the tumor thrombus before making an incision.
- When CPB with deep hypothermic circulatory arrest is anticipated, surgeons at some institutions will also perform preoperative coronary angiography. Coronary lesions can be repaired concurrently during CPB.
- When reconstructing the IVC the lumen can be safely narrowed by half and closed primarily. To maintain the lumen in larger resections the cava can be reconstructed with a pericardial graft or PTFE.
- When performing right radical nephrectomy with tumor thrombectomy the suprarenal vena cava can be resected, but only if the left renal vein has been ligated distal to its venous tributaries (i.e., gonadal, lumbar, and adrenal veins).
- Given the lack of venous tributaries on the right side, the suprarenal vena cava should not be resected for a left-sided tumor unless one provides alternative venous drainage for the right kidney with autotransplantation or a saphenous vein graft to the splenic, portal, or inferior mesenteric vein.
- Radical nephrectomy with excision of an intrahepatic or suprahepatic IVC thrombus is a challenging procedure requiring special techniques, including CPB, owing to the difficulty of obtaining vascular control above the tumor thrombus. CPB with deep hypothermic circulatory arrest is recommended for a thrombus within 2 cm of the hepatic veins and cephalad.
- The Lahey minimally invasive approach to CPB eliminates the median sternotomy, reduces the dose of postoperative analgesics, avoids reoperative sternotomy in patients with a prior coronary artery bypass, and results in a shorter operative time, shorter hospital stays, and decreased transfusion and mechanical ventilatory support.
- Alternatives to CPB may include venovenous bypass and extensive liver mobilization.

symptoms. In contrast, cytoreductive nephrectomy is performed with the goal of improving cancer outcome. A combined analysis of two trials (Southwest Oncology Group S8949 and EORTC 30947) elucidated the benefits of cytoreductive nephrectomy and revealed a survival benefit for interferon-alfa combined with nephrectomy versus interferon alone (Lara et al, 2009; Mickisch et al, 2001). Additional studies show potential for cytoreductive nephrectomy in combination with tyrosine kinase inhibitors (sunitinib [Sutent] and sorafenib) (Thomas et al, 2009). Analyses indicate that excellent preoperative performance status (ECOG 0 to 1 or Karnofsky performance status <80) and lung-only metastatic disease are good prognostic variables (Tables 54–13 and 54–14). Proponents of cytoreductive therapy cite anecdotal cases of spontaneous metastasis resolution, referred to as the Lazarus effect. A reduction in angiogenesis and growth factors after nephrectomy may enhance the efficacy of systemic immunotherapy compared with immunotherapy without prior cytoreductive nephrectomy. Unresectable lung lesions can serve as markers for chemotherapy efficacy and may be resected if their volume decreases significantly. In the authors' experience the presence of disease outside the chest and poor performance status are contraindications for surgical intervention, unless for pure palliative purposes such as with intractable edema, ascites, cardiac dysfunction, associated pain, or hematuria.

First described by Barney and Churchill in 1939, the resection of pulmonary metastasis remains an effective treatment for select patients. Utilizing a thoracoabdominal approach for the radical

Table 54–13.

Eastern Cooperative Oncology Group (ECOG) Status

GRADE	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework and office work)
2	Ambulatory and capable of all self care but unable to carry out any work activities Up and about more than 50% of waking hours
3	Capable of only limited self care Confined to bed or chair more than 50% of waking hours
4	Completely disabled Cannot perform any self care Totally confined to bed or chair
5	Dead

From Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649–55.

Table 54–14.

Karnofsky Performance Score

SCORE	DESCRIPTION
100	Normal no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospital admission is indicated although death not imminent
20	Very sick; hospital admission necessary; active supportive treatment necessary
10	Moribund, fatal processes progressing rapidly
0	Dead
Ranges	
80-100	Able to carry on normal activity and to work. No special care needed
50-70	Unable to work. Able to live at home and care for most personal needs
0-40	Unable to care for self. Requires institutional or hospital care

From Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol 1984;2(3):187–93.

nephrectomy and metastasectomy, the authors resect anterior lower lobe lesions using Doyle clamps and endovascular staplers. Favorable prognostic factors for isolated pulmonary metastasis include preoperative performance status, completeness of resection, number of lesions (less than six), limited lymph node involvement, and disease-free interval. Properly selected patients may have 5-year survival rates exceeding 50% (Hofmann et al, 2005). Metastasectomy in nonpulmonary sites such as the liver and brain are controversial and should be considered investigational. Preoperative imaging using biologic markers, such as monoclonal antibodies to carbonic anhydrase IX, may better help to identify occult metastatic disease and better stratify these patients with complex disease (Divgi et al, 2007) (Fig. 54–129).

Partial Nephrectomy for Malignant Disease

From its 19th century roots, nephron-sparing surgery has emerged as a sophisticated and continually ground-breaking component of contemporary open renal surgery. Partial nephrectomy is a demanding endeavor that involves complete resection of a tumor with a negative margin, with maximal preservation of functioning renal parenchyma. Although radical nephrectomy is oncologically sound, technically straight forward, and boasts a favorable perioperative complication rate, the more challenging nephron-sparing approach is indicated in a growing number of patients.

Indications

Traditionally, the treatment of choice for renal cortical tumors was radical nephrectomy. Partial nephrectomy was reserved for patients in whom radical nephrectomy would result in dependence on dialysis, such as those patients with a solitary kidney, bilateral or familial renal tumors, or chronic renal insufficiency. In recent years, indications for nephron-sparing surgery have broadened. **Partial nephrectomy has supplanted radical nephrectomy as the treatment of choice for T1 renal tumors when feasible, even in the absence of identifiable renal insufficiency or threat** (Russo et al, 2002; Russo and Huang, 2008). Partial nephrectomy provides the same long-term oncologic results as radical nephrectomy for tumors of 7 cm or less (Fergany et al, 2000; Russo et al, 2002; Dash et al, 2006; Pahernik et al, 2008).

For tumors other than T1, partial nephrectomy may be indicated in patients with a contralateral kidney that is threatened by stone disease, chronic infection, renovascular disease, vesicoureteral reflux, or systemic diseases that threaten renal function such as hypertension or diabetes mellitus (Licht et al, 1994). In recent years, the adverse consequences of chronic renal insufficiency, even in the absence of dialysis, have become clear. Urologists are increasingly aware of the importance of preservation of renal function. The literature does not support partial nephrectomy for patients with a tumor that is T2 or higher with a normal contralateral kidney.

Contraindications to open partial nephrectomy include lymph node metastasis because the prognosis for these patients is poor. Biopsy of enlarged or suspicious-looking lymph nodes should be done before the renal resection is initiated. For renal cortical tumors in a solitary kidney with venous extension, partial nephrectomy with tumor thrombectomy may be feasible, but this remains investigational (Tollefson et al, 2005).

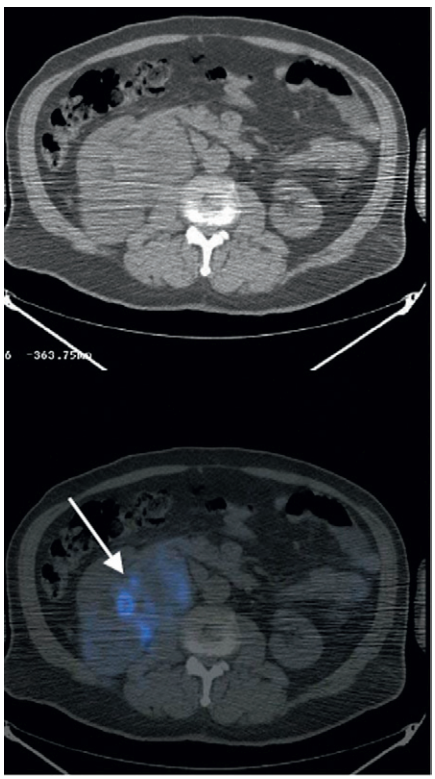


Figure 54–129. CT scans obtained for large right renal mass using antibodies to carbonic anhydrase IX (G250 antibody). Note in the lower picture the uptake of tracer. Surgical pathology confirmed a renal cell carcinoma (clear cell).

Nephron-Sparing Surgery and the Adverse Effects of Renal Insufficiency

In the past, partial nephrectomy was not thought to be necessary in patients with a normal contralateral kidney, owing to a mistaken belief that patients with a normal contralateral kidney would suffer no ill effect from radical nephrectomy. This idea dates back to the 19th century. In 1869, Simon performed the first nephrectomy in a human for a benign condition (Simon, 1870). He did so only after first removing a kidney in 30 dogs, thereby demonstrating that survival with a solitary kidney is possible. Nevertheless, 140 years later, it is apparent that the deficit in glomerular filtration due to radical nephrectomy can have far-reaching negative consequences.

The majority of patients with renal cortical tumors have unrecognized comorbid medicorenal disease. In a pathologic review of radical nephrectomy specimens, only 10% of specimens had normal renal parenchyma adjacent to the tumor (Bijol et al, 2006). More than 60% of patients had pathologic evidence of medicorenal disease and nearly 30% had demonstrable renal arteriosclerosis. In a study from Memorial Sloan-Kettering Cancer Center, 26% of patients with renal cortical tumors who underwent surgery had a preoperative estimated GFR less than 60 mL/min/1.73 m^2 despite having two apparently normal kidneys and a serum creatinine concentration in the normal range (Huang et al, 2006).

In comparison to partial nephrectomy, radical nephrectomy is associated with a higher risk of postoperative renal insufficiency (Lau et al, 2000; McKiernan et al, 2002). In a retrospective study from Memorial Sloan-Kettering Cancer Center regarding patients with a renal cortical tumor 4 cm or smaller, normal preoperative serum creatinine concentration,

and two intact kidneys, radical nephrectomy was an independent risk factor for new onset of chronic kidney disease. The 3-year probability of freedom from new onset of GFR less than 60 mL/min/1.73 m^2 was 80% after partial nephrectomy but only 35% after radical nephrectomy ($P < .01$) (Huang et al, 2006).

There is a dose-response association between chronic kidney disease and hospitalizations, cardiovascular events, and death (Go et al, 2004). **Recent efforts have demonstrated that radical nephrectomy may be associated with increased cardiovascular events and decreased survival.** A study combining Surveillance, Epidemiology and End Results (SEER) cancer registry data with Medicare claims demonstrated that radical nephrectomy, in comparison to partial nephrectomy, is associated with a higher risk of overall mortality (HR 1.38, $P < .01$) and a 1.4-fold higher number of cardiovascular events ($P < .05$) (Huang et al, 2009). For patients younger than 65 years old with single unilateral renal cortical tumors measuring 4 cm or less with a normal contralateral kidney, data from the Mayo Clinic suggests that radical nephrectomy is associated with decreased overall survival in comparison to partial nephrectomy (response rate [RR] = 2.16; $P = .02$) (Thompson et al, 2008).

Partial Nephrectomy is Underutilized

Despite the growing number of small renal masses and ample evidence in favor of the oncologic efficacy of partial nephrectomy for T1 tumors and the potential adverse impact of radical nephrectomy, a large percentage of tumors amenable to partial nephrectomy are still removed with radical surgery (Nuttall et al, 2005; Hollenbeck et al, 2006). In a study from a tertiary care center, more than 70% of renal cortical tumors smaller than 4 cm were treated by laparoscopic radical nephrectomy in 2002 (Scherr et al, 2003). In a nationwide sample from 1988 to 2002, partial nephrectomy comprised fewer than 8% of operations for renal tumors (Hollenbeck et al, 2006). In another sample, only 20% of renal cortical tumors measuring 2 to 4 cm were treated with partial nephrectomy (Miller et al, 2006). The desire to use a minimally invasive modality may be contributing to excessive use of radical surgery (Scherr et al, 2003). This imbalance needs to be rectified.

Open Partial Nephrectomy: An Increasingly Challenging Endeavor

Because the majority of renal cortical lesions are now discovered incidentally on cross-sectional imaging, tumors of 4 cm or less now make up the principal share of newly diagnosed masses (Nguyen et al, 2006). Despite this general trend, in the senior author's experience the lesions referred for open partial nephrectomy have become more complex. Lesions managed with open partial nephrectomy at the Lahey Clinic are now larger, more often hilar, more central, deeper, and involve the collecting system to a greater degree than in the past. This observation is consistent with experience at other tertiary care centers. When compared with the era before laparoscopy, tumors undergoing open partial nephrectomy in the laparoscopic era at the Cleveland Clinic are more often in a solitary kidney (40.0% vs. 15.6%), centrally located (55.6% vs. 37.3%), and higher grade (Fuhrman 3 or 4) (43.1% vs. 27.8%, each $P < .01$) (Weight et al, 2008).

The increasing complexity of open partial nephrectomy is attributable, at least in part, to widespread adoption of minimally invasive techniques (e.g., laparoscopic radical and partial nephrectomy, cryoablation, and radiofrequency ablation) (Weight et al, 2008). In a multi-institutional comparison of 1800 open and laparoscopic partial nephrectomies, patients undergoing open partial nephrectomy had larger tumors, which were more centrally located and more often malignant. Patients undergoing open surgery were more often symptomatic at presentation and more frequently had impaired renal function, worse performance status, and solitary kidney (Gill et al, 2007).

New surgical techniques, which will be integrated into the technical descriptions in this chapter, have been adopted so the nephron-sparing approach can be applied to these increasingly complex masses with limited impact on renal function. Contemporary open partial nephrectomy is a cutting-edge operation that is rooted in powerful evidence favoring both oncologic efficacy and renal preservation.

Preoperative Evaluation and Preparation

Patients undergoing partial nephrectomy should have an extensive preoperative workup as described earlier in the chapter, including cardiac, pulmonary, and renal evaluation. Autologous blood donation should be offered to patients because perioperative blood transfusion may be necessary. A preoperative urine culture is mandatory. It is the practice of the senior author to treat bacteriuria, even if asymptomatic, before surgery. Urine should be sterile before partial nephrectomy given the risk of entry into the collecting system. Patients should be intravascularly fluid replete before surgery. Although it is no longer the authors' practice to admit patients for volume resuscitation on the day before partial nephrectomy, it is the belief of the senior author that patients benefit from vigorous intravenous hydration on the morning of surgery.

Before partial nephrectomy, evaluation of patients with renal cortical tumors should include imaging to identify locally extensive or metastatic disease. Preoperative imaging should also delineate relevant regional anatomy, intrarenal anatomy, and vasculature to minimize blood loss and damage to adjacent renal parenchyma. Invasive renal arteriography has largely been replaced by noninvasive 3D CT angiography, which offers excellent anatomic detail. 3D CT integrates information from arteriography, venography, excretory urography, and conventional two-dimensional CT into a single imaging modality (Fig. 54–130). In addition to tumor staging, 3D reconstructions of contrast-enhanced CT angiograms, MR images, or MR venograms are useful for planning site and extent of planned resection and to determine proximity to the renal hilum, intrarenal vasculature, and collecting system (Fig. 54–131). 3D CT accurately demonstrates involvement of the collecting system by tumor (Derweesh et al, 2003).

In general, the authors prefer not to administer an intravenous contrast load within 1 week of surgery. Appropriate precautions including oral *N*-acetylcysteine, vigorous hydration with normal saline, and use of low osmolality contrast agents should be taken in patients at risk of contrast nephropathy (Barrett and Parfrey, 2006). After administration of a contrast medium, renal function is reevaluated before partial nephrectomy to exclude contrast nephropathy.

Bilateral Tumors

Bilateral tumors represent a special circumstance that is considered a firm indication for nephron-sparing surgery. The simpler partial nephrectomy is performed first. A MAG3 renogram is used to document preservation of renal function in the postoperative kidney. Once the patient has fully recovered from the initial surgery, the more complicated partial or radical nephrectomy is performed on the contralateral kidney.

Fundamentals of Partial Nephrectomy

Open partial nephrectomy is a technically demanding procedure. **Although individual techniques may vary, the fundamental steps begin with the surgical approach, vascular control, and mobilization of the kidney. After complete excision of the tumor with maximal preservation of normal parenchyma and minimization of ischemic injury, renorrhaphy is completed. Renorrhaphy includes hemostasis, watertight closure of the collecting system, and repair of the renal defect.** The basic techniques are outlined here, followed by a more detailed discussion of the various types of partial nephrectomy.

Approach. Good functional exposure through a properly selected incision is essential to the success of the procedure. For partial nephrectomy the incision should be chosen to optimize exposure of the tumor, kidney, and renal pedicle. The authors most often employ an extrapleural, extraperitoneal supra-11th rib incision. The level of incision is determined by the position of the kidney in relation to the ribs as seen on preoperative radiographic studies and by the location and size of the tumor. The thoracoabdominal approach is useful in large or upper pole tumors. Partial nephrectomy can also be accomplished through an anterior subcostal incision, although this typically affords inferior exposure. The rib-resecting approach is not employed. In rare circumstances, extracorporeal partial nephrectomy with autotransplantation is necessary, in which case a supracostal 11th rib incision is used to harvest the kidney and a semilunar Gibson incision is used to autotransplant the kidney.



Figure 54–130. Three-dimensional CT reconstruction demonstrating hilar tumor and peripheral tumor.

Prompt Vascular Control and Mobilization of the Kidney. **With few exceptions, the first priority in partial nephrectomy is identification, dissection, and nonocclusive control of the renal artery and vein with vessel loops** (see Fig. 54–132 on the Expert Consult website). This protects the renal pedicle in the ensuing dissection and, in emergencies, permits the surgeon to rapidly occlude the renal artery to stop life-threatening hemorrhage. One may be able to safely resect small, peripheral renal tumors without first obtaining control of the main renal artery.

The ureter is identified and encircled with a vessel loop. Dissection of the ureter is carried superiorly to the renal pelvis, with special care to avoid devascularization. The uninvolved portion of the kidney is mobilized within the Gerota fascia, while the perirenal fat overlying the tumor is left undisturbed. The kidney must be adequately mobilized to permit resection of a renal tumor with negative margins and minimal injury to adjacent vasculature, parenchyma, and collecting system.

Fully Perfused Partial Nephrectomy: A New Model of Nephron Sparing. Although clamping of the renal artery and vein may reduce the technical difficulty of the procedure by providing a nearly bloodless field, this maneuver leads to renal ischemia that may adversely affect renal function (Thompson et al, 2007). At the Lahey Clinic, the senior author prefers to perform fully perfused partial nephrectomy.

Duration of renal ischemia is the strongest modifiable risk factor for renal insufficiency after partial nephrectomy (Lane et al, 2008). In patients with a solitary kidney, clamping is associated with greater risk of urine leak, renal failure, and

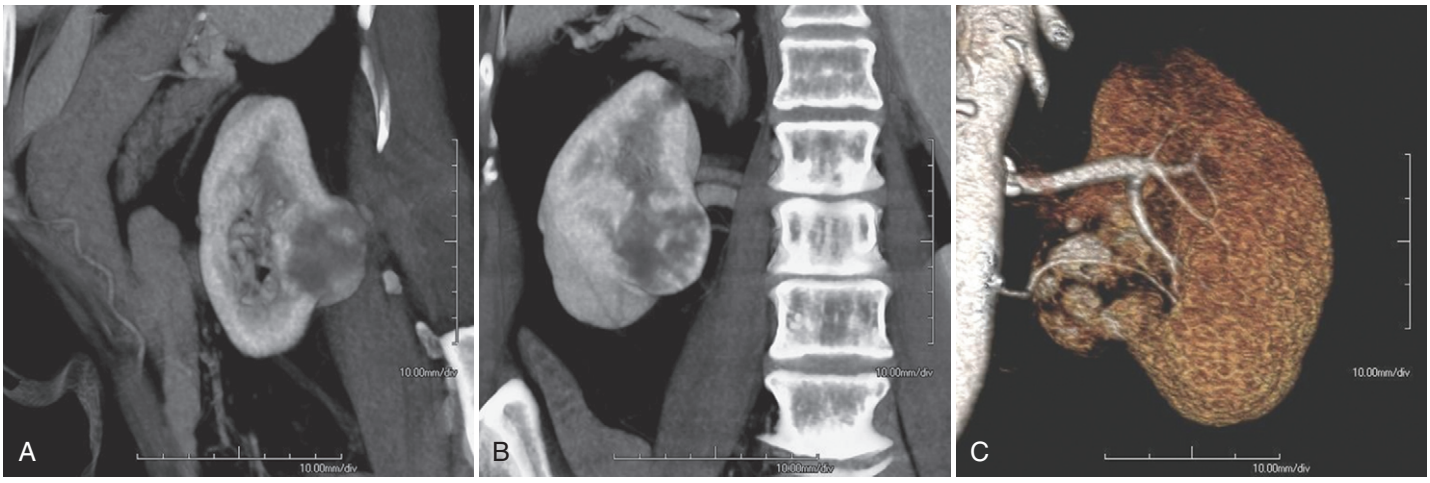


Figure 54–131. **A,** Contrast-enhanced CT scan demonstrating right renal mass. **B,** Three-dimensional reconstruction demonstrates a large intrarenal component to the mass. **C,** Arterial reconstruction shows lower pole renal artery in close proximity to the renal mass.

temporary dialysis (Thompson et al, 2007). The senior author considers clamping of the pedicle to be antithetical to the philosophy of nephron-sparing surgery. The authors perform the majority of open partial nephrectomies with the kidney fully perfused. In a retrospective review of 112 patients with a solitary kidney or preoperative renal dysfunction (serum creatinine concentration >1.5 mg/dL) who underwent partial nephrectomy by the senior author, only 18% required arterial clamping (Smith et al, 2008). **The fully perfused partial nephrectomy technique may result in excellent sparing of renal function.** The majority of patients had either no change in serum creatinine concentration (37%) or a less than a 50% change (46%). Others have advocated a similar approach when feasible (Russo and Huang, 2008).

In the nonclamping method, a vessel loop is placed around the renal artery after it has been mobilized but the vessels are never clamped or compressed. Although this nonclamping technique has frequently been coupled with enucleation, a method of excision characterized by minimal blood loss and trauma to surrounding parenchyma, the senior author has expanded nonclamping to more difficult tumors requiring complex resection. In a retrospective review of 273 patients at the Lahey Clinic who underwent fully perfused partial nephrectomy, 37% of tumors were 4 cm or smaller and 33% were hilar or central. There were multiple tumors in 17% of patients, and 26% of patients had a solitary kidney (Kurteva et al, 2008). The median estimated blood loss was 685 mL (mean 1100 mL). With fully perfused partial nephrectomy, the authors believe the risk of durable deficit in renal function is lowered, as demonstrated in patients with solitary kidneys or preoperative renal dysfunction, albeit at the cost of an increased risk of blood loss and a higher level of technical difficulty (Kurteva et al, 2008).

On rare occasions, some form of transient compression may be required to aid in tumor excision, pelvicalyceal suture repair, and hemostasis. Even in cases of brisk bleeding, the authors prefer not to clamp the main renal artery with instruments or tourniquets, given the threat of ischemia and the small but real risk of intimal damage, thrombosis, and loss of the kidney. It is often sufficient to have the assistant gently compress the renal parenchyma adjacent to the cut surface or use a Kitner to compress the bleeding vessel while the surgeon places shallow 4-0 monocryl figure-of-eight sutures into the transected vessels.

Traditional Partial Nephrectomy with Vascular Clamping. Although the authors have largely abandoned vascular clamping, partial nephrectomy has traditionally been performed with temporary occlusion of the main renal artery or a segmental artery supplying the tumor. Proposed benefits of clamping include limitation of intraoperative bleeding, improved visualization, and reduction in renal tissue turgor, which may improve access to intrarenal structures (Novick, 2007).

When clamping of the renal artery is required, in-situ renal hypothermia is used to protect against ischemic renal injury (Novick, 2007). Surface cooling of the kidney with ice slush allows up to 3 hours of safe ischemia without permanent renal injury. The entire kidney should be covered with ice slush for 10 to 15 minutes immediately after the renal artery is occluded and before the partial nephrectomy is begun (Fig. 54–133). This amount of time is needed to obtain core renal cooling to a temperature (approximately 20° C) that optimizes in-situ renal preservation. During excision of the tumor, invariably, large portions of the kidney are no longer covered with ice slush; and in the absence of adequate prior renal cooling, rapid rewarming and ischemic renal injury can occur. Cooling by perfusion of the kidney with a cold solution instilled through the renal artery is not recommended because of the theoretical risk of tumor dissemination. Mannitol is given intravenously 5 to 10 minutes before temporary renal arterial occlusion. Systemic or regional anticoagulation to prevent intrarenal vascular thrombosis is not necessary (Novick, 2007).

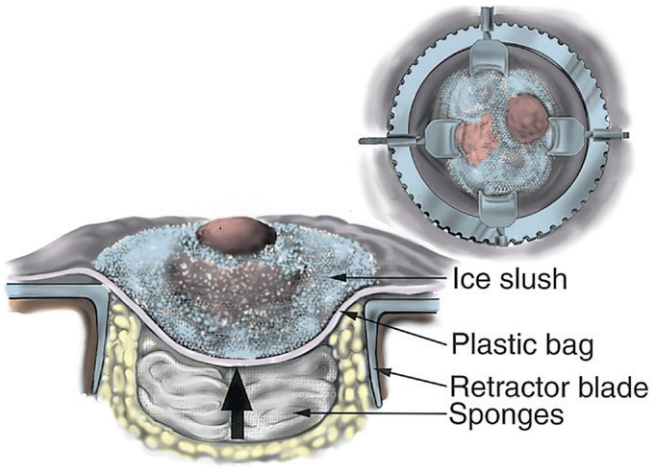


Figure 54–133. Elevation of the mobilized kidney to skin level is demonstrated by placement of sponges under the plastic bag containing the kidney and ice slush.

Even with the artery clamped it is preferable to leave the renal vein patent to reduce ischemia and permit identification of venous bleeding. When large veins are transected, such as in large centrally located tumors, some find it necessary to clamp the renal vein (Novick, 2007).

Tumor Excision. The goal of partial nephrectomy is complete excision of the tumor with negative margins and maximal preservation of benign adjacent parenchyma. Various techniques can be employed to remove the tumor, including enucleation, polar segmental nephrectomy, transverse resection, wedge resection, and extracorporeal partial nephrectomy with renal autotransplantation (see later for a detailed discussion). When performing partial nephrectomy for a suspected malignancy, the overlying renal capsule is not preserved for renorrhaphy but is excised along with the tumor.

Complete resection must be ensured in the operating room. Local recurrence may be due to incomplete resection of the primary lesion or synchronous lesions that were unrecognized at the time of surgery. Intraoperative ultrasonography is used to delineate tumor from normal parenchyma and may help localize intrarenal lesions that are not visible or palpable from the surface of the kidney (Assimos et al, 1991; Campbell et al, 1996) (see Fig. 54–134 on the Expert Consult website; see also Fig. 54–135). Intraoperative ultrasonography is especially useful in the patient with von Hippel-Lindau disease with multiple lesions. The tumor should be inked and cut by the pathologist to be certain that the capsule has not been violated. Intraoperative biopsies should be obtained from the tumor bed if the capsule has been violated. Frozen sections should be examined, and additional tissue should be excised if the frozen section reveals persistent tumor. The width of a tumor-free resection margin has no biologic or prognostic significance (Castilla et al, 2002).

Renorrhaphy: Hemostasis, Closure of the Collecting System, and Repair of the Renal Defect. After excision of the tumor the transected blood vessels on the renal surface are secured with figure-of-eight 4-0 monocryl sutures. The argon beam coagulator can be

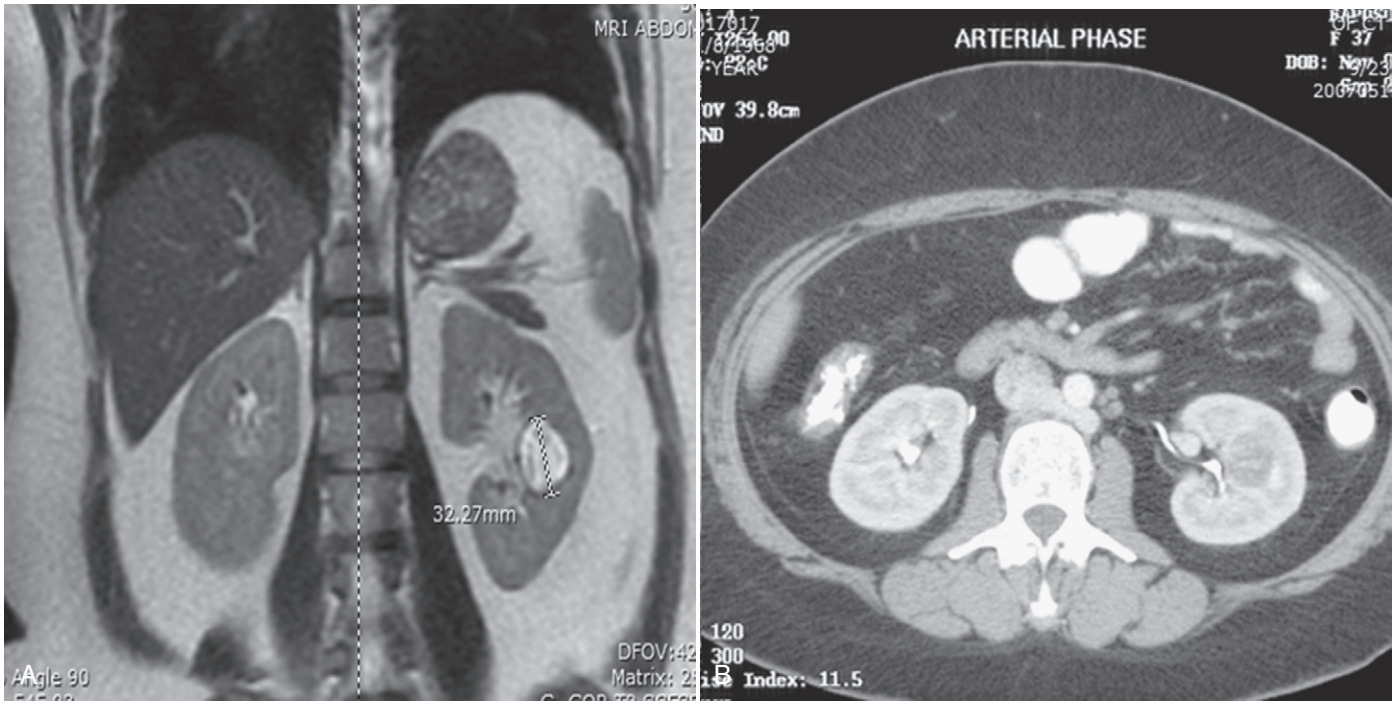


Figure 54–135. **A** and **B,** Preoperative MR and CT images show a left 3-cm enhancing hilar mass closely abutting the collecting system.

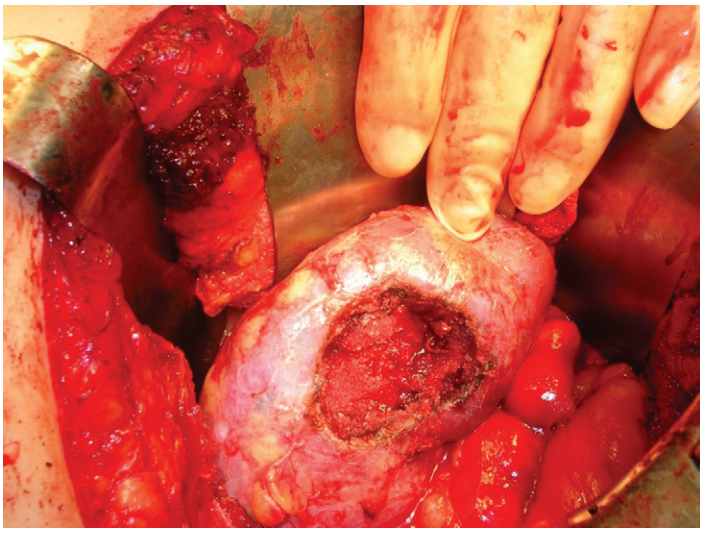


Figure 54–136. Floseal is used to provide hemostasis after removal of the tumor and to identify areas of collecting system leaks after intravenous administration of indigo carmine.

used to achieve hemostasis on the cut renal surface. At the Lahey Clinic, use of Floseal hemostatic matrix (Baxter International, Deerfield, IL) has obviated use of the argon beam coagulator, which can disrupt the figure-of-eight sutures or devitalize the collecting system (Fig. 54–136).

Collecting system defects can be identified by administration of methylene blue or indigo carmine, either intravascularly or directly into the renal pelvis, to dye the urine (see Fig. 54–137 on the Expert Consult website). The collecting system is closed with interrupted or running 4-0 monocryl suture. A ureteral stent can be placed in a retrograde fashion at the start of the procedure if significant repair of the intrarenal collecting system is anticipated. Alternatively, before repair of the collecting system, a wire can be placed antegrade into the bladder through the opening in the collecting system followed by a double-J stent (see Fig. 54–138 on the Expert Consult website).

After closure of the renal vasculature and collecting system, a hemostatic bolster composed of rolled Surgicel is placed at the base of the defect. Floseal hemostatic matrix is applied to the resection site around the bolster. The cortical edges are approximated over the bolster with simple, pledgeted interrupted 2-0 polyglactin sutures (Fig. 54–139; see Fig. 54–140 on the Expert Consult website). The suture line should be tension free, and the kidney should be reconstructed in such a way that the renal pedicle is not kinked. If the renal artery was clamped, circulation is restored after the renorrhaphy is complete. Nephropexy to the posterior musculature with interrupted 2-0 polydioxanone may prevent postoperative migration or rotation of the remnant kidney (Fig. 54–141). A retroperitoneal drain is externalized through a counter incision and is left in place approximately 1 week, or longer if it is draining urine.

Recently, the senior author has utilized an alternative method of approximating the cortical edges that is adapted from the laparoscopic technique. Interrupted 2-0 polyglactin sutures are used to approximate the cortical margins, which are secured in a novel, knotless fashion (see Fig. 54–142 on the Expert Consult website). The suture is secured at the first cortical surface with a Weck ligating clip (Pilling Weck Canada, L.P., Markham, ON, Canada), followed by a Lapra-Ty clip (Ethicon Endosurgery, Cincinnati, OH). A Weck clip is then placed on the suture where it exits the other cortical surface. It is cinched snugly into position, causing the cortical margins to come together, and secured with a second Lapra-Ty clip. This may permit tighter closure of the cortical margins than the traditional repair, provide good closure of parenchyma over the repaired collecting system, and eliminate the need for a bolster.

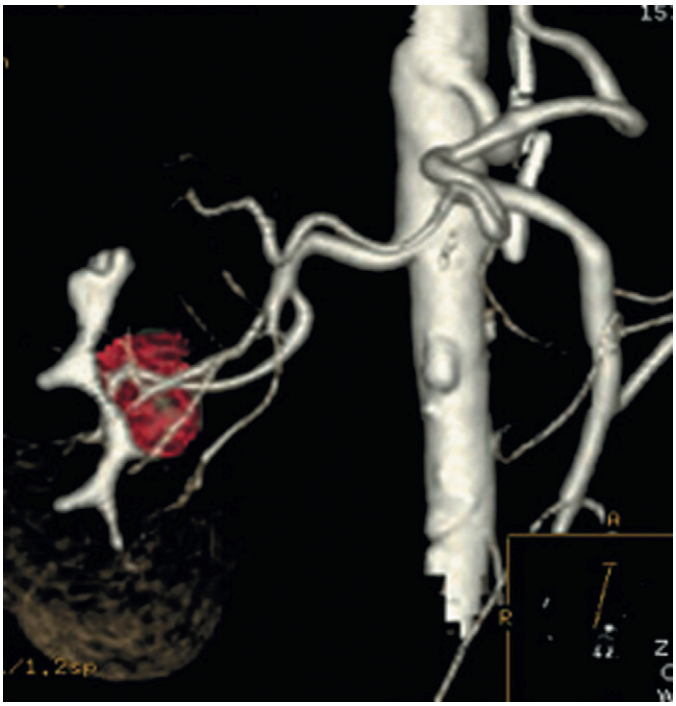


Figure 54–139. Three-dimensional CT reconstruction demonstrating a centrally located tumor.

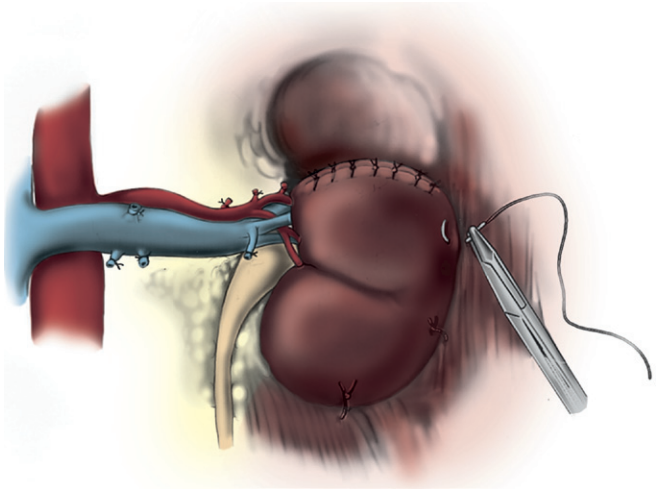


Figure 54–141. Nephropexy of the remnant kidney to the retroperitoneum is achieved with several interrupted sutures.

Techniques of Tumor Excision

Enucleation. Pure enucleation involves removing a renal tumor with blunt dissection along the natural plane provided by the tumor pseudocapsule. Although this technique is convenient and is associated with minimal blood loss, several studies have demonstrated that tumor may extend beyond the pseudocapsule and might therefore be left behind after a pure enucleation. For instance, an analysis of 82 radical nephrectomy specimens for tumors measuring less than 4 cm demonstrated that nearly 20% of specimens had tumor beyond the pseudocapsule, at a mean of 0.5 mm from the capsule. No cancer was found to extend beyond 5 mm, and fewer than 3% extended beyond 4 mm (Li et al, 2003). Other studies have also suggested a higher risk of leaving cancer in the kidney when pure enucleation is performed (Rosenthal et al, 1984; Marshall et al, 1986; Blackley et al, 1988). In response, some authors have advocated using pure enucleation followed by ablation of the tumor base with argon beam or laser energy, such as with the neodymium:yttrium-aluminum-garnet (Nd-YAG) laser, to destroy remaining tumor cells (Kutikov et al, 2008).

Given the risk of incomplete resection with pure enucleation, it is the practice of the senior author to enucleate tumors along with a thin rim of grossly normal renal parenchyma. It is a rapid, precise technique with the benefit of limited blood loss and excellent preservation of normal parenchyma. The kidney is approached and mobilized as described previously, leaving the perirenal fat overlying the tumor intact. The limits of the tumor are defined by palpation and ultrasonography. An incision is made in the renal capsule around the base of the tumor, using the coagulation setting of the Bovie device (see Fig. 54–143 on the Expert Consult website). The Bovie device is inserted into the cut renal capsule and the tumor is circumferentially inscribed. A small tenotomy scissor is used to divide the renal parenchyma. A Penfield spatula is used to retract the normal parenchyma from the specimen. Small vessels in the cortex are palpated with the Frazer pediatric suction device by gently moving it along the cut surface of the parenchyma. These vessels are then grasped with a delicate Gerald forceps, coagulated, and divided with the tenotomy scissors (see Fig. 54–144 on the Expert Consult website). Cautery should not be used deeper than the corticomedullary junction or near the collecting system because it will cause ischemic damage. Nonhealing of the collecting system due to cautery injury may result in a urinary fistula.

Closer to the base of the lesion the tumor is meticulously dissected with the surgeon's thumb protecting the specimen. Larger intrarenal vessels are clamped with pediatric right-angle clamps, divided, and ligated (see Fig. 54–145 on the Expert Consult website). Frozen sections are obtained to be certain that the margins are negative. If there is any question about the margin, additional tissue at the margins is resected and reevaluated. The specimen is inked, and the integrity of the capsule is determined. Floseal is applied to the cut surface of the kidney. In the absence of renal artery clamping, indigo carmine can be given intravenously (see Fig. 54–146 on the Expert Consult website). An opening in the collecting system is identified by the appearance of a blue dot on the surface of the Floseal, which is then closed with 4-0 monocryl suture (see Fig. 54–138). If possible, the renal parenchyma should be closed over the opening in the collecting system. Otherwise, perinephric fat or omentum can be used to cover the renal parenchymal defect. The perinephric fat is approximated over the kidney. This is accomplished without clamping the renal artery or manual compression of the parenchyma. A Penrose drain is externalized through a separate stab incision.

Deep-seated tumors can be resected using a similar approach. After the tumor is located with ultrasound, a Y-shaped incision is made in the parenchyma over the tumor. The incision is opened, and the tumor is dissected meticulously from the kidney using the techniques described earlier. The incision is then closed with absorbable suture (see Fig. 54–147 on the Expert Consult website).

Polar Nephrectomy. Polar nephrectomy is useful for tumors confined to the upper or lower pole of the kidney. The kidney is approached and mobilized as previously explained. The authors typically use a vessel loop to obtain nonocclusive control of the segmental artery supplying the tumor and perform the polar nephrectomy with the kidney fully perfused, as described earlier. The limits of the resection are determined by the tumor rather than by the territory supplied by the segmental apical or basilar artery. This technique permits resection of a polar tumor with a

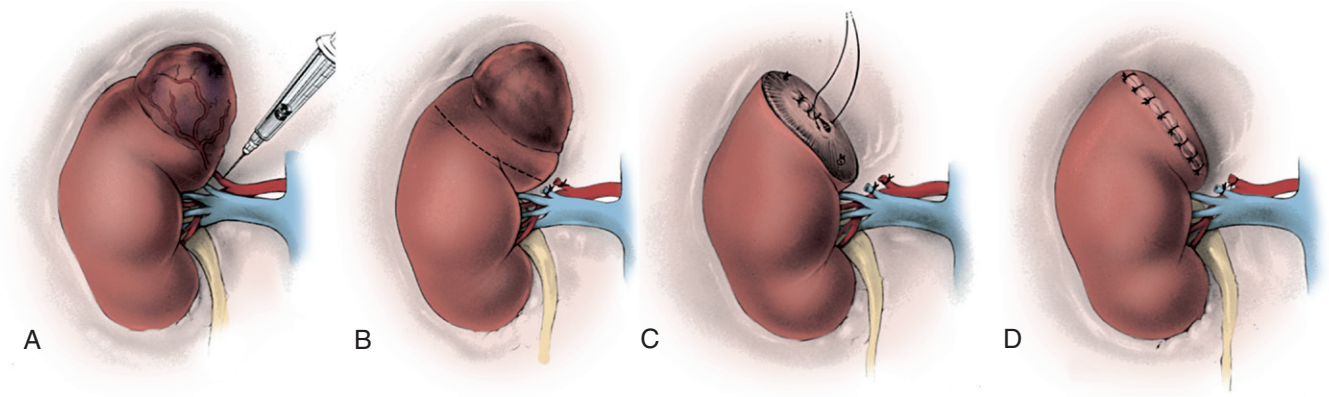


Figure 54–148. **A** to **D,** Technique of segmental (apical) polar nephrectomy with preliminary ligation of apical arterial and venous branches. (From Novick AC. Partial nephrectomy for renal cell carcinoma. Urol Clin North Am 1987;14:419.)

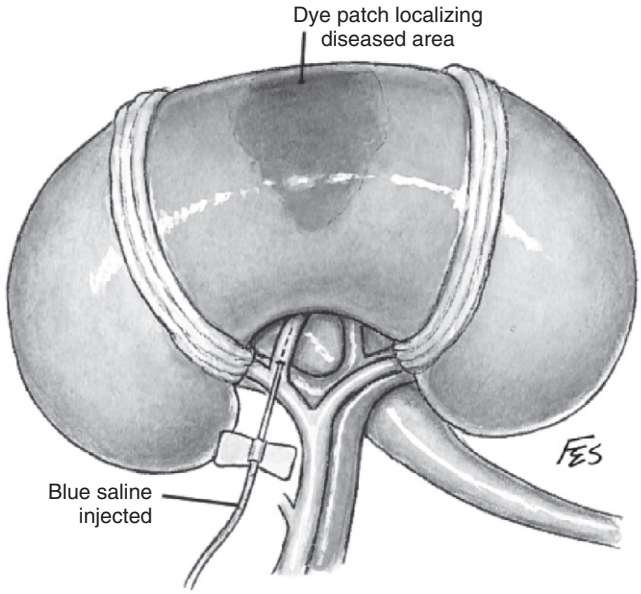


Figure 54–149. Identification of the small blood vessel, such as one that supplies part of the diseased parenchyma, is achieved by injecting a diluted solution of indigo carmine dye into the lumen with a scalpel vein needle and correlating the region stained with that seen angiographically. (© The Lahey Clinic.)

thin margin of normal parenchyma and preservation of uninvolved polar parenchyma.

A more traditional approach is to isolate, ligate, and divide the segmental apical or basilar artery, leaving the remainder of the kidney perfused (Fig. 54–148). The corresponding venous branch is also divided. A line marking the ischemic segment will appear. If this ischemic line is not apparent, injection of methylene blue into the distal aspect of the ligated artery will delineate the involved renal segment (Fig. 54–149). The renal cortex is incised at the line of ischemia, which should be at least several millimeters away from the visible edge of the tumor. Renal parenchyma is divided with a small tenotomy scissor. A neurosurgical spatula is used to provide exposure. Whereas renal parenchyma is easily divided, vessels and collecting system structures are sturdier and elastic. With careful technique, this difference can aid in identification of vessels and the collecting system structures before they are divided. By placing gentle tension on the polar segment to be excised, the gap between specimen and remnant kidney is enlarged, which helps identify larger blood vessels before they are transected. The polar segment is removed. Renorrhaphy with hemostasis, closure of the collecting system, and repair of the renal defect proceeds as described earlier. Surgicel is placed at the base of the defect. If the cortical margins cannot be approximated to each other, a hemostatic bolster is employed.

Knowledge of the renovascular anatomy is essential for polar nephrectomy. If the segmental artery supplying the tumor has been identified with a preoperative CT angiogram, it can be isolated and controlled with a minimal amount of dissection. Alternatively, one is obligated to dissect the main renal artery and identify the various branches. The main renal artery often enters the upper third of the kidney and branches downward to supply the rest of the kidney. In upper pole partial nephrectomy it is therefore possible to damage the main renal artery during tumor excision or occlude a segmental artery supplying the lower portion of the kidney during renorrhaphy.

Heminephrectomy. Heminephrectomy, also referred to as a transverse resection, is used to remove large tumors that extensively involve the upper or lower portion of the kidney (see Figs. 54–150 and 54–152 on the Expert Consult website; see also Fig. 54–151). It is the authors' preference to perform transverse resections without clamping to maintain perfusion to what will be the remnant parenchyma. The kidney is approached and mobilized as previously described. The main renal artery is isolated and surrounded with a vessel loop. With nonocclusive control of the renal artery the parenchyma is sharply divided, leaving several millimeters of grossly normal parenchyma around the tumor (Fig. 54–153). Transected vessels are controlled with shallow 4-0 monocryl figure-of-eight sutures. If needed, bleeding can be slowed transiently by gentle manual compression on the cut parenchyma of the kidney. For more severe bleeding the bleeding vessel can be compressed digitally or with a Kitner. Alternatively, Libertino clamps can be briefly applied until hemostasis has been obtained (Fig. 54–154). Renorrhaphy proceeds as previously described.

A more traditional approach is to perform a major transverse resection with arterial clamping and renal hypothermia. Before clamping the main renal artery, major branches of the renal artery and vein supplying the tumor-bearing portion of the kidney are identified in the renal hilum, ligated, and divided (Fig. 54–155). Renal artery clamping and tissue hypothermia are then obtained. Once adequate hypothermia has been obtained, the transverse resection proceeds as described previously.

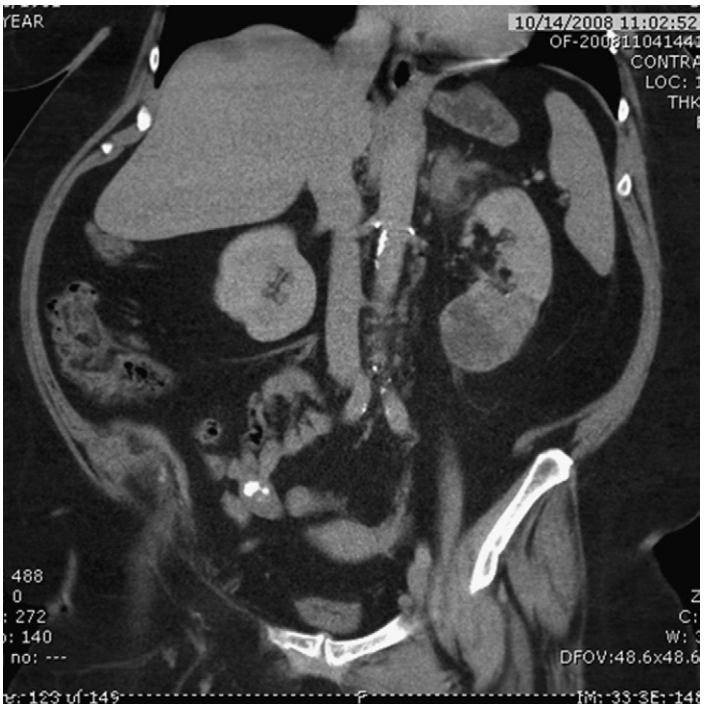


Figure 54–151. Left renal mess noted on CT scan.

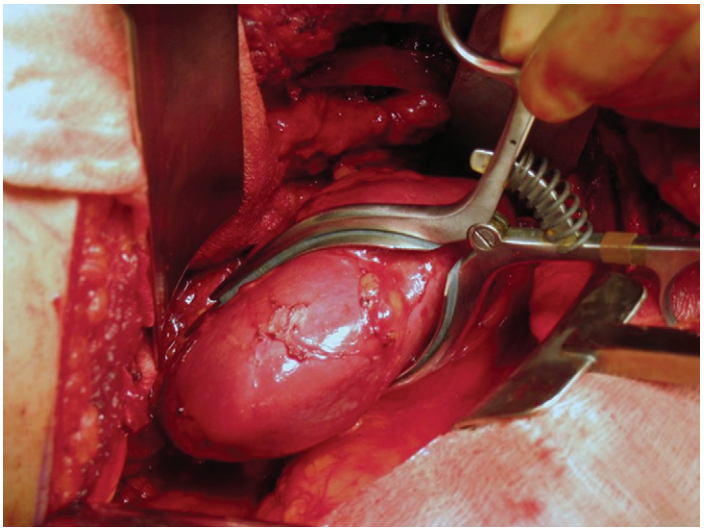


Figure 54–154. Large kidney clamps can be helpful for heminephrectomy and large polar masses.

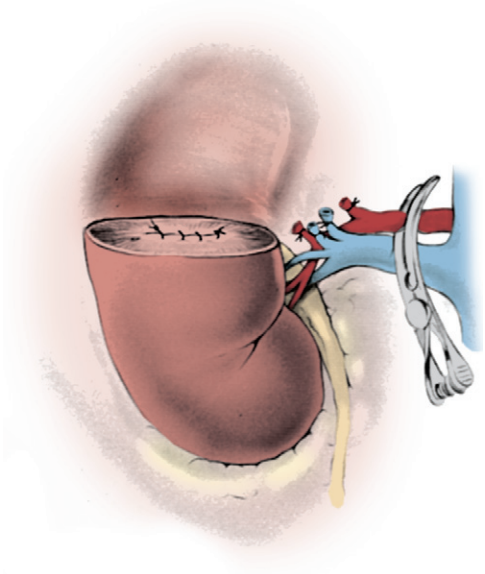


Figure 54–153. Technique of transverse resection for a tumor involving the upper half of the kidney. (From Novick AC. Partial nephrectomy for renal cell carcinoma. Urol Clin North Am 1987;14:419.)

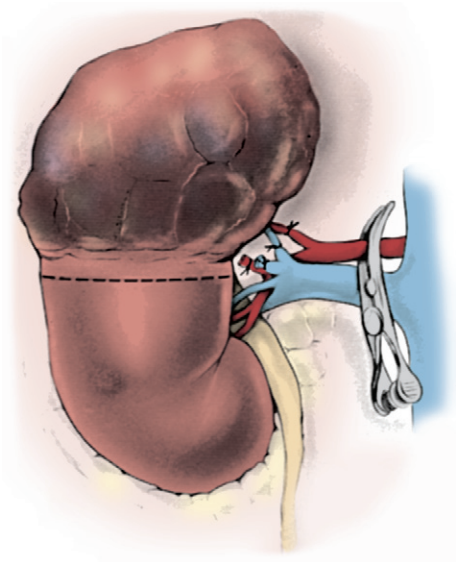


Figure 54–155. Technique of transverse resection for a tumor involving the upper half of the kidney. (From Novick AC: Partial nephrectomy for renal cell carcinoma. Urol Clin North Am 1987;14:419.)

The relevant renovascular anatomy should be identified on a preoperative CT angiogram. The posterior segmental renal artery can be injured during transverse resection. The basilar renal artery, which typically arises from the anterior segmental renal artery, may occasionally arise from the posterior segmental artery. In that case, injury to the posterior segmental artery would devascularize a major portion of the remnant kidney during an upper pole transverse resection (Fig. 54–156).

Midsegmental Partial Nephrectomy. Midsegmental partial nephrectomy is a complicated and rarely employed nephron-sparing technique that is utilized for predominantly endophytic

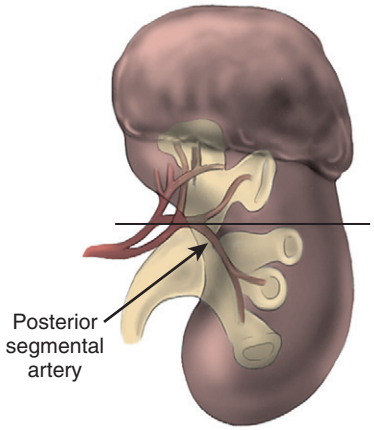


Figure 54–156. Injury to the posterior segmental renal arterial branch must be avoided.

interpolar tumors. The kidney is approached and mobilized as described. The hilar structures are dissected free from each other and cleaned of adherent fat. The arterial branches are carefully identified. Vessel loops or loose loops of silk are placed around the primary and secondary arterial branches supplying the segment of parenchyma to be removed. The secondary arterial branches are injected with a dilute solution of indigo carmine or methylene blue, which demarcates the territory supplied by the vessels. If the demarcated area includes the tumor with an acceptable margin, the appropriate segmental arteries are ligated. The corresponding veins are doubly tied and divided. The caliceal infundibulum draining the targeted tissue is transected and ligated.

The main renal artery is clamped and surface hypothermia is obtained as previously described. A fingertip is placed under the midparenchyma to protect the hilar vessels. With a scalpel, a central section of the kidney that includes the tumor and a clean margin is excised from the convex through to the concave surfaces of the kidney (Fig. 54–157). Hemostasis is obtained with figure-of-eight sutures of 4-0 monocryl. The collecting system is closed. No calyces of the remaining lower or upper pole should be left open. The clamp is removed from the main renal artery. The cut surfaces and hilar branches are checked for significant bleeding. The two poles are approximated with horizontal mattress sutures (Fig. 54–158). During renorrhaphy, one must ensure that the blood vessels supplying the remnant kidney are free of significant angulation or kinking.

Wedge Resection. Wedge resection can be employed to excise large tumors that are predominantly located on the surface of the kidney and that are not limited to the upper or lower pole. A wedge shape that contains the tumor along with several millimeters of grossly normal renal parenchyma is removed. Wedge resection is traditionally performed with clamping of the renal artery and surface hypothermia, although it is the authors' practice to avoid clamping whenever possible. The parenchyma is divided by a combination of sharp and blunt dissection, as previously described. The tumor is excised. The collecting system and vasculature are repaired as previously described.

Surgicel is placed at the base of the defect, which is then obliterated by closing the kidney on itself using simple interrupted 2-0 polyglactin sutures to approximate the cut cortical edges (Fig. 54–159). Alternatively, if closing the kidney would produce tension on the suture line or kinking of the blood supply, the base of the renal defect is covered with perirenal fat, which is sutured to the parenchymal margins with interrupted 4-0 monocryl sutures. The renal artery is then unclamped.

Central Tumors. Centrally located tumors present unique challenges for partial nephrectomy given their proximity to the hilum and the collecting system (see Fig. 54–160 on the Expert Consult website). The kidney is approached and mobilized as described. With central tumors extending into the renal hilum there may be no overlying perirenal fat to preserve. As mentioned previously, very deep-seated tumors can be resected without clamping by making a Y-shaped incision in the parenchyma overlying the tumor (see Figs. 54–147 and 54–161 on the Expert Consult website). The tumor and a thin rim of normal parenchyma is meticulously dissected and extracted from the kidney using the techniques described in the enucleation section. The incision is closed with absorbable suture.

A more conventional technique for tumors adjacent to the hilum is to perform partial nephrectomy with temporary occlusion of both the renal artery and vein using individual vascular clamps. Before clamping the main renal artery, segmental renal vessels adjacent to the tumor that supply the uninvolved portion of kidney are dissected away from the tumor and preserved. Because intrarenal venous branches freely anastomose, providing collateral venous drainage, one may divide small venous branches to access central tumors in the renal hilum without causing ischemia. In this way the main renal vein can be mobilized and

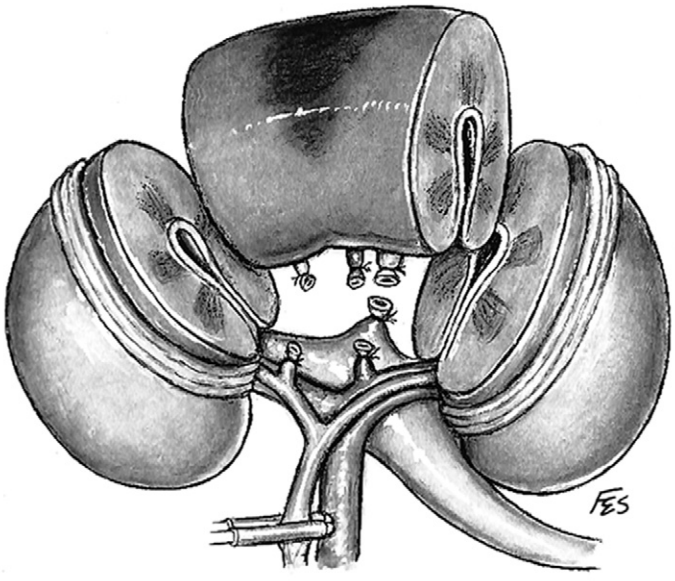


Figure 54–157. Excision is completed by division of tertiary vascular branches and of the infundibulum draining the involved calix. (© The Lahey Clinic.)

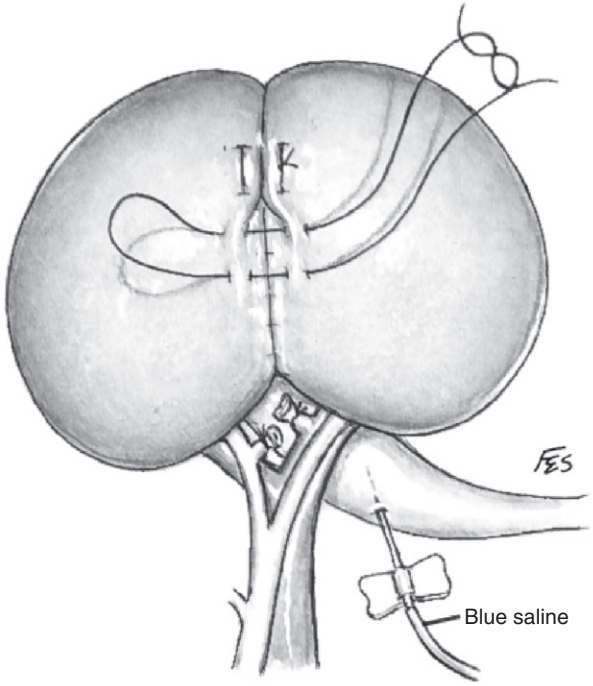


Figure 54–158. Polar remnants are rejoined after releasing the arterial clamp and achieving hemostasis. Closure of the collecting system is tested with colored saline solution. (© The Lahey Clinic.)

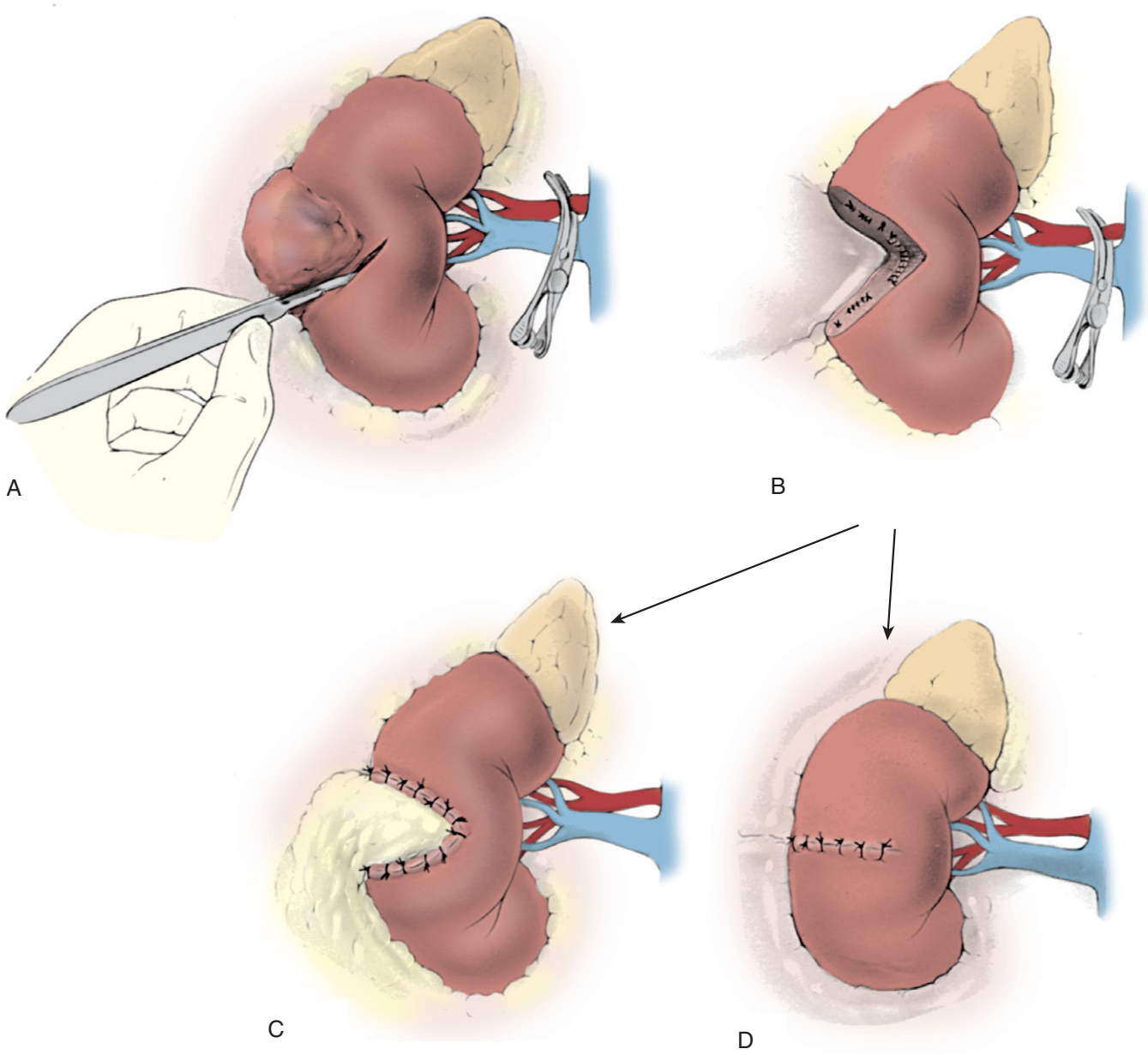


Figure 54–159. **A** to **D,** Technique of wedge resection for a peripheral tumor on the surface of the kidney. The renal defect may be closed on itself or covered with perirenal fat. (From Novick AC. Partial nephrectomy for renal cell carcinoma. Urol Clin North Am 1987;14:419.)

retracted in a fairly extensive fashion to expose a central tumor (Fig. 54–162). Segmental arterial branches that directly supply the tumor are divided. The renal artery and vein are clamped, and the kidney is cooled. The tumor is excised using a combination of blunt and sharp dissection as described previously. These tumors should be removed with neighboring renal sinus fat and with a 3- to 4-mm margin of surrounding normal parenchyma where feasible. Hilar tumors may border the central collecting system; this may limit the margin of normal tissue. Renorrhaphy proceeds with the previously described methods. The vessels are unclamped. As mentioned previously, one must be vigilant to avoid injury to the posterior segmental renal artery

Extracorporeal Partial Nephrectomy and Autotransplantation. Extracorporeal partial nephrectomy with autotransplantation of the renal remnant can facilitate excision of large complex tumors involving the renal hilum (see Fig. 54–76). Proposed benefits of an extracorporeal approach include excellent exposure, a bloodless surgical field, maximal conservation of renal parenchyma, and greater protection of the kidney from prolonged ischemia. The technique, which is associated with longer operative time, need for renovascular and ureteral anastomoses, and risk of renal insufficiency, is infrequently employed and is discussed previously in this chapter.

COMPLICATIONS OF OPEN RENAL SURGERY

Although much can be done to avoid surgical complications, some complications are due to the nature of the disease being treated and may be unavoidable. Meticulous attention to preoperative evaluation, surgical technique, and postoperative care will minimize avoidable morbidity and mortality. Complications are to be

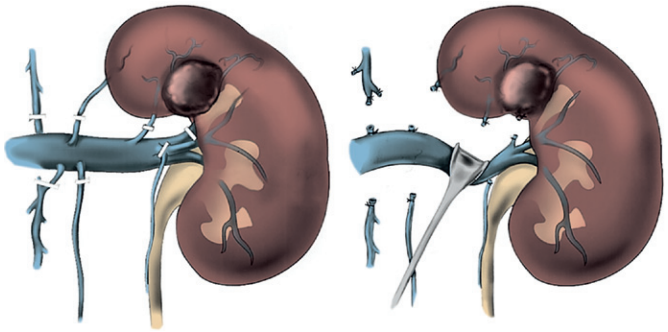


Figure 54–162. Mobilization of the left renal vein to obtain better exposure of the tumor in the renal hilum by ligation and division of small renal venous branches.

Key Points: Partial Nephrectomy for Malignant Disease

- Partial nephrectomy has supplanted radical nephrectomy as the treatment of choice for T1 renal tumors when feasible, even in the absence of identifiable renal insufficiency or threat.
- For tumors other than T1, partial nephrectomy may be indicated in patients with a contralateral kidney that is threatened by stone disease, chronic infection, renovascular disease, vesicoureteral reflux, or systemic diseases that threaten renal function such as hypertension or diabetes mellitus.
- Bilateral tumors represent a special circumstance that is considered a firm indication for nephron-sparing surgery.
- The majority of patients with renal cortical tumors have unrecognized comorbid medicorenal disease. In comparison to partial nephrectomy, radical nephrectomy is associated with a higher risk of postoperative renal insufficiency. There is a dose-response association between chronic kidney disease and hospitalizations, cardiovascular events, and death. Radical nephrectomy may be associated with increased cardiovascular events and decreased survival.
- A large percentage of tumors amenable to partial nephrectomy are still removed with radical surgery.
- The fundamental steps of partial nephrectomy include the surgical approach, vascular control, mobilization of the kidney, complete excision of the tumor with maximal preservation of normal parenchyma, minimization of ischemic injury, and renorrhaphy, which includes hemostasis, watertight closure of the collecting system, and repair of the renal defect.
- The goal of partial nephrectomy is complete excision of the tumor with negative margins and maximal preservation of benign adjacent parenchyma. Various techniques can be employed to remove the tumor, including enucleation, polar segmental nephrectomy, transverse resection, wedge resection, and extracorporeal partial nephrectomy with renal autotransplantation.
- Partial nephrectomy has traditionally been performed with temporary occlusion of the main renal artery or a segmental artery supplying the tumor. Duration of renal ischemia is the strongest modifiable risk factor for renal insufficiency after partial nephrectomy. The fully perfused partial nephrectomy technique may result in improved sparing of renal function.

avoided at all costs, but they also should be regarded as an invaluable teaching tool for surgeons in training.

Patients with significant comorbidity may be at higher risk of complications, and some procedures are inherently perilous. Ideal surgical outcomes and safety should be relentlessly pursued, but the risk of complications should not deter surgeons from performing an indicated operation for a patient in need. Unlike vigilance and confidence, timidity and apprehension on the part of a surgeon do not benefit the patient.

Pulmonary and Thoracic Complications

Pulmonary complications of open renal surgery include atelectasis, pneumothorax, pneumonia, and injury to the lung parenchyma. As discussed previously, use of the flank positions can have deleterious effects on cardiopulmonary function. Postoperative atelectasis, which is cited as a common cause of postoperative fever, is best managed with early ambulation, vigilant fluid management, deep breathing, and incentive spirometry. Atelectasis and pneumonia may be prevented by postoperative pulmonary toilet, including incentive spirometry, bronchodilators when indicated, and postural drainage.

In addition, the pleura or parenchyma of the lung can be injured during open renal surgery, especially through a thoracoabdominal or flank incision. When the pleura is injured, the authors prefer to leave a 8-Fr "dart" chest drain one or two rib levels above the incision. On the contrary, after a nephrectomy with wedge resection of the lung for metastasectomy, a standard-caliber chest tube is used.

When an air leak is not anticipated, a well-described alternative to a chest tube is to evacuate the air from the pleural cavity with a red rubber catheter while the anesthesiologist hyperinflates the lungs. With hyperinflation and suction on the catheter, air and fluid in the hemithorax are forced out through the catheter, which is then removed as a preplaced purse-string suture is tied. Chest films are obtained in the postanesthesia care unit. A significant pneumothorax (15%-20%) or tension pneumothorax requires standard (28 to 32 Fr) chest tube placement. The less common complications of urinothorax or hemothorax are best managed with drainage of the chest and treatment of the root causes of urine leak and bleeding, respectively.

Injured lung parenchyma can be identified by gently pouring water over the parenchyma while the anesthesiologist hyperinflates the lungs. One can oversew the injured areas with 3-0 chromic sutures while the lungs are hyperinflated. Alternatively, a wedge resection of the injured lung using a gastrointestinal stapler can be performed. In the absence of definitive injury to the lung parenchyma, a clinically significant pneumothorax will rarely occur.

Diaphragmatic palsy is a hazard of any approach that puts the phrenic nerve at risk of injury. In addition, renal tumors may be adherent to and require partial resection of the diaphragm, especially when performing a thoracoabdominal incision. Small- to medium-sized defects can be repaired with figure-of-eight 2-0 silk sutures. A PTFE patch can be used to reconstruct larger defects along with chest tube drainage. Omental flaps interposed between the diaphragm and abdominal organs provide additional vasculature to promote healing.

Renal Complications

Renal insufficiency is a risk of any renal surgery, from ischemic injury from vascular clamping, excision of functional renal tissue,

or renal unit loss. Hemodialysis, either temporary or permanent, may be necessary. As discussed earlier, duration of renal ischemia is the strongest modifiable risk factor for renal insufficiency after partial nephrectomy (Lane et al, 2008). In addition, clamping of the renal artery is associated with greater risk of urine leak, renal failure, and temporary dialysis (Thompson et al, 2007).

Ligation of the right renal vein during radical nephrectomy and IVC thrombectomy will result in failure of the right renal unit due to lack of venous collateral vessels. On the left, the renal insufficiency should be transient and resolve once adequate venous collateral vessels have developed (Clark, 1961; Pathak, 1971).

Urine leak is a risk of any renal surgery involving entrance into the colleting system, such as partial nephrectomy. This complication should resolve with placement of a ureteral stent, and urinomas should be managed with percutaneous drainage.

Neurologic Complications

Patients undergoing CPB and circulatory arrest are at risk for cerebral ischemic insults when the total arrest time exceeds 40 minutes. Retrograde cerebral perfusion and "trickle" maintenance blood flow (5 to 10 mL/kg/min) can be employed when the ischemic period is expected to be long. When the foramen ovale remains patent, tumor thrombus that dislodges can cause massive stroke. After a single instance of this devastating complication, the authors abandoned the median sternotomy technique to gain distal control via the minimally access approach, which was hoped to reduce the risk of embolism of the thrombus.

Compression neurapraxia is a recognized complication of the flank position for nephrectomy (Garland and Moorhouse, 1952). In addition, intraoperative hypothermia, which is used in IVC thrombectomy, is a risk factor for development of nerve injury (Graham et al, 1981). Nerve injury due to intraoperative positioning is caused by stretch, ischemia, or compression. Risk factors include thin body habitus, diabetes mellitus, existing neuropathy, peripheral vascular disease, malnutrition, and intraoperative hypothermia or hypotension (Winfree and Kline, 2005). Particular care should be taken, especially in high-risk patients, to properly pad and position all areas at risk (Winfree and Kline, 2005). The authors advocate a team approach with the anesthesiologists for positioning and make an effort to reposition the arms every 2 to 3 hours during prolonged operations.

The bulk of neurapraxia injuries resolve with conservative measures. Postoperative complaints should be addressed with physical therapy and neurology evaluations if symptoms persist or worsen. Pain is treated with analgesics. Physical therapy will help preserve range of motion and joint flexibility in the presence of motor deficits. The physical examination and electromyography findings should normalize over time, although surgical intervention may be indicated if the deficit does not improve.

The flank approaches risk injury to the intercostal nerves and subcostal nerve, which can result in denervation and paresis of the flank musculature. Consequences can include chronic pain or flank bulge, as discussed earlier.

Intra-Abdominal Complications

Abdominal complications include injury to adjacent structures such as the colon, liver, spleen, pancreas, and duodenum. Injury to the bowel can be a devastating complication of renal surgery. Intraoperative vigilance can help prevent and recognize bowel injury, which should be repaired and drained. Adhesions from prior surgery increase the risk of injury to the small bowel. The small bowel can suffer injury when packed away under a retractor. The authors close simple serosal tears or enterotomies with interrupted polyglactin 3-0 sutures in a two-layered Lembert fashion. When necessary, small bowel resection is performed using gastrointestinal staplers and a side-to-side anastomosis. The large bowel can be injured when it is mobilized, especially during adhesiolysis or resection of locally advanced tumors invading the colon or mesocolon.

Right radical nephrectomy requiring Kocher mobilization can lead to injuries of the second or third portions of the duodenum. A duodenal injury should be treated with sharp debridement of nonviable tissue. Two-layered closure in Lembert fashion with an omental patch is the optimal closure to limit leaks and provide additional blood support for healing. Complete mobilization of the small bowel mesentery can maximize exposure of the duodenum and the degree of medial reflection. Use of moist sponges and gentle retraction will limit undue pressure. The same approach should be taken on left-sided tumors to minimize damage to the fourth portion of the duodenum and the tail of the pancreas.

Left-sided tumors requiring mobilization and division of the splenorenal ligament can lead to inadvertent splenic injury. Simple lacerations can be addressed with electrocautery or the argon laser. Larger defects can be managed with bolster repairs utilizing Surgicel or Gelfoam. Omental patches can provide additional support. Persistent bleeding necessitates splenectomy. The spleen is first mobilized anterior and medially, and the short gastric vessels are ligated with 2-0 silk sutures or controlled with Harmonic shears (Ethicon Endo Surgery, Inc., Cincinnati, Ohio). The splenic artery and vein should be ligated individually with suture ligatures of 2-0 silk. Postoperative immunizations to encapsulated bacteria are given before discharge.

Liver lacerations can be very troublesome depending on the location. Superficial lacerations can be managed with electrocautery or an argon beam laser. Alternatively, hemostatic bolsters of Surgicel can be sewn over defects. In the case of severe bleeding from liver injury, partial hepatectomy with assistance of hepatobiliary surgeons may be necessary.

Pancreatic injuries for the most part tend to result from inadequate mobilization or excess traction during exposure. Pancreatic injuries recognized at the time of surgery require that the capsule of the pancreas be closed with nonabsorbable suture and drained with a Jackson-Pratt suction device. In the rare instance that a pancreatectomy is necessary, a consult with hepatobiliary or general surgeons should be obtained. The tail of the pancreas, which can be injured in left nephrectomy, can be resected in a straightforward manner. The pancreas is mobilized and the tail resected with a gastrointestinal stapler. The resected edge may be oversewn with nonabsorbable nylon or polypropylene suture and use of a Surgicel bolster.

Postoperative ileus with significant pain should alert one to possible pancreatitis. Conservative management with parental nutrition and bowel rest remains the primary therapy. A pancreatic fistula usually presents as acute pancreatitis and is confirmed by measuring the amylase level and pH of the draining fluid. Serum chemistries should be obtained and CT performed to delineate the extent of disease. Pancreatic leak is managed by percutaneous or surgical drainage of the fluid collection, hyperalimentation, and administration of somatostatin until the drainage ends or requires surgical management. Most fistulas close spontaneously with adequate drainage. Early drainage of peripancreatic collections can limit pseudocyst or abscess formation. Surgical closure by excision of the fistulous tract and construction of an anastomosis between the pancreas and a Roux-en-Y limb of

the jejunum is only occasionally necessary in patients with prolonged drainage.

Prolonged ileus and small bowel obstruction are potential complications of any surgery, especially the transperitoneal approach.

Incisional Complications

Incisional hernias can be a vexing complication. Anterior midline hernias may result from a technical error in failing to identify and reapproximate the rectus fascia. Patients with multiple prior incisions may be best served by closure with mesh or retention sutures.

Flank bulges after nephrectomy are often not hernias but rather result from paresis of the flank musculature due to intercostal or subcostal nerve injury. An effort should be made to spare the intercostal nerve, which lies between the internal oblique and the transverse abdominal muscles, by padding and retracting the nerve out of the surgical field.

Flank incisional hernias are rare and may result from inappropriate closure of the fascia of the oblique muscles. A fascial defect is often palpable. Closing flank incisions in multiple layers will reduce the incidence of hernia.

Partial or complete dehiscence of the operative wound can occur in 1% to 4% of midline incisions and less than 1% of all flank incisions. Most occur between postoperative days 6 to 8 when tensile strength is relatively weak. Risk factors include poor surgical technique, immunosuppression, malnutrition, poorly controlled diabetes, and sepsis (Riou et al, 1992). The key to management of this complication is prevention with a well-planned incision and solid tissue approximation. Retention sutures should be considered in those patients at risk. A complete revision with retention sutures and synthetic mesh reinforcement should be considered in treating wound dehiscences.

Infectious Complications

Preoperative antibiotics are administered per guidelines discussed in earlier sections. Superficial wound infections are treated by opening the wound to allow purulent material to drain. Deep wound infections, and those accompanied by cellulitis or systemic symptoms, are treated with drainage and antibiotics. Small wounds can be managed with wet-to-dry packing two to three times per day to allow for secondary intention healing. Larger wounds with intact fascia heal faster with vacuum devices.

Asymptomatic lymph or serous collections in the surgical site are best managed conservatively. Infection or respiratory impingement from mass effect are indications to percutaneously drain the collection. Infected hematomas or urinomas should be drained. Prolonged drainage should raise the possibility of a retained foreign body or enteric fistula.

Vascular Injury and Hemorrhage. Blood loss in renal surgery can be significant due to the high percentage of cardiac output delivered to the kidneys. Preparation is essential. Cross-matched blood should be available. Two larger-bore peripheral intravenous catheters and an arterial catheter are standard. Any patient with an extensive cardiac or pulmonary history is managed with a pulmonary artery catheter to facilitate fluid management and determine the need for inotropic support. Vascular instruments should be open before the initial incision is made. Preoperative images should be reviewed for anomalous vasculature.

Injury to the main renal artery often will require proximal exposure at the aortic takeoff to get adequate control. In patients without significant atherosclerotic disease a side clamp can be placed for temporary occlusion until a 4-0 polypropylene repair suture can be placed. Inadvertent injury to the aorta is best repaired with gentle pressure over the aortotomy and polypropylene figure-of-eight repair sutures. Very small holes are best treated with Surgicel, absorbable gelatin sponge such as Gelfoam, or microfibrillar collagen such as Avitene, along with gentle pressure and patience. Segmental branch injuries can be difficult to manage and may require excellent hilar exposure with proximal control for clamping.

The vascular nature of renal tumors and the presence of venous tumor thrombus can lead to extensive venous collateral patterns. These veins are fragile and easily torn. Lumbar tributaries lie in difficult positions and may be injured before they are detected. If the distal end can be identified, the authors like to use a small Allis clamp for hemostasis with figure-of-eight polypropylene sutures. If complete circumferential control cannot be gained, a small snap can be used along with a gentle twisting motion followed by suture ligation. In the rare instance that a lumbar vein retracts into the deep musculature of the retroperitoneum, a large figure-of-eight suture is placed through the muscle in wide bites. Likewise, these vessels can retract into the foramina of vertebral bodies requiring figure-of-eight sutures into the vertebral periosteum. Large lesions with parasitizing vessels can bleed extensively and may be best treated with tumor extirpation and a damage control approach to bleeding after exposure is increased.

Injuries to the IVC are manageable if recognized early with adequate exposure. As a general rule the key principle is to avoid making more than one hole at a time. When a venotomy is encountered the initial move is get proximal and distal control with gentle pressure using one's fingers or sponge sticks. An Allis clamp(s) can be used for hemostasis and a running polypropylene suture can be placed. For larger rents one can temporary occlude the vena cava using Fogarty clamps.

Postoperative bleeding after open renal surgery may be characterized by pain, signs of shock, abdominal or flank swelling, and drainage of blood through the incision or a drain site. Potential sources of postoperative bleeding include the kidney itself, the renal pedicle, and unrecognized injury to the spleen, the liver, or a mesenteric vessel. In some cases it may be best to explore the surgical site, evacuate the hematoma, and obtain hemostasis. In the event of diffuse bleeding from a clotting disorder it may be necessary to temporarily pack the wound with gauze, which can then be removed after 24 to 48 hours. Arteriovenous malformations are an additional significant complication of renal surgery that may present in a delayed fashion. They can often be treated percutaneously (Fig. 54–163). Patients should be given blood and fluid replacement as needed.

Key Points: Complications

- Although much can be done to avoid surgical complications, some complications are due to the nature of the disease being treated and may be unavoidable.
- Meticulous attention to preoperative evaluation, surgical technique, and postoperative care will minimize avoidable morbidity and mortality.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

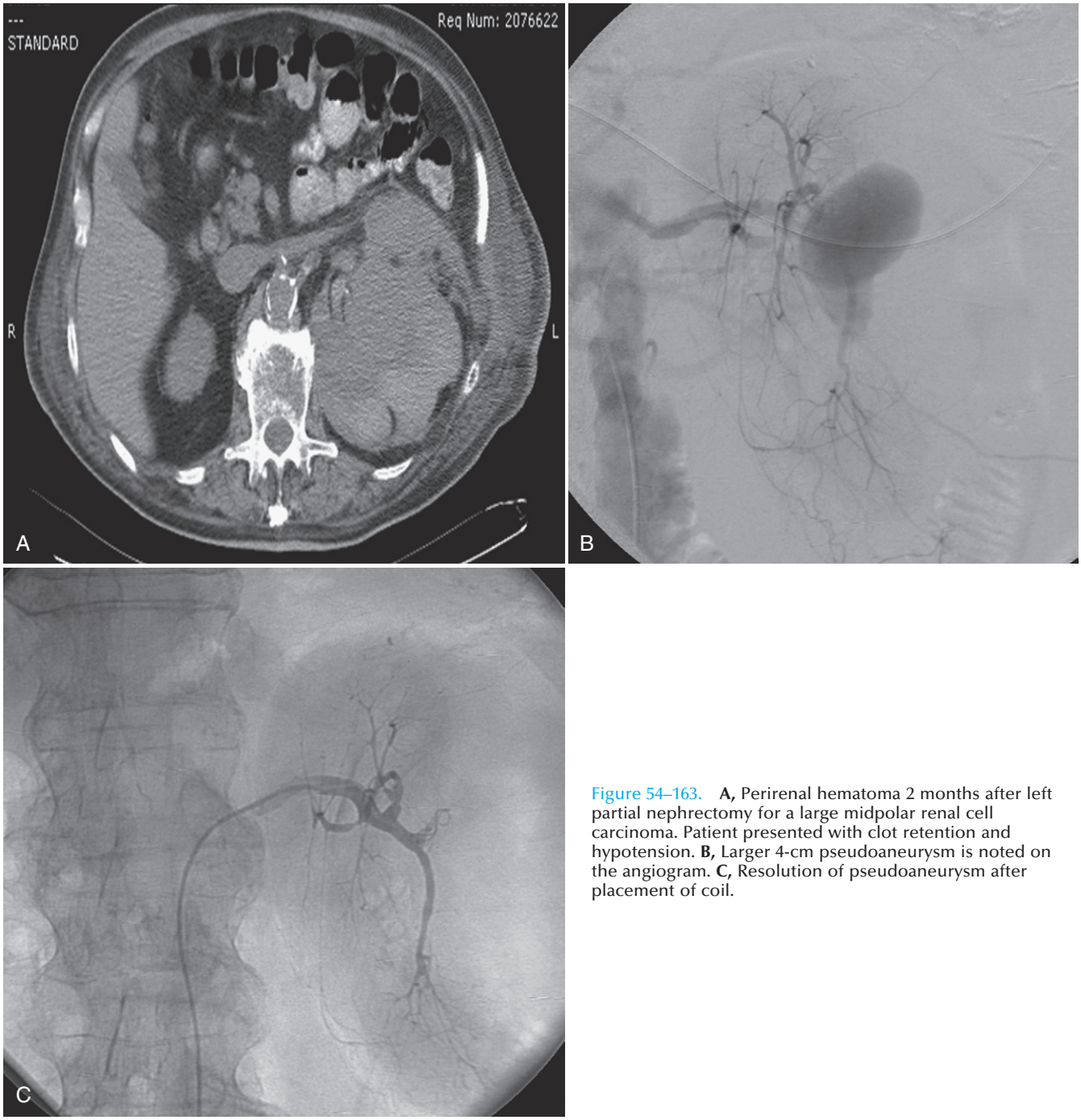


Figure 54–163. **A,** Perirenal hematoma 2 months after left partial nephrectomy for a large midpolar renal cell carcinoma. Patient presented with clot retention and hypotension. **B,** Larger 4-cm pseudoaneurysm is noted on the angiogram. **C,** Resolution of pseudoaneurysm after placement of coil.

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chapter
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Laparoscopic Surgery of the Kidney

Louis R. Kavoussi, MD, MBA ● Michael J. Schwartz, MD ● Inderbir S. Gill, MD, MCh

Patient Evaluation and Preparation
Surgical Approaches and Obtaining Access
Simple Nephrectomy
Renal Cystic Disease
Renal Biopsy for Medical Renal Disease
Pyelolithotomy, Nephrolithotomy, and Ureterolithotomy
Nephropexy
Calyceal Diverticulectomy
Nephrolysis
Radical Nephrectomy
Radical Nephrectomy: Special Considerations
Partial Nephrectomy
Warm Ischemia
Laparoscopic Partial Nephrectomy: Contemporary Outcomes
Laparoscopic Ablative Techniques
Laparoendoscopic Single-Site (Less) Surgery of the Kidney
Complications of Laparoscopic Renal Surgery
Penetrance of Laparoscopic Renal Surgery for the Community Urologist

Surgical treatment is central to addressing many urologic conditions affecting the kidneys. Decades of experience have demonstrated the efficacy and durability of operative excision for malignancies, as well as reconstruction for obstruction. Unfortunately, traditional open surgical approaches, although extremely effective, are associated with significant postoperative discomfort and recuperation. Studies also demonstrate permanent body surface alterations with flank incisions resulting in significantly larger postoperative surface area and volume changes on the operated flank compared to the noninvolved flank. Indeed, patients report dissatisfaction with the body changes occurring in up to 60% of flank incisions (Chatterjee et al, 2004; Kobayashi et al, 2004).

Minimally invasive surgical approaches were born out of the desire to address secondary issues related to surgery, including incisional pain, convalescence, and cosmesis. Initially applied to treat stone disease, advances in video technology and surgical tools have now been used to treat the most complex of renal pathologies, with less morbidity compared to standard operative approaches. Clayman and associates initiated this revolution in renal surgery in 1990 when they introduced the laparoscopic nephrectomy (Clayman et al, 1991). This was performed in an octogenarian with a kidney mass, and although the procedure took over 7 hours, its impact on postoperative recovery was immediately apparent. Subsequently, this approach has been applied to treat every aspect of operative renal disease.

Multiple studies have demonstrated that laparoscopic renal surgery provides recuperative as well as cosmetic advantages in contrast to open surgery (Kerbl et al, 1994a; Dunn et al, 2000; Gill et al, 2003). **With experience, this is now routinely accomplished without compromise to surgical outcomes**. As such, the laparoscopic technique has evolved into the preferred alternative in treating surgical diseases of the kidney. This chapter will discuss indications, present techniques, review results, and outline potential complications of laparoscopy applied to the kidney.

PATIENT EVALUATION AND PREPARATION

Basic laparoscopic principles are thoroughly discussed in Chapter 9. Patient selection and preparation for renal surgery is similar to that for comparable open surgery. A pertinent history and physical are necessary to identify potential issues that could arise during surgery. **Prior abdominal, retroperitoneal, or renal surgery is not a contraindication to laparoscopic surgery; however, type and extent of prior abdominal surgery**

will drive trocar location, as well as choice of transperitoneal or extraperitoneal access (Chen et al, 1998; Cadeddu et al, 1999). In addition, degree of obesity may influence the type of access and location of trocars (Fugita et al, 2004; Hedican et al, 2004; Kapoor et al, 2004). Surgeon experience and available equipment will facilitate or deter use of the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA) in treating renal pathology. Informed consent is obtained with a detailed discussion of potential complications including the potential for open conversion.

Coagulopathies should be corrected to minimize chances of intraoperative or postoperative bleeding. With the increased use of cardiac stenting, more patients are on chronic antiplatelet therapy. A conversation should occur with the patient's cardiologist to plan cessation of therapy to minimize risk of perioperative coronary artery thrombosis. If necessary, complex laparoscopic renal procedures have been performed while patients continue aspirin therapy. Uremic patients with prolonged bleeding time may benefit from desmopresssin acetate (desamino-D-arginine vasopressin [DDAVP] 0.3 to 0.4 μg/kg) given intravenously an hour before surgery to improve platelet function (Mannucci et al, 1983). A side effect of this therapy, iatrogenic hyponatremia, has been reported (Pruthi et al, 2002).

Laboratory and imaging studies are obtained as indicated by each patient's medical history. Patients should have blood typed and screened. Cross matching of blood is at the discretion of each surgeon and based on operative experience and complexity of the procedure. Bowel preparation is helpful to improve visualization and working space.

Imaging studies that define the pathology should be available in the operative suite to define anatomy and, along with operative site marking, minimize the risk of wrong side surgery. Angiography, embolization, and stent placement are not routine and related to each individual procedure.

Anesthesic Considerations in Laparoscopy

The majority of laparoscopic renal procedures require a general anesthetic, and a patient's pulmonary and cardiac function must tolerate this anesthetic approach (Monk and Weldon, 1992). The pneumoperitoneum can impact upon patients with severe cardiopulmonary disease by compromising ventilation and venous return (Arthure, 1970; Hodgson et al, 1970; Nunn 1987; Lew et al, 1992). Patients with chronic pulmonary disease may not be able to compensate for the pneumoperitoneum-induced hypercarbia and may require working at lower pressures, use of helium as an insufflant, or open conversion (Monk and Weldon, 1992; Wolf et al, 1996; Makarov et al, 2007). The use of valveless trocar systems has also been associated with less carbon dioxide absorption (Herati et al, 2009).

Considerations in Obese Patients

Obesity is not a contraindication for laparoscopic surgery, but can make retraction and identification of anatomic structures challenging. It is for these reasons that laparoscopy in obese patients is associated with an increased risk of open conversion when compared with nonobese patients (Fazeli-Matin et al, 1999). In addition, although complication rates for laparoscopy in obese patients are higher when compared with laparoscopy in the general population (Mendoza et al, 1996), pulmonary and wound complications are lower with laparoscopy when compared with an open approach (Kapoor et al, 2004; Montgomery et al, 2005). Other factors to account for in the obese population include the increased distance to the operative field, which calls for modifying trocar location and number, as well as the use of longer instrumentation (Doublet and Belair, 2000; Jacobs et al, 2000). Consideration must also be given to the weight of the pannus, which may raise the intra-abdominal pressure and limit working space. The potential for rhabdomyolysis, a rare but devastating complication in the obese as well as very muscular individuals, must also be considered (Troppmann and Perez, 2003).

SURGICAL APPROACHES AND OBTAINING ACCESS

There are now five laparoscopic approaches to renal surgery: transperitoneal, retroperitoneal, hand-assisted, robotic, and laparoendoscopic single-site surgery (LESS)/natural orifice transluminal endoscopic surgery (NOTES). Each approach can have discrete advantages and limitations depending upon the clinical situation and surgeon familiarity. To date there have been no studies that have shown a definitive recuperative advantage of any one of these approaches. Potential differences in cosmesis may exist, but have also not been well studied to date.

Transperitoneal Laparoscopy

The transperitoneal approach is the traditional and most widely used method of addressing renal pathology. It provides the largest working space, facilitates orientation by providing readily identifiable anatomic landmarks, affords greater versatility in angles and direction of laparoscopic trocars and instruments, and can result in the smallest size and number of ports. The equipment is mature and techniques are well defined and, like any approach, it requires significant expertise in instrument manipulation and suturing.

Patient Positioning and Trocar Placement

For most transperitoneal renal surgery, the patient is initially positioned supine for intravenous (IV) access, the induction of general anesthesia, and endotracheal intubation. A bladder catheter and orogastric tube are placed for decompression of the bladder and stomach during insufflation, trocar placement, and dissection. Sequential compression stockings are placed for deep venous thrombosis prophylaxis. When performing transperitoneal procedures, including robotic and LESS surgeries, patients are positioned in a 30- to 45-degree flank-up position. Care is taken to pad

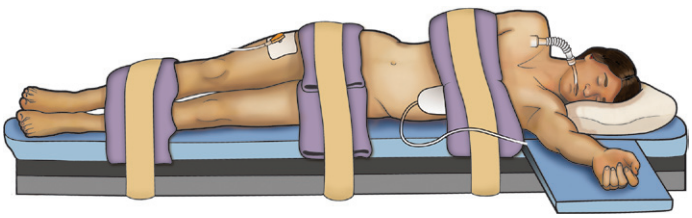


Figure 55–1. The patient is placed in a modified flank position, with the operative side tilted up 30 to 45 degrees using a gel roll or a rolled blanket supporting the back. The lower arm is placed on a padded armrest, and the other arm is flexed at the elbow and rested over the chest. Wide cloth or silk tape is used to secure the patient to the operating table to allow for table rotation during the surgery.

all pressure points. The patient is secured to the operating table to allow lateral tilting of the table (Fig. 55–1). Tilting the table away from the affected kidney will help move bowel out of the operative field. There is no need to flex the table or use a kidney rest as there is with open surgery. The equipment in the operating room is situated to maximize the use of space and allow all members of the surgical team to view the procedure (Fig. 55–2). During the skin preparation and draping, the entire flank and abdomen are included in case conversion to an open procedure is required.

Once a pneumoperitoneum is established, three to five trocars are initially placed to complete the dissection (Fig. 55–3). There are a variety of trocar configurations that are effective for each procedure.

A 12-mm trocar is placed lateral to the rectus at the level of the umbilicus; this trocar is used for instrumentation and the passage of sutures, bulldog clamps, or staplers to secure and divide hilar vessels. In short patients, this may be placed in the midline, halfway between the umbilicus and pubis. **A 10-mm trocar is placed at the umbilicus for the camera, and a 5- or 10-mm port is inserted in the midline 2 cm below the xiphoid process.** In obese patients, all trocar sites are moved laterally (see Fig. 55–3C). Additional trocars for retraction may be needed for visualization or assist with organ entrapment (Fig. 55–4).

Retroperitoneal Laparoscopy

The retroperitoneal approach mimics open surgery because the peritoneal cavity is avoided. A potential space is created to visualize the surgical field. It may be preferred for selected cases of laparoscopic partial nephrectomy, cyst marsupialization, pyeloplasty, renal biopsy, or in patients who have had peritonitis or who have undergone multiple prior abdominal surgeries.

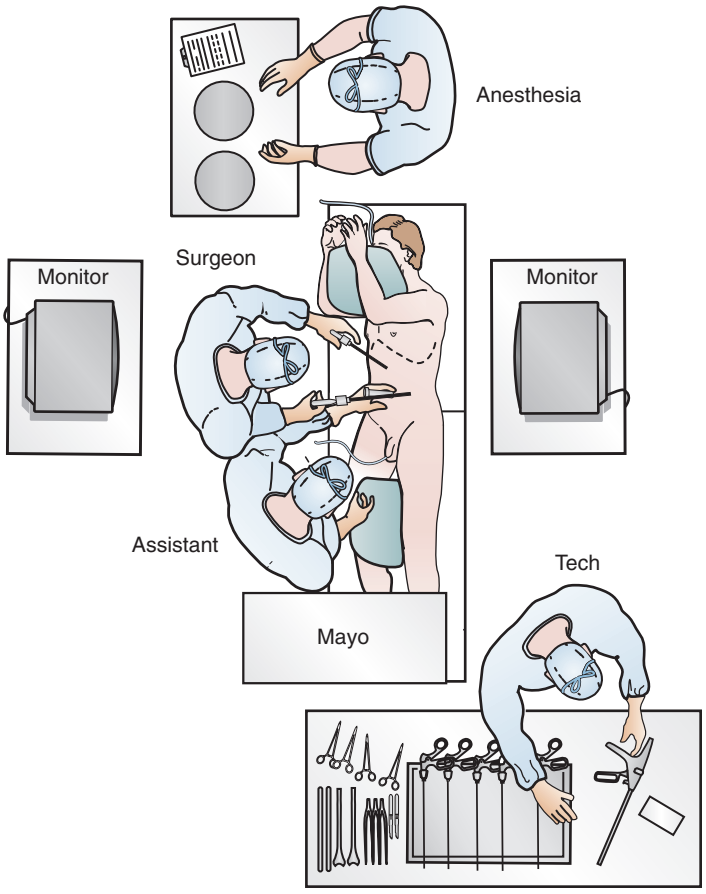


Figure 55–2. The operating room configured for left nephrectomy. Two monitors allow the assistant to follow the procedure. The scrub tech is positioned to easily assist with instrument passage and exchange.

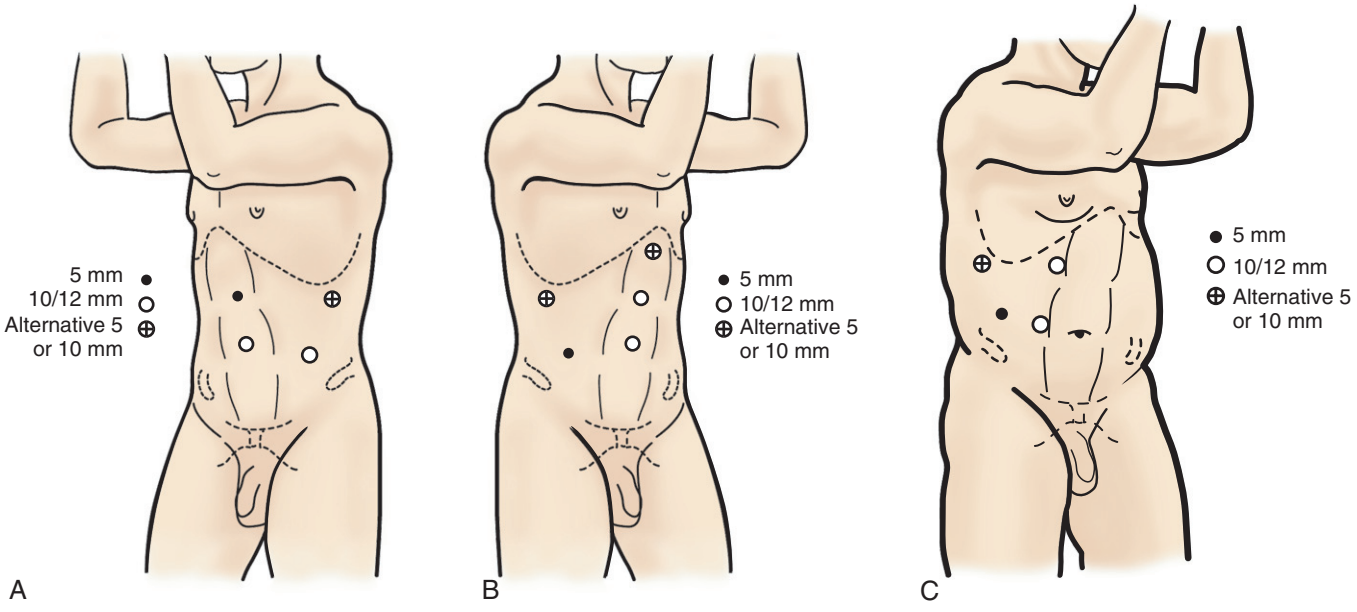


Figure 55–3. Trocar sites for left-sided **(A)** and right-sided **(B)** procedures. A 12-mm trocar is placed lateral to the rectus at the level of the umbilicus, a second 10-mm trocar is placed at the umbilicus, and a 5-mm trocar is inserted in the midline between the umbilicus and the xiphoid process. **C,** In obese patients, all trocars are shifted laterally. Optional accessory subcostal, subxiphoid, and low midline trocar positions, which may be helpful for retraction, are also shown.

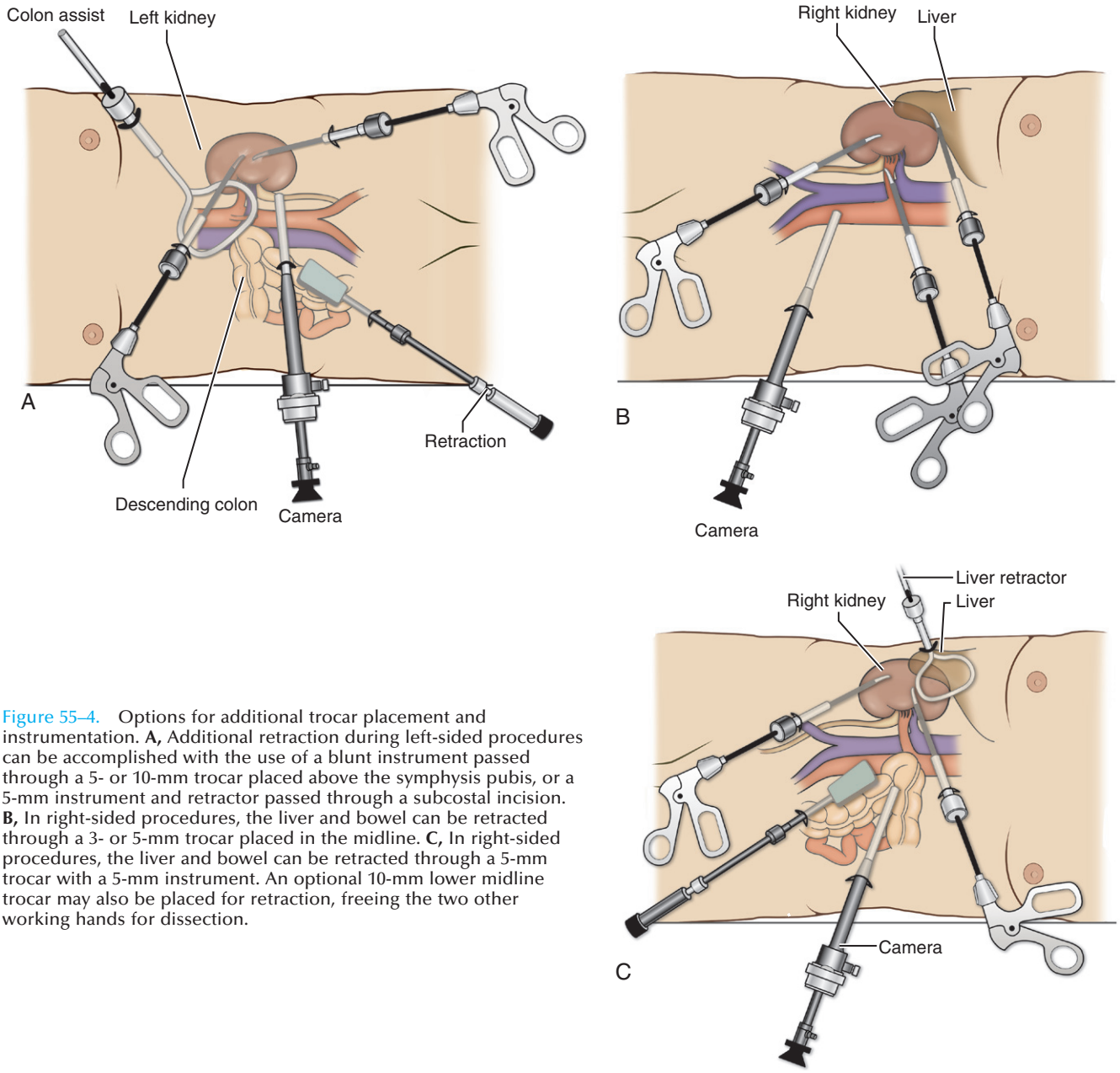


Figure 55–4. Options for additional trocar placement and instrumentation. **A,** Additional retraction during left-sided procedures can be accomplished with the use of a blunt instrument passed through a 5- or 10-mm trocar placed above the symphysis pubis, or a 5-mm instrument and retractor passed through a subcostal incision. **B,** In right-sided procedures, the liver and bowel can be retracted through a 3- or 5-mm trocar placed in the midline. **C,** In right-sided procedures, the liver and bowel can be retracted through a 5-mm trocar with a 5-mm instrument. An optional 10-mm lower midline trocar may also be placed for retraction, freeing the two other working hands for dissection.

Patient Positioning and Trocar Placement

Using this approach, patients are placed in a full-flank position. Modest table flexion can help increase the distance between the ribs and iliac crest to facilitate trocar placement. An axillary roll is required, as well as care in securing the patient to the bed. Arms may be secured on pillows or a purpose-built armrest. A 15-mm transverse incision is made in the posterior axillary line, midway between the tip of the 12th rib and the iliac crest (Fig. 55–5A). After deepening the dissection downward through the lumbodorsal fascia, the retroperitoneum is entered, and a working space may be developed using blunt dissection with the tip of a finger in the space between the psoas muscle and the kidney (Fig. 55–5B). A simple balloon created from two fingers of a size-8 or -9 glove may then be inserted and filed with CO_2 or saline to further develop the retroperitoneal working space (Fig. 55–5C). A blunt tip trocar is then passed through the incision, and the trocar cuff is expanded and cinched to the skin to prevent leakage of CO_2 (Fig. 55–5D). An alternative entry approach involves entry with the 0-degree lens and visual obturator through the initial incision (Fig. 55–6A). Entry into the retroperitoneum may be confirmed by the appearance of the characteristic yellow retroperitoneal fat, insufflation is initiated, and blunt dissection using only the laparoscope is performed to develop a working space (Fig. 55–6B). Caution must be used not to enter too anteriorly because inadvertent **peritoneal entry or colon injury may occur; entering too posteriorly may result in bleeding from the quadratus lumborum or psoas muscles.** Once the working space is established through either approach, pertinent structures may be identified for orientation and additional trocars placed. Typically, a 5-mm trocar is placed just off the tip of the 12th rib, and a 12-mm trocar is placed posteriorly and superiorly relative to the camera port (see Fig. 55–5A).

The greatest limitations of the retroperitoneal approach are the limited working space and more subtle anatomic landmarks. The smaller working space limits the distance between trocars,

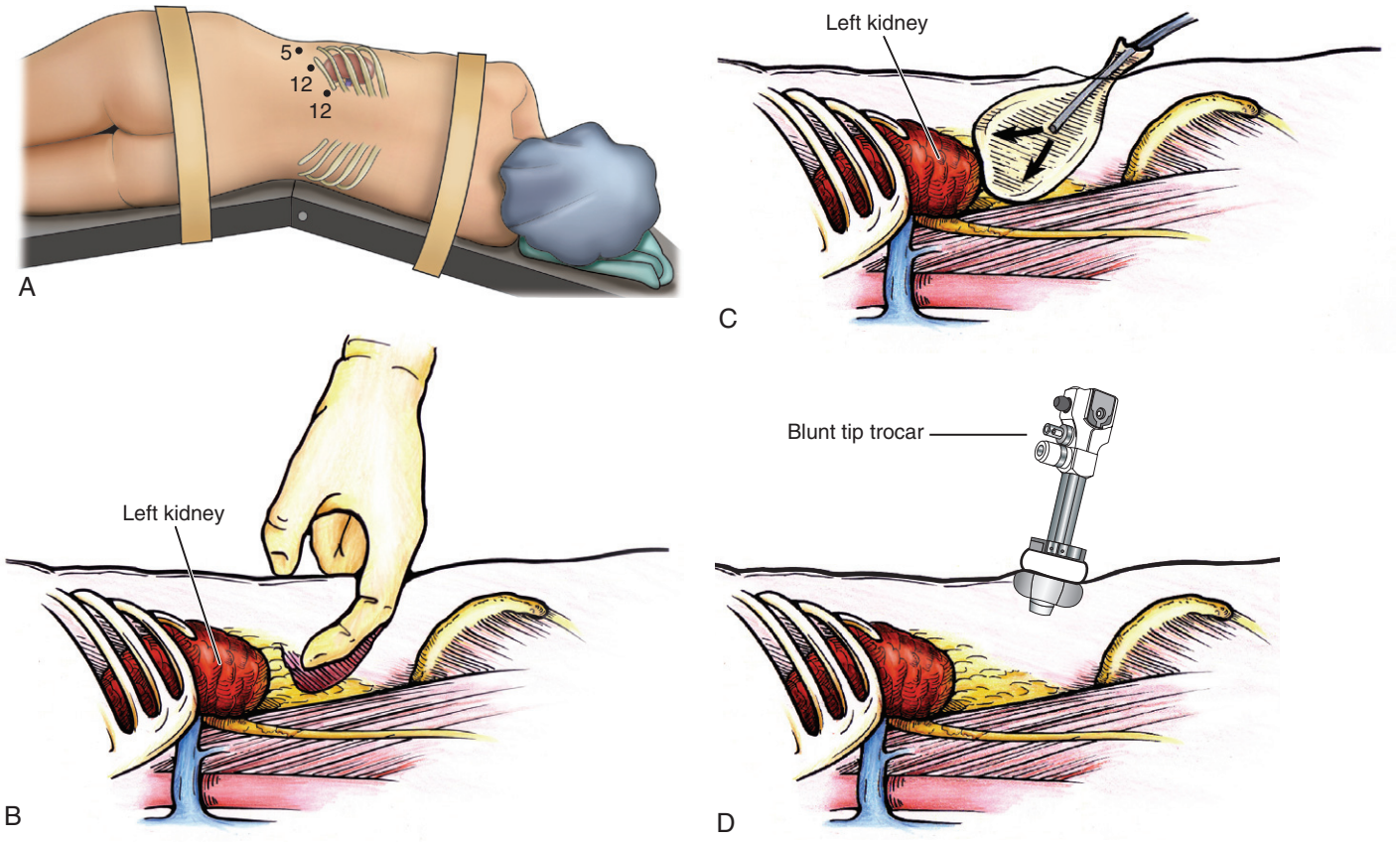


Figure 55–5. Trocar placement for retroperitoneal kidney surgery. **A,** With the patient in the full lateral position, the hips flexed, and the kidney rest elevated, a 15-mm incision is made 2 cm below the tip of the 12th rib, between the rib and the anterior superior iliac spine. **B,** The index finger is inserted through the incision and used for blunt dissection to create a hole from the skin through the muscle into the retroperitoneal space. If the finger is in the correct position, the surgeon should feel the smooth surface of psoas muscle and the lower pole of the kidney covered by Gerota fascia. **C,** To quickly create the working space, insert a balloon created from the finger of a size 8 or 9 glove, secured with silk suture over a simple red rubber catheter. The balloon is then filled with 600 to 800 mL of saline. **D,** A Blunt Tip Trocar (U.S. Surgical, Norwalk, CT) is used to seal the trocar site. Because of its low profile, it will not obstruct the view or take up useful space in the retroperitoneum. The balloon/collar configuration eliminates the need for sutures and allows 360-degree rotation.

potentially leading to awkward hand positioning. Also, the pathology is much closer to the lens, and frequent smudging of the tip may occur. If additional space is needed during the procedure, initial retroperitoneal access can be expanded to a transperitoneal approach through opening the peritoneum under direct vision. Despite these limitations, the retroperitoneal approach may be preferred in some cases, and with adequate experience, a wide variety of laparoscopic renal surgery may be performed.

Hand-Assisted Laparoscopy

Hand assistance offers a bridge between open surgery and laparoscopy (Nakada et al, 1997). It offers more intuitive assistance from the human hand with dissection and retraction, simultaneously providing tactile feedback to the surgeon. Several manufacturers make devices for this purpose. An incision large enough for the hand must be created and can also be used as an extraction site. This incision site is usually larger than one used for intact extraction during pure laparoscopic surgery. This technique may be advantageous for the novice laparoscopic surgeon and in patients with significant scaring about the kidney, or if a difficult dissection is anticipated. Hand assistance may also be employed in the event of an emergency, such as bleeding, by extending a trocar site and placing a hand port to assist in repair of an injury or vascular control. Indications are identical to those for laparoscopic nephrectomy or laparoscopic partial nephrectomy.

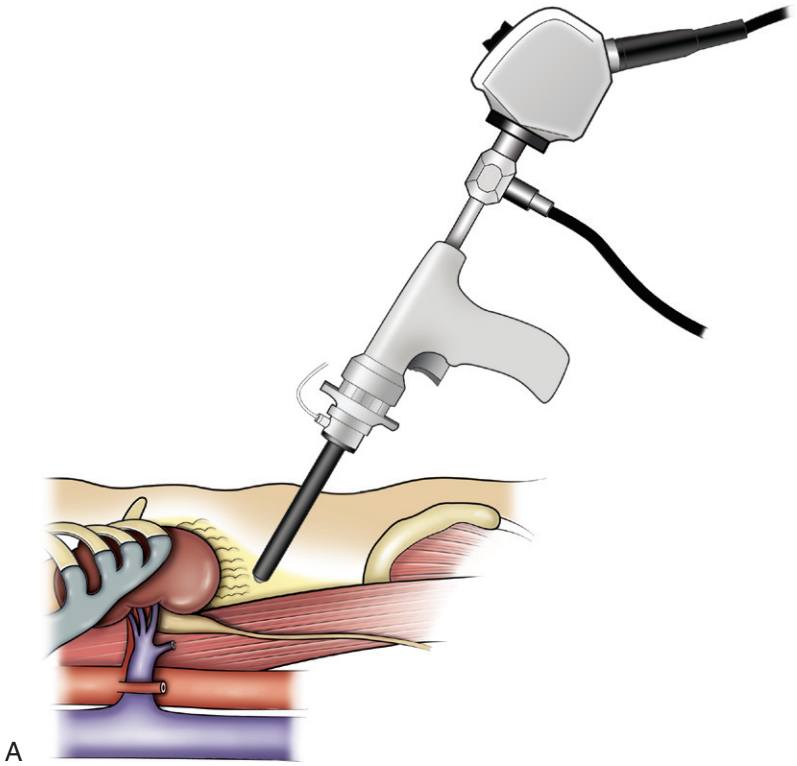
Patient Positioning and Trocar Placement

The patient is positioned just as for pure laparoscopic kidney surgery. The initial incision is for the hand port that is made through the skin and fascia and into the peritoneal cavity. Location will depend on handedness of the surgeon, operative side, and body habitus of the patient (Figs. 55–7 and 55–8). Care must be taken to avoid making the incision too large, because gas may escape, making the procedure more difficult due to decreased working space. Once the hand-assisted device is placed, the peritoneum is insufflated, and the additional trocars may be placed under direct vision by placing the camera through the hand port.

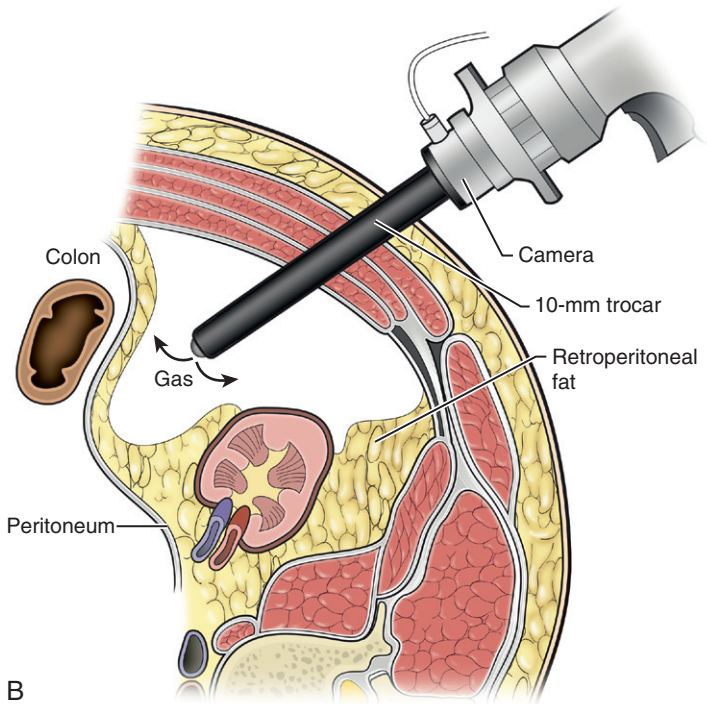
There are some limitations in location of port placement, and the hand may potentially get in the way of visualization or dissection instrumentation. Some leakage of gas may occur about the device, resulting in difficulty in maintaining the pneumoperitoneum. These devices exert 30 to 100 mm Hg of pressure on the arm, which may account for surgeons developing tingling, numbness, or pain in the forearm or hand (Monga et al, 2004).

Robotic-Assisted Laparoscopy

The da Vinci computer–aided surgical system has been used to perform what has commonly become known as robotic surgery. This device uses a computer system and a series of mechanical arms to translate surgeon movements familiar to open surgery to



A



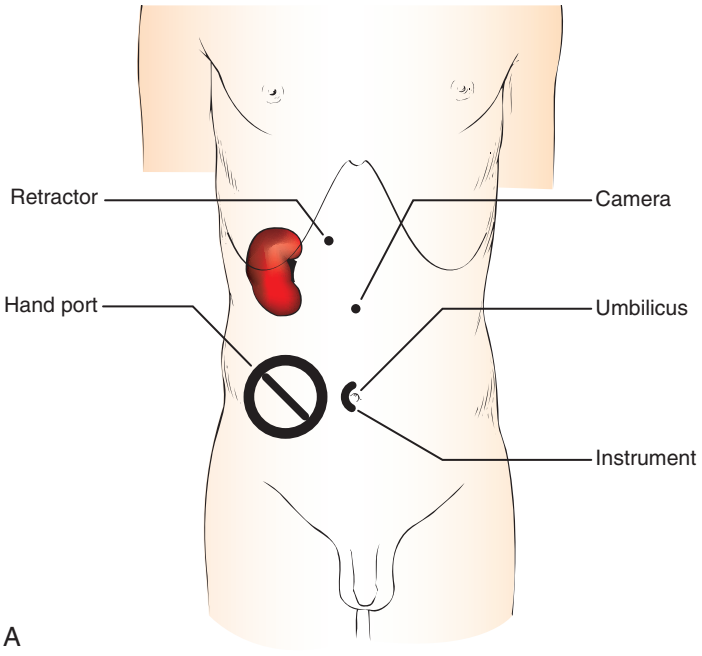
B

Figure 55–6. **A,** Standing behind the patient, the surgeon initially develops a space bluntly between the psoas muscle and the kidney using the visual obturator with the 0-degree laparoscope through it. **B,** Together, they are used to bluntly push the peritoneum medially, creating a working space large enough to allow placement of additional trocars.

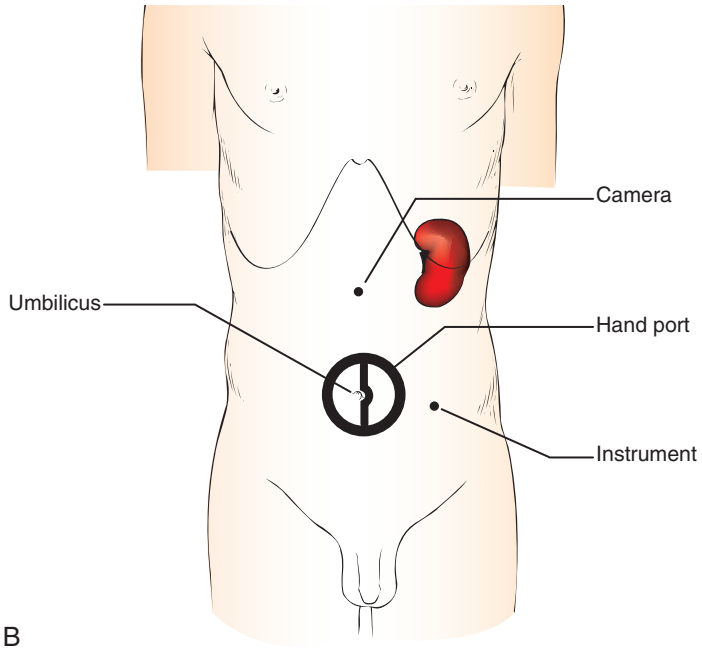
a laparoscopic platform. As such, instrument movement of right and left is preserved, as opposed to pure laparoscopic surgery where it is reversed. Also, hand-eye association is preserved and, a dual lens system provides 3-dimensional (3D) depth perception. The addition of instrument articulation facilitates dissection and suturing for those lacking laparoscopic abilities. These additions have obviated the need for high-level laparoscopic skills, in some instances to allow more surgeons to offer a minimally invasive approach to their patients.

Patient Positioning and Trocar Placement

Patient positioning will depend, in part, upon tumor location if partial nephrectomy is to be undertaken. In addition, the timing of docking the robot must be considered because with the robot docked, table rotation will not be possible. The entire procedure may be performed with the aid of the robot, or the initial part of the operation may be performed using standard laparoscopy, with use of the robot only for tumor excision and renorrhaphy.

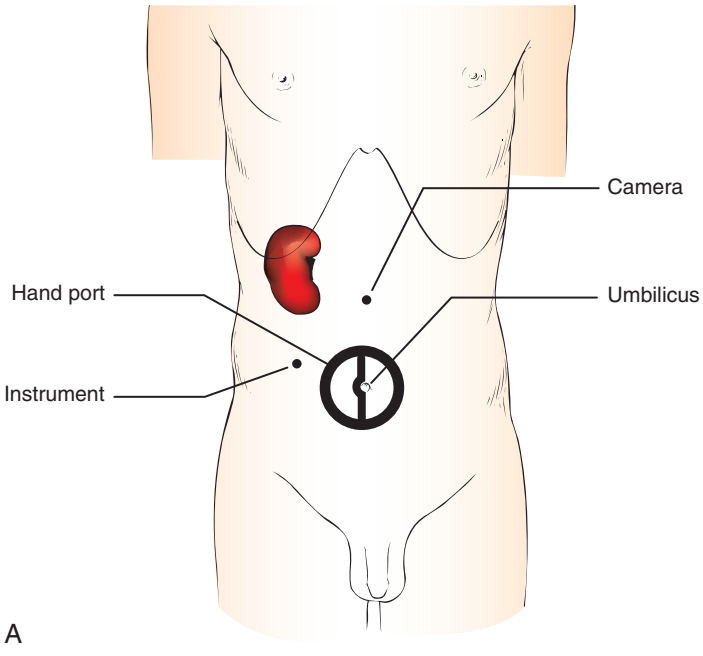


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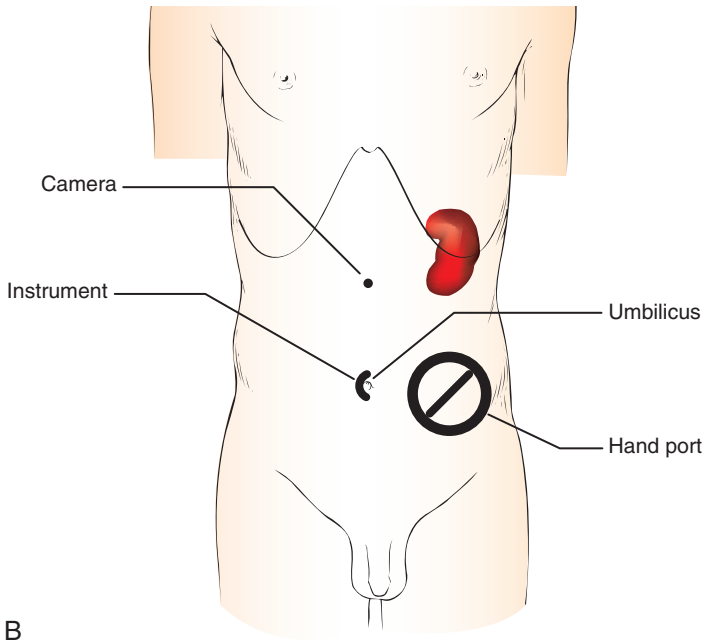


B

Figure 55–7. Port placement for a right-handed surgeon for hand assistance. **A,** For a right-sided kidney, the hand-assisted device is placed in the right lower quadrant for insertion of the left hand, and dissection is performed with instruments in the right hand placed through an umbilical trocar. The camera is placed several centimeters above the umbilicus in the midline. On the right side, retraction of the liver is usually necessary to allow visualization and dissection of the renal hilum. A liver or bowel retractor can be placed through a subcostal trocar to assist with visualization or irrigation/aspiration. **B,** For the left kidney, the hand-assisted device and left hand are placed though a periumbilical incision and dissection is performed with the right hand using an instrument placed in the subcostal margin just medial to the nipple. The camera is placed several centimeters lateral to the edge of the actual hand-assisted device (not the edge of the incision). Additional assistance can be delivered through the most lateral trocar site.



A



B

Figure 55–8. Port placement for a left-handed surgeon for hand assistance **A,** When operating on the right kidney, a left-handed surgeon places the hand-assisted port in the periumbilical location for insertion of the right hand. The working port for the left hand is placed lateral to the rectus muscle, in line with or just inferior to the level of the umbilicus. The camera is placed through a lateral trocar in the anterior axillary line. Additional assistance with retraction of the liver can be accomplished through a subcostal trocar. **B,** For a left-handed surgeon operating on the left kidney the hand-assisted port is placed in the left lower quadrant for insertion of the right hand. The left hand works with the instrument passed through an umbilical trocar, and the camera is placed midway between the umbilicus and the xiphoid process. Additional assistance with retraction or aspiration can be accomplished through a fourth trocar placed at the subcostal margin.

Most authors prefer a flank position with the table modestly flexed (Aron et al, 2008; Deane et al, 2008; Benway et al, 2009). As the robotic procedure requires more trocars than standard laparoscopy, this allows more adequate spacing of instruments and less clashing of the robotic arms. Inclining the table may provide additional space at the back of the patient for the robot and other equipment (Fig. 55–9).

Robotic trocars plus the additional assistant and camera ports are typically used for the procedure. A port-in-port technique of robotic-assisted partial nephrectomy (RaPN) has also been described, wherein the righthand and lefthand working ports are actually standard 12-mm laparoscopic ports (Aron et al, 2008). The robotic 8-mm ports are inserted through these 12-mm ports to perform RaPN. This arrangement can be advantageous in event of an intraoperative complication or robotic malfunction, wherein emergent conversion to pure laparoscopic surgery is necessary. The robot can be undocked expeditiously and standard LPN performed in the usual fashion without requiring additional time to insert new ports or working through 8-mm robotic ports that preclude passage of the necessary CT-1 or CT-X needles.

A three-arm configuration includes four to five total trocars, a 12-mm periumbilical camera port, an 8-mm subcostal robotic trocar in the anterior axillary line, an 8-mm robotic trocar in the posterior axillary line placed above the iliac crest, and one 12-mm assistant trocar in the low midline to allow passage of sutures, bulldog clamps, suction, or retraction. An additional 12-mm subxiphoid trocar may be used, if necessary, for additional retraction or passage of bulldog clamps if the angle is more optimal (Fig. 55–10A). A four-arm configuration involves five to six total trocars, using the same general configuration as the three-arm technique, but shifting the robotic trocars slightly to avoid clashing of the arms (Fig. 55–10B).

The shortcomings of the device include the initial capital investment and ongoing disposable expenses that make robotic procedures more expensive than other laparoscopic approaches. In case of instrument malfunction, the surgeon must either have laparoscopic skills or abort and perform the surgery in an open manner. Robotic cases also require a skilled bedside assistant and use more, and potentially larger, port sites, whereas most laparoscopic renal procedures can be completed in a solo fashion using a mechanical endoscope holder and two working trocars.

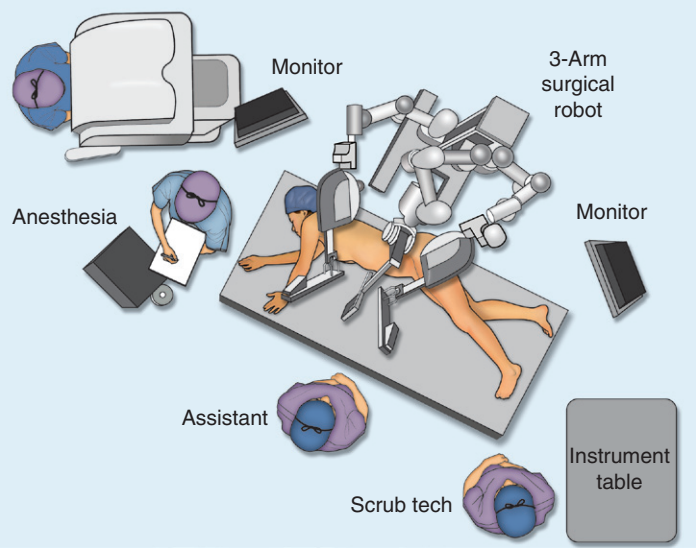


Figure 55–9. Operating room configured for left-sided robotic-assisted laparoscopic partial nephrectomy.

Laparoendoscopic Single-Site Surgery (LESS) and Natural Orifice Transluminal Endoscopic Surgery (NOTES)

Laparoendoscopic single-site (LESS) surgery describes laparoscopic techniques that consolidate all ports within a single skin incision, often concealed within the umbilicus (Box et al, 2008). It has evolved to improve upon cosmesis associated with standard laparoscopic surgery and uses commercially available multichannel working ports placed in the umbilicus or below the lower abdominal hair line to minimize postoperative visible scars. Initial clinical cases of virtually every type of extirpative and reconstructive urologic procedures have now been performed by LESS surgery.

Patient Positioning and Trocar Placement

Because LESS surgery remains a procedure in evolution, there is no widely accepted method of positioning or gaining access. Modified and full-flank positioning have been described and are identical to standard transperitoneal or retroperitoneal kidney surgery,

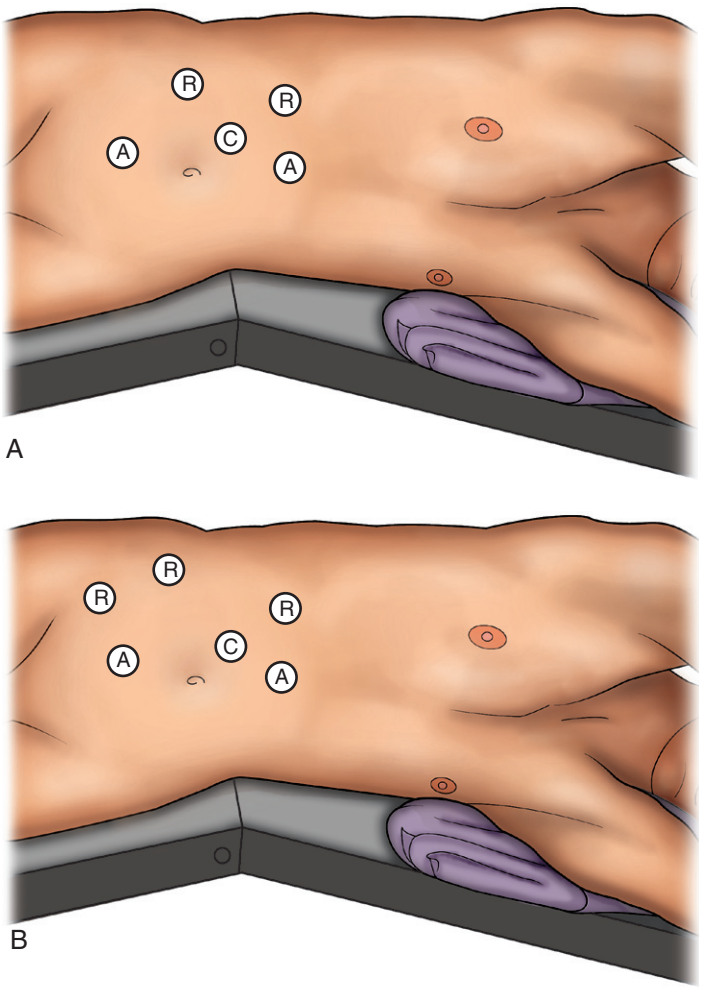


Figure 55–10. Trocar placement for robotic-assisted laparoscopic renal surgery. **A,** Three-arm system configuration. **B,** Four-arm system configuration. A, assistant trocars, R, robotic trocars, C, camera port.

respectively. Once pneumoperitoneum has been established, one may cluster multiple traditional low-profile trocars close together within a single, small extraction incision (Fig. 55–11). Alternatively, newer purpose-specific access devices (Fig. 55–12) may be used in combination with conventional laparoscopic or flexible instrumentation. The devices are secured using preplaced fascial sutures or with an inner and outer ring drawn together with a cylindrical sleeve. Characteristics of single-site access options are described in Table 55–1.



Figure 55–11. Laparoendoscopic single-site surgery performed using three low-profile trocars inserted through a single small extraction incision. A flexible laparoscope and flexible instrumentation may be used. (From Tracy CR, Raman JD, Cadeddu JA, Rane A. Laparoendoscopic single-site surgery in urology: where have we been and where are we heading? Nat Clin Pract Urol 2008;5:561–8.)

These approaches are technically challenging and the most difficult of the minimally invasive techniques. To date, no differences in postoperative morbidity or recovery have been reported (Raman et al, 2009). Advances in instrumentation may increase applicability and dissemination into mainstream urologic practice.

NOTES involves using a natural orifice to perform the entire operation. In the gastrointestinal (GI) and surgical literature, the mouth, vagina, and rectum have been used to remove organs such as the appendix and gall bladder (Rao et al, 2006; Zorron et al, 2007; Palanivelu et al, 2008). In urology, to date experience with pure NOTES surgery in humans is limited (Kaouk et al, 2009). Several authors have reported hybrid approaches with NOTES and standard laparoscopic techniques, using the vagina as an access and extraction site for nephrectomy (Branco et al, 2008; Alcaraz et al, 2010; Sotelo et al, 2010).

SIMPLE NEPHRECTOMY

Benign Indications

Laparoscopic simple nephrectomy is indicated in the treatment of most benign renal diseases. **Renovascular hypertension that is not correctable with medication or angiographic repair** may be managed with a simple nephrectomy. Patients with **chronic pain syndromes** may benefit from nephrectomy, including **symptomatic acquired renal cystic disease, autosomal dominant polycystic kidney disease (ADPKD), chronic hydronephosis not amenable to surgical repair, loin pain/hematuria syndrome. Chronic infectious processes** that are recalcitrant to antibiotic therapy may also be approached laparoscopically, including **chronic pyelonephritis, xanthogranulomatous pyelonephritis (XGP), and renal tuberculosis**. These conditions are associated with a higher rate of conversion to open surgery due to perinephric inflammatory changes and loss of tissue planes (Gupta et al, 1997; Bercowsky et al, 1999). In some cases, subcapsular nephrectomy

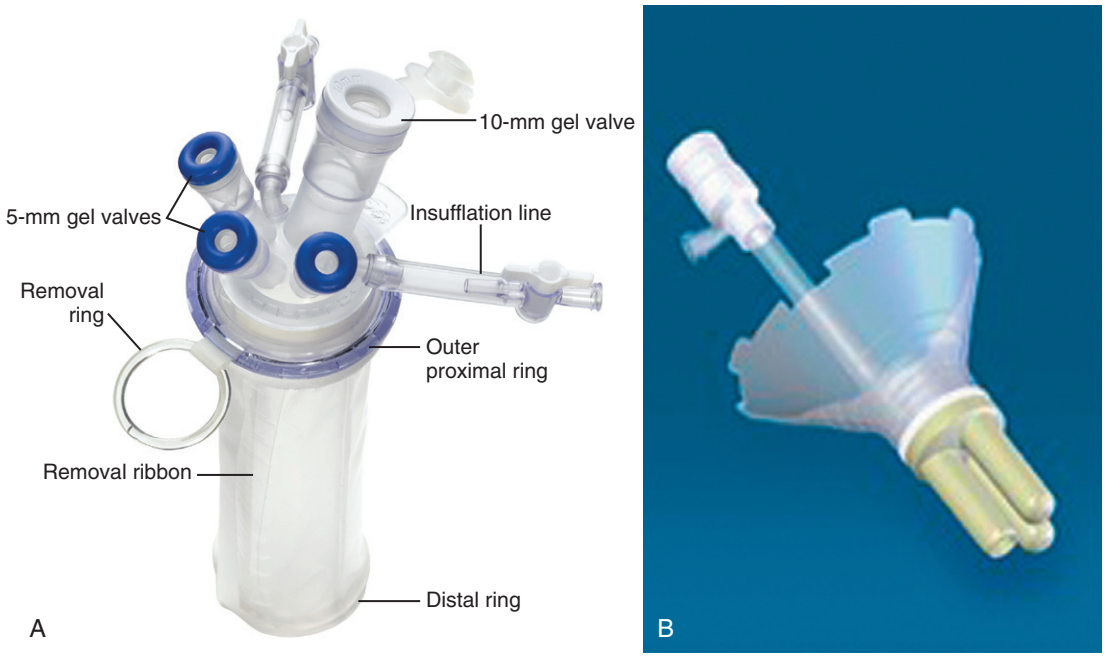


Figure 55–12. Purpose-specific devices for laparoendoscopic single-site surgery. **A,** The TriPort system (Advanced Surgical Concepts, Bray, Ireland). **B,** The Uni-X system (Pnavel Systems, Cleveland, OH). Both allow for passage of multiple instruments through a single incision.

Table 55–1.

Access Options for Laparoendoscopic Single Site (LESS) Surgery

ACCESS TYPE	DESCRIPTION
Keyhole	Use of three closely approximated periumbilical trocars placed side by side in a single skin incision or three separate incisions No additional device required Typically used with articulating camera and specialized instrumentation Insufflation through trocar
TriPort (Advanced Surgical Concepts, Bray, Ireland)	Open or closed access, may be used with multiple incision sizes (5-mm to hand-assisted incision) Anchored by inner (intra-abdominal) and outer rings drawn together with cylindrical sleeve 3-Port (one 12-mm and two 5-mm) configuration or 4-port (two 12-mm and two 5-mm) configuration available (Quadport) Insufflation through valve housing
Uni-X (Pnavel Systems, Cleveland, OH)	Open access technique, requires 2-cm fascial incision Anchored with preplaced fascial sutures Single port encompassing three 5-mm access ports Typically used with articulating camera and specialized instrumentation Insufflation through valve housing
Gelport (Applied Medical, Rancho Santa Margarita, CA)	Open access technique, requires 2.5- to 5-cm fascial incision Anchored by inner and outer rings drawn together with cylindrical sleeve Can accommodate all trocar sizes May allow for wider spacing of trocars Insufflation through trocar placed through device

may be necessary to complete the procedure. Hand assistance may also be of benefit and avoid open conversion in cases with dense scar tissue formation or inflammatory reaction (Rosoff et al, 2006). Successful retroperitoneal laparoscopic simple nephrectomy has also been reported in 30 of 31 patients with nonfunctioning kidneys secondary to tuberculosis (Lee et al, 2002). Other benign conditions that may call for nephrectomy include patients with a multicystic dysplastic kidney or a symptomatic failed renal transplant. Again, in this later case, a subcapsular dissection may be required.

Procedure

Reflection of the Colon

For a left nephrectomy and all renal surgery, the line of Toldt is incised from below the lower pole of the kidney inferiorly to above the spleen superiorly (Fig. 55–13). The inferior limit of this incision may be extended inferiorly, if the bowel does not move sufficiently. The lienocolic ligament should be incised to allow the spleen to fall medially along with the pancreas and the colon (see Fig. 55–13). Care must be taken to avoid injuring the diaphragm

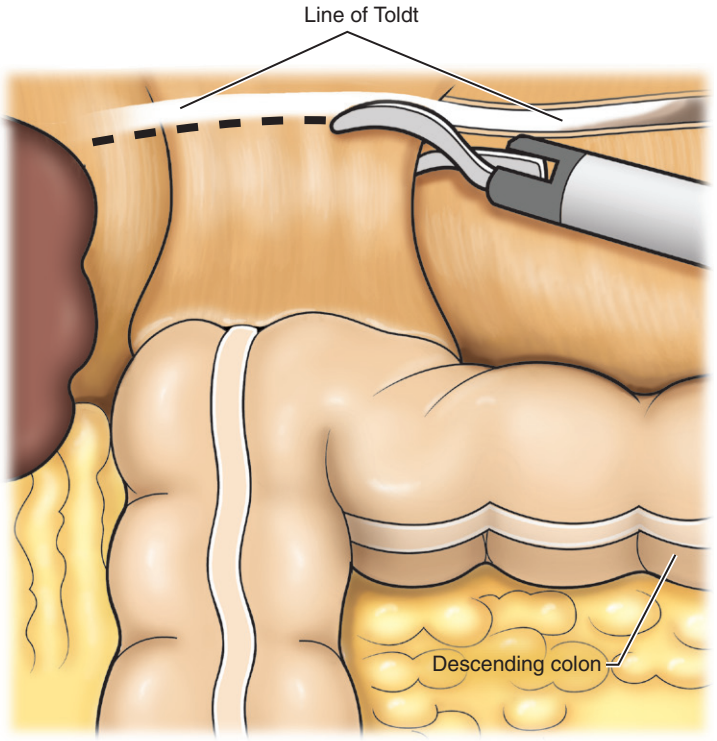


Figure 55–13. Incision of the white line of Toldt with endoshears, bipolar cautery, or ultrasonic energy allows reflection of the colon. Continuing superiorly allows incision of the lienocolic ligament, facilitating reflection of the spleen, pancreas, and colon.

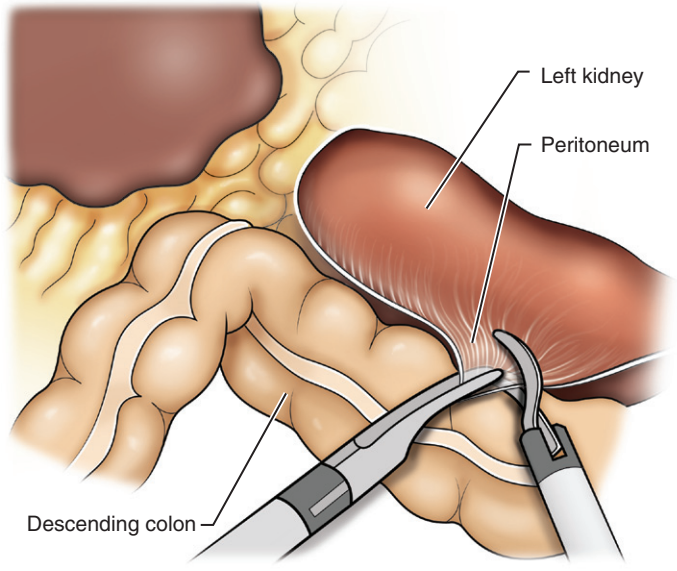


Figure 55–14. Medial traction on the colon helps identify additional colorenal attachments and assists in differentiating the undersurface of the large bowel mesentery. Care must be taken at this step to avoid creating a mesenteric window.

with this maneuver. The thin colorenal attachments are incised and the colon is swept medially (Fig. 55–14). Care should be taken to avoid making a hole in the mesentery. Mesenteric fat has a brighter hue of yellow compared with the retroperitoneal or Gerotas fat, which allows for identification of the correct plane of

dissection. If the operative field is not adequately visualized, a paddle retractor may be placed in an additional lower midline trocar to aid in retracting the colon, pancreas, and spleen medially (see Fig. 55–4A). Blunt and sharp dissection is necessary to move these structures off the anterior surface of the kidney and hilum.

During a right-sided nephrectomy, the peritoneal incision is carried medially and parallel to the lateral border of the venacava and duodenum. A lateral (anterior axillary line) or high midline port may be needed to retract the liver anteriorly (see Fig 55–4B and C). Care must be taken to avoid thermal injury to the duodenum and gall bladder during incision of the peritoneum. Medial traction on the colon reveals colorenal attachments that must be divided to complete the colon dissection. Again, a low midline retractor may be helpful for visualization. A Kocher maneuver may be required to fully expose the medial portion of the kidney and the connective tissue overlying the renal hilum (Fig. 55–15).

Dissection of the Ureter

Once the colon has been adequately mobilized, the psoas muscle and tendon should be identified. Following this structure medially, the gonadal vessels are usually first encountered. These should be swept medially and the ureter is usually located just deep to these vessels. Peristalsis of the ureter can help differentiate between these two structures. **Once identified, the ureter is elevated and followed proximally to the lower pole of the kidney. The ureter is not divided at this time, because it can be used to help elevate the kidney** (Fig. 55–16). The tissue posterior to the ureter and lower pole of the kidney is swept anteriorly to further expose the psoas muscle. Care should be taken to try and stay above the psoas fascia to minimize postoperative thigh numbness. The instrument in the subxyphoid trocar is used to slide under the kidney all the way to the sidewall. This allows the surgeon to lift the kidney and place medial lymphatic and vascular attachments on stretch.

Identification of the Renal Hilum

Safe dissection of the renal hilum requires medial retraction of the colon and bowel by gravity or an additional retractor, as well as anterior retraction of the kidney, lifting it out of the renal fossa. With the ureter and lower pole of the kidney elevated, vessels entering the renal hilum can be identified and bluntly dissected using the tip of the irrigator-aspirator. **Firm elevation of the lower pole assists in identification and dissection of the renal hilar vessels** (Fig. 55–17). This is accomplished by gently placing the lateral grasper under the ureter and kidney until it abuts the abdominal sidewall. It is important to be sure that the

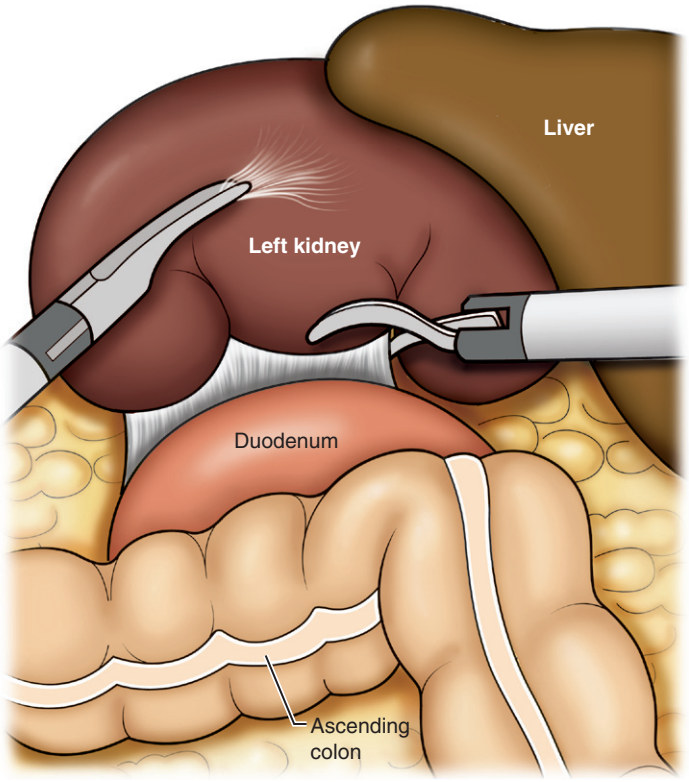


Figure 55–15. On the right side, the colon is reflected, and a Kocher maneuver may be performed to completely expose the kidney and the renal hilum.

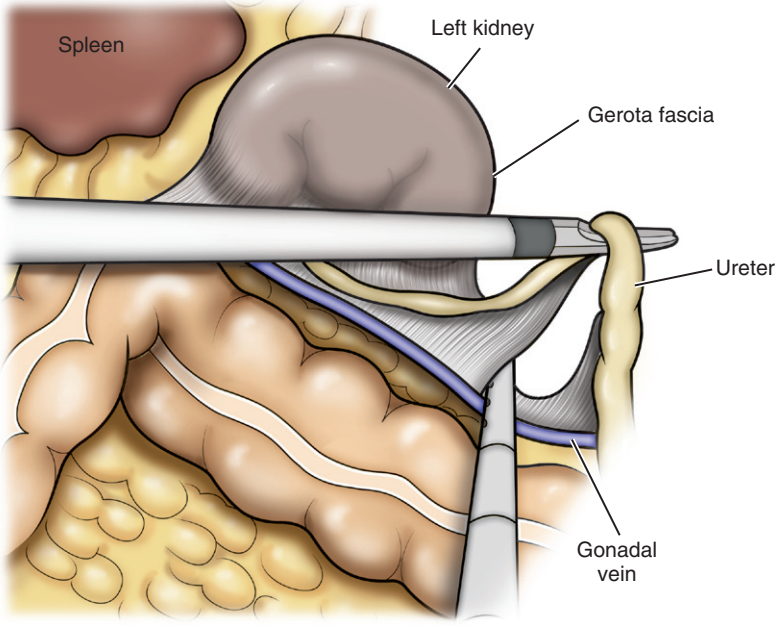


Figure 55–16. A curved dissector, in the left hand, is placed beneath the ureter and used to provide anterolateral elevation. On the right side the angle of insertion from the gonadal to the vena cava can be a source of significant bleeding if torn during elevation.

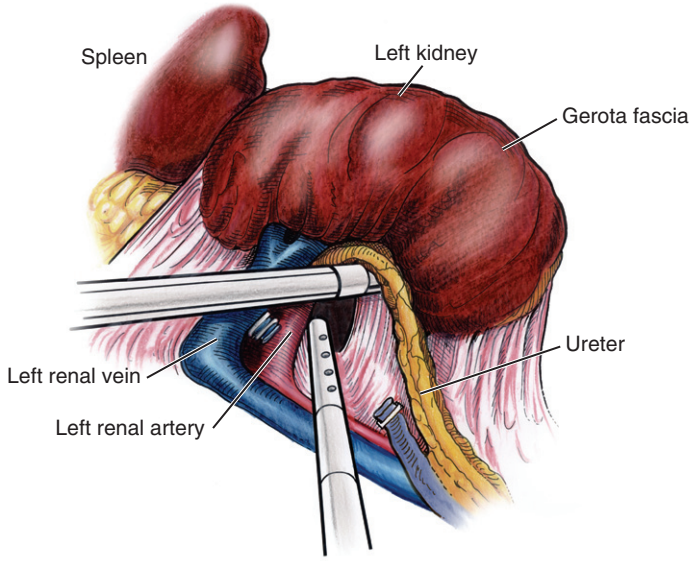


Figure 55–17. The lower pole of the kidney and ureter are firmly retracted anterolaterally, placing the hilum on stretch. The left gonadal vein has been ligated and divided.

grasper is against the muscle and not into the renal parenchyma. A gentle, layer-by-layer dissection is performed with the irrigator-aspirator until the renal vein is uncovered. There is usually an anterior bundle of connective tissue that needs to be incised in order to fully expose and visualize the vein. Gonadal, lumbar, and accessory venous branches can be clipped and divided as necessary.

Securing the Renal Blood Vessels

By clearing off inferior attachments and lymphatics, one can identify the renal artery. If the irrigator-aspirator tip is not precise enough for meticulous dissection, a hook electrode can be used to dissect the lymphatic vessels free of the vein and artery. **With an endovascular gastrointestinal anastomosis (GIA) stapler, the artery is divided first, followed by the vein** (Fig. 55–18). We prefer to use staples in this area because three rows of staples will be left on the vessel stump and are unlikely to be dislodged during subsequent dissection. In some instances clips may be needed. We prefer to use at least five clips on the patient side, when possible.

Isolation of the Upper Pole

Once the hilar vessels have been divided, the dissection continues posteriorly and superiorly to the upper pole. The adrenal gland is preserved in cases of simple nephrectomy by staying close to the upper pole (Fig. 55–19). This is accomplished by incising the Gerota fascia anteriorly, just above the hilum. Gerota fat is then gently peeled off circumferentially above the upper pole of the kidney. At this point during the dissection, it may be necessary to clip and transect the ureter. This allows the kidney to be rotated anteriorly above the liver (right) or spleen (left) to facilitate incision of the uppermost attachments under direct vision. In cases of extreme fibrosis, a subcapsular nephrectomy can be performed once the artery and vein have been controlled (Moore et al, 1998). Long, blunt instruments, such as the closed stapler or the 10-mm Ligasure Atlas (Valleylab, Boulder, CO) are particularly well suited for reaching and freeing the upper pole attachments.

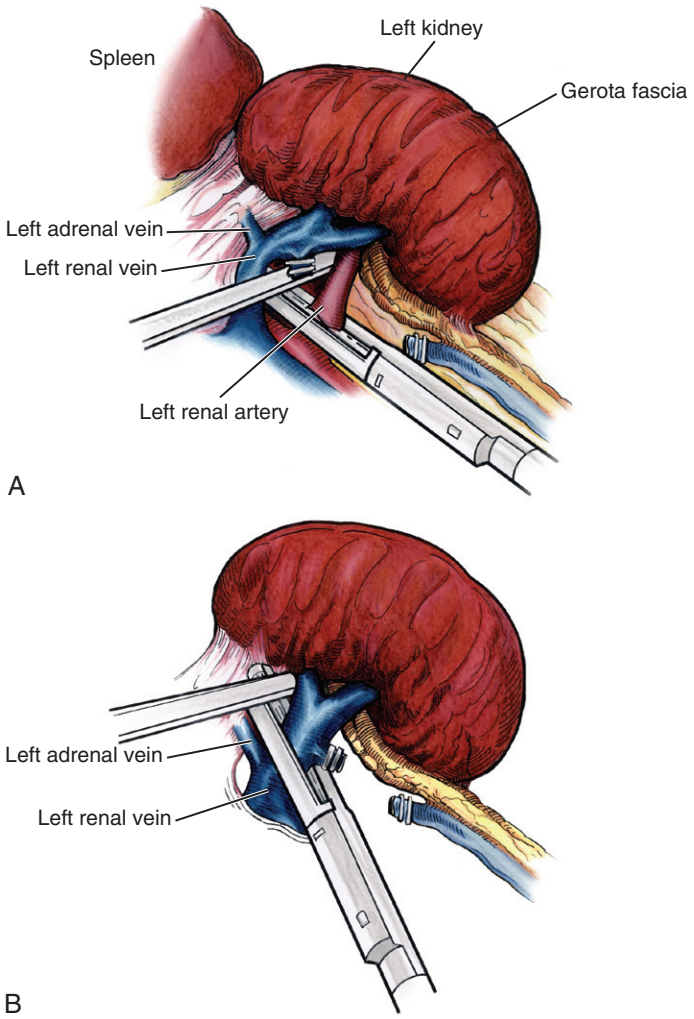


Figure 55–18. **A,** First, the renal artery is stapled using an endovascular gastrointestinal anastomosis (GIA) stapler. **B,** The renal vein is secured lateral to the adrenal vein with the GIA stapler. If clips are used on the gonadal or adrenal vessels, the surgeon must be careful to exclude them from the jaws of the stapler.

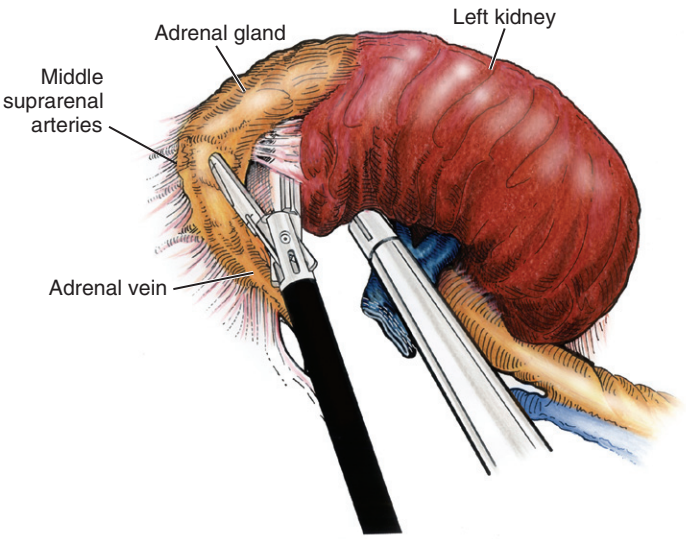


Figure 55–19. The adrenal gland can be preserved during simple nephrectomy or radical nephrectomy as indicated by dissecting it from the superior pole of the kidney.

Organ Entrapment and Extraction

The kidney can be removed intact or through morcellation. When morcellation is performed, the specimen should be placed into a sturdy entrapment sac (Urban et al, 1993). This minimizes the risk of rupture during mechanical morcellation of the tissue (Landman et al, 2000; Pautler et al, 2002). Using ring forceps and a Kocher clamp, the kidney and collecting system can be morcellated and removed in small pieces (Fig. 55–20). Alternatively, the kidney can be removed intact through an incision after placement into a sac (Fig. 55–21). The kidney can be worked out of an extended trocar site or Pfannenstiel incision. For trocar sites greater than 5 mm, it is helpful to place the closure sutures before removing the kidney. Once the sutures are placed, trocars can be reinserted for kidney entrapment and removal.

Postoperative Management

The orogastric tube is removed at the conclusion of the procedure. The patient can begin a diet as tolerated. The Foley catheter should be removed once the patient is comfortably ambulating. The patient is discharged when tolerating a regular diet. Unrestricted activity can usually be resumed according to the patient's comfort.

Results

The postoperative results of laparoscopic nephrectomy are comparable to that of open surgery, with much less pain and shorter convalescence. **Postoperative pain control requirements are approximately four times less than with traditional open incisions. Hospital stays have been decreased by 50%, and the time to full convalescence has been reported to be markedly less than with open removal.** In early series, the mean operative times were greater than 300 minutes. However, with advances in techniques, experience, and equipment, current operative times have decreased dramatically (Kerbl et al, 1994a, 1994b; Nicol et al, 1994; Parra et al, 1995; Baba et al, 1996; Rassweiler et al, 1998).

RENAL CYSTIC DISEASE

Renal cysts are extremely common and are present in more than one third of patients more than 50 years old (Laucks and McLachlan, 1981; Carrim et al, 2003). **They rarely require surgical intervention, but indications include cyst-associated pain, infection, or obstruction** (Hoenig et al, 1997; Wolf, 1998; Roberts et al, 2001; Doumas et al, 2004; Camargo et al, 2005). The increased use of cross-sectional imaging has also increased the detection of indeterminate renal cystic lesions and complex renal cysts, bringing an increased number to the attention of urologists. Classification schema have been developed to help clinicians make determinations regarding management, the most popular being the Bosniak system (Table 55–2) (Israel and Bosniak, 2005). Although these schema can be extremely useful, they are not diagnostic, and surgery may be required in some cases to exclude malignancy.

Indications

First-line therapy and diagnosis of symptomatic renal cysts often involves percutaneous image-guided needle aspiration, with or without the use of a sclerosing agent, to prevent recurrence. If symptoms temporarily resolve and recur when fluid reaccumulates, this increases the likelihood that surgical treatment will be successful in resolving the pain (Rané et al, 2004). Caution should be exercised in use of cyst aspiration and sclerosing agents in peripelvic cysts, because fibrosis may occur (Wehle and Grabstald, 1986; Hulbert et al, 1988; Santiago et al, 1998; McDougall, 2000).

In addition to causing pain, cysts may compress the renal parenchyma or other adjacent organs, cause ureteral obstruction and obstructive uropathy, spontaneously bleed, cause hypertension, or become infected. Laparoscopic decortication or unroofing may be used to treat these cysts, which are typically simple in character (Fig. 55–22). Cysts with complex appearance, such as thickened septa, calcification, or enhancement (Bosniak class III-IV), may be explored and sampled laparoscopically to rule out renal cell carcinoma due to their increased risk of harboring

Table 55–2.

Renal Cyst Classification Based on Updated Bosniak Criteria

TYPE	DESCRIPTION	RECOMMENDED MANAGEMENT
I	A benign simple cyst with a hairline thin wall that does not contain septa, calcifications, or solid components. It measures water density and does not enhance.	No follow-up necessary
II	A benign cyst that may contain a few hairline thin septa in which "perceived"* enhancement may be present. Fine calcification or a short segment of slightly thickened calcification may be present in the wall or septa. Uniformly high-attenuation lesions (3 cm) (so-called high-density cysts) that are well marginated and do not enhance are included in this group.	No follow-up necessary
IIF	Cysts that may contain multiple hairline thin septa or minimal smooth thickening of their wall or septa. Perceived enhancement of their septa or wall may be present. Their wall or septa may contain calcification that may be thick and nodular, but no measurable contrast enhancement is present. These lesions are generally well marginated. Totally intrarenal nonenhancing high-attenuation renal lesions >3 cm are also included in this category.	Follow-up imaging required
III	"Indeterminate" cystic masses that have thickened irregular or smooth walls or septa in which measurable enhancement is present. These are surgical lesions, although some will prove to be benign (e.g., hemorrhagic cysts, chronic infected cysts, and multiloculated cystic nephroma), some will be malignant, such as cystic renal cell carcinoma and multiloculated cystic renal cell carcinoma.	Surgical treatment
IV	These are clearly malignant cystic masses that can have all the criteria of category III, but also contain enhancing soft tissue components adjacent to, but independent of, the wall or septum. These lesions include cystic carcinomas and require surgical removal.	Surgical treatment

From Israel GM, Bosniak MA. An update of the Bosniak renal cyst classification system. Urology 2005;66:484–8.

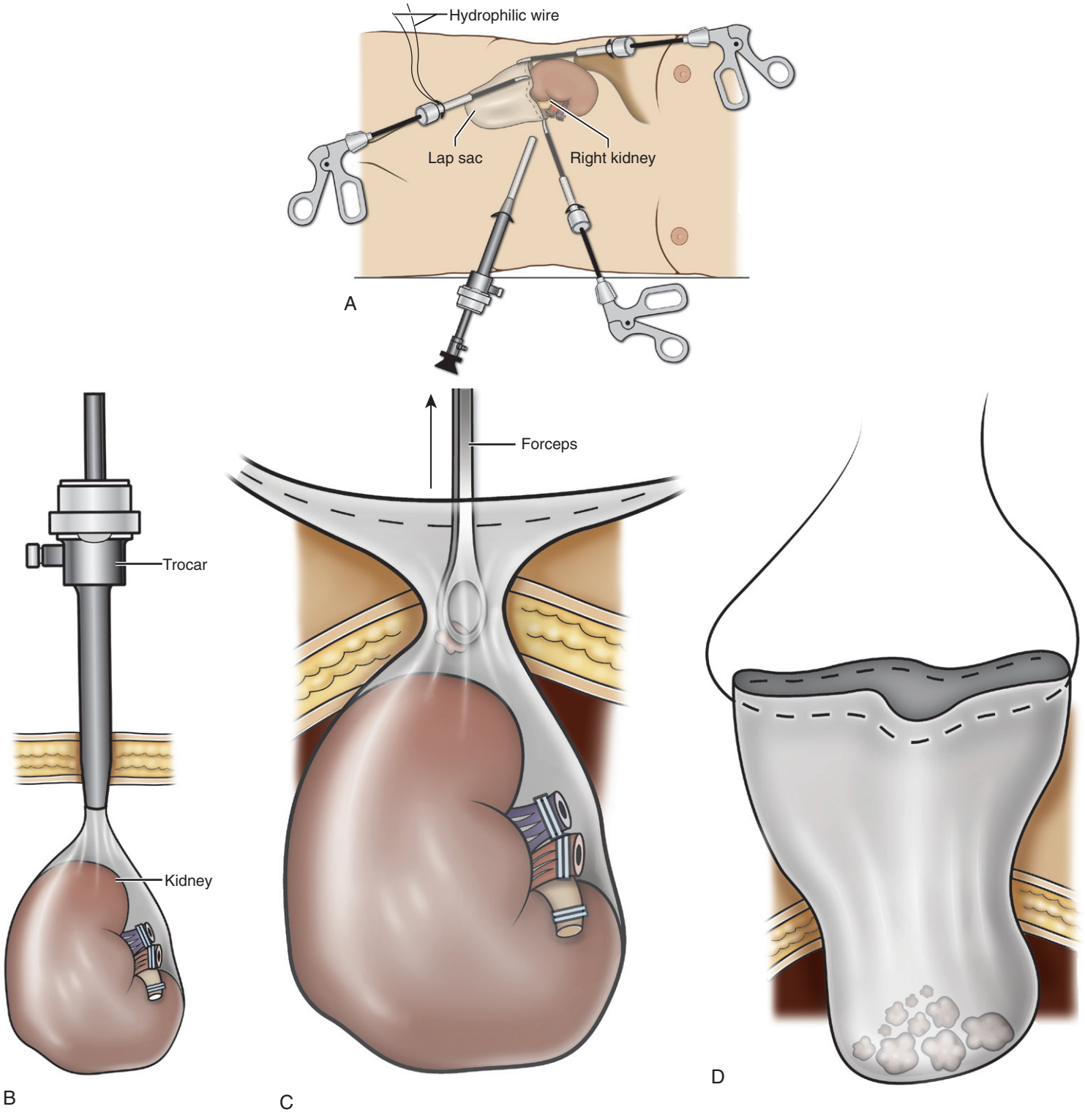


Figure 55–20. Removal of the morcellated specimen. **A,** The LapSac (Cook Urological, Spencer, IN) entrapment sac is introduced through the lateral 10-mm trocar site after passing a hydrophilic wire through the opening of the LapSac. The entrapment sac is then released within the abdomen. The wire facilitates opening the bag and placement of the specimen. A lateral 5- or 3-mm port may be necessary to assist with holding placement of the specimen inside the LapSac. **B,** Once the specimen is within the LapSac, the wire is removed, the bag cinched closed, and the opening withdrawn through the 10-mm trocar site. **C,** The entrapment sac is pulled tightly up against the abdominal wall, with two hands pushing part of the specimen to appear through the opening of the LapSac. After the site is carefully draped, manual morcellation with ring forceps or a Kelly clamp can be used. **D,** The entrapment sac is removed once the remaining specimen fragments are small enough to be extracted through the trocar site. Only the tissue visible from the opening is grasped. Blind passes into the bag may injure surrounding bowel segments.

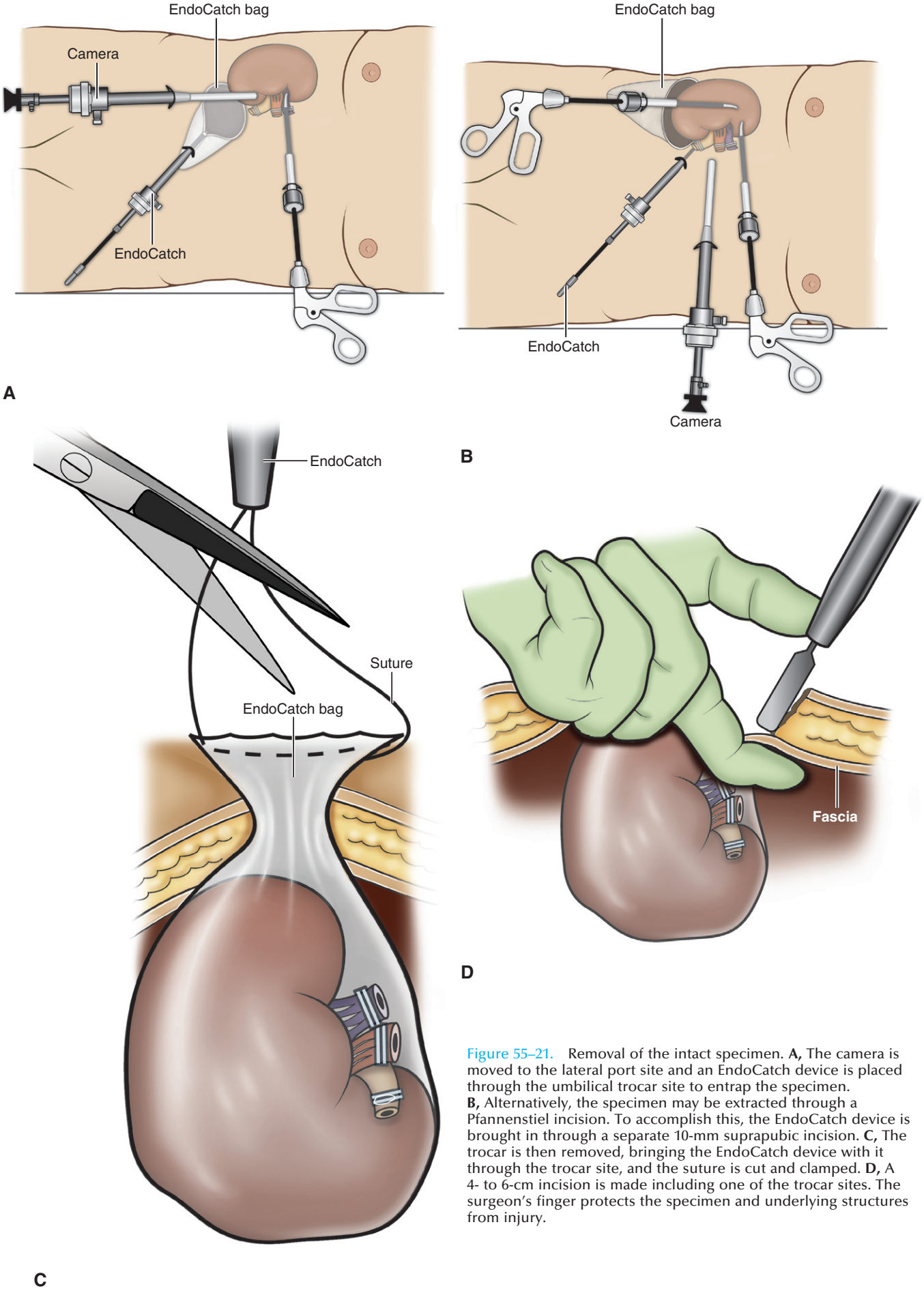


Figure 55–21. Removal of the intact specimen. **A,** The camera is moved to the lateral port site and an EndoCatch device is placed through the umbilical trocar site to entrap the specimen. **B,** Alternatively, the specimen may be extracted through a Pfannenstiel incision. To accomplish this, the EndoCatch device is brought in through a separate 10-mm suprapubic incision. **C,** The trocar is then removed, bringing the EndoCatch device with it through the trocar site, and the suture is cut and clamped. **D,** A 4- to 6-cm incision is made including one of the trocar sites. The surgeon's finger protects the specimen and underlying structures from injury.

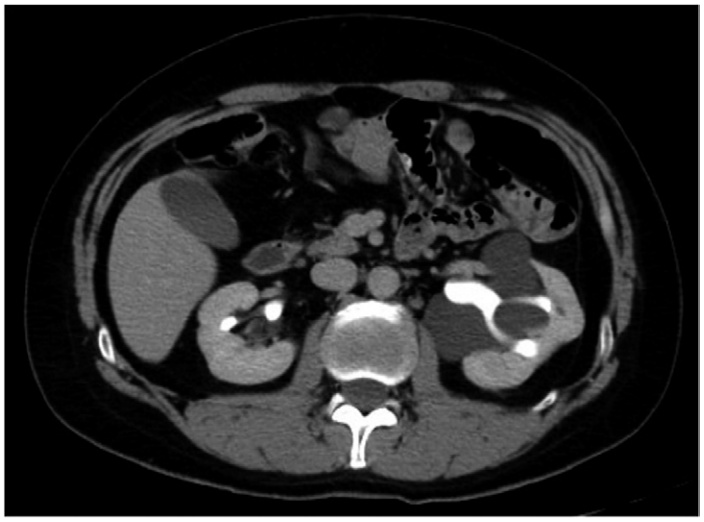


Figure 55–22. Axial CT scan in delayed phase after IV contrast administration, demonstrating peripelvic cysts in a patient who presented with left flank pain.

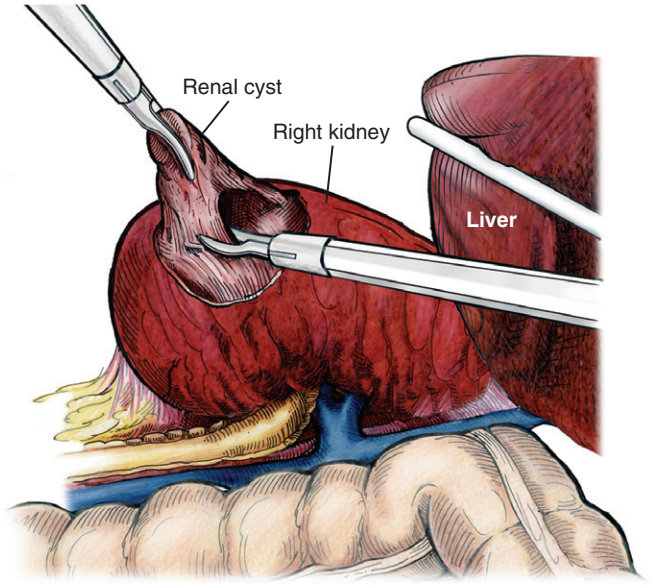


Figure 55–23. The cyst fluid is aspirated with a laparoscopic aspiration needle. After decompression of the cyst, the wall can easily be grasped and manipulated. The cyst is elevated with a grasper and scissors or ultrasonic shears to circumferentially excise the cyst wall. The edge of the cyst is carefully inspected, and biopsies are performed using the 5-mm laparoscopic biopsy forceps as needed.

malignancy (Cloix et al, 1996; Santiago et al, 1998). Options include cryoablation, enucleation, partial nephrectomy, or radical nephrectomy. If there is any question of cyst proximity to the collecting system, cystoscopy and placement of an open-ended ureteral catheter may be performed to ensure the integrity of the collecting system after cyst excision.

A subset of patients with autosomal dominant polycystic kidney disease (ADPKD) may develop cyst-associated pain. Laparoscopic cyst decortication, marsupialization, or unroofing can be of benefit to these patients by offering a minimally invasive treatment that is successful in relieving pain in up to 83% of cases (Lifson et al, 1998; Dunn et al, 2001; Lee et al, 2003). In patients with end-stage renal disease, bilateral synchronous laparoscopic nephrectomy may be performed in patients with enlarged, symptomatic, or infected kidneys (Gill et al, 2001; Rehman et al, 2001; Bendavid et al, 2004; Desai et al, 2008). Because an incision will be required to remove kidneys that are often quite enlarged, a hand port may be placed in the midline and used bilaterally to facilitate the dissection (Rehman et al, 2001; Jenkins et al, 2002).

Procedure

Depending on cyst location, a transperitoneal or retroperitoneal approach may be used as previously described. Intraoperative ultrasonography may be used to identify the cyst or cysts in question. It is usually easier to dissect out the cyst wall before evacuating fluid. The wall of the cyst can then be grasped and excised, cutting along the junction between the cyst wall and the renal parenchyma (Fig. 55–23). If suspicious lesions are noted in the base, biopsies may be taken using the 5-mm biopsy forceps. If no evidence of malignancy is seen, the remaining cyst wall may be fulgarated with either electrocautery or the argon beam coagulator. Care should be taken when ablating the surface, because inadvertent entry into the collecting system can easily occur (Cherullo et al, 1999). Moreover, these surfaces can be friable and prone to significant bleeding. Packing with hemostatic agents or suturing may be necessary. One should have a low level of suspicion for entry into the collecting system and, as such, a low threshold for leaving a drain (Fig. 55–24). If malignancy is noted, extirpative surgery or cryoablation may be used to treat the remainder of the lesion.

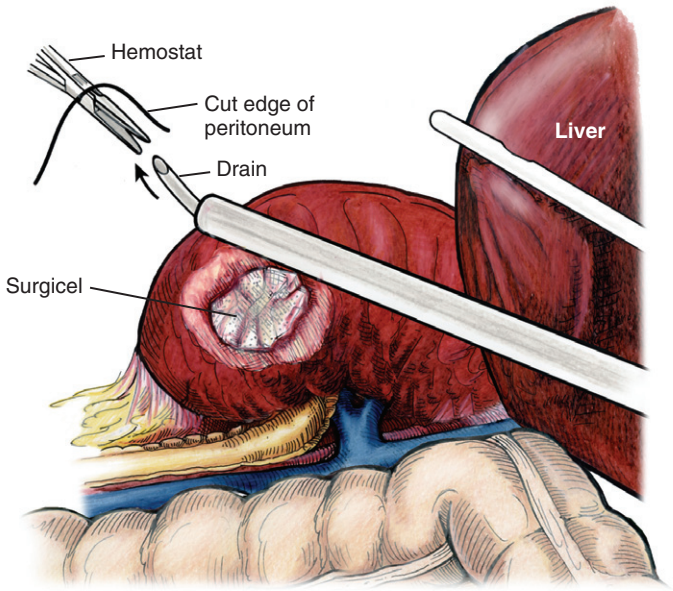


Figure 55–24. Drain placement after renal cyst excision. If the collecting system has been entered, it is closed and a drain placed. To insert the drain, a hemostat is passed through a small stab incision in the side and advanced into the abdominal cavity under direct vision. A drain is placed through a trocar site and advanced toward the open hemostat using the trocar to direct the drain. The colon is brought back over the kidney and attached to the sidewall to "reperitonealize" the kidney and drain.

When treating central or perihilar cysts, it may not be feasible to remove a large portion of the cyst wall. In these cases, it is helpful to place a pedicle of autologous fat into the defect to act as a wick (Nieh and Bihrle, 1993).

Results

Laparoscopic treatment of symptomatic renal cysts has been found to be effective in both decompression and pain control. A study evaluating treatment durability at a mean follow-up of 26 months demonstrated a 100% pain-free rate in patients treated for a solitary symptomatic renal cyst (Lifson et al, 1998). In a separate study with a mean follow-up of 60 months, 80% to 90% of patients have complete resolution of pain after laparoscopic cyst decortication. In patients with ADPKD, additional benefits of cyst decortication have been noted, including decreased blood pressure (Dunn et al, 2001; Lee et al, 2003). Recurrence of pain in this group is higher than with simple cysts, and durability is moderate (Brown et al, 1996). No significant changes in renal function were noted postoperatively.

Patients undergoing surgery for cystic renal disease are inherently a heterogeneous group, made up of patients with simple renal cysts, complex or indeterminate cysts, and ADPKD. Interpretation of incidence reports of renal cell carcinoma in these series must take this fact into account. That said, the reported incidence of renal cell carcinoma in cystic lesions is between 3% and 20% (Rubenstein et al, 1993; Lifson et al, 1998; Roberts et al, 2001; Limb et al, 2002).

RENAL BIOPSY FOR MEDICAL RENAL DISEASE

Histologic information is a key component in making treatment decisions and for prognosis in patients with proteinuria or unexplained renal insufficiency (Morel-Maroger, 1982; Gault and Muehrcke, 1983; Manaligod and Pirani, 1985). Although the modality of choice is typically ultrasound-guided percutaneous renal biopsy, laparoscopic biopsy may be preferred in certain situations, such as failed percutaneous biopsy, renal anatomic anomalies, risk of bleeding complications, morbid obesity, multiple renal cysts, or solitary kidneys.

Procedure

The patient is placed in the full-flank position with the table flexed to increase working space between the costal margin and the iliac crest. Retroperitoneal access is preferred and obtained using techniques described later in this chapter. Renal biopsy is accomplished with the use of two trocars. With blunt dissection, Gerota fascia is opened, and the lower pole of the kidney is exposed (Fig. 55–25A). **In obese patients, intraoperative ultrasonography may be required to localize the kidney when copious retroperitoneal or perinephric fat is present.** A 5-mm biopsy forceps is used to take samples of cortical tissue; hemostasis is achieved with the argon beam coagulator; and adjunctive hemostatic measures are used as necessary (Fig. 55–25B).

Results

A multi-institutional series reporting on outcomes of laparoscopic renal biopsy in 74 patients over 9 years showed a mean operative time of 123 minutes, mean estimated blood loss of 67 cc, and discharge within 24 to 48 hours unless other preexisting medical conditions required a longer stay (Shetye et al, 2003). Tissue obtained from 96% of patients was adequate for diagnosis, with a complication rate of 13.5%. The authors concluded that laparoscopic renal biopsy may be performed safely with a high success

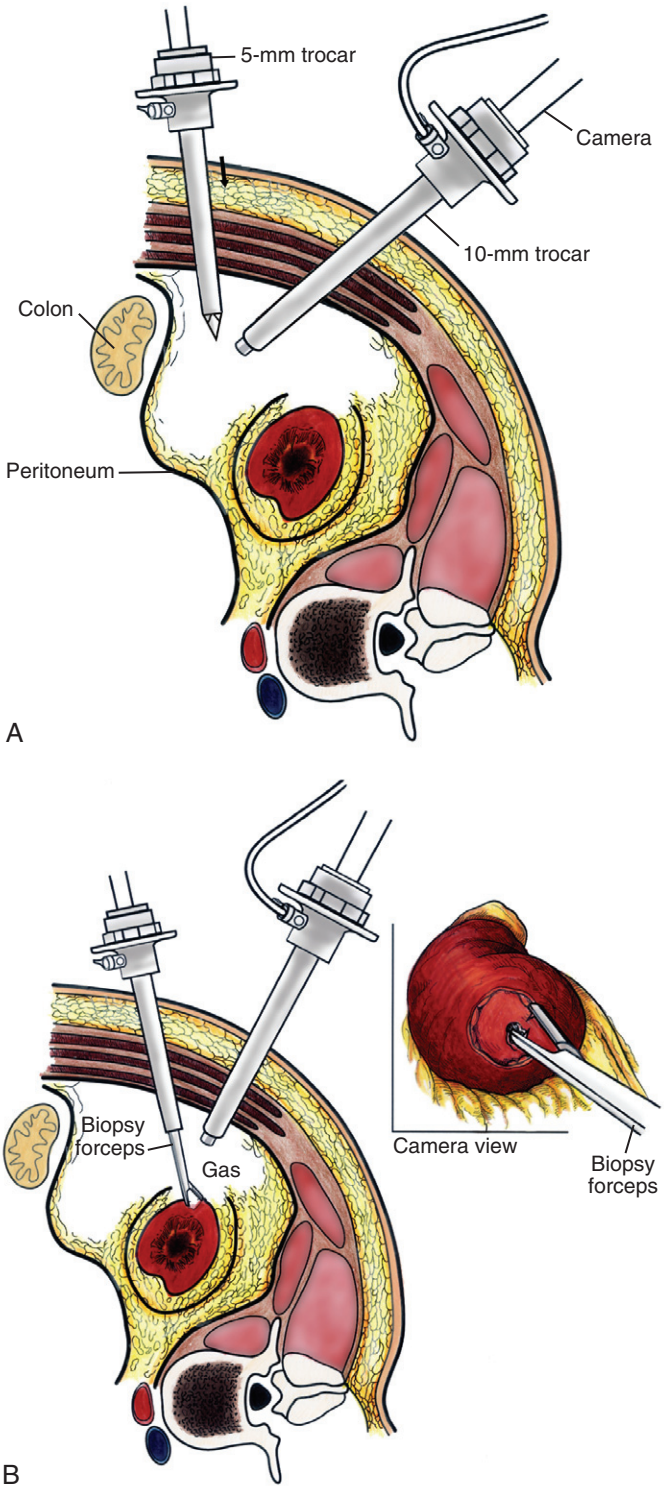


Figure 55–25. **A,** After establishing a working space, a 5-mm trocar is placed under direct vision. The working instruments are passed through this port. The camera can be used to assist with dissection and is frequently cleaned to maintain adequate visualization. **B,** Gerota fascia is opened with the use of the scissors. A 5-mm two-tooth laparoscopic biopsy forceps is used to take two to three samples from the lower pole of the kidney.

rate, and, that as experience grows, the complication rate and operative duration would likely decrease. In another series of 17 patients, using balloon dilatation to create the working space demonstrated 100% success in obtaining renal tissue adequate for diagnosis. Mean operative time was 35 minutes (excluding anesthesia time), complication rate was 11%, and 15 of 17 patients were discharged within 24 hours. **In published series of laparoscopic renal biopsy, hemorrhage is the most common complication. Caution should be used in resumption of anticoagulation in patients who require it postoperatively. If signs or symptoms of postoperative anemia or hypovolemia occur, a low threshold should be used to evaluate the patient with computed tomography (CT).**

PYELOLITHOTOMY, NEPHROLITHOTOMY, AND URETEROLITHOTOMY

Advances in stone therapy have made pyelolithotomy, nephrolithotomy, and ureterolithotomy almost obsolete. However, a select subgroup of stone patients will benefit from these approaches. Depending on local demographics and incidence of stone disease, the **indications for laparoscopic stone extraction may vary but primarily include patients with renal stones who are undergoing simultaneous laparoscopic pyeloplasty** (Ball et al, 2004; Stein et al, 2008). **In these patients, a flexible cystoscope may be passed through one of the trocars to remove stones. A laparoscopic grasper may also be used to remove stones, but patients should always undergo a complete nephroscopy to ensure stone clearance. Other patients who may benefit include those with unusual anatomy (pelvic kidney)** (Chang and Dretler, 1996; Harmon et al, 1996; Hoenig et al, 1997), **stones resistant to fragmentation** (Jordan et al, 1997), **and failed extracorporeal shock wave lithotripsy (ESWL), ureteroscopy, or percutaneous procedures.**

Treating stone disease in ectopic kidneys can be particularly challenging. Ectopic kidneys frequently have anomalous vasculature, and therefore access into the collecting system carries a higher risk of bleeding. Laparoscopy may be used to assist in the placement of percutaneous access to minimize the risk of bleeding complications (Eshghi et al, 1985; Tóth et al, 1993; Troxel et al, 2002).

A retrospective comparative study of 12 patients who underwent percutaneous nephrolithotomy (PCNL), and 16 patients who underwent laparoscopic retroperitoneal pyelolithotomy, revealed no benefit to the laparoscopic approach. Laparoscopy was also associated with longer operative time, longer recovery, inferior cosmesis, and required more advanced skills (Goel and Hemal, 2003). The authors concluded that PCNL should remain the gold standard for treating large renal stones, unless the patient is undergoing surgery for concomitant pathology.

Robotic approaches to stone disease have also been described for the treatment of staghorn calculi, with or without simultaneous pyeloplasty. In a study of 12 patients undergoing robotic extended pyelolithotomy, 11 were stone free after surgery as assessed by postoperative CT scan. Mean operative time was 158 minutes, with mean estimated blood loss of 100 cc (Badani et al, 2006).

Laparoscopic anatrophic nephrolithotomy has been reported in animal models and small case series (Kaouk et al, 2003; Simforoosh et al, 2008). Initial reports are encouraging, but, to date, renal functional outcomes in humans have not been evaluated with nuclear renal scans. Further studies are required to assess the feasibility of this procedure.

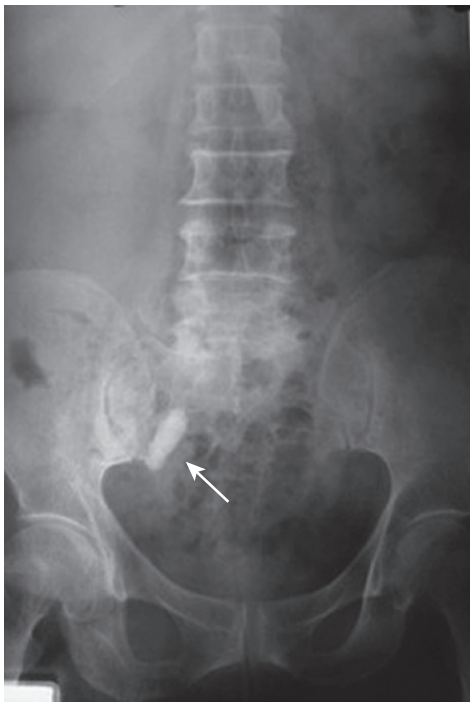


Figure 55–26. Abdominal radiograph demonstrating a large, impacted, distal right ureteral stone that was addressed with ureterolithotomy.

Large or impacted ureteral stones may be managed laparoscopically with ureterolithotomy (Fig. 55–26). In a series of 93 patients undergoing this procedure, successful stone removal was achieved in 85 patients, with eight failures due to inability to locate the stone (Gaur et al, 2002). Mean operative time was reported as 80 minutes, and in many of the patients, the ureter was left open, leading to shorter operative time but more complications with prolonged urinary leakage. Other authors have also reported this approach for impacted or large ureteral stones (Hemal et al, 2003). In this series of 31 patients, success was reported in all cases, no stent was used, and closure of the ureterolithotomy in all cases resulted in a prolonged urinary leakage rate of 6.5% at 48 hours.

NEPHROPEXY

Renal ptosis, although rare, is a real cause of chronic flank or upper abdominal pain. The precise origin of symptoms is unknown, but is likely secondary to either transient ischemia or urinary obstruction (Moss, 1997). It is usually defined as the descent of the kidney by more than two vertebral bodies, but before a definitive diagnosis is made, objective proof that is associated with pain should be obtained. The typical patient with a ptotic kidney is a young, thin female who complains of pain while in an upright position. **Supine and erect intravenous pyelography (IVP) can be used for diagnosis, with the finding of interest being descent of the symptomatic kidney by two vertebral bodies** (Fig. 55–27)**. Nuclear imaging may also quantify obstruction of blood flow or drainage in the upright position. Color Doppler sonography in both the supine and upright positions can also be used to evaluate differential blood flow.** If a ptotic kidney is present, the expected

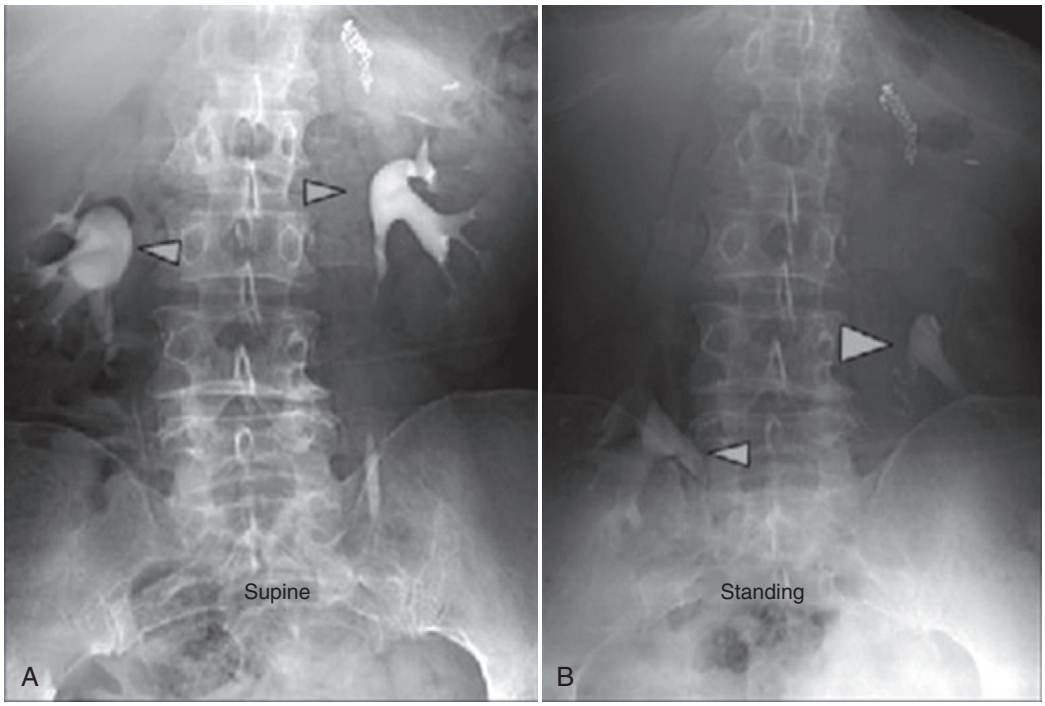


Figure 55–27. Intravenous pyelogram demonstrating bilateral ptotic kidneys in the supine **(A)** and standing **(B)** positions. (From El-Moula MG, Izaki H, Kishimoto T, et al. Laparoscopic nephropexy. J Laparoendosc Adv Surg Tech A 2008;18:230–6.)

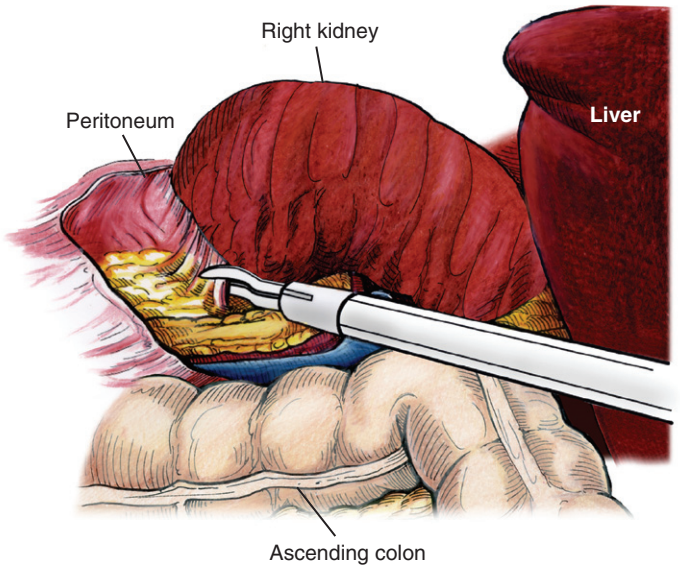


Figure 55–28. The kidney is stripped of overlying Gerota fascia down to the surface of the renal capsule. All remaining attachments are divided, allowing full mobility for repositioning.

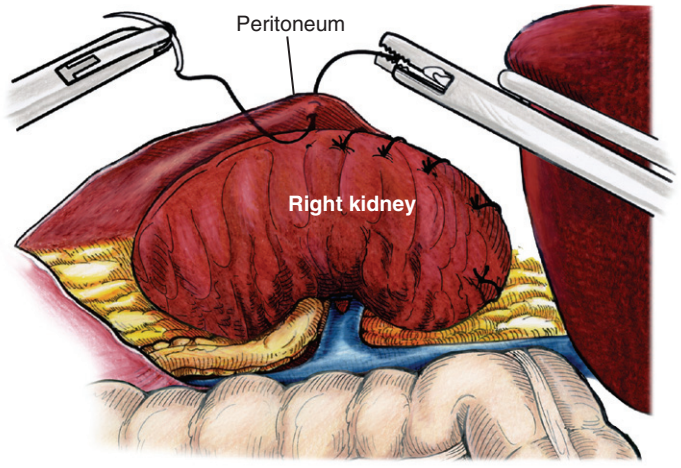


Figure 55–29. Nephropexy. Once the kidney is free of lateral and posterior attachments, multiple 2-0 sutures are placed into the capsule and the lateral edge of the fascia overlying the abdominal wall. Sutures may also be placed between the anterior renal capsule and the parietal peritoneum for additional support.

finding would be diminished blood flow while in the erect position. **Before surgical repair, obstruction, decreased blood flow, or significant descent correlating with pain should be documented.**

Procedure

Surgical repair is performed using either a standard transperitoneal or retroperitoneal approach to fully mobilize the affected kidney and expose the fascia overlying the psoas and quadratus lumborum muscles (Chueh et al, 2002; Matsui et al, 2004) (Fig. 55–28). Beginning at the upper pole, interrupted sutures are placed to secure the lateral edge of the renal capsule to the fascia overlying the muscle (Fig. 55–29). Sutures may also be placed between the anterior renal capsule and the parietal peritoneum for additional support. Using sutures with preplaced Lapra-Ty clips (Ethicon Endosurgery, Cincinnati, OH), the initial pass is made through the fascia or peritoneum, and a second clip is placed on the suture after the pass through the kidney. An alternative technique describes the use of tension-free vaginal tape to secure the kidney (Hübner et al, 2004). By placing the needles such that the tape is passed around the lower pole of the kidney and out through the abdominal wall, the kidney is secured. Sometimes this is found in

conjunction with a ureteropelvic junction obstruction that should be adressed simultaneously (Boylu et al, 2009).

Results

A retrospective study of 30 patients undergoing laparoscopic nephropexy with a median follow-up of 5.9 years demonstrated improvement in all patients, 11 with complete relief of symptoms (Plas et al, 2001). Significant improvement in renal function was measured by renal scan in 9 of 10 patients undergoing the study postoperatively. Two patients developed a recurrent ptotic kidney with greater than 5 cm of descent documented by IVP. An additional study of 48 patients, with a median follow-up of just more than 8 years, revealed that 94% of patients had no signs of significant ptosis on postoperative imaging, and 91% of patients had improvement in their pain symptoms (Gözen et al, 2008). Mean operative time was 95 minutes, and mean estimated blood loss was 50 cc. Patient satisfaction was high, and the authors concluded that laparoscopic nephropexy provided a minimally invasive approach to these patients with good long-term clinical outcomes.

CALYCEAL DIVERTICULECTOMY

Patients with symptomatic calyceal diverticula containing stones can be managed laparoscopy. ESWL and ureteroscopy may be employed, but due to infundibular stenosis, stone clearance rates are low (Jones et al, 1991; Pang et al, 1992; Stream et al, 1992). **The principles of treatment include the removal of stones and widening of the infundibular stenosis to prevent urine stasis or ablation of the diverticula cavity.** In the past, symptomatic calyceal diverticula have been managed with partial nephrectomy, with marsupialization and fulgaration of the diverticulum, and occasionally simple nephrectomy. More recently, percutaneous treatment has been used, but stones or symptoms may recur if the cavity is not fully ablated (Donnellan et al, 1999). **A laparoscopic approach may be indicated with large, peripheral diverticula, or for centrally located diverticula with proximity to the renal hilum.**

Procedure

The location of the diverticula will be the primary driver for choosing either a transperitoneal or retroperitoneal approach. Once the renal dissection is completed, locating the diverticulum may prove difficult. The presence of dense adhesions on the surface of the kidney overlying the divericulum may be present along with a "dimpling" effect on the renal capsule. Intraoperative ultrasonography may also be used to aid in the location of the divertiulum or to confirm a suspected location. Once localized, the overlying parenchyma is incised and opened to expose the diverticulum, which is subsequently opened with cautery. Stones may then be removed, and the argon beam coagulator or monopolar cautery device can be used to fulgarate the diverticular lining. The collecting system is closed with suture, and perirenal fat may be placed into the defect to further decrease the likelihood of recurrence. A drain is usually left in place.

Results

Published reports on laparoscopic calyceal diverticulectomy are limited to small series and case reports. Excellent results have been reported by numerous authors, demonstrating the definitive nature of this treatment modality (Miller et al, 2002; Gluckman et al, 1993; Ruckle and Segura et al, 1994; Harewood et al, 1996; Wolf, 2000; Canales and Monga, 2003; Wyler et al, 2005). Probably due to the rarity of this surgery, complications are also rare and have not been reported yet in the literature.

NEPHROLYSIS

Chyluria is caused by lymphatic rupture or fistulous connection into the pyelocalyceal system. It is a rare problem worldwide but is commonly seen in tropical countries when filariasis (*Wuchereria bancrofti* or *Brugia malayi*), the most common cause, is endemic (Tandon et al, 2004). Rarely, schistosomiasis may also be a cause of chyluria, and nonparasitic chyluria is rare. Other reported etiologies include tuberculosis (Wilson and White, 1976), idiopathic lymphorenal fistula (Eisner et al, 2009), prior surgery (Kim and Joudi, 2009), pregnancy (Onyeije et al, 1997), thoracic duct obstruction (Garrido et al, 1995), mesenteric adenitis (Cohen et al, 1984), renal vasculitis (El-Reshaid et al, 1998), and metanephric adenoma (McNeil et al, 2008).

Diagnosis

Patients typically present with milky white urine and may have nephrotic range proteinuria. Initial evaluation includes urinalysis and culture, urine for chyle, and complete blood count to check for eosinophila. Evaluation to localize the fistula may include cystoscopy with retrograde pyelogram, CT, magnetic resonance imaging (MRI), or lymphangiography (Fig. 55–30).

Treatment

Chyluria is often self-limited, and many patients may be managed conservatively. In filariasis-associated cases, this involves treatment with a course of diethylcarbamazine (DEC) in combination with a low-fat diet (Tandon et al, 2004). Retrograde instillation of silver nitrate or povidone iodine into the collecting system as a sclerosing agent has also been described, and these agents are commonly used as first-line treatment with comparable success rates of approximately 80% (Dalela et al, 2004a; Goel et al, 2004). When conservative management fails or if cases are particularly severe, surgical intervention is undertaken.

Procedure and Results

Nephrolysis involves the complete mobilization of the kidney and skeletonization of the renal hilar vessels and upper ureter with ligation of the lymphatic channels. The procedure may be performed laparoscopically by either a transperitoneal or retroperitoneal approach and ensures complete lymphatic dissociation of the affected kidney (Chiu et al, 1995, Gomella et al, 1998). The use of an omental wrap around the hilum has also been described to provide an additional barrier against recurrence (Dalela et al, 2004b). Authors commonly performing this procedure report excellent success rates—approaching 100%.

RADICAL NEPHRECTOMY

Indications for Malignancy

Laparoscopic approaches to malignancy have been performed for over 20 years. The indications for radical nephrectomy are similar to those for open surgery. Kidneys with tumors as large as 25 cm

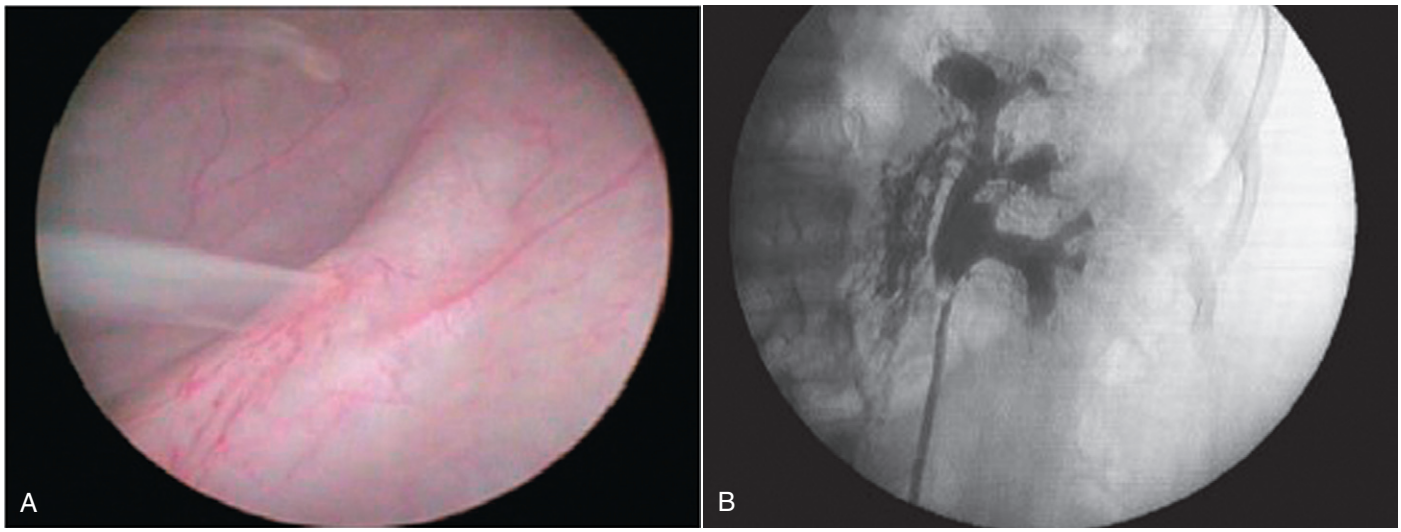


Figure 55–30. Chyluria. **A,** Cystoscopy demonstating milky white efflux from the left ureteral orifice. **B,** Retrograde pyelogram demonstrating lymphorenal fistula. (From Eisner BH, Tanrikut C, Dahl DM. Chyluria secondary to lymphorenal fistula. Kidney Int 2009;76:126.)

have been successfully removed laparoscopically, and cytoreductive nephrectomy has been performed in patients with metastatic disease (Walther et al, 1999). Moreover, tumors with low- level caval thrombi have also been removed (Martin et al, 2008).

Transperitoneal

Procedure

Access and trocar placement are similar to what has been described for simple nephrectomy. With larger masses, caval involvement or organ invasion, additional trocars or a hand port may be needed. The procedure for laparoscopic radical nephrectomy (LRN) is essentially identical to laparoscopic simple nephrectomy. The main distinguishing feature is that Gerota fascia is left intact during dissection. The adrenal may be removed en bloc with the kidney when indicated (Fig. 55–31A). Alternatively, this fascia is opened over the upper medial aspect of the kidney when adrenal-sparing nephrectomy is performed (Fig. 55–31B). Suspect lymph nodes may be removed, and a full hilar or retroperitoneal dissection can be carried out if deemed necessary. Excision of part of adjacent muscle or involved organs, such as the pancreas, liver, spleen, and bowel, has also been reported (Molina et al, 2004).

Results

Long-term cancer-specific survival data is now widely available from multiple centers around the world that perform laparoscopic radical nephrectomy (Table 55–3). Five- and 10-year outcomes show oncologic equivalence to open radical nephrectomy in treatment of renal cancer. Indeed, LRN has become the standard of care for most renal malignancies.

A multi-institutional study from centers performing LRN compared the surgical and disease-specific outcomes between open and laparoscopic radical nephrectomy, with long-term follow-up (Portis et al, 2002). Median follow-up was 54 months, and recurrence-free survival was 91% and 92%, respectively, for the two groups at 5 years. The 5-year cancer-specific survival was 98% for the laparoscopic cohort and 92% for the open cohort.

A comparative analysis of 67 patients undergoing LRN, with 54 patients undergoing open radical nephrectomy, evaluated perioperative and oncologic outcomes (Permpongkosol et al, 2005). The LRN group showed a longer mean operative time (256 vs. 193 minutes). However, this finding likely reflects the learning curve for laparoscopy, because the first 34 patients and last 33 patients in the LRN group had a significant operative time difference. Complications occurred in 15% of patients in the LRN and open groups, and blood transfusions were required in 6% and 20% of the patients, respectively. Most importantly, **the calculated disease-free survival rates for laparoscopic and open radical nephrectomy were 95% and 89%, respectively, at 10 years. The actuarial survival rates for laparoscopic and open radical nephrectomy were 87% and 75%, respectively, at 10 years.** These differences were not found to be statistically significant.

Most recently, 10-year oncologic outcomes data following LRN were reported. Recurrence-free, cancer-specific, and overall survival rates were 86%, 92%, and 65%, respectively, at 10 years postnephrectomy (Berger et al, 2009). **Of 73 patients undergoing LRN, no patient developed local recurrence, and 6 (8.2%) developed metastatic disease at a mean time to recurrence of 74 months.** Although outcomes in this study were not compared with an open radical nephrectomy cohort, results are quite comparable to those for open surgery.

Perioperative outcomes in contemporary groups undergoing laparoscopic and open radical nephrectomy have also been extensively studied. In a series of 54 laparoscopic and 34 open radical nephrectomies, no differences in age, body mass index (BMI), American Society of Anesthesiologists (ASA) score, tumor size, specimen weight, or operative time were noted (Gill et al, 2000). **The laparoscopic approach was shown to have less blood loss, shorter hospital course, lower analgesic requirement, and shorter return to convalescence.** Complications were noted in 13% of patients in the laparoscopic group and 24% of patients in the open group. Similar findings have been previously reported by multiple authors (Kerbl et al, 1994a; McDougall et al, 1996; Hemal et al, 2007).

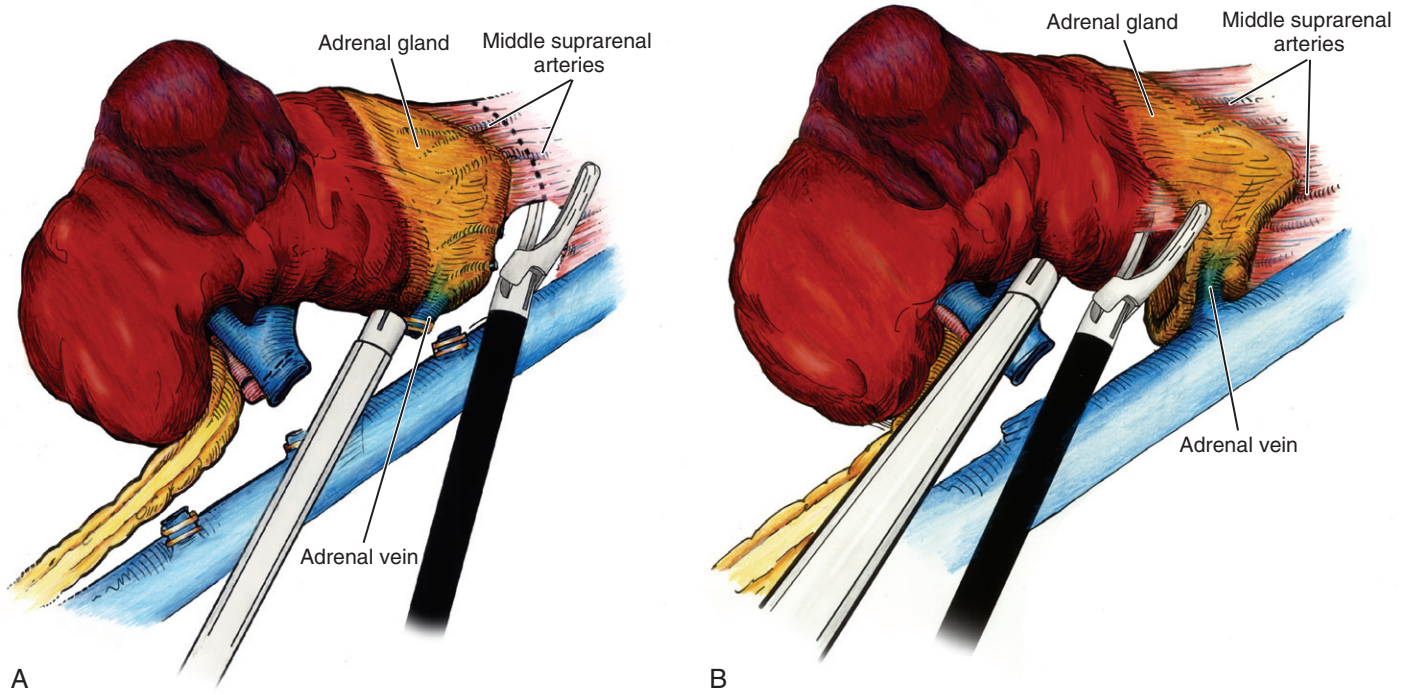


Figure 55–31. **A,** Inclusion of the adrenal gland during right laparoscopic radical nephrectomy can be readily accomplished using ultrasonic or bipolar shears to control the multiple arterial branches to the adrenal gland. Inferior retraction of the specimen facilitates exposure of this surgical plane. **B,** Adrenal-sparing, right radical nephrectomy. Use of a blunt instrument above the hilum to put anterior and inferior traction on the kidney helps to expose the correct plane and place the connective tissue on stretch. Ultrasonic or bipolar shears are again useful to avoid any bleeding that may be encountered in this plane.

Retroperitoneal

Procedure

The patient is positioned, and trocars are placed for retroperitoneal access as described earlier in the chapter. After identifying the psoas muscle and tendon, medial dissection in this plane will reveal the ureter. Elevation of the ureter will allow visualization and subsequent elevation of the lower pole of the kidney. This will place the main renal vessels on stretch, facilitating their dissection. The arterial pulsation may be indirectly visualized through overlying connective tissue, and just as with the transperitoneal approach, gentle layer-by-layer dissection with the suction-irrigator will allow the renal vessels to come more directly into view. Use of the right-angle dissector will allow the artery to be circumferentially freed from the surrounding tissue, and the endovascular stapler or clips are used to divide the artery and vein sequentially. When operating on the left kidney, a lumber vein will typically require dissection, ligation, and division to allow unencumbered access to the main hilum. **Care must be taken to continuously reorient to anatomic relationships to ensure that the inferior vena cava is not mistakenly identified as the renal vein**. The kidney may be removed intact or after morcellation, as previously described.

Results

When compared with transperitoneal laparoscopic radical nephrectomy, outcomes of the retroperitoneal approach are quite similar with regard to complication rates, analgesic requirements, hospital course, and return to convalescence.

A randomized study comparing transperitoneal and retroperitoneal laparoscopic approaches was performed in 102 patients (52 transperitoneal, 50 retroperitoneal) with a mean tumor size of 5 cm (Desai et al, 2005). No difference was seen in blood loss, narcotic requirement, hospital stay, or complication rate. However, there was a significant difference noted in operative time, which favored the retroperitoneal approach (150 vs. 207 minutes). A second randomized study of 40 patients compared the number and size of trocars, pathologic stage, blood loss, operative time, complication rate, and hospital stay (Nambirajan et al, 2004). No statistical difference was noted in any of these outcomes, including operative time.

Hand-Assisted

Procedure

The patient is positioned, and the hand port and trocars are placed as previously described. The steps in hand-assisted laparoscopic nephrectomy (HALN) are similar to those for pure laparoscopic surgery, but the nondominant hand is used throughout for retraction and dissection. To incise the white line of Toldt, the nondominant hand retracts the colon medially while the dominant hand uses an endoscopic scissors to divide the attachments (Fig. 55–32). The irrigator-aspirator is then used to help identify and dissect the correct plane posterior to the large bowel mesentery and anterior to Gerota fascia. The surgeon's hand and fingers may be used to simultaneously place lateral traction on the kidney and medial traction on the bowel, helping to demonstrate the correct plane. For a left nephrectomy, the hand may also be used to gently retract the spleen and pancreas medially while the lienorenal

Table 55–3.

Oncologic Outcomes of Laparoscopic Radical Nephrectomy

A. Comparative Series Analyzing Laparoscopic and Open Radical Nephrectomy

AUTHOR	APPROACH	TOTAL NO. OF PATIENTS	NO. PATIENTS WITH RCC	MEAN AGE AT SURGERY	MEAN TUMOR SIZE	CLINICAL STAGE ≥ T2	PATIENTS WITH FUHRMAN GRADE 3 OR 4	MEDIAN FOLLOW-UP	LOCAL RECURRENCE	PROGRESSION TO METASTATIC DISEASE	MEAN TIME TO RECURRENCE OR METASTASIS	CANCER-SPECIFIC DEATHS	5-YEAR RECURRENCE-FREE/ CANCER-SPECIFIC/ OVERALL SURVIVAL	10-YEAR RECURRENCE-FREE/CANCER-SPECIFIC/ OVERALL SURVIVAL
Dunn et al, 2000	Laparoscopic	60	44	63.5 yr	5.3 cm	NR	NR	25 mo (mean)	1 (2.3%)	2 (4.5%)	Not specified	2	—	—
	Open	30	30	61.8 yr	7.4 cm	NR	NR	27 mo (mean)	0 (0%)	3 (10%)	Not specified	0	—	—
Ono et al, 2001	Laparoscopic	103	103	57.2 yr	3.1 cm	0%	3.9%	29 mo	1 (1%)	3 (2.9%)	31.5 mo	0	95.1%/NR/95%	—
	Open	46	46	56.7 yr	3.3 cm	0%	6.5%	39 mo	0 (0%)	3 (6.5%)	22.3 mo	2	89.7%/NR/95.6%	—
Portis et al, 2002	Laparoscopic	64	64	60.6 yr	4.3 cm	14.1%	9.4%	54 mo	1 (1.6%)	3 (4.7%)	31.8 mo	1	92%/98%/81%	—
	Open	69	69	61.3 yr	6.2 cm	34.8%	13.0%	69 mo	1 (1.4%)	10 (14.5%)	47.5 mo	6	91%/92%/89%	—
Saika et al, 2003	Laparoscopic	195	195	57.3 yr	3.7 cm	NR	4.1%	40 mo	1 (0.5%)	10 (5.1%)	33.6 mo	5	91%/NR/94%	—
	Open	68	68	58.4 yr	4.4 cm	NR	7.3%	65 mo	0 (0%)	10 (14.7%)	Not specified	6	87%/NR/94%	—
Harano et al, 2005	Laparoscopic	96	96	61.1 yr	4.3 cm	NR	NR	25 mo	0 (0%)	3 (3.1%)	24.3 mo	0	88%/NA/100%*	—
	Open	86	86	58.5 yr	4.9 cm	NR	NR	86 mo	0 (0%)	5 (5.8%)	Not specified	0	93%/NA/100%*	—
Permpongkosol et al, 2005	Laparoscopic	67	67	61 yr	5.1 cm	31.3%	26.9%	73 mo	0 (0%)	4 (6%)	29.5 mo	2	94%/97%/85%	94%/97%/76%
	Open	54	54	59 yr	5.4 cm	25.9%	29.6%	80 mo	0 (0%)	7 (13%)	Not specified	6	87%/89%/72%	87%/86%/58%
Hemal et al, 2007†	Laparoscopic	41	39	52.5 yr	9.9 cm	100%	NR	51 mo	0 (0%)	3 (7.7%)	Not specified	2	92.6%/95.1%/87.8%	—
	Open	71	68	52.7 yr	10.1 cm	100%	NR	57 mo	0 (0%)	7 (10.3%)	Not specified	4	90.1%/94.4%/88.7%	—
Hattori et al, 2009†	Laparoscopic	52	52	56 yr	8.8 cm	100%	11.5%	41 mo	1.9%	19.2%	Not specified	6	75%/90%/NR	60%/90%/NR
	Open	79	79	62 yr	8.9 cm	100%	11.4%	51 mo	2.5%	20.3%	Not specified	20	77%/87%/NR	70%/75%/NR

B. Noncomparative Series of Laparoscopic Radical Nephrectomy

AUTHOR	NO. PATIENTS WITH RCC	MEDIAN AGE AT SURGERY	MEAN TUMOR SIZE	PATIENTS WITH FUHRMAN GRADE 3 OR 4	MEDIAN FOLLOW-UP	LOCAL RECURRENCE	PROGRESSION TO METASTATIC DISEASE	MEAN TIME TO RECURRENCE OR METASTASIS	CANCER-SPECIFIC DEATHS	5-YEAR RECURRENCE-FREE/ CANCER-SPECIFIC/ OVERALL SURVIVAL	10-YEAR RECURRENCE-FREE/ CANCER-SPECIFIC/ OVERALL SURVIVAL
Cadeddu et al, 1998	157	61 yr	NR	8.9%	19.2 mo (mean)	1 (0.6%)	4 (2.5%)	14.8 mo	0	91%/NA/NA	NA
Wille et al, 2004	118	63 yr	5.1 cm	NR	23.5 mo	0 (0%)	3 (2.5%)	9.7 mo	NR	NR	NA
Hemal et al, 2007	132	51.6 yr	6.9 cm	7.6%	56 mo	0 (0%)	17 (12.9%)	34.1 mo	16	87.1%/87.9%/85.6%	NA
Bandi et al, 2008	65	59 yr	5.8 cm	14.0%	46 mo (mean)	1 (1.5%)	4 (6.2%)	18 mo	3	90.2%/94.4%/80%	NA
Berger et al, 2009	73	59 yr	5 cm	24.6%	131 mo	0 (0%)	8.2%	74 mo	8	NR	86%/92%/65%

*Four-year survival reported in this series.
†Series inclusive of tumors only ≥7 cm in size.
NA, not available; NR, not reported; RCC, renal cell carcinoma.

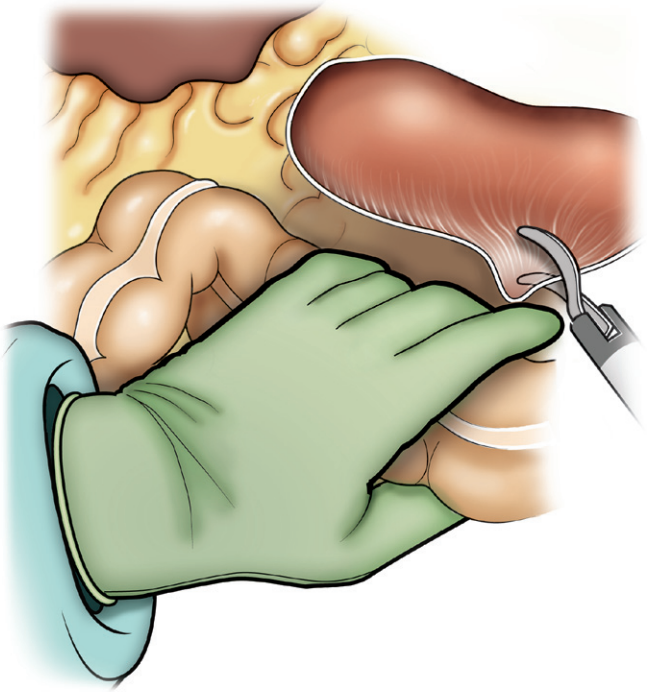


Figure 55–32. The nondominant hand is used to retract the colon medially and to dissect tissue planes, while the dominant hand uses endoscopic scissors to divide colon attachments.

attachments are divided. Similarly, on the right, the hand is used to retract the liver anteriorly, exposing the upper pole and facilitating its dissection.

After the colon is sufficiently mobilized, the psoas muscle is identified, which will allow the ureter to be elevated. On the left, the gonadal vein is typically elevated in the packet along with the ureter, but on the right, the gonadal vein is reflected medially. With the ureter elevated, the hand can bluntly dissect and elevate the entire kidney off the psoas muscle, and the ureter is then followed up to the renal hilum. The fingers are then used to place anterolateral traction on the kidney, while the thumb pushes the bowel and mesentery medially. The hilum should begin to come into view at this point, and the irrigator-aspirator can be used to gently dissect the overlying connective tissue while the hand is used to keep the vessels on stretch. Once the vessels are sufficiently skeletonized, the endovascular stapler or clips are used to ligate and divide the artery and vein sequentially (Fig. 55–33A and B). The lateral and superior attachments may then be divided, using a Ligasure device or harmonic scalpel while the hand keeps them on traction. The hand should not be used to dissect the adrenal gland free from the upper pole of the kidney, because this will typically result in bleeding. Ultrasonic energy, Ligasure, or bipolar cautery may be used to divide the fragile attachments between the kidney and the adrenal gland, just as with pure laparoscopy.

A rolled laparotomy sponge is often placed through the hand port at the beginning of the procedure to assist with retraction, absorb blood, and to allow the surgeon to hold pressure if needed. In addition, the tip of the irrigator-aspirator can be placed into the compressed sponge to facilitate suction when needed. It is critical to remember removal of the sponge at the end of the case. The previously made hand-port incision allows rapid removal of sponge and the intact specimen. However, hand-port metastases have been reported, and it is recommended to place the specimen in a removal device before extraction to prevent any possibility of direct contact with wound edges.

The inserted hand can also facilitate closure of trocar sites greater than 10 mm with a suture-passing device. **Wound complications such as hernias and infections have been reported at the hand-port site, with hernias typically presenting 3 months or more after surgery and with an overall 4% incidence** (Okeke et al, 2002; Wolf, 2005). Care must be taken to copiously irrigate and close the hand-port incision, ideally closing the peritoneum separately from the fascia to minimize chance of hernia.

Results

Most outcomes are comparable between pure laparoscopy and the hand-assisted technique including efficacy, operative times, complication rates, narcotic requirements, length of hospital stay, and return to convalescence. Some comparative studies between laparoscopic and hand-assisted techniques have demonstrated that the hand-assisted procedures can require shorter operative times, but patients had more abdominal pain and wound complications (Nelson and Wolf, 2002).

Comparative studies between HALN and standard laparoscopic approaches have shown that choice of approach does not impact on oncologic outcome. Gabr and colleagues (2009) studied and compared 147 patients who underwent standard laparoscopic nephrectomy and 108 who underwent hand-assisted laparoscopic nephrectomy. Patients were followed for a mean of 35.2 months, and multivariate analysis showed that the approach did not impact recurrence-free, cancer-specific, or overall survival. A multi-institutional study of 95 patients undergoing HALN evaluated the impact of tumor size on outcome (Stifelman et al, 2003). Patients were grouped into those with tumors larger than 7 cm and those with tumors smaller than 7 cm. Short-term outcomes at mean follow-up of 12 months were not different between the two groups, including positive margin rate, local recurrence, and metastasis. An additional short-term outcome study investigating a series of 60 patients undergoing HALN for T1 or T2 tumors demonstrated no recurrence or trocar site seeding at mean follow-up of 11 months (Patel and Leveillee, 2003).

RADICAL NEPHRECTOMY: SPECIAL CONSIDERATIONS

Large Tumors

Experience with laparoscopy for large tumors (>7 cm) has grown substantially as confidence with renal laparoscopy has increased (Steinberg et al, 2004; Hemal et al, 2007; Berger et al, 2008; Rosoff et al, 2009). Large tumors present several surgical challenges. The bulk of the mass can decrease working space and alter normal anatomic landmarks. This can result in disorientation with potential injury to surrounding structures. Continuous intraoperative reference to preoperative imaging as well as use of ultrasonography is helpful. Flexible endoscopes may be used to see around structures. The weight of large tumors may cause the surgeon to apply additional force for manipulation, potentially resulting in tumor rupture. It may be beneficial to use a hand port in these instances or additional trocars. Consideration may also be given to lymphadenectomy with larger tumors as indicated.

En Bloc Stapling

En bloc stapling of the renal hilum has been reported from several centers. An evaluation of 80 patients with mean follow-up of 35.2

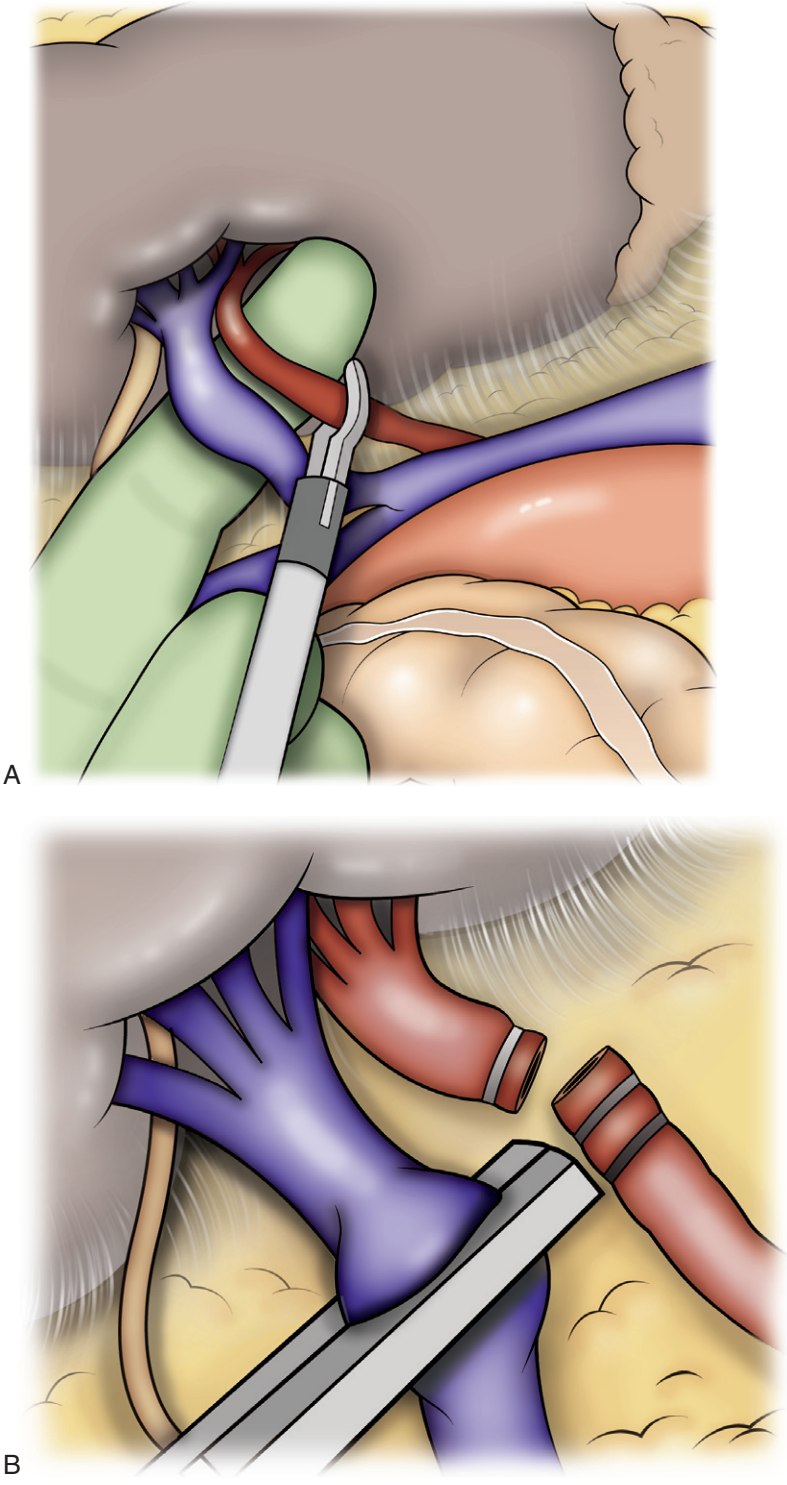


Figure 55–33. **A,** With the renal hilum on stretch and the bowel retracted medially to expose the vessels, the fingers can be used to palpate the renal artery and guide a stapler or clip applier to secure and divide the artery. **B,** Once the artery is divided, the renal vein is freed circumferentially and divided with an endovascular stapler.

months after either open or laparoscopic radical nephrectomy, with routine use of en bloc hilar stapling, demonstrated no clinical evidence of arteriovenous fistula (White et al, 2007). Half of the patients also underwent CT arteriography at a minimum interval of 12 months postoperatively, and no patient had radiographic evidence of arteriovenous fistula. Another study evaluated patient outcomes in 433 patients undergoing laparoscopic radical nephrectomy or nephroureterectomy, of whom 26 (6%) underwent en bloc stapling only when hilar dissection was deemed "difficult" by the surgeon (Rapp et al, 2004). No cases of arteriovenous fistula were noted at a mean follow-up of 26 months. However, the authors noted that arteriovenous fistula may be a more long-term complication after en bloc hilar stapling, and thus longer follow-up is needed to properly assess these patients.

Port-Site Recurrence

Since its inception, a concern for port-site seeding and recurrence continues to be raised for performance of laparoscopic surgery for urologic malignancy. In an international survey of 20 centers

performing 2604 laparoscopic radical nephrectomies, no port-site seeding was reported (Micali et al, 2004). A recent review of all reported cases of port-site seeding in laparoscopy for urologic malignancy revealed a total of 28 cases. The majority involved aggressive upper tract transitional cell carcinoma, and six involved renal cell carcinoma (Eng et al, 2008). The etiology of port-site recurrence is thought to be multifactorial and related to tumor aggressiveness, immune status of the patient, local wound factors, and surgical technique. The effect of pneumoperitoneum, aerosolization of tumor cells, insufflation gas type, and laparoscopic wound closure techniques have been studied by multiple authors and is noncontributory (Ikramuddin et al, 1998; Tsivian et al, 2000; Gupta et al, 2002; Burns et al, 2005; Halpin et al, 2005; Jingli et al, 2006). As with open surgery, the most common etiology is technical error and associated tumor spillage. Animal studies demonstate that direct contact between tumor and port-site enhances tumor growth (Bouvy et al, 1996), and the use of an impermeable specimen retrieval bag is recommended in all cases. Although the overall incidence of port-site metastasis is low—estimated at 0.09% to 0.18% (Micali et al, 2004; Rassweiler et al, 2003)—care should be taken in specimen handling and extraction to help minimize risk factors over which the surgeon has the most control.

Specimen Extraction

An area of controversy surrounding specimen extraction has been morcellation due to the concerns for inadequate pathology and staging, peritoneal or port-site seeding, bag rupture, and recurrence. Although there is an advantage in terms of shorter incision length, there has been no benefit demonstrated in postoperative analgesic requirement (Hernandez et al, 2003). A multi-institutional study of the safety and efficacy of specimen morcellation in 188 patients with clinical stage T1 or T2 renal cell carcinomas revealed 11 patients with recurrent disease (10 metastatic to lungs or viscera and 1 patient with port-site, renal fossa, and lymph node recurrence) (Wu et al, 2009). This demonstrates that mechanical morcellation may be safely performed in selected patients. However, the ability to properly stage the patient remains in question, with studies demonstrating conflicting results. The feasibility of pathologic evaluation has been studied in comparative fashion by evaluating both fresh and formalin-fixed specimens before and after morcellation (Landman et al, 2000). No alteration in determination of histology, grade, or local invasiveness of tumor was seen. Only specimen size could not be assessed following morcellation. A separate study on 23 morcellated specimens concluded that pathologic tumor stage in both renal cell and transitional cell carcinoma is severely limited by morcellation and must rely partially on diagnostic imaging for lesion size, capsule, and renal vein involvement (Rabban et al, 2001). Additionally, the incidence of pathologic stage T3a tumors was evaluated retrospectively in a series of 1781 patients and found to be 7.2% overall (Granberg et al, 2007). Imaging in the overwhelming majority of these patients did not predict stage pT3a disease. The authors concluded that without imaging that can more reliably predict fat invasion, accurate staging would be difficult if morcellation is performed.

If the specimen is to be morcellated, the surgeon should strictly adhere to proper technique including the use of a purpose-built sac, adequate draping, and change of gowns, gloves, and instruments after morcellation. The LapSac (Cook Urological, Spencer, IN) has been shown to be impermeable to bacteria and tumor cells, even after its use for morcellation (Urban et al, 1993). The sac is prepared by passing a moistened hydrophilic wire alternating through every third hole in the sac, which is then rolled from the bottom up and passed through a 12-mm trocar site. The trocar is replaced leaving the wire and drawstrings outside the trocar. Graspers are used to place the specimen in the sac, which is held open by the wire, and the wire is removed (Wakabayashi et al, 2003). The drawstrings are grasped and brought through the periumbilical incision along with the neck of the sac, which is held tightly against the abdomen. Enlarging the trocar site by 1 cm will allow small amounts of tissue to protrude through the mouth of the sac. The morcellation process is performed with a ring forceps, working with alternating bites on the protruding tissue. Deep passes with the forceps should be avoided to prevent unintentional incorporation of bowel into the forceps. Pneumoperitoneum should also be maintained during the process to allow monitoring of the sac intracorporeally to avoid injury to structures resting against the sac or sac perforation.

Lymphadenectomy

Lymphadenectomy at the time of nephrectomy, open or laparoscopic, remains controversial. It has been shown that presence of two or more adverse pathologic predictors (grade, sarcomatoid features, tumor size, stage, and necrosis) results in a higher likelihood of lymph node metastasis (Blute et al, 2004). In addition, patients with preoperatively or intraoperatively suspicious lymph nodes have been shown to have improved survival (median of 5-month benefit) when undergoing a lymph node dissection compared with those who did not (Pantuck et al, 2003). A retrospective study of 50 patients undergoing LRN alone versus 50 undergoing LRN with laparoscopic lymph node dissection (LND) determined that 10% of the patients undergoing LND had positive nodes (Chapman et al, 2008). All patients were preoperatively node negative by cross-sectional imaging evaluation, and those with positive nodes all had high-grade lesions, stages T3 or T4. However, a randomized study comparing groups undergoing radical nephrectomy, with or without lymphadenectomy at the time of surgery, has demonstrated no survival benefit of lymph node dissection in patients with clinically negative lymph nodes (Blom et al, 2009).

It is clear that not every patient with renal cell carcinoma requires lymphadenectomy. However, a subset of patients with suspicious lymph nodes may derive benefit from lymphadenectomy. Of note, there is no consensus on the extent of node dissection to be performed. The additional group that may benefit includes those with higher-stage tumors in the absence of suspicious lymph nodes, although survival data to support lymphadenectomy in this population is lacking.

Local Recurrence

The incidence of isolated local recurrence after nephrectomy with curative intent is approximately 1.8% (Itano et al, 2000; Margulis et al, 2009). Isolated local recurrence is defined as recurrence in the ipsilateral retroperitoneal lymph nodes, renal fossa, or adrenal gland without evidence of distant metastasis (Fig. 55–34). In a study of 54 patients with isolated local recurrence managed with open surgical resection, median recurrence-free and cancer-specific survival of 11 and 61 months, respectively, were observed (Margulis et al, 2009). Perioperative systemic therapy with various combinations of immunotherapy, chemotherapy, and targeted tyrosine kinase inhibitors was used in 69% of cases. Given their rarity, published laparoscopic experience in surgically addressing these recurrences is quite limited to date. A series of five patients

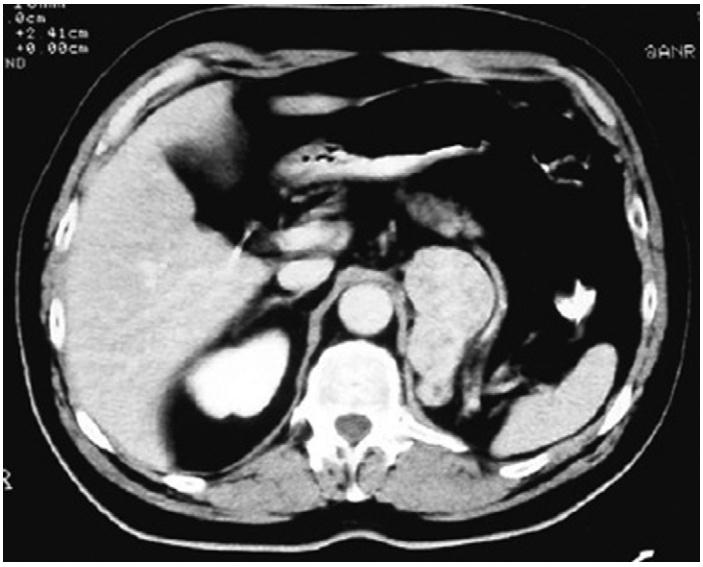


Figure 55–34. Renal fossa recurrence. (From Nóbrega de Jesus CM, Silva Casafus FA, Agostinho AD. Surgical treatment of renal cell carcinoma recurrence at the renal fossa following radical nephrectomy. Sao Paulo Med J 2008;126:194–6.)

(one open conversion for vena caval invasion) undergoing a hand-assisted approach to isolated local recurrence has demonstrated that the procedure may be safely performed in selected patients (Bandi et al, 2008). At a mean follow-up of 43 months, cancer-specific and disease-free survival rates were 60% and 20%, respectively. The small number of patients in this report makes the results difficult to interpret. An open surgical resection can offer durable local control and cancer-specific survival in carefully selected patients; larger comparative laparoscopic series with sufficient follow-up are clearly needed to determine the efficacy of laparoscopy in these scenarios.

Renal Vein and Caval Tumor Thrombus

Several centers have now published their experiences with laparoscopy for renal cancers with associated tumor thrombus into the renal vein or inferior vena cava (Desai et al, 2003; Hsu et al, 2003; Martin et al, 2008; Guzzo et al, 2009). After complete laparoscopic mobilization of the kidney and ligation of the renal artery, a laparoscopic DeBakey procedure, vessel loop, or hand assistance is typically employed to "milk" the tumor thrombus distally toward the kidney. This allows either the endovascular stapler to be deployed proximal to the thrombus, or a laparoscopic Satinsky clamp to be placed to isolate a cuff of the vena cava such that the cuff may be excised to allow intact specimen extraction. When using a hand port, the vena cava may then be oversewn using proline suture. The use of intraoperative ultrasonography has also been described to aid in assessing the location of the proximal extent of the tumor thrombus (Hsu et al, 2003). To date, the approach has been limited to low-level caval thrombi, but results have been comparable with the open surgical experience.

Cytoreductive Nephrectomy

Patients with advanced renal cell carcinoma may require cytoreductive nephrectomy before the initiation of systemic secondary therapies. A comparative study of open versus laparoscopic cytoreductive nephrectomy in a selected group of patients with metastatic disease—but without local invasion, venous involvement, or bulky adenopathy—demonstrated similar one-year survival between the two groups (61% vs. 65%) (Rabets et al, 2004). In addition, the laparoscopic group had less blood loss, shorter hospital stay, and shorter interval between surgery and the initiation of systemic therapy (36 vs. 61 days). Other studies have shown similar results (Eisenberg et al, 2006; Matin et al, 2006a), although the shorter interval to systemic therapy has not been consistently observed.

Surgical Salvage after Failed Ablative Therapies

Nephrectomy following ablation is technically challenging due to resulting loss of tissue planes surrounding the lesion. A multi-institutional review of treatment outcomes for primary radiofrequency ablation (RFA) or cryotherapy revealed residual or recurrent disease in a median of 8.7% of patients (Matin et al, 2006b). Although a subgroup of these patients will undergo successful salvage ablative therapy, some may not be candidates for repeat ablation due to disease progression, tumor size, or failed repeat ablation. A report of 10 patients undergoing salvage surgery in this patient population has shown that laparoscopic nephrectomy was only possible in 4 patients, and the remainder required either open partial or radical nephrectomy (Nguyen et al, 2008). Extensive perinephric fibrosis was cited as the main factor complicating surgery.

PARTIAL NEPHRECTOMY

Kidney tumors are increasingly being diagnosed incidentally, at a small size and early stage, in asymptomatic healthy patients (Jayson et al, 1998; Leslie et al, 2003). Although the majority of imaging-detected incidentally found renal lesions are benign simple cysts, one must be vigilant to not miss an early renal cancer. **Recent data regarding the prevalence of unsuspected, early-stage chronic kidney disease underscore an important point: Renal functional preservation and nephron-sparing strategies are important considerations when making management decisions in patients with a small renal mass (SRM)** (Huang et al, 2006)**.** The desire to provide a minimally invasive alternative to treat patients with small renal masses led to the application of laparoscopic techniques to nephron-sparing surgery.

The first transperitoneal laparoscopic partial nephrectomy (LPN) was reported in 1993 by Winfield and colleagues, with the retroperitoneal approach introduced one year later (Gill et al, 1994). Initially, LPN was applied to treat small clinical T1a exophytic renal masses (Fig. 55–35). With increasing laparoscopic confidence and experience, the indications of LPN have been expanded to almost all patients with challenging tumor anatomy in complex clinical settings.

Expanded Indications

Clinical Stage T1b Tumors (4 to 7 cm)

LPN was initially restricted to patients with tumors less than or equal to 4 cm in size. Technical advances in laparoscopic techniques, along with demonstration of equivalent results to open surgery for T1a tumors, provided the groundwork for approaching

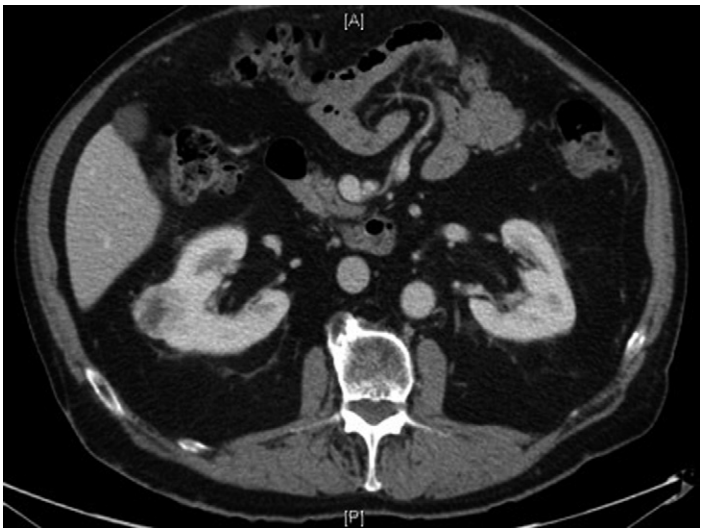


Figure 55–35. CT scan with IV contrast demonstrating a partially exophytic midpole clinical T1a lesion in the right kidney.

larger lesions (Leibovich et al, 2004; Dash et al, 2006; Mitchell et al, 2006). Simmons and colleagues (2009) reported perioperative outcomes of LPN in 58 patients for T1b tumors. Mean tumor size was 6 cm, and 55% of tumors were centrally located. Although patients with pT1b tumors more often underwent pelvicalyceal repair ($P = .004$) and heminephrectomy ($P < .001$), they had similar operative time, blood loss, and hospital stay but longer warm ischemia time than patients with tumors less than 4 cm. Tumor size greater than 4 cm did not increase risk for positive cancer margins, intraoperative complications, or postoperative urologic complications. Of note, in patients with tumors less than 2 cm, 2 to 4 cm, and 4 to 7 cm (stage ≥III), chronic kidney disease (CKD) existed preoperatively in 31%, 35%, and 44% of patients, respectively, and postoperatively in 52%, 53%, and 63%, respectively (P = ns). This underscores the importance of attempting to provide a nephron-sparing approach to all patients. **Given adequate laparoscopic experience and judicious patient selection, the perioperative outcomes of LPN for clinical T1b tumors greater than 4 cm appear comparable to those achieved for clinical T1a tumors less than or equal to 4 cm.**

Laparoscopic Heminephrectomy

Finelli and colleagues (2005) compared outcomes of laparoscopic heminephrectomy (excising greater than 30% of renal parenchyma) in 41 patients, with a contemporary group of 41 consecutive patients who underwent LPN with less than 30% resection. Except for a longer ischemia time (39 vs. 33 minutes) in the heminephrectomy cohort, there were no differences between the two groups regarding blood loss, operation room (OR) time, analgesic requirement, hospital stay, postoperative serum creatinine, and overall complications. All surgical margins were negative. Specific technical considerations inherent to laparoscopic heminephrectomy include routinely performing deeper renal parenchymal resections, transection of sizable intraparenchymal blood vessels, and intentional entry into the pelvicalyceal system. The primary goals of laparoscopic heminephrectomy and LPN are the same: achieve negative surgical margins, perform clipping or suture repair to secure renal vessels, and where necessary, repair the collecting system while minimizing ischemia time.

Central and Hilar Tumors

Central tumors are defined as those abutting or invading the central renal sinus fat and/or the collecting system on preoperative CT. These tumors deeply infiltrate the renal parenchyma, and their excision requires intentional entry into and potentially suture-repair of the pelvicalyceal system along with complex parenchymal reconstruction, all within the time constraints of renal ischemia. The technical complexity of such cases depends upon the location of the individual tumor, and the type of suturing angles available for laparoscopic instruments in the dominant and nondominant hand. Frank and colleagues (2006) compared experience with LPN for 154 central tumors with LPN for 209 peripheral tumors. Although blood loss was similar, central tumors were associated with somewhat longer operative time, ischemia time, and hospital stay, and more early postoperative complications. There was only one positive margin for cancer in each group. These data reflect the initial outcomes of the LPN experience; at this writing, the authors routinely perform LPN for central tumors without any increase in operative morbidity as noted above.

Hilar tumors, defined as tumors located in the renal hilum in direct contact with the renal artery and/or vein on cross-sectional imaging, were initially considered by many to be a contraindication to LPN. In 2005, an initial experience with LPN outcomes for hilar tumors in 25 patients was reported (Gill et al, 2005). Mean tumor size was 3.7 cm (range 1 to 10.3). LPN was successful in all cases, without any open conversions or operative reinterventions. Postoperative hemorrhage occurred in three early patients. Preoperative 3D video reconstruction of triphasic spiral CT was important in detailing the number, interrelationship, anatomical course, and position of the renal vessels in relation to the tumor.

Tumor in a Solitary Kidney

Partial nephrectomy for tumor in a solitary kidney, open or laparoscopic, is challenging. The margin for error is small because a complication could result in temporary dialysis, or worse, render the patient anephric. In the largest reported series of patients (n = 22) undergoing LPN for a tumor in a solitary kidney mean warm ischemia time was 29 minutes (Gill et al, 2006). Two patients (9%) were electively converted to open surgery. Median pre- and postoperative serum creatinine (1.2 and 1.5 mg/dL, respectively) and estimated glomerular flow rate (eGFR) (67.5 and 50 mL/min/1.73 m^2, respectively) reflected changes of 33% and 27%, respectively, which correlates with approximately 25% nephron volume loss. One kidney was lost due to hemorrhage. The authors concluded that LPN for tumor in a solitary kidney was feasible.

Multiple Tumors

Increasingly, nephron-sparing surgery (NSS) is the preferred treatment for patients with multiple, small ipsilateral tumors, due to the potential for contralateral recurrence. LPN has been applied in this clinical setting as well. Steinberg and colleagues (2004) published their experience in 13 patients (92% of patients had an imperative indication for nephron preservation) undergoing laparoscopic NSS for two or more ipsilateral renal tumors. LPN was performed in six patients either by itself, or in conjunction with cryotherapy. At a mean follow-up of 16.4 months (range 1 to 54), no ipsilateral recurrences were noted. When performing LPN for multiple tumors, depending upon their geographic proximity, tumor excision can be performed either en bloc or individually. With the short-term oncologic outcome data available to date, LPN, when judiciously combined with cryotherapy, can provide

clearance of the ipsilateral tumor burden, while keeping ischemia time to a minimum.

Cystic Tumors

LPN for radiographically suspicious cystic tumors is technically more challenging due to the potential for inadvertent cyst rupture and tumor spillage. Spaliviero and colleagues (2005) compared 50 patients undergoing LPN for a cystic renal lesion with 50 consecutive patients undergoing LPN for a solid renal mass. LPN was successful in all cases, and intraoperative complications were similar in the two groups. All surgical margins were negative. However, one patient in the cystic tumor group developed retroperitoneal recurrence at 1 year, despite an unremarkable intraoperative course and negative histological margins. The authors concluded that extreme caution and careful technique is necessary to avoid inadvertent cyst rupture and local tumor spillage.

Other Indications

LPN has also been performed in the following unique clinical settings: adrenal involvement from an upper pole tumor requiring excision with concomitant adrenalectomy (Ramani et al, 2003), repair of concomitant renal artery disease (Steinberg et al, 2003), tumor in congenitally anomalous kidney, such as horseshoe kidney (Tsivian et al, 2007), in obese patients (Romero et al, 2008), and after prior ipsilateral renal surgery (Turna et al, 2008).

Procedure

Technical Issues

The principal technical challenge during LPN stems from the complexity of laparoscopic tumor excision and sutured renal reconstruction in a time-sensitive manner. **The primary objectives are to complete tumor excision with negative margins, obtain hemostasis, and minimize warm ischemia time.** Successful LPN for complex tumors requires an in-depth understanding of 3D renal anatomy, real-time appreciation of visual cues during laparoscopy, and facility with precise and relatively efficient suturing.

Transperitoneal LPN

The transperitoneal approach offers many features that are crucial for performance of advanced LPN: larger working space, more familiar landmarks, greater versatility of instrument angles, and technical ease of suturing. The initial portion of the procedure is performed as previously described for transperitoneal LRN.

Tumor Localization and Excision

Once the initial dissection is complete, including isolation of the hilar vessels, intraoperative ultrasonography is used to confirm location, width, and depth of the tumor (Fig. 55–36). Ultrasonography may also be used to confirm absence of additional lesions in the kidney. The Gerota fascia is entered away from the lesion to expose the renal capsule. Using the monopolar scissor, the capsule is scored circumferentially around the tumor (Fig. 55–37), and the hilum is then clamped using laparoscopic bulldog clamps (Fig. 55–38). The scored line may then be incised using cold shears (Fig. 55–39), and with the assistance of a suction-irrigator device to provide both countertraction and a clear operative field, the tumor excision is completed. In some patients, adherent fat will necessitate a subcapsular dissection to identify the visual borders of the tumor.

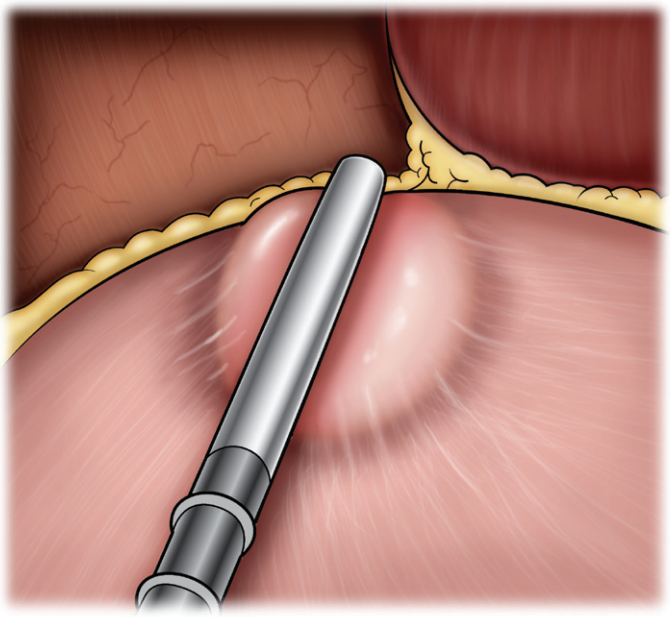


Figure 55–36. Intraoperative ultrasonography is used to confirm location, width, and depth of the tumor.

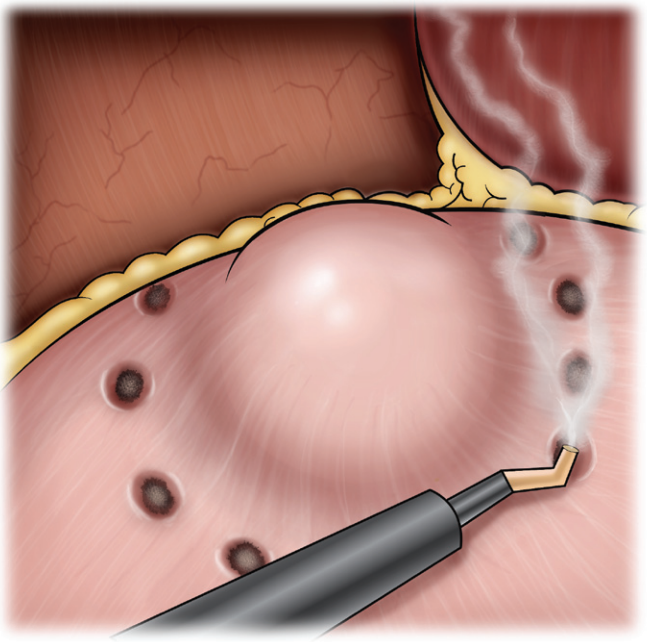


Figure 55–37. After Gerota fascia is cleared to expose the lesion and the renal capsule. Using the monopolar scissor or hook cautery, the capsule is scored circumferentially around the tumor.

Hemostasis

Achieving hemostasis is very important during LPN. Several strategies have been advocated for this purpose. The most widely employed technique to achieve hemostasis of the partial nephrectomy bed is by primarily using freehand laparoscopic suturing with or without adjunctive biologic hemostatic/sealant agents, or a Surgicel bolster (Johnson and Johnson, New Brunswick, NJ) (Fig. 55–40). Alternatively, surgical clips can be used while coming across the surface of the parenchyma. A number of tissue sealants

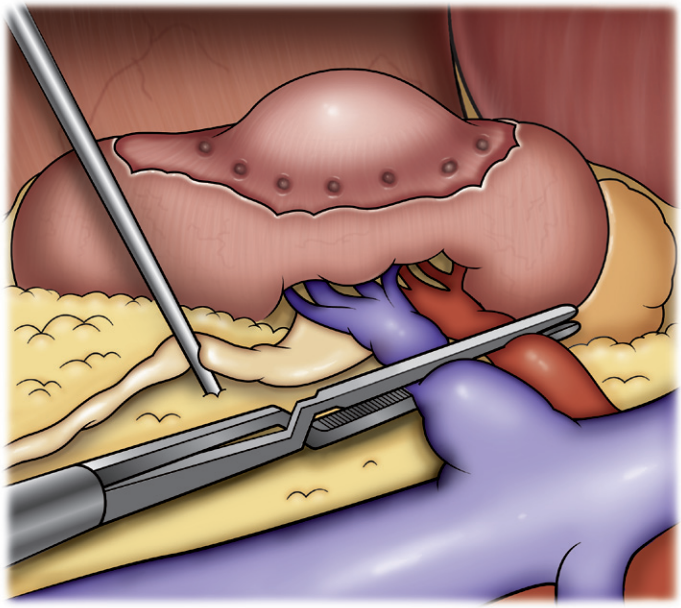


Figure 55–38. Once the margin around the tumor has been scored, the hilum is clamped either en bloc using a laparoscopic Satinsky clamp, or the artery and vein are clamped separately using bulldog clamps.

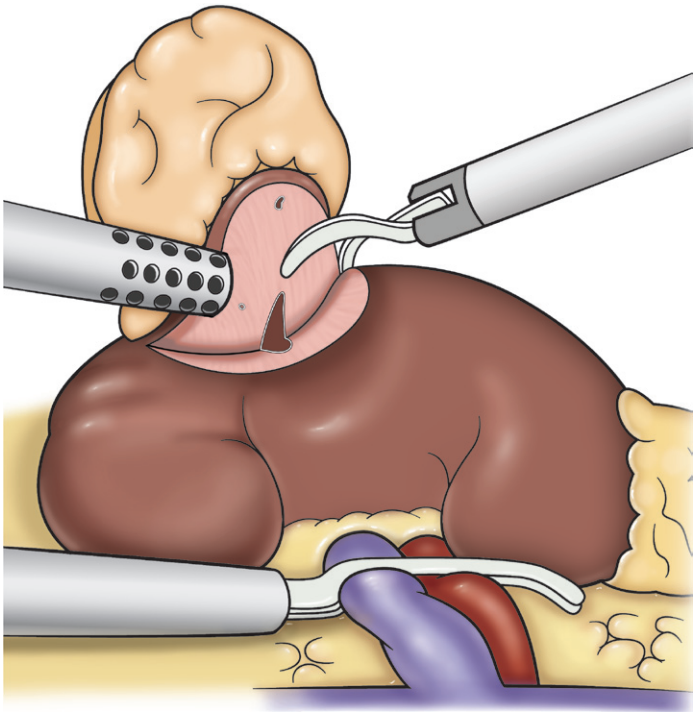


Figure 55–39. The scored margin around the tumor is incised using cold shears with the renal hilum clamped. The suction-irrigator provides both countertraction and helps to maintain a clear operative field and adequate margin of normal renal tissue.

are available: gelatin matrix thrombin sealant (Floseal; Baxter, Deerfield, IL), fibrin glue (Tisseel; Baxter), polyethylene glycol hydrogel (Coseal; Baxter), cyanoacrylate glue (Dermabond; Ethicon, Somerville, NJ), and Bioglue (CryoLife, Atlanta, GA).

During LPN for selected small, superficial, exophytic tumors, various thermal (radiofrequency, microwave, ultrasonic) and novel alternative (laser, water-jet) energy sources have been employed for hemostasis clinically and in the laboratory. Herrell and Levin (2005) evaluated the TissueLink radiofrequency device (TissueLink Medical, Dover, DE) during unclamped LPN in 25 human cases. Fibrin glue was used as a hemostatic adjunct. There were no intraoperative complications. Mean estimated blood loss was 98 mL (range 10 to 337). This device could potentially have a role in unclamped LPN for small, peripheral, and exophytic tumors. Lasers have been used as an energy source for performing unclamped LPN in the animal model. The potassium-titanyl-phosphate laser (KTP) (GreenLight PVP; Laserscope, San Jose, CA) and the holmium : yttrium aluminum garnet (Ho : YAG) laser have been employed with initial success (Lotan et al, 2004; Hindley et al, 2006; Liu et al, 2006). Moinzadeh and colleagues (2005) also evaluated the water-jet device (Helix Hydro-jet; Erbe-USA, Marietta, GA) to perform LPN without renal hilar control in the calf model. They were able to perform 18 of 20 cases without hilar control, with a mean estimated blood loss of 174 mL. Further technological improvements are necessary to achieve reliable hemostasis using these technologies.

Hilar Control

Select superficial, exophytic, noninfiltrating tumors can be excised during LPN without hilar clamping. However, tumors that are larger, deeper, central, or hilar require a substantial LPN, necessitating transient hilar clamping to provide a bloodless operative field. Guillonneau and colleagues (2003) compared LPN with (n = 12) and without (n = 16) hilar clamping using ultrasonic shears and bipolar cautery. The authors concluded that hilar clamping provided decreased blood loss, shorter operating time, and superior surgical performance. From a technical standpoint, hilar control can be achieved by using bulldog clamps individually on the renal artery and vein, or by using a Satinsky clamp across both vessels to achieve en bloc hilar clamping.

Renal hypothermia

Three techniques have been described for laparoscopic renal hypothermia: surface cooling with ice slush, instillation of cold saline through a retrograde ureteral catheter, and intra-arterial perfusion of cold saline or lactated Ringer solution (Gill et al, 2003; Landman et al, 2003; Janetschek et al, 2004). Although all of these techniques are clinically feasible and reasonably effective, they are rarely employed during clinical LPN. This is not only because of their complexity, but also because the majority of tumors subjected to LPN do not currently require an inordinately long period of warm ischemia.

Collecting System Repair

Central tumors abutting the renal sinus fat and collecting system may require deliberate entry into the pelvicalyceal system (PCS) to ensure negative surgical margins during tumor excision. For this reason, PCS entry is a common occurrence in contemporary LPN practice. Retrograde injection of dilute indigo carmine through a 5-Fr ureteral catheter inserted into the renal pelvis can be used to help identify the site of PCS entry and confirm repair. Prospective comparison of perioperative outcomes in 27 LPN with pelvicalyceal entry to 37 LPN with no pelvicalyceal entry (Desai et al, 2003) revealed similar operating room (OR) time, tumor excision time, and blood loss. However, PCS suture repair was associated with a somewhat longer warm ischemia time and hospital stay. None of the patients undergoing PCS suture repair developed a urinary leak. The results of this early study showed that intentional entry into the PCS system for central tumors could be safely and effectively repaired (Fig. 55–41). Suture repair of the PCS with a running

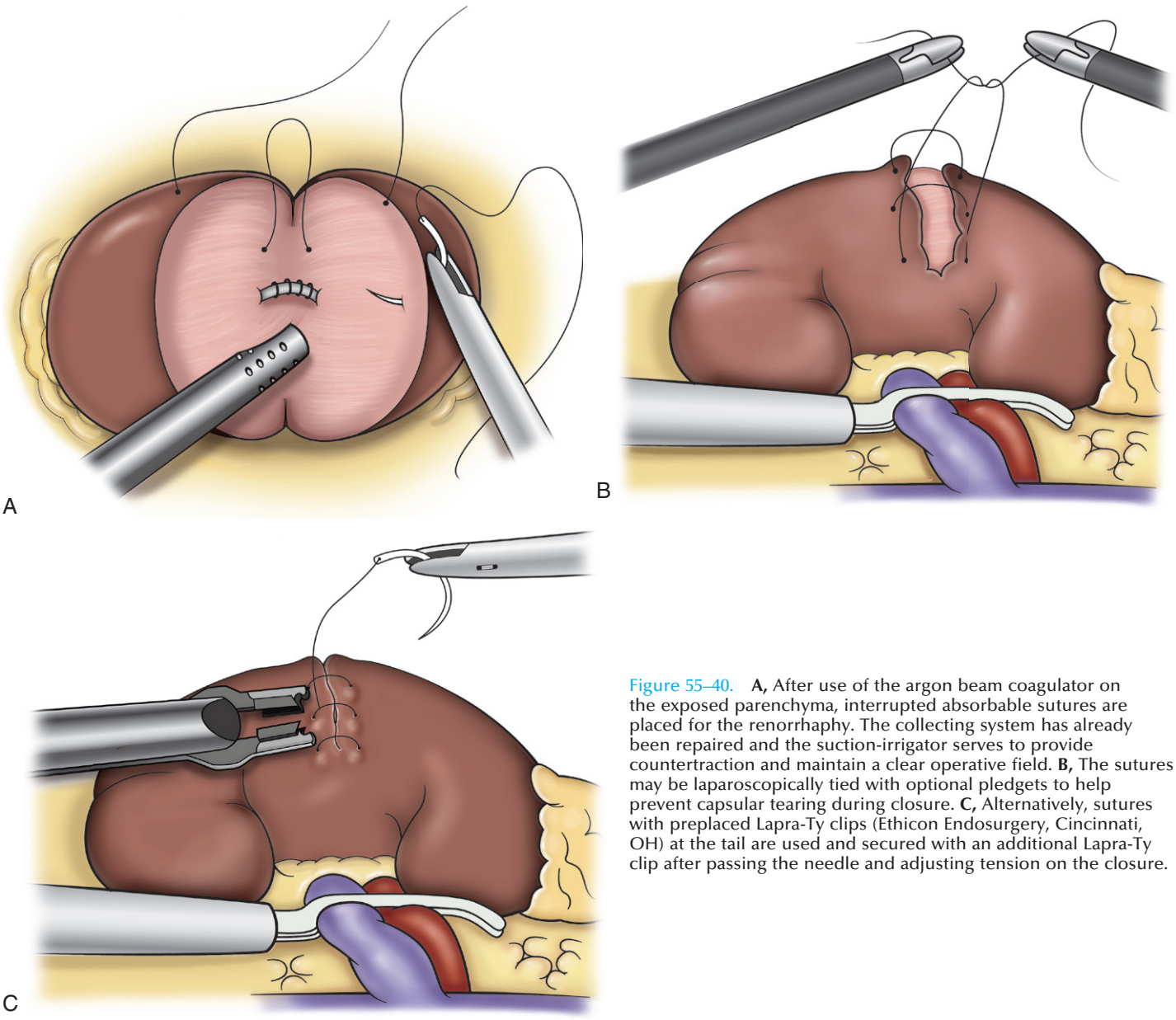


Figure 55–40. **A,** After use of the argon beam coagulator on the exposed parenchyma, interrupted absorbable sutures are placed for the renorrhaphy. The collecting system has already been repaired and the suction-irrigator serves to provide countertraction and maintain a clear operative field. **B,** The sutures may be laparoscopically tied with optional pledgets to help prevent capsular tearing during closure. **C,** Alternatively, sutures with preplaced Lapra-Ty clips (Ethicon Endosurgery, Cincinnati, OH) at the tail are used and secured with an additional Lapra-Ty clip after passing the needle and adjusting tension on the closure.

3-0 polyglactin suture can be accomplished, and the integrity of the repair tested with retrograde injection of dilute methylene blue. Alternatively, one may close the renal capsule over the defect. In either case, a drain should be placed for postoperative monitoring.

Retroperitoneal LPN

Although most LPN surgeons prefer the transperitoneal approach for most tumors, some employ the retroperitoneal approach, which has advantages for select posteriorly located upper pole apical tumors. After entry into the retroperitoneum and establishment of a working space as previously described, the kidney may be lifted anteriorly off the psoas muscle to allow visualization of the arterial pulsation. The dissection of the renal hilum can then proceed to facilitate bulldog clamp placement when deemed necessary. Tumor localization and excision, hemostatic control, collecting system repair, and renorraphy are performed as described for the transperitoneal approach. In a comparison of 32 retroperitoneal with 19 transperitoneal LPN, choice of approach was based on tumor location (Wright and Porter, 2005). The retroperitoneal approach was associated with shorter operating time, decreased blood loss, quicker return of bowel function, and shorter hospitalization. These authors preferred the retroperitoneal approach for polar and posterolateral masses, while the transperitoneal approach was preferred for anterior and medial lesions. Another comparison of 100 transperitoneal with 63 retroperitoneal LPN demonstrated that blood loss, perioperative complications, postoperative serum creatinine, analgesic requirements, and histological outcomes were comparable in the two groups (Ng et al, 2005). As such, the choice of LPN approach is dictated primarily by surgeon experience and tumor location. Other factors include tumor size, number of tumors, number of arteries supplying the kidney, amount of visceral fat surrounding the kidney, and route

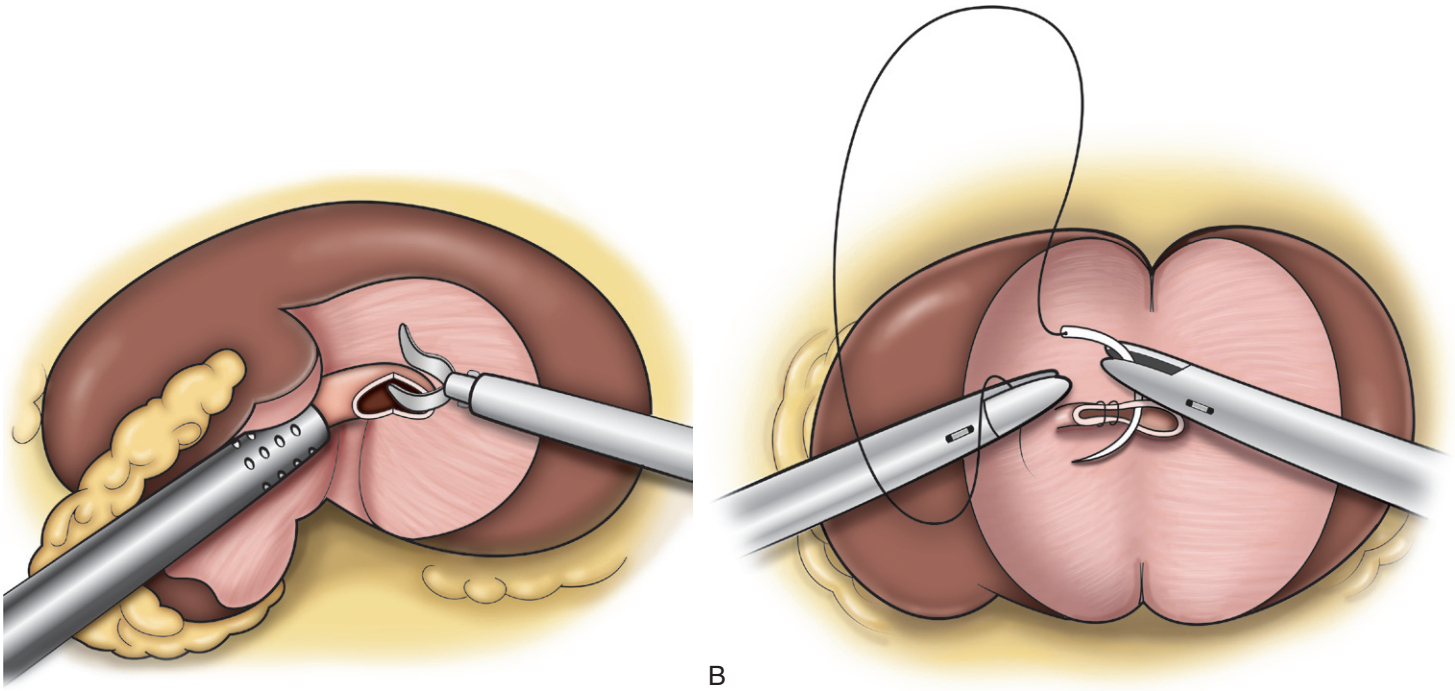


Figure 55–41. **A,** When deep resection is required, the collecting system will often be transected. With occlusion of the renal vessels, these defects can easily be identified and closed using absorbable sutures. The cut edge of the collecting system is identified with the tip of the needle and elevated. **B,** An interrupted figure-of-eight suture or running suture is used to completely close the collecting system. The integrity of the repair can be determined by intravenous indigo carmine administration or retrograde instillation, if a ureteral catheter was placed at the beginning of the case. Care must be taken not to destroy the suture, if argon beam coagulation of the parenchyma surface will be performed.

of any prior open surgery on the quadrant of interest. The transperitoneal approach for all renal tumors is usually easier, except those that are located posteriorly or posteromedially on the upper pole.

Early Unclamping LPN Technique

The standard LPN technique involves en bloc hilar clamping of the renal artery and vein followed by cold endoshear excision of the tumor with adequate margins. Control of transected intrarenal blood vessels and pelvicalyceal repair are obtained with an initial, central, running suture. Subsequent parenchymal reconstruction involves parenchymal mattress sutures tied over a bolster, with adjunctive use of biologic hemostatic agent. Thus the entire renal repair is performed in the ischemic kidney, with the hilar vessels clamped.

More recently, an early unclamping technique has been developed in an attempt to decrease ischemia time (Nguyen and Gill, 2008). In this technique, the renal hilum is clamped only for the duration of tumor excision and placement of the initial, central, running suture. In conjunction with suturing, clips are used selectively for preemptive control of the larger intrarenal blood vessels before transection. The hilum is then unclamped, reperfusing the kidney. All subsequent suturing in the partial nephrectomy bed to ensure parenchymal hemostasis and pelvicalyceal repair is now performed in the perfused, revasularized kidney. This includes specific figure-of-eight sutures to control any remaining active arterial and/or venous bleeding sites. Horizontal mattress sutures are also placed, if indicated, to undersew various clips, thereby excluding them from immediate proximity to the underlying pelvicalyceal system. If desired, the partial nephrectomy bed can be covered with biologic, hemostatic, or adhesive agents. Given that this technique allows hemostasis to be visually confirmed in the perfused kidney, the compression bolster is rarely used in contemporary practice. The benefits of early unclamping are twofold: (1) it decreases ischemia time, and (2) it leads to decreased incidence of postoperative hemorrhage.

Robotic-Assisted Partial Nephrectomy

Robotic-assisted PN (RaPN) is being explored at several centers with the aim of facilitating the precise intracorporeal suturing necessary during LPN. In its early days, RaPN remains a procedure in evolution (Gettman et al, 2004; Caruso et al, 2006; Kaul et al, 2007; Rogers et al, 2008).

The responsibilities of the table-side assistant include clamping the renal hilum, providing suction and retraction to maintain a clean operative field, delivery and cutting of sutures, and clip placement as needed. The console-side surgeon performs tumor excision, hemostatic suturing, and pelvicalyceal and parenchymal suture reconstruction robotically. Upon completion of renal reconstruction, the hilum is unclamped, and additional parenchymal sutures are placed, as needed, to ensure hemostasis. The robot is undocked and laparoscopic exit completed. The early unclamping LPN technique may be easily adapted for use during RaPN with good success.

Since 2004, several centers have reported initial experiences with RaPN (Gettman et al, 2004; Caruso et al, 2006; Kaul et al, 2007; Rogers et al, 2007). As such, the technical feasibility of RaPN has been established. More recently, initial data comparing outcomes with LPN have become available in a matched-pair analysis comparing RaPN and LPN (Aron et al, 2008). Patients were matched for age, gender, body mass index (BMI), ASA score, tumor side, tumor size, tumor location, and specific technique employed (early vs. conventional unclamping). Perioperative outcomes were

similar between the RaPN and LPN cohorts with regard to estimated blood loss, warm ischemia time, OR time, and length of stay. Renal functional outcomes, transfusion rate, and complication rates were also comparable. Two RaPN cases required conversion to standard LPN. In a subset analysis of patients undergoing the early unclamping technique, the LPN cohort had a shorter warm ischemia time (14 vs. 21 minutes, $P = .05$), despite larger tumors in the LPN cohort (3 cm vs. 2.4 cm, $P < .01$). The authors concluded that RaPN, an evolving procedure, is technically feasible and safe, albeit with a longer ischemia time compared to LPN in the initial experience. Analysis of a larger number of cases is necessary to determine the relative merits of RaPN. However, it is likely that the growing familiarity of urologists with robotic surgery will facilitate the application of minimally invasive nephron-sparing surgery in a larger cohort of patients. Unfortunately, the robotic approach is associated with increased cost and cosmetic inferiority due to the need for additional access ports.

WARM ISCHEMIA

The limit of safe renal warm ischemia time has historically been considered to be 30 minutes. Although supported by canine and anecdotal clinical data, no scientifically rigorous clinical study has defined an ischemic dose-response curve to date. Indeed, recent data suggests that up to 90 minutes may be reasonable (Orvieto et al, 2005). Until this issue is better understood, all efforts should be made to keep warm ischemia time as short as possible. With regard to surgical renal ischemia, various myths abound due to insufficient data.

Pneumoperitoneum

There is ongoing debate regarding the effects of pneumoperitoneum on renal functional outcomes. It has been demonstrated that 20 mm Hg of intraperitoneal pressure can cause decreased renal cortical capillary perfusion, increased renal venous outflow resistance, and transient oliguria in pigs (Shuto et al, 1995). In contrast, a report by Cisek and colleagues (1998) showed that 6 hours of 20-mm Hg pneumoperitoneum in pigs, rendered renally insufficient with prior left nephrectomy and right heminephrectomy, had no long-term impact on renal function. The debate regarding the negative impact of pneumoperitoneum remains unresolved; however, these studies suggest that when applied for less than 6 hours in patients with normal preoperative renal function, its ultimate impact is likely negligible and reversible. There is general consensus, however, that pneumoperitoneum during laparoscopic surgery should not be maintained with sustained pressures of greater than 20 mm Hg. Attempts at completely eliminating potential effects of pneumoperitoneum on the kidney have also been reported with donor nephrectomy using gasless laparoscopy (Watanabe et al, 2002), but it is unclear whether there are any long-term benefits of this approach.

Renal Artery-Only versus Artery-Plus-Vein Clamping

It is theorized that artery-only clamping during partial nephrectomy would allow retrograde venous blood flow with potentially partial oxygenation to the renal parenchyma. In a solitary kidney pig model, Orvieto and associates (2007) found that artery-only clamping resulted in lower serum creatinine rises, during postoperative days 1 to 3, than in animals that underwent complete hilar occlusion. Interestingly, this effect was not observed in animals that underwent laparoscopic surgery. It was concluded that artery-only clamping provided immediate postoperative benefit, and that this benefit was likely offset by pneumoperitoneum-induced venous compression during laparoscopy. In contrast, the same group found a benefit to artery-only clamping in a case-control study of patients undergoing LPN with artery-only ($n = 25$) versus simultaneous clamping of the artery and vein ($n = 53$) (Gong et al, 2008). A significant decrease in serum creatinine and creatinine clearance was observed in those patients undergoing simultaneous clamping of the artery and vein compared to preoperative levels. This effect was not observed in those undergoing artery-only clamping. Additionally, there were no statistically significant differences observed in either blood loss or positive margin rate between the groups. These findings need validation in larger patient cohorts. From a practical standpoint, leaving the renal vein unclamped can lead to increased intraoperative renal parenchymal bleeding, which can obscure the surgical field, leading to increased blood loss and prolonged ischemia time. In the majority of partial nephrectomy cases at the authors' institutions, both the renal artery and vein are clamped routinely to achieve vascular control and optimize visualization during tumor excision and renorrhaphy.

Manual Compression of Renal Parenchyma versus Vascular Clamping

Some advocate the use of manual compression of the kidney during tumor excision and renorrhaphy, while others contend that vascular clamping is preferable. Manual compression can be effective for small exophytic tumors, although the renal vasculature should always be accessible to allow emergent clamping in the case of hemorrhage. No controlled clinical study examining this issue has been conducted. Issues to consider include the possibility of tissue trauma due to excessive compression, and the limitation of this approach to peripheral tumors during open and hand-assisted laparoscopic procedures only. Manual compression techniques would not be feasible in partial nephrectomy of central, hilar, or large tumors, or for pure laparoscopic surgery.

Intermittent versus Continuous Clamping

Controversy exists regarding the possible deleterious effects of intermittent perfusion by sequential clamping and unclamping during partial nephrectomy. Intermittent ischemic "preconditioning" has been extensively studied as a method for protecting against ischemic organ injury, especially in liver surgery (Centurion et al, 2007; Saidi et al, 2007). Wilson and colleagues (1971) compared renal function in canine kidneys subjected to intermittent versus continuous occlusion for 1 to 2 hours. Occlusion and reperfusion times were 15 minutes and 3 minutes, respectively, repeated for 2 hours of occlusion time. In subjects with intermittent occlusion, GFR was significantly decreased after 7 days compared with continuous occlusion subjects. Contrary to these findings, Frank and colleagues (1993) found that rats undergoing cycled occlusion-reperfusion (15 minutes occlusion followed by 5 minutes reperfusion) for 45 minutes had lower serum creatinine levels and decreased pathologic evidence of tubular

injury at 3 days compared with the continuous occlusion subjects. Another study confirmed a protective effect of intermittent ischemic preconditioning in rats, and established the optimal occlusion and reperfusion intervals at 15 and 10 minutes, respectively (Wu et al, 2009). It is possible that species differences may account for discrepancies within the literature. No clinical trials of renal ischemic preconditioning have been conducted; only anecdotal reports guide practice. Because of insufficient and conflicting data regarding intermittent clamping, ischemic preconditioning is not recommended.

Parenchymal Clamping

Several authors have published their initial experiences in a small number of patients using techniques of parenchymal clamping in selected patients with peripheral renal cortical tumors (Verhoest et al, 2007; Simon et al, 2009). Use of a parenchymal clamp can allow the surgeon to induce ischemia only in the immediate area surrounding the tumor. All patients in these two studies had negative surgical margins, and no changes in renal function were reported. The potential benefits of this technique are multiple: It facilitates a bloodless operative field in the area of the tumor; the majority of the normal parenchyma is spared from ischemic injury; and the time-sensitivity of tumor excision and renorrhaphy is markedly reduced. However, the limitation of the technique is that only selected patients with peripherally located tumors are candidates. Larger numbers of patients are necessary to validate this technique, but due to the reduction in time sensitivity, parenchymal clamping may allow a larger cohort of surgeons to perform LPN with increased confidence.

Solitary Kidney May Be "More Tolerant" to Ischemic Injury

It is known that contralateral normally-functioning kidneys will hypertrophy to compensate for decreased function after unilateral nephrectomy. The extent of this response has been shown to be species- and age-dependent (Funahashi et al, 2009). Fried and colleagues (1984) studied functional recovery in rats with or without nephrectomy 2 weeks before a 40-minute ischemic insult. Nephrectomized rats demonstrated improved inulin clearance at 48 hours compared with non-nephrectomized controls. In contrast, Stackl and colleagues (1983) failed to show a difference in renal blood flow (RBF) or GFR in rabbits with or without preischemic nephrectomy. For obvious reasons, a human clinical study of this effect is impossible. Clinical anecdotal evidence points to the possibility that solitary kidneys may be more resistant to ischemic injury. It is plausible that some aspect of this increased tolerance to ischemic injury is attributable to the increased intraoperative vigilance and postoperative support measures taken in this high-risk patient cohort.

LAPAROSCOPIC PARTIAL NEPHRECTOMY: CONTEMPORARY OUTCOMES

An 1800-patient retrospective multi-institutional study compared a mature series of 1029 OPN cases with the initial LPN cases for solitary T1 tumors less than or equal to 7cm (Gill et al, 2007). Tumors in the OPN group were larger (3.3 vs. 2.6 cm), and more often located centrally (53% vs. 34%) or in a solitary kidney ($P < .001$ for all comparisons). LPN had less blood loss, and shorter operative time, hospital stay, and convalescence ($P < .001$ for all comparisons). Overall postoperative complications (25% vs. 19%) and conversion to radical nephrectomy (1% vs. 0%) were somewhat greater in the LPN group. Importantly, LPN and OPN were similar with regard to intraoperative complications (1.8% vs. 1%), positive surgical margins for cancer (1.6% versus 1%), 3-year oncological outcomes, and 3-year renal functional outcomes. However, LPN had a 10-minute longer ischemia time (30 vs. 20 minutes), and somewhat higher postoperative hemorrhage (4.2% vs. 2%) and reintervention rate.

With increasing LPN experience and standardization of the early unclamping technique, contemporary LPN outcomes have improved significantly. Specifically, the two remaining concerns for higher postoperative hemorrhage and longer ischemia time with LPN have now been addressed, leading to significantly decreased ischemia time and reduced occurrence of post-operative hemorrhage. The initial report of the early unclamping technique in LPN has decreased ischemia to a mean of 13.9 minutes (55% reduction), and reduced postoperative hemorrhage rate to 2% (Nguyen and Gill, 2008).

Gill and colleagues (2010) reported a single-surgeon series of 800 laparoscopic partial nephrectomy (LPN) cases encompassing a 9-year period (1999 to 2008). The authors divided the entire cohort into three chronologic eras: era I: 1999 to 2003 ($n = 276$), era II: 2004 to 2006 ($n = 289$), and era III: 2007 to 2008 ($n = 235$). **On comparing eras I, II, and III, tumors in the most recent era were larger, more commonly greater than or equal to 4 cm and central, and, less often, peripheral and less than 4 cm (*P* value significant for all). Despite such increasing tumor complexity, mean warm ischemia times were shorter in the most recent era: 32 minutes, 32 minutes, and 14 minutes, respectively, ($P < .0001$). Also, overall, postoperative and urologic complications were significantly lower in the most recent era. Finally, renal functional outcomes were superior in era III, as documented by lesser percent decreases in estimated GFR (18%, 20%, and 11%, respectively).**

Kamoi and Gill also retrospectively compared 150 contemporary patients undergoing OPN (2006 to 2008) with 150 contemporary patients undergoing LPN (2007 to 2008) (author's unpublished data). Notably, all OPNs were performed by one surgeon experienced with open procedures, and all LPNs were performed by one surgeon experienced with laparoscopy procedures. LPN patients had a shorter ischemia time (21 vs. 13 minutes, $P < .0001$); more LPN patients had ischemia time of less than or equal to 20 minutes (52% vs. 97%); and fewer had an ischemia time greater than 30 minutes (9% vs. 0%; $P < .0001$ for both). Postoperative complications were fewer in the LPN group (19% vs. 8.7%; $P = .01$), including hemorrhage (3.3% vs. 2.7%; $P =$ ns) and urine leak (7.3% vs. 1.3%; $P = .02$). Patients undergoing elective PN had similar outcomes, and those undergoing imperative PN or PN in a solitary kidney had superior renal functional outcomes in the LPN cohort, probably because of the reduced ischemic insult during LPN. A recent study compared 86 off-clamp LPN with traditional clamped LPN (Herati et al, submitted). Significant differences ($P < .05$) in the off-clamp group relative to the on-clamp group included shorter operative time (132 vs. 146 minutes), a higher proportion of exophytic lesions (51% vs. 28%), smaller tumor volume (26 vs. 41 cm^3), and fewer hilar tumors (15% vs. 29%). Short-term elevation in serum creatinine was significantly

less (6% vs. 29%) although long-term significance of this finding is unknown. There were no significant differences in blood loss, transfusion rate, or complications. As experience improves, an increasing number of procedures may be performed off clamp.

These new data indicate that, despite increasing tumor complexity, three key outcomes of contemporary LPN (ischemia time, complications, and renal function) have improved significantly and now approach outcomes of open partial nephrectomy.

Positive Surgical Margin

The clinical significance of a pathologic positive surgical margin after partial nephrectomy, whether laparoscopic or open, has prompted several studies evaluating outcomes specifically in these patients. In a group of 1344 patients undergoing open partial nephrectomy, positive surgical margins were noted in 77 cases (5.5%) (Yossepowitch et al, 2008). The 10-year probability of freedom from local recurrence and progression to metastatic disease was 93% for both. There were no significant differences noted between those with positive and negative margins. Several laparoscopic surgeons have reported similar results. Of 511 patients undergoing LPN for renal cell carcinoma, 9 patients (1.8%) had a positive surgical margin (Permpongkosol et al, 2006a). Two underwent completion nephrectomy with no evidence of residual tumor, one patient with von Hippel-Lindau disease died of metastatic disease at 10 months, and six patients were observed to have no evidence of recurrence at mean follow-up of 32 months. **Although these data demonstrate that many patients with pathologically positive margins may be observed, negative surgical margins should always be the goal in any oncologic procedure.**

Long-Term Outcomes

Long-term data on LPN are now available (Table 55–4), and appear similar to open partial nephrectomy (OPN). **Five-year cancer-specific survival after LPN is 100%** (Lane et al, 2007). Most recently, a retrospective comparative study of 7-year outcomes compared 77 patients undergoing LPN with 310 patients undergoing open partial nephrectomy (OPN) for single clinical stage T1 (≤7 cm) tumors between 1999 and 2001 (Lane and Gill, 2010). Cancer recurred infrequently, and only rarely caused mortality, after either LPN or OPN. At 7 years, metastasis-free survival was 97.5% and 97.3% ($P = 0.47$) after LPN and OPN, respectively. After accounting for baseline differences between the cohorts, using propensity score–matching, 7-year metastasis-free survival was similar after LPN and OPN. On multivariate analysis, predictors of all-cause mortality included advancing age ($P < .0001$), comorbidity ($P < .0001$), preoperative renal dysfunction ($P = .0001$), but not tumor size ($P = .6$) or operative approach (LPN vs. OPN, $P = .06$). **The authors concluded that LPN and OPN provide similarly excellent long-term overall and cancer-specific survival, with the vast majority (97%) of patients experiencing metastasis-free survival.**

In experienced hands, LPN now is equivalent to OPN, with shorter ischemia times, and equivalent complication rates and renal functional outcomes. As a result, several centers routinely offer LPN for the majority of tumors (Permpongkosol et al, 2006b; Kamoi et al, submitted). These include technically challenging SRMs, including tumors which are hilar, central, completely intrarenal, larger (4 to 7 cm, pT1b) or located in a solitary kidney (Turna et al, 2008).

LAPAROSCOPIC ABLATIVE TECHNIQUES

As the incidence of the small renal mass has increased with the prevalence of cross-sectional imaging, a stage migration has occurred such that a rising number of patients are presenting with low-stage disease. Although the standard of care for these lesions remains surgical excision, due to cancer-specific survival rates in excess of 95% (Frank et al, 2005; Lane et al, 2007), cryoablation and radiofrequency ablation (RFA) have emerged as alternative treatment options for patients with a small renal mass. High-intensity focused ultrasonography, microwave therapy, and high-intensity radiation have also been investigated. The primary goals of these techniques are complete tumor destruction while minimizing morbidity. The potential advantages include less blood loss, less dissection, and fewer complications. Indications are similar for all of the ablative technologies and include lesions in patients with significant comorbidities, solitary kidneys, and hereditary renal cell carcinoma. The percutaneous approach is preferred for treatment of small renal masses due to its lower morbidity, but in some instances may not be possible due to tumor location or proximity to adjacent organs. For these reasons, laparoscopy is required for direct visualization and manipulation to make treatment delivery feasible. As cryoablation and RFA are the most prevalent in clinical applications, these ablative techniques will be discussed here in further detail.

Cryoablation

Laparoscopic cryoablation may be delivered using either a transperitoneal or retroperitoneal approach, with the decision resting primarily on tumor location. The kidney is mobilized using a three-port technique, and Gerota fascia is opened in a manner similar to that employed for LPN. The fat overlying the tumor may be excised and placed in a specimen bag for extraction and pathologic analysis. Biopsy samples of the tumor itself may also be taken with a 14- or 18-gauge biopsy needle for pathologic diagnosis. Placement of the cryoablation probes into the tumor can be performed percutaneously, leaving the ports free for instrumentation. Direct visualization of probe placement and depth of placement are confirmed with the laparoscope and intraoperative ultrasonography, respectively. Number and spacing of probes is dictated by probe-specific ablative diameter, and they should be positioned to ensure cryolesion overlap, typically parallel to one another in a triangular or quadratic configuration. The tip of the probes should be advanced just beyond the deepest margin of the tumor.

Cryoablation is believed to work by two distinct mechanisms: at the cellular level by intracellular ice formation and solute damage, and at the vascular level, secondary to thrombosis and subsequent coagulative and ischemic necrosis. It uses thin probes cooled with compressed gas, such as argon or carbon dioxide, to achieve very low temperatures. Tissue destruction and necrosis occur consistently at temperatures at or below –19.4° C and temperatures of –20° C are achieved 3.1 mm inside of the leading edge of a 3.2-cm iceball (Campbell et al, 1998; Chosy et al, 1998). Typically, an active double freeze-thaw cycle is used to enhance tumor destruction (Gill et al, 1998; Nakada et al, 1998). Clamping of the renal artery during freezing, to theoretically avoid the heat-sink effect of renal blood flow, has been shown to make no difference in the freezing effect (Orihuela et al, 1999).

Table 55–4.

Oncologic Outcomes of Laparoscopic Partial Nephrectomy

A. Comparative Series Analyzing Laparoscopic and Open Partial Nephrectomy

AUTHOR	APPROACH	TOTAL NO. OF PATIENTS	NO. PATIENTS WITH RCC	MEAN AGE AT SURGERY	MEAN TUMOR SIZE	PATIENTS WITH FUHRMAN GRADE 3 OR 4	MEDIAN FOLLOW-UP	NO. POSITIVE MARGINS (RATE)	LOCAL RECURRENCE	PROGRESSION TO METASTATIC DISEASE	MEAN TIME TO RECURRENCE OR METASTASIS	CANCER-SPECIFIC DEATHS	5-YEAR RECURRENCE-FREE/CANCER-SPECIFIC/OVERALL SURVIVAL
Permpongkosol et al, 2006	Laparoscopic	85	85	58.2 yr	2.4 cm	17.6%	40.5 mo (mean)	2 (2.35%)	2 (2.35%)	1 (1.18%)	31.1 mo	1	91.4%/NR/93.8%
	Open	58	58	57 yr	2.9 cm	6.7%	49.7 mo (mean)	1 (1.72%)	1 (1.72%)	1 (1.72%)	43.3 mo	0	97.6%/NR/95.8%
Gill et al, 2007	Laparoscopic	771	554	59.4 yr	2.7 cm	28.9%	14.4 mo	12 (1.6%)	1.4%	0.9%	NR	NR	97.7%/99.3%/NR (3-year)
	Open	1028	853	61.6 yr	3.5 cm	34.0%	33.6 mo	10 (1.0%)	1.5%	2.1%	NR	NR	96.4%/99.2%/NR (3-year)
Marszalek et al, 2009	Laparoscopic	100	81	62.3 yr	2.8 cm	NR	43.2 mo (mean)	4.0%	2 (2.4)%	1 (1.2%)	NR	NR	96.2%/NR/96%
	Open	100	66	62.5 yr	2.9 cm	NR	42 mo (mean)	2.0%	1 (1.5%)	3 (4.5%)	NR	NR	94.5%/NR/85%

B. Noncomparative Series of Laparoscopic Partial Nephrectomy for Malignancy

AUTHOR	TOTAL NO. OF PATIENTS	NO. PATIENTS WITH RCC	MEAN AGE AT SURGERY	MEAN TUMOR SIZE	MEDIAN FOLLOW-UP	PATIENTS WITH FUHRMAN GRADE 3 OR 4	POSITIVE MARGIN RATE	LOCAL RECURRENCE	PROGRESSION TO METASTATIC DISEASE	MEAN TIME TO RECURRENCE OR METASTASIS	CANCER-SPECIFIC DEATHS	5-YEAR RECURRENCE-FREE/CANCER-SPECIFIC/OVERALL SURVIVAL
Allaf et al, 2004	48	48	59.7 yr	2.4 cm	37.7 mo (mean)	20.8%	1 (2.1%)	2 (4.2%)	0 (0%)	32 mo	0	—
Moinzadeh et al, 2006	100	68	65 yr	3.1 cm	42 mo	23.5%	1 (1.5%)	0 (0%)	0 (0%)	NA	0	100%/100%/86%
Lane et al, 2007	58	37	64 yr	2.9 cm	68.4 mo	NR	1 (2.7%)	1 (2.7%)	0 (0%)	12 mo	0	97.3%/100%/86%
Pyo et al, 2008	110	70	62 yr	2.4 cm	23.4 mo (mean)	16.5%	0 (0%)	1 (2.1%)	0 (0%)	12 mo	0	—
Gill et al, 2010	800	594	59.5 yr	3.1 cm	36 mo	19.5%	6 (1.0%)	NR	NR	NR	NR	97.8%/99%/92.5%

NR, not reported; RCC, renal cell carcinoma.

The progress of the ice-ball formation may be monitored in real time using intraoperative ultrasonography, and the iceball should extend approximately 1 cm beyond the edge of the tumor. Keeping in mind that the progress of the iceball cannot be abruptly stopped, caution should be exercised to avoid contact of the iceball with the renal collecting system, ureter, renal vasculature, or adjacent organs. After the freeze-thaw cycles are complete, the probes are removed with a gentle twisting motion. If any bleeding occurs, it can usually be controlled by applying pressure, or, if necessary, hemostatic agents such as fibrin glue or Floseal.

Radiofrequency Ablation

Similar to cryoablation, RFA may be administered laparoscopically using either a transperitoneal or retroperitoneal approach. After ultrasound confirmation of tumor location and size, the RFA probe is introduced into the tumor, and the tines are deployed to a diameter that ensures ablation of the tumor and a 1-cm margin of normal renal tissue. The size of the thermal lesion is determined by temperature- or impedance-based monitoring. **The probe uses an alternating current of high-frequency radio waves, causing ion vibration. The resistance in the tissue causes generation of sufficient heat to result in thermal tissue damage—tumor coagulation, protein denaturation, and cell membrane disintegration all occur** (Goldberg et al, 2000; Aron and Gill, 2007). Immediate histopathology after RFA shows hypereosinophila and pyknosis, which is subsequently replaced by coagulative necrosis within days to weeks (Crowley et al, 2001). To achieve these effects, optimal temperatures for ablation range between 60° C and 100° C and avoid tissue vaporization, which may occur at temperatures over 105° C (Goldberg et al, 2000; Crowley et al, 2001).

Unfortunately, unlike cryoablation, real-time ultrasonography cannot be used to monitor the thermal lesion induced by RFA. RFA itself may interfere with ultrasound imaging, and the affected tissue does not have any immediate change in echotexture. Color Doppler ultrasonography has been evaluated during RFA, but does not reliably contribute to monitoring the lesion (Crowley et al, 2001). Although MRI has been used to monitor the changing appearance of ablated lesions at the time of percutaneous treatment (Lewin et al, 2004), there is no current imaging technique that effectively monitors the progress of RFA lesions intraoperatively. Questions have been raised about temperature-based monitoring of the lesion, due to the observation that temperatures measured at the limit of the ablated area are actually 20° C to 30° C cooler than what is measured by the probe thermocouples. A potential solution involves the use of independent temperature probes to monitor temperature at the edge of the desired treatment area (Wingo et al, 2008). This allows a more definitive end point in the ablation cycle. Alternatively, an impedance-based system may be used. Instead of direct temperature measurement, this method relies on tissue impedance; sufficiently desiccated tissue becomes an insulator, and at an impedance level of 200 Ω, further progression of the thermal lesion is unlikely to occur (Lewin et al, 1998).

Imaging Follow-up

While cross-sectional imaging serves as the mainstay to determine treatment efficacy, there is debate about how to interpret the appearance of ablated lesions on postoperative imaging studies. Lack of enhancement on postprocedure CT scan or MRI is generally considered to define success for both cryoablation and RFA. Studies evaluating the appearance of cryolesions by CT or MRI demonstrated that peripheral rim enhancement is a common finding after laparoscopic cryoablation, and not necessarily cause for concern as demonstrated by follow-up percutaneous biopsy of these lesions (Remer et al, 2000; Bolte et al, 2006; Beemster et al, 2008). Cryolesions were generally noted to decrease in size over time, up to 94% at one year (Remer et al, 2000). Nonenhancing infiltrated fat may also be noted in the area overlying the lesion. Findings to elicit cause for concern for residual or recurrent disease were new rim enhancement, internal enhancement, or increase in size of the cryolesion. RFA lesions followed with MRI tend to be hypointense with a surrounding bright rim on T2-weighted imaging, and hyperintense on T1-weighted images. Tumor recurrence by most authors is defined as hyperintense soft tissue signal within the ablation zone, along its margin on T2-weighted images, or in areas of abnormal contrast enhancement within the treated region on the postcontrast images. Over time, RFA lesions also involute, causing a decrease in their size as measured by MRI or CT.

Treatment Outcomes

Several studies have reported promising short-term outcomes of laparoscopic cryoablation (Gill et al, 2000; Cestari et al, 2004). A study of 59 patients undergoing laparoscopic cryoablation, with a median tumor size of 2.5 cm and median follow-up of 26.8 months, documented 2 patients with tumor recurrence (Lawatsch et al, 2006). In a study of 81 patients undergoing laparoscopic cryoablation, 31 were presented with a minimum 3-year follow up (Weld et al, 2007). Biopsy of these lesions demonstrated that 61% were malignant and 39% were benign. Follow-up imaging performed at 1, 3, 6, 12, 24, and 36 months showed one patient who developed return of enhancement that was suspicious for recurrence at 36 months.

A comparison of 66 patients undergoing laparoscopic or percutaneous cryoablation demonstrated equivalent oncologic control at 30-months mean follow-up with no progression to metastasis (Malcolm et al, 2009). However, the percutaneous approach had a significantly higher primary treatment failure rate (25% vs. 3.8%). These patients either underwent salvage treatment or were observed with serial imaging. A similar comparative study of 37 patients with median follow-up of approximately 12 months demonstrated no difference in recurrence (4.2% vs. 5.3%) or need for re-treatment between the laparoscopic and percutaneous groups (Finley et al, 2008).

A multi-institutional study of RFA and cryoablation outcomes in 616 patients demonstrated residual or recurrent disease in 13.4% of patients undergoing RFA and 3.9% of patients undergoing cryoablation (Matin et al, 2006). Overall, 8.7% of patients failed primary therapy, and, after salvage ablative therapy, the failure rate was reduced to 4.2%. The authors noted that the majority of failures were detected after less than 3 months, and that cross-sectional imaging should be obtained 3 to 4 times at spaced intervals for the first year after undergoing treatment. A subsequent meta-analysis of patients undergoing partial nephrectomy, ablative therapies, or observation noted a higher risk of recurrence in patients undergoing cryoablation (RR = 7.45) or RFA (RR = 18.23) when compared with partial nephrectomy (Kunkle et al, 2008). Treatment failure was also linked to tumor size. However, no significant difference in rates of progression to metastatic disease was observed, regardless of treatment modality (Kunkle et al, 2008). Other studies have demonstrated that endophytic status may be linked to treatment failure after laparoscopic cryoablation, perhaps explained by increased difficulty with

ultrasound-guided targeting of the lesion without direct visualization afforded by exophytic lesions (Wright et al, 2007).

Complications

A multi-institutional experience with 148 laparoscopic cryoablation procedures on 144 patients reported a complication rate of 15.5% (Laguna et al, 2009). Significant independent predictors of negative outcomes and complications included tumor size, preexisting cardiac disease, and female gender. Although larger tumor size and cardiac disease would intuitively lead one to predict increased complication rate, the association of female gender is unclear. A second multi-institutional study investigated complications of both percutaneous and laparoscopic cryoablation and radiofrequency ablation of small renal tumors (Johnson et al, 2004). A total of 139 cryoablations were performed along with 133 RF ablations. An overall 11% complication rate was observed with 1.8% classified as major, 9.2% as minor. Major complications included significant hemorrhage, ileus, uteropelvic junction (UPJ) obstruction necessitating nephrectomy, urinoma, conversion to open surgery, and death (aspiration pneumonia). In the laparoscopic group (90 patients), a 9% complication rate was reported, with the most common complication being pain or paresthesia at the ablation probe insertion site.

LAPAROENDOSCOPIC SINGLE-SITE (LESS) SURGERY OF THE KIDNEY

Clinical Experience of Renal LESS Surgery

Initially reported for nephrectomy in the urologic literature (Raman et al, 2007), LESS has now been used to perform a variety of transumbilical procedures. Adjunctive 3-mm subxiphoid ports and 2-mm needlescopic ports have been required in some cases for liver retraction and laparoscopic suturing, respectively. Reported operative times and complication rates have been comparable to traditional laparoscopic approaches.

After gaining substantial experience with LESS techniques, several authors have now reported the use of LESS with more time-sensitive surgeries such as donor nephrectomy and partial nephrectomy. A retrospective comparative study between 17 LESS donor nephrectomies and 17 matched patients undergoing a standard laparoscopic approach has now been reported (Canes et al, 2010). All LESS procedures were completed with the use of a purpose-specific access device; at the discretion of the surgeon, an adjunctive 2-mm needlescopic port was used to aid in retraction, hilar dissection, and extraction (Fig. 55–42). Mean warm ischemia time was longer in the LESS group (3 vs. 6.1 minutes), while blood loss and operative times were similar. The median length of harvested renal artery, vein, and ureter were 3.2 cm, 3.6 cm, and 14.9 cm, respectively, in the LESS cohort; measurements for standard laparoscopy were not reported. Complications included one corneal abrasion and one postoperative allograft thrombosis. A more rapid return to convalescence was noted in the LESS donor nephrectomy group, with fewer days on oral pain medication, faster return to work, and days to "100% recovery" (self determined). LESS Pfannenstiel donor nephrectomy has also been reported and may add to the cosmetic benefit afforded by the single-site approach (Andonian et al, 2009). Prospective studies are certainly needed to determine if this approach is warranted in this patient population.

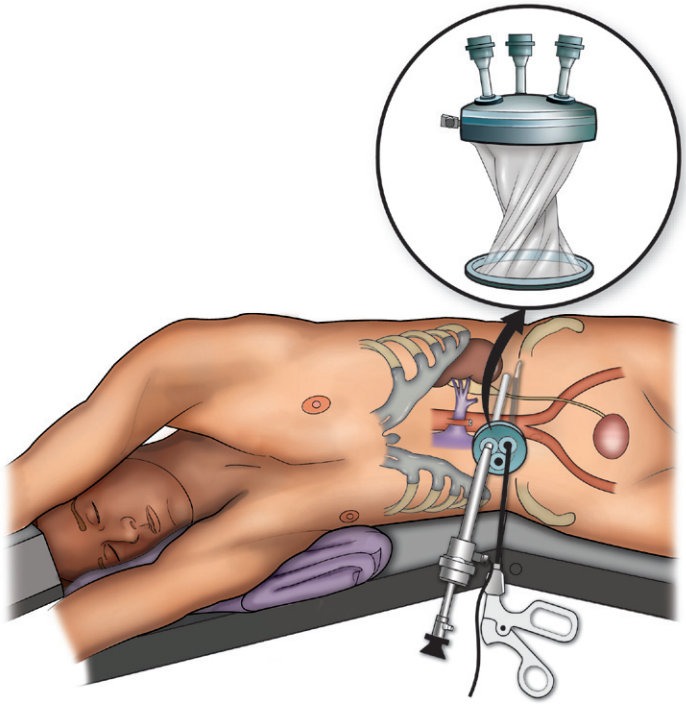


Figure 55–42. Laparoendoscopic single-site surgery donor nephrectomy using a purpose-specific device with multichannel instrument access. A 2-mm instrument is also used to aid in retraction, hilar dissection, and extraction.

An initial series of LESS partial nephrectomy was reported in four patients with a median tumor size of 3-cm (range, 1 to 5.9 cm) (Aron et al, 2009). Median operating time was 270 minutes, and median blood loss was 150 cc. Median warm ischemia time was 20 minutes (range 11 to 29 minutes), and median hospital stay was 3 days. One patient had postoperative hemorrhage and pulmonary embolism.

The two largest LESS series each encompass 100 patients, where LESS has been employed to perform a variety of urologic surgeries (Desai et al, 2009; White et al, 2009). The cases performed have included nephrectomy (simple, partial, radical, and donor), nephroureterectomy, renal cyst excision, renal tumor cryoablation, pyeloplasty, ureteroneocystostomy, ileal ureter, adrenalectomy, hysterectomy, varicocelectomy, radical prostatectomy, transvesical simple prostatectomy, radical cystectomy, sacral colpopexy, and mesh sling removal. These series demonstrate the breadth of urologic procedures that can be performed with LESS techniques.

Raman and colleagues (2009) reported the first comparative study between traditional laparoscopic and LESS applications. The investigators compared 11 LESS nephrectomies with 22 standard laparoscopic nephrectomies. The groups were matched at a 2:1 ratio for patient age, surgical indication, and tumor size. Similar outcomes between the two groups were noted regarding operative time (122 vs. 125 minutes), analgesic use, length of stay, and complication rate.

Robotic LESS (R-LESS) Surgery

The da Vinci-S Robotic System (Intuitive Surgical, Sunnyvale, CA) has been used in conjunction with a Tri-Port single-port access device to perform radical prostatectomy, pyeloplasty, and radical nephrectomy (Kaouk et al, 2009). A 12-mm 3D camera and 5-mm

grasper were placed through the Tri-Port, while an additional 8-mm port was placed alongside the port in the same incision for another robotic instrument. Operative times (radical prostatectomy = 5 hours, pyeloplasty = 4.5 hours, radical nephrectomy = 2.5 hours), estimated blood loss (80 to 250 cc), and hospital stay (2 days) were acceptable. Significant "clashing" of robotic arms was noted. R-LESS surgery has also been performed using the GelPort laparoscopic access system (Stein et al, 2010). The authors reported more adequate spacing for the robotic instruments and easier assistant access. However, the need for novel purpose-specific, possibly flexible, robotic instrumentation or platforms was noted in both studies.

The prospect of LESS surgery is potentially attractive from the patient perspective, with possible benefit in decreasing postoperative pain and improving cosmesis. This may be especially true in the case of extirpative surgery, when an extraction site is required or if cosmesis is of particular concern. However, these potential benefits have not yet been proven in prospective trials. Moreover, although a large body of surgical literature clearly demonstrates benefits of traditional laparoscopy versus open surgical techniques for analgesic requirements, length of stay, return to convalescence, and cosmesis, the benefits of LESS versus traditional laparoscopy remain in question at this time. Larger comparative series between traditional laparoscopic techniques and LESS are required to further study outcomes relevant to each specific procedure and to evaluate for potential benefits.

COMPLICATIONS OF LAPAROSCOPIC RENAL SURGERY

Complications are an unavoidable consequence of surgical practice and even the most experienced clinicians will face problems. Organic factors related to the patient, operating room environment, and chaotic forces can lead to an untoward event. Thus efforts at prevention through knowledge of each given procedure and its potential pitfalls should be maximized. Moreover, patient education about the risks of surgery is essential.

Patient selection is important to minimize risk of complications. This needs to be paired with each surgeon's experience and ability. Several situations require caution when considering a laparoscopic approach. True contraindications include an uncorrected coagulopathy, untreated infection, and hypovolemic shock (Capelouto and Kavoussi, 1993). **Previous surgery is not a contraindication to laparoscopic renal surgery. Prior abdominal surgery may have caused intra-abdominal adhesions and increased the possibility of injury to bowel during insufflation, trocar placement, or dissection.** The initial entry site in these patients should be away from scars and prior surgical fields. Open trocar placement or a retroperitoneal approach, may be necessary to minimize access injuries (Hasson, 1971). Extraperitoneal access may also help avoid adhesions. If additional space is required, the peritoneum may be opened under direct vision.

Patients with large, dilated loops of bowel from either functional or obstructive ileus should be approached cautiously, because the dilated intestinal segments can limit the working space and may be injured during access, dissection, and trocar site closure (Borten, 1986).

Care is taken to keep anatomic orientation at all times, because confusion in landmarks can lead to catastrophic consequences. Prior surgery or bulky pathology can alter normal anatomic relationships. It is thus necessary to have preoperative imaging studies available in the room. Intraoperative ultrasonography can be a valuable tool to help identify structures. When visual clues are inadequate to allow safe progress, palpation by hand assistance may provide additional information. Alternatively, open conversion may be indicated.

When complications occur, the consequences can often be minimized through early recognition and appropriate intervention. Laparoscopic renal surgery shares several potential risks with traditional open approaches; however, there are differences in the type and presentation of these complications. It must be kept in mind that all situations are individual, and unique problems may arise and call for innovative actions.

General complications of laparoscopic surgery have been covered in Chapter 9, however, specific pitfalls require review. Reported complications from laparoscopic kidney surgery are reviewed in Table 55–5. The combined incidence of bowel injury in the urologic literature is 0.8%, and injury may occur at any point during the dissection (Schwartz et al, 2010). When reflecting the colon or duodenum, avoid thermal energy adjacent to the bowel. This is the most common cause of unrecognized injury and may not be diagnosed until postoperative day 3 to 5. When recognized, superficial thermal injuries may be oversewn with 3-0 silk suture to imbricate the affected area. Transmural injuries should be debrided and, as with primary sharp injury, may be closed primarily in two layers. The area should be irrigated thoroughly and inspected to rule out a through and through injury. Drain placement is optional and oral intake is held until bowel function has returned.

Table 55–5.

Reported Complications of Laparoscopic Kidney Surgery

Vascular injury
Adjacent organ injury (liver, spleen, pancreas, bowel, stomach, diaphragm)
Wound infection
Abscess
Seroma
Wound dehiscence
Internal hernia
Incisional hernia
Pulmonary complications (pneumothorax, pulmonary edema, pleural effusion, pneumonia)
Pulmonary embolism
Deep vein thrombosis
Neuromuscular pain
Postoperative bleeding/transfusion
Atrial fibrillation
Myocardial infarction
Adrenal insufficiency
Testicular infarction or ischemia
Epididymitis
Ureteral stricture
Nonelective open conversion
Chylous ascites
Urinoma
Completion nephrectomy (after partial nephrectomy)
Tumor fragmentation
Renal insufficiency (transient or chronic)
Delayed bleeding
Urinary tract infection
Urinary retention

One of the most devastating complications occurring as a result of laparoscopic surgery is unrecognized bowel injury (Fig. 55–43). **Only a small portion of the laparoscopic instrument is in the visual field so that injuries can occur out of the surgeon's view during introduction or retraction.** In the urologic literature, the overall incidence of bowel injury during laparoscopic surgery of the retroperitoneum, both recognized and unrecognized, is 0.65% (Schwartz et al, 2010). **Unrecognized injuries result in high-grade complications in 100% of cases in series reporting on laparoscopic bowel injuries.** Blunt, sharp, and cautery dissection account for the majority of bowel injuries (60%), while access-related injuries are far less common (6%). **The presentation of bowel injuries in patients undergoing laparoscopy differs from that described with open surgery. Patients with unrecognized bowel injury after laparoscopy typically present with persistent and increased trocar-site pain at the site closest to the bowel injury. The area around this site becomes edematous and doughy in consistency. Signs and symptoms may also include abdominal distention, nausea, diarrhea, anorexia, low-grade fever, persistent bowel sounds, and a low or normal white blood cell count. The patient's condition can rapidly deteriorate to hemodynamic instability and death, if the injury is not recognized and treated** (Bishoff et al, 1999). CT with oral contrast is the initial diagnostic modality of choice (Cadeddu et al, 1997), and open exploration is usually required to evacuate bowel spillage and perform the necessary repair. In rare cases, when a controlled fistula develops, conservative management with bowel rest and hyperalimentation may be used, but this can take months to resolve.

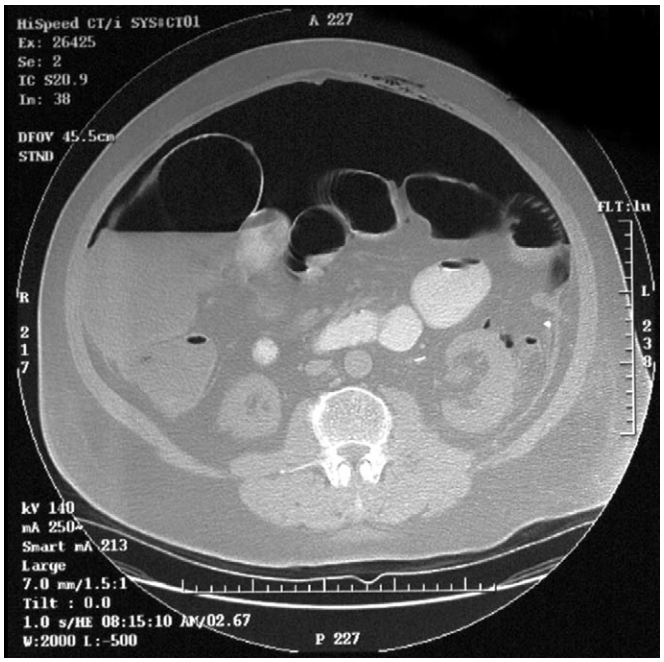


Figure 55–43. CT scan taken 9 days after partial nephrectomy when the patient presented to the clinic for routine follow-up complaining of distention and worsening abdominal pain for the past 3 days, low-grade fever, leukopenia, and pain out of proportion at a single trocar site. CT shows dilated loops of large bowel and significant amounts of free air. Exploration revealed a small perforation in the cecum.

In reflecting the bowel on the left side, care must be taken to avoid making a hole in the mesentery. Any mesenteric defects should be closed as postoperative bowel herniation is possible (Regan et al, 2003). During closure of the mesentery, care also should be taken to avoid compromising the vascular supply to the colon. Retractors not in the operative field may also injure the bowel, and one should check for inadvertent injury at the conclusion of the procedure.

Vascular injuries are the most common complication of urologic laparoscopy (Permpongkosol et al, 2007). Life-threatening vascular injuries can occur during laparoscopic renal surgery and usually occur during dissection of the renal hilum. Injury to arteries, veins, branches, and accessory vessels can result in bleeding that may require conversion to open surgery. The renal vein can have multiple branches that can easily be torn. Care should be taken in assuring ligation and transection without tension. Venous bleeding can be brisk. Many times, applying direct pressure with gauze for several minutes will be sufficient to control bleeding. Resist the temptation to continually explore the area of venous bleeding, if all is quiescent once the gauze is removed. On the right side, the vena cava can be injured. Avulsion of the gonadal or adrenal vein can cause significant bleeding. If a hole is visible, placement of a clip or suture may be attempted once a grasper has controlled the situation. Blind clip placement or suturing can lead to a worsening of the situation and additional complications. Again, direct pressure with gauze over several minutes may abate bleeding. Dissection may continue with the gauze in place.

Arterial injuries can occur when structures are not fully identified before transection. Also, past pointing of scissors can cut an underlying vessel. If the opening is identified, suture placement or clips may be used for control. A hand may be placed in a lower abdominal midline incision to hold pressure if bleeding is brisk. In this manner, laparoscopic suturing or open conversion can proceed in a controlled manner.

Cases of inadvertent stapling of important anatomic structures have been reported. The vena cava and aorta have been mistaken for the renal vessels (McAllister et al, 2004). Several instances of transection of the small mesenteric artery (SMA) or contralateral renal vessels have also occurred. This can occur readily with the novice who is unfamiliar with the retroperitoneal approach. Unfortunately, many of these are not recognized intraoperatively and mortality is high. The best way to avoid this is through continuous anatomic orientation and vigilant self-questioning.

Equipment failure can result in bleeding. A multi-institutional review of endovascular stapler complications showed a malfunction rate of 1.7% (10/565), with eight cases involving the renal vein and two cases the renal artery (Chan et al, 2000). Blood loss resulting from the malfunction was between 200 to 1200 cc. Conversion to open surgery for hemostasis was required in 20% of the malfunction cases. The etiology of stapler failure was due directly to the instrument in three cases and due to preventable causes in seven cases. Preventable causes included stapling over clips or incomplete transection due to incorrect placement. **The abdominal cavity should be inspected for bleeding at the conclusion of surgery. Common areas of postoperative intra-abdominal bleeding include the bed of the dissection, adrenal gland, mesentery, gonadal vessels, and ureteral stump.**

Postoperative hemorrhage can occur following partial nephrectomy. Hypotension with associated tachycardia and a drop in hematocrit may imply postoperative bleeding. **Following partial nephrectomy, an arteriovenous malformation or pseudoaneurysm may form** (Benway et al, 2009; Shapiro et al,

2009). **These patients present with persistent gross hematuria, hypotension, and tachycardia.** If there is a question, CT scanning may be appropriate in identifying the source of bleeding; **however, in the majority of patients, immediate renal angiography with embolization of the bleeding site is indicated.**

Persistent urine leakage may occur following a partial nephrectomy or cyst ablation. Unless there is distal obstruction to the site of leakage, most will resolve with conservative therapy after several weeks (Meeks et al, 2008). After approximately one week, a controlled fistula develops, and the drain can be taken off continous suction and checked intermittantly to be sure fluid is not accumulating. If conservative management fails, such as in cases of distal obstruction, additional intervention may be required, such as percutaneous drainage of a urinoma or ureteral stent and bladder decompression.

Upper pole renal dissection can result in diaphragmatic injury. This is usually immediately recognized because peak airway pressures suddenly increase, and ventilation of the patient becomes difficult. The diaphragm can be seen billowing on endoscopic inspection. Immediate treatment is needed to prevent a tension pneumothorax. The diaphragm can be sutured directly while a central line catheter is placed into the ipsilateral anterior second intercostals space and placed to a water seal. At the conclusion of the procedure, the patient is ventilated, a chest radiograph obtained, and, if resolved, the catheter is removed. When significant gas remains, a chest tube can be inserted (Del Pizzo et al, 2003; Aron et al, 2007).

On the left side, splenic and pancreatic injuries may occur. Bleeding from the spleen is usually controlled with topical agents and argon beam coagulations (Canby-Hagino et al, 2000; McGinnis et al, 2000). Injuries to the pancreas may be insidious, and inspection is needed at the conclusion of surgery. Superficial pancreatic injuries are observed with drain placement. Deeper injuries may require formal repair or isolation of the segment with a GIA stapler (Varkarakis et al, 2004). Right-sided dissections may cause injury to the liver or gall bladder. Liver injuries are managed with topical therapy and argon beam coagulation. Gall bladder injuries are best managed by cholecystectomy.

Patients undergoing laparoscopic renal surgery are at risk of intravascular volume overload if fluid replacement is not modified relative to open surgery. The laparoscopic approach is associated with far less insensible fluid loss compared with open procedures, and there is also a vascular-mediated oliguria. As such, urine output should not be a barometer of fluid status. Typically, intravenous fluids should be minimized with the exception of laparoscopic donor nephrectomy. Aggressive replacement can cause volume overload in patients with diminished cardiac reserve and can result in postoperative congestive heart failure. Poor urine output or hemodynamic instability in the postoperative period should initiate an evaluation to rule out bleeding; if the work-up is negative, diuresis can be induced if clinically indicated.

Several authors have reported cases of chronic pain syndrome or nerve injury after laparoscopic radical nephrectomy. Patients may experience a burning discomfort in the ipsilateral flank; paresthesias around port sites or over the thigh and upper extremity can occur (Wolf et al, 2000; Oefelein and Bayazit, 2003). In a series of 381 laparoscopic donor nephrectomies, ipsilateral orchialgia was reported in 10% of patients (Kim et al, 2003). Onset of pain occurred at a mean of 5 days after surgery (range 6 to 52 months) and at 6 months; 50% had complete spontaneous resolution. Thigh paresthesias may be avoided by preserving the psoas fascia during posterior renal dissection. Additional reported complications include incisional hernia after intact specimen removal, port-site hernia, prolonged ileus, pulmonary embolus, and pneumonia.

In a multi-institutional review of 185 patients, Gill and coworkers (1995) reported an overall complication rate of 12% for benign disease, with 5% of patients requiring conversion to open surgery. In their series, the incidence of complications decreased markedly with increasing experience. **In fact, 70% of the complications occurred during the first 20 cases at each institution. A learning curve of approximately 20 laparoscopic nephrectomy cases is also supported by other reports** (Keeley and Tolley, 1998; Rassweiler et al 1998; Fahlenkamp et al, 1999). In a recently reported series of partial nephrectomies, the complication rate continued to decrease even after 750 cases. This implies a longer learning curve for more complex procedures.

In a series of 482 laparoscopic nephrectomies (444 procedures for benign disease) performed by 20 surgeons at 14 different European medical centers, a 6% overall complication rate was reported, with 10% of the cases converted to open surgery (Rassweiler et al, 1998). **The majority of patients converted to open surgery had infectious causes of renal abnormality as the leading indication for kidney removal.** Bleeding was the most common cause of open conversion in these cases, followed by the surgeon's inability to visualize the renal hilum for dissection.

In series comparing open, hand-assisted, and laparoscopic nephrectomy for malignancy, the complication rates were 10%, 17%, and 12% respectively (P = .133) (Chan et al, 2001; Shuford et al, 2004).

Two comparative studies examining complication rates in the elderly population, greater than 75 and greater than 80 years, respectively, found no difference in surgical or long-term morbidity when compared with younger patient populations (Varkarakis et al, 2004b; Thomas et al, 2009). In patients at high risk for perioperative complications, as determined by an American Society of Anesthesiologists score greater than or equal to 3, there were no significant differences in complication rates between hand-assisted, laparoscopy, and open radical nephrectomy (Baldwin et al, 2003).

PENETRANCE OF LAPAROSCOPIC RENAL SURGERY FOR THE COMMUNITY UROLOGIST

A recent study using information gathered from the SEER-Medicare–linked database showed the serious underutilization of laparoscopic and nephron-sparing techniques (Miller et al, 2008). Of 4872 radical nephrectomies performed for kidney cancer between 1997 and 2002, only 515 (10.6%) were performed laparoscopically. After controlling for variables such as demographics, tumor size, and comorbidities, surgeon-attributable factors were consistently the most significant predictor of the type of surgery performed. Stated otherwise, the surgeon's practice style was the determining factor for the surgical approach, not patient characteristics or characteristics of the renal cancer. This conclusion should be cause for some alarm in the urologic community. Laparoscopic procedures such as cholecystectomy and appendectomy are quite commonplace and were rapidly adopted by general surgeons. Historically, urologists have been receptive to new technology, a fact most recently demonstrated by the rapid increase in the number of robotic prostatectomies performed in the United States. However, the same does not hold true for laparoscopic nephrectomy, despite its longevity and proven benefits. This

would suggest significant barriers to the diffusion of laparoscopy specifically for renal surgery. A complex array of reasons may account for this observation, including the differential incidence of kidney and prostate cancer, marketing of robotics, referral patterns, consumer demand, etc. (Richstone et al, 2008). As physicans, we must be aware of barriers that affect the use of procedures with proven and meaningful patient benefits, and work toward dismantling them such that every patient may gain from progress in our field.

SUMMARY

Laparoscopy has emerged as the preferred treatment modality for many types of renal pathology. Patients have undoubtedly gained from the benefits laparoscopy offers in terms of perioperative morbidity without sacrificing therapeutic outcomes. As surgical tools continue to evolve, even more minimally invasive options such as laparoendoscopic single-site surgery and natural orifice transluminal endoscopic surgery may become more pervasive and potentially offer additional perioperative benefit to patients.

Key Points

- Laparoscopy can be used to treat the majority of renal pathology with equal efficacy as open surgery while providing less pain, shorter convalescence, and optimal cosmesis.
- Basic principles of oncologic surgery must be maintained when using a laparoscopic approach to treat renal tumors.
- Unrecognized bowel injuries are associated with high mortality, because the presentation of bowel injuries in patients undergoing laparoscopy differs from that described with open surgery. Presentation is typically characterized by normal to low white blood count (WBC), focal abdominal pain (often worst at the trocar site nearest the injury), mild ileus, and lack of fever.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter
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Ablative Therapy for Renal Tumors

Wesley M. White, MD ● Jihad H. Kaouk, MD

Cryoablation
Radiofrequency Ablation
Surgical Technique
Oncologic Outcomes
Complications
Future Trends
Conclusions

The management of renal cell carcinoma has undergone a paradigm shift over the last two decades. The widespread use and refinement of modern imaging during this period has led to a dramatic increase in the number of incidentally discovered and low-stage renal lesions (Jayson and Sanders, 1998; Volpe et al, 2004). This fortunate trend has allowed urologists to explore alternative and less invasive forms of therapy, among them nephron-sparing surgery and renal ablative technologies (Colombo and Kaouk, 2007; Pinto, 2009). Cancer-specific survival, preservation of renal function, avoidance of treatment-related morbidity, and patient-centered quality-of-life outcomes now constitute the ultimate goals for management of early-stage renal cell carcinoma.

The preponderance of evidence-based data champions the role of partial nephrectomy in the treatment of localized unilateral small renal masses (Herr, 1999; Fergany et al, 2000). Nephron-sparing surgery, in this setting (tumors < 4 cm), offers comparable oncologic outcomes (>95% cancer-specific survival) as compared with radical nephrectomy and is associated with improved preservation of renal function, superior cardiac outcomes, and improved overall survival (Thompson et al, 2008; Huang et al, 2009; Zini et al, 2009). Moreover, nephron-sparing surgery avoids overtreatment of indolent or benign tumors, a particularly germane concern, because nearly 20% of malignant-appearing, small renal masses are pathologically benign (Frank et al, 2003). For these reasons, open partial nephrectomy is currently considered the gold standard treatment for radiographically enhancing small renal masses (Novick, 2004).

Despite its aforementioned long-term advantages, open partial nephrectomy is nevertheless associated with significant short-term morbidity, namely substantial postoperative pain, prolonged hospitalization, and a protracted convalescence (Gill et al, 2007). Because a large proportion of patients who are candidates for partial nephrectomy demonstrate concomitant co-morbidities or are of advanced age, this short-term morbidity must be taken into consideration during patient counseling, and less invasive alternatives, if appropriate, should be discussed.

Laparoscopic partial nephrectomy (LPN) replicates the principles of open nephron-sparing surgery but with less attendant surgical morbidity (Gill et al, 2002). Indeed, laparoscopic partial nephrectomy offers markedly improved convalescence and equivalent disease-free survival as compared with open partial nephrectomy (Aron and Gill, 2007; Andonian et al, 2008; Marszalek et al, 2009). However, laparoscopic partial nephrectomy remains a technically challenging procedure with significantly higher complication rates, even among experienced surgeons at centers of excellence (Gill et al, 2007). Further, renal hilar occlusion is nearly universally required during LPN to minimize blood loss and facilitate tumor resection in a bloodless field. In expert hands, warm ischemia times during LPN approach 30 minutes (Kural et al, 2009; Thomas et al, 2009). Although controversial and dependent on the inherent renal function status, warm ischemia times that approach or exceed 30 minutes may place the kidney at considerable risk for postischemic injury (Thompson et al, 2007; Lane et al, 2008).

Irrespective of the surgical approach chosen, nephron-sparing surgery is underutilized in the United States owing to the comparative risks and attendant technical demands associated with the procedure (Abouassaly et al, 2009). Recent Surveillance, Epidemiology, and End Results (SEER) data found that partial nephrectomy is performed in only 11.1% of patients, with the remaining 88.9% undergoing radical nephrectomy (Miller et al, 2008). Furthermore, when adjusted for patient demographics and tumor size, surgeon preference was significantly more important than patient characteristics with regard to the type of operation selected.

Energy-based, in-situ tumor ablation was developed in an attempt to broaden the minimally invasive treatment options available to patients with ostensibly localized, low-stage renal tumors (Goel and Kaouk, 2008a). Focal ablative therapy confers myriad advantages compared with extirpative surgery. Principally, renal tumor ablation is associated with fewer complications, less morbidity, and a shortened convalescence (Desai et al, 2005). Second, prospective studies have demonstrated no significant impact on renal function following treatment (Shingleton and Sewell, 2003; Raman et al, 2008). Although a modicum of parenchymal loss does occur, renal hilar occlusion is not performed during tumor ablation, and postischemic injury is therefore avoided. Next, ablation offers considerable treatment flexibility. That is, tumors may be treated open, laparoscopically, or percutaneously with the approach tailored to the specifics of the patient and tumor (Rukstalis et al, 2001; Deane and Clayman, 2006).

Finally, renal tumor ablation is technically less demanding to perform than either open or laparoscopic partial nephrectomy. Complex reconstruction is not required following treatment, and dissection and isolation of the renal hilum is not requisite. Given these advantages, ideal candidates for ablative treatment have traditionally included patients with small multifocal tumors, those with one or more tumors in a solitary kidney in which surgical warm ischemia would place the kidney at risk, and those who desired treatment but were not appropriate candidates for extirpative surgery (Lehman and Landman, 2008).

Although well tolerated and technically less challenging than alternative extirpative options, concern exists regarding the oncologic efficacy of ablative techniques. A recent meta-analysis demonstrated a higher relative risk of local recurrence with cryoablation (RR = 7.45) and radiofrequency ablation (RR = 18.23) as compared with partial nephrectomy, but with no significant difference in progression to metastatic disease between the three groups (Kunkle et al, 2008). However, nonuniform criteria were used to define tumor recurrence in these series and pathology was not obtained for all specimens.

Evolving technology that includes treatment guidance systems, more robust operator experience, and improved patient selection may position renal ablative technologies as a treatment of choice for small renal masses. Probe ablative treatments are considerably less invasive than open partial nephrectomy, are less technically challenging and more easily learned than laparoscopic partial nephrectomy, and are associated with fewer complications as compared with open or laparoscopic partial nephrectomy.

Key Points: Management of the Small Renal Mass

- Widespread use of cross-sectional imaging has led to a dramatic increase in the number of incidentally discovered, low-stage renal lesions.
- Nephron-sparing surgery offers comparable cancer-specific survival and superior overall survival when compared with radical nephrectomy for small renal masses.
- In-situ ablative technologies including cryoablation and radiofrequency ablation were developed as a minimally invasive nephron-sparing alternative to extirpative surgery.

CRYOABLATION

Mode of Action and Experimental Data

The concept of applying cold temperatures to destroy tissue is credited to an English physician, Dr. James Arnott (1797 to 1883). Using a combination of ice and salt, he was able to topically palliate tumors of the cervix and breast with variable success. Over the course of the ensuing decades, investigators developed more sophisticated, reproducible, and pragmatic methods of handling and applying topical cryogens (Gage, 1998). In 1963, a neurosurgeon from New York, Dr. Irving S. Cooper, introduced a probe capable of achieving a controlled temperature of –196° C in deep-seated tissues (Cooper, 1963). Using pressurized liquid nitrogen, this self-contained probe was employed to ablate otherwise inoperable brain tumors, as well as portions of the thalamus in patients with Parkinson disease. Cooper's innovative concept ushered in a new era in cryosurgery in which larger volumes of tissue in less accessible locations could be successfully and reproducibly ablated.

Although Cooper's experience provided the proof in principle for cryoablation, its practical application for abdominopelvic tumors was not immediately realized. Early cryogen delivery systems could not unfailingly control the extent of tissue death owing to a generalized lack of cryoprobe sophistication and an unreliable system of monitoring the freezing process (Weber and Lee, 2005). As such, irreparable collateral damage was often a consequence of treatment, and the technique was transiently abandoned. It was not until the development of cryoablation under real-time image guidance with intraoperative ultrasonography that the procedure became a safe and pragmatic treatment choice.

The application of intraoperative ultrasonography during cryosurgery addressed many of its aforementioned short-comings (Onik et al, 1984, 1985). First, ultrasonography offered an excellent method for evaluating the patient's anatomy. The relative size and location of the area to be treated could be visualized and documented, and the entirety of the organ could be evaluated for occult metastatic disease. Second, precise probe placement could be assured by following its echogenic tip under ultrasound guidance. Lastly and most importantly, the freezing process could finally be monitored in real time by observing the formation and propagation of the highly echogenic leading edge of the iceball (Fig. 56-1). Because animal studies had already confirmed a close correlation between the sonographically visible iceball and the zone of cell death, surgeons now had a reliable and reproducible method of targeting and destroying tumors without attendant collateral damage (Steed et al, 1997; Campbell et al, 1998; Weber et al, 1998).

Following treatment under image guidance, the next significant breakthrough with cryoablation was the introduction of argon gas–driven treatment systems (Rewcastle et al, 1999). Through the mid- to late 1990s, cryoablation was performed exclusively with liquid nitrogen-based systems that were relatively inefficient. Newer argon gas systems were developed, ones that use the Joule-Thomson principle (low temperatures are achieved by the rapid expansion of high-pressure, inert gas) to generate temperatures of –185.7° C within the treatment tissues. These systems require shorter treatment times and allow for smaller, more proficient

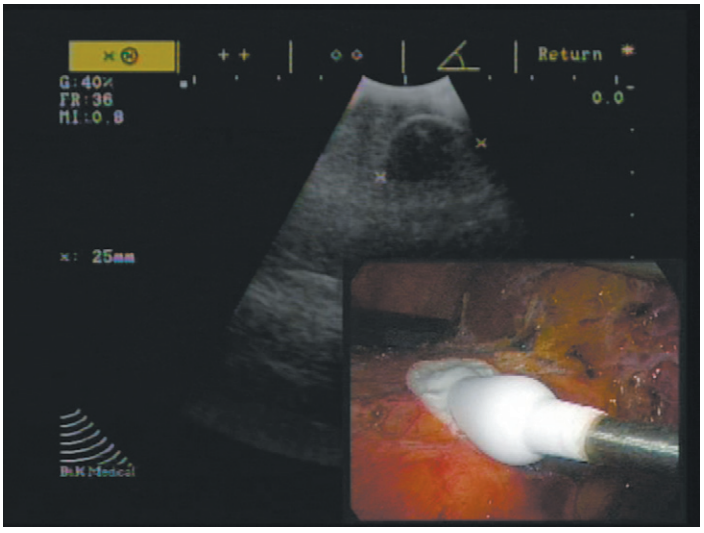


Figure 56–1. Intraoperative ultrasound image during renal tumor laparoscopic cryoablation. Note the hyperechoic semicircular edge with a posterior shadow of the developing iceball. *Inset:* laparoscopic view of the cryoablated mass with the cryoprobe positioned in the center of the tumor that is covered with ice.

cryoprobes that can be employed laparoscopically with fused ultrasound guidance or percutaneously under computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound guidance. The majority of commercially available cryoablation units (CryoHit, Galil Medical, Plymouth Meeting, PA; CryoCare, CryoCare CS, Endocare, Irvine, CA; SeedNet, Oncura, Philadelphia, PA) now employ argon gas–based systems as described.

The mechanism of tissue injury with cryoablation is multifaceted, reflecting direct cellular damage during the freezing phase and indirect reperfusion injury during the thawing phase (Mazur, 1977; Ishiguro and Rubinsky, 1994; Hoffman and Bischof, 2002). During rapid freezing or freezing at extremely low temperatures, ice crystals form within the intracellular spaces, causing cell death by direct injury to either the cellular membrane or structures within the cell. With gradual freezing, extracellular ice formation creates an osmotic gradient that results in intracellular fluid moving into the extracellular space. The result of this fluid shift is dehydration, cell membrane rupture, and subsequent cell death. During the thawing phase, reperfusion injury occurs that results in microcirculatory failure and small-vessel thrombosis (Weber et al, 1997; Kahlenberg et al, 1998). Although speculative, this may represent the dominant mechanism of cell kill during cryosurgery. The summative pathologic consequence of treatment is coagulative necrosis and fibrous scar formation.

The adequacy and reproducibility of tissue destruction during cryoablation is dependent upon several parameters:

1. *Treatment Temperature.* Based on experimental evidence, it is clear that a certain threshold temperature must be reached in order to effect adequate tumor destruction. Although susceptibility to cryoablation is dependent upon the tissue treated, it is widely estimated that the critical temperature for irreparable tissue destruction is between –20° C and –50° C (Neel, 1971; Tatsutani et al, 1996; Woolley et al, 2002). In general, normal renal parenchyma is destroyed at –19.4° C with tumor cells requiring lower temperatures, likely owing to their more fibrous nature (Chosy et al, 1998; Larson et al, 2000). Tissue with high-collagen and elastin content appear to be the most resilient to freezing (Shepherd and Dawber, 1984). For this reason, the renal collecting system and renal vasculature tolerate cryoablation without appreciable long-term adverse effects (Sung et al, 2003). Conversely, the urethra, bowel, and ureter are more cryosensitive and are thus subject to stricture, sloughing, and perforation if protective measures are not employed (Wong et al, 1997). With the use of modern cryoablation units, core treatment temperatures of –130° C to –150° C are achieved. **Currently, the minimum preferred target temperature during renal cryoablation is at or below –40° C.**
2. *Double Freeze-Thaw Cycle.* In-vivo animal studies initially demonstrated adequate cell kill in normal tissue employing a single freeze-thaw cycle (Weber et al, 1997). However, when applied to tumor cells in small animal models, the single freeze-thaw cycle was found to be inferior to a double freeze-thaw cycle with respect to adequacy of tissue ablation and local tumor control. This finding was confirmed by Woolley and associates (2002) who prospectively compared treatment outcomes in 16 female dogs who underwent either a single or double freeze-thaw cycle. A significantly larger and more adequate area of liquefaction necrosis was noted following a double freeze-thaw cycle. **As such, a double freeze-thaw cycle is currently the standard of care during renal tumor cryoablation.**
3. *Determining an Adequate Ablation Zone.* Campbell and colleagues (1998) demonstrated that the aforementioned threshold temperature of –40° C (as evidenced by tissue necrosis) was achieved 3.1 mm inside the edge of the evolving iceball. To guarantee that the tumor is completely ablated with a margin of normal tissue, the iceball is generally carried 5 to 10 mm beyond the edge of the tumor when viewed under real-time imaging (Gill et al, 2000). In addition, thermosensors may be positioned at the tumor margin to ensure that adequate treatment temperatures (–40° C) are achieved at the periphery (Rukstalis et al, 2001). The ability to shape the iceball by placing multiple probes at different locations and to deliver varying amounts of flow through these probes such that target temperatures are consistently achieved constitutes a distinct advantage over single-probe ablation devices such as radiofrequency ablation (Weber and Lee, 2005). **Currently, cryoablation of renal tumors should be performed under real-time imaging with the treatment area approximately 1 cm beyond the margin of the tumor.**
4. *Duration of Treatment.* Little data exists regarding the optimal duration of freezing during cryoablation. Auge and colleagues (2006) performed a prospective study in nine female farm pigs in which cryoablation was performed for either 5, 10, or 15 minutes. When the specimens were examined histologically, the pigs treated for 5 minutes demonstrated inadequate tissue necrosis and experienced more postprocedural bleeding. Pigs that were treated for 15 minutes exhibited uniform and consistent necrosis but with a high rate of tissue fracture. The pigs treated in the 10-minute cohort demonstrated adequate cell kill and minimal complications. Although the optimal duration of freezing is not known, **in our clinical experience, most tumors can be adequately treated with an initial freeze cycle of 8 to 10 minutes and a second freeze cycle of approximately 6 to 8 minutes.**
5. *Active versus Passive Thaw.* Modern argon-based cryoablation units employ helium gas to actively thaw tissue following iceball formation. Alternatively, the flow of argon gas may be discontinued and the tissue allowed to passively thaw without the use of helium. Although active thawing is clearly more efficient and translates into shorter overall operative times, scant data is available regarding the superiority of tissue destruction with active versus passive thawing (Desai and Gill, 2002). Experimental data from Woolley and colleagues (2002) suggests no difference in the degree or reproducibility of tissue destruction with active or passive thaw processes. Conversely, Klossner and colleagues (2007) examined variables that impacted cryosurgical outcomes using human prostate PC-3 and LNCaP cultures and found passive thawing yielded greater tissue destruction owing to

Key Points: Cryoablation

- Cryoablation employs argon gas–based systems to achieve treatment temperatures of less than –40° C.
- Cryoablation of renal tumors should be performed under real-time imaging with the treatment area approximately 1 cm beyond the margin of the tumor.
- A double freeze-thaw cycle is currently the standard of care during renal tumor cryoablation.

increased solute effects and increased recrystallization at temperatures between –20° C and –30° C. Unfortunately, no prospective clinical data exists that specifically addresses the issue. **We prefer to use a passive thaw following our initial freeze cycle such that temperatures of less than –40° C are maintained for a longer period of time. We employ an active thaw following the second freeze cycle such that potential bleeding can be more rapidly addressed following probe removal.**

RADIOFREQUENCY ABLATION

Mode of Action and Experimental Data

Cushing and Bovie (1928) introduced the Bovie knife, an instrument that employed pulsed or continuous monopolar radiofrequency current to cauterize or cut tissue, respectively. Although this forerunner to modern electrocautery revolutionized and defined contemporary surgical techniques, it also provided the foundation for present-day radiofrequency ablation (RFA).

Radiofrequency energy effects cell kill by transferring alternating radiofrequency current (450 to 1200 kHz) through insulated interstitial needle electrodes (Raj et al, 2003). This energy transfer generates ionic friction and agitation within tissue that results in heating (Organ, 1976-1977; LeVeen, 1997; Rehman et al, 2004). When tissue is heated in excess of 60° C, irreversible coagulative necrosis and tissue desiccation occurs (Hsu et al, 2000). Much like cryoablation, the adequacy and reproducibility of tissue destruction during RFA is dependent upon several parameters:

1. *Amount of RF Energy/Treatment Temperature:* The volume of tissue necrosis is directly correlated to the total amount of RF energy deposited into the tissue less local and systemic heat loss (Zevas and Kuwayama, 1972; McGahan and Dodd, 2001). As stated, alternating RF current creates cellular agitation and, as a result of electrical impedance of the tissue, local heating. Provided that electrical impedance remains low, an expanding sphere of tissue damage emanates outward from the treatment probe. If current is administered too rapidly or the amount of RF energy applied is too high, charring occurs, which reduces the water content of the tissue, abruptly increases impedance, decreases energy transfer, and halts the heating process (Djavan et al, 2000; Finelli et al, 2003). The lesion volume is then either smaller than desired or lacks uniformity. In general, treatment temperatures well above 105° C are avoided for this reason (Goldberg et al, 2000). **In clinical practice, a mean treatment temperature of 105° C is preferred** (Carraway et al, 2009).
2. *Duration of RF Treatment:* In general, irreversible protein denaturation and cell kill occurs if a temperature of 46° C is maintained for 1 hour, or 50° C is maintained for between 4 to 6 minutes (Goldberg and Dupuy, 2001). Tissue destruction is nearly instantaneous when treatment temperatures exceed 60° C. As most modern RFA treatment systems consistently achieve temperatures at or above 100° C, the duration of treatment would not appear to be a defining parameter. With modern temperature-based and impedance-based generators, the duration of ablation is largely determined by the treatment system and the size of the lesion. **Although no clinical data explicitly addresses the optimal duration of RF treatment, tumors less than 2 cm are typically treated with two cycles of 5 minutes; tumors 2 to 3 cm are treated with two cycles of 7 minutes; and tumors greater than 3 cm are treated with two cycles of 8 minutes** (Park et al, 2006a).
3. *Wet versus Dry RF:* Radiofrequency energy can be applied using needles placed directly into tissue (dry RFA), or with ionic solutions perfused into tissues to decrease carbonization and act as an energy conductor (wet RFA). Early dry RFA systems were highly successfully in treating small lesions but encountered tissue impedance and an attendant lack of efficacy in treating lesions greater than 4 cm. In the late 1990s, Lorentzen and colleagues (1997) and Goldberg and colleagues (1996) independently introduced the concept of driving chilled saline through the shaft of the treatment needle (wet RFA). By cooling the tip of the probe, they discovered that tissue charring immediately adjacent to the electrode was minimized; impedance and ionic agitation was preserved as a consequence, and a larger overall treatment lesion was ultimately created. The success of wet RFA in producing a reliably larger area of necrosis was confirmed in subsequent studies (Collyer et al, 2001; Leveillee and Hoey, 2003; Pereira et al, 2004). Internally cooled ablation probes and the use of hypertonic saline have both been proposed as an alternative to cooled saline and have demonstrated mixed success (Miao et al, 1997; Muvner et al, 2002).
4. *Single-Tine versus Multitine Electrode:* The original RF needle electrodes were dry RF devices, with varying amounts of insulation at the distal tip governing the approximate size of the treatment lesion. That is, the size of the lesion and the approximate depth of treatment could be modified by exposing varying amounts of tissue to the uninsulated needle. However, the initial ablation probes were capable of treating tumors no greater than 2 cm (McGahan et al, 1993). Larger tumors or the acquisition of an adequate tumor margin required additional treatment probes or re-treatment of overlapping regions. In an attempt to achieve a larger overall treatment volume, LeVeen (1997) introduced an insulated monopolar probe with multiple uninsulated prongs that function as RF antennae for the wider dispersion of current. These prongs are deployed in an even fashion to create a spherical lesion. When high impedance is encountered at one prong, current is redirected to areas of lower impedance. **Clinical validation studies have demonstrated more complete necrosis and superior treatment outcomes with multitine electrodes** (Rossi et al, 1998; Curley et al, 2000; Rehman et al, 2004).
5. *Monopolar versus Bipolar RF:* RF energy can be delivered through bipolar or monopolar electrodes. Monopolar RF devices achieve this effect by dispersing current from the device through the patient to a grounding pad on the skin of the patient. Conversely, bipolar RF devices generate current between two electrodes (one active and one negative) in the target tissue. The purported advantage of bipolar energy is that significantly higher temperatures are induced compared with those of monopolar devices (Nakada et al, 2003). It is unclear whether this theoretical advantage translates into improved operative outcomes.
6. *Heat-Based versus Impedance-Based Generators:* RF energy can be delivered using impedance or temperature-based feedback. As is implied by the name, impedance-based systems (Cool-tip, Valleylab, Boulder, CO; RF 3000, Boston Scientific, Natick, MA) constantly monitor the level of impedance at the tip(s) of the electrode(s) and terminate treatment when

"infinite impedance" is encountered. This implies complete desiccation and charring such that electrical current is unable to pass through tissue. Conversely, temperature-based systems (RITA Model 1500X, AngioDynamics, Queensbury, NY) determine completion of treatment when the tissues adjacent to the probe have reached a target temperature for a predetermined duration of time. Experimental data is contradictory. Rehman and colleagues (2004) noted areas of incomplete necrosis with impedance-based systems and complete necrosis with temperature-based systems. However, a dedicated animal study by Gettman and colleagues (2002a) demonstrated similar efficacy in ablating renal tissue with the two types of generators. **There is no explicit clinical data that supports the superiority of impedance or temperature-based systems.**

7. *"Heat-Sink" Phenomenon:* Treatment efficacy is dependent on the total amount of RF energy applied to the tissue, multiplied by local tissue interactions, less systemic and local heat loss (the "bioheat transfer equation") (Pennes, 1948; Goldberg et al, 2000). When the target zone is highly vascularized or is adjacent to large vessels, thermal energy is preferentially dispersed to the comparatively cooler blood within these vessels. This heat-sink effect may therefore spare tumor cells in close proximity to large blood vessels and lead to treatment failures. In response to this shortcoming, investigators within and outside urology have evaluated and employed methods to temporarily interrupt blood flow to the target organ (Corwin et al, 2001; Chang et al, 2004). The collective experience with hepatovascular occlusion (by transcatheter arterial embolization/balloon occlusion or the Pringle maneuver) during RFA has been favorable with significantly larger treatment areas and improved overall outcomes (Curley et al, 1999; Rossi et al, 2000). Success with renovascular occlusion has not yet been demonstrated. No significant difference in lesion size was noted between the clamped and unclamped cohorts in two separate studies (Corwin et al, 2001; Marcovich et al, 2002). Given the risk of postischemic injury and the technical complexity of hilar dissection and cross-clamping, renal vascular occlusion is not routinely performed during RFA.
8. *Treatment under Image Guidance:* Perhaps the most significant limitation of RFA, to date, has been the inability to reliably monitor treatment under image guidance. With cryoablation, the evolving iceball can be monitored in real time and its hyperechoic edge used as direct clinical evidence of treatment adequacy. Owing to the low intrinsic contrast between untreated and ablated tissue, as well as the formation of gas bubbles during heating, monitoring the RF ablation zone with ultrasonography, CT, and/or MRI has proven difficult (Rendon et al, 2001; Renshaw, 2004). Certainly, accurate probe positioning can be achieved with intraoperative ultrasonography (laparoscopic RFA) or under ultrasonography, CT, or MRI guidance (percutaneous RFA). However, once the probe is appropriately positioned, the desired treatment zone becomes entirely dependent on the deployed diameter and configuration of the electrode. And although impedance and temperature-based feedback ensures tissue destruction at the tip(s) of the electrode(s), the global geometric treatment area cannot be directly appreciated as readily as with cryoablation. In order to compensate for these "indirect" cues and to ensure a negative treatment margin, an ablation zone 5 to 10 mm beyond the maximum radiographic tumor diameter is preferred (Carraway et al, 2009).

Key Points: Radiofrequency Ablation

- Transfer of RF energy generates ionic friction and agitation within tissue that results in heating. When temperatures exceed 60° C, irreversible coagulative necrosis and tissue desiccation occurs.
- Myriad probe configurations and treatment systems are available.
- Treatment cannot be monitored under image-guidance owing to the low intrinsic contrast between untreated and ablated tissue, as well as the formation of gas bubbles during heating.

SURGICAL TECHNIQUE

Transperitoneal/Retroperitoneal Laparoscopic Renal Cryoablation/ Radiofrequency Ablation

See Chapter 55 for these modalities.

Percutaneous Renal Cryoablation/ Radiofrequency Ablation under Ultrasonography, CT, or MRI

Percutaneous tumor ablation can be performed under conscious sedation with local anesthesia or under general endotracheal anesthesia. Controversy exists regarding the optimal method of sedation. General endotracheal anesthesia allows controlled respiration during probe placement that may translate into more accurate targeting and improved overall outcomes. Conversely, conscious sedation minimizes the morbidity of the procedure and allows the procedure to be performed on an outpatient basis. Following induction, a 16-Fr urinary catheter is placed and intravenous antibiotics are administered. The patient is positioned on the CT or MRI gantry in the prone or flank position.

Intravenous contrast (iodinated or gadolinium contrast, depending on the imaging technique chosen and the patient's renal function) is administered and the lesion identified and characterized. A 20-gauge "finder needle" or access sheath is placed near the expected location of the tumor, and imaging is repeated to confirm localization. It is important to note the depth of the finder needle for subsequent biopsy and probe placement. Using this finder needle as a guide, an 18-gauge Tru-Cut (Cardinal Health, Dublin, OH) core biopsy needle is inserted percutaneously, and positioning is again confirmed with repeat imaging. Specimens are obtained and sent for permanent section. The cryoprobe(s) or RFA probe is/are next inserted in a manner similar to that of the core biopsy needle. Cryoprobe positioning and positioning of the RFA probe, and prongs are again confirmed with repeat imaging. Treatment is carried out in a fashion similar to that described for laparoscopic cryoablation/radiofrequency ablation (Fig. 56-2). Again, a "track burn" can be performed with percutaneous RFA. With percutaneous cryoablation, the cryoprobe is removed and repeat imaging performed to evaluate for potential bleeding. With either technique, a postablation contrasted imaging study is performed to determine the adequacy of treatment.

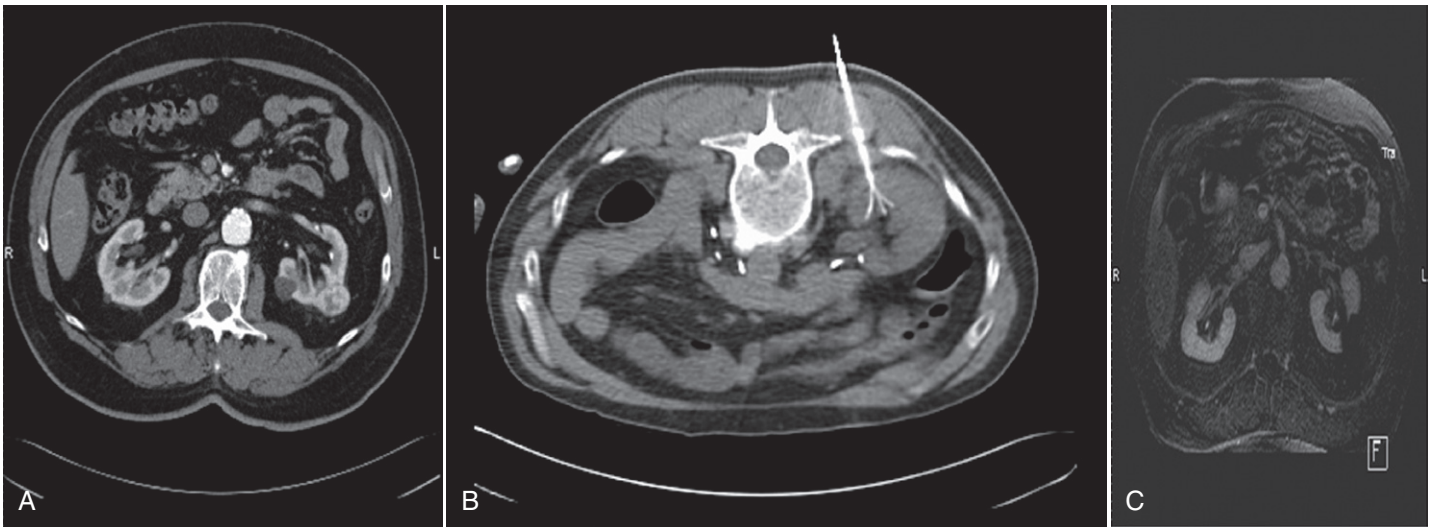


Figure 56–2. **A,** Preoperative CT scan noting a 2.4-cm solid enhancing mass in the left kidney. **B,** Intraoperative CT scan with the patient in prone position and a multitine radiofrequency ablation needle deployed into the renal mass. **C,** Postoperative CT scan at 6 months follow-up showing complete ablation of the left renal mass as demonstrated by the lack of enhancement at the site of the preexisting renal tumor.

Patients who underwent percutaneous ablation under conscious sedation are discharged in a same-day fashion. If the patient required general endotracheal anesthesia or in those patients with significant comorbidities, overnight admission is standard. Again, a CT of the abdomen without contrast is obtained prior to discharge.

Interpretation of Success and Follow-up after Tumor Ablation

Interpretation of treatment success following renal tumor ablation remains a controversial subject. Much of this confusion stems from a lack of uniformity with regard to follow-up protocols (frequency of follow-up and the type of imaging study chosen), as well as a lack of consensus regarding radiographic parameters of success and the role of renal biopsy. **The aggregate duration of follow-up with either cryoablation or RFA is inadequate to determine if radiographic follow-up alone is a sufficient surrogate of treatment efficacy** (Boorjian and Uzzo, 2009). Routine postablative biopsy may serve a role in corroborating radiographic findings. **However, the interpretation of biopsy findings following ablation is highly contentious, and the overall utility of biopsy in this setting is unresolved.** Selective biopsy is appropriate and indicated in cases of suspected recurrence. Given these ambiguities, urologists who employ ablative technologies should be familiar with existing and ongoing evidence-based literature and must place these findings in the context of clinical judgment and the overall well being of the patient.

Radiographic Interpretation of Success. As no pathologic margins are rendered with in-situ ablation, imaging characteristics serve as a surrogate marker of treatment efficacy. In general, the **complete loss of contrast enhancement on follow-up CT or MRI is considered evidence of complete tissue destruction and attendant treatment success** (Matsumoto et al, 2004; McAchran et al, 2005). **If a lesion demonstrates persistent contrast enhancement following treatment or requires more than one ablation session to achieve loss of contrast enhancement, this is considered incomplete ablation** (Matin et al, 2006). **Conversely, if a lesion demonstrates an initial complete loss of contrast enhancement and later demonstrates enlargement of the lesion and/or contrast enhancement, this is considered local tumor recurrence or progression** (Novick et al, 2009).

In addition to contrast-related characteristics, lesions that undergo cryoablation or RFA demonstrate characteristic but strikingly different appearances on follow-up imaging. **The majority of lesions treated with cryoablation demonstrate a greater than 50% reduction in size in the first year following treatment** (Deane and Clayman, 2006; Kawamoto et al, 2009). This contraction is due to cellular breakdown and phagocytosis. Conversely, **lesions treated with RFA often do not demonstrate postablative contraction, and failure to do so should not be interpreted as a treatment failure. Enlargement of a lesion, regardless of the treatment modality or the enhancement characteristics, should be construed as an ominous sign of local tumor recurrence** with biopsy and/or treatment (observation vs. repeat ablation vs. extirpative surgery) dictated by the size and location of the lesion, the response to the original treatment, and the patient's overall and renal functional status.

Recommended Radiographic Follow-up Protocol. The optimal radiographic follow-up regimen is not yet defined. The plurality of high-volume centers have determined that **CT with intravenous contrast or MRI with gadolinium contrast should be performed at 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months following treatment** (Deane, 2006; Matin et al, 2006; Carraway et al, 2009; Crouzet et al, 2009). **Imaging should be repeated annually thereafter.** There is no available data that cites the superiority of MRI or CT in routine follow-up although some experts contend that CT better distinguishes tumor margins and enhancement in the evaluation of renal tumors (Cadeddu, 2008). Ultrasonography is not routinely employed to evaluate lesions following ablation.

Role of Pre- and Postablation Biopsy. One of the chief criticisms of in-situ renal ablation has been the inability to render definitive pathologic evidence of treatment success. Efficacy with ablative technologies is therefore predicated solely on indirect radiographic cues as previously discussed. In an attempt to address this issue

and substantiate the role of postablation radiographic evaluation, biopsy of the lesion before and after treatment has been advocated (Kunkle and Uzzo, 2008).

Historically, biopsy of suspected renal cell carcinoma (RCC) has rarely been performed prior to treatment owing to perceived diagnostic inaccuracies in specimen interpretation, as well as the high overall diagnostic accuracy of cross-sectional imaging (Wang and Wood, 2009). Unfortunately, this reticence to perform biopsy prior to extirpative surgery has likewise carried over to cryoablation and RFA. A recent meta-analysis performed by Kunkle and Uzzo (2008) demonstrated that preablation biopsy was performed in 83.2% of cryoablation cases and 62.2% of RFA cases ($P < .0001$). Among those that underwent biopsy and subsequent ablation, 53.9% demonstrated pathologic evidence of RCC. The remaining 46.1% of lesions were either benign (12.7%) or indeterminate (33.5%). In light of these ambiguities, accurately interpreting cancer specific outcomes following cryoablation and RFA is extremely challenging. **To establish a diagnosis and provide uniformity and improved outcomes-based data, the American Urological Association Small Renal Mass (AUA SRM) Guidelines Panel recently recommended that tumor biopsy be universally performed at the time of ablation** (Novick et al, 2009).

Much of the controversy surrounding the oncologic efficacy of ablative technologies has centered on the inherent reliability of postoperative cross-sectional imaging to accurately predict disease-free status. It was originally thought that the high overall diagnostic accuracy of CT or MRI in predicting malignancy preoperatively would translate into equally accurate predictions of postablation tumor destruction or tumor recurrence. However, recent studies have questioned this bias and invoked uncertainty regarding the utility and adequacy of radiographic imaging as the sole surrogate of treatment success, especially following RFA.

In 2002, Rendon and colleagues (2002) performed laparoscopic or percutaneous RFA prior to partial or radical nephrectomy in 10 patients (11 tumors), with a mean tumor size of 2.4 cm. Hematoxylin and eosin (H&E) staining demonstrated residual viable tumor in 7 of the 11 tumors that underwent treatment. Four years later, Park and colleagues (2006b) reported on three patients who underwent delayed nephrectomy at a mean follow-up of 18 months following RFA. Intervention was performed due to new enhancement at the periphery of the treated lesion in two cases and treatment-related ureteropelvic junction obstruction in the remaining patient. No evidence of residual tumor was noted in any of the specimens.

Weight and colleagues (2008) attempted to correlate the radiographic appearance of ablated renal masses with pathological outcomes. The group examined a total of 109 renal lesions in 88 patients who underwent percutaneous RFA and 192 lesions in 176 patients who underwent laparoscopic cryoablation. At 6 months following treatment, radiographic success (no evidence of contrast enhancement) was noted in 90% of patients who underwent cryoablation and in 85% of patients who underwent RFA. Biopsy at 6 months was then performed in 134 lesions (45%). Pathologic evidence of success was 93.8% with cryoablation and only 64.8% with RFA. Of note, 6 of the 13 patients who underwent RFA and demonstrated viable residual tumor on follow-up biopsy demonstrated no contrast enhancement on follow-up imaging. Conversely, all cryoablation patients who had residual tumor on follow-up biopsy demonstrated definitive contrast enhancement. The authors concluded that radiographic imaging results following cryoablation correlated well with pathologic results, whereas a poor correlation was noted between radiographic imaging and pathologic results following RFA. Routine biopsy following RFA was advocated by the authors.

Although the Weight and colleagues study (2008) was criticized for potential selection bias, it nevertheless highlights the long-standing dilemma of post-RFA biopsy interpretation. **Standard H&E staining may be misleading immediately following RFA, because cellular architecture is largely preserved despite cell death** (Margulis et al, 2004). The duration of this "architectural preservation" is unknown. Stern attempted to address this issue by performing tumor biopsy of 20 radiographically negative lesions at least 1 year following RFA (Stern et al, 2008). No evidence of disease was noted. The authors concluded that RFA imparts definitive cellular necrosis, and radiographic imaging results correlate well with histopathology. **Given such conflicting information, the ultimate utility of H&E staining following RFA remains unknown.**

Cell viability stains, primarily reduced nicotinamide adenine dinucleotide (NADH) diaphorase, have been proposed as an alternative and more accurate method of determining cell death following tumor ablation. Much like the aforementioned H&E studies, results with NADH staining have been conflicting. Marcovich and coworkers (2003) performed a porcine study in which renal tumors were ablated and later resected and examined histologically. Tumor architecture was variably preserved on H&E staining (as previously discussed) but no NADH diaphorase staining was noted (implying complete cell death). Conversely, Matlaga and colleagues (2002) performed biopsy following RFA in 10 patients and noted an absence of NADH activity in 8 patients. The remaining two patients stained positive for NADH but technical (maximum treatment temperature of 41° C) and tumor-related (8-cm lesion) confounders may account for these failures. Michaels and colleagues (2002) likewise performed RFA in 15 patients and noted positive NADH staining in 4 of 5 tumors that underwent completion nephrectomy. **The inherent value and accuracy of NADH staining following RFA remains controversial.**

Key Points: Follow-up After Tumor Ablation

- Interpretation of treatment success following renal tumor ablation remains a controversial and divisive subject.
- Complete loss of contrast enhancement on follow-up CT or MRI is considered evidence of complete tissue destruction and attendant treatment success.
- The majority of lesions treated with cryoablation demonstrate a greater than 50% reduction in size in the first year following treatment. Lesions treated with RFA often do not demonstrate postablative contraction and failure to do so should not be interpreted as a treatment failure.
- Enlargement of a lesion, regardless of the treatment modality or the enhancement characteristics, should be construed as an ominous sign of local tumor recurrence.
- The American Urological Association Small Renal Mass Guidelines Panel recently recommended that tumor biopsy be universally performed at the time of ablation.
- The accuracy and utility of H&E and NADH staining following RFA is controversial.

ONCOLOGIC OUTCOMES

The interpretation of oncologic outcomes following renal tumor ablation is challenging. In general, ablative technologies have been thought to offer inferior cancer control compared to better-established extirpative alternatives. A recent meta-analysis demonstrating a higher relative risk of recurrence with cryoablation and RFA would seem to support this (Kunkle et al, 2008). However, the majority of published studies on cryoablation and RFA have enrolled small numbers of patients and employed disparate operative and follow-up protocols. As was explained, pathology is either not obtained or is difficult to interpret, and the reliability of radiographic imaging remains unknown. A veritable litany of commercially available and ever-evolving treatment systems and probes have further compounded the issue. Perhaps most importantly, collective follow-up is too short to derive meaningful conclusions. Much like radiation treatment for prostate cancer, a **discussion of oncologic efficacy regarding ablative technologies must focus less on defined and immediately gratifying end points, such as margin status, and more on long-term markers of success, such as metastasis-free survival, cancer-specific survival, and quality-of-life outcomes.** In an attempt to minimize inherent flaws with single institutional series, we have elected to present oncologic outcomes in a more evidence-based and systematic fashion. Individual salient studies of cryoablation and RFA are found in Tables 56–1 and 56–2.

Local Recurrence-Free Survival (LRFS)

Recent meta-analyses have evaluated the risk of local tumor recurrence following cryoablation and RFA (Kunkle et al, 2008; Novick et al, 2009). Local recurrence was defined as "any disease presence in the treated kidney or associated renal fossa posttreatment" and for ablation studies was defined as "any localized disease remaining in the treated kidney at any point after the first ablation." The AUA SRM Guidelines Panel examined 10 studies of cryoablation and 10 studies of RFA and determined a local recurrence-free survival of 90.6% (83.8% to 94.7%) for cryoablation and 87.0% (83.2% to 90%) for RFA. **When compared to alternative extirpative treatments, both cryoablation and RFA demonstrated significantly higher rates of local recurrence despite a shorter overall duration of follow-up.** There was no significant difference in local recurrence-free survival between cryoablation and RFA.

Kunkle and colleagues (2008) performed a landmark meta-analysis in which treatment outcomes with partial nephrectomy, cryoablation, RFA, and active surveillance were evaluated. A total of 99 studies and 6,471 tumors were included in the analysis. The relative risk of local recurrence was significantly higher with cryoablation (RR = 7.45) and RFA (RR = 18.23), respectively, when compared to partial nephrectomy. This same group performed a follow-up subanalysis including 1,375 renal tumors (47 total published series from 45 institutions) that underwent cryoablation ($n = 600$) or RFA ($n = 775$) alone (Kunkle and Uzzo, 2008). The rate of local tumor progression was 5.2% following cryoablation and 12.9% following RFA. The risk of local recurrence was significantly higher in the RFA cohort on univariate ($P = .001$) and multivariate ($P = .003$) analysis.

Metastatic Recurrence-Free Survival (MRFS)

The AUA SRM Guidelines Panel additionally examined the risk of metastatic recurrence, which was defined as "any disease presence in the body other than in the treated kidney or associated renal

Table 56–1.

Cumulative Outcomes of In-Situ Tumor Cryoablation for the Treatment of Small Renal Masses

AUTHOR	APPROACH	MEAN TUMOR SIZE	*N*	FOLLOW-UP	TREATMENT SUCCESS/RFS	CANCER-SPECIFIC SURVIVAL
Davol et al, 2006	Open/laparoscopic	2.6 cm	48	64 mo	87.5%	100%
Gill et al, 2005	Laparoscopic	2.3 cm	56	36 mo	94.4%	98%
O'Malley et al, 2006	Laparoscopic	2.7 cm	15	11.9 mo	100%	100%
Lawatsch et al, 2006	Laparoscopic	2.5 cm	59	26.8 mo	96.6%	N/A
Nadler et al, 2003	Laparoscopic	2.15 cm	15	15 mo	93.3%	N/A
Lee et al, 2003	Laparoscopic	2.56 cm	20	14.2 mo	100%	100%
Cestari et al, 2004	Laparoscopic	2.57 cm	37	20.5 mo	94.3%	N/A
Weight et al, 2008	Laparoscopic	2.4 cm	176	6 mo	94%*	N/A
Bandi et al, 2007	Laparoscopic	2.7 cm	58	22 mo	98.3%	100%
	Percutaneous	2.2 cm	20	12 mo	100%	100%
Weld et al, 2007	Laparoscopic	2.1 cm	31	45.7 mo	98.8%	100%
Finley et al, 2008	Laparoscopic	3.0 cm	19	13.4 mo	95.8%	100%
	Percutaneous	2.7 cm	18	11.4 mo	94.7%	100%
Derweesh et al, 2008	Laparoscopic	2.9 cm	34	25 mo	97.1%	100%
	Percutaneous	3.1 cm	26		88.5%	100%
Malcolm et al, 2009	Laparoscopic	2.33 cm	66	30 mo	96.2%	100%
	Percutaneous				75%	
Hinshaw et al, 2008	Laparoscopic	2.5 cm	60	14.6 mo	93.3%	100%
	Percutaneous	2.1 cm	30	14.5 mo	90%	100%
Shingleton and Sewell, 2004	Percutaneous	3.0 cm	90	30 mo	98%	100%
Gupta et al, 2006	Percutaneous	2.5 cm	20	5.9 mo	N/A	N/A
Atwell et al, 2008	Percutaneous	3.3 cm	80†	13.3 mo	100%	N/A

N/A, not available; RFS, recurrence-free survival.
*Based on biopsy results.
†80 patients with 115 total tumors.

Table 56–2.

Cumulative Outcomes of In-Situ Tumor Radiofrequency Ablation for the Treatment of Small Renal Masses

AUTHOR	APPROACH	MEAN TUMOR SIZE	*N*	FOLLOW-UP	TREATMENT SUCCESS/RFS	CANCER-SPECIFIC SURVIVAL
Zagoria et al, 2007	Percutaneous	2.7 cm	104	13.8 mo	93%	100%
Lewin et al, 2004	Percutaneous	2.3 cm	10	25 mo	100%	100%
Roy-Choudhury et al, 2003	Percutaneous	3.0 cm	8	17.1 mo	88%	88%
McDougal et al, 2005	Percutaneous	3.2 cm	16	60 mo	N/A	93.8%
Breen et al, 2007	Percutaneous	3.2 cm	97	17 mo	79%	N/A
Stern et al, 2009	Percutaneous Laparoscopic	2.1 cm	63	34 mo	98%	100%
Gervais et al, 2005	Percutaneous	3.2 cm	85	28 mo	90%	N/A
Park et al, 2006a	Percutaneous Laparoscopic	2.4 cm	78	25 mo	96.8%	98.5%
Levinson et al, 2008	Percutaneous	2.0 cm	31	61.6 mo	79%	100%
Varkarakis et al, 2005	Percutaneous	2.2 cm	46	27.5 mo	86.9%	N/A
Veltri et al, 2004	Percutaneous	3.65 cm	13	14 mo	94%	N/A
Farrell et al, 2003	Percutaneous	1.7 cm	20	9 mo	100%	100%
Schenk et al, 2005	Percutaneous	2.5 cm	115	12 mo	95%	N/A
Su et al, 2003	Percutaneous	2.2 cm	29	9 mo	94%	100%
Weight et al, 2008	Percutaneous	2.5 cm	88	6 mo	65%*	N/A
Matsumoto et al, 2005	Percutaneous Laparoscopic	2.4 cm	91	19.4 mo	98%	100%
Pavlovich et al, 2002	Percutaneous	2.4 cm	21	N/A	79.1%	N/A
Hwang et al, 2004	Percutaneous Laparoscopic	2.26 cm	17	12 mo	93%	100%

N/A, not available; RFS, recurrence-free survival.
*Based on biopsy results.

fossa post-treatment." Mean metastatic recurrence-free survival was 95.3% (91.1% to 97.5%) for cryoablation and 97.5% (94.8% to 98.8%) for RFA (Novick et al, 2009). Interestingly, **there was no significant difference in metastatic recurrence-free survival between the ablative technologies and alternative extirpative treatments** including open partial nephrectomy and laparoscopic radical nephrectomy. There was a significant difference in MRFS in favor of laparoscopic partial nephrectomy. The authors did note that duration of follow-up was inadequate to draw conclusions and selection bias may have confounded the analysis.

In Kunkle's initial meta-analysis, the relative risk of metastatic disease was not significantly different between cryoablation, RFA, active surveillance, and partial nephrectomy (Kunkle et al, 2008). Subsequent analysis of ablation patients alone demonstrated progression to metastatic disease in 1% of patients who underwent cryoablation and 2.5% of patients who underwent RFA ($P = .06$) (Kunkle and Uzzo, 2008).

Cancer-Specific Survival (CSS)

The AUA meta-analysis additionally examined the risk of dying from RCC following cryoablation (six studies were included) or RFA (eight studies were included). **CSS was 95.2% (89.2% to 97.9%) with cryoablation and 98.1% (95.2% to 99.2%) with RFA.** CSS was significantly higher with laparoscopic partial nephrectomy than for cryoablation but there was no significant difference in CSS between LPN and RFA. There was no significant difference in CSS between cryoablation and RFA. Again, selection bias and short duration of follow-up may confound these results.

Overall Survival

Mean overall survival rate following cryoablation was 95.8% (87.2% to 98.7%) and 93.7% (85.4% to 97.4%) for RFA. **There was no significant difference in overall survival between cryoablation and RFA.** Again, limited follow-up and selection bias may confound these results.

Cryoablation versus RFA

Any debate regarding the superiority of cryoablation versus RFA is subject to the same faults, confounders, and ambiguities as the aforementioned comparisons between in-situ tumor ablation and extirpation. Beyond issues of ill-defined radiologic and pathologic end points, there is considerable variability in patient selection, tumor size and location, technique, and approach (laparoscopic vs. percutaneous), as well as inherent bias for a particular ablative modality. To our knowledge, there is no data that directly compares percutaneous and laparoscopic cryoablation to its respective RFA counterparts.

Hegarty and colleagues performed the only published comparative study of cryoablation and RFA in 2006. This retrospective cohort study was performed to determine complications, impact on renal function, follow-up imaging, and oncologic outcomes comparing 164 laparoscopic cryoablation procedures and 82 percutaneous RFA procedures. There was no significant difference in tumor size between the two groups, but the RFA cohort demonstrated more central tumors and tumors in solitary renal units. Radiographic evidence of disease persistence or recurrence was noted in 1.8% of patients who underwent cryoablation and in 11.1% of patients who underwent RFA. There was no significant impact on renal function with either modality. At a median follow-up of 3 years, the CSS for cryoablation was 98%; at a median follow-up of 1 year, the CSS for RFA was 100%. Although the study was successful in articulating the need for improved comparative analysis, its results are difficult to fully embrace given the incongruent patient cohorts and treatment approaches.

Ultimately, the results of the three recent meta-analyses discussed previously offer the most insight into the comparative

oncologic merit and potential limitations of cryoablation and RFA (Kunkle et al, 2008; Kunkle and Uzzo, 2008; Novick et al, 2009). **Although some data is conflicting, it appears that there is no significant difference in the risk of local tumor recurrence, disease progression/metastasis, cancer-specific survival, and overall survival between the two modalities.**

Laparoscopic versus Percutaneous Renal Tumor Ablation

One proposed explanation for the higher local recurrence rate with RFA in some series centers on the adequacy of tumor ablation by the percutaneous approach. Indeed, the vast majority of cryoablation procedures are approached laparoscopically, while nearly 90% of RFA procedures are performed percutaneously (Deane, 2006; Carraway et al, 2009). Crouzet and colleagues (2009) retrospectively compared 244 laparoscopic renal cryoablation procedures with 63 percutaneous renal cryoablation procedures. Patient and tumor characteristics were similar with both cohorts. There was a trend toward prior renal surgery or a solitary renal unit with percutaneous cryoablation. There was no significant difference in renal functional outcomes between the two groups. Duration of hospitalization was shorter in the percutaneous cohort. With a minimum follow-up of 2 years, the percutaneous cohort demonstrated a higher incomplete treatment rate and the need for re-treatment. There was no difference in overall survival, CSS, and recurrence-free survival between the two groups. Similar studies comparing laparoscopic and percutaneous tumor ablation have confirmed these findings (Derweesh et al, 2008; Hinshaw et al, 2008; Hui et al, 2008; Malcolm et al, 2009).

In contradistinction to these studies, Finley and colleagues (2008) reported their 4-year experience with laparoscopic and percutaneous renal cryoablation in 37 patients with 43 tumors. Operative time and duration of hospitalization were significantly shorter with the percutaneous approach, and there was no significant difference in the number of incomplete ablations.

Key Points: Oncologic Outcomes

- The interpretation of oncologic outcomes following renal tumor ablation is challenging.
- When compared to alternative extirpative treatments, both cryoablation and RFA demonstrate significantly higher rates of local recurrence, despite a shorter overall duration of follow-up.
- There is no apparent significant difference in metastatic recurrence-free survival between the ablative technologies and alternative extirpative treatments.
- Any discussion of oncologic efficacy regarding ablative technologies must focus less on defined and immediately gratifying end points, such as margin status, and more on long-term markers of success, such as metastasis-free survival, cancer-specific survival, and quality-of-life outcomes.
- Although some studies demonstrate inferior local recurrence rates with RFA when compared with cryoablation, these results are controversial and subject to considerable debate. There is no apparent difference in cancer-specific or overall survival between the two modalities.

Researchers have investigated exclusive use of general anesthesia and advanced navigational systems as mechanisms to improve outcomes with percutaneous ablation (Gupta et al, 2009; Haber et al, 2009).

COMPLICATIONS

Complications with in-situ tumor ablation are relatively low. A recent meta-analysis compared urologic and nonurologic complications following cryoablation, radiofrequency ablation, and alternative extirpative approaches (Novick et al, 2009). Major urologic complications were defined as postoperative hemorrhage requiring transfusion or intervention, urinary leak, abscess, and unanticipated loss of renal function. **The incidence of major urologic complications with renal cryoablation was 4.9% (range 3.3% to 7.4%). Postoperative hemorrhage is the most commonly cited major adverse risk,** with ureteral obstruction, splenic hematoma, and perirenal abscess additionally reported. **The risk of major urologic complications with RFA is 6.0% (4.3% to 8.2%).** Reported major complications with RFA include ureteral obstruction, pyelocalyceal injury, bowel injury, pancreatic injury, and/or gross hematuria requiring intervention. Of note, **the risk of major urologic complications was lower with ablative techniques than with either laparoscopic or open partial nephrectomy, and there was no significant difference in urologic complications with cryoablation versus RFA.**

Major nonurologic complications occurred in 4.9% (3.4% to 7.2%) of cryoablation patients and in 4.4% (3.2% to 6.2%) of RFA patients. Of note, nonurologic complications were significantly more common with cryoablation than with RFA or open partial nephrectomy. This higher complication rate with cryoablation may reflect the older patient population in the cryoablation cohort. **Commonly cited minor complications with cryoablation and RFA include pain and paresthesia at the probe insertion site, urinary tract infections, and self-limited hematuria.**

Conversion was defined in the meta-analysis as a deviation from the intended surgical procedure or approach. The overall conversion rate for cryoablation was 3.5% with bleeding, adhesions, and respiratory difficulty cited as common reasons for conversion. The conversion rate for RFA was 1.6% with proximity to bowel as the only cited reason. Of note, only one RFA study was included in the analysis. Deriving meaningful conclusions regarding the superiority of RFA versus cryoablation with regard to conversions is therefore difficult.

The cited rate of transfusion with cryoablation is 3.2% (2.0% and 20%) and is 2.4% (1.4% to 40%) with RFA. Indeed, the most commonly encountered complication with cryoablation is bleeding, especially in the setting of tumor or renal fracture (up to 17% of patients with renal fracture require transfusion). Lehman and colleagues (2008) additionally noted that tumors greater than 3.0 cm in size were significantly more likely to require a blood transfusion (38%). Bleeding following RFA is relatively uncommon given the ability to perform a hemostatic "track burn" on probe withdrawal.

Reintervention was defined in the meta-analysis as any unplanned operation occurring during or after the planned renal surgery. Reintervention occurred in 2.6% (1.5% to 4.3%) of cryoablation patients and 3.2% (1.9% to 5.1%) of RFA patients. **The risk of reintervention was significantly higher in patients undergoing laparoscopic partial nephrectomy than with either ablative technique.**

Key Points: Complications Following Tumor Ablation

- The incidence of major urologic complications with renal cryoablation is estimated at 4.9%. Postoperative hemorrhage is the most commonly cited major adverse risk.
- The risk of major urologic complications with RFA is 6.0%. Bleeding is not a significant risk factor following RFA.
- The risk of major urologic complications is lower with ablative techniques than with either laparoscopic or open partial nephrectomy. There is no significant difference in urologic complications between cryoablation and RFA.
- Commonly cited minor complications with cryoablation and RFA include pain and paresthesia at the probe insertion site, urinary tract infections, and self-limited hematuria.

FUTURE TRENDS

Extracorporeal High-Intensity Focused Ultrasonography (HIFU)

As an acoustic wave is propagated through tissue, a portion of its energy is absorbed and converted into heat (Madersbacher et al, 1995; Vricella et al, 2009). When ultrasound beams are tightly concentrated, temperature levels approach or exceed the threshold for cell kill (65° C to 85° C) within this focused field, while adjacent tissue is spared. At high enough intensities (>3500 W/cm^3), cavitation and microbubble formation occurs that yields extremely high temperatures and a mechanically disrupting "shock wave" effect similar to that seen with extracorporeal shock wave lithotripsy (Kieran et al, 2007). Cavitary forces are extremely difficult to control during HIFU and are generally avoided.

HIFU employs a transducer that is used for treatment and monitoring. The ultrasound beams are focused geometrically through the transducer by employing an acoustic lens or a concave shape. Under real-time guidance, the HIFU beam is focused on the treatment zone and a defined area is ablated. The transducer can then be refocused to ablate a larger overall volume of tissue. Treatment times can be lengthy with a mean reported duration of nearly 5½ hours (1.5 to 9 hours) (Köhrmann et al, 2002; Marberger et al, 2005; Häcker et al, 2006). Myriad parameters, including focal length, type of transducer employed, and type of treatment system, have been investigated and are beyond the scope of this chapter.

Certainly, the promise of a noninvasive ablative technology that offers favorable and reproducible outcomes is extremely attractive. However, existing studies have yielded mixed results. Vallancien and colleagues (1993) performed a pilot study in which eight patients underwent targeted transcutaneous HIFU ablation followed by specimen excision. Approximately 10% of the cohort exhibited skin burns, and all specimens demonstrated pathologic evidence of viable tumor. Marberger and colleagues (2005) evaluated 18 renal units treated with HIFU followed by specimen extraction. Similar to the findings of Vallencien, incomplete ablation was noted in all cases. Häcker and colleagues (2006) additionally assessed the efficacy of HIFU by treating normal portions of 24 kidneys prior to preplanned completion radical nephrectomy. Coagulative necrosis was sporadic and inconsistent with the number of treatments applied. Again, skin burns were noted in two patients. Purported explanations for these collective incomplete treatments have included poor targeting secondary to respiratory movement and acoustic interference (acoustic shadowing, reverberation, and refraction), as well as system limitations including limited focal zone depth and an inability to monitor treatment progression in real time. Recently, laparoscopic HIFU has been investigated in an attempt to circumvent issues related to targeting, acoustic interference, and respiratory movement (Klingler et al, 2008). Results are anecdotal but favorable. **In summary, outcomes with renal HIFU have proven inferior to alternative ablative technologies, and its use in this regard should be considered investigational.**

Radiation Therapy

Historically, radiation therapy has been considered ineffective in the treatment of renal cell carcinoma. Although RCC is widely considered "radioresistant," it is unclear if this assertion is justifiable. It remains unclear if poor outcomes with radiation therapy for RCC are due to an inherent resistance to radiation or due to limitations with radiation delivery (Camphausen and Coia, 2008). Modern external beam radiation systems are inadequately designed to deliver high doses in a focal manner. With conventional treatment systems, high-dose radiation is associated with significant radiation scatter and attendant damage to adjacent tissues. Brachytherapy is better tailored for focal ablation, but its logistic application (seed placement in the kidney) for renal indications remains impractical.

Stereotactic radiosurgery (SRS) employs 3-dimensional coordinates to target and focally ablate tissue using high-dose external beam radiation. As opposed to conventional radiation delivery techniques, modern stereotactic treatment systems compensate for respiratory movement and radiation scatter by automatically tracking, detecting, and correcting for tumor and/or organ movement without interrupting the treatment or repositioning the patient. This tracking system is image guided and dependent on a constant reference point (fiducial marker) that is continually recognized by the linear accelerator. High-dose radiation beams move in real time with the respiratory cycle and are therefore extremely accurate (Ponsky et al, 2007). Not only is radiation scatter minimized, but higher doses may be applied in a focal manner that effectively ablates masses in the kidney without compromising overall renal function. The most commonly used stereotactic radiosurgical system is termed CyberKnife (Accuray, Palo Alto, CA). The CyberKnife is a 6-MV frameless linear accelerator mounted on a computer-controlled robotic arm. An image-guidance system as described above is employed to continually monitor movement of the target organ and deliver high-dose radiation in a focused fashion.

Ponsky and colleagues (2003) evaluated stereotactic radiosurgery in the treatment of renal tissue. Eight pigs underwent bilateral renal irradiation using the CyberKnife treatment system. Treatment doses of between 24 to 40 Gy were administered. The pigs were sacrificed 4 to 8 weeks following ablation. The treatment zone demonstrated complete tissue ablation with no collateral damage to adjacent tissue. Building on this initial animal experiment, Ponsky subsequently performed a Phase I study on three human patients with a mean renal tumor size of 2.03 cm. A total of 16 Gy were administered in a fractionated fashion. Patients were followed for 8 weeks, after which a partial nephrectomy was performed (a so-called treat and cut study). No adverse events or radiation toxicities were noted. Examination for pathology demonstrated residual RCC in two patients and no evidence of

viable tumor in the remaining patient. However, low doses were used in this initial feasibility study, and dose escalation trials are ongoing.

Svedman and colleagues (2006) performed a retrospective study evaluating the efficacy and safety of stereotactic radiosurgery in the management of inoperable or metastatic primary renal cell carcinoma. Thirty patients with 82 lesions underwent treatment with varied dose/fractionation schedules. At a median follow-up of 52 months, complete response was noted in 21% of patients, with another 58% demonstrating a partial/stable response. Overall survival was 32 months.

Certainly, the responsiveness of RCC to stereotactic radiosurgery in the aforementioned trials argues against its radioresistant reputation. **Although its use should still be considered experimental, with improved treatment protocols and well-designed prospective trials, SRS may ultimately play a significant role in the treatment of RCC.**

Microwave Thermotherapy (MWT)

MWT delivers energy through flexible antennae that are inserted directly into the target lesion. Microwave energy creates an electromagnetic field that causes rapid ion oscillation and frictional heat. Although ostensibly similar in design and technique to RFA, MWT is capable of achieving treatment temperatures (>60° C) with greater rapidity. Moreover, MWT is not limited by tissue charring and desiccation and is able to achieve high treatment temperatures over a broader area. These advantages may translate into more efficient treatments and improved cell kill. Although theoretical, there is also some evidence that MWT is less susceptible to the heat-sink phenomenon and may therefore be applied in the treatment of highly vascular lesions (Liang and Wang, 2007).

MWT was initially designed for the percutaneous treatment of hepatocellular carcinoma and has enjoyed considerable success in this capacity. Its use in the management of renal tumors remains investigational, with sporadic feasibility studies supporting its use. MWT was initially employed during unclamped open partial nephrectomy to create an avascular plane prior to tumor resection. More recently, MWT has been investigated as a therapeutic in-situ renal ablative device. Clark and colleagues (2007) performed a Phase I study in which 10 patients underwent MWT of suspected RCC at the time of radical nephrectomy. When examined pathologically, ablation lesions as large as 5.7 cm × 4.7 cm × 3.8 cm were achieved with complete and uniform tissue necrosis. The authors advocated "treat and leave" studies to confirm their findings. In 2008, Liang and colleagues published their series of 12 patients who underwent percutaneous MWT under ultrasound guidance (a so-called treat and leave protocol). All patients demonstrated pathologically proven unilateral renal cell carcinomas that were less than 4 cm, not adjacent to the collecting system or bowel, and were accessible through a percutaneous approach. One or two antennae were employed (depending on tumor size) to ablate the renal lesion, and thermocouples were used to monitor treatment temperatures in real time. No significant adverse events were reported following treatment. All patients underwent follow-up imaging at 1 day, 1 month, 3 months, and 6 months following treatment. At a median follow-up of 11 months, no cancer recurrence was noted on imaging.

MWT offers considerable promise as yet another minimally invasive ablative technology. However, until prospective studies are available, its use should remain investigational.

Laser Interstitial Thermal Therapy (LITT)

LITT employs specialized laser fibers to delivery energy directly into tissue. These fibers emit laser light that is converted to heat. Treatment temperatures of greater than 55° C are achieved, and tissue necrosis results. Thus far, LITT has relied on neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers and diode lasers. Results have been difficult to interpret owing to the small number of treated patients and a lack of clinical follow-up (Dick et al, 2002; Gettman et al, 2002b; Williams et al, 2000). **The use of LITT remains investigational.**

Navigational Systems

In an attempt to better localize, control, and predict the area of treatment during percutaneous cryoablation, novel navigational and targeting systems have been developed. Haber and colleagues (2009) performed percutaneous renal cryoablation of 13 lesions in 10 patients using a stereotactic navigational system (CT-Nav; Keolis, La Tronche, France) designed to direct renal biopsy and probe placement. Patients underwent preoperative CT scan with a preplaced tracking sensor taped to the body of the patient. Using a stereoscopic infrared camera, the tracking sensor was located three-dimensionally and a tracking handle used to guide probe placement. The mean calculated error in targeting with use of the navigational device was 4.2 mm. The most significant variability occurred in the cephalad/caudad axis consistent with respiratory movement. Although purely experimental, these tracking and targeting systems may represent a significant advance in the percutaneous application of ablative technologies.

Single Port Surgery/NOTES

Developed as an extension of standard laparoscopy, laparoendoscopic single-site (LESS) surgery seeks to minimize patient discomfort, shorten convalescence, and improve cosmesis by placing all instruments through a 2 cm incision, sometimes concealed in the umbilicus (Kaouk et al, 2008).

In 2008, Goel and colleagues published their clinical experience with single-port access renal cryoablation (SPARC) in six patients with small renal masses (Goel and Kaouk, 2008b). Using either a transperitoneal or retroperitoneal approach, all procedures were successfully completed without intraoperative complications. A subsequent publication from the same group cited eight total single-port cryoablation procedures (White et al, 2009). Mean tumor size was 2.64 cm. Mean operative time was 171 minutes. Two patients required postoperative blood transfusions. No recurrences were noted on follow-up imaging. The authors stated that renal ablative procedures may represent an attractive and natural transition into single-port surgery as limited dissection and reconstruction are needed.

Natural orifice translumenal endoscopic surgery (NOTES) employs a natural orifice, such as the vagina, bladder, stomach, or colon, as the entry point to the peritoneal cavity. Ostensibly, NOTES should offer superior cosmesis and decreased pain compared to conventional laparoscopy. However, operating through a natural orifice is technically very challenging with only two NOTES extirpative urologic procedures successfully completed (Kaouk et al, 2009). Much like single-port surgery, NOTES is ideally suited for ablative procedures that require minimal dissection and

reconstruction. Crouzet and colleagues (2009) reported bilateral transgastric and transvesical renal cryoablation in two female farm pigs. All four procedures were successfully completed without the need for additional ports. There were no intraoperative complications.

Chemoablation and Combined Chemoablation with RFA

The percutaneous injection of 95% ethanol to ablate renal cysts was originally described by Bean in 1981. This conceptual approach was later applied in the treatment of hepatocellular carcinoma with moderate success. Clayman and colleagues later evaluated injectable 95% ethanol, 24% hypertonic saline gel, and 50% acetic acid gel alone or in combination with RFA in a porcine study (Rehman et al, 2004). The authors demonstrated inadequate tissue necrosis with any of the injectables alone but noted enhanced tissue necrosis with the use of chemoablative agents in conjunction with RFA. The combined use of hypertonic saline with RFA produced the largest overall lesions. A second study from Fotiadis and colleagues (2007), in the United Kingdom, evaluated combined RFA and ethanol injection in 27 patients (28 total tumors) with a mean tumor size of 2.87 cm. Absolute ethanol was injected into the tumor just prior to RFA treatment. At a mean follow-up of approximately 18 months, 27 of 28 tumors were completely ablated with one (21 tumors) or two (6 tumors) treatments. No local recurrence or metastases occurred. **Currently, injectable chemoablation agents are difficult to reproducibly control and provide inferior tissue necrosis. Combined RFA/injectable chemoablation remains investigational.**

Targeted Embolization and Ablation

Owing to the heat-sink phenomenon with RFA, highly vascular central lesions or lesions positioned adjacent to the renal hilum are often inadequately ablated. Studies estimate treatment failures as high as 40%. In an attempt to address conductive heat loss, investigators have performed selective arterial embolization prior to RFA (Yamakado et al, 2006; Gebauer et al, 2007; Mahnken et al, 2009). Theoretically, selective embolization should allow for more homogenous heating and improved tissue necrosis. **Clinical reports are sporadic and anecdotal. Therefore the use of targeted angioembolization prior to RFA remains investigational.**

CONCLUSIONS

The role of in-situ ablation in the management of small renal masses is rapidly evolving. Once considered experimental and appropriate only for patients with significant comorbidities, cryoablation and radiofrequency ablation are currently considered viable alternatives to extirpative management. In-situ ablation confers less treatment-related morbidity than either open or laparoscopic partial nephrectomy and offers superior renal preservation compared with open or laparoscopic nephrectomy. Cryoablation and RFA are technically less challenging than other nephron-sparing approaches and may allow general urologists without advanced laparoscopic training to selectively provide their patients with a minimally invasive nephron-sparing treatment. Results from recent meta-analyses demonstrate inferior local tumor control compared with partial and radical nephrectomy, but with equivalent or superior cancer-specific and overall survival. Interpretation of treatment success remains challenging with existing protocols, and long-term follow-up is needed to confirm these findings. No prospective literature currently exists that addresses the superiority of cryoablation or RFA. Some evidence exists that percutaneous tumor ablation offers incomplete primary treatment, but with improved recovery and decreased morbidity. Without question, prospective, comparative trials with uniform radiographic and pathologic follow-up are needed to address many of these uncertainties. Ultimately, the decision to treat a small renal mass with an ablative technology should take into account tumor-related characteristics, patient demographics and comorbidities, and the values and desires of the patient.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter 57

Pathophysiology, Evaluation, and Medical Management of Adrenal Disorders

Alexander Kutikov, MD • Paul L. Crispen, MD • Robert G. Uzzo, MD

Historical Background
Adrenal Anatomy and Embryology
Adrenal Physiology
Adrenal Disorders
Evaluation of Adrenal Lesions in Urologic Practice

The adrenal glands are small and deceptively simple. Formerly known as the suprarenal glands, given their location above the kidneys, this paired triangular organ sits at an anatomical crossroads in the upper abdomen adjacent to major vessels, nerves, and other vital organs, which they help to monitor and regulate. The complexities of adrenal endocrine and neurocrine function only recently have been more fully recognized. Indeed, **adrenals are now known to be central to homeostasis.** Moreover, pathology involving the glands is responsible for major human ailments.

Given the varied systemic adrenal functions and dysfunctions, medical management is primarily within the purview of endocrinologists, nephrologists, and cardiologists. Similarly, surgical management of adrenal diseases historically has been divided among urologists, general surgeons, surgical oncologists, and, more recently, endocrine surgeons with referral patterns often dependent on traditions established at individual institutions. With the urologist's advanced minimally invasive surgical skills, comfort with both retroperitoneal anatomy and surgical approaches to retroperitoneal organs, and the close relationship between renal and adrenal pathophysiology, **it is natural that the evaluation and surgical management of adrenal disorders remain firmly in the domain of practicing urologic surgeons.**

HISTORICAL BACKGROUND

The diminutive adrenal glands were easily overlooked by early physicians. Distinguished anatomists such as Galen, da Vinci, and Vesalius omitted the adrenal glands in their descriptions of the retroperitoneum. Bartholomaeus **Eustachius was the first to describe the organs in the mid-16th century** (Scott, 1990). Not until the mid-19th century was the critical importance of the adrenal recognized when **Thomas Addison,** an English physician, described a series of patients with the condition of **adrenal insufficiency** that now carries his name. He linked the disease to the adrenal glands upon careful inspection of the organs at autopsy (Addison, 1855). Soon thereafter, **Charles Brown-Sequard,** through a series of animal experiments demonstrated that **bilateral adrenalectomy uniformly resulted in death,** suggesting that the adrenals were indispensable to the survival of the host (Brown-Sequard, 1856). William Osler was the first to report treatment of Addison disease with hormonal replacement in 1896. He administered crude extract from the adrenal glands of pigs to a patient with Addison disease and produced significant weight gain in this one individual (Oliver and Sharpey-Schafer, 1895). In the ensuing half-century "adrenalin" was discovered, and its production was localized to the adrenal medulla (Oliver and Sharpey-Schafer, 1895). The ability of adrenaline to produce a sustained rise in blood pressure was subsequently determined (Abell and Crawford, 1897). Moreover, the failure of this substance, later termed "epinephrine" to sustain life following bilateral adrenalectomy underscored the complexity and multifunctionality of the adrenal gland and established Addison disease as an ailment of the adrenal cortex (Scott, 1990; Porterfield et al, 2008). Discovery and **isolation of cortisol from the adrenal gland** in the 1930s and subsequent work on its use to treat rheumatoid arthritis produced a **1950 Nobel Prize** in Physiology and Medicine for Edward Kendall, Philip Hench, and Tadeus Reichstein (Scott, 1990). Aldosterone was ultimately isolated from the bovine adrenal in 1952 (Grundy et al, 1952). The latter part of the 20th century witnessed a rapid transformation in our understanding and treatment of adrenal disorders lead by pioneers such as Jerome Conn, Lawson Wilkins, Grant Liddle, and Earl Sutherland (Scott, 1990).

ADRENAL ANATOMY AND EMBRYOLOGY

Overview

The adrenal glands are paired retroperitoneal organs composed of a cortex and medulla. Gross examination reveals a distinct spiculated mustard-yellow–colored cortex that is distinct from the surrounding perinephric fat and the inner medulla, which can be

distinguished macroscopically on cross section by its central brown color (see Figs. 57–1 and 57–2 on the Expert Consult website). The normal adrenal gland weighs an average of 4 to 5 g each and range in size from 4 to 6 cm in length and 2 to 3 cm in width (Mitty, 1988; Silverman and Lee, 1989; Avisse et al, 2000). Morphologically, the right adrenal gland is triangular in shape while the left adrenal gland is crescent shaped (Avisse et al, 2000). They may sit either immediately superior to the kidney, "capping" the upper pole, or superior medially to the upper pole, "cradled" by the kidney just above the renal vessels. Once understood, this difference can be appreciated by either computed tomography (CT) scan or magnetic resonance imaging (MRI) and is a relevant surgical distinction, particularly in patients with substantive perinephric fat and on the left side when identifying the adrenal vein.

Embryology

The adrenal cortex and the medulla are two embryologically and functionally distinct units. The cortex is derived from the intermediate mesoderm of the urogenital ridge (Mitty, 1988; Barwick et al, 2005). Beginning in the 5th week of gestation, mesenchymal cells located at the urogenital ridge and the root of the mesentery proliferate and form the cortex of the fetal adrenal gland. During the 6th and 7th weeks of gestation, additional mesothelial cells surround the fetal adrenal cortex, which will later form the adult adrenal cortex (Mitty, 1988; Barwick et al, 2005). By the end of the 8th week of gestation the mesothelial cells forming the cortex are encapsulated by connective tissue and have separated from the peritoneal mesothelium. In distinction, the adrenal medulla is derived from neural crest cells, located in adjacent sympathetic ganglia, which migrate into the medial aspect of the fetal adrenal cortex by the 9th week of gestation (Kempna and Fluck, 2008). The neural crest cells continue to invade the adrenal cortex until they achieve a central position surrounding the adrenal vein by the 18th week of gestation. This embryologic relationship explains the brown stippling of the adrenal cortex.

At birth, the fetal adrenal gland is twice the weight of an adult adrenal gland, but has not completed development. After birth, the fetal cortex begins to atrophy and will be completely resorbed by 12 months of age (Mitty, 1988). As the fetal cortex is being resorbed, the zona glomerulosa and fasciculata of the adult cortex continue to develop, but the zona reticularis will not complete differentiation until 3 years of age, reflecting the relative late importance of sex steroid production by this part of the adrenal cortex (Barwick et al, 2005; Kempna and Fluck, 2008).

Cases of unilateral adrenal agenesis are rare and are often associated with unilateral renal agenesis (Nakada et al, 1988; Else and Hammer, 2005). However, because adrenal and renal development are separate processes, this association is likely spurious and is the result of limited radiographic evaluation of the ipsilateral adrenal gland in cases of renal agenesis. **Most often, adrenal gland development occurs normally in the absence of ipsilateral renal unit development, malrotation, or malascent. In these cases, the adrenal glands are often discoid in shape and located in their normal position within the retroperitoneum** (Mitty, 1988).

More common anomalies of adrenal gland development include accessory adrenal tissue and adrenal heterotopia. Accessory renal tissue, also known as adrenal rests, can be composed of cortical or medullary tissues. Due to the close proximity of the adrenal gland and genitourinary organ development, adrenal rests can be found anywhere along the path of gonadal descent within the retroperitoneum. Although adrenal rests can be found in up to 50% of neonates, the tissue typically atrophies and is found in only approximately 1% of adults (Barwick et al, 2005). In cases of congenital adrenal hyperplasia (CAH), adrenal rest within the testis may become hyperplastic and present as a testicular mass. This is an important consideration prior to performing an orchiectomy for a testicular mass in patients with CAH. Adrenal heterotopia results from incomplete separation of primitive adrenal mesoderm from adjacent organs such as the liver or kidney, resulting in partial or complete incorporation of the gland into the adjacent organ.

Anatomy

The right and left adrenal glands are located within Gerota fascia at the levels of the 11th and 12th ribs and share several important anatomic relationships, including being located cephalad to the upper pole of the kidneys and anterior to the crus of the diaphragm. The right adrenal is bounded medially by the inferior vena cava and anteriorly by the liver, while the left adrenal gland is bounded medially by the aorta and anteriorly by the stomach, pancreas, and splenic vessels. The close juxtaposition of these organs to the adrenal explains why lesions of adjacent organs, such as leiomyomas of the greater curvature of the stomach, may be confused for an adrenal mass.

As with most endocrine organs, the blood supply to the adrenal gland is redundant. Although variable, the arterial supply of each adrenal gland may arise from three main sources: superior adrenal arteries (branches from the inferior phrenic arteries), middle adrenal arteries (direct visceral branches from the aorta), and inferior adrenal arteries (branches from the ipsilateral renal artery (see Fig. 57–1). The main adrenal arteries then branch to form a subcapsular plexus. From the subcapsular plexus some branches continue directly to the medulla, while others form sinusoids supplying the adrenal cortex. On the venous side, medullary veins coalesce to form the adrenal vein, which is surrounded by medullary tissue within the adrenal gland. The short right adrenal vein drains directly into the vena cava. On the left, the adrenal vein is long compared with the right and is joined by the inferior phrenic vein prior to draining into the left renal vein. The overlapping of both arterial and venous anatomy makes partial adrenalectomy possible with little risk of subsequent adrenal infarction. The principal lymphatic drainage of the adrenal glands is through the paracaval lymph nodes on the right and the para-aortic lymph nodes on the left.

The autonomic innervation of the adrenal glands includes predominantly preganglionic sympathetic fibers off the sympathetic trunk directly to the chromaffin cells of the adrenal medulla, while postganglionic fibers originating from the splanchnic ganglia provide innervation to the adrenal cortex. Parasympathetic innervation to the adrenal cortex and medulla is not well defined; however, animal models suggest that parasympathetic branches originating from the vagus nerve may be present.

Histology

Each adrenal gland is enclosed within a fibrous capsule (see Fig. 57–2). Directly beneath the capsule is the cortex, which comprises three zones: the zona glomerulosa, the zona fasciculata, and the zona reticularis. The zona glomerulosa consists of small polyhedral cells with scant eosinophilic cytoplasm and dark round nuclei. The essential function of the glomerulosa is the production of mineralocorticoids, predominantly aldosterone. The broad layer of large pale cells arranged in vertical columns beneath the zona

glomerulosa is the zona fasciculata responsible for the production of glucocorticoids such as cortisol. The zona reticularis, the innermost layer of the cortex, consists of round dark staining cells and predominantly produces sex steroids, such as adrenal estrogens and androgens (Mitty, 1988; MacLennan et al, 2003) (Table 57–1).

Key Points: Anatomy and Embryology

- The adrenal glands are composed of two embryologically and functionally distinct components: the cortex and the medulla (the former endocrine, the latter neurocrine).
- The arterial supply of the adrenal glands is variable and can arise from several sources. However, the venous drainage is more predictable with the right adrenal vein emptying into the inferior vena cava and the left adrenal vein draining into the left renal vein in the majority of patients.

ADRENAL PHYSIOLOGY

Other than their juxtaposed anatomic associations, the adrenal cortex and the adrenal medulla are best conceptualized as two distinct organs, the former endocrine and the latter neurocrine.

Adrenal Cortex Physiology

As part of a multistep synthetic pathway, numerous enzymes of the adrenal cortex catalyze conversion of essential steroid hormones from the common precursor cholesterol. Low-density lipoprotein (LDL) serves as the primary source of cholesterol for the adrenal (Arlt and Stewart, 2005). **Ratios and types of enzymes in each zone of the adrenal cortex vary, resulting in different hormonal products for each region** (Fig. 57–3) (Rainey, 1999).

Steroid hormone receptors are absent on cellular membranes of target tissues. Instead, steroids diffuse passively into the cell and bind to their respective receptors intracellularly. Gene transcription is then modulated by direct binding of the hormone receptor complex to target DNA (Arlt and Stewart, 2005). As discussed previously, the three main zones of the adrenal cortex are zona glomerulosa, zona fasciculata, and zona reticularis with each zone primarily responsible for mineralocorticoid (100 to 150 mcg/day), glucocorticoid (10 to 20 mg/day), and androgen synthesis (>20 mg/day), respectively (Arlt and Stewart, 2005).

Table 57–1.
Primary Effects of Mineralocorticoids

ACTION	EFFECT	SITE OF ACTION
Renal sodium reabsorption	Increased blood volume Increased blood pressure Decrease in urine sodium	Distal tubule Connecting segment Collecting duct
Renal chloride reabsorption	Increase in serum chloride Decrease in urine chloride	Distal tubule Connecting segment Collecting duct
Renal potassium secretion	Decrease in serum potassium Increase in urine potassium	Distal tubule Connecting segment Collecting duct
Renal proton secretion	Increased urine NH_4	Collecting duct—a result of sodium reabsorption

NH_4, ammonia.

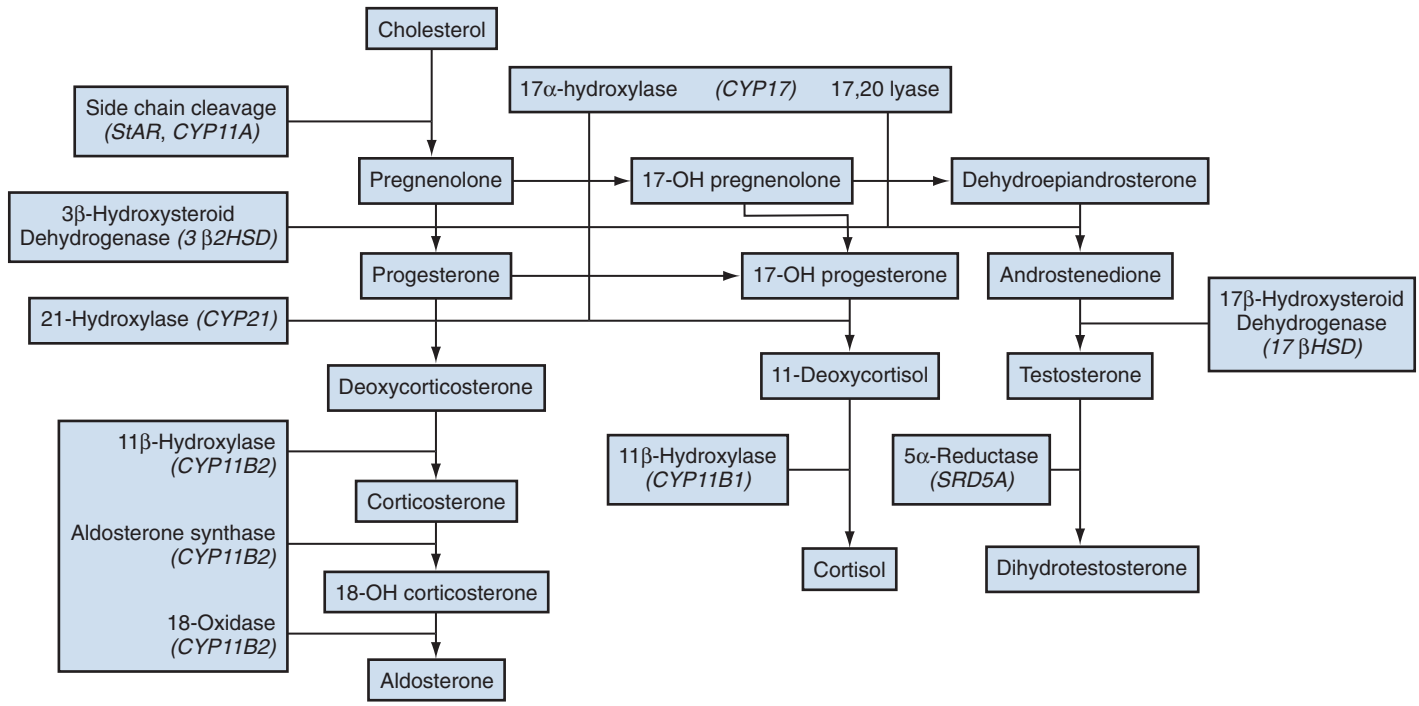


Figure 57–3. Steroid hormone synthesis beginning with cholesterol and resulting in mineralocorticoid, glucocorticoid, and androgen production in the adrenal cortex. Enzymes are listed in boxes and genes in parentheses. (From Hyun G, Kolon TF. A practical approach to intersex in the newborn period. Urol Clin N Am 2004;31:435–43.)

Zona Glomerulosa

The zona glomerulosa is the outermost region of the adrenal cortex and is the only zone of the adrenal gland that contains the enzyme aldosterone synthase (CYP11B2). As a result, the glomerulosa cells of this tissue are **the sole source of aldosterone**—the primary human mineralocorticoid (Rainey, 1999). Aldosterone regulates electrolyte metabolism by stimulating epithelial cells of the distal nephron to reabsorb Na^+ and Cl^-, while secreting H^+ and K^+. Although aldosterone levels have a profound effects on total body Na^+, concentration of the ion does not change, whereas reabsorbtion of sodium is accompanied by reuptake of free water. Therefore aldosterone primarily affects total body volume and not sodium concentration (White, 1994; Arlt and Stewart, 2005). Electrolyte balance in epithelial cells of the submaxillary salivary glands and the large intestine are also under mineralocorticoid control; however, the physiologic importance of this phenomenon is likely minimal (Bastl and Hayslett, 1992).

Aldosterone levels are primarily regulated by angiotensin II through the renin-angiotensin-aldosterone system and directly by serum potassium levels. A rise in adrenocorticotropic hormone (ACTH) can also increase aldosterone secretion, but this is a much less potent stimulus (White, 1994; Arlt and Stewart, 2005). For this reason the zona glomerulosa is the only region of the adrenal cortex that does not atrophy upon pituitary failure (Hubbard et al, 1990). Atrial natriuretic peptide is the main inhibitory regulator of aldosterone secretion providing an important link between cardiac, adrenal and renal function; although, somatostatin, dopamine, and others may also play a role (Spat and Hunyady, 2004). A working knowledge of the renin-angiotensin-aldosterone system is critical in conceptualizing and managing hyperaldosteronism. The pathophysiology of this pathway is discussed in the section on Conn syndrome.

Zona Fasciculata

The zona fasciculata is the site of glucocorticoid production due to zonal expression of 17α-hydroxylase, 21-hydroxylase, and 11β-hydroxylase enzymes (see Fig. 57–3) (Arlt and Stewart, 2005). **Cortisol is the primary glucocorticoid in humans, and its secretion is under tight control of the ACTH.** As such, cortisol and ACTH are a part of a classic hormonal negative feedback system that features the hypothalamus, the pituitary gland, and the adrenal. The physiology of this axis is discussed in more detail in the section on Cushing syndrome (Jacobson, 2005). Production of cortisol by the adrenal follows a strict circadian schedule with the majority of the hormone being secreted in the early morning (Jacobson, 2005). Glucocorticoids are essential to life and modulate complex physiologic pathways that include metabolism, immunity, maintenance of intravascular volume, regulation of blood pressure, and complex modulation of the central nervous system with significant effects on mood, sleep, and potentially memory (Arlt and Stewart, 2005) (Table 57–2).

Zona Reticularis

The zona reticularis is the innermost zone of the adrenal cortex. The presence of 17α-hydroxylase and 17,20-lyase results in the production of dehydroepiandrosterone (DHEA), sulfated DHEA (DHEA-S) and androstenedione to this region, although some androgen synthesis also occurs in the zona fasciculata. Adrenal androgen secretion appears to be under control of ACTH, and, like cortisol, exhibits circadian patterns (Arlt and Stewart, 2005). DHEA, DHEA-S, and androstenedione comprise the greatest portion of steroid hormone that is produced by the adrenals (>20 mg/day), but appear to be the least important for adult physiologic homeostasis (Nguyen and Conley, 2008); however, **pharmacologic manipulation of adrenal androgen production remains a viable and increasingly targeted strategy for advanced prostate cancer** (see Chapter 133). Moreover, aberrations in production of these hormones during development are responsible for significant pathology and result in the clinical entity known as congenital adrenal hyperplasia (CAH) (Finkelstein and Shaefer, 1979; Hubbard et al, 1990). CAH is discussed in detail in Chapter 110.

Table 57–2.

Primary Effects of Glucocorticoids

EFFECTS	CLINICAL IMPLICATIONS
Enhance skeletal and cardiac muscle contraction	Absence results in weakness
Cause protein catabolism	Excess results in muscle wasting and weakness
Inhibit bone formation	Excess decreases bone density
Inhibit collagen synthesis	Excess causes thin skin and fragile capillaries
Increase vascular contractility and decrease permeability	Absence makes it difficult to maintain blood pressure
Have anti-inflammatory activity	Exogenous steroid is useful in treating inflammatory diseases
Have anti-immune system activity	Exogenous steroids are useful in promoting transplant tolerance and in treating autoimmune disorders
Maintain normal glomerular filtration (GFR)	Absence reduces glomerular filtration rate

From Howards SS, Carey RM. The adrenals. In: Gillenwater JY, Grayhack JT, Howards SS, Duckett JW, editors. Adult and pediatric urology. 2nd ed. Chicago: Year Book; 1991.

Adrenal Medulla Physiology

The **adrenal medulla** comprises less than 10% of total adrenal mass. Neither its function nor its embryology are related to the neighboring cortex. Instead, this portion of the adrenal, which **lies at the center of the gland, is an integral part of the autonomic nervous system.** Chromaffin cells of the medulla are innervated by preganglionic sympathetic fibers of T-11 through L-2, making them analogous to cells of the sympathetic ganglia. The medulla secretes epinephrine (80%), norepinephrine (19%), and dopamine (1%). These substances, collectively known as catecholamines, are produced from the amino acid tyrosine and modulate the systemic stress response (Fig. 57–4) (Robertson, 1990; de Diego et al, 2008). The effects of these catecholamines are mediated through their binding to adrenoreceptors located on target organs. The nature of these effects depend on the adrenoreceptor types or subtypes located and stimulated on a particular end organ (Table 57–3) (Robertson, 1990; Guimaraes and Moura, 2001). Interestingly, the enzyme phenylethanolamine-*N*-methyl transferase (PNMT), which catalyzes the conversion of norepinephrine to epinephrine, is relatively unique to the adrenal medulla (the brain and organ of Zuckerkandl also express this enzyme). The function of this enzyme is potentiated by the presence of glucocorticoids, thereby creating one of the few physiologic links between the adrenal cortex and the medulla. **Localization of PNMT to the adrenal medulla explains**

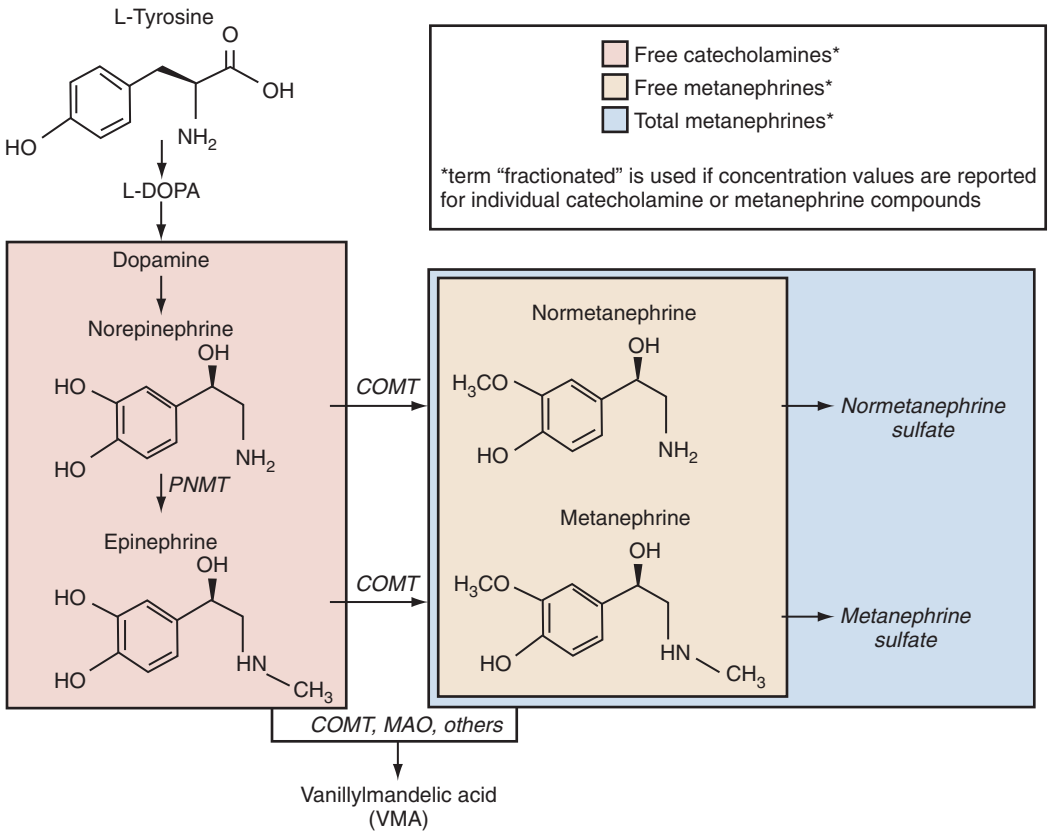


Figure 57–4. Summary of catecholamine metabolism. The figure simplifies the metabolic pathway of norepinephrine and epinephrine degradation to highlight those metabolic products that play a role in routine clinical practice. Key enzymes involved in catalysis of metabolic conversions are indicated in italic font. COMT, catechol-*O*-methyltransferase; MAO, monoamine oxidase; PNMT, phenylethanolamine-*N*-methyltransferase. NB: The central role that the MAO enzyme plays in catecholamine degradation is not fully reflected in this figure, because most metabolites that are produced by MAO catalysis are not routinely measured in laboratory assessments for pheochromocytoma.

why the gland is the primary source of systemic epinephrine, despite the presence of similar chromaffin cells elsewhere in the sympathetic nervous system (Robertson, 1990). Similar to the physiology that controls norepinephrine release at synaptic nerve terminals, the storage and release of adrenal catecholamines involves intracellular vesicles. Liberation of these vesicles through exocytosis results in release of adrenal catecholamines into the blood stream (Eisenhofer et al, 2004b).

The metabolism of catecholamines is complex and some controversy still exists about the physiologic relevance of each pathway (Eisenhofer et al, 2004b). The majority of adrenal catecholamine metabolism occurs at the scene of production in cells of the adrenal medulla themselves (Eisenhofer et al, 2003a). **For clinical purposes, three metabolites (metanephrine, normetanephrine, and vanillylmandelic acid) and two enzymes (catechol-O-methyltransferase and monoamine oxidase) are important.** Metanephrine and normetanephrine result from respective methylation of epinephrine and norepinephrine by catechol-*O*-methyltransferase (COMT). Although large amounts of this enzyme are present in the liver and kidneys, the majority of adrenal catecholamine metabolites are methylated by COMT within the cells of the adrenal medulla (Eisenhofer et al, 2003a). Indeed, **over 90% of metanephrine (epinephrine metabolite) and some 20% or more of normetanephrine (a norepinephrine metabolite) in the blood stream are derived from the adrenal medulla.** Therefore a measurable rise in the level of these metabolites is very useful when diagnosing potential pheochromocytomas (see

Key Points: Physiology

- Adrenal cortex and the adrenal medulla are best conceptualized as two distinct organs, the former endocrine and the latter neurocrine.
- Three main zones of the adrenal cortex are zona glomerulosa, zona fasciculata, and zona reticularis, with each zone primarily responsible for mineralocorticoid, glucocorticoid, and androgen synthesis, respectively.
- Ratios and types of enzymes in each zone of the adrenal cortex vary, resulting in different hormonal products for each region.
- Aldosterone levels are primarily regulated by angiotensin II through the renin-angiotensin-aldosterone system and directly by serum potassium levels. ACTH is less important in regulation of this region's function; therefore zona glomerulosa is the only region of the adrenal cortex that does not atrophy upon pituitary failure.
- Cortisol is the primary glucocorticoid in humans, and its secretion is under tight ACTH control.
- Pharmacologic manipulation of adrenal androgen production is an increasingly targeted strategy for treatment of advanced prostate cancer.
- Substances collectively known as catecholamines—epinephrine, norepinephrine, and dopamine—are produced from the amino acid tyrosine and modulate the systemic stress response.

Table 57–3.

Primary Effects of Catecholamines

EFFECTOR ORGANS	RECEPTOR TYPE	RESPONSES	MOST RELEVANT CLINICAL MANIFESTATIONS
Eye			
Radial muscle, iris	α_1	Contraction (mydriasis) + +	Blurry vision
Ciliary muscle	β_2	Relaxation for far vision +	
Heart			
SA node	β_1, β_2	Increase in heart rate + +	Palpitations, angina
Atria	β_1, β_2	Increase in contractility and conduction velocity + +	Palpitations, angina
AV node	β_1, β_2	Increase in automaticity and conduction velocity + + +	Palpitations, angina
His-Purkinje system	β_1, β_2	Increase in automaticity and conduction velocity + + +	Palpitations, angina
Ventricles	β_1, β_2	Increase in contractility, conduction velocity, automaticity, and rate of idioventricular pacemakers + + +	Palpitations, angina
Arterioles			
Coronary	α_1, α_2, β_2	Constriction +; dilations + +	Angina
Skin and mucosa	α_1, α_2	Constriction + + +	Pallor
Skeletal muscle	α, β_2	Constriction + +; dilations + +	Hypertension
Cerebral	α_1	Constriction (slight)	Stroke
Pulmonary	α_1, β_2	Constriction +; dilations + +	Edema
Abdominal viscera	α_1, β_2	Constriction + + +; dilations +	E.g., bowel ischemia
Salivary glands	α_1, α_2	Constriction + + +	
Renal	α_1, α_2, β_1, β_2	Constriction + + +; dilations +	Renal failure
Veins (systemic)	α_1, α_2, β_2	Constriction + +; dilations + +	Orthostatic hypotension
Lung			
Tracheal and bronchial muscle	β_2	Relaxation +	
Bronchial glands	α_1, β_2	Decreased secretion; increased secretion	
Stomach			
Motility and tone	α_1, α_2, β_2	Decrease (usually) +	Early satiety, discomfort
Sphincters	α_1	Contraction (usually) +	
Intestine			
Motility and tone	α_1, α_2, β_1, β_2	Decrease +	Constipation, ileus
Sphincters	α_1	Contraction (usually) +	
Secretion	α_2	Inhibition	Constipation
Gallbladder and ducts	β_2	Relaxation +	Gallstones
Kidney			
Renin secretion	α_1, β_2	Decrease +; increase ++	
Urinary bladder			
Detrusor	β_2	Relaxation (usually) +	Urinary retention
Trigone and sphincter	α_1	Contraction + +	Urinary retention
Ureter			
Motility and tone	α_1	Increase	
Uterus	α_1, β_2	Pregnant; contraction; relaxation Nonpregnant; relaxation	
Sex organs, male	α_1	Ejaculation + +	
Skin			
Pilomotor muscles	α_1	Contraction + +	
Sweat glands	α_1	Localized secretion +	Sweating
Spleen capsule	α_1, β_2	Contraction + + +; relaxation +	
Skeletal muscle	β_2	Increased contractility; glycogenolysis; K^+ uptake	Hyperglycemia, glycosuria
Pancreas			
Acini	α	Decreased secretion +	
Islets (β cells)	α_2	Decreased secretion + + +	Hyperglycemia, glycosuria
	β_2	Increased secretion +	Hypoglycemia
Fat cells	α_2, β_1, β_2	Lipolysis + + + (thermogenesis)	Feeling warm
Salivary glands	α_1	K^+ and water secretion +	
	β	Amylase secretion +	
Lacrimal glands	α	Secretion +	Lacrimation
Pineal gland	β	Melatonin synthesis	
Posterior pituitary	β_1	Antidiuretic hormone secretion	Decreased diuresis

Highest (+ + +) to lowest (+) intensity of adrenergic nerve activity in the control of various organs and functions listed. Where (+) is not given, intensity is not specified.
SA, sinoatrial; AV, atrioventricular.
Adapted from Pacak K. Preoperative management of the pheochromocytoma patient. J Clin Endocrinol Metab 2007;92(11):4069–79, Table 2.

section on Assessment of Function of Adrenal Masses) (Eisenhofer et al, 1995). In the urine, the majority of these metabolites are excreted in a sulfonated form. Furthermore, monoamine oxidase (MAO) and other enzymes subsequently participate in the conversion of catecholamine metabolites to vanillylmandelic acid (VMA), the primary catecholamine metabolic end product that is largely formed by the liver. Nonadrenal catecholamines from the sympathetic nervous system are similarly converted to VMA (Eisenhofer et al, 2004b). Figure 57–4 summarizes the most clinically relevant aspects of the catecholamine metabolism pathway.

ADRENAL DISORDERS

Disorders of Increased Adrenal Function

Cushing Syndrome

Introduction and Epidemiology. **Hypercortisolism secondary to excessive production of glucocorticoids by the adrenal cortex is defined as Cushing syndrome** (Orth and Liddle, 1971). The disease is rare and occurs in 2 to 5 of every million people per year (Lindholm et al, 2001; Findling and Raff, 2005). Diagnosis and treatment of Cushing syndrome is multifaceted, often requiring cooperation of internists, endocrinologists, neurosurgeons, and adrenal surgical experts (Newell-Price et al, 2006). The urologist must understand the comprehensive pathophysiology of hypercortisolism and have particularly advanced expertise in the aspects of this complex disease for which adrenalectomy is required.

Pathophysiology

Introduction. The zona fasciculata of the adrenal cortex secretes more than 20 mg of cortisol every day (Arlt and Stewart, 2005). Regulation of this secretion is controlled through the hypothalamic-pituitary-adrenal (HPA) axis (Jacobson, 2005). A fluent understanding of this classic neuroendocrine negative feedback system is critical for the successful management of every Cushing patient.

Normal Hypothalamic-Pituitary-Adrenal (HPA) Axis Physiology. **Corticotrophic cells of the anterior pituitary secrete ACTH, also known as corticotrophin, under the influence of neuronal innervations from the hypothalamus.** Synthesis of ACTH is a result of cleavage of the pro-opiomelanocortin (POMC) precursor molecule. Physiologically, the most important promoter of ACTH release is corticotropin-releasing hormone (CRH), but oxytocin and vasopressin also play a role (Jacobson, 2005; Sam and Frohman, 2008). **Stress, whether physiologic or psychologic, appears to be the most important variable in modulating activity of the HPA axis** (Jacobson, 2005).

ACTH is not only responsible for promoting production of glucocorticoids and androgens by the adrenal cortex, but it also plays a critical role in maintaining adrenal cortical vitality. Indeed, without ACTH (e.g., when its secretion is suppressed by exogenous steroid intake), all but the mineralocorticoid-producing cells of the adrenal cortex arrest hormone production and undergo apoptosis (Arlt and Stewart, 2005; Jacobson, 2005). In addition to ACTH, splanchnic nerves that innervate the adrenals also appear to affect glucocorticoid production (Jacobson, 2005).

Glucocorticoids bind receptors in the hypothalamus and the pituitary and complete the negative feedback loop by inhibiting production of CRH and ACTH by these structures, respectively (Jacobson, 2005). Figure 57–5 summarizes the salient features of the HPA axis.

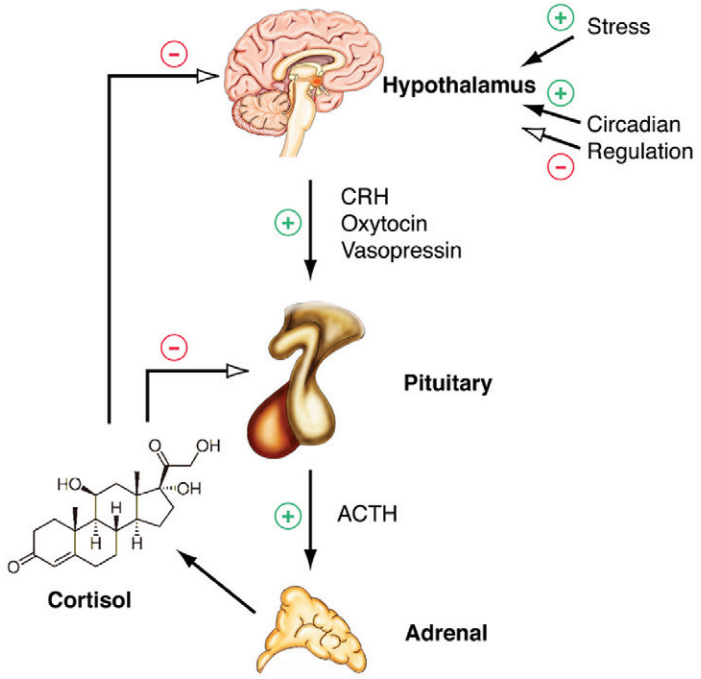


Figure 57–5. The hypothalamic-pituitary-adrenal axis and feedback loop. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone.

It is important to understand that CRH secretion is under tight control of the hypothalamic suprachiasmic nucleus and follows circadian patterns. The highest level of cortisol in healthy subjects is detected in the mornings, while the nadir is observed at approximately 11 PM. Even small perturbations of this physiologic rhythm are considered pathologic (Jacobson, 2005; Sam and Frohman, 2008).

Overview of Cushing Syndrome. Given the sophistication of the HPA axis, hypercortisolism can result from a number of different pathologies that result in oversecretion of cortisol by the adrenal glands. **Causes of Cushing syndrome can be divided into three main groups: (1) exogenous, (2) ACTH-dependent, and (3) ACTH-independent** (Fig. 57–6). Exogenous Cushing syndrome is a result of iatrogenic glucocorticoid administration. ACTH-dependent disease results from an elevated serum corticotropin level due to pathology extrinsic to the adrenal gland and accounts for up to 85% of cases of endogenous Cushing syndrome. **ACTH-independent hypercortisolism, on the other hand, results from unregulated overproduction of glucocorticoids by the adrenal(s) and is relatively rare.** The adrenal surgeon has long been involved in management of ACTH-independent disease, but with advent of laparoscopy, adrenal surgery for ACTH-dependent Cushing syndrome is becoming more commonplace (Porterfield et al, 2008).

Exogenous Cushing Syndrome. **Exogenous Cushing syndrome is the most common cause of hypercortisolism in patients of the Western world** (Newell-Price et al, 2006). Synthetic glucocorticoids are frequently employed in treatment of many conditions, and Cushing syndrome can result even from the administration of even low doses of exogenous steroids administered orally, topically, or by inhaled preparations (Hopkins and Leinung, 2005; Newell-Price et al, 2006). A careful patient history is therefore essential in the evaluation of all patients with Cushing syndrome. The clinician also must be cognizant of the possibility

that the patient is either unaware of his or her steroid use (e.g., use of herbal remedies, nasal sprays) or is surreptitiously self-administering glucocorticoids (e.g., for performance enhancement) (Hopkins and Leinung, 2005).

ACTH-Dependent Cushing Syndrome

OVERVIEW. **ACTH-dependent hypercortisolism accounts for 80% to 85% of endogenous Cushing syndrome. Approximately 80% of ACTH-dependent disease is due to primary pituitary pathology and is known as Cushing *disease*. Ectopic ACTH production is the other main cause of ACTH-dependent hypercortisolism** (Newell-Price et al, 2006). Ectopic CRH syndrome is a third cause of ACTH-dependent Cushing syndrome and is extremely uncommon (see Fig. 57–6) (Orth, 1995).

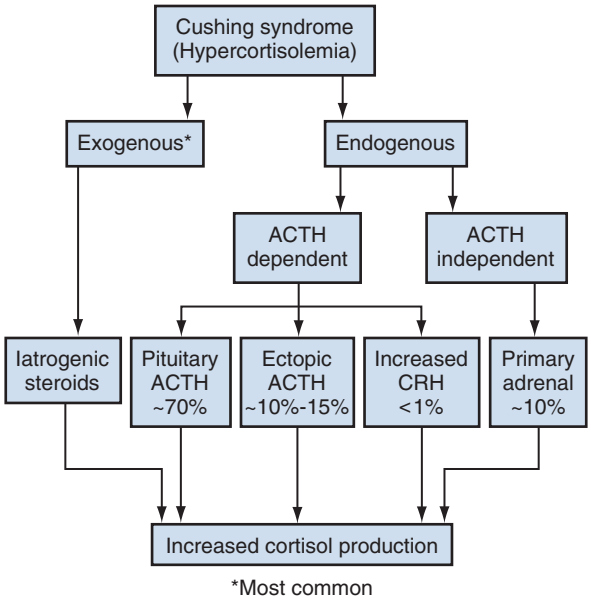


Figure 57–6. Clinically relevant causes of excess cortisol production. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone.

CUSHING DISEASE. **Described by the neurosurgical pioneer Harvey Cushing in 1932, Cushing disease causes hypercortisolism through excessive secretion of ACTH by the pituitary gland** (Cushing, 1932). The condition accounts for nearly 70% of endogenous Cushing syndrome. The most common culprit is a corticotropin-producing microadenoma. Large macroadenomas of 1 cm in size or greater are found in only about 5% of cases (Newell-Price et al, 2006). Fifteen percent of functional pituitary adenomas exhibit the ability to secrete ACTH (Shimon and Melmed, 1998). Hyperplasia of ACTH-producing cells and pituitary carcinoma can also oversecrete ACTH but are extremely rare (Orth, 1995). Up to two thirds of individuals with Cushing disease are female (Scott and Orth, 1990).

ECTOPIC ACTH SYNDROME. **Production of ACTH by nonpituitary tumors can also result in hypercortisolism. These corticotropin-producing tissues are nearly always malignant and account for approximately 10% of Cushing syndrome** (Porterfield et al, 2008). Liddle and associates first described the phenomenon in the early 1960s and termed it "ectopic ACTH syndrome" (Meador et al, 1962; Scott and Orth, 1990). The timing and onset of hypercortisolism varies and can precede the diagnosis of an extra-adrenal malignancy by many years, resulting in diagnostic difficulties and the clinical conundrum, whereby a subclinical pituitary adenoma is suspected but not radiographically identified (Aniszewski et al, 2001). Moreover, hypercortisolism in end-stage debilitated cancer patients is almost certainly underdiagnosed (Orth, 1995). As a result of higher ACTH levels, the adrenal glands of patients with ectopic ACTH syndrome are generally more markedly hyperplastic and thereby larger than those of patients with Cushing disease (Jenkins et al, 1999). Table 57–4 summarizes primary malignancies implicated in ectopic ACTH production, which notably includes pheochromocytoma.

ECTOPIC CRH. Production of CRH by malignancies is extremely rare and is responsible for less than 1% of cases of Cushing syndrome. Bronchial carcinoma is the most common culprit, and

Table 57–4.

Sources of Ectopic ACTH

PARAMETER	CURRENT STUDY	FINDLING 1986*	IMURA 1975	DOPPMAN 1989	HOWLETT 1986
No. of patients	106	49	30	28	16
No tumor found (%)	16	12		32	
Islet cell tumor (%)	16	4	7	11	13
Bronchial carcinoid (%)	25	49	7	46	38
Thymic carcinoid (%)	5	16			13
Medullary thyroid cancer (%)	8				
Disseminated neuroendocrine tumor (%)	7				
Disseminated GI carcinoid (%)	1				
Small cell lung cancer (%)	11	10	33		19
Miscellaneous (%)	8	6	17		13†
Pancreatic adenocarcinoma (%)		2			
Adenocarcinoma of the bronchus (%)			10		
Squamous cell carcinoma of the bronchus (%)			3		
Undifferentiated carcinoma of the bronchus (%)			10		
Malignant thymoma (%)			13		
Pheochromocytoma (%)	3			11	6
TOTAL	100	100	100	100	100

*Includes a literature review.
†Carcinoid of the gallbladder and colon cancer.
Adapted from Aniszewski JP, Young WF Jr, Thompson GB, et al. Cushing syndrome due to ectopic adrenocorticotropic hormone secretion. World J Surg 2001;25(7): 934–40.

concurrent ACTH secretion is not unusual (Carey et al, 1984; Orth, 1995).

ACTH-INDEPENDENT CUSHING SYNDROME. **Uncontrolled hypersecretion of cortisol by adrenal tissues accounts for a minority of endogenous hypercortisolism and is classified as ACTH-independent Cushing syndrome.** Adrenal neoplasms and rare forms of bilateral adrenal disease are responsible for this group of conditions (Lacroix and Bourdeau, 2005; Newell-Price et al, 2006).

ADRENAL TUMORS. **Cortisol-secreting benign adenomas of the adrenal gland are responsible for approximately 10% of Cushing syndrome** and often result from a dominant unilateral hyperplastic nodule, although multifocal bilateral functional adrenal hyperplasia may also occur. Less than 10% of adrenal masses are bilateral and often present a diagnostic challenge (Lacroix and Bourdeau, 2005; Porterfield et al, 2008; Young et al, 2008). Radiographically undetectable benign adrenal cortisol-producing lesions may also be responsible for cases of subclinical Cushing syndrome (Rossi et al, 2000). Cortisol production by adrenocortical carcinomas account for approximately 8% of patients with Cushing syndrome (Lindsay and Nieman, 2005a).

ACTH-INDEPENDENT MACRONODULAR ADRENAL HYPERPLASIA (AIMAH). ACTH-independent bilateral macronodular adrenal hyperplasia (AIMAH) gives rise to less than 1% of Cushing syndrome. The condition is characterized by multiple large (up to 4 cm) nodules replacing the glands with each adrenal weighing over 60 g (Lacroix and Bourdeau, 2005; Iacobone et al, 2008). Weights in excess of 200 g have been reported for each gland affected by AIMAH (Swain et al, 1998). It is essential that this disease entity must be distinguished from adrenal enlargement caused by chronic adrenal stimulation in ACTH-dependent Cushing syndrome, whereas radiographics of the adrenals appear similar in both conditions. Bilateral macronodular hyperplasia is observed as a feature of the McCune-Albright syndrome, which also includes polyostotic fibrous dysplasia, dermatologic manifestations, and other endocrine abnormalities (Lacroix and Bourdeau, 2005).

PRIMARY PIGMENTED NODULAR ADRENOCORTICAL DISEASE (PPNAD). Like AIMAH, primary pigmented nodular adrenocortical disease (PPNAD) is exceedingly rare, accounting for less than 1% of cases of Cushing syndrome. Unlike AIMAH, however, the adrenal glands in this condition remain normal in size and exhibit black or brown cortical nodules (Young et al, 1989). The cortical tissue surrounding the nodules is atrophic and the adrenal medulla is free of disease (Lacroix and Bourdeau, 2005). Approximately half of PPNAD is found in patients with the autosomal-dominant Carney complex, which is also responsible for spotty skin and mucous membrane lesions, and a variety of neoplasms that include Sertoli-cell tumors. The other half of cases of PPNAD are nonhereditary with no known cause (Lacroix and Bourdeau, 2005).

Clinical Characteristics

Classical Cushing Syndrome. **Clinical characteristics of Cushing syndrome vary considerably among affected patients. Many of the classic symptoms of hypercortisolism, such as central obesity, moon faces, buffalo hump, proximal muscle weakness, easy bruisability, and abdominal striae, are non-specific. It is the combination of these and other clinical signs that should raise suspicion and prompt potential screening for Cushing syndrome** (Findling and Raff, 2005). **Cushing syndrome also results in systemic symptomatology, such as central obesity, dyslipidemia, insulin resistance, and hypertension, that is identical to the highly-prevalent metabolic syndrome** (Pivonello et al, 2005, 2008). Figure 57–7 depicts the effects of glucocorticoids on organ systems, and Table 57–5 summarizes signs and symptoms of the disease and indicates their frequency. Screening for Cushing syndrome is usually beyond the scope of urologic practice; however, it is important for urologists to appreciate the **relatively common occurrence of hypogonadal hypogonadism in men with Cushing syndrome.** A low threshold for initiating a hypercortisolism workup should exist in these men with libido or erectile problems, low testosterone, and low gonadotropin levels (Findling and Raff, 2005; Pivonello et al, 2008). **Up to 50% of patients with Cushing syndrome exhibit urolithiasis;** therefore stone formers with cushinoid features also deserve a hypercortisolemia evaluation. Interestingly, definitive treatment of Cushing syndrome in these patients reduces the risk of stone formation, but does not bring the risk back to that of the general population (Faggiano et al, 2003).

Subclinical Cushing Syndrome. Subclinical Cushing syndrome is a relatively new disease entity that describes hypercortisolemia in the absence of an overt cushinoid phenotype. Obvious clinical signs of Cushing syndrome are absent, and the diagnosis is made when a metabolic workup for an incidentally-discovered adrenal mass reveals hypercortisolemia (Sippel and Chen, 2004). In the past, the disease entity was referred to as "pre-Cushing syndrome," "noncushingoid Cushing syndrome," and "preclinical Cushing syndrome"; however, the term "subclinical Cushing" has gained acceptance. Recently, the term "subclinical autonomous glucocorticoid hypersecretion" also has been introduced (Tsagarakis et al, 2006). Classically, the disease entity applies to patients who are found to have elevated cortisol levels upon a metabolic workup of an adrenal incidentaloma. **Nearly 10% of patients in one large series of adrenal incidentalomas were found to have the condition** (Mantero et al, 2000). Patients can also fall under the umbrella of this diagnosis when Cushing syndrome

Table 57–5.

Signs and Symptoms of Cushing Syndrome

SYMPTOMS AND SIGNS	PREVALENCE (%)
Central obesity	90-100
Rounded face ("moon face")	
Facial plethora	
Decreased libido	
Purple striae	70-90
Menstrual disturbances	
Hirsutism	
Erectile dysfunction	
Hypertension	
Muscle weakness	50-70
Posterior neck fat deposit ("buffalo hump")	
Body bruising	
Glucose intolerance/diabetes	
Osteopenia/osteoporosis	
Emotional lability/depression	
Headache	20-50
Backache	
Limb edema	
Recurrent infections	
Hypokalemic alkalosis	
Nephrolithiasis	
Acne	0-20
Alopecia	

Adapted from Pivonello R, De Martino MC, De Leo M, et al. Cushing's syndrome. Endocrinol Metab Clin North Am 2008;37(1):135–49, ix.

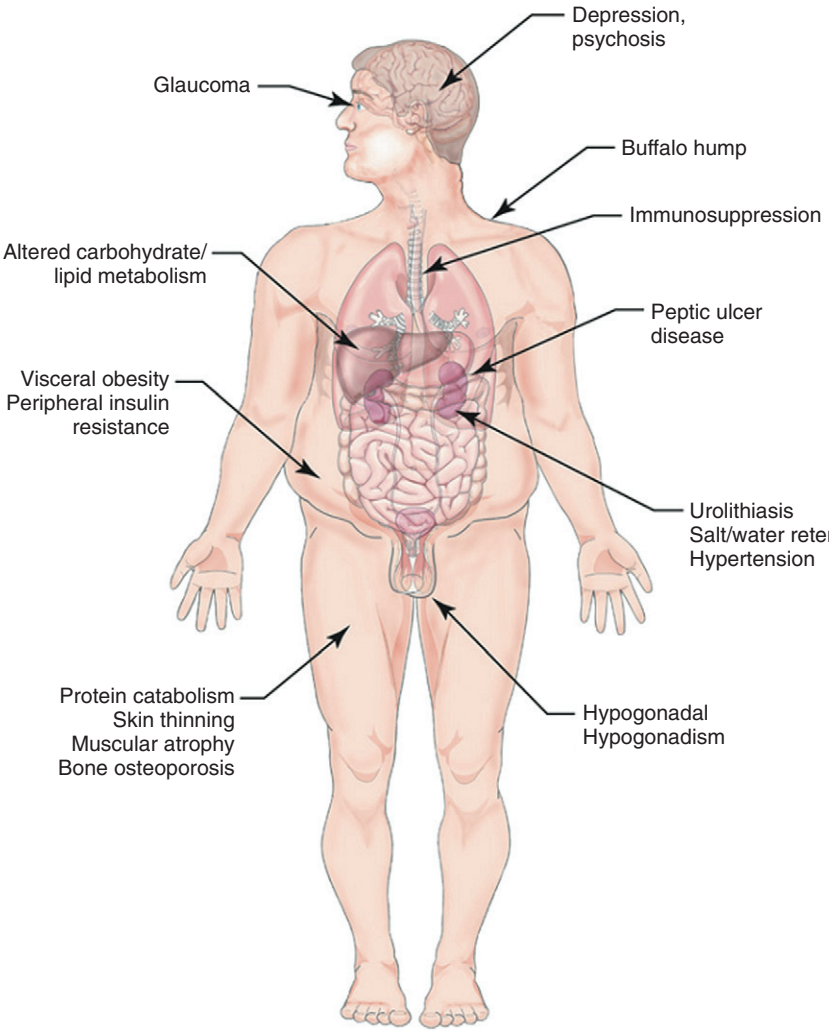


Figure 57–7. Diverse effects of hypercortisolism on organ systems.

is discovered during screening. For instance, when patients with type II diabetes and poor glucose control are screened for hypercortisolism, some 2% have subclinical Cushing syndrome (Catargi et al, 2003).

Adrenalectomy in the setting of subclinical Cushing may improve glucose control, hypertension, and result in weight loss (Midorikawa et al, 2001; Mitchell et al, 2007). Surgical indications and benefits for subclinical Cushing syndrome, however, are still a matter of debate (Sippel and Chen, 2004; Tsagarakis et al, 2006). Some authors argue that adrenalectomy should be performed only in patients who are potentially symptomatic and exhibit clinical signs, such as hypertension, obesity, glucose intolerance, or osteopenia. Others propose that surgery must be offered to all patients in order to prevent the sequelae of hypercortisolism (Sippel and Chen, 2004; Pivonello et al, 2005; Tsagarakis et al, 2006). Patients with subclinical Cushing syndrome may be at higher risk for postadrenalectomy adrenal insufficiency than those patients with non-cortisol-secreting adrenal pathologies, because functionality of the contralateral gland may be suppressed (Tsagarakis et al, 2006).

Diagnostic Tests. The diagnosis of Cushing syndrome is one of the most complex and difficult tasks in clinical endocrinology and most often falls outside of the realm of medical or surgical urological practice (Findling and Raff, 2005). Nevertheless, the urologist must be familiar with these diagnostic strategies and how they relate to the etiology of hypercortisolism. Moreover, the urologist who offers adrenalectomy must be well versed in the basic metabolic evaluation for Cushing syndrome in patients with adrenal masses.

Establishing the Diagnosis of Cushing Syndrome. When the diagnosis of Cushing syndrome is suspected, the clinician can choose among several laboratory studies. **The two evaluations performed most frequently are the 24-hour urinary free cortisol evaluation and the overnight low-dose dexamethasone suppression test (LD-DST). The sensitivity of the former test, however, may not be adequate for screening patients with incidentalomas** (Nieman et al, 2008). **Late-night salivary cortisol is a test that is becoming increasingly popular.** Second-line tests include the 2-day LD-DST and midnight plasma cortisol testing (Arnaldi et al, 2003; Newell-Price et al, 2006, Nieman et al, 2008; Pivonello et al, 2008). The physiologic principles underlying these tests are important to understand and are described in this section (Findling and Raff, 2005). The section Evaluation of Adrenal Pathology in Urologic Practice outlines practical algorithms for the metabolic evaluation of adrenal lesions. Tests such as random serum cortisol, plasma ACTH level, urinary 17-ketosteroid level, insulin tolerance testing, and loperamide testing have fallen out of favor and are no longer recommended (Nieman et al, 2008).

Administration of low-dose dexamethasone followed by measurement of serum cortisol the next morning probes the patient's glucocorticoid negative feedback

system. In subjects without hypercortisolism, dexamethasone acts on the corticotrophic cells of the anterior pituitary, suppresses ACTH production, and thereby results in a reduction of serum cortisol levels (Findling and Raff, 2005). A key element to understanding this test is that despite the "low-dose" designation, the dosage of dexamethasone administered for this study corresponds to three- to fourfold levels of physiologic glucocorticoid. Importantly, the exogenous dexamethasone is not detected by the serum cortisol assay. The fact that patients with ACTH-independent Cushing syndrome and those with ectopic ACTH secretion fail to suppress cortisol production during such testing is intuitive; however, the reason for the failure of patients with ACTH-producing pituitary adenomas (Cushing disease) to suppress cortisol secretion following low-dose dexamethasone administration is less obvious. The phenomenon is best understood by the relative insensitivity of pituitary adenomas to the inhibitory effects of glucocorticoid stimulation (Raff and Findling, 2003). In summary, a patient's failure to suppress cortisol levels following an overnight low-dose dexamethasone administration is indicative of Cushing syndrome. **This test does not delineate the etiology of hypercortisolism, but simply suggests its presence.** Administration of low-dose dexamethasone over a 48-hour period is less practical and is reserved for second-line testing.

Urinary free cortisol evaluation is a 24-hour direct measurement of free bioavailable cortisol. Unlike serum cortisol testing, which measures both free and bound cortisol, urinary cortisol measurements are independent from the variables that influence corticosteroid-binding globulin levels (Arnaldi et al, 2003). Moreover, the test is an integrated measurement of cortisol secretion over a 24-hour period. This feature of the study is critical, because serum cortisol levels exhibit some circadian variation even in many patients with Cushing syndrome (Orth, 1995). **The urologist must be cognizant that this test may not possess sufficient sensitivity for diagnosis of subclinical Cushing syndrome, and the Endocrine Society recommends against it for metabolic evaluation of adrenal incidentalomas** (Nieman et al, 2008).

Late-night salivary cortisol and midnight plasma cortisol measurements take advantage of a common feature of all causes of Cushing syndrome—a perturbation and in some cases complete disruption in the diurnal variation of cortisol levels. The abnormality, even in very mild cases of Cushing syndrome, is the inability to suppress cortisol levels at night. As previously mentioned, peak morning cortisol levels in patients with Cushing syndrome are often within the normal range; however, persistent elevation at night may signal the loss of diurnal variance associated with Cushing. While midnight plasma cortisol measurements are clinically impractical in an outpatient setting, late-night salivary cortisol measurements are becoming a popular diagnostic tool for identification of hypercortisolism (Raff and Findling, 2003; Findling and Raff, 2005).

It is important to note that other conditions can stimulate the hypothalamic-pituitary-adrenal axis and emulate Cushing syndrome (Table 57–6); **therefore endocrinologic expertise is recommended when definitively diagnosing hypercortisolism** (Nieman et al, 2008).

Identifying the Cause of Cushing Syndrome. Once Cushing syndrome is diagnosed, its etiology must be localized. Due to the nuanced complexity of this process, some authors believe that this is best done by endocrinologists at major referral centers (Newell-Price et al, 2006). Briefly, the algorithm is as follows.

First, ACTH-dependent disease must be distinguished from the ACTH-independent causes. This is done by measurement of serum ACTH. Low serum ACTH points to ACTH-independent pathology, and abdominal imaging is indicated to identify the adrenal source. If the adrenals are unremarkable on cross-sectional imaging, exogenous steroids as a cause of Cushing syndrome, or much less commonly PPNAD, must be suspected (Arnaldi et al, 2003). Interestingly, the presence of PPNAD often can be confirmed by a delayed "paradoxical rise" in the 24-hour urinary cortisol sampling following dexamethasone administration (Lacroix and Bourdeau, 2005). Up to 10% of patients with adrenal Cushing syndrome have bilateral adrenal lesions (Lacroix, 2008). Adrenal venous sampling may be helpful in this setting (Young et al, 2008).

Table 57–6.

Causes of Hypercortisolism in the Absence of Cushing Syndrome

Conditions
Some clinical features of Cushing syndrome may be present
Pregnancy
Depression
Alcohol dependence
Glucocorticoid resistance
Morbid obesity
Poorly controlled diabetes mellitus
Unlikely to have any clinical features of Cushing syndrome
Physical stress (hospitalization, surgery, pain)
Malnutrition, anorexia nervosa
Intense chronic exercise
Hypothalamic amenorrhea
CBG excess (increased serum but not in urine cortisol)

Whereas Cushing syndrome is unlikely in these conditions, it may rarely be present. If there is a high clinical index of suspicion, the patient should undergo testing, particularly those within the first group.

Adapted from Nieman LK, Biller BM, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2008;93(5):1526–40.

The true diagnostic difficulty lies in distinguishing Cushing disease from the ectopic ACTH syndrome for patients who have high serum ACTH levels. This problem stems from the fact that both pituitary microadenomas and ACTH-producing tumors can be very difficult to localize with modern imaging. Meanwhile, incidental imaging findings in the lungs, pancreas, and pituitary are relatively common, often clouding the diagnostic waters (Newell-Price et al, 2006). For instance, 10% of the general population exhibit an abnormality upon imaging of the pituitary gland, while some 50% of patients with Cushing disease have no abnormality on pituitary MRI (Fig. 57–8) (Arnaldi et al, 2003; Porterfield et al, 2008).

Direct measurements of ACTH in a downstream venous plexus that drains the pituitary—the inferior petrosal sinus—following CRH stimulation has become the gold standard approach for distinguishing ectopic ACTH production from Cushing disease. High levels of ACTH in the inferior petrosal sinus, when compared to those in peripheral blood, indicate Cushing disease, while levels similar to peripheral plasma suggest an ectopic ACTH source (Findling and Raff, 2006; Porterfield et al, 2008).

High-dexamethasone suppression testing was used in the past to differentiate pituitary and ectopic ACTH sources, but the value of the test is limited. The study is based on the principle that high enough doses of dexamethasone should suppress ACTH production by pituitary adenomas, while ectopic ACTH production continues despite the high-dose

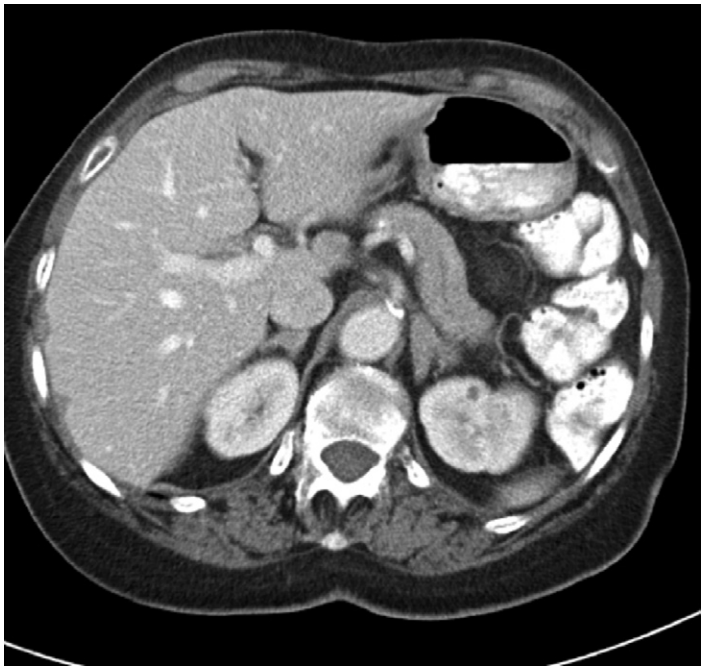


Figure 57–8. Bilateral adrenal enlargement in a patient with advanced metastatic adenocarcinoma of the pancreas.

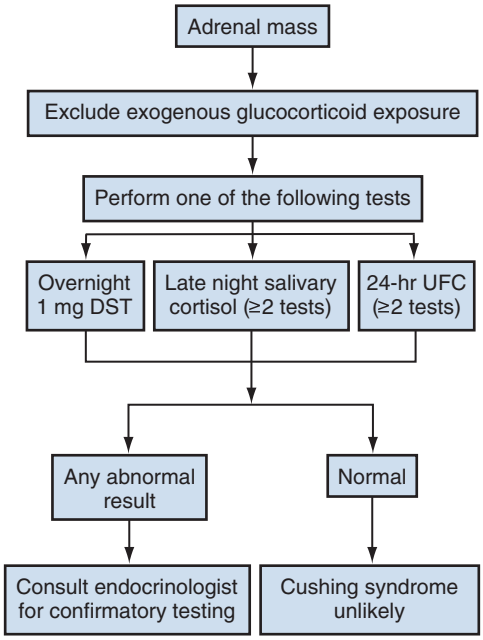


Figure 57–9. Testing algorithm for ruling out hypercortisolemia secondary to an adrenal mass. In case of a positive result during late-night salivary cortisol or 24-hour urinary–free cortisol evaluations, repeat testing is often prudent. DST, dexamethasone suppression test; UFC, urinary–free cortisol.

glucocorticoid administration (Arnaldi et al, 2003). Unfortunately, it is now clear that some nonpituitary ACTH-producing tumors possess the glucocorticoid receptor and also reduce ACTH production upon high-dose dexamethasone administration (Aron et al, 1997; Raff and Findling, 2003). Currently, high-dexamethasone suppression testing is not routinely employed (Fig. 57–9) (Findling and Raff, 2006; Porterfield et al, 2008).

Treatment. The treatment of Cushing syndrome must be approached as a multidisciplinary endeavor. Primary care physicians, endocrinologists, neurosurgeons, and the adrenal surgical experts must effectively communicate not only with the patient but also with each other. Treatment goals involve correction of hypercortisolemia, restoration of the hypothalamic-pituitary-adrenal axis, and management of Cushing syndrome sequelae (Porterfield et al, 2008).

Exogenous Cushing Syndrome. Correction of exogenous Cushing syndrome, when appropriate, must be handled with proper care. Cessation of glucocorticoid administration must be gradual, so that hypothalamic-pituitary-adrenal axis has ample time to recover. The process can take weeks to months and varies greatly from patient to patient. The physician must be aware of the clinical entity known as "steroid withdrawal syndrome" where the patient cannot tolerate steroid dose reduction despite apparent normalization in hypothalamic-pituitary-adrenal axis testing (Hopkins and Leinung, 2005).

ACTH-Dependent

CUSHING DISEASE. **The current standard of care for ACTH-secreting pituitary adenomas is transsphenoidal surgical resection** (see Fig. 57–10 on the Expert Consult website). **Unfortunately, cure is seen in only 60% to 80% of patients** (Newell-Price et al, 2006; Pivonello et al, 2008). **Furthermore, long-term follow-up is necessary, because up to 25% of individuals relapse** (Patil et al, 2008). Macroadenomas are additionally resistant to neurosurgical treatment, and less than 15% of patients are cured following excision of tumors 1 cm in size or greater (Newell-Price et al, 2006). Following resection, a severe addisonian state is common, and careful glucocorticoid replacement is necessary in the year following surgery (Utz et al, 2005). Hypopituitarism after resection of a pituitary adenoma is a known complication, with rates varying from less than 5% to greater than 50% for the various pituitary metabolic products in various surgical series. Careful patient monitoring by expert endocrinologists is essential (Utz et al, 2005; Porterfield et al, 2008). Neurosurgic reoperation following initial failure is challenging and success rates vary. Moreover, the risk of hypopituitarism also significantly rises with secondary resections (Utz et al, 2005; Porterfield et al, 2008). Salvage radiation therapy is an option, but the patient must be warned about significant delays in reduction of ACTH secretion and the possibility of hypopituitarism (Estrada et al, 1997; Utz et al, 2005; Porterfield et al, 2008).

The urologist must be involved when adrenalectomy is contemplated or required. **Currently bilateral adrenalectomy is most often recommended when at least one attempt to treat the primary tumor has failed. It is also necessary in rare instances when hypercortisolism is life-threatening and swift definitive treatment is mandatory.** The advantages of the procedure include a lack of postoperative hypopituitarism and an extremely high success rate with rapid resolution of hypercortisolism (Vella et al, 2001; Chow et al, 2008; Lacroix, 2008). Nevertheless, lifelong mineralocorticoid and glucocorticoid replacement is required in all patients. **Moreover, the patients are at risk for progressive growth of their pituitary adenoma, mainly resulting in complications such as ocular chiasm compression, oculomotor deficiencies, and, rarely, a rise in intracranial pressure** (Assie et al, 2007). **This results in the Nelson-Salassa syndrome (also known as Nelson syndrome), which is found in 8% to 29% of patients following bilateral adrenalectomy in large series.** Prophylactic radiation therapy has been shown to prevent the phenomenon in some but not all published reports (Gil-Cárdenas et al, 2007). Currently, routine use of prophylactic radiotherapy to prevent Nelson syndrome following

bilateral adrenalectomy is controversial (Porterfield et al, 2008). **When counseling patients regarding bilateral adrenalectomy for ACTH-dependent Cushing syndrome, the urologist must also warn of the rare possibility of residual, functioning adrenal tissue remaining following the procedure** (Kemink et al, 1992).

ECTOPIC ACTH SYNDROME. Resection of the primary ACTH-producing tumor is the single best therapeutic approach to normalizing cortisol levels in patients with ectopic ACTH syndrome. In large series, however, primary tumor resection is only possible in approximately 10% of patients (Aniszewski et al, 2001). **For patients with unresectable primary tumors or whose primary ACTH-producing tissue cannot be identified (up to 35% of cases), bilateral adrenalectomy with lifelong replacement therapy is an excellent therapeutic option** (Aniszewski et al, 2001; Porterfield et al, 2008).

ACTH-Independent. Patients with unilateral cortisol-secreting adrenal masses are treated with ipsilateral adrenalectomy. Partial adrenalectomy is possible when preservation of adrenal tissue is deemed essential (Walz, 2004). Case reports of bilateral partial adrenalectomies for cortisol-producing masses exist in the literature (Inoue et al, 2006). The current standard of care for AIMAH and PPNAD patients is bilateral adrenalectomy with lifelong replacement therapy. Success with unilateral resection of the largest gland in AIMAH patients also has been reported (Iacobone et al, 2008).

Medical Treatment of Hypercortisolism. Medical therapy for hypercortisolism is employed for bridging a patient to surgery or when surgical intervention is not possible. Medications that block enzymes of steroid synthesis, such as metyrapone, aminoglutethimidine, trilostan, ketoconazole, and etomidate are often employed. Mitotate, a medication that is discussed in further detail in the section Adrenal Carcinomas, can also be used (Porterfield et al, 2008). In the future, inhibitors of 17α-hydroxylase (cyp17), such as aberaterone, may also be of some utility; however, at this point such use of these drugs remains largely unexplored (Attard et al, 2009). Medical treatment of hypercortisolemia requires significant expertise and should be left to expert endocrinologists.

Prognosis. Life expectancy for patients with Cushing syndrome falls short of those of patients with normal cortisol levels. Normalization of hypercortisolemia may reduce but not eradicate this risk (Swearingen et al, 1999; Pivonello et al, 2005). Aggressive management of cardiovascular risk factors under the watchful eyes of experienced medical experts is paramount even in patients whose laboratory values return to normal following successful treatment.

Key Points: Cushing Syndrome

- Serum cortisol levels are under tight control. In healthy subjects peaks occur in the morning, while the nadir is observed at approximately 11:00 PM.
- Adrenal tumors that secrete cortisol cause ACTH-independent Cushing syndrome and account for approximately 10% of Cushing syndrome that is not caused by steroid intake.
- Patients with undiagnosed Cushing syndrome can present to the urologist with hypogonadal hypogonadism or with urolithiasis.
- Testing of adrenal masses for cortisol hypersecretion is mandatory.

Summary. Cushing syndrome is a complex disorder that requires a multidisciplinary approach. The urologist plays a critical role in management of the hypercortisolemic patient when unilateral or bilateral adrenalectomy is required. A thorough understanding of relevant pathophysiology is necessary not only for diagnosis and treatment, but also for appropriate perioperative counseling of patients with Cushing syndrome.

Primary Aldosteronism

Introduction and Epidemiology. Dr. Jerome Conn first described primary aldosteronism in 1955 in a 34-year-old female presenting with hypertension and hypokalemia (Conn, 1955). Urine assays demonstrated a markedly elevated level of mineralocorticoid activity. The patient's condition greatly improved following the removal of a 4-cm unilateral adrenal tumor. Since this initial case report, several subtypes of primary aldosteronism, which require distinct evaluation and treatment, have been identified. Given the prevalence of primary aldosteronism, which ranges from 5% to 13% of hypertensive patients in contemporary series, urologists must be familiar with appropriate diagnostic and management strategies (Mulatero et al, 2004; Rossi et al, 2006a; Young, 2007a).

Pathophysiology. The renin-angiotensin-aldosterone-system (RAAS) is a key regulator of blood pressure and extracellular fluid volume (Fig. 57–11). The release of renin from the juxtaglomerular cells is the rate-limiting step in the RAAS cascade. Under normal physiologic conditions, renin release is stimulated by several conditions including low renal perfusion pressure, increased renal sympathetic nervous activity, and low sodium concentration sensed by the macula densa (Gibbons et al, 1984). Renin then cleaves angiotensinogen to angiotensin I, which in turn is cleaved by angiotensin-converting enzyme to angiotensin II. Angiotensin II functions as both a potent vasoconstrictor and triggers the release of aldosterone from the zona glomerulosa. Additional regulators of aldosterone release include potassium and ACTH. **In primary aldosteronism, aldosterone secretion is independent of the RAAS, and plasma renin levels will be suppressed.** This finding is in contrast to patients with secondary

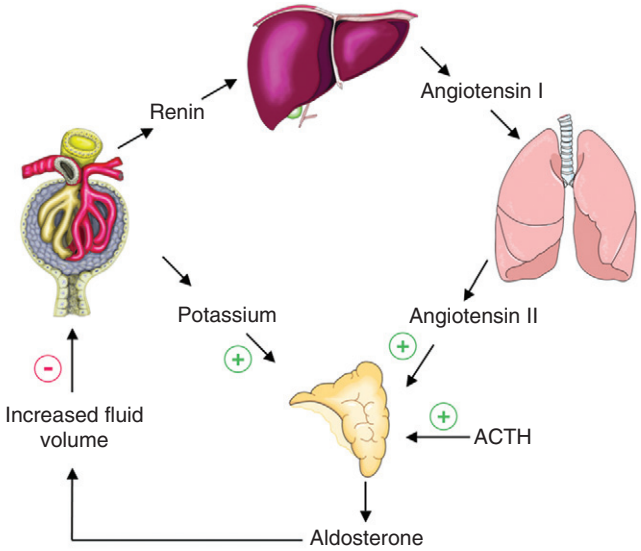


Figure 57–11. Renin-angiotensin-aldosterone-system. Under normal conditions, aldosterone secretion is under the control of angiotensin II, serum potassium levels, and adrenocorticotropic hormone (ACTH). In primary aldosteronism, aldosterone is autonomously released, resulting in decreased plasma renin levels.

hyperaldosteronism, where elevated renin levels are the cause of elevations in aldosterone secretion. This distinction between plasma renin levels in primary and secondary hyperaldosteronism is a critical concept used when screening for primary aldosteronism (see Diagnosis section later).

Following release from the adrenal cortex, aldosterone increases sodium reabsorption and potassium secretion in the distal nephron (Nyirenda and Padfield, 2007). Hypernatremia does not occur as sodium reabsorption is accompanied by water uptake, thereby maintaining isotonicity. The resultant volume expansion is limited by mineralocorticoid escape. Mineralocorticoid escape is mediated by pressure-natriuresis, atrial natriuretic peptide secretion, and changes in electrolyte transporters in the distal nephron, which result in limiting volume expansion to approximately 1.5 kg or less (Burnett et al, 1985; Yokota et al, 1994; Knepper et al, 2003).

Although the finding of increased plasma aldosterone and decreased plasma renin activity is common to all patients with primary aldosteronism, individual subtypes of the disorder have distinct underlying pathophysiology. Differentiation between subtypes of primary aldosteronism is essential to ensure proper treatment. The causes of primary aldosteronism are presented in Figure 57–12. Idiopathic hyperplasia and aldosterone-producing adenomas are by far the most common subtypes encountered, accounting for over 95% of cases. Although idiopathic hyperplasia is the most common subtype diagnosed, the prevalence of aldosterone-producing adenomas may be greater than previously thought due to lack of routine lateralization studies in patients diagnosed with primary aldosteronism (Mulatero et al, 2004).

The underlying pathophysiology of idiopathic hyperplasia, also referred to as bilateral adrenal hyperplasia, remains unknown. Macronodular hyperplasia is rarely the cause, with most cases attributed to micronodular hyperplasia (Schirpenbach and Reincke, 2007). Clinically, patients with idiopathic hyperplasia have less severe hypertension and are less likely to be hypokalemic compared with patients with aldosterone-producing adenomas (Rossi et al, 2006a). Whereas both adrenal glands are responsible for increased aldosterone production in idiopathic hyperplasia, unilaterally adrenalectomy is not therapeutic. Unilateral adrenal hyperplasia is distinctly uncommon, but when appropriately diagnosed is potentially curable with adrenalectomy following confirmation of lateralizing aldosterone secretion (see Subtype Differentiation section). In comparison with idiopathic hyperplasia, aldosterone-producing adenomas are associated with more profound hypertension and hypokalemia (Rossi et al, 2006a).

Less common causes of primary aldosteronism include adrenal cortical carcinomas, ectopic aldosterone producing tumors, and familial hyperaldosteronism (FH). Primary aldosteronism associated with adrenal cortical carcinoma is rare, representing less than 1% of cases of primary aldosteronism and 2.5% to 5% of adrenal cortical carcinomas (Ng and Libertino, 2003; Seccia et al, 2005). Ectopic aldosterone-producing tumors are extremely rare and should raise suspicion for the presence of accessory adrenal tissue or adrenal heterotopia (Abdelhamid et al, 1996).

Two types of FH have been described, type I and type II (Mulatero et al, 2004). FH type I, also known as glucocorticoid-remediable aldosteronism, is an autosomal-dominant genetic disorder driven by the chimeric fusion of the promoter region of the 11β-hydroxylase gene (*CYP11B1*) and the coding region of the aldosterone synthase gene (*CYP11B2*). This combination results in aldosterone synthase activity being controlled by ACTH. Thus aldosterone is secreted according to the circadian rhythm of ACTH instead of the RAAS (Lifton et al, 1992). Patients with FH type I will often have early-onset refractory hypertension and a family history of early onset hypertension or cerebral vascular accidents (Litchfield et al, 1998; McMahon and Dluhy, 2004). FH type II is a genetically heterogeneous disease with an autosomal-dominant inheritance pattern. Effected families will demonstrate either idiopathic hyperplasia or aldosterone-producing adenomas that are clinically and morphologically indistinguishable from sporadic cases of primary aldosteronism. Linkage analysis suggests that mutations in the 7p22 region are responsible for FH type II in some families (Mulatero et al, 2004; So et al, 2005).

Clinical Characteristics. The diagnosis of primary aldosteronism is usually made during the third to sixth decades of life. There are no specific symptoms of primary aldosteronism with the vast majority of patients being diagnosed during the evaluation of hypertension. The degree of hypertension is typically graded as moderate to severe with the mean blood pressure of 184/112 noted in a retrospective series of 262 patients with primary aldosteronism (Young and Klee, 1988). In the prospective series by Rossi and colleagues (2006a), which evaluated the prevalence of primary aldosteronism in 1125 newly diagnosed hypertensive patients, the mean blood pressure (154/98) was significantly higher than in patients without primary aldosteronism (147/95) (Rossi et al, 2006a). The association between primary aldosteronism and the severity of hypertension has been demonstrated by Mosso and colleagues (2003), who noted a 2%, 8%, and 13% prevalence of primary aldosteronism in hypertensive patients stratified by stage 1 (140 to 159/90 to 99), stage 2 (160 to 179/100 to 109), and stage 3 (>180/>110) hypertension, respectively.

Although hypokalemia has been classically described as a common finding in primary aldosteronism, in contemporary

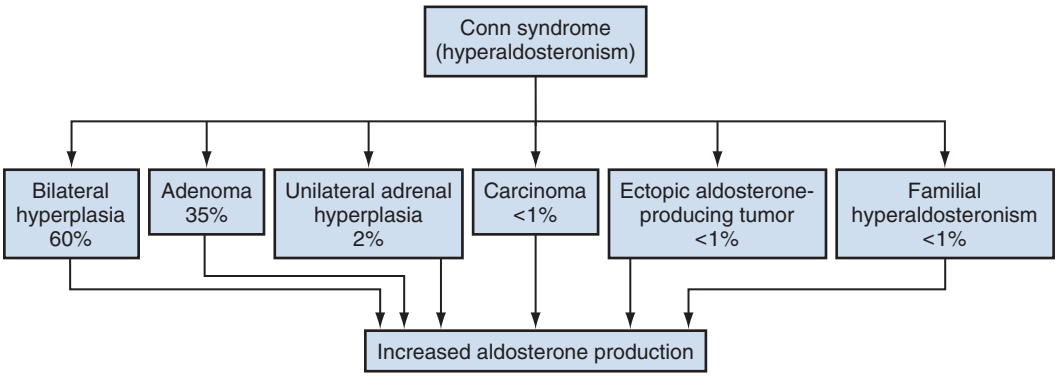


Figure 57–12. Subtypes of primary aldosteronism. (Adapted from Young WF. Primary aldosteronism: renaissance of a syndrome. Clin Endocrinol [Oxf] 2007;66:607–18.)

series, between 63% and 91% of newly diagnosed patients are normokalemic at the time of diagnosis (Mulatero et al, 2004). In a minority of patients, hypokalemia is associated with symptoms including headaches, polydipsia, palpitations, polyuria, nocturia, and muscle weakness (Young, 2007a). Due to mineralocorticoid escape, hypernatremia is an uncommon finding in primary aldosteronism with serum sodium levels similar to other forms of hypertension (Rossi et al, 2006a; Young, 2007a).

Cardiovascular and renal damage is a concern for all patients with hypertension and underlies the need for treatment. The incidence and severity of target organ damage appears to be increased in patients with primary aldosteronism compared with other forms of hypertension. Cardiac abnormalities, including left ventricular filling and diastolic dysfunction, increased left ventricular mass measurement, and prolonged QP interval have all been associated with primary aldosteronism (Rossi et al, 1996; Tanabe et al, 1997). These findings may help to explain the significant increase of cardiovascular events noted in patients with primary aldosteronism by Milliez and colleagues. In a retrospective series of 589 patients with hypertension, patients with primary aldosteronism were 4 times more likely to be diagnosed with a stroke, 6.5 times more likely to be diagnosed with a myocardial infarction, and 12 times more likely to be diagnosed with atrial fibrillation compared with patients with essential hypertension (Milliez et al, 2005; Gonzaga and Calhoun, 2008). The increased risk of cardiovascular disease may be associated with the increased prevalence of metabolic syndrome that has been noted in this patient population (Fallo et al, 2006). Additionally, patients with primary aldosteronism demonstrate increased rates of proteinuria when compared with patients with essential hypertension (Fox et al, 2006; Rossi et al, 2006b).

Diagnostic Tests. The diagnosis of primary aldosteronism is made in a systematic fashion and involves screening, confirmatory testing, and subtype differentiation. Indications for screening are listed in Table 57–7. The accurate diagnosis of primary aldosteronism and subtype differentiation is critical due to the associated increased risk of target organ damage and the potential of surgical cure in appropriately selected patients.

Screening. Prior to initiating screening, hypokalemia should be corrected and all contraindicated medications discontinued. Although patients can continue the majority of antihypertensive agents during screening, mineralocorticoid receptor antagonists are contraindicated and should be stopped at least 6 weeks prior to testing (Seifarth et al, 2002; Young, 2007a). Patients requiring these agents for control of severe hypertension should be transitioned to agents, such as α_1-receptor blockers or long-acting calcium channel blockers, with minimal effects on screening test results (Rossi et al, 2008a). Other antihypertensive agents can alter screening values, but not to the extent that mandates their discontinuation (see Fig. 57–32).

Screening for primary aldosteronism begins by obtaining a morning (between 8 and 10 AM) plasma aldosterone concentration (PAC) and plasma renin activity (PRA) (Funder et al, 2008). From these tests, the PAC and aldosterone to renin ratio are used to screen for autonomous aldosterone secretion. Whereas the aldosterone to renin ratio is dependent on PRA, it is recommended that the lowest PRA value be set at 0.2 ng/mL/hr to avoid falsely elevated ratios (Rossi et al, 2006a). The plasma aldosterone concentrations and aldosterone to renin ratios that define a positive screen and suggest the diagnosis of primary aldosteronism are subject to laboratory variability, thus standard thresholds have not been established. The National Institutes of Health (NIH) Consensus Statement (2002) on the management of the clinically inapparent adrenal mass suggests cutoffs of greater than 30 for the aldosterone to renin ratio and greater than 20 ng/dL for the plasma aldosterone concentrations. However, other institutions have recommended lowering the cutoffs to greater than 20 and greater than 15 ng/dL, respectively (Young, 2007a; Rossi et al, 2008a). Although lowering the thresholds for a positive screening test may increase the rate of false-positive results, all positive tests must be confirmed with further testing prior to making the diagnosis of primary aldosteronism.

Measurement of PRA can be time consuming and varies between different laboratories. For this reason, plasma renin concentration has been evaluated as a possible replacement for PRA in screening for primary aldosteronism (Ferrari et al, 2004; Perschel et al, 2004). Although initial series evaluating the utility of plasma renin concentration in primary aldosteronism screening have demonstrated promise, these findings require further standardization and validation prior to the widespread use (Young, 2007a; Rossi et al, 2008b).

Confirmatory Testing. Following a positive screening test, a confirmatory test must be performed prior to securing the diagnosis of primary aldosteronism. Of the patients with positive screening tests, only 50% to 70% will be diagnosed with primary aldosteronism on confirmatory testing (Mosso et al, 2003; Seiler et al, 2004; Giacchetti et al, 2006). As with screening for primary aldosteronism, proper patient preparation is required with the correction of hypokalemia and discontinuation of mineralocorticoid receptor antagonists. Of the confirmatory tests available, three evaluate for the suppression of aldosterone following sodium loading, and one evaluates for the suppression of the aldosterone to renin ratio following the administration of an angiotensin-converting enzyme inhibitor. The underlying theory behind the sodium loading tests is that loading will decrease plasma renin and aldosterone production in patients without autonomous aldosterone secretion (Mattsson and Young, 2006). The selection of the confirmatory test used depends on individual patient characteristics and physician preferences. Blood pressure should be monitored closely in all patients during confirmatory testing.

The fludrocortisone suppression test requires the administration of the synthetic mineralocorticoid fludrocortisone (0.1 mg every 6 hours) and sodium chloride (2 g every 8 hours) for 4 days. Following 4 days of fludrocortisone and sodium loading, plasma aldosterone concentrations are measured in the upright position. Failure to suppress plasma aldosterone concentrations to less than 6 ng/dL is diagnostic of primary aldosteronism. Once considered the gold standard in the diagnosis of primary aldosteronism, the fludrocortisone suppression test has been supplanted by the oral sodium loading test and the intravenous infusion test due to the

Table 57–7.

Indications for Primary Aldosterone Screening

Hypertension with hypokalemia
Resistant hypertension (three or more oral agents with poor control)
Adrenal incidentaloma with hypertension
Early-onset hypertension (<20) or stroke (<50 years)
Severe hypertension (≥160/≥110)
Whenever considering secondary causes of hypertension (i.e., pheochromocytoma or renovascular disease)
Unexplained hypokalemia (spontaneous or diuretic induced)
Evidence of target organ damage disproportionate to degree of hypertension

risks of severe hypertension and hypokalemia (Schirpenbach and Reincke, 2007).

The oral sodium loading test is conducted by administering a high-sodium diet for 3 days, followed by 24-hour urine measurements of aldosterone, sodium, and creatinine. Supplemental sodium chloride can be given to ensure the intake of at least 12.8 g of sodium per day. Twenty-four-hour sodium should be greater than 200 mmol to ensure adequate sodium loading. The diagnosis of primary aldosteronism is then made when the 24-hour aldosterone is greater than 12 µg per day.

The intravenous saline infusion test spares the patient from several days of sodium loading by the administration of 2 L of 0.9% sodium chloride intravenously over 4 hours. The infusion is performed in the morning after an overnight fast, while the patient is in a recumbent position. Following the intravenous infusion of saline, plasma aldosterone concentrations are measured, with a level of greater than 5 ng/dL being diagnostic of primary aldosteronism, and levels greater than 10 ng/dL are suggestive of aldosterone-producing adenomas (Mulatero et al, 2005; Young, 2007a).

The captopril suppression test is performed by administering 25 to 50 mg of the angiotensin-converting enzyme inhibitor captopril, followed by the measurement of plasma aldosterone concentrations while the patient remains recumbent. Suppression of the RAAS should be noted in patients without primary aldosteronism following the acute administration of captopril, while those with autonomous aldosterone secretion will have persistently elevated plasma aldosterone concentrations greater than 15 ng/dL (Young and Klee, 1988). Further standardization and validation of the captopril suppression test is needed before it is used routinely to confirm the diagnosis of primary aldosteronism when sodium loading tests are available. At this time, the captopril suppression is recommended for patients with cardiac and renal disease, which prohibits sodium loading (Giacchetti et al, 2008).

Subtype Differentiation. Following the diagnosis of primary aldosteronism, attention is then paid to defining the etiology of autonomous aldosterone secretion. Subtype differentiation of primary aldosteronism is essential in selecting the appropriate therapy, because surgical therapy is only successful for select subtypes (Table 57–8). **In patients who are not surgical candidates, subtype differentiation is of little consequence because medical therapy will be instituted; thus these patients can forgo further evaluation, and medical management can be initiated** (Fig. 57–13). **Given the rarity of FH type I, genetic screening should not be performed in all patients. However, patients with a family history of primary aldosteronism, early age of onset (<20 years), or patients with a family history of cerebral vascular accidents at a young age should be considered for genetic testing** (Fig. 57–14). An adrenal CT scan should be obtained in

Table 57–8.

Subtypes of Primary Aldosteronism

SURGICALLY CORRECTABLE	NOT CORRECTABLE BY SURGERY
Aldosterone-producing adenoma	Bilateral adrenal hyperplasia
Primary unilateral adrenal hyperplasia	Familial hyperaldosteronism type I
Ovarian aldosterone-secreting tumor	Familial hyperaldosteronism type II
Aldosterone-producing carcinoma	

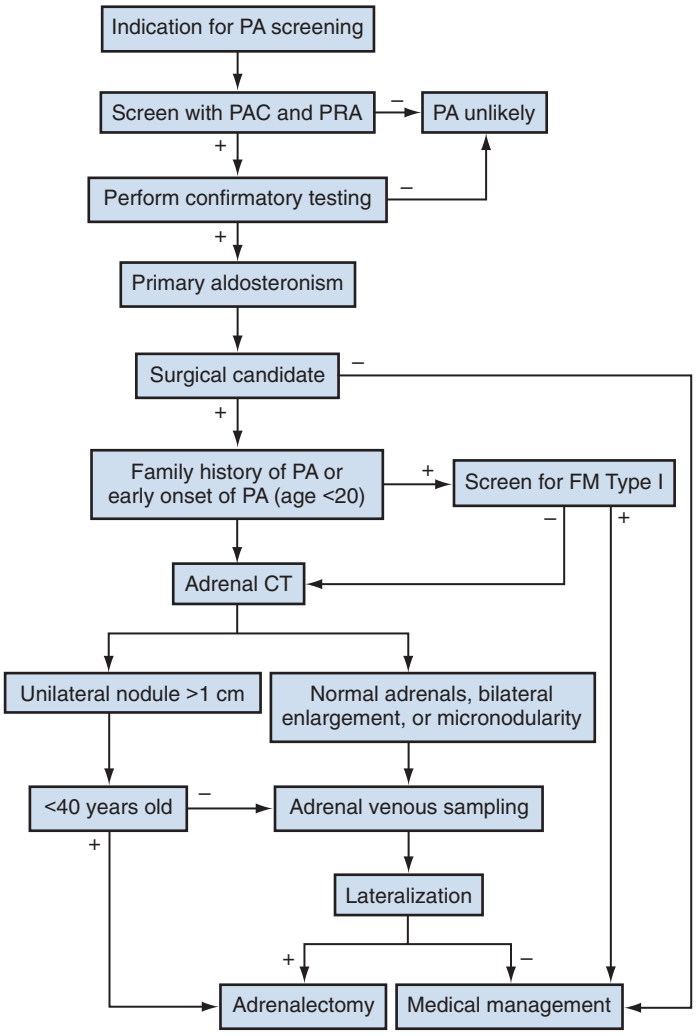


Figure 57–13. Primary aldosteronism diagnosis and treatment algorithm. CT, computed tomography; FM, familial hyperaldosteronism; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity.

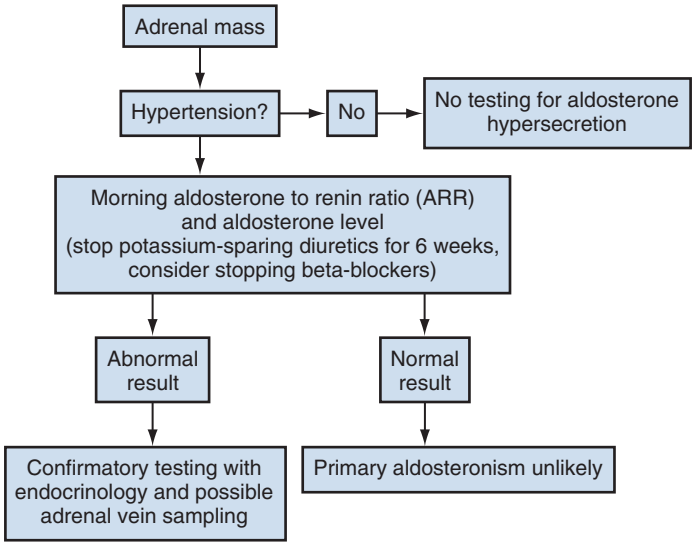


Figure 57–14. Testing algorithm for of aldosterone hypersecretion by an adrenal mass.

all patients with primary aldosteronism who are potential surgical candidates.

Although imperfect in delineating the subtype of primary aldosteronism, an adrenal CT scan should be obtained to evaluate for the presence of adrenal nodules. Radiographic characteristics of aldosterone-producing adenomas include the presence of a unilateral low-density non-enhancing lesion of less than 10 Hounsfield units (HU), with an average size of 1.6 to 1.8 cm and a normal-appearing contralateral adrenal gland. However, given that approximately 20% of aldosterone-producing adenomas will be less than 1 cm in size, lateralization is not based on CT findings alone (Simon and Palese, 2008). Radiographic characteristics of idiopathic hyperplasia can include the presence of multiple unilateral or bilateral adrenal nodules, bilateral adrenal enlargement with increased limb size, or the presence of normal-appearing glands. The combination of the small-size, aldosterone-producing adenomas, and the potential for the presence of nonfunctional adrenal adenomas makes CT imaging flawed in delineating lateralization of aldosterone hypersecretion. Because MRI does not offer an advantage in delineating primary aldosteronism subtypes, and is associated with increased cost, routine use is not currently recommended.

To establish lateralization of aldosterone secretion in surgical candidates, adrenal vein sampling should be performed. By establishing lateralization, one can differentiate between subtypes of primary aldosteronism and identify patients in which adrenalectomy is potentially beneficial. **The value of adrenal vein sampling in evaluating the presence of lateralized aldosterone secretion was illustrated by** Young and colleagues (2004), **who noted that 22% of patients would have been incorrectly excluded from adrenalectomy, and 25% would have been inappropriately recommended to undergo adrenalectomy based on CT findings instead of adrenal vein sampling studies.** As with all other evaluations performed for primary aldosteronism, proper patient selection, patient preparation, and an accurate interpretation of results are essential (Young and Stanson, 2009). A decision-making strategy when performing adrenal vein sampling is depicted in Figure 57–15.

After appropriate patient selection, adrenal vein sampling is performed in the morning after an overnight fast. Percutaneous access to the femoral vein is obtained, and catheter tips are positioned to collect samples from three sites: the right adrenal vein, left adrenal vein, and inferior vena cava (IVC) (see Fig. 57–15A). Samples are then evaluated for aldosterone and cortisol concentrations. Appropriate specimen collection from the adrenal vein is determined by comparing the cortisol concentrations from the adrenal vein samples to the cortisol concentration from the IVC sample, which should be less. The ratio of adrenal vein cortisol to IVC cortisol should be greater than 1.1 : 1 to 5 : 1, depending upon the use of ACTH stimulation (Young and Stanson, 2009). If ACTH stimulation is used, a higher ratio is expected in properly collected samples. Adrenal vein sampling that demonstrates adrenal vein to IVC ratios below the cutoff, on either side, should be considered "nonselective" and discarded. An adrenal vein to IVC ratio above the cutoff, bilaterally, is considered "selective," and comparisons between aldosterone concentrations can be made to determine the presence of lateralization.

Lateralization of aldosterone secretion is determined by comparing the aldosterone to cortisol ratios of the dominant to

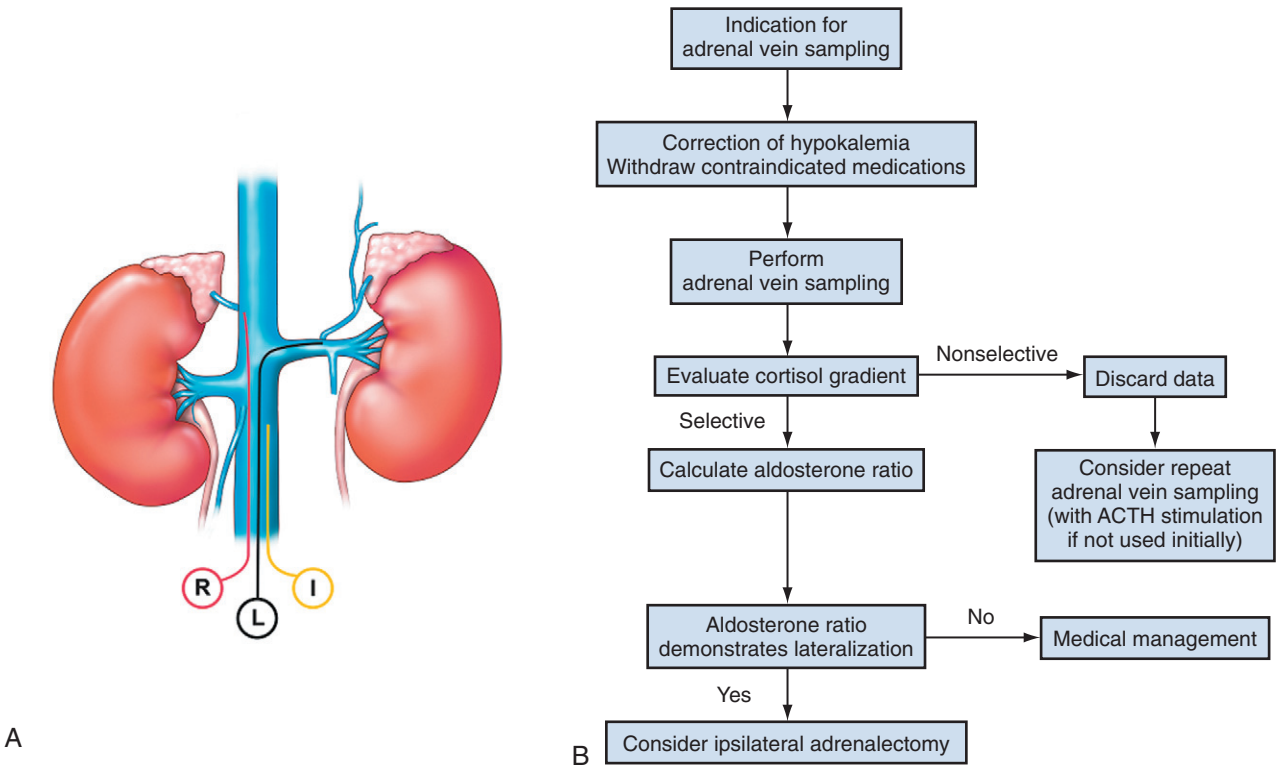


Figure 57–15. Adrenal vein sampling protocol. **A,** Proper catheter positioning for sampling R, right adrenal vein sample; L, left adrenal vein sample; I, inferior vena cava (IVC) sample. **B,** Following sample collection, the cortisol gradient is evaluated using the ratios $R_{cortisol}/I_{cortisol}$ and $L_{cortisol}/I_{cortisol}$. If the cortisol gradients confirm appropriate sample collection, lateralization of aldosterone secretion can be evaluated. Lateralization of aldosterone secretion is determined by the ratio of aldosterone secretion of the dominant to the nondominant adrenal gland while correcting for ipsilateral cortisol secretion using the formula $(A_{dominant}/C_{dominant})/(A_{nondominant}/C_{nondominant})$, where A = plasma aldosterone concentration [PAC] and C = cortisol. ACTH, adrenocorticotropic hormone.

nondominant sides using the formula $(A_{dominant}/C_{dominant})/(A_{nondominant}/C_{nondominant})$. Aldosterone secretion is considered to be lateralized if the ratio is greater than 2 to 4:1, depending on the use of ACTH stimulation (Rossi et al, 2008a; Young and Stanson, 2009). When performed and interpreted correctly, adrenal vein sampling has a sensitivity of 95% and specificity of 100% in detecting lateralized autonomous aldosterone secretion (Young et al, 2004).

The routine use of ACTH stimulation during adrenal vein sampling is controversial. Potential advantages of ACTH stimulation include minimizing stress-induced fluctuations in aldosterone secretion, maximizing the cortisol gradient, and maximizing the aldosterone secretion from aldosterone-producing adenomas (Young, 2007a; Young and Stanson, 2009). In a prospective study investigating these potential benefits, ACTH stimulation was noted to facilitate the ascertainment of proper specimen collection when evaluating the cortisol gradient between adrenal and IVC specimens. However, the authors also noted that ACTH stimulation was also associated with a small risk (3% to 12%) of incorrectly assigning the side of lateralization of aldosterone-producing adenomas, and a moderate risk (36% to 37%) of incorrectly classifying aldosterone-producing adenomas as idiopathic hyperplasia (Seccia et al, 2009).

When adrenal vein sampling is inconclusive due to sampling error, alternative studies are available that may help guide treatment decisions, including nuclear scintigraphy, postural stimulation testing, and measurement of cortisol metabolites. Of these modalities, only nuclear scintigraphy can provide both functional and anatomic data, which is necessary when considering surgical intervention.

^{131}I-6β-iodomethyl-norcholesterol (NP59) is a cortisol analog that can label adrenal cortical cells in order to evaluate for areas of hypersecretion (Heinz-Peer et al, 2007). Prior to injection of the radiotracer, saturated potassium iodine (Lugol solution) is administered to protect the thyroid from uptake of free ^{131}I. Additionally suppression of ACTH with dexamethasone (1 mg every 6 hours for 7 days) is necessary. Evaluation of radiotracer uptake is begun 4 days after NP59 injection and may continue through day 10. Characteristics that suggest the presence of aldosterone-producing adenomas include unilateral uptake of radiotracer less than 5 days after injection, while bilateral uptake is suggestive of idiopathic hyperplasia (Simon and Palese, 2008). The ability to detect a hyperfunctioning adenoma using NP59 is directly proportional to the tumor size and function, with a diminished ability to detect lesions less than 1.5 cm in size (Hogan et al, 1976; Nomura et al, 1990; Mansoor et al, 2002).

The posture stimulation test is designed to distinguish between aldosterone-producing adenomas and idiopathic hyperplasia based on changes in plasma aldosterone concentration levels in response to changes in posture. The test is performed by comparing plasma aldosterone concentration levels after the patient has been recumbent overnight, and again after 4 hours of being upright. In theory, the increase of angiotensin induced with being upright leads to an increase of plasma aldosterone concentration in normal patients that is two- to fourfold greater when compared with recumbent levels. In comparison, patients with idiopathic hyperplasia will demonstrate an increase of at least 33% over baseline, while patients with aldosterone-producing adenomas or FH type I will not demonstrate an increase of plasma aldosterone concentration levels with changes in posture (Ganguly et al, 1973; Young, 2007a). Although the test can be helpful in distinguishing between aldosterone-producing adenomas and idiopathic hyperplasia, it does not provide information regarding the location of the adenoma (right vs. left). Additionally, the reliability of the posture stimulation test is limited by the observation that 30% to 50% of aldosterone-producing adenomas demonstrate an increase of plasma aldosterone concentration, while 20% of idiopathic hyperplasia patients do not demonstrate any elevation with postural changes (Mulatero et al, 2004; Schirpenbach and Reincke, 2007).

Another potential method for differentiating aldosterone-producing adenomas from idiopathic hyperplasia is the measurement of 18-hydroxycortisone (18-OH-B). 18-OH-B is formed by the 18-hydroxylation of corticosterone and may be the immediate precursor of aldosterone. Elevated 18-OH-B (>100 ng/dL) suggests an aldosterone-producing adenoma, while levels of less than 100 ng/dL suggest idiopathic hyperplasia (Biglieri and Schambelan, 1979). However, the accuracy of this test in distinguishing aldosterone production from an adenoma versus hyperplasia is thought to be less than 80%. Additionally, the test does not provide information about tumor location (right vs. left) in cases of functional adenomas (Young and Klee, 1988).

Treatment and Prognosis. The goal of treatment in primary aldosteronism is to control and prevent the morbidity associated with mineralocorticoid access. Therefore the treatment strategies used in therapy aim to remove the source of mineralocorticoid access or block the effect of aldosterone on target organs (Young, 2007a). Treatment strategies for primary aldosteronism are primarily dependent on subtype classification and surgical candidacy (see Fig. 57–13). Patients who are acceptable surgical candidates and have been diagnosed with a surgically correctable subtype of primary aldosteronism can be offered unilateral adrenalectomy, while other patients can be managed effectively with medical therapy.

In patients with confirmed lateralizing aldosterone secretion, adrenalectomy should be considered. Given the small size of aldosterone-producing adenomas, the majority of patients are candidates for a laparoscopic adrenalectomy. In patients suspected of having hypersecretion of aldosterone associated with adrenal cortical carcinoma, an open procedure may be recommended (Kebebew et al, 2002; Gonzalez et al, 2005; Schlamp et al, 2007). **Improvements in blood pressure are noted in the majority of patients undergoing adrenalectomy for primary aldosteronism, with 33% to 73% of patients not requiring antihypertensives postoperatively** (Sawka et al, 2001; Meyer et al, 2005; Schirpenbach and Reincke, 2007). Several predictors of persistent hypertension following adrenalectomy for primary aldosteronism have been described, including age greater than 50 years, the use of two or more antihypertensive agents preoperatively, having a first-degree relative with hypertension, prolonged duration of hypertension prior to adrenalectomy, and renal insufficiency (Celen et al, 1996; Sawka et al, 2001). In patients less than 40 years of age with a unilateral adenoma greater than 1 cm, a unilateral adrenalectomy can be performed without adrenal vein sampling due to the rarity of incidental adenomas in this population (Schirpenbach and Reincke, 2007; Young, 2007a; Zarnegar et al, 2008). In the immediate postoperative period, plasma aldosterone concentration and aldosterone to renin ratios should be evaluated to ensure biochemical cure. Additionally, patients should maintain a high-sodium diet and be monitored for hyperkalemia for several weeks following surgery (Mattsson and Young, 2006; Funder et al, 2008).

Medical treatment of primary aldosteronism is indicated in patients with nonsurgically correctable subtypes and those who are not surgical candidates. **Aldosterone receptor antagonists, spironolactone and eplerenone, are successful in**

lowering the blood pressure and are the antihypertensive agents of choice in patients with primary aldosteronism. Spironolactone therapy is initiated at doses of 25 to 50 mg per day and can be titrated up to 400 mg per day, depending on blood pressure, serum potassium levels, and side effects. Side effects of spironolactone include gynecomastia, impotence, and menstrual disturbances. Eplerenone may provide a more favorable side-effect profile compared with spironolactone, due to increased selectivity for the aldosterone receptor. Treatment should be initiated with 25 mg twice per day and titrated up to 100 mg per day. Despite treatment with an aldosterone receptor antagonist, other antihypertensive agents will often be needed. Additionally, several lifestyle modifications may contribute to the success of medical therapy, including weight loss, maintaining a low- sodium diet, and a regular exercise program (Young, 2007a).

Unlike other forms of primary aldosteronism, FM type I can be treated with oral glucocorticoids. Glucocorticoid administration will reduce ACTH release, leading to decreased aldosterone production in this select group of patients. In FM type I patients whose blood pressure is not controlled with glucocorticoids alone, or those who develop iatrogenic Cushing syndrome, the addition of an aldosterone receptor antagonist should be considered (Funder et al, 2008).

Summary. Successful identification and treatment of primary aldosteronism is critical due to the increased risk of cardiovascular morbidity associated with the diagnosis. Because primary aldosteronism comprises several distinct subtypes that significantly impact management strategy, subtype differentiation is critical prior to surgical intervention.

Key Points: Primary Aldosteronism

- Most patients with primary aldosteronism in contemporary series are normokalemic.
- Primary aldosteronism is associated with an increased risk of end organ damage compared to essential hypertension.
- Accurate subtype differentiation is essential to ensure appropriate treatment of primary aldosteronism.

Pheochromocytoma

Introduction and Epidemiology. Pheochromocytoma is a tumor of the catecholamine-producing cells of the adrenal medulla. Approximately 1 to 2 per 100,000 individuals are diagnosed annually with pheochromocytoma, albeit reports on incidence vary (Bravo and Tagle, 2003). Given its rarity, it is estimated that pheochromocytoma is responsible for only approximately 0.5% of cases of hypertension (Lenders et al, 2005). **Among patients with incidental adrenal masses, approximately 5% will have a pheochromocytoma** (Mantero et al, 2000; Young, 2000). Indeed, incidentally discovered lesions now account for 10% to 25% of all pheochromocytomas diagnoses (Bravo and Tagle, 2003; Lenders et al, 2005).

Some 1% to 25% of pheochromocytomas originate outside of the adrenal gland (Fig. 57–16). These extra-adrenal pheochromocytomas are known as paragangliomas, because they arise from paraganglia, a network of chromaffin-producing neural crest tissue that anatomically parallels the sympathetic and parasympathetic ganglia (Scott et al, 1990; Ilias and Pacak, 2004). Paragangliomas can arise in the head, neck, thorax, abdomen, and pelvis (including bladder). The chromaffin bodies that lie between the aortic bifurcation and the root of the inferior mesenteric artery are known as the organ of Zuckerkandl, and are a common site for paragangliomas (Scott et al, 1990). Of note, some authors reserve the term paraganglioma for tumors only in the head and neck, locations where extra-adrenal pheochromocytomas tend to be nonfunctional (Neumann et al, 2004).

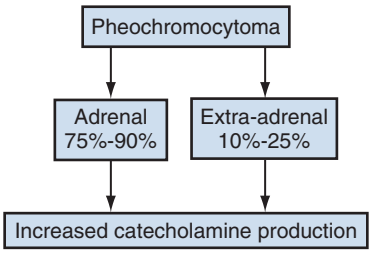


Figure 57–16. Causes of excess catecholamines.

Pathophysiology

Overview. As discussed in the Adrenal Physiology section, cells of the adrenal medulla are analogous to the chromaffin cells of the sympathetic ganglia. Unlike sympathetic ganglia cells, however, cells of the adrenal medulla, and therefore of adrenal pheochromocytomas, possess the enzyme phenylethanolamine-*N*-methyl transferase (PNMT), which gives them the ability to synthesize epinephrine from norepinephrine (Eisenhofer et al, 2004b). Pheochromocytomas vary in their enzymatic composition and in their ability to self-metabolize the catecholamines within each tumor's secretory vesicles. Therefore there is great variability in the amount and ratio of catecholamines secreted by pheochromocytomas (Eisenhofer et al, 2001). Indeed these differences in norepinephrine, epinephrine, and dopamine secretion explain the heterogeneity in clinical behavior of pheochromocytomas. For instance, patients with the rare tumors that secrete primarily epinephrine (usually limited to those that arise from the adrenals or from the organ of Zuckerkandl), tend to experience syncopal or hypotensive episodes due to epinephrine's vasodilatory action through the β_2 receptor, while those patients with predominantly norepinephrine-secreting tumors (e.g., patients with von Hippel–Lindau syndrome [VHL]) present with hypertension and sweating, given the compound's affinity for the vasoconstricting α-adrenoreceptor (Pacak, 2007).

Pathophysiology of Hereditary Pheochromocytoma. Familial cases account for nearly one third of pheochromocytomas (Benn and Robinson, 2006). **Indeed, a significant percentage of cases that initially appear sporadic are later deemed hereditary upon genetic testing. In a 2002 report, Neumann and colleagues** (2002) **demonstrated that 24% of patients (*n* = 271) who presented with isolated pheochromocytoma and lacked any significant family history exhibited a germ-line mutation that predisposed them to the disease.** At least five genes—*RE*arranged *T*ransfection proto-oncogene *(RET)*, von Hippel–Lindau *(VHL)*, neurofibromatosis type 1 *(NF1)*, and mitochondrial succinate dehydrogenase subunits D and B genes *(SDHD, SDHB)*, are now associated with familial pheochromocytomas. Some investigators believe that these genetic abnormalities all modulate neuronal apoptosis and are related through signal transduction pathways downstream from the nerve growth factor (NGF) (Nakamura and Kaelin, 2006). Nevertheless, the phenotypes produced by each gene mutation are quite diverse. Table 57–9 summarizes the clinical features associated with each gene mutation.

In general urologic practice, VHL is the most relevant syndrome associated with pheochromocytoma, because these patients

Table 57–9.

Hereditary Forms of Pheochromocytoma

SYNDROME	CLINICAL CHARACTERISTICS	RISK OF PHEOCHROMOCYTOMA	GENE	CHROMOSOME/ INHERITANCE	PROTEIN	% GERM-LINE MUTATION IN APPARENTLY SPORADIC CASES	RATE OF MALIGNANT DISEASE
Multiple endocrine neoplasia type 2A	• Medullary cancer of thyroid • Hyperparathyroidism • Cutaneous lichen • Amyloidosis	50%	*RET*	10q11.2 Autosomal dominant	Tyrosine kinase receptor	<5	3
Multiple endocrine neoplasia type 2B	• Medullary cancer of thyroid • Multiple neuromas • Marfanoid body habitus • Rare hyperparathyroidism	50%	*RET*	10q11.2 Autosomal dominant	Tyrosine kinase receptor	<5	3
von Hippel-Lindau syndrome type 2	• Renal cell carcinomas and renal cysts • CNS and retinal hemangioblastomas • Pancreatic cysts • Epididymal cystadenomas • Endolymphatic cyst tumors	10%-20%	*VHL*	3p25.26 Autosomal dominant	pVHL19 pVHL30	2-11	5
Neurofibromatosis type 1	• Neurofibromas • Café-au-lait skin spots	1%	*NF1*	17q11.2 Autosomal dominant	Neurofibromin	Unknown	11
Familial paraganglioma syndrome type 4 (PGL-4)	• Carotid body tumors (chemodectomas) • Vagal, jugular, tympanic, abdominal, thoracic paragangliomas	≈20%	*SDHB*	1p36.13 Autosomal dominant	Catalytic iron-sulfur protein	3-10	30-50
Familial paraganglioma syndrome type 1 (PGL-1)	• Carotid body tumors (chemodectomas) • Vagal, jugular, tympanic, abdominal, thoracic paragangliomas	≈20%	*SDHD*	11q23 Maternal imprinting	CybS (membrane-spanning subunit)	4-7	<3

CNS, central nervous system; Pheo, pheochromocytoma.

Data from Dluhy RG. Pheochromocytoma—death of an axiom. N Engl J Med 2002;346(19):1486–8; and Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. Lancet 2005;366(9486):665–75.

usually are already under urologic care due to their propensity to develop renal cell carcinoma (RCC). Patients with VHL and no family history of pheochromocytoma are classified as having the type 1 variant of the syndrome, while type 2 patients are those who carry a family history of pheochromocytoma. Additionally, the type 2 variant of VHL is further subdivided. Type 2A patients are those with concomitant RCC, and type 2B patients are those who do not exhibit evidence of renal malignancy (Walther et al, 1999). A type 2C variant is defined as patients with pheochromocytoma in the setting of a VHL mutation, but no other stigmata of the VHL syndrome (Hes et al, 2003). Interestingly, a genotype phenotype has been established with VHL-associated pheochromocytomas (type 2), whereby these patients are more likely to exhibit a missense mutation of the VHL gene (Walther et al, 1999). Whereas VHL type 2C patients appear to maintain HIF regulation, pheochromocytoma pathogenesis may occur through HIF-independent pathways (Nakamura and Kaelin, 2006). Furthermore, pheochromocytomas in patients with VHL, unlike those in cases of sporadic or multiple endocrine neoplasia 2 (MEN2)-related disease, tend to produce less epinephrine. As a result, metanephrine (but not normetanephrine) levels in these patients are nearly always normal (Eisenhofer et al, 1999; Walther et al, 1999; Pacak, 2007).

Pathophysiology of Malignant Pheochromocytoma. Malignant pheochromocytoma is an aggressive life-threatening neoplasm. **Currently, malignancy can only be defined by the presence of clinical metastases. Pathologic appearance and even local invasion are of only limited value in determining metastatic potential of a given lesion** (Scholz et al, 2007). A number of pathologic criteria to differentiate benign from malignant disease have been proposed, but, to date, there is no single histologic criterion agreed upon (Thompson, 2002; Kimura et al, 2005; Pacak et al, 2007; Scholz et al, 2007). Some pathologic criteria employ immunohistochemical strategies including Ki-67 staining, which may be the best indicator of malignancy thus far; although, it has not yet been validated due to methodologic heterogeneity (Kimura et al, 2005; Pacak et al, 2007).

Malignant pheochromocytoma in patients with MEN-2 and VHL is exceedingly rare (see Table 57–9). The *SDHB* mutation is the single genetic abnormality most strongly associated with malignancy. In one international series, 11 of 32 patients with this mutation exhibited clinically malignant pheochromocytoma (Neumann et al, 2004).

Clinical Characteristics

Overview. **Classically, pheochromocytoma has been called the "10% tumor": 10% extra-adrenal, 10% familial, 10% bilateral, 10% pediatric, and 10% malignant** (Scott et al, 1990; Dluhy, 2002; Lenders et al, 2005). **However, this rule has been challenged repeatedly. As already mentioned, up to 25% of pheochromocytomas can be extra-adrenal** (Ilias and Pacak, 2004). **Similarly, familial cases account for up to 30% of tumors at presentation** (Benn and Robinson, 2006). **Malignancy is rare in both sporadic cases of adrenal pheochromocytoma (up to 5%) and in most cases of hereditary disease** (see Table 57–9). **However, for unclear reasons, it occurs in over one third of patients with extra-adrenal disease** (Lenders et al, 2005). **Nonhereditary cases of pheochromocytoma are most often diagnosed in the fourth and fifth decades of life, while familial tumors tend to occur at a younger age** (Lenders et al, 2005). Despite being uncommon, pediatric pheochromocytoma is the most frequently encountered endocrine neoplasm in children. Up to 40% of such tumors are familial, and over 20% are bilateral (Pacak et al, 2007; Havekes et al, 2009). For reasons that are unclear, tumors arising from the right adrenal are more common, tend to be larger, and recur more frequently than those that arise in the left gland (Amar et al, 2005b).

Paroxysmal hypertension is the classic presenting symptom in patients with pheochromocytoma. Nevertheless, such episodic spikes in blood pressure are only documented in approximately 30% to 50% of patients and can occur in the backdrop of baseline essential hypertension. The remainder of patients demonstrate persistently elevated blood pressure, and a minority are entirely normotensive (Scott et al, 1990). **The triad of headache, episodic sudden perspiration, and tachycardia is a classic hallmark of pheochromocytoma** (Bravo and Tagle, 2003). Table 57–10 lists common clinical signs and symptoms of pheochromocytoma. More than 20% of patients can be asymptomatic (Adler et al, 2008). Indeed, depending on the catecholamine milieu of each tumor, its ability to self-metabolize the catecholamine reserve, and the patient's varied response to catecholamine surges, symptomatology can drastically differ from patient to patient (Pacak, 2007). This heterogeneity in mode of presentation, symptomatology and difficulty in establishing firm diagnostic criteria for pheochromocytoma is illustrated by an autopsy series that includes 54 patients over 50 years from the Mayo Clinic, where more than 75% of tumors were not suspected prior to the patient's death (Sutton et al, 1981).

Clinical Characteristics of Hereditary Pheochromocytoma. Hereditary pheochromocytomas occur at a younger age and tend to be multifocal and/or bilateral at presentation (Adler et al, 2008). Table 57–9 summarizes the clinical features of each gene mutation. Pheochromocytomas in patients with MEN-2 nearly always arise from the adrenal gland, while tumors in patients with VHL and neurofibromatosis-1 (NF1) are outside the adrenal in approximately 12% and 6% of cases, respectively (Lairmore et al, 1993; Walther et al, 1999; Benn and Robinson, 2006; Karagiannis et al, 2007). *SDHB* and *SDHD* mutations mostly result in extra-adrenal and often multifocal phenotypes; nevertheless, solitary adrenal masses, as a result of these genetic abnormalities, may also arise (Neumann et al, 2004; Pacak et al, 2007). Unlike other hereditary forms of pheochromocytoma, mutations in the *SDHB* gene is associated with a very high risk of malignancy (Neumann et al, 2004). As mentioned previously, pheochromocytomas in patients with VHL mainly secrete norepinephrine and lack significantly

Table 57–10.

Clinical Manifestations of Pheochromocytoma

	FREQUENCY
Headache	60%-90%
Palpitations	50%-70%
Sweating	55%-75%
Pallor	40%-45%
Nausea	20%-40%
Flushing	10%-20%
Weight loss	20%-40%
Tiredness	25%-40%
Psychologic symptoms (anxiety, panic)	20%-40%
Sustained hypertension	50%-60%
Paroxysmal hypertension	30%
Orthostatic hypotension	10%-50%
Hyperglycemia	40%

Adapted from Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. Lancet 2005;366(9486):665–75.

elevated epinephrine secretion. As a result, normetanephrine, but not metanephrine, levels are elevated in these patients (Eisenhofer et al, 1999; Walther et al, 1999; Pacak, 2007).

Clinical Characteristics of Malignant Pheochromocytoma. Metastatic disease is much more common in extra-adrenal lesions (Scholz et al, 2007). The *SDHB* mutation is the one genetic abnormality that is strongly associated with metastatic disease (see Table 57–9). Classically, the majority of patients with an *SDHB* abnormality exhibit extra-adrenal disease; however, a significant proportion of patients (28% of patients in one series) have adrenal lesions at presentation (Neumann et al, 2004). Malignant lesions are more likely to exhibit elevated dopamine levels and tend to be larger (>5 cm); however, as mentioned previously, in the absence of metastatic deposits, a preclinical diagnosis of malignant potential is not possible (John et al, 1999; Lenders et al, 2005). Bone, lungs, liver, and lymph nodes constitute the most common sites of metastases (Scholz et al, 2007).

Metastatic pheochromocytoma can be present at diagnosis or be detected during surveillance after excision of the primary tumor. Most metastases are discovered within 5 years of the original diagnosis, but metastatic spread more than 15 years following initial excision has been reported (Eisenhofer et al, 2004a; Lenders et al, 2005).

Diagnostic Tests. Biochemical testing is the first step in the evaluation of patients suspected of pheochromocytoma. If metabolic testing is positive, appropriate imaging is undertaken to localize the source of the catecholamine excess (Adler et al, 2008). Timely and appropriate diagnosis of pheochromocytoma continues to be a clinical challenge (Zendron et al, 2004; Harding et al, 2005; Yu et al, 2009). In urologic practice, diagnosis of pheochromocytoma typically begins with the evaluation of an adrenal mass as a catecholamine hypersecreting lesion. Given the potentially catastrophic consequences of misdiagnosis, the possibility of pheochromocytoma must also be considered in patients with a known history of malignancy, and with a solitary adrenal mass in those whom a metastatic adrenal lesion is suspected (Weismann et al, 2006; Adler et al, 2007). Clinical evaluation depends on both radiographic imaging and, more importantly, on biochemical testing.

Imaging. Here we briefly discuss imaging of pheochromocytoma. Please refer to Imaging of Adrenal Masses section for further details on adrenal imaging.

CROSS-SECTIONAL IMAGING. On cross-sectional imaging, adrenal pheochromocytomas appear as well-circumscribed lesions. **Given their rich vascularity and low lipid content, pheochromocytomas typically measure an attenuation of greater than 10 HU on unenhanced CT (mean ≈35 HU). This property affords the ability to differentiate them from lipid-rich adenomas** (Motta-Ramirez et al, 2005). Furthermore, pheochromocytomas can be distinguished from lipid-poor adenomas using CT contrast washout strategies. Although nonspecific, pheochromocytomas, unlike adenomas, do not exhibit rapid contrast washout on delayed imaging (Szolar et al, 2005), rare examples of low-density pheochromocytomas that exhibit an unenhanced attenuation of less than 10 HU and demonstrate brisk contrast washout have been reported (Blake et al, 2003; Blake et al, 2005). Such examples, underscore the importance of a complete metabolic evaluation for every adrenal mass. In the past, iodinated intravenous (IV) contrast was believed to be a possible trigger for a hypertensive crisis. No evidence exists to support this misconception (Pacak, 2007).

Similar to CT, magnetic resonance imaging is an excellent imaging modality for characterizing adrenal lesions. Again, differentiation of pheochromocytoma from adenoma centers on an assessment of the lesion's lipid content. Unlike lipid-rich adenomas, pheochromocytomas do not exhibit signal dropout on out-of-phase sequences (Namimoto et al, 2001). Classically, bright signal intensity on T2-weighted imaging (best seen on fat suppression sequences)—termed the "light bulb" sign—was believed to be diagnostic for pheochromocytoma. It is now clear that this imaging characteristic is neither specific nor sensitive enough to secure a diagnosis and must be interpreted with caution (Varghese et al, 1997; Elsayes et al, 2005).

FUNCTIONAL IMAGING

METAIODOBENZYLGUANIDINE (MIBG) SCINTIGRAPHY

MIBG is a small-molecule analogue of norepinephrine. When tagged with either ^{131}I or ^{123}I, MIBG scintigraphy has been used since the 1980s to evaluate patients with pheochromocytoma. ^{123}I-MIBG, the preferred radiographic agent, affords a high sensitivity (83% to 100%) and superb specificity (95% to 100%) for identification of pheochromocytoma (Ilias and Pacak, 2004). Details regarding this imaging modality are discussed in the Imaging section. Here, we review clinical applications of MIBG.

MIBG is an integral part of a thorough workup for patients with extra-adrenal, metastatic, or recurrent pheochromocytoma. It is also often employed to localize diseases in patients with biochemical evidence of pheochromocytoma but negative cross-sectional imaging. Nevertheless, currently no consensus exists on the role of MIBG in the most common and urologically most relevant clinical scenario—a solitary adrenal mass on cross-sectional imaging in the setting of a biochemical evaluation indicative of pheochromocytoma (Pacak et al, 2007; Koch, 2009). Advocates for MIBG testing argue that in this context, MIBG affords the opportunity to verify that the mass in question is indeed a pheochromocytoma and that metastatic disease was not missed on cross-sectional imaging (Ilias and Pacak, 2004). Some clinical data, however, suggest that MIBG in this situation can safely be omitted, because it only serves to confirm what is already known and does not alter management (Miskulin et al, 2003; Bhatia et al, 2008; Greenblatt et al, 2008). Nevertheless, MIBG imaging for large (>5 cm) tumors is likely prudent in order to assess for presence of metastatic disease prior to surgery and thereby counsel the patient appropriately (Lenders et al, 2005). Rarely, MIBG scanning may also be employed in cases where metabolic workup of an adrenal mass reveals exclusive excess of norepinephrine and normetanephrine, but not epinephrine or metanephrine. In such unusual circumstances, MIBG can, at times, demonstrate that the actual functioning lesion is extra-adrenal (Pacak et al, 2007).

OTHER FUNCTIONAL IMAGING MODALITIES

Whole-body functional imaging with MIBG has its limitations. For instance, tumors in patients with *VHL* and *SDHB* gene mutations may exhibit cold MIBG scans (Timmers et al, 2007b; Havekes et al, 2008). Furthermore, aggressive metastatic lesions may lose their ability to accumulate MIBG (Havekes et al, 2008). As discussed under Imaging, several modalities using radiolabeled somatostatin analogues and PET radiopharmaceuticals have been developed to serve as alternatives to MIBG in these instances. Most have limited clinical utility; however, PET imaging with ^{18}F-dopamine has gained acceptance at some institutions (Timmers et al, 2007a). Furthermore, FDG-PET was recently shown as a useful clinical tool for patients with the *SDHB* mutation (Fig. 57–17) (Timmers et al, 2007b).

Biochemical Evaluation

OVERVIEW. Catecholamines and their metabolites, including metanephrines, are conjugated with a sulfate moiety in the

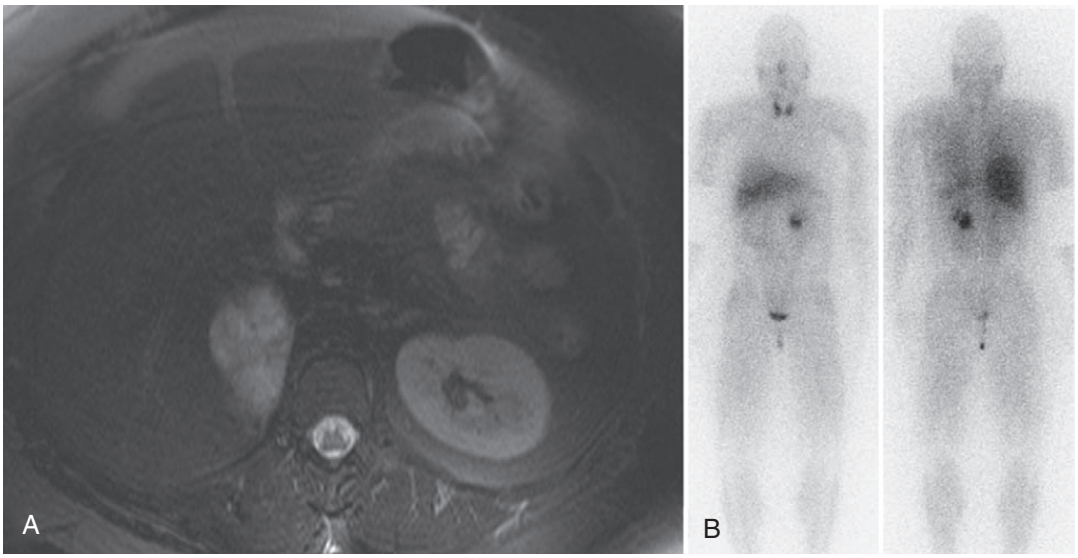


Figure 57–17. Imaging of pheochromocytoma. **A,** Axial T2-weighted MR image of a right adrenal mass that proved to be pheochromocytoma. **B,** Metaiodobenzylguanidine scan of a different patient with a localized left pheochromocytoma. Normal uptake can be seen in the liver, salivary glands, the thyroid, liver, and bladder. (**A,** Courtesy of Dr. Rosaleen Parsons, Fox Chase Cancer Center, Philadelphia, PA. **B,** Courtesy of Dr. Michael Yu, Fox Chase Cancer Center, Philadelphia, PA.)

Table 57–11.

Test Characteristics for Diagnosis of Pheochromocytoma from a Large Multicenter Cohort Study (*n* = 858, 214 Patients with Pheochromocytoma and 644 Controls)

	Sensitivity, %		Specificity, %	
	Hereditary	Sporadic	Hereditary	Sporadic
Plasma-free metanephrines	97 (74/76)	99 (137/138)	96 (326/339)	82 (249/305)
Catecholamines	69 (52/75)	99 (126/137)	89 (303/339)	72 (220/304)
Urine-fractionated metanephrines	96 (26/27)	97 (76/78)	82 (237/288)	45 (73/164)
Catecholamines	79 (54/68)	91 (97/107)	96 (312/324)	75 (159/211)
Total metanephrines	60 (27/45)	88 (61/69)	97 (91/94)	89 (79/89)
Vanillylmandelic acid	46 (30/65)	77 (66/86)	99 (310/312)	86 (132/153)

From Lenders J, Pacak K, Walther M, et al. Biochemical diagnosis of pheochromocytoma: which test is best? J Am Med Assoc 2002;287(11):1427–34, Table 3.

bloodstream. The term "free" refers to compounds that are not conjugated and lack this sulfate group. In the past, assays that measured "total" amounts of catecholamine metabolites were employed. These assays were not able to discriminate between "free" and "sulfonated" compounds, and were largely inferior in their test characteristics compared with current methods (Eisenhofer et al, 2003a). Moreover, in the past, assays did not always distinguish compound subtypes and reported the aggregate level of catecholamines or metanephrines. Today, the term "fractionated" is used when the laboratory report details not only the amount of each compound type (e.g., metanephrines), but also the relative concentrations of each compound (e.g., normetanephrine and metanephrine) (Eisenhofer et al, 2004b) (Table 57–11).

CATECHOLAMINE TESTING. Catecholamines—dopamine, norepinephrine, and epinephrine—are produced by pheochromocytomas in varying amounts. Release of these compounds into the bloodstream is often paroxysmal. In the past, measurement of both urinary and serum catecholamine levels was the mainstay for evaluation of pheochromocytoma. Due to the sensitivity (≈85%) and specificity (≈85%) of these tests, this strategy has been largely replaced by measurements of levels of metanephrines—the methylated metabolites of catecholamines (Lenders et al, 2002; Lenders et al, 2005). Measurement of urinary catecholamines, nevertheless, is still recommended in conjunction with urinary–fractionated metanephrine testing (Young, 2007b).

METANEPHRINE TESTING. *O*-Methylation of catecholamines is catalyzed by the catechol-*O*-methyltransferase (COMT) enzyme. *O*-Methylation of norepinephrine produces normetanephrine, while epinephrine's methylation results in formation of metanephrine. Together normetanephrine and metanephrine are known as metanephrines (see Fig. 57–4) (Eisenhofer et al, 2001). Historically, formation of metanephrines was believed to take place by COMT in the liver and kidneys after catecholamines were released into the peripheral circulation by the tumor. Now it is clear that the vast majority of metanephrine synthesis occurs within the adrenal medulla and/or pheochromocytoma and only then do they enter the bloodstream (Eisenhofer et al, 1998; Eisenhofer et al, 2004b). **Because this conversion of catecholamines to metanephrines is an uninterrupted process within pheochromocytomas, measurement of plasma concentration of metanephrines is a much more sensitive means of tumor detection than the measurement of rises in plasma catecholamines, which may be paroxysmal** (Eisenhofer et al, 2003a, b). Today, measurement of metanephrine levels in plasma or urine represents the foundation for pheochromocytoma diagnosis and is extremely sensitive (Fig.

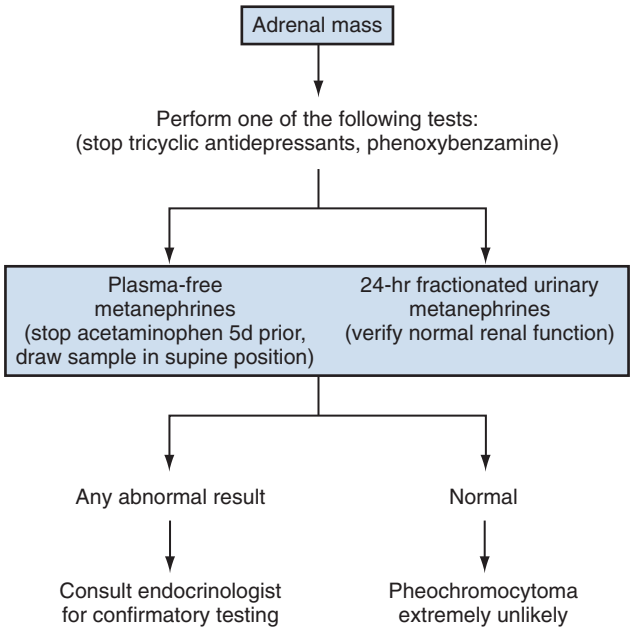


Figure 57–18. Testing algorithm to evaluate adrenal mass for catecholamine secretion.

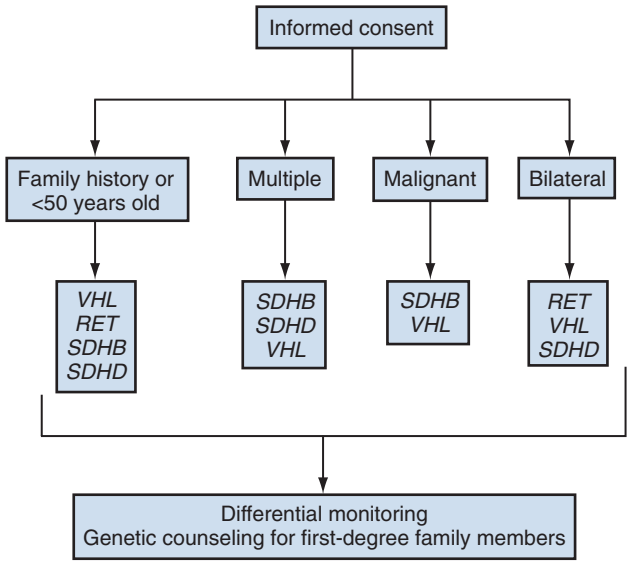


Figure 57–19. Algorithm for genetic screening of patients with pheochromocytoma with risk factors for hereditary disease. (From Pacak K. Preoperative management of the pheochromocytoma patient. J Clin Endocrinol Metab 2007;92:4069–79.)

57–18). Controversy exists regarding whether measurement of plasma-free metanephrines versus urinary–fractionated metanephrines should be used as the initial test (Lenders et al, 2002; Sawka et al, 2003; Young, 2007b; Eisenhofer et al, 2008). Please refer to the section Assessment of Function of Adrenal Masses: Testing for Catecholamine Hypersecretion for a complete discussion of the two testing strategies. Traditionally, when tests for fractionated urine or total metanephrines are ordered, urine catecholamine levels are also obtained (Eisenhofer et al, 2003a).

VMA TESTING. Because vanillylmandelic acid (VMA) is the primary end metabolite of catecholamines, its measurement in urine has long been used for diagnosis of pheochromocytoma. Nevertheless, synthesis of VMA requires deamination of catecholamines, or their metabolites, by the monoamine oxidase (MOA) enzyme, and occurs not only in the adrenal medulla but also in the sympathetic nervous system. Moreover, the sympathetic nervous system lacks the ability to produce epinephrine, due to the absence of the PNMT enzyme, and therefore only contributes to the serum level of normetanephrine (from norepinephrine) but not metanephrine (from epinephrine). Therefore the relative rise of VMA levels in the presence of a pheochromocytoma is much less dramatic than the rise seen in the levels of metanephrines, and the sensitivity of urine VMA levels is therefore low (below 65% in some series) (Lenders et al, 2005). However, the specificity of the test is high, especially in nonfamilial cases (99%) (Lenders et al, 2002).

CLONIDINE SUPPRESSION TESTING. Clonidine, an α_2 agonist, suppresses catecholamine (specifically norepinephrine) production by the sympathetic nervous system but not by pheochromocytoma. Comparison of normetanephrine levels before and after clonidine administration has been shown to yield results with favorable test characteristics (Eisenhofer et al, 2003b). This evaluation is suggested by some experts for secondary testing in patients with pheochromocytoma who exhibit mild or borderline elevations in metanephrine levels. When embarking on clonidine suppression testing, one must be cognizant that clonidine administration can result in significant hypotension in certain patients (Eisenhofer et al, 2003b).

CHROMOGRANIN A TESTING. Chromogranin A belongs to a group of compounds known as granins, which exist in the secretory vesicles of the neuroendocrine and the nervous systems. Elevation of serum chromogranin A levels has been documented in patients with pheochromocytoma. Although the sensitivity of the test for detecting pheochromocytoma is suboptimal (≈85%), some have suggested that chromogranin A–level evaluation has a role for confirmatory testing in patients who have mild or moderate (less than a fourfold) elevation in free-plasma metanephrine levels (Bravo and Tagle, 2003; Algeciras-Schimnich et al, 2008). Chromogranin A is renally cleared, and the specificity of the test decreases significantly in patients with glomerular filtration rates less than 80 mL/min (Bravo and Tagle, 2003).

Screening for Hereditary Pheochromocytoma. A hereditary pattern is responsible for more than one third of pheochromocytomas. Furthermore, nearly one quarter of patients who appear to have sporadic nonfamilial disease at diagnosis demonstrate germline mutations upon genetic testing (Neumann et al, 2002; Benn and Robinson, 2006). Despite this, the consensus of The First International Symposium on Pheochromocytoma in 2005 did not endorse universal genetic testing in all patients diagnosed with pheochromocytoma. Instead, this panel of experts established guidelines for screening and evaluation for pheochromocytoma. Figure 57–19 summarizes how clinical history and disease characteristics at presentation should guide genetic testing. Others have suggested similar algorithms (Amar et al, 2005a). All patients under age 50 deserve genetic testing for the *RET*, *VHL*, *SDHB*, and *SDHD* gene mutations (Pacak, 2007). Routine testing for the *NF1* gene is not recommended in patients who do not meet clinical criteria for neurofibromatosis (Plouin and Gimenez-Roqueplo, 2006b). Before initiating genetic testing, the patient should be counseled about implications and benefits of genetic testing. Professional genetic counseling is strongly recommended (Pacak, 2007).

Treatment

Overview. Pheochromocytoma is a surgical disease. Complete resection of the tumor is advised whenever possible (Khorram-Manesh et al, 2005). Laparoscopic adrenalectomy constitutes the

standard of care for most tumors; although open approaches have been advocated for large and/or surgically difficult tumors (Pacak et al, 2007). Please see Chapter 58 regarding surgical considerations when treating patients with pheochromocytoma. The urologist must be familiar with the peri-operative management of catecholamine-producing tumors before taking the patient to the operating room. Lifelong follow-up is necessary for all patients. Patients with familial and malignant disease require a tailored approach that should include cardiology, endocrinology, and, if needed, medical oncology.

Preoperative Management

OVERVIEW. Catecholamine release during intraoperative tumor manipulation can result in hazardous blood pressure elevation and cardiac arrhythmias. In the era before routine initiation of preoperative catecholamine blockade, some reported mortality rates as high as 50% (Pacak et al, 2001b). **In 2005, the First International Symposium on Pheochromocytoma recommended that all patients with pheochromocytoma and an abnormal metabolic evaluation undergo preoperative catecholamine blockade, including patients who do not exhibit evidence of blood pressure elevation and lack classic symptomatology** (Pacak, 2007). Contemporary series demonstrate mortality rates of less than 3%, which has been attributed in part to optimized anesthetic care and routine preoperative blockade (Lenders et al, 2005). In the absence of appropriately conducted clinical studies comparing preoperative management strategies, no level I evidence exists regarding optimal pre- or perioperative management (Pacak, 2007). Here, we review pre-operative blockade strategies relevant to aggressive α blockade, a central theme recommended by the team from the National Institutes of Health. Option 1 in Figure 57–20 summarizes their approach. We also outline an alternative strategy (see Fig. 57–20, option 2) that focuses on calcium channel blockade and that has been popularized by other authors (Ulchaker et al, 1999). Other permutations on approaches to preoperative catecholamine blockade exist but are less widely discussed in the literature (Pacak, 2007).

Thoughtful preoperative cardiac evaluation is paramount, because patients with pheochromocytoma are at risk for cardiomyopathy. Some experts recommend routine pre-operative echocardiography (Kinney et al, 2002). We suggest that the patient undergo either a cardiology or an anesthesia consultation prior to surgery.

ALPHA BLOCKADE. **Phenoxybenzamine is the most common α blocker used for preoperative catecholamine blockade of pheochromocytoma.** The agent irreversibly blocks the α receptor. As such, intraoperative catecholamine surges generally do not override its actions, because reversal of the blockade is only possible through synthesis of new receptor molecules (Pacak, 2007). Phenoxybenzamine is started 7 to 14 days prior to surgery. Oral dosing of 10 mg twice daily is initiated and titrated by increases of 10 to 20 mg to a blood pressure of 120 to 130/80 mm Hg in a seated position. Mild postural hypotension with systolic pressures greater than 80 mm Hg is acceptable (Kinney et al, 2002). Experience shows that final dosing of 1 mg/kg is usually sufficient to achieve adequate blockade (Pacak, 2007). In children, 0.2 mg/kg (maximum dose of 10 mg) four times daily with increases in 0.2 mg/kg increments is recommended (Lenders et al, 2005). Due to the irreversible nature of α blockade, following tumor resection patients may require transient blood pressure support (Pacak, 2007).

Selective reversible α_1 blockers, such as terazosin, doxazosin, or prazosin, are used at some centers in lieu of or in combination with phenoxybenzamine. Although these agents may have fewer side effects than phenoxybenzamine, data regarding their efficacy is contradictory (Lenders et al, 2005; Pacak, 2007).

BETA BLOCKADE. Beta blockade should be used with caution in patients with pheochromocytoma; however, its use is at times necessary due to reflex tachycardia and arrhythmias that can result upon initiation of α blockade. **It is important to understand that β blockade should never be started prior to appropriate α blockade.** Indeed, in the absence of α blockade, β antagonists cause a potentiation of the action of epinephrine on the α_1 receptors, due to blockade of the arteriolar dilation at the β_2 receptor. For this reason, selective β_1 adrenoreceptor blockers, such as atenolol and metoprolol, are generally preferred. Dosing for these agents is summarized in Figure 57–20 (Pacak, 2007).

CATECHOLAMINE SYNTHESIS BLOCKADE. Alpha-methyltyrosine, better known as metyrosine, blocks the rate-limiting step in the biosynthesis of catecholamines by inhibiting the tyrosine hydroxylase enzyme and thereby preventing the conversion of tyrosine to L-dihydroxyphenylalanine (L-DOPA) (see Fig. 57–4) (Pacak et al, 2001b). Approximately 3 days are necessary to achieve full clinical effect following initiation of this agent. Because blockade of catecholamine synthesis is incomplete, the use of metyrosine is generally coupled with α blockade by phenoxybenzamine. Use of this agent largely depends on institutional preferences and availability. Some centers avoid routine use of this agent and reserve it for refractory or metastatic patients due to its central nervous system side effects, including sedation, mood depression, and galactorrhea. Extrapyramidal symptoms resembling parkinsonism can result and require cessation of phenoxybenzamine use if present (Pacak et al, 2007). Dosing and titration strategies are summarized in Figure 57–20.

CALCIUM CHANNEL BLOCKADE. Calcium channel blockade in the context of catecholamine excess lowers blood pressure by generating smooth muscle relaxation (Ulchaker et al, 1999). The use of agents such as nicardipine has been suggested by some as an adjunct to traditional α-blockade therapy in refractory patients. Other groups, however, report that sole use of calcium channel blockers (see Fig. 57–20, option 2) is sufficient for safe pheochromocytoma resection (Ulchaker et al, 1999; Lebuffe et al, 2005). Indeed, advocates of this strategy argue that this approach avoids reflex tachycardia and postoperative hypotension that is seen with use of phenoxybenzamine (Ulchaker et al, 1999). The team from the National Institutes of Health suggests that this strategy (Fig. 57–20, option 2) be reserved for patients with only mild symptomatology at presentation (Pacak, 2007).

INTRAVASCULAR VOLUME MANAGEMENT. Restoration of intravascular volume is perhaps the most important component of preoperative management of patients with pheochromocytoma. Intake of salt and fluid is encouraged once catecholamine blockade has been initiated (Lenders et al, 2005). Moreover, most centers admit patients the day before surgery and initiate aggressive intravenous fluid resuscitation. The last dose of phenoxybenzamine and/or metyrosine is usually given on the night prior to surgery, and the next morning's dose is held. This approach minimizes potentially prolonged hypotension following tumor resection (Pacak, 2007).

Postoperative Management.

In the immediate postoperative period, the patient must be actively monitored. If phenoxybenzamine was employed for preoperative α blockade, hypotension is common, given the lasting effects of the agent (Pacak et al, 2001b). Moreover, in a high catecholamine state, α_2-adrenoreceptor stimulation inhibits insulin release. The withdrawal of this adrenergic stimulus following tumor resection, may result in rebound hyperinsulinemia and subsequent hypoglycemia (Kinney et al, 2002).

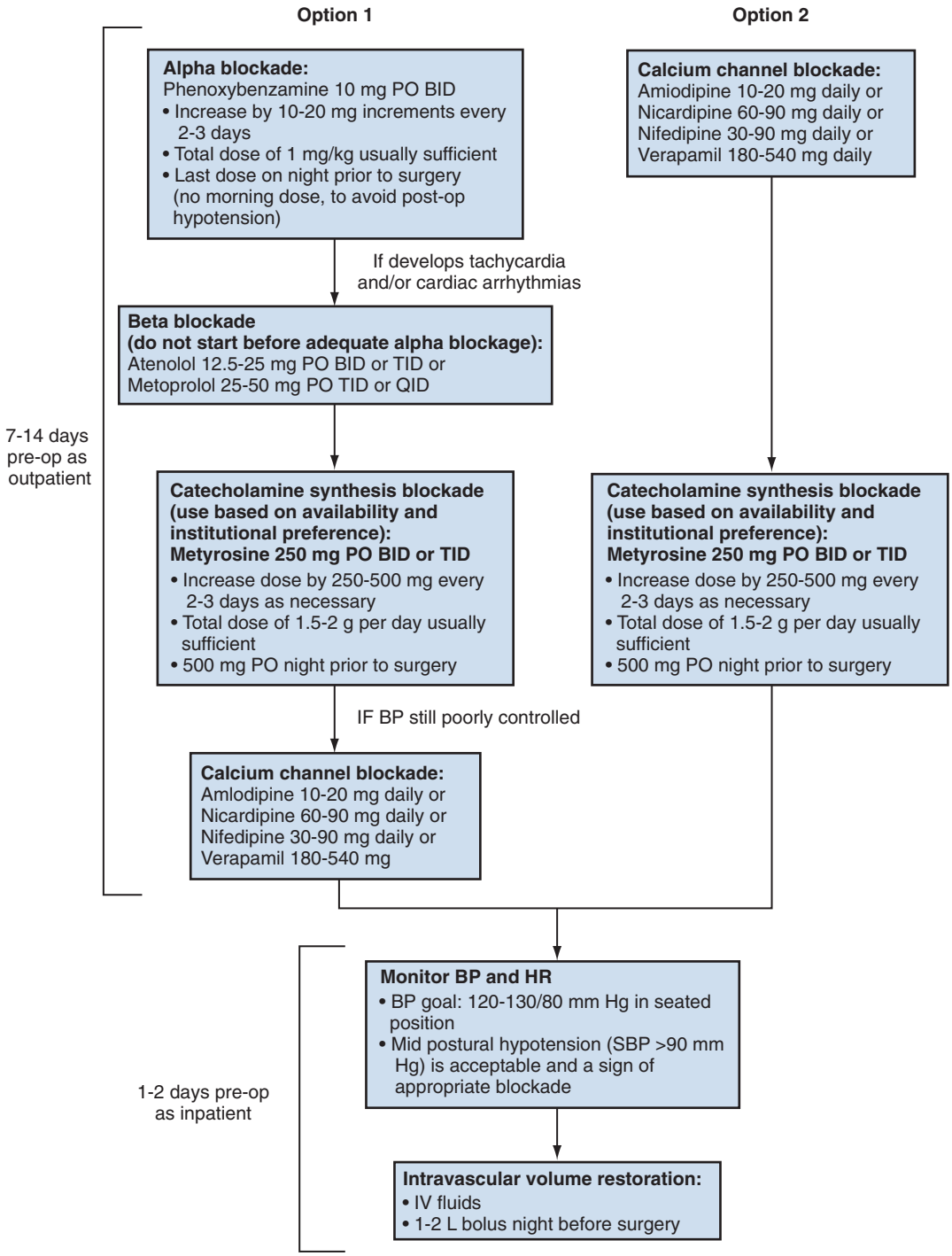


Figure 57–20. Preoperative medical management in patients with pheochromocytoma. BP, blood pressure; HR, heart rate; IV, intravenous. (Adapted from Pacak K. Preoperative management of the pheochromocytoma patient. J Clin Endocrinol Metab 2007;92:4069–79.)

Hence, given the necessity for close monitoring, some experts advise overnight admission to the intensive care unit following pheochromocytoma resection (Lenders et al, 2005).

Follow-up. Repeat metabolic testing should be performed approximately 2 weeks after adrenalectomy to document normalization of chromaffin cell function (Pacak et al, 2007). In patients in whom metanephrine levels remain elevated, MIBG imaging may be helpful. MIBG uptake by previously unseen metastases may now be unveiled following resection of the primary tumor (Plouin and Gimenez-Roqueplo, 2006a).

Long-term vigilant postoperative follow-up of patients with pheochromocytoma is essential (Lenders et al, 2005; Pacak et al, 2007). **Lifelong screening for recurrence is recommended by some experts, because 10-year recurrence rates are as high as 16% in some series of fully resected lesions** (Amar et al, 2005b; Plouin and Gimenez-Roqueplo, 2006a). Indeed, recurrent disease has been noted in patients more than 15 years following resection of the original tumor (Plouin et al, 1997; Goldstein et al, 1999). Annual biochemical follow-up is mandatory for all patients with resected pheochromocytoma (Eisenhofer et al,

2004a; Lenders et al, 2005). No consensus on follow-up protocols exists; however, biochemical testing at 6 months after surgery, followed by annual testing, has been suggested (Pacak et al, 2001b, 2007). Post-operative cross-sectional imaging is reasonable to document tumor resection and appropriate healing of the resection bed. Need for subsequent imaging should be guided by results of biochemical testing (Pacak et al, 2001b).

Treatment of Hereditary Pheochromocytoma. Patients with hereditary pheochromocytoma require a unique approach. Given that for patients with MEN-2 and VHL, the risk of malignancy is low (see Table 57–9) while risk of bilateral disease is significant, partial cortical-sparing adrenalectomy has been advocated. This strategy is employed to avoid lifelong hormonal replacement, with its associated morbidity (Løvås et al, 2002; Yip et al, 2004; Diner et al, 2005). Successful surgical outcomes require advanced surgical expertise and careful preoperative radiographic planning (Mitterberger et al, 2006). Nevertheless, the patient must be counseled that hormonal replacement may still be necessary despite a seemingly successful cortex-sparing procedure. Life-threatening addisonian crisis can also occur despite close postoperative monitoring (Yip et al, 2004; Asari et al, 2006). Close long-term biochemical and radiographic follow-up is essential, whereas recurrence rates are poorly defined but appear to be significant (Yip et al, 2004; Asari et al, 2006).

Treatment of Malignant Pheochromocytoma. Currently therapy for metastatic pheochromocytoma is largely palliative. Surgical metastatectomy of resectable disease is the standard of care; however, little evidence exists to demonstrate that it prolongs patient survival or is more effective for symptomatic relief than medical treatment with α/β blockade and α-methyl-paratyrosine (Eisenhofer et al, 2004a; Lenders et al, 2005; Pacak, 2007). Local palliative tumor control is also described using ablation techniques and embolization (Pacak et al, 2001a; Eisenhofer et al, 2004a).

Given selective uptake of MIBG by pheochromocytoma cells, systemic treatment of metastatic patients with radioactive ^{131}I-MIBG may be instituted. Before initiation of therapy, MIBG uptake by tumor targets should be demonstrated with traditional MIBG imaging (Scholz et al, 2007). Symptomatic response is seen in up to 2 of 3 patients. Over 40% of patients exhibit a reduction in catecholamine levels. Tumor volume reduction occurs in approximately 30% of patients, but complete responses are seen in less than 5% (Loh et al, 1997; Scholz et al, 2007). High-dose therapy has been reported. Rose and colleagues (2003) described a multi-institutional study where 12 patients were treated with ^{131}I-MIBG at 2 to 3.5 times its usual dose. Although toxicity was not trivial, 25% of patients ($n = 3$) exhibited a lasting complete response. Two of these patients had both bony and soft tissue metastatic lesions. Given significant toxicity, routine use of high-dose MIBG radiotherapy continues to be controversial (Lenders et al, 2005; Pacak et al, 2007; Scholz et al, 2007).

The best-studied chemotherapy regimen for malignant pheochromocytoma entails a combination of cyclophosphamide, vincristine, and dacarbazine (CVD). Although response rates can be significant (over 50% radiographic tumor response and nearly 75% biochemical response), they are generally short-lived (2 years) (Scholz et al, 2007; Huang et al, 2008). Chemotherapy is primarily used in patients who have failed MIBG therapy, or in those whose tumors do not demonstrate MIBG uptake on initial MIBG imaging studies. Combination therapy with CVD and MIBG has been explored, but, to date, its risks and benefits remain poorly defined (Scholz et al, 2007).

Prognosis. Following surgical resection, patients with pheochromocytoma generally do exceedingly well. Surgical mortality rates in the current era are less than 3% (Lenders et al, 2005). Hypertension usually resolves following resection, but not in all cases (Plouin et al, 1997). **Despite excellent prognosis, the disease can recur many years following resection in up to 16% of patients, necessitating vigilant lifelong follow-up** (Plouin et al, 1997; Goldstein et al, 1999; Eisenhofer et al, 2004a; Amar et al, 2005b). In one large series, patients with extra-adrenal disease (hazard ratio [HR] 11.2), hereditary pheochromocytomas (HR 3.4), right adrenal tumors (HR 3.1), bilateral tumors (HR 1.4), and larger tumors (HR 1.2 per cm of diameter) were more likely to recur. **Some 50% of the recurrences were malignant** (Amar et al, 2005b).

Some patients with metastatic disease progress rapidly, while others exhibit nonaggressive disease and can live in excess of 20 years (Huang et al, 2008). Bone metastases appear to carry the most benign prognosis (Pacak, 2007; Scholz et al, 2007). For all-comers, 5-year survival statistics vary but are believed to be approximately 50% (John et al, 1999; Lenders et al, 2005; Pacak et al, 2007; Scholz et al, 2007).

Summary. Pheochromocytoma is a rare catecholamine-producing tumor. Awareness of its potential presence and familiarity with its management are critical for every urologist. Misdiagnosis or management is often associated with dire consequences. Pheochromocytoma must be considered in every adrenal mass and referral to a tertiary care facility made if the physician is unfamiliar with the care of these complex patients.

Key Points: Pheochromocytoma

- Nearly 25% of cases of pheochromocytoma that initially appear sporadic are later deemed hereditary upon genetic testing.
- Testing for urinary or serum metanephrines (normetanephrine and metanephrine) represents the underpinning of modern biochemical testing for pheochromocytoma.
- Malignancy of pheochromocytoma can be defined only by presence of metastases. Pathologic appearance is unreliable. Long-term follow-up is paramount, since recurrences are reported even after 15 years following the initial resection of a localized lesion.
- Familiarity with perioperative management of patients with pheochromocytoma is paramount.

Disorders of Decreased Adrenal Function

Introduction and Epidemiology

Adrenal insufficiency, also known as Addison disease, is a condition whose management typically is beyond the scope of most urologic practices. Nonetheless, a working knowledge of the condition is essential for the urologic surgeon, because it may result from either resection or pharmacologic inhibition of functioning adrenal tissues. Failure to consider and diagnose is potentially lethal and therefore warrants review. **Indeed, if not anticipated and appropriate proactive therapies instituted, addisonian crises following simultaneous or staged bilateral adrenalectomy can result in death** (Asari et al, 2006).

Adrenal insufficiency may be due to primary adrenal failure or secondary to extra-adrenal mechanisms. Its estimated prevalence is 39 to 60 per million (Oelkers, 1996).

Pathophysiology

In the Western world, the most frequent cause of primary adrenal insufficiency is autoimmune adrenalitis. This condition can occur in isolation or as a constellation of pathologies known as autoimmune polyendocrine syndrome (APS), where adrenal insufficiency coexists with hypoparathyroidism, autoimmune thyroid disease, hypogonadism, diabetes, and other autoimmune conditions. Depending on the extent of endocrinologic involvement, APS is classified as either type 1 or the more common type 2 (Arlt and Allolio, 2003). In developing countries, as was true in the age of Thomas Addison, tuberculosis remains the major etiology of adrenal failure (Løvås and Husebye, 2005). Other infectious causes, such as cytomegalovirus in the setting of HIV infection and rare fungal adrenalities, can also destroy the adrenal cortex. Bilateral adrenal hemorrhage or infiltrative diseases, such as amyloidosis, sarcoidosis, along with hemochromatosis may also affect the function of the glands (Oelkers, 1996). Bilateral metastatic disease involving the adrenals, while classically described as a potential cause of adrenal insufficiency, is a very rare cause of clinically significant Addison disease (Lutz et al, 2000). In urologic practice, relevant clinical scenarios include simultaneous or staged surgical loss of bilateral adrenal tissue following treatment of adrenal or renal disease, and pharmacologic adrenalectomy with inhibitors of steroid hormone synthesis, such as ketoconazole, or new 17α-hydroxylase (CYP-17) inhibitors, such as aberiterone (Arlt and Allolio, 2003).

Secondary adrenal insufficiency is caused by abnormalities in the pituitary gland or, less frequently, the hypothalamus. Tumors, radiation, autoimmune conditions, pituitary apoplexy (also known as Sheehan syndrome, when it occurs peripartally), and trauma are less common causes of the condition. Rare congenital conditions marked by a metabolic error in the production of pituitary hormones, including ACTH, are rare causes of secondary Addison disease (Arlt and Allolio, 2003). Figure 57–21 summarizes the major causes of Addison disease. Importantly, given that aldosterone secretion by the adrenals does not depend on ACTH, the zona glomerulosa continues to function appropriately in patients with secondary adrenal insufficiency. **Mineralocorticoid deficiency is therefore only present in patients with primary Addison disease** (White, 1994).

Exogenous chronic administration of glucocorticoids accompanied by suppression of the hypothalamic-pituitary-adrenal axis, resulting in secondary adrenal insufficiency is particularly relevant to the surgeon (Krasner, 1999). Although overt adrenal crises due to this clinical scenario are exceedingly rare, the possibility exists in surgical patients on chronic steroids (Axelrod, 2003). Postoperatively the urologist must also be cognizant of hypothalamic-pituitary-adrenal axis failure in critically-ill patients. This condition, recently termed "critical illness–related corticosteroid insufficiency" is an important, albeit controversial, clinical entity (Marik et al, 2008; Marik, 2009).

Clinical Characteristics

Clinical signs and symptoms of Addison disease are generally nonspecific and constitutional in most outpatients, who may complain of profound fatigue and anorexia for many months prior to definitive diagnosis. Hyperpigmentation, a hallmark of primary adrenal insufficiency, results from high serum concentrations of ACTH in response to increased hypothalamic release of pro-opiomelanocortin (POMC)-derived peptides that stimulate the melanocortin (MC-1) receptor of the skin (Arlt and Allolio, 2003). Table 57–12 summarizes the clinical manifestations of adrenal insufficiency.

Acute adrenal insufficiency, or adrenal crisis, is a life-threatening condition often preceded by hypotension unresponsive to fluid resuscitation. Patients are easily and often misdiagnosed with an acute abdomen, whereas abdominal pain, nausea, vomiting, and fever frequently accompany hypovolemia in these individuals. Pediatric patients can exhibit hypoglycemic seizures (Arlt and Allolio, 2003; Bouillon, 2006).

Adrenal insufficiency (an addisonian state) following adrenalectomy in the setting of a normally functioning contralateral adrenal gland is unlikely, but possible.

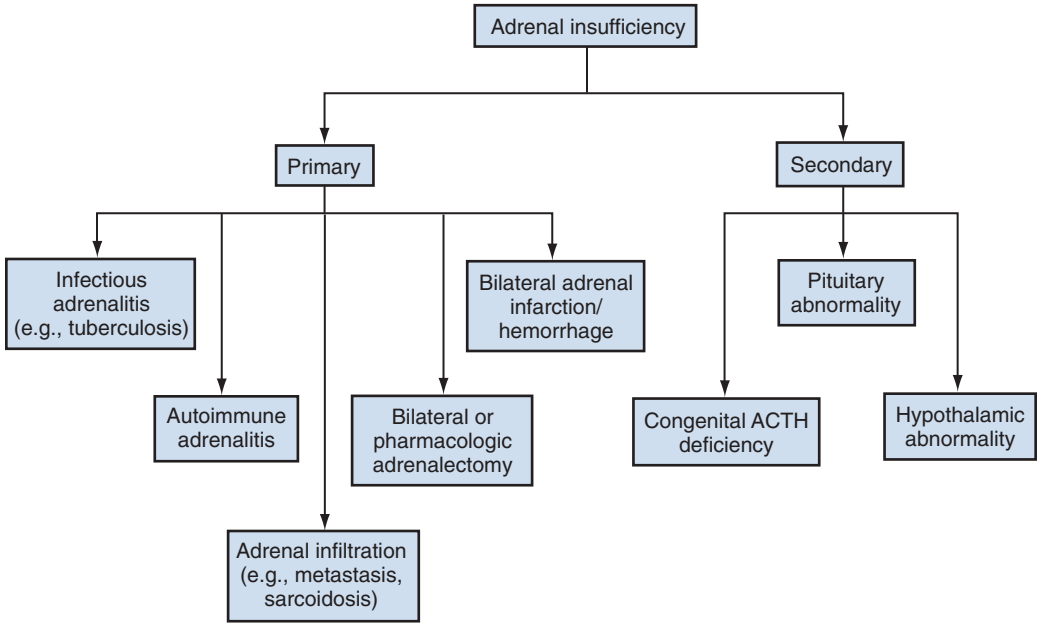


Figure 57–21. Causes of adrenal insufficiency. ACTH, adrenocorticotropic hormone.

Table 57–12.

Clinical Manifestations of Adrenal Insufficiency

SYMPTOMS	PATHOPHYSIOLOGY
Fatigue, lack of energy or stamina, reduced strength	Glucocorticoid deficiency, adrenal androgen deficiency
Anorexia, weight loss (in children failure to thrive)	Glucocorticoid deficiency
Gastric pain, nausea, vomiting (more frequent in primary adrenal insufficiency)	Glucocorticoid deficiency, mineralocorticoid deficiency
Myalgia, joint pain	Glucocorticoid deficiency
Dizziness	Mineralocorticoid deficiency, glucocorticoid deficiency
Salt craving (primary adrenal insufficiency only)	Mineralocorticoid deficiency
Dry and itchy skin (in women)	Adrenal androgen deficiency
Loss or impairment of libido (in women)	Adrenal androgen deficiency
Signs	
Skin hyperpigmentation (primary adrenal insufficiency only)	Excess of pro-opiomelanocorticoid-derived peptides
Alabaster-colored pale skin (secondary adrenal insufficiency only)	Deficiency of pro-opiomelanocortin-derived
Fever	Glucocorticoid deficiency
Low blood pressure (systolic RR < 100 mm Hg), postural hypotension (pronounced in primary adrenal insufficiency)	Mineralocorticoid deficiency, glucocorticoid deficiency
Raised serum creatinine (primary adrenal insufficiency only)	Mineralocorticoid deficiency
Hyponatremia	Mineralocorticoid deficiency, glucocorticoid deficiency (leading to SIADH)
Hyperkalemia (primary adrenal insufficiency only)	Mineralocorticoid deficiency
Anemia, lymphocytosis, eosinophilia	Glucocorticoid deficiency
Increased thyroid stimulating hormone (primary adrenal insufficiency only)	Glucocorticoid deficiency (or autoimmune thyroid failure)
Hypercalcemia (primary adrenal insufficiency only)	Glucocorticoid deficiency (mostly concurrent hyperthyroidism)
Hypoglycemia	Glucocorticoid deficiency
Loss of axillary or pubic hair (in women), absence of adrenarche or pubarche in children	Adrenal androgen deficiency

From Arlt W, Allolio B. Adrenal insufficiency. Lancet 2003;361(9372):1881–93.

This is especially true for patients who are undergoing adrenalectomy for a cortisol-secreting lesion, because functionality of the contralateral gland can be suppressed (Tsagarakis et al, 2006). **Furthermore, patients with a history of contralateral partial or radical nephrectomy clearly represent a high-risk group. The integrity of the adrenal gland on the side of previous surgery may be compromised, or that gland may be altogether absent. Close examination of preoperative imaging and review of old operative and pathology reports, as to the status of the adrenal gland in the previous surgical field, is paramount.**

Diagnostic Tests

The diagnosis of primary adrenal insufficiency is primarily made on clinical grounds, with a high index of suspicion given a patient's history, exam, and laboratory evaluation. It is ultimately secured by measurements of morning serum cortisol and ACTH. Patients with primary Addison disease exhibit abnormal aldosterone and renin levels. Confirmatory testing involves assessing the adrenal response to ACTH stimulation in the form of the corticotropin test. The majority of patients with autoimmune adrenalitis demonstrate detectable levels of anti–21-hydroxylase antibodies (Oelkers et al, 1992; Arlt and Allolio, 2003).

The appropriate workup for secondary adrenal insufficiency often requires sophisticated probing of the hypothalamic-pituitary-adrenal axis that goes beyond the scope of this text and requires endocrinologic expertise. In-depth reviews of the topic are available (Oelkers et al, 1992; Oelkers, 1996).

Treatment

The treatment of Addison disease involves adrenal hormonal repletion. Cortisol is replaced with hydrocortisone (15 to 25 mg per day) or with cortisone acetate (25 to 37.5 mg per day). To mimic physiologic circadian glucocorticoid cycling, the majority (half or two thirds) of the daily dosing is given in the morning, with the rest administered in one or two doses later in the day (Arlt and Allolio, 2003). Mineralocorticoid replacement is only required for patients with primary adrenal insufficiency, and is achieved with fludrocortisone 0.05 to 0.2 mg daily (Løvås and Husebye, 2005). Supplementation of adrenal androgens is advised by some experts (dehydroepiandrosterone 25 to 50 mg daily), but is often limited to those who experience constitutional complaints despite adequate glucocorticoid and mineralocorticoid supplementation (Arlt and Allolio, 2003). Careful monitoring of patients on hormone replacement for adrenal insufficiency is required and is often best left to experienced endocrine experts.

The necessity of perioperative stress-dose steroid administration continues to be controversial. Although continuing the patient's usual steroid dose is usually sufficient, given the negligible downside of perioperative steroid coverage and the potential catastrophic consequences of failure to prevent an adrenal crisis, surgeons continue to administer stress-dose steroids perioperatively. Tables 57–13 and 57–14 summarize contemporary recommendations (Salem et al, 1994; Krasner, 1999; Axelrod, 2003). Again, because aldosterone physiology is not altered in these patients, mineralocorticoid replacement is unnecessary (White, 1994).

Prognosis

The impact on life expectancy in cases of primary adrenal insufficiency has not been established; however, a significant impact on a patient's quality of life has been demonstrated (Løvås et al, 2002). Many patients complain of decreased energy, loss of libido, and psychologic maleffects (Arlt and Allolio, 2003). Secondary adrenal insufficiency due to hypopituitary disease is an established cause of premature death (Tomlinson et al, 2001).

Table 57–13.

Perioperative Glucocorticoid Dosing in Patients on Chronic Steroid Therapy

DEGREE OF SURGICAL STRESS	DEFINITION	GLUCOCORTICOID DOSE
Minor	Procedure under local anesthesia and less than 1 hour in duration (e.g., inguinal hernia repair)	Hydrocortisone 25 mg or equivalent
Moderate	Procedure such as vascular surgery of a lower extremity or a total joint replacement	Hydrocortisone 50 to 75 mg or equivalent This could be continuation of usual daily steroid dose (e.g., prednisone 10 mg per day) and hydrocortisone 50 mg intravenously during surgery
Major	Procedure such as esophagogastrectomy or operation on cardiopulmonary bypass	Usual glucocorticoid (e.g., prednisone 40 mg or the parenteral equivalent within 2 hours before surgery) and hydrocortisone 50 mg intravenously every 8 hours after the initial dose for the first 48 to 72 hours of the postoperative period

Data from Salem M, Tainsh RE Jr, Bromberg J, et al. Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. Ann Surg 1994;219(4):416–25; and Axelrod L. Perioperative management of patients treated with glucocorticoids. Endocrinol Metab Clin North Am 2003;32(2):367–83.

Table 57–14.

Relative Potency of Common Glucocorticoid Preparations

NAME	BIOLOGIC HALF-LIFE (hr)	RELATIVE ANTI-INFLAMMATORY POTENCY	APPROXIMATE ADULT PHYSIOLOGIC REPLACEMENT DOSE (mg/day)
Hydrocortisone (cortisol)	8-12	1	20
Cortisone acetate		0.8	25
Prednisone	18-36	4	5
Prednisolone		4	5
Methylprednisolone		5	4
Triamcinolone		5	4
Dexamethasone	36-54	25-50	0.5

Adapted from Krasner AS. Glucocorticoid-induced adrenal insufficiency. JAMA 1999;282(7):671–6.

Summary

In urologic practice, adrenal insufficiency can result from simultaneous or staged surgical excision or pharmacologic ablation with steroid–hormone synthesis blockade agents. Diagnosis requires a high index of suspicion. Any patient having undergone ipsilateral partial or radical nephrectomy and presenting for contralateral surgery represents an at-risk population. Obtaining old operative or pathology reports and examining cross-sectional imaging for the presence or absence of adrenal tissue is essential in this setting. Postoperative adrenal insufficiency must be considered in patients on chronic glucocorticoid therapy or in the critically ill. There should be a low threshold to consult advanced endocrinologic expertise given the complexity and the potentially grave consequences of the condition.

Key Points: Adrenal Insufficiency

- Mineralocorticoid deficiency is present only in patients with primary Addison disease (e.g., autoimmune adrenalitis, surgical absence of adrenal tissue). Abnormalities in the pituitary gland or, less frequently, the hypothalamus (e.g., in patients with suppressed ACTH secretion due to chronic steroid use) do not result in suppression of aldosterone production.
- Any patient who has undergone ipsilateral partial or radical nephrectomy presenting for contralateral renal or adrenal surgery is at risk for a postoperative adrenal crisis. Obtaining old operative or pathology reports and examining cross-sectional imaging for the presence or absence of adrenal tissue is essential in this setting.

Disorders of Abnormal Adrenal Function

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is a disorder that is characterized by low cortisol production due to a metabolic enzymatic abnormality in the cholesterol-steroid biosynthesis pathway (see Fig. 57–3). The disorder is autosomal recessive and associated with a deficiency in the enzyme 21-hydroxylase in over 95% of cases. In the absence of negative feedback, ACTH production by the pituitary is increased, resulting in hyperplasia of the adrenal cortex and overproduction of adrenal androgens (Merke and Bornstein, 2005). Diagnosis of the condition is most often established in childhood and is discussed in detail in Chapter 110. Patients with known CAH, as well as carriers of the *CAH* gene, appear to have a high propensity for developing benign adrenal cortical adenomas but are not at known increased risk for malignant adrenal lesions (Jaresch et al, 1992; Barzon et al, 2007). Patients with undiagnosed nonclassical 21-hydroxylase deficiency can present with adrenal neoplasms later in life (Ravichandran et al, 1996; Nigawara et al, 2008). Given the relatively low incidence, genetic screening of patients with adrenal incidentalomas has not demonstrated an increased incidence of undiagnosed CAH. Therefore screening of incidentaloma patients for CAH is not indicated (Kjellman et al, 1999; Barzon et al, 2003; Wagnerova et al, 2008).

Adrenal Lesions

Malignant

Adrenal Carcinoma

Introduction and Epidemiology. Adrenocortical carcinoma (ACC) is a rare malignancy with an incidence of 0.5 to 2 per million (Aubert et al, 2002; Roman, 2006; Fassnacht and Allolio, 2009). It has a bimodal age distribution that peaks in children in the first decade of life and adults in the fourth to fifth decades of life, although most patients with ACC are adults, with a slight female predominance of 1.5 to 2.1 (Roman, 2006). Several important differences exist between the pediatric and adult ACC populations, including symptoms at presentation, staging systems used, and prognosis. Compared with the adult population, children with ACC will more often present with lower-stage functional tumors, which is associated with improved survival (Liou and Kay, 2000).

The majority of ACCs are sporadic and unilateral; however, 2% to 6% of patients will present with bilateral disease that may be associated with a hereditary disorder (Ng and Libertino, 2003). Although the etiology of sporadic ACC remains unknown, several syndromes are associated with an increased incidence of ACC, including Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, Carney complex, multiple endocrine neoplasia type 1, and McCune-Albright syndrome. Although the underlying molecular defect of these syndromes has advanced our understanding of the tumorigenesis of ACC, significant improvements in treatment regimens and survival are yet to be realized. Currently, surgical resection remains the cornerstone of treatment and, when localized, offers the best chance of cure; however, multimodal therapy including systemic chemotherapy and radiation therapy are often required for locally advanced and metastatic disease.

Pathophysiology. **Two hereditary disorders, Li-Fraumeni and Beckwith-Wiedemann syndrome, have provided valuable insight into the tumorigenesis of sporadic ACC. Loss of TP53 function, as found in Li-Fraumeni syndrome, has been noted in 20% to 33% of sporadic ACC cases compared with 0% to 6% of adrenal cortical adenomas. Increased insulin-like growth factor (IGF) expression, as found in Beckwith-Wiedemann syndrome, has been noted in up to 90% of sporadic cases of ACC, compared with only 8.5% of adrenal cortical adenomas** (Herbet et al, 2009). **These findings suggests that loss of TP53 function and increased IGF expression represent late events in the tumorigenesis of sporadic ACC. Additional alterations of several oncogenes and peptides have been associated with the ACC, including squamous cell carcinoma–related oncogene (SCCRO), inhibin, activin, epidermal growth factor receptor, and vascular endothelial growth factor (VEGF)** (Boulle et al, 1998; Kolomecki et al, 2001; Beuschlein et al, 2004; Sarkaria et al, 2004).

Clinical Characteristics. Incidental detection of adrenal cortical carcinoma has increased with the routine use of cross-sectional imaging; however, the majority of patients still present with advanced disease and tumor-related symptoms. Figure 57–22 shows a CT image of a large right-sided ACC. **Tumor-related symptoms of ACC can be secondary to local or systemic disease burden and/or hypersecretion of adrenal hormones, which has been noted in 50% to 79% of adult and 90% of pediatric ACCs** (Roman, 2006). Adrenal cortical carcinomas that are associated with the hypersecretion of adrenal hormones are characterized as being functional. However, the presence of a functional tumor does not always lead to clinical symptoms, as in the case of tumors that secrete high concentrations of steroid precursors. This is especially relevant given the increasing sensitivity of assays used when evaluating serum hormone levels. Furthermore, it is common to have several hormones secreted by a single tumor, and it has been theorized that a tumor's functional status and hormones secreted may change throughout the tumor's development and growth (Phan, 2007).

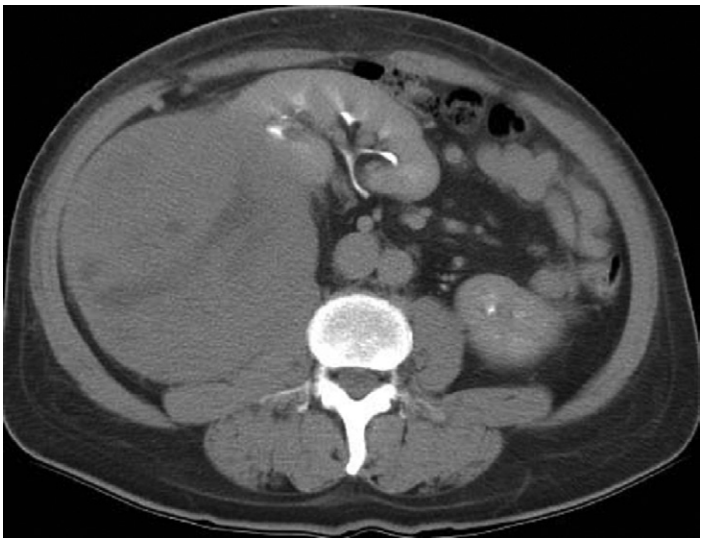


Figure 57–22. Axial cut in excretory phase of a computed tomography scan demonstrating a large right adrenal carcinoma. The right kidney is shifted anteriorly and medially. Similar-sized masses that arise from the kidney itself generally do not displace the renal unit. Importantly, even at this large size the adrenal carcinoma appears relatively homogeneous and well circumscribed—features deceptively camouflaging its deadly biologic potential. Surgical resection demonstrated a 25-cm, stage II (pT2N0M0), localized adrenocortical carcinoma (ACC). (Courtesy of Dr. David Y.T. Chen, Fox Chase Cancer Center, Philadelphia, PA.)

Table 57–15.

Functional Breakdown of Adrenal Cortical Carcinomas

Nonfunctional	21%-50%
Functional	50%-79%
Cushing syndrome	33%-53%
Cushing syndrome + virilization	20%-24%
Virilization alone	10%-20%
Feminization	6%-10%
Hyperaldosteronism	2.5%-5%

The most common hormone secreted by adrenal cortical carcinoma is cortisol, resulting in the clinical manifestations of Cushing syndrome (Table 57–15). Hypercortisolism in ACC is ACTH-independent, and the Cushing-associated virilization has been noted to be more pronounced compared with that resulting from functional adenomas. The observed increase in virilization may be due to increased rates of cosecretion of 17-ketosteroids and de-hydroepiandrosterone (DHEA) in patients with ACC (Roman, 2006). Androgen-secreting tumors in women can lead to virilization, characterized by male-pattern baldness, hirsutism, and oligoamenorrhea, which are typically related to elevated 17-ketosteroids. When virilization is present in the absence of elevated 17-ketosteroids, free testosterone hypersecretion from an adrenal or ovarian source should be considered. Feminization in

men, characterized by testicular atrophy and gynecomastia, may result from peripheral conversion of androstenedione to estrogen and is highly suggestive of malignancy when present. Although hypersecretion of aldosterone is rarely associated with ACC, when present, it is associated with profound hypertension and hypokalemia. Moreover, the symptoms of hypertension and hypokalemia are more likely secondary to other adrenal steroids produced by ACC, rather than the hypersecretion of aldosterone. Although considered functional, ACCs can present with high levels of steroid precursors, such as androstenedione and 17α-hydroxyprogesterone, which may not cause any overt clinical symptoms (Fassnacht and Allolio, 2009). Nonfunctional ACC may present with more generalized tumor related symptoms, such as abdominal fullness, back pain, nausea, vomiting, or other constitutional symptoms.

Diagnostic Tests. Suspicion for adrenal cortical carcinomas is based on clinical symptoms or radiographic findings and warrants the complete extent of disease evaluation, given the implications of this malignancy. Evaluating the functional status of adrenal tumors suspicious for ACC is essential, not only for making the diagnosis of ACC but also for consideration of postoperative cortisol replacement and the potential use of tumor secreted hormones as markers during postoperative surveillance. **When considering the functional status of a tumor suspicious for adrenal cortical carcinomas, glucocorticoid, mineralocorticoid, catecholamine, sexual steroid, and steroid precursor excesses should be evaluated** as outlined in Table 57–16.

The radiographic characteristics of an adrenal tumor provide valuable information regarding the lesion's malignant potential, and may be obtained using several modalities including CT, MRI, and FDG-PET imaging. **On cross-sectional imaging, adrenal cortical carcinomas tend to be larger than benign adrenal tumors with an average size of 10 to 12 cm on presentation. Indeed over 90% of ACCs are greater than 5 cm** (Ng and Libertino, 2003; Fassnacht and Allolio, 2009). In incidentally detected adrenal tumors, size is a relative indicator of malignancy, with 4% to 5% of tumors less than 4 cm, 10% of tumors larger than 4 cm, and 25% of tumors greater than 6 cm found to be adrenal carcinomas (Sturgeon and Kebebew, 2004; Walz et al, 2005). Given the relationship between adrenal tumor size and malignancy, it is currently recommended that adrenal tumors greater than 4 to 6 cm be surgically excised (Schteingart et al, 2005). Although a complete metastatic evaluation should be completed for all adrenal tumors suspicious for adrenal cortical carcinomas, the presence of lymphadenopathy and local tumor extension into the inferior vena cava and other adjacent organs are ominous indicators of locally advanced or distant metastatic disease. The most common sites of metastases in adrenal carcinoma are the lung and liver. Therefore metastatic evaluation at presentation should include cross-sectional imaging of the chest, abdomen, and pelvis. Evaluation for bone and central nervous system metastases need only be performed in patients with site-specific symptoms. **Common radiographic characteristics of adrenal carcinomas on CT imaging include the presence of irregular borders, irregular enhancement, calcifications, and necrotic areas with cystic degeneration. Mean attenuation on noncontrast CT scan in ACC is significantly higher (39 HU) compared with adenomas (8 HU).** Moreover, they will not demonstrate the contrast washout characteristics of benign adrenal adenomas (Szolar et al, 2005; Roman, 2006) (see Imaging section).

MRI provides valuable information when evaluating adrenal tumors. ACCs appear isointense relative to the liver or spleen on T1-weighted images and demonstrate intermediate to increased intensity on T2-weighted images. On gadolinium-enhanced images, adrenal carcinomas demonstrate marked contrast uptake (Ilias et al, 2007). In cases of suspicion for venous tumor thrombus, MRI can be an essential tool in detecting the presence of a tumor clot and delineating its extent.

Experience with FDG-PET in evaluating adrenal tumors suspicious for ACC is limited. In currently available series, all malignant adrenal tumors demonstrated FDG uptake (Tenenbaum et al, 2004). However, given the established value of CT and MRI in distinguishing benign from malignant disease and the limited experience with FDG-PET, the routine use of FDG-PET in evaluating adrenal tumors cannot be recommended at this time.

When diagnosing adrenal cortical carcinomas, percutaneous needle biopsy is generally not performed prior to surgical excision due to a clinically unacceptable risk of needle-tract seeding (Fassnacht et al, 2004; Schteingart et al, 2005). In cases of surgically resectable disease, the information obtained from biochemical and radiographic evaluation should be enough to justify extirpation. The primary indication for needle biopsy is in cases of unresectable, locally advanced, or metastatic disease, to confirm the diagnosis prior to systemic medical therapy.

Pathologic Evaluation. Although the presence of distant metastasis and local invasion are clear indications of malignancy, the differentiation between benign and malignant neoplasms in organ-confined tumors can be pathologically challenging (Fig. 57–23). The Weiss criteria, developed in 1984, have been established to distinguish benign from malignant adrenal tumors using nine pathologic features (Weiss, 1984). The classification system is based on tumor structure, cytology, and invasion (Table 57–17. The presence of three or more of the Weiss criteria are associated with malignancy, with a sensitivity of 100% and a specificity of 96% (Aubert et al, 2002). In cases of pediatric adrenal tumors, and in adult adrenal tumors that demonstrate oncocytic features, the Weiss criteria should be employed with caution, and alternative diagnostic criteria are recommended (Lau and Weiss, 2009).

Staging. In 2004, the Union Internationale Contre Cancer and World Health Organization created a staging system for ACC

Table 57–16.

Functional Evaluation of Adrenal Tumors Suspicious for Adrenal Cortical Carcinoma

TYPE OF ADRENAL HYPERSECRETION	FUNCTIONAL EVALUATION
Glucocorticoid excess	Low-dose dexamethasone suppression test or Late night salivary or 24-hour urine cortisol
Sexual steroids and steroid precursors	DHEA-S 17-OH-progesterone Androstenedione Testosterone 17β-estradiol (only in men and postmenopausal women)
Catecholamine excess	Serum or urinary metanephrines
Mineralocorticoid excess	Aldosterone to renin ratio (only in patients with hypertension or hypokalemia)

DHEA-S, dehydroepiandrosterone sulphate.

Adapted from Fassnacht M, Kenn W, Allolio B. Adrenal tumors: how to establish malignancy? J Endocrinol Invest 2004;27(4):387–99.

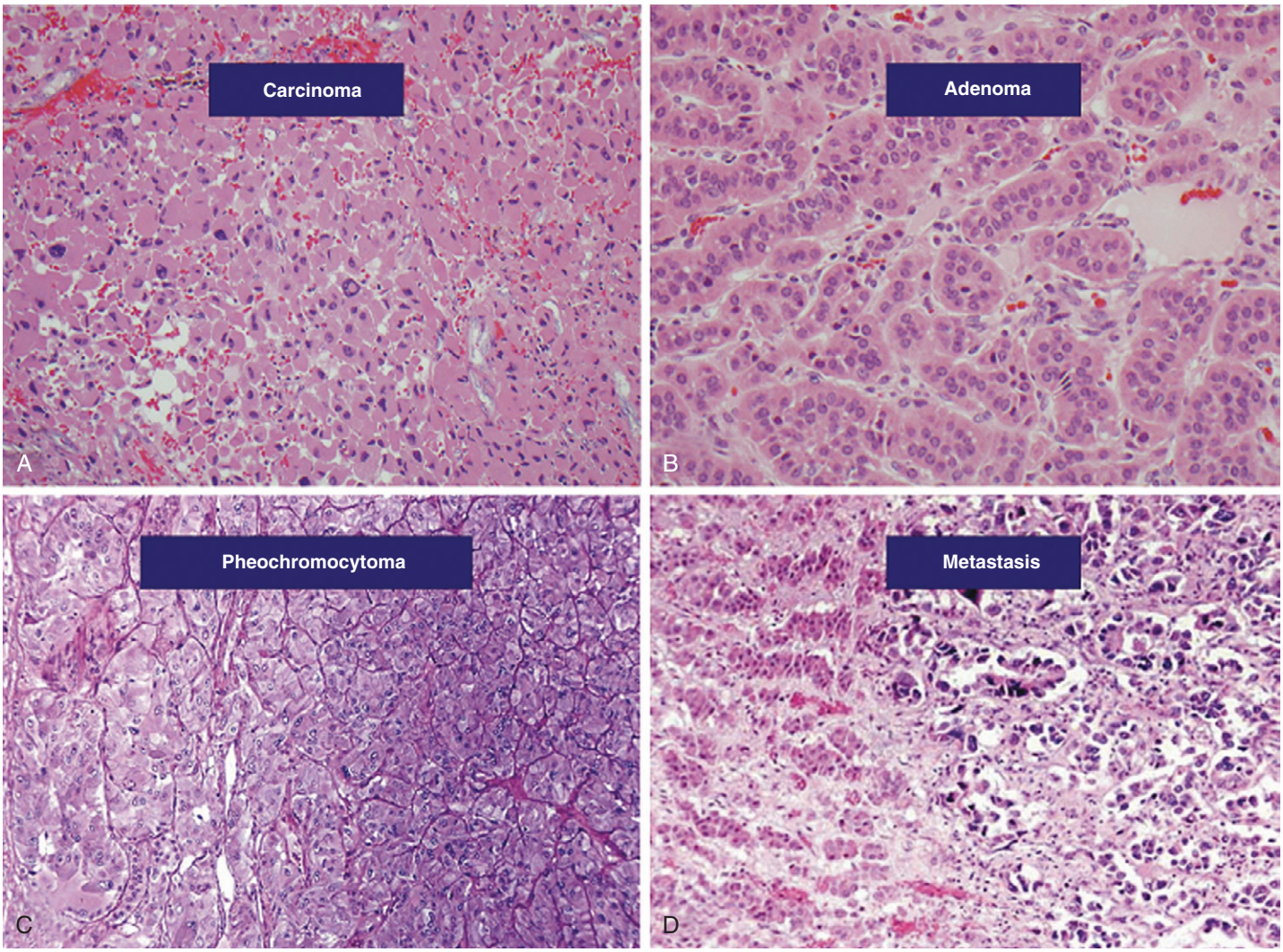


Figure 57–23. Histologic appearance of adrenal tumors (hematoxylin and eosin [H&E] staining). **A,** Adrenocortical carcinoma: high-grade nuclear atypia with necrosis in other sections. **B,** Adrenocortical adenoma: well-organized trabecular pattern with relatively uniform cells and minimal atypia. **C,** Pheochromocytoma: alveolar and trabecular pattern, eosinophilic, and amphophilic finely granular cytoplasm. **D,** Metastatic adenocarcinoma: hyperchromatic pleomorphic cells *(right)* compared with the eosinophilic cells with organized trabecular pattern *(left)* of the residual adrenal gland. (Images courtesy of Tahseen Al-Saleem, MD, Department of Pathology, Fox Chase Cancer Center, Philadelphia, PA and Dr. Thomas J. Sebo, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN.)

Table 57–17.

Weiss Pathologic Criteria for Differentiating Benign and Malignant Adrenal Tumors

High nuclear grade (Furman grade 3 to 4)
High mitotic rate (greater than 5 mitoses per HPF)
Presence of atypical mitoses
Character of cytoplasm (low percentage of clear cells)
Diffuse architecture of tumor cells
Presence of necrosis
Invasion of venous structures
Invasion of sinusoidal structures
Invasion of tumor capsule

From Weiss LM. Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. Am J Surg Pathol 1984;8(3):163–9.

Table 57–18.

Staging of Adrenocortical Carcinoma Including Stage at Diagnosis and 5-Year Survival Data

STAGE	2004 UICC/WHO	AT DIAGNOSIS	5-YEAR SURVIVAL
1	T1N0M0	3%-4%	33%-66%
2	T2N0M0	29%-46%	20%-58%
3	T1-2N1M0 T3N0M0	11%-19%	18%-24%
4	T1-4N0-1M1 T3N1M0 T4N0-1M0	39%-49%	<5%

T1 = <5 cm; T2 = >5 cm; T3 = infiltration of surrounding adipose tissue; T4 = invasion into adjacent organs.
UICC, Union Internationale Contre Le Cancer; WHO, World Health Organization.

(Table 57–18) (DeLellis et al, 2004). Stage I and II tumors are confined to the adrenal gland and are distinguished by a size cutoff of 5 cm. Stage III disease includes tumor extension into adjacent adipose tissue or having regional lymph node involvement. Stage IV disease includes tumors invading adjacent organs and the presence of distant metastatic disease. A modified staging system has recently been proposed by the European Network for the Study of Adrenal Tumors (ENSAT), in an attempt to improve the prognostic accuracy of the 2004 WHO staging system. The ENSAT staging system maintains the tumor-node-metastasis (TNM)

classifications used in the 2004 staging system (version 6); however, stage III disease includes patients with positive lymph nodes (N1), infiltration of surrounding tissues (T3-4) and venous tumor thrombus, while stage IV disease is reserved for any tumor associated with distant metastatic disease (Fassnacht et al, 2009). Further changes in the staging of ACC may be forthcoming with the release of the 2009 American Joint Committee on Cancer Staging Manual.

Management. Unfortunately, the majority of patients with adrenal cortical carcinomas present with advanced disease (see Table 57–18), and those who do have localized disease are at a high risk of local recurrence and metastatic progression. For this reason, treatment of ACC often includes multimodal therapy directed by a team of surgeons, medical oncologists, endocrinologists, and radiation oncologists. **Despite aggressive surgical resection, adrenal carcinoma is associated with a high rate (60% to 80%) of recurrent disease** (Pommier and Brennan, 1992; Stojadinovic et al, 2002; Meyer et al, 2004). Thus adjuvant therapy is often administered, frequently involving both local and systemic modalities. Unfortunately, the impact of adjuvant therapy on survival is not established, making the routine administration of adjuvant treatments controversial. Given the low incidence of ACC, no randomized prospective trials have been completed to evaluate the efficacy of current treatment regimens; thus existing treatment strategies are based on the collective experience of nonrandomized retrospective series.

SURGERY. Complete surgical excision is essential in the management of adrenal cortical carcinomas and offers the best chance of cure, control of symptoms secondary to hypersecretion of adrenal hormones, and other tumor-related symptoms. En bloc resection of surrounding organs involved with locally advanced disease should be performed whenever possible. Regional retroperitoneal lymph node dissection can provide additional disease control and staging information. Cases of venous tumor thrombus involving the IVC may require vascular bypass techniques, IVC replacement, and/or IVC interruption. Given the extent of resection frequently required, open abdominal/retroperitoneal exploration is commonly employed. Smaller radiographically organ- confined disease can be approached laparoscopically, but should be performed with caution due to the risk of tumor spillage (Kebebew et al, 2002; Gonzalez et al, 2005; Schlamp et al, 2007). **In cases of metastatic adrenal carcinoma, cytoreductive removal of the primary tumor and debulking metastatectomy should be considered if greater than 90% of the disease burden can be removed** (Schteingart et al, 2005). **Although debulking surgery may not improve survival, it may alleviate tumor-related side effects and facilitate additional therapies** (Fassnacht et al, 2004)**. Local or distant disease recurrences, following initial resection, should be considered for surgical excision and have been associated with improved survival in retrospective series** (Meyer et al, 2004). Locally recurrent disease and select metastatic lesions may be treated with ablative therapy using radiofrequency ablation or angioembolization, if surgical excision cannot be performed (Wood et al, 2003; Schteingart et al, 2005; Soga et al, 2009).

Follow-up should include CT examination of the chest, abdomen, and pelvis every 3 months for the first 2 years. The value of routine PET imaging in disease surveillance has not been established. In patients with evidence of functional tumors, measurement of the initially elevated hormones postoperatively may help to reveal early disease recurrence despite negative radiographic studies. After a disease-free interval of 2 years, surveillance should continue, but the frequency of imaging may decrease (Fassnacht et al, 2004; Schteingart et al, 2005).

RADIATION. Currently there is a limited role for radiation therapy in the treatment of primary adrenal cortical carcinomas; however, radiation therapy remains the treatment of choice in the management of bone and CNS metastasis (Schteingart et al, 2005). Adjuvant radiation has been noted to decrease local recurrence rates following complete tumor resection, with reported local recurrence rates of 14% and 79%, with and without adjuvant radiation therapy, respectively (Fassnacht et al, 2004; Polat et al, 2009). Unfortunately, a significant improvement in disease-free or overall survival was not observed. Patients believed to benefit the most from adjuvant radiation therapy are those without evidence of metastatic disease and positive or indeterminant surgical margins.

MEDICAL THERAPY. Mitotane is an oral synthetic derivative of the insecticide dichlorodiphenyltrichloroethane (DDT) and is the most commonly used chemotherapeutic agent in the treatment of adrenal cortical carcinoma. The agent has demonstrated clinical benefit in the adjuvant setting following surgical resection and in patients with metastatic disease (Phan, 2007). Three mechanisms of action of mitotane against ACC have been proposed, including the direct cytotoxicity of cells in the adrenal cortex, oxidative damage through the production of free radicals, and/or inhibition of enzymes involved with steroid synthesis (Fassnacht and Allolio, 2009). Due to the adrenolytic effect of mitotane, steroid replacement is typically necessary during therapy. In addition to adrenal insufficiency, common side effects include gastrointestinal upset, lethargy, depression, feminization in males, rash, elevation of hepatic enzymes, elevation of hormone-binding globulins, hypothyroidism, dyslipidemia, and thrombocytopenia. Given its significant adverse effect profile and its marginal therapeutic benefit, administration must be closely monitored and dosage titrated according to patient tolerability and serum levels (Fassnacht and Allolio, 2009).

The efficacy of adjuvant mitotane following surgical resection has been evaluated by several small retrospective series with varying results. A more contemporary retrospective series by Terzolo and colleagues (2007) evaluated the impact of adjuvant mitotane on recurrence-free survival and overall survival in 177 patients with ACC. A significant increase in recurrence-free survival and overall survival was noted in patients receiving mitotane compared with controls, after multivariate adjustments. Additionally, treatment-related toxicity appeared acceptably low. Currently, significant questions remain regarding the routine use of adjuvant mitotane following surgical resection, including which patients will derive the greatest benefit from adjuvant therapy and what is the optimal dosage and duration of adjuvant mitotane therapy (Terzolo et al, 2007, 2009).

In patients who are not candidates for complete tumor debulking, surgery should not be performed because it will delay systemic therapy. Currently, mitotane remains the primary systemic therapy, either as a single agent or in combination with other cytotoxic drugs for adrenal cortical carcinomas. **As a single agent, overall responses to mitotane range from 14% to 36%, with few studies demonstrating a significant survival benefit** (Roman, 2006; Phan, 2007). **A series by** Khan and colleagues (2000), **investigating the combination of mitotane and streptozotocin, noted a response rate of 36%. In a report by** Berruti (2005), **a response rate of 49% was noted with the combination of mitotane, etoposide, doxorubicin, and cisplatin.** These series have led to the currently ongoing randomized First International Randomized Trial

in Locally Advanced and Metastatic Adrenocortical Carcinoma Treatment (FIRM-ACT) trial, in which patients with advanced ACC are randomized to receive mitotane in combination with streptozotocin or etoposide, doxorubicin, and cisplatin. With the known limited success of first-line mitotane therapy for advanced disease, salvage therapy is often required. Multiple ongoing trials are investigating targeted therapies and other agents in patients who progress following first-line systemic therapy (Roman, 2006; Fassnacht and Allolio, 2009).

Control of symptoms secondary to the hypersecretion of hormones is often necessary in patients with metastatic disease. Although mitotane has adrenolytic activity, given its delayed onset of action and associated toxicity, other agents are often necessary to help control symptoms of hormone hypersecretion. Adrenostatic drugs, such as ketoconazole, metyrapone, aminoglutethimide, and etomidate have been used to decrease circulating levels of cortisol in symptomatic patients (Fassnacht et al, 2004).

Prognosis. Overall 5-year survival in adrenal cortical carcinomas is poor, ranging from 20% to 47% (Fassnacht and Allolio, 2009; Roman, 2006). The observed poor prognosis associated with ACC reflects the advanced stage frequently noted at presentation, the high rate of recurrent disease in patients with localized disease, and the limited efficacy of current systemic treatment regimens. Five-year survival based on tumor stage is presented in Table 57–18. In addition to advanced stage, several clinicopathologic features have been associated with decreased survival, including tumor size greater than 12 cm, high mitotic rate, tumor necrosis, atypical mitotic figures, and high Ki-67 staining (Fassnacht and Allolio, 2009). The impact of a tumor's functional status on outcome has been widely debated and remains controversial (Luton et al, 1990; Favia et al, 2001; Chen et al, 2004; Vaughan, 2004).

Pediatric ACC. The presentation, staging, and prognosis of pediatric adrenal cortical carcinomas differ from that in adults (Liou and Kay, 2000). More than 90% of ACCs in children are functional at the time of presentation, with virilization being the most common clinical manifestation occurring in 55% to 70% of patients. Unlike adults, the female to male ratio is equal in children under the age of 12, while the female to male ratio sharply increases to 6:1 in children aged 13 to 20. Genetic syndromes should be considered in pediatric cases of adrenal carcinoma, particularly Li-Fraumeni syndrome, because a high rate of *TP53* mutations has been noted in prior series. The staging system in pediatric patients defines stage I and II tumors as being completely excised with negative margins and with a tumor weight of greater than 200 g differentiating stage I and II disease. Stage III disease is defined by the presence of microscopic or macroscopic residual disease following surgical resection or inoperable tumors, while stage IV disease is defined by the presence of hematogenous metastasis. The overall 5-year survival rate is 54.2%, with several clinicopathologic features associated with diminished survival, including tumors weighing more than 400 g, tumor size greater than 10.5 cm, necrosis, frequent and atypical mitotic bodies, and presentation after 5 years of age (Michalkiewicz et al, 2004).

Summary. Adrenal cortical carcinoma is a rare malignancy requiring multispecialty care. Given the aggressive natural history of the disease, ACC must be considered in the differential diagnosis in all patients presenting with an adrenal tumor, particularly if greater than 6 cm. Evaluation of tumor functional status is critical for preoperative planning and supportive care, even in asymptomatic patients. Complete surgical resection of the primary tumor and any associated metastatic lesions should be performed whenever possible. Adjuvant therapy or enrollment into a clinical trial should be considered in most patients, given the high rate of local recurrence and metastatic progression despite complete surgical resection. Systemic therapy with mitotane therapy alone, or in combination with other cytotoxic agent, is recommended as first-line therapy in patients with metastatic ACC. Unfortunately, the prognosis for patients with ACC is poor, and improved therapeutic regimens are needed to improve outcomes.

Key Points: Adrenal Cortical Carcinoma

- Increasing adrenal tumor size is significantly associated with an increased risk of malignancy.
- The majority of adrenal cortical carcinomas will be functional at the time of presentation.
- Multimodal treatment, surgical resection, radiation therapy, and systemic chemotherapy is often necessary for patients with adrenal cortical carcinoma.

Neuroblastoma. Neuroblastoma, a malignancy derived from the cells of the neural crest, which give rise to the adrenal medulla and sympathetic ganglia, is the most common solid extracranial tumor of childhood. Chapter 137 is dedicated to the clinical and pathologic features of this entity (Park et al, 2008).

Metastases

Introduction and Epidemiology. **The adrenal glands are a common site of metastases.** Large autopsy series have demonstrated that over 25% of patients with melanoma and lung carcinoma have metastases to their adrenals (Bullock and Hirst, 1953). Renal cell carcinoma, breast cancer, medullary thyroid carcinoma, contralateral adrenocortical carcinoma, gastrointestinal malignancies, prostate adenocarcinoma, cervical cancer, basal cell, pancreatic tumors, cholangiocarcinoma, urothelial carcinoma, squamous cell carcinoma, seminoma, thymoma, chronic myelogenous leukemia, and other malignancies can all exhibit metastatic deposits within the adrenals (Bullock and Hirst, 1953; Lenert et al, 2001). Indeed diagnostic challenges arise when an adrenal incidentaloma is discovered in patients with a known malignancy. **It has been estimated that in patients with a history of a previous malignancy, over 50% of newly discovered adrenal lesions are metastatic** (Lenert et al, 2001; Frilling et al, 2004). Current imaging modalities supplemented by adrenal biopsy, when necessary, can frequently differentiate metastases from a primary adrenal tumor.

Renal cell carcinoma can involve the adrenal by direct invasion or systemic metastases (Lau, 2003; Antonelli, 2006). O'Malley and colleagues (2009) provide a recent review of these data as they relate to the need for adrenalectomy during surgery for RCC. Management of solitary metastases to the adrenal from other malignancies often falls within the purview of the practicing urologist. **Indeed, for some malignancies, specifically melanoma and non–small cell lung carcinoma, a survival benefit has been suggested in patients who undergo resection of an isolated adrenal metastasis** (Mercier et al, 2005; Collinson et al, 2008; Mittendorf et al, 2008; Tanvetyanon et al, 2008).

Pathophysiology and Clinical Characteristics. Remarkably few patients with metastatic disease to the adrenal gland exhibit evidence of adrenal insufficiency. Indeed, although an addisonian state secondary to metastatic carcinoma was described by Addison in his original series, the scenario is exceedingly rare (Addison, 1855; Lutz et al, 2000). Some reports suggests that bulky (>4 cm)

bilateral disease is necessary to produce biochemical evidence of adrenal insufficiency (Lutz et al, 2000). The statement that adrenal insufficiency exists in 20% of patients with metastatic RCC is, at times, quoted in the urologic literature. This supposition is based on an isolated report from the 1980s (involving a cohort of 15 patients) that, to our knowledge, has only been published in abstract form (Schorr et al, 1986). Indeed, patients with advanced malignancy may exhibit symptoms of an addisonian state (i.e., nausea, vomiting, fatigue, weight loss, etc.) in the absence of biochemical evidence of adrenal insufficiency (Lutz et al, 2000).

Diagnostic Tests. Radiographically metastatic lesions, similar to benign adenomas, appear well circumscribed, homogeneous, and most often lack areas of macroscopic necrosis (Boland et al, 2008). Nevertheless, metastatic disease almost always can be differentiated from the typical adrenal adenoma based on its lack of substantial lipid content. As is discussed in the Imaging section of this chapter, metastatic lesions exhibit greater than 10 HU in attenuation on noncontrast imaging and fail to demonstrate significant contrast loss on adrenal "washout" studies (Fig. 57–24) (Boland et al, 2008). Furthermore, adrenal biopsy can be helpful with newly found adrenal lesions in the setting of a known history of malignancy when imaging is equivocal. Unlike with metastases to the kidney, which are frequently associated with widespread metastatic disease, metastases to the adrenals can occur early and may be the sole focus of radiographically identifiable disease, making therapeutic resection feasible. (See Adrenal Biopsy section for more details.)

Nonetheless, a standard metabolic workup is warranted to rule out functionality of any new adrenal lesion (Lenert et al, 2001). Indeed, some small series report no difference in the incidence of metabolically active tumors, when patients with and without a history of extra-adrenal malignancy are compared (Tsvetov et al, 2007). Importantly, reports of pigmented pheochromocytomas being mislabeled as metastatic melanoma exist in the literature (Lenert et al, 2001).

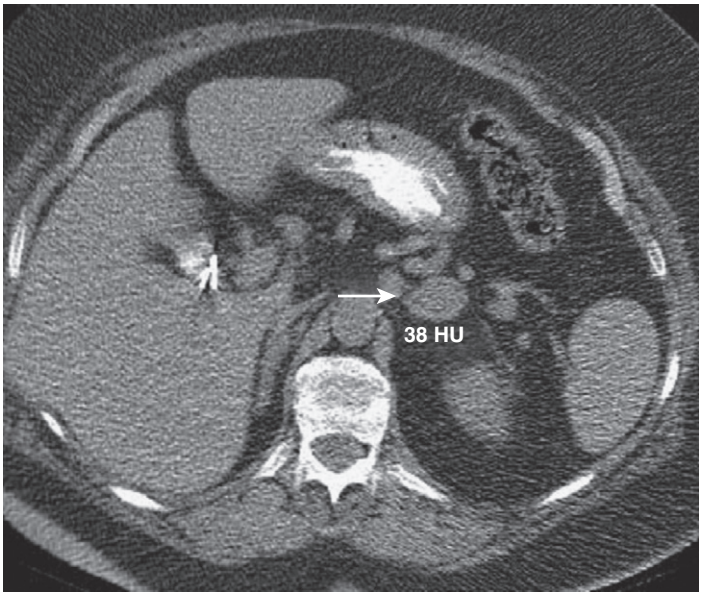


Figure 57–24. Unenhanced CT of a patient with a left adrenal metastasis from right-sided renal cell carcinoma (RCC) that was resected several years earlier. At presentation, unenhanced imaging revealed a lesion with an attenuation of greater than 10 Hounsfield units (HU), indicating that the adrenal mass was not a lipid-rich adenoma. Washout study (not shown) revealed poor contrast washout, significantly reducing the possibility that the lesion was a lipid-poor adenoma. Metabolic evaluation ruled out pheochromocytoma. Laparoscopic adrenalectomy confirmed metastatic RCC.

Treatment and Prognosis. Resection of metastases to the contralateral or ipsilateral adrenal gland from renal cell carcinoma is advocated in the context of a cytoreductive approach for a select group of patients. Nevertheless, benefits to adrenal metastatectomy are as yet unproven in a prospective fashion. Moreover, the role of resection may change with antiangiogenic targeted therapies (Lau, 2003; Antonelli, 2006; O'Malley et al, 2009). **Treatment of metastatic disease of the adrenals in patients with nonurologic malignancies requires a multidisciplinary approach. The urologist must work closely with the patient's primary medical oncologist regarding the surgical and biologic prudence of resection.** Lenert and colleagues (2001) have reported their experience with adrenalectomy for solitary adrenal metastases from over 20 separate primary malignancies. Currently, the best data regarding adrenal metastasectomy exist for patients with non–small cell lung carcinoma and melanoma (Branum et al, 1991; Mittendorf et al, 2008).

In patients with non–small cell lung cancer, adrenal metastases are most frequently encountered in the setting of systemic disease. An isolated adrenal metastasis is rare, and may be due to nonhematogenous lymphatic spread (Tanvetyanon et al, 2008). Surgical resection of solitary adrenal metastases has been associated with 5-year overall survival rates of over 25% (Mercier et al, 2005; Strong et al, 2007; Tanvetyanon et al, 2008). Although the prognosis following resection in patients with metachranous metastasis and longer disease-free intervals is thought to be better than in those patients found to have an isolated adrenal metastasis at the time of their initial diagnosis, a meta-analysis from 2008 demonstrated that the 5-year overall survival is equivalent in both groups (Tanvetyanon et al, 2008). In patients with metastatic melanoma, adrenalectomy has been reported to be associated with long-term survival and even rare regression of distant disease (Branum et al, 1991; Collinson et al, 2008). Nevertheless, data is limited to retrospective reports describing highly selected patient populations (Mittendorf et al, 2008).

Summary. Metastatic disease to the adrenal is common and must be suspected when patients with a history of malignancy are found to have adrenal incidentaloma. Radiographic and functional studies are essential and often secure the diagnosis. Percutaneous biopsy is safe but its success depends on the size and location of the lesion and the technical aspects of the procedure. Adrenalectomy for patients with solitary adrenal metastasis is a viable option for a select group of individuals.

Key Points: Adrenal Metastases

- Metastatic disease to the adrenals is common, yet it appears that bilateral and bulky disease (>4 cm) is necessary to produce biochemical evidence of adrenal insufficiency.
- More than 50% of newly discovered adrenal lesions in patients with a history of previous malignancy represent metastatic disease; nevertheless, metabolic work-up in these patients is recommended.

Malignant Pheochromocytoma. Malignant pheochromocytomas are discussed in the section Disorders of Increased Adrenal Function: Pheochromocytoma.

Benign

Adenoma

Introduction and Epidemiology. Adenomas are the most common neoplasms arising from the adrenal gland and are most often associated with the cortex. These lesions are found in approximately 6% of patients at autopsy (Kloos et al, 1995). Clinically adrenal adenomas are most often incidentally discovered on cross-sectional imaging obtained for other indications and are thus termed "incidentalomas." More than 85% of adrenal neoplasms incidentally discovered on imaging are ultimately clinically proven to be adenomas (Young, 2000, 2007b). **The incidence of adenomas rises with age, as inferred from the observation that incidentalomas are found in less than 0.5% of individuals in their 20s and in up to 7% of those 70 years of age or older** (Young, 2000). Similar trends are observed in historical autopsy series (Commons and Callaway, 1948; Russell et al, 1972). Despite benign behavior, a small percentage of adrenal adenomas can exhibit metabolic activity, and, as such, can represent "surgical" lesions. The essential evaluation of the small adrenal mass requires differentiating the nonfunctional benign adenoma from functional or malignant lesions.

Pathophysiology and Clinical Characteristics. Adenomas possess a yellowish color on gross pathological examination due to presence of abundant lipid. Histologically, they may be difficult to distinguish from adrenal adenocarcinomas. As discussed above (see Table 57–17), pathologists use a set of criteria proposed by Weiss along with modern immunohistochemical methods to differentiate the two clinical entities (Weiss, 1984; Aubert et al, 2002; Sasano et al, 2006).

Adrenal adenomas are by definition benign and the vast majority are metabolically silent. An analysis of the 13 largest series of incidental adrenal masses (n = 2005) reveals that nearly 90% (n = 1779) of these lesions are clinically benign adenomas. Of these, only 127 lesions (7.1% of adenomas) exhibited metabolic activity, 107 (6% of adenomas) hypersecreted glucocorticoids, and 20 (1.1% of adenomas) were functioning hyperaldosteronomas. The overwhelming majority (93%) of adenomas displayed no evidence of metabolic activity (Young, 2000, 2007b). Hypersecretion of sex steroids by benign adrenal adenomas is exceedingly rare but has been reported. Interestingly, these rare lesions may secrete testosterone and possess Reinke crystals, normally identified in testosterone-producing Leydig cells of the testes (Ryan et al, 1995). The implications of glucocorticoid and mineralocorticoid hypersecretion by adrenal adenomas are discussed in detail in the sections Cushing Syndrome and Primary Aldosteronism, respectively. Finally, it has been hypothesized that nonfunctional adrenal adenomas may be associated with physiologic derangements, such as insulin resistance and left ventricular dysfunction; however, such reports are isolated to small single-institution series and await confirmation (Midorikawa et al, 2001; Ermetici et al, 2008).

The growth kinetics of adrenal adenomas is reviewed below (see discussion on incidentalomas). In brief, an analysis of 18 reported series following over 850 patients with adrenal incidentalomas revealed that the vast majority of these benign masses remain stable in size; however, approximately 9% of lesions increased by more than 1 cm in diameter over a mean follow-up of 3 years (Barzon et al, 2003). The size and growth of adrenal lesions are discussed in detail in a later section of this chapter.

The current literature suggests that adenomas that are initially metabolically inert are unlikely to gain function. An analysis of 18 published series, reporting over 1100 incidental adrenal masses (not all of them adenomas) revealed that only 1.7% became metabolically active in follow-up, including 0.65% that developed subclinical Cushing syndrome, 0.3% with subsequent overt Cushing syndrome, and 0.05% who were identified as becoming functional secretors of catecholamines. No lesion produced new onset hyperaldosteronism during endocrinologic reevaluation (Barzon et al, 2003).

Diagnostic Tests. The evaluation of incidental adrenal lesions, the primary way that adenomas come to clinical attention, is discussed in detail elsewhere in this chapter. In this section, we review the salient points of the clinical workup, as it relates to adenomas. The goal in evaluating any adrenal lesion is twofold: (1) rule out the possibility of malignancy and (2) document metabolic inactivity of the lesion in question.

Noncontrast CT scan is arguably the most valuable imaging study for the diagnosis of an adrenal adenoma. Computed tomography affords accurate measurements of a lesion's density, uniformity, and size. The vast majority of adrenal adenomas are smooth-bordered, homogeneous tumors that are less than 4 cm in diameter (Grumbach et al, 2003). High intracytoplasmic lipid content is unique to adenomas, and this attribute affords accurate differentiation of adenomas from other adrenal lesions on cross-sectional imaging. **According to an NIH 2002 consensus panel, an adrenal mass with an attenuation of less than 10 Hounsfield units (HU) on unenhanced CT is "strongly suggest[ive of] a benign adrenal adenoma"** (Grumbach et al, 2003). Indeed, a large contemporary series of resected adrenal masses from Cleveland Clinic demonstrated 100% specificity when the threshold of less than 10 HU was applied to lesions in this cohort (Hamrahian et al, 2005). The 100% specificity for adenoma was retained if only masses equal to 4 cm were considered and the threshold was raised to 20 HU (Hamrahian et al, 2005). Nevertheless, not all adenomas have sufficient intracytoplasmic fat content to result in attenuation below 10 HU on noncontrast CT. Approximately 30% of adrenal adenomas register a density greater than 10 HU on unenhanced computed tomography (Korobkin et al, 1998; Pena et al, 2000; Szolar et al, 2005). However, even in these cases a diagnosis of adenoma is still possible employing the "washout" technique, whereby loss of attenuation of the lesion is noted on delayed contrast-enhanced CT imaging. Lesions that "washout" more than 40% to 60% of gained enhancement can be identified as adenomas with specificity that approaches 100% (Fig. 57–25) (Korobkin et al, 1998; Pena et al, 2000; Szolar et al, 2005; Heinz-Peer et al, 2007). MRI also can be used to successfully characterize adrenal adenomas. Chemical-shift ratios relating to in- and out-of-phase imaging substitute for CT attenuation values. Refer to the Imaging section for further details on imaging of adrenal adenomas (Outwater et al, 1996; Hussain and Korobkin, 2004; Heinz-Peer et al, 2007).

Classically, incidentalomas are evaluated for excess cortisol and catecholamine secretion. In patients with history of hypertension, hyperaldosteronemia also should be ruled out (Grumbach et al, 2003). Adenomas themselves only have the potential to secrete cortisol or aldosterone; therefore, strictly speaking if a diagnosis of adenoma is unequivocal on imaging, metabolic workup for pheochromocytoma risks false-positive results given the imperfect specificity of testing. Nevertheless, current recommendations suggest serum or urine metanephrine testing for all adrenal lesions (Grumbach et al, 2003; Young, 2007b). Indeed, pheochromocytomas that mimic adenomas on imaging have been reported validating the

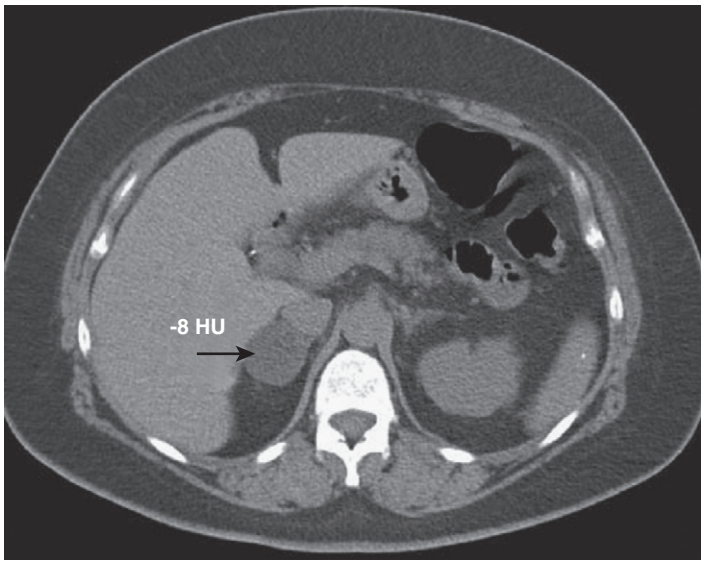


Figure 57–25. Axial cut of an unenhanced computed tomography scan in a patient with a 3.5-cm, right, lipid-rich adrenal adenoma, demonstrating an attenuation of less than 10 Hounsfield units (HU).

recommendation for metanephrine testing of all adrenal lesions (Blake et al, 2003). Despite the 2002 NIH consensus statement that all adrenal lesions greater than 1 cm should undergo a metabolic evaluation, current literature suggests that greater than 80% of adrenal masses are not appropriately radiographically or functionally evaluated in routine clinical practice (Eldeiry and Garber, 2008).

Treatment. **Adenomas that are metabolically active should undergo resection in acceptable surgical candidates.** In patients with nonfunctional adenomas, the size of lesion and its growth characteristics dictate management. Notwithstanding benign imaging features, experts suggest that resection of all adrenal masses greater than 6 cm is prudent given that adenomas of this size are rare and the risk of malignancy is substantial. The one exception to this may be a definitively diagnosed adrenal myelolipoma (Grumbach et al, 2003). Others argue that a cutoff of 4 cm should be used (Young, 2007b). Lesions that are not resected should undergo at least initial radiographic follow-up to ascertain growth kinetics. Reimaging at 6, 12, and, potentially, 24 months has been recommended in order to verify benign clinical biology and indolent growth (Grumbach et al, 2003; Young, 2007b). Suspicious and unusual tumors may necessitate imaging at earlier or more frequent intervals or removal (Young, 2007b). As already discussed, although reports in the literature vary, on average approximately 2% of incidentalomas that are initially metabolically silent result in superphysiologic hormone production during follow-up (Barzon et al, 2003). Despite this low rate of "metabolic transformation," the most recent consensus statement by a panel of NIH-convened experts suggests that annual metabolic hormonal screening for the first 3 to 4 years following diagnosis is prudent, especially for masses that are equal to 3 cm in diameter (Grumbach et al, 2003). Nevertheless, given lack of strong data supporting this recommendation, the need for metabolic reevaluation of adrenal adenomas in patients who show no clinical signs of hormonal hypersecretion remains controversial (Barry et al, 1998; Bulow et al, 2006; Young, 2007b).

Prognosis. Normalization of serum cortisol levels following resection of adenoma likely reduces but does not eradicate heightened cardiovascular risk in patients with Cushing syndrome (Swearingen et al, 1999; Pivonello et al, 2005). For patients with hyperaldosteronism, serum aldosterone and blood pressure often return to normal within 3 months of adrenalectomy (Young, 2007a), although those with baseline essential hypertension may remain medication-dependent. Generally, patients with nonfunctional adrenal adenomas appear to be unaffected by their diagnoses. **A large surveillance series from the Mayo Clinic (n = 231) demonstrated that no patients succumbed to a condition that could be ascribed to adrenal pathology after a mean follow-up of 7 years** (Barry et al, 1998).

Summary. Adrenal adenomas account for more than 80% of incidental adrenal neoplasms. Due to their abundance of intracellular lipid, these lesions possess characteristic imaging features. More than 90% of these lesions are metabolically silent and require no treatment; however, all should be subjected to an initial metabolic evaluation. Lesions greater than 4 to 6 cm and metabolically-active lesions should be resected in patients who are appropriate surgical candidates.

Key Points: Adenoma

- Incidence of adrenal adenoma rises with age.
- Approximately 7% of adrenal adenomas exhibit metabolic hyperactivity. Those that are metabolically inert at diagnosis only rarely (<2%) gain function on follow-up.
- Radiographic diagnosis of adrenal adenoma pivots on its high lipid content.

Oncocytoma

Introduction and Epidemiology. Oncocytomas are familiar to the urologist given their relatively common renal origin (Chang and Harawi, 1992). Oncocytic tumors can also arise from the salivary gland and the endocrine organs. Adrenal lesions are exceedingly rare (Bisceglia et al, 2004), with approximately 50 cases having been reported in the literature (Juliano et al, 2008).

Pathophysiology and Clinical Characteristics. Like oncocytic tumors in other organs, histologically oncocytic adrenal lesions are characterized by mitochondria-rich, large, eosinophilic cells with abundant granulations (Chang and Harawi, 1992). The pathogenesis of oncocytic neoplasias is poorly understood (Chang and Harawi, 1992). Females have been reported to be affected 2.5 times more frequently than males, and left-sided lesions outnumber those in the right adrenal 3.5 to 1. Tumors can grow up to 20 cm, and at least two cases have been reported in pregnancy (Bisceglia et al, 2004; Juliano et al, 2008). Most lesions that are documented in the literature are metabolically inactive; however, some oncocytic adrenal neoplasms (n = 6, or approximately 10% of all cases reported) hypersecrete sex steroids, cytokines, and/or cortisol (Akatsu et al, 2008; Juliano et al, 2008; Lee et al, 2008). Classically, these lesions have been considered benign (Vaughan and Blumenfeld, 2007); however, over 30% of reported lesions have been classified as malignant with an additional 23% having been designated as pathologically indeterminant (Juliano et al, 2008). These reports include a lesion that locally invaded the inferior venal cava (El-Naggar et al, 1991).

Diagnostic Tests and Treatment. Because the diagnosis of adrenal oncocytic tumor is nearly always made upon surgical resection, the evaluation and treatment of oncocytic lesions follows the same strategy as that of other adrenal masses. On imaging, adrenal oncocytic lesions are not reported to regularly possess the central stellate scar that may characterize such cases in the kidney (Lee

et al, 2006). The optimal treatment for malignant oncocytic lesions is unknown; however, in at least one report, metastatectomy and radiation treatment for local recurrence may play a role (Juliano et al, 2008).

Prognosis. Given the emerging appreciation for the heterogeneity of the biologic behavior of adrenal oncocytic lesions, the prognosis of patients with these lesions is uncertain but leans toward the more benign. Some reports suggest that even patients with widely metastatic disease can exhibit slow disease progression with long-term survival (Juliano et al, 2008).

Summary. **Adrenal oncocytic tumors are extremely rare neoplasms. Despite predominantly benign classical descriptions, a proportion of lesions can exhibit malignant potential.**

Key Point: Oncocytoma

- Unlike renal oncocytomas, a large proportion of adrenal lesions are malignant.

Myelolipoma

Introduction and Epidemiology. Myelolipomas are rare, benign, metabolically silent lesions that arise primarily from the adrenal gland and arise in patients in all age groups (Han et al, 1997). Based on historical autopsy series, the incidence of these lesions is estimated at less than 0.1% percent (Olsson et al, 1973; Bishop et al, 2006). Some reports suggest that 15% of all myelolipomas are extra-adrenal, with up to a half of these arising in the presacral area. Thoracic, retroperitoneal, pelvic, renal, hepatic, and gastric lesions have all been reported (Patel et al, 2006).

Pathophysiology. **Myelolipomas appear to result from clonal stem cell proliferation and are composed of an unusual mixture of mature adipose tissue and relatively normal trilineage hematopoietic elements** (Bishop et al, 2006). Overabundance of megakaryoctyes has been reported. Unlike normal bone marrow, cellularity within myelolipomas varies greatly and does not decrease with increasing patient age. These lesions do not appear to contribute hematopoietic cells to the circulation, which may be due to irregularities in stromal support and a lack of appropriate microvasculature. Specifically, normal capillary venous sinuses that are critical to functional bone marrow are nearly always absent in myelolipomas (Bishop et al, 2006).

Experimentally, myelolipoma generation has been induced in the adrenals of rats following injection with necrotic tumor tissues and ACTH (Seyle and Stone, 1950). This observation has resulted in the hypothesis that myelolipomas are a result of an adrenal stress response. Additional theories exist, and the etiology of these unusual tumors remains unknown (Han et al, 1997; Bishop et al, 2006).

Clinical Characteristics. Men and women are affected with relatively equal frequency. The tumor does not appear to have a predilection for either the right or left adrenal. Bilateral lesions have been reported (Bishoff et al, 1997; Han et al, 1997; Russell et al, 2000). Tumors vary greatly in size, and can grow in excess of 10 cm. In a single institutional series of 21 lesions, the average tumor size was 5.1 cm (Han et al, 1997). As with most retroperitoneal tumors, these lesions are usually asymptomatic, although some proportion of patients do present to medical attention with abdominal or flank pain (Han et al, 1997). Spontaneous rupture of myelolipomas has been reported; however, this event is rare. Indeed, the mean tumor size of myelolipomas that ruptured exceeds 10 cm (range 6.3 to 14.7 cm) (Russell et al, 2000).

Classically, myelolipomas are metabolically nonfunctional lesions. Nevertheless, over two dozen cases are present in the literature in which myelolipomas are associated with adrenal metabolic hyperactivity. The most common abnormality appears to be hypercortisolemia (Hisamatsu et al, 2004). In the majority of patients, the myelolipoma is not the source of excess hormone production but coexists with a hyperfunctional adrenal adenoma. Indeed, some have suggested that these cases substantiate the early animal model where rat adrenal hyperstimulation with pituitary extract resulted in myelolipoma formation (Seyle and Stone, 1950; Hisamatsu et al, 2004).

Diagnostic Tests. In the majority of cases, diagnosis of myelolipoma can be made accurately on cross-sectional imaging. **Computed tomography reveals a well-circumscribed adrenal lesion with varying amounts of mature adipose tissue (30 HU) interdigitated with higher-density myeloid components, which enhance upon contrast administration** (Fig. 57–26). Over a quarter of the lesions may exhibit evidence of

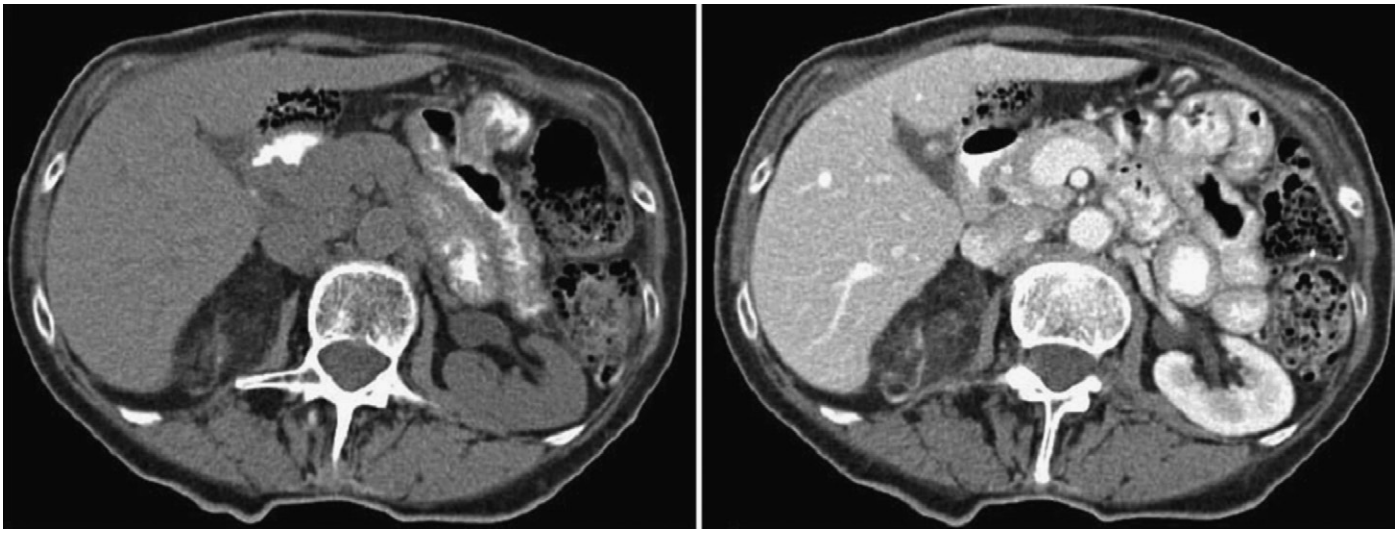


Figure 57–26. Pre- and postcontrast axial cuts of a CT scan demonstrating a right 6- × 3.5-cm adrenal myelolipoma in a 76-year-old, otherwise asymptomatic female. (Courtesy of Dr. Rosalia Viterbo, Fox Chase Cancer Center, Philadelphia, PA.)

calcifications, and a large proportion have areas of hemorrhage (Kenney et al, 1998). Macroscopic adipose tissue can also be easily identified within myelolipomas on magnetic resonance imaging (Cyran et al, 1996). **The presence of macroscopic fat in an adrenal mass is virtually diagnostic of a myelolipoma.** Nevertheless, exceedingly rare exceptions exist, and adrenal lipomas, teratomas, angiomyolipomas, metastases, and liposarcomas with macroscopic fat on imaging have been reported (Han et al, 1997; Lam and Lo, 2001). Careful interpretation of cross-sectional imaging is mandatory to distinguish an adrenal myelolipoma from an upper pole renal angiomyelolipoma. In contrast to the benign appearance of a myelolipoma, liposcarcomas tend to be aggressive lesions that lack regular borders and have a propensity for infiltrating surrounding tissues (Schaeffer and Kavoussi, 2005). When the diagnosis is in doubt, some experts believe that percutaneous biopsy may be helpful (Han et al, 1997).

As discussed earlier, although myelolipomas are themselves metabolically silent, they have been associated with metabolically active adenomas and pheochromocytomas that may not be readily differentiated on imaging. Therefore it is not unreasonable to perform a standard adrenal metabolic workup in the rare patient that is diagnosed with a myelolipoma (Daneshmand and Quek, 2006; Patel et al, 2006). Nevertheless, some experts believe a metabolic workup is only necessary when the index of suspicion for a concomitant metabolically active tumor is high (Han et al, 1997). The National Institutes of Health Consensus Panel on adrenal incidentaloma concluded that myelolipoma can be regarded as an exception to the mandatory metabolic work-up of a newly discovered adrenal mass (Grumbach et al, 2003).

Treatment. **Classically asymptomatic myelolipomas are treated conservatively.** No standard protocols for reimaging exist, but serial reevaluation with ultrasonography or CT every several years has been suggested (Han et al, 1997). **Surgery is usually reserved for symptomatic lesions** (Schaeffer and Kavoussi, 2005).

Prognosis. Tumor growth rates vary. Not only do some lesions remain stable, but some may actually decrease in size over time (Han et al, 1997). Based on available literature, resections are considered definitive. As discussed previously, although spontaneous rupture of myelolipomas has been reported, this event appears to be extremely rare and, on average, has been reported in lesions greater than 10 cm in size (range 6.3 to 14.7 cm) (Russell et al, 2000).

Summary. Myelolipoma is a rare lesion of the adrenal gland that contains hematopoietic elements and mature adipose tissues. Extra-adrenal lesions have also been reported. In general, lesions do not require resection and follow a benign clinical course.

Key Points: Myelolipoma

- Myelolipoma possess tissue components identical to healthy bone marrow.
- Clinical course is benign and surgery is indicated only for extremely large or symptomatic lesions.

Ganglioneuroma

Introduction and Epidemiology. Ganglioneuromas are extremely rare benign neuroectodermal neoplasms that are composed of ganglion and Schwann cells (Enzinger and Weiss, 1995). Although uncommon, the diagnosis must be considered during the evaluation of an adrenal mass (Maweja et al, 2007). In one large series (n = 88), 21% of cases arose from the adrenal gland itself. Other sites of origin included the mediastinum (39%), retroperitoneum (31%), and isolated cases in the pelvis and neck (Enzinger and Weiss, 1995). The tumor appears to have a predilection for the young, with only 20% of cases affecting individuals over age 40, and some 50% of cases found in patients between 10 and 29 years of age (Enzinger and Weiss, 1995).

Pathophysiology/Clinical Characteristics. Ganglioneuromas are benign, but isolated case reports of ganglioneuromas undergoing malignant transformation are reported (Enzinger and Weiss, 1995). Furthermore, cases of peripheral nerve sheath tumors (PNST) arising within ganglioneuromas, and composite tumors of ganglioneuroma and pheochromocytoma, also exist in the literature (Radin et al, 1997). Interestingly, reports of ganglioneuroma cells in lymph nodes surrounding an apparently benign tumor exist, and some authors presume that such cases represent neuroblastomas that have matured (Enzinger and Weiss, 1995).

Tumors can grow extremely large and have a propensity to encase vessels without impinging on the vessel lumen (Radin et al, 1997). Ganglioneuromas have been reported to secrete vasoactive intestinal polypeptide (VIP), and some patients complain of diarrhea (Enzinger and Weiss, 1995). Nevertheless, the majority of individuals with ganglioneuromas are largely asymptomatic (Radin et al, 1997).

Diagnostic Tests. On both enhanced and unenhanced CT, ganglioneuromas exhibit attenuation less than that of muscle (Radin et al, 1997). Calcifications within the tumor are not uncommon and have been reported present in as many as a third of ganglioneuromas (Enzinger and Weiss, 1995; Radin et al, 1997). Some authors suggest that a metabolically silent adrenal mass with unenhanced attenuation of less than 40 HU and presence of stippled calcifications should raise suspicion for a ganglioneuroma (Maweja et al, 2007).

Treatment/Prognosis. Because the diagnosis of ganglioneuroma is nearly always made upon resection, natural history of unresected gangioneuromas has not been clearly defined. Nevertheless, the urologist must be aware that the tumors can grow quite large and can surround critical structures such as retroperitoneal vessels (Radin et al, 1997).

Summary. Ganglioneuromas are rare tumors that can arise from the adrenal gland. Diagnosis is largely pathologic and the clinical course is nearly always benign.

Key Point: Ganglioneuroma

- Ganglioneuromas are rare, benign tumors that tend to occur in the young and can grow to encase critical structures.

Adrenal Cysts

Introduction/Epidemiology. Adrenal cysts have been noted in 0.064% to 0.18% of patients in autopsy series and account for 1% to 5% of incidentally detected adrenal lesions (Elsayes et al, 2004; Guo et al, 2007; Song et al, 2008). Cystic adrenal lesions can be diagnosed throughout life and as early as the prenatal period. Cyst size can range widely from several millimeters to greater than 20 cm, with either unilocular or multilocular components. Although the majority of adrenal cysts are unilateral, bilateral cysts have been noted in 8% to 10% of cases (Rozenblit et al, 1996). An increased incidence of adrenal cysts has been noted in women, with a peak incidence between the third and sixth decades of life (Sanal et al, 2006). Several medical conditions have been

associated with adrenal cysts, including polycystic renal disease, Klippel-Trenaunay-Weber syndrome, and Beckwith-Wiedemann syndrome (Erickson et al, 2004).

Pathophysiology. **Four histologic types of adrenal cysts have been described, including pseudocysts, endothelial, epithelial, and parasitic cysts.** Among these, the most common are pseudocysts and endothelial adrenal cysts. Adrenal pseudocysts do not possess a cellular lining and are believed to be the result of previous intra-adrenal hemorrhage or infarction. Endothelial cysts include lymphangiomatous and angiomatous subtypes. Epithelial cysts can be further characterized as glandular and embryonal cysts. Paracystic adrenal cysts may occur in association with disseminated *Echinococcus* infections; however, it is extremely rare for a parasitic adrenal cyst to be the only site of infection (Otal et al, 1999; Guo et al, 2007).

It can be difficult to distinguish a benign adrenal cyst from cystic adrenal neoplasms. This is especially true of adrenal neoplasms with associated hemorrhage or cystic degeneration, which may radiographically resemble an adrenal pseudocyst. In a series of 41 adrenal lesions macroscopically characterized as cysts, 7 were associated with adrenal neoplasms, including 2 adrenal cortical carcinomas, 2 adenomas, and 3 pheochromocytomas (Erickson et al, 2004). Furthermore, 6 of the 7 adrenal neoplasms in this series were associated with adrenal pseudocysts. **A review of multiple series accounting for 515 adrenal cysts noted that 7% of the lesions were associated with malignancy, all of which were pseudocysts** (Neri and Nance, 1999). Additionally, cases of cystic adrenal carcinoma and pheochromocytomas have been reported (Rozenblit et al, 1996). Compared with benign cysts, cystic adrenal neoplasms tend to be larger (>7 cm) and have thicker walls. When considering the reported incidence of malignancy associated with adrenal cysts it should be noted that histology in most series is based upon surgical specimens, so the incidence of malignancy may be overestimated because small radiographically benign lesions likely remain unresected.

Clinical Characteristics. Although most adrenal cysts are diagnosed incidentally, some become large in size and are symptomatic on presentation. The origin of large adrenal cysts is often difficult to distinguish from other organs, including the kidney, pancreas, spleen, and liver (Otal et al, 1999).

Diagnostic Tests. Although the majority of adrenal cysts are benign, and nonfunctional, routine endocrinologic evaluation should be performed to exclude active lesions. Due to the relative rarity of adrenal cysts, well-defined diagnostic criteria have not been established. The suggested radiographic criteria for diagnosing an adrenal cyst include a well-defined, sharply marginated mass of fluid attenuation without any evidence of enhancement (Fig. 57–27). Cysts with higher fluid attenuation (>30 HU) may be attributed to hemorrhage, intracystic debris, or calcification (Rozenblit et al, 1996; Sanal et al, 2006). The presence of peripheral calcifications has been noted in 15% to 70% of adrenal cysts (Song et al, 2008). Calcifications are typically rimlike, but occasionally will be nodular in appearance (Rozenblit et al, 1996). When evaluated with MRI, simple cysts will appear hypointense on T1-weighted images and hyperintense on T2-weighted images. Unfortunately, radiographic criteria alone cannot rule out malignancy in adrenal cystic lesions, thus cyst aspiration or surgical excision is often performed to rule out malignancy. Aspiration of cystic adrenal lesions should only be performed after chemical evidence of pheochromocytoma has been excluded. Adrenal cyst aspiration may be both diagnostic and potentially therapeutic in select patients (Pradeep et al, 2006). If aspiration is performed, the collected fluid should be sent for Gram stain, cytology, triglycerides, cortisol, and amylase (for left-sided cysts). Additionally, a contrast injection of the cyst cavity (cystogram) can be performed at the time of aspiration to evaluate the cyst wall texture.

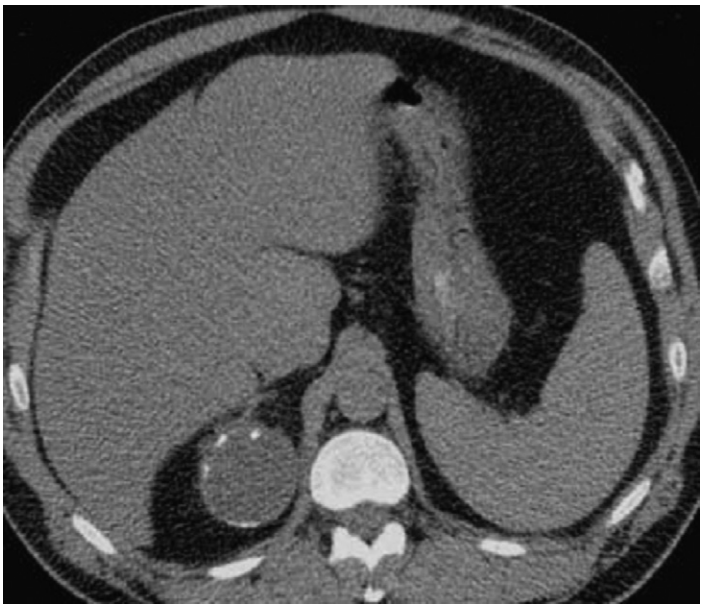


Figure 57–27. Unenhanced CT of a right adrenal cyst. Stippled calcifications within the cyst wall are not unusual in these lesions, as can be seen in this particular lesion.

Treatment. Factors influencing the treatment of adrenal cysts include functional status, chances of incidental malignancy, and cyst-related symptoms. With the known, albeit low, risk of associated malignancy with cystic adrenal lesions, active surveillance must be done with caution. Small, asymptomatic thin-walled lesions containing homogeneous near-water attenuation may be safely observed, and future surveillance of cystic lesions is warranted (Rozenblit et al, 1996). Adrenal cysts that are heterogeneous, large, thick walled, or symptomatic warrant further evaluation and surgical excision. Because of the known risk of associated malignancy, simple decortication is not advocated and should be undertaken with caution. Due to the inadequacies of radiographic evaluation, surgical resection remains the standard of care in patients with a normal-appearing contralateral adrenal gland.

Prognosis. The prognosis and subsequent follow-up following resection of an adrenal cyst is dependent upon histology. Benign adrenal cysts warrant follow-up to monitor potential reaccumulation, and warrant re-treatment if symptoms return. Adrenal cysts associated with malignancy require follow-up in accordance to the malignant histology detected.

Summary. Adrenal cysts are rare, and their diagnosis can be challenging. Symptomatic adrenal cysts should be surgically removed, while small nonfunctional asymptomatic lesions with benign radiographic appearance may be treated conservatively with regular follow-up.

Key Point: Adrenal Cysts

- Due to the known chance of associated malignancy, observation of adrenal cysts must be done with caution.

Benign Pheochromocytoma. Benign pheochromocytomas are discussed in the section Disorders of Increased Adrenal Function: Pheochromocytoma.

EVALUATION OF ADRENAL LESIONS IN UROLOGIC PRACTICE

In urologic practice, the evaluation of adrenal pathology is typically in the setting of patients referred with a diagnosis of a new adrenal mass or in existing patients in whom a new adrenal mass is discovered incidentally. Occasionally, patients are identified by astute clinicians based on clinical symptoms in the absence of prior radiographic identification of an adrenal lesion. This section of the chapter reviews clinically relevant evaluation and management of adrenal masses. It is important to note that the pregnant patient diagnosed with an adrenal mass requires a carefully planned, multidisciplinary, tailored approach. This subject matter is beyond the scope of this chapter; however, reviews on this topic are available (Harrington et al, 1999; Lindsay and Nieman, 2005b, 2006; Klibanski et al, 2006).

Overview of the Adrenal Incidentaloma

Adrenal incidentalomas are unsuspected adrenal masses greater than 1 cm in diameter identified on cross-sectional imaging performed for seemingly unrelated causes. Strictly speaking, patients who are undergoing a staging evaluation for another malignancy or who are later found to have symptoms relating to the adrenal lesion are excluded from the term "adrenal incidentaloma," given the possible relationship of the primary indication for the study and the adrenal lesion (Young, 2000, 2007b; Mazzaglia and Monchik, 2009). **The frequency of adrenal incidentalomas is relatively high, with contemporary imaging series reporting an incidence of approximately 5%,** (Song et al, 2008) **similar to that found in historical autopsy data** (Commons and Callaway, 1948; Russell et al, 1972). **The incidence of the incidental adrenal mass increases with age, with a risk of less than 0.5% in individuals in their 20s and up to 7% in those 70 years of age or older** (Young, 2000).

It is important to emphasize that "incidental" does not mean "insignificant." Table 57–19 summarizes collective data available regarding pertinent clinical characteristics of over 2000 newly discovered adrenal lesions and demonstrates that **nearly 20% of adrenal incidentalomas are found to be potential surgical lesions.** The two characteristics of primary clinical relevance are imaging and metabolic activity or functional status. Biopsy is rarely indicated but can be a useful tool in specific clinical circumstances. This section of the chapter describes in details the clinical indications and processes of imaging, biopsy, and metabolic testing.

Table 57–19.

Characteristics of Incidental Adrenal Masses as Described in a Systematic Review of Published Series of Adrenal Incidentalomas That Include ≥20 Patients (Total *n* = 2005)

ADRENAL LESION	PERCENT OF TOTAL (*n* = 2005)
Metabolically active	11.2%
Cortisol-producing adenoma	5.3%
Aldosterone-producing adenoma	1.0%
Pheochromocytoma	5.1%
Malignant	7.2%
Adrenocortical carcinoma	4.7%
Metastasis	2.5%
TOTAL POTENTIALLY SURGICAL LESIONS	18.4%

Data from Young WF Jr. Management approaches to adrenal incidentalomas. A view from Rochester, Minnesota. Endocrinol Metab Clin North Am 2000;29(1):159–85, x; and Young WF Jr. The incidentally discovered adrenal mass. N Engl J Med 2007b;356(6):601–10.

Imaging of Adrenal Masses

Imaging Modalities

Appropriate management and follow-up of the adrenal incidentaloma largely depends on ordering the proper test, carrying out accurate image-acquisition protocols, and interpreting the information obtained. Urologists must be well versed in adrenal imaging modalities and limitations and be able to speak knowledgeably to their radiology colleagues. Numerous imaging modalities can be used to assess both morphologic and functional features of adrenal masses. This section will summarize the salient features of each imaging modality as they pertain to characterization of adrenal incidentalomas. Please also refer to the Adrenal Lesions section of this chapter for details regarding imaging characteristics of each specific type of adrenal lesion.

Ultrasonography. Ultrasonography is a suboptimal imaging modality for detecting and fully characterizing adrenal lesions. Nevertheless, many incidentalomas will be discovered on ultrasound imaging performed for unrelated reasons. Indeed, in parts of the world where ultrasonography is employed as the primary imaging modality, the majority of adrenal incidentalomas are discovered using this modality (Bhargav et al, 2008). Moreover, in series where ultrasonography is responsible for identifying individuals with adenomas, right-sided lesions appear to be more common, whereas ultrasonography is less sensitive in identifying left-sided adrenal lesions than those in the right gland, based on anatomic differences. On the right, the IVC and liver provide a better window to the adrenal gland by ultrasonography, whereas on the left, the adrenal can be overlooked or mistaken as part of the splenic, pancreatic, para-aortic lymphatic, or gastric anatomy (Barzon et al, 2003).

Computed Tomography and Magnetic Resonance Imaging. Imaging with computed tomography (CT) and magnetic resonance (MR) permit cross-sectional and reconstructed anatomical image characterization of the adrenals and serve as the cornerstone for adrenal evaluation. Size, laterality, homogeneity, density, vascularity (enhancement and washout), and anatomic relationships can be accurately assessed using these modalities. Indeed, the size of an adrenal lesion, a characteristic reliably assessed by cross-sectional imaging, is a primary factor driving management decisions (see discussion in Size and Growth section). Often the differential diagnosis of an adrenal lesion can be immediately narrowed based on their imaging characteristics. For instance, the presence of macroscopic fat identifies an adrenal myelolipoma, while large heterogeneous masses that invade surrounding structures are most indicative of adrenal adenocarcinomas (Cyran et al, 1996). Adrenal cysts and acute or subacute hemorrhage also exhibit characteristic imaging findings (Burks et al, 1992). **Nevertheless, most adrenal incidentalomas are small homogeneous masses with regular**

contours that cannot be immediately given a pathologic label. Further characterization of these common lesions relies on the ability of modern cross-sectional imaging to identify the presence of intracytoplasmic lipid that differentiates a benign adrenal adenoma from other adrenal pathology (Korobkin et al, 1996b). Although adenomas can be differentiated from nonadenomas based on this single imaging characteristic, the need for a metabolic workup is not eliminated based upon identification of lipid within an adrenal mass. Radiographic differentiation between metabolically functional and nonfunctioning adenomas has been investigated and, to date, no reliable radiographic test or characteristic is sensitive enough to obviate endocrinologic evaluation based solely on imaging (Korobkin et al, 1996b; Fujiyoshi et al, 2003; Hussain and Korobkin, 2004).

Unenhanced CT. **An unenhanced CT scan is the first, and perhaps single best, and most easily interpreted test for intracellular lipid and therefore can diagnose an adrenal adenoma in more than 70% of cases. Low attenuation (<10 HU) on unenhanced CT corresponds to high intracytoplasmic lipid content and is diagnostic for an adrenal adenoma** (Lee et al, 1991; Korobkin et al, 1996b). Using a threshold of 0 or less HU, there is 100% specificity for an adrenal adenoma, meaning that if the lesion meets this criterion, it is always an adenoma. Unfortunately, the sensitivity of noncontrast CT density measurements is imperfect, meaning that not all adenomas will meet this criterion. Indeed only 41% of adenomas exhibit an attenuation of 0 HU (Boland et al, 1998), and therefore a threshold of 10 HU is currently used. This cutoff affords a sensitivity of 71% and a specificity of 98% for the diagnosis of adrenal adenomas (Boland et al, 1998; Boland et al, 2008). In other words, 98% of lesions that exhibit an attenuation of 10 HU or less on nonconstrast CT are adrenal adenomas, while less than 30% of adrenal adenomas are lipid-poor (also known as "atypical adenomas") and exhibit an attenuation of greater than 10 HU. Similar test characteristics have been confirmed in purely surgical series (Hamrahian et al, 2005). In urologic practice, this criterion on unenhanced CT is quite useful, because the vast majority of renal imaging for stones or lesions of the upper urinary tracts includes an unenhanced precontrast phase. Despite the high specificity of the 10 HU cutoff, few low-density (<10 HU) pheochromocytomas have been reported, underscoring the importance of a metabolic workup for all adrenal lesions (Blake et al, 2003; Blake et al, 2005). It should be mentioned that in an era of digital radiology, density measurements of adrenal lesions can easily be measured at the time of evaluation for definitive evaluation, even when the interpreting radiologist may not provide the values in their dictation. Diligence in this regard by the clinician is essential to avoid additional unnecessary imaging tests, even if improperly recommended.

Enhanced CT. Some adrenal masses may be discovered on contrast-enhanced imaging without the benefit of precontrast films. Unfortunately, the diagnostic information that can be obtained from attenuation values of these single-phase studies (approximately 1 minute after the contrast bolus) is limited. Unlike unenhanced CT, there is tremendous overlap in postcontrast attenuation values of adenomas and nonadenomas (Korobkin et al, 1996a; Szolar and Kammerhuber, 1998).

Recently, some authors demonstrated that enhanced CT may indeed contain diagnostic information that is helpful in identifying lipid-rich adenomas when histogram analysis of the lesion's region of interest (ROI) is performed. This technique is available on most modern workstations, and it graphs the quantity of pixels in an ROI against their attenuation value (Boland et al, 2008). Some suggest that if more than 10% of pixels exhibit a density below 0 HU, the lesion is likely an adenoma (Bae et al, 2003). Nevertheless, this technique is not yet fully validated (Boland et al, 2008).

CT Washout Study. **Approximately 30% of adrenal adenomas exhibit an attenuation of greater than 10 HU on unenhanced CT due to their lower lipid content. These "atypical adenomas" are indistinguishable from nonadenomas using noncontrast CT density measurements alone** (Boland et al, 1998)**. Fortunately lipid-poor adenomas possess identical properties to lipid-rich adenomas regarding their rapid loss (washout) of enhancement following CT contrast load** (Caoili et al, 2000; Pena et al, 2000). Indeed in the last decade, "washout" of contrast enhancement has become a routine technique to differentiate lipid-poor adenomas from other adrenal lesions (Korobkin et al, 1998; Szolar and Kammerhuber, 1998; Szolar et al, 2005). An absolute percent washout (comparing noncontrast values to 15-minute postcontrast density values) of greater than 60%, or a relative percent washout (comparing arterial phase density measurements to 15-minute postcontrast density values) of greater than 40% on delayed (washout) imaging, are indicative of adenoma (Fig. 57–28) (Caoili et al, 2002; Boland et al, 2008). Remarkably, test characteristics for these CT washout studies approach nearly perfect sensitivity and specificity parameters (Boland et al, 2008). Figure 57–29 summarizes when CT washout studies should be used and how the percent washout is calculated.

Reports on washout studies using a 10-, instead of a 15-minute, delay exist. Originally, a relative percent washout (RPW) of greater than 50% was believed to be necessary to diagnose adenomas using such protocols (Pena et al, 2000). However, more recent reports suggest that just as with a 15-minute delayed study, an RPW of greater than 40% is sufficient (Blake et al, 2005). Nevertheless, despite the potential added efficiency of a 10-minute study, the 15-minute delayed protocols are most often employed (Boland et al, 2008).

Given these data, it is imperative that the knowledgeable urologist orders a proper adrenal CT study to include noncontrast 5-mm images through the adrenal with enhanced (1-minute postbolus imaging) and 15-minute washout imaging, and speaks to the radiologists to assure the test uses the proper protocol. In the absence of a properly performed test, nondiagnostic images may lead to a recommendation for subsequent unnecessary and anxiety-provoking tests.

MR Imaging. Similar to adrenal imaging by CT, magnetic resonance imaging of the adrenal incidentaloma relies on its ability to accurately quantify the lesion's lipid content. **While CT uses unenhanced attenuation to identify lipid-rich adenomas, MRI harnesses the interference between signal collected from fat and water tissue to evaluate for intracellular lipid content** (Hussain and Korobkin, 2004). **On such opposed phase chemical-shift imaging, signal intensity loss on out-of-phase sequences, when compared to in-phase imaging, signifies the presence of intracellular lipid and definitively identifies the lesions in question is an adenoma** (Korobkin et al, 1996b; Namimoto et al, 2001). The loss of signal intensity can be quantified by several methods (for example, using the spleen as an internal reference); however, in clinical practice, qualitative assessments are most often employed (Outwater et al, 1996; Fujiyoshi et al, 2003; Boland et al, 2008). Most reports demonstrate that the test characteristics of MR chemical shift imaging are similar to those of unenhanced CT, albeit

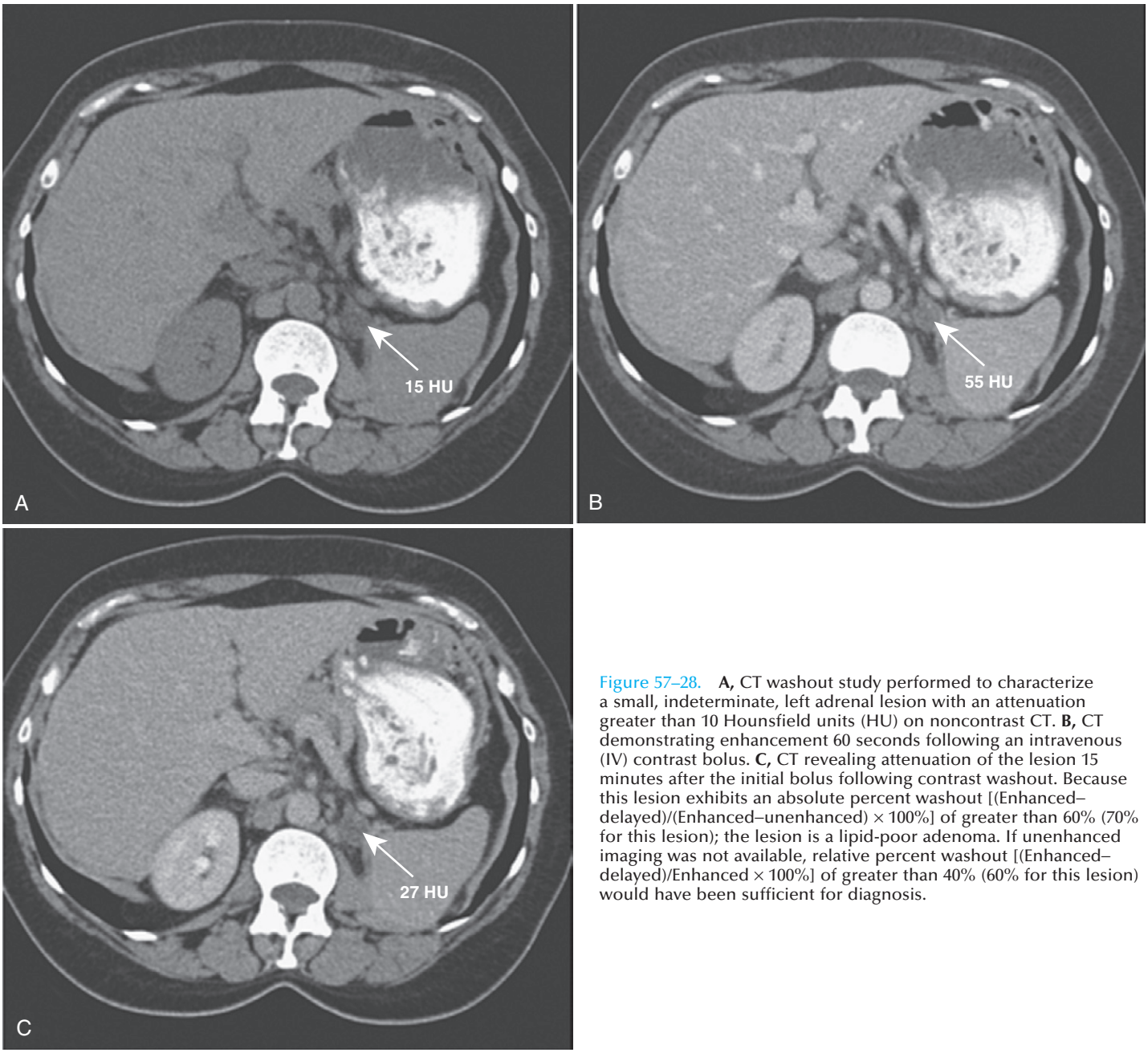


Figure 57–28. **A,** CT washout study performed to characterize a small, indeterminate, left adrenal lesion with an attenuation greater than 10 Hounsfield units (HU) on noncontrast CT. **B,** CT demonstrating enhancement 60 seconds following an intravenous (IV) contrast bolus. **C,** CT revealing attenuation of the lesion 15 minutes after the initial bolus following contrast washout. Because this lesion exhibits an absolute percent washout [(Enhanced–delayed)/(Enhanced–unenhanced) × 100%] of greater than 60% (70% for this lesion); the lesion is a lipid-poor adenoma. If unenhanced imaging was not available, relative percent washout [(Enhanced–delayed)/Enhanced × 100%] of greater than 40% (60% for this lesion) would have been sufficient for diagnosis.

significantly more expensive. Several reports suggest that MRI may be superior in characterizing *lipid-poor* adenomas than unenhanced CT (Haider et al, 2004; Israel et al, 2004). **Nevertheless, CT washout studies are considered the gold standard and appear to surpass opposed phase chemical-shift MR imaging in their sensitivity for identifying adenomas** (Caoili et al, 2000; Hussain and Korobkin, 2004; Park et al, 2007; Boland et al, 2008). **It is important to note that gadolinium-enhanced MR washout studies do not exhibit the diagnostic strength of iodine-based CT washout studies, and are not currently employed in clinical practice.** This shortcoming of MR imaging may be explained by the fact that gadolinium-induced signal intensity is less dose-dependent than enhancement from iodinated contrast on computed tomography imaging (Hussain and Korobkin, 2004).

Functional Imaging. The high diagnostic accuracy provided by biochemical evaluation and cross-sectional radiographic imaging of adrenal incidentalomas limits the indications for the routine use of functional imaging. However, functional adrenal imaging can provide valuable information when the origin of the adrenal tumor is unclear or when malignancy is highly suspected but has not been confirmed with other diagnostic modalities (Avram et al, 2006; Gross et al, 2009).

Radionuclide scintigraphy with the radiolabeled cholesterol analogue ^{131}I-6β-iodomethyl-norcholesterol (NP59) can help determine whether or not an adrenal lesion originated in the adrenal cortex or is from another source, because adrenocortical cells demonstrate increased uptake of the cholesterol analog. Based upon the pattern of NP59 uptake, adrenal adenomas can be distinguished from other space-occupying lesions of the adrenal gland

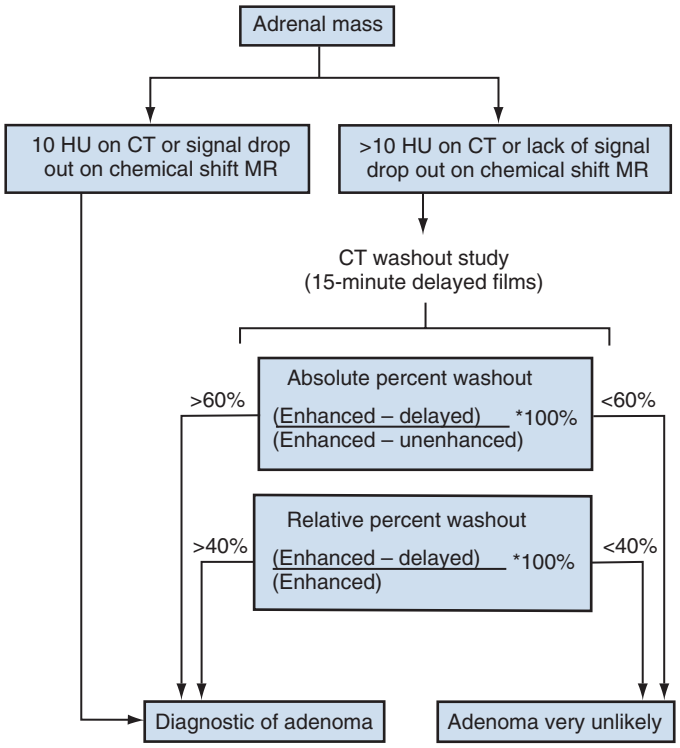


Figure 57–29. Summary of evaluation of adrenal mass using modern cross-sectional imaging.

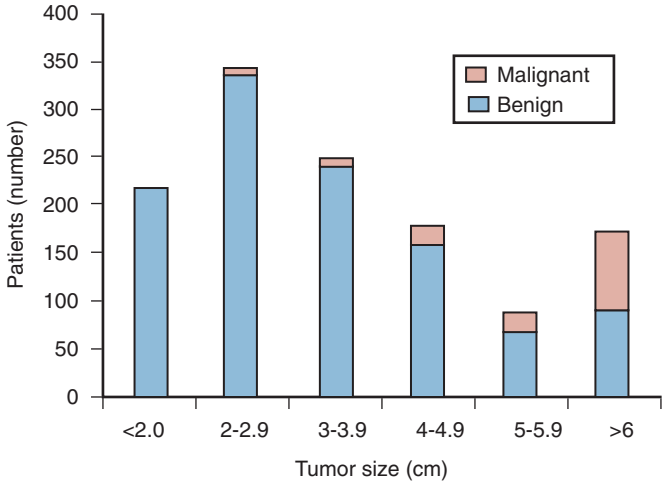


Figure 57–30. Distribution of benign versus malignant adrenal masses based on lesion size (total $n = 1322$). (Adapted from Barzon L, Sonino N, Fallo F, et al. Prevalence and natural history of adrenal incidentalomas. Eur J Endocrinol 2003;149:273–85.)

with high sensitivity and specificity (Kloos et al, 1995; Kloos et al, 1997). Although the characterization of lesions greater than 2 cm is limited with planar scintigraphy, the use of single photon emission-computed tomography (SPECT) may enhance the ability of NP59 to detect smaller lesions (La Cava et al, 2003). Despite the apparent benefits of NP59 scintigraphy in detecting adrenal adenomas, the test is time consuming and is not currently approved by the U.S. Food and Drug Administration. Moreover, it cannot reliably exclude the presence of adrenal cortical carcinoma (Tauchmanova et al, 2004).

Another radiotracer used to identify tumors of adrenocortical origin is ^{11}C-metomidate. Metomidate is an inhibitor of 11β-hydroxylase and aldosterone synthase that is preferentially taken up by adrenocortical cells (see Fig. 57–3). Although several studies have demonstrated the ability of ^{11}C-metomidate PET to correctly identify tumors of adrenocortical origin, the test is significantly limited by its inability to differentiate benign adrenal adenomas from adrenal cortical carcinomas (Minn et al, 2004; Hennings et al, 2006).

The role of functional imaging for the diagnosis of pheochromocytoma is limited given that most pheochromocytomas can be accurately diagnosed with cross-sectional imaging and metabolic evaluation for catecholamines and their metabolites. Therefore ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) imaging has a limited role in the routine evaluation of adrenal incidentalomas. MIBG is a functional and structural analog of norepinephrine that is incorporated into catecholamine storage vesicles. Increased uptake of MIBG suggests the presence of a chromaffin tumor, such as a pheochromocytoma or paraganglioma. In a small series of 23 patients with nonfunctioning adrenal masses, ^{131}I-MIBG scintigraphy was performed prior to pathologic evaluation and demonstrated a sensitivity of 100% and a specificity of 94% in identifying the presence of pheochromocytomas and paragangliomas (Maurea et al, 2001). Although there are alternatives to MIBG imaging for the detection of pheochromocytomas, including ^{18}F-dopamine PET and the somatostatin analogue ^{111}In-octreotide, their utility in the routine evaluation of adrenal incidentalomas has not been evaluated to date (Mayo-Smith et al, 2001; Timmers et al, 2007a).

The differentiation of benign and malignant adrenal tumors may be facilitated with the use of PET. Multiple reports have demonstrated a high sensitivity (93% to 100%) and specificity (80% to 100%) using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET to identify malignant adrenal tumors, including adrenal cortical carcinomas and metastatic lesions to the adrenal (Yun et al, 2001; Blake et al, 2006; Chong et al, 2006). However, the use of ^{18}F-FDG-PET is best reserved for cases in which CT imaging and clinical data are inconclusive (Boland et al, 2008).

Key Points: Imaging

- Low attenuation on unenhanced CT (<10 HU) corresponds to high intracellular lipid and is extremely specific for identification of adrenal adenoma.
- MR imaging is similar in its test characteristics to unenhanced CT.
- CT washout studies are considered the gold standard for adrenal imaging. Rapid loss of contrast enhancement can differentiate even lipid-poor adenomas (~30% of adenomas) from other lesions. Gadolinium-enhanced MR washout studies do not exhibit the diagnostic strength of iodine-based CT washout studies and are not currently employed in clinical practice.

Size and Growth

The retroperitoneal space allows for relatively asymptomatic growth of most adrenal lesions, which may reach beyond 20 cm in size before clinically manifesting. Nevertheless, at presentation, the median radiographic diameter of an adrenal incidentaloma is approximately 3 cm (Mantero et al, 2000). **A relationship does exist between the size of an adrenal lesion and its malignant potential with larger masses more likely to exhibit adverse clinical and pathologic features** (Angeli et al, 1997). Figure 57–30 summarizes the

relationship between adrenal mass size and its risk of malignancy in over 1300 reported incidentalomas (Barzon et al, 2003). Masses less than 4 cm are considered to possess low malignant potential (2% are adrenal carcinomas) and, if nonfunctional, can be observed safely (Grumbach et al, 2003; Cicala et al, 2008). **Masses that exceed 6 cm should be considered malignant until proven benign, which generally requires definitive resection. Management of incidentalomas between 4 and 6 cm is more controversial. In this intermediate size range, the rate of malignancy is estimated to be only 6%** (Cicala et al, 2008)**. Nonetheless, in otherwise healthy individuals with acceptable perioperative risk profile, most experts recommend 4 cm as the cutoff diameter that warrants resection** (Barry et al, 1998; Mantero et al, 2000; Young, 2000, 2007b; Thompson and Young, 2003). In the largest adrenal incidentaloma series to date ($n = 1004$), Mantero and colleagues (2000) reported that the 4-cm cutoff afforded a 93% sensitivity and 42% specificity for detecting malignancy. Sensitivity dropped to 74% and specificity rose to 73% when a 6-cm cutoff was applied. It is important to note that the relationship between the radiographic and pathologic size of an adrenal lesion is imperfect, with pathologic assessment usually resulting in a larger measurement (Cerfolio et al, 1993; Kouriefs et al, 2001).

The urologic oncologist must remember that the incidence of benign adrenal adenomas increases with age; therefore adrenal lesions in younger patients, even those less than 4 cm, must be managed with greater caution than similar lesions in an older age group. Likewise, lesions greater than 4 cm in older patients with significant comorbidities may be better served with observation than resection (Young, 2007b). Moreover, the radiographic characteristics of individual adrenal lesions (regularity of borders, enhancement) must be considered in addition to the lesion's size when deciding whether to treat. In the absence of level I evidence, large population-based reports must be integrated with sound clinical judgment.

The growth kinetics of unresected adrenal lesions should be followed; although, most lesions that are resected due to an increased growth kinetics ultimately prove benign. In a prospectively followed multi-institutional Swedish cohort ($n = 229$, median follow-up 25 months), 7.4% ($n = 17$) of masses grew at least 5 mm, with 5.2% ($n = 12$) adding at least 1 cm to their diameter. All patients who underwent resection because of an increase in lesion size exhibited benign pathology (Libe et al, 2002). Similarly, an earlier review of the literature ($n = 873$) revealed that at a mean follow-up of 3 years, 9% of adrenal incidentalomas grew over 1 cm in diameter while a smaller number decreased in size. In this series, only one lesion proved malignant. The authors concluded that the rate of malignant transformation of adrenal incidentalomas is approximately 1 in 1000 (Barzon et al, 2003). **Reimaging at 6, 12, and, as possible, at 24 months is currently recommended in order to verify oncologic indolence** (Grumbach et al, 2003; Young, 2007b). Suspicious and unusual tumors may require imaging at earlier or more frequent intervals, while small (<2 cm) homogeneous, well-circumscribed, nonfunctional lesions can be followed less closely (Young, 2007b). **A rather arbitrary criterion of 1-cm growth has been proposed as an indication for resection; however, the patient must be counseled that the chance of malignancy is low if growth kinetics are flat** (Young, 2007b).

Key Points: Size and Growth

- Masses >6 cm should be considered malignant until proved otherwise. Although management of masses between 4 and 6 cm is controversial, thought leaders in the field advise that in otherwise healthy individuals masses 4 cm or larger should be resected.
- Kinetics of growth should be followed. Current recommendation is to resect masses that grow over 1 cm; however, incidence of malignancy among these patients is low.

Biopsy of Adrenal Masses

Overview

The role for adrenal biopsy has been limited for the following reasons: (1) modern imaging in the context of clinical characteristics affords superb diagnostic capabilities, (2) histologically adenomas cannot be reliably differentiated from adrenal carcinomas, and (3) adrenal biopsy is not without risk (Thompson and Young, 2003; Young, 2007b). Nevertheless, it is useful to review data that is available with regard to safety and diagnostic utility of adrenal biopsy, and the procedure can occasionally be a useful tool in the diagnostic armamentarium of the adrenal surgeon.

Test Characteristics of Biopsy

Welch and colleagues (1994) reported on 277 percutaneous biopsies performed at the Mayo Clinic. Most biopsies in the series were performed in patients with a known nonadrenal malignancy. The authors report a sensitivity of 81% and specificity of 99%. The accuracy of right-sided biopsies was higher than those on the left (94% vs. 87%). Larger biopsy needles (18 or 19 gauge) resulted in better diagnostic yield and equivalent complication rates when compared with biopsies performed with smaller needles.

The reported positive predictive value of adrenal biopsy is high, meaning that a positive biopsy for malignancy has a high correlation on final pathology. This is especially relevant in patients with a history of an unrelated primary, and in whom an adrenal metastasis is suspected (Silverman et al, 1993; Harisinghani et al, 2002). Although the overall specificity is imperfect, in the same clinical scenario, the test's negative predictive value is nevertheless impressive when nondiagnostic biopsies are excluded (Silverman et al, 1993; Harisinghani et al, 2002). In a series of 225 adrenal biopsies performed in patients with a known primary malignancy at the Massachusetts General Hosptial, 18% of biopsies demonstrated adrenal tissue without evidence of malignancy. The authors reported the negative predictive value of these negative biopsies based on lack of tumor growth at follow-up, autopsy findings, or a rebiopsy result of 100%; although selection and research biases may have existed (Harisinghani et al, 2002). In skilled hands, nondiagnostic biopsies appear infrequent when the majority of sampling is performed with 18-gauge needles (Paulsen et al, 2004).

The probability of a positive adrenal biopsy for metastatic disease appears highest in patients with known lung (>90%) and renal cell carcinomas (80%) (Mazzaglia and Monchik, 2009). In contrast, an adrenal mass in a patient without a previous history of malignancy and without evidence of a synchronous nonadrenal mass is highly unlikely to be present as a metastasis (Lutz et al, 2000). Biopsy in this setting is rarely helpful. Instead, other

criteria, such as radiographic morphology and size, must be used to characterize adrenal masses in such patients (Thompson and Young, 2003; Mazzaglia and Monchik, 2009).

Complications of Biopsy

The complication rates of adrenal biopsies in some large series are as low as 2.8% (Welch et al, 1994). Bleeding is the most common postbiopsy issue with pneumo-/hemothoraces also being reported (Silverman et al, 1993; Welch et al, 1994; Quayle et al, 2007). Needle-track seeding in patients with adrenocortical carcinoma remains a concern, and some authors suggest that biopsy should be avoided in patients in whom adrenal carcinoma is suspected (Quayle et al, 2007). Surgically, there has been a suggestion that biopsy, especially if followed by hemorrhage, can complicate or even prevent laparoscopic resection (Quayle et al, 2007).

The NIH consensus statement mandates that the possibility of pheochromocytoma is metabolically excluded prior to biopsy, whereas percutaneous biopsies of pheochromocytomas have been reported to result in life-threatening hypertensive crises (Grumbach et al, 2003; Quayle et al, 2007). Interestingly, inadvertent biopsy of pheochromocytomas has resulted in no ill effects in some patients (Quayle et al, 2007); however, in real-world practice due diligence to rule out pheochromocytoma prior to biopsy is prudent (Mazzaglia and Monchik, 2009).

Clinical Utility of Biopsy

Despite the fact that adrenal biopsies—when used to differentiate benign from metastatic disease—afford favorable accuracy, some clinicians argue that most adrenal biopsies performed today are unnecessary (Quayle et al, 2007; Mazzaglia and Monchik, 2009). For instance, Quayle and colleagues retrospectively reviewed their experience with patients who were sent to their tertiary referral center following an adrenal biopsy performed in the community. They concluded that in no case did the biopsy affect their clinical management. Moreover, these and other investigators have raised the issue of radiology reports recommending adrenal biopsies or stating that the lesions are "amenable" to biopsy. The authors suggested that such language in radiology reports must be strongly discouraged, because it leads to unnecessary and, at times, deleterious procedures by physicians who are not familiar with standard management of the adrenal mass (Quayle et al, 2007; Mazzaglia and Monchik, 2009).

In conclusion, adrenal biopsy should be pursued only when limitations of imaging have been reached and when the physician and patient are certain that the result of biopsy will influence management. Indeed, perhaps the biggest role for adrenal mass biopsy is in patients with primary malignancies that have potentially recurred in the adrenal gland and whose management will be affected by the biopsy results. Figure 57–31 summarizes the salient points that must be considered when making a decision regarding whether to perform a biopsy of a patient's adrenal mass.

Key Points: Biopsy of Adrenal Masses

- When used to differentiate benign from metastatic disease, adrenal biopsy carries favorable test characteristics.
- Always exclude possibility of pheochromocytoma before biopsy.

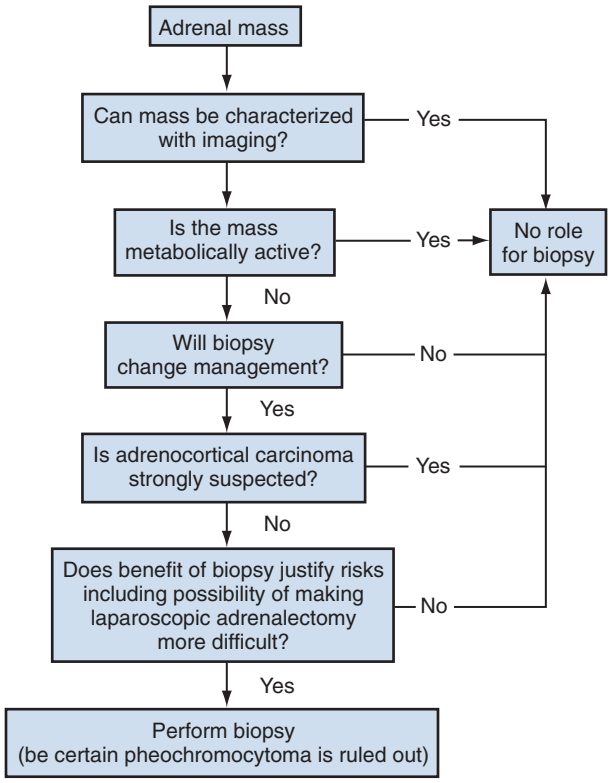


Figure 57–31. Algorithm summarizing decision making regarding whether to subject the patient to an adrenal biopsy. Perhaps the most clinically valuable role for adrenal mass biopsy is in patients with primary malignancies that have potentially recurred in the adrenal gland and whose management will be affected by the biopsy results.

Assessment of Function of Adrenal Masses

Overview

The NIH consensus statement recommends metabolic testing for all adrenal incidentalomas (Grumbach et al, 2003). **This recommendation is supported by the observation that more than 10% of adrenal incidentalomas are metabolically active** (see Table 57–19). **Current practice is to test all new adrenal masses for cortisol and catecholamine hypersecretion. In patients with a history of hypertension, aldosterone hypersecretion should also assessed** (Grumbach et al, 2003; Young, 2007b). Despite this recommendation as a standard of care, routine clinical practice remains inadequate in this domain, whereas it is estimated that greater than 80% of adrenal masses do not receive appropriate evaluation (Eldeiry and Garber, 2008).

Testing for Cortisol Hypersecretion

A systematic review of the literature reveals that 5% to 8% of adrenal incidentalomas produce excessive glucocorticoids (Young, 2000; Barzon et al, 2003). The NIH consensus guidelines state that all adrenal lesions should be tested for glucocorticoid hypersecretion (Grumbach et al, 2003). **Three first-line tests are available to screen patients with incidentalomas for Cushing syndrome: (1) an overnight low-dose dexamethasone suppression test (OST), (2) a late-night salivary cortisol test, and (3) a 24-hour urinary–free cortisol evaluation**

(UFC). A meta-analysis of the published literature demonstrates that these tests afford relatively equivalent accuracy; however, the UFC and the OST are supported by more abundant evidence than the late-night salivary cortisol approach (Elamin et al, 2008). **Nonetheless, reports suggest that UFC is not sufficiently sensitive to detect subclinical Cushing syndrome** (Tsagarakis et al, 2006; Mitchell et al, 2007). Indeed, recent practice guidelines from the The Endrocrine Society, recommend the use of either the OST or the late-night salivary cortisol test to screen patients with adrenal incidentalomas as part of a complete endocrinologic evaluation (Nieman et al, 2008). The section on Cushing syndrome reviews the physiologic rationale for both first-line testing discussed here and other testing that may be necessary. In this section, we review practical considerations of evaluating adrenal incidentalomas for excess glucocorticoid secretion within the scope of urologic practice. As mentioned in prior sections, the physician must verify that exogenous steroids, including creams and nasal sprays, are not in use by the patient prior to testing.

Overnight Low-Dose Dexamethasone Suppression Test. Administration of low-dose dexamethasone followed by measurement of serum cortisol probes the patient's glucocorticoid negative feedback system (see section on Cushing syndrome for discussion of physiology). A patient's failure to suppress cortisol levels following low-dose dexamethasone administration is indicative of Cushing syndrome (Findling and Raff, 2005).

Despite the test's arguably complex physiologic considerations, its administration is remarkably simple. **The patient is given a prescription for 1 mg of dexamethasone and instructed to take it between 11 PM and 12 AM (Newell-Price et al, 2006). The next morning, a serum cortisol is obtained between 8 AM and 9AM.** In patients without hypercortisolemia, the cortisol level should be suppressed below 5 mcg/dL (140 nmol/L). Specificity at this threshold is greater than 95% (Nieman et al, 2008). The trade-off, however, is sensitivity. In some reports up to 18% of patients with Cushing syndrome exhibited false-negative results (Findling et al, 2004). Therefore, a threshold-suppressed cortisol level of 1.8 mcg/dL (50 nmol/L) has been suggested, raising the sensitivity to over 90% (Findling et al, 2004) with a specificity of 80% (Nieman et al, 2008). The test's performance is similar to other first-line tests used to diagnose Cushing syndrome and is recommended as an alternative to the late-night salivary cortisol test for initial screening of incidentalomas (Elamin et al, 2008; Nieman et al, 2008).

Unlike the 24-hour urinary–free cortisol testing, OST is not affected by the patient's glomerular flow rate (GFR). Table 57–20 lists the most common pharmacologic agents that can alter testing. **Most importantly, the urologist must be aware that the test can yield as high as a 50% false-positive rate in women using oral contraceptives, because the contraceptives increase total (but not bioavailable) cortisol levels by raising the patient's cortisol-binding globulin concentrations** (Nickelsen et al, 1989). Administration of low-dose dexamethasone over a 48-hour period is less practical but may improve accuracy and is preferred by some endocrinologists.

Late-Night Salivary Cortisol. Late-night cortisol measurements probe the perturbation and, in some cases, complete disruption in the diurnal variation of cortisol levels that is seen in Cushing syndrome. The abnormality, even in very mild cases of Cushing syndrome, is the inability to suppress cortisol levels at night (Raff and Findling, 2003; Findling and Raff, 2005). Because late-night serum cortisol measurements are impractical, salivary testing has gained acceptance, because salivary cortisol levels reflect near real-time serum cortisol levels. Measurements of cortisol in saliva samples collected between 11 PM and midnight or at bedtime should not exceed 145 ng/dL when the tandem mass spectrometry (LC-MS/MS) assay is used (Nieman et al, 2008). The sensitivity and specificity of the test exceeds 90% and is similar to both UFC and OST; however, a large meta-analysis concluded that the data supporting salivary cortisol testing, to date, is inferior to the data available for UFC and the OST (Elamin et al, 2008; Nieman et al, 2008). Furthermore, the test's utility in diagnosing subclinical Cushing syndrome has been questioned (Nunes et al, 2009).

Unacceptably high false-positive rates may occur in patients with depression, altered sleep patterns, and chronic illness, because normal circadian variation in cortisol levels can be altered in these individuals. Tobacco use can affect salivary cortisol levels and should be avoided on the day of testing (Nieman et al, 2008). Some clinicians instruct patients to avoid oral food or liquid intake, brushing teeth, or undergoing stimulating activity within 30 minutes of salivary collection. Collection is rescheduled if the patient feels ill (Nunes et al, 2009). Some experts advise repeating salivary testing at least twice, regardless of the initial result (Nieman et al, 2008).

24-Hour Urinary–Free Cortisol Evaluation. Urinary–free cortisol evaluation is a 24-hour direct measurement of free bioavailable cortisol. This test is an integrated measurement of cortisol secretion over a 24-hour period and does not depend on variables

Table 57–20.

Pharmaceuticals That Affect Testing for Cushing Syndrome

Drugs That Accelerate Dexamethasone Metabolism by Induction of CYP 3A4
Phenobarbital
Phenytoin
Carbamazepine
Primidone
Rifampin
Rifapentine
Ethosuximide
Pioglitazone
Drugs That Impair Dexamethasone Metabolism by Inhibition of CYP 3A4
Aprepitant/fosaprepitant
Itraconazole
Ritonavir
Fluoxetine
Diltiazem
Cimetidine
Drugs That Increase CBG and May Falsely Elevate Cortisol Results
Estrogens
Mitotane
Drugs That Increase UFC Results
Carbamazepine
Fenofibrate (increase if measured by HPLC)
Some synthetic glucocorticoids (immunoassays)
Drugs that inhibit 11β-HSD2 (licorice, carbenoxolone)

This should not be considered a complete list of potential drug interactions. Data regarding CYP3A4 obtained from http://medicine.iupui.edu/flockhart/table.htm.
From Nieman LK, Biller BM, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2008;93(5):1526–40.

that influence corticosteroid-binding globulin levels (e.g., oral contraceptives) (Arnaldi et al, 2003). This study has been recommended as an initial test to screen patients with incidentalomas for Cushing syndrome (Orth, 1995); however, some recent evidence suggests that the study may not be sensitive enough to detect subtle glucocorticoid metabolism perturbations in patients with cortisol-secreting adrenal lesions (Terzolo et al, 2005; Tsagarakis et al, 2006; Mitchell et al, 2007). **Practice guidelines issued by the Endocrine Society in 2008 recommend that the dexamethasone suppression test or the late-night salivary cortisol test supplant the 24-hour urinary–free cortisol evaluation in initial metabolic screening of patients with incidentalomas** (Nieman et al, 2008). Nevertheless, this test remains the test of choice in pregnant patients. In the second and third trimester, cutoff values two- to threefold above the normal laboratory threshold must be used to account for the physiologic hormonal changes associated with pregnancy (Nieman et al, 2008).

As in all 24-hour urine collections, the patient is instructed to discard the morning's first voided urine and begin to collect all subsequent voided samples. The last sample that is collected is the first morning's void of the following day. Collection and analysis of two separate samples from each patient is advised. The test is most accurate in patients with a GFR greater 60 mL/min because false-negative results may arise in patients with poor renal function (Nieman et al, 2008). Creatinine levels in the collection must be checked to verify completeness of the collection.

As for all tests, sensitivity and specificity of the UFC depend on the population that is being tested and the normal cutoff values that are selected. Normal cutoff values of approximately 50 mcg to 100 mcg per 24 hours of urine volume are usually used, but these vary depending on the laboratory where the test is performed and the assay employed (Orth, 1995; Lin et al, 1997; Pecori Giraldi et al, 2007). Again, cutoff values in the second and third trimester of pregnancy must be raised approximately threefold to account for physiologic changes. As stated previously, the sensitivity of UFC for patients proven to exhibit hypercortisolism secondary to an adrenal adenoma has been reported to be as low as 85% (Invitti et al, 1999), while the specificity of the test in a population of patients with suspected Cushing syndome appears to be in the 90% range (Pecori Giraldi et al, 2007).

Testing for Aldosterone Hypersecretion

Hypersecretion of aldosterone by adrenal masses is extremely rare, with only approximately 1% of adrenal adenomas responsible for Conn syndrome (Young, 2000). Nevertheless, recent data demonstrates that nearly 5% of newly hypertensive patients may harbor an aldosterone-secreting adenoma (Rossi et al, 2006a). Indeed, testing of hypertensive patients with adrenal lesions for hyperaldosteronemia is clinically recommended. Testing of nonhypertensive patients, however, currently is not recommended. The section on Primary Aldosteronism describes the physiologic rationale for each test. In this section, we review the practical implications of evaluating adrenal incidentalomas for excess aldosterone secretion.

In the past, low serum potassium level has been used as a screening tool to assess for presence of aldosterone hypersecretion. Despite this prior teaching, contemporary series reveal that less than 40% of patients with hyperaldosteronism exhibit hypokalemia (Mulatero et al, 2004). **Today the screening test of choice for Conn syndrome is a morning plasma aldosterone (ng/dL) to renin (ng/mL/hr) ratio (ARR). An ARR of 20 (some suggest 30) along with a concomitant aldosterone concentration above 15 ng/mL are indicative of Conn syndrome** (Grumbach et al, 2003; Mulatero et al, 2004; Vierhapper, 2007; Young, 2007b). **The concurrent elevated aldosterone level appears important for cases in which the ARR is elevated simply due to a low renin level.** The test's characteristics have not been fully defined; however, sensitivities and specificities in the 90th percentile have been reported (Montori and Young, 2002; Young, 2007a).

Blood samples should be drawn between 8 AM and 10 AM, preferably in the sitting position. Note that this timing is also ideal for drawing the morning cortisol level for low-dose dexamethasone suppression testing. Some experts believe that hypokalemia may result in false-positive studies due to physiologic aldosterone elevation, and, therefore, patients with low potassium levels should undergo repletion prior to testing (Young, 2007a). **Potassium-sparing diuretics such as amiloride, and especially mineralocorticoid receptor blockers such as spironolactone, alter the renin-angiotensin-aldosterone system and will affect test results. These agents should be stopped approximately 6 weeks prior to testing** (Young, 2007a). Also, historically, there has been great concern about ARR reliability in patients who are on other antihypertensive medications. Indeed, until recently, cessation of all antihypertensive therapy was recommended for a minimum of several days prior to ARR testing. Data now suggest that this may be unnecessary. Figure 57–32 summarizes the effects of various antihypertensive agents on aldosterone and renin levels and on the ARR. The urologist must remember that patients on β blockers, who continue therapy through testing, may show a false-positive rise in ARR. Interpretation in these cases should be unaffected because the concurrent aldosterone level remains within normal limits (Young, 2007a). Nevertheless, some experts recommend cessation of β blockade prior to testing (Seifarth et al, 2002). Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs)

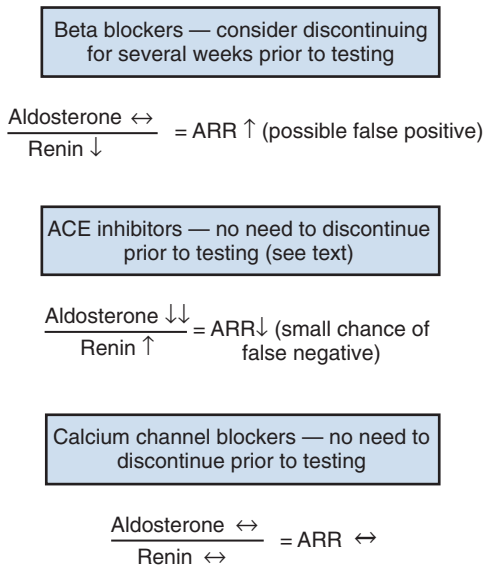


Figure 57–32. Effect of antihypertensives on screening for hyperaldosteronism. Potassium-sparing diuretics and mineralocorticoid receptor blockers are not included in the figure, because they greatly alter the renin-angiotensin-aldosterone axis and should be stopped at least 6 weeks prior to aldosterone renin ratio (ARR) testing. The ARR must be interpreted in the context of the aldosterone and renin levels (see text).

can lower aldosterone levels while raising renin levels in normal subjects. The ARR in patients with and without hyperaldosteronism, who are on these medications, has been shown to fall. Cessation of ACE inhibitors and ARBs, however, is not required. First, aldosterone levels are unlikely to fall in patients with hypersecreting adrenal lesions in the setting of ACE inhibitor/ARB use, due to the fact that this hypersecretion is independent of the renin-angiotensin-aldosterone system. Second, undetectable renin levels can be used as an additional screen for the diagnosis of hyperaldosteronism. Indeed, renin levels rise in normal subjects, and undetectable renin concentrations should be used as a trigger for secondary (confirmatory) testing even in the setting of an ARR within the normal limits (Seifarth et al, 2002; Young, 2007a).

Confirmatory testing is mandatory in patients who test positive during the initial screen for Conn syndrome. Briefly, this testing involves a 72-hour oral sodium challenge followed by measurements of a 24-hour urinary aldosterone level. The intravenous saline infusion test and the fludocortisone suppression tests are also used for confirmatory testing by some experts, although the latter test has fallen out of favor (Mulatero et al, 2004; Young, 2007a). We strongly recommend that the patient be referred to an experienced endocrinologist at this point in his or her care. Once hyperaldosteronism is confirmed, further workup with adrenal vein sampling may be necessary. Please refer to the Primary Aldosteronism section for further discussion.

Testing for Adrenal Sex Steroid Hypersecretion

Hypersecretion of adrenal sex steroids by adrenal masses, especially incidentalomas, is exceedingly rare. The most common adrenal mass that hypersecretes sex steroid is an adrenal carcinoma that concomitantly exhibits cortisol hypersecretion (Wajchenberg et al, 2000; Cordera et al, 2003). Tumors that exclusively hypersecrete androgens, both testosterone and/or 17-ketosteroids, have been reported primarily in women. Approximately 50% of such lesions ultimately prove benign (Cordera et al, 2003; Moreno et al, 2004). **Routine testing of incidentalomas for sex hormones is currently not recommended** (Grumbach et al, 2003; Stanczyk, 2006; Young, 2007b).

Previously, for patients who presented with virilization, dexamethasone suppression testing was used to differentiate adrenal androgen excess from an ovarian androgen source; however, this approach has proven unreliable and has been largely replaced by radiographic imaging strategies (Derksen et al, 1994; Cordera et al, 2003).

Testing for Catecholamine Hypersecretion

Pheochromocytoma is found in approximately 5% of patients who present for adrenal incidentaloma. Therefore all patients, including those in whom metastatic disease is suspected, should undergo functional testing to rule out pheochromocytoma (Adler et al, 2007; Young, 2007b). The section on Pheochromocytoma describes the physiologic rationale for each test. Here we discuss the practical details regarding testing.

Free-fractionated plasma metanephrines and the 24-hour urinary–fractionated metanephrine tests constitute the mainstay for pheochromocytoma testing, given their superb sensitivity and suitable specificity. Indeed, the 2005 International Symposium on pheochromocytoma concluded that one of these two tests should be used for initial diagnosis and screening for pheochromocytoma (Grossman et al, 2006; Pacak et al, 2007). Currently there is an ongoing debate regarding which one of these tests is superior (Young, 2007b; Eisenhofer et al, 2008).

Plasma-Free Metanephrines. The measurement of plasma-free (fractionated) metanephrines has gained popularity due to ease of testing and excellent test characteristics. In a study of over 850 patients ($n = 214$ with pheochromocytoma, $n = 644$ without pheochromocytoma), Lenders and colleagues (2002) concluded that the test is superior to all other methods for diagnosing and excluding pheochromocytoma. Investigators in this multicenter study showed that the test affords nearly perfect sensitivity in cases of sporadic (99%) and familial (97%) pheochromocytoma. Specificity was reported to be 82% for sporadic and 96% for familial cases (Lenders et al, 2002). Indeed, the test's low specificity (reported as low as 77%) in patients older than 60, may lead to false-positive results. For this reason, some experts advise against first-line use of plasma-free metanephrines in all patients with incidentalomas (Sawka et al, 2003; Young, 2007b). Nevertheless, supporters of the test contend that the true specificity of the test is closer to 92% and that insufficient evidence exists to prove superiority of urinary testing and to eliminate plasma-free metanephrines from routine first-line use (Eisenhofer et al, 2008). Further arguments for and against using plasma-free metanephrines are summarized in Table 57–21.

Ideally, patients should not consume food or liquids after midnight prior to the study. Caffeinated beverages must be avoided especially (Lenders et al, 2002). **Acetaminophen can produce a false-positive result due to cross reactivity in the assay and should be stopped for at least 5 days prior to testing. Tricyclic antidepressants and phenoxybenzamine should also be stopped, because these have been shown to be**

Table 57–21.

Relative Merits for and against Using Plasma-Free Metanephrines and Urinary-Fractionated Metanephrines in Diagnosis of Pheochromocytoma

URINARY FRACTIONATED METANEPHRINES	PLASMA-FREE METANEPHRINES
Well-established, widely available test	Relatively new test with limited availability
Urinary concentrations (200-2000 nmol) make analysis relatively easy	Plasma concentrations (0.1-0.5 nmol) can make analysis difficult
Easy for clinicians to implement with minimal expenditure of time and effort	Blood collections require some time and effort by medical staff
Twenty-four–hour collections can be inconvenient for patients	Blood sampling relatively more convenient for patients
Problems with reliability of incomplete timed urine collections	Collection and handling of blood samples can be better regulated
Difficult to control dietary and daily life influences on symphathoadrenal function	Influences of diet and sympathoadrenal function more easily controlled
In children, 24-hour collections are difficult to interpret without age-appropriate reference intervals	In children blood sampling may be stressful, but results are more easily interpreted without age-appropriate reference intervals
Urine collections may be inappropriate in patients with renal failure	Test is applicable in patients with renal failure

From Grossman A, Pacak K, Sawka A, et al. Biochemical diagnosis and localization of pheochromocytoma: can we reach a consensus? Ann N Y Acad Sci 2006;1073:332–47.

responsible for false-positive results (Eisenhofer et al, 2003b). Usual antihypertensive therapy can be continued. Although β blockade can potentially result in a false-positive test result, the current recommendation is to stop the medication only on repeat testing (Eisenhofer et al, 2003b). Ideally, the serum sample should be drawn in the supine position following at least 20 minutes of supine rest. Position is especially important if a positive result has been obtained and confirmatory testing is being performed (Grossman et al, 2006).

The upper limit of normal for the test is usually set at 0.61 nmol/L (112 ng/L) for normetanephrine and 0.31 nmol/L (61 ng/L) for metanephrine (Lenders et al, 2002; Eisenhofer et al, 2003; Pacak et al, 2007). Elevation beyond 2.2 nmol/L (400 ng/L) for normetanephrine and/or 1.2 nmol/L (236 ng/L) for metanephrine is substantial and is highly indicative of pheochromocytoma. Lesser elevation in plasma-free metanephrine levels require repeat testing (Eisenhofer et al, 2003b). No consensus exists regarding the best strategy for repeat testing; however, such strategies as repeating plasma-free metanephrine under ideal conditions (supine for 20 minutes, off β blockers, etc.), performing urinary–fractionated metanephrine testing, evaluating for elevated chromogranin A levels, and subjecting the patient to clonidine suppression testing have all been suggested (Eisenhofer et al, 2003b; Lenders et al, 2005; Algeciras-Schimnich et al, 2008). At this point in the patient's care, we strongly suggest involving an experienced endocrinologist.

24-Hour Urinary–Fractionated Metanephrines. Some experts believe that 24-hour urinary–fractionated metanephrines along with fractionated urinary catecholamine testing represent the best first-line test for pheochromocytoma (Perry et al, 2007; Young, 2007b). When measured with tandem mass spectrometry, and when an elevation in either metanephrine (>1531 nmol/day), normetanephrine (>4001 nmol/day), or total metanephrines (>1563 nmol/day) level is considered as a positive result, sensitivity for detecting pheochromocytoma is reported to exceed 97% with a specificity of approximately 91%. Supporters contend that given this specificity, the test is superior to plasma-free metanephrines, because it avoids unnecessary false-positive results, especially in patient populations with relatively low pretest probabilities, such as those with incidentaloma (Sawka et al, 2003, Perry et al, 2007; Young, 2007). Nevertheless, critics argue that high specificity is achieved by raising reference limits, potentially compromising sensitivity (Eisenhofer et al, 2008). Furthermore, they point to results of Lenders and colleagues (2002) that showed urinary–fractionated metanephrine to be inferior to plasma-free metanephrines. Given strong opinions on both sides of the argument, the 2005 International Symposium on Pheochromocytoma failed to reach a consensus regarding the superiority of either test (Grossman et al, 2006; Pacak et al, 2007). Table 57–21 summarizes some additional arguments for and against urinary metanephrine testing.

As in all 24-hour urine collections, the patient is instructed to discard the morning's first voided urine and begin to collect all subsequent voided samples. The last sample that is collected is the first morning's void of the following day. Creatinine levels in the collection must be checked to verify completeness of the collection. The test is most accurate in patients with normal renal function. Tricyclic antidepressants and phenoxybenzamine should be stopped.

Follow-up

A small percentage (approximately 2%), of metabolically silent adrenal incidentalomas are reported to show new metabolic activity during follow-up evaluation (Barzon et al, 2003). **The most recent consensus statement by a panel of experts recommends annual metabolic hormonal screening for the first 3 to 4 years following diagnosis, especially for masses that are 3 cm in diameter** (Grumbach et al, 2003). Nevertheless, given a lack of strong data for this recommendation, the need for metabolic reevaluation of adrenal adenomas in patients who show no clinical signs of hormonal hypersecretion remains controversial (Barry et al, 1998; Bulow et al, 2006; Young, 2007b).

Key Points: Assessment of Function of Adrenal Masses

- All adrenal incidentalomas demand a metabolic evaluation.
- Annual follow-up for 3 to 4 years is recommended for metabolically silent masses; however, de-novo development of metabolic activity is rare.

Summary of Surgical Indications

Every urologist must clearly understand the indications for surgical intervention in patients with adrenal pathology. The decision making and management algorithm for patients with adrenal incidentalomas are summarized in Figure 57–33. Table 57–22 also details the major surgical indications for resection of the adrenal gland. The table also includes existing recommendations for adrenal resection during radical nephrectomy (O'Malley et al, 2009).

Table 57–22.

Summary of Surgical Indications for Adrenalectomy

Functional adrenal mass
• Cortisol hypersecretion
• Pheochromocytoma
• Aldosterone hypersecretion
Mass > 4 cm (see Imaging of Adrenal Masses: Size and Growth) with exception of myelolipoma
Mass with imaging findings that are suggestive of malignancy (lipid-poor, heterogeneous, irregular borders, infiltrates surrounding structures, etc.)
Adrenal incidentaloma that grow greater than 1 cm on follow-up imaging
Extremely large and/or symptomatic myelolipoma (see Adrenal Lesions: Benign: Myelolipoma)
Isolated adrenal metastasis (multidisciplinary decision making required)
During radical nephrectomy for renal cell carcinoma if:
• Adrenal abnormal or not visualized due to large renal tumor size on imaging
• Large (≥7 cm) upper pole mass
• Vein thrombus to level of adrenal vein
Failed neurosurgical treatment of Cushing disease, requiring bilateral adrenalectomy
Select patients with ectopic adrenocorticotropic hormone (ACTH) syndrome, requiring bilateral adrenalectomy
ACTH-independent macronodular adrenal hyperplasia (AIMAH)
Primary pigmented nodular adrenocortical disease (PPNAD)

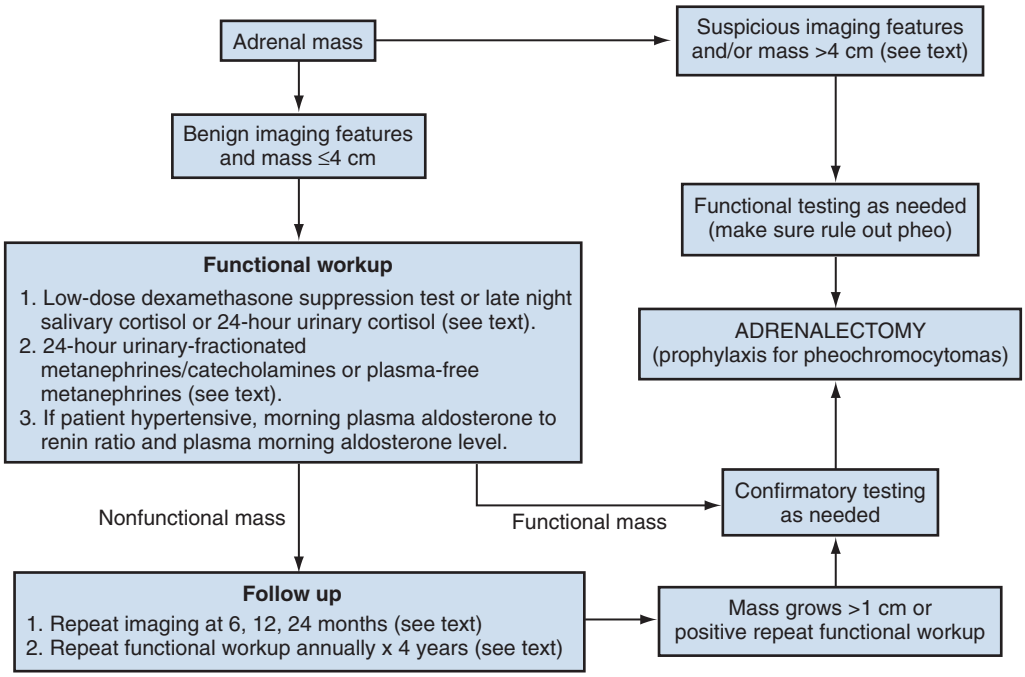


Figure 57–33. Management algorithm for newly diagnosed incidental adrenal mass.

CONCLUSIONS

The adrenal glands have long been recognized for their essential role in regulation of critical homeostatic functions. Indeed, these deceptively simple glands are central to a myriad of essential life-sustaining human functions. Despite the frequency of incidental adrenal lesions, relative to other essential organs, the adrenal glands are infrequent primary initiators of human diseases. Nonetheless, clinically significant abnormalities of the adrenal gland require a systematic multidisciplinary approach. With the urologist's advanced minimally invasive surgical skills, comfort with both retroperitoneal anatomy and surgical approaches to retroperitoneal organs and the close relationship between renal and adrenal pathophysiology, it is natural that he or she participate in the evaluation of adrenal disorders and provide primary surgical management for these patients.

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chapter 58

Surgery of the Adrenal Glands

George K. Chow, MD ● Michael L. Blute, Sr., MD

History
Surgical Anatomy
Clinical Indications and Selection of Patients
Preoperative Management
Open Adrenalectomy
Laparoscopic Adrenalectomy
Hand-Assisted Surgery
Robotic Surgery
Intraoperative Ultrasonography
Postoperative Management
Outpatient and Short-Stay Laparoscopic Adrenalectomy
Outcomes
Complications
Special Considerations
Nonsurgical Alternatives

Surgery of the adrenal gland consists of operative procedures to correct endocrine abnormalities or to treat malignant disease. As outlined in Chapter 57, various adrenal disorders can be identified and treated medically. When medical therapy is ineffective or does not exist for a particular adrenal disease, surgery becomes necessary.

Traditional open adrenal surgery has been performed since the late 19th century. Various techniques and anatomic approaches have been described for adrenalectomy, but the essential surgical principles have remained unchanged for a century. The introduction of laparoscopic adrenalectomy has revolutionized adrenal surgery and largely supplanted the open approach. However, we are not yet ready to relegate open adrenal surgery to the history books. There is a diminished but vital role for open adrenal surgery in the management of invasive adrenal carcinoma. Furthermore, all urologic surgeons should be familiar with the open techniques in the event that emergent open surgical conversion is necessary.

The future of adrenal surgery is evolving. New technology, such as robotics and percutaneous ablation, is being developed. These minimally invasive nonsurgical approaches may obviate the skills of the surgeon. Nevertheless, it is important that the urologist be part of the treatment team, either as direct practitioner of the technique or as a direct consultant guiding therapy.

HISTORY

The first adrenalectomy was performed by Thornton in 1889 for a large tumor in a 36-year-old woman (Thornton, 1890). At the time, Thornton was unaware of the adrenal origin of the patient's disease and removed the adrenal en bloc with the kidney. Sargent performed the first planned adrenalectomy in 1914 for a large adrenal adenoma. Charles Mayo (1927) performed the first flank adrenalectomy for pheochromocytoma in 1927. As was often the case in these early forays, Mayo was not aware of the exact nature of the pathologic process with which he was dealing and assumed that he was removing an aberrant retroperitoneal nerve.

Young (1936) described the posterior approach using a "hockey stick" incision to access both adrenal glands simultaneously. The thoracoabdominal incision for management of large retroperitoneal masses was first described by Chute and colleagues (1949). In 1965, Turner-Warwick developed and described a supracostal transdiaphragmatic variation of Young's posterior approach.

Gagner performed the first laparoscopic adrenalectomy in 1991 (Gagner et al, 1992). He used a transperitoneal approach to gain access to the adrenal gland. Also in 1992, Gaur developed and described the first device for balloon dilation of the retroperitoneum. Retroperitoneal access has been developed for both flank (Gasman et al, 1998) and posterior (Baba et al, 1997) approaches.

SURGICAL ANATOMY

The adrenal glands are situated in the retroperitoneum within the Gerota fascia. The right adrenal gland tends to lie more cephalad than the left adrenal gland. The anatomic borders of the right adrenal gland are the liver anteriorly, the vena cava medially, the right kidney laterally and inferiorly, and the diaphragm along its superior and posterior aspects. The medial aspect of the right adrenal gland will often be retrocaval, and the right adrenal vein will enter the inferior vena cava in a posterolateral position.

The left adrenal gland is bordered by the aorta medially, the stomach and body of the pancreas anteriorly, the kidney inferiorly, the spleen superiorly, and the diaphragm posteriorly. The left adrenal gland is often more elongated than the right adrenal gland and will lie in a more superomedial position to the kidney. This tends to place the gland closer to the left renal hilum, and these structures must be accounted for during dissection. The anatomic relationships of the adrenal glands are summarized in Fig. 58–1.

The arterial blood supply to the adrenal gland can be variable but tends to derive from three major sources on each side. Each

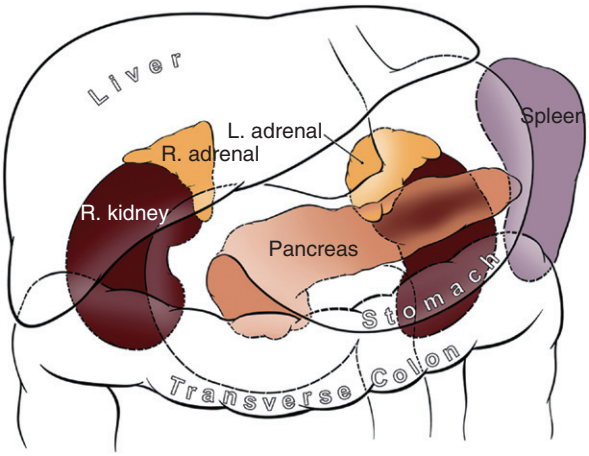


Figure 58–1. Regional anatomy of adrenal glands.

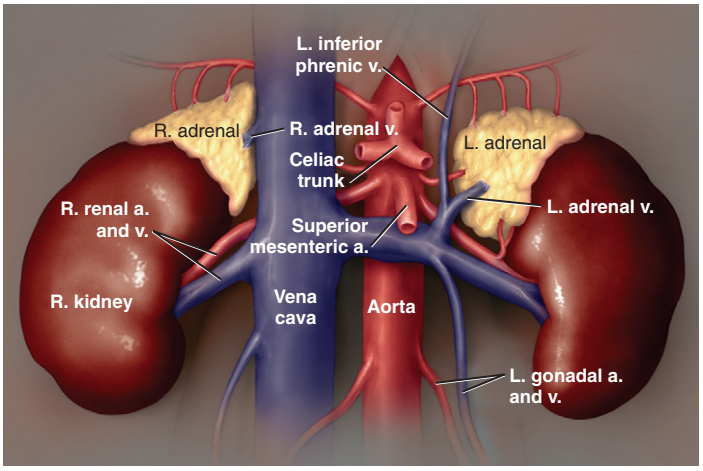


Figure 58–2. Vascular supply of adrenal glands.

adrenal gland receives branches from its ipsilateral inferior phrenic artery (superior adrenal arteries), aorta (middle adrenal arteries), and renal artery (inferior adrenal arteries). The venous drainage is typically simple; a single adrenal vein drains into the vena cava directly on the right and into the left renal vein on the left. Accessory veins (5% to 10%) that drain into the right renal vein, right hepatic vein, or inferior phrenic vein can be present (Fig. 58–2).

Lymphatic drainage from the adrenal glands consists of a lateral aortic lymph node chain extending from the diaphragm to the ipsilateral renal artery.

CLINICAL INDICATIONS AND SELECTION OF PATIENTS

Clinical Indications

The clinical indications for adrenalectomy are summarized in Table 58–1. The pathophysiology, diagnosis, and treatment of these diseases are detailed in Chapter 57.

Exclusion Criteria

Severe coagulopathy and poor cardiopulmonary performance status are absolute contraindications to adrenalectomy by any technique. As far as laparoscopy is concerned, the shrinking number of contraindications attests to the high level of skill exhibited by pioneering laparoscopic surgeons. These relative contraindications include previous open surgery, tumor size, obesity, and adrenal cortical carcinoma.

Table 58–1.

Clinical Indications for Adrenalectomy

Primary aldosteronism (solitary adenoma versus bilateral adrenal hyperplasia)
Cushing syndrome
Pheochromocytoma
Adrenal adenoma
Myelolipoma
Adrenal cyst
Metastatic tumor
Adrenocortical carcinoma
Neuroblastoma (pediatric)
Incidentally discovered adrenal mass or “incidentaloma”

Table 58–2.

Surgical Options (Open Adrenalectomy)

DISEASE	APPROACH
Primary hyperaldosteronism	Posterior (left or right) Modified posterior (right) 11th rib (left > right) Posterior transthoracic
Cushing adenoma	11th rib (left or right) Thoracoabdominal (large) Posterior (small)
Cushing disease (bilateral hyperplasia)	Bilateral posterior Bilateral 11th rib (alternating)
Adrenal carcinoma	Thoracoabdominal 11th rib Transabdominal
Bilateral adrenal ablation	Bilateral posterior
Pheochromocytoma	Transabdominal chevron Thoracoabdominal (large, usually right) 11th rib
Neuroblastoma	Transabdominal 11th rib

From Vaughn ED. Adrenal surgery. In: Marshall F, editor. Operative urology. Philadelphia: WB Saunders; 1996. p. 222.

Indications for Open Surgery

The current indications for open adrenalectomy are few but important. First, **adrenal cortical carcinoma with radiographic evidence of extra-adrenal tumor invasion of adjacent organs may benefit from maximal surgical exposure. Similarly, the extension of adrenal vein tumor thrombus into the inferior vena cava necessitates a more invasive approach.** Finally, in developing countries, the resources for laparoscopic surgery may be lacking, and the open approach will be preferred out of necessity. The choice of open surgical approach is dictated by the surgeon’s experience and the pathologic process in question. Table 58–2 summarizes the best surgical approach for a given adrenal disease.

Past Surgical History

Is open surgery indicated when there is a history of previous surgery close to the adrenal gland? The laparoscopic approach can be tailored to deal with past surgical history; a patient with previous transabdominal surgery could have a retroperitoneal laparoscopic procedure (Caddedu et al, 1999), and a history of previous open flank surgery could be addressed by performing a transperitoneal laparoscopic procedure. Furthermore, Gill and colleagues (2001) have reported their experience with a transthoracic laparoscopic approach that may be ideally suited for this situation. The thoracic cavity is entered thorascopically, the diaphragm is divided, and the adrenal gland is approached superiorly.

Size

Tumor size is a relative contraindication to laparoscopic surgery. In the initial experience of many laparoscopists, a cutoff of 5 or 6 cm was chosen because of the increased risk of treating an adrenal cortical carcinoma. Subsequently, ample empirical evidence has accumulated to suggest that specimen size is not necessarily a contraindication to laparoscopic adrenalectomy. MacGillivray and colleagues (2002) noted no difference in operative time, blood loss, complication rate, and hospital stay among 12 patients with large tumors (mean, 8.2 cm; range, 6 to 12 cm) and 36 patients with small tumors (mean, 2.5 cm; range, 0.4 to 5.6 cm).

In contrast, Hobart and colleagues (2000) noted increased operative time (205 minutes vs. 158 minutes; $P = .07$), increased blood loss (400 mL vs. 113 mL; $P = .009$), higher complication rate (21.4% vs. 8.9%; $P = .21$), and higher open conversion rate (14.3% vs. 2.2%; $P = .14$) in comparing 14 large tumors (mean, 8 cm) with 45 small tumors (mean, 2.2 cm). However, Hobart did find that operative time, blood loss, hospital stay, narcotic use, and complication rate were lower with laparoscopic adrenalectomy than with traditional open adrenalectomy for large tumors. Although a higher morbidity could be expected with larger tumors, morbidity was still less than with open surgery.

Conversion to open surgery is most often due to infiltrative adrenal cortical carcinoma. In the largest series, conversion occurred electively after initial laparoscopic exploration and not because of hemorrhage or other emergent causes. MacGillivray and colleagues (1996) concluded that **preoperative computed tomographic scanning can identify those infiltrative tumors that are likely to be invasive carcinoma.**

MacGillivray and coworkers (2002) and Henry and colleagues (1999) recommend an upper size limit of 12 cm for laparoscopic adrenalectomy. However, keep in mind that computed tomographic scanning can underestimate specimen size by as much as 16% (Lau et al, 1999).

Obesity

With a worldwide epidemic of obesity, it is an increasingly common occurrence to operate on morbidly obese patients. Rather than obesity being a relative contraindication, laparoscopy may offer a less morbid alternative for adrenalectomy on obese patients. Comparing results between obese patients (body mass index greater than 30) who underwent laparoscopic adrenal or renal surgery and those who underwent open surgery, Fazeli-Matin and colleagues (1999) noted that patients who underwent laparoscopic surgery had fewer complications (18% vs. 47%; $P = .21$), less blood loss (50 mL vs. 300 mL; $P = .03$), less narcotic use ($P = .01$), and shorter hospital stay (<24 hours vs. 5.5 days; $P = .01$). However, these surgeries were performed by a veteran laparoscopist, and obesity may remain a relative contraindication for less experienced surgeons.

Adrenal Cortical Carcinoma

Laparoscopic adrenalectomy on adrenal cortical carcinoma can be a daunting task. Adrenal carcinomas tend to be larger (>6 cm). Henry and colleagues (2002) noted that of 150 consecutive laparoscopic adrenalectomies, none of the smaller (<4 cm) tumors ($N = 102$) was malignant. In contrast, 12.5% of tumors larger than 4 cm ($N = 48$) were malignant. Using a 6-cm cutoff, Prager and coworkers (2004) noted that 21.2% of tumors larger than 6 cm were malignant versus 1.9% of lesions smaller than 6 cm. Also, the prospect of invasion by infiltrative lesions into surrounding structures can prohibit successful laparoscopic surgery. However, if computed tomography indicates that no local invasion is present and the lesion is not excessively large, laparoscopic adrenalectomy is possible.

Known adrenal vein or vena caval involvement is an absolute contraindication to laparoscopic surgery. However, in one case report, Kim and colleagues (2004) described an intraoperatively discovered adrenal vein thrombus with a 7-cm adrenal mass. With use of atraumatic vascular clamps, the renal vein was entered, and the intact tumor thrombus was removed en bloc with the adrenalectomy specimen.

Cancer control is dependent on adherence to the same oncologic principles as in open surgery. Wide local excision with perirenal fat is necessary for good local control to be obtained. Adrenal cortical carcinoma tends to be an aggressive disease, and locoregional recurrence can develop as often as 60% (Vassilopoulou-Sellin and Schultz, 2001). Most reports of postoperative adrenal cortical carcinoma recurrence have been in case reports. Henry and colleagues (2002) published a summary of 12 cases of carcinoma recurrence in the medical literature. In 25% of the cases, the authors admitted to specimen disruption during the case.

PREOPERATIVE MANAGEMENT

It is important to correct any electrolyte abnormalities that may result from an endocrinologically active adrenal tumor. Most notably, aldosteronoma can result in hypokalemia that may require potassium repletion and administration of a potassium-sparing diuretic. Hypertension should also be treated before surgery.

With a pheochromocytoma, α-adrenergic blockade should be started 2 weeks before surgery. Phenoxybenzamine is most often used for adrenergic blockade prior to surgery. Some patients with tachycardia may benefit from concurrent β blockade. Alternatively, an α_1-selective blocker such as prazosin or doxazosin can be used. Intraoperatively, high blood pressure can be treated with nitroprusside or a short-acting β blocker like esmolol. Volume repletion is important to prevent the postoperative hypotension secondary to loss of tonic vasoconstriction after removal of a pheochromocytoma.

Patients with Cushing syndrome require correction of electrolyte abnormalities and hyperglycemia before surgery. These patients may benefit from administration of adrenolytic agents such as mitotane or aminoglutethimide.

Potential errors in preoperative preparation are summarized in Table 58–3.

Table 58–3.
Errors in Preparation of Patients for Adrenal Surgery

Primary Aldosteronism
Potassium repletion
Blood pressure control
Cushing Syndrome
Inhibition of glucocorticoid production when there is severe manifestation with metyrapone
Control of diabetes
Preoperative antibiotics
Operative steroid administration
Incidentalomas
Anesthetic preparation for pheochromocytoma; 5% have normal diagnostic studies
Adrenal Carcinoma
Consent for adjacent organ removal
Failure to identify vena cava involvement
Pheochromocytoma
Preoperative catecholamine blockade
Volume expansion
Anesthetic consultation

Modified from Vaughn ED. Complications of adrenal surgery. In: Taneja SS, Smith RB, Ehrlich RM, editors. Complications of urologic surgery: prevention and management. 3rd ed. Philadelphia: WB Saunders; 2001. p. 363.

A mechanical bowel preparation can be helpful for open or laparoscopic transperitoneal surgery. Retroperitoneal surgery may not require this bowel preparation. All patients should receive appropriate preoperative antibiotics. A nasogastric or orogastric tube can be placed to decompress the bowel, especially helpful for transperitoneal cases. The placement of a urinary catheter to help measure urine output and to decompress the bladder is essential.

OPEN ADRENALECTOMY

Open adrenalectomy can be performed through either a transperitoneal or retroperitoneal approach. The transperitoneal approaches include midline, subcostal, and thoracoabdominal. The retroperitoneal approaches include flank and posterior lumbodorsal. The advantages of the transperitoneal approaches are better exposure for larger tumors and excellent access to the great vessels and retroperitoneum. The main disadvantages are prolonged ileus and difficult exposure in morbidly obese patients. The retroperitoneal approach results in less ileus and may result in shorter hospital stays. There is a smaller operative field, and access to larger tumors and surrounding involved organs may be difficult. The best surgical approach for a given adrenal disease is indicated in Table 58–2.

Flank Retroperitoneal Approach

Right Side. The patient is placed in flank position with the right side facing up (Fig. 58–3). The bed is placed in maximal flexion, and the kidney rest is deployed to accentuate the space between the costal margin and iliac crest. Palpation is used to identify the course of the 11th rib. The skin and fat overlying the 11th rib are incised, and the fascia and muscle overlying the rib are divided. (Fig. 58–4).

Once the anterior surface of the rib is exposed, the anterior periosteum is cauterized, and the periosteal elevator is used to scrape it off the anterior rib surface. The edges of the periosteum

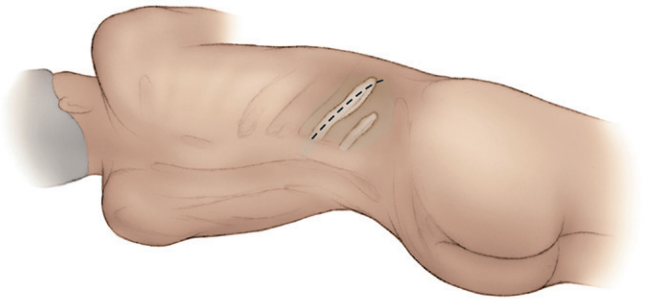


Figure 58–3. Surgical incision over 11th rib for flank adrenalectomy. The patient is in flexion, with the kidney rest deployed to maximally expose the right retroperitoneum.

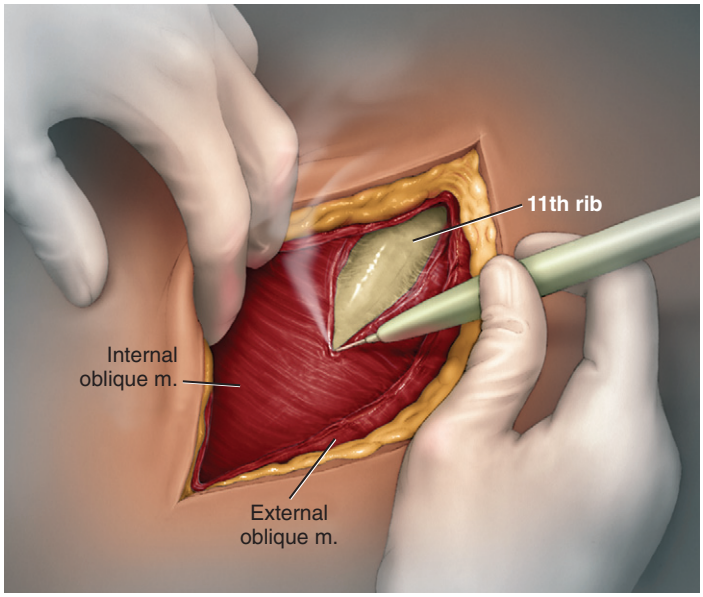


Figure 58–4. Flank approach. Incision of muscle overlying 11th rib.

on the superior and inferior aspects of the rib should now be visible. The periosteal elevator is used to develop a plane between the posterior rib surface and the posterior leaf of the periosteum. The Doyen instrument and surgical cautery are used to strip the periosteum off the rib from the tip of the rib back toward the paraspinal muscles. With the rib cutter, the 11th rib is excised (Fig. 58–5). A rongeur can be used to remove any sharp remnants on the rib stump. Cautery or bone wax can be used to render the marrow hemostatic.

Next, the neurovascular bundle is identified and freed with sharp and blunt dissection to avoid injury during subsequent dissection and closure (Fig. 58–6). The lumbodorsal fascia is entered sharply with Metzenbaum scissors, and blunt dissection is used to dissect the peritoneum off the transverse fascia anteriorly. The flank muscles and their accompanying fasciae are divided anteriorly—the external oblique, internal oblique, and transverse abdominal. Next, the posterior muscle diaphragmatic attachments are divided with cautery. The pleura is sharply and bluntly dissected off the superior edge of the 12th rib.

The plane between the Gerota fascia and the peritoneum can be started with the cautery or sharp dissection. Once it is identified, this plane can be maximally developed with blunt dissection. The peritoneum needs to be freed from the superior aspect of the

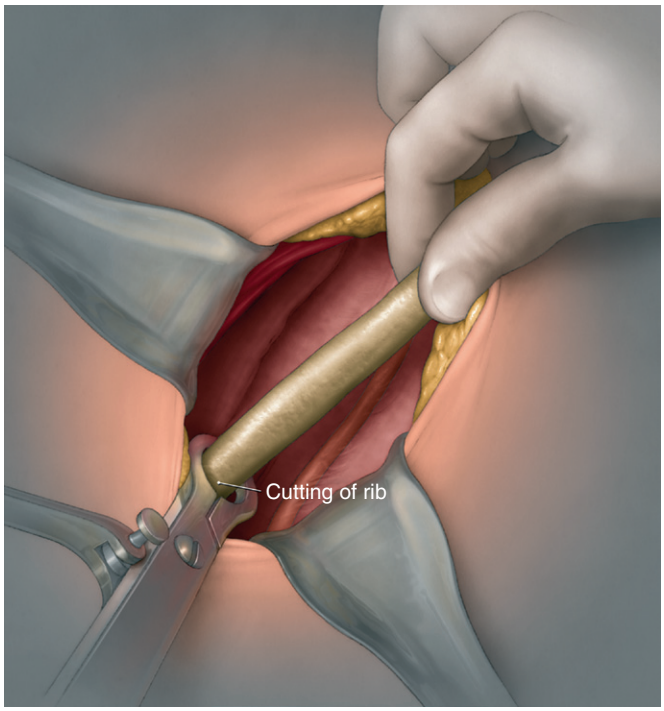


Figure 58–5. Flank approach. Excision of 11th rib.

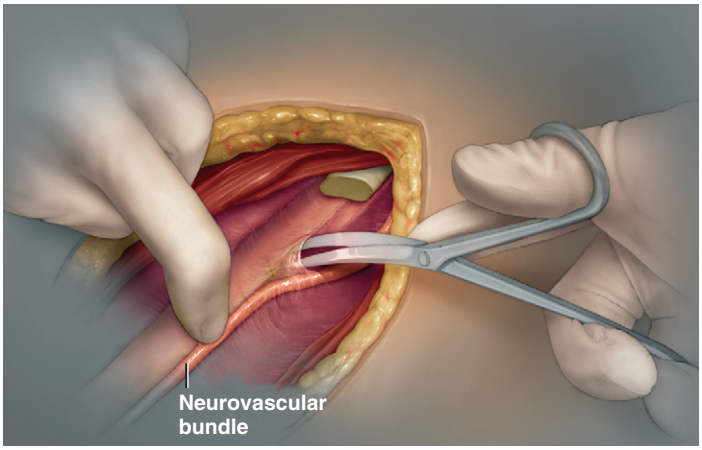


Figure 58–6. Flank approach. Mobilization of the intercostal neurovascular bundle from the 11th rib. This is performed with a combination of blunt dissection with a Kittner dissector and sharp dissection with Metzenbaum scissors.

Gerota fascia as well. Once the peritoneum is mobilized, on the right side, the vena cava can be visualized, and with cephalad dissection, the adrenal gland and renal vein can be seen as well. Placement of a self-retaining retractor is essential for maximal exposure to be obtained.

Dissection of the adrenal gland typically begins along the medial border of the gland with the vena cava. The overlying peritoneum is divided, and blunt dissection is used to expose the plane between the medial surface of the adrenal gland and the lateral surface of the vena cava. The adrenal vein is often difficult to identify until this plane is developed. The adrenal vein is dissected out with a right-angled instrument such as a Mixter forceps. Surgical ties or clips can be placed to ligate the adrenal vein. In our opinion, surgical ties are more reliable than standard titanium clips. However, locking surgical clips may be substituted for added security. There are numerous arterial branches to the gland that can be ligated and divided individually. Alternatively, many authors attest to the utility of the harmonic scalpel in hemostatically dividing arterial attachments. Once this is done, the psoas muscle is often visible posteriorly. Superior attachments are divided with the aid of surgical cautery or harmonic scalpel. Downward traction on the kidney assists with this dissection. Inferomedial attachments to the kidney are taken with sharp or cautery hook dissection.

Dissection of the left adrenal gland is similar except that the aorta is visualized, and the adrenal vein originates from the renal vein. Other authors have described supracostal technique with intentional violation of the pleura. This approach may be helpful for larger tumors.

Closure of the incision consists of a two-layer closure with a running No. 1 polydioxanone suture. The deep layer consists of the transverse abdominal muscle, internal oblique muscle, and fascia. The outer layer consists of the external oblique muscle and fascia. Skin closure can be completed with surgical staples or absorbable subcuticular suture.

Lumbodorsal Posterior Approach

The main advantage of this approach is the ability to easily access both adrenal glands for bilateral surgery. The disadvantages include a limited operative field and respiratory limitation. If bleeding is extensive, it can be difficult to control from this position. The posterior approach requires prone positioning of the patient with arms extended cephalad. The procedure has been extensively modified over time—with or without rib resection, transthoracic through the diaphragm, or diaphragm sparing. A rib-resecting, diaphragm-sparing approach is described.

Right Side. An incision is made along the course of the right 11th rib (Fig. 58–7). This is taken down to the periosteum, and the rib resection is performed in a manner similar to that described for flank incision. The diaphragm is dissected off the underlying peritoneum and liver. The peritoneum is then dissected off the Gerota fascia, which is retracted inferiorly. If a bilateral procedure is undertaken, a Finochietto retractor can be used to assist in bilateral exposure (Fig. 58–8). With division of the final hepatic attachments, the adrenal gland becomes visible. The vena cava often becomes visible at this point, and the right adrenal vein is easily identified at its posterolateral origin. After division of arterial branches to the adrenal that course behind the vena cava and anterior to the paraspinal muscles, the adrenal gland can be mobilized posteriorly away from the paraspinal muscles, exposing the anterior vena cava. Given the small operative field, manual retraction of the kidney to assist dissection is not usually possible. Fortunately, division of the vascular attachments is relatively simple, and direct manipulation of the adrenal gland is possible. **The posterior approach should not be used for large tumors or adrenocortical carcinoma.**

Subcostal Anterior Approach

The anterior approach is useful for larger tumors and can be extended to the contralateral side as a chevron incision for treatment of bilateral lesions (Fig. 58–9). This approach also affords excellent exposure of the great vessels, in the event that lymph nodes or venous tumor thrombus needs to be addressed.

Left Side. The patient is placed supine on the surgical table. If needed, a body roll can be placed under the back at the level of the costal margin to accentuate the costal margin. A skin incision



Figure 58–7. Posterior approach—possible incisions for lumbodorsal incisions.

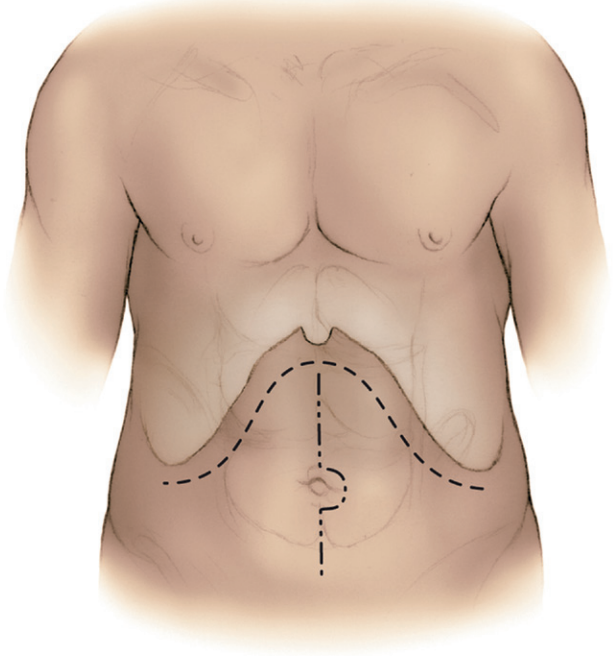


Figure 58–9. Anterior approach. The transperitoneal approach may be attempted through a midline incision or subcostal incision. The subcostal incision can be extended into a full chevron for bilateral adrenalectomy or if a large unilateral tumor is encountered.

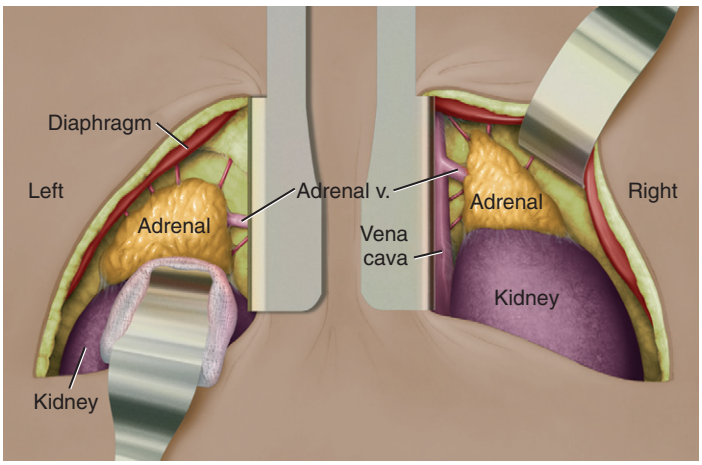


Figure 58–8. Bilateral posterior approach—anatomic relations to the adrenal gland as seen from behind.

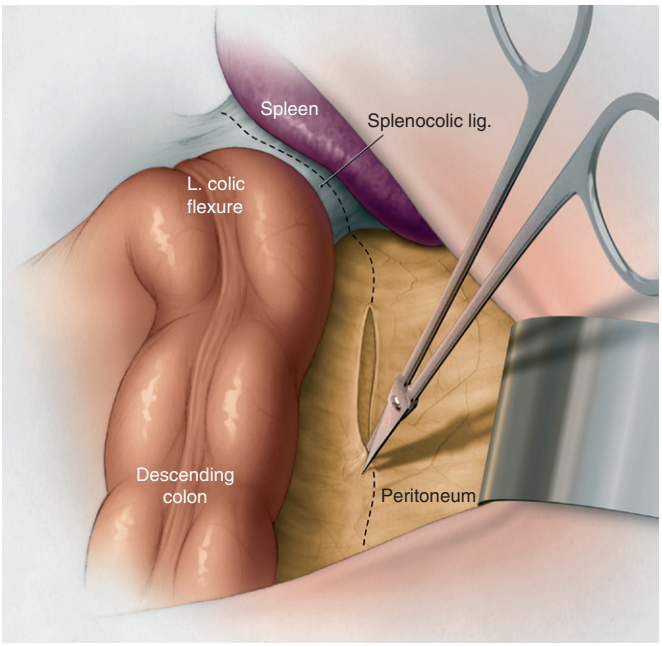


Figure 58–10. Anterior approach. Peritoneum lateral to left colon is incised at the line of Toldt and extended cephalad to the splenocolic ligament and inferiorly.

is made approximately two fingerbreadths below the costal margin. This incision is extended medially to the midline or beyond, depending on the degree of exposure needed. The external oblique, internal oblique, and transverse abdominal muscles, and their corresponding fasciae, are divided laterally; the rectus muscle and the rectus sheath are divided medially. The peritoneum is entered sharply, and the falciform ligament is divided after it is clamped and ligated with a large-gauge vascular tie (No. 0 or 1 silk). The line of Toldt is incised, and the left colon is mobilized medially. The splenic flexure is taken down by dividing the splenocolic ligament (Fig. 58–10). Division of the lienorenal ligament will allow medial mobilization of the spleen. The tail of the pancreas may come into view at this point. In a thin individual, the adrenal may be visible at this point. The left adrenal vein is identified on dissecting out the left renal vein (Fig. 58–11). After ligation and division of the left adrenal vein, medial attachments to the aorta can be taken with the harmonic scalpel or with careful dissection and ligation of small arterial vessels while gentle lateral traction is placed on the gland. The lateral and inferior attachments to the kidney can be taken by blunt and sharp dissection off of the renal

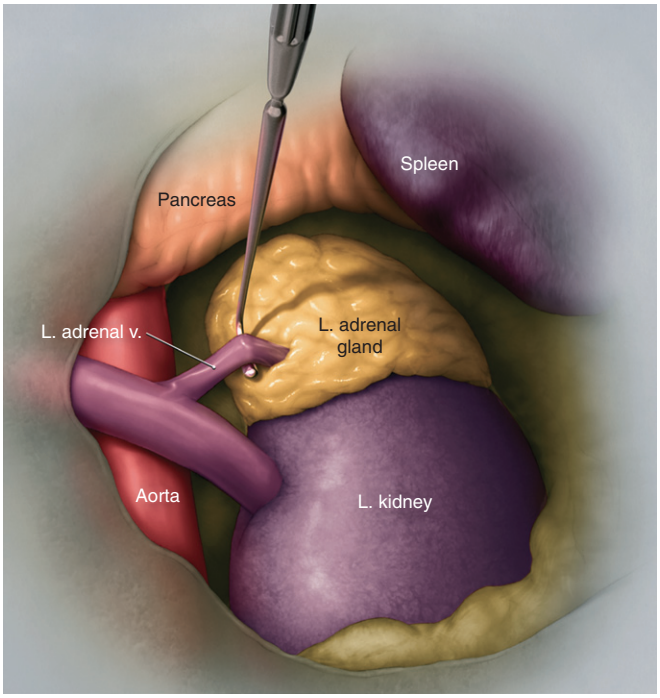


Figure 58–11. Anterior approach. The left adrenal vein is dissected out and ligated.

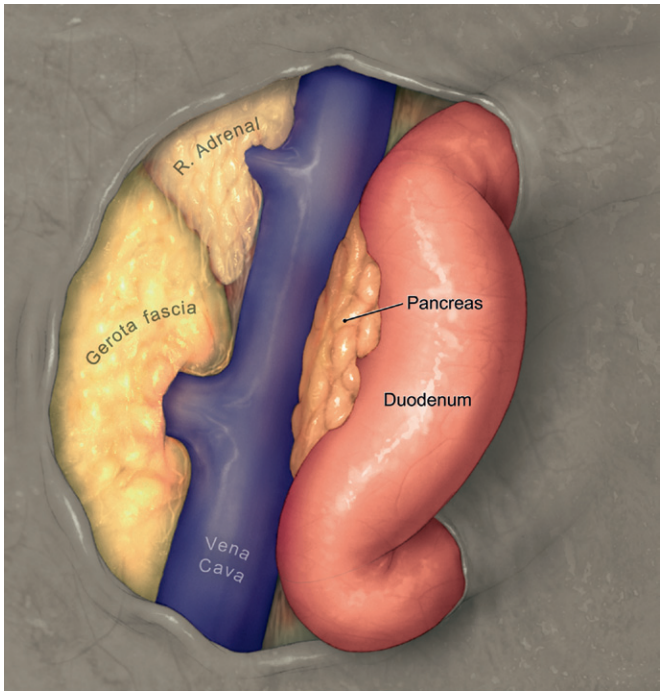


Figure 58–12. Kocher maneuver. The peritoneum is incised, and sharp dissection and blunt dissection are used to mobilize the second stage of the duodenum away from the renal hilum.

capsule. Care must be taken to avoid hitting upper pole renal vascular attachments. After removal of the left adrenal gland, closure of the incision is performed with a running No. 1 polydioxanone suture in two layers. The deep layer consists of the transverse abdominal muscle, transverse fascia, internal oblique muscle and fascia, and posterior rectus sheath, and the superficial layer consists of the external oblique muscle and fascia, and the anterior rectus sheath.

For right-sided tumors, the dissection is similar except for the need to dissect the duodenum medially by the Kocher maneuver (Fig. 58–12).

Thoracoabdominal Approach

This approach is a maximally invasive way to ensure superb surgical exposure of the retroperitoneum, adrenal gland, and great vessels. However, this exposure comes at a price: increased incisional pain, prolonged ileus, pulmonary morbidity, and a chest tube. **The thoracoabdominal approach is reserved for large or invasive adrenal carcinomas.**

Right Side. The patient is placed in an oblique position with the upper torso at a 45-degree angle to the table and the lower body flat on the table. A body roll is used to achieve the 45-degree position, and the right arm is placed in a sling with the arm bent at the elbow (Fig. 58–13). The left arm is secured to an arm board. The incision is made through the eighth or ninth intercostal space (Fig. 58–14), dividing the intercostal muscles and fasciae. The costal cartilage is divided with the surgical cautery. The incision is carried farther through the anterior and posterior rectus sheaths and the rectus abdominal muscle. The pleura is entered, and the lung is packed away with laparotomy sponges (Fig. 58–15). The diaphragm is divided with the cautery. Do not cut directly to the center of the diaphragm because the phrenic nerve can be damaged. Once the diaphragm is divided, a Finochietto

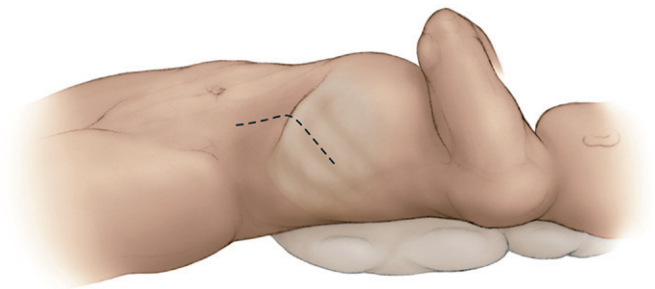


Figure 58–13. Positioning for thoracoabdominal surgery. A body roll elevates the flank on the side of surgery, and the arm and shoulder are rotated away, supported by a sling.

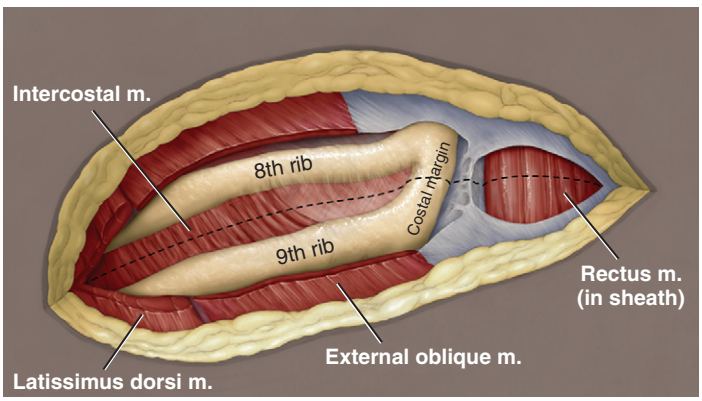


Figure 58–14. Thoracoabdominal approach. Incision at the eighth intercostal space. The costal margin, external intercostal muscle and fascia, and anterior rectus sheath are divided.

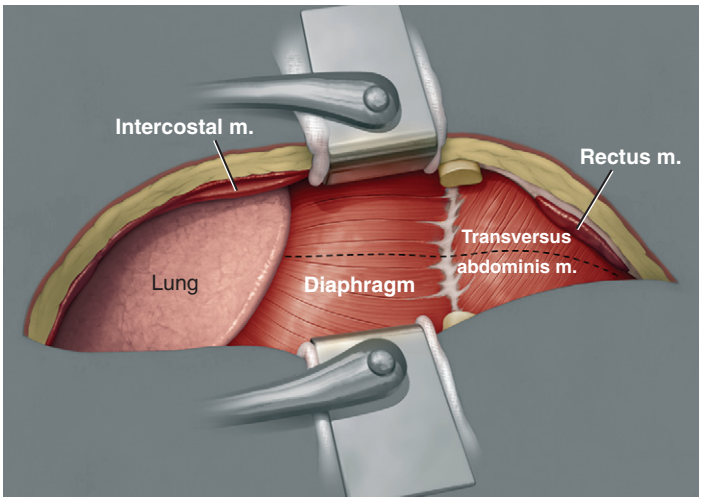


Figure 58–15. Thoracoabdominal approach. The Finochietto retractor is placed to expose the anatomy. The lung visible in this view is packed away with laparotomy sponges.

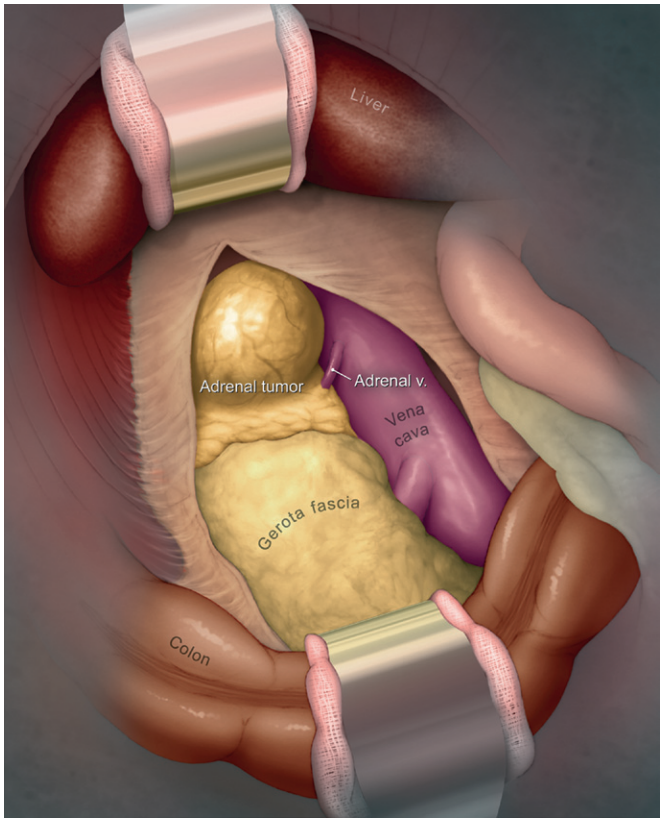


Figure 58–16. Thoracoabdominal approach. Exposure of the adrenal.

self-retaining retractor is placed to expose the surgical area. The rest of the dissection is similar to that of the previously described techniques. The relationship of the thoracoabdominal incision to the adrenal gland is illustrated in Figures 58–16 and 58–17.

Closure of the incision requires closure of the diaphragm and reapproximation of the ribs. The diaphragm is closed with interrupted figure-of-eight stitches with nonabsorbable suture. A chest tube is placed before the anterior thorax is closed. The anterior thorax is closed with several interrupted No. 0 chromic sutures on blunt-tip liver needles around the superior border of the eighth

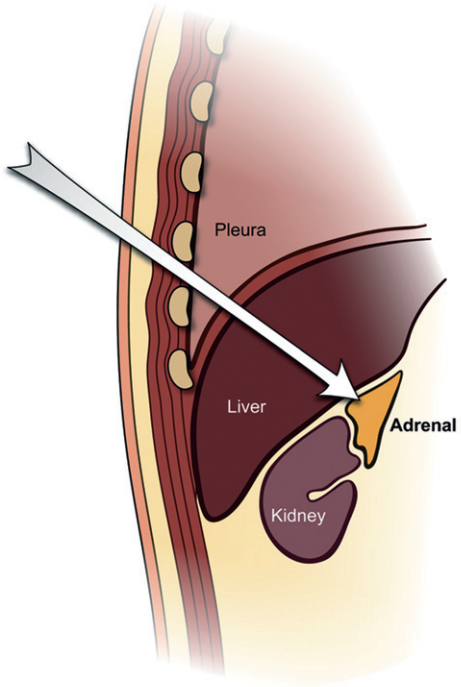


Figure 58–17. Demonstration of the route of surgical dissection during thoracoabdominal incision.

rib and inferior border of the ninth rib. A No. 0 Prolene suture on a tapered needle is placed through the cut costal cartilage to bring the costal margin together. The chest tube is placed to a water seal and suction.

LAPAROSCOPIC ADRENALECTOMY

Transperitoneal Approach

Transperitoneal laparoscopic adrenalectomy can be performed through either an anterior supine approach or a lateral approach. In general, the anterior supine approach allows bilateral adrenalectomy without having to reposition the patient. The lateral position is advantageous because greater workspace is available secondary to gravity-assisted retraction of the bowel. The flank approach is described in detail.

Left Side. The patient is positioned in a modified flank position. The patient is angled back about 30 to 45 degrees. After insufflation of the abdomen, four trocars are placed along the left costal margin (Fig. 58–18). The line of Toldt is incised and the left colon medially mobilized (Fig. 58–19). The lienorenal and splenocolic ligaments are divided. The lateral and superior attachments of the spleen can be divided to facilitate medial mobilization of the spleen if necessary. In many cases, the spleen may fall away sufficiently by gravity without having to extend the dissection above the spleen. The renal vein and adrenal vein are dissected free (Fig. 58–20). The left adrenal vein is dissected out, ligated, and divided (Fig. 58–21). Surgical clips are used to control the adrenal vein. It is advisable to leave two clips on the body side of the vein and one on the specimen side. Adrenal arterial supply is divided as the adrenal is dissected free (Fig. 58–22). The harmonic scalpel is effective for performing this dissection. The remaining attachments to the kidney are divided bluntly and with the hook cautery (Fig. 58–23). The specimen is placed in an endoscopic sac and extracted (Fig. 58–24).

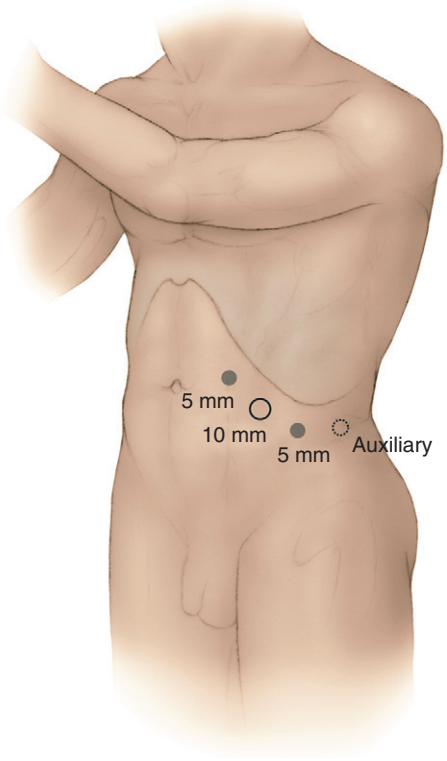


Figure 58–18. Four-trocar configuration for left transperitoneal laparoscopic adrenalectomy.

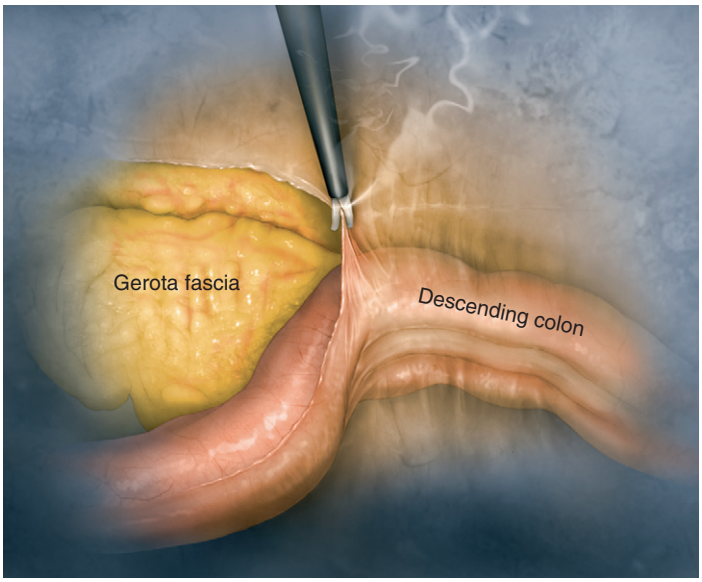


Figure 58–19. Transperitoneal laparoscopic adrenalectomy. Incision of the line of Toldt and medial dissection of the left colon with cautery endoscopic scissors.

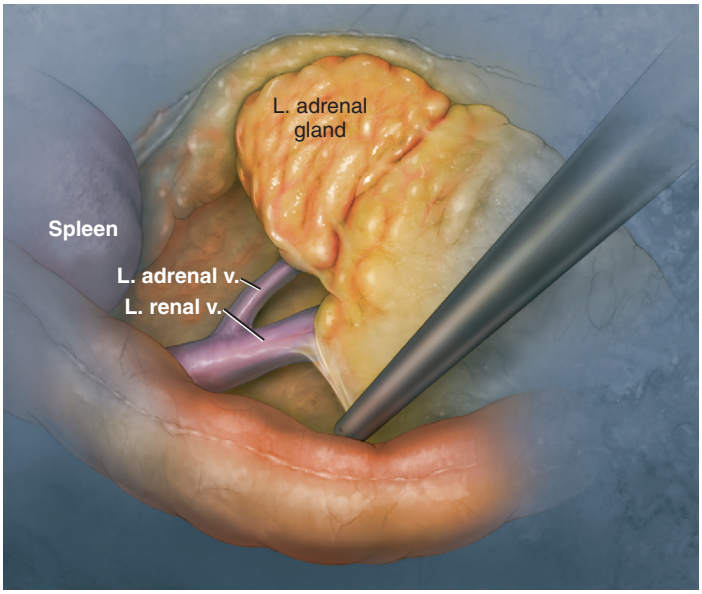


Figure 58–20. Transperitoneal laparoscopic adrenalectomy. Exposure and dissection of the renal vein and left adrenal vein.

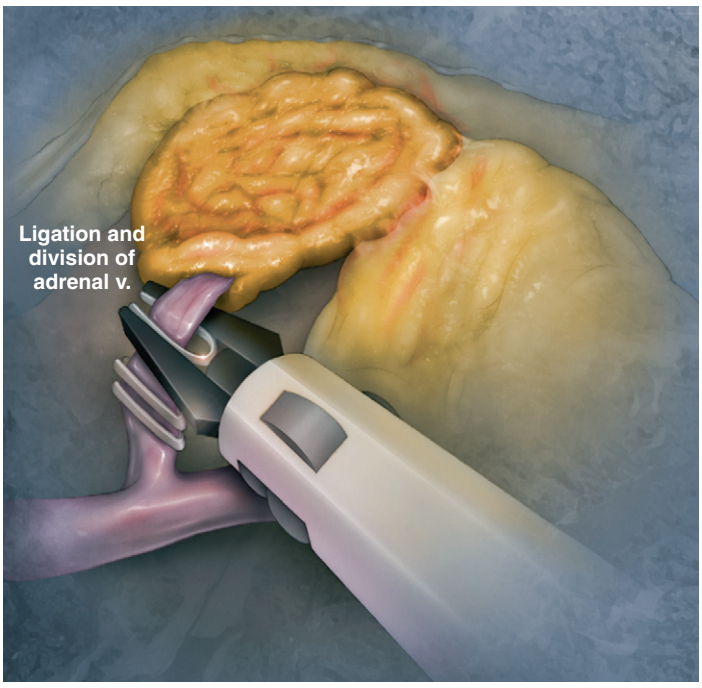


Figure 58–21. Transperitoneal laparoscopic adrenalectomy. Ligation and division of left adrenal vein.

The operative field is examined with the insufflation pressure turned down to 5 mm Hg. If it is hemostatic, the trocar sites are closed with absorbable suture. A drain usually does not need to be placed.

On the right side, the approach is similar. However, the duodenum must be dissected away by the Kocher maneuver. As on the left side, a four-trocar configuration is used (Fig. 58–25). The most medial trocar is used for liver retraction. A 2-mm trocar can be used with a 2-mm locking grasper to fashion a self-retaining retractor of the liver (Fig. 58–26).

Retroperitoneal Approach

Left Side. The patient is placed in flank position with the left side up. The patient is placed in flexion, and the kidney rest is deployed to accentuate the left flank. A 12-mm incision is made near the tip of the 12th rib under the 11th rib. The underlying muscle and fasciae are divided with cautery until the lumbodorsal fascia is visible or palpable. The lumbodorsal fascia is divided with cautery or Metzenbaum scissors, and blunt finger dissection is

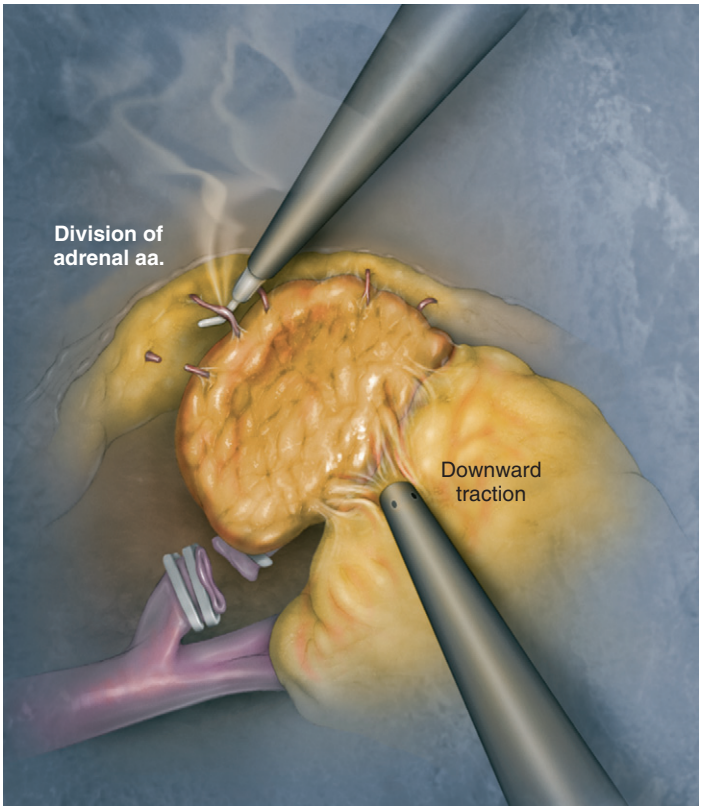


Figure 58–22. Transperitoneal laparoscopic adrenalectomy. Division of adrenal arterial supply and superomedial dissection with downward traction on the kidney.



Figure 58–24. Transperitoneal laparoscopic adrenalectomy. Placement of specimen in endoscopic extraction sac.

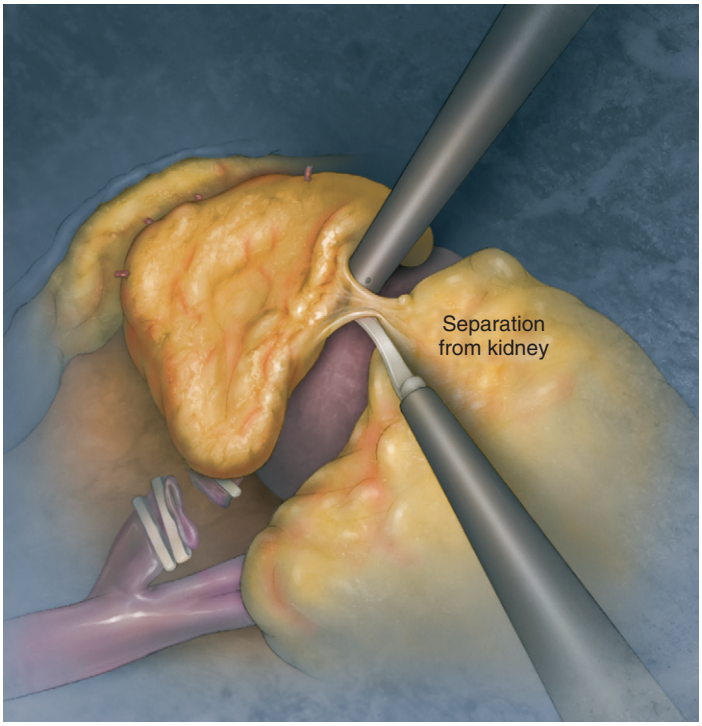


Figure 58–23. Transperitoneal laparoscopic adrenalectomy. The adrenal gland is mobilized off the medial aspect of the kidney.

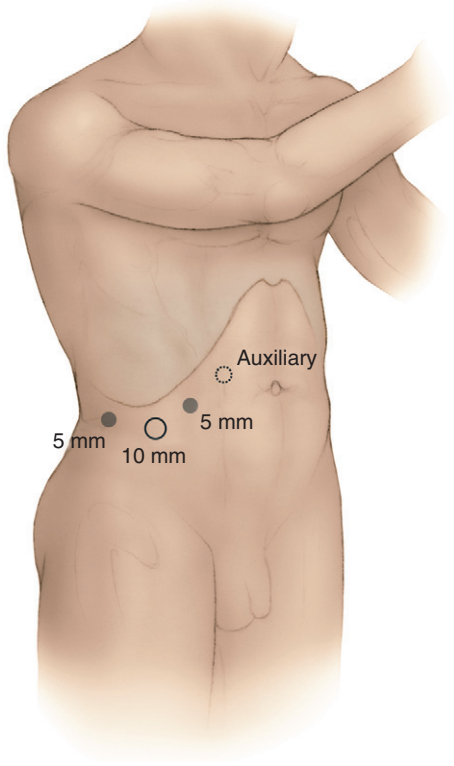


Figure 58–25. Four-trocar configuration for right transperitoneal laparoscopic adrenalectomy. Auxiliary site can be used for liver retraction.

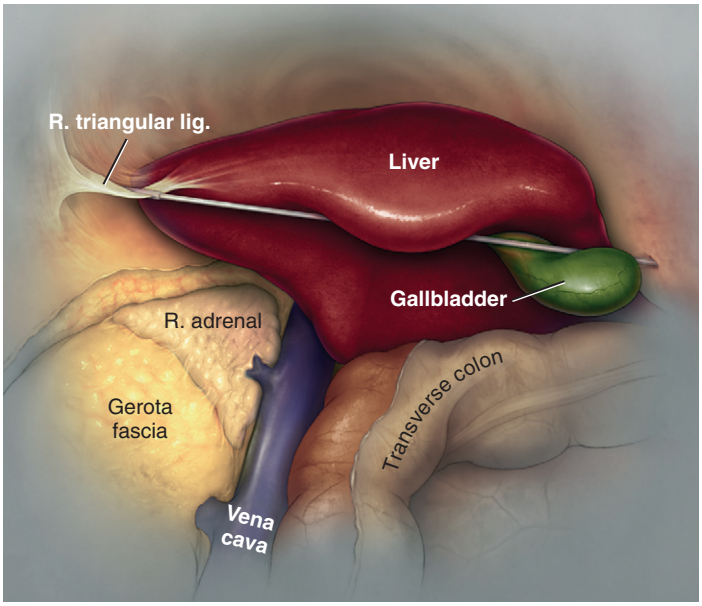


Figure 58–26. A 2-mm trocar and locking grasping forceps can be used instead of a larger-caliber fan retractor to act as a self-retaining liver retractor. It is important that the trocar be placed just below the xiphoid process to ensure adequate retraction.

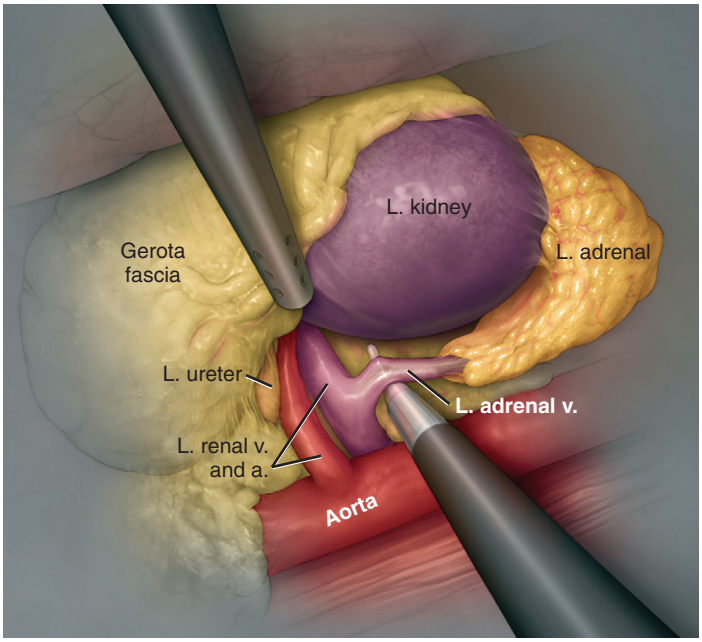


Figure 58–28. Retroperitoneal laparoscopic adrenalectomy. Dissection of the left adrenal vein by the retroperitoneal approach.

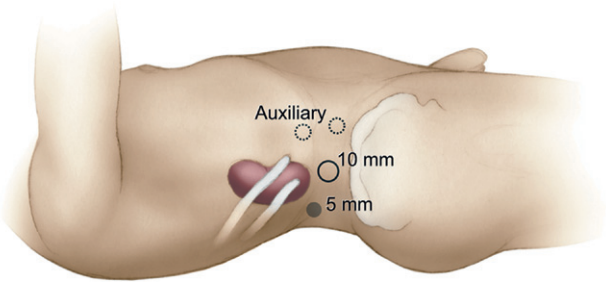


Figure 58–27. Trocar placement for retroperitoneal laparoscopy. The dotted circles represent alternative sites for placement of a third port.

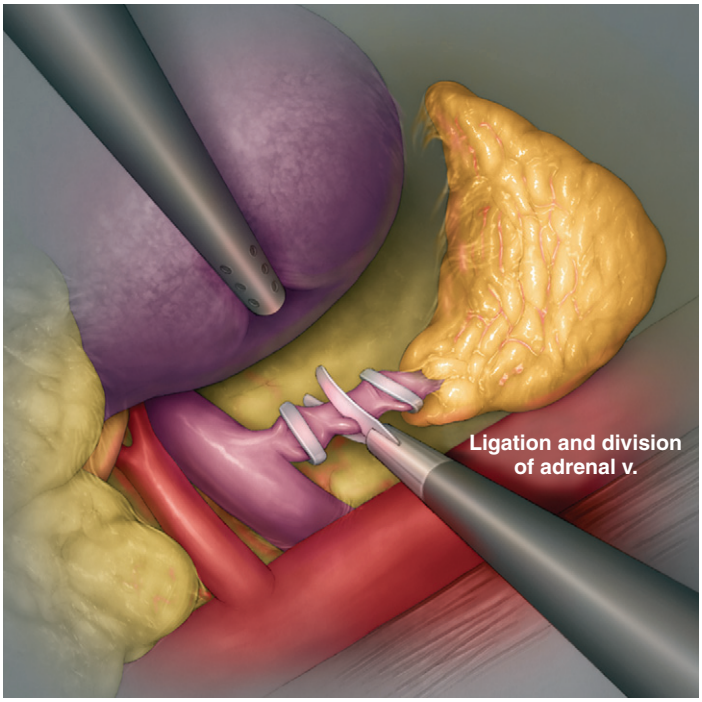


Figure 58–29. Retroperitoneal laparoscopic adrenalectomy. Ligation and division of left adrenal vein. The kidney is dissected away from the adrenal gland.

used to develop a plane between the posterior Gerota fascia and the psoas fascia. With this plane developed, a retroperitoneal dissection balloon is placed and inflated. Typically, a laparoscope can be placed down the hollow shaft of the dissection balloon to visually confirm the accurate anatomic placement of the balloon between the kidney and psoas. A balloon-tip trocar is placed into the defect and secured in position. After insufflation of the retroperitoneum, a 5- or 10-mm trocar is placed at the angle of the paraspinal muscle and the origin of the 12th rib. A 5- or 10-mm trocar is placed about two fingerbreadths above the iliac crest near the anterior superior iliac spine (Fig. 58–27).

The renal hilum is usually located fairly rapidly in the retroperitoneal approach by direct visualization of arterial pulsations. The left adrenal vein can be isolated from its origin on the left renal vein (Fig. 58–28). The left adrenal vein is dissected out and ligated with surgical clips and divided (Fig. 58–29). The left adrenal gland is then dissected out as described previously; small arterial branches can be clipped or divided hemostatically with a harmonic scalpel. The specimen is placed in a specimen bag and extracted. The trocar sites are closed with absorbable suture after hemostasis is ensured. The right adrenalectomy is performed in similar fashion; anatomic relations of this approach are illustrated in Fig. 58–30.

HAND-ASSISTED SURGERY

The advantage of hand assistance stems from the addition of tactile sensation. This may result in faster dissection and added security in the event of bleeding complications. Also, the learning curve may be shorter with hand assistance. Only case reports exist regarding hand-assisted laparoscopic adrenalectomy. This may be

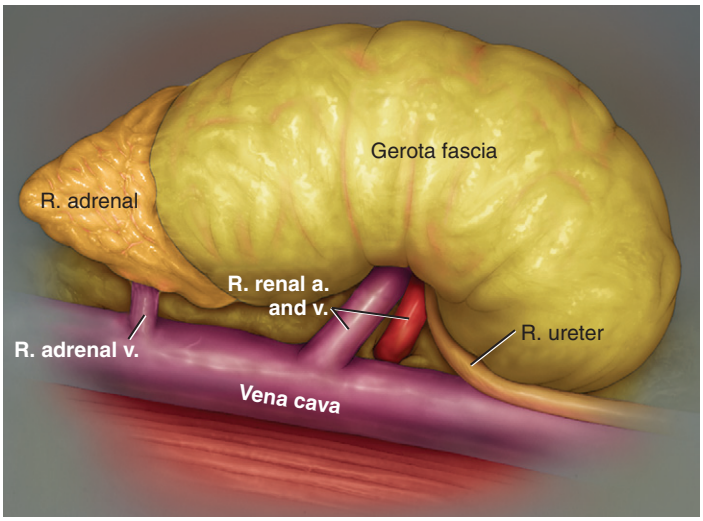


Figure 58–30. Anatomic view of right adrenal gland from laparoscopic retroperitoneal approach.

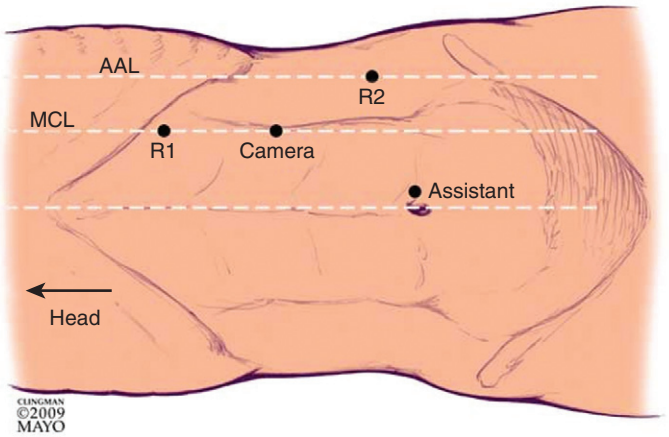


Figure 58–31. Left robotic adrenalectomy trocar placement. A total of four ports are placed. One 12-mm camera port, one 12-mm assistant port, and the two 8-mm robotic arm ports. AAL, anterior axillary line; MCL, mid clavicular line. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

especially advantageous for large adrenal tumors that may require an incision for extraction. Bilateral tumors may also be treated in this fashion.

ROBOTIC SURGERY

There is growing interest in applying robotic technology to adrenal surgery. Currently, the da Vinci Surgical Robotic System (Intuitive Surgical, Sunnyvale, CA) is the only commercially available product to perform these procedures. Desai and colleagues reported the first case of robotic adrenalectomy in 2002. Since the initial case report, there have been many larger experiences that show that robotic adrenalectomy is safe and effective.

It remains to be seen if robotic adrenalectomy is superior to laparoscopy. The advantages of robotics should be the superior three-dimension visualization and hand-like dexterity of the robotic arms to perform the microdissection of the plane between the adrenal and the great vessels. However, these technical advantages do not appear to translate to any tangible benefit in operative outcomes. In a quality-of-life study comparing laparoscopic to robotic adrenalectomy, Brunaud and colleagues (2004) demonstrated no major difference in all parameters assessed. Likewise, in a prospective randomized study comparing laparoscopic and robotic adrenalectomy, Morino and colleagues (2004) showed that laparoscopic surgery was actually superior to robotic adrenalectomy in operative time, morbidity, and cost. Winter and colleagues (2006) reported on 30 consecutive adrenalectomies and showed that the cost was higher for robotic surgery ($12,977 vs. $11,599), but this was not statistically significant.

Robotic Adrenalectomy Technique

This transperitoneal technique is a variant on the laparoscopic approach. The patient is placed in flank position. After the patient is prepared and draped, pneumoperitoneum is established in the same manner as laparoscopic surgery. Based on the side treated, a total of 4 to 5 trocars are placed as outlined by diagrams. The remainder of the dissection and excision of the adrenal gland are similar to the laparoscopic surgery. To facilitate access to the upper areas of the retroperitoneum, the robot is docked at an angle at the head of the table as outlined in diagram. The third robotic

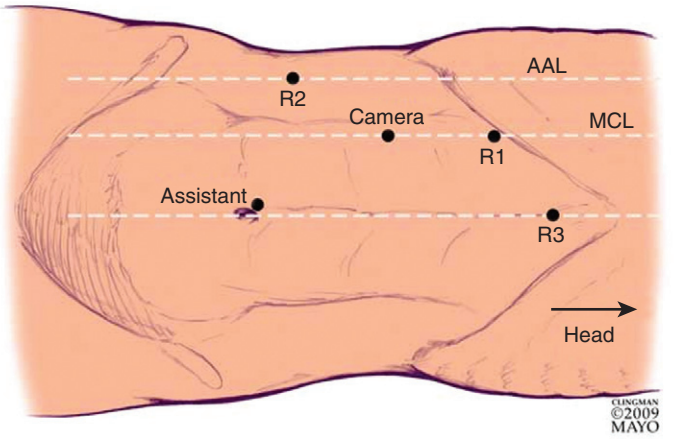


Figure 58–32. Right robotic adrenalectomy trocar placement. A total of five ports are placed. One 12-mm camera port, one 12-mm assistant port, and two 8-mm robotic arm ports. To retract the liver, a third robotic arm is available, or a 3- or 5-mm trocar may be placed with a retraction device such as a locking Babcock clamp or fan retractor. AAL, anterior axillary line; MCL, mid clavicular line. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

arm or a locking forceps can be used to elevate and retract the liver during right adrenalectomy (Figs. 58–31 to 58–33).

INTRAOPERATIVE ULTRASONOGRAPHY

It can be difficult, at times, to locate the adrenal gland, especially if the patient is obese and there is a lot of intra-abdominal fat. Without tactile feedback, unless the lesion is grossly evident, it can be difficult to localize the adrenal gland during surgery. Ultrasonography of the adrenal gland is extremely difficult as an extracorporeal technique. The ability to directly apply the ultrasound probe to the operative area under laparoscopic guidance facilitates identification of the adrenal gland. Furthermore, **intraoperative ultrasonography can help identify the adrenal vein,** especially on the left side.

Brunt and colleagues (1999) used intraoperative ultrasonography in 28 adrenalectomies and had 100% success in identifying

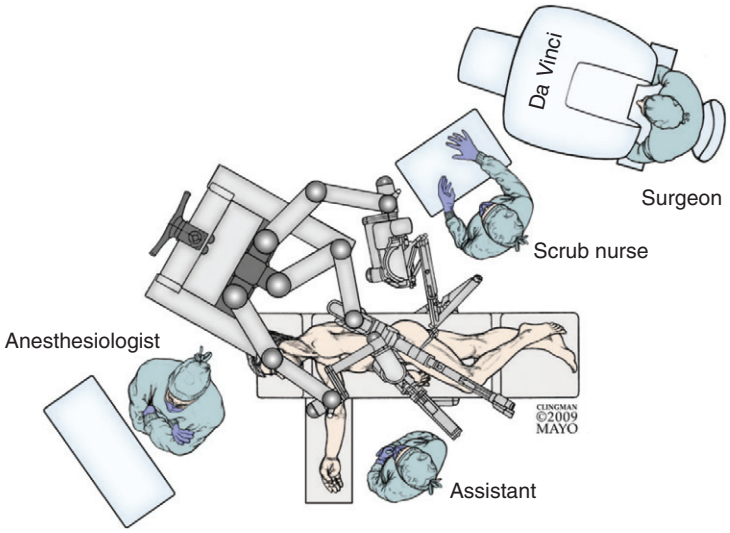


Figure 58–33. Surgical room set-up for left robotic adrenalectomy. The slave unit of the robot is brought in over patient's left shoulder as indicated in the diagram. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

the adrenal gland. Lucas and colleagues (1999) had similar success with 42 adrenalectomies.

Intraoperative ultrasonography is especially helpful in laparoscopic partial adrenalectomy. It can delineate the tumor within the adrenal gland to facilitate adrenal-sparing surgery. Pautler and colleagues (2002) successfully performed laparoscopic partial adrenalectomy on seven patients with ultrasound assistance. There were no complications and no open conversions.

POSTOPERATIVE MANAGEMENT

Electrolyte values are checked the night of surgery and each morning; this is especially important for patients with Conn or Cushing syndrome. The urinary catheter can usually be removed on the first postoperative day when the patient is ambulatory. If a nasogastric tube was placed for open surgery, it can be removed with return of bowel sounds. Diet resumption is usually started on the first postoperative day for laparoscopic surgery, and when bowel sounds resume for open surgery.

Blood pressure is carefully evaluated for hypertension or hypotension. Unexplained hypotension, confusion, lethargy, nausea, vomiting, or fever could represent addisonian crisis (adrenal insufficiency). **Adrenal insufficiency is most commonly seen after surgery for Cushing syndrome, because of contralateral cortisol suppression.** Stress-dose steroid administration may be necessary. Corticosteroid replacement and mineralocorticoid (fludrocortisone) may be required for the long term. Hospital stay may be prolonged by the necessary adjustment of antihypertensive medications and steroids.

OUTPATIENT AND SHORT-STAY LAPAROSCOPIC ADRENALECTOMY

In select patients who underwent uneventful surgery, same-day or less than 24-hour hospital discharge has been attempted. Gill and colleagues (2000) were able to discharge 9 of 27 patients who underwent laparoscopic adrenalectomies within 8 hours of surgery. One patient was readmitted for abscess formation. Edwin and colleagues (2001) described 13 patients with aldosteronoma who underwent laparoscopic adrenalectomy. All were discharged within 3 to 6 hours of surgery. None was readmitted. The satisfaction of patients was high for all but one patient who had poorly controlled pain after discharge. Rayan and Hodin (2000) performed 19 laparoscopic adrenalectomies and were able to discharge 47% of patients within 24 hours.

OUTCOMES

Retrospective studies demonstrate a clear advantage to laparoscopic surgery over open surgery in terms of analgesia, hospital stay, blood loss, and complication rate. The laparoscopic surgeries typically had longer operative times than the open surgery did. There are no randomized prospective studies comparing laparoscopic with open adrenalectomy. In a rare nonrandomized prospective study, Prager and colleagues (2004) assigned patients to laparoscopic or open surgery on the basis of a cutoff of 6 cm; lesions smaller than 6 cm were removed laparoscopically. As one would expect, operative times, complication rate, and blood loss were higher in the open surgery group. It is difficult to compare these two groups fairly because the patients assigned to open surgery had larger tumors and a higher incidence of malignant disease (1.9% vs. 29.1%) than the laparoscopic cohort did.

Comparison of retroperitoneal with transperitoneal laparoscopy tended to favor the retroperitoneal approach. Bonjer and colleagues (1997) showed an advantage in operative time (75 minutes vs. 150 minutes; $P = .005$), blood loss (20 mL vs. 150 mL; $P = .01$), postoperative analgesia (6 mg vs. 20 mg of morphine sulfate; $P = .003$), and hospital stay (4 vs. 6 days; $P = .027$) for retroperitoneal over transperitoneal approach. Suzuki and colleagues (2001) also found less blood loss, shorter convalescence, and faster resumption of oral intake with retroperitoneal surgery than with anterior and lateral transperitoneal procedures. Interestingly, Bonjer and colleagues initially attempted to perform a prospective randomized study, but patients expressed strong preference for retroperitoneal surgery.

Is laparoscopic adrenalectomy too costly? In the current era of soaring medical costs, the cost effectiveness of laparoscopic surgery must be proven to justify its use. Initially, the cost of laparoscopic adrenalectomy was much higher than the cost of open surgery. Thompson and colleagues (1997) noted that hospital charges for laparoscopic adrenalectomy were $1000 higher than for open adrenalectomy. With increased use of disposables and with growing surgical experience, the costs are becoming manageable. Hobart and colleagues (1999) have shown that with 2-mm instrumentation, laparoscopic adrenalectomy resulted in 17.9% less cost than open adrenalectomy. The laparoscopic adrenalectomy had an 18.1% increased intraoperative cost but a 63.4% less postoperative cost. In Spain, Ortega and colleagues (2002) calculated that laparoscopic adrenalectomy was not more expensive in terms of direct surgical cost (€6306 vs. €7581; P = NS). However, hospital stay was significantly shorter and cheaper (€742 vs. €1191; $P = .004$). Interestingly, the most expensive part of the entire therapeutic process was the preoperative hospitalization for diagnostic workup. In the United States, most diagnostic tests are carried out on an ambulatory outpatient basis, and these costs would be considerably less. Aside from the direct cost of surgery and hospitalization, laparoscopic adrenalectomy is often less expensive than long-term medical therapy for certain adrenal disorders. In Canada, aldosteronoma management with surgery represents a savings of C$31,132 over the lifetime of each patient (Sywak and Pasieka, 2002).

Table 58–4.

Operative Complications of Adrenal Surgery

Hemorrhage	Adjacent Organ Injury
Inferior vena cava	Pneumothorax
Adrenal vein	Pancreas
Lumbar vein	Liver
Hepatic vein	Spleen
Vascular	Stomach
Ligation of renal artery branch	Colon
Ligation of mesenteric artery	Kidney
Inferior vena cava involvement	

From Vaughn ED. Complications of adrenal surgery. In: Taneja SS, Smith RB, Ehrlich RM, editors. Complications of urologic surgery: prevention and management. 3rd ed. Philadelphia: WB Saunders; 2001. p. 366.

COMPLICATIONS

Operative Complications (Table 58–4)

As expected, adrenal surgery, both open and laparoscopic, can involve injury to adjacent organs. Hemorrhage is a potentially catastrophic complication of adrenal surgery. Bleeding can result from injury to the adrenal vein, inferior vena cava, lumbar vein, or renal vein. These injuries are managed initially by application of direct pressure to the injury. Grasping a small injury with an Allis clamp and closing it with suture or by placement of a vascular clamp for a larger vena cava injury may be curative. For laparoscopic cases, the management is more of a problem. In the early days of laparoscopic adrenalectomy, open conversion was the typical consequence of vascular injury. However, with increasing experience with laparoscopic suturing techniques, these injuries are often managed as in the open surgery.

Nonhemorrhagic vascular injuries can occur as well. An upper pole renal artery branch can be divided inadvertently during dissection. If the branch is small and supplies a minimal portion of the kidney, it can be ignored. More substantial injuries may require a revascularization attempt. If the patient has a large tumor, there can be distortion of the regional anatomy, and inadvertent ligation of the superior mesenteric vein is possible. This is a potentially fatal injury, and one must have a high index of suspicion to restore vascular supply to the bowel as soon as possible.

The adjacent organs can be injured during dissection of the adrenal gland. The liver can be injured during right adrenalectomy. Liver lacerations can be treated with argon beam coagulation and application of hemostatic agents such as methyl cellulose. More serious injuries may require hemostatic sutures with a blunt-tip liver needle. The spleen can be injured during left adrenalectomy. As with hepatic injury, argon beam coagulation and hemostatic agents can be used to control bleeding. If this is not sufficient, splenorrhaphy can be attempted. If these measures are unsuccessful, splenectomy may be necessary. It is important to remember to give pneumonia vaccination to these patients during postoperative care.

The pancreas can be injured during surgery on either the right or left adrenal gland. If an injury to the tail of the pancreas occurs, distal pancreatectomy may be performed. If the injury is to the pancreatic duct, this may be repaired and surgical drains left. If there is uncertainty of pancreatic injury, leaving closed-suction surgical drains behind is advisable. Postoperative drainage high in triglycerides is indicative of pancreas injury. Management consists of bowel rest with parenteral nutrition. The administration of octreotide can decrease pancreatic secretions while the pancreas heals.

The proximity of the kidney to the adrenal gland can be a problem in cases of large adrenal cortical carcinomas. **It is imperative for all patients undergoing surgery for large adrenal masses to be counseled about the possibility of concurrent en bloc nephrectomy.**

During 11th-rib flank adrenalectomy, it is not unusual for pleural injury to be incurred. These injuries can be repaired with a purse-string chromic suture and a red rubber catheter to water seal. Expulsion of air from the pleura followed by cinching of the purse-string usually repairs the defect. Postoperative chest radiography should be routinely performed after flank or thoracoabdominal nephrectomy. If a significant pneumothorax is present, a chest tube should be placed.

With pheochromocytoma, blood pressure fluctuations can be life-threatening. The anesthesiologist typically manages high blood pressure with short-acting β blockade, α blockers, or nitroprusside. Arrhythmias are usually treated with β blockers. When the adrenal vein is ligated, there can be a sudden drop in blood pressure. It is important to inform the anesthesiologist just before the adrenal vein is ligated to avoid any nasty surprises. Fluid repletion and pressors may be necessary to bring the pressure to normal.

Postoperative Complications

Table 58–5 summarizes the postoperative complications that can occur. Disease-specific complications must be accounted for to ensure an uneventful postoperative course.

Patients with primary hyperaldosteronism require close monitoring of potassium levels because they can be either hypokalemic or hyperkalemic. Hyperkalemia, secondary to contralateral adrenal zona glomerulosa suppression, should be managed medically with the typical hyperkalemia regimens. Hypokalemia can persist in the immediate period after adrenalectomy, and this should be corrected with potassium repletion. In patients who had only one adrenal gland to begin with, mineralocorticoid replacement with fludrocortisone is essential.

Patients with Cushing syndrome will require steroid replacement after surgery, until the contralateral gland recovers function. Measurements of plasma cortisol can be useful in determining when steroid replacement can be tapered. Furthermore, these patients have increased risk of fracture secondary to osteoporosis, hyperglycemia, and poor wound healing.

Patients with pheochromocytoma may have hypotension secondary to α blockade. These patients need to be monitored closely until α blockade wears off, often in the intensive care unit. If α blockade was not used preoperatively, as it is done at the Cleveland Clinic, intensive care stay is unnecessary in most cases.

Laparoscopy versus Open Adrenalectomy

Brunt (2002) compiled the complication statistics of 50 laparoscopic studies and 48 open studies to evaluate the impact of laparoscopy on adrenalectomy. To limit selection bias, open surgical series with adrenal cortical carcinoma cases were excluded. Laparoscopy resulted in a lower complication rate (10.9% vs. 25.2%; $P \leq .0001$) than did open adrenalectomy. Specifically, **pulmonary, wound, and infectious complications were statistically less common with laparoscopic surgery.** There were also fewer injuries to adjacent organs (0.7% vs. 2.4%; $P = .05$). Splenic injuries decreased dramatically in incidence (laparoscopic,

Table 58–5.
Postoperative Complications of Adrenal Surgery

Primary Aldosteronism
Hypokalemia: secondary to continued potassium loss immediately postoperative
Hyperkalemia: secondary to failure of contralateral adrenal to secrete aldosterone
Cushing Syndrome
Inadequate steroid replacement leading to hypocorticoidism
Fracture secondary to osteoporosis
Hyperglycemia
Poor wound healing
Increased risk of infections
Pheochromocytoma
Hypotension secondary to α-adrenergic blockade after tumor removal
Generic Complications
Hemorrhage
Inferior vena cava
Adrenal arteries
Pneumothorax
Pancreatitis
Pneumonia
Hiccups

From Vaughn ED. Complications of adrenal surgery. In: Taneja SS, Smith RB, Ehrlich RM, editors. Complications of urologic surgery: prevention and management. 3rd ed. Philadelphia: WB Saunders; 2001. p. 368.

0.2%; open, 2.0%). A number of factors account for this decrease, including division of the splenocolic and lienorenal ligaments under magnification and the assistance of gravity in retracting the spleen rather than manual retraction. With retroperitoneal surgery, the spleen would not even be in the surgical field to be injured. A decrease in cardiac complications was observed, but some of the improvement in complication rate was thought to be attributable to improvements in perioperative management of vasoactive tumors. The most common complication of laparoscopic adrenalectomy is bleeding (4.7%). Bleeding is also the most common reason for open conversion of laparoscopic adrenalectomy (30%). Bleeding results from vascular injury to the adrenal vein, injury to the vena cava, direct injury to the adrenal gland, renal capsular tear, or surgical clip dislocation.

SPECIAL CONSIDERATIONS

Pediatric

There are relatively few cases of laparoscopic adrenalectomy for pediatric patients. The small body habitus of the patients makes surgery more technically challenging. Neuroblastoma is the most common adrenal tumor in this age group, and this tumor tends to be large and infiltrative, complicating laparoscopic extraction.

Nevertheless, laparoscopic surgery has been successfully performed on pediatric patients. The first case was performed on a small asymptomatic neuroblastoma identified by mass screening of children in Japan (Yamamoto et al, 1996). Comparing open with laparoscopic biopsies and excisions, Iwanaka and colleagues (2001) showed that laparoscopy was associated with shorter hospitalization and rapid resumption of diet. Bilateral laparoscopic adrenalectomy can be performed safely as well (Schier et al, 1998).

In financial terms, laparoscopic adrenalectomy is cost saving when postoperative stay is accounted for (Stanford et al, 2002). Even though laparoscopic adrenalectomy was more expensive as a procedure ($12,941 vs. $4,714; $P < .001$), the overall cost difference between the two procedures was statistically insignificant.

Pregnancy

The pregnant patient can present with an endocrinologically active adrenal tumor. Pheochromocytoma must be distinguished from preeclampsia or pregnancy-induced hypertension, a more medically accurate term. The main distinguishing factors are the absence of proteinuria in pheochromocytoma and the fact that pregnancy-induced hypertension tends to occur in the third trimester. When pheochromocytoma is diagnosed late in pregnancy, the pregnancy can be taken to term with medical management and the child delivered by cesarean section. If pheochromocytoma is diagnosed in the first or second trimester, the risk of surgery must be weighed against the risk of the pheochromocytoma to the pregnancy (Martinez Brocca et al, 2001).

Laparoscopic adrenalectomy can be successfully performed on a pregnant patient. Several reports exist of successful surgery. Maneuvers to minimize risk include keeping insufflation pressure below 15 mm Hg, using open Hasson technique to gain access, and monitoring fetal heart rate and maternal arterial blood gases.

Partial Adrenalectomy

The main indications for partial adrenalectomy are solitary adrenal gland, bilateral disease, and patients with familial syndromes. Pheochromocytoma has been treated with partial adrenalectomy, especially in patients with von Hippel-Lindau syndrome (Al-Sobhi et al, 2002; Baghai et al, 2002), familial pheochromocytoma, or multiple endocrine neoplasia type IIA (Sackett and Bambach, 2003; Brauckhoff et al, 2004). Aldosteronomas have been removed laparoscopically (Sasagawa et al, 2000; Jeschke et al, 2003).

Partial adrenalectomy is usually performed with an endoscopic stapler. Dividing the adrenal vein does not affect viability of the adrenal gland, so it can be taken with the mass. However, Sasagawa and colleagues (2000) described a technique using the ultrasonic scalpel. Intraoperative ultrasonography can help identify the mass to facilitate surgery (Pautler et al, 2002).

NONSURGICAL ALTERNATIVES

Radiofrequency Ablation

Radiofrequency ablation has been used successfully to treat adrenal lesions, primarily adrenal metastases (Rohde et al, 2003) or metastases of adrenal cortical carcinoma (Abraham et al, 2003; Wood et al, 2003) and malignant pheochromocytoma. In the largest series to date, Mayo-Smith and Dupuy (2004) described performing 13 procedures on 12 patients without incident. These procedures can be safely and comfortably employed on an outpatient or overnight-stay basis. However, life-threatening hypertension has been reported in one case of adrenal ablation (Chini et al, 2004). The lesion may have been a pheochromocytoma. Unfortunately, no pathologic examination or preoperative workup for vasoactive adrenal masses was performed. Presumably, **catecholamine release can be caused by thermal injury to the adrenal in the absence of pheochromocytoma.** Onik and colleagues (2003) described their experience with two cases of hypertensive crisis in patients undergoing hepatic radiofrequency ablation. Both cases involved radiofrequency ablation of the posterior right lobe of the liver, close to the right adrenal. In one

patient in whom catecholamine levels were measured, the values were 10-fold greater than the upper limit of normal.

Cryoablation

The clinical experience with cryoablation is fairly limited (Munver and Sosa, 2004). Canine experiments have confirmed that cryotherapy can be delivered to the adrenal gland effectively (Schulsinger et al, 1999). Furthermore, the ability to observe the ice ball under ultrasound examination in a live dynamic fashion allows it to be applied in a controlled, reproducible fashion.

Key Points

- Laparoscopic adrenalectomy is the current standard of care for adrenal lesions with the exception of invasive adrenocortical carcinoma or adrenocortical carcinoma with caval thrombus.
- Preoperative computed tomography can help distinguish invasive from noninvasive adrenocortical carcinoma.
- Percutaneous ablative technologies are an increasingly attractive alternative to surgery for small incidental masses.
- If you suspect pheochromocytoma, avoid percutaneous ablation because of the risk for catecholamine release.
- Open adrenal surgery is reserved for lesions not amenable to minimally invasive techniques (i.e., invasive, large carcinomas, or carcinoma with caval involvement).
- When operating on patients for large invasive adrenocortical carcinoma, be sure to obtain consent for possible en bloc resection of adjacent organs.

Acknowledgment

Special thanks to Dr. E. Darracott Vaughan for permission to use tables published in previous chapters on adrenal surgery.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter 59

Physiology and Pharmacology of the Renal Pelvis and Ureter

Robert M. Weiss, MD

Cellular Anatomy
Development of the Ureter
Electric Activity
Contractile Activity
Mechanical Properties
Role of the Nervous System in Ureteral Function
Urine Transport
Pathologic Processes Affecting Ureteral Function
Effect of Age on Ureteral Function
Effect of Pregnancy on Ureteral Function
Effect of Drugs on the Ureter

The function of the ureter is to transport urine from the kidney to the bladder. Under normal conditions, ureteral peristalsis originates with electric activity at pacemaker sites located in the proximal portion of the urinary collecting system (Bozler, 1942; Weiss et al, 1967; Constantinou, 1974; Gosling and Dixon, 1974; Tsuchida and Yamaguchi, 1977; Zhang and Lang, 1994; Lammers et al, 1996). The electric activity is then propagated distally and gives rise to the mechanical event of peristalsis, ureteral contraction, which propels the bolus of urine distally. Efficient propulsion of the urinary bolus depends on the ureter's ability to completely coapt its walls (Woodburne and Lapides, 1972). Urine passes into the bladder through the ureterovesical junction (UVJ), which, under normal conditions, permits urine to pass from the ureter into the bladder but not from the bladder into the ureter.

CELLULAR ANATOMY

The primary functional anatomic unit of the ureter is the ureteral smooth muscle cell. The cell is extremely small, approximately 250 to 400 μm in length and 5 to 7 μm in diameter. The **nucleus,** which is separated from the remainder of the cell by a nuclear membrane, is ellipsoidal and **contains a darkly staining body, the nucleolus, and the genetic material of the cell. Surrounding the nucleus is the cytoplasm or sarcoplasm, which contains the structures involved in cell function.** Frequently, in conjunction with the nucleus, **mitochondria** in the cytoplasm **perform many of the nutritive functions of the cell. Endoplasmic or sarcoplasmic reticulum dispersed in the cytoplasm serve as Ca^{2+} storage sites.**

Dispersed in the sarcoplasm are the **contractile proteins, actin, and myosin**. Depending on the local calcium ion (Ca^{2+}) concentration, they interact to produce contraction or relaxation. **Any process that leads to a significant increase in the Ca^{2+} concentration in the region of the contractile proteins results in contraction; conversely, any process that leads to a significant decrease in the Ca^{2+} concentration in the region of the contractile proteins results in relaxation.** Actin is dispersed throughout the sarcoplasm in hexagonal clumps and is interspersed among the less numerous clumps of more deeply staining myosin. Dark bands along the cell surface are referred to as *attachment plaques*. Along with dense bodies dispersed in the cytoplasm, they serve as attachment devices for the actin.

Around the periphery of the cell are numerous cavitary structures, some of which open to the outside of the cell and are referred to as ***caveolae.*** These **caveolae contain a cytoskeletal protein, caveolin, and a variety of signal transduction molecules and receptors for growth factors and cytokines** (William and Lisanti, 2004). **A double-layer cell membrane surrounds the cell. The inner plasma membrane surrounds the entire cell, but the outer basement membrane is absent at areas of close cell-to-cell contact, referred to as intermediate junctions.**

DEVELOPMENT OF THE URETER

The ureter, a 25- to 30-cm tube extending from the renal pelvis to the bladder, arises as an outpouching from the mesonephric duct. This begins on embryonic day (E) 10.5 in mice and E28 in humans. Signals from the metanephric mesenchyme, stroma, and angioblasts induce the ureteral bud to arise from the mesonephric duct, invade the mesenchyme, and undergo branching. Formation of the ureteric bud and its subsequent branching is induced by glial cell line–derived neurotrophic factor (GDNF), derived from adjacent metanephrogenic mesenchyme (Pepicelli et al, 1997; Sainio et al, 1997; Shakya et al, 2005). GDNF signals through the c-RET receptor tyrosine kinase (Vega et al, 1996), which results in increased phosphatidylinositol-3-kinase (P13-kinase) activity and AKT/PKB phosphorylation (Tang et al, 2002). Expression of *GDNF* or c-*RET* is activated by a transcription factor present in the metanephric mesenchyme, paired box 2 (from *PAX-2* gene) (Brophy

et al, 2001; Clarke et al, 2006). A number of other growth factors, including transforming growth factor–β (TGF-β); hepatocyte growth factor (HGF); fibroblast growth factors (FGF 1, 2, 7, and 10); transcription factors, from *Foxd1, Wnt11,* and *Spry1* genes; and matrix molecules, such as heparin sulphate proteoglycans, laminins, integrins, and matrix metalloproteinases (MMP9) are involved in stimulation or inhibition of growth and branching of the ureteral bud (Davies et al, 1995; Mendelsohn et al, 1999; Qiao et al, 1999; Pohl et al, 2000; Davies, 2001; Qiao et al, 2001; Takemura et al, 2002; Majumdar et al, 2003; Sakurai, 2003; Bush et al, 2004; Chen et al, 2004; Basson et al, 2006). Activin A, a member of the TGF-β family, is an endogenous inhibitor of ureteric bud outgrowth from the wolffian duct (Maeshima et al, 2006). Activin A inhibits GDNF-induced ureteral bud formation, and this is accompanied by inhibition of cell proliferation, reduced expression of *PAX-2*, and decreased phosphorylation of PI3-kinase and MAP kinase in the wolffian duct. The tip of each ureteral bud is capable of inducing adjacent metanephric mesenchyme to undergo a mesenchymal-to-epithelial transition (MET), with the formation of the nephron (Ekblom, 1989; Shah et al, 2004).

Programmed cell death, or apoptosis, is involved in branching of the ureteric bud and subsequent nephrogenesis. Inhibitors of caspases, which are involved in the apoptotic signaling pathway, inhibit ureteral bud branching (Araki et al, 1999). **During development, the ureteral lumen is obliterated, and then it recanalizes** (Russo-Gil et al, 1975; Alcaraz et al, 1991). **It appears that angiotensin, acting through the angiotensin II receptor, is involved in the recanalization process** (Yerkes et al, 1998) and in the inhibition of aberrant ureteral budding (Oshima et al, 2001). Knockout mice for the *ATR2* gene have congenital anomalies of the kidney and urinary tract, including duplicated collecting systems with a hydronephrotic upper pole moiety, multicystic dysplastic kidneys, megaureters, and ureteropelvic junction (UPJ) obstructions. Mutant mice lacking angiotensin II type I receptors fail to develop a renal pelvis and lack ureteral peristaltic activity (Miyazaki et al, 1998). Angiotensin II, acting through angiotensin II type I receptors, also is involved in ureteric bud cell branching, a process that depends on phosphorylation of the epidermal growth factor (EGF) receptor (Iosipiv and Schroeder, 2003; Yosypiv et al, 2006).

Calcineurin, a Ca^{2+}–dependent serine/threonine phosphatase also appears to be an essential signaling molecule in urinary tract development. Mutant mice in which calcineurin function is removed are noted to have reduced proliferation of smooth muscle and mesenchymal cells in the developing urinary tract, with abnormal development of the renal pelvis and ureter with resultant defective pyeloureteral peristalsis (Chang et al, 2004).

ELECTRIC ACTIVITY

The electric properties of all excitable tissues depend on the distribution of ions on both the inside and the outside of the cell membrane and on the relative permeability of the cell membrane to these ions (Hodgkin, 1958). The ionic basis for electric activity in ureteral smooth muscle has not been fully described; however, many of its properties resemble those in other excitable tissues.

Resting Potential

When a ureteral muscle cell is in a nonexcited or resting state, the electric potential difference across the cell membrane, transmembrane potential, is referred to as the resting membrane potential (RMP). The RMP is determined primarily by the distribution of potassium ions (K^+) across the cell membrane and by the permeability of the membrane to K^+ (Hendrickx et al, 1975). In the resting state, the K^+ concentration on the inside of the cell is greater than that on the outside of the cell, that is, $[K^+]_i > [K^+]_o$, and the membrane is preferentially permeable to K^+. Because of the tendency for the positively charged K^+ ions to diffuse from the inside of the cell, where they are more concentrated, to the outside of the cell, where they are less concentrated, an electric gradient is created, with the inside of the cell membrane being more negative than the outside (Fig. 59–1A). The electric gradient that is formed tends to oppose the further movement of K^+ outward across the cell membrane along its concentration gradient, and an equilibrium is reached.

If the membrane in the resting state were exclusively permeable to K^+, the measured RMP of the ureteral smooth muscle cell would

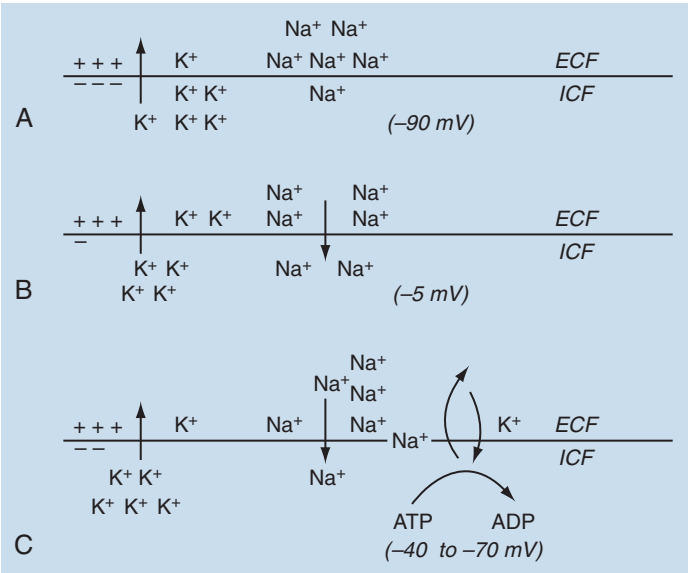


Figure 59–1. Ionic basis for the resting membrane potential (RMP) in smooth muscle. In the resting state, the K^+ concentration inside the cell is greater than the K^+ concentration outside the cell, and the Na^+ concentration outside the cell is greater than the Na^+ concentration inside the cell. **A,** Electrochemical changes that would occur if the membrane were solely permeable to potassium. Potassium would diffuse from the inside of the cell, where it is more concentrated, to the outside of the cell, where it is less concentrated. The outward movement of the positively charged K^+ ions would make the inside of the cell membrane negative with respect to the outside of the cell membrane. **B,** Electrochemical changes that would occur if the resting membrane were also permeable to sodium. An inward movement of Na^+ along its concentration gradient would make the inside of the cell membrane less negative with respect to the outside of the cell membrane than is depicted in **A**. **C,** Pump mechanism for extruding Na^+ from within the cell against concentration and electrochemical gradients. Inward movement of K^+ is coupled with outward movement of Na^+. This mechanism helps to maintain a steady state of ion distribution across the cell membrane and a stable RMP. ECF, extracellular fluid; ICF, intracellular fluid. (**A** to **C,** From Weiss RM. Ureteral function. Urology 1978;12:114.)

approximate –90 mV, the K^+ equilibrium potential, as predicted by the Nernst equation:

$$E_k = -RT/nF \ln[K^+]_i/[K^+]_o$$

where E_k is the potential difference attributable to the concentration difference of K^+ across the cell membrane, R is the molar gas constant, T is the absolute temperature, n is the number of moles of K^+, and F is the faraday constant (Nernst, 1908). However, in the ureter and in other smooth muscles, the RMP is considerably less than the K^+ equilibrium potential, with values of –33 to –70 mV, the inside of the cell being negative relative to the outside (Kuriyama et al, 1967). Studies from single isolated ureteral cells show spontaneous transient hyperpolarizations, with the RMP transiently becoming more negative (Imaizumi et al, 1989). This phenomenon appears to be due to spontaneous release of calcium ions (Ca^{2+}) from the sarcoplasmic reticulum, with activation of tetraethylammonium (TEA) and charbydotoxin-sensitive Ca^{2+}-dependent K^+ channels ($I_{K(Ca)}$). Although the low resting potential of ureteral cells may be explained in part by a relatively small resting K^+ conductance (Imaizumi et al, 1989), it also may be due to the contribution of other ions.

One such ion that could account for the relatively low RMP of the ureter and other smooth muscles is the sodium ion (Na^+) (Kuriyama, 1963). In the resting state, the Na^+ concentration on the outside of the cell membrane is greater than that on the inside, that is, $[Na^+]_o > [Na^+]_i$. If the resting membrane were somewhat permeable to Na^+, both the concentration and the electric gradient would support an inward movement of Na^+ across the cell membrane, with a resultant decrease in the electronegativity of the inner surface of the cell membrane (Fig. 59–1B).

If such an inward movement of Na^+ went unchecked, the RMP would be expected to decrease to a level lower than that actually observed, and the concentration gradient for Na^+ might become reversed. In order to maintain a steady-state ion distribution across the cell membrane with $[K^+]_o < [K^+]_i$ and $[Na^+]_o > [Na^+]_I$, and to prevent the transmembrane potential from becoming lower than the measured ureteral RMP, an active mechanism capable of extruding Na^+ from within the cell against a concentration and electrochemical gradient is required (Fig. 59–1C). Such an outward Na^+ pump that is coupled with an inward movement of K^+ derives its energy requirements from the dephosphorylation of ATP (Casteels, 1970). Na^+/Ca^{2+} exchange also may play a role in Na^+ extrusion, especially when the Na^+ pump is inhibited (Aickin, 1987; Aickin et al, 1987; Lamont et al, 1998).

The dynamic processes illustrated in Figure 59–1 enable the ureter in its resting state to maintain a relatively low RMP. In addition to the mechanisms described, the distribution of chloride ions (Cl^-) across the cell membrane and the relative permeability of the membrane to Cl^- may be factors in the maintenance of the RMP in the ureter and other smooth muscles (Kuriyama, 1963; Washizu, 1966).

Action Potential

The transmembrane potential of an inactive or resting ureteral cell remains stable until it is excited by an external stimulus—electric, mechanical (stretch), or chemical—or by conduction of electric activity (action potential) from an already excited adjacent cell. **When a ureteral cell is stimulated, depolarization occurs, with the inside of the cell membrane becoming less negative than it was before stimulation. If a sufficient area of the cell membrane is depolarized rapidly enough to reach a critical level of transmembrane potential, referred to as the threshold potential, a regenerative depolarization, or action potential, is initiated.**

The changes that occur are diagrammatically depicted in Figure 59–2. If a stimulus is very weak, as shown by *arrow a,* the transmembrane potential may remain unchanged. A slightly stronger, yet subthreshold, stimulus may result in an abortive displacement of the transmembrane potential, but not to such a degree that an action potential is generated *(arrow b).* If the stimulus is strong enough to decrease the transmembrane potential to the threshold potential, the cell becomes excited and develops an action potential *(arrow c).* The **action potential,** which **is the primary event in the conduction of the peristaltic impulse,** has the capability to act as the stimulus for excitation of adjacent quiescent cells **and, through a complicated chain of events, gives rise to the ureteral contraction.**

When the ureteral cell is excited, its membrane loses its preferential permeability to K^+ and becomes more permeable to Ca^{2+} ions that move inward across the cell membrane, primarily through fast L-type Ca^{2+} channels and give rise to the upstroke of the action potential (Fig. 59–3A) (Kobayashi, 1965; Kuriyama and Tomita, 1970; Imaizumi et al, 1989; Lang, 1989, 1990; Sui and Kao, 1997a, b; Smith et al, 2002). This channel is inhibited by the calcium channel blocker nifedipine and by cadmium ions (Cd^{2+}), and it is potentiated by barium ions (Ba^{2+}). As the positively charged Ca^{2+} ions move inward across the cell membrane, the inside of the membrane becomes less negative relative to the outside and may even become positive at the peak of the action potential, a state referred to as ***overshoot***. Na^+ ions also may play a role in the upstroke of the ureteral action potential (Kobayashi, 1964, 1965; Muraki et al, 1991). The rate of rise of the upstroke of the ureteral action potential is relatively slow, 1.2 ± 0.06 V/sec in the cat (Kobayashi, 1969). This compares with a 610 V/sec rate of rise in dog cardiac Purkinje fibers (Draper and Weidmann, 1951) and a 740 V/sec rate of rise in skeletal muscle (Ferroni and Blanchi, 1965). The slow rate of upstroke rise of the ureteral action potential accounts for the slow conduction velocity in the ureter.

After reaching the peak of its action potential, the ureter maintains its potential for a period of time

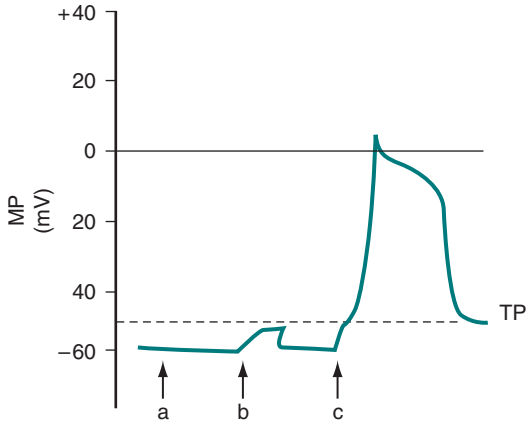


Figure 59–2. Response of ureteral transmembrane potential to stimuli. At *arrow a,* a weak stimulus is applied that does not alter the resting membrane potential (MP). At *arrow b,* a stimulus is applied that decreases the transmembrane potential but not to the level of the threshold potential TP (subthreshold stimulus). At *arrow c,* a stimulus is applied that decreases the transmembrane potential to TP, and an action potential is initiated (suprathreshold stimulus). (From Weiss RM. Ureteral function. Urology 1978;12:114.)

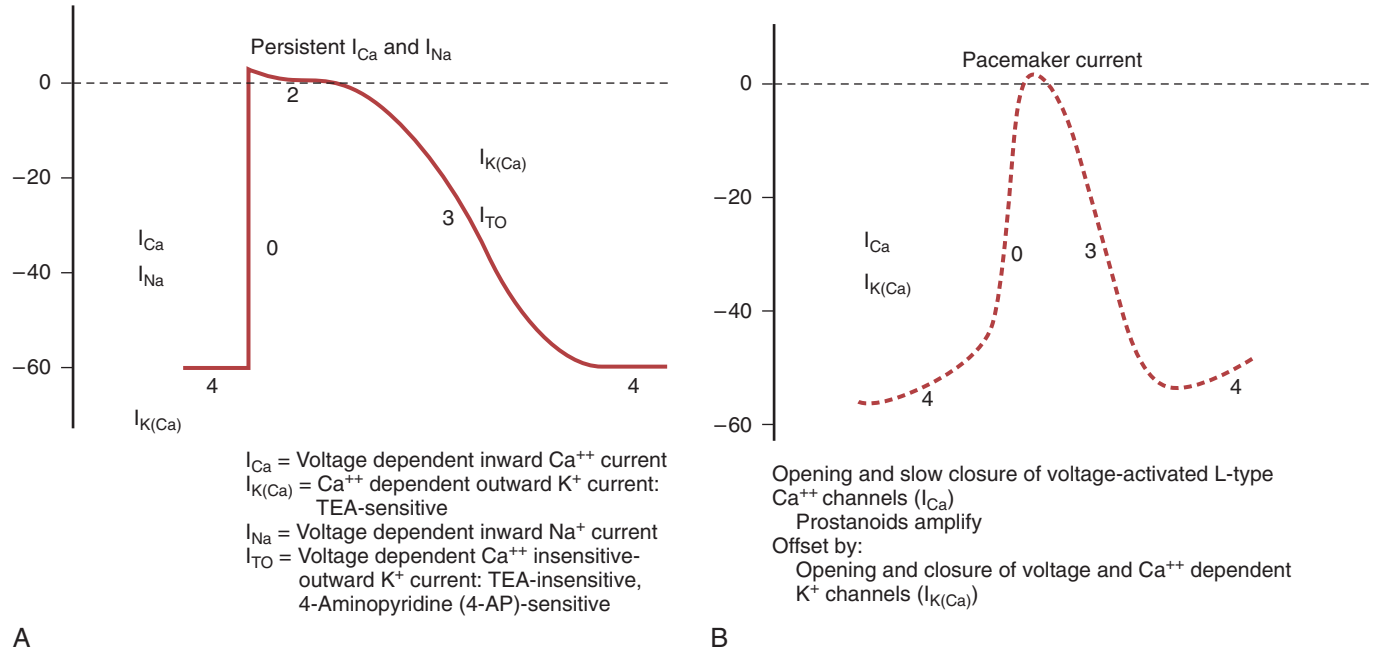


Figure 59–3. Schematic representation of ionic currents in **(A)** nonpacemaker *(solid line)* and **(B)** pacemaker *(dashed line)* action potentials: (0) upstroke or depolarization phase; (2) plateau phase; (3) repolarization phase; and (4) resting potential of the nonpacemaker cell and spontaneous depolarization phase of the pacemaker cell. A spontaneous decrease in the transmembrane potential of pacemaker cells accounts for their spontaneous activity.

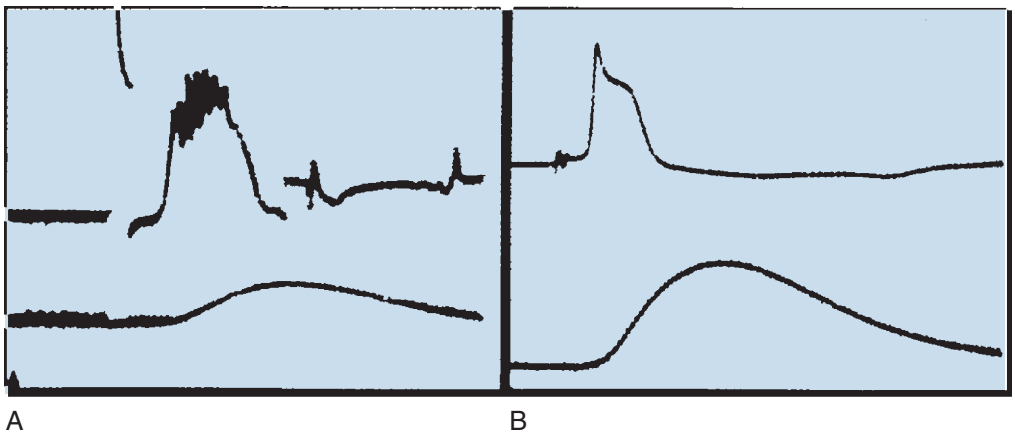


Figure 59–4. Intracellular recordings of ureteral action potentials *(upper tracings)* and isometric recordings of contractions (lower tracings) in response to electrical stimuli. Action potentials precede contractions. **A,** Guinea pig ureter; oscillations on the plateau of the action potential. **B,** Cat ureter; no oscillations on the plateau of the action potential. (**A** and **B,** From Weiss RM. Ureteral function. Urology 1978;12:114.)

(plateau of the action potential) before the transmembrane potential returns to its resting level (repolarization) (Kuriyama et al, 1967). The plateau phase of the guinea pig action potential is superimposed with multiple oscillations, a phenomenon not observed in the rat, rabbit, or cat (Fig. 59–4) (Bozler, 1938). The plateau phase appears to depend on the persistence of an inward Ca^{2+} current and on Na^+ influx through a voltage-dependent Na^+ channel (see Fig. 59–3A) (Kuriyama and Tomita, 1970; Imaizumi et al, 1989; Sui and Kao, 1997b). Also involved in the plateau formation is the maintenance of depolarization by an inward calcium-dependent chloride current ($I_{Cl(Ca)}$) which is countered by outward voltage-gated (I_{70}) and Ca^{2+}-activated K^+ currents ($I_{(KCa)}$) (Smith et al, 2002). There are species differences in the ionic currents involved in the formation of the action potential, with the Ca^{2+}-activated chloride current being present in the rat but not in the guinea pig ureter. The inward Cl^- current can be inhibited by niflumic acid and by Ba^{2+} (Smith et al, 2002). The oscillations on the plateau of the guinea pig action potential appear to depend on the repetitive activation of an inward Ca^{2+} current (Kuriyama and Tomita, 1970) and of a Ca^{2+}-dependent outward K^+ current (Imaizumi et al, 1989). Prolongation of the inward calcium current and the duration of the action potential correlate with an increased force of contraction (Burdyga and Wray, 1999b).

The activation of a Ca^{2+}-dependent K^+ current that is involved in repolarization is mainly due to Ca^{2+} release from the endoplasmic reticulum, which is triggered by the influx of extracellular Ca^{2+} through voltage-dependent Ca^{2+} channels. The increase in intracellular Ca^{2+} concentration during the upstroke and plateau of the

action potential finally may activate the outward Ca^{2+}-dependent K^+ current ($I_{K(Ca)}$) to such a degree that repolarization occurs with return of the transmembrane potential to its resting level (see Fig. 59–3A) (Imaizumi et al, 1989; Sui and Kao, 1997c). This $I_{K(Ca)}$ is sensitive to inhibition by tetraethylammonium (TEA). Based on this, TEA increases the amplitude and duration of in-vitro ureteral contractions (Floyd et al, 2008). A voltage-dependent, Ca^{2+} insensitive outward K^+ current (I_{TO}) also appears to be involved in the repolarization (Lang, 1989; Imaizumi et al, 1990). These currents are TEA-insensitive and 4-aminopyridine (4-AP)–sensitive. In the rat, but not the guinea pig, ureter there is a late TEA-, Cd^{2+}- and Ca^{2+}-insensitive outward K^+ current that also is involved in the repolarization process. The duration of the action potential in the cat ranges from 259 to 405 milliseconds (Kobayashi and Irisawa, 1964).

In summary, **the RMP of the ureteral cell is approximately –33 to –70 mV and is determined primarily by the distribution of K^+ ions across the cell membrane and the relatively selective permeability of the resting cell membrane to K^+. When excited by a suprathreshold stimulus, the membrane becomes less permeable to K^+ and more permeable to Ca^{2+}, which moves inward across the cell membrane and provides the ionic mechanism for the development of the upstroke of the action potential. After reaching the peak of its action potential, the membrane maintains a depolarized state—plateau of the action potential—for a period of time before the membrane potential of the activated cell returns to its resting level (repolarization). The plateau appears to be related to a persistent inward Ca^{2+} current and to an influx of Na^+. Repolarization of the membrane is related to a renewed increase in permeability to K^+.**

Pacemaker Potentials and Pacemaker Activity

Electric activity arises in a cell either spontaneously or in response to an external stimulus. If the activity arises spontaneously, the cell is referred to as a pacemaker cell. Pacemaker fibers differ from nonpacemaker fibers in that their transmembrane resting potential is lower (less negative) than that of nonpacemaker fibers (Lang and Zhang, 1996) and does not remain constant but, rather, undergoes a slow spontaneous depolarization (see Fig. 59–3B). If the spontaneously changing membrane potential reaches the threshold potential, the upstroke of an action potential occurs. The **ionic conduction underlying pacemaker activity in the upper urinary tract is due to the opening and slow closure of voltage-activated L-type Ca^{2+} channels that are amplified by prostanoids** (Santicioli et al, 1995a). This is opposed by the opening and closure of voltage and Ca^{2+}-dependent K^+ channels. It has been suggested that prostaglandins and excitatory tachykinins, released from sensory nerves, help maintain autorhythmicity in the upper urinary tract through maintenance of Ca^{2+} mobilization (Lang et al, 2002). **Tetrodotoxin and blockers of the autonomic nervous system, both parasympathetic and sympathetic, have little effect on peristalsis, suggesting that autonomic neurotransmitters have a small role in maintaining pyeloureteral motility** (Lang et al, 2001, 2002). Changes in the frequency of action potential development may result from a change in the level of the threshold potential, a change in the rate of slow spontaneous depolarization of the resting potential, or a change in the level of the resting potential.

Gosling and Dixon (1971, 1974) provided morphologic evidence of specialized pacemaker tissue in the proximal portion of the urinary collecting system and described species differences. **In species with a multicalyceal system, such as the pig, sheep, and human, the "pacemaker cells" are located near the pelvicalyceal border** (Dixon and Gosling, 1973). In species with a unicalyceal system, such as the dog, cat, rat, rabbit, and guinea pig, the "pacemaker cells" extend from the pelvicalyceal border to the ureteropelvic junction (UPJ). These **atypical smooth muscle cells that give rise to pacemaker activity** in the rat and guinea pig, in contrast to typical smooth muscle cells, have less than 40% of their cellular area occupied by contractile elements and demonstrate sparse immunoreactivity for smooth muscle and actin (Klemm et al, 1999; Lang et al 2001). These spindle-shaped cells are 90 to 230 μm in length, and their electrical activity consists of simple waveforms of alternating depolarizing and repolarizing phases that occur at a relatively rapid frequency of 8 to 15/min (Fig. 59–5A) (Tsuchida and Suzuki, 1992; Klemm et al, 1999). Pacemaker potentials have a lower resting membrane potential (RMP), a slower rate of rise, and a lower amplitude than action potentials recorded from nonpacemaker cells. In the guinea pig, these atypical, presumably pacemaker cells comprise greater than 80% of the cells at the pelvicalyceal junction, about 15% of the cells in the proximal renal pelvis, but are not present in the distal renal pelvis or ureter (Klemm et al, 1999). Electrical recordings correlate with histologic findings in that pacemaker potentials were not observed in the distal renal pelvis or ureter (Klemm et al, 1999).

Driven action potentials that fire at lower frequency (3 to 5/min) than pacemaker potentials are recorded from longer (150 to 400 μm) spindle-shaped typical smooth muscle cells (Fig. 59–5B) (Klemm et al, 1999). Most muscle cells of the ureter (100%), distal renal pelvis (97.5%), and proximal renal pelvis (83% are typical nonpacemaker smooth muscle cells with typical action potentials. Lang et al (1998) described fibroblast-like cells resembling the interstitial cells of Cajal (ICC), which serve as pacemaker cells in the intestine, in the proximal portion of the guinea pig renal pelvis. These "ICC-like" cells are irregularly shaped with oval nuclei and many branching interconnecting processes and contain numerous mitochondria, caveolae, and prominent endoplastic reticulum. The ICC-like cells in the guinea pig are not immunoreactive for α-smooth muscle actin, which is present in typical smooth muscle cells, or for c-KIT, a tyrosine kinase receptor that is expressed in intestinal ICC pacemaker cells (Klemm et al, 1999). The immunoreactivity to c-KIT appears to be species specific, because ICC-like cells that are immunoreactive to antibodies raised against the c-*KIT* proto-oncogene are present in the upper urinary tract of a number of mammals (Lang and Klemm, 2005; Metzger et al, 2005). Electrical recordings from these cells demonstrate action potentials with properties intermediate to the pacemaker and driven action potentials. These intermediate action potentials in the guinea pig have a single spike, a plateau without the superimposed spikes seen in driven action potentials and a rapid repolarization phase (Fig. 59–5C). Intermediate action potentials are noted in 11% to 17% of cells at the pelvicalyceal junction and the proximal and distal renal pelvis (Lang et al, 2002). These **ICC-like cells in the upper urinary tract do not appear to be primary pacemaker cells but, rather, may provide for preferential conduction of electrical signals from pacemaker cells to typical smooth muscle**

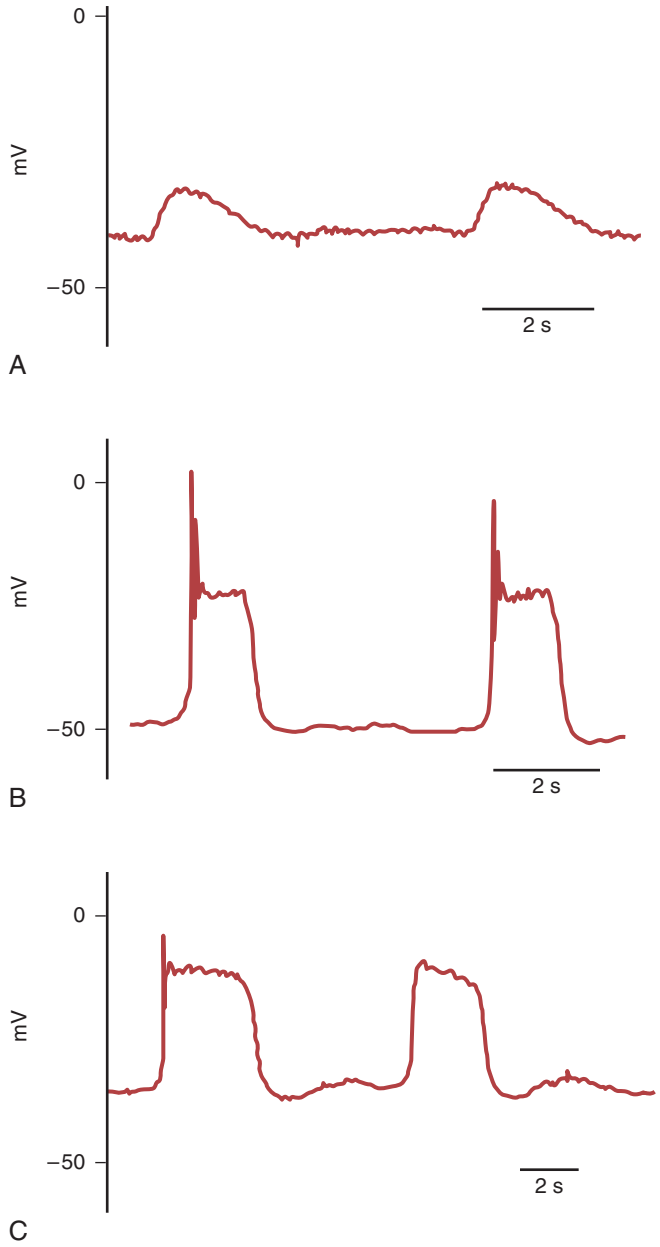


Figure 59–5. Action potentials in the upper urinary tract of the guinea pig. **A,** Pacemaker potentials. **B,** Driven action potentials. **C,** Intermediate action potentials. (Modified with permission from Klemm MF, Exintaris B, Lang RJ. Identification of the cells underlying pacemaker activity in the guinea pig upper urinary tract. J Physiol [Lond] 1999;519:867.)

cells of the renal pelvis and ureter (Klemm et al, 1999). **In the mouse ureteropelvic junction, c-KIT–positive ICC-like cells have been identified that showed high-frequency spontaneous transient inward currents that often occurred in bursts to sum and produce long-lasting large inward currents** (Lang et al, 2007b). **It is postulated that in the absence of a proximal pacemaker drive these ICC-like cells could act as pacemaker cells and trigger contractions in adjacent smooth muscle cells in the ureteropelvic junction. Thus both atypical smooth muscle cells and ICC-like cells both may play a pacemaker role in the initiation and propagation of pyeloureteric peristalsis** (Lang et al, 2006; Lang et al, 2007a).

c-KIT is a tyrosine kinase receptor that promotes cell migration and proliferation of melanoblasts, hematopoietic progenitors and primordial germ cells. Mice expressing mutant inactivating **c-*Kit*** alleles, lack intestinal interstitial cells of Cajal (ICC), have abnormal intestinal peristalsis, and develop bowel obstruction, showing that **c-*Kit* is important in the development of pacemaker activity and peristalsis of the gut** (Der-Silaphet et al, 1998). Pezzone et al (2003) identified c-Kit positive cells in the mouse ureter. They suggested that the difference from previous studies in the guinea pig upper urinary tract, in which c-Kit–positivity was not identified in ICC-like cells (Klemm et al, 1999), may be due to species differences, the c-Kit antibody used, and/or the fixation methods. **c-*Kit* gene expression** was noted to be **upregulated in the embryonic murine ureter prior to its development of unidirectional peristaltic contractions** (David et al, 2005). Incubation of isolated cultured embryonic murine ureters with antibodies that neutralize c-Kit activity altered ureteral morphology and inhibited unidirectional peristalsis. These data suggest that c-Kit–containing cells, which are probably ICC-like cells, have an important role in pyeloureteric peristalsis. c-Kit–positive cells have been identified in the human ureter (Metzger et al, 2004; van der Aa et al, 2004) and in the human UPJ (Solari et al, 2003). In the presence of obstruction, c-Kit–positive cells ICC-like cells at the UPJ were sparse or absent (Solari et al, 2003).

Bozler (1942), using small extracellular surface electrodes, demonstrated the characteristic slow spontaneous depolarization of pacemaker-type fibers in the proximal portion of the isolated ureter of a unicalyceal upper collecting system. In a multicalyceal kidney, Morita and associates (1981), using extracellular electrodes, recorded low-voltage potentials that appeared to be pacemaker potentials from the border of the pig minor calyces and the major calyx with the contraction rhythm varying between each calyx. Multiple pacemakers fire simultaneously as coupled oscillators, or individually, as pacemaker activity shifts from one site to another along the renal pelvis of the unicalyceal kidney or the pelvicalyceal border of the multicalyceal pig and sheep kidney (Golenhofen and Hannappel, 1973; Constantinou et al, 1977; Constantinou and Yamaguchi, 1981; Lammers et al, 1996).

Although the primary pacemaker for ureteral peristalsis is located in the proximal portion of the collecting system, other areas of the ureter may act as **latent pacemakers**. Under normal conditions, the latent pacemaker regions are dominated by activity arising at the primary pacemaker sites. When the latent pacemaker site is freed of its domination by the primary pacemaker, it, in turn, may act as a pacemaker. To demonstrate latent pacemaker sites, Shiratori and Kinoshita (1961) transected the in-vivo dog ureter at various levels. Before transection, peristaltic activity arose proximally from the primary pacemaker. When the ureter was transected at the UPJ, antiperistaltic waves of lower frequency than the previous normoperistaltic waves originated from the UVJ. Division of the ureter at the UVJ did not affect the normoperistaltic waves. After division of the midureter, the normoperistaltic waves in the upper segment remained unchanged, and the lower segment demonstrated antiperistaltic waves, which originated at the UVJ at a frequency less than that of the normoperistaltic waves in the upper segment. Thus cells at the UVJ of the dog may act as pacemaker cells when freed of control from the primary proximally located pacemaker. **Latent pacemaker cells are present in all regions of the ureter** (Imaizumi et al, 1989; Meini et al, 1995).

Propagation of Electric Activity

Excitable cells possess resistive and capacitative membrane properties similar to those of a cable or core conductor. The transverse resistance of the membrane is higher than the longitudinal resistance of the extracellular or intracellular fluid; this allows current resulting from a stimulus to propagate along the length of the fibers. The spread of current is referred to as *electrotonic spread* (Hoffman and Cranefield, 1960). The space constant (λ) determines the degree to which the electrotonic potential dissipates with increasing distance from an applied voltage. In a cable, this relation is expressed by

$$P = P_o\, e^{-X/\lambda}$$

where X is the distance from the applied voltage, P is the displacement of the membrane potential at X, P_o is the displacement of the membrane potential at the site of the applied voltage, e is the base of the natural logarithm, and λ is the space constant. Thus the electrotonic potential decreases by 1/e in one space constant. The space constant of the guinea pig ureter measured by extracellular stimulation is 2.5 to 3 mm (Kuriyama et al, 1967).

The time constant τ_m is expressed by

$$\tau_m = RC$$

where R is the membrane resistance and C is the membrane capacity. The time constant τ_m signifies that a small displacement of potential is decreased by 1/e of its value in one τ_m. The time constant of the guinea pig ureter measured by extracellular stimulation is 200 to 300 milliseconds (Kuriyama et al, 1967).

The ureter acts as a **functional syncytium**. Engelmann (1869, 1870) showed that stimulation of the ureter produces a contraction wave that propagates proximally and distally from the site of stimulation. Under normal conditions, **electric activity** arises proximally and is **conducted distally from one muscle cell to another across areas of close cellular apposition referred to as intermediate junctions** (Uehara and Burnstock, 1970; Libertino and Weiss, 1972). The similarity of these close cellular contacts to nexuses, which have been shown to be low-resistance pathways for cell-to-cell conduction in other smooth muscles (Barr et al, 1968), suggests that a similar mechanism for conduction may be present in the ureter. **Gap junctions, consisting of groups of channels in the plasma membrane of adjacent smooth muscle cells, enable exchange of ions and small molecules and play a role in electrical coupling between adjacent cells and electromechanical coupling** (Gabella, 1994; Santiciolli and Maggi, 2000). 18β-glycyrrhetinic acid, a gap junction inhibitor, inhibits cell-to-cell electrical coupling in the guinea pig renal pelvis and ureter and dissociates electrical and mechanical events (Santicioli and Maggi, 2000). **Conduction velocity in the ureter is 2 to 6 cm/sec** (Kobayashi, 1964; Kuriyama et al, 1967); it has been shown to vary with temperature, the time interval between stimuli (van Mastrigt et al, 1986), and the pressure within the ureter (Tsuchiya and Takei, 1990). This compares to conduction velocities ranging from 1.5 to 2 m/sec in cardiac Purkinje fibers (Rosen et al, 1981) and from 10 to 100 m/sec in the dorsal and ventral roots of the spinal cord (Biscoe et al, 1977). Conduction in the ureter is similar to that in cardiac tissue, even to the extent that the Wenckebach phenomenon (a partial conduction block) has been demonstrated in the ureter, as it has been in specialized cardiac fibers (Weiss et al, 1968).

CONTRACTILE ACTIVITY

The contractile event is dependent on the concentration of free sarcoplasmic Ca^{2+} in the region of the contractile proteins, actin and myosin. Any process that results in a significant increase in Ca^{2+} in the region of the contractile proteins favors the development of a contraction; any process that results in a significant decrease in Ca^{2+} in the region of the contractile proteins favors relaxation (Fig. 59–6).

Contractile Proteins

In skeletal muscle, Ca^{2+} appears to act as a derepressor. It is thought that in the relaxed state, a regulator system, consisting of the proteins troponin and tropomyosin, prevents the interaction of actin and myosin. In the relaxed state, troponin that is attached to tropomyosin is inactive, and tropomyosin prevents the interaction between actin and myosin. With activation, there is an increase in the sarcoplasmic Ca^{2+} concentration. The Ca^{2+} binds to troponin, producing a conformational change that results in the displacement of tropomyosin, thus allowing the interaction of actin and myosin and the development of a contraction.

In smooth muscle, on the other hand, Ca^{2+} appears to act as an activator. The most widely accepted theory suggests that **phosphorylation of myosin is involved in the contractile process** and that a troponin-like system does not constitute the

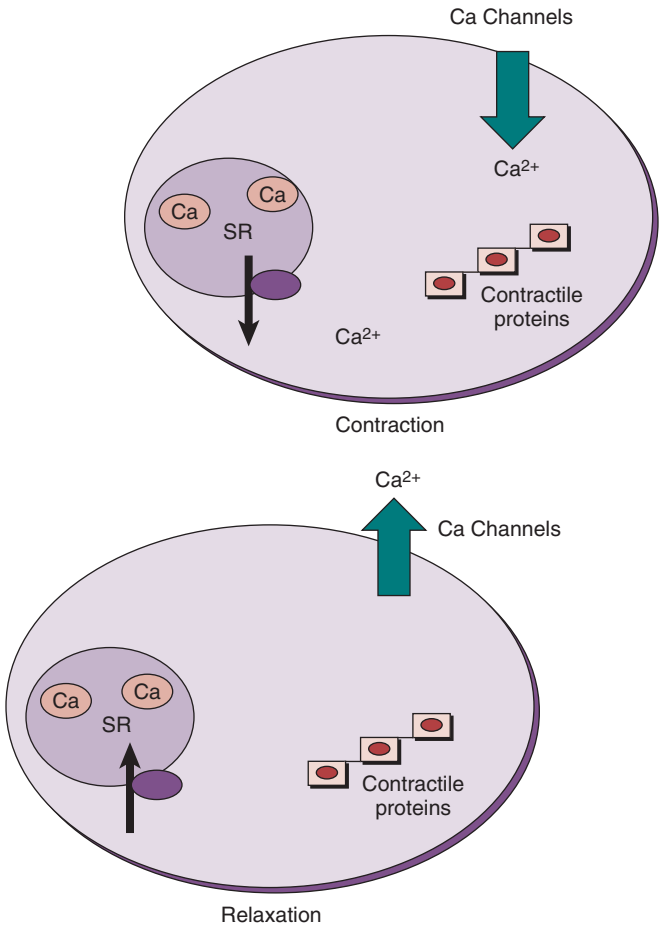


Figure 59–6. Schematic representation of calcium ion movements during contraction and relaxation. SR, sarcoplasmic reticulum.

primary regulatory mechanism, as it does in skeletal muscle. **With excitation, there is a transient increase in the sarcoplasmic Ca^{2+} concentration** from its steady-state concentration of 10^{-8} to 10^{-7} M to a concentration of 10^{-6} M or higher. At this higher concentration, **Ca^{2+} forms an active complex with the Ca^{2+}–binding protein calmodulin** (Watterson et al, 1976; Cho et al, 1988). Calmodulin without Ca^{2+} is inactive (Fig. 59–7). **The Ca^{2+}–calmodulin complex activates a calmodulin-dependent enzyme, myosin light-chain kinase** (see Fig. 59–7). **The activated myosin light-chain kinase, in turn, catalyzes the phosphorylation of the 20,000-D light chain of myosin** (Fig. 59–8). **Phosphorylation of the myosin light chain allows actin to activate myosin Mg^{2+}-ATPase activity, leading to hydrolysis of ATP and the development of smooth muscle tension or shortening** (Fig. 59–9). Actin cannot activate the ATPase activity of the dephosphorylated myosin light chain.

When the Ca^{2+} concentration in the region of the contractile proteins is low, the myosin light-chain kinase is not active, because calmodulin requires Ca^{2+} to activate the enzyme. This prevents activation of the contractile apparatus, because the myosin light chain cannot be phosphorylated, a process that must precede tension development. Furthermore, a phosphatase dephosphorylates the myosin light chain, thus preventing actin activation of myosin ATPase activity, and relaxation results.

Evidence indicates that phosphorylation of the enzyme myosin light-chain kinase by a cAMP-dependent protein kinase decreases myosin light-chain kinase activity by decreasing the affinity of this enzyme for calmodulin (Adelstein et al, 1981).

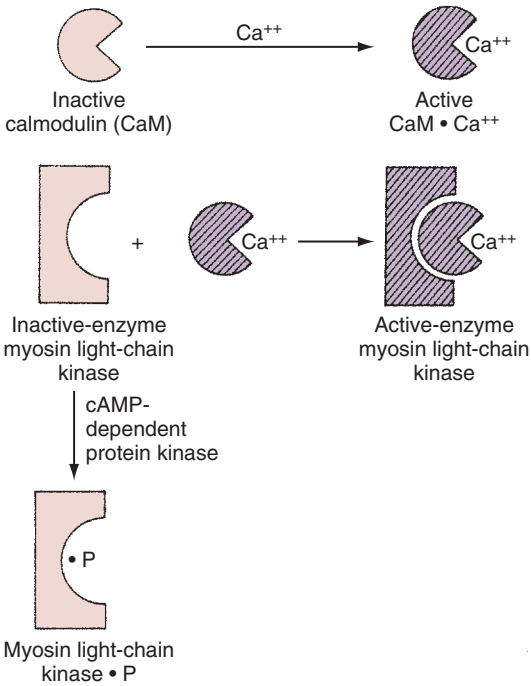


Figure 59–7. Schematic representation of the contractile process in smooth muscle. Calmodulin is activated by Ca^{2+}. The activated calcium-calmodulin complex activates the enzyme myosin light-chain kinase, which phosphorylates the light chain of myosin. Phosphorylation of myosin light-chain kinase decreases the rate of activation of the enzyme by the Ca^{2+}-calmodulin complex.

Although Ca^{2+} is required for most smooth muscle contractile events, there is evidence in some smooth muscles, including in the rabbit and human bladder, that Ca^{2+}-independent contractions can occur (Yoshimura and Yamaguchi, 1997). Carbachol, a muscarinic cholinergic agonist, and phorbol ester, which activate protein kinase C (PKC), can induce contraction in Ca^{2+}-depleted bladder strips that can be inhibited by a PKC inhibitor, H7. It is suggested that activation of PKC, coupled with agonist stimulation of the muscarinic receptor, can induce a Ca^{2+}-independent contraction.

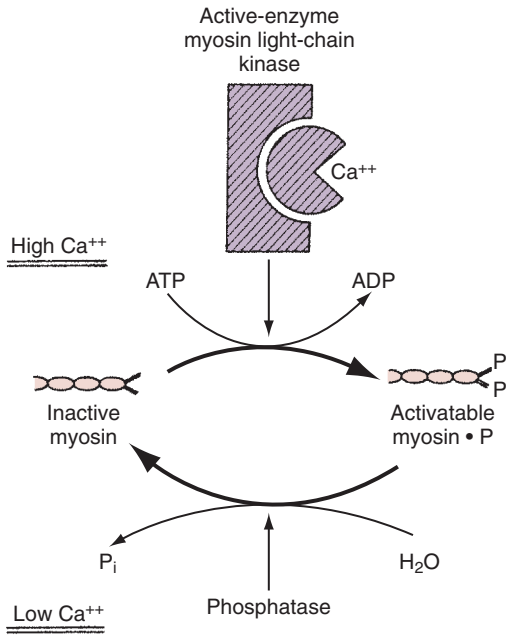


Figure 59–8. Schematic representation of the contractile process in smooth muscle. The activated enzyme myosin light-chain kinase catalyzes the phosphorylation of myosin. Myosin must be phosphorylated in order for actin to activate myosin ATPase. ADP, adenosine diphosphate; ATP, adenosine triphosphate.

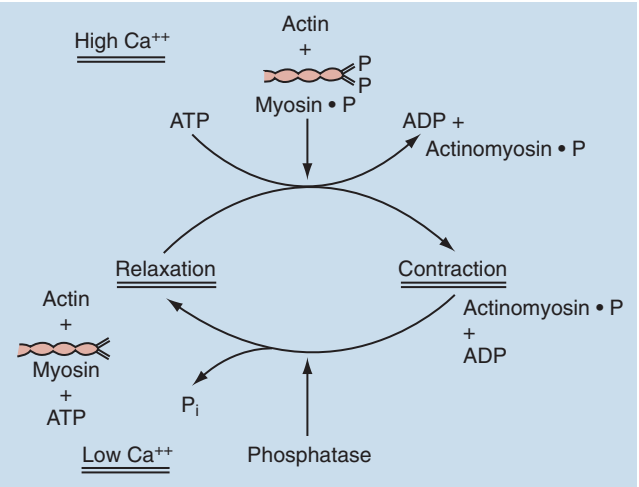


Figure 59–9. Schematic representation of the contractile process in smooth muscle. Actin activates ATPase activity of phosphorylated myosin. This allows interaction of actin and myosin with the development of a contraction. ADP, adenosine diphosphate; ATP, adenosine triphosphate.

Calcium and Excitation-Contraction Coupling

The mechanical event of ureteral peristalsis follows an electric event to which it is related. The Ca^{2+} involved in the ureteral contraction is derived from two main sources. Because smooth muscle cells have a very small diameter, the **inward movement of extracellular Ca^{2+} into the cell through L-type Ca^{2+} channels during the upstroke of the action potential provides a significant source of sarcoplasmic Ca^{2+}** (Brading et al, 1983; Hertle and Nawrath, 1989; Yoshida et al, 1992; Maggi et al, 1994a; Maggi and Giuliani, 1995; Floyd et al, 2008) (see Fig. 59–6). This inward movement across the cell membrane is the major source of calcium used for contraction in most smooth muscles. Na^+-Ca^{2+} exchange, with an outward movement of Na^+ and an inward movement of Ca^{2+}, also plays a role in the ureteral contraction (Lamont et al, 1998). Furthermore, in response to an excitatory impulse, Ca^{2+} release from tightly bound storage sites (i.e., the endoplasmic or sarcoplasmic reticulum) also increases the Ca^{2+} concentration in the sarcoplasm (Burdyga et al, 1998; Burdyga and Wray, 1999a; Lang et al, 2002). Calcium may be released from the sarcoplasmic reticulum (SR) of smooth muscle by an inositol 1,4,5-trisphosphate (IP_3)–induced release mechanism or by Ca^{2+}-induced Ca^{2+} release (CICR) (Somlyo and Somlyo, 1994). These processes appear to be species dependent. CICR, which involves ryanodine receptors, appears to be the sole mechanism for calcium release from the SR in the guinea pig ureter, whereas the SR stored in the rat ureter appears to be exclusively under the control of IP_3 receptors (Burdyga et al, 1995). IP_3 and ryanodine receptors are expressed in the human ureter (Floyd et al, 2008). The opening of caffeine-sensitive ryanodine receptors produces small local elevations of Ca^{2+} that are termed Ca^{2+} sparks (Nelson et al, 1995). In addition to providing a source of calcium for contraction, Ca^{2+} released from the SR activates Ca^{2+}–sensitive surface membrane channels and modulate membrane excitability (Imaizumi et al, 1989; Carl et al, 1996). Both calcium-activated outward potassium currents (K_{Ca}), or STOCS (spontaneous transient outward currents), and calcium-activated inward chloride currents (Cl_{Ca}), or STICS (spontaneous transient inward currents), have been identified in smooth muscles. These currents affect membrane potential and thus affect calcium entry through L-type Ca^{2+} channels in the membrane. The Ca^{2+}–activated chloride currents are present in rat but not guinea pig ureteral smooth muscle (Burdyga and Wray, 2002). Thus some Ca^{2+} released from SR results in contraction, but it has been shown that caffeine-induced release of SR Ca^{2+}, in the form of Ca^{2+} sparks, increases outward potassium currents (K_{Ca}), or STOCS, with an inhibitory effect on action potentials and contractility (Borisova et al, 2007). At least in the guinea pig ureter, this increase in the outward potassium current hyperpolarizes the membrane and determines the refractory period, which is important in determining the frequency of ureteral peristalsis and may have a protective effect on the kidney (Burdyga and Wray, 2005).

Support for use of a dual source of Ca^{2+} in the ureter has been provided by Vereecken and coworkers (1975), who noted that it took approximately 45 minutes for spontaneous contractions of isolated guinea pig ureters to cease when the tissue was placed in a Ca^{2+}-free medium. They interpreted this to indicate that some of the Ca^{2+} involved in the contractile process is derived from tightly bound intracellular stores. They also noted that recovery of the contractile response to electric stimuli was almost immediate when the tissue was returned to a physiologic solution containing a normal concentration of Ca^{2+}. This suggests that free extracellular Ca^{2+} entering the cell during excitation also provides a source of Ca^{2+} for the contractile machinery. A similar conclusion was reached by Hong and associates (1985). There is, however, some evidence that Ca^{2+} release from the sarcoplasmic reticulum may not play a significant role in ureteral contractions, at least in the guinea pig (Maggi et al, 1994a, 1995, 1996), and some perturbations of contractility may be related to movements of ions other than Ca^{2+}. The increase in developed force in the guinea pig ureter, with intracellular acidification and decrease with intracellular alkalinization, appear to result from modulation of outward K^+ currents rather than effects on inward Ca^{2+} currents (Smith et al, 1998). That is, alkalinization (increasing intracellular pH) enhances outward K^+ currents, and this reduces excitability; acidification has the opposite effect. Relaxation results from a decrease in the concentration of free sarcoplasmic Ca^{2+} in the region of the contractile proteins. The decrease in sarcoplasmic Ca^{2+} can result from the uptake of Ca^{2+} into intracellular storage sites (Maggi et al, 1994a, 1995) or from extrusion of Ca^{2+} from the cell (Burdyga and Magura, 1988).

In addition to the Ca^{2+}- signaling cascade that affects contractility, there is a Rho/Rho-kinase signaling pathway that affects contractility by altering the Ca^{2+}-sensitivity of the contractile system (Somlyo and Somlyo, 2003). The Rho-kinase pathway is involved in ureteral contractions in a number of species (Levent and Buyukafsar, 2004; Shabir et al, 2004; Hong et al, 2005). Rho-kinase inhibits myosin phosphatase by phosphorylation of its regulatory subunit, which prevents dephosphorylation of myosin light chain, which, in turn, leads to Ca^{2+} sensitization of the smooth muscle with a subsequent increase in contractility. Y-27632, an inhibitor of Rho-kinase, decreases both spontaneous and EFS-induced contractile responses of in vitro human ureteral segments (Hong et al, 2005). Y-27632 inhibits kinase activity by competing with ATP for binding to the Rho-kinases.

Urothelial Effects on Contractile Activity

Furchgott (1999) showed that **the endothelium produced a factor that had a relaxing action on the smooth muscle layer of blood vessels.** This factor was originally termed **endothelium-derived relaxing factor (EDRF)** and was subsequently shown to be **nitric oxide (NO).** Mastrangelo et al (2003) showed that the urothelium of rat ureter produced NO, which inhibited contractile responses of the rat ureter. Recently in the rat ureter, it was shown that the urothelium inhibited spontaneous contractions of isolated ureteral segments and that removal of the urothelium potentiated the stimulatory effects of neurokinin A, vasopressin, carbachol, bradykinin, and angiotensin II (Mastrangelo and Iselin, 2007). In intact ureteral segments, cyclooxygenase inhibitors potentiated the stimulatory effects of neurokinin A, vasopressin, carbachol, bradykinin, and angiotensin II. Cyclooxygenase inhibitors had no effect on the responses to these agents in urothelium-free ureters. These data suggest that the inhibitory effects of the urothelium on ureteral contractile events may involve the participation of a urothelial cyclooxygenase product such as prostacyclin.

Second Messengers

The functional response to a number of hormones, neurotransmitters, and other agents is mediated by means of *second messengers*. The agonist, or first messenger, interacts with a specific

membrane-bound receptor (Alquist, 1948; Furchgott, 1964); the agonist-receptor complex then activates or inactivates an enzyme, which leads to alteration of a second messenger within the cell. These **second messengers include cyclic AMP (cAMP), cyclic GMP (cGMP), Ca^{2+}, inositol 1,4,5-trisphosphate (IP_3), and diacylglycerol (DG).** They mediate the functional response to the agonist (first messenger) through a process that frequently involves protein phosphorylation.

Although relaxation of smooth muscle may occur independently of changes in cyclic nucleotides (Vesin and Harbon, 1974), cAMP is believed to mediate the relaxing effects of β-adrenergic agonists in a variety of smooth muscles (Triner et al, 1971; Andersson, 1972). According to this concept, a β-adrenergic agonist, such as isoproterenol, serves as the first messenger and combines with a receptor on the outer surface of the cell membrane (Fig. 59–10). Isoproterenol itself does not enter the cell. The **β-adrenergic agonist–receptor** complex activates the enzyme adenylyl cyclase on the inner surface of the cell membrane, in close morphologic relation to the receptor. **In the presence of magnesium ions (Mg^{2+}) and a guanine nucleotide (GTP), adenylyl cyclase catalyzes the conversion of ATP to cAMP within the cell.**

$$\text{ATP} \xrightarrow[Mg^{2+},\,GTP]{\text{adenylyl cyclase}} \text{cAMP}$$

A stimulatory guanine nucleotide–regulatory protein, or G protein (G_S), acts as a functional link between the agonist-receptor complex and the catalytic, or active unit, of the enzyme adenylyl cyclase. cAMP acts as a second, or "internal," messenger of the response elicited by the β-adrenergic agonist. It has been suggested that the increase in cAMP through activation of an enzyme, that is, a protein kinase, and phosphorylation of proteins leads to the uptake of Ca^{2+} into intracellular storage sites (i.e., the endoplasmic or sarcoplasmic reticulum) with the resultant decrease of free sarcoplasmic Ca^{2+} in the region of the contractile proteins (Andersson and Nilsson, 1972). The decrease in sarcoplasmic Ca^{2+} in the region of the contractile proteins leads to relaxation of the smooth muscle. β-Adrenoceptor–induced relaxation of smooth muscle also may be due to the opening of Ca^{2+}-activated K^+ channels (Uchida et al, 2005; Ferro, 2006).

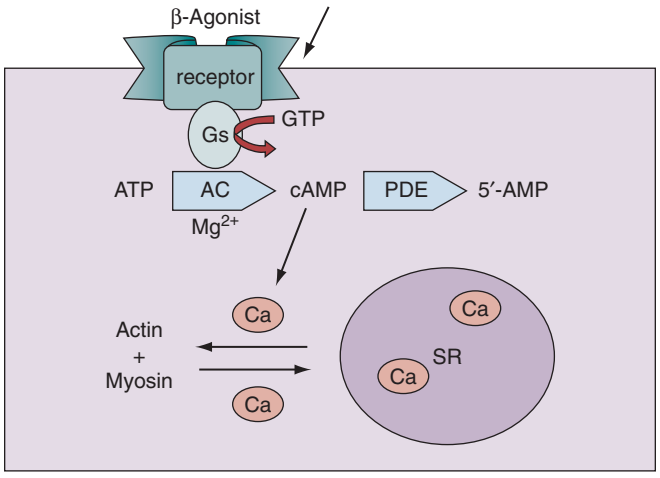


Figure 59–10. Schematic representation of the role of cAMP in β-adrenergic agonist–induced relaxation of smooth muscle. Agonist combines with receptor on the outer side of the cell membrane. The receptor-agonist complex, in turn, by a stimulatory G protein (G_s), activates the enzyme adenylyl cyclase (AC) on the inner surface of the cell membrane, which in the presence of Mg^{2+} and GTP results in the conversion of ATP to cAMP. cAMP is postulated to cause an increased uptake of Ca^{2+} into intracellular storage sites with a resultant decrease in Ca^{2+} in the region of the contractile proteins that results in relaxation. cAMP may also have other actions (not shown) that inhibit the contractile process. The enzyme phosphodiesterase (PDE) degrades cAMP to 5′-AMP. SR, sarcoplasmic reticulum.

cAMP levels may be increased within the cell in two ways. One is by increasing synthesis, which involves activation of the enzyme adenylyl cyclase; the other is by decreasing degradation. **The degradation of cAMP involves activation of an enzyme, a phosphodiesterase:**

$$\text{cAMP} \xrightarrow{\text{phosphodiesterase}} \text{5′-AMP}$$

Thus **agents that either increase adenylyl cyclase activity, such as the β-adrenergic agonist isoproterenol, or decrease phosphodiesterase activity, that is, phosphodiesterase inhibitors such as theophylline and papaverine, increase intracellular cAMP levels and cause smooth muscle relaxation.**

Weiss and associates (1977) demonstrated the presence of both adenylyl cyclase and phosphodiesterase activities in the ureter. They showed, in the ureter, that isoproterenol stimulates adenylyl cyclase activity and theophylline inhibits phosphodiesterase activity. These two agents that relax ureteral smooth muscle would be expected to increase cAMP levels—isoproterenol by increasing synthesis and theophylline by decreasing degradation. Further support of **a role for cAMP in smooth muscle relaxation** can be derived from the finding that dibutyryl cAMP, which more readily diffuses into the intact cell and is less likely to be broken down by phosphodiesterase than is cAMP, has been shown to relax a variety of smooth muscles, including the ureter (Takago et al, 1971; Wheeler et al, 1990), and forskolin, which activates the catalytic subunit of adenylyl cyclase, relaxes the ureter (Wheeler et al, 1986; Hernández et al, 2004).

In addition to receptors and G proteins that are involved in stimulation of adenylyl cyclase and the formation of cAMP, as in the actions of β-adrenergic agonists, other receptors and G proteins inhibit adenylyl cyclase activity (Londos et al, 1981). Some actions of α_2-adrenergic and muscarinic cholinergic agonists involve stimulation of these inhibitory G proteins (Gi) with subsequent inhibition of adenylyl cyclase activity.

Another cyclic nucleotide, **cGMP, can also cause smooth muscle relaxation**. The **cGMP is synthesized from GTP by the enzyme guanylyl cyclase and is degraded to 5′-GMP by a phosphodiesterase**. Phosphodiesterase activity that can degrade both cAMP and cGMP has been demonstrated in the canine ureter, and various inhibitors can preferentially inhibit the breakdown of one of the cyclic nucleotides (Weiss et al, 1981; Stief et al, 1995). Insulin has been shown to activate cAMP phosphodiesterase activity in the ureter (Weiss and Wheeler, 1988), and 8-bromo-cGMP has been shown to cause relaxation of a number of smooth muscles (Schultz et al, 1979), including the ureter (Cho et al, 1984).

Nitric oxide (NO) stimulates soluble guanylyl cyclase activity and causes smooth muscle relaxation (Dokita et al, 1991, 1994). **Nitric oxide synthase (NOS) converts L-arginine to NO and L-citrulline in a reaction that requires reduced nicotinamide adenine diphosphate (NADPH). There are three NOS isoforms. Neuronal NOS (nNOS) is present in neuronal tissues and is Ca^{2+} and NADPH dependent** (Bredt and Snyder, 1990). It is thought that neuronal excitation increases

Ca^{2+} concentration within nerves, which leads to the synthesis of NO from L-arginine. **NO** released from the nerve **activates** the enzyme **guanylyl cyclase in the smooth muscle cell, with the resultant conversion of GTP to cGMP and thus smooth muscle relaxation** (Fig. 59–11). It also is possible that a yet-to-be-determined neurotransmitter is released from the neuron, stimulating NO production in the smooth muscle cell, which, in turn, leads to cGMP formation and smooth muscle relaxation. **Endothelial NOS (eNOS), is also Ca^{2+} and NADPH dependent** (Sessa, 1994). Similar to neuronal NOS, eNOS produces small amounts of NO for prolonged periods of time. An **inducible NOS isoform, iNOS, is NADPH dependent but Ca^{2+} independent** and has been identified in ureteral smooth muscle (Smith et al, 1993). iNOS produces larger amounts of NO for short periods of time.

NOS-containing nerves have been demonstrated in the human ureter (Stief et al, 1993, 1996; Goessl et al, 1995; Iselin et al, 1998), and NOS has been demonstrated in the pig UVJ (Hernández et al, 1995; Phillips et al, 1995) and the upper ureter and calyces of pigs and humans (Iselin et al, 1998, 1999). NOS co-localizes with vasoactive polypeptide and neuropeptide Y (NPY) in nerves supplying the human ureter, including the intravesical segment (Smet et al, 1994; Iselin et al, 1997). NOS seems to localize in parasympathetic and sensory nerves but not in adrenergic neurons. In primary cultures of rat ureteral cells, NO production was detected in urothelial but not in smooth muscle cells (Mastrangelo et al, 2003). These cells contain both eNOS and iNOS.

There is evidence that the NO pathway is involved in human ureteral relaxation (Stief et al, 1996; Iselin et al, 1997). The NO donor, SIN-1, relaxes human ureteral segments, an action that is inhibited by the **guanylyl cyclase inhibitor methylene blue.** NO donors also inhibit agonist-induced contractions of isolated pig calyceal and rat, pig, and human intravesical ureteral segments, an action that is associated with an increase in cGMP. Furthermore, NO has been shown to be involved in nonadrenergic, noncholinergic–induced relaxation of the pig UVJ (Hernández et al, 1995). There is also evidence that adenosine relaxes the pig intravesical ureter through a process independent of NO (Hernández et al, 1999).

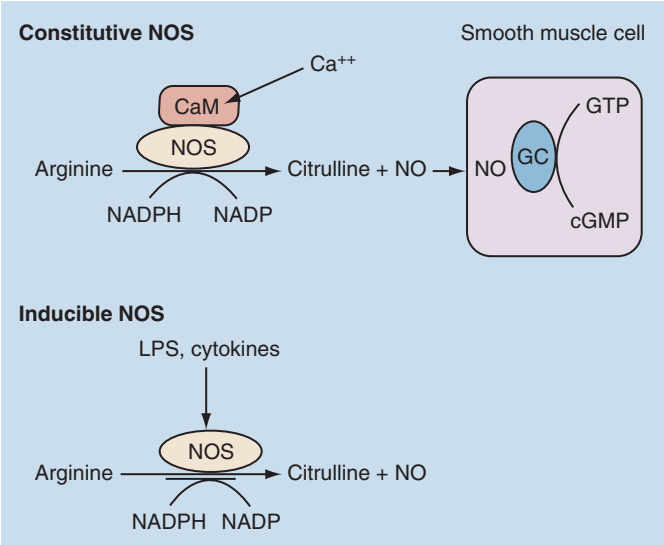


Figure 59–11. Schematic representation of inducible and constitutive nitric oxide synthase (NOS). CaM, calmodulin; GC; guanylyl cyclase; LPS, lipopolysaccharide.

Some actions of **α_1-adrenergic and muscarinic cholinergic agonists** and a number of other hormones, neurotransmitters, and biologic substances are associated with an increase in intracellular Ca^{2+} and are related to changes in inositol lipid metabolism. These agonists **combine with a receptor on the cell membrane, and the agonist-receptor complex, in turn, activates an enzyme, phospholipase C, that leads to the hydrolysis of polyphosphatidylinositol 4,5-bisphosphate, with the formation of two second messengers: inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DG)** (Berridge, 1984) (Fig. 59–12). The activation of phospholipase C involves a G protein. **IP_3 mobilizes Ca^{2+} from intracellular stores (i.e., endoplasmic or sarcoplasmic reticulum)** with an initiation of a cascade of events through the calmodulin branch of the Ca^{2+} messenger system. In smooth muscles, **IP_3 is thought to be involved in brief contractile responses or in the initial phase of sustained responses** (Park and Rasmussen, 1985).

The other second messenger, **DG, binds to an enzyme, protein kinase C (PKC),** translocates to the cell membrane, and, by reducing the concentration of Ca^{2+} required for PKC activation, results in an increase in this enzyme's activity. The **actions of PKC, and** thus **DG, involve the phosphorylation of proteins** (Nishizuka, 1984). The **PKC branch of the Ca^{2+} messenger system is thought to be responsible for the sustained phase of the contractile response in smooth muscle** (Park and Rasmussen, 1985) and is responsive to hormonally induced changes in intracellular Ca^{2+}. PKC has been implicated in Ca^{2+}-independent smooth muscle contractions (Yoshimura and Yamaguchi, 1997). Numerous PKC isoforms have been identified.

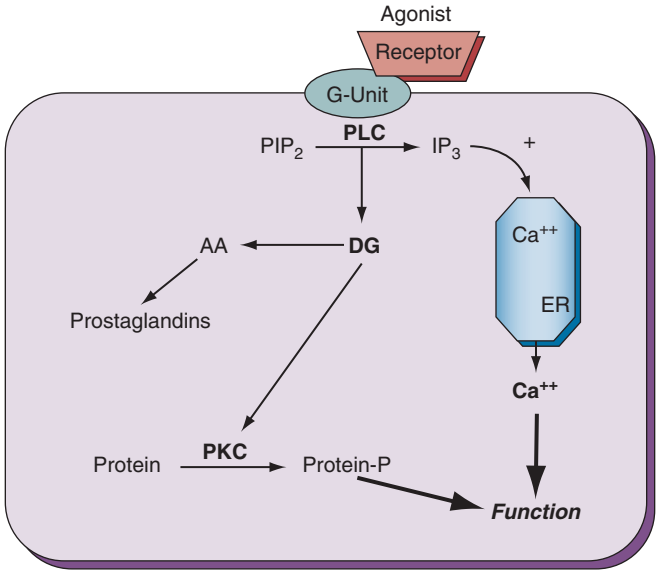


Figure 59–12. Schematic representation of the role of inositol lipid metabolism in smooth muscle function. The agonist combines with the receptor on the outer side of the cell membrane. The receptor-agonist complex in turn activates the enzyme phospholipase C (PLC), which leads to the hydrolysis of polyphosphatidylinositol 4,5-bisphosphate (PIP_2), with the formation of two second messengers, inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DG). The activation of PLC involves a G protein. IP_3 mobilizes calcium from intracellular stores (i.e., endoplasmic reticulum), and this leads to a functional response. DG binds to an enzyme, protein kinase C (PKC), which results in phosphorylation of proteins and a subsequent functional response. AA, arachidonic acid; ER, endoplasmic reticulum.

The functional activity and specificity of function of these isoforms appear to be primarily determined by the state of phosphorylation of the isoenzyme and its subcellular localization (Dempsey et al, 2000).

DG also activates the enzyme phospholipase A, which serves as a source of arachidonic acid, the substrate for prostaglandin synthesis (Mahadevappa and Holub, 1983). Arachidonic acid, in turn, may stimulate guanylate cyclase activity with the subsequent formation of cGMP (Berridge, 1984), and this would explain the Ca^{2+}-dependent increase in cGMP levels associated with muscarinic cholinergic and α_1-adrenergic agonist–induced contractions in smooth muscle. The observed increases in cGMP levels follow, rather than precede, the onset of contractions induced by these agonists.

Thus a group of second messengers are involved in the transduction of the signal that is initiated when an agonist combines with a specific receptor on the cell membrane of the smooth muscle. This process of **signal transduction** ultimately results in the functional response to the agonist.

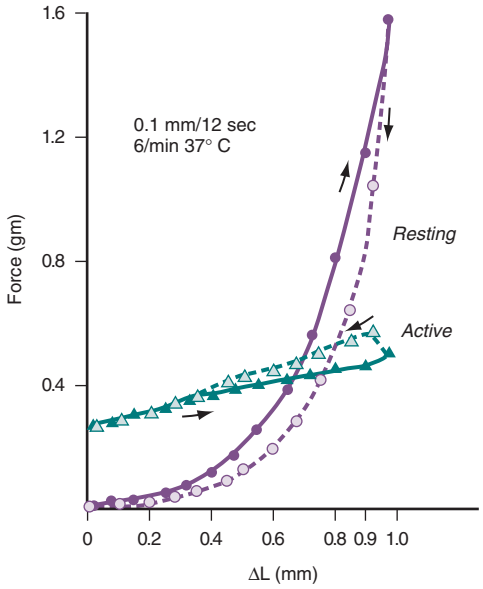


Figure 59–13. Hysteresis. Resting and contractile (active) force of cat ureter during muscle lengthening and shortening. Force is on the ordinate; change in length (ΔL) is on the abscissa. *Solid symbols* and *solid lines* show data obtained during muscle lengthening. *Open symbols* and *dashed lines* show data obtained during muscle shortening. *Circles* show resting force, and *triangles* show active or contractile force. Length and the direction of length change influence resting and contractile force. (From Weiss RM, Bassett AL, Hoffman BF. Dynamic length-tension curves of cat ureter. Am J Physiol 1972;222:388.)

MECHANICAL PROPERTIES

Mechanical characteristics of muscle are commonly assessed by defining force-length and force-velocity relations. Isometric force-length measurements depend on the number of linkages between the contractile proteins actin and myosin, which are brought into action during contraction. Force-velocity relations depend on the rate of formation and breakdown of linkages between the contractile proteins. Interventions may affect force-velocity relations, with or without affecting force-length relations. In addition to these methods of assessing mechanical properties of the ureter, the bidimensional nature of the ureter has lent itself to studies of pressure-length-diameter relations.

Force-Length Relations

Force-length relations express the relation between the force developed by muscle when it is stimulated under isometric conditions and the resting length of the muscle at the time of stimulation. With stretching of the ureter (muscle lengthening), the resting force (i.e., the tension present when the muscle is not excited) increases at a progressive rate (Weiss et al, 1972). The force developed during isometric contraction also increases with elongation until a length is reached at which the maximal contractile force is achieved. With further lengthening, the developed force decreases (Weiss et al, 1972; Thulesius et al, 1989). The ureter at this length is overstretched, or beyond the peak of its force-length curve. Ureteral resting tension is high at the length at which maximal contractile force is developed.

Because the ureter is a viscoelastic structure (Weiss et al, 1972), **the resting or contractile force developed at any given length depends on the direction in which the change in length is occurring and on the rate of length change** (Weiss et al, 1972; Vereecken et al, 1973). **This is referred to as hysteresis;** for the ureter, at any given length, the resting force is less, and the contractile force is greater when the ureter is allowed to shorten than when the ureter is being stretched (Fig. 59–13).

When the ureter is stretched, the resting force increases. If the length is kept constant at its new longer length after a stretch, changes occur that result in a decrease in the resting force, or stress relaxation (Fig. 59–14) (Weiss et al, 1972). Within certain limits, when the ureter is stretched to a length beyond the peak of the force-length curve—that is, when the ureter is stretched to a length at which the contractile force declines in the face of increasing muscle length—the degree of stress relaxation may be such that, within a period of time, the developed force no longer declines, even though the increased length is kept constant (Weiss et al, 1972). Stress relaxation can thus be considered a compensatory mechanism of a viscoelastic structure to stretch.

Force-Velocity Relations

Force-velocity curves depict the relation between the load and the velocity of shortening. A typical force-velocity curve, as predicted by Hill's equation for muscle shortening, has a hyperbolic configuration (Fig. 59–15) (Hill, 1938). From the force-velocity curve, one can extrapolate the **maximal velocity of shortening (V_{max}),** which **represents the velocity of shortening at zero load (i.e., at isotonic conditions).** V_{max} is determined by the level at which the force-velocity curve crosses the ordinate. V_{max} values in the ureter are in the range of 0.5 to 0.7 lengths per second (Biancani et al, 1984). The force-velocity curve intersects the abscissa at zero shortening, that is, at isometric conditions at which the load is great. Shortening depends on the total load lifted, with the ureter shortening to a lesser extent with heavier loads. At conditions near those of zero load, that is, conditions of free shortening (isotonic conditions), the in-vitro guinea pig ureter shortens by 25% to 30% of its initial length (Biancani et al, 1984).

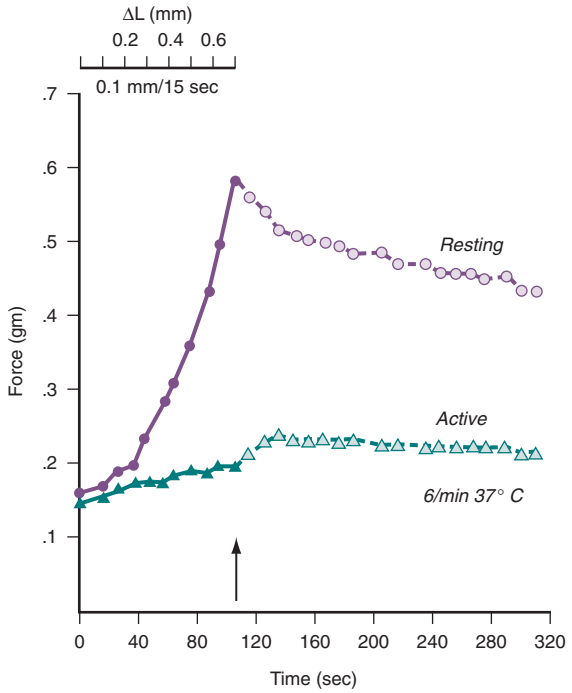


Figure 59–14. Stress relaxation. The resting and contractile (active) force of cat ureter is on the ordinate, the time from the onset of stretching is on the lower abscissa, and the change in length (ΔL) is on the left upper corner abscissa. Muscle is stretched by a given amount and then held at a fixed length. *Solid symbols* and *solid lines* show data obtained during muscle lengthening; *open symbols* and *dashed lines* show data obtained after stretching has ceased *(arrow)* and muscle is maintained at a constant length. Resting force decreases when muscle is held at a constant length after a stretch (stress relaxation). Contractile (active) force increases during this period of time. (From Weiss RM, Bassett AL, Hoffman BF. Dynamic length-tension curves of cat ureter. Am J Physiol 1972;222:388.)

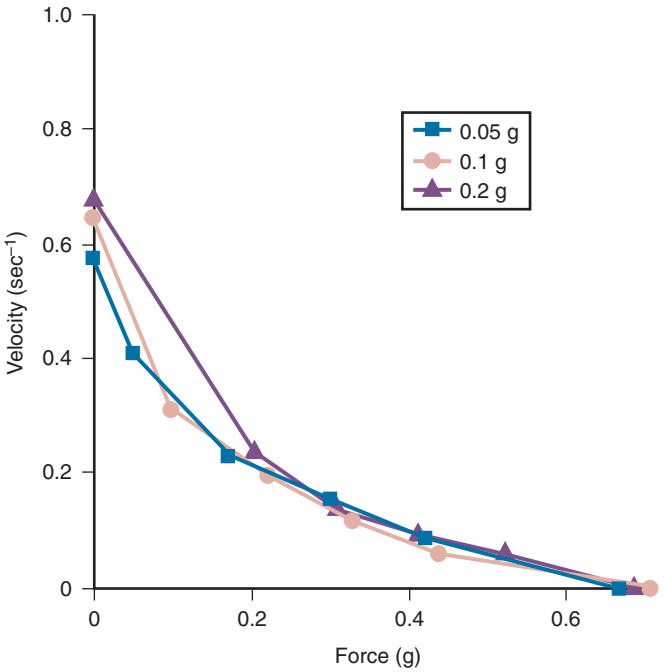


Figure 59–15. Force-velocity relation of guinea pig ureter. Specimens were stretched by three different preloads (0.05, 0.1, and 0.2 g). The velocity of shortening on the ordinate is plotted as a function of the total load lifted on the abscissa. V_{max} is obtained by extrapolating the experimental curves to intersect the ordinate. Isometric force is given by data points where velocity equals zero. (From Biancani P, Onyski JH, Zabinski MP, Weiss RM. Force-velocity relationships of the pig ureter. J Urol 1984;131:988. Copyright by Williams & Wilkins, 1984.)

Pressure-Length-Diameter Relations

Because ureteral muscle fibers are arranged in a longitudinal, circumferential, and spiral configuration (Tanagho, 1971), longitudinal and diametral deformation of the ureter are interrelated. Simultaneous studies of length and diameter changes in response to an intraluminal pressure load are another means of assessing the mechanical properties of a tubular structure. After application of an intraluminal pressure, the ureter increases in both length and diameter, a process known as *creep* (Biancani et al, 1973). Deformation in response to a given intraluminal pressure load is greater in vitro than in vivo; this difference is partially negated if the in-vivo preparation is pretreated with reserpine to suppress adrenergic influences (Fig. 59–16). Such data provide support for a role of the adrenergic nervous system in the control of ureteral function.

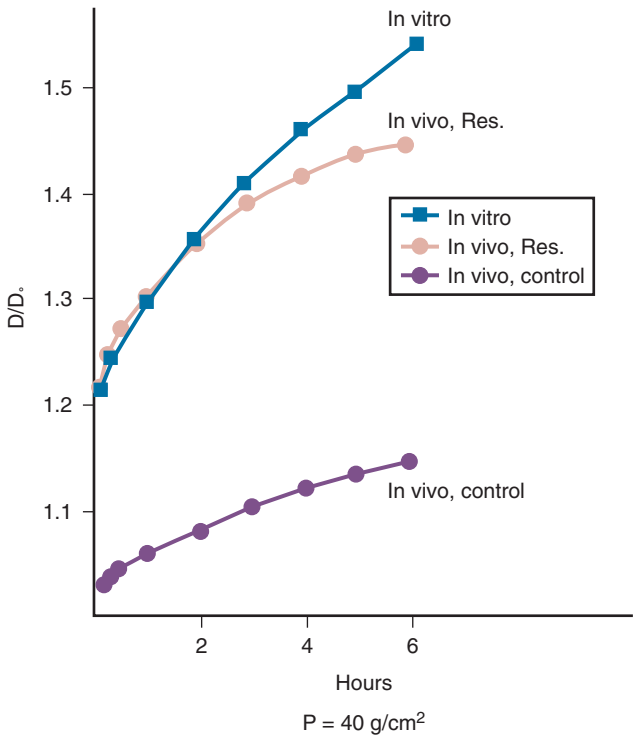


Figure 59–16. Pressure-diameter relations. An intraluminal pressure (P) load of 40 g/cm^2 is applied to rabbit ureters, and the change in diameter (D/D_0) is measured as a function of time. *Blue squares* show data obtained from in-vitro ureters. *Pink circles* show data obtained in vivo. *Purple circles* show data obtained in vivo from animals previously treated with reserpine. D_0, Initial diameter; D, diameter during deformation.

ROLE OF THE NERVOUS SYSTEM IN URETERAL FUNCTION

Some smooth muscles have a specific innervation of each smooth muscle fiber, whereas other, syncytial-type smooth muscles lack discrete neuromuscular junctions and depend on a diffuse release of transmitter from a bundle of nerves, with a subsequent spread

of excitation from one muscle cell to another. **The ureter is a syncytial type of smooth muscle without discrete neuromuscular junctions** (Burnstock, 1970).

Because peristalsis may persist after transplantation (O'Conor and Dawson-Edwards, 1959) or denervation (Wharton, 1932), because spontaneous activity may occur in isolated in-vitro ureteral segments (Finberg and Peart, 1970), and because normal antegrade peristalsis continues after reversal of a segment of ureter in situ (Melick et al, 1961), it is apparent that **ureteral peristalsis can occur without innervation**. However, analysis of the data in the literature clearly indicates that the **nervous system plays at least a modulating role in ureteral peristalsis**. Morita and colleagues (1987) have provided evidence that the autonomic nervous system may affect urine transport through the ureter by affecting both peristaltic frequency and bolus volume. Catecholamine fluorescence and acetylcholine (ACh) release studies indicate that the human ureter is supplied by sympathetic (noradrenaline-containing) and parasympathetic (ACh-containing) neurons (Duarte-Escalante et al, 1969; DelTacca, 1978).

Parasympathetic Nervous System

Although the role of the parasympathetic nervous system in the control of ureteral peristalsis has not been well defined, muscarinic cholinergic receptors have been demonstrated in the ureter of a number of species including the human (Latifpour et al, 1989, 1990; Hernández et al, 1993; Sakamoto et al, 2006), and acetylcholinesterase-positive nerve fibers have been demonstrated in the equine ureter (Prieto et al, 1994). The cholinergic innervation is especially rich in the distal and intravesical ureter (Hernández et al, 1993). Furthermore, ACh has been shown to be released from isolated guinea pig, rabbit, and human ureters in response to electric-field stimulation (DelTacca, 1978), and this release is inhibited by the neural poison tetrodotoxin. These data suggest but do not prove that the parasympathetic nervous system has at least a modulatory role in the control of ureteral activity.

The prototypic cholinergic agonist is acetylcholine (Ach), which serves as the neurotransmitter at (1) neuromuscular junctions of somatic motor nerves (nicotinic sites), (2) preganglionic parasympathetic and sympathetic neuroeffector junctions (nicotinic sites), and (3) postganglionic parasympathetic neuroeffector sites (muscarinic sites). ACh synthesis involves

$$\text{Acetyl CoA} + \text{Choline} \xrightarrow[\text{acetyltransferase}]{\text{choline}} \text{Ach}$$

where CoA is coenzyme A. The ACh is stored in vesicles within the synaptic terminal; its release depends on the influx of Ca^{2+} into the terminal, which presumably causes vesicle fusion with the presynaptic terminal membrane, thereby expelling ACh into the synaptic cleft. ACh subsequently is hydrolyzed by acetylcholinesterase. The muscarinic effects of cholinergic agonists can be blocked by atropine. The effects of nicotinic agonists can be blocked by nondepolarizing ganglionic blocking agents or by high concentrations of the nicotinic agonist itself, which may cause ganglionic blockade by desensitization of receptor sites after an initial period of ganglionic stimulation.

Cholinergic Agonists

Cholinergic agonists, including ACh, methacholine (Mecholyl), carbamylcholine (carbachol), and bethanechol (Urecholine), in general have been observed to have an excitatory effect on ureteral and renal pelvic function, that is, to increase the frequency and force of contractions (Vereecken, 1973; Longrigg, 1974; Rose and Gillenwater, 1974; Morita et al, 1986, 1987; Maggi and Giuliani, 1992; Hernández et al, 1993; Prieto et al, 1994). The excitatory effect of carbachol on isolated canine ureter has been attributed to be mediated by the M3-receptor subtype, and carbachol-induced inhibition of KCl-induced contractions of longitudinal canine ureteral preparations appears to be mediated primarily by the M4-receptor subtype (Tomiyama et al, 2003). ACh also has been shown to increase the duration of the guinea pig and rat ureteral action potential (Prosser et al, 1955; Ichikawa and Ikeda, 1960) and the number of oscillations on the plateau of the guinea pig ureteral action potential (Ichikawa and Ikeda, 1960). **The excitatory effects of cholinergic agonists may be related to an indirect release of catecholamines**—supported by the findings that the excitatory effects of bethanechol can be blocked by the α-adrenergic blocking agent phentolamine (Rose and Gillenwater, 1974), and that the increased frequency of canine ureteral peristalsis induced by ACh can be blocked by adrenalectomy (Labay et al, 1968) or to a direct effect of the drug on muscarinic receptors (Vereecken, 1973; Hernández et al, 1993; Tomiyama et al, 2003).

Nicotinic agonists, such as nicotine, tetramethylammonium, and dimethylphenylpiperazin, cause an initial stimulation of nicotinic receptors followed by desensitization of the receptor sites; the receptors then become unresponsive to nicotinic agonists and also to endogenous ACh, with a resultant transmission blockade. Nicotine, as would be expected, has been shown to have excitatory (Boyarsky et al, 1968), biphasic (Satani, 1919; Labay and Boyarsky, 1967), or inhibitory (Prosser et al, 1955; Vereecken, 1973) actions on the ureter that may be dose dependent.

Anticholinesterases

Anticholinesterases prevent the hydrolysis of ACh by cholinesterases and thus increase the duration and intensity of ACh action at both muscarinic and nicotinic receptor sites. With prolonged administration in high doses, they can result in desensitization blockade at nicotinic sites. The effects of **anticholinesterases**, such as **physostigmine and neostigmine**, parallel the excitatory effects of ACh and other parasympathomimetics on the ureter (Satani, 1919; Vereecken, 1973).

Parasympathetic Blocking Agents

Atropine is a competitive antagonist of the muscarinic effects of ACh. The inhibitory effects of atropine may be preceded by a transitory stimulatory effect on muscarinic receptors. Although atropine has been shown to inhibit the excitatory effects of parasympathomimetic agents (Vereecken, 1973; Longrigg, 1974) and physostigmine (Macht, 1916a) on a variety of ureteral and calyceal preparations, the majority of studies have shown that **atropine itself has little direct effect on ureteral activity in a number of species** (Gibbs, 1929; Gould et al, 1955; Butcher et al, 1957; Washizu, 1967; Vereecken, 1973; Reid et al, 1976), including humans (Kiil, 1957). **Even when atropine has been observed to inhibit ureteral activity, its effects are frequently minimal and inconsistent** (Ross et al, 1967), **thus providing little rationale for its use in the treatment of ureteral colic.**

Reports of the direct effects on ureteral activity of two other parasympathetic blocking agents, methantheline (Banth[i-macron]ne) and propantheline (Pro-Banth[i-macron]ne), also have been

inconsistent (Draper and Zorgniotti, 1954; Kiil, 1957; Reid et al, 1976).

Sympathetic Nervous System

The sympathetic nervous system appears to modulate ureteral activity as evidenced by the demonstration of adrenergic receptors in the ureter (Latifpour et al, 1989, 1990; Morita et al, 1994), the identification of catecholaminergic neurons in the ureter as determined by labeling tyrosine hydroxylase as a marker (Edyvane et al, 1994), and the demonstration that catecholamines are released from the ureter (Weiss et al, 1978) and renal calyx (Longrigg, 1975) in response to electric-field stimulation.

The ureter contains excitatory α-adrenergic and inhibitory β-adrenergic receptors (McLeod et al, 1973; Rose and Gillenwater, 1974; Weiss et al, 1978) that have been demonstrated with receptor-binding techniques (Latifpour et al, 1989, 1990). In the human ureter, α_{1D} and α_{1A} adrenoceptor subtypes are more prevalent than the α_{1B} adrenoceptor subtype (Sigala et al, 2005; Itoh et al, 2007). The highest density of α_1 adrenoceptors is found in the distal ureter with the relative density being $\alpha_{1D} > \alpha_{1A} > \alpha_{1B}$. **Norepinephrine**, **primarily an α-adrenergic agonist** (although it also can stimulate β-adrenergic receptors), increases the force of electrically induced ureteral contractions (Weiss et al, 1978). When administered in the presence of **phentolamine** (Regitine), **an α-adrenergic blocking agent,** norepinephrine, decreases the force of ureteral contractions (Weiss et al, 1978). A similar reversal of action occurs in the in-vivo ureter (McLeod et al, 1973) and can be explained by norepinephrine's primary action on inhibitory β-adrenergic receptors when the excitatory α-adrenergic receptors are blocked. Propranolol (Inderal), a β-adrenergic antagonist, potentiates the increase in contractile force induced by norepinephrine (Weiss et al, 1978). This can be explained by norepinephrine acting more exclusively on excitatory α-adrenergic receptors when the inhibitory β-adrenergic receptors are blocked. Furthermore, **isoproterenol, a β-adrenergic agonist,** depresses contractility (Weiss et al, 1978). These data provide evidence for excitatory α-adrenergic and inhibitory β-adrenergic receptors in the ureter and are in accord with the observations of McLeod and associates (1973) and Rose and Gillenwater (1974) on in-vivo ureters.

Further support for the presence of excitatory α-adrenergic and inhibitory β-adrenergic receptors in the ureter includes the demonstration of adenylyl cyclase activity in the ureter (Weiss et al, 1977; Wheeler et al, 1986) and the finding that the ureters of rabbits depleted of catecholamines by the administration of reserpine undergo greater degrees of deformation when a given intraluminal pressure is applied than would result from the application of the same pressure load to the ureters of normal, non–reserpine-treated animals (see Fig. 59–16) (Weiss et al, 1974). Finally, electric stimulation with high-intensity, high-frequency, short-duration stimuli has been shown to release neurotransmitter, presumably from intrinsic neural tissue within the wall of the ureter (Weiss et al, 1978) and renal calyx (Longrigg, 1975).

Adrenergic Agonists

Norepinephrine, the chemical mediator responsible for adrenergic transmission, is synthesized in the neuron from tyrosine. After its release from the nerve terminal, some of the norepinephrine combines with receptors in the effector organ, leading to a physiologic response. The greatest percentage of the norepinephrine is actively taken up (reuptake or neuronal uptake) into the neuron. Neuronal reuptake regulates the duration that norepinephrine is in contact with the innervated tissue and thus regulates the magnitude and duration of the catecholamine-induced response. Agents such as cocaine and imipramine (Tofranil), which inhibit neuronal uptake, potentiate the physiologic response to norepinephrine. The enzymes monoamine oxidase and catechol-*O*-methyltransferase provide degradative pathways for norepinephrine.

According to the general consensus, **agents that primarily activate α-adrenergic receptors, such as norepinephrine and phenylephrine, tend to stimulate ureteral and renal pelvic activity** (McLeod et al, 1973; Vereecken, 1973; Hannappel and Golenhofen, 1974; Rose and Gillenwater, 1974; Hernández et al, 1992; Rivera et al, 1992; Danuser et al, 2001), and **agents that primarily activate β-adrenergic receptors, such as isoproterenol and orciprenaline, tend to inhibit ureteral and renal pelvic activity** (Finberg and Peart, 1970; Ancill et al, 1972; McLeod et al, 1973; Vereecken, 1973; Hannappel and Golenhofen, 1974; Rose and Gillenwater, 1974; Weiss et al, 1978; Hernández et al, 1992; Rivera et al, 1992; Danuser et al, 2001). The β-adrenergic subtypes involved in ureteral relaxation are species specific: β_1 adrenoceptors in rats, β_2 adrenoceptors in rabbits, mainly β_3 adrenoceptors in dogs, and β_2 and β_3 adrenoceptors in pigs and humans (Tomiyama et al, 1998; Park et al, 2000; Tomiyama et al, 2003; Wanajo et al, 2004). A synthesized β_2/β_3-adrenoceptor agonist, KUL-7211 was a more potent relaxant of isolated dog ureteral segments than the α-adrenergic antagonists tamsulosin and prazosin, the calcium channel blocker verapamil, and the phosphodiesterase inhibitor papaverine (Wanajo et al, 2005). Intraluminal isoproterenol has been shown to lower renal pelvic pressures during ureteroscopy, with the presumption that this would decrease intrarenal backflow that has potential harmful effects (Jung et al, 2008). In the rabbit renal pelvis, β_2-adrenergic agonists inhibit contractile activity of the distal renal pelvis, and β_1-adrenergic agonists potentiate contractile activity of the proximal renal pelvis (Kondo et al, 1989). Tyramine, whose adrenergic agonist effects are due primarily to the release of norepinephrine from adrenergic terminals, also has a stimulatory effect on the upper urinary tract (Boyarsky and Labay, 1969; Finberg and Peart, 1970; Longrigg, 1974). The reported stimulatory effects of cocaine on ureteral activity (Boyarsky and Labay, 1969) may be explained by blockage of norepinephrine reuptake into adrenergic nerve endings, with a resultant increase in the magnitude and duration of the effect of norepinephrine.

Adrenergic Antagonists

The α-adrenergic antagonists phentolamine and phenoxybenzamine (Dibenzyline) have been shown to inhibit the stimulatory effects of norepinephrine and other α-adrenergic agonists in a variety of preparations (Finberg and Peart, 1970; Gosling and Waas, 1971; McLeod et al, 1973; Vereecken, 1973; Hannappel and Golenhofen, 1974; Longrigg, 1974; Rose and Gillenwater, 1974; Weiss et al, 1978; Hernández et al, 1992). The α-adrenergic antagonist doxazosin has been shown to slightly reduce spontaneous contractility of in-vitro pig ureter and to inhibit the contractile effects of epinephrine and phenylephrine (Nakada et al, 2007), and tamsulosin inhibited the contractility of human ureters in vitro (Rajpathy et al, 2008) and in vivo (Davenport et al, 2007). The β-adrenergic antagonist propranolol has been shown to block or attenuate the inhibitory effects of β-adrenergic agonists, such as isoproterenol, in a variety of preparations (McLeod et al, 1973; Vereecken, 1973; Longrigg, 1974; Rose and Gillenwater, 1974; Weiss et al, 1978).

Sensory Innervation and Peptidergic Agents in the Control of Ureteral Function

Sensory nerves can play both a sensory afferent and motor efferent role in a given tissue. Tachykinins and calcitonin gene–related peptide (CGRP) are neurotransmitters released from peripheral endings of sensory nerves (Maggi, 1995). **Tachykinins stimulate and CGRP inhibit electrical and contractile activity. Capsaicin-sensitive sensory nerves are located in the ureter** (Maggi et al, 1986; Maggi and Meli, 1988; Dray et al, 1989; Ammons, 1992) and contain the tachykinins, substance P, neurokinin A, and neuropeptide K (Hua et al, 1985; Sann et al, 1992), as well as CGRP (Gibbins et al, 1985; Sann et al, 1992; Tamaki et al, 1992). Immunoreactivity for tachykinins and CGRP is less in the human than in the guinea pig ureter (Su et al, 1986; Hua et al, 1987; Edyvane et al, 1992, 1994). Capsaicin in low doses inhibits ureteral activity, presumably due to the release of CGRP, but in high doses it increases ureteral activity, presumably due to release of the tachykinins neurokinin A, neuropeptide K, and substance P (Hua and Lundberg, 1986). Neonatal capsaicin administration causes degeneration of CGRP-containing sensory nerves in the rat ureter, which is accompanied by an increase in sympathetic (noradrenergic) innervation (Sann et al, 1995). Because NGF (nerve growth factor) is responsible for both increased sensory and noradrenergic innervation, capsaicin-induced degeneration of sensory nerves decreases NGF uptake into sensory neurons with a resultant increase in the amount of NGF available for stimulating sympathetic innervation (Schicho et al, 1998). The excitatory effects of the tachykinins are more prominent in the renal pelvis than in the ureter, and the inhibitory effects of CGRP are more prominent in the ureter than in the renal pelvis (Maggi et al, 1992b). The excitatory effects of tachykinins involve excitation of neurokinin-2 (NK-2) receptors in the human, pig, and guinea pig ureter; pig intravesical ureter; and guinea pig renal pelvis (Patacchini et al, 1998; Jerde et al, 1999; Bustamante et al, 2001; Nakada et al, 2001). The inhibitory actions of the neurotransmitter CGRP appear to involve multiple mechanisms (Maggi and Giuliani, 1991; Maggi et al, 1994b). By opening ATP-sensitive K^+ channels, CGRP causes membrane hyperpolarization with a resultant blocking of voltage-sensitive Ca^{2+} channels that are involved in generation of the ureteral action potential and ureteral contraction (Maggi et al, 1994c; Santicioli and Maggi, 1994; Meini et al, 1995). CGRP-induced ureteral relaxation may also result from stimulation of adenylyl cyclase activity with a resultant increase in cAMP (Santicioli et al, 1995b). The action of CGRP on the ureter may be regulated by an endopeptidase that degrades the CGRP released from the sensory nerves (Maggi and Giuliani, 1994).

Histochemical studies show that the tachykinins and CGRP co-localize in the same nerves in the ureter (Hua et al, 1987). Peptidergic neurons containing neuropeptide Y (NPY) and vasoactive intestinal polypeptide (VIP) also are present in the ureter (Allen et al, 1990; Edyvane et al, 1992; Prieto et al, 1997). VIP and pituitary adenylate cyclase–activating polypeptide (PACAP) have been shown to relax pig intravesical ureteral segments through a cyclic AMP–dependent mechanism (Hernández et al, 2004). Edyvane and associates (1994) have provided evidence of at least four, and possibly six, different immunohistochemical populations of nerve fibers in the human ureter. The predominant types include noradrenergic nerves containing NPY, neurons containing NPY and vasoactive polypeptide, neurons containing substance P and CGRP, and neurons containing CGRP. NPY potentiates the excitatory effects of norepinephrine on the ureter (Prieto et al, 1997). Rare coexistences also were observed between CGRP and vasoactive polypeptide, CGRP and NPY, and CGRP and tyrosine hydroxylase, a marker of noradrenergic neurons. These investigators demonstrated regional differences in the innervation of the ureter, with a more extensive innervation noted in the lower than in the upper ureter.

Renal pelvic sensory nerves contain both substance P and CGRP. Increases in renal pelvic pressure result in the release of substance P and a subsequent increase in afferent renal nerve activity. CGRP potentiates the afferent renal nerve activity responses to substance P (SP) by retarding the metabolism of SP, thus resulting in increased amounts of SP available for potentiating afferent renal nerve activity (Gontijo et al, 1999). Prostaglandins also contribute to sensory receptor activation (Kopp et al, 2000).

Nonadrenergic, noncholinergic (NANC) excitatory neurotransmission is functional in the pig intravesical ureter (Bustamante et al, 2000, 2001). In the presence of agents that block adrenergic neurotransmission, muscarinic cholinergic receptors, NO synthase activity, prostaglandin synthesis, and A_1/A_2 adenosine receptors, electrical-field stimulation (EFS, 5 Hz) induced contractions that were potentiated by the tachykinins SP and NKA, and that were inhibited by a sensory neurotoxin, capsaicin, and by a NK_2 receptor antagonist, GR94800. The EFS-induced contractions were abolished by tetrodotoxin, providing evidence that the contractions were neurogenic in origin. It has been suggested that tachykinins, especially neurokinin A (NKA), released from capsaicin-sensitive afferent nerves and activating NK_2 receptors are involved in NANC excitatory neurotransmission.

Purinergic Nervous System

Burnstock and associates (1972) postulated that ATP could act as an excitatory transmitter in the bladder. It was subsequently shown that ATP is released along with acetylcholine in response to nerve stimulation (Kasakov and Burnstock, 1983) and that the excitatory response in the bladder is mediated through P2X receptors (Theobald, 1995). ATP activation of P2X purinoceptors promotes influx of extracellular Ca^{2+} into the muscle cells with resultant contraction. **Although there is no evidence for ATP mediating contractions in the ureter, there is evidence to suggest that ATP is involved in nociceptive processes.** P2X receptors are present in the ureter (Lee et al, 2000), and release of ATP from the urothelium, in response to ureteral distention (Knight et al, 2002), stimulates afferent terminals by interacting with multiple purinergic receptors (Rong and Burnstock, 2004).

Two classes of mechanosensitive afferent fibers have been identified in the guinea pig ureter (Cervero and Sann, 1989). It would appear that one group of fibers are tension receptors that respond to normal ureteral peristalsis, whereas the others are involved in the signaling of noxious events, such as kidney stones and increased intraluminal pressures. Both groups are chemosensitive, being excited by K^+, bradykinin, and capsaicin (Sann, 1998). Because both ureteral distention and exogenous ATP increase afferent nerve discharge (Rong and Burnstock, 2004), ATP may be involved in signaling visceral pain with ureteral dilatation (Burnstock, 2006). It has been proposed that ureteral distension causes release of ATP from the urothelium, which, in turn, activates purinoceptors on suburothelial nociceptive sensory nerves. Consistent with this postulation, ATP has been shown to be

released with distention of isolated human ureteral segments, and this was accompanied by staining of P2X(3) and capsaicin receptors (Calvert et al, 2008).

URINE TRANSPORT

Physiology of the Ureteropelvic Junction

At normal urine flows, the frequency of calyceal and renal pelvic contractions is greater than that in the upper ureter, and there is a relative block of electric activity at the UPJ (Morita et al, 1981). At these flows, the renal pelvis fills; as renal pelvic pressure rises, urine is extruded into the upper ureter, which is initially in a collapsed state (Griffiths and Notschaele, 1983). Ureteral contractile pressures that move the bolus of urine are higher than renal pelvic pressures, and a closed UPJ may be protective of the kidney in dissipating back-pressure from the ureter. As the flow rate increases, the block at the UPJ ceases and a 1:1 correspondence between pacemaker and ureteral contractions develops (Constantinou and Hrynczuk, 1976; Constantinou and Yamaguchi, 1981).

With UPJ obstruction, there may be areas of narrowing or valve-like processes (Maizels and Stephens, 1980) or mucosal folds (Takeyama and Sakai, 2007). In other instances, there is no gross narrowing at the UPJ, and abnormal propagation of the peristaltic impulse is a causative factor in the obstruction. In these instances, there appears to be a functional obstruction at the UPJ, because a large-caliber catheter can be passed readily through the UPJ, even though urine transport is inadequate. Murnaghan (1958) related the functional abnormality to an alteration in the configuration of the muscle bundles at the UPJ, and Foote and associates (1970) observed a decrease in musculature at the UPJ. Hanna (1978), in an electron microscopic study of severe UPJ obstructions, noted abnormalities in the musculature of the renal pelvis and disruption of intercellular relations at the UPJ itself. Increased accumulation of collagen has been described in the region of the UPJ with obstruction (Murakumo et al, 1997), and it has been suggested that differences in types I and III collagen in the region of the obstructed UPJ may be age dependent (Yoon et al, 1998). Increases in smooth muscle, myosin heavy-chain isoforms also have been described in congenital UPJ obstruction (Hosgor et al, 2005). Studies also have shown a decrease in nerves and in nerve growth factor mRNA expression in UPJ obstruction specimens compared with controls (Wang et al, 1995; Murakumo et al, 1997). An increase in apoptosis of smooth muscle cells in the region of congenital UPJ obstruction has been reported to accompany a decrease in smooth muscle and nerve terminals and an increase in collagen and elastin (Kajbafzadeh et al, 2006). Defective contractility of UPJ segments obtained at the time of pyeloplasty has been described (Pontincasa et al, 2006). A vessel or adhesive band crossing the UPJ may potentiate the degree of dilatation in any of the forms of UPJ obstruction.

The differences in the reported findings suggest a histopathologic spectrum in the group of cases referred to as *UPJ obstructions*. **It appears possible that, at least in some instances, disruption of cell-to-cell propagation of peristaltic activity results in impairment of urine transport across the UPJ.**

One must consider input and output when predicting whether or not dilatation will occur; the effects of diuresis and obstruction appear to be complementary and additive regarding the development of renal pelvic and calyceal dilatation. Some UPJs can handle urine flow regardless of the magnitude of diuresis; others cause dilatation at even the lowest flows, and still others can handle low flows but cause massive dilatation at high flows (Fig. 59–17).

Propulsion of Urinary Bolus

The theoretical aspects of the mechanics of urine transport within the ureter have been described in detail by Griffiths and Notschaele (1983); these are depicted in Figure 59–18.

At normal flow rates, as the renal pelvis fills, a rise in renal pelvic pressure occurs and urine is extruded into the upper ureter, which is initially in a collapsed state. The contraction wave originates in the most proximal portion of the ureter and moves the urine in front of it in a distal direction. The urine that had previously entered the ureter is formed into a bolus. To propel the bolus of urine efficiently, the contraction wave must completely coapt the ureteral walls (Woodburne and Lapides, 1972; Griffiths and Notschaele, 1983), and the pressure generated by this contraction wave provides the primary component of what is recorded by intraluminal pressure measurements. The bolus that is pushed in front of the contraction wave lies almost entirely in a passive, noncontracting part of the ureter (Fung, 1971; Weinberg, 1974).

Baseline, or resting, ureteral pressure is approximately 0 to 5 cm H_2O, and superimposed ureteral contractions ranging from 20 to 80 cm H_2O occur two to six times per minute (Kiil, 1957; Ross et al, 1972). The urine traverses the UVJ to enter the bladder; when functioning properly, the UVJ ensures one-way transport of urine. The bolus is forced into the bladder by the advancing contraction wave that then dissipates at the UVJ.

As with any tubular structure, the ureter can transport a set maximal amount of fluid per unit time. Under normal flows, in which bolus formation occurs, the amount of urine transported per unit time is significantly less than the maximal transport capacity of the ureter. **At extremely high flows, as are employed in the standard perfusion studies** (Whitaker, 1973), **the ureteral walls do not coapt, and a continuous column of fluid, rather than a series of boluses, is transported.**

When transport becomes inadequate, stasis of urine occurs with resultant ureteral dilatation. **Inadequate transport can result either from too much fluid entering the ureter per unit time or from too little fluid exiting the ureter per unit time**. Both input and output must be considered in predicting whether or not ureteral dilatation will occur. For example, a minor degree of obstruction to outflow will cause more dilatation at high flow rates than at low flow rates. Even a normal nonobstructed ureter will impede urine transport if the rate of flow is great enough.

Changes in ureteral dimensions that occur in pathologic states may, per se, result in inefficient urine transport, even if the contractile force of the individual fibers is unchanged. The Laplace equation expresses the relation between the variables that affect intraluminal pressure:

$$\text{Pressure} = \frac{\text{tension} \times \text{wall thickness}}{\text{radius}}$$

An increase in ureteral diameter, itself, can decrease intraluminal pressure and result in inefficient urine transport. Such dimensional changes may, at least theoretically, be deleterious (Griffiths, 1983). Another factor may be the histologic composition of the dilated ureter, as evidenced by the description of different amounts of type I and type III collagen in primary obstructed and refluxing megaureters (Lee et al, 1998).

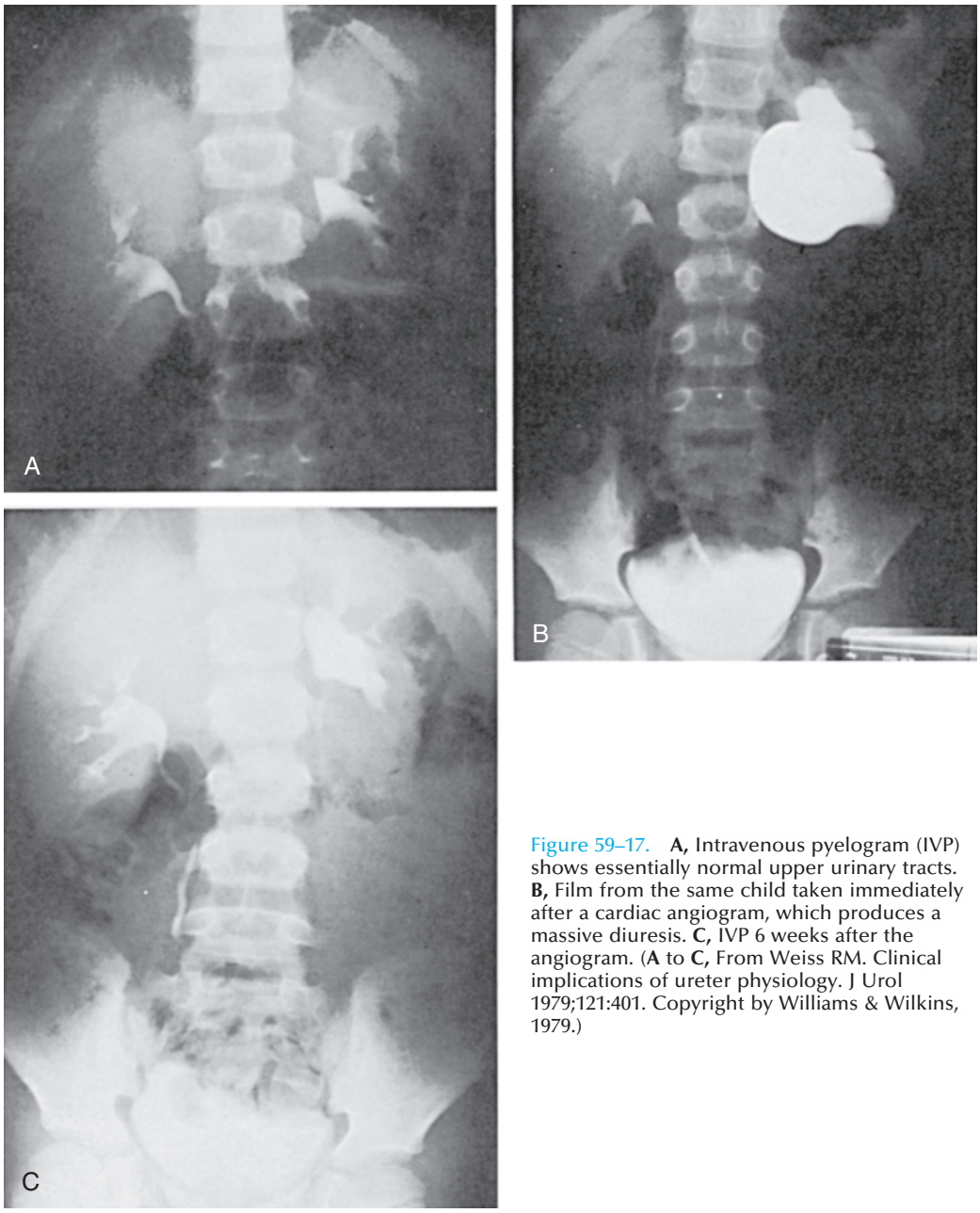


Figure 59–17. **A,** Intravenous pyelogram (IVP) shows essentially normal upper urinary tracts. **B,** Film from the same child taken immediately after a cardiac angiogram, which produces a massive diuresis. **C,** IVP 6 weeks after the angiogram. (**A** to **C,** From Weiss RM. Clinical implications of ureter physiology. J Urol 1979;121:401. Copyright by Williams & Wilkins, 1979.)

Effect of Diuresis on Ureteral Function

With increasing urine flow rates, the initial response of the ureter is to increase peristaltic frequency. After the maximal frequency is achieved, further increases in urine transport occur by means of increases in bolus volume (Morales et al, 1952; Constantinou et al, 1974). At relatively low flow rates, small increases in flow result in large increases in peristaltic frequency. At higher flow rates, relatively large increases in flow result in only small increases in peristaltic frequency. As the flow rate continues to increase, several of the boluses coalesce, and finally the ureter becomes filled with a column of fluid and dilates. At these high flow rates, urine transport is through an open tube.

Effects of Bladder Filling and Neurogenic Vesical Dysfunction on Ureteral Function

Ureteral dilatation can result either from an increase in fluid input or from a decrease in fluid output from the ureter. The relation between ureteral intraluminal pressure and intravesical pressure is important in determining the efficacy of urine passage across the UVJ into the bladder. In the case of the normal ureter under normal physiologic rates of flow, ureteral contractile pressure exceeds intravesical pressure, resulting in passage of urine into the bladder. In the dilated, poorly contracting ureter or in the normal ureter at extreme flow rates, the ureter does not coapt its walls to form boluses, and the baseline pressure in the column of urine

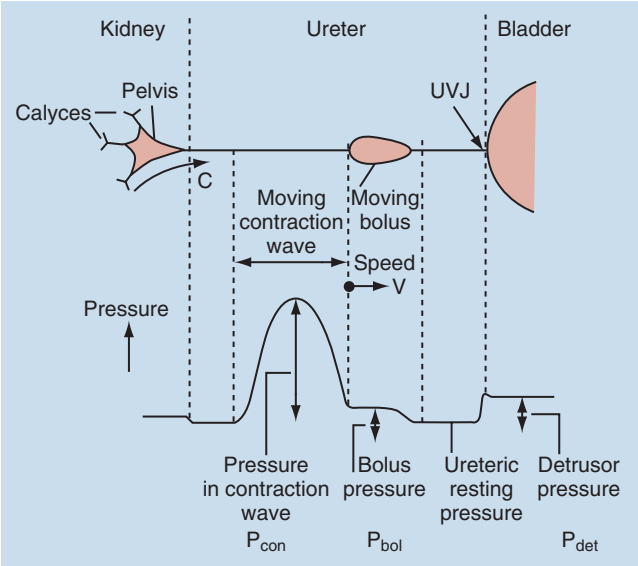


Figure 59–18. Schematic representation of a single bolus in the ureter moving away from the renal pelvis and toward the bladder. Arrow C indicates the direction of bolus transport. The corresponding distribution of pressure within the urinary tract is shown in the lower tracing. UVJ, ureterovesical junction. (From Griffiths DJ, Notschaele C. The mechanics of urine transport in the upper urinary tract. Neurourol Urodyn 1983;2:155.)

within the ureter must exceed intravesical pressure in order for urine to pass into the bladder.

The pressure within the bladder during the storage phase is of paramount importance in determining the efficacy of urine transport across the UVJ. This is the pressure that the ureter needs to work against for the longest period of time. During filling of the normal bladder, sympathetic impulses and the viscoelastic properties of the bladder wall inhibit the magnitude of the intravesical pressure rise, that is, the tonus limb. With filling, the normal bladder maintains a relatively low intravesical pressure (McGuire, 1983) that facilitates the transport of urine across the UVJ and prevents ureteral dilatation. In the noncompliant fibrotic bladder and in some forms of neurogenic vesical dysfunction, the bladder is autonomous, and relatively small increases in bladder volume result in large increases in intravesical pressure with resultant impairment of ureteral emptying. The ureter initially responds to its decreased ability to empty by increasing its peristaltic frequency (Zimskind et al, 1969; Rosen et al, 1971; Fredericks et al, 1972). Ultimately, stasis occurs with the development of ureteral dilatation. **The ureter has been shown to decompensate when intravesical pressure approaches 40 cm H_2O** (McGuire et al, 1981).

Physiology of the Ureterovesical Junction

Griffiths (1983) has analyzed the factors involved in urine transport across the UVJ. Under normal conditions and at normal flow rates, the contraction wave, which occludes the ureteral lumen, propagates distally with the urine bolus in front of it. When the bolus reaches the UVJ, the pressure within the bolus must exceed intravesical pressure so that the bolus of urine can pass across the UVJ into the bladder. Under these conditions, when the contraction wave can coapt the ureteral wall and move the urinary bolus distally, the pressure generated by the contraction wave exceeds the pressure within the urinary bolus. The contracted ureteral ring, just proximal to the ureteral orifice at the UVJ, is relevant in the antireflux mechanism (Roshani et al, 1996). As the bolus is ejected into the bladder, the distal ureter retracts within its sheaths; this telescoping of the ureter within its sheaths aids in decreasing UVJ resistance to flow and thus facilitates urine passage into the bladder (Blok et al, 1985). The UVJ does not relax (Weiss and Biancani, 1983). **Impediment of efficient bolus transfer across the UVJ into the bladder can occur when there is an obstruction at the UVJ, when intravesical pressure is excessive, or when flow rates are so high as to exceed the transport capacity of the normal UVJ. Under such conditions, when the bolus of urine cannot pass freely into the bladder, the pressure within the bolus increases and may exceed the pressure in the contraction wave. This results in an inability of the contraction wave to completely occlude the ureter; there is retrograde flow of urine from the bolus, and only a fraction of the urinary bolus passes across the UVJ into the bladder.** Griffiths (1983) has presented theoretical evidence to show that a similar situation of impaired bolus transport across the UVJ would be expected if the ureter was wide or weakly contracting, even if the UVJ was perfectly normal. The wider and more weakly contracting the ureter, the lower the UVJ resistance must be in order not to interfere with bolus transport. The resistance to flow at the UVJ has been variously attributed to forces in the trigone (Tanagho et al, 1968) and to detrusor pressure (Coolsaet et al, 1982).

The theoretical considerations outlined by Griffiths (1983) have direct clinical implications. **If the UVJ is obstructed (i.e., has an abnormally high resistance to flow) or if the detrusor pressure is excessive, large boluses occurring at high-flow conditions would not be completely discharged into the bladder, because the contraction wave pushing the bolus would be forced open and intraureteral reflux would occur.** Such obstruction at the UVJ would be detected by perfusion studies as popularized by Whitaker (1973) (i.e., the Whitaker test). On the other hand, Griffiths' (1983) theory suggests that a similar breakdown of bolus discharge into the bladder can occur in the wide or weakly contracting ureter at high flow rates even if the UVJ is normal, and that such a condition would go undetected by a Whitaker perfusion test.

There is evidence that gravity may assist urine transport and that the erect position may aid urine transport across the UVJ, especially in individuals with dilated upper tracts (Schick and Tanagho, 1973). From a practical standpoint, George and associates (1984) suggested that bed rest may be deleterious to renal function in individuals with urinary retention and wide upper urinary tracts.

PATHOLOGIC PROCESSES AFFECTING URETERAL FUNCTION

Effect of Obstruction on Ureteral Function

General

The effect of obstruction on ureteral function depends on the degree and duration of the obstruction, on the rate of urine flow, and on the presence or absence of infection. After the onset of obstruction, a backup of urine occurs within the urinary collecting system, along with an associated increase in baseline (resting) ureteral

intraluminal pressure and an increase in ureteral dimensions, that is, an increase in both length and diameter (Fig. 59–19) (Rose and Gillenwater, 1973; Biancani et al, 1976). **The increase in intraluminal pressure depends on the kidney's continued production of urine that cannot pass beyond the site of obstruction; the increase in ureteral dimensions results from the increased ureteral intraluminal pressure and the increased volume of urine retained within the ureter. A transient increase in the amplitude and frequency of the peristaltic contraction waves accompanies these initial dimensional and ureteral baseline (resting) pressure changes** (Rose and Gillenwater, 1978). **With time, as the ureter fills with urine, the peristaltic contraction waves become smaller and are unable to coapt the ureteral wall. Urine transport then becomes dependent on hydrostatic forces generated by the kidney** (Rose and Gillenwater, 1973). **Superimposed infection may result in a complete absence of contractions in the obstructed ureter and contributes to impairment of urine transport** (Rose and Gillenwater, 1973).

Within a few hours after the onset of obstruction, the intraluminal baseline ureteral pressure reaches a peak and then declines to a level only slightly higher than the normal baseline pressure. This occurs at a time when dimensional changes remain stable (Biancani et al, 1976). The decrease in ureteral pressure can be attributed to changes in intrarenal hemodynamics, such as a reduction in renal blood flow (Vaughan et al, 1971), with resultant decreases in the glomerular filtration rate and intratubular hydrostatic pressure (Gottschalk and Mylle, 1956). Fluid reabsorption into the venous and lymphatic systems and a decrease in wall tension also may play a role in the reduction in baseline ureteral pressure (Rose and Gillenwater, 1978). The persistence of dimensional changes in the face of a decrease in intraluminal pressure depends on the **hysteretic properties** of the viscoelastic ureteral structure (Fig. 59–20) (Weiss et al, 1972; Biancani et al, 1973, 1976; Vereecken et al, 1973).

As the obstruction persists, there is a gradual increase in ureteral length and diameter to considerable dimensions. This occurs even though ureteral pressure remains at a relatively low and constant level. This process, observed in viscoelastic structures, is referred to as creep (Biancani et al, 1973). Continued, albeit small, urine production is required for the continuing increase in intraureteral volume. Such changes account for the relatively low intrapelvic pressures clinically observed in the massively dilated, chronically obstructed upper urinary tract (Backlund et al, 1965; Struthers, 1969; Vela-Navarrete, 1971; Djurhuus and Stage, 1976); and in

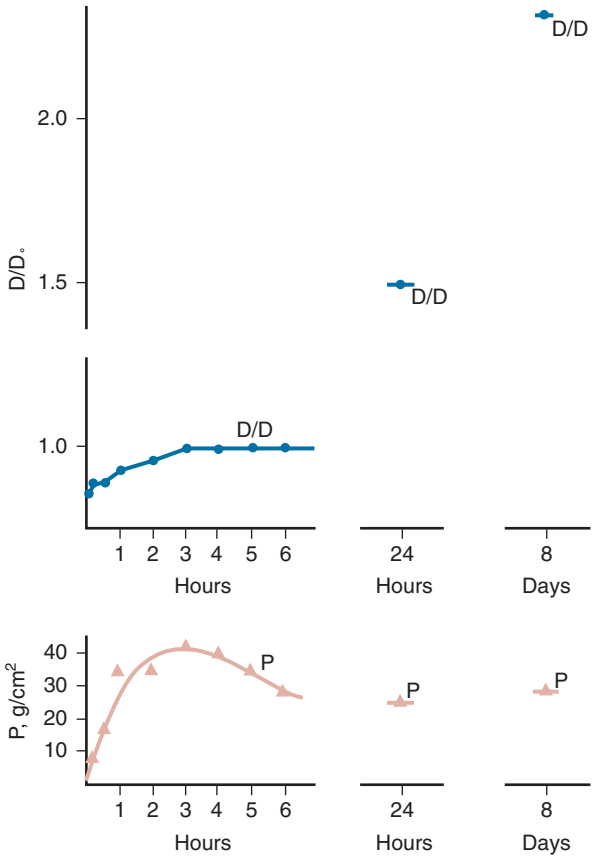


Figure 59–19. Intraluminal pressure and diameter changes after obstruction of rabbit ureter. The time from the onset of obstruction is on the abscissa. The change in diameter (D/D_0) is on the upper ordinate, and the intraluminal pressure is on the lower ordinate. During the initial 3 hours of obstruction, intraluminal pressure increased to reach a maximum and was associated with an increase in diameter. Between 3 and 6 hours after the onset of obstruction, pressure declined, although diametral deformation persisted. After 6 hours, pressure remained essentially unchanged, although the diameter continued to increase. Do, initial diameter; D, diameter during deformation; P, intraluminal pressure. (Adapted from Biancani P, Zabinski MP, Weiss RM. Time course of ureteral changes with acute and chronic obstruction. Am J Physiol 1976;231:393.)

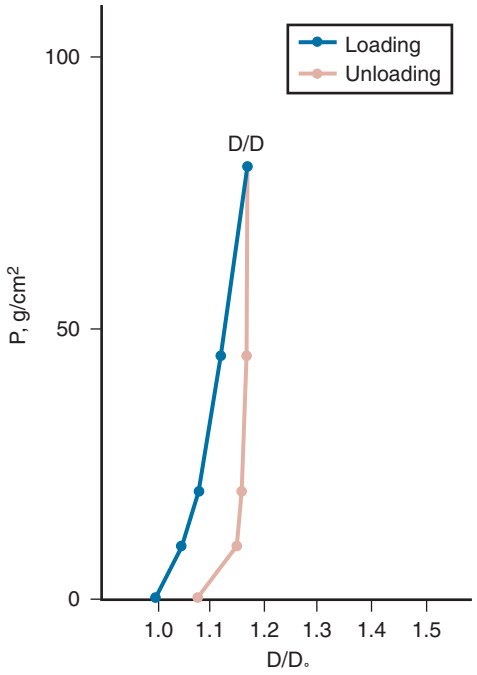


Figure 59–20. Demonstration of hysteretic properties of ureter show that dimensional changes depend on intraluminal pressure and on the direction of change of that pressure. At comparable pressures, deformations are greater during ureteral emptying than during ureteral filling. The *blue line* shows data obtained during loading; the *pink line,* data obtained during unloading. D_0, initial diameter; D, diameter during deformation; P, intraluminal pressure in grams per square centimeter. (Adapted from Biancani P, Zabinski MP, Weiss RM. Time course of ureteral changes with acute and chronic obstruction. Am J Physiol 1976;231:393.)

experimentally produced obstruction (Schweitzer, 1973; Koff and Thrall, 1981a). One could postulate that with prolonged complete obstruction, the total cessation of urine output ultimately occurs. A subsequent decrease in ureteral dimensions would depend on whether urine is reabsorbed and on the mechanical properties of the ureter at that time.

To determine the effect of obstruction on the contractile properties of the ureter, a rabbit model, in which the ureter is totally obstructed for 2 weeks, has been employed (Hausman et al, 1979; Biancani et al, 1982). After 2 weeks of obstruction, the cross-sectional muscle area increases by 250%, ureteral length by 24%, and ureteral outer diameter by 100%. In addition to undergoing **muscle hypertrophy**, in-vitro segments from obstructed ureters develop greater contractile forces, in both longitudinal and circumferential directions, than do segments from control ureters (Fig. 59–21). With experimental obstruction at the UPJ, there also is an increase in the frequency and amplitude of spontaneous mechanical contractions of the renal pelvis and an increase in the amplitude of phenylephrine and 5-hydroxytryptamine (5-HT)–induced contractions (Ekinci et al, 2004). Determinations of stress (force per unit area of muscle) provide a means of determining whether the observed increases in developed force result from an increase in contractility or from an increase in muscle mass alone. The increases in force were associated with an increase in maximal active circumferential stress but no change in maximal active longitudinal stress (Fig. 59–22). Because there is an increase in circumferential stress and no change in longitudinal stress, the sum of the stresses (total stress) or overall contractility increases after 2 weeks of obstruction. In order for these differences in longitudinal and circumferential stresses to occur after obstruction, rotation of muscle bundles must occur; otherwise, longitudinal and circumferential stresses would increase equally. The rotation could result from the greater increase in diameter than in length after obstruction, from remodeling of the muscle fibers, or from both. In addition to an increase in EFS-induced ureteral contractions with obstruction, carbachol, phenylephrine, and KCl also caused a greater increase in contractions in obstructed ureters, and the Rho-kinase inhibitor Y-27632 has a more pronounced effect in inhibiting these contractile events in the obstructed ureters (Turna et al, 2007). The expression of the two Rho kinase isoforms ROCK-1 and ROCK-2 is increased in the obstructed ureter (Turna et al, 2007).

Thus the ureter dilated after 2 weeks of obstruction is not mechanically decompensated but, rather, undergoes changes that result in an increase in contractility. **Despite both the muscle hypertrophy and the increase in contractility, it is clinically and experimentally evident that the obstructed, dilated ureter is less able than the normal ureter to generate the contractile pressures required for urine transport** (Rose and Gillenwater, 1973). The decrease in the ability to generate an intraluminal pressure, despite an increase in contractility, results from the increase in ureteral diameter that occurs after obstruction and can be explained by the **Laplace relation:**

$$\text{Pressure} = \frac{\text{stress} \times \text{wall thickness}}{\text{radius}}$$

Although contractility (stress) increases after 2 weeks of obstruction, the decrease in the wall's thickness-to-radius ratio, resulting from the marked increase in intraluminal diameter and thinning of the muscle layer, accounts for the decrease in pressure. It must be realized that a longer duration of obstruction or the presence of infection may alter these relations.

Estimates of intraluminal pressures as a function of diameter (pressure-diameter curves) can be calculated from in-vitro circumferential force-length data (Fig. 59–23) (Biancani et al, 1982; Weiss

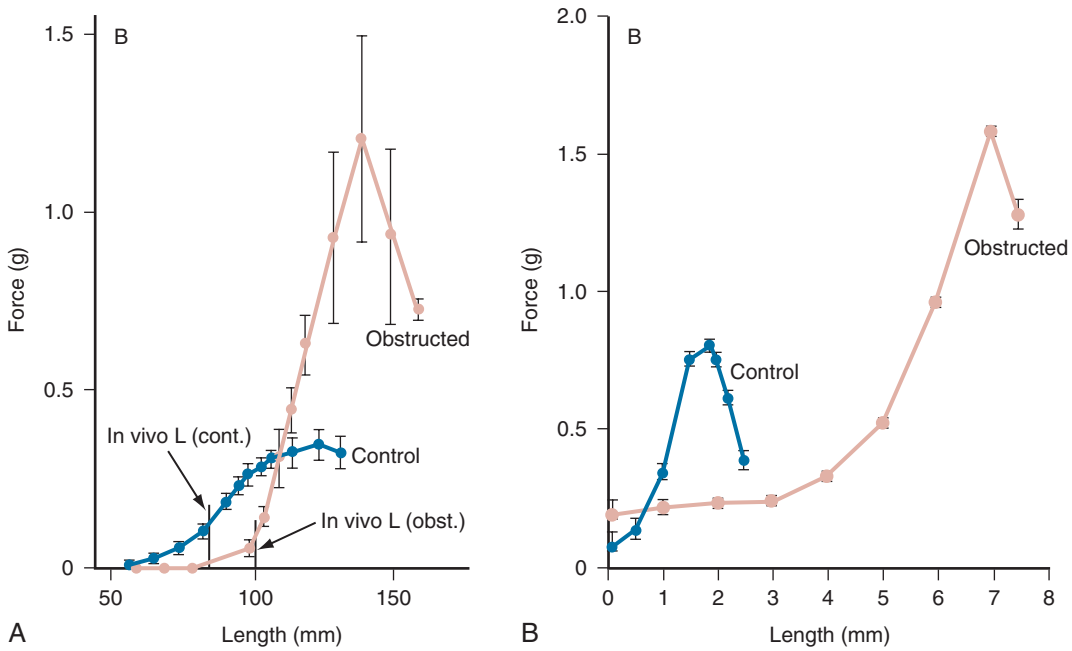


Figure 59–21. **A,** Active (contractile) longitudinal force-length relations of control *(blue circles)* and obstructed *(pink circles)* rabbit ureters. Each data point represents mean ± SEM. **B,** Active (contractile) circumferential force-length relations of obstructed *(pink)* and control *(blue)* ureteral rings. *Vertical bars* correspond to in-vivo lengths of control and obstructed segments. (**A,** From Hausman M, Biancani P, Weiss RM. Obstruction induced changes in longitudinal force-length relations of rabbit ureter. Invest Urol 1979;17:223. Copyright by Williams & Wilkins, 1979; **B,** from Biancani P, Hausman, M, Weiss RM. Effect of obstruction on ureteral circumferential force-length relation. Am J Physiol 1982;243:F204.)

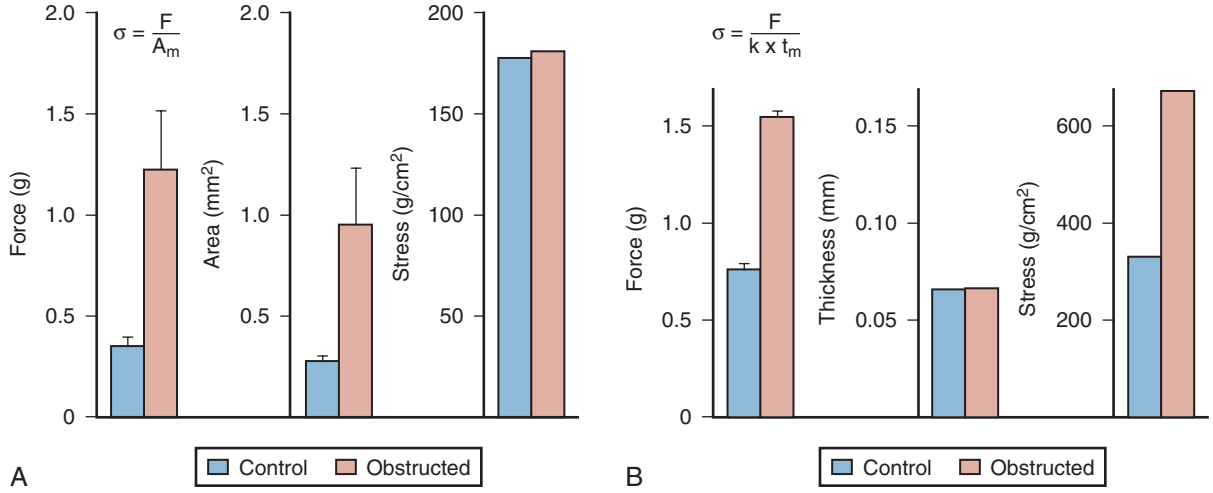


Figure 59–22. **A,** Longitudinal force, cross-sectional muscle area, and longitudinal stress at the length of maximal active force development. **B,** Circumferential force, average muscle thickness, and circumferential stress at the length of maximal active force development. σ, stress; F, force; A_m, cross-sectional muscle area; t_m, average thickness of muscle layer, a constant. (From Weiss RM, Biancani P. A rationale for ureteral tapering. Urology 1982;20:482.)

and Biancani, 1982) and provide insight as to how obstruction interferes with urine transport. The validity of such calculations is supported by their correspondence to actual in-vivo measurements (Rose and Gillenwater, 1973; Biancani et al, 1976). The obstructed ureter at in- vivo dimensions has a higher resting (baseline) pressure and a lower contractile (active) pressure than does a control ureter. In the control ureter, the total (active plus passive or resting) pressure developed at all diameters exceeds the passive pressure marked by the *horizontal dotted line,* and thus the generated active or contractile pressures are able to fully coapt the ureteral lumen and propel the urine bolus. In the obstructed ureter at diameters less than 3.3 mm, the passive pressure, as marked by the horizontal dotted line, exceeds the total pressure. The contraction ring therefore is incapable of contracting below this diameter, and the pressure in the whole ureter remains approximately uniform and equal to the passive pressure. The principal effect of the contraction wave in the obstructed dilated ureter is to slightly reduce the ureteral volume and thereby slightly raise the overall resting pressure. Thus although the obstructed ureter is able to develop greater circumferential contractile forces than the control ureter, the expected intraluminal pressure generated by the obstructed ureter would differ little from baseline (resting) pressure, and the contraction wave occurring during propagation of peristalsis would be incapable of coapting the ureteral lumen and propelling the urine bolus in an effective manner.

It should be noted that the calculated active pressure in the obstructed ureter estimates the pressure that would develop if the whole ureter contracted simultaneously and uniformly throughout its whole length, rather than the pressure measured in a peristaltic contraction wave, which involves contraction of only a small segment of ureter at a given time. The fact that the calculated pressures in the obstructed ureter are, if anything, a slight overestimate of expected pressures only further supports the conclusion that **the obstructed ureter is incapable of coapting its lumen and efficiently propelling the urine bolus. If, however, the urine were removed from the lumen of the ureter (e.g., by relieving the obstruction), the ureter obstructed for 2 weeks would be able to immediately coapt its lumen and produce pressures comparable with those of control ureters.** This can be appreciated from

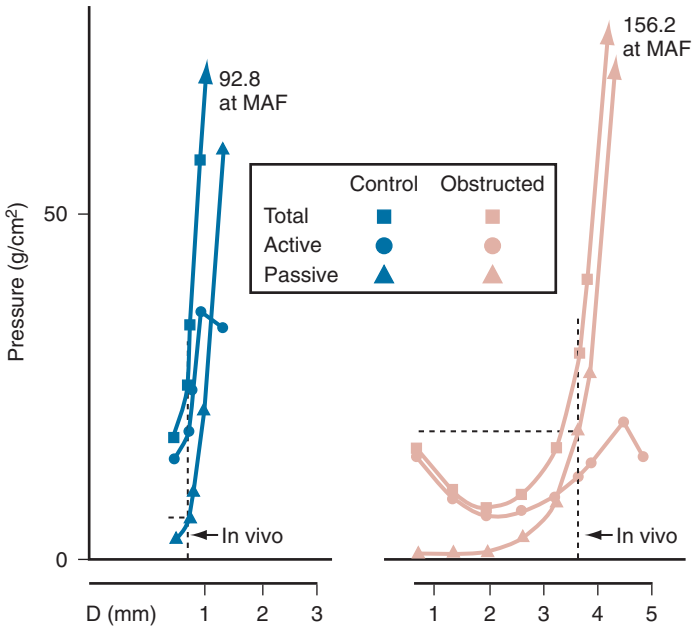


Figure 59–23. Pressure-diameter relationships of control and obstructed ureters. Calculated total, active, and passive pressures are shown as a function of intraluminal diameter (D). In-vivo passive pressures are indicated by *horizontal dashed lines* and in-vivo dimensions by *vertical dashed lines*. MAF, maximum active force. (Adapted from Biancani P, Hausman M, Weiss RM. Effect of obstruction on ureteral force-length relations. Am J Physiol 1982;243:F204.)

Figure 59–23, in which the total pressure in the obstructed ureter of near zero diameter is comparable to the total pressure in the control ureter of a similar diameter. Thus **2 weeks of obstruction results in an increase in ureteral contractility but a decrease in contractile intraluminal pressures.** This decrease in the ability to generate an active intraluminal pressure and to coapt the ureteral lumen impairs urine transport in the obstructed ureter.

Obstruction of the fetal ureter also is accompanied by an increase in ureteral weight, smooth muscle mass, extracellular

matrix, and the frequency and amplitude of spontaneous ureteral contractile activity (Santis et al, 2000). Obstructed and refluxing dilated ureters have an increase in type I and type III collagen and an increased ratio of collagen to smooth muscle (Gearhart et al, 1995; Lee et al, 1998). Hydrocortisone, verapamil (a calcium channel blocker), and D-penicillamine reduce collagen III production, which is increased in a variety of obstructed ureteral states and in ureteral cell cultures (Wolf et al, 1996). Obstruction also has been shown to alter the hierarchic organization of the multiple coupled pacemakers that normally coordinate peristaltic activity (Constantinou and Djurhuus, 1981; Djurhuus and Constantinou, 1982). Such disruption causes discoordination of pelvic contractility with resultant incomplete emptying of the renal pelvis that contributes to upper urinary tract dilatation.

Physiologic Methodologies for Assessing Clinical Obstruction

A variety of radiographic methodologies, the rationale for whose use is based on physiologic principles, are employed in the evaluation and differentiation of upper urinary tract dilatation and obstruction. Description of these examinations, which include diuretic urograms, diuretic MR urography, diuretic ultrasonography, diuretic radionuclide renograms, pulsed Doppler sonographic assessment of renal vascular resistance, and ultrasonographic evaluation of ureteral peristalsis are beyond the scope of this chapter. The best methods now available for differentiating obstructive from nonobstructive dilatation depend on assessing the efficacy of urine transport. When transport becomes inadequate, urine stagnates, and dilatation occurs. **Dilatation depends on the compliance of the system and can result either from too much fluid entering the system per unit time or from too little fluid exiting the system per unit time.** The properly functioning upper urinary tract should transport urine over the entire range of physiologically possible flow rates without undergoing marked deformational changes or increases in intraluminal pressure of a magnitude that would be deleterious to the function of the ureter, renal pelvis, or kidney.

Measurement of basal or resting intraluminal pressures does not help in differentiating obstructive from nonobstructive dilatation, because the pressures may be low even when obstruction is present (Backlund et al, 1965; Struthers, 1969; Vela-Navarrete, 1971). The values obtained vary with the state of hydration, the degree of renal function, the severity and duration of obstruction, and the compliance of the system. **Perfusion studies are used in an attempt to differentiate dilated systems that are obstructed from those that are not obstructed** (Backlund and Reuterskiöld, 1969a, b; Reuterskiöld, 1969, 1970; Whitaker, 1973, 1978). The technique involves cannulating the dilated upper urinary tract and perfusing the system at a rate of 10 mL/min. Pressures are measured after the achievement of steady-state conditions, which occur when an equilibrium is reached between the flow into and out of the system. Fluoroscopic monitoring aids in the interpretation of the data. **The basic hypothesis in perfusion studies is that if the dilated upper urinary tract can transport 10 mL/min (a fluid load greater than it would ever be expected to handle during usual physiologic states) without an inordinate increase in pressure, any degree of obstruction that is present is not clinically significant.** Whitaker (1978) and associates (1981) concluded from a large clinical experience that under these flow conditions, a pressure less than 15 cm H_2O correlates with a nonobstructive state, whereas pressures greater than 22 cm H_2O invariably correlate with clinically significant obstruction (Whitaker, 1978; Witherow and Whitaker, 1981). With this definition, minor degrees of obstruction could go undetected; however, **the presumption is that if at high flows the hydrostatic pressure in the system is not at a level that would produce renal deterioration, then lower and more physiologic flows surely will be tolerated.** The high flows are used to stress the system and thus to detect the slightest propensity to obstruction. The interpretation of data obtained by perfusion studies is schematically shown in Figure 59–24.

In order to obtain relevant information, strict adherence to detail is required in the performance of perfusion studies. Care must be taken to ensure that an equilibrium state has been reached before making pressure measurements. Extrinsic factors that affect the resistance to flow, such as the needle size, length and compliance of extrinsic tubing, viscosity of the perfusion fluid, temperature, and flow rate, must be considered when quantitative data are obtained (Toguri and Fournier, 1982). Furthermore, the bladder should be continuously drained to eliminate the bladder's effect on urine transport.

When performed and interpreted properly, perfusion studies may provide clinically relevant information in selected cases. The basic problem in the interpretation of data with this and other

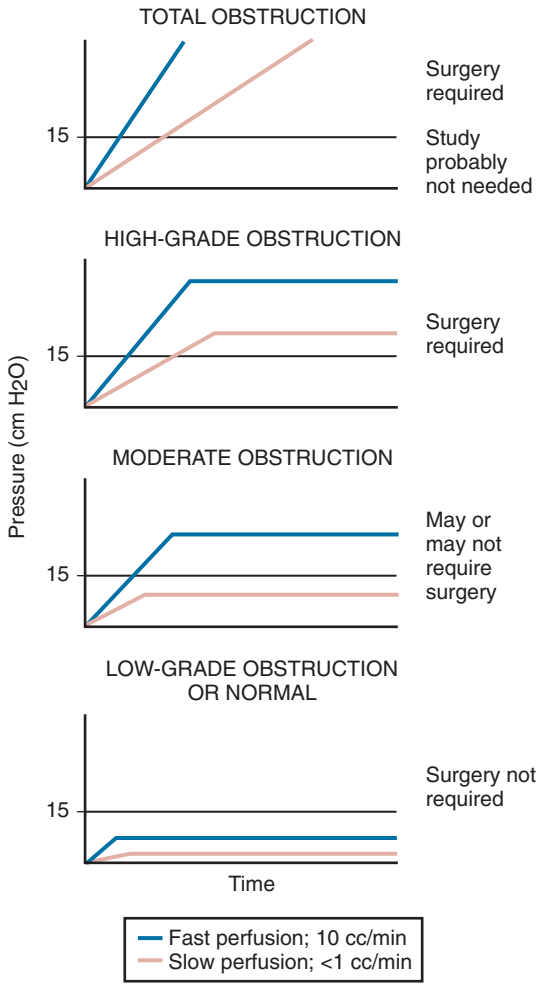


Figure 59–24. Schematic representation of data that can be obtained with perfusion studies. A fast perfusion rate, 10 mL/min, would be used in a standard Whitaker test. A slow perfusion rate, less than 1 mL/min, would be closer to more physiologic rates of flow. (From Weiss RM. Clinical implications of ureteral physiology. J Urol 1979;121:401. Copyright by Williams & Wilkins, 1979.)

diagnostic methods is the definition of "clinically relevant obstruction"—that is, just how much resistance to flow or increase in pressure is required to produce renal functional or anatomic deterioration as a function of time, taking into account the compliance of the system (Koff and Thrall, 1981b). Also, it is theoretically possible that the wide or weakly contracting ureter at high flow rates may interfere with bolus transport even if the UVJ is normal (Griffiths, 1983). Such an obstructive process would not be detected by perfusion studies.

These theoretical considerations provide a rationale for **ureteral tapering** (Hendren, 1970). The Laplace relation provides a possible explanation for anticipated improvement in function resulting from tapering. With ureteral tapering, muscle thickness and the ability of the ureteral fibers to contract (stress) are unchanged. The decrease in radius resulting from tapering itself, according to the Laplace relation, could account for higher intraluminal pressures, which could improve urine transport. Thus the tapered ureter may coapt its walls more readily and generate higher intraluminal pressures even though the material itself has not changed (Weiss and Biancani, 1982). Although the possibility of deleterious effects of the wide "nonobstructed" ureter remains controversial, one should consider such effects when interpreting data obtained with the present modalities for diagnosing obstruction and when determining management.

Relation between Vesicoureteral Reflux and Ureteral Function

Factors that have been implicated in the development of vesicoureteral reflux include (1) anatomic and functional abnormalities at the UVJ, (2) inordinately high intravesical pressures, and (3) impaired ureteral function. The normal intravesical ureter is approximately 1.5 cm in length and takes an oblique course through the bladder wall. It is composed of an intramural segment surrounded by detrusor muscle and a submucosal segment that lies directly under the bladder urothelium (Tanagho et al, 1968). The relation between the length and the diameter of this intravesical segment of ureter appears to be a factor in the prevention of vesicoureteral reflux (Paquin, 1959). Reflux may occur when the intravesical tunnel is destroyed. Trigonal function may also be a factor in the prevention of vesicoureteral reflux. Tanagho and associates (1965) created vesicoureteral reflux in the cat by disruption of the trigone or by sympathectomy and, conversely, increased the pressure within the intravesical ureter by electric stimulation of the trigone or by administration of IV epinephrine. The development of vesicoureteral reflux in individuals with bladder outlet obstruction and neurogenic vesical dysfunction provides evidence that increased intravesical pressures may also be a factor in certain instances of reflux.

A significant percentage of units with vesicoureteral reflux improve spontaneously with age. In a study by Jorgensen et al (1984), 35% of young pigs had vesicoureteral reflux that disappeared with age. In the pig, significant growth and organization of smooth muscle and increase in innervation occurs during the postnatal period, and this might be the anatomic correlate of maturation of the UVJ during infancy and the spontaneous functional disappearance of reflux (Pirker et al, 2007).

Although an abnormality of the UVJ is the primary etiologic factor in most cases of reflux, there is evidence to suggest that decreased ureteral peristaltic activity can be a contributory factor. This may explain why a normal ureter may not reflux even when reimplanted into a bladder without a submucosal tunnel (Debruyne et al, 1978), or why a defunctionalized refluxing ureter may cease to reflux when a proximal diversion is taken down (Teele et al, 1976; Weiss, 1979). The observation that vesicoureteral reflux may temporarily cease after ureteral electric stimulation (Melick et al, 1966) further supports this possibility.

Even the mildest forms of vesicoureteral reflux are associated with a decreased frequency of ureteral peristalsis (Kirkland et al, 1971; Weiss and Biancani, 1983). Although this may offer further evidence that decreased peristaltic activity is a possible etiologic factor in the development of reflux, an alternative interpretation is that the decreased peristaltic activity reflects changes in ureteral or renal function resulting from the reflux. Finally, the success rate of antireflux procedures is lower with poorly functioning dilated ureters, and, although this may be related to technical factors, decreased peristaltic activity may be another reason for failure in many instances.

Studies in normal and mildly refluxing systems have shown that there is a high-pressure zone in the distal ureter, with a resultant pressure gradient across the UVJ (Weiss and Biancani, 1983). Although the cause of the UVJ gradient is not known, the weight of the fluid within the bladder compressing the intravesical ureter may be a factor. Another causative factor may be bladder or trigonal tension involving myogenic or neurohumoral mechanisms. With bladder filling, there is an increase in the amplitude of the high-pressure zone that is greater in nonrefluxing than in refluxing systems. With bladder filling, the resultant UVJ–bladder pressure gradient increases in nonrefluxing systems, whereas it decreases and may disappear in refluxing systems (Fig. 59–25) (Weiss and Biancani, 1983). This decrease in pressure gradient may correspond to the time when reflux occurs and may be related to lateralization of the ureteral orifice and shortening of the intravesical tunnel. More recent studies have shown a decrease in basal and maximum pressures at the UVJ of refluxing ureters that correlated with histologic changes (Arena et al, 2007). The histologic changes included a degree of smooth muscle deterioration and atrophy, an increase in collagen deposition and fewer c-KIT–positive ICC-like cells at the UVJ in patients with vesico-ureteral reflux (Oswald et al, 2004; Schwentner et al, 2005; Arena et al, 2007). Contraction of the longitudinal muscles at the UVJ also may function as an active antireflux mechanism (Schwentner et al, 2005).

Effect of Infection on Ureteral Function

Infection within the upper urinary tract may impair urine transport. Pyelonephritis in the monkey has been associated with decreased peristaltic activity (Roberts, 1975). Furthermore, Rose and Gillenwater (1973) have shown that infection can potentiate the deleterious effects of obstruction on ureteral function. In 1913, Primbs showed that *Escherichia coli* and staphylococcal toxins inhibited contractions of in-vitro guinea pig ureteral segments. A number of studies have confirmed that bacteria and *E. coli* endotoxin can inhibit ureteral activity (Grana et al, 1965; King and Cox, 1972), although these findings have not been universal (Struthers, 1976). Thulesius and Araj (1987) also failed to suppress ureteral activity with *E. coli* endotoxin but noted that growth supernatants from *E. coli*, *Pseudomonas aeruginosa,* and *Klebsiella pneumoniae* inhibited ureteral contractility. These investigators suggested that the inhibition of peristaltic activity is due to an exotoxin.

In humans, irregular peristaltic contractions with often-decreased amplitude have been recorded with infection, and an absence of activity has been noted in the more severe cases (Ross

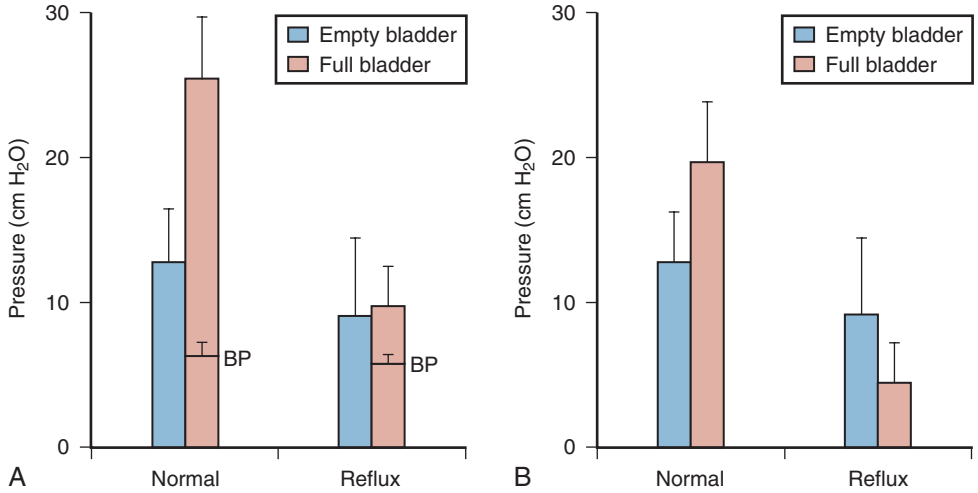


Figure 59–25. **A,** Ureterovesical junction pressures. Bladder pressure is approximately 0 cm H_2O with the bladder empty and is labeled BP with the bladder full. **B,** Pressure gradient across the ureterovesical junction, obtained by subtracting the bladder pressure from the ureterovesical junction pressure. (From Weiss RM, Biancani P. Characteristics of normal and refluxing ureterovesical junctions. J Urol 1983;129:858. Copyright by Williams & Wilkins, 1983.)

et al, 1972). Furthermore, ureteral dilatation has been reported to result from retroperitoneal inflammatory processes secondary to appendicitis, regional enteritis, ulcerative colitis, or peritonitis (Makker et al, 1972). Infection may also reduce the compliance of the intravesical ureter and permit reflux to occur in situations in which the UVJ is intrinsically of marginal competence (Cook and King, 1979).

Effect of Calculi on Ureteral Function

Factors that affect the spontaneous passage of calculi are (1) the size and shape of the stone (Ueno et al, 1977), **(2) intrinsic areas of narrowing within the ureter, (3) ureteral peristalsis, (4) hydrostatic pressure of the column of urine proximal to the calculus** (Sivula and Lehtonen, 1967), **and (5) edema, inflammation, and spasm of the ureter at the site at which the stone is lodged** (Holmlund and Hassler, 1965).

In an attempt to understand the physiologic processes that contribute to or hinder the passage of stones through the ureter, Crowley and associates (1990) created acute ureteral obstruction in the dog with an intraluminal balloon catheter and measured intraluminal ureteral pressures and peristaltic activity above and below the acutely obstructed site. The peristaltic rate and baseline, peak, and delta (peak minus baseline) pressures increased proximal to the site of obstruction. In contrast, the peristaltic rate remained unchanged distal to the obstruction, despite decreases in the baseline, peak, and delta pressures. It was suggested that failure of transmission of effective peristalsis across the site of obstruction may hinder stone passage; however, this remains to be proved. In a more recent study, implantation of an artificial calculus in a rat ureter resulted in an increase in the amplitude of contraction, a decrease in the rate of contractions, and a decrease in baseline pressure (Laird et al, 1997). These changes persisted for a period after spontaneous passage of the calculus. It was suggested that the increased motility caused by a stone contributes to the visceral pain associated with ureteral stone passage.

Two factors that appear to be most useful in facilitating stone passage are an increase in hydrostatic pressure proximal to a calculus and relaxation of the ureter in the region of the stone. In support of the theory that hydrostatic pressure facilitates stone passage, artificial concretions with holes were shown to move more slowly in the rabbit and dog ureter than those without holes (Sivula and Lehtonen, 1967). Furthermore, ureteral ligation proximal to a concretion, which decreases hydrostatic pressure by decreasing urine output and decreases peristaltic activity proximal to a stone, hampers stone passage (Sivula and Lehtonen, 1967).

With respect to the potential facilitative effect of ureteral relaxation on stone passage, the spasmolytic agents phentolamine (an α-adrenergic antagonist), and orciprenaline and isoproterenol (β-adrenergic agonists), have been shown to dilate the ureteral lumen or decrease ureteral wall tension at the level of an artificial concretion and thus permit increased fluid flow beyond the concretion (Peters and Eckstein, 1975; Miyatake et al, 2001). In a human study, renal colic was relieved by meperidine in 83% of patients, by phentolamine in 63%, and by propranolol, a β-adrenergic antagonist that presumably would interfere with the β-adrenergic inhibitory actions of catecholamines, in 0% (Kubacz and Catchpole, 1972). These data suggest that drugs with spasmolytic effects on the ureter may relieve renal colic, whereas those with spasmogenic actions do not.

Pharmacologic data can be interpreted to imply that ureteral relaxation in the region of a concretion could aid in stone passage. Agents such as theophylline (Weiss et al, 1977; Green et al, 1987), with strong relaxant effects on the ureter have potential value in facilitating stone passage. In a rabbit in-vivo model, rolipram, a cAMP-specific phosphodiesterase (PDE) inhibitor (PDE 4 inhibitor), caused a more marked ureteral relaxation than did the nonspecific PDE inhibitors papaverine and theophylline, and without the circulatory side effects seen with the nonspecific PDE inhibitors (Becker et al, 1998). Because the relaxant effect of rolipram was similar in human and rabbit in-vitro ureteral segments, it was suggested that rolipram could potentially be beneficial in the treatment of renal colic and in the facilitation of stone passage (Becker et al, 1998). Rolipram also has been shown to relax pig intravesical ureteral segments (Hernández et al, 2004). In addition to the PDE 4 inhibitor rolipram, PDE 5 inhibitors (cGMP-specific PDE inhibitor) relax in-vitro human ureteral segments (Kuhn et al, 2000). The relaxant effects of the PDE

4 and PDE 5 inhibitors were paralleled by an increase in cAMP and cGMP, respectively. Gratzke and coworkers (2007) showed that PDE 5 inhibitors reversed KCl-induced increases in tension of isolated human ureteral segments, with a rank order of efficacy of vardenafil (Levitra) > sildenafil (Viagra) > tadalafil (Cialis). Species differences in PDE subtypes may exist. Although the nonspecific PDE inhibitor papaverine decreased the frequency of ureteral peristalsis in the pig, the PDE 4 inhibitor rolipram had no effect (Danuser et al, 2001).

A combination of the calcium channel blocker nifedipine, which causes ureteral relaxation, and the corticosteroid deflazacort, which reduces edema, was shown to facilitate spontaneous passage of 1-cm or smaller distal ureteral stones (Borghi et al, 1994; Porpiglia et al, 2000). Spontaneous expulsion of 79% of stones (average size 5.8 ± 1.8 mm) occurred in an average of 7 days in patients treated with nifedipine and deflazacort, compared with spontaneous passage of 35% of stones (average size 5.5 ± 1.4 mm) within an average of 20 days in untreated patients (Porpiglia et al, 2000). In a subsequent study, this same group showed that both nifedipine and the α-adrenergic antagonist tamsulosin, when combined with deflazacort, increased the rate of spontaneous passage of lower ureteral calculi, and in addition, tamsulosin, a selective $\alpha_{1A/1D}$-adrenergic receptor antagonist, reduced the time to spontaneous expulsion (Porpiglia et al, 2004, 2006). They showed that tamsulosin alone was effective in facilitating expulsion of distal ureteral stones, and that this effect was potentiated by steroids. Steroids alone were ineffective. α_1-Adrenergic receptors are present throughout the human ureter, with the greatest quantity of α_1-adrenergic receptors being in the distal ureter (Sigala et al, 2004, 2005). α_{1D} mRNA was expressed throughout the human ureter, with significantly greater amounts than the α_{1A}- and α_{1B}-receptor subtypes in the proximal and distal ureter. $\alpha_{1A/1D}$-adrenergic receptors are present in the distal ureter. A number of other studies have noted an increased spontaneous stone expulsion rate and expulsion rate after extracorporeal shock wave lithotripsy (ESWL), a decrease in renal colic, and an improved tolerance of ureteral stents with the administration of tamsulosin and other α-adrenergic antagonists (Cervenakov et al, 2002; Dellabella et al, 2003; Kupeli et al, 2004; Autorino et al, 2005; Gravina et al, 2005; Resim et al, 2005; Yilmaz et al, 2005; De Sio et al, 2006; Gravas et al, 2007; Liatsikos et al, 2007; Damiano et al, 2008; Losek and Mauro, 2008). Although most of the studies address the efficacy of tamsulosin in facilitating stone passage, Yilmaz and associates (2005) reported that doxazosin and terazosin were equally effective in facilitating stone passage. Dellabella and colleagues (2005) reported that tamsulosin was more effective than the calcium channel blocker nifedipine in facilitating stone expulsion.

Effect of Diabetes on Ureteral Function

In cases of diabetes, changes in bladder function affect the ureter. Additionally, there is some evidence of a direct effect of diabetes on the ureter. The length and velocity of movement of the urinary bolus is decreased in the streptozotocin (STZ) diabetic rat (Watanabe and Miyagawa, 2002). Although the frequency of contractions of in-vitro segments of the renal pelvis and ureter of STZ-induced diabetic rats are unchanged, the amplitude of contractions are increased in comparison with renal pelvic and ureteral segments from control sucrose-induced diuretic rats (Davidson and Lang, 2007). Capsaicin is known to release tachykinins from sensory nerves, and it is postulated that a supersensitivity of the upper urinary tract of STZ-induced diabetic rats to the sensory neurotoxin capsaicin, and to the sensory excitatory neuropeptides substance P and neurokinin A, results from a sensory neuropathy (Davidson and Lang, 2007).

EFFECT OF AGE ON URETERAL FUNCTION

Clinically, the response of the ureter to pathologic conditions varies with age. **More marked degrees of ureteral dilatation are observed in the neonate and young child than in the adult.** Experimental data corroborating this clinical impression can be derived from observed age-dependent differences in the response of in-vitro ureteral segments to an intraluminal pressure load. The neonatal rabbit ureter undergoes a greater degree of deformation in response to an applied intraluminal pressure than does the adult rabbit ureter (Akimoto et al, 1977). Furthermore, norepinephrine decreases the diametral deformation of the neonatal rabbit ureter in response to an applied intraluminal pressure but has little effect on the deformation of the adult rabbit ureter (Fig. 59–26). Thus the in-vitro neonatal rabbit ureter appears to be more compliant and more sensitive to norepinephrine than the adult rabbit ureter.

Age also affects the response of the ureter to β-adrenergic agonists; with aging, there is a decrease in the relaxant response to the β-adrenergic agonist isoproterenol (Wheeler et al, 1990). The relaxant response to β-adrenergic agonists is related, in part, to cAMP levels. It has been shown that with aging there is a decrease in the enzymatic activities involved in the synthesis of cAMP (Wheeler et al, 1986) but no change in the enzymatic activities involved in cAMP degradation (Cho et al, 1988). These data suggest that the decrease in the ability of isoproterenol to relax the ureter with aging is due to a decrease in the ability of isoproterenol to activate adenylyl cyclase, the enzyme involved in cAMP synthesis. Developmental differences in the response of the ureter to metabolic inhibitors are evident, with cyanide causing a larger decrease in force in the adult than in the neonatal guinea pig ureter (Bullock and Wray, 1998a, 1998b).

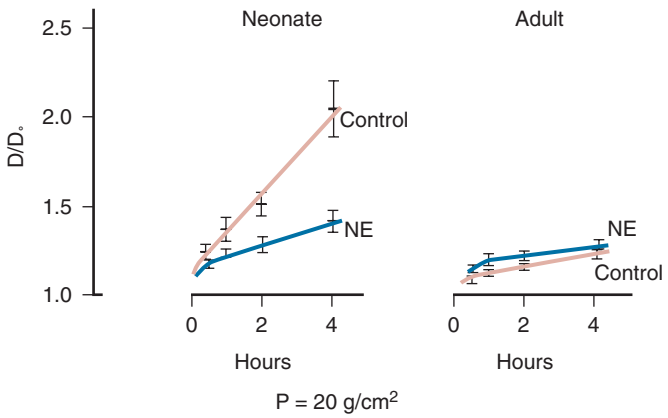


Figure 59–26. Changes in diameter of neonatal and adult rabbit ureteral segments as a function of time after the application of a constant intraluminal pressure (P) of 20 g/cm^2. Diametral deformation (D/D_0) of control neonatal ureters was significantly greater than that of control adult ureters. Norepinephrine (NE) (10^{-5} M) decreased the diametral deformation of the neonatal ureters but had no significant effect on the deformation of the adult ureteral segments. D_0, initial diameter; D, diameter during deformation; P, pressure. (From Akimoto M, Biancani P, Weiss RM. Comparative pressure = length – diameter relationships of neonatal and adult rabbit ureters. Invest Urol 1977;14:297.)

A progressive increase in ureteral cross-sectional muscle area is observed in the guinea pig between 3 weeks and 3 years of age. This is in accord with the findings of Cussen (1967), who noted in a human autopsy study (subjects ranging in age from 12 weeks of gestation to 12 years of age) that there is a progressive increase in the population of smooth muscle cells and a small increase in the overall size of the individual smooth muscle cells. In addition, an irregular increase in the number of elastic fibers was observed with increasing age.

The contractility of the ureter is also affected by age. The maximal active force of isolated guinea pig ureteral segments increases between 3 weeks and 3 years of age (Fig. 59–27) (Hong et al, 1980). The increase in force developed between 3 weeks and 3 months of age seems to be attributable to an increase in contractility, because there is an associated increase in active stress (force per unit area of muscle). The increase in force developed between 3 months and 3 years of age can be explained by an increase in muscle mass alone because there is no change in active stress between these two age groups (see Fig. 59–27).

Although changes in the force-length relations of guinea pig ureter occur with age, the force-velocity relations do not change with age (Biancani et al, 1984). Thus although ureteral contractility increases during early development, as shown by an increase in force per unit area of muscle, or stress, no significant change is apparent in the rate of the driving reactions that control the contractile process, that is, no change in shortening, velocity, work, or power.

EFFECT OF PREGNANCY ON URETERAL FUNCTION

Hydroureteronephrosis of pregnancy begins in the second trimester of gestation and subsides within the first month after parturition. It is more severe on the right side, and the ureteral dilatation does not occur below the pelvic brim. Roberts (1976) has presented a strong case in favor of obstruction as the etiologic factor in the development of hydroureteronephrosis of pregnancy, whereas other investigators have suggested a hormonal mechanism for the ureteral dilatation of pregnancy (van Wagenen and Jenkins, 1939).

Roberts (1976) emphasized the following: (1) Elevated baseline (resting) ureteral pressures consistent with obstructive changes have been recorded above the pelvic brim in pregnant women, and these pressures decrease when positional changes permit the uterus to fall away from the ureters (Sala and Rubi, 1967). (2) Normal ureteral contractile pressures recorded during pregnancy suggest that hormonally induced ureteral atony is not the prime factor in ureteral dilatation of pregnancy. (3) Women whose ureters do not cross the pelvic brim (i.e., those with pelvic kidneys or ileal conduits) do not develop hydronephrosis of pregnancy. (4) Hydronephrosis of pregnancy usually does not occur in quadrupeds, whose uterus hangs away from the ureters (Traut and Kuder, 1938). (5) Elevated ureteral pressures in the pregnant monkey return to normal when the uterus is elevated from the ureters at laparotomy or when the fetus and placenta are removed from the uterus.

Observed hormonal effects on ureteral function have been used to implicate a hormonal mechanism in the ureteral dilatation of pregnancy, although difficulties in interpretation arise from inconsistencies in the data. Several studies have shown an inhibitory effect of **progesterone** on ureteral function (Kumar, 1962). Progesterone has been noted to increase the degree of ureteral dilatation during pregnancy and to retard the rate of disappearance of hydroureter in postpartum women (Lubin et al, 1941). Other studies, however, have failed to demonstrate an effect of progesterone on ureteral activity in animals (McNellis and Sherline, 1967) or in humans (Lapides, 1948), and still others have failed to induce changes in ureteral activity in women through the

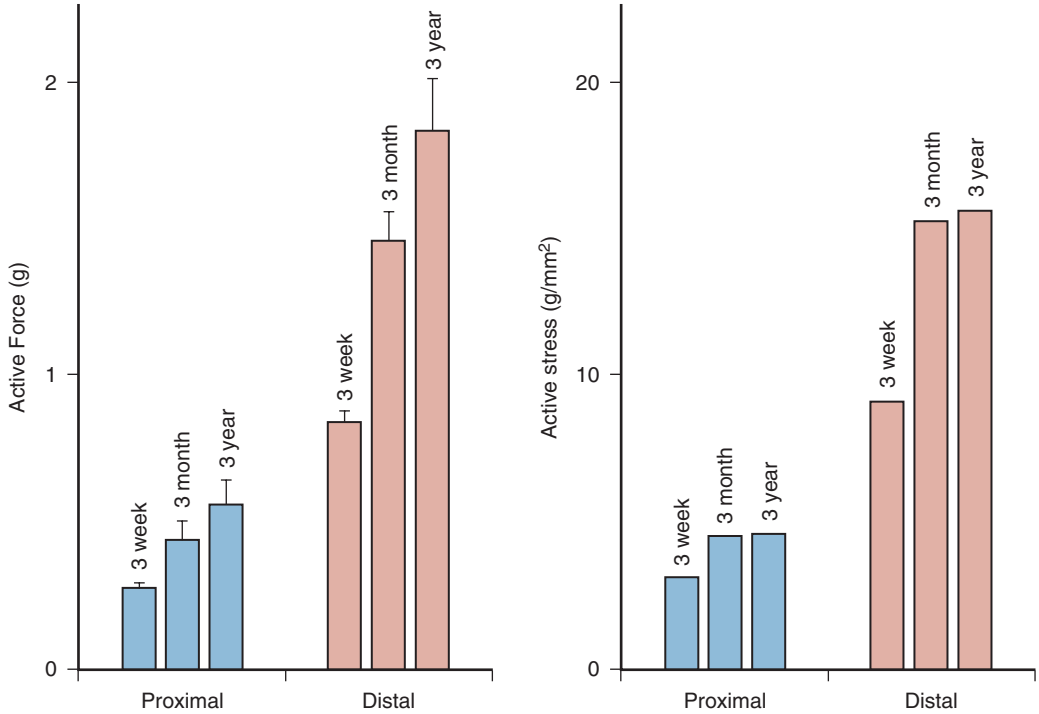


Figure 59–27. Maximal active (contractile) force and maximal active stress of proximal and distal guinea pig ureteral segments as a function of age.

administration of estrogens, progesterone, or a mixture of these drugs (Marchant, 1972; Clayton and Roberts, 1973). Although some workers have noted that estrogens increase ureteral activity (Hundley et al, 1942), the majority of investigators have failed to observe an effect of estrogens in animal models (Abramson et al, 1953) or in humans (Kumar, 1962). Thus **obstruction appears to be the primary factor in the development of hydronephrosis of pregnancy**, although some evidence suggests that a combination of hormonal and obstructive factors is involved (Fainstat, 1963).

EFFECT OF DRUGS ON THE URETER

This section provides an assessment of the effects of the major classes of drugs on ureteral function. Many of the studies referred to were performed in animal models, and extrapolation of the data to the intact human ureter is often difficult. In the clinical situation, the relatively sparse blood supply to the ureter limits the distribution of drugs to the ureter, and the pharmacokinetics is quite different in the laboratory than in the clinic. In addition, many drugs with potential usefulness in the management of ureteral abnormalities have potential untoward side effects when used in concentrations required to affect the ureter.

To assess the effect of drugs on the ureter, it is necessary to understand the anatomic, physiologic, and biochemical properties of the ureter, in addition to understanding the principles of drug action. For a drug to elicit a given response, it is necessary to achieve and maintain an appropriate concentration of that drug at its site of action. Factors that can influence the achievement of an effective concentration of drug at a site of action are (1) the route of administration and cellular distribution of the drug; (2) the dosage of the drug administered; (3) the biotransformation, including metabolism and excretion, of the drug; (4) the binding of the drug to plasma and tissue proteins; and (5) the effects of age and disease on the absorption, distribution, metabolism, and elimination of the drug.

The literature contains considerable confusing and conflicting information concerning the effects of drugs on the ureter. To some extent, the discrepancies in the available data are due to poorly controlled experimental procedures or to attempts to compare dissimilar functional responses of the ureter with a given drug. To simplify the present section, no attempt is made to analyze the validity of each pharmacologic study or to rationalize discrepancies in the literature; rather, an overview is presented with an attempt to provide a consensus that, at times, may be prejudiced by personal bias. Furthermore, discussion of drugs related to the nervous system, pregnancy, and a variety of pathologic states is included in earlier sections of this chapter.

Histamine and Its Antagonists

Histamine has a dual action on smooth muscle; it may (1) release catecholamines from sympathetic nerve endings or (2) act directly on receptors within the smooth muscle. In addition, **histamine may have excitatory or inhibitory effects on ureteral function**. The majority of studies have shown an excitatory effect of histamine on ureteral function (Borgstedt et al, 1962; Sharkey et al, 1965; Vereecken, 1973; Benedito et al, 1991; Smita et al, 2006), a finding that may be species dependent (Tindall, 1972). **Histamine's excitatory effect on the ureter and UVJ appears to be mediated by H_1 receptors** because they are inhibited by the H_1-receptor antagonists mepyramine, pheniramine, and dimethindene but not by the H_2-receptor antagonists cimetidine and ranitidine (Benedito et al, 1991; Dodel et al, 1996; Smita et al, 2006). An H_1 agonist, 2-(2-pyridyl)ethylamine, increases ureteral contractility (Dodel et al, 1996). The H_1 inhibitor pheniramine has no effect on spontaneous activity of isolated goat ureter (Smita et al, 2006). The excitatory effect of histamine on the sheep UVJ is partially blocked by scopolamine, suggesting an indirect stimulatory action of histamine on intramural parasympathetic nerves. H_1 histamine receptors are expressed in the smooth muscle and urothelium of the human ureter (Floyd et al, 2008). The antihistamines diphenhydramine (Benadryl) and tripelennamine have been shown to inhibit the effects of histamine on the ureter (Borgstedt et al, 1962; Sharkey et al, 1965). **The H_2 receptor mediates inhibitory effects of histamine**. Histamine and the H_2-receptor agonist impromidine relax precontracted ureteral segments, actions that are inhibited by the H_2-receptor antagonist cimetidine (Dodel et al, 1996).

Serotonin

Serotonin (5-hydroxytryptamine [5-HT]) has been reported to stimulate (Vereecken, 1973; Dodel et al, 1996; Hauser et al, 2002; Hernández et al, 2003), inhibit (Mazzella and Schroeder, 1960), or have no effect (Finberg and Peart, 1970) on a variety of ureteral preparations. In the pig ureter, the contractile effects appear to be mediated by 5-HT_2 receptors (Hauser et al, 2002; Hernández et al, 2003). Gidener et al (1999) showed that 5-hydroxytryptamine induces concentration-dependent contractions of isolated human ureteral segments. However, their studies suggested no involvement of 5-HT_2 receptors in the contractile effects of 5-hydroxytryptamine. Tetrodotoxin, guanethidine, and phentolamine had an inhibitory effect on 5-HT–induced contractions of pig isolated intravesical ureteral segments, suggesting that part of the contractile effects of 5-HT are indirectly mediated through release of norepinephrine from sympathetic nerves (Hernández et al, 2003).

Kinins

The kininskallidin, eledoisin, and bradykinin increase the frequency of contraction and baseline intraluminal pressure of the dog ureter (Boyarsky et al, 1966a, b; Labay and Boyarsky, 1966), and bradykinin decreases the contractile force of the sheep ureter (Kaygisiz et al, 1995).

Angiotensin

Angiotensin has a stimulatory effect on the ureter. Angiotensin II (ANG II) and mRNA for angiotensinogen, a principal precursor of ANG II, renin, angiotensin-converting enzyme (ACE), and type I angiotensin receptor are expressed in the human ureter (Santis et al, 2003). Losartin, an ANG II-receptor antagonist, decreases the amplitude and frequency of spontaneous contractions of human ureteral segments. ANG II induces phasic contractions of rat ureteral segments, an effect that is inhibited by losartin (Fujinaka et al, 2000). The ANG II type I receptor also is expressed in the rat ureter (Paxton et al, 1993).

Narcotic Analgesics

Morphine has been reported to increase ureteral tone or the frequency and amplitude of ureteral contractions or both in a variety of experimental preparations and in humans (Macht, 1916b; Gruber, 1928; Ockerblad et al, 1935; Vereecken, 1973). Others,

however, have failed to observe an effect of morphine on ureteral function (Gould et al, 1955; Kiil, 1957; Weinberg and Maletta, 1961; Ross et al, 1967).

Meperidine (Demerol) appears to have a similar excitatory effect on the activity of the intact dog ureter (Sharkey et al, 1968). Kiil (1957), however, failed to observe an effect of meperidine on ureteral peristalsis in humans. **If one considers only the effects on ureteral activity, there is no basis to preferentially favor morphine or meperidine in the treatment of renal colic. Both agents may have ureteral spasmogenic effects that theoretically would detract from their value in the management of ureteral colic. They certainly do not have potentially valuable spasmolytic actions. Their efficacy in treating colic depends on their central nervous system (CNS) actions, which decrease the perception of pain.**

Prostaglandins

Prostaglandins are derived from fatty acids and have a variety of biologic actions in various systems of the body. Their effects vary with the species, type of prostaglandin, endocrine status of the tissue, experimental conditions, and origin of the smooth muscle. **The "primary" prostaglandins (PGs), PGE_1, PGE_2, and $PGF_{2\alpha}$, are synthesized from the fatty acid arachidonic acid by enzymatic reactions involving two cyclooxygenase (COX) isoforms, COX-1 and COX-2** (Vane, 1998). In most tissues, COX-1 is constitutively expressed and is involved in the regulation of normal physiologic processes, whereas COX-2 is induced in response to processes such as inflammation and mitogenesis (Mitchell and Warner, 1999). **These enzymatic reactions can be inhibited by indomethacin and aspirin, and by a number of COX-1 and COX-2 inhibitors.** COX-1 and COX-2 receptors have been identified in the human ureter (Chaignat et al, 2008).

Indomethacin has been employed in the management of ureteral colic (Holmlund and Sjöden, 1978; Flannigan et al, 1983; Jönsson et al, 1987). The beneficial effects probably are due to indomethacin's inhibition of the prostaglandin-mediated vasodilatation that occurs subsequent to obstruction (Allen et al, 1978; Sjöden et al, 1982). The vasodilatation theoretically would result in an increase in glomerular capillary pressure and a subsequent increase in pelviureteral pressure. Indomethacin, by reducing pelviureteral pressure and thus pelviureteral wall tension, might eliminate some of the pain of renal colic that is dependent on distention of the upper urinary tract. An upregulation of COX-2 mRNA and protein with obstruction supports the potential use of selective COX-2 inhibitors in the treatment of obstructive ureteral disease (Nakada et al, 2002). **A potential problem with the use of indomethacin for the treatment of renal colic is that prostaglandin-mediated vasodilatation aids in preserving renal function; thus, indomethacin may provide pain relief, but it may be potentially deleterious to renal function** (Perlmutter et al, 1993; Kristova et al, 2000).

PGE_1 inhibits the activity of the dog (Boyarsky et al, 1966b; Wooster, 1971; Abrams and Feneley, 1976) and guinea pig ureter (Vermue and Den Hertog, 1987). PGE_1 inhibition of ureteral activity in the guinea pig is associated with an increase in cAMP levels (Vermue and Den Hertog, 1987). In the ureter, PGE_1 activates adenylyl cyclase, and this may account for the increase in cAMP (Wheeler et al, 1986). Johns and Wooster (1975) suggested that the inhibitory effects of PGE_1 on ureteral activity depended on the sequestration of Ca^{2+} at the inner surface of the cell membrane, with a resultant increase in outward K^+ conductance and hyperpolarization of the membrane. Although reports have indicated that PGE_2 relaxes the ureter (Vermue and Den Hertog, 1987), other reports describe an excitatory action of PGE_2 on sheep (Thulesius and Angelo-Khattar, 1985) and human (Angelo-Khattar et al, 1985; Cole et al, 1988) ureters and on renal pelvic smooth muscle (Lundstam et al, 1985). PGE_2 increases the contractility of chronically obstructed human ureters, and although it relaxed normal porcine ureter, it increased the contractility of acutely obstructed porcine ureters (Ankem et al, 2005; Lowry et al, 2005). In contrast to the inhibitory effects of PGE_1, PGE_2 increases the frequency of ureteral peristalsis in the dog (Boyarsky and Labay, 1969). In human ureteral preparations PGE_1 and PGE_2 have been shown to decrease spontaneous contractions, whereas PGF_{2a} increased ureteral contractility (Abrams and Feneley, 1976). In human renal pelvis and ureter there is a higher concentration of $PGF_{2\alpha}$ than PGE_2 (Zwergel et al, 1991). $PGF_{2\alpha}$ increased contractility of porcine ureteral segments (Ankem et al, 2005). The prostanoid PGI_2 is synthesized in the urothelium of the ureter (Ali et al, 1998). COX inhibitors such as indomethacin have been shown to inhibit the activity of rat (Davidson and Lang, 2000), guinea pig (Davidson and Lang, 2000), sheep (Thulesius and Angelo-Khattar, 1985), and human ureters (Angelo-Khattar et al, 1985; Cole et al, 1988) and renal pelvic smooth muscle (Lundstam et al, 1985; Zhang and Lang, 1994; Santicioli et al, 1995a; Davidson and Lang, 2000). The nonspecific COX inhibitor diclofenac and the selective COX-2 inhibitors NS-398 and celecoxib have been shown to be equipotent in inhibiting agonist-induced contractions of isolated pig and human ureter (Mastrangelo et al, 2000; Nakada et al, 2000), and diclofenac also has been shown to relax human ureteral segments that were precontracted with KCl (Sivrikaya et al, 2003). The COX-2 selective inhibitor celecoxib, and indomethacin, inhibited porcine ureteral contractility and TNF-α–induced prostanoid release (Jerde et al, 2005). Diclofenac, but not the COX-2 selective inhibitor valdecoxib, decreased the contractile amplitude of electrically stimulated in-vitro human ureteral segments and valdecoxib decreased the contractility of nonobstructed, but not obstructed, ureters of the pig in vivo (Chaignat et al, 2008). Species differences may exist, with COX-2 being the primary enzyme involved in synthesizing PGs in the guinea pig upper urinary tract, and COX-1 being the primary enzyme involved in PG synthesis in the rat upper urinary tract (Davidson and Lang, 2000).

Chronic obstruction upregulates COX-2 activity in the human ureter (Nakada et al, 2002). Upon stretching of the porcine ureter, there is COX-2 induction in both the urothelial and smooth muscle layers of the porcine ureter, with a more significant induction in the urothelium (Jerde et al, 2006). In the normal rat ureter COX-1, but not COX-2, mRNA was detected, and following obstruction, there was an increase in COX-2 mRNA and protein expression but no change in COX-1 expression (Norregaard et al, 2006). In addition to an increased synthesis of prostanoids with obstruction, there is a decrease in prostanoid degradation contributing to the increase in prostanoids with obstruction. 15-Hydroxyprostaglandin dehydrogenase (PGDH), the enzyme responsible for prostaglandin degradation is suppressed in the human ureter with obstruction (Jerde et al, 2004). The dilated ureter following obstruction has an increase expression of COX-2, PGE_2, $TGF\beta_1$, α-smooth muscle actin (α-SMA), fibrosis, apoptotic cells, and proliferation cell nuclear antigen (PCNA) (Chuang et al, 2007). The administration of the COX-2 selective inhibitor celecoxib abolished the expression of COX-2 and PGE_2, decreased the expression of TGF-β_1 and α-SMA, and decreased apoptotic cells

and fibrosis but increased the expression of PCNA in the smooth muscle in the dilated obstructed ureter (Chuang et al, 2007). These investigators concluded that the COX-2 inhibitor might ameliorate, in part by inhibition of COX-2 and TGF-β_1 expression, ureteral damage resulting from obstruction.

Cardiac Glycosides

Ouabain, a cardiac glycoside, has an effect on ureteral activity that appears to be species dependent. In the isolated cat ureter, ouabain produces a marked increase in contractility, which usually is followed by a late decrease in excitability (Weiss et al, 1970). In the guinea pig ureter, ouabain inhibits activity without a preliminary potentiation of contractility (Washizu, 1968; Hendrickx et al, 1975). The inhibitory effects of ouabain are accompanied by a shortening of the action potential duration, a decrease of the number of oscillations on the plateau of the guinea pig action potential, and a decrease in the RMP.

Calcium Antagonists

Because Ca^{2+} is necessary for the development of the action potential and contraction of the ureter, agents that block the movement of Ca^{2+} into the cell would be expected to depress ureteral function. Voltage-dependent Ca^{2+} channel antagonist binding sites (receptors) have been demonstrated in the ureter, and their density decreases with age (Yoshida et al, 1992). These dihydropyridine-sensitive, **L-type, voltage-dependent Ca^{2+} channels appear to provide the main inward current for generation of the ureteral action potential and the phasic contractile response** (Shuba, 1977; Brading et al, 1983; Aickin et al, 1984; Imaizumi et al, 1989; Lang, 1989). Potassium-induced ureteral contractions depend on the inward movement of Ca^{2+} through L-type voltage-dependent Ca^{2+} channels (Maggi and Giuliani, 1995). The dihydropyridine Ca^{2+} channel agonist Bay K 8644 has an excitatory effect on ureteral activity (Maggi et al, 1994a; Floyd et al, 2008) and potentiates K^+-induced contractions. The Ca^{2+} channel blockers verapamil, D-600 (a methoxy derivative of verapamil), diltiazem, and nifedipine have been shown to inhibit ureteral activity (Golenhofen and Lammel, 1972; Vereecken et al, 1975; Hertle and Nawrath, 1984; Hong et al, 1985; Sakanashi et al, 1985, 1986; Maggi et al, 1994a; Davenport et al, 2006). These inhibitory effects are accompanied by decreases in the duration of the action potential, the number of oscillations on the plateau of the guinea pig action potential, excitability, and the rate of rise and amplitude of the action potential. High concentrations of verapamil and D-600 cause a complete cessation of electric and mechanical activity.

Potassium Channel Openers

Potassium channel openers such as cromakalim, nicorandil, BRL 38227, and PFK217-744b hyperpolarize smooth muscle membranes and **inhibit renal pelvic and ureteral activity** (Kontani et al, 1993; Maggi et al, 1994c; Weiss et al, 2002; Smita et al, 2006; Floyd et al, 2008). Glibenclamide, a blocker of K^+/ATP channels had no effect on contractility (De Moura and De Lemos Neto, 1996). The inhibitory effects of cromakalim and nicorandil are prevented by glibenclamide, providing evidence that ATP-sensitive K^+ channels are involved in these processes (Maggi et al, 1994c; Smita et al, 2006). Activation of these K^+ channels may reduce the probability of the opening of voltage-sensitive Ca^{2+} channels, inhibit agonist-induced increases in inositol 1,4,5-trisphosphate, or reduce Ca^{2+} sensitivity of contractile elements processes that are important in the generation of the ureteral action potential and the contractile response (Cook and Quast, 1990; Quayle et al, 1997).

The tricyclic antidepressant amitriptyline (Elavil) has been shown to relax isolated pig and human ureteral strips by opening potassium channels (Achar et al, 2003). This relaxation response is inhibited by 4-aminopyridine (4-AP), a voltage-dependent K^+ channel blocker. Nicorandil, a K^+ channel opener and nitric oxide (NO) donor, stimulates guanylyl cyclase activity with formation of cyclic GMP and hyperpolarizes the smooth muscle with resultant relaxation of rabbit, guinea pig, and human ureter (Klaus et al, 1989, 1990; Weiss et al, 2002). The relaxant effects of nicorandil can be inhibited by both the K_{ATP} antagonist glibenclamide and the guanylyl cyclase inhibitor methylene blue (Weiss et al, 2002).

Endothelins

Endothelins are potent vasoconstrictor peptides that exist in three isoforms: ET-1, ET-2, and ET-3. These peptides interact with their specific receptors: ET_A, ET_B, and ET_C. Endothelin binding sites (receptors) have been identified in the ureter and renal pelvis (Eguchi et al, 1991; Latifpour et al, 1995; Wada et al, 2001), where they are primarily of the ET_A subtype (Latifpour et al, 1995; Wada et al, 2001). Diabetes results in upregulation of the expression of ureteral endothelin receptors (Nakamura et al, 1997). Endothelins have been shown to initiate contractions in isolated guinea pig and porcine ureters (Eguchi et al, 1991; Maggi et al, 1992a) and increase the contractile force of renal pelvis smooth muscle (Wada et al, 2001).

Antibiotics

Ampicillin causes relaxation of the ureter and antagonizes the stimulatory effects of barium chloride ($BaCl_2$), histamine, serotonin, and carbachol on the ureter, thus suggesting that its action is directly on the smooth muscle (Benzi et al, 1970b). Chloramphenicol, the isoxazolyl penicillins, and gentamicin also have spasmolytic effects on the ureter (Benzi et al, 1970a, 1971, 1973). The tetracyclines, on the other hand, potentiate the contractile effects of $BaCl_2$ on the ureter (Benzi et al, 1973).

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chapter
60

Physiology and Pharmacology of the Bladder and Urethra

Naoki Yoshimura MD, PhD ● Michael B. Chancellor, MD

Relevant Anatomy and Biomechanics
The Urinary Bladder
The Urethra
Neural Control of the Lower Urinary Tract
Pharmacology
Mechanisms of Detrusor Overactivity
Summary
Future Research

The medical, social, and economical impact of urinary incontinence, overactive bladder, and voiding dysfunction is staggering (Yoshimura and Chancellor, 2002). In the United States, there are an estimated 34 million community-dwelling men and women with an overactive bladder (Hu et al, 2004). It costs an estimated $19.5 billion and $12.6 billion a year in the United States to manage urinary incontinence and the overactive bladder, respectively (Hu et al, 2003; Hu et al, 2004). With the continued aging of the populations in all developed countries, the problems associated with bladder control will certainly continue to increase. In this chapter, we review the neuromuscular physiology and pathophysiology of the bladder and urethra. We will discuss what is new in pharmacology that may better help our patients with voiding dysfunction. Finally, we will speculate about future treatment methods to conquer urinary incontinence.

The micturition process can be visualized as a complex of neural circuits in the brain and spinal cord that coordinate the activity of smooth muscle in the bladder and urethra (Torrens and Morrison, 1987; de Groat et al, 1993a; Yoshimura and de Groat, 1997). **These circuits act as on-off switches to alternate the lower urinary tract between two modes of operation: storage and elimination.**

Injuries or diseases of the nervous system in adults can disrupt the voluntary control of micturition, causing the reemergence of reflex micturition and resulting in detrusor overactivity and urgency incontinence (Fig. 60–1) (Torrens and Morrison, 1987; Wein, 1992; de Groat et al, 1993a; Yoshimura and de Groat, 1997). Because of the complexity of the central nervous control of the lower urinary tract, urgency incontinence can result from a variety of neurologic disorders. In addition, urgency incontinence may be due to intrinsic detrusor myogenic abnormalities, resulting in detrusor overactivity (Brading, 1997b). The morphology and function of the detrusor wall are reviewed, including new insights into the urothelium.

Urethral dysfunction can also be an important cause of urinary incontinence in both women and men. Many health care professionals who are not trained in urology erroneously believe that urethral dysfunction can cause only genuine stress urinary incontinence. This is not true. Urethral dysfunction can also cause urgency incontinence. Increased bladder outlet urethral resistance in men with benign prostatic hyperplasia and in younger men and women with detrusor-sphincter dyssynergia (e.g., spinal cord injury, multiple sclerosis) causes secondary bladder changes. Increased bladder outlet resistance causes secondary bladder remodeling and can result in urgency incontinence. In addition, it can be speculated that in patients with mixed stress and urgency incontinence, stress incontinence can cause urgency incontinence. Leakage of urine into the urethra (stress incontinence) may stimulate urethral afferents that induce an involuntary voiding reflex (urgency incontinence).

This chapter reviews studies in humans and animals that provide insights into

- organization of neural pathways controlling the lower urinary tract;
- neurotransmitters involved in storage and voiding reflexes;
- function of the detrusor wall, including urothelium and smooth muscle;
- contribution of the smooth and skeletal muscle urethral function and interaction of urethra with bladder function;
- action of drugs on the bladder; and
- mechanisms that contribute to overactive bladder.

Speculation about what the future holds in terms of research and treatment of lower urinary tract dysfunction ends the chapter. With the mapping of the human genome now completed, we believe that we are on the verge of a paradigm shift in clinical medicine. The future will bring molecular medicine into the hands of the practicing urologists.

RELEVANT ANATOMY AND BIOMECHANICS

General Concepts

The bladder can be divided into two parts: a **body** lying above the ureteral orifices and a **base** consisting of the trigone and bladder neck, because the two areas are different but homogeneous within themselves regarding neuromorphology and

neuropharmacology (Elbadawi and Schenk, 1966). Histologic examination of the bladder body reveals that myofibrils are arranged into fascicles in random directions (Donker et al, 1982). This architecture differs from the discrete circular and longitudinal smooth muscle layers in the ureter or gastrointestinal tract.

The bladder outlet is composed of the bladder base, urethra, and external urethral sphincter (Fig. 60–2). The bladder base has a laminar architecture with a superficial longitudinal layer lying beneath the trigone. A muscle layer deep to the superficial layer is continuous with the detrusor (Tanagho, 1982; Dixon and Gosling, 1987; Zderic et al, 1996). The smaller muscle bundles of the deep muscle layer in the bladder base exhibit a predominantly circular orientation.

The urethra begins at the internal meatus of the bladder and extends to the external meatus. In the male, four segments are readily identified. The first is the preprostatic portion, or the bladder neck. The prostatic urethra then extends throughout the length of the gland, terminating at its apex. The membranous urethra extends from the prostatic apex through the pelvic floor musculature until it becomes the bulbous and penile urethra (fourth segment) at the base of the penis. In women, the urethra extends throughout the distal third of the anterior vaginal wall from the bladder neck to the meatus. **The urethra is composed of tissues that aid continence rather than a single discrete and visible "sphincter." A network of vascular subepithelial tissue in women contributes to a urethral seal effect.**

It is debatable whether the detrusor or trigone muscles project into the proximal urethra (see Fig. 60–2). Embryologic data support the concept of a separate origin for muscles of the bladder and urethra (Dixon and Gosling, 1987; Zderic et al, 1996). Histologic studies show that the longitudinal muscle of the bladder base extends distally into the urethra to form an inner longitudinal layer (Hutch and Rambo, 1967; Tanagho, 1982). Examination of adult and fetal specimens shows that striated and smooth muscles coalesce in the urethra and interdigitate with the fibrous prostatic capsule (Oelrich, 1980). Conversely, a complete and competent ring of smooth muscle at the male bladder neck has been described (Gosling, 1999). No such collar of muscle is identified in the female. The maintenance of continence in men and some women with destruction or opening of the bladder neck argues that the bladder neck may not be the principal site of urinary continence (Chapple et al, 1989). **The importance of the bladder neck as the principal zone of maintaining continence remains controversial.**

The bladder neck serves an important function in reproduction. **In men, closure of the bladder neck facilitates antegrade ejaculation. This is accompanied through a rich noradrenergic innervation by sympathetic nerves that actively contract the bladder neck during ejaculation**. However, **in women, the density of adrenergic innervation in the**

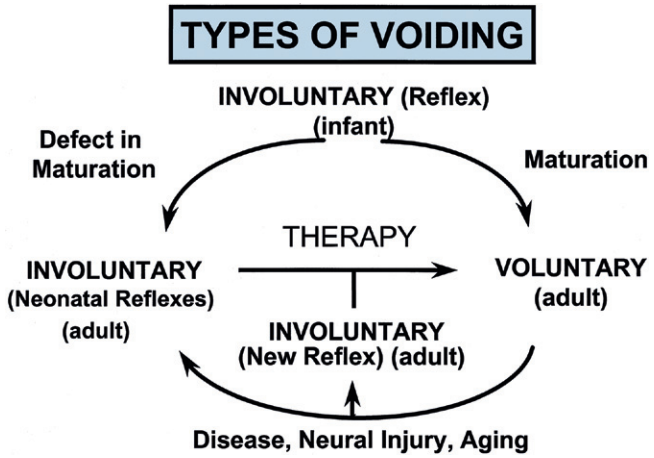


Figure 60–1. Bladder's "circle of life" by influence of maturation, pathologic processes, and aging. In infants, voiding is initiated and coordinated by reflex circuits. After maturation of central neural pathways, voiding is controlled voluntarily by neural circuitry in higher centers in the brain. A defect in neural maturation allows involuntary voiding to persist in adults. Aging, neural injury, or diseases, such as benign prostatic hyperplasia, can disrupt the central voluntary micturition neural pathways. Pathologic processes can lead to the formation of new reflex circuitry by reemergence of primitive reflex mechanisms that were present in the infant or that appear as the result of synaptic remodeling. The goal of therapy is to reverse the pathologic process and to reestablish normal voluntary control of voiding.

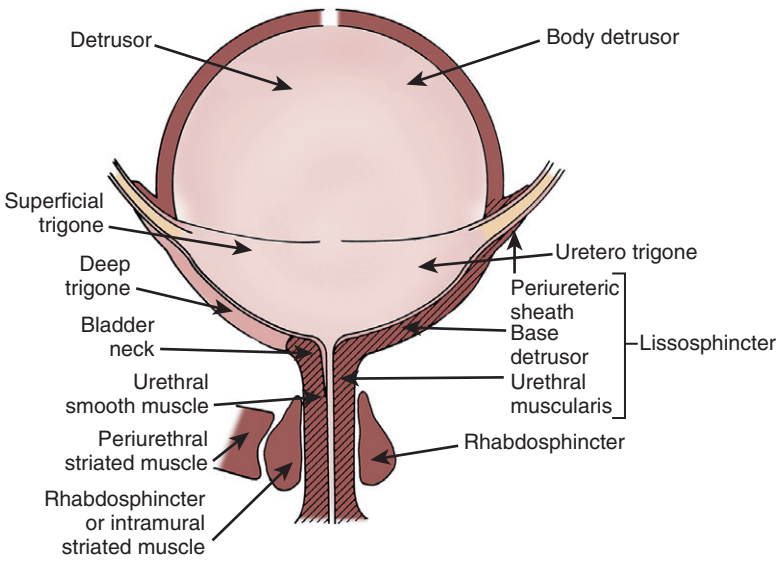


Figure 60–2. Anatomy of the bladder and its outlet, as defined by Gosling and Dixon *(left)* versus Elbadawi and coworkers *(right)*. (From Torrens M, Morrison JFB. The physiology of the urinary bladder. Berlin: Springer-Verlag; 1987. p. 1.)

bladder neck is reportedly less than that in men (de Groat and Booth, 1993).

Understanding voiding and continence requires some working knowledge of the contractile properties of smooth and striated muscle. The contractile properties of bladder smooth muscle cells are well suited for either urine storage or release. Filling the bladder at a slow physiologic rate maintains an intravesical pressure of less than 10 cm H_2O (Klevmark, 1974). Acute denervation of the bladder does not appreciably alter this low filling pressure (Langley and Whiteside, 1951). This concept has been used to support the hypothesis that the **intrinsic myogenic or viscoelastic properties of cellular and extracellular components are major contributors to low-pressure bladder filling and compliance** (see the section Mechanisms of Detrusor Overactivity). Conversely, neural input is required for the rapid and sustained smooth muscle contraction accompanying voiding.

Bladder Biomechanics

What basic bladder hydrodynamics and biomechanical properties should practicing urologists know, and why should they know them? These are some of the questions we attempt to answer in this section. We lay the foundation of the relationship between bladder shape, size, pressure, and tension as expressed by the Laplace law (Chancellor et al, 1996). Marquis Pierre-Simon de Laplace (1779 to 1827) has been called the Newton of France. **Laplace** made the keen observation that the **tension in the wall of a container necessary to contain a given pressure is directly proportional to the radius of curvature at any point**. This is the Laplace law.

It is intuitive to urologists that there is a relationship between intravesical pressure and the size of the bladder and that this affects the tension in the bladder wall. Increased wall tension activates bladder afferent nerves that evoke the sensation of bladder filling and also can evoke involuntary bladder contractions. Large increases in intravesical pressure, especially in a hypertrophic, small-capacity bladder, can dramatically elevate bladder wall tension, producing ischemia, vesicoureteral reflux, and bacterial emptying into the venous or lymphatic systems. Elevated wall tension and intravesical pressure may be the cause of bladder rupture sometimes seen after enterocystoplasty.

The Laplace equation states that there is a direct relationship between wall tension and intravesical pressure and bladder size. In this equation, T is tension, P is intravesical pressure, R is bladder radius, and d is wall thickness. During bladder filling, Pves is relatively constant. With a fully distended bladder, d, because of its relative thinness, is ignored relative to the other parameters unless a hypertrophied wall exists. Thus, T = P • R/2 approximates tension in the full normal bladder (Fig. 60–3).

Filling Mechanics

The viscoelastic behavior of the bladder and urethra depends on both neuromuscular and mechanical properties. Mechanical properties vary with the magnitude of stretch (distention), even in tissue deprived of adenosine triphosphate (ATP) (e.g., postmortem). Mechanical properties are extremely sensitive to tissue structure and composition. In the bladder and urethra, collagen and elastin content have a profound influence on the viscoelastic properties when these tissues are subjected to stress (force per area). **Besides smooth muscle, the human bladder is composed of roughly 50% collagen and 2% elastin. With injury, obstruction, or denervation, collagen content increases** (Macarak and Howard, 1999). When contractile protein content exceeds collagen, greater distensibility is achieved (compliance). **Conversely, when collagen levels increase, compliance falls.** Bladder compliance (C) is defined as the change in volume (V) relative to the corresponding change in intravesical pressure (P):

$$C = \Delta V / \Delta P$$

A decrease in compliance or efferent neural input can alter wall tension, cause afferent firing, and thereby change bladder sensations and the volume threshold for micturition. With increasing bladder volume, wall stress or tension (T) increases, as defined by the Laplace equation (see Fig. 60–3).

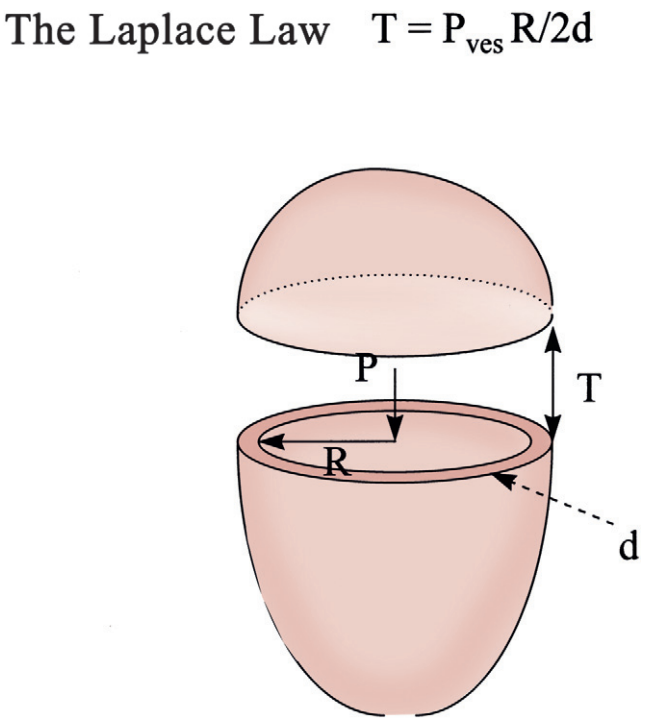


Figure 60–3. The Laplace equation describing wall tension (T) as a function of the bladder radius (R), intravesical pressure (Pves), and wall thickness (d).

Bladder Accommodation

The bladder surface undergoes incredible change in size going from empty to full. The percentage change is truly unmatched by any other organ in the body. The change is accommodated by both the urothelium and the bladder wall smooth muscle and connective tissue.

The changes in the thickness of the lamina propria and the detrusor are mechanical requirements for the bladder to accommodate increasing urine volume. During filling, the lamina propria thins at a faster rate than the muscle wall. It has been proposed that bladder wall thinning during filling is the result of a rearrangement of the muscle bundles and also alteration of collagen coil structure (Macarak and Howard, 1999). A combination of muscle and connective tissue spatial changes is required to accommodate urine at low intravesical pressures (Chang et al, 1999).

During filling, the detrusor reorganizes and muscle bundles shift position from a top-to-bottom to a side-to-side configuration. During reorganization, the coiled type III collagen fibers connecting the muscle bundles orthogonally become extended, longer, and taut and assume an orientation such that the fibers become oriented parallel to the lumen.

Voiding Mechanics

Intravesical pressure reflects the combined factors of abdominal (Pabd) and detrusor (Pdet) pressures. Therefore,

$$Pdet = Pves - Pabd$$

Micturition relies on a neurally mediated detrusor contraction, causing Pdet to rise without a significant change in Pabd. To assess the strength of a detrusor contraction, Pdet alone is an insufficient measure. A muscle can use energy either to generate force or to shorten its length. Because the bladder is a hollow viscus, the force developed contributes to Pdet, whereas the velocity of shortening relates to urine flow (Q). There is a trade-off between generating Pdet and urine flow. This has been nicely reviewed by Griffiths (1988). **If urethral resistance is low, as in women with sphincter insufficiency and even in normal continent women, Pdet may be almost undetectable; yet, these women with modest Pdet would have normal flow rates. The trade-off between Pdet and Q resembles a curve for constant mechanical power (W) in which**

$$W = Pdet \times Q$$

The equation explains why a woman could have normal detrusor contractility and normal detrusor power despite low voiding pressure. During micturition, Pdet reflects outlet resistance. When the urethra opens widely with a high flow (Q), little Pdet is needed to achieve the work necessary to empty the bladder. The key message is that low voiding pressure in a woman does not equate with impaired detrusor contractility; she may simply be able to open her urethra widely. Moreover, pressure-flow nomograms developed for men for diagnosis of obstruction should not be applied to women without validation.

Tissue Biomechanics and Bladder Function

In addition to important molecular and cellular parameters, tissue- and organ-level bladder properties are important to the function of the bladder during filling (Damaser, 1999). Fundamental mechanical properties include the stress-strain relationship, viscoelasticity, and deformation of bladder tissue. Whole-bladder properties include bladder shape, mass, and distention. Organ-level pressure-volume assessment is usually achieved by the cystometrogram. Although it is an essential tool for the urologist, the cystometrogram *alone* cannot rigorously distinguish between the effects of changes in tissue compliance, and the shape and wall stress distribution of the whole organ. For example, changes in the cystometrogram in spinal cord injury could be a result of alterations in both bladder shape (Ogawa et al, 1988) and tissue properties. Thus to assess intrinsic changes in bladder wall properties, proper assessment of the changes in bladder function requires an understanding of bladder wall biomechanical properties. The biomechanical components contributing to tissue mechanical responses have been studied in isolated detrusor tissue (Wagg and Fry, 1999). However, an ongoing problem is to determine whether clinically observed alterations in detrusor function are due to changes in the contractile apparatus or in the surrounding extracellular matrix.

The complexity of the bladder shape raises similar questions. The bladder can be mechanically idealized as a thin-walled shell. In the theory of thin shells, surface geometry is an integral part of how wall tensions are spatially distributed (Flügge, 1973). That is, a change in surface geometry can alter the stress distributions independent of changes in the mechanical properties. Thus focal points of high curvature on the bladder surface (Fig. 60–4) can potentially induce regions of localized stress concentrations and may be related to bladder deformity, for example, during the spinal cord injury disease process. These phenomena have been underscored by the bladder shape modeling work of Damaser and Lehman (1995), who demonstrated the sensitivity of bladder wall stress distribution on bladder shape.

Although it is typically modeled as a spheroid, the bladder is probably one of the more irregularly shaped anatomic structures.

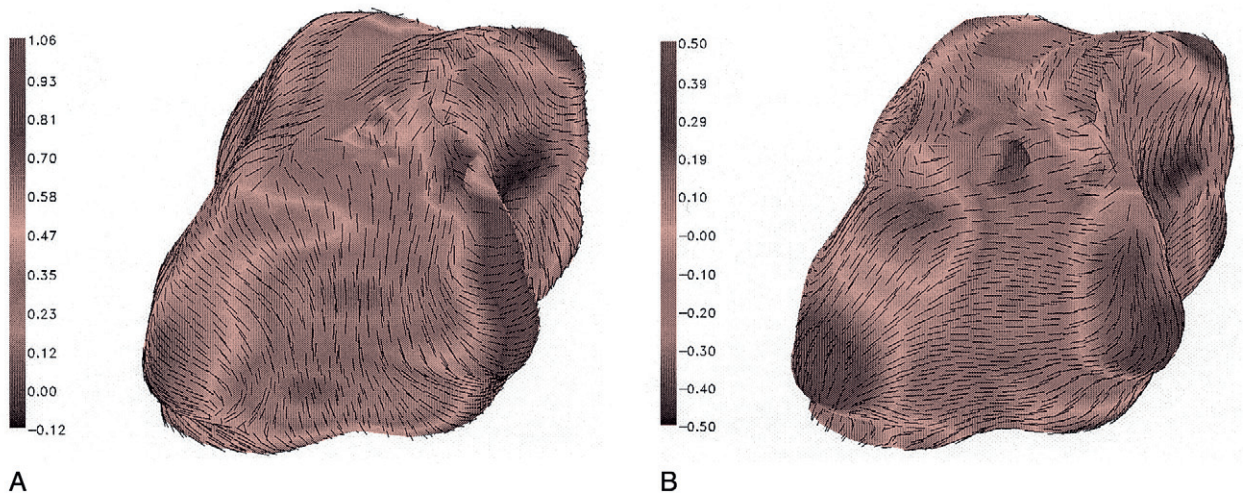


Figure 60–4. Major principal curvature **(A)** and minor principal curvature **(B)** for the bladder. Curvature magnitudes are indicated by gray scale and directions by vectors. When the bladder is full, as in this case, wide variations in curvature exist because of contact with the surrounding pelvic structures.

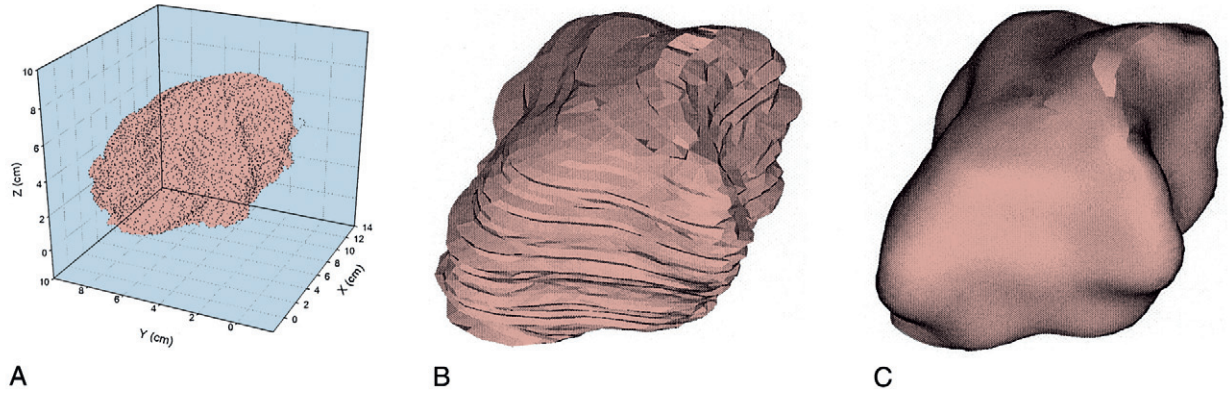


Figure 60–5. Three-dimensional reconstruction of the bladder. **A,** "Point cloud" of 3146 digitized surface points from a normal human bladder from computed tomographic images. **B,** The resulting reconstructed bladder surface, revealing a complex, nonspheroidal surface. **C,** Same surface as in **B** but with the surface roughness from imaging noise removed.

Irregularity in bladder shape, especially when it is full, is due to contact with surrounding pelvic structures. Note in particular the complex spatial distribution of surface curvatures, including pointed regions of high curvature and rapid transitions between elliptical (both principal curvatures are positive) and hyperbolic (or saddle-shaped, where one principal curvature component is negative) regions (see Fig. 60–4). By use of the techniques developed by Sacks and colleagues (1993, 1999), this roughness can be removed and the original smooth in-vivo surface recovered (Fig. 60–5).

THE URINARY BLADDER

The bladder performs several important functions. First, it must store a socially adequate volume of urine. The bladder wall must be able to stretch and rearrange itself to allow an increase in bladder volume without significant rise in pressure. In other words, the bladder wall must be highly compliant. Second, the smooth muscle and intrinsic nerves have to be protected from exposure to urine by the urothelium, which itself must also expand readily during filling. Third, bladder emptying requires synchronous activation of all the smooth muscle of the bladder body, because if only part of the wall contracted, the uncontracted compliant areas would stretch and prevent the increase in pressure necessary for urine to be expelled through the urethra. This is the problem often seen in an elderly man with benign prostatic hyperplasia who develops urinary retention and a bladder diverticulum.

In this section, we review the various components of the bladder, including smooth muscle, stroma, and blood vessels. First, we focus on the detrusor smooth muscle by contrasting the characteristics of smooth and striated muscle, the activation of smooth muscle contractility, the maintenance of bladder tone, and its neural regulation. In addition, we concentrate on the urothelium, because there is now a resurgence of research interest in this thin but complex membrane. Some exciting studies are presented that discuss the barrier, transport, and neurocommunication properties of the urothelium that are just beginning to be understood. Last, we briefly discuss ion channels and how they might contribute to detrusor dysfunction.

Smooth Muscle

There are several universal characteristics of smooth muscle:

Smooth muscle consists of a sheet containing many small, spindle-shaped cells linked together at specific junctions. Smooth muscle cells contain actin and myosin, but these proteins are not arranged in a regular sarcomere pattern. Instead, each smooth muscle cell consists of a more variable matrix of contractile proteins that is attached to the plasma membrane at the junctional complexes between neighboring cells. Smooth muscle maintains a steady level of tension that can be modulated by circulating hormones, by local factors such as nitric oxide, or by activity in the autonomic nerves. Smooth muscle is more adaptable than skeletal muscle and is able to adjust its length over a much wider range than skeletal muscle.

Based on the assumption of a spherical bladder, the circumference of a 400-mL capacity bladder is approximately 30 cm. If the bladder empties to a residual urine volume of 10 mL, the circumference would be only 8 cm. To accomplish this feat, the detrusor would have a change in muscle length of 75%. If the bladder were to be made of skeletal muscle instead, the maximum length change would be only about 30%. The maximum "skeletal muscle bladder" emptying would be only 70% of its contents, leaving a residual urine of 120 mL. Thus the bladder requires the unique property of smooth muscle to accomplish its job. What is assumed to be the stronger skeletal muscle is not up to the job of bladder emptying (Gabella, 1995; Brading et al, 1996; Brading, 1999).

Morphology

The individual smooth muscle cells in the bladder wall are small spindle-shaped cells with a central nucleus; fully relaxed, they are several hundred micrometers long with a 5- to 6-μm maximum diameter. Skeletal muscle fibers are some 20 times wider and thousands of times longer (Smet et al, 1996).

Smooth muscle has a unique range of physiologic properties and consists of sheets containing many small spindle-shaped cells linked together at specific junctions. Each cell has a single nucleus. No cross striations are visible under the microscope, but like skeletal and cardiac muscle, smooth muscle cells contain actin and myosin. In addition, they contain cytoskeletal intermediate

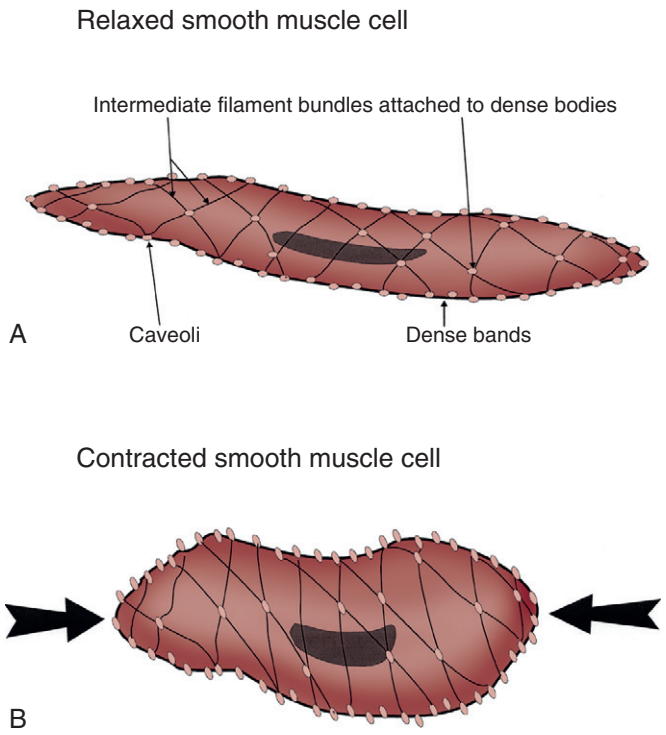


Figure 60–6. The organization of the contractile elements of smooth muscle fibers by a simple model of the contraction of smooth muscle. **A,** Relaxed smooth muscle cell. **B,** Contracted smooth muscle cell. Intermediate filaments, dense bodies, and dense bands of smooth muscle fibers harness the pull generated during myosin cross-bridge activity. Intermediate filaments attach to dense bodies scattered throughout the sarcoplasm and occasionally anchor to the dense bands situated between caveolae (invaginations of the sarcolemma). As the obliquely running contractile elements contract, the muscle shortens.

Table 60–1.

Comparison of the Properties of Skeletal and Smooth Muscle

PROPERTY	SKELETAL MUSCLE	SMOOTH MUSCLE
Cell characteristics	Long cylindrical cells with many nuclei	Spindle-shaped cells with a single nucleus
Maximum cell size (length × diameter)	30 cm × 100 μm	200 μm × 5 μm
Visible striations	Yes	No
Ultrastructure	Sarcomere pattern No immediate filaments	No sarcomere pattern Intermediate filaments Dense bodies
Motor innervation	Somatic	Autonomic
Type of contracture	Phasic	Mostly tonic, some phasic
Contractile activity	Disinhibition of tropomyosin Sliding filaments Rapid contraction	Active myosin phosphorylation ? Sliding filaments Formation of "latch state"
Calcium regulation	Rapid Ca^{2+} influx via T tubule	Voltage- and receptor-operated Ca^{2+} channels Release from internal stores
Basic muscle tone	Neural activity	Intrinsic, extrinsic factors
Force of contraction regulated by hormone	No	Yes

filaments that assist in transmission of the force generated during contraction to the neighboring smooth muscle cells and connective tissue. Although there are no Z lines in smooth muscle, they have a functional counterpart in dense bodies that are distributed throughout the cytoplasm and that serve as attachments for both the thin and the intermediate filaments. The thin and thick filaments of smooth muscle fibers are arranged as myofibrils that cross the fibers obliquely in a lattice-like arrangement. The filaments of contractile proteins are attached to the plasma membrane at the junctional complexes between neighboring cells (Fig. 60–6). A comparison of some of the properties of smooth and skeletal muscle is listed in Table 60–1 (Chacko et al, 1999).

Smooth Muscle Cellular Mechanics

Detrusor smooth muscle contracts and shortens by interaction between thin and thick filaments. The thin actin filaments are anchored at the membranes on the dense bands, or in the cytoplasm on the dense bodies, and interact with the thick filaments through cross bridges formed from the heads of myosin molecules. In both cases, the contractile mechanism is a myosin-activated system. **Cross-bridge cycling is initiated when the ATPase activity of the myosin heads is switched on. This is achieved by phosphorylation of two light chains on the cross bridge, through a specific enzyme, myosin light-chain kinase, that is activated by a rise in the intracellular calcium concentration** (Hai and Murphy, 1989; Gunst et al, 1993; Andersson and Arner, 2004). Changes in the contractile proteins occur in developing bladders and also during bladder hypertrophy (Wang et al, 1995; Wu et al, 1995; Sjuve et al, 1996).

The bladder muscle has a broad length-tension relationship, allowing tension to be developed over a large range of resting muscle lengths (Uvelius and Gabella, 1980). The tissue shows viscoelasticity that influences muscle tension and is manifested as total bladder wall tension (Venegas, 1991). Isolated detrusor strips show spontaneous mechanical activity to a variable extent. It is more frequently seen in bladders from small mammals (Sibley, 1984) but can also be seen in muscle strips from human detrusor. However, spontaneous fused tetanic contractions, such as those commonly seen in smooth muscles from the gastrointestinal tract and uterus, are almost never seen in normal bladders.

Membrane Electrical Properties and Ion Channels. The smooth muscle of the detrusor is able to support a regenerative action potential from a resting potential of –50 to –60 mV (Montgomery and Fry, 1992; Fry et al, 2002). The action potentials have marked after-hyperpolarizations, and several different K^+ channels, such as delayed rectifier and transient outward channels and both small and large calcium-activated K^+ channels (SKCa and BKCa, respectively), appear to be involved in determining their shape (Fujii et al, 1990; Brading and Turner, 1996; Heppner et al, 1997; Andersson and Arner, 2004). The upstroke is supported by calcium influx through L-type Ca^{2+} channels (Rivera, 1998). In addition, a K^+ channel opened by reduced intracellular ATP has been

demonstrated (Bonev and Nelson, 1993), which, on activation, is profoundly inhibitory to the spontaneous activity (Foster et al, 1989). Several other conductances, which include a nonspecific cation channel linked to the P2X receptor (Inoue and Brading, 1990) and stretch-activated cation channels (Wellner and Isenberg, 1993), have been demonstrated in detrusor smooth muscle.

In response to acetylcholine released from parasympathetic nerve terminals, muscarinic M_3 receptors are thought to induce detrusor muscle contractions by calcium entry through nifedipine-sensitive L-type Ca^{2+} channels (Andersson and Arner, 2004; Andersson and Wein, 2004; Schneider et al, 2004a, 2004b), **in addition to increased polyphosphoinositide hydrolysis resulting in inositol 1,4,5-trisphosphate (IP_3) production and release of intracellular calcium stores** (Iacovou et al, 1990; Eglen et al, 1994; Harriss et al, 1995; Hashitani, Bramich et al, 2000; Fry et al, 2002; Braverman et al, 2006a), although the importance of L-type channel activation in muscarinic M_3 receptor–mediated detrusor bladder contractions is still a matter of debate (Fry et al, 2002; Hashitani et al, 2000; Schneider et al, 2004a, 2004b; Braverman et al, 2006a, 2006b; Frazier et al, 2008). **The calcium influx through L-type Ca^{2+} channels also triggers calcium-induced calcium release through ryanodine receptors and activates BKCa channels to generate the membrane after-hyperpolarization** (Hashitani and Brading, 2003). **The opening of the K^+ channel repolarizes the membrane potential by the efflux of positively charged potassium ions from the cell** (Mostwin, 1986). In addition, increased polyphosphoinositide hydrolysis after M_3 receptor activation can also generate diacylglycerol in the membrane; diacylglycerol can activate protein kinase C, which may be involved in generating the tonic element of the response through modulation of Ca^{2+} and K^+ channels (Zhao et al, 1993).

Calcium also activates a variety of cellular responses when it enters the cytoplasm of a cell by means of transmembrane channels. To be effective as a signal, its concentration must be returned to submicromolar levels, driven by ATP pumps. The Ca^{2+} pump is a membrane-bound, Ca^{2+}-activated ATPase, similar to the Na^+–K^+ pump that controls ion balance and membrane potential in all animal cells. These pumps belong to a superfamily of ATPases known as P type, because they depend on the autophosphorylation of a conserved aspartic acid residue using ATP.

Excitation-Contraction Coupling in Smooth Muscle. Like skeletal and cardiac muscle, smooth muscle contracts when intracellular calcium concentration rises. Because smooth muscle does not possess the tubules of the "T system," the rise in calcium concentration occurs through calcium influx through voltage-gated Ca^{2+} channels in the plasma membrane or release from the sarcoplasmic reticulum after activation of receptors that increase the formation of IP_3. Although calcium serves the same triggering role in all muscle types, the mechanism of activation is different in smooth muscle. The contractile response is slower and longer lasting than that of skeletal and cardiac muscle. This can be explained by the slowness with which smooth muscle is able to hydrolyze ATP during the contractile process. A calcium-binding protein called calmodulin regulates the interaction between actin and myosin. The thin filaments lack troponin and are always ready for contraction. The slow and relatively steady generation of tension enables smooth muscle to generate and to maintain tension with relatively little expenditure of energy (Fig. 60–7 and Table 60–2).

The rise in cytoplasmic calcium concentration brought on by the action potential results in binding of calcium to calmodulin. Calcium-bound calmodulin is then capable of activating myosin light-chain kinase, permitting it to phosphorylate the myosin type II light chain. Phosphorylation of the light chain allows the myosin to interact with actin, leading to force generation (White et al, 1993; Chacko et al, 1994; Andersson and Arner, 2004). The actual geometric arrangement of the actin-myosin complex that permits force generation is unclear. Different isoforms of the myosin heavy chain have been defined by Chacko and associates (1994), as well as the components of the regulatory system linking cytoplasmic calcium levels to contraction (White et al, 1993). The smooth muscle myosin heavy chain is encoded by a single gene, and two heavy-chain variants formed by alternative splicing are identified (SM1 and SM2). Two additional myosin heavy-chain

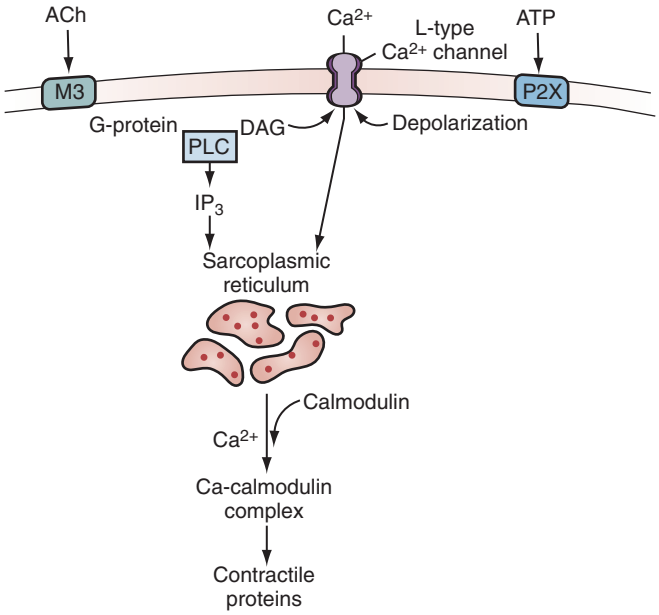


Figure 60–7. Acetylcholine (ACh) and adenosine triphosphate (ATP) pathway in the bladder. Acetylcholine interacts with M_3 muscarinic receptors and activates phospholipase C (PLC) through a G protein. Phospholipase activation leads to the production of inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 elicits release of calcium from the sarcoplasmic reticulum through IP_3 receptors, and DAG may modulate voltage-sensitive Ca^{2+} channels in the plasma membrane. ATP acting through P2X purinergic receptors opens nonselective cation channels in the membrane, leading to depolarization that opens voltage-sensitive Ca^{2+} channels. Both lead to entry of calcium. This triggers release of more calcium from the stores through ryanodine receptors. The rise in intracellular free calcium concentration triggers contraction and may also open calcium-activated channels in the membrane, such as calcium-activated K^+ channels, that can modulate the response. (Redrawn from Brading A. Cellular biology. In: Abrams P, Khoury S, Wein A, editors. Incontinence. Plymouth [UK]: Health Publications; 1999. p. 73.)

Table 60–2.

Detrusor Smooth Muscle Contraction Sequence

Ca^{2+} binds to calmodulin, activating it.
Calmodulin activates the kinase enzyme.
Kinase enzyme catalyzes phosphate transfer from adenosine triphosphate to myosin, allowing myosin to interact with actin of the thin filaments.
Smooth muscle relaxes to widen intracellular decrease in Ca^{2+} levels.

isoforms, SM-A and SM-B, are then formed by alternative splicing in the amino-terminal region, enabling four possible isoforms: SM1-A, SM1-B, SM2-A, and SM2-B (Babu et al, 2000). Because the SM-B isoform is shown to propel actin at a faster velocity (Lauzon et al, 1998), the relatively high expression of SM-B isoform in the bladder shown at the mRNA level (Arafat et al, 2001) would contribute to a comparatively fast smooth muscle type of the bladder (Andersson and Arner, 2004).

Propagation of Electrical Responses. The lack of fused tetanic contractions in normal detrusor smooth muscle strips suggests that there is poor electrical coupling between smooth muscle cells (Uvelius and Mattiasson, 1986). **Measurements of tissue impedance support the observation that the detrusor is less well coupled electrically than other smooth muscles** (Brading and Mostwin, 1989; Parekh et al, 1990)**. Poor coupling could be a feature of a normal detrusor that prevents synchronous activation of the smooth muscle cells during bladder filling.** Nevertheless, some degree of coupling within a muscle bundle clearly does exist, because it is possible to measure the length constant of a bundle (Seki et al, 1992). There is also evidence for gap-junction coupling between detrusor cells in humans and guinea pigs, detected by whole-cell patch clamp recordings (Wang et al, 2006) and Ca^{2+} imaging (Neuhaus et al, 2002), respectively. Significant expression of connexins 43 and 45, gap-junction proteins, is found in human detrusor muscles (John et al, 2003; Wang et al, 2006). However, electrical couplings between detrusor cells seem to be reduced during postnatal development because coordinated, large-amplitude, low-frequency contractile activity is seen in the neonate rat bladder declines and is replaced by low-amplitude, high-frequency, more irregular activity in older rats, which appears to depend on the disruption of the intercellular smooth muscle communication (Szell et al, 2003). It has also been suggested that a change in the properties of the cell coupling may underlie the generation of the uninhibited detrusor contractions occurring in overactive and aging bladders (Seki et al, 1992; Brading, 1997b; Brading, 2006).

Smooth Muscle during Filling. As the bladder fills, the myocytes are stretched, leading to activation of nonselective cation channels that permit rapid entry of sodium and of some calcium (Wellner and Isenberg, 1993). Entry of cations depolarizes the smooth muscle membrane potential. If the extent of stretch is mild, there is low activation, and the membrane potential rests at a more depolarized level, predisposing the cell to activation by lower levels of muscarinic agonists. If the extent of the stretch is more significant, the activation of cation channels may be sufficient to depolarize the cell sufficiently for initiation of an action potential. **Although individual cells may contract spontaneously, contraction of the bladder as a whole generally requires stimulation by parasympathetic nerves** (Andersson, 1993). **When the membrane is sufficiently depolarized, L-type Ca^{2+} channels open and Ca^{2+} channels in the sarcoplasmic reticulum open, flooding the cell with calcium and resulting in an action potential, thereby leading to spontaneous phasic activity in the bladder** (Mostwin, 1986; Kumar et al, 2005).

Between contractions, the sarcoplasmic reticulum accumulates calcium to levels far above those of the cytosol by means of a calcium ATPase (Wall et al, 1990). Calcium stores in the sarcoplasmic reticulum can be released in the absence of action potentials by exposure to caffeine, which renders the Ca^{2+} channels sensitive to normal ambient cytoplasmic calcium levels.

Interstitial Cells. Recent evidence suggests that the "normal" bladder may be spontaneously active and that exaggerated spontaneous contractions could contribute to the development of detrusor overactivity. In a rat model for detrusor overactivity, local areas of spontaneous contractions are increased and more coordinated in partial outlet-obstructed rat bladders (Drake et al, 2003). However, it is still not clear which cells generate spontaneous activity in the bladder. As mentioned before, detrusor myocytes could be spontaneously active, and electrical coupling through gap junctions could trigger spontaneous contractions (Brading, 1997b, 2006). Alternatively, **another population of cells in the bladder known as interstitial cells, or myofibroblasts, has been proposed for a pacemaking role in spontaneous activity of the bladder** (Andersson and Arner, 2004; Kumar et al, 2005). Interstitial cells have been identified in the human and guinea pig ureter, urethra, and bladder body (Kumar et al, 2005; Hashitani, 2006; Fry et al, 2007).

Suburothelial Interstitial Cells. In the human bladder, subepithelial interstitial cells, which are also called myofibroblasts, stain for vimentin and α–smooth muscle actin but not for desmin (Fry et al, 2004). These cells are linked by gap junctions consisting of connexin 43 proteins and make close appositions with C-fiber nerve endings in the submucosal layer of the bladder, suggesting that there is a network of functionally connected interstitial cells immediately below the urothelium that may be modulated by other nerve fibers (Fry et al, 2004) (Fig. 60–8). ATP can induce inward currents associated with elevated intracellular Ca^{2+} in isolated suburothelial interstitial cells (Fry et al, 2007). Immunohistochemical studies show the expression of P2Y receptors, most notably $P2Y_6$ receptors, and M_3 muscarinic receptors in suburothelial interstitial cells from guinea pigs (Fry et al, 2007; Grol et al, 2009). In the human bladder, increased expression of muscarinic M_2 and M_3 receptors in vimentin-stained suburothelial interstitial cells is found and correlates with the urgency score in humans with idiopathic detrusor overactivity (Mukerji et al, 2006). Because

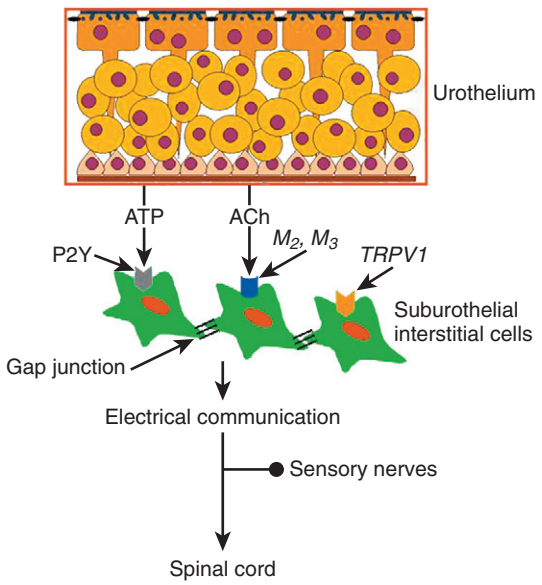


Figure 60–8. Schematic representation of suburothelial interstitial cells (IC), which are also called myofibroblasts. Substances released from the basolateral surface during stretch, such as adenosine triphosphate (ATP) and acetylcholine (ACh), activate afferents in the suburothelial layer through the intermediation of suburothelially located interstitial cells, which express purinergic P2Y receptors, muscarinic M_2 and M_3 receptors, or capsaicin TRPV1 receptors, and are connected to each other by gap-junction proteins.

ATP or acetyl choline (ACh) is known to be released from the urothelium during bladder stretch, suburothelial interstitial cells are in an ideal position between the urothelium and nerve endings to modify a sensory feedback mechanism. Application of a nitric oxide donor sodium nitroprusside (SNP) also attenuates an increase in intracellular Ca^{2+} and current responses to ATP in guinea pig interstitial cells, suggesting the cGMP-dependent inhibition of cell activity (Sui et al, 2008).

Intradetrusor Interstitial Cells. Interstitial cells are also found in the detrusor layer and shown to be spontaneously active (Kumar et al, 2005). These cells are stained for c-Kit and located along both boundaries of muscle bundles in the guinea pig bladder (McCloskey and Gurney, 2002; Hashitani et al, 2004; Hashitani, 2006). These cells can fire Ca^{2+} waves in response to cholinergic stimulation by M_3 muscarinic receptor activation and can be spontaneously active, suggesting that they could act as pacemakers or intermediaries in transmission of nerve signals to smooth muscle cells (McCloskey and Gurney, 2002; Johnston et al, 2008) (Fig. 60–9). However, Hashitani and colleagues (2004) have also suggested that interstitial cells in the detrusor may be more important for modulating the transmission of Ca^{2+} transients originating from smooth muscle cells rather than being the pacemaker of spontaneous activity because spontaneous Ca^{2+} transients occur independently in smooth muscles and interstitial cells. It has also been demonstrated that the c-Kit tyrosine kinase inhibitor Glivec decreased the amplitude of spontaneous contractions in the guinea pig bladder (Kubota et al, 2004, 2006) and in muscle strips from the overactive human bladder, in which c-KIT–positive cells were increased compared with normal subjects (Biers et al, 2006), suggesting that targeting these receptors expressed in intradetrusor interstitial cells may provide a new approach for treating overactive bladder. In addition, following application of SNP (a nitric oxide [NO] donor), interstitial cells throughout the bladder, but not detrusor muscle cells, demonstrate cyclic guanosine monophosphate (cGMP) immunoreactivity (Smet et al, 1996; Gillespie et al, 2004). Thus increased levels of cGMP found in interstitial cells by using phosphodiesterase-5 inhibitors, for example, may diminish synchronicity between detrusor muscle bundles (Hashitani, 2006). These cells are also a source of prostaglandin E_2 (PGE_2) because of their expression of cyclooxygenase and a reduction in spontaneous activity of bladder muscle strips by use of prostaglandin E_2 receptor (EP) antagonists in rabbits (Collins et al, 2009).

Further research is definitely required to fully understand the role of suburothelial/intradetrusor interstitial cells and their contribution to spontaneous contractions or detrusor overactivity.

Smooth Muscle Tone. The bladder smooth muscle maintains a steady level of contracture and tone. Tone is important in maintaining the capacity of the bladder. Smooth muscle tone depends on many factors, some intrinsic and some extrinsic. Extrinsic factors include activity in the autonomic nerves and circulating hormones; intrinsic factors include the response to stretch, local metabolites, and locally secreted agents such as nitric oxide, and temperature. Consequently, smooth muscle tone does not depend solely on activity in the autonomic nerves or on circulating hormones.

The contraction of smooth muscle is slow, sustained, and resistant to fatigue. Smooth muscle takes 30 times longer to contract and relax than does skeletal muscle and can maintain the same contractile tension for prolonged periods at less than 1% of the energy cost.

Length-Tension Relationship. If a smooth muscle is stretched, there is a corresponding increase in tension immediately after the stretch. This is followed by a progressive relaxation of the tension toward its initial value. This property is unique to smooth muscle and is called stress relaxation (Chancellor et al, 1996).

Compared with skeletal or cardiac muscle, smooth muscle can shorten to a far greater degree. A stretched striated muscle can shorten by perhaps as much as a third of its resting length, whereas a normal resting muscle would shorten by perhaps a fifth. This is perfectly adequate for it to perform its normal physiologic role. In contrast, a smooth muscle may be able to shorten by more than two thirds of its initial length. This unusual property is conferred by the loose arrangement of the thick and thin myofilaments in smooth muscle cells. It is a crucial adaptation because the volume contained by the bladder depends on the cube of the length of the individual muscle fibers. The ability of the detrusor smooth muscle to change its length to such a large degree permits the bladder to adjust to a much wider variation in volume than would be possible for skeletal muscle.

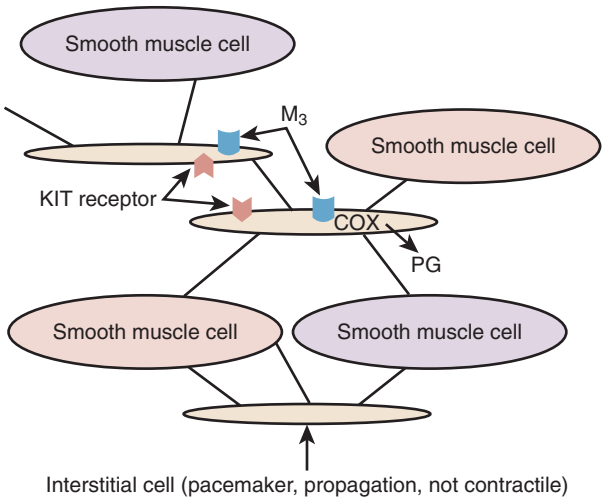


Figure 60–9. Schematic representation of interstitial cells in the detrusor muscle layers. These cells are not contractile but may be pacemakers with spontaneous activity and propagate signals between detrusor muscles. They also express KIT receptors and muscarinic M_3 receptors, and can produce prostaglandins (PG), such as PGE_2, through activation of cyclooxygenase (COX).

Key Points: Smooth Muscle Mechanics

- Muscarinic receptors induce detrusor contraction, in response to acetylcholine released from parasympathetic nerve terminals, by calcium entry through Ca^{2+} channels
- Although calcium serves the same triggering role in all muscle types, the mechanism of activation is different in smooth muscle. The contractile response is slower and longer lasting than that of skeletal and cardiac muscle.
- Recent evidence suggests that the "normal" bladder may be spontaneously active and that exaggerated spontaneous contractions could contribute to the development of an overactive bladder. A population of cells in the bladder known as interstitial cells or myofibroblasts has been proposed for a pacemaking role in spontaneous activity of the bladder.

Stroma

The main constituents of bladder wall stroma are collagen and elastin in a matrix composed of proteoglycans. The main cells are fibroblasts. **The passive mechanical properties of the bladder wall depend on the viscoelastic properties of the stroma and of the relaxed detrusor muscle** (Cortivo et al, 1981). The stroma has commonly been considered a passive low-metabolic tissue that fills out the space between muscle bundles, vessels, and nerves. In recent years, the important role of the stroma in the adaptation of the bladder to pathophysiologic conditions has been more appreciated (Macarak and Howard, 1999). Bladder hypertrophy is likely to involve an interaction of stroma and smooth muscle. In arteries, disruption of elastin in the stroma can stimulate proliferation of smooth muscle (Li et al, 1998). Although no such mechanisms are yet known in the bladder, it is possible that there could be a more intimate relationship between changes in the composition of the stroma and muscle function and growth than is appreciated at present.

Bladder Wall Collagen

Most of the bladder wall collagen is found in the connective tissue outside the muscle bundles. Changes in the relative amounts of muscle and nonmuscle tissue in the bladder wall would therefore influence collagen concentration. A number of different collagen types have been identified. In the bladder, **types I, III, and IV are the most common** (Macarak et al, 1995; Andersson and Arner, 2004). Landau and coworkers (1994) developed morphometric and histochemical techniques to determine the percentage volume of connective tissue in the bladder wall and to measure the two major types (I and III) of collagen. These methods quantitate three parameters of bladder ultrastructure: percentage volume of connective tissue, ratio of connective tissue to smooth muscle, and ratio of type III to type I collagen. These parameters have been shown to be abnormally elevated in patients with bladder disease compared with normal patients. They further studied the ultrastructural changes that occur in the wall of dysfunctional bladders to determine the ability of new urodynamic techniques to reliably detect the clinical effect of these histologic changes. The study included 29 consecutive patients undergoing bladder augmentation. Preoperative urodynamic evaluation included measurement of the total bladder capacity, pressure-specific bladder volume, and dynamic analysis of bladder compliance. Full-thickness bladder biopsy specimens were obtained from the dome of the bladders during augmentation. The percentage of connective tissue and the ratio of connective tissue to smooth muscle were determined for all patients. These histologic results were compared with previously established normal values. All 29 patients had decreased bladder compliance, even though 9 had a normal bladder capacity. **The ratio of connective tissue to smooth muscle was significantly increased in poorly compliant versus normal bladders. The ratio of type III to type I collagen was also significantly elevated. One can conclude that the poor storage function of poorly compliant bladders is secondary to an alteration in the connective tissue content of the bladder wall, especially increased collagen type III.**

In the rat, infravesical obstruction or bladder denervation induces hypertrophy of the detrusor smooth muscle and, in turn, a decrease in the collagen concentration (Uvelius and Mattiasson, 1984, 1986). Aging is associated with a relative decrease in smooth muscle, in both men and women, relative to collagen content (Susset et al, 1978; Lepor et al, 1992). This could perhaps be related to the decreased packing density of submucosal collagen during aging (Levy and Wight, 1990).

Perhaps the most comprehensive work on bladder collagen has been performed by Macarak and Howard (1999), who have speculated that connections must exist between the tension-generating elements (i.e., the smooth muscle cells) and the other components of the bladder. In bladders that become noncompliant (e.g., from spinal cord injury), it is likely that there is some interference with the ability of the collagen fibers to alter their tortuosity. This, predictably, would reduce total bladder capacity. Further studies are required to establish the relationship between compliance changes and the passive mechanical elements of the bladder wall that make up its structural protein matrix.

Bladder Wall Elastin and Matrix

Elastic fibers are amorphous structures composed of elastin and a microfibrillar component located mainly around the periphery of the amorphous component (Rosenbloom et al, 1995). In the mature fiber, the amorphous component composes about 90%. The microfibrils contain a number of glycoproteins. Elastin fibers are sparse in the bladder, compared with collagen, but are found in all layers of the bladder wall (Murakumo et al, 1995). In spinal cord–injured rats, the elastin/collagen ratio first increased and is well correlated with increased bladder compliance due to bladder overdistention up to 6 weeks after injury, including a bladder areflexia phase. Then the ratio is reduced as bladder compliance is decreased due to the emergence of detrusor overactivity 10 weeks after injury, suggesting a potential role for elastin in the modulation of bladder compliance (Nagatomi et al, 2005; Toosi et al, 2008).

The nonfibrillar matrix in the stroma is largely composed of a gel of proteoglycans and water. Proteoglycans are glycoproteins with glycosaminoglycans covalently attached. The arrangement of the proteoglycans in the matrix creates a compartment of tissue water that has a viscous behavior when it is subjected to deformation.

Blood Vessels

The bladder has a multilayer vascular plexus, and this fact has morphologic as well as functional implications. When it is carefully examined, the underside of the epithelium is depressed by numerous grooves that are occupied by a dense network of blood capillaries. These vascular grooves allow a large number of capillaries to run at a distance of only a few tenths of a micron from the epithelium (Inoue and Gabella, 1991). The subepithelial capillary plexus may be associated with maintenance of the barrier function of the urothelium, reducing any exposure of the detrusor smooth muscle to substances diffusing from the urine (Hossler and Monson, 1995). It may also play a role in epithelial transport function and be necessary for urothelial metabolism.

Because of the large increase in surface area of the bladder wall during filling, the blood vessels must be able to lengthen considerably. To maintain good blood flow, mechanisms may be needed to ensure that the overall resistance of the vessels, as they lengthen, does not increase sufficiently to reduce the effective perfusion of the tissue. Several groups have investigated the effects of bladder filling on the blood flow. The majority of reports have shown that the blood flow is reduced by distention (Batista et al, 1996; Greenland and Brading, 1996). In patients with a low compliant bladder, there is a marked increase in the intravesicular pressure and a more pronounced decrease in bladder blood flow compared with normal controls (Ohnishi et al, 1994). **The principal determinant of**

blood flow in the bladder wall seems to be intramural tension. During normal filling, the blood flow is able to adapt to the large increase in surface area until the pressure increases in the bladder (Greenland and Brading, 1996).

When the detrusor is deprived of oxygen or a metabolic substrate, as would occur in ischemia, its contractile ability rapidly declines (Levin, 1983; Zhao et al, 1991; Pessina et al, 1997; Levin et al, 2003). **It has been suggested that ischemia and reperfusion might lead to damage to intramural neurons and result in the patchy denervation and altered smooth muscle function seen in bladders of patients with detrusor overactivity** (Brading, 1997a).

Urothelium

The basic functions of the bladder are storage of urine, maintenance of urine composition, and facilitation of voiding at appropriate time intervals. The urothelium has physiologic functions in relation to all parts of these basic functions and, as such, can no longer be thought of as an inert barrier between urine and plasma.

Structure

The urothelium consists of a variable number of cell layers, depending on the species (Fawcett, 1984). There are generally three distinct layers. A layer of basal cells are germinal in nature and 5 to 10 μm in diameter. Intermediate cells are superficial to these and approximately 20 μm in diameter, and a layer of umbrella cells forms the luminal surface of the urothelium (Lewis, 2000; Apodaca, 2004). These umbrella cells are the largest epithelial cells in the body, measuring 100 to 200 μm in diameter; they are polyhedral, are generally hexagonal, and can flatten and have more surface area with stretching. They may also be multinucleate (Kelly, 1984). The surface of the umbrella cells is covered with a glycosaminoglycan layer (Fig. 60–10).

Glycosaminoglycan Layer. The glycosaminoglycan (GAG) layer has been a controversial subject of research into urothelial barrier function. Parsons and associates (Parsons et al, 1990) reported that intravesical treatment of the rabbit bladder with protamine sulfate increased urothelial permeability, to water, urea, and calcium both in vivo and in vitro. This effect was reversed with pentosan polysulfate. They concluded that the protamine sulfate affected the GAG layer and that this was repaired by pentosan polysulfate. However, no microscopic evidence of the anatomic changes was presented in this paper. This study was confirmed by Nickel and coworkers (1998), who compared pentosan polysulfate, heparin, and hyaluronic acid as treatments. The authors concluded that heparin was the best of the three agents in efficacy but pointed out that this may be due to its anti-inflammatory properties. Indeed, the role of the GAG layer may be more in line with an antibacterial adherence function as outlined by Hanno and coworkers (1981). The GAG layer may also be important for the formation and attachment of particulates to the urothelium and stone formation (Hurst, 1994; Grases et al, 1996). However, there are a number of problems with the theory that the GAG layer is the urothelial plasma barrier:

- The GAG layer does not prevent small molecules, such as amiloride, from reaching the Na^+ channels expressed on the surface of the umbrella cells and interfering with them (Niku et al, 1994).
- The polyene antibiotic nystatin can reach the urothelium, as evidenced by increases in the short-circuit currents and reduction of transepithelial resistance to insignificant values, as it generates nonspecific cation pores in the cholesterol-containing luminal membrane of the umbrella cells.
- With the use of microelectrodes, the first resistive barrier is found on entry into the cell. Addition of monomeric arginine or polyvalent cations does not alter transepithelial ion permeability based on electrical measurements.
- Use of hydrolytic agents, such as neuraminidase, hyaluronidase, and chondroitinase, or of proteolytic agents, such as trypsin and kallikrein (to deliberately strip the urothelium of the GAG layer), does not alter the ability of protamine to increase the urothelial permeability (Lewis et al, 1995). This implies that the protamine acts not at the level of the GAG layer but rather at the surface of the luminal cells.

Protamine sulfate increases the apical membrane (luminal surface of umbrella cells) permeability to both

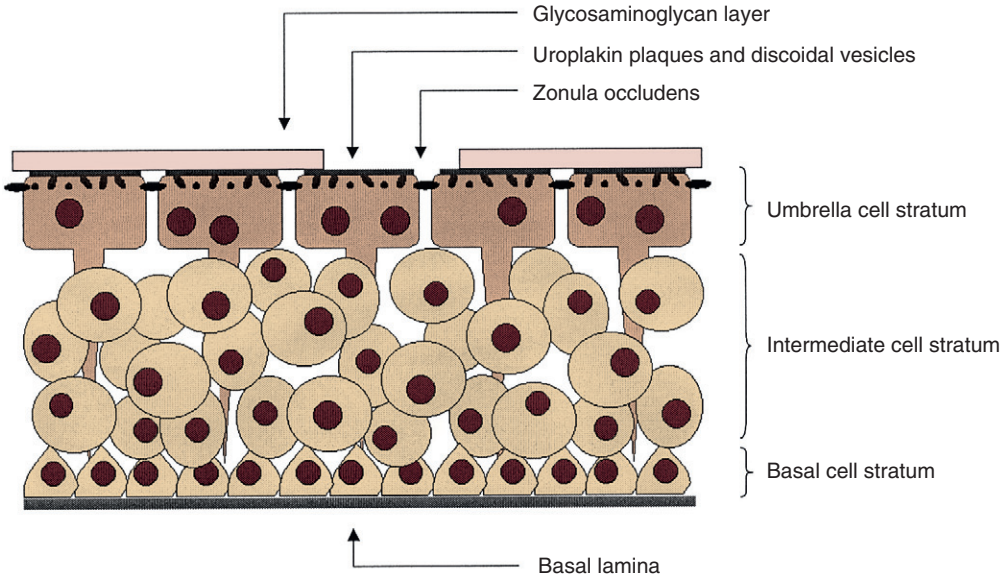


Figure 60–10. Diagrammatic representation of the bladder urothelium. The lumen of the bladder is on top and the lamina propria is below. The glycosaminoglycan layer is shown as discontinuous for illustrative purposes, enabling labeling of deeper structures.

monovalent cations and anions. This may be reversed on the basis of the concentration of the protamine, the composition of the bathing solution, and the exposure time of the urothelium to protamine. Prolonged exposure to protamine (>15 minutes) is poorly reversible and is thought to be caused by a decrease in paracellular resistance from cell lysis (Tzan et al, 1993, 1994).

In an indirect method of examining the GAG layer, Madin-Darby canine kidney (MDCK) cells were transfected with MUC-1, the major GAG of the bladder, with different tandem repeat units to vary the length of the glycosylated chain outside the cell. After this treatment, no difference in the transcellular water and urea permeability was found (Lavelle et al, 1997). **In summary, the GAG layer may have importance in bacterial antiadherence and in prevention of urothelial damage by large macromolecules. However, there is no definite evidence that the GAG layer acts as the primary epithelial barrier between urine and plasma.**

The Umbrella Cells. **The large umbrella cells that form the primary urine-plasma barrier are unique in several ways. First, they have the ability to increase and to decrease considerably their surface area primarily at the apical (luminal) surface. Second, they may be multinucleate. Third, they have an unusual apical surface membrane, which is described as an asymmetrical unit membrane, with the outer leaflet consisting of protein plaques and lipid and with a lipid inner leaflet. Fourth, these cells maintain an extremely high gradient between the plasma and the urine in terms of water concentration, urea concentration, potassium concentration, osmolality, and pH.**

Umbrella cells are so called for their shape, in that they look like umbrellas over the intermediate cell layer. They may cover several intermediate cells and have a stem that may extend to the lamina propria of the urothelium. They are capable of changing shape and can increase their surface area as the bladder fills and, conversely, decrease their surface area as the bladder empties. How this phenomenon occurs is still under debate. The primary theory is that there are a large number of subapical discoid vesicles with an asymmetrical membrane structure just under the apical membrane. These vesicles decrease in number with bladder stretch and increase the electrical capacitance of the luminal surface of the umbrella cells. This is consistent with the exocytosis of these vesicles to increase the cell surface area (Porter et al, 1967). Conversely, the discoid vesicles may be infoldings of membrane that stretch out and disappear with the requirement for increased surface area (Staehelin et al, 1972). These discoid vesicles are associated with a dense network of filaments (Hicks, 1965), which may be connected to the uroplakin plaques (Minsky and Chlapowski, 1978). The insertion of these vesicles into the apical membrane is a microfilament-dependent system, requiring ATP for insertion but not collapse, (Sarikas and Chlapowski, 1986) that does not require an intact microtubule system (Lewis and de Moura, 1982).

In membrane physiology, the primary determinant of the permeability of the lipid bilayer is the permeability of the individual leaflets. The leaflet that is least permeable will determine the overall permeability of the membrane (Negrete et al, 1996). In the umbrella cell luminal membrane, there is a unique structure where the membrane has most (70% to 90%) of the apical surface covered with protein plaque, with the remaining area consisting of hinge-like regions. The composition of the hinge regions is unclear but may be a protein or lipid. The large plaque units are 0.5 μm to 12 nm thick, with subunits approximately 16 nm from center to center (Walz et al, 1995). They are composed of a class of proteins called uroplakins, which are highly conserved across several species (human, monkey, sheep, pig, dog, rabbit, rat, and mouse). There are four uroplakin proteins: UP Ia (27 kD), UP Ib (28 kD), UP II (15 kD), and UP III (47 kD). Antibodies raised against UP I proteins have shown them to be present only in the umbrella cells of the urothelium, and therefore they may act as specific markers of terminally differentiated umbrella cells (Yu et al, 1994; Sun et al, 1999).

The primary function of the uroplakin proteins is hypothesized to be part of the primary plasma-urine barrier. Uroplakins have also been shown to act as the primary attachment site of type 1 piliated uropathogenic *Escherichia coli* in mice, leading to apoptosis of the umbrella cells that were inhibited by the caspase inhibitor Boc-aspartyl(OMe)-fluoromethylketone (BAF) (Mulvey et al, 1998). Given the highly conserved nature of uroplakins, the same is likely to happen in humans.

Coupled with the theory that the apical asymmetrical membrane of the umbrella cells is the primary barrier of the bladder to urine is the observation that cells are joined by tight junctions consisting of four to six interconnecting strands (Peter, 1978). It is the combination of the umbrella cells and tight junction connections that creates the physical barrier to the movement of substances between urine and blood. Once the umbrella cell layer of the urothelium is breached, there is little morphologic (Peter, 1978) or electrophysiologic (Lewis et al, 1976) diffusive permeability evidence (Negrete et al, 1996; Lavelle et al, 1998, 2000) for a barrier to the movement of water and urea.

Urothelial Permeability

Epithelial permeability, including that of the urothelium, depends on a number of factors. These are passive diffusion, osmotically driven diffusion, active transport, and inertness of the membrane to the solutes to which it is exposed.

Descriptions of finite passage of substances across the urothelium are well known. In 1856, Kaupp reported that the composition and volume of urine were altered with 12-hour voiding patterns instead of hourly voiding. These changes in volume have also been noted in rats during isovolumetric cystometrograms during 3-hour periods (Sugaya et al, 1997), and the rate of water loss has also been estimated by direct measurement of passive water diffusion in vitro in the rabbit (Negrete et al, 1996). There is a passive permeability to most substances in the blood or urine (Hicks, 1975).

The diffusive permeability of the mammalian bladder to water and urea has been directly measured in several species (Lavelle et al, 2000). The permeability of water in the bladder remains remarkably constant, ranging from 4.01 to 5.74×10^{-5} cm/sec, and that of urea, 1.5 to 4.51×10^{-6} cm/sec. Water permeability value in humans is similar at 6.5×10^{-5} cm/sec (Fellows and Marshall, 1972). This value was obtained by estimating the absorption of tritiated water into the plasma after instillation of the tritiated water into the bladder of volunteers. A direct measurement of urothelial diffusive permeability in the human has not yet been made.

Breakdown of the umbrella cells in animal models of cystitis has shown increased water and urea permeability. Presumably, leakage of urine into the detrusor is also responsible for the symptoms of cystitis (Lavelle et al, 1998, 2000). This increase in urothelial permeability with cystitis is increased further by distention of the bladder. The hypothesis is that with distention of the bladder, the weakened urothelium with denuded apical umbrella

cells and no real barrier in the intermediate or basal cells is further disrupted, thus allowing further egress of urine constituents into the detrusor. Similar breakdown of the apical cells is thought to occur in most forms of infectious cystitis and also in radiation cystitis.

Direct measurements of the osmotic effect on permeability have not been performed on urothelium. However, the urothelium maintains an osmotic gradient between plasma (300 mOsm/kg approximately) and urine (100 to 1500 mOsm/kg), depending on the level of water balance and diuresis of the individual. In the normal bladder, the osmotic effects of the urine appear to go unnoticed, and the patients have few or no symptoms. However, once the bladder is inflamed, such as in bladder pain syndrome/interstitial cystitis (BPS/IC), the effects of osmotic gradients become important (Gao et al, 1994).

Patients with spinal cord injury or with myelodysplasia tend to have chronic cystitis with bacteriuria and inflamed urothelium. When detrusor activity was increased in the rat by instillation of hyperosmolar compounds, this was accompanied by neurogenic inflammation, including plasma extravasation of Evans blue that could be decreased by pretreatment with the C-fiber afferent neurotoxin capsaicin (Maggi et al, 1990) indicating that hyperosmolar solutions excite afferent nerves. With increased osmolality, detrusor contractions were much stronger and accompanied by blood pressure elevations. These effects were enhanced when the bladder was pretreated with dimethyl sulfoxide to simulate cystitis conditions (Hohlbrugger and Lentsch, 1985; Hohlbrugger, 1987).

Increased permeability of the urothelium in inflammatory conditions has become the basis of the potassium sensitivity test, during which the bladder is distended with 400 mM of potassium chloride solution. Potassium penetrates the urothelium in the inflamed bladder and causes pain by activation of bladder afferent nerves (Parsons, 1996). This does not occur in normal bladders. The validity and accuracy of the intravesical potassium chloride test has not yet been proven clinically by multicenter randomized double-blind studies.

The fact that changes in the osmolality, pH, and ionic composition of the urine can influence the activity of the detrusor is important in the performance of cystometry. The nature of the infusate could alter the outcome of the test, particularly in the neurogenic bladder, where there are usually some changes in the urothelium because of the chronic bacteriuria (Hohlbrugger, 1995).

Ionic Transport

The apical membrane of the urothelium has a high electrical resistance (Lavelle et al, 1998, 2000), whereas the basolateral membrane resistance is approximately 10-fold lower (Clausen et al, 1979). Active sodium transport across the urothelium has been demonstrated (Wickham, 1964; Lewis and Diamond, 1976). Na^+ channels that exist on the apical surface of the umbrella cells and in the cytoplasmic vesicles below the apical surface are primarily amiloride sensitive (inhibition) and aldosterone responsive. However, amiloride-insensitive, cation-selective, as well as amiloride-insensitive, unstable cation channels have also been identified. Both of these channels were found to be degradation products of the amiloride-sensitive Na^+ channel. The amiloride-sensitive Na^+ channel is hydrolyzed by serine proteases such as kallikrein and urokinase and plasmin (normally found in the urine but produced by the kidney) (Lewis et al, 1995).

Sodium that is transported into the cell is removed at the basolateral membrane by a Na^+–K^+ exchanger. This leaves the cell with a negative intracellular charge. The basolateral membrane contains K^+ and Cl^- channels, Na^+–H^+ exchangers, and Cl^-–HCO_3^- exchangers. These channels and exchangers are important in recovery of cell volume during an increase in serosal osmolality (Donaldson and Lewis, 1990). Unfortunately, the precise role of the Na^+ channel in the apical membrane of the umbrella cell is unknown. It is possible that the degradation of the channel might follow the filling of the bladder and that the changes in conductance of sodium may be a signaling factor for the bladder and micturition when it reaches capacity. Alternatively, it may be involved in the signaling pathway that allows insertion or removal of apical membrane on expansion of the bladder.

Key Points: Urothelium

- Uroplakin proteins may be a key part of the primary plasma-urine barrier. Uroplakins have also been shown to act as the primary attachment site of type 1 piliated uropathogenic *Escherichia coli*.
- Protamine sulfate increases the luminal surface of umbrella cells permeability to cations and anions.
- The GAG layer may have importance in bacterial antiadherence and in prevention of urothelial damage, but there is no definite evidence that the GAG layer acts as the primary epithelial barrier between urine and plasma because the GAG layer does not prevent small molecules such as amiloride from reaching the cationic channels on the surface of the umbrella cells.

THE URETHRA

The urethra is composed of striated and smooth muscles. Contraction of the longitudinal smooth muscle could play a role in stabilizing the urethra and allowing force generated by the circular muscle elements to occlude the lumen or in aiding in the opening of the bladder neck during micturition. There is controversy about the relative roles of the urethral smooth and striated circular muscles and the lamina propria in generating the urethral pressure profile, but it seems likely that both contribute (Thind, 1995). **Blocking striated sphincter activity with nicotinic neuromuscular blocking agents has variable effects and may reduce urethral tone, but rarely by more than 40%, suggesting that the smooth muscles are important. Blocking sympathetic tone with α-adrenoceptor blockers may also reduce urethral pressure by about a third** (Torrens and Morrison, 1987). There is little evidence for the involvement of the cholinergic innervation in generating urethral pressure.

Urethral Muscle

The smooth muscle cells in the urethra are gathered into small bundles and linked to each other by many adherens-type junctions but no gap junctions. The smooth muscle bundles in the urethral wall are thinner than in the detrusor and arranged in obvious layers. **In humans and larger mammals, there is a relatively thick inner layer that is predominantly longitudinally arranged, and outside this, there is a thinner circular muscle layer.** In the lamina propria of the urethra, scattered small bundles of only a few cells are often found.

Striated muscle occurs in the walls of the male and female urethra, where it forms a rhabdosphincter that is separate from the periurethral skeletal muscle of the

pelvic floor. In the male, the striated muscle extends from the base of the bladder and the anterior aspect of the prostate to the full length of the membranous urethra. In the female, the striated muscle extends from the proximal urethra distally. The striated sphincter is horseshoe shaped, and the muscle cells are smaller than ordinary skeletal muscle, being 15 to 20 μm in diameter.

Morphology

The urethral stroma has been less extensively studied than the bladder stroma, but it is known to contain primarily longitudinally arranged collagen fibers and elastin fibers (Hickey et al, 1982; Huisman, 1983). The vascular filling of the urethral lamina propria is known to be of importance for urinary continence, although the magnitude of its contribution to continence is still not understood (Rud et al, 1980). Estrogen is known to increase the urethral blood flow, resulting in an increased distention of the lamina propria blood vessels (Brading, 1997a).

Impaired arterial blood supply to the urethra decreases the intraluminal pressure (Rud et al, 1980), but at present, it is not known whether it is the decrease in vascular filling or the urethral hypoxia that mediates the decrease in urethral pressure. It has been suggested that both these mechanisms may be involved because it was shown that the initial drop in urethral pressure was mediated through decreased vascular filling, whereas the later phase was due to a hypoxic effect on the urethral smooth muscle (Greenland and Brading, 1996).

Sphincter Configuration

An issue of continuing confusion is what composes the external sphincter and what the distinction is between the rhabdosphincter and the external striated sphincter proper. **In the membranous urethra, a thin smooth muscle layer extends along the entire urethra in the female and throughout the prostate and its capsule in the male** (Tanagho, 1982; Dixon and Gosling, 1987). **On the anterior surface of the male urethra, an outer layer of circularly oriented striated muscle forms a horseshoe configuration in the adult near the prostatic apex.** This striated muscle develops as a complete ring in the fetus and neonate and forms the external urethral sphincter or rhabdosphincter. **The periurethral striated muscles of the pelvic floor lie external to the rhabdosphincter** (see Fig. 60–2).

Despite the horseshoe configuration with the open end in the posterior direction, urethral pressure recording at the external sphincter during bladder filling increases uniformly along the entire circumference like an iris (Morita, 1989). Norepinephrine or hypogastric nerve stimulation augments this pressure, suggesting a role for adrenergic receptors and sympathetic nerves in the function of the external urethral sphincter (Kakizaki et al, 1991).

The arrangement of muscle forming the distal sphincter of the female differs from that in the male. **The female has an attenuated striated sphincter mechanism, as well as additional muscle structures termed the compressor urethrae and urethrovaginal sphincter** (DeLancey, 1989). The posterior wall remains rigid if there is adequate pelvic support from muscle and connective tissues. **As in the male, the striated components are deficient posteriorly.** This relative deficiency of periurethral striated musculature contributes to the difficulty in obtaining reliable external sphincter electromyography results during urodynamic studies in women. This attenuation of distal sphincteric muscles may contribute to urinary incontinence in females after resection of the bladder neck.

In women, urinary continence is maintained during elevations in intra-abdominal pressure by three processes. First, there is passive transmission of abdominal pressure to the proximal urethra. A guarding reflex involving an active contraction of striated muscle of the external urethral sphincter can transiently help continence (Enhorning, 1961; Tanagho, 1982). **However, mere transmission of abdominal pressure to proximal urethra does not account for the entire increase in urethral pressure** (Constantinou and Govan, 1982). **Urethral pressure rises before cough transmission** (Fig. 60–11). **These findings implicate an active urethral continence (neural) mechanism in women** (Constantinou and Govan, 1982). **DeLancey proposes the "hammock hypothesis" that abdominal pressure transmitted through the proximal urethra presses the anterior wall against the posterior wall. The posterior wall remains rigid if there is adequate pelvic support from muscle and connective tissues. More distally, based on morphologic data, DeLancey and colleagues** (DeLancey 1989, 1997; Sampselle and DeLancey, 1998) **have postulated that the urethral attachments to the pubis (pubourethral) and vaginal connections to pelvic muscles and fascia actively change the position of the bladder neck and proximal urethra with voiding. This**

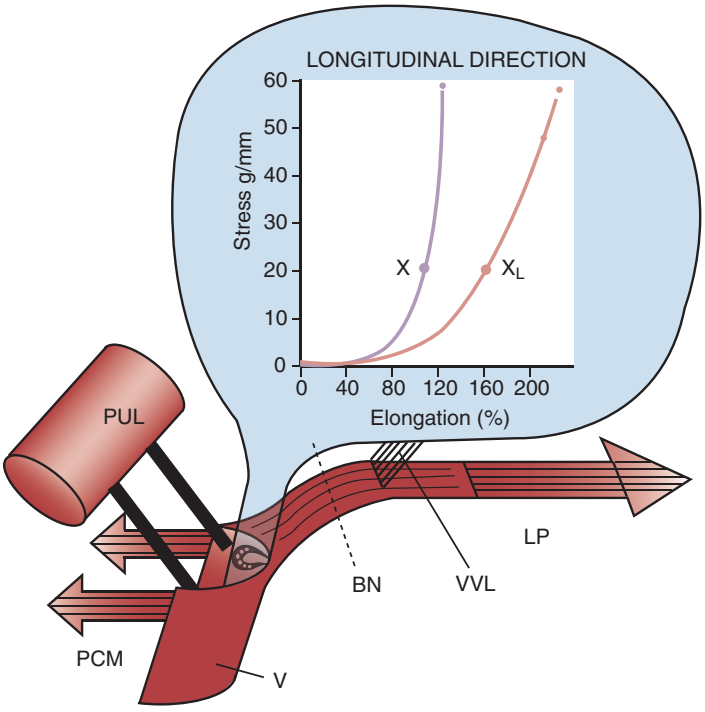


Figure 60–11. Influence of vaginal laxity on muscle force transmission and urinary continence. *Inset,* Stress extension curve of vagina. BN, bladder neck; LP, levator plate; PCM, pubococcygeus muscle; PUL, pubourethral ligament; V, vaginal hammock; VVL, vaginal attachment to the bladder base; X, normal elasticity; X_L, vaginal laxity. The authors propose that an increase in urethral pressure before cough transmission proves that an active continence mechanism is involved in preventing stress urinary incontinence. (From Petros PE, Ulmsten U. An integral theory and its method for the diagnosis and management of female urinary incontinence. Scand J Urol Nephrol 1993;27[Suppl. 153]:1–93.Copyright 1993, Scandinavian University Press, Stockholm, Sweden.)

arrangement compresses the urethra against the pubis during bladder filling and straining. These attachments contain both fascia and smooth muscle (Oelrich, 1983; DeLancey, 1988, 1989). **Thus urinary continence results from the combination of active muscle tone and passive anatomic coaptation.**

Fiber Types of Urethral Striated Muscle

Striated muscles are characterized as **slow type** and **twitch type**. **Twitch-type myofibrils can be further classified as slow and fast on the basis of functional and metabolic characteristics** (Padykula, 1967). Slow-twitch fibers seem ideally suited to maintaining sphincter tone for prolonged periods, whereas fast-twitch fibers may be needed to add to sphincter tone rapidly to maintain continence when intra-abdominal pressure is abruptly increased. Similar to smooth muscle, contraction of striated muscle fibers is governed by intracellular calcium, through interactions with troponin.

The fast-twitch fibers can be recruited rapidly but also fatigue rapidly, and perform predominantly anaerobic metabolism (Markwardt and Isenberg, 1992). Fast-twitch fibers exhibit rapid bursts of contractile force and are rich in myosin ATPase that catalyzes the actin–myosin interaction. The speed of contraction may be correlated with the histochemical reaction of this ATPase and alkaline pH. In addition, fast-twitch muscles are supplied with a fast isoform of the Ca^{2+}-ATPase, which translocates the cytosolic calcium into the abundant sarcoplasmic reticulum to allow rapid relaxation.

In contrast, slow-twitch fibers are found in greater percentage in muscles that require sustained tension, such as the pelvic levators and urethral sphincter. These muscle fibers are recruited and fatigue slowly and can perform high rates of oxidative metabolism because they possess less of the myosin ATPase activity and contain an increased expression of a slow isoform of the Ca^{2+}-ATPase (Markwardt and Isenberg, 1992). These fibers give rise to the background electromyographic activity seen during a urodynamic evaluation.

The external urethral sphincter is composed of two parts. The periurethral striated muscle of the pelvic floor contains both fast-twitch and slow-twitch fibers. The striated muscle of the distal sphincter mechanism contains predominantly slow-twitch fibers (Elbadawi, 1984) **and provides more than 50% of the static resistance** (Tanagho et al, 1989). **Gosling and colleagues** (2000) **presented histochemical evidence in humans that striated muscle within the distal urethra is composed primarily of slow-twitch myofibrils in contrast to the periurethral striated muscles of the pelvic floor, which contain fast-twitch and slow-twitch fibers. In the male, the rhabdosphincter consists of 35% fast-twitch and 65% slow-twitch fibers** (Padykula and Gauthier, 1970). **In the female, the ratio of slow-twitch to fast-twitch fibers is 87% slow-twitch and 13% fast-twitch.**

The majority of the fast-twitch fibers and about a fourth of the slow-twitch fibers in the intramural striated muscle of the human membranous urethral sphincter show positive staining for nitric oxide synthase in the sarcolemma (Ho et al, 1998). Moreover, the striated periurethral muscles of the pelvic floor are adapted for the rapid recruitment of motor units required during increases in abdominal pressure. **It has been speculated that the successful treatment of stress incontinence by pelvic floor exercises or electrostimulation is caused by the conversion of fast-twitch to slow-twitch striated muscle fibers** (Bazeed et al, 1982).

In addition to striated muscle, the external sphincter appears to contain smooth muscle, which receives noradrenergic innervation. Investigators have shown that stimulation of the hypogastric nerve elicits myogenic potentials in the external urethral sphincter (Kakizaki et al, 1991). Whether this activity is the result of smooth or striated muscle is unclear. Because these potentials persist after α-adrenergic blockade, investigators postulate that it arises from striated muscle.

Lamina Propria and Paraurethral Tissue

Results are divergent regarding the clinical significance of connective tissue outside the urethra. Paraurethral tissue biopsy specimens from premenopausal women with stress incontinence contain 30% more collagen, and the diameter of the fibrils is 30% larger than in controls (Falconer et al, 1998a). Postmenopausal stress-incontinent women, on the other hand, have no difference in collagen concentration compared with their age-matched controls (Falconer et al, 1998b). Others, however, have found a decreased periurethral collagen concentration (Rechberger et al, 1993) and a decreased collagen I to collagen III ratio (Keane et al, 1997) in patients with stress incontinence.

NEURAL CONTROL OF THE LOWER URINARY TRACT

Peripheral Nervous System

The lower urinary tract is innervated by three sets of peripheral nerves involving the parasympathetic, sympathetic, and somatic nervous systems (Fig. 60–12). **Pelvic parasympathetic nerves arise at the sacral level of the spinal cord, excite the bladder, and relax the urethra. Lumbar sympathetic nerves inhibit the bladder body and excite the bladder base and urethra. Pudendal nerves excite the external urethral sphincter.** These nerves contain afferent (sensory) as well as efferent axons (Wein, 1992; de Groat et al, 1993a; Sugaya et al, 1997; Yoshimura et al, 2008).

Parasympathetic Pathways

Parasympathetic preganglionic neurons innervating the lower urinary tract are located in the lateral part of the sacral intermediate gray matter in a region termed the sacral parasympathetic nucleus (Nadelhaft et al, 1980; Morgan et al, 1981; de Groat et al, 1993a; Morgan et al, 1993; de Groat et al, 1996). Parasympathetic preganglionic neurons send axons through the ventral roots to peripheral ganglia, where they release the excitatory transmitter acetylcholine (de Groat and Booth, 1993). **Parasympathetic postganglionic neurons in humans are located in the detrusor wall layer as well as in the pelvic plexus. This is an important fact to remember because patients with cauda equina or pelvic plexus injury are neurologically decentralized but may not be completely denervated. Cauda equina injury allows possible afferent and efferent neuron interconnection at the level of the intramural ganglia** (de Groat et al, 1993a; de Groat et al, 1996).

Sympathetic Pathways

Sympathetic outflow from the rostral lumbar spinal cord provides a noradrenergic excitatory and inhibitory input to the bladder and

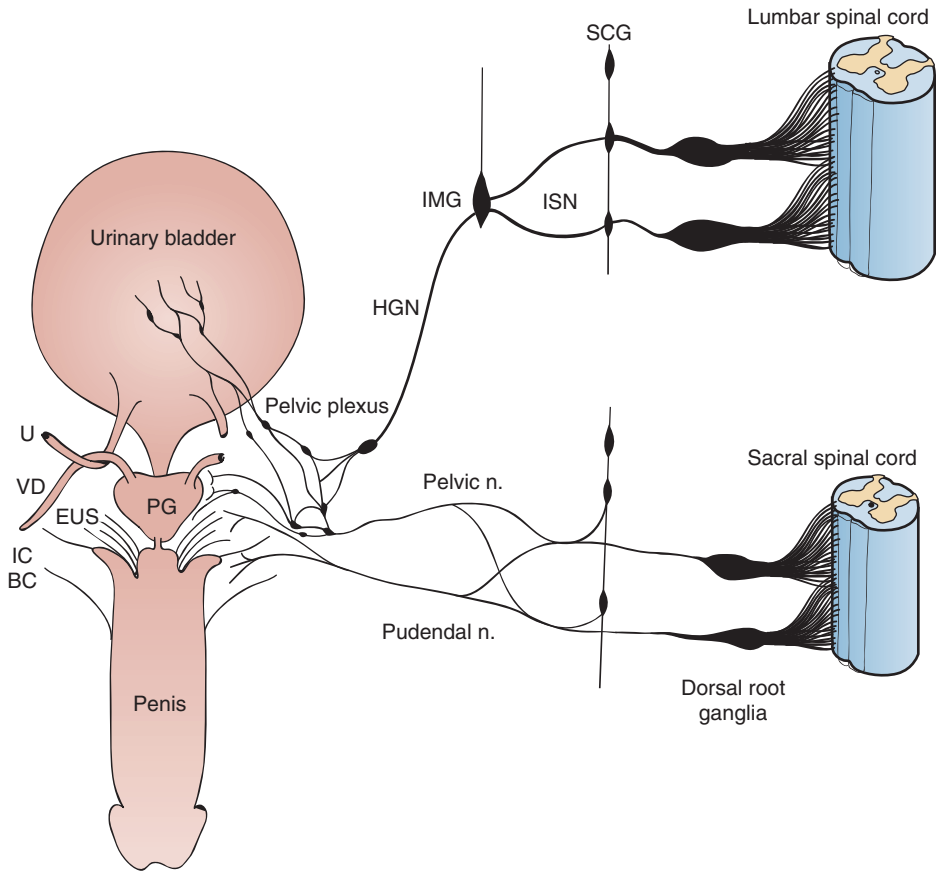


Figure 60–12. Diagram showing the sympathetic, parasympathetic, and somatic innervation of the urogenital tract of the male cat. Sympathetic preganglionic pathways emerge from the lumbar spinal cord and pass to the sympathetic chain ganglia (SCG) and then through the inferior splanchnic nerves (ISN) to the inferior mesenteric ganglia (IMG). Preganglionic and postganglionic sympathetic axons then travel in the hypogastric nerve (HGN) to the pelvic plexus and the urogenital organs. Parasympathetic preganglionic axons that originate in the sacral spinal cord pass in the pelvic nerve to ganglion cells in the pelvic plexus and to distal ganglia in the organs. Sacral somatic pathways are contained in the pudendal nerve, which provides an innervation to the penis and the ischiocavernosus (IC), bulbocavernosus (BC), and external urethral sphincter (EUS) muscles. The pudendal and pelvic nerves also receive postganglionic axons from the caudal sympathetic chain ganglia. These three sets of nerves contain afferent axons from the lumbosacral dorsal root ganglia. PG, prostate gland; U, ureter; VD, vas deferens.

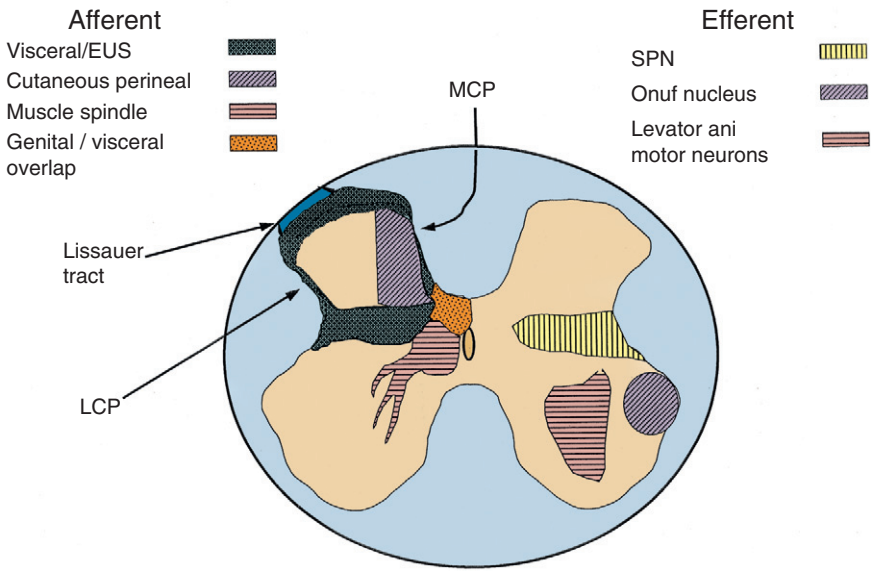


Figure 60–13. Cross section of sacral spinal cord; neuroanatomic distribution of primary afferent and efferent components of storage and micturition reflexes. For purposes of clarity, afferent components are shown only on the *left*, and efferent components are shown only on the *right*. Both components are, of course, distributed bilaterally and thus overlap extensively. Visceral afferent components represent bladder, urethral, and genital (glans penis or clitoris) afferent fibers contained in the pelvic and pudendal nerves. Cutaneous perineal afferent components represent afferent fibers that innervate the perineal skin contained in the pudendal nerve. Muscle spindle afferent components represent Ia/b afferent fibers contained in the levator ani nerve that innervate muscle spindles in the levator ani muscle. EUS, external urethral sphincter; LCP, lateral collateral projection; MCP, medial collateral projection; SPN, sacral parasympathetic nucleus.

urethra (Andersson, 1993). Activation of sympathetic nerves induces relaxation of the bladder body and contraction of the bladder outlet and urethra, which contribute to urine storage in the bladder. **The peripheral sympathetic pathways follow a complex route that passes through the sympathetic chain ganglia to the inferior mesenteric ganglia and then through the hypogastric nerves to the pelvic ganglia.**

Somatic Pathways

The external urethral sphincter motoneurons are located along the lateral border of the ventral horn, commonly referred to as the Onuf nucleus (Fig. 60–13) (Thor et al, 1989). Sphincter motoneurons also exhibit transversely oriented dendritic bundles that project laterally into the lateral funiculus, dorsally into the intermediate gray matter, and dorsomedially toward the central canal.

Afferent Pathways

Afferent axons in the pelvic, hypogastric, and pudendal nerves transmit information from the lower urinary tract to the lumbosacral spinal cord (de Groat, 1986; Janig and Morrison, 1986; Yoshimura et al, 2008). **The primary afferent neurons of the pelvic and pudendal nerves are contained in sacral dorsal root ganglia (DRG), whereas afferent innervation in the hypogastric nerves arises in the rostral lumbar DRG.** The central axons of the DRG neurons carry the sensory information from the lower urinary tract to second-order neurons in the spinal cord (Morgan et al, 1981; de Groat, 1986; Thor et al, 1989; de Groat et al, 1996) (see Fig. 60–13). Visceral afferent fibers of the pelvic (Morgan et al, 1981) and pudendal (Thor et al, 1989) nerves enter the cord and travel rostrocaudally within the Lissauer tract.

Pelvic nerve afferents, which monitor the volume of the bladder and the amplitude of the bladder contraction, consist of myelinated (Aδ) and unmyelinated (C) axons (Table 60–3). **During neuropathic conditions and possibly inflammatory conditions, there is recruitment of C fibers that form a new functional afferent pathway that can cause urgency incontinence and possibly bladder pain.**

Sensing bladder volume is of particular relevance during urine storage. On the other hand, afferent discharges that occur during a bladder contraction have an important reflex function and appear to reinforce the central drive that maintains the detrusor contraction. Afferent nerves that respond to both distention and contraction, that is, "in-series tension receptors," have been identified in the pelvic and hypogastric nerves of cats and rats (see Table 60–3) (Iggo, 1955; Floyd et al, 1976; Morrison, 1997). Afferents that respond only to bladder filling have been identified in the rat bladder (Morrison, 1998) and appear to be volume receptors, possibly sensitive to stretch of the mucosa. In the cat bladder, some in-series tension receptors may also respond to bladder stretch (Downie and Armour, 1992). In the rat, there is evidence that many C bladder afferents are volume receptors that do not respond to bladder contractions, a property that distinguishes them from in-series tension receptors (Morrison, 1998).

In the mouse pelvic nerve, four classes of bladder afferents (serosal, muscular, muscular/urothelial, and urothelial) have been identified based on responses to receptive field stimulation with different mechanical stimuli, including probing, stretch, and stroking the urothelium. Both low-threshold, representing 65% to 80% of the total population, and high-threshold stretch-sensitive muscular afferents are present (Daly et al, 2007; Xu and Gebhart, 2008). The muscular afferents can be sensitized by application of a combination of inflammatory mediators (bradykinin, serotonin, prostaglandin, and histamine at pH 6.0) (Xu and Gebhart, 2008).

In the guinea pig bladder, four classes of C-fiber afferents have also been detected (Zagorodnyuk et al, 2006, 2007). The first class, muscle mechanoreceptors, are activated by stretch but not by mucosal stroking with light (0.05 to 0.1 mN) von Frey hairs or by hypertonic saline, α,β-methylene ATP or capsaicin. Removal of the urothelium did not affect their stretch-induced firing. The second class, muscle-mucosal mechanoreceptors, are activated by both stretch and mucosal stroking, by hypertonic solution, α,β-methylene-ATP but not by capsaicin. Stroking- and stretch-induced firing is significantly reduced by removal of the urothelium. The third class of afferents, mucosal high-responding mechanoreceptors, are stretch insensitive but can be activated by mucosal stroking, hypertonic solution, α,β-methylene-ATP, and capsaicin. Stroking-induced activity is reduced by removal of the urothelium. The fourth class of afferents, mucosal low-responding mechanoreceptors, are stretch insensitive but can be weakly activated by mucosal stroking but not by hypertonic solution, α,β-methylene-ATP, or capsaicin. Removal of the urothelium reduces stroking-induced firing. A recent study by Zagorodnyuk and colleagues (2009) also showed that mechanotransduction during stretch or mucosal stroking in the second and third classes of afferents, stretch-sensitive muscle-mucosal mechanoreceptors, and stretch-insensitive, mucosal high-responding afferents, are not dependent upon Ca^{2+}-dependent exocytotic release of mediators or ATP, but are likely to be induced by benzamil-sensitive, stretch-activated ion channels on nerve endings. This is because stretch- or stroking-induced firing of these afferents are not affected by the nonselective P2 purinoreceptor antagonist or Ca^{2+}-free solution, but are inhibited by benzamil, a mechanogated channel blocker. These results suggest that substances released from the urothelium during mechanical stimulation, such as ATP, may not be involved in the modulation of the activity of bladder afferents located in the vicinity of the urothelium, at least in the normal condition, which is against the current theory of the urothelium–afferent interaction by urothelially released substances during bladder stretch.

Species differences, as well as differences of nomenclature, might account for some of the variations in reported properties of bladder afferents. For example, the conduction velocity that differentiates Aδ and C fibers is 2 m/sec in the cat, whereas it is 1.3 m/sec in the rat (Waddell et al, 1989). In the cat, Aδ bladder afferents appear to be low-threshold mechanoreceptors (Häbler et al, 1993), whereas C-bladder afferents (Häbler et al, 1990) are generally mechanoinsensitive ("silent C fibers") (see Table 60–3). Some of the latter may be nociceptive and have been found to be sensitized by intravesical administration of chemicals (such as high potassium), low pH, high osmolality, and irritants such as capsaicin (Fig. 60–14) (Maggi et al, 1987; McMahon and Abel, 1987; Häbler et al, 1990; Wen et al, 1994; Wen and Morrison, 1994, 1996; Zagorodnyuk et al, 2009). After exposure to these

Table 60–3.

Bladder Afferent Properties

FIBER TYPE	LOCATION	NORMAL FUNCTION	INFLAMMATION EFFECT
Aδ (finely myelinated axons)	Smooth muscle	Sense bladder fullness (wall tension)	Increase discharge at lower pressure threshold
C fiber (unmyelinated axons)	Mucosa	Respond to stretch (bladder volume sensors)	Increase discharge at lower threshold
C fiber (unmyelinated axons)	Mucosa muscle	Nociception to overdistention	Sensitive to irritants
		Silent afferent	Becomes mechanosensitive and unmasks new afferent pathway during inflammation

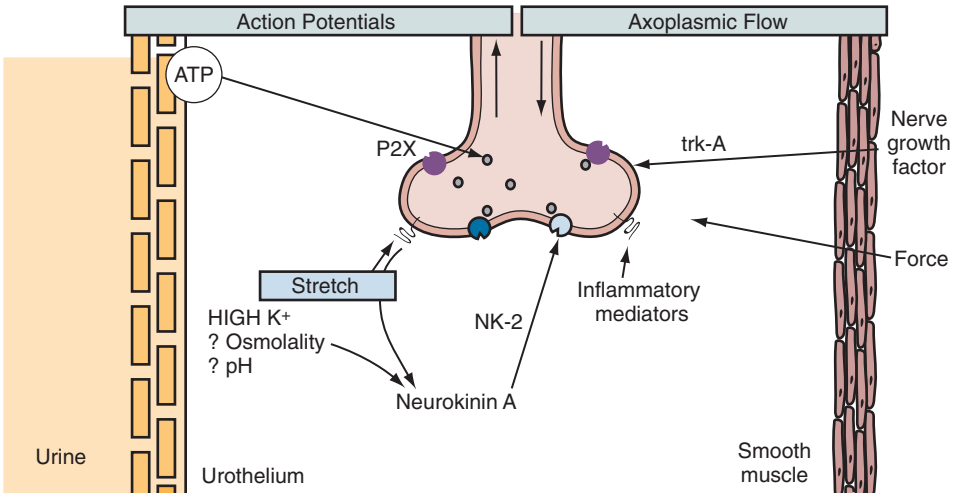


Figure 60–14. Actions of chemical mediators that may sensitize mechanosensory nerve endings in the bladder mucosa. Adenosine triphosphate (ATP) can be released from the urothelium and may sensitize the mechanoreceptors, which respond to stretch of the mucosa during bladder distention. Neuropeptides transported to the sensory ending by axoplasmic transport may be released during distention and chemical stimulation, and neurokinin A can act on NK_2 autoreceptors, which sensitize the mechanosensitive endings. This mechanism can be induced by high urinary potassium concentrations and possibly by other sensitizing solutions within the bladder lumen, such as those with high osmolality or low pH; the presence in the tissues of inflammatory mediators may also sensitize the endings. The smooth muscle can generate force that may influence some mucosal endings, and the production of nerve growth factor is another mechanism that can influence the mechanosensitivity of the sensory ending through the TrkA receptor.

substances, the sensitivity of bladder mechanoreceptors to distention increases, and some "silent" afferents become mechanoreceptive.

In the urethra, afferent nerves are distributed between the muscle fibers, around blood vessels, in the urothelium, and in a dense suburothelial plexus (Crowe et al, 1986; Tainio, 1993; Fahrenkrug and Hannibal, 1998). In some species, afferent nerves extend to the luminal surface of the urothelium. The striated sphincter muscle that surrounds the urethra receives a very sparse afferent innervation that is localized primarily to nerve bundles passing between the muscle bundles. Specialized tension receptors (muscle spindles) that are innervated by large-diameter myelinated group IA afferents and that are prominent in most striated muscles are absent (Gosling et al, 1981) or are present in low density (Lassmann, 1984) in striated sphincter muscles.

Afferent Nerves and Interorgan Cross Sensitization. Axonal tracing studies revealed that a subpopulation (6% to 21%) of afferent neurons in dorsal root ganglia of the rat and mouse can innervate multiple pelvic organs (Keast and de Groat, 1992; Christianson et al, 2007). In the rat, the largest percentage of these neurons is present in the thoracolumbar DRG; whereas in the mouse the larger percentage is in the lumbosacral DRG. Subsequent studies provided evidence that **chemical irritation of one organ (either the urinary bladder or the colon) can facilitate/sensitize the activity of the other organ** (Pezzone et al, 2005). Electrophysiologic experiments showed that acute colonic irritation can sensitize bladder C-fiber afferents to mechanical and chemical stimuli (Ustinova et al, 2006, 2007) and enhance the firing of lumbosacral spinal interneurons receiving afferent input from the bladder (Qin et al, 2005). Lumbosacral afferent neurons in the L6-S2 DRG innervating both the colon and bladder ("convergent neurons") exhibited decreased voltage and current thresholds for action potential firing three days after colonic irritation with trinitrobenzene sulfonic acid (TNBS) in rats (Malykhina et al, 2006). The effect persisted for 30 days in the absence of overt colonic inflammation. Colitis also enhanced the responses to capsaicin and increased the peak amplitude of tetrodotoxin-resistant Na^+ currents in bladder afferent neurons isolated from the L6-S2 DRG (Malykhina et al, 2004).

Changes in bladder function after colonic inflammation also appear to be mediated by a change in the cholinergic efferent pathway to the bladder (Noronha et al, 2007). During the active colonic inflammation, three days after TNBS instillation into the colon, the bladder was not inflamed, but the contractions of bladder strips induced by electrical field stimulation or carbachol, a muscarinic receptor agonist, were reduced, while the contractions induced by potassium (KCl) were not changed. During and after recovery of the colonic inflammation (15 to 30 days), the contractile responses of the bladder returned to normal. It was suggested that bladder dysfunction was mediated by visceral organ cross talk induced by sensitization of a subpopulation of afferents innervating both the bladder and colon.

Key Points: Afferent Pathways

- Studies of the properties of bladder afferents in the pelvic nerve, particularly in the rat, indicate that in series tension receptors, volume receptors and silent afferents (including nociceptors) are present.
- Intravesical irritant chemicals reduce the pressure thresholds of most of these endings, including the high-threshold receptors.
- A substantial proportion of the C-fiber afferent population is silent (i.e., insensitive to normal distention). However, these fibers become mechanosensitive after the action of various chemical mediators.
- During inflammation and possibly other pathologic conditions, there is recruitment of mechanosensitive C fibers that form a new functional afferent pathway. This is the rationale for intravesical C-fiber neurotoxin capsaicin and resiniferatoxin (RTX) therapy (Chancellor and de Groat, 1999).

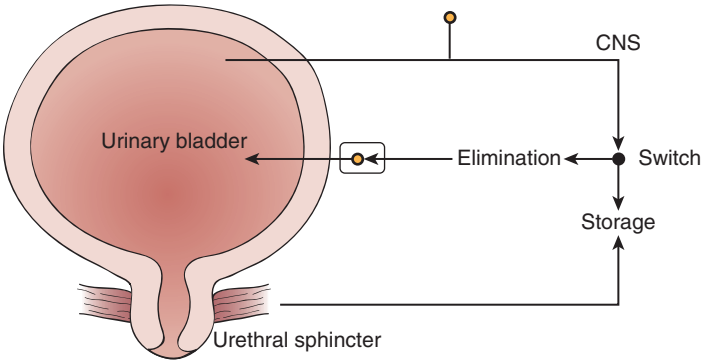


Figure 60–15. Diagram illustrating the anatomy of the lower urinary tract and the "switchlike" function of the micturition reflex pathway. During urine storage, a low level of afferent activity activates efferent input to the urethral sphincter. A high level of afferent activity induced by bladder distention activates the switching circuit in the central nervous system (CNS), producing firing in the efferent pathways to the bladder, inhibition of the efferent outflow to the sphincter, and urine elimination.

Table 60–4.

Reflexes to the Lower Urinary Tract

AFFERENT PATHWAY	EFFERENT PATHWAYS	CENTRAL PATHWAY
Urine Storage		
Low-level vesical afferent activity (pelvic nerve)	External sphincter contraction (somatic nerves) Internal sphincter contraction (sympathetic nerves) Detrusor inhibition (sympathetic nerves) Ganglionic inhibition (sympathetic nerves) Sacral parasympathetic outflow inactive	Spinal reflexes
Micturition		
High-level vesical afferent activity (pelvic nerve)	Inhibition of external sphincter activity Inhibition of sympathetic outflow Activation of parasympathetic outflow to the bladder Activation of parasympathetic outflow to the urethra	Spinobulbospinal reflex

Reflex Circuitry Controlling Micturition

Multiple reflex pathways organized in the brain and spinal cord mediate coordination between the urinary bladder and the urethra. The central pathways controlling lower urinary tract function are organized as simple on-off switching circuits (Fig. 60–15) that maintain a reciprocal relationship between the urinary bladder and the urethral outlet (de Groat, 1975; de Groat et al, 1993a). The principal reflex components of these switching circuits are listed in Table 60–4 and illustrated in Figure 60–16. Some reflexes promote urine storage, whereas others facilitate voiding. It is also possible that individual reflexes might be linked together in a serial manner to create complex feedback mechanisms. For example, **the bladder to external urethral sphincter guarding reflex that triggers sphincter contractions during bladder filling could, in turn, activate sphincter muscle afferents that initiate an inhibition of the parasympathetic excitatory pathway to the bladder. Thus a bladder to sphincter to bladder reflex pathway could, in theory, contribute to the suppression of bladder activity during urine storage. Alterations in these primitive reflex mechanisms may contribute to neurogenic bladder dysfunction.** Direct activation of these reflexes by electrical stimulation of the sacral spinal roots very likely contributes to therapeutic effects of sacral nerve root neuromodulation (Dijkema et al, 1993; Chancellor and Chartier-Kastler, 2000).

The Storage Phase of the Bladder

Intravesical pressure measurements during bladder filling in both humans and animals reveal low and relatively constant bladder pressures when bladder volume is below the threshold for inducing voiding (Fig. 60–17). **The accommodation of the bladder to increasing volumes of urine is primarily a passive phenomenon dependent on the intrinsic properties of the vesical smooth muscle and stroma, as well as the quiescence of the parasympathetic efferent pathway** (Torrens and Morrison, 1987; de Groat et al, 1993a; Yoshimura et al, 2008). **The bladder to sympathetic reflex also contributes as a negative feedback or urine storage mechanism that promotes closure of the urethral outlet and inhibits neurally mediated contractions of the bladder during bladder filling** (de Groat and Theobald, 1976) (see Table 60–4). Reflex activation of the sympathetic outflow to the lower urinary tract can be triggered by afferent activity induced by distention of the urinary bladder (de Groat and Theobald, 1976; de Groat et al, 1993a). This reflex response is organized in the lumbosacral spinal cord and persists after transection of the spinal cord at the thoracic levels (Fig. 60–18). **However, this bladder to sympathetic mechanism to suppress bladder contractions during urine storage may be weak in humans**, given that bilateral retroperitoneal lymph node dissection, in which the sympathetic chains are destroyed, has no discernible alteration of filling or storage function in humans.

During bladder filling, the activity of the sphincter electromyogram also increases (see Fig. 60–17), **reflecting an increase in efferent firing in the pudendal nerve and an increase in outlet resistance that contributes to the maintenance of urinary continence. Pudendal motoneurons are activated by bladder afferent input (the guarding reflex)** (Park et al, 1997), **whereas during micturition the motoneurons are reciprocally inhibited** (de Groat et al, 1993a). External urethral sphincter motoneurons are also activated by urethral or perineal afferents in the pudendal nerve (Fedirchuk et al, 1992). This reflex may represent, in part, a continence mechanism that is activated by proprioceptive afferent input from the urethra or pelvic floor and that induces closure of the urethral outlet. These excitatory sphincter reflexes are organized in the spinal cord. **Inhibition of external urethral sphincter reflex activity during micturition is dependent, in part, on supraspinal mechanisms, because it is weak or absent in chronic spinal animals and humans, resulting in simultaneous contractions of bladder and**

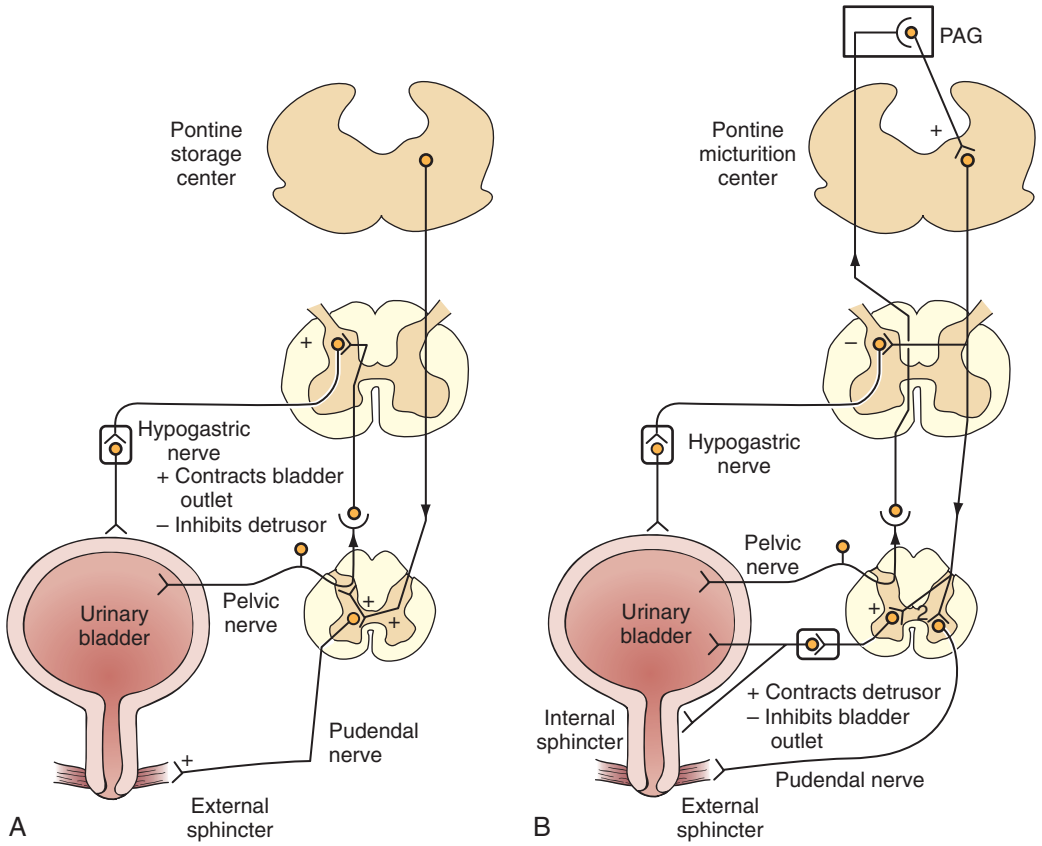


Figure 60–16. Mechanism of storage and voiding reflexes. **A,** Storage reflexes. During the storage of urine, distention of the bladder produces low-level bladder afferent firing. Afferent firing, in turn, stimulates the sympathetic outflow to the bladder outlet (base and urethra) and pudendal outflow to the external urethral sphincter. These responses occur by spinal reflex pathways and represent "guarding reflexes," which promote continence. Sympathetic firing also inhibits detrusor muscle and transmission in bladder ganglia. **B,** Voiding reflexes. At the initiation of micturition, intense vesical afferent activity activates the brainstem micturition center, which inhibits the spinal guarding reflexes (sympathetic and pudendal outflow to the urethra). The pontine micturition center also stimulates the parasympathetic outflow to the bladder and internal sphincter smooth muscle. Maintenance of the voiding reflex is through ascending afferent input from the spinal cord, which may pass through the periaqueductal gray matter (PAG) before reaching the pontine micturition center.

sphincter (i.e., detrusor-sphincter dyssynergia) (Rossier and Ott, 1976; Blaivas, 1982).

Sphincter to Bladder Reflexes. It is well known that **stimulation of somatic afferent pathways projecting in the pudendal nerve to the caudal lumbosacral spinal cord can inhibit voiding function. The inhibition can be induced by activation of afferent input from various sites, including the penis, vagina, rectum, perineum, urethral sphincter, and anal sphincter** (de Groat et al, 1979, 1993a, 2001). Electrophysiologic studies in cats showed that the inhibition was mediated by suppression of interneuronal pathways in the sacral spinal cord and also by direct inhibitory input to the parasympathetic preganglionic neurons (de Groat et al, 1982).

On the basis of experiments in our laboratory and the review of medical literature, we believe that contractions of the external urethral sphincter, and possibly other pelvic floor striated muscles, stimulate firing in muscle proprioceptive afferents, which then activate central inhibitory mechanisms to suppress the micturition reflex (Fig. 60–19). A similar inhibitory mechanism has been identified in monkeys by directly stimulating the anal sphincter muscle (McGuire et al, 1983). In monkeys, at least part of the inhibitory mechanism must be localized in the spinal cord, because it persisted in T4 chronic paraplegic animals.

The Emptying Phase of the Bladder

The storage phase of the bladder can be switched to the voiding phase either involuntarily (reflexively) or voluntarily. The former is readily demonstrated in the human infant or in patients with neuropathic bladder when the bladder wall tension due to increased volume of urine exceeds the micturition threshold. At this point, increased afferent firing from tension receptors in the bladder reverses the pattern of efferent outflow, producing firing in the sacral parasympathetic pathways and inhibition of sympathetic and somatic pathways. The expulsion phase consists of an initial relaxation of the urethral sphincter (see Fig. 60–17) **followed in a few seconds by a contraction of the bladder, an increase in bladder pressure, and the flow of urine. Relaxation of the urethral smooth muscle during micturition is mediated by activation of a parasympathetic pathway to the urethra that triggers the release of nitric oxide, an inhibitory transmitter** (Andersson, 1993; Bennett et al, 1995), **and by removal of excitatory inputs to the urethra. Secondary reflexes elicited by flow of urine through the urethra facilitate bladder emptying** (Torrens and Morrison, 1987; de Groat et al, 1993a; Jung et al, 1999). These reflexes

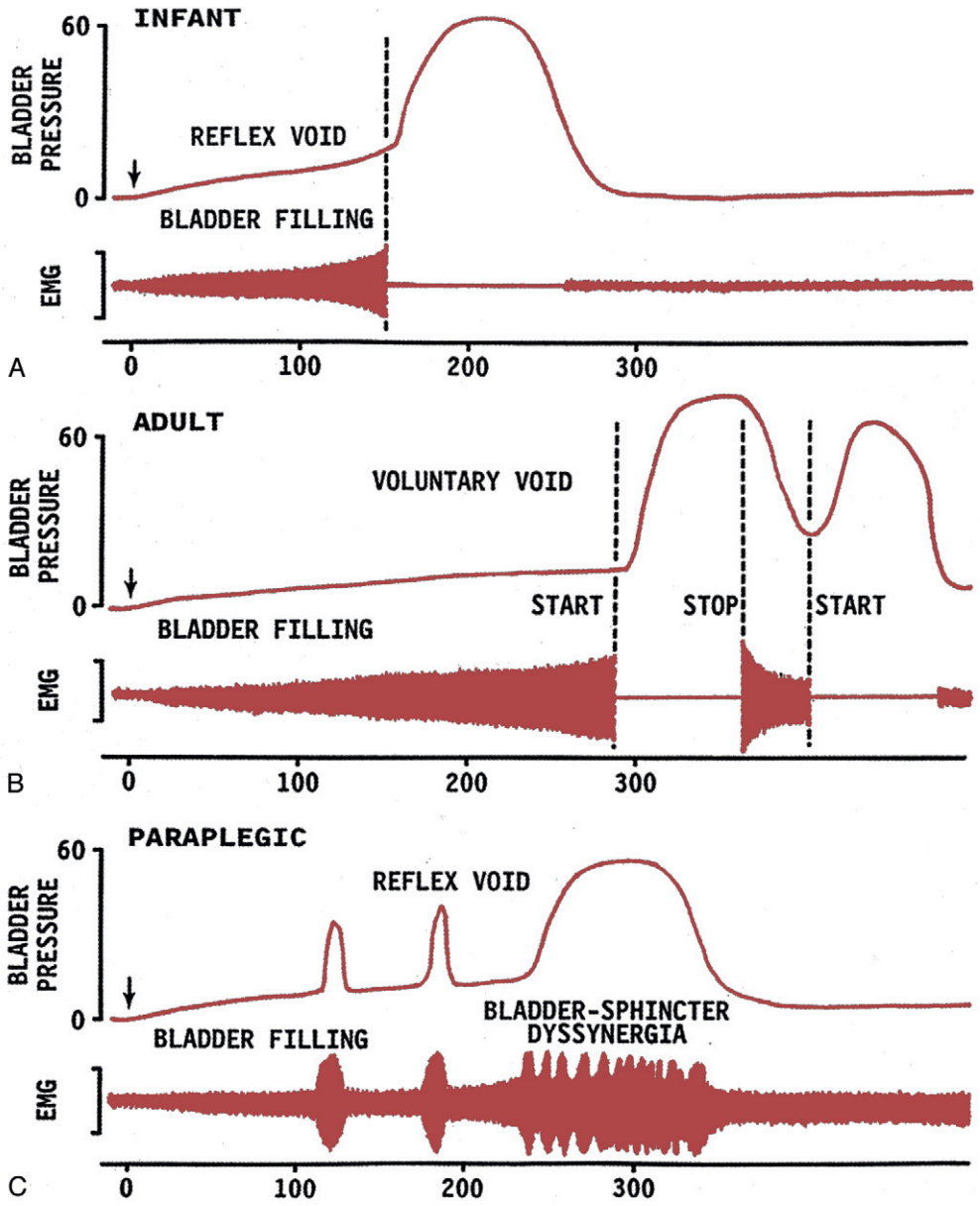


Figure 60–17. Combined cystometrogram and sphincter electromyogram (EMG) comparing reflex voiding responses in an infant **(A)** and in a paraplegic patient **(C)** with a voluntary voiding response in an adult **(B).** The x-axis in all records represents bladder volume in milliliters, and the y-axis represents bladder pressure in centimeters of water and electrical activity of the electromyographic recording. On the *left* side of each trace, the arrows indicate the start of a slow infusion of fluid into the bladder (bladder filling). Vertical *dashed lines* indicate the start of sphincter relaxation that precedes by a few seconds the bladder contraction in **A** and **B.** In **B,** note that a voluntary cessation of voiding (stop) is associated with an initial increase in sphincter electromyographic activity followed by a reciprocal relaxation of the bladder. A resumption of voiding is again associated with sphincter relaxation and a delayed increase in bladder pressure. On the other hand, in the paraplegic patient **(C),** the reciprocal relationship between bladder and sphincter is abolished. During bladder filling, transient uninhibited bladder contractions occur in association with sphincter activity. Further filling leads to more prolonged and simultaneous contractions of the bladder and sphincter (bladder-sphincter dyssynergia). Loss of the reciprocal relationship between bladder and sphincter in paraplegic patients interferes with bladder emptying. (From de Groat WC. Basic neurophysiology and neuropharmacology. In: Abrams P, Khoury S, Wein A, editors. Incontinence. Plymouth [UK]: Health Publications; 1999. p. 112.)

require the integrative action of neuronal populations at various levels of the neuraxis (see Fig. 60–16A). **The parasympathetic outflow to the detrusor and urethra has a more complicated central organization involving spinal and spinobulbospinal pathways passing through a micturition center in the pons (pontine micturition center)** (see Fig. 60–16B).

Urethra to Bladder Reflexes. A landmark in the historical progress of neurourology is the contribution of Barrington. Using his keen observational skills, Barrington (1931, 1941) reported that urine flow or mechanical stimulation of the urethra with a catheter could excite afferent nerves that, in turn, facilitated reflex bladder contractions in the anesthetized cat (see Fig. 60–19). **He proposed that this facilitatory urethra to bladder reflex could promote complete bladder emptying.** Barrington identified two components of this reflex. One component was activated by a somatic afferent pathway in the pudendal nerve and produced facilitation by a supraspinal mechanism involving

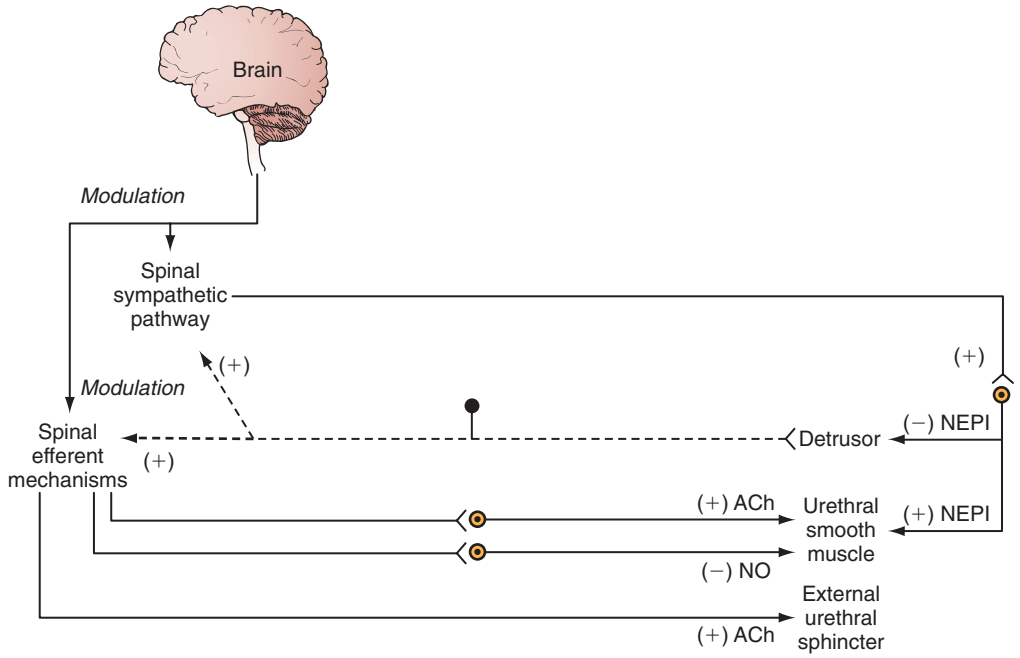


Figure 60–18. Diagram showing bladder to urethra reflex pathways. Afferent pathway *(dashed line)* from the detrusor activates spinal reflex mechanisms that induce firing in somatic cholinergic nerves to the external urethral sphincter, sympathetic adrenergic nerves to the urethral smooth muscle, and cholinergic and nitrergic nerves to the urethral smooth muscle. Bulbospinal pathways from the brain can modulate these spinal reflex mechanisms. ACh, acetylcholine; NEPI, norepinephrine; NO, nitric oxide; excitatory (+) and inhibitory (–) mechanisms.

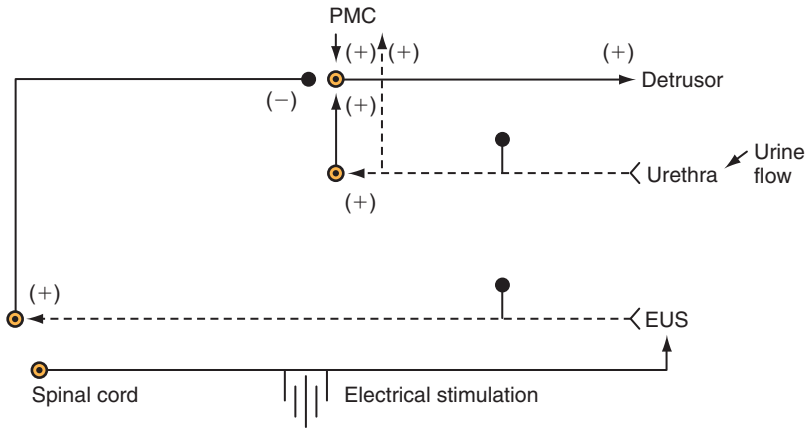


Figure 60–19. Urethra to bladder reflexes. Activity in afferent nerves *(dashed lines)* from the urethra can facilitate parasympathetic efferent outflow to the detrusor by means of a supraspinal pathway passing through the pontine micturition center (PMC), as well as a spinal reflex pathway. Afferent input from the external urethral sphincter (EUS) can inhibit parasympathetic outflow to the detrusor through a spinal reflex circuit. Electrical stimulation of motor axons in the S1 ventral root elicits an EUS contraction and EUS afferent firing that, in turn, inhibits reflex bladder activity, excitatory (+) and inhibitory (–) mechanisms.

the pontine micturition center (Barrington, 1931) (see Fig. 60–19). Studies have confirmed the existence of this type of reflex by the pudendal nerve because low-frequency electrical stimulation of afferent axons in the pudendal nerve in humans, or the deep perineal nerve (a caudal branch of the pudendal nerve) in cats, can initiate reflex bladder contractions and voiding (Shefchyk and Buss, 1998; Boggs et al, 2005). The other component was activated by a visceral afferent pathway in the pelvic nerve and produced facilitation by a spinal reflex mechanism (Barrington, 1941).

Studies (Jung et al, 1999) in the anesthetized rat have also provided additional support for Barrington's findings (Dokita et al, 1991). Measurements of reflex bladder contractions, under isovolumetric conditions during continuous urethral perfusion (0.075 mL/min), revealed that the frequency of micturition reflexes was significantly reduced when urethral perfusion was stopped or after infusion of lidocaine (1%) into the urethra. Intraurethral infusion of nitric oxide donors (*S*-nitroso-*N*-acetylpenicillamine [SNAP], or nitroprusside, 1 to 2 mM) markedly decreased urethral perfusion pressure (approximately 30%) and decreased the frequency of reflex bladder contractions (45% to 75%) but did not change the amplitude of bladder contractions (Fig. 60–20). Desensitization of the urethral afferent with intraurethral capsaicin also dramatically altered the micturition reflex (Fig. 60–21). It was concluded that activation of urethral afferents during urethral perfusion could modulate the micturition reflex in the rat. This may be an explanation of why stress incontinence and urgency incontinence often occur together in women. Jung and colleagues (1999) speculated that **in women with mixed incontinence, leakage of urine into the urethra can stimulate afferents and induce or increase detrusor overactivity. The theory is that stress incontinence can induce urgency incontinence** (Lavelle et al, 2000). Surgical cure of the stress incontinence of women with mixed incontinence has resolved the urgency incontinence in up to half of the patients.

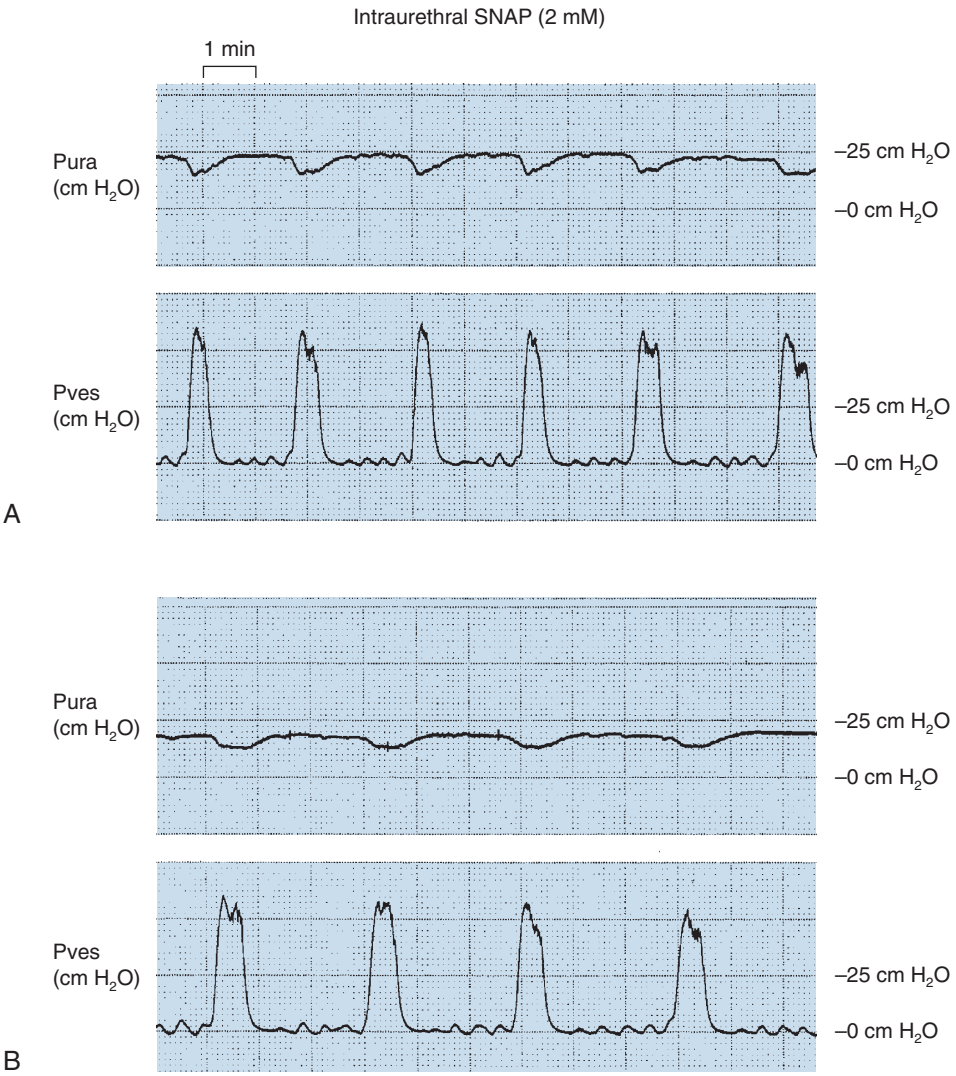


Figure 60–20. Effects of intraurethral *S*-nitroso-*N*-acetylpenicillamine (SNAP) on the bladder pressure (Pves) and urethral pressure (Pura) in normal female rats. **A,** Before treatment. **B,** After intraurethral administration of SNAP (2 mM). Urethral perfusion pressure immediately decreased. In addition, bladder contraction frequency was significantly decreased. The duration of reflex urethral relaxation was increased. (From Jung SY, Fraser MO, Ozawa H, et al. Urethral afferent nerve activity affects the micturition reflex: implication for the relationship between stress incontinence and detrusor instability. J Urol 1999;162:204–12.)

Spinal and Supraspinal Pathways Involved in the Micturition Reflex

Spinal Cord

In the spinal cord, afferent pathways terminate on second-order interneurons that relay information to the brain or to other regions of the spinal cord, including the preganglionic and motor nuclei. Because disynaptic or polysynaptic pathways, but not monosynaptic pathways, mediate bladder, urethral, and sphincter reflex, interneuronal mechanisms must play an essential role in the regulation of lower urinary tract function. Electrophysiologic (de Groat et al, 1981; Araki and de Groat, 1997) and neuroanatomic (Birder and de Groat, 1993; Vizzard et al, 1995; Nadelhaft and Vera, 1996; Sugaya et al, 1997) techniques have identified lower urinary tract interneurons in the same regions of the cord that receive afferent input from the bladder.

As shown in Figure 60–13, horseradish peroxidase labeling techniques in the cat revealed that afferent projections from the external urethral sphincter and levator ani muscles (i.e., pelvic floor) project into different regions of the sacral spinal cord. The external urethral sphincter afferent terminals are located in the superficial layers of the dorsal horn and at the base of the dorsal horn (laminae V to VII and lamina X), whereas the levator ani afferents project into a region just lateral to the central canal and extend into the medial ventral horn. The external urethral sphincter afferents overlap closely with the central projections of visceral afferents in pelvic nerve that innervate the bladder and urethra (Morgan et al, 1981). Intracellular labeling experiments also showed that the dendritic patterns of external urethral sphincter motoneurons (Sasaki, 1994) and parasympathetic preganglionic neurons (Morgan et al, 1993) are similar. **Pharmacologic experiments revealed that glutamic acid is the excitatory transmitter in these pathways.** In addition, approximately 15% of interneurons medial to the sacral parasympathetic nucleus in laminae V through VII make inhibitory synaptic connections with the preganglionic neurons (de Groat et al, 1996). **These inhibitory neurons release γ-aminobutyric acid (GABA) and glycine. Reflex pathways that control the external sphincter muscles also use glutamatergic excitatory and GABAergic and glycinergic inhibitory interneuronal mechanisms.**

Tracing with neurotropic viruses, such as pseudorabies virus, has been particularly useful. Pseudorabies virus can be injected into a target organ and then move intra-axonally from the periphery to the central nervous system. In the nervous system, the virus can

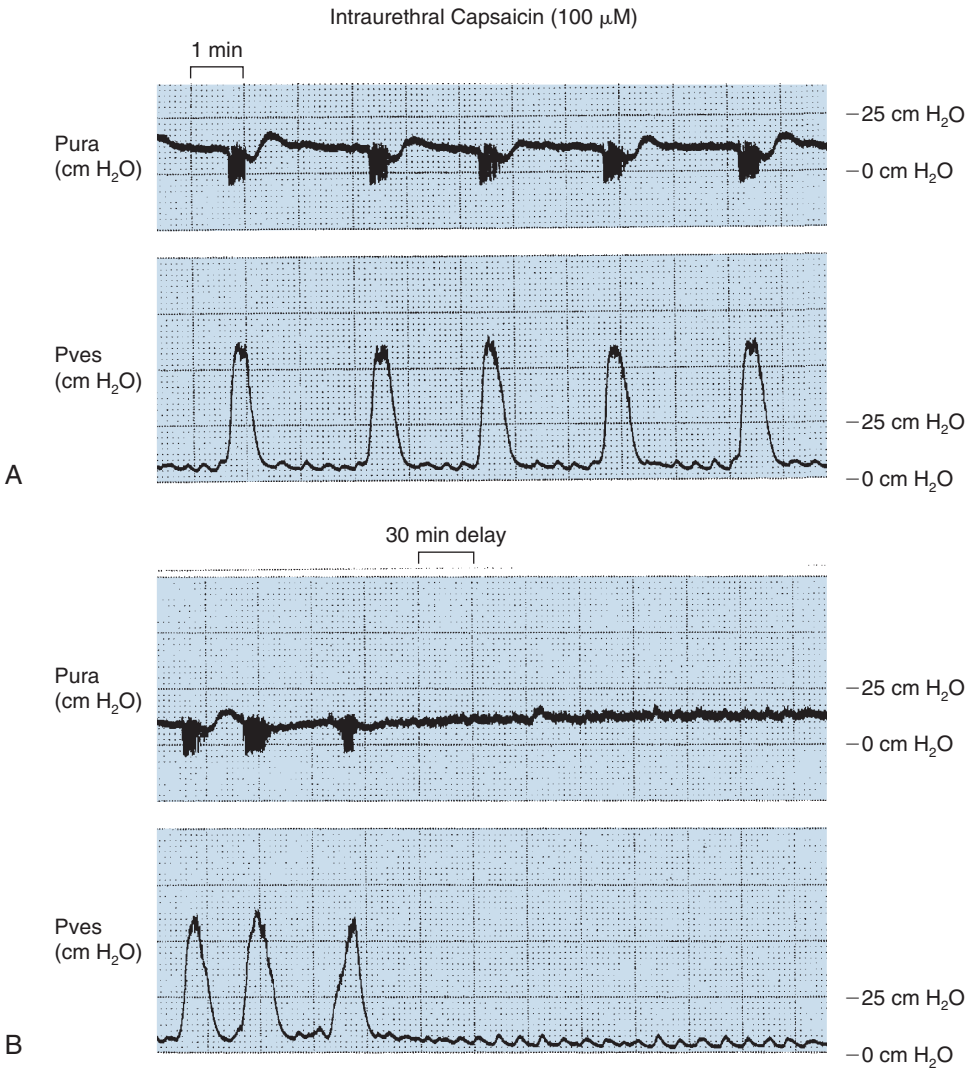


Figure 60–21. Effects of intraurethral capsaicin on the bladder pressure (Pves) and urethral pressure (Pura) in normal female rats. **A,** Before treatment. **B,** After intraurethral administration of capsaicin (100 μM). Initially, intraurethral capsaicin instillation increased the bladder contraction frequency, but 30 minutes after continuous infusion, the activity was blocked. (From Jung SY, Fraser MO, Ozawa H, et al: Urethral afferent nerve activity affects the micturition reflex: implication for the relationship between stress incontinence and detrusor instability. J Urol 1999;162:204–12.)

replicate and then pass retrogradely across synapses to infect second- and third-order neurons in the neural pathways (Vizzard et al, 1995; Nadelhaft and Vera, 1996; Sugaya et al, 1997). Because pseudorabies virus can be transported across many synapses, it could sequentially infect all the neurons that connect directly or indirectly to the lower urinary tract. Interneurons identified by retrograde transport of pseudorabies virus injected into the urinary bladder are located in the region of the sacral parasympathetic nucleus, the dorsal commissure, and the superficial laminae of the dorsal horn (de Groat et al, 1996; Nadelhaft and Vera, 1996; Sugaya et al, 1997). A similar distribution of labeled interneurons has been noted after injection of virus into the urethra (Vizzard et al, 1995) or the external urethral sphincter (Nadelhaft and Vera, 1996), indicating a prominent overlap of the interneuronal pathways controlling the various target organs of the lower urinary tract.

The micturition reflex can be modulated at the level of the spinal cord by interneuronal mechanisms activated by afferent input from cutaneous and striated muscle targets. Micturition reflex can also be modulated by inputs from visceral organs (de Groat et al, 1975; McGuire, 1977; de Groat, 1978; de Groat et al, 1981; McMahon and Morrison, 1982; Torrens and Morrison, 1987; de Groat et al, 1993a; Morrison et al, 1995; Yoshimura et al, 2008). Stimulation of afferent fibers from various regions (anus, colon-rectum, vagina, uterine cervix, penis, perineum, pudendal nerve) can inhibit the firing of sacral interneurons evoked by bladder distention (de Groat et al, 1981). This inhibition may be a result of presynaptic inhibition at primary afferent terminals or be due to direct postsynaptic inhibition of the second-order neurons. Direct postsynaptic inhibition of bladder preganglionic neurons can also be elicited by stimulation of somatic afferent axons in the pudendal nerve or visceral afferents from the distal bowel (de Groat and Ryall, 1969; de Groat, 1978). **Suppression of detrusor overactivity in patients by sacral root stimulation may reflect, in part, activation of the afferent limb of these visceral-bladder and somatic-bladder inhibitory reflexes** (Wheeler et al, 1992; Bosch and Groen, 1995; Chancellor and Chartier-Kastler, 2000).

Pontine Micturition Center and Brainstem Modulatory Mechanisms

Various studies indicate that the micturition reflex is normally mediated by a spinobulbospinal reflex pathway passing through relay centers in the brain (see Fig. 60–16B) (de Groat, 1975; Torrens and Morrison, 1987; de Groat et al, 1993a; Yoshimura et al, 2008). Studies in animals by use of brain-lesioning techniques revealed that neurons in the brainstem at the level of the inferior colliculus have an essential role in the control of the parasympathetic component of micturition (Torrens and Morrison, 1987; de Groat et al, 1993a; Yoshimura and de Groat, 1997; Yoshimura et al, 2008). **Removal of areas of brain above the colliculus by intercollicular decerebration usually facilitates micturition by elimination of inhibitory inputs from more rostral centers. However, transections at any point below the colliculi abolish micturition.**

The dorsal pontine tegmentum has been firmly established as an essential control center for micturition in normal subjects. First described by Barrington (1921), it has subsequently been called the **Barrington nucleus,** the **pontine micturition center** (Blok and Holstege, 1997), or the **M region** (Blok and Holstege, 1996; Holstege et al, 1996) because of its medial location.

In addition to providing axonal inputs to the locus ceruleus and the sacral spinal cord (Ding et al, 1995; Otake and Nakamura, 1996; Valentino et al, 1996), neurons in the pontine micturition center (PMC) also send axon collaterals to the paraventricular thalamic nucleus, which is thought to be involved in the limbic system modulation of visceral behavior (Otake and Nakamura, 1996). Some neurons in the PMC also project to the periaqueductal gray region (PAG) (Blok et al, 1998), which regulates many visceral activities as well as pain pathways (Valentino et al, 1995). Thus neurons in the PMC communicate with multiple supraspinal neuronal populations that may coordinate micturition with other functions of the organism. Although the circuitry in humans is uncertain, brain imaging studies have revealed increases in blood flow in this region of the pons during micturition (Blok et al, 1997b). This change presumably reflects increases in neuronal activity. Thus the PMC appears critical for micturition across species.

Neurons in the PMC provide direct synaptic inputs to sacral preganglionic neurons (Blok and Holstege, 1997) **as well as to GABAergic neurons in the sacral dorsal commissure region** (Blok et al, 1997a). **The former neurons carry the excitatory outflow to the bladder, whereas the latter neurons are thought to be important in mediating an inhibitory influence on external urethral sphincter motoneurons** (Blok et al, 1998). Because of these reciprocal connections, the PMC can promote bladder–sphincter synergy. Studies in rats indicate that activation of bladder preganglionic neurons by input from the PMC can be blocked by inotropic glutamate receptor antagonists, suggesting that neurons in the PMC use glutamate as a neurotransmitter (Matsumoto et al, 1995a).

Besides the PMC region, transneuronal virus tracing methods have identified many populations of neurons in the brainstem that are involved in the control of bladder, urethra, and the urethral sphincter, including medullary raphe nuclei, which contain serotonergic neurons; the locus coeruleus, which contains noradrenergic neurons; PAG; and the A5 noradrenergic cell group (Nadelhaft and Vera, 1992; Vizzard et al, 1995; Sugaya et al, 1997). Other anatomical studies in which anterograde tracer substances were injected into brain areas and then identified in terminals in the spinal cord are consistent with the virus tracing data. **Projections from neurons in the lateral pons (L-region or nucleus locus subcoeruleus) terminate rather selectively in the sphincter motor nucleus to enhance the contraction of pelvic floor muscle and increased urethral pressure during the storage phase in cats, providing evidence that this area in the lateral pons functions as "the pontine continence center"** (Blok, 2002; Sugaya et al, 2003). The parabrachial nuclei (PBN) at the dorsolateral pons, which send projections to the sacral spinal cord neurons, are also known to be involved in the control of micturition (Lumb and Morrison, 1987; de Groat et al, 1993b). A recent study in rats has shown that firing of PBN neurons corresponds to bladder contraction during cystometry and that the medial subnuclei of PBN plays an important role in the mediation of normal bladder contractions (Liu et al, 2007).

In the midbrain, there is increasing evidence that the mesencephalic PAG, which directly receives information of bladder fullness by ascending spinal tract neurons and sends projections to the PMC, seems to play an important role in the integration of the micturition reflex (Blok, 2002; Holstege, 2005). Stimulation of the pelvic nerve results in short latency potentials in the caudal periaqueductal gray (Noto et al, 1991). Electrical and chemical stimulation of the ventrolateral PAG induces micturition in rats and cats (Matsuura et al, 2000; Taniguchi et al, 2002), and this PAG-mediated micturition reflex seems to be induced by subsequent activation of the PMC following PAG stimulation (Matsuura et al, 2000). In cats, there are different patterns of neuronal firing in response to storage/micturition cycles in the PAG, and stimulation of the rostral PAG can inhibit the micturition reflex (Liu et al, 2004; Numata et al, 2008). **Thus the PAG appears to function as a relay center between the PMC and spinal cord neurons that are critically involved in the excitatory and inhibitory control of the micturition reflex.**

Central Pathways That Modulate the Micturition Reflex

Transneuronal virus tracing methods have identified virus-infected cells in several regions of the hypothalamus and the cerebral cortex after injection of pseudorabies virus into the lower urinary tract in animals (Nadelhaft and Vera, 1992; Vizzard et al, 1995; Sugaya et al, 1997). Neurons in the cortex were located primarily in the medial frontal cortex. Tracers injected into the paraventricular nucleus of the hypothalamus labeled terminals in the sacral parasympathetic nucleus as well as the sphincter motor nucleus (Holstege and Mouton, 2003). The influence of the cortex on voiding function could be mediated by a number of pathways, including direct cortical projections from the prefrontal cortex and insular cortex to the PMC or projections through the hypothalamus and the extrapyramidal system (de Groat et al, 1993a). **Studies in humans indicate that voluntary control of voiding is dependent on connections between the frontal cortex and the septal-preoptic region of the hypothalamus, as well as on connections between the paracentral lobule and the brainstem. Lesions to these areas of cortex appear to directly increase bladder activity by removing cortical inhibitory control** (de Groat et al, 1993a).

Human Brain Imaging Studies

In the last decade, **the areas of the brain involved in the control of micturition have been examined in human brain imaging studies using single photon emission–computed tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI)** (DasGupta et al, 2007; Griffiths and Tadic, 2008) (Fig. 60–22). Some studies evaluated the brain areas responsible for the perception of bladder fullness and the sensation of the desire to void during bladder filling, whereas others examined brain activity during micturition, voluntary contractions of the pelvic floor during urine withholding, or during cold stimulation of the bladder. **PET scan studies in normal men and women revealed that during voiding two cortical areas (the dorsolateral prefrontal cortex and anterior cingulate gyrus) were active** (i.e., exhibited increased blood flow). **The hypothalamus, including the preoptic area, as well as the pons and the PAG, also showed activity in concert with voluntary micturition** (Blok et al, 1997c, 1998). Another PET study during voiding also confirmed that micturition was associated with increased activity in the pons, inferior frontal gyrus, hypothalamus, and PAG, while also showing activity in several other cortical areas (postcentral gyrus, superior frontal gyrus, thalamus, insula, and globus pallidus) and the cerebellar vermis (Nour et al, 2000).

Other PET studies that examined the changes in brain activity during filling of the bladder revealed that increased activity occurred in the PAG, the midline pons, the anterior and midcingulate gyrus, anterior insula, and bilaterally in the frontal lobes (Athwal et al, 1999; Athwal et al, 2001; Matsuura et al, 2002). The results were consistent with the notion that the PAG receives information about bladder fullness and then relays this information to other brain areas involved in the control of bladder storage**. In fMRI studies in men and women, activation during urinary storage is found in the supplementary motor area, midcingulate cortex, insula, and right prefrontal cortex,** and the right anterior insula and midbrain PAG were more active at higher than at lower bladder volumes (Kuhtz-Buschbeck et al, 2005, 2009). Other fMRI studies also addressed the effect of pelvic floor contraction with a full bladder, and reported activation of the parietal cortex, cerebellum, putamen and supplementary motor area (Zhang et al, 2005), or the frontal cortex, basal ganglia, and cerebellum (Seseke et al, 2006).

Brain imaging studies have also been performed to identify changes in cerebral perception of detrusor overactivity. A PET study in patients with Parkinson disease reported activation of the PAG, supplementary motor area, basal ganglia, and cerebellum during detrusor overactivity, (Kitta et al, 2006). When comparing healthy control subjects and those with confirmed overactivity using fMRI, infusion into the bladder is associated with activity in the PAG, thalamus, insula, and anterior cingulated gyrus; however, weak responses or deactivation in the prefrontal cortex or the limbic system, as well as exaggerated responses in the anterior cingulate gyrus at large bladder volumes, are observed in urgency-incontinent patients (Griffiths et al, 2005, 2007). Based on the results in human imaging studies, **Griffiths proposes that (1) during urine storage in healthy subjects, bladder and urethral afferents received in the PAG and mapped in**

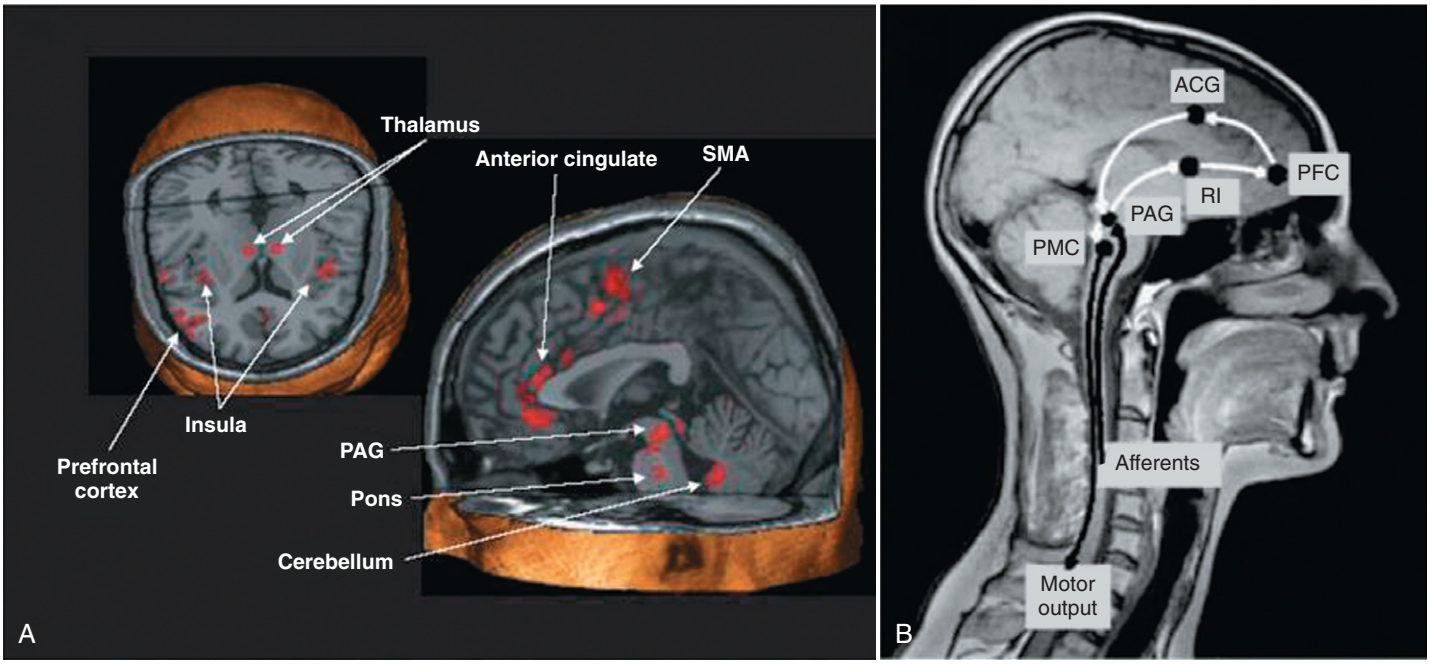


Figure 60–22. **A,** Areas of brain activation during the urinary storage phase based on human imaging studies using PET and fMRI. SMA, supplementary motor area. PAG, periaqueductal gray. **B,** Simplified model of supraspinal control system. Ascending afferent fibers (afferents) carrying the information from the bladder synapse in the PAG and are relayed to the right insula (RI), forming the substrate for sensation. The anterior cingulate gyrus (ACG) is responsible for monitoring, arousal, and efferent output to the PAG and pontine micturition center (PMC). The prefrontal cortex (PFC) is involved in voluntary decision about voiding and generates efferent signals to control ACG and ultimately PMC. The PMC then provides motor output to cause voiding. (**A,** Modified from Fowler A, Griffiths CJD, et al. The neural control of micturition. Nat Rev Neurosci 2008;9:453–66; **B,** modified from Griffiths D, Tadic SD. Bladder control, urgency, and urge incontinence: evidence from functional brain imaging. Neurourol Urodyn 2008; 27:466–74.)

the insula form normal sensations of desire to void, which is monitored by the anterior cingulate gyrus, and the voiding reflex is continuously inhibited until the decision to void is made in the prefrontal cortex; and (2) urgency-incontinent patients have weak responses or deactivation observed in the prefrontal cortex or the limbic system, leading to a defect of supraspinal bladder control, which may cause urgency incontinence, and enhanced responses in the anterior cingulate gyrus, which may be due to abnormal bladder afferents or related to a loss of control in other brain areas, and could be correlated with the urgency sensation (Griffiths and Tadic, 2008) (see Fig. 60–22). Radiographic imaging of the central nervous system (CNS), with control and dysregulation of the lower urinary tract, is an exciting area of research, but the results are preliminary. Subjects are conscious and thinking about their bladder during the test and may have an indwelling catheter that may alter what parts of the brain are activated naturally or artificially.

Hypothesis of Mechanism of Action of Sacral Neuromodulation

Neuromodulation of the sacral nerves and, more recently, pudendal nerves is now commonly used for the treatment of refractory overactive bladder and urinary retention relating to pelvic floor dysfunction (Das et al, 2004; Leng and Chancellor, 2005). Some have criticized the inconsistency that electrical stimulation of the sacral nerve can paradoxically inhibit incontinence in the overactive bladder (OAB) group of patients and yet aid the retentive patients to void. But neuromodulation has worked for both these groups of patients. **The effects of sacral neuromodulation may depend on electrical stimulation of afferent axons in the spinal roots that, in turn, modulate voiding and continence reflex pathways in the central nervous system.** The afferent system is the most likely target, because beneficial effects can be elicited at intensities of stimulation that do not activate movements of striated muscles (Vadusek et al, 1986; Thon et al, 1991; de Groat et al, 1997). Sacral neuromodulation activates somatic afferent axons that modulate sensory processing and micturition reflex pathways in the spinal cord. Urinary retention and dysfunctional voiding can be resolved by inhibition of the guarding reflexes. Detrusor overactivity can be suppressed by direct inhibition of bladder preganglionic neurons. Inhibition of interneuronal transmission in the afferent limb of the micturition reflex can also block detrusor overactivity. **Thus the principle behind sacral neuromodulation can be summarized as somatic afferent inhibition of sensory processing in the spinal cord**.

Rational for Neuromodulation to Facilitate Voiding. In adults, brain pathways are necessary to turn off sphincter and urethral guarding reflexes to allow efficient bladder emptying. Thus spinal cord injury produces bladder-sphincter dyssynergia and inefficient bladder emptying by eliminating the brain mechanisms involved (Fig. 60–23). This may also occur after more subtle neurologic lesions in patients with idiopathic urinary retention, such as after a bout of prostatitis or urinary tract infection. Before the development of brain control of micturition, at least in animals, the stimulation of somatic afferent pathways passing through the pudendal nerve from the perineum can initiate efficient voiding by activating bladder efferent pathways and turning off the excitatory pathways to the urethral outlet (de Groat et al, 1993a; Kruse and de Groat, 1993). Tactile stimulation of the perineum in the cat also inhibits the bladder–sympathetic reflex component of the guarding reflex mechanism. The sacral nerve stimulation may elicit similar responses in patients with urinary retention, and it may turn off excitatory outflow to the urethral outlet and promote bladder emptying. Because sphincter activity can generate afferent input to the spinal cord that can, in turn, inhibit reflex bladder activity, an indirect benefit of suppressing sphincter reflexes would be a facilitation of bladder activity.

Rationale for Neuromodulation to Inhibit the Overactive Bladder. Several reflex mechanisms may be involved in the sacral neuromodulation suppression of detrusor overactivity. Afferent pathways projecting to the sacral cord can inhibit bladder reflexes in animals and humans. The source of afferent input may be from sphincter muscles, distal colon, rectum, anal canal, vagina, uterine cervix, and cutaneous afferents from the perineum (Fig. 60–24). As mentioned previously, two mechanisms have been identified in animals for somatic and visceral afferent inhibition of bladder reflexes. The most common mechanism is suppression of interneuronal transmission in the bladder reflex pathway (de Groat and Theobald, 1976; Kruse et al, 1990; Kruse and de Groat, 1993). It is assumed that this inhibition occurs, in part, on the ascending limb of the micturition reflex and therefore blocks the transfer of information from the bladder to the PMC. This action would prevent

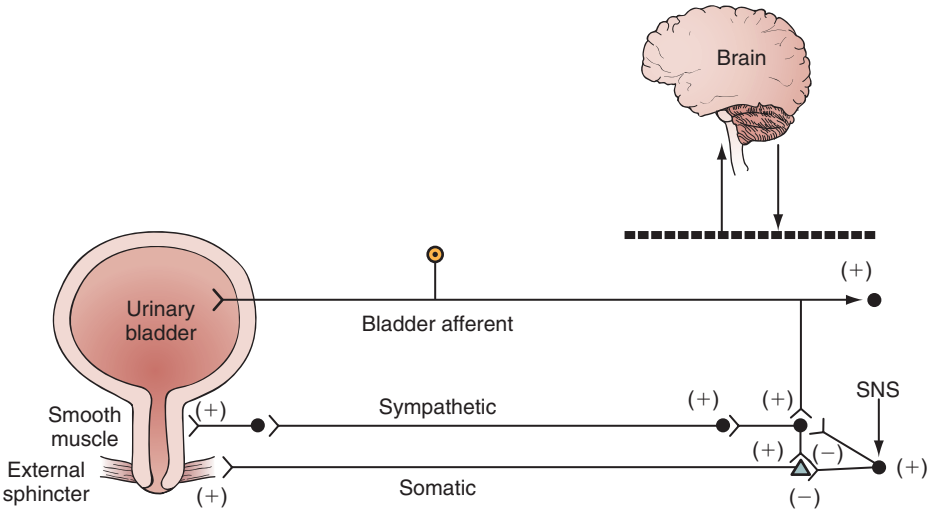


Figure 60–23. When there is a sudden increase in intravesical pressure, such as during a cough, the urinary sphincter contracts by means of the spinal guarding reflex to prevent urinary incontinence (guarding reflex). The spinal guarding reflexes can be turned off by the brain for urination. In cases of neurologic diseases, the brain cannot turn off the guarding reflex and retention can occur. The sacral nerve stimulation (SNS) restores voluntary micturition in cases of voiding dysfunction and urinary retention but inhibits the guarding reflex.

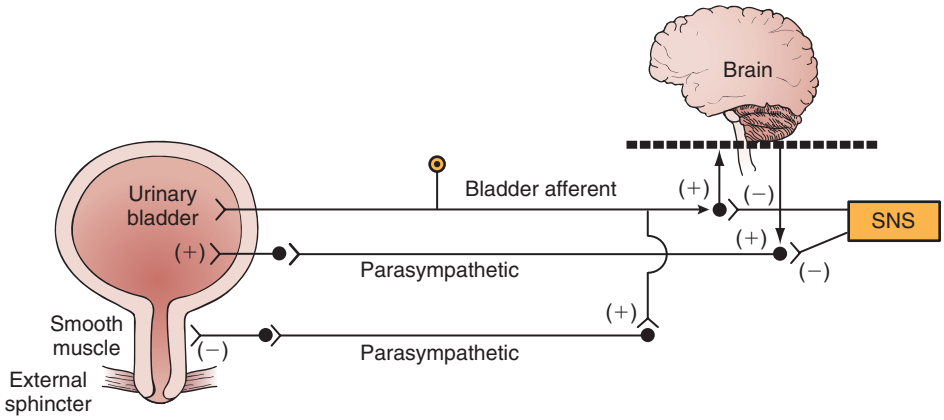


Figure 60–24. The voiding reflex involves afferent neurons from the bladder that project on spinal tract neurons that ascend to the brain. Descending pathways connect to parasympathetic efferent nerves to contract the bladder (bladder-bladder reflex). A spinal bladder-urethra reflex is activated by a similar bladder afferent innervation. In cases of supraspinal dysfunction, overactive micturition reflexes occur. The sacral nerve stimulation (SNS) inhibits urinary urgency, frequency, and urge incontinence by inhibiting the bladder-bladder and bladder-urethra reflexes.

involuntary (reflex) micturition but not necessarily suppress voluntary voiding that would be mediated by descending excitatory efferent pathways from the brain to the sacral parasympathetic preganglionic neurons. A second inhibitory mechanism is mediated by a direct inhibitory input to the bladder preganglionic neurons. This can be induced by electrical stimulation of the pudendal nerve or by mechanical stimulation of the anal canal and distal bowel. It is not elicited by tactile stimulation of penile or perineal afferents; this mechanism would be much more effective in turning off bladder reflexes, because it would directly suppress firing in the motor outflow from the spinal cord.

Pudendal Nerve Stimulation. The pudendal nerve is a peripheral branch of the sacral nerve roots, and stimulating the pudendal allows afferent stimulation to all three of the sacral nerve roots (S2, S3, S4), and that may raise the stimulation threshold needed for micturition and inhibit detrusor activity. Because this is a more peripheral nerve, it is less likely that stimulation of the sciatic and sural nerves will occur, thus decreasing the potential risk for discomfort in the thighs, calves, and feet as seen on occasion with sacral stimulation at the S3 nerve root. The pudendal nerve arises from the sacral plexus within the pelvis; it must go around the pelvic floor to reach the ischioanal fossa. In the pelvis, it runs on the piriformis and then passes laterally through the greater sciatic foramen to enter the gluteal region. Here it lies inferior to the piriformis as does the sciatic nerve, the inferior gluteal neurovascular bundle, and the nerve to the quadratus femoris. The pudendal nerve curls around the spine of the ischium, lying superficial to the sacrospinous ligament, and then passes into the lesser sciatic notch to enter the ischioanal fossa. The nerve then divides into the inferior rectal, the perineal, and the dorsal nerve of the penis or clitoris.

Afferent pudendal nerve stimulation has been demonstrated to inhibit the micturition reflex, abolish uninhibited detrusor contractions, and increase bladder capacity in animals and humans (Fall and Lindstrom, 1991). Peters and colleagues (2005) compared the effectiveness of sacral and pudendal nerve stimulation for voiding dysfunction in a prospective, single-blinded, randomized crossover trial of 30 subjects (22 with urgency/frequency, 5 with urgency incontinence, and 3 with urinary retention) scheduled for sacral implantation a tined quadripolar lead consented to the placement of a second pudendal lead. Twenty-four of the 30 subjects demonstrated a significant clinical response and had an implantable pulse generator placed. Sacral nerve stimulation resulted in 46% improvement in symptoms, while pudendal nerve stimulation demonstrated 63% improvement in symptoms. Urgency-incontinence episodes were reduced by approximately 47%; however, this did not reach statistical significance because of small sample size ($n = 5$).

Inhibitory and Excitatory Stimulation Frequencies of the Pudendal-Bladder Reflexes. The exact mechanism of action of neuromodulation is unknown. In addition, there are no studies involving neuromodulation that look at programming parameters (pulse width, intensity, or frequency) and their impact on voiding function. The pudendal nerve may have a dual mechanism depending on the frequency and continuity of stimulation. A recent study by Tai et al (2007) in anesthetized spinal cord–injured cats demonstrated that at 3 Hz, stimulation of the pudendal nerve inhibited bladder function and decreased bladder pressures, whereas intermittent stimulation at 20 Hz improved the efficiency of the bladder to empty (Tai et al, 2007). Furthermore, the clinical outcomes of continuous (which potentially can fatigue the urethral sphincter and accommodate the nerve) and intermittent stimulation have not been explored. It would directly suppress firing in the motor outflow from the spinal cord.

Developmental Changes of Bladder Reflexes

The neonatal bladder is a conduit of urine more than a storage organ. Without cerebral control, the bladder will reflexively empty into a diaper when it reaches functional capacity. Therefore by definition, a normal toddler has detrusor overactivity. Neonatal animal bladder strips have repetitive spontaneous contraction, which can be initiated by pacemaker cells within the bladder and propagated by gap junctions between cells (see Fig. 60–1) (Pezzone et al, 1999; Szell et al, 2003) and/or directly induced by enhanced smooth muscle activity due to the low level expression of Ca^{2+}-activated K^+ channels (Ng et al, 2007).

The neonatal pathways responsible for bladder overactivity do not disappear with growth and development; rather, increasing cerebral maturation actively inhibits them. Inhibition rather than resolution of neonatal reflexes may be difficult to grasp initially, but this concept holds true across most concepts of neuroscience. **With disease processes such as neurologic diseases and aging, the neonatal reflexes are released and involuntary detrusor contractions recur** (de Groat, 1975).

One of the most interesting clinical demonstrations of the reemergence of the primitive neonatal micturition reflex is the bladder ice-water test. The bladder ice-water cooling test is performed by quickly instilling up to

100 mL of 4° C sterile saline solution. The normal adult will sense cold but maintain a stable bladder. However, infants and neuropathic patients will develop involuntary detrusor contractions with this test (Chancellor and de Groat, 1999).

The bladder cooling response is triggered by activation of cold receptors within the bladder wall. The receptors are supplied by unmyelinated C-fiber afferent neurons (Chancellor and de Groat, 1999). The cooling response represents a neonatal reflex that may be unmasked by central neuropathologic processes, analogous to the appearance of the Babinski reflex in pyramidal tract lesions. The cooling response is present (development of involuntary detrusor contraction) in neurologically normal infants and children until about the age of 4 years. **The reflex becomes absent with further maturation of the nervous system, but the response may be unmasked by pathologic processes that disturb the descending neuronal control of normal voiding** (Geirsson et al, 1999). It has also been suggested that men with prostatic bladder outlet obstruction also have an ice-water test response. Chai and colleagues (1998) reported an ice-water test response in 12 of 17 patients (71%) with bladder outlet obstruction, but their method of ice-water infusion has been criticized (Geirsson et al, 1999). Hirayama and colleagues (2003) have also reported that an ice-water test response was found in 35 (27%) of 127 patients with benign prostatic hyperplasia and that the patients with the ice-water test response had detrusor overactivity and higher bladder outlet obstruction index than the nonresponders on the pressure flow study.

PHARMACOLOGY

Peripheral Pharmacology

Traditional teaching in uropharmacology is that if a drug works on the bladder or urethra, it is working on the postjunctional receptors. In this section, we present evidence for prejunctional as well as postjunctional actions of drugs.

Muscarinic Mechanisms

Detrusor strips from normal human bladders are contracted by cholinergic muscarinic receptor agonists and by electrical stimulation of intrinsic cholinergic nerves. Contractile responses can be completely abolished by atropine (Sibley, 1984). **There are at least five receptor subtypes based on molecular cloning and four different receptor subtypes based on pharmacology (M_1 to M_5)** (Somogyi et al, 1994; Wang et al, 1995; Eglen et al, 1996; Yamaguchi, 1996; Hegde et al, 1997).

Pharmacologically, M_1, M_2, and M_3 receptor subtypes have been found in the human bladder by receptor binding assays (Kondo et al, 1995); **all M_1 to M_5 receptor mRNAs are detected by reverse transcription–polymerase chain reaction assays** (Andersson and Wein, 2004; Mansfield et al, 2005). **Although ligand receptor binding studies revealed that M_2 receptors predominate, M_3 receptors mediate cholinergic contractions** (Eglen et al, 1994; Harriss et al, 1995; Yamaguchi, 1996; Hegde et al, 1997; Lai et al, 1998). **Stimulation of M_3 receptors by acetylcholine leads to IP_3 hydrolysis due to phospholipase C activation and then to the release of intracellular calcium and a smooth muscle contraction** (Harriss et al, 1995; Fry et al, 2002) (Fig. 60–25). **The involvement of transmembrane flux of calcium ions through nifedipine-sensitive L-type Ca^{2+} channels has also been indicated in M_3 receptor–mediated detrusor muscle contractions** because the L-type Ca^{2+} channel inhibitor nifedipine strongly suppressed carbachol-induced detrusor contractions, whereas the phospholipase C inhibitor or the store-operated Ca^{2+} channel inhibitor caused little inhibition in rats and humans (Andersson and Arner, 2004; Andersson and Wein 2004; Schneider et al, 2004a, 2004b; Frazier et al, 2008) (see Fig. 60–25). However, other studies have indicated the major contribution of the phospholipase C–mediated mechanism to M_3 receptor–induced detrusor contractions, because phospholipase C inhibitors significantly suppressed carbachol-induced detrusor contractions in rats (Braverman et al, 2006a, 2006b), and intracellular calcium elevation after carbachol application was observed without membrane depolarization in human bladders, which is required for the opening of L-type Ca^{2+} channels (Fry et al, 2002). Hashitani and colleagues (2000) have reported that the stimulation of muscarinic receptors activates both calcium influx through L-type Ca^{2+} channels and calcium release from intracellular calcium stores in guinea pig bladders.

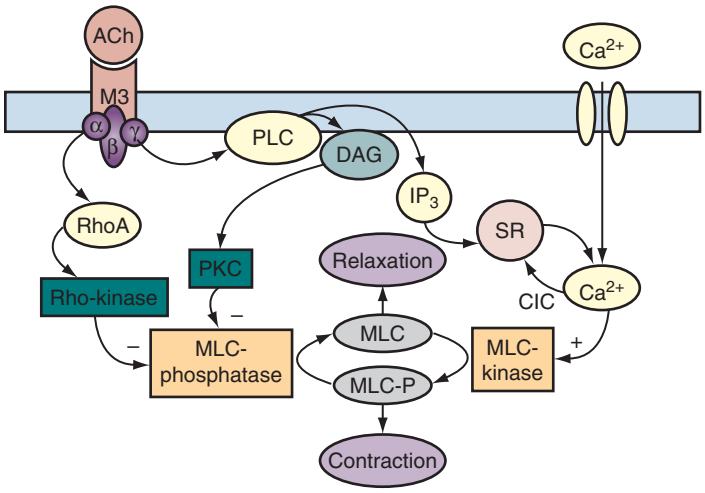


Figure 60–25. Transmitter signal pathways involved in activation of detrusor contractions through muscarinic M_3 receptors. There seem to be differences between species in the contribution of the different pathways in contractile activation. ACh, acetylcholine; CIC, calcium-induced calcium release; DAG, diacylglycerol; IP_3, inositol 1.4.5-trisphosphate; MLC, myosin light chain; PKC, protein kinase C; PLC, phospholipase C; SR, sarcoplasmic reticulum. (From Andersson KE, Wein AJ. Pharmacology of the lower urinary tract: basis for current and future treatments of urinary incontinence. Pharmacol Rev 2004;56:581–631.)

It has also been proposed (Hegde et al, 1997; Ehler et al, 2005) that **coactivation of M_2 receptors could enhance the response to M_3 stimulation by (1) inhibition of adenylate cyclase, thereby suppressing sympathetically mediated depression of detrusor muscle; (2) inactivation of K^+ channels; or (3) activation of nonspecific cation channels.** In addition, because the specific Rho-kinase inhibitor Y-27632 reportedly suppresses carbachol-induced detrusor contractions in rats and humans, **muscarinic receptor activation in detrusor smooth muscles is likely to stimulate the Rho-kinase pathway, leading to a direct inhibition of myosin phosphatase that induces calcium sensitization to enhance the ability of the muscle to generate the same contractile force with lower levels of intracellular calcium** (Andersson and Wein, 2004; Schneider et al, 2004a, 2004b; Frazier et al, 2008). Although the involvement of M_3 receptors for the Rho-kinase activation has been suggested (Andersson

Table 60–5.

Drugs with Bladder Action

CLASSIFICATION	EXAMPLES	PHARMACOLOGIC ACTION
Anticholinergic agents	Atropine Glycopyrrolate Oxybutynin Propantheline Tolterodine	Inhibit muscarinic receptors, thus reducing the response to cholinergic stimulation; used to reduce pressure during bladder filling and for the treatment of unstable bladder contractions
Smooth muscle relaxants	Dicyclomine Flavoxate	Direct smooth muscle relaxation reduces intravesical pressure during filling and reduces severity and presence of unstable bladder contractions; most of these agents have some degree of anticholinergic action
Calcium antagonists	Diltiazem Nifedipine Verapamil	Used in the treatment of unstable bladder contractions to reduce the magnitude of the spikes by reducing the entrance of calcium during an action potential
Potassium channel openers	Cromakalim Pinacidil	Act to increase the membrane potential and thus reduce the myogenic initiation of unstable bladder contractions
Prostaglandin synthesis inhibitors	Flurbiprofen	Prostaglandins have been implicated in increased smooth muscle tone and in the induction of spontaneous activity. Inhibition of prostaglandin synthesis could promote relaxation of the bladder during filling and decrease spontaneous activity of the bladder.
β-Adrenergic agonists	Isoproterenol Terbutaline	Stimulation of β receptors induces relaxation of the bladder body, resulting in a decrease in intravesical pressure during filling.
Tricyclic antidepressants	Amitriptyline Imipramine	These agents have anticholinergic, direct smooth muscle relaxant, and norepinephrine reuptake inhibition properties.
α-Adrenergic agonists	Ephedrine Phenylpropanolamine Midodrine Pseudoephedrine	Increase urethral tone and closure pressure by direct stimulation of α-adrenergic receptors
Afferent nerve inhibitors	DMSO Capsaicin Resiniferatoxin	Reduce the sensory input from bladder and thereby increase bladder capacity and reduce detrusor overactivity
Estrogen	Estradiol	Direct application to the vagina or oral therapy may increase the thickness of the urothelial mucosa, making a better seal and reducing the incidence of incontinence. Other actions may include increasing adrenergic effects on the urethra and increasing blood flow.

DMSO, dimethyl sulfoxide.

and Arner, 2004; Andersson and Wein, 2004; Schneider et al, 2004a) (see Fig. 60–25), a study has also suggested the participation of M_2 receptors in this mechanism because Y-27632 not only suppressed carbachol-induced muscle contractions but also increased the affinity of darifenacin, an M_3 receptor antagonist with approximately a 30-fold selectivity for M_3 over M_2 receptors, for inhibiting carbachol-induced contractions of rat bladders (Braverman et al, 2006a, 2006b). It has also been reported that the muscarinic receptor subtype–mediated detrusor contractions shift from M_3 to M_2 receptor subtype in certain pathologic conditions, such as obstructed or denervated hypertrophied bladders in rats (Braverman and Ruggieri, 2003; Braverman et al, 2006a, 2006b), as well as in bladder muscle specimens from patients with neurogenic bladder dysfunction (Pontari et al, 2004).

Studies using constructed mutant mice lacking the M_3 receptor or the M_2 and M_3 receptors have demonstrated that this subtype plays key roles in salivary secretion, pupillary constriction, and detrusor contractions (Matsui et al, 2000, 2002; Igawa et al, 2004). However, M_3-mediated signals in digestive and reproductive organs are dispensable, probably because of redundant mechanisms through other muscarinic acetylcholine receptor subtypes or other mediators (Matsui et al, 2000). In addition, it has also been found that male M_3 knockout mice had a distended bladder and larger bladder capacity compared with females, indicating a considerable sex difference in the micturition mechanism (Matsui et al, 2002; Igawa et al, 2004). Thus M_3 or M_2 and M_3 double-knockout mice should provide a useful animal model for the detrusor overactivity pathophysiology and pharmacology.

Muscarinic receptor antagonists tolterodine and oxybutynin (Table 60–5) are the most widely prescribed drugs for urinary incontinence. Oxybutynin is a nonspecific muscarinic antagonist with additional smooth muscle relaxant properties. The smooth muscle relaxation properties of oxybutynin may be clinically relevant only with intravesical instillation of the drug. Because new antimuscarinic drugs are such a hot topic for pharmaceutical development, all urologists should be aware of the existence of muscarinic receptor subtypes and their distribution in the lower urinary tract and other organs.

We will briefly present two additional issues regarding the effect of antimuscarinic drugs on the bladder and salivary glands that have clinical relevancy. First, antimuscarinic drugs are metabolized, and their metabolites have pharmacologic effects. It has been shown that oxybutynin has less of a dry mouth effect than does its metabolite desethyoxybutynin (Gupta and Sathyan, 1999). Therefore the controlled-release formulation of oxybutynin maintains the efficacy of immediate-release oxybutynin but with significantly fewer side effects. Tolterodine and solifenacin have been shown in cats and rats, respectively, to have less activity on the salivary gland muscarinic receptors than on the bladder muscarinic receptors (Nilvebrant et al, 1997; Ohtake et al, 2004).

Second, the site and speed of antimuscarinic metabolism appear to have profound effects in terms of clinical efficacy and side effects.

Muscarinic receptors are also located prejunctionally on cholinergic nerve terminals in the bladder (D'Agostino et al, 1986; Somogyi and de Groat, 1992; Somogyi et al, 1996; D'Agostino et al, 1997; Braverman et al, 1998; D'Agostino et al, 2000). Activation of M_1 prejunctional receptors facilitates acetylcholine release (Somogyi and de Groat, 1992; Somogyi et al, 1996), whereas activation of M_2 to M_4 receptors inhibits the release (D'Agostino et al, 1997; Braverman et al, 1998). It has been proposed that inhibitory M_2 to M_4 receptors are preferentially activated by autofeedback mechanisms during short periods of low-frequency nerve activity and thereby suppress cholinergic transmission during urine storage (Somogyi and de Groat, 1992). Conversely, M_1 receptors are activated during more prolonged, high-frequency nerve firing that would occur during voiding and thus participate in an amplification mechanism to promote complete bladder emptying. M_1-mediated facilitation of transmitter release involves the activation of a phospholipase C–protein kinase C signaling cascade that appears to facilitate the opening of L-type Ca^{2+} channels that are necessary for prejunctional facilitation of acetylcholine release from parasympathetic nerve terminals (Somogyi et al, 1996, 1997). Inhibitory and facilitatory muscarinic receptors are also present in the central nervous system (de Groat et al, 1993a; Yoshimura and de Groat, 1997; Ishiura et al, 2001) and in bladder parasympathetic ganglia, where they modulate nicotinic transmission (de Groat and Booth, 1993). The ability to modulate neurotransmission in the bladder through the selective activation and inhibition of specific presynaptic receptors may lead, in the future, to novel forms of pharmacologic therapy for specific forms of lower urinary tract dysfunction.

Muscarinic Selectivity. Pharmacologically defined subtype-selective drugs have been developed. Darifenacin and vamicamide have been demonstrated to be relatively selective for the M_3 subtype (Yamamoto et al, 1995; Andersson, 1997; Steers, 2006). However, they are not necessarily tissue selective, because salivary glands and other tissues also contain M_3 muscarinic receptors. Currently, several drugs are being tested for their tissue selectivity. Tolterodine appears to be a muscarinic antagonist that has selectivity for the bladder compared with the salivary gland, even though it may not be an M_3 subtype–selective antagonist (Nilvebrant et al, 1997; Andersson, 1998). More recently, solifenacin has also shown selectivity to the bladder over the salivary gland; the receptor selectivity of solifenacin to M_3 receptors over M_2 receptors (10-fold) is similar to that of oxybutynin (Ikeda et al, 2002; Ohtake et al, 2004). Thus, therapeutically, it is more important to be tissue selective than subtype selective (Nilvebrant, et al. 1997; Andersson, 1998). A truly bladder-selective antimuscarinic drug with *no* side effects is the "holy grail" of overactive bladder drug therapy.

Key Points: Muscarinic Mechanisms

- There are at least five muscarinic receptor subtypes. Pharmacologically, M_1, M_2, and M_3 receptor subtypes have been found in the human bladder.
- Stimulation of M_3 receptors by acetylcholine induces calcium influx through L-type Ca^{2+} channels, as well as IP_3 hydrolysis due to phospholipase C activation, resulting in the release of intracellular calcium, both of which contribute to a smooth muscle contraction.
- Muscarinic receptor subtype–mediated detrusor contractions shift from M_3 to M_2 receptor subtype has been reported in bladder muscle specimens from neurogenic bladder dysfunction patients.

Purinergic Mechanisms

Purinergic contribution to parasympathetic stimulation in vivo, or field stimulation in vitro, has been proved to exist in a variety of species including rat, rabbit, and guinea pig (Burnstock et al, 1972; Chancellor et al, 1992; Burnstock, 1996). **However, there is less evidence that purinergic neurotransmission exists in humans, at least regarding normal responses to stimulation, but it may play a role in pathologic conditions such as detrusor overactivity or bladder outlet obstruction** (Palea et al, 1993; Burnstock, 2000; O'Reilly et al, 2001a).

ATP acts on two families of purinergic receptors: an ion channel family (P2X) and a G protein–coupled receptor family (P2Y) (Inoue and Brading, 1990; Inoue and Gabella, 1991; McMurray et al, 1997). Seven P2X subtypes and eight P2Y subtypes have been identified. Analysis of the structure-activity relationships of a series of excitatory purinergic agonists on the guinea pig bladder revealed an order of potency consistent with $P2X_1$ or $P2X_2$ receptors (Burnstock, 2001; Zhong et al, 2001). In other species (rabbit, cat, and rat), various studies suggested that multiple purinergic excitatory receptors are present in the bladder (Burnstock, 2000). Immunohistochemical experiments with specific antibodies for different P2X receptors showed that $P2X_1$ receptors are the dominant subtype in membranes of rat detrusor muscle and vascular smooth muscle in the bladder (Lee et al, 2000). Clusters of $P2X_1$ receptors were detected on rat bladder smooth muscle cells, some of which were closely related to nerve varicosities. Northern blotting and in-situ hybridization revealed the presence of $P2X_1$ and $P2X_4$ mRNA in the bladder (Valera et al, 1995). **The predominant expression of $P2X_1$ receptors has also been confirmed in the human bladder** (O'Reilly et al, 2001a, 2001b). **Investigators also found that the amount of $P2X_1$ receptors was increased in the obstructed bladder compared with the control bladder, suggesting upregulated purinergic mechanisms in the overactive bladder due to bladder outlet obstruction** (O'Reilly et al, 2001a). In addition, ATP also seems to act through P2Y receptors in the smooth muscle to suppress cholinergic and purinergic contractions (Lee et al, 2000; Burnstock, 2001).

Purinergic nerves are likely to have other functions in the lower urinary tract, because excitatory receptors for ATP are present in parasympathetic ganglia (Theobald and de Groat, 1989; Nishimura and Tokimasa, 1996; Zhong et al, 1998, 2001), afferent nerve terminals (Dmitrieva et al, 1998; Namasivayam et al, 1999; Lee et al, 2000; Burnstock, 2001), and urothelial cells (Buffington et al, 1999; Vlaskovska et al, 2001). Excitatory purinergic receptors in pelvic ganglia have been demonstrated in the cat (Theobald and de Groat, 1989), rabbit (Nishimura and Tokimasa, 1996), and rat (Zhong et al, 1998, 2001).

$P2X_3$ receptors that have been identified in small-diameter afferent neurons in DRG have also been detected immunohistochemically in the wall of the bladder and ureter in a suburothelial plexus of afferent nerves (Lee et al, 2000). Studies using patch clamp recordings in rats have also demonstrated that the majority (90%) of bladder afferent neurons projecting by pelvic nerves responded to ATP and α,β-methylene ATP with persistent currents, suggesting that bladder afferent pathways in the pelvic nerve express

predominantly $P2X_{2/3}$ heteromeric receptors rather than $P2X_3$ homomeric receptors (Zhong et al, 2003; Dang et al, 2005). Intravesical or intra-arterial administration of ATP- or 2-methylthio-ATP–activated bladder afferent fibers and enhanced reflex bladder activity (Dmitrieva et al, 1998; Namasivayam et al, 1999; Pandita and Andersson, 2002; Zhang et al, 2003; Nishiguchi et al, 2005). On the other hand, desensitization of purinergic receptors by intravesical administration of α,β-methylene ATP, a purinergic receptor agonist, or administration of a receptor antagonist, suramin, depressed bladder afferent activity (Dmitrieva et al, 1998; Namasivayam et al, 1999). **In $P2X_3$ knockout mice, afferent activity induced by bladder distention was significantly reduced** (Burnstock, 2000; Cockayne et al, 2000; Cook and McCleskey, 2000; Souslova et al, 2000). Furthermore, deletion of the gene encoding $P2X_2$ and loss of heteromeric $P2X_{2/3}$ receptors also result in a marked urinary bladder hyporeflexia, as evidenced by increased thresholds for bladder contractions during bladder filling (Cockayne et al, 2005). These data indicate that **purinergic receptors are involved in mechanosensory as well as nociceptive signaling in the bladder.**

ATP is also released by afferent nerves and might act in an autofeedback manner to regulate afferent excitability. Two studies (Dmitrieva et al, 1998; Morrison, 1998) presented evidence for purinergic sensitization of bladder afferent nerve endings. Intra-arterial injection of ATP can activate bladder afferent nerves (Dmitrieva et al, 1998), whereas suramin, an antagonist of certain types of ATP receptors (P2X purinergic receptors), given intravesically reduced by 50% the firing of bladder mechanoreceptors induced by bladder distention (Morrison, 1998). Intravesical administration of α,β-methylene ATP also reduced the firing of mechanosensitive afferents, presumably by desensitizing purinergic receptors on the afferent terminals.

In addition, adenosine, which can be formed by the metabolism of ATP, can depress parasympathetic nerve-evoked bladder contractions by activating P1 inhibitory receptors in parasympathetic ganglia (Akasu et al, 1984), in postganglionic nerve terminals, and in the bladder muscle (Cockayne et al, 2000; Burnstock, 2001). Adenosine P1 receptors have been further classified into a number of subtypes (i.e., A_1, A_{2A}, A_{2B}, and A_3) (Olah et al, 1995). A study has demonstrated that adenosine reduces the force of nerve-mediated contractions by acting predominantly at presynaptic sites at the nerve-muscle junction through a subtype of an adenosine receptor (the A_1 receptor in guinea pigs), although these actions of adenosine are less evident in human detrusor muscles (Fry et al, 2004).

Key Points: Purinergic Mechanisms

- $P2X_3$ receptors that have been identified in small-diameter afferent neurons in dorsal root ganglion have also been detected immunohistochemically in the wall of the bladder and ureter in a suburothelial plexus of afferent nerves.
- Deletion of the gene encoding $P2X_2$ and loss of heteromeric $P2X_{2/3}$ receptors also result in a marked urinary bladder hyporeflexia, as evidenced by increased thresholds for bladder contractions during bladder filling.

Adrenergic Mechanisms

β-Adrenergic. Stimulation of β_2- and β_3-adrenergic receptors that exist in the human detrusor results in the direct relaxation of the detrusor smooth muscle (Andersson, 1993; Morita et al, 1993; Nishimoto et al, 1995; Levin and Wein, 1995). In addition, β-adrenergic–stimulated relaxation is mediated through the stimulation of adenylate cyclase and the accumulation of cyclic AMP (cAMP) (Levin et al, 1986; Andersson, 1993; Andersson and Arner, 2004). Because β-adrenoceptor–mediated relaxation of the human detrusor was not blocked by selective β_{1-} or β_2-adrenoceptor antagonists, such as dobutamine and procaterol, but was blocked by selective β_3-adrenoceptor antagonists, **the relaxation induced by adrenergic stimulation of the human detrusor is mediated mainly through β_3-adrenoceptor activation** (Igawa et al, 1999; Yamaguchi, 2002; Andersson and Arner, 2004). A quantitative analysis by reverse transcription–polymerase chain reaction has also confirmed that the β_3-adrenergic receptor is the most highly expressed subtype among α– and β-adrenoceptor subtypes at the mRNA level in human bladders (Nomiya and Yamaguchi, 2003). Therefore β_3-receptor agonists have been proposed to be effective for treatment of detrusor overactivity, and this is an exciting area of research for overactive bladder (Andersson and Arner, 2004; Tyagi et al, 2009). β-Adrenergic blockers have also been advocated for urinary incontinence due to inappropriate reflex urethral relaxation, because propranolol prevents the reduction in urethral pressure after sacral root stimulation (McGuire, 1978). However, β-adrenergic antagonists are not particularly useful in treating bladder or urethral disorders (Castleden and Morgan, 1980; Naglo et al, 1981; Takeda et al, 1997).

A second pharmacologic method of increasing cAMP levels is with phosphodiesterase (PDE) inhibitors. PDE is the enzyme that catalyzes the degradation of cAMP to AMP and thus limits the action of cAMP (Andersson, 1997; Longhurst, et al, 1997). There are several classes of PDEs that have individual substrate affinities, specific species and tissue distributions, and pharmacologic selectivities (Truss et al, 1996; Longhurst et al, 1997). **Currently, there is considerable research trying to identify the specific isoform of PDE present in the bladder as opposed to that in the penis** (Truss et al, 1996). **Selective inhibition of bladder PDE would result in both an increase in the basal levels of cAMP (and possibly relaxation of the detrusor) and enhancement of the sensitivity and efficacy of β-adrenergic agonists. In the isolated guinea pig bladder, the frequency of agonist-induced phasic activity is slowed by cAMP, and degradation of intracellular cAMP in the cells responsible for phasic activity appears to involve primarily PDE4** (Gillespie 2004). PDE4 inhibitors are shown to suppress detrusor overactivity in a rat model of bladder outlet obstruction induced by partial urethral ligation (Kaiho et al, 2008). Thus a selective β agonist and a selective PDE inhibitor might be an effective combination for the relaxation of the detrusor in the future.

α-Adrenergic. Although α-adrenergic stimulation is not prominent in the normal bladder, recent evidence indicates that **under pathologic conditions, such as detrusor overactivity associated with bladder outlet obstruction, the α-adrenergic receptor density, especially the α_{1D}-receptor subtype, can increase to such an extent that the norepinephrine-induced responses in the bladder are converted from relaxation to contraction** (Andersson and Arner, 2004). In rats with outflow obstruction, the proportion of α_{1D}-receptor subtype in the total α_1-receptor mRNA in the bladder is increased to 70% from 25% in normal rat bladders (Hampel et al, 2002), and urinary frequency is suppressed by an inhibition of α_{1D} and α_{1A} receptors by tamsulosin, whereas α_{1A}-receptor suppression by 5-methyl-urapidil has no effect. Moreover, α_{1D}-receptor knockout mice have larger bladder capacity and voided volumes

than do their wild-type controls, which supports an important role of α_{1D} receptors in the control of bladder function (Chen et al, 2005). **However, in humans, there is the predominant expression of α_{1D} receptors already in the normal bladder** (Malloy et al, 1998), **and the level of expression of α-adrenoceptor mRNA, which is considerably low compared with β_3 adrenoceptors in normal bladders, was not increased in the bladder with outflow obstruction** (Nomiya and Yamaguchi, 2003). Thus the contribution of α_{1D} receptors to detrusor overactivity observed in a variety of pathologic conditions, including obstructive uropathy and incontinence, still needs to be established (Andersson and Arner, 2004).

α-Adrenergic mechanisms are more important in urethral function. Substantial pharmacologic and physiologic evidence indicates that **urethral tone and intraurethral pressure are influenced by α-adrenergic receptors.** The presence of α_1 and α_2 adrenoceptors has been shown in the urethra of various species including humans. Among α_1 adrenoceptors, **the α_{1A} adrenoceptor is the major subtype expressed in urethral smooth muscle** at the mRNA and protein levels (Yono et al, 2004; Michel and Vrydag, 2006). Isolated human urethral smooth muscle contracts in response to α-adrenergic agonists (Yalla et al, 1977; Awad et al, 1978; Nordling, 1983; Mattiasson et al, 1984). It is also reported in the rabbit that the urethral contraction is mediated by the α_{1A}-adrenoceptor subtype (Testa et al, 1993; Michel and Vrydag, 2006). Likewise, **hypogastric nerve stimulation and α-adrenergic agonists raise intraurethral pressure, which is blocked by α_1-adrenergic antagonists** (Awad et al, 1976; Yalla et al, 1977). These findings provide the rationale for use of α-adrenergic agonists to promote urine storage by increasing urethral resistance.

Conversely, α-adrenergic receptor antagonists facilitate urine release in conditions of functionally increased urethral resistance, such as benign prostatic hyperplasia. Although the α_{1A} adrenoceptor is the major subtype in the prostate and urethra, highly selective α_{1A}- adrenoceptor antagonists (e.g., RS-17053) do not alter lower urinary tract symptom (LUTS) scores in men with BPH, but these agents are effective at relaxing prostate smooth muscle and increasing urine flow in men (Schwinn and Roehrborn, 2008). In contrast, α_1-adrenoceptor antagonists that contain α_{1D}-adrenoceptor blocking activity improve bladder-based symptoms in humans (Nishino et al, 2006), suggesting the important role of the α_{1D} adrenoceptors for storage symptoms associated with bladder outlet obstruction, receptors potentially located at the bladder or the spinal cord (Schwinn and Roehrborn, 2008).

α_2-Adrenergic antagonists increase the release of norepinephrine from urethral tissues through a presynaptic mechanism, but this does not affect the contractility of urethral smooth muscle in vitro (Mattiasson et al, 1984; Willette et al, 1990; Michel and Vrydag, 2006). The human urethra lacks postjunctional α_2-adrenergic receptors, although in-vitro prejunctional activation of these receptors produces a feedback inhibition of norepinephrine release. Pharmacologic and electrophysiologic data suggest that adrenergic nerves influence excitatory cholinergic transmission in pelvic ganglia. de Groat and Booth (1993) have shown, in the cat, that hypogastric nerves inhibit excitatory cholinergic transmission in vesical ganglia by activation of α_2-adrenergic receptors (Fig. 60–26). Conversely, β-adrenergic agonists facilitate transmission in vesical ganglia.

Urethral Tone in Women. Taki and associates (1999) separated the entire length of the human female urethra into several parts and studied regional contractile effect to norepinephrine, clonidine, acetylcholine, and potassium chloride. Their findings suggest that sympathetic innervation helps maintain resting urethral tonus, mainly through α_1 adrenoceptors. With the recent identification of at least three distinct subtypes of α_1 adrenoceptors with distinct pharmacologic profiles, it may be possible to develop urethra-specific adrenergic agonists for the treatment of stress urinary incontinence. A small-scale, placebo-controlled clinical study has demonstrated that activation of the $\alpha_{1A/1L}$-adrenoceptor subtype, which is a pharmacologic isoform of the α_{1A}-adrenoceptor gene product, was effective in reducing the number of incontinence episodes in women with mild to moderate stress urinary incontinence (Musselman et al, 2004), suggesting an important role of α_1 adrenoceptors in the urethral continence mechanism, although the data are still preliminary.

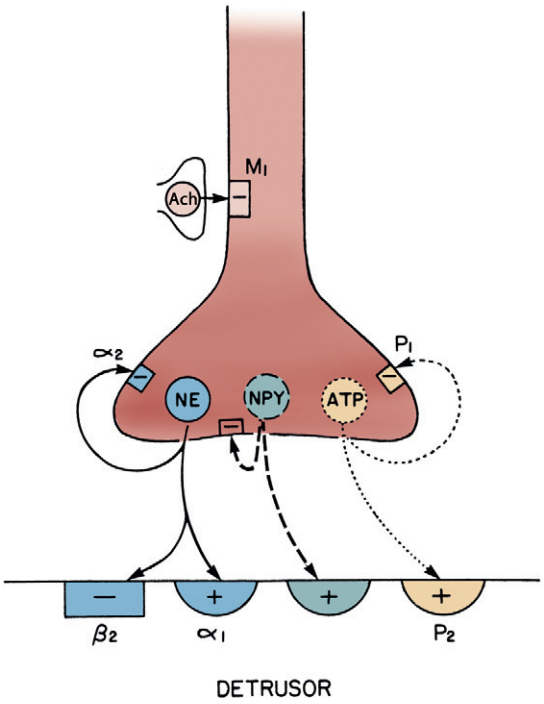


Figure 60–26. Diagram of possible transmitters in an adrenergic terminal supplying the bladder or urethra. Norepinephrine (NE) release can activate α_1-adrenergic receptors and produce contraction (+) or β receptors and cause relaxation (–) of the detrusor. Feedback inhibition of NE release through α_2 receptors can also occur. Neuropeptide Y (NPY) can produce smooth muscle contraction (+) or inhibit acetylcholine (ACh) release (not shown), or feedback can inhibit NE release. Adenosine triphosphate (ATP) can activate P2 receptors in the detrusor, which elicit contraction (+) or inhibit (–) further ATP release through P1 prejunctional receptors. ACh release from terminals in synaptic contact with an adrenergic varicosity can inhibit firing of adrenergic axons by activation of M_1 receptors.

Nitric Oxide

Nitric oxide (NO) has been identified as a major inhibitory transmitter mediating relaxation of the urethral smooth muscle during micturition (Andersson et al, 1992; Andersson, 1993; Andersson and Persson, 1995; Bennett et al, 1995). In 1931, Barrington hypothesized that stimulation of the pelvic nerve, in addition to evoking a bladder contraction, produces urethral relaxation. Indeed, urodynamic studies document a reduction in urethral pressure just before a bladder contraction (Scott et al, 1964; van Waalwijk van Doorn et al, 1991). In support of the contention that parasympathetic nerves mediate

Key Points: Adrenergic Mechanisms

- β-Adrenergic–stimulated relaxation is mediated through the activation of adenylate cyclase and the accumulation of cyclic AMP (cAMP).
- The β_3-adrenergic receptor is the most highly expressed subtype among α- and β-adrenoceptor subtypes, and β_3-receptor agonists are in clinical trial for treatment of detrusor overactivity.
- In the human, there is a predominant expression of α_{1D} receptors present in the normal bladder, and the level of expression of α-adrenoceptor mRNA, which is considerably low compared with β_3 adrenoceptors in normal bladders, was not increased in the bladder with outflow obstruction.
- Urethral tone and intraurethral pressure are influenced by α-adrenergic receptors. The α_{1A} adrenoceptor is the major subtype in the prostate and urethra, and all three α_1 adrenoceptor subtypes (α_{1A}, α_{1B}, α_{1D}) are present in blood vessels.

this urethral relaxation, sacral root stimulation reduces urethral pressure (McGuire, 1978; Torrens, 1978). Cholinergic innervation to the urethra has been supported by histochemical identification of acetylcholinesterase-staining fibers and ultrastructural data showing varicosities containing small clear vesicles in the human urethra (Ek, 1977; Gosling et al, 1977). Exogenous cholinergic agonists do not relax but rather contract urethral smooth muscle in vivo (Nergardh and Boreus, 1972; Ek et al, 1978) and in vitro (Ek et al, 1978). Therefore parasympathetic pathways mediating urethral relaxation must rely on a noncholinergic transmitter.

In the rat, NO is released by postganglionic nerves arising from neurons in the major pelvic ganglia (Fraser et al, 1995) (see Fig. 60–18). These neurons contain nitric oxide synthase (NOS), the enzyme that synthesizes NO, as well as nicotinamide adenine dinucleotide phosphate diaphorase, a marker for NOS (Vizzard et al, 1994). Electrophysiologic studies in female rats showed that electrical stimulation of the lumbosacral (L6-S1) spinal roots elicits simultaneous bladder contractions and urethral relaxation (Fraser et al, 1995). The urethral relaxation was inhibited by NOS inhibitors, which did not alter the bladder responses. The inhibition was reversed by administration of L-arginine, a precursor of NO. The electrically evoked urethral relaxation was abolished by ganglionic blocking agents, indicating that it was mediated by stimulation of preganglionic parasympathetic axons in the lumbosacral roots.

NO is also involved in controlling bladder afferent nerve activity. Inhibitors of NOS, given systemically or intrathecally, do not affect normal micturition in conscious or anesthetized rats. However, detrusor overactivity that accompanies irritation with turpentine, acetic acid, or cyclophosphamide is ameliorated by spinal application of NOS inhibitors (Rice, 1995; Kakizaki and de Groat, 1996; Lagos and Ballejo, 2004). However, intravesically administered capsaicin induces detrusor overactivity that is not influenced by an intrathecally applied NOS inhibitor, although the behavioral effects of the irritation are reduced (Pandita et al, 1997). It is believed that NO is involved in mediating *N*-methyl-D-aspartate (NMDA) receptor–dependent effects but not those involving neurokinin 2 (NK_2) receptors. **Overall, the NO mechanism at the spinal level has an excitatory effect on the micturition reflex.**

However, NO seems to have an inhibitory effect in the bladder. Intravesical application of NO can suppress bladder overactivity due to cyclophosphamide-induced bladder irritation in rats (Ozawa et al, 1999)**.** Intravesical oxyhemoglobin, an NO scavenger, also induces bladder overactivity as evidenced by reductions in bladder capacity and micturition volume, which is prevented by L-arginine or enhanced by the guanylate cyclase inhibitor in rats (Pandita et al, 2000). Masuda and colleagues (2007) also showed that bladder overactivity induced by intravesical capsaicin instillation was enhanced by a NOS inhibitor (L-NAME) administered intravenously or intravesically, and that these L-NAME–induced excitatory effects were significantly suppressed by desensitization of C-fiber afferent pathways by capsaicin pretreatment. **Thus NO released locally in the bladder can mediate inhibitory effects by modulation of bladder afferent activity** (Yoshimura et al, 2001).

Possible Gender Difference in Cholinergic and Nitrergic Innervation in the Urethra. A parasympathetic cholinergic excitatory input to the urethra (see Fig. 60–18) has been identified in male but not in female rats (Flood et al, 1995; Kakizaki et al, 1997). This was demonstrated by measuring intraurethral pressure during voiding after blockade of striated external urethral sphincter activity with a neuromuscular blocking agent. Under these conditions, urethral pressure increased during micturition in male rats. This urethral reflex was blocked by hexamethonium (a ganglionic blocking agent), markedly reduced by atropine, and increased by an NOS inhibitor. However, it was not changed by transection of sympathetic nerves or administration of an α_1-adrenergic blocking agent (prazosin). These results indicate that in male rats, parasympathetic nerve activity induces a predominant cholinergic muscarinic contraction of the urethra and a subordinate NO-mediated relaxation. These studies implicate possible gender differences in parasympathetic and especially nitrergic pathways in the human urethra.

Smooth Muscle Tone and Nitric Oxide. NO-mediated smooth muscle relaxation is due to increased production of intracellular cyclic guanosine monophosphate (cGMP). The second messengers cAMP and cGMP are synthesized from the corresponding nucleoside triphosphates by their respective membrane-bound or soluble adenylate or guanylate cyclases. cAMP and cGMP are inactivated by PDEs by hydrolytic cleavage of the 3′-ribose phosphate bond. Therefore the level of intracellular second messengers can be regulated by PDE isoenzymes (Truss et al, 1999, 2001).

Because of their central role in regulating smooth muscle tone and the considerable variation of PDE isoenzymes among species and tissues, PDEs have become an attractive target for drug development. So far, 7 PDE families, 16 genes, and 33 individual enzyme proteins have been defined. The hope is that bladder-specific PDEs can be developed.

Studies have reported that **PDEs 1 to 5 exist in human detrusor smooth muscle** (Truss et al, 1996). The PDE1-selective inhibitor vinpocetine has been tested, with encouraging but preliminary results, in patients with detrusor overactivity who did not respond to conventional anticholinergic drugs (Truss et al, 1997, 2001).

Afferent Neuropeptides

Afferent neurons innervating the lower urinary tract exhibit immunoreactivity for various neuropeptides, such as substance P (SP), calcitonin gene–related peptide (CGRP), pituitary adenylate cyclase–activating polypeptide (PACAP), leucine enkephalin, corticotropin-releasing factor, and vasoactive intestinal polypeptide (VIP) (de Groat, 1986; de Groat, 1989; Keast and de Groat, 1992; Maggi,

1993; Vizzard, 2001, 2006), as well as growth-associated protein-43 (GAP43), nitric oxide synthase (NOS) (Vizzard et al, 1996), glutamic acid, and aspartic acid (Keast and Stephensen, 2000). These substances have been identified in many species and at one or more locations in the afferent pathways including (1) afferent neurons in lumbosacral dorsal root ganglia, (2) afferent nerves in the peripheral organs, and (3) afferent axons and terminals in the lumbosacral spinal cord (Kawatani et al, 1985, 1986, 1996; Morrison et al, 2005). The majority (>70%) of bladder DRG neurons in rats appear to contain multiple neuropeptides—CGRP, substance P, or PACAP being the most common. In cats, VIP is also contained in a large percentage of bladder DRG neurons (de Groat, 1989).

Many of these peptides, which are contained in capsaicin-sensitive, C-fiber bladder afferents, are released in the bladder by noxious stimulation and contribute to inflammatory responses by triggering plasma extravasation, vasodilation, and alterations in bladder smooth muscle activity (Maggi, 1993; Ishizuka et al, 1994, 1995b). **These agents also function as transmitters at afferent terminals in the spinal cord.**

Tachykinins. The tachykinins are a family of small peptides sharing a common C-terminal sequence, Phe-Xaa-Gly-Leu-Met-NH_2, whose main members are **substance P**, **neurokinin A, and neurokinin B**. Tachykinins are found in both central and peripheral nervous systems. In the peripheral nerves, tachykinins are predominantly located in the terminals of nonmyelinated, sensory C fibers. **The diverse biologic effects of the tachykinins are mediated through three receptors, designated NK_1, NK_2, and NK_3**, which belong to the superfamily of seven transmembrane-spanning G protein–coupled receptors (Khawaja and Rogers, 1996). Substance P is the most potent tachykinin for the NK_1 receptor, whereas neurokinin A exhibits the highest affinity for the tachykinin NK_2 receptor, and neurokinin B for the tachykinin NK_3 receptor (Table 60–6). All receptor subtypes have been identified in the bladder of humans and animals such as rats, mice, and dogs (Lecci and Maggi, 2001; Andersson and Arner, 2004).

Tachykinins released from capsaicin-sensitive sensory C fibers in response to irritation in the bladder can act on (1) NK_1 receptors in blood vessels to induce plasma extravasation and vasodilation, (2) NK_2 receptors to stimulate bladder contractions, and (3) NK_2 receptors on primary afferent terminals to increase the excitability during bladder filling or during bladder inflammation (de Groat, 1989; Andersson, 1993; Morrison et al, 1995; Lecci and Maggi, 2001). A study by Kamo and associates (2005) also demonstrated that **activation of NK_3 receptors on capsaicin-sensitive C-fiber afferents in the rat bladder can increase the excitability during bladder filling**.

Intrathecal administration of NK_1 antagonists (RP 67580 and CP 96345) or systemic application of centrally acting NK_1 antagonists (GR 205171 and CP 99994) increased bladder capacity in normal rats and guinea pigs, respectively, without changing voiding pressure, whereas NK_2, NK_3, or peripherally acting NK_1 antagonists were ineffective (Lecci et al, 1993; Yamamoto et al, 2003). Detrusor overactivity in rats induced by chemical cystitis, intravesical administration of capsaicin, or intravenous injection of L-dopa was also suppressed by intrathecal injection of NK_1 antagonists (Ishizuka et al, 1994, 1995b; Lecci et al, 1994). Detrusor overactivity induced by capsaicin was reduced by an NK_2 antagonist (SR 48965) that did not influence normal voiding (Lecci et al, 1997). In the anesthetized guinea pigs, TAK-637, an NK_1 receptor antagonist, administered orally or intravenously, also increased the volume threshold for inducing micturition and inhibited the micturition reflex induced by capsaicin applied topically to the bladder (Doi et al, 1999). In a clinical study, an NK_1 receptor antagonist, aprepitant, is also shown to effectively decrease the average daily number of micturitions and urgency episodes compared with placebo at 8 weeks in women with idiopathic overactive bladder (Green et al, 2006). These results indicate that **sensory input to the spinal cord from nonnociceptive bladder afferents is mediated by tachykinins acting on NK_1 receptors, whereas input from nociceptive afferents in the bladder can be mediated by NK_1, NK_2, and NK_3 receptors.** In addition, tachykinin NK_3 receptor activation in the spinal cord can inhibit the micturition reflex through an activation of the spinal opioid mechanism (Kamo et al, 2005).

Autofeedback mechanisms may also be important at afferent nerve terminals (see Fig. 60–14). As mentioned earlier, some stimuli are known to release neuropeptides from afferent nerves, and these neuropeptides may, in turn, sensitize the afferents. NK_2 agonists were found (Wen and Morrison, 1996) to sensitize bladder mechanoreceptors by acting on NK_2 autoreceptors in the sensory endings in the bladder mucosa to produce the combination of effects found previously for other sensitizing agents (Morrison, 1998). The NK_2 receptor blocker SR 48968 decreases the sensitivity of bladder mechanoreceptors and also blocks the sensitization produced by NK_2 agonists and high urinary potassium levels. This suggests that the sensitization produced by intravesical chemical stimuli may be due to a mechanism using the NK_2 receptor. On the basis of these findings, it could be hypothesized that high urinary potassium concentration or higher levels of bladder distention release neurokinin A from sensory endings, and that the sensitization is due to the action of the peptide on local NK_2 autoreceptors on the sensory endings. It has also been shown that sensory neurons obtained from rat DRG can be excited by NK_2 agonists and inhibited by NK_3 agonists through modulation of Ca^{2+} channel activity mediated by protein kinase C activation (Sculptoreanu and de Groat, 2003). NK_2 receptor activation also leads to PKC-induced phosphorylation of TRPV1 channels, resulting in an increase in capsaicin-evoked currents in rat DRG neurons (Sculptoreanu and de Groat, 2007; Sculptoreanu et al, 2008).

Other Neuropeptides. Other afferent neuropeptides have effects on the peripheral organs or the central reflex pathways controlling the lower urinary tract. However, the effects can vary in different species and at different sites in the lower urinary tract. **CGRP** applied exogenously or released from primary afferents relaxes smooth muscle and produces vasodilation. The effect of CGRP on bladder is prominent in the guinea pig and dog but is absent in the rat and human bladder (Andersson 1993). **VIP**, which is contained in C-fiber afferents, as well as in postganglionic neurons (de Groat and Booth, 1993), inhibits spontaneous contractile activity in isolated bladder muscle from several species, including humans. However, VIP usually has little effect on bladder

Table 60–6.

Tachykinins and Tachykinin Receptors

TACHYKININ	RECEPTOR
Substance P	NK_1
Neurokinin A	NK_2
Neurokinin B	NK_3

contractions induced by muscarinic receptor agonists or by nerve stimulation (Andersson, 1993). In-vivo studies in the cat revealed that VIP facilitates muscarinic, but not nicotinic transmission, in bladder parasympathetic ganglia and also depresses neurally evoked contractions of the bladder (de Groat and Booth, 1993).

In the spinal cord, VIP-containing afferent pathways have been implicated in the recovery of bladder reflexes after spinal injury. In cats with chronic spinal injury, VIP immunoreactivity, which is a marker for C-fiber afferent terminals, is distributed over a wider area of the lateral dorsal horn, suggestive of afferent axonal sprouting after spinal injury (Yoshimura and de Groat, 1997; Doi et al, 1999). In addition, the effects of intrathecal administration of VIP are changed. In normal cats, VIP inhibits the micturition reflex; whereas in paraplegic cats, VIP facilitates the micturition reflex. These findings suggest that the action of a putative C-fiber afferent transmitter may underlie the emergence of C-fiber bladder reflexes in the paraplegic cat. In the normal rat, VIP and **PACAP**, another member of the secretin-glucagon-VIP peptide family, also facilitate the micturition reflex by actions on the spinal cord (Ishizuka et al, 1995a; Yoshiyama and de Groat, 2008). In rats with spinal cord injury, an increase in expression of PACAP-immunoreactivity in bladder DRG neurons and expansion of PACAP-IR afferent axons in the lumbosacral spinal cord are observed, and intrathecal administration of PACAP6-38, a PAC1 PACAP–receptor antagonist, reduces premicturition contractions during bladder filling and reduces maximal voiding pressure, suggesting that activation of PAC1 receptors by endogenous PACAP contributes to the micturition reflex and bladder overactivity in spinalized rats (Zvarova et al, 2005; Zvara et al, 2006).

Patch clamp studies in neonatal rat spinal-slice preparations revealed that PACAP has a direct excitatory action on parasympathetic preganglionic neurons due in part to blockade of K^+ channels (Miura et al, 2001). In addition, PACAP has an indirect action by activating excitatory interneurons.

Prostanoids, Endothelins, and Hormones

Prostanoids. Prostanoids (prostaglandins and thromboxanes), which comprise a family of oxygenated metabolites of arachidonic acid, by the enzymatic activity of cyclooxygenases 1 and 2, are manufactured throughout the lower urinary tract and have been implicated in bladder contractility, inflammatory responses, and neurotransmission. Biopsy specimens of human bladder mucosa contain prostaglandin (PG) I_2, PGE_2, $PGE_{2\alpha}$, and thromboxane A. **In decreasing order of potency, $PGF_{2\alpha}$, PGE, and PGE_2 contract the human detrusor** (Andersson, 1993; Andersson and Arner, 2004). The actions of prostanoids are mediated by specific receptors on cell membranes. The receptors include the DP, EP, FP, IP, and TP receptors that preferentially respond to PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, and thromboxane A_2, respectively. Furthermore, EP is subdivided into four subtypes: EP_1, EP_2, EP_3, and EP_4 (Breyer et al, 2001, 2003). **The slow onset of action for these substances suggests a modulatory role for prostaglandins. Some prostaglandins may affect neural release of transmitters, whereas others inhibit acetylcholinesterase activity.** These actions provide mechanisms whereby prostaglandins could potentially augment the amplitude of cholinergic-induced detrusor contractions (Borda et al, 1982).

Attempts to use prostaglandins to facilitate voiding have had mixed results. Intravesical PGE_2 has been shown to enhance bladder emptying in women with urinary retention and patients with neurogenic voiding dysfunction (Bultitude et al, 1976; Vadyanaathan et al, 1981; Tammela et al, 1987). Others have failed to find PGE_2 useful to facilitate complete evacuation of the bladder ((Delaere et al, 1981; Wagner et al, 1985). Intravesical PGE_2 does produce urgency and involuntary bladder contractions (Schussler, 1990). Consistent with this finding, inhibition of prostaglandin synthesis with indomethacin reduces detrusor overactivity (Cardozo and Stanton, 1980).

Endothelins. Endothelins (ETs), a family of 21–amino acid peptides (originally isolated from bovine aortic endothelial cells), include ET-1, ET-2, and ET-3, which are encoded by separate genes and mediate a variety of biologic actions through two distinct G protein–coupled receptor subtypes, the endothelin-A (ETA) and the endothelin-B (ETB) receptor (Yanagisawa et al, 1988; Masaki, 2004). The ETA receptor subtype has a higher affinity for ET-1 and ET-2 than for ET-3; the ETB receptor subtype binds all ETs with equal affinity (Rubanyi and Polokoff, 1994). ET-1, which is known to be primarily produced by human endothelial cells, can induce prolonged contractile responses in isolated urinary bladder muscle strips in various species (Maggi et al, 1990; Khan et al, 1999). In humans and rabbits, ET-like immunoreactivity is identified in almost all cell types in the bladder, including bladder epithelium, vascular endothelium, detrusor, and vascular smooth muscles, and fibroblasts; **it plays a role in control of bladder smooth muscle tone, regulation of local blood flow, and bladder wall remodeling in pathologic conditions** (Saenz de Tejada et al, 1992). In a rabbit model of bladder outlet obstruction, ET-1 and ETA receptor binding sites in detrusor smooth muscle and urothelium, as well as ETB receptor binding sites in detrusor smooth muscle, were significantly increased (Khan et al, 1999). In addition, the endothelin-converting enzyme inhibitor WO-03028719, which suppresses ET-1 production, can improve voiding efficiency and suppress detrusor overactivity in a rat model of bladder outlet obstruction (Schroder et al, 2004). YM598, a selective ETA receptor antagonist, also reduces detrusor overactivity in urethral obstructed rats (Ukai et al, 2006). These results suggest that **the increase in ET-1 expression and ET receptors could be involved in detrusor hyperplasia and overactivity seen in patients with bladder outlet obstruction resulting from benign prostatic hyperplasia.**

There is also evidence that ETs have a role in modulation of sensory function in the peripheral and central nervous system. The activation of ET_A receptors in capsaicin-sensitive C-fiber afferents in the bladder induces detrusor overactivity, whereas ET_A receptor activation in the spinal cord can inhibit the micturition reflex through activation of a spinal opioid mechanism in rats (Ogawa et al, 2004). In spinal cord–injured rats, the bladder ET-1 level was increased, and the application of ABT-627, an ET_A antagonist, suppresses C-fiber–mediated detrusor overactivity. Taken together, modulation of ET_A receptor activity in bladder afferent pathways or the spinal cord could be effective in treating bladder overactivity or painful conditions (Ogawa et al, 2008).

Parathyroid Hormone–Related Peptide. Some locally released substances cause **detrusor relaxation**. Parathyroid hormone–related peptide is **manufactured by bladder smooth muscle**. **Stretch** in vivo (Yamamoto et al, 1992) and in vitro (Steers et al, 1998) **increases parathyroid hormone–related peptide**. Slow or gradual distention could release local relaxants, thereby maintaining low filling pressures.

Sex Steroids. Differences in responses of human and animal bladders to the effect of drugs suggest that sex steroids play a role in detrusor contractility. It is not unusual for women to note changes in voiding, bladder pain, or continence at different times of their menstrual cycle. **Sex steroids do not directly affect bladder contractility, but they modulate receptors and**

influence growth of bladder tissues. Estrogen receptors are expressed by the trigone in women (Iosif et al, 1981). Levin and associates (1980) noted that bladder body muscle from young female rabbits treated with estrogens exhibits increased responsiveness to α-adrenergic, cholinergic, and purinergic agonists. Others have seen a decreased density of adrenergic and muscarinic receptors in the bladder after estrogen administration (Shapiro, 1986; Batra and Andersson, 1989). In contrast to the study by Levin and coworkers (1980), Elliot and associates (1992) showed that bladder smooth muscle from estrogen-treated rats exhibited decreased contractions.

Estrogens also increase adrenergic receptors in the urethra (Callahan and Creed, 1985). Ekstrom and associates (1993) reported that estrogen administration to ovariectomized rabbits unmasked contractile responses to α-adrenergic agonists, whereas contracted and normal rabbit bladders demonstrated no response to these agents. Some clinicians have combined these agents to elevate urethral pressure in patients with stress incontinence (Wilson et al, 1987). However, the clinical efficacy of the combined use of estrogen with α agonists has been questioned (Walter et al, 1978). **The effect of estrogens on urinary continence in females probably reflects the multiple actions of this hormone on adrenergic receptors, vasculature, and urethral morphology. In addition, progesterone increases electrical and cholinergic contractions of the bladder.** Exogenous estrogens and progesterones also induce NOS activity in bladders of female guinea pigs (Ehren et al, 1995). This effect is postulated to contribute to relief of detrusor overactivity with hormonal treatment. However, the use of estrogens alone to treat either stress urinary incontinence or urgency incontinence has given disappointing results (Abrams et al, 2005), and studies have suggested that estrogen may be associated with an increase in urinary incontinence in postmenopausal women (Hendrix et al, 2005).

Androgen treatment in the male rat has been reported to have similar effects on synaptic connections, as well as effects on motoneuronal somatic and dendritic size in the androgen-sensitive motoneurons innervating the bulbocavernosus and levator ani muscles of the rat (Jordan, 1997; Matsumoto, 1997). Testosterone treatment can also influence the size of postganglionic neurons in the major pelvic ganglion of the male rat (Keast and Saunders, 1998). Thus further studies are needed to evaluate the influence of changes in hormonal environment on the neural pathways controlling the lower urinary tract.

"Transducer" Function of the Urothelium

Whereas the urothelium has historically been viewed primarily as a "barrier," **there is increasing evidence that urothelial cells display a number of properties similar to sensory neurons (nociceptors and mechanoreceptors) and that both types of cells use diverse signal-transduction mechanisms to detect physiologic stimuli.** Examples of "sensor molecules" (i.e., receptors and ion channels) associated with neurons that have been identified in urothelium include receptors for bradykinin (Chopra et al, 2005), neurotrophins (TrkA and p75) (Murray et al, 2004), purines (P2X and P2Y) (Lee et al, 2000; Hu et al, 2002; Birder et al, 2004; Tempest et al, 2004; Chopra et al, 2008), norepinephrine (α and β) (Birder et al, 1998; Birder et al, 2002), acetylcholine (nicotinic and muscarinic) (Chess-Williams, 2002; Beckel et al, 2006; Kullmann et al, 2008a), protease-activated receptors, amiloride-/mechanosensitive Na^+ channels such as ENaC (Smith et al, 1998; Wang et al, 2003; Araki et al, 2004), and a number of TRP channels (TRPV1, TRPV2, TRPV4, TRPM8) (Birder and de Groat, 1998; Birder et al, 2001, 2002, 2007; Stein et al, 2004; Gevaert et al, 2007).

When urothelial cells are activated through these receptors and ion channels in response to mechanical as well as chemical stimuli, they can, in turn, release chemical mediators such as NO, ATP, acetylcholine, and substance P (Ferguson et al, 1997; Birder et al, 1998; Burnstock, 2001; Birder et al, 2003; Chess-Williams, 2004). **These agents are known to have excitatory and inhibitory actions on afferent nerves that are close to or in the urothelium** (Bean et al, 1990; Dmitrieva et al, 1998; Birder et al, 2001; Yoshimura et al, 2008). **Chemicals released from urothelial cells may act directly on afferent nerves or indirectly through an action on suburothelial interstitial cells** (also referred to as myofibroblasts) that lie in close proximity to afferent nerves. Myofibroblasts are extensively linked by gap junctions and can respond to chemicals that in turn modulate afferent nerves (Fowler et al, 2008). **Thus it is believed that urothelial cells and myofibroblasts can participate in sensory mechanisms in the urinary tract by chemical coupling to the adjacent sensory nerves.**

NO can be released by the urothelium, particularly during inflammation (Birder et al, 1998). The release of NO may be evoked by the calcium ionophore A-23187, norepinephrine, and capsaicin. Substance P also acts on receptors on urothelial cells to release NO. The adrenergic release of NO from bladder strips was reduced by 85% after removal of the urothelium. Denervation of the bladder did not completely block the release of capsaicin-induced NO production, suggesting other sites of production. This is consistent with the observations that capsaicin released NO from cultured rat, cat, rabbit, and human urothelial cells and that the TRPV1 capsaicin receptor is expressed in cultured urothelial cells. NOS expression in afferent neurons is also increased in chronic bladder inflammation. Given that NO does not have much effect on the detrusor muscle but does inhibit Ca^{2+} channels in rat bladder afferent neurons (Yoshimura et al, 2001), **the role of NO in the urothelium has still to be clarified**. However, **NO released locally in the bladder appears to have an inhibitory effect on afferent activity in the bladder** because suppression of endogenous NO by intravesical oxyhemoglobin, an NO scavenger, or L-NAME, a NOS inhibitor, enhances bladder activity in rats (Pandita et al, 2000; Masuda et al, 2007).

ATP released from urothelial cells during stretch can activate a population of suburothelial bladder afferents expressing $P2X_3$ receptors, signaling changes in bladder fullness and pain (Ferguson et al, 1997; Burnstock, 2001). Accordingly, **$P2X_3$ null mice exhibit a urinary bladder hyporeflexia, suggesting that this receptor, as well as neural–epithelial interactions, are essential for normal bladder function** (Cockayne et al, 2000). This type of regulation may be similar to epithelium-dependent secretion of mediators in airway epithelial cells, which are thought to modulate submucosal nerves and bronchial smooth muscle tone and may play an important role in inflammation (Homolya et al, 2000; Jallat-Daloz et al, 2001). Thus it is possible that activation of bladder nerves and urothelial cells can modulate bladder function directly or indirectly by the release of chemical factors in the urothelial layer. ATP released from the urothelium or surrounding tissues may also play a role in the regulation of membrane trafficking. This is supported by studies in the urinary bladder in which urothelium-derived ATP release purportedly acts as a trigger for exocytosis, in part by autocrine activation of urothelial purinergic (P2X, P2Y) receptors (Wang et al, 2005).

These findings suggest a mechanism whereby urothelial cells sense or respond to ATP and thereby translate extracellular stimuli into functional processes.

Prostaglandins are also released from the urothelium. These are assigned two possible functions: regulation of detrusor muscle activity and cytoprotection of the urothelium, based on effective treatment of hemorrhagic cystitis by prostaglandins (Jeremy et al, 1987). The predominant forms found in human urothelium from biopsy specimens are 6-oxo-$PGF_{2\alpha}$ > PFE_2 > $PGF_{2\alpha}$ > thromboxane B_2. PGI_2 (prostacyclin) is also produced. These findings were confirmed and further developed in the guinea pig, in which it was found that the major production of prostaglandins occurred in the urothelium. The production of prostaglandins also increased greatly with inflammation (Saban et al, 1994). Prostaglandin synthesis also occurs in the ureter, where it is speculated to be important in the regulation of ureteral peristalsis and also in reducing the development of blood clots in the lumen of the ureter (Ali et al, 1998).

Evidence also suggests that the involvement of the muscarinic receptor in bladder function extends beyond detrusor contractility and into afferent sensory functioning. Muscarinic receptors are found on the urothelium at high density (Hawthorn et al, 2000), **and there is a basal release of acetylcholine from the urothelium that is increased by stretch and aging** (Yoshida et al, 2006). **Thus activation of the muscarinic receptors in the urothelium releases substances that modulate afferent nerves and smooth muscle activity** (Hawthorn et al, 2000; de Groat, 2004; Kullmann et al, 2008b).

The urothelium also releases substances called urothelium-derived inhibitory factors, which decrease the force of detrusor muscle contraction in response to muscarinic stimulation (Hawthorn et al, 2000; Kumar et al, 2005). The molecular identity of this factor is not known; however, pharmacologic studies suggest that it is not NO, a prostaglandin, prostacyclin, adenosine, catecholamine, GABA, or one that acts through apamine-sensitive, small-conductance K^+ channels. It has been shown that an inhibitory response through this factor is attenuated in a fetal model of bladder outlet obstruction (Thiruchelvam et al, 2003). Further studies are required to clarify the identity of this substance and its role in bladder function.

Serotonin

Serotonin (5-HT) has been found in neuroendocrine cells along the urethra and in the prostate ((Hanyu et al, 1987). In animals, 5-HT_2 and, possibly, 5-HT_3 agonists contract the urethra. If inflammatory conditions promote release of serotonin from paraurethral cells, irritative symptoms, such as the urethral syndrome, may arise because of serotonergic mechanisms. The 5-HT_2 antagonist ketanserin has been shown to reduce urethral pressure in humans (Horby-Petersen et al, 1985). However, the reduction in urethral pressure after ketanserin administration can also be the result of blockade of α-adrenergic receptors (Thor and Katofiasc, 1995).

5-HT also has several pharmacologic effects on mammalian urinary bladders, both in vitro and in vivo. Human and pig isolated detrusor muscles are known to contract in a concentration-dependent manner in response to 5-HT (Klarskov and Horby-Petersen, 1986). In human isolated urinary bladder, there was potentiation of the contractions induced by electrical field stimulation, mediated by the 5-HT_4 receptor subtype (Candura et al, 1996; Darblade et al, 2005). A similar response is present on guinea pig detrusor muscle through 5-HT_{2A} and 5-HT_4 receptors, whereas in the rabbit and the rat, the receptors involved are the 5-HT_3 and 5-HT_7 subtypes, respectively (Palea et al, 2004).

TRP Channels and C-Fiber Pharmacotherapy

The superfamily of TRP **(transient receptor potential)** channels expressed in mammals are subdivided into six subfamilies: TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin), and TRPA (ankyrin) groups, which are **Ca^{2+}-permeable cation channels and activated by physical (depolarization, hot/cold temperature, mechanical stress) or chemical (pH, osmolality) stimuli and binding to specific ligands** (vanilloids, menthol) (Krause et al, 2005; Everaerts et al, 2008). The available evidence suggests that TRP channels have a four-subunit combination, in either a homotetrameric or heterotetrameric complex, to form functional ion-permeation complexes (Krause et al, 2005).

TRPV1

TRPV1, the most extensively studied TRP channel, is expressed on capsaicin-sensitive afferent pathways, predominantly C-fiber nociceptors, and responds to increases in temperature to the noxious range (>43° C) and to protons, suggesting that it functions as a **transducer of painful thermal stimuli and acidity in vivo**. When it is activated, the channel opens, allowing an influx of Ca^{2+} and Na^+ ions that depolarizes the nociceptive afferent terminals, initiating a nerve impulse that travels through afferent nerves into the central nervous system. Noxious temperature uses the same elements, which explains why the mouth feels hot when eating chili peppers (Clapham, 1997). **In the lower urinary tract, TRPV1 is expressed in suburothelial afferent fibers, urothelium, detrusor smooth muscle, and other non-neuronal cells such as suburothelial interstitial cells** (see Fig. 60–8). Studies using TRPV1 knockout mice showed that TRPV1 receptors are not essentially involved in conscious voiding but have a role in afferent sensitization due to cystitis because bladder overactivity induced by chemical cystitis, using cyclophosphamide or acrolein, was not observed in TRPV1 knockout mice (Birder et al, 2002; Charrua et al, 2007; Wang et al, 2008). In addition, TRPV1 expressed in the bladder urothelium may function as a stretch sensor because the release of ATP and NO from cultured urothelial cells during hypotonic stretch is reduced in TRPV1 knockout mice compared with the wild type (Birder et al, 2002).

Activation of TRPV1 by vanilloids, such as capsaicin and its ultrapotent analog resiniferatoxin (RTX), results in spikelike currents (Liu and Simon, 1996) **and selectively excites and subsequently desensitizes TRPV1-expressing C fibers.** Desensitization induced by capsaicin is defined as a long-lasting, reversible suppression of sensory neuron activity (Craft et al, 1995). Thus because **of the unique ability to desensitize TRPV1-expressing C fibers, the vanilloids have been used for treatment of pain/overactivity of the bladder** (Cheng et al, 1995; Chancellor and de Groat, 1999). The normal sensations of bladder filling appear to be mediated by small myelinated Aδ fibers. In the cat, Aδ fibers have pressure thresholds in the range of those at which humans report the first sensation of bladder filling (Janig and Morrison, 1986). **C-fiber afferents, which are small and unmyelinated, have high mechanical thresholds and do not normally respond to**

even high levels of intravesical pressure in the cat (Häbler et al, 1990). **C-fiber afferents are activated by noxious chemical irritation** (Häbler et al, 1990) **or by cold** (Fall et al, 1990). **In the irritated state, C-fiber afferents become responsive to low-pressure bladder distention such as mechanoreceptive Aδ fibers. C fibers, therefore, are normally "silent." C-fibers have the specific function of signaling of inflammatory or noxious events in the bladder** (Chancellor and de Groat, 1999) (Figs. 60–27 and 60–28).

RTX is the principal active ingredient in the drug euphorbium that is derived from the air-dried latex (resin) of the cactus-like plant *Euphorbia resinifera*. *E. resinifera* belongs to the Euphorbiaceae, commonly known as the spurge family, one of the most important families of medicinal plants. In 1975, the principal active ingredient in euphorbium was isolated and named **resiniferatoxin** (Hergenhahn et al, 1975). In 1989, **RTX was recognized as an ultrapotent analog of capsaicin; however, it has unique pharmacologic effects as well** (Szallasi and Blumberg, 1990), **such as desensitization without prior excitation of the pulmonary chemoreflex pathway** (Szolcsanyi, 1990). In patients with spinal cord injury–induced detrusor overactivity, clinical response to intravesical therapy with RTX led to a marked decrease of nerve fibers positively stained for PGP9.5, a neuronal marker, and TRPV1. Six of 17 patients in this investigation showed a satisfactory clinical response to RTX treatment, with marked improvements on cystometry and other parameters (Brady et al, 2004). Spinal-injury patients who did not respond to RTX showed no decrease in nerve fiber population, similar to controls. In addition, intravesical RTX administered to patients with idiopathic detrusor overactivity delayed or suppressed involuntary detrusor contractions during filling cystometry. The mean interval to the first involuntary contraction more than doubled versus baseline at 30 and 90 days; mean maximal cystometric capacity increased; the mean number of episodes of urinary incontinence daily fell to fewer than one; and mean daily frequency also decreased significantly (Silva et al 2002). It has also been reported that C-fiber desensitization induced by intravesical application of high-dose capsaicin and resiniferatoxin (RTX) is effective for treating painful symptoms in IC patients (Lazzeri et al, 1996, 2000) although a prospective, randomized clinical trial using intravesical RTX application showed no effect in patients with IC (Payne et al, 2005).

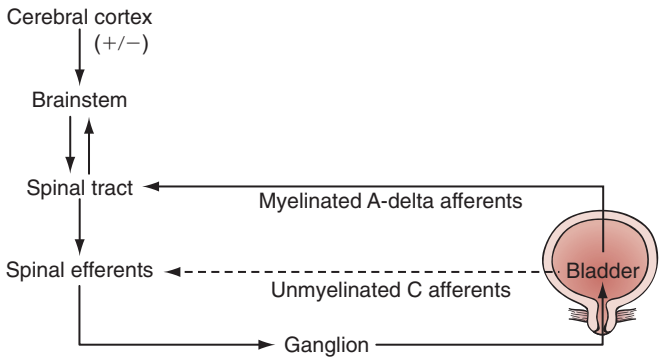


Figure 60–27. Illustration depicting the predominant Aδ afferent contribution to the normal micturition reflex.

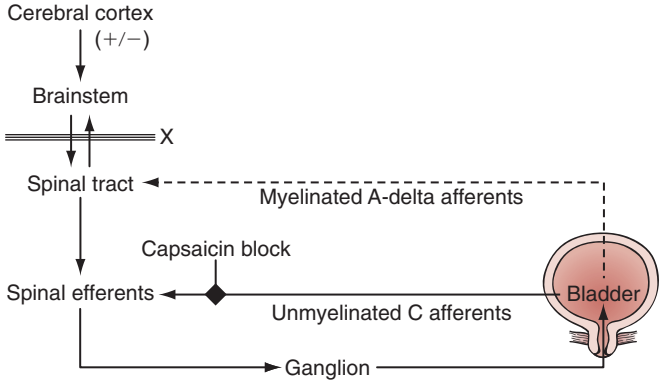


Figure 60–28. Illustration depicting the switch in afferent contribution to the micturition reflex from Aδ-fiber predominant to C-fiber predominant with neurologic diseases, aging, and possibly inflammatory disease. Note that capsaicin (and other vanilloids) can block the C-fiber contribution under these conditions.

More recently, selective antagonists of TRPV1 channels are being evaluated as potential analgesics in clinical trials (Everaerts et al, 2008). GRC-6211, a new oral TRPV1 antagonist, has been shown to decrease bladder overactivity and noxious bladder input in cystitis animal models (Charrua et al, 2009), suggesting the **possibility of TRPV1 antagonists for the treatment of bladder pain/overactivity.**

TRPM8 and TRPA1

TRPM8 is a member of the temperature-sensitive TRP channels that responds to cold temperature of less than 23° C. Pharmacologic agents that evoke cool sensation, such as menthol and ilicin, can activate TRPM8. In sensory pathways, TRPM8 is expressed in DRG and trigeminal ganglion neurons that do not express TRPV1, isolectin-B4, or CGRP, which are usually markers of C-fiber afferents. Thus TRPM8 is considered to be **expressed in a subpopulation of thermoceptive and nociceptive afferents that are different from the TRPV1-expressing subpopulation.** In the human lower urinary tract, TRPM8 expression is found in the prostate, the testes, scrotal skin, and bladder (Stein et al, 2004). In addition, although the study by Stein and colleagues showed that expression in the human bladder was limited to the urothelium, Mukerji and colleagues (2006) showed TRPM8 immunoreactivity in the bladder urothelium, as well as in fine nerve fibers in the suburothelial layer, and that the number of TRPM8-positive C-fibers in the bladder suburothelium is increased in patients with idiopathic detrusor overactivity. In animal studies, activation of TRPM8 channels in the guinea pig bladder by intravesical application of menthol reduces volume threshold for micturition and increases sensitivity to bladder cooling (Tsukimi et al, 2005), while a TRPM8 antagonist, ammonium/methyl ammonium transport B (AMTB), decreases bladder contraction frequency without affecting contraction amplitude in cystometry, as well as the visceromotor reflex of abdominal muscle in response to noxious urinary bladder distention in rats (Lashinger et al, 2008). Therefore **TRPM8 in bladder afferent pathways and urothelium could be involved in modulation of sensory function of the lower urinary tract.**

TRPA1 is the only member of the ankyrin TRP channel and a receptor for several pungent chemicals that evoke pain, such as allyl-isothiocyanate (the pungent compound in mustard oil), allicin (garlic), cinnamaldehyde (in cinnamon), and acrolein (a metabolite of cyclophosphamide). TRPA1 also functions as a receptor-operated channel that can be activated by growth factors or proinflammatory peptides such as bradykinin, which increases intracellular Ca^{2+} levels using G protein–coupled receptors. TRPA1 is expressed in sensory neurons, in which it is coexpressed with TRPV1, but not with TRPM8. Although TRPA1 can be activated by

cold (<17° C) by an increase in intracellular Ca^{2+} concentration when expressed in heterologous systems, its role as a cold sensor in native peripheral sensory neurons, including DRG cells, remains uncertain. In mice, cooling does not evoke unspecific rises in Ca^{2+} concentration in DRG neurons, while visceral sensory neurons in nodose ganglia exhibit a strong correlation between cold sensitivity and TRPA1 expression (Fajardo et al, 2008), suggesting that TRPA1 may contribute to cold transduction in visceral sensory neurons rather than somatic neurons (Caspani and Heppenstall, 2009). In the bladder, TRPA1 is expressed in the urothelium, TRPV1 and CGRP-positive suburothelial afferent nerves, and detrusor muscles in mice, rats, and humans (Nagata et al, 2005; Du et al, 2007, 2008; Streng et al, 2008). TRPA1 receptor activation by intravesical application of hydrogen sulfide, allyl isothiocyanate, and cinnamaldehyde induces frequent voiding as evidenced by a reduction in intercontraction intervals, which is suppressed by capsaicin-induced C-fiber desensitization in rats (Du et al, 2007; Streng et al, 2008). In addition, TRPA1 mRNA expression in the bladder mucosa from male patients with lower urinary tract symptoms due to bladder outlet obstruction is significantly increased compared with control subjects (Du et al, 2008). Thus TRPA1 expressed in the bladder urothelium and sensory pathways **may have a role in sensory transduction in pathologic conditions, including overactive bladder.**

In patients with various types of overactive bladder, the ice-water test, in which infusion of ice cold water in the bladder causes reflex detrusor contraction, has been used as a diagnostic tool to detect hyperexcitability of C-fiber bladder afferent pathways (Chancellor and de Groat, 1999). TRPM8 and TRPA1, both of which can be activated by cooling, may be responsible for activation of the bladder cooling reflex in the ice-water test, although the involvement of TRPA1 in cold transduction is still equivocal.

TRPV4

TRPV4 is a member of vanilloid TRPV channels and a nonselective cation channel **activated by mechanical pressure, osmolality (hypotonicity), moderate warmth (>27° C), and chemical stimuli** such as phorbol derivates. Its expression **has been detected in urothelial cells and detrusor muscle**, but not in the suburothelial layer, in the bladder of mice, rats, and guinea pigs (Birder, 2007; Gevaert et al, 2007; Thorneloe et al, 2008; Xu et al, 2009; Yamada et al, 2009). The TRPV4 agonist, 4α-phorbol 12,13-didecanoate, and hypotonic cell swelling promote Ca^{2+} influx and evoke ATP release in cultured urothelial cells from mice (Gevaert et al, 2007) or rats (Birder, 2007). In cultured urothelial cells from TRPV4 knockout mice, the intracellular Ca^{2+} increase and ATP release in response to stretch stimulation were significantly attenuated compared to the wild-type mice (Mochizuki et al, 2009). Cystometric experiments revealed that TRPV4 knockout mice exhibit a lower frequency of voiding contractions, as well as a higher frequency of nonvoiding contractions (Gevaert et al, 2007), and that intravesical application of TRPV4 agonists induces bladder overactivity as evidenced by increased micturition pressure in rats (Birder, 2007) or reduced contraction frequency in mice (Thorneloe et al, 2008). These results suggest that **urothelial TRPV4 channels act as a pressure sensor to enhance bladder activity, predominantly through activation of bladder afferent pathways by urothelially released ATP**.

Botulinum Toxin

In recent years, there has been increasing evidence for the therapeutic efficacy of botulinum neurotoxin (BoNT) for the treatment of various urethral and bladder dysfunctions (Smith and Chancellor, 2004; Apostolidis and Fowler, 2008).

Botulinum toxins act by **inhibiting acetylcholine release at the presynaptic cholinergic nerve terminal, thereby inhibiting striated and smooth muscle contractions**. The toxins are synthesized as single-chain polypeptides with a molecular weight of about 150 kD (DasGupta, 1994). Initially, the parent chain is cleaved into its active dichain polypeptide form, consisting of a heavy chain (approximately 100 kD) connected by a disulfide bond to a light chain (approximately 50 kD) with an associated zinc atom (Schiavo et al, 1992). Four steps are required for toxin-induced paralysis: binding of the toxin heavy chain to an as yet unidentified nerve terminal receptor, internalization of the toxin within the nerve terminal, translocation of the light chain into the cytosol, and inhibition of neurotransmitter release. Neurotransmitter release involves the ATP-dependent transport of the vesicle from the cytosol to the plasma membrane (Barinaga, 1993). Vesicle docking requires the interaction of various cytoplasm, vesicle, and target membrane proteins (i.e., synaptosome-associated membrane receptor [SNARE] proteins), some of which are specifically targeted with clostridial neurotoxins (Fig. 60–29). For example, BoNT-A cleaves the cytosolic translocation protein SNAP-25, thus preventing vesicle fusion with the plasma membrane (Fig. 60–30) (Schiavo et al, 1993).

Seven immunologically distinct neurotoxins are designated types A, B, C, D, E, F, and G. Clinically, the urologic community has used commercial preparations of BTX-A to treat patients with neurogenic and idiopathic detrusor overactivity (Dykstra et al, 1988; Dykstra and Sidi, 1990; Schurch et al, 1996; Petit et al, 1998; Schurch et al, 2000; Apostolidis et al, 2009). **Although acetyl choline (ACh) release from bladder parasympathetic efferent terminals is the primary target of BoNT treatment, suppression of bladder afferent activity with BoNT treatment is also evident** because the reduction of urgency symptom in patients with neurogenic and idiopathic detrusor overactivity is associated with reduced expression of the capsaicin receptor (TRPV1) and the ATP receptor ($P2X_3$) in C-fibers (Apostolidis et al, 2005). In addition, **in basic research, botulinum toxins are shown to suppress not only efferent nerve activity by inhibition of the release of acetylcholine but also afferent nerve activity by release of inhibition of neurotransmitters, such as substance P and CGRP, from sensory terminals** (Chuang et al, 2004; Dressler et al, 2005). There is also evidence that the toxin can reduce the release of ATP from urothelial cells in spinalized rats (Khera et al, 2004; Smith et al, 2005; Smith et al, 2008). Thus the use of the toxins has been expanded to treat women with pelvic floor spasticity, as well as patients with non-neurogenic overactive bladder and even bladder pain syndrome (Smith et al, 2003; Smith and Chancellor, 2004; Smith et al, 2005; Apostolidis and Fowler, 2008). The efficacy of botulinum toxins was also recently identified in patients with benign prostatic hyperplasia, in whom BoNT-A injection into the prostate induced an atrophy of the prostate by inducing apoptosis, inhibiting proliferation, and downregulating α_{1A}-adrenergic receptors (Chuang et al, 2006).

Actions of Drugs on Bladder Smooth Muscle

Two major classes of pharmacologic agents that are used clinically to inhibit spontaneous activity of the bladder are calcium channel

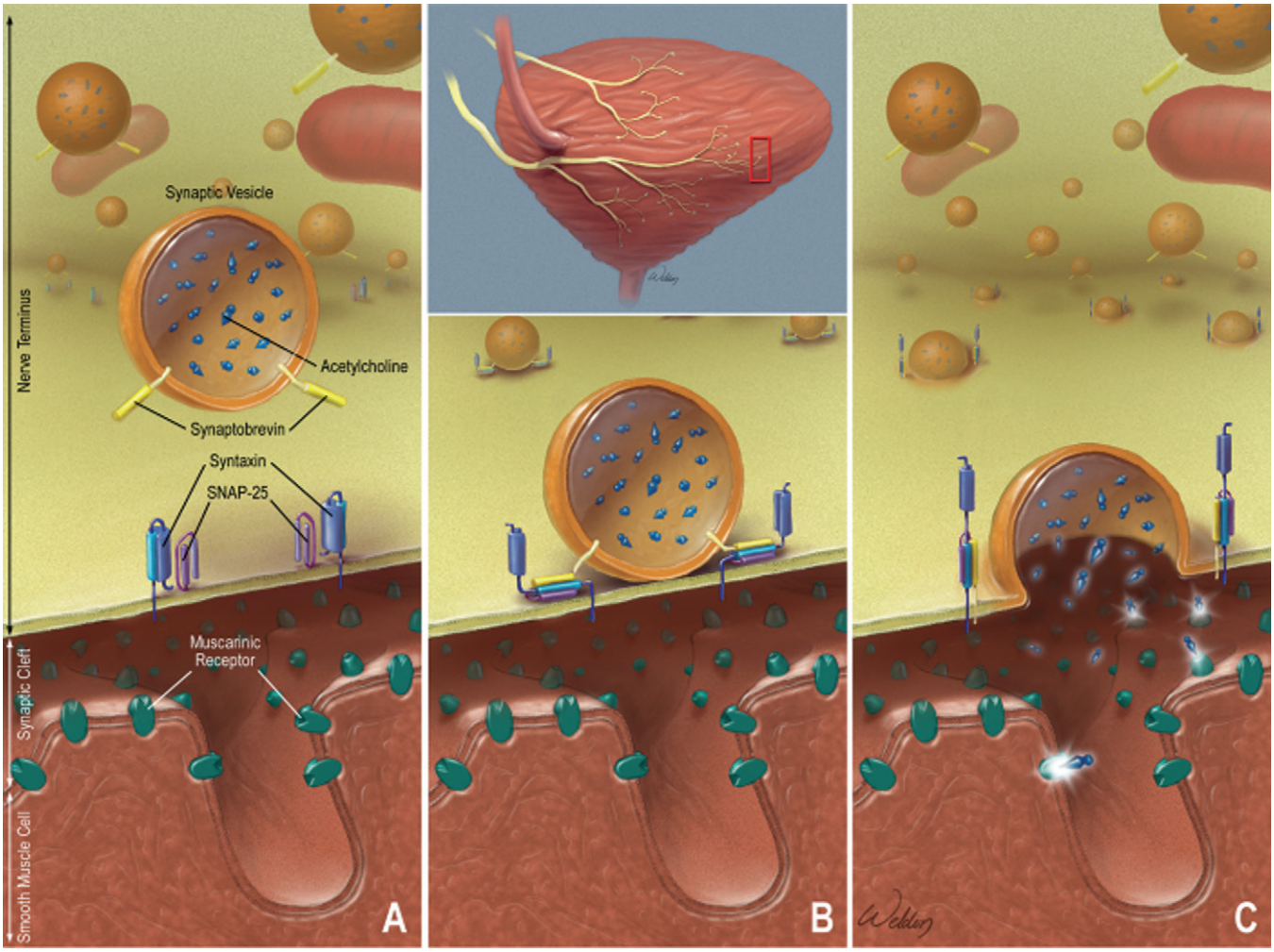


Figure 60–29. Schematic diagram demonstrating normal fusion and release of acetylcholine from nerve terminals through interaction of vesicle and membrane-bound (SNARE) proteins. Parasympathetic nerves innervate the urinary bladder *(inset)* with **(A)** nerve terminal in an unactivated state displaying numerous vesicles containing the neurotransmitter acetylcholine. **B,** After nerve activation, assembly of the SNARE protein complex (e.g., synaptobrevin, SNAP-25, and syntaxin) leads to **(C)** release of acetylcholine and activation of postjunctional muscarinic receptors, resulting in bladder contraction.

blockers, such as diltiazem and verapamil, and potassium channel openers, such as cromakalim and pinacidil (see Table 60–5) (Andersson, 1993, 1997; Andersson et al, 1999). Also, the direct effect of tricyclic antidepressants on the bladder is briefly discussed.

Calcium Channel Blockers

In the bladder smooth muscle, both spontaneous and evoked contractile activities are mediated by membrane depolarization and the movement of calcium into the smooth muscle cell through L-type Ca^{2+} channels (Brading, 1997b; Fry and Wu, 1997; Brading, 2006). In addition, Ca^{2+} channels and nonselective stretch-activated divalent ion channels have been demonstrated in detrusor smooth muscle (Brading, 1997b; Fry and Wu, 1997; Martin et al, 1997). The one thing in common is that **all contractile activity involves the entrance of extracellular calcium. Some forms of contractile responses are mediated by both the entrance of extracellular calcium and the release of intracellular calcium from the sarcoplasmic reticulum** (Levin and Wein, 1995; Zderic et al, 1996; Brading, 1997b; Fry and Wu, 1997; Martin et al, 1997).

The relationship between various forms of contractile response and calcium translocation and release has been the subject of a large number of studies. Inhibition of the entrance of calcium can inhibit spontaneous and evoked contractile activity (Levin et al, 1991). L-type Ca^{2+}-blocking agents, such as nifedipine, can reduce the level and severity of spontaneous myogenic contractile activity, which depends primarily on the entrance of extracellular calcium through L-type Ca^{2+} channels. Ca^{2+} channel blockers are less effective in suppressing nerve-mediated contractions, which are dependent on both the entrance of extracellular calcium and the stimulated release of intracellular calcium from the sarcoplasmic reticulum through IP_3-mediated mechanisms (Levin and Wein, 1995; Zderic et al, 1996; Brading, 1997b; Andersson and Arner, 2004). This leads to the possibility of developing selective Ca^{2+}-channel blocking agents that eliminate spontaneous contractions without affecting micturition contractions.

Potassium Channel Openers

K^+ channel openers, such as cromakalim and pinacidil (see Table 60–5), **stimulate the movement of potassium out of the cell, resulting in membrane hyperpolarization and a**

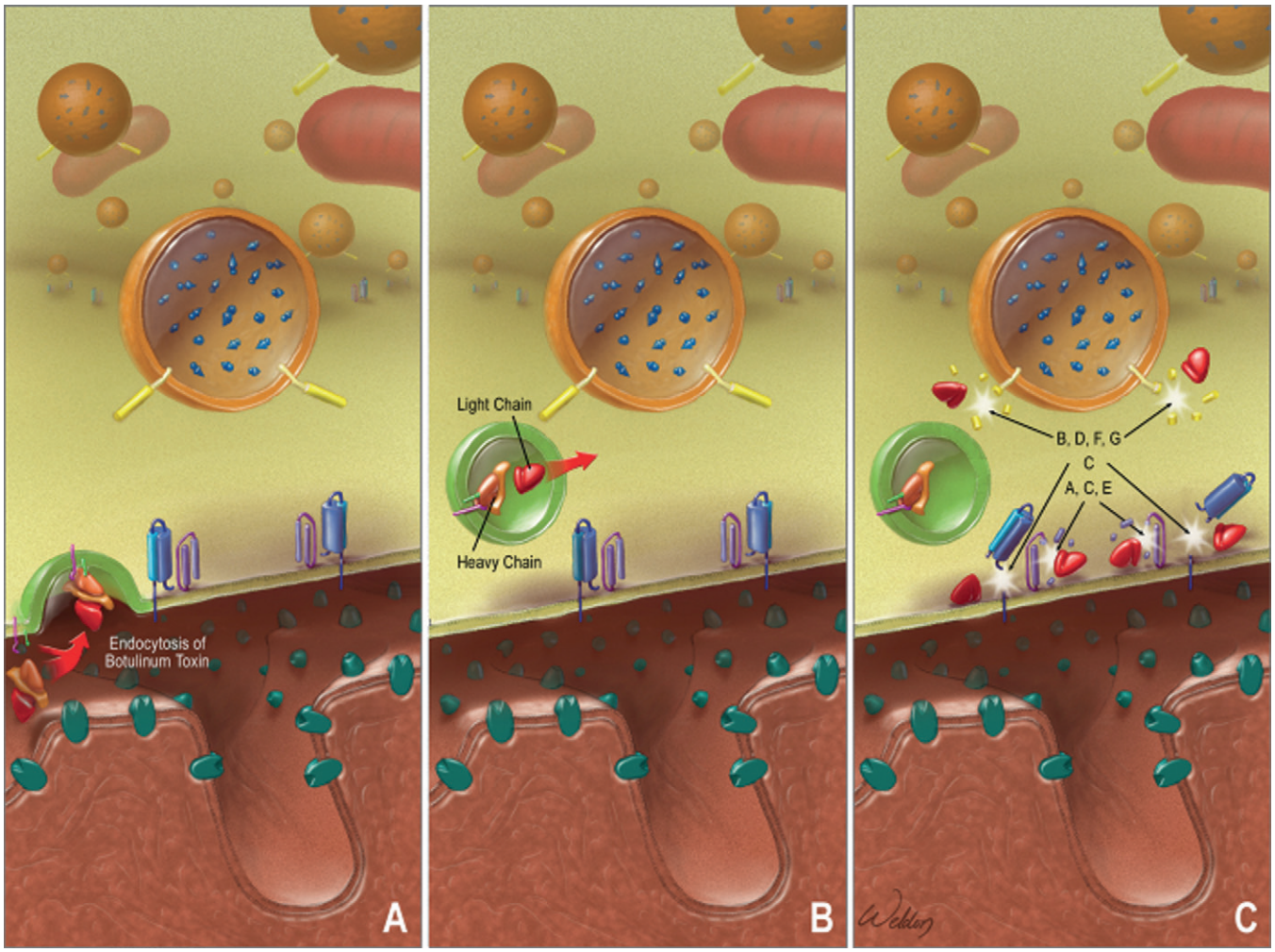


Figure 60–30. Diagram of parasympathetic nerve terminal demonstrating **(A)** binding of the toxin heavy chain to an as yet unidentified receptor and internalization of the toxin within the nerve terminal; **(B)** translocation of the light chain into the cytosol; and **(C)** inhibition of neurotransmitter release by cleavage of specific SNARE proteins. A to G represent different botulinum toxin serotypes.

reduction in spontaneous contractile activity (Andersson, 1993; Andersson, 1997; Andersson et al, 1999). In the detrusor, various types of K^+ channels have been identified, including ATP-sensitive (K_{ATP}), calcium-dependent small conductance (SKCa), and calcium-dependent large conductance (BKCa) channels (Andersson, 1992; Trivedi et al, 1995; Andersson and Arner, 2004; Gopalakrishnan and Shieh, 2004). It is currently still under investigation what the relationship is between each of these K^+ channels and the different forms of contractile activity (myogenic contractions, neurogenic contractions, and micturition contractions). However, **it is apparent that pharmacologic manipulation of both Ca^{2+} and K^+ channels can result in reduced spontaneous contractile activity** (Levin et al, 1991; Andersson, 1992; Trivedi et al, 1995; Brading, 1997b; Fry and Wu, 1997; Martin et al, 1997; Andersson and Arner, 2004). It has been documented that **intravesical instillation of the bladder-selective K_{ATP} channel opener ZD6169 significantly reduced detrusor overactivity in bladder outlet–obstructed rats** (Pandita and Andersson, 1999). **The mechanisms of action may be both direct smooth muscle action and action on the afferent nerve endings near the urothelium** (Hu and Kim, 1997; de Groat et al, 1999). Another K_{ATP} channel opener ZD0947 caused detrusor muscle relaxation through activation of glibenclamide-sensitive K_{ATP} channels in human and guinea pig urinary bladders (Aishima et al, 2006; Yunoki et al, 2008). Moreover, mice with the gene deletion of *mSlo1* for the pore-forming subunit of the BKCa channel exhibit increased urinary bladder spontaneous and nerve-evoked contractions, as well as a marked elevation in urination frequency (Meredith et al, 2004). It has also been demonstrated that local injection of *hSlo* cDNA into the bladder lumen to increase BKCa channel activity eliminated detrusor overactivity in rats with bladder outlet obstruction (Christ et al, 2001), suggesting an important role of BKCa channels in urinary bladder function and overactive bladder. Thus **there is considerable interest in the development of specific K^+ channel openers for therapeutic use in the treatment of bladder overactivity** (Pandita and Andersson, 1999; Andersson and Arner, 2004).

Tricyclic Antidepressants

Tricyclic antidepressants, such as imipramine and amitriptyline, have been shown to be clinically effective in reducing the level of detrusor overactivity under specific conditions (Wein, 1998). Their effectiveness has been linked to antimuscarinic activity, inhibition of calcium translocation, and direct smooth muscle relaxant properties, and possibly to an action on the central nervous system (Maggi et al, 1989). Each of these actions would relax the bladder and reduce the level of spontaneous activity. Because these are

nonselective agents with multiple mechanisms of action, there is little research in the development of more bladder-selective tricyclic agents.

Spinal Ascending and Descending Pathways

It is possible to conjecture about the sites of action of drugs in the spinal cord on the basis of certain experimental designs. For example, alterations in the volume threshold for inducing micturition (in the absence of other changes of bladder activity) are interpreted as indicating an effect on the ascending limb of the micturition reflex. Alterations in the magnitude of bladder contractions (or pelvic nerve discharge) produced by PMC stimulation (Matsumoto et al, 1995b) may be taken to indicate an action on the descending limb of the micturition reflex.

Glutamatergic Mechanisms

Intrathecal or intravenous administration of glutamatergic NMDA or α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) antagonists in urethane-anesthetized rats depressed reflex bladder contractions and electromyographic activity of the external urethral sphincter in animals with an intact spinal cord, as well as in animals with chronic spinal injury (Yoshiyama et al, 1994, 1997). These results indicate that **spinal reflex pathways controlling bladder and sphincter functions use NMDA and AMPA glutamatergic transmitter mechanisms**. In spinal cord–injured rats, external sphincter muscle activity was more sensitive than bladder reflexes to glutamatergic antagonists, raising the possibility that the two reflex pathways might have different glutamatergic receptors (Yoshiyama et al, 1994). This was confirmed with in-situ hybridization techniques, which revealed that sacral parasympathetic preganglionic neurons in the rat express high mRNA levels of GluR-A and GluR-B AMPA receptor subunits and NR1, but not NR2 NMDA receptor subunits (Shibata et al, 1999). Conversely, motoneurons in the urethral sphincter nucleus express all four AMPA receptor subunits (GluR-A, GluR-B, GluR-C, and GluR-D) in conjunction with moderate amounts of NR2A and NR2B, as well as high levels of NR1 receptor subunits. It seems likely that this difference in expression accounts for the different sensitivity of bladder and sphincter reflexes to glutamatergic antagonists. In addition, intrathecal application of an mGluR agonist inhibits isovolumetric bladder contractions (Tanaka et al, 2003), although intrathecal application of an mGluR antagonist has no effects on bladder activity in rats (Yoshiyama and de Groat, 2007), suggesting that spinal mGluR are not tonically active, but can inhibit the micturition reflex when stimulated.

Glutamate also plays a role as an excitatory transmitter in the afferent limb of the micturition reflex. The c-*FOS* expression induced in spinal interneurons by activation of bladder afferents is suppressed by the administration of both NMDA and non-NMDA glutamatergic receptor antagonists (Birder and de Groat, 1992; Kakizaki et al, 1996).

Inhibitory Amino Acids

Intrathecal injection of either $GABA_A$ or $GABA_B$ agonists increases bladder capacity and decreases voiding pressure and efficiency in rats (Igawa et al, 1993). **Glycine and GABA inhibitory mechanisms have also been identified in the neonatal rat spinal cord** in local interneuronal inhibitory pathways projecting directly to the preganglionic neurons (Araki, 1994). Clinical studies have revealed that intrathecal administration of a $GABA_B$ receptor agonist (baclofen) increased the volume threshold for inducing the micturition reflex (Bushman et al, 1993). Intrathecally administered baclofen also produced a phaclofen-sensitive inhibition of distention-evoked micturition in conscious rats that appears to be resistant to capsaicin (substance P depletion) or parachlorophenylalanine (5-HT depletion) pretreatment. Because baclofen also inhibits field stimulation–evoked release of CGRP from primary afferent terminals in dorsal horn slices, one possible site for this action is suppression of transmitter release from primary afferent terminals in the spinal cord. In addition, studies by Miyazato and colleagues (2003, 2005) have revealed that the level of glycine in the spinal cord is decreased by approximately 50% in rats with detrusor overactivity induced by chronic spinal cord injury compared with spinal intact rats, and that dietary supplement with glycine can restore bladder function, along with an increase in the serum level of glycine in spinal cord–injured rats. The level of glutamic acid decarboxylase, a GABA synthesis enzyme, is also reduced in lumbosacral DRG and the spinal cord in spinal cord–injured rats, and intrathecal application of $GABA_A$ or $GABA_B$ receptor agonists suppresses detrusor overactivity and sphincter-detrusor dyssynergia (Miyazato et al, 2008). These results suggest that downregulation of the spinal glycinergic and GABAergic mechanisms may contribute to the emergence of neurogenic detrusor overactivity associated with spinal cord injury.

Adrenergic Mechanisms

In the spinal cord, α adrenoceptors can mediate excitatory and inhibitory influences on the lower urinary tract. In anesthetized cats, α_1 adrenoceptors were implicated in a bulbospinal noradrenergic excitatory pathway from the locus ceruleus to the sacral parasympathetic outflow to bladder (Yoshimura et al, 1988, 1990), although subsequent studies could not confirm these findings in conscious cats (Espey et al, 1992).

Experiments in conscious or anesthetized rats (Ishizuka et al, 1996; de Groat et al, 1999) revealed that intrathecal administration of an α_1-adrenergic antagonist (doxazosin) decreased the amplitude of bladder contractions (Ishizuka et al, 1996, 1997). The bladder inhibitory effect of the intrathecal α_1-adrenergic antagonist was more prominent in animals with chronic outlet obstruction (Ishizuka et al, 1996). Also, intrathecal administration of doxazosin suppressed detrusor overactivity (unstable bladder contractions) in spontaneously hypertensive rats (Persson et al, 1997). Although intrathecal injection of doxazosin suppressed the amplitude of reflex bladder contractions in anesthetized rats, it increased the frequency of isovolumetric contractions, indicating the presence of a tonic adrenergic inhibitory mechanism (de Groat et al, 1999). This was supported by the finding that phenylephrine, an α_1-adrenergic agonist, applied intrathecally, decreased the frequency of bladder contractions without changing contraction amplitude (de Groat et al, 1999). Thus it appears that **efferent and afferent limbs of the micturition reflex receive excitatory and inhibitory input, respectively, from spinal noradrenergic systems.**

Evidence for a modulatory role of α_2 adrenoceptors in micturition is conflicting because both facilitatory and inhibitory roles of α_2 adrenoceptors have been documented (Ishizuka et al, 1996; de Groat et al, 1999). Atipamezole, an α_2-adrenergic antagonist given intrathecally, can increase micturition pressure in the conscious rat, implying that there is a tonic inhibitory adrenergic control (Ishizuka et al, 1996). However, yohimbine, an α_2-adrenergic

antagonist, inhibits micturition in rats anesthetized with chloralose-urethane (Kontani et al, 1992). In paraplegic patients, intrathecal injection of clonidine suppressed detrusor overactivity (Denys et al, 1998). Conversely, in conscious spinal cats, clonidine, an α_2-adrenergic agonist, increased bladder pressures and facilitated voiding (Galeano et al, 1986).

Pharmacologic experiments showed that the bladder-sympathetic reflex pathway is modulated by central noradrenergic mechanisms (Danuser and Thor, 1995; de Groat et al, 1999; de Groat and Yoshimura, 2001). In the chloralose-anesthetized cat, prazosin or doxazosin, α_1- adrenoceptor antagonists, suppressed spontaneous firing (Ramage and Wyllie, 1995) or the reflex discharge recorded on the hypogastric nerve in response to pelvic nerve afferent stimulation (Danuser and Thor, 1995). Administration of α_2-adrenergic agonists also suppresses reflex sympathetic activity (Danuser and Thor, 1995). These observations suggest that bulbospinal noradrenergic pathways provide a tonic α_1-excitatory control of the bladder-sympathetic reflex in the spinal cord. α_2-Adrenergic inhibitory mechanisms are not active under control conditions in anesthetized animals but can be upregulated by elevating endogenous norepinephrine levels with an inhibitor (tomoxetine) of norepinephrine reuptake (Danuser and Thor, 1995). These results suggest that the lumbar sympathetic outflow is controlled by α_1-excitatory and α_2-inhibitory mechanisms.

The activation of urethral sphincter motoneurons by stimulation of bladder (pelvic nerve) or urethral or perineal (pudendal nerve) afferents is part of a continence-maintaining mechanism. These reflexes, recorded as efferent discharges on the pudendal nerve in chloralose-anesthetized cats, were suppressed by the α_1-adrenoceptor antagonist prazosin (Gajewski et al, 1984; Danuser and Thor, 1995; Downie, 1999), but not by the α_2 blocker idazoxan (Danuser and Thor, 1995). Conversely, clonidine, an α_2-adrenoceptor agonist, suppressed the reflex in anesthetized cats (Downie and Bialik, 1988). The norepinephrine uptake blocker tomoxetine produced a slight inhibition alone and only a slightly greater inhibition after prazosin. However, it greatly facilitated the reflex when given after idazoxan (Danuser et al, 1995). These data indicate the existence of α_2 adrenoceptor–mediated inhibition and α_1 adrenoceptor–mediated tonic facilitation of sphincter function, and that the α_2 adrenoceptor–dependent inhibitory mechanism is the dominant adrenergic modulator of the pudendal nerve reflex (Thor and Donatucci, 2004). These excitatory α_1 and inhibitory α_2 adrenoceptor–mediated modulations of external sphincter function are also involved in the urethral continence reflexes during passive intravesical pressure rises and sneezing. Nisoxetine, a norepinephrine uptake blocker, induces an increase in pressure responses at the middle urethra measured by a microtransducer-tipped catheter during sneezing, which is antagonized by prazosin, an α_1 adrenoceptor antagonist, in normal rats and rats with simulated birth trauma induced by vaginal distention (Kaiho et al, 2007). On the contrary, external urethral sphincter–electromyographic (EUS-EMG) activity that increased during lower abdominal wall compression was reduced by medetomidine, an α_2-adrenoceptor antagonist, in rats (Furuta et al, 2009).

Serotonergic Mechanisms

Neurons containing 5-HT in the raphe nucleus of the caudal brainstem send projections to the dorsal horn, as well as to the autonomic and sphincter motor nuclei in the lumbosacral spinal cord. In cats, activation of raphe neurons or 5-HT receptors in the spinal cord inhibits reflex bladder contractions and firing of the sacral efferent pathways to the bladder (McMahon and Spillane, 1982; Chen et al, 1993; de Groat et al, 1993a; de Groat, 2002) and also inhibits firing of spinal dorsal horn neurons elicited by stimulation of pelvic nerve afferents (Fukuda and Koga, 1991). In rats, administration of 5-HT_{2C} receptors agonists, such as *m*-chlorophenylpiperazine, Ro 60-0175, and WAY 161503, suppresses efferent activity on bladder nerves and/or the micturition reflex (Steers and de Groat, 1989; Mbaki and Ramage, 2008). These effects are blocked by mesulergine, a 5-HT_2 receptor antagonist (Steers and de Groat, 1989; Guarneri et al, 1996), or by SB 242084, a 5-HT_{2C} antagonist (Mbaki and Ramage, 2008). Intrathecal administration of methysergide, a 5-$HT_{1/2}$ antagonist, or zatosetron, a 5-HT_3 antagonist, decreases the micturition volume threshold in cats (Espey et al, 1998), implying that **descending serotonergic pathways tonically depress the afferent limb of the micturition reflex.**

8-OH-DPAT, a 5-HT_{1A} agonist, administered intrathecally, facilitated bladder activity in both normal and spinal cord–injured rats but not in rats in which bladder afferents were damaged by treatment with capsaicin at birth (Lecci et al, 1992). Conversely, administration of the 5-HT_{1A} receptor antagonist WAY 100635, which increases the firing rate of raphe neurons by blocking 5-HT_{1A} inhibitory autoreceptors, inhibits reflex bladder contractions (Testa et al, 1999). The inhibition is antagonized by pretreatment with mesulergine, a 5-HT_2 receptor antagonist, indicating that 5-HT_2 receptors are involved in descending raphe and spinal inhibitory mechanisms (Testa et al, 1999). When the effects of intrathecal administration of WAY 100635 on the ascending and descending limbs of the micturition reflex pathway were examined in anesthetized rats, WAY 100635 depressed bladder contractions evoked by electrical stimulation of the PMC but did not alter the evoked field potentials in the region during electrical stimulation of afferent axons in the pelvic nerve, indicating that the drug suppresses the pathway from the brainstem to the spinal cord but does not alter the afferent pathway from the bladder to the PMC (Kakizaki et al, 2001; de Groat, 2002). However, in contrast to 5-HT_{1A} receptor-mediated facilitatory effects on bladder activity in rats, 5-HT_{1A} receptor activation exerts inhibitory effects in cats, especially when C-fiber afferent function is unregulated because 8-OH-DPAT induces dose-dependent increases in threshold volume and bladder capacity in cats with acetic acid–induced cystitis (Thor et al, 2002) or spinal cord injury (Gu et al, 2004; Gu et al, 2007). Thus micturition in the rat is facilitated by stimulation of 5HT_{1A} inhibitory autoreceptors, whereas in the cat 5HT_{1A} receptor activation appears to act primarily through postsynaptic mechanisms to suppress bladder activity.

The sympathetic autonomic nuclei, as well as the sphincter motor nuclei, also receive a serotonergic input from the raphe nucleus (de Groat et al, 1979; Downie, 1999; Thor and Donatucci, 2004). Serotonergic activity mediated by 5-HT_2 and 5-HT_3 receptors enhances urine storage by facilitating sphincter reflexes in acts and rats (Danuser and Thor, 1996; Espey et al, 1998; Mbaki and Ramage, 2008). The role of 5-HT_{1A} receptors in the control of EUS activity may be different depending on animal species or experimental conditions. Activation of 5-HT_{1A} receptors with 8-OH-DPAT increased external sphincter activity during stimulation of the pelvic nerve in normal and spinalized rats, and this effect was reversed by WAY-100635 (Chang et al, 2006, 2007). In cats, both 8-OH-DPAT and 5-methoxy-*N,N*-dimethyltryptamine (5-MeODMT), 5-HT_{1A} receptor agonists, cause dose-dependent decreases in bladder activity and increases in EUS-EMG activity especially when acetic acid was infused into the bladder to induce bladder irritation (Thor et al, 2002). However, another study in

urethane-anesthetized chronic spinal cord injured rats has shown that 8-OH-DPAT induces periodic external urethral sphincter relaxation during voiding, suggesting the 5-HT_{1A}-mediated suppression of sphincter activity (Dolber et al, 2007).

Duloxetine, a combined norepinephrine and 5-HT reuptake inhibitor (Sharma et al, 2000), **has been shown, in a bladder-irritated model, to increase the neural activity of both the urethral sphincter and the bladder** (Thor and Katofiasc, 1995; Thor and Donatucci, 2004). Duloxetine appears to have effects on both the bladder and the sphincter and has been proposed for treatment of both stress incontinence and urgency incontinence (Cannon et al, 2003; Thor and Donatucci, 2004). Duloxetine increases the neural activity to the external urethral sphincter and decreases bladder activity through effects on the central nervous system in cats (Thor and Donatucci, 2004). In a rat study, duloxetine also enhances the urethral continence reflex during sneezing as evidenced by an increase in sneeze-induced pressure responses at the middle urethra, although the effect appears to be mainly mediated by α_1 adrenoceptors (Miyazato et al, 2008). Clinical trials have also shown the efficacy of duloxetine for the treatment of stress urinary incontinence; the drug has been approved in Europe and is already available in several countries (Castro-Diaz and Amoros, 2005), although it has been withdrawn from the Food and Drug Administration approval process in the United States by the manufacturer.

Opioid Peptides

Opioid peptides have an inhibitory action on reflex pathways in the spinal cord. In the cat spinal cord, inhibition of reflex bladder activity is mediated by δ receptors, whereas inhibition of sphincter activity is mediated by κ receptors (de Groat et al, 1993a; Yoshimura and de Groat, 1997; de Groat and Yoshimura, 2001; Gu et al, 2004). In the rat, both μ and δ receptors mediate bladder inhibition (Dray and Metsch, 1984b). Enkephalin gene transfer to bladder afferent pathways using herpes simplex virus vectors reduces pain behavior and bladder overactivity induced by capsaicin injection into the bladder by activation of spinal opioid receptors in rats (Yokoyama et al, 2008).

Purinergic Mechanisms

Adenosine A_1 (and perhaps A_2) receptor activation by intrathecal agonist administration has produced a caffeine-sensitive increase in volume threshold in conscious rats. Based on the known distribution of adenosine receptors in the spinal cord, excitatory interneurons are the presumed site of inhibitory action of adenosine A_1 agonist (Sosnowski et al, 1989).

Key Points: Spinal Circuitry Neurotransmitters

- Glutamate plays an important role in the spinal efferent circuitry supporting micturition.
- The spinal noradrenergic system, mediated by α_1 adrenoceptors, has a modulatory role in controlling micturition by inhibiting afferent inputs from the bladder and facilitating the descending limb of the spinal micturition reflex to increase bladder contractility.
- Transmitters such as 5-HT, purines, glycine, and GABA appear to selectively modulate the volume threshold by actions in the sacral spinal cord.
- These mechanisms seem to be favorable for development of novel drug therapies.

Pontine Micturition Center and Supraspinal Mechanisms

Glutamatergic Mechanisms

Glutamic acid also has a role in excitatory transmission at supraspinal sites in the micturition reflex pathway (See Fig. 60–31 on the Expert Consult website). Exogenous L-glutamate, or its analog, were injected at sites (locus ceruleus or parabrachial nucleus) in the brainstem of supracollicular decerebrate cats, where electrical stimulation–evoked bladder contractions elicited voiding or increased frequency and amplitude of rhythmic bladder contractions (Kruse et al, 1990; Mallory et al, 1991).

Administration of glutamatergic agonists into the region of the PMC in cats and rats elicits voiding or increases frequency and amplitude of bladder contractions (Mallory et al, 1991; de Groat et al, 1999), whereas injection of agonists at other brainstem nuclei known to have inhibitory functions in micturition elicits inhibitory effects (Chen et al, 1993). Intracerebroventricular injection of AMPA or NMDA receptor antagonists blocks reflex bladder contractions in anesthetized rats, indicating that glutamatergic transmission in the brain is essential for voiding function (Yoshiyama and De Groat, 1996; Yoshiyama and de Groat, 2005). Similarly, Yokoyama and colleagues (1999) have shown that glutamate plays an important role, especially through NMDA receptors, in the rat middle cerebral artery occlusion model of detrusor overactivity.

Cholinergic Mechanisms

Excitatory and inhibitory cholinergic influences on the micturition pathway have been identified at the supraspinal level. A decreased volume threshold and increased micturition pressure were detected after administration of bethanechol, a muscarinic agonist, into the central circulation of the cross-perfused dog (O'Donnell, 1990). One site of action can be localized to the midbrain-pons region, because cholinergic agonists are effective after supracollicular decerebration in rats (Sillen et al, 1982). In the rat brain, muscarinic receptor–mediated cholinergic mechanisms may be involved in both inhibitory and facilitatory modulation of the micturition reflex (Ishiura et al, 2001; Yokoyama et al, 2001; Ishizuka et al, 2002), and the muscarinic inhibitory mechanism seems to involve an activation of M_1 muscarinic receptors (Yokoyama et al, 2001; Masuda et al, 2009) and protein kinase C (Nakamura et al, 2003). In the brainstem, microinjection of acetylcholine to the PMC in cats increased or decreased the threshold volume for inducing a reflex contraction of the bladder (Sugaya et al, 1987; Yoshimura and de Groat, 1997). These effects were blocked by atropine, indicating a role for muscarinic receptors. Nicotinic receptors are also involved in the control of voiding function because a nicotinic receptor agonist, epibatidine, injected into the lateral ventricle suppressed the micturition reflex in the rat (Lee et al, 2003).

GABAergic Mechanisms

GABA has been implicated as an inhibitory transmitter at supraspinal sites where it can act on both $GABA_A$ and $GABA_B$ receptors (de Groat and Booth, 1993; Yoshimura and de Groat, 1997; de Groat et al, 1999; Kanie et al, 2000; de Groat and Yoshimura, 2001). Injection of GABA or muscimol, a $GABA_A$ receptor agonist, into the PMC of decerebrate cats suppressed reflex bladder activity and increased the volume threshold for inducing micturition (Mallory et al, 1991). These effects were reversed by

bicuculline, a $GABA_A$ receptor antagonist. Because bicuculline alone stimulated bladder activity and lowered the volume threshold for micturition, the micturition reflex pathway in the PMC must be tonically inhibited by a GABAergic mechanism. Intracerebroventricular baclofen, a $GABA_B$ agonist, suppressed distention-evoked micturition in urethane-anesthetized rats, but the effect was not blocked by phaclofen, a $GABA_B$ receptor antagonist (de Groat and Yoshimura, 2001; de Groat et al, 1993a).

Dopaminergic Mechanisms

In the central nervous system, dopaminergic pathways exert inhibitory and facilitatory effects, respectively, on the micturition reflex through D_1-like (D_1 or D_5 subtype) and D_2-like (D_2, D_3, or D_4 subtype) dopaminergic receptors (Albanese et al, 1988; Kontani et al, 1990; Yoshimura et al, 1992; Yoshimura et al, 1993, 1998, 2003; Yokoyama et al, 1999; Seki et al, 2001; Hashimoto et al, 2003) (see Fig. 60–31 on the Expert Consult website). In anesthetized cats, activation of dopaminergic neurons in the substantia nigra inhibits reflex bladder contractions through D_1-like receptors (Yoshimura et al, 1992). A study also revealed that a D_1 dopaminergic antagonist (SCH 23390) facilitated the micturition reflex, whereas a D_1 agonist (SKF 38393) had no effect on the reflex bladder contractions in awake rats, suggesting that D_1 receptor–mediated suppression of bladder activity is tonically active in the normal awake state (Seki et al, 2001). Disruption of this tonic dopaminergic inhibition by destroying the nigrostriatal pathway with the neurotoxin methyphenyltetrahydropyridine (MPTP) produces Parkinson-like motor symptoms in monkeys accompanied by detrusor overactivity (Albanese et al, 1988), as reported in patients with Parkinson disease (Albanese et al, 1988; Yoshimura et al, 1993; Steers et al, 1996). Similarly, a rat model of Parkinson disease induced by a unilateral 6-hydroxydopamine lesion of the nigrostriatal pathway also exhibits detrusor overactivity. In these parkinsonian animals, detrusor overactivity was suppressed by stimulation of D_1-like receptors with SKF 38393 or pergolide (Yoshimura et al, 1993, 1998, 2003).

Conversely, activation of central D_2-like dopaminergic receptors with quinpirole or bromocriptine facilitates the micturition reflex pathway in rats, cats, and monkeys (Kontani et al, 1990; Yoshimura et al, 1993, 1998, 2003; Yokoyama et al, 1999). D_2-like receptor-mediated facilitation of the micturition reflex may involve actions on brainstem because microinjection of dopamine to the PMC reduced bladder capacity and facilitated the micturition reflex in cats (de Groat et al, 1993a) D_2-like receptors are also involved in detrusor overactivity induced by middle cerebral artery occlusion in rats (Yokoyama et al, 1999). Thus **central dopaminergic pathways exhibit different effects on micturition through actions on multiple receptors at different sites in the brain.**

It is also known in cats that neurons in the substantia nigra pars compacta and the ventral tegmental area, which are the major dopamine-containing nuclei in the midbrain, respond to the storage/micturition cycles of isovolumetric cystometry (Sakakibara et al, 2002), and that the dopamine level in the striatum, where nigrostriatal dopaminergic nerves terminals are found, is shown to increase during the urine storage phase (Yamamoto et al, 2005). For the control of urethral function, activation of D_2-like receptors at a supraspinal site suppresses the activity of the striated sphincter muscle to reduce urethral pressure. Inhibition of dopamine D_1- or D_2-like receptors has a minimal effect on urethral function in anesthetized rats, suggesting the dopaminergic control of urethral function is minimally active in the normal condition (Ogawa et al, 2006).

Opioid Peptides

Intracerebroventricularly administered morphine suppressed isovolumic bladder contractions, and this effect was blocked by naloxone (Dray and Metsch 1984a). Naloxone administered intracerebroventricularly also reversed the effects of systemically administered morphine. **Naloxone administered alone intracerebroventricularly or injected directly into the PMC facilitates the micturition reflex** (Hisamitsu and de Groat, 1984). Both μ and δ opioid receptors mediate inhibitory effects that are blocked by naloxone (Hisamitsu and de Groat, 1984; Mallory et al, 1991; Downie, 1999). In a recent study, activation of μ and δ_1, but not δ_2, opioid receptors in the brain increases bladder capacity in both normal rats and rats with cerebral infarction that exhibit frequent voiding; however, κ receptor activation increases bladder capacity only in cerebral infarct rats (Nagasaka et al, 2007).

Key Points: Supraspinal Circuitry Neurotransmitters

- Glutamate appears to be involved as an excitatory transmitter in the supraspinal circuitry controlling micturition.
- Glutamate may also be a mediator of detrusor overactivity after neural injury.
- Transmitters such as 5-HT, purines, glycine, and GABA appear to selectively modulate the volume threshold by actions in the sacral spinal cord. The role of other potential excitatory transmitters remains to be examined.
- Several substances can exert significant modulatory influences on the supraspinal circuits (see Fig. 60–31 on the Expert Consult website) and can have dramatic influences on micturition.
- The receptors for these substances represent potential sites for therapeutic intervention.

MECHANISMS OF DETRUSOR OVERACTIVITY

A variety of models have been used to explore the pathogenesis of detrusor overactivity and to formulate treatments for overactive bladder and urgency incontinence. Models for detrusor overactivity in several species have been developed that are relevant to spinal cord injury, obstruction, denervation, Parkinson disease, interstitial cystitis, diabetes, multiple sclerosis, and aging (de Groat et al, 1993a; Dupont et al, 1994). In addition, the spontaneously hypertensive rat has provided a useful genetic model for detrusor overactivity (Steers et al, 1999). A common feature of many of these models is that changes in smooth muscle function can elicit long-term changes in nerves. Investigators are accustomed to examining short-term effects. However, there is now a greater appreciation that long-term events involving growth factors lead to plasticity in neural pathways with implications for disorders of micturition.

Neurotransmitters, prostaglandins, and neurotrophic factors, such as nerve growth factor (NGF), are substances that provide mechanisms for communication between muscle and nerve. Disturbances in these mechanisms can cause detrusor overactivity by alterations in autonomic reflex pathways. This detrusor overactivity can, in turn, lead to urgency incontinence. Cystometry and

urinary frequency are commonly used to define detrusor overactivity and can be used to monitor responses to drugs or other therapies. A multidisciplinary approach incorporating biochemical, molecular, pharmacologic, physiologic, and behavioral methods can provide insight into the pathogenesis of detrusor overactivity. In addition, recent advances in constructing mutant mice lacking specific genes provide a useful tool to study the contribution of specific molecules to the lower urinary tract function or the emergence of detrusor overactivity. For example, bladder function has been investigated in knockout mice lacking muscarinic receptors (M_1 to M_5) (Matsui et al, 2002; Igawa et al, 2004), purinergic receptors ($P2X_2$, $P2X_3$) (Cockayne et al, 2000, 2005), TRPV1 (Birder et al, 2002), *hSlo* for BKCa channels (Meredith et al, 2004), serotonin reuptake transporter (Cornelissen et al, 2005), or TRP channels (Birder et al, 2002; Mochizuki et al, 2009).

Please see the Expert Consult website for additional discussion of **Spinal Cord Injury and Neurogenic Detrusor Activity, Bladder Outlet Obstruction, Inflammation, Aging, and Neurogenic Mechanisms Underlying Detrusor Activity, as well as Figures 60–31 and 60–32.**

SUMMARY

This chapter began with the premise that the lower urinary tract has two main functions: storage and periodic elimination of urine. These functions are regulated by the unique biomechanics of bladder and urethral muscles, as well as by a complex neural control system located in the brain and spinal cord. The neural control system performs like a simple switching circuit to maintain a reciprocal relationship between the reservoir (urinary bladder) and the outlet components (urethra and urethral sphincter) of the urinary tract. The switching circuit is modulated by various neurotransmitters and is sensitive to a variety of drugs. In infants, the switching circuits function in a purely reflex manner to produce involuntary voiding; however, in adults urine storage and release are subject to voluntary control (see Fig. 60–1).

Injuries or diseases of the nervous system in adults can disrupt the voluntary control of micturition, causing the reemergence of reflex micturition, resulting in detrusor overactivity and incontinence. Because of the complexity of the central nervous control of the lower urinary tract, incontinence can result from a variety of neurologic disorders. Experimental studies indicate that detrusor overactivity occurs after a wide range of neurologic diseases, including interruption of cortical inhibitory circuits, disruption of basal ganglia function in models of Parkinson disease, damage to pathways from the brain to the spinal cord (multiple sclerosis, spinal cord injury), and sensitization of bladder afferents. Various mechanisms contribute to the emergence of bladder dysfunction, including reorganization of synaptic connections in the spinal cord, changes in the expression of neurotransmitters and receptors, alterations in neural target organ interactions mediated by neurotrophic factors, and changes in smooth muscle function. **An understanding of the physiologic events mediating micturition and continence provides a rational basis for the management of lower urinary tract dysfunction.**

FUTURE RESEARCH

During the past few years, research in neurourology and female urology has led to the development of new concepts regarding the etiology of unstable bladder dysfunction and urinary incontinence. The breakthroughs outlined in this chapter have stimulated the development of new therapeutic approaches for incontinence, including the local administration of botulinum toxin and afferent neurotoxins, such as capsaicin and RTX. What are the research priorities for the future? It will be important to focus on the development of neuropharmacologic agents that can suppress the unique components of abnormal bladder reflex mechanisms and thereby act selectively to diminish symptoms without altering normal voiding function.

Neurourologic research with a clinical application is intensifying at major medical centers and also in the pharmaceutical industry. With the aging population across all the developed nations and public education that is demystifying the stigma of bladder control problems and urinary incontinence, more patients are seeking help. The dramatically expanding commercial markets and need for improved medications for the lower urinary tract have been recognized and publicized. We need better drugs and approaches to help the 85% of people with detrusor overactivity and urinary incontinence who have not yet sought medical help.

To end this chapter, we would like to look into our crystal ball and speculate about a few areas of research that we think may pay off within the next 5 years with new and better treatments of urinary incontinence.

1. NGF has been implicated as one of the key factors inducing bladder overactivity and pain conditions. Can the tissue or urinary level of NGF be a biomarker for the diagnosis and/or evaluation of therapeutic efficacy of bladder dysfunction?
2. Can the drug companies develop a truly bladder-specific and effective anticholinergic drug with *no* dry mouth? β_3-Agonists are currently in phase 3 studies internationally.
3. Tachykinin or TRP channel antagonists are appealing, because they may be effective for unstable and painful bladder conditions without increasing residual urine volumes. Can clinically useful and safe oral antagonists be developed?
4. We need an effective drug for stress incontinence, such as one based on urethral smooth muscle– or skeletal muscle–specific agonists/antagonists or norepinephrine/5-HT reuptake inhibitors.
5. Although not as clinically obvious as the ideas just listed, we believe that drugs that can affect urothelial trafficking and permeability may be tremendously helpful. These types of drugs not only can aid the overactive and painful bladder but may have indications for bladder cancer and even urinary tract infection.
6. In addition, given that spontaneous activity in the detrusor muscle and interstitial cells in the urothelium and bladder wall has an important role in the regulation of bladder activity, targeting detrusor muscles or interstitial cells could be effective for treating detrusor overactivity, especially that of myogenic origin.

Beyond the horizon of near-term advances, we predict a brave new paradigm in neurourology. What has already started is the evolution of unstoppable forces of change in medicine that include pharmacogenomics, tissue engineering, and gene therapy. These will change how we practice urology.

Drug by Design (Pharmacogenomics). Medicine will be tailored to the genetic makeup of each individual. Through microarray gene chip technology, we will know how a patient metabolizes medications, or a patient's receptor profile and allergy risks. These factors can be used to screen against a list of medications before therapy. A urologist will then be able to always prescribe the best drug for each patient without the risk of side effects.

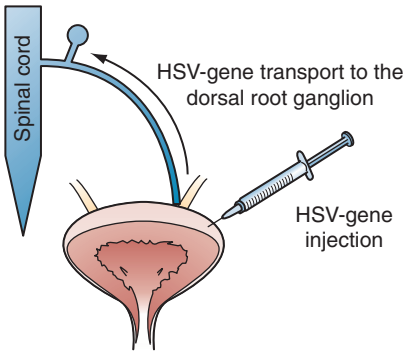


Figure 60–33. Illustration depicting the concept of gene therapy for neurogenic bladder, voiding dysfunction, and pain. Herpes simplex virus (HSV) is used as a vector for directed transfection of nerves that innervate the urinary bladder. Such an approach has interesting potential for the treatment of bladder dysfunction.

Stem Cells and Tissue Engineering. Rapid advances are being made in tissue engineering (Atala, 2004) and organ reconstruction with autologous tissue and stem cells (Chancellor et al, 2000). We envision a day, in the not too distant future, when stress incontinence is cured not with a cadaver ligament and metal screws into the bones but rather with minimally invasive injection of muscle stem cells that will not only bulk up the deficient sphincter but actually improve the deficient sphincter's contractility.

Gene Therapy. Benign prostatic hyperplasia (Marcelli et al, 2000), diabetic neurogenic bladder (Phelan et al, 2000; Goins et al, 2001; Sasaki et al, 2004), neurogenic detrusor overactivity (Miyazato et al, 2009), and even BPS/IC (Yokoyama et al, 2008) may be cured with one or more treatments with a gene vector that the urologist will inject into the bladder or prostate. The injection of a viral vector expression apoptotic factor can direct the hypertrophied prostate to shrink. Injection of NGF through a herpes simplex virus vector into the bladder of a diabetic person may promote the recovery of bladder sensation and innervation (Fig. 60–33). Finally, what about the single condition most troubling to just about every urologist, BPS/IC? Can the introduction of a viral vector that is targeted to nerves, and that carries a gene for an endogenous opioid peptide that blocks pain pathways, be used to help alleviate pain, regardless of the cause of BPS/IC?

Acknowledgments

We want to thank Dr. William C. (Chet) de Groat for reviewing this chapter. Around the world, Dr. de Groat is warmly regarded as the godfather of neurourology, but to the two of us, Dr. de Groat is much more. Chet is the father of our laboratory and our research. His intellectual brilliance is matched only by his decency of heart. Chet is always there to help us in developing research ideas and writing papers and grants. Chet is there when we run into trouble and need guidance. We dedicate our research in honor of our teacher, Dr. Chet de Groat. We would also like to thank Dr. John Lavelle at the University of North Carolina for his assistance with the section on bladder urothelium and Dr. Michael Sacks at the University of Pittsburgh for helping us with the bladder biomechanics section.

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chapter

61

Pathophysiology and Classification of Lower Urinary Tract Dysfunction: Overview

Alan J. Wein, MD, PhD (Hon), FACS

Normal Lower Urinary Tract Function: Overview

Mechanisms Underlying the Two Phases of Function: Overview

Micturition Cycle: Simplification and Overview

Abnormalities of Filling/Storage and Emptying/Voiding: Overview of Pathophysiology

Classification Systems

The lower urinary tract functions as a group of interrelated structures whose joint function in the adult is to bring about efficient and low-pressure bladder filling, low-pressure urine storage with perfect continence, and periodic complete voluntary urine expulsion, again at low pressure. This should occur with appropriate sensation, meaning that a sense of deferrable bladder fullness should gradually occur between voluntary voids up to a volume that is sufficient to prevent urinary frequency and without any pain or sudden compelling desires to void, which are difficult to defer (urgency). Because in the adult the lower urinary tract is normally under voluntary neural control, it is clearly different from other visceral organs innervated by the autonomic nervous system whose regulation is solely by involuntary mechanisms.

For the purposes of description and teaching, the micturition cycle is best divided into two relatively discrete phases: bladder filling/urine storage and bladder emptying/voiding. The micturition cycle normally displays these two modes of operation in a simple on-off fashion. The cycle involves switching from inhibition of the voiding reflex and activation of storage reflexes to inhibition of the storage reflexes and activation of the voiding reflex—and back again. This chapter begins with a functional, physiologic, and pharmacologic overview of normal and abnormal lower urinary tract function. A simple way of looking at the pathophysiology of all types of voiding dysfunction is then presented, followed by a discussion of various systems of classification and categorization. Consistent with the author's philosophy and prior attempts to make the understanding, evaluation, and management of voiding dysfunction as logical and simple as possible (Wein and Barrett, 1988; Wein, 2002), a functional and practical approach is favored.

As an apology and explanation to significant contributors to the field whose works have not been specifically referenced by name as frequently as they could have been, citations have been chosen primarily because of their comprehensive review or informational content and not because of originality or initial publication on a particular subject, except where noted.

NORMAL LOWER URINARY TRACT FUNCTION: OVERVIEW

Two-Phase Concept of Function: Filling/Storage and Emptying/Voiding

Whatever disagreements exist regarding the anatomic, morphologic, physiologic, pharmacologic, and mechanical details involved in both the storage and the expulsion of urine by the lower urinary tract, the author has always taken the rather simple-minded view that the "experts" would agree on certain general points (Wein, 1981; Wein and Barrett, 1988; Wein, 2007; Wein and Moy, 2007). The first is that **the micturition cycle involves two relatively discrete processes: (1) bladder filling and urine storage and (2) bladder emptying or voiding.** The second is that, whatever the details involved, **one can succinctly summarize these processes from a conceptual point of view as follows:**

Bladder filling and urine storage require:

Accommodation of increasing volumes of urine at a low intravesical pressure (normal compliance) and with appropriate sensation.

A bladder outlet that is closed at rest and remains so during increases in intra-abdominal pressure.

Absence of involuntary bladder contractions (detrusor overactivity).

Bladder emptying/voiding requires:

A coordinated contraction of the bladder smooth musculature of adequate magnitude and duration.

A concomitant lowering of resistance at the level of the smooth and striated sphincter (no functional obstruction).

Absence of anatomic (as opposed to functional) obstruction.

The **smooth sphincter** refers to the smooth musculature of the bladder neck and proximal urethra. This is a physiologic but not an anatomic sphincter and one that is not under voluntary control. The **striated sphincter** refers to the striated musculature that is a part of the outer wall of the proximal urethra in both the male and the female (this portion is often referred to as the **intrinsic or intramural striated sphincter or rhabdosphincter)** and the bulky skeletal muscle group that closely surrounds the urethra at the level of the membranous portion in the male and primarily the middle segment in the female (often referred to as the **extrinsic or extramural striated sphincter**). The extramural portion is the classically described **external urethral sphincter** and is under voluntary control (for a detailed discussion see Chapter 60; DeLancey et al, 2002; Zderic et al, 2002).

MECHANISMS UNDERLYING THE TWO PHASES OF FUNCTION: OVERVIEW

This section briefly summarizes pertinent points regarding the physiology and pharmacology of the various mechanisms underlying normal bladder filling/storage and emptying/voiding abnormalities, which constitute the pathophysiologic mechanisms seen in the various types of dysfunction of the lower urinary tract. The general information is consistent with that detailed in Chapter 60 and in previous source materials and their supporting references: Wein and Barrett, 1988; deGroat et al, 1993, 1999, 2001; Zderic et al, 2002; Andersson and Arner, 2004; Andersson and Wein, 2004; Morrison et al, 2005; Mostwin et al, 2005; Yoshimura and Chancellor, 2007; Fowler et al, 2008; Birder et al, 2009; and Koelbl et al, 2009. Other specific references are provided only when particularly unique or applicable.

Bladder Response during Filling

The normal adult bladder response to filling at a physiologic rate is an almost imperceptible change in intravesical and detrusor pressure. During at least the initial stages of bladder filling, after unfolding of the bladder wall from its collapsed state, **this high compliance (Δ volume/Δ pressure) of the bladder is due primarily to its elastic and viscoelastic properties. Elasticity** allows the constituents of the bladder wall to stretch to a certain degree without any increase in tension. **Viscoelasticity** allows stretch to induce a rise in tension followed by a decay ("stress relaxation") when the filling (stretch stimulus) slows or stops. The viscoelastic properties are considered to be primarily due to the characteristics of the extracellular matrix in the bladder wall. Andersson and Arner (2004) cite references demonstrating that the main extracellular components are elastic fibers and collagen fibrils present in the serosa, between muscle bundles, and between the smooth muscle cells in the muscle bundles. Brading and colleagues (1999) add that they believe that there is continuous contractile activity in the smooth muscle cells to adjust their length during filling but without the type of synchronous activity that would increase intravesical pressure, impede filling, and could cause urinary leakage. Clinically and urodynamically, therefore, the bladder seems "relaxed." The urothelium also expands but must preserve its barrier function while doing so.

There may also be a non-neurogenic active component to the storage properties of the bladder. Hawthorn and colleagues (2000) have suggested that an as yet unidentifiable relaxing factor is released from the urothelium during filling and storage, and Andersson and Wein (2004) have suggested that urothelium-released nitric oxide may have an inhibitory effect on afferent mechanisms as well.

The viscoelastic properties of the stroma (bladder wall less smooth muscle and epithelium) and the urodynamically relaxed detrusor muscle thus account for the passive mechanical properties and normal bladder compliance seen during filling. The main components of the stroma are collagen and elastin. In the usual clinical setting, filling cystometry seems to show a slight increase in intravesical pressure, but Klevmark (1974, 1999) elegantly showed that **this pressure rise is a function of the fact that cystometric filling is carried out at a greater than physiologic rate and that, at physiologic filling rates, there is essentially no rise in bladder pressure until bladder capacity is reached.**

When the collagen component of the bladder wall increases, compliance decreases. This can occur with chronic inflammation, bladder outlet obstruction, neurologic decentralization, and various other types of injury. Bladder muscle hypertrophy, which can result from outlet obstruction, can also result in decreased compliance because it is said to be less elastic than normal detrusor; it also can synthesize increased amounts of collagen (Mostwin, 2006). **Once decreased compliance has occurred because of a replacement by collagen of other components of the stroma, it is generally unresponsive to pharmacologic manipulation, hydraulic distention, or nerve section.** Most often, under those circumstances, augmentation cystoplasty is required to achieve satisfactory reservoir function.

Does the nervous system affect the normal bladder response to filling? At a certain level of bladder filling, **spinal sympathetic reflexes** facilitatory to bladder filling/storage are clearly evoked in animals, a concept developed over the years by deGroat and others (deGroat et al, 1993; deGroat and Yoshimura, 2001; Chancellor and Yoshimura, 2002; Zderic et al, 2002; Yoshimura and Chancellor, 2007; see Chapter 60), who have also cited indirect evidence to support such a role in humans. **This inhibitory effect is thought to be mediated primarily by sympathetic modulation of cholinergic ganglionic transmission.** Through this reflex mechanism, **two other possibilities exist for promoting filling/storage.** One is neurally mediated stimulation of the predominantly α-adrenergic receptors (α_1) in the area of the smooth sphincter, the net result of which would be to cause an increase in resistance in that area. The second is neurally mediated stimulation of the predominantly β-adrenergic receptors (β_3 inhibitory) in the bladder body smooth musculature, which would cause a decrease in bladder wall tension. McGuire and colleagues (1983) have also proposed a direct inhibition of detrusor motor neurons in the sacral spinal cord during bladder filling related to increased afferent pudendal nerve activity generated by receptors in the striated sphincter. **Good evidence also seems to exist to support an inhibitory effect of other neurotransmitters (e.g., glycine, gamma amino butyric acid [GABA], opioids, purines, the noradrenergic system) on the micturition reflex at various levels of the neural axis.** Bladder filling and consequent wall distention may also result in the release of factors from the urothelium that may influence contractility (e.g., acetylcholine [Ach], adenosine triphosphate [ATP], nitric oxide, prostaglandins, other peptides, as yet unidentified inhibitory factors).

Outlet Response during Filling

There is a gradual increase in urethral pressure during bladder filling, contributed to at least by the striated sphincteric element and perhaps by the smooth sphincteric element as well. The rise in urethral pressure seen during the filling/storage phase of micturition can be correlated with an increase in efferent pudendal nerve impulse frequency and in electromyographic activity of the striated sphincter. This constitutes the efferent limb of a spinal somatic reflex, the so-called **guarding reflex,** which results in a gradual increase in striated sphincter activity during normal bladder filling and storage. Although it seems logical and certainly compatible with neuropharmacologic, neurophysiologic, and neuromorphologic data to assume that the muscular component of the smooth sphincter also contributes to the change in urethral response during bladder filling, probably through sympathetically induced contraction, it is extremely difficult to prove this either experimentally or clinically. The direct and circumstantial evidence in favor of such a hypothesis has been summarized by Wein and Barrett (1988), Brading (1999), and Andersson and Wein (2004).

The passive properties of the urethral wall certainly deserve mention because these undoubtedly play a role in the maintenance of continence (Zinner et al, 1983; Brading, 1999). Urethral wall tension develops within the outer layers of the urethra; however, urethral pressure is a product not only of the active characteristics of smooth and striated muscle but also of the passive characteristics of the elastic, collagenous, and vascular components of the urethral wall because this tension must be exerted on a soft or plastic inner layer capable of being compressed to a closed configuration—the **"filler material"** representing the submucosal portion of the urethra. The softer and more pliable this area is, the less pressure required by the tension-producing area to produce continence. Finally, whatever the compressive forces, the lumen of the urethra must be capable of being obliterated by a watertight seal. This **"mucosal seal mechanism"** explains why a thin-walled rubber tube requires less pressure to close an open end when the inner layer is coated with a fine layer of grease than when it is not, the latter case being much like scarred or atrophic urethral mucosa.

Voiding with a Normal Bladder Contraction

Although many factors are involved in the initiation of micturition, in adults it is **intravesical pressure producing the sensation of distention that is primarily responsible for the initiation of normal voluntarily induced emptying of the lower urinary tract. Although the origin of the parasympathetic neural outflow to the bladder, the pelvic nerve, is in the sacral spinal cord, the actual coordinating center for the micturition reflex in an intact neural axis is in the rostral brainstem.** The complete neural circuit for normal micturition includes the ascending and descending spinal cord pathways to and from this area and the facilitatory and inhibitory influences from other parts of the brain, particularly the cerebral cortex. **The final step in voluntarily induced micturition involves inhibition of the somatic neural efferent activity to the striated sphincter and an inhibition of all aspects of any spinal sympathetic reflexes evoked during filling. Efferent parasympathetic pelvic nerve activity is ultimately what is responsible for a highly coordinated contraction of the bulk of the bladder smooth musculature.**

A decrease in outlet resistance occurs with adaptive shaping or funneling of the relaxed bladder outlet. Besides the inhibition of any continence-promoting reflexes that have occurred during bladder filling, the change in outlet resistance may also involve an active relaxation of the smooth sphincter area through a noradrenergic noncholinergic (NANC) mechanism, proposed to be mediated by nitric oxide (Andersson and Arner, 2004; Andersson and Wein, 2004). **The adaptive changes that occur in the outlet are probably also due at least in part to the anatomic interrelationships of the smooth muscle of the bladder base and proximal urethra.** Longitudinal smooth muscle continuity (Mostwin, 2006; see Chapter 60) would promote shortening and widening of the proximal urethra during a coordinated emptying bladder contraction. Other reflexes that are elicited by bladder contraction and by the passage of urine through the urethra may reinforce and facilitate complete bladder emptying. Superimposed on these autonomic and somatic reflexes are complex, modifying supraspinal inputs from other central neuronal networks. These facilitatory and inhibitory impulses, which originate from several areas of the nervous system, allow the full conscious control of micturition in the adult.

Urinary Continence during Abdominal Pressure Increases

During voluntarily initiated micturition, the bladder pressure becomes higher than the outlet pressure and certain adaptive changes occur in the shape of the bladder outlet with consequent passage of urine into and through the proximal urethra. One could reasonably ask, **why do such changes not occur with increases in intravesical pressure that are similar in magnitude but that are produced only by changes in intra-abdominal pressure such as straining or coughing?** First, a coordinated bladder contraction does not occur in response to such stimuli, clearly emphasizing the fact that increases in total intravesical pressure are by no means equivalent to emptying ability. Secondly, for urine to flow into and through the proximal urethra in an individual who does not have sphincteric incontinence, there must be (1) an increase in intravesical pressure that is primarily a product of a coordinated, neurally mediated bladder contraction and that is (2) associated with characteristic tension and conformational changes in the bladder neck and proximal urethral areas.

Assuming that the bladder outlet is competent at rest, a major factor required for the prevention of urinary leakage during increases in intra-abdominal pressure is that there is **at least equal pressure transmission to the proximal urethra (the midurethra, as well as in the female) during such activity.** This phenomenon was first described by Enhorning (1961) and has been confirmed in virtually every urodynamic laboratory since that time. **Failure of this mechanism is an invariable correlate of effort-related urinary incontinence in the female and male. The urethral closure pressure increases with increments in intra-abdominal pressure, indicating that active muscular function related to a reflex increase in striated sphincter activity or other factors that increase urethral resistance is also involved in preventing such leakage.** Tanagho (1978) was the first to provide direct evidence of this. A more complete description of the factors

involved in sphincteric incontinence can be found later in this chapter and in Chapters 60 and 63.

Sensory Aspects

Most of the afferent input from the bladder and urethra reaches the spinal cord through the pelvic nerve and dorsal root ganglia and some through the hypogastric nerve.

Afferent input from the striated muscle of the sphincter and pelvic floor travels in the pudendal nerve. The most important afferents for initiating and maintaining normal micturition are those in the pelvic nerve, relaying to the sacral spinal cord. These convey impulses from tension, volume, and nociceptive receptors located in the serosal, muscle, and urothelial and suburothelial layers of the bladder and urethra. In a neurologically normal adult the sensation of filling and distention, but not urgency or pain, is what develops during normal filling/storage and initiates the reflexes responsible for emptying/voiding (deGroat and Yoshimura, 2001; Chancellor and Yoshimura, 2002; Morrison et al, 2005; Birder et al, 2009; see Chapter 60). Alterations in this finely tuned pathway can be responsible for significant alterations in lower urinary tract function.

MICTURITION CYCLE: SIMPLIFICATION AND OVERVIEW

Filling/Storage

Bladder accommodation during filling is a primarily passive phenomenon dependent on the elastic and viscoelastic properties of the bladder wall and the lack of parasympathetic excitatory input. An increase in outlet resistance occurs by means of the striated sphincter somatic guarding reflex. In at least some species, a sympathetic reflex also contributes to storage by (1) increasing outlet resistance by increasing tension in the smooth sphincter, (2) inhibiting bladder contractility through an inhibitory effect on parasympathetic ganglia, and (3) causing a decrease in tension of bladder body smooth muscle. Continence is maintained during increases in intra-abdominal pressure by the intrinsic competence of the bladder outlet (bladder neck and proximal/middle urethra) and the pressure transmission ratio to this area with respect to the intravesical contents. A further increase in striated sphincter activity, on a reflex basis, is also contributory.

Emptying/Voiding

Emptying (voiding) can be voluntary or involuntary and involves an inhibition of the spinal somatic and sympathetic reflexes and activation of the vesical parasympathetic pathways, the organizational center for which is in the rostral brainstem. Initially, there is a decrease in outlet resistance, mediated not only by the cessation of the somatic and sympathetic spinal reflexes but possibly also by a relaxing factor released by parasympathetic stimulation or by some effect of bladder smooth muscle contraction itself. A highly coordinated parasympathetically induced contraction of the bulk of the bladder smooth musculature occurs, with shaping or funneling of the relaxed outlet, owing at least in part to smooth muscle continuity between the bladder base and the proximal urethra. With amplification and facilitation of the bladder contraction from other peripheral reflexes and from spinal cord supraspinal sources, and in the absence of anatomic obstruction between the bladder and urethral meatus, complete emptying occurs.

ABNORMALITIES OF FILLING/STORAGE AND EMPTYING/VOIDING: OVERVIEW OF PATHOPHYSIOLOGY

Excluding psychologic reasons, the pathophysiology of failure of the lower urinary tract in the adult to fill with or store urine adequately or to empty adequately must logically be secondary to reasons related to the bladder, the outlet, or a combination (Wein, 1981; Wein and Barrett, 1988).

Filling/Storage Failure

Absolute or relative failure of the bladder to fill with and store urine adequately results from bladder overactivity (involuntary contraction or decreased compliance), decreased outlet resistance, heightened or altered sensation, or a combination.

Bladder Overactivity

Overactivity of the bladder during filling/storage can be expressed as phasic involuntary contractions, as low compliance, or as a combination. Involuntary contractions are most commonly seen in association with **neurologic disease or injury, bladder outlet obstruction, stress urinary incontinence** (perhaps because of sudden entry of urine into the proximal urethra, eliciting a reflex contraction), **aging** (probably related to neural degeneration), or may be truly **idiopathic.** However, they may also be associated with **increased afferent input** related to inflammation or irritation of the bladder or urethral wall. Excitatory neurotransmitters may be released from the urothelium during filling/storage and activate afferent receptors/nerves, ultimately resulting, in some individuals, in involuntary contractions or altered (heightened) sensation, either a premature sensation of distention or fullness, true urgency (a sudden compelling desire to void, which is difficult to defer), or pain. If an individual has urgency urinary incontinence, it can be assumed that an involuntary contraction (DO) has occurred. The symptom of urgency without incontinence suggests DO, but this is often not demonstrable on urodynamic study. Conversely, urodynamically demonstrable DO may not be associated with clinically troublesome filling/storage symptomatology.

The possible pathophysiologies of the symptom syndrome "overactive bladder" (defined by the ICS as urgency with or without urge incontinence, usually with frequency and nocturia) can be summarized as (1) reduced suprapontine inhibition, (2) damaged axonal paths in the spinal cord, (3) damaged axonal paths in the periphery, (4) loss of peripheral inhibition, (5) enhancement of excitatory neurotransmission in the micturition reflex pathway, (6) increased lower urinary tract afferent

input, and (7) idiopathic. Staskin (2001) and Mostwin and colleagues (2005) also hypothesized that decreased stimulation from the pelvic floor can contribute to phasic bladder overactivity. **Decreased compliance** during filling/storage may be secondary to neurologic injury or disease, usually at a sacral or infrasacral level, but may result from any process that impairs or destroys the viscoelastic or elastic properties of the bladder wall.

Filling/Storage Failure due to Altered Sensation

Bladder-related storage failure may also occur in the absence of overactivity because of increased afferent input from inflammation, irritation, other causes of hypersensitivity, and pain. The causes may be chemical, psychologic, or idiopathic. One classic example is *painful bladder syndrome,* a term that is replacing *interstitial cystitis* (see Chapter 12). Increased afferent activity can then be responsible for true detrusor overactivity (an involuntary contraction), true urgency without DO, a premature feeling of fullness or distention without urgency or DO, or the sensation of pain during filling.

Outlet Underactivity

Decreased outlet resistance may result from any process that damages the innervation of structural elements of the smooth or striated sphincter, or both, or damages or impairs the support of the bladder outlet in the female. This may occur with **neurologic disease or injury, surgical or other mechanical trauma, or aging. Classically, sphincteric incontinence in the female was categorized into relatively discrete entities:** (1) so-called **genuine stress incontinence** and (2) **intrinsic sphincter deficiency,** originally described as type III stress incontinence (DeLancey et al, 1994; Mostwin et al, 2005; Koelbl et al, 2009; see Chapters 60, 63, 71, and 73). **Genuine stress incontinence in the female** was described as associated with hypermobility of the bladder outlet because of poor pelvic support and with an outlet that was competent at rest but lost its competence only during increases in intra-abdominal pressure. **Intrinsic sphincter deficiency** (ISD) described a nonfunctional or poorly functional bladder neck and proximal urethra at rest. **The implication of classic ISD was that a surgical procedure designed to correct only urethral hypermobility would have a relatively high failure rate, as opposed to one designed to improve urethral coaptation and compression. The contemporary view is that the majority of cases of effort-related incontinence in the female involve varying proportions of support-related factors and ISD.** It is possible to have outlet-related incontinence that is due only to ISD but not due solely to hypermobility or poor support—some ISD must exist.

Stress or effort-related urinary incontinence is a symptom that arises primarily from **damage to muscles, nerves, or connective tissue, or a combination, within the pelvic floor** (DeLancey et al, 2002; Mostwin et al, 2005; Koelbl et al, 2009). Urethral support is important in the female, the urethra normally being supported by the action of the levator ani muscles through their connection to the endopelvic fascia of the anterior vaginal wall. Damage to the connection between this fascia and this muscle, damage to the nerve supply, or direct muscle damage can therefore influence continence. Bladder neck function is likewise important, and loss of normal bladder neck closure can result in incontinence despite normal urethral support. In older writings, the urethra was sometimes ignored as a factor contributing to continence in the female, and the site of continence was thought to be exclusively the bladder neck. However, in approximately 50% of continent women, urine enters the urethra during increases in abdominal pressure. The continence point in these women (highest point of pressure transmission) is at the midurethra.

Urethral hypermobility implies weakness of the pelvic floor support structures. During increases in intra-abdominal pressure, there is descent of the bladder neck and proximal urethra. If the outlet opens concomitantly, stress urinary incontinence ensues. In the classic form of urethral hypermobility, there is rotational descent of the bladder neck and urethra. However, the urethra may also descend without rotation (it shortens and widens), or the posterior wall of the urethra may be pulled (sheared) open while the anterior wall remains fixed. However, urethral hypermobility is often present in women who are not incontinent, and thus the mere presence of urethral hypermobility is not sufficient to make a diagnosis of a sphincter abnormality unless urinary incontinence is also demonstrated. The **"hammock hypothesis"** of John DeLancey (1994) proposes that for stress incontinence to occur within hypermobility, there must be a lack of stability of the suburethral supportive layer. This theory proposes that the effect of abdominal pressure increases on the normal bladder outlet, if the suburethral supportive layer is firm, is to compress the urethra rapidly and effectively. If the supportive suburethral layer is lax or movable, or both, compression is not as effective. **Intrinsic sphincter dysfunction** denotes an intrinsic malfunction of the urethral sphincter mechanism itself. In its most overt form, it is characterized by a bladder neck that is open at rest and a low abdominal leak point pressure and urethral closure pressure (see Chapter 62) and is usually the result of prior surgery, trauma with scarring, or a neurologic lesion.

Urethral instability refers to the rare phenomenon of episodic decreases in outlet pressure unrelated to increases in bladder or abdominal pressure. The term urethral instability is probably a misnomer because many believe that the drop in urethral pressure represents simply the urethral component of what would otherwise be a bladder contraction/urethral relaxation in an individual whose bladder does not measurably contract, for either myogenic or neurogenic reasons. Little has appeared in the literature about this entity since the last edition of this text.

In theory at least, categories of outlet-related incontinence in the male are similar to those in the female. Sphincteric incontinence in the male is not, however, associated with hypermobility of the bladder neck and proximal urethra but is similar to what is termed *intrinsic sphincter dysfunction* in the female. There is essentially no information regarding the topic of urethral instability in the male.

The treatment of filling/storage abnormalities is directed toward inhibiting bladder contractility, decreasing sensory output, or mechanically increasing bladder capacity; and/or toward increasing outlet resistance, the latter either continuously or just during increases in intra-abdominal pressure.

Emptying/Voiding Failure

Absolute or relative failure to empty the bladder results from decreased bladder contractility (a decrease in magnitude or duration), increased outlet resistance, or a combination.

Bladder Underactivity

Absolute or relative failure of bladder contractility may result from temporary or permanent failure or impairment in one of the neuromuscular mechanisms necessary for initiating and maintaining a normal detrusor contraction. Inhibition of the voiding reflex in a neurologically normal individual may also occur; it may be by a reflex mechanism secondary to increased afferent input, especially from the pelvic and perineal areas, or may be psychogenic. **Non-neurogenic causes** also include impairment of bladder smooth muscle function, which may result from overdistention, various centrally or peripherally acting drugs, severe infection, or fibrosis.

Outlet Overactivity or Obstruction

Pathologically increased outlet resistance is much more common in men than in women. Although it is most often secondary to anatomic obstruction, it may be secondary to a failure of relaxation or active contraction of the striated or smooth sphincter during bladder contraction (see Chapter 65). **Striated sphincter dyssynergia** is a common cause of functional or nonanatomic (as opposed to fixed anatomic) obstruction in patients with neurologic disease or injury. Except for the true smooth sphincter contraction, which occurs in conjunction with autonomic hyperreflexia (see Chapter 65), true dyssynergia at the level of the bladder neck–proximal urethra is unusual at best. Incomplete opening of an anatomically normal bladder neck during voluntary or involuntary voiding is termed *bladder neck dysfunction,* an uncommon entity found almost exclusively in young and middle-aged men, and also sometimes known as *primary bladder neck obstruction, smooth sphincter dyssynergia,* and *dysfunctional bladder neck* (see Chapter 65). The common causes of anatomic outlet obstruction include prostatic enlargement, bladder neck contracture, and urethral stricture. A common cause of outlet obstruction in the female is compression or fibrosis following surgery for sphincteric incontinence.

The treatment of emptying failure generally consists of maneuvers to increase intravesical/detrusor pressure, facilitate the micturition reflex, decrease outlet resistance, or a combination. If other means fail or are impractical, intermittent (or continuous) catheterization is an effective way to circumvent emptying failure.

CLASSIFICATION SYSTEMS

On the basis of the data obtained from the neurourologic evaluation, a given voiding dysfunction can be categorized in an ever-increasing number of descriptive systems. The purpose of any classification system should be to facilitate understanding and management and to avoid confusion among those who are concerned with the problem for which the system was designed. A good classification should serve as **intellectual shorthand** and should convey, in a few key words or phrases, the essence of a clinical situation. An ideal system for all types of voiding dysfunction would include or imply a number of factors: (1) the conclusions reached from urodynamic testing, (2) expected clinical symptoms, and (3) approximate site and type of a neurologic lesion or lack of one. If the various categories accurately portray pathophysiology, treatment options should then be obvious, and a treatment "menu" should be evident. **Most systems of classification for voiding dysfunction were formulated primarily to describe dysfunction secondary to neurologic disease or injury. The ideal system should be applicable to all types of voiding dysfunction.** On the basis of the data obtained from the neurourologic evaluation, a given voiding dysfunction can be categorized in a number of descriptive systems. **No one system is perfect.** Most major systems or types of systems in use are reviewed, along with their advantages and applicability. Understanding the rationale and shortcomings of each system significantly improves one's knowledge of voiding function and dysfunction.

Functional System

Classification of voiding dysfunction can be formulated on a simple functional basis, describing the dysfunction in terms of whether the deficit produced is primarily one of the filling/storage or the emptying/voiding phase of micturition (Table 61–1) (Wein, 1981; Wein and Barrett, 1988). The genesis of such a system was proposed initially by F. Brantley Scott's group (Quesada et al, 1968). This simple-minded scheme assumes only that, whatever their differences, all "experts" would agree on the two-phase concept of micturition (filling/storage and emptying/voiding), on the simple overall mechanisms underlying the normality of each phase (see previous discussion), and on the possibilities for dysfunction.

Storage failure results from either **bladder or outlet abnormalities or a combination.** The proven **bladder abnormalities** simply include only involuntary bladder contractions, low compliance, and heightened or altered sensation. The **outlet abnormalities** can include only an intermittent or continuous decrease in outlet resistance.

Emptying failure, likewise, can occur because of **bladder or outlet abnormalities or a combination.** The bladder side includes only inadequate or unsustained bladder contractility, and the outlet side includes only anatomic obstruction and sphincter dyssynergia or dysfunction.

There are indeed some types of voiding dysfunction that represent combinations of filling/storage and emptying voiding abnormalities. Within this scheme, however, these become readily understandable and their detection and treatment can be logically described. Various aspects of physiology and pathophysiology are always related more to one phase of micturition than another. **All aspects of urodynamic and videourodynamic evaluation can be conceptualized in this functional manner as to exactly what they evaluate in terms of either bladder or outlet activity during filling/storage and emptying/voiding** (Table 61–2)**. In addition, one can easily classify all known treatments for voiding dysfunction under the broad categories of whether they facilitate filling/storage and emptying/**

Table 61–1.

Functional Classification

Failure to Store
Because of the bladder
Because of the outlet
Failure to Empty
Because of the bladder
Because of the outlet

Table 61–2.

Urodynamics Simplified

	BLADDER	OUTLET
Filling/storage phase	Pves[1] Pdet[2] (FCMG[3]) DLPP[4]	UPP[5] VLPP[6] FLUORO[7]
Emptying phase	Pves[8] Pdet[9] (VCMG)[10]	MUPP[11] FLUORO[12] EMG[13]
	(_____ _____) _____FLOW[14]_____ _____RU[15]_____	

This functional conceptualization of urodynamics categorizes each study as to whether it examines bladder or outlet activity during the filling/storage or emptying phase of micturition. In this scheme, uroflow and residual urine integrate the activity of the bladder and the outlet during the emptying phase.
[1,2]Total bladder (Pves) and detrusor (Pdet) pressures during a filling cystometrogram (FCMG).
[3]Filling cystometrogram.
[4]Detrusor leak point pressure.
[5]Urethral pressure profilometry.
[6]Valsalva leak point pressure.
[7]Fluoroscopy of outlet during filling/storage.
[8,9]Total bladder and detrusor pressures during a voiding cystometrogram (VCMG).
[10]Voiding cystometrogram.
[11]Micturitional urethral pressure profilometry.
[12]Fluoroscopy of outlet during emptying.
[13]Electromyography of periurethral striated musculature.
[14]Flowmetry.
[15]Residual urine.

voiding and whether they do so by an action primarily on the bladder or on one or more of the components of the bladder outlet (Tables 61–3 and 61–4).

Failure in either category generally is not absolute but more often is relative. Such a functional system can easily be "expanded" and made more complicated to include etiologic or specific urodynamic connotations (Table 61–5). However, the simplified system is perfectly workable and avoids argument in the complex situations in which the exact etiology or urodynamic mechanism for a voiding dysfunction cannot be agreed on.

Proper use of the functional system for a given voiding dysfunction obviously requires a reasonably accurate notion of what the urodynamic data show. However, **an exact diagnosis is not required for treatment.** It should be recognized that **some patients do not have only a discrete storage or emptying failure, and the existence of combination deficits must be recognized to use this system classification properly.** For an example, the "classic" T10 paraplegic patient after spinal shock generally exhibits a relative failure to store because of involuntary bladder contraction and a relative failure to empty the bladder because of striated sphincter dyssynergia. With such a combination deficit, to use this classification system as a guide to treatment, one must assume that one of the deficits is primary and that significant improvement will result from its treatment alone or that the voiding dysfunction can be converted primarily to a disorder of either storage or emptying by means of nonsurgical or surgical therapy. The resultant deficit can then be treated or circumvented. Using this example, the combined deficit in a T10 paraplegic patient can be converted primarily to a storage failure by procedures directed at the dyssynergic striated sphincter; the resultant incontinence (secondary to involuntary contraction) can be circumvented (in a male) with an external collecting device. Alternatively, the deficit can be converted primarily to an emptying failure by pharmacologic or surgical measures designed to abolish or reduce the involuntary contraction, and the resultant emptying failure can then be circumvented with clean intermittent catheterization. Other examples of combination deficits include impaired bladder contractility or overactivity with sphincter dysfunction, bladder outlet obstruction with detrusor overactivity, bladder outlet obstruction with sphincter malfunction, and detrusor overactivity with impaired contractility.

One of the advantages of this functional classification is that it allows the clinician the liberty of "playing" with the system to suit his or her own preferences without an alteration in the basic concept of "keep it simple but accurate and informative." For instance, one could easily substitute the terms overactive or oversensitive bladder and underactive outlet for because of the bladder and because of the outlet under "Failure to Store" in Table 61–1. One could choose to categorize the bladder reasons for overactivity (see Table 61–5) further in terms of neurogenic, myogenic, or anatomic causes and further subcategorize neurogenic in terms of decreased inhibitory control, increased afferent activity, increased sensitivity to efferent activity, and so on. The system is flexible.

The classification system proposed by the International Continence Society (ICS) (Table 61–6) is **in essence an extension of a urodynamic classification system.** The storage and voiding phases of micturition are described separately, and, within each, various designations are applied to describe bladder and urethral function (Abrams et al, 1988, 1992). Some of the definitions were changed by the standardization subcommittee of the International Continence Society in 2002, and the relevant changes are indicated here (Abrams et al, 2002, 2003). **Normal bladder function during filling/storage implies no significant rises in detrusor pressure (stability). Overactive detrusor function indicates the presence of "involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked."** If the condition is caused by neurologic disease, the term ***neurogenic detrusor overactivity*** (previously, *detrusor hyperreflexia*) is applied. If not, the term ***idiopathic detrusor overactivity*** (previously, *detrusor instability*) is applied. **Bladder sensation** can be categorized only in qualitative terms as indicated. **Bladder capacity and compliance** (Δ volume/Δ pressure) are cystometric measurements. Bladder capacity can refer to cystometric capacity, maximum cystometric capacity, or maximum anesthetic cystometric capacity (Abrams et al, 2002). **Normal urethral function during filling/storage indicates a positive urethral closure pressure (urethral pressure minus bladder pressure) even with increases in intra-abdominal pressure, although it may be overcome by detrusor overactivity. Incompetent urethral function during filling/storage** implies urine leakage in the absence of a detrusor contraction. This may be secondary to genuine stress incontinence, intrinsic sphincter dysfunction, a combination, or an involuntary fall in urethral pressure in the absence of detrusor contraction.

During the voiding/emptying phase of micturition, normal detrusor activity implies voiding by a voluntarily initiated sustained contraction that leads to complete bladder emptying within a normal time span. An **underactive detrusor** defines a contraction of inadequate magnitude or duration, or both, to empty the bladder within a normal time span. An **acontractile detrusor** is one that cannot be demonstrated to contract during urodynamic testing. **Areflexia** is defined as acontractility due to an abnormality of neural control, implying

Table 61–3.

Therapy to Facilitate Urine Storage/Bladder Filling

Bladder Related (Inhibiting Bladder Contractility, Decreasing Sensory Input, and/or Increasing Bladder Capacity)

Behavioral therapy including any or all of the following:
- Education
- Bladder training
- Timed bladder emptying or prompted voiding
- Fluid restriction
- Pelvic floor physiotherapy ± biofeedback

Pharmacologic therapy (oral, intravesical, intradetrusor)
- Anticholinergic agents
- Drugs with mixed actions
- Calcium antagonists
- Potassium channel openers
- Prostaglandin inhibitors
- β-Adrenergic agonists
- α-Adrenergic antagonists
- Tricyclic antidepressants; serotonin and norepinephrine reuptake inhibitors
- Dimethyl sulfoxide (DMSO)
- Polysynaptic inhibitors
- Capsaicin, resiniferatoxin, and like agents
- Botulinum toxin

Bladder overdistention

Electrical stimulation and neuromodulation

Acupuncture and electroacupuncture

Interruption of innervation
- Very central (subarachnoid block)
- Less central (sacral rhizotomy, selective sacral rhizotomy)
- Peripheral motor and/or sensory

Augmentation cystoplasty (auto, bowel, tissue engineering)

Outlet Related (Increasing Outlet Resistance)

Behavioral therapy
- Education
- Bladder training
- Timed bladder emptying or prompted voiding
- Fluid restriction
- Pelvic floor physiotherapy ± biofeedback

Electrical stimulation

Pharmacologic therapy
- α-Adrenergic agonists
- Tricyclic antidepressants; serotonin and norepinephrine reuptake inhibitors
- β-Adrenergic antagonists, agonists

Vaginal and perineal occlusive and/or supportive devices; urethral plugs

Nonsurgical periurethral bulking
- Collagen, synthetics, cell transfer (tissue engineering)

Vesicourethral suspension ± prolapse repair (female)

Sling procedures ± prolapse repair (female)

Closure or compression of the bladder outlet (balloons, surgical closure)

"Sling/Tape" procedure (male)

Artificial urinary sphincter

Bladder outlet reconstruction

Myoplasty (muscle transposition)

Circumventing the Problem

Absorbent products

External collecting devices

Antidiuretic hormone-like agents

Short acting diuretics

Intermittent catheterization

Continuous catheterization

Urinary diversion

the complete absence of centrally coordinated contraction. **Normal urethral function** during voiding indicates a urethra that opens and is continuously relaxed to allow bladder emptying at a normal pressure. **Abnormal urethral function during voiding** may be due to either mechanical obstruction or urethral overactivity. **Dysfunctional voiding** describes an intermittent or fluctuating flow rate due to involuntary intermittent contractions of the periurethral striated muscle in neurologically normal individuals. **Detrusor sphincter dyssynergia** defines a detrusor contraction concurrent with an involuntary contraction of the urethral or periurethral striated muscle, or both. **Nonrelaxing urethral sphincter obstruction** usually occurs in individuals with a neurologic lesion and is characterized by a nonrelaxing obstructing urethra resulting in reduced urine flow.

Lower urinary tract dysfunction in a classic T10-level paraplegic patient after spinal shock has passed would be classified in the ICS system as follows:

- Storage phase—overactive neurogenic detrusor function, absent sensation, low capacity, normal compliance, normal urethral closure function.
- Voiding phase—overactive obstructive urethral function, overactive detrusor function.

The micturition dysfunction of a stroke patient with urgency incontinence would most likely be classified during storage as overactive neurogenic detrusor function, normal sensation, low capacity, normal compliance, and normal urethral closure function. During voiding, the dysfunction would be classified as normal detrusor activity and normal urethral function, assuming that no anatomic obstruction existed.

Urodynamic Classification

As urodynamic techniques have become more accepted and sophisticated, systems of classification have evolved solely on the basis of objective urodynamic data (Table 61–7). Among the first to popularize this concept were Krane and Siroky (1984). When exact urodynamic classification is possible, such a system can provide a truly exact description of the voiding dysfunction that occurs. If a normal or hyperreflexic (overactive) detrusor exists with coordinated smooth and striated sphincter function and without anatomic obstruction, normal bladder emptying should occur. **Detrusor hyperreflexia** (now termed ***neurogenic detrusor overactivity*** in ICS parlance) is most commonly associated with neurologic lesions above the sacral spinal cord.

Table 61–4.

Therapy to Facilitate Bladder Emptying/Voiding

Bladder Related (Increasing Intravesical Pressure or Facilitating Bladder Contractility)

- External compression, Valsalva
- Promotion or initiating of reflex contraction
  - Trigger zones or maneuvers
  - Bladder "training"; tidal drainage
- Pharmacologic therapy (oral, intravesical)
  - Parasympathomimetic agents
  - Prostaglandins
  - Blockers of inhibition
    - α-Adrenergic antagonists
    - Opioid antagonists
- Electrical stimulation
  - Directly to the bladder or spinal cord
  - Directly to the nerve roots
  - Intravesical (transurethral)
  - Neuromodulation
- Reduction cystoplasty
- Bladder myoplasty (muscle wrap)
- Tissue engineering

Outlet Related (Decreasing Outlet Resistance)

- At a site of anatomic obstruction
  - Pharmacologic therapy—decrease prostate size or tone
    - α-Adrenergic antagonists
    - 5 α-reductase inhibitors
    - Luteinizing hormone releasing hormone-agonists/antagonists
    - Antiandrogens
  - Prostatectomy, prostatotomy (diathermy, heat, laser)
  - Bladder neck incision or resection
  - Urethral stricture repair or dilation
  - Intraurethral stent
  - Balloon dilatation of stricture/contracture
- At level of smooth sphincter
  - Pharmacologic therapy
    - α-Adrenergic antagonists
    - β-Adrenergic agonists
    - Botulinum toxin (injection)
  - Transurethral resection or incision
  - Y-V plasty
- At level of striated sphincter
  - Behavioral therapy ± biofeedback
  - Pharmacologic therapy
    - Benzodiazepines
    - Baclofen
    - Dantrolene
    - α-Adrenergic antagonists
    - Botulinum toxin (injection)
  - Urethral overdilation
  - Surgical sphincterotomy
  - Urethral stent
  - Pudendal nerve interruption

Circumventing the Problem

- Intermittent catheterization
- Continuous catheterization
- Urinary diversion (conduit)

Striated sphincter dyssynergia is most commonly seen after complete suprasacral spinal cord injury, following the period of spinal shock. **Smooth sphincter dyssynergia** is seen most classically in autonomic hyperreflexia (see Chapter 65) when it is characteristically associated with detrusor overactivity and striated sphincter dyssynergia. **Detrusor areflexia** (actually this category includes acontractile and areflexic bladder) may be secondary to bladder muscle decompensation or to various other conditions that produce inhibition at the level of the brainstem micturition center, the sacral spinal cord, bladder ganglia, or bladder smooth muscle. Patients with a voiding dysfunction secondary to detrusor areflexia generally attempt bladder emptying by abdominal straining, and their continence status and the efficiency of their emptying efforts are determined by the status of their smooth and striated sphincter mechanisms.

This classification system is easiest to use when detrusor hyperreflexia (overactivity) or normoreflexia exists. Thus a typical T10-level paraplegic patient after spinal shock exhibits detrusor hyperreflexia, smooth sphincter synergia, and striated sphincter dyssynergia. When a voluntary or a hyperreflexic contraction cannot be elicited, the system is more difficult to use because it is not appropriate to speak of true sphincter dyssynergia in the absence of an opposing bladder contraction. There are obviously many variations and extensions of such a system. **Such systems can work well only when total urodynamic agreement exists among classifiers. Unfortunately, there are many voiding dysfunctions that do not fit neatly into a urodynamic classification system that is agreed on by all experts. Compliance is not mentioned in this particular version, nor is sensation or the concept of deficient but not absent detrusor contractile function.** As sophisticated urodynamic technology and understanding improve, this type of classification system may become more commonly used. The ICS system (see previous discussion) is in reality a logical and more complete extension of such a system.

Lapides Classification

Lapides (1970) contributed significantly to the classification and care of the patient with neuropathic voiding dysfunction by slightly modifying and popularizing a system originally proposed by McLellan in 1939 (Table 61–8). Lapides' classification differs from that of McLellan in only one respect, and that is the division of the group of "atonic neurogenic bladder" into sensory neurogenic and motor neurogenic bladder. This remains a familiar system to urologists and nonurologists because it describes in recognizable shorthand the clinical and cystometric conditions of many types of neurogenic voiding dysfunction.

A sensory neurogenic bladder results from disease that selectively interrupts the sensory fibers between the bladder and the spinal cord or the afferent tracts to the brain. **Diabetes mellitus, tabes dorsalis, and pernicious anemia** are the most responsible. The first clinical changes are described as those of impaired sensation of bladder distention. Unless voiding is

Table 61–5.

Expanded Functional Classification

I. Failure to store
- A. Because of the bladder
  - 1. Overactivity
    - a. Involuntary contractions
      - Neurologic disease, injury, or degeneration
      - Bladder outlet obstruction
      - Stress urinary incontinence
      - Increased afferent input
        - Inflammation
        - Increased neurotransmitter release
      - Idiopathic
    - b. Decreased compliance
      - Neurologic disease or injury
      - Fibrosis
      - Bladder muscle hypertrophy
      - Idiopathic
    - c. Combination
  - 2. Hypersensitivity
    - a. Inflammatory/infectious
    - b. Neurologic
    - c. Increased neurotransmitter release
    - d. Psychologic
    - e. Idiopathic
  - 3. Decreased pelvic floor activity (?)
  - 4. Combination
- B. Because of the outlet
  - 1. Combination (GSI and ISD)
  - 2. Genuine stress urinary incontinence (GSI)
    - a. Lack of suburethral support
    - b. Pelvic floor laxity, hypermobility
  - 3. Intrinsic sphincter deficiency (ISD)
    - a. Neurologic disease or injury
    - b. Fibrosis
- C. Combination

II. Failure to empty
- A. Because of the bladder
  - 1. Neurogenic
  - 2. Myogenic
  - 3. Psychogenic
  - 4. Idiopathic
- B. Because of the outlet
  - 1. Anatomic
    - a. Prostatic obstruction
    - b. Bladder neck contracture
    - c. Urethral stricture
    - d. Urethral compression, fibrosis
  - 2. Functional
    - a. Striated sphincter dyssynergia
    - b. Smooth sphincter dyssynergia or dysfunction
    - c. Dysfunctional voiding
- C. Combination

Table 61–6.

International Continence Society Classification

STORAGE PHASE	VOIDING PHASE
Bladder Function	**Bladder Function**
Detrusor activity	Detrusor activity
Normal or stable	Normal
Overactive	Underactive
Neurogenic	Acontractile
Idiopathic	Areflexic
Bladder sensation	**Urethral Function**
Normal	Normal
Increased or hypersensitive	Abnormal
Reduced or hyposensitive	Mechanical obstruction
Absent	Overactivity
Bladder capacity	Dysfunctional voiding
Normal	Detrusor sphincter dyssynergia
High	Non-relaxing urethral sphincter dysfunction
Low	
Urethral Function	
Normal closure mechanism	
Incompetent closure mechanism	

Modified from Abrams P, Blaivas J, Stanton S, et al. ICS standardization of terminology of lower urinary tract function. Scand J Urol Nephrol 1988;114:5–19; Abrams P, Blaivas J, Stanton S, et al. ICS 6th report on the standardization of terminology of lower urinary tract function. Neurol Urodyn 1992;11:593–603; Abrams P, Cardozo L, Fall M, et al: The standardization of terminology in lower urinary tract function: report from the standardization subcommittee of the International Continence Society. Neurol Urodyn 2002;21:167–78.

Table 61–7.

Urodynamic Classification

Detrusor Hyperreflexia (or Normoreflexia)

Coordinated sphincters
Striated sphincter dyssynergia
Smooth sphincter dyssynergia
Nonrelaxing smooth sphincter

Detrusor Areflexia

Coordinated sphincters
Nonrelaxing striated sphincter
Denervated striated sphincter
Nonrelaxing smooth sphincter

Modified from Krane RJ, Siroky MB. Classification of voiding dysfunction: value of classification systems. In Barrett DM, Wein AJ, editors. Controversies in neurourology. New York: Churchill Livingstone; 1984. p. 223–38.

Table 61–8.

Lapides Classification

Sensory neurogenic bladder
Motor paralytic bladder (motor neurogenic bladder)
Uninhibited neurogenic bladder
Reflex neurogenic bladder
Autonomous neurogenic bladder

initiated on a timed basis, varying degrees of bladder overdistention can result with resultant hypotonicity. If bladder decompensation occurs, significant amounts of residual urine result, and at that time the cystometric curve generally demonstrates a large capacity bladder with a flat, high-compliance, low-pressure filling curve.

A **motor paralytic bladder** results from disease processes that destroy the parasympathetic motor innervation of the bladder. **Extensive pelvic surgery or trauma** may produce this. **Herpes zoster** has been listed as a cause as well, but recent evidence suggests that the voiding dysfunction seen with herpes may be more related to a problem with afferent input (see Chapter 65). The early symptoms of a motor paralytic bladder may vary from painful urinary retention to only a relative inability to initiate and maintain normal micturition. Early cystometric filling is normal but without a voluntary bladder contraction at capacity. Chronic overdistention and decompensation may occur, resulting in a large-capacity bladder with a flat, low-pressure filling curve; a large residual urine may result.

An **uninhibited neurogenic bladder** was described originally as resulting from injury or disease to the "corticoregulatory tract." The sacral spinal cord was presumed to be the micturition reflex center, and this corticoregulatory tract was believed normally to exert an inhibitory influence on the sacral micturition reflex center. A destructive lesion in this tract would then result in overfacilitation of the micturition reflex. **Cerebrovascular accident, brain or spinal cord tumor, Parkinson disease, and demyelinating disease** were listed as the most common causes in this category. The voiding dysfunction is most often characterized symptomatically by frequency, urgency, and urge incontinence and urodynamically by normal sensation with involuntary contraction at low filling volumes. Residual urine is characteristically low unless anatomic outlet obstruction or true smooth or striated sphincter dyssynergia occurs. The patient generally can initiate a bladder contraction voluntarily but is often unable to do so during cystometry because sufficient urine storage cannot occur before involuntary contraction is stimulated.

Reflex neurogenic bladder describes the post–spinal shock condition that exists after complete interruption of the sensory and motor pathways between the sacral spinal cord and the brainstem. Most commonly, this occurs in **traumatic spinal cord injury and transverse myelitis,** but it may occur with **extensive demyelinating disease or any process that produces significant suprasacral (cord) spinal cord destruction.** Typically, there is no bladder sensation, and there is inability to initiate voluntary micturition. Incontinence without sensation generally results from low-volume involuntary contraction. Striated sphincter dyssynergia is the rule. This type of lesion is essentially equivalent to a complete upper motor neuron (UMN) lesion in the Bors-Comarr system (see later).

An autonomous neurogenic bladder results from complete motor and sensory separation of the bladder from the sacral spinal cord. This may be caused by **any disease that destroys the sacral cord or causes extensive damage to the sacral roots or pelvic nerves.** There is inability to initiate micturition voluntarily, no bladder reflex activity, and no specific bladder sensation. This type of bladder is equivalent to a complete lower motor neuron (LMN) lesion in the Bors-Comarr system and is also the type of dysfunction seen in patients with spinal shock. The characteristic cystometric pattern is initially similar to the late stages of the motor or sensory paralytic bladder, with a marked shift to the right of the cystometric filling curve and a large bladder capacity at low intravesical pressure. However, decreased compliance may develop, secondary either to chronic inflammatory change or to the effects of denervation/decentralization with secondary neuromorphologic and neuropharmacologic reorganizational changes. Emptying capacity may vary widely, depending on the ability of the patient to increase intravesical pressure and on the resistance offered during this increase by the smooth and striated sphincters.

These classic categories in their usual settings are generally understood and remembered, and this is why this system provides an excellent framework for teaching some fundamentals of neurogenic voiding dysfunction to students and nonurologists. Unfortunately, **many patients do not exactly fit into one or another category.** Gradations of sensory, motor, and mixed lesions occur, and the patterns produced after different types of peripheral denervation/defunctionalization may vary widely from those that are classically described. **The system is applicable only to neuropathic dysfunction.**

Bors and Comarr (1971) made a remarkable contribution by logically deducing a classification system from clinical observation of their patients with traumatic spinal cord injury (Table 61–9). **This system, primarily of historical interest at present, applies only to patients with neurologic dysfunction and considers three factors: (1) the anatomic localization of the lesion, (2) the neurologic completeness or incompleteness of the lesion, and (3) whether lower urinary tract function is *balanced* or *unbalanced*.** The last terms are based solely on the percentage of residual urine relative to bladder capacity. **Unbalanced** signifies the presence of greater than 20% residual urine in a patient with a UMN lesion or 10% in a patient with an LMN lesion. This relative residual urine volume was ideally meant to imply coordination (synergy) or dyssynergia between the smooth and the striated sphincters of the outlet and the bladder during bladder contraction or during attempted micturition by abdominal straining or the Credé maneuver. The determination of the completeness of the lesion is made on the basis of a thorough neurologic examination.

Table 61–9.

Bors-Comarr Classification

Sensory Neuron Lesion
Incomplete, balanced
Complete, balanced
Motor Neuron Lesion
Balanced
Imbalanced
Sensory-Motor Neuron Lesion
Upper motor neuron lesion
Complete, balanced
Complete, imbalanced
Incomplete, balanced
Incomplete, imbalanced
Lower motor neuron lesion
Complete, balanced
Complete, imbalanced
Incomplete, balanced
Incomplete, imbalanced
Mixed lesion
Upper somatomotor neuron, lower visceromotor neuron
Lower somatomotor neuron, upper visceromotor neuron
Normal somatomotor neuron, lower visceromotor neuron

The system erroneously assumes that the sacral spinal cord is the primary reflex center for micturition. LMN implies collectively the preganglionic and postganglionic parasympathetic autonomic fibers that innervate the bladder and outlet and originate as preganglionic fibers in the sacral spinal cord. The term is used in an analogy to efferent somatic nerve fibers such as those of the pudendal nerve, which originate in the same sacral cord segment but terminate directly on pelvic floor striated musculature without the interposition of ganglia. **UMN** is used in a similar analogy to the somatic nervous system to describe the descending autonomic pathways above the sacral spinal cord (the origin of the motor efferent supply to the bladder).

In this system, **UMN bladder** refers to the pattern of micturition that results from an injury to the suprasacral spinal cord after the period of spinal shock has passed, assuming that the sacral spinal cord and the sacral nerve roots are intact and that the pelvic and pudendal nerve reflexes are intact. **LMN bladder** refers to the pattern resulting if the sacral spinal cord or sacral roots are damaged and the reflex pattern through the autonomic and somatic nerves that emanate from these segments is absent. This system implies that if skeletal muscle spasticity exists below the level of the lesion, the lesion is above the sacral spinal cord and is by definition a UMN lesion. This type of lesion is characterized by involuntary bladder contraction during filling. If flaccidity of the skeletal musculature below the level of a lesion exists, an LMN lesion is assumed to be present, implying that detrusor areflexia is present. Exceptions occur and are classified in a **"mixed lesion group"** characterized either by involuntary bladder contraction with a flaccid paralysis below the level of the lesion or by detrusor areflexia with spasticity or normal skeletal muscle tone neurologically below the lesion level.

The use of this system is illustrated as follows. A **"UMN lesion, complete, imbalanced"** implies a neurologically complete lesion above the level of the sacral spinal cord that results in skeletal muscle spasticity below the level of the injury. Involuntary bladder contraction occurs during filling, but a residual urine volume of greater than 20% of the bladder capacity is left after bladder contraction, implying obstruction in the area of the bladder outlet during the involuntary detrusor contraction. This obstruction is generally due to striated sphincter dyssynergia, typically occurring in patients who are paraplegic or quadriplegic with lesions between the cervical and the sacral spinal cord. Smooth sphincter dyssynergia may be seen as well in patients with lesions above the level of T6, usually associated with autonomic hyperreflexia (see Chapter 65). An **"LMN lesion, complete, imbalanced"** implies a neurologically complete lesion at the level of the sacral spinal cord or of the sacral roots, resulting in skeletal muscle flaccidity below that level. Detrusor areflexia results, and whatever measures the patient may use to increase intravesical pressure during attempted voiding are not sufficient to decrease residual urine to less than 10% of bladder capacity.

This classification system applies best to spinal cord injury patients with complete neurologic lesions after spinal shock has passed. It is difficult to apply to patients with multicentric neurologic disease and cannot be used at all for patients with non-neurologic disease. The system fails to reconcile the clinical and urodynamic variability exhibited by patients who, by neurologic examination alone, seem to have similar lesions. The period of spinal shock that immediately follows severe cord injury is generally associated with bladder areflexia, whatever the status of the sacral somatic reflexes. Temporary or permanent changes in bladder or outlet activity during filling/storage and emptying/voiding may occur secondary to a number of factors such as chronic overdistention, infection, and reinnervation or reorganization of neural pathways following injury or disease; such changes make it **impossible to always accurately predict lower urinary tract activity solely on the basis of the level of the neurologic lesion.** Finally, although the terms *balanced* and *imbalanced* are helpful, in that they describe the presence or absence of a certain relative percentage of residual urine, they do not necessarily imply the true functional significance of a lesion, which depends on the potential for damage to the lower or upper urinary tracts and also on the social and vocational disability that results.

Table 61–10.

Hald-Bradley Classification

Suprasacral lesion
Suprasacral spinal lesion
Infrasacral lesion
Peripheral autonomic neuropathy
Muscular lesion

Hald-Bradley Classification

Hald and Bradley (1982) described what they termed a simple neurotopographic classification (Table 61–10). The system is of historical interest only. A **supraspinal lesion** is characterized by synergy between detrusor contraction and the smooth and striated sphincters, but defective inhibition of the voiding reflex exists. Involuntary bladder contraction generally occurs, and sensation is usually preserved. However, depending on the site of the lesion, detrusor areflexia and defective sensation may be seen. A **suprasacral spinal lesion** is roughly equivalent to what is described as a UMN lesion in the Bors-Comarr classification. An **infrasacral lesion** is roughly equivalent to an LMN lesion. **Peripheral autonomic neuropathy** is most frequently encountered in the diabetic patient and is characterized by deficient bladder sensation, gradually increasing residual urine, and ultimate decompensation, with loss of detrusor contractility. A **muscular lesion** can involve the detrusor itself, the smooth sphincter, or any portion, or all, of the striated sphincter. The resultant dysfunction is dependent on which structure is affected. Detrusor dysfunction is the most common and generally results from decompensation, following long-standing bladder outlet obstruction. In my opinion, this system is as confusing as the word neurotopographic and adds little to the understanding of lower urinary tract dysfunction.

Bradley Classification

Bradley's "loop system" of classification is a primarily neurologic system based on his conceptualization of central nervous system control of the lower urinary tract that identifies four neurologic "loops" (Hald and Bradley, 1982). Dysfunctions are classified according to the loop affected. Occasional reference is made to this system, primarily by nonurologists.

Loop 1 consists of neuronal connections between the cerebral cortex and the pontine mesencephalic micturition center; this coordinates voluntary control of the detrusor reflex. **Loop 1 lesions** are seen in conditions such as **brain tumor, cerebrovascular accident or disease, and cerebral atrophy with dementia.** The final result is characteristically **involuntary bladder contractions.**

Loop 2 includes the intraspinal pathway of detrusor muscle afferents to the brainstem micturition center and the motor impulses from this center to the sacral spinal cord. Loop 2 is thought to coordinate and provide for a detrusor reflex of adequate temporal duration to allow complete voiding. Partial interruption by spinal cord injury results in a detrusor reflex of low threshold and in poor emptying with residual urine. **Spinal cord transection of loop 2 acutely produces detrusor areflexia and urinary retention—spinal shock. After this has passed, involuntary bladder contractions result.**

Loop 3 consists of the peripheral detrusor afferent axons and their pathways in the spinal cord; these terminate by synapsing on pudendal motor neurons that ultimately innervate periurethral striated muscle. Loop 3 was thought to provide a neurologic substrate for coordinated reciprocal action of the bladder and striated sphincter. **Loop 3 dysfunction could be responsible for detrusor striated dyssynergia or involuntary sphincter relaxation.**

Loop 4 consists of two components. Loop 4A is the suprasacral afferent and efferent innervation of the pudendal motor neurons to the periurethral striated musculature. Loop 4B consists of afferent fibers from the periurethral striated musculature that synapse on pudendal motor neurons in Onuf nucleus—the segmental innervation of the periurethral striated muscle. Bradley conceptualized that, in contrast to the stimulation of detrusor afferent fibers, which produced inhibitory postsynaptic potentials in pudendal motor neurons through loop 3, pudendal nerve afferents produced excitatory postsynaptic potentials in those motor neurons through loop 4B. These provided for contraction of the periurethral striated muscle during bladder filling and urine storage. The related sensory impulses arise from muscle spindles and tendon organs in the pelvic floor musculature. **Loop 4 provides for volitional control of the striated sphincter.** Abnormalities of the suprasacral portion result in abnormal responses of the pudendal motor neurons to bladder filling and emptying, manifested as detrusor striated sphincter dyssynergia or loss of the ability to contract the striated sphincter voluntarily, or both.

The Bradley system is sophisticated and reflects the ingenuity and neurophysiologic expertise of its originator, himself a neurologist. For neurologists, this method may be an excellent way to conceptualize the neurophysiology involved, assuming that there is, in fact, agreement on the existence and significance of all four loops—a big assumption. Most urologists find this system difficult to use for many types of neurogenic voiding dysfunction and not at all applicable to non-neurogenic voiding dysfunction. Urodynamically, it may be extremely difficult to test the intactness of each loop system, and multicentric and partial lesions are difficult to describe.

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chapter 62

Urodynamic and Video-Urodynamic Evaluation of the Lower Urinary Tract

Victor W. Nitti, MD

Role of Urodynamic Testing in Clinical Practice
Functional Classification of Voiding Dysfunction: Applicability to Urodynamic Testing
Conducting a Urodynamic Study: Patient and Technical Factors
Components of the Urodynamic Study
Urodynamic Equipment
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Filling and Storage Phase
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Clinical Utility of Ambulatory Urodynamics
Clinical Applications of Urodynamic Studies: Evidence-Based Review
Evaluation of Women with Stress Incontinence
Evaluation of Men with Lower Urinary Tract Symptoms
Evaluation of Neuropathic Lower Urinary Tract Dysfunction
Evaluation of Children

Urodynamics (UDS) is the term used to describe testing and measurements of the function of the lower urinary tract. The lower urinary tract has two essential functions: the storage of urine at low pressure and the voluntary evacuation of urine. Low-pressure storage is essential to protect kidneys and ensure continence, whereas voluntary evacuation allows for the elimination of urine in socially acceptable situations without fear of leakage or overdistention. It is clear that a number of conditions and diseases affect the lower urinary tract and disrupt the storage and/or evacuation of urine. This can lead to bothersome symptoms (e.g., urinary incontinence or pain from failure to empty) or, in some cases, potentially harmful sequela. In many cases, a precise assessment of storage and emptying is necessary to optimally treat patients. **UDS is the dynamic study of the transport, storage, and evacuation of urine. It is composed of a number of tests that individually or collectively can be used to gain information about urine storage and evacuation.** UDS involves the assessment of the function and dysfunction of the urinary tract and includes the actual tests that are performed (UDS studies) and the observations during the testing (UDS observations) (Abrams et al, 1988, 2002). In this chapter we discuss the use of urodynamics to help in the assessment and treatment of voiding dysfunction. We keep that discussion in practical terms and supplement it with evidence for the technical performance and clinical utility of UDS.

ROLE OF URODYNAMIC TESTING IN CLINICAL PRACTICE

UDS has been used for decades, yet clear-cut, level 1, evidenced-based "indications" for its use are surprisingly lacking. There are a number of reasons for this. It is difficult to conduct proper randomized controlled trials on UDS for conditions in which lesser levels of evidence and expert opinion strongly suggest clinical utility and in which "empiric treatment" is potentially harmful or even life threatening (e.g., neurogenic voiding dysfunction). Additionally, symptoms can be caused by a number of different conditions and it is difficult to study pure or homogeneous patient populations. **Given the current state of evidence for UDS studies, what is most important is that the clinician has clear-cut reasons for performing the study and that the information obtained will be used to guide treatment of**

the patient. Therefore it is probably more useful to describe the role of UDS in clinical practice rather than precise "indications" for its use.

In practical terms, UDS is most useful when history, physical examination, and simple tests are not sufficient to make an accurate diagnosis and/or institute treatment. This has clinical applicability in two general scenarios:

1. To obtain information needed to make an accurate diagnosis for what condition(s) is causing symptoms (e.g., lower urinary tract symptoms or incontinence).
2. To determine the impact of a disease that has the potential to cause serious and irreversible damage to the upper and lower urinary tract (e.g., neurologic diseases like spinal cord injury and multiple sclerosis, radiation cystitis). Sometimes profound abnormalities can be found in the relative absence of symptoms.

Rather than refer to a list of "indications for UDS" that often are not evidence based at all, it is more useful for clinicians to think of how UDS should be used in a broader clinical perspective. In keeping with that theme, the role of UDS in clinical practice has been nicely summarized by Hosker and colleagues (2009) **for the following situations:**

1. **To identify or rule out factors contributing to lower urinary tract dysfunction (e.g., urinary incontinence) and assess their relative importance**
2. **To obtain information about other aspects of lower urinary tract function or dysfunction**
3. **To predict the consequences of lower urinary tract dysfunction on the upper urinary tract**
4. **To predict the outcome including undesirable side effects of a contemplated treatment**
5. **To confirm the effects of intervention or understand the mode of action of a particular type of treatment (especially a new one)**
6. **To understand the reasons for failure of previous treatments for symptoms (e.g., urinary incontinence) or for lower urinary tract function in general**

In order to use UDS in a practical and effective way, it is important that the clinician has the proper expertise to know when and why to perform a UDS study. Despite many technical advances in the recording, processing, and printing of UDS studies, careful attention to technical details to ensure accurate collection of data remains the cornerstone of a good study. Because not all patients undergo UDS for the same reasons, the clinician should "customize" UDS to the patients' symptoms and condition. **That means deciding on the questions to be answered before starting each study and designing that study to obtain the answers to those questions.** It is important to remember that UDS is performed in an "unnatural setting" and therefore does not always duplicate real life. A UDS study that does not duplicate complaints or symptoms when an abnormality is recorded is not necessarily diagnostic. In addition, failure to record an abnormality does not always rule out its existence (e.g., failure to demonstrate detrusor overactivity in a patient with urge incontinence). Finally, not all UDS observations are clinically significant. **Therefore it is important to interpret UDS studies in the context of the patient's history including symptoms and concomitant diseases/conditions, as well as other information like postvoid residual volumes and frequency volume charts (voiding and intake diaries) when clinically applicable.**

FUNCTIONAL CLASSIFICATION OF VOIDING DYSFUNCTION: APPLICABILITY TO URODYNAMIC TESTING

In order to formulate a set of questions to be answered by a urodynamic test, an understanding of the possible causes of symptoms and the possible urodynamic manifestations of a preexisting condition is necessary. In order to accomplish this, a practical classification of voiding dysfunction is invaluable. The system proposed and popularized by Wein (1981) is simple and allows one to classify voiding dysfunction according to urodynamic findings. **Functional abnormalities of the lower urinary tract can be divided into the following:**

1. **Storage dysfunction (failure to properly store urine)**
2. **Emptying dysfunction (failure to empty the bladder normally)**
3. **Combined dysfunction (failure to store and empty)**

In addition, functional abnormalities can be subclassified to the anatomic region of the lower urinary tract that is affected and how it is affected. Thus storage and emptying abnormalities can be caused by the following:

1. **Bladder dysfunction: overactive (causing failure to store) or underactive (causing failure to empty)**
2. **Bladder outlet dysfunction: overactive (causing failure to empty) or underactive (causing failure to store)**
3. **Combined bladder and bladder outlet dysfunction**

The beauty of a functional classification system is that it helps to clarify treatment options for a given patient. Thus in practical terms, the UDS evaluation should help to determine if there is bladder or bladder outlet dysfunction (or both) and whether there is a storage and/or emptying problem. By providing answers to these simple questions, the urodynamic test can lead to a correct diagnosis and, equally as important, institution of appropriate treatment. Obviously, an understanding of the physiology of urine storage and voiding and the pathophysiology of voiding dysfunction (see Chapter 61) is required to formulate appropriate questions to be answered by a urodynamic study. However, all too often clinicians get caught up in the intricate neurophysiologic aspects of voiding and storage dysfunction and fail to think in practical terms. One should always focus on the possible urodynamic findings in a given case and how each of the findings may ultimately affect the patient and his or her treatment. Obviously, these potential findings will be determined by symptoms and/or underlying conditions or diseases.

CONDUCTING A URODYNAMIC STUDY: PATIENT AND TECHNICAL FACTORS

Preparing for Urodynamic Study: Clinician, Patient, and Facility

Once the decision has been made to perform UDS on a particular patient, it is important to consider what information is expected from the test. The simple fact that a patient has symptoms or a disorder that may affect the lower urinary tract is not sufficient to

start the UDS evaluation. **A list of problems or questions that should be solved or answered by UDS should be made before any testing is performed.** All patients are not alike, so each urodynamic evaluation may be different depending on the information needed to answer the questions relevant to a particular patient. **We follow three important rules before starting the UDS evaluation** (Nitti and Combs, 1998):

1. **Decide on questions to be answered before starting a study.**
2. **Design the study to answer these questions.**
3. **Customize the study as needed.**

By following these simple rules, one can maximize the chance of obtaining useful information from a study. If a particular question is not answered, the study can be repeated in the same session. Most people who do urodynamics regularly would concur that a urodynamic test is not always perfect in answering all important questions, but by defining the information needed before starting the study, "unanswered questions" can be kept to a minimum. As mentioned earlier, one of the most important parts of UDS is its proper performance with careful attention to technical details so that accurate interpretation is possible. It is beyond the scope of this chapter to describe the proper performance of UDS in detail; however, the reader is referred to Schafer and colleagues (2002) for good urodynamic practices and Abrams and colleagues (2002) for terminology. The International Continence Society (ICS) has now defined the term "urodynamic observations" to denote those observations that occur during and are measured by the UDS test itself. In order to be consistent, it is recommended that all clinicians performing and interpreting UDS use the current ICS terminology (Abrams et al, 2002). A list of common UDS terms is provided in Table 62–1.

Ideally a room of suitable size should be dedicated to urodynamics (Nitti and Combs, 1998). This area does not have to be exclusively for urodynamics, but when a study is being performed, there should not be distractions from people walking into and out of the area for other reasons. A quiet, private area is the best. It is difficult enough to recreate a natural environment during testing without outside distractions. The room should be large enough to allow for the patient to lie down to have catheters placed and also to be able to stand and sit on a commode as needed. Many patients

Table 62–1.

Terminology for Common Urodynamic Terms and Observations According to the International Continence Society Standardization Subcommittee

The ICS has now defined the term urodynamic observations to denote observations that occur during and are measured by the urodynamics (UDS) test itself. In order to be consistent, it is recommended that all clinicians performing and interpreting UDS use the current ICS terminology (Abrams et al, 2002).

Two principal methods of urodynamic investigation exist:
- Conventional urodynamic studies: normally take place in the urodynamic laboratory involving artificial bladder filling.
- Ambulatory urodynamic studies: a functional test of the lower urinary tract using natural filling and reproducing the subject's everyday activities.

The following are required of both types of studies:
- Intravesical pressure: the pressure within the bladder.
- Abdominal pressure: the pressure surrounding the bladder; currently it is estimated from rectal, vaginal, or extraperitoneal pressure or a bowel stoma.
- Detrusor pressure: the component of intravesical pressure created by forces on the bladder wall that are both passive and active.
- Filling cystometry: the method by which the pressure and volume relationship of the bladder is measured during bladder filling.
- Physiologic filling rate: a filling rate less than the predicted maximum. Predicted maximum is the body weight in kilograms divided by 4 and expressed as milliliters per minute.
- Nonphysiologic filling rate: a filling rate greater than the predicted maximum.

Bladder sensation during filling cystometry:
- Normal bladder sensation, defined by three points noted during filling cystometry and evaluated in relation to the bladder volume at that moment and in relation to the patient's symptomatic complaints.
- First sensation of bladder filling: the volume at which the patient first becomes aware of the bladder filling.
- First desire to void: the feeling during filling cystometry that would lead the patient to pass urine at the next convenient moment.
- Strong desire to void: a persistent desire to void without the fear of leakage.
- Increase that occurs at low bladder volumes and persists.
- Reduced bladder sensation: diminished sensation throughout bladder filling.
- Absent bladder sensation: the individual has no bladder sensation.
- Nonspecific bladder sensation: the individual is aware of bladder filling because of other sensations such as abdominal fullness or vegetative symptoms.
- Bladder pain: a self-explanatory term that is abnormal.
- Urgency: a sudden compelling desire to void.
- Normal detrusor function: allows bladder filling with little or no change in pressure, no involuntary contractions despite provocative maneuvers.
- Detrusor overactivity: involuntary detrusor contractions during the filling phase, spontaneous or provoked.
- Phasic detrusor overactivity: a characteristic waveform that may or may not lead to urinary incontinence.
- Terminal detrusor overactivity: a single involuntary detrusor contraction occurring at cystometric capacity that cannot be suppressed, resulting in incontinence with bladder emptying.
- Detrusor overactivity incontinence: incontinence related to involuntary detrusor contractions. This may be qualified according to cause.
- Neurogenic detrusor overactivity: overactivity accompanied by a neurologic condition; this term replaces the term *detrusor hyperreflexia*.
- Idiopathic detrusor overactivity: detrusor overactivity without concurrent neurologic etiology. This term replaces the term *detrusor instability*.

Continued

Table 62–1.

Terminology for Common Urodynamic Terms and Observations According to the International Continence Society Standardization Subcommittee—cont'd

Provocative maneuvers: techniques used during urodynamic border to provoke detrusor overactivity.
Cystometric capacity: the bladder volume at the end of the filling cystogram when permission to void is given.
Maximum cystometric capacity: the volume at which the patient feels he or she can no longer delay micturition and has a strong desire to void.
Maximum anesthetic bladder capacity: the volume to which the bladder can be filled under deep general or spinal anesthesia. This should be qualified as to what type of anesthesia is used, the rate of filling, the length of time of filling, and the pressure to which the bladder is filled.
Normal urethral closure mechanism: this maintains a positive urethral closure pressure during bladder filling even in the presence of increased abdominal pressure.
Incompetent urethral closer mechanism: this is defined as one allowing leakage of urine in the absence of detrusor contraction.
Urethral relaxation incontinence: leakage related to urethral relaxation in the absence of raised abdominal pressure or detrusor overactivity.
Urodynamic stress incontinence: noted during filling cystometry and defined as the involuntary leakage of urine during increased abdominal pressure in the absence of a detrusor contraction. This currently replaces genuine stress incontinence.
Urethral pressure measurements:
- Urethral pressure: the fluid pressure needed to just open a closed urethra.
- Urethral pressure profile: a graph indicating the intraluminal pressure along the length of the urethra.
- Urethral closure pressure profile: the subtraction of intravesical pressure from urethral pressure.
- Maximum urethral pressure: the maximum pressure of the measured profile.
- Maximum urethral closure pressure (MUCP): the maximum difference between the urethral pressure and the intravesical pressure.
- Functional profile length: the length of the urethra along which the urethral pressure exceeds intravesical pressure in women.
- Pressure transmission ratio: the increment in urethral pressure on stress as a percentage of the simultaneously recorded increment in intravesical pressure.

Abdominal leak point pressure: the intravesical pressure at which urine leakage occurs because of increased abdominal pressure in the absence of a detrusor contraction.
Detrusor leak point pressure: the lowest detrusor pressure at which urine leakage occurs in the absence of either a detrusor contraction or increased abdominal pressure.
Pressure-flow studies: the method by which the relationship between pressure in the bladder and urine flow rate is measured during bladder emptying.
Pressure measurements during pressure-flow studies:
- Premicturition pressure: the pressure recorded immediately before the initial isovolumetric contraction.
- Opening pressure: the pressure recorded at the onset of urine flow.
- Opening time: the elapsed time from original rise in detrusor pressure to onset of flow.
- Maximum pressure: the maximum value of the measured pressure.
- Pressure at maximum flow: the lowest pressure recorded at maximum measured flow rate.
- Closing pressure: the pressure measured at the end of measured flow.
- Minimum voiding pressure: the minimum pressure during measurable flow.
- Flow delay: the time delay between a change in bladder pressure and the corresponding change in measured flow rate.

From Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Subcommittee of the International Continence Society. Neurourol Urodyn 2002;21:167–78; and Schafer W, Abrams P, Liao L, et al. Good urodynamic practices: uroflowmetry, filling, cystometry, and pressure-flow studies. Neurourol Urodyn 2002;21:261–74.

undergoing urodynamic testing will have neurologic problems that limit mobility and will require assistance with positioning. This includes patients in wheelchairs. This must be considered when determining the size of the room. Centers that perform video-urodynamics (VUDS) will require a larger area to allow for x-ray equipment.

The importance of a well-trained, attentive, and supportive staff involved with the UDS study cannot be overemphasized. With that said, in general, UDS is well tolerated. **However, patients should be properly prepared and told why the test is being done, how the results may affect treatment, and what to expect during the actual UDS test.** Scarpero and colleagues (2005) used a questionnaire-based study to assess patient expectations of anxiety, pain, embarrassment, and apprehension before UDS and compared it with the patient's actual experience. They found that UDS was associated with minimal to moderate degrees of anxiety, discomfort, and embarrassment. After testing, most respondents (>90% per question) thought that the test was the same or better than expected and had an expected or less than expected level of pain and embarrassment. This did not vary between the sexes, but a higher number of younger individuals found that the test experience was worse than expected, whereas a higher number of older individuals found that it was better than expected. Therefore younger patients may require more reassurance and attention in preparation for the procedure.

Many patients undergoing urodynamic testing will have been placed on medications that affect bladder function (e.g., antimuscarinics). For such patients the clinician should decide in advance what information is desired and whether or not the study should be done on or off medication. For example, if the goal of the study is to determine the therapeutic effect of a medication, obviously the UDS should be done with the patient on a regular dosing schedule for that medication. On the other hand, if medication was started empirically to treat symptoms and the goal of the urodynamic test is to uncover the etiology of those symptoms, then consideration can be given to discontinuing the medication before testing because this may give the highest yield.

COMPONENTS OF THE URODYNAMIC STUDY

Before discussing the details of the UDS test itself, it is useful to be familiar with its different components. These tests within the test can be used individually or in combination depending on the information desired. For the purposes of this chapter we discuss each component as part of the entire multichannel UDS or video UDS study. Uroflow and postvoid residual (PVR) determination are two simple, noninvasive tests that can be used to evaluate voiding function and perhaps prompt further testing. In addition, both are part of a multichannel UDS study.

PVR is an excellent assessment of bladder emptying. It can be performed by ultrasound (bladder scan) or catheterization. Elevation of PVR indicates a problem with emptying but does not tell why. An elevated PVR may prompt further testing.

Uroflowmetry is measurement of the rate of urine flow over time. It is also an assessment of bladder emptying. Normal uroflow is a bell-shaped curve. When the flow rate is reduced or the pattern is altered, this could indicate bladder (underactive) or bladder outlet (obstruction) dysfunction (Fig. 62–1).

Cystometrogram (CMG): Cystometry or, more appropriately, "filling cystometry" is the method by which the pressure/volume relationship of the bladder is measured during bladder filling. The filling phase starts when filling commences and ends when the patient and urodynamicist decide that "permission to void" has been given. CMG can be performed by the single measurement of bladder pressure via a bladder catheter (urethral or suprapubic); however, changes in bladder pressure can represent a change in detrusor pressure (Pdet) or a change in abdominal pressure (Pabd) (see later). Therefore it is recommended that CMG be performed by measuring both the total vesical pressure (Pves) and Pabd (measured by a catheter placed in the rectum or vagina). To calculate Pdet, the following equation is used: **Pdet = Pves – Pabd** (Fig. 62–2).

Electromyography (EMG) is the study of the electronic potentials produced by the depolarization of muscle membranes. In the case of UDS, EMG measurement of the striated sphincteric muscles of the perineum is done to evaluate possible abnormalities of perineal muscle function, which are often associated with lower urinary tract symptoms and dysfunction. EMG activity is measured during both filling and emptying. EMG is obtained via electrodes placed in or near the muscle to be measured.

Urethral pressure profile (UPP) is a graph indicating the intraluminal pressure along the length of the urethra. Urethral pressure is defined as the fluid pressure needed to just open a closed urethra. UPP is obtained by the withdrawal of a pressure sensor (catheter) along the length of the urethra.

Pressure-flow studies (PFS) of voiding are the method by which the relationship between pressure in the bladder and urine flow rate is measured during bladder emptying. Detrusor pressure is measured as explained earlier with the simultaneous measurement of flow rate by a uroflowmeter. The voiding phase starts when "permission to void" is given, or when uncontrollable voiding begins, and ends when the patient considers voiding has finished.

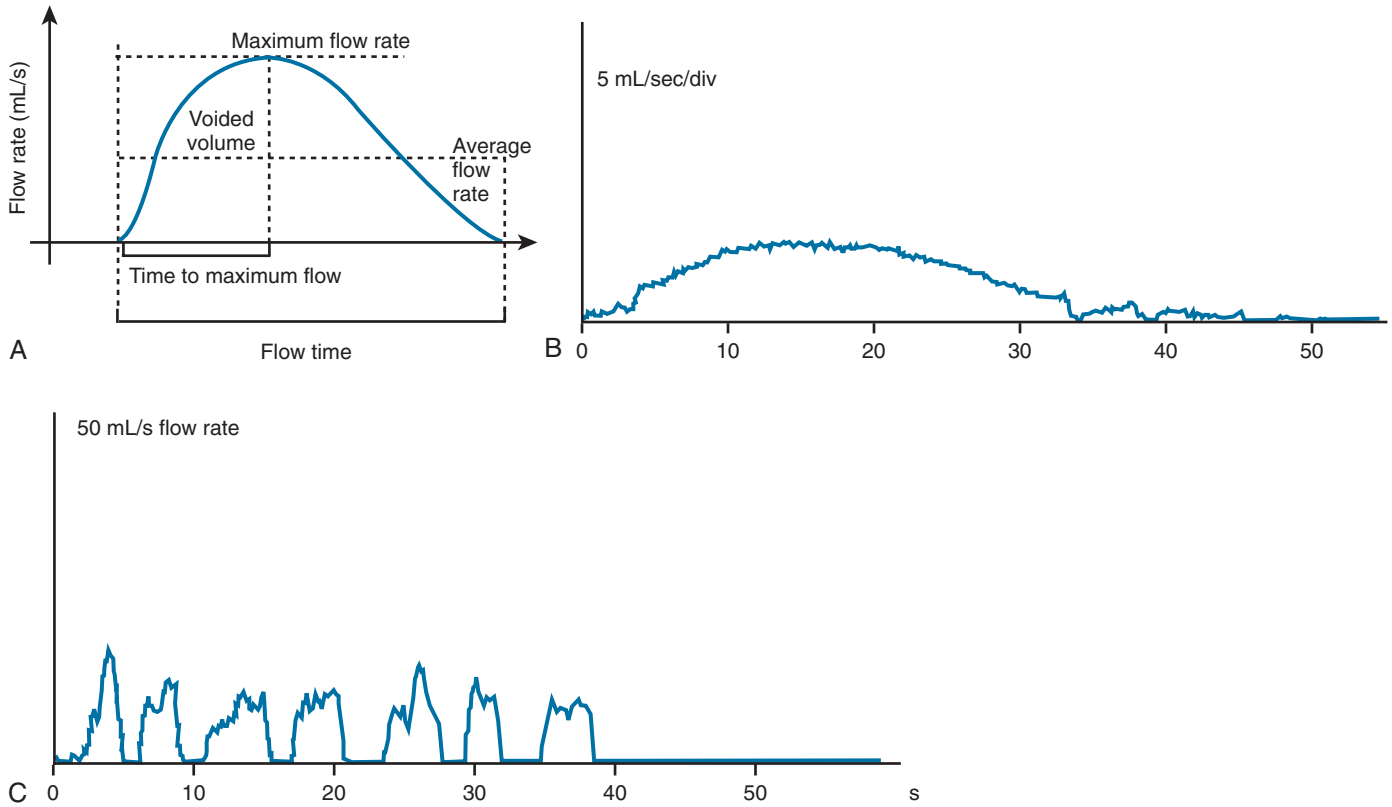


Figure 62–1. Examples of uroflow curves. **A,** Normal bell-shaped flow curve of flow rate versus time. **B,** A flattened pattern is usually indicative of obstruction. **C,** An interrupted or straining pattern, which can be seen with impaired bladder contractility, obstruction, or voiding with or by abdominal straining. (**A** from Wein AJ, English WS, Whitemore KE. Office urodynamics. Urol Clin North Am 1988;15:609; **B** and **C** from Boone TB, Kim YH. Uroflowmetry. In: Nitti VW, editor. Practical urodynamics. Philadelphia: WB Saunders; 1998. p. 28–51.)

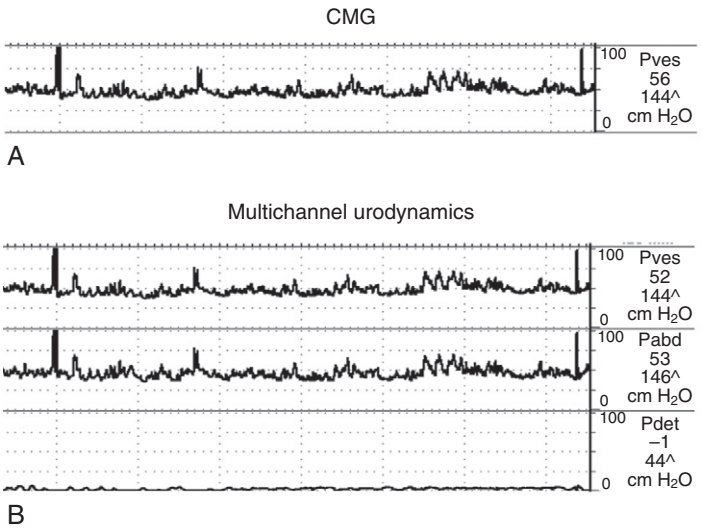


Figure 62–2. Cystometrogram (CMG) measures the pressure in the bladder as the bladder fills over time. Standard fill rates in adults are 30 to 100 cm/H_2O per minute. Adding intra-abdominal pressure monitoring gives a better representation of the true detrusor pressure. **A,** Single-channel CMG where only the total vesical pressure (Pves) is measured. Note the multiple spikes and rises in pressure. Without having simultaneous monitoring of intra-abdominal pressure, it is impossible if these pressure spikes are due to a rise in detrusor or abdominal pressure. **B,** This same tracing with intra-abdominal pressure (Pabd) monitoring added (Multichannel UDS). This allows for the determination of (subtracted) detrusor pressure (Pdet). Now it can be clearly seen that changes in Pves were due to the changes in Pabd (e.g., movement, coughing). The Pdet curve is noted to be flat and without any rises in pressure. (From Nitti VW. Cystometry and abdominal pressure monitoring. In Nitti VW, editor. Practical urodynamics. Philadelphia: WB Saunders; 1998. p. 38–51.)

URODYNAMIC EQUIPMENT

Urodynamic Systems

Various urodynamic systems are available today. They range in price from several thousand dollars to more than 100,000 dollars depending on their complexity and the features they contain. Most high-end systems are computer-based digital systems that allow for easy data storage and postprocessing of the study. In addition, they allow for hardware and software upgrades as needed. It is beyond the scope of this chapter to describe in detail the options available for UDS systems. However, it is recommended that, when choosing a system, one must consider the patient population and spectrum of diseases frequently encountered, space, convenience of operation (if a factor), and the need for data storage and processing. In addition, it is recommended that a multichannel system in which channels are available to measure vesical pressure, abdominal pressure (and subtracted detrusor pressure), and flow rate is used. Some clinicians may also desire channels for electromyography and urethral pressure measurement. The UDS system and software market is constantly changing, so what is state-of-the-art today may seem "outdated" tomorrow. However, despite all the advances, the clinician performing the study remains the most important constant in data collection and interpretation. For the most realistic assessment, the infusant should be a liquid (e.g., normal saline or radiographic contrast) that will most approximate urine. The use of gas such as carbon dioxide is no longer recommended. Many advanced urodynamic centers now perform VUDS. Adding this capability is expensive but allows one to perform the most comprehensive study possible. There are certain clinical settings in which VUDS is the test of choice (see later). In addition to the necessary urodynamic hardware and software, a fluoroscopy unit and room of adequate size are required. Obviously, this is not practical or necessary in every setting. Video-urodynamic studies also require a greater time commitment on the part of the clinician to ensure accurate data collection.

Signal Transmission and Transducers

Transducers are the hardware that allows pressure in the patient to be measured and transferred to the UDS system. External strain-gauge transducers located "between" the patient and the urodynamic machine have been popular for years. Pressurized tubing (to avoid dampening or dissipation of the pressure) extends from the pressure transducer to the catheters placed in the patient. An electronic cable or "wireless transmission" brings the signal from the transducer to the urodynamic machine. Traditionally a water-filled system in which the entire system from transducer to patient is filled with water has been used. Since this system depends on the transmission of pressure through fluid (water), it is crucial that there are no air bubbles in the transducer or tubing. The pressurized tubing transmission lines should be lucent to allow for easy recognition of air in the line. The transducers are usually set at the level of the patient's bladder (symphysis pubis) at the start of the study. This is important because if the patient changes position during the test (e.g., standing to sitting), the height of the transducer can be adjusted so that it remains at the level of the bladder.

More recently, **air-charged catheters** have become popular for pressure measurement (T-Doc, Wenonah, NJ). This catheter uses a miniature, air-filled balloon placed circumferentially around a polyethylene catheter. External forces on the balloon of the catheter are transmitted to the air-filled catheter lumen and communicated to an external semiconductor transducer. The technology of the balloon system allows circumferential measurement readings. The catheters are disposable and single use. Air-charged catheters have several practical advantages over fluid-filled pressure lines because there is no fluid connection between the patient and the urodynamic equipment—just air. This means there is no hydrostatic pressure effect to account for so that there is no need to position anything at the level of the symphysis pubis and there is no need to flush the system through to exclude air (essential when using a fluid-filled system). Also, there are no artifactual fluctuations in pressure produced when the patients move. It must also be remembered that **many UDS nomograms and other "standards of measurement" were determined using fluid-filled systems. Although there is comparative evidence for the use of air-charged catheters to measure urethral pressure** (Pollak et al, 2004), **no studies have shown definitively that air-charged catheters provide an acceptable alternative to fluid-filled lines for measuring intravesical and intra-abdominal pressure in UDS.** Thus it is recommended that investigators planning to use air-charged catheters for intravesical and intra-abdominal pressure monitoring check for themselves that they have an equivalent performance to their current system for measuring pressure (Hosker et al, 2009).

Finally a microtip or fiberoptic system can be used to process pressure transmission. Here the transducer is contained within the catheter. This in turn is connected directly into the urodynamic machine via a cable. These catheters are quite expensive but reusable. They must be sterilized before each use.

Uroflowmeters

Urine flow rate or uroflow can be determined by a number of different types of devices or uroflowmeters. Modern uroflowmeters use weight, electrical capacitance, or a rotating disc to determine urinary flow rates. The two most common techniques used today are the weight transducer or load cell method and the rotating disc method. With the load cell the voided "weight" is measured and is then differentiated with respect to time to determine the flow rate. In the rotating disc method the urine stream is directed onto a rotating disc, and the power necessary to keep a disc rotating at a constant rate is measured. This power is proportional to the flow rate. The electronic dipstick flowmeter measures the electrical capacitance of a dipstick mounted in a collecting chamber. The output of the signal is proportional to the accumulated volume, and the volumetric flow rate is determined by differentiation. Each of these methods has advantages and disadvantages. The weight transducer method is simple, reliable, and accurate regardless of the site of stream impact but requires that the density of urine must be set. The rotating disc method is also reliable and accurate, and it provides a direct measurement without need for differentiation of volume with respect to time. Electronic flowmeters provide a range of electronically read flow parameters with graphical depiction of the uroflow and have sufficient precision for clinical use with error rates of 1% to 8% in voided volume and 4% to 15% in flow rate (Susset, 1983). Variations in specific gravity of the fluid voided (infusant when doing UDS studies) can affect the calculated flow rate. Most systems allow for calibrations for various fluids such as radiographic contract.

Electromyography

Muscle depolarization must be detected by an electrode placed in or near the muscle. Several different methods are available to do this including surface electrodes and needle electrodes (the two most common methods), as well as anal plug or urethral catheter–mounted electrodes (O'Donnell, 1998). Surface electrodes are self-adhesive skin patch electrodes that are applied over the skin of the anal sphincter. Except in some neurologic diseases, the external anal sphincter EMG will be the same as the external urethral sphincter EMG. Surface electrodes have a significant advantage compared with the needle electrode regarding patient convenience and comfort. However, the surface electrodes provide an inferior signal source and must be precisely placed to provide an adequate signal source. Most clinicians feel that the concentric needle electrode is the superior technique for obtaining a signal source of EMG activity of the striated external sphincter muscles. Compared with the surface electrode, placement of the needle electrode has the disadvantage of being uncomfortable for the patient, especially if more than one attempt at placement of the electrode is required to obtain an adequate signal. Also, the needle electrode is easily dislodged and may require replacement during the study. Patients typically have a low tolerance for replacement of the needle electrode during urodynamic studies. The performance of an EMG and the selection of the type of electrode to be used depend on the UDS question to be answered.

URODYNAMIC STUDY: ANALYSIS AND INTERPETATION

The author has found it useful to divide the UDS test into filling/storage and voiding phases. This allows for ease of classification of voiding dysfunction according to the functional classification system mentioned previously. The filling/storage phase consists primarily of the CMG, provocative testing (e.g., measurement of abdominal leak point pressure), and urethral pressure measurement during storage. The voiding phase evaluates bladder contractility, bladder outlet resistance, and sphincter coordination by pressure-flow analysis and EMG.

FILLING AND STORAGE PHASE

The CMG assesses the bladder's response to filling. The CMG can measure filling pressure, sensation, involuntary contractions, compliance, and capacity. Sensation is the part of cystometry that is truly subjective and therefore requires an alert and attentive patient and clinician. Several subjective parameters that can be recorded during filling are recognized by the ICS (see Table 62–1).

Normal Filling and Storage

Normally, the bladder should store urine at low pressure and not contract involuntarily. Once capacity is reached or voluntary voiding is desired, intravesical pressure will increase (voluntary detrusor contraction). In actuality this is preceded by a relaxation of the external sphincter. A normalized adult CMG is shown in Figure 62–3. **Normally detrusor pressure should remain near zero during the entire filling cycle until voluntary voiding is initiated. That means baseline pressure stays constant (and low) and there are no involuntary contractions.**

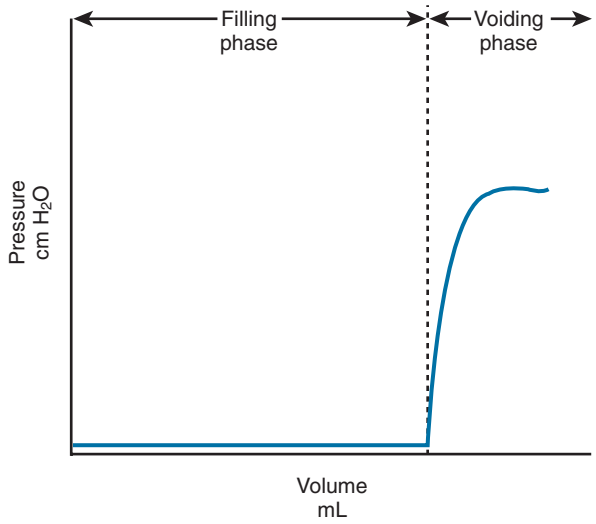


Figure 62–3. Normal, idealized adult cystometrogram with low pressure storage until the patient is given the command to void and the voiding phase starts. Note that the baseline bladder pressure is near zero (compliant) and there are no involuntary contractions.

As mentioned previously, the simultaneous measurement of Pabd, usually by a rectal or vaginal catheter, and Pves during urodynamics provides a means of calculating the true Pdet. **The ability to calculate subtracted Pdet allows one to distinguish between a true rise in detrusor pressure (either via a contraction or loss of compliance) and the effect of increased abdominal pressure** (e.g., straining, Valsalva). This is especially important when rises in detrusor pressure are small or when they are accompanied by changes in abdominal pressure.

Abnormalities of Bladder Filling—Detrusor Overactivity and Impaired Compliance

During filling, involuntary detrusor contractions (IDCs) can occur. These are often associated with urgency and even urgency incontinence. **Detrusor overactivity (DO) is a *urodynamic observation* characterized by IDCs during the filling phase, which may be spontaneous or provoked** (Fig. 62–4)**. DO may be further characterized as *neurogenic DO,* which means it is associated with a relevant neurologic condition (e.g., spinal cord injury, multiple sclerosis) or *idiopathic DO,* which means there is "no defined cause" (non-neurogenic)** (Abrams et al, 2002). The term *idiopathic* is a bit of a misnomer in that the cause of DO in a non-neurogenic patient may be readily apparent (e.g., bladder outlet obstruction, inflammatory process) or may be truly "unknown." Thus from a practical standpoint, the terms neurogenic and non-neurogenic DO make sense but do not fit the ICS definitions. (It should be noted that the term *neurogenic DO* replaced the term *detrusor hyperreflexia,* and the term *idiopathic DO* replaced the term *detrusor instability* in previous ICS terminology). Neurogenic and idiopathic DO may look identical on CMG. These terms are strictly defined by the patient's neurologic status and not the CMG appearance of the IDCs.

The presence of DO during UDS must be interpreted in the context of the patient's symptoms and condition. Ideally, a patient's symptoms should be reproduced during UDS, so we would expect DO to be accompanied by urgency or urgency incontinence, although it can occur and be significant without being symptomatic, particularly in neurogenic DO. However, DO can also be "test induced" or clinically insignificant. It has been reported in 14% to 18% of healthy asymptomatic volunteers undergoing UDS (van Waalwijk van Doorn et al, 1992; Robertson, 1999; Wyndaele et al, 2002). This is even more dramatic in ambulatory UDS studies where DO has been found in up to 69% of asymptomatic females (van Waalwijk van Doorn, et al, 1996). Conversely, failure to demonstrate DO on UDS does not rule out its existence. It is well known that up to 50% of women with urgency incontinence do not demonstrate DO on UDS. However, the ability to suppress DO during UDS test may in and of itself be significant. For example, Osman (2003) showed that patients with mixed incontinence and a normal CMG (no DO) not only had excellent cure rates for stress incontinence but also had an 87% cure rate for urgency incontinence (compared with only 43% cure for urgency incontinence for women randomized to receive antimuscarinic medication instead of stress incontinence surgery).

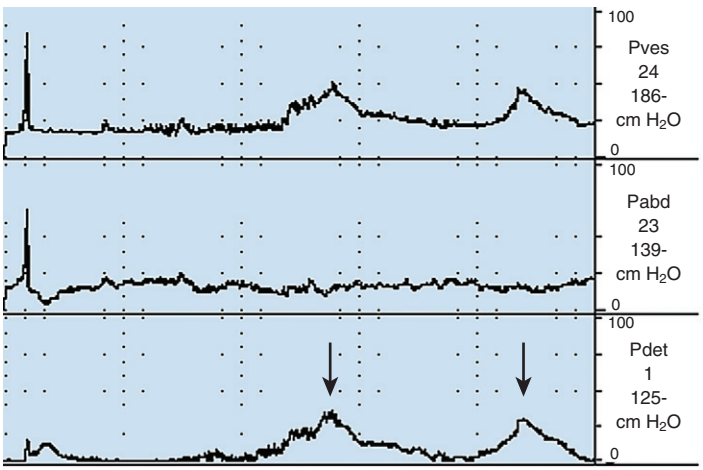


Figure 62–4. Detrusor overactivity. In this tracing there are two involuntary detrusor contractions *(arrows)*. There is a rise in Pves with no associated rise in Pabd, and therefore the subtracted Pdet looks identical to the Pves.

It is important that the person performing the UDS study be absolutely sure that the contraction is indeed involuntary. Sometimes a patient may become confused during the study and actually void as soon as the desire is felt. The volume at which contractions occur and the pressure of the contractions should be recorded. It is often worthwhile to repeat the CMG at a slower filling rate if the patient experiences uncharacteristic symptoms associated with DO. If the patient experiences incontinence during an involuntary contraction (DO incontinence), this should be noted.

In addition to the presence of DO, its characteristics can be noted. DO can be observed as a single event or as multiple IDCs. It can be phasic (continuous), sporadic, or terminal (occurring at the end of filling near capacity). It can also be suppressed or nonabortable and may lead to leakage or precipitant micturition. Classifying DO in such a way can be valuable in certain circumstances. For example, overactivity bladder symptoms associated with obstruction have been shown to have a higher likelihood of resolving with intervention (e.g., transurethral resection of the prostate [TURP]) when DO occurs as a single terminal IDC rather than continuous or sporadic IDCs (Kageyama et al, 2000).

The viscoelastic properties of the bladder, on the basis of its composition of smooth muscle, collagen, and elastin, normally produce a highly compliant structure. Therefore as the bladder fills there is little change in pressure (**see normalized CMG** Fig. 62–3). **Compliance** is the relationship between change in bladder volume and change in detrusor pressure (Δ volume/Δ pressure) and is measured in mL/cm H_2O. The ICS recommends two standard points, the Pdet at the start of bladder filling (usually zero) and the Pdet at cystometric capacity or before the start of any detrusor contraction that results in significant leakage (Abrams et al, 2002). Both points are measured excluding any detrusor contractions. **It is difficult to define what "normal compliance" is in terms of mL/cm H_2O.** Several authors have shown that mean values for compliance in healthy subjects range from 46 to 124 mL/cm H_2O (Sorensen et al, 1988; van Waalwijk van Doorn et al, 1992; Hosker, 2004). However, there is great variation. For example, van Waalwijk van Doorn and colleagues (1992) showed a variation of compliance from 11 to 150 mL/cm H_2O (mean 46) in 17 healthy subjects. Some of the variation in "normal" is likely due to the fact that compliance per se is dependent on bladder capacity. Furthermore, various definitions of impaired compliance have been used (e.g., between 10 and 20 mL/cm H_2O); however, there is no consistent definition based on mL/cm H_2O. Stohrer and colleagues (1999) suggest that a value of less than 20 mL/cm H_2O is consistent with impaired compliance and implies a poorly

accommodating bladder. However, examples in which this may not be the case can be cited (e.g., small cystometric capacity). Therefore **in practical terms, absolute pressure is probably more useful than a "compliance number" or value.** For example, it has been shown that storage greater than 40 cm H_2O is associated with harmful effects on the upper tracts (McGuire et al, 1981) (Fig. 62–5). Also, depending on the clinical scenario, a particular compliance in terms of mL/cm H_2O can mean different things (Fig. 62–6). As a general rule, **prolonged storage at high pressures can lead to upper tract deterioration.** Elevated storage pressures and impaired compliance should be interpreted in the context of the clinical scenario. It appears that **conventional cystometry may provoke filling pressures higher than natural filling in some cases.** Robertson (1999) showed that for six patients with neuropathic bladder and severely impaired compliance on conventional cystometry, compliance was actually normal on ambulatory monitoring with natural filling.

Impaired compliance is seen in a variety of neurologic conditions (spinal cord injury/lesion, spina bifida) and usually results from increased outlet resistance (e.g., detrusor-external sphincter dyssynergia [DESD]) or decentralization in the case of lower motor neuron lesions. It can also result from long-term bladder outlet obstruction (e.g., BPH) (Leng and McGuire, 2003) or structural changes like radiation cystitis or tuberculosis.

The measurement of compliance can be affected by a number of factors. Sometimes an increase in Pdet during cystometry is seen as a result of rapid filling (filling during cystometry is almost always faster than physiologic filling). This is more of an accommodation problem rather than a true decrease in compliance. When Pdet is seen to be rising, filling may be stopped or reduced to see if the effect is real. An IDC, particularly if it is of sustained and low amplitude, can be confused with impaired compliance. If filling is stopped and the pressure returns to baseline, then the compliance is not impaired. Finally, a number of "pop-off" mechanisms can make compliance seem better than it actually is. Vesicoureteral reflux and bladder diverticulum are two examples. With reflux, pressure is actually transferred to the refluxing renal unit and may be harmful. The author has seen instances where the upper tract holds more urine than the bladder. VUDS (see later) is useful in these cases. Because a bladder diverticulum is actually part of the bladder, it may provide a protective effect for the upper tracts. Finally, an incompetent outlet may be a pop-off mechanism. This may only become apparent when outlet resistance is increased, which can be done during cystometry by occluding the outlet but may not be seen until the outlet resistance is surgically increased (e.g., with an artificial urinary sphincter or sling procedure).

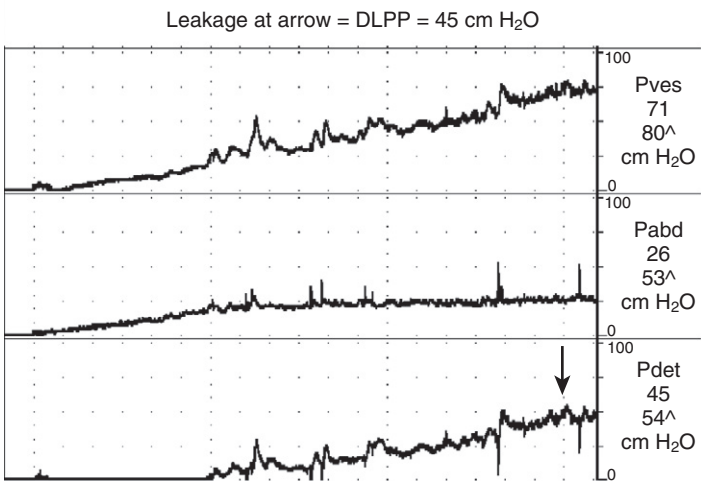


Figure 62–5. Impaired compliance. Note the rise in Pves (and Pdet) with bladder filling. The Pdet at the end of filling is approximately 45 cm H_2O, which is a potentially dangerous situation. In this case the bladder was filled to a volume of 300 mL, so the compliance is 6.67 mL/cm H_2O. The *arrow* is the point at which incontinence was demonstrated, which is the detrusor leak point pressure (DLPP).

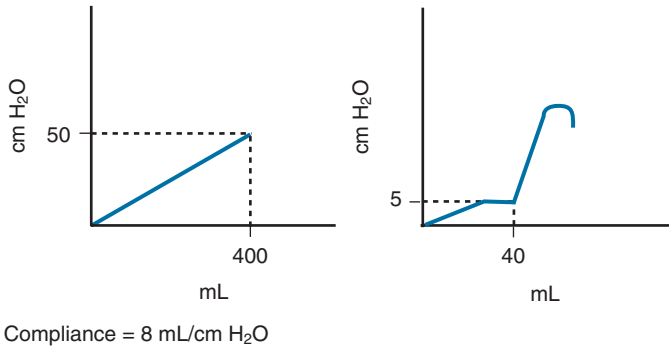


Figure 62–6. A problem with measuring compliance. Shown are two theoretical cystometrograms. The one on the left demonstrates impaired compliance with a constant rise in Pdet throughout filling. At 400 mL the Pdet is 50 cm H_2O (8 mL/cm H_2O), a dangerous situation. There is significant storage time where the det is greater than 40 cm H_2O. The CMG on the right could represent a small-capacity bladder with DO and precipitant micturition. At a volume of only 40 mL, an IDC occurs. The Pdet just before this was only 5 cm H_2O. The calculated compliance would be 6 mL/cm H_2O, the same as the one on the left. Yet the CMG on the right does not demonstrate a dangerous situation, just a highly symptomatic (incontinent) patient.

Key Points: Abnormalities of Bladder Filling

- DO is often a significant UDS finding and may explain a number of storage symptoms.
- In addition to its presence, the characteristics of DO should be noted.
- It is also important that clinicians recognize normal test-retest variation and also that "usual lower urinary tract behavior" is not always replicated in the test setting.
- Impaired compliance with prolonged elevated storage pressures is a urodynamic risk factor and usually needs to be treated to prevent renal damage.

Leak Point Pressures

Two distinct types of leak point pressures can be measured in the incontinent patient: abdominal leak point pressure (ALPP) and detrusor leak point pressure (DLPP). The two are independent of each other and conceptually measure completely different things.

ALPP is a measure of sphincteric strength or the ability of the sphincter to resist changes in abdominal pressure (McGuire et al, 1993). **ALPP is defined as the intravesical pressure at which urine leakage occurs due to increased**

abdominal pressure in the absence of a detrusor contraction (Abrams et al, 2002). **This measure of intrinsic urethral function is applicable to patients with stress incontinence. An ALPP can only be demonstrated in a patient with stress urinary incontinence (SUI). Conceptually, the lower the ALPP, the weaker the sphincter. There is no normal ALPP because patients without stress incontinence will not leak any physiologic abdominal pressure. ALPP should be measured as the total abdominal pressure required to cause leakage, not the change in pressure** (McGuire et al, 1993). Therefore if ALPP is measured in the standing position, it should include the baseline Pabd (or Pves), which is usually about 20 to 40 cm H_2O. Classically, **the reading is taken from the Pves channel as long as there is no involuntary contraction** (Fig. 62–7). In cases where patients do not leak with a urethral catheter in place, the ALPP can be measured from the abdominal pressure channel either rectally or vaginally (Stohrer et al, 1999). The original description of ALPP was done at an arbitrary bladder volume of 150 milliliters; however, in some cases it is necessary to fill the bladder more. The volume at which ALPP is determined should be noted as some investigators have found that it decreases at higher volumes (Faerber and Vashi, 1998). As a general rule, one should start testing at 150 mL and then every 50 mL thereafter until SUI is demonstrated. If there is no SUI demonstrated at capacity, the urethral catheter is removed and ALPP is measured via the rectal catheter (provided there is no increase in Pdet from DO or impaired compliance).

Attempts have been made to quantify intrinsic sphincter deficiency (ISD) in women using ALPP. In 1993 McGuire and colleagues measured ALPP in 125 women with SUI. When the ALPP was less than 60 cm H_2O, all patients had high-grade incontinence with 81% having continuous leakage and 75% having a fixed urethra (no urethral hypermobility). When ALPP was between 61 and 89 cm H_2O, 80% had pronounced urethral hypermobility and moderate to high-grade incontinence. When ALPP was greater than 90 cm H_2O, patients had lesser grades of incontinence and minimal to gross urethral hypermobility. The inferences are that:

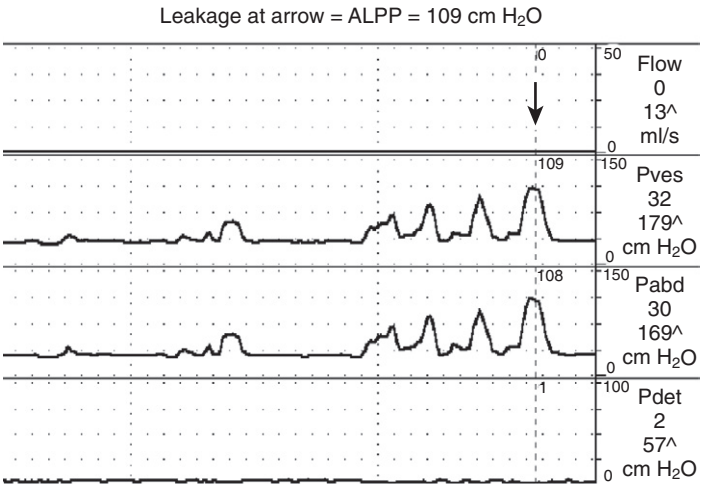


Figure 62–7. Abdominal leak point pressure measurement. After progressive Valsalva maneuvers, leakage is demonstrated on the last one at 109 cm H_2O *(arrow)*. There is no rise in Pdet.

ALPP less than 60 cm H_2O signifies ISD.
ALPP between 60 and 90 cm H_2O is equivocal (there is a component of ISD).
ALPP greater than 90 cm H_2O indicates little or no ISD.

Current technology does not permit a method to distinguish between ISD in the face of urethral hypermobility in women. Therefore although these ALPP values are often used as guidelines, **they should be interpreted with caution.** For example, **if there is no urethral hypermobility, SUI must be caused by ISD, regardless of the ALPP**. Furthermore, Fleischmann and colleagues (2003) found that urethral hypermobility was equally common in women with lower versus higher ALPP. ISD and urethral hypermobility may coexist, and they do not define discrete classes of patients with stress urinary incontinence. Thus an isolated measure of ALPP without considering other factors such as cystometry and urethral mobility is of limited utility in predicting success for commonly performed female SUI procedures (Hosker et al, 2009).

The term *ALPP* has been used interchangeably with "Valsalva" leak point pressure (VLPP); however, this is not entirely correct. An ALPP can be measured during UDS testing by a voluntary Valsalva maneuver (VLPP) or by a cough (cough leak point pressure or CLPP). In the same person, **VLPP tends to be significantly lower than CLPP.** Therefore exact terminology and methods should be used when describing an ALPP. ALPP can also be influenced by the presence or the size of a urethral catheter (Bump et al, 1995; Huckabay et al, 2005; Türker et al, 2010). It has been shown in women with SUI that the larger the catheter, the lower the ALPP. ALPP can also be measured without a urethral catheter by assessing the abdominal pressure via a rectal (or vaginal) catheter. It has been shown that 15% of women with SUI (Türker et al, 2010) and 35% of men with postprostatectomy SUI (Huckabay et al, 2005) will demonstrate an ALPP only with the urethral catheter removed.

The second type of leak point pressure is the detrusor leak point pressure (DLPP), which is a measure of detrusor pressure in patients with decreased bladder compliance. It is defined as the lowest detrusor pressure at which urine leakage occurs in the absence of either a detrusor contraction or increased abdominal pressure (Abrams et al, 2002) (see Fig. 62–5). The higher the urethral resistance, the higher the DLPP. One can imagine that in a poorly compliant bladder, if outlet resistance is low, incontinence will occur at a relatively low or "safe" pressure. However, if outlet resistance is high, the pressure in the bladder will continue to increase as the bladder fills. There is potentially less incontinence, but eventually the pressure is transmitted to the upper tracts (Fig. 62–8).

From a clinical perspective, DLPP is most useful in patients with lower motor neuron disease causing "decentralization" and in non-neurogenic patients with low bladder compliance (after multiple bladder surgeries, radiation, and tuberculous cystitis). The higher the DLPP, the more likely is upper tract damage because intravesical pressure is transferred to the kidneys. McGuire (1981) documented the deleterious effects that a detrusor high-leak point pressure has on the upper urinary tracts; **detrusor leak point pressures greater than 40 cm H_2O result in hydronephrosis or vesicoureteral reflux in 85% of myelodysplastic patients.**

The significance of an elevated DLPP is that bladder pressures are getting too high before the "pop-off" mechanism of urethral leakage occurs. In most cases treatment is aimed at lowering bladder pressures, so the DLPP is never reached. In some cases

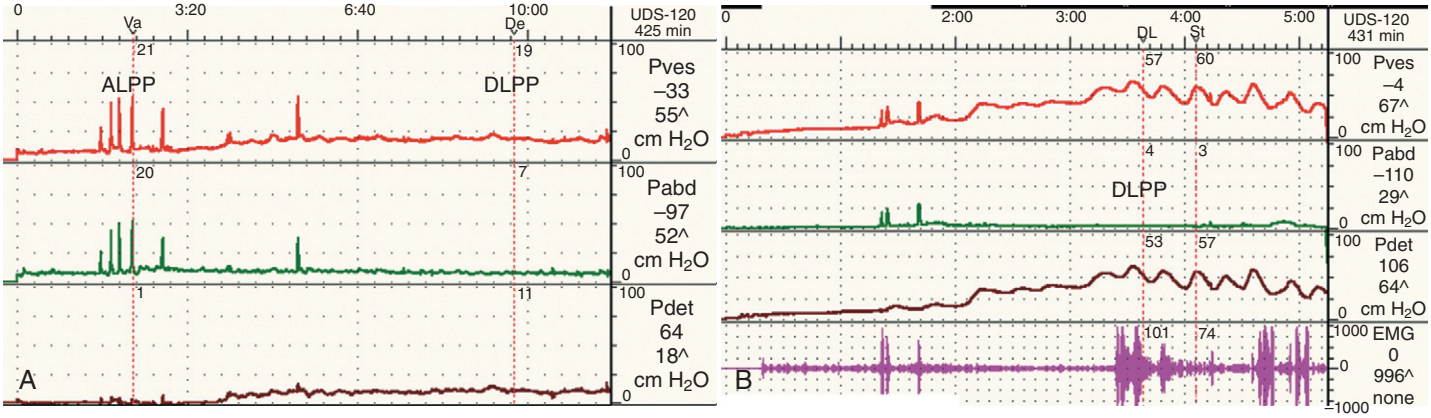


Figure 62–8. Outlet resistance causes impaired compliance. Urodynamic (UDS) studies of two children with the same neurologic problem and symptoms but dramatically different findings. **A**, UDS tracing of a young boy with spina bifida who is incontinent in between catheterizations. The study shows a low-pressure system with poor outlet resistance and stress incontinence (ALPP demonstrated) and a low DLPP. His upper tracts are protected. **B**, UDS tracing of a young girl with spina bifida who is incontinent in between catheterizations. The study shows a high-pressure system with strong outlet resistance and a high DLPP. There was no stress incontinence. Her upper tracts are at risk. The difference in these two cases is difference in storage pressures caused by the difference in outlet resistance.

DLPP can be lowered by decreasing outlet resistance, for example, with a sphincterotomy in a patient with DESD.

Key Point: Leak Point Pressures

- ALPP and DLPP, although both called "leak point pressure," are completely different. The ALPP measures the sphincter response to increased abdominal pressure. The lower the ALPP, the "weaker" the sphincter. The DLPP measures the injured bladder response to increased outlet resistance. The higher the resistance (e.g., detrusor-external sphincter dyssynergia), the higher the DLPP, which is potentially dangerous to the upper tracts.

Stress-Induced Detrusor Overactivity

Sometimes detrusor overactivity can be triggered by a rise in abdominal pressure (Fig. 62–9). Thus the symptom may appear to be stress incontinence, but the condition causing the symptom is actually an involuntary contraction, not sphincteric weakness. In a patient with stress-induced detrusor overactivity (SIDO), it is important to note if there is also urodynamic SUI and/or DO independent of the SIDO.

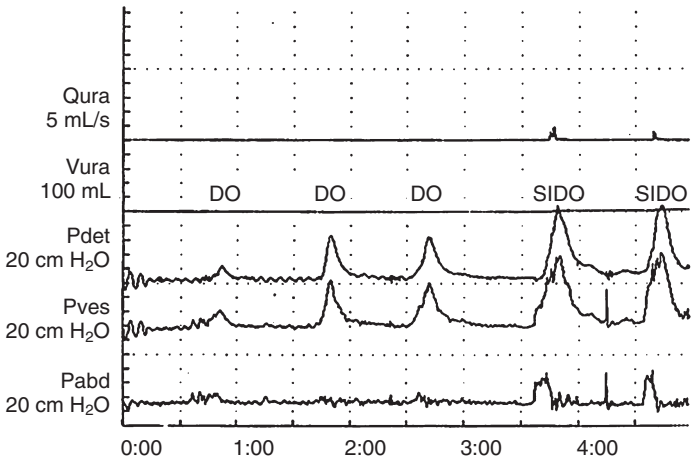


Figure 62–9. Stress-induced detrusor overactivity. In this case, there are three episodes of detrusor overreactivity (DO) preceding two episodes of stress-induced DO (SIDO). In the case of SIDO, note that as Pabd increases, so does Pves. Shortly *after* this, Pdet rises and continues long after Pabd returns to baseline. With both episodes of stress-induced instability, incontinence occurred, as can be seen on the flow (Qura) curve. (From Nitti VW: Cystometry and abdominal pressure monitoring. In Nitti VW, editor. Practical urodynamics. Philadelphia: WB Saunders; 1998. p. 38–51.)

Occult Stress Incontinence

Stress incontinence that is demonstrated in a clinically continent woman with pelvic prolapse, only when the prolapse is reduced, is referred to as *occult incontinence* (Ballert et al, 2009). Prolapse reduction can be done with a pessary, a packing, a forceps, or manually. Technically, if this is demonstrated during urodynamic testing, it may be referred to as *urodynamic occult SUI.*

Urethral Pressure Profilometry

The method of urethral pressure profilometry (UPP) was popularized by Brown and Wickman in 1969 using a small catheter with lateral apertures. Fluid is continuously infused through this type of catheter. Simultaneous bladder and urethral pressure is measured as the catheter is slowly withdrawn along the course of the urethra. The urethral pressure transducer measures the fluid pressure required to lift the urethral wall off the catheter side holes and thus elevates the circumferential and radial stresses induced by the presence of the catheter in the urethra and the slow urethral profusion. **Thus urethral pressure is defined as the fluid pressure needed to just open a closed urethra** (Abrams et al, 2002). Accurate measurements are recorded only in those cases in which the urethra is distensible and therefore able to create a perfect seal.

Despite an abundant literature on urethral profilometry, **its clinical relevance is controversial.** Many urologists do not routinely perform urethral profilometry. The urethral pressure profile (UPP) represents the intraluminal pressure along the length of the urethra in graphic form (Fig. 62–10). Several parameters can be obtained from the UPP:

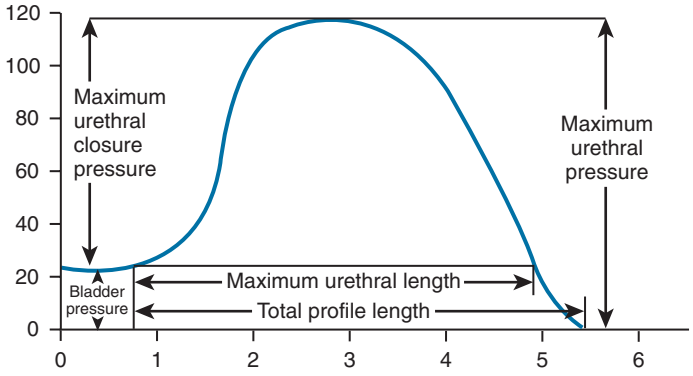


Figure 62–10. Urethral pressure profile with appropriate parameters identified.

The urethral closure pressure profile (UCP) is given by the subtraction of intravesical pressure from urethral pressure.

Maximum urethral pressure (MUP) is the highest pressure measured along the UPP.

Maximum urethral closure pressure (MUCP) is the maximum difference between the urethral pressure and the intravesical pressure.

Functional profile length is the length of the urethra along which the urethral pressure exceeds intravesical pressure in women.

In most continent women, the functional urethral length is approximately 3 cm and the MUCP is 40 to 60 cm H_2O, but normal values vary widely. MUCP has also been used to define ISD. McGuire (1981) performed a retrospective evaluation of women who failed SUI surgery and found that a preoperative MUCP less than 20 cm H_2O resulted in higher surgical failure rates. These patients represented a specific subtype of SUI caused by a fixed, open urethra (type III SUI). In 1992 the term was redefined as *ISD*. **Many authors have used the definition of MUCP less than 20 to define ISD; however, this definition has many of the same problems as ISD definitions for ALPP.** Another caveat of UPP is that its measurement does not diagnose stress incontinence and SUI is not required to measure it (contrary to ALPP). MUCP in incontinent women has been shown to be lower than in continent women, but there is certainly overlap (Schick et al, 2004). In addition, MUCP is not always indicative of the severity of incontinence. For example, there is a difference between the urethra of an incontinent patient whose MUCP equals 38 cm H_2O and that of a continent woman with the same MUCP.

In 2002 the ICS standardization subcommittee concluded that the clinical utility of urethral pressure measurement is unclear (Lose et al, 2002). **Furthermore, there are no urethral pressure measurements that (1) discriminate urethral incompetence from other disorders; (2) provide a measure of the severity of the condition; and (3) provide a reliable indicator to surgical success and return to normal after surgical intervention** (Lose et al, 2002).

VOIDING AND EMPTYING PHASE

Normal Voiding and Emptying

Evaluation of the voiding phase provides an assessment of both detrusor contractility and bladder outlet resistance, the two parameters that are critical for normal bladder emptying. In simple terms, abnormalities of bladder emptying are caused by too much outlet resistance, inadequate (strength or duration) bladder contractility, or a combination of both. The simultaneous measurement of detrusor pressure and urinary flow rate during voluntary voiding, known as a PFS, is the most accurate way to access these two critical parameters (Fig. 62–11).

In order to understand the relationship between bladder contractility and outlet resistance, one must start with an understanding of the normal micturition process. Normal voiding is accomplished by activation of the micturition reflex, which involves the following (Fig. 62–12):

1. Relaxation of striated urethral sphincter
2. Contraction of detrusor muscle
3. Opening of vesical neck and urethra
4. Onset of urine flow

This occurs as a result of coordination between pontine and sacral micturition centers with suprapontine input, which allows for voluntary control of the micturition reflex.

UDS can evaluate the critical parameters during the voiding phase: detrusor contractility, relaxation of the bladder outlet, and coordination of sphincters (Fig. 62–13).

According to the ICS, *normal detrusor function* is characterized by a voluntarily initiated continuous contraction that leads to complete bladder emptying within a normal time span, and in the absence of obstruction. *Detrusor underactivity* is defined as a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span. Finally, an *acontractile detrusor* is when there is no demonstrable contraction during UDS (Abrams et al, 2002). Normal detrusor function and detrusor underactivity are "nebulously defined" in terms of absolute pressure because that will depend on outlet resistance. When evaluating detrusor function urodynamically, UDS must be correlated with clinical findings. For example, if a patient who normally voids is unable to void during a UDS study, one cannot make a definitive diagnosis of "acontractile detrusor."

Urinary flow rate in combination with PVR is a useful clinical tool to assess emptying. When flow rate is reduced or PVR is elevated, it tells us that emptying is not complete but does not tell us why (e.g., obstruction vs. impaired contractility). Flow rate also depends on voided volume because there is a linear relationship between Q_{max} and voided volume with a voided volume above and a hyperbolic relationship below a voided volume of 150 mL (Drach et al, 1979). Therefore many authors have recommended a minimum voided volume of 150 mL to accurately assess uroflow. However, establishing a minimum voided volume puts major limitations on uroflowmetry because many patients with voiding dysfunction do not routinely void large enough volumes to be evaluable. The corrected form of Q_{max}, Q_{max} divided by the square root of voided volume, may provide useful information in such patients (Boone and Kim, 1998). Over the years several nomograms have been developed to define normal flow rates for a specified population and correct for voided volume. These include the Siroky nomogram (Siroky et al, 1979, 1980) for men and the Liverpool nomogram (Haylen et al, 1989) for men and women.

The bethanechol supersensitivity test has been used to help distinguish the cause of detrusor underactivity as neurogenic or myogenic. It is based on the Cannon theory of denervation, which states that denervated structures develop increased sensitivity to chemical stimulation. This concept was applied to the bladder by Lapides and colleagues (1962). The original

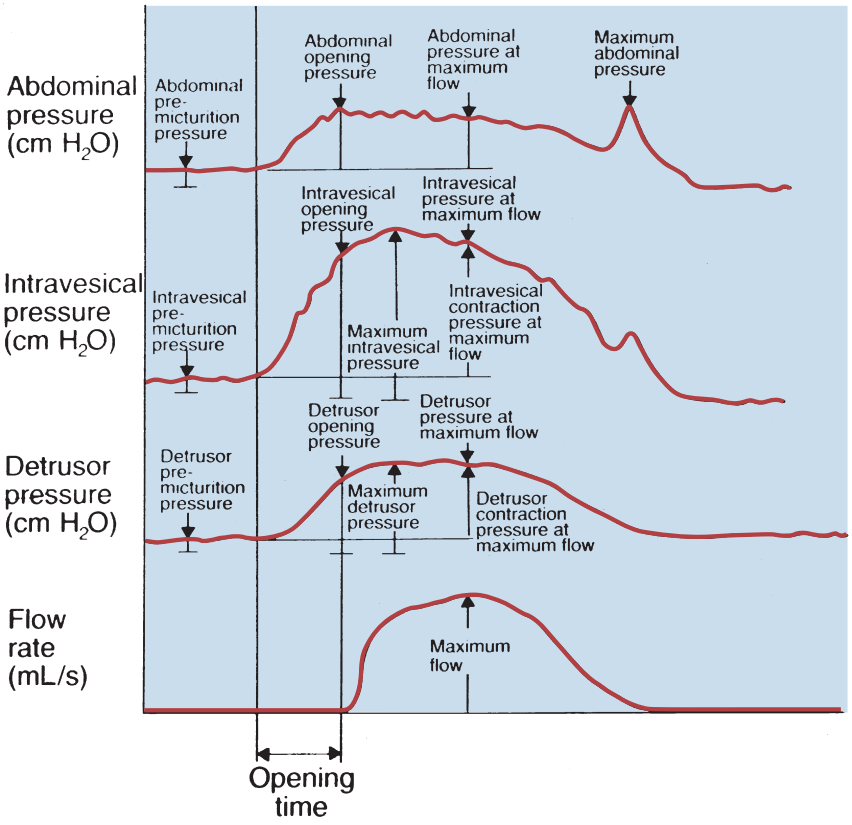


Figure 62–11. Schematic pressure-flow study labeled with recommended terminology.

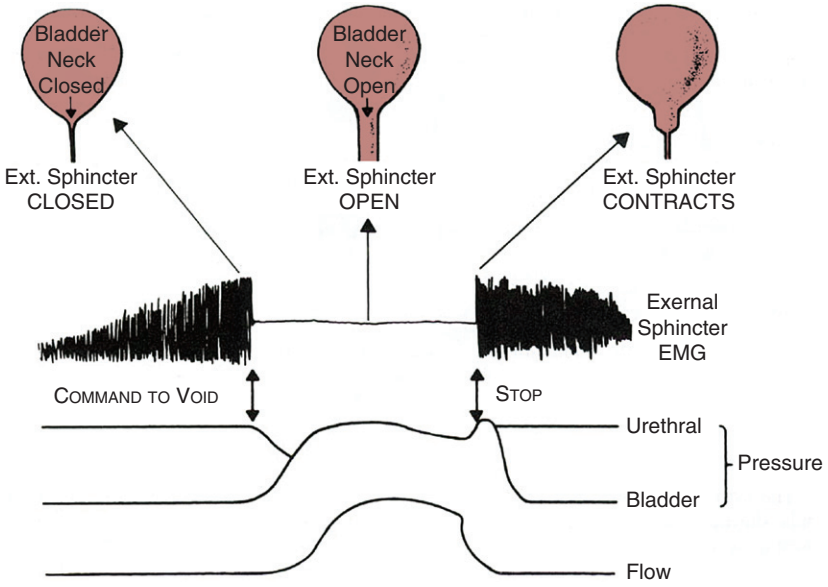


Figure 62–12. Physiology of micturition. See text for details. (From Blaivas JG. Pathophysiology of lower urinary tract dysfunction. Clin Obstet Gynecol 1885;12:295–309.)

bethanechol supersensitivity test described by these authors was performed by infusing liquid at a rate of 1 mL/sec to a volume of 100 mL, where the pressure is measured. This can be done up to three times, and the pressure values averaged. The patient is then given 2.5 mg of bethanechol chloride (later revised to 0.035 mg/kg) subcutaneously, and the study is repeated at 10, 20, and 30 minutes. A normal bladder (or myogenically impaired bladder) should show an increase of less than 15 cm H_2O above control value at 100 mL at 30 minutes. This is considered a negative study. A positive study, indicating a sensory or motor paralytic bladder, is a response of at least 15 cm H_2O above the control value. More recent studies have indicated that the bethanechol supersensitivity test is rather unreliable in predicting "neurogenic bladder." Blaivas and colleagues (1980) reported only 76% sensitivity and 50% specificity in doing this. Another problem is that even if the test is able to differentiate between neurogenic and myogenic dysfunction, treatment is often the same (e.g., clean intermittent catheterization). Bethanechol chloride, whether administered subcutaneously or orally, has not proved to be a consistently effective treatment for the underactive detrusor (Wein et al, 1978, 1980). In addition, a positive test does not predict improved voiding when it is used therapeutically**. Therefore we feel that there is a limited role for the use of the bethanechol supersensitivity test**.

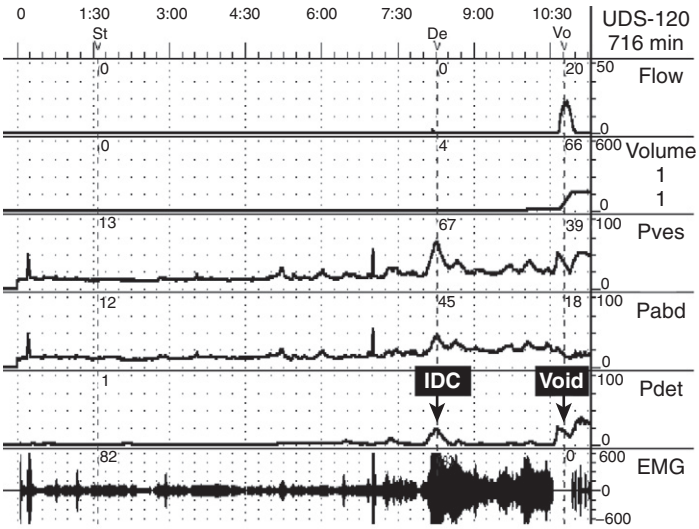


Figure 62–13. Multichannel urodynamics study showing filling and voiding phases with pressure and electromyography (EMG) readings. In this case, the patient experienced an involuntary detrusor contraction (IDC) that led to increased external sphincter contraction and an increase in EMG activity (guarding reflex). However, shortly after that the patient is given permission to void. First there is quieting of the EMG (sphincter relaxation) followed by an increase in Pdet and volitional voiding with a normal-appearing uroflow curve.

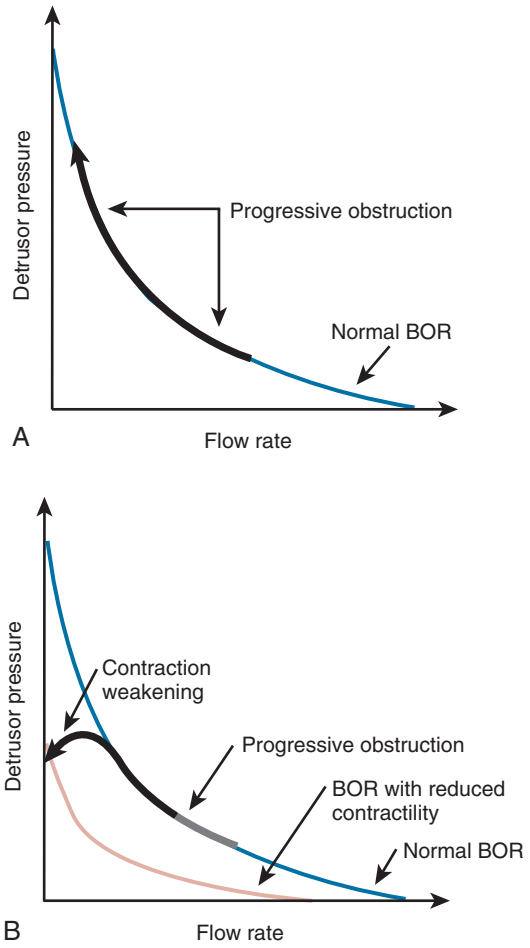


Figure 62–14. **A** and **B**, Relationship between detrusor pressure and flow in a given person—the bladder outlet relation (BOR). See text for details. (From Griffiths DJ. The mechanics of the urethra and of micturition. Br J Urol 1973;45:497–507.)

Pressure-Flow Relation

As mentioned previously, detrusor pressure during voiding is a function of outlet resistance. For a normal detrusor, the greater the outlet resistance is, the higher the detrusor pressure during voiding will be. This is accompanied by a reduced flow rate. A healthy bladder is able to overcome obstruction by contracting more forcefully. Although the flow may be slower, the bladder can empty itself. Over time, the detrusor may decompensate and no longer be able to generate the necessary pressure to overcome obstruction. When this occurs, the result will be incomplete bladder emptying or retention of urine. **Thus the urodynamic manifestation of bladder outlet obstruction (BOO) is high-pressure and low-flow voiding** (or more practically speaking, increased pressure and reduced flow). Over time, if bladder decompensation results, detrusor underactivity or impaired contractility can result.

In order to use the common measures of obstruction and impaired contractility that are used today, it is important to understand basic bladder output and urethral resistance relations. Attempts to mathematically define urethral resistance date back to 1962 (Gleason and Lattimer). Early equations calculating urethral resistance followed standard hydrodynamic formulas calculating outlet resistance. These concepts failed to consider that the urethra is not a rigid tube but rather has an active and a distensible nature. They also failed to consider the importance of bladder volume. Rigid tube hydrodynamics were abandoned in favor of more dynamic ways to analyze micturition. In 1972 Griffiths introduced Bladder Output Relation (BOR), which depicts the interrelations between bladder pressure and uroflow at a given volume and essentially measures the function of the bladder independent of the function of the urethra. Griffiths further defined a method to evaluate urethral resistance independent of bladder function, the urethral resistance relation (URR). According to this relation, as bladder pressure rises the flow rate will be zero until the intrinsic bladder pressure equals the intrinsic urethral pressure. At this point flow will start and the flow rate will rise rapidly with further increases in the intrinsic bladder pressure. If pairs of simultaneously measured values of detrusor pressure and flow rate are plotted against one another throughout the course of a micturition event, a curve is obtained. The curve shows the resistance to flow independent of detrusor function, representing the urethral resistance relation. If the urethra were relaxed or tightened during voiding, the URR would move toward the left or right, respectively. Because the BOR represents the function of the bladder independent of the urethra and the URR depicts urethral function independent of bladder function, the actual detrusor pressure and flow rate are determined by the intersection of the bladder output relation and the urethral resistance relation, which is the point at which intrinsic bladder pressure equals urethral pressure (Fig. 62–14). A change in one of these relations during micturition would not affect the curve representing the other relation but would result in the point of intersection to moving along that curve.

Bladder Outlet Obstruction in Men

The value of making a precise diagnosis of obstruction in men comes from the assumption that the outcomes of surgery to treat

benign prostatic hyperplasia (BPH) and its consequent lower urinary tract symptoms (LUTS) are improved when obstruction can be documented. Because BPH and benign prostatic obstruction (BPO) are highly prevalent conditions, it was intuitive to use them as a model for defining obstruction. Most of the analytic work has focused on defining obstruction-based PFS. Three well-known nomograms based on PFS have been described to diagnose men as obstructed, equivocal, or unobstructed. These are the Abrams Griffiths nomogram (Abrams and Griffiths, 1979); the Urethra Resistance Factor (URF) (Griffiths et al, 1989); and the Linear Passive Urethral Resistance Relation or Schafer nomogram (Schafer, 1990). The categories of obstruction described in these nomograms are based on observations of men who underwent surgery for LUTS (mainly transurethral resection of the prostate, TURP). After surgery, the detrusor pressure at maximum flow ($PdetQ_{max}$) was reduced in the obstructed group, reduced unpredictably in the equivocal group, and unchanged in the unobstructed group. Subsequently, Lim and Abrams (1995) showed that patients were similarly classified by all three methods. **They described a number, the AG number (now known as the bladder outlet obstruction index [BOOI]), derived from the equation for the slope of the line dividing obstructed from equivocal in the Abrams Griffiths nomogram, which is the same line dividing obstructed from slightly obstructed in the Schafer nomogram: BOOI = $PdetQ_{max} - 2(Q_{max})$. Subsequently, Griffiths and colleagues** (1997) (Fig. 62–15) **described the ICS provisional nomogram, which is now suggested for use in diagnosing obstruction in men with LUTS suggestive of BPH** (Abrams, 1999). **Men are considered obstructed if BOOI is greater than 40, unobstructed if BOO is less than 20, and equivocal if BOOI is 20 to 40.**

Voiding PFS show consistent reproducibility in the diagnosis of BOO in men. In a review of the topic, Abrams and colleagues (2001) concluded that random variations of about 9 to 14 cm H_2O in pressure measurement and about 0.4 to 2 mL/sec in maximum flow rate occur. In repeated studies during the same session there is usually a systematic decrease of up to 4 cm H_2O in detrusor pressure and 0.4 mL/sec in maximum flow rate. These variations have little clinical importance because they cause only 10% to 16% of patients to change classification on the ICS nomogram, and in all but about 1% that change is only by one class (e.g., from equivocal to unobstructed or from obstructed to equivocal).

Although much effort has focused on defining outlet resistance (i.e., obstruction), an index for bladder contractility can also be derived from the contractility groups Schafer (1995) described (strong, normal, weak, very weak). The **slope of Schafer's lines, now known as the bladder contractility index (BCI), is given by the formula: $PdetQ_{max} + 5(Q_{max})$** (Abrams, 1999). **Strong contractility is a BCI greater than 150, normal contractility a BCI of 100 to 150, and weak contractility a BCI of less than 100** (Fig. 62–16).

Although contractility and obstruction can be independently measured, it is sometimes difficult to diagnosis obstruction in the face of impaired contractility using the ICS or other nomograms. For example, in order to make a diagnosis of unequivocal obstruction, BOOI must be at least 40 cm H_2O. That means that a Pdet of at least 40 cm H_2O must be generated and that assumes flow is zero. If the Q_{max} is 5 mL/sec, then $PdetQ_{max}$ must be at least 50 cm H_2O. Thus the ICS nomogram can exclude obstructed patients whose impaired contractility is the result of long term obstruction. In such cases, clinical judgment becomes important.

BOO is associated with abnormalities of storage as well. This is presumably due to changes in ultrastructure that occur with obstruction. Detrusor overactivity and impaired compliance occur in conjunction with obstruction. For example, about two thirds of men with symptomatic BPO have DO that resolves 50% to 67% of the time with treatment of obstruction (Abrams et al, 1979). Reduced compliance is also associated with obstruction and has been shown to improve with treatment of obstruction (TURP) (Leng and McGuire, 2003).

An alternative to voiding PFS as a way of measuring outlet resistance is the **micturitional urethral pressure profile** (MUPP), or voiding profilometry. This technique, popularized by Yalla, can both diagnose and localize obstruction (Yalla et al, 1980, 1981). The MUPP is performed with a triple-lumen catheter under fluoroscopic guidance similar to the static UPP described earlier. During voiding the catheter is slowly withdrawn and the pressure is measured from the bladder neck through the anterior urethra (Steele et al, 1998). Normally during voiding, the pressure in the bladder is isobaric with the prostatic urethra and then pressure decreases across the membranous urethra and gradually decays along the rest of the anterior urethra. The membranous urethra is the narrowest segment of the bladder outlet during voiding, which accounts for the expected pressure drop of 20 to 30 cm H_2O. In patients with obstruction secondary to BPH, the MUPP is quite different. One will typically see a pressure disparity somewhere along the prostatic urethra. When this pressure disparity is greater than 5 cm H_2O, obstruction at the point of pressure drop is present. MUPP has been shown to be as effective in diagnosing bladder outlet obstruction as standard pressure-flow studies (DuBeau et al, 1995). An analysis of symptomatic BPH patients has shown that

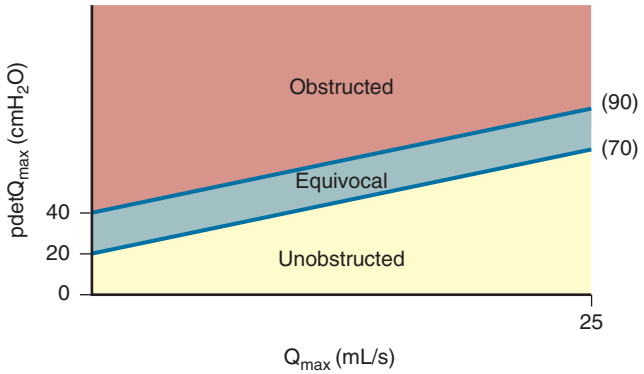


Figure 62–15. Provisional International Continence Society nomogram. See text for details.

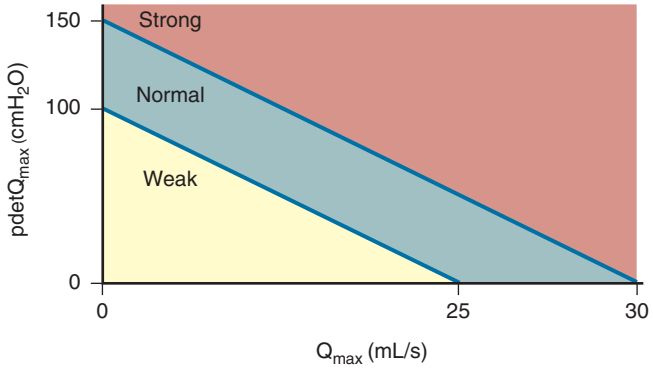


Figure 62–16. The Bladder Contractility Nomogram. See text for details.

successful treatment outcomes have been achieved with treatment based on MUPP results (Lecanwasam et al, 1994).

Bladder Outlet Obstruction in Women

Bladder outlet obstruction in women can present more of a diagnostic dilemma than in men. Because there is no highly prevalent condition (like BPH) that causes female obstruction, it is difficult to establish nomograms. Furthermore, nomograms derived for men cannot be applied to women because voiding dynamics differ. In addition, anatomic differences allow many women to empty their bladders by simply relaxing the pelvic floor, and some will augment voiding by abdominal straining. Minor elevations in detrusor pressure or decreases in flow rate, which might be considered insignificant in the male population, might signify BOO in women. Accordingly, clinicians must have a high index of suspicion on the basis of the presence of lower urinary tract symptoms, incomplete emptying, persistent urinary tract infections, and a history of anti-incontinence surgery, prolapse, or other conditions.

In an effort to develop cut-off values for pressure and flow for the diagnosis of obstruction in women, Chassagne and colleagues (1998) studied a group of "clinically obstructed women" (after incontinence surgery; secondary to cystocele; or "other etiologies") and compared them with a group of controls (women with stress incontinence). Using receiver operator (ROC) curve analysis, they found the optimum sensitivity and specificity for predicting obstruction was obtained with a Q_{max} less than 15 mL/sec and a $PdetQ_{max}$ of greater than 20 cm H_2O (74.3% sensitivity and 91.1% specificity). In 2000 with an expanded population, the authors (Lemack and Zimmern, 2000) revised this to Q_{max} = 11 mL/sec and $PdetQ_{max}$ = 21 cm H_2O as optimal for the selection of patients with BOO. In the most recent publication (Defreitas et al, 2004), these authors used normal asymptomatic women as the control group and found the highest sensitivity and specificity for predicting obstruction was obtained with **Q_{max} less than 12 mL/sec and $PdetQ_{max}$ greater than 25 cm H_2O**. These cut point studies have some limitations, namely that obstruction was predefined clinically and only patients with anatomic obstruction were included. Women with functional obstruction (e.g., from primary bladder neck obstruction or dysfunctional voiding) were not included in any of the cut point analyses. This would be a difficult group of women to define "clinically" without any testing.

In 1999 Nitti and colleagues showed that the addition of fluoroscopic imaging to urodynamics was helpful in diagnosing female BOO (see section on VUDS). In this study, patients were classified as obstructed if there was radiographic evidence of obstruction between the bladder neck and distal urethral in the presence of a sustained detrusor contraction of any magnitude. In addition to diagnosing BOO, it also localizes the site of obstruction and allows for the diagnosis of obstruction in the face of impaired contractility if indeed the site can be localized. **With both the video-urodynamic and cut point criteria there is a significant difference in mean Q_{max} and $PdetQ_{max}$ in the group of obstructed versus the group of unobstructed women, but there is a large overlap of values between obstructed and unobstructed patients. This demonstrates that absolute pressure and flow values are imprecise and that another parameter (e.g., radiographic or clinical evidence of obstruction) is necessary for diagnosis**.

Blaivas and Groutz (2000) presented a nomogram for defining female BOO. Citing the fact that in their series there was a significantly higher flow rate in the same woman without a catheter, they chose to use noninvasive flow rate in their nomogram. Also, because they found no statistical difference between $PdetQ_{max}$ and $Pdet_{max}$ in obstructed or unobstructed patients, they chose $Pdet_{max}$ as the pressure parameter. Using cluster analysis to classify patients with low- and moderate-grade obstruction, they formulated the nomogram. The nomogram places women into four zones: no, mild, moderate, and severe obstruction. An obvious criticism of the nomogram is that it is based on two separate voids (invasive and noninvasive), and one must assume that the pressure characteristics of the void are the same. Akikwala and colleagues (2006) compared the three methods of diagnosing BOO in women and found good concordance between the video-urodynamic and cut point criteria. They also noted that the Blaivas Groutz nomogram over diagnosed obstruction compared with the other two methods.

Obstruction in women cannot be defined by the ICS nomogram or the BOOI because these will grossly underestimate female BOO. This is because normally women void at much lower pressures than men, and therefore the obstructed female bladder outlet may not respond as dramatically (or at least with the same pressures) as in the male. Unfortunately there is no condition in women that causes BOO as commonly as BPO in men, and therefore creating a consistent standard is difficult. Thus concepts are the same (higher pressure and lower flow), but the values are different and less well defined. Those who are interested are referred to suggested readings (Nitti et al, 1999; Blaivas and Groutz, 2000; Defreitas et al, 2004; Akikwala et al, 2006).

Sphincter Coordination

External Sphincter. Normal voiding requires external sphincter relaxation followed by contraction of the detrusor. The external sphincter (and internal sphincter) should remain relaxed until voiding is complete. In normal voluntary voiding, a rise in detrusor pressure is preceded by a fall in urethral pressure and relaxation of the external sphincter as measured by electromyography (EMG). The sphincter and urethral pressure remain low during voiding and then increase when voiding is completed (Fig. 62–17). **Failure of the sphincter to relax or stay completely relaxed during micturition is abnormal** (Abrams et al, 2002). **Thus normally EMG activity decreases before a voluntary bladder contraction; however, it is not abnormal for EMG activity to increase with an involuntary contraction as part of a guarding reflex to inhibit the IDC** (see Fig. 62–11).

Several abnormalities are related to external sphincter relaxation (or lack thereof). **DESD occurs when there is an involuntary increase external sphincter associated with DO and also with voiding** (see Fig. 62–17). **It is caused by a neurologic lesion in the suprasacral spinal cord. DESD can produce profound changes as the detrusor involuntarily contracts against a relatively closed sphincter. This will result in high pressures and can even cause impaired bladder compliance over time. Because long periods of elevated detrusor pressure during bladder filling or (abnormally prolonged) voiding put the upper urinary tract at risk** (McGuire et al, 1996; Kurzrock and Polse, 1998; Tanaka et al, 1999). **DESD may be considered a urodynamic risk factor for upper tract deterioration. True DESD only occurs when there is a known neurologic lesion above the sacral micturition center.** The higher the lesion, the more likely DESD will occur (Blaivas, 1982). If there is no neurologic lesion, then the "dyssynergia" is considered to be

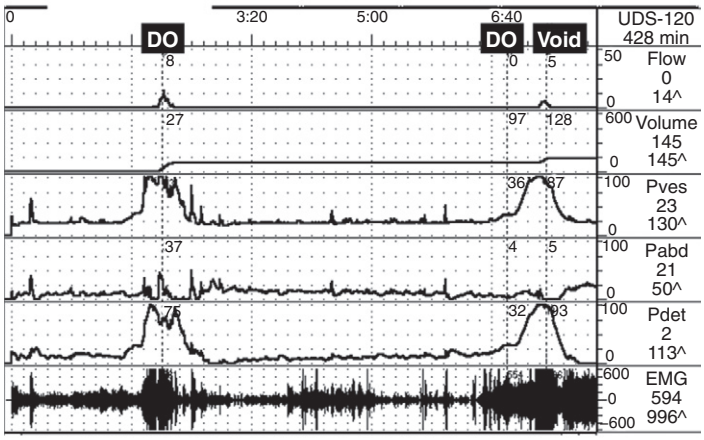


Figure 62–17. Urodynamic tracing of a patient with myelodysplasia and neurogenic detrusor overactivity (DO) and detrusor-external sphincter dyssynergia (DESD). Note the initial involuntary detrusor contraction associated with DESD and incontinence (measured on the flow channel). With refilling there is again DO with DESD. Then the patient is told to voluntarily void, and there is persistent increased electromyographic activity. As a result there is high-pressure, low-flow voiding (obstruction from the dyssynergic sphincter).

a learned behavior and is known as *dysfunctional voiding*. The term *dysfunctional* describes malfunction (failure to relax or involuntarily contraction of the external sphincter) during the voiding phase only and says nothing about the storage phase (Nevéus et al, 2006). However, it is entirely possible and quite common for a patient to experience storage symptoms (and UDS abnormalities) associated with dysfunctional voiding. Although the condition has been extensively described in children, it has also been described in adult men (Kaplan et al, 1997; Nitti et al, 2001; He et al, 2009) and women (Carlson et al, 2001) and can be a major cause of LUTS. It is recommended that when dysfunctional voiding is diagnosed by UDS, the flow pattern (reduced and/or intermittent) is confirmed by noninvasive uroflowmetry to rule out a test-induced phenomenon (Barrett and Wein, 1981; Carlson et al, 2001). He and colleagues (2010) used the following diagnostic criteria in men: nothing abnormal detected in the history and no symptoms on an examination for neurologic diseases; transient and intermittent closure of the external sphincter during voiding detected by EMG and fluoroscopic cystourethrography; a higher external sphincter EMG activity with no abdominal pressure increase in the voiding phase. Uroflowmetry was assessed individually to show any discontinuity in a diagram of urinary flow, in conditions with as little external interference as possible.

Internal Sphincter. Just as there can be a lack of coordination of the detrusor and external sphincter, so too can there be dyscoordination of the internal sphincter or bladder neck. In the case of neurologic disease, if a suprasacral spinal cord lesion is above the level of the sympathetic ganglia (T10-L1), detrusor-internal sphincter-dyssynergia may occur in conjunction with external sphincter dyssynergia (Pan et al, 2009). In non-neuropathic men, women, and children the phenomenon of bladder neck dyssynergia or primary bladder neck obstruction is a well-known cause of LUTS, although its exact etiology is not known (Diokno et al, 1984; Norlen and Blaivas, 1986; Combs et al, 2005). Conditions of internal sphincter dysfunction require VUDS for an exact diagnosis and are described later in the next section.

Key Points: Urodynamic Risk Factors

- The following urodynamics findings are potentially dangerous and usually require intervention to prevent upper and lower urinary tract decompensation:
  - Detrusor-external sphincter dyssynergia
  - Detrusor-internal sphincter dyssynergia
  - High-pressure detrusor overactivity present throughout filling
  - Elevated detrusor leak point pressure (>40 cm H_2O)
  - Poor emptying with high storage pressures
  - Impaired compliance

VIDEO-URODYNAMICS

VUDS consists of the simultaneous measurement of UDS parameters and imaging of the lower urinary tract. It provides the most precise evaluation of voiding function and dysfunction and is particularly useful when anatomic structure and function are important (Keane at al, 1993; McGuire et al, 1996). Examples of where VUDS are useful include the localization of obstruction, detecting incontinence not seen on physical examination, and evaluating vesicoureteral reflux during storage and/or voiding. It can be particularly useful in cases of neuropathic voiding dysfunction. VUDS is the only way to evaluate bladder neck dysfunction and can confirm sphincteric dysfunction diagnosed by EMG. Also, there are instances where a known anatomic abnormality exists and simultaneous imaging can determine if that abnormality is playing a role in voiding dysfunction (e.g., bladder or urethral diverticulum, vesicoureteral reflux).

VUDS can be performed using various different methods. Most commonly fluoroscopy is employed using a C-arm. This gives the most flexibility in allowing patient positioning. However, a fixed unit with a fluoroscopy table that can move from 90 to 180 degrees may also be used. It is important that the patient can be positioned properly to evaluate the desired function and anatomy. For example, SUI in men and women is best evaluated in the standing position. Voiding is best evaluated in the position that the patient characteristically voids (usually sitting for women and standing for men). It is always recommended that fluoroscopy time be limited and focus on situations of high yield such as during provocative maneuvers to demonstrate SUI, during rises in pressure associated with impaired compliance or involuntary contractions, and during voiding.

VUDS can be extremely useful for the diagnosis of bladder outlet obstruction in women (Nitti el al, 1999; Blaivas and Groutz, 2000). In fact, Nitti and colleagues (1999) described the VUDS criteria for the diagnosis obstruction in which radiographic evidence of obstruction between the bladder neck and urethral meatus during voluntary voiding defines and localizes obstruction. Primary bladder neck obstruction can only be diagnosed on VUDS. Figures 62–18 and 62–19 distinguish between the two most common causes of functional obstruction in women, primary bladder neck obstruction, and dysfunctional voiding.

Similarly, VUDS can be used to evaluate LUTS in young men and in particular make a diagnosis of primary bladder neck obstruction (Norlen and Blaivas, 1986; Kaplan et al, 1996). Although obstruction can be diagnosed by PFS alone, many surgeons would not feel comfortable performing surgical intervention on a young man without localizing that obstruction. In addition, sometime bladder neck obstruction can present without

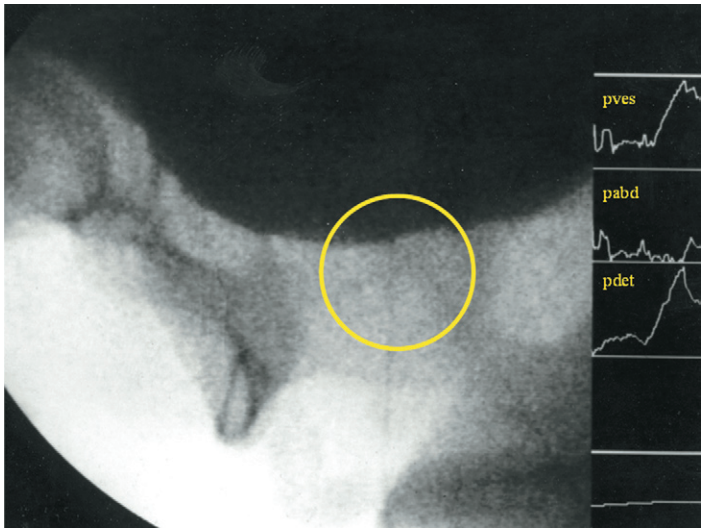


Figure 62–18. Primary bladder neck obstruction in a 35-year-old woman with obstructive voiding symptoms and intermittent urinary retention. Note the failure of the bladder neck to open at all, despite a detrusor contraction of greater than 60 cm H_2O. (From Nitti VW. Primary bladder neck obstruction in men and women. Rev Urol 2005;7[Suppl 8]:S12–7.)

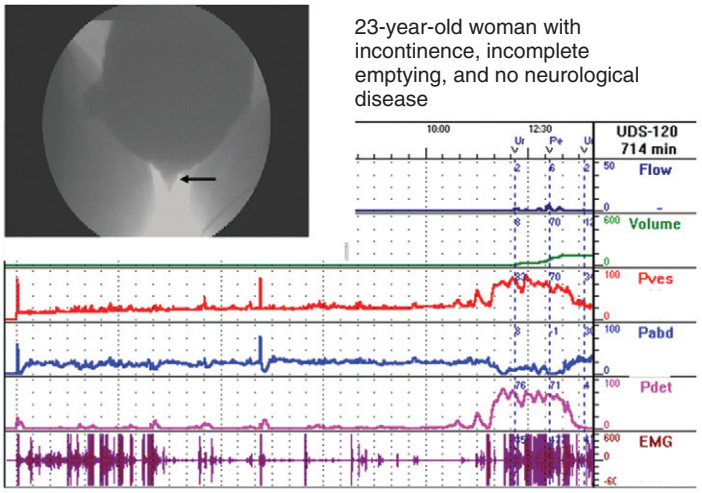


Figure 62–19. Dysfunctional voiding—a urodynamics study of a 23-year-old woman with urgency incontinence, incomplete emptying, and no neurologic disease. Just before voiding there is an involuntary detrusor contraction. With voiding there is increased EMG activity. The fluoroscopic picture taken during voiding shows a characteristic "spinning top urethra" with the level of obstruction at the external sphincter. The high-pressure–low-flow voiding is also characteristic of obstruction.

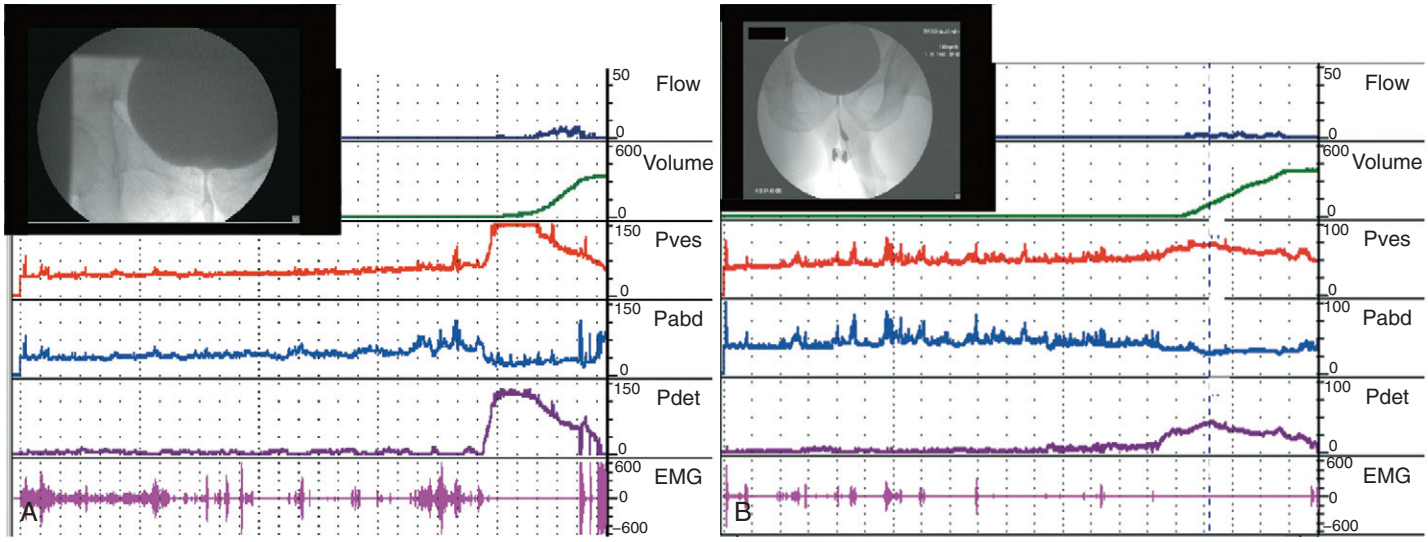


Figure 62–20. Primary bladder neck obstruction (dysfunction). **A**, Type 1—high-pressure, low-flow voiding in a 45-year-old male with severe lower urinary tract symptoms (LUTS) including frequency, urgency, and decreased force of stream. Image is taken during voiding—note the incompletely opened bladder neck. **B**, Type 2—normal-pressure, low-flow voiding in a 35-year-old male with similar LUTS as **A**. There is also an incompletely open bladder neck during voiding. The much lower voiding pressures compared with **A** should still be enough to empty normally, though there may be a component of impaired contractility because the bladder is unable to compensate for the increased resistance at the bladder neck. (From Nitti VW. Primary bladder neck obstruction in men and women. Rev Urol 2005;7[Suppl 8]:S12–7.)

classical findings of high pressure and low flow. Three distinct types have been described (Nitti et al, 2001): classic high pressure—low flow (type I); normal pressure—low flow with narrowing at the bladder neck (type II); and delayed opening of the bladder neck (type III). Figure 62–20 shows types I and II male primary bladder neck obstruction. Fluoroscopy is critical to the diagnosis, especially in types II and III.

VUDS is an important aid in diagnosing neuropathic voiding dysfunction, as well as other conditions that may cause elevated storage pressures. In cases where vesicoureteral reflux occurs, the volume and pressure at which it starts can be documented. In fact, in cases of impaired compliance, in which there is compensation by the "pop-off" mechanism of vesicoureteral reflux, the impaired compliance might not be identified unless the reflux is also recognized by fluoroscopy. In addition, an accurate DLPP can be obtained in cases where it would otherwise be impossible to position a patient to observe leakage (e.g., some tetraplegics). Furthermore, in cases of possible internal sphincter dyssynergia (often found in conjunction with external sphincter dyssynergia), VUDS is the only way to make the diagnosis and can dramatically change treatment (Fig. 62–21). The latest ICI recommendations (Hosker et al, 2009) include that VUDS be used, if possible, to evaluate patients with suspected neuropathic lower urinary tract dysfunction to "establish the state and function of the lower urinary

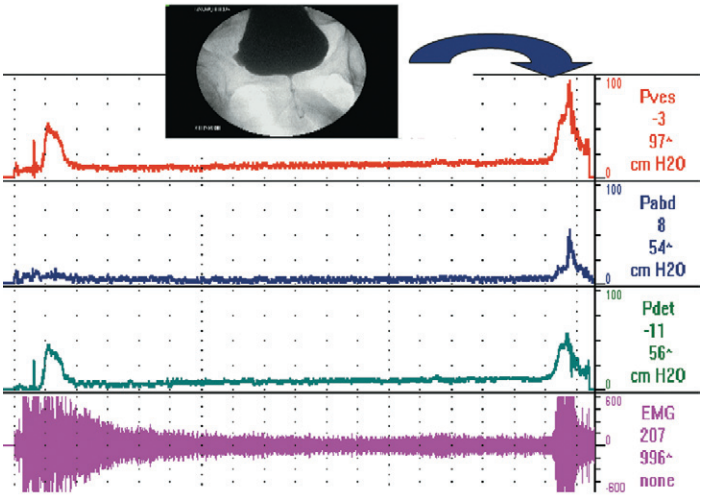


Figure 62–21. Video-urodynamics evaluation of a cervical spine–injured man with neuropathic voiding dysfunction with incontinence and incomplete emptying. The urodynamic tracing clearly shows detrusor overactivity with detrusor-external sphincter dyssynergia (increased electromyographic activity with involuntary contraction). However, it is only with the fluoroscopic view of the bladder outlet during an involuntary contraction that detrusor-internal sphincter dyssynergia is diagnosed (the bladder neck remains relatively closed).

tract." Although VUDS can be helpful in many cases, it is not readily available to all physicians.

Key Points: Video-Urodynamics

- VUDS is the procedure of choice for documenting bladder neck dysfunction in men and women.
- Patients at high risk for complicated voiding dysfunction such as those with known or suspected neuropathic voiding dysfunction, unexplained urinary retention in women, prior radical pelvic surgery, urinary diversion, prerenal or postrenal transplant, or prior pelvic radiation should be considered for referral to a center with VUDS capabilities if a complete and accurate diagnosis cannot otherwise be obtained (Scarpero, 2009).

AMBULATORY URODYNAMICS

Ambulatory urodynamic studies are defined as a functional test of the lower urinary tract, using natural filling and reproducing the subject's everyday activities (Abrams et al, 2002). The development of natural and slow-filling urodynamic studies was initially undertaken in the investigation of neuropathic patients by Comarr (1957) using diuresis-induced natural filling. He demonstrated an increase in bladder capacity and decreases in bladder pressures during filling when compared with CMG. Similar investigations of spinal injury patients by Tsiju and colleagues (1960) demonstrated increased phasic activity associated with incontinence during natural filling. Today it is a well-established method for investigating lower urinary tract function under the conditions of normal daily activities. Ambulatory UDS has its greatest value in patients in whom conventional UDS is not suitable or is unable to reproduce symptoms in question.

In 2000 the ICS published guidelines for the performance of ambulatory UDS (van Waalwijk van Doorn et al, 2000). Before the investigation, patients receive detailed information describing the test and the necessary preparation. Patients are instructed on how to accurately record symptoms and how to identify catheter displacement and hardware failure. A sample diary is given to record all relevant events so that UDS findings can be correlated with symptoms. Most systems employ microtip transducer catheters, which allow the most mobility. These are placed transurethrally to record bladder pressure and transrectally to record abdominal pressure. These catheters are firmly secured to the patient and are connected to a portable recording device. Some systems contain a third channel, which can be used for measuring urinary leakage objectively using an absorbent electronic (capacitance change) nappy pad (Robertson and Neil, 1998). This allows accurate data on the relationship of urinary leakage to detrusor activity to be obtained. Home uroflowmetry units are also available. After the completion of testing, ambulatory UDS tracings are analyzed, and this can be a time-consuming process depending on the length of the study. This must be done with great care and frequent quality checks to make sure that urethral and abdominal catheters are properly transducing pressure (e.g., using cough tests). In addition, the reader must be able to identify physiologic artifacts (after contractions and aberrant rectal pressures) and technical artifacts (movement or variation in pressure and lack of balance in the transducer lines), which could affect the interpretation of the study. The ambulatory study should be designed to reproduce symptoms. For example, if the patient complains of stress incontinence, a standard protocol of exercises can be performed and recorded (e.g., jumping up and down, squatting, coughing).

CLINICAL UTILITY OF AMBULATORY URODYNAMICS

Ambulatory UDS is performed in an effort to capture more realistic or more physiologic observations, especially of incontinence episodes (Hosker et al, 2009). It attempts to increase sensitivity by providing a longer time for DO (and other abnormalities) to manifest itself. Practically speaking, ambulatory UDS is most useful when standard UDS is inconclusive and diagnosis and, more importantly, treatment are uncertain. Ambulatory UDS has been most commonly used to diagnose the cause of urinary incontinence, but it has also been applied to the diagnosis of male bladder outlet obstruction and neuropathic voiding dysfunction.

It has been shown that ambulatory monitoring detects more actual incontinence than conventional cystometry (Cassidenti and Ostergard, 1999). Several studies have shown ambulatory UDS to be more sensitive than conventional CMG for the diagnosis of DO (Robertson et al, 1994; Heslington and Hilton, 1996). Radley and colleagues (2001) found that ambulatory monitoring revealed DO in 70 of 106 women with symptoms suggestive of DO (twice as many as conventional cystometry with provocation by hand washing) and it detected DO incontinence (DOI) in 40 of the 70. The observation of DOI was correlated with symptom severity, but it is not clear how many women complaining of urgency incontinence showed DOI. Thus the sensitivity is unknown. The finding of higher rates (and sensitivity) of DO found on ambulatory monitoring must be weighed against the fact that ambulatory UDS has found rates of DO asymptomatic volunteers. DO has been found in asymptomatic females as often as 69% versus 18% for conventional CMG (vanWaalwijk van Doorn et al, 1996) and in 38% versus 17% in asymptomatic men and women (Robertson et al, 1994). Thus some degree of detrusor overactivity may be normal

in the setting of a urethral catheter for a prolonged period of time, making some sort of standardization important.

In a review of 422 female ambulatory UDS studies over a 12-year period, Patravali (2007) argued for the value of the study. It was seen that 85% of patients complaining of urinary incontinence showed detectable leakage with a diagnosable mechanism on ambulatory study, and in 77% of 74 women with a normal CMG ambulatory UDS diagnosed the cause of incontinence and provided "clear added value." DO was a component in 42 of these 57 patients (76%). What is unknown is exactly what was meant by "clear added value" and how treatment was affected. In a smaller study of 25 patients, Pannek and Pieper (2008) had similar findings but a more useful interpretation of those findings. They found that ambulatory UDS was helpful (versus standard UDS) in diagnosing lower urinary tract dysfunction in 72% of the evaluable examinations. However, 24% of the studies done were not evaluable owing to technical problems or catheter dislocation. Thus ambulatory UDS was clinically useful in only 48% of the patients who underwent this examination. When a diagnosis was made on ambulatory UDS, successful treatment was established in 42% of the patients. However, when ambulatory UDS was not helpful and patients were treated on the basis of clinical symptoms, 33.3% were treated successfully. Gorton and Stanton (2000) also looked at the effect of ambulatory UDS on clinical management. In a retrospective review of 71 women there were technical difficulties in 42% of the studies with 2 being uninterpretable. DO was found in 45% of the women, and nearly all were treated with medication. Among the remainder without DO, fewer received medication. However, less than half of those who received medication improved. The authors concluded that ambulatory UDS was not helpful in deciding on management.

Ambulatory UDS has been used for the diagnosis of obstruction in men with LUTS and inconclusive (borderline or nondiagnostic) conventional PFS. Rosario and colleagues (1999) reclassified 24% of such patients as either obstructed or nonobstructed. However, Robertson and colleagues (1996) found no difference in the classification of patients with ambulatory versus conventional PFS. It has been demonstrated that storage pressures in patients with chronic obstruction and neuropathic voiding dysfunction are lower on ambulatory, natural-fill UDS than on conventional CMG (Webb et al, 1989, 1992). Patients with poor compliance (high filling pressures) and hydronephrosis on conventional CMG were found to have normal compliance but significant phasic DO on ambulatory monitoring. It has been suggested that phasic DO and not impaired compliance may lead to upper tract deterioration in these patients. Although this may be true, it needs to be proven in a series of patients followed over time, and for now, on the basis of the available evidence, one must still conclude that significantly impaired compliance on conventional CMG is a risk factor for upper tract damage.

Key Points: Ambulatory Urodynamics

- Ambulatory UDS may be useful in a select group of patients where conventional UDS is nondiagnostic and the information provided will affect treatment, counseling, or follow-up.
- Ambulatory UDS and its interpretation are time consuming and technically challenging.
- The data obtained for ambulatory UDS studies must be weighed against the fact that for many findings, both normal and abnormal standards have not been established.

CLINICAL APPLICATIONS OF URODYNAMIC STUDIES: EVIDENCE-BASED REVIEW

Thus far this chapter has described the technical aspects of UDS and general indications for its use. This final section provides an evidence-based review of UDS for different common clinical applications. In many situations there is not enough evidence in the literature to conclude how useful UDS is for a particular case, and as such, its use should be based on a clinical impression. Nevertheless, there are some instances and indications where the evidence is strong enough to provide guidance as to how useful UDS will be. In cases where recommendations are made, these are based on the Oxford system: Grade A recommendation usually depends on consistent level 1 evidence and often means that the recommendation is effectively mandatory and placed within a clinical care pathway. Grade B recommendation usually depends on consistent level 2 and/or 3 evidence studies or "majority evidence" from randomized controlled trials. Grade C recommendation usually depends on level 4 evidence studies or "majority evidence" from level 2/3 studies or from "expert opinion." Four areas in which UDS is commonly used for evaluation are addressed. Enough evidence exists to make valid conclusions or recommendations for women with SUI, men with LUTS, neuropathic voiding dysfunction, and pediatric urologic conditions.

EVALUATION OF WOMEN WITH STRESS INCONTINENCE

Several studies have shown that **for women with pure SUI without urge symptoms who empty normally and demonstrated SUI on physical examination, UDS will not provide much useful information.** For example, in a randomized trial comparing the efficacy of Burch procedure versus pubovaginal sling in 655 *selected* women with pure or predominate SUI who had fewer than 12 micturitions/day, a positive standardized stress test (volume < 300 mL), a maximum cystometric capacity of at least 200 mL, a PVR of less than 150 mL and unobstructed voiding (Q_{max} > 12 mL/sec, $PdetQ_{max}$ < 50 cm H_2O), UDS including ALPP, and presence of DO added little to help determine surgical outcomes with respect to efficacy (Nager et al, 2008) or postoperative voiding dysfunction (Lemack et al, 2008). In 2006, in the United Kingdom, the National Institute for Health and Clinical Excellence issued guidelines that UDS was recommended before surgery for urinary incontinence only if (1) there is a clinical suspicion of DO, (2) there has been previous surgery for stress incontinence or anterior compartment prolapse, or (3) there are symptoms suggestive of voiding dysfunction. In other words, urodynamics is not routinely recommended for women before surgery for a "clearly defined clinical diagnosis of stress urinary incontinence."

However, many women with SUI who are considering surgical correction have mixed symptoms or emptying difficulties and it is here that UDS probably has its most significant role for female SUI. In addition, previous studies have found significant variation of the predictive value of symptoms in identifying the three UDS observations of urodynamic SUI, DOI, and mixed urinary incontinence (Harvey and Versi, 2001; Homma, 2002; Agur et al, 2009). This variation is probably explained by the nonhomogeneous patient populations and an

inconsistency in the clinical and the UDS diagnosis between the studies.

UDS does seem to have a valuable role in the preoperative evaluation of patients with mixed symptoms. In fact, several studies have shown excellent cure rates for both stress and urge symptoms in women with urodynamic SUI and a normal CMG (no DO) for pubovaginal sling (Chou, 2003; Osman, 2003); Burch procedure (Osman, 2003); and tension-free vaginal tape (Rezapour and Ulmstem, 2001).

In view of these discrepancies between symptoms and urodynamic findings, the soundest basis for the clinical diagnosis and evaluation of stress urinary incontinence and urgency urinary incontinence remains to be established, as does the significance of the corresponding urodynamic observations such as USI, DOI, and DO (Hosker et al, 2009). In cases of straightforward SUI with no significant urgency symptoms and with normal bladder emptying, it seems reasonable to forego UDS evaluation if the clinician and patient are comfortable with the limitations of symptoms as a predictor of all possible lower urinary tract abnormalities. These considerations are best reflected in the following grade A recommendation from the Fourth ICI Committee on Dynamic Testing (Hosker, 2009):

> "the cost effectiveness of urodynamic testing is kept in mind when discussing 'cost and gain' of the various methods of diagnosis for urinary incontinence, in relation to the method of treatment."

Many attempts to measure and quantify the severity of SUI urodynamically have been made using urethral pressure profilometry and leak point pressure measurements. In a review of static urethral pressure profilometry parameters such as MUCP or cough profile parameters such as pressure transmission ratio, Weber (2001a) concluded that these measures cannot be used to characterize the severity of incontinence. Another review by the same author (Weber, 2001b) suggested that ALPP might be a useful tool to quantify urethral dysfunction associated with SUI. However, other studies have found no correlation between leak point pressures and the severity of urinary incontinence as measured by bladder diaries and quality of life instruments (Theofrastous et al, 1995; Nager et al; 2001; Fleischmann et al, 2003; Albo et al, 2007; Chen et al, 2008). Leak point pressures have also been criticized as a diagnostic tool because of a lack of standardization of the technique (Rodrigues et al, 2006). Furthermore, leak point pressure and urethral pressure profilometry have not been shown to consistently predict outcomes for surgical treatment of SUI. In a review of this topic, Lemack (2004) found little evidence to suggest that women with "more severe forms" of SUI as measured urodynamically fare more poorly after commonly performed surgical procedures than those with "less severe forms." Recently it has been suggested that lower urethral pressure cut points are predictive of failure for transobturator versus retropubic midurethral slings (Miller et al, 2006; O'Connor et al, 2006; Guerette et al, 2008). However, this has not been confirmed by randomized studies to date. Other investigators have shown that MUCP is not a predictor or surgical failure (Homma, 2002; Bai et al, 2007). Finally, in the prospective, randomized Stress Incontinence Surgical Treatment Efficacy (SISTEr) trial comparing Burch colposuspension and pubovaginal sling, leak point pressures were not found to be predictive of surgical outcome for either procedure (Nager et al, 2008).

In 2009 the Fourth ICI Committee on Dynamic Testing made the following grade B/C recommendations on the basis of available evidence-based literature (Hosker et al, 2009):

1. **Urethral function measurements of leak point pressures and urethral closure pressures are not used as a single factor to grade the severity of incontinence.**
2. **Use caution with the prediction of the outcome of any surgical treatment on the basis of contemporary urethral function tests.**

EVALUATION OF MEN WITH LOWER URINARY TRACT SYMPTOMS

LUTS are common among men of 50 years and older. The cause of male LUTS is multifactorial, comprising at least four conditions: (1) BOO, (2) impaired contractility, (3) detrusor overactivity, and (4) sensory urgency (Blaivas, 1988). Often storage symptoms of frequency and urgency accompany voiding symptoms of decreased force of stream and hesitancy. Urgency incontinence can also occur as a result of DO with or without BOO. It has been established that coexistence of BOO and DO increases with age and with the degree of BOO (Vesely et al, 2003; Oelke et al, 2008). In such cases UDS can be helpful to establish the underlying bladder and/or bladder outlet abnormality.

The question of how much help UDS is in the evaluation and treatment of male LUTS has been debated for years. How necessary is a diagnosis of BOO before transurethral prostate resection, for example? The answer depends on how comfortable the clinician is making a diagnosis and treating with less invasive and less definitive testing. Few would argue that in order to institute an α blocker for the treatment of LUTS in a man with relatively normal bladder emptying, UDS is not required. However, as the scenario becomes more complex and the treatment more invasive and potentially morbid, a precise diagnosis will be helpful in many cases. Often it is ultimately up to the clinician to decide how much information is useful or necessary to make a treatment decision and properly counsel patients.

It is well documented that in men with BOO, surgery such as transurethral prostate resection (by any means) reduces obstruction and relieves symptoms. However, storage symptoms like urgency frequency and urgency incontinence will persist in about one third of cases. It has been shown that when storage symptoms are associated with DO and BOO, UDS can help predict resolution of those symptoms. In such a scenario, storage symptoms have a higher likelihood of resolving with intervention (e.g., TURP) when DO occurs as a single terminal IDC rather than continuous or sporadic IDCs (Kageyama et al, 2000). Such information can be quite valuable when counseling patients. For example, given the same UDS presentation of BOO plus continuous IDCs, a patient primarily concerned with his inability to empty may opt for surgery, whereas a patient who is primarily concerned about OAB symptoms may not.

As for the utility of UDS before surgical treatment or no treatment of LUTS thought to be secondary to BPH, the literature is mixed. Several studies support its necessity (Javle et al, 1998; Rodrigues et al, 2001; Porru et al, 2002; Thomas et al, 2004), whereas others have concluded that UDS is not necessary (Pannek et al, 1998; Kanik et al, 2004) or necessary only in inconclusive cases (Ignjatovic, 1997). Three reviews (Abrams et al, 2001; Homma, 2001; Clemens, 2003) have suggested that UDS has some but not strong predictive value for the outcome of treatment. Another review by Bhargava and colleagues (2004) concluded that conventional urodynamic studies are useful in providing preoperative information about detrusor function and to exclude

patients less likely to benefit from prostate surgery. Despite this, some regard the need for performing urodynamic evaluation routinely, before transurethral resection of the prostate, as still controversial. **This led the experts at the Sixth International Consultation on New Developments in Prostate cancer and Diseases to conclude that although almost all evidence for the advantages of UDS before invasive therapy for BPO is level 3 (good-quality retrospective "case-control studies" or "case series"), the quantity of evidence allows a grade B recommendation** (Abrams et al, 2006).

Most of the time when BOO is treated, it is done so because of symptoms. However, "symptomatic" BOO, if not relieved in time, may lead to progression of the disease and affect organ function. For many years attention was paid only to the backpressure effects of obstruction on the kidneys (from high voiding pressures and/or impaired compliance). However, it is now known that BOO affects bladder function, leading to structural changes. Because the changes may eventually become irreversible, some would argue that management should be directed toward early relief of significant obstruction (Flanigan et al, 1998; Lu et al, 2000; Brierly et al, 2003). **However, at this time, a critical level of obstruction (e.g., based on the BOOI) has not been defined. No evidence-based studies suggest when surgical relief is indicated to prevent bladder decompensation. However, many papers have shown that if there is no evidence of obstruction on PFS, the results of surgical relief are not as good** (Porru et al, 2002; Thomas, 2004). **Significantly impaired compliance remains the only "absolute urodynamic indication" for treating BOO.**

EVALUATION OF NEUROPATHIC LOWER URINARY TRACT DYSFUNCTION

Neuropathic lower urinary tract dysfunction usually presents clinically as incontinence and/or inability to empty the bladder. Incontinence may be of bladder origin (detrusor overactivity or impaired compliance) or sphincter origin. Poor emptying can also be of bladder origin (impaired detrusor contractility) of sphincter origin (dyssynergia). In addition to symptomatic presentation, neuropathic lower urinary tract dysfunction can present as upper urinary tract decompensation with hydroureteronephrosis and renal insufficiency without bothersome symptoms. The goal of management in these patients is to prevent upper tract decompensation and relieve symptoms. A specific understanding of the pathophysiology of the condition in each individual is essential for the correct choice of therapy (Stohrer, 1990; Stohrer et al, 1994; Rivas and Chancellor, 1995). **UDS probably has its most important role in the diagnosis and management of patients with neuropathic voiding dysfunction.**

The aims of therapy for neuropathic lower urinary tract dysfunction are to achieve physiologic filling (and if possible voiding) conditions, as well as to control symptoms and create a management situation acceptable to the patient in daily life. Much of the evidence base for management of the lower urinary tract in the neuropathic patient consists of level 3 evidence. This is primarily because of the potential negative consequences of untreated neuropathic dysfunction. As such, randomized, controlled trials are thought by many to be dangerous and unethical. Because prolonged periods of elevated detrusor pressure during bladder filling or abnormally prolonged elevated pressures during voiding have been found to put the upper urinary tract at risk (McGuire et al, 1996; Kurzrock and Polse, 1998; Tanaka et al, 1999), primary aim of therapy in patients with such problems is conversion to a low pressure bladder during filling even if this leads to incomplete emptying and the need to supplement emptying with catheterization. Adequate therapy depends on whether the detrusor is overactive or has reduced compliance, and only urodynamics can answer those questions unequivocally. Timely and adequate diagnosis of DO and impaired compliance is thought to be of paramount importance for the patient's quality of life (Stohrer, 1990; Stohrer et al, 1994; Bomalaski et al, 1995; Cardenas et al, 1995). UDS is also essential for assessing the response to treatment and following any sequelae of the disease and its management (Hosker et al, 2009).

In 2009 the Fourth Consultation on Incontinence committee on dynamic testing made the following grade B/C recommendation on the basis of the available evidence-based literature (Hosker et al, 2009): **Patients with suspected neurogenic dysfunction of the LUT should receive comprehensive UDS evaluation including VUDS, if possible, to establish the state and function of the lower tract. In addition, UDS testing in this group of patients should be done in a specialized environment with trained personnel.**

EVALUATION OF CHILDREN

Many of the conditions for which UDS is used in children involve anatomic and neurologic abnormalities in which lower urinary tract function is variable and unpredictable. UDS is used to establish as clearly as possible the baseline situation so that changes as a result of treatment and/or growth can be assessed, and some guidance is obtained in the choice of treatment even if the result of UDS testing is not necessarily the deciding factor (Hosker et al, 2009). In the pediatric population, the aim of UDS is not only to provide precise knowledge of lower urinary tract function but also to provide an understanding of the current and future condition to the caregiver and to the patient (and his or her parents). Of course, it is still imperative that the testing should be relevant, reliable, and reproducible. We briefly describe the evidence base for several commonly studied pediatric conditions. The reader is referred to the relevant chapters on pediatric urology for a more detailed discussion.

Pediatric Neurologic Conditions: Myelodysplasia, Occult Spinal Dysraphism, and Sacral Agenesis

When evaluating children with myelodysplasia, a number of effects on the lower urinary tract can be seen. Detrusor overactivity (on filling) or underactivity (on voiding), DESD, impaired compliance, and elevated DLPP are the key parameters evaluated on UDS testing in this population (McGuire et al, 1981; Bauer et al, 1984). Retrospective and prospective studies have shown that the urodynamic diagnosis of DO and/or reduced detrusor compliance in patients with myelodysplasia or (occult) spinal dysraphism is not predictable on the basis of clinical signs, symptoms, or level of lesion (Dator et al, 1992; Landau et al, 1994; Pontari et al, 1995; Kaefer et al, 1997; Palmer et al, 1997), making UDS an important tool in assessing the lower urinary tract. Furthermore, these studies reveal clinically relevant results with regard to detrusor storage function. In a retrospective study of 64 children, Rendeli and

colleagues (2007) showed that UDS evaluation and the presence of neurologic impairment have crucial roles in determining the optimal timing of surgery in patients with lipomeningocele and in diagnosing the onset of tethered cord. Finally, it has been demonstrated that lower urinary tract function may change over time (McGuire et al, 1981; Bauer et al, 1984; Sidi et al, 1986; Wang et al, 2006) and repeat evaluation may be necessary. However, no studies have helped to determine the optimum timing and frequency of UDS follow-up.

Sacral agenesis is often missed in infancy because of its subtle clinical manifestations and no obvious loss of lower extremity motor and sensory function. Similar to myelodysplasia, patients can present with a variety of lower urinary tract dysfunctions. Several studies have shown that 30% to 40% of patients present with DO and an intact but dyssynergic sphincter (upper motor neuron lesion), 25% to 50% will have an acontractile detrusor with a denervated sphincter (lower motor neuron lesion), and 15% to 20% have normal lower urinary tract function (Koff et al, 1977; Guzman et al, 1983, Jabokson et al, 1985). In eight reports that provide adequate data, UDS has been 90% accurate in delineating the neurologic deficit and in managing incontinence and upper urinary tract abnormalities (Koff et al, 1977, 1983; Jabokson et al, 1985; Gotoh et al, 1991; Saito et al, 1991; Boemers et al, 1994, 1996; Wilmshurst et al, 1999; Torre et al, 2002).

In 2009 the Fourth Consultation on Incontinence committee on dynamic testing made the following recommendations for children with myelodysplasia or occult spinal dysraphism and sacral agenesis on the basis of the available evidence-based literature (Hosker et al, 2009):

1. **Comprehensive UDS testing is advised in all patients with myelodysplasia or occult spinal dysraphism (grade B/C).**
2. **Video-urodynamic testing should be considered in all children with myelodysplasia or occult spinal dysraphism (grade C).**
3. **Timing and technique of UDS testing in children with myelodysplasia or occult spinal dysraphism should be selected on an individual basis (grade C).**
4. **To help identify children at risk for subsequent urinary tract deterioration or a changing neurologic picture, initial UDS studies early in the neonatal period are recommended for children with myelodysplasia or occult spinal dysraphism (grade C).**
5. **Clinicians should consider UDS testing in children with sacral agenesis when clinical signs of lower urinary tract dysfunction or relevant neurologic abnormalities exist (grade C).**

Pediatric Anatomic Abnormalities: Posterior Urethral Valves, Bladder Extrophy, Vesicoureteral Reflux

A number of congenital and acquired anatomic abnormalities can affect lower urinary tract function. Because of a lack of prospective data, it is recommended that for each of the abnormalities presented, clinicians should consider UDS, depending on the clinical scenario (Hosker et al, 2009). Studies on posterior urethral valves have shown that some boys will have significant lower urinary tract dysfunction, namely DO and impaired compliance (Kim et al, 1997; Kajbafzadeh et al, 2007). When storage pressures are considered to be dangerously elevated, improvements in DO and compliance after valve ablation have been documented (De Gennaro et al, 1996, 2000; Holmdahl et al, 1996; Kim et al, 1997; Donohoe et al, 2004). Myogenic failure and poor emptying are late sequela of posterior urethral valves, and persistence of upper tract changes is related to high storage pressure and/or incomplete emptying. Several studies have shown the predictability of developing upper tract decompensation on the basis of UDS parameters of persistent poor compliance, high detrusor pressures, and impaired contractility during voiding (Bauer et al, 1979; Peters et al, 1990; Holmdahl et al, 1995, 1996; Lopez Pereira et al, 2002).

Bladder extrophy is another condition in which UDS may be helpful. A few studies have shown that after bladder neck reconstruction, the prevalence of DO increases and compliance worsens in up to 50% of cases (Hollowell et al 1992, 1993; Diamond et al, 1999; Caione et al, 2005; Burki, 2006). Although there is no prospective information regarding long-term outcomes based on UDS finding, this information may be helpful in management.

There is increasing evidence that a significant number of vesicoureteral reflux cases are due to bladder dysfunction (DO) and not necessarily an anatomic abnormality at the ureterovesical junction (Koff et al, 1979; Griffiths and Scholtmeijer, 1987; Sillen et al, 1996; Capitanucci, 2000; Greenfield and Wan, 2000; Podesta, 2004). DO may be a result of high voiding pressures, particularly in boys, or dysfunctional voiding. Four separate studies have shown that treating DO and/or voiding with antimuscarinics leads to a rapid rate of reflux resolution (63% to 92%) within 1 year (Homsy et al, 1985; Scholtmeijer and Nijmanl, 1994; Batista Miranda et al, 1997). This is higher than the 25% to 54% rate of reflux resolution seen with treatment using antibiotics alone to prevent recurrent infection (Seruca, 1989). Treating dysfunctional voiding with biofeedback has also been shown to reduce the grade of reflux (Kuo and Liu, 2006). Because of these findings, many clinicians advocate UDS for children with high-grade vesicoureteral reflux, especially those with incontinence, renal damage, or pending surgery to correct reflux (Scholtmeijer and Nijman, 1994; Moran Penco et al, 2004; Musquera et al, 2004; Fotter and Riccabona, 2005). **On the basis of the available literature, the Fourth ICI Committee had the following grade C recommendation regarding UDS testing of children with anatomic abnormalities discussed earlier: Clinicians should consider complete urodynamic testing, at least once, in children with posterior urethral valves, urethral stricture, ectopic ureterocele, vesicoureteral reflux, and bladder extrophy. Clinicians should consider regular uroflowmetry and PVR in the management and follow-up of children with posterior urethral valves, urethral stricture, ectopic ureterocele, vesicoureteral reflux, and bladder extrophy.**

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chapter 63

Urinary Incontinence and Pelvic Prolapse: Epidemiology and Pathophysiology

Christopher R. Chapple, MD, FRCS (Urol), FEBU ● Ian Milsom, MD, PhD

Definition and Classification of Urinary Incontinence
Definition and Classification of Pelvic Organ Prolapse
Relationship Between Incontinence and Prolapse
Pathophysiology of Incontinence and Prolapse
Pelvic Floor Support Mechanisms
Epidemiology of Urinary Incontinence and Prolapse
Epidemiology of Overactive Bladder
Epidemiology of Pelvic Organ Prolapse

DEFINITION AND CLASSIFICATION OF URINARY INCONTINENCE

Urinary incontinence (UI) has a considerable social and economic impact. Indeed, it has been estimated that UI in women was the primary cause for more than 1.1 million office visits in 2000 in the United States (Litwin et al, 2005). Hu and colleagues (2004) estimated the total direct and indirect cost of incontinence in the United States in the year 2000 to be approximately $19.5 billion. Incontinence has a larger economic impact than many chronic conditions and diseases.

The lower urinary tract comprises the bladder and urethra and should be considered as a single functioning vesicourethral unit required to store urine and empty efficiently. Most of the bladder's functional time is spent in storing urine. Dysfunction occurs when there is a breakdown of these fundamental tasks, resulting in storage and/or voiding symptoms, urinary retention, or incontinence. The bladder tends to be an "unreliable witness," its symptoms often being nonspecific and neither diagnosing the underlying dysfunction nor paralleling the severity of the underlying functional disorder. The customary evaluation of patients with both storage and voiding dysfunction includes an in-depth history and physical examination, as well as appropriate laboratory studies. Endoscopy and radiography provide useful structural information and are used when clinically indicated. Urodynamic studies provide the only objective functional tests of bladder and urethral function and are a valuable adjunct to the investigation of patients with lower urinary tract dysfunction (LUTD). Urodynamics, when properly selected and accurately interpreted, provides health care professionals with an improved diagnostic capability useful in formulating treatment strategies, educating patients, and ultimately improving therapeutic outcome. The results of urodynamics should not be interpreted as a free-standing study but in conjunction with the clinical presentation. Although the interpretation of urodynamics can be complex on occasion, in the majority of cases the indications for urodynamic investigation are evident and its application provides an essential complement to the modern practice of urology, gynecology, and associated specialties.

The "storage" component of **lower urinary tract symptoms (LUTS),** of which incontinence is unarguably the most troublesome, is a common and important cause of morbidity and impairment of quality of life, in both men and women (Chapple et al, 2008). In order to effectively consider the subject of incontinence, it is important to think in terms of symptoms, signs, urodynamic observations, and conditions, as defined by the International Continence Society (ICS) and summarized in their published standardization report (Abrams, 2002; Abrams et al, 2002).

When a condition cannot be documented by urodynamic observation, it may be "presumed" by clinical documentation.

In this chapter we widely quote the ICS standardization documents, which underpin all clinical and academic evaluation of patients and should form the basis for all therapy. The authors of this chapter want to acknowledge the hard work of all of the authors and contributors to these documents. **Signs** are observed by the physician by simple means (e.g., observation of the loss of urine with a cough) or by the use of diaries, pad **tests, symptoms scores, and validated quality of life instruments. Urodynamic observations** are made during urodynamic studies and reflect the definitive pathophysiologic condition that is causing the incontinence (e.g., detrusor overactivity or sphincteric weakness).

Lower Urinary Tract Symptoms

Symptoms are the subjective indicator of a disease or change in condition as perceived by the patient, caregiver, or partner and may lead him or her to seek help from health care professionals. They may be volunteered or described during the patient interview. They are usually qualitative. In general, LUTS cannot be used

to make a definitive diagnosis. LUTS can also indicate pathologies other than LUTD such as urinary infection.

Signs Suggestive of Lower Urinary Tract Dysfunction

Signs are observed by the physician including simple means to verify symptoms and quantify them. For example, a classical sign is the observation of leakage on coughing. Observations from frequency volume charts, pad tests, and validated symptom and quality-of-life questionnaires are examples of other instruments that can be used to verify and quantify symptoms.

Urodynamic Observations

Urodynamic observations are observations made during urodynamic studies. For example, an involuntary detrusor contraction (detrusor overactivity) is a urodynamic observation. In general, a urodynamic observation may have a number of possible underlying causes and does not represent a definitive diagnosis of a disease or condition and may occur with a variety of symptoms and signs or in the absence of any symptoms or signs.

Conditions

Conditions are defined by the presence of urodynamic observations associated with characteristic symptoms or signs and/or nonurodynamic evidence of relevant pathologic processes.

LUTS are best considered as three groups of symptoms: **storage, voiding,** and **postmicturition.** Storage symptoms will be considered in detail later, and the reader is directed to other chapters for a consideration of the other categories of LUTS.

Storage symptoms are experienced during the storage phase of the bladder and include daytime frequency and nocturia.

- **Increased daytime frequency** is the complaint by the patient who considers that he or she voids too often by day (equivalent to the term *pollakisuria* used in many countries).
- **Nocturia** is the complaint that the individual has to wake at night one or more times to void. **This is sleep-disturbing voiding.**

  Night-time frequency differs from nocturia because it includes voids that occur after the individual has gone to bed but before he or she has gone to sleep and voids that occur in the early morning, which prevent the individual from getting back to sleep as he or she desires.
- **Urgency** is the complaint of a sudden, compelling desire to pass urine, which is difficult to defer.
- **UI** is the complaint of any involuntary leakage of urine.

The International Continence Society (ICS) has defined the symptom of UI as "the **complaint of any involuntary loss of urine that is a social or hygienic problem."** When considering incontinence, it is important to particularly consider relevant factors such as **type, frequency, severity, precipitating factors, social impact, effect on hygiene and quality of life, the measures used to contain the leakage, and whether or not the individual seeks or desires help** because of UI. Urinary leakage may need to be distinguished from sweating or vaginal discharge.

- Stress UI is the:

  symptomatic complaint of involuntary leakage on effort or exertion, or on sneezing or coughing.

  sign of involuntary urinary loss from the urethra synchronous with exertion, sneezing, or coughing.

  urodynamic diagnosis of the involuntary leakage of urine during increases in abdominal pressure in the absence of a detrusor contraction—so-called **urodynamic stress incontinence.**

  The term "stress," although unsatisfactory in the English language because of its mental connotations, has been retained because although the terms "effort or exertion incontinence" are preferable, they do not capture some of the common precipitating factors for stress incontinence such as coughing or sneezing.
- Urgency UI is the:

  symptomatic complaint of involuntary leakage accompanied by or immediately preceded by urgency as *contrasted* to urge, which is a normal sensation (Abrams et al, 2009). The current term *urge* has therefore been replaced by **urgency UI.**

  sign of involuntary urinary loss from the urethra that is accompanied by or immediately preceded by urgency.

  urodynamic diagnosis of incontinence related to an involuntary detrusor contraction during urodynamics—so-called **detrusor overactivity associated incontinence.**

Urgency incontinence can present in different symptomatic forms (e.g., as frequent small losses between micturitions or as a catastrophic leak with complete bladder emptying).

- Mixed UI is the:

  symptomatic complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing, or coughing.

  sign of involuntary urinary loss from the urethra synchronous with exertion, sneezing, or coughing and of involuntary urinary loss from the urethra that is accompanied by or immediately preceded by urgency.

  urodynamic diagnosis of both involuntary leakage of urine during increases in abdominal pressure. It is related to an involuntary detrusor contraction during urodynamics and is present in approximately 40% of women with stress incontinence.

Overactive bladder (OAB), or the urgency frequency symptom syndrome, comprises urgency, with or without **urgency incontinence,** usually with frequency and nocturia. Urgency is widely held to be a key symptom driving the clinical sequence as demonstrated by Figure 63–1.

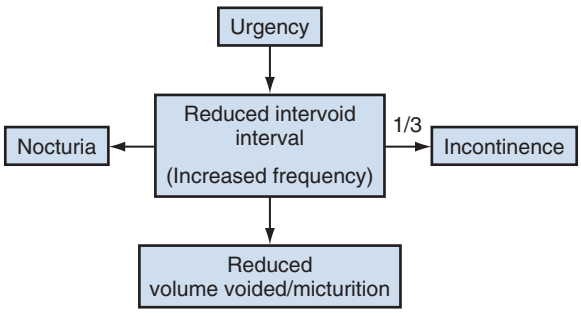


Figure 63–1. The overactive bladder symptom complex. (From Chapple CR, Artibani W, Cardozo LD, et al. The role of urinary urgency and its measurement in the overactive bladder symptom syndrome: current concepts and future prospects. BJU Int 2005;95:335–40.)

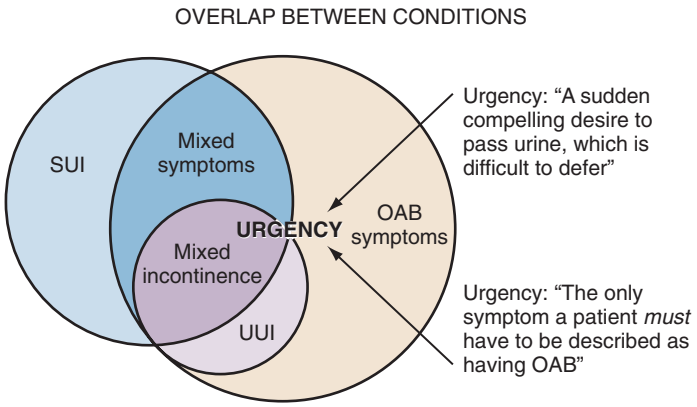


Figure 63–2. Overlap between conditions. OAB, overactive bladder; SUI, stress urinary incontinence; UUI, urgency urinary incontinence. (From Wein AJ, Rackley RR. Overactive bladder: a better understanding of pathophysiology, diagnosis and management. J Urol 2006;175:S5–10.)

- **Mixed urinary symptoms** is a term applied to the presentation of a patient with a combination of OAB dry (without urgency incontinence) and stress incontinence (Fig. 63–2).
- **Enuresis** means any involuntary loss of urine. If it is used to denote incontinence during sleep, it should always be qualified with the adjective "nocturnal."
- **Nocturnal enuresis** is the complaint of loss of urine occurring during sleep.
- **Continuous UI** is the complaint of continuous leakage.
- **Other types of UI** may be situational (e.g., the report of incontinence during sexual intercourse, giggle incontinence).

  Overflow incontinence is not a symptom or condition but rather a term used to describe leakage of urine associated with urinary retention.

  Postmicturition dribble is the complaint of an involuntary loss of urine. Both are voiding symptoms.

  Extraurethral incontinence is the observation of urine leakage through channels other than the urethra (e.g., fistula or ectopic ureter) immediately after passing urine.

  Bladder sensation is an important factor to take into account when interpreting storage disorders affecting the lower urinary tract and can be categorized during history taking into five broad categories:

  1. **Normal:** The individual is aware of bladder filling and increasing sensation up to a strong desire to void.
  2. **Increased:** The individual feels an early and persistent desire to void.
  3. **Reduced:** The individual is aware of bladder filling but does not feel a definite desire to void.
  4. **Absent:** The individual reports no sensation of bladder filling or desire to void.
  5. **Nonspecific:** The individual reports no specific bladder sensation but may perceive bladder filling as abdominal fullness, vegetative symptoms, or spasticity. These nonspecific symptoms are most frequently seen in neurologic patients, particularly those with spinal cord trauma and in children and adults with malformations of the spinal cord.

  Physical examination is essential in the assessment of all patients with LUTD. It should include abdominal, pelvic, perineal, and a focused neurologic examination. For patients with possible neurogenic lower urinary tract dysfunction, a more extensive neurologic examination is necessary. Clinical assessment of pelvic floor anatomy is determined by physical examination of the external genitalia and vaginal canal.

  Abdominal: The bladder may be felt by abdominal palpation or by suprapubic percussion. Pressure suprapubically or during bimanual vaginal examination may induce a desire to pass urine.

  Perineal/Genital Inspection allows the description of the skin (e.g., the presence of atrophy or excoriation, any abnormal anatomic features, observation of incontinence).
- **UI (the sign)** is defined as urine leakage seen during examination: This may be urethral or extraurethral. **Extraurethral incontinence** is defined as the observation of urine leakage through channels other than the urethra.
- **Stress UI** is the observation of involuntary leakage from the urethra, synchronous with exertion/effort, or sneezing or coughing. Stress leakage is presumed to be due to raised abdominal pressure.

Coughing may induce a detrusor contraction—hence the sign of stress incontinence is only a reliable indication of urodynamic stress incontinence when leakage occurs synchronously with the first proper cough and stops at the end of that cough.

- **Uncategorized incontinence** is the observation of involuntary leakage that cannot be classified into one of the above categories on the basis of signs and symptoms.

DEFINITION AND CLASSIFICATION OF PELVIC ORGAN PROLAPSE

More than 40% of women with urethral sphincter incompetence will have a significant cystocele (Cardozo and Stanton, 1980). Conversely, a history of stress incontinence associated with a mild or moderate cystocele is not specific for diagnosing genuine stress incontinence (Summitt et al, 1992). **"Occult or latent" incontinence is urethral sphincteric incompetence masked by the presence of pelvic prolapse** (Rosenzweig et al, 1992a, 1992b). Not infrequently, incontinent women may note the decrease or disappearance of stress incontinence episodes as the degree of prolapse worsens. The sign of occult stress incontinence is facilitated by the use of a speculum or pessary to reduce the prolapse while a stress maneuver is performed. The method to reduce vaginal prolapse to evaluate latent incontinence is not universally agreed on or standardized at this time.

A large rectocele may cause incomplete bowel evacuation and tenesmus. Sexual function consists of a complex interaction of biologic, psychologic, and social factors that affect both patient and partner. A complex relationship exists between anatomic descent of pelvic organs and physiologic function, and often these components do not correlate well with each other.

Vaginal examination allows the description of observed and palpable anatomic abnormalities and the assessment of pelvic floor muscle function. Segments of the lower reproductive tract should be considered as a substitute for terms as "cystocoele, rectocoele, enterocoele, or urethrovesical junction" because these terms convey an unrealistic certainty relating to the structures associated with the vaginal bulge, especially following previous prolapse surgery. This section draws heavily on the ICS standardization report, which commented on the evaluation of pelvic organ prolapse (Bump et al, 1996) as modified by the ICS standardization report 2002.

- **Pelvic organ prolapse** is defined as the descent of one or more of the following: anterior vaginal wall, posterior vaginal wall, and apex of the vagina (cervix/uterus) or vault (cuff) after hysterectomy. Absence of prolapse is defined as stage 0 support; prolapse can be staged from stage I to stage IV.

Pelvic organ prolapse can occur in association with UI and other lower urinary tract dysfunction and may on occasion mask incontinence.

- **Anterior vaginal wall prolapse** is defined as descent of the anterior vagina so that the urethrovesical junction (a point 3 cm proximal to the external urinary meatus) or any anterior point proximal to this is less than 3 cm above the plane of the hymen.
- **Prolapse of the apical segment of the vagina** is defined as any descent of the vaginal cuff scar (after hysterectomy) or cervix, below a point that is 2 cm less than the total vaginal length above the plane of the hymen.
- **Posterior vaginal wall prolapse** is defined as any descent of the posterior vaginal wall so that a midline point on the posterior vaginal wall 3 cm above the level of the hymen or any posterior point proximal to this is less than 3 cm above the plane of the hymen.

Pelvic floor muscle function can be qualitatively defined by the tone at rest and the strength of a voluntary or reflex contraction as strong, weak, or absent or by a validated grading system (e.g., Oxford 1 to 5). A pelvic muscle contraction may be assessed by **visual inspection, palpation**, **electromyography,** or **perineometry**. Factors that must be assessed are **strength, duration, displacement, and repeatability. Rectal examination** allows the description of observed and palpable anatomic abnormalities and is the easiest method of assessing pelvic floor muscle function in children and men. In addition, rectal examination is essential in children with UI to rule out fecal impaction.

RELATIONSHIP BETWEEN INCONTINENCE AND PROLAPSE

Patients with severe prolapse may develop voiding symptoms as a result of urethral kinking, leading to obstruction that is worsened during straining effort (Richardson et al, 1983). For instance, a moderate or severe cystocele may promote urethral compression and kinking, pressure dissipation, and an increase in maximum urethral closure pressures (Bergman et al, 1988; Versi et al, 1998). Clearly, a number of storage urinary symptoms may occur in combination with prolapse. Risk factors contributing to the symptoms of urgency and frequency include age and urogenital atrophy. One study found that women with mild cystoceles had a 20% incidence of detrusor overactivity, and the incidence increased to 52% in those with moderate to severe cystoceles (Enhorning, 1961).

More than 40% of women with urethral sphincter incompetence will have a significant cystocele (Cardozo and Stanton, 1980). A complaint of stress incontinence associated with the appearance of a mild or moderate cystocele, however, is not specific for diagnosing genuine stress incontinence (Walters and Shields, 1988; Summitt et al, 1992).

Occult or latent incontinence is urethral sphincteric incompetence masked by the presence of pelvic prolapse (Rosenzweig et al, 1992). Not infrequently, incontinent women may note the decrease or disappearance of stress incontinence episodes as the degree of prolapse worsens. The office demonstration of the sign of occult stress incontinence is facilitated by the use of a speculum or pessary to reduce the prolapse while a stress maneuver is performed. Its presence may influence management options given to the patient. However, the method to reduce vaginal prolapse to evaluate latent incontinence is not universally agreed on or standardized at this time.

A large rectocele may cause incomplete bowel evacuation and tenesmus, leading some to splint or manually reduce the posterior vaginal segment or perineum to assist in defecation. Patients may describe stool becoming trapped in the rectocele pocket itself. Constipation and straining may worsen the symptoms and lead to left lower quadrant abdominal pain if impaction occurs.

The prevalence of fecal incontinence increases to 17% in populations with pelvic organ prolapse and UI (Jackson et al, 1997) compared with 2% to 3% in the general population (Leigh and Turnberg, 1982; Thomas et al, 1984). The most common mechanisms are an incompetent sphincteric mechanism (secondary to a structural defect or pudendal nerve damage) and overflow incontinence.

Sexual function consists of a complex interaction of biologic, psychologic, and social factors that affect both patient and partner. Various studies have described the presence of sexual problems in patients who present with pelvic organ prolapse and UI (Haase and Skibsted, 1988; Field and Hilton, 1993).

Key Points: Conditions Associated with Pelvic Organ Prolapse

- Patients with severe prolapse may develop voiding symptoms as a result of urethral kinking leading to obstruction.
- More than 40% of women with urethral sphincter incompetence will have a significant cystocele.
- Occult or latent incontinence is urethral sphincteric incompetence masked by the presence of pelvic prolapse.
- A large rectocele may cause incomplete bowel evacuation and tenesmus.
- The prevalence of fecal incontinence increases in populations with pelvic organ prolapse and UI.
- Sexual problems are an important issue in patients who present with pelvic organ prolapse and urinary incontinence.

PATHOPHYSIOLOGY OF INCONTINENCE AND PROLAPSE

Continence

To understand the pathophysiology of urinary incontinence, it is important to be familiar with the micturition cycle and the physiology of normal storage and emptying of urine. The details of the physiology of micturition are provided in Chapter 60. The **function of the lower urinary tract is to temporarily store a continuously increasing amount of urine at low pressure and expel it under appropriate circumstances.** This is dependent on the coordinated activity of smooth and striated muscles in the bladder, urethra, and pelvic floor. The bladder and urethra constitute a functional unit, which is controlled by a complex interplay between the central and peripheral nervous systems and local regulatory factors (Andersson and Wein, 2004).

Bladder emptying and, conversely, urine storage rely on a complex series of finely tuned and integrated neuromuscular events that involve anatomic and neurologic mechanisms. It is a complex pattern of efferent and afferent signaling in parasympathetic, sympathetic, somatic, and sensory nerves. Malfunction at various levels may result in bladder control disorders, which roughly can be classified as disturbances of filling/storage or disturbances of voiding/emptying. Failure to store urine may lead to various forms of incontinence (mainly urgency and stress incontinence), and failure to empty can lead to urinary retention, which may result in overflow incontinence. A disturbed filling/storage function can, at least theoretically, be improved by agents decreasing detrusor activity, increasing bladder capacity, and/or increasing outlet resistance.

During bladder filling at physiologic rates, detrusor pressure remains nearly constant because of this property of **accommodation** (Klevmark, 1974), otherwise known as "tonus" or receptive relaxation. Accommodation accounts for the nearly flat cystometric curve that is seen during normal bladder filling. **The viscoelastic properties of the bladder, based on its composition of smooth muscle, collagen, and elastin, normally produce a highly compliant structure. When accommodation is impaired, low bladder compliance ensues. This is manifest as a steep rise in detrusor pressure during bladder filling.** In addition to the viscoelastic properties of the bladder, the neural control of the lower urinary tract and the anatomy and support of the sphincteric unit are important factors in the maintenance of urinary continence. **The micturition reflex is normally under voluntary control** and is organized in the rostral brainstem (the pontine micturition center [PMC]). Micturition results from a release from the negative inhibitor effect of the higher centers on the PMC. It requires integration and modulation by the parasympathetic and somatic components of the sacral spinal cord (the sacral micturition center) and the thoracolumbar sympathetic components (Fowler et al, 2008).

The reservoir function of the bladder requires a permanently low intravesical pressure over a wide volume range and a bladder outlet that remains firmly closed, even under conditions of abdominal pressure rises, during the filling phase of the bladder, which represents the majority of its activity cycle. Conversely, during voiding the bladder should be able to develop a sustained contraction of sufficient strength with opening of the bladder outlet offering a low resistance to urinary flow to assure adequate emptying of the bladder. During micturition, the first recorded event is sudden and complete relaxation of the striated sphincteric muscles, characterized by complete electrical silence of the sphincter electromyogram (Tanagho and Miller, 1970). This is followed almost immediately by a rise in detrusor pressure and concomitant fall in urethral pressure as the bladder and proximal urethra become isobaric (Yalla et al, 1980). The bladder neck and urethra open, and voiding ensues. Voluntary interruption of the stream is accomplished by a sudden contraction of the striated periurethral musculature, which, through a reflex mechanism, shuts off the detrusor contraction, aborting micturition. The sphincteric system is also designed to resist physiologic increases in abdominal pressure and thereby prevent the development of incontinence.

Normal storage of urine is therefore dependent on the following:

1. **An intact normally functioning innervated lower urinary tract (bladder, urethra, sphincters, and pelvic floor)**
2. **Spinal reflex mechanisms that allow centripetal afferent nerve traffic to activate sympathetic and somatic pathways to the bladder outlet**
3. **Tonic inhibitory systems in the brain that suppress parasympathetic excitatory outflow to the bladder** (Morrison et al, 2005)

It is important to identify the underlying bladder abnormality in a reproducible manner. Bladder abnormalities that cause UI include detrusor overactivity and low bladder compliance.

Disordered lower urinary tract function can result from the following:

- **Disruption of the normal peripheral or central nervous system (CNS) control mechanisms**
- **Disordered bladder muscle function, either primary (of unknown etiology) or secondary to an identifiable pathology such as prostatic-mediated bladder outflow obstruction**

Patients who have disordered lower urinary tract function in routine clinical practice represent a heterogeneous collection for most of whom there is no identifiable neurologic abnormality. Some of these patients will have a primary neural or muscular disorder (e.g., primary idiopathic detrusor overactivity) in contrast to postobstructive secondary detrusor overactivity, in which the major etiologic factor is likely to be peripheral disruption of local neuromuscular function.

Detrusor overactivity is a urodynamic observation characterized by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked. Detrusor overactivity may be phasic, terminal, or both (Abrams et al, 2002). There are certain patterns of detrusor overactivity:

- **Phasic detrusor overactivity** is defined by a characteristic wave form and may or may not lead to urinary incontinence. Phasic detrusor contractions are not always accompanied by any sensation or may be interpreted as a first sensation of bladder filling or as a normal desire to void.
- **Terminal detrusor overactivity** is defined as a single, involuntary detrusor contraction, occurring at cystometric capacity, which cannot be suppressed and results in incontinence usually resulting in bladder emptying (voiding). *Terminal detrusor overactivity* is a new ICS term: It is typically associated with reduced bladder sensation (e.g., in the elderly stroke patient when urgency may be felt as the voiding contraction occurs). However, in complete spinal cord injury patients there may be no sensation whatsoever.
- **Detrusor overactivity incontinence** is incontinence due to an involuntary detrusor contraction. In a patient with normal sensation, urgency is likely to be experienced just before the leakage episode.
- **Other patterns of detrusor overactivity** are seen (e.g., the combination of phasic and terminal detrusor overactivity, the sustained high pressure detrusor contractions seen in spinal cord injury patients when attempted voiding occurs against a dyssynergic sphincter).

Provocative maneuvers are used during urodynamics in an effort to provoke detrusor overactivity (e.g., rapid filling, use of cooled or acid medium, postural changes, hand washing).

Detrusor overactivity may also be qualified, when possible, according to cause. Examples follow:

- **Neurogenic detrusor overactivity,** when there is a relevant neurologic condition. This term replaces the term *detrusor hyperreflexia*.

Table 63–1.

Causes of Detrusor Overactivity

Neurogenic Detrusor Overactivity
Supraspinal neurologic lesions
Stroke
Parkinson disease
Hydrocephalus
Brain tumor
Traumatic brain injury
Multiple sclerosis
Suprasacral spinal lesions
Spinal cord injury
Spinal cord tumor
Multiple sclerosis
Myelodysplasia
Transverse myelitis
Diabetes mellitus
Idiopathic Detrusor Overactivity
No neurologic abnormality is evident, but associated abnormalities include the following:
Bladder infection
Bladder outlet obstruction
Men—prostatic and bladder neck, strictures
Women—pelvic organ prolapse, postsurgical, urethral diverticulum, primary bladder neck, strictures
Bladder tumor
Bladder stones
Foreign body
Aging

- **Idiopathic detrusor overactivity** when there is no defined cause. This term replaces *detrusor instability.*

In clinical and research practice, the extent of neurologic examination/investigation varies. It is likely that the proportion of neurogenic-to-idiopathic detrusor overactivity will increase if a more complete neurologic assessment is carried out (Table 63–1).

Interpretation of Vesicourethral Dysfunction

Because so many different aspects of vesicourethral function can be impaired in neurologic conditions, interpretation may be difficult. The most important points to clarify in clinical practice are **the presence or absence of neurogenic detrusor overactivity** and **the behavior of the distal urethral sphincter mechanism during voiding.**

High-pressure bladders with detrusor–sphincter dyssynergia are prone to develop vesicoureteral reflux, which may ultimately lead to renal impairment. This can be clearly demonstrated by videocystometrography (VCMG). Preservation of renal function is of utmost importance in the management of patients who have chronic neurologic conditions. As a rule of thumb, those patients with a competent bladder outflow and an end filling pressure of 40 cm H_2O or higher before leakage occurs—(the **detrusor leak point pressure**) are at particular risk of developing upper urinary tract problems due to back pressure (McGuire et al, 1996).

Neurogenic detrusor overactivity can be defined as abnormal function of the bladder and urethra due to lesions affecting their innervation, either within the central nervous system or in the peripheral nerves of the lower urinary tract.

Urodynamic investigations are essential to characterize the nature of the detrusor and sphincteric abnormality to do the following:

- **Identify patients who are at risk of deteriorating renal function as a result of the abnormally high bladder pressures**
- **Formulate the best treatment strategies to achieve efficient bladder emptying and continence and reduce the incidence of urinary tract infections and autonomic dysreflexia**

The interpretation of urodynamics in such complex cases is often difficult and is best performed in specialist centers using VCMG.

Neurologic conditions can alter vesicourethral function by impairing the following:

- Detrusor activity
- Striated sphincter activity
- Bladder and urethral sensation
- Urethral smooth muscle activity

These alterations may occur in isolation or in combination. Identical abnormalities may also occur without clinical evidence of a neurologic deficit.

Classification of Neuropathic Bladder Dysfunction

Neuropathic bladder dysfunction may be classified into supraspinal, suprasacral, and infrasacral, according to the level of the lesion in relation to the pontine and sacral micturition centers:

- Supraspinal lesions include all cerebral diseases such as cerebral hemorrhage and thrombosis, dementia, tumors, arteriosclerosis, and Parkinson disease.
- Suprasacral lesions are all spinal cord lesions above the conus.
- Infrasacral lesions involve the conus or sacral roots and may be further subdivided into cauda equina lesions (within the spinal canal) and peripheral lesions (outside the spinal canal).

Neurologic lesions generally affect bladder and urethral function in a relatively consistent fashion, depending on the area affected and the completeness of the lesion. A basic understanding of the bladder dysfunction associated with each level of injury is necessary to interpret the results of urodynamics properly.

Supraspinal Lesions

Patients who have supraspinal lesions generally empty their bladders efficiently unless they have associated bladder outlet obstruction. Preexisting bladder dysfunction is not uncommon, and urodynamics plays a major role in defining the abnormality and formulating treatment strategies.

Suprasacral Lesions

Patients who have cord lesions above the sacral micturition center initially go through a period of spinal shock in which there is loss of neurologic activity below the level of the injury. Detrusor areflexia (the inability to generate a detrusor contraction due to neurologic causes) and maintenance of some residual sphincteric competence usually results in urinary retention requiring either indwelling or intermittent catheterization.

Recovery is characterized by the gradual return of reflex bladder activity or neurogenic detrusor overactivity mediated through the sacral micturition center, which is intact but separated from higher centers. It usually occurs within 2 to 3 months, but in a small number of patients it may take up to 2 years for reflex activity to return. As reflex bladder activity increases during the recovery phase, the bladder may empty well at the expense of incontinence

or high detrusor voiding pressures may develop, resulting in hydronephrosis.

Infrasacral Lesions

Detrusor activity may be absent or diminished if there are lesions of the cell bodies or parasympathetic efferents to the bladder from the sacral roots (S2 to S4). This may be due to trauma to the spinal cord or pelvic nerves or destruction of the cord segment by lesions such as a plaque of multiple sclerosis.

Injury to the conus or sacral roots results in the following:

- Detrusor areflexia
- A denervated open bladder neck
- A paralyzed closed external sphincter
- In most patients, urinary retention

The weakened urethral sphincter mechanism and paralyzed pelvic floor make patients prone to stress incontinence, especially women.

Some patients empty their bladders by abdominal straining or suprapubic compression (Credé's maneuver), but the majority need clean intermittent self-catheterization to empty efficiently. For poorly understood reasons, a minority of patients are at risk of developing poorly compliant high-pressure bladders that can lead to renal damage.

Partial infrasacral lesions may result in a mixed pattern of weak or absent detrusor activity, poor compliance, and considerable reflex activity in the pelvic floor muscles.

Idiopathic Detrusor Overactivity

Idiopathic detrusor overactivity can be associated with a variety of non-neurogenic clinical conditions such as bladder outlet obstruction, dysfunctional voiding, and inflammatory reactions (Hebjorn et al, 1976; Awad and McGinnis, 1983; Blaivas, 1988; Resnick et al, 1989; Fantl et al, 1990; Brading and Turner, 1994; Carlson et al, 2001). Elbadawi and colleagues (1993a, 1993b, 1993c) have proposed a possible explanation for age-related detrusor overactivity based on detailed ultrastructural studies of the bladder. They showed a characteristic structural pattern in bladder biopsy specimens obtained from elderly patients with detrusor overactivity. Electron microscopic changes (abundant, distinctive protrusion junctions and abutments) in patients with detrusor overactivity are thought to result in a diminished electrical resistance between detrusor muscle cells and, hence, a hyperexcitable state that results in involuntary detrusor contractions.

Bladder outlet obstruction causes increased voiding pressures and a prolonged duration of voiding. It has been hypothesized that this results in ischemic damage to the intramural ganglia and consequently to a partial denervation of the detrusor muscle (Brading and Turner, 1994). Experiments have shown that denervation of smooth muscle cells may result in supersensitivity to agonists, increased excitability, and increased electrical coupling. These changes may make the detrusor muscle susceptible to the development of involuntary contractions. The detrusor muscle hypertrophy on obstruction does not necessarily play a causative role (Brading and Turner, 1994). A somewhat contrasting and more evidence-based explanation comes from the observation of increased levels of nerve growth factor in the bladders of obstructed rats and humans and increased dimensions of afferent and efferent rat neurons (Steers et al, 1991).

In many cases the etiology is unclear—the cause of idiopathic detrusor overactivity is likely to be neurogenic rather than myogenic, particularly in view of the association between detrusor overactivity and aging. An increased number of putative afferent nerves in the bladder wall of female patients has been reported (Smet et al, 1997). Although no effect of intravesical capsaicin on idiopathic detrusor overactivity was found (Fowler, 2002), efficacy was found in 12 patients treated with the more potent analog resiniferatoxin (Cruz, 2002). This suggests the involvement of the afferent C fibers. The role of non-neurogenic factors cannot be excluded because abnormal cell-to-cell communications have been reported in the bladders of patients with idiopathic overactivity (Elbadawi et al, 1993b).

Bladder Compliance during Filling Cystometry

Bladder compliance describes the relationship between change in bladder volume and change in detrusor pressure. The observation of reduced bladder compliance during conventional filling cystometry is often related to relatively fast bladder filling: the incidence of reduced compliance is markedly lower if the bladder is filled at physiologic rates, as in ambulatory urodynamics.

- **Compliance** is calculated by dividing the volume change (ΔV) by the change in detrusor pressure ($\Delta Pdet$) during that change in bladder volume ($C = V/\Delta Pdet$). It is expressed in mL/cm H_2O.
- A variety of means of **calculating bladder compliance** has been described. The ICS recommends that two standard points be used for compliance calculations, but the investigator may define additional points. The standards points are as follows:
  1. the detrusor pressure at the start of bladder filling and the corresponding bladder volume (usually zero), and
  2. the detrusor pressure (and corresponding bladder volume) at cystometric capacity or immediately before the start of any detrusor contraction that causes significant leakage (and therefore causes the bladder volume to decrease, affecting compliance calculation). Both points are measured excluding any detrusor contraction.

The viscoelastic properties and neurologic innervation of the bladder under normal conditions allow it to store increasing volumes of urine at low pressure. Thus with **normal compliance** there is little or no pressure change as the bladder fills. Compliance (Δvolume/Δpressure) is expressed as mL/cm H_2O.

Although it is well established that high storage pressures can lead to incontinence and upper tract deterioration (McGuire et al, 1981; Comiter et al, 1997), at the present time there are no standardized or international agreed values to define normal, high, and low compliance. **The calculated value of compliance is probably less important than the actual bladder pressure during filling.** This is because the compliance value can change depending on the volume over which it is calculated. For this reason, numeric values of compliance are rarely reported. For example, **sustained detrusor pressures of 35 to 40 cm H_2O or greater during storage, regardless of the bladder volume, can lead to upper tract damage, but similar damage can also occur at lower pressures** (McGuire et al, 1981; Churchill et al, 1987). When the detrusor pressure exceeds the pressure capacity of the sphincter to resist that pressure, incontinence results.

Low bladder compliance denotes an abnormal volume-pressure relationship in which there is a high incremental rise in detrusor pressure during bladder filling. Low bladder compliance may be caused by changes in the elastic and viscoelastic properties of the bladder, changes in detrusor muscle tone, or combinations of the two. Clinically, low bladder compliance is most commonly

Table 63–2.
Causes of Low Bladder Compliance

Neurogenic
Myelodysplasia
Shy-Drager syndrome
Suprasacral spinal cord injury/lesion
Radical hysterectomy
Abdominoperineal resection
Non-Neurogenic (Increased Collagen)
Tuberculous cystitis
Radiation cystitis
Chronic indwelling catheter
Bladder outlet obstruction

seen in a variety of neurologic conditions, especially lower motor neuron lesions such as spina bifida and cauda equina syndrome. Obstructive uropathy, because of its effect on bladder ultrastructure, is known to cause low bladder compliance and has been identified as a urodynamic risk factor. Leng and McGuire (2003) showed that relief of obstruction by transurethral incision or resection of the prostate can improve compliance.

The clinical causes of low bladder compliance are listed in Table 63–2.

Sphincteric Mechanisms

The urethra has two main functions:

- **Provide an effective continence mechanism, for the majority of the time (>99%) (storage phase)**
- **Allow adequate emptying from the bladder with minimal resistance during micturition (voiding phase)**

The innermost mucosal layer in both sexes is organized in longitudinal folds, and during the storage phase, when the urethra is "closed," this appears in a stellate configuration on cross section. Such a configuration allows significant distensibility, which is necessary during urethral "opening."

The submucosal layer contains a vascular plexus, which may be involved in improving the seal of a "closed urethra" by transmitting the tension of the urethral muscle to the mucosal folds.

Apart from the obvious anatomic differences (the longer urethra and presence of a prostate gland in men), there are important differences in the configuration of the sphincter mechanisms between males and females. There are two powerful sphincter mechanisms in the male compared with the single weaker intrinsic sphincter mechanism with a weaker bladder neck and also a shorter urethra in the female.

Traditionally, the urethral sphincter is considered to be composed of two components: the internal sphincter, which represents a direct continuation of the detrusor smooth muscle, and the striated external sphincter (Tanagho, 1992). From a clinical standpoint, the bladder neck–proximal urethra normally functions as a sphincter in both sexes. Anatomically there is a unique mixture of smooth and striated muscle, intracellular matrix, and mucosal components contributing to the functional sphincter.

Male Sphincteric Mechanisms

In the male there are **two important sphincteric mechanisms:** (Hadley et al, 1986).

1. **A proximal "bladder neck mechanism"** consisting of the bladder neck, prostate, and prostatic urethra to the level of the verumontanum. This receives a dual innervation from the autonomic nervous system via parasympathetic and sympathetic fibers. The main motor control is likely to be provided by the sympathetic component, although there is some evidence for a contribution from the detrusor muscle where the predominant innervation is parasympathetic. This portion of the continence mechanism is removed during prostatectomy, leaving only the distal urethral sphincter mechanism to prevent urinary leakage.
2. **A distal urethral mechanism at the apex of the prostate.** This extends from the verumontanum to the proximal bulb and is composed of a number of structures that help to maintain continence. The male distal sphincter complex is composed of the prostatomembranous urethra, cylindrical rhabdosphincter (external sphincter muscle) surrounding the prostatomembranous urethra, and extrinsic paraurethral musculature and connective tissue structures of the pelvis. The rhabdosphincter is a concentric muscular structure consisting of longitudinal smooth muscle and slow-twitch (type I) skeletal muscle fibers that can maintain resting tone and preserve continence (Gosling et al, 1981; Turner-Warwick, 1983). Skeletal muscle fibers of the rhabdosphincter have been shown to intermingle with smooth muscle fibers of the proximal urethra, suggesting a dynamic and coordinated interaction (Burnett and Mostwin, 1998). The rhabdosphincter is invested in a fascial framework and supported below by a musculofascial plate that fuses with the midline raphe, which is also a point of origin for the rectourethralis muscle (Burnett and Mostwin, 1998). Superiorly, the fascial investments of the rhabdosphincter fuse with the puboprostatic ligaments (Steiner, 2000). This dorsal and ventral support probably contributes to the competence of the sphincter. The striated fibers of the extrinsic paraurethral muscle (levator ani complex), on the other hand, are of the fast-twitch (type II) variety (Gosling et al, 1981). During sudden increases in abdominal pressure, these fibers can contract rapidly and forcefully to provide continence. Continence has been shown to be maintained after inducing paralysis of the striated sphincter (Lapides et al, 1957; Krahn and Morales, 1965), indicating that this structure is not solely responsible for continence in men with an intact functioning bladder neck.

The proximal sphincter in the male bladder neck provides a powerful mechanism in both maintaining urinary continence and also prevents retrograde ejaculation of semen during sexual activity. **In patients with a damaged distal urethral sphincter** (e.g., a pelvic fracture-associated urethral disruption), **continence can be maintained solely by the proximal bladder neck mechanism.** Ultrastructurally, it consists of a powerful inner layer of muscle bundles arranged in a circular orientation.

The distal sphincteric mechanism is also extremely important, as evidenced by its **ability to also maintain continence even when the proximal bladder neck mechanism has been rendered totally incompetent by surgical bladder neck incision or a prostatectomy.** It is confined to the 3- to 5-mm thickness of the wall of the membranous urethra from the level of the verumontanum down to the distal aspect of the membranous urethra. It is composed mainly of extrinsic striated muscle, which is capable of the sustained contraction necessary for continence and to a lesser degree by intrinsic smooth muscle.

Table 63–3.

Comparison of Male and Female Sphincteric Mechanisms*

	MALE	FEMALE
Proximal bladder neck mechanism	Powerful	Weak
Distal urethral mechanism	Powerful	Extending along the majority of the length of the female urethra and prone to the effect of exogenous influences such as pelvic floor weakness and damage or denervation consequent on childbirth
Prostate	Further increases bladder outlet resistance	Not present
Urethra	Long	Short (≈3.5 cm)

*Indicates why females are much more likely to develop an incompetent urethral mechanism and are prone to urinary incontinence from intrinsic sphincter deficiency.

Unlike that in the female, where urethral support can be compromised as a result of childbirth and aging, in the male, compromise to the rhabdosphincter usually occurs after trauma or surgery (e.g., prostatectomy).

Female Sphincteric Mechanisms

Females are much more likely to suffer from UI due to sphincteric deficiency than males because of the much less powerful sphincteric mechanisms. The **bladder neck is a far weaker structure than the male bladder neck and is often incompetent,** even in nulliparous young women (Chapple et al, 1989). The bladder neck is poorly defined with the muscle fibers having a mainly longitudinal orientation.

Urinary continence usually relies on the integrity of the urethral sphincteric mechanism in females (analogous to the distal sphincter in men). Like the male distal mechanism, it is composed of a longitudinal intrinsic urethral smooth muscle and a larger extrinsic striated muscle component. This sphincter extends throughout the proximal two thirds of the urethra, being most developed in the middle one third of the urethra. **Therefore in women the majority of the urethra should be considered to be sphincter active.** Damage to the innervation of the urethral sphincter (in particular the pudendal nerve) by obstetric trauma reduces the effectiveness of this mechanism and predisposes to stress UI (Table 63–3).

The principles underlying normal sphincteric function are integrated interactions among a number of factors:

1. **Watertight apposition of the urethral lumen.** Four urethral wall factors promote continence: (1) wall tension or external compression, (2) inner wall softness, (3) a filler material beneath the mucosa that helps to deform the mucosal folds into apposition, and (4) a lining of mucus provides the stickiness that enables cooptation of these mucosal folds (Zinner et al, 1980). Histologic cross sections of the urethra show that the urethra is not simply a closed tube; rather, there are numerous mucosal folds, between which are potential spaces for urine leakage. In women, estrogen and a cushion effect of the submucosal vasculature have been suggested as ancillary factors (Raz et al, 1972; Tulloch, 1974).
2. **Compression of the wall around the lumen.** External compression of the urethral lumen is achieved by (1) smooth and striated muscle tone, (2) phasic contractions of the smooth and striated musculature, (3) elastic and viscoelastic properties of the extracellular matrix, (4) mechanical factors related to transmission of abdominal pressure, and (5) structural (anatomic) support of the posterior urethral wall.
3. **Structural support to keep the proximal urethra from moving during increases in pressure**
4. **A means of compensating for abdominal pressure changes (pressure transmission)**
5. **Neural control**

Conditions Causing Sphincter Abnormalities

The causes of sphincteric dysfunction are different in men and women.

In men, sphincter abnormalities are most commonly caused by anatomic disruption after prostate surgery or, less commonly, by trauma or neurologic abnormalities.

In women with stress incontinence it is likely that there is a degree of sphincter weakness in all cases. The sphincter abnormality will lie on a spectrum from a mild degree where the predominant pathophysiologic abnormality is urethral hypermobility (urethral support defect), to those where irrespective of the urethral support defect there is severe intrinsic sphincteric insufficiency (ISD). Urethral hypermobility and support defects in women are most commonly associated with pregnancy and vaginal delivery, pelvic surgery, and chronic abdominal straining (e.g., chronic constipation). In some cases, loss of support many be secondary to neurologic injury. In such cases, nerve injury (e.g., pudendal nerve) can lead to muscle atrophy and subsequent failure of the support mechanism.

Sphincter Abnormalities in Women

Labor and delivery have long been thought to be risk factors for stress incontinence, urogenital prolapse, and anal incontinence. Vaginal delivery may be associated with direct injury to the pelvic soft tissues, as well as partial denervation of the pelvic floor and thus may play a role in the etiology of stress urinary incontinence (SUI).

There are four major mechanisms by which vaginal delivery might lead to sphincteric damage and incontinence:

1. **Injury to connective tissue support by the mechanical process of vaginal delivery**
2. **Vascular damage to the pelvic structures as a result of compression by the fetus**
3. **Damage to the pelvic nerves or muscles or both as a result of trauma during parturition**
4. **Direct injury to the urinary tract during labor and delivery**

Vaginal delivery can cause partial denervation with consequent reinnervation in most first deliveries (Allen et al, 1990). A growing body of evidence indicates that **multiparity; forceps delivery; increased duration of the second stage of labor, partially related to epidural anesthesia; third-degree perineal tear; and high birth weight (>4000 g) are important factors leading to pudendal nerve injury**

(Snooks et al, 1986; Handa et al, 1996; Brown and Lumley, 1998; Rortveit et al, 2003). Snooks and colleagues (1984) studied the postpartum innervation of the external anal sphincter and found that the external anal sphincter and its innervation might be damaged by vaginal delivery but not by cesarean section. The abnormalities found were most marked in multiparas and correlated most strongly with a prolonged second stage of labor and forceps delivery.

Several conditions are associated with increased risk for ISD in women:

1. **Previous urethral or periurethral surgery** (e.g., anti-incontinence surgery, urethral diverticulectomy) may result in postoperative ISD from periurethral fibrosis, scarring, or denervation (Haab et al, 1996). Prevalence of ISD after two or more failed anti-incontinence operations was found to be as high as 75% (McGuire et al, 1980).
2. **Neurologic insult** may cause ISD. Sacral neurologic lesions have a variable effect on micturition, depending on the extent to which the neurologic injury affects the parasympathetic, sympathetic, and somatic systems (Gerstenberg et al, 1980; Blaivas and Barbalias, 1983; Wheeler et al, 1986; McGuire et al, 1988). In complete parasympathetic lesions, the bladder is areflexic and the patient is in urinary retention. When, in addition to a parasympathetic lesion, there is a sympathetic lesion, the proximal urethra loses its sphincteric function. Clinically, this results in incomplete bladder emptying, caused by the acontractile detrusor, and sphincteric incontinence, caused by the nonfunctioning proximal urethra (Gerstenberg et al, 1980; Blaivas and Barbalias, 1983). Somatic neurologic lesions affect pudendal afferent and efferent nerves (Blaivas, 1982). In addition to loss of perineal and perianal sensation, these lesions abolish the bulbocavernosus reflex and impair the ability to contract the urethral and anal sphincters voluntarily. Sacral neurologic lesions are caused by herniated disks, diabetic neuropathy, multiple sclerosis, and spinal cord tumors. They are also commonly encountered after extensive pelvic surgery such as abdominoperineal resection of the rectum and radical hysterectomy (Gerstenberg et al, 1980; Blaivas and Barbalias, 1983; Chang and Fan, 1983; McGuire et al, 1988).
3. **Pelvic radiation therapy** has been associated with damage to the mucosal seal coaptation of the urethra and local neurologic damage (Haab et al, 1996).

Sphincter Abnormalities in Men

Sphincter abnormalities in men are **caused by trauma or neurologic injury.** With **prostatectomy,** whether for benign disease or with radical prostatectomy, the distal urethral sphincter (particularly the rhabdosphincter) can be damaged by direct injury or injury to the nerve supply or supporting structures (Nitti, 2002). In some cases, there may be preexisting damage to the sphincter that cannot be accurately diagnosed preoperatively (Nitti, 2002). As in women (as noted earlier), **radiation** and **neurologic lesions** can cause sphincteric dysfunction. Finally, **pelvic trauma** or instrumentation that results in trauma to the distal urethral sphincter can result in incontinence, particularly when the PUS is absent or deficient.

Postprostatectomy incontinence, like any urinary incontinence, may be caused by bladder dysfunction, sphincter dysfunction, or a combination of both and may be associated with other lower urinary tract symptoms. Urodynamic investigations are helpful to rule out bladder outlet obstruction or significant bladder dysfunction. **Urodynamic studies have demonstrated that the sphincter incompetence occurs as the sole cause in more than two thirds of patients.** Isolated bladder dysfunction (detrusor overactivity, poor compliance, detrusor underactivity during voiding) is uncommon, occurring in less than 10% (Ficazzola and Nitti, 1998; Groutz et al, 2000). However, **sphincter and bladder dysfunction can coexist in at least one third of incontinent patients.**

Bladder dysfunction may occur de novo after prostatectomy, perhaps induced by bladder denervation; may be caused by outlet obstruction; or may be related to preexisting factors such as age. Impaired detrusor contractility and poor compliance resolved in the majority of patients within 8 months (Giannantoni et al, 2004). Decreased sphincter resistance may be due to tissue scarring in some cases and is reflected by a low urethral compliance; however, this parameter is difficult to measure (Groutz et al, 2000). Scarring may lead to an anastomotic stricture and is clinically suspected when both incontinence and decreased force of stream coexist. The preoperative length of the membranous urethra determined on magnetic resonance imaging (MRI) has been shown to be significantly related to time to postoperative continence. When urethral length was greater than 12 mm, 89% of the patients were continent at 1 year, versus 77% with 12 mm or less than this length (Coakley et al, 2002). Urodynamic studies revealed that a reduced functional urethral length was a predictive parameter of incontinence (Hammerer and Huland, 1997; Van Kampen et al, 1998; Wei et al, 2000). Different components of the urethra may also be involved. The urethral intrinsic component responsible for passive continence, as well as the extrinsic component responsible for active continence, may be involved as has been demonstrated in a study using urodynamic evaluation and alpha blockade (Pfister et al, 2002). This may explain passive incontinence despite a high voluntary urethral pressure or that measured during an active squeeze by the patient. Postoperative disruption of the innervation of the posterior urethra may also be involved and can affect both motor and sensory function (John et al, 2000; Bader et al, 2001).

Risk factors for incontinence after transurethral resection of the prostate (TURP) have not been clearly defined, probably because the incidence is so low. However, previous brachytherapy does predispose to post-TURP incontinence, as does significant bladder overactivity and preoperative urinary incontinence. Preoperative lower urinary tract symptoms including urgency incontinence and "overflow incontinence" may improve with de-obstruction secondary to extirpative surgery. **Whenever a functional abnormality of the bladder or sphincter abnormalities is suspected, preoperative urodynamic assessment is advised before TURP.**

UI occurring after radical prostatectomy (RP) is a significant problem. Although its rate has lessened in recent years primarily due to a better understanding of pathophysiology and improvements in surgical technique, its prevalence has increased due to the dramatic increase of laparoscopic and robotic-assisted laparoscopic radical prostatectomy as standard treatments for men with prostate cancer in developed countries (Hu et al, 2003, 2004) within the past decade. Based on the body of available data on postoperative continence, it would appear that **incontinence rates are similar between open and laparoscopic/robotic approaches.** Several studies have compared the techniques either prospectively in nonrandomized fashion (Anastasiadis et al, 2003; Jacobsen et al, 2007) retrospectively (Ahlering et al, 2004) or via limited meta-analysis (Rassweiler et al, 2003; Salomon et al, 2004),

and similar continence rates were found. Further prospective comparative studies with open surgery are necessary. Perineal prostatectomy is done by only a limited number of urologists but is still advocated for obese patients. The continence rate was reported as similar to the retropubic route (Weldon et al, 1997; Gray et al, 1999; Harris, 2003).

Data from large multicenter studies and prostate cancer databases suggest that **following RP, 1% to 40% of patients complain of persistent urinary incontinence. The incidence of postprostatectomy incontinence (PPI) depends on the definition of UI and the length of follow-up** (Olsson et al, 2001; Krupski et al, 2003; Rodriguez et al, 2006). Recent reports of large cohorts use definitions that include "total control/perfect continence," "occasional leakage but no pad," and "less than one pad." Because one third to one half of men who do not wear pads will have occasional leakage of urine, it is important to distinguish among those men who leak enough to require pad use and those who do not. It has been demonstrated that health-related quality of life is strongly correlated with the level of incontinence, and wearing a pad more significantly affects the quality of life than wearing no pad (Litwin et al, 2000). In addition, not all men who leak will elect to have further treatment. Most **large cohort studies indicate that between 6% and 9% of patients undergo subsequent surgical treatment for PPI following prostate cancer surgery** (Stanford et al, 2000; Begg et al, 2002; Steineck et al, 2002; Penson et al, 2005).

Reported risk factors for incontinence following radical prostatectomy include the following:

- Patient age at surgery
- Stage of disease
- Surgical technique including nerve sparing
- Preoperative bladder function and urinary continence status
- Prior radiation therapy
- Preoperative length of the membranous urethra
- Prior TURP
- Vascular comorbidities

Preoperative sphincteric insufficiency (demonstrated by either the preexisting clinical sign of SUI or the urodynamic finding of lower maximal urethral closure pressure) predicts postoperative SUI (Wei et al, 2000; Majoros et al, 2006). Preoperative bladder dysfunction can also contribute to postoperative incontinence. Preexisting abnormalities of detrusor function may predispose to leakage following surgery, especially neurogenic detrusor overactivity due to Parkinson disease, dementia, or spinal cord injury (Khan et al, 1991).

Advancing age as a risk factor is supported by several studies (Leandri et al 1992; Zincke at al, 1994; Eastham et al, 1996; Catalona et al, 1999; Horie et al, 1999; Moore et al, 2007). Others have found advancing age and the number of comorbidities to have a negative impact on the recovering time for continence during the first year after radical prostatectomy (Young et al, 2003). Rogers and colleagues demonstrated that age affected postoperative continence status following laparoscopic RRP. In those younger than 50 years old, 100% achieved 0 to 1 pad per day continence at 1 year, which decreased to 91% and 81% for those 50 to 59 years old and older than 60 years, respectively ($P < 0.01$) (Rogers et al, 2006). Strasser and colleagues (1998) hypothesized that age-related sphincteric changes may be responsible for the age-related increase in postoperative SUI and successfully demonstrated a progressive reduction in sphincter striated muscle cells with age.

Most large series have found no correlation between the stage of disease and incontinence rates (Eastham et al, 1996; Jonler et al, 1996; Lowe, 1996; Catalona et al, 1999; Pierorazio et al, 2007). However, in certain cases, the stage of disease may affect the surgical technique (i.e., nerve sparing) and incontinence rates may be higher, but this appears to be a reflection on surgical technique and not disease stage (Zincke et al, 1994).

Regarding surgical technique, the many parameters involved in continence have resulted in difficulties in understanding the benefit of certain technical points.

Bladder neck preservation has been reported to improve continence at 3 months (Lowe, 1996), but no difference was evident at 6 and 12 months (Poon et al, 2000; Srougi et al, 2001).

The role of nerve sparing on subsequent continence is debated. Nerve sparing has no significant impact according to Steiner and colleagues (1991), and Lepor and colleagues (2004) recently confirmed this. Others did find benefit (Wei et al, 2000). In particular, Nandipati and colleagues reported that in a cohort of 152 patients followed prospectively, bilateral nerve-sparing surgery was associated with a shorter time to regain continence, as well as improved long-term continence rates compared with non–nerve-sparing surgery. They additionally found that increased age was a risk factor for postprostatectomy incontinence (Nandipati et al, 2007). Burkhard and colleagues similarly demonstrated a positive effect of nerve-sparing surgery on postoperative continence. In a prospective cohort study of 536 patients, PPI developed in 1 of 75 (1.3%), 11 of 322 (3.4%), and 19 of 139 (13.7%) with attempted bilateral, attempted unilateral, and without attempted nerve sparing, respectively. Attempted nerve sparing was, in fact, the only statistically significant factor influencing urinary continence after RRP in this cohort (Burkhard et al, 2006).

PELVIC FLOOR SUPPORT MECHANISMS

Two major factors govern the predisposition of the human female to develop either stress UI or prolapse, or both.

1. After the evolutionary changes in pelvic floor anatomy resulting from the change from a four-limb to an upright two-limb posture; the pelvic floor has had to adapt from its mainly muscular utility (of moving the tail) in four-legged animals to a supportive function in the human. This has generated a decrease in reliance on muscle mass and an increase in the importance of connective tissue support mechanisms.
2. The human reproductive process consists of a relatively large fetus with a large bony cranium that must pass through the pelvic floor during labor and delivery.

Certainly, repeated episodes of vaginal traction can stretch, tear, or weaken urethral muscles and contribute to a chronically weakened urethra characterized by low VLPP or low urethral closure pressures. This is suggested to be typical of intrinsic sphincter deficiency (ISD). Clearly, however, there is no adequate categorization of ISD because most of the measures have limited sensitivity by virtue of their nature and inability to separate out the different components of urethral function. Electrophysiologic studies, MRI, and sonography can be used to quantify the morphologic and functional decline in striated sphincter tone, but analysis of the etiologic factors is difficult because the pathophysiology develops over many years. Successful operations can restore urethral position but probably do not reverse damage to urethral sphincter function, and there are still many question marks about whether this is ever possible.

The complex etiology of stress UI and pelvic organ prolapse and the long time period over which these complications and problems develop strongly supports the need for prospective studies taking account of both nature and nurture. This may allow the investigation of early timely interventions to prevent the further deterioration of their support tissues and urethral closure mechanisms.

From Dichotomy to Continuum between Hypermobility and Intrinsic Sphincter Deficiency

An integrated approach involving anatomy and physiology is essential to an improved understanding of pathophysiology. Clearly a continent bladder outlet in the females depends on multiple factors (resting tone, active contraction, external compression, pressure transmission, integrity of configuration), and the focal point appears to be the midpoint of the urethra. **In patients with stress incontinence there is clearly a spectrum between the two components of ISD and urethral hypermobility.** Clearly, some patients have primary sphincteric problems, whereas others have an adequately functioning sphincter but significant hypermobility. The majority lie somewhere between these two extremes.

In recent years there has been a gradual change from this dichotomic classification of stress incontinence: hypermobility or ISD. ISD alone is rare, and urethral hypermobility may occur commonly without significant ISD, but usually there is a combination of both in individual patients.

Figure 63–3 demonstrates the potential balance between the relative proportions of ISD and pelvic floor muscle weakness hypermobility seen in any individual patient.

This evolution in our understanding in part followed the development of the concept of Valsalva leak point pressure (VLPP) introduced by McGuire in 1995 and also from analysis of long-term results of incontinence surgery. Despite lacking standardization of recording methods, as well as lacking consensus on how to deal with any associated prolapse, low VLPP (inferior to 60 cm H_2O has been suggested) has been widely considered as an indicator of ISD. Reports in the literature vary considerably regarding the extent of correlation between VLPP and outcome. Similarly, urethral pressure profilometry has been extensively studied in this context but there is a similar lack of correlation both in terms of predictive value and outcome. For instance, a low-pressure urethra may not leak, whereas the high-pressure urethra may. Also, a number of studies have failed to show any correlation between postoperative UPP and outcome. Cystography, although an invasive technique requiring radiologic input, provides a reproducible and easily interpreted technique, which allows the relative contribution of both sphincteric weakness and hypermobility to be assessed (Blaivas and Olsson, 1988).

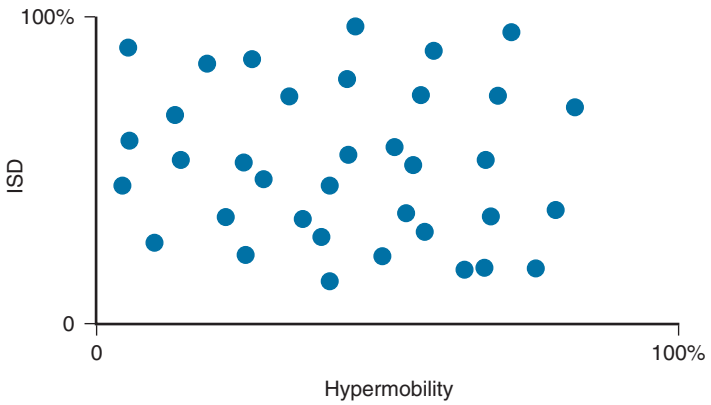


Figure 63–3. The potential balance between the relative proportions of intrinsic sphincter deficiency (ISD) and pelvic floor muscle weakness hypermobility seen in any individual patient.

Consequently, some degree of ISD may exist in many patients where hypermobility is believed to be the only cause of stress incontinence (Kayigil et al, 1999). This understanding supports the increasing use of suburethral slings to treat stress incontinence, whereas formerly this procedure was exclusively suggested for patients with recurrent stress incontinence or severe ISD (Chaikin et al, 1998). Clearly, vaginal support is an important factor in maintaining urinary continence, but in addition one needs to consider the importance of ISD, a discussion hampered by the lack of adequate techniques to evaluate ISD at present.

Urethral Support Mechanisms

The urethral support mechanism comprises all the structures extrinsic to the urethra that offer a supportive backplate on which the proximal urethra and midurethra lie.

The anatomic support is derived from the following:

1. **Fascial structures**

In recent years the important potential role of connective tissue in the overall physiologic function of the lower urinary tract and pelvic floor has been progressively recognized. The age-related weakening of connective tissues can influence both tissue and organ function, and it is likely that the increasing attention on connective tissue changes will provide a better understanding of pathophysiology, which hopefully will be useful in leading to the more effective management of stress UI and vaginal prolapse.

2. **Musculature**

Urethral hypermobility (increased mobility) is thought to be due to loss of the normal extrinsic support of the urethra by a weakness of both endopelvic fascia and pelvic floor muscles, usually initiated by childbirth but worsened by aging and alterations of hormone level. Stretching, tearing, and avulsion of the levator muscles results in the urogenital hiatus becoming longer and wider. This results in chronic anterior displacement of pelvic organs with loss of any organ support at rest and especially during straining. Stretching or tearing of the cardinal and utero-sacral ligaments may result in anterior displacement of the uterus at rest or during straining. This results in stretching of the vaginal wall and loss of the normal superior vaginal sulcus and vaginal folds.

The consequence of this is a rotational descent of the proximal urethra away from its retropubic position and the eventual development of SUI.

Certainly in lateral cystourethrograms, the main anatomic change is loss of the posterior urethra-vaginal angle with the urethra and trigone falling into the same plane (Jeffcoate and Roberts, 1952; Hodgkinson, 1953; Hodgkinson, 1970).

Consequently, radiographic studies cannot distinguish between lateral or central defects in vaginal wall support because they appear in the same sagittal plane. It is necessary to examine the patient to determine which defect is present and to what extent. Because the proximal urethra rotates out of the focal plane of ultrasonographic probes or MRI, coronal images of vaginal relaxation cannot provide adequate anatomic information during leakage.

Despite the extensive data about anatomic defects, it is difficult to correlate the influence of these defects, the vaginal position,

and the urethral closure mechanism. Not all women with stress incontinence have vaginal prolapse; clearly, prolapse repairs do not always cure the stress incontinence and, conversely, women who redevelop stress incontinence after an apparently successful operation do not always have a recurrence of prolapse (Wall et al, 1994).

In conclusion, **support and suspension of the pelvic organs is dependent on a healthy pelvic floor striated muscle, intact robust connective tissue, and their attachment to the bony frame of the pelvis.** A useful analogy to visualize these factors is to consider a ship lying moored in dock. One can consider the ligaments as the mooring ropes and the pelvic floor musculature as the water on which the ship sits. If the dock is emptied, the influence of the support of the water disappears, leaving all of the tension applied to the mooring robes, which will inevitably weaken and fracture (Fig. 63–4).

Berglas and Rubin (1953) showed that in the nulliparous patient, the lower one third of the vagina is oriented more vertically, while the upper two thirds deviate horizontally, thereby maintaining the vaginal axis in an almost horizontal position (Fig. 63–5A and B). This configuration is maintained by the posterior attachments of the cervix with the cardinal and utero-sacral ligaments and by the anterior position of the urogenital hiatus. During stressful maneuvers such as coughing or straining, the levator hiatus is shortened anteriorly by contraction of the pubococcygeus muscles (Fig. 63–5C). In the case of genital prolapse when the levator ani support is lost, the vaginal axis becomes more vertical, the urogenital hiatus broadens, and fascial supports are strained (Fig. 63–5D).

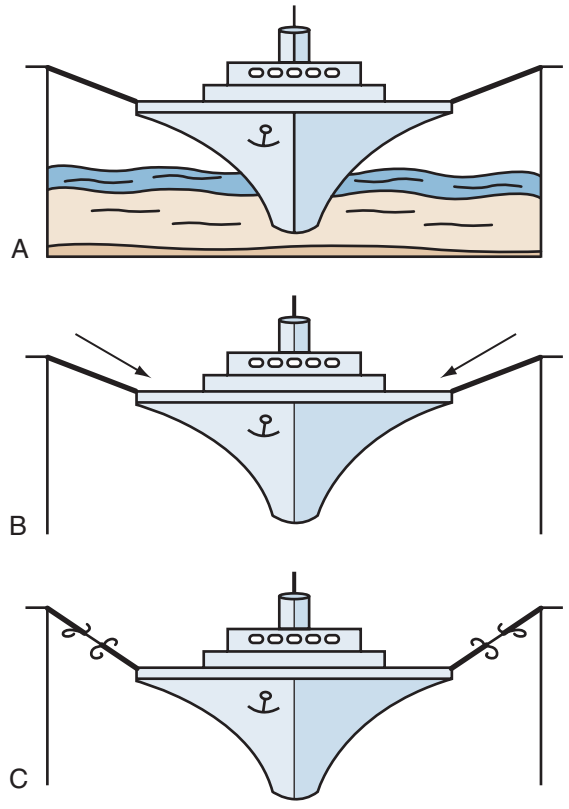


Figure 63–4. Analogy demonstrating the support provided by the **A,** pelvic floor (water) and ligaments (ropes) to the pelvic organs (ship). **B,** Consequences of a pelvic floor muscle weakness with increasing strain placed on ligamentous structures. **C,** Ligamentous damage as a consequence of loss of pelvic floor muscle weakness.

Connective Tissue

The **pubourethral ligament** attaches the midurethra to the inferior side of the pubic symphysis and prevents its downward rotational descent (Zacharin, 1963). It works in conjunction with the pubourethralis muscle, a subdivision of the levator ani muscle that forms a sling around the proximal urethra. Together they form the midurethral complex. In **particular it has been postulated that an elongation of the posterior pubourethral ligaments may be a significant contributory factor to the loss of urethral support seen in stress incontinence.** An important fascial support for the urethra is provided by the **urethro-pelvic ligament,** which attaches the urethra to the tendineus arc (Rovner et al, 1997).

In addition, the **endo-pelvic fascia/pubocervical fascia,** extending between the bladder and the vagina, suspends and attaches the vagina and cervix to the pelvic sidewall and to each arcus tendineus fascia pelvis, thereby offering posterior support to the bladder and bladder neck. It has two surfaces: the perivesical fascia on the vaginal side and the endo-pelvic fascia on the abdominal side. Its upper zone supports the bladder above the cervix, the middle zone supports the trigone, and the lower zone supports the bladder neck. Laxity of the fascia in each of the zones will result in uterine prolapse, cystocele, and urethrocele, respectively (DeLancey, 2001).

The **arcus tendineus fasciae pelvis** are tensile structures located bilaterally on either side of the urethra and vagina that act like the ropes of a suspension bridge and provide the necessary support needed to hang the urethra on the anterior vaginal wall. They originate as fibrous bands from the pubic bone and broaden out as aponeurotic structures moving dorsally to insert into the ischial spine (Fig. 63–6).

The **cardinal ligaments** and the more medially placed **utero-sacral ligaments** support the uterus and cervix; their relaxation results in uterine prolapse (Fig. 63–7).

Pelvic Floor Musculature

The pelvic floor musculature, represented by the **levator ani muscles,** carries the weight of the pelvic contents and prevents the abdominal pressure from stretching the ligamentous support structures. The levator ani includes the **puborectalis muscle,** which surrounds the rectum connecting the pubic bones anteriorly in a U-shaped configuration, the **pubococcygeus muscle,** which crosses from the pubis to the coccyx, and the **iliococcygeus muscle.** The last one arises laterally from the arcus tendineus levator ani and forms a horizontal sheet that spans the posterior opening of the pelvis, providing a shelf on which the pelvic organs lie. The urethra and vagina pass through an aperture in the levator musculature, the urogenital hiatus. The levator ani contains not only type I fibers providing resting tone but also type II (fast-twitch) fibers that, under stress, maintain the urethral closure and prevent stretching of the pelvic ligaments.

The constant muscle tone (Critchley et al, 1980) maintained by predominantly type I (slow-twitch) striated muscle fibers compresses the vagina and urethra anteriorly toward the pubic bone and keeps the hiatus closed (DeLancey and Hurd, 1998).

The pudendal nerve provides somatic innervation to the striated muscle of levator ani, as well as to the striated muscle within the external anal and urethral sphincters. The intrapelvic somatic

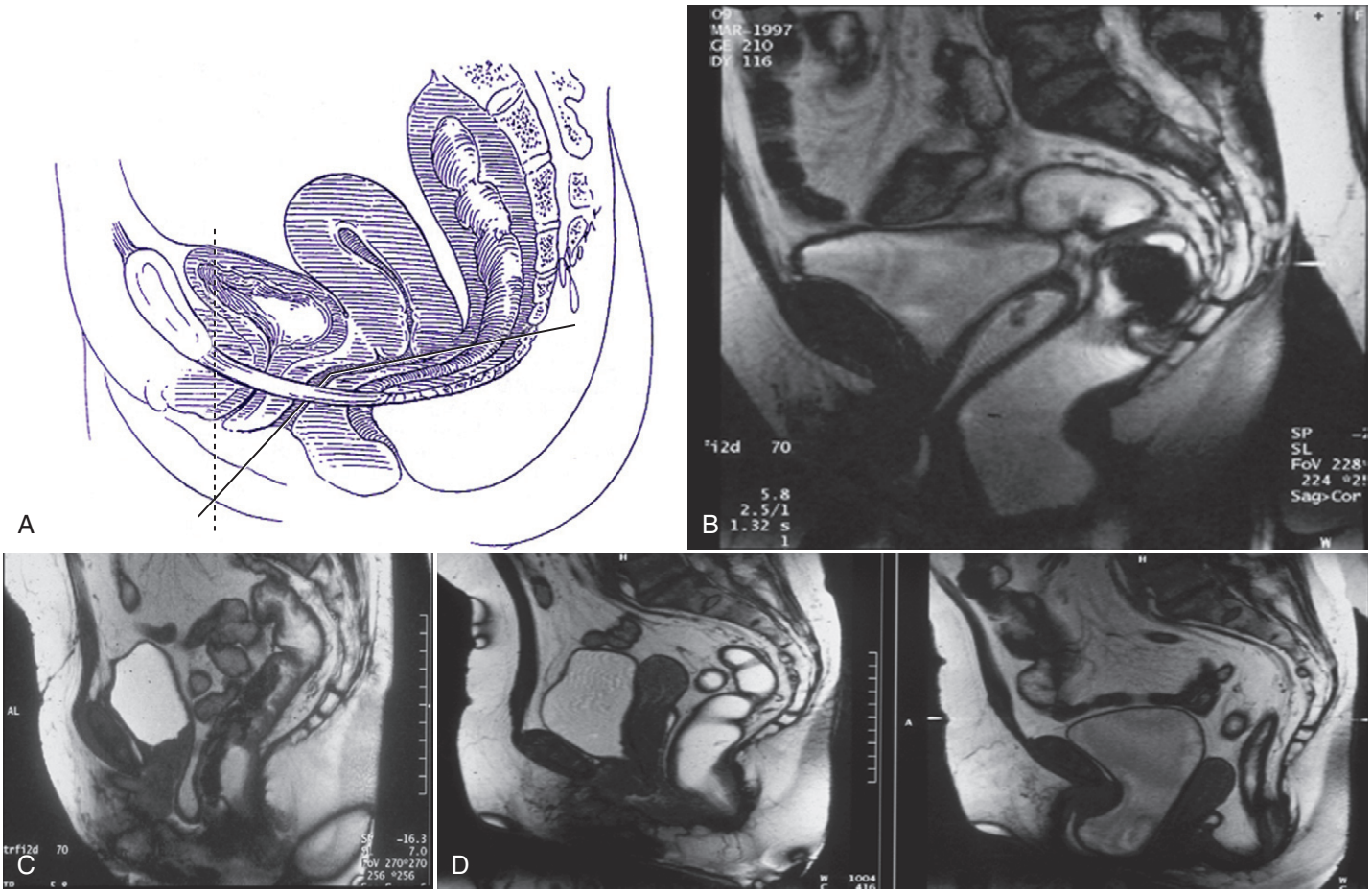


Figure 63–5. **A,** In the nulliparous patient, the lower one third of the vagina is oriented more vertically, whereas the upper two thirds deviate horizontally, thereby maintaining the vaginal axis in an almost horizontal position. **B,** In the nulliparous patient, the lower one third of the vagina is oriented more vertically, whereas the upper two thirds deviate horizontally, thereby maintaining the vaginal axis in an almost horizontal position. **C,** During stressful maneuvers such as coughing or straining, the levator hiatus is shortened anteriorly by contraction of the pubococcygeus muscles. **D,** In the case of genital prolapse when the levator ani support is lost, the vaginal axis becomes more vertical, the urogenital hiatus broadens, and fascial supports are strained.

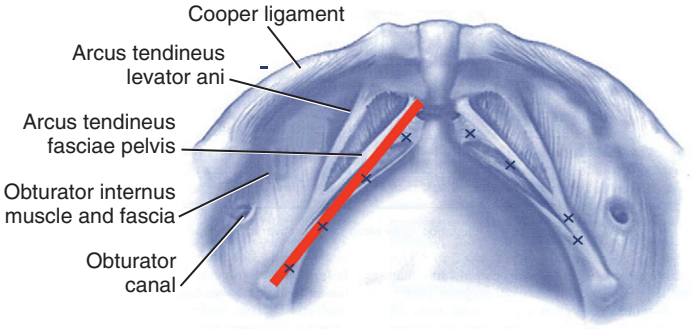


Figure 63–6. The arcus tendineus fasciae pelvis and its relationship to bony structures. The *x's* refer to placement of sutures during a paravaginal or vagino–obturator repair.

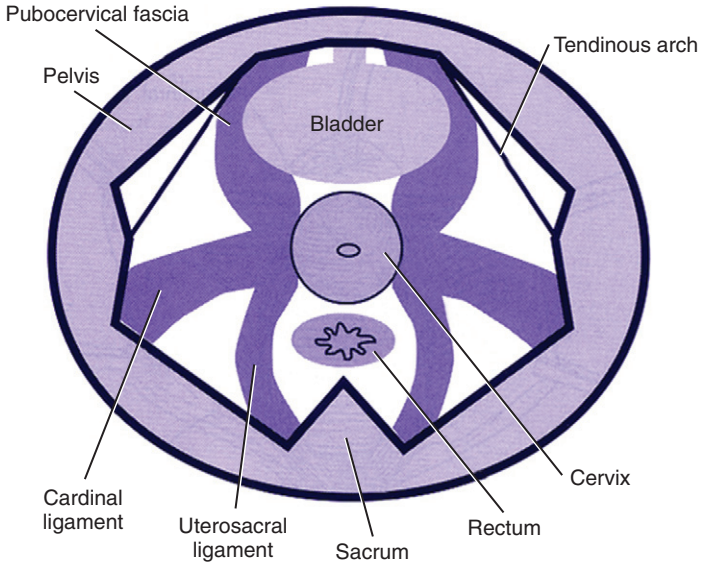


Figure 63–7. Relationship of ligaments to pelvic organs.

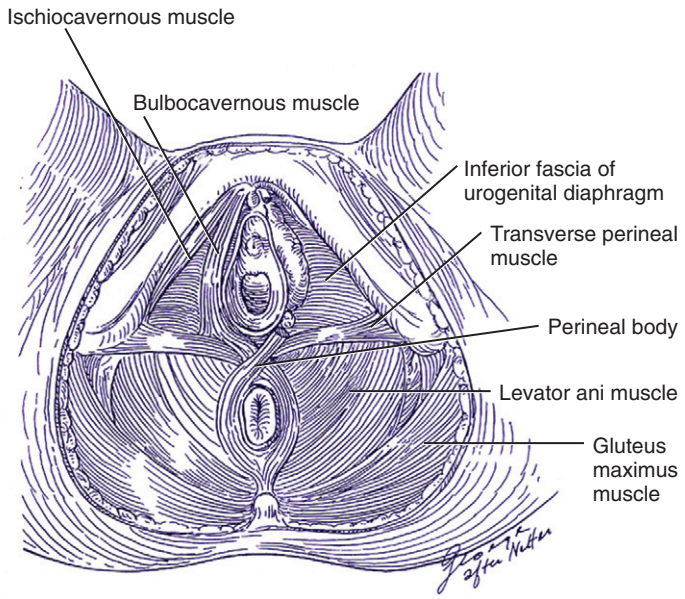


Figure 63–8. Disposition of the levator ani.

fibers travel along the anterior vaginal wall from the sacral segments S2 to S4 to provide asomatic nerve supply to the pelvic floor (Borirakchanyavat et al, 1997). Neuromuscular injuries have been proposed as an important factor in predisposing to pelvic floor dysfunction. Childbirth and age are the two major factors predisposing to pelvic floor denervation (Smith et al, 1989). Other factors include pelvic surgery (rectal and vaginal surgery with extensive pelvic dissection), radiotherapy, and congenital neurologic conditions such as spina bifida and muscular dystrophy (Fig. 63–8).

Current Theories Relating to the Maintenance of Continence

The traditional view has been that urethral support is critical to the maintenance of continence during increases in abdominal pressure. It was thought that loss of structural urethral support resulted in varying degrees of descent of the bladder neck and urethra, and it was thought that the resultant urethral hypermobility is the principal cause of SUI (Hodgkinson, 1953; Green, 1968; McGuire et al, 1976; Hodgkinson, 1978; Blaivas, 1988; Walters and Jackson, 1990). It was also thought that the normally supported bladder neck and proximal urethra sit in a high retropubic position and that increased intra-abdominal pressure is transmitted equally to both bladder and urethra. In cases of stress-induced urethral descent, the urethra attains a low, dependent position. Increased intra-abdominal pressure is then transmitted unequally to the urethra and bladder, and when bladder pressure exceeds urethral pressure, SUI ensues (McGuire and Herlihy, 1977; Constantinou and Govan, 1982; Westby et al, 1982; Constantinou, 1985; Bump et al, 1988; Rosenzweig et al, 1991). However, the fact that many women are totally continent despite clinical evidence of urethral hypermobility somewhat refutes that theory. This implies that the normal urethra remains closed even during stress-induced descent (Walters and Diaz, 1987).

The most commonly held view of the pathophysiology of stress incontinence secondary to urethral hypermobility is based on DeLancey's theory of urethral support, the so-called hammock theory (DeLancey, 1994). In anatomic specimens in which increases in abdominal pressure were simulated, he found that the urethra lies in a position where it can be compressed against a hammock-like musculofascial layer on which the bladder and urethra rest (DeLancey, 1994). **In this model, it is the stability of this supporting layer rather than the position of the urethra that determines stress continence.** Urethral support is supplied by connective tissue and muscle arranged to resist the downward pressure created by increases in abdominal pressure. The urethra is intimately connected to the anterior vaginal wall, and the connections of these two structures to the levator ani muscle complex and arcus tendineus fascia pelvis (ATFP) determine the stability of the urethra. The ATFP is a fibrous fascial band that stretches from the pubic bone anteriorly to the ischial spine. The fascial covering of the levator ani consists of two leaves: the endopelvic fascia (abdominal side) and the pubocervical fascia (vaginal side). The two leaves fuse laterally to attach on to the ATFP, creating a hammock of support under the urethra and bladder neck. **Normally, with rises in intra-abdominal pressure, the urethra is compressed against the supporting structures, which act like a backboard and prevent loss of urine** (DeLancey, 1997). When the supporting structures fail, there can be rotational descent of the bladder neck and proximal urethra during increases in abdominal pressure. If the urethra opens concomitantly, SUI ensues. If this supporting layer establishes its stability, although at a lower level, continence may still be preserved (DeLancey, 1996). **These findings have important clinical implications that support the contention that the primary goal of surgery for sphincteric incontinence in women is to provide a backboard against which the bladder neck and proximal urethra can be compressed during increases in abdominal pressure.** In fact, some of the most popular procedures for the treatment of stress incontinence do not change the position of the urethra or even correct mobility (Lo et al, 2001; Sarlos et al, 2003; Minaglia et al, 2005). An additional observation by DeLancey (1990) is that the medial portion of the levator ani muscle has a direct connection to the endopelvic fascia and the vaginal wall, and contraction of the levators contributes to stabilization of the urethra during sudden increases in abdominal pressure (e.g., a cough).

In a series of elegant MRI studies of the pelvic floor, stress incontinence was found to occur when there was unequal movement of the anterior and posterior walls of the bladder neck and proximal urethra during stress. With good anterior wall support and a lax posterior wall, the urethral lumen is literally pulled open as the posterior wall moves away from the anterior wall, resulting in incontinence (Yang et al, 1991; Yang et al, 1993; Mostwin et al, 1995). Conversely, one would expect less incontinence if there is similar laxity of the anterior wall.

Furthermore, ultrasound imaging of the bladder neck and proximal urethra, in both normal and stress-incontinent patients, demonstrated that opening (funneling) of the bladder neck was the common denominator underlying stress incontinence, not urethral hypermobility. Anterior support of the urethra is provided by the pubourethral ligaments, attaching the midurethra to the inferior aspect of the pubic bone. These work in conjunction with the pubourethralis muscle of the levator ani complex, which forms a sling around the proximal urethra and prevents rotational descent (Plzak and Staskin, 2002). Together, the two structures form the **midurethral complex,** which is now thought to play a significant role in the maintenance of stress continence along with the suburethral hammock described

earlier. According to Mostwin and colleagues (1995): **"It is the relative, not the absolute, position of the urethra with respect to the pubis that may contribute to urethral opening in stress incontinence. The length and strength of the suburethral complex may vary in patients. In those with shorter, stronger anterior fascial support, only a small loss of suburethral support may be sufficient to permit distraction (of the anterior and posterior urethral walls) during rotational descent."** In contrast to the explanation that proposes a pure transmitted pressure effect, the mechanism of shear force suggests that transmitted energy mechanically opens the proximal and middle urethra (Plzak and Staskin, 2002).

The exact point of continence in the urethra, if such a point exists, has been debated. For years it was thought to be the bladder neck; however, the work of Constantinou and Govan (1981) and Petros and Ulmstem (1990, 1998) **suggested that the midurethra supported anteriorly by the pubourethral ligaments is the most important zone of continence.** Constantinou and Govan (1981) showed that pressure change ratios in the urethra/bladder are highest at the midurethra in continent control patients and in postsurgical patients after endoscopic bladder neck suspension, whereas the high midurethral pressure is lost in women with stress incontinence. In 1990 Petros and Ulmstem published the **integral theory of stress and urge incontinence.** According to the theory, female stress incontinence and urgency incontinence have a common etiology. They proposed that support of the anterior vaginal wall is provided by three separate but synergistic mechanisms. The anterior pubococcygeus muscle lifts the anterior vaginal wall to compress the urethra; the bladder neck is closed by traction of the underlying vaginal wall in a backward and downward fashion; and the pelvic floor musculature, under voluntary control, draws the hammock upward, closing the bladder neck. Overall laxity of the anterior vaginal wall causes dissipation of all of these forces, resulting in stress incontinence. They further suggested that laxity of the anterior vaginal wall causes activation of stretch receptors in the bladder neck and proximal urethra that can trigger an inappropriate micturition reflex, resulting in detrusor overactivity. These theories are not mutually exclusive, and there is probably a least some truth in each. The fact that both bladder neck and midurethral slings have been shown to be successful in treating stress incontinence supports all these theories (Ulmsten et al, 1998; Olsson and Kroon, 1999; Nilsson and Kuuva, 2001; Rezapour and Ulmsten, 2001; Nilsson et al, 2004). Further reports of successful treatment of mixed incontinence with slings lend credence to the integral theory.

In 1980 **McGuire and colleagues first introduced the concept of intrinsic sphincteric deficiency** (ISD) when, in a retrospective analysis of the results of anti-incontinence surgery, they noted that some women who had undergone multiple retropubic operations had a deficient sphincteric mechanism characterized by an open bladder neck and proximal urethra at rest with minimal or no urethral descent during stress. They stated that ISD denotes an intrinsic malfunction of the urethral sphincter, regardless of its anatomic position. **Contemporary theories suggest that all patients with sphincteric incontinence have some degree of ISD.** Considerations that support this theory include the fact that the normal urethra is intended to remain closed no matter what the degree of stress or rotational descent. Furthermore, many women with urethral hypermobility remain continent (Versi et al, 1986). Finally, urethral hypermobility and ISD may (and often do) coexist in the same patient. Because urethral hypermobility and ISD often coexist, we believe that they do not necessarily define discrete classes of patients (Nitti and Combs, 1996; Fleischmann et al, 2003). Thus these parameters may be used to characterize incontinence but not necessarily classify patients. Classification systems have been devised to characterize stress incontinence by the presence or absence of urethral mobility, the degree of mobility, and the presence of rotational descent (Green, 1962; McGuire et al, 1976; Blaivas and Olsson, 1988). However, it is recommended **that rather than "classifying" stress incontinence, it makes more sense to simply characterize it by two parameters—the degree of urethral mobility and sphincter strength.**

EPIDEMIOLOGY OF URINARY INCONTINENCE AND PROLAPSE

The authors would like to acknowledge the major contribution made by the International Consultation on Incontinence Committee 1 on Epidemiology of Urinary and Faecal Incontinence and Pelvic Organ Prolapse (Milsom et al, 2009), on which the following section is based.

Background Terminology

Epidemiology is the scientific study of the distribution and determinants of disease in people. The epidemiology and natural history of UI vary greatly between the genders. Causes and risk factors are different. Therefore it is most practical to discuss the epidemiology of incontinence in men and women separately.

Prevalence is defined as the probability of experiencing a symptom or having a condition or a disease within a defined population and at a defined time point. The concept is important for establishing the distribution of the condition in the population and for projecting the need for health and medical services.

Incidence is defined as the probability of developing the condition under study during a defined time period. Incidence is usually reported for a 1-, 2-, or 5-year time interval.

When discussing the epidemiology and impact of incontinence, it is important to distinguish between its prevalence and incidence.

The relative risk (RR) estimates the magnitude of an association between exposure and a condition and indicates the likelihood of having the condition in the exposed group relative to those who are not exposed (e.g., do not have the risk factor). An RR of 1.0 indicates that the rates in the exposed and nonexposed groups are identical and thus that there is no association between the exposure and the condition in that specific dataset. A value greater than 1.0 indicates a positive association or an increased risk. An RR of 2.5 for UI indicates that there is a 2.5 times increased risk or that the persons in question are 250% more likely to have incontinence than those without the risk factor.

The odds ratio (OR) is the odds for having a risk factor in persons with a condition divided by the odds among those without the condition. An OR of 2.5 for UI may be interpreted as meaning that in this sample the odds in favor of having incontinence are 2.5 times higher among those with the risk factor than among those without.

For a condition with high prevalence, like UI or pelvic organ prolapse, OR and RR will not be identical, but in practice the results can be interpreted similarly. Results should always be given with a 95% confidence interval (CI).

Incontinence

UI is a common symptom that may affect women at all ages, and there is a wide range of severity and nature of symptoms. UI is not a life-threatening disease, but the symptoms may seriously influence the physical, psychologic, and social well-being of the affected individuals.

1. **Pregnancy, labor, and vaginal delivery** versus caesarean section are significant risk factors for later UI, but the strength of this association diminishes substantially with age (level 1 evidence).
2. Although several specific parturition factors such as **instrumental delivery and birth weight are risk factors for UI in the postpartum period, their association with UI in later life is weak or nonexistent,** suggesting that changes in birthing practices in developed countries are unlikely to affect UI in older age (level 2 evidence).
3. Additional evidence has now established **body mass** as important, modifiable risk factors for UI (level 1 evidence).
4. **Physical function** also appears to be an independent risk factor for UI in older women. Whether improvement in physical function leads to a reduction in UI remains to be established (level 2 evidence).
5. Evidence from two blinded, randomized controlled trials indicate **that oral estrogen, with or without progestogen,** is a significant risk factor for UI in women age 55 and older (level 1 evidence).
6. **Diabetes** is a risk factor for UI in most studies. Although diabetic neuropathy and/or vasculopathy are possible mechanisms by which diabetes could lead to UI, **no mechanism has been established, nor is it clear whether prevention or treatment of diabetes, separate from weight reduction, will reduce the risk of UI** (level 2 evidence).
7. **Menopause,** as generally defined, **does not appear to be an independent risk factor for stress UI** (level 2 evidence).
8. **Hysterectomy** remains a **possible risk factor** for later UI, but the evidence is inconsistent (level 2 evidence).
9. **Moderate to severe dementia** in older women is a **moderate to strong independent risk factor for UI** (level 2 evidence). Whether interventions to maintain or improve cognitive functioning also reduce UI has not been evaluated.
10. **Mild loss of cognitive function** in community-dwelling women, separated from physical function and other factors, **increases the risk of UI slightly,** if at all, but **may increase the impact of UI** (level 2 evidence).
11. Data from twin studies suggests that there is a **substantial genetic component** to UI (level 1 evidence).
12. Other potential risk factors including **smoking, diet, depression, constipation, UTIs, and exercise, although associated with UI, have not been established as etiologic risk factors** and are, in fact, difficult to study with observational data because of the potential for unmeasured confounding and questions of direction of the association (level 3 evidence).

General Comments

Virtually all epidemiologic studies rely on participant self-reporting of UI. Multiple studies have examined the association between self-reported incontinence and clinically demonstrable incontinence and by type of incontinence based on self-reported compared with type based on clinical diagnosis. Although self-reporting and clinical diagnosis are highly correlated, they are inherently different. Sandvik and colleagues (1995) validated diagnostic questions used in a survey against a final diagnosis made by a gynecologist after urodynamic evaluation. The percentage of stress-only incontinence increased from 51% to 77%, and mixed incontinence was reduced from 39% to 11% while the proportion with urgency-only UI remained virtually the same (10% vs. 12%). For public health purposes, self-report has the advantage of reflecting the woman's experience and allows further characterization of the incontinence by frequency and quantity of urine loss. Despite the uncertainty in determining the type of incontinence, the differences in the epidemiology of urgency and stress incontinence are potentially important given the presumed differences in underlying pathophysiology. Differences in the association of stress and urgency UI (based on self-report) with respect to age, race/ethnicity, and risk factors suggest that questionnaire-based determination of UI type is useful and should be included in all epidemiologic studies of UI (Thom, 1998).

Usually incontinence is defined by the episode frequency (e.g., one or more episodes in the past year or past month or typically leaking at least once a week or daily). **UI can also be defined by severity (a combination of frequency and quantity).** Probably the most widely used measure of severity is the Sandvik Severity index (Sandvik et al, 1993, 2000), which is calculated by multiplying the reported frequency (four levels) by the amount of leakage (three levels). **Incontinence can also be characterized by impact,** which is usually assessed either in terms of bothersomeness or by the degree to which it restricts a woman's activity (e.g., the Incontinence Impact Questionnaire) (Shumaker et al, 1994).

The vast majority of epidemiologic studies of female UI have been conducted in the United States, Canada, Europe, Australia, or Japan. A few additional studies have been reported from other Asian countries. Thus we know little about the prevalence, incidence, and risk factors for UI in Africa or other parts of the developing world.

Prevalence

Estimates of UI prevalence differ for a variety of reasons other than variation in true prevalence:

1. **Sampling frame.** Representative samples drawn from a large, usually geographically defined population (e.g., via random digit dialing) are thought to provide prevalence estimates that are the most generalizable.
2. **Response rates.** Even population-based studies can provide biased prevalence estimates due to poor response rates (Fultz and Herzog, 1993). Although the degree of bias is often unknown, as a general rule response rates above 80% are considered good and those between 60% and 80% are marginal.
3. **Threshold definition of UI.** Usually incontinence is defined by a threshold frequency (e.g., one or more episodes in the past year or past month, or typically leaking at least once a week or daily). Severity of degree of bother may also be used. The threshold chosen to define UI obviously affects the prevalence and incidence.

4. **Types of UI.** UI in women is typically classified as stress, urgency, or mixed. Prevalence estimates for each type of UI are sensitive to the wording of the questions and to definitions used.
5. **Survey methods.** Although there are few data comparing differences in prevalence based on method of ascertainment (Herzog and Fultz, 1990; Fultz and Herzog, 2000), variation in ascertainment (e.g., in-person interviews, phone interviews, mailed questionnaires, diaries) affects prevalence estimates for other socially sensitive conditions.
6. **Culture and language.** Although this area has not been investigated, it is likely that there are cultural differences in the perception of and terms used to describe UI that may affect prevalence estimates. Similarly, differences in language may lead to differences in ascertainment.

Prevalence in General Population of Adult Women

A review of 36 general population studies from 17 countries in the 2004 Third ICI edition (Hunskaar, 2005) found that the prevalence estimates for the most inclusive definitions of UI ("ever," "any," or "at least once in the past 12 months") ranged from 5% (Van Oyen and Van Oyen, 2002) to 69% (Swithinbank et al, 1999), **with most studies reporting a prevalence of any UI in the range of 25% to 45%. For daily incontinence, prevalence estimates typically range between 5% and 15% for middle-aged and older women** (Thomas et al, 1980; Yarnell et al, 1981; Holst and Wilson, 1988; Rekers et al, 1992; Lara and Nacey, 1994; Hannestad et al, 2000). Studies reported since 2004 have added important information on prevalence of incontinence in women younger than 30 and older than 80 years of age, particularly for prevalence of incontinence by type. These studies are consistent with previous studies reporting that **older women are more likely to have mixed and urgency incontinence** (Diokno et al, 1986; Molander et al, 1990; Roberts et al, 1998; Nuotio et al, 2003), whereas **young and middle-aged women generally report stress incontinence** (Hording et al, 1986; Holst and Wilson, 1988; Burgio et al, 1991; Samuelsson et al, 1997; Hannestad et al, 2000). **Overall, approximately half of all incontinent women are classified as stress incontinent. A smaller proportion are classified as mixed incontinent, and the smallest fraction as urgency incontinent.** A recent study that included the entire adult age range by Hannestad and colleagues (2000) demonstrated a fairly regular increase in prevalence of mixed incontinence across the age range and a decrease in prevalence of stress incontinence from the 40- to 49-year-old age group through the 60- to 69-year-old group.

Prevalence in Long-Term Care Facilities

Several studies have documented a **higher prevalence** of UI in women residing in long-term care facilities compared with community-dwelling women (Ouslander et al, 1982; Sgadari et al, 1997; Hunskaar et al, 1998; Aggazzotti et al, 2000; Saxer et al, 2008). Because UI is associated with dementia, limited mobility, and other comorbid conditions, **prevalence of UI is higher in facilities with residents requiring a higher level of care.** In addition to being more frequent, **UI in long-term care residents tends to be more severe, costly, and more burdensome on caregivers** compared with UI in the community (Ouslander and Schnelle, 1995).

Prevalence during Pregnancy and Postpartum

Studies of UI during pregnancy have reported **period prevalences of 32% to 64% for all UI and 40% to 59% for stress (including mixed) UI. Period prevalence is higher in parous than in nulliparous women** (Dimpfl et al, 1992; Marshall et al, 1998; Morkved and Bo, 1999; Hvidman et al, 2002), whereas new-onset UI (cumulative incidence) during pregnancy is higher in primigravida women (Marshall et al, 1998; Morkved and Bo, 1999; Hvidman et al, 2002). **Point prevalence of UI is low in the first trimester, rises rapidly in the second trimester, and increases further, though less rapidly, in the third trimester** (Marshall et al, 1998; Morkved and Bo, 1999). **Severity of incontinence appears to increase during pregnancy as well** (Burgio et al, 1996). Data recently reported from the Norwegian Mother and Child Cohort Study, a large (N = 43,279) population-based study, confirms these observations (Wesnes et al, 2007). In this study the prevalence of stress incontinence from before to during pregnancy rose from 9% to 31% in nulliparous women and from 24% to 42% in parous women. In contrast, mixed incontinence showed a similar rise in both groups (from 6% to 16% and from 8% to 20%, respectively). Urgency incontinence remained virtually unchanged in both groups at less than 5%.

Estimating the postpartum prevalence of UI is complex because in addition to differences in study design, method of ascertainment, and choices of definition of incontinence, prevalence may also depend on the number of previous births, type of delivery, and history of previous incontinence. **Nearly all postpartum UI is stress related.** Most studies did not provide information on the frequency of leakage or degree of bother. Overall, it appears that **any incontinence is reported by 15% to 30% of women during the postpartum year, weekly or greater incontinence is reported by 5% to 10%, and daily UI is reported by less than 5% of women.** Excluding women with UI before pregnancy reduced the prevalence of postpartum incontinence by 3% to 4% in the one study reporting separate prevalences for each group (Glazener et al, 2006). Studies that included women delivered by caesarean section and delivered vaginally consistently found **a lower prevalence in those delivered by caesarean section. Studies reporting prevalence in women delivered by elective caesarean section** and by caesarean section after initiation of labor showed a substantially lower prevalence of postpartum UI in the elective caesarean section group.

Prevalence in Different Racial and Ethnic Groups

Although most epidemiologic studies of UI have been conducted on Caucasian populations in the United States, Canada, and Europe, there are now a substantial number of studies in Asian countries (Herzog and Fultz, 1990; Dimpfl et al, 1992; Burgio et al, 1996; Marshall et al, 1998; Morkved and Bo, 1999; Hvidman et al, 2002; Jumadilova et al, 2005; Anger et al, 2006b; Glazener et al, 2006; Waetjen et al, 2007; Wesnes et al, 2007). Studies have also been conducted on racial/ethnic groups in the United States (Burgio et al, 1991; Fultz et al, 1999; Sampselle et al, 2002; Grodstein et al, 2003; Nygaard et al, 2003; Jackson et al, 2004; Anger et al, 2006a; Danforth et al, 2006; Thom et al, 2006; Waetjen

et al, 2007; Dooley et al, 2008; Fenner et al, 2008; Markland et al, 2008, 2009). Because of the substantial variation in prevalence of incontinence between studies, it is best to examine differences by race and ethnicity in the same study. Most striking is the **lower prevalence of stress UI in black and Asian compared with white women**. In most studies, blacks have half to a quarter the prevalence of stress UI compared with white women but the same or slightly higher prevalence of urgency UI and a slightly lower prevalence of mixed UI. Thus the difference in prevalence of UI between white and black women appears to be almost entirely the result of a markedly lower prevalence of stress UI symptoms in black women. In contrast, the lower prevalence of UI seen in Asian women compared with white women reflects a lower prevalence of both stress and urgency UI. The comparison of prevalences between Hispanic and non-Hispanic white women is complex in that some studies have found a lower prevalence of UI in Hispanic women while others have reported the prevalence to be higher in this group. This heterogeneity may be explained, at least in part, by differences in prevalence among a subpopulation of Hispanic women. Studies such as the SWAN study (Sampselle et al, 2002) that include Hispanic women who are primarily of Caribbean origin have reported lower UI prevalence, whereas those enrolling primarily Mexican-American women have reported higher UI prevalences (Thom et al, 2006; Daneshgari et al, 2008; Dooley et al, 2008). This relationship is further supported by the NHANES data reported by Anger and colleagues, which found prevalences of any UI to be 36% in Mexican-American women and 30% in other Hispanic women (Anger et al, 2006a; Daneshgari et al, 2008).

Key Points: Prevalence of Urinary Incontinence

- The estimated prevalence of UI in middle-aged and older women in the general population appears to be in the range of 30% to 60% (increasing with age). The prevalence of daily UI ranges from 5% to 15%, rising to more than 15% in women older than age 70 who are institutionalized. Some studies have found prevalences outside theses ranges, demonstrating that there remains a large variation in the estimated prevalence of UI in women, even after taking into account differences in definitions, ascertainment, and demographic characteristics. At least part of this variation is likely to be due to the sensitivity of the subject and subtle differences in the conduct of studies (level 1 evidence).
- Multiple observational studies have confirmed that white, non-Hispanic women have a substantially higher prevalence of stress UI than black or Asian women that is not explained by differences in known risk factors for UI (level 1 evidence).

Potential Risk Factors

Many epidemiologic studies have investigated potential risk factors for UI. The design of most of these studies has been cross sectional using prevalent UI. In cross-sectional studies, the temporal relationship between some potential risk factors such as diet, physical activity, medications, or body weight is ambiguous because the development of UI can lead to changes in behavior. Since 2004, several prospective studies have examined risk factors for incident UI that have allowed for evaluation of the temporal relationship. Associations in all observational studies are subject to potential confounding, necessitating multivariate analysis to estimate the independent association between risk factors and UI. The risk factors of estrogen use and body mass (obesity) have been examined in randomized, controlled trials. With the exception of age, the following risk factors are considered to be at least potentially modifiable.

Impact and Consequences

The impact of UI is typically assessed by degree of bother or by scales that measure the impact of incontinence on functional status and quality of life. A single question asking patients to report the degree of bother they experience from their incontinence provides an important dimension to characterizing UI in addition to frequency and amount of urine lost. Typically, **incontinence that is more severe, of longer duration, and is urgent or mixed is also more bothersome** (van der Vaart et al, 2002). Validated scales measure the impact of UI. One of the first scales, the Incontinence Impact Questionnaire (Shumaker et al, 1994), uses 30 items asking whether incontinence limits activities in four domains. Several other similar scales exist, some specific for urgency or stress incontinence or for overactive bladder (Shumaker et al, 1994; Uebersax et al, 1995; Jackson et al, 1996; Wagner et al, 1996; Kelleher et al, 1997; Brown et al, 1999; DuBeau et al, 1999). **In addition to severity of UI, interference with sexual activities and incontinence at night is associated with greater reported impact on quality of life** (Huang et al, 2006).

Incontinence has been identified as a **potential risk factor for falls and nursing home admissions.** In a prospective study of more than 6000 older women, women with weekly urgency, but not stress, incontinence were more likely to fall during the 3-year follow-up, adjusting for multiple other factors (adjusted OR = 1.3, 95% CI = 1.1 to 1.4) (Brown et al, 2000). Similarly, in a study of 472 long-term care residents in Germany, UI at baseline predicted falls over the next 12 months after adjusting for a variety of patient factors and comorbid conditions (Kron et al, 2003). UI was the second strongest predictor of falls (a history of falls being first). However, it is possible that both falls and UI are markers for frailty that cannot completely be adjusted for. Whether treatment of UI would reduce the number of falls has not been established.

UI has also been reported as a **risk factor for nursing home admissions even after adjusting for multiple comorbid conditions** (Thom et al, 1997a, 1997b). However, another study that also adjusted for additional measures of frailty including activities of daily living found that the association became weaker and nonsignificant (Holroyd-Leduc et al, 2004).

UI has substantial, well-documented economic consequences as well. Annual costs of UI are estimated to be more than $20 billion in direct costs (primarily costs of routine care including out-of-pocket costs) (Wilson et al, 2001), which is greater than the annual costs for breast, cervical, uterine, and ovarian cancer combined (Subak et al, 2006). There are also substantial indirect costs from work loss and missed volunteer work (Thom et al, 2005).

Treatment Seeking and Treatment

The proportion of women with any UI in the past 12 months who report having sought medical treatment ranges from 12% (Sampselle et al, 2002) **to 53%** (Mardon et al, 2006) **with about half the studies showing 25% to 30%** (Rekers et al, 1992; Hannestad et al, 2002; Hagglund et al, 2003; Hsieh et al, 2008). All studies that have examined treatment seeking by type of incontinence have found that **women with urgency or mixed incontinence are more likely to seek**

Key Points: Conditions Predisposing to Urinary Incontinence (Milsom et al, 2009)

- Age: Virtually all studies have found an increase of UI prevalence with age. As a result, while stress incontinence predominates in younger and middle-aged women, urgency and mixed incontinence are more common in older women.
- Pregnancy, parity, and parturition events: Stress UI is reported by most women at some time during pregnancy, usually in the third trimester, but is generally self-limited and resolves after delivery. The interpretation of this association is not clear. It may be that physiologic changes during pregnancy cause incontinence later in life, but it is also possible that the temporary physiologic changes during pregnancy may "uncover" women with a predisposition to incontinence who are destined to become incontinent later in life regardless of the effects of pregnancy. The vast majority of studies have found an association between parity and later UI.
- The effect of parturition on risk of incontinence is difficult to separate from the effect of pregnancy. Possible mechanisms by which vaginal birth could lead to incontinence include stretching damage to pudendal and other nerves and tearing of connective tissue, which reduces pelvic floor support for urethral competence.
- Obesity and body mass: Obesity is well established as a factor that can cause UI or contribute to the severity of the condition. It is believed that the added weight of obesity, like pregnancy, may bear down on pelvic tissues causing chronic strain, stretching, and weakening of the muscles, nerves, and other structures of the pelvic floor. Intervention studies for weight reduction have reported that loss of weight is associated with partial remission or complete resolution of UI. Thus there is strong evidence to support the causal role of excess weight in the development of UI.
- Hormones: Current evidence suggests that although oral estrogen as a risk factor for stress UI may be unexpected, it is likely to be important, at least in women age 55 and older.
- Diabetes: Many, though not all, cross-sectional studies have reported UI to be more common in women with type 2 diabetes than among women with normal glucose levels even after adjusting for common risk factors including age and obesity.
- Hysterectomy: Approximately 600,000 women have hysterectomies in the United States each year, usually for noncancerous conditions. There has been concern that hysterectomy may be associated with development of UI via damage to the pelvic nerves and pelvic supportive structures. On the basis of the available data, hysterectomy does not appear to increase the risk of UI in the short term.
- Urinary tract infections and lower urinary tract symptoms: Urinary tract infection (UTI) has long been considered to be a cause of transient UI. The role of UTIs with respect to the development of chronic UI is less clear. Without additional data, it is not possible to say if UTIs actually increase the risk of later UI, if UI increases the risk of being diagnosed with a UTI, or if both UI and UTIs are manifestations of a common underlying process.
- Impaired physical function: Functional impairments, particularly mobility limitations, a history of falls, arthritis, dizziness, the need to use a walking aid, and poor lower extremity strength, have been correlated with UI in many community-based and nursing home studies.
- Cognitive impairment: Research on UI in nursing home residents has consistently supported an association between UI and dementia. In studies using multivariate analyses, patients lacking mental orientation had a 3.6 times greater risk of being incontinent than those with normal mental status and the presence of dementia increased the odds of UI by 1.5 to 2.3.
- Depression: Although depression may predispose a woman to developing UI, it is also possible that UI leads to depression (e.g., by reducing a woman's social network); that depression and UI share one or more common neurochemical or hormonal pathways; or that women with depression are more likely than nondepressed women to be bothered by, and hence report, having incontinence.
- Menopause: Historically, menopause has been considered a risk factor for UI. However, establishing a relationship between menopause and UI has been difficult, probably in part because changes in endogenous hormone levels vary over a period of at least several years and only approximately correspond to amenorrhea or vasomotor symptoms used to define clinical menopause.
- Physical activity: Evaluating physical activity as a potential risk factor or protective factor for incontinence has been difficult. Incontinence, particularly stress UI, can be a barrier to exercise, which could lead to the spurious appearance of a protective effect of physical activity on UI. Alternatively, engaging in physical activity could "unmask" an existing propensity toward stress incontinence by increasing intra-abdominal pressure, resulting in physical activity being identified as a risk factor in the short term even if it is protective in the long term.
- Smoking, cough, and chronic lung disease: Conflicting data from cross-sectional studies and lack of association between smoking and incident UI in prospective studies suggest that smoking per se is probably not an independent risk factor for UI.
- Diet: Studying diet as a risk factor for UI is challenging. Although some dietary constituents such as coffee, alcohol, or carbonated beverages have been suspected as worsening UI, there is little reason to suspect other dietary constituents as causing, or protecting from, UI.
- Family history and genetics: Several family history studies have found a twofold to threefold greater prevalence of stress UI among first-degree relatives of women with stress UI compared with first-degree relatives of continent women.
- Ischemic heart disease: It is not clear if heart disease is an independent risk factor for UI.
- Other factors: Additional variables reported as associated with UI include constipation; fecal incontinence; genital prolapse; congestive heart failure; use of diuretics, benzodiazepines, and other drugs; and childhood enuresis.

treatment than women with stress incontinence (Hannestad et al, 2002; Danforth et al, 2006; Zhu et al, 2008). As expected, **the proportion of women seeking treatment is strongly associated with frequency, severity, and bothersomeness,** with several studies reporting proportions of 50% to 80% of women with daily, moderate to severe, or bothersome incontinence (Hannestad et al, 2002; Kinchen et al, 2003; Diokno et al, 2004; Gasquet et al, 2006).

Reasons given by people for not seeking help include not regarding incontinence as abnormal or serious, embarrassment, considering incontinence to be a normal part of aging, having low expectations of treatment, and thinking they should cope on their own. Other characteristics such as age, general health, or attitude toward health care may also play a role.

Key Points: Consequences of Urinary Incontinence

- Typically, incontinence that is more severe, of longer duration, and is urgency or mixed incontinence is more bothersome.
- In addition to severity of UI, interference with sexual activities and incontinence at night are associated with greater reported impact on quality of life.
- Incontinence has been identified as a potential risk factor for falls and nursing home admissions.
- UI has also been reported as a risk factor for nursing home admissions even after adjusting for multiple comorbid conditions.
- UI therefore has substantial, well-documented, economic consequences.
- The proportion of women with any UI in the past 12 months who report having sought medical treatment ranges from 12% to 53% with about half the studies showing 25% to 30%.
- Women with urgency or mixed incontinence are more likely to seek treatment than women with stress incontinence.
- The proportion of women seeking treatment is strongly associated with frequency, severity, and bothersomeness.

Key Points: Urinary Incontinence in Men

- The epidemiology of UI in men has not been investigated to the same extent as for females. But it appears that **UI is at least twice as prevalent in women as compared with men.** There seems to be a more **steady increase in prevalence with increasing age than for women** (level 1 evidence).
- Most studies find a **predominance of urgency incontinence, followed by mixed forms of UI and stress incontinence the least.** Most studies have a large fraction of other/unclassified types (level 2 evidence).
- Literature on incidence and remission of male UI is still scarce.
- Few clear risk factors have been scientifically documented, but several medical correlates have been reported. **Established risk factors** predisposing men to UI include **increasing age, presence of lower urinary tract symptoms (LUTS), urinary tract infections, functional and cognitive impairment, neurologic disorders, and prostatectomy** (level 2 evidence).
- UI after radical prostatectomy is frequent, ranging from 2% to 57%. Rates steadily decline from the time of surgery and plateau at 1 to 2 years (level 1 evidence).
- Factors affecting **postprostatectomy UI** include the **age at surgery, type of prostatectomy, and the modifications in the technique involving nerve and bladder neck preservation** (level 2 evidence).

Urinary Incontinence in Men

General Comments

Prevalence

A systematic review of 21 studies reported a **prevalence of UI in older men ranging from 11% to 34%** (median = 17, pooled mean = 22%). In the same review, the **prevalence of daily UI in men ranged from 2% to 11%** (median = 4%, pooled mean = 5%) (Thom, 1998). A wide definition of UI, older age, inclusion of institutionalized men, and the use of self-reporting methods tend to result in higher prevalence rates (Koyama et al, 1998; Thom, 1998). The wide span of results may be explained by the variation in the population studied, the definition of incontinence used, and the methods used in the surveys.

For any definition of UI, there is a **steady increase in prevalence with increasing age.**

Incontinence Subtypes

Due to differences in pathologic anatomy and pathophysiology of UI in men and women, there is a different distribution in incontinence subtypes. Recent studies confirmed our previous reports of the **predominance of urgency incontinence (40% to 80%), followed by mixed forms of UI (10% to 30%) and stress incontinence (<10%)** (Herzog and Fultz, 1990).

The higher percentages of the urgency and mixed types of incontinence are more significant in studies involving older people. In fact, the increasing prevalence of any UI by age in men is largely due to the contribution of urgency incontinence rather than stress incontinence. One study demonstrated an increasing rate of urgency UI from 0.7% between ages 50 and 59 to 2.7% between 60 and 69 to 3.4% for respondents 70 years and older. Stress UI was steady at 0.5%, 0.5%, and 0.1% for these groups, respectively (Ueda et al, 2000). On the other hand, Maral and colleagues (2001) reported increasing prevalence of SUI with age: 0.9% between ages 35 and 44, 1.2% between ages 45 and 54, 3.8% between ages 55 and 64, and 4.9% at age 65 and older.

Most studies report a significant fraction of other/unclassified type of urinary incontinence. One study reported that a majority of men with UI had overflow and functional types of incontinence (Bortolotti et al, 2000), whereas another found constant dribbling in 7% of their respondents (Damian et al, 1998). **Terminal dribbling or postvoid dribbling is another type of leakage in men that is difficult to assign to the conventional subtypes of UI.** In an Australian survey, **12%** of respondents reported frequent terminal dribbling (Sladden et al, 2000).

Severity

When it comes to severity, the distribution in men follows that of the women. Estimates for severe UI in older women tend to be about twice as high as for older men (Herzog and Fultz, 1990).

Race/Ethnicity

Few studies have looked at the impact of race or ethnicity on the prevalence of UI among men. A four-country study presented lower prevalences of reported UI among men from Korea (4%) and France (7%) than in men from Britain (14%) and Denmark (16%) (Boyle et al, 2003). On the other hand, unpublished data from the MESA study did not indicate differences in prevalence among white male respondents compared with African-American respondents.

Incidence and Remission

Literature on the incidence of male UI is scarce. The MESA study (Herzog and Fultz, 1990) found a 1-year incidence rate for men older than 60 years of 9% to 10%. In a population-based survey in the UK among men at least 40 years of age, the 1-year incidence of UI was noted to be 3.8% (McGrother et al, 2004). A review of a health organization database of males at least 65 years old revealed a UI incidence of 23.8 per 1000 person years. Malmsten (1997) analyzed the age of onset of UI for each age cohort. Mean starting age for all men was 63 years. The mean duration was about 8 to 10 years in the cohorts. Substantial remission rates for UI in males were noted by the MESA study, higher among men (27% to 32%) than women (11% to 13%) (Herzog and Fultz, 1990). A similarly high 1-year remission rate of 39.6% was noted among British males (McGrother et al, 2004). One possible explanation for the difference in the published incidence and remission rates in men compared with women is the predominance of urgency type incontinence among men and its close relation to overactive bladder with and without incontinence. Another factor is the close association among urgency UI and prostate gland disease, infections, or bowel dysfunction, all of which are relatively amenable to treatment or may improve even without treatment.

Potential Risk Factors for Urinary Incontinence

There is relatively little research concerning conditions and factors that may be associated with UI in men, and clear risk factors are poorly documented. However, a few available studies have identified potential risk factors, which are described next.

Age

As in women, **increasing age is correlated with increasing prevalence of UI.** Multivariate analysis in several studies has shown that age is an independent risk factor for incontinence (Muscatello et al, 2001; Boyle et al, 2003; Landi et al, 2003; Nelson and Furner, 2005; Diokno et al, 2007). Compared with women, however, there seems to be a steadier increase in prevalence in men with increasing age.

Lower Urinary Tract Symptoms and Infections

LUTS, like urgency, nocturia, a feeling of incomplete voiding, and reduced flow, are typically associated with UI (Diokno et al, 1986; Hunskaar, 1992; Schmidbauer et al, 2001). In one study, UI was reported by 15% of men without voiding symptoms, frequency, or urgency and by 34% of those with such symptoms (Diokno et al, 1986).

Studies have also reported that urinary tract infections and cystitis are strongly associated with male UI (Damian et al, 1998; Ueda et al, 2000), with an OR of 3.7 for UI in men reporting cystitis (Ueda et al, 2000) and an OR of 12.5 among men with recurrent infections (Bortolotti et al, 2000). It should be noted that reports indicating a positive association between UTI and incontinence involved men older than 60 years.

Functional and Cognitive Impairment, Physical Activity

Mobility problems such as use of a wheelchair or aids to walking, as well as diagnosed arthritis or rheumatism or having a fall during the past year, were **significantly greater among incontinent than continent men** (Diokno et al, 1990; Damian et al, 1998).

Neurologic Disorders

Many specific neurologic diseases may lead to UI (Resnick and Yalla, 1987). **Neurogenic detrusor overactivity** is seen commonly in meningo-myelocele patients and in spinal injuries, Parkinson disease, and multiple sclerosis. **Underactive bladder dysfunction** due to a cauda equina lesion or diabetes **might cause overflow or a paralyzed pelvic floor and hence stress incontinence.** Men who have suffered a stroke were at increased risk for incontinence with an OR of 7.1 (Ueda et al, 2000). A case control study of age-matched, long-term stroke male survivors with controls showed a higher prevalence of UI among stroke survivors compared with controls (17% vs. 9%). In addition, among UI sufferers, the stroke survivors were found to have higher frequency and more leakage than controls. In a study of 235 stroke patients, the occurrence of UI correlated with motor weakness (OR 5.4), visual defects (OR 4.8), and dysphagia (OR 4.0).

Prostatectomy

A well-known iatrogenic cause of male incontinence is prostatectomy, but the attributable risk for this factor in the population of men with UI is unknown. In a Norwegian survey of elderly men with UI, almost a third had undergone prostatectomy (Hunskaar, 1992).

In a cross-sectional study among men in Vienna, Schmidbauer and colleagues identified previous prostatectomy to be associated with UI (Schmidbauer et al, 2001).

TURP seems to be followed by an incidence of stress incontinence of about 1%. A randomized controlled trial comparing TURP, laser prostatectomy, and evaporization of the prostate for benign disease showed comparable incontinence rates immediately and up to 12 months postoperatively (van Melick et al, 2003).

Radical prostatectomy seems to induce UI at a much higher rate than TURP. The overall **prevalence of postradical prostatectomy incontinence ranges from 2% to nearly 60%.** This wide range may be explained by many factors including differences in study characteristics, population characteristics, study site, definition used, and timing of assessment of continence in relation to the surgery. The era of development of the procedure has also been found to be associated with the prevalence rates (Hu et al, 2003), as well as the various procedural modifications of the surgery (see later). **Postprostatectomy incontinence rates elicited from symptoms reported by patients are generally two to three times higher than those from physicians' observations.** Studies that have performed both assessments in the same population confirm this observation that **doctors underestimate postprostatectomy incontinence by as much as 75%** (Ojdeby et al, 1996; Donnellan et al, 1997; McKammon et al, 1997; Olsson et al, 2001).

Incontinence rates after prostatectomy seem to decline steadily with time and plateau 1 to 2 years after surgery (Lowe, 1996; Weldon et al, 1997; Goluboff et al, 1998; Horie et al, 1999; Walsh et al, 2000; Moinzadeh et al, 2003). This emphasizes the need for a long follow-up period to establish continence status postprostatectomy. An actuarial study among 647 postprostatectomy men estimated UI rate of 13% at 1 year and 7% at 2 years postsurgery (Saranchuk et al, 2005).

The **technique of radical prostatectomy** affects UI rates. Modifications associated with lower UI rates include the perineal approach (Bishoff et al, 1998; Gray et al, 1999) and preservation of neurovascular bundle (Eastham et al, 1996; Van Kampen et al, 1998; Wei et al, 2000). Bladder neck preservation affords earlier return to continence compared with bladder neck resection, but with similar UI rates after 1 year (Poon et al, 2000; Srougi et al, 2001). One study showed earlier recovery of UI after tennis racquet reconstruction and bladder neck preservation compared with bladder neck resection with puboprostatic ligament preservation, but with similar UI rates at 1 year (Lowe, 1996; Noh et al, 2003). However, continence status assessed more than 12 months after surgery showed even lower rates of UI after bladder neck preservation (11.6%) compared with resection (4.9%) in one study (Lowe, 1996). UI after laparoscopic procedures seems to be higher initially but approximates that of open techniques by 1 year (Jacobsen et al, 2007).

Older age at time of surgery has been found to be associated with a higher prevalence of postprostatectomy UI (Eastham et al, 1996; Goluboff et al, 1998; Van Kampen et al, 1998; Gray et al, 1999; Wei et al, 2000; Kundu et al, 2004). One study showed a doubled risk for every 10 years of age beginning at age 40 (Catalona et al, 1999). Another study suggested that rather than absolutely affecting final continence prevalence, elderly men need a longer time to achieve continence after surgery (Horie et al, 1999). Two studies found no relation between age at surgery and UI (Donnellan et al, 1997; Kao et al, 2000).

Other factors have been found to be associated with a higher prevalence of postprostatectomy UI, although not consistently. Such factors include prior TURP, preoperative lower urinary tract symptoms, obesity, clinical stage, prostate-specific antigen (PSA), prostate volume, and Gleason score (Eastham et al, 1996; Moul et al, 1998; Van Kampen et al, 1998; Kundu et al, 2004; Lee et al, 2006). A retrospective analysis of 156 patients who had undergone preoperative MRI of the prostate and were followed up postprostatectomy showed that time to return to continence was associated with the variation in the shape of the prostatic apex. The prostatic apex that does not overlap with the membranous urethra was found to be significantly associated with an early return of continence (Lee et al, 2006). The 5-year cohort study of the Prostate Cancer Outcomes Study found that among prostatectomy patients, race and ethnic differences were related to urinary incontinence, with African-Americans having better recovery compared with non-Hispanic whites and Hispanics (Johnson et al, 2004).

Adjuvant radiotherapy has not been found to affect postprostatectomy incontinence rates when assessed beyond 1 year (Formenti et al, 2000; Hofmann et al, 2003; Kundu et al, 2004).

Factors of Unclear Association with Urinary Incontinence in Men

A 9-year study of Janssen (2007) showed increasing rates of UI with increasing body mass index (BMI) among the older men and women. However, multivariate analysis failed to show increased BMI (overweight and obese levels) as an independent risk factor for the development of UI. In a study including a younger population in Australia, obesity was noted to be associated with UI with an OR of 3.2 (1.2 to 9.0) (Muscatello et al, 2001). In this study, however, being merely overweight was not associated with UI. Several studies in the older persons have shown an association between physical activity and UI among women that is not seen among men (Boyle et al, 2003; Kikuchi et al, 2007).

Key Points: Epidemiology of Male Incontinence

- Relatively little research concerning conditions and factors that may be associated with UI in men has been conducted, and clear risk factors are poorly documented.
- Increasing age is correlated with increasing prevalence of UI.
- LUTS, like urgency, nocturia, feeling of incomplete voiding, and reduced flow, are typically associated with UI.
- Many specific neurologic diseases may lead to UI.
- TURP seems to be followed by an incidence of stress incontinence of about 1%.
- The overall prevalence of postradical prostatectomy incontinence ranges from 2% to nearly 60%.
- Postprostatectomy incontinence rates elicited from symptoms reported by patients are generally two to three times higher than those from physicians' observations.
- Doctors underestimate postprostatectomy incontinence by as much as 75%.
- The technique of radical prostatectomy affects UI rates.
- Older age at time of surgery has been found to be associated with a higher prevalence of postprostatectomy.
- Other factors associated with a higher prevalence of postprostatectomy UI include prior TURP, preoperative lower urinary tract symptoms, obesity, clinical stage, PSA, prostate volume, and Gleason score.

EPIDEMIOLOGY OF OVERACTIVE BLADDER

The studies reported in the literature have used different populations and ways of selecting samples, and the definition of OAB has changed slightly after its initial description, although this was standardized after the 2002 ICS standardization report.

The prevalence of OAB in adult males varies from 10.2% to 17.4% and in females from 7.7% to 31.3%. Clearly different definitions, the different age groups studied and maybe cultural differences affect the rates (level 2 evidence). OAB_{wet} was less prevalent than OAB_{dry} except for one implausible-looking result. The response rate was quite low in many of these studies, and sometimes it was impossible to know the response rate (e.g., when quota sampling was used).

A common finding was that the **rates increased with age,** but this was not universal (level 2 evidence). Some studies found that after adjusting for state of health, the relationship with age went away, and some found that it only applied to OAB_{wet}. **Usually OAB was more prevalent in females, and this was much more pronounced for OAB_{wet}, which sometimes meant that OAB_{dry} was the same for males and females**. OAB was related to **general health problems** and in particular **diabetes.** It is likely to be related to urinary problems in childhood.

Key Points: Epidemiology of Overactive Bladder

- The prevalence of OAB in adult males varies from 10.2% to 17.4% and in females from 7.7% to 31.3%.
- Rates of OAB increase with age.
- OAB is more prevalent in females, particularly OAB_{wet} to the extent that the prevalence of OAB_{dry} can be the same for males and females.
- OAB is related to general health problems and in particular diabetes and probably urinary problems in childhood.

EPIDEMIOLOGY OF PELVIC ORGAN PROLAPSE

General Comments and Definitions

Pelvic organ prolapse (POP) refers to loss of support for uterus, bladder, colon, or rectum leading to prolapse of one or more of these organs into the vagina. The ICS Pelvic Organ Prolapse Quantification (POPQ) examination defines prolapse by measuring the descent of specific segments of the reproductive tract during Valsalva strain relative to a fixed point, the hymen. As noted earlier, the **POPQ system describes the anatomic findings of pelvic organ prolapse without consideration for symptoms and bother** perceived by the woman. Validation of this system has shown it to be highly reliable (Hall et al, 1996). The stages of prolapse severity are arbitrarily defined, and **there is no clear differentiation between normal anatomic variation and mild POP.** For research purposes there is consensus for use of the POPQ system until further evidence might clarify the distinction between normal variation and mild prolapse (Weber et al, 2001).

Determining POP on the basis of self-reported symptoms is difficult because of the lack of specificity and sensitivity of most symptoms attributed to pelvic organ prolapse (Ellerkmann et al, 2001) **and the fact that prolapse above the level of the hymenal ring is usually asymptomatic** (Lukacz et al, 2005). The only exception appears to be a sensation of bulging into the vagina, which is most strongly associated with prolapse at or below the hymeneal ring (Swift, 2000; Hendrix et al, 2002). A recent study of 110 women found that a question asking about a feeling of something bulging in or dropping out of their vagina had a sensitivity of 84% and a specificity of 94% for POP at or beyond the hymeneal ring on examination (Lukacz et al, 2005). Seeing prolapse would presumably be even more specific but is too uncommon to be useful as a definition.

Prevalence of PELVIC ORGAN PROLAPSE

The prevalence of POP based on a sensation of a mass bulging into the vagina was remarkably consistent, ranging between 5% and 10%. The study by Eva and colleagues (2003) reported a substantially higher prevalence included in the definition of POP, pelvic heaviness, or digital pressure on the perineum or in the vagina to aid with defecation. Reports from the Women's Health Initiative (WHI) Oestrogen Plus Progestin Trial and randomized controlled trial (Handa et al, 2004; Nygaard et al, 2004; Bradley et al, 2007), although not actually population based, recruited the women in the trial from the community rather than from women seeking gynecologic care and provided important information on the prevalence of POP based on pelvic examination. The prevalence of observed prolapse in women enrolled in the WHI trial is similar to the prevalence found in the population-based study that also used pelvic examination (Samuelsson et al, 1999), although the prevalence of each type of prolapse was higher in the WHI study (Hendrix et al, 2002). In both studies, **prolapse occurs most frequently in the anterior compartment, next most frequently in the posterior compartment, and least in the apical compartment.**

Two studies that examined prolapse by race found that black women had the lowest prevalence and Hispanic women the highest after controlling for multiple other factors in multivariate analysis (Hendrix et al, 2002; Rortveit et al, 2007). The study reported by Rortveit and colleagues (2007) based on symptoms found adjusted ORs of 0.4 (95% CI = 0.2 to 0.8) for black and 1.3 (95% CI = 0.8 to 2.2) for Hispanic women, with white women as the referent group. Hendrix and colleagues (2002) reported adjusted ORs of 0.6 (95% CI = 0.5 to 0.8) for black and 1.2 (95% CI = 1.0 to 1.5) for Hispanic women compared with white women for POP based on genital examination.

Key Points: Epidemiology of Pelvic Organ Prolapse

- Most studies have used a cross-sectional design and there are limited longitudinal data to suggest a causal relationship between symptoms of obstructed defecation and pelvic organ prolapse or vice versa.
- Posterior vaginal wall prolapse and perineal descent are the compartment-specific defects most clearly associated with symptoms of obstructive defecation.
- A number of studies suggest that hysterectomy and other pelvic surgery may increase the risk for pelvic organ prolapse (level 2 evidence).
- Hysterectomy due to pelvic organ prolapse and other pelvic floor surgery are the strongest predictors of secondary pelvic floor surgery (level 2 evidence).
- SUI and pelvic organ prolapse have familial transmission patterns mediated by either genetic or environmental factors (level 2 evidence).
- SUI is more common in Caucasian women and pelvic organ prolapse in Caucasian and Hispanic women when compared with African-American women (level 2 evidence).
- Twin studies suggest that heritability contributes to the liability of developing pelvic floor disorders, but environmental effects are substantial.
- Childbirth is associated with an increased risk for pelvic organ prolapse later in life. Current evidence also suggests that increasing number of childbirths increases the risk (level 2 evidence).
- It remains undecided if caesarean section prevents the development of pelvic organ prolapse but most studies indicate that caesarean is associated with a decreased risk for subsequent pelvic floor morbidity in comparison to giving vaginal birth (level 2 evidence).
- There is a dearth in the understanding of how specific obstetrical events and the process of labor and delivery affect the risk for pelvic organ prolapse.
- Lifestyle factors and socio-economic indices appear to be associated with the risk for pelvic organ prolapse.
- A number of somatic diseases and conditions have been linked to the occurrence of prolapse, but the cause-effect relationship is undetermined.

Incidence

Only two studies that reported the incidence of new POP could be located. Both studies were done on subgroups of women enrolled in the WHI Oestrogen Plus Progestin Trial. The first study of 412 women enrolled at the University of California, Davis site used a standardized pelvic examination repeated every 2 years over 8 years (Handa et al, 2004). The incidence of new cystocele, rectocele, and uterine prolapse was 9%, 6%, and 2%, respectively. Annual rates of remission from grade 1 (prolapse to above introitus) were relatively common for each type of POP (24%, 22%, and 48%, respectively) but less common from grade 2 or 3 (prolapse to or beyond introitus) (9%, 3%, and 0%, respectively). In a second study of 259 women, postmenopausal women with a uterus were examined using the POP-Q at baseline and annually for 3 years. POP was defined as prolapse to or beyond the hymeneal ring. The incidence of new POP was 26% at 1 year and 40% at 3 years, with remission rates of 21% at 1 year and 19% at 3 years (Bradley et al, 2007).

Several studies have reported the annual incidence of surgery for POP in the United States and at least one in the United Kingdom. A longitudinal study of more than 17,000 women in the United Kingdom, age 25 to 39 at baseline, reported an annual rate of prolapse surgery of 0.16% (Mant et al, 1997). This rate is consistent with the rate of approximately 0.2% per year reported in the United States (Brown et al, 2002; Boyles et al, 2003). One U.S. study reported an annual incidence rising with age from 0.05% in women age 30 to 39 to 0.5% in women age 70 to 79 with an estimated lifetime cumulative risk of surgery from prolapse of 7% to 11% (Olsen et al, 1997). A recent U.S. study reported similar surgical rates: 0.07% for women age 18 to 39, 0.24% for women age 40 to 59, and 0.31% for women age 60 to 79 (Shah et al, 2008). Surgical rates drop substantially after age 80 (Olsen et al, 1997; Shah et al, 2008). Estimating rates of prolapse surgery has the advantage of use of hospital discharge data on procedures, which is highly accurate for the procedure performed but less accurate for the indications for the procedures, particularly when a procedure may have more than one indication.

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The complete reference list is available online at www.expertconsult.com.

chapter
64

Evaluation of Patients with Urinary Incontinence and Pelvic Prolapse

Kathleen C. Kobashi, MD

Definition and Impact of Pelvic Floor Disorders
Diagnostic Evaluation
History
Physical Examination
Supplemental Evaluation
Management
Incontinence Treatment Overview
Pelvic Prolapse Treatment Overview

DEFINITION AND IMPACT OF PELVIC FLOOR DISORDERS

Pelvic floor disorders (PFDs), which include urinary incontinence, fecal incontinence, and pelvic organ prolapse (POP), pose a prevalent worldwide health concern. (For the purposes of this chapter, "incontinence" will refer to *urinary* leakage unless otherwise specified.) **On the basis of 2001-2004 data from the National Health and Nutrition Examination Survey (NHANES), an overall prevalence of incontinence of 49.6% in 4229 women older than age 20 was reported. Of those who reported incontinence, 49.8%, 15.9%, and 34.3% reported pure stress urinary incontinence (SUI), pure urgency incontinence (UI), and mixed incontinence, respectively** (Dooley et al, 2008). Interestingly, there appears to be a racial disparity with regard to pure SUI and pure UI with the odds of pure SUI being at least 2.5-fold higher in white and Mexican-American women than black women (Dooley et al, 2008; Fenner et al, 2008). The NHANES data from 2004-2005 showed that 23.7% of 1961 women described at least one PFD, and the proportion of women who reported a PFD increased with increasing age and body mass index (BMI) (Nygaard et al, 2008).

The overall prevalence of incontinence in community-dwelling men is 17% and varies with age, race, and socioeconomic status (Abrams et al, 2005; Anger et al, 2006). NHANES data revealed an 11% prevalence in those aged 60 to 64 and 31% in men 85 years or older. Daily incontinence occurs in 42% and weekly incontinence in 24%, with only 22% of those who leaked weekly seeking medical care for the problem (Harris et al, 2007). **Unlike in women, there is a prevalence of urgency incontinence (40% to 80%) as compared with mixed incontinence (10% to 30%) or pure SUI (<10%) in men.** Overall prevalence is higher in African-American men (21%) than in white men (16%).

Risk factors for development of POP include advanced age, increased parity (vaginal childbirth), genetic predisposition (Twiss et al, 2007), **estrogen deficiency, compromised pelvic floor muscle strength, and smoking** (Miedel et al, 2009; Samuelsson et al, 2000). Interestingly, recent studies indicate that current or past use of exogenous hormones in the form of oral contraception or hormone replacement therapy may paradoxically serve as a risk factor for the development of urinary incontinence (Samuelsson et al, 2000; Townsend et al, 2009). **In men, comorbidities, poor general health, cognitive impairment, stroke, radiation, urinary tract infections, prostate diseases, and diabetes are all associated with incontinence** (Shamliyan et al, 2009).

One questionnaire study of 4103 women, conducted in a large managed health care plan, found the prevalence of POP to be 6% (Lawrence et al, 2008). This and other studies have evaluated and found a high co-occurrence of PFDs. Lawrence and colleagues (2008) reported a co-occurrence of at least one additional PFD in approximately 80% of women with SUI or overactive bladder (OAB), 69% of women with POP, and 48% of women with anal incontinence. On the basis of the 2005-2006 NHANES data, Nygaard and colleagues (2008) found that the weighted prevalence of at least one PFD was 23.7%, increasing incrementally with age and parity. Although the prevalence of at least one PFD was 9.7% and 49.7% in women between ages 20 and 39 and those aged 80 or older, respectively, the prevalence was 12.8%, 18.4%, 24.6%, and 32.4% for those who had zero, one, two, and three or more deliveries, respectively. De Boer and colleagues (2010) reported a higher prevalence of OAB in patients with POP than in those without POP, although there was no relationship noted to exist between the grade and stage of POP and the presence of OAB symptoms. Wu and colleagues (2009) used U.S. Census Bureau population projections to forecast the change in PFD prevalence in women between 2010 and 2050. The current estimate of 28.1 million women with at least one PFD in 2010 is projected to increase substantially to 43.8 million in 2050.

The impact of PFDs is far-reaching, carrying a significant potential to affect patient quality of life (QoL), notwithstanding the psychologic burden it produces. Additionally, incontinence creates

a tremendous cost to the individual and to society. Hu and colleagues (2004) estimated that the evaluation and management of incontinence and productivity lost due to the condition resulted in a $19.5 billion (year 2000 dollars) cost to society, although sensitivity analysis suggested a potential cost range of between $9.32 and $28 billion. Contemporary numbers might predictably be higher in 2009, although Hu's most recent analysis demonstrated a 26% cost decrease compared with the 1995 report, which estimated $26.29 billion. The decrease was speculated to be due to various factors including decreased hospital stays and adjusted methods of assessing nursing home stays, routine care product use, and prevalence data. Other reports have demonstrated that medical expenditures for incontinence in the female Medicare population nearly doubled between 1992 and 1998, due primarily to increased outpatient expenditure from 9.1% to 27.3% of total Medicare costs in approximately the same time frame (Thom et al, 2005; Anger et al, 2006).

As a result of increasing awareness of the societal impact of PFDs in addition to the growing emphasis on maximizing QoL in our aging population, tremendous research efforts are under way to improve our understanding of the pathophysiology of these disorders, thereby improving both diagnostic and therapeutic techniques. The importance of evidence-based medicine and meticulous follow-up of patients is driving improvement in the science on which advancements in this subspecialty of urology are being made.

DIAGNOSTIC EVALUATION

General Considerations

A recent upsurge in research efforts has resulted in the emergence of new diagnostic and therapeutic techniques to address PFDs. As QoL impact has become a focus, many current research efforts include detailed QoL assessment and attempts to quantify and assess the relationship between PFDs and their effects on QoL. Correlating the bother caused by a given PFD with the risk of available therapies is an important consideration.

The type of incontinence affecting an individual must be defined and quantified in order to guide proper treatment planning. Transient or unrelated conditions that can cause leakage should be identified before proceeding with definitive therapy. Table 64–1 contains a mnemonic of transient causes of incontinence (Resnick, 1984). Table 64–2 lists current International Continence Society (ICS) nomenclature and definitions for types of incontinence (Abrams et al, 2002, 2009b). The terminology continues to adjust to reflect the evolving understanding of the condition. The importance of this flexibility has been realized and acknowledged by leaders in the subspecialty of pelvic floor medicine (Chapple, 2009).

Table 64–1.

Causes of Transient Incontinence (DIAPPERS)

Delerium
Infection (urinary tract infection)
Atrophic vaginitis/urethritis
Psychologic (e.g., severe depression, neurosis)
Pharmacologic
Excess urine production
Restricted mobility
Stool impaction

From Resnick NM. Urinary incontinence in the elderly. Med Grand Rounds 1984;3:281–90.

The classification of POP is categorized according to the affected compartment. Simply put, anterior compartment prolapse (cystocele) generally involves descent of the bladder toward the vaginal lumen, posterior prolapse (rectocele) involves the rectum compressing the posterior vaginal wall into the vagina, and apical prolapse is associated with descent of the uterus (uterine procidentia) and/or the bowel (enterocele) at the top of the vagina. Several grading systems exist to quantify the severity of POP and are discussed later and illustrated in Figure 64–1.

Regarding incontinence specifically, the substantiation of a proper diagnosis requires direct observation of urinary leakage by the clinician (Nitti and Blaivas, 2007). It is the belief of many experts that no patient should undergo invasive or irreversible therapies without definitive establishment of the cause of their incontinence. Complete and extensive evaluation can facilitate accurate diagnosis of PFDs to promote optimal treatment planning and counseling of patients.

HISTORY

A careful history should always be obtained from the patient. However, several studies have indicated that patient history alone is not completely accurate as the

Table 64–2.

Standard International Continence Society Terminology of Lower Urinary Tract Symptoms Pertaining to Continence

TERMINOLOGY	DESCRIPTION
Urinary incontinence	The complaint of any involuntary leakage of urine
Enuresis	Any involuntary loss of urine (should be specified if it is nocturnal)
Urgency	The complaint of a sudden compelling desire to pass urine that is difficult to defer
Urgency incontinence	The complaint of involuntary leakage accompanied by or immediately preceded by urgency
Stress urinary incontinence	The complaint of involuntary leakage on effort or exertion, or on sneezing or coughing
Mixed incontinence	The complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing, or coughing
Continuous urinary incontinence	The complaint of continuous leakage
Other types of urinary incontinence	Situational incontinence (e.g., during sexual intercourse or giggle incontinence)
Dependent continence	Situation in which the individual would suffer a recurrence of incontinence if management was withdrawn
Contained incontinence	Situation in which incontinence is controlled by being contained in an absorbent product or collecting device (previously "social continence")
Overactive bladder	Urgency with or without urgency incontinence usually with increased daytime frequency and nocturia

Data from Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-Committee of the International Continence Society. Neurourol Urodyn 2002;21:167–78 (reprinted in Urology 2003;61:37–49).

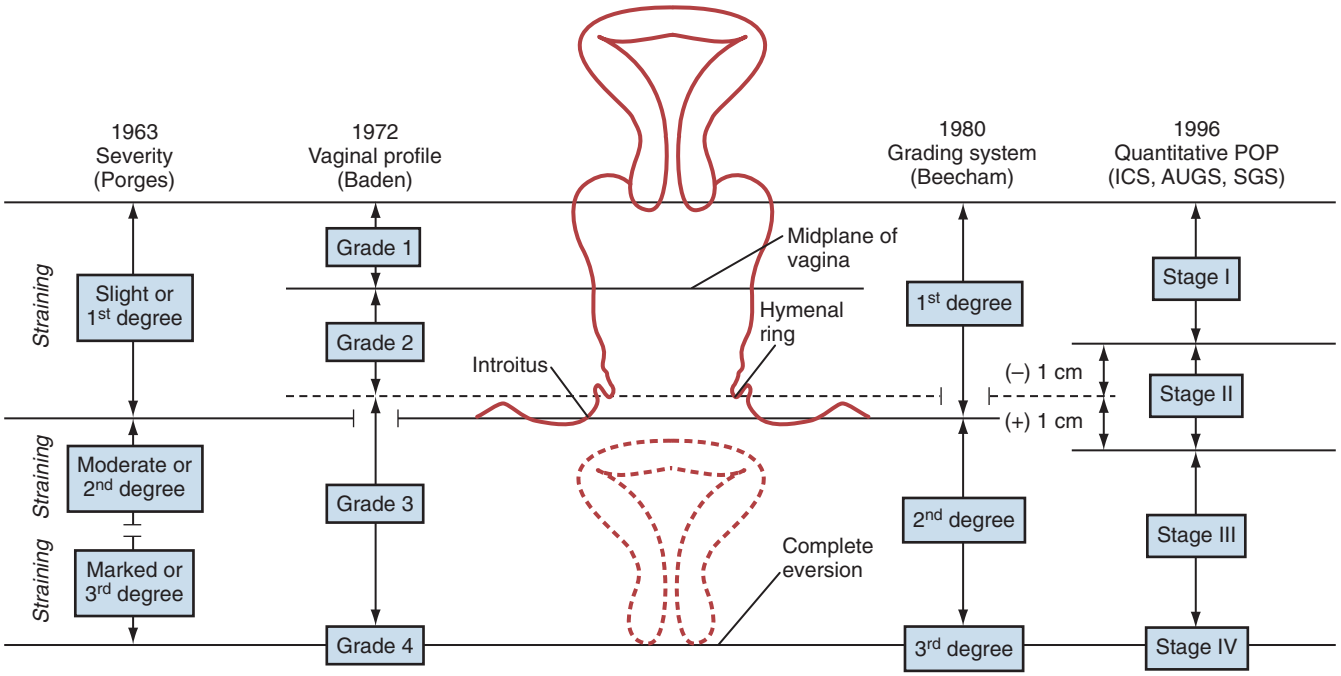


Figure 64–1. Visual comparison of systems used to quantify pelvic organ prolapse (From Theofrastous JP, Swift SE. The clinical evaluation of pelvic floor dysfunction. Obstet Gynecol Clin North Am 1998;25:783–804.)

Key Points: General Considerations

- Pelvic floor disorders (PFDs) are a prevalent worldwide health concern.
- Careful history and physical examination are integral in the proper evaluation of patients with PFDs.
- Supplementary evaluation including urinalysis, postvoid residual, urodynamics, endoscopy, and radiologic imaging can be helpful in arriving at a complete and accurate diagnosis.
- A variety of surgical and nonsurgical treatment options are available for treatment of urinary incontinence and pelvic organ prolapse.

sole determinant of incontinence type (Summitt et al, 1992; Jensen et al, 1994). Bates and colleagues (1973) are credited with the dictum, "The bladder is an unreliable witness," which has been corroborated by many investigators in various forms. **Accordingly, all available information including that which is obtained by supplementary examinations should be integrated into the diagnosis.**

History of Present Illness

A thorough history is imperative in the evaluation of incontinence. Several queries should be included in a continence and pelvic floor history in order to best portray the patient's symptoms (Holroyd-Leduc et al, 2008). **The incontinence should first be characterized subjectively.** Does the leakage occur (1) with physical activity? (2) with a sense of urgency? or (3) without sensory awareness? If the nature of the incontinence is mixed, does one component cause more bother or occur more frequently than the other? **Second, the leakage should be quantified if possible.** Appraisal of the degree of leakage before therapy can be helpful during postoperative assessment of treatment impact. For the purposes of routine outpatient assessment, this quantification can be achieved on the basis of the number of pads used per day or the frequency of clothing changes due to urinary leakage. In the setting of research or an academic practice, more stringent and objective measures such as pad weight testing are often used (see "Supplemental Evaluation" later). **Third, the voiding pattern should be defined.** What is the frequency of urination during the day? During the night? Are there any obstructive symptoms? Does the patient feel as though he or she empties the bladder completely? Is the stream strong or does it "trickle"? Does the stream fluctuate during the void? Is it necessary to push or strain or change posture to void or empty the bladder? **Fourth, establishment of the duration of symptoms and any inciting events that contributed to the onset of leakage is important.** Did the leakage follow a pregnancy or a vaginal delivery? How long ago? Did the leakage start after a strain, a fall, or trauma? Has the patient undergone pelvic or back surgery? In males, has there been any prostate or urethral surgery for benign or malignant disease? Has there been any lower urinary tract instrumentation? Are there any accompanying neurologic symptoms such as numbness or tingling in the extremities, blurry/double vision, balance or coordination changes, or tremor? **Finally, it is helpful to determine the impact that the leakage has on the patient's daily life and activities.** Does the incontinence limit the individual's activity? Has the patient changed his or her lifestyle due to the threat of leakage?

Regarding pelvic prolapse specifically, important questions focus on whether or not the patient is aware of any prolapse and what, if any, symptomatology and bother the prolapse may be causing. Does the patient feel that anything is falling down out of place in the vagina? Does she need to reduce the prolapse for comfort? Or empty her bladder completely? Or facilitate evacuation of her bowels?

Past medical and surgical histories are vital to the assessment of incontinence insofar as medical conditions and surgeries can affect urinary tract function. Childhood and adult urologic history

should be obtained, as should a neurologic history. **Neurologic conditions** such as Parkinson disease, multiple sclerosis, stroke, spinal cord injury, back surgery, and myelodysplasia can have a considerable impact on lower urinary tract (LUT) function. **Medical diagnoses** such as diabetes mellitus and dementia can affect continence. Similarly, a history of **radiation therapy** or neurologic or urologic **trauma** can affect LUT function, specifically with regard to outlet resistance and/or bladder contractility, stability, and compliance. Although outlet resistance may be compromised by trauma or LUT surgery, urethral strictures related to trauma or neurologic dysfunction that abnormally increase outlet resistance during voiding can cause obstruction and secondary symptoms related to the obstruction.

In women the **gynecologic and obstetric history** including gravity, parity, and hormonal status is important. Determination of whether the patient is premenopausal, perimenopausal, or postmenopausal, and whether or not she has used any exogenous hormones such as oral contraceptives or local or systemic hormone replacement therapy can be helpful in her overall assessment. As mentioned earlier, although beneficial effects of local hormone replacement therapy are well-established, there have been reports that exogenous hormone therapy can actually increase the risk of SUI (Townsend et al, 2009).

Clearly, **previous pelvic surgery** can affect LUT function. Anti-incontinence surgery, POP repair, and hysterectomy can contribute to a variety of urinary symptoms in women. Similarly, a history of prostate surgery can give rise to voiding or leakage complaints in men. Abdominoperineal resection can result in neurologic injury that can affect the function of either the bladder or the sphincter (Petrelli et al, 1993), and back surgery can cause a variety of symptoms dependent on the level affected.

Medications

An accurate assessment of medications is critical, particularly in the elderly patient population in whom polypharmacy is common. Many agents can affect urine production, LUT function, and mental status, all of which can have an impact on continence. Special attention should focus on agents that can affect bladder/sphincteric function. Table 64–3 categorizes some commonly used classes of medications by mechanism of action and potential effect on the LUT.

Other

As **genetics** can influence connective tissue integrity, it stands to reason that there may be a potential hereditary role in continence and POP (Twiss et al, 2007). Therefore inquiry about family history of POP may be helpful. Additionally, a thorough review of systems may reveal symptoms that suggest other conditions that could affect pelvic floor function.

Male incontinence, also a prevalent health issue, should be assessed in much the same way as female incontinence, although specific consideration of the impact of the anatomy specific to the male should be considered. **Benign prostatic hyperplasia,** the evaluation of which is covered in detail in Chapter 92, can cause secondary urgency and urgency incontinence in addition to more "typical" obstructive symptoms such as a decreased force of stream, urinary hesitancy, intermittency, and incomplete bladder emptying. **Prostate surgery for benign or malignant disease** can contribute to SUI. With this in mind, full assessment of male LUT symptoms (LUTS) should be performed to facilitate proper treatment planning.

Table 64–3.

Pharmacologic Agents That Can Affect the Lower Urinary Tract

PHARMACOLOGIC EFFECTS	POTENTIAL EFFECTS ON URINARY TRACT
Sympathomimetics	Can increase outlet resistance and exacerbate obstructive symptoms/overactive bladder symptoms Can decrease detrusor contractility and precipitate retention
Sympatholytics	Can decrease outlet resistance and exacerbate stress incontinence
Anticholinergics	Can contribute to urinary retention, particularly in patients with outlet obstruction
Diuretics	Do not affect bladder directly, but because of increased urine production, can aggravate incontinence problems

Key Points: Evaluation—History

- A thorough history is essential in the diagnostic evaluation of patients with PFDs.
- Queries specific to the character, severity, duration, and quantity of incontinence and other symptoms related to pelvic floor function should be presented.
- Attention should be paid to the impact of PFD symptoms on QoL.
- When appropriate, the clinician should present questions specific to the female with potential pelvic organ prolapse and the male with potential prostate issues.
- Queries regarding past medical and surgical history, obstetric and gynecologic history, radiation therapy, trauma, and medications may provide important information.

PHYSICAL EXAMINATION

The general appearance of a patient including details such as age, gait, stature, and fragility can provide important information regarding performance status, neurologic status, and other factors that may direct proper treatment planning. Similarly, an abdominal examination evaluating for incisions, hernias, organomegaly or bladder distention, and habitus is important, particularly if any abdominal surgery may be considered.

Per Medicare coding guidelines (Centers for Medicare/Medicaid, 1997), **a female pelvic examination includes at least 7 of the 11 bullet items listed in** Table 64–4**.** The external genitalia should be evaluated with regard to general appearance, estrogen status, lesions, and labial size and adhesions. **Estrogen status** can be evaluated on the basis of the presence or absence of a urethral caruncle, urethral prolapse, and/or labial adhesions, all of which, if present, may indicate estrogen deficiency. Likewise, attention to the overall tissue appearance and color is important. Hormonally deficient vaginal tissue has a pale, flat, dry appearance with no rugae, as opposed to the healthy, pink rugae of well-estrogenized tissue.

Urethral position and mobility should be assessed at rest and with straining and coughing. The **Q-tip test** was developed to objectify the evaluation of urethral mobility (Bergman and Bhatia, 1987; Walters and Diaz, 1987). The discomfort caused

Table 64–4.

Components of a Focused Pelvic Examination

- Inspection and palpation of breasts (e.g., masses or lumps, tenderness, symmetry nipple discharge)
- Digital rectal examination including sphincter tone, presence of hemorrhoids, rectal masses

Pelvic examination (with or without specimen collection for smears and cultures) including:

- External genitalia (e.g., general appearance, hair distribution, lesions)
- Urethral meatus (e.g., size, location, lesions, prolapse)
- Urethra (e.g., masses, tenderness, scarring)
- Bladder (e.g., fullness, masses, tenderness)
- Vagina (e.g., general appearance, estrogen effect, discharge, lesions, pelvic support, cystocele, rectocele)
- Cervix (e.g., general appearance, lesions, discharge)
- Uterus (e.g., size, contour, positions, mobility, tenderness, consistency, descent or support)
- Adnexa/parametria (e.g., masses, tenderness, organomegaly, nodularity)
- Anus and perineum

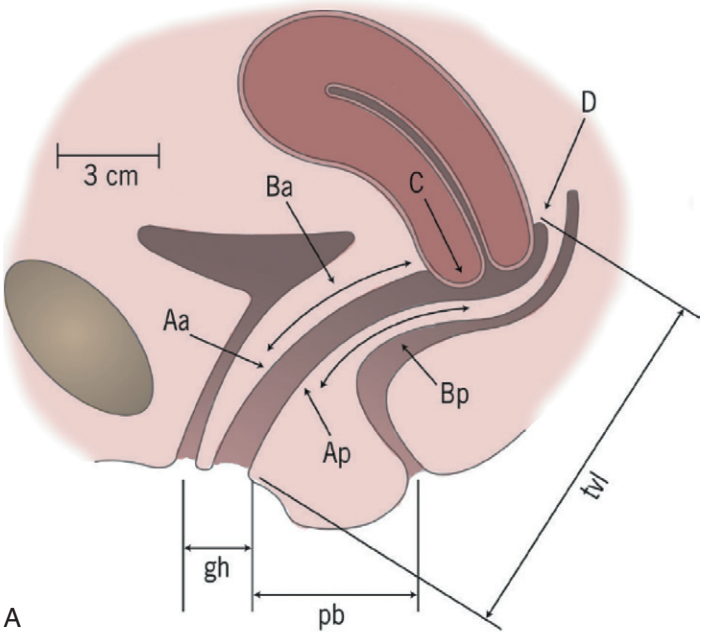
At press time, 7 of 11 bullet points listed above are required to be considered a complete female genitourinary examination. However, other organ systems/body areas not limited to the genitourinary system may be included in a report to accomplish the requirements of various levels of examination.

Data from Centers for Medicare/Medicaid (CMS): Single organ system examination—Genitourinary: 1997 Documentation Guidelines for Evaluation and Management (E/M) Services, jointly approved by the American Medical Association and HCFA with revisions November, 1997.

to the patient during insertion of the Q-tip can be minimized with the use of intraurethral lidocaine jelly. The Q-tip is inserted into the bladder through the urethra, and the angle that the Q-tip moves from horizontal to its final position with straining is measured. Hypermobility is defined as a Q-tip angle of greater than 30 degrees from horizontal.

Assessment of prolapse should ideally be performed in both the lithotomy and standing positions, the latter facilitated by having the patient stand with one foot elevated on a short stool. Each compartment—the anterior, posterior, and apical (uterus/cervix or vaginal cuff)—should be evaluated methodically and the perineal body assessed for laxity. A complete systematic examination is performed using two posterior blades of a split Grave speculum with and without straining. First, one blade is used to retract the posterior wall to facilitate anterior compartment examination. The blade is then repositioned to retract anteriorly for examination of the posterior compartment. Finally, both blades are inserted simultaneously, one anteriorly and one posteriorly, to isolate the vaginal apex and facilitate examination of the cervical or cuff support. The posterior blade is slowly withdrawn to examine the posterior wall. Next, with the posterior blade in place, the patient is asked to strain. Foreshortening of the posterior wall causes expulsion of the blade and suggests a compromise in the level I support (Delancey, 1992) (cardinal-uterosacral ligament complex) of the vault; if the blade remains in place, this could represent an isolated rectocele or enterocele without vault prolapse. Evaluation for occult SUI should be performed with the anterior wall supported. SUI can be masked if significant prolapse "kinks" the urethra and outlet.

Several classification systems are used to quantify POP, the most widely used of which are the **Baden-Walker classification** (Baden et al, 1968) and the **Pelvic Organ Prolapse Quantification system,** known as the "POP-Q" (Bump et al, 1996). The



A

Point	Description	Range of values
Aa	Anterior vaginal wall 3 cm proximal to the hymen	–3 cm to +3 cm
Ba	Most distal position of remaining upper anterior vaginal wall	–3 cm to +tvl
C	Most distal edge of cervix or vaginal cuff scar	–
D	Posterior fornix (N/A if post-hysterectomy)	–
Ap	Posterior vaginal wall 3 cm proximal to the hymen	–3 cm to +3 cm
Bp	Most distal position of remaining upper posterior vaginal wall	–3 cm to +tvl
gh (genital hiatus)	Measured from middle of external urethral meatus to posterior midline hymen	–
pb (perineal body)	Measured from posterior margin of gh to middle of anal opening	–
tvl (total vaginal length)	Depth of vagina when point D or C is reduced to normal position	–

B

Figure 64–2. **A,** Landmarks for the POP-Q system. **B,** POP-Q Points of Reference. (**A,** From Bump RC, Mattiasson A, Bo K, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol 1996;175:10–7.)

two systems are juxtaposed in Figure 64–1. **In the POP-Q system, which was created in an effort to provide objectivity to POP quantification, nine specific points of measurement are obtained in relation to the hymenal ring as illustrated in** Figure 64–2A and B. Six vaginal points labeled Aa, Ba, C, D, Ap, and Bp are measured during Valsalva maneuver. Points above the hymen are considered negative and points below the hymen are positive. The genital hiatus (gh) represents the size of the vaginal opening, and the perineal body (pb) represents the distance between the vagina and the anus. The total vaginal

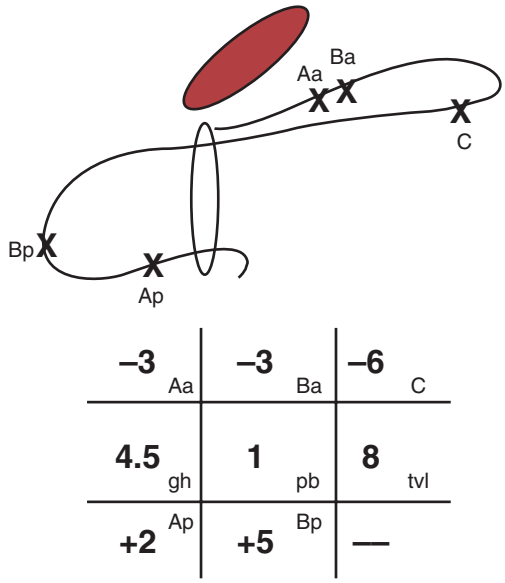


Figure 64–3. Line drawing example of posterior support defect. The anterior compartment is well supported. The leading point of the prolapse is point Bp (+5), which is 5 cm beyond the hymen. Total vaginal length is 8 cm, and point C (–6), the cuff position, has descended 2 cm. (From Bump RC, Mattiasson A, Bo K, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol 1996;175:10–7.)

Table 64–5.

POP-Q Staging Criteria

STAGE	CRITERIA
0	Aa, Ap, Ba, Bp at –3 cm *and* C or D ≤ –(tvl – 2) cm
I	Stage 0 criteria not met and leading edge < –1 cm
II	Leading edge ≥ –1 cm but ≤ +1 cm
III	Leading edge > +1 cm but < +(tvl – 2) cm
IV	Leading edge ≥ +(tvl – 2) cm

length (tvl) is measured by reducing the prolapse and measuring the depth of the vagina. Table 64–5 contains the **POP-Q staging criteria,** a simplified presentation of the POP-Q system, and Figure 64–3 illustrates an example of the application of the system.

A **neurologic examination** is important in any patient with a known or suspected neurologic condition. Attention to the patient's gait, speech, cognitive status, facial symmetry, sensation in the lower extremities, perineal and perianal regions, lower extremity motor strength, and vaginal and pelvic floor strength can provide helpful information. Mobility and cognitive status can play a role in urinary continence insofar as both can affect a patient's ability to reach the facilities in a timely fashion. The **bulbocavernosus reflex (BCR),** which is representative of sacral nerve root levels 2-4 (S2-4), is present in 70% of normal females and 100% of normal males. The BCR is considered positive when squeezing of the glans penis or clitoris results in anal and pelvic floor contraction that can be detected visually or by rectal examination. Alternatively, applying traction to an indwelling Foley catheter to pull the balloon against bladder neck should also precipitate a BCR.

A **digital rectal examination (DRE)** is important in men to assess the prostate for size, nodularity, or tenderness. In the female, the DRE can facilitate assessment of the rectovaginal septum. Demonstration of a rectocele can be facilitated via anterior pressure applied by a finger placed in the rectum. Anal sphincter tone, which is a reflection of the function at S2-4, is particularly important in neurologic patients with PFD. Patients are asked to voluntarily tighten the pelvic floor as if attempting to stop the flow of urine midstream. Laxity in the rectal sphincter tone may suggest a possible neurologic defect, but it may also be due to patient lack of understanding regarding how to voluntarily control the specific muscle groups necessary for contraction.

In men, genitourinary examination as it pertains to voiding function should also include evaluation of the penis for meatal stenosis and, particularly in the post-prostatectomy patient, visible urinary leakage with coughing and straining. Examination for leakage is ideally performed with the patient in the standing position.

Key Points: Evaluation—Physical Examination

- A properly performed physical examination is imperative in the evaluation of patients with PFDs.
- The Centers for Medicare/Medicaid require specific elements of both male and female genitourinary examination in order to meet coding guidelines (see Table 64–4).
- Assessment of pelvic organ prolapse (POP) should ideally be performed in both the supine and standing positions.
- Several classification and quantification systems are available for assessment of POP, the most widely used of which (Baden-Walker and POP-Q) are illustrated in Figures 64–1 and 64–2.
- A neurologic examination and rectal examination should be performed in appropriate patients in order to obtain complete clinical information important in the assessment of lower urinary tract and pelvic floor function.

SUPPLEMENTAL EVALUATION

A variety of measures are available to supplement the history and physical examination in patients with PFDs. Instruments exist to quantify symptoms, their effects on QoL, and the degree of bother experienced by patients with PFDs. **Most experts concur that a urinalysis and postvoid residual measurement should be considered in the majority of patients undergoing evaluation for incontinence. However, beyond this, there are no universally agreed-upon guidelines regarding the roles of other studies, such as endoscopy, urodynamics (UDS), and various modalities of radiographic imaging.** In circumstances in which further investigation is considered, the value and accuracy (sensitivity and specificity) of the information provided by the given assessment method should be considered in relation to the cost and morbidity of the examination.

Symptom Quantification Instruments

Voiding Diaries

Instruments such as voiding diaries, questionnaires, and pad tests have been developed to aid in the quantification of urinary loss, both symptomatically and volumetrically. **Voiding diaries can provide both diagnostic and therapeutic advantages. The use of diaries often helps patients realize their**

pattern of urination and is more accurate than recall (Larsson et al, 1984; McCormack et al, 1992; Siltberg et al, 1997). **Furthermore, the diary can provide patients with insights into those behaviors that can be altered to decrease urinary frequency** (Burgio, 2004).

Several studies have demonstrated the adjunctive role that diaries can have in the diagnosis and management of incontinence. Diaries can be helpful over routine subjective history because patient recall is often not as accurate as a formal voiding diary in ascertaining urinary frequency. In a retrospective review of 601 patients who underwent sling surgery and completed bladder diaries, only 47% were accurate about their daytime frequency; 51% overestimated their diurnal frequency, and this overestimation was exaggerated in those who reported voiding more than 10 times a day (Stav et al, 2009). Overestimation rates were similar between patients with and without overactive bladder (OAB) symptoms. Interestingly, 93% of women in this study were accurate about their nighttime frequency. In another study of women with UI, it was noted that the overestimation of incontinence episode frequency occurred more often in those patients who were more bothered by their incontinence. Conversely, Ku and colleagues (2004) found a poor correlation between subjective nocturnal frequency and that noted by 164 patients on their frequency volume charts. Wyman and colleagues (1987) similarly showed a higher correlation of diary-reported frequency in the daytime versus the night.

Martin and colleagues (2006) performed a meta-analysis of 121/6099 papers that compared two or more diagnostic techniques for incontinence and showed that diaries are most cost-effective when used in conjunction with history, particularly in patients undergoing treatment for detrusor overactivity (DO). It should be noted, however, that diaries should not substitute for more formal studies in select patients. One study that retrospectively assessed the Larsson frequency/volume chart as compared with the cystometrogram in 216 patients demonstrated the sensitivity and specificity of the chart with regard to DO to be 52% and 70%, respectively, and with regard to SUI, 66% and 65%, respectively (Tincello and Richmond, 1998). For daily clinical practice, 24-hour diaries should suffice to obtain valuable clinical information regarding LUT function; in academic studies, longer diaries may be requested, but this should be balanced with the well-established knowledge that the more complex a given instrument is (i.e., the more data requested), the lower patient compliance will be in completing it (Groutz et al, 2000).

Questionnaires and Quality of Life Instruments

Questionnaires can provide a helpful complement to the patient history and patient-reported outcomes (PROs). A plethora of instruments to evaluate symptoms, degree of bother, and QoL in patients with incontinence and PFDs have been developed in an effort to provide optimal assessment of outcomes and to eliminate the confounding issue of physician bias; many have been validated. Table 64–6 contains validated questionnaires highly recommended by the International Consultation on Incontinence (ICI). One such instrument, the modular ICIQ, was developed by the ICI in an effort to collaboratively develop a universally applicable instrument that could be used internationally to assess pelvic floor function in both clinical practice and research settings (Abrams et al, 2005) and has accordingly been translated in 38 languages. The short form of the ICI questionnaire (ICIQ-SF) has been shown to correlate nicely with both the 1-hour (Franco et al, 2008) and 24-hour (Karantanis et al, 2004) pad test for evaluation of the severity of SUI. Another comparison of the 24-hour pad test, the ICIQ-SF, the International Prostate Symptom Score (IPSS), and the Postoperative Patient Global Impression of Improvement (PGI-I) score in 26 men following perineal sling placement confirmed the construct validity of these instruments (Twiss et al, 2007). There was a strong correlation demonstrated between the ICIQ-SF and PGI-I scores and the percentage reduction in 24-hour pad weight. Appendices 1 to 6 on the Expert Consult website contain the ICIQ-MLUTS (male LUTS), ICIQ-FLUTS (female LUTS), ICIQ-SF (short form), ICIQ-OAB (overactive bladder), ICIQ-VS (vaginal symptoms), and the recently developed ICIQ-B (bowel). At the time of this writing, additional modules covering QoL, sexual function, pediatric LUTS, neurogenic LUTS, nocturia, and bowel function are available or are in development and are or will be available through the ICI (2010).

A study examining the incontinence- and nonincontinence-related pelvic floor symptoms evaluated by two widely used symptom tools, the UDI-6 and the ICIQ-UI, demonstrated that both symptom questionnaires were sound and correlated with each other and independently with the QoL scores, as measured by the IIQ-7 and IQOL (van de Vaart et al, 2010). This study also uncovered the interesting finding that the delay in time to consultation with a physician was associated with greater bother, emphasizing the importance of heightened awareness of PFDs in the female patient population.

In Martin's meta-analysis, two studies showed a high sensitivity (0.82 to 0.92) of question 3 in the Urogenital Distress Inventory for SUI; the specificity was 0.51 to 0.69 (Martin et al, 2006). In this study, history alone had a pooled sensitivity of 0.92 (95% CI) and a specificity of 0.56 for the diagnosis of SUI and a sensitivity of 0.61 and specificity or 0.87 for the diagnosis of DO. **It should be borne in mind, however, that for higher-risk interventions such as surgery, the most accurate testing available remains multichannel UDS studies.**

Pad Tests

Pad tests are generally used for academic purposes. **The ICS recommends both a three-day bladder diary and pad weight test as proper measures for symptom quantification in incontinence research** (Lose et al, 2001). However, although pad tests can be helpful in quantifying leakage, they are tedious and cumbersome for the patients. Moreover, they do not provide information that is necessary for daily routine clinical practice. **The Fourth ICI Committee on initial assessment did not recommend pad tests as part of the initial evaluation in the incontinent patient** (Staskin, 2009). **From an *academic* standpoint, however, many investigators advocate for pad tests in clinical trials because pad tests can provide objective, precise information for assessment of actual volume of urine lost over an established period of time.**

According to the Third ICI, greater than 1.3 g of urine loss is considered a "positive" 24-hour pad test (Tubaro, 2005), **whereas others consider up to 8 g of urine loss in 24 hours to be normal** (Lose et al, 1989). Vaginal secretions should also be taken into consideration, although the volume attributable to normal vaginal secretions may be as low as 0.3 g in 24 hours (Karantanis et al, 2003). O'Sullivan et al (2004) evaluated 110 women with incontinence with two 1-hour pad tests and 7 consecutive days of 24-hour pad tests. The severity of the leakage

Table 64–6.

Instruments Highly Recommended by the International Consultation on Incontinence (Fourth ICI) for Urinary Incontinence, Overactive Bladder (OAB), Lower Urinary Tract Symptoms (LUTS), and Pelvic Organ Prolapse Patient Reported Outcomes (PRO)

QUESTIONNAIRE	POPULATION	PURPOSE OF INSTRUMENT
Health-Related Quality of Life (HRQOL)		
BFLUTS (Bristol Female Lower Urinary Tract Symptoms Questionnaire) aka ICIQ-FLUTS (Jackson et al, 1996)	Women, incontinence	To assess female LUTS, particularly incontinence, measure impact on QOL and evaluate treatment outcome
DAN-PSS-1 (Danish Prostatic Symptom Score) (Hansen et al, 1995)	Men, BPH	To evaluate males with LUTS suggestive of uncomplicated BPH
ICIQ-UI-SF (ICIQ Urinary Incontinence Short Form) (Avery et al, 2004)	Men and women, urinary symptoms	To assess symptoms and impact of urinary incontinence in clinical practice and research
ICSmale (ICIQ-MLUTS) (Donovan et al, 1996)	Men with LUTS and possible BPH	To provide evaluation of occurrence and bothersomeness of LUTS and their impact on the lives of men with BPH
ICS-QoL (Donovan et al, 1997)	Men with LUTs and possible BPH	To assess impact of LUTS on the lives of men with LUTS
IIQ (Incontinence Impact Questionnaire (Wyman et al, 1988)	Women, UI, SUI	To assess impact of incontinence on HRQOL, primarily in patients with SUI
IIQ-7 (IIQ-short form) (Uebersax et al, 1995)	Women, UI, SUI	To assess impact of urinary incontinence on HRQOL
I-QOL (ICIQ-Uiqol) (Urinary incontinence-specific QoL instrument) (Wagner et al, 1996)	Women, UI	To assess AOL of women with urinary incontinence
KHQ (King's Health Questionnaire) (ICIQ-LUTSqol) (Kelleher et al, 1997)	Men and women, OAB	To assess the impact of LUTS on HRQOL
N-QoL (ICIQ-Nqol; Nocturia QOL) (Abraham et al, 2004)	Men and women	To assess the impact of nocturia on QOL
OABq-SF (Coyne et al, 2002)	Men and women, OAB	Shortened version of OAB-q to evaluate both continence and incontinence symptoms of OAB and their impact on QOL
OAB-q (ICIQ-OABqol) (Coyne et al, 2002)	Men and women with OAB wet and OAB dry	To evaluate both OAB-wet and OAB-dry symptoms and their impact on HRQOL
PRAFAB (Protection, Amount Frequency, Adjustment, Body image) (Hendriks et al, 2007)	Women, UI	To evaluate treatment effects for UI in women
UISS (Urinary incontinence severity score) (Stach-Lempinen et al, 2001)	Women, UI	To assess symptom severity and impact of urinary incontinence on everyday life
Urolife (BPH-QoL9) (Lukacs et al, 1997)	Men, BPH	To assess the impact of BPH and its treatment on the QOL of patients
Screeners		
B-SAQ (Bladder-Self-Assessment Questionnaire) (Basra et al, 2007)	Women	Screening tool for the presence of bothersome LUTS in women
LUSQ (Leicester Urinary Symptom Questionnaire) (Shaw et al, 2002)	Men and women, LUTS	Condition-specific screener of storage LUTS (urgency, frequency, nocturia, and incontinence)
OAB-SS (OAB Symptom Score) (Blaivas et al, 2007)	Men and women, LUTS with and without OAB	7-item tool to measure overall symptom severity due to the 4 index symptoms of OAB
OAB-V8 (OAB Awareness Tool) (Coyne et al, 2005)	Men and women, OAB	8-item screening tool for use in primary care setting to identify patients who may have OAB
QUID (Questionnaire for Urinary Incontinence Diagnosis) (Bradley et al, 2005)	Women, UI and SUI	6-item tool to diagnose SUI and UI
Symptom Bother		
PPBC (Patient Perception of Bladder Condition) (Coyne et al, 2006)	Men and women	To assess patients' subjective impression of their current urinary problems. Developed as a global assessment of bladder condition
UDI-6 (Urogenital Distress Inventory-6/short form) (Uebersax et al, 1995)	Women	To assess LUTS bother, including incontinence, in women
Urgency		
IUSS (Indevus Urgency Severity) (Nixon et al, 2005)	OAB with urgency incontinence, men and women	To quantify the level of urgency associated with each toilet void as measured during standard voiding diaries
POP Symptoms and QOL		
PFDI (Pelvic Floor Distress Inventory) (Barber et al, 2001)	Women	To quantify the symptoms caused by pelvic prolapse
PFIQ (Pelvic Floor Impact Questionnaire) (Barber et al, 2001)	Women	To quantify the effects of pelvic prolapse on quality of life

BPH, benign prostatic hypertrophy; HRQOL, health-related QOL; ICIQ, International Consultation on Incontinence Questionnaire; ICS, International Continence Society; MLUTS/FLUTS, male/female lower urinary tract symptoms; OAB, overactive bladder; QoL, quality of life; SF, short form; SUI, stress urinary incontinence; UI, urgency incontinence.

Data from Staskin DR. In: Patient-Reported Outcome Assessment. Fourth International Consultation on Incontinence, report of Committee 5, part 5B. 2009. p. 363–412.

was analyzed in relation to UDS parameters, age, parity, and pelvic floor muscle strength, showing increased severity with increasing age and parity and in those women who demonstrated DO. The authors proposed that 24-hour loss of 1.3 to 20 g, 21 to 74 g, and greater than 75 g signifies "mild," "moderate," and "severe" incontinence, respectively. Another study of 144 randomly selected Danish women who underwent 24-hour pad testing revealed a similar loss of urine in the self-reported continent and incontinent groups, or 3.1 and 3.3 g, respectively (Ryhammer et al, 1998).

It is generally agreed that the 24-hour pad test is a clinically more useful tool than the 1-hour pad test (Lose et al, 1989; Matharu et al, 2004); in fact, the test-retest reliability and the predictive value of the 1-hour test in the diagnosis of female incontinence has been shown to be poor (Lose et al, 1986; Lose et al, 1988; Simons et al, 2001; Constantini et al, 2008). Others have advocated the opposite extreme, suggesting that a 20-minute pad test with a standardized bladder volume of 250 mL instilled into the bladder via catheterization had superior sensitivity as compared with the 1-hour test conducted via the ICS standardized method of pad testing (Wu et al, 2006). The ICS method, described in 1988, requires the patient to drink 500 mL of sodium-free liquid in 15 minutes followed by a 30-minute resting period before proceeding with the recommended physical activity (Abrams et al, 1988). One potential concern about this method is the lack of standardization of bladder volume.

Parenthetically, pad use per day (PPD) obtained via patient history is a measure frequently used to quantify urine loss, but one study demonstrated that this is an unreliable measure of incontinence (Dylewski et al, 2007). A retrospective chart review of 145 males and 116 females who underwent artificial urinary sphincter placement and sling surgery, respectively, and who had completed a self-reported pad-use query was performed, and the patients were asked to bring three pads into their clinic visit: one dry "reference" pad and the incontinence pads used for the 24-hour periods preceding and including the day of their visit. The pads were quantified and weighed to determine the grams of urine per pad (GPP). All patients also underwent a 24-hour pad weight test. Only a weak correlation was found between reported pad usage and the 24-hour pad weight, with pad usage measuring only 38% of the variability of incontinence volume. Additionally, although the PPD decreased, the GPP increased with increasing age.

Dye Testing

Dye testing can be helpful to verify that the leakage represents urine versus another fluid such as vaginal discharge or peritoneal fluid and to substantiate the diagnosis of urinary tract fistulae. **Oral phenazopyridine** 200 mg three times a day colors the urine orange, and this simple test can confirm that the leaking fluid is indeed urine. Diagnosis of a vesicovaginal or urethrovaginal fistula can be supported by blue or orange staining of an intravaginal tampon following **intravesical instillation of methylene blue or phenazopyridine hydrochloride (Pyridium) dissolved in sterile water or saline.** In the case of a suspected *ureter*ovaginal fistula, **intravesical methylene blue with concurrent oral Pyridium** can elucidate the fistula location on the basis of the staining pattern on the vaginal tampon. Orange staining suggests a ureteral communication, whereas blue staining connotes a bladder communication (Raghavaiah, 1974). The clinician must keep in mind that simultaneous vesicovaginal and ureterovaginal fistulae can occur.

Key Points: Supplementary Evaluation

- It has been demonstrated that patient subjective history alone often does not reflect an accurate or complete picture of their symptomatology complex.
- Several instruments designed to facilitate symptom quantification have been developed and include tools such as voiding diaries, symptom and QoL questionnaires, and pad tests.
- Voiding diaries can be both diagnostic and therapeutic because they can provide patients with insights into behaviors that may be contributing to their voiding symptoms.
- Pad tests may be helpful, particularly in the academic setting, to quantify incontinence symptoms. Loss of up to 8 g of urine in 24 hours may be considered normal, although the International Consultation on Incontinence (ICI) considers loss of greater than 1.3 g to be a positive 24-hour test.
- Validated questionnaires are available to assess symptoms and quality of life in patients with PFDs.

Urinalysis

It is generally agreed that urinalysis plays a fundamental role in the evaluation of the incontinent patient or the patient with lower urinary tract symptoms (LUTS) (Abrams et al, 2009a). The urinalysis provides information such as the presence of hematuria, pyuria, glucosuria, or proteinuria that can be indicative of conditions that can cause *secondary* incontinence. As indicated by the screening dipstick analysis, a microanalysis and/or culture should be performed that may provide guidance regarding further testing or therapy for conditions related to or independent of urinary incontinence.

Postvoid Residual

The volume of urine left in the bladder following routine voiding is termed the postvoid residual (PVR) and should be evaluated in all incontinent patients (Tubaro, 2005; Gormley, 2007). This simple test, which can be performed via in-and-out catheterization or using noninvasive transabdominal ultrasonography, evaluates the bladder's emptying ability and can be helpful in the diagnosis of overflow incontinence. **It is also essential to establish baseline bladder emptying, particularly in stress incontinent patients who may be considered for an anti-incontinence procedure or patients with urinary urgency who may be candidates for therapies aimed at decreasing bladder contractility.**

A number of studies have demonstrated that ultrasound is comparable to catheterization in evaluating the PVR, although **there are no officially established volumes that define normal or impaired emptying.** The Agency for Healthcare Policy and Research (AHCPR) suggests that PVR less than 50 mL represents adequate emptying and PVR greater than 200 mL represents inadequate emptying (U.S. Department of Health and Human Services, 1992). There is no consensus recommendation regarding the significance of PVR between 50 and 200 mL. In one study, Gehrich and colleagues (2007) enrolled 96 healthy women who presented for routine "well-women" checkups. Exclusion criteria included urinary incontinence more than twice a week, urinary retention, neurologic disease, or symptomatic POP. The mean and median PVRs were 19 mL (0 to 145 mL) and 24 ± 29 mL. Fifteen percent

had PVR greater than 50 mL, and 95% had PVR less than 100 mL. Another study compared PVR measurements obtained by 3-D bladder scan versus catheterization in 170 women who were undergoing evaluation for SUI but who had never undergone previous pelvic surgery (Tseng et al, 2008). In addition, 35.5% had PVR greater than 50 mL and 15.9% had PVR greater than 100 mL. Ultrasound offered a sensitivity of 64.7% and a specificity of 94.3% in detecting PVR greater than 100 mL. Although several studies support the accuracy of the bladder scan (Al-Shaikh et al, 2009), some suggest that certain sonographic devices may provide more accurate information than others (Ghani et al, 2008).

Cystoscopy

Endoscopic examination of the bladder is important as a means to evaluate for intravesical or intraurethral pathology that may be contributing to the patient's symptomatology. Bladder tumors, bladder stones, cystitis, and intravesical or intraurethral foreign bodies such as mesh or suture can contribute to irritative voiding symptoms, recurrent urinary tract infections (UTIs), and incontinence. Patients with a history of previous pelvic floor reconstructive surgery should be evaluated for eroded materials into the LUT. The ureteral orifices should be identified and evaluated for morphology, position, number, and efflux. The bladder mucosa is examined for trabeculation (which can be indicative of bladder outlet obstruction [BOO] and/or overactivity) and estrogen status, and the urethra is assessed for foreign bodies, stricture, diverticulum or fistula, and position.

The role of preoperative cystourethroscopy has been addressed by few authors. Anger and colleagues (2007) analyzed Medicare claims data to assess the effects of preoperative cystoscopy and UDS studies on sling outcomes. The data of a random 5% sample of Medicare beneficiaries during an established 18-month period were used to assess the likelihood of undergoing postoperative studies in those who did and did not undergo the same studies preoperatively. Although patients who underwent preoperative cystoscopy were less likely to undergo postoperative cystoscopy (23.4% vs. 35.2%, $P < 0.0001$) or UDS (19.3% vs. 34%, $P < 0.0001$), there were no significant differences in complications or repeat incontinence procedures between the groups. However, Cundiff and Bent (1996) reported that cystoscopy changed the diagnosis and management in 6 of 84 women (7%) who underwent both cystoscopy and UDS for evaluation of LUT dysfunction. Findings included transitional cell carcinoma, cystitis glandularis, intravesical suture, and a urethral diverticulum.

Although the use of routine cystoscopy in the evaluation of the "index" stress urinary incontinence patient is controversial, it should be performed in patients who present with urinary urgency, hematuria, or other irritative symptoms, particularly if they have previously undergone a previous anti-incontinence procedure, pelvic radiation, or pelvic prolapse repair.

Urodynamics

Similar to cystourethroscopy, the routine use of UDS is the subject of much debate; however, one should strongly consider UDS in patients who have failed previous pelvic floor reconstruction or who complain of mixed incontinence, urinary urgency, or obstructive symptoms, and in those who have elevated PVRs or neurologic disease. The benefit of UDS in these situations is to establish baseline bladder capacity, compliance, sensation, stability, and sphincter function before further surgical or therapeutic manipulation. A comprehensive review of UDS is presented in Chapter 62.

LUT function can be simply categorized into storage and emptying. Each of these categories is affected by the bladder (detrusor) and the outlet. **Two main questions should be considered in the evaluation of the incontinent patient: (1) Is the problem at hand a storage issue, an emptying issue, or a combination of the two? *and* (2) Is the etiology of the first question due to a detrusor issue, an outlet issue, or a combination of both?**

"Eyeball UDS" is a simple economically favorable alternative to full multichannel UDS that can be helpful in selected patients. The study can determine bladder sensation, compliance, stability, and capacity, as well as outlet competence and PVR. Following voiding, the patient is placed in the lithotomy position and a Foley catheter is placed and the PVR measured. A 60-mL catheter tip syringe with the barrel removed is placed into the end of the catheter. With the syringe held upright, the bladder is filled with sterile fluid through the syringe. The height of the meniscus above the bladder represents the intravesical pressure. The volumes at first sensation, sensation to void, and strong sensation are recorded. During the filling phase, the meniscus in the syringe is observed for a rise and fall that may represent bladder overactivity or a consistent gradual rise that suggests compromised detrusor compliance. The catheter is removed, and a cough stress test is performed by observing the urethra for incontinence during coughing and straining.

Multichannel UDS offers an extensive evaluation of LUT function. This degree of accuracy is important in a variety of circumstances including when conservative treatment methods fail, when the diagnosis is unclear or when previous diagnostic procedures are inconclusive, in patients with clinical pictures complicated by radiation therapy, neurologic disease, or prior failed pelvic floor reconstruction or anti-incontinence surgery, or when patients describe symptoms that cannot be confirmed by the clinician. A complete UDS study evaluates the ***filling/storage phase*** by filling cystometrogram and the ***voiding/emptying phase*** by uroflowmetry.

Catheters are placed into the bladder and the rectum. The bladder catheter measures the actual pressure within the bladder, termed the *vesical pressure* (Pves). The rectal catheter measures the abdominal pressure (Pabd). The detrusor pressure (Pdet) is a calculated value (Pves – Pabd) that represents the pressure created by the detrusor independent of the influences of intra-abdominal pressure. During the filling phase, the Pdet is expected to remain low and stable to allow for low-pressure bladder filling. Poorly compliant bladders will show a gradual steady rise in the Pdet as the bladder volume increases. Detrusor overactivity is manifest by intermittent and unpredictable rises in the Pdet. During the voiding phase, the Pdet may rise as the urine flows. Many women normally void with virtually no rise in Pdet. High Pdet with low flow during voiding suggests BOO. Inability to produce a flow with no Pdet, particularly when accompanied by abdominal straining (represented by an undulant Pabd), may indicate an atonic or hypotonic detrusor.

Electromyogram (EMG) and fluoroscopic imaging ("videourodynamics," VURDS) are helpful adjuncts to the UDS study in selected patients and are covered in detail in Chapter 62. EMG activity is reflective of the activity of the striated muscles of the urethral and anal sphincters and the perineal musculature and can be measured using either surface electrodes or needle electrodes. Although the latter provides more accurate

readings, the discomfort caused to the patient and the expertise required for the technique render it far less popular than surface electrodes. The coordination of the EMG and detrusor activity is most helpful during the voiding phase, when failure to relax the pelvic floor can be indicative of pathology. Similarly, recruitment of activity should be noted with BCR and increased abdominal pressure, such as occurs during coughing. VURDS can be useful in the demonstration of anatomy in the upright position, and because the bladder and outlet are visualized "real time," VURDS can confirm incontinence in patients in whom the diagnosis is difficult and can provide an accurate measure of leak point pressure. It is also helpful to assess the bladder outlet in patients in whom detrusor-sphincter dyssynergia or primary bladder neck obstruction is suspected. Patients can be evaluated for vesicoureteral reflux (VUR). Assessment of detrusor pressures in the face of reflux can provide important information that would be missed without video-imaging.

Recent attention has been placed on scientifically establishing the role and clinical value of UDS. The worth of a test is not solely in its diagnostic accuracy but also in the improvement of the outcomes of subsequent interventions. UDS is frequently used in the evaluation of patients with PFDs. Suboptimal outcomes of anti-incontinence procedures are generally attributed to intrinsic sphincter deficiency (ISD), DO, or baseline dysfunctional voiding. The deliberation regarding the merit of these theories and the ability of UDS to accurately establish these conditions continues. In a study of 655 women with positive stress tests, 10% did not demonstrate urodynamic-SUI (UDS-SUI) (Nager et al, 2007). A meta-analysis based on a Medline search of the literature between 1975 and 1998 suggested that UDS has a positive predictive value (PPV) of only 56% and 79% for pure SUI and SUI with other abnormalities, respectively, while a positive cough test has PPVs for the same of 55% and 91%, respectively (Harvey and Versi, 2001). The Urinary Incontinence Treatment Network (UITN) reported that UDS did not predict postoperative voiding dysfunction or the risk for need of postoperative surgical intervention (Lemack et al, 2008). In another retrospective study in women who underwent retropubic midurethral sling placement for treatment of mixed incontinence, the median opening detrusor pressure was higher in women with postoperative DO than in those with normal postoperative UDS (Panayi et al, 2009).

Much of the literature to date has been limited by the retrospective design and small cohorts of the available studies. The UITN found that the success of anti-incontinence surgery in patients who demonstrated UDS-SUI was nearly twice that of those with non-UDS-SUI (type 0 SUI), although this trend did not reach statistical significance (Nager et al, 2008). Similarly, although the study by Anger and colleagues (2007) did not definitively establish an effect of preoperative UDS specifically on sling outcomes, there was a clear demonstration of a twofold (significant) increased likelihood of undergoing postoperative UDS studies in those patients who did not undergo the study preoperatively as compared with those who did.

With healthcare reform increasingly at the forefront of discussion, cost-effectiveness continues to be a subject of great debate. On the basis of decision-analytic (hypothetical) models, one group deemed UDS not cost-effective relative to the basic office evaluation (Weber and Walters, 2000; Weber et al, 2002). However, one must remain mindful that UDS provides information, not only about the overall diagnosis but also regarding important subtle findings that may direct the clinician in treatment planning and counseling (Summitt et al, 1992; Patel and Chapple, 2008). Although it has been suggested that UDS may not be necessary or useful in straightforward, non-neurologic patients who would be considered for initial conservative management (Colli et al, 2003; NICE, 2006), others have shown that up to 20% of patients with presumed pure SUI may have UDS findings that might alter their treatment or outcomes (Digesu et al, 2009).

Reproducibility of UDS studies, as well as the interpretation of the examination, has been questioned by several studies (Van de Beek et al, 1997; Gupta et al, 2004; Zimmern et al, 2006; Gacci et al, 2007). Others have demonstrated that intraobserver (interpretation repeated by the same individual) interpretation is superior to interobserver (same study read by two different individuals) interpretation for both pressure-flow analyses (Digesu et al, 2003) and filling/voiding studies (Whiteside et al, 2006). Still others have demonstrated no difference in interobserver and intraobserver interpretation, but that live interpretation of a study provides different readings than post hoc interpretation, suggesting that intangible experiential factors may play a role in the interpretation of UDS studies (Smith et al, 2009).

Approximately 40% of patients with POP describe SUI symptoms (Grody, 1998), **and UDS-SUI is demonstrated in 70% to 75% of prolapse patients** (Roovers and Oelke, 2007). **Occult SUI unmasked by reduction of prolapse is reported to be present in 36% to 80%** (Richardson et al, 1983; Bergman et al, 1988; Chaikin et al, 2000), and **11% to 50% of clinically continent patients will develop de novo SUI following repair of high-grade prolapse** (Bergman et al, 1988; Borstad and Rud, 1989; Gallantine and Cespedes, 2001). Women who demonstrated preoperative UDS-SUI before sacrocolpopexy were more likely to develop postoperative SUI irrespective of whether they received a concomitant Burch colposuspension (Visco et al, 2008). Conversely, following a retrospective review of the records of 76 patients who underwent POP repair, Roovers and colleagues (2007) reported that no UDS parameters predicted postoperative incontinence. In an effort to determine the need for prophylactic sling placement in patients undergoing surgery for high-grade POP, Ballert and colleagues (2009) followed a UDS protocol designed to address the urethra in a standardized fashion. They concluded that in patients who did not subjectively describe or urodynamically demonstrate SUI preoperatively, the risk of intervention due to BOO following sling placement was equivalent to the risk of intervention for SUI in patients who did not receive a sling.

In select patients, particularly those with OAB symptoms and/or known neurogenic bladder, UDS can be helpful in determining the risk of progression to upper tract deterioration. DO, poor compliance, detrusor–external sphincter dyssynergia (DESD), high detrusor storage pressures, VUR, and BOO all represent potential risk factors or the development of upper tract disease, particularly in those patients with sustained Pdet greater than 40 cm H_20 (McGuire et al, 1981; Blaivas and Barbalias, 1984; Ghoniem et al, 1989, 1990).

Although multichannel UDS remains the most accurate tool with which to evaluate LUT function, it is clear that multiinstitutional randomized prospective studies are of dire importance in addressing many of the unanswered questions regarding the role and contribution of UDS. The accuracy of the study and impact of the findings on treatment outcomes must be established.

Radiographic Imaging

Voiding Cystourethrogram

Standard imaging studies are not necessary in the initial evaluation of women with uncomplicated incontinence

Key Points: Evaluation—Urodynamics

- Urodynamics (UDS) is the most accurate tool available for the assessment of LUT function and provides information regarding urine storage and emptying as they are affected by the bladder and the bladder outlet.
- Although the use of routine UDS for straightforward incontinence is a subject of debate, UDS should be strongly considered before intervention in patients who have a complex clinical picture due to failed previous treatment or surgery, mixed incontinence, obstructive symptoms, neurologic disease, or other medical conditions that may contribute to the LUT function such as diabetes mellitus, pelvic prolapse, or history of radiation therapy.
- "Eyeball UDS" may provide a rough picture of the bladder capacity, sensation, stability, compliance, and outlet resistance when formal UDS is not available.
- Multichannel UDS offers extensive evaluation of LUT function. It involves direct measurement of bladder and intra-abdominal pressure (Pves and Pabd, respectively) and a calculated assessment of detrusor pressure independent of abdominal pressure (Pdet). Pves – Pabd = Pdet.
- Fluoroscopic imaging provides useful adjunctive information such as the position and status of the bladder base and bladder neck, the presence of vesicoureteral reflux, and direct visualization of urinary leakage under real-time circumstances. Video imaging should be considered when the diagnosis cannot be made with certainty without simultaneous understanding of the anatomy in conjunction with the functional findings.

(Artibani et al, 2002; Artibani and Cerruto, 2005). However, **upper and lower urinary tract imaging in patients in whom renal damage or pelvic pathology are suspected should be performed. Voiding cystourethrogram** (VCUG) is optional in patients with recurrent UTIs but can be helpful in the diagnosis of a urethral diverticulum or VUR. VCUG can provide valuable information regarding the contour of the bladder, the presence of VUR, the position of the bladder base with and without straining with the patient in an upright posture, and the position and configuration of the bladder neck during voiding. VCUG can also provide visualization of subtle leakage with coughing or Valsalva maneuver that may be difficult to detect with direct examination.

Ultrasound

Upper tract imaging is recommended in patients with neurogenic detrusor dysfunction considered to be at high risk for renal damage, chronic urinary retention, suspected extraurethral incontinence, and untreated severe POP. The latter group may develop upper tract obstruction and hydroureteronephrosis related to ureteral "kinking" due to the prolapse. **Ultrasonography** provides a noninvasive sensitive and specific method of assessing the upper tracts for hydronephrosis. Ultrasonic imaging of the bladder neck for urinary leakage and descent during stress has also been used to diagnose SUI with documented pooled sensitivity and specificity rates in the range of 0.84 to 0.89 and 0.82 to 0.89, respectively (Martin et al, 2006).

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has been proposed as an ideal method by which to evaluate the anatomy of the bladder neck and urethra with good correlation with functional studies (Macura, 2006; Macura and Genadry, 2008; Macura et al, 2006). MRI has also been advocated for evaluation of pelvic floor relaxation and POP (Boyadzhyan et al, 2008), particularly in patients undergoing evaluation for complex multicompartmental pelvic floor reconstruction (Macura, 2006; Boyadzhyan et al, 2008), and has been shown to identify changes related to the uterosacral ligaments before and following surgical repair of prolapse (Martin et al, 2006). MRI may also be helpful in identifying those patients in whom a urethral diverticulum may be present. Although urethral diverticula can cause symptoms of urinary leakage, pelvic pain, obstructive voiding symptoms, recurrent urinary tract infections, dyspareunia, and a multitude of nonspecific symptoms, up to 20% of diverticula may be completely asymptomatic (Rovner, 2007). In patients with complaints of SUI who are found to have a urethral diverticulum, a simultaneous anti-incontinence surgery can be offered, in which case proper radiographic imaging such as that which can be obtained with MRI can provide anatomic information germane to optimal surgical planning.

High-resolution MRI allows detailed visualization of the urethra, external sphincter, and supporting structures. Magnetic resonance evaluation focusing specifically on the muscle volume of the sphincter, defects in the sphincteric musculature, funneling of the bladder neck, asymmetry of the pubococcygeus muscle or urethral supporting ligaments, increase in the size of the retropubic space or urethrovesical angle, and abnormal vaginal shape may be helpful in the diagnosis of SUI due to ISD or urethral hypermobility (Macura, 2006). To facilitate assessment of POP using MRI, the HMO (H-line, M-line, organ prolapse) system was developed (Pannu et al, 2000).

Evaluation is performed using rapid half-Fourier T2-weighted images in the midsagittal plane during maximal patient straining. Three fixed points are in the HMO system: **A**, the inferior margin of the pubic symphysis, **B**, the posterior levator plate, and **C**, the junction between the first and second coccygeal segments. Two fixed reference points include the pubococcygeal line ***(PCL)***, drawn between points A and C, and point B. ***Line H***, drawn between A and B, represents the anterior-posterior hiatal dimension. ***Line M***, which is the shortest distance between point B and the PCL, represents the degree of pelvic descent. The ***O component*** comprises the shortest distance between the H line and the most caudal aspect of the evaluated organ during Valsalva maneuver. Prolapse is graded on the basis of the organ location relative to the H-line in centimeters.

Dynamic MRI can provide integral information in the preoperative assessment of POP, particularly in patients in whom the pelvic examination is difficult and inconclusive. The sensitivity, specificity, and positive predictive value (PPV) of MRI for cystoceles has been reported to be 70% to 100%, 83% to 100%, and 97% to 100%, respectively; 42% to 100%, 54% to 81%, and 33% to 60%, respectively, for vaginal vault prolapse; 87% to 100%, 80% to 83%, and 75% to 91%, respectively, for enteroceles; 83%, 100%, and 100%, respectively, for uterine prolapse, and 87%, 72%, and 66%, respectively, for rectoceles (Gousse et al, 2000; Deval et al, 2003). Other authors have found that dynamic MRI does not correlate well with clinical findings in patients with middle compartment (i.e., apical) prolapse, and much of the literature suggests that the study should be used only as an adjunct to clarify anatomy in complex cases (Cortes et al, 2004) or under investigational circumstances (Tubaro, 2005). Similarly, many authors agree that the posterior compartment is not as easily visualized on dynamic MRI. A study using intrarectal air during MRI did not demonstrate any value of dynamic MRI for

evaluation for rectoceles over videoproctography, the latter of which was more sensitive in identifying rectoceles (Matsuoka et al, 2001). For optimal visualization of rectoceles, intrarectal gel is used to provide hyperintensity on T2-weighted images (Macura 2006; Boyadzhyan et al, 2008; Law and Fielding, 2008).

MANAGEMENT

Incontinence Treatment Overview

The approach to treatment of incontinence is contingent on a clear understanding of the etiology and pathophysiology underlying the patient's symptoms. The clinician must first determine whether the cause of the symptomatology complex is a bladder or an outlet problem or, not uncommonly, a combination of both. Therapeutic options should be considered with the goal of providing an individualized patient-directed treatment plan on the basis of the patient goals and risk-benefit and cost-benefit ratios.

Management of incontinence can be categorized into nonsurgical and surgical options. Underlying causes such as UTI, BOO, bladder stones, foreign body, or bladder tumor should be identified and addressed first. Table 61–3 in Chapter 61 provides an overview of the treatment options available for the management of incontinence; a detailed review of the various therapeutic options is presented in Chapters 68 through 79.

Treatment of incontinence must be tailored to the patient's needs, goals, and expectations and requires proper counseling on the part of the clinician. Some patients may be satisfied with protective garments and/or urine collection devices such as indwelling or condom catheters or barriers such as urethral plugs or external occlusion devices. Intervention for patients with urgency incontinence may range from behavioral and dietary modification to biofeedback or pharmacotherapy. Sacral neuromodulation, off-label botulinum toxin A detrusor injection, and enteric augmentation of the bladder may be considered in patients with refractory symptoms.

Similarly, patients with SUI may benefit variably from conservative measures using pelvic floor muscle exercises, biofeedback, electrical stimulation, and pharmacotherapy. Urethral bulking injection therapy can provide an intermediate option between nonsurgical and surgical therapies, but surgery remains the mainstay of treatment for SUI. Although needle suspensions remain only as a point of historic discussion, retropubic suspensions have persisted as a reasonable treatment option for SUI. However, slings, using a variety of materials, insertion approaches, and anchoring techniques, have effectively become the standard of care for women with SUI. Injection therapy has not proven a particularly viable option for the treatment of male SUI (which occurs most commonly following prostatectomy for treatment of adenocarcinoma of the prostate), and follow-up of the outcomes with male slings is still early. The artificial urinary sphincter (AUS) remains the prevailing treatment option for postprostatectomy incontinence. The AUS has rarely been used for treatment of SUI in women. In the fortunately rare cases of complete urethral devastation, bladder neck closure or urinary diversion can be considered.

PELVIC PROLAPSE TREATMENT OVERVIEW

New techniques have been explored to improve on the traditional pelvic floor reconstructive approaches that depend on the inherently compromised tissues of the POP patient. The use of synthetic and biologic graft materials to improve the integrity and durability of POP repairs have become popularized over the past decade. Novel anatomic approaches and "kits" have been developed and have resulted in a dramatic increase in the number of clinicians participating in pelvic floor reconstruction.

The goal of POP repair is to restore the normal anatomy and function of the vagina and the lower urinary and GI tracts. The decision regarding whether to proceed with a transvaginal or a transabdominal approach is dependent on which of the three compartments is affected, the degree of prolapse, and patient and surgeon preference. Apical prolapse involving the uterus typically results in a hysterectomy, although uterine-sparing techniques can be performed. Posthysterectomy apical prolapse can be addressed transvaginally with a uterosacral ligament suspension or a sacrospinous ligament fixation. Several contemporary devices that aim to facilitate high prolapse reduction have been introduced. Nevertheless, the sacrocolpopexy, a transabdominal approach that can be performed either open or minimally invasively using laparoscopy or robotic assistance, remains the gold standard repair for apical prolapse. A Y-shaped mesh typically composed of polypropylene is attached to the apex of the vagina and bridged to the sacrum to return the vagina to its normal axis.

New techniques of pelvic floor reconstruction continue to emerge parallel with increasing efforts to understand pelvic floor anatomy and function. A comprehensive overview of current surgical management of pelvic prolapse is presented in Chapter 72.

CONCLUSION

The ultimate goal of pelvic floor reconstruction is to restore the normal anatomy and function of the vagina, bladder, and surrounding structures. Proper evaluation of the pelvic floor anatomy and function should theoretically maximize the probability of favorable outcomes. Additionally, with a growing emphasis on QoL-enrichment and a simultaneously increasing cost of health care, economically sound and durable treatments are the aspiration. Accordingly, efforts to develop methods by which to measure symptoms and evaluate outcomes continue. New techniques designed to provide robust, minimally invasive options to achieve this objective have been developed, and as our appreciation of the pelvic floor continues to advance, further approaches will undoubtedly arise.

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chapter 65

Neuromuscular Dysfunction of the Lower Urinary Tract

Alan J. Wein, MD, PhD (Hon), FACS ● Roger R. Dmochowski, MD, FACS

Objectives
General Patterns of Neuropathic Lower Urinary Tract Dysfunction
Disease at or above the Brainstem
Diseases Primarily Involving the Spinal Cord
Disease Distal to the Spinal Cord
Miscellaneous Neurologic Diseases Causing Voiding Dysfunction
Miscellaneous Conditions Definitely, Probably, or Possibly Related to Neuromuscular Dysfunction
Treatment of Neurogenic Lower Urinary Tract Dysfunction: Overview

OBJECTIVES

This chapter begins with a summary of the abnormalities of the micturition cycle produced by different types of neuromuscular disease, injury, or dysfunction. The source material for the central and peripheral factors involved in the physiology and pharmacology of lower urinary tract function (and dysfunction) are thoroughly discussed in Chapter 60. Most chronic voiding dysfunctions secondary to neurologic disease or injury are logical, meaning that they can be inferred from a knowledge of the normal physiology and pharmacology and the type(s) and location(s) of the pathologic process(es). Certain secondary factors that can modify the type of voiding dysfunction seen and that, once established, can cause persistence of a filling/storage or voiding/emptying abnormality, even after the initial precipitating factor or factors have disappeared or been corrected, are considered. The specific types of voiding dysfunction that occur secondary to the most common categories of neuromuscular disease, injury, or dysfunction are then described in detail. Ideally, in any such discussion, the expected states of the following parameters should be described (see Chapter 61 for specific definitions of terms):

- Detrusor activity (normal, overactive, areflexic, impaired contractility)
- Detrusor compliance (normal, decreased, increased)
- Smooth sphincter activity (synergic, dyssynergic)
- Striated sphincter activity (synergic, dyssynergic, bradykinetic, impaired voluntary control, fixed tone)
- Sensation (normal, absent, impaired)

In Table 65–1 an attempt has been made to summarize many of these dysfunctions on the basis of the most common type of abnormal pattern that results from a given disease or injury, insofar as the parameters just listed are concerned. This abbreviated classification is not meant to be all inclusive but simply to indicate that, for the most part, an individual with a specific neurologic abnormality, and voiding dysfunction because of it, will, in general, have the type of dysfunction shown.

The chapter concludes with a general consideration of the principles that should guide the selection of therapy(ies) for the dysfunctions considered. The individual therapies, and potential consequences thereof, are discussed in great detail in other chapters. The types and management of voiding dysfunction in the pediatric age group are specifically covered in Chapters 127 and 128.

As an apology to others in the field whose works have not been specifically cited or not cited as frequently as they could have been, please note that citations have generally not been chosen, except where noted, because of initial publication or original thinking on a particular subject but primarily because of their review or informational content.

GENERAL PATTERNS OF NEUROPATHIC LOWER URINARY TRACT DYSFUNCTION

Discrete neurologic lesions generally affect the filling/storage and emptying/voiding phases of lower urinary tract function in a relatively consistent fashion. This fashion is dependent on (1) the area(s) of the nervous system affected; (2) the physiologic function(s) and the contents and location of the area(s) affected; and (3) whether the lesion or process is destructive, inflammatory, or irritative. The acute dysfunction produced may differ, for a variety of reasons, from the chronic one.

Plasticity

When used in the context of the nervous system and the structures it innervates, **plasticity refers to the inherent capacity to undergo structural and functional modification.** These induced changes can be reflected on a number of levels: (1) structural, (2) metabolic, and (3) neurologic. In addition, the neurologic changes can then be reflected on a number of levels: (1)

Table 65–1.

Most Common Patterns of Voiding Dysfunction Seen with Various Types of Neurologic Disease or Injury*

DISORDER	DETRUSOR ACTIVITY	COMPLIANCE	SMOOTH SPHINCTER	STRIATED SPHINCTER	OTHER
Cerebrovascular accident	O	N	S ±VC	S	There may be decreased sensation of lower urinary tract events.
Brain tumor	O	N	S	S	There may be decreased sensation of lower urinary tract events.
Cerebral palsy	O	N	S	S D (25% of those with detrusor overactivity) ±VC	
Parkinson disease	O I	N	S	S Bradykinesia	
Multiple system atrophy	O I	N †	O	S	Striated sphincter may exhibit denervation.
Multiple sclerosis	O	N	S	S D (30%-65%)	Dyssynergia figures refer to percentage of those with detrusor activity.
Spinal cord injury					
Suprasacral	O	N	S	D	Smooth sphincter may be dyssynergic if lesion is above T7.
Sacral	A	N † (may develop)	CNR O (may develop)	F	
Autonomic hyperreflexia	O	N	D	D	
Myelodysplasia	A	N O	O † (may develop)	F	Findings vary widely in different series. Striated sphincter commonly shows some evidence of denervation.
Tabes, pernicious anemia	I A	N ‡	S	S	Primary problem is loss of sensation. Detrusor may become decompensated secondary to overdistention.
Disk disease	A	N	CNR	S	Striated sphincter may show evidence of denervation and fixed tone.
Radical pelvic surgery	I A	† N	O	F	
Diabetes	I A O	N ‡	S	S	Sensory loss contributes, but there is a motor neuropathy as well.

Compliance: N, normal; †, decreased; ‡, increased.
Detrusor activity: A, areflexia ; I, impaired; O, overactive.
Smooth sphincter: CNR, competent, nonrelaxing; D, dyssynergic; O, open, incompetent at rest; S, synergic.
Striated sphincter: D, dyssynergic; F, fixed tone; S, synergic; ±VC, voluntary control may be impaired.
*See chapter content for percentages of patients with dysfunction.

Key Point: Lesions above the Brainstem

- Neurologic lesions above the brainstem (with rare exceptions) that affect micturition generally result in involuntary bladder contractions with coordinated sphincter function (smooth and striated sphincter synergy). Sensation and voluntary striated sphincter function are generally preserved, but sensation may be deficient or delayed. Detrusor areflexia may, however, occur, either initially or as a permanent dysfunction. Urinary incontinence may occur due to the detrusor overactivity.

Key Point: Complete Spinal Cord Lesions from Spinal Cord Level T6 to S2

- Patients with complete lesions of the spinal cord between spinal cord level T6 and S2, after they recover from spinal shock, generally exhibit involuntary bladder contractions without sensation, smooth sphincter synergy, but striated sphincter dyssynergia. Those with lesions above spinal cord level T6 may experience, in addition, smooth sphincter dyssynergia and autonomic hyperreflexia (see later). Incontinence may occur due to detrusor overactivity, but the outlet obstruction can also cause urinary retention and overflow incontinence.

Key Point: Trauma or Disease below Spinal Cord Level S2

- Patients with significant spinal cord or nerve root trauma or disease below spinal cord level S2 generally do not manifest involuntary bladder contractions per se. Detrusor areflexia is initially the rule after spinal shock, and, depending on the type and extent of neurologic injury, various forms of decreased compliance during filling (usually due to bladder wall fibrosis) may occur. An open smooth sphincter area may result, but whether this is caused by sympathetic or parasympathetic decentralization/defunctionalization (or both or neither) has never been determined. Various types of striated sphincter dysfunction may occur, but commonly the area retains a residual resting sphincter tone (not the same as dyssynergia) and is not under voluntary control.

Key Point: Interruption of the Peripheral Reflex Arc

- The dysfunctions that occur with interruption of the peripheral reflex arc may be similar to those of distal spinal cord or nerve root injury. Detrusor areflexia often develops, low compliance may result, the smooth sphincter area may be relatively incompetent, and the striated sphincter area may exhibit fixed residual tone not amenable to voluntary relaxation. True peripheral neuropathy can be motor or sensory, with the usual expected sequelae, at least initially.

morphologic, (2) neurochemical, (3) electrical, and (4) organizational. Each of these changes can be studied at a variety of different levels, from investigating the end product (e.g., the clinical manifestations) to the initial molecular correlates and the factors that induce or affect them. The chronic clinical manifestations that we associate with a particular voiding dysfunction may, in fact, be the ultimate results of the phenomena that fall under the rubric "plasticity." To a certain point, the changes may be reversible. After a certain point the changes may not be reversible, and thus **plasticity may account for the persistence of clinical symptoms after the initial stimulus for dysfunction has been removed or corrected.** Perhaps the most obvious changes that occur as a result of plasticity are (1) chronic changes in neural organization of the micturition reflex that occur after complete spinal cord transaction above the level of S2 and (2) the changes in peripheral neural organization that occur after damage to or transection of the peripheral parasympathetic innervation of the lower urinary tract. Specific details are contained in the relevant sections of this chapter.

What may be less obvious as a phenomenon related to plasticity are many of the changes that occur subsequent to bladder outlet obstruction. The most obvious changes that occur are those related to muscle and collagen content. However, these are themselves initiated by molecular events that ultimately cause increased contractile protein synthesis and hypertrophic bladder tissue growth (Levin et al, 1995). The initial stimulus might be stretched from overdistention (Cheng et al, 1999) or ischemia, likewise from distention (Chen et al, 1996). Compensation of the bladder smooth muscle cells to initially overcome the increased demand associated with obstruction is associated with alterations in the expression and function of many proteins involved in excitation/contraction coupling and active force generation of bladder smooth muscle (Chacko et al, 1999). Although urodynamic studies reflect obstruction, satisfactory emptying is generally preserved. Changes in the composition of the extracellular matrix occur as well, presumably also caused by an initial stretch stimulus. The ratio of type 3 collagen to type 1 collagen increases, and the localization of type 3 collagen changes as well (within and around some muscle bundle) (Macarak and Howard, 1999). The increase in connective tissue could be related to an increase in certain growth factors emanating from the smooth muscle or to a decrease in the activity of certain metabolic pathways contributing to the breakdown of various forms of collagen (Borer et al, 1999). Ischemia, which itself can be caused by obstruction or atherosclerosis, has also been hypothesized to contribute to remodeling of the extracellular matrix and fibrosis (Azadzoi et al, 1999; Mostwin et al, 2005).

Bladder outlet obstruction has also been postulated to be associated with partial denervation, owing to damage to the intrinsic innervation of the bladder smooth muscle from a combination of pressure and ischemia (Turner and Brading, 1997; Mostwin et al, 2005). With all of these potential adverse changes occurring, it seems almost miraculous that the bladder can maintain its function, but it does for variable periods of time under different circumstances. However, there does come a point when the ability to fill/store and empty is adversely affected, but not necessarily to the same extent. Filling/storage changes seem related primarily to (1) changes in the extracellular matrix, leading to decreased compliance; and (2) to the appearance of phasic bladder overactivity. This overactivity could be myogenic in origin (caused by partial denervation—see Turner and Brading, 1997), or it could be neurogenic and related to another facet of plasticity. Afferent neuroplasticity mediated by nerve growth factors occurs experimentally in response to bladder outlet obstruction, a phenomenon that is inhibited by autoimmunization against nerve growth factor (Steers et al, 1996). The ability to empty can be adversely affected by factors related to neurogenic or myogenic mechanisms. The myogenic mechanisms could include a reversal of the compensatory changes that initially occur (see Chacko et al, 1999) or a breakdown of the structure and function of the proteins that enable the smooth muscle cells to take up, store, and release calcium, affecting the calcium activation of the contractile apparatus (Zderic et al, 1998; Chacko et al, 1999).

Furthermore, these neurogenic changes associated with outflow obstruction may alter the neurotransmitter milieu of the lower urinary tract. In a model of fetal sheep bladder outlet obstruction, ligation of the urachus at midgestation in fetal sheep for 1 month resulted in a shifting of muscarinic, purinergic, and nitrergic mechanisms normally present during fetal development and growth. With outflow obstruction, bladder hypocontractility was induced and contractile forces decreased during stimulated conditions, consistent with denervation and the possibility of atropine resistance. Normal urothelial exerted negative inotropic effects (nitric oxide mediated) were also lost after obstruction. Additionally, loss of compliance resulted in reduced elasticity in the obstructed bladders, consistent with denervation (Thiruchelvam et al, 2003). Other evidence exists suggesting that bladder outlet obstruction alters the milieu of the lower urinary tract. Mirone and coworkers (2007) summarized changes related to bladder outlet obstruction on the ultrastructure of the bladder in prior animal models. These changes include alterations in the cytoskeleton and contractile protein matrix of the bladder, increasing expression of several growth factors and COX-2, swelling and structural destruction of the detrusor mitochondria, augmented extracellular matrix deposition with significant increase of the

type III/I collagen ratio, downregulation of matrix metalloproteinases, and upregulation of tissue inhibitors of metalloproteinases, increased afferent neural activity from epithelial cells due to higher density of mechanosensitive epithelial sodium channels, and activation of normal cell and unmyelinated C fibers. All of these factors appear to be related to bladder dysfunction associated with obstruction.

At this time, one cannot reverse certain precipitating factors for the initiation of voiding dysfunction such as spinal cord transection and peripheral nerve injury.

Thus the fact that the changes resulting from the neuroplasticity induced by these insults are permanent is not surprising. However, **there are instances in which the initiating "cause" of a particular voiding dysfunction can be removed and yet the symptoms do not entirely disappear. This may be another instance in which neuroplasticity is a major factor.** For instance, irritative voiding symptoms fail to disappear in a certain percent of patients with outlet obstruction who undergo surgical correction. Chai and colleagues (1998) found an increased incidence of a positive ice water test in patients with bladder outlet obstruction, indicating the presence of a primitive reflex circuitry capable of mediating an abnormal micturition reflex. Because the ice water test is mediated by C-afferent fibers, the findings support the hypothesis that bladder outlet obstruction is associated with afferent neuroplasticity, detectable in this case by ice water cystometry. Furthermore, persistence of this afferent neural plasticity after relief of the obstruction could account for at least a proportion of the symptomatic treatment failures after urodynamically successful outlet reduction.

Vizzard (1999, 2000a, 2000b, 2000c, 2000d; Qiao and Vizzard, 2004) has written prolifically about various aspects of neuroplasticity, specifically on the occurrence and potential role of such changes in altered lower urinary tract dysfunction after spinal cord injury (SCI) and irritant-induced cystitis. Changes in spinal cord protein expression from retrogradely transported bladder neurotrophic factors could play a role in the neurochemical, electrophysiologic, and organizational properties of the lower urinary tract seen in both of these conditions and could account, in the latter case, for persistence of symptomatic and/or urodynamic abnormalities after the irritating stimulus is removed (e.g., in patients with interstitial cystitis). Those especially interested in this area should consult Vizzard's articles and associated references.

DISEASE AT OR ABOVE THE BRAINSTEM

Cerebrovascular Disease

Cerebrovascular Accident (Stroke)

Cerebrovascular accident (CVA) is a common cause of death and one of the most common causes of disability in the United States and Europe. CVA is the most devastating manifestation of cerebrovascular disease, with an **annual incidence in the United States that has been variably cited as approximately 550,000** (Blaivas et al, 1998a) **and 83 to 160 per 100,000** (Blaivas and Chancellor, 1995a). Approximately one third are fatal, and another third require long-term nursing care (Marinkovic and Badlani, 2001). The prevalence of stroke in persons older than 65 years has been cited as approximately 60 in 1000, and in persons older than 75, 95 per 1000 (Khan et al, 1990). Wyndaele and colleagues (2005) estimate that 1 in 200 individuals will suffer from a CVA. Although CVA is the third leading cause of death in the United States (Marinkovic and Badlani, 2001), approximately 75% of stroke victims survive (Blaivas et al, 1998a) and, of these, only 10% are unimpaired, 40% have a mild residual, 40% have a significant disability, and 10% require institutionalization (Arunable and Badlani, 1993). Thrombosis, occlusion, and hemorrhage are the most common causes of stroke, leading to ischemia and infarction of variably sized areas in the brain, usually around the internal capsule. Marinkovic and Badlani (2001) cite evidence that arterial occlusion is found in 80% of patients.

After the initial acute episode, urinary retention from detrusor areflexia may occur. The neurophysiology of this "cerebral shock" is unclear. After a variable degree of recovery from the neurologic lesion, a fixed deficit may become apparent over a few weeks or months. **The most common long-term expression of lower urinary tract dysfunction after CVA is phasic detrusor overactivity** (Wein and Barrett, 1988; Khan et al, 1990; Fowler, 1999; Wyndaele et al, 2005). **Sensation is variable but is classically described as generally intact, and thus the patient has urgency and frequency with detrusor overactivity. The appropriate response is to try to inhibit the involuntary bladder contraction by forceful voluntary contraction of the striated sphincter. If this can be accomplished, only urgency and frequency result; if not, urgency with incontinence results.**

The exact acute and chronic incidence of any voiding dysfunction after CVA, and specifically of incontinence, is not readily discernable. **The cited prevalence of urinary incontinence on hospital admission for stroke ranges from 32% to 79%, on discharge from 25% to 28%, and some months later, from 12% to 19%** (Brittain et al, 1998). Sakakibara and colleagues (1999), based on their own experience and that of others, estimate that some voiding dysfunction occurs in 20% to 50% of patients with focal brain lesions from tumor and CVA. They cite nocturnal frequency as the most common manifestation, affecting 36% of their patients. Urgency incontinence occurred in 29%, "voiding difficulty" in 25%, urgency without incontinence in 25%, diurnal frequency in 13%, and enuresis in 6%. Acute retention occurred in only 6%. Fowler (1999) cites studies showing that the presence of urinary incontinence within 7 days of a stroke is a more powerful prognostic indicator for poor survival and functional dependence than a depressed level of consciousness. Urinary incontinence at admission was found by Garibella (2003) to have a hazard ratio of 2.8 as a predictor of stroke death at 3 months. Stroke patients who were incontinent had an increased risk of infectious complications and were malnourished, possible confounders of the increased death risk. Patel and colleagues (2001) reported that urinary incontinence was associated with age older than 75 years, dysphagia, visual field defect, and motor weakness. Certain specific types of strokes also appear to be associated with unusual forms of incontinence. Lenticulo-capsular strokes have been noted to be associated with incontinence. Fifty-two percent of patients with strokes in this area of the brain demonstrated poststroke emotional incontinence, which was not related to other aspects of stroke or gender (Kim, 2002). Lesions centrally located in the globus pallidus, especially dorsally located, were more prone to be associated with an emotional incontinence. This area of the brain is noted to have high density of serotonergic fibers, which has been attributed as an explanation as to why this occurs.

Previous descriptions of the voiding dysfunction after CVA have all cited the preponderance of detrusor overactivity with coordinated sphincter activity

(Kolominsky-Rabas et al, 2003; Wyndaele et al, 2005). **It is difficult to reconcile this with the relatively high incontinence rate that occurs, even considering the probability that a percentage of these patients had an incontinence problem before the CVA.** Tsuchida and colleagues (1983) and Khan and colleagues (1990) made early significant contributions in this area by correlating the urodynamic and computed tomographic (CT) pictures after CVA. They reported that patients with lesions in only the basal ganglia or thalamus have normal sphincter function. This means that when an impending involuntary contraction or its onset was sensed, these patients could voluntarily contract the striated sphincter and abort or considerably lessen the effect of an abnormal micturition reflex. The majority of patients with involvement of the cerebral cortex or internal capsule or both were unable to forcefully contract the striated sphincter under these circumstances. Although the authors and others have called this problem "uninhibited relaxation of the sphincter" (Marinkovic and Badlani, 2001), it really is not, but certainly the term does imply that a profound abnormality exists in these patients in the cerebral to corticospinal circuitry that is necessary for voluntary control of the striated sphincter.

Griffiths (2004) has summarized the evidence, obtained by electrical stimulation, positron emission tomography (PET), and functional magnetic resonance imaging (fMRI), implicating Barrington nucleus, the so-called M region, as responsible for coordinated striated sphincter relaxation followed by detrusor contraction (i.e., normal voiding). He summarizes evidence that a second region in the pons—the L region—may be responsible for maintaining striated sphincter tone between voids, although the evidence for this is less convincing. Griffiths (1998), studying the results of single-proton emission computer tomography (SPECT) in a group of geriatric patients with established urinary incontinence, found urge incontinence in approximately 50%; and, in half of these there was reduced sensation of bladder filling, more so in men than in women. True urgency incontinence with reduced bladder sensation was associated with global underperfusion of the cerebral cortex, especially the frontal areas, especially on the right. **Thus there are two possible mechanisms for the incontinence associated with involuntary bladder contractions in patients who have sustained a CVA: (1) impaired striated sphincter control and (2) lack of appreciation of bladder filling and impending bladder contraction.**

Smooth sphincter activity is generally unaffected (synergic) by CVA. Some authors describe striated sphincter dyssynergia in 5% to 21% of patients with brain disease and voiding dysfunction (Sakakibara et al, 1999). This is incompatible with accepted neural circuitry. The authors of this chapter agree with those who believe that **true detrusor–striated sphincter dyssynergia does not occur in this situation. Pseudodyssynergia may indeed occur** during urodynamic testing of these patients (Wein and Barrett, 1982). This refers to an electromyographic (EMG) sphincter "flare" during filling cystometry that is secondary to attempted inhibition of an involuntary bladder contraction by voluntary contraction of the striated sphincter. The guarding reflex is generally intact (Siroky and Krane, 1982).

Detrusor hypocontractility or areflexia may persist after CVA. The exact incidence of areflexia as a cause of chronic voiding symptoms after CVA is uncertain. In our patient population, this is rare, but some estimates place it as high as 20% (Arunable and Badlani, 1993). In a group of incontinent male stroke patients, Linsenmeyer and Zorowitz (1992) found 35% had involuntary bladder contractions with urodynamic evidence of bladder outlet obstruction and 6% had detrusor areflexia. In women in this group, 13% had involuntary contraction with a large residual urine volume and 19% had areflexia. **Poor flow rates and high residual urine volumes in a male with pre-CVA symptoms of prostatism generally indicate prostatic obstruction, but a full urodynamic evaluation is advisable before committing a patient to mechanical outlet reduction, primarily to exclude detrusor overactivity with impaired contractility as a cause of symptoms.**

Key Point: Lower Urinary Tract Dysfunction after CVA

- In the **functional system of classification** (see Chapter 66), the most common type of voiding dysfunction after stroke would then be characterized as a failure to store secondary to bladder overactivity, specifically involuntary bladder contractions. In the **ICS Classification System,** the dysfunction would most likely be classified as overactive neurogenic detrusor function, normal sensation, low capacity, normal compliance, and normal urethral closure function during storage; during voiding the description would be normal detrusor activity and normal urethral function assuming that no anatomic obstruction existed. Treatment, in the absence of coexisting significant bladder obstruction or significantly impaired contractility, is directed at decreasing bladder contractility and increasing bladder capacity (see Tables 61–3 and 61–4).

Other important modifying factors should be considered in the case of these patients. This is generally a problem of the elderly, some of whom have preexistent lower urinary tract pathologic processes. Previously, the problems may have been manageable, but the additional difficulty may make the situation intolerable. As Andrews (1994) notes, other aspects of the brain damage can affect general rehabilitation and control of the lower urinary tract dysfunction. These may include cognitive impairment, dysphasia, inappropriate and aggressive behavior, impaired mobility, and low motivation. Finally, the entire voiding dysfunction may be adversely affected by treatment regimens that concentrate on detrusor overactivity alone (e.g., anticholinergic or antispasmodic therapy). Many such patients are depressed, and confusion and disorientation often result, which compounds the problem. Vigorous pharmacologic therapy of detrusor overactivity with agents that cross the blood-brain barrier and inhibit M_1 receptor function may make these associated problems of mentation worse.

The underlying basic mechanisms of bladder overactivity after CVA remain unclear. Experimental models of middle cerebral artery occlusion have been described, most recently followed by reperfusion to simulate the clinical condition (Pehrson et al, 2003). Shimizu and colleagues (2003) described the development of a rat model involving an electrolytic lesion of the right basal forebrain. Following at least middle cerebral artery occlusion, the overactivity seems to involve glutaminergic, dopaminergic, and γ-aminobutyric acid (GABA)-ergic innervations (Kanie et al, 2000; Yokoyama et al, 2002). In addition, Fu and colleagues (2004) have shown upregulation of proinflammatory cytokines and neuronal nitric oxide synthetase gene in the spinal cord and bladder. Such findings raise interesting theoretic possibilities for pharmacologic management other than or in addition to antimuscarinic therapy.

Brainstem Stroke

Sakakibara and colleagues (1996b) studied 39 patients with brainstem stroke. Nineteen of these had voiding symptoms. The major problems were nocturnal frequency and voiding difficulty in six, urinary retention in eight, and urinary incontinence in three. Problems were more common after damage from bleeding than from infarction. Symptoms did not occur in those with strictly midbrain lesions but occurred in 18% of patients with medullary stroke and in 35% of patients with pontine lesions. Eleven patients were symptomatic and underwent urodynamic study. Detrusor overactivity was found in 8 of the 11 and low compliance in 1. What was interpreted as striated sphincter dyssynergia was reported in 5 of the 11 patients, and what was called uninhibited sphincter relaxation occurred in 3. The authors concluded that lesions of the dorsolateral pons involving the pontine reticular nucleus, reticular formation, and the locus coeruleus were mainly responsible for the micturition disturbances in patients with brainstem lesions and that these findings corroborated the presence of a pontine micturition center in humans, corresponding to the pontine storage and micturition centers reported in animal studies.

Dementia

Dementia is a poorly understood disease complex involving atrophy and the loss of gray and white matter of the brain, particularly of the frontal lobes. Problems result with memory and the performance of tasks requiring intellectual mentation. Associated conditions include widespread vascular disease, Alzheimer disease, Pick disease, Jakob-Creutzfeldt disease, syphilis, heat trauma, and encephalitis. Alzheimer disease is the principal cause of dementia in the elderly (Wyndaele et al, 2005, 2009). **When voiding dysfunction occurs, the result is generally incontinence. It is difficult to ascertain whether the pathophysiology and considerations are similar to those in the stroke patient or whether the incontinence reflects a situation in which the individual has simply lost the awareness of the desirability of voluntary urinary control.** Even if the person has voluntary sphincter control, such individuals may void when and where they please, because mentation fails to dictate why they should not. Such activity may be caused by detrusor overactivity or an otherwise normal, but inappropriately timed, micturition reflex. An accurate estimate of the prevalence of dementia-associated incontinence is confounded by the difficulty in distinguishing this from age-related changes in the bladder and from other concomitant diseases, as pointed out by Wyndaele and colleagues (2005, 2009), who cite figures of 30% to 100%. Treatment is obviously difficult without a desire for improvement. Additionally, therapy that inhibits muscarinic brain receptors may be contraindicated in Alzheimer disease if current theories about its etiology are valid (cortical cholinergic loss).

Traumatic Brain Injury

Traumatic brain injury has been cited as the most common form of severe neurologic impairment as a result of trauma (Blaivas and Chancellor, 1995a). **When voiding dysfunction occurs, there may be an initial period of detrusor areflexia. With lesions above the pontine micturition center, involuntary bladder contractions are the most frequent manifestation of chronic lower urinary tract dysfunction. Coordinated sphincter function is the rule. In patients who have more isolated brainstem injuries with involvement below the pontine micturition center, detrusor striated sphincter dyssynergia may occur in addition.**

Chua and colleagues (2003) assessed 66 males and 18 females within 6 weeks of acute traumatic brain injury. Sixty-two percent of patients had urinary incontinence on admission with retention (defined as >100 mL), noted in 9.5%. Sixty-two percent required either indwelling catheters or external collecting devices for urinary maintenance. Urinary incontinence was associated with poor functional status and bilateral lesions, whereas urinary retention was more commonly noted in patients with comorbid diabetes mellitus or fecal impaction. After rehabilitation, 36% remained incontinent (Chua et al, 2003).

Brain Tumor

Both primary and metastatic brain tumors have been reported to be associated with disturbances of bladder function. When dysfunction results, it is related to the localized area involved rather than to the tumor type. **The areas that are most frequently involved with associated micturition dysfunction are the superior aspects of the frontal lobe** (Blaivas, 1985). **When voiding dysfunction occurs, it generally consists of detrusor overactivity and urinary incontinence.** These individuals may have a markedly diminished awareness of all lower urinary tract events and, if so, are totally unable to even attempt suppression of the micturition reflex. **Smooth and striated sphincter activity is generally synergic.** Pseudodyssynergia may occur during urodynamic testing. Fowler (1999) has reviewed the literature on frontal lobe lesions and bladder control. She cites instances of resection of a tumor relieving the micturition symptoms for a period of time, raising the question of whether the phenomenon of tumor-associated bladder overactivity was a positive one (activating some system) rather than a negative one (releasing a system from control). **Urinary retention has also been described** in patients with space-occupying lesions of the frontal cortex, in the absence of other associated neurologic deficits (Lang et al, 1996). Posterior fossa tumors may be associated with voiding dysfunction (32% to 70%, based on references cited by Fowler, 1999). Retention or difficulty voiding is the rule, with incontinence being rarely reported.

Cerebellar Ataxia

This group of diseases involves pathologic degeneration of the nervous system generally involving the cerebellum, but with a possible extension to the brainstem, spinal cord, and dorsal nerve roots (Leach et al, 1982). Poor coordination, depressed deep tendon reflexes, dysarthria, dysmetria, and choreiform movements result because of the cerebellar involvement. **Voiding dysfunction is generally manifested by incontinence, usually associated with detrusor overactivity and sphincter synergia. Retention or high residual urine volume may occur as well. Poor emptying, when present, is most commonly caused by detrusor areflexia, but it may be associated with detrusor–striated sphincter dyssynergia, presumably secondary to spinal cord involvement.** Sakakibara and colleagues (1998b) reported micturitional symptoms in 184 patients with spinocerebellar degeneration. Twenty-nine (15.8%) showed stress urinary incontinence. Although 20 of these 29 also had detrusor overactivity and/or low compliance and/or residual urine, 9 had none of these findings. The authors

speculate that in some such patients, spinal lesions affecting Onuf nucleus and consequently pudendal nerve function were responsible.

Normal-Pressure Hydrocephalus

This is a disease of progressive dementia and ataxia occurring in patients with normal cerebrospinal fluid pressure and distended cerebral ventricles but with no passage of air over the cerebral convexities by pneumoencephalography (Blaivas, 1985). When voiding dysfunction occurs, it is generally incontinence secondary to detrusor overactivity with sphincter synergia.

Cerebral Palsy

Cerebral palsy (CP) is the name applied to a nonprogressive injury of the brain in the prenatal or perinatal or postnatal period (generally during the first year of life, but some say up to 3 years) that produces neuromuscular disability and/or specific symptom complexes of cerebral dysfunction. The etiology is generally infection or a period of hypoxia. Affected children exhibit delayed gross motor development, abnormal motor performance, altered muscle tone, abnormal posture, and exaggerated reflexes. **Most children and adults with only CP have urinary control and what seems to be normal filling/storage and normal emptying.** The actual incidence of voiding dysfunction is somewhat vague because the few available series report findings predominantly in those who present with voiding symptoms. Andrews (1994) estimates that a third or more of children with CP are so affected. Roijen and colleagues (2001) surveyed children and adolescents from six rehabilitation centers and cited the prevalence of "primary urinary incontinence" as 23.5%. The most important factors influencing the occurrence of incontinence were spastic tetraplegia and low intellectual capacity. Wyndaele and colleagues (2005, 2009) cite the occurrence of lower urinary tract dysfunction as 36%. When an adult with CP presents with an acute or subacute change in voiding status, however, it is most likely unrelated to CP.

Reid and Borzyskowski (1993) described findings in 27 patients, aged 3 to 20 years, referred for voiding dysfunction. Incontinence (74%), frequency (56%), and urgency (37%) were the most common presenting symptoms, and detrusor overactivity was the most common urodynamic abnormality (87% of those undergoing urodynamics), with 25% of these exhibiting apparent striated sphincter dyssynergia. Mayo (1992) reported on 33 CP patients referred for evaluation, of whom 10 were older than 20 years. Difficulty urinating was the predominant symptom in about half the patients, but half of these also had overactivity and urgency when the bladder was full. The cause of the difficulty in voluntarily initiating micturition was thought to be a problem with relaxing the pelvic floor and not true striated sphincter dyssynergia. Incontinence was the major presenting symptom in the other half, associated in 14 of 16 with detrusor overactivity; all exhibited normal voiding otherwise. Decreased sensation was reported in 17 of 23 patients younger than 20 years of age and in 4 of 10 older than 20. The more serious manifestations such as retention were found only in the adults, prompting the author to suggest that difficulty urinating may progress in adulthood.

Reid and Borzyskowski (1993) note that incontinence can be significantly improved in most CP patients and that, in their experience, intellectual delay is not a barrier to successful management. However, one special problem that is encountered in some of these individuals that makes their management difficult is a severe degree of mental retardation, such that any evaluation or treatment that requires cooperation is virtually impossible. With such individuals, sometimes the best that one can do is to check the upper tracts with renal ultrasonography, measure serum creatinine levels, and obtain an estimate of postvoid residual urine, either by catheterization or ultrasound, and proceed accordingly. **In those individuals with CP who exhibit significant dysfunction, the type of damage that one would suspect from the most common urodynamic abnormalities seems to be localized anatomically above the brainstem. This is commonly reflected by phasic detrusor overactivity and coordinated sphincters. However, spinal cord damage can occur,** and perhaps this accounts for those individuals with CP who seem to have evidence of striated sphincter dyssynergia or of a more distal type of neural axis lesion.

Parkinson Disease

Parkinson disease (PD) is a neurodegenerative disorder of unknown cause that affects primarily the dopaminergic neurons of the substantia nigra but also heterogeneous populations of neurons elsewhere (Lang and Lozano, 1998). The most important site of pathology is the substantia nigra pars compacta, the origin of the dopaminergic nigrostriatal tract to the caudate nucleus and putamen. **Dopamine deficiency in the nigrostriatal pathway accounts for most of the classic clinical motor features of PD.** The classic major signs of PD consist of tremor, skeletal rigidity, and bradykinesia, a symptom complex often referred to as *parkinsonism*. Positron-emission tomography (PET) has shown alteration in brain activation in response to bladder filling in PD. PET revealed changes in nine patients in brain activation associated with detrusor overactivity, specifically in the periaqueductal gray, the supplementary motor area, the cerebellar vermis, the insula, putamen, and thalamus. The most prominent degree of increased activation was noted in the cerebellum, with no change in pons during detrusor overactivity (Kitta et al, 2006).

The role of alterations in dopaminergic receptor subtypes has been assessed in animal models of PD. D-2 agonists and D-1 antagonists appear to result in a reduction of bladder capacity in these models. Brusa and colleagues (2006) studied a group of 87 patients with mild PD who were evaluated by symptomatic change and urodynamics after administration of selective dopaminergic agents. Agents resulting in acute central D-2 stimulation result in bladder capacity and worsened detrusor overactivity, as compared with peripheral dopaminergic antagonists (Brusa et al, 2006). There are causes of parkinsonism other than PD, and in an excellent review, Lang and Lozano (1998) discuss clinical distinguishing features of these other causes of parkinsonism from PD. These other causes consist of (1) multiple system atrophy (MSA: includes striatonigral degeneration, sporadic olivopontocerebellar atrophy, and Shy-Drager syndrome); (2) progressive supranuclear palsy; (3) cortical-basal ganglionic degeneration; (4) so-called vascular parkinsonism; and (5) dementia with Lewy bodies. **The combination of asymmetry of symptoms and signs, the presence of a resting tremor, and a good response to levodopa best differentiates PD from parkinsonism produced by other causes, although none of these is individually specific for PD.** Wyndaele and colleagues (2005) endorse additional criteria for distinguishing lower urinary tract symptoms caused by MSA from those caused by PD. The following suggest MSA: (1) urinary symptoms precede or present with parkinsonism; (2) urinary incontinence; (3) significant postvoid residual; (4) initial erectile failure; and (5) abnormal striated sphincter electromyogram. Five percent of patients initially diagnosed with PD are

found to have Parkinson's Plus Syndromes. These syndromes are characterized by early dementia and/or falls, symmetric symptoms such as a wide-based gait, normal eye movements, autonomic dysfunction, and marked disability. These variants tend to have a worse prognosis than does idiopathic PD. Urinary function is not well described in this subgroup of patients (Nutt and Wooten, 2005).

The "gold standard" for the diagnosis of PD is the neuropathologic examination. In addition to the characteristic pattern of the loss of selected populations of neurons, there is the presence of degenerating ubiquitin-positive neuronal processes or neurites (Lewy neurites) found in all affected brainstem regions. The Lewy body is an intracytoplasmic eosinophilic hyaline inclusion consistently observed in selectively vulnerable neuronal populations, although these are not specific to PD, being found in small numbers in other neurodegenerative disorders. PD affects both sexes roughly equally. The prevalence is cited as 0.3% of the general population and 3% of people older than 65 years (Lang and Lozano, 1998).

Voiding dysfunction occurs in 35% to 70% of patients with PD (Berger et al, 1990; Sotolongo and Chancellor, 1993; Blaivas et al, 1998a; Wein and Rovner, 1999; Wyndaele et al, 2005, 2009). Preexisting detrusor or outlet abnormalities may be present, and the symptomatology may be affected by various types of treatment for the primary disease. **When voiding dysfunction occurs, symptoms generally (50% to 75%) consist of urgency, frequency, nocturia, and urge incontinence.** The remainder of patients have "obstructive" symptoms or a combination. **The most common urodynamic finding is detrusor overactivity.** The pathophysiology of detrusor overactivity most widely proposed (Fowler, 1999) is that the basal ganglia normally have an inhibitory effect on the micturition reflex, which is abolished by the cell loss in the substantia nigra. Whether the dopamine D_1 or D_2 receptor (or both) are primarily responsible does not seem to have been settled as yet. It has been suggested that loss of inhibitory D_1-like receptors causes detrusor overactivity, allowing D_2 receptors to facilitate micturition (Andersson and Wein, 2004). **The smooth sphincter is synergic. There is some confusion regarding EMG interpretation.** Sporadic involuntary activity in the striated sphincter during involuntary bladder contraction has been reported in up to 60% of patients; however, this does not cause obstruction and cannot be termed *true* dyssynergia, which generally does not occur. **Pseudodyssynergia may occur, as well as a delay in striated sphincter relaxation (bradykinesia) at the onset of voluntary micturition, both of which can be urodynamically misinterpreted as true dyssynergia. Impaired detrusor contractility may also occur, either in the form of low amplitude or poorly sustained contractions or a combination. Detrusor areflexia is relatively uncommon in PD.**

It should be recognized, however, that **many cases of "PD" in the older literature may actually have been MSA, and citations regarding symptoms and urodynamic findings may not therefore be accurate.** A good and important example of this is the inference from the publication by Staskin and colleagues (1988) that transurethral prostatectomy (TURP) in the patient with PD is associated with a high incidence of urinary incontinence (because of poor striated sphincter control). Retrospective interpretation (Fowler, 1999, 2001; Wyndaele et al, 2005) has shown that these were patients with MSA and not PD and that **TURP should not be contraindicated in patients with PD because external sphincter acontractility is extremely rare** in such patients. However, one must be cautious with such patients, and a complete urodynamic or video-urodynamic evaluation is advisable. Poorly sustained bladder contractions, sometimes with slow sphincter relaxation, should make one less optimistic regarding the results of outlet reduction in the male. PD has been shown to impact voiding dysfunction in postradical prostatectomy patients. Routh and colleagues (2006) noted that in a study of retrospective evaluation of 20 patients with PD who had undergone radical prostatectomy that de novo incontinence rate was 24% and was of a minimal nature on the basis of pad utilization. However, the conclusion of the study was that advanced evaluation preoperatively including urodynamic or video-urodynamic evaluation would seem advisable for purposes of counseling given the higher rates of incontinence in this particular population.

Christmas and colleagues (1988) demonstrated that subcutaneous administration of a dopamine receptor agonist (apomorphine) can reliably and rapidly reverse parkinsonian "off" periods (periods of worsening symptoms mainly caused by the timing of previous medication doses and the unpredictable nature of motor fluctuations). By repeating video-urodynamic studies during the motor improvement after administration of apomorphine, bladder outlet obstruction secondary to benign prostatic hyperplasia (BPH) may be able to be distinguished from voiding dysfunction secondary to PD. The authors also point out that apomorphine might be useful in such patients who have severe off-phase voiding dysfunction (e.g., those with disabling nocturnal frequency and incontinence). **Voiding dysfunction secondary to PD defies "routine" classification within any system. It is most manifest by storage failure secondary to bladder overactivity, but detailed urodynamic evaluation is mandatory before any but the simplest and most reversible therapy.** The therapeutic menus (see Tables 66–3 and 66–4) are perfectly applicable, but the disease itself may impose certain limitations on the use of certain treatments (e.g., limited mobility for rapid toilet access, hand control insufficient for clean intermittent catheterization [CIC]).

Animal models of PD have been developed, using injections of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine or 6-hydroxydopamine into the nigrostriatal pathway (Yoshimura et al, 2003; Andersson and Wein, 2004; Wyndaele et al, 2005).

Subthalamic nucleus deep brain stimulation has been shown to be effective for motor symptoms and dyskinesias in patients with moderate to severe PD. Clinical studies have shown that this type of stimulation improves urinary function in these patients by ameliorating bladder sensation and also improving functional bladder capacity. Herzog and colleagues (2006) studied 11 patients undergoing deep brain stimulation with positron emission tomography assessments of regional cerebral blood flow. Subjects were studied with urodynamics both with stimulation on and stimulation off. At urodynamic capacity, significant increases in anterior cingulate regional blood flow were noted. They were increased when deep brain stimulation was off. At bladder capacity, there was also an increase in lateral frontal cortical blood flow with stimulation off. These results were felt to be indicative of deep brain stimulation improvement of bladder function by the modulation of afferent bladder information to cortical and subcortical areas (Herzog et al, 2006).

Multiple System Atrophy

Multiple system atrophy is a progressive neurodegenerative disease of unknown etiology. The symptoms encompass parkinsonism and cerebellar, autonomic (including urinary and erectile

problems), and pyramidal cortical dysfunction in a multitude of combinations. The clinical features and the differentiation from PD are nicely described in a consensus statement by Gilman and colleagues (1999). These investigators advocate a designation of MSA-P if parkinsonian features predominate and one of MSA-C if cerebellar features predominate. Older names such as "striatonigral degeneration," "sporadic olivopontocerebellar atrophy," and "Shy-Drager syndrome" (Wein, 2002a) should be discarded in favor of these.

The neurologic lesions of MSA consist of cell loss and gliosis in widespread areas, much more so than with PD, and this more diffuse nature of cell loss probably explains why bladder symptoms may occur earlier than in PD and be more severe and why erection may be affected as well (Kirby et al, 1986; Beck et al, 1994; Chandiramani et al, 1997). Affected areas have been identified in the cerebellum, substantia nigra, globus pallidus, caudate, putamen, inferior olives, intermediolateral columns of the spinal cord, and Onuf nucleus. Males and females are equally affected, with the onset in middle age. MSA is generally progressive and associated with a poor prognosis.

Shy-Drager syndrome has been described in the past as characterized clinically by orthostatic hypotension, anhidrosis, and varying degrees of cerebellar and parkinsonian dysfunction. Voiding and erectile dysfunction are common. Some consider this as late-stage MSA (Chandiramani et al, 1997).

Chandiramani and colleagues (1997) **compared the clinical features of 52 patients with probable MSA and 41 patients with PD.** Of patients with MSA, 60% had their urinary symptoms precede or present with their symptoms of parkinsonism. Of patients with PD, 94% had been diagnosed for several years before the onset of urinary symptoms. In patients with MSA, urinary incontinence was a significant complaint in 73%, whereas 19% had only frequency and urgency without incontinence. Sixty-six percent of the patients with MSA had a significant postvoid residual volume (100 to 450 mL). In patients with PD, frequency and urgency were the predominant symptoms in 85%, whereas incontinence was the primary complaint in 15%. In only 5 of 32 patients with PD in whom residual urine volume was measured was it significant. Eleven men with MSA underwent TURP. Nine of these had deterioration of their urinary incontinence afterward. All three women with MSA were incontinent after pelvic floor repair. Five men with PD underwent prostatectomy, and three reported a good result. Ninety-three percent of the men with MSA questioned about erectile function reported erectile failure, and in 13 of 27 of these the erectile dysfunction preceded the diagnosis of MSA. Seven of the 21 men with PD had erectile failure, but in all these men the diagnosis of erectile dysfunction followed the diagnosis of PD by 1 to 4 years. Fowler (2001) lists the clinical urogenital criteria favoring a diagnosis of MSA as (1) urinary symptoms precede or present with parkinsonism; (2) male erectile dysfunction precedes or presents with parkinsonism; (3) urinary incontinence; (4) significant postvoid residual; and (5) worsening lower urinary tract dysfunction after urologic surgery.

The initial urinary symptoms of MSA are urgency, frequency, and urgency incontinence, occurring up to 4 years before the diagnosis is made, as does erectile failure. **Detrusor overactivity is frequently found, as one would expect from the central nervous system areas affected, but decreased compliance may occur, reflecting distal spinal involvement of the locations of the cell bodies of autonomic neurons innervating the lower urinary tract. As the disease progresses, difficulty in initiating and maintaining voiding may occur, probably from pontine and sacral cord lesions, and this is generally associated with a poor prognosis. Cystourethrography or videourodynamic studies may reveal an open bladder neck (intrinsic sphincter deficiency), and many patients exhibit evidence of striated sphincter denervation on motor unit electromyography. The smooth and striated sphincter abnormalities predispose women to sphincteric incontinence and make prostatectomy hazardous in men.** Berger and coworkers (1990) described a useful urodynamic differentiation of what was termed Shy-Drager syndrome (probable late stage MSA) from PD. Parkinsonian patients with voiding dysfunction generally have detrusor overactivity and normal compliance. An open bladder neck was seen only in patients with "Shy-Drager syndrome," excluding those patients with PD who have had a prostatectomy. EMG evidence of striated sphincter denervation was seen much more commonly in those diagnosed as having Shy-Drager syndrome.

The treatment of significant voiding dysfunction caused by MSA is difficult and seldom satisfactory. Treatment of detrusor overactivity during filling may worsen problems initiating voluntary micturition or worsen impaired contractility during emptying. Patients generally have sphincteric insufficiency, so an outlet-reducing procedure is rarely indicated. Drug treatment for sphincteric incontinence may further worsen emptying problems. Generally, the goal in these patients is to facilitate storage, and CIC would often be desirable. Unfortunately, patients with advanced disease often are not candidates for CIC.

DISEASES PRIMARILY INVOLVING THE SPINAL CORD

Multiple Sclerosis

Multiple sclerosis (MS) is primarily a disease of young and middle-aged adults with a twofold predilection for women. Litwiller and colleagues (1999) detailed current prevalence rates for MS as 1/1000 Americans, 2/1000 northern Europeans, and 20 to 40/100,000 first-degree relatives of patients with MS. **The disease is believed to be immune mediated and is characterized by neural demyelination, generally characterized by axonal sparing, in the brain and spinal cord** (Noseworthy et al, 2000). This demyelination causes impairment of saltatory conduction and of conduction velocity in axonal pathways, resulting in various neurologic abnormalities that are subject to exacerbation and remission. Lesions, known as plaques, range from 1 mm to 4 cm and are scattered throughout the white matter of the nervous system (Chancellor and Blaivas, 1993). **The demyelinating process most commonly involves the lateral corticospinal (pyramidal) and reticulospinal columns of the cervical spinal cord,** and it is thus not surprising that voiding dysfunction and sphincter dysfunction are so common. Autopsy studies have revealed almost constant evidence of demyelination in the cervical spinal cord, but involvement of the lumbar and sacral cord occurs in approximately 40% and 18%, respectively (Blaivas and Kaplan, 1988). Lesions may also occur in the optic nerve and in the cerebral cortex and midbrain, the latter accounting for the intellectual deterioration and/or euphoria that may be seen as well (Kirby, 1994; Noseworthy et al, 2000), ultimately in up to 43% to 65% of patients (Litwiller et al, 1999). A rat model for a demyelinating disease resembling MS has been described using myelin basic protein as an antigen for inducing experimental allergic encephalomyelitis (Mizusawa et al, 2000).

The incidence of voiding dysfunction in MS is related to the disability status. Of patients with MS, **50% to 90% complain of voiding symptoms at some time; the prevalence of incontinence is cited as 37% to 72%** (Wyndaele et al, 2005). Litwiller and colleagues (1999), in their excellent review article, cite symptoms of frequency or urgency in 31% to 85% of patients in various series, with corresponding percentages of incontinence as 37% to 72% and of obstructive symptoms with urinary retention in 2% to 52%. Lower urinary tract involvement may constitute the sole initial complaint or be part of the presenting symptom complex in up to 15% of patients, usually in the form of acute urinary retention of "unknown" etiology or as an acute onset of urgency and frequency, secondary to overactivity (Wyndaele et al, 2005).

Detrusor overactivity is the most common urodynamic abnormality detected, occurring in 34% to 99% of cases in reported series (Blaivas and Kaplan, 1988; Chancellor and Blaivas, 1993; Sirls et al, 1994; Litwiller et al, 1999). **Of the patients with overactivity, 30% to 65% have coexistent striated sphincter dyssynergia. Impaired detrusor contractility or areflexia may also exist; estimates of prevalence range from 12% to 38%** (Wyndaele et al, 2005), **a phenomenon that can considerably complicate treatment efforts.** Other estimates suggest that 62% of patients with MS have neurogenic detrusor overactivity with bladder outlet obstruction, 25% have neurogenic detrusor overactivity with detrusor sphincter dyssynergia, 20% have detrusor under activity, and 10% have no initial abnormal urodynamic findings. The variability and potential multiplicity of lesions associated with MS, however, prohibit accurate diagnosis on the basis of urodynamics alone (Ukkonen et al, 2004). Bladder dysfunction associated with MS, as compared with women with non-neurogenic detrusor activity, has been shown to demonstrate significant differences. The amplitude of the first overactive contraction is greater in patients with MS as compared with those patients with idiopathic detrusor overactivity, as is the maximal detrusor contraction. The threshold volume at which detrusor overactivity occurs in patients with neurogenic detrusor overactivity, however, is somewhat higher than in those patients with idiopathic detrusor overactivity, which may be related to residual volume and which is noted in patients with detrusor overactivity. Using threshold values for prediction of type of voiding dysfunction, 30 cm of H_2O and above was predictive of patients having neurogenic detrusor activity as compared with those who have non-neurogenic detrusor overactivity. These differences in neurogenic detrusor overactivity urodynamic findings may be representative of direct neurogenic influences on the detrusor muscle from abnormal bladder interpolation and/or signaling as compared with non-neurogenic patients (Lemack, 2006).

Generally, **the smooth sphincter is synergic.** Chancellor and Blaivas (1993) reviewed urodynamic findings in multiple series of patients with MS and voiding dysfunction and summarized the incidence of three basic patterns: (1) detrusor overactivity, striated sphincter synergia 26% to 50% (average 38%); (2) detrusor overactivity, striated sphincter dyssynergia 24% to 46% (average, 29%); and (3) detrusor areflexia 19% to 40% (average, 26%). Litwiller and colleagues (1999) tabularized 22 references, reporting approximately the same ranges. It is also possible to see relative degrees of sphincteric flaccidity caused by MS, a phenomenon cited as occurring in less than 15% of patients (Litwiller et al, 1999); this finding could predispose and contribute to sphincteric incontinence. De Ridder and colleagues (1998) reported weakness of pelvic floor contraction in nearly all 30 women they studied with MS. Spasticity of the pelvic floor was present in all patients with striated sphincter dyssynergia but in none with detrusor overactivity alone.

Because sensation is frequently intact in these patients, one must be careful to distinguish urodynamic pseudodyssynergia from true striated sphincter dyssynergia. Blaivas and colleagues (1981) subcategorized true striated sphincter dyssynergia in patients with MS and identified some varieties that are more worrisome than others. For instance, in a female with MS, a brief period of striated sphincter dyssynergia during detrusor contraction but one that does not result in excessive intravesical pressure during voiding, substantial residual urine volume, or secondary detrusor hypertrophy may be relatively inconsequential, whereas those varieties that are more sustained—resulting in high bladder pressures of long duration—are most associated with urologic complications. Giannantoni and colleagues (1998) reviewed 116 of their patients and likewise concluded that there was a significant relationship between the maximum amplitude of the involuntary bladder contractions and upper urinary tract deterioration. Chancellor and Blaivas (1993) emphasized what they believed were **the most important parameters predisposing patients with MS to significant urologic complications: (1) striated sphincter dyssynergia in men; (2) high detrusor filling pressure (>40 cm H_2O); and (3) an indwelling catheter. Interestingly, however, Wyndaele's committee** (Wyndaele et al, 2005) **concluded that progressive neurologic disease, MS included, rarely causes upper urinary tract damage, even when, in MS, severe spasticity and disability exist. The reason for this is unknown, but they believe that the situation and concerns with respect to this are unlike those for SCI.**

Key Point: Multiple Sclerosis

- The most common functional classification applicable to patients with voiding dysfunction secondary to MS would thus be storage failure secondary to detrusor overactivity. This is commonly complicated by striated sphincter dyssynergia, with varying effects on the ability to empty completely at acceptable pressures. Other abnormalities and other combined deficits, are obviously possible, however. Once the dysfunction is broadly characterized, the treatment options should be obvious from the therapeutic menus (see Tables 61–3 and 61–4).

Aggressive and anticipatory medical management can obviate most significant complications. Sirls and colleagues (1994) reported that only 7% (the author calculated 10.4%) of their patients required surgical intervention because of failure of aggressive medical management and that none developed hydronephrosis on such therapy. The regimens used were (1) drugs to decrease detrusor overactivity plus CIC (57%); (2) such drugs alone (13%); (3) CIC alone (15%); and (4) behavioral therapy. **A significant proportion of patients with MS with and without new symptoms will develop changes in their detrusor compliance and urodynamic pattern** (Ciancio et al, 2001). **Caution should therefore be exercised in recommending irreversible therapeutic options.** No factors appear to be predictive of upper tract changes in MS. In a 4-year follow-up of multiple sclerosis patients, 113 patients were evaluated, of whom 66 patients

had both urodynamic and renal ultrasound testing. Sixteen percent (11 patients) had abnormal ultrasound findings. The most significant finding was minor caliectasis, which was of no clinical significance. Neither creatinine nor urodynamic findings were associated with the abnormal renal ultrasound findings (Lemack et al, 2005). Surgical intervention for multiple sclerosis appears to be diminishing with improved pharmacologic management and the realization of the alternating neurologic picture of lower urinary dysfunction associated with MS (Ukkonen et al, 2004).

No consensus on optimal bladder management has identified for multiple sclerosis, and most commonly, management is predicated on symptomatic and urodynamic findings. According to consensus agreement, De Ridder and colleagues (2005) concluded that in early multiple sclerosis, anticholinergics and intermittent catheterization were considered to be cornerstones of therapy. For advanced MS (with an EDSS > 7), specific guidelines remain lacking. In general, crédé voiding or Valsalva voiding are contraindicated, especially in the presence of detrusor sphincter dyssynergia. They further recommended that indwelling catheters be reserved for patients for whom all other possible treatments have failed. In the approximately 30% of patients with MS using indwelling urinary catheters, the suprapubic route is the preferred route in both men and women. This form of management is considered reasonable for that subpopulation, as long as long-term follow-up is continued (De Ridder et al, 2005).

Spinal Cord Injury

Epidemiology, Morbidity, General Concepts

SCI may occur as a consequence of acts of violence, fracture, or dislocation of the spinal column secondary to motor vehicle, diving accidents or falls, vascular injuries or repair, infection, disk prolapse, or sudden or severe hyperextension from other causes. Altered lower urinary tract and sexual function frequently occur secondary to SCI and significantly affect quality of life; SCI patients are at risk urologically for urinary tract infection, sepsis, upper and lower urinary tract deterioration, upper and lower urinary tract calculi, autonomic hyperreflexia (dysreflexia), skin complications, and depression (which can complicate their urologic management). Failure to properly address the lower urinary tract dysfunction can lead to significant morbidity and mortality. There is great variation in urologic practice regarding initial evaluation, follow-up, and surveillance among spinal injury units (Bycroft et al, 2004), a problem that Boone (2004) properly attributes to a lack of evidence-based decision making.

Complete anatomic transection of the spinal cord is rare, and the degree of neurologic deficit varies with the level and severity of the injury. **Spinal column (bone) segments are numbered by the vertebral level, and these have a different relationship to the spinal cord segmental level at different locations. One must be careful to specify cord or column level when discussing SCI. The sacral spinal cord begins at about spinal column level T12 to L1. The spinal cord terminates in the cauda equina at approximately the spinal column level of L2.** Multiple level injuries may occur, and, even with a single initial injury, cord damage may not be confined to a single cord segment and may extend cephalad, caudad, or both.

Stover and Fine (1987) reviewed the epidemiology and other general aspects of SCI. The annual rate was reported as 30 to 32 new SCIs per million persons at risk in the United States; the prevalence was approximately 906 per million. This coincides roughly with the estimate by DeVivo (1997) of approximately 10,000 new cases of SCI in the United States yearly and an estimate of 12,000 per year by Rabchevsky and Smith (2001). DeVivo (1997) reported the most common mechanisms of injury, as collected by the National Spinal Cord Injury Statistical Center, as motor vehicle accidents (35.9%), violence (29.5%), falls (20.3%), and sports-related injuries (7.3%). Males account for 71% to 80% of patients with SCI. The average age at injury is 31.5 years. Children comprise 3% to 5% of all patients with SCI (Generao et al, 2004). Stover and Fine (1987) reported that neurologically incomplete quadriplegics constituted the largest group of SCI patients at the time of hospital admission (28%), followed by complete paraplegics (26%), complete quadriplegics (24%), and incomplete paraplegics (18%). This seems to have changed little during the 1990s. The majority occur at or above the T12 spinal column (vertebral) level.

Although earlier data (Hackler, 1977) **indicated that renal disease was the major cause of death, at least in the paraplegic patient, a retrospective study of more than 5000 patients who sustained SCI between 1973 and 1980 revealed that the leading causes of death at that time were pneumonia, septicemia, heart disease, accidents, and suicide** (Stover and Fine, 1987; Soden et al, 2000). These figures seemingly indicate a distinct improvement in the urologic care of these patients. Impaired mobility is commonly noted in the spinal cord–injured patient and may substantially affect urinary habit and incontinence (Biering-Sorensen et al, 2004). Urologic phenomena also figure prominently in chronic SCI. Within 10 years after SCI, approximately 7% of patients with spinal cord will develop an initial kidney stone with the greatest risk occurring during the first 3 months after injury. Ninety-eight percent of these stones will be apatite or struvite in composition. There appear to be two time frames for stone formation in this population, one being the acute phase associated with immobilization and immobilization hypercalciuria. The other is a more chronic phase stone formation period, usually associated with chronic catheter management years after injury and predominately involving the lower tract (Post and Noreau, 2005).

Controlled and coordinated lower urinary tract function depends on an intact neural axis. Bladder contractility and the occurrence of reflex contractions depend on an intact sacral spinal cord and its afferent and efferent connections (see Chapter 61).

An impressive amount of literature is continuously building on the neurobiology of the spinal cord and its acute and chronic alteration after SCI. These topics are not specifically considered in

Key Point: Spinal Cord Injury

- Generally, complete spinal cord lesions above the sacral spinal cord, but below the area of the sympathetic outflow, result in detrusor overactivity, absent sensation below the level of the lesion, smooth sphincter synergia, and striated sphincter dyssynergia. Lesions at or above the spinal cord level of T7 or T8 (the spinal column level of T6) may result in smooth sphincter dyssynergia as well. However, although the correlation between neurologic and urodynamic findings is good, it is not perfect, and a neurologic examination is no substitute for a urodynamic evaluation in these patients when one is determining risk factors and treatment (see later).

detail here, nor are the ramifications of this information relative to potential improvement of spinal cord function after injury by stem cell implant or reinnervation. Earlier reviews can be found by Olson (1997), Fawcett (1998), and Kakulas (1999); later ones were presented by Rabchevsky and Smith (2001) (this also includes a discussion of pathophysiology and experimental models), Cao and colleagues (2002) (stem cell repair), Fawcett (2002) (repair of SCI), Rossi and Cattaneo (2002) (stem cell therapy), Mitsui and colleagues (2003) (stem cell repair), Kakulas (2004) (neuropathology and natural history of the spinal cord changes), and Livshits and colleagues (2004) (reinnervation). Sexual and reproductive dysfunction in the patient with SCI is a topic that deserves much attention in the overall rehabilitation plan. Pertinent general and specific concepts of sexual and reproductive dysfunction and their normalization in this special group of patients can be found in Chapters 23, 27 (male), and 30 (female). Other excellent reviews on the specifics of sexual function in SCI can be found by Bennett and colleagues (1988), Stone and MacDermott (1989), Smith and Bodner (1993), and Biering-Sorensen and Sonksen (2001), and on infertility by Linsenmeyer and Perkash (1991), Rajaskaran and Monga (1999), and Rutkowski and colleagues (1999).

Spinal Shock

After a significant SCI, a period of decreased excitability of spinal cord segments at and below the level of the lesion occurs, referred to as "spinal shock." There is **absent somatic reflex activity and flaccid muscle paralysis below this level.** Although classic teaching refers to generalized areflexia below the level of the lesion for days to months, Thomas and O'Flynn (1994) confirm that the most peripheral somatic reflexes of the sacral cord segments (the anal and bulbocavernosus reflexes) may never disappear or, if they do, may return within minutes or hours of the injury. However, functions proximal to the level of the injury may be depressed as well (Atkinson and Atkinson, 1996). Although the course of spinal shock is well known, the actual phenomenon remains poorly understood, with little or no basic research evident recently.

Spinal shock includes a suppression of autonomic activity, as well as somatic activity, and the bladder is acontractile and areflexic. Radiologically, the bladder has a smooth contour with no evidence of trabeculation. The bladder neck is generally closed and competent unless there has been prior surgery or in some cases of thoracolumbar and presumably sympathetic injury (Sullivan and Yalla, 1992). **The smooth sphincter mechanism seems to be functional. Some EMG activity may be recorded from the striated sphincter, and the maximum urethral closure pressure is lower than normal but still maintained at the level of the external sphincter zone; however, the normal guarding reflex (striated sphincter response during filling) is absent and there is no voluntary control** (Fam and Yalla, 1988). Because sphincter tone exists, urinary incontinence generally does not result unless there is gross overdistention with overflow. In evolving lesions, every attempt should be made to preserve as low a bladder storage pressure as possible and to avoid any measures that might impair this. Urinary retention is the rule, and catheterization is necessary to circumvent this problem. Although virtually all would agree that CIC is an excellent method of management during this period and advocate its use, Lloyd and colleagues (1986) reported their own experience and cite that of others that indicate no differences in outcome when a small-bore Foley catheter or suprapubic tube is used at this stage.

If the distal spinal cord is intact but is simply isolated from higher centers, there is generally a return of reflex detrusor contractility. At first, such reflex activity is poorly sustained and produces only low-pressure changes, but the strength and duration of such involuntary contractions increase, producing involuntary voiding, usually with incomplete bladder emptying. This return of reflex bladder activity is generally manifested by involuntary voiding between catheterizations and occurs along with the recovery of lower extremity deep tendon reflexes. Spinal shock generally lasts 6 to 12 weeks in complete suprasacral spinal cord lesions but may last up to 1 or 2 years. It may last a shorter period of time in incomplete suprasacral lesions and only a few days in some patients.

Suprasacral Spinal Cord Injury

There is no unanimous agreement on the neurobiology of the development of reflex bladder contraction in response to bladder distention after suprasacral SCI. de Groat and colleagues (1997) have studied this phenomenon and related events extensively in cats and listed four potential mechanisms for the recovery of such micturition and the development of C-fiber afferent evoked bladder reflexes (see also the description by Yoshimura and Chancellor in Chapter 60): (1) elimination of bulbospinal inhibitory pathways; (2) strengthening of existing synapses or formation of new synaptic connections from axonal sprouting in the spinal cord; (3) changes in synthesis, release, or actions of neurotransmitters, and (4) alterations in afferent input (afferent axonal sprouting) from peripheral organs. Recent reports of specific alterations in animal models are summarized by Morrison and colleagues (2005) as (1) increased sensitivity of C-fiber afferents, possibly involving nerve growth factor; (2) enlargement of dorsal root ganglion cells; (3) increased electrical excitability of afferents associated with a shift in expression of sodium channels from a high-threshold tetrodotoxin-resistant type to a low-threshold tetrodotoxin-sensitive type. Other findings possibly related to the development of lower urinary tract dysfunction after SCI have been reported as (1) increased concentrations of glutamate, glycine, and taurine (Smith et al, 2002); (2) disruption of bladder epithelium barrier function (Apodaca et al, 2003); (3) change from low affinity M_1 to high affinity M_3 receptors at prejunctional cholinergic nerve endings (Somogyi et al, 2003); (4) increased release of adenosine triphosphate from bladder urothelium (Khera et al, 2004); (5) increased spinal cord nerve growth factor (Seki et al, 2004); and (6) alterations in smooth muscle myosin heavy chain gene expression (Wilson et al, 2005). Recently, in murine models of acute SCI, nicotinic or purinergic receptor mechanisms have been shown to be the primary mechanism for ATP release as atropine has been shown to be only partially effective in stimulating ATP release (predominantly a muscarinic receptor phenomenon in the absence of injury).These findings further indicate a change in receptor-mediated bladder activity associated with SCI (Salas et al, 2007).

The characteristic pattern that results when a patient has a complete lesion above the sacral spinal cord is detrusor overactivity, smooth sphincter synergia (with lesions below the sympathetic outflow), and striated sphincter dyssynergia (Sullivan and Yalla, 1992; Thomas and O'Flynn, 1994; Chancellor and Blaivas, 1995b). **Neurologic examination shows spasticity of skeletal muscle distal to the lesion, hyperreflexic deep tendon reflexes, and abnormal plantar responses. There is impairment of superficial and deep sensation.** Figures 65–1 to 65–3 typify the cystourethrographic and urodynamic patterns. The guarding

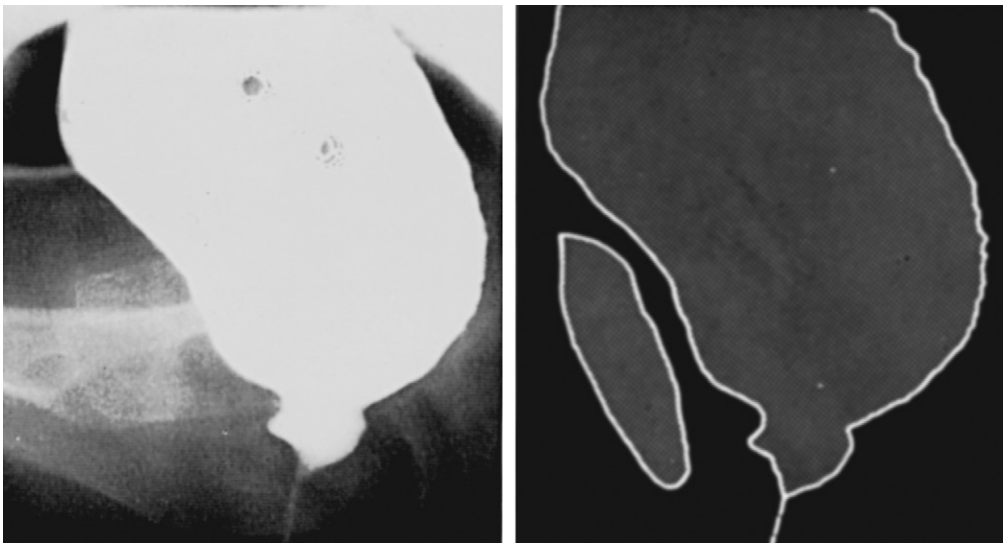


Figure 65–1. Cystourethrogram in a 19-year-old woman with detrusor–striated sphincter dyssynergia secondary to a complete spinal cord injury at vertebral level T11. Image was taken during an involuntary bladder contraction with exaggerated bladder neck opening caused by the obstruction below. (From Nordling J, Olesen KP. Basic urographic and cystourethrographic patterns. In: Pollack HM, editor. Clinical urography. Philadelphia: WB Saunders; 1990, p. 1953.)



Figure 65–2. Typical cystourethrographic configuration of a synergic smooth sphincter and a dyssynergic striated sphincter in a man during a bladder contraction. (From Nanninga JB: Radiological appearances following surgery for neuromuscular diseases affecting the urinary tract. In: Pollack HM, editor. Clinical urography. Philadelphia: WB Saunders; 1990, p. 2003.)

reflex is absent or weak in most patients with a complete suprasacral SCI. In incomplete lesions the reflex is often preserved but variable (Morrison et al, 2005).

The striated sphincter dyssynergia causes a functional obstruction with poor emptying and high detrusor pressure. In an effort to subclassify detrusor sphincter dyssynergia, Karsenty and colleagues (2005) retrospectively evaluated videourodynamic recordings of patients with complete SCI with untreated neurogenic overactive bladder and detrusor sphincter dyssynergia. They identified two time periods within the tracings, with Delay A being defined as that period between the onset of external urethral sphincter (EUS) pressure increase and the subsequent onset of bladder pressure increase. Delay B was defined as the period between the onset of urethral sphincter pressure increase and the moment at which bladder pressure increase reached a level of 10 cm H_2O or greater above the baseline value. The recordings of 20 patients were assessed, with the Delay A timeframe found to be significant in 16 of 20 patients, with a meantime for delay of 2.2 seconds. There was a positive association between this delay and the completeness of the SCI and the presence of continuous DSD on electromyogram. Delay B was positive in all patients with a mean delay time of 7.6 seconds. The authors concluded that EUS contraction starts before the onset of bladder contraction in most patients with coexistent SCI and detrusor sphincter dyssynergia. **Occasionally, incomplete bladder emptying may result from what seems to be a poorly sustained or absent detrusor contraction.** This seems to occur more commonly in lesions close to the conus medullaris than with more cephalad lesions. This may result from a second occult lesion or may be caused by locally functioning reflex arcs, which result in detrusor inhibition from strong striated pelvic floor muscle contraction, or to a loss of higher

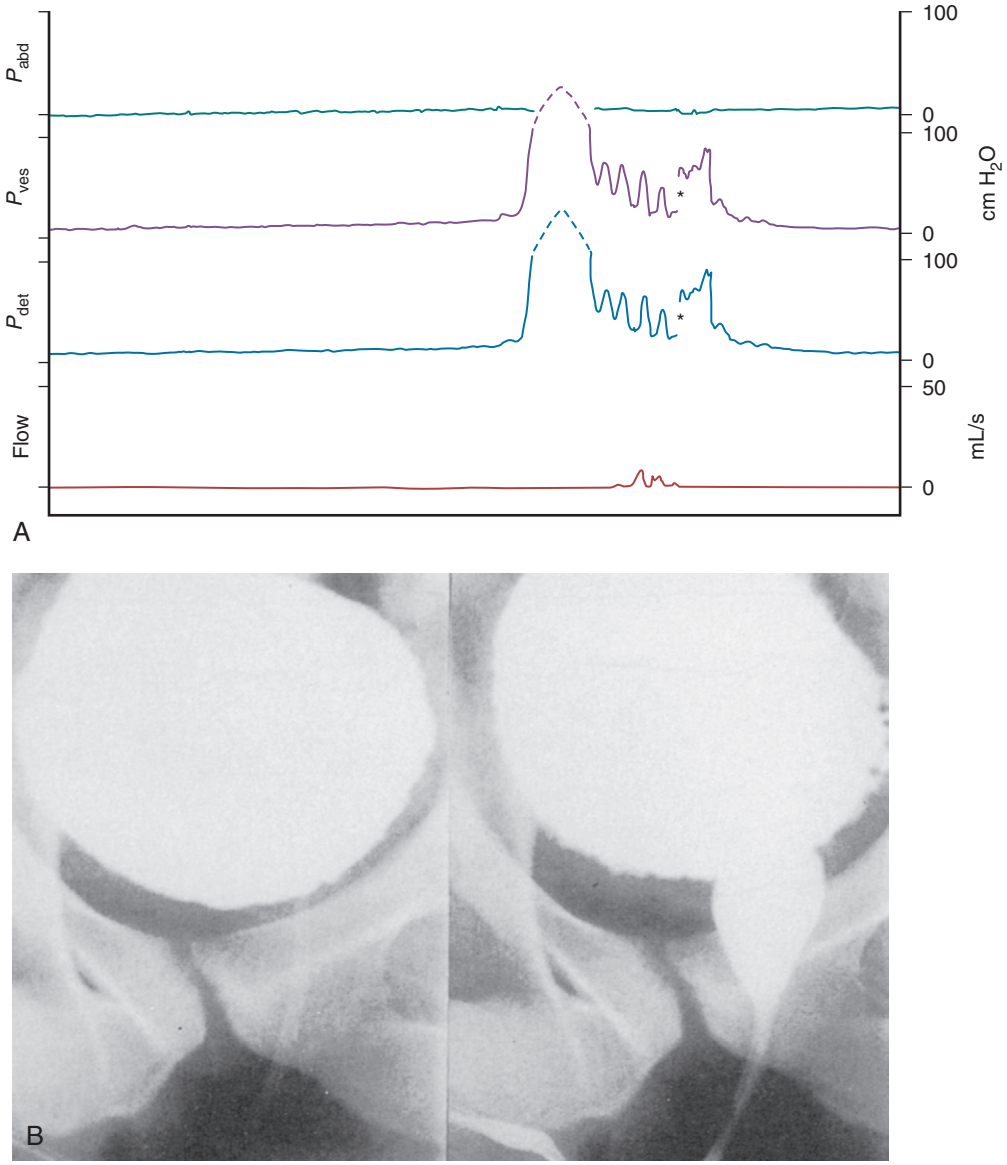


Figure 65–3. Video images in **B** at corresponding points of the urodynamic tracings in **A**. Detrusor hyperreflexia (P_{det} 150 cm H_2O), synergic bladder neck, dyssynergic striated sphincter. The *asterisk* represents a range change from a scale of 0 to 100 cm H_2O. (From Lawrence WT, Thomas DC. Urodynamic techniques in the neurologic patient. In: O'Reilly PH, George NJR, Weiss RM, editors. Diagnostic techniques in urology. Philadelphia: WB Saunders; 1990. p. 360.)

center–mediated detrusor facilitation, which normally occurs after the initial increase in pressure during a bladder contraction (Thomas and O'Flynn, 1994). Once reflex voiding is established, it can be initiated or reinforced by the stimulation of certain dermatomes, as by tapping the suprapubic area. The urodynamic and upper tract consequences of the striated sphincter dyssynergia vary with severity (generally worse in complete lesions than in incomplete ones), duration (continuous contraction during detrusor activity is worse than intermittent contraction), and anatomy (male is worse than female) (Linsenmeyer et al, 1998).

The type of dyssynergia also appears to be associated with degree of injury and potential for progression of dysfunction. Schurch and colleagues (2005) evaluated 105 male patients with SCI to determine if neurologic examination could predict the type of detrusor sphincter dyssynergia present. A correlation was noted between type of dyssynergia and completeness of spinal cord lesion. More commonly, patients with incomplete sensory and motor lesions presented with type 1 DSD. Complete sensory and motor lesions were more commonly associated with either type 2 or type 3 detrusor sphincter dyssynergia. There was no correlation, however, noted between the type of DSD and the lesion level. At chronic follow-up DSD type was noted to evolve from type 2 or type 3 DSD in approximately a quarter of the studied patients, whereas 65% of patients remained stable with the same type of DSD at follow-up (Schurch et al, 2005).

Sacral Spinal Cord Injury

After the patient recovers from spinal shock, there **is generally a depression of deep tendon reflexes below the level of a complete lesion with varying degrees of flaccid paralysis. Sensation is generally absent below the lesion level. Detrusor areflexia with high or normal compliance is the common initial result, but decreased compliance may develop,** a change seen in some neurologic lesions at or

Key Point: Management of Patients with Suprasacral Spinal Cord Injury

- From a functional standpoint the voiding dysfunction most commonly seen in suprasacral SCI represents both a filling/storage and an emptying failure. Although the urodynamics are "safe" enough in some individuals to allow only periodic stimulation of bladder reflex activity, many will require some treatment. If bladder pressures are suitably low or if they can be made suitably low with nonsurgical or surgical management, the problem can be treated primarily as an emptying failure. CIC can be continued, when practical, as a safe and effective way of satisfying many of the treatment goals. Alternatively, sphincterotomy, stenting, or intrasphincteric injection of botulinum toxin can be used in males to lower the detrusor leak point to an acceptable level, thus treating the dysfunction primarily as one of emptying. The resultant storage failure can be obviated either by timed stimulation or with an external collecting device. In the dexterous SCI patient, the former approach using CIC is becoming predominant. Electrical stimulation of the anterior sacral roots with some form of deafferentation is also now a distinct reality (Creasey et al, 2001; Seif et al, 2004). As with all patients with neurologic impairment, a careful initial evaluation and periodic follow-up evaluation must be performed to identify and correct the following risk factors and potential complications: bladder overdistention, high-pressure storage, high detrusor leak point pressure, vesicoureteral reflux (VUR), stone formation (lower and upper tracts), and complicating infection, especially in association with reflux.

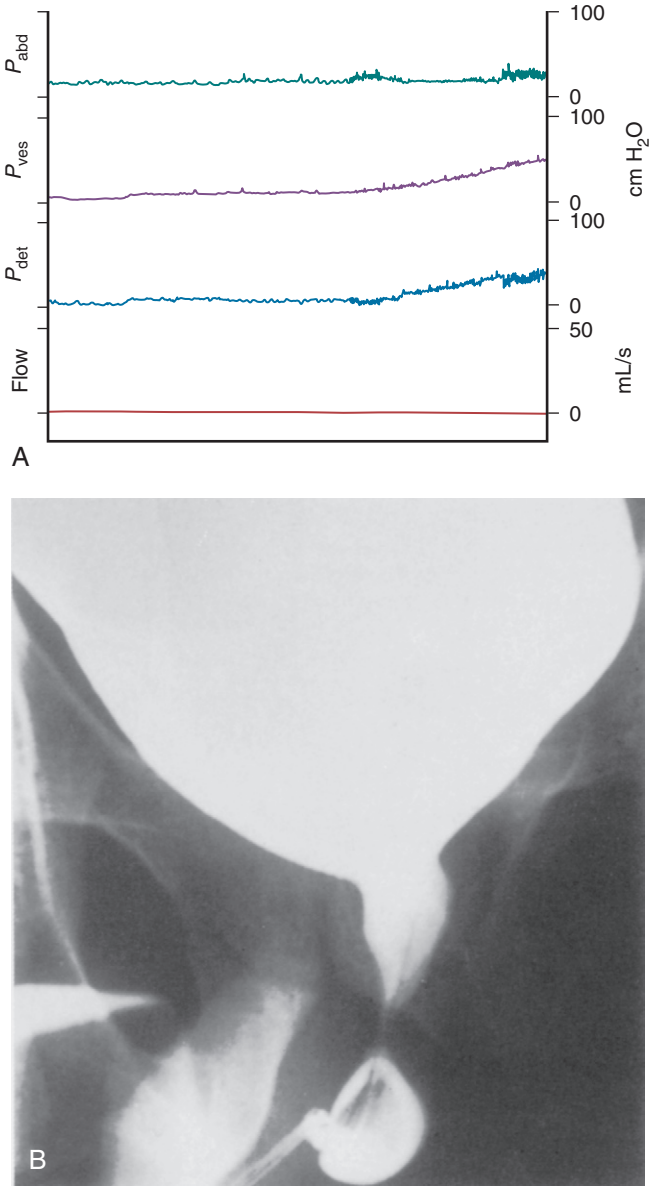


Figure 65–4. Simultaneous video **(B)** and urodynamic study **(A)** from a 28-year-old man whose bladder has been filled with 420 mL of contrast material. There is low compliance; the bladder neck is incompetent; and with straining the distal sphincter mechanism does not open—a pattern often seen in sacral spinal cord or efferent nerve root injury or disease. (From Lawrence WT, Thomas DC. Urodynamic techniques in the neurologic patient. In: O'Reilly PH, George NJR, Weiss RM, editors. Diagnostic techniques in urology. Philadelphia: WB Saunders; 1990, p. 362.)

distal to the sacral spinal cord that most likely represents a complex response to neurologic decentralization probably involving reorganization and plasticity of neural pathways (Fam and Yalla, 1988; de Groat et al, 1997; Blaivas et al, 1998b). There is surprisingly little consensus on the evolution of the appearance or function of the bladder neck or smooth sphincter area after sacral spinal cord damage. **The classic outlet findings are described as a competent but nonrelaxing smooth sphincter and a striated sphincter that retains some fixed tone but is not under voluntary control. Closure pressures are decreased in both areas** (Sullivan and Yalla, 1992; Thomas and O'Flynn, 1994). However, the late appearance of the bladder neck may be "open" (Kaplan et al, 1991). Attempted voiding by straining or Credé's maneuver results in "obstruction" at the bladder neck (if closed) or at the distal sphincter area by fixed sphincter tone (Fam and Yalla, 1988; Thomas and O'Flynn, 1994). Figure 65–4 illustrates the typical cystourographic and urodynamic pictures of the late phases of such a complete lesion.

Neurologic and Urodynamic Correlation

Although generally correct, the correlation between somatic neurologic findings and urodynamic findings in suprasacral and sacral SCI patients is not exact. A number of factors should be considered in this regard. First, whether a lesion is complete or incomplete is sometimes a matter of definition, and a complete lesion, somatically speaking, may not translate into a complete lesion autonomically and vice versa. Multiple injuries may actually exist at different levels, even though what is seen somatically may reflect a single level of injury. Even considering these situations, however, all such discrepancies are not explained. This is further demonstrated in patients with incomplete lesions. Patki and colleagues (2006) assessed a group of 43 men and 21 women with incomplete SCI (ASA grades D and E) during a 2-year period. In this group, 40 patients who were initially assessed as having a bladder not at risk for deterioration ultimately experienced deterioration requiring clean, intermittent catheterization. Conversely, 5 of 20 patients, who initially required clean intermittent catheterization, no longer required this with time. In chronic follow-up, 68% of patients continued to have abnormal urodynamic findings and 37% of patients required a

change in urologic management in the absence of perceptible change in neurologic status, indicating the potential of continued bladder changes in the absence of other detectable neurologic disease (Patki et al, 2006).

Key Point: Management of Patients with Sacral Cord Injury

- **Potential risk factors and complications are those previously described, with particular emphasis on storage pressure, which can result in silent upper tract decompensation and deterioration in the absence of VUR. The treatment of such a patient is generally directed toward producing or maintaining low-pressure storage while circumventing emptying failure with CIC when possible.** Pharmacologic and electrical stimulation may be useful in promoting emptying in certain circumstances (see Tables 66–3 and 66–4).

In a classic article, Blaivas (1982) **correlated clinical and urodynamic data from 550 patients with voiding dysfunction.** In 155 patients with complete and incomplete suprasacral neurologic lesions, physiologically normal voiding was reported in 41%. Detrusor–striated sphincter dyssynergia was demonstrated in 34%, and, surprisingly (and seemingly paradoxically), detrusor areflexia was noted in 25%. Other authors have noted detrusor areflexia with suprasacral SCI or disease, and the causes have been hypothesized as a coexistent distal spinal cord lesion or a disordered integration of afferent activity at the sacral root or cord level (Light et al, 1985; Beric and Light, 1992). Detrusor–striated sphincter dyssynergia was reported in 45% of 119 patients with suprasacral spinal cord lesions. None of 36 patients with supraspinal neurologic lesions had striated sphincter dyssynergia. **These data certainly support prior conclusions that (1) coordinated voiding is regulated by neurologic centers above the spinal cord and (2) a diagnosis of striated sphincter dyssynergia implies a neurologic lesion that interrupts the neural axis between the pontine-mesencephalic reticular formation and the sacral spinal cord.** All 27 patients with neurologic lesions above the pons and who were able to void did so synergistically—with relaxation of the striated sphincter preceding detrusor contraction. Twenty of these patients had detrusor overactivity, but 12 of these 20 had voluntary control of the striated sphincter, supporting a thesis of separate neural pathways governing voluntary control of the bladder and of the periurethral striated musculature. Most of these patients with detrusor overactivity secondary to lesions above the pons were able to voluntarily contract the striated sphincter, but without abolishing bladder contraction. This seems to indicate that the inhibition of bladder contraction by pudendal motor activity is not merely a simple sacral reflex but, rather, a complex neurologic event. Twenty-two of these patients had evidence of either sacral or infrasacral neurologic impairment of bladder function with suprasacral control of striated sphincter function or vice versa; this provides a clinical correlate to the separate anatomic locations of the parasympathetic motor nucleus and the pudendal nucleus in the sacral spinal cord (see Chapter 60).

A subsequent study from the same center analyzed the results of urodynamic evaluation in 489 consecutive patients with either congenital or acquired SCI or disease and correlated these with the diagnosed neurologic deficit (Kaplan et al, 1991). Although there was a general correlation between the neurologic level of injury and the expected vesicourethral function, it was neither absolute nor specific. Twenty of 117 cervical lesions exhibited detrusor areflexia; 42 of 156 lumbar lesions, detrusor–striated sphincter dyssynergia; and 26 of 84 sacral lesions, either detrusor overactivity or detrusor–striated sphincter dyssynergia. The patients were further classified on the basis of the integrity of the sacral dermatomes (intact sacral reflexes or not). This helps to explain some, but not all, of the apparent discrepancies. Of the patients with suprasacral cord lesions who had detrusor areflexia, 84% also had abnormal sacral cord signs (absent bulbocavernosus reflex, lax anal sphincter tone, or sphincter EMG abnormalities indicative of lower motor neuron degeneration). All suprasacral cord lesion patients who had no evidence of sacral cord involvement had either detrusor overactivity or detrusor striated sphincter dyssynergia.

Patients were also classified according to the three most common neurologic causes for their lesion: trauma, myelomeningocele, and spinal stenosis. Of the 284 trauma patients, all with thoracic cord lesions had either detrusor overactivity or detrusor striated dyssynergia and negative sacral cord signs. In contrast, in patients with traumatic lesions affecting other parts of the spinal cord, there was a wide distribution of both urodynamic and sacral cord sign findings. For example, of patients with traumatic lumbar cord injury, 38% had detrusor areflexia and positive sacral cord signs, 25% had detrusor–striated sphincter dyssynergia and negative sacral cord signs, 25% had detrusor overactivity and negative sacral cord signs, and 14% had either detrusor overactivity or detrusor–striated sphincter dyssynergia and negative sacral cord signs. Of 25 patients with lumbar myelomeningocele, 20 had either detrusor areflexia or detrusor–striated sphincter dyssynergia. All patients with lumbar myelomeningocele and detrusor areflexia had positive sacral cord signs. Of 48 patients with sacral myelomeningocele, 37 had detrusor areflexia and 35 had positive sacral cord signs. Of 54 patients with spinal stenosis, all those with cervical and thoracic cord lesions had either detrusor overactivity or detrusor–striated sphincter dyssynergia and negative sacral cord signs. Patients with a lumbar cord stenosis had no consistent pattern of detrusor activity or sacral cord signs. An open bladder neck at rest was found in 21 patients. All had either lumbar or sacral SCI. Sixteen of these had sacral cord lesions and detrusor areflexia. Decreased bladder compliance was noted in 54 patients, 41 of whom had sacral cord injury and 43 of whom had detrusor areflexia.

Koh et al (2006) reported urodynamic evaluation of five patients with myelomeningocele who underwent prenatal closure of the spinal dysraphism as compared with a large group of 88 patients who underwent postnatal closure. All five of the reported patients had lower lumbosacral lesions. They noted that there is no spontaneous electromyographic activity in the five prenatally intervened children as compared with only 39% identification in the postnatal group. Additionally, all five patients in the prenatal cohort exhibited detrusor overactivity as compared with 38% in the postnatal group. These findings were similar both at baseline and at 1 year. The finding of the complete innervation of the EUS suggested the need for close postnatal surveillance to exclude the possibility of tethering of the spinal cord and other events postsurgical intervention. The value of intervention in these patients has been noted in patients undergoing detethering. In a study of 120 children with myelomeningocele, Abrahamsson and colleagues (2007) identified 20 who underwent cord detethering at a

median age of 8 years. Preintervention and postintervention urodynamic evaluation was performed (median of 5 months preoperatively and a median of 12 months postoperatively). Of the 20 that underwent detethering in this group, 7 had improvement of their voiding dysfunction to a milder level of dysfunction with 1 experiencing deterioration. Six patients actually experienced deterioration of bladder dysfunction before detethering, all of whom returned to a less significant level postoperatively. Ten patients had no change in bladder function on urodynamics after intervention, one of whom actually deteriorated on urodynamic findings. The overall 35% improvement underscored the need for regular evaluation of bladder function in these children. Metcalfe and colleagues (2006) reported 36 patients who underwent sectioning of the filum terminale as management of tethered cord. They estimated 0.4% of pediatric clinic visits in the urology department resulted in neurosurgical referral for the potential exclusion of occult tethered cord. Symptoms included daytime incontinence in 83% of the patients and 47% with encopresis. Preintervention urodynamics showed a mean of a 55% reduction of expected bladder capacity in the affected patients. Clinical improvement was noted in 72% of patients undergoing intervention with 42% becoming clinically continent. Additionally, 88% of cases noted improvement in bowel symptomatology including 53% of patients noting improvement in encopresis after 3 months of surgery. Urodynamic improvement was likewise documented in 57% of patients on the basis of improved bladder capacity. No specific factors were identified that would improve surgical success on the basis of either urodynamic findings or symptomatic presentation. In yet another cohort of tethered cord patients (Guerra et al, 2006), 24 patients (10 male, 14 female) between the ages of 1 month and 12 years were treated for this condition. Diurnal incontinence was noted in 50% and constipation was noted in 42%. Incontinence resolved in all but 1 patient postoperatively with improvement in constipation in 4 of 10 patients with preoperative constipation. Forty-eight percent of children had resolution of urodynamic abnormalities postoperatively with 10 of 17 with detrusor overactivity normalizing and 7 remaining unchanged. Four patients with either diminished bladder capacity or low compliance did not improve postoperatively after intervention on urodynamics. Similarly, two of three patients with normal preoperative urodynamic evaluation developed detrusor overactivity and/or poor compliance postoperatively. They found there was no relationship between the level of conus on magnetic resonance imaging and predictive findings of urodynamics. The authors did raise concern regarding the potential for decompensation even after surgery.

Kessler and colleagues (2006) assessed 123 patients with myelomeningocele retrospectively on the basis of urodynamic patterns. The patients were classified into four categories: detrusor overactivity with overactive sphincter (43 patients), overactive detrusor and underactive or acontractile sphincter (37 patients), underactive acontractile detrusor with overactive spastic sphincter (8 patients), and underactive acontractile detrusor and underactive acontractile sphincter (35 patients). Patients were assessed for urinary incontinence and the need for adjunctive incontinence surgery between the four groups. At mean follow-up of 10 years, social continence was highest in groups one and three (86% and 87%, respectively) and lowest in groups two and four (57% and 74% respectively). There was statistical significance between interventions among the groups. The study concluded that initial urodynamics were useful in counseling families regarding the ultimate status of urinary incontinence in patients with myelomeningocele including rates of social continence.

Wyndaele (1997) correlated the neurologic and urodynamic data in 92 patients with SCI and came to the same general conclusion: **Although there was a general correlation between the neurologic level of injury and the expected vesicourethral function, it was neither absolute nor specific, especially in the group of patients with paraplegia resulting from spinal cord lesions at column level T10 to L2.** With reference to this latter group, Pesce and colleagues (1997) reported on 46 patients with complete SCIs from vertebral lesions between T11 and L2. Fifty percent of the patients had detrusor areflexia, and 50% had overactivity; 16 of the latter group also had striated sphincter dyssynergia. Of 22 patients with lesions above vertebral level L1, 8% showed areflexia and 14 showed overactivity, of whom 9 demonstrated sphincter dyssynergia. Of 9 patients with a lesion between T12 and L1, 3 showed detrusor areflexia and 6 overactivity, of whom 4 showed striated sphincter dyssynergia. Of 15 patients with a lesion at L1 or lower, 3% showed detrusor overactivity and striated sphincter dyssynergia.

Weld and Dmochowski (2000) agreed that the correlation between somatic neurologic findings or spinal imaging studies and urodynamic findings in patients with SCI is not exact, based on their review of 243 post-traumatic SCI patients who had complete spinal CT or MRI studies. It should be noted, however, that their correlation between level of injury and urodynamic findings was in fact better than those previously reported, most likely because of the more exact determination of the level of injury and the detection of multiple levels of injury, attributable to the precision of the radiologic imaging studies. Of 196 patients with suprasacral injuries, 94.9% demonstrated overactivity and/or striated sphincter dyssynergia, 41.8% had low bladder compliance (defined as 12.5 mL/cm H_2O), and 40.3% had detrusor leak point pressures greater than 40 cm H_2O. Of the 14 patients with sacral injuries, 85.7% demonstrated detrusor areflexia; 78.6%, low compliance; and 85.7%, high leak point pressures. Of 33 patients with combined suprasacral and sacral injuries, 68% demonstrated detrusor overactivity and/or detrusor dyssynergia; 27%, areflexia; 58%, low compliance; and 61%, high leak point pressures.

The degree and magnitude of SCI also impacts the overall management of these patients. Patki and colleagues (2006) assessed a group of 43 men and 21 women with incomplete SCI (ASA grades D and E) during a 2-year period. In this group, 40 patients who were initially assessed as having a bladder not at risk for deterioration ultimately experienced deterioration requiring clean, intermittent catheterization. Conversely, 5 of 20 patients, who initially required clean intermittent catheterization, no longer required this with time. In chronic follow-up, 68% of patients persisted with abnormal urodynamic findings, and 37% of patients required a change in urologic management in the absence of perceptible neurologic disease, indicating the potential of continued bladder changes in the absence of other detectable neurologic disease. Other factors such as underlying histology may also contribute to upper tract deterioration. Ozkan studied a group of patients undergoing augmentation for neurogenic detrusor overactivity, requiring augmentation cystoplasty. Patients underwent perioperative full-thickness bladder biopsies during the augmentation cystoplasty. A relationship between the degree of and severity of detrusor fibrosis was noted to be a significant risk factor of upper tract deterioration. Additionally, leak-point pressures of greater than 75 cm of water were also found to be consistent with upper tract deterioration (Ozkan et al, 2006).

All these data make the point, as cogently as possible, that **management of the urinary tract in such patients must be based on urodynamic principles and findings rather**

than inferences from the neurologic history and evaluation. Similarly, although the information regarding "classic" complete lesions is for the most part valid, one should not make neurologic conclusions solely on the basis of urodynamic findings.

Autonomic Hyperreflexia

First described by Guttmann and Whitteridge in 1947, autonomic hyperreflexia (autonomic dysreflexia) is a potentially fatal emergency unique to the SCI patient. Excellent sources of information include the reviews by Trop and Bennett (1991), Vaidyanathan and colleagues (1998), and Karlsson (1999). **Autonomic hyperreflexia represents an acute massive disordered autonomic (primarily sympathetic) response to specific stimuli in patients with SCI above the cord level of T6 to T8 (the sympathetic outflow).** It is more common in cervical (60%) than thoracic (20%) injuries. Onset after injury is variable (usually soon after spinal shock) but may be up to years after injury. Distal cord viability is a prerequisite.

Symptomatically, autonomic hyperreflexia is a **syndrome of exaggerated sympathetic activity in response to stimuli below the level of the lesion. The symptoms are pounding headache, hypertension, and flushing of the face and body above the level of the lesion with sweating. Bradycardia is a usual accompaniment, although tachycardia or arrhythmia may be present. Hypertension may be of varying severity,** from causing a mild headache before the occurrence of voiding to life-threatening cerebral hemorrhage or seizure. **The stimuli for this exaggerated response commonly arise from the bladder or rectum and generally involve distention, although other stimuli from these areas can be precipitating. Precipitation may be the result of simple lower urinary tract instrumentation, tube change, catheter obstruction, or clot retention; and, in such cases, the symptoms resolve quickly if the stimulus is withdrawn. Other causes or exacerbating factors may include other upper or lower urinary tract pathology (e.g., calculi), gastrointestinal pathology, long bone fracture, sexual activity, electrocoagulation, and decubiti.**

Striated sphincter dyssynergia invariably occurs, and smooth sphincter dyssynergia is generally a part of the syndrome as well, at least in males. The pathophysiology is that of a nociceptive stimulation via afferent impulses that ascend through the cord and elicit reflex motor outflow, causing arteriolar, pilomotor, and pelvic visceral spasm and sweating. Normally, the reflexes would be inhibited by secondary output from the medulla, but because of the SCI this does not occur below the lesion level. Vaidyanathan and colleagues (1998) emphasized that the SCI disrupts control of the sympathetic preganglionic neurons because bulbospinal input has been lost, and the remaining regulation is accomplished by spinal circuits consisting of dorsal root afferent and spinal interneurons. Karlsson (1999), however, points out that the underlying pathogenic mechanisms may not be as simple as they first appear. The amplitude of the blood pressure reaction indicates involvement of a large vascular bed, perhaps larger than that of the skin and skeletal muscle. It may be that the splanchnic vascular bed is involved as well, either from the standpoint of active vasoconstriction or simply from a lack of the ability to exhibit compensatory vasodilatation. Afferent and efferent plasticity in the sympathetic nervous system may also be involved.

Ideally, any endoscopic procedure in susceptible patients should be done under spinal anesthesia or carefully monitored general anesthesia. Acutely, the hemodynamic effects of this syndrome may be managed with β- and/or α-adrenergic blocking agents. Ganglionic blockers had previously been the mainstay of treatment (Wein, 2002a), but their usage has essentially been abandoned. Sublingual nifedipine had been reported to be capable of alleviating this syndrome when given during cystoscopy (10 to 20 mg) and of preventing it when given orally 30 minutes before cystoscopy (10 mg) (Dykstra et al, 1987). The rationale was that this presumably prevented smooth muscle contraction through its calcium antagonist properties and thereby prevented the increase in peripheral vascular resistance normally seen with sympathetic stimulation. The use of sublingual nifedipine, however, has been prohibited in the authors' particular medical center and doubtless in some others as well. It has been reported that the sublingual absorption of nifedipine is negligible and that the favorable therapeutic results obtained from such administration are probably caused by swallowing the drug (van Harten et al, 1987). These particular authors believe that if a fast onset of action of nifedipine is desired, the patient should be instructed to bite the capsule and swallow the contents with water, thereby rapidly achieving therapeutic plasma levels of the drug. Before electroejaculation, Steinberger and colleagues (1990) recommended oral prophylaxis with 20 mg of nifedipine, finding this markedly lowered pressure rises during treatment. Captopril, hydralazine, or diazoxide are still occasionally recommended but are less advantageous. Other rapidly acting agents have been reported to be beneficial. Many anesthesiologists recommend labetalol (Bycroft et al, 2005).

Chancellor and colleagues (1994) reported on the use of terazosin (a selective α_1-adrenergic blocker) for long-term management (3-month study) and prophylaxis. A nightly dose of 5 mg reduced severity, whereas erectile function and blood pressure were unchanged. Vaidyanathan and colleagues (1998) affirmed the success of the prophylactic use of terazosin. They treated 18 adults with tetraplegia and 3 with paraplegia with graduated increasing doses of the drug, ultimately varying from 1 to 10 mg daily, and reported complete subsidence of dysreflexic symptoms in all patients. Only one patient, a tetraplegic, required discontinuation of the drug because of persistent dizziness. Such prophylaxis may be particularly important in view of the fact that significant elevations in blood pressure can occur without other symptoms of autonomic hyperreflexia (Linsenmeyer et al, 1996). Similar salubrious results have also been reported with prazosin as prophylaxis for this condition (Bycroft et al, 2005).

Prophylaxis, however, does not eliminate the need for careful monitoring during provocative procedures. There are patients with severe dysreflexia that is intractable to oral prophylaxis and correction by urologic procedures. For these unfortunate individuals, a number of neurologic ablative procedures have been used—sympathectomy, sacral neurectomy, sacral rhizotomy, cordectomy, and dorsal root ganglionectomy (Trop and Bennett, 1991). Hohenfellner and colleagues (2001) advocate sacral bladder denervation by sacral rhizotomy as a moderately invasive, relatively low-risk procedure that, along with intermittent catheterization, produces good results in refractory patients.

Vesicoureteral Reflux

Surprisingly little is written about VUR in the SCI patient. The reported incidence varies between 17% and 25% of such patients (Thomas and Lucas, 1990) and is more common in those with

suprasacral SCI. Contributing factors include (1) elevated intravesical pressure during filling and emptying and (2) infection. Persistent reflux can lead to chronic renal damage and may be an important factor in the long-term survival of SCI patients. In the series of SCI patients reported by Hackler and colleagues (1965), persistent reflux was present in 60% of patients of those dying of renal disease. In patients with only transient reflux over a 5- to 15-year period, the urogram was normal in 83% and calyceal changes were only minimal. It should be noted, however, that high storage and voiding pressures without reflux can be responsible for renal damage (McGuire, 1984; Vega and Pascual, 2001). Ku and colleagues (2005) studied 179 men undergoing annual follow-up for SCI. The average duration of follow-up after injury was 29 years. The incidence of reflux in this group was 15.1%. Thirty-four percent of the patients were diagnosed with pyelonephritis at some point during their course of follow-up, and 24.6% developed renal stones. Thirty-two percent experienced upper tract deterioration as manifested by hydronephrosis. Upper tract degeneration was more prevalent in those managed with urethral catheters (51%) than in those managed with either spontaneous voiding or intermittent catheterization. Urethral catheter drainage was found to be inferior to all other forms of bladder drainage in terms of protection of the upper urinary tract, suggesting the inadvisability of urethral catheterization chronically in these patients (Ku et al, 2005).

The best initial treatment for reflux in a patient with voiding dysfunction secondary to neurologic disease or injury is to normalize lower urinary tract urodynamics as much as possible. Depending on the clinical circumstances, this may be by pharmacotherapy, urethral dilatation (in the myelomeningocele patient), neuromodulation, deafferentiation, augmentation cystoplasty, or sphincterotomy (Flood et al, 1994; Perkash et al, 1998). If this fails, the question of whether to operate on such patients for correction of the reflux or to correct the reflux while performing another procedure (e.g., augmentation cystoplasty) is not an easy one because correction of reflux in an often thickened bladder may not be an easy task.

Transureteroureterostomy for unilateral reflux is feasible, but even experienced urologists have had difficulties with ureteral calculi trapping, recurrent reflux, and obstruction at the vesicoureteral junction following such procedures in this difficult group of patients (Van Arsdalen and Hackler, 1983). Submucosal trigonal injection of bulking substances may add a new dimension to the treatment of this difficult problem.

One must remember the potential artifact that significant reflux can introduce into urodynamic studies. Measured bladder capacity appears artifactually large, and measured pressures at given inflow volumes may appear lower than after reflux correction. The apparent significance of detrusor overactivity may thus be underestimated.

Urinary Tract Infection

Urinary tract infection (UTI) is relatively common in patients with SCI. Fifty-seven percent of patients with SCI experience UTI or bacteriuria in the first year after initial hospitalization (Morton et al, 2002). Recurrent infections may be a manifestation of upper or lower tract calculi, symptomatic or silent pyelonephritis, or lower urinary tract dysfunction causing persistent residual urine. In conjunction with poor urodynamic function, UTI can lead to high morbidity, poor quality of life, and decreased life expectancy in patients with SCI (Sauerwein, 2002). The use of antibiotics in SCI patients remains a topic of discussion. **Virtually all who have written on the subject agree that bacteriuria should be treated only when signs or symptoms present, a consensus reached by the National Institute on Disability and Rehabilitation Research Group (1992)** (Penders et al, 2003). Biering-Sorensen and colleagues (2001) authored a nicely organized, well-written, and referenced article on the subject. They recommended the following: (1) treat bacteriuria only if symptomatic; (2) use antimicrobial agents, if possible, with little or no impact on normal flora; (3) treat at least 5 days; those with reinfection or relapse, treat 7 to 14 days; (4) repair structural and functional risk factors; (5) use prophylaxis only in those with recurrent UTI when no underlying cause can be found and especially if the upper tracts are dilated; (6) do not use antibiotics to prevent UTI in patients with an indwelling catheter. They regard the use of prophylactic antibiotics in patients on CIC as controversial.

Morton and colleagues (2002) concluded from a meta-analysis of 15 controlled trials that prophylactic antibiotics were not generally helpful but added that they could not exclude a clinically important effect, especially in those who had recurrent UTI that limited their functioning and well-being. Sauerwein (2002) recommends beginning antibiotic prophylaxis in patients on CIC and stopping after 1 year if there has been one or fewer UTIs. Some (Burns et al, 2001) believe that significant pyuria, defined as 8 to 10 or more white blood cells per high-power field, connotes tissue invasion and is an indication for antibiotic treatment. Evidence-based data in this area are sparse.

Spinal Cord Injury in Women

There are many aspects of management of the lower urinary tract affected by SCI that are specific to women (Yang and Cardenas, 2001). McColl (2002) summarized some of these. The problem of osteoporosis places women at a much increased risk of fracture. The symptoms of menopause (e.g., hot flashes) may be difficult to distinguish from those of autonomic dysreflexia. Incontinence and UTI become worse with age in women in the general population and particularly in those with SCI. Body composition of SCI women shows deficient protein and bone mass and excess fat, predisposing them to an increased incidence of fractures and the risk of skin breakdown. The incidence of SCI is highest among young men and older women. Psychologic outcomes (e.g., depression) have been shown to improve after 30 years' duration of disability. Women injured at a modal age of 60 are unlikely to enjoy this benefit.

Special difficulty in this category of patients is encountered because of the lack of an appropriate external collecting device. Suitable bladder reservoir function can usually be achieved either pharmacologically or surgically, and paraplegic women can generally master CIC. Although a few quadriplegic women can be trained to self-CIC, for the majority there is no practical alternative to indwelling catheterization (Lindan et al, 1987). McGuire and Savastano (1986) point out that indwelling catheter drainage on a long-term basis in women may not be, however, as is sometimes written, well tolerated because significant incontinence around the catheter and upper tract changes may develop.

For those SCI female patients who can assume CIC or who have around-the-clock medical or family care, creation of adequate bladder reservoir function is reasonable. For those not in this category, the alternatives are limited and difficult. Bennett and colleagues (1995) compared the incidence of major complications in a group of female SCI patients who were managed long term

by (1) CIC; (2) reflex voiding and incontinence padding; and (3) an indwelling catheter. There were 10 major complications in the 25 patients in group 2 and 58 in the 22 patients in group 3, compared with only 4 major complications in group 1. Singh and Thomas (1997) looked at the results of treatment in a group of female tetraplegics. Twenty-three of 27 patients with complete lesions wound up using an indwelling catheter, 3 underwent diversion, and in 1 patient the caregiver performed CIC. In 20 patients with incomplete lesions, all with poor functional recovery, 14 had permanent indwelling catheters, 3 were able to perform CIC, and 3 used reflex voiding by triggering. Of 37 patients with incomplete lesions with good functional recovery, only 3 required indwelling catheterization; 4 used CIC, and most were able to use reflex voiding by triggering. The authors noted also that 55% of the women with permanent catheters had bladder calculi, 35% had leakage around the catheter, and 33% had recurrent symptomatic infection. Although upper tract changes were seen in only 5%, it is obvious that the authors consider that, for the most part, female patients with voiding dysfunction secondary to cervical SCI who exhibit poor functional recovery represent urologic failures of management.

Spinal Cord Injury and Bladder Cancer

The development of carcinoma of the bladder in 6 of 59 patients with SCIs who had long-term indwelling catheters was reported by Kaufman and colleagues (1977). All were squamous cell lesions. Four of these patients had no obvious tumors visible at endoscopy, and the diagnosis was made by bladder biopsy. Five of these patients also had transitional cell elements in their tumor. Broecker and colleagues (1981) surveyed 81 consecutive SCI patients with an indwelling urinary catheter for more than 10 years. Although the investigators did not find frank carcinoma in any patients, they found squamous metaplasia of the bladder in 11 and leukoplakia in 1. Locke and colleagues (1985) noted two cases of squamous cell carcinoma of the bladder in 25 consecutive SCI patients catheterized for a minimum of 10 years. Bickel and colleagues (1991) reported eight cases of bladder cancer in SCI men, although the denominator was uncertain. Four of the men had been managed by indwelling catheterization for 7, 10, 14, and 19 years, respectively. All of these four men had transitional cell carcinoma, whereas in the other four, there were two cases of transitional and two of squamous cell carcinoma. In Chao and colleagues' series (1993), 6 patients developed bladder cancer, 3 of whom had indwelling catheters (of a total of 32) and 3 of whom (of 41) did not. Stonehill and colleagues (1996) retrospectively reviewed all bladder tumors in their SCI patients for 7 years and compared these with matched controls. They found 17 malignant and 2 benign bladder tumors. Indwelling catheters and a history of bladder calculi were statistically significant risk factors.

Hess and colleagues (2003) reported their own series and summarized one view of the literature regarding SCI and bladder cancer: (1) the relative risk in SCI patients is 16% to 28% greater than the general population; (2) the overall incidence is 2.3% to 10%; (3) there is a higher proportion of squamous cell than transitional cell carcinoma; (4) the prevalence peaks at an earlier age than in the general population; (5) diagnosis is made at a more advanced stage; (6) risk factors include chronic indwelling catheterization, bladder stones, and chronic UTI; (7) neither cystoscopy nor cytology is an entirely reliable diagnostic tool; and (8) those with multiple risk factors should have a more aggressive evaluation.

Tempering this are reports by Pannek (2002), who reviewed the data from 43,561 SCI patients in three countries and concluded the incidence of bladder cancer is comparable with that of the general population, but more than 60% of those affected presented initially with muscle invasive disease. Chronic indwelling catheters and persistent or recurrent UTI are suggested as the risk factors rather than the SCI itself. Subramonian and colleagues (2004) reported similar conclusions regarding age-standardized incidence of bladder cancer relative to the general population. Seventy-five percent of the affected patients in the series had indwelling catheters for 18 to 32 years.

The incidence of bladder cancer in MS patients with indwelling catheters is estimated at 0.29%, as compared with 0.004% in the general population of females and 0.018% in the population of males. The incidence of bladder cancer in SCI patients has been recorded to range from 0.27% to 9.6%; however, in larger series, the overall incidence is 0.27% to 0.37%. The natural history of bladder cancer is thought to be more highly aggressive in neurogenic patients and is responsible for 0.3% to 2.8% of known deaths in the SCI population.

Follow-Up

Linsenmeyer and Culkin (1999) reported the American Paraplegic Society (APS) Guidelines for urologic care of SCI. **Annual follow-up is recommended for the first 5 to 10 years after injury. If the patient is doing well, then follow-up every other year is advised. Upper and lower tract evaluation should be done initially and yearly for 5 to 10 years, then every other year.** Burns and colleagues (2001) recommended at least plain films and nuclear renal scans, with a decrease of more than 20% in renal plasma flow warranting further investigation. **Urodynamic evaluation was recommended by the APS at the same intervals as upper and lower tract screening. Cystoscopy was recommended annually in those with an indwelling catheter.**

Cervical Myelopathy

Cervical myelopathy is generally caused by compression, secondary to either spondylosis, ossification of the posterior longitudinal ligament, or cervical disk herniation (Sakakibara et al, 1995a; Mochida et al, 1996). Sakakibara and colleagues (1995a) studied 128 affected patients, of whom 95 had voiding symptoms, 61 had irritative symptoms, 71 had obstructive symptoms, and 25 had urinary incontinence. Urodynamic studies revealed involuntary bladder contractions in 61 patients and detrusor sphincter dyssynergia (DESD) in 22. Mochida and colleagues (1996), on the other hand, reported on 60 patients undergoing surgery for cervical myelopathy, 22 of whom (37%) were found to have neuropathic bladder dysfunction on urodynamic study. Of these, 9 (41%) were found to have detrusor overactivity but 13 (59%) were characterized as having an underactive detrusor. Because this is at odds with what one would expect with only cervical spinal cord pathology, it reinforces the need for urodynamic study to optimally guide therapy in patients with neurogenic bladder.

Acute Transverse Myelitis

Acute transverse myelitis is a rapidly developing condition with motor, sensory, and sphincter abnormalities, generally with a well-defined upper sensory limit and no signs of spinal cord compression or other neurologic disease (Kalita et al, 2002). It may result from a variety of mechanisms—parainfectious, autoimmune, vascular, or demyelinating (Ganeson and Borzyskowski, 2001). The condition usually stabilizes within 2 to 4 weeks, is not progressive

afterward, and is followed by variable recovery with some residual neurologic deficits. Although recovery is more variable, and the prognosis, in general, is more favorable, the development and nature of voiding dysfunction has been reported to be similar, level by level, to that of SCI (Sakakibara et al, 1995b). Kalita and colleagues (2002), however, reported on 18 patients with acute transverse myelitis whose 6-month outcome included persistent retention in 6 and storage symptoms in 10, of whom 5 had emptying problems as well; 2 patients had regained normal voiding. In the acute state, urodynamics showed an areflexic or contractile bladder in 10, detrusor overactivity with poor compliance in 2, and DESD in 3. Seventeen had presented in urinary retention. As in SCI, because the activity of the bladder and outlet during filling/storage and emptying/voiding does not always correspond to what they "should" be, based on the level of pathology, urodynamic studies are necessary to guide irreversible therapy.

Neurospinal Dysraphism

These topics are covered primarily in Chapters 127 and 128. However, certain considerations regarding the adult with these abnormalities should be mentioned. Spinal dysraphism refers to the malformation of the vertebral arches and, commonly, malformation of the neural tube. The term includes spina bifida occulta, which involves only a bony (vertebral) arch defect, and spina bifida cystica (aperta), which involves a bony defect and a neural tube (spinal cord) defect. The two primary subclasses of spina bifida cystica are myelomeningocele (the nerve roots or portions of the spinal cord have evaginated beyond the vertebral bodies) and meningoceles (contain only a herniated meningeal sac with no neural elements). If fatty tissue is present in the sac in either, the prefix "lipo-" is added (Churchill et al, 2001). **Myelomeningocele accounts for more than 90% of spina bifida cystica and is the most devastating condition in terms of sequelae. Of myelomeningoceles, 2% are cervical, 5% thoracic, 26% lumbar, 47% lumbosacral, and 20% sacral. The level(s) of the lesion correlates poorly with urodynamic findings** (Churchill et al, 2001). **Myelomeningocele occurs in approximately 1/1000 live births** (Wyndaele et al, 2005). **The incidence of lower urinary tract dysfunction is not absolutely documented, but most studies suggest an incidence of greater than 90%** (Wyndaele et al, 2005).

McGuire and Denil (1991) and Woodhouse (2005) point out that, secondary to progress in the overall care of children with myelodysplasia, urologic dysfunction often becomes a problem of the adolescent or adult with this disease. In McGuire and Denil's (1991) experience, **the "typical" myelodysplastic patient shows an areflexic bladder with an open bladder neck. The bladder generally fills until the resting residual fixed external sphincter pressure is reached, and then leakage occurs. Stress incontinence occurs also,** related to changes in intra-abdominal pressure. A small percentage (10% to 15%) of patients demonstrate detrusor striated sphincter dyssynergia, but these individuals show normal bladder neck function that, if detrusor reflex activity is controlled, is associated with continence. After puberty, most authors report that most myelodysplastic patients note an improvement in continence, but, at that age and after, they are less inclined than children to tolerate any degree of incontinence. In adult patients, the problems encountered in myelodysplastic children still exist but are often compounded by prior surgery, upper tract dysfunction, and one form of urinary diversion or another.

In adult females, the treatment strategy is generally to increase urethral sphincter efficiency without causing a major enough increase in urethral closing pressure that will result in a change in bladder compliance (McGuire and Denil, 1991). **Periurethral injection therapy to achieve continence may replace the pubovaginal sling and artificial sphincter in this circumstance. These authors also point out that continence in adult male myelodysplastic individuals follows the same general rules as in females, and injectable materials may give good results in this group as well. When the urethra is widely dilated and somewhat rigid, and neither procedure alone will provide sufficient coaptation, it may be possible to combine a "prostatic sling" with periurethral collagen injection. Dry individuals, of course, will be on intermittent self-catheterization.**

"Classic" may imply different urodynamic findings to different groups of clinicians. **Nowhere is the failure of a neurologic examination to predict urodynamic behavior more obvious than in patients with myelomeningocele.**

Van Gool and colleagues (2001) summarized the urodynamic findings in 188 children with myelomeningocele and categorized these into five groups. Seven percent had normal detrusor and sphincter activity; 11% had detrusor overactivity and an inactive sphincter; 45% had detrusor overactivity and an overactive sphincter; 23% had an inactive detrusor and inactive sphincter; and 14% had an inactive detrusor and an overactive sphincter. Sakakibara and colleagues (2003a) reported on urodynamic results in 16 adult patients with myelomeningocele. Detrusor overactivity was found in 38%, low compliance in 81%, impaired bladder sensation in 25%, DESD in 50%, low maximum urethral pressure in 56%, and silent sphincter electromyogram in 25%. Webster and colleagues (1986) urodynamically classified a large number of myelomeningocele patients as follows: 62% had detrusor overactivity, whereas 38% had detrusor areflexia, with 30 of 34 of these having low compliance with high terminal filling pressure. Striated sphincter behavior was characterized as follows: true detrusor–striated sphincter dyssynergia in 15%, an apparently innervated but fixed nonrelaxing sphincter in 15%, and some evidence of striated sphincter denervation in 69%.

It is clear, however, that whatever the pattern of voiding dysfunction in the adult, all authors would agree that a prime directive of therapy is still the avoidance of high storage pressures (McGuire and Denil, 1991; Persun et al, 1999; Woodhouse, 2005).

Voiding dysfunction secondary to occult spinal dysraphism may not present in childhood, and such patients may be referred as adults for symptoms as mundane as incontinence or recurrent urinary infection. Jakobsen and colleagues (1985) reported seven such patients ranging in age from 10 to 51 years. Delayed diagnosis of such voiding dysfunction was also reported by Yip and colleagues (1985). There was no characteristic abnormality, and the specific dysfunction is dependent on the level and extent of the neurologic injury.

The urologic rehabilitation of patients with spinal dysraphism relies primarily on medical management with the selective use of augmentation or urinary diversion after failure thereof. However, surgery does not necessarily yield superior results. In a review of 421 patients managed for spina bifida, 45% were medically treated, either with intermittent catheterization, spontaneous voiding, or no specific method utilized. Two-hundred and thirty patients were surgically treated. Overall incontinence episodes were higher in the surgical versus medical management group. These results may

have been reflective of the aggressiveness of management, as well as the severity of disease (Lemelle et al, 2006).

Recently, neural rerouting has been proposed as a potential option for some of these individuals. Ziao and colleagues have performed microanastomosis of the fifth lumbar ventral root to the third sacral ventral root in order to bypass low-level spina bifida injury. Initial improvements in bladder compliance and urinary incontinence were noted in patients and paralleled similar findings in spinal cord patients (Joseph, 2005).

Tethered cord syndrome (TCS) is defined as a stretch-induced functional disorder of the spinal cord with its caudal part anchored by inelastic structures. Vertical movement is restricted. The anchoring structures can include scar from prior surgery, fibrous or fibroadipose filum terminale, a bony septum, or tumor (Yamada et al, 2004a, 2004b). Adults with TCS can be divided into those with a prior history of spinal dysraphism with a previously stabilized neurologic status who present with subtle progression in adulthood and those without associated spinal dysraphism who present with new subtle neurologic symptoms (Yamada et al, 2004a, 2004b). **Symptoms can include back pain, leg weakness, foot deformity, scoliosis, sensory loss, and bowel or lower urinary tract dysfunction** (Phuong et al, 2002). **TCS is reported to occur in 3% to 15% of patients with myelomeningocele. There is no typical dysfunction in TCS, and treatment must be based on contemporary urodynamic evaluation.** Voiding dysfunction may not be present until the teenage years or later (Kaplan and Blaivas, 1988; Husmann, 1995). Giddens and colleagues (1999) point out that, whereas children often develop symptoms of tethered cord after growth spurts, in adults presenting symptomatology often follows activities that stretch the spine such as sports or motor vehicle accidents. In adults, urologic presentation can include irritative voiding symptoms, incontinence, or retention. These authors reported neurourologic and urodynamic findings in a group of adult patients. At presentation, urgency (67%) and urge incontinence (50%) were the most common findings. Pretreatment urodynamics in 18 patients revealed detrusor overactivity in 13 (72%), DESD in 4 (22%), decreased sensation in 4 (22%), decreased compliance in 3 (17%), and what was called a "hypocontractile" detrusor in 2 (11%). It is interesting that postoperative urodynamic findings were improved in only 4 patients (29%) and unchanged in 10 (71%). Steinbok and colleagues (2007) assessed eight children undergoing section of the filum inducing the tethered cord and compared them with seven children who had abnormal urodynamic findings and did not undergo filum release. Clinical improvement occurred in seven of the eight children at a mean follow-up of 3 years with improved urodynamics in four of seven children tested after surgery. These improvements were also associated with nonurologic functional improvements (motor leg function). At a mean follow-up of 3 years in the nonsurgical group, two patients had urologic improvement but three patients required surgical intervention and five had persistence of nonurologic symptoms. Section of the cord appeared to improve function as compared with conservative management (Steinbok et al, 2007).

Tabes Dorsalis, Pernicious Anemia

Although syphilitic myelopathy is disappearing as a major neurologic problem, involvement of the spinal cord dorsal columns and posterior sacral roots can result in a loss of bladder sensation and large residual urine volumes and therefore be a cause of "sensory neurogenic bladder" (see Chapter 61). Although this represents the "classic" tabetic bladder (Wheeler et al, 1986), Hattori and colleagues (1990) reported on some patients with only tabes as an obvious cause of their voiding dysfunction who had low compliance or detrusor overactivity. Another spinal cord cause of the classic "sensory bladder" is the now uncommon pernicious anemia that produced this disorder by virtue of subacute combined degeneration of the dorsolateral columns of the spinal cord.

Poliomyelitis

When seen, voiding dysfunction in polio is that of a typical "motor neurogenic bladder" (see Chapter 61) with urinary retention, detrusor areflexia, and intact sensation. The reported incidence of voiding dysfunction in patients with polio was described as ranging from 4% to 42% by Bors and Comarr (1971).

DISEASE DISTAL TO THE SPINAL CORD

Disk Disease

Goldman and Appell (2000a) nicely summarize the anatomic and neurologic considerations applicable to voiding dysfunction from lumbar disk disease. **In the adult, the sacral segments of the spinal cord are at the level of the L1 and L2 vertebral bodies.** In this distal end of the spinal cord, commonly called the ***conus medullaris,*** the spinal cord segments are named for the vertebral body at which the nerve roots exit the spinal canal. Thus although the sacral spinal cord segment is located at vertebral segment L1, its nerve roots run in the subarachnoid space posterior to the L2 to L5 vertebral bodies until reaching the S1 vertebral body, at which point they exit the canal. Thus all of the sacral nerves that originate at the L1 and L2 spinal column levels run posterior to the lumbar vertebral bodies until they reach their appropriate site of exit from the spinal canal. This group of nerve roots running at the distal end of the spinal cord is commonly referred to as the **cauda equina.**

Usually, disk prolapse is in a posterolateral direction, which does not affect the majority of the cauda equina. However, in 1% to 15% of the cases (Goldman and Appell, 2000a), central disk prolapse occurs and compression of the cauda equina may result. Thus disk prolapse anywhere in the lumbar spine could interfere with the parasympathetic and somatic innervation of the lower urinary tract, striated sphincter and other pelvic floor musculature, and afferent activity from the bladder and affected somatic segments to the spinal cord. **Most disk protrusions compress the spinal roots in the L4-L5 or L5-S1 vertebral interspaces. Voiding dysfunction may result and, when present, generally occurs with the usual clinical manifestations of low back pain radiating in a girdle-like fashion along the involved spinal root areas. Examination may reveal reflex and sensory loss consistent with nerve root compression. The most characteristic findings on physical examination are sensory loss in the perineum or perianal area (S2-S4 dermatomes), sensory loss on the lateral foot (S1-S2 dermatomes), or both.**

Goldman and Appell (2000a) also reviewed the literature on voiding dysfunction associated with lumbar disk disease. The incidence of such dysfunction in their review ranged from 27% to 92%. The true incidence is a bit difficult to ascertain because many reported series on this subject describe findings only in patients who present with voiding dysfunction. Bartolin and colleagues (1998) reported on findings in 114 patients with lumbar disk

protrusion who were prospectively studied. They found detrusor areflexia in 31 (27.2%) and normal detrusor activity in the remaining 83. **All 31 patients with detrusor areflexia reported difficulty voiding with straining. Patients with voiding dysfunction generally presented with these symptoms or in urinary retention. The most consistent urodynamic finding was that of a normally compliant areflexic bladder associated with normal innervation or findings of incomplete denervation of the perineal floor musculature.** In a later report, Bartolin and colleagues (2002) describe findings in 122 patients with lumbar disk protrusion. Detrusor areflexia was found in 32 (26%) and normal bladder urodynamic findings in 90 (74%). All with areflexia complained of difficulty voiding; 8 could not void at all, 14 had an interrupted flow, and 10 had a continuous but low flow. Occasionally, patients may show detrusor overactivity, attributed to irritation of the nerve roots (O'Flynn et al, 1992).

The detrusor areflexia associated with lumbar disk protrusion shows a lower incidence of decreased compliance than in the voiding dysfunction caused by myelomeningocele. Sandri and colleagues (1987) offered two possible explanations for this difference: (1) the effect of the disk represents a more incomplete lesion of the preganglionic parasympathetic fibers and (2) the lesion is more sensory than motor, implying that the decreased compliance seen with the type of neural lesion in myelomeningocele is primarily caused by injury of the preganglionic parasympathetic motor fibers to the bladder.

Laminectomy may not improve bladder function, and prelaminectomy urodynamic evaluation is therefore desirable because it may be difficult postoperatively in these cases to separate causation of voiding dysfunction owing to the disk sequelae from changes secondary to the surgery. Bartolin and colleagues (1999) reported on the results of surgery in a group of patients with lumbar disk protrusion. Of 27 patients with detrusor areflexia preoperatively, detrusor activity returned to normal in only 6. The patients were studied up to a year after surgery. Of the 71 patients with normal urodynamic findings preoperatively, 4 developed detrusor overactivity and 3 developed detrusor areflexia postoperatively. The medicolegal implications of a presurgical and postsurgical urodynamic evaluation are obvious.

Cauda equina syndrome **is a term applied to the clinical picture of perineal sensory loss with loss of voluntary control of both anal and urethral sphincter and of sexual responsiveness.** This can occur not only secondary to disk disease (severe central posterior disk protrusion) but to other spinal canal pathologic processes as well. Yamanishi and colleagues (2003) place the incidence of cauda equina syndrome at 1% to 5% of all prolapsed lumbar disks. They reported on eight patients undergoing emergency corrective surgery for this entity. All had an acontractile detrusor with no bladder sensation, and four of seven had an inactive sphincter electromyogram. Follow-up urodynamics showed that all continued with an acontractile detrusor, three had normal EMG activity, and three had EMG activity but with denervation potentials in two and low activity in two.

Spinal Stenosis

Spinal stenosis is a term applied to any narrowing of the spinal canal, nerve root canals, or intervertebral foramina. It may be congenital, developmental, or acquired. Compression of the nerve roots or cord by such a problem may lead to neuronal damage, ischemia, or edema. **Spinal stenosis may occur without disk prolapse. Symptoms may range from those consequent to cervical spinal cord compression to a cauda equina syndrome, with corresponding urodynamic findings** (Smith and Woodside, 1988). Back and lower extremity pain, cramping, and paresthesias related to exercise and relieved by rest are the classic symptoms of lumbar stenosis caused by lumbar spondylosis and are believed to result from a sacral nerve root ischemia. The urodynamic findings are dependent on the level and the amount of spinal cord or nerve root damage. Deen and colleagues (1994) reported subjective improvement in more than 50% of such patients with bladder dysfunction who were treated by decompressive laminectomy. In cervical spondylitic spinal stenosis, detrusor overactivity or underactivity may occur, depending on whether the primary pathologic process affecting the micturition neural axis is compression of the inhibitory reticulospinal tracts or myelopathy in the posterior funiculus, which carries proprioceptive sensation (Tammela et al, 1992). Because there is no consistent pattern of dysfunction with any type of spinal stenosis, urodynamic studies again are the cornerstone of rational therapy. Podnar and colleagues (2006) assessed 65 cauda equina patients with neuro-urologic examination, electromyography, and urodynamics. Severe LUT dysfunction was noted in 14% of women and 15% of men, whereas moderate dysfunction was noted in 27% of men and 46% of women. Incomplete emptying was the most common symptom (>90%), and urinary incontinence was next with 56% of men and 71% of women. Reduced capacity was noted in 9% and 15%, respectively. Poor detrusor contractility was noted in 59% of men and 85% of women. Using multiple linear regression, perianal sensory loss and female gender had the most significant positive predictive value for urinary incontinence.

Radical Pelvic Surgery

Voiding dysfunction after pelvic plexus injury occurs most commonly after abdominoperineal resection and radical hysterectomy. The true incidence of neurogenic vesicourethral dysfunction after various types of pelvic surgery is unknown because there are few prospectively studied series of patients with preoperative and postoperative urodynamic evaluation. **The incidence has been estimated to range from 20% to 68% of patients after abdominoperineal resection, 16% to 80% after radical hysterectomy, 20% to 25% after anterior resection, and 10% to 20% after proctocolectomy** (Blaivas and Chancellor, 1995b). These are estimates drawn from past literature, and the current incidence is most likely significantly lower owing to the use of nerve-sparing techniques during these types of pelvic surgery. It has been estimated, however, that **in 15% to 20% of affected individuals, the voiding dysfunction is permanent** (McGuire, 1984; Mundy, 1984). The injury may occur consequent to denervation or neurologic decentralization, tethering of the nerves or encasement in scar, direct bladder or urethral trauma, or bladder devascularization. Adjuvant treatment such as chemotherapy or irradiation may play a role as well. The type of voiding dysfunction that occurs is dependent on the specific nerves involved, the degree of injury, and any pattern of reinnervation or altered innervation that results over time (see Chapter 60 and the previous section on neuroplasticity).

Literature on the effects of parasympathetic decentralization on neuromorphology and neuropharmacology of the lower urinary tract in many animal models is abundant (Wein and Barrett, 1988). Parasympathetic decentralization has been reported to lead to a marked increase in adrenergic innervation of the bladder in

some experimental models, with the resultant conversion of the usual β (relaxant) response of the bladder body in response to sympathetic stimulation to an α (contractile) effect (Sundin et al, 1977). Hanno and colleagues (1988) confirmed that, in the cat model, parasympathetic decentralization does result in adrenergic hyperinnervation of the detrusor but that pelvic plexus neurectomy alone or parasympathetic decentralization plus hypogastric neurectomy yields no detectable increase in adrenergic innervation. In their experimental model, decentralization did result in synaptic reorganization in bladder wall ganglia with new cholinergic excitatory inputs from the hypogastric nerves. Koyanagi was the first to call attention to what he referred to as supersensitivity of the urethra to α-adrenergic stimulation in a similar group of patients with neurologic decentralization of the lower urinary tract, implying a similar change in adrenergic receptor function in the urethra after parasympathetic decentralization (Koyanagi et al, 1988). Nordling and colleagues (1981) described a similar change in females after radical hysterectomy and ascribed this change to damage to the sympathetic innervation of the lower urinary tract.

When permanent voiding dysfunction occurs after radical pelvic surgery, the pattern is generally one of a failure of voluntary bladder contraction, or impaired bladder contractility, with obstruction by what seems urodynamically to be residual fixed striated sphincter tone, which is not subject to voluntarily induced relaxation. Often, the smooth sphincter area is open and nonfunctional. Whether this appearance of the bladder neck/proximal urethra is caused by parasympathetic damage or terminal sympathetic damage or whether it results from the hydrodynamic effects of obstruction at the level of the striated sphincter is debated and unknown. **Decreased compliance is common in these patients, and this, with the "obstruction" caused by fixed residual striated sphincter tone, results in both storage and emptying failure. These patients often experience leaking across the distal sphincter area and, in addition, are unable to empty the bladder because although intravesical pressure may be increased, there is nothing that approximates a true bladder contraction. The patient often presents with urinary incontinence that is characteristically most manifest with increases in intra-abdominal pressure.** This is usually most obvious in females because the prostatic bulk in males often masks an equivalent deficit in urethral closure function. Alternatively, patients may present with variable degrees of urinary retention.

Urodynamic studies may show decreased compliance, poor proximal urethral closure function, loss of voluntary control of the striated sphincter, and a positive bethanechol supersensitivity test, findings similar to those in Figure 65–4. **Upper tract risk factors are related to intravesical pressure and the detrusor leak point pressure, and the therapeutic goal is always low-pressure storage with periodic emptying. The temptation to perform a prostatectomy should be avoided unless a clear demonstration of outlet obstruction at this level is possible.** Otherwise, prostatectomy simply decreases urethral sphincter function and thereby may result in the occurrence or worsening of sphincteric urinary incontinence. **Most of these dysfunctions will be transient, and the temptation to "do something" other than perform CIC initially after surgery in these patients, especially in those with little or no preexistent history of voiding dysfunction, cannot be too strongly criticized.** Our general practice in such patients is to discharge them on CIC and then have them return for a full urodynamic evaluation at a later date. Six to 12 months may elapse before detrusor function returns to an acceptable level (Blaivas and Chancellor, 1995b). Many of the changes after radical pelvic surgery are similar to those seen in sacral cord injury or disease. Sislow and Mayo (1990), in an excellent study on decreased bladder compliance after decentralization, noted a higher prevalence of this finding in patients who had undergone radical pelvic surgery than in those who had sustained conus medullaris or cauda equina injury.

Finally, to answer questions as to whether some types of nonradical pelvic surgery such as simple hysterectomy are ultimately responsible for filling/storage or emptying abnormalities on the basis of neurologic damage, more series that include sophisticated preoperative and early and late postoperative urodynamic evaluation are necessary.

Herpesvirus Infections

Invasion of the sacral dorsal root ganglia and posterior nerve roots with herpes zoster virus may produce urinary retention and detrusor areflexia days to weeks after the other primary viral manifestations (Ryttov et al, 1985). Generally, painful cutaneous eruptions secondary to the virus are also present, but initially there may be just fever and malaise with perineal and thigh paresthesias and obstipation. **Urinary incontinence secondary to detrusor overactivity may also occur, but the pathophysiology is uncertain.** It may be related to nerve root irritation, inflammation of the meninges or spinal cord, or "zoster cystitis" (Broseta et al, 1993). Cystoscopy may reveal vesicles in the bladder mucosa similar to those seen on the skin. **Spontaneous resolution generally occurs in 1 to 2 months.** Broseta and colleagues (1993) reported on 57 patients with herpes zoster infection whose records were reviewed retrospectively. Fifteen (26%) of these patients showed urologic manifestations, but in only two of these did frank urinary retention occur. Three patients demonstrated urinary incontinence; urodynamically, all of those showed involuntary bladder contractions. Ten patients demonstrated irritative voiding symptoms with dysuria and frequency.

Chen and colleagues (2002) reported on the incidence of voiding dysfunction in 423 patients admitted with a diagnosis of herpes zoster. Seventeen (4%) had voiding dysfunction. Excluding those with cranial rather than spinal nerve involvement, the incidence was 8.8%; when only lumbosacral dermatome patients were considered, the figure rose to 28.6%. The authors subdivided the bladder disorders into three types. The most common is associated with a herpetic cystitis. Patients in this group may present with dysuria, frequency, retention, pyuria, or hematuria. Twelve of the 17 affected patients (71%) were in this group; they presented with dysuria and frequency or retention. The second type is neuritis associated, presumably affecting the sacral motor neurons. Four of the 17 (24%) were in this group and presented in urinary retention and with a "flaccid bladder." Myelitis-associated voiding dysfunction is the third type, associated with spinal cord involvement and presenting with detrusor overactivity. One of their patients was in this group. All patients regained a normal or "balanced bladder" within 8 weeks, and no major urologic sequelae were noted.

Urinary retention has also been reported to occur in association with anogenital herpes simplex virus infection. Caplan and colleagues (1977) reported 11 such patients with the typical clinical picture of herpes genitalis, all of whom

developed urinary retention 2 to 7 days after the genital eruption. Hemrika and colleagues (1986) reported three such patients, each of which showed pleocytosis of the cerebrospinal fluid, a finding that they believed was indicative of central nervous system involvement. They termed the coexistence of bilateral involvement of the sacral nerve roots of rapid onset accompanied by sphincteric incontinence with cerebrospinal fluid pleocytosis the ***Elsberg syndrome*** and tabulated 47 such cases reported before their article. Haanpaa and Paavonen (2004) added two cases, in which both patients had transient urinary retention but developed chronic neuropathic pain in the sacral area. The lower urinary tract dysfunction was transient, as with herpes zoster.

Diabetes Mellitus

Diabetes is the most common cause of peripheral neuropathy in Europe and North America. The exact prevalence of diabetes in the United States is somewhere between 1% and 6%, depending on whether one includes only diagnosed patients or diagnosed and undiagnosed patients and on what fasting blood glucose criteria one uses for inclusion (the higher estimate of prevalence represents a recent reduction in blood glucose criteria to 126 mg/dL) (Chancellor and Blaivas, 1995a; Goldman and Appell, 2000b). The clinical spectrum of voiding dysfunction thought to be caused by diabetes has been well reviewed by a number of authors, each of whom has cited the same historical articles up to their date of publication and added their personal experience at that time (Kaplan and Blaivas, 1988; Kaplan and Te, 1992; Beck et al, 1994; Chancellor and Blaivas, 1995a; Kaplan et al, 1995; Wein and Rovner, 1999; Goldman and Appell, 2000b). The exact incidence of voiding dysfunction caused by diabetes is, however, uncertain. Unselected patients generally do not complain of bladder symptoms. **If specifically questioned, anywhere from 5% to 59% of patients with diabetes report symptoms of voiding dysfunction.** However, the symptoms may or may not be caused by just the diabetes. In trying to come to conclusions regarding the incidence and types of voiding dysfunction specifically from diabetes, one has to carefully discriminate between articles that consider patients referred for voiding symptoms versus those that have evaluated unselected patients from a population known to have diabetes.

Current evidence points to both a sensory and a motor neuropathy as being involved in the pathogenesis, the motor aspect per se contributing to the impaired detrusor contractility. **The typically described classic urodynamic findings include impaired bladder sensation, increased cystometric capacity, decreased bladder contractility, impaired uroflow, and, later, increased residual urine volume.** The main differential diagnosis, at least in men, is generally bladder outlet obstruction because both conditions commonly produce a low flow rate. Pressure/flow urodynamic studies easily differentiate the two. **Smooth or striated sphincter dyssynergia is generally not seen in classic diabetic cystopathy,** but these diagnoses can easily be erroneously made on a poor or incomplete urodynamic study—voiding may involve abdominal straining, which will produce an interference EMG pattern (pseudodyssynergia), and abdominal straining alone will not open the bladder neck area.

Other articles have appeared, however, suggesting that this "classic" diabetic cystopathy may not be the predominant form of lower urinary tract dysfunction. Starer and Libow (1990) reported on a group of 23 elderly diabetic nursing home patients who presented with symptoms of urinary dysfunction. In these 19 women and 4 men, 61% had involuntary bladder contractions, 17% had voluntary contractions of decreased magnitude, 13% had normal detrusor contractility, and 9% were unable to initiate a detrusor contraction at all. Kaplan and colleagues (1995) reported on another group of patients with diabetes referred because of voiding symptoms. Fifty-five percent were found to have involuntary bladder contractions; 23%, impaired detrusor contractility; 10%, detrusor areflexia; and 11%, "indeterminate findings." In the 42 patients in this group with sacral cord neurologic signs, 50% had impaired detrusor contractility and 24% had detrusor areflexia. Chancellor and Blaivas (1995a) detailed the urodynamic findings in 43 diabetic patients at Chancellor's institution: 33% had involuntary bladder contractions with normal contractility; 23% had involuntary bladder contractions with impaired contractility but were able to void; 9% had impaired bladder contractility alone but were able to void; 23% had detrusor areflexia; and only 12% had a normal urodynamic study. Ueda and colleagues (1997) also found involuntary bladder contractions in a moderate percentage of diabetic patients (25%) but noted that all these patients had a history of cerebrovascular disease and that no patient had involuntary bladder contractions who did not have such a history. Although it is obvious that some (or even many) of the patients with diabetes who exhibited involuntary bladder contractions may have had factors other than diabetes to account for their bladder overactivity, the importance of urodynamic study in diabetic patients before the institution of therapy cannot be overemphasized.

A variety of animal models have been able to replicate the diabetic state; however, different models demonstrate different patterns of disease expression. Alloxan-induced diabetic rats demonstrated detrusor overactivity. Sucrose-fed rats demonstrated normal bladder contractions. Streptozotocin-induced diabetic rats demonstrate pyuria more commonly (raising the question of an inflammatory component). Therefore the type of model used should be considered when attempting to interpret experimental findings (Yoshimura et al, 2005).

Liu and Daneshgari (2005) concluded that bladders of diabetic and diuretic rats weighed more than control animals and that diabetes and diuresis caused a significant increase in overall fluid intake, urine output, and bladder size. An increased response after field stimulation was noted in both diabetic and diuretic conditions, and a reduced response to cholinergic activity was noted as compared with controls. The authors noted this finding indicated the possibility of neurogenically mediated bladder contraction in the diabetic rat (Liu and Daneshgari, 2005). Numerous articles

Key Point: Diabetes Mellitus

- Cai Frimodt-Moller (1976) coined the term *diabetic cystopathy* to describe the involvement of the lower urinary tract by this disease. The classic description of voiding dysfunction secondary to diabetes is that of a peripheral and autonomic neuropathy that first affects sensory afferent pathways, causing the insidious onset of impaired bladder sensation. As the classic description continues, a gradual increase in the time interval between voiding results, which may progress to the point at which the patient voids only once or twice a day without ever sensing any real urgency. If this continues, detrusor distention, overdistention, and decompensation ultimately occur. Detrusor contractility, therefore, is classically described as being decreased in the end-stage diabetic bladder.

describe potential pathophysiologic mechanisms that could account for the various types of voiding dysfunction seen in diabetes. Clark and Lee (1995) describe the basic mechanism of interference with physiologic mechanisms as increases in blood glucose increasing the intercellular accumulation of both glucose and its subsequent metabolic products. Hyperglycemia is then proposed to lead to microvascular and neurologic complications, the neurologic sequelae ultimately resulting in a loss of myelinated and unmyelinated fibers, wallerian degeneration, and blunted nerve fiber reproduction and function. The proposed mechanisms include increased accumulation of polyols (sorbitol) from glucose through the aldolase-reductase pathway, inhibiting both glomerular and neural synthesis of myoinositol. The decrease in myoinositol synthesis depresses phosphoinositide metabolism, decreasing Na^+,K^+-ATPase activity. Hyperglycemia also leads to the formation of advanced glycosylation end products, inhibition of the formation of which in animals has been shown to improve response to functional and structural abnormalities of peripheral nerves.

Nerve growth factor (NGF) and its primary receptor p75NTR expression have been shown to be altered in rodent diabetic models. Tong and Cheng (2005) evaluated NGF levels in streptozotocin-treated rats by means of ELISA expressions for MRNAs of NGF and its primary receptor. NGF levels were found to be significantly lower in streptozotocin-induced diabetic rats, as compared with controls for both NGF and its primary receptor. In a treatment group managed with insulin, with normal glycemia, NGF levels and expressions of NGF, MRNAs, and primary receptor MRNAs were normalized.

Another aspect of diabetic bladder dysfunction may occur at the organelle level. In rodent models, morphologic changes in chronic diabetes have also included mitochondrial abnormalities, especially in the urothelium. Increased collagen was noted to be deposited in capillary walls, with an interruption or extensive widening of the gap junctions between myocytes in the bladder muscularis. Reduced mitochondrial counts were noted in the urothelium and bladder muscle. Degenerated nerve fibers and myelin bodies were identified between myocytes with increased collagen, and mast cells inflammatory aggregates were noted in the stroma of diabetic rats as compared with nondiabetic controls. The duration of diabetes appeared to amplify these changes, and the authors concluded that diabetic changes were a time-dependent phenomenon (Rizk et al, 2006).

In addition to this overall hypothesis, there are tantalizing "chunks" of data from various investigators that may or may not prove to be involved in the pathogenesis of voiding dysfunction secondary to diabetes. In streptozotocin-induced diabetic rats, Hashitani and Suzuki (1996) report reduced spontaneous spike activity, failure of neuromuscular transmission, reduced potency of the smooth muscle sodium-potassium pump, and the development of a postjunctional, muscarinic supersensitivity, but without alteration of the adenosine triphosphate receptor sensitivity. Tong and colleagues (1999) reported an upregulation of M2 receptor protein in the bladder of streptozotocin-induced diabetic rats and an upregulation of M2 receptor protein in bladder body tissue (Tong and Juei-Tang, 2002). Presumably, this could be related to detrusor overactivity and conceivably account for a differential effect of various anticholinergic agents, depending on their receptor specificity. Mumtaz and colleagues (1999) reported an impairment of nitric oxide–mediated urethral smooth muscle relaxation in alloxan-induced diabetic rabbits along with a significant impairment of noradrenergic, noncholinergic, nerve-mediated relaxation in this area. They hypothesize that nitric oxide may be functionally inactive and/or unavailable in this type of diabetes, and this lack may contribute to non–BPH-related outlet obstruction in patients with long-term diabetes and to detrusor overactivity, although it is a bit unclear as to how changes in only the outlet might influence overactivity. Gupta and colleagues (1996) and Gupta and Wein (1999) suggested that diabetes diminishes sodium pump activity, thereby inhibiting agonist-induced contractions in bladder smooth muscle by an increase in intracellular sodium concentration, the latter acting to diminish calcium influx. In abstract form, Chacko's group (Su et al, 2004) has hypothesized a translocation of protein kinase C isoforms as being involved in decreased detrusor contractility in alloxan-induced diabetes in rabbits. Cardozo and colleagues (2002) reported enhancement of bladder contractions to substance P and des-Arg-BK in a streptozotocin model. Sasaki and colleagues (2002) described decreased nerve growth factor in bladder tissue and L6 to S1 dorsal root ganglia. In alloxan-induced diabetic animals, Khan and colleagues (2002) noted decreased apoptosis of bladder urothelial cells. In this same model, Su and colleagues (2004) reported increased myosin light chain phosphorylation and decreased sensitivity to activator calcium; Changolkar and colleagues (2005) reported decreased smooth muscle force associated with increased lipid peroxides and sorbitol and an overexpression of aldolase reductase and polyol pathway activation. Another interesting pathophysiologic explanation is that attributed to autoimmune phenomena. In a murine model, antibody-mediated bladder dysfunction in type 1 diabetes has been identified. In diabetic mice, anti–voltage-gated calcium channel antibodies induce urodynamic findings compatible with overactive bladder such as phasic detrusor contractions and also loss of bladder wall compliance. This autoimmune dysfunction was reversed by the administration of agonists for voltage-gated calcium channels. The possible reversibility of this phenomenon remains intriguing for early-stage treatment (Wan et al, 2007).

Early institution of timed voiding will avoid the proportion of the impaired detrusor contractility from chronic distention and detrusor decompensation. Experimental studies are currently directed at inhibiting the proposed mechanisms by which hyperglycemia produces neuropathy (Clark and Lee, 1995). Ayan and colleagues (1999) cite references showing that intensive therapy for diabetes can slow its progression and slow the development of abnormal autonomic tests. As a corollary, they showed on a short-term basis in alloxan-induced diabetic rabbits that insulin therapy prevented the urodynamic (increased bladder capacity and compliance) and histopathologic changes seen in a similar but non–insulin-treated group of animals. Insulin reversed most of the changes reported by Cardozo and colleagues (2002).

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is **an inflammatory demyelinating disorder of the peripheral somatic and autonomic nervous system** that may be life threatening. It is described as a recognizable clinical entity characterized by rapidly evolving symmetrical limb weakness, loss of tendon reflexes, absent or mild sensory signs, and variable autonomic dysfunctions (Hahn, 1998). It results from aberrant immune responses directed against peripheral nerve components (Hartung et al, 1995; Hahn, 1998). It is triggered by a preceding bacterial or viral infection, with the immune responses directed toward the infecting organisms cross-reacting with neural tissues. The immune reactions against Schwann cell surface membrane or myelin result in acute inflammatory demyelinating neuropathy (accounting for 85% of cases), whereas reactions against axonal membrane components cause

acute motor-sensory axonal neuropathy, accounting for 15% of cases. Two thirds of patients report an antecedent acute infectious illness, most commonly a respiratory tract infection or gastroenteritis, that has resolved by the time the neurologic symptoms begin. Several anecdotal case reports have linked GBS to vaccination by temporal association alone. About 75% of cases reach their nadir within 2 weeks and 94% within 4 weeks. After a brief plateau phase, improvement begins, with gradual resolution of paralysis over weeks to months. The outcome is generally favorable, but Hahn (1998) quotes a mortality rate of 5% to 8% despite the most aggressive management. **Autonomic neuropathy is a common complication.** Cardiac arrhythmia; hypertension and hypotension; and bowel, bladder, and sexual dysfunction may occur. **The prevalence of lower urinary tract dysfunction has been reported as ranging from 25% to more than 80%** (Wyndaele et al, 2005). Zochodne (1994) reviewed multiple series and reported a urinary retention rate of 11% to 30%. Sakakibara and colleagues (1997a) reported 7 of 28 patients with voiding dysfunction. Of these, three had transient urinary retention; two had urgency, nocturia, and urge incontinence; one had stress incontinence; and one had voiding difficulty, otherwise unexplained. Many of these patients will have an indwelling catheter to monitor output while in the intensive care unit. Otherwise, **their voiding dysfunction should be managed by reversible therapy** (e.g., CIC, anticholinergic therapy) while waiting and hoping for resolution.

MISCELLANEOUS NEUROLOGIC DISEASES CAUSING VOIDING DYSFUNCTION

Lyme Disease

The associated neurologic symptoms of Lyme disease (neuroborreliosis) fall broadly into three syndromes: (1) encephalopathy, (2) polyneuropathy, and (3) leukoencephalitis. The Lyme spirochete can also (rarely) invade the bladder itself. Chancellor and colleagues (1993) described seven patients who also had lower urinary tract dysfunction. Five had detrusor overactivity, none had dyssynergia, and two had detrusor areflexia. In two women, urinary retention was the presenting symptom of Lyme disease. Other subjective symptoms noted were urgency, frequency, nocturia, and urge incontinence. Follow-up at 6 months to 2 years after treatment revealed residual urgency and frequency in three patients.

Hereditary Spastic Paraplegia

Hereditary spastic paraplegia is a genetically transmitted disorder, generally autosomal dominant, less commonly autosomal recessive, and rarely sex linked. There is a pattern of central demyelination with axon loss and progressive lower extremity spasticity generally with muscle weakness. Bushman and colleagues (1993) reported three patients, two of whom had detrusor overactivity (one with striated sphincter dyssynergia), one who had significantly decreased compliance, and one who was urodynamically normal except for a high maximum urethral pressure of uncertain significance.

Jensen and colleagues (1998) reported the voiding characteristics of 11 patients with autosomal dominant pure spastic paraplegia linked to chromosome 2p21-p24. These were culled from six of eight families with the disorder, the authors commenting that lower urinary tract symptoms were present in 16 of 44 definitely affected family members. One patient had an indwelling catheter, and thus an accurate description of symptomatology was not possible. For the other patients, urinary urgency and frequency were the dominant complaints, with 6 of these 10 patients regularly experiencing urgency incontinence. Urodynamically, three patients showed detrusor overactivity, six demonstrated normal detrusor activity, and one demonstrated "hyporeflexia" with delayed first sensation. Satisfactory sphincter EMG recordings were obtained from seven patients, and all were normal. Postvoid residual urine volumes were raised in 8 of 10 patients. The bulbocavernosus reflex was absent in six patients and was truly normal in only one. The authors commented that the frequency of urinary symptoms in their patients (36%) correlated well with other reports in the literature. The authors proposed that the lower urinary tract symptoms (and bowel and sexual dysfunction) in patients with this disorder are caused by a combination of somatic and autonomic nervous system involvement, supporting a multisystem involvement.

Tropical Spastic Paraparesis

Tropical spastic paraparesis is primarily a spinal cord myelopathy caused by a retrovirus (human T-cell leukemia virus 1 [HTLV-1]) similar to HIV. Progressive lower limb weakness and back pain are typically the primary complaints, but voiding dysfunction occurs in up to 60% of those affected (Walton and Kaplan, 1993). Eardley and colleagues (1991) studied six such patients with voiding dysfunction. Two had detrusor areflexia, and three had overactivity, one of whom with dyssynergia. Walton and Kaplan (1993) found four of five consecutive patients had detrusor overactivity and striated sphincter dyssynergia, whereas one had overactivity and synergia. The type of voiding dysfunction depends on whether the damage is primarily to the descending spinal tracts, to the sacral nuclei, or to the sacral outflow. The disease must be distinguished from other myelopathic conditions associated with voiding dysfunction such as MS.

Acquired Immunodeficiency Syndrome

Infection with HIV can affect both the central and peripheral nervous systems, and so it is not unexpected that symptoms of lower urinary tract dysfunction occur, although there is some disagreement as to the overall prevalence of such symptoms in this population. Khan and colleagues (1992) were among the first to report on the types of voiding dysfunctions seen in patients with AIDS. They reported 11 such patients. Urinary retention occurred in six. On urodynamic evaluation, three had detrusor overactivity, four had detrusor areflexia, two had a hypocontractile detrusor, and two had outlet obstruction secondary to BPH. Hermieu and colleagues (1996) prospectively studied 39 patients with HIV infection and voiding symptoms. Clinical symptoms included frequency, urgency, and incontinence in 41% of patients, acute urinary retention in 28%, dysuria and frequency in 18%, and decreased flow in 13%. Seventeen of the patients had involuntary bladder contractions; of these, eight had striated sphincter dyssynergia or a lack of sphincter relaxation during micturition, five patients had detrusor areflexia, four patients had what was termed a "hypertonic urethra," three had "hypersensitivity," and five patients had a normal urodynamic evaluation. The authors characterized the voiding dysfunctions broadly as inability to void in 41% of the cases and frequency/urgency/incontinence in 41%. The authors comment that the appearance of neurogenic voiding disturbances

heralds a poor prognosis. Eighteen HIV-positive patients, 13 with AIDS, who presented with voiding dysfunction were urodynamically characterized by Kane and colleagues (1996). Chief presenting complaints were daytime frequency in eight patients; retention in three; nocturia in two; and having to strain to void, feeling incompletely empty, incontinence, split stream, and groin pain in one each. Five patients (28%) showed detrusor overactivity, five showed DESD, and one (6%) showed detrusor areflexia. The authors remarked that there was a correlation between cytomegalovirus infection, polyradiculopathy, and detrusor areflexia, a phenomenon reported by others as well. Other common causes of voiding dysfunction exist as well because four patients had outlet obstruction secondary to BPH and in one patient it was secondary to urethral stricture. In another study, Lima and colleagues (2002) evaluated a group of 26 men with HIV-induced bladder dysfunction. Eighty percent of those patients demonstrated detrusor overactivity, and 34% had detrusor-sphincter dyssynergia. These findings are indicative of the myopathy associated with HIV (Lima et al, 2002). Additionally, impaired micturition in the HIV complex may be due to infestations (cerebral toxoplasmosis or viral encephalitis), demyelination disorders, cytomegalovirus, polyradiculopathy, and AIDS-related dementia. Thirty to forty percent of patients with AIDS will develop neurologic involvement with 20% presenting initially with some neurologic symptom. In those patients presenting with urologic symptoms, an underlying neurologic cause is present in approximately 60% of those patients, and 90% of those patients will have already developed an AIDS-associated neoplasm or infestation. Detrusor-sphincter dyssynergia, poor bladder contractility, detrusor overactivity, and bladder outlet obstruction have all been reported in this population. AIDS-related neurogenic voiding dysfunction is associated with a poor outcome, with a mortality rate of approximately 40% within 8 months of development of urologic symptoms (Heyns and Fisher, 2005). How common are voiding problems overall in patients with HIV infection and AIDS? Gyrtrup and colleagues (1995) prospectively investigated voiding function in 77 men and 4 women with HIV infection or AIDS consecutively attending an outpatient clinic. Eight of these (10%) had moderate subjective voiding problems, whereas two (2%) had severe problems. The authors believed that in only 4% of patients did the nature of the disturbance warrant urodynamic examination and concluded that urinary voiding symptoms are only a modest problem overall in an HIV/AIDS population. They concluded that neuropathic bladder dysfunction is rare and occurs mostly in the late stages of the disease.

Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is an acute inflammatory demyelinating disorder of the central nervous system of unknown etiology. It is also sometimes known as *parainfectious* or *postinfectious encephalomyelitis*. The sites of lesions are multifocal and can include the cerebral white matter, cerebellum, brainstem, and spinal cord. The records of 11 patients with ADEM were reviewed and commented on by Sakakibara and colleagues (1996a). Nine patients had presented in urinary retention; the other two had urgency, frequency, nocturia, and difficulty voiding, one of whom had enuresis and urgency incontinence as well. The urodynamic findings are difficult to correlate with the presenting symptoms because in four of the patients the studies were done considerably after the onset of the disease. During the follow-up period, seven of the nine patients who originally had retention became able to urinate. Five had difficulty voiding, and four developed irritative symptoms. Six of the patients ultimately had a near-complete neurologic recovery, but voiding symptoms persisted in three. The authors concluded that the supranuclear and nuclear types of pelvic and pudendal nerve dysfunction were primarily responsible for the micturitional disturbances in patients with this disease and that voiding dysfunction was common in these patients.

Syringomyelia

Syringomyelia is a chronic disorder of the spinal cord characterized by dissociated sensory loss and brachial amyotrophy. It usually affects the cervical spinal cord but can extend caudally. Voiding dysfunction has been reported in 9% to 25% of patients. Fourteen patients with syringomyelia were studied urologically by Sakakibara and colleagues (1996d). Eleven of these had urinary symptoms: difficulty voiding in eight, retention in three, nocturnal and daytime frequency in three, incontinence in two, and urgency and enuresis in one. The urinary symptoms appeared from 2 months to 13 years after the initial neurologic symptoms. Urodynamic studies revealed detrusor overactivity in seven, detrusor-sphincter dyssynergia in four, detrusor areflexia in four, and "uninhibited sphincter relaxation" in two. It is interesting that motor unit EMG recordings disclosed findings compatible with denervation of the striated sphincter in five of six patients. The authors concluded that both supranuclear and nuclear types of peripheral autonomic and somatic nerve dysfunction are responsible for the voiding dysfunctions seen. It is also interesting that the micturitional status gradually improved in four of six patients after syringosubarachnoid shunts.

Schistosomal Myelopathy

In addition to causing voiding dysfunction secondary to bladder neck obstruction and impaired muscle contractility as a result of infiltration of the bladder smooth muscle itself, schistosomiasis can rarely cause spinal cord involvement, either as a granulomatous intrathecal mass or as an acute transverse myelitis (Razdan et al, 1997). Two such patients presented with urinary incontinence as their chief urologic complaint. Both had detrusor overactivity: one without dyssynergia and with minimal motor weakness and the other with striated sphincter dyssynergia and a T11 sensory level. It was believed that the findings in the former patient were characteristic of a partial spinal cord or cerebral lesion and that the second patient had a suprasacral transverse myelopathy. In the first patient, the urinary symptoms developed approximately 2 months after exposure and after the development of systemic symptoms; in the second case, symptoms developed some 5 years after the initial diagnosis. Gomes and colleagues (2002) reviewed the records of 14 patients with schistosomal myelopathy referred for voiding dysfunction. Of five patients with acute disease, three presented with retention and two had incontinence. Urodynamics were performed in three of these. Two (one in retention, one with hesitancy and incontinence) demonstrated detrusor areflexia, and one (in retention) showed detrusor overactivity and striated sphincter dyssynergia. Of the 9 chronic patients, 5 showed detrusor overactivity with dyssynergia, 1 with decreased compliance; 2 showed overactivity with synergic sphincters; and 25 showed detrusor areflexia, 1 with decreased compliance.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a disease in which there is widespread inflammatory change in the connective tissues and

small vessels of the skin and systemic organs, probably autoimmune in origin (Hahn cited by Sakakibara et al, 2003b). The prevalence of nervous system involvement is cited from 18% to 75%. Myelopathy occurs in 1% to 3% of SLE patients. Sakakibara and colleagues (2003b) reported on eight patients with SLE who presented with voiding dysfunction, six with voiding difficulty (two in retention) and four with urinary incontinence. Five exhibited decreased flow, three had increased residual urine, five had detrusor overactivity, five had impaired detrusor contractility, four had detrusor–striated sphincter dyssynergia, and two of four exhibited abnormal striated sphincter EMG potentials. Sensation was impaired in two patients. Although three patients had subacute encephalomyelopathy (one subacute myelopathy, four chronic myelopathy), the lower urinary tract dysfunction seemed related mainly to the myelopathy. Yu and colleagues (2003) studied 152 women with lupus. Urodynamics and an AUA-7 symptom index were administered and compared with 227 age-matched healthy women. A significantly higher percentage of women with SLE experienced emptying and storage dysfunction with higher symptom scores in the lupus group, as compared with the control group. There was a correlation between symptomatic presentation and Lupus index, but no correlation with disease duration. However, there was a significant relationship between symptom degree and magnitude of symptoms and central nervous system involvement in the lupus group. The lupus patients more commonly manifested a diminished cystometric capacity and a decreased flow rate.

Reflex Sympathetic Dystrophy

Reflex sympathetic dystrophy is a disabling syndrome characterized by severe pain with autonomic changes such as vasomotor disturbances. The condition usually follows a traumatic injury. The exact etiology and pathogenesis are unclear. The prevalence of voiding dysfunction in patients with reflex sympathetic dystrophy is unknown, but it must be more than a rare occurrence because Chancellor and colleagues (1996) were able to collect 20 consecutive patients with neurologically verified reflex sympathetic dystrophy who were referred for voiding symptoms, none of which existed before the initial trauma that induced the reflex sympathetic dystrophy. Seven of the patients presented with urinary retention, although some of these had had various types of surgery designed to treat the symptoms of the dystrophy. Five presented with urgency incontinence, one of whom also had stress incontinence. Six had urgency as a primary complaint, one had daytime frequency, and one had severe nocturia. Detrusor overactivity was demonstrated in eight patients, DESD in one, detrusor areflexia in eight, and hypersensitivity on filling in three. Because the authors excluded patients with acute development of voiding dysfunctions after back surgery and with herniated disks and included only those in whom voiding symptoms developed concurrently with progressive symptoms of reflex sympathetic dystrophy, one must conclude that significant lower urinary tract dysfunction can develop as a direct result of or an association with this problem, although the cause-and-effect relationship is unknown.

Other Conditions

A number of other conditions have been associated with voiding dysfunction, most of which have been reported as individual cases or small groups of cases. These are associated with neurologic symptoms typical of central and/or peripheral neural involvement. The interested reader is referred to relevant articles on amyloidosis (Sakamoto and Wheeler, 1997), adult polyglucosan body disease (Gray et al, 1988), Behçet disease (Theodorou et al, 1999; Saito and Miyagawa, 2000; Sakakibara et al, 2000), neurofibromatosis (Brownlee et al, 1998), spinal muscular atrophy (Von Gontard et al, 2001), Duchenne muscular dystrophy (MacLeod et al, 2003), and familial dysautonomia (Saini et al, 2003).

MISCELLANEOUS CONDITIONS DEFINITELY, PROBABLY, OR POSSIBLY RELATED TO NEUROMUSCULAR DYSFUNCTION

Detrusor Sphincter Dyssynergia

Dyssynergia refers to the kinesiologic disassociation of two groups of muscles that generally work in harmony. Sphincter dyssynergia refers to an involuntary contraction or lack of relaxation of either the striated sphincter (the striated muscle surrounding the proximal urethra and the striated muscle that forms a part of the urethra for a variable distance from the "urogenital diaphragm" to the bladder neck) or the smooth sphincter (the smooth muscle of the bladder neck and proximal urethra). **Detrusor sphincter dyssynergia,** unless specified otherwise, refers to dyssynergia of the striated sphincter and is sometimes abbreviated DSD or DESD. This is discussed in Chapter 61 and in the earlier parts of this chapter, especially in the section on SCI. It is discussed as a separate entity here as well to emphasize its importance in terms of recognition and proper management in patients with neurogenic voiding dysfunction.

True DESD should exist only in patients who have an abnormality in pathways between the sacral spinal cord and the brainstem pontine micturition center, generally caused by neurologic injury or disease (Blaivas, 1982; Rudy, 1993; Chancellor and Rivas, 1995; Wein and Rovner, 1999). The diagnosis of DESD should be suspected in any patient with a neurologic lesion in this area. Common causes include traumatic SCI, multiple sclerosis, and the various forms of transverse myelitis. Conversely, **in patients without such a lesion, this diagnosis should always be viewed with skepticism,** and, without such apparent pathology, such a patient deserves exhaustive study to exclude a neural diagnosis. One exception to this precept is in infants and children with dysfunctional voiding or the Hinman syndrome (see later).

Blaivas and colleagues (1981) have described three main types of DESD. In type 1, there is concomitant increase in both detrusor pressure and EMG activity; at the peak of the detrusor contraction, the sphincter suddenly relaxes and unobstructed voiding occurs. In type 2, there are sporadic contractions of the striated sphincter throughout the detrusor contraction. In type 3, there is a crescendo-decrescendo pattern of sphincter contraction that results in outlet obstruction throughout the entire detrusor contraction. Schurch and colleagues (2005) have correlated neurologic status and DESD type after SCI. Those with an incomplete sensory and motor lesion generally present with type 1 DESD; those with complete sensory and motor lesions present with type 2 and type 3. Weld and colleagues (2000) prefer to classify DESD as intermittent or continuous but note that in their experience the clinical significance of DESD type is not crucial because both types require urodynamic surveillance and expedient treatment to minimize complications. No significant association between type and level of injury was

found. Continuous DESD was more associated with complete injuries.

Sphincter EMG activity that increases simultaneously with intravesical or detrusor pressure does not always indicate true DESD, however. These other instances are referred to as pseudodyssynergia (Wein and Barrett, 1982), and such a misdiagnosis may be accompanied by adverse therapeutic consequences. **Common causes of pseudodyssynergia include (1) abdominal straining to either initiate or augment a bladder contraction or in response to discomfort and (2) attempted inhibition of a bladder contraction either because of its involuntary nature or because of discomfort.** Rudy (1993) has reported that pseudodyssynergia can reliably be differentiated from true DESD urodynamically by analyzing the patterns of detrusor and EMG activity, but others have not always found this to be the case.

Without proper treatment, more than 50% of men with DESD will develop significant complications such as VUR, upper tract deterioration, urolithiasis, urosepsis, and ureterovesical obstruction (Chancellor and Rivas, 1995). In women, these complications are much less common, probably because of the decreased detrusor pressures generated. Using Blaivas' categorization, type 1 DESD is generally managed with observation alone unless there is persistent reflux, hydronephrosis, or autonomic hyperreflexia. Types 2 and 3 are generally treated. In assessing success or failure of treatment, Kim and colleagues (1998) have used bladder leak point pressure greater than 40 cm H_2O as an indicator of the failure of at least sphincterotomy, because in their experience there was a significantly higher incidence of upper tract damage and persistent DESD in such patients. This most likely applies to other treatments as well. **Therapy for DESD is designed to either eliminate or significantly lessen the abnormal sphincter activity or to circumvent it. Oral medical therapy directed toward the striated sphincter has not enjoyed wide success, and the most common current approaches are (1) CIC (usually combined with therapy to control detrusor overactivity), (2) sphincterotomy, (3) stent placement across the sphincter, (4) injection of botulinum toxin into the sphincter, (5) continuous catheterization, and (6) urinary diversion.**

Experimental small animal models of DESD have been reported by Burnett and colleagues (1997) in mice with targeted deletion of the gene for neuronal nitric oxide synthase and by Cheng and colleagues (1997) by instillation of cold water into the urinary bladder of rats.

Dysfunctional Voiding

This subject is more extensively considered in Chapters 127-128 but is mentioned here because individuals with a history of unexplained lower urinary tract dysfunction symptomatology may not present to the urologist or be definitively diagnosed with this entity until adulthood. **This syndrome, also described by various authors as *non-neurogenic neurogenic bladder, occult voiding dysfunction, occult neuropathic bladder, learned voiding dysfunction,* and the *Hinman syndrome,* presents the unusual circumstance of what appears urodynamically to be involuntary obstruction at the striated sphincter level existing in the absence of demonstrable neurologic disease** (Hinman, 1986). It is difficult to prove urodynamically that an individual has this entity, and it should further be noted that the diagnoses in many of the patients reported have been made on the basis of only history, isolated flowmetry, isolated measurements of total intravesical pressure, and pelvic floor EMG activity (Wein and Barrett, 1988). I believe unequivocal demonstration of this entity requires pressure-flow-EMG evidence of bladder emptying occurring simultaneously with involuntary striated sphincter contraction in the absence of any element of abdominal straining, either in an attempt to augment bladder contraction or as a response to discomfort during urination. Such reports do exist and confirm the existence of this syndrome. The etiology is uncertain and may represent a persistent transitional phase in the development of micturitional control or persistence of a reaction phase to the stimulus of lower urinary tract discomfort during voiding, long after the initial problem that caused this has disappeared (Jorgensen et al, 1982).

Bladder Neck Dysfunction

Bladder neck dysfunction is defined here as **an incomplete opening of the bladder neck during voluntary or involuntary voiding.** It has also been referred to as *smooth sphincter dyssynergia, proximal urethral obstruction, primary bladder neck obstruction,* and *dysfunctional bladder neck*. **The term *smooth sphincter dyssynergia* or *proximal sphincter dyssynergia* is generally used when referring to this urodynamic finding in an individual with autonomic hyperreflexia.** In male patients with autonomic hyperreflexia, the neurologic pathophysiology is clear. **The term *bladder neck dysfunction* more often refers to a poorly understood non-neurogenic condition first described over a century ago but first fully characterized by** Turner-Warwick and colleagues in 1973**. The dysfunction is found almost exclusively in young and middle-aged men, and characteristically they complain of long-standing voiding/emptying (obstructive) and filling/storage (irritative) symptoms** (Webster et al, 1980; Norlen and Blaivas, 1986; Wein and Barrett, 1988; Trockman et al, 1996; Yamanishi et al, 1997). **These patients have often been seen by many urologists and have been diagnosed as having psychogenic voiding dysfunction because of a normal prostate on rectal examination, a negligible residual urine volume, and a normal endoscopic bladder appearance.** The differential diagnosis also includes anatomic bladder neck contracture, BPH, dysfunctional voiding, prostatitis/prostatosis, neurogenic dysfunction, and low pressure/low flow (see later). **Objective evidence of outlet obstruction in these patients is easily obtainable by urodynamic study. Once obstruction is diagnosed, it can be localized at the level of the bladder neck by video-urodynamic study, cystourethrography during a bladder contraction, or micturitional urethral profilometry** (see Chapter 62). The diagnosis may also be made indirectly by the urodynamic findings of outlet obstruction in the typical clinical situation in the absence of urethral stricture, prostatic enlargement, and striated sphincter dyssynergia. Involuntary bladder contractions or decreased compliance may occur. Noble and colleagues (1994) cite the incidence as 50%, but this seems high. Trockman and colleagues (1996) quote it as 34%.

The exact cause of this problem is unknown. Some have proposed that there is an abnormal arrangement of musculature in the bladder neck region, so coordinated detrusor contractions cause bladder neck narrowing instead of the normal funneling (Bates et al, 1975). The occurrence of this problem in young, anxious, and high-strung individuals and its partial relief by α-adrenergic blocking agents have prompted some to speculate that it may in some way be related to sympathetic hyperactivity.

When prostatic enlargement develops in individuals with this problem, a double obstruction results, to which Turner-Warwick (1984) **has applied the term *trapped prostate.*** The lobes of the prostate cannot expand the bladder neck and therefore expand into the urethra. A patient so affected generally has a lifelong history of voiding dysfunction that has gone relatively unnoticed because he has always accepted this as normal, and exacerbation of these symptoms occurs during a relatively short and early period of prostatic enlargement. Although α-adrenergic blocking agents provide improvement in some patients with bladder neck dysfunction, definitive relief in the male is best achieved by bladder neck incision. In patients with this and a trapped prostate, marked relief is generally effected by a "small" prostatic resection or ablation that includes the bladder neck or a transurethral incision of the bladder neck and prostate. Such patients often note afterward that they have "never" voided as well as after their treatment.

Bladder Outlet Obstruction in Women

The female counterpart of non-neurogenic bladder neck dysfunction in men does exist, although it is rare. **Bladder outlet obstruction in women in general is uncommon.** Dionko and colleagues (1984) were among the first to clearly define this entity in women on the basis of video-urodynamic studies. Nitti and colleagues (1999) evaluated the video-urodynamic studies of 261 of 331 women who underwent multichannel studies for non-neurogenic voiding dysfunction. **They defined *bladder outlet obstruction* as radiographic evidence of obstruction between the bladder neck and the distal urethra in the presence of a sustained detrusor contraction of any magnitude, which is usually associated with reduced or delayed urinary flow rate. Obstruction at the level of the bladder neck was diagnosed when the bladder neck was closed or narrowed during voiding. Obstruction of the urethra was diagnosed as a discrete area of narrowing, associated with proximal dilatation.** Strict pressure-flow criteria were not used to classify cases as obstructed or not obstructed. Using these criteria they found 76, or 23%, of their cases to be obstructed. Of those obstructed, only 16% (12 patients) were diagnosed as having primary bladder neck obstruction (the counterpart to non-neurogenic bladder neck dysfunction in the male). Thirty-three percent of the cases of obstruction were caused by dysfunctional voiding (see earlier for description), 28% by cystocele, 14% by obstruction created by prior incontinence surgery, 4% by urethral stricture, 3% by uterine prolapse, and 1% each by urethral diverticulum and rectocele. Groutz and colleagues (2000) reviewed their urodynamic database of 587 consecutive women referred for evaluation of voiding symptoms. **They defined obstruction as a persistent, low, noninvasive maximum flow rate less than 12 mL/sec on repeated study combined with a detrusor pressure at maximum measured flow rate of more than 20 cm H_2O in a pressure-flow study.** Only 38 women (6.5%) met these criteria of bladder outlet obstruction. Of those, only 8% (three women) were characterized as having primary bladder neck obstruction. Twenty-six percent (10 women) had obstruction on the basis of prior anti-incontinence surgery, 24% because of severe genital prolapse, 13% because of urethral stricture, 5% because of dysfunctional voiding, 5% because of true detrusor striated sphincter dyssynergia, and 3% because of urethral diverticulum. In 16%, there was no definable etiology. **Most authors would agree that surgical treatment of this problem in women should be approached with caution because sphincteric incontinence is a significant risk.** Smith and Appell (2006) commented on the importance of urodynamics in distinguishing dysfunctional voiding versus bladder neck dysfunction. They commented on the importance of evaluation inclusive of symptom assessment, uninstrumented uroflow patterns, simultaneous urodynamic and EMG assessment of voiding, as well as the addition of fluoroscopy to assess function of the bladder neck during voiding. They further stressed multidisciplinary therapy including pelvic floor therapy (biofeedback), behavioral modification, and the addition of pharmacotherapy. Neuromodulation may have a role in select patients, as well as rare surgical intervention for primary bladder neck dysfunction.

Low-Pressure/Low-Flow Voiding in Younger Men: Bashful Bladder

Low-pressure/low-flow voiding **can be the result of a number of causes, most notably a decompensating detrusor** (generally from bladder outlet obstruction—see Chapters 62 and 92) or as a part of the syndrome known as *detrusor hyperactivity with impaired contractility* (DHIC—see Chapters 62 and 76). **When this occurs in a young man, it is generally characterized by frequency, hesitancy, and a poor stream.** The entity is readily demonstrated on urodynamic assessment and with no coexisting endoscopic abnormality. **The patient usually notes marked hesitancy when attempting to initiate micturition in the presence of others,** and some have therefore described this condition as an "anxious bladder" or a "bashful bladder." The estimate of the incidence of this problem in younger male patients referred for urodynamic assessment varies between 6% (Barnes et al, 1985) and 19% (George and Slade, 1979).

Barnes and colleagues (1985) suggested that these men are psychologically unusual but in the direction of being obsessional rather than anxious. They suggest that these individuals have a lifelong tendency to overcontrol the process of micturition and are thus vulnerable to lower urinary tract symptoms under stress, and they recommend that a behavioral modification program be considered. Rosario and colleagues (2000) performed ambulatory urodynamic studies on 40 consecutive symptomatic men with a mean international prostate symptom score of 19 who were unable to "perform" during conventional video-urodynamic study. They concluded that a surgically correctable cause of the symptoms could be found in about 20% of men, but only in those older than 40 years. They believed therefore that the contribution of ambulatory urodynamic monitoring in such cases in men younger than 40 years was negligible. They also stated that they thought evidence from the literature suggested that a significant proportion of such nonobstructed cases would respond to drug therapy or behavioral therapy. The authors' experiences have been similar to those of others who have stated that, in the younger nonobstructed male with this condition, neither empirical pharmacologic treatment nor transurethral surgery has had any consistent beneficial effect.

Urinary Retention; the Fowler Syndrome in Young Women

Urinary retention is encountered fairly commonly by the urologist, especially in adult men secondary to anatomic obstruction from benign prostatic enlargement. Although unusual, urinary

retention in women is not rare. As in the male, **the potential causes are classically cited as neurologic, pharmacologic, anatomic, myopathic, functional, and psychogenic.** A particularly excellent review of the various causes of urinary retention in women along with an algorithm for evaluation and treatment has been published by Smith and colleagues (1999).

The Fowler syndrome (Fowler et al, 1988; Noble et al, 1994; Fowler, 1999, 2007; Swinn and Fowler, 2001) refers to **a syndrome of urinary retention in young women in the absence of overt neurologic disease. The typical history is that of a woman younger than 30 years of age who has found herself unable to void for a day or more with no urinary urgency but increasing lower abdominal discomfort. A bladder capacity of more than 1 L with no sensation of urgency is necessary for the diagnosis. There are no neurologic or laboratory features to support a diagnosis of any neurologic disease. MRI of the brain and the entire spinal cord is normal. On concentric needle electrode examination of the striated muscle of the urethral sphincter, however, Fowler and colleagues described a unique EMG abnormality.** This abnormal activity, localized to the urethral sphincter, consists of a type of activity that would be expected to cause inappropriate contraction of the muscle. Sphincter activity consists of two components: complex repetitive discharges and decelerating bursts. This abnormal activity impairs sphincter relaxation. These patients often have polycystic ovaries, raising the possibility that the activity is linked in some way to impaired muscle membrane stability, allowing direct spread of electrical impulses throughout the muscle, owing possibly to a hormonal abnormality; and thus the disorder may possibly be the manifestation of a focal, hormonally dependent "channelopathy." This would explain why the condition is seen only in premenopausal women. Efforts to treat this condition by hormonal manipulation, pharmacologic therapy, or injections of botulinum toxin have been unsuccessful. This condition is highly responsive to neuromodulation (success rate approaching 70%) even in women who have been in retention for many months or years.

Kavia and colleagues (2006) assessed a large group of women (247) for assessment of either complete (42%) or partial (58%) retention. Completeness was defined as inability to void whatsoever. These women had previously been diagnosed with abnormality of the striated urethral sphincter electromyogram (Fowler syndrome), which led to the referral. These women were assessed with a combination of urethral profilometry (71%), transvaginal ultrasonographic measurement of sphincter volume (57%), and sphincter electromyogram (39%). Those patients with complete retention showed a significant difference in sphincter volume between those who were EMG positive, as opposed to those who were EMG negative. The authors concluded that on the basis of this, the most common diagnosis for women referred for urinary retention was Fowler syndrome, which led to the potential use of neuromodulation for those patients.

The urodynamic problem is detrusor acontractility. The same EMG abnormality, however, is found sometimes in women with obstructed voiding. This type of EMG activity is not uncommon (Fitzgerald and colleagues [2000] cite an incidence of 8% in a series of women undergoing routine urodynamic and EMG studies), but its correlation with complete retention is relatively rare.

Neuromodulation has been advocated for Fowler syndrome (nonobstructive urinary retention in women). De Ridder and colleagues (2007) reported 62 women who underwent sacral nerve stimulation, 30 of whom had findings compatible with Fowler syndrome and 32 with idiopathic retention. Somatoform disorder was found in 26% of the Fowler's patients and 43.8% of the idiopathic group. Depression was also higher in the Fowler syndrome group (30% vs. 18.8%). Neither of these findings, however, had correlation with outcome. Nine patients with Fowler syndrome as compared with 19 without failed neuromodulation. The authors concluded that Fowler syndrome was actually a positive predictive factor for SNS response in patients with female urinary retention. They did advocate preimplant psychologic testing including the patient health questionnaire; however, there was no correlation with outcomes in this population.

Postoperative Urinary Retention

Postoperative urinary retention is a well-recognized but poorly understood event. Its incidence is generally quoted overall as 4% to 25%. It occurs more frequently after lower urinary tract, perineal, gynecologic, and anorectal surgery. In the placebo arms of four trials of α-adrenergic blocker prophylaxis after these types of surgery, the incidence of postoperative retention ranged from 18.8% to 57% (Velanovich, 1992). **Contributing factors, which are not mutually exclusive, include the following eight factors:**

1. Traumatic instrumentation
2. Bladder overdistention
3. Diminished awareness of bladder sensation
4. Decreased bladder contractility
5. Increased outlet resistance
6. Decreased micturition reflex activity
7. Nociceptive inhibitory reflex
8. Preexistent outlet pathology (e.g., BPH)

Anesthesia and analgesia can contribute to factors 2, 3, 4, and 6. The idea of a nociceptive inhibitory reflex, initiated by pain or discomfort, is an attractive one because a sympathetic efferent limb could directly affect factors 4, 5, and 6 (see Chapter 60).

Bladder decompression for 18 to 24 hours postoperatively decreased the incidence of retention in patients undergoing joint replacement surgery by 52% versus 27% (Michelson et al, 1988) and 65% versus 0% (Carpiniello et al, 1988), compared with CIC. The incidence of urinary infection with continuous catheterization was no different in the Michelson and colleagues' study (15% vs. 11%) and was less in the Carpiniello and colleagues' study (16% vs. 43%), in which straight catheterization was carried out in the recovery room as well. The avoidance of acute bladder overdistention to prevent postoperative urinary retention is supported by the experimental observation of a reduced bladder response to sacral neural stimulation during overdistention (>80% reduction) and, as well, after overdistention (19% reduction) (Bross et al, 1999).

α-Adrenergic blockade with phenoxybenzamine historically has seemed effective prophylactically in decreasing the incidence of postoperative retention. Velanovich (1992) performed a meta-analysis on the use of phenoxybenzamine (only randomized placebo-controlled studies) and concluded that this agent reduced the occurrence by 29.1%. In a retrospective review of colorectal patients treated with and without phenoxybenzamine, Goldman and colleagues (1988) found a 54.7% incidence of retention in patients not given this agent versus a 19.2% incidence in those who were. The regimen for those not catheterized preoperatively was 10 mg orally the evening before and 1 hour before surgery, 2 hours after, and 10 mg twice daily for 3 days. For those who were catheterized before the procedure, the regimen was 10 mg twice daily, initiated the day before catheter removal. The mechanism of action is uncertain. If an inhibitory nociceptive reflex is

initiated, and this is similar to the sympathetic reflex elicited by bladder filling (see Chapter 60), the mechanism is multifactorial. Alternatively, the drug may act only on the outlet to decrease resistance, which may be pathologically increased by anxiety, pain, and other factors related to surgery. Whether other α-adrenergic blockers are as effective is uncertain (Cataldo and Senagore, 1991).

Hyperthyroidism

Patients with thyrotoxicosis often present with symptoms caused by sympathetic overactivity and autonomic nervous system imbalance. Goswami and colleagues (1997) reported that 12 of 30 patients (40%) experienced the onset of voiding symptoms 1 to 6 months after the onset of the symptoms of thyrotoxicosis. Four of these patients had enuresis. Urodynamic studies were done in five patients; all had reduced flow rates, and four had a significant postvoid residual, three of whom had an enlarged bladder capacity and increased perineal EMG activity during voiding. The voiding dysfunction and urodynamic abnormalities resolved after resolution of the hyperthyroidism. The bladder symptoms were more common in females than in males. The authors hypothesize that increased β-adrenergic activity in thyrotoxicosis is responsible for a reduced flow rate and increased bladder capacity because of the inhibitory β-adrenergic activity on detrusor muscle contractility. Stoffer (1988) cited a much lower incidence of voiding dysfunction in thyrotoxicosis: a 7% prevalence of urgency and hesitancy and a 1% prevalence of enuresis.

Schizophrenia

Bonney and colleagues (1997) proposed that a significant subset of schizophrenic patients have involuntary bladder contractions secondary to brain pathology. In a previous study (Gupta et al, 1995), the same group demonstrated involuntary bladder contractions in 4 of 10 evaluable patients with schizophrenia who were referred for voiding dysfunction or incontinence. All of these patients had significant childhood incontinence, urge incontinence, bedwetting, and a small bladder capacity. In the later report (Bonney et al, 1997) the prevalence of urinary incontinence and related symptoms in a group of chronic schizophrenic patients was compared with a group of comparatively hospitalized patients with mood disorders. There was a significant difference in the prevalence of urge incontinence (34% vs. 17%) and bedwetting (46% vs. 20%). There were no significant differences in urinary urgency, overall voiding dysfunction, fecal incontinence, or sexual dysfunction. The hypothesis of a neurobiologic correlate between schizophrenic patients and the occurrence of involuntary bladder contractions in these patients is an intriguing one.

Gastroparesis

Gastroparesis is a condition characterized by symptoms from impaired transit of intraluminal gastric contents into the duodenum but in the absence of mechanical obstruction. It may be caused by diabetes, occur after gastric surgery, or be idiopathic. Goldman and Dmochowski (1997) characterized the voiding dysfunction of 17 patients with gastroparesis who were referred for voiding symptoms, 10 of whom had idiopathic gastroparesis and in 7 of whom the condition was secondary to diabetes. Seven patients had abnormal detrusor contraction and delayed sensation, five had poor detrusor function and normal sensation, three had normal detrusor function and poor sensation, and two had normal detrusor contraction and sensation. There was no difference between the occurrence of the dysfunctions in the two groups. Predominant symptoms were urinary frequency in 7 and difficulty emptying in 10. Patients with idiopathic gastroparesis were more likely to note difficulty emptying (70%), whereas those with diabetic gastroparesis were more likely to have urinary frequency (71%). The authors postulated an association between idiopathic gastroparesis and bladder dysfunction and proposed that a common autonomic neuropathic syndrome may account for the bladder dysfunction in both the idiopathic and the diabetic forms of this syndrome.

Myasthenia Gravis

Any neuromuscular disease that affects the tone of the smooth or striated muscle of the distal sphincter mechanism can predispose an individual patient to a greater chance of urinary incontinence after even a well-performed transurethral or open prostatectomy. Myasthenia gravis is an autoimmune disease caused by autoantibodies to acetylcholine nicotinic receptors. This leads to neuromuscular blockade and hence to weakness in a variety of striated muscle groups. The incidence of incontinence after prostatectomy is indeed greatly increased in patients with this disease (Greene et al, 1974; Khan and Bhola, 1989). Sandler and colleagues (1998), in addition, reviewed three cases of de novo voiding dysfunction in patients with myasthenia gravis (one woman with intrinsic sphincter deficiency, poor pelvic muscle contractility, and detrusor hyperreflexia; one male with detrusor hyporeflexia complaining of urgency and incontinence; and one young woman with an acontractile bladder) and added a personal report of a fourth patient with urinary retention from detrusor areflexia. They hypothesize that such autonomic dysfunction in a patient with myasthenia might indicate a unique subset with a worse prognosis.

Isaacs Syndrome

Isaacs syndrome is a rare neurologic disorder characterized by continuous muscle contraction, fasciculations, myokymia, excessive sweating, and elevated creatinine kinase level. It is shown to be secondary to antibodies possibly directed against potassium channels on peripheral nerves and is associated with peripheral neuropathy, autoimmune diseases, malignancies, and endocrine disorders. Tiguert and colleagues (1999) present a case with urinary retention associated with a picture of acute demyelinating neuropathy. Their patient was in painful urinary and fecal retention; the urinary retention was presumed to be caused by spasm of the periurethral striated sphincter, diagnosed by an inability to pass a catheter beyond this. Rectal sphincter spasm was also diagnosed. The condition was treated with plasmapheresis and pharmacologic agents to relax skeletal muscle. Suprapubic drainage was instituted. The condition subsided, and normal urinary function was ultimately restored.

Wernicke Encephalopathy

Wernicke encephalopathy is a rare but well-documented condition caused by a deficiency in thiamine (vitamin B_1) in both alcoholic and nonalcoholic populations. Pathologic lesions are characteristically distributed periventricularly at the levels of the third and fourth ventricles including the mammillary body, medial thalamic nucleus, hypothalamus, superior cerebellar vermis, periaqueductal gray matter, and midbrain tegmentum.

The two major clinical manifestations of thiamine deficiency involve the cardiovascular and neurologic systems. The latter manifests generally as peripheral neuropathy, the condition being known as Wernicke encephalopathy. The initial symptoms of the polyneuropathy range from simply burning feet to muscle weakness. Sakakibara and colleagues (1997b) report a case of a pregnant woman with multiple neurologic manifestations of central and peripheral neuropathy and with urge incontinence, manifested urodynamically by involuntary bladder contractions and a decreased bladder volume. **Resolution of the urinary symptoms occurred after thiamine replacement.** The authors hypothesize that lesions in the medial thalamic-hypothalamic area and periaqueductal gray matter were primarily responsible for the micturitional disturbance. Tjandra and Janknegt (1997) reported a case of a chronic alcoholic male with seemingly isolated erectile and voiding dysfunction, the latter consisting of complaints referable to emptying, correlated with flowmetry during a prolonged void with a peak flow rate of 6.4 mL/sec with an interrupted pattern, suggesting poor detrusor contractility. The erectile dysfunction was determined to be neurogenic. Both resolved with thiamine replacement.

Systemic Sclerosis (Scleroderma)

Scleroderma is a disease of the connective tissue characterized by thickening and fibrosis of the skin, abnormalities of the small arteries, and involvement of the gastrointestinal tract, heart, lung, and kidneys. The pathogenesis is unknown but thought to be caused by overexpression of the collagen gene DNA, contributing to excessive production of collagen in these patients. Lazzeri and colleagues (1995) report the urodynamic assessment and histologic evaluation of nine such women, of whom five had hesitancy; four, decreased stream; two, frequency and nocturia; and two, suprapubic pain. Four patients had detrusor areflexia, one of whom also had decreased compliance. Another patient with decreased stream also had decreased compliance. Three of the patients with areflexia demonstrated collagen accumulation on histologic examination of bladder biopsies. The authors review five literature reports of various aspects of lower urinary tract function and histology in patients with scleroderma but fail to find a consistent pattern in these. They hypothesize that in their patients the areflexia resulted from impaired neurologic modulation owing to the histologic changes in the detrusor tissue.

Minervini and colleagues (1998), conversely, carried out urodynamic and bladder morphologic evaluations in 23 female patients with systemic sclerosis, 9 of whom complained of urinary symptoms, and found urodynamic alterations in only 3 cases. They were unable to correlate voiding symptoms, urodynamic changes, and the degree of bladder wall fibrosis or visceral involvement. Evidence of autonomic nervous system dysfunction was found outside the urinary tract in 13 of these patients. The authors speculate that voiding dysfunction, when it occurs, could be caused by the fibrotic replacement of bladder smooth muscle, but they did not exclude some degree of autonomic dysfunction as well.

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome refers to a heterogeneous group of disorders characterized by inherited abnormalities of connective tissue. The main clinical manifestations are skin fragility, skin hyperextensibility, and joint mobility. More than 10 subtypes of the syndrome have been defined on the basis of clinical, genetic, and biochemical criteria. Bladder diverticula have been associated with this disorder, with operative repair characterized by an increased recurrence rate over that which would ordinarily be expected. Deveaud and colleagues (1999) reviewed the literature on this subject and reported on the intensive study of one such patient with a large left-sided diverticulum that did not empty, along with a greatly enlarged bladder capacity and residual urine. Simultaneously, they reported a second patient without Ehlers-Danlos syndrome who presented with a urinary tract infection and left pyelonephritis. This patient also reported decreased force of stream, and evaluation disclosed left VUR with a left (presumably congenital) periureteral diverticulum. The diverticulum enlarged with voiding, and the patient left a large postvoid residual. Both patients were treated surgically (successfully). The authors thought the tissue from the nonperiureteral diverticulum was more closely related to the pathophysiology of Ehlers-Danlos syndrome, noting the tissue from that diverticulum to be more compliant, and attributed this to changes in the extracellular matrix protein caused by the Ehlers-Danlos syndrome. Nonspecific joint hypermobility may also be associated with voiding dysfunction. Manning and colleagues (2003) prospectively evaluated 1000 women referred for urodynamic evaluation and noted benign joint hypermobility to be associated with increasing bowel dysfunction and a higher degree of urinary tract symptomatology. Also noted was a significant childhood history for both of these phenomena. Generalized joint hypermobility (GJH) has been associated with non-neurogenic bladder dysfunction in children. de Kort and colleagues (2003) reported 89 children with GJH and found that 19% of males, as compared to 4% of control, had constipation. Fecal soiling also occurred more commonly in the GJH group (34% vs. 18%). In girls, day and night urinary incontinence was more prevalent in the joint hypermobility group (38% and 14%, respectively), as compared with controls (13% and 2%). Urinary tract infections also tended to occur more commonly in joint hypermobility with 24% being noted, as compared with 11% in the control group. The generalized hypermobility is a mild form of a genetic, inheritable connective-tissue disease, which is related to Ehlers-Danlos syndrome, Marfan syndrome, and osteogenesis imperfecta. Hypermobility in these children has been reported in multiple organ systems. Additionally, an increased incidence of genitourinary prolapse in women with joint hypermobility has been attributed to connective tissue deficit.

Myotonic Dystrophy

Myotonic dystrophy is an autosomal dominant hereditary multiorgan disease characterized by myotonia and distal muscle atrophy, and in later stages by cataracts, endocrine disturbances, mental retardation or dementia, testicular atrophy and infertility, progressive frontal alopecia, and disturbances in cardiac conduction. Although myotonic activity has not been found in the sphincter or pelvic floor, many patients appear to have voiding complaints. Bernstein and colleagues (1992) reported on 10 patients, 8 of whom had urinary complaints by history (4 infrequent voiders, 1 with urge and stress incontinence, 1 with urge and urge incontinence, 1 with slight urgency without incontinence, and 1 with obstructive symptoms only in the morning). There were no characteristic urodynamic patterns observed, and urodynamic findings did not correlate particularly well with symptoms. Sakakibara and colleagues (1995b) also reported lower urinary tract symptoms in such patients, but the message seems to be that there is **no characteristic pattern of dysfunction,** and thus such patients

need to be characterized urodynamically before making any assumptions regarding therapy based on symptoms alone.

Corticobasalar Degeneration

Corticobasalar degeneration is a rare neurodegenerative disorder of the corticobasalar tracts in the cerebral cortex and basal ganglia, most likely in the supranuclear parasympathetic system. The disorder tends to have a unilateral predominance. Cortical, extrapyramidal, long-tract, and urinary symptoms are commonly noted in this disease process. Sakakibara and colleagues (2004b) assessed 10 patients with this disorder compared with 11 age-matched controls. As compared with controls, the degeneration patients had more common urinary symptoms (80% of study group). Urinary symptoms usually appeared within 1 to 3 years after onset of the disease and became more common with longer disease duration. Nocturnal frequency tended to be the initial urinary symptom, followed by incontinence, urgency, and frequency. Urodynamic findings included decreased bladder capacity, detrusor overactivity (most commonly), detrusor hypocontractility, and low compliance in individual patients. Detrusor sphincter dyssynergia was not noted (Sakakibara et al, 2004b).

SACRAL COCCYGEAL TERATOMA

Sacral coccygeal teratoma can produce significant neuro-urologic dysfunction and can be associated with upper tract deterioration due to high-grade reflux and abnormal bladder storage pressures. Öskan and colleagues identified 14 patients with sacral coccygeal teratoma, of whom detrusor overactivity was seen in 8, underactivity in 2. There was also abnormal urethral sphincteric activity in 54% of the patients, and 38% demonstrated sphincter dyssynergia. Eleven of 14 patients required clean intermittent catheter drainage for bladder emptying, and additionally, 5 required anticholinergics. Six patients had hydronephrosis, and seven had reflux (Ozkan et al, 2006).

Radiation

Vale and colleagues (1993) summarized their experience with the occurrence of voiding dysfunction after external-beam irradiation. **They describe an early radiation reaction most prominent at 4 to 6 weeks with an incidence as high as 70%. Symptoms are predominantly of the filling/storage type, and urodynamic studies have demonstrated reduced volume at first desire to void, reduced cystometric capacity, and reduced compliance. These parameters tend to return to pretreatment values by 6 months. Symptoms associated with later radiation effects are less common but may be progressive and intractable. Filling/storage symptoms predominate, and urodynamic studies, when positive, demonstrate reductions in first desire to void, maximum cystometric capacity, involuntary bladder contractions (in up to a third of patients), and an increase in maximum subtracted detrusor pressure during filling.** Historical explanations have concentrated on urothelial injury and ulceration with fibrosis. These authors attempted to develop an experimental model in rats. They found a biphasic reduction in compliance, the first reduction developing at 4 to 6 weeks after irradiation, followed by recovery. A second reduction phase in compliance started at 10 to 12 weeks and persisted. Interestingly, only half the irradiated bladders demonstrated fibrotic infiltration of muscle bundles, and there was no association between the presence of fibrosis and the magnitude of reduction and compliance. Mast cells were more abundant in irradiated bladders than in controls. Electron microscopic studies showed, in the irradiated bladders, the presence of areas displaying focal degeneration of smooth muscle cells, these cells showing disaggregation of filaments and in some cases cytoplasmic organelles free in the intracellular space. In scattered foci, selective degeneration of unmyelinated axon profiles was noted, ranging from marked to lesser degrees of axonal injury. The authors were thus unable to confirm a fibrosis-based hypothesis of postirradiation bladder dysfunction in their experimental model but did show other changes that could contribute to such dysfunction: neural degeneration and changes in the detrusor muscle itself.

Choo and colleagues (2002) reported on video-urodynamic parameters in 15 of 17 patients completing studies at baseline and at 3 and 18 months after external-beam irradiation for prostate cancer. Between baseline and 18 months there were no statistically significant changes in detrusor pressure, peak flow rate, voided volume, postvoid residual, compliance, occurrence of detrusor overactivity, or outlet obstruction. There was a mean reduction in bladder capacity of 100 mL in the supine position and 54 mL in the upright position. There was no change in self-assessed qualitative urologic function (International Prostate Symptom Score, Quality of Life Assessment Index, and urinary frequency). There were, however, individual patients who developed decreased compliance (four patients) and detrusor overactivity (two patients), urgency (five patients), and urgency incontinence (three patients).

Defunctionalized Bladder

The timing of bladder defunctionalization and the age on the individual at time of defunctionalization may be predictive of bladder functionality. In fetal sheep urinary diversion results in loss of overall bladder weight with marked connective tissue infiltration and loss of smooth muscle organization. Also, a reduced response to carbachol stimulation and increased response to field stimulation was noted in tissue from animals undergoing early diversion (Matsumoto et al, 2003).

The previously normal defunctionalized bladder will often show decreased capacity and involuntary bladder contractions and/or decreased compliance. Previously abnormal bladders will generally demonstrate their prior pathology, many times with these additional abnormalities. Rehabilitation of a defunctionalized bladder is certainly possible and should definitely be attempted by cycling with progressively increasing volumes. Serrano and colleagues (1996) considered this subject while evaluating the outcome of transplantation into five long-term defunctionalized bladders. Successful bladder rehabilitation was accomplished, and the transplantation was successful without bladder augmentation, although one patient required CIC. Normal compliance was inferred by the fact that there was no evidence of hydronephrosis after long-term allograft function up to 10 years. The authors recommend that transplantation can be accomplished into a previously defunctionalized bladder when a capacity greater than 100 mL and a voiding pressure less than 100 cm/H_2O are demonstrated during bladder rehabilitation.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is associated with mixed urinary symptoms. Davies and colleagues (2005) studied 19 women with congenital adrenal hyperplasia (16 of whom had

undergone childhood feminizing surgery). These were compared with age-matched controls. The CAH population had a higher incidence of urge incontinence (68%) and stress incontinence (47%) as compared with age-matched controls. The effects of congenital adrenal hyperplasia are uncertain and may be due to either the result of feminizing surgery (possible direct neuropraxia induced by surgery) or a primary affect of CAH (Davies et al, 2005).

Aging

Lower urinary tract symptoms and disorders are prevalent and bothersome in the elderly population. These problems are specifically and extensively considered in Chapter 76. When considering the effects of aging on the lower urinary tract, one cannot separate the effects of chronologic age itself from the various anatomic, neuromorphologic, neurophysiologic, neuropharmacologic, metabolic, and hormonal changes that coexist with aging, along with the effects of other coexisting disease processes. In addition to the material contained in Chapter 76, there is an excellent review of this area that was carried out by the Committee on Pathophysiology of the Urinary Bladder and Obstruction and Aging for the 4th International Consultation on BPH (Nordling et al, 2001).

Additionally, neurologic phenomena may masquerade as lower urinary tract symptoms associated with bladder outlet obstruction. These phenomena may include multiple cerebral infarctions, cervical spondylosis, and lumbar spondylosis. These findings were noted in the Olmsted County longitudinal study and are indicative of the need for urodynamics in older men with complex urinary symptoms (Woderich and Fowler, 2006).

Other Conditions

The effect of disordered function of other organs within the pelvis is also potentially contributory to lower urinary tract dysfunction. Some of this disordered function may arise due to altered afferent neurologic activity induced by other organ disorders. The potential for visceral "cross talk" has been proposed as an etiology for patients with lower urinary tract dysfunction including syndromes such as interstitial cystitis and irritable bowel syndrome. In a rodent, the short- and long-term effects of acid-induced colitis on bladder function have been assessed. Bladder detrusor muscle contractility and histology were evaluated, both acutely and subacutely after induction of chemical colitis. During the active phase (3 days postinjury), bladder muscle structure appeared histologically normal and without inflammation. However, some abnormalities in detrusor muscle contractility in response to electrical field stimulation were noted. During the subacute period and after recovery of colitis (15 and 30 days), bladder muscle contractility returned to control levels with no discernible histologic change. These reversible changes were postulated to result from altered afferent input from the colon, resulting in "field" type changes affecting the bladder (Noronha et al, 2007).

Parturition, Caesarean Section, and Simple Hysterectomy

No clear consensus yet exists as to the independent effects of child birth and hysterectomy on lower urinary tract function. A variety of explanations have been put forth regarding whether or not, in fact, lower urinary tract dysfunction is induced by these events and, if so, what the underlying pathophysiology may be.

In a multicenter Danish trial, patients undergoing hysterectomy (either total or subtotal) for benign uterine diseases were assessed. A total of 319 women were randomized to either total abdominal hysterectomy (158) or subtotal abdominal hysterectomy (161). At 1-year follow-up after intervention, urinary incontinence was less often noted in patients undergoing total abdominal hysterectomy. Both groups, however, did experience an increase in incomplete emptying requiring double voiding. Interestingly, both groups experienced an overall decrease in urinary incontinence frequency as compared with baseline (Gimbel et al, 2005).

No prospective trials, as yet, document the long-term follow-up relationship between urinary dysfunction and method of delivery, and no prospective clinical trials have been done to determine if caesarean section is protective against the development of incontinence. The debate regarding caesarean section as an alternative to spontaneous vaginal delivery and impact of each on the lower urinary tract also continues. The EPINCONT study assessed 15,307 women for the development of voiding dysfunction during longitudinal follow-up. The risk of urinary incontinence of all types was noted to be higher in women who had caesarean sections as compared with nulliparous women and those who had vaginal deliveries. However, the risk of moderate to severe incontinence was actually less in section patients than in patients who had had vaginal deliveries. Urgency incontinence was the only exception, being equal across all groups. The adjusted ratio for any incontinence in women after caesarean section was 1.5 versus 1.7 for women with vaginal deliveries. Stress incontinence appeared to be associated with mode of delivery (Rortveit, 2003a, 2003b).

McKinnie and colleagues (2005) studied 1004 women over an 18-month period to determine the relationship between urinary and fecal incontinence and type of delivery. In this study, pregnancy was identified as increasing the overall risk of urinary and fecal incontinence, and there was no apparent relationship to mode of delivery (McKinnie et al, 2005).

As of yet no agreement exists as to the putative causation of voiding dysfunction related to pregnancy and parturition. It would seem reasonable to believe that mass effect of the gravid uterus combined with peripheral nerve changes (neuropraxia related to stretch) may be contributory.

Any neurologic disease or injury can affect lower urinary tract function. Many have been mentioned in this chapter, but case reports and small series exist that document many others. The dysfunction produced by some is logically deducible on the basis of similarity to other neurologic lesions; for others the lower urinary tract dysfunctions are inconsistent and seemingly at odds with what would be predicted on the basis of neuroanatomic and neurophysiologic principles. For those who want to further pursue this subject, the following referenced list may be helpful:

Adrenoleukodystrophy (Silveri et al, 2004)
Adrenomyeloneuropathy (Sakakibara et al, 1998a)
Brown-Séquard syndrome (Sakakibara et al, 2001)
Central cord syndrome (Newey et al, 2000; Smith et al, 2000)
Incontinence in cystic fibrosis (Dodd and Langman, 2005)
Down syndrome (Handel et al, 2003)
Intramedullary epidermoid cyst (Ferrara et al, 2003)
Lambert-Eaton myasthenic syndrome (Satoh et al, 2001)
Machado-Joseph disease (Sakakibara et al, 2004a)
Pituitary adenomas and urinary symptoms (Yamamoto et al, 2005)
Sjögren syndrome (Kovacs et al, 2003)
Spinal cord tumors (Uchiyama et al, 2004)

TREATMENT OF NEUROGENIC LOWER URINARY TRACT DYSFUNCTION: OVERVIEW

In later chapters, the various therapies available for the treatment of lower urinary tract dysfunction are considered. Only a discrete number of such therapies are available, and these are easily categorized on a functional "menu" basis according to whether they are used primarily to assist urine filling/storage or voiding/emptying and according to whether their primary effect is on the bladder or on the outlet (see Tables 66–3 and 66–4).

The initial choice of a mode of management for a given problem is multifactorial. Although many of us who lecture and write about the management of neurogenic lower urinary tract dysfunction are associated primarily with one approach or another, **all would doubtless agree on certain goals of management for voiding dysfunction** (Table 65–2). The fact that these goals have remained relatively unchanged over the past few editions of this text attest to their general validity. As a corollary, absolute or relative indications for changing or augmenting a particular regimen exist, and, likewise, there is general agreement on these, although the relative importance of the indication for change might be disputed (Table 65–3). It should be remembered that the term *inadequate,* when applied to storage and emptying, applies not only to volumes (capacity, voided volume, residual) but also to unacceptably high detrusor pressures during either or both of the two phases of the micturition cycle. In the planning of goals of therapy and reasons for change, the concept of a "hostility score" such as that of Galloway (1989) is attractive. His hostility score includes five urodynamic characteristics—bladder compliance, overactivity, dyssynergia, outlet resistance, and VUR. Each is allocated a score of 0, 1, or 2. The best possible score is 0 and implies normal compliance, no inappropriate detrusor activity, a synergic sphincter, a low leak pressure, and no reflux.

The results of treatment of voiding dysfunction are rarely perfect, and they do not have to be. The goals are satisfaction and avoidance of adverse outcomes. A flexible approach must be adopted in choosing therapy that takes into account the individual wishes of each patient and family and the practicality of each proposed solution for that particular patient (Table 65–4). The therapeutic decisions are thus made with the patient and with the family. In every case, within the limits of practicality, the following should be discussed: reversibility, side effects that occur with some regularity, ultimate best and worst possible scenario, frequency and extent of follow-up, and alternate methods of management. Treatment should always begin with the simplest most reversible form(s) of therapy, proceeding gradually up the ladder of complexity, but with the knowledge that it is only the patient (and/or family) who is (are) empowered to say when "enough is enough." Again, avoidance of adverse outcomes and satisfaction are the primary goals. A combination of therapeutic maneuvers can sometimes be used to achieve a particular end, especially if these modalities act through different mechanisms and their side effects are not synergistic or additive. There are circumstances and locales in which health care resources and hospital bed use must also be considered.

New therapies continue to be proposed for those patients with neurogenic lower urinary tract dysfunction refractory to medical therapies. The use of dorsal penile or clitoral nerve stimulation for controlled neurogenic detrusor overactivity has been recently described. Hansen and colleagues (2005) studied a group of 16 patients (2 women and 14 men) with neurogenic detrusor overactivity and diminished bladder capacity associated with complete or incomplete SCI. After stimulation of the dorsal nerve, 13 of 16 were noted to have increased bladder capacity and improved storage pressures during stimulation. The average bladder capacity increase was 53% in the study group. Detrusor pressures were also modulated below those associated with ureterovesical reflux (Hansen et al, 2005).

Pudendal nerve stimulation has been used for improving neurogenic voiding dysfunction. Spinelli and colleagues treated 15 patients with neurogenic voiding dysfunction (varied causes). After pudendal stimulation, there was a significant decrease in incontinence episodes, with 8 of 15 patients becoming continent during stimulation, and two with improvement approximating 90%. Twelve of 15 ultimately progressed to permanent implantation. In the chronically implanted patients, maximal cystometric capacity was noted to significantly increase and maximum

Table 65–2.

Voiding Dysfunction: Goals of Management

Upper urinary tract preservation or improvement
Absence or control of infection
Adequate storage at low intravesical pressure
Adequate emptying at low intravesical pressure
Adequate control
No catheter or stoma
Social acceptability and adaptability
Vocational acceptability and adaptability

Table 65–3.

Reasons to Change or Augment a Given Regimen

Upper urinary tract deterioration
Recurrent sepsis or fever of urinary tract origin
Lower urinary tract deterioration
Inadequate storage
Inadequate emptying
Inadequate control
Unacceptable side effects
Skin changes secondary to incontinence or collecting device

Table 65–4.

Patient Factors to Consider in Choosing Therapy

Prognosis of underlying disease, especially if progressive or malignant
General health
Limiting factors: inability to perform certain tasks (e.g., hand dexterity, ability to transfer, body habitus)
Mental status
Motivation
Desire to remain catheter or appliance free
Desire to avoid surgery
Sexual activity status
Reliability
Educability
Psychosocial environment, interest, reliability, and cooperation of family
Economic resources

detrusor pressure was also noted to decrease substantially. Neurophysiologic guidance was considered critical for adequate implantation (Spinelli et al, 2005).

Another form of neuromodulatory therapy for which more experience is being reported in SCI is anterior root stimulation. One of the largest experiences with sacral deafferentation and anterior root stimulator implantation was reported by Kutzenberger and colleagues (2005). Four-hundred and sixty-four paraplegic patients received this intervention, with most patients receiving the intradural approach. Four-hundred and forty of these patients were available for long-term follow-up with a mean of 6.6 years. Complete deafferentation was successful in 94% of the patients. Four-hundred and twenty patients used the sacral anterior root stimulator for voiding, and 401 used it for defecation. Overall, 364 (83%) of patients were continent. Urinary tract infections decreased from a mean of six to a mean of one, postoperatively, and kidney function remained stable in this population. Complications included cerebral spinal fluid leaks in six and infected implants in five. Additionally, later complications included device failure or cable failure in 35 patients. Interestingly, autonomic dysreflexia also disappeared or was resolved in most of these cases (Kutzenberger et al, 2005).

As a treatment of last resort, urinary diversion may provide significant functional improvement in addition to improved quality of life in selected patients with neurologic dysfunction. For patients with significant lower urinary tract dysfunction who are unable to catheterize, an alternative may also be urinary diversion. Stein and colleagues (2005) reported 24 patients undergoing Mainz pouch diversion. Urinary diversion was associated with stability of the upper tracts and daytime continence but with some nocturnal incontinence per stoma. Comparing this group with a separate group of patients undergoing bladder augmentation with suburethral fascial sling, all patients in the augmentation group had stability of the upper tracts and 8 of 10 were continent. Both alternatives were considered adequate for neurogenic voiding dysfunction (Stein et al, 2005).

Acknowledgment

The authors want to express their utmost appreciation to Rosemarie Larmer and Edna Johnson for their forbearance and expertise in assisting in the production of this chapter.

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The complete reference list is available online at www.expertconsult.com.

chapter 66

Overactive Bladder

Marcus Drake, DM, MA, FRCS (Urol) ● Paul Abrams, MD

Pathophysiology and Etiology
Prevalence
Clinical Assessment
Initial Treatment
Urodynamic Evaluation
Management

The overactive bladder (OAB) is a prevalent problem, with considerable effects on the quality of life of affected individuals and substantial health economic costs. The condition is symptom based and defined by the International Continence Society (ICS) standardization committee as **urgency, with or without urgency incontinence, usually with frequency and nocturia, if there is no proven infection or other obvious pathology** (Abrams et al, 2002). A correction had to be put forward when it was realized that the term "urge incontinence" had been used in the original definition (Abrams et al, 2009). OAB is thus a syndrome in which several of the lower urinary tract symptoms (LUTS) relating to the storage of urine coexist, with urinary urgency as the essential parameter. Because urgency will frequently arise at comparatively small bladder volumes, patients tend to describe frequent voids with a low typical voided volume. Nocturia as a symptom is somewhat variable in OAB because the supine position and reduced physical exertion overnight seem to be less provocative in eliciting OAB. A difficulty with the ICS definition is that some patients may void preemptively (defensive voiding), passing urine before urgency arises; they will thus clearly have storage-phase LUTS yet lack the urgency symptom, which is the defining characteristic of OAB.

Urgency with at least one other symptom is essential to diagnose OAB. Thus urgency is the pivotal symptom, defined by the ICS as **the complaint of a sudden compelling desire to void that is difficult to defer**. However, there remains plenty of room for confusion. For example, a normal "urge to void" is not synonymous with abnormal urgency; the ICS therefore suggested that the term "desire to void" is more appropriate for describing normal filling sensation. Furthermore, there are grounds to consider including "for fear of leakage" alongside the sudden compelling desire to void that is difficult to defer—indeed this was included in earlier ICS definitions. Many OAB patients certainly feel as if they are going to leak, even if they say they never have, commonly expressing anxieties exemplified by, "When I want to go, I have to rush because I think I may wet myself."

In many OAB patients, urgency incontinence occurs, defined as involuntary leakage of urine, accompanied or immediately preceded by urgency (Abrams et al, 2002). This standardized definition abandoned the requirement that the leakage should be a "social or hygienic problem" to be called incontinence because considerable leakage can occur, which in some individuals may not be a problem to them, particularly in children and the elderly. In a prevalence survey, 69% of women had "any incontinence," but only 30% found this a "social or hygienic problem" (Swithinbank et al, 1999).

The symptom of "increased daytime frequency" is the complaint by the patient who considers that he or she voids too often by day. There is no minimum number of voids included in the standardized definition. **The symptom of nocturia is the complaint that the individual has to wake at night one or more times to void**. No agreement has been reached for individuals with differing sleep patterns such as night-shift workers.

Before the introduction of the standardized definitions, the use of several overlapping terms resulted in a confusing situation, hampering many aspects of research and management. The English-speaking world had adopted Patrick Bates' term *unstable bladder* to describe involuntary detrusor contractions seen during urodynamic studies as the bladder was filled, while the Scandinavians used the term *detrusor hyperreflexia*. To resolve the discrepancy, the ICS designated the term *unstable bladder* to be applied where there was no obvious cause for the contractions and *detrusor hyperreflexia* for patients whose involuntary contractions had a neurologic cause (Bates et al, 1980); ***overactive detrusor*** was used as the generic, overarching term. Nonetheless, the use of different terms in neurologic and non-neurologic patient groups became increasingly difficult. Firstly, several studies showed considerable overlap in the underlying mechanisms. In addition, explaining the terms to the patients and the wider medical profession highlighted the incongruity of the differing terminology. Furthermore, physicians had to be careful not to insult the sensibilities of the patient by inadvertently implying mental instability by using the word "unstable" in relation to bladder symptoms. "Overactive Bladder" was used as the title of a consensus conference, and a formal definition was proposed in 1999 (Abrams and Wein, 1999), culminating in the ICS definition used currently.

Crucially, the current definition of OAB is based on symptoms; in contrast, **detrusor overactivity (DO) is a urodynamic observation, characterized by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked** (Abrams et al, 2002). **OAB and DO are thus not interchangeable terms,** and the clinician must be specific in their use. Clinicians need to be clear on this among themselves and when discussing urgency with patients. All measures, for example "warning time" (between first sensation of urgency and eventual voiding), depend on the patients and the clinicians reaching a consensus as to the meaning of urgency. The

ICS terminology committee excluded "for fear of leakage" in the new definition of urgency, mainly because many OAB patients do not leak. Perhaps this was not entirely logical because patients can certainly feel as if they are going to leak, even if they have never actually done so. A couple of phrases are often used by patients:

- "When I've got to go, I've got to go."
- "When I want to go, I have to rush because I think I may wet myself."

Hence "fear of leakage" is an important concept to patients.

Key Points: OAB Terminology

- The International Continence Society updated its definitions for OAB and other lower urinary tract dysfunctions in 2002.
- OAB is a symptomatic diagnosis and is distinct from detrusor overactivity (DO), which is a urodynamic diagnosis.
- Other causes of similar symptoms must be excluded before diagnosing OAB.
- OAB is defined by the presence of urinary urgency with at least one other relevant symptom.
- "Fear of leakage" is not part of the ICS definition of urgency, but it is a concept that OAB patients feel is important.

PATHOPHYSIOLOGY AND ETIOLOGY

The reliance on urgency in defining OAB is a problem for investigation into its scientific basis because it complicates the development of reliable animal models, with which evaluation of subjective symptoms is not possible. Accordingly, research focus has particularly concentrated on abnormalities of afferent signaling and mechanisms underlying DO, the former as the presumed basis of urgency, the latter as it is likely to contribute in a large number of people with OAB. In addition, some hypothetical reasoning has been used to translate scientific observations into clinical reality.

Hypotheses of Detrusor Overactivity

Until recently, insight into the pathophysiologic basis of DO has generally focused on cellular mechanisms by which unregulated motor activity could arise. **The neurogenic hypothesis states that DO arises from generalized, nerve-mediated excitation of the detrusor muscle** (de Groat, 1997). There are several interdependent mechanisms by which this may arise. First, damage to the brain can induce DO by reducing suprapontine inhibition. Second, damage to axonal pathways in the spinal cord allows the expression of primitive spinal bladder reflexes. Third, synaptic plasticity leads to reorganization of sacral activity, with the emergence of new reflexes, which may be triggered by C-fiber bladder afferent neurons. Finally, sensitization of peripheral afferent terminals in the bladder can trigger DO.

The myogenic hypothesis suggests that overactive detrusor contractions result from a combination of an increased likelihood of spontaneous excitation within smooth muscle of the bladder and enhanced propagation of this activity to affect an excessive proportion of the bladder wall (Brading and Turner, 1994; Brading, 1997). Patchy denervation is a common observation in DO, regardless of etiology (German et al, 1995; Charlton et al, 1999; Drake et al, 2000; Mills et al, 2000). A smooth muscle cell deprived of its innervation shows an upregulation of surface membrane receptors and may have altered membrane potential, which increases the likelihood of spontaneous contraction in that cell. DO is also associated with characteristic changes in ultrastructure (Elbadawi et al, 1993; Haferkamp et al, 2003a, 2003b), which could facilitate the propagation of the contraction over a wider proportion of the body of the detrusor than normal. However, the observations in different models of DO and from clinical specimens do not uniformly describe these features.

Afferent Mechanisms in Overactive Bladder and Detrusor Overactivity

The afferent nerve endings are widely distributed in the bladder wall and are particularly dense in the connective tissue underneath the urothelium. In this location, they may be influenced by several cell types. **Urothelial cells possess sensory and signaling properties that allow them to respond to their chemical and physical environments and to communicate with subjacent structures** (Birder, 2001). **Suburothelial interstitial cells lie in close physical proximity to nerve fibers, suggesting a role in sensory transduction or regulation** (Wiseman et al, 2003). The number of impulses fired by an afferent ending at any level of distention can be varied physiologically; that is, the gain of the sensory nerve endings can be changed to vary the "afferent sensitivity." Thus the rate of firing in a particular afferent normally associated with a high vesical volume can occur at lower volumes if the afferent ending has been sensitized. Accordingly, the release of substances from the urothelium, as well as the direct interaction between afferent nerve endings and other cell types, may physiologically influence central reporting of the bladder state and could well contribute pathophysiologically. In theory, **OAB may arise if the level of sensory activity is inappropriately high for any given degree of bladder distention, resulting from pathologically sensitized or abnormally numerous afferent nerve endings.** The interaction among afferents, urothelium, and interstitial cells is thus interesting, in that modulating their interactions may result in amelioration of symptom severity. The expression of various receptors on urothelium and afferents, particularly members of the transient receptor potential (TRP) family, may thus be relevant in the development of future clinical management options. The sensory information is carried to the spinal cord by myelinated Aδ fibers and unmyelinated C fibers. As a general rule, **the Aδ fibers are regarded as responding to passive bladder distention and active detrusor contraction ("in series" mechanoreceptors** [Iggo, 1955]), **thus conveying information about bladder filling** (Janig and Morrison, 1986). **C fibers are regarded as responding primarily to chemical irritation of the bladder mucosa** (Habler et al, 1990) **or to thermal stimulus** (Fall et al, 1990). Accordingly, they may be less active in the physiologic state than the Aδ fibers. Nonetheless, there is almost certainly considerable overlap in the sensory information carried by the two types of afferent, and the C fibers may take on a more prominent role in the pathologic state.

Integrative Physiology of Overactive Bladder

The afferent, neurogenic, and myogenic mechanisms alluded to earlier are essentially based on physiology of individual cell types.

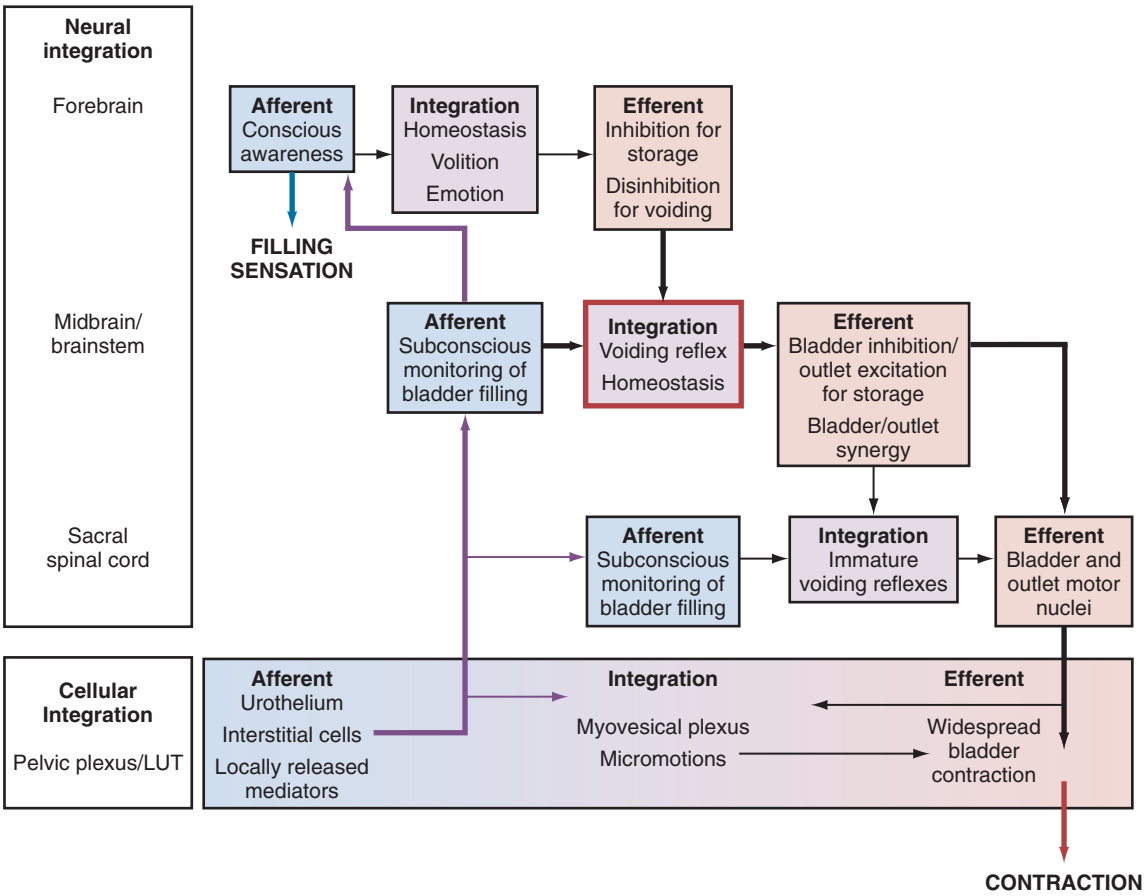


Figure 66–1. The integrative hypothesis of overactive bladder and detrusor overactivity. Neural circuits in the central nervous system and cellular interactions in the periphery integrate afferent input and modulatory influences, in a hierarchy of regulatory structures underpinning normal bladder function. Storage function is characterized by sensations of filling and desire to void at suitable volumes, whereas voiding function is characterized by volitional control and complete emptying. Lesions at various levels have seemingly similar effects because their effects are mediated by final common pathways of sensation and bladder contraction.

However, the complexity of lower urinary tract function is substantially increased by the potential interactions between differing cell types and their humoral/paracrine environments. The integrative properties determining the interaction between cell types is manifest in the neural circuits of the central nervous system, as well as the periphery (Fig. 66–1)—the latter working through networks (neural, interstitial cells) and by direct cell communication in the urothelium or muscle cell–to–muscle cell. The presence of interstitial cells in the bladder led to the proposal of a regulatory "myovesical plexus" comprising nerves (excitatory and inhibitory, peripheral and central) and interstitial cells loosely, akin to gut myenteric plexuses. The integrative hypothesis of OAB draws on the various contributory factors to understand the normal micturition cycle, OAB, and DO (Drake et al, 2001). Several observations can be understood by focusing on activity within the bladder wall itself:

1. Generation of normal and increased filling sensations in the absence of pressure change; the sensations of normal desire and strong desire to void arise in the absence of change in detrusor pressure. This could arise as a consequence of localized contractions (Drake et al, 2001), which are active in only a small part of the bladder wall, so they do not measurably affect intravesical pressure but result in small distortions that are detected by the afferent nerves. Such activity, termed "micromotions," is seen in various animal models and humans (Van Os-Bossagh et al, 2001; Drake et al, 2003a, 2003b; Gillespie et al, 2003; Drake et al, 2005). Exaggerated micromotions would then increase filling sensations pathologically, again without affecting pressure (i.e., OAB without DO). Local mediator release in inflammatory situations such as cystitis could cause temporary urgency sensations by increasing localized contractions.
2. Generation of DO; the myogenic hypothesis describes the abnormal propagation of localized excitation through direct muscle-to-muscle communication, which causes a substantial proportion of the bladder to contract synchronously as the basis of DO. In the integrative hypothesis, the possible routes of abnormal propagation extend to interstitial cell networks, innervation, and urothelium. The relative degree of local distortion and wider propagation will determine whether the individual patient manifests OAB, DO, or both together.
3. Completeness of bladder emptying; complete bladder emptying relies on sustaining detrusor contraction for a sufficient duration, and this could result from the myovesical plexus driving detrusor contraction during voiding (Drake, 2007). The hypothetical existence of feedback from bladder afferents into the myovesical plexus could ensure contraction is sustained for sufficient duration, and a lesion impairing this feedback would result in a postvoid residual (PVR).

The **crucial factors in the integrative hypothesis are the level of excitation and degree of propagation in the myovesical plexus structures of the bladder wall.** Both will be at low levels during normal bladder filling. Local excitability is high in OAB, whereas propagation alone is high in asymptomatic DO; both are increased where DO is symptomatic. Propagation is high in normal voiding (driven by efferent commands from the central nervous system [CNS]). Increased local excitation with impaired propagation could explain why patients have OAB and a PVR (detrusor hyperactivity with impaired contractility (Resnick and Yalla, 1987).

Central Nervous System

The development of functional brain imaging technology allows estimation of gross activity in specific brain areas and has been used to study bladder filling in normal and symptomatic individuals. Intriguing insights into contributions from various parts of the cerebral cortex such as the insula and the prefrontal cortex have resulted. Alterations in the regional brain activity of symptomatic individuals with OAB have been reported (Griffiths et al, 2007). Understanding brain responses to lower urinary tract activity through autonomic afferent processing networks, as is already under investigation for the gastrointestinal tract, will be crucial in the endeavor to develop improved clinical management options.

Etiology

Neurologic disease is associated with a high prevalence of LUT dysfunction, and this is to be anticipated given the fundamental regulatory influence of innervations on bladder and bladder outlet. Aging is associated with increased LUTS; this may be through the attritional effects on inhibitory innervation and brain function. Bladder outlet obstruction has long been considered an etiologic factor in generation of DO and OAB, but there is now some doubt as to whether this is correct.

Key Points: OAB Pathophysiology

- Normal lower urinary tract function derives from a complex interplay of cellular physiology and hierarchical neural control.
- DO may result from increased cellular excitability with abnormal propagation, arising within the detrusor muscle (myogenic), other cell types in the bladder (integrative), or the CNS (neurogenic).
- Altered afferent nerve function peripherally, or altered CNS processing, may underpin changes in urinary sensation.

PREVALENCE

Using the standardized ICS definition of OAB, the EPIC study reported the prevalence of OAB in four European countries and in Canada, reporting an **overall OAB prevalence of 11.8%, in the context of a prevalence of 64.3% for at least one LUTS** (Irwin et al, 2006). The EPIC study also catalogued multidimensional impact including effects on employment (Coyne et al, 2008; Irwin et al, 2009).

Older studies have to be interpreted according to the definitions they used for LUTS. One prevalence study (Milsom et al, 2001) reported prevalence of OAB symptoms that "occurred singly or in combination," estimating overall OAB prevalence at 16%. In the studied population, 9.2% had urgency, and this is perhaps closer to the true prevalence of OAB in the community.

The NOBLE study (Stewart et al, 2003) established the prevalence of OAB in more than 5000 community-dwelling individuals in the United States using a validated computer-assisted telephone interview. Men and women had the same prevalence of OAB overall (16.0% and 16.9%, respectively) as defined by the ICS. However, **men were shown to have a higher prevalence of "OAB dry"** (13.4% as opposed to 7.6% in women) and **women had a higher prevalence of "OAB wet"** (9.3% as opposed to 2.6% in men). **It is assumed that the difference in the prevalence of incontinence is due to the relative weakness of the bladder neck and urethral sphincter mechanism in women,** particularly in those who have had children. **In women the prevalence of "OAB wet" rose from 2.0% in the youngest group (ages 18 to 24) to 19.1% in those 65 to 74 years of age. Men, on the other hand, did not experience an increase in "OAB wet" until older: 8.22% for those 65 to 74 and 10.2% for those 75 years and older**.

In addition to simple prevalence, effect on quality of life needs to be evaluated. Both types of OAB have a significant impact on the patients' quality of life, as measured by generic quality of life instruments. It is not difficult to understand that being "OAB wet" has a profound impact. However, in some studies, the symptom of urgency was shown to have a greater effect on quality of life than incontinence (Coyne et al, 2004, 2008). EpiLUTS was an Internet-based survey of 30,000 people in the United States, United Kingdom, and Sweden documenting symptoms, symptom bother, and health-related quality of life. It derived a substantial amount of information about the impact of LUTS, individually and categorized as storage, voiding, and postmicturition including consequent anxiety and depression. It concluded that storage symptoms were significantly associated with greater impact (Sexton et al, 2009). Many studies in women have shown that urgency incontinence is more bothersome than stress incontinence. In some women, stress incontinence may occur several times a day and urgency incontinence only once or twice a week, but it is for the latter that the patient may demand treatment. This is probably because stress incontinence occurs more predictably and can usually be better contained by pads. OAB is a long-term condition, and ongoing quality of life impairment can be anticipated in many patients (Garnett et al, 2009).

Key Points: OAB Prevalence

- Overall prevalence of OAB in the EPIC study, using ICS standardized definitions, was 11.8%.
- Storage LUTS have a greater impact on health-related quality of life than other LUTS.
- Both genders have similar rates of OAB, but "OAB wet" is more prevalent in women and "OAB dry" is more prevalent in men.

CLINICAL ASSESSMENT

Patients with OAB may present to health care workers in various disciplines in either the community or the hospital service. It is vital that the doctor or nurse caring for such individuals is both

knowledgeable and sympathetic, taking into account the patient's psychosocial circumstances. OAB always requires management, and "cure" is not a realistic aspiration; appropriate expectations and honest explanation are therefore crucial. An appropriate initial assessment gives a presumptive diagnosis and thus the basis for empirical treatment. It should also establish the patient's desire for treatment and which therapies are open to consideration; for example, treatments likely to impair voiding contractility should not be employed if intermittent catheterization is unfeasible or indwelling catheterization will not be tolerated.

History should cover the following:

1. Presence or absence, incidence, severity, bother and effect on quality of life for each of the OAB symptoms including urgency incontinence. Other LUTS should also be assessed.
2. Presence or absence of dysuria and hematuria.
3. Nature and volume of fluid intake.
4. Whether occult neurologic disease could be present.
5. Obstetric and gynecologic history, previous surgery/radiotherapy, bowel symptoms, and drug history.
6. Other medical issues (e.g., closed-angle glaucoma and cognitive impairment can limit treatment options).

Focused physical examination requires abdominal and pelvic examination, as well as basic neurologic examination. Assessment of bladder emptying is necessary (most simply by palpating the lower abdomen, if the patient is slim). Urinalysis is important in all patients. The algorithms from the fourth International Consultation on Incontinence 2008 (Abrams et al, 2009) summarize the basic assessment necessary in the evaluation of lower urinary tract dysfunction in men, women, and the frail elderly (Fig. 66–2).

Instruments for Measuring Bladder Sensations and Storage Symptoms

Normal LUT sensations during cystometry are (1) first sensation of filling, (2) normal desire to void, and (3) strong desire to void (Wyndaele and De Wachter, 2002). Whether an individual with OAB also experiences normal sensations is not yet established but seems likely. Commonly, OAB patients have increased daytime frequency, but only a proportion of voids are associated with urgency. Tools for evaluating urgency thus have to deal with the subjective nature of the symptom, the habit of preemptive voiding at low bladder volumes, and the consequent increased frequency with low levels of urgency. A validation process is necessary to ensure tools employed are suitable for clinical or research use (Avery et al, 2004; Abrams et al, 2006).

The **urinary sensation scale** (Abrams et al, 2005) is as follows:

1. No urgency: "I felt no need to empty my bladder but did so for other reasons."
2. Mild urgency: "I could postpone voiding as long as needed without fear of wetting myself."
3. Moderate urgency: "I could postpone voiding for a short time without fear of wetting myself."
4. Severe urgency: "I could not postpone voiding but had to rush to the toilet in order not to wet myself."
5. Urgency incontinence: "I leaked before arriving at the toilet."

The **urgency percentage scale** (Cardozo et al, 2002) has three possible responses:

1. I am usually not able to hold urine.
2. I am usually able to hold urine until I reach the toilet if I go immediately.
3. I am usually able to finish what I am doing before going to the toilet.

The Indevus **"Urgency Severity Scale"** (Bowden et al, 2003), used in trials of trospium, has four responses:

0. None, no urgency
1. Mild, awareness of urgency but easily tolerated
2. Moderate, enough urgency/discomfort that it interferes with usual activities/tasks
3. Severe, extreme urgency/discomfort that abruptly stops all activities/tasks

A related strategy used an **"urgeometer"** (Oliver et al, 2003) in cystometry, asking patients sequentially to press a series of five buttons during bladder filling according to their degree of urgency:

0. None
1. Mild
2. Moderate
3. Strong
4. Desperate

However, the lower three of these scales do not explain to the patients how urgency is defined; thus **they are inappropriately named because they actually measure intensity of bladder sensation in differing parts of the sensation spectrum. Other measures such as "warning time"** (between first sensation of urgency and eventual voiding) also depend on the patients and clinicians reaching a consensus as to the meaning of *urgency* (Cardozo and Dixon, 2005).

Storage symptoms questionnaires are now available in a modular format, developed to address recommendations made by the International Consultation on Incontinence (Abrams et al, 2006), known as the *ICIQ*. The ICIQ has adopted several validated tools and developed new ones where necessary. The King's Health Questionnaire (Kelleher et al, 1997) and the OAB-q (Coyne et al, 2002) have been adopted as ICIQ modules.

Urgency assessment is a component of more generic LUTS assessment tools and may be of more practical use in clinical practice. For example, the "Patient Perception of Bladder Condition" is straightforward to administer and captures the clinical significance that patients attribute to their OAB (Coyne et al, 2008).

The frequency volume chart (FVC) (Abrams and Klevmark, 1996) remains the principal method of evaluating frequency and nocturia in an objective way. **In OAB, the pattern of voided volumes is characteristically erratic. On the FVC, frequency is defined as the number of voids recorded during waking hours including the last void before sleep and the first void after waking and rising in the morning** (Abrams et al, 2002). **Nocturia is the number of voids recorded during a night's sleep: each void is preceded and followed by sleep. The FVC is valuable in highlighting nocturnal urine output because nocturia due to nocturnal polyuria must be considered with other LUTS** as likely to mitigate against successful OAB management. The bladder diary additionally collects information on fluid intake and incontinence episodes.

Two symptom scales are undergoing evaluation in nonselected populations. The **bladder sensation scale,** for use with an FVC, is shown in Table 66–1. The **cystometry sensation scale,** for use during urodynamic study, is shown in Table 66–2. The approach of using complementary modalities of assessment in conjunction allows a more comprehensive baseline evaluation and is informative for evaluation of treatment response.

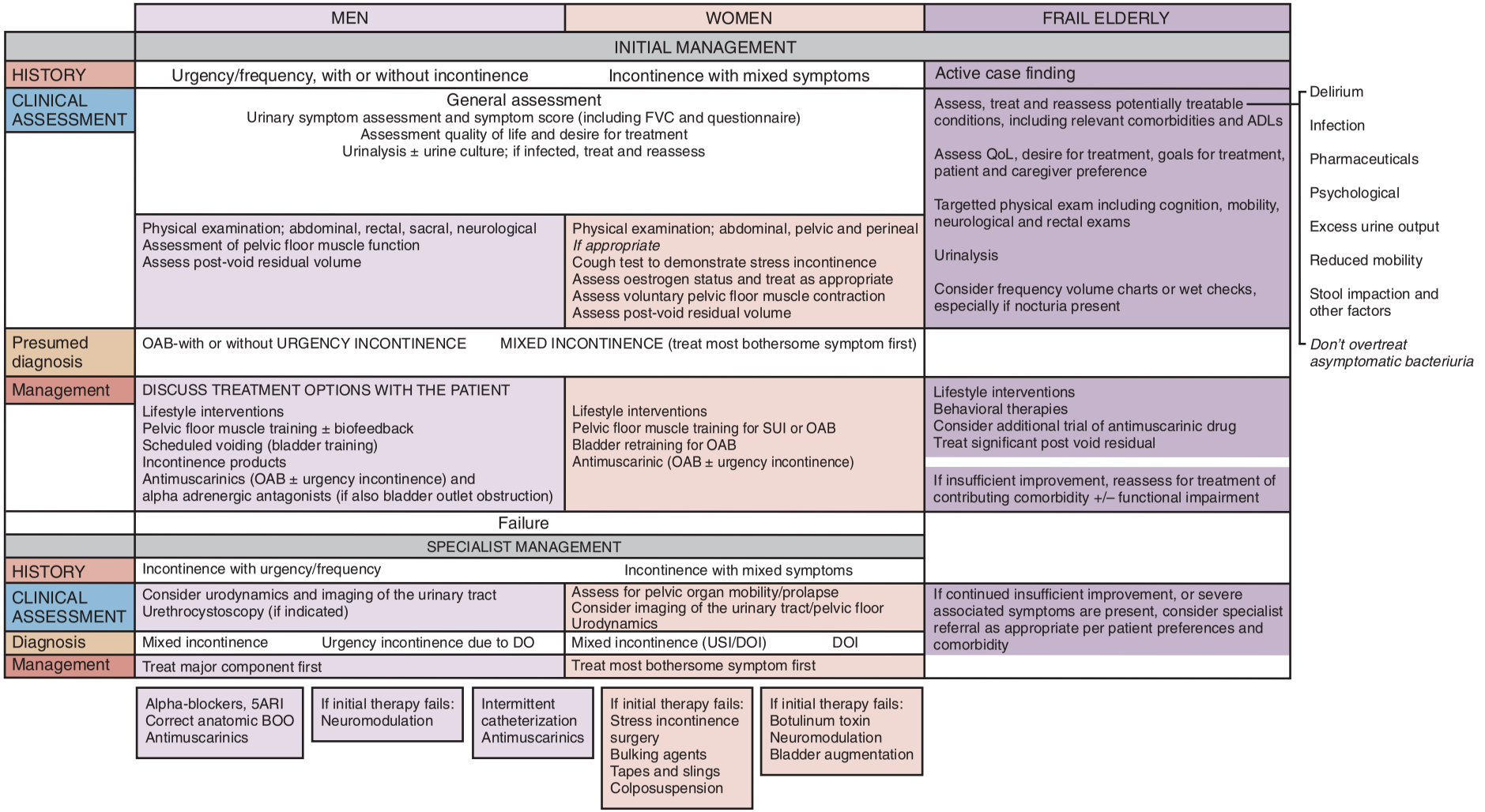


Figure 66–2. Overactive bladder in men, women, and the frail elderly; assessment and management, derived from the respective algorithms of the fourth International Consultation on Incontinence. (From Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence. 4th ed. Plymouth [MA]: Health Publications; 2009.)

Table 66–1.

Bladder Sensation Scale

1. No sensation of needing to pass urine but passed urine for "social reasons" (e.g., just before going out, unsure where next toilet is); no urgency.
2. Normal desire to pass urine; no urgency.
3. Urgency but urgency passed away before had to visit bathroom; went later with normal desire to pass urine.
4. Urgency but managed to get to bathroom, still with urgency, yet did not leak urine.
5. Urgency and could not get to bathroom in time, so leaked urine.

Table 66–2.

Cystometry Sensation Scale

0. No bladder sensation: "I don't feel anything."
1. First sensation of filling: "I'm beginning to feel my bladder."
2. First desire to pass urine: "I feel like I want to pass urine."
3. Urgency is graded.
   Mild: "I think I can hold on."
   Moderate: "I don't know if I can hold on."
   Serious: "I have to go now or I will leak any moment."
4. Strong desire to pass urine: "I'm getting uncomfortable, I'd like to pass urine now."

Mixed Urinary Incontinence and Mixed Incontinence

OAB can coexist with stress urinary incontinence (SUI). Mixed urinary incontinence (MUI) is the **complaint of involuntary leakage associated with urgency and with exertion, effort, sneezing, or coughing** (Abrams et al, 2002). Figure 66–3 describes the relationships among SUI, MUI, and OAB in women. The group illustrated with SUI and "OAB dry" could be described as having "mixed symptoms" because they have key features of SUI and urgency symptoms, but their OAB is not associated with urgency incontinence, so they do not have MUI. In general, MUI is associated with more severe levels of leakage, although it is currently unclear which component, urgency or stress, is responsible: possibly either or both types will prove culpable. Mixed incontinence refers to the coexistence of urinary and fecal incontinence. Clarity of communication is necessary to ensure all parties are aware of the specific situation for each individual under consideration.

Distinguishing Overactive Bladder from Bladder Pain Syndrome

Urgency in the old ICS terminology included a comment as to the reason underpinning the need to pass urine related to "fear of leakage or pain." Pain aspects now fall into bladder pain syndrome (BPS), which constitutes a symptom complex clearly distinguished from OAB (Abrams et al, 2005; Hanno et al, 2008). BPS is defined **as the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology**. Figure 66–4 illustrates the relationship between OAB and BPS, and Figure 66–5 indicates the difference in bladder sensation/pain.

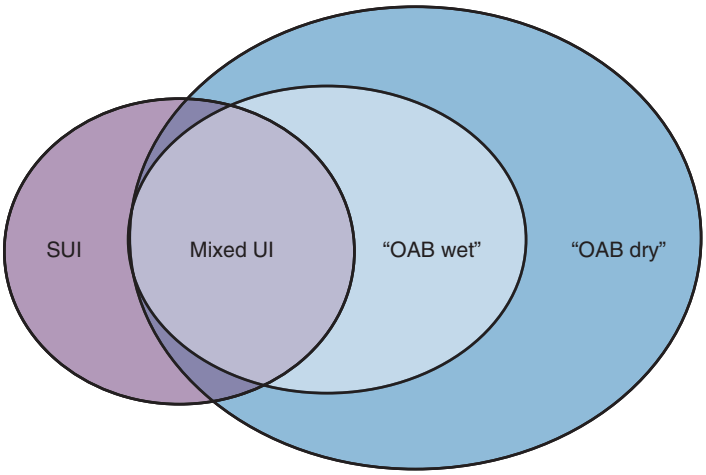


Figure 66–3. Incontinence in women may be stress urinary incontinence (SUI), mixed urinary incontinence (MUI), or urgency urinary incontinence ("OAB wet"). SUI can coexist with OAB dry, giving rise to mixed symptoms of stress incontinence and urgency.

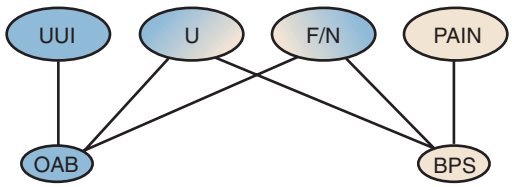


Figure 66–4. Overactive bladder (OAB) and bladder pain syndrome (BPS) both give rise to urgency (U), frequency (F), and nocturia (N); pain, but not urgency urinary incontinence (UUI), is seen in BPS.

Differences that help to distinguish BPS include the painful nature of symptoms, the steady increase in pain with filling, the more consistent voided volumes compared with OAB, and the ability to defer voiding (albeit at the cost of greater pain). In BPS, suprapubic pain is usual and additional perineal (urethral/vaginal/penile) discomfort/pain can also occur (Fitzgerald et al, 2005); in OAB, urgency is typically felt in the perineum/base of penis or vagina/urethra.

Key Points: OAB Clinical Assessment

- A comprehensive clinical history and physical examination are essential in the assessment of OAB.
- Symptom assessment questionnaires provide valuable information for baseline assessment and follow-up of treatment response.
- The FVC/bladder diary is essential for assessing OAB and excluding additional problems such as polydipsia or nocturnal polyuria.
- Dipstick urinalysis is necessary to exclude hematuria or urinary tract infection.
- A significant postvoid residual volume must be considered when evaluating OAB.

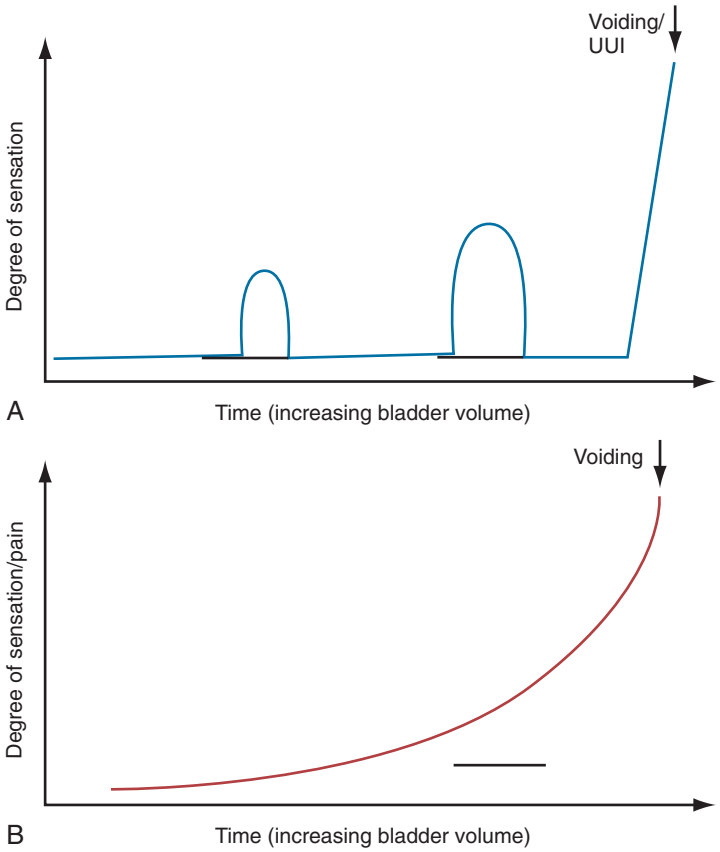


Figure 66–5. The differences in the development of bladder sensation in overactive bladder (OAB) and bladder pain syndrome (BPS). **A,** In OAB, phasic increases in urgency arise and recede as filling progresses, until severe urgency compels the patient to void or an urgency urinary incontinence (UUI) episode sets in. **B,** In BPS, pain increases throughout filling, accelerating as filling progresses.

INITIAL TREATMENT

Basic evaluation allows diagnosis of OAB and baseline severity assessment, at which point initial treatment can be instigated:

1. Lifestyle interventions; attention to the nature and volume of fluid intake, dietary irritants, and cessation of smoking foster a sense of engagement in their care for the patient.
2. Bladder training and pelvic floor muscle training help patients to reestablish inhibitory control over bladder storage and allow them to resist and abort urgency episodes.
3. Drug treatments should be employed once conservative approaches have been attempted. Antimuscarinic drugs are described in more detail in Chapter 68. Prescribers should warn the patient as to potential side effects including dry mouth, constipation, cognitive effects, visual impairment, and others. A range of agents and doses is available, and patients should be advised that the idiosyncratic nature of responses means that it may take some adjustment to find an optimum regimen.

In addition to the patient's perceptions regarding response, repeat measures using symptom assessment tools and the frequency volume chart are valuable in providing objective markers because subjective perceptions and recollections of LUTS are notoriously unreliable. Should these initial therapies fail both subjectively and objectively, and invasive treatment be contemplated by the patient and clinician, then urodynamic evaluation is usually desirable.

URODYNAMIC EVALUATION

It is common practice to employ conservative management and oral pharmacotherapy without a urodynamic diagnosis. Where the initial treatment is deemed inadequate and specialist referral is made, it is incumbent on the specialist clinician to ensure that conservative measures have been followed fully. Before urodynamic tests are requested, the reasons for "failure" of drug therapy should be explored:

1. Insufficient duration of prescription or poor patient compliance
2. Insufficient dose; individual patients absorb and metabolize drugs differently, so dose titration may be necessary to achieve a therapeutic level. Presence of dry mouth symptoms is a useful rule of thumb for deciding whether dose is adequate
3. Idiosyncrasy of response; some people appear to find better efficacy with certain agents
4. Adverse effects; some patients do have therapeutic improvement in symptoms but tolerate adverse effects poorly

For each circumstance, altered drug dose or agent may achieve sufficient improvement to obviate the need to consider more invasive investigation and treatment. Only when considerable efforts have been made should conservative therapy and antimuscarinic medications be considered unsuccessful.

Urodynamic evaluation should be considered where conservative and drug therapy fails adequately to manage OAB in a patient who is sufficiently healthy and is considering more invasive therapeutic interventions due to the impact of the symptoms on his or her quality of life. Whether to discontinue antimuscarinic drugs before the test can be argued either way; stopping the drugs gives the best chance of observing DO if present, while continuing them allows evaluation of the mechanism underlying residual refractory symptoms.

The primary aim of urodynamic studies is to reproduce the patient's symptoms and identify additional factors likely to influence management decisions. **The two main urodynamic diagnoses associated with OAB are DO and increased filling sensation.** Figure 66–6 shows the relationship between the symptom-based diagnosis of OAB and the urodynamic-based diagnosis of DO. It is worth emphasizing that DO may not be present in some patients with OAB, especially women (Hashim and Abrams, 2006), and that some patients with DO are asymptomatic (i.e., do not have OAB). OAB without DO could be a consequence of bladder wall micromotions, causing distortion that leads to sensations, but without affecting a sufficient proportion of the bladder wall to cause pressure change (Drake et al, 2005). **In some patients considered to have OAB on the basis of their symptoms, the ultimate diagnosis turns out to be urodynamic stress incontinence (USI),** perhaps because contact of urine with urethral receptors can trigger a reinforcement reflex. **Additional diagnoses relevant to management include bladder outlet obstruction and inefficient bladder emptying** because treatment measures aiming to improve bladder reservoir function may cause collateral problems with voiding, perhaps necessitating intermittent self-catheterization.

Ideally, the patient should be seated or standing for filling cystometry because OAB symptoms are usually experienced when

upright. However, where there is severe DO at low volumes, it may be difficult to ascertain if urinary stress incontinence (USI) is also present. In these patients, a second filling cycle in the supine position generally makes DO less overt (Al-Hayek et al, 2008), allowing more fluid to be instilled for determining whether USI is an additional diagnosis.

The urodynamic report must clearly state whether the patients' symptoms were reproduced completely, reproduced in part, or not reproduced to ensure that due caution is exercised in major treatment decisions where there is diagnostic uncertainty.

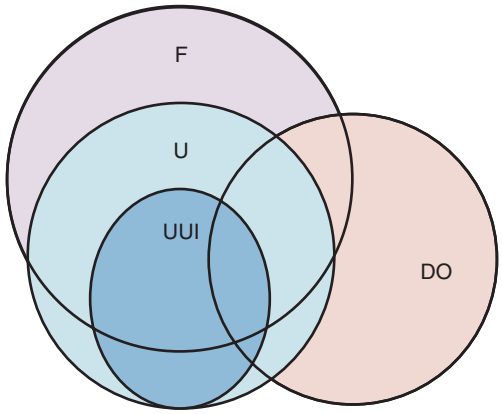


Figure 66–6. Correlation between the symptom-based diagnosis of overactive bladder (F, frequency; U, urgency; UUI, urgency urinary incontinence) and the urodynamic diagnosis of detrusor overactivity (DO). The correlation is best for urgency incontinence and least good for frequency (day and/or night).

Subclassification of Detrusor Overactivity and Technical Aspects of Urodynamics

The presence of a relevant neurologic condition distinguishes neurogenic DO from idiopathic DO, when there is no defined cause. Some clinicians feel that DO can arise as a consequence of BOO, but prevalence of DO is 60% in men who have had transurethral resection of the prostate previously (Thomas et al, 2005), despite the fact that they remain unobstructed. Accordingly, relief of BOO does not lead to permanent disappearance of DO. Although symptomatic improvement is seen in many of these men, it is probably less reliable than in men without DO.

DO has a variety of patterns on urodynamic traces. The ICS report describes two types:

1. **Phasic DO** has a characteristic waveform and may or may not lead to incontinence. It tends to be characterized by contractions of increasing amplitude as the bladder volume increases (Fig. 66–7) and is the characteristic pattern seen in most idiopathic DO.
2. **Terminal DO** is a single involuntary detrusor contraction occurring at cystometric capacity, which causes incontinence, often resulting in complete bladder emptying. It is most characteristically seen in the elderly person with "precipitant voiding" such as elderly patients who have suffered a cerebrovascular accident. Such patients appear to lose awareness of impending micturition and the ability to inhibit what turns out to be a voiding contraction.

Nonphasic changes in detrusor pressure before micturition should be regarded as changes in bladder compliance rather than as DO. Technical artifacts are easily introduced by moving a patient during urodynamics. Sometimes this change in pressure

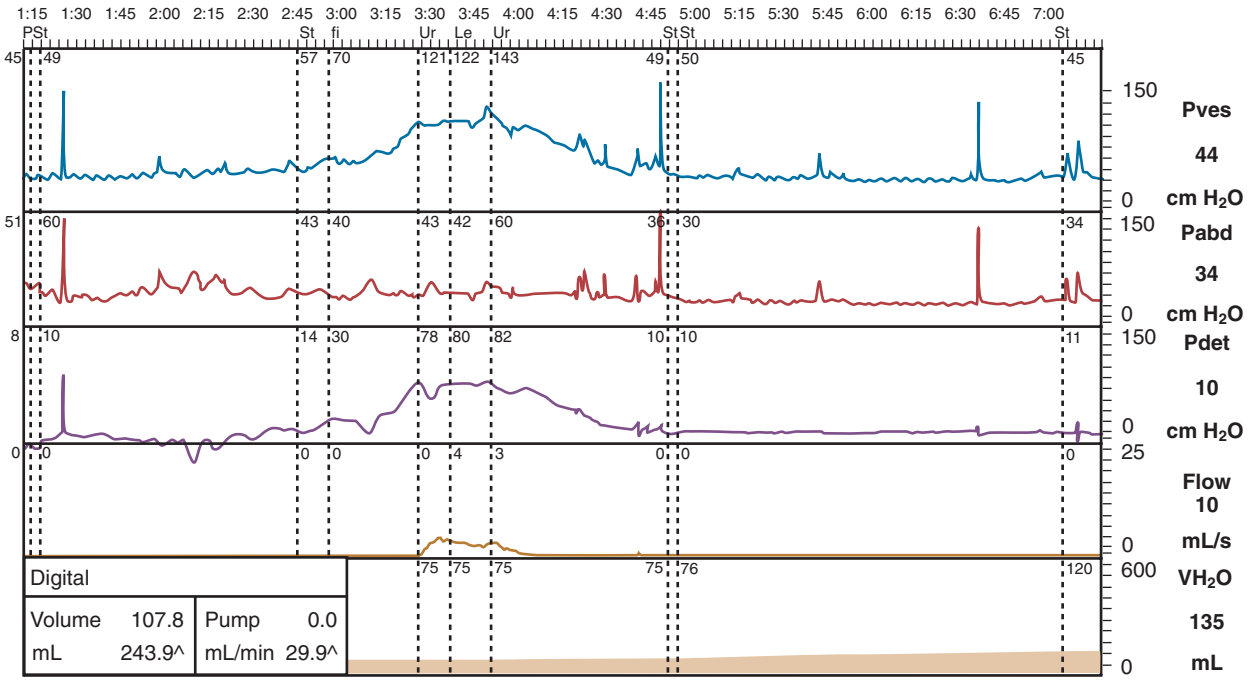


Figure 66–7. Detrusor overactivity trace. Bladder pressure is plotted in blue, rectal pressure in red, detrusor pressure in purple, flow in orange, and filling in light brown. This is a filling cystometry, so the presence of flow signifies incontinence. Incontinence in this individual is seen as a consequence of a phasic rise in detrusor pressure, at a comparatively low bladder volume.

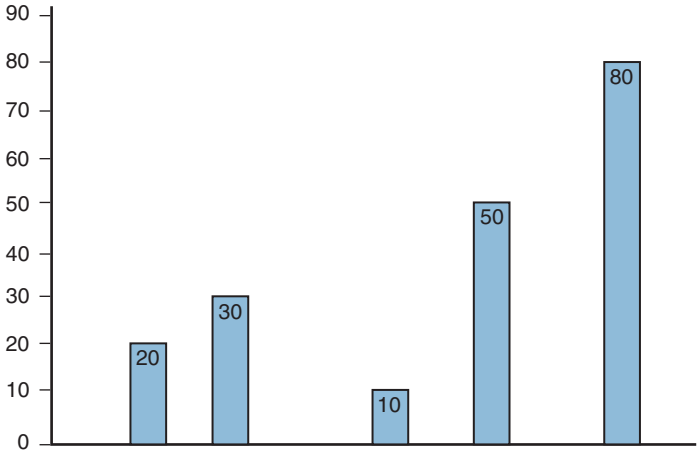


Figure 66–8. Detrusor overactivity (DO) index: a simple means of quantifying DO. It is calculated by summing the amplitude of the phasic DO contractions and dividing by the bladder volume. In this example, the DO index is (20 + 30 + 10 + 50 + 80)/300 = 0.63 cm H_2O/mL.

occurs if the patient is moved to the standing or sitting position, having had the bladder filled while supine.

If DO is not seen during filling, the investigator should attempt to use any provocations that the patient says lead to OAB symptoms such as the sound of running water. In some individuals, DO can be elicited by asking the patient to cough, but this must not be confused with stress urinary incontinence. Filling rate needs to be considered carefully; a short period of rapid filling can provoke the emergence of DO. However, fast filling can mask DO and cause low compliance, particularly in neurogenic DO.

There is no minimum value of amplitude below which a phasic detrusor contraction during filling does not constitute DO (Abrams et al, 2002). Earlier ICS reports (Bates et al, 1980) stated that, in order to diagnose "detrusor instability," the contraction should be at least 15 cm H_2O. However, it was later recognized that involuntary detrusor contractions of lower amplitude can cause significant symptoms, so the 1988 ICS report (Abrams et al, 1988) was altered accordingly. Measurement of the amplitude has been used as a way of describing the severity of DO (Abrams, 1984) (Fig. 66–8).

Ambulatory Urodynamics

The advent of ambulatory urodynamics has complicated the discussion because DO may be apparent in up to 60% of asymptomatic women (Heslington and Hilton, 1996). Does DO in these circumstances have any clinical relevance? It is not clear from the papers whether DO during ambulatory urodynamics in normal individuals is symptomatic or asymptomatic. If it were symptomatic, but this was a symptom the individual did not experience in everyday life, then the conclusion would be that the DO was artifactual, perhaps due to the presence of the pressure-measuring catheter "irritating" the bladder wall. Thus the requirements of good urodynamic practice to document the reproduction of a patient's symptoms are particularly pertinent in this context.

MANAGEMENT

The fourth International Consultation of Incontinence has produced a comprehensive review of the spectrum of incontinence management, using the International Consultation on Urological Diseases' adaptation of the AHCPR/ Oxford System of levels of evidence and grades of recommendation to evaluate the evidence from the scientific literature. The initial and specialized management algorithms for women show the care pathways for OAB and DO (Abrams et al, 2009) (see Fig. 66–2). Management of OAB is covered in detail elsewhere in this book. In brief, therapy for OAB can be divided into four classes of treatment:

1. Conservative management including weight loss, cessation of smoking, and dietary factors (decreased use of caffeine, decreased fluid intake, decreased alcohol intake, changes in food and drink). Lifestyle interventions include pelvic floor muscle training, to resist and occasionally to terminate overactivity when it arises, and bladder retraining, to encourage inhibitory influences on the lower urinary tract.
2. Pharmacotherapy; the antimuscarinics are the mainstay of treatment and can be given orally, transdermally, or intravesically. Other drug classes are in development, with β_3-adrenergic agonists currently in phase 3 trials. Vanilloid agonists, exemplified by capsaicin and resiniferatoxin, have been used in neurogenic DO; although not currently in use, analogous treatments may become available in the future.
3. Surgical therapy; sacral nerve stimulation, tibial nerve stimulation, intravesical botulinum injections, augmentation cystoplasty, and detrusor myectomy.

For intractable OAB, options are appliances, catheters (urethral or suprapubic), urethral closure, and urinary diversion.

Key Points: OAB Treatment

- Lifestyle interventions are the starting point in managing OAB including advice on fluid intake and bladder training.
- Antimuscarinic drugs may be used where symptoms remain bothersome, but due consideration of collateral effects is essential.
- Urodynamic studies are indicated in a patient with refractory symptoms who is willing to consider proceeding to more invasive treatment.
- The main urodynamic diagnoses in OAB are DO and increased filling sensation. Symptoms are not always reproduced in a urodynamic test.
- Management of refractory OAB is a challenging problem requiring specialist expertise.

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chapter
67

Nocturia

Marcus Drake, DM, MA, FRCS (Urol)

Definitions and Terminology
Prevalence and Impact of Nocturia
Physiology and Pathophysiology
Clinical Assessment
Management

Nocturia is a common problem that presents to the urologist. It represents a considerable diagnostic and therapeutic challenge because failure to appreciate the extent of potential contributory factors predictably leads to poor treatment outcomes. Extensive knowledge of internal medicine and ready availability of multidisciplinary support are invaluable for achieving patient satisfaction. The clinician needs to apply a systematic approach in diagnosing underlying mechanisms so that treatments can be selected appropriately, avoiding untailored prescribing.

DEFINITIONS AND TERMINOLOGY

The term "nocturia" relates to passage of urine overnight. In common with other lower urinary tract symptoms (LUTS), the Standardisation Committee of the International Continence Society (ICS) has proposed definitions (Abrams et al, 2002) for general use to allow comparisons between studies, with a specific initiative for nocturia (Van Kerrebroeck, 2002; Van Kerrebroeck et al, 2002). Key terms are listed in Table 67–1. At its most basic, the symptom of **nocturia is the complaint that the individual has to wake at night one or more times to void.** There is no inclusion of degree of symptom bother in this definition, and many individuals will not regard nocturia on only one occasion per night as being of clinical significance. On the other hand, some people can be substantially bothered by nocturia once per night. Several reported studies disregarded nocturia if it was only a single episode per night; the outcomes have to be interpreted accordingly.

Defining "night-time" is contentious. In this context it does not specifically relate to the hours of dark, but rather to the hours of sleep. On this basis, shift workers who are active during the hours generally regarded as overnight can still manifest nocturia during their repose periods in daylight hours. For this specific group it is essential to ensure that frequency volume chart (FVC) documentation is explicit and unambiguous as to sleeping hours. Changing time zones (jet lag) also complicates interpretation, and it is best to allow recovery from jet lag before asking a patient to complete an FVC.

Nocturia frequency includes only those voids preceded and followed by sleep. Thus the first morning void after a night's sleep is counted toward daytime (diurnal) frequency rather than nocturia. An estimate of nocturnal functional bladder capacity is given by summing the volumes of all the nocturia episodes (nocturnal voided volume) and dividing the total by the nocturnal frequency. **The nocturnal urine production is given by adding the first morning void to the nocturnal voided volume. It is the nocturnal urine production that determines the diagnosis of nocturnal polyuria (NP). The ICS Standardisation Committee defined NP as nocturnal urine production exceeding 20% of 24-hour output in younger adults and 33% in older adults** (Abrams et al, 2002). In measuring nocturnal urine production, allowance has to be made for any significant delay between waking and the first morning void, particularly if there has been consumption of fluid in that time. Some studies have used alternative approaches (e.g., defining NP as a nocturnal diuresis of greater than or equal to 0.9 mL per minute overnight [Asplund et al, 1998], regarding "night" as time spent in bed). Alternatively, it has been defined as nocturnal urine volume exceeding 10 mL per kilogram, here referring to night as patient-reported sleeping time (Homma et al, 2000).

The **functional reservoir capacity of the lower urinary tract and the renal output volume it receives overnight can be linked using a nocturia index** (Ni) derived from a frequency volume chart (FVC) (Weiss et al, 1999). Ni in excess of 1.0 signifies that **nocturnal urine production exceeds the largest voided volume, such that it will be inevitable that the person has to get up at night to pass urine.**

Defining the reason people wake is intrinsically subjective and somewhat unreliable, particularly if the patient affected may not be certain in his or her own mind. The clinician should attempt to ascertain whether nocturia is the fundamental cause of sleep disturbance. Where sleep is disturbed for other reasons, voiding is a secondary issue, perhaps a habitual response or an action to assist subsequent return to sleep; sometimes this will not be clear from the history.

Nocturnal enuresis signifies voiding while remaining asleep, constituting part of the nocturnal voided volume. Nocturnal enuresis does not count as nocturia because the patient fails to wake when passing urine, but it clearly must be factored into any evaluation of LUTS and nocturnal urine production. Primary nocturnal enuresis in adults is a particularly difficult management challenge because the individual involved may have failed to establish cortical neuronal systems inter-relating toileting and arousal; once adulthood is reached, such links are unlikely to be acquired.

Key Points: Voided Volume and Frequency

- Nocturia is the number of voids recorded during a night's sleep: each void is preceded and followed by sleep.
- Nocturnal polyuria means overnight urine production exceeds 20% to 33% of total 24-hour volume and is age dependent.
- Polyuria in a 70-kg adult is diagnosed by a 24-hour voided volume in excess of 2.8 L (>40 mL/kg).
- If nocturnal urine production exceeds the largest voided volume (nocturia index >1), it will be inevitable that the person has to get up at night to pass urine.

Table 67–1.

Key Terms and Definitions

TERM	DEFINITION
Nocturia	The number of voids recorded during a night's sleep: each void is preceded and followed by sleep
Nocturnal urine volume	Total volume of urine passed during the night including the first morning void
Nocturnal polyuria	Nocturnal volume >20%-33% of total 24-hr volume (age dependent)
Polyuria	24-hour voided volume of >2.8 L in a 70-kg adult (>40 mL/kg)
Night	The period of time between going to bed with the intention of sleeping and waking with the intention of arising
Nighttime frequency	The number of voids recorded from the time the individual goes to bed with the intention of sleeping, to the time the individual wakes with the intention of rising
First morning void	The first void after waking with the intention of rising
Maximum voided volume	The largest single voided volume in a 24-hr period
Nocturnal enuresis	Voiding occurring during sleep

From Van Kerrebroeck P. Standardization of terminology in nocturia: commentary on the ICS report. BJU Int 2002;90(Suppl. 3):16–7.

PREVALENCE AND IMPACT OF NOCTURIA

Prevalence

Overall prevalence of nocturia for 5500 people in the Boston Area Community Health (BACH) study was 28.4%, affecting 25.2% of men and 31.3% of women (Fitzgerald et al, 2007). Prevalence of nocturia was 48.6% of men and 54.5% in the EPIC study in Europe and Canada, evaluating 19,000 adults with or without overactive bladder (OAB) (Irwin et al, 2006). In a subgroup analysis for men in the EPIC study, nocturia was the most prevalent LUTS (Irwin et al, 2009). In a European survey of nearly 3000 men aged 55 to 75 years in several primary care practices, nocturnal voiding frequency was zero in 20%, one in 45.8%, two in 20.8%, three in 7.1%, four 2.4%, and five or more in 2.6% (Gourova et al, 2006). In the hospital setting, prevalence of nocturia was 87% in a population of 700 women of mean age 59, with greater bother associated with higher number of nocturia episodes and with mixed incontinence (Lowenstein et al, 2007). Differences according to ethnicity are apparent, with an overall prevalence of 38.5% in blacks, 30.7% in Hispanics, and 23.2% in whites (Fitzgerald et al, 2007).

There is a clear impact of aging on prevalence of nocturia. Between the ages of 30 and 39 years old, nocturia prevalence is 19.9% and in those aged between 60 and 79 it is 41.2% (Fitzgerald et al, 2007). In people younger than the age of 40, nocturia is slightly more prevalent in women than men; above the age of 60, prevalence in the two genders is similar (Irwin et al, 2006). In general, younger people are more likely to manifest decreased nocturnal bladder capacity, whereas nocturnal urine overproduction increasingly accounts for nocturia as people age (Weiss et al, 2007). Presence of NP cannot be reliably predicted from daytime LUTS (Swithinbank et al, 2004).

Approaches to diagnosing NP (absolute, relative or functional) were compared in an epidemiologic study (Rembratt et al, 2002). In older patients showing at least two voids per night, 70% fulfilled all three diagnostic approaches. For those people with up to one void per night, 67% fulfilled at least one definition, but only 5% fulfilled all three definitions. Overall, the prevalence of NP in older nocturia patients was 45% to 100% when there were greater than or equal to two voids per night, 8% to 37% of people with up to one void per night, and 4% to 25% of people who did not void overnight.

Quality of Life and Wider Health Impact of Nocturia

The overall duration of sleep can be divided into specific stages according to various parameters including electro-encephalogram, muscle tone, respiration, heart rate, and eye movement. A **slow-wave sleep pattern, regarded as the restorative component of sleep, predominately occurs in the first part of the night. Thus early sleep disturbance may result in a more substantial impact on health and ability to carry out activities of daily living.** A series of potential causes of sleep disturbance was surveyed by the National Sleep Foundation "Sleep in America Poll" (Foley et al, 2004). These comprised nocturia, physical pain, caregiving, health concerns, cough, nighttime heartburn, headache, money problems, family problems, and uncomfortable bed. Nocturia was found to be the leading cause of sleep disturbance in older adults (aged 55 to 84) (Bliwise et al, 2009).

A high proportion of people with nocturia describe themselves as having impaired quality of life as a consequence. Nocturia is one of the main predictors of symptoms (Coyne et al, 2009a, 2009b) and drug treatment (Asplund et al, 2005) of anxiety and depression in people with LUTS. Increased nocturia severity was shown to increase absence from work for health reasons (Asplund et al, 2005). Nocturia impairs work productivity and activity in a nonlinear fashion (Kobelt et al, 2003). **Where nocturia of at least two voids per night is reported, impact on quality of life is more problematic at a population level** (Fiske et al, 2004; Yu et al, 2006), **becoming a major impact at three voids per night or more** (Tikkinen et al, 2010), **though this is subject to considerable individual variation.** Self-reported health status was impaired in people documented as having at least two voids per night in a Dutch population (van Dijk et al, 2002). Consequently, a greater proportion will seek medical input at this level of severity (Chen et al, 2007). In elderly residential care, falls are common at night and are frequently

reported to occur in relation to toilet visits. **The odds ratio of a fall is 1.84 where there are at least two voids per night, rising to 2.15 for more than three voids per night.** Observation of increasing prevalence of hip fracture as a consequence of nocturia has been documented (Asplund, 2006).

Key Points: Prevalence and Impact

- Overall prevalence of nocturia in the BACH study was 28.4%, affecting 25.2% of men and 31.3% of women.
- Aging affects the prevalence of nocturia; between the ages of 30 and 39 years prevalence is 19.9%, rising to 41.2% between 60 and 79.
- Younger people are more likely to manifest decreased nocturnal bladder capacity, whereas nocturnal urine overproduction increases with age.
- Slow-wave sleep is the restorative component of sleep, occurring mainly in the first part of the night.
- Overall, presence of nocturia of two or more episodes per night has a greater impact on quality of life, but there is considerable individual variation.

PHYSIOLOGY AND PATHOPHYSIOLOGY

Influences determining urine output and storage are diverse, and the large range of potential mechanisms underlying nocturia is outlined in Table 67–2.

Table 67–2.

Nocturia Pathophysiology

Nocturnal Polyuria

1. Behavioral (e.g., excessive evening/nighttime fluid intake, polydipsia, drug-induced diuresis)
2. Global polyuria (e.g., poorly controlled diabetes mellitus, diabetes insipidus, DIDMOAD syndrome, panhypopituitarism)
3. Release of fluid and electrolyte sequestration (e.g., congestive heart failure, peripheral edema, venous stasis)
4. Obstructive sleep apnea
5. Renal tubular dysfunction (e.g., diuretic phase of acute tubular necrosis, nephrotic syndrome)
6. Hepatic failure
7. Hypoalbuminemia

Diminished Nocturnal Bladder Capacity and/or Global Bladder Capacity

1. Storage failure
   a) detrusor overactivity; *idiopathic or nocturnal detrusor overactivity, neurogenic bladder dysfunction*
   b) increased filling sensation; *overactive bladder*
2. Voiding failure leading to postvoid residual; *bladder outflow obstruction, reduced detrusor contractility, dysfunctional voiding, neurogenic bladder dysfunction*
3. Inflammatory or painful conditions of the urinary tract *(e.g., urinary tract or genital infection, bladder pain syndrome, bladder or ureteric calculi, malignancy)*

Sleep Impairment

1. Environmental
2. Anxiety disorders
3. Stimulants
4. Circadian disruption *(e.g., melatonin deficiency of aging)*

Regulation of Body Water Balance; Diuresis and Natriuresis

Tight regulation of total body water and electrolyte loads; relative distribution across the intracellular, extracellular, and intravascular compartments; and specific concentrations within each compartment are crucial homeostatic functions, regulated by hormonal and physical properties (Verbalis, 2006). Balance is achieved by interplay of diverse physiologic influences, in which renal regulation of glomerular filtration and tubular reabsorption play a foremost role, reflected in the composition and rate of production of urine. As a consequence, **the lower urinary tract, and hence LUTS, are subordinate to the greater physiologic needs of the organism as a whole.** Focusing on nocturia, without consideration of the pathophysiologic context, may prove counterproductive.

Aquaporins (Agre et al, 1998) **are a family of regulated channels with a key role in fluid and electrolyte balance.** For a recent review of renal aquaporins, read the work of Kwon and colleagues (2009). Various aquaporins are present in the kidney, with a major role attributed to aquaporin-2. **Key to rapid adjustment of fluid balance is the process of "trafficking," the short-term variation of aquaporin-2 channel density and function.** Changes in aquaporin-2 and aquaporin-3 can arise over periods of days, influenced by numerous factors. Some aquaporins have been identified in the urothelium of the bladder (Rubenwolf et al, 2008), where their roles have yet to be ascertained (reviewed in Khandelwal et al, 2009).

Arginine vasopressin is a key endocrine determinant of water retention, hence its alternative name of antidiuretic hormone (ADH). It modifies the structure of aquaporin-2 and causes increased insertion of aquaporin water channels at key locations in the nephron, consequently enhancing permeability for reabsorption of water. Human volunteers given ADH show an increase of body weight and a corresponding dilutional decrease in their serum sodium concentration, if not fluid restricted (Leaf et al, 1958). By extrapolation, retained water in the syndrome of inappropriate ADH secretion (SIADH) leads to increased body weight, hyponatremia, and blood pressure problems (Verbalis, 2006). Where there is chronic exposure to elevated levels of ADH, the phenomenon of "escape from antidiuresis" can occur as a result of desensitization of the renal tubules (Leaf et al, 1958), with downregulation of the aquaporin-2 channel (Verbalis, 2006). Accordingly, the **chronic nature of impaired fluid and electrolyte balance can lead to a refractory clinical situation unless the overall balance is corrected, and time allowed for recovery. Recognition that other hormones can also influence aquaporin-2 is more recent, including secretin** (Chu et al, 2009) **or oxytocin** (reviewed in (Cheng et al, 2009). These may yield alternative pharmaceutic strategies in the future (Bouley et al, 2008).

Natriuresis is the process of excretion of sodium in the urine and is a consideration in the clinical context (Matthiesen et al, 1996) that is often underestimated. The renin-angiotensin-aldosterone system makes major adjustments to the rates of renal sodium secretion, though at a comparatively slow rate. **Brain and atrial natriuretic peptides (BNP and ANP, respectively) cause net sodium excretion, whereas sodium is conserved by aldosterone. Natriuresis lowers the blood sodium concentration and lowers blood volume, as osmotic forces make water follow sodium into the urine.** Sympathetic innervation can make rapid adjustments to salt

balance. This may explain why global polyuria is common following renal transplantation, with a high prevalence of nocturnal polyuria (Mitsui et al, 2009). There are also intrarenal mechanisms including ATP influence on epithelial sodium channels (Wildman et al, 2009). Excess natriuresis can be caused by medullary cystic disease, Bartter syndrome, Gitelman syndrome, the diuretic phase of acute tubular necrosis, primary renal diseases affecting the renal tubules, and congenital adrenal hyperplasia.

Cardiac Impairment

Impaired cardiac function can result in accumulation of fluid in dependent parts of the body ("third-spacing"), which can then return to the circulating volume when the patient is recumbent. Older patients can demonstrate an increased body weight during the daytime, which is greater in patients with nocturia (mean daytime weight change 0.93 kg compared with 0.60 kg in asymptomatic patients) (Kaye, 2008). This led to a significant difference in overall urine volume passed overnight, along with significant differences in the sodium, potassium, and chloride output.

Ordinarily, blood pressure should reduce overnight ("dipping"). In hypertensive patients, dipping of the blood pressure overnight becomes less apparent, signifying an increased prevalence of cardiac disease and being associated with an increased risk of nocturia (Fitzgerald et al, 2007). Men with benign prostate enlargement (BPE) are significantly more likely to lose the overnight dip in blood pressure, particularly men with nocturia (Turgut et al, 2008). **Underlying pathophysiology of nocturia can be related to increased mean arterial blood pressure and blunted circadian variation in ADH** (Graugaard-Jensen et al, 2006).

Global Polyuria and Increased Fluid Intake

Urine output in excess of 40 mL per kilogram per 24 hours (equating to 2.8 L per 24 hours in a 70-kg adult) defines polyuria and is likely to lead to increased voiding frequency both day and night. The patient's fluid intake, either in the form of fluid drunk or free fluid in ingested food, will influence urine output. In many cases, patients deliberately increase their fluid intake volitionally. **Evaluation of sustained polyuria has to include consideration of whether there is excessive fluid intake (polydipsia); it is also important to consider whether the polydipsia is a cause of the polyuria or whether it is secondary to thirst induced by other pathologic causes of polyuria.** The best known medical examples of secondary polydipsia are poorly controlled diabetes mellitus and diabetes insipidus (DI), where thirst results from excessive fluid loss. Fluid loss in diabetes mellitus results from increased solute load (glucose) in the glomerular filtrate; **if polyuria is present in a seemingly well-controlled diabetic, breakthrough hyperglycemia and other causes of polyuria (e.g., impaired renal tubular function) should be considered**. DI can be a consequence of impaired ADH secretion (neurogenic/central DI) or impaired renal responsiveness to ADH (nephrogenic DI). DI can occur in conjunction with other problems such as panhypopituitarism, and it is part of DIDMOAD syndrome (DI, diabetes mellitus, optic atrophy, and deafness) (Barrett et al, 1995).

Nocturnal Polyuria

Ordinarily there is a circadian reduction in urine production overnight, which is largely regulated by endocrine or neural mechanisms but which is yet to be fully explained. This **circadian pattern relates to increased secretion of ADH during the hours of sleep** (Graugaard-Jensen et al, 2006), thus lower volumes of more concentrated urine (Asplund and Aberg, 1991). Loss of circadian reduction in overnight urine production is important clinically (Matthiesen et al, 1996). Plasma ADH levels may be pathologically undetectable during the night in elderly subjects with nocturia (Asplund and Aberg, 1991). Central nervous system lesions due to CVA can affect the hypothalamic-pituitary axis, causing a loss of ADH circadian rhythmicity (Ozawa et al, 1998). However, there remains a strong possibility of further underlying mechanisms yet to be elucidated.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) results from intermittent occlusion of the airway during sleep, leading to profound hypoxia, which is relieved by a gasping respiratory pattern. **The fluctuating hypoxia pattern impairs sleep patterns directly. In addition, the gasping intakes of breath substantially raise intrathoracic pressures. The increased right atrial transmural pressure resulting from hypoxia-induced pulmonary vasoconstriction leads to an elevation in ANP, which precipitates increased urine output** (Yalkut et al, 1996). Risk factors for OSA include morbid obesity, acromegaly, asthma, hypertension, adult onset diabetes mellitus, and craniofacial abnormalities. New-onset snoring in an older patient should prompt evaluating clinicians to consider overnight oximetry monitoring or polysomnographic sleep studies.

Increasing severity of OSA has been corresponded with nocturia (Fitzgerald et al, 2006), with reduction in nocturia episodes achieved by OSA treatment using continuous positive airway pressure. Elderly patients with severe sleep disordered breathing have a greater number of nocturia episodes (Endeshaw et al, 2004). The link between nocturia and OSA is sufficiently close that it has even been suggested that nocturia is as sensitive as snoring as a predictive symptom of OSA (Romero et al, 2010). OSA should be considered in any nocturia patient, even where OAB is clearly apparent in the daytime (Lowenstein et al, 2008).

Impaired Renal Function

Impaired renal tubular function leads to failure of reabsorption of glomerular filtrate and thus overall urine output rises. In a long-term cohort study to evaluate risk factors for end-stage renal disease, risk factors were identified as male gender, family history of renal disease, older age, proteinuria, diabetes mellitus, African-American race, higher blood pressure, higher body mass index, and higher creatinine level (Hsu, 2009). Proteinuria and excess weight were identified as the two greatest risk factors. In addition, self-reported history of nocturia was identified as a possible novel risk factor (Hsu, 2009). **Nocturia is an independent predictor of albuminuria, and this may underpin the value of the symptom as a predictor of chronic kidney disease,** as found by the PolNef Study (Krol et al, 2009). Numerous influences and conditions alter renal expression of aquaporins. For example, hypokalemia and hypercalcemia can lead to nephrogenic DI.

When polyuria is seen on the FVC, a water-deprivation test may be used to distinguish between DI and polydipsia. If the water deprivation test is abnormal, a renal concentrating capacity test can distinguish between central and nephrogenic DI by measuring urine osmolality a few hours after a dose of desmopressin under conditions of water restriction. If renal concentrating capacity is normal, any DI will be neurogenic/endocrine, for which desmopressin therapy is usually effective. Reduced concentrating capacity (urine osmolalities <550 mOsm/kg) signifies nephrogenic DI.

Multiple Medical Disorders

The treating clinician should not lose sight of the fact that nocturia represents a multifactorial problem (Tikkinen et al, 2009), extending substantially beyond the urinary tract. Particularly in elderly patients, the pathophysiology is complex (Wagg et al, 2005). A multivariate logistic regression analysis showed that nocturia in elderly men is significantly related to bladder/prostate cancer, cerebrovascular disease, treatment of voiding disorders, cardiovascular disease, hypertension, and moderate alcohol consumption (Gourova et al, 2006). Nocturia is an important nonmotor symptom in Parkinson disease; severity of neurological impairment is the main predictor, and nocturia ranks alongside urinary frequency as the greatest LUTS-derived adverse influence on quality of life. **Nocturia in Parkinson disease generally responds inadequately to dopamine-targeted treatment** (Kim et al, 2009; Sammour et al, 2009) **or antimuscarinics** (Sammour et al, 2009). In stroke patients, the most frequent bothersome LUTS is nocturia, with a prevalence of 53% (Tibaek et al, 2008).

Obesity is associated with nocturia (Shiri et al, 2008). Metabolic syndrome, defined as the presence of at least three of waist circumference greater than 102 cm; systolic blood pressure (BP) 130 mm Hg or greater or diastolic BP 85 or greater; high-density lipoprotein (HDL) cholesterol less than 40 mg/dL or lipid medication use; type 2 diabetes mellitus or increased blood sugar or diabetes medication use; or triglycerides greater than 150 mg/dL (Kupelian et al, 2006), is associated with an increased overall risk of nocturia (odds ratio 1.69) (Kupelian et al, 2009).

Medications

Drugs that can increase urine output include diuretics, selective serotonin reuptake inhibitors (SSRIs), calcium channel blockers, and tetracyclines. Lithium can cause nephrogenic DI in 40% of users (Grunfeld and Rossier, 2009).

Certain medications can be associated with insomnia, thereby causing additional sleep disturbance problems that may be correctable. Such agents include **central nervous system stimulants (e.g., dextroamphetamine and methylphenidate); antihypertensives (including alpha-adrenergic antagonists, beta blockers, methyldopa); respiratory medications (albuterol, theophylline); decongestants (phenylephrine, pseudoephedrine); hormones (corticosteroids, thyroid medications); psychotropics (atypical antidepressants, monoamine oxidase inhibitors, SSRIs); carbidopa; and phenytoin. In addition, chronic use of hypnotics and sedatives** to induce sleep can lead to tolerance and dependence. As a consequence, rebound insomnia and anxiety can arise when the medication is stopped (hypnotic-dependent insomnia).

Pregnancy

Pregnancy increases LUTS including nocturia, which is presumed to be a consequence of increased glomerular filtration rate and subsequent urine output. Symptoms tend to begin early in pregnancy, increasing with each trimester, with a high prevalence of nocturia by term (Aslan et al, 2003; FitzGerald and Graziano, 2007).

Impaired Lower Urinary Tract Reservoir Function

Urologic causes of low nocturnal and global bladder capacity include OAB, infravesical obstruction, idiopathic detrusor overactivity, neurogenic bladder, bladder inflammation (e.g., cystitis), and bladder pain syndrome (BPS). Bladder or ureteric calculi and neoplasms of the bladder, prostate, or urethra should also be considered.

Nocturia is an element in the definition of OAB (urgency, with or without urgency urinary incontinence, usually with frequency and nocturia in the absence of other causes of similar symptoms). The symptom of nocturia alone does not constitute a basis for diagnosing OAB. Indeed, lying recumbent reduces detrusor overactivity in many patients (Al-Hayek et al, 2008). Nonetheless, **the most prevalent combination of OAB symptoms is urgency with nocturia** (Irwin et al, 2008).

Nocturia is commonly reported in bladder pain syndrome. The original National Institute of Diabetes and Digestive and Kidney Diseases criteria of exclusion for diagnosing interstitial cystitis state that it should not be diagnosed if nocturia is absent (Hanno, 1994). In this context, waking is often caused by pain in the bladder. Because the cause of waking is the pain, rather than a desire to void, use of the term *nocturia* in this context is not consistent with the ICS standardized LUTS terminology, even though the pain may be reduced by voiding.

Insomnia

Insomnia can arise as a result of remarkably diverse causes. By definition, nocturia is preceded and followed by sleep. Thus complete failure to fall asleep or return to sleep will formally exclude nocturia. Nonetheless, more subtle sleep disruption can reflect failure of key sleep phases that underpin the restorative effects of a normal night's slumber. Thus specialist appraisal of a sleep may be necessary to detect whether fatigue reflects primary sleep disruption or whether the sleep disruption is secondary to nocturia.

CLINICAL ASSESSMENT

Patients are likely to present with either nocturia or fatigue-related symptoms. A practical aid for remembering key aspects in patient assessment is given in Figure 67–1 (Wein et al, 2002). Evaluation requires a focused history and physical examination to evaluate the following:

1. Sleep
2. Conditions that might account for excessive nocturnal urine output (cardiovascular, endocrine, neurologic, renal impairment)
3. LUTS and conditions impairing bladder capacity including OAB
4. Fluid intake and medication use

Key Points: Fluid and Electrolyte Balance

- Compartmental distribution of body water and electrolyte loads are homeostatic priorities.
- Short- and medium-term variation of renal aquaporin levels are important determinants of urine volume and composition.
- The antidiuretic hormone, arginine vasopressin, is the main endocrine regulator of aquaporin-2 expression.
- Natriuresis, net sodium loss in urine, is regulated by the renin-angiotensin-aldosterone system, brain- and atrial-natriuretic peptides, the sympathetic nervous system, intrarenal mechanisms, and other incompletely understood influences.
- Chronic fluid and electrolyte imbalance, as well as involvement of less well-recognized hormonal influences, can create a refractory clinical problem.
- Accumulated fluid in dependent parts of the body ("third-spacing") returns to the circulating volume when the patient is recumbent.
- Altered cardiovascular function in nocturia includes deficiency of the overnight dip in BP.
- Polyuria and polydipsia need careful evaluation to exclude underlying endocrine or renal dysfunction.
- Circadian reduction in nocturnal urine production is regulated by ADH and other influences.
- Obstructive sleep apnea causes natriuresis by release of atrial natriuretic peptide.
- Nocturia is an independent predictor of albuminuria, substantiating the high prevalence of nocturnal polyuria in renal tubular dysfunction.
- Patients with metabolic syndrome have a high prevalence of nocturia.
- Certain drugs influence nocturia directly by increasing urine production or indirectly by causing sleep disturbance.
- Lower urinary tract dysfunction including OAB can contribute to nocturia frequency by reducing bladder reservoir function.

The FVC is of particular importance to document the volume and time of each void, the time of retiring for sleep, and the time of rising, ideally over a 3- or 4-day period or longer if patient compliance allows (Matthiesen et al, 1999). On the basis of the FVC, the following observations should be considered: **diurnal or nocturnal frequency, global or nocturnal polyuria, reduced bladder capacity (overall or solely nocturnal), or a mixed disorder** (Weiss et al, 2008). Additional aspects included in a more comprehensive bladder diary could be nature and timing of fluid intake, LUTS such as urgency, potential contributory factors, sleep pattern, and confounding factors (e.g., staying in bed for a long time after waking). Nocturia due to diminished bladder capacity is of two types: **a global decrease in bladder capacity as expressed by reduced maximal voided volume or typical voided volume or decreased bladder capacity apparent primarily at nighttime.** Sleep duration is an independent factor for nocturia (Udo et al, 2009).

FVCs can be supplemented by quantifying symptom severity and bother using validated questionnaire-based symptom assessment tools. Nocturia can constitute the main assessment target (as in the nocturia quality of life "N-QoL" tool [Abraham et al, 2004]). Alternatively, nocturia may be an element in a global LUTS tool such as the International Prostate Symptom Score (IPSS) (Homma et al, 2002) or the ICI-Q (Abrams et al, 2006); this approach can reduce the ability to discern symptom severity and treatment response in situations where nocturia reflects systemic disease rather than being a dependent variable of LUTS.

MANAGEMENT

Management considerations are outlined in Table 67–3. **Individualized treatment plans are beneficial, and a tailored approach based on evaluation of risk factors is appropriate, integrating advice and specific instructions.** Objective data to corroborate subjective impressions is valuable; an FVC before and during treatment allows greater sensitivity when evaluating treatment response and facilitating self-management (Yap et al, 2009).

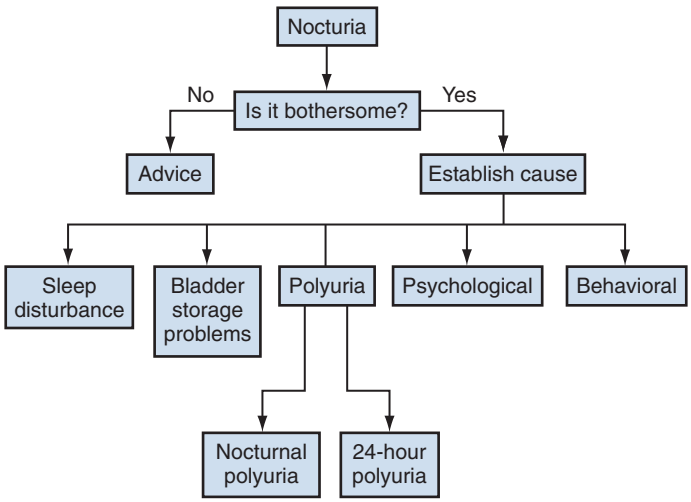


Figure 67–1. Key aspects of nocturia assessment. (From Wein A, Lose GR, Fonda D. Nocturia in men, women and the elderly: a practical approach. BJU Int 2002;90[Suppl. 3]:28–31.)

Table 67–3.

Key Considerations in Management of Nocturia

1. Health and lifestyle issues affecting sleep quality
2. Optimizing management of systemic conditions
   a) Optimizing management of known conditions likely to affect nocturnal urine output
   b) Identifying previously unrecognized conditions likely to affect nocturnal urine output
   c) Adjusting nature and timing of drugs used to treat otherwise-unrelated systemic conditions
3. Managing renal fluid and solute load
   a) Overall volume of oral intake
   b) Nature and timing of fluid and solute intake
   c) Endogenous fluid shifts
4. Increasing bladder reservoir capacity
   a) Reducing storage LUTS
   b) Improving bladder emptying in voiding dysfunction (bladder outlet obstruction, reduced detrusor contractility)
5. Hypnotics and restoration of circadian pattern
6. Pharmaceutic suppression of nocturnal renal output

Health and Lifestyle Issues Affecting Sleep Quality

In its wider context, nocturia is one of a range of interdependent sleep disturbances, such that attention has to be given to improving the sleep environment. In general, cognitive behavior therapy and relaxation techniques are preferred where there is comorbid insomnia (McCrae, 2009). Educating patients on consistent bedtimes, room temperature, noise, and lighting ("sleep hygiene") are appropriate. Gentle exercise leads to the deeper sleep, thence increasing the "arousal threshold bladder volume"—this also improves day-time urinary frequency and other health-related parameters (Sugaya et al, 2007). Several of the potential disturbances found in the Sleep in America Poll (Foley et al, 2004) may sometimes be correctable by simple measures (particularly physical pain, cough, headache, nighttime heartburn, headache, and uncomfortable bed), whereas some others (health concerns, money problems, family problems) should receive self-help coping measures and appropriate support. Depressive symptoms increase the incidence of nocturia (Hakkinen et al, 2008), so mental state needs to be considered.

Optimizing Management of Systemic Conditions

Some of the underlying nonurologic diseases that can contribute to nocturia merit treatment priority because major morbidity can ensue if appropriate intervention is not instigated (Schneider et al, 2009). This requires optimizing management of known conditions and consideration that a patient could have undiagnosed conditions that might affect nocturnal urine output. The list includes cardiovascular disease, endocrine disorders, renal failure, and OSA. However, improvement in nocturia severity as a consequence of optimizing treatment cannot be relied on. For example, in elderly people with hypertension, addition of a thiazide for management of nocturia in people who are already using losartan provides no additional benefit (Kojima et al, 2008). Part of the optimization of treatment requires adjusting the nature and timing of certain drugs (particularly diuretics, SSRIs, calcium channel blockers, and lithium) used to treat otherwise unrelated systemic conditions, in liaison with the relevant physicians caring for that aspect of the patient's management.

Managing Renal Fluid and Solute Load

Evaluating overall volume of oral intake and understanding the nature and timing of fluid and solute intake are fundamental aspects of managing nocturia. Engaging the patient in their own management is a key factor in the likelihood of treatment success. Behavioral interventions to manage exogenous fluid intake include patient education, caffeine and alcohol reduction, and restriction of nighttime fluids. Evening fluid restriction appears to reduce nocturnal urine excretion by a comparatively small amount (Griffiths et al, 1993). In fact, a high proportion of people with nocturia, in excess of two voids per night, have already instigated evening fluid restrictions themselves (Asplund and Aberg, 1992).

Endogenous fluid shifts, the return of free water and solutes to the circulation from sequestration sites, also need to be considered. Lower limb elevation (so that ankles are above the level of the heart), sometimes combined with compression stockings to reduce gravity-induced third-spacing of fluid in the lower extremities, is often advised (Vaughan et al, 2009). However, clinical evidence to support their efficacy is limited. A peripheral edema score (grade 1: ankle edema; grade 2: edema of the tibial and pretibial region; grade 3: ascites; grade 4: extreme generalized edema (anasarca); upgrading for jugular vein distention) has been used to evaluate nocturia in men with heart failure (Siniorakis et al, 2008). The study proposed that edema within the prostate gland is an element underlying the symptomatology. Diuretics taken in the late afternoon or early evening conceivably will decrease third-spacing of fluid and appear to help nocturia (Reynard, 1998; Williams and Donaldson, 1998). Nocturia response to diuretic therapy is partly predicted by alterations in baseline ANP levels (Fujikawa et al, 2001). Combination therapy employing a diuretic with an α blocker can achieve some benefit in a subgroup of patients, particularly those with nocturnal polyuria (Cho et al, 2009).

Increasing Impaired Bladder Capacity

Storage LUTS and increased filling sensation counteract the reservoir function of the bladder. Voiding dysfunction must also be considered because the presence of a significant postvoid residual will impair reservoir function; instigating intermittent self catheterization at bedtime may help nocturia in this subgroup of patients.

For patients with OAB, antimuscarinic drugs appear to be a logical choice (Chapple et al, 2006; Nitti et al, 2006; Rackley et al, 2006; Brubaker and FitzGerald, 2007). Generally, evening administration of the drug is recommended, though timing of administration for individuals should consider relative bother impact of daytime and overnight LUTS. The presence of NP reduces the prospect of clinical success (Brubaker and FitzGerald, 2007). Furthermore, **reduction of nocturia frequency with these drugs is marginal relative to placebo** (Michel and de la Rosette, 2005), **and there is no significant difference compared with behavioral therapy** (Fitzgerald et al, 2008). **They are not currently licensed for nocturia as an isolated symptom**.

In men, α-adrenergic antagonists are sometimes beneficial (Paick et al, 2006), but NP does not generally improve with α blocker therapy alone (Koseoglu et al, 2006). Naftopidal has been used to treat men with nocturia who have not improved with tamsulosin; benefits were seen in men with nocturia of three or more times per night (Oh-oka, 2008). Celecoxib, a cyclooxygenase-2 inhibitor, can improve nocturnal frequency and IPSS in men with BPE (Falahatkar et al, 2008). Combination pharmaceutic therapy with α-adrenergic antagonists and 5α-reductase inhibitors can improve symptom severity, but changes beyond 1 year are of doubtful clinical significance (Johnson et al, 2007). In men with OAB and nocturia, combined treatment including antimuscarinic drugs can improve symptom severity (Kaplan et al, 2006). Combination treatment including a nonsedating hypnotic (zolpidem) leads to a subjective reduction in nocturia episodes in men with LUTS (Song and Ku, 2007). Chinese herbal medicines have been used with apparent improvement of nocturia in older men (Ogushi and Takahashi, 2007). Nocturia scores and quality of life can improve as a result of surgical treatment in men (Cai et al, 2006). Following TURP, nocturia improvement is more clearly apparent in men of a lower age and with a lower preoperative maximum flow rate (Seki et al, 2009). TURP can improve nocturia frequency and quality of life, hours of undisturbed sleep, and the longest sleep interval between voids (Margel et al, 2007). However,

in nocturia-predominant LUTS, the physician should fully investigate the pathophysiology underlying the nocturia, evaluate whether bladder outlet obstruction is actually present, and warn patients that improvement of nocturia with surgical intervention is not reliable and of uncertain longevity (Neal, 1997).

Hypnotics and Restoration of Circadian Pattern

Hypnotic sedatives administered to elicit sleep pharmaceutically can affect nocturia (Fujikawa et al, 2001). The benzodiazepine oxazepam reduced nocturia 63%, but with no effect on urine volume (Kaye, 2008). The benefits of sedative agents may be in improving return to sleep, rather than in improving nocturia frequency (Takami and Okada, 1993). Those patients taking in excess of 30 minutes to return to sleep after awakening can be prescribed a nonbenzodiazepine sedative hypnotic to take once per night after a first nocturia episode between 23.00 and 03.00 hours (Vaughan et al, 2009). These drugs can be associated with hangover sedation when rising the following morning.

The pineal gland hormone melatonin is secreted during nocturnal hours and is a major determinant of physiologic circadian rhythm. **This release is affected in some older patients with sleep impairment; exogenously administered melatonin can counteract some of the associated sleep impairment** (Garfinkel et al, 1995) **and is not associated with hangover sedation.** Melatonin in isolation has been used for treatment of nocturia in men with BPE, showing marginal changes in the overall study group but with more overt benefits in a small subgroup of patients in whom nocturnal frequency fell by more than one void per night (Drake et al, 2004). Effect of melatonin supplementation has been compared with the hypnotic agent rilmazafone in elderly patients; both groups showed reduction in the number of nocturnal voids (Sugaya et al, 2007).

Pharmaceutic Suppression of Nocturnal Renal Output

Desmopressin can achieve significant improvement in nocturia symptoms for the isolated symptom and when nocturia is a component of OAB. Desmopressin is increasingly used for management of nocturnal polyuria (van Kerrebroeck et al, 2007), and randomized double-blind trials have been reported in both men (Mattiasson et al, 2002) and women (Lose et al, 2003). Thirty-three percent of men and 46% of women showed at least a 50% reduction in the mean number of voids per night relative to baseline; a greater proportion of patients showed at least a 50% reduction in the number of nocturnal voids in longer-term use (Lose et al, 2004). **Dilutional hyponatremia occurs in 7.6% of patients** (Weatherall, 2004); **risk factors include age older than 65 years and low serum sodium at baseline** (Rembratt et al, 2006). **The serum sodium concentration should be checked within a few days of instigating treatment, and dose titration should be employed. In long-term use, sodium should be assessed at least every 6 months** (Bae et al, 2007). Desmopressin is licensed for management of nocturia in multiple sclerosis (MS); its influence on renal urine output is exerted in the 6-hour period following administration (Bosma et al, 2005). Its value is more likely to be clinically beneficial if maximal bladder capacity is adequate (Zahariou et al, 2008). Clinical response to vasopressin analogue treatment was not predicted by water-deprivation tests (Johnson et al, 2007). Cannabis extracts also appear to help nocturia in MS (Brady et al, 2004).

Nonsteroidal anti-inflammatory drugs including oral loxoprofen (Saito et al, 2005) and indomethacin suppositories (Al-Waili et al, 2005) have been administered at bed-time for the treatment of nocturia. The mechanism of action appears to be a reduction in nocturnal urine volume (Araki et al, 2008). It is not clear whether this approach risks any long-term effects on renal function.

Key Points: Assessment and Treatment

- The FVC is used to document key parameters determining diurnal or nocturnal frequency, global or nocturnal polyuria, reduced bladder capacity (overall or nocturnal), or a mixed disorder.
- Symptom assessment tools are used to capture subjective elements of nocturia.
- Individualized treatment plans based on evaluation of risk factors should integrate advice and specific instructions with directed interventions.
- Improved sleep environment, self-help, depression management, cognitive behavior therapy, relaxation techniques, and gentle exercise are used to manage comorbid insomnia.
- Major nonurologic diseases that can contribute to nocturia are prioritized in management.
- Volume, nature, and timing of fluid and solute intake can be adjusted, while endogenous fluid shifts also need to be considered.
- Storage and voiding dysfunction have to be managed to restore bladder reservoir function; intermittent self-catheterization, antimuscarinic drugs, and combination treatments can be considered.
- For nocturia-predominant LUTS in men, comprehensive evaluation is necessary before considering surgery to reduce the risk of a poor symptomatic outcome.
- The benefits of sedative agents may be in improving return to sleep, rather than nocturia frequency. Treatment with melatonin can counteract sleep impairment and reduces nocturia in some patients.
- Desmopressin can achieve significant improvement in nocturia symptoms for the isolated symptom, as well as when nocturia is a component of OAB. Dilutional hyponatremia occurs in 7.6% of patients.

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chapter 68

Pharmacologic Management of Lower Urinary Tract Storage and Emptying Failure

Karl-Erik Andersson, MD, PhD ● Alan J. Wein, MD, PhD (Hon), FACS

Pharmacologic Therapy to Facilitate Bladder Filling and Urine Storage

Pharmacologic Therapy to Facilitate Bladder Emptying

The function of the lower urinary tract (LUT) is to effect efficient and low-pressure bladder filling, low-pressure urine storage with normal sensation and perfect continence, and periodic complete voluntary emptying, again at low pressure. The structures involved include the smooth musculature of the bladder and the bladder outlet and the striated muscle, both intrinsic (to the bladder outlet) and extrinsic (the striated musculature surrounding the bladder outlet and the striated musculature of the pelvic floor). These component structures are controlled by a complex interplay between the central and peripheral nervous systems and local regulatory factors. Pharmacologic alteration of LUT function can occur at any point along the afferent or efferent limb of this complex neuromuscular cascade, either by receptor activation/stimulation or blockade, by affecting the concentration of neurotransmitter at an activation site, or by stimulating or inhibiting signal transduction mechanisms (Andersson and Wein, 2004; Andersson et al, 2009; Birder et al, 2009; Fry et al, 2009; see also Chapter 60).

The focus of this chapter is the pharmacologic management of bladder filling/storage and bladder emptying/voiding dysfunction. The conceptual basis is that of the expanded functional classification seen in Table 61–5 and the division of therapies in the relatively simple-minded manner of those that facilitate urine storage/bladder filling and those that facilitate bladder emptying/voiding (see Tables 61–3 and 61–4). Although the principles expressed are generally applicable to all ages, specifics concerning usage in the elderly and pediatric age groups are considered in detail in Chapters 75, 126, and 127. Specific information regarding the pharmacologic management of LUT dysfunction secondary to obstruction by benign prostatic enlargement is considered in detail in Chapter 91, whereas drug therapy for the treatment of bladder and pelvic pain disorders is considered in detail in Chapters 11 and 12.

As an apology in explanation to significant contributors to the field whose works have not been specifically referenced by name as frequently as they could have been, please note the citations have been chosen primarily because of their comprehensive review or specific informational content and not because of originality or initial publication on a particular subject, except where noted.

PHARMACOLOGIC THERAPY TO FACILITATE BLADDER FILLING AND URINE STORAGE

Inhibiting Bladder Contractility, Decreasing Sensory Input, Increasing Bladder Capacity

Bladder Contraction and Muscarinic Receptors

The major portion of the neurohumoral stimulus for physiologic bladder contraction is acetylcholine-induced stimulation of postganglionic parasympathetic muscarinic cholinergic receptor sites in the bladder (detrusor smooth muscle and possibly other sites) (see Chapter 60). Atropine and atropine-like agents will depress normal bladder contractions and involuntary bladder contractions of any cause (Andersson, 1988; 1993; Andersson and Wein, 2004). In patients with involuntary contractions, the volume to the first involuntary contraction will generally be increased, the amplitude of the contraction decreased, and the total bladder capacity increased (Jensen, 1981).

Previously, it has been stated (Wein, 1998) that bladder compliance in normal individuals and in those with neurogenic detrusor overactivity (NDO; Abrams et al, 2002), in whom the initial slope of the filling curve on cystometry is normal before the involuntary contraction, does not seem to be significantly altered by antimuscarinic agents and that the effect of pure antimuscarinics in those patients who exhibit only decreased compliance had not been well studied. Regarding the subject of bladder tone during filling, Andersson (1999a, 1999b, 2004; Andersson and Yoshida, 2003) has pointed out that, although it is widely accepted that there is normally no sacral parasympathetic outflow to the bladder during filling, antimuscarinic drugs increase, and anticholinesterase inhibitors decrease, bladder capacity. **Because antimuscarinic drugs do seem to affect the sensation of urgency during filling, this suggests an ongoing acetylcholine-mediated stimulation of detrusor tone** (see later). **If this is correct,**

agents inhibiting acetylcholine release or activity would be expected to contribute to bladder relaxation or the maintenance of low bladder tone during filling with a consequent decrease in filling/storage symptomatology unrelated to the occurrence of an involuntary contraction. Outlet resistance, at least as reflected by urethral pressure measurements, does not seem to be clinically affected.

Although the antimuscarinic agents usually produce significant clinical improvement in patients with involuntary contractions and associated symptoms, generally only partial inhibition results. In many animal models, atropine only partially antagonizes the response of the whole bladder to pelvic nerve stimulation and of bladder strips to field stimulation, although it does completely inhibit the response of bladder smooth muscle to exogenous cholinergic stimulation. This phenomenon, which is called ***atropine resistance,*** is secondary to release of a transmitter other than acetylcholine (see Andersson, 1993; Andersson et al, 1999c; Andersson and Wein, 2004; see also Chapter 60). Atropine resistance is the most common hypothesis invoked to explain the clinical difficulty in eradicating involuntary contractions with antimuscarinic agents alone, and it is also invoked to support the rationale of combined treatment of DO with agents that have different mechanisms of action (Andersson, 2006).

Andersson and Wein (2004) cite references stating that atropine resistance seems to be of little importance in normal human bladder muscle but point out that atropine-resistant (nonadrenergic, noncholinergic) contractions have been reported in human detrusor smooth muscle and in morphologically and/or functionally changed bladders in individuals with various types of voiding dysfunction. Thus, **the importance or nonimportance of an atropine-resistant component to detrusor contraction in the treatment of DO in humans remains to be established.**

Muscarinic Receptors

In the human bladder, where the mRNAs for all the five pharmacologically defined receptors, M_1 to M_5, have been demonstrated (Sigala et al, 2002; Abrams et al, 2006a; Giglio and Tobin, 2009), **there is a predominance of mRNAs encoding M_2 and M_3 receptors** (Yamaguchi et al, 1996; Sigala et al, 2002; Abrams et al, 2006a; Giglio and Tobin, 2009). This seems to be the case also in the animal species investigated (Hegde and Eglen, 1999; Chess-Williams, 2002; Andersson and Arner, 2004). **Both M_2 and M_3 receptors can be found on detrusor muscle cells, where M_2 receptors predominate at least 3:1 over M_3 receptors, but also in other bladder structures, which may be of importance for detrusor activation.** Thus, muscarinic receptors can be found on **urothelial cells, on suburothelial nerves, and on other suburothelial structures, such as interstitial cells** (Chess-Williams, 2002; Gillespie et al, 2003; Gillespie, 2004b; Mansfield et al, 2005; Bschleipfer et al, 2007; Giglio and Tobin, 2009).

In human as well as animal detrusor, the M_3 receptors are believed to be the most important for contraction (Andersson, 1993; Chess-Williams, 2002; Abrams et al, 2006a; Giglio and Tobin, 2009). No differences between genders could be demonstrated in rat and human bladders (Kories et al, 2003). **The functional role for the M_2 receptors has not been clarified,** and even in M_3 receptor knockout mice they seem responsible for less that 5% of the carbachol-mediated detrusor contraction (Matsui et al, 2000). Stimulation of M_2 receptors has been shown to oppose sympathetically (β-adrenoreceptor [β-AR]) mediated smooth muscle relaxation (Hegde et al, 1997). However, based on animal experiments, M_2 receptors have been suggested to directly contribute to contraction of the bladder in certain disease states (denervation, outflow obstruction). Experiments on human detrusor muscle by Stevens and associates (2007) could not confirm this; however, Pontari and colleagues (2004) analyzed bladder muscle specimens from patients with neurogenic bladder dysfunction to determine whether the muscarinic receptor subtype mediating contraction shifts from M_3 to the M_2 receptor subtype, as found in the denervated, hypertrophied rat bladder. They concluded that normal detrusor contraction is mediated by the M_3 receptor subtype whereas contractions can be mediated by the M_2 receptors in patients with neurogenic bladder dysfunction.

Muscarinic receptors are coupled to G proteins, but the signal transduction systems may vary. **Generally, M_1, M_3, and M_5 receptors are considered to couple preferentially to $G_{q/11}$, activating phosphoinositide hydrolysis, in turn leading to mobilization of intracellular calcium (Ca^{2+}). M_2 and M_4 receptors couple to pertussis toxin–sensitive $G_{i/o}$, resulting in inhibition of adenylate cyclase activity.** In the human detrusor, Schneider and coworkers (2004), confirming that the muscarinic receptor subtype mediating carbachol-induced contraction is the M_3 receptor, also demonstrated that the phospholipase-C inhibitor U73122 did not significantly affect carbachol-stimulated bladder contraction, despite blocking inositol 1,4,5-triphosphate generation. They concluded that carbachol-induced contraction of the human urinary bladder is mediated via M_3 receptors and largely depends on Ca^{2+} entry through nifedipine-sensitive channels and activation of the Rho-kinase pathway. Thus, **it may be that the main pathways for muscarinic receptor activation of the detrusor via M_3 receptors are Ca^{2+} influx via L-type Ca^{2+} channels and increased sensitivity to Ca^{2+} of the contractile machinery via inhibition of myosin light-chain phosphatase through activation of Rho-kinase.**

The signaling mechanisms for the M_2 receptors are less clear than those for M_3 receptors. As mentioned previously, **M_2 receptor stimulation may oppose sympathetically induced smooth muscle relaxation, mediated by β-ARs via inhibition of adenylyl cyclase** (Hegde et al, 1997). In agreement with this, Matsui and colleagues (2003) suggested, based on results obtained in M_2 receptor knockout mice, that a component of the contractile response to muscarinic agonists in smooth muscle involves an M_2 receptor–mediated inhibition of the relaxant effects of agents that increase cyclic adenosine monophosphate (cAMP) levels. M_2 receptor stimulation can also activate nonspecific cation channels and inhibit K_{ATP} channels through activation of protein kinase C (Bonev and Nelson, 1993; Kotlikoff et al, 1999).

Muscarinic receptors may also be located on the presynaptic nerve terminals and participate in the regulation of transmitter release. The inhibitory prejunctional muscarinic receptors have been classified as muscarinic M_2 in the rabbit (Tobin and Sjögren, 1995) and rat (Somogyi and de Groat, 1992) and as M_4 in the guinea pig (Alberts, 1995) and human bladder (D'Agostino et al, 2000). Prejunctional facilitatory muscarinic receptors appear to be of the M_1 subtype in the bladders of rats, rabbits (Somogyi and de Groat, 1992; Tobin and Sjögren, 1995, 1998), and humans (Somogyi and de Groat, 1999; Giglio and Tobin, 2009). The muscarinic facilitatory mechanism seems to be upregulated in overactive bladders from chronic spinal cord–transected rats. The facilitation in these preparations is primarily mediated by M_3 muscarinic receptors (Somogyi and de Groat, 1999).

The relative roles of the different presynaptic and postsynaptic receptor subtypes in normal and abnormal bladder function still require clarification, and thus speculation regarding optimal drug therapy based only on in-vitro receptor selectivity profiles represents, at the very least, a gross oversimplification of assumptions regarding the muscarinic regulation of bladder function. The muscarinic receptor functions may be changed in different urologic disorders, such as outflow obstruction, neurogenic bladders, DO without overt neurogenic cause, and diabetes (Andersson, 2000b). **However, it is not always clear what the changes mean in terms of changes in detrusor function.**

In general, **all drug therapy for LUT dysfunction is hindered by a concept that can be expressed in one word: "uroselectivity"** (Andersson, 1998). **The clinical utility of available antimuscarinic agents is limited by their lack of selectivity, which is responsible for the classic peripheral antimuscarinic side effects of dry mouth, constipation, blurred vision, and increase in heart rate and for the effects on cognitive functions.** Although M_3 receptor selective agents have the potential to eliminate some of these side effects, it would appear that the M_3 receptors in tissues of the LUT are identical to those elsewhere in the body (Caulfield and Birdsall, 1998). It may be speculated, however, that there is some heterogeneity among M_3 receptors, and this has prompted many pharmaceutical companies to continue to search for the "ideal" antimuscarinic agent to treat DO, one that would be relatively selective for muscarinic receptors involved in the regulation of bladder contraction. Receptor selectivity, however, is not the only basis on which a drug may be "uroselective." From a clinical standpoint it would seem particularly important to be able to describe in relative terms the ratio between a drug dose required for a desired therapeutic action and the dose producing side effects. A differential effect could be based not only on receptor selectivity but also on other known and as yet undefined physiologic, pharmacologic, or metabolic characteristics. Organ selectivity would thus seem to be the "holy grail" of such therapy. The same problematic set of concepts applies to virtually all drugs used for the treatment of LUT dysfunction.

Drugs Used for Treatment of Detrusor Overactivity/Overactive Bladder Symptomatology

The prevalence of the overactive bladder (OAB) syndrome varies with the criteria for diagnosis. According to Irwin and associates (2006), using the 2002 International Continence Society (ICS) definition, the overall prevalence (the EPIC study) was 11.8%. The rates were similar in men and women and increased with age. A similar study by Herschhorn and coworkers (2008) found the prevalence to be 13% in Canadian men and 14% in Canadian women. It appears that OAB/DO may be the result of several different mechanisms, both myogenic and neurologic (Morrison et al, 2002; Birder et al, 2009; Koebl et al, 2009). Most probably, both factors contribute to the genesis of the disease.

An abundance of drugs has been used for the treatment of OAB/DO. It should be stressed that in many trials on OAB/DO there has been such a high placebo response that meaningful differences between placebo and active drug cannot be demonstrated (Thüroff et al, 1998). However, drug effects in individual patients may be both distinct and useful.

The 4th International Consultation on Incontinence (ICI) (2008) **assessed drugs used for treatment of incontinence** (Andersson et al, 2009). **The assessment criteria** (Table 68–1) **were based on the Oxford guidelines, and the drugs included are given in** Table 68–2**.**

Antimuscarinic (Anticholinergic) Agents

Mechanism of Action. **For many years, antimuscarinic drugs have been the gold standard for treatment of OAB. Still, the way(s) by which they exert their beneficial effect has (have) not yet been established.**

Acetylcholine stimulates both muscarinic and nicotinic receptors. Antimuscarinic agents block selectively muscarinic receptors, and they are currently the mainstay of treatment of OAB/DO (Abrams and Andersson, 2007). The **traditional view** is that in OAB/DO the drugs act by blocking the muscarinic receptors on the detrusor muscle, which are stimulated by acetylcholine released from activated cholinergic (parasympathetic) nerves. Thereby, they decrease the ability of the bladder to contract. **However, antimuscarinic drugs act mainly during the storage phase, decreasing urgency and increasing bladder capacity; and during this phase there is normally no parasympathetic input to the LUT** (Morrison et al, 2002; Andersson, 2004). Furthermore, antimuscarinic agents are usually competitive antagonists. This implies that when there is a massive release of acetylcholine, as during micturition, the effects of the drugs should be decreased, otherwise the reduced ability of the detrusor to contract would eventually lead to urinary retention. Undeniably, high doses of antimuscarinic agents can produce urinary retention in humans, **but in the dose range used for beneficial effects in OAB/DO there is little evidence for a significant reduction of the voiding contraction** (Finney et al, 2006) (Fig. 68–1). There is indirect clinical evidence for release of acetylcholine during bladder filling in certain abnormal conditions. Smith and colleagues (1974) found that in patients with recent spinal cord injury, inhibition of acetylcholine breakdown by use of cholinesterase inhibitors could increase resting tone and induce rhythmic contractions in the bladder. Yossepowitch and coworkers (2001) inhibited acetylcholine breakdown with edrophonium in a series of patients with disturbed voiding or urinary incontinence. They found a significant change in sensation and decreased bladder capacity, induction or amplification of involuntary detrusor contractions, or significantly decreased detrusor compliance in 78% of the patients with the symptom pattern of OAB but in no patients without specific complaints suggesting DO. Thus, **during the storage phase,**

Table 68–1.

International Consultation on Incontinence (ICI) Assessments 2004, 2008: Oxford Guidelines (Modified)

Levels of Evidence

Level 1: Systematic reviews, meta-analyses, good quality randomized controlled clinical trials
Level 2: Randomized controlled trials, good quality prospective cohort studies
Level 3: Case-control studies, case series
Level 4: Expert opinion

Grades of Recommendation

Grade A: Based on level 1 evidence (highly recommended)
Grade B: Consistent level 2 or 3 evidence (recommended)
Grade C: Level 4 studies or "majority evidence"(optional)
Grade D: Evidence inconsistent/inconclusive (no recommendation possible)

Table 68–2.

Drugs Used in the Treatment of Detrusor Overactivity (ICI, 2008; Andersson et al, 2009)

ANTIMUSCARINIC DRUG	LEVEL OF EVIDENCE	GRADE OF RECOMMENDATION
Tolterodine	1	A
Trospium	1	A
Solifenacin	1	A
Darifenacin	1	A
Fesoterodine	1	A
Propantheline	2	B
Atropine, hyoscyamine	3	C
Drugs Acting on Membrane Channels		
Calcium antagonists	2	D
Potassium channel openers	2	D
Drugs with Mixed Actions		
Oxybutynin	1	A
Propiverine	1	A
Flavoxate	2	D
Antidepressants		
Imipramine	3	C
Duloxetin	2	C
α-Adrenergic Receptor Antagonists		
Alfuzosin	3	C
Doxazosin	3	C
Prazosin	3	C
Terazosin	3	C
Tamsulosin	3	C
β-Adrenergic Receptor Antagonists		
Terbutaline (β_2)	3	C
Salbutamol (β_2)	3	C
YM178 (β_3)	2	BPDE-
Phosphodiesterase-5 Inhibitors		
Sildenafil, Tadalafil, Vardenafil	2	B
Cyclooxygenase Inhibitors		
Indomethacin		C
Flurbiprofen	2	C
Toxins		
Botulinum toxin (neurogenic)*	2	A
Botulinum toxin (idiopathic)*	3	B
Capsaicin†	2	C
Resiniferatoxin†	2	C
Other Drugs		
Baclofen‡	3	C
Hormones		
Estrogen	2	C
Desmopressin§	1	A

*Bladder wall.
†Intravesical.
‡Intrathecal.
§Nocturia.

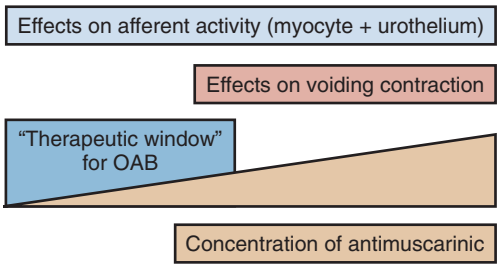


Figure 68–1. Rationale for use of antimuscarinic agents in overactive bladder (OAB).

acetylcholine may be released from both neuronal and non-neuronal sources (e.g., the urothelium/suburothelium) **and directly or indirectly (by increasing detrusor smooth muscle tone) excite afferent nerves in the suburothelium and within the detrusor. There is also good experimental evidence that antimuscarinic agents act during the storage phase by decreasing the activity in afferent nerves (both C and Aδ fibers) from the bladder** (De Laet et al, 2006; Iijima et al, 2007).

Muscarinic receptors are found on bladder urothelial cells where their density can be even higher than in detrusor muscle. The role of the urothelium in bladder activation has attracted much interest (Andersson, 2002a; de Groat, 2004; Birder and de Groat, 2007; Birder et al, 2009; Giglio and Tobin, 2009), but whether the muscarinic receptors on urothelial cells can influence micturition has not yet been established. Yoshida and colleagues (2004, 2006, 2008) found that there is basal acetylcholine release in the human bladder. This release was resistant to tetrodotoxin and much diminished when the urothelium was removed; thus, the released acetylcholine was probably of non-neuronal origin and, at least partly, generated by the urothelium. Thus, during the storage phase, acetylcholine and adenosine triphosphate (ATP) may be released from both neuronal and non-neuronal sources (e.g., the urothelium) and directly or indirectly (by increasing detrusor smooth muscle tone) excite afferent nerves in the suburothelium and within the detrusor. These mechanisms may be important in the pathophysiology of OAB and represent possible targets for antimuscarinic drugs.

Pharmacologic Properties. Generally, antimuscarinic agents can be divided into tertiary and quaternary amines (Guay, 2003; Abrams and Andersson, 2007). They differ with regard to lipophilicity, molecular charge, and even molecular size, with tertiary compounds generally having higher lipophilicity and molecular charge than quaternary agents. **Atropine, darifenacin, fesoterodine (and its active metabolite 5-hydroxymethyl-tolterodine), oxybutynin, propiverine, solifenacin, and tolterodine, are tertiary amines. They are generally well absorbed from the gastrointestinal tract and should theoretically be able to pass into the central nervous system (CNS),** dependent on their individual physicochemical properties. **High lipophilicity, small molecular size, and less charge will increase the possibilities to pass the blood-brain barrier, but for some of the drugs this is counteracted by active transport out of the CNS by P-glycoprotein. Quaternary ammonium compounds, such as propantheline and trospium, are not well absorbed, pass into the CNS to a limited extent, and have a low incidence of CNS side effects** (Guay, 2003). They still produce well-known peripheral antimuscarinic side effects, such as accommodation paralysis, constipation, increase in heart rate, and dryness of mouth.

Many antimuscarinic drugs are metabolized by the cytochrome P450 enzyme system to active and/or inactive metabolites (Guay, 2003). **The most commonly involved P450 enzymes are CYP2D6 and CYP3A4. The metabolic conversion creates a risk for drug-drug interactions, resulting in either reduced (enzyme induction) or increased (enzyme inhibition, substrate competition)**

plasma concentration/effect of the antimuscarinic and/or interacting drug. Antimuscarinic agents secreted by the renal tubules (e.g., trospium) may theoretically be able to interfere with the elimination of other drugs using this mechanism.

Antimuscarinic drugs are still the most widely used treatment for urgency and urgency incontinence (Andersson, 2004; Andersson et al, 2009). However, currently used drugs lack selectivity for the bladder, and effects on other organ systems (Table 68–3) may result in side effects that limit their usefulness. For example, all antimuscarinic drugs are contraindicated in patients with untreated narrow-angle glaucoma.

Theoretically, drugs with selectivity for the bladder could be obtained if the subtype(s) mediating bladder contraction, and those producing the main side effects of antimuscarinic drugs, were different. Unfortunately this does not seem to be the case. One way of avoiding many of the antimuscarinic side effects is to administer the drugs intravesically. However, this is practical only in a limited number of patients.

Clinical Efficacy. Several antimuscarinic drugs are and have been used for treatment of OAB/DO. For many of them documentation of effects is not based on randomized controlled trials (RCTs) satisfying currently required criteria, and some drugs can be considered as obsolete (e.g., emepronium). Information on these drugs is found elsewhere (Andersson, 1988; Andersson et al, 1999c).

The clinical relevance of efficacy of antimuscarinic drugs relative to placebo has been questioned. Herbison and associates (2003) stated in a widely discussed article: "Anticholinergics produce significant improvements in overactive bladder symptoms compared with placebo. The benefits are, however, of limited clinical significance." **Large meta-analyses of studies performed with the currently most widely used drugs** (Chapple et al, 2005, 2008a; Novara et al, 2008) **clearly show that antimuscarinic drugs are of significant clinical benefit.** Novara and colleagues (2008) reviewed 50 RCTs and 3 pooled analyses that they considered of good methodologic quality. They concluded that still more clinical studies are needed to decide which of the drugs should be used as first-, second-, or third-line treatment. Reviewing information from more than 12,000 references, Chapple and colleagues (2008a) based their conclusions ("antimuscarinics are efficacious, safe, and well tolerated treatments") on 73 RCTs selected for their meta-analysis. It was recommended that because the profiles of each drug and dosage differ that these factors should be considered in making treatment choices.

The consequence of this is that, in the authors' opinion, none of the antimuscarinic drugs in common clinical use (darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine, or trospium) is ideal as a first-line treatment for *all* OAB/DO patients. Optimal treatment should be individualized, implying that the patient's comorbidities and concomitant medications, and the pharmacologic profiles of the different drugs, should be taken into consideration (Chapple et al, 2008a).

Behavioral therapy (see Chapter 69) **should always be used in conjunction with drug therapy for OAB/DO because most studies show the effects of the two combined are greater than the effect of either alone** (Burgio et al, 2000; Mattiasson et al, 2003; Klutke et al, 2009).

Tolerability and Safety. An extensive literature supports that antimuscarinic drugs for the treatment of OAB symptoms are generally well tolerated. The adverse effect profiles of the different drugs are determined by their organ and muscarinic receptor subtype selectivities and pharmacokinetic parameters. **The most commonly reported adverse effects are dry mouth, constipation, headache, and blurred vision.**

Among the more serious possibilities related to antimuscarinic use is **the potential risk of cardiac adverse effects,** particularly **increases in heart rate** and **QT prolongation and induction of polymorphic ventricular tachycardia** (torsades de pointes). **QT prolongation and its consequences are not related to blockade of muscarinic receptors but rather linked to inhibition of the hERG potassium (K^+) channel in the heart** (Roden, 2004). **Thus QT prolongation is not a class effect of antimuscarinic drugs.** In general the cardiovascular safety for antimuscarinic drugs seems to be good. However, **the potential of the different agents to increase heart rate or to prolong the QT time has not been extensively explored.** Differences between the drugs cannot be excluded, but risk assessments based on available evidence are not possible.

Another concern is that antimuscarinic drugs commonly used to treat OAB can be associated with CNS side effects, including cognitive dysfunction, memory impairment, dizziness, fatigue, and headache. With the exception of oxybutynin IR, CNS-related side effects are not commonly found when investigated. The potential to cause CNS-related adverse effects may differ between drugs, but in the absence of comparative trials, relative risk assessments are not possible.

Atropine Sulfate. Atropine (*dl*-hyoscyamine) is rarely used for treatment of OAB/DO because of its systemic side effects, which preclude its use as an oral treatment. However, in patients with neurogenic DO, intravesical atropine may be effective for increasing bladder capacity without causing any systemic adverse effects, as shown in open pilot trials (Ekström et al, 1992; Glickman et al, 1995; Deaney et al, 1998; Enskat et al, 2001; Fader et al, 2007). It appears that intravesical atropine may be as effective as intravesical oxybutynin in patients with neurogenic DO (Fader et al, 2007). The pharmacologically active antimuscarinic component of atropine is *l*-hyoscyamine. Although it is still used, few clinical studies are available to evaluate the antimuscarinic activity of *l*-hyoscyamine sulfate (Muskat et al, 1996). For assessment, see Table 68–2.

Table 68–3.

Muscarinic Receptors: Distribution and Function

REGION	SUBTYPE OF MUSCARINIC RECEPTOR	FUNCTION
Bladder	$M_2 > M_3$ (3:1)	M_3: mediates human detrusor contraction
Salivary glands, parotid gland	M_1, M_3	M_1: high viscosity lubrication M_3: salivation
Gastrointestinal tract	$M_2 > M_3$ (4:1)	M_3: stimulation of gastrointestinal motility
Brain	M_1 to M_5 (M_3 sparse)	Involved in higher cognitive processes such as learning and memory (mostly M_1)
Eye	M_1 to M_5 (M_3 predominates)	Controls iris sphincter contraction
Heart	M_2	Modulates pacemaker activity, atrioventricular conduction, and the force of contraction

Data from Abrams P, Andersson K-E, Buccafusco JJ, et al. Muscarinic receptors: their distribution and function in body systems, and the implications for treating overactive bladder. Br J Pharmacol 2006;148:565.

Propantheline Bromide. **Propantheline bromide (Pro-Banthine, others) is a quaternary ammonium compound,** nonselective for muscarinic receptor subtypes, that has a low (5% to 10%) and individually varying biologic availability. It is metabolized (metabolites inactive) and has a short plasma half-life (<2 hr) (Beermann et al, 1972). It is usually given in a dose of 15 to 30 mg four times daily, but, to obtain an optimal effect, individual titration of the dose is necessary and often higher dosages are required. Using this approach in 26 patients with DO, Blaivas and associates (1980) in an open study obtained a complete clinical response in all patients but one, who did not tolerate more than propantheline, 15 mg, four times daily. The range of dosages varied from 7.5 to 60 mg four times daily. In contrast, Thüroff and coworkers (1991) comparing the effects or oxybutynin 5 mg three times a day, propantheline 15 mg three times a day, and placebo in a randomized, double-blind, multicenter trial on the treatment of frequency, urgency, and incontinence related to DO (154 patients) found no differences between the placebo and propantheline groups. In another randomized comparative trial with crossover design (23 women with idiopathic DO), and with dose titration, Holmes and associates (1989) found no differences in efficacy between oxybutynin and propantheline. There is a surprising lack of evaluable data on the effectiveness of propantheline for the treatment of DO. The Agency for Health Care Policy and Research (AHCPR) Clinical Practice Guidelines (U.S. Department of Health and Human Services, 1992) lists five randomized controlled trials reviewed for propantheline, with 82% female patients. Percent cures (all figures refer to percent effect on drug minus percent effect on placebo) are listed as 0% to 5%, reduction in urgency incontinence as 0% to 53%, and percent side effects and percent dropouts as 0% to 50% and 0% to 9%, respectively. RCTs (n = 6) reviewed by Thüroff and associates (1998) confirmed a positive, but varying, response to the drug.

Although the effect of propantheline on OAB/DO has not been well documented in controlled trials satisfying standards of today, it can be considered effective and may, in individually titrated doses, be clinically useful (see Table 68–2). No new studies on the use of this drug for the treatment of OAB/DO seem to have been performed during the past decade.

Trospium Chloride. **Trospium is a quaternary ammonium compound with a biologic availability of less than 10%** (Fusgen and Hauri, 2000; Doroshyenko et al, 2005). The drug has a plasma half-life of approximately 20 hours and is mainly (60% of the dose absorbed) eliminated unchanged in the urine. The concentration obtained in urine seems to be enough to affect the mucosal signaling system in a rat model (Kim et al, 2006). Whether it contributes to the clinical efficacy of the drug remains to be established. Trospium is not metabolized by the cytochrome P450 enzyme system (Beckmann-Knopp et al, 1999; Doroshyenko et al, 2005). **It is expected to cross the blood-brain to a limited extent and seems to have no negative cognitive effects** (Fusgen and Hauri, 2000; Todorova et al, 2001; Wiedemann et al, 2002).

Trospium has no selectivity for muscarinic receptor subtypes. In isolated detrusor muscle it was more potent than oxybutynin and tolterodine to antagonize carbachol-induced contractions (Uckert et al, 2000).

Several RCTs have documented positive effects of trospium both in neurogenic (Stöhrer, et al, 1991; Madersbacher et al, 1995; Menarini et al, 2006) and non-neurogenic DO (Allousi et al, 1998; Cardozo et al, 2000; Jünemann and Al-Shukri, 2000; Halaska et al, 2003; Zinner et al, 2004a; Rudy et al, 2006; Staskin et al, 2007; Dmochowski et al, 2008). In a placebo-controlled, double-blind study on patients with neurogenic DO (Stöhrer et al, 1991) the drug was given twice daily in a dose of 20 mg over a 3-week period. It increased maximum cystometric capacity, decreased maximum detrusor pressure, and increased compliance in the treatment group, whereas no effects were noted in the placebo group. Side effects were few and comparable in both groups. In another RCT including patients with spinal cord injuries and neurogenic DO, trospium and oxybutynin were equally effective; however, trospium seemed to have fewer side effects (Madersbacher et al, 1995). The effect of trospium in urgency incontinence has been documented in several RCTs. Allousi and associates (1998) compared the effects of the drug with those of placebo in 309 patients in a urodynamic study of 3 weeks' duration. Trospium, 20 mg, was given twice daily. Significant increases were noted in volume at first involuntary contraction and in maximum bladder capacity. Cardozo and coworkers (2000) investigated 208 patients with DO who were treated with trospium, 20 mg twice daily, for 2 weeks. Also in this study, significant increases were found in mean volume at first unstable contraction (from 233 to 299 mL; placebo 254 to 255 mL) and in maximum bladder capacity (from 329 to 356 mL; placebo 345 to 335 mL) in the trospium-treated group. Trospium was well tolerated with similar frequency of adverse effects as in the placebo group. Jünemann and Al-Shukri (2000) compared trospium, 20 mg twice daily, with tolterodine, 2 mg twice daily, in a placebo-controlled double-blind study on 232 patients with urodynamically proven DO, urgency incontinence without demonstrable DO, or mixed incontinence. Trospium reduced the frequency of micturition, which was the primary end point, more than tolterodine and placebo and also reduced the number of incontinence episodes more than the comparators. Dry mouth was comparable in the trospium and tolterodine groups (7% and 9%, respectively). Halaska and colleagues (2003) studied the tolerability and efficacy of trospium chloride in doses of 20 mg twice daily for long-term therapy in patients with urgency syndrome. The trial comprised a total of 358 patients with urgency syndrome or urgency incontinence. After randomization in the ratio of 3:1, participants were treated continuously for 52 weeks with either trospium chloride (20 mg twice daily) or oxybutynin (5 mg twice daily). Urodynamic measurements were performed at the beginning and at 26 and 52 weeks to determine the maximum cystometric bladder capacity. Analysis of the micturition diary clearly indicated a reduction of the micturition frequency, incontinence frequency, and a reduction of the number of urgency episodes in both treatment groups. Mean maximum cystometric bladder capacity increased during treatment with trospium chloride by 92 mL after 26 weeks and 115 mL after 52 weeks ($P = .001$). Further comparison with oxybutynin did not reveal any statistically significant differences in urodynamic variables between the drugs. Adverse events occurred in 65% of the patients treated with trospium and 77% of those treated with oxybutynin. The main symptom encountered in both treatment groups was dryness of the mouth. An overall assessment for each of the drugs revealed a comparable efficacy level and a better benefit-risk ratio for trospium than for oxybutynin due to better tolerability. Zinner and coworkers (2004a) treated 523 patients with symptoms associated with OAB and urgency incontinence with trospium 20 mg twice daily or placebo in a 12-week, multicenter, parallel, double-blind, placebo-controlled trial. Dual primary end points were change in average number of toilet voids and change in urgency incontinent episodes per 24 hours. Secondary efficacy variables were change in average of volume per void, voiding urgency severity, urinations during day and night, time to onset of action, and change in

Incontinence Impact Questionnaire. By week 12, trospium significantly decreased average frequency of toilet voids per 24 hours (–2.37; placebo –1.29) and urgency incontinent episodes (–59%; placebo –44%). It significantly increased average volume per void (32 mL; placebo: 7.7 mL) and decreased average urgency severity and daytime frequency. All effects occurred by week 1, and all were sustained throughout the study. Nocturnal frequency decreased significantly by week 4 (–0.43; placebo: 0.17), and Incontinence Impact Questionnaire scores improved at week 12. Trospium was well tolerated. The most common side effects were dry mouth (21.8%; placebo 6.5%), constipation (9.5%; placebo 3.8%). and headache (6.5%; placebo 4.6%). In a large U.S. multicenter trial with the same design, and including 658 patients with OAB, Rudy and coworkers (2006) confirmed the data by Zinner and associates (2004a), both with respect to efficacy and adverse effects. An extended-release formulation of trospium allowing once-daily dosing (60 mg) has been introduced and its effects tested in controlled trials (Staskin et al, 2007; Dmochowski et al, 2008). These RCTs demonstrated similar efficacy as found with previous formulations.

The most frequent side effects were dry mouth (12.9%; placebo 4.6%) and constipation (7.5%; placebo 1.8%) (Dmochowski et al, 2008).

Intravesical application of trospium may be an interesting alternative. Fröhlich and colleagues (1998) performed a randomized, single-blind, placebo-controlled, monocenter clinical trial in 84 patients with urgency or urgency incontinence. Compared with placebo, intravesical trospium produced a significant increase in maximum bladder capacity and a decrease of detrusor pressure accompanied by an increase of residual urine. There was an improvement in uninhibited bladder contractions. No adverse events were reported. Interestingly, intravesical trospium does not seem to be absorbed (Walter et al, 1999), thus offering an opportunity for treatment with minimal systemic antimuscarinic effects.

Trospium is a well-documented alternative for treatment of OAB/DO and seems to be well tolerated.

Tolterodine Tartrate. **Tolterodine is a tertiary amine, rapidly absorbed and extensively metabolized by the cytochrome P450 system (CYP2D6). The major active 5-hydroxymethyl metabolite (5-HMT) has a similar pharmacologic profile as the mother compound** (Nilvebrant et al, 1997b) **and significantly contributes to the therapeutic effect of tolterodine** (Brynne et al, 1997, 1998). Both tolterodine and 5-HMT have plasma half-lives of 2 to 3 hours, but the effects on the bladder seem to be more long lasting than could be expected from the pharmacokinetic data. Urinary excretion of tolterodine accounted for less than 1.0% to 2.4% of the dose; 5% to 14% of 5-HMT is eliminated in the urine (Brynne et al, 1997). Whether the total antimuscarinic activity of unchanged tolterodine and 5-HMT excreted in urine is sufficient to exert any effect on the mucosal signaling mechanisms has not been established. However, the preliminary studies by Kim and coworkers (2006) and Chuang and colleagues (2008) do not support such an effect. The relatively low lipophilicity of tolterodine and even lesser one of 5-HMT implies **limited propensity to penetrate into the CNS,** which may explain a low incidence of cognitive side effects (Hills et al, 1998; Clemett et al, 2001; Salvatore et al, 2008). However, tolterodine may disturb sleep in subjects unable to form the even less lipophilic 5-HMT due to a low activity of CYP2D6 (Diefenbach et al, 2008).

Tolterodine has **no selectivity for muscarinic receptor subtypes** but is claimed to have functional selectivity for the bladder over the salivary glands (Stahl et al, 1995; Nilvebrant et al, 1996, 1997a, 1997c). In healthy volunteers, orally given tolterodine in a high dose (6.4 mg) had a powerful inhibitory effect on micturition and also reduced stimulated salivation 1 hour after administration of the drug (Stahl et al, 1995); however, 5 hours after administration, the effects on the urinary bladder were maintained whereas no significant effects on salivation could be demonstrated. Tolterodine is available as immediate-release (TOLT-IR; 1 or 2 mg; twice-daily dosing) and extended-release (TOLT-ER) forms (2 or 4 mg; once-daily dosing). The ER form seems to have advantages over the IR form in terms of both efficacy and tolerability (Van Kerrebroeck et al, 2001).

Several randomized, double-blind, placebo-controlled studies on patients with OAB/DO (both idiopathic and neurogenic DO) have documented a significant reduction in micturition frequency and number of incontinence episodes (Hills et al, 1998; Clemett et al, 2001; Salvatore et al, 2008). Comparative RCTs such as the OBJECT (Overactive Bladder: Judging Effective Control and Treatment) and the OPERA (Overactive Bladder; Performance of Extended Release Agents) studies have further supported its effectiveness. The OBJECT trial compared oxybutynin ER (OXY-ER) 10 mg once daily with TOLT-IR 2 mg twice daily (Appell et al, 2001) in a 12-week randomized, double-blind, parallel-group study including 378 patients with OAB. Participants had between 7 and 50 episodes of urgency incontinence per week and 10 or more voids in 24 hours. The outcome measures were the number of episodes of urgency incontinence, total incontinence, and micturition frequency at 12 weeks adjusted for baseline. At the end of the study, OXY-ER was found to be significantly more effective than TOLT-IR in each of the main outcome measures adjusted for baseline (see also later discussion on oxybutynin chloride). Dry mouth, the most common adverse event, was reported by 28% and 33% of participants taking OXY-ER and TOLT-IR, respectively. Rates of CNS and other adverse events were low and similar in both groups. The authors concluded that OXY-ER was more effective than TOLT-IR and that the rates of dry mouth and other adverse events were similar in both treatment groups. In the OPERA study (Diokno et al, 2003), OXY-ER at 10 mg/day or TOLT-ER at 4 mg/day was given for 12 weeks to women with 21 to 60 urgency incontinence episodes per week and an average of 10 or more voids per 24 hours. Episodes of incontinence episodes (primary end point), total (urgency and nonurgency) incontinence, and micturition were recorded in seven 24-hour urinary diaries at baseline and at weeks 2, 4, 8, and 12 and compared. Adverse events were also evaluated. Improvements in weekly urgency incontinence episodes were similar for the 790 women who received OXY-ER (n = 391) or TOLT-ER (n = 399). OXY-ER was significantly more effective than TOLT-ER in reducing micturition frequency, and 23.0% of women taking OXY-ER reported no episodes of urinary incontinence compared with 16.8% of women taking TOLT-ER. Dry mouth (usually mild) was more common with OXY-ER. Adverse events were generally mild and occurred at low rates, with both groups having similar discontinuation of treatment due to adverse events. The conclusions were that reductions in weekly urgency incontinence and total incontinence episodes were similar with the two drugs. Dry mouth was more common with OXY-ER, but tolerability was otherwise comparable, including adverse events involving the CNS.

In the ACET (Antimuscarinic Clinical Effectiveness Trial) (Sussman and Garely, 2002) study, which consisted of two trials, patients with OAB were randomized to 8 weeks of open-label treatment with either 2 mg or 4 mg of once-daily TOLT-ER (study 1) and to 5 mg or 10 mg of OXY-ER (study 2). A total of 1289 patients were included. Fewer patients prematurely withdrew from the trial

in the TOLT-ER 4-mg group (12%) than either the OXY-ER 5-mg (19%) or OXY-ER 10-mg groups (21%). More patients in the OXY-ER 10-mg group than the TOLT-ER 4-mg group withdrew because of poor tolerability (13% vs. 6%). After 8 weeks, 70% of patients in the TOLT-ER 4-mg group perceived an improved bladder condition, compared with 60% in the TOLT-ER 2-mg group, 59% in the OXY-ER 5-mg group and 60% in the OXY-ER 10-mg group. Dry mouth was dose dependent with both agents, although differences between doses reached statistical significance only in the oxybutynin trial (OXY-ER 5 mg vs. OXY-ER 10 mg; $P = .05$). Patients treated with TOLT-ER 4 mg reported a significantly lower severity of dry mouth compared with OXY-ER 10 mg. The conclusion that the findings suggest improved clinical efficacy of TOLT-ER (4 mg) over OXY-ER (10 mg) is weakened by the open-label design of the study.

Zinner and associates (2002) evaluated the efficacy, safety, and tolerability of TOLT-ER in older (≥65) and younger (<65) OAB patients in a 12-week RCT including 1015 patients with urgency incontinence and urinary frequency. Patients were randomized to treatment with TOLT-ER 4 mg once daily (n = 507) or placebo (n = 508) for 12 weeks. Efficacy, measured with micturition charts (incontinence episodes, micturitions, volume voided per micturition) and subjective patient assessments, safety, and tolerability end points were evaluated, relative to placebo. Compared with placebo, significant improvements in micturition chart variables with TOLT-ER showed no age-related differences. Dry mouth (of any severity) was the most common adverse event in both the TOLT-ER and placebo treatment study arms, irrespective of age (<65: TOLT-ER 22.7%, placebo 8.1%; ≥65: TOLT-ER 24.3%, placebo 7.2%). A few patients (<2%) experienced severe dry mouth. No CNS (cognitive functions were not specifically studied), visual, cardiac (per electrocardiogram), or laboratory safety concerns were noted in this study. Withdrawal rates due to adverse events on TOLT-ER 4 mg once daily were comparable in the two age cohorts (<65: 5.5%; ≥65: 5.1%).

The central symptom in the OAB syndrome is urgency. Freeman and coworkers (2003) presented a secondary analysis of a double-blind, placebo-controlled study evaluating the effect of once-daily TOLT-ER on urinary urgency in patients with OAB. Patients with urinary frequency (eight or more micturitions per 24 hours) and urgency incontinence (five or more episodes per week) were randomized to oral treatment with TOLT-ER 4 mg once daily (n = 398) or placebo (n = 374) for 12 weeks. Efficacy was assessed by use of patient perception evaluations. Of patients treated with TOLT-ER, 44% reported improved urgency symptoms (compared with 32% for placebo) and 62% reported improved bladder symptoms (placebo, 48%). The proportion of patients unable to hold urine on experiencing urgency was decreased by 58% with TOLT-ER, compared with 32% with placebo ($P < .001$). In the IMprovement in Patients: Assessing symptomatic Control with Tolterodine ER (IMPACT) study (Elinoff et al, 2006), the efficacy of TOLT-ER for patients' most bothersome OAB symptom was investigated in an open-label, primary care setting. Patients with OAB symptoms for more than 3 months received TOLT-ER (4 mg once daily) for 12 weeks. By week 12 there were significant reductions in the patients' most bothersome symptom—incontinence—urgency episodes, and nocturnal and daytime frequency. The most common adverse events were dry mouth (10%) and constipation (4%), and it was concluded that, in primary care practice, bothersome OAB symptoms can be effectively and safely treated with TOLT-ER, even in patients with comorbid conditions.

Various aspects of the efficacy and tolerability of tolterodine have been further documented in a number of RCTs (Dmochowski et al, 2007a, 2007b; Barucha et al, 2008; Choo et al, 2008; Coyne et al, 2008; Rogers et al, 2008; Rovner et al, 2008b; for further discussion see Chapple et al, 2008b; Novara et al, 2008). Importantly, the QTc effects of tolterodine were determined in a crossover-designed QT study of recommended (2 mg twice daily) and supratherapeutic (4 mg twice daily) doses of tolterodine, moxifloxacin (400 mg once daily), and placebo. No subject receiving tolterodine exceeded the clinically relevant thresholds of 500 msec absolute QTc or 60 msec change from baseline, and it was concluded that tolterodine does not have a clinically significant effect on QT interval (Malhotra et al, 2007). Olshansky and colleagues (2008) compared, in a randomized, placebo-controlled, double blind crossover study, the effects on heart rate of TOLT-ER 4 mg/day with those of darifenacin 15 mg/day and placebo in 162 healthy volunteers. They found that tolterodine, but not darifenacin and placebo, significantly increased mean heart rate per 24 hours. The treatment difference in adjusted mean change from baseline was +1.84 beats per minute ($P = .0004$) for tolterodine versus darifenacin and +1.42 beats per minute ($P < .001$) for tolterodine versus placebo. The proportion of subjects with an increase greater than 5 beats per minute was significantly greater in those receiving TOLT-ER (1 of 4) than with darifenacin (1 of 10). The clinical significance of this has yet to be established.

In a prospective, open study, Song and associates (2006) compared the effects of bladder training and/or tolterodine as first-line treatment in female patients with OAB. One hundred and thirty-nine female patients with OAB were randomized to treatment with bladder training, tolterodine (2 mg twice daily), or both for 12 weeks. All treatments were efficacious; however, combination therapy was the most effective. Mattiasson and colleagues (2003) compared the efficacy of tolterodine 2 mg twice daily plus simplified bladder training with tolterodine alone in patients with OAB in a multicenter single-blind study. At the end of the study the median percentage reduction in voiding frequency was greater with tolterodine plus bladder training than with tolterodine alone (33% vs. 25%; $P < .001$), whereas the median percentage increase in volume voided per void was 31% with tolterodine plus bladder training and 20% with tolterodine alone ($P < .001$). There was a median of 81% fewer incontinence episodes than at baseline with tolterodine alone, which was not significantly different from that with tolterodine plus bladder training (–87%). It was concluded that the effectiveness of tolterodine 2 mg twice daily can be augmented by a simplified bladder training regimen. However, Millard and colleagues (2004) investigated whether the combination of tolterodine plus a simple pelvic floor muscle exercise program would provide improved treatment benefits compared with tolterodine alone in 480 patients with OAB. Tolterodine therapy for 24 weeks resulted in significant improvement in urgency, frequency, and incontinence; however, no additional benefit was demonstrated for a simple pelvic floor muscle exercise program.

The beneficial effect of TOLT-ER in men with benign prostatic enlargement and LUTS, including OAB, has been well documented. Both as monotherapy, but particularly in combination with an α-adrenergic receptor (AR) antagonist, TOLT-ER was found effective (Kaplan et al, 2006; Höfner et al, 2007; Kaplan et al, 2008a; 2008b; Roehrborn et al, 2009; Rovner et al, 2008a). This effect was obtained irrespective of prostate size and was not associated with increased incidence of acute urinary retention (Roehrborn et al, 2009).

Tolterodine, in both the immediate- and extended-release forms, has a well-documented effect in OAB/DO.

Darifenacin Hydrobromide. **Darifenacin is a tertiary amine with moderate lipophilicity, well absorbed from the**

gastrointestinal tract after oral administration, and extensively metabolized in the liver by the cytochrome P450 isoforms CYP3A4 and CYP2D6, the latter saturating within the therapeutic range (Skerjanec 2006). UK-148,993, UK-73,689, and UK-88862 are the three main circulating darifenacin metabolites, of which only UK-148,993 is said to have significant antimuscarinic activity. However, available information suggests that various metabolites of darifenacin contribute little to its clinical effects (Michel and Hegde, 2006). The metabolism of darifenacin by CYP3A4 suggests that coadministration of a potent inhibitor of this enzyme (e.g., ketoconazole) may lead to an increase in the circulating concentration of darifenacin (Kerbusch et al, 2003). **Darifenacin is a relatively selective muscarinic M_3 receptor antagonist.** In vitro, it is selective for human cloned muscarinic M_3 receptors relative to M_1, M_2, M_4, or M_5 receptors. Theoretically, drugs with selectivity for the M_3 receptor can be expected to have clinical efficacy in OAB/DO with reduction of the adverse events related to the blockade of other muscarinic receptor subtypes (Andersson, 2002b). However, the clinical efficacy and adverse effects of a drug are dependent not only on its profile of receptor affinity but also on its pharmacokinetics and on the importance of muscarinic receptors for a given organ function.

Darifenacin has been developed as a controlled-release formulation, which allows once-daily dosing. Recommended dosages are 7.5 and 15 mg/day. The clinical effectiveness of the drug has been documented in several RCTs (Haab et al, 2004; Cardozo and Dixon 2005; Chapple et al, 2005, 2007a; Foote et al, 2005; Steers et al, 2005; Haab et al, 2006; Hill et al, 2006; Zinner et al, 2006; Abrams et al, 2008, Chancellor et al, 2008b; Dwyer et al, 2008; for reviews, see Guay, 2005; Zinner, 2007; Chapple et al, 2008; Novara et al, 2008). Haab and coworkers (2004) reported a multicenter, double-blind, placebo-controlled, parallel-group study that enrolled 561 patients (age 19 to 88; 85% female) with OAB symptoms for more than 6 months and included some patients with prior exposure to antimuscarinic agents. After washout and a 2-week placebo run-in, patients were randomized (1:4:2:3) to once-daily oral darifenacin controlled-release tablets: 3.75 mg (n = 53), 7.5 mg (n = 229) or 15 mg (n = 115) or matching placebo (n = 164) for 12 weeks. Patients recorded daily incontinence episodes, micturition frequency, bladder capacity (mean volume voided), frequency of urgency, severity of urgency, incontinence episodes resulting in change of clothing or pads, and nocturnal awakenings due to OAB using an electronic diary during weeks 2, 6, and 12 (directly preceding clinic visits). Tolerability data were evaluated from adverse event reports. Darifenacin 7.5 mg and 15 mg had a rapid onset of effect, with significant improvement compared with placebo being seen for most parameters at the first clinic visit (week 2). Darifenacin 7.5 mg and 15 mg were significantly superior to placebo for (median) improvements in micturition frequency (7.5 mg: –1.6; 15 mg: –1.7; placebo –0.8), frequency of urgency per day (–2.0; –2.0; –0.9), and number of incontinence episodes leading to a change in clothing or pads (–4.0; –4.7; –2.0). There was no significant reduction in nocturnal awakenings due to OAB. The most common adverse events were mild-to-moderate dry mouth and constipation with a CNS and cardiac safety profile comparable to that of placebo. No patients withdrew from the study as a result of dry mouth, and discontinuation related to constipation was rare (0.6% placebo vs. 0.9% darifenacin).

In a dose titration study on 395 OAB patients, darifenacin, allowing individualized dosing (7.5 or 15 mg), was found to be effective and well tolerated (Steers et al, 2005). A 2-year open-label extension study of these investigations (i.e., Haab et al, 2004; Steers et al, 2005) confirmed a favorable efficacy tolerability and safety profile (Haab et al, 2006). A review of the pooled darifenacin data from the three phase 3, multicenter, double-blind clinical trials in patients with OAB was reported by Chapple and coworkers (2005). After a 4-week washout/run-in period, 1059 adults (85% female) with symptoms of OAB (urgency incontinence, urgency and frequency) for at least 6 months were randomized to once-daily oral treatment with darifenacin: 7.5 mg (n = 337) or 15 mg (n = 334) or matching placebo (n = 388) for 12 weeks. Efficacy was evaluated using electronic patient diaries that recorded incontinence episodes (including those resulting in a change of clothing or pads), frequency and severity of urgency, micturition frequency, and bladder capacity (volume voided). Safety was evaluated by analysis of treatment-related adverse events, withdrawal rates, and laboratory tests. Relative to baseline, 12 weeks of treatment with darifenacin resulted in a dose-related significant reduction in median number of incontinence episodes per week: 7.5 mg, –8.8 (–68.4%; placebo –54%, $P < .004$); 15 mg, –10.6 (–76.8%; placebo 58%, $P < .001$). Significant decreases in the frequency and severity of urgency, micturition frequency, and number of incontinence episodes resulting in a change of clothing or pads were also apparent, along with an increase in bladder capacity. Darifenacin was well tolerated. The most common treatment-related adverse events were dry mouth and constipation, although together these resulted in few discontinuations (7.5 mg, 0.6% of patients; 15 mg, 2.1%; placebo, 0.3%). The incidence of CNS and cardiovascular adverse events was comparable to that of placebo. The results were confirmed in other RCTs, including also a pooled analysis of three phase 3 studies in older patients (>65 years), showing that darifenacin (7.5 and 15 mg) had an excellent efficacy, tolerability, and safety profile (Foote et al, 2005; Zinner et al, 2005; Hill et al, 2006).

One of the most noticeable clinical effects of antimuscarinic agents is their ability to reduce urgency and allow patients to postpone micturition. A study was conducted to assess the effect of darifenacin on the "warning time" associated with urinary urgency. This was a multicenter, randomized, double-blind, placebo-controlled study consisting of 2 weeks' washout, 2 weeks' medication-free run-in, and a 2-week treatment phase (Cardozo and Dixon, 2005). Warning time was defined as the time from the first sensation of urgency to voluntary micturition or incontinence and was recorded via an electronic event recorder at baseline (visit 3) and study end (visit 4) during a 6-hour clinic-based monitoring period, with the subject instructed to delay micturition for as long as possible. During each monitoring period, up to three urgency-void cycles were recorded. Of the 72 subjects who entered the study, 67 had warning time data recorded at both baseline and study end and were included in the primary efficacy analysis (32 on darifenacin, 35 on placebo). Darifenacin treatment resulted in a significant ($P < .004$) increase in mean warning time with a median increase of 4.3 minutes compared with placebo (darifenacin group, from 4.4 to 1.8 minutes; placebo, from 7.0 to –1.0 minute). Overall, 47% of darifenacin-treated subjects compared with 20% receiving placebo achieved a 30% or more increase in mean warning time. There were methodologic problems associated with this study; it utilized a dose of 30 mg (higher than the dose recommended for clinical use), the treatment period was short, it was conducted in a clinic-centered environment, the methodology carried with it a significant potential training effect, and the placebo group had higher baseline values than the treatment group. In another warning time study (Zinner et al, 2006) with 445 OAB patients, darifenacin treatment (15 mg) resulted in

numerical increases in warning time; however, these were not significant compared with placebo.

Further studies have demonstrated that darifenacin treatment is associated with clinically relevant improvements on health-related quality of life in patients with OAB (Abrams et al, 2008), and such improvements were sustained as shown in a 2-year extension study (Dwyer et al, 2008). It was shown that the positive effects neither on micturition variables nor on health-related quality of life produced by darifenacin (7.5 and 15 mg) were further enhanced by a behavioral modification program including timed voiding, dietary modifications, and Kegel exercises (Chancellor et al, 2008b). Several studies have been devoted to study possible effect on cognition by darifenacin. Neither in healthy volunteers (19 to 44 years) and healthy subjects (>60 years) nor in volunteers 65 years or older could any effect of darifenacin (3.75 to 15 mg/day) be demonstrated compared with placebo (Kay and Wesnes, 2005; Lipton et al, 2005; Kay et al, 2006; Kay and Ebinger, 2008).

To study whether darifenacin had any effect on QT/QTc intervals, Serra and associates (2005) performed a 7-day, randomized, parallel-group study (n = 188) in healthy volunteers receiving once-daily darifenacin at steady-state therapeutic (15 mg) and supratherapeutic (75 mg) doses alongside control subjects receiving placebo or moxifloxacin (positive control, 400 mg) once daily. No significant increase in QTcF interval could be demonstrated compared with placebo. Mean changes from baseline at pharmacokinetic Tmax versus placebo were –0.4 and –2.2 msec in the darifenacin 15-mg and 75-mg groups, respectively, compared with +11.6 msec in the moxifloxacin group ($P < .01$). The conclusion was that darifenacin does not prolong the QT/QTc interval. Darifenacin 15 mg/day given to healthy volunteers did not change heart rate significantly compared with placebo (Olshansky et al, 2008).

Darifenacin has a well-documented effect in OAB/DO, and the adverse event profile seems acceptable.

Solifenacin Succinate. **Solifenacin is a tertiary amine and well absorbed from the gastrointestinal tract (absolute bioavailability 90%).** The mean terminal half-life is 45 to 68 hours (Kuipers et al, 2004; Smulders et al, 2004). **It undergoes hepatic metabolism involving the cytochrome P450 enzyme system (CYP3A4).** In subjects who received a single oral dose of 10 mg solifenacin on day 7 of a 20-day regimen of ketoconazole administration (200 mg) Cmax and AUC0-inf were increased by only approximately 40% and 56%, respectively (Swart et al, 2006). **Solifenacin has a modest selectivity for M_3 over M_2 receptors and a marginal selectivity over M_1 receptors** (Ikeda et al, 2002; Abrams and Andersson, 2007).

Two large-scale phase 2 trials with parallel designs, comprising men and women, were performed (Smith et al, 2002; Chapple et al, 2004a). The first dose-ranging study evaluated solifenacin (2.5 mg, 5 mg, 10 mg, and 20 mg) and tolterodine (2 mg twice daily) in a multinational placebo-controlled study of 225 patients with urodynamically confirmed DO (Chapple et al, 2004a). Patients received treatment for 4 weeks followed by 2 weeks of follow-up. Inclusion criteria for this and subsequent phase 3 studies of patients with OAB included at least eight micturitions per 24 hours and either one episode of incontinence or one episode of urgency daily as recorded in 3-day micturition diaries. Micturition frequency, the primary efficacy variable, was statistically significantly reduced in patients taking solifenacin 5 mg (–2.21), 10 mg (–2.47), and 20 mg (–2.75) but not in patients receiving placebo (–1.03) or tolterodine (–1.79). This effect was rapid, with most of the effect observed at the earliest assessment visit, 2 weeks after treatment initiation. In addition there were numerically greater reductions in episodes of urgency and incontinence when compared with placebo. Study discontinuations due to adverse events were similar across treatment groups, albeit highest in the 20-mg solifenacin group. Because the 5-mg and 10-mg doses caused lower rates of dry mouth than tolterodine, and superior efficacy outcomes relative to placebo, these dosing strengths were selected for further evaluation in large-scale phase 3 studies. The second dose-ranging study of solifenacin 2.5 mg to 20 mg was carried out in the United States (Smith et al, 2002). This trial included 261 evaluable men and women receiving solifenacin or placebo for 4 weeks followed by a 2-week follow-up period. Micturition frequency was statistically significantly reduced relative to placebo in patients receiving 10 mg and 20 mg solifenacin. The number of micturitions per 24 hours showed reductions by day 7 and continued to decrease through day 28; day 7 was the earliest time point tested. Efficacy was demonstrated at this time. The 5-mg, 10-mg, and 20-mg dosing groups experienced significant increases in volume voided; the 10-mg solifenacin dose was associated with significant reductions in episodes of incontinence.

In one of the early RCTs, a total of 1077 patients were randomized to 5 mg solifenacin, 10 mg solifenacin, tolterodine (2 mg twice daily), or placebo (Chapple et al, 2004b). This study was powered only to compare active treatments to placebo. Compared with placebo (–8%), mean micturitions per 24 hours were significantly reduced with solifenacin 10 mg (20%), solifenacin 5 mg (17%), and tolterodine (15%). Solifenacin was well tolerated, with few patients discontinuing treatment. Incidences of dry mouth were 4.9% with placebo, 14.0% with solifenacin 5 mg, 21.3% with solifenacin 10 mg, and 18.6% with tolterodine 2 mg given twice daily.

Cardozo and colleagues (2004b) randomized 911 patients to 12-week once-daily treatment with solifenacin 5 mg, solifenacin 10 mg, or placebo. The primary efficacy variable was change from baseline to study end point in mean number of micturitions per 24 hours. Secondary efficacy variables included changes from baseline in mean number of urgency, nocturia, and incontinence episodes per 24 hours and mean volume voided per micturition. Compared with changes obtained with placebo (–1.6), the number of micturitions per 24 hours was statistically significantly decreased with solifenacin 5 mg (–2.37) and 10 mg (–2.81). A statistically significant decrease was observed in the number of all incontinence episodes with both solifenacin doses (5 mg: –1.63, 61%; 10 mg: –1.57, 52%), but not with placebo (–1.25, 28%). Of patients reporting incontinence at baseline, 50% achieved continence after treatment with solifenacin (based on a 3-day micturition diary); placebo responses were not given. Episodes of nocturia were statistically significantly decreased in patients treated with solifenacin 10 mg versus placebo. Episodes of urgency and mean volume voided per micturition were statistically significantly reduced with solifenacin 5 mg and 10 mg. Treatment with solifenacin was well tolerated. Dry mouth, mostly mild in severity, was reported in 7.7% of patients receiving solifenacin 5 mg and 23% receiving solifenacin 10 mg (vs. 2.3% with placebo). A 40-week follow-up of these studies (i.e., Chapple et al, 2004b and Cardozo et al, 2004b) demonstrated that the favorable profile, both in terms of efficacy and tolerability, was maintained over the study period (Haab et al, 2005).

The STAR trial (Chapple et al, 2005, 2007b) was a prospective, double-blind, double-dummy, two-arm, parallel-group, 12-week study conducted to compare the efficacy and safety of solifenacin 5 or 10 mg and TOLT-ER 4 mg once daily in patients with OAB.

The primary effect variable was micturition frequency. After 4 weeks of treatment, patients had the option to request a dose increase but were dummied throughout, because approved product labeling only allowed an increase for those on solifenacin. The results showed that solifenacin, with a flexible dosing regimen, was "non-inferior" to tolterodine concerning the primary effect variable of micturition frequency. However, solifenacin showed significantly greater efficacy to tolterodine in decreasing urgency episodes (–2.85 vs. –2.42), incontinence (–1.60 vs. –0.83), urgency incontinence (–1.42 vs. –0.83), and pad usage (–1.72 vs. –1.19). More solifenacin-treated patients became continent by study end point (59% vs. 49%) and reported improvements in perception of bladder condition (1.51 vs. –1.33) assessments. However, this was accompanied by an adverse event incidence that was greater with solifenacin than with tolterodine. Dry mouth and constipation (mild + moderate + severe) were the most common (solifenacin 30% and 6.4%, tolterodine 23% and 2.5%). The majority of side effects were mild to moderate, and discontinuations were comparable and low (5.9 and 7.3%) in both groups.

A number of studies and reviews have further documented the effects of solifenacin (Cardozo et al, 2006; Chapple et al, 2006a, 2007b; Maniscalco et al, 2006; for further discussion see also Chapple et al, 2008; Novara et al, 2008). In a pooled analysis of four RCTs, Abrams and Swift (2005) demonstrated positive effects on urgency, frequency, and nocturia symptoms in OAB dry patients. In an analysis of four phase 3 clinical trials, Brubaker and FitzGerald (2007) confirmed a significant effect of solifenacin 5 and 10 mg on nocturia in patients with OAB (reductions of nocturia episodes with 5 mg: –0.6, $P < .025$; with 10 mg: –0.6, $P < .001$ vs. placebo: –0.4) but without nocturnal polyuria. Kelleher and colleagues (2006) and Staskin and Te (2006) presented data showing efficacy in patients with mixed incontinence. A pooled analysis of four studies confirmed the efficacy and tolerability of solifenacin 5 and 10 mg in elderly (>65 years) patients and also showed a high level of persistence in a 40-week extension trial (Wagg et al, 2006). Improvement of quality of life by solifenacin treatment has been documented in several studies (Kelleher et al, 2005; Garely et al, 2006). In female volunteers, aged 19 to 79 years, the effect of 10 mg and 30 mg solifenacin on the QT interval was evaluated at the time of peak solifenacin plasma concentration in a multiple-dose, randomized, double-blind, placebo- and positive-controlled (moxifloxacin 400 mg) trial. The QT interval prolonging effect appeared greater for the 30 mg (8 msec, 4, 13: 90% confidence interval [CI]) compared with the 10 mg (2 msec, –3, 6) dose of solifenacin. Although the effect of the highest solifenacin dose (three times the maximum therapeutic dose) studied did not appear as large as that of the positive control moxifloxacin at its therapeutic dose, the confidence intervals overlapped. This study was not designed to draw direct statistical conclusions between the drugs or the dose levels.

Michel and colleagues (2008) studied cardiovascular safety and overall tolerability of solifenacin in routine clinical use in a 12-week, open-label, post-marketing surveillance study. They concluded that "in real-life conditions, that is, with inclusion of large numbers of patients with cardiovascular comorbidities and taking comedications, therapeutically effective doses of solifenacin did not increase heart rate or blood pressure."

Solifenacin has a well-documented effect in OAB/DO, and the adverse event profile seems acceptable.

Fesoterodine Fumarate. **Fesoterodine functions as an orally active prodrug that is converted to the active metabolite 5-hydroxymethyltolterodine (5-HMT) by nonspecific esterases** (Michel, 2008; McKeage and Keating, 2009). **This compound, which is chemically identical to the 5-hydroxy metabolite of tolterodine, is** (like fesoterodine itself) **a non-subtype selective muscarinic receptor antagonist** (Ney et al, 2008). **All of the effects of fesoterodine in humans are thought to be mediated via 5-HMT,** because the parent compound remains undetectable on oral dosing. **5-HMT is metabolized in the liver, but a significant part of 5-HMT is excreted renally without additional metabolism.** Because the renal clearance of 5-HMT is about 250 mL/min, with more than 15% of the administered fesoterodine dose excreted as unchanged 5-HMT, this raises the possibility that 5-HMT also could work from the luminal side of the bladder (Michel, 2008).

Fesoterodine is indicated for use at doses of 4 and 8 mg once daily. In clinical studies, both doses of fesoterodine were consistently superior to placebo in improving the symptoms of OAB (Chapple et al, 2007c, 2008b; Nitti et al, 2007; McKeage and Keating, 2009), with 8 mg/day having significantly greater effects than 4 mg/day (Khullar et al, 2008). Analysis of pooled data on quality of life, using King's Health Questionnaire and ICI Questionnaire-Short Form, showed that both doses of the drug caused a significant improvement in quality of life. Compared with TOLT-ER (4 mg), fesoterodine (8 mg) had statistically significant advantages for improving incontinence episodes, severe urgency with incontinence, mean voided volumes, and number of continent days a week (Chapple et al, 2008b; Khullar et al, 2008). Adverse events were characteristic for an antimuscarinic drug, with dry mouth being the most frequently reported and rated as mild to moderate in most cases. In one phase 3 study it was seen in 7%, 16%, and 36% of patients receiving placebo and 4 and 8 mg/day fesoterodine, respectively (Nitti et al, 2007), whereas in the another phase 3 study the findings were 7.1%, 21.7%, and 33.8% in the same groups (16.9% for 4 mg/day TOLT-ER) (Chapple et al, 2007c). Kelleher and colleagues (2008) evaluated the effect of fesoterodine on health-related quality of life in patients with OAB syndrome. Pooled data from two randomized placebo-controlled phase 3 studies were analyzed. Eligible patients were randomized to placebo or fesoterodine 4 or 8 mg for 12 weeks; one trial also included TOLT-ER 4 mg. By the end of treatment, all active-treatment groups had significantly improved health-related quality of life compared with those on placebo. A study on possible effects on QT intervals has been performed (Michel, 2008). This included parallel groups of 64 to 68 subjects each who were treated for 3 days with 4 mg/day fesoterodine, the highly supratherapeutic dose of 28 mg/day fesoterodine, the active control moxifloxacin 400 mg/day, or placebo. Both the standard dose of 4 mg/day and the highly supratherapeutic dose of 28 mg/day did not provide any evidence of QT interval prolongation (e.g., QTc for 28 mg/day from 404.5 ± 16.7 to 400.1 ± 14.0 msec, delta: –5.0 ± 7.9 msec).

Fesoterodine has a well-documented beneficial effect in OAB (see Table 68–2), **and the adverse event profile seems acceptable.**

Drugs Acting at Membrane Channels

Calcium Antagonists. **Activation of detrusor muscle, both through muscarinic receptor and nonadrenergic, noncholinergic pathways, seems to require influx of extracellular Ca^{2+} through Ca^{2+} channels, as well as via mobilization of intracellular Ca^{2+}** (Andersson, 1993; Andersson and Arner, 2004). **The influx of extracellular Ca^{2+} can be blocked by Ca^{2+} antagonists, blocking L-type Ca^{2+} channels;** and, theoretically, this would be an attractive way of inhibiting DO. However, there have been few clinical studies of the effects of Ca^{2+} antagonists in patients with DO and the ones

that have been done suggest no beneficial effect. For example, Naglie and coworkers (2002) evaluated the efficacy of nimodipine for geriatric urgency incontinence in a randomized, double-blind, placebo-controlled crossover trial. Thirty milligrams of nimodipine was given twice daily for 3 weeks in older persons with DO and chronic urgency incontinence. A total of 86 participants with a mean age of 73.4 years were randomized. The primary outcome was the number of incontinent episodes, as measured by the self-completion of a 5-day voiding record. Secondary outcomes included the impact of urinary incontinence on quality of life measured with a modified incontinence impact questionnaire and symptoms, as measured by the American Urological Association (AUA) symptom score. In the 76 (88.4%) participants completing the study there was no significant difference in the number of incontinent episodes with nimodipine versus placebo. Scores on the incontinence impact questionnaire and the AUA symptom score were not significantly different with nimodipine versus placebo, and the authors concluded that treatment of geriatric urgency incontinence with 30 mg nimodipine twice daily was unsuccessful.

Available information does not suggest that systemic therapy with Ca^{2+} antagonists is an effective way to treat OAB/DO.

Potassium Channel Openers. **Opening of K^+ channels and subsequent efflux of K^+ will produce hyperpolarization of various smooth muscles, including the detrusor** (Andersson, 1992; Andersson and Arner, 2004). **This leads to a decrease in Ca^{2+} influx by reducing the opening probability of Ca^{2+} channels with subsequent relaxation or inhibition of contraction.** Theoretically, such drugs could be active during the filling phase of the bladder, abolishing bladder overactivity with no effect on normal bladder contraction. The K^+ channel openers, such as pinacidil and cromakalim, have been effective in animal models (Andersson, 1992; Andersson and Arner, 2004), but clinically the effects have not been encouraging. The first generation of openers of ATP-sensitive K^+ channels, such as cromakalim and pinacidil, were found to be more potent as inhibitors of vascular preparations than of detrusor muscle, and in clinical trials performed with these drugs no bladder effects have been found at doses already lowering blood pressure (Hedlund et al, 1991; Komersova et al, 1995). However, new drugs with K^+ ATP-sensitive channel opening properties have been described, which may be useful for the treatment of OAB (Andersson and Arner, 2004). Although K^+ channel openers are believed mainly to act directly on smooth muscle cells (Gopalakrishnan and Shieh, 2004), they may also at least in part affect bladder function by modulating the activity of afferent neurons (Tanaka et al, 2003).

Although the previous data demonstrate the potential of K^+ channel openers to inhibit nonvoiding detrusor contractions these channels are expressed not only in bladder but also, for example, in vascular smooth muscle. Therefore, K^+ channel openers **may also affect cardiovascular function** and in effective doses may considerably lower blood pressure (Howe et al, 1995; Shieh et al, 2007). Although some compounds of this class have a certain degree of selectivity for the bladder as compared with the cardiovascular system, it remains unclear whether the degree of selectivity offers a sufficiently large therapeutic window for clinical use. This consideration has led to a considerable hesitancy to study K^+ channel openers in patients with OAB. Nevertheless, one randomized, placebo-controlled clinical study on the K^+ ATP opener ZD0947 has been reported (Chapple et al, 2006b). Although ZD0947 at the chosen dose did not lower blood pressure or cause adverse events typical for a vasodilating drug, it failed to achieve superiority relative to placebo for the treatment of OAB symptoms. Therefore, **despite promising preclinical efficacy data, K^+ channel openers at present are not a therapeutic option and may never become one owing to a lack of selectivity for bladder over cardiovascular tissues.**

At present there is no evidence from RCTs to suggest that K^+ channel openers represent a treatment alternative.

Drugs with "Mixed" Actions

Some drugs used to block DO have been shown to have more than one mechanism of action. **They all have a more or less pronounced antimuscarinic effect and, in addition, an often poorly defined "direct" action on bladder muscle.** For several of these drugs the antimuscarinic effects can be demonstrated at much lower drug concentrations than the direct action, which may involve blockade of voltage-operated Ca^{2+} channels. **Most probably, the clinical effects of these drugs can be explained mainly by their antimuscarinic action.** Among the drugs with mixed actions was terodiline, which was withdrawn from the market because it was suspected to cause polymorphic ventricular tachycardia (torsades de pointes) in some patients (Connolly et al, 1991; Stewart et al, 1992).

Oxybutynin Chloride. **Oxybutynin is a tertiary amine that is well absorbed and undergoes extensive upper gastrointestinal and first-pass hepatic metabolism via the cytochrome P450 system (CYP3A4) into multiple metabolites. The primary metabolite, *N*-desethyloxybutynin (DEO), has pharmacologic properties similar to those of the parent compound** (Waldeck et al, 1997) **but occurs in much higher concentrations after oral administration** (Hughes et al, 1992). **It has been implicated as the major cause of the troublesome side effect of dry mouth** associated with the administration of oxybutynin. It seems reasonable to assume that the effect of oral oxybutynin to a large extent is exerted by the metabolite. The occurrence of an active metabolite may also explain the lack of correlation between plasma concentration of oxybutynin itself and side effects in geriatric patients reported by Ouslander and associates (1995). The plasma half-life of oxybutynin is approximately 2 hours, but with wide interindividual variation (Douchamps et al, 1988; Hughes et al, 1992).

Oxybutynin has several pharmacologic effects in vitro, some of which seem difficult to relate to its effectiveness in the treatment of DO. It has both an antimuscarinic and a direct muscle relaxant effect, and, in addition, local anesthetic actions. The latter effect may be of importance when the drug is administered intravesically but probably plays no role when it is given orally. In vitro, oxybutynin was **500 times weaker as a smooth muscle relaxant than as an antimuscarinic agent** (Kachur et al, 1988). Most probably, when given systemically, oxybutynin acts mainly as an antimuscarinic drug. Oxybutynin has a high affinity for muscarinic receptors in human bladder tissue and effectively blocks carbachol-induced contractions (Waldeck et al, 1997). The drug was shown to have **slightly higher affinity for muscarinic M_1 and M_3 receptors than for M_2 receptors** (Nilvebrant and Sparf, 1986; Norhona-Blob et al, 1991), **but the clinical significance of this is unclear.**

The immediate release (IR) form of oxybutynin (OXY-IR) is recognized for its efficacy, and most of the newer antimuscarinic agents have been compared with it once efficacy over placebo has been determined. In general, the new formulations of oxybutynin and other antimuscarinic agents offer patients efficacy roughly equivalent to that of OXY-IR and the advantage of the newer formulations lies in improved dosing schedules and side effect

profile (Appell et al, 2001; Dmochowski et al, 2002; Diokno et al, 2003). An extended-release oxybutynin (OXY-ER) once-daily oral formulation, an oxybutynin patch transdermal delivery system (OXY-TDS), and an oxybutynin gel are available. OXY-TDS offers a twice-weekly dosing regimen and the potential for improved patient compliance and tolerability. The gel requires once-daily application. Available formulations of oxybutynin were overviewed by McCrery and Appell (2006). Clinical use of the gel was first described by Staskin and coworkers (2009).

Immediate-Release Oxybutynin (OXY-IR). Several controlled studies have shown that OXY-IR is effective in controlling DO, including neurogenic DO (Yarker et al, 1995; Andersson and Chapple, 2001). The recommended oral dose of the IR form is 5 mg three times daily or four times daily, even if lower doses have been used. Thüroff and associates (1998) summarized 15 randomized controlled studies on a total of 476 patients treated with oxybutynin. The mean decrease in incontinence was recorded as 52%, and the mean reduction in frequency per 24 hours was 33% (data on placebo not presented). The overall "subjective improvement" rate was reported as 74% (range 61% to 100%). The mean percent of patients reporting an adverse effect was 70% (range 17% to 93%). Oxybutynin, 7.5 to 15 mg/day, significantly improved the quality of life of patients suffering from OAB in a large open multicenter trial. In this study, patient compliance was 97% and side effects, mainly dry mouth, were reported by only 8% (Amarenco et al, 1998). In nursing home residents (n = 75), Ouslander and colleagues (1995) found that oxybutynin did not add to the clinical effectiveness of prompted voiding in a placebo-controlled, double-blind, crossover trial. On the other hand, in another controlled trial in elderly subjects (n = 57), oxybutynin with bladder training was found to be superior to bladder training alone (Szonyi et al, 1995).

Several open studies in patients with spinal cord injuries have suggested that oxybutynin, given orally or intravesically, can be of therapeutic benefit (Kim et al, 1996; Szollar and Lee, 1996). The therapeutic effect of OXY-IR on DO is associated with a high incidence of side effects (up to 80% with oral administration). These are typically antimuscarinic in nature (dry mouth, constipation, drowsiness, blurred vision) and are often dose limiting (Baigrie et al, 1988; Jonville et al, 1992). The effects on the electrocardiogram of oxybutynin were studied in elderly patients with urinary incontinence (Hussain et al, 1996); no changes were found. It cannot be excluded that the commonly recommended dose of 5 mg three times a day is unnecessarily high in some patients and that a starting dose of 2.5 mg twice daily with following dose titration would reduce the number of adverse effects (Malone-Lee et al, 1992; Amarenco et al, 1998).

Extended-Release Oxybutynin (OXY-ER). This formulation was developed to decrease liver metabolite formation of desethyloxybutynin (DEO) with the presumption that it would result in decreased side effects, especially dry mouth, and improve patient compliance with remaining on oxybutynin therapy. The formulation utilizes an osmotic system to release the drug at a controlled rate over 24 hours distally primarily into the large intestine where absorption is not subject to first-pass metabolism in the liver. This reduction in metabolism is meant to improve the rate of dry mouth complaints when compared with OXY-IR. DEO is still formed through the hepatic cytochrome P450 enzymes, but clinical trials have indeed demonstrated improved dry mouth rates compared with OXY-IR (Appell et al, 2003). Salivary output studies have also been interesting. Two hours after administration of OXY-IR or TOLT-IR, salivary production decreased markedly and then gradually returned to normal. With OXY-ER, however, salivary output was maintained at predose levels throughout the day (Chancellor et al, 2001).

The effects of OXY-ER have been well documented (Siddiqui et al, 2004). In the OBJECT study (Appell et al, 2001) the efficacy and tolerability of 10 mg OXY-ER was compared with a twice-daily 2-mg dose of TOLT-IR. OXY-ER was statistically more effective than the TOLT-IR in weekly urgency incontinence episodes (OXY-ER from 25.6% to 6.1%; TOLT-IR 24.1% to 7.8%), total incontinence (OXY-ER from 28.6% to 7.1%; TOLT-IR 27.0% to 9.3%), and frequency (OXY-ER from 91.8% to 67.1%; TOLT-IR 91.6% to 71.5%), and both medications were equally well tolerated. The basic study was repeated as the OPERA study (Diokno et al, 2003) with the difference that this study was a direct comparison of the two extended-release forms, OXY-ER (10 mg) and TOLT-ER (4 mg); and the results were quite different. In this study there was no significant difference in efficacy for the primary end point of urgency incontinence; however, TOLT-ER had a statistically lower incidence of dry mouth. OXY-ER was only statistically better at 10 mg than TOLT-ER 4 mg in the reduction of the rate of urinary frequency. These studies made it clear that in comparative studies IR entities of one drug should not be compared with ER entities of the other. Greater reductions in urgency and total incontinence have been reported in patients treated in dose escalation studies with OXY-ER. In two randomized studies, the efficacy and tolerability of OXY-ER were compared with OXY-IR. In the 1999 study (Anderson et al, 1999), 105 patients with urgency or mixed incontinence were randomized to receive 5 to 30 mg OXY-ER once daily or 5 mg of OXY-IR one to four times a day. Dose titrations began at 5 mg, and the dose was increased every 4 to 7 days until one of three end points was achieved. These were (1) the patient reported no urgency incontinence during the final 2 days of the dosing period; (2) the maximum tolerable dose was reached; and (3) the maximum allowable dose (30 mg for OXY-ER or 20 mg for OXY-IR) was reached. The mean percentage reduction in weekly urgency and total incontinence episodes was statistically similar between OXY-ER and OXY-IR, but dry mouth was reported statistically more often with OXY-IR. In the 2000 study (Versi et al, 2000), 226 patients were randomized between OXY-ER and OXY-IR with weekly increments of 5 mg/day up to 20 mg/day. As in the 1999 study, OXY-ER again achieved a greater than 80% reduction in urgency and total incontinence episodes and a significant percentage of patients became dry. A negative aspect of these studies is that there were no naive patients included, as all patients were known responders to oxybutynin. Similar efficacy results have been achieved, however, with OXY-ER in a treatment-naive population (Gleason et al, 1999). In an RCT comparing different daily doses of oxybutynin (5, 10, and 15 mg), Corcos and colleagues (2006) found a significant dose-response relationship for both urgency incontinence episodes and dry mouth. The greatest satisfaction was with 15 mg oxybutynin/day.

Transdermal Oxybutynin (OXY-TDS). Transdermal delivery also alters oxybutynin metabolism reducing DEO production to an even greater extent than OXY-ER. A study (Davila et al, 2001) comparing OXY-TDS with OXY-IR demonstrated a statistically equivalent reduction in daily incontinence episodes (from 7.3 to 2.3: 66% for OXY-TDS, and 7.4 to 2.6: 72% for OXY-IR) but much less dry mouth (38% for OXY-TDS and 94% for OXY-IR). In another study (Dmochowski et al, 2002), the 3.9-mg daily dose patch significantly (vs. placebo) reduced the mean number of daily incontinence episodes (from 4.7 to 1.9; placebo from 5.0 to 2.9), while reducing average daily urinary frequency confirmed by an increased average voided volume (from 165 to 198 mL; placebo from 175 to 182 mL). Furthermore, the dry mouth rate was similar

to that of placebo (7% vs. 8.3%). In a third study (Dmochowski et al, 2003b), OXY-TDS was compared not only with placebo but also with TOLT-ER. Both drugs equivalently and significantly reduced daily incontinence episodes and increased the average voided volume, but TOLT-ER was associated with a significantly higher rate of antimuscarinic adverse events. **The primary adverse event for OXY-TDS was application site reaction pruritus in 14% and erythema in 8.3%** with nearly 9% feeling that the reactions were severe enough to withdraw from the study, despite the lack of systemic problems.

The pharmacokinetics and adverse effect dynamics of OXY-TDS (3.9 mg/day) and OXY-ER (10 mg/day) were compared in healthy subjects in a randomized, two-way crossover study (Appell et al, 2003). Multiple blood and saliva samples were collected, and pharmacokinetic parameters and total salivary output were assessed. OXY-TDS administration resulted in greater systemic availability and minimal metabolism to DEO compared with OXY-ER, which resulted in greater salivary output in OXY-TDS patients and less dry mouth symptomatology than when taking OXY-ER. Dmochowski and coworkers (2005) analyzing the combined results of two RCTs concluded that OXY-TDS was shown to be efficacious and well tolerated. The most common systemic side effect was dry mouth (7.0% vs. placebo 5.3%). Application-site erythema occurred in 7% and pruritus in 16.1%. Also Cartwright and Cardozo (2007), reviewing published and presented data, concluded that OXY-TDS has a good balance between efficacy and tolerability with a rate of systemic antimuscarinic side effects lower than that with oral antimuscarinic agents; however, this benefit was offset by the rate of local skin reaction. Sahai and associates (2008) largely confirmed these conclusions.

Oxybutynin Gel. Oxybutynin topical gel was introduced in 2009 as a transdermal formulation applied once daily to the abdomen, thigh, shoulder, or upper arm area (Staskin et al, 2009). The 1-g application dose delivers approximately 4 mg of drug to the circulation with stable plasma concentration. Staskin and associates (2009) reported a randomized controlled double-blind trial of patients (89% women) with urgency-predominant urinary incontinence. The mean number of urgency-predominant urinary incontinence episodes on a 3-day voiding diary was reduced by 3 episodes per day versus 2.5 in the placebo study arm ($P < .0001$). Urinary frequency was decreased by 2.7 episodes per day versus 2.0 episodes ($P = .0017$), and voided volume increased by 21 mL versus 3.8 mL ($P = .0018$). Dry mouth was reported in 6.9% of the treatment group versus 2.8% in the placebo group. Skin reaction at the application site occurred in 4.5% of the treatment group versus 1% in the placebo arm. It was believed that the **improved skin tolerability over the transdermal patch** system was secondary to a lack of adhesive and of skin occlusion. Person-to-person transference via skin contact is a risk but largely eliminated if clothing is worn over the application site.

Other Administration Forms. Rectal administration (Collas and Malone-Lee, 1997; Winkler and Sand, 1998) was reported to have fewer adverse effects than the conventional tablets. Administered intravesically, oxybutynin has in several studies been demonstrated to increase bladder capacity and produce clinical improvement with few side effects, both in neurogenic and in other types of DO, and both in children and adults (Weese et al, 1993; Lose and Norgaard, 2001; Fader et al, 2007; George et al, 2007; Guerra et al, 2008), although adverse effects may occur (Kasabian et al, 1994; Palmer et al, 1997). **Intravesical administration** of oxybutynin is a conceptually attractive form of drug delivery, especially for patients who already perform clean intermittent catheterization (CIC). However, a specific intravesical formulation is not available, and, currently, the oral formulation, either liquid or crushed tablet in solution, is delivered by periodic insertion through a catheter. There does appear to be some systemic absorption of oxybutynin placed intravesically. Plasma oxybutynin but not DEO levels were measured after intravesical and oral administration by Madersbacher and Jilg (1991). It is still not entirely clear what portion of the effects of the drug are due to local versus absorbed parent drug and primary metabolite. Certainly this is a circumstance in which the non-antimuscarinic actions of oxybutynin (see earlier) might be relevant.

Effects on Cognition. Several studies have documented the possibility that oxybutynin may have negative effects on cognitive functions, particularly in the elderly population but also in children (see Kay et al, 2006; Klausner al Steers, 2007; Kay and Ebinger, 2008). This factor should be taken into consideration when prescribing the drug.

Oxybutynin has a well-documented efficacy in the treatment of OAB/DO (see Table 68–2). **Despite the adverse effect profile, it is still an established therapeutic option.**

Dicyclomine. Dicyclomine (Bentyl) has attributed to it both a direct relaxant effect on smooth muscle and an antimuscarinic action (Downie et al, 1977). An oral dose of 20 mg three times a day in adults was reported to increase bladder capacity in patients with neurogenic DO (Fischer et al, 1978). Beck and associates (1976) compared the use of 10 mg of dicyclomine, 15 mg of propantheline, and placebo three times a day in patients with DO. The reported cure or improved rates, respectively, were 62%, 73%, and 20%. Awad and coworkers (1977) reported that 20 mg of dicyclomine three times a day caused resolution or significant improvement in 24 of 27 patients with involuntary bladder contractions.

Even if published experiences of the effect of dicyclomine on DO are favorable, the drug is not widely used, and controlled clinical trials documenting its efficacy and side effects are scarce.

Propiverine Hydrochloride. Several aspects of the preclinical, pharmacokinetic, and clinical effects of propiverine have been reviewed by Madersbacher and Murz (2001). **The drug is rapidly absorbed (Tmax 2 hr), but has a high first-pass metabolism, and its biologic availability is about 50%.** Propiverine is an inducer of hepatic cytochrome P450 enzymes in rats in doses about 100 times above the therapeutic doses in man (Walter et al, 2003).

Several active metabolites are formed that quantitatively and qualitatively differ from the mother compound (Haustein et al, 1988; Muller et al, 1993; Wuest et al, 2006; Sugiyama et al, 2008; Zhu et al, 2008). Most probably these metabolites contribute to the clinical effects of the drug, but their individual contributions have not been clarified (Michel and Hegde, 2006). The half-life of propiverine is 11 to 14 hours. An extended-release preparation was shown to be effective (Jünemann et al, 2006; May et al, 2008).

Propiverine has combined antimuscarinic and Ca^{2+} antagonistic actions (Haruno, 1992; Tokuno et al, 1993). The importance of the Ca^{2+} antagonistic component for the drug's clinical effects has not been established. Propiverine has **no selectivity for muscarinic receptor subtypes.** The drug is not available in the United States.

Propiverine has been shown to have beneficial effects in patients with DO in several investigations. Thüroff and coworkers (1998) collected nine randomized studies on a total of 230 patients and found a 17% reduction in micturitions per 24 hours, a 64-mL increase in bladder capacity, and a 77% (range 33% to 80%) subjective improvement. Side effects were found in 14% (range 8%

to 42%). In patients with neurogenic DO, controlled clinical trials have demonstrated propiverine's superiority over placebo (Stöhrer et al, 1999). Propiverine also increased bladder capacity and decreased maximum detrusor contractions. Controlled trials comparing propiverine, flavoxate, and placebo (Wehnert et al, 1989) and propiverine, oxybutynin, and placebo (Wehnert et al, 1992; Madersbacher et al, 1999) have confirmed the efficacy of propiverine and suggested that the drug may have equal efficacy and fewer side effects than oxybutynin. In a comparative RCT including 131 patients with neurogenic DO, propiverine and oxybutynin were compared (Stöhrer et al, 2007). The drugs were found to be equally effective in increasing bladder capacity and lowering bladder pressure. Propiverine caused a significantly lower frequency of dry mouth than oxybutynin. Also in children and adolescents with neurogenic DO, propiverine was found to be effective (Grigoleit et al, 2006; Schulte-Baukloh et al, 2006), with a low incidence rate of adverse events: less than 1.5% (Grigoleit et al, 2006).

Madersbacher and colleagues (1999) compared the tolerability and efficacy of propiverine (15 mg three times daily), oxybutynin (5 mg twice daily), and placebo in 366 patients with urgency and urgency incontinence in a randomized, double-blind placebo-controlled clinical trial. Urodynamic efficacy of propiverine was judged similar to that of oxybutynin, but the incidence of dry mouth and the severity of dry mouth were judged less with propiverine than with oxybutynin. Dorschner and coworkers (2000) investigated in a double-blind, multicenter, placebo-controlled randomized study the efficacy and cardiac safety of propiverine in 98 elderly patients (mean age 68 years) suffering from urgency, urgency incontinence, or mixed urgency stress urinary incontinence (SUI). After a 2-week placebo run-in period the patients received propiverine (15 mg three times daily) or placebo (three times daily) for 4 weeks. Propiverine caused a significant reduction of the micturition frequency (from 8.7 to 6.5) and a significant decrease in episodes of incontinence (from 0.9 to 0.3 per day). The incidence of adverse events was very low (2% dryness of the mouth under propiverine—2 of 49 patients). Resting and ambulatory electrocardiograms indicated no significant changes.

In a randomized, double-blind multicenter clinical trial, patients with idiopathic DO were treated with 15 mg propiverine twice daily or 2 mg TOLT-IR twice daily over a period of 28 days (Jünemann et al, 2005). The maximum cystometric capacity was determined at baseline and after 4 weeks of therapy. The difference of both values was used as the primary end point.

Secondary end points were voided volume per micturition, evaluation of efficacy (by the investigator), tolerability, postvoid residual urine, and quality of life. It was found that the mean maximum cystometric capacity increased significantly ($P < .01$) in both groups. The volume at first urgency and the frequency/volume chart parameters also showed relevant improvements during treatment. The most common adverse event, dry mouth, occurred in 20 patients in the propiverine group and in 19 patients in the tolterodine group. The scores for the quality of life improved comparably in both groups. Abrams and associates (2006b) compared the effects of propiverine and oxybutynin on ambulatory urodynamic monitoring parameters, safety, and tolerability in OAB patients. Patients (n = 77) received two of the following treatments during two 2-week periods: propiverine 20 mg once daily, propiverine 15 mg three times daily, oxybutynin 5 mg three times daily, and placebo. They found that oxybutynin 15 mg was more effective than propiverine 20 mg in reducing symptomatic and asymptomatic involuntary detrusor contractions in ambulatory patients. Oxybutynin had a higher rate of dry mouth, and propiverine had a more pronounced effect on gastrointestinal, cardiovascular, and visual function.

A randomized, double-blind, placebo-controlled trial with parallel-group design in children aged 5 to 10 years was performed by Marschall-Kehrel and coworkers (2009). Of 171 randomized children, 87 were treated with propiverine and 84 with placebo. Decrease in voiding frequency per day was the primary efficacy parameter; secondary end points included voided volume and incontinence episodes. There was a significant decrease in voiding frequency episodes for propiverine versus placebo. Superiority could also be demonstrated for voided volume and incontinence episodes per day. Propiverine was well tolerated: 23% of side effects were reported for propiverine and 20% for placebo.

Yamaguchi and colleagues (2007) performed a multicenter, 12-week, double-blind phase III trial in Japanese men and women with OAB (1593 patients were randomized and 1584 were treated), comparing solifenacin 5 or 10 mg, propiverine 20 mg, and placebo. Changes at end point in number of voids per 24 hours, urgency, incontinence, urgency incontinence and nocturia episodes, volume voided/void, restoration of continence, and quality of life were examined. It was found that at end point there were greater reductions in mean (SD) voids per 24 hours with all drug regimens than with placebo. All active treatments improved the volume voided and quality of life versus placebo; solifenacin 10 mg reduced nocturia episodes and significantly improved urgency episodes and volume voided versus propiverine 20 mg, and solifenacin 5 mg caused less dry mouth. Solifenacin 10 mg caused more dry mouth and constipation than propiverine 20 mg.

Propiverine has a documented beneficial effect in the treatment of OAB/DO (see Table 68–2) **and seems to have an acceptable side effect profile.**

Flavoxate Hydrochloride. Flavoxate is well absorbed, and oral bioavailability appeared to be close to 100% (Guay, 2003). The drug is extensively metabolized, and plasma half-life was found to be 3.5 hours (Sheu et al, 2001). Its main metabolite (3-methylflavone-8-carboxylic acid [MFCA]) has been shown to have low pharmacologic activity (Cazzulani et al, 1988; Caine et al, 1991). The main mechanism of flavoxate's effect on smooth muscle has not been established. The drug has been found to possess a moderate Ca^{2+} antagonistic activity, to have the ability to inhibit phosphodiesterase (PDE), and to have local anesthetic properties; no antimuscarinic effect was found (Guarneri et al, 1994). Uckert and associates (2000) found that in strips of human bladder the potency of flavoxate to reverse contraction induced by muscarinic receptor stimulation and by electrical field stimulation was comparable. Tomoda and coworkers (2005) studied the effects of flavoxate on K^+-induced tension using strips prepared from human urinary bladder and also investigated the effects of flavoxate on voltage-dependent nifedipine-sensitive Ba^{2+} currents (i.e., L-type Ca^{2+} currents) in single freshly dispersed human detrusor smooth muscle myocytes by use of whole-cell patch-clamp techniques. They found that flavoxate caused a concentration-dependent reduction of the K^+-induced contraction of the bladder strips and that in the human detrusor myocytes, flavoxate inhibited the peak amplitude of voltage-dependent, nifedipine-sensitive inward Ba^{2+} currents in a voltage- and concentration-dependent manner. They concluded that flavoxate caused muscle relaxation through the inhibition of L-type Ca^{2+} channels in the human detrusor.

It has been suggested that pertussis toxin-sensitive G proteins in the brain are involved in the flavoxate-induced suppression of the micturition reflex, since intracerebroventricularly or

intrathecally administered flavoxate abolished isovolumetric rhythmic bladder contractions in anesthetized rats (Oka et al, 1996).

The clinical effects of flavoxate in patients with DO and frequency, urgency, and incontinence have been studied in both open and controlled investigations, but with varying rates of success (Ruffmann, 1988). Stanton (1973) compared emepronium and flavoxate in a double-blind, crossover study of patients with detrusor instability and reported improvement rates of 83% and 66% after flavoxate or emepronium, respectively, both administered as 200 mg three times daily. In another double-blind, crossover study comparing flavoxate 1200 mg/day with that of oxybutynin 15 mg daily in 41 women with idiopathic motor or sensory urgency and utilizing both clinical and urodynamic criteria, Milani and associates (1993) found both drugs effective. No difference in efficacy was found between them, but flavoxate had fewer and milder side effects. Other investigators, comparing the effects flavoxate with those of placebo, have not been able to show any beneficial effect of flavoxate at dosages up to 400 mg three times daily (Briggs et al, 1980; Chapple et al, 1990; Dahm et al, 1995).

In general, few side effects have been reported during treatment with flavoxate. On the other hand its efficacy, compared with other therapeutic alternatives, is not well documented. No RCTs seem to have been performed with flavoxate during the past decade.

α-Adrenergic Receptor Antagonists

Even if it is well known that α_1-AR antagonists can ameliorate lower urinary tract symptoms (LUTS) in men with benign prostatic enlargement (Andersson et al, 2002) **there are no controlled clinical trials showing that they are an effective alternative in the treatment of OAB/DO in this patient category.** In an open-label study, Arnold (2001) evaluated the clinical and pressure-flow effects of tamsulosin 0.4 mg once daily in patients with LUTS caused by benign prostatic obstruction. He found that tamsulosin produced a significant decrease in detrusor pressure, an increase in flow rate, and a symptomatic improvement. In a study in which tamsulosin was given alone, or together with tolterodine, to male patients with LUTS, monotherapy with the drug was not effective (Kaplan et al, 2006). An RCT, comprising 364 women with OAB, revealed no effect of tamsulosin versus placebo (Robinson et al, 2007). On the other hand, voiding symptoms in women with functional outflow obstruction, or LUTS, were reported as successfully treated with an α_1-AR antagonist (Kessler et al, 2006; Low et al, 2008).

α_1-AR antagonists have been used to treat patients with neurogenic DO (Abrams et al, 2003); however, the success has been moderate. Thus there is no convincing evidence that α_1-AR antagonists are effective in patients with storage symptoms. Although α_1-AR antagonists may be effective in selected cases, convincing effects documented in RCTs are lacking (see Table 68–2). **In women, these drugs may produce or aggravate SUI** (Dwyer and Teele, 1992).

β-Adrenergic Receptor Agonists. In isolated human bladder, nonsubtype selective β-AR agonists such as isoprenaline have a pronounced inhibitory effect, and administration of such drugs can increase bladder capacity in humans (Andersson, 1993). However, the β-ARs of the human bladder were shown to have functional characteristics typical of neither β_1- nor β_2-ARs, because they could be blocked by propranolol but not by practolol or metoprolol (β_1) or butoxamine (β_2) (Nergardh et al, 1977; Larsen, 1979). On the other hand, early receptor binding studies using subtype selective ligands suggested that the β-ARs of the human detrusor are primarily of β_2 subtype (Andersson, 1993), and favorable effects on DO were reported in open studies with selective β_2-AR agonists such as terbutaline (Lindholm and Lose, 1986). In a double-blind investigation clenbuterol 0.01 mg three times daily was shown to have a good therapeutic effect in 15 of 20 women with DO (Gruneberger, 1984). Other investigators, however, have not been able to show that β-AR agonists represent an effective therapeutic principle in elderly patients with DO (Castleden and Morgan, 1980) or in young patients with myelodysplasia and DO (Naglo et al, 1981).

However, **three subtypes (β_1, β_2, and β_3) have been identified in the detrusor of most species, including humans** (Andersson and Arner, 2004; Michel and Vrydag, 2006). Also the human urothelium contains all three receptor subtypes (Otsuka et al, 2008). Studies, using real-time polymerase chain reaction, have revealed a **predominant expression of β_3-AR mRNA** in human detrusor muscle (Nomiya and Yamaguchi, 2003; Michel and Vrydag, 2006); and the functional evidence for an important role in both normal and neurogenic bladders is convincing (Fujimura et al, 1999; Igawa et al, 1999, 2001; Takeda et al, 1999; Morita et al, 2000; Biers et al, 2006; Michel and Vrydag, 2006; Badawi et al, 2007; Leon et al, 2008). **The human detrusor also contains β_2-ARs, and most probably both receptors are involved in the physiologic effects (relaxation) of norepinephrine in this structure** (Andersson and Arner 2004; Michel and Vrydag, 2006).

The generally accepted mechanism by which β-ARs induce detrusor relaxation in most species is activation of adenylyl cyclase with the subsequent formation of cAMP. However, there is evidence suggesting that, in the bladder, K^+ channels, particularly BK_{Ca} channels, may be more important in β-AR–mediated relaxation than cAMP (Hudman et al, 2000; Frazier et al, 2005; Uchida et al, 2005; Frazier et al, 2008).

Because β-ARs are present in the urothelium, their possible role in bladder relaxation has been investigated (Murakami et al, 2007; Otsuka et al, 2008). Murakami and coworkers (2007) found that the relaxation responses of the detrusor were not influenced by the urothelium. However, isoprenaline was more potent at inhibiting carbachol contractions in the presence of the urothelium than in its absence. It was suggested that this might reflect the release of an inhibitory factor from the urothelium. Further support for this hypothesis was given by Otsuka and associates (2008). However, to what extent a urothelial signaling pathway contributes in vitro and in vivo to the relaxant effects of β-AR agonists in general, and β_3-AR agonists specifically, remains to be elucidated.

The in-vivo effects of β_3-AR agonists on bladder function have been studied in several animal models. It has been shown that compared with other agents (including antimuscarinic drugs), β_3-AR agonists increase bladder capacity with no change in micturition pressure and the residual volume (Fujimura et al, 1999; Woods et al, 2001; Kaidoh et al, 2002). For example, Hicks and associates (2007) studied the effects of the selective β_3-AR agonist GW427353 in the anesthetized dog and found that the drug evoked an increase in bladder capacity under conditions of acid-evoked bladder hyperactivity, without affecting voiding.

A number of β_3-AR selective agonists are currently being evaluated as potential treatment for OAB in humans, including GW427353 (solabegron) and YM178 (Colli et al, 2007). Takasu and associates (2007) found that the selective β_3-AR agonist YM178 mediated muscle relaxation of human bladder strips. Chapple and coworkers (2008c) reported the results of a controlled clinical trial

with this drug in patients with OAB. Tolterodine and placebo served as controls. The primary efficacy analysis showed a statistically significant reduction in mean micturition frequency, compared with placebo (–2.19 vs. –1.18). With respect to secondary variables YM178 (100 mg) was significantly superior to placebo concerning mean volume voided per micturition (26 vs. 11 mL), mean number of incontinence episodes (–2.17 vs. –1.01), and urgency episodes per 24 hour (–2.30 vs. –1.03). The drug was well tolerated, and the most commonly reported side effects were headache and gastrointestinal adverse effects. The results of this proof of concept study showed that **the principle of β_3-AR agonism may be useful for treatment of patients with OAB** (see Table 68–2). However, to show that this class of drugs offers a viable therapeutic alternative or complement to current treatment of LUTS/OAB requires further well-designed RCTs.

Phosphodiesterase Inhibitors

Drugs stimulating the generation of cAMP are known to relax smooth muscles, including the detrusor (Andersson, 1999b; Andersson and Arner, 2004). I**t is also well established that drugs acting through the nitric oxide/cyclic guanosine monophosphate (NO/cGMP) system can relax the smooth muscle of the bladder outflow region** (Andersson and Arner, 2004). Use of PDE inhibitors to enhance the presumed cAMP- and cGMP-mediated relaxation of LUT smooth muscles (detrusor prostate, urethra) should then be a logical approach (Andersson et al, 2007). There are presently 11 families of PDEs, some of which preferentially hydrolyze either cAMP or cGMP (Andersson et al, 2007).

As a basis for PDE inhibitor treatment of LUTS, Truss and colleagues (2001) investigated human bladder tissue, revealing mRNA for PDE1, PDE2, PDE4, and PDE5; **most of these PDEs preferably inhibit the breakdown of cAMP.** In vitro, human detrusor muscle responded poorly to sodium nitroprusside and to agents acting via the cGMP system (Truss et al, 2001). However, significant relaxation of human detrusor muscle, paralleled by increases in cyclic nucleotide levels, was induced by papaverine, vinpocetine (a low affinity inhibitor of PDE1), and forskolin (stimulating the generation of cAMP), suggesting that the cAMP pathway and PDE1 may be important in regulation of detrusor smooth muscle tone. Significant dose-dependent relaxations were also induced by human cAMP analogues (Truss et al, 2001). With these studies as a background, Truss and colleagues (2000) presented preliminary clinical data with vinpocetine in patients with urgency/urgency incontinence or low compliance bladders and not responding to standard antimuscarinic therapy. This initial open pilot study suggested a possible role for vinpocetine in the treatment of OAB. However, the results of a larger RCT in patients with DO showed that vinpocetine showed statistically significant results only for one parameter (Truss et al, 2001). Studies with other PDE1 inhibitors than vinpocetine (which may not be an optimal drug for elucidating the principle) do not seem to have been performed.

PDE4 (which also preferably hydrolyzes cAMP) has been implicated in the control of bladder smooth muscle tone. PDE4 inhibitors reduced the in-vitro contractile response of guinea pig (Longhurst et al, 1997) and rat (Nishiguchi et al, 2007; Kaiho et al, 2008) bladder strips and also suppressed rhythmic bladder contractions of the isolated guinea pig bladder (Gillespie, 2004a). Previous experiences with selective PDE4 inhibitors showed emesis to be a dose-limiting effect (Giembycz, 2005). If this side action can be avoided, PDE4 inhibition seems to be a promising approach.

NO has been demonstrated to be an important inhibitory neurotransmitter in the smooth muscle of the urethra, and its relaxant effect is associated with increased levels of cGMP (Andersson and Wein, 2004). However, few investigations have addressed the cAMP- and cGMP-mediated signal transduction pathways and its key enzymes in the mammalian urethra. Morita and associates (1994) examined the effects of isoproterenol, prostaglandin E_1 and E_2, and sodium nitroprusside on the contractile force and tissue content of cAMP and cGMP in the rabbit urethra. They concluded that both cyclic nucleotides can produce relaxation of the urethra. Werkström and associates (2006) characterized the distribution of PDE5, cGMP, and PKG1 in female pig and human urethra and evaluated the effect of pharmacologic inhibition of PDE5 in isolated smooth muscle preparations. After stimulation with the NO donor, DETA NONO-ate, the cGMP-immunoreactivity in urethral and vascular smooth muscles increased. There was a wide distribution of cGMP- and vimentin-positive interstitial cells between pig urethral smooth muscle bundles. PDE5 immunoreactivity could be demonstrated within the urethral and vascular smooth muscle cells but also in vascular endothelial cells that expressed cGMP immunoreactivity. Nerve-induced relaxations of urethral preparations were enhanced at low concentrations of sildenafil, vardenafil, and tadalafil, whereas there were direct smooth muscle relaxant actions of the PDE5 inhibitors at high concentrations.

The distribution of PDEs in the male urethral structures does not seem to have been studied.

The observation that patients treated for erectile dysfunction with PDE5 inhibitors had an improvement of their LUTS has sparked a new interest in using these drugs also for treatment of LUTS and OAB. After the report in an open study (Sairam et al, 2002) that treatment with sildenafil appeared to improve urinary symptom scores in men with erectile dysfunction and LUTS, this observation has been confirmed in several well-designed and conducted RCTs (McVary et al, 2007a, 2007b; Stief et al, 2008).

McVary and colleagues (2007a) evaluated the effects of sildenafil (50 to 100 mg daily for 12 weeks) on erectile dysfunction and LUTS in men 45 years or older who scored 25 or less on the erectile function domain of the International Index of Erectile Function (IIEF) and 12 or greater on the International Prostate Symptom Score (IPSS). In 189 men receiving sildenafil, significant improvements were observed in IPPS (–6.32 vs. –1.93, $P < .0001$), Benign Prostatic Hyperplasia Impact Index (–2.0 vs. –0.9, $P < .0001$), mean IPSS quality of life score (–0.97 vs. –0.29, $P < .0001$) and total Self-Esteem and Relationship questionnaire scores (24.6 vs. 4.3, $P < .0001$). Interestingly there was no difference in urinary flow between the groups ($P = .08$). Significantly more sildenafil versus placebo-treated patients were satisfied with treatment (71.2 vs. 41.7, $P < .0001$). Sildenafil was well tolerated.

In an RCT, treatment with tadalafil once daily, in addition to improving erectile function in men with LUTS, was demonstrated to produce a clinically meaningful and statistically significant symptomatic improvement of LUTS (McVary et al, 2007b). In another RCT, vardenafil given twice daily for 8 weeks to men with erectile dysfunction and LUTS was shown to significantly improve LUTS, erectile function, and quality of life (Stief et al, 2008).

The mechanism behind the beneficial effect of the PDE inhibitors on LUTS/OAB and their site(s) of action largely remain to be elucidated. If the site of action were the smooth muscles of the outflow region (and the effect relaxation), an increase in flow rate should be expected. In none of the trials referred to, such an effect was found. However, there are several other structures in the LUT that may be involved, including those in the urothelial signaling

pathway (urothelium, interstitial cells, and suburothelial afferent nerves).

PDE5 inhibitors have a documented effect in men with LUTS/OAB (see Table 68–2). The place of PDE5 inhibitors in the treatment of OAB/DO remains to be established. Specifically, there seems to be no published information on the effects of these drugs in women with OAB/DO.

Antidepressants

Many clinicians believe that tricyclic antidepressants, particularly **imipramine** (Tofranil, others), are useful agents for facilitating urine storage, both by decreasing bladder contractility and by increasing outlet resistance (Wein, 1995a, 1995b). These agents have been the subject of a voluminous amount of highly sophisticated pharmacologic investigation to determine the mechanisms of action responsible for their varied effects (Maggi et al, 1989b; Richelson, 1994; Baldessarini, 2006). Most data have been accumulated as a result of trying to explain the antidepressant properties of these agents and are thus primarily from CNS tissue. The results, conclusions, and speculations inferred from the data are extremely interesting, but it should be emphasized that it is essentially unknown whether they apply to or have relevance for the LUT.

Tricyclic antidepressants possess varying degrees of at least three major pharmacologic actions: (1) they have central and peripheral antimuscarinic effects at some, but not all, sites; (2) they block the active transport system in the presynaptic nerve ending that is responsible for the reuptake of the released amine neurotransmitters norepinephrine and serotonin; and (3) they are sedatives, an action that occurs presumably on a central basis but is perhaps related to antihistaminic properties (at H_1 receptors, although they also antagonize H_2 receptors to some extent). There is also evidence that they desensitize at least some α_2- and some β-AR agonists. Paradoxically, they also have been shown to block some α-AR agonists and 5-hydroxytryptamine type 1 receptors.

Imipramine. As indicated earlier, imipramine has complex pharmacologic effects, and its mode of action in OAB/DO has not been established (Hunsballe and Djurhuus, 2001). **Even if it is generally considered that imipramine is a useful drug in the treatment of OAB/DO, no good quality RCTs that can document this have been retrieved.**

It has been known for a long time that imipramine can have favorable effects in the treatment of nocturnal enuresis in children with a success rate of 10% to 70% in controlled trials (Hunsballe and Djurhuus, 2001; Glazener et al, 2003).

The risks (see later) and benefits of imipramine in the treatment of voiding disorders do not seem to have been assessed. Very few studies have been performed during the past decade (Hunsballe and Djurhuus, 2001). No good quality RCTs have documented that the drug is effective in the treatment DO. However, a beneficial effect has been documented in the treatment of nocturnal enuresis.

Doxepine. Doxepine is another tricyclic antidepressant that was found to be more potent, using in-vitro rabbit bladder strips, than other tricyclic compounds with respect to antimuscarinic and musculotropic relaxant activity (Levin and Wein, 1984). Lose and associates (1989), in a randomized, double-blind crossover study of females with involuntary bladder contractions, and either frequency, urgency, or urgency incontinence, found that this agent caused a significant decrease in urine loss (pad weighing test) and in the cystometric parameters of first sensation and maximum bladder capacity. The dosage of doxepin used was either a single 50-mg bedtime dose or this dose plus an additional 25 mg in the morning. The number of daytime incontinence episodes decreased in both doxepin and placebo groups, and the difference was not statistically significant. Doxepine treatment was preferred by 14 patients, whereas 2 preferred placebo. Three patients had no preference. Of the 14 patients who stated a preference for doxepine, 12 claimed that they became continent during treatment whereas 2 claimed improvement; the 2 patients who preferred placebo claimed improvement. The AHCPR Guidelines combine results for imipramine and doxepine, citing only three randomized controlled trials, with an unknown percent of female patients. Percent cures (all figures refer to percent drug effect minus percent effect on placebo) are listed as 31%, percent reduction in urgency incontinence as 20% to 77%, and percent side effects as 0% to 70% (U.S. Department of Health and Human Services, 1992).

Duloxetine. Duloxetine is a serotonin-norepinephrine reuptake inhibitor that has been shown to significantly increase sphincteric muscle activity during the filling/storage phase of micturition in the cat acetic acid model of irritated bladder function (Thor et al, 1995; Katofiasc et al, 2002). **Bladder capacity was also increased in this model,** both effects mediated centrally through both motor efferent and sensory afferent modulation (Fraser et al, 2003). The effects of duloxetine were studied in a placebo-controlled study comprising 306 women (aged 21 to 84 years) with OAB, randomly treated with placebo (153) or duloxetine (80 mg/day for 4 weeks, which was increased to 120 mg/day for 8 weeks (Steers et al, 2007). The primary efficacy analysis compared the treatment effects on mean change from baseline to end point in the mean number of voiding episodes per 24 hours. Patients randomized to duloxetine had significant improvements over those randomized to placebo for decreases in voiding and incontinence episodes (–1.81 vs. –0.62, for increases in the daytime voiding intervals (29 vs. 7 minutes), and for improvements in Incontinence Quality of Life scores at both doses of duloxetine. Urodynamic studies showed no significant increases in maximum cystometric capacity or in the volume threshold for DO. The most common treatment-emergent adverse events with duloxetine (nausea 31%, placebo 4.6%; dry mouth 16%, placebo 1.3%; dizziness 14%, placebo 0.7%; constipation 14%, placebo 3.3%; insomnia 13%, placebo 1.3%; and fatigue 11%, placebo 2.0%) were the same as those reported by women with SUI (see later) and were significantly more common with duloxetine than placebo. Also in females with mixed incontinence, improvement of the OAB component has been demonstrated (Bent et al, 2008; Schagen van Leeuwen et al, 2008). For assessment, see Table 68–2.

When used in the generally larger doses employed for antidepressant effects **the most frequent side effects of the tricyclic antidepressants are those attributable to their systemic antimuscarinic activity** (Richelson, 1994; Baldessarini, 2006). Allergic phenomena, including rash, hepatic dysfunction, obstructive jaundice, and agranulocytosis may also occur but rarely. CNS side effects may include weakness, fatigue, parkinsonian effect, a fine tremor noted most in the upper extremities, a manic or schizophrenic picture, and sedation, probably from an antihistaminic effect. Postural hypotension may also be seen, presumably on the basis of selective blockade (a paradoxical effect) of α_1-AR agonists in some vascular smooth muscle. Tricyclic antidepressants can also cause excess sweating of obscure etiology and a delay of orgasm or orgasmic impotence, the cause of which likewise is unclear. They can also produce arrhythmias and interact in deleterious ways with other drugs, and so caution must be

observed in their use in patients with cardiac disease (Baldessarini, 2006). Whether cardiotoxicity will prove to be a legitimate concern in patients receiving the smaller doses (than for treatment of depression) for LUT dysfunction remains to be seen but is a potential matter of concern. Consultation with a patient's internist or cardiologist is always helpful before instituting such therapy in questionable situations. It is well established that **therapeutic doses of tricyclic antidepressants, including imipramine, may cause serious toxic effects on the cardiovascular system** (orthostatic hypotension, ventricular arrhythmias). Imipramine prolongs QTc intervals and has an antiarrhythmic (and proarrhythmic) effect similar to that of quinidine (Bigger et al, 1977; Giardina et al, 1979). Children seem particularly sensitive to the cardiotoxic action of tricyclic antidepressants (Baldessarini, 2006).

With respect to the potential cardiovascular risks of antidepressant medication, two additional points need to be made. First of all, it may be depression itself that is associated with an increased risk of myocardial infarction, cardiovascular disease, and all-cause mortality (see references in Cohen et al, 2000). Although treatments for depression, including antidepressive medications, are certainly a potential factor underlying this association, the separation from disease association and treatment association is difficult at best. The second point relates to whether there is a difference in this regard between the use of tricyclic antidepressants and selective serotonin reuptake inhibitors. Data presented by Cohen and coworkers (2000) suggest with respect to long-term adverse cardiovascular outcome there is an association between the use of tricyclic antidepressants but not selective serotonin reuptake inhibitors, a conclusion that differs from earlier data that indicated no significant differences in the safety or efficacy of these two groups of agents (AHCPR Report, cited by Cohen et al, 2000). As a closing statement on this subject, it should be noted that data in the literature refer to therapeutic doses of these medications for depression and not the smaller (in comparison) doses of imipramine used for the treatment of voiding dysfunction.

The use of imipramine is contraindicated in patients receiving monoamine oxidase inhibitors, because severe CNS toxicity can be precipitated, including hyperpyrexia, seizures, and coma. Some potential side effects of the antidepressants may be especially significant for the elderly, specifically weakness, fatigue, and postural hypotension. Psychotropic drugs in general have been shown to increase the risk of falls and hip fractures in the elderly (Liu et al, 1998). If imipramine or any of the tricyclic antidepressants is to be prescribed for the treatment of voiding dysfunction, the patient should be thoroughly informed of the fact that this is not the usual indication for this drug and that potential side effects exist. Reports of significant side effects (severe abdominal distress, nausea, vomiting, headache, lethargy, and irritability) after abrupt cessation of high doses of imipramine in children would suggest that the drug should be discontinued gradually, especially in patients receiving high doses.

Cyclooxygenase Inhibitors

Human bladder mucosa has the ability to synthesize eicosanoids (Jeremy et al, 1987), and these agents can be liberated from bladder muscle and mucosa in response to different types of trauma (Downie and Karmazyn, 1984; Leslie et al, 1984). Even if prostaglandins cause contraction of human detrusor (Andersson, 1993) **it is still unclear whether prostaglandins contribute to the pathogenesis of DO. More important than direct effects on the bladder muscle may be sensitization of sensory afferent nerves, increasing the afferent input produced by a given degree of bladder filling.** Involuntary bladder contractions can then be triggered at a small bladder volume. If this is an important mechanism, treatment with prostaglandin synthesis inhibitors could be expected to be effective. However, **clinical evidence for this is scarce.**

Cardozo and colleagues (1980) performed a double-blind controlled study of 30 women with DO using the prostaglandin synthesis inhibitor flurbiprofen at a dosage of 50 mg three times daily. The drug was shown to have favorable effects, although it did not completely abolish DO. There was a high incidence of side effects (43%) including nausea, vomiting, headache, and gastrointestinal symptoms. Palmer (1983) studied the effects of flurbiprofen 50 mg four times daily versus placebo in a double-blind, crossover trial in 37 patients with idiopathic DO (27% of the patients did not complete the trial). Active treatment significantly increased maximum contractile pressure, decreased the number of voids, and decreased the number of urgent voids compared with baseline. Indomethacin 50 to 100 mg/day was reported to give symptomatic relief in patients with DO, compared with bromocriptine in a randomized, single-blind, crossover study (Cardozo and Stanton, 1980). The incidence of side effects was high, occurring in 19 of 32 patients. However, no patient had to stop treatment because of side effects.

The few controlled clinical trials on the effects of prostaglandin synthesis inhibitors in the treatment of DO, and the limited number of drugs tested, make it difficult to evaluate their therapeutic value (see Table 68–2). **No new RCTs on the effects of COX inhibitors in OAB/DO patients seem to have been published during the past decade.**

Dimethyl Sulfoxide

Dimethyl sulfoxide (DMSO) is a relatively simple, naturally occurring organic compound that has been used as an industrial solvent for many years. It has multiple pharmacologic actions (membrane penetrant, anti-inflammatory, local analgesic, bacteriostatic, diuretic, cholinesterase inhibitor, collagen solvent, vasodilator) and has been used for the treatment of arthritis and other musculoskeletal disorders, generally in a 70% solution. The formulation for human intravesical use is a 50% solution. Sant (1987) has summarized the pharmacology and clinical use of DMSO and has tabulated "good to excellent" results in 50% to 90% of collected series of patients treated with intravesical instillation for interstitial cystitis. **However, DMSO has not been shown to be useful in the treatment of neurogenic or idiopathic DO or in any patients with urgency/frequency but without interstitial cystitis.** The subject of interstitial cystitis and its treatment is considered in Chapter 12.

Polysynaptic Inhibitors

Baclofen (Lioresal) is discussed primarily along with agents that decrease outlet resistance secondary to striated sphincter dyssynergia. Baclofen is a γ-aminobutyric acid type B ($GABA_B$) receptor agonist that depresses monosynaptic and polysynaptic motoneurons and interneurons in the spinal cord (Andersson et al, 1999, 2000a). It has also been shown capable of depressing neurogenic DO secondary to a spinal cord lesion (Kiesswetter and Schober, 1975). Taylor and Bates (1979), in a double-blind crossover study, reported it to be very effective also in decreasing daytime and night-time urinary frequency and incontinence in patients with idiopathic DO. Cystometric changes were not recorded, however, and considerable improvement was also obtained in the placebo

group. Effective intrathecal use of baclofen for treatment of neurogenic DO was reported by Kums and Delhaas (1991), Steers and associates (1992), and Bushman and colleagues (1993). Little on this subject has appeared during the past decade.

Toxins

Vanilloids. By means of **capsaicin,** a subpopulation of primary afferent neurons innervating the bladder and urethra, the "capsaicin-sensitive nerves," has been identified. It is believed that capsaicin exerts its effects by acting on specific "vanilloid" receptors on these nerves (Szallasi, 1994). Capsaicin exerts a biphasic effect: initial excitation is followed by a long-lasting blockade, **which renders sensitive primary afferents (C fibers) resistant to activation by natural stimuli. In sufficiently high concentrations, capsaicin is believed to cause "desensitization" initially by releasing and emptying the stores of neuropeptides and then by blocking further release** (Maggi, 1993). **Resiniferatoxin** (RTX) is an analogue of capsaicin, approximately **1000 times more potent for desensitization than capsaicin** (Ishizuka et al, 1995a) **but only a few hundred times more potent for excitation** (Szallasi and Blumberg, 1999). **Possibly, both capsaicin and RTX can have effects on Aδ fibers.** It is also possible that capsaicin at high concentrations (mM) has additional, nonspecific effects (Kuo, 1997).

The rationale for intravesical instillations of vanilloids is based on the involvement of C fibers in the pathophysiology of conditions such as bladder hypersensitivity and neurogenic DO. In the healthy human bladder C fibers carry the response to noxious stimuli, but they are not implicated in the normal voiding reflex. After spinal cord injury major neuroplasticity appears within bladder afferents in several mammalian species, including humans. C-fiber bladder afferents proliferate within the suburothelium and become sensitive to bladder distention. Those changes lead to the emergence of a new C-fiber–mediated voiding reflex, which is strongly involved in spinal neurogenic DO. Improvement of this condition by defunctionalization of C-fiber bladder afferents with intravesical vanilloids has been widely demonstrated in humans and animals.

Cystometric evidence that capsaicin-sensitive nerves may modulate the afferent branch of the micturition reflex in humans was originally presented by Maggi and colleagues (1989a), who instilled capsaicin (0.1 to 10 μM) intravesically in five patients with hypersensitivity disorders with attenuation of their symptoms a few days after administration. Intravesical capsaicin, given in considerably higher concentrations (1 to 2 mM) than those administered by Maggi and colleagues (1989a), has since been used with success in neurologic disorders such as multiple sclerosis or traumatic chronic spinal lesions (Fowler et al, 1992b, 1994; Geirsson et al, 1995; DeRidder et al, 1997; for more discussion see de Seze et al, 1999; DeRidder and Baert, 2000; Andersson et al, 2002, 2009; Cruz, 2004; de Seze et al, 2004). Side effects of intravesical capsaicin include discomfort and a burning sensation at the pubic/urethral level during instillation, an effect that can be overcome by prior instillation of lidocaine, which does not interfere with the beneficial effects of capsaicin (Chandiramani et al, 1996). No premalignant or malignant changes in the bladder have been found in biopsy specimens of patients who had repeated capsaicin instillations for up to 5 years (Dasgupta et al, 1998).

The beneficial effect of **RTX** has been demonstrated in several studies (see Andersson 2002a, 2009; Kim et al, 2003; Kuo et al, 2003; de Seze et al, 2004; Giannantoni et al, 2004; Watanabe, 2004).

de Seze and associates (2004) compared the efficacy and tolerability of nonalcohol capsaicin (1 mM) versus RTX (100 nM) in 10% alcohol in a randomized, double-blind, parallel-group study in 39 spinal cord–injured adult patients with neurogenic DO (hyperreflexia). Efficacy (voiding chart and cystomanometry) and tolerability were evaluated during a 3-month follow-up. On day 30, clinical and urodynamic improvement was found in 78% and 83% of patients with capsaicin versus 80% and 60% with RTX, respectively, without a significant difference between the two treated groups. The benefit remained in two thirds of the two groups on day 90. There were no significant differences in regard to the incidence, nature, or duration of side effects in capsaicin- versus RTX-treated patients. The data suggested that capsaicin and RTX are equally efficient for relieving the clinical and urodynamic symptoms of neurogenic DO and that glucidic capsaicin is as well tolerated as ethanolic RTX.

Available information (including data from RCTs) suggests that **both capsaicin and RTX may have useful effects in the treatment of neurogenic DO. There may be beneficial effects also in non-neurogenic DO in selected cases refractory to antimuscarinic treatment, but further RCT-based documentation is desired.** RTX is an interesting alternative to capsaicin, but the drug is currently not in clinical development owing to formulation problems.

Neither capsaicin nor RTX is approved in the United States for clinical use. It is obvious, however, that the intravesical use of such agents has the potential to significantly contribute to the treatment of DO in patients with neurogenic and other types of LUT dysfunction. Various techniques of administration of intravesical capsaicin and RTX differ slightly among experienced users and are described in detail in the articles by Chancellor and de Groat (1999), Fowler (2000), and DeRidder and Baert (2000).

Botulinum Neurotoxin (BoNT). **BoNT** is produced by *Clostridium botulinum*. **Of the seven subtypes of BoNT, subtype A (BoNT/A) is the most relevant clinically.** Most of the intravesical experience reported on BoNT/A deals with Botox. However, BoNT/A toxin is also available under the trade names of Dysport and Xeomin. Bladder experience with the latter was, however, never reported. Available information indicates that Botox is roughly three times more potent than Dysport (Cruz and Silva, 2004; Nitti et al, 2006). However, this relation has never been clearly defined. Therefore in a bladder setting these equivalents should be approached with caution (for clinical reviews, see Nitti et al, 2006; Patel et al, 2006; Cruz and Dinis, 2007; Karsenty et al, 2008). In addition to subtype A, recent reports have investigated the detrusor injection of BoNT subtype B (Neurobloc, Miobloc). BoNT was shown to exert a prolonged local effect when injected directly into skeletal muscles, and the effects are dose dependent and reversible.

BoNT consists of a heavy and a light chain linked by a disulfide bond. In the synaptic cleft the toxin binds to synaptic vesicle protein or SV2 (Dong et al, 2006) through its heavy chain and is internalized by the nerve terminal. On cleavage, the light chain is released in the cytosol, where it impedes binding of neurotransmitter-containing synaptic vesicles to the plasma membrane. This is achieved through the *N*-ethylmaleimide-sensitive factor attachment protein (SNARE) complex made up of synaptosome-associated protein 25 kD (SNAP 25), synaptobrevin (vesicle-associated membrane protein [VAMP]), and syntaxin. BoNT/A cleaves SNAP 25 rendering the SNARE complex inactive (Humeau et al, 2000; Chancellor et al, 2008a). Subtype B acts preferentially through the inactivation of VAMP (Humeau et al, 2000).

The rationale for using BoNT to treat human DO is based on the assumption that effects of the toxin on skeletal muscle would be replicated in bladder smooth muscle (Schurch et al, 2000a, 2000b) **and that detrusor muscle paralysis would reduce the symptoms of OAB** (Duthie et al, 2007). **BoNT has been developed as a second-line treatment option (after failure of, or intolerance to, appropriate antimuscarinic therapy) for patients with NDO with urinary incontinence or other neurogenic OAB symptoms and who are able and willing to perform CIC.**

The first report of the application of BoNT/A in NDO appeared in 2000 (Schurch et al, 2000b). Injection of BoNT/A 200 to 300 units at 20 to 30 detrusor muscle sites restored continence in 17 of 19 patients (89.5%) with severe neurogenic DO and incontinence secondary to traumatic spinal cord injury at the 6-week follow-up. No side effects were reported, mean reflex volume and mean maximum cystometric bladder capacity increased significantly from baseline, and there was a significant decrease in mean maximum detrusor pressure. Since then, the efficacy of BoNT/A injection into the detrusor muscle in adult patients with NDO refractory to, and/or intolerant of, antimuscarinic agents has been confirmed in a number of studies, which have been the subject of systematic review (Karsenty et al, 2008; Apostolidis et al, 2009; see also Andersson et al, 2009). The analysis by Karsenty and colleagues (2008) evaluated 18 trials with Botox, involving a total of 698 patients, of whom 83% had NDO with urinary incontinence. Significant benefits were seen in clinical variables (micturition frequency and number of incontinence episodes) as well as urodynamic variables (maximum detrusor pressure, maximum cystometric capacity). Complete continence was achieved in 40% to 80% of patients. Efficacy has also been demonstrated in spinal cord–injured patients with detrusor–striated sphincter dyssynergia (Dykstra et al, 1990, 1998; Schurch et al, 1996). A significant response to BoNT/A is seen as early as 1 week after treatment; however, maximum effects were seen between 1 and 4 weeks. **The efficacy of BoNT/A appears to persist for at least 3 to 4 months and up to 1 year but does decline over time** (Grosse et al, 2005), meaning that **repeat injections are required for continued therapeutic effect.** Repeat injections have been shown to be effective and well tolerated (Grosse et al, 2005; Karsenty et al, 2006; Giannantoni et al, 2009), and there is **no reported evidence of a reduction in response** over time, after two to nine repeat injections. The beneficial clinical and urologic effects of BoNT/A in adults with NDO are accompanied by improvement in patients' quality of life (Kalsi et al, 2006; Schurch et al, 2007).

BoNT/A is generally well tolerated. Data from a systematic review of the role of BoNT/A in NDO indicated that the most frequent adverse events are injection site pain, procedure-related urinary tract infection, and mild hematuria (Karsenty et al, 2008). A potential adverse effect resulting from the use of BoNT in patients not using CIC is an increase in postvoid residual volume that may result in de novo CIC (6% to 88% of patients), with associated impact on quality of life (Karsenty et al, 2008; Shaban et al, 2008). Systemic side effects, although rare, could be very disabling for patients with spinal cord injury (De Laet et al, 2005).

Important factors to consider in relation to the risk of adverse events during urologic use of BoNT/A are the drug dosage, the formulation used, and the injection technique. Available data indicate that Dysport may be associated with a higher risk of side effects related to drug migration (e.g., muscle weakness) than Botox (Dmochowski and Sand, 2007). The doses typically evaluated in clinical trials in urologic indications differ between the commercially available formulations of BoNT/A. Additionally, systemic adverse reactions, including respiratory compromise and death, have been reported after the use of BoNT/A and BoNT/B for both U.S. Food and Drug Administration (FDA) approved and unapproved uses (Dmochowski and Sand, 2007). The most serious cases involved treatment of children for cerebral palsy–associated limb spasticity, and the FDA is currently reviewing safety data relating to marketed BoNT products.

Accumulating evidence indicates that BoNT/A may be a useful option for treating children with NDO and urinary incontinence and whose disorders are refractory to antimuscarinic therapy. A systematic review on the use of BoNT/A (Botox) in children with NDO identified six small (10 to 26 patients) prospective studies primarily involving children with myelomeningocele (Game et al, 2009). BoNT/A treatment resulted in a reduction in urinary incontinence of 40% to 80%, and between 65% and 87% of patients became completely continent between CIC. In addition, all studies showed a significant impact of treatment on urodynamic variables, including maximum detrusor pressure and maximum cystometric capacity. Improvement was observed within 2 weeks of BoNT/A injection and persisted for up to 6 months. The amount of Botox injected ranged from 5 to 12 units/kg, with a maximum dose of 360 units. Repeat administration of BoNT/A was associated with similar therapeutic effects to the first dose. Available data therefore indicate that BoNT/A may have the ability to prevent or delay the need for surgery in children with NDO, but further studies with the appropriate design and with a longer follow-up are required to confirm this. The safety profile in children has not been established, and there is a need for studies that evaluate the effect of long-term, repeated administration on the bladder wall. Although the value of BoNT for the treatment of NDO is now recognized in European and U.S. consensus reports (Naumann et al, 2008; Apostolides et al, 2009), at the time of this writing, the only approval for BoNT/A in a urologic indication is for Botox for the treatment of OAB in Brazil. On the whole, studies on BoNT/A are small (<50 patients), short term, and are largely restricted to patients with spinal cord injury or multiple sclerosis. Indeed, several questions remain unanswered. These include the optimal dose and frequency of administration to balance efficacy with safety, the most appropriate method and location of administration, and how to identify patients who would benefit the most. Considerable systematic research is still required to answer these questions. Large phase 3 registration studies are being conducted to support the registration of this treatment for NDO, including the optimal dose recommendation.

There are limited data on the use of **botulinum toxin B (BoNT/B)** for incontinence, particularly in patients with NDO. In the only two published trials on the use of BoNT/B in urologic indications, the vast majority of patients had non-neurogenic OAB (Dykstra et al, 2003a, 2003b; Ghei et al, 2005). Data on the use of BoNT/B in patients with NDO come primarily from three case reports (Dykstra et al, 2003b; Pistolesi et al, 2004; Reitz and Schurch, 2004). In one report, BoNT/B 5000 units was injected into 10 different areas of the bladder wall in a patient with multiple sclerosis whose disease was refractory to oral and topical antimuscarinic agents. The patient reported a positive response within 24 hours and had no adverse effects. The beneficial effects of BoNT/B began to decline after 4 months, and a repeat BoNT/B dose of 7500 units was given that also provided therapeutic benefit for 4 months (Dykstra et al, 2003b). BoNT/A and BoNT/B interfere with different presynaptic proteins, meaning that a primary nonresponse to the type A toxin does not necessarily imply a

non-response to the type B toxin. Indeed, data from the other two case reports indicate that BoNT/B may have a place for the management of patients with NDO resistant to therapy with the type A toxin. However, the duration of effect was only 4 to 6 weeks (Pistolesi et al, 2004; Reitz and Schurch, 2004). There are no data on the use of BoNT/B in children.

Estrogens for Urgency Urinary Incontinence and Overactive Bladder Symptoms

Estrogen has been used to treat postmenopausal urgency and urgency incontinence for many years, but there have been **few controlled trials to confirm that it is of benefit** (Hextall, 2000; for assessment, see Table 68–2). A double-blind multicenter study of 64 postmenopausal women with "urgency syndrome" failed to show efficacy (Cardozo et al, 1993). All women underwent pretreatment urodynamic investigation to ensure that they had either "sensory urgency" or DO. They were randomized to treatment with oral estriol 3 mg daily or placebo for 3 months. Compliance with therapy was confirmed by a significant improvement in the maturation index of vaginal epithelial cells in the active but not the placebo group. Estriol produced subjective and objective improvements in urinary symptoms but was not significantly better than placebo.

Another recent RCT from the same group using 25 mg estradiol implants confirmed the previous findings (Rufford et al, 2003) and additionally found a high complication rate in the estradiol-treated patients (i.e., vaginal bleeding).

Evidence from Recent Large Clinical Trials. The **HERS study** included 763 postmenopausal women younger than the age of 80 years with coronary heart disease and intact uteri (Grady et al, 2001). It was designed to evaluate the use of estrogen in secondary prevention of cardiac events. In a secondary analysis, 1525 participants who reported at least one episode of incontinence per week at baseline were included. Participants were randomly assigned to 0.625 mg of conjugated estrogens plus 2.5 mg of medroxyprogesterone acetate in one tablet (n = 768) or placebo (n = 757) and were followed for a mean of 4.1 years. Severity of incontinence was classified as improved, unchanged, or worsened. The results showed that incontinence improved in 26% of the women assigned to placebo compared with 21% assigned to hormones whereas 27% of the placebo worsened compared with 39% of the hormone group ($P = .001$). This difference was evident by 4 months of treatment, for both urgency incontinence and SUI. The number of incontinent episodes per week increased an average of 0.7 in the hormone group and decreased by 0.1 in the placebo group ($P < .001$). The authors concluded that **daily oral estrogen plus progesterone therapy was associated with worsening urinary incontinence in older postmenopausal women with weekly incontinence and did not recommend this therapy for treatment of incontinence.** However, it is possible that the progestogen component may have had an influence on the results of this study.

The **Women's Health Initiative (WHI)** was a multicenter double-blind, placebo-controlled RCT of menopausal hormone therapy in 27,347 postmenopausal women aged 50 to 79 years enrolled between 1992 and 1998 for whom urinary incontinence symptoms were known in 23,296 participants at baseline and 1 year. The women were randomized based on hysterectomy status to active treatment or placebo. Those with a uterus were given 0.625 mg/day of conjugated equine estrogen (CEE) plus 2.5 mg/day of medroxyprogesterone acetate (CEE+MPA), whereas those who had undergone hysterectomy received estrogen alone (CEE). **At 1 year hormone therapy was shown to increase the incidence of all types of urinary incontinence among women who were continent at baseline.** The risk was highest for SUI, with results as follows: CEE+MPA: relative risk [RR] 1.7, 95% CI 1.61 to 2.18; CEE alone: RR 2.15, 95% CI 1.77 to 2.62; followed by mixed urinary incontinence CEE+MPA: RR 1.49, 95% CI 1.10 to 2.01. Results for CEE alone were RR 1.79 and 95% CI 1.26 to 2.53. The combination of CEE and MPA had no significant effect on developing urgency urinary incontinence: RR 1.15, 95% CI 0.99 to 1.34; but CEE alone increased the risk: RR 1.32, 95% CI 1.10 to 1.58. **For those women experiencing urinary incontinence at baseline, frequency worsened in both active groups:** CEE+MPA: RR 1.38, 95% CI 1.28 to 1.49; CEE alone: RR 1.47, 95% CI 1.35 to 1.61. Quantity of urinary incontinence worsened at 1 year in both active groups: CEE+MPA: RR 1.20, 95% CI 1.06 to 1.76; CEE alone: RR 1.59, 95% CI 1.39 to 1.82. Those women receiving hormone therapy were more likely to report that urinary incontinence limited their daily activities: CEE+MPA: RR 1.18, 95% CI 1.06 to 1.32; CEE alone: RR 1.29, 95% CI 1.15 to 1.45 at 1 year. Thus based on this secondary analysis of data from a huge study, **conjugated equine estrogen alone or in combination with medroxyprogesterone acetate was shown to increase the risk of urinary incontinence among continent women and worsen urinary incontinence among symptomatic women after 1 year of therapy.**

The **Nurses Health Study** (Grodstein et al, 2004) was a biennial postal questionnaire starting in 1976. In 1996, 39,436 postmenopausal women aged 50 to 75 years who reported no urinary leakage at the start of the study were followed-up for 4 years to identify incident cases of urinary incontinence: 5060 cases of occasional and 2495 cases of frequent incontinence were identified. The risk of developing urinary incontinence was increased among postmenopausal women taking hormones compared with women who had never taken hormones, respectively (oral estrogen: RR 1.54, 95% CI 1.44, 1.65; transdermal estrogen: RR1.68, 95% CI 1.41, 2.00; oral estrogen with progestin: RR 1.34, 95% CI 1.24, 1.44; transdermal estrogen with progestin: RR 1.46, 95% CI 1.16, 1.84). After cessation of hormone therapy there was a decreased risk of incontinence such that 10 years after stopping hormones the risk was identical in women who had and who never had taken hormone therapy.

Conclusions. Estrogen has an important physiologic effect on the female LUT and its deficiency is an etiologic factor in the pathogenesis of a number of conditions. However, the use of estrogen either alone or in combination with progestogen has yielded poor results. The current **level 1 evidence against the use of estrogens for the treatment of urinary incontinence comes from studies powered to assess their benefit in the prevention of cardiovascular events and therefore the secondary analyses have been based only on self-reported symptoms of urinary leakage without any objective data.** Despite this, **all of these large randomized controlled trials show a worsening of preexisting urinary incontinence (both stress and urgency) and an increased new incidence of urinary incontinence with both estrogen and estrogen plus progesterone.** However, the majority of patients in all of these studies were taking combined equine estrogen and this may not be representative of all estrogens taken by all routes of administration.

In a systematic review of the effects of estrogens for symptoms suggestive of an OAB, the conclusion was that estrogen therapy may be effective in alleviating OAB symptoms and that local administration may be the most beneficial route of administration (Cardozo et al, 2004c). It is quite possible that the reason for this

is that the symptoms of urinary urgency, frequency, and urgency incontinence may be a manifestation of urogenital atrophy in older postmenopausal women rather than a direct effect on the LUT (Robinson and Cardozo, 2003). Although there is good evidence that the symptoms and cytologic changes of urogenital atrophy may be reversed by low dose (local) vaginal estrogen therapy there is **currently no evidence that estrogens with or without progestogens should be used in the treatment of urinary incontinence.** Of interest would be studies looking at (1) the role of prophylactic versus therapeutic estrogen and (2) a double-blind study of transvaginal estrogen in various but low doses.

Concerns about the use of estrogen are summarized by Loose and Stancel (2006). **Unopposed estrogen for hormone treatment in postmenopausal women increases the risk of endometrial carcinoma by 5 to 15 fold, but this increased risk can be prevented if a progestin is coadministered with the estrogen, and this is now standard practice. In the WHI study** (see earlier), **an estrogen-progestin combination increased the total risk of breast cancer by 24%, translating into an absolute increase in attributable cases of disease of 6 per 1000 women requiring 3 or more years of treatment. In women without a uterus who received estrogen alone, the relative risk of breast cancer was actually decreased by 23%,** and the decrease only narrowly missed reaching statistical significance. **It appears to be the progestin component that plays a major role in the increased risk of breast cancer.** Estrogens increase cholesterol levels in bile and cause a relative twofold to threefold increase in gallbladder disease. The HERS study and the WHI study indicate that combination estrogen-progestin does not protect against coronary heart disease, but the specific populations studied and the specific preparations utilized may prohibit generalization of these conclusions to other preparations, doses, and patient populations. It is clear, however, that the **risk of thromboembolic disease is clearly elevated in women taking oral estrogen, both healthy women and women with preexisting cardiovascular disease. In the WHI study the estrogen-progestin combination was associated with an increase in eight cases of stroke per 10,000 women and a similar increase in pulmonary embolism.** Loose and Stancel (2006) also mention as possibilities altered cognition, changes in carbohydrate and lipid metabolism, hypertension, nausea, migraine, and changes in mood.

Future Possibilities

Peripherally Acting Drugs. A few new peripheral targets suitable for treatment have been identified and are under evaluation.

Vitamin D_3 Receptor Analogues. Rat and human bladders were shown to express receptors for vitamin D (Crescioli et al, 2005), which makes it conceivable that the bladder may also be a target for vitamin D. Analogues of vitamin D_3 have also been shown to inhibit benign prostatic hyperplasia (BPH) cell proliferation and to counteract the mitogenic activity of potent growth factors for BPH cells (Crescioli et al, 2002, 2003, 2004). Experiments in rats with bladder outflow obstruction (Schröder et al, 2006) showed that one of the analogues, BXL-628, at nonhypercalcemic doses, did not prevent bladder hypertrophy but reduced the decrease in contractility of the bladder smooth muscle that occurred with increasing bladder weight (Schröder et al, 2006). The mechanism of action for the effects has not been clarified. However, elocalcitol was shown to have an inhibitory effect on the RhoA/Rho kinase pathway (Morelli et al, 2007). Upregulation of this pathway has been associated with bladder changes associated with diabetes, outflow obstruction, and DO (Peters et al, 2006; Christ and Andersson, 2007). The effect of elocalcitol on prostate volume was evaluated in patients with BPH, and it was found that BXL628 was able to arrest prostate growth within 12 weeks in men aged 50 years or older with prostatic volume of 40 mL or more (Colli et al, 2006). In an RCT enrolling 120 female patients with OAB, in which the primary end point was an increase in the mean volume voided, a significant increase versus placebo (22% vs. 11%) was demonstrated (Colli et al, 2007). **Whether vitamin D receptor agonism (monotherapy or in combination) will be a useful alternative for the treatment of LUTS/OAB requires further RCTs.**

Centrally Acting Drugs. Many parts of the brain seem to be activated during storage and voiding (see, Griffiths 2007; Fowler et al, 2008; Griffiths and Tadic, 2008), and there is increasing interest in drugs modulating the micturition reflex by a central action (Andersson and Pehrson, 2003). Several drugs used for pain treatment also affect micturition, with morphine and some antiepileptic drugs being a few examples. However, CNS mechanisms have so far not been preferred targets for drugs aimed to treat OAB, because selective actions may be difficult to obtain. Holstege (2005), reviewing some of the CNS mechanisms involved in micturition, including the periaqueductal gray matter and the pontine micturition center, suggested that the problem in OAB or urgency incontinence is at the level of the periaqueductal gray matter or pontine micturition center and their connections, and possible treatments for this condition, should target the micturition pathways at that level.

Gonadotropin-Releasing Hormone Antagonists. The beneficial effects of the 5α-reductase inhibitors finasteride and dutasteride in the treatment of male LUTS are well documented. The efficacy of other hormonal treatments, for example, antiandrogens or gonadotropin-releasing hormone (GNRH; also known as luteinizing hormone-releasing hormone [LHRH]) agonists is either poor or at the expense of unacceptable side effects such as medical castration associated with hot flushes, decrease of potency and libido, and negative effects on bone density and cardiac health after long-term androgen ablation (Schroeder et al, 1986; Peters et al, 1987; Bosch et al, 1989; Eri and Tveter, 1993). With LHRH antagonists, submaximal, noncastrating blockade of the androgen testosterone and consequently of dihydrotestosterone can be achieved, thus avoiding medical castration.

Debruyne and coworkers (2008) demonstrated in a phase 2 RCT that the LHRH antagonist cetrorelix given subcutaneously weekly for 20 weeks to 140 men with LUTS (IPSS ≥ 13, peak urinary flow rates 5 to 13 mL/sec) rapidly caused a significant improvement in the mean IPSS: the peak decrease was –5.4 to –5.9 versus –2.8 for placebo. All dosage regimens tested were well tolerated, and the authors concluded that the drug offered a safe and effective treatment of male LUTS. **Further studies are needed to assess whether this therapeutic principle is a useful addition to the current treatment alternatives.**

Gabapentin. Gabapentin is one of the new first-generation antiepileptic drugs that expanded its use into a broad range of neurologic and psychiatric disorders (Striano and Striano, 2008). It was originally **designed as an anticonvulsant γ-aminobutyric acid (GABA) mimetic capable of crossing the blood-brain barrier** (Maneuf et al, 2003). The effects of gabapentin, however, do not appear to be mediated through interaction with GABA receptors, and its mechanism of action remains controversial (Maneuf et al, 2003). It has been suggested that it acts by binding to a subunit of the $\alpha_2\delta$ unit of voltage-dependent Ca^{2+} channels

(Gee et al, 1996; Striano and Striano, 2008). Gabapentin is also widely used not only for seizures and neuropathic pain but also for many other indications, such as anxiety and sleep disorders, because of its apparent lack of toxicity.

Carbone and coworkers (2006) reported on the effect of gabapentin on neurogenic DO. They found a positive effect on symptoms and significant improvement in urodynamic parameters and suggested that the effects of the drug should be explored in further controlled studies in both neurogenic and non-neurogenic DO. Kim and colleagues (2004) studied the effects of gabapentin in patients with OAB and nocturia not responding to antimuscarinic agents. They found that 14 of 31 patients experienced improvement of their symptoms with orally administered gabapentin. The drug was generally well tolerated, and the authors suggested that it can be considered in selective patients when conventional modalities have failed. It is possible that gabapentin and other $\alpha_2\delta$ ligands (e.g., pregabalin and analogues) will offer new therapeutic alternatives.

Tramadol. Tramadol is a well-known analgesic drug (Grond and Sablotzski, 2004). By itself it is a weak μ-receptor agonist, but it is metabolized to several different compounds, some of them almost as effective as morphine at the μ receptor. However, the drug (metabolites) also inhibits serotonin (5-HT) and norepinephrine reuptake (Grond and Sablotzski, 2004). This profile is of particular interest because both μ-receptor agonism and amine reuptake inhibition may be useful principles for treatment of LUTS/OAB/DO, as shown in a placebo-controlled study with duloxetine (Steers et al, 2008).

In rats, tramadol abolished experimentally induced DO caused by cerebral infarction (Pehrson et al, 2003). Tramadol also inhibited DO induced by apomorphine in rats (Pehrson and Andersson, 2003), a crude model of bladder dysfunction in Parkinson disease. Singh and associates (2008) gave tramadol epidurally and found the drug to increase bladder capacity and compliance and to delay filling sensations without adverse effects on voiding. Safarinejad and Hosseini (2006) evaluated in a double-blind, placebo-controlled randomized study the efficacy and safety of tramadol in patients with idiopathic DO. A total of 76 patients 18 years or older were given 100 mg tramadol in sustained-release form every 12 hours for 12 weeks. Clinical evaluation was performed at baseline and every 2 weeks during treatment. Tramadol significantly ($P < .01$) reduced the number of incontinence periods per 24 hours from 3.2 ± 3.3 to 1.6 ± 2.8 and induced improvements in urodynamic parameters. The main adverse event was nausea. It was concluded that, in patients with non-neurogenic DO, tramadol provided beneficial clinical and urodynamic effects. Even if tramadol may not be the best suitable drug for treatment of LUTS/OAB the study suggests efficacy for modulation of micturition via the μ receptor.

NK1-Receptor Antagonists. The main endogenous tachykinins substance P (SP), neurokinin A (NKA), and neurokinin B (NKB) and their preferred receptors NK1, NK2, and NK3, respectively, have been demonstrated in various CNS regions, including those involved in micturition control (Lecci and Maggi, 2001; Covenas et al, 2003; Saffroy et al, 2003). NK1 receptor–expressing neurons in the dorsal horn of the spinal cord may play an important role in DO, and tachykinin involvement via NK1 receptors in the micturition reflex induced by bladder filling has been demonstrated (Ishizuka et al, 1994) in normal and, more clearly, rats with bladder hypertrophy secondary to bladder outlet obstruction. Capsaicin-induced DO was reduced by blocking NK1 receptor–expressing neurons in the spinal cord, using intrathecally administered substance P/saponin conjugate (Seki et al, 2005). Furthermore, blockade of spinal NK1 receptor could suppress detrusor activity induced by dopamine receptor (levodopa) stimulation (Ishizuka et al, 1995b).

In conscious rats undergoing continuous cystometry, antagonists of both NK1 and NK2 receptors inhibited micturition, decreasing micturition pressure and increasing bladder capacity at low doses and inducing dribbling incontinence at high doses. This was most conspicuous in animals with outflow obstruction (Gu et al, 2000). Intracerebroventricular administration of NK1 and NK2 receptor antagonists to awake rats suppressed detrusor activity induced by dopamine receptor (levodopa) stimulation (Ishizuka et al, 2000). Taken together, available information suggests that spinal and supraspinal NK1 and NK2 receptors may be involved in micturition control.

Aprepitant, an NK-1 receptor antagonist used for treatment of chemotherapy-induced nausea and vomiting (Massaro and Lenz, 2005), was reported to improve symptoms of OAB in postmenopausal women with a history of urgency incontinence or mixed incontinence (with predominantly urgency urinary incontinence), as shown in a well-designed pilot RCT (Green et al, 2006). The primary end point was percent change from baseline in average daily micturitions assessed by a voiding diary. Secondary end points included average daily total urinary incontinence and urgency incontinence episodes and urgency episodes. Aprepitant significantly ($P < .003$) decreased the average daily number of micturitions (–1.3 ± 1.9) compared with placebo (–0.4 ± 1.7) at 8 weeks. The average daily number of urgency episodes was also significantly ($P < .047$) reduced (–23.2 ± 32%) compared with placebo (–9.3 ± 40%) and so were the average daily number of urgency incontinence and total urinary incontinence episodes, although the difference was not statistically significant. The large standard errors and the low placebo results are atypical for OAB trials. Aprepitant was generally well tolerated, and the incidence of side effects, including dry mouth, was low. The results of this initial proof of concept study suggest that NK-1 receptor antagonism holds promise as a potential treatment approach for OAB.

Drug Treatment of Overactivity in Augmented or Intestinal Neobladders

With regard to the subject of overactivity in bowel augmented or intestinal neobladders, Andersson and associates (1992) reviewed this subject and its pharmacologic treatment. They noted a few instances of positive results with drugs given systematically, but locally applied agents were believed to offer more promise. Pure antimuscarinic agents had produced few good results, either locally or systemically. Oxybutynin had shown some good results with local therapy but poor results with systemic therapy. The α- and β-AR agonists had shown little or no effects. Other possibilities mentioned included opioid agonists (diphenoxylate and loperamide), Ca^{2+} antagonists, K^+ channel openers, and nitric oxide donors. Apostolidis and colleagues (2007) reported a case of successful treatment with BoNT-A after failed augmentation ileocystoplasty.

Increasing Outlet Resistance

Many factors seem to be involved in the pathogenesis of SUI: urethral support, vesical neck function, and function of the nerves and musculature of the bladder, urethra, and pelvic floor (DeLancey, 1997; Mostwin et al, 2005). Anatomic factors cannot be treated pharmacologically. However, **women with SUI have lower resting urethral pressures than age-matched continent women** (Henriksson et al, 1979; Hilton and Stanton,

1983), **and because it seems likely that there is a reduced urethral closure pressure in most women with SUI it seems logical to increase urethral pressure to improve the condition.**

Factors that may contribute to urethral closure include tone of urethral smooth and striated muscle and the passive properties of the urethral lamina propria, in particular its vasculature. The relative contribution to intraurethral pressure of these factors is still subject to debate. However, there is ample pharmacologic evidence that a substantial part of urethral tone is mediated through stimulation of α-ARs in the urethral smooth muscle by released norepinephrine (Andersson, 1993; Andersson and Wein, 2004). A contributing factor to SUI, mainly in elderly women with lack of estrogen, may be lack of mucosal function. **The pharmacologic treatment of SUI aims at increasing intraurethral closure forces by increasing the tone in the urethral smooth and striated muscles. Several drugs may contribute to such an increase** (Andersson, 1988; Zinner et al, 2004b), **but relative lack of efficacy and/or side effects have limited their clinical use** (Table 68–4).

α-Adrenergic Receptor Agonists

Several drugs with agonistic effects on α-ARs have been used in the treatment of SUI (Table 68–5). However, **ephedrine** and norephedrine (**phenylpropanolamine** [PPA]) seem to have been the most widely used (Andersson et al, 2002). The original Agency for Healthcare Policy and Research Guidelines (1992) reported eight RCTs with PPA 50 mg twice daily for SUI in women. Percent cures (all figures refer to percent effect on drug minus percent effect on placebo) were listed as 0% to 14%, percent reduction in continence as 19% to 60%, and percent side effects and percent dropouts as 5% to 33% and 0% to 4.3%, respectively. The most recent Cochrane review on the subject (Alhasso et al, 2005) assessed RCTs or quasi-RCTs in adults with SUI that included an adrenergic agonist drug in at least one arm of the trial. There were no controlled studies reported on the use of such drugs in men. Twenty-two eligible trials were identified, 11 of which were crossover trials, which included 1099 women, 673 of whom received an adrenergic drug (PPA in 11, midrodrine in 2, norepinephrine in 3, clenbuterol in 3, terbutaline in 1, eskornade in 1, and RO 115-1240 in 1). The authors concluded "there was weak evidence to suggest that use of an adrenergic agonist was better than placebo treatment." The limited evidence suggested that such drugs were better than placebo in reducing the number of pad changes and incontinence episodes and in improving subjective symptoms. There was not enough evidence to evaluate the merits of an adrenergic agonist compared with estrogen, whether used alone or in combination. Regarding adverse events, the review reported similar numbers with adrenergic, placebo, or alternative drug treatment. Over 25% of subjects reported such effects, but when these consisted of effects due to adrenergic stimulation they caused discontinuation in only 4% of the total.

The date of the most recent amendment to this review is listed as May 15, 2007; no new trials were identified at that time. The update of 2005 (Alhasso et al, 2005) included seven new RCTs over the 2003 report, cited in the last consultation. The final statement on "what's new" reads, **"The conclusions still provide limited support for the use of adrenergics but side effects may cause dropout, and some side effects may be dangerous.** Further trials are needed."

Ephedrine and PPA lack selectivity for urethral α-ARs and can increase blood pressure and cause sleep disturbances, headache, tremor, and palpitations (Andersson et al, 2002). Kernan and coworkers (2000) reported **the risk of hemorrhagic stroke to be 16 times higher in women younger than 50 years of age who had been taking PPA as an appetite suppressant** (statistically significant) and 3 times higher in women who had been taking the drug for less than 24 hours as a cold remedy (not statistically significant). There was no increased risk in men. **PPA has been removed from the market in the United States.**

Numerous case reports of adverse reactions due to ephedra alkaloids exist, and some (Bent et al, 2003) had suggested that sale of these compounds as a dietary supplement be restricted or banned. In December 2003 the U.S. FDA decreed such a ban, a move that has survived legal appeal.

Midodrine and methoxamine stimulate α_1-ARs with some degree of selectivity. According to the RCTs available, the effectiveness of these drugs is moderate and the clinical usefulness seems to be limited by adverse effects (Weil et al, 1998; Radley et al, 2001; Alhasso et al, 2003).

Attempts continue to develop agonists with relative selectivity for the human urethra. Musselman and associates (2004) reported on a phase 2 randomized crossover study with Ro

Table 68–4.

Drugs Used in the Treatment of Stress Incontinence (ICI, 2008; Andersson et al, 2009)

DRUG	LEVEL OF EVIDENCE	GRADE OF RECOMMENDATION
Duloxetine	1	B
Imipramine	3	D
Clenbuterol	3	C
Methoxamine	2	D
Midodrine	2	C
Ephedrine	3	D
Norephedrine (phenylpropanolamine)	3	D
Estrogen	2	D

Table 68–5.

Drugs Used in the Treatment of Overflow Incontinence (ICI 2004)

DRUG	LEVEL OF EVIDENCE	GRADE OF RECOMMENDATION
α-Adrenoceptor Antagonists		
Alfuzosin	4	C
Doxazosin	4	C
Prazosin	4	C
Terazosin	4	C
Tamsulosin	4	C
Phenoxybenzamine	4	NR
Muscarinic Receptor Agonists		
Bethanechol	4	D
Carbachol	4	D
Cholinesterase Inhibitors		
Distigmine	4	D
Other Drugs		
Baclofen	4	C
Benzodiazepines	4	C
Dantrolene	4	C

NR, not recommended.

115-1240, a peripheral active selective $\alpha_{1A/1L}$ adrenergic receptor partial agonist (Blue et al, 2004) in 37 women with mild to moderate SUI. A moderate, positive effect was demonstrated, but side effects have apparently curtailed further development of the drug.

β-Adrenergic Receptor Antagonists

The theoretical basis for the use of β-AR antagonists in the treatment of SUI is that blockade of urethral β-ARs may enhance the effects of norepinephrine on urethral α-ARs. Propranolol has been reported to have beneficial effects in the treatment of SUI (Gleason et al, 1974; Kaisary, 1984) **but there are no RCTs supporting such an action.** In Gleason and colleagues' (1974) study the beneficial effects become manifest only after 4 to 10 weeks of treatment—a phenomenon difficult to explain. Donker and Van der Sluis (1976) reported that β blockade did not change the urethral pressure profile in normal women. Although suggested as an alternative to α-AR agonists in patients with SUI and hypertension, these agents may have major potential cardiac and pulmonary side effects of their own, related to their therapeutic β-AR blockade.

β-Adrenergic Receptor Agonists

β-AR stimulation is generally conceded to decrease urethral pressure (Andersson, 1993), but **β_2-AR agonists have been reported to increase the contractility of some fast-contracting striated muscle fibers and suppress that of slow-contracting fibers of others** (Fellenius et al, 1980). **Some β-AR agonists also stimulate skeletal muscle hypertrophy—in fast-twitch more so than slow-twitch fibers** (Kim et al, 1992). **Clenbuterol** has been reported to potentiate the field stimulation–induced contraction in rabbit isolated periurethral muscle preparations, an action that is suppressed by propranolol and greater than that produced by isoproterenol (Kishimoto et al, 1991). These authors were the first to report an increase in urethral pressure with clinical use of clenbuterol and to speculate on its potential for the treatment of SUI. Yamanishi and associates (1994) reported an inotropic effect of clenbuterol and terbutaline on the fatigued striated urethral sphincter of dogs that was abolished by β-AR blockade.

Yasuda and coworkers (1993) described the results of a double-blind placebo-controlled trial with clenbuterol agent in 165 women with SUI. Positive statistical significance was achieved for subjective evaluation of incontinence frequency, pad usage per day, and overall global assessment. Pad weight decreased from 11.7 ± 17.9 g to 6.0 ± 12.3 g for drug and from 18.3 ± 29.0 g to 12.6 ± 24.7 g for placebo, raising questions about the comparability of the two groups. The "significant" increase in maximum urethral closure pressure was from 46.0 ± 18.2 cm H_2O to 49.3 ± 19.1 cm H_2O, versus a change of –1.5 cm H_2O in the placebo group. Fifty-six of 77 patients in the clenbuterol group reported some degree of improvement versus 48 of 88 in the placebo group. The positive effects were suggested to be a result of an action on urethral striated muscle and/or the pelvic floor muscles. Ishiko and associates (2000) investigated the effects of clenbuterol on 61 female patients with SUI in a 12-week randomized study, comparing drug therapy to pelvic floor exercises. The frequency and volume of SUI and the patient's own impression were used as the basis for the assessment of efficacy. The improvement of incontinence was 76.9%, 52.6%, and 89.5% in the respective groups. In an open study, Noguchi and colleagues (1997) reported positive results with clenbuterol (20 mg twice daily for 1 month) in 9 of 14 patients with mild to moderate SUI after radical prostatectomy. No subsequent published reports have appeared. **Further well-designed RCTs documenting the effects of clenbuterol are needed to adequately assess its potential as a treatment for SUI.**

Serotonin-Norepinephrine Uptake Inhibitors

Imipramine. Imipramine, among several other pharmacologic effects, inhibits the reuptake of norepinephrine and serotonin in adrenergic nerve endings. In the urethra this can be **expected to enhance the contractile effects of norepinephrine on urethral smooth muscle.** Gilja and colleagues (1984) reported in an open study on 30 women with SUI that imipramine 75 mg daily produced subjective continence in 21 patients and increased mean maximum urethral closure pressure from 34 to 48 mm Hg. A 35% cure rate was reported by pad test and, in an additional 25%, a 50% or more improvement.

Lin and coworkers (1999) assessed the efficacy of imipramine (25 mg imipramine three times a day for 3 months) as a treatment of genuine SUI in 40 women. A 20-minute pad test, uroflowmetry, filling and voiding cystometry, and stress urethral pressure profile were performed before and after treatment. The efficacy of "successful treatment" was 60% (95% CI 11.8 to 75.2). **There are no RCTs on the effects of imipramine on SUI.** No subsequent published reports have appeared.

Duloxetine. As mentioned previously, duloxetine is a serotonin-norepinephrine reuptake inhibitor that has been shown **to significantly increase sphincteric muscle activity during the filling/storage phase of micturition in the cat acetic acid model of irritated bladder function** (Thor et al, 1995; Katofiasc et al, 2002). The sphincteric effects were reversed by α_1-adrenergic (prazosin) and 5-HT_2 serotonergic (LY 53857) antagonism, whereas the bladder effects were mediated by temporal prolongation of the actions of serotonin and norepinephrine in the synaptic cleft (Fraser et al, 2003). Duloxetine is lipophilic, well absorbed, and extensively metabolized (CYP2D6). Its plasma half-life is approximately 12 hours (Sharma et al, 2000).

There are many studies, including RCTs, documenting the effects of duloxetine in SUI (Norton et al, 2002; Dmochowski et al, 2003a; Cardozo et al, 2004a; Millard et al, 2004; Van Kerrebroeck et al, 2004; Ghoneim et al, 2005; Kinchen et al, 2005; Hurley et al, 2006; Castro-Diaz et al, 2007; Bump, 2008). A Cochrane review of the effects of duloxetine for SUI in women is available, the last substantive amendment listed as May 25, 2005 (Mariappan et al, 2005). Fifteen reports were deemed eligible for analysis, nine primary studies, and six additional reports related to one or two of the primary references. An additional analysis "performed under the auspices of the Cochrane Incontinence Group" was performed on just the nine primary trials comparing duloxetine and placebo and published separately (Mariappan et al, 2007). The results can be summarized as follows. **Subjective "cure" in the duloxetine 80 mg daily (40 mg twice daily) group was higher than in the placebo group** (10.8% vs. 7.7%, overall RR = 1.42; 95% CI, 1.02 to 1.98; $P = .04$). The **estimated absolute size of effect was about 3 more patients cured of every 100 treated. Objective cure data, available from only one trial, showed no clear drug/placebo difference. Duloxetine showed greater improvement in Incontinence Quality of Life score (weighted mean difference for 80 mg:** 4.5; 95% CI 2.83 to 6.18, $P < .00001$). **Patient global impression of improvement (PGI-I) data also favored the drug** (RR for better health status 1.24, 95% CI 1.14 to 1.36; $P < .00001$). Adverse effects in six trials were analyzed. These were reported by 71% of drug subjects and 59% of those allocated to placebo. **Nausea was the most common adverse event,**

and the incidence ranged from 23% to 25% and was the main reason for discontinuation. **Other side effects reported were vomiting, constipation, dry mouth, fatigue, dizziness, and insomnia** for an overall RR of 1.30 (95% CI 1.23 to 1.37). Across these six trials 17% in the drug group and 4% in the placebo study arms withdrew. In the 2007 article the authors conclude by saying that **further research is needed as to whether management policies incorporating duloxetine are clinically effective and cost effective compared with other current minimally invasive and more invasive approaches in patients with varying severity of SUI and that "longer term experience is now a priority to determine whether there is sustained efficacy during and after duloxetine use and to rule out complications."** Hashim and Abrams (2006) suggested that to reduce the risk of nausea that therapy start with a dose of 20 mg twice daily for 2 weeks and then to increase to the recommended 40 mg twice-daily dosage.

Duloxetine is **licensed at 40 mg twice daily for the treatment of SUI in the European Union** (European Medicines Agency, 2005) for women with moderate to severe SUI (defined as 14 or more episodes per week). It was **withdrawn from the U.S. FDA consideration process for the treatment of SUI but is approved for the treatment of major depressive disorder (20 to 30 mg twice daily initially, 60 mg once-daily maintenance), diabetic peripheral neuropathic pain (60 mg once daily), and generalized anxiety disorder (60 mg once daily). The product information contains a "black box" warning of "increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for major depressive disorder and other psychiatric disorders,"** noting also that "depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide" (Prescribing Information, revised December 2007, Eli Lilly and Company, Indianapolis, IN). Other warnings and precautions in the U.S. product information for psychiatric indications, not SUI, include hepatotoxicity (not to be used in patients with substantial alcohol use or chronic liver disease), orthostatic hypotension, serotonin syndrome (general statement regarding selective serotonin reuptake inhibitors, abrupt discontinuation (may result in dizziness, paresthesias, irritability, and headache), inhibitors of CYP1H2 or thioridazine (do not administer concomitantly), potent inhibitors of CYP2D6 (may increase concentration), and others.

Male Stress Urinary Incontinence

Although a problem of significant magnitude, especially after total prostatectomy for cancer, the pharmacologic treatment of male SUI is an area that has received relatively little attention. Tsakiris and coworkers (2008) searched for articles on this subject published between 1966 and June 2007 and did a generalized database search in addition. Nine trials were identified using α-AR agonists, β_2 antagonists, or serotonin-norepinephrine reuptake inhibitors. Only one of these included a comparison arm (Filocamo et al, 2007), 40 mg twice daily duloxetine plus pelvic floor exercises versus pelvic floor exercises with placebo. The results suggested a positive effect of drug but were a bit confusing. Of those patients completing the 4-month trial (92/112), 78% of the drug-treated patients versus 52% of those in the placebo group were dry. However, 1 month after the end of the study the corresponding figures were 46% versus 73%, a shift still observed 2 months later. The authors of the review article suggest further larger and well-designed studies on duloxetine for this potential usage.

Estrogens for Stress Incontinence

Estrogen-sensitive tissues of the bladder, urethra, and pelvic floor are all potentially important in maintaining the continence mechanism in women. For women to remain continent during increases in intra-abdominal pressure the urethral pressure must exceed the intravesical pressure at all times except during micturition. **There are four estrogen-sensitive functional layers that could play a part in the maintenance of a positive urethral pressure and closure mechanism: (1) the epithelium, including the mucosal seal mechanism; (2) the vasculature; (3) the connective tissue component; and (4) the muscular components,** including the smooth muscle of the bladder neck and urethra and the striated muscle, which is both intrinsic to the urethra and extrinsic (a part of the pelvic floor striated musculature). If estrogen did have a positive effect on SUI it could be by means of an effect on any or all of the structures (Andersson et al, 2009).

The role of estrogen in the treatment of SUI has been controversial, even though there are a number of reported studies (see Hextall, 2000). Some have given promising results, but this may be because they were observational, not randomized, blinded, or controlled. The situation is further complicated by the fact that a number of different types of estrogen have been used with varying doses, routes of administration, and durations of treatment. Fantl and coworkers (1996) treated 83 hypoestrogenic women with urodynamic evidence of genuine SUI and/or detrusor instability with conjugated equine estrogens 0.625 mg and medroxyprogesterone 10 mg cyclically for 3 months. Controls received placebo tablets. At the end of the study period the clinical and quality of life variables had not changed significantly in either group. Jackson and associates (1999) treated 67 postmenopausal women with genuine SUI or mixed incontinence with estradiol valerate 2 mg or placebo daily for 6 months. There was no significant change in objective outcome measures.

There have been two meta-analyses performed that have helped to clarify the situation further. In the first, a report by the Hormones and Urogenital Therapy (HUT) committee, the use of estrogens to treat all causes of incontinence in postmenopausal women was examined (Fantl et al, 1994). Of 166 articles identified, which were published in English between 1969 and 1992, only 6 were controlled trials and 17 uncontrolled series. The results showed that there was a significant subjective improvement for all patients and those with genuine SUI. However, assessment of the objective parameters revealed that there was no change in the volume of urine lost. Maximum urethral closure pressure did increase significantly, but this result was influenced by only one study showing a large effect. In the second meta-analysis, Sultana and Walters (1990) reviewed 8 controlled and 14 uncontrolled prospective trials and included all types of estrogen treatment. They also found that estrogen therapy was not an efficacious treatment of SUI but may be useful for the often associated symptoms of urgency and frequency. **Estrogen when given alone therefore does not appear to be an effective treatment for SUI.** However, several studies have shown that it may have a role in combination with other therapies (for combination with α-AR agonists, see earlier). In a randomized trial, Ishiko and coworkers (2001) compared the effects of the combination of pelvic floor exercise and estriol (1 mg/day) in 66 patients with postmenopausal SUI. Efficacy was evaluated every 3 months based on stress scores obtained from a questionnaire. They found a significant decrease in stress score in mild and moderate SUI patients in both groups 3 months after the start of therapy and concluded

that combination therapy with estriol plus pelvic floor exercise was effective and capable of serving as first-line treatment for mild SUI.

These conclusions still seem valid. Thus **reviews of recent literature agree on the fact that "estrogen therapy has little effect in the management of urodynamic SUI"** (Al-Badr et al, 2003; Robinson and Cardozo, 2003a, 2003b).

Circumventing the Problem

Vasopressin Analogues: Desmopressin

Desmopressin (1-desamino-8-D-arginine vasopressin; DDAVP) is a **synthetic vasopressin analogue with a pronounced antidiuretic effect but practically lacking vasopressor actions** (Andersson et al, 1988; Vande Walle et al, 2006). It is now widely used as **a treatment for primary nocturnal enuresis** (Nevéus et al, 1999; Glazener and Evans, 2002; Andersson et al, 2009). Studies have shown that one of the factors that can contribute to nocturnal enuresis in children, and probably in adults, is lack of a normal nocturnal increase in plasma vasopressin, which results in high nocturnal urine production (Rittig et al, 1989; Matthiesen et al, 1996; Nørgaard et al, 1997; Hjalmas, 1999). By decreasing the nocturnal production of urine, beneficial effects may be obtained in enuresis and nocturia. However, the drug may also have stimulatory effects on the CNS, as found in rats (DiMichele et al, 1996). Several, controlled, double-blind investigations have shown intranasal administration of desmopressin to be effective in the treatment of nocturnal enuresis in children (Nevéus et al, 1999; Glazener and Evans, 2002; Andersson et al, 2009). The dose used in most studies has been 20 µg intranasally at bedtime. However, the drug is orally active, even if the bioavailability is low (less than 1% compared with 2% to 10% after intranasal administration), and its efficacy in primary nocturnal enuresis in children and adolescents has been documented in randomized, double-blind, placebo-controlled studies (Janknegt et al, 1997; Skoog et al, 1997; Andersson et al, 2009).

Positive effects of desmopressin on nocturia in adults have been documented (Månsson et al, 1980; Hilton and Stanton, 1982; Asplund and Aberg, 1993; Asplund et al, 1999; Chancellor et al, 1999; Andersson et al, 2009). Nocturnal frequency and enuresis due to idiopathic DO responded favorably to intranasal desmopressin therapy even when previous treatment with "antispasmodics" had been unsuccessful (Hilton and Stanton, 1982). Also in patients with multiple sclerosis, desmopressin was shown in controlled studies to reduce nocturia and micturition frequency (Hilton et al, 1983; Kinn and Larsson 1990; Eckford et al, 1994; Fredrikson et al, 1996; Ferreira and Letwin, 1998; Andersson et al, 2009). In multiple sclerosis, effects on daytime frequency also have been documented (Hoverd and Fowler, 1998). Furthermore, desmopressin was shown to be successful in treating nocturnal enuresis in patients with spina bifida with diurnal incontinence (Horowitz et al, 1997).

Oral desmopressin also has proved to be effective in the treatment of nocturia. In a randomized double-blind study, Mattiasson and colleagues (2002) investigated the efficacy and safety of oral desmopressin in the treatment of nocturia in men. A 3-week dose-titration phase established the optimum desmopressin dose (0.1, 0.2, or 0.4 mg); and, after a 1-week "washout" period, patients who responded in the dose-titration period were randomized to receive the optimal dose of desmopressin or placebo in a double-blind design for 3 weeks. In all, 151 patients entered the double-blind period (86 treated with desmopressin, 65 with placebo). In the desmopressin group, 28 (34%) patients and in the placebo group, 2 (3%) patients had significantly fewer than half the number of nocturnal voids relative to baseline; the mean number of nocturnal voids decreased from 3.0 to 1.7 and from 3.2 to 2.7, respectively, reflecting a mean decrease of 43% and 12%. The mean duration of the first sleep period increased by 59% (from 2.7 to 4.5 hours) in the desmopressin group, compared with an increase of 21% (from 2.5 to 2.9 hours) in the placebo group. The mean nocturnal diuresis decreased by 36% (from 1.5 to 0.9 mL/min) in the desmopressin group and by 6% (from 1.7 to 1.5 mL/min) in the placebo group. The mean ratio of night per 24-hour urine volume decreased by 23% and 1%, and the mean ratio of night/day urine volume decreased by 27% and increased by 3% for the desmopressin and placebo groups, respectively. In the double-blind treatment period, similar numbers of patients had adverse events: 15 (17%) patients in the desmopressin and 16 (25%) patients in the placebo group. Most adverse events were mild. Serum sodium levels were less than 130 mmol/L in 10 (4%) patients, and this occurred during dose titration. The authors concluded that orally administered desmopressin is an effective and well-tolerated treatment for nocturia in men.

Lose and associates (2003) found similar results in women. In the double-blind phase of their study, 144 patients were randomly assigned to groups (desmopressin, n = 72; placebo, n = 72). For desmopressin, 33 (46%) patients had a 50% or greater reduction in nocturnal voids against baseline levels compared with 5 (7%) patients receiving placebo. The mean number of nocturnal voids, duration of sleep until the first nocturnal void, nocturnal diuresis, and ratios of nocturnal per 24 hours and nocturnal per daytime urine volumes changed significantly in favor of desmopressin versus placebo. In the dose-titration phase, headache (22%), nausea (8%), and hyponatremia (6%) were reported.

Robinson and colleagues (2004) introduced antidiuresis as a new concept in managing female daytime urinary incontinence. In a multicenter, multinational, randomized, double-blind, placebo-controlled, crossover exploratory study of women (aged 18 to 80 years) complaining of severe daytime urinary incontinence, 60 received study medication (safety population) and 57 completed the study. The primary efficacy end point was the number of periods with no leakage for 4 hours after dosing. There was a higher mean incidence of periods with no leakage in the first 4 hours on desmopressin, at 62 (35)%, than on placebo, at 48 (40)%, and during the first 8 hours, at 55 (37)% versus 40 (41)%. There was also a higher frequency of dry days on desmopressin than on placebo; 36% of patients had no leakage on virtually all treatment days (6 or 7) for 4 hours after dosing. The time from dosing to first incontinence episode was longer on desmopressin, at 6.3 (2.5) hours versus 5.2 (3.3) hours whereas the volume leaked per incontinence episode was lower on desmopressin than placebo. The total volume voided was consistently lower on desmopressin, at 1180 (58) mL versus 1375 (57) mL, over the 24-hour period after administration. There were no serious or severe adverse events reported, and it was concluded that desmopressin is an effective and safe treatment in women with daytime urinary incontinence.

Even if side effects are uncommon during desmopressin treatment there is a risk of water retention and hyponatremia (Robson et al, 1996; Schwab and Ruder, 1997). In elderly patients it was recommended that the serum sodium concentration should be measured before and after a few days of treatment (Rembratt et al, 2003). **Currently there are no predictive factors about who may be at increased risk of developing hyponatremia** (Andersson et al, 2009). However,

to reduce the risk of hyponatremia it is recommended that patients older than age 79 years or with a 24-hour urine volume more than 28 mL/kg should not be given desmopressin (Rembratt et al, 2006). In those older than age 65 years, serum sodium levels should be checked at baseline and at 3 days and 7 days after beginning treatment or changing dose. **It is probably good medical practice that these serum sodium measurements are also applied to those younger than 65 years of age, as well as checking sodium levels at 3 weeks after treatment or change of dose because there is the potential for levels of sodium to mean change within a 3-week period** (Callreus et al, 2005). One study showed that hyponatremia can develop after 6 months of administration, although this is not clinically significant (Bae et al, 2007), and therefore serum sodium levels may be checked at 6 months after administration and then every 6 months thereafter. Long-term use of desmopressin does not seem to affect baseline antidiuretic hormone secretion (Bae et al, 2007). The fluid intake will need to be limited to a minimum from 1 hour before the dose until 8 hours afterward, and there needs to be periodic blood pressure and weight measurements to monitor for fluid overload.

Desmopressin is a well-documented therapeutic alternative in pediatric nocturnal enuresis and also is effective in adults with nocturia of polyuric origin. Whether it will be an alternative for managing daytime OAB symptomatology, including urgency, frequency, and urinary incontinence, requires further documentation.

Diuretics

Another circumventive pharmacologic approach is to give a rapid-acting loop diuretic 4 to 6 hours before bedtime. This, of course, assumes the nocturia is not caused by obstructive uropathy. A randomized, double-blind crossover study on this approach using bumetanide in a group of 14 general practice patients was reported by Pedersen and Johansen (1988). Control nocturia episodes per week averaged 17.5; with placebo this decreased to 12 (!) and with drug to 8. Bumetanide was preferred to placebo by 11 of 14 patients.

PHARMACOLOGIC THERAPY TO FACILITATE BLADDER EMPTYING

Increasing Intravesical Pressure/Bladder Contractility

Parasympathomimetic Agents

Because a major portion of the final common pathway in physiologic bladder contraction is stimulation of parasympathetic postganglionic muscarinic cholinergic receptor sites, agents that imitate the actions of acetylcholine might be expected to be effective in treating patients who cannot empty their bladder because of inadequate bladder contractility. Acetylcholine, which is a quaternary amine, cannot be used for therapeutic purposes because of its action at both muscarinic and nicotinic receptors; it is rapidly hydrolyzed by acetylcholinesterase and by butyrylcholinesterase (Brown and Taylor, 2006). Many acetylcholine-like drugs exist, but only bethanechol chloride exhibits a relatively selective in-vitro action on the urinary bladder and gut with little or no nicotinic action (Brown and Taylor, 2006). **Bethanechol is cholinesterase resistant and causes an in-vitro contraction of smooth muscle from all areas of the bladder** (see Chapter 60).

Bethanechol, or agents similar to it, has historically been recommended for the treatment of postoperative or postpartum urinary retention, but only if the patient is awake and alert and if there is no outlet obstruction. The recommended dose has been 5 to 10 mg subcutaneously. For more than 50 years, bethanechol has been recommended for the treatment of the atonic or hypotonic bladder and has been reported as effective in achieving "rehabilitation" of the chronically atonic or hypotonic detrusor (Sonda et al, 1979). This drug has also been reported to stimulate or facilitate the development of reflex bladder contractions in patients in spinal shock secondary to suprasacral spinal cord injury (Perkash, 1975).

Although bethanechol has been reported to increase gastrointestinal motility and has been used in the treatment of gastroesophageal reflux, and although anecdotal success in specific patients with voiding dysfunction seems to occur, **there is little or no evidence to support its success in facilitating bladder emptying in a series of patients in whom the drug was the only variable** (Finkbeiner, 1985; Barendrecht et al, 2007). In one set of trials a pharmacologically active subcutaneous dose (5 mg) did not demonstrate significant changes in flow parameters or residual urine volume in (1) a group of women with a residual urine volume greater than or equal to 20% of bladder capacity but no evidence of neurologic disease or outlet obstruction; (2) a group of 27 "normal" women of approximately the same age; or (3) a group of patients with a positive bethanechol supersensitivity test (Wein et al, 1980a, 1980b). This dose did increase cystometric filling pressure and also decreased bladder capacity threshold, findings previously described by others (Sonda et al, 1979). Short-term studies in which the drug was the only variable have generally failed to demonstrate significant efficacy in terms of flow and residual urine volume data (Barrett, 1981). Farrell and colleagues (1990) conducted a double-blind randomized trial that looked at the effects of two catheter management protocols and the effect of bethanechol on postoperative retention after gynecologic incontinence surgery and concluded that bethanechol was not helpful in this setting. Although bethanechol is capable of eliciting an increase in bladder smooth muscle tension, as would be expected from in-vitro studies, its ability to stimulate or facilitate a coordinated and sustained physiologic-like bladder contraction in patients with voiding dysfunction has been unimpressive (Finkbeiner, 1985; Andersson, 1988).

It is difficult to find reproducible urodynamic data that support recommendations for the use of bethanechol in any specific category of patients. Most, if not all, "long-term" reports in such patients are neither prospective nor double blind and do not exclude the effects of other simultaneous regimens (e.g., treatment of urinary infection, bladder decompression, timed emptying, or other types of treatment affecting the bladder or outlet), an important observation to consider when reporting such drug studies. Whether repeated doses of bethanechol or any cholinergic agonist can achieve a clinical effect that a single dose cannot is speculative, as are suggestions that bethanechol has a different mode of action or effect on atonic or decompensated bladder muscle than on normal tissue.

Bethanechol, administered subcutaneously, does cause an increased awareness of a distended bladder (Downie, 1984). This could facilitate more frequent emptying at lower volumes and thereby help to avoid overdistention, but, it would seem, only in a bladder that is capable of a contraction. O'Donnell and Hawkins (1993) administered 5 mg of bethanechol subcutaneously to 10 neurologically intact males and made the following cystometric observations: bladder volume at first desire to void

decreased (220 mL to 85 mL), maximum bladder capacity decreased (380 mL to 160 mL), first desire to void occurred at a higher pressure (5 cm H_2O vs. 28 cm H_2O), and compliance was reduced. They concluded that bethanechol affects the ability of the bladder to accommodate volume. Patients were comfortable at a resting bladder pressure of 20 cm H_2O (uncommon in their population), and the pressures at maximum bladder capacity were considerably higher than commonly seen under normal conditions. This suggested to them that either bladder pressure alone is not a significant factor in the perception of a sensation of first desire to void or that bethanechol somehow alters the threshold at which perception of desire to void occurs (because these patients showed a tolerance for increased intravesical pressure before first desire to void and at maximum bladder capacity). De Wachter and Wyndaele (2001) determined the bladder electrical threshold in healthy volunteers receiving 5 mg bethanechol subcutaneously. They found a marked decrease in the volume at which various filling sensations occurred and that the electrical threshold decreased after drug administration. De Wachter and coworkers (2003) treated 18 women with impaired detrusor contraction with subcutaneous bethanechol (5 mg four times daily) for 10 days. At the end of treatment, 61% of the patients voided without a postvoid residual volume. These investigators also found that in these women the sensation of filling and the electrical sensitivity were significantly increased compared with before treatment. The authors suggested that patients likely to respond to bethanechol can be identified by determination of the bladder electrical perception threshold.

Riedl and colleagues (2000) performed a clinical study in 45 patients with detrusor areflexia. They were tested with electromotive administration of intravesical bethanechol. Bethanechol 25 mg given orally once daily were then prescribed for 15 patients and voiding control was assessed after 6 weeks of therapy. A mean pressure increase of 34 cm H_2O during the electromotive administration of bethanechol was found in 24 of 26 patients with areflexia and neurologic disease compared with only 3 cm H_2O in 3 of 11 with a history of chronic bladder dilatation. Oral bethanechol restored spontaneous voiding in 9 of 11 patients who had had a positive response to the electromotive administration of bethanechol, whereas all 4 without a pressure increase during the electromotive administration of bethanechol did not void spontaneously. Riedl and coworkers (2000) concluded that electromotive administration of intravesical bethanechol can identify patients with an atonic bladder and adequate residual detrusor muscle function who are candidates for restorative measures, such as oral bethanechol and intravesical electrostimulation. Those who do not respond to the electromotive administration of bethanechol do not benefit from oral bethanechol and are candidates for catheterization.

No agreement exists as to whether cholinergic stimulation produces an increase in urethral resistance (Wein et al, 1980a, 1980b). It would appear that pharmacologically active doses do, in fact, increase urethral closure pressure, at least in patients with neurogenic DO (Sporer et al, 1978). This would of course tend to inhibit bladder emptying. As to whether cholinergic agonists can be combined with agents to decrease outlet resistance to facilitate emptying and achieve an additive or synergistic effect, the authors' own experience with such therapy, using even 200 mg (50 mg four times a day) of oral bethanechol daily, has been extremely disappointing. Certainly, most clinicians would agree that a total divided daily dose of 50 to 100 mg rarely affects any urodynamic parameter at all. In a prospective, single-blind randomized study comprising 119 patients with underactive detrusor, Yamanishi and colleagues (2004) studied the effect of combination of a cholinergic drug (bethanechol 60 mg/day or distigmine 15 mg/day) and an α-AR antagonist (urapidil 60 mg/day). The effectiveness of each therapy was assessed 4 weeks after initialization of the therapy using the IPSS. The IPSS results remained unchanged after the cholinergic therapy but were significantly lower after the α-AR antagonist treatment and the combination therapy. With regard to the total IPSS, there were significant differences between the cholinergic and the α-AR antagonist groups and also between the cholinergic and combination groups, in favor of the latter. The average and maximum flow rates did not increase significantly after monotherapy with either the cholinergic drug or the α-AR antagonist, but they significantly increased after combination therapy compared with baseline values. Postvoid residual volume did not decrease significantly after the cholinergic drug therapy but decreased significantly after the α-AR antagonist and the combination therapies. The authors concluded that combination therapy with a cholinergic drug and an α-AR antagonist appeared to be more useful than monotherapy for the treatment of an underactive detrusor.

The question of whether bethanechol may be efficacious in a particular patient can be answered by a brief urodynamically controlled trial in which institution of therapy is the only variable. In the laboratory, a functioning micturition reflex is an absolute requirement for the production of a sustained bladder contraction by a subcutaneous injection of the drug (Downie, 1984). **Patients with incomplete lower motor neuron lesions constitute the most reasonable group for a trial of bethanechol** (Awad, 1985), although subcutaneous administration may be required. **It is generally agreed that, at least in a "denervated" bladder, an oral dose of 200 mg is required to produce the same urodynamic effects as a subcutaneous dose of 5 mg** (Diokno and Lapides, 1977).

The **potential side effects of cholinomimetic drugs** include flushing, nausea, vomiting, diarrhea, gastrointestinal cramps, bronchospasm, headache, salivation, sweating, and difficulty with visual accommodation (Brown and Taylor, 2006). Intramuscular and intravenous use can precipitate acute and severe side effects, resulting in an acute circulatory failure and cardiac arrest and are therefore prohibited. Contraindications to the use of this general category of drug include bronchial asthma, peptic ulcer, bowel obstruction, enteritis, recent gastrointestinal surgery, cardiac arrhythmia, hyperthyroidism, and any type of bladder outlet obstruction.

One potential avenue of increasing bladder contractility is cholinergic enhancement or augmentation. Such an action might be useful alone or in combination with a parasympathomimetic agent. **Metoclopramide** is a dopamine receptor antagonist with cholinergic properties (Pasricha et al, 2006). It has a central antiemetic effect in the chemoreceptor trigger zone and peripherally increases the tone of the lower esophageal sphincter, promoting gastric emptying. Its effects seem to be related to its ability to antagonize the inhibitory action of dopamine, to augment acetylcholine release, and to sensitize the muscarinic receptors of gastrointestinal smooth muscle. Some data in the dog suggest that this agent can increase detrusor contractility (Mitchell and Venable, 1985), but there are no controlled studies documenting a useful clinical effect in the treatment of detrusor underactivity.

Cisapride is a substituted piperidinyl benzamide with a number of different pharmacologic activities, including a possible direct stimulation of smooth muscle (Pasricha, 2006). Until

recently it was commonly used as a prokinetic agent, particularly for gastroesophageal reflux and gastroparesis. It was also suggested that it could improve bladder contractility (Carone et al, 1993; Binnie et al, 1988; Steele et al, 2001). However, there was never any particularly convincing data that the drug improved voiding function, and it is no longer available in the United States because of its potential to induce serious and occasional cardiac arrhythmias (Smalley et al, 2000; Pasricha, 2006). The concept, however, of cholinergic enhancement or augmentation remains attractive but awaits the development of a bladder selective compound.

Prostaglandins

The reported use of prostaglandins to facilitate emptying is based on hypotheses that these substances contribute to the maintenance of bladder tone and bladder contractile activity (see Chapter 60 and Andersson, 1993; Zderic et al, 1995; Andersson, 1999a, 1999b, 1999c; Andersson and Wein, 2004, for a complete discussion). **Prostaglandins and thromboxane A_2 (TXA_2) have been shown to be present in human bladder in the following quantitative order: $PGE_2 > PGE_1 > PGF_{2\alpha} > TXA_2$; isolated detrusor muscle is contracted by $PGF_{2\alpha}$, PGE_1, PGE_2, and TXA_2** (see references in Andersson and Wein, 2004). **Prostanoids are synthesized locally in both bladder muscle and mucosa, with synthesis being initiated by various physiologic stimuli such as detrusor muscle stretch, mucosal injury, and neural stimulation; by ATP; and by mediators of inflammation** (Andersson and Wein, 2004). Prostanoids may affect bladder activity directly by effects on the smooth muscle or indirectly through effects on neurotransmission. **Possible roles mentioned by** Andersson (2000a) **include (1) neuromodulators of efferent and afferent neurotransmission; (2) sensitization or perhaps (3) activation of certain sensory nerves; and (4) potentiation of acetylcholine release from cholinergic nerve terminals through prejunctional prostanoid receptors. PGE_2 seems to cause a net decrease in urethral smooth muscle tone; $PGF_{2\alpha}$ causes an increase.**

Bultitude and colleagues (1976) first reported that instillation of 0.5 mg PGE_2 into the bladders of females with varying degrees of urinary retention resulted in acute emptying and in improvement of longer-term emptying (several months) in two thirds of the patients studied (n = 22). Desmond and associates (1980) reported results with intravesical use of 1.5 mg of this agent (diluted with 20 mL of 0.2% neomycin solution) in patients whose bladders exhibited no contractile activity or in whom bladder contractility was relatively impaired. Twenty of 36 patients showed a strongly positive immediate response, and 6 showed a weakly positive one. Fourteen patients were reported to show prolonged beneficial effects, all but 1 of whom had shown a strongly positive immediate response. Stratification of the data revealed that an intact sacral reflex arc was a prerequisite for any type of positive response. Tammela and coworkers (1987) reported that one intravesical administration of 10 mg of $PGF_{2\alpha}$ facilitated voiding in women who were in retention 3 days after surgery for SUI. The drug was administered in 50 mL of saline solution as a single dose and retained for 2 hours. However, in these "successfully" treated patients, the average maximum flow rate was 10.6 mL/sec with a mean residual urine volume of 107 mL, and the authors stated that "bladder emptying deteriorated in most patients on the day after treatment." Koonings and colleagues (1990) reported that daily intravesical $PGF_{2\alpha}$ and intravaginal PGE_2 reduced the number of days required for catheterization after SUI surgery when compared with a control group receiving intravesical saline solution.

Others, however, have reported negative results. Grignaffini and Bazzani (1998) reported on instillation of 1.5 mg of PGE_2 in 50 mL of saline solution into the bladder of 50 patients on their fourth day after vaginal hysterectomy and cystourethropexy, with a control group of 60 patients. The results are presented in an interesting fashion. After catheter removal, following the PGE_2 or control treatment, 58% of the PGE_2-treated group voided spontaneously as compared with 48.3% of the control group. This difference was not significant. Thus, 42% of the treated group and 51.7% of the control group were in retention. Of those who were in retention, the number who were in retention for fewer than 3 days was greater in the PGE_2 group (32%) versus the control group (25%), and this was statistically significant. Likewise, the number who remained in urinary retention for 3 days or longer after the initial treatment was 10% in the PGE_2-treated group versus 26.7% in the control group. Stanton and colleagues (1979) and Delaere and associates (1981) reported on success utilizing intravesical PGE_2 in doses similar to those reported earlier; Delaere and associates (1981) similarly reported no success using $PGF_{2\alpha}$ in a group of women with emptying difficulties of various causes. Wagner and coworkers (1985) used PGE_2 in doses of 0.75 to 2.25 mg and reported no effect on urinary retention in a group of patients after anterior colporrhaphy.

In a prospective randomized double-blind study, Hindley and colleagues (2004) tested the hypothesis that the combination of intravesical PGE_2 and oral bethanechol are additive or synergistic in improving bladder emptying. Nineteen patients with detrusor underactivity (17 men and 2 women) were eligible and randomized to one of two treatments. One group (9 patients) received once-weekly intravesical PGE_2 (1.5 mg in 20 mL 0.9% saline) plus bethanechol 50 mg four times daily for a total of 6 weeks. A second group of 10 patients received a once-weekly instillation of saline together with placebo tablets, again for 6 weeks. Although there was evidence of a pharmacologic effect, bethanechol and PGE_2 had a limited therapeutic effect compared with placebo. The authors did not recommend this treatment as routine but suggested that it may be considered for the occasional treatment of a patient with detrusor underactivity.

There has been little recent activity in this area, a fact that generally means that clinicians have lost interest or that the initial optimistic results have not been confirmed. **Prostaglandins have a relatively short half-life, and it is difficult to understand how any effects after a single application can last up to several months. If such does occur, it must be the result of a "triggering effect" on some as yet unknown physiologic or metabolic mechanism. Because of the number of conflicting positive and negative reports with various intravesical preparations, double-blind, placebo-controlled studies would obviously be helpful to see whether there are circumstances in which prostaglandin use can reproducibly facilitate emptying or treat postoperative retention.** Potential systemic side effects of prostaglandin use include vomiting, diarrhea, pyrexia, hypertension, and hypotension (Campbell and Halushka, 1996).

Blockers of Inhibition

de Groat and coworkers (see Chapter 60; de Groat et al, 1993; Zderic et al, 1995) have demonstrated a sympathetic reflex during bladder filling that, at least in the cat, promotes urine storage partly by exerting an α-AR–mediated inhibitory effect on pelvic parasympathetic ganglionic transmission. Some have suggested that α-AR blockade, in addition to decreasing outlet resistance, may, in fact, facilitate transmission through these ganglia and

thereby enhance bladder contractility. On this basis, Raz and Smith (1976) were the first to advocate a trial of an α-AR blocking agent for the treatment of nonobstructive urinary retention. A complete discussion of postoperative retention, including the use of α-AR antagonists for its treatment, is presented elsewhere (see Chapter 65).

Opioid Receptor Antagonists

Endogenous opioids have been hypothesized to exert a tonic inhibitory effect on the micturition reflex at various levels (see Chapter 60) (Zderic et al, 1995), and agents such as opioid receptor antagonists therefore may offer possibilities for stimulating reflex bladder activity.

Thor and associates (1983) were able to stimulate a micturition contraction with naloxone, an opioid receptor antagonist, in unanesthetized chronic spinal cord–injured cats. The effects, however, were transient, and tachyphylaxis developed. Vaidyanathan and associates (1981) reported that an intravenous injection of 0.4 mg of naloxone enhanced detrusor reflex activity in five of seven patients with neuropathic bladder dysfunction caused by incomplete suprasacral spinal cord lesions. The maximum effect occurred within 1 to 2 minutes after intravenous injection and was gone by 5 minutes. Murray and Feneley (1982) reported that the same dose of naloxone caused, in a group of patients with idiopathic DO, an increase in detrusor pressure at zero volume and at first desire to void, a decrease in the maximum cystometric capacity, and a worsening of the degree of instability. Galeano and coworkers (1986) reported that although naloxone increased bladder contractility in the cat with chronic spinal cord injury, it also aggravated striated sphincter dyssynergia and spasticity—a potential problem in the treatment of emptying failure. Wheeler and colleagues (1987) noted no significant cystometric changes in a group of 15 spinal cord–injured patients after intravenous administration of naloxone, whereas 11 showed decreased perineal electromyographic (EMG) activity. **Although an intriguing area, the concept of reversing an inhibitory opioid influence to stimulate reflex bladder activity is of little practical use at present.**

Decreasing Outlet Resistance

At a Site of Anatomic Obstruction

This topic includes the treatment of bladder outlet obstruction secondary to benign prostatic enlargement, and a full discussion is appropriately found in Chapters 92 and 93.

At the Level of the Smooth Sphincter

α-Adrenergic Receptor Antagonists. Whether one believes that there is significant innervation of the bladder and proximal urethral smooth musculature by postganglionic fibers of the sympathetic nervous system, one must acknowledge the existence of α- and β-AR sites. **The smooth muscle of the bladder base and proximal urethra contains predominantly α-ARs, although β-ARs are present. The bladder body contains both varieties of adrenergic receptors, with the β-ARs (β_3) variety being more common** (see Chapter 60) (Zderic et al, 1995; Andersson, 2000a). **The human LUT contains more α_2 than α_1 ARs, but adrenergically induced prostatic smooth muscle contraction and human LUT smooth muscle contraction are mediated largely, if not exclusively, by α_1 ARs.** There are at least three subtypes of α_1 ARs, designated α_{1A}, α_{1B}, and α_{1D}. **Adrenergically induced smooth muscle contraction in the human LUT is mediated largely by the α_{1A}** (and in the detrusor α_{1D}) subtype (Docherty, 1998; Harada and Fujimura, 2000; Michel et al, 2000; Schwinn, 2000; Andersson and Wein, 2004; Andersson and Gratzke, 2007). In addition to the three cloned α_1 ARs, there is a possible fourth, α_{1L}, although the α_{1L}-AR is probably a variant of the α_{1A}. There is a tremendous amount of information and controversy in the literature regarding the selectivity of certain α-AR blocking agents for these respective receptor subtypes. Conclusions are drawn regarding "the best" α_1-AR antagonist for the treatment of at least BPH on the basis of in-vitro and in-vivo pharmacologic selectivity, but many authors note that this does not necessarily translate into functional selectivity in a given patient (Andersson, 2002c; Djavan et al, 2004). The various α-AR antagonists are dealt with in more detail in Chapter 60 (see also Andersson, 2007).

Krane and Olsson (1973) **were among the first to promote the concept of a physiologic internal sphincter partially controlled by tonic sympathetic stimulation of contraction-mediating α-ARs in the smooth musculature of the bladder neck and proximal urethra. Furthermore, they hypothesized that some obstructions at this level during bladder contraction are a result of inadequate opening of the bladder neck and/or of an inadequate decrease in resistance in the area of the proximal urethra. They also theorized and presented evidence that α-AR blockade could be useful in promoting bladder emptying in such a patient with an adequate detrusor contraction but without anatomic obstruction or detrusor–striated sphincter dyssynergia.** They and many others (see Wein and Barrett, 1988) have confirmed the usefulness of α-AR blockade in the treatment of what is now usually referred to as smooth sphincter or bladder neck dyssynergia or dysfunction. Successful results, usually defined as an increase in flow rate, a decrease in residual urine, and an improvement in upper tract appearance (where pathologic), could often be correlated with an objective decrease in urethral profile closure pressure.

One would expect success with such therapy to be most evident in patients without detrusor–striated sphincter dyssynergia, as reported by Hachen (1980). Mobley (1976), however, reported a startling 86% subjective success rate in 21 patients with a reflex neurogenic bladder, with a corresponding success rate of 66% in what was called "flaccid" and 57% of what was called "autonomous" neurogenic bladder dysfunction, with success being defined as postvoid residual urine volume consistently less than 100 mL. Scott and Morrow (1978), on the other hand, noted excellent results with phenoxybenzamine therapy in 9 of 10 patients with a flaccid bladder and a flaccid external sphincter and in a single patient with an upper motor neuron bladder with intact sympathetic innervation, but in only 8 of 21 patients with hyperreflexia and autonomic dysreflexia, and in none of 6 patients with an upper motor neuron bladder and sympathetic denervation (lesion between T10 and L2).

Although most would agree that α-AR blocking agents exert their favorable effects on voiding dysfunction by affecting the smooth muscle of the bladder neck and proximal urethra, **information in the literature suggests that they may decrease striated sphincter tone as well;** and other information suggests that they may exert some of their effects on at least the filling/storage symptoms of voiding dysfunction by decreasing bladder contractility (see previous discussion). Much of the confusion relative to whether α-AR blocking agents have a direct (as opposed to indirect) inhibitory effect on the striated sphincter relates to the interpretation of clinical observations and

experimental data referable to their effect on urethral pressure in the region of the urogenital diaphragm and on EMG activity in the periurethral striated muscle of this area. One cannot tell by pressure tracings alone whether decreased resistance in this area of the urethra is secondary to a decrease in smooth or striated muscle activity. Nanninga and associates (1977) found that the EMG activity of the external sphincter decreased after phentolamine administration in three paraplegic patients and attributed this effect to a direct inhibition of sympathetic action on the striated sphincter. Nordling and associates (1981) demonstrated that clonidine and phenoxybenzamine (both of which pass the blood-brain barrier) also decreased urethral pressure in this area and yet had no effect on EMG activity. They concluded (1) that the effect of phentolamine was from smooth muscle relaxation alone; (2) that the effect of clonidine, and possibly phenoxybenzamine, was elicited mostly through centrally induced changes in striated urethral sphincter tonus; and (3) that these agents also had an effect on the smooth muscle component of urethral pressure. None of the three drugs, however, affected the reflex rise in either urethral pressure or EMG activity seen during bladder filling, and none decreased the urethral pressure or EMG activity response to voluntary contraction of the pelvic floor striated musculature. Gajewski and colleagues (1984) concluded that α-AR blockers do not influence the pudendal nerve dependent urethral response in the cat through a peripheral action but that at least prazosin can significantly inhibit this response at a central level. Thind and associates (1992) reported on the effects of prazosin on static urethral sphincter function in 10 healthy females. They found a reduction—predominantly in the midurethral area—and hypothesized that the response was caused by a decrease in both smooth and striated sphincter activity, the latter as a result of a reduced somatomotor output from the CNS. Clinically, Chancellor and coworkers (1994) reported that terazosin, a selective α_1-AR antagonist, had little or no effect on striated sphincter function in spinal cord–injured patients and had no effect on functional obstruction caused by sphincter dyssynergia in these patients.

α-AR blocking agents have also been used to treat both bladder and outlet abnormalities in patients with so-called autonomous bladders—such as those with myelodysplasia, sacral spinal cord or infrasacral neural injury, and voiding dysfunction after radical pelvic surgery (Wein and Barrett, 1988). Decreased bladder compliance is a common clinical problem in such patients, and this, along with a fixed urethral sphincter tone, results in the paradoxical occurrence of both storage and emptying failure.

Phenoxybenzamine. This was the α-AR antagonist originally used for the treatment of voiding dysfunction (see Te, 2002). Phenoxybenzamine has **blocking properties at both α_1- and α_2-AR sites.** The initial adult dosage of this agent is 10 mg/day, and the usual daily dose for voiding dysfunction is 10 to 20 mg. **After discontinuation, the effects of administration may persist for days, because the drug irreversibly inactivates α-ARs** and the duration of effect depends on the rate of receptor synthesis (Hoffman and Lefkowitz, 1996). Side effects affect approximately 30% of patients (Kirby, 1999) and include orthostatic hypotension, reflex tachycardia, nasal congestion, diarrhea, miosis, sedation, nausea, and vomiting (secondary to local irritation). It has mutagenic activity in the Ames test, and repeated administration to animals can cause peritoneal sarcomas and lung tumors (Westfall and Westfall, 2006). Although this agent has been in clinical use for some 35 years without clinically apparent oncologic associations, one must now consider the potential medicolegal ramifications of long-term therapy, especially in younger persons. A reassessment of the use of phenoxybenzamine for treatment of urinary tract disorders was made by Te (2002).

Prazosin. **Prazosin was the first potent selective α_1-AR antagonist** (see Westfall and Westfall, 2006) used to lower outlet resistance (Andersson et al, 1981). The duration of action is 4 to 6 hours; therapy is generally begun in daily divided doses of 2 to 3 mg. The dose may be very gradually increased to a maximum of 20 mg daily, although seldom has anyone used more than 9 to 10 mg daily for voiding dysfunction. The potential side effects of prazosin are consequent to its α_1-AR blockade. Occasionally there occurs a "first-dose phenomenon," a symptom complex of faintness, dizziness, palpitation, and, infrequently, syncope, thought to be caused by acute postural hypotension. The incidence of this can be minimized by restricting the initial dose of the drug to 1 mg and administering this at bedtime. Other side effects associated with chronic prazosin therapy are generally mild and rarely necessitate withdrawal of the drug.

Terazosin and Doxazosin. Terazosin and doxazosin are two highly selective postsynaptic α_1-AR antagonists. They are readily absorbed with high bioavailability and a long plasma half-life, enabling their activity to be maintained over 24 hours after a single oral dose. Both of these agents have been evaluated with respect to their efficacy in patients with LUTS and decreased flow rates presumed secondary to BPH. Their efficacy in decreasing symptoms and raising flow rates has been shown to be superior to placebo and similar to that of prazosin (Kirby, 1999). Their safety profiles have been well documented as a result of their widespread use over several years for the treatment of hypertension. Side effects are related to peripheral vasodilatation (postural hypotension), and both drugs have to be started at a low dose and titrated to obtain an optimum balance between efficacy and tolerability. Dizziness and weakness are sometimes observed, and these are presumed secondary to CNS actions. These drugs are marketed for the treatment of hypertension as well as LUTS presumed secondary to BPH.

Alfuzosin and Tamsulosin. **Alfuzosin and tamsulosin, both highly selective α_1-AR blockers, have appeared and are marketed solely for the treatment of BPH because of some reports suggesting preferential action on prostatic rather than vascular smooth muscle** (Kirby, 1999; Djavan et al, 2004). **Marketing claims aside, whether there is any difference in the efficacy/side effect profiles of these individual agents remains a topic of controversy.** Both are able to be administered once daily and without titration. **Available data suggest that retrograde ejaculation and rhinitis are more common with tamsulosin, whereas dizziness and asthenia are more common with terazosin and doxazosin** (Djavan et al, 2004).

Silodosin. Silodosin is a novel highly selective α_{1A}-AR antagonist (Yoshida et al, 2007). Clinical data (Kawabe et al, 2006) showed that silodosin showed significant improvement in LUTS associated with BPH, as well as in quality of life. The improvements were observed in both voiding and storage symptoms. Long-term study revealed that the efficacy and safety was sustained for 1 year. The most common adverse event in the silodosin group was abnormal ejaculation, which occurred in 22% of cases (Kawabe et al, 2006). Adverse events associated with lowering of blood pressure were low.

Summary. Agents with α-AR blocking properties at various levels of neural organization have been used in patients with very varied types of voiding dysfunction—functional outlet obstruction, urinary retention, decreased compliance, and DO. The authors' own experience would suggest that a trial of such an agent is

certainly worthwhile, because the effect or noneffect will become obvious in a matter of days and any pharmacologic side effects are, of course, reversible. However, our results with such therapy for non–BPH-related voiding dysfunction have been somewhat less spectacular than those of at least some other investigators.

Nitric Oxide. In the future there may be other pharmacologic mechanisms that are explored to produce relaxation in the smooth muscle of the bladder neck, urethra, or prostatic stroma. **Nitric oxide is a neurotransmitter capable of producing smooth muscle relaxation, at least in the female rabbit urethra, pig urethra, and human bladder neck** (Andersson and Persson, 1993; Andersson and Wein, 2004). A selective nitrergic action on bladder neck and urethral smooth muscle is an interesting theoretical possibility, and Mumtaz and coworkers (2000) suggest that a topical intraurethral nitric oxide donor could induce urethral smooth muscle relaxation without affecting bladder smooth muscle function and that this is a possible clinical avenue of exploration. Mamas and associates (2001, 2003) hypothesized that augmentation of external sphincter nitric oxide could be an effective pharmacologic therapy for detrusor–striated sphincter dyssynergia. In a functional urodynamic study, Reitz and coworkers (2004a) assessed the effect of the nitric oxide donor isosorbide dinitrate on the external urethral sphincter. Magnetic stimulation of the sacral roots was performed in eight healthy males to evoke reproducible contractions of the external urethral sphincter. Sublingual administration of isosorbide dinitrate (10 mg) could significantly reduce the resting pressure of the external urethral sphincter for at least 1 hour. The maximum contractile strength measured as the maximum urethral closure pressure during single pulse and continuous magnetic stimulation of the sacral roots also decreased significantly. Nitric oxide did not induce a significantly faster fatigue of the external urethral sphincter during continuous magnetic stimulation of the sacral roots. The authors suggested that nitric oxide donors could offer a new pharmacologic approach to treat urinary retention due to an overactive or nonrelaxing external urethral sphincter. In a later study on 12 male spinal cord–injured patients presenting with neurogenic DO and detrusor–striated sphincter dyssynergia, Reitz and coworkers (2004b) found that nitric oxide significantly reduced external urethral sphincter pressures at rest ($P < .05$) and during dyssynergic contraction ($P < .05$) while bladder pressures at rest and during contraction as well as the reflex volume remained unchanged. In patients who used suprapubic tapping for bladder emptying the mean post-triggering residual volume was significantly reduced ($P < .05$). Their conclusion based on their findings was that nitric oxide donors could offer a potential pharmacologic option to treat detrusor–striated sphincter dyssynergia in spinal cord–injured patients.

At the Level of the Striated Sphincter

There is no class of pharmacologic agents that will selectively relax the striated musculature of the pelvic floor. Three different types of drugs have been used to treat voiding dysfunction secondary to outlet obstruction at the level of the striated sphincter: the benzodiazepines, dantrolene, and baclofen. The benzodiazepines are classified as antianxiety agents (Baldessarini, 2006) and as sedative/hypnotics, muscle relaxants, and anticonvulsants (Charney et al, 2006). Dantrolene and baclofen are characterized as antispasticity agents (Standaert and Young, 2006; Taylor, 2006). Baclofen and diazepam exert their actions predominantly within the CNS, whereas dantrolene acts directly on skeletal muscle. Unfortunately **there is no completely satisfactory form of therapy for alleviation of skeletal muscle spasticity.** Although these drugs are capable of providing variable relief in given circumstances, their efficacy is far from complete; and troublesome muscle weakness, adverse effects on gait, and a variety of other side effects minimize their overall usefulness as treatments of spasticity (Standaert and Young, 2006; Taylor, 2006).

GABA and glycine have been identified as major inhibitory transmitters in the CNS (Andersson and Wein, 2004; Bloom, 2006). GABA is the most widely distributed inhibitory neurotransmitter in the mammalian CNS. GABA receptors have been divided into three types. The $GABA_A$ receptor directly gates a chloride ionophore and has modulatory binding sites for benzodiazepines, barbiturates, neurosteroids, and ethanol (Bloom, 2006). The $GABA_B$ or metabotropic receptor couples to Ca^{2+} and K^+ channels by means of G proteins and second messenger systems. It inhibits adenylate cyclase, activates K^+ channels, and reduces Ca^{2+} conductance. The $GABA_B$ receptor is activated by baclofen and is resistant to drugs that modulate $GABA_A$ receptors. There is a third type of GABA receptor, the $GABA_C$, that is less widely distributed than the A and B subtypes (Bloom, 2006). GABA appears to mediate the inhibitory actions of local interneurons in the brain and presynaptic inhibition within the spinal cord (Bloom, 2006). Glycine receptors are prominent in the brain stem and spinal cord and have many features analogous to the $GABA_A$ receptor.

Benzodiazepines. **Benzodiazepines potentiate the action of GABA by promoting GABA binding to the $GABA_A$ receptor** (Baldessarini, 2006; Charney, 2006). Benzodiazepines are extensively used for the treatment of anxiety and related disorders (Baldessarini, 2006), although pharmacologically they can also be classified as centrally acting muscle relaxants. The generalized anxiety disorder that is responsive to pharmacotherapy with these agents is characterized by unrealistic and/or excessive anxiety and worry about life circumstances (Shader and Greenblatt, 1993). Specific symptoms can be related to motor tension, autonomic hyperactivity (frequent urination can be a manifestation of this, as well as nausea, vomiting, diarrhea, and abdominal distress), and excessive vigilance. Other common uses have included treatment of insomnia, stress-related disorders, muscle spasm, and epilepsy and as preoperative sedation (Lader, 1987). Side effects include nonspecific CNS depression—manifested as sedation, lethargy, drowsiness, a feeling of slowing of thought processes, ataxia, and decreased ability to acquire or store information (Shader and Greenblatt, 1993; Baldessarini, 2006). Some believe that any muscle relaxation effect in clinically utilized doses is caused by the CNS depressant effects and cite a lack of clinical studies showing any advantages of these agents over placebo or aspirin in this regard (Baldessarini, 2006; Charney et al, 2006). Effective total daily doses of diazepam, the most widely used agent of this group, range from 4 to 40 mg. Other benzodiazepine anxiolytic agents include chlordiazepoxide, clorazepate, prazepam, halazepam, clonazepam, lorazepam, oxazepam, and alprazolam.

Few references are available that provide evaluable data on the use of any of the benzodiazepines in the treatment of functional obstruction at the level of the striated sphincter. Opinions, however, are commonly expressed, at least in regard to diazepam. The authors have not found the recommended oral doses of diazepam to be effective in controlling the classic type of detrusor–striated sphincter dyssynergia secondary to neurologic disease. If the etiology of incomplete emptying in a neurologically normal patient is obscure, and the patient has what appears to be inadequate relaxation of the pelvic floor striated musculature urodynamically (e.g., dysfunctional voiding, occult neuropathic bladder, the Hinman syndrome), a trial of such

an agent may be worthwhile. The rationale for use is either that of relaxation of the pelvic floor striated musculature during bladder contraction or that of such relaxation removing an inhibitory stimulus to reflex bladder activity. Improvement under such circumstances may simply be caused, however, by the antianxiety effect of the drug, or by the intensive explanation, encouragement, and modified biofeedback therapy that usually accompanies such treatment in these patients.

Baclofen. **Baclofen depresses monosynaptic and polysynaptic excitation of motor neurons and interneurons in the spinal cord by activating $GABA_B$ receptors** (Standaert and Young, 2006). Baclofen's primary site of action is in the spinal cord, but it is also reported to have activity at more rostral sites in the CNS. Baclofen has been found useful in the treatment of skeletal spasticity from a variety of causes (especially amyotrophic lateral sclerosis) (Standaert and Young, 2006). Determination of the optimal dose in an individual patient requires careful titration. Treatment is started at an initial dose of 5 mg twice daily, and the dose is increased every 3 days up to a maximum daily dose of 20 mg four times a day. With reference to voiding dysfunction, Hachen and Krucker (1977) found a daily oral dose of 75 mg ineffective in patients with striated sphincter dyssynergia from traumatic paraplegia, whereas they found a daily intravenous dose of 20 mg highly effective. Florante and colleagues (1980) reported that 73% of their patients with voiding dysfunction secondary to acute and chronic spinal cord injury showed lower striated sphincter responses and decreased residual urine volumes after baclofen treatment, but only with an average daily oral dose of 120 mg. Potential side effects of baclofen include drowsiness, insomnia, rash, pruritus, dizziness, and weakness. This drug may impair a person's ability to walk or stand and is not recommended for the management of spasticity caused by cerebral lesions or disease. Sudden withdrawal has been shown to provoke hallucinations, anxiety, and tachycardia; hallucinations during treatment, which have been responsive to reductions in dosage, have also been reported (Roy and Wakefield, 1986).

Drug delivery often frustrates adequate pharmacologic treatment, and baclofen is a good example of this. GABA's hydrophilic properties prevent its crossing the blood-brain barrier in sufficient amounts to make it therapeutically useful. For oral use, the more lipophilic analogue baclofen was developed. However, its passage through the barrier is likewise limited, and it has proved to be a generally insufficient drug when given orally to treat severe somatic spasticity and micturition disorders secondary to neurogenic dysfunction (Kums and Delhaas, 1991).

Intrathecal infusion bypasses the blood-brain barrier; cerebrospinal fluid levels 10 times higher than those reached with oral administration are achieved with infusion amounts 100 times less than those taken orally (Penn et al, 1989). Direct administration into the subarachnoid space by an implanted infusion pump showed initially promising results for not only skeletal spasticity but also striated sphincter dyssynergia and DO.

Nanninga and colleagues (1989) reported on such administration to seven patients with intractable spasticity. All patients experienced a general decrease in spasticity, and the amount of striated sphincter activity during bladder contraction decreased; six showed an increase in bladder capacity. Four previously incontinent patients were able to stay dry with CIC. The action on DO is not unexpected, given its spinal cord mechanism of action, and this inhibition of bladder contractility when administered intrathecally may in fact prove to be its most important benefit. Laubser and associates (1991) studied nine spinal cord–injured patients with refractory spasticity using an external pump to initially test the response. Eight showed objective improvement in functional abilities; three of the seven studied urodynamically showed an increase in bladder capacity. Kums and Delhaas (1991) reported on nine paraplegic or quadriplegic males (secondary to trauma or multiple sclerosis) with intractable muscle spasticity treated with intrathecal baclofen. After a successful test period through an external catheter, a drug delivery system was implanted and connected to a spinal catheter. Doses per 24 hours ranged from 74 to 840 μg. Patients were studied before and 4 to 6 weeks after initiation of therapy. Mean residual urine volume fell from 224 to 110 mL ($P = .01$), mean urodynamic bladder capacity rose from 162 to 263 mL ($P = .005$), and pelvic floor spasm decreased at both baseline and at maximum bladder capacity ($P < .005$ and $< .025$, respectively). Three subjects became continent. Additionally, CIC was no longer complicated by adductor spasm. Bushman and associates (1993) reported an increase in bladder storage in three individuals with hereditary spastic paraplegia treated with intrathecal baclofen. Tolerance to intrathecal baclofen with a requirement for increasing doses may prove to be a problem with long-term chronic use, and studies are under way to investigate this. Vaidyanathan and colleagues (2004) reported a case with insidious development of autonomic dysreflexia and hydronephrosis due to dyssynergic voiding after discontinuation of intrathecal baclofen therapy. They recommended that in spinal cord–injured patients, in whom intrathecal baclofen therapy is terminated, close monitoring of the urologic status is needed.

Dantrolene

Dantrolene exerts its effects by a direct peripheral action on skeletal muscle (Standaert and Young, 2006; Taylor, 2006). **It is thought to inhibit the excitation-induced release of Ca^{2+} ions from the sarcoplasmic reticulum of striated muscle fibers,** thereby inhibiting excitation-contraction coupling and diminishing the mechanical force of contraction. The blockade of Ca^{2+} release is not complete, however, and contraction is not completely abolished. It reduces reflex more than voluntary contraction, probably because of a preferential action on fast-type, as compared with slow-type, skeletal muscle fibers. It has been shown to have therapeutic benefits for chronic spasticity associated with CNS disorders.

The drug has been reported to improve voiding function in some patients with classic detrusor–striated sphincter dyssynergia and was initially reported as being very successful in doing so (Murdock et al, 1976). Therapy in adults is recommended to begin at a dose of 25 mg daily, and this is gradually increased by increments of 25 mg every 4 to 7 days to a maximum oral dose of 400 mg given in four divided doses. Hackler and coworkers (1980) achieved improvement in voiding function in approximately half of their patients treated with dantrolene but found that such improvement required oral doses of 600 mg daily. Although no inhibitory effect on bladder smooth muscle seems to occur (Harris and Benson, 1980), the generalized weakness that dantrolene can induce is often significant enough to compromise its therapeutic effects. Other potential side effects include euphoria, dizziness, diarrhea, and hepatotoxicity. Fatal hepatitis has been reported in 0.1% to 0.2% of patients treated with the drug for 60 days or longer, and symptomatic hepatitis may occur in 0.5% of patients on treatment for more than 60 days, whereas chemical abnormalities of liver function are noted in up to 1%. The risk of hepatic injury is twofold greater in females (Ward et al, 1986).

One agreed-on use of dantrolene is to acutely manage malignant hyperthermia, a rare hereditary syndrome characterized by vigorous contraction of skeletal muscle precipitated by

excess release of Ca^{2+} from the sarcoplasmic reticulum, generally in response to neuromuscular blocking agents or inhalational anesthetics. Almost all hospital pharmacies stock parenteral dantrolene for this purpose. **Virtually no one currently uses dantrolene for the treatment of voiding dysfunction.**

Botulinum Toxin

As mentioned previously, BoNT is an inhibitor of the release of acetylcholine and other transmitters at the neuromuscular junction of somatic nerves in striated muscle and of autonomic nerves in smooth muscle (Simpson, 2004). It is interesting that it produces enough weakness of the muscle to prevent or considerably ameliorate spasm or involuntary contraction but not to completely block voluntary control, a phenomenon hypothesized to occur because more active neuromuscular junctions are more likely than less active junctions to be blocked by the effect of the drug (Hallett, 1999). **Its urologic use for the treatment of detrusor–striated sphincter dyssynergia** was first reported by Dykstra and colleagues (Dykstra and Sidi, 1990; Dykstra et al, 1998). Injections were performed weekly for 3 weeks, achieving a duration of effect averaging 2 months. The only side effects reported in these articles were transitory limb paresis and transitory exacerbation of autonomic hyperreflexia. Fowler and coworkers (1992a) used BoNT in six women with difficult voiding/urinary retention secondary to what is now called the Fowler syndrome (manifested by abnormal myotonus-like EMG activity in the striated urethral sphincter). Although no patient had improved voiding characteristics (a fact attributed to the type of repetitive discharge activity), three women did develop transient SUI, a positive effect of sorts, indicating that the sphincter muscle had indeed been weakened. Petit and associations (1998) reported on the endoscopic injection of BoNT, 150 IU, into the striated urethral sphincter, using a four-point injection technique (the medication was diluted to 4 mL with saline solution). Seventeen patients with spin cord injury or spinal cord disease were treated, and evaluation 1 month after treatment disclosed the following positive results: (1) a decrease in postvoid residual by an average of 176 mL; (2) a decrease in bladder pressure during an emptying contraction by an average of 19 cm H_2O; and (3) a decrease in urethral pressure during an emptying bladder contraction by an average of 24 cm H_2O. The authors judged voiding to be improved in 10 patients. Side effects included the new appearance of SUI in 2 patients and exacerbation of preexisting incontinence in 3 patients. The duration of the effect was variable, but no less than 2 to 3 months. There were no adverse effects on striated muscle elsewhere. The authors concluded that BoNT was a promising treatment for striated sphincter dyssynergia in certain patients refractory to CIC or surgery. Gallien and associates (1998) injected BoNT transperineally in five men with traumatic quadriplegia and striated sphincter dyssynergia. Using a total initial dose of 100 units, divided into four injections of 25 units each, the authors noted what they called improved bladder function in all patients, with a significant decrease in residual urine volume (however, on examining the figures, the mean reduction was only 14 mL, with one of the patients requiring a second set of injections). The maximum urethral closure pressure on average did not change, the maximum detrusor pressure during an emptying episode decreased 5 cm H_2O, and the functional detrusor capacity increased by an average of 89 mL. Urinary catheterization was able to be stopped in two patients, and autonomic hyperreflexia dramatically decreased in intensity in four patients. The time to improvement was 10 to 21 days, and the duration was 3 to 5 months. No patient had significant side effects. Wheeler and associates (1998) reported on three men with spinal cord injury, all with emptying problems related to striated sphincter dyssynergia. The sphincter was injected transperineally with BoNT, using EMG control for localization. Two of the patients reported excellent results. Schurch and associates (1996) used both transurethral and transperineal injections in 24 male spinal cord–injured patients with voiding dysfunction secondary to striated sphincter dyssynergia. They judged that in 21 of these patients, striated sphincter dyssynergia was significantly improved with a concomitant decrease in postvoid residual urine volume in "most cases." Nine of 24 patients had a decreased postvoid residual volume from 450 to 50 mL; in 7 patients, the residual urine volumes were less than 50 mL to begin with and remained unchanged; and in 8 patients, the postvoid residual urine volumes were high and remained unchanged. The authors commented that transurethral injections appeared to be more effective, at least in reductions in maximum urethral closure pressure, than did transperineal injections. They noted no side effects. de Seze and colleagues (2002) performed a double-blind lidocaine-controlled study in 13 patients with spinal cord disease and detrusor–striated sphincter dyssynergia and demonstrated the superiority of BoNT compared with lidocaine in improving clinical symptoms and increased urethral pressure.

There are several reviews summarizing the uses of BoNT injection (Cruz and Silva, 2004; Rackley and Abdelmalak, 2004; Reitz et al, 2004; Smith and Chancellor, 2004; Ghei et al, 2005; Sahai et al, 2005; Dmochowski and Sand, 2007; Karsenty et al, 2008; Andersson et al, 2009). A potential side effect is the spread to nearby muscles, particularly when high volumes of BoNT are injected. Distant effects can also occur, but distant weakness or generalized weakness, owing to the toxins spreading in the blood, is very rare. BoNT should be used only under close supervision in patients with already disturbed neuromuscular transmission or during treatment with aminoglycosides.

Theoretically, any agent that promotes striated sphincter relaxation in a uroselective manner could be used to decrease outlet resistance and facilitate voiding dysfunction. Yoshiyama and associates (2000) describe the intravenous use of α-bungarotoxin as improving voiding in spinal cord–injured rats. The drug is a toxin extracted from the venom of a Formosan snake; it selectively blocks nicotinic receptors without influencing transmission in autonomic ganglia. Although a long way from clinical use, nicotinic receptors in the striated sphincter have been shown to be a potential target for drug therapy for striated sphincter dyssynergia.

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chapter 69

Conservative Management of Urinary Incontinence: Behavioral and Pelvic Floor Therapy, Urethral and Pelvic Devices

Christopher K. Payne, MD

General Considerations
The Tools of Conservative Therapy
Concept of "Therapeutic Package"
Pelvic Floor Rehabilitation
Devices
Practical Approach to Treatment
Conclusion

GENERAL CONSIDERATIONS

Impact of Urinary Incontinence

Urinary incontinence (UI) affects people in all strata of society—the young and the old, male and female, rich and poor, all ethnic and racial backgrounds—although women and older individuals bear a disproportionate share of the burden. The impact is enormous. The most recent comprehensive accounting estimated the total annual direct and indirect costs for UI in the United States alone to be $19.5 billion (in year 2000 dollars; Hu et al, 2004). **In a 2000 report to Congress, the National Institutes of Health (NIH) estimated the direct cost of UI at $12.5 billion, a figure comparable to other important diseases such as Alzheimer disease, chronic obstructive pulmonary disease, and human immunodeficiency virus infection/acquired immunodeficiency syndrome** (Table 69–1). **Although medical insurance covers some expenses, patients with UI bear a considerable percentage of the overall disease costs for protective pads, laundry, and other expenses not covered by individual insurance plans.** The median out-of-pocket costs to women with weekly or more UI were $186/year (2005 dollars), but those with severe UI spent $372/year and those with very severe UI spent $1148/year (Subak et al, 2007). These costs appear to be increasing rapidly; Medicare expenditures on women with UI increased 57%, adjusted for inflation, between 1992 and 1998 (Anger et al, 2006). As summarized in the Third International Consultation on Incontinence (ICI) Economics Committee (Hu et al, 2005) the consequences of UI lead to serious morbidity, including falls and fractures; urinary tract infections; skin breakdown, including pressure ulcers; and admission to nursing homes. Logically, the presence of lower urinary tract symptoms, including overactive bladder (OAB)/UI symptoms, was found to be associated with approximately 50% increased emergency department visits, hospitalizations, and medical provider visits (Kannan et al, 2009). Despite these figures, and despite markedly increased efforts to inform the public about UI in the past decades, the majority of patients suffer quietly; in one study, fewer than one third of women with bothersome UI in a prepaid health care plan had been diagnosed in the prior 5 years and few had been treated (Kinchen et al, 2007).

The Urologic Diseases in America project has published detailed analyses of expenditures by the U.S. health care system for UI in both men (Stothers et al, 2005) and women (Thom et al, 2005). Among the more interesting findings was a dramatic increase in Medicare expenditures for women from $128.1 to $234.4 million between 1992 and 1998, despite decreasing hospitalizations and length of stay. In men, the prevalence of incontinence was estimated at 17% for those older than 60 years of age (any incontinence over the past 12 months) and the annual expenditures for privately insured male adults with UI were $7702 compared with $3204 for a man without UI. Demographic trends producing increasing numbers of elderly individuals will make this problem a critical challenge to urologists for the coming decades. Those interested in further information are referred to the report of the Epidemiology Committee of the Fourth ICI (Milsom et al, 2009) which provides excellent summaries of prevalence, incidence, remission, and risk factors.

The impact of UI cannot be measured in dollars alone. A "social cancer," UI impacts every facet—social, physical, sexual, psychological, and medical—of human life at work and at home. Numerous reports continue to document the serious impact of UI and overactive bladder (OAB) on quality of life using high-quality methodology (Coyne et al, 2003, 2004; Avery et al, 2004; Hajjar, 2004). Incontinent patients are more likely to have poor self-esteem, feeling shame and guilt, which may keep them from working effectively and partaking in social activities. UI is strongly associated with depression and vice versa

Table 69–1.

Cost of Illness and National Institutes of Health Support

DISEASE/CONDITION	YEAR OF COST DATA	TOTAL COST (IN BILLIONS $)	POPULATION	FY 1999 NIH SPENDING (IN MILLIONS $)
Asthma	1997	100.0	Total	140.4
Alzheimer disease and other dementias	1996	14.0	Older than 65	406.5
Cerebrovascular disease (stroke)	1998	43.3	Total	186.0
Chronic obstructive pulmonary disease	1998	37.3	Total	997.0
Diabetes	1997	98.2	Total	457.6
HIV infections/AIDS	1999	28.9	Total	1792.7
Incontinence	1995	26.3	Older than 65	6.9

(Steers and Lee, 2001), although the nature of this relationship is not established. Stress urinary incontinence (SUI) restricts the physical activity of patients, many of whom are otherwise healthy young women. The long-term deleterious effects of exercise reduction on health are unclear but may be important. **Urgency urinary incontinence (UUI) affects quality of life even more than SUI because of its unpredictable nature.** It may lead to loss of sleep as well as the limitations just mentioned. Sexual activity and interpersonal relationships suffer due to UI. Despite this, many and perhaps most individuals still do not seek help for UI for a variety of reasons, including misguided perceptions that UI is a normal consequence of aging and that there is no effective treatment (Shaw, 2001). **Even more importantly, expenditures for UI research are a small fraction of that spent on other conditions; NIH-funded UI research is less than 2% than that for stroke or Alzheimer disease** (see Table 69–1).

Rationale for Conservative Therapies

This "silent" epidemic was brought to national attention with the 1988 NIH consensus conference (Consensus Conference, 1989) followed by the publication of the first Agency for Health Care Policy and Research (AHCPR) practice guideline on UI in adults in 1992 (Urinary Incontinence Guideline Panel, 1992). Two of the principal recommendations of the guideline relate directly to improving the recognition of UI and validating it as an important medical problem:

- "The guideline calls for vigorous efforts to educate health care professionals about this condition so that they are sufficiently knowledgeable to diagnose and treat it."
- "It recommends that the public be advised to report incontinence problems once they occur and be informed that incontinence is not inevitable or shameful but is a treatable or at least manageable condition."

A third recommendation of the 1992 AHCPR guideline applies directly to the focus of this chapter:

- "The guideline recommends that surgery, except in very specific cases, should be considered only after behavioral and pharmacologic interventions have been tried."

The rationale for a conservative approach is clear. UI is not an inexorably progressive disease. A moderate delay in surgical therapy does not make such treatment more difficult. As will be amply documented, "conservative" therapies are effective, well tolerated, and safe. In addition, they are preferred by many patients. In the fifth National Association for Continence (NAFC) survey of 130,000 members, 52% of men and 48% of women ranked conservative therapies in general as "most helpful" (NAFC, 1999). Because the impact of UI varies greatly from patient to patient, the patient's feelings and goals must be taken into consideration in treatment planning. Thus, it is generally appropriate that the least invasive treatment that takes into account patient preferences and offers a reasonable chance for success be used first.

Description: What Is "Conservative," Who Is it for?

Traditionally, treatments that are totally reversible have been considered "conservative." Depending on the reviewer, this may or may not include drugs. However, given the data just presented regarding the costs associated with UI, a more considered assessment is in order. It can no longer be acceptable to call all nonpharmacologic, nonsurgical therapy "conservative" and recommend that such treatments routinely be employed as initial therapy. "Conservative" therapies must be held to the same standards as pharmacologic and surgical treatments. Effectiveness and safety must be determined in the context of patient satisfaction—it does little good to identify a treatment as safe and effective if patients are ultimately not satisfied and go on to "second line" treatments. Ultimately, the clinician and patient need to know the long-term outcomes for continence, adverse events, and cost-effectiveness to develop appropriate treatment algorithms. Ultimately, specific patient factors should be identified that will help predict the likelihood of response to a given therapy. Only then will the precious resources spent on UI be used most effectively.

To this end, levels of evidence and grades of recommendation are used whenever possible and conclusions drawn from systematic literature reviews and the ICI are highlighted. The AHCPR has used specified evidence levels to justify recommendations for the investigation and treatment of a variety of conditions, and the Oxford Centre for Evidence Based Medicine produced a widely accepted adaptation of the work of the AHCPR (Oxford Centre, 2001). The highest level of evidence (level 1) is based on systematic reviews and/or randomized controlled trials. The highest grade of recommendation (grade A) stems from consistent level 1 evidence. When possible these terms are used in the chapter, although there is a great need for further high-quality research and there is a notable lack of long-term follow-up of treatment effect for almost all of the therapies discussed.

Overview

The challenge to the urologist is to understand all of the treatments for UI, to be able to assess the patient efficiently yet thoroughly, and then to construct an appropriate treatment plan with the patient, taking into account the problem and the goals of the

individual patient. A review is presented of the basic nonsurgical tools used in treating UI—behavioral therapy, pelvic floor muscle training and biofeedback, external devices, and peripheral electrical and magnetic stimulation. Pharmacologic therapy is discussed in Chapter 68, surgical and injection therapy in Chapters 71 to 74, and neuromodulation in Chapter 70. The detailed evaluation of the incontinent patient is discussed in Chapter 64. Although it is important to rule out serious underlying or associated conditions, invasive testing is rarely required before initiating treatment with the measures discussed here. The focus here is on only that part of the evaluation that directly relates to treatment planning. It is generally sufficient to have a working diagnosis classifying the patient as having stress, urgency, or mixed UI. Patients with symptoms of OAB (the generic term for urgency and frequency with or without UI) are treated in the same manner as those with UUI. Practical algorithms are presented that provide a rational means of applying these varied treatments to an individual patient.

Key Points: General Considerations

- The consequences of UI lead to serious morbidity, including falls and fractures, urinary tract infections, skin breakdown including pressure ulcers, and admission to nursing homes.
- UI is not an inexorably progressive disease. Conservative therapies are effective, well tolerated, safe, and preferred by many patients. Thus it is generally appropriate that the least invasive treatment that takes into account patient preferences and offers a reasonable chance for success be used first.
- Although it is important to rule out serious underlying or associated conditions, invasive testing is rarely required before initiating treatment with conservative measures.

THE TOOLS OF CONSERVATIVE THERAPY

Behavioral Therapy

Behavioral therapy describes a group of treatments grounded in the concept that the incontinent patient can be educated about his or her condition and develop strategies to minimize or eliminate UI. It is sometimes erroneously reduced to the combination of fluid restriction and timed voiding but is actually a far richer therapy. In fact, one of the main problems with the term *behavioral therapy* is that it has been used so differently by various practitioners that its meaning has become diluted and vague. There is no one standard protocol or "best" methodology. The shared aims of behavioral therapy are illustrated in Figure 69–1 (Payne, 2000). Although various practitioners may have different emphasis, the different treatment approaches are unified by education about normal urinary tract function. The individual elements of behavioral therapies discussed here are centered on basic educational techniques such as operant learning, which is intended to model activity so as to reproduce normal behavior, in this case urinary continence (Palmer, 2004). All of the individual techniques discussed fall into this category, although pelvic floor muscle training is both a behavioral therapy (education about anatomy and function of the muscles, learning to use the muscles properly to control lower urinary tract function) and a physical therapy (strengthening the muscles to improve function). In any case, education binds the various techniques together and plays the central role in behavioral therapy.

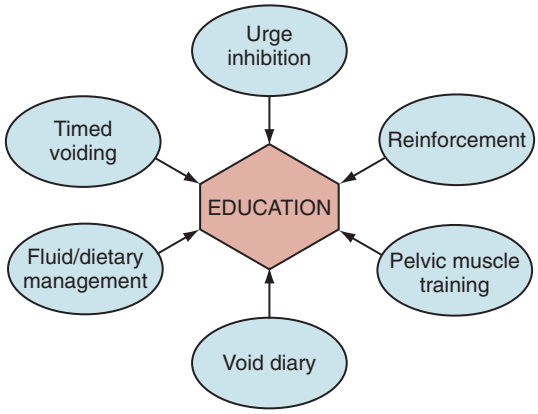


Figure 69–1. Behavioral therapy has many different components, all of which center on patient education. Education leads to understanding of normal lower urinary tract function and the patient's ability to self-regulate those functions.

Pelvic Floor Education

In a pure form of behavioral therapy there would simply be education about the normal anatomy of the pelvic floor musculature and the function of these muscles in maintaining continence. Pelvic muscle exercises could be explained along with the use of repeated rapid contractions ("quick flicks") to inhibit urgency by activating the spinal reflex pathway. However, the literature also includes sophisticated biofeedback techniques and treatment by physiotherapists in many trials of behavioral therapy. In most of these cases the purpose of the treatment is aimed at improving muscle strength and control; therefore the detailed discussion of this approach is included in the section on pelvic floor rehabilitation (see later).

Bladder Training/Timed Voiding

The term ***scheduled voiding*** is the generic term preferred for describing voiding regimens used for home-dwelling cognitively intact patients as opposed to ***prompted voiding*** **or** ***toileting***, terms properly applied to institutionalized or otherwise dependent patients. The most commonly used technique for patients with OAB and UUI is **"bladder training" ("bladder drill," "bladder retraining").** Bladder training starts a patient voiding on a fixed time interval schedule with the intention that, most of the time, the patient will urinate before experiencing urgency and UI. The interval is gradually increased with clinical improvement. Early practitioners of bladder training first established the effectiveness of intensive inpatient bladder training temporarily supplemented by medications (Frewen, 1978). Next, outpatient treatment was proven to be effective (Elder and Stephenson, 1980; Frewen, 1980). Finally, the durability of response, with 85% initial and 48% three-year response rates was reported (Holmes et al, 1983). **Bladder training should always be combined with urge inhibition techniques and is often combined with anticholinergic medical therapy,** particularly for more severe cases and for patients with neurogenic bladder. In contrast, **"timed voiding"** involves having a patient void on a fixed schedule, typically every 2 to 3 hours, and is intended to normalize frequency in a patient with infrequent voiding and/or diminished bladder sensation. This technique can be employed for patients with SUI with the idea that leakage will be less if the bladder is less full when physical stress occurs. It can also be used in a variety of patients with UUI who have a good bladder capacity (the classic example is that of patients with diabetic neurogenic

bladder; they do not have proper bladder sensation and thus delay voiding inappropriately).

Although there is no evidence as to the optimal program of bladder training, a common approach is to start at a safe interval based on the patient's bladder diary and increase the interval by 15 to 30 minutes as the patient achieves continence. The ultimate goal is a comfortable interval between voids with continence—a "retraining" of the bladder. Wilson and colleagues (2005) concluded that if no improvement is made after 3 weeks "the patient should be reevaluated and other treatment options considered." **The ICI authors acknowledge that the quantity of evidence is low but still make a grade A recommendation that "bladder training is recommended as a first line treatment of UI in women"** (Hay-Smith et al, 2009). Medical therapy is commonly employed initially, and there are rather limited studies comparing bladder training to anticholinergic medications for detrusor overactivity and UUI. One study demonstrated superior results with the combination of behavioral therapy and anorectal biofeedback in comparison to anticholinergic medication alone (oxybutynin chloride in titrated dosing) in a group of patients with urge and mixed UI (Burgio et al, 1998). Subsequent work by Burgio and colleagues (2000) confirms the clear truth that **behavioral and drug therapy are complementary, not competitive treatments;** the primary value of this research is to underscore the value of the behavioral component in the treatment plan. Logically, all patients should have behavioral therapy with medications used on an individualized basis. **The ICI committee** (Hay-Smith et al, 2009) **found level 2 evidence that the effect of bladder training may be enhanced by drug therapy and that, for women already taking an antimuscarinic drug, there was no additional benefit from adding brief written instructions on bladder training.**

Smoking

Aside from being a major risk factor for bladder cancer, smoking has been proposed as a risk factor for SUI by increasing coughing episodes and for OAB through bladder irritation from nicotine and toxins excreted in the urine. However, to date, epidemiologic studies of tobacco use have produced inconsistent findings. In women, some studies suggest that smoking increases the risk of UI, or at least severe UI, but others demonstrate no increased risk. A 1-year longitudinal study of 6424 women older than 40 years of age found that current smokers were at higher risk for both SUI and OAB than those who had never smoked, although statistical significance was seen only for OAB (Table 69–2). Former smokers had intermediate risk (Dallosso et al, 2004a). The same group also published a longitudinal study of 4887 men showing no association between smoking and OAB symptoms (Dallosso et al, 2004b). Another population-based study suggested that the risk of UI is limited to subjects with a history of more than 15 pack-years or current consumption of more than 20 cigarettes a day (Hannestad et al, 2003). One group of researchers found that smoking was associated with the severity of UI in women seeking surgical treatment (Richter et al, 2005). **As of yet there have been no adequate studies of smoking cessation on prevention or treatment of UI symptoms, and the ICI committee could make no evidence-based recommendation** (Hay-Smith et al, 2009). Despite these conflicting results, smoking cessation can logically be recommended as a general health measure, to reduce the risk of bladder cancer, and for those smokers with SUI particularly related to coughing. More research, particularly on the effectiveness of smoking cessation in treating UI and on the relationship between smoking and OAB, would be welcomed.

Table 69–2.

Risk Factors for Stress Urinary Incontinence and Overactive Bladder (Multivariate Analysis)

	Overactive Bladder		Stress Urinary Incontinence	
	RR	CI	RR	CI
Smoking vs. Never Smoked				
Former smoker	1.24	0.97-1.44	—	—
Current smoker	1.44	1.05-1.63	—	—
Obesity vs. Acceptable Weight				
Underweight	0.69	0.38-1.26	0.82	0.46-1.44
Overweight	1.25	0.94-1.67	1.24	0.93-1.63
Obese	1.74	1.22-2.12	1.46	1.07-1.99

RR, relative risk; CI, confidence interval.

Caffeine

Caffeine is well known as a nervous system stimulant and has demonstrable effects on detrusor muscle in vivo and in vivo, promoting detrusor overactivity. In one study of community-dwelling elderly women subjects who decreased caffeine and increased fluid intake, increased voiding volumes and fewer accidents were experienced (Tomlinson et al, 1999). High caffeine intake (>400 mg/day average) also correlated with urodynamic detrusor overactivity compared with stress-incontinent women (<200 mg/day average) (Arya et al, 2000). Caffeine has thus been postulated to be a cause of OAB symptoms, and **caffeine reduction has been advised for OAB patients.** Epidemiologic data are less clear. Reports usually break down consumption by type of beverage rather than actual caffeine consumption as is typically found in smaller studies of dietary intervention. Such small studies have typically shown a correlation between caffeine reduction and reduction of UI (Tomlinson et al, 1999; Bryant et al, 2002). Although larger studies would be helpful, it seems appropriate to recommend restriction, particularly in those patients with very high intake of caffeine. The ICI committee concluded that, "while large cross-sectional surveys indicate no association (level 3 evidence), small clinical trials do suggest that decreasing caffeine intake improves continence (level of evidence 2)" (Hay-Smith et al, 2009).

Fluid Management

Fluid restriction has been advocated in the treatment of both SUI and OAB. The rationale is that abdominal leak pressures appear to be volume dependent; therefore, physical stress occurring at lower bladder volumes both will be less likely to cause UI and will be associated with lower volume loss when leakage does occur. Similarly, OAB is believed to be a volume-driven phenomenon and slower filling promotes bladder compliance and lower pressures. This concept appears to be well accepted, as manifest by a recent U.S. study in which 38% of incontinent women had tried limiting fluids compared with 21% who tried Kegel exercises and 6% using prescription medications (Diokno et al, 2004a). On the other hand, extreme fluid restriction produces concentrated urine, which has been postulated to be a bladder irritant, leading to detrusor overactivity as well as constipation, which can negatively affect bladder function. Indeed, there is conflict regarding fluid management, with some investigators showing improvement with fluid reduction (Swithinbank et al, 2005) and others finding that increasing fluid intake improved UI (Dowd et al, 1996). Hashim and Abrams (2008) studied this controversy using

a crossover trial in which patients with OAB were instructed to first decrease fluid intake 25% to 50% below baseline and then to increase intake 25% to 50% above the baseline (or the reverse). A significant improvement in continence was noted with decreasing fluids (and increased UI was noted with increasing fluids). **It certainly seems reasonable to obtain a baseline frequency-volume chart and advise those patients with normal to increased fluid intake to try moderately restricting fluid intake. Any potential benefit must be balanced against possible problems with bladder infections and constipation.**

The types of fluid intake may also be significant; caffeinated beverages, acidic juices, and alcohol have been suggested to be bladder irritants. Caffeine was discussed earlier. Tea consumption correlated with UI in the EPINCONT study, but alcohol and coffee consumption did not (Hannestad et al, 2003). Although it is possible that caffeine is not the critical component, there is no clear hypothesis as to why tea (which has less caffeine than coffee) would be a relevant dietary factor but not coffee. Unless confirmed in other studies this may turn out to be a statistical aberration. In a population of Chinese women, alcohol consumption correlated with SUI but not UUI (Song et al, 2005), but other studies have shown no link between alcohol use and UI symptoms. Epidemiologic data support a link between consumption of carbonated beverages with both SUI and OAB (Dallosso et al, 2003) with level 2 to 3 evidence. Data on the effects of other beverages are scarce.

Other Dietary Management

A variety of different dietary maneuvers have been recommended for incontinent patients, including avoidance of alcohol, carbonated beverages, acid foods, salt, and others. A detailed study examining dietary factors noted an association between intake of vegetables with lower risk of OAB and intake of fruit with lower risk of SUI (Dallosso et al, 2003). These observations have yet to be reproduced in other populations. A follow-up report (Dallosso et al, 2004a) examined details of the diet in relationship to SUI and found that "intakes of total fat, saturated fatty acids and monounsaturated fatty acids were associated with an increased risk of SUI onset one year later. Of the micronutrients studied, zinc and vitamin B_{12} were positively associated with SUI onset." Because these observations are not hypothesis driven, confirmation is mandated before any recommendation can be given. No similar connection was identified with alcohol consumption in the same or other studies, and one study actually suggested a lower risk of OAB in men who were beer drinkers (Dallosso et al, 2004b). Once again, **the best advice for incontinent patients would seem to be to follow established guidelines for overall health with moderation in alcohol use and adequate intake of fruits and vegetables.**

Obesity/Weight Reduction

In no area of behavioral therapy has there been more advancement than in the recent work delineating **obesity as a serious, modifiable, and indeed reversible cause of UI.** There has long been an assumption that obesity is linked to UI, particularly SUI, by straining and potentially damaging the supportive structures of the bladder and pelvic organs. However, until recently little has been known about the true risk of obesity or about the effectiveness of weight loss as a therapy for UI.

Epidemiologic data provide persuasive support for a causal association between obesity and UI. The Nurses' Health Study identified 6,790 women with incident UI over a 2-year period among 35,754 women initially reporting no UI (Townsend et al, 2008a). There were highly significant trends of increasing risk of UI with increasing BMI and waist circumference (P for trend < .001 for both). The same research group showed that not only was obesity a risk for UI but also that weight gain was an independent risk for incident UI (Townsend et al, 2007). Gaining 5 to 10 kg after age 18 increased the risk of developing weekly UI by 44% (OR 1.44, CI 1.05 to 1.97) compared with women who maintained their weight within 2 kg—regardless of the initial weight! Gaining 30 kg increased the risk fourfold. The relationship between obesity, weight gain, and incident UI held for both SUI and UUI. Another powerful study from the United Kingdom followed 1201 women from their birth in 1946 annually from 48 to 54 years (Mishra et al, 2008). At the age of 20, 26, 36, and 43, body mass index (BMI) was positively associated with stress symptoms and severe UI in midlife and there appeared to be a cumulative effect. These relationships existed even after accounting for the effects of aging, childhood enuresis, childbirth characteristics, menopause, educational attainment, and smoking status. Interestingly, these researchers found that BMI was not significantly associated with symptoms of UUI. Finally, in a 1-year longitudinal study of 6424 women older than 40 years of age there was a strong correlation between BMI and the risk of both OAB and SUI (Dallosso et al, 2003) (see Table 69–2). Work in other populations consistently confirms the relationship between obesity and UI (Thom et al, 1997; Brown et al, 1999; Fornell et al, 2004; Larrieu et al, 2004; Melville et al, 2005b). The work in this field provides consistent findings describing a linear relationship between obesity and UI that cumulatively produce conclusive evidence for obesity as an important modifiable risk factor for UI.

More importantly, it is now clear that weight loss is an effective treatment for UI. A prospective randomized controlled trial (RCT) studied 338 overweight and obese women at two centers in the United States (Subak et al, 2009). All had BMI greater than 25 (mean 36) and at least 10 UI episodes per week (>75% with mixed UI). Subjects were randomized to an intensive 6-month weight loss program that included diet, exercise, and behavior modification (226 patients) or to a structured education program (112 patients). Weight loss was moderate (–8 kg vs. –1.6 kg), yet statistically significant decreases were found for all UI (–47% vs. –28%) and SUI (–58% vs. –33%). There was a trend to reduction in UUI (–42% vs. –14%, $P = .14$). More patients rated themselves to be moderately or very satisfied with the change in UI (75.8% vs. 46.8%, $P < .001$). These strong results were mirrored in a 2-year open-label trial in the United Kingdom of 64 obese women who were offered a commercially run program of diet and exercise (Rosemary Conley Diet and Fitness Clubs) aiming for weight loss of 5% to 10% over 6 months (Auwad et al, 2008) and by the initial pilot RCT by Subak and colleagues (2005). The high value of bariatric surgery for morbidly obese patients with UI has been clearly documented in four different case series, all showing dramatic reduction in UI episodes (Burgio et al, 2007; Kuruba et al, 2007; Maher et al, 2008, Laungani et al, 2009) (Table 69–3).

In summary, **it is clear that obesity is a cause for UI and weight loss is an effective treatment that also provides many other health benefits.** Weight loss should be first-line therapy for obese patients with UI, particularly SUI. More research is needed as to the role of obesity and weight loss in patients who are only overweight (BMI 25 to 30) and into the intriguing but less well defined relationship with UUI.

Urge Inhibition

Urgency is the predominant symptom for most patients with OAB and UUI. In many cases, UI has become a reflex as the patient has

Table 69–3.

The Value of Bariatric Surgery for Morbidly Obese Patients with Urinary Incontinence

CITATION	POPULATION	FOLLOW-UP	MEAN WEIGHT LOSS	ANY UI	ANY SUI	UUI
Kuruba et al, 2007	44 women/1 man	≥6 mo	64% of excess body weight	50% resolution/95% improved		
Maher et al, 2008	Unknown number, 80.5% female	1 yr	66% of excess body weight		87.7%	
Burgio et al, 2007	101 women	12 mo	18.8 ± 4.5 kg/m^2	66.7%-37%	59.8%-31.5%	35.9%-15.2%
Laungani et al, 2009	58 women	12 mo	66% of excess body weight	64% resolved/92% improved		

developed dysfunctional behavior in response to urgency. It is important to break the cycle of rushing to the toilet in response to urgency. The patient is instructed to stop, sit if possible, and use pelvic muscle contractions, distraction, or other techniques until urgency passes. There are no data on use of this practice as an isolated therapy, but it is a critical part of the overall treatment of patients with OAB; patients who learn to delay or overcome urgency may eventually be cured of their condition.

Other Lifestyle Issues

As summarized by Wilson and associates (2005), "there are many other lifestyle interventions suggested either by health care professionals or the lay press for the treatment of UI, including reducing emotional stress, wearing non-restrictive clothing, utilizing a bedside commode, decreasing lower extremity edema, treating allergies and coughs, wearing cotton underwear, and increasing sexual activity. These interventions are, however, all anecdotal in nature."

It has been shown (level 2 evidence) that stress-induced urine loss can be reduced by positional changes, that is, having a woman cross her legs with coughing, although this was only examined in the acute urodynamic testing situation (Norton and Baker, 1994). **The ICI panel** (Hay-Smith et al, 2009) **concluded that constipation and chronic straining may be a risk factor for the development of UI (level 3 evidence) but that there were no data on the effect of intervention.**

There is inadequate knowledge about the relationship of strenuous activity, sports, and work. It has long been known that low-grade SUI is common in female college athletes (Nygaard et al, 1994). However, the long-term clinical significance of this is unknown. Because women are universally advised to restrict activity after surgical treatment for SUI one might assume that the effect of postoperative activity on outcome had been investigated, but there are actually no useful data. One study has examined the association between physical activity and risk of developing UI by analysis of data from incident cases of UI in the Nurses' Health Study of women aged 54-79 years (Danforth et al, 2007). The authors found that increasing levels of total physical activity (which was mainly walking) were significantly associated with a reduced risk of UI and SUI although not with UUI (Table 69–4). The same researchers examined the dataset to explore the relationship for younger women, age 37 to 54 (Townsend et al, 2008b). They again found that activity was inversely correlated with incident UI and that the protective effect of exercise appeared to be present for both SUI and UUI. Accounting for the independent effect of BMI attenuated the findings, but exercise remained a significant independent factor. Although it is possible that these data may not apply to women engaged in very high level, chronic, strenuous activity, the important lesson is that good health habits clearly correlate with a lower risk of UI.

Table 69–4.

Physical Activity and Urinary Incontinence

	Any Incontinence	
	Cases*	OR† (95% CI)
Physical Activity (MET-hr/wk)		
Quintile 1	524	Referent
Quintile 2	534	1.04 (0.92-1.18)
Quintile 3	465	0.90 (0.79-1.02)
Quintile 4	434	0.85 (0.75-0.98)
Quintile 5	398	0.81 (0.71-0.93)
P for trend		<.01
Walking (MET-hr/wk)‡		
Quintile 1	524	Referent
Quintile 2	524	1.01 (0.88-1.14)
Quintile 3	470	0.91 (0.80-1.04)
Quintile 4	463	0.90 (0.78-1.04)
Quintile 5	374	0.74 (0.63-0.88)
P for trend		<.01

*Incontinence cases were defined as leaking urine at least once per week.
†Odds ratios were adjusted for age, race or ethnicity, body mass index, parity, cigarette smoking, and postmenopausal hormone therapy.
‡Walking analyses were controlled for total activity.
MET, metabolic equivalent task; OR, odds ratio; CI, confidence interval.
From Danforth KN, Shah AD, Townsend MK, et al. Physical activity and urinary incontinence among healthy, older women. Obstet Gynecol 2007;109(3):721–7.

The **ICI committee concluded** that "strenuous exercise is likely to unmask the symptoms of SUI during the provocation. There is currently no evidence that strenuous activity causes the condition of UI" and **"there is good prospective cohort information suggesting that moderate exercise decreases the incidence of UI in middle aged and older women"** (level of evidence II) (Hay-Smith et al, 2009).

Other Health Issues

Increasing attention has been paid to the relationship between **diabetes** and UI. Data from the Nurses' Health Study and the Nurses' Health Study II were examined to study associations between diabetes and UI type in 71,650 women (Danforth et al, 2009). Incident UI cases were identified over a 2-year period. The incidence of at least weekly UI was 5.3% among women without type 2 diabetes and 8.7% among women with diabetes (adjusted odds ratio 1.2; 95% CI 1.0 to 1.3; $P = .01$). This increase appeared largely explained by significantly greater odds of UUI (OR 1.4; 95% CI 1.0 to 1.9; $P = .03$). A cross-sectional mail survey of community dwelling women screened women for pelvic floor disorders while diabetes status and other risk factors were obtained from medical record review. Of 3,962 women, 393 (10%) had diabetes. Among women with diabetes, being obese was associated with SUI and

OAB (Lawrence et al, 2007). This finding was supported by analysis of an RCT comparing treatment of diabetics with UI using oral hypoglycemics (metformin) versus lifestyle intervention (weight loss and exercise) (Brown et al, 2006). The researchers found that the prevalence of UI was lower in women randomized to lifestyle intervention than those on medication or placebo.

There is a strong relationship between UI and **depression.** In one study, patients with UI were almost three times more likely to have major depression than those without (6.1% vs. 2.2%) and patients with UI and depression had significantly greater decrements in quality of life and functional status than those with UI alone (Melville et al, 2005a).

A specific investigation into comorbidities and UI was undertaken by a research group in the United Kingdom who note, "The bladder forms part of a sensitive and complex system of the body that operates largely autonomously but remains under voluntary control. As such, it is vulnerable to general disease processes related to ageing. Thus, associations with poor health and obesity could represent pathogenic as well as functional involvement of the bladder." (McGrother et al, 2006). They used a postal survey of a random sampling of over 19,000 community dwelling women older than 40 years of age with 1-year follow-up surveys. There were strong correlations between poorer health and increased prevalence of both SUI and OAB. There are many interesting findings but one of the most important is that **"OAB was independently predicted by poor health ... The association with old age, although consistent with other studies, disappeared after controlling for a full range of specific comorbidities, suggesting that the condition is age related rather than age dependent."**

CONCEPT OF "THERAPEUTIC PACKAGE"

It is, of course, logical and appropriate that these various behavioral treatments be used together in a therapeutic package. They are inherently complementary, are completely reversible, and lack significant adverse effects. They also can be (and typically are) combined with the pelvic floor rehabilitation techniques discussed later. Patients who are motivated to avoid surgical or pharmacologic interventions will be inclined to seek out such treatments; the problem remains as to the most efficient way to deliver therapy to the average patient.

Such an approach showed utility in an RCT in which patients were randomized to receive a package of behavioral therapy including individualized counseling about fluid and caffeine intake, quick pelvic floor muscle contraction, voiding frequency, and management of constipation or placed on a waiting list (Kincade et al, 2007). This design provides a good starting point for use in many patients with UI. In addition, Diokno and colleagues (2004b) demonstrated that two simple group sessions were effective in preventing UI. The trial randomized 359 continent women older than age 55 years who were recruited and observed for 1 year. The treatment group received a single 2-hour group session teaching pelvic floor muscle training (PFMT) and bladder training as well as an audiotape on PFMT for reinforcement; the control group was not treated. There was one follow-up office visit with a nurse specialist in 2 to 4 weeks. At the end of 1 year, 56% of the treatment group reported the same or better continence compared with only 41% of controls; 37% of the treatment group reported "absolute continence" compared with 28% of the controls. Several other studies using various combinations of therapies led the ICI group (Wilson et al, 2005) to a **level A recommendation that "women with stress, urge, or mixed incontinence should be offered a conservative management program as first line therapy for UI" while acknowledging that there were inadequate data to define the optimal treatment package and that most of the data comes from trials in older women.**

Key Points: The Tools of Conservative Therapy: Behavioral Therapy

- Behavioral therapy describes a group of treatments grounded in the concept that the incontinent patient can be educated about his or her condition and develop strategies to minimize or eliminate UI. There is no one standard protocol or "best" methodology. The different treatment approaches are unified by education about normal urinary tract function.
- Bladder training starts a patient voiding on a fixed time interval schedule with the intention that the patient will urinate before experiencing urgency and UI. It can be used with or without medical therapy. There is a grade A recommendation that "bladder training is recommended as a first line treatment of UI in women."
- There have been no adequate studies of smoking cessation on prevention or treatment of UI symptoms.
- There is level 2 evidence suggesting that decreasing caffeine intake improves continence.
- One prospective study showed improvement in UI with fluid restriction; the potential benefit must be balanced against possible problems with bladder infections and constipation.
- Epidemiologic data support a link between consumption of carbonated beverages with UI, with level 2 to 3 evidence.
- Epidemiologic studies provide consistent findings describing a linear relationship between obesity and UI that cumulatively provide strong evidence for obesity as an important modifiable risk factor for UI.
- There is level 1 evidence that weight improves continence, and the effect appears to be on both SUI and UUI symptoms. Weight loss should be first-line therapy for obese patients with UI, particularly SUI. However, effect of weight loss for the overweight population (BMI 25 to 30) is less clear.
- There is level 2 evidence that moderate exercise decreases the incidence of UI in middle-aged and older women.
- Although the prevalence of OAB/UUI increases with age it appears that this is due to comorbid conditions and not aging itself.
- Although acknowledging that the optimal treatment package is unknown, combinations of conservative therapies are logical and appropriate, leading to a level A recommendation that "women with stress, urge, or mixed incontinence should be offered a conservative management program as first line therapy for UI."

PELVIC FLOOR REHABILITATION

The term *pelvic floor rehabilitation* should be applied to any treatment intended to increase the strength, bulk, and function of the pelvic floor/levator muscles. Muscle rehabilitation can be achieved through a variety of tools, which

can be classified as "basic" or "advanced," depending on the cost and complexity of the therapy. **Basic treatments (Kegel exercises, vaginal cones, and simple home perineometry) are used in the home setting, require no or inexpensive equipment, and can be administered by a relatively unskilled therapist. Advanced treatments are used in an office setting, are administered by a trained therapist, and/or require more sophisticated equipment.**

Pelvic Floor Muscle Training

Pelvic floor exercises (PFE) or "Kegels" have been advocated in the treatment of UI since the 1950s (Kegel 1948a, 1948b, 1956). Dr. Kegel taught his patients to forcefully contract the pelvic muscles to treat and prevent postpartum UI. Unfortunately, **half of patients are unable to perform a proper contraction with simple instructions** (Bump et al, 1991), **and up to one fourth will actually promote UI with their efforts.** Indiscriminant recommendation of this therapy to all incontinent patients has created a negative bias that PFE are just "something to do" before pharmacologic or definitive surgical treatment. It should also be acknowledged that Dr. Kegel routinely employed a perineometer with his patients in one of the first documented uses of biofeedback in medicine. This implies that Kegel exercises alone should not be considered the standard treatment for pelvic floor rehabilitation.

Currently, ***PFMT* is the currently accepted term,** replacing *Kegels* and *PFE.* It is defined as "any program of repeated voluntary pelvic floor muscle contractions taught by a health care professional" (Wilson et al, 2005) and is advocated for both prevention and treatment of UI. "Training" is preferred over "exercises" to emphasize the importance of a regimen of repeated exercise over time. **The therapy is intended to improve the function of the pelvic floor muscles; whether this happens primarily by increasing the strength, power, and speed and/or improving the timing and coordination of a contraction is not known. Much more is known about the clinical effectiveness of the therapy than the exact physiologic changes that produce the outcomes.** With repeated exercise a muscle will develop improved responsiveness that may lead to a faster and/or stronger contraction before any increase in actual bulk. Over longer periods of time the muscle fibers will progressively hypertrophy, producing increased bulk. The ICI committee (Hay-Smith et al, 2009) points out that (1) an increase in strength occurs before visible hypertrophy, (2) early improved strength results from neural adaptation, and (3) hypertrophy begins only after a minimum of 8 weeks and may continue for some years. In any case, muscle bulk is clearly not a prerequisite for improved continence with PFMT, and many studies have failed to show a correlation between improved strength and improved continence.

Although a huge number of studies have investigated PFMT it is challenging to draw clear conclusions for a variety of reasons:

1. Treatment regimens vary widely.
   a. Type of exercises
   b. Number and frequency of exercises
   c. Initial confirmation of correct technique
   d. Use of various forms of biofeedback in teaching
2. Patient types are often widely mixed.
   a. Type of UI
   b. Severity of UI
   c. Temporal relationship of therapy to childbearing (or prostate surgery in males)
3. Outcome measures vary.
   a. Self-reported versus objective
   b. "Cure" versus "improved"
4. Duration of effect is not well defined.

When possible these issues are addressed in the following discussion. The interested reader is strongly encouraged to study the comprehensive review performed by the ICI committee (Hay-Smith et al, 2009).

It is difficult to analyze the literature on PFMT because training is commonly combined with other modalities. The combination can range from general advice about management of UI, specific strategies such as bladder diaries/timed voiding, and biofeedback training. **It is important to realize how differently PFMT is applied in research trials and in European practice compared with standard U.S. clinical practice.** The definition of PFMT clearly states that it is "taught by a health care professional." In clinical trials this is always the case; the instructor is typically a skilled physiotherapist who may apply a variety of techniques to promote learning as needed by an individual patient. In U.S. clinical practice a patient is often given only verbal instruction. In more ideal cases the patient will have written instruction after an initial assessment including a pelvic examination and assessment of and instruction in pelvic muscle contraction. Regular follow-up is not an option in most health care settings owing to poor or absent reimbursement. This divergence in care means that results obtained in research trials may be difficult or impossible to obtain in standard clinical practice and that the difference between stand-alone PFMT and PFMT with adjunctive treatments may be much greater in U.S. clinical practice than in research studies. The following discussion of PFMT results is based on the published literature; it remains a challenge for the clinician to translate these somewhat idealized results into clinical practice.

Does PFMT Prevent Urinary Incontinence in Childbearing Women?

PFMT has been used to prevent UI in pregnant women, because pregnancy and vaginal birth are strong risk factors for UI. Three prospective RCTs have investigated this question (Sampselle et al, 1998; Reilly et al, 2002; Mørkved et al, 2003), producing a **grade A recommendation that primiparous women "should be offered a supervised and intensive strengthening antepartum PFMT programme to prevent post-partum UI"** (Hay-Smith et al, 2009). In all three trials the PFMT group had less postpartum UI; and in one study (Reilly et al, 2002), the effect was still present at 4 years postpartum, although only 100 of 268 patients were available for follow-up. There was no evidence supporting the utility of PFMT in pregnant, previously continent, multiparous women. The **evidence reviewed by the ICI group for postpartum PFMT was less compelling, but it was concluded that the evidence also supports a grade C recommendation for supervised intensive PFMT for women after delivery utilizing instruments or delivery of a large infant** (≥4000 g) (Hay-Smith et al, 2009).

Is PFMT an Effective Treatment for Urinary Incontinence and Which Patients Are Good Candidates?

The most important question is whether PFMT is effective in the management of established UI and, if so, how to most effectively apply the therapy to the large population of incontinent women. Seventeen RCTs comparing PFMT to no intervention, placebo, sham, or control in childbearing women were summarized by

Hay-Smith and colleagues (2009) and are based on the findings of a Cochrane review (Dumoulin et al, 2008). Although the magnitude and duration of the expected effect is not well defined, the overwhelming majority of the trials showed effectiveness of PFMT, leading to a **grade A recommendation that "PFMT should be offered, as first line therapy, to all women with stress, urge or mixed incontinence."** This recommendation is, of course, based on the combination of demonstrable effectiveness with essentially no risk to the patient. It does not mandate that all patients undertake a formal course of PFMT before surgical treatment. **However, there are as yet no studies that adequately define patient groups who are unlikely to respond to PFMT** based on clinical factors such as age, obesity, and so on. In most cases, studies have been too small to examine such predictive factors and there may well be a role for individualized therapeutic recommendations if proper studies could be done. A single trial investigating PFMT for UI in pregnancy did not show efficacy (Woldringh et al, 2007), but this has been criticized owing to lack of specificity about the intervention. The ICI committee specifically points out the need for a large scale, pragmatic trial of PFMT with detailed reporting of long-term (>5 years) follow-up (Hay-Smith et al, 2009). The authors also describe what they believe are the key components of an effective program: (1) it is based on sound principles (specificity, overload, and progression), (2) correct contraction is confirmed before training, and (3) women are supported to maintain treatment adherence (level of evidence 4).

The quality of the data for men with postprostatectomy UI is less robust with too many single-center, underpowered trials. Research has focused on use of pelvic floor therapies to hasten return of continence. **A systematic review of the literature concluded that although training may hasten return of continence after surgery it does not affect long-term outcome** (MacDonald et al, 2007). Others have found that there is no difference between routine preoperative and postoperative PFMT (Filocamo et al, 2005). In contrast, one RCT found that significantly more men were completely continent 1 year after prostatectomy when performing PFMT with a physiotherapist than without (Overgard et al, 2008). When PFMT is used for established postprostatectomy UI, the results similarly do not establish long-term benefit of therapy, with or without biofeedback. Interested readers are referred to a Cochrane review on the subject (Hunter et al, 2004).

Within these overarching categories it is likely that specific patient subgroups are more or less likely to benefit from PFMT (and probably other conservative techniques). However, studies have not been designed to specifically identify such groups and subgroup analysis of relatively small trials is fraught with error. In one retrospective series of 447 women with SUI, 49% of patients were "successfully treated." Success appeared to be more likely in patients with milder degrees of UI (not using pads: 67% success; not having daily UI: 63% success; no leakage at first cough: 60% success). Independent risk factors for failure included two or more leaks per day, presence of leakage at first cough, and use of antidepressant/anxiolytic medications (Cammu et al, 2004). Burgio (2004) argues that PFMT is equally effective in treating UI with stress, urge, and mixed UI, whereas Goode (2004) commented that there are as yet no reliable predictors of treatment outcomes.

Other Benefits of PFMT

A small pilot study demonstrated effectiveness of PFMT in symptoms of prolapse and in objective prolapse stage for women with symptomatic stage I or II prolapse (Hagen et al, 2009). If confirmed in larger studies with long-term follow-up this could have a major impact on women's health.

Implementing PFMT in Clinical Practice

If PFMT is to be accepted as standard therapy, one must also define how to implement training in clinical practice. Many articles have evaluated different regimens and use of ancillary tools, but in many cases quality is lacking. In evaluating the literature it is important to ensure that groups being compared are truly equivalent in all parameters other than that being tested. Key elements include the usual demographic characteristics, the degree of supervision (expertise and contact time), the intensity of the exercise program (number, frequency, and duration of contractions), use of ancillary tools, and, of course, the length of the program and follow-up. **The ICI group** (Hay-Smith et al, 2009) **concluded that:**

1. **Clinicians should provide the most intensive heath care professional–led PFMT program that is possible within service constraints because programs taught and supervised by health care professionals are superior to self-directed programs.**
2. **No PFMT regimen has been proven most effective; treatments should be based on the exercise physiology literature.**
3. **There is no demonstrable benefit of adding clinic or home biofeedback to a PFMT program.**

A representative strengthening program for PFMT used by the author suggests:

1. **Sets of 8 to 12 near-maximal contractions are recommended.**
2. **Each contraction is held 6 to 8 seconds with an equivalent rest period.**
3. **At the end of each set a series of 5 to 10 rapid contractions are performed.**
4. **The exercises are repeated five times per day, every other day.**

In addition to the strengthening program **the author recommends use of the "knack" maneuver to promote timing of the contraction coincident to coughing for SUI patients** (Miller et al, 2001, 2008) **and "quick flicks," which are short, rapid contractions intended to inhibit urgency for those with OAB symptoms.**

Long-Term Results of PFMT

The need to practice PFMT is probably lifelong, and patients should be counseled to integrate exercise into their normal routines. Bo and colleagues (2005) reported a 15-year follow-up of a randomized trial between intensive exercise therapy and home exercises in women with SUI. Ninety percent of the subjects were located and responded to a questionnaire. Half of the women in both groups eventually underwent surgical treatment. It is clear that exercises were not continued (28% exercise at least weekly and 36% never exercise). Although most women in both groups were satisfied with their current condition, "the marked benefit of intensive PFMT seen short-term was not maintained 15 years later." The author suggests that training one to two times a week at high intensity is enough to maintain muscle strength. A second group was able to query 79 of 123 women with SUI or mixed UI initially treated with PFMT after 8 years. Again, less than 10% continued training throughout the interval (Kondo et al, 2007). Yet 39% of the group considered the treatment to be successful (>50% improvement). On the other hand, Cammu and

colleagues (2000) found that 16 of 24 patients (67%) originally satisfied with PFMT remained so after 10 years and only 2 of 24 (8%) went on to surgical therapy. They attributed sustained improvement to patients' use of a voluntary pelvic muscle contraction ("perineal lock" or "knack") before physical stress.

PFMT versus Other "Conservative" Modalities

PFMT has also been compared against other therapies, including various forms of vaginal cones, electrical stimulation, bladder training, and pharmacologic therapy. Again, most of the individual trials are relatively underpowered, often differ in the degree of therapist contact/supervision, and have a short follow-up. In addition there is always a selection bias because some women will not accept use of vaginal devices such as cones, biofeedback probes, or stimulators. **The following conclusions regarding first-line therapy came from the ICI committee** (Hay-Smith et al, 2009):

For women with SUI:

- PFMT is superior to electrical stimulation, particularly if PFMT is intensively supervised (grade B).
- PFMT is better than bladder training (grade B).
- PFMT has equivalent efficacy to duloxetine with fewer adverse effects (grade C).
- PFMT and surgery are both effective therapies but PFMT is better as a first-line treatment because it is less invasive (grade C).

For women with SUI or mixed UI:

- PFMT is better than vaginal cones (grade B).
- PFMT is better than phenylpropanolamine or clenbuterol because of the side effects with the medications (grade B).

For women with UUI or mixed UI:

- PFMT and bladder training are both effective first-line therapy (grade B).
- PFMT is superior to oxybutynin (grade B).

Although it is scientifically desirable to understand the relative value of each of these conservative treatments, the practical fact is that these are generally complementary tools. In particular, **bladder training and PFMT are useful for all types of UI and require no specialized equipment.** Wyman and colleagues (1998) found that adding PFMT to bladder training produced superior short-term results. Another clinical trial demonstrated the feasibility of using a booklet to provide an initial "package" therapy to be used without ongoing supervision (Goode et al, 2003). The standardized booklet was compared with one group receiving office behavioral training and another that used home vaginal electrical stimulation. Episodes of UI were reduced by 52.5%, 68.6%, and 71.9%, respectively. Although the booklet approach was inferior to the more intensive treatment, the results, including a statistically significant improvement in quality of life in all groups, suggest that **most cost-effective way to deliver therapy would be to begin with such a booklet, reserving office-based therapy requiring expert clinicians for those not satisfied with the initial results.**

Key Points: Pelvic Floor Rehabilitation: Pelvic Floor Muscle Training

- The term *pelvic floor rehabilitation* should be applied to any treatment intended to increase the strength, bulk, and function of the pelvic floor/levator muscles.
- Basic treatments are used in the home setting, require no or inexpensive equipment, and can be administered by a relatively unskilled therapist. Advanced treatments are used in an office setting with a trained therapist or require more sophisticated equipment.
- *Pelvic floor muscle training* (PFMT) is the currently accepted term, replacing *Kegels* and *pelvic floor exercises*. It is defined as "any program of repeated voluntary pelvic floor muscle contractions taught by a health care professional."
- Evidence supports the effectiveness of routine PFMT to prevent UI in primiparous women and for supervised intensive PFMT for all women after instrumental delivery or delivery of a large infant (grade C recommendation).
- The overwhelming majority of the trials showed effectiveness of PFMT in treating established UI, leading to a grade A recommendation that "PFMT should be offered, as first line therapy, to all women with stress, urge or mixed incontinence."
- No role has been established for pelvic floor rehabilitation in the treatment or prevention of postprostatectomy UI.
- Success with PFMT appears to be more likely in patients with milder degrees of UI. Independent risk factors for failure included two or more leaks per day, presence of leakage at first cough, and use of antidepressant/anxiolytic medications.
- The principles of a quality PFMT program include:
  1. Clinicians should provide the most intensive PFMT supervision that is possible within service constraints.
  2. No PFMT regimen has been proven most effective; treatments should be based on the exercise physiology literature.
  3. There is no demonstrable benefit of biofeedback over PFMT alone, although properly powered quality trials are probably warranted to study this issue further.
- A representative strengthening program for PFMT could include sets of 10 to 12 near-maximal contractions, with each contraction held 6 to 8 seconds with equivalent rest period and repeated three to five times per day, every other day.

Biofeedback

Biofeedback is any method of training a patient to control a bodily function by providing him or her with information about that function. In this case, the patient hopes to gain control of, and strengthen, the pelvic muscles. The tools range from inexpensive vaginal cones to office systems costing thousands of dollars. One must remember, however, that no study has ever demonstrated that a particular device is responsible for restoring continence. On the contrary **it is clear that the motivation of the patient and the experience and ability of the therapist are the critical factors for success** (Bo et al, 1990a). Published articles in the UI literature typically involve trained physical therapists specializing in UI and pelvic floor problems. In contrast, the biofeedback therapist in the "real world" setting is often a nurse or technician possessing only brief training in the subject. Finally, **biofeedback is only a tool, a teaching technique; real improvement in muscle strength and continence is dependent on the patient's work outside the office.** The bottom line with all of these pelvic floor therapies is that no piece of equipment is as important as the effort the patient puts into the program.

Palpation Only

Most of the literature on PFMT assumes at least initial basic evaluation and teaching by digital assessment of a pelvic floor muscle contraction during pelvic examination. This may or may not be performed at all follow-up visits. Although this is clearly an example of biofeedback, in the PFMT literature the term *biofeedback* is generally reserved for studies using sophisticated electronic or pressure devices to record pelvic floor activity.

Vaginal Cones

Sets of cones sold with varying numbers of cones ranging from 3 to 9, each of different weight, have been marketed for treatment of UI for many years (Fig. 69–2). The patient is instructed to insert a cone in the vagina above the levator muscles and hold it in for 15 to 20 minutes while in the erect position. **The concept is that the sensation of the cones slipping down or falling out of the vagina will provide biofeedback to the patient to learn to identify and contract the pelvic muscles.** Initially, the patient may only be able to hold the cone at rest for a short time but as she gains strength she will be able to retain the cone with normal activity. She then progresses to the next heaviest cone. This provides additional biofeedback and may encourage the patient to continue with therapy. It is unlikely that this is equivalent to the effect of a skilled therapist, but this approach offers convenience at a very low cost. There are many limitations in the use of cones. Many patients will not use any vaginal device, a substantial group will not even be able to retain the lightest cone, and some patients will retain the cones with use of thigh adductor muscles without proper levator contraction. They are obviously not useful for the incontinent male patient.

The clinical effectiveness of vaginal cones has been examined in a Cochrane systematic review (Herbison et al, 2004). The authors identified 15 studies involving 1126 women, of whom 466 received cones. However, the trials were small, many were published only as abstracts, and "the quality was hard to judge." Cones were believed to be better than no treatment but not clearly different from PFMT or electrical stimulation. Hay-Smith and colleagues (2009) concluded that there was grade B evidence that vaginal cones could be offered to women with SUI **"who can and are prepared to use them" but cones were inferior to PFMT (grade B). Cones were equally effective to electrical stimulation in four trials reviewed (grade B) and adding cones to PFMT does not appear to offer additional benefit.**

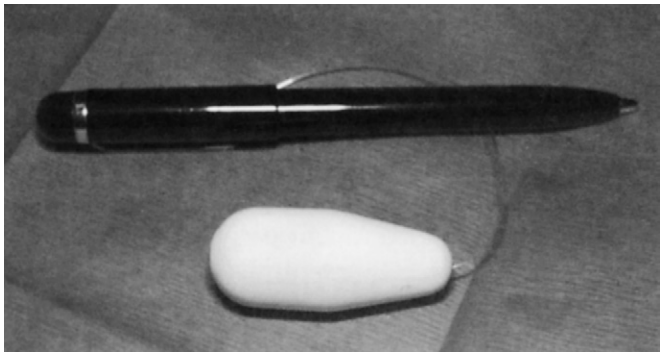


Figure 69–2. Small, weighted cones placed in the vagina provide biofeedback when the patient feels the cone slipping out and must tighten the pelvic floor muscles to retain it. They are typically sold in sets of five with progressively greater weight. (From Payne CK. Advances in nonsurgical treatment of urinary incontinence and overactive bladder. Campbell's Urology Update 1999;1[1]:6.)

Other Biofeedback Techniques

Most modern biofeedback units employ vaginal/anal sensors that display either pressure or electromyographic (EMG) activity on a computer screen for visual biofeedback (Fig. 69–3). In some cases, auditory biofeedback corresponding to the muscle contraction is provided, and this can be beneficial for those patients with visual limitations. Perineometers measure vaginal or anal squeeze pressure (as per Arnold Kegel), are available for about $100, and, in theory, might be more effective in teaching a patient to identify the proper muscles than vaginal cones. In practice, however, **pressure-based biofeedback has been criticized because abdominal pressure is also transmitted to the probe** (Bo et al, 1990b). A patient may perform a Valsalva maneuver, which is counterproductive, because the pelvic muscles are contracting. The devices are more expensive and have the same problems with patient acceptance as vaginal cones. **Pressure-based biofeedback has largely been supplanted by EMG systems,** which are more expensive ($250 to $400 and up). These reduce the problem with Valsalva maneuvers but **do not guarantee proper muscle isolation because they only register activity of one muscle group.** Devices used with vaginal sensors, rectal sensors, and perineal patches are available. Although many randomized controlled trials have been performed examining exercises with and without biofeedback, the results are mixed, and a recent review concluded, "The evidence for firm recommendations to include biofeedback in these conservative strategies is lacking, and further research is needed to clarify the role of biofeedback" (Weatherall, 2000). **The ICI review data presented earlier** (Hay-Smith et al, 2009) **concluded that there is no benefit to adding biofeedback to a good PFMT program.**

Peripheral Stimulation

Dissatisfaction with the time, effort, and expertise required for office-based biofeedback generates an interest in passive pelvic floor therapy. The two modalities used in this manner are peripheral electrical stimulation and magnetic stimulation.

Electrical Stimulation

There have been innumerable different devices used to assist and promote rehabilitation of the pelvic floor muscles. The type of stimulation varies by location, current type, waveform, and intensity. **High-frequency stimulation (50 to 200 Hz) generally has been used with vaginal or anal electrodes for SUI; the proposed mechanism of action is to directly stimulate the pelvic floor and urethral muscles thereby causing contractions.** Exactly how this improves continence—by changing muscle reaction or increasing bulk/strength—is not well documented in the literature. **Electrical stimulation can also be used to treat patients with urge or mixed UI.** Low-frequency stimulation **(5 to 20 Hz)** is typically employed, **intending to activate inhibitory bladder reflexes and reduce detrusor overactivity.** Although most devices employ vaginal or anal electrodes, the effect can also be achieved less invasively with peripheral stimulation using patch electrodes in the perianal or posterior tibial nerve distribution (McGuire et al, 1983; Hasan et al, 1996). Male patients may find this mode of therapy more acceptable than anal electrodes.

The advantage of this modality is that it is dependent only on patient compliance, not effort. The initial expense

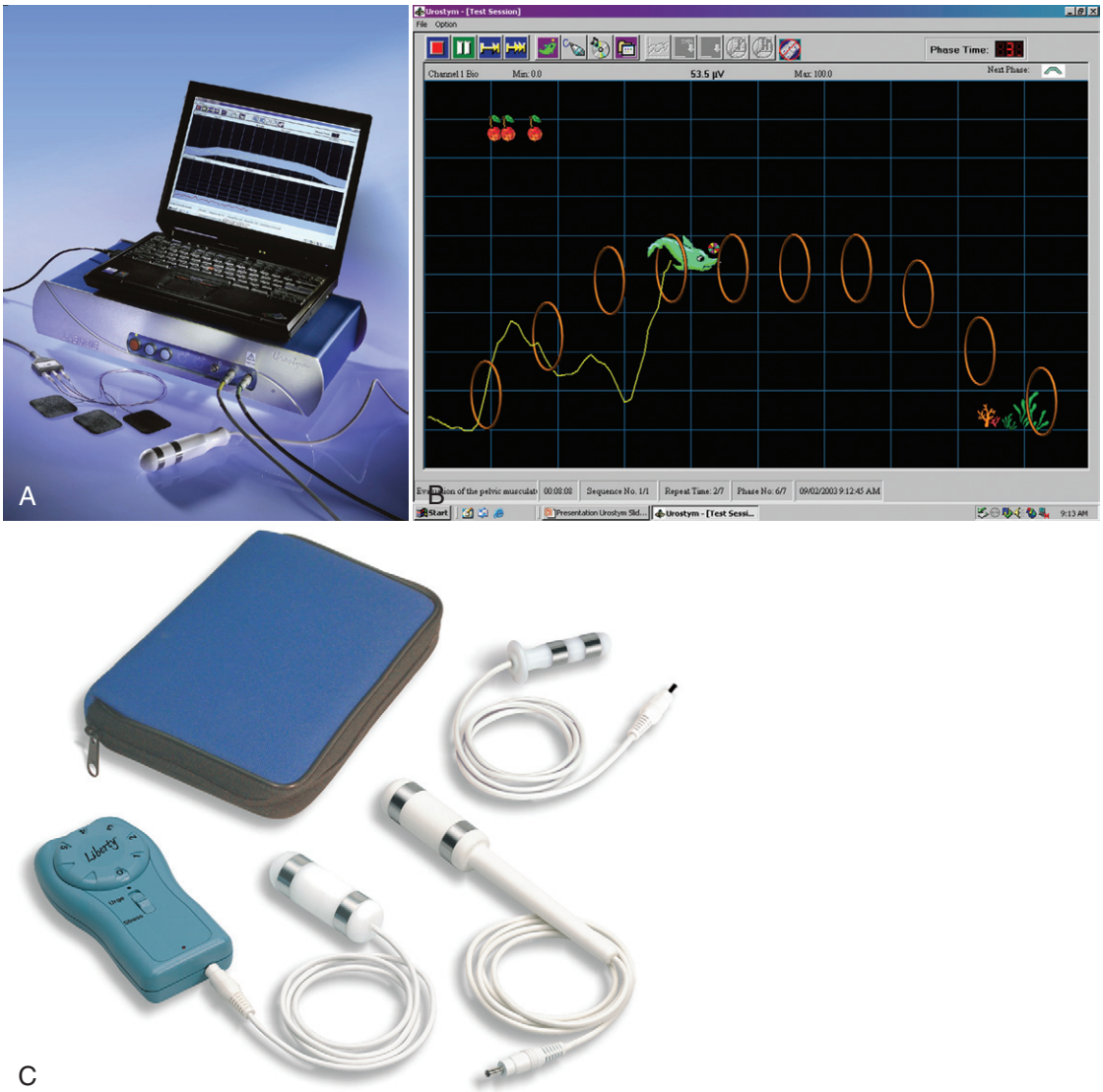


Figure 69–3. Tools for pelvic floor rehabilitation. **A,** Laptop-based office biofeedback system with probe and patches. **B,** Animated screen for pediatric biofeedback. **C,** Typical home electrical stimulation unit. (**A** and **B,** Courtesy of Laborie Corporation, Williston, VT; **C,** Courtesy of Utah Medical Products, Midvale, UT.)

($600 to $800) can be partially offset by home administration of treatments. Electrical stimulation can be combined with office biofeedback using the same probe on some systems.

Electrical stimulation has potentially wide applicability and reasonable cost. Unfortunately, the electrical stimulation literature is characterized by case series with small numbers of patients using different devices and widely varying treatment algorithms, few of which provide any follow-up after the initial assessment of response. In addition, the role of dual stimulation for mixed UI has not been adequately evaluated; this treatment would seem to be ideal for such patients using the high frequency for the sphincter and low frequency for the bladder. The various types of protocols for stimulation are well summarized by the ICI committee (Hay-Smith et al, 2009).

The most clinically useful data come from three RCTs using the EMPI product (EMPI Corporation, St. Paul, MN). One study including 121 women with UI found no significant changes in any of the clinical variables examined (frequency, incontinence, subjective improvement) even though active treatment produced an improvement in urodynamics for the subset with detrusor overactivity (Brubaker et al, 1997). In a second study investigating women with SUI, electrical stimulation was demonstrated to be significantly better than sham therapy. Patients were treated with home vaginal stimulation for 15 minutes twice per day for 12 weeks. Leakage episodes decreased from 3.1 to 1.8 (42%) per day, and pad use decreased from 6.2 to 4.1 (34%) per week in the treatment group; there were small, statistically insignificant increases in the placebo group. Importantly, the clinical improvement correlated with improvement in pelvic muscle strength on perineometry (10.6 mm Hg baseline and 15.2 mm Hg at the end of treatment compared with a small decrease in strength in the placebo group) (Sand et al, 1995). The final study examined the optimal treatment regimen; there was no difference in outcome between daily and every-other-day stimulation (Richardson et al, 1996). In a literature review of 361 cumulative patients with UUI, detrusor overactivity, and neurogenic detrusor overactivity, the overall results were 20% dry and another 37% significantly improved using a variety of definitions for outcome (Payne, 1996). **The ICI committee concluded that electrical stimulation might be better than no treatment for women with SUI**

or DO, that low-intensity home electrical stimulation may be superior to maximal stimulation in an office setting, and that adding electrical stimulation does not improve the outcome of a proper PFMT program (all grade C) (Hay-Smith et al, 2009).

The "new" treatment option for peripheral electrical stimulation is peripheral neuromodulation of the posterior tibial nerve using 34-gauge solid needles connected to an external stimulator (PTNS). The idea was initially developed and promoted by Stoller (Payne, 2002). The initial multicenter open-label trial found a 71% response in 53 patients with a variety of lower urinary tract disorders after 12 weekly treatments (Govier et al, 2001). In 2005 a small RCT showed no difference in response between three times per week and weekly treatment (Finazzi Agrò, 2005). The therapy was ultimately approved by the U.S. Food and Drug Administration (FDA) in 2007 as the Urgent PC (Uroplasty, Minnetonka, MN). Since then, further work has shown that the device has considerable promise in the treatment of OAB. Peters and colleagues (2009) compared PTNS with pharmacologic therapy with long-acting tolterodine 4 mg/day in 100 adults with OAB. The results were very similar with near-identical responses in reduction of frequency, nocturia, UUI, and urgency episodes. More subjects reported cure or improvement in OAB symptoms with PTNS than tolterodine (79.5% compared with 54.8%, $P = .01$). Constipation and dry mouth were significantly less common in the PTNS group, and local adverse effects from PTNS appear to have been minor. A follow-up manuscript reported the durability of PTNS at 1 year (MacDiarmid et al, 2010). Patients initially randomized to PTNS were offered an additional 9 months of therapy but could not use any supplemental anticholinergic medications. Treatments were given at the discretion of the patient and physician. There were 35 responders of the initial 44 patients randomized to PTNS. Thirty-three agreed to enter the continuation trial and 25 continued for 1 year (71% or 56% of those initially assigned to PTNS), and all but 1 continued to self classify as "cured or improved." Improvement in all voiding diary variables was sustained.

The ICI committee (Hay-Smith et al, 2009) was able to come to **several conclusions and recommendations about the use of peripheral electrical stimulation for UI:**

1. Home-based electrical stimulation is superior to no treatment for women with DO or SUI (grade C).
2. There was inadequate evidence to conclude that electrical stimulation was superior to sham therapy.
3. For women with SUI low-intensity home-based electrical stimulation daily for 6 months might be better than 16 sessions of maximal clinic-based electrical stimulation (grade C).
4. The addition of electrical stimulation to a biofeedback-assisted PFMT program does not appear to add benefit (grade C).
5. There was inadequate evidence to compare electrical stimulation to any alternative therapy.
6. Older women may respond to electrical stimulation as well as younger women and should not be excluded from studies of this therapy.

Magnetic Stimulation

One commercial device has been available in the United States to treat UI by extracorporeal magnetic stimulation since 1998. The NeoControl (Neotonus Corporation, Marietta, GA) device provides noninvasive, passive stimulation to the pelvic floor. The patient sits in the treatment chair, which emits electromagnetic waves focused on the expected area of the pelvic floor muscles. The recommended treatment session lasts 20 minutes and includes both high- and low-frequency stimulation, regardless of the type of UI. The low-frequency stimulus elicits a pulselike contraction of the levator muscles, whereas the higher frequency produces more of a tetanic contraction. There is some flexibility for the clinician to program the treatment, and the patient adjusts the intensity to comfort level. **The potential advantages of this therapy are as follows:**

- No internal probe—increased patient acceptance
- Patient can wear street clothes—convenience
- Operated by a technician with minimal training
- No supervision required

The disadvantage is that the twice-weekly treatments must be administered in the clinician's office, which is quite inconvenient for many patients in comparison to home electrical stimulation. The stimulation is nonspecific, and magnetic waves are not significantly attenuated by interaction with tissue. Thus, other muscles, nerves, and even the uterus could respond to stimulus, although most patients tolerate treatment well. Although magnetic stimulation is usually thought to act by improving pelvic floor muscle function, stimulation has been shown to suppress detrusor overactivity in the acute setting (McFarlane et al, 1997).

The initial case series suggested that magnetic stimulation might be effective for both SUI and UUI (Galloway et al, 1999; Yokoyama et al, 2004). Subsequent RCTs have had mixed results. Two sham-controlled trials have studied women with urodynamically proven SUI using the NeoControl device. Gilling and colleagues (2009) found that active treatment was not superior to sham therapy in 70 women treated three times per week for 6 weeks. Enrollment in another trial using twice-weekly treatment for 8 weeks was stopped early, having recruited only 48 of 60 patients, owing to poor results and a high dropout rate with adverse events in half of the subjects (Ismail et al, 2009). These results contrast to a case series of women with SUI treated with a similar device, most of whom had a sustained good response for 1 year but then suffered deterioration during the second year (Hoscan et al, 2008). Yet another device developed in Japan was studied in 39 patients with UUI who had failed PFMT (Suzuki et al, 2007). A double-blind crossover design with weekly treatment for 10 weeks was employed. The authors found improvement in UI episodes and urodynamic parameters with active treatment. These results were supported by a long-term follow-up of 48 women with OAB in which 26 of 27 subjects who were considered "cured" at 2 weeks continued to be improved at 24 months (Choe et al, 2007). Another trial using a different type of device (PULSEGEN by Power of Nature, Ft. Myers, FL) included 39 women with urge-predominant mixed UI (But et al, 2005) treated at 18.5 Hz. Those receiving active treatment had statistically significant improvements in several outcome variables, and symptoms improved in 42% with active therapy compared with 23% in the placebo-treatment group. However, this device is worn in a small pocket of specially designed underwear with stimulation used day and night for 2 months.

Thus, **the small trials performed to date suggest that extracorporeal magnetic stimulation is not effective for female SUI but may be useful for OAB/UUI.** The ICI committee (Hay-Smith et al, 2009) could only conclude that magnetic stimulation was "worthy of further investigation in women with UI." Several authors have suggested that the therapy might be best used with patients who are unable to perform a pelvic muscle contraction, but this has not been specifically studied. Very limited investigation into the durability of response in patients initially treated successfully suggests that the relapse rate is not

unreasonable; whether failures might respond to "booster" therapy is unknown. It is clear that larger-scale trials with pragmatic design are needed before the role of magnetic stimulation can be defined. The most important question is whether any of the advanced pelvic floor rehabilitation techniques provide more consistent or better durability of response than PFMT. Until such data exist, biofeedback, electrical stimulation, and electromagnetic therapy are all potential competitive treatment options to rehabilitate the pelvic floor when PFMT is insufficient.

Key Points: Biofeedback and Peripheral Stimulation

- Biofeedback is any method of training a patient to control a bodily function by providing him or her with information about that function. For UI, the patient hopes to gain control of, and strengthen, the pelvic muscles.
- The simplest form of biofeedback is direct palpation by a skilled therapist.
- Vaginal cones are inexpensive devices for home biofeedback. The evidence suggests that cones are better than no treatment but not clearly different from PFMT.
- More sophisticated office biofeedback machines may be useful for certain subgroups of patients but have not been proven to be superior to PFMT.
- High-frequency stimulation (50 to 200 Hz) has been used with vaginal or anal electrodes for SUI, and low-frequency stimulation (5 to 20 Hz) is employed to reduce OAB/UUI.
- There is a single trial showing PTNS to be superior to anticholinergic medication in the treatment of OAB with good durability at 1 year follow-up.
- Both electrical and magnetic stimulation are passive treatments that offer an opportunity to treat patients who may not be motivated to perform regular PFMT.

DEVICES

Vaginal Support (Pessaries) for Stress Urinary Incontinence

Vaginal support prostheses are among the oldest of medical devices. Although primarily used to treat pelvic organ prolapse, these products have been used to treat SUI and there has been an interest in developing devices specifically for SUI in recent years. Older devices, initially developed for lower-stage pelvic organ prolapse, such as the Smith and Hodge pessaries, have been used in treating SUI with limited clinical data as to their effectiveness (Bhatia et al, 1983; Bergman and Bhatia, 1984; Nygaard, 1995). The Incontinence Dish (Milex Corp., Chicago, IL) is another pessary commonly used in treating SUI; although there are no published clinical trials, a urodynamic investigation (Noblett et al, 2008) revealed that the mean Q-tip straining angle without and with the pessary, respectively, was 57.8 (+19.5) and 34.4 (+29.7), the maximum urethral closure pressure was significantly increased by 19.7 cm H_2O ($P < .001$), and 60% of the subjects did not experience any leaking with the device in place. In addition, any of the variety of devices that support the bladder neck have been used to estimate the response to surgical therapy in patients with mixed UI, although the predictive value of the trial is not established.

Advantages of vaginal support devices include:

- They are potentially applicable to the majority of the incontinent population (those with pure stress or mixed UI and urethral hypermobility).
- They do not require specific testing, such as urodynamics.
- They can be used "as needed" for predictable SUI (as can the other devices).
- They have mild side effects limited to occasional vaginitis and minor local discomfort.
- Some devices can be used to treat both pelvic prolapse and SUI.

Disadvantages of vaginal support devices include:

- They do not correct intrinsic sphincter deficiency and thus are not as likely to help patients without urethral hypermobility.
- They do not definitively treat potentially curable problems. If the problem worsens over time, the patient's health may make surgical therapy less attractive and, in rare cases, impossible.

The Introl bladder neck support prosthesis (Fig. 69–4) was the first device specifically approved for SUI in the United States, and it has subsequently been withdrawn from the market. The Introl was a simple device to mechanically support the hypermobile bladder neck. Clinical trials showed good objective relief of SUI without creating emptying difficulty (Davilla and Ostermann, 1994). One problem may have been relative difficulty in fitting because the Introl prosthesis had 25 sizes whereas traditional pessaries have about 10 sizes. There now appear to be three devices in use, but only one is currently available in the United States. All show promising results in small clinical trials.

The ConTIPI (Fig. 69–5) was developed and is sold in Israel. In contrast to other pessaries, it is disposable and intended for single-daily or as-needed use. It consists of a flexible core with the ends made of resin to provide anchoring. It is covered with a nylon mesh, and a string is attached to the cover for easy removal. This device has been tested in one prospective case series of women

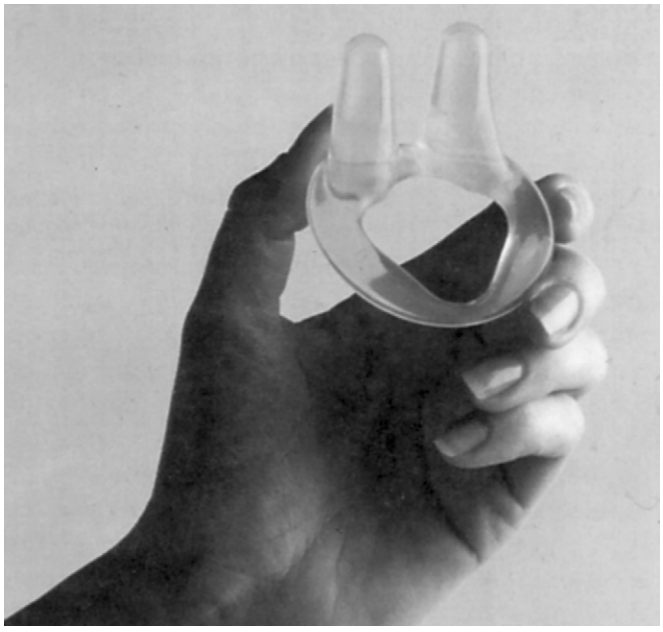


Figure 69–4. The Introl bladder neck support prosthesis. (Courtesy of UroMed Corporation, Needham, MA.)



Figure 69–5. The ConTIPI Intravaginal Device (ConTIPI LTD, Caesarea, Israel). (From Ziv E, Stanton SL, Abarbanel J. Efficacy and safety of a novel disposable intravaginal device for treating stress urinary incontinence. Am J Obstet Gyncol 2008;198:594.)



Figure 69–6. The Contiform device (Contiform International, Blacktown, New South Wales, Australia). (From www.contiform.com.)



Figure 69–7. The Uresta pessary (EastMed Inc., Halifax, Nova Scotia, Canada). (From www.uresta.com/sites/default/files/PPP%20Fitting%20Dec%208%2C%202009.pdf.)

with urodynamically proven SUI who were considered surgical candidates (Ziv et al, 2008). There was a 7-day "run in" followed by 28 days using the device. Eighty-five percent of the 60 women tested were considered responders, having achieved 70% or more reduction in home pad testing ($P = .01$). Improvements in overall quality of life, subjective perception of UI, and satisfaction with the device were observed. There were no changes in flow rates or residual urine, but 67% of subjects experienced some genital tract adverse event, including 25% with pain and 23% with spotting.

Another device, the "Contiform" (Fig. 69–6), is being used in Australia. It is intended for women with a main complaint of SUI but no pelvic organ prolapse. It comes in four sizes. Studies by Allen and associates (2008) showed that of 73 women invited to participate, 65 enrolled, 52 were successfully fitted (80% of those willing), and 37 completed the study protocol (71% of those fitted, 57% of those willing). At the end of 1 month, 20 (54%) of patients were dry after a 24-hour pad test. Only 8 of 37 (22%) chose to proceed with surgical therapy, whereas the rest were satisfied to continue using the device for a longer term. The patients had relatively mild SUI, with all having less than 25 g of urine loss on the baseline 24-hour pad test. This study points out one of the limitations of using pessaries; patients with prior surgery causing vaginal distortion or introital scarring may not be successfully fit, and those with an overly large genital hiatus may not retain a device.

The third device, the Uresta (Fig. 69–7), is marketed in the United States and Canada. It was studied in a small group of women with 1-year follow-up (Farrell et al, 2007). Thirty-two women started the trial, and 11 dropped out in the first 2 weeks. Among women successfully fitted at 2 weeks, 16 of 21 (76%, or 50% of the initial cohort) continued using their pessary at 1 year. Weekly UI episodes decreased from 20 to 4 ($P = .028$) and provocative pad test weight decreased from 20 to 9 g ($P = .06$).

Vaginal Support (Pessaries) for Prolapse (Overflow/Bladder Outlet Obstruction/ Urgency Urinary Incontinence)

Pessaries have been used for years as a treatment for pelvic organ prolapse and diseases of the uterus (Miller, 1991). In fact, most

devices used for SUI in the United States are pessaries primarily designed for pelvic organ prolapse. The Milex Corporation (Chicago, IL) and the Mentor Company (Santa Barbara, CA) offer a full range of pessaries for prolapse and have developed devices intended for SUI alone (Fig. 69–8) or that associated with pelvic organ prolapse (Fig. 69–9). These devices include a "knob" oriented anteriorly in the distal vagina at the level of the proximal urethra to improve closure. Such devices put pressure directly on the urethra and are thus more likely to be obstructive. This design could at least theoretically be useful for the patient with intrinsic sphincter deficiency because there is direct compression of the urethra. No direct comparison has ever been made between any of the various pessaries for any indication. **Pessaries used for prolapse only should be fitted with an empty bladder** for patient comfort. However, all **pessaries intended for use in SUI should be fitted with the bladder at a comfortable fullness.** The patient can then cough and strain to get an immediate assessment of effectiveness, and the patient should always urinate adequately before leaving the clinic because obstruction and retention can be a problem.

Vaginal pessaries have specific roles in diagnosis and treatment of lower urinary tract symptoms in at least three distinct situations:

1. Identification of "occult" SUI in a patient with cystocele
2. Identification/treatment of symptomatic prolapse causing OAB symptoms
3. Identification/treatment of symptomatic cystocele causing voiding symptoms and/or urinary retention

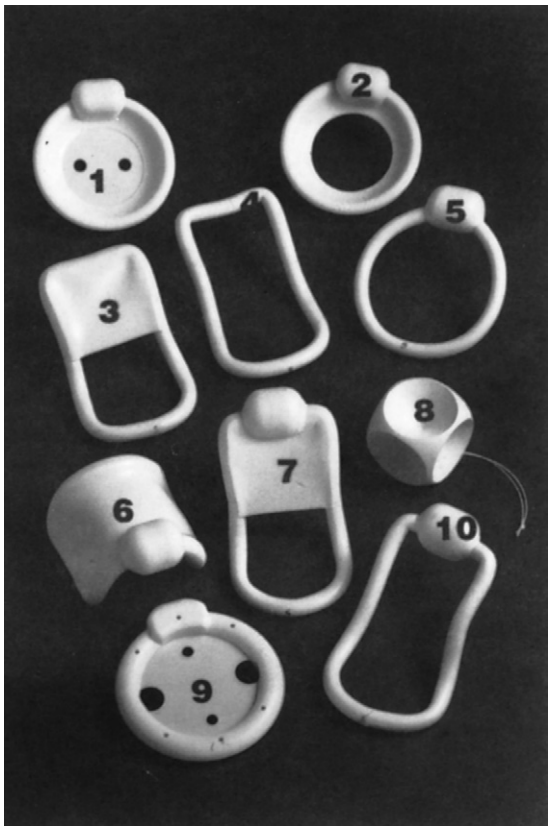


Figure 69–8. Pessaries available from Milex Corporation, Chicago. All provide varying anatomic support; those with "knobs" apply direct pressure to close the urethra to manage stress incontinence. 1, Incontinence dish with support; 2, Incontinence dish; 3, Hodge with support; 4, Hodge; 5, Incontinence ring; 6, Gehrung with knob; 7, Hodge with support and knob; 8, Cube; 9, Ring with support and knob; 10, Hodge with knob.

Prolapse, primarily from the anterior compartment, can impair voiding by mechanically obstructing the urethra through local pressure or by a kinking effect. This same mechanism could prevent clinical manifestations of SUI, and prolapse further diminishes SUI by dissipating abdominal pressure on the bladder neck and proximal urethra. Many authors have advocated using a vaginal pack or pessary test during preoperative evaluation before prolapse surgery (Fianu et al, 1985; Bergman et al, 1988; Ghoneim et al, 1994; Cross, 1998; Hextall et al, 1998; Chaikin et al, 2000; Klutke and Ramos, 2000). The use of a pessary or other means of prolapse reduction before surgery for apical prolapse was studied prospectively in the CARE trial (Colpopexy And urinary Reduction Efforts) by the NIH-sponsored Pelvic Floor Disorders Network. When clinically continent women were demonstrated to leak with stress with prolapse reduction during urodynamics they had a much worse result if no SUI procedure was performed (58% incontinent vs. 32% of those undergoing a Burch suspension) (Brubaker et al, 2003, 2008; Visco et al, 2008). Unfortunately, a negative stress test did not have a good predictive value because 38% of these patients had stress leakage after the prolapse repair. The pessary was the least specific of the five different methods of prolapse reduction tested (although a ring pessary was used that may not be suitable for higher grades of prolapse).

It thus seems reasonable to encourage prolapse patients considering surgery to undergo a trial of a pessary and evaluate the clinical response to the device. If OAB or other lower urinary tract symptoms resolve with the pessary, the patient may elect to use the device either temporarily until a convenient time for surgery or as a long-term solution. Similarly, if symptoms do not resolve after appropriate support with a pessary the patient should be counseled that the symptoms are more likely to persist even after successful repair of the anatomic defect. A pessary trial has an advantage over the packing tests during urodynamics in that the patient can be evaluated chronically and during day-to-day activities. However, **many patients with high-grade prolapse cannot retain any pessary and surgical decisions must be made using common sense, urodynamic data, and best clinical judgment.** If "de novo" SUI is uncovered, anti-UI surgery is clearly indicated. Even if no SUI is noticed with the pessary, consideration should be given to performing anti-UI surgery, providing the patient empties the bladder normally.

Urethral Meatal Occlusive Devices

At least three devices have been marketed for female SUI that were applied directly to the urethral meatus. The exact mechanism of action for these devices is not clear. The devices generally have a small reservoir or some absorptive capacity. They may create a "dam" to prevent leakage, work through absorption, or increase urethral closure by eliminating "pop off." The Capsure, Femassist, and Impress devices were approved for marketing, but all have been withdrawn from the market.

These were simple devices that could be more attractive to patients than a pad because they actually prevent leakage rather than simply absorbing the fluid. This would reduce odor and skin irritation. Good effectiveness was demonstrated for mild to moderate SUI, as detailed by Dmochowski (1998):

- Capsure: 84/100 completed 3 months, 48% dry/97% improved by pad test

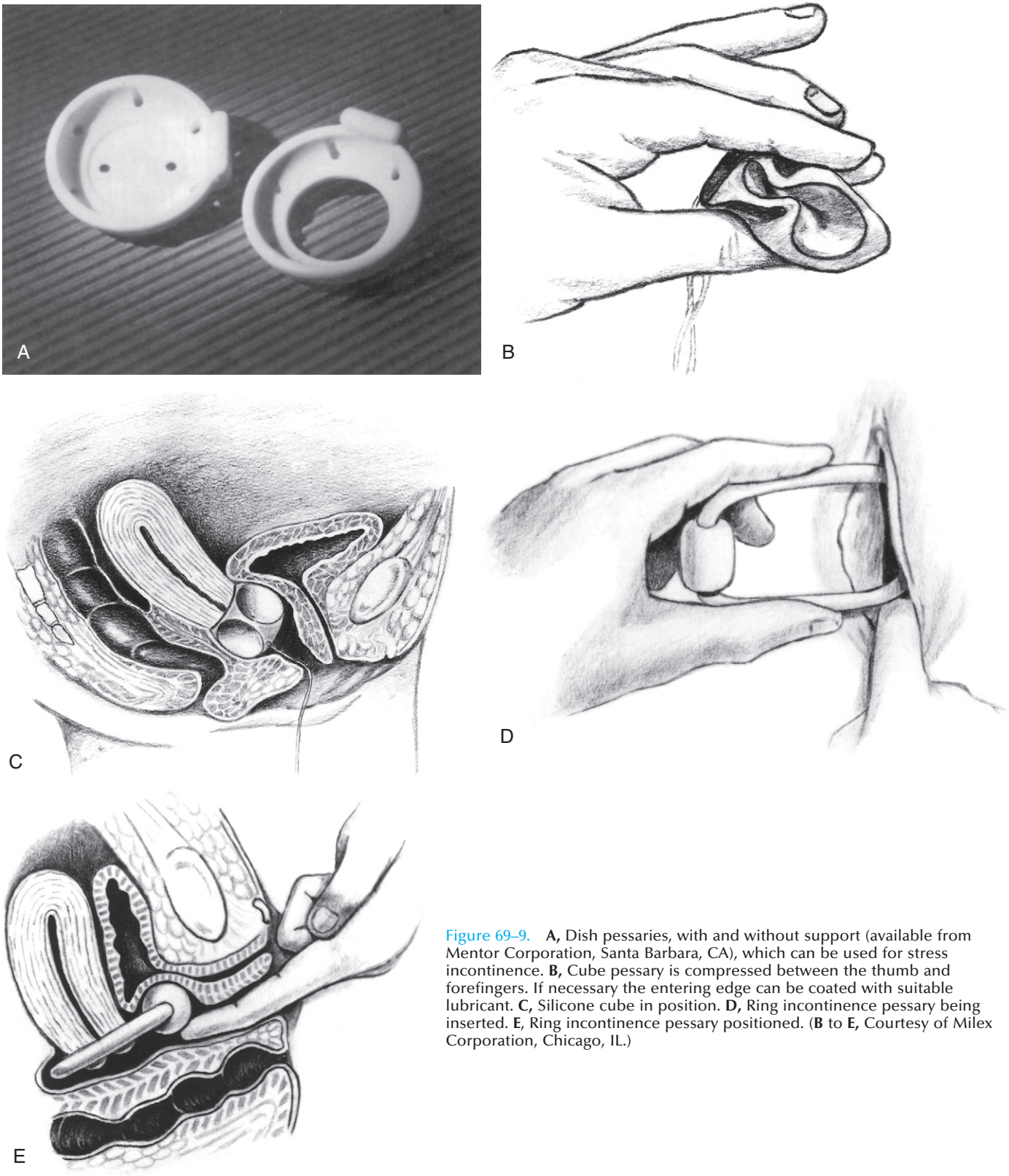


Figure 69–9. **A,** Dish pessaries, with and without support (available from Mentor Corporation, Santa Barbara, CA), which can be used for stress incontinence. **B,** Cube pessary is compressed between the thumb and forefingers. If necessary the entering edge can be coated with suitable lubricant. **C,** Silicone cube in position. **D,** Ring incontinence pessary being inserted. **E**, Ring incontinence pessary positioned. (**B** to **E,** Courtesy of Milex Corporation, Chicago, IL.)

- Femassist: 20/56 improved, 15 would use long term
- Impress: 17/19 cured/improved by a pad test

On the other hand, application was not uniformly easy and patients did not always have resources to help them get through initial problems in utilization. For some types of body habitus it was simply not possible to apply the device. The devices have a limited ability to oppose leakage and were not effective for severe stress leakage or any urge leakage. Finally, local tissue irritation was a minor but common problem. The future role for improved products in this area is unclear.

Urethral Inserts

Sometimes referred to as urethral stents or plugs, the urethral inserts for SUI passively occlude and/or coapt the urethra and must be removed for voiding. The first urethral insert to be approved for marketing by the U.S. FDA, the Reliance (UroMed, Inc., Needham, MA) (Fig. 69–10), has been withdrawn from the market. The second-generation FemSoft stent (Rochester Medical Corporation, Stewartville, MN) (Fig. 69–11) was FDA approved in 1997 and is currently available.

The multicenter study that led to the approval of the Reliance device enrolled 255 patients from eight centers. Of these, 135 completed at least 4 months with the device and were considered evaluable. The results were unquestionably good, with 80% of the subjects dry using the device and 95% improved (Staskin et al, 1998). At 1-year follow-up, the efficacy was maintained and there were significant but mostly minor complications, including urinary tract infection (30%), gross hematuria (24%), and local changes on cystoscopy (9%) (Miller and Bavendam, 1996). The device was also studied in a small comparative trial against a novel device, the NEAT, that never came to market. Both were effective against SUI with seemingly reasonable adverse events (Robinson et al, 2003).

In comparison, the one published study of the FemSoft insert was a 5-year, multicenter trial involving 150 women with mean follow-up of 15 months (Sirls et al, 2002). Pad testing and bladder diaries demonstrated efficacy. This device appears to be useful for a wide spectrum of the incontinent population, including those with urgency, low leak point pressure, failed surgery, and advanced age. In contrast, the Reliance was believed to be applicable only for pure SUI; if urgency was present it tended to be exacerbated by the device, resulting in loss of both urine and the device with an involuntary bladder contraction. Adverse events with the FemSoft were again common but not severe, including symptomatic urinary tract infection in 31.3%, mild trauma with insertion in 6.7%, hematuria in 3.3%, and migration in 1.3% of women.

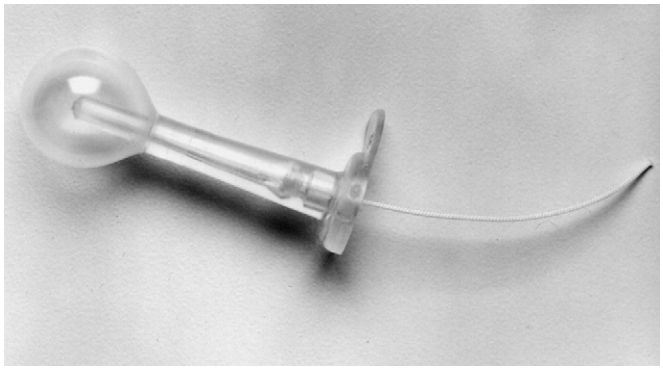


Figure 69–10. Reliance urethral insert. (Courtesy of Uromed Corporation, Needham, MA.)

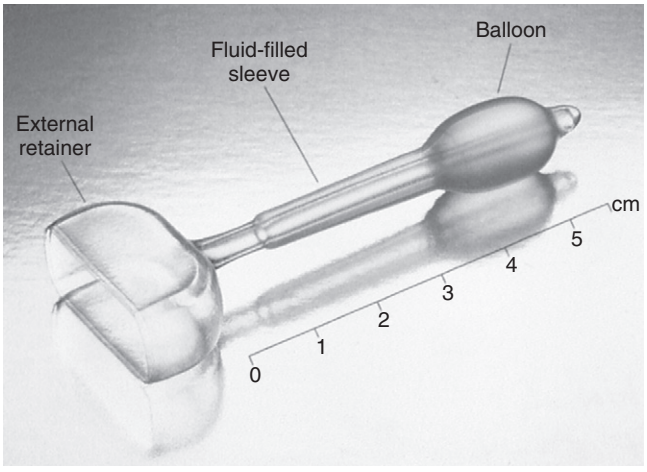


Figure 69–11. FemSoft urethral insert. (Courtesy of Rochester Medical Corporation, Stewartville, MN.)

Although urethral inserts are potentially applicable to almost all women with pure SUI and possibly some of those with mixed UI, it must be remembered that the device must be removed and replaced for each void. Despite the new soft, hydrophilic materials, only a small percentage of the SUI population seems to be willing to instrument the urethra to be dry. The highest patient acceptance seems to be among those with very predictable, episodic SUI, such as during sports or dancing. Such patients might use a device several times each week and have complete elimination of leakage. Many of these patients believe that their problem is too mild to undergo a surgical procedure but are happy to have this minimally invasive alternative.

Current practitioners and those who may design and market future devices might be informed by one study of women's knowledge of anatomy and their attitudes toward devices and genital touching. An Australian team questioned 104 consecutive women with UI using a 10-item questionnaire (Prashar et al, 2000). They found that only 30% of the women felt "quite comfortable" about the concept of touching their genitalia: this attitude was age dependent. Only 21% were quite willing to insert a continence device into their vagina: this attitude varied weakly with age but was significantly affected by previous tampon or diaphragm usage. Only 15% felt very comfortable about placing a continence device onto their urethra, but the likelihood of a positive response to this concept was not at all affected by age and was only slightly more common in previous tampon users. Thus older women are less likely to understand the anatomy of their genitalia or to be comfortable about the idea of exploring it, but age is no barrier to willingness to employ urethral or vaginal continence devices per se.

Urethral Stents

Urethral stents that allow for intermittent voiding through the device have been tested in both men and women with urinary retention/overflow UI. None has ever been approved in the United States. Most of the catheters that have been designed have internal motors that allow the patient to expel urine without removing the device, but one device, the ContiCath (ContiMed Corporation, Minneapolis, MN), works by allowing urine to pass around the catheter through three deep grooves. In contrast to the motorized stents, this device will be effective only for retention due to obstruction with intact detrusor function. In a preliminary trial (Corujo et al, 1999) 33 of 37 patients (90%) with a non-neuropathic cause and retention of 1 week or less were able to establish controlled voiding. The device was ineffective for neurogenic and chronic retention.

PRACTICAL APPROACH TO TREATMENT

General Issues—Patient Goals

Treatment of UI is more challenging and potentially more rewarding than many of the tasks facing the urologist because it requires

Key Points: Devices

- Bladder neck support devices are potentially applicable to the majority of the incontinent population (those with pure stress or mixed UI plus urethral hypermobility).
- Devices do not require specific testing such as urodynamics.
- Devices can be used "as needed" for predictable SUI.
- Supportive and occlusive devices have mild, reversible side effects limited to occasional vaginitis and minor local discomfort.
- Some supportive devices can be used to treat both pelvic prolapse and SUI.
- Devices do not definitively treat potentially curable problems. If the problem worsens over time, the patient's health may make surgical therapy less attractive and, in rare cases, impossible.
- Short-term trials using supportive devices can be a useful method to predict response to surgical therapy for prolapse and mixed UI.

a true partnership with the patient. **In most instances there is no one "best" treatment for the particular problem. Even when there is a superior treatment option, the nature of the disorder—not directly threatening to life and not necessarily progressive—not only allows but also mandates an individualized approach to therapy. The patient's personal goals should always be the prime concern.** A 40-year-old aerobics instructor may be highly motivated to be completely dry, whereas another woman might only want to attend church without fear of leakage; an incontinent man might be much more bothered by getting up three to four times at night than by daytime UI. Brubaker and Shull (2005) point out that it is "the patient's perspective that drives decisions about further treatment [in quality of life disorders]" in a review describing **the term *EGGS*, which has been coined to facilitate communication about patient-centered treatment outcomes. EGGS—Expectations, Goal setting, Goal achievement, and Satisfaction—describes a process in which the patient's point of view is explored to develop an individualized treatment plan.** This process is equally relevant for medical, surgical, and physical therapies; the importance of the patient perspective in surgical treatment has been demonstrated in prospective clinical trials. In a surgical series, **patient satisfaction was moderately correlated to goal achievement but was not related to objective cure of SUI or prolapse** (Elkadry et al, 2003), and goal achievement appeared to be durable at longer-term follow-up (Hullfish et al, 2004). Although less is known about expectations and goals as they relate to nonsurgical therapy, a clinician will do well to be aware of the patient's goals lest he or she lose the patient or find an unsatisfied customer. **The very nature of conservative therapies—safe, reversible, and effective—means that most patients will choose these options for first-line treatment. When the treatments are skillfully delivered, most patients will be very satisfied with the results.**

Treatment Planning—Data Collection

The clinician needs three primary pieces of information to develop a treatment plan for a given patient: the type of UI, the baseline voiding diary, and an assessment of anatomy with particular emphasis on pelvic floor muscle strength and function. In most cases a clinical diagnosis of stress, urge, or mixed UI is easily made but detailed evaluations are sometimes necessary before beginning treatment. **The voiding diary is important for four reasons.** First, **it is a reasonable substitute for cystometry, because the largest voided volume on a diary has been shown to correlate with the cystometric capacity** defined by urodynamic testing (Diokno et al, 1987). Given the high false-negative rate for cystometry and detrusor overactivity, determining a general sense of the bladder's capacity to store urine is at least as valuable as knowing whether involuntary contractions are present on cystometry. Second, **the voiding diary allows the clinician to objectively determine a "safe" voiding interval to begin a program of bladder training.** Third, **the "baseline" diary becomes the comparison for the clinician to objectively measure change with therapy.** Finally, **the process of keeping the voiding diary involves the patient in the treatment program,** starting the education essential to behavioral therapy. The assessment of baseline pelvic muscle strength is critical because that allows the clinician to intelligently prescribe pelvic floor rehabilitation therapy.

Pelvic floor rehabilitation has a unique role in UI therapy in that all types of UI can benefit and, potentially, be cured. Pelvic floor rehabilitation has long been identified as a treatment for SUI. It has been variously proposed that such treatments increase the resting tension, the contractile force, or the speed of recruitment of the voluntary sphincter. Such changes could increase resting urethral closure and improve the reflex closure that occurs with increases in abdominal pressure. Pelvic floor rehabilitation has been relatively overlooked in treating bladder-related UI. Pelvic floor therapy is theoretically valuable to the patient with OAB in three ways. First, the simple mechanics of voluntary sphincter closure oppose the unstable bladder contraction and prevent or minimize urine leakage. Second, there are inhibitory local reflexes between the pelvic floor muscles and the bladder. At least in theory, increased muscle tone and strength should decrease overactivity. Finally, many patients can use repeated quick, active contractions ("quick flicks") to inhibit an involuntary contraction once it starts. Thus, improved muscle function can improve continence for the patient with OAB through both passive and active mechanisms. Although pelvic floor therapy is of unquestioned value, it has not been properly appreciated, perhaps owing to confusion about the inappropriate use of the various tools described previously and improper referrals for therapy. A simple assessment of pelvic floor muscle function at physical examination may be useful in triaging patients with UI.

Patients are classified into three groups based on the assessment of pelvic floor muscle strength at baseline examination: (1) those with no or minimal ability to isolate and contract the levator muscles, (2) those who can isolate the correct muscles with poor strength, and (3) those with good pelvic floor muscle strength and isolation on the initial examination. There is no universally accepted objective method of evaluating pelvic muscle strength by digital vaginal examination. It is principally important that the clinician be internally consistent in his or her assessment. The author has used a convention proposed by Laycock (Tries and Eisman, 1995). A 6-point scale is used for contraction strength: 0, absent; 1, flicker; 2, weak; 3, moderate; 4,

good; 5, strong. A second score is given to indicate the endurance time in seconds. Romanzi and associates (1999) examined a similar system. Patients can have a maximum score of 9; a score less than 4 correlated with self-reported UI in a small test group. Scores correlated well (*r* values ~ 0.8) for both intra-rater and inter-rater observations. There was also a reasonable correlation to surface EMG determinations (*r* values ~ 0.5).

Regardless of which system a clinician chooses to score pelvic muscle strength, it is proposed that patients be stratified into three clinically relevant groups by the physical examination as described earlier. It is possible to assign treatment to patients in the three clinical groups by applying these basic principles. **It seems illogical to prescribe home exercises in the first group (inappropriate or absent baseline function), and anecdotal experience suggests that significant improvement is uncommon. These patients need some form of teaching/biofeedback (or passive stimulation) just to get started. Office-based training should be considered to be superior to other forms of biofeedback until proved otherwise.** Many of these patients are older and will not accept home therapy. The author's strategy has been to offer weekly office sessions and convert the patient to a home unit once there is consistent objective and subjective response. Alternatively, passive treatment with peripheral electrical stimulation or magnetic stimulation can be investigated.

The second group of patients demonstrate weak contractions but appropriate isolation and should be good candidates for some form of pelvic muscle rehabilitation; biofeedback has not yet been conclusively proved to be better than PFMT alone in this general population. The lesson learned from biofeedback in SUI is that results are primarily dependent on the motivation of the patient and the skill and enthusiasm of the therapist. The author recommends exercise therapy for most of these patients. They are given written instructions and a follow-up office appointment with a nurse to review their progress. Home therapy with cones or simple EMG/pressure devices is a practical option that is generally well accepted by patients who have a basic knowledge and comfort about their bodies. Definitive clinical trials focusing on this patient population would be welcome.

In the final category (strong baseline pelvic contraction) the value of pelvic floor "rehabilitation" is unclear. If these patients have significant UI there is generally severe urethral incompetence and/or severe bladder dysfunction; and they require more aggressive treatment. The author's general practice is to instruct the patient in "quick flicks" to inhibit urgency and offer vaginal cones to motivated patients. With these patients the onus is on the clinician to demonstrate effectiveness of more complex and expensive treatment.

Treatment of Female Stress Urinary Incontinence

The two principal treatments of pure female SUI are pelvic floor rehabilitation and surgery. These options have been compared in three trials with similar results. Klaskov and coworkers (1986) randomized 50 consecutive women with SUI to immediate surgery versus five weekly visits with a physical therapist, without complex biofeedback. Ten of 24 (42%) patients treated initially with pelvic floor therapy were satisfied and declined surgery after the training program. Tapp and associates (1989) followed 81 consecutive patients with SUI who were randomized to three groups: PFE, PFE plus electrical stimulation, or immediate surgery. The group treated with pelvic floor therapy again had a 43% satisfaction rate (19/44), although only 4 (9%) were cured of UI. Finally, in a group of 39 women awaiting surgery for SUI, 30 completed 1 month of therapy using vaginal cones for home biofeedback. Seventy percent were considered cured or improved, 11 of 30 chose surgery, and thus 49% of the initial group avoided an operation (Peattie et al, 1988). **It thus seems proper to counsel women who might appropriately choose surgery that although surgery is the single most effective treatment for SUI there is a 40% to 50% chance that they can avoid an operation and be satisfied with the outcome by going through PFMT.**

In practice, it seems that one could do better than simply giving the same advice to all patients. **Certain patients might logically benefit from immediate surgery. These would include those who have significant associated prolapse (beyond the hymenal ring) that may be corrected at the same time, those who are highly motivated to be completely dry or who have high levels of physical stress due to lifestyle or occupation, those with relatively severe SUI, and especially those with good pelvic floor function on initial examination (group 3 mentioned earlier).** On the other hand, patients with poorer pelvic floor function might reasonably be expected to have better odds of improvement than those cited earlier; thus a trial of pelvic floor therapy should be strongly encouraged. Those with weak muscles and good isolation may benefit from home pelvic muscle exercises alone, but those with absent voluntary contractions or poor isolation probably absolutely require a therapist or are best treated by immediate use of one of the advanced techniques: biofeedback or pelvic floor stimulation. Even those patients who eventually go on to surgery may be pleased with progress and may have better surgical outcomes because they will be better able to manage postoperative irritative bladder symptoms.

Surgery and pelvic floor therapy are the leading treatments of SUI because they are potentially curative. However, some patients will prefer other options for a variety of reasons. **The devices mentioned previously are particularly attractive to the patient who really only needs "PRN therapy," that is, a patient whose leakage is infrequent but predictable and bothersome.** An example would be a patient who only leaks during twice-a-week exercise classes or sports. She may feel that surgery would be too much treatment for such a problem but is not really satisfied with protective pads. Similarly, a patient may really prefer surgery but for personal or financial reasons may need to delay definitive treatment. The devices can provide good palliation of symptoms during the interim. Devices are also, of course, indicated for the nonsurgical patient with severe comorbidities. It is simply uncommon that a patient is too ill to undergo one of the minimally invasive operations yet still is active enough to have significant SUI. When such a patient has significant hypermobility, a vaginal support device may be used. Patients without hypermobility can usually be treated with periurethral injection therapy.

Finally, the role of behavioral therapy in SUI should not be overlooked. Fantyl and associates (1991) demonstrated more than 50% improvement in leakage episodes and volume of urine lost with their program, getting essentially equal results in patients with both SUI and UUI. This is enough improvement to satisfy many patients.

Overactive Bladder and Detrusor-Related Incontinence

Successful treatment of the patient with OAB mandates a complete understanding of the pathophysiology. **Although anticholinergic medications are quite effective for most patients with OAB, medical therapy should not be a reflexive initial treatment and should rarely be used in isolation.** Abnormal bladder activity is often central to the problem, but it is inappropriate to focus only on the bladder. Dysfunctional behaviors and physical limitations strongly impact and can be the primary cause of OAB symptoms. The patient with OAB with UI almost always has poor pelvic floor muscle function (or the symptoms would be limited to urge frequency without UI). Thus, most patients can benefit from multimodality therapy (Fig. 69–12).

Once underlying causes for OAB have been ruled out in the initial history, physical examination, and testing as required, treatment planning should begin with a review of the voiding diary and the patient's behaviors. The diary reveals the maximum functional bladder capacity, which gives a strong indication as to the severity of the underlying bladder dysfunction. A low functional capacity (<150 to 200 mL) typically correlates with more severe bladder dysfunction, whereas a good functional capacity (>300 mL) indicates better potential bladder function. The clinician may find an unusually large fluid intake to be a factor aggravating the symptoms. **A timed voiding regimen is prescribed based on a time interval determined by the patient's baseline diary. Usually a patient is instructed to void at the longest consistently dry interval. When the patient becomes dry, the interval is increased by 15 to 30 minutes per week until a normal voiding pattern is established.** Some patients will benefit from use of a watch with a timing alarm for prompted voiding. Finally, the patient's response to urge should be reviewed. Inappropriate behaviors such as running to the bathroom must be replaced by proper urge inhibition techniques.

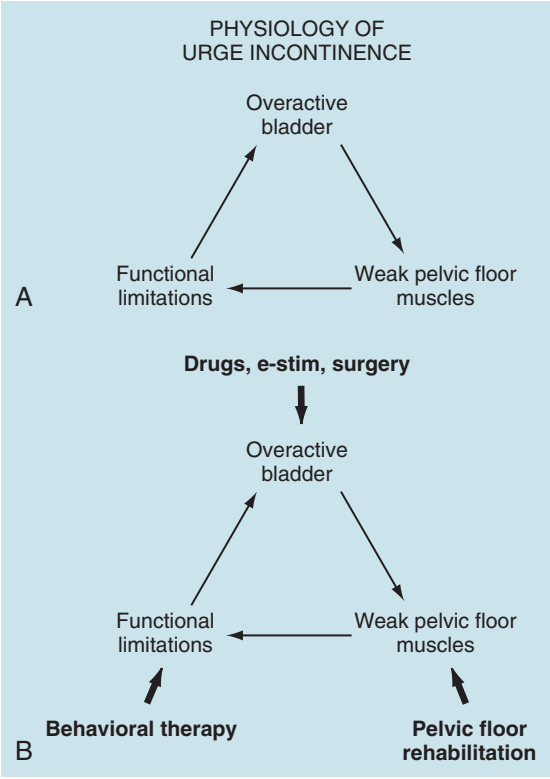


Figure 69–12. **A,** The clinical manifestation of urgency incontinence is caused not only by bladder overactivity but also by poor pelvic floor muscle function, functional limitations, and dysfunctional behaviors. **B,** Multimodality treatment is the most effective approach to managing urgency incontinence because each area can be addressed.

One of the key methods of urge inhibition is use of the pelvic muscle contraction and particularly "quick flicks" of short rapid contractions. The advantage of quick contractions is that the muscles are less likely to fatigue. If the patient can inhibit the urge for about 30 seconds it is likely to pass. Few incontinent patients can hold a maximal contraction that long; therefore, they leak when the muscles fatigue. Some therapists recommend teaching the patient to practice half-strength contractions for the same reason. In any case, pelvic floor therapy will be the appropriate second step for the vast majority of OAB patients who have suboptimal muscle function. The same classification system discussed in the context of SUI is also useful for triage of patients with OAB.

The key question in the treatment of OAB is when to introduce pharmacologic therapy. Unfortunately, most patients have been given drugs as first-line therapy without supplementing treatment with behavioral and pelvic floor therapy. This approach has the tandem problems of exposing many patients to expense and side effects unnecessarily. More importantly, drug therapy is rarely curative alone, whereas the other conservative measures can cure many patients, especially those who start with a reasonable bladder capacity and no underlying neurologic abnormality. Although the **newer medications have greatly improved patient acceptance of medical therapy, it still seems appropriate to use drugs selectively and with an eye toward ultimately rehabilitating the bladder and titrating the patient off of medicine.** Early use of medication is particularly indicated for patients with a low maximal voided volume on the diary, patients with underlying neurologic disease, and patients who seem uninterested or unable to participate in behavioral techniques. **Medications are relatively contraindicated in patients with a very large bladder capacity, medical reasons to avoid anticholinergics, the very old, and the very young.** Some clinicians prefer to start anticholinergic therapy on all patients (along with behavioral techniques) as in the original British bladder training protocols (Frewen, 1978; Holmes et al, 1983). This is reasonable because it improves the odds of the patient making an immediate improvement. However, whether drugs are used on all patients or selectively, consideration should be given to the ultimate goal of bladder retraining. Patients who become completely continent with good capacity on the voiding diary probably have approximately a 50% chance of being able to go off medication and stay dry in long-term follow-up (Holmes et al, 1983). Titration off medication should be suggested after 3 to 6 months when drug therapy is successful.

Refractory Overactive Bladder

In a small group of patients, OAB will prove to be refractory to the basic methods described previously. **These patients should have further evaluation with sophisticated urodynamic testing and cystoscopy to carefully define the nature of the lower urinary tract dysfunction and to rule out**

other causes for the symptoms. The patient who truly has refractory detrusor overactivity can be tried on combination medical therapy with a standard anticholinergic plus imipramine. When satisfactory continence is not achieved at the maximal tolerable medical therapy, the remaining options have been sacral neuromodulation or surgical reconstruction (e.g., augmentation, diversion).

Advances with botulinum neurotoxin type A (BoNT/A) injection therapy for detrusor overactivity challenge this algorithm. Although not yet FDA approved for use in the urinary system the drug is commonly used "off label." Treatments are performed cystoscopically, typically injecting 200 units divided into 20 sites around the bladder. The procedure can be performed on an outpatient basis under local anesthesia or sedation. BoNT/A injections have been proven effective for refractory neurogenic detrusor overactivity in one well-designed randomized controlled trial (Schurch et al, 2005). Fifty-nine patients with multiple sclerosis or spinal cord injury were randomized to receive injections with 200 units of BoNT/A, 300 units of BoNT/A, or a placebo. Dramatic improvements in bladder capacity and continence were seen in both active treatment arms compared with placebo. The gains were maintained for 24 weeks of follow-up. A small prospective randomized trial demonstrated similar results in idiopathic detrusor overactivity (Sahai et al, 2007). **More research is needed to define the optimal dose, mode of injection, the length of response, and most importantly the risk for urinary retention and catheterization for those patients who void normally before treatment.**

When comparing neuromodulation to BoNT/A injections, the most obvious difference is that the neuromodulation data are almost exclusively from the non-neurogenic population in contradistinction to the neurogenic patients treated with injections. The second key factor is that neuromodulation is FDA approved for UUI, urge-frequency syndrome, and idiopathic urinary retention. **BoNT/A injections are not currently FDA approved for any application in the urinary tract.** Nevertheless, some patients may prefer a trial of BoNT/A injections, and it would seem reasonable to offer this therapy to a well-informed patient. The advantages of BoNT/A include a lower initial cost, a somewhat simpler procedure, and elimination of the permanent implant (the implant precludes performing magnetic resonance imaging and can complicate travel). The disadvantages of BoNT/A include the need for repeated injections indefinitely over time. Long-term response to neuromodulation is somewhat better established than BoNT/A, but a great deal of research is needed in both areas and a head-to-head study would greatly advance this field.

The Problem of Mixed Incontinence

Mixed UI presents a special challenge to the clinician. These patients have typically been approached by offering a trial of anticholinergic medication first and then operating on those whose disorder does not adequately respond. There are certainly clues that can be used to define the primary component of the UI in at least some of the patients and develop more individualized treatment strategies.

The history can be helpful; the primary problem in mixed UI is often that component (the stress or the urge) that occurred first chronologically. The voiding diary can provide important clues. When OAB is the predominant problem the void volumes should be small both day and night. In contradistinction, if there are small daytime voids with little or no nocturia and a large first morning void the urgency symptoms tend to be a manifestation of SUI, perhaps stimulated as a few drops of urine leak into the proximal urethra with activity and trigger a sense of urgency. Pelvic organ prolapse can have a similar effect. When SUI is suspected to be the primary component, a short-term trial of one of the vaginal support devices may clarify the picture. If the symptoms are relieved by the device the patient may decide to continue using it or feel more confident that surgical intervention will be successful. **A pessary trial is doubly important before correcting pelvic organ prolapse (with or without UI). Elevation of a cystocele will unmask occult sphincteric incompetence in approximately 50% of patients who are continent with the prolapse.** If an ambulatory trial of a pessary is not performed, then a pessary or vaginal packing may be used during preoperative urodynamic testing as discussed in the pessary section previously. The urethral stent/plug devices are relatively contraindicated in

Key Points: Practical Approach to Treatment

- The patient's personal goals should always be a prime concern. Patient satisfaction was moderately correlated to goal achievement but was not related to objective cure of SUI or prolapse in prospective studies.
- Three primary pieces of information are required to develop a treatment plan for a patient with UI: the type of UI, the baseline voiding diary, and an assessment of anatomy with particular emphasis on pelvic floor muscle strength and function. In most cases, a clinical diagnosis of stress, urge, or mixed UI is easily made but detailed evaluations are sometimes necessary before beginning treatment.
- The largest voided volume on a diary correlates with the cystometric capacity defined by urodynamic testing.
- Patients are classified into three groups based on the assessment of pelvic floor muscle strength at baseline examination: (1) those with no or minimal ability to isolate and contract the levator muscles, (2) those who can isolate the correct muscles with poor strength, and (3) those with good pelvic floor muscle strength and isolation on the initial examination.
- Those with no voluntary pelvic muscle contraction should be offered biofeedback training and/or passive stimulation.
- Those with strong, coordinated muscle contractions will probably require medical or surgical therapy.
- Although surgery is the single most effective treatment for SUI there is a 40% to 50% chance that women can avoid an operation and be satisfied with the outcome by going through PFMT.
- Early surgical intervention is more appropriate for patients with significant associated prolapse (beyond the hymenal ring) that may be corrected at the same time, those who are highly motivated to be completely dry or who have high levels of physical stress due to lifestyle or occupation, those with relatively severe SUI, and especially those with good pelvic floor function on initial examination.
- Most OAB patients can benefit from multimodality therapy including bladder training, PFMT, and medical therapy.
- When OAB symptoms are cured, a trial of titration off medication is warranted.
- After appropriate evaluation, sacral neuromodulation, botulinum toxin injections, and surgical reconstruction/diversion are options for refractory OAB.

this patient population because clinical experience suggests that they typically aggravate the underlying urge and become totally ineffective.

The patient with mixed UI can usually benefit from each form of conservative treatment: behavioral, pelvic floor, and medical therapies. When medications are prescribed, it is particularly important to obtain voiding records before and during treatment. A patient who is not satisfied with treatment may be shown to have the same number of leaks but a significant improvement in bladder capacity. This would again argue for success with surgical therapy for residual SUI symptoms. Pelvic floor rehabilitation is probably the most important treatment in this patient group, and there may be a special role for electrical stimulation because, at least theoretically, stimulation may specifically improve both urethral and bladder function. The patient uses low- and high-frequency stimulation on alternate days. Any of the other therapies can be combined with stimulation.

CONCLUSION

Urinary incontinence is a pervasive and increasing problem throughout all segments of our society that produces a severe impact on our health care system and patients' quality of life. The incontinence specialist of the 21st century must be familiar with all types of therapies: conservative/behavioral treatments, medical therapy, and surgical options. There is a great need for quality research that compares various treatment options to determine the initial effectiveness and durability, the adverse effects, and the advantages for specific groups of patients. In the meantime, the therapist must be able to match treatment to the problems and goals of individual patients. Nonsurgical treatments are unquestionably effective and are preferred by many patients. Mastering of all types of therapies will keep the urologist the recognized expert in incontinence. Ignoring nonsurgical therapies will pass the mantle, and the surgery, to other providers.

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Electrical Stimulation and Neuromodulation in Storage and Emptying Failure

Sandip P. Vasavada, MD ● Raymond Robert Rackley, MD

History of Electrical Stimulation
Neurophysiology of Electrical Stimulation for Storage and Emptying Disorders
Electrical Stimulation for Storage Disorders
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Future Research and Conclusions

For the past century, the development of electrical neurostimulation and neuromodulation to alter physiologic processes responsible for lower urinary tract symptoms and dysfunctions has largely been the result of important landmark discoveries in the clinical application of electricity and in the understanding of neuromuscular physiology. **In neurostimulation the use of electrical stimuli on nerves and muscles has mainly been developed to achieve immediate clinical responses in neurogenic conditions of pelvic organ dysfunction; in neuromodulation the application of electrical stimuli to nerves has been developed to alter neurotransmission processes in non-neurogenic and neurogenic conditions.** In this chapter the focus is on reviewing the application (Table 70–1) and clinical outcomes of neurostimulation and neuromodulation therapies for pelvic organ dysfunction with respect to the development of our knowledge of pelvic neuromuscular physiology and its role in translational innovations.

HISTORY OF ELECTRICAL STIMULATION

Although the field of electrical stimulation of nerves to achieve muscle contractions was not truly realized until the early 1800s, its roots can be traced into the 1700s, when inadvertent electrical impulses were found to generate strong muscle convulsions (Galvani, 1786; Bell, 1811). Magendie (1822) **was one of the first to conduct physiologic investigations of the spinal nerve roots, documenting in young dogs that transection of the posterior (dorsal) segments resulted in a lack of sensation but persistence of motor function, whereas anterior (ventral) root transection yielded preservation of sensation yet abolishment of motor function.** These important findings created the foundation for our understanding of basic neurophysiology of micturition and led to further discoveries on bladder function in the setting of selective rhizotomy of both the pelvic and hypogastric nerves (Giannuzzi, 1863; Langley, 1895). Ultimately, Saxtorph in 1878 used these principles to directly stimulate the bladder in patients with urinary retention via a metal transurethral catheter (Madersbacher, 1999). His early findings allowed others to develop enthusiasm for direct stimulation of the bladder through both transurethral and direct detrusor routes (see section on direct stimulation).

Because Saxtorph had significant influence on the idea that direct bladder stimulation may lead to bladder contractility, McGuire used some of these same principles to perform direct bladder stimulation in dogs (Boyce et al, 1964). He concluded that multiple pairs of electrodes were required to achieve a more uniform pressure rise within the bladder during the stimulated contraction. Research continued throughout the late 1900s and moved toward development of new electrodes (Susset and Boctor, 1967) and differing wire configurations (Timm and Bradley, 1969; Tscholl et al, 1971).

Direct pelvic nerve stimulation and pelvic floor muscle stimulation were not well-known or well-studied concepts until the mid 1900s because emphasis was clearly on different areas of direct stimulation (i.e., bladder). Dees (1965) studied the bladder contraction state after stimulation to the pelvic nerve. He achieved contraction of both the detrusor muscle and urethral sphincter in a cat model and produced pain and hind leg contraction as well. Others demonstrated similar findings of nonspecific contraction of the bladder and pelvic floor and other areas with direct pelvic nerve stimulation and ultimately realized that direct pelvic nerve stimulation may not be suitable for treatment of bladder dysfunction (Burghele et al, 1962; Hald et al, 1966; Holmquist and Olin, 1968). It appears that direct pelvic nerve stimulation elicits pudendal nerve activity such that outlet resistance is increased, as is pain, through simultaneous hypogastric nerve stimulation. Thus, with the limited-potential clinical utility of the pelvic nerve for stimulation, efforts focused on the pelvic floor muscles, spinal cord, and sacral roots. Caldwell first reported experience with pelvic floor muscle stimulation with the goal of improving fecal continence and later urinary incontinence (Caldwell, 1963;

Table 70–1.

Potential Applications of Electrical Stimulation in the Treatment of Voiding Dysfunction

PURPOSE	SITES OF STIMULATION	MECHANISM
Facilitate Filling-Storage		
Inhibit detrusor contractility	V, A, SP, PT	Neuromodulation
Increase bladder capacity	CP, SR, IV	
Decrease urgency and frequency		
Decrease nociception	V, A, SP, SR	Neuromodulation
Increase outlet resistance	V, A, SR	Direct stimulation (efferent nerves or roots)
Facilitate Emptying		
Stimulate detrusor contraction (spinal cord–injured patient)	SAR	Direct stimulation (efferent nerves or roots)
Restore micturition reflex (idiopathic retention)	SR, IV	Neuromodulation

A, anal; CP, common peroneal; IV, intravesical; PT, posterior tibial; SAR, sacral anterior (ventral) roots; SP, suprapubic; SR, sacral roots; V, vaginal.

Table 70–2.

Sacral Nerve Responses

SACRAL NERVE	MOTOR AND SENSORY RESPONSE
S2	*Motor:* Plantarflexion of the entire foot with lateral rotation and clamp movement of the anal sphincter
	Sensory: Sensations in the leg and buttock
S3	*Motor:* Dorsiflexion of the great toe and bellows reflex (anal wink)
	Sensory: Paresthesias or sensation of pulling in the rectum, scrotum, or vagina
S4	*Motor:* Bellows reflex only
	Sensory: Sensation of pulling in the rectum only

Caldwell et al, 1965). Subsequently, interest increased and efforts toward external stimulation were described by anal, vaginal pessary, and direct vaginal stimulation (Hopkinson and Lightwood, 1967; Alexander and Rowan, 1968; Erlandson et al, 1977; Fall et al, 1977).

Spinal cord stimulation, by attempting to directly activate the micturition center, was thought to be a promising avenue of therapy (Nashold et al, 1971; Jonas et al, 1975; Jonas and Tanagho, 1975). **Still, as in pelvic nerve stimulation, voiding was initiated; however, simultaneous sphincter activity precluded proper emptying.** The subsequent series of developments pursued therapy for incomplete emptying by affecting not only bladder stimulation but, in some way, sphincter relaxation as well.

In 1972, Brindley began experimentation of sacral root stimulation that led to implantation of sacral anterior root stimulators in paraplegic patients with urinary incontinence (Brindley, 1972, 1974, 1977). **Evolving data showed that, for optimal bladder emptying to be achieved, sacral anterior root stimulation with posterior rhizotomies of S2, S3, and S4 would be required** (Sauerwein, 1990). **The posterior rhizotomy would decrease the reflex activity of the detrusor and improve bladder compliance.** Tanagho and coworkers then began further examining the sacral roots and their individual contributions to bladder and outlet function. In 1982, Tanagho and Schmidt presented initial experience in sacral root stimulation in paraplegic dogs. In this initial study they realized the design of a spiral electrode to minimize nerve damage and fixed the lead wire to the sacral lamina, thereby preventing tension on the electrode itself. They ultimately attained good bladder contraction in these dogs, with minimal sphincteric response. From these initial good results, Tanagho and coworkers then began human trials and characterized the sacral root stimulation patterns and the corresponding muscle responses (Table 70–2). **In the course of the neurostimulation developments these researchers realized that sphincteric contraction abolished detrusor activity, and the role of the pudendal nerve and its modulation of bladder capacity began to evolve** (Tanagho and Schmidt, 1988; Schmidt, 1989). Thus, neuromodulation was introduced as a concept by which activation of the sacral roots may, in fact, modulate external sphincter function and in turn inhibit detrusor activity as a normal reflex. These early discoveries created the platform for the current and future concepts and technologies that are used for neurostimulation and neuromodulation.

NEUROPHYSIOLOGY OF ELECTRICAL STIMULATION FOR STORAGE AND EMPTYING DISORDERS

The exact mechanisms of how neuromodulation works are not completely understood, but several plausible theories with testable hypotheses are under investigation. Most are founded on the basic neurophysiologic mechanisms that result in the normal storage and emptying functions of the bladder. Although there is an expanding amount of information on our knowledge of micturition neurophysiology as discussed in this chapter, in this section the specifics of the micturition pathway in relation to neuromodulation are addressed.

Normal detrusor function appears to be a sacral balance under suprasacral influences of the sympathetic and parasympathetic nervous systems in their respective abilities to maintain continence. The sympathetic tone, for the most part, is dominant for the majority of time and thus provides continence or storage of urine; the parasympathetic nervous system allows detrusor contractions for emptying of the bladder. Thus, the micturition reflex pathway is activated by initial bladder afferent excitation that then results in a bladder efferent excitation leading to a detrusor muscle contraction. The acquired and unique ability to void volitionally is due to either negative feedback (inhibition of voiding) or positive feedforward (induction of voiding) influences of supraspinal inputs from the pontine micturition center on this sacral micturition reflex pathway. Any loss of either central supraspinal inhibitory influences or increased sensitization of bladder afferent signaling can lead to unmasking of involuntary voiding. As such, this has been proven only in animals and, by deference, relates then to humans. There may be primitive reflexes that reside within the spinal cord that can be "awakened" by somatic and afferent nerve stimulation and may have something to do with the mechanism of action of neuromodulation (de Groat, 1975, 1976; de Groat and Ryall, 1968a, 1968b).

Bladder afferent nerve signaling sends information about pain and bladder fullness to the brain that will in turn initiate the micturition reflex. Bladder overactivity may be in part mediated by the loss of voluntary control of the voiding reflex and, furthermore, emergence of primitive voiding reflexes. In certain states of neurologic or inflammatory disease of the bladder, the previously silent C fibers may emerge and trigger the micturition reflex. Accordingly, blockade of this pathway by electrical neuromodulation, similar to pharmacologic blockade by capsaicin (a C-fiber blocker), may suppress detrusor overactivity (Maggi and Meli, 1988; Chen et al, 1993).

Reflexes That Promote Bladder Storage

Two important reflexes may play an important role in modulation of bladder function: the guarding reflex and the bladder afferent loop reflex. Both reflexes promote urine storage (guarding reflex under somatic influence and bladder loop reflex under sympathetic tone). The guarding reflex guards or prevents urine loss from times of cough or other physical stress that would normally trigger a micturition episode. Suprapontine input from the brain turns off the guarding reflex during micturition to allow efficient and complete emptying. The bladder afferent reflex works through sacral interneurons that then activate storage through pudendal nerve efferent pathways directed toward the urethral sphincter. As such, the activity has truly been realized only in cats but has been postulated to exist in humans and to function the same. Similar to the guarding reflex, **the bladder afferent reflex promotes continence during periods of bladder filling and is quiet during micturition** (Fig. 70–1).

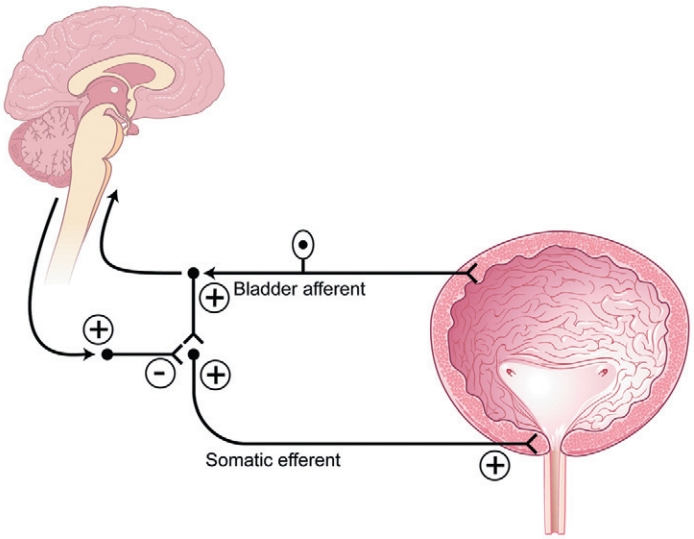


Figure 70–1. The guarding reflex promotes continence and allows the outlet to contract the urinary sphincter during periods of stress (e.g., cough). The brain can turn this reflex off during voiding. (Modified from Leng WW, Chancellor MB. How sacral nerve stimulation neuromodulation works. Urol Clin North Am 2005;32:11–8.)

Reflexes That Promote Bladder Emptying

Signals from the bladder that may modulate the need to void with fullness, pain, pressure, or stretch may elicit bladder afferent activity through the Aδ or even C fibers. These bladder afferent nerve fibers then synapse with both parasympathetic efferents (bladder-bladder reflex) and parasympathetic urethral efferents (bladder-urethral) reflex. The urge to void may then be translated as an initial activity (inhibitory) of the bladder-urethral reflex to allow the pressure in the urethral outlet to drop immediately before a bladder contraction ensues and simultaneously permit the bladder-bladder reflex to allow a smooth bladder contraction to occur as the reflex is maintained throughout the entire void (de Groat, 1978; de Groat et al, 1981, 1996).

Putative Mechanism of Action of Sacral Neuromodulation

Although our knowledge of how neuromodulation works is evolving, two main theories exist: (1) direct activation of efferent fibers to the striated urethral sphincter reflexively causes detrusor relaxation and (2) selective activation of afferent fibers causes inhibition at spinal and supraspinal levels. **Accumulating evidence suggests that activation of somatic sacral afferent inflow at the sacral root level that in turn affects the storage and emptying reflexes in the bladder and central nervous system accounts for the positive effects of neuromodulation on both storage and emptying functions of the bladder** (Yoshimura and de Groat, 1992, 1997; Leng and Chancellor, 2005). Malaguti and coworkers (2003), using detection of somatosensory evoked potentials during sacral neuromodulation, concluded that sacral neuromodulation therapy works by sacral afferent activity and concomitant activation of the somatosensory cortex. Because sacral neuromodulation has been clinically proven for both storage (urgency/frequency and urgency urinary incontinence) and emptying (nonobstructive urinary retention) dysfunctions of the bladder, isolating the mechanism of action to the micturition reflex pathway of sacral afferent and efferent pathways alone is challenging. However, by understanding the reflexes that influence the promotion of urine storage or emptying of the sacral micturition reflex pathway one begins to realize how neuromodulation may affect these reflexes and elicit symptomatic and functional improvement of voiding function (Fowler et al, 2000). Animal models of sacral neuromodulation for detrusor overactivity are now being developed and may shed more light on how this technology achieves its benefits (Riazimand and Mense, 2004; Vignes et al, 2009)

Putative Mechanism of Action of Sacral Neuromodulation in Overactive Bladder

The bladder storage and emptying reflexes are modulated by several centers in the brain and may be altered by neurologic injury that effectively unmasks involuntary bladder contractions. Thus, sacral neuromodulation of these primitive reflexes may restore normal micturition (de Groat, 1976). Animal data exist to support the fact that somatic afferent input to the spinal cord can affect the guarding and bladder-bladder reflexes (de Groat, 1978; Chen et al, 1993). It is believed that suppression of interneuronal transmission in the bladder reflex pathway may be how sacral neuromodulation affects detrusor overactivity (de Groat, 1976;

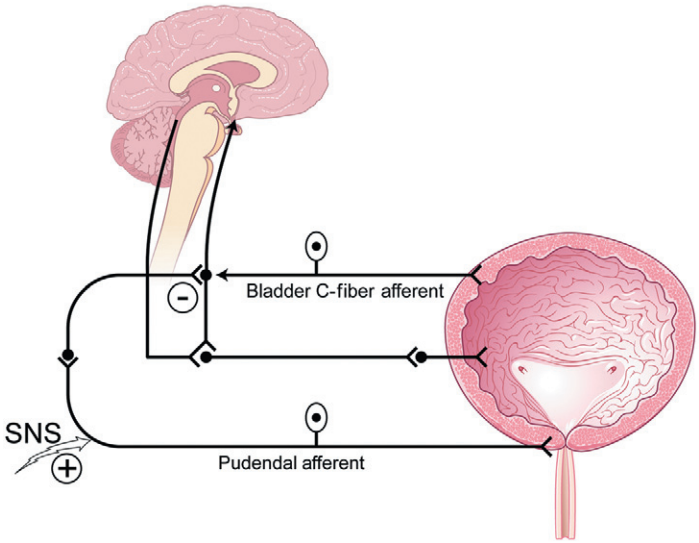


Figure 70–2. Pudendal nerve afferent firing can modulate and accordingly inhibit the bladder micturition reflex. SNS, sacral nerve stimulation. (Modified from Leng WW, Chancellor MB. How sacral nerve stimulation neuromodulation works. Urol Clin North Am 2005;32:11–8.)

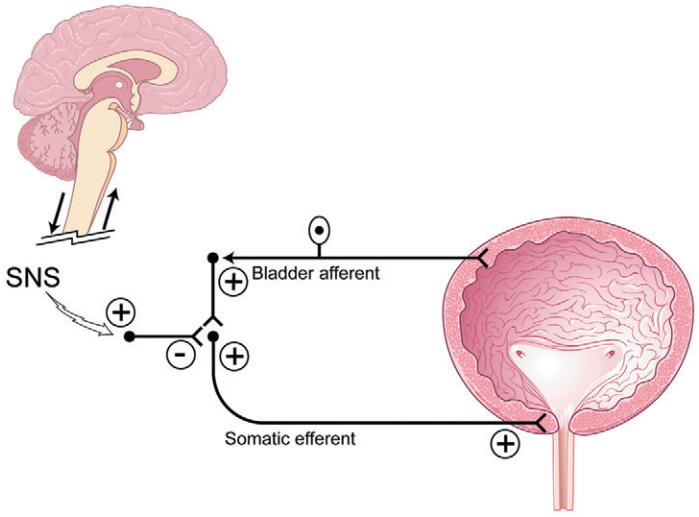


Figure 70–3. In neurologic disease the supraspinal circuitry is "disconnected" and therefore cannot turn off the spinal guarding reflex, and thus retention occurs. Sacral neuromodulation (SNS) can restore the normal voluntary pattern of micturition by inhibition of the spinal guarding reflex. (Modified from Leng WW, Chancellor MB. How sacral nerve stimulation neuromodulation works. Urol Clin North Am 2005;32:11–8.)

Kruse and de Groat, 1993; Leng and Chancellor, 2005). **The inhibition by electrical neuromodulation may, in part, modulate the sensory outflow from the bladder through the ascending pathways to the pontine micturition center, thereby preventing involuntary contractions by modulating the micturition reflex circuit but allowing voluntary voiding to occur** (Fig. 70–2). The preservation of voluntary voiding may be due to selective avoidance of normal sensory ascending outflow pathways of the bladder from Aδ fibers to the pontine micturition center as well as initiation of the descending pathways from the pontine micturition center to sacral efferent outflow pathways. Therefore, as is seen in clinical practice, sacral neuromodulation may affect and improve the abnormal bladder sensations, involuntary voids, and detrusor contractions but still maintain normal bladder sensations and voluntary voiding patterns.

Putative Mechanism of Action of Sacral Neuromodulation in Urinary Retention

Sphincteric activity can be turned off by brain pathways to allow efficient and complete bladder emptying. **If the suprasacral pathways are altered, the guarding and urethral reflexes still exist and cannot be turned off. This may cause retention, as in the spinal cord–injured patient who in turn has detrusor-sphincter dyssynergia resulting in urinary retention. Thus, inhibition of the guarding reflexes may allow urinary retention states to be improved** (Fig. 70–3). Originally for urinary retention due to functional outlet obstruction, sacral neuromodulation was thought to directly turn off excitatory flow to the urethral outlet and facilitate bladder emptying. This may be an efferent effect of the primary afferent mechanism of sacral neuromodulation as reported by Dasgupta and colleagues (2005), who described novel neuroimaging evidence for the existence of abnormal interaction between the brainstem and cortical centers in women with urinary retention due to Fowler syndrome or overactive sphincteric activity. The direct therapeutic effect of sacral neuromodulation in patients with sphincter overactivity or functional outlet obstruction appears to be in the afferent restoration of a normal pattern of midbrain activity and decreased cortical activity leading to inhibition of the guarding reflexes.

ELECTRICAL STIMULATION FOR STORAGE DISORDERS

Criteria for Selection of Patients

Because many lower urinary tract symptoms and dysfunctions are secondary to a neuromuscular etiology, a thorough history and physical examination will often reveal the nature (acute vs. chronic) and help classify the cause (neurogenic, anatomic, postsurgical, functional, inflammatory, or idiopathic). In addition to the unique evaluation of pelvic floor muscle dysfunction (Siegel, 2005), a urinalysis is routinely performed; urine cytology should be considered in patients who present with refractory symptoms of dysuria, urgency, or frequency of urination, because carcinoma in situ and bladder tumors may present as irritative bladder symptoms without hematuria. Further assessment of the bladder function, urodynamic studies including cystometrography, pressure-flow studies, and electromyography of sphincters and pelvic floor muscles are performed on a selected basis, because most non-neurogenic assessments are completed routinely with the use of a voiding diary and a focused physical examination of the pelvis. Electromyography is recommended in suspected cases of neurogenic bladder dysfunction, detrusor-sphincter dyssynergia, or Fowler syndrome and may be considered for evaluation of inappropriate pelvic floor muscle behavior (Dasgupta and Fowler, 2003). As of now, urodynamics have not yielded adequate predictive factors that allow enhanced

selection for patients undergoing sacral neuromodulation (Groenendijk et al, 2007). **The characteristics of neurogenic bladders, as seen in patients with multiple sclerosis and spinal cord injury, can change with time and disease progression. Therefore, reevaluation with urodynamics and assessment of the upper urinary tracts may be needed when symptoms change despite active medical intervention.**

Cystourethroscopy may yield information helpful in making a diagnosis. Anatomic lesions such as urethral stricture, bladder neck fibrosis, trabeculation, and bladder lesions have been found even in women with bladder outlet obstruction. Baseline upper tract imaging is performed in patients with neurologic disease or, if indicated, by physical or baseline studies or a patient's history.

Sacral neuromodulation is frequently attempted in patients in whom traditional conservative measures (e.g., bladder retraining, pelvic floor biofeedback, and medications) have failed and before more invasive surgical procedures (e.g., enterocystoplasty and urinary diversion). **Despite all the studies done to date there are no defined preclinical factors, such as urodynamic findings, that can predict which patients will or will not respond to sacral neuromodulation.**

Although most patients are considered candidates for neurostimulation and neuromodulation therapies when more conservative treatment has failed **there are some clinical considerations for excluding patients from this therapy. These include significant anatomic abnormalities in the spine or sacrum that may present challenges to gaining access; mental incapacitation of patients who cannot manage their device or judge the clinical outcome; physical limitations that prevent the patient from achieving normal pelvic organ function, such as functional urinary incontinence; and noncompliance of the patient.**

Relative contraindications for patients who may be considering or who have an implantable electrical stimulation device are magnetic resonance imaging (MRI) and pregnancy. Magnetic fields produce currents in neuroelectrodes, and there is some concern that the magnetic field from MRI may damage the pulse generator, as discussed later. Many radiologists are reluctant to provide MRI services for patients with implantable electrical stimulation devices despite the anecdotal evidence that no adverse event has occurred when MRI has inadvertently or purposefully been done for emergent reasons or in small trials (Hassouna and Elkelini, 2005). For patients who have InterStim devices in place (see later), the authors advocate removal of the device in preparation for elective MRI based on current manufacturer recommendations. After the MRI procedure, a new neuroelectrode and generator may be placed. Anecdotal reports of patients safely undergoing the study (MRI) with the InterStim implant in place have occurred, but patients should have the devices turned off in anticipation. Because of the potential for teratogenicity or abortion from the effect of electrical stimulation, electrical stimulation has been considered contraindicated in pregnant women with various voiding dysfunctions. However, whether electrical stimulation can cause abortion or malformation is not known. Wang and Hassouna (1999) reported no adverse effects of electrical stimulation on pregnant rats and that termination of pregnancy is not advised for prospective mothers when electrical stimulation has been performed unknowingly in early pregnancy. Women with electrical stimulation devices for pelvic health conditions who become pregnant may simply turn off their devices during pregnancy.

Electrical Stimulation of the Bladder

Transurethral electrical bladder stimulation (TEBS) has been pursued not only for initiating sensory awareness of bladder filling and stimulating detrusor contractility (see later section) **but also for increasing bladder capacity at low pressure in pediatric patients with myelomeningocele** (Kaplan et al, 1989; Decter et al, 1994). The authors in these two cited references carried on an interesting point-counterpoint discussion in publications regarding the practical benefit of TEBS (Kaplan, 2000; Decter, 2000), which remains controversial.

Both authors seem to be saying the same thing with respect to results but attach a totally different significance to the practical implications of the results. Kaplan (2000) points out that when the procedure was initiated the goal was to provide children with neurogenic bladder dysfunction, mostly secondary to spina bifida, enough sensation to detect a filling or full bladder and to have them synergistically void or catheterize in a timely manner. As the results of treatment have been evaluated over the years, the real benefit of this program, to Kaplan at least, was the potential to increase bladder capacity while maintaining or decreasing end-filling bladder pressure (in essence, improving compliance). Decter (2000) gives what seems to be a reasonable summation of the largest multi-institutional report of this therapy involving 568 patients who underwent TEBS at 11 institutions, only 335 of whom had adequate pretreatment and post-treatment urodynamics for evaluation. Bladder capacity increased by 20% or more in 56% of the 335 patients, whereas pressure at bladder capacity decreased by 25% or more in 16% of those in whom the bladder capacity increased. Decter (2000) calculated that only 30 of 335 patients had both a 20% or more increase in bladder capacity and a 25% decrease in compliance. He reports his experience with 25 patients during a 4-year period as showing that bladder capacity increased more than 20% (values referred to a comparison to age-adjusted bladder capacity) and end-filling bladder pressures showed clinically significant decreases in 29% of patients. Putting this in perspective, he believes "the practical benefits our patients derive seem limited…the urodynamic improvements we achieved after stimulation did not materially alter daily voiding routine (i.e., clean intermittent catheterization) of these children." Pugach and associates (2000) also reported the results of TEBS in a group of pediatric patients; only 7 of 44 (16%) had safe storage pressures with continence after treatment. There exist limited new data since 2000 on this treatment modality probably owing to other better potential nerve targets.

Sacral Rhizotomy

In most cases, **bilateral anterior and posterior sacral rhizotomy or conusectomy converts a overactive detrusor to an areflexic one.** This alone may be inappropriate therapy because it also adversely affects the rectum, anal and urethral sphincters, sexual function, and the lower extremities. In an attempt to leave sphincter and sexual function intact, **selective motor nerve section was originally introduced as a treatment to increase bladder capacity by abolishing only the motor supply responsible for involuntary contractions.** The initial use of this procedure followed the observation that the third anterior (ventral) sacral root provided the dominant motor innervation of the human bladder. **To enhance the clinical response and to minimize side effects, differential sacral rhizotomy should always be preceded by stimulation**

and blockade of the individual sacral roots with cystometric and sphincterometric control.

Although technique refinements, such as percutaneous radiofrequency selective sacral rhizotomy and cryoneurolysis, have occurred, **there is still controversy about the role of anterior rhizotomy procedures within a treatment plan for detrusor overactivity.** Torrens (1985) summarized successful results in collected groups of patients that ranged from 48% for idiopathic overactivity to 81% for patients classified as having a "paraplegic bladder." However, as he astutely pointed out, the definition of success varies from one series and from one patient to another. When these procedures are used, they should certainly be preceded by urodynamics and urologic evaluation of the effects of selective nerve blocks before performance, especially in patients without fixed neurologic disease or injury. Even then, **unintended effects on pelvic and lower extremity sensory or motor functions may occur with disastrous medical and legal sequelae.**

Both Tanagho and Schmidt (Tanagho and Schmidt, 1988; Tanagho et al, 1989) **and Brindley** (Brindley and Rushton, 1990) **have popularized the concept of sensory deafferentation by dorsal or posterior rhizotomy to increase bladder capacity as part of their overall plan to simultaneously rehabilitate storage and emptying problems in patients with significant spinal cord injury or disease. These are patients in whom electrical stimulation also was used to alleviate emptying deficits** (see section on emptying disorders). McGuire and Savastano (1984) **also mentioned dorsal root ganglionectomy alone in such patients to increase bladder capacity.**

Gasparini and colleagues (1992) reported durability of the deafferentation response to selective dorsal sacral rhizotomy up to 64 months after section. The technique involves selecting nerve roots whose intraoperative stimulation provokes an adequate detrusor response. The dorsal and ventral components of these roots are then separated and the dorsal root or roots severed. An increase in bladder capacity of 259 to 377 mL was noted in 16 of 17 patients studied (24 in the original series), with an increase in the volume to the first contraction of 99 to 270 mL. Fourteen patients were cured of incontinence, and 2 improved; the technique failed in 1 patient. Of seven potent men, two experienced a decrease in erectile frequency but were still able to achieve penetration. Bowel and sphincter function were unaffected. Koldewijn and associates (1994) reported on the effects of intradural bilateral posterior root rhizotomies from S2 to S5 with implantation of an anterior root stimulator in a group of patients with suprasacral spinal cord injury. All showed persistent detrusor areflexia afterward, although 2 required subsequent secondary rhizotomy at the level of the conus. A majority showed decreased bladder compliance up to 5 days postoperatively, followed by a rapid increase thereafter.

Brindley (1994) **summarized the advantages of bilateral posterior sacral rhizotomy in treatment of voiding dysfunction after spinal cord injury as abolishing reflex incontinence, improving compliance, and abolishing striated sphincter dyssynergia without altering resting tone. Partial or selective procedures are considered only in such patients who retain some sensation or have excellent reflex erections.** Madersbacher (2000) comments that posterior sacral rhizotomy for sacral deafferentation of the bladder is best achieved by the intradural approach, which has the advantage that, in this location, motor and sensory fibers can easily be separated, whereas distal to the spinal ganglion, motor and sensory fibers are intermingled and a clear separation is no longer possible. If an intradural procedure is not possible, he believes that a deafferentation at the level of the conus medullaris is preferable to an extradural sacral approach. He mentions that he has treated 65 tetraplegic or paraplegic patients with post–spinal cord injury reflex urinary incontinence who were resistant to all other means of conservative treatment. Incontinence was abolished in 90% of these patients.

Sacral Neuromodulation

Neuromodulation is an innovative treatment of lower urinary tract symptoms and dysfunctions of bladder storage secondary to neuromuscular causes. In addition to the application of evolving technologies for sacral neuromodulation therapy, expanding clinical indications such as neurogenic detrusor overactivity, post–sling-related voiding dysfunction, interstitial cystitis, pelvic pain, pediatric voiding dysfunction, and bowel disorders as well as novel forms of transcutaneous and implantable neuromodulation devices for different nerve roots are under investigation.

Technique

Sacral nerve stimulation (SNS) by the InterStim (Medtronic, Minneapolis, MN) procedure is performed in two stages: stage I, a clinical trial of a temporary or permanent lead for external stimulation; and stage II, implantation of a subcutaneous implantable pulse generator (IPG). Each stage can be performed with monitored anesthesia care supplemented by local anesthesia. During the initial introduction of sacral neuromodulation therapy, patients underwent a percutaneous nerve evaluation by the placement of a unilateral percutaneous lead in the S3 foramen with use of local injectable anesthesia. The lead was connected to an external pulse generator and worn by the patient for several days. A large number of false-negative results with therapy are attributed to improper lead placement and migration. Whereas some physicians still prefer to perform the first stage by a percutaneous nerve evaluation approach, most have adopted a permanent tined lead placement for the first stage in an attempt to avoid the issues related to high false-negative results with the first stage and high false-positive results with the second stage. Changes in lower urinary tract symptoms and postvoid residuals are recorded in a detailed bladder diary. If improvement is minimal or absent, revision or bilateral percutaneous lead placement may be attempted. If more than 50% improvement in symptoms of urgency/frequency or urgency urinary incontinence is attained, a permanent IPG is implanted. The length of the trial with the external pulse generator may vary slightly from patient to patient, by the indication, and by the surgeon's practice preference. In patients with urgency/frequency and urgency urinary incontinence, a 1- to 2-week trial is generally adequate. For retention, a longer trial of 3 to 4 weeks or more may be necessary before a desired clinical response is obtained.

Previous lead placement required a more time-consuming surgical dissection of the layers above the sacral foramen and unreliable lead fixation with anchors. Recent technical advances have made implantation of the percutaneous lead easier and less prone to migration. Spinelli and colleagues (2003) were the first to present the advantages of the tined lead that used a percutaneous approach for placement and fixation (Fig. 70–4). Subsequent large-scale clinical experience worldwide confirms that the tined lead is less prone to migration and has decreased false-negative results with the screening trial. Furthermore, the false-positive rate of the screening trial is reduced when placement of a permanent lead

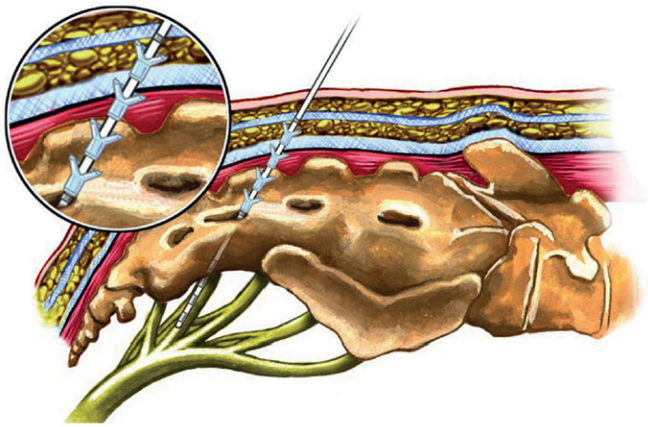


Figure 70–4. The tined lead is introduced typically into the S3 nerve foramen. The "tines" allow the lead to be fixed into the fascial layers above the sacrum. This lead has a quadripolar configuration (four contact points). (Courtesy of Medtronic, Minneapolis, MN.)

with reliable fixation during the screening trial ensures that the same location of stimulation is achieved when the IPG is implanted. With a percutaneous nerve evaluation or similar temporary lead electrode during the screening trial, a different clinical outcome may occur when the permanent lead is placed at the time of the IPG implantation.

For the first stage of the procedure, preoperative intravenous antibiotics are given before the procedure and aseptic techniques of foreign body implants are implemented. The patient is placed in the prone position, and the buttocks are held apart by wide tape retraction so that the anus is visible during test stimulation. The anus and tape are prepared in a sterile fashion and then covered with a separate plastic drape until visualization is needed during the procedure. The sterile drape covering the feet must be folded back such that the feet can be visualized during the procedure as well.

The location of the S3 foramen is approximated by measuring 9 cm cephalad to the dropoff of the sacrum and 1 to 2 cm lateral to the midline on either side. Alternatively, the site may also be localized by palpating the cephalad portions of the sciatic notches bilaterally and drawing a connecting line that intersects the midline of the sacrum; one fingerbreadth on either side of the midline of the sacrum at this intersection will define the location of the S3 foramen (Fig. 70–5). The foramen needle is then inserted into the S3 foramen. The pelvic plexus and pudendal nerve run alongside the pelvis, and therefore the needle should be placed just inside the ventral foramen. The position of the needle is confirmed by fluoroscopy. The nerve is tested for the appropriate motor response, which is dorsiflexion of the great toe and bellows contraction of the perineal area, which represents contraction of the levator muscles (bellows reflex). Simultaneous sensory responses determined at the time of lead placement help optimize positioning. Although this is controversial, if one can localize the stimulation at the time of lead positioning to the vagina-rectum juncture in females and perineoscrotal area in males this is proper localization of the device. The foramen needle stylet is then removed and replaced with the introducer sheath. The distal aspect of the lead consists of four electrodes numbered 0 through 3. The lead is placed into the introducer sheath as directed to expose the electrodes. Typically, electrodes are positioned such that electrodes 2 and 3 straddle the ventral surface of the sacrum

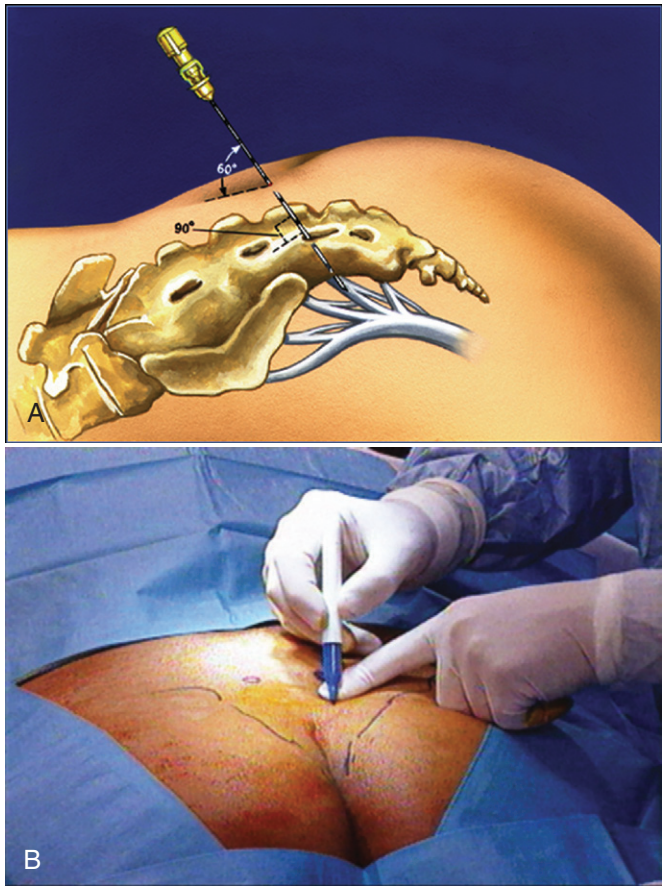


Figure 70–5. **A,** The percutaneous test stimulation is performed in an outpatient setting. A small lead wire is placed into S3 and connected to an external stimulator for 1 week to administer stimulation to the nerve roots. **B,** Measurement of the S3 nerve foramen is typically 9 cm to the coccyx and 11 cm to the anal verge. One measures 1 to 2 cm lateral to this mark to find the rough site of the S3 nerve foramen. The "cross hair" technique can be used to find the midline fluoroscopically and the lower aspect of the sacroiliac joints laterally to find the S3 nerve foramen as well. (Courtesy of Medtronic, Minneapolis, MN.)

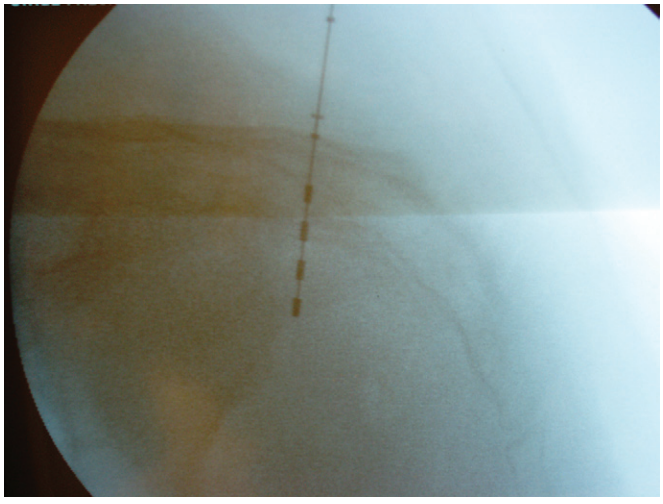


Figure 70–6. Fluoroscopy is used to confirm lead placement, typically with the lead configurations to obtain optimal muscle (bellows response and ipsilateral toe contractions) and sensory (vaginal, penile, or scrotal "pulsating" feeling) responses. The lead may then be deployed.

(Fig. 70–6). Test stimulation is repeated on each electrode, and the responses are observed. An S3 response should be noted on at least two of the electrodes (see Table 70–2). Once the surgeon is satisfied with the position, the sheath is removed, releasing the tines that anchor the lead. A sensory response, sensation of stimulation in the perineum, is not needed to confirm proper placement if the correct S3 motor response is observed. However, when a motor response is absent, raising the conscious level of the patient during the procedure and detecting the correct sensory response will confirm proper localization, and a clinical response may still be obtained during the screening trial period despite the absence of the motor response.

A 3- to 4-cm incision into the subcutaneous tissues in the upper lateral buttock is made below the beltline or below the level of the ischial wings for connecting the permanent lead to the percutaneous extension lead wire. If the screening trial is successful, this connection site will be the site of implantation for the IPG. With use of the tunneling device provided in the commercial kit, the permanent lead is transferred to the medial aspect of the lateral buttock incision. The lead is then connected to the extension wire, and the tunneling device is used again to transpose the extension wire from the medial aspect of the incision to an exit point on the contralateral side of the back. This transfer and long tunnel reduce the occurrence of infection from the percutaneous exit site of the wire. The extension wire is connected to the external pulse generator. Patients are able to resume their normal activities immediately but are advised to limit excessive movement-related activities, such as high-impact exercises, for the duration of the trial period.

The external generator can be flexibly programmed for the duration of the intended trial while the patient records symptoms and bladder function in a voiding diary. If there is more than 50% improvement in the symptoms or voiding function, a stage II procedure is performed.

A stage II procedure entails placement of the IPG. No fluoroscopy is required during stage II when a permanent neuroelectrode has been placed for the stage I procedure; however, if a percutaneous nerve evaluation was performed for stage I, fluoroscopic confirmation of the neuroelectrode placement is advised. The patient may be placed in the prone position or a lateral position with the site of the previous lateral incision for the lead connections placed upward (Fig. 70–7). The lateral position may improve ventilation during sedation. The previous buttock incision overlying the lead connections is opened, the percutaneous extension wire is removed, and the extension lead is secured to the permanent lead and subsequently to the IPG. A pocket is made in the subcutaneous tissue that is large enough to avoid tension on closure and at a depth to provide a covering layer of subcutaneous tissue anterior to the pulse generator to prevent erosion.

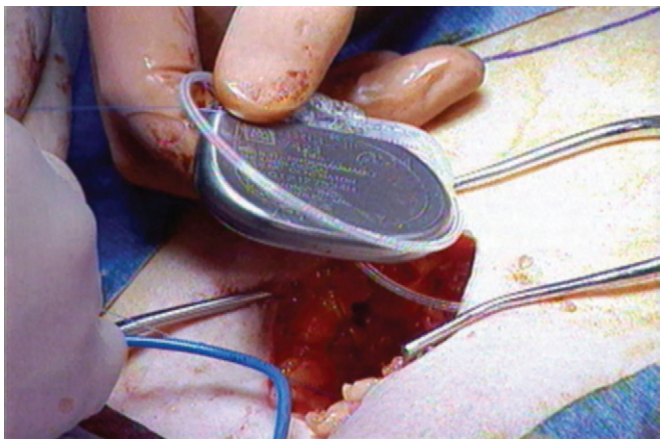


Figure 70–7. A 3- to 4-cm counterincision in the upper gluteal crease is made for a deep subcutaneous pocket to allow implantation of the implantable pulse generator.

Outcomes

Urinary urgency, frequency, and urgency incontinence have a significant impact on medical health and quality of life. Neuromodulation offers an alternative to patients who may be considering irreversible surgical options when pelvic floor muscle reeducation and pharmacologic therapy have failed. Outcomes of SNS for the indications of idiopathic urgency/frequency and urgency urinary incontinence are derived from only two studies that have randomized patients to active or delayed therapy as well as reports from numerous prospective and retrospective reviews of case series and registry databases.

Schmidt and coworkers (1999) reported on SNS therapy in 76 patients with refractory urgency urinary incontinence from 16 centers worldwide randomized to active or delayed therapy (control group) during the study period of 6 months. Of the 34 patients receiving active SNS therapy compared with the delayed group, 16 (47%) were completely dry and an additional 10 (29%) demonstrated more than 50% reduction in incontinence episodes. Complications were IPG site pain in 16%, implant infections in 19%, and lead migration in 7%.

In a similar study design, Hassouna and colleagues (2000) reported the outcomes of SNS on refractory urgency/frequency conditions in 51 patients randomized from 12 centers during an initial 6-month period that was extended to 2 years. Outcomes at 6 months in the active SNS group showed improvement in the number of daily voids (16.9 ± 9.7 to 9.3 ± 5.1), volume voided (118 ± 74 mL to 226 ± 124 mL), degree of urgency (rank score of 2.2 ± 0.6 to 1.6 ± 0.9), and SF-36 quality of life measures. At 6 months after implantation, stimulators in the active group were turned off and urinary symptoms returned to baseline values. After reactivation of SNS, sustained efficacy was documented at 12 and 24 months.

Limited but conformational results of the earlier randomized trials have been obtained from prospective series (Shaker and Hassouna, 1998; Siegel et al, 2000; Janknegt et al, 2001) and registry studies (Spinelli et al, 2001; Hedlund et al, 2002) evaluating efficacy, safety, and quality of life measures. The results for the registration trial that led to approval by the U.S. Food and Drug Administration (FDA) for SNS (Pettit et al, 2002) reveal that 37 of 62 patients (60%) with refractory urgency/frequency or urgency urinary incontinence achieved an improvement of 50% or more in their condition. van Kerrebroeck and coworkers (2007) have reported on a 5-year prospective worldwide series for patients with the InterStim device for varying indications and for the urgency/frequency and urgency urinary incontinence populations, and good success was achieved in all groups. Of note is that the analysis was of patients including those in the initial registration trial who then "crossed over" to the prospective 5-year trial. This study, unfortunately, was influenced by several patients who did not attend all follow-up visits and, therefore, had missing data points, a problem reflective of this challenging subgroup. Outcomes data were based on "last observation carried forward," which is of concern for not being statistically optimal, but nonetheless these are still the longest-term data this technology has available.

Special Populations

With the success of neuromodulatory therapies for refractory detrusor overactivity and urinary retention it should be no surprise that indications are expanding. Despite the fact that there is no true FDA-approved indication for neuromodulation in select populations, these groups all have some component of the indicated symptom-complex that includes urgency, frequency, urgency urinary incontinence, or urinary retention. The current expansion of indications for neuromodulation has developed into areas of neurogenic bladder (Parkinson disease, multiple sclerosis, spinal cord injury), interstitial cystitis (painful bladder syndrome), pelvic pain, fecal incontinence and bowel disorders, and pediatric voiding dysfunction.

Neurogenic Bladder. Patients with neurogenic bladder may have several urodynamic events that lead to their symptomatic voiding dysfunction. This may include neurogenic detrusor overactivity, detrusor-sphincter dyssynergia, and flaccid areflexia. Whereas neuromodulation has not been well examined in cases of obvious areflexia (possibly because of the need for some end-organ response for neuromodulation to have any benefit), it has been studied in small subgroups of patients with detrusor overactivity and possibly detrusor–external sphincter dyssynergia, although few published reports exist.

Because the spectrum of neurologic diseases with potential bladder **manifestations is wide, one must be cognizant of a few important relative contraindications before contemplating current neuromodulatory therapies, as follows: significant bone abnormalities in the spine or sacrum that may present challenges to gaining access; mental incapacity of patients, who cannot manage the device; physical limitations that prevent voiding (functional incontinence); future need of MRI; and noncompliance.**

Multiple Sclerosis. **Multiple sclerosis (MS) is a chronic demyelinating disease of the central and peripheral nervous system that can cause a variety of voiding dysfunction scenarios including neurogenic detrusor overactivity, detrusor-sphincter dyssynergy, areflexia, and combinations of these.** Because many patients have been refractory to standard therapies, neuromodulation or neurostimulation (to be addressed later in the section on neurostimulation for retention) may be considered a part of their treatment options. In an appropriately selected patient with MS, neuromodulation truly has some promise because it may balance the function of the bladder itself as well as that of the outlet (two of the main components of MS-related voiding dysfunction). This may be considered off-label use of neuromodulation because it is not approved specifically for MS-related voiding dysfunction, but approval may be based on symptoms such as urgency, frequency, or often urgency urinary incontinence and even nonobstructive urinary retention.

No prospective randomized trials exist on the use of neuromodulation in management of MS-related bladder dysfunction. Small series with encouraging results in patients with MS demonstrate that neuromodulation may have a role in treatment of MS-related voiding dysfunction (Bosch and Groen, 1996; Wallace et al, 2007). It appears that the best candidates are ones with mild, nonprogressive MS, with few functional issues, who also have detrusor overactivity or even retention but not areflexia. One of the major issues that arises in the patient with MS in particular is the potential change in the disease state that may be potentiated by neuromodulation. Although this may be theoretical, it was one of the factors cited by the FDA in the original sacral neuromodulation trials and precluded MS patients from being enrolled (Hassouna et al, 2000).

A secondary issue that may arise if a patient with MS is implanted with the lead and IPG system is the potential need for MRI in the future. One should maintain close contact with the patient's neurologist as to the decision to place a neuromodulatory device to prevent any future need for MRI or selection of a patient in an active phase of disease who requires routine MRI. **The main concern with MRI and implantable stimulator or pacemaker-type devices is that heating of the leads has been demonstrated in vivo and in vitro** (Roguin et al, 2004; Martin, 2005). Whereas some question the clinical significance of the small temperature changes with the leads, the potential exists to elicit nerve damage with heating of the lead, and the magnetic field may change the generator itself (Gimbel and Kanal, 2004). At present, it is contraindicated to perform MRI of a patient with an implantable neurostimulator system.

Spinal Cord Injury. Many specialists who treat neurogenic disorders due to spinal cord injury realize that a patient may present with a variety of clinical and urodynamic findings. Many patients have neurogenic detrusor areflexic situations, but perhaps more often and sometimes more challenging is the subset who may be incontinent from neurogenic detrusor overactivity with or without concomitant sphincteric dyssynergy. Furthermore, the adverse sequelae of treated or untreated spinal cord injury may include infections, urolithiasis, reflux, or obstruction. The goal, then, is not only to prevent these adverse events but also to ensure a bladder that functions well, empties at a low pressure to protect the upper tracts, and maintains a good capacity and continence. **Whereas it is implied that an intact reflex arc should be in place for neuromodulation to work, this has not been proved in clinical studies. Basic science data suggest that at least some communication should exist between sacral outflow and the pontine micturition center to allow processing for the reflexes that may be inhibited by the brain** (de Groat et al, 1981). Thus, a patient with a complete spinal cord lesion may not have the same potential benefit from neuromodulation as does one with an incomplete lesion. Again, this fact has yet to be proved clinically in patients. Shaker and colleagues (2000) described their observations in a group of female rats that developed bladder overactivity 3 weeks after spinal cord transection, associated with an increase in neuropeptide content of the dorsal root ganglion of L6. The spinal cord transections were at level T10. Electrostimulation of S1 was carried out and abolished overactivity while still attaining the rise in neuropeptide content in the L6 dorsal root ganglion. This suggested that blockade of C-fiber afferent pathways may have been one of the mechanisms of action of neuromodulation of the sacral root. In addition, they believed the time course of the reduction in neuropeptide content may explain the long-term changes that occur with chronic neuromodulation and the time needed for detrusor overactivity to return toward baseline after neuromodulation is initiated.

From a clinical perspective, few studies exist in neurogenic patients alone for whom sacral neuromodulation was performed. Andrews and Reynard (2003) described a T8 paraplegic with residual urinary urgency and urgency urinary incontinence who underwent percutaneous tibial nerve stimulation (see later section in this chapter) for his problem. This patient experienced an almost twofold increase in bladder capacity; this was repeated, and again, increased cystometric capacity was demonstrated on follow-up. Patients with incomplete spinal cord injury may respond in a

similar fashion to the remainder of the population, with fairly high success rates in motivated individuals (Lombardi and Del Popolo, 2010).

It is clear that this is an emerging area of interest in current techniques, and some have postulated a role for selective stimulation in neurogenic patients as a means to achieve better results. Future research will clearly need to be done in this challenging subset of patients.

Voiding Dysfunction after Prior Sling or Anti-Incontinence Surgery. It is well known that patients may develop urinary retention or some form of voiding dysfunction after vaginal sling surgery or other forms of surgical management for urinary incontinence. Whereas the mainstay of therapy is to surgically "undo" the operation, many patients who have been obstructed for some period of time may manifest long-term voiding difficulty. This problem may vary from urgency, frequency, to urgency urinary incontinence or to continued problems with retention and incomplete emptying despite adequate urethrolysis. This patient population (when refractory symptoms continue) may be ideally suited to the placement of a sacral neuromodulation device (Starkman et al, 2008). After implantation, patients had improved quality of life scores, improved urgency and frequency scores, with diminished urgency urinary incontinence in a small retrospective series.

Interstitial Cystitis (Painful Bladder Syndrome). Chronic pelvic pain and interstitial cystitis are challenging and frustrating conditions for both the physician and the patient. Therapeutic options are limited and frequently ineffective. Whereas neuromodulation therapy in patients with interstitial cystitis has typically been reserved for patients considering major surgery (e.g., cystectomy and urinary diversion) when behavioral and pharmacologic therapies have failed, more innovative consideration has been given to earlier application of this therapy before chronic neuroplastic changes become irreversible.

Interstitial cystitis is not a true FDA-approved indication for neuromodulation; however, the symptom-complex of urinary urgency and frequency is well within the standard approved criteria. **It may be realized that neuromodulation for interstitial cystitis may be best in combination with other therapies, because interstitial cystitis is thought to require a multimodal approach and neuromodulation should be considered only one part of the multimodal therapy.**

Comiter (2003) performed a prospective evaluation of 25 patients with refractory interstitial cystitis. Seventeen of the 25 patients demonstrated more than 50% improvement in average pain score and voiding symptoms and therefore qualified for permanent IPG placement. At a mean of 14 months of follow-up, improvements were seen in frequency, nocturia, and mean voided volume. Average pain scores decreased from 5.8 to 1.6 on a 10-point scale, and Interstitial Cystitis Symptom Index (ICSI) and Problem Index (ICPI) scores decreased significantly. Furthermore, 94% of patients implanted had a sustained improvement in symptoms. Similar findings were noted by Whitmore and associates (2003) in 33 patients who had statistically improved parameters in frequency, pain, average voided volume, and maximum voided volume as well as ICSI and ICPI scores.

Peters and colleagues (2003) retrospectively evaluated 21 patients with refractory interstitial cystitis with pelvic pain who underwent permanent implantation of the IPG. The patients were contacted by mail and asked to respond to a questionnaire that addressed the use of narcotic pain medication. There was an average decrease in morphine dose-equivalents after implantation of 36%. In addition, subjects were asked to rate their pelvic pain complaints on a 7-point scale. Most patients reported a moderate to marked improvement in pain after sacral neuromodulation. Approximately one fourth of the patients were able to discontinue narcotics completely, and patients overall were satisfied with this form of therapy compared with previous ones.

Chai and coworkers (2000) have reported that perhaps some of the effects of neuromodulation in patients with interstitial cystitis may be due to changes in antiproliferative factor. His group has shown that levels of antiproliferative factor and epidermal growth factor were elevated in the urine of patients with interstitial cystitis and that these levels subsequently normalized after a short trial of sacral neuromodulation.

Chronic Pelvic Pain. Pelvic pain, much like interstitial cystitis, has been investigated with therapy like neuromodulation; again, this affects a challenging subset of patients who no other treatments seem to benefit. Bemelmans (1999) described the mechanism in pain inhibition as involving the gate control mechanism at the spinal segmental level. At this point, large somatic sensory fibers inhibit the activity in small Aδ or unmyelinated C fibers via sacral segmental interneurons or perhaps supraspinally by way of the spinobulbospinal reflex system. The hypothesis is that sacral root stimulation for the treatment of many disorders may result from decreasing pelvic floor spasticity.

Multimodal therapy is likely to be of benefit; however, results may not be optimal in all cases. **Spinal cord stimulation at higher centers has been used by pain therapists and with moderate success; however, trial design and consistent entry criteria are debated** (Feler, 2003; Mailis-Gagnon et al, 2004). Small series have looked at more selective stimulation, primarily at sacral roots. Aboseif and colleagues (2002) examined the effect of sacral neuromodulation on pelvic floor dysfunction in 41 of 64 patients thought to have chronic pelvic or perineal pain. Patients with chronic pelvic pain had decreased pain scores on average (5.8 to 3.7) after neuromodulation based on validated pain scales. Siegel and associates (2001) examined patients with intractable pelvic or genitourinary pain in the absence of neurologic or pelvic disease. Sacral neuromodulation did benefit patients, and they described a decrease in severity of pain and quality of life improvements. Bilateral caudal sacral stimulation may yield almost 40% improvement in pain scores in patients with mixed symptoms of voiding dysfunction and pelvic pain (Zabihi et al, 2008). Still, some form of placebo effect is likely to exist and is challenging to control in these small series.

Pediatric Voiding Dysfunction. Children often experience voiding dysfunction in fairly high rates and may in fact have refractory bladder problems that require advanced management schemes. **Neuromodulation has been considered in this population because of the variety of lower tract dysfunctions that pediatric patients may have, including overactive bladder, urinary retention, and non-neurogenic neurogenic bladder (the Hinman bladder syndrome).** Because neuromodulation truly represents a minimally invasive option for refractory management, it follows that this may be an approach to be used in pediatric lower urinary tract dysfunction. **Still, sacral neuromodulation is not approved by the FDA for use in pediatric patients, perhaps owing to lack of data on what the sacral lead would do with concomitant growth of the spinal cord, nerve roots, and foramina. Accordingly, efforts in the past have been centered on alternative means of delivering electrical stimulation to the bladder and pelvic floor in these patients.** Few studies exist of pediatric patients and sacral neuromodulation. Guys and coworkers (2004) prospectively examined 21 patients aged 5 to 21

years with sacral neuromodulation in the setting of neurologic disease consisting predominantly of spina bifida. The neuromodulation implant group had improved compliance and bladder capacity at 6 and 9 months but not at 12 months. Of the 21 patients, 9 improved their intestinal transit times and 1 patient had complete disappearance of urinary incontinence. No patients in the control group experience an improvement of their condition. McGee and associates (2009) described the use of an incisionless first- and second-stage sacral neuromodulation procedure with fairly high success rates in pediatric patients with dysfunctional elimination syndromes and had minimal complications.

Transcutaneous electrical nerve stimulation (TENS) has been used in pediatrics because it is noninvasive. One usually places a patch electrode on both sides of the S3 nerve foramen, and it is connected to a pulse generator and amplifier. Hoebeke and associates (2001) reported on this use in 41 children. In this case series, patients had urodynamically proven detrusor overactivity, and anticholinergic therapy had failed in all. Patients had daily therapy with the patch electrodes placed at S3, and stimulation was delivered at 2 Hz. A 76% response rate was observed, and this was due in part to increase in bladder capacity and reduction in urgency urinary incontinence and urgency symptoms. Of 41 patients, 21 (51%) were definitively cured; the remainder experienced relapse in the ensuing 1 year of follow-up. Bower and colleagues (1998) reported a similar fairly high success rate with 17 children treated with S3 transcutaneous stimulation and demonstrated dryness in 73.3% of patients and improved urgency and bladder capacity based on visual analog scales and voiding diaries. A more recent study by Malm-Buatsi and associates (2007) also showed continued benefit in patients when 8 of 12 (75%) subjects received statistically significant benefits when therapy was completed. Although this technology seems to have fairly good success there has been no trial in a randomized prospective controlled fashion that may increase its acceptance.

Posterior tibial nerve stimulation (PTNS), much like TENS, has been studied in pediatric patients because of its lack of invasiveness. DeGennaro and colleagues (2004) reported on PTNS in children in a subset of patients with refractory non-neurogenic voiding dysfunction; 80% of patients had symptom improvement and 44% were totally dry, and 62.5% had improvement in bladder capacity. Furthermore, 71% had improvement in urinary retention symptoms. No patients had significant problems from the therapy, and it was overall thought to be both safe and well tolerated. Hoebeke and associates (2002), in a pilot study of PTNS, demonstrated similar success with 32 children. Of the 28 children with urgency before therapy, the urgency disappeared after therapy in 7 and improved in 10. Of the 23 children with daytime incontinence before treatment, 4 became dry after stimulation, and in 12 patients the incontinence decreased. Of the 19 patients who reported abnormal voiding frequency of either less than 4 or more than 8 voids per day, 16 of 19 achieved a normal frequency of 4 to 6 voids daily.

Fecal Incontinence and Bowel Disorders. **Sacral neuromodulation was investigated for bowel disorders on the basis of some of the early experience in bladder patients who exhibited treatment benefits with regard to the bowel symptoms** (Pettit et al, 2002). The use of sacral neuromodulation in bowel disorders is being actively examined, but it is not yet approved for use in the United States. **There exist two major areas of interest with regard to neuromodulation and bowel disorders: fecal incontinence and constipation.**

Fecal Incontinence. Several studies have been done to examine the utility of sacral neuromodulation in fecal incontinence (Kenefick et al, 2002a, 2002b; Uludag et al, 2002; Melenhorst et al, 2007). It appears that patients with a variety of causes of the fecal incontinence seem to have benefited from sacral neuromodulation therapy in this setting. The Cleveland Clinic scoring system allows comparisons to be made with regard to outcome measures including incontinent episodes (solid, liquid, and flatus), pad use, and lifestyle changes. **Several studies have used this scoring system, and all have shown improvements in these assessed parameters** (Matzel et al, 2003; Jarrett et al, 2004). **Sacral stimulation has been shown to be more effective than medical management based on randomized controlled trials for fecal incontinence** (Tjandra et al, 2008). **The mean incontinent (fecal) episodes decreased from 9.5 per week to 3.1 ($P < .001$), and perfect continence was gained in 47.2%. Similar improvements were demonstrated in quality of life parameters. The exact prognostic indicators for success have yet to be defined, particularly as they relate to etiology of the fecal incontinence (sphincter defect, neurologic, functional). The use of sacral neuromodulation is currently being investigated by the FDA for use in fecal incontinence.**

Constipation. *Constipation* as such is a broad term, with the definition being in evolution. It is thought to be representative of difficult evacuation of feces and infrequent or inadequate defecation. Other refinements to the definition may include bowel frequency of fewer than three stools per week. The ROME II criteria categorize constipation into subtypes, including constipation-predominant irritable bowel syndrome, functional constipation, and pelvic floor dyssynergia (Drossman and Corazziari, 2000). Sacral neuromodulation has been examined in this regard and has had favorable results on the basis of some of the criteria listed for improvement. Ganio and associates (2001) described 16 patients who underwent permanent implantation of sacral leads for constipation whereby they had more than 50% decrease in difficulty emptying the rectum and more than 80% improvement in the Cleveland Clinic constipation score that persisted during the course of 1 year of follow-up. Other series (Kenefick et al, 2002a, 2002b) have shown similar improvements, although in smaller numbers. Still, with the small series available, it is difficult to make any meaningful analyses. The more important parameters, perhaps, in this setting relate to quality of life; these have been assessed with SF-36 questionnaires and have proved to be beneficial at least in Kenefick and associates' study. **All of these results suggest, at least, that there is some benefit of sacral neuromodulation in refractory constipation cases. Further study is warranted to assess prognostic factors to better decide on future candidates for this therapy.**

Bilateral Stimulation and Neuromodulation

The current technique for sacral neuromodulation involves a unilateral lead at the S3 nerve foramen to achieve results in cases of urgency, frequency, urgency urinary incontinence, and idiopathic nonobstructive urinary retention. **Bilateral stimulation has been suggested as an alternative, particularly in failed unilateral lead placements, for potential salvage or added benefit as the bladder receives bilateral innervation** (van Kerrebroeck et al, 2005). The initial consideration of bilateral stimulation was based on animal studies

demonstrating that bilateral stimulation yielded a more profound effect on bladder inhibition than did unilateral stimulation (Schultz-Lampel et al, 1998a, 1998b). An animal model of unilateral versus bilateral stimulation has suggested that bilateral stimulation may be more effective overall (based on reduction of detrusor overactive contractions) than unilateral stimulation (Kaufmann, 2008).

There has been only one prospective clinical study to demonstrate the differences in unilateral versus bilateral stimulation (Scheepens et al, 2002). This study was a prospective randomized crossover design in which all patients underwent unilateral as well as bilateral test stimulations to assess the benefits of bilateral stimulation. Both unilateral and bilateral test stimulation was continued for 72 hours, and the patients were randomly assigned to start with unilateral or bilateral stimulation. No significant difference was found in the unilateral versus bilateral group with regard to urgency urinary incontinence, frequency, or severity of leakage in the overactive bladder group, although overall results were impressive in both categories. The retention group had better parameters of emptying (volume per void) in bilateral compared with unilateral stimulation. Still, the numbers were too small in the retention group for adequate conclusions to be made. **It appears that the data as presented, at least from a clinical perspective, do not suggest a large role for routine bilateral stimulation for most patients.** Perhaps there will be subgroups that may benefit more than others (e.g., retention patients), but larger-scale studies with good methodology as shown in the Scheepens study will be required. Still, if one could increase the overall success rates of patients undergoing sacral neuromodulation, one could ultimately help more patients. Accordingly, Pham and colleagues (2008) examined 124 patients undergoing stage I sacral neuromodulation and stratified patients into unilateral and bilateral groups, retrospectively. Successful stage 1 trials were noted in 58% of unilateral patients and 76% of bilateral patients. An important component that still needs to be evaluated is whether it is cost effective to "routinely" place bilateral leads in the setting of most unilateral lead success rates approaching 70% and 80%.

Selective Nerve Stimulation

Pudendal Nerve

Because the bladder afferent reflex works through sacral interneurons that then activate storage through pudendal nerve efferent pathways directed toward the urethral sphincter, the pudendal nerve is a logical target for developing neuromodulation therapies. The earliest attempts to manipulate this reflex through electrical stimulation were based on direct pelvic floor muscle stimulation by Caldwell (1963, 1965) and others with the development of the first implantable and external pelvic floor stimulators, anal plug stimulator (Hopkinson and Lightwood, 1966, 1967), and intravaginal pessary stimulation (Alexander and Rowan, 1968; Erlandson et al, 1977; Fall et al, 1977; Fall, 1985). To deliver optimal stimulation to the nerve directly, selective pudendal nerve stimulation was introduced by Vodusek and coworkers (1986) and shown to have an inhibitory effect on the micturition reflex.

Neurophysiologic studies reveal that SNS works for bladder storage disorders by a similar inhibition of the micturition reflex as a result of electrical stimulation of sensory afferent fibers, in particular by depolarization of Aα and Aγ somatomotor fibers that affect the pelvic floor and external sphincter and thus inhibit detrusor activity (Hohenfellner et al, 1992). Because many of the sensory afferent nerve fibers contained in the sacral spinal nerves originate in the pudendal nerve, the pudendal nerve afferents are important targets for neuromodulating the inhibitory reflex on the micturition reflex (Peng et al, 2008; Woock et al, 2008; Yoo et al, 2008). Furthermore, high-frequency electrical stimulation of this nerve may achieve blockade of external sphincter contractions leading to sphincter relaxation (Gaunt and Prochazka, 2009). Direct pudendal nerve neuromodulation stimulates more pudendal afferents than SNS provides and may do so without the side effects of off-target stimulation of leg and buttock muscles. Thus, techniques for direct pudendal nerve stimulation at alternative locations to the sacral foramen are being developed. Spinelli and associates (2005) modified existing sacral neuromodulation technology and adapted it to pudendal nerve stimulation and realized the need for more sensitive neurophysiologic guidance to better guide stimulation to the pudendal nerve target. Trials using different techniques and devices are under way for selective pudendal nerve stimulation within the ischial rectal fossa and the pure sensory afferent branch of the pudendal nerve at the level of the symphysis bone referred to as the dorsal genital nerve.

The Bion device (Boston Scientific, Natick, MA) is a minimally invasive implantable mini-stimulator with an integrated electrode for nerve neuromodulation. Early feasibility trial results of the Bion device placed at the level of the pudendal nerve exiting the Alcock canal indicate that a considerable reduction in the degree of detrusor overactivity incontinence can be obtained in refractory cases, including those cases of failed SNS neuromodulation (Bosch, 2005). Clinical trials of the rechargeable Bion device were halted in the United States and Europe.

External Periurethral Nerve

A relatively new way to stimulate the bladder has been investigated and is now underway with clinical trials in the use of external periurethral neuromodulation (Nissenkorn et al, 2004, 2005). This device basically entailed placement of a lead and generator apparatus in the periurethral location while the generator was in the lower abdomen subcutaneous space. The lead then stimulated the sphincter apparatus and nerves associated with this structure presumably. Whereas their early results are fairly impressive, the device may help both urgency and stress urinary incontinence (16 patients with stress urinary incontinence were treated and 9 were dry during electrostimulation and the remainder had a 74% reduction in pad weights). The exact positioning of the electrodes seems to be in the area proximate to the external urethral sphincter, thereby allowing for direct access to afferent nerve fibers (Whiteside et al, 2009). How this therapy benefits patients will be interesting because it has many potential uses, including stress and urgency urinary incontinence, pain syndromes, and neuromuscular disorders of the pelvic outlet.

Dorsal Genital Nerve

The dorsal genital nerves (dorsal nerve of the penis in males, clitoral nerve in females) are the terminal and most superficial branches of the pudendal nerve found at the level of the symphysis pubis. The nerves are afferent nerves that carry sensory information from the glans of the penis or clitoris. Proximally, the dorsal genital nerves form a component of the pudendal nerve and then the sacral spinal roots. As a pure sensory afferent nerve branch of the pudendal nerve, the dorsal genital nerve contributes to the pudendal-pelvic nerve reflex that has been proposed as a mechanism of bladder inhibition. Whereas squeezing the glans penis or manipulation of the clitoris is clinically known to help

suppress bladder contractions as observed in behaviors of voiding avoidance, direct electrical stimulation of these organs does not produce a significant effect on the micturition reflex as measured by urodynamics during the storage phase (Yalla et al, 1978; Kondo et al, 1982). However, direct dorsal genital nerve electrical stimulation in experimental and clinical studies appears promising in producing an inhibition of the micturition reflex.

Results in laboratory animals and in persons with spinal cord injury have demonstrated that electrical stimulation of the dorsal genital nerves inhibits bladder contractions (Craggs and McFarlane, 1999). In anesthetized cats (Sundin et al, 1974; Jiang and Lindstrom, 1999) and in unanesthetized chronic spinal cord–injured cats, reflex bladder contractions could be inhibited by stimulation of the genital nerves (Walter et al, 1993). Conditioning stimulation of afferents in the dorsal clitoral nerves has also been shown to suppress reflex bladder contractions in anesthetized cats (Jiang and Lindstrom, 1999). Similarly, recent work in anesthetized cats has shown that low-amplitude electrical stimulation of the S1 dorsal root (which in the cat carries the dorsal genital afferents) inhibits or abolishes ongoing reflex bladder contractions (Jezernik et al, 2001), resulting in significantly shorter bladder contractions. The micturition reflex can be activated and inhibited by stimulation of these dorsal penile afferent fibers in animal models (Woock et al, 2008).

Stimulation of the dorsal penile nerve has been tested in humans to control incontinence in individuals with spinal cord injury and increase bladder volume and reduce bladder overactivity (Wheeler et al, 1992, 1994). Penile nerve stimulation was painless with no side effects, was effective for inhibiting detrusor overactivity, and may be adaptable for chronic home use as an alternative to current therapy (Wheeler et al, 1992). Similar experiments have shown that stimulation of the dorsal nerve of the penis abolishes reflexive bladder contractions and increases bladder capacity in persons with spinal cord injury (Lee and Creasey, 2002). These results demonstrate that electrical stimulation of the dorsal genital nerves can abolish detrusor overactivity and increase bladder capacity in individuals with neurogenic detrusor overactivity due to spinal injury. Feasibility trials with this approach have been completed and demonstrate in a small series that 81% of patients experienced a 50% or greater improvement in urgency and 47% reported a 50% or greater reduction in incontinence episodes (Goldman et al, 2008). This approach seems to have further advantages in being minimally invasive, office based, and without the need for fluoroscopy or prone positioning.

Posterior Tibial Nerve

The posterior tibial nerve is a mixed sensory and motor nerve containing fibers originating from spinal roots L4 through S3 that modulate the somatic and autonomic nerves to the pelvic floor muscles, bladder, and urinary sphincter. On the basis of translational findings of the traditional Chinese practice of using acupuncture points over the common peroneal or posterior tibial nerve to inhibit bladder activity, McGuire and associates (1983) used transcutaneous stimulation of the common peroneal or posterior tibial nerve for inhibition of detrusor overactivity. PTNS (Urgent PC, CystoMedix, Anoka, MN) as approved by the FDA currently consists of weekly 30-minute stimulation treatments provided by insertion of a small-gauge stimulating needle approximately 5 cm cephalad from the medial malleolus and just posterior to the margin of the tibia with the grounding electrode pad placed on the medial surface of the calcaneus (Govier et al, 2001; Cooperberg and Stoller, 2005).

Clinical trials of PTNS have been performed in detrusor overactive conditions with and without pelvic pain (Klingler et al, 2000; van Balken et al, 2003; Vandoninck et al, 2003; Congregado Ruiz et al, 2004; Zhao et al, 2008) and urinary retention (van Balken et al, 2001; Vandoninck et al, 2003). Although clinical trials have produced variable results, PTNS is minimally invasive, demonstrates efficacy, and is easily applicable and well tolerated in all the lower urinary tract conditions studied. Recent urodynamic outcomes have been shown in an MS subpopulation and improvements during PTNS have been demonstrated, including increases in mean first involuntary detrusor contractions and mean cystometric capacity (Kabay et al, 2008). One major limitation of PTNS is that there does appear to be the need for chronic treatment that may be better derived from an implantable subcutaneous stimulation device (van Balken et al, 2003) and even continuous stimulation (Oliver et al, 2003). Perhaps the use of a sham control can help us better understand the potential clinical benefits of this therapy in the long run. A novel sham has been developed, and widespread study of PTNS with use of a sham control may help determine outcomes and eliminate placebo rates (Peters et al, 2009).

Transcutaneous Electrical Stimulation

Other methods of electrical stimulation have been used that seem to occupy a place midway between anal, vaginal, or perineal stimulation and sacral root stimulation. TENS devices have been used to limited degrees to achieve better tolerability to bladder filling and may have some efficacy in postponing voiding. Fall and associates (1980) described TENS use suprapubically in patients with interstitial cystitis, and subsequent studies have been done to gain wider use of this modality (Lindstrom et al, 1983; Fall and Lindstrom, 1991). The exact stimulation parameters are not agreed on because different frequencies have been used; 2 Hz may stimulate pudendal afferents, whereas 50 Hz may stimulate striated paraurethral musculature. Similarly, low-frequency TENS may have some use in abolishing detrusor contractility (Bower et al, 1998). As such, this technology is easy to do and apply, but it may be required for extended periods to gain treatment benefits. S2 or S3 TENS may make some sense, because direct stimulation transcutaneously of this area may yield better results than suprapubic stimulation. Positive results have been demonstrated on the basis of urodynamic data, with improved bladder capacity, delay in first urge to void, and reduced detrusor instability (Bower et al, 2001; Hoebeke et al, 2001). For adequate maintenance of the benefits of this therapy it must also be continued for longer durations. McGuire and associates (1983) described 16 patients with involuntary bladder contractions of varying etiology who were treated with common peroneal or posterior tibial nerve patch electrode stimulation: 12 patients initially were dry, 3 were improved, and 1 was "possibly improved." Vereecker and colleagues (1984), however, were unable to suppress hyperactivity by this method in patients with suprasacral spinal cord injury or disease. Okada and associates (1998) reported a positive experience with transcutaneous stimulation of the thigh muscle in 19 patients with detrusor overactivity; the maximal cystometric capacity was increased by 57% in 11 of 19 patients.

Noninvasive magnetic stimulation of the sacral roots will also inhibit bladder contractions and cause effects that will persist for short times beyond the period of stimulation. This type of stimulation at present cannot be applied for prolonged periods and is currently unsuitable for long-term treatment, although it

may be helpful for preliminary assessment of candidates for chronic sacral root neuromodulation. The extracorporeal magnetic stimulation provided by the "chair" has been used clinically for potential use in overactive bladder, stress incontinence, and pelvic pain (Galloway et al, 2000). No other prospective data on this technology are available for overactive bladder and, furthermore, the exact mechanism of action, if effective, remains to be explained, namely, magnetic, nerve root or peripheral nerve, or intramural nerve stimulation.

Complications and Troubleshooting of Sacral Neuromodulation

With the widespread adoption of sacral neuromodulation, an increasing need has developed to understand complications of this therapy and to learn how to troubleshoot the devices when responses change. It appears that the introduction of the tined lead concept has changed the frequency and profile of the complications that were once only technology related while keeping the patient-related complications at the same frequency.

Published Series

The SNS study group has published several reports on the efficacy and safety of the procedure for individual indications (Siegel et al, 2000). The complications were pooled from the different studies on the basis of the fact that the protocols, devices, efficacy results, and safety profiles were identical. The studies recruited 581 patients, 219 of whom underwent implantation of the InterStim system. The complications were divided into percutaneous test stimulation–related and postimplant-related problems. Of the 914 test stimulation procedures done on the 581 patients, 181 adverse events occurred in 166 of these procedures (18.2% of the 914 procedures). **Most complications were related to lead migration (108 events, 11.8% of procedures). Technical problems and pain represented 2.6% and 2.1% of the adverse events, respectively. For the 219 patients who underwent implantation of the InterStim system (lead and generator), pain at the neurostimulator site was the most commonly observed adverse effect at 12 months (15.3%). Surgical revision of the implanted neurostimulator or lead system was performed in 33.3% of cases (73 of 219 patients) to resolve an adverse event. This included relocation of the neurostimulator because of pain at the subcutaneous pocket site and revision of the lead for suspected migration. Explant of the system was performed in 10.5% for lack of efficacy. One should consider the fact that, at the time, the generator was implanted in the lower abdomen.**

Everaert and associates (2004) reported specifically on the complications with SNS. This was a retrospective study of 53 patients who had undergone implantation of the quadripolar electrode (Medtronic InterStim, model 3886 or 3080) and subcutaneous pulse generator in the abdominal site (Medtronic Itrel 2 IPG) between 1994 and 1998. Device-related pain was the most frequent problem and occurred equally in all implantation sites (sacral, flank, and abdominal). This occurred in 18 of the 53 patients (34%) and was more frequent in patients with dysuria and retention or perineal pain. Pain responded to physiotherapy in 8 patients, and no explantation was done for pain reasons. Current-related complications occurred in 11%. They performed 15 revisions in 12 patients. Revisions for prosthesis-related pain (n = 3) and for late failures (n = 6) were not successful. Similar series have been published by White and associates (2009) and show relatively low rates (30%) of adverse events and may have been predicted by trauma, body mass index and enrollment into a pain clinic, and history of adverse events.

A review (Hijaz and Vasavada, 2005) of the tined lead approach was performed at the Cleveland Clinic from June 2002 to June 2004 when 167 patients underwent sacral neuromodulation for indications of refractory overactive bladder, idiopathic and neurogenic urinary retention, and interstitial cystitis. In this cohort, 180 stage I operations used the tined lead approach. After 2 to 4 weeks of test stimulation, 130 (72.2%) patients proceeded to stage II implantation of the IPG.

Stage I complications can lead to explantation or revision of the tined lead. The reasons for either fall under response related, mechanical, or infection related. In this series, 50 tined leads were explanted (27.8%). The majority of lead explantations were performed for unsatisfactory or poor clinical response (46 of 50; 92%). The rest of the explantations were done for infection (4 of 50; 8%). Explantation for response reasons is not truly considered a complication as much as it is an integral part of the procedure. Stage I revisions totaled 22 of the 180 operations (12.2%). Revisions were done for marginal response (13 of 22), frayed subcutaneous extension wire (6 of 22), lead infection (3 of 22), and improper localization of stimulus (1 of 22). Eleven (50%) of the revisions proceeded to stage II generator implantation. When the revision was done for a marginal response (13 of 22), the response was ultimately clinically satisfactory in 5 of 13 (38.5%), and patients proceeded to generator implantation. Typically, when the patient reported a marginal or equivocal response during the test stimulation in the absence of infection or mechanical problems, a lead revision was offered with intraoperative sensory testing. Because 38.5% of these revisions eventually were successful and patients proceeded to stage II, this is an option to keep in mind in motivated patients with equivocal response.

As in stage I, stage II complications can be divided into explantation (generator and lead) or revision. Explantation was performed in 16 of 130 (12.3%). Explantations were done for infection and failure to maintain response in 56.3% and 43.7%, respectively. Revisions were done for infection, mechanical (generator related), and response causes. The revision rate of stage II in this series was 20% (26 of 130).

When infection at the generator site is diagnosed, the best management is explantation of the whole system.

Response-related complications necessitating revision are more common (18 of 26). The algorithm for management of a patient who presents with a decreased or absent response after a successful interval is outlined in Figure 70–8.

The outlined algorithm includes testing of impedances (Fig. 70–9). **Impedance describes the resistance to the flow of electrons through a circuit. Impedance or resistance is an integral part of any functioning circuit. However, if there is too much resistance, no current will flow (open). If there is too little resistance, excessive current flow results in diminished battery longevity (short). The electrical circuit that we are referring to starts at the neurostimulator's circuitry and goes through the connectors to the extension wires, through the extension connector to the lead wires, through the lead's electrodes to the patient's tissue, and back either through another electrode and up the same path to the circuitry (bipolar) or to the neurostimulator case and into the circuitry (unipolar).**

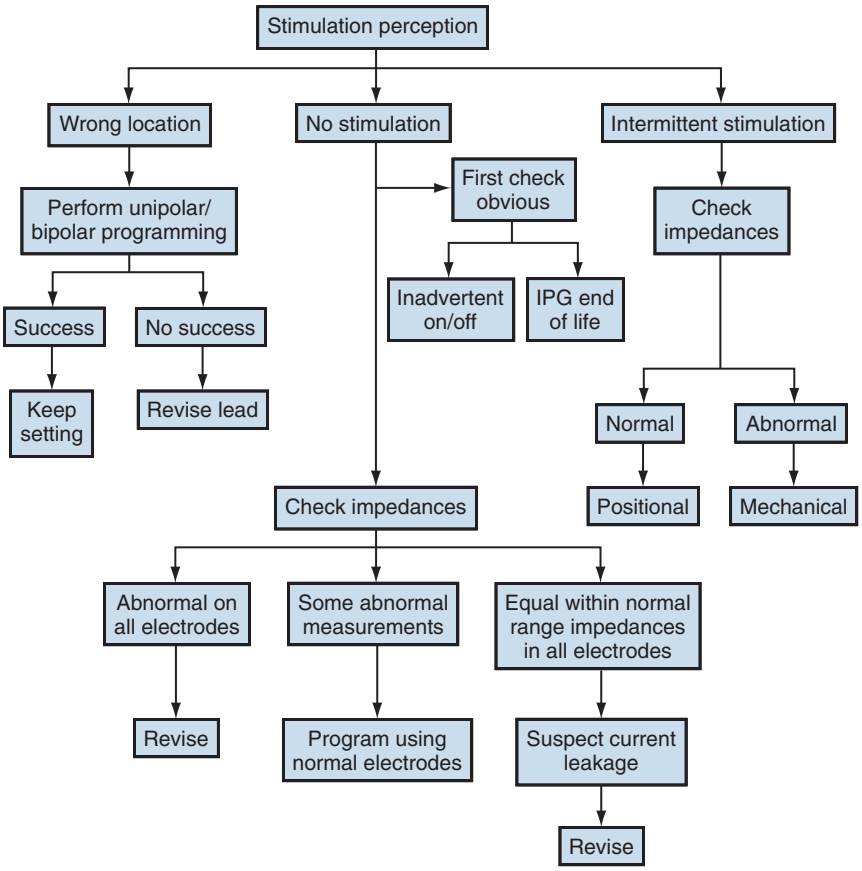


Figure 70–8. Diagnostic algorithm and troubleshooting for recurrent symptoms. IPG, implantable pulse generator.

If the circuit is broken somehow, electrons cannot flow. **This is called an open circuit, and impedance measurements are high.** Open circuits can be caused by a fractured lead or extension wires and loose connections. Patients generally feel no stimulation if an open circuit is present. In measurement of impedances by the programmer, **unipolar measurements are most useful for identifying open circuits** because they take one lead wire measurement at a time, immediately identifying which connection or wire has the problem.

Short circuits, which are reflected in **low impedance measurements,** can be caused by body fluid intrusion into the connectors or crushed wires that are touching each other. The electrons will always follow the path of least resistance. Patients may or may not feel stimulation, or stimulation may not be present in the correct area (i.e., the generator site) or may vary in strength (i.e., a surging sensation). In measurement of impedances by the programmer, **bipolar measurements are most useful for identifying shorts between two wires.**

Therefore, impedance measurement is used as a troubleshooting tool to check the integrity of the system when a patient presents with a sudden or gradual disappearance of stimulation. Many measurements fall within the 400- to 1500-ohm range. High levels (>4000 ohms) identify open circuits, and low levels (<50 ohms) identify short circuits. Medtronic (manufacturer of the InterStim) recommends performing the impedance measurements at the time of closure of the incision, at the first programming session, to get a baseline measurement and at any time a problem is suspected. These measurements will identify which electrodes, if any, are intact and allow the programmer to proceed with programming of only those with acceptable impedance measurements. If all electrode measurements read above 4000 ohms, a revision may be necessary.

The intraoperative algorithm for management of impedance problems includes initial testing of impedances (see Fig. 70–9). First, the tined lead is disconnected from the extension to the IPG and then dried. The connection may be irrigated with sterile water, and then the connection is dried with the 3-Fr ENT suction device before it is reconnected again. At this stage the impedances are repeated. If they normalize, the revision can be concluded at this stage. If impedances continue to be abnormal, one can evaluate or change the 10-cm extension and retest impedances. If they continue to be abnormal, the lead is revised. It has been the authors' experience that the connections to the IPG and the IPG itself seldom have anything to do with abnormal impedance values.

Troubleshooting Algorithm

After successful completion of stage II, a number of events can occur, and the treating physician should develop an algorithm to handle these events in a timely and efficient manner. These events with their probable causes and the troubleshooting algorithm are covered in this section.

Pocket (IPG Site) Discomfort. The probable causes of this symptom are pocket related or output related. Pocket-related causes of discomfort include infection, pocket location (waistline), pocket dimension (too tight, too loose), seroma, and erosion. Output-related causes include sensitivity to unipolar stimulation if this mode is used or current leak. To troubleshoot this problem the evaluating specialist is advised to do the following (Fig. 70–10):

1. Turn off the device and ask the patient if the discomfort is still present to differentiate pocket-related from output-related causes.

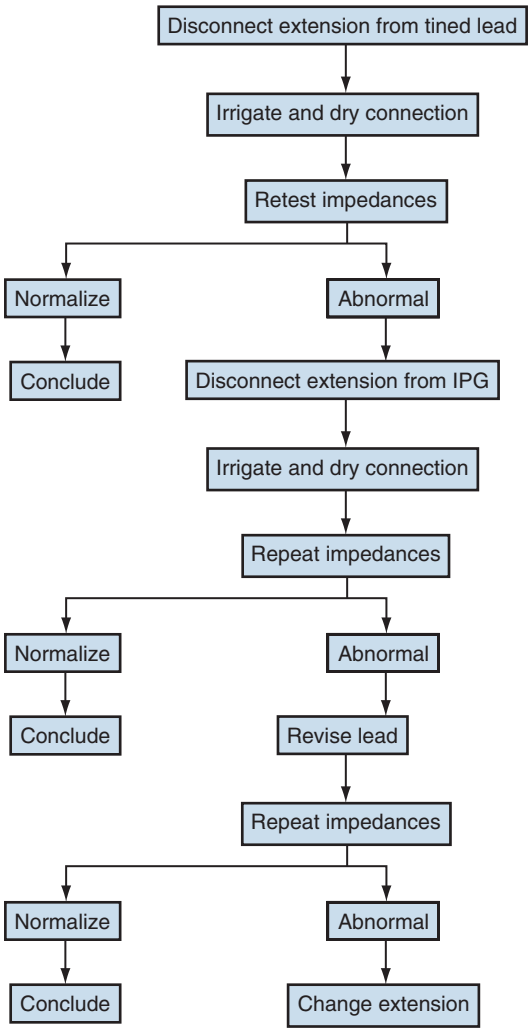


Figure 70–9. Intraoperative algorithm for impedance problem management. IPG, implantable pulse generator.

2. If the discomfort persists, the cause is not related to the device output. In the absence of clinical signs of infection, pocket-related causes such as pocket size, seroma, and erosion must be considered.
3. If the discomfort disappears, device output is probably causing discomfort. If the stimulation program is unipolar, switch to bipolar and see whether that eliminates discomfort. Some patients are sensitive to the unipolar mode of stimulation, because the positive pole is the neurostimulator itself. Another possibility is leakage of fluid into the connector. This somehow creates a short circuit whereby the current from the device now follows this fluid pathway out to the patient's tissue. Most patients report this as a burning sensation. Even though current is following this fluid out to the patient's tissue, some of the current may also be getting to the electrodes as well, so some patients feel both burning in the pocket and stimulation in the perineum. One can try reprogramming around this by using different electrode combinations. If reprogramming is unsuccessful, the patient is asked if the "burning" sensation is tolerable (it will not harm the patient's tissues); if it is not tolerable, a revision may be necessary to dry out the connection sites.

Recurrent Symptoms. When the patient presents with recurrent symptoms, evaluation of the stimulation perception is necessary.

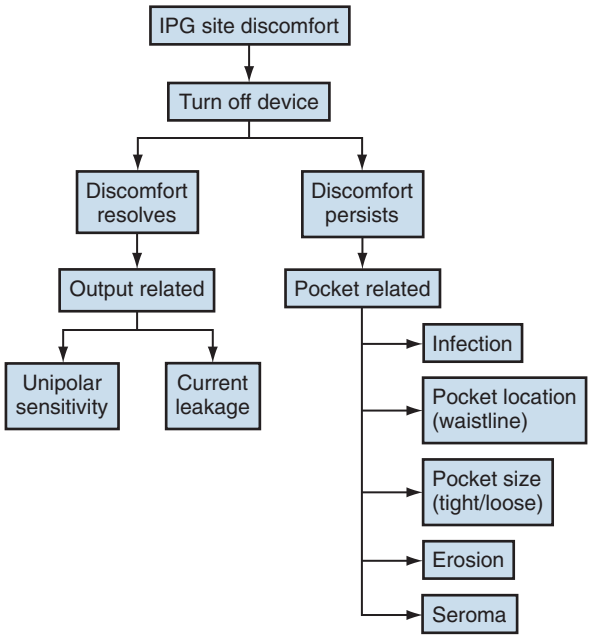


Figure 70–10. Troubleshooting algorithm for implantable pulse generator site discomfort.

The possibilities are that the patient perceives the stimulation in a wrong location compared with baseline, has no stimulation, or has intermittent stimulation.

Wrong Location. If the patient reports that the stimulation location or pattern has changed, it is best to go back to each unipolar setting and "map" out where the patient feels the stimulation. The device is set to 0–, case+ and the patient is asked where she or he feels the sensation; next it is set to 1–, case+ and the patient again is asked about the sensation; next it is set to 2–, case+ and finally to 3–, case+. If these combinations do not confirm the target area, the next step is to start programming bipolar combinations. When those are exhausted, sometimes increasing the pulse width widens the stimulation area. If the programming possibilities are exhausted, then revision for lead repositioning or relocation to the other side may be necessary.

No Stimulation. The obvious is checked first. The device parameters must be set high enough, an inadvertent on-off is checked (set magnet switch off to avoid inadvertent magnet activations), and whether the IPG is nearing the end of its life is checked. Next impedance readings are performed, paying close attention to unipolar impedances. These impedances measure one lead wire with the case, so it is easy to isolate a problem. Using unipolar impedances, it is possible to tell which lead wires are still intact and which ones are not, as mentioned previously. Programming of the electrodes is then continued with acceptable impedance measurements. Bipolar measurements are checked to rule out short circuits as well (very low impedance measurements). If programming around the malfunctioning lead does not restore the stimulation, the patient will often need to undergo revision.

Intermittent Stimulation. Again, inadvertent on-off is checked. Intermittent stimulation can be caused by either a loose connection or positional sensitivity. If a loose connection is suspected, palpating the connection site and re-creating the intermittency is a good clue as to where the problem lies. Taking impedances while the patient reports the stimulation intermittently determines whether the problem is positional (acceptable impedances are still present) or mechanical (when the patient feels stimulation go off,

the impedances are high). With positional sensitivity, the lead position shifts when a patient moves in a certain direction (for instance, the patient reports that the stimulation goes away on standing). The lead position may have moved farther from the nerve during standing, and the amplitude may just need to be increased. Intermittent stimulation represents a challenging dilemma to troubleshoot.

ELECTRICAL STIMULATION FOR EMPTYING DISORDERS

There exists strong evidence to suggest that neuromodulation works through supraspinal pathways (see the section on neurophysiology of electrical stimulation). The question of how it works for refractory detrusor overactivity as well as for urinary retention is based on changes in supraspinal pathways and perhaps the guarding reflex. It is important to understand that before neuromodulation, neurostimulation was applied in different forms to achieve bladder emptying. Still, neurostimulation has a role today in management of disorders of bladder emptying and has evolved through many different versions before its current techniques.

Electrical Stimulation Directly to the Bladder or Spinal Cord

Clinical trials of direct electrical stimulation of the bladder to facilitate emptying originated in 1940 but have met with only partial success and intermittent enthusiasm since then (Wein and Barrett, 1988). **Direct electrical stimulation was most effective in patients with hypotonic and areflexic bladders.** Initial success, defined as low postvoid residual urine volume with sterile urine, was achieved in only 50% to 60% of patients, and **secondary failure often supervened, usually related to fibrosis, electrode malfunction, bladder erosion, or other equipment malfunction. The spread of current to other pelvic structures with a stimulus threshold lower than that of the bladder often resulted in abdominal, pelvic, and perineal pain; a desire to defecate or defecation; contraction of the pelvic and leg muscles; and erection and ejaculation in male patients. It was also noted that the increase in intravesical pressure was generally not coordinated with bladder neck opening or with pelvic floor relaxation and that other measures to accomplish these ends could be necessary.** Direct electrical stimulation of the sacral spinal cord was also performed as an attempt to take advantage of the remaining motor pathways to initiate micturition. Although some short-term success was noted, many of the side effects seen with direct bladder stimulation occurred as well because the stimulus applied in this way was also unphysiologic. **Enthusiasm for both of these approaches has waned considerably, and resurrection seems unlikely.**

Electrical Stimulation to the Nerve Roots

For the past 25 to 30 years, Brindley (1993) and the Tanagho group (Tanagho and Schmidt, 1988; Tanagho et al, 1989) have pursued neurostimulation for the treatment of voiding dysfunction. The use of electrical stimulation for storage disorders and pelvic floor dysfunction has been covered. **The focus of this section is on the use of anterior root electrical stimulation to facilitate emptying.**

The Brindley device is the one most commonly used. Prerequisites for such use are described by Madersbacher and Fischer (Fischer et al, 1993) **as (1) intact neural pathways between the sacral cord nuclei of the pelvic nerve and the bladder and (2) a bladder that is capable of contracting. The chief applications are in patients with inefficient or nonreflex micturition after spinal cord injury. Simultaneous bladder and striated sphincter stimulation is obviated by sacral posterior rhizotomy, usually complete, which eliminates reflex incontinence and improves low bladder compliance,** if it is present (Brindley, 1994). The stimulation sequences and parameters themselves and their neurophysiologic consequences lead to less striated sphincter dyssynergia, even without posterior rhizotomy, than is seen in reflex micturition in a spinal cord–injured patient. Complete sacral deafferentation is usually performed, however, with the exception listed by Brindley as those patients who have genital sensation or useful reflex erections. **Electrodes are applied intradurally** to S2, S3, and S4 nerve roots, but the pairs can be activated independently (Fig. 70–11). **The detrusor is usually innervated primarily by S3 and to a smaller extent by S2 or S4. Rectal stimulation is by means of all three roots equally. Erectile stimulation is chiefly by S2 with a small contribution from S3 and none from S4.** Micturition, defecation, and erection programs are possible, with stimulus patterns set specifically for each patient (Brindley, 1994). The ventral sacral roots, however, carry both parasympathetic fibers to the bladder and somatic fibers to the striated sphincter. Ventral root stimulation therefore occasionally results in detrusor–striated sphincter dyssynergia.

The current Brindley stimulator uses the principle of *post-stimulus voiding*, a term first introduced by Jonas and Tanagho (1975) **to obviate this. Relaxation time of the striated sphincter after a stimulus train is shorter than the relaxation time of the detrusor smooth muscle. When interrupted pulse trains are used, voiding is achieved between the pulse trains because of the sustained high intravesical pressure.** This concept and other methods that are available to overcome the stimulation-induced sphincter dyssynergia and allow low-pressure emptying are nicely reviewed by Rijkhoff and colleagues (1997). **Post-stimulus voiding has a few shortcomings, described in this article as follows: voiding occurs in spurts at above-normal bladder pressures; when the stimulus parameters are not properly adjusted the detrusor pressures can become too high, putting the upper tracts at risk; and movement of the lower limbs occurs during stimulation because the nerve roots also contain fibers innervating leg musculature, and this movement can be cumbersome for the patient.**

Brindley (1994) carefully reviewed the experience in the first 500 patients treated with his prosthesis with a total follow-up, at that time, of 2033.5 years. Of the total, 2 patients were lost to follow-up and 21 had died. Of the deaths, two were from septicemia (one definitely unrelated to the implant and the specifics of the other unmentioned) and one from related renal failure; the causes of five were unknown. Ninety-five reoperations were required for repair, six stimulators were removed (four infected), and two were awaiting repair. In 45 patients the stimulator was believed to be intact but not used for various reasons. In all others the stimulators were in use (411 for micturition and in most for defecation and in 13 for defecation alone) and the users were

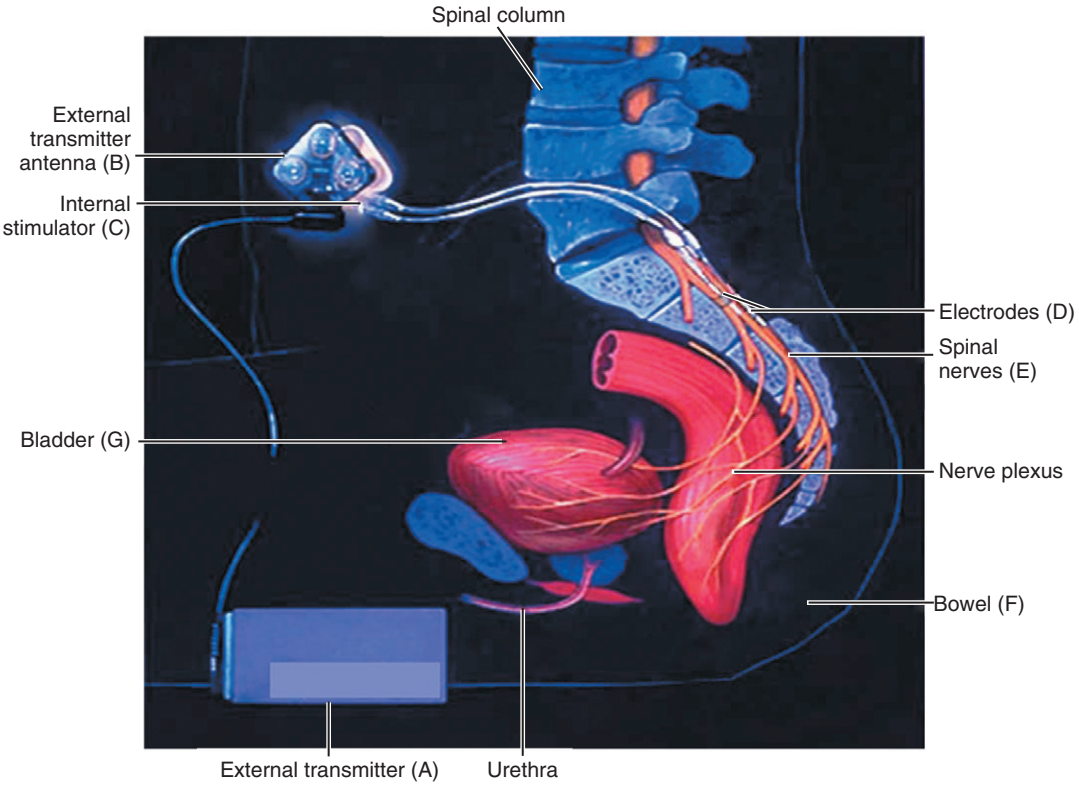


Figure 70–11. Brindley-Finetech system for sacral root stimulation. (Courtesy of NDI Medical, Cleveland, OH.)

believed to be "pleased." Upper tract deterioration was reported in only 2 of 365 patients with full deafferentation and in 10 of 135 with incomplete or no deafferentation. Two of these 10 had impaired renal function, and 1 died of this condition.

van Kerrebroeck and associates (1997) reported the results of use of the Finetech-Brindley stimulator in 52 patients. These patients were selected by screening 226 patients; complete posterior sacral root rhizotomies were performed in all. Thirty-seven of the patients had 6 months of follow-up; in these patients, complete daytime continence was achieved in 73% and night-time continence in 86%. There were significant increases in bladder capacity and bladder compliance, and residual urine was reduced significantly. Complications included cerebrospinal fluid leaks, which resolved spontaneously in 23 patients; nerve damage that resolved in 1 patient; and one implant failure caused by a cable fracture, which was successfully repaired. Sauerwein and colleagues (1999) reported in abstract form the results of sacral deafferentation and implantation of an anterior sacral root stimulator in 294 patients with spinal cord injury. Bladder spasticity was relieved in all. In 50%, micturition was achieved by stimulating S4 and S5 sacral ventral roots; in the remaining cases, it was achieved by stimulating the S2 and S3 roots. **Variations in surgical approaches designed to achieve stimulation of only bladder contraction are described by** Dahms and associates (2000), **who also summarize overall success rates for sacral ventral root stimulation in spinal cord–injured patients at about 75%. Recent laparoscopic access techniques have minimized the invasiveness of this procedure and may have a role in the future in this select group of patients** (Possover, 2009).

Extradural stimulation has been used by the Tanagho group (Tanagho and Schmidt, 1988; Schmidt, 1989; Tanagho et al, 1989) in the treatment of 19 patients with serious and refractory neuropathic voiding disorders. Extensive dorsal rhizotomy was performed, and a stimulator was implanted on the ventral component of S3 or S4 with selective peripheral neurotomy (Tanagho et al, 1989). In eight patients (42%), complete success was achieved with reservoir function, continence, and low-pressure/low residual voiding with electrical stimulation. Ten patients qualified as achieving partial success, regaining reservoir function and obtaining continence.

Electrical stimulation of the ventral sacral roots with some techniques to reduce detrusor hyperactivity and obviate striated sphincter dyssynergia has become an accepted treatment modality for lower urinary tract dysfunction in spinal cord–injured patients. Although more detailed follow-up is necessary, and further evolution will doubtless occur, these techniques have achieved remarkable improvements and success rates, which now seem to have stabilized at a high level.

Transurethral Electrical Bladder Stimulation

Intravesical electrotherapy is an old technique that has been resurrected with some interesting and promising results. The use of this technique to increase bladder capacity and to increase compliance has previously been discussed. This section deals with **the use of TEBS to facilitate bladder emptying by establishing conscious control of the initiation and completion of a micturition reflex.** Fischer and colleagues (1993) describe their concept of the basis for this use as follows. **In patients with incomplete central or peripheral nerve lesions—**and only these patients are suitable for this method—**at least some nerve pathways between the bladder and the cerebral centers**

are preserved but are too weak to be efficient under normal circumstances. TEBS in this situation is hypothesized to activate specific mechanoreceptors in the bladder wall. With depolarization of these receptors, activation of the intramural motor system is said to occur, resulting in small local muscle contractions that further depolarize the receptor cells. As soon as this local motor reaction reaches a certain strength, "vegetative afferentation" begins, meaning that stimuli travel along afferent pathways to the corresponding cerebral structures with the occurrence of sensation. This, in time, reinforces efferent pathways, and their stimuli create centrally induced and more coordinated and stronger detrusor contractions. Ebner and coworkers (1992) **simply conceptualize the mechanism as involving an artificial activation of the normal micturition reflex and further suggest that repeated activation of this pathway may "upgrade" its performance during voluntary micturition.**

Children with congenital neurogenic bladder dysfunction who have never experienced the urge to void require a biofeedback system to realize the nature and meaning of this new sensation induced by TEBS. This exteroceptive stimulation is also important for other groups of patients because it signals detrusor contractions and whether, and to what degree, voluntary detrusor control is or has become possible and, by demonstrating progress, serves as positive feedback.

This technique involves direct intraluminal monopolar electrical stimulation with a special catheter equipped with a stimulation electrode. Saline solution is used as the current-leading fluid medium in the bladder. Exteroceptive reinforcement is achieved by visual recording of detrusor contractions on a water manometer connected to the stimulation catheter. An intensive bladder training program has to be combined with TEBS and must be highly individualized. **Only patients with an incomplete spinal cord lesion and with receptors still capable of reactivity and with a detrusor still capable of contractility will benefit from this technique. The achievement of conscious control requires, in addition, an intact cortex.**

Fischer and colleagues (1993) have used this technique in patients with incomplete spinal cord injury and other incomplete central or peripheral lesions of bladder innervation, in pediatric patients with congenital neurogenic lower urinary tract dysfunction, and in patients, especially children, with non-neurogenic dysfunction voiding. Only patients with preserved pain sensation in sacral dermatomes S2 through S4 improved with this technique. The technique is time consuming because stimulation must be performed on a daily basis for weeks and months, with an individual treatment time of about 90 minutes. Kaplan and Richards (1988) reported on such therapy in myelodysplastic children, performing the treatment for 60 minutes (during a 90-minute catheterization), 3 to 5 days a week for 15 to 30 daily sessions. Of 62 patients evaluated, 42 completed at least one series of treatment. "Success" was defined differently for infants than for older children. For infants, success implied a decrease in filling pressure, an increase in the quality of bladder contraction, and a decrease in residual urine. For older children, this type of result implied a heightened awareness of detrusor contractions before and during a contraction, maintenance of low-pressure filling, effectively emptying detrusor contractions with low residual urine, and either a conscious urinary control or timely enough sensory input to allow clean intermittent catheterization for continence. Of children who initially had some detrusor contraction on initial evaluation, 80% were said to have achieved some or all of the success parameters. Of those with no initial detrusor activity, 33% achieved some success.

Other reports have been less optimistic. Lyne and Bellinger (1993) **reported the results of TEBS treatment of 17 patients with neurologic dysfunction, 10 with myelomeningocele, and 2 with lipomeningocele. Ultimately, all patients showed detrusor contraction during therapy (12 did so initially), but results related to increased bladder capacity and improved continence were disappointing. Five patients showed minor positive changes in continence. After completion of therapy in 12 patients who had serial cystometry, 5 experienced an increase in capacity (14% to 158%) and 4 a decrease (7% to 37%).** Decter and associates (1994) used TEBS in 25 patients with neurogenic voiding dysfunction. TEBS was correlated with an increase from 18 to 24 in the number of patients who manifested contraction on stimulation and from 3 to 12 in the number who sensed contraction during stimulation. However, cystometry showed a more than 20% increase in the age-adjusted bladder capacity in only 6 of 18 patients with serial studies and clinically significant improvements in end-filling pressures in 5 of these. A telephone questionnaire revealed that 10 of 18 patients or parents perceived an improvement in bladder function, but the authors stated that "the limited urodynamic benefits our patients achieved have not materially altered the daily voiding regimen and, because of these factors, we are not enrolling any new patients in our…program." **This technique is certainly controversial.** Some question the theoretical basis and the definitions of "success" applied to patients treated. **Currently, even** Kaplan (2000) **does not seem enthusiastic about the use of this technique to attain the goal of volitional voiding, and** Decter (2000), **as previously pointed out, stated that, in his opinion, TEBS is a modality with limited clinical efficacy for facilitation of filling-storage and emptying.**

Sacral Neuromodulation of Emptying Disorders

Sacral neuromodulation has been successful in patients with idiopathic nonobstructive retention, in patients with retention secondary to deafferentation of the bladder after hysterectomy, and in patients with Fowler syndrome (Dasgupta et al, 2004; De Ridder et al, 2007). Patient factors predictive of success have been sought, and increasing numbers of reports are differentiating results of sacral neurostimulation in urinary retention based on the functional disorders causing the condition, detrusor acontractility, and functional outlet obstruction. Bross and coworkers (2003) evaluated the predictive ability of the carbachol test and concomitant diseases in patients with an acontractile bladder. Whereas 33% of patients had a successful bilateral percutaneous nerve evaluation, a positive carbachol test result was not predictive of success. Goh and Diokno (2007) in a retrospective study of patients implanted for nonobstructive urinary retention found a statistically significant difference in predicting success of test stimulation for patients with a preimplantation ability to void (>50 mL) versus non-voiders. Further evidence of the predictive role of detrusor function was reported by Bertapelle and colleagues (2008) in developing a detrusor contractility test using urodynamics in conjunction with sacral neurostimulation in urinary retention as an exclusion criteria for sacral neurostimulation; this test appears to be a reliable tool to rule out detrusor acontractility due to irreversible bladder

myopathy or complete neurogenic lesion and to predict success of permanent sacral neuromodulation.

A large, prospective, randomized multicenter trial to evaluate the efficacy of SNS for urinary retention was performed by Jonas and colleagues (2001). After a percutaneous nerve evaluation period of 3 to 7 days, 68 patients (38% of those evaluated) with chronic urinary retention qualified for permanent implantation. Patients were randomly assigned to the treatment or control group, in which treatment was delayed for 6 months. Successful results were initially achieved in 83% of patients who received the implant, with 69% able to discontinue intermittent catheterization completely. At 18 months, 71% of patients available for follow-up had sustained improvement. These results have been corroborated by others with longer follow-up (Datta et al, 2008; White et al, 2008).

Aboseif and coworkers (2002) **evaluated the efficacy and change in quality of life in patients with idiopathic, chronic, nonobstructive functional urinary retention. Thirty-two patients with idiopathic retention requiring intermittent catheterization underwent percutaneous nerve evaluation. Permanent implants were placed in 20 patients (17 women) who showed more than 50% improvement in symptoms.** Eighteen patients were subsequently able to void and no longer required intermittent catheterization; one patient required bilateral SNS implants. Average voided volumes increased from 48 to 198 mL, and postvoid residual volume decreased from 315 to 60 mL. Eighteen patients reported more than 50% improvement in quality of life, although the questionnaire used in the study was not described. Significant score improvements in the Beck Depression Inventory and SF-36 after sacral root neuromodulation for retention have been demonstrated by Shaker and Hassouna (1998). **Overall success rates of the percutaneous nerve evaluation range from 33.3% to 100%** (Koldewijn et al, 1994; Scheepens et al, 2002; Spinelli et al, 2003). Improvement in patients with retention may not be as rapid as in patients undergoing sacral root stimulation for other reasons. A percutaneous nerve evaluation period of at least 2 to 3 weeks and a permanent implant lead evaluation of 4 weeks or more have generally been recommended. **Furthermore, bilateral or caudal SNS for urinary retention may be considered initially or for unilateral SNS trial failures, although this technique is performed infrequently and is less studied to date** (van Kerrebroeck et al, 2005; Maher et al, 2007; Pham et al, 2008).

FUTURE RESEARCH AND CONCLUSIONS

During the past century, neurostimulation and neuromodulation that originated in the 19th century have been clinically adopted. Advances in electrical innovations and our understanding of neurophysiology have provided important discoveries for the care of people with neuromuscular causes of their pelvic organ dysfunctions. To date, influencing these dysfunctions at the level of the sacral roots appears to have stood the test of time and has become generalizable to physicians worldwide. At the start of our next century of using this expanding therapy, we will need to urgently focus on developing the supportive clinical research needed to drive further innovations and acceptance of wider clinical indications and applications. Long-term surveillance studies and randomized clinical trials to compare different techniques and nerve locations and to evaluate placebo effects are critically needed, as are more studies to elucidate modes of action to improve stimulation applications, selection of patients, and therapeutic results.

The introduction of new stimulation methods as well as application of these methods to different nerve locations will continue to provide improved treatment alternatives. In addition, these innovations will provide the ability to further develop testable hypotheses of more basic questions on electrical neurostimulation, neuromodulation, and neurophysiology of the autonomic, somatic, and central pathways that regulate pelvic organ function. Such questions need to address the observed lack of neural plasticity-induced changes with long-term neuromodulation and neurostimulation despite acute cellular changes identified in nerve signaling molecules secondary to magnetic and electrical field changes.

In their present form, neurostimulation and neuromodulation work acutely through continuous electrical activity without inducing long-term neuroplastic changes. Therefore, future technologies are likely to provide closed-loop conditional stimulation, much in the same manner as "on-demand" cardiac pacemakers and defibrillators do, as a means to obtain better efficacy without additional adverse electric field effects. The development of change from the present open-loop stimulation to closed-loop conditional stimulation will necessitate innovations in neurosensing of pathologic neuromuscular events of the pelvis that will lead to on-demand therapeutic electrical activity. These innovations will in turn have a profound effect on our diagnostic ability to predict clinical responses to neurostimulation and neuromodulation as we seek to maximize our benefit-risk and benefit-cost ratios in patient care.

Key Points: Electrical Stimulation

- Neuromodulation is a field clearly in its infancy.
- Current techniques of sacral neuromodulation are indicated for treatment of refractory urgency/frequency, urgency urinary incontinence, and nonobstructive urinary retention.
- Sacral neuromodulation has yielded successful stage I to stage II conversion rates based on 50% symptom improvement in more than 60% of patients for urgency/frequency and urgency urinary incontinence.
- The exact best nerves to stimulate have yet to be realized, but data seem to be focusing on more selective nerve stimulation, particularly in complex subgroups such as patients with neurogenic bladders. Focused research on risk factor analysis of who is the best candidate for therapy will be beneficial to selection criteria.
- Transurethral electrical stimulation has fallen out of favor for the most part.
- Transcutaneous electrical stimulation, although demonstrating good efficacy, seems to have a more limited role because of the constant need to administer the therapy but its minimal invasiveness may allow a resurgence in interest in this therapy.
- Expanding indications for neuromodulation are likely to dominate the literature in the coming years as comfort with neuromodulation increases and more challenging subgroups are addressed.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter 71

Retropubic Suspension Surgery for Incontinence in Women

Christopher R. Chapple, MD, FRCS (Urol), FEBU

Therapeutic Options
Choice of Surgical Technique
Assessing Outcomes of Therapy
Indications for Retropubic Repair
General Technical Issues
Marshall-Marchetti-Krantz Procedure
Burch Colposuspension
Paravaginal Repair
Vagino-Obturator Shelf Repair
Laparoscopic Retropubic Suspension
Complications of Retropubic Repairs
Comparisons Between Incontinence Procedures

Continence in the woman results from a complex interplay of anatomic and physiologic properties of the lower urinary tract (bladder, urethra and sphincter, and pelvic floor) acting under the coordinating control of an intact central and peripheral nervous system. The role of the pelvic floor is to provide support to both the bladder and urethra and to facilitate normal abdominal pressure transmission to the proximal urethra, thereby maintaining continence.

Stress incontinence is a symptom, a sign, and a clinical diagnosis; the clinical symptom is that of involuntary loss of urine associated with increased intra-abdominal pressure, such as occurs during coughing and sneezing. The International Continence Society (ICS) defines *urodynamic stress incontinence* as the involuntary loss of urine during increased intra-abdominal pressure during filling cystometry, in the absence of detrusor (bladder wall muscle) contraction (Abrams et al, 2002). Thus, urodynamic evaluation is a prerequisite for the diagnosis of urodynamic stress incontinence. Therefore, in discussing stress incontinence, this review refers to women with stress urinary incontinence (SUI) diagnosed on the basis of symptoms alone or urodynamically proven, so-called urodynamic stress incontinence.

Treatment options for SUI include conservative techniques and both pharmacologic and surgical interventions. Surgical procedures to treat SUI generally aim to improve the support to the urethrovesical junction and to correct deficient urethral closure. There is a contemporary lack of consensus, however, regarding the precise mechanism by which continence is achieved in the "normal asymptomatic female" and therefore not surprisingly in how "normality" is restored by surgical manipulation. Anti-incontinence surgery is generally used to address the failure of normal anatomic support of the bladder neck and proximal urethra and intrinsic sphincter deficiency. **Anti-incontinence surgery does not necessarily work by restoring the same mechanism of continence that was present before the onset of incontinence. Rather, it works by a compensatory approach, creating a new mechanism of continence** (Jarvis, 1994a).

THERAPEUTIC OPTIONS

The surgeon's preference, coexisting problems, and anatomic features of the patient and her general health condition influence the choice of procedure. Numerous surgical methods have been described, but they essentially fall into seven categories (Table 71–1).

This wide variety of treatment options for stress incontinence indicates the lack of a clear consensus as to which procedure is the most effective. Several groups have reviewed the literature, often using systematic and methodical analyses of well-designed randomized controlled trials (Jarvis, 1994b; Black and Downs, 1996; Fantl et al, 1996; Leach et al, 1997; Moehrer et al, 2002, 2003; Lapitan et al, 2003). **Most of these reviews, however, are hampered by the quality of the existing evidence base, and these reviews are based on studies of mixed quality with little standardization of the points in** Table 71-2.

A review of existing literature on confounding variables affecting outcome of therapy (Smith et al, 2005) concluded the following:

1. **Age may not be a contraindication to colposuspension,** with equivalent success rates in the elderly at long-term follow-up (Gillon and Stanton, 1984; Tamussino et al, 1999), although others reported less success with increasing age (Langer et al, 2001; Chilaka et al, 2002). Smith and associates (2009), from their review of the literature, concluded that the affect of age on outcomes is poorly undefined. The affect of aging on the lower urinary tract includes a higher rate of detrusor overactivity, as well as

Table 71–1.

Surgical Methods

Open retropubic colposuspension
Laparoscopic retropubic colposuspension
Suburethral sling procedure
Needle suspension
Periurethral injection
Artificial sphincter
Vaginal anterior repair (anterior colporrhaphy)

Table 71–2.

Standardization Needed for Studies

The patients under study (with regard to age, history of prior surgery, body mass)
The nature of the surgical technique, taking account of the surgeon's experience
Outcome measures and follow-up

urgency incontinence and intrinsic sphincteric deficiency. In addition, older patients are more likely to have had prior interventions and may, therefore, have a higher rate of periurethral fibrosis and/or other abnormalities in the area tissues surrounding the lower urinary tract. The presence of multiple comorbidities may also affect overall surgical outcome, including creating the possibility for increased complications and prolonged postoperative course.

2. The influence of the level of postoperative activity has been inadequately studied, so that no recommendations can be made (Smith et al, 2009).
3. There is level 4 evidence that medical comorbidity may have an impact on surgical outcomes, depending on the outcomes selected. There is level 3 evidence that psychologic factors have an impact on subjective and objective outcomes in different ways (Smith et al, 2005).
4. Obesity as a confounding variable is the subject of conflicting evidence in the literature and has not been studied in a prospective fashion. Obesity has been studied only retrospectively in case series as a risk factor for success or morbidity in stress incontinence surgery (level 4 evidence). There are no prospective, randomized trials that suggest superiority of one surgical technique over another in the obese population. Some studies have suggested increased failure rates in obese patients undergoing retropubic colposuspension (Brieger and Korda, 1992; Alcalay et al, 1995). Conversely, in a retrospective study of 198 women undergoing anti-incontinence surgery, cure rates were markedly better in those undergoing Burch colposuspension (Zivkovic et al, 1999).
5. **Surgery for recurrent stress incontinence has a lower success rate.** One study has reported that Burch colposuspension has an 81% success rate after one previous surgical procedure has failed, but this drops to 25% after two previous repairs and to 0% after three previous operations (Petrou and Frank, 2001). Other series report excellent results for colposuspension carried out after prior failed surgery. Maher and colleagues (1999) and Cardozo and associates (1999) have shown good objective (72% and 79%) and subjective (89% and 80%) success rates with repeated colposuspension at a mean follow-up of 9 months. Nitahara and coworkers (1999) reported a 69% subjective success at a mean follow-up of 6.9 years.
6. Berglund and associates (1996) reported that the duration of symptoms is a predictor of outcome, with a better response in those with a shorter history, which as a finding was independent of type of approach (e.g., vaginal versus retropubic). Ward and Hilton (2002), in a randomized comparison of colposuspension and tension-free vaginal tape, found no significant impact of symptom severity on outcomes for either procedure. Tamussino and coworkers (1999), in a review of 327 women assessed a minimum of 5 years postoperatively, noted that women with moderate or severe incontinence fared worse than those with milder symptoms. In their series, only Burch colposuspension was unaffected by the severity of preoperative symptoms.
7. It has been reported that as many as 23% of women undergoing urodynamics have mixed urodynamic stress incontinence and detrusor overactivity (Clarke, 1997). In a retrospective cohort study, Colombo and associates (1996b) compared 44 women with mixed incontinence with a matched group with urodynamic stress incontinence. The cure rate was 95% in the latter group compared with 75% in the former. Other studies report a less favorable outcome of 24% to 43% in those with detrusor overactivity combined with stress incontinence (Stanton et al, 1978; Milani et al, 1985; Lose et al, 1988). Smith and associates (2009) conclude that **surgery for urodynamic stress incontinence should not be considered contraindicated in women with mixed symptoms of SUI and overactive bladder syndrome or mixed urodynamic findings of urodynamic stress incontinence and detrusor overactivity (grade B).** All patients undergoing surgery for SUI should be appropriately counseled to allow realistic expectations of outcome; this is particularly important in those with mixed symptoms or mixed urodynamic incontinence (grade B).
8. The International Consultation on Incontinence (ICI), although allowing the fact that there is no consensus on the definition of intrinsic sphincter deficiency, concluded that there are limited evidence-based data to support that intrinsic sphincter deficiency influences either the outcomes of surgery or the type of surgical treatment (Smith et al, 2005, 2009). It would appear that a low leak point pressure is less predictive of outcome when compared with the presence or absence of urethral hypermobility (Smith et al, 2009).

CHOICE OF SURGICAL TECHNIQUE

Two types of stress incontinence have been suggested: one associated with a hypermobile but otherwise healthy urethra, a manifestation of weakened support of the proximal urethra, and one arising from a deficiency of the urethral sphincter mechanism itself, thereby compromising the ability of the urethra to act as a watertight outlet. **Hypermobility of the bladder neck and proximal urethra results from a weakening or loss of their supporting elements (ligaments, fasciae, and muscles), which in turn may be a consequence of aging, hormonal changes, childbirth, and prior surgery. It seems likely that the majority of women with SUI will also have an element of intrinsic sphincteric weakness with a variable degree of loss of the normal anatomic support of the bladder neck and proximal urethra,**

resulting in hypermobility. The compelling observation that one can cite for this is that a normal asymptomatic individual will not leak however much she strains.

Differentiating Relative Contributions of Hypermobility and Intrinsic Sphincter Deficiency

The influence of urethral function defined by leak point pressure or maximum urethral closure pressure (MUCP) is difficult to define on account of the large variation in outcome measures employed. Furthermore, other variables such as urethral mobility are often not controlled. Intrinsic sphincteric deficiency (ISD) is usually defined as a leak point pressure of less than 60 or MUCP of less than 20. A standardized test is not available to differentiate the relative contributions of intrinsic sphincter deficiency and hypermobility; therefore few studies have been able to accurately separate their individual contributions to the development of incontinence (Chapple et al, 2005). Retropubic procedures act to restore the bladder neck and proximal urethra to a fixed, retropubic position and are used when hypermobility is believed to be an important factor in the development of that woman's stress incontinence. This may facilitate the function of a marginally compromised intrinsic urethral sphincter mechanism, but if significant intrinsic sphincter deficiency is present it is likely that SUI will persist despite efficient surgical repositioning of the bladder neck and proximal urethra; at present this hypothesis remains unproven. In such circumstances then a sling procedure (particularly a "snug" fascial sling) or an artificial sphincter is most likely to be the therapy of choice.

In the normal continent woman, the bladder neck and proximal urethra are supported in a retropubic position, with the bladder base being dependent. Increases in intra-abdominal pressure are transmitted to both the bladder and the proximal urethra such that the pressure difference between the two is unchanged, promoting continence (Einhorning, 1961). A valvular effect at the bladder neck created by the transmission of abdominal pressure to the dependent bladder base may also be operative here (Penson and Raz, 1996). Furthermore, with proper bladder neck support, reflex contraction of the pelvic floor muscles during Valsalva maneuvers and coughing acts as a backboard for urethral compression (Staskin et al, 1985).

Surgical Procedures

Retropubic surgical procedures, usually chosen as surgical therapy for patients with SUI in which there is a significant component of hypermobility, are discussed here.

Open retropubic colposuspension is the surgical approach of lifting the tissues near the bladder neck and proximal urethra into the area of the pelvis behind the anterior pubic bones. When it is an open procedure the approach is through an incision over the lower abdomen. There are four variations of open retropubic colposuspension: Marshall-Marchetti-Krantz (MMK), Burch, vaginoobturator shelf (VOS), and paravaginal.

The term *colposuspension* was originally used to denote suspension of the urethra by the vaginal wall; however, by common usage, it now generally includes the paraurethral fascia and sometimes only this without the vagina. Retropubic colposuspension urethral repositioning can be achieved by three distinctly different procedures; these are all based on a similar underlying principle but in a spectrum in relation to the degree of the support/elevation they achieve, and their outcomes differ somewhat in the longer term.

The Burch colposuspension (Fig. 71–1A) is the elevation of the anterior vaginal wall and paravesical tissues toward the iliopectineal line of the pelvic sidewall with use of two to four sutures on either side (Burch, 1961). The VOS repair (see Fig. 71–1B) aims to anchor the vagina to the internal obturator fascia and is a modification of a combination of the Burch and paravaginal defect repair, with placement of the sutures laterally anchored to the internal obturator fascia rather than hitching the vagina up to the iliopectineal line (Turner-Warwick, 1986), although a more recent modification does, where appropriate, insert sutures into both the internal obturator and iliopectineal line (see Fig. 71–1C). The paravaginal defect repair (see Fig. 71–1D) aims to close a presumed fascial weakness laterally at the site of attachment of the pelvic fascia to internal obturator fascia (Richardson et al, 1976). The MMK procedure (see Fig. 71–1E) is the suspension of the vesicourethral junction (bladder neck) toward the periosteum of the symphysis pubis (Marshall et al, 1949) and was thought to act by buttressing the paraurethral area and bringing the vesicourethral junction into a more elevated "intra-abdominal" position.

The Degree of Urethral Elevation

The extent of the urethral elevation achieved by both the Burch (see Fig. 71–1A) and the VOS suspensions (see Fig. 71–1B and C) is higher than the arcus tendineus anchorage of the paravaginal defect repair (see Fig. 71–1D).

The Configuration of the Suspensions

A particular advantage of the horizontal urethral elevation achieved by both the VOS and the paravaginal repair suspensions is the significantly less susceptibility to tension on the urethra and to obstructive problems than with the V-shaped configuration of the Burch suspension (see Fig. 71–1A).

Tissue Approximation

Both the VOS and the paravaginal repair suspensions are anchored by tissue-approximating sutures; thus, unlike the Burch colposuspension, neither the VOS nor the paravaginal repair suspension is suture dependent in the longer term once the initial healing is complete because there is direct tissue adhesion. The VOS anchorage and suspension is significantly more robust than that of the paravaginal defect repair; the elevation it achieves can be further augmented by additionally including the iliopectineal ligament in the upper sutures (see Fig. 71–1C).

Laparoscopic colposuspension is the most popular of the laparoscopic incontinence procedures that were first introduced in the early 1990s (Vancaillie and Schuessler, 1991) with the premise that as minimally invasive procedures they would benefit patients by avoiding the major incision of conventional open surgery and shorten the time for a return to normal activity. As in open colposuspension, sutures are inserted into the paravaginal tissues on either side of the bladder neck and then attached to the iliopectineal ligaments on the same side. There are, however, technical variations in surgery with respect to the laparoscopic approach (transperitoneal into the abdominal cavity or extraperitoneal) and in the number and types of sutures, the site of anchor, and the use of mesh and staples (Jarvis et al, 1999).

ASSESSING OUTCOMES OF THERAPY

Before the best procedure can be determined, several issues regarding outcome reporting need to be addressed.

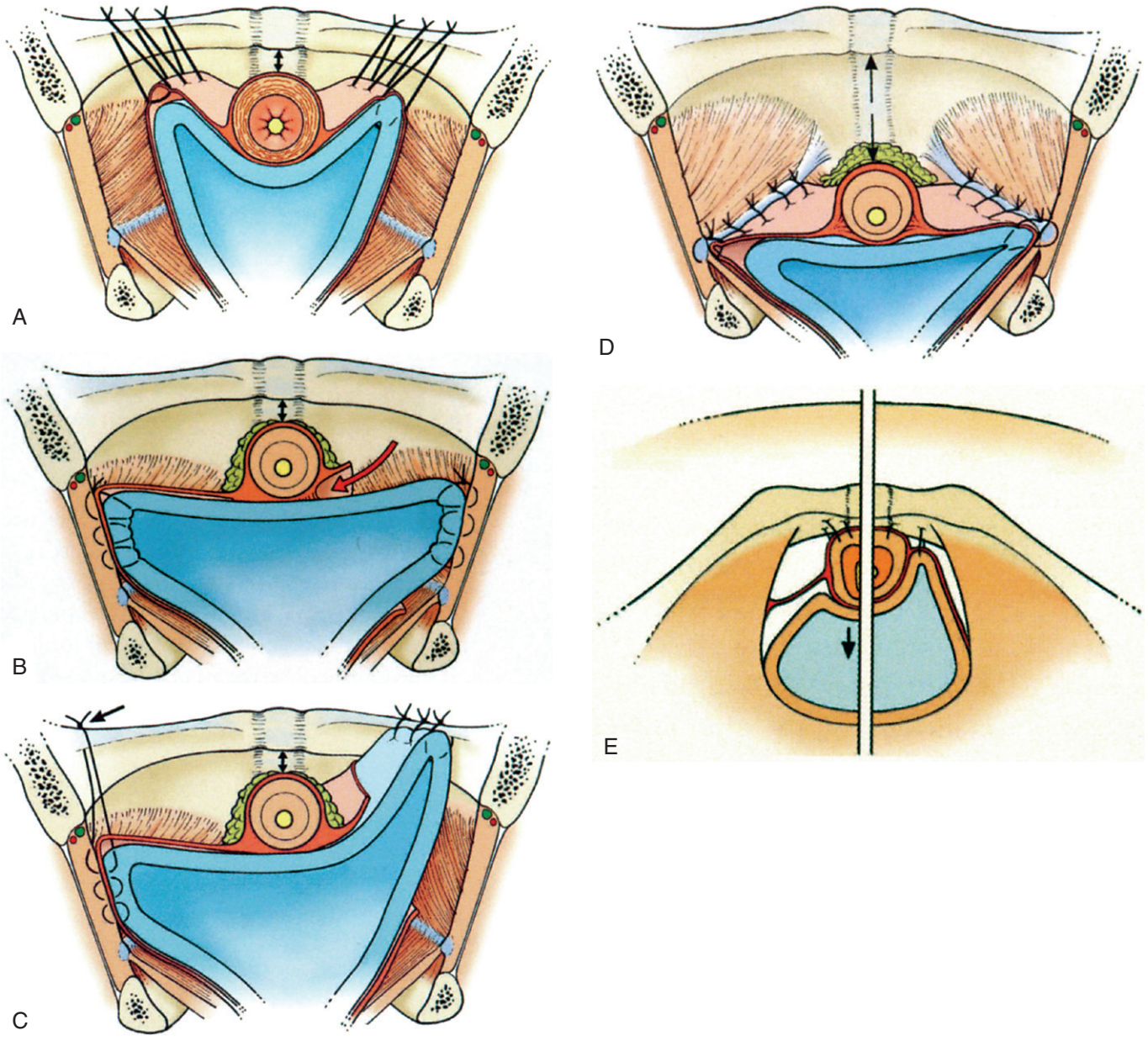


Figure 71–1. **A,** Coronal view, diagram of a Burch colposuspension. **B,** Coronal view, diagram of a vagino-obturator shelf procedure. **C,** Coronal view, diagram of a vagino-obturator shelf procedure on the left, augmented by suturing to the iliopectineal line, and a Burch colposuspension on the right. **D,** Coronal view, diagram of a paravaginal repair. **E,** Diagram showing the sutures in a Marshall-Marchetti-Krantz procedure and their proximity to the urethra.

Duration of Follow-up

It is recognized that prolonged follow-up is required to assess the true benefit of an incontinence procedure. **Short-term follow-up should be considered to have begun in all studies after participants have reached 1 year of follow-up** (Abrams et al, 2005). In the short term (2 years), most procedures are successful and success rates between procedures are similar (Leach et al, 1997). However, with longer follow-up (>5 years), failures become manifest and the true benefit of the better procedures is realized. Most studies report outcomes after short-term follow-up, and thus results must be interpreted with caution.

The Issue of Intrinsic Sphincter Deficiency

There is no consistency in the existing literature database to support the likelihood that intrinsic sphincter deficiency can influence either the outcomes or the type of surgical treatment. The main problem is that there is no consensus on the meaning of intrinsic sphincter deficiency and how to diagnose it (Smith et al, 2005, 2009). Nevertheless it is likely in the author's view (unsubstantiated by any unequivocal evidence) that mild degrees of intrinsic sphincter

deficiency coexist with hypermobility in most cases. In a situation in which intrinsic sphincter deficiency is the predominant problem, then a repositioning procedure such as a colposuspension is less likely to be successful than a tight fascial sling or artificial sphincter.

The Definition of Cure

The definition of cure varies between studies. Some authors report cure of SUI only, whereas others define cure as complete continence postoperatively, implying the absence of urgency incontinence as well. The assessment of cure may vary. Some authors report subjective cure based on patient history, questionnaire, bladder diary, or medical chart review; others use more objective measures, such as pad tests, stress tests, and urodynamics.

Finally, one must question whether the goal of complete continence is reasonable, given that the condition of SUI is generally a degenerative one and corrective surgery does not replace the defective components. As well, **even in normal healthy women, urinary continence is a spectrum of dryness; approximately 40% of nulliparous 30- to 49-year-olds experience some degree of incontinence with exercise** (Nygaard et al, 1990). It seems unreasonable to expect surgery for a degenerative condition to achieve results that are better than the nondegenerative state.

The Patient's versus the Physician's Perspective

A patient's satisfaction with treatment is often based on the difference between her expectations and her experiences (Sofaer and Firminger, 2005). Thus, fulfillment of positive expectations is a key element of a patient's satisfaction (Sitzia and Wood, 1997). Because expectations vary widely, satisfaction is not a standard concept. Consequently, treatment plans must be tailored to meet a nonstandard goal. An integral step in achieving this goal is the development of a patient-physician partnership that promotes the negotiation of realistic expectations.

Logically, agreement of patient and physician with respect to treatment plan and goals should improve outcomes. When a diagnosis has been made, asking patients what they already know about the condition may give clues to expectations for treatment. The "ask-tell-ask" method may be employed to mend the gaps between the physician's and the patient's expectations. The physician explains the proposed treatment plan and expectations for the outcome, then encourages the patient to ask questions. The physician provides the information requested and invites questions again, continuing the process until a mutual understanding of treatments and expectations is reached (Barrier et al, 2003). This approach may prevent "surprises" such as unexpected pain of treatment, adverse events of medication, and prolonged recovery time. Elkadry and associates (2003) emphasized this point by demonstrating a significant association between feeling unprepared for surgery and the patient's dissatisfaction after pelvic reconstruction. The same investigators also reported that achievement of patient-defined goals was more predictive of a patient's satisfaction than were objective measures of surgical success.

Clearly, one or more high-quality validated symptom and quality of life instruments should be chosen at the outset of a clinical trial representing the patient's viewpoint, accurately defining baseline symptoms as well as any other areas in which treatment may be beneficial and assessing the objective severity and subjective impact of both.

Whereas many, including the author, think that urodynamic studies are helpful in defining the underlying pathophysiologic process in cases with incontinence, they have not been proved to have adequate sensitivity, specificity, or predictive value (Chapple et al, 2005). **The ICI meeting concluded that although urodynamic studies, such as frequency-volume charts and pad tests, are useful there is inadequate evidence to justify pressure-flow studies for routine testing as either entry criteria or outcome measures in clinical trials. It was recommended that most large-scale clinical trials enroll subjects by using carefully defined symptom-driven criteria when the treatment will be given on an empirical basis** (Abrams et al, 2005).

INDICATIONS FOR RETROPUBIC REPAIR

The treatment of SUI in women must be tailored to the individual patient. Once evaluation has identified contributing factors, a trial of conservative therapy should be pursued and surgery considered for patients who fail to respond to these conservative measures. Careful assessment of the patient is essential in making an accurate diagnosis (Fig. 71–2).

The selection of technique is largely based on the surgeon's preference and prior experience; bladder base and urethral hypermobility may be surgically corrected by either a vaginal or a retropubic approach. Although it has been suggested that a retropubic colposuspension should be considered in patients who frequently generate high intra-abdominal pressure (e.g., those with chronic cough from obstructive pulmonary disease and women in strenuous occupations) (Appell, 1993), it could also be argued that these patients may be better served by a pubovaginal sling as well.

Specific Indications

A retropubic approach for the correction of anatomic SUI is indicated (1) for a patient undergoing a laparotomy for concomitant abdominal surgery that cannot be performed vaginally and (2) where there is limited vaginal access.

Potential Contraindications

If there is a history of prior failed incontinence procedures the existence of significant sphincteric deficiency must be suspected, even if hypermobility exists, and consideration given to performing a pubovaginal sling, although retropubic colposuspensions may be successful in this scenario as well (Cardozo et al, 1999; Maher et al, 1999; Nitahara et al, 1999).

In the author's view, when SUI exists solely due to intrinsic sphincter deficiency (i.e., a fixed, nonfunctional proximal urethra with intrinsic urethral sphincter dysfunction), a retropubic suspension procedure is less likely to be successful because there is no hypermobility to correct and the patient is better served by a pubovaginal sling, collagen injections, or an artificial sphincter (Bergman et al, 1989b). This represents a personal view that is at variance with the ICI's conclusion statement on the role of urethral occlusive forces, which reads as follows: "It would appear that a low leak point pressure is less predictive of outcome on this

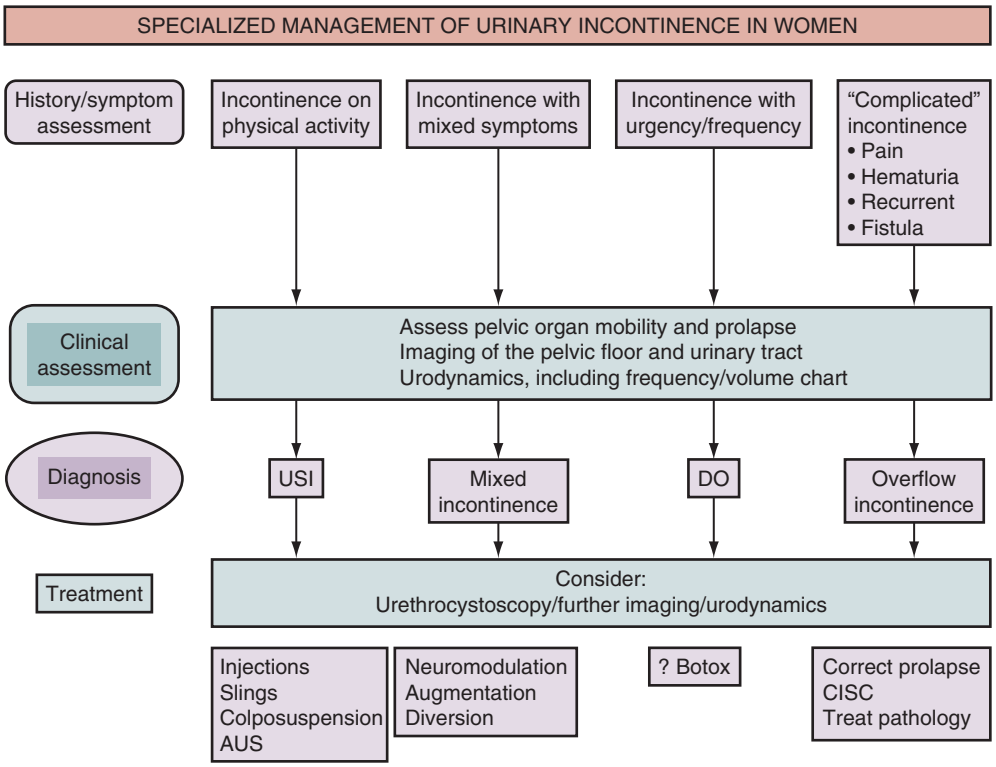


Figure 71–2. Algorithm for the specialized management of stress urinary incontinence (after the Third International Consultation on Incontinence, Monaco [Abrams et al, 2005]). USI, urodynamic stress incontinence; DO, detrusor overactivity; AUS, artificial urinary sphincter; CISC, clean intermittent self-catheterization.

data when compared to the presence or absence of urethral hypermobility" (Smith et al, 2009).

In cases with a pan–pelvic floor weakness, a colposuspension should not be used in isolation but should be part of a comprehensive approach to the pelvic floor and combined as appropriate with other alternative pelvic floor repair procedures. A retropubic colposuspension does not always adequately correct the associated vaginal prolapse that frequently coexists with bladder neck hypermobility. Although lateral defect cystocele and enterocele lend themselves to retropubic repair, a central defect cystocele, rectocele, and introital deficiency do not.

A retropubic colposuspension is contraindicated **when there is an inadequate vaginal length or mobility of the vaginal tissues, for example, after prior vaginal surgery or radiotherapy or such as that after a prior vaginal incontinence procedure** (Appell, 1993). The lysis of retropubic adhesions can be performed adequately and safely by a vaginal approach in conjunction with a needle suspension procedure or pubovaginal sling.

Vaginal versus Retropubic Surgery

From a review of the literature there is clearly a difference in the success rate of vaginal versus retropubic surgery alone with respect to correction of stress incontinence. An anterior colporrhaphy can certainly be efficacious for the correction of prolapse, with a reported efficacy in randomized controlled studies of 42% and 57% in the management of cystoceles (Sand et al, 2001; Weber et al, 2001). For the treatment of both a cystocele and SUI, an anterior colporrhaphy should be combined with a sling procedure. Goldberg and colleagues (2001), in a case-control series, demonstrated that in women with a cystocele and SUI the addition of a pubovaginal sling to an anterior colporrhaphy significantly decreased the recurrence rate from 42% in the control group to 19% in the anterior colporrhaphy group.

Glazener and Cooper (2001) reviewed the literature on randomized or quasi-randomized trials that included anterior vaginal repair for the treatment of urinary incontinence. Nine trials were identified that included 333 women having an anterior vaginal repair and 599 who received comparison interventions. They concluded that anterior vaginal repair was less effective than open abdominal retropubic suspension on the basis of patient-reported cure rates in eight trials both in the medium term (failure rate within 1 to 5 years after anterior repair, 97 of 259 [38%] versus 57 of 327 [17%]; relative risk [RR], 2.29; 95% confidence interval [CI], 1.7 to 3.08) and in the long term (after 5 years, 49 of 128 [38%] versus 31 of 145 [21%]; RR, 2.02; 95% CI, 1.36 to 3.01). There was evidence from three of these trials that this was reflected in a need for more repeated operations for incontinence (25 of 107 [23%] vs. 4 of 164 [2%]; RR, 8.87; 95% CI, 3.28 to 23.94). These findings held irrespective of the coexistence of prolapse (pelvic relaxation), although fewer women had a prolapse after anterior repair (RR, 0.24; 95% CI, 0.12 to 0.47) and later prolapse operation appeared to be equally common after either a vaginal (3%) or an abdominal (4%) operation.

Long-term follow-up beyond the first year is available in only three randomized controlled trials (Bergman et al, 1989a; Liapis et al, 1996; Colombo et al, 2000). There is a low morbidity with vaginal repair, but long-term success rates decrease with time to the extent that a 63% cure rate at 1 year fell to 37% at 5 years of follow-up (Bergman and Elia, 1995).

It can be concluded that with short-term follow-up vaginal and open retropubic suspension procedures have

similar success rates in the treatment of stress incontinence. However, with longer follow-up (and with the exception of the pubovaginal sling and loose midurethral tapes (see later) **patients who have retropubic procedures fare better than those undergoing vaginal repairs.**

The recommendation from the ICI committee (Smith et al, 2009) **is that anterior colporrhaphy should not be used in the management of SUI alone (grade A).**

GENERAL TECHNICAL ISSUES

Retropubic Dissection

In open retropubic suspension procedures good access to the retropubic space is crucial. This is best performed with the patient in the supine position with the legs abducted, in either a low or a modified dorsal lithotomy position with the use of stirrups, allowing access to the vagina during the procedure and a perineal-abdominal progression. A urethral Foley catheter is inserted; the catheter balloon is used for subsequent identification of the urethra and bladder neck, and, indeed, it is invaluable in allowing palpation of the edges of the bladder by appropriate manipulation. A Pfannenstiel or lower midline abdominal incision is made, separating the rectus muscles in the midline and sweeping the anterior peritoneal reflection off the bladder. It is essential to optimize the access to the retropubic space, and if a Pfannenstiel skin incision is made it is advisable to use the suprapubic V-shaped modification described by Turner-Warwick and colleagues (1974). Likewise, whatever incision is made, extra valuable access to the retropubic space is obtained by extending the division of the rectus muscles down to the pubic bone and elevating the aponeurotic insertion of the rectus muscle off the upper border of the pubic bone.

The retropubic space is then developed by teasing away the retropubic fat and underlying retropubic veins from the back of the pubic bone. The bladder neck, anterior vaginal wall, and urethra are then easy to identify, often facilitated by the presence of the Foley balloon. In patients who have had previous retropubic surgery, the dissection is performed sharply and it is important to take down all old retropubic adhesions, particularly in the presence of a prior failed repair. If difficulty is encountered in the identification of the bladder neck, the bladder may be partially filled or even opened to identify its limits and an examining finger in the vagina is invaluable in aiding the dissection (Symmonds, 1972; Gleason et al, 1976).

It is important to identify the lateral limits of the bladder as it reflects off the vaginal wall because only in this manner can one avoid inadvertent suturing of the bladder itself. Dissection over the bladder neck and urethra in the midline is to be avoided so as not to damage the intrinsic musculature. The lateral bladder wall may be "rolled off" medially and cephalad from the vaginal wall with a mounted swab and by use of countertraction with a finger in the vagina. In the author's experience it is necessary to incise the endopelvic fascia. Occasional venous bleeding from the large vaginal veins is controlled by suture ligature, although it often resolves with tying of elevating sutures. To aid in the identification of the lateral margin of the bladder it is helpful to displace the balloon of the Foley catheter into the lateral recess, where it easily can be palpated through the bladder wall.

Suture Material

Absorbable sutures were used in the original descriptions of the MMK procedure (chromic catgut), Burch colposuspension (chromic catgut), and VOS procedure (polyglycolic acid or polydioxanone), whereas the original paravaginal repair used nonabsorbable sutures (silicon-coated Dacron). Fibrosis during subsequent healing is likely to be the most important factor in providing continued fixation of the perivaginal fascia to the suspension sites (Tanagho, 1996); nevertheless, some surgeons believe that a nonabsorbable suture material is better because of the risk of suture dissolution before the development of adequate fibrosis (Penson and Raz, 1996). Clearly, the choice of suspension suture material is a personal choice, but erosion of nonabsorbent sutures into the lumen of the bladder is a not uncommon complication and a not uncommon source of medical litigation (Woo et al, 1995).

Bladder Drainage

Some degree of immediate postoperative voiding difficulty can be expected after retropubic suspensions (Lose et al, 1987; Colombo et al, 1996a). Immediately postoperatively, bladder drainage may take the form of a urethral or a suprapubic catheter, generally based on the surgeon's preference. A voiding trial is usually performed around the fifth day postoperatively. However, there is some evidence that a suprapubic catheter may be advantageous with respect to a lower incidence of asymptomatic and febrile urinary tract infection and earlier resumption of normal bladder function (Andersen et al, 1985; Bergman et al, 1987). In addition, the use of a suprapubic tube is generally more comfortable, allows the patient to participate in catheter management, and avoids the need for clean intermittent self-catheterization. Catheterization can be discontinued when efficient voiding has resumed, which is usually indicated by a postvoid residual urine volume either less than 100 mL or less than 30% of the functional bladder volume.

Drains

A tube drain may be placed in the retropubic space when there is concern about ongoing bleeding from perivaginal veins that may prove difficult to control with suture and electrocautery. Often, tying the suspension sutures is sufficient to stop this bleeding; but when the bleeding persists, drainage of the retropubic space is indicated. The drain is generally removed on the first to third day, when minimal output is noted.

MARSHALL-MARCHETTI-KRANTZ PROCEDURE

Technique

Marshall, Marchetti, and Krantz in 1949 described a retropubic approach for the elevation and fixation of the anterolateral aspect of the urethra to the posterior aspect of the pubic symphysis and the adjacent periosteum. Technically, the original description of the MMK procedure reported a double suture bite of the paraurethral tissue included with the vaginal wall; this may be generically entitled a cystourethropexy. In 1949, Marshall and coworkers described their retropubic vesicourethral suspension in 50 patients; 38 of the patients had symptoms of SUI, 25 of whom had failed prior gynecologic operations for urinary incontinence. A simple suprapubic procedure was described by which the vesical outlet was suspended to the pubis (Marshall et al, 1949). In the original description, three pairs of sutures (taking double bites of tissue) were placed on each side of the urethra, incorporating full-thickness vaginal wall (excluding mucosa) and lateral urethral wall

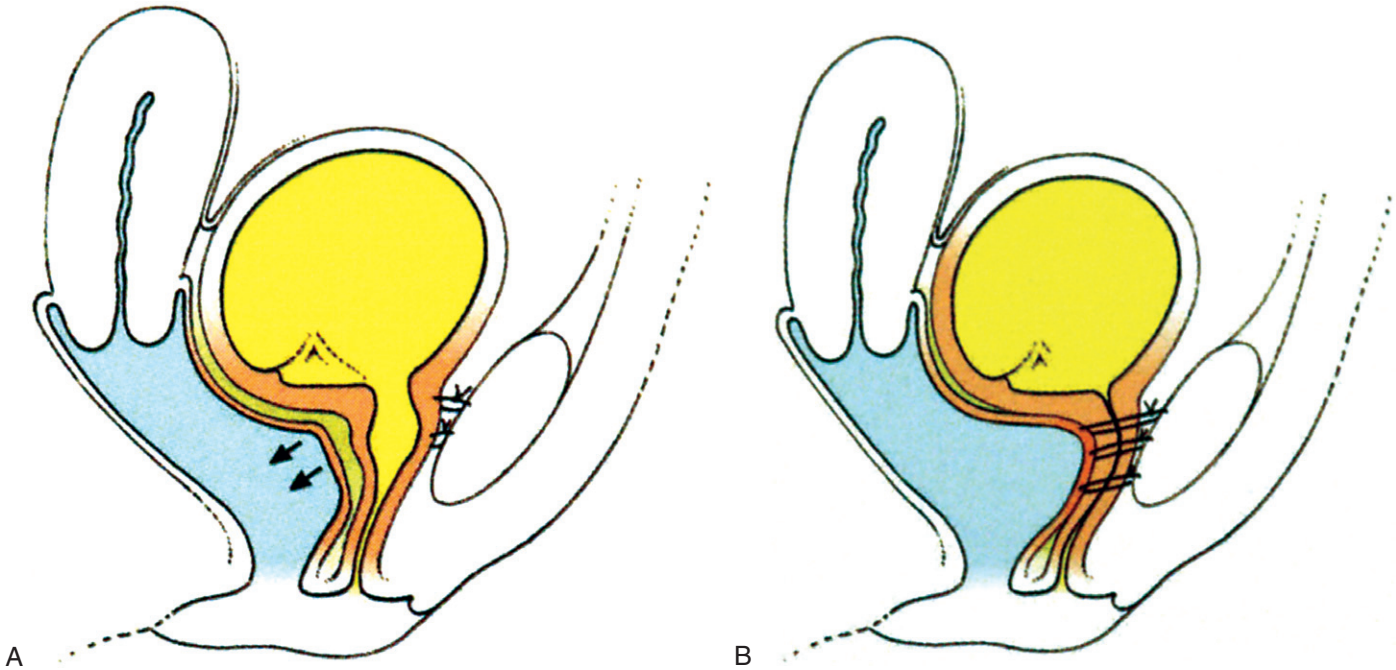


Figure 71–3. **A,** Potential risk of tethering the urethra with the Marshall-Marchetti-Krantz (MMK) procedure, influencing the function of the urethral sphincter mechanism. **B,** Potential risk of obstruction of the urethra with the paraurethral sutures of the MMK procedure.

(excluding mucosa) (Marshall et al, 1949). Marchetti (1949) then modified the procedure to omit the tissue bite through the urethral wall because of concern about urethral injury. Apart from modifications in suture number and material over the years, the procedure remains the same today.

Cystourethropexy was often used as a secondary procedure for the resolution of persistent leaking after an anterior colporrhaphy. A cystourethropexy does not support the posterior wall of the urethra unless the sutures include the paraurethral vaginal wall, nor does it positively reduce an anterior vaginal wall prolapse in the same way that the true retropubic colposuspension procedures do. If there is a significant urinary residual after colporrhaphy with associated laxity of the anterior vagina wall, then with the descent, this applies traction to the posterior aspect of the bladder neck and tends to "tent" it open because the anterior aspect is tethered by sutures to the back of the pubis (see Fig. 71–1E). Sutures are placed on either side of the urethra (avoiding the urethral wall), taking bites through the paraurethral fascia and anterior vaginal wall (excluding mucosa). The most proximal sutures are placed at the level of the bladder neck. Each suture is then passed into an appropriate site in the cartilaginous portion of the symphysis (Fig. 71–3). However, the main technical problem relating to the MMK procedure is the difficulty of obtaining an adequately robust anchorage of the anterior wall of the urethra and the paraurethral fascia to the symphysis and the periosteum of the pubis where the suture bites are relatively insecure. As shown in Figure 71–3 these sutures can potentially either distort the bladder neck and impair sphincter function (see Fig. 71–3A) or obstruct the bladder neck (see Fig. 71–3B). All sutures are inserted; and while an assistant elevates the anterior vaginal wall, each suture is individually tied, starting with the more distal pair. The proximal, or bladder neck, suture frequently needs to be passed through the insertion of the rectus abdominis. Additional sutures may or may not be placed between the anterior bladder wall and the rectus muscles to pull the bladder farther anteriorly.

Results

Krantz described a personal series of 3861 cases with a follow-up of up to 31 years and a 96% subjective cure rate (Smith et al, 2005). Short- and medium-term results with the MMK procedure have been good. Mainprize and Drutz (1988) reviewed 58 articles (predominantly retrospective) published between 1951 and 1988 for treatment outcomes in 3238 cases. The cure rate, mostly based on subjective criteria, was 88%, with an improvement rate of 91%. Jarvis's meta-analysis of studies in the literature (1994b) noted subjective continence in 88.2% (range, 72% to 100%) of 2460 patients with 1- to 72-month follow-up and objective continence in 89.6% (range, 71% to 100%) of 384 patients with 3- to 12-month follow-up. Whether the procedure was being done primarily or secondarily affected the outcome, with subjective continence in 92% if it was done primarily versus 84.5% if it was done secondarily. Longer-term data are limited in amount. McDuffie (1981) reported 75% success at 15 years. More recently, Clemens and coworkers (1998) noted subjective cure or improvement (SUI and urgency urinary incontinence) in only 41% of patients with a mean follow-up of 17 years, and Czaplicki and colleagues (1998) noted decreasing continence rates from 77% at 1 year to 57% at 5 years to 28% at 10 years, with a mean duration of continence of 78.5 months. There are significant limitations to the data since most series are retrospective, with preoperative assessment based mainly on the history and physical examination and few studies using objective data as outcome measures.

Complications occur in up to 21% of cases (Mainprize and Drutz, 1988), and the placement of sutures through the pubic symphysis incurs the risk of osteitis pubis, a potentially devastating complication of the MMK procedure that has been reported in 0.9% to 3.2% of patients (Lee at al, 1979; Mainprize and Drutz, 1988; Zorzos and Paterson, 1996). Patients usually present 1 to 8 weeks postoperatively with acute pubic pain radiating to the inner thighs, aggravated by moving. Physical examination reveals tenderness over the pubic symphysis, and radiography demonstrates

haziness to the borders of the pubic symphysis and possibly lytic changes. Treatment is with bed rest, analgesics, and possibly corticosteroids (Lee at al, 1979). Other specific complications of the MMK procedure have included the occasional erosion of nonabsorbable cystourethropexy sutures into the bladder lumen with stone formation. Also, the positioning of sutures in the endopelvic fascia close to the bladder neck can result in a significant outlet obstruction.

Whereas the MMK procedure produces a cure rate similar to that of colposuspension, the complication of osteitis pubis means that there is little to support its use as an alternative to other colposuspension procedures. Indeed the ICI committee (Smith et al, 2009) **concluded that although short-term results indicate comparable cure rates to colposuspension there is limited evidence that the longer-term outcome is poorer after MMK (level 1) and declines further over time (level 3). There is no evidence to support the continued use of MMK over colposuspension.**

The recommendation from the ICI committee (Smith et al, 2009) **is that the MMK procedure is not advised for the treatment of SUI (grade A).**

BURCH COLPOSUSPENSION

Technique

Burch's original description of the colposuspension in 1961 followed his original procedure, which was essentially a paravaginal repair attaching the paravaginal fascia to the white line of the pelvis, the arcus tendineus. The Burch colposuspension was a novel approach to restore the urethrovesical junction to a retropubic location by approximating the periurethral fascia to the tough bands of fibrous tissue running along the superior aspect of the pubic bone (Cooper [iliopectineal] ligament) with three pairs of sutures. The original Burch retropubic colposuspension is appropriate only if the patient has adequate vaginal mobility and capacity to allow the lateral vaginal fornices to be elevated toward and approximated to the Cooper ligament on either side. This technique has been modified. Tanagho's modification (1978) approximated the vaginal wall to the lateral pelvic wall, with the sutures holding the anterior vaginal wall to the Cooper ligament, being tied loosely so that two fingers could be placed between the symphysis and urethra. This achieved broad support for the urethra and bladder neck and potentially minimized the risk of postoperative voiding dysfunction. A more recent modification (Shull and Baden, 1989; Turner-Warwick and Chapple, 2002) involves a hybrid approach whereby the vaginal tissues are approximated to the internal obturator fascia with an anchoring bite to the iliopectineal ligament (see VOS repair later).

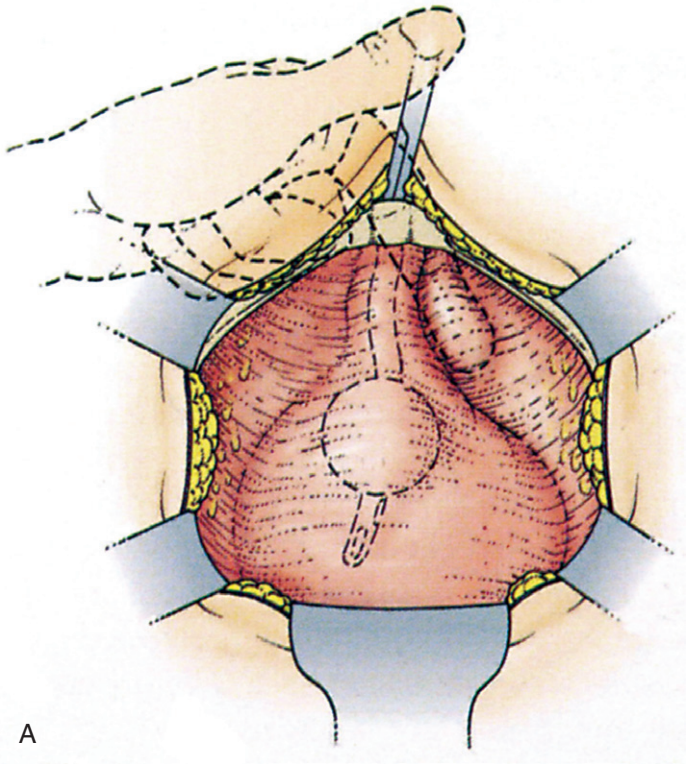
Suture placement is facilitated by the elevation of the dissected anterolateral vaginal wall into the field by the surgeon's fingers inserted in the vagina (Fig. 71–4). The bladder is retracted to the opposite side with a mounted swab. Two to four sutures are placed on each side, each suture taking a good bite of fascia and vaginal wall, with care taken not to pass through the vaginal mucosa. Some recommend taking double bites of tissue to lessen the risk of suture pull-through (Jarvis, 1994a). The most distal suture is at the level of the bladder neck and placed no closer than 2 cm lateral to it, although some place distal sutures at the midurethral level (Tanagho, 1978). The suspension suture bites of the paraurethral fascia should not be positioned too close to the bladder neck and the urethra, as they are in the cystourethropexy procedures (MMK), because the unwanted effect of lateral traction-tension created by their anchorage to the iliopectineal ligaments may tether the sphincteric occlusive effect on the urethra or create a degree of obstructed voiding. Subsequent sutures are placed proximal to the level of the bladder neck, at about 1-cm intervals. The sutures are then placed into corresponding sites in the Cooper ligament, the emphasis being on a mediolateral direction for the sutures. The exact mechanism of continence of the Burch colposuspension is still unknown. Burch (1968) thought it to be secondary to elevation and stabilization of the bladder neck and urethra. In support of the suggestion regarding suture placement, Digesu and colleagues (2004) reviewed magnetic resonance imaging findings before and 1 year after open Burch colposuspension in 28 women to see if this would explain the mechanism. In the 86% who were cured the distance between the levator ani muscle and bladder neck was significantly shorter than in those whose treatment failed. Their suggestion is that insertion of sutures in a medial-lateral direction as opposed to an anteroposterior direction may better appose the levator ani muscle and bladder neck. The highly vascular vaginal wall may bleed profusely during suture placement, and large vaginal veins often need to be oversewn, but most bleeding ceases once the sutures are tied and the vagina is suspended. To facilitate tying of the sutures, the assistant elevates the appropriate portion of the vaginal wall as each suture is tied, beginning with the more distal pair.

No attempt should be made to tie the sutures tightly. Often, the vaginal wall does not approximate to the Cooper ligaments, and free suture material is seen between the vagina and the ligaments. The principle is to approximate the vaginal wall to the lateral pelvic wall, where it will heal and promote adhesion formation (Tanagho, 1978; Shull and Baden, 1989; Turner-Warwick and Chapple, 2002), **thereby creating a broad support for the urethra and bladder neck.**

Results

As in the MMK procedure, short- and medium-term outcomes with the Burch colposuspension have been good. In Jarvis's meta-analysis (1994b), subjective continence was achieved in 91% (range, 63% to 97%) of more than 1300 patients with 3 to 72 months of follow-up and objective continence in 84% of more than 1700 patients with 1 to 60 months of follow-up. Lapitan and associates (2003) reviewed 33 trials involving a total of 2403 women who underwent open colposuspension and found an overall cure rate between 68.9% to 88.0%, with a 1-year cure rate of 85% to 90%. This decreased to 70% at 5 years. Although there may be a decline in the cure rate of only 15% to 20% beyond 5 years, Alcalay and colleagues (1995) noted a subjective and objective SUI cure rate of 69% with a mean follow-up of 13.8 years. Baessler and Stanton (2004) examined the impact of surgery on coital incontinence. Of the 30 women available for postoperative evaluation, 73% preoperatively had incontinence with penetration, 10% with orgasm only, and 17% with both. Postoperatively, 70% were cured of their coital incontinence. Moreover, in those who were subjectively cured of their stress incontinence, 87% were also cured of their coital incontinence.

Unlike with the MMK procedure, the good results with the Burch colposuspension appear to be durable with longer follow-up. Lapitan and associates (2003) **reached the conclusion from a review of two trials comparing the Burch colposuspension and the MMK procedure that the Burch technique results in higher cure rates. Thus,**



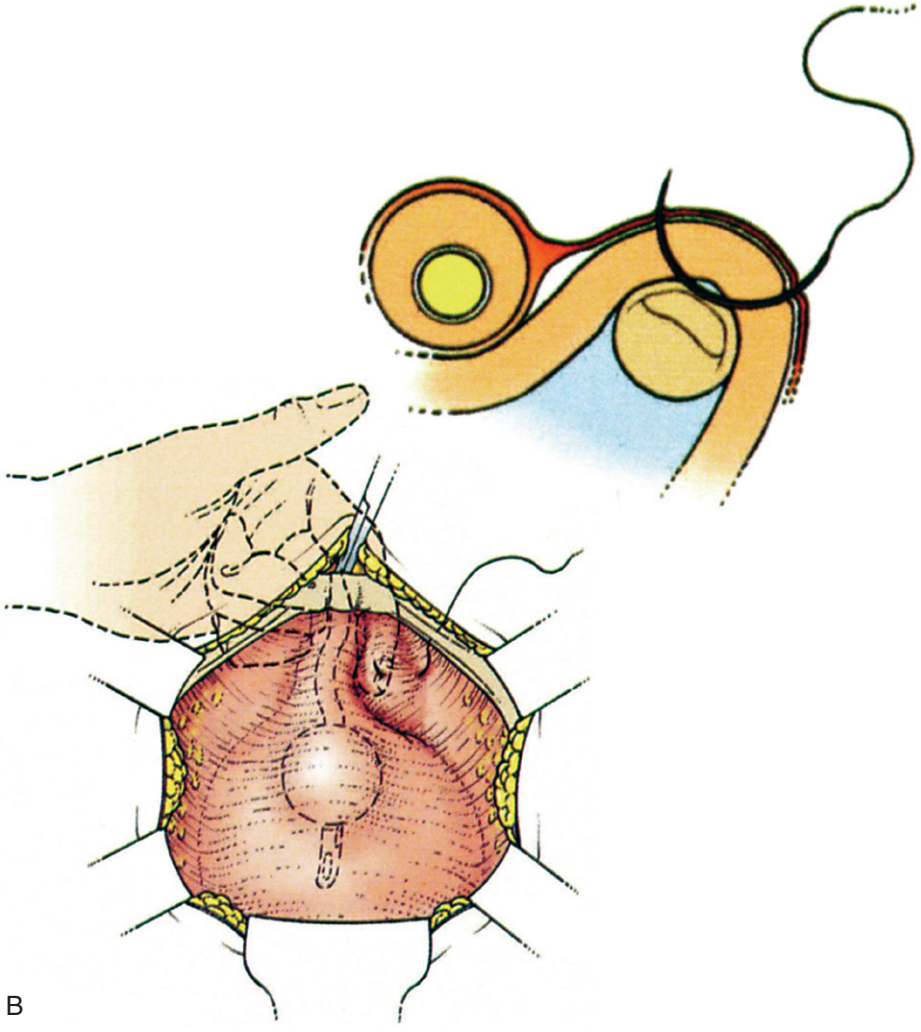
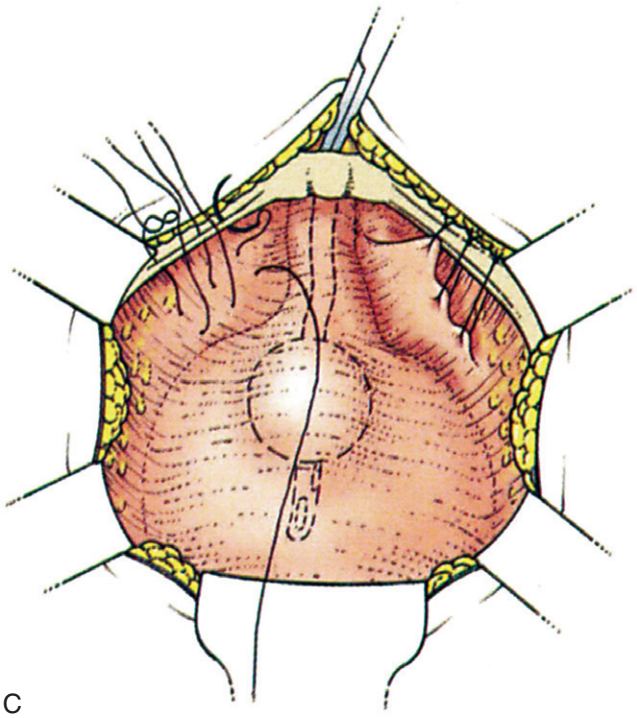
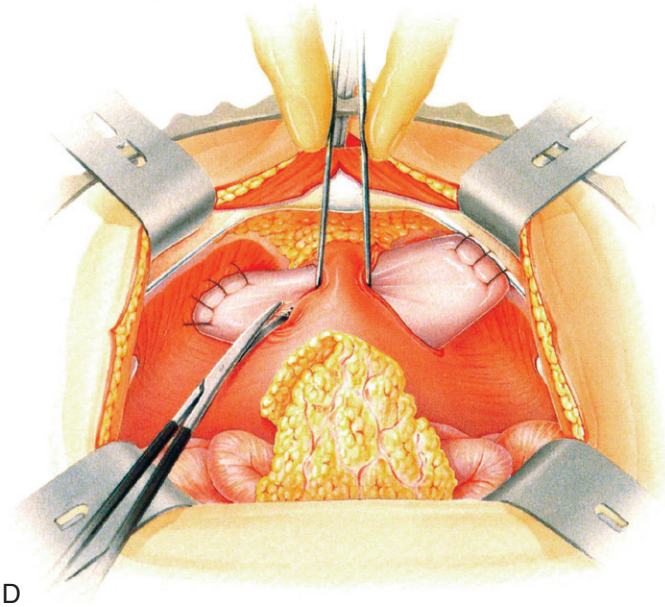


Figure 71–4. **A,** The use of a finger in the vagina when the pelvic tissues are dissected superomedially off of the vagina. **B,** Medial suture placement; note the role of the finger in steering the suture *(inset)*.



C



D

Figure 71–4, cont'd. **C,** Note the mediolateral orientation of the sutures. **D,** Completion of a retropubic colposuspension with a vaginoobturator hitch on the left and a Burch colposuspension on the right.

it should be regarded as the *standard* open retropubic colposuspension procedure.

Open colposuspension is as effective as any other procedure in primary or secondary surgery at curing SUI with proven long-term success (level 1 evidence, grade A recommendation) (Smith et al, 2005).

Prophylactic Colposuspension

In 2006, the Colpopexy and Urinary Reduction Efforts trial demonstrated that the postoperative risk of stress incontinence in stress-continent women undergoing open abdominal sacrocolpopexy could be substantially reduced by the addition of a Burch colposuspension (Brubaker et al, 2006). Initial results at 3 months after the procedure demonstrated reduction of de novo stress incontinence from 44% in the untreated group to 24% in the Burch group, without increased rates of voiding dysfunction or urgency symptoms. Subsequent 1- and 2-year outcomes from this trial showed continued benefit in patients who received the concomitant Burch colposuspension (Burgio et al, 2007; Brubaker et al, 2008).

Reoperative Surgery

Poorer results are likely to occur when the procedure is performed secondarily. Scarring and fibrosis from previous surgery can prevent adequate suspension in some cases, and suture cut-through is more likely. Furthermore, after failed surgery, patients may often have coexisting sphincteric weakness that places them at greater risk of recurrence after colposuspension (Bowen et al, 1989; Koonings et al, 1990).

Nevertheless, Maher and colleagues (1999) and Cardozo and associates (1999) have both shown good objective (72% and 79%) and subjective (89% and 80%) success with repeated colposuspension at a mean follow-up of 9 months. Nitahara and coworkers (1999) reported a 69% subjective success at a mean follow-up of 6.9 years. Urgency incontinence and sphincteric weakness are the main causes of failure and dissatisfaction. Urgency incontinence accounted for 63% (12 of 19) of failures; the remaining 7 with persistent stress incontinence in Nitahara's series demonstrated sphincteric deficiency with mean Valsalva leak point pressures of 65 cm H_2O. The low-pressure urethra has often been quoted as an adverse risk factor for colposuspension (Haab et al, 1996; Bowen et al, 1989; Koonings et al, 1990), but this topic also remains controversial. Several authors have studied the urethral pressure profilometry changes after colposuspension and have noted a statistically significant increase in the postoperative pressure transmission ratio but minimal changes in the postoperative MUCP, functional urethral length, and continence area (Faysal et al, 1981; Weil et al, 1984; Feyersiel et al, 1994). Although a low-pressure urethra (MUCP ≤ 20 cm H_2O) is considered a contraindication to the Burch procedure, a modification of the standard Burch operation has had some success in managing SUI associated with the low-pressure urethra. Bergman and colleagues (1989c) combined a standard Burch procedure with the Ball procedure (Ball, 1963) whereby, before the Cooper ligament suspension is performed, two or three sutures are used to plicate the anterior urethral wall at the level of the proximal and middle urethra. They retrospectively noted greater success with this technique than with a standard Burch procedure for the low-pressure urethra, and this was comparable to the success obtained with a standard Burch procedure in patients with a normal-pressure urethra (MUCP > 20 cm H_2O). With longer follow-up, the Ball-Burch procedure continued to yield better results than the standard Burch procedure in patients with a low-pressure urethra, with a documented 5-year cure rate of SUI of 84% (Bergman et al, 1991; Elia and Bergman,

1995). However, there are no randomized studies addressing the issue, and whether these results can be extrapolated for the use of this technique in patients with intrinsic sphincter deficiency is debatable.

As with any major abdominal or pelvic surgical procedure, intraoperative and perioperative complications that may occur after a retropubic suspension include bleeding, injury to genitourinary organs (bladder, urethra, ureter), pulmonary atelectasis and infection, wound infection or dehiscence, abscess formation, and venous thrombosis or embolism. Other complications more specific to retropubic suspension procedures include postoperative voiding difficulty, detrusor overactivity, and vaginal prolapse. These are discussed in more detail along with other reported complications in a later section in this chapter.

The recommendations from the ICI committee (Smith et al, 2009) **are as follows: Open retropubic colposuspension can be recommended as an effective treatment for primary SUI, which has longevity (grade A). Although open colposuspension has to a large extent been superseded by the less invasive midurethral tapes, it should still be considered for those women in whom an open abdominal procedure is required concurrently with surgery for SUI (grade D).**

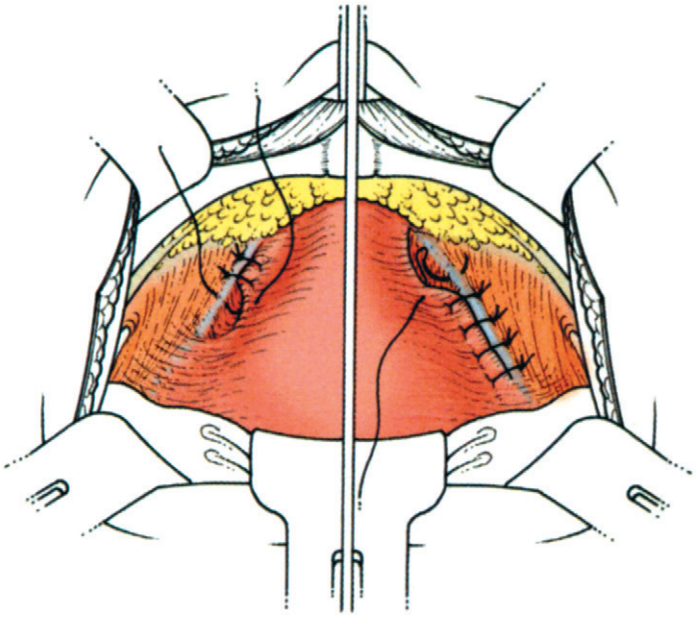


Figure 71–5. A paravaginal repair procedure.

PARAVAGINAL REPAIR

Technique

The origins of the paravaginal repair date to White (1912), who described the importance of the "white line" of the pelvis (arcus tendineus) as an integral structure supporting the proximal urethra and bladder base to the pelvic wall and the development of paravaginal fascial tears predisposing to cystocele formation. He performed the paravaginal repair by a vaginal approach but envisioned that it would be easier if it was performed abdominally (White, 1912). Later, in his original description, Burch (1961) attached the vaginal wall to the arcus tendineus in seven patients, only to realize that the attachment may not be secure, prompting him to use the Cooper ligament as an attachment site. In the 1970s, Richardson and coworkers (1976) reintroduced the concept of a lateral defect cystourethrocele as an etiologic factor in the genesis of SUI and popularized the paravaginal repair as a technique for management.

The patient is placed in a low lithotomy position, just as for the MMK procedure and Burch colposuspension. If there are retropubic adhesions resulting from prior surgery they are sharply incised; the dissection is facilitated by placement of two fingers of the surgeon's left hand in the vagina. The bladder and urethra are not mobilized from the vaginal attachments. Richardson and colleagues (1981) describe an extensive reattachment of the lateral vaginal sulcus with its overlying fascia to the arcus tendineus fasciae pelvis from the back of the lower edge of the symphysis pubis to the ischial spine, using six to eight sutures placed at 1-cm intervals. The vaginal wall in the region of the bladder neck is identified, and these interrupted sutures are placed at approximately 1-cm intervals through the paravaginal fascia and vaginal wall (excluding vaginal mucosa) beginning at the urethrovesical junction. The sutures are then passed through the adjacent obturator fascia and underlying muscle at the site of the arcus tendineus fascia (Fig. 71–5). If the arcus is not visible, the obturator foramen may be used as a landmark. It is situated 1.5 to 2 cm above the white line.

The end point that should be achieved is the reestablishment of the urethral axis in an anatomic position, easily allowing three fingerbreadths between the pubic symphysis and the proximal urethra but providing secure fixation and preventing rotational descent. Consequently, it has been reported that postoperative voiding difficulties are uncommon (Richardson et al, 1981).

Results

Few reports on the use of this technique have been published. With variable follow-up, cure rates greater than 90% have been reported for the paravaginal repair (Richardson et al, 1981; Shull and Baden, 1989). There is only a single randomized comparison of colposuspension with paravaginal repair including 36 patients who were randomly allocated to treatment by either colposuspension or paravaginal repair with nonabsorbable suture material. At 6 months of follow-up there was an objective cure rate of 100% for those undergoing colposuspension and 72% for those undergoing paravaginal repair (Colombo et al, 1996a).

Small series have reported on vaginal approach paravaginal repairs (Scotti et al, 1998; Mallipeddi et al, 2001). In particular, Mallipeddi and colleagues observed 45 patients (21 with SUI) after this approach for a mean of 1.6 years, and 57% had persistent stress incontinence; their conclusion was that this technique had limited applicability for SUI. **It can be concluded that there is level 1/2 evidence that abdominal paravaginal repair is less effective than colposuspension. There are limited data (level 3/4) on laparoscopic and vaginal paravaginal repairs, but interpretation of these data is hampered by the small numbers of patients, the short follow-up, and a combination of this procedure with other types of incontinence procedures** (Smith et al, 2005).

There is limited evidence (level 2) that abdominal paravaginal defect repair is less effective than open colposuspension (Smith et al, 2009).

The recommendation from the ICI committee (Smith et al, 2009) **is that paravaginal defect repair is not recommended for the treatment of SUI alone (grade A).**

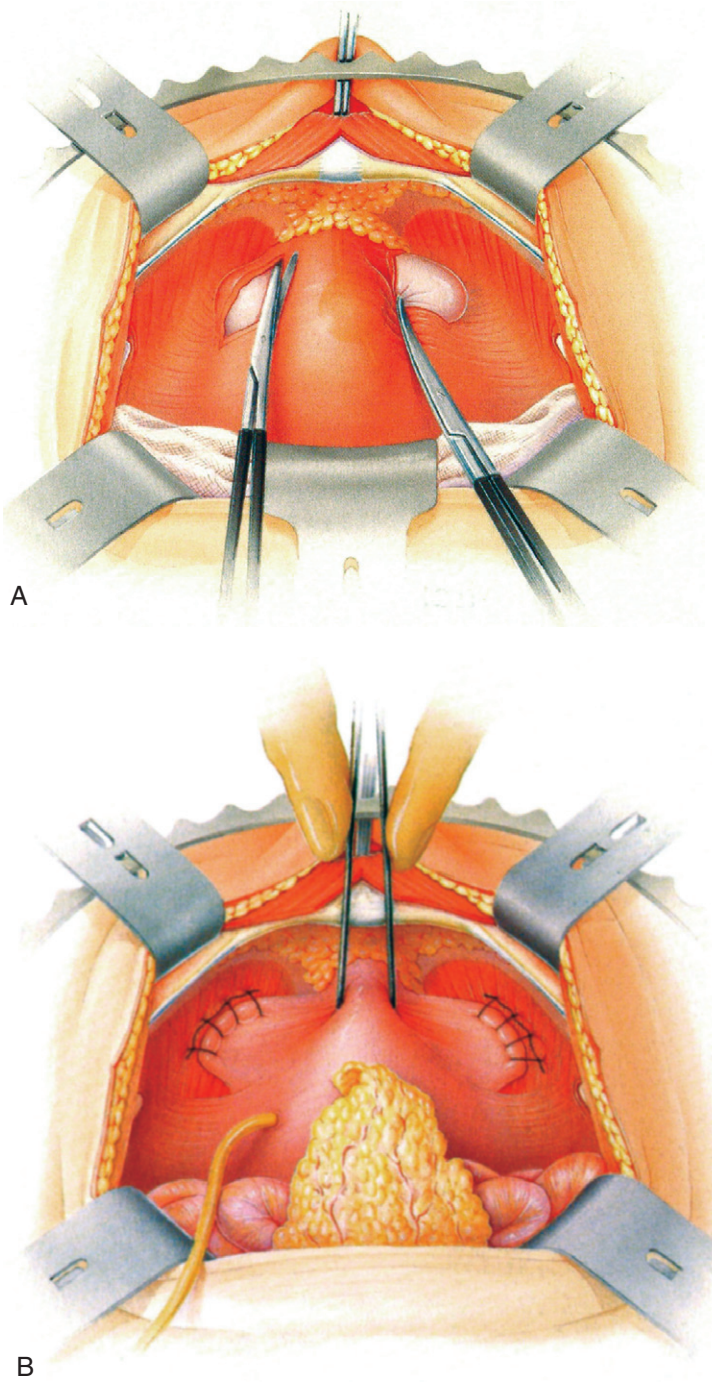


Figure 71–6. **A,** Mobilizing the tissues. The tissues should be stripped by blunt dissection with a mounted swab or the edge of a pair of scissors; only occasionally is sharp dissection necessary, provided the stripping action starts far laterally adjacent to the pubic bone. **B,** Completed vagino-obturator shelf procedure.

VAGINO-OBTURATOR SHELF REPAIR

Technique

Turner-Warwick (1986; Turner-Warwick and Chapple, 2002) reported his variant of the paravaginal repair, which he called the vagino-obturator shelf (VOS) repair. The premise for this is that there should be no restriction to the intrinsic sphincteric function of the urethra by fixation or paraurethral tethering, and there should be no urethral compression (Turner-Warwick and Kirby, 1993).

Just as for other retropubic suspension procedures (Fig. 71–6), the anterior wall of the lower segment of the bladder wall is exposed and the position of the bladder neck is identified by gentle traction on a balloon catheter in the urethra. The surgeon's forefinger in the vagina elevates its anterior wall and the overlying endopelvic fascia on either side of the urethra. Lateral displacement of the catheter balloon with the finger in the vagina facilitates the identification of the inferolateral margin of the bladder, lateral to the bladder neck; and its separation from the paraurethral endopelvic fascia is achieved by simple blunt dissection with a sponge or scissor-tip retraction. This naturally exposes the surface of the obturator muscle and the arcus tendineus origin of the levator muscles deep in the sulcus below this, the site of suture placement in the paravaginal repair (which is well below the vaginal anchorage point in the VOS procedure). The obturator nerves lie superolaterally; their canals run high up in a groove under the superior pubic ramus so that once they are identified,

injury to them can be avoided. The full thickness of the vagina and its overlying layer of endopelvic fascia are elevated by the surgeon's finger in the vagina and are approximated to the internal obturator muscle and anchored to the bulk of this with absorbable 0 or 1 sutures mounted on robust 35- to 40-mm half-circle needles. Slight flexion of the fingertip tents the vaginal wall and facilitates the full-thickness insertion of these suture bites through it, thus avoiding inclusion of the surgical glove. Three or four successive sutures are inserted. For knot security these are best tied continuously, head to tail, as they are inserted, rather than separating them individually. Each tied suture bite facilitates the insertion of the next (unlike in the Burch procedure, in which the sutures are not tied until they have all been inserted). A similar obturator suspension of the elevated protrusion of the vagina and its overlying endopelvic fascia is achieved on the opposite side. Some additional elevation of the lateral anchorage of the VOS by the inclusion of a bite of the iliopectineal ligament within the suture bite approximating the vagina to the obturator muscle (like a Burch procedure) may be used to reinforce the repair (Shull and Baden, 1989). This modification is one the author favors and represents a hybrid with the Burch procedure, facilitating reattachment of the pubocervical fascia to the arcus tendineus fasciae pelvis, tissue apposition to the lateral pelvic wall, and nonobstructive elevation of the urethra and urethrovesical junction. In addition, obliteration of the pouch of Douglas (culdoplasty) may be needed to prevent enterocele (Shull and Baden, 1989; Turner-Warwick and Kirby, 1993).

Results

There are limited data available for the VOS repair, which has had reported cure rates of 60% to 86%, depending on whether the procedure was performed primarily or secondarily (Turner-Warwick, 1986; German et al, 1994). German and colleagues (1994) reported that the VOS procedure is less likely to be successful in those patients who had undergone previous surgery.

Ultimately, as with all such reconstructive surgery, the surgeon should select the correct procedure for the individual patient. Although the VOS, which is a synthesis of the principles of the paravaginal repair and the Burch colposuspension, is of interest, further clinical results are necessary before definitive conclusions can be drawn.

LAPAROSCOPIC RETROPUBIC SUSPENSION

Laparoscopic techniques for retropubic suspension were introduced by Vancaillie and Schuessler in 1991. They essentially performed an MMK urethropexy laparoscopically and, since that time, laparoscopic techniques have been applied to both the Burch procedure and the paravaginal repair. Subsequent modifications to the suspension suturing techniques have been introduced, including the use of mesh (Ou et al, 1993), staples (Lyons, 1994), and fibrin sealant (Kiilholma et al, 1995), but all adhere to the same principles of their open counterparts. Proposed advantages to the laparoscopic approach include improved intraoperative visualization, less postoperative pain, shorter hospitalization, and quicker recovery times (Liu, 1993). Disadvantages include greater technical difficulty with resultant longer operating times and higher operating costs (Paraiso et al, 1999).

The procedure may be performed extraperitoneally or transperitoneally, and each approach has its proponents. Although the extraperitoneal technique may be associated with shorter operating times, easier dissection, and fewer bladder injuries (Frankel and Kantipong, 1993; Raboy et al, 1995), the transperitoneal approach provides a larger operating space and the ability to perform concomitant intraperitoneal procedures and apical prolapse repair (Paraiso et al, 1999). The specifics of the different procedures are beyond the scope of this chapter.

Short- and medium-term outcomes with the laparoscopic retropubic suspensions have become available. In their review of 13 studies of laparoscopic retropubic suspensions, Paraiso and colleagues (1999) found cure rates to range from 69% to 100% with follow-up of 1 to 36 months. This is comparable to outcomes of the open procedures as already noted. Both retrospective (Polascik et al, 1995) and randomized, prospective comparisons (Summitt et al, 2000) between open and laparoscopic techniques have demonstrated similar short-term success. However, with longer follow-up, laparoscopic retropubic suspensions appear to fail more frequently. McDougall's group (1999) retrospectively noted only 30% cure of SUI and 50% cure or improvement by a laparoscopic Burch procedure with 45 months of follow-up, and this was no different from the results with a Raz procedure.

Five trials summarized in a Cochrane review have compared laparoscopic with open colposuspension (Burton, 1997, 1999; Su et al, 1997; Carey et al, 2000; Summitt et al, 2000; Fatthy et al, 2001; Moehrer et al, 2002). All had different lengths of follow-up: 6 months (Carey et al, 2000); 1 year (Su et al, 1997; Summitt et al, 2000); 6 and 18 months (Fatthy et al, 2001); and 6 months, 1 year, 3 years, and 5 years (Burton, 1997, 1999). Outcome data for 6 months to 18 months were therefore available for all studies. Longer-term data are currently available only for Burton's study. The ability to synthesize data was also limited by the variable tests and definitions used to measure subjective and objective outcomes across the trials (Moehrer et al, 2003). Moehrer and colleagues, in their meta-analysis, noted that a total of 233 women received a laparoscopic and 254 women an open colposuspension, and the confidence intervals are generally all wide as a consequence. Four trials comparing laparoscopic with open colposuspension were otherwise of good quality (Burton, 1997, 1999; Carey et al, 2000; Summitt et al, 2000; Fatthy et al, 2001). Burton's study had the potentially confounding factors of use of absorbable sutures and of the surgeons having performed only a relatively small number of laparoscopic colposuspensions (<20) before beginning the trial. These factors may have influenced his results, in particular since there is believed to be a definite albeit relatively steep learning curve associated with laparoscopic colposuspensions. The fifth trial had methodologic problems with corrupted randomization and confounding factors of performance of additional surgery in some patients and the use of a different number of sutures for laparoscopic (one suture) and open (three sutures) colposuspension (Su et al, 1997). The number of sutures used appears to have a significant influence on the cure rate, with more sutures resulting in a significantly higher success rate. Persson and Wolner-Hanssen (2000) compared different numbers of paravaginal sutures and found a significantly higher objective 1-year cure rate (dry on "ultrashort" pad test) for women randomized to two sutures compared with one suture, with a cure rate of 83% for two sutures and 58% for one suture. Only one trial currently has data beyond 18 months of follow-up (Burton, 1997, 1999). This suggested poorer long-term results after laparoscopic surgery. This finding should be interpreted cautiously, however, because there are concerns that the surgeon's laparoscopic performance may have been suboptimal because he had performed few laparoscopic colposuspensions when the trial started. Data from other larger trials with

multiple operators are now needed to assess whether this is a real effect. All the other trials had data up to a maximum of 18 months. These show some inconsistencies. Outcome assessed by the women participating (arguably the most important outcome) appeared equally good in the two groups. Urodynamic investigations were used to assess cure objectively in all five studies. Overall, there was a significantly higher success rate after open colposuspension (RR, 0.89; 95% CI, 0.82 to 0.98) equivalent to an absolute difference of an additional 9% risk of failure after laparoscopic surgery. No significant differences between the two groups were observed for postoperative urgency, voiding dysfunction, or de novo detrusor overactivity. A trend was shown toward a higher complication rate, less postoperative pain, shorter hospital stay, and more rapid return to normal function for laparoscopic colposuspension. The operating time tended to be longer, the intraoperative blood loss less, and the duration of catheterization shorter for laparoscopic compared with open colposuspension (Moehrer et al, 2003).

In a previous review of laparoscopic colposuspension, Paraiso and colleagues (1999) noted major intraoperative and short-term complications in up to 25% of cases, with bladder injury being the most common complication and declining with experience; ureteric injury has also been reported (Aslan and Woo, 1997). The use of mesh and tacks or staples may be complicated by foreign body erosion (Arunkalaivanan and Arunkalaivanan, 2002; Kenton et al, 2002), and in a randomized study (Ankardal et al, 2004) it was reported that the use of sutures was superior to the laparoscopic mesh and staple technique.

A previous Cochrane review (Moehrer et al, 2002) was dependent on small trials, recruiting a total of 487 women between them, with mostly only medium-term follow-up data (18 months) and limited evidence from other small studies and concluded that laparoscopic colposuspension had the benefit of a more rapid recovery but might have a higher complication rate and be more expensive and possibly less effective in the long term than open colposuspension. This highlighted the need for further well-designed clinical studies.

Carey and colleagues (2006) have reported a randomized trial that recruited 200 women during 1997 and 1998, with 2-year follow-up available for 83% of participants and longer-term subjective data from a similar proportion. The primary outcome measure was objective cure (absence of urodynamic stress incontinence) at 6 months, powered to detect a difference of 20% between the two study arms. Secondary measures included patient satisfaction, quality of life and general well-being, and complications. In the same year Kitchener and coworkers (2006) reported the results of the COLPO trial, which recruited 291 women between 1999 and 2001, with a 2-year follow-up rate of more than 80%. The primary outcomes were objective (dry pad test) and subjective (symptom report) cure at 24 months. Secondary outcomes included recovery time, complications, and a formal cost-benefit analysis. The trial was powered to show noninferiority of laparoscopic colposuspension to open colposuspension, assuming a cure rate of 80% for the open procedure. Both studies were well designed, well conducted, and clearly reported.

Carey and coworkers found no difference in urodynamic cure rate, incidence of detrusor overactivity, or patient satisfaction at 6 months, with an overall objective cure rate of 75%. Detrusor overactivity occurred in 12% of women; 66% of women were urodynamically "normal." If the raw data are converted to percentage scores, there was 89% satisfaction with the treatment outcomes and 88% satisfaction with the care received. The overall satisfaction was 87%. At 24 months after surgery there were no significant differences between the two treatment groups with respect to reporting SUI, urgency, and urgency incontinence and a satisfaction score of greater than or equal to 80. Across both treatment groups, by 24 months after surgery, 66% of women reported no SUI, 38% reported no urgency, 47% reported no urgency incontinence, and 64% reported a satisfaction score of greater than or equal to 80. Although follow-up information was only available on approximately 80% of all subjects by 24 months, a sensitivity analysis was performed assuming that all women who did not complete the 24-month follow-up had either occasional or frequent SUI. With these assumptions, cure rates decreased to 61% for open colposuspension and 50% for laparoscopic colposuspension. There was no significant difference between the two groups treatment groups, even when adjusted for surgeon experience (P = .08). The study population was contacted by telephone for further follow-up at a mean of 3.7 years (range 3 to 5 years) after surgery. This follow-up was undertaken at a single point in time. A total of 164 women were contacted, 88 of whom underwent open colposuspension and 76 of whom underwent laparoscopic colposuspension. There were no significant differences between the two treatment groups at 3 to 5 years after surgery and the findings were similar to the 24-month data. Mean operating time was approximately twice as long for laparoscopic colposuspension, but surgeon's estimates of blood loss and patient's estimates of immediate postoperative pain at rest were significantly less after the laparoscopic procedure with a return to normal activities, on average, 5 days earlier (P = .01).

Kitchener and colleagues also found no difference in the objective cure rate (79% for laparoscopic vs. 70% for open) or subjective cure rate (55% vs. 54%) between the study arms, again showing the now well-recognized mismatch between objective and subjective outcomes. The intention-to-treat analysis indicated no significant difference in cure rates between open and laparoscopic surgery. The study was slightly underpowered based on the sample size calculations, but the analyses clearly demonstrated that laparoscopic colposuspension is not inferior to open colposuspension. The complication rate was low in both arms, with more bowel and bladder injuries in the laparoscopic arm and more wound infections in the open arm. Each demonstrated comparable improvements in generic quality-of-life scores. Other points of note include the careful selection of surgeons who had experience of both open and laparoscopic surgery and interestingly as contrasted to the Carey study contrary to the previously held beliefs of laparoscopic surgery is that it would be associated with longer operating times, less postoperative pain, and shorter hospital stay. For hospital stay there was only a small advantage for laparoscopic surgery, with a median stay of 5 days compared with 6 days for open surgery. The operating times were fairly similar in terms of "knife to skin" to completion of surgery, there being a median time of 65 and 51 minutes for laparoscopic and open surgery, respectively, but postoperative pain was significantly less in the laparoscopic surgery group. But there were no differences in time of return to work identified in this study. Complications of surgery were low generally, with a higher bladder injury rates in the laparoscopic procedure and a higher wound infection with open surgery as would be expected. The impact of these differences was analyzed in a cost-benefit analysis accompanying this study that suggested that a greater quality-adjusted life year total is achieved in the laparoscopic arm at both 6 and 24 months, suggesting that laparoscopic surgery may confer an additional benefit of well-being (Manca et al, 2006). But the additional costs of laparoscopic surgery were only recouped after 24 months of follow-up, thus highlighting the need to address long-term outcomes in any surgical study.

The last major publication in this field was a meta-analysis of all of the comparative studies published between 1995 and 2006 of laparoscopic versus open colposuspension (Tan et al, 2007). End points evaluated were operative outcomes and subjective/objective cure. A random-effect model was used and sensitivity analysis performed to account for bias in patient selection. Sixteen studies matched the selection criteria, reporting on 1807 patients, of whom 861 (47.6%) underwent laparoscopic and 946 (52.4%) underwent open colposuspension. Length of hospital stay and return to normal life were significantly reduced after laparoscopic surgery. These findings remained consistent on sensitivity analysis. Bladder injuries occurred more often in the laparoscopic group, but only with marginal statistical significance. Comparable bladder injury rates were found when studies were matched for quality, year, and randomized trials. Cure rates were similar between the two procedures at 2 years follow-up.

The current evidence would suggest that in adequately experienced hands there is no difference in overall safety and efficacy between laparoscopic and open colposuspension. Clearly another concern is how generalizable the data are on laparoscopic colposuspension because the majority of reported studies are from expert laparoscopists or surgeons working in specialized units. The evidence base on both laparoscopic and open colposuspension is limited by relatively short-term follow-up (robust data are needed out to 5 years) and the tendency toward small numbers, and poor methodology limits the interpretation of most studies with the exception of those reported by Carey and coworkers (2006) and Kitchener and colleagues (2006). Laparoscopic colposuspension shows comparable subjective outcome, but poorer objective outcome than both open colposuspension and tension-free vaginal tape procedure in the short to medium term; longer term outcomes are unknown (level 2). It may not be good value for money when compared with open colposuspension in the short term (i.e., first 6 months after surgery), but it could be a cost-effective alternative over 24 months (level 1); other comparisons, however, suggest that minimally invasive midurethral tape procedures may be dominant in health economic terms.

Recommendations from the ICI committee (Smith et al, 2009) **include the following:**

- **Laparoscopic colposuspension is not recommended for the routine surgical treatment of SUI in women (grade A).**
- **Laparoscopic colposuspension might be considered for the treatment of SUI in women who also require concurrent laparoscopic surgery for other reasons (grade D).**
- **Laparoscopic colposuspension should be performed only by surgeons with specific training, expertise, and appropriate workload in laparoscopic surgery and in the assessment and management of urinary incontinence in women (grade D).**

COMPLICATIONS OF RETROPUBIC REPAIRS

As with any major abdominal or pelvic surgical procedure, intraoperative and perioperative complications that may occur after a retropubic suspension include bleeding, injury to genitourinary organs (bladder, urethra, ureter), pulmonary atelectasis and infection, wound infection or dehiscence, abscess formation, and venous thrombosis or embolism. Other common complications more specific to retropubic suspension procedures include postoperative voiding difficulty, detrusor overactivity, and vaginal prolapse. Potentially, it is overcorrection of the urethrovesical angle that may be a major contributory factor in the development of the long-term complications of de novo urgency, voiding dysfunction, and enterocele formation.

Nevertheless, the reported incidence of these problems is relatively low. In their meta-analysis, Leach and associates (1997) noted a 3% to 8% transfusion rate for retropubic suspensions and no significant difference in the overall medical and surgical complication rates between retropubic suspensions, needle suspensions, anterior colporrhaphy, and pubovaginal slings. Mainprize and Drutz (1988), in their review of the MMK procedure literature (2712 patients), noted an overall complication rate of 21%, with wound complications and urinary infections making up the majority (5.5% and 3.9%, respectively). Direct surgical injury to the urinary tract occurred in only 1.6%, and genitourinary tract fistulas occurred in 0.3%. Ureteral obstruction has been reported rarely after Burch colposuspension, and it usually results from ureteral kinking after elevation of the vagina and bladder base, although direct suture ligation of the ureter can occur (Applegate et al, 1987). If it is identified intraoperatively, it is best remedied by removal of the offending ligature and temporary placement of a ureteral stent. The so-called post-colposuspension syndrome, which has been described as pain in one or both groins at the site of suspension, has been noted in up to 12% of patients after a Burch procedure (Galloway et al, 1987). More recently, Demirci and colleagues (2001, 2002) reported the occurrence of groin or suprapubic pain in 15 of 220 women (6.8%) after Burch colposuspension with a follow-up of 4.5 years.

Postoperative Voiding Difficulty

Postoperative voiding difficulty after any type of retropubic suspension is not uncommon, and undoubtedly its occurrence is more likely if there is preexisting detrusor dysfunction or denervation resulting from extensive perivesical dissection. In most cases, however, it is the result of overcorrection of the urethral axis from inappropriately placed or excessively tightened sutures. If the sutures are placed too medially, they may also transfix the urethra or distort it.

Preoperatively, at-risk patients may be identified by their history of prior voiding dysfunction or episodes of urinary retention. These women should be carefully counseled preoperatively about the potential for postoperative voiding difficulty and the possible need for self-catheterization intermittently. Their incontinence should be of sufficient magnitude that its correction offsets the risk of the need for self-catheterization.

Women with postcystourethropexy voiding problems who have obstruction often do not exhibit the classic urodynamic features of obstruction. However, the history of postoperative voiding symptoms and associated new-onset bladder storage symptoms and a finding of a retropubically angulated and fixed urethra generally indicate that obstruction does exist (Carr and Webster, 1997). In such cases, revision of the retropubic suspension by releasing the urethra into a more anatomic position resolves voiding symptoms in up to 90% of cases (Webster and Kreder, 1990; Nitti and Raz, 1994; Carr and Webster, 1997).

The meta-analysis by Leach and coworkers (1997) **noted that the risk of temporary urinary retention lasting more than 4 weeks postoperatively is 5% for all retropubic suspensions, and the risk for permanent retention is estimated to be less than 5%. These risks are not**

significantly different from those for needle suspensions or pubovaginal slings. Mainprize and Drutz's review of the literature (1988) yielded a 3.6% incidence of postoperative voiding problems after an MMK procedure, whereas the Burch procedure literature reports an incidence of postoperative voiding disorders ranging from 3% to 32% (Hilton and Stanton, 1983; Galloway et al, 1987; Eriksen et al, 1990; Alcalay et al, 1995; Colombo et al, 1996a). In more recent literature, voiding dysfunction may be persistent, as noted in 3.5% of a series of 310 women with a mean follow-up of 36 months (Viereck et al, 2004). Nonpersistent voiding dysfunction has been reported in 12.5% (6% to 37.2%) after primary surgery (Smith et al, 2005). After colposuspension conducted as a secondary procedure, Bidmead and associates (2001) reported voiding difficulties requiring intermittent self-catheterization in 6% of cases.

Because the paravaginal repair aims to restore normal anatomy there is theoretically little chance of overcorrection of the urethral axis, which should translate into a lower risk of postoperative obstruction. In Richardson and coworkers' study (1981), 80% of patients were able to void immediately after paravaginal repair, and "all patients had satisfactory bladder function at the time of discharge." However, temporary voiding difficulty has been noted in up to 17% of patients after a VOS procedure (German et al, 1994), and chronic (>2 years) voiding difficulty has been noted in up to 11% of patients after the paravaginal repair (Colombo et al, 1996a).

All patients should be counseled before surgery about the potential need for intermittent self-catheterization.

Bladder Overactivity

Bladder overactivity commonly accompanies anatomic SUI, and its incidence preoperatively has been reported to be as high as 30% in patients undergoing either first correction or repeated operations (McGuire, 1981). **Provided it is considered as a diagnosis, urodynamic evaluation is performed to show whether detrusor overactivity is present, an attempt at treatment of the related overactive bladder symptoms has been made (with or without success), and the patient has been advised that the presence of detrusor overactivity will increase the risk of continuing storage symptoms postoperatively, then preoperative bladder overactivity does not contraindicate a retropubic suspension procedure, provided that anatomic SUI has also been demonstrated.** In the majority of cases, the bladder overactivity symptoms resolve after surgical repair (McGuire, 1988). Leach and coworkers' meta-analysis (1997) found the risk of urgency after a retropubic suspension to be 66% if urgency and detrusor overactivity were present preoperatively, 36% if there was urgency but no documented overactivity preoperatively, and only 11% if there was neither urgency nor overactivity preoperatively. There was no significant difference in the incidence of postoperative urgency between retropubic suspensions, needle suspensions, and pubovaginal slings. Postoperative urgency was noted in only 0.9% of MMK procedures in Mainprize and Drutz's meta-analysis of 15 series (1988), although Parnell and associates (1982) reported that 28.5% of their patients developed postoperative storage symptoms. Jarvis's meta-analysis (1994b) of Burch procedures found the incidence of de novo bladder overactivity to be 3.4% to 18%. More recently, Smith and colleagues (2005) quoted a figure for postoperative detrusor overactivity of 6.6% for colposuspension (range, 1.0% to 16.6%), whereas the incidence of postoperative urgency or of urgency incontinence after the paravaginal/VOS repair has been reported to be 0% to 6% (Shull and Baden, 1989; German et al, 1994; Colombo et al, 1996a).

For those patients in whom postoperative storage symptoms persist, proven to be associated with detrusor overactivity and intractable to management with anticholinergic therapy and behavioral modification, surgical techniques including intravesical botulinum toxin therapy, neuromodulation, augmentation cystoplasty, or detrusor myectomy may be indicated.

Bladder storage symptoms arising de novo after retropubic suspension may be associated with bladder outlet obstruction. This premise is supported by the frequent coexistence of these symptoms with impaired voiding after suspension procedures and confirmed by the finding that urethrolysis, by freeing the urethra from an obstructed position, often resolves both storage and voiding symptoms (Raz, 1981; Webster and Kreder, 1990).

Vaginal Prolapse

Retropubic suspensions alter vaginal and bladder base anatomy, and thus postoperative vaginal prolapse is a potential complication. Genitourinary prolapse has been reported as a sequel to Burch colposuspension in 22.1% of women (range, 9.5% to 38.2%) by Smith and colleagues (2005) in their review of the literature. **The Burch colposuspension, because of lateral vaginal elevation, may aggravate posterior vaginal wall weakness, predisposing to enterocele.** The incidence varies between 3% and 17% (Burch, 1961, 1968; Galloway et al, 1987; Wiskind et al, 1992); **because of this, prophylactic obliteration of the cul-de-sac of Douglas is sometimes considered in performing retropubic suspensions** (Shull and Baden, 1989; Turner-Warwick and Kirby, 1993). However, simultaneous hysterectomy is not recommended prophylactically because it does not enhance the outcome of a retropubic suspension and should be performed only if there is concomitant uterine disease (Milani et al, 1985; Langer et al, 1988). Although the Burch colposuspension and paravaginal/VOS repair both correct lateral defect cystourethroceles, recurrent cystourethroceles were noted in 11% and 39% of Burch colposuspensions and paravaginal repairs, respectively (Colombo et al, 1996a). In Mainprize and Drutz's review (1988), postoperative cystocele was noted in only 0.4% of patients after an MMK procedure.

Wiskind and coworkers (1992) noted that 27% of patients who had undergone a Burch colposuspension developed prolapse requiring surgery: rectocele in 22%, enterocele in 11%, uterine prolapse in 13%, and cystocele in 2%. More recently, it has been suggested that most women are asymptomatic, and less than 5% have been reported to request further surgery (Smith et al, 2005). Ward and Hilton (2004) reported that 4.8% of women needed a posterior repair, whereas Kwon and associates (2003) reported that 4.7% required subsequent pelvic reconstruction.

Auwad and colleagues (2006) have reported the findings of the first prospective study to determine the prevalence of pelvic organ prolapse (POP) after colposuspension and to investigate possible preoperative and operative risk factors. Seventy-seven women who underwent colposuspension between 1996 and 1997 were investigated. POP was assessed before colposuspension using the pelvic organ prolapse quantification (POP-Q) system (Bump et al, 1988). Women were reassessed at 1 and at 7 to 8 years (or when referred with symptomatic POP). By 7 to 8 years, of the 77 women, 29 (38%) had developed symptomatic prolapse, 29 (38%)

had asymptomatic prolapse, 7 (9%) had no symptoms and no prolapse, and 12 (15%) could not be assessed. POP at 1 year was significantly associated with the presence of posterior vaginal descent before colposuspension (odds ratio 3.07, 95% CI 1.10 to 8.60, $P = .03$). No potentially predisposing variable reached statistical significance by 8 years after colposuspension. The results add support to the view that there is an association between colposuspension and the development of symptomatic POP (requiring surgery).

Because retropubic suspensions are unable to correct central defect cystoceles, patients must be carefully examined preoperatively to exclude their presence and must be counseled if undergoing a colposuspension of the high risk of needing further surgery in the long term. Particularly those in whom a weakness of the posterior compartment is identified preoperatively and with a past history of hysterectomy might be at increased risk.

COMPARISONS BETWEEN INCONTINENCE PROCEDURES

Retropubic Repair versus Needle Suspension and Anterior Repair

Three articles that reviewed the literature on incontinence procedures all found retropubic suspensions to be more effective than either needle suspensions or anterior colporrhaphies (Jarvis, 1994b; Black and Downs, 1996; Leach et al, 1997). Cure rates were approximately 85% for the retropubic suspensions compared with 50% to 70% for the needle suspensions and anterior colporrhaphies. Results were more durable for the retropubic suspensions and better if the procedure was primary.

Overall therefore there is now high-level evidence that indicates that needle suspension procedures are as effective as anterior colporrhaphy but less effective than colposuspension even in the short-term (level 1). Long-term studies indicate lack of longevity even of the initial modest results; long-term complications remain a concern (level 3) (Smith et al, 2009).

The recommendation from the ICI committee (Smith et al, 2009) **is that endoscopic and nonendoscopic bladder neck needle suspension procedures, with and without bone anchors, are not recommended for the treatment of SUI (grade A).**

Retropubic Repair versus Pubovaginal Sling

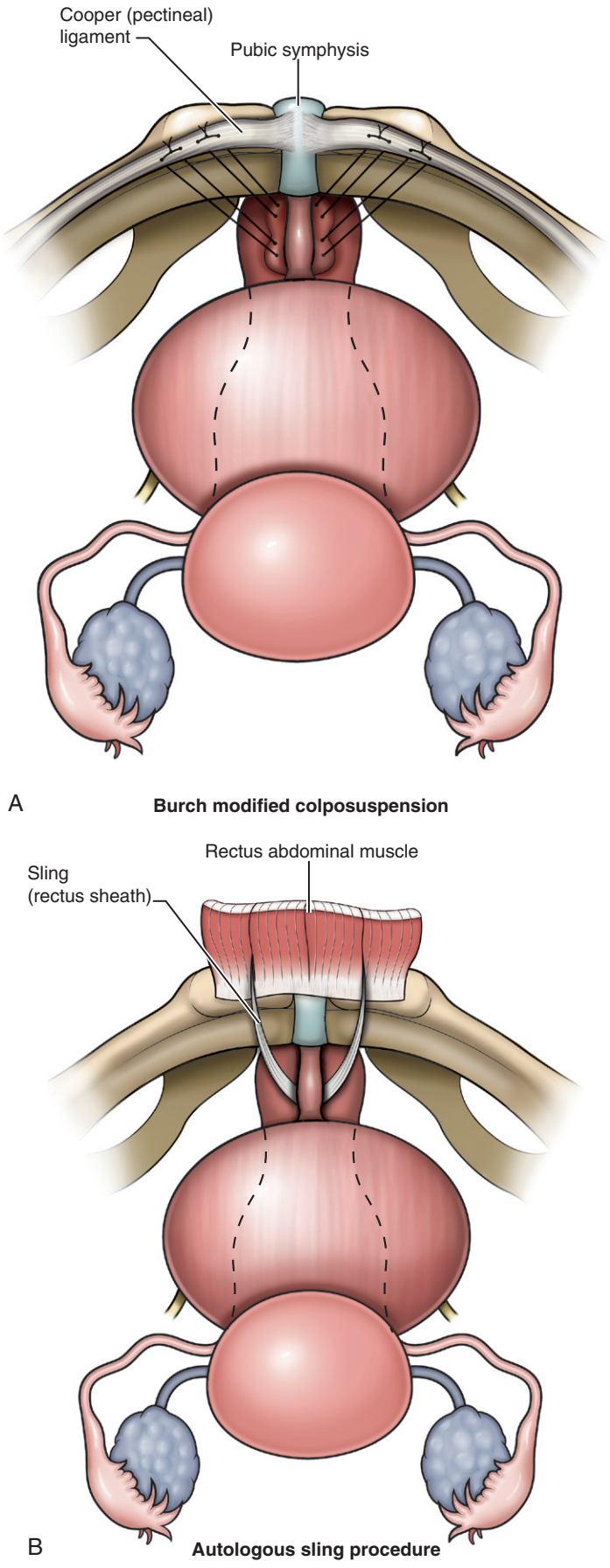
Most studies in the historical literature have not demonstrated a significant difference in cure rates between retropubic suspensions (generally a Burch colposuspension) and pubovaginal slings (Jarvis, 1994b; Black and Downs, 1996; Leach et al, 1997). However, often, selection bias exists in that the pubovaginal sling is generally reserved for patients with multiple prior failed incontinence procedures and with less prolapse, and the presence of presumed intrinsic sphincter deficiency (a fixed urethra with periurethral fibrosis) is often used in clinical practice as a contraindication to a retropubic suspension. In an interesting randomized study in patients with a prior failed incontinence procedure (anterior repair) but without a low-pressure urethra (i.e., MUCP > 20 cm H_2O), Enzelsberger's group (1996) found no significant difference in cure (subjective or objective) at 32 to 48 months between the Burch colposuspension and the Lyodura sling. However, they noted significantly more postoperative voiding difficulty with the pubovaginal sling (13% vs. 3%) and more vaginal prolapse (enterocele or rectocele) with the Burch colposuspension (13% vs. 3%).

A recent high-quality multicenter randomized clinical trial in women with stress incontinence compared the Burch colposuspension with a pubovaginal sling using autologous rectus fascia (Aldo et al, 2007). Women were eligible for the study if they had predominant symptoms associated with the condition, a positive stress test, and urethral hypermobility. The primary outcomes were success in terms of overall urinary incontinence measures, which required a negative pad test, no urinary incontinence (as recorded in a 3-day diary), a negative cough and Valsalva stress test, no self-reported symptoms, no re-treatment for the condition, and success in terms of specific measures of stress incontinence as well as an assessment of postoperative urgency incontinence, voiding dysfunction, and adverse events. A noteworthy aspect of the study was the careful approach to standardization (using the recommendations from the standardization committees of the ICI with regard to clinical terms, urodynamic nomenclature, and methods of evaluation of patients across all sites. Key elements of the two surgical procedures were standardized among all participating surgeons and included the use of preoperative antibiotics, skin-incision length, number and type of Burch sutures, fascial-sling length and width, and cystoscopic evaluation of the bladder. A criticism that can be leveled at the study is the choice of technique for the Burch colposuspension with very medial paraurethral sutures. The techniques utilized are demonstrated in Figure 71–7.

Because these procedures are frequently performed in conjunction with surgery for pelvic prolapse, abdominal and vaginal approaches for both pelvic prolapse repair and hysterectomy were permitted; however, surgeons were required to declare before randomization which concomitant procedures would be performed.

A total of 655 women were randomly assigned to study groups: 326 to undergo the sling procedure and 329 to undergo the Burch procedure; 520 women (79%) completed the outcome assessment. At 24 months, success rates were higher for women who underwent the sling procedure than for those who underwent the Burch procedure, for both the overall category of success (47% vs. 38%, $P = .01$) and the category specific to stress incontinence (66% vs. 49%, $P < .001$). There was no significant difference between the sling and Burch groups in the percentage of patients who had serious adverse events (13% and 10%, respectively; $P = .20$). However, more women who underwent the sling procedure had adverse events than in the Burch group, with 415 events among 206 women in the sling group as compared with 305 events among 156 women in the Burch group. This difference was due primarily to urinary tract infections; 157 women in the sling group (48%) had 305 events and 105 women in the Burch group (32%) had 203 events. When urinary tract infections were excluded, the rates of adverse events were similar in the two groups.

The distribution of time to return to normal voiding differed significantly between the two groups ($P < .001$). Voiding dysfunction was more common in the sling group than in the Burch group (14% vs. 2%, $P < .001$). Consequently, surgical procedures to reduce voiding symptoms or improve urinary retention were performed exclusively in the sling group, in which 19 patients underwent 20 such procedures (63% vs. 47%, $P < .001$). Treatment



satisfaction rates for the 480 subjects who answered the satisfaction question at 24 months were significantly higher in the sling group than in the Burch group (86% vs. 78%, $P = .02$).

A further analysis of this study focused on sexual activity as assessed by the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) among those sexually active at baseline and 2 years after surgery (Brubaker et al, 2009). This report demonstrated that sexual function improves after successful surgery and does not differ between the Burch and sling operations.

It therefore can be reliably concluded that in specialist centers working in a standardized fashion, the autologous fascial sling results in a higher rate of successful treatment of stress incontinence but also greater morbidity than the Burch colposuspension.

Burch Colposuspension versus Marshall-Marchetti-Krantz Procedure versus Paravaginal Repair

Comparisons between the MMK and the Burch procedures have generally yielded similar results. Jarvis, in his meta-analysis of the literature (1994b), noted that overall continence rates were 89.6% and 83.9% for the MMK and the Burch procedures, respectively. When he looked at the effect of prior incontinence surgery, the continence rates were 92.1% and 94% when there was no prior surgery and 84.5% and 84% when there was a history of prior incontinence surgery for the MMK and Burch procedures, respectively. Similarly, Black and Downs (1996), in reviewing five studies (one randomized) that directly compared the MMK procedure with the Burch procedure, found that there was no significant difference in cure rates between the two procedures, although the Burch procedure generally yielded better results. However, they pointed out that overall the studies were of poor quality with small sample sizes.

Two randomized studies that assessed urethral sphincteric function by urethral pressure profilometry had conflicting results. Quadri's group (1999) compared the MMK procedure with the Burch procedure in women with a hypermobile, low-pressure urethra (MUCP ≤ 20 cm H_2O) and noted significantly higher subjective and objective 1-year cure rates with the MMK procedure. They used urethroscopy to facilitate MMK suture placement. On the other hand, Colombo's group (1994) excluded women with a low-pressure urethra (MUCP < 30 cm H_2O) and performed a cystotomy to facilitate MMK suture placement. With 2- to 7-year follow-up (mean, 3 years), they noted higher subjective and objective cure rates with the Burch procedure, although these were not statistically significant. In addition, significantly more MMK patients had persistent postoperative voiding difficulties (28% vs. 8%).

Figure 71–7. **A,** In the Burch colposuspension, sutures are placed in the anterior vaginal wall at the level of the bladder neck and proximal urethra and sutured to the iliopectineal ligament. **B,** In the autologous sling procedure a strip of rectus fascia is harvested and permanent sutures placed at both ends. The sling is positioned beneath the urethra via a vaginal incision. The two ends of the sling are then secured to the anterior abdominal wall, either together or to the rectus fascia. (Modified from Aldo ME, Richter HE, Brubaker L, et al. Burch colposuspension versus fascial sling to reduce urinary stress incontinence. N Engl J Med 2007;356:2143–55.)

The literature on the paravaginal repair is sparse. The only randomized study that compared the Burch procedure with a paravaginal repair found significantly greater subjective and objective cure with the Burch procedure (Colombo et al, 1996a). Until large, randomized studies with prolonged follow-up are available, the issue of which is the best procedure will remain unresolved.

Tension-Free Vaginal Tape Procedure versus Colposuspension

Since its introduction in 1996 by Ulmsten and colleagues, the tension-free vaginal tape (TVT) procedure has gained widespread acceptance for treatment of SUI, given its low morbidity, short-term success rates, and ability to be performed as an outpatient procedure under local or regional anesthesia. The 7-year objective and subjective success rate for TVT is 81% (Nilsson et al, 2004). More recently in reviewing this series, 77% of the initial cohort of 90 women and 89% of those alive and capable of cooperating were assessed 11.5 years after the TVT operation. Ninety percent of the women had both a negative stress test and a negative pad test and were considered to be objectively cured. Subjective cure by patients' global impression was found in 77%, 20% being improved and only 3% regarding the operation as a failure. No late-onset adverse effects of the operation were found, and no case of tape erosion was seen (Nilsson et al, 2008).

There have been a number of well-designed, prospective, randomized trials comparing the Burch colposuspension (two open and two laparoscopic) with TVT.

Liapis and coworkers (2002) reported a prospective randomized comparative study of Burch colposuspension (n = 35) and TVT (n = 36). They concluded that at 2-year follow-up the TVT and Burch procedures were equally effective with an objective pad test cure rate of 84% and 86%, respectively. TVT had a shorter operative time and entailed less postoperative pain with a faster return to normal activity.

Ward and Hilton (2004) published a 2-year follow-up of their landmark prospective randomized trial comparing TVT and open Burch colposuspension. At 2 years, 74% of the initial TVT and 69% of the open colposuspension patients completed the evaluation. The objective cure rates for the TVT (81%) and colposuspension (80%) were not significantly different. However, if the missing patients were evaluated by the last observation carried forward analysis, the cure rates would favor TVT (78% vs. 68%). It is interesting that the subjective cure rates differ from the objective rates dramatically, with only 43% and 37% reporting subjective cure of stress incontinence after TVT and colposuspension, respectively. At 2 years the colposuspension group still had significantly lower scores on mental and emotional health. The incidences of enterocele and vault prolapse were higher in the colposuspension group, requiring significantly more prolapse surgery. Likewise, the number of patients still requiring intermittent catheterization was higher in the colposuspension group. The intraoperative complications were higher in the TVT group, whereas the postoperative complications were higher in the colposuspension group. The authors' conclusion at 2 years, because of patients lost to follow-up, is unchanged from their conclusion at 6 months, namely, that TVT may be better than, worse than, or the same as colposuspension.

A Cochrane review of open colposuspension examined a total of seven trials comparing TVT with open colposuspension (Lapitan et al, 2005), although the trial by Ward and Hilton noted earlier dominated the analysis. The review concluded that TVT and open colposuspension were equally effective but that TVT carried an increased risk of complications, particularly bladder perforation. A further cost-benefit analysis based on the Ward and Hilton study showed that TVT was a cost-effective alternative to colposuspension, largely based on shorter hospital stay and rapid return to work (Manca et al, 2003).

In a further report from the Ward and Hilton study, 98 of those who had TVT and 79 of those having colposuspension returned for 5-year follow up; 72 in the TVT group and 49 in the colposuspension group had full subjective and objective data (Ward et al, 2008). The primary outcome in this analysis was a negative 1-hour pad test and this was not significantly different between the two groups, being recorded in 58/72 (81%) women in the TVT group and 44/49 (90%) in the colposuspension group (P = .21, Fisher's exact test) at 5 years. Significantly, more women in the colposuspension group (11 [7.5%]) underwent surgery for prolapse during the follow-up period than those in the TVT group (3 [1.8%]). Tape-related complications were seen in six women. In the first year, one tape was divided for obstructed voiding; there was one suprapubic extrusion and one vaginal erosion. Two further vaginal erosions were detected at 5-year follow-up; and, in addition, one woman was found to have tape within the bladder at cystoscopy after complaining of symptoms of overactive bladder. There were no reported suture-related complications in the colposuspension group.

The effect of both procedures on cure of incontinence and improvement in quality of life appears from this follow-up of a proportion of the originally treated patients to be maintained in the long term out to 5 years (Ward et al, 2008), **with 81% of the women who had undergone TVT and 90% who had undergone colposuspension as satisfied or very satisfied with the results of their surgery at 5 years. The key messages in terms of adverse events are that vault and posterior vaginal wall prolapse are seen more commonly after colposuspension and that late tape erosion may occur several years after surgery.**

Persson and coworkers (2002) were one of the first groups to compare TVT and laparoscopic Burch colposuspension. At 1-year follow-up there was no difference between objective and subjective cure rates. Valpas and associates (2004) conducted a prospective randomized trial comparing TVT and laparoscopic mesh colposuspension at 1-year follow-up. The objective cure rate (negative stress test, 86% vs. 57%), satisfaction, and quality of life were statistically better for the TVT group.

Paraiso and colleagues (2004) prospectively randomized 72 patients into laparoscopic Burch colposuspension and TVT at a mean follow-up of 20 months, but only 17 and 16 patients were available in the laparoscopic and TVT groups, respectively. Whereas objective and subjective cure rates were significantly higher in the TVT group, satisfaction of patients was equal in each group and no difference was reported in voiding dysfunction, urgency, or symptomatic pelvic prolapse. All these laparoscopic studies require longer follow-up with greater power to demonstrate a persistent difference between TVT and Burch colposuspension.

A meta-analysis of the literature has been reported by Novara and colleagues (2007) in which they combined the results of open and laparoscopic colposuspension. To date, nine RCTs compared TVT to Burch colposuspension as primary treatment for SUI (Liapis et al, 2002; Persson et al, 2002; Ward et al, 2002, 2004; Ustun et al, 2003; Paraiso et al, 2004; Valpas et al, 2004; Bai et al, 2005; El-Barky et al, 2005). A further study compared the suprapubic arc sling to laparoscopic Burch colposuspension (Foote et al, 2006). TVT was followed by significantly higher continence rates compared with Burch colposuspension, considering success rates

evaluated according to any definition of continence (OR = 0.58; 95% CI = 0.42 to 0.79; $P = .0007$), presence of negative stress test (OR = 0.38; 95% CI = 0.25 to 0.57; $P < .0001$), and negative pad test (OR = 0.59; 95% CI = 0.41 to 0.85; $P = .005$).

A recent study has contrasted direct health care costs of treatment of SUI in Sweden to four different procedures: (1) open Burch colposuspension (OBC), (2) laparoscopic colposuspension with sutures (LCS), (3) laparoscopic colposuspension with mesh and staples (LCM), and (4) tension-free vaginal tape (TVT) (Ankardal et al, 2007). A model was constructed representing a hospital with standardized surgical equipment, staff, and average unit costs in 2003 euros. The time used for anesthesia and surgery was calculated. Clinical data were collected from three different sources: a multicenter, randomized, prospective study comparing OBC with LCM with 1-year follow-up; a three-armed, prospective study in which women were randomized to either OBC, LCM, or LCS with 1-year follow-up; and a descriptive study reporting results of TVT with 5-year follow-up. Data collected from the studies and hospital cost data were put into the model to create the different cost elements. The total cost per individual, showed a lower cost for TVT compared with the other alternatives. The direct costs for a TVT were only 56% of the costs for an OBC ($P < .001$) and 59% of the costs for an LCS ($P < .001$). Thus, when using a model and comparing health care costs for surgical treatment of female SUI in Sweden, the TVT procedure generated a lower direct cost than both open and laparoscopic colposuspension.

The shift in practice pattern away from Burch colposuspension for the treatment of SUI to midurethral slings as the primary treatment of SUI shows one of the difficulties in conducting surgical randomized controlled trials, especially when the field has changed as quickly as it has in recent years in the treatment of urinary incontinence. A recent survey of urogynecology fellows found that the average third-year fellow had performed 257 midurethral sling procedures and only 13 Burch procedures (LeBrun et al, 2008). It would be interesting to determine if a surgeon's experience with Burch colposuspension is correlated with outcomes. Indeed, the outcomes reported in the existing literature base are likely to be very different to those seen in many clinicians' clinical

Key Points

- Anti-incontinence surgery does not necessarily work by restoring the same mechanism of continence that was present before the onset of incontinence. It works by a compensatory approach.
- The surgeon's preference, coexisting problems, and anatomic features of the patient and her general health condition influence the choice of procedure.
- There is lack of a clear consensus as to which surgical procedure for stress incontinence is most effective, but contemporary practice is shifting to the "loose" urethral sling being the most widely used and having largely replaced the colposuspension.
- A number of variables may influence surgical outcome: age, postoperative activity, medical comorbidity, obesity, duration of symptoms, coexistence of detrusor overactivity, prior surgery, and intrinsic sphincter deficiency.
- There is no consensus on how to differentiate the relative contributions of hypermobility and sphincteric weakness.
- There remains no consensus on how to assess the outcomes of surgery, but this requires careful assessment with adequate follow-up and use of simple objective measures as well as taking particular account of patient-perceived outcomes.
- During short-term follow-up, vaginal and open retropubic suspension procedures have similar success rates. With longer follow-up (and with the exception of the pubovaginal sling), patients who have retropubic procedures fare better.
- With the MMK procedure, placement of sutures through the pubic symphysis incurs the risk of osteitis pubis in 0.9% to 3.2% of patients.
- The Burch colposuspension is as effective as any other procedure in primary or secondary surgery at curing SUI, with proven long-term success. Thus, it should be regarded as the *standard* open retropubic procedure for incontinence.
- Abdominal paravaginal repair is less effective than other forms of colposuspension.
- As with any major abdominal or pelvic surgical procedure, intraoperative and perioperative complications that may occur after a retropubic suspension include bleeding, injury to genitourinary organs (bladder, urethra, ureter), pulmonary atelectasis and infection, wound infection or dehiscence, abscess formation, and venous thrombosis or embolism. Other common complications more specific to retropubic suspension procedures include postoperative voiding difficulty, detrusor overactivity, and vaginal prolapse.
- The risk of temporary urinary retention lasting more than 4 weeks postoperatively is 5% for all retropubic suspensions. The risk of permanent retention is estimated to be less than 5%. These risks are not significantly different from those of needle suspensions or pubovaginal slings.
- All patients should be counseled before surgery about the potential need for intermittent self-catheterization.
- Because retropubic suspensions are unable to correct central defect cystoceles, patients must be carefully examined preoperatively to exclude their presence. The Burch colposuspension, because of lateral vaginal elevation, may aggravate posterior vaginal wall weakness, predisposing to enterocele.
- Retropubic suspensions are more effective than either needle suspensions or anterior colporrhaphies.
- Laparoscopic colposuspension is not recommended as a routine surgical procedure and when performed should only be carried out by a surgeon skilled in laparoscopic surgery.
- Most studies in the literature have not demonstrated a significant difference in cure rates between retropubic suspensions (generally a Burch colposuspension) and pubovaginal slings.
- Comparisons between the MMK procedure and the Burch procedure have generally yielded similar results.
- The literature on the paravaginal repair is sparse. The only randomized study that compared the Burch colposuspension with a paravaginal repair found significantly greater subjective and objective cure rates with the Burch colposuspension.
- At this time, the TVT procedure appears to be at least equivalent to the Burch colposuspension and in general is probably better.

practices in which this has become a rare operation and where many have had very limited experience of performing the procedure during their training over the past decade.

At this time the TVT appears to be an equivalent operation to the open or laparoscopic Burch colposuspension. A recent meta-analysis (Novara et al, 2007) **suggested superiority for the TVT, but this combined open and laparoscopic procedures and studies of variable quality. It is likely that greater reliability should be placed on single high-quality comparative studies** (Ward et al, 2004, 2008). **The TVT has now largely supplanted the colposuspension in contemporary practice. An open colposuspension should still be considered as a surgical option in patients undergoing open surgery and still has a role when there is associated prolapse. The laparoscopic colposuspension has been shown in the short term to have some advantages over open colposuspension in experienced hands but as a procedure has largely been supplanted by the TVT in contemporary practice.**

Acknowledgment

I would like to thank Richard Turner-Warwick for allowing the use of figures from our book in this chapter.

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chapter 72

Vaginal and Abdominal Reconstructive Surgery for Pelvic Organ Prolapse

Jack Christian Winters, MD ● Joanna Maya Togami, MD ● Christopher J. Chermansky, MD

Surgical Anatomy of the Pelvic Floor
Site-Specific Defects by Compartment (Identification)
Preparing the Patient for Prolapse Surgery
Biologic and Synthetic Materials in Prolapse Surgery
Surgical Management of Pelvic Organ Prolapse

Surgical treatment of pelvic organ prolapse (POP) is one of the most challenging problems faced by surgeons who perform procedures to correct disorders of the pelvic floor. The cause is usually multifactorial, and the clinical presentation and the impact on a patient's quality of life may vary considerably. Surgical correction is aimed at addressing defects in the supporting structures, which requires a comprehensive understanding of pelvic floor anatomy and function. Pelvic floor defects have been traditionally named for the prolapsing visceral organs; however, it is important to conceptualize that these disorders have less to do with the prolapsing organs and more to do with compartmental defects in the supportive tissues. Just as any hernia represents a defect in the fascia, POP represents herniations or descensus of the bladder, rectum, bowel, uterus, and urethra through defects in the pelvic floor connective tissues. Procedures must be tailored to the patient's unique presenting factors, such as comorbidities and concomitant pathology of the pelvic floor, as well as patient goals and expectations in surgical restoration of pelvic organ support. The aim of this chapter is to provide a practical overview of the surgical anatomy and discuss the vaginal and open abdominal techniques for the treatment of POP.

Pelvic organ defects occur as compartmental defects of vaginal support. Patients may present with any combination of compartmental defects, and multiple defects are very common. **The aims of surgical management include restoration of normal vaginal anatomy while maintaining visceral and sexual function.** It is critical to understand the patient's goals and expectations of treatment to ensure that the prescribed treatment will meet these goals. This is the art of tailoring the appropriate treatment for each individual surgical patient.

SURGICAL ANATOMY OF THE PELVIC FLOOR

Anatomy

Supporting Structures

Bony Scaffolding. The bones of the pelvis provide the scaffold on which the soft tissue supports (muscles, ligaments, and fascia) are anchored. They include paired innominate or hip bones on either side of the sacrum, which comprise the pelvic girdle. The innominate bones are further divided into the ileum, the ischium, and the pubis. The ischial spine provides attachment for the arcus tendineus fasciae pelvis (ATFP), the sacrospinous ligament, and the coccygeus muscle (Fig. 72–1). The obturator foramen is formed by the superior pubic ramus above, the pubic body and inferior ramus medially, and the anterior border of the ischial body below (Newell, 2005) (Fig. 72–2).

Muscular Supports of the Pelvic Floor. The pelvic floor comprises all of the soft tissues that essentially hold the pelvic viscera in place at the base of the bony pelvis and the levator ani muscle complex. The pelvic floor is a three-dimensional structure that functions as a unit (Hurt, 2000). The pelvic diaphragm is composed of the striated pubococcygeus, iliococcygeus, and coccygeus (Fig. 72–3). The levator ani muscles are composed of the pubococcygeus and iliococcygeus. The coccygeus is also termed the ischiococcygeus and is attached to the lateral margins of the coccyx and fifth sacral segment (Mundy, 2005). It is attached laterally to the ischial spine. The iliococcygeus is attached to the ischial spine, the arcus tendineus levator ani laterally and posteriorly, the tip of

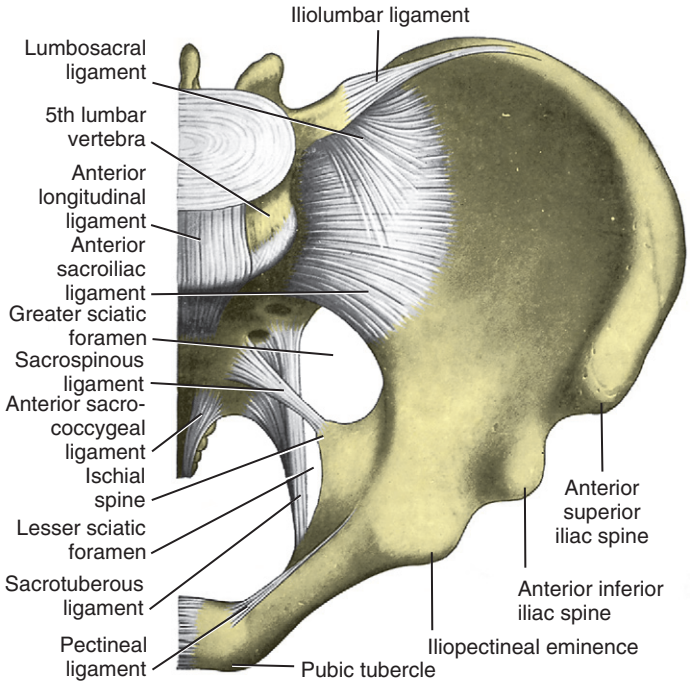


Figure 72–1. Left hemipelvis with ligaments. (From Newell R. Pelvic girdle, gluteal region and hip joint. In: Standring S, editor. Gray's anatomy: the anatomical basis of clinical practice. 39th ed. New York: Elsevier; 2005.)

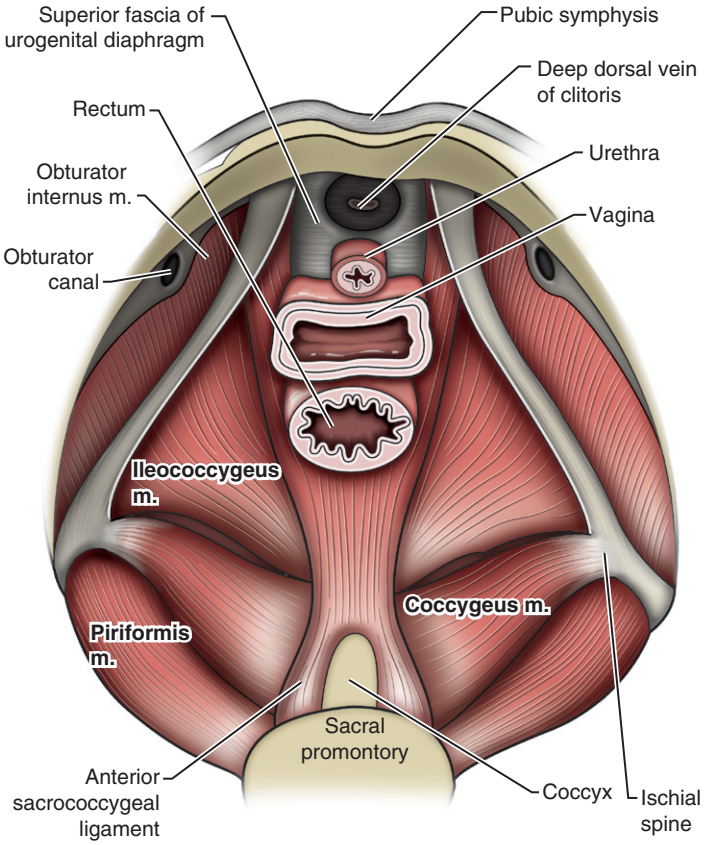


Figure 72–3. Muscles of the female pelvic diaphragm. (From Anderson J, Genadry R. Anatomy and embryology. In: Novak's text of gynecology. 13th ed. Philadelphia: Lippincott Williams & Wilkins; 2002, with permission.)

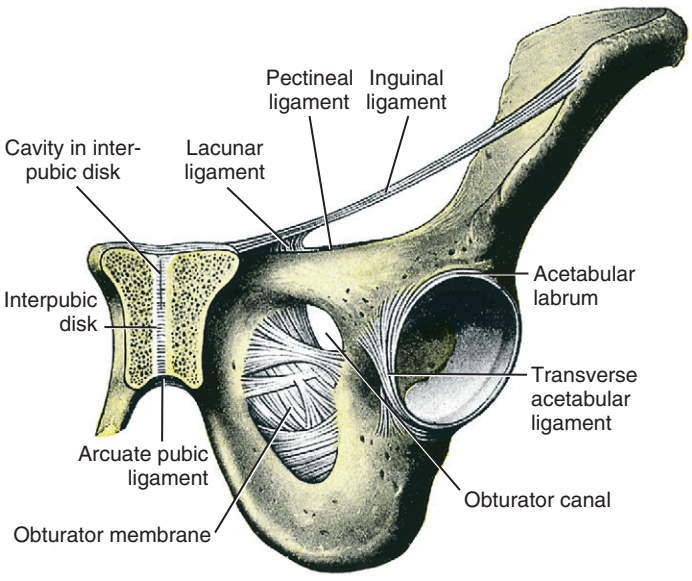


Figure 72–2. Left obturator foramen and membrane. (From Newell R. Pelvic girdle, gluteal region and hip joint. In: Standring S, editor. Gray's anatomy: the anatomical basis of clinical practice. 39th ed. New York: Elsevier; 2005.)

the sacrum, and the coccyx. The pubococcygeus is attached to the back of the pubis, and it courses lateral to the urethra (in males it is the puboure thralis, and in females, because it forms a sling around the vagina, it is the pubovaginalis). In both men and women, fibers of the pubococcygeus attach to the perineal body (Mundy, 2005). The pubococcygeus compresses the visceral canals, which cross the pelvic floor. The puborectalis portion of the pubococcygeus helps to create the anorectal angle. Contraction of the puborectalis causes the rectoanal junction to move toward the pubic symphysis, which is critical in maintaining fecal continence (Rogers, 2003). **Although the muscles are referred to separately, like other structures of the pelvic floor the boundaries are often difficult to delineate and they perform similar physiologic functions** (Mundy, 2005). The posterior levator ani group (iliococcygeus and coccygeus) fuses in the midline and attaches to the coccyx. The complex formed by this fusion is the levator plate, which serves as a supporting structure for the upper vagina and cervix, This serves not only to stabilize the upper vagina in a horizontal plane but also to provide a protective mechanism preventing downward forces onto the perineal body (Wall and Menafee, 2002).

Beneath the pelvic diaphragm is the diamond-shaped urogenital diaphragm (Fig. 72–4). The boundaries are the pubic symphysis anteriorly, the tip of the coccyx posteriorly and laterally, and the ischiopubic rami on either side. It can be further divided anteriorly and posteriorly by imagining a line between each ischial tuberosity. This results in the urogenital triangle anteriorly and the anorectal triangle posteriorly. The deep transversus perinei muscle, also referred to as the perineal membrane, is contained by the urogenital triangle, in which the urethra and vagina traverse. In contrast to the perineal membrane in males, which is a sheetlike structure, the perineal membrane in females is a three-dimensional structure that has two regions, dorsal and ventral (DeLancey, 1999; Stein and DeLancey, 2008) (Fig. 72–5). The dorsal region is attached to the perineal body and the lateral wall of the vagina via the ischiopubic rami. The ventral region is part of a solid

three-dimensional mass that is contiguous with the paraurethral and paravaginal connective tissues. This portion contains the compressor urethrae and urethrovaginal sphincter muscles of the distal urethra (Stein and DeLancey, 2008).

The anorectal triangle contains the external anal sphincter, which attaches to the anococcygeal ligament and fuses to the superficial transverse perinei muscle. External to the urogenital triangle are the external genital muscles, bulbospongiosus, ischiospongiosus, and superficial transversus perinei. The hymen is located just inside the labia minora and is the fixed point of reference recommended by the International Continence Society Committee on Standardisation of Terminology, Subcommittee on Pelvic Organ Prolapse and Pelvic Floor Dysfunction to grade prolapse (Bump et al, 1996). This is in contrast to the term *introitus,* which is ill defined.

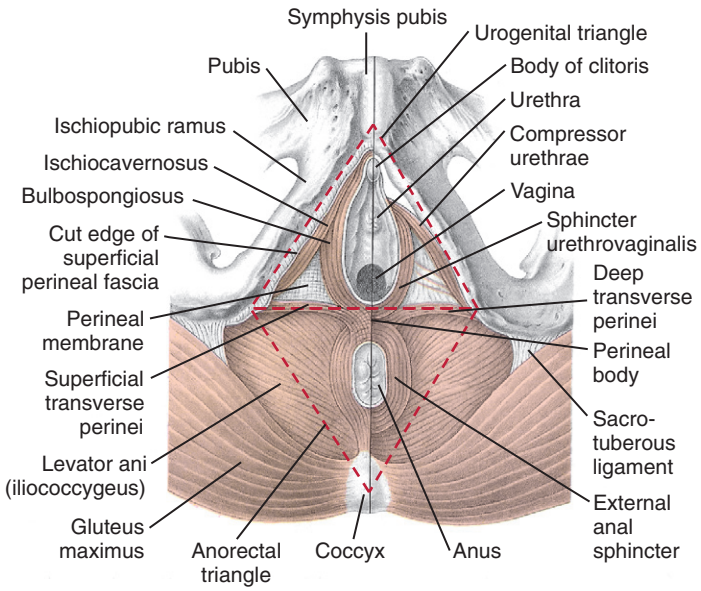


Figure 72–4. Muscles of the female perineum. The cut edge on the right side is the cut edge of the superficial fascia that has been removed. The left side depicts the deep perineal muscles (seen without the superficial perineal muscles and overlying fascia. (From Mundy A. True pelvis, pelvic floor and perineum. In: Standrinak W, editor. Gray's anatomy: the anatomical basis of clinical practice. 39th ed. New York: Elsevier; 2005.)

The urogenital hiatus is the opening within the levator ani muscle through which the urethra and vagina pass. Because the rectum is attached directly to the muscles at this level it is not within the urogenital hiatus. The hiatus is supported anteriorly by the pubic bones and levator ani muscles and posteriorly by the perineal body and external anal sphincter (Ashton-Miller and DeLancey, 2007). The urogenital hiatus elongates and descends with POP.

Endopelvic Fascia and Connective Tissue Supports. The endopelvic fascia is a network of fibromuscular tissue located between the peritoneum and the levator muscles. It surrounds and attaches the bladder, uterus, vagina, and rectum to the pelvic walls, thereby stabilizing the pelvic viscera. The endopelvic fascia is one continuous unit; however, distinct areas are named separately. The parametrium (broad, cardinal, and uterosacral ligaments) attaches the uterus and upper vagina to the pelvic sidewall. The paracolpium (the arcus tendineum levator ani and the ATFP) attaches the vagina to the pelvic sidewalls. In his landmark article, DeLancey (1992) described the supports of the vagina and conceptually divided them into three parts according to the region of vaginal support (Fig. 72–6). The structures supporting the uterus and the cephalad 2 to 3 cm of the vagina comprise level I support, and these fibers originate from the greater sciatic foramen, the sacroiliac region, and the lateral sacrum. The fibers are primarily vertical in their orientation and are the longest fibers of the endopelvic fascia, thereby suspending the uterus and upper vagina, and comprise the cardinal/uterosacral ligament complex. Level II support is at the mid vagina. These fibers are shorter than level I support but longer than those at level III. The orientation of the attaching fibers is lateral, and they are more dense than the cardinal/uterosacral ligament complex. The endopelvic fascia splits at this level to encompass the bladder and urethra such that the abdominal leaf is still named the endopelvic fascia and the vaginal leaf is the pubocervical and periurethral fascia. Posteriorly, the endopelvic fascia, which attaches laterally to the superior fascia of the levator ani muscles, is the rectovaginal fascia. Level III support of the vagina starts at the introitus and extends 2 to 3 cm above the

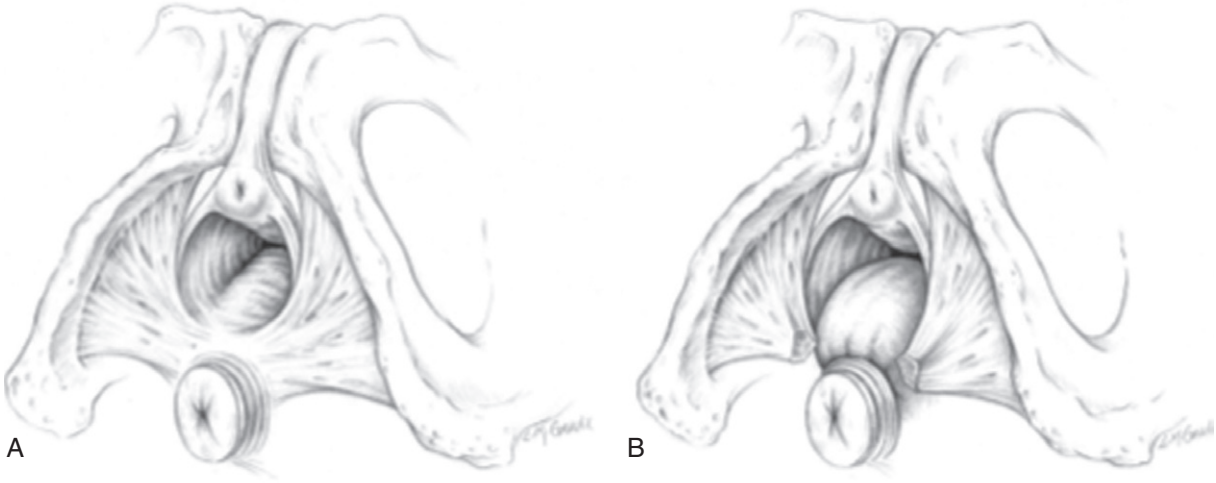


Figure 72–5. **A** and **B,** Perineal membrane. The two halves of this triangular sheet of fibromuscular connective tissue form a central tendon referred to as the perineal body. (From DeLancey JO. Structural anatomy of the posterior pelvic compartment as it relates to rectocele. Am J Obstet Gynecol 1999;180:815–23.)

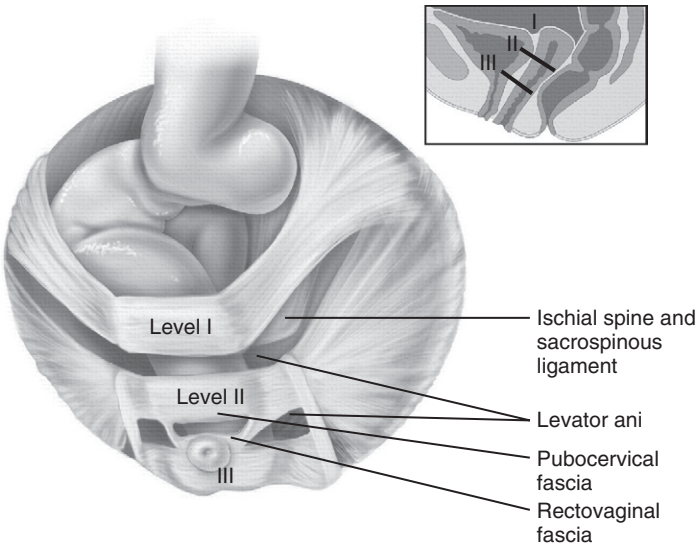


Figure 72–6. Vaginal and visceral supportive structures as defined by DeLancey. The fibers of level I support are oriented vertically and suspend the uterus and upper vagina. Level II support is more horizontal in its orientation and attached to the mid vagina. Distally, level III support fuses directly into the support structures. (From DeLancey JO. Anatomic aspects of vaginal eversion after hysterectomy. Am J Obstet Gynecol 1992;166:1717–28.)

hymenal ring. In this most distal location there is no intervening paracolpium and the vagina is fused directly to the urethra and is embedded in the connective tissue of the perineal membrane (urogenital diaphragm). Laterally it blends into the medial margins of the levator ani muscles, and posteriorly it blends into the perineal body.

The endopelvic fascia is a composite of tissues of fibers embedded in a matrix. The variability of this tissue matrix may lead to its inherent weakness and inconsistency in reconstructive surgery. In fact, fresh strips of pubocervical fascia have been shown to shorten 15% to 20% of its length (Richardson, and DeLancey, 2000). Thus, these tissues are supportive and contractile. Histologically, this tissue is unlike abdominal wall fascia or the fascial coverings of other muscles such that they lack the organization of the fascial coverings of the skeletal muscle.

Support by Compartment

Anterior Compartment Supports. Because the urethra is fused to the anterior vaginal wall for much of its length, the supporting structures of the urethra and distal anterior vagina are one in the same. The major components are the endopelvic fascia (periurethral and pubocervical fascia), ATFP, and the levator ani muscles (Ashton-Miller and DeLancey, 2007). At this level the endopelvic fascia surrounds the vagina and attaches to the ATFP bilaterally. Each ATFP is attached to the pubic bone anteriorly and to the ischial spine dorsally. This structure appears as a band closer to the pubic bone, and as it courses toward the ischial spine it fans out into a broad aponeurotic structure. Laterally it merges with the levator ani muscles at the confluence of the iliococcygeus and obturator internus.

Apical (Middle) Compartment Supports. This support is provided by the cardinal/uterosacral ligament complex, which are level I supports as described by DeLancey (1992). They originate from fibers of the pelvic sidewall and extend to the area around the greater sciatic foramen and extend to the second, third, and fourth sacral segments. From there they fan out as they attach to the cervix and the upper vagina. The medial edge of this complex is the area of the uterosacral ligaments. The uterosacral ligaments are visible and palpable with traction of the cervix or the cuff of the vagina after hysterectomy. The fibers encircle the cervix and in aggregate are called the pericervical ring.

Posterior Compartment Supports. The rectovaginal fascia is also sometimes referred to as Denonvilliers fascia in the female (Richardson and DeLancey, 2000). It has more dense strands of elastin and less smooth muscle compared with the pubocervical fascia. It is stabilized in the upper vagina by the cardinal/uterosacral ligament complex, because it is contiguous with this structure. The uterosacral ligament inserts into the rectovaginal fascia just below the attachment to the posterior cervix. Because the rectovaginal fascia is connected to the sacrum and the perineal body it provides continuous posterior support.

The perineal body is a condensation of fibromuscular tissue and collagen that is located in the midline between the vagina and the anus. It serves as a point of fixation for the rectovaginal fascia, the levator ani muscles, the transverse perinei muscles, and the external anal sphincter (Rosenblum et al, 2005).

Pathophysiology of Pelvic Organ Prolapse: Surgical Correlation

The levator ani muscles comprise both type I and type II fibers. Type I muscle fibers are slow twitch and provide sustained tonicity of the pelvic floor. This function serves a crucial role in providing dynamic pelvic floor support, thus taking the mechanical stress off of the endopelvic connective tissue attachments. Type II fibers consists of fast-twitch fibers that are mainly responsible for the reflex contractions of the pelvic floor associated with sudden increases in intra-abdominal pressure. Thus, the levator ani muscle complex fulfills multiple functions. First, the tonic contraction of the pubococcygeus muscle narrows the genital hiatus. Second, contraction of the pelvic floor leads to the elongation and elevation of the pelvic organs facilitating urinary and fecal continence. Additionally, posterior levator ani tonicity elevates the upper vagina and stabilizes it into a horizontal plane near the hollow of the sacrum (Fig. 72–7) (Wall and Menafee, 2002). Direct muscular damage, neuromuscular dysfunction, and inherent tissue defects may predispose to a dysfunction of the levator ani musculature. As a result, the burden of support shifts mostly to the endopelvic connective tissues. As these structures weaken, various “breaks” occur that lead to vaginal support defects.

It is most useful to define defects by compartment while keeping in mind that many patients present with multicompartmental defects. Additionally, some patients will present with several defects within the same compartment.

SITE-SPECIFIC DEFECTS BY COMPARTMENT (IDENTIFICATION) (Table 72–1)

Anterior Compartment

Within the anterior compartment two types of defects can lead to cystoceles. The central cystocele results from attenuation or separation of the pubocervical fascia, resulting in a protrusion of anterior compartment structures through this defect. This protrusion results in the classic appearance of a loss of the rugae or vaginal

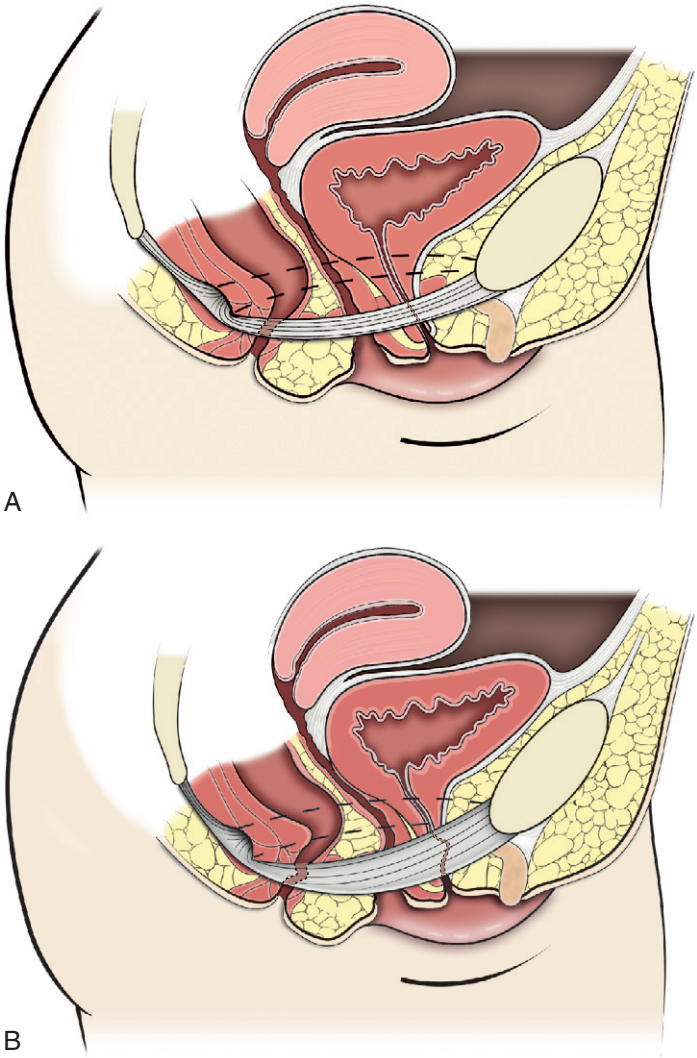


Figure 72–7. Function of the levator ani. The tonic contraction of the pubococcygeus muscle narrows the genital hiatus and leads to elongation and elevation of the pelvic organs, facilitating continence (**A** at rest; **B** contracted). The posterior levator ani elevate the upper vagina and stabilize it on the levator plate, which provides a supportive role to the perineal body. (From Wall LL, Menefee S. Incontinence, prolapse and disorders of the pelvic floor. In: Berek JS, editor. Novak's textbook of gynecology. 13th ed. Philadelphia: Lippincott Williams & Wilkins; 2002, with permission.)

Table 72–1.

Compartmental Anatomy: POP-Q Sites and Organ Involvement

COMPARTMENT	POP-Q SITE	PROLAPSED ORGAN	VAGINAL WALL SITE
Anterior	Aa	Urethra (urethrocele)	Distal anterior vaginal wall
	Ab	Bladder (cystocele)	Proximal and distal anterior vaginal wall
Middle	C	Cervix	Cervix
	D	Small bowel (enterocele)	Uterosacral scar
Posterior	Ap	Small bowel (enterocele)	Proximal posterior vaginal wall
	Bp	Rectum (rectocele)	Proximal and distal posterior vaginal wall
		Perineal body	Perineal body

folds of the anterior vaginal wall. Detachment of the pubocervical fascia and the pubourethral ligaments to the ATFP results in a lateral cystocele and can also involve the urethra. This usually results in a preservation of the rugal folds of the vaginal wall and a "rotational" prolapse of the anterior wall (Fig. 72–8). Urethroceles, which are distal anterior compartment defects, usually result in urethral hypermobility (Weber and Walter, 1997).

Apical Compartment

Apical compartment defects involve a disruption in the uterosacral/cardinal ligament complex. This defect may lead to prolapse of the uterus, the vaginal cuff after hysterectomy, and the peritoneum cul-de-sac with or without bowel (enterocele). Enteroceles are most commonly associated with apical or high posterior compartment defects; however, enteroceles may rarely occur anteriorly. Enteroceles can occur with or without vaginal vault prolapse. Complete vaginal vault prolapse contains enteroceles in 75% of patients. Waters (1956) described four types of enteroceles by etiology: congenital, pulsion, traction, and iatrogenic. Congenital enteroceles occur either from the failure of the peritoneum to fuse with the perineal body or from reopening of previously fused structures. Pulsion defects occur with increased intra-abdominal pressures, and traction enteroceles occur by a pulling of the vaginal epithelium from other prolapsing organs. Iatrogenic enteroceles are created when a surgical procedure is performed that alters the normal vaginal axis or when the pubocervical fascia and the rectovaginal septum are not reapproximated after hysterectomy (Wiskind et al, 1992).

Uterine prolapse occurs with loss of support of the cardinal and uterosacral ligaments. The broad ligaments also provide uterine support and are located above insertion of the cardinal uterosacral ligaments. They are located within the leaves of the anterior and posterior peritoneum. Within this fused structure are the fallopian tubes and the round and ovarian ligaments along with their blood supply (Rosenblum et al, 2005). It is difficult to differentiate other prolapsing organs with loss of apical support high in the vagina. As such, careful dissection is often needed to identify other prolapsing organs with uterine prolapse. **This reinforces the concept that the endopelvic fascia is best considered as a contiguous unit that can fail together. Consequently, the bladder, small bowel, and rectum are often found prolapsing with the uterus.**

Vaginal vault prolapse can occur after hysterectomy if support of the vault is not reconstituted by suspending it to the cardinal/uterosacral ligament complex. Incidence of vaginal vault prolapse after hysterectomy has been reported to be as high as 18.2%, and it can contribute to prolapse in other compartments (Richter, 1982). Because of the redundancy of the support by the endopelvic fascia, failure to reattach the suspensory component does not lead to immediate vaginal eversion after hysterectomy (DeLancey, 1992). Complex vaginal eversion is vaginal eversion associated with cystocele, rectocele, or both (DeLancey, 1992). Complex vaginal eversion has been reported as high as 67% of vault prolapse (Morley and DeLancey, 1988). In this group of patients, 7% had apical prolapse and cystocele, 30% had apical prolapse

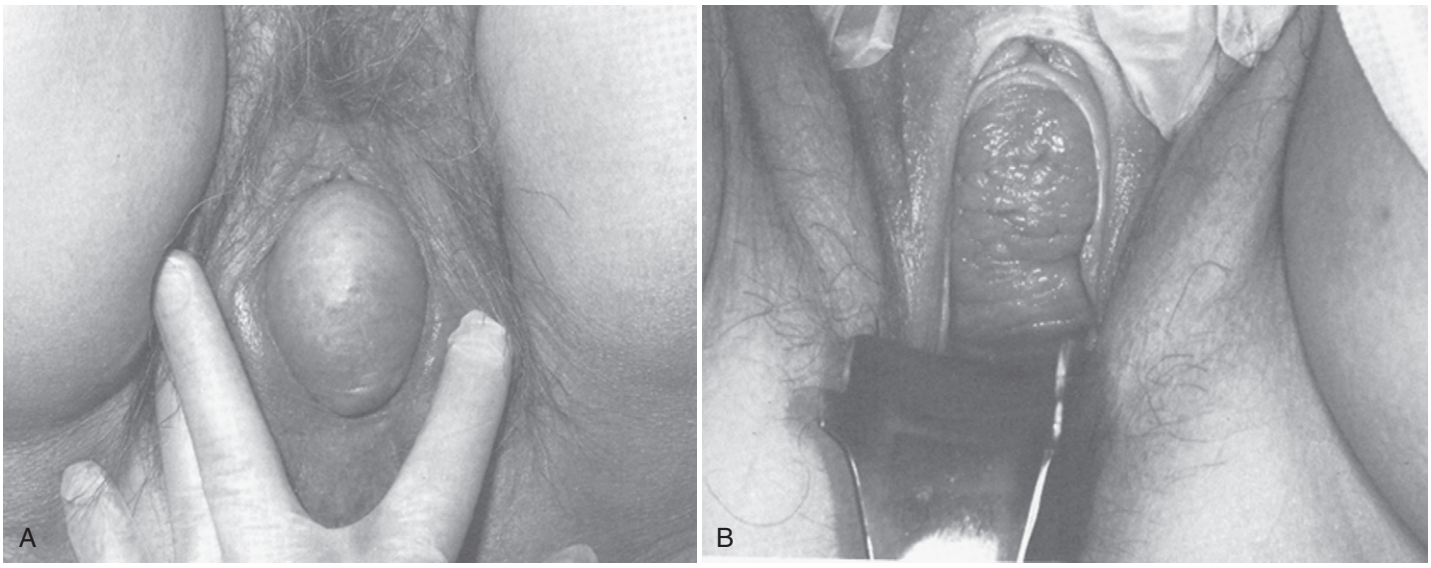


Figure 72–8. **A** and **B,** Cystoceles. (From DeLancey JO. Relation of prolapse syndromes to symptoms. In: Kursh E, McGuire E, editors. Female urology. Philadelphia: JB Lippincott; 1994.)

with rectocele, and 30% had prolapse with both cystocele and rectocele.

Posterior Compartment

The posterior vaginal compartment comprises the peritoneum of the cul-de-sac, the rectum, and the perineum. Defects in the rectovaginal fascia either in the form of attenuated fascia or site-specific tears will result in herniation of the rectum and sometimes the small bowel into the vagina. Rectoceles may be divided into low, midvaginal, or high depending on the location of loss of support, and it may present as a combination of defects. Richardson was the first to describe site-specific defects of the rectovaginal fascia in 1993 (Fig. 72–9). Defects in the cardinal/uterosacral ligament complex can result in high rectoceles and can involve enteroceles. Enteroceles are estimated to be present in 0.1% to 16% of women undergoing surgery for POP (Chou et al, 2000). Loss of support in the mid vagina from the lateral attachments to the arcus tendineus fascia rectovaginalis will result in a bulging in the midportion of the posterior compartment. The perineal body is suspended from the sacrum by the contiguous support of the uterosacral ligaments and rectovaginal septum. Any break in this support system will lead to a hypermobile perineal body that descends with increases in intra-abdominal pressures (Richardson, 1993). Separation of the perineal body at the level of the rectovaginal fascia results in perineal descent or a low rectocele. The rectocele will be visible just inside the hymen posteriorly (Fig. 72–10). If perineal body detachment is left untreated at the time of rectocele repair, a perineal rectocele can occur in which the rectum bulges into the perineal body, termed a *perineal rectocele* (Richardson, 1995).

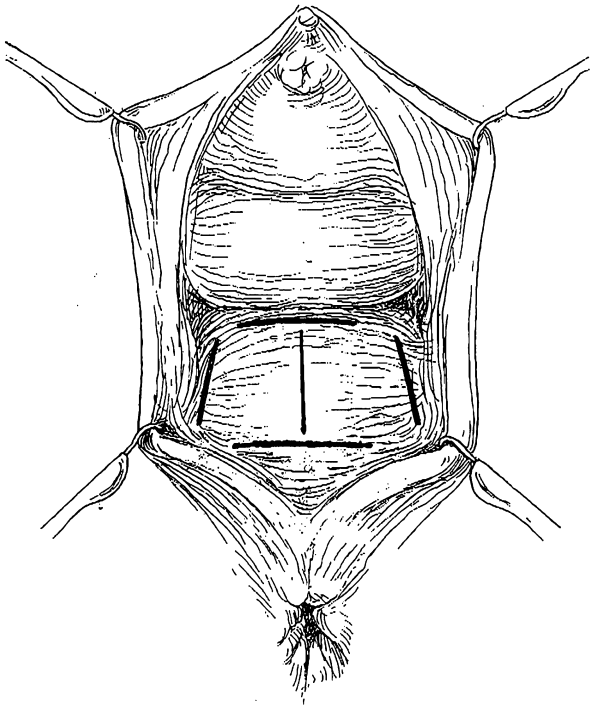


Figure 72–9. Locations where breaks in the rectovaginal septum have been observed in patients with posterior defects. (From Richardson AC. The rectovaginal septum revisited: its relationship to rectocele and its importance in rectocele repair. Clin Obstet Gynecol 1993;36:976–83.)

PREPARING THE PATIENT FOR PROLAPSE SURGERY

Because pelvic organ prolapse is, for the most part, a quality of life issue, consideration must be given to the grade of prolapse, patient's symptoms, and the degree to which the patient's quality of life is impaired (Novara and Artibani, 2005). In selecting surgical procedure(s), one must individualize management based on the unique clinical presentation of each patient, taking into account physiologic age, comorbidities, previous surgeries, and level of physical and sexual activity (Flynn and Webster, 2002). Once the decision has been made to proceed with surgery, it is imperative to recall that the best chance at restoring normal support and function is to reapproximate normal anatomy during

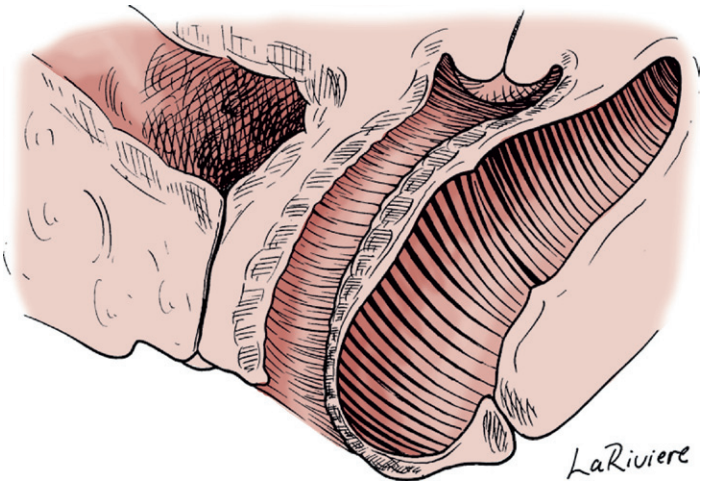


Figure 72–10. Large rectocele with perineal body defect. (From Nichols DH. Rectocele and perineal defect. In: Nichols DH, editor. Gynecologic and obstetric surgery. St. Louis: CV Mosby; 1993. p. 363–85.)

the first surgery (Rogers, 2003). After the first procedure, the normal anatomic planes will no longer be present, which may add to the difficulty and complexity of subsequent surgeries. Recurrence rates increase with each attempt to surgically correct the defect(s) (Birch, 2005; Maher et al, 2006). In addition, the surgeon who operates in the region of the pelvic floor must understand the anatomic alterations that result from each technique and how that surgery will affect the continuity and function of the endopelvic fascia and its related viscera (Rogers, 2003).

Repairs can be defined as restorative, compensatory, and obliterative (Van Rooyen and Cundiff, 2005). In patients whose comorbidities preclude prolonged surgery, obliterative procedures provide symptom relief with minimal morbidity. These procedures are contraindicated in patients who wish to remain sexually active. For those patients who have discrete defects in the fibromuscular layer of the endopelvic fascia, restorative repairs are an appropriate option. These repairs correct the defined defects in the native tissues by utilizing endogenous support structures. For patients whose native tissues are particularly weak or in those who have had failed surgeries, compensatory procedures have been used. These procedures involve placing a graft to reinforce the repair. Grafts are made of synthetic materials and biologic and autologous tissues.

In assessing tension of the repair at the time of surgery, the pelvic floor surgeon should recall that the muscles of the pelvic floor are relaxed under anesthesia (general or spinal). Postoperatively, these muscles will contract along with the endopelvic fascia due to its own contractile fibers. Furthermore, scarring and postmenopausal atrophy may also cause further narrowing (Segal and Karram, 2002). Although the etiology of postsurgical dyspareunia is not fully understood, these factors should be kept in mind when repairing the pelvic floor.

Pelvic floor reconstruction may be performed through a vaginal, open abdominal, laparoscopic approach or any combination of these techniques. Because POP is often mixed, surgery commonly involves a combination of repairs addressing any affected compartments. In addition, an anti-incontinence procedure may be performed at the same time. In comparing the vaginal approach with the abdominal approach there is a benefit with the vaginal approach in that complications and recovery time are less with the vaginal approach (Weber and Richter, 2005). The operative time is generally less with the vaginal approach, as is the hospital stay and recovery time (Morley and DeLancey, 1988; Shull, 1999). However, there is evidence that the abdominal approach is more durable compared with a vaginal technique (Benson et al, 1996). This fact should be considered in younger and more active patients.

Preoperative Counseling of Patient for Vaginal POP Surgery

Over the past decade the definition of success has been expanded to include patient satisfaction and symptom improvement in addition to objective measures. Patients' expectations and readiness to undergo surgery for POP have been shown to impact their satisfaction and how they perceive their improvement (Kenton et al, 2007). In the first article to examine patient-selected goals and surgical outcomes, Elkadry and coworkers (2003) found that patient satisfaction after surgery for POP correlated highly with achievement of self-described goals. In contrast, patient satisfaction correlated poorly with objective measures of surgical success. Dissatisfaction was highly associated with feeling unprepared for surgery. Furthermore, patients perceived the experience of routine postoperative events such as pain, hospital discharge with a catheter, constipation, urgency incontinence, and minor effects of anesthesia as surgical complications. These perceived complications were also associated with dissatisfaction. Additionally, they also demonstrated dissatisfaction despite high cure rates. **Thus, patient perception of perioperative events and bother from recurrent symptoms equate largely to postoperative dissatisfaction even in the presence of high objective cure rates. It is vitally important to recognize that the absence of symptoms influences patient satisfaction greater than the elimination of anatomic prolapse.** Kenton and associates (2007) evaluated patients with standardized counseling using a three-page handout on what to expect after surgery. Women who perceived they were fully prepared for surgery were more likely to be improved on the Patient Global Impression of Improvement (PGI-I) scale (Yalcin and Bump, 2003) and had lower postoperative scores on the Pelvic Organ Prolapse Distress Inventory (POPDI) (Barber et al, 2001) and Urogenital Distress Inventory (UDI) (Shumaker et al, 1994). Also, they found that objective measures of cure did not differ by preparedness. In conclusion, **the preoperative surgeon-patient interaction is a key time that can be used to improve postoperative patient satisfaction. Therefore it is recommended to complete a thorough consent about the surgery, alternatives to surgery, the purpose of planned surgery (what it can and cannot accomplish), the benefits of surgery (what symptoms can be improved), the risks, and complications. In addition, it is useful to review what to expect while the patient is in the hospital, what to expect at home, and strategies on coping with a catheter both in the hospital and at home if needed** (Kenton et al, 2007).

In 2001 the Agency for Healthcare Research and Quality (AHRQ) identified perioperative interventions to improve patient safety (Shojania et al, 2001). These include asking the patient to recall and restate what she was told during the informed consent process, administering appropriate antibiotic prophylaxis to prevent postoperative infections, and implementing prophylaxis to prevent venous thromboembolism in patients at risk.

The second most common source of nosocomial infections is infection at the surgical site (Bratzler and Houck, 2004). Current

guidelines by the Centers for Medicare and Medicaid Services recommend that prophylactic antibiotics be administered within 60 minutes of incision time and discontinued within 24 hours of surgery (Centers for Medicare and Medicaid Services, 2008). The antibiotic chosen should be active against the likely infectious organisms to be encountered during the surgery performed. Although the American College of Obstetricians and Gynecologists has provided recommendations for antibiotic prophylaxis in patients undergoing hysterectomy there are no current guidelines addressing prolapse operations without hysterectomy (ACOG, 2009). Most favor the use of prophylactic antibiotics in reconstructive vaginal surgery, especially in surgery involving synthetic and biologic grafts.

The risk of deep venous thrombosis (DVT) after major gynecologic surgery in patients not receiving prophylaxis is between 15% and 40% (Gutt et al, 2005). Risk factors include increasing age, previous venous thromboembolism, gynecologic malignancy surgery, and major pelvic reconstructive surgery. Waetjen and associates (2003) found that 42% of patients having surgery for POP were older than 60. The Centers for Medicare and Medicaid Services has endorsed a risk stratification presented by Geerts and colleagues (2004) that states that patients older than age 60 undergoing major surgery are at high risk for DVT. Without prophylaxis, high-risk patients have a 20% to 40% risk for calf DVT, a 2% to 4% risk for pulmonary embolism, and a 1% risk of fatal pulmonary embolism. They have recommended both anticoagulant-based and mechanical prophylaxis in patients at high risk for DVT. Specifically, heparin 5000 units three times a day and low-molecular-weight heparin with or without sequential compression devices are acceptable choices.

Patients with advanced POP and incomplete bladder emptying may be taught to perform clean intermittent catheterization (CIC) preoperatively in the event that complete bladder emptying becomes a problem postoperatively. **In postmenopausal women, local estrogen therapy with vaginal cream to treat atrophic vaginitis is started 6 weeks preoperatively.** The administration of unopposed low-dose vaginally administered estrogen has been shown to be both safe and effective (Robinson and Cardozo, 2003). Also, local estrogens may increase vascularity and facilitate healing (Cervigni, 1996). The use of yellowfin (Allen, Acton, MA) or comparable stirrups, careful positioning of the patient in a neutral anatomic position, and avoiding leaning on or into the patient will minimize the risk of neuropathy, specifically to the lateral peroneal nerves.

BIOLOGIC AND SYNTHETIC MATERIALS IN PROLAPSE SURGERY

Although there has been an increased use of interposition graft materials in the area of pelvic floor reconstruction there are little controlled data to recommend their use. Graft materials have been used in an effort to improve outcomes of transvaginal prolapse repairs. The risk factors for failure of prolapse surgery include age, vaginal parity, smoking, deficient tissue quality, conditions that impair wound healing (diabetes mellitus and corticosteroid use), and conditions that stress the repair (chronic constipation, chronic obstructive pulmonary disease, and obesity). **When examining the issue of failed prolapse surgery there are limitations. The definition of failure is not standardized, and many studies are short term, lacking controls. However, in spite of the limitations it is clear that failure of prolapse surgery is not uncommon.** Some patients with POP have specific deficiencies in their tissues, which may predispose them to failure with traditional restorative procedures. Abnormal type I to type III collagen ratios have been identified, leading to a less organized collagen matrix (Falconer et al, 1998). Normal collagen protects fibroblasts from apoptosis, whereas abnormal fibroblasts are not protective (He et al, 2002). Decreased numbers and impaired function of fibroblasts have also been cited (Poncet et al, 2005). Overexpression of matrix metalloproteinases that break down extracellular matrix proteins have been demonstrated in women with prolapse (Jackson et al, 1996). These factors imply that these affected tissues may be less likely to respond to the dynamic forces placed on the female pelvic floor (Chen et al, 2004). As a result of these potential tissue disorders and inherent tissue weakness, graft interposition has been utilized with increased frequency. Although there is level I evidence supporting the use of synthetic graft materials for abdominal sacrocolpopexy (Davila et al, 2005) there is little evidence regarding the most appropriate usage of transvaginal mesh in prolapse repairs.

Classification of Graft Materials

The ideal prosthetic implant would be biocompatible, chemically inert, noncarcinogenic, mechanically strong, and sterile, have minimal allergic or inflammatory reaction, and avoid shrinkage and mechanical stress (Birch, 2005). In addition, the ideal implant should be readily available and affordable. Grafts may be categorized as either synthetic or biologic, and both graft types are used in pelvic floor reconstruction. Synthetic graft materials are usually classified as absorbable or nonabsorbable (permanent). Permanent graft materials are usually classified by pore size (macroporous, microporous, submicroporous, and combined) and by material structure (monofilament or multifilament). Biologic grafts are classified by source—autologous or heterologous—and further categorized as allografts or xenografts (Fig. 72–11).

Basic Science: Graft-versus-Host Interaction

Graft incorporation of the tissues involves a foreign body response. Although many materials used for synthetic grafts are reported to be chemically and physically inert and nonimmunogenic (Davila

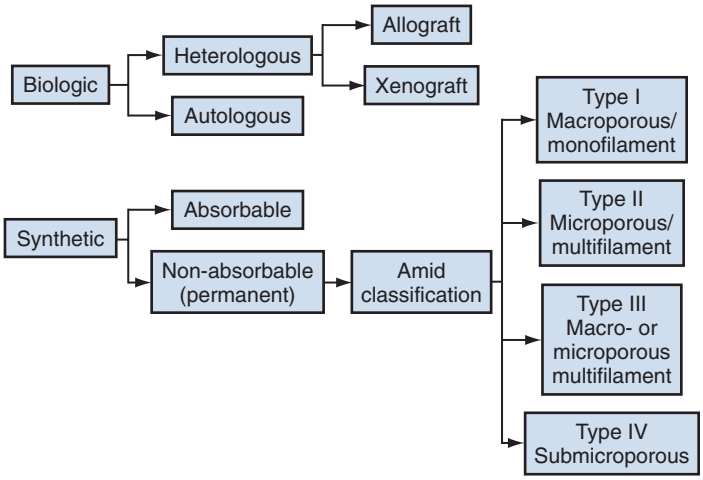


Figure 72–11. Classification of graft materials. (From Togami J, Krlin R, et al. Graft materials in prolapse surgery. AUA Update Series 2008;27[31]:294–303, with permission.)

et al, 2005; Deprest et al, 2006), none is biologically inert. Regardless of the material type, wound healing with a graft follows a stepwise cascade. Initially a biofilm is produced in response to tissue injury. Low-molecular-weight protein adsorption occurs quickly at the interface and does not require a cellular response. Complex proteins such as fibrinogen, immunoglobulins, and extracellular matrix proteins follow. If bacteria are incorporated into the biofilm at this point later wound healing can be affected (Deprest et al, 2006). These complex proteins undergo a conformational change to become more immunogenic, which leads to an inflammatory cascade by activating complement, binding antibodies, leukocytes, blood clotting, and fibrinolysis (Tang and Eaton, 1995). At this point the acute inflammatory response becomes chronic and granulation tissue forms. This involves fibroblasts, macrophages, giant cells, and, later, neovascularization and fibrosis. At this point the implant is mechanically stable. The amount of foreign body reaction is proportional to the surface area of the material exposed to the host. **The degree of response and amount of tissue ingrowth is determined by the nature of the material, its structure, and the amount implanted for biologic grafts** (Deprest et al, 2006). Ideally, host-tissue integration into the graft takes place, leading to long-term graft function after this biologic transformation. This illustrates an important concept in that the graft, biologic or synthetic, acts as a scaffold to provide a substrate to facilitate tissue ingrowth, rather than it functioning as a permanent mechanical support (Birch, 2005).

Once a graft has been implanted into the human host, one of four processes may occur: (1) rejection in which there is severe and chronic inflammatory reaction around the implant, (2) degeneration (the result is necrosis from in-situ exothermic polymerization by the host), (3) encapsulation (minimal foreign body response in which there is fibrosis around the graft), or (4) incorporation into the human host tissue (a response in which there are inflammatory cells and giant cells leading to ingrowth of host tissues into the graft) (Williams, 1973). **For long-term graft survival it appears that incorporation by the host through a process known as graft remodeling is necessary** (Fig. 72–12).

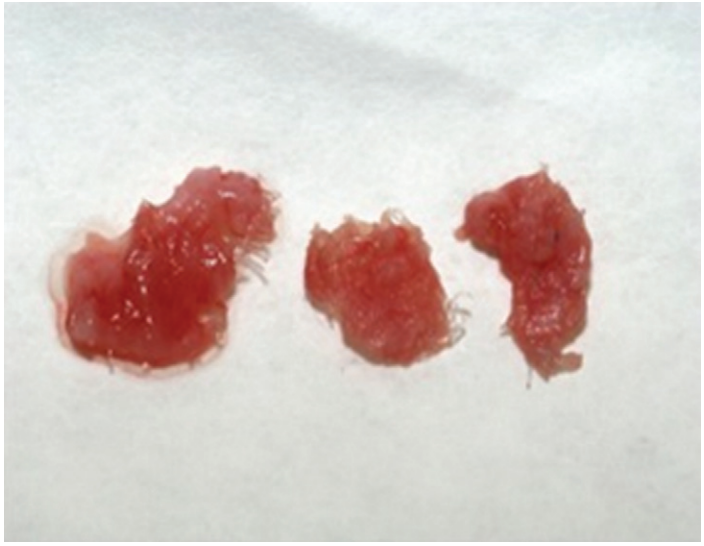


Figure 72–12. Host tissue ingrowth (process of graft remodeling) into polypropylene mesh. (From Woodruff A, Cole E, Scarpero H, et al. A histologic analysis of sling graft materials: a comparative study. Urology 2008;72:85–9, with permission.)

Pore size affects host fibroblast infiltration, flexibility, and mechanical integration of the graft (Klinge et al, 2002). Large pore size has been shown to facilitate this process by enhancing host tissue infiltration and reducing the amount of inflammatory reaction with increased fibroblast infiltration. The large pores become integrated in a loose network of perifilament granulomas filled with fat, which maintains elasticity. After ingrowth of host tissue, a process of transformation occurs to complete the process of remodeling. Solid products or products with small pores (< 50 μm) induce a foreign body reaction that fills the entire pore. This promotes the bridging of the filaments to each other, thereby predisposing to encapsulation (Beets et al, 1996).

Kaupp and colleagues (1979) described four histologic stages of the host to biologic graft implantation:

- Stage 1 occurs over the first 7 days. This is marked by intense inflammation around the graft, which induces capillary proliferation, formation of granular tissue, and presence of giant cells.
- Stage 2 encompasses the next 7 days. Granular tissues are still present, and foamy histiocytes appear. Giant cells may increase or decrease at this point.
- Stage 3 spans 21 and 28 days, when the acute inflammation dissipates with decreased capillaries. Foamy histiocytes and giant cells increase in number.
- Stage 4 happens after 28 days. Giant cells are present on the surface of the implant along with dense fibrotic tissue. This initiates the process of the host-graft interaction.

Once the entire graft is infiltrated with host tissue the transformation process is complete. If this remodeling process characterized by ingrowth and transformation occurs before the graft substrate dissolves, long-term viability of the implant may be ensured. Although synthetic mesh material is a permanent substrate, the principles of tissue incorporation are necessary to prevent infection, extrusion, or erosion. Extrusion is thought to be secondary to exposed graft, which is attributable to localized infection, inadequate closure of the wound, or poor tissue quality (decreased vascularity or thickness) (Birch, 2005). Erosion is thought to be a chronic process related to host inflammatory response at the tissue-graft interface.

Clinical Application of Graft Materials

Biologic Grafts

Because of concerns regarding potential complications associated with synthetic grafts, some authors have turned to biologic grafts to circumvent these complications (Togami et al, 2008). Biologic grafts are categorized as autologous (patient serves as the donor), heterologous (same species, different individual [cadaveric]), and xenogenic (obtained from other species, typically porcine). The advantages of biologic grafts include in-vivo tissue remodeling, histologic similarity, and decreased propensity to elicit local complications (Silva and Karram, 2005).

The donor sites for autologous grafts include rectus fascia, fascia lata, and vaginal epithelium, with the most common being rectus fascia and fascia lata. **Autologous grafts are ideal in that they are well incorporated, pose no threat of disease transmission, and have minimal risk of encapsulation or rejection.** The major drawback is the harvesting process, with increased morbidity, time, and potential for complications at the donor site. These factors are eliminated by using allografts and xenografts (Jarvis et al, 1985). Allografts are obtained from cadaveric donors and include dura mater, fascia lata, and dermis.

Cadaveric fascia lata and dermis are used most commonly. A major concern when utilizing biologic materials is the potential for disease transmission. Choe and Bell (2001) demonstrated intact DNA in freeze-dried/irradiated cadaveric fascia lata and freeze-dried cadaveric dermal allograft. Fitzgerald and associates (2000) also examined irradiated freeze-dried or solvent dehydrated cadaveric fascia lata and found that it retained the donor human leukocyte antigen (HLA) class I and II antigens. Although extensive steps are taken to prevent infection exposure, risk of prion and human immunodeficiency virus transmission is estimated to be 1 in 1.7 million (Buck et al, 1989). To date there have not been any reports of disease transmission from grafts used for POP.

The harvesting techniques of nonautologous biologic graft materials are standardized. In their review, Chen and colleagues (2007) described the process of allograft acquisition. Before allografts are harvested the donor undergoes serologic testing for hepatitis B and C, human immunodeficiency virus, and human T-lymphotropic virus type 1. Aseptic technique is used during harvest, and cultures are obtained at the time. The source animals for xenografts are specifically raised for medical purposes with production being strictly controlled by U.S. Food and Drug Administration (FDA) guidelines (Deprest et al, 2006). Materials available are derived from porcine subintestinal mucosa, porcine dermis, bovine dermis, and bovine pericardium, although the most commonly used are from porcine sources. These function as acellular collagen–based scaffolds to serve as a platform for host infiltration.

Allografts and xenografts must undergo tissue processing before implantation, and, unlike harvesting, there is a variance in the processing techniques of these materials. This variance may affect the biologic and biomechanical properties of the grafts. There is no consensus as to which method should be used to optimize tissue properties. In some cases, processing is carried out to affect the long-term effects of the tissue to decrease graft breakdown and increase host tissue ingrowth. Sterilization is achieved by freeze-drying, solvent dehydration, and/or gamma irradiation. Lemer and associates (1999) demonstrated that freeze-dried cadaveric fascia demonstrated the least desirable characteristics when compared with autologous rectus fascia, cadaveric dermis, and solvent dehydrated cadaveric fascia lata. The freeze-dried cadaveric fascia demonstrated a reduced maximum load to failure and stiffness. In addition there was greater variability in the tissue's strength and stiffness throughout its entire length.

Cross-linking is another processing technique that can affect graft performance. This is done to delay reabsorption by collagenases (Badylak et al, 2002). Several methods are used, including aldehyde cross-linking and hexamethylene di-isocyanate (HMDI). Aldehydes are cytotoxic in high concentrations and may increase concentrations of gelatinases, which may actually increase the rate of degradation (Jorge-Herrero et al, 2001). In addition, aldehydes may cause calcification of the grafts, adversely affecting their function. Studies performed in rats have shown no graft mineralization with HMDI cross-linked dermal implantation at 2 years in contrast to aldehydes (Oliver, 1987).

Local complications such as encapsulation may occur after the use of porcine dermis grafts (Cole et al, 2003). Graft fenestrations have been reported to enhance ingrowth and angiogenesis (Taylor et al, 2008). They may also decrease seroma formation and local complications. Porcine small intestine submucosa (Surgisis, Cook Medical, Bloomington, IN) is a non–cross-linked graft processed so that the complex extracellular matrix and natural growth factors are left intact (Cook Medical, 2007). There is histologic evidence that by 1 month the strength and histology of the graft is identical to native material and at 2 years it exceeds the strength of native tissue (Konstantinovic et al, 2005).

The lack of in-vivo data limits the study of many biologic and synthetic grafts. Naturally it would be of benefit to demonstrate how the biomechanical properties of these materials are altered or remodeled by the host. Several animal models have been used to study grafts and meshes. In the rabbit model a free or pedicle flap of autologous rectus fascia decreased 37% in length, 63% in width, and 53% in tensile strength after implantation for 12 weeks. Neovascularization, minimal inflammation, and fibrosis was noted only along the permanent suture used to secure the graft (Fokaefs et al, 1997). In a rabbit model, freeze-dried, irradiated cadaveric fascia lata had a 90% decrease in tensile strength 12 weeks after implantation (Walter et al, 2003). There was variability in tensile strength from lot to lot and from grafts taken from different areas in the same lot. In an extensive rabbit study examining six different graft materials, tensile strength and stiffness of human cadaveric fascia and porcine xenografts decreased by 60% to 89%. Polypropylene (Prolene) mesh and anterior rectus fascia had no change in tensile strength from baseline (Dora et al, 2004). When comparing a tension-free vaginal tape (TVT) (Ethicon, Somerville, NJ) polypropylene sling to a cadaveric fascia lata sling in the rat model there was an advantage for the polypropylene sling in the breakload and maximum average load compared with cadaveric fascia lata (Spiess et al, 2004). **There is a wide variation in the types of grafts available and tissue processing they undergo. It is unclear how this affects the performance of the grafts because there are little data comparing them.** Before implantation, dermal allografts, solvent dehydrated fascia lata, and synthetic mesh have equal or higher tensile strength compared with autologous fascia. In some studies, freeze-dried grafts have a decreased tensile strength compared with similar grafts that have been solvent dehydrated. After implantation, autologous fascia and synthetic mesh seem to retain more of their tensile strength compared with allografts or xenografts (Chen et al, 2007).

Synthetic Grafts

Synthetic mesh can be permanent or absorbable. Absorbable mesh has several desirable characteristics. It promotes postoperative fibroblast activity, has less infectious disease risk, is not rejected, and has not been reported to be harmful to the viscera. One disadvantage is that the resultant scar tissue may not be as strong as the native tissue it is reinforcing (Klinge et al, 2001). Classification of the synthetic meshes occurs by type of mesh (absorbable or nonabsorbable), pore size (macroporous or microporous), and filament type (monofilament or multifilament). Two types of absorbable meshes are available: polyglycolic acid (Dexon, Davis and Geck, American Cyanamid, Danbury, CT) and polyglactin 910 (Vicryl, Ethicon, Somerville, NJ). They differ in the duration in the tissues. Polyglactin 910 starts to hydrolyze by 21 days and loses its mechanical support by 30 days. Polyglycolic acid takes 90 days for absorption.

The most important characteristic of a synthetic mesh is its pore size. Meshes are divided into macroporous (>75 μm) or microporous (<10 μm). Pore size is important from an infectious standpoint because it allows cellular elements such as macrophages and granulocytes to enter the mesh construct. In addition, it is important for tissue ingrowth with fibroblasts, blood vessels, and collagen fibrils (Amid, 1997; Deprest et al, 2006; Dwyer, 2006) (Fig. 72–13). Most bacteria are less than 1 μm; granulocytes and macrophages are greater than 10 μm in diameter, but 75 μm is the key

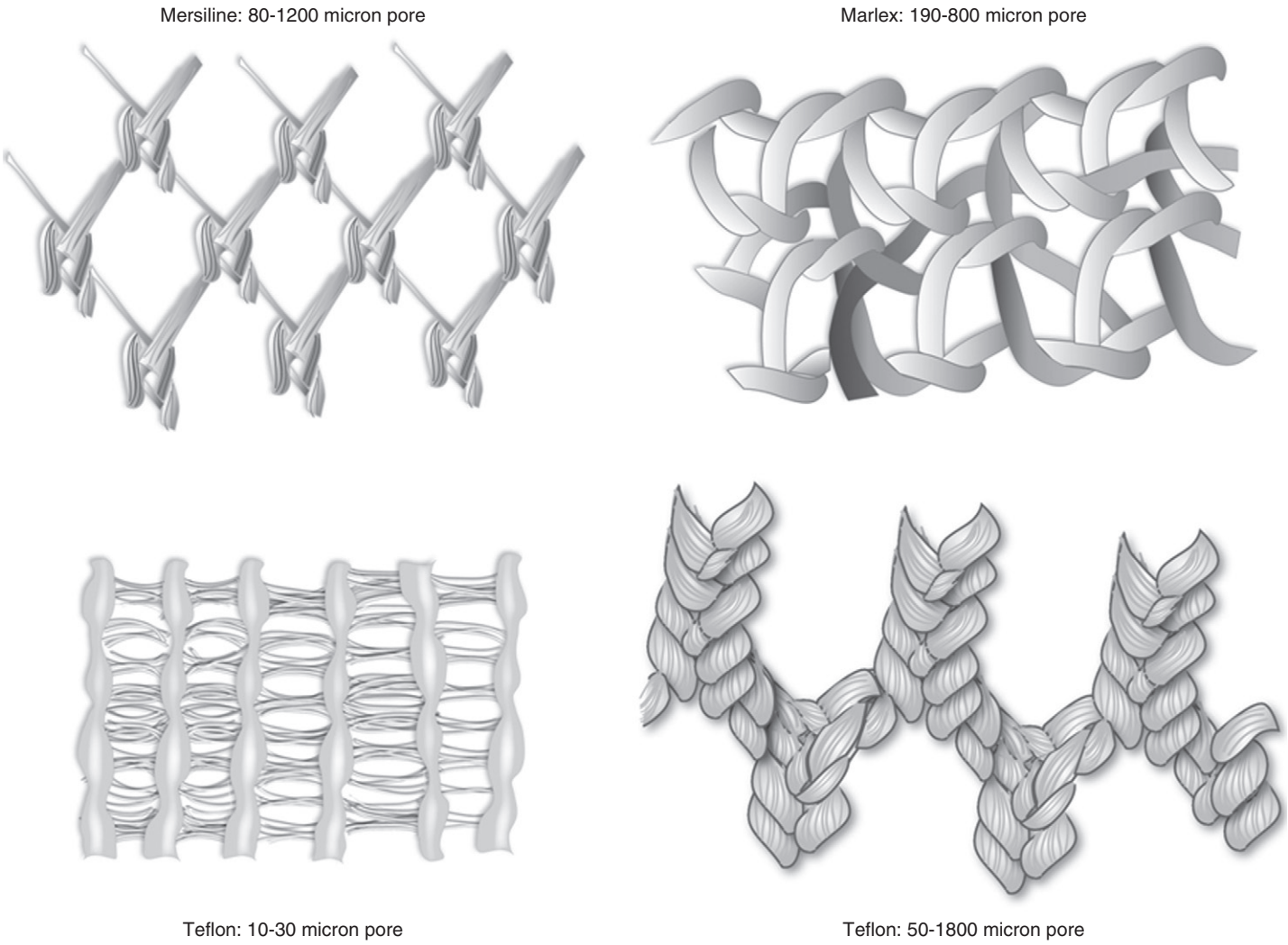


Figure 72–13. Synthetic graft pore and interstices: Note the multifilamentous nature of Mersilene, which may promote bacterial adherence. (From Togami J, Krlin R, et al. Graft materials in prolapse surgery. AUA Update Series 2008;27(31):294–303.)

size that allows the tissue ingrowth. Pore size also determines the flexural rigidity. The larger the pore size, the more flexible the mesh (Dietz et al, 2003). This property may impact local tissue trauma and erosive risk (Birch, 2005).

Synthetic mesh can be monofilament or multifilament. Multifilament synthetics may have pore sizes that allow them to be classified as macroporous; however, between the fibers the size is less than 10 µm, owing to the way they are either woven or knitted. The spaces are small enough to allow bacteria into confines less than 10 µm, which carries a greater theoretical risk than a monofilament mesh. The construct of the mesh affects pore size, and the interstitial distance is measured between the synthetic fibers (Fig. 72–14). Woven mesh has small pore size and interstices, whereas knitted materials are able to assume a macroporous configuration and are flexible with high tissue conformity.

Although there is no classification system specifically used for mesh in pelvic floor reconstruction, the Amid classification, which was originally used to describe mesh used in the treatment of abdominal wall hernias, is currently the standard (Amid, 1997).

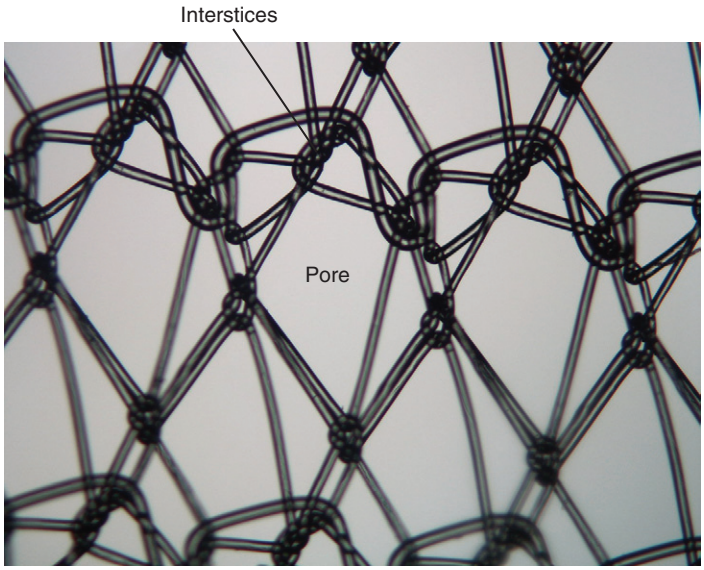


Figure 72–14. Polypropylene mesh depicting pore and interstices.

This classification emphasizes the importance of pore size and filament type (see Fig. 72–11).

Type I promotes host defenses and tissue infiltration. Type II and type III meshes result in a greater foreign body response and are associated with greater rates of erosion (Julian, 1996; Debodinance et al, 1999). **The most desirable synthetic for pelvic floor reconstruction are monofilament, macroporous mesh, most commonly polypropylene mesh.**

SURGICAL MANAGEMENT OF PELVIC ORGAN PROLAPSE (Table 72–2)

Anterior Compartment

Anterior Colporrhaphy

Kelly described his method of cystocele repair as a treatment for urinary incontinence in 1913. He emphasized the importance of repairing the pubocervical fascia with plication sutures to repair the central defect. This procedure eventually became known as the anterior colporrhaphy, and it corrects the central defect in the anterior compartment. However, **anterior compartment defects are commonly combined central and lateral defects. Thus, an isolated anterior colporrhaphy is not recommended except in rare circumstances.** In addition, the American Urological Association Female Stress Urinary Incontinence Clinical Guidelines Panel, in 1997, performed a meta-analysis and found that the failure rate of anterior colporrhaphy as a treatment for stress urinary incontinence (SUI) was close to 40% after 4 years of follow-up (Leach et al, 1997). **As such, anterior colporrhaphy is not recommended as treatment for SUI.**

Technique (Fig. 72–15)**.** After placement of the patient in the dorsal lithotomy position an indwelling urethral catheter is placed and the bladder is kept drained throughout the procedure. Hydrodissection may be utilized to facilitate the dissection. A midline incision is made in the anterior vaginal wall, extending from the vaginal apex to the bladder neck. The incision should not extend to the urethra when a simultaneous midurethral sling is performed. Optimally the sling should be placed through a separate, suburethral incision. However, when performing a pubovaginal sling, it is desirable to create one incision that extends to the distal urethra and facilitates more precise sling location. The vaginal epithelium is dissected off the pubocervical fascia, and the dissection should be carried out sufficiently to delineate the defect. Usually, the incision should extend as far laterally as possible. Allis clamps or a self-retaining ring retractor may be utilized to provide optimal exposure. The bladder is then reduced with a finger or instrument, and this facilitates exposure and reapproximation of the pubocervical tissues. Once these tissues are identified, interrupted 2-0 delayed absorbable plication sutures are then placed from the bladder neck to the apex. The plication sutures are then tied. Care must be taken to avoid excessively deep suture placement to avoid ureteral injury. If the pubocervical fascia is too attenuated, a piece of allograft or mesh can be placed under the vaginal wall on one side to strengthen the repair and prevent suture pull-through (Chesson et al, 1999). After completion of the colporrhaphy, cystoscopy is performed after the administration of indigo carmine or methylene blue to inspect the bladder for any iatrogenic injury and to visualize urine effluxing from each ureteral orifice. Finally, the vaginal wall is trimmed and closed with a 2-0 absorbable suture.

Results. In earlier studies, the reported cure rate of cystocele approached 95% (Table 72–3). In a large, retrospective study that

Table 72–2.
Surgical Approach to Pelvic Organ Prolapse

POP-Q SITE	VAGINAL	ABDOMINAL
Aa Urethra	Anterior repair Pereyra/Raz Sling	Retropubic urethropexy
Ba Bladder	Anterior repair Paravaginal repair Four or six-corner repairs	Wedge colpectomy Paravaginal repair
C Cervix/cuff	Uterosacral ligament suspension Iliococcygeus suspension Sacrospinous fixation Manchester operation Vaginal hysterectomy Colpocleisis	Abdominal hysterectomy Uterosacral ligament suspension Abdominal sacrocolpopexy Uterine suspension
D Cul-de-sac	McCall culdoplasty	Halban culdoplasty Moschkowitz culdoplasty
Ap	Rectovaginal plication (posterior repair) Site-specific repairs	Colpoperineopexy

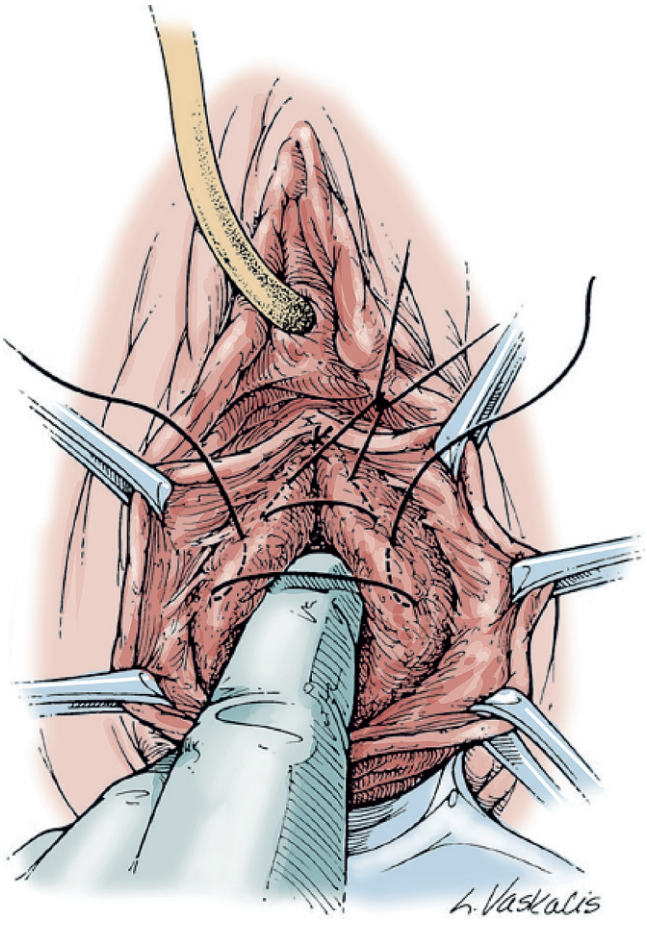


Figure 72–15. Anterior colporrhaphy. The anterior submucosal layer is imbricated with 2-0 delayed absorbable continuous or interrupted suture. (From Nicholas DH. Cystocele. In Nichols DH, editor. Gynecologic and obstetric surgery. St. Louis: CV Mosby; 1993. p. 334–62.)

Table 72–3.

Results of Anterior Compartment Repair without Graft

TECHNIQUE	STUDY	NO. PATIENTS	MEAN FOLLOW-UP (mo)	SUCCESS RATE	EVALUATION	COMPLICATIONS
Vaginal anterior colporrhaphy	Porges and Smilen, 1994	299	31	97%	Baden-Walker classification	Pelvic abscess
	Colombo et al, 2000; Khan et al,1997	33	60	97%	Baden-Walker classification, questionnaire	Dyspareunia
Vaginal paravaginal repair	Shull et al, 1994	56	19	73%	Baden-Walker classification	Femoral nerve paresis, UTI
	Elkins et al, 2000	25	1.5	92% lateral 76% central	Baden-Walker classification	Hemorrhage
	Young et al, 2001; Maher et al, 2004	100	11	98% lateral 78% central	Baden-Walker classification	Hemorrhage, LE neuropathy
	Mallipeddi et al, 2001; Singh et al, 2003	35	19	97%	Baden-Walker classification, IIQ-7 and UDI-6	Pelvic abscess, ureteric obstruction
Needle suspension	Raz et al, 1991	22	31	89%	Baden-Walker classification	De novo UUI, urinary retention
	Miyazaki and Miyazaki, 1994	22	42	59%	Baden-Walker classification	
	Dmochowski et al, 1997	47	37	57%	Baden-Walker classification, questionnaire	De novo UUI
	Safir et al, 1999; Porter et al,1999	112	21	92%	Baden-Walker classification, questionnaire	De novo UUI
Abdominal paravaginal repair	Richardson et al, 1981	233	5	95%	Examination (degree not specified)	Pneumonia
	Scotti et al, 1998	49	39	98% lateral 91% central	Baden-Walker classification	De novo UUI
	Bruce et al, 1999	52	17	85%	Baden-Walker classification	Urinary retention (post sling)

IIQ-7, Incontinence Impact Questionnaire; LE, lower extremity; UDI-6, Urogenital Distress Inventory, Short Form; UTI, urinary tract infection; UUI, urgency urinary incontinence.

included 299 patients with anterior vaginal wall prolapse, Porges and Smilen (1994) reported a recurrence rate of only 3%, with a mean follow-up of 31 months. Recurrence was defined as only symptomatic descent for which further surgery was performed or recommended. Also, in a prospective, randomized trial between Burch colposuspension versus anterior colporrhaphy, Colombo and colleagues (2000) reported a recurrence rate again of only 3% in the 33 patients who underwent anterior colporrhaphy. The mean follow-up was 5 years. All of the patients in both groups underwent concomitant hysterectomy and uterosacral ligament fixation. **Recent series have reported recurrence rates for standard anterior colporrhaphy that approach 40%** (Table 72–4). Recurrence in these series included asymptomatic grade 2 or stage 2 anterior compartment prolapse. Sand and associates (2001) reported on 161 women randomized to either anterior colporrhaphy with polyglactin suture or anterior colporrhaphy with a free polyglactin mesh inlay, which was placed underneath the trigone after plicating the pubocervical fascia. After 1 year of follow-up, the women randomized to polyglactin mesh had a failure rate of 25% compared with the 43% failure rate in those women who underwent the plication with suture alone ($P = .02$). Weber and colleagues (2001) compared anterior colporrhaphy reinforced with polyglactin mesh to traditional plication without tension using polydioxanone suture and "ultralateral" plication using both polydioxanone suture and tension. In this study, 114 women with symptomatic cystoceles (mostly stages 2 and 3 on the pelvic organ prolapse quantification [POP-Q] system) were randomized between the three groups. With a mean follow-up of 23 months there was no significant difference in failure rate (defined as stage 2 or greater on the POP-Q) between the three groups. The failure rate was 30% in those who underwent traditional plication, 46% in those who underwent ultralateral plication, and 42% in those who underwent traditional plication augmented with polyglactin mesh. Unfortunately, the study did not recruit enough women to achieve statistical power to detect differences between the groups. This is in contrast to an earlier paper by the same author that stated that anterior vaginal wall prolapse recurs after standard anterior colporrhaphy in 20% of patients (Weber and Walter, 1997). The Sand and Weber trials are not similar enough to do a meta-analysis. **Yet, the high recurrence rates observed with anterior colporrhaphy illustrates the main concern regarding the durability of this procedure in most women with moderate- or high-grade anterior compartment defects. The most likely contributing factor is the concomitant presence of other compartmental defects.**

Complications. Reported complications from anterior colporrhaphy include de novo SUI (if the patient had SUI masked by a high-grade cystocele), de novo detrusor overactivity, postoperative urinary retention, incomplete bladder emptying, significant bleeding of more than 350 mL, wound infection, bladder or ureteral injuries, vaginal shortening, and dyspareunia. De novo detrusor overactivity can occur in 5% to 7% of patients after standard colporrhaphy (Raz et al, 1991). Yet, preexisting detrusor overactivity has been reported to resolve in up to 63% of patients after surgical repair of pelvic organ prolapsed (Nguyen and Bhattia, 2001).

Table 72–4.

Results of Anterior Compartment (AC) Repair with Graft

TECHNIQUE	STUDY	NO. PATIENTS	MEAN FOLLOW-UP (mo)	SUCCESS RATE	EVALUATION	COMPLICATIONS
Polyglactin 910 mesh	Weber et al, 2001	114	23	AC alone 70% AC + mesh 58%	POP-Q, reported symptoms, visual analog scale	Hemorrhage, vaginal mesh extrusion
	Sand et al, 2001	161	12	AC alone 57% AC + mesh 75%	Baden-Walker classification	Urinary retention (post sling)
Polypropylene mesh	Nicita, 1998	44	13.9	93%	SEAPI QMM scale	Vaginal mesh extrusion and dyspareunia in one patient
	de Tayrac et al, 2002	48	18	97.9%	POP-Q	Vaginal mesh extrusion and dyspareunia
	de Tayrac et al, 2005	87	24	91.6%	POP-Q	Vaginal mesh extrusion and dyspareunia
	Hiltunen et al, 2007	202	12	AC alone 61% AC + mesh 93%	POP-Q and questionnaire	Vaginal mesh extrusion and dyspareunia
	Rodriguez et al, 2005	98	Not reported	85%	POP-Q, UDI-6, validated global QOL question	De novo SUI and de novo UUI
Cadaveric fascia	Groutz et al, 2001	21	20	100%	Baden-Walker classification, 24-hour pad test	Persistent SUI
	Gandhi et al, 2005	154	12	AC alone 71% AC + fascia 79%	POP-Q, Likert questionnaire	Excessive bleeding
	Frederick and Leach, 2005	251	60	93%	Baden-Walker classification, validated questionnaires	Persistent SUI, de novo UUI, urinary retention
	Chung et al, 2002	19	28	89%	Baden-Walker classification, questionnaire	Graft infection and removal
	Clemons et al, 2003	33	18	59% objective 97% subjective	POP-Q, questionnaire	Suture erosion
Porcine dermis	Gomelsky et al, 2004	70	24	87%	Baden-Walker classification, questionnaire	De novo UUI, vaginal wound separation
	Meschia et al, 2007	201	12	AC alone 81% AC + dermis 93%	POP-Q, visual analog scale	Vaginal graft extrusion
	Handel et al, 2007	119	13.5	AC alone 94% AC + mesh 96% AC + dermis 64%	Baden-Walker classification, questionnaire	Vaginal graft extrusion and hemorrhage

POP-Q, Pelvic Organ Prolapse Quantification System; QOL, quality of life; SUI, stress urinary incontinence; UDI-6, Urogenital Distress Inventory, Short Form; UUI, urgency urinary incontinence.

Urinary retention usually happens in cases during which an anti-incontinence procedure is performed. In most instances, the retention resolves after a brief period of CIC. If the retention persists and the patient had a concomitant anti-incontinence procedure, urethrolysis is often required. When impaired bladder emptying is due to preexisting hypocontractility, the patient may require chronic CIC or neuromodulation.

Bleeding during anterior colporrhaphy is usually due to both the high vascularity of the vagina and to the venous complex beneath the inferior pubic bone. **During transvaginal anterior colporrhaphy, problematic bleeding can occur if the dissection is carried out in the wrong plane. During anterior colporrhaphy, the vaginal wall should be dissected off of the pubocervical fascia directly on its white shiny surface.** In patients undergoing repeat anterior colporrhaphy, scarring will often obscure the correct dissection plane. As such, these patients are at higher risk for bleeding.

Bladder or ureteral injuries are rare during standard anterior colporrhaphy. **Bladder injuries can occur when perforation into the retropubic space occurs. Ensuring bladder drainage before perforating the endopelvic fascia may reduce this.** Should an inadvertent bladder injury occur, a two-layer closure should be performed with absorbable suture. If the patient has a history of pelvic irradiation or if the repair quality seems tenuous, a labial fat pad interposition should be considered to prevent vesicovaginal fistula formation (Kreder, 1993). **Cystoscopy after the administration of indigo carmine should be routinely performed with every anterior colporrhaphy.** If blue-stained urine is not seen effluxing from either ureteral orifice, ureteral catheterization should be considered before taking down the plication sutures. In some cases the ureter is patent and an alternative reason will explain the lack of efflux. Appropriate steps must be taken to ensure ureteral patency if the ureter cannot be catheterized. This may include taking down the repair.

Procedures for Lateral and Combined Defects

Vaginal Paravaginal Repair. In his first description of a vaginal paravaginal repair, George White (1909) described a cystocele repair that involved suturing the lateral sulci of the vagina to the white line of the pelvic fascia. White believed that the cause of a cystocele was weakness of the lateral vaginal attachments to the ATFP. As Kelly's anterior colporrhaphy became the primary technique of cystocele repair for the next 70 years, White's concept fell into disfavor. In 1976, Richardson and coworkers (1976) reintroduced the paravaginal defect repair, but they described the technique using an abdominal approach. Regardless of the approach the goal of a paravaginal repair is to repair a lateral compartment defect by reattaching the pubocervical fascia to the ATFP. A vaginal

paravaginal repair may be combined with anterior colporrhaphy in patients with combined lateral and central defects.

Technique (Fig. 72-16)**.** A midline anterior vertical incision is made through the vaginal epithelium from the bladder neck to the vaginal apex. After the vaginal epithelium is sharply dissected off the attenuated pubocervical fascia and bladder the dissection is carried laterally to the pelvic sidewall. Blunt dissection can be used to facilitate this. Access to the pelvic sidewall is achieved by either continued lateral dissection or perforation of the endopelvic fascia. On entry into the retropubic space, palpation is utilized to identify the ATFP as it courses from the ischial spine to the inferior aspect of the pubic ramus. Deep, lighted retractors may be useful to facilitate exposure. With the bladder retracted medially, five to seven interrupted nonabsorbable sutures are placed at 1-cm intervals through the ATFP. A Capio Suture Capturing Device (Boston Scientific, Natick, MA) may expedite placement of these sutures. These sutures are then passed through the lateral edge of the detached pubocervical fascia. No sutures should be tied until all are placed on either one side or both sides (if bilateral defects). At this point, if indicated, central defect plication sutures may be placed to complete a combined repair. As with anterior colporrhaphy, cystoscopy must be performed to confirm ureteral patency and the absence of intravesical sutures. The vaginal wall is trimmed and closed with a 2-0 absorbable suture. Vaginal packing is placed.

Results (see Table 72–4)**.** Shull and colleagues (1994) reported that 41 patients (73%) had no cystocele recurrence with vaginal paravaginal repair after a mean follow-up of 1.6 years. Of the 15 recurrences, only 4 developed to or through the hymen, and in these the prolapse was less than what was noted preoperatively. Elkins and associates (2000) reported an 8% lateral cystocele recurrence rate and a 22% central cystocele recurrence rate 0.5 to 3 years after vaginal paravaginal repair in 25 patients with grade 3 or greater anterior wall vaginal prolapse. Midline central defects were common, leading surgeons to perform joint repairs with an anterior colporrhaphy. Young and coworkers (2001) retrospectively evaluated 100 patients with symptomatic grade 2 to 4 combined central and lateral cystoceles. All 100 patients underwent both vaginal paravaginal repair and concomitant anterior colporrhaphy. With a mean follow-up of 11 months, the lateral cystocele recurrence rate was only 2% and the central cystocele recurrence rate was 22%. Mallipeddi and colleagues (2001) reported a 3% central cystocele recurrence 20 months after vaginal paravaginal repair in 35 patients with grades 2 to 4 anterior vaginal wall prolapse. Of the 21 patients with concomitant SUI, 12 (57%) had persistent SUI after the paravaginal repair. **The paravaginal repair, like standard anterior colporrhaphy, is ineffective in the treatment of SUI.** Finally, there are no studies comparing paravaginal defect repair with or without midline anterior repair to standard anterior colporrhaphy alone.

Although complications after vaginal paravaginal repair are infrequent, they are significant. Young and associates (2001) reported 21 major complications, including three major intraoperative hemorrhagic complications. Two patients developed lower extremity neuropathy, one of whom was in the lithotomy position for a prolonged period of time. Elkins and associates (2000) reported a transfusion rate of 12%. Mallipeddi and coworkers (2001) reported 2 patients with vaginal abscesses that required drainage, 1 patient with retropubic hematoma who required reexploration, and 1 patient with bilateral ureteric obstruction that resolved after takedown of the repair and suture replacement.

The vaginal paravaginal repair as described is technically more challenging than the standard anterior colporrhaphy. Complication rates are higher and usually more serious. In addition, the conventional vaginal paravaginal repair relies on suture placement through weakened pubocervical fascia. To compensate for these factors, most surgeons describe transvaginal correction of lateral defects using placement of grafts, which are attached to the pelvic sidewalls bilaterally.

Anterior Compartment Repairs Utilizing Grafts

Technique. The incision and dissection into the retropubic space are performed in a similar manner as for the vaginal paravaginal repair. Once access to the pelvic sidewall is achieved, the bladder is retracted medially, and 2 to 3 sutures (permanent or delayed absorbable) are placed into the ATFP and/or obturator internus fascia, which will serve as adequate lateral fixation for the graft. A Capio Suture Capturing Device (Boston Scientific, Natick, MA) may expedite placement of these sutures (Fig. 72–17). Before fashioning the graft it is useful to estimate the distance between the proximal and distal ipsilateral sutures and the distance between the sutures on each side. These measurements serve to determine the dimensions of the graft material, which is trimmed to size. At this point, central plication sutures may be placed. The previously placed pelvic sidewall sutures are then brought out to the corresponding locations on the graft. The sutures are then tied, securing the graft to the pelvic sidewall. It is useful to leave the sutures long until after cystoscopy confirms patency of the ureters. The vaginal wall is trimmed and closed with a 2-0 absorbable suture. Vaginal packing is placed at the end of the case.

Results

POLYPROPYLENE MESH (see Table 72–4). Nicita (1998) described the use of polypropylene mesh for the treatment of anterior vaginal wall prolapsed. He sutured the mesh to the anterior aspect of the ATFP on each side using 3-0 polypropylene sutures. With 2 years of follow-up, only 3 of the 44 patients (7%) had prolapse recurrence. The only patient who developed dyspareunia had vaginal mesh extrusion (exposure), and this was managed with mesh trimming and vaginal closure.

de Tayrac and associates, in 2002, described placement of polypropylene mesh (Gynemesh; Ethicon, Somerville, NJ) into the retropubic space in a tension-free fashion without suture fixation. The lateral extensions of the mesh were placed in contact with the ATFP and anchored with a transobturator approach. A total of 48 women with grade 3 and 4 cystoceles underwent this procedure. After a mean follow-up of 18 months the authors reported an anatomic success rate of 97.9%. Vaginal mesh extrusion was noted in 8.3%. In a subsequent series with 87 women and with 24 months of follow-up, de Tayrac and associates again (2005) used GyneMesh and found that 77 women (91.6%) were cured of their symptomatic anterior vaginal wall prolapse, defined as POP-Q stage 0 or 1. Of the 7 patients with recurrent cystoceles, 5 were asymptomatic. Vaginal mesh extrusion was again noted in 8.3%, and the de novo dyspareunia rate was 16.7%.

In a randomized controlled trial of 202 women with anterior vaginal wall prolapse, Hiltunen and coworkers (2007) compared anterior colporrhaphy (n = 97) to the same procedure reinforced with low-weight polypropylene mesh (n = 105). After 1 year of follow-up the addition of the polypropylene mesh to the anterior repair did statistically decrease the risk of recurrent stage 2 or greater anterior prolapse. **Recurrence was noted in 7 of 104 women in the mesh group versus 37 of 96 women in the group with no graft ($P < .001$). However, there was no statistically significant difference in symptomatic outcomes (pelvic pressure, vaginal bulging, or difficulty with bladder emptying) between the groups.**

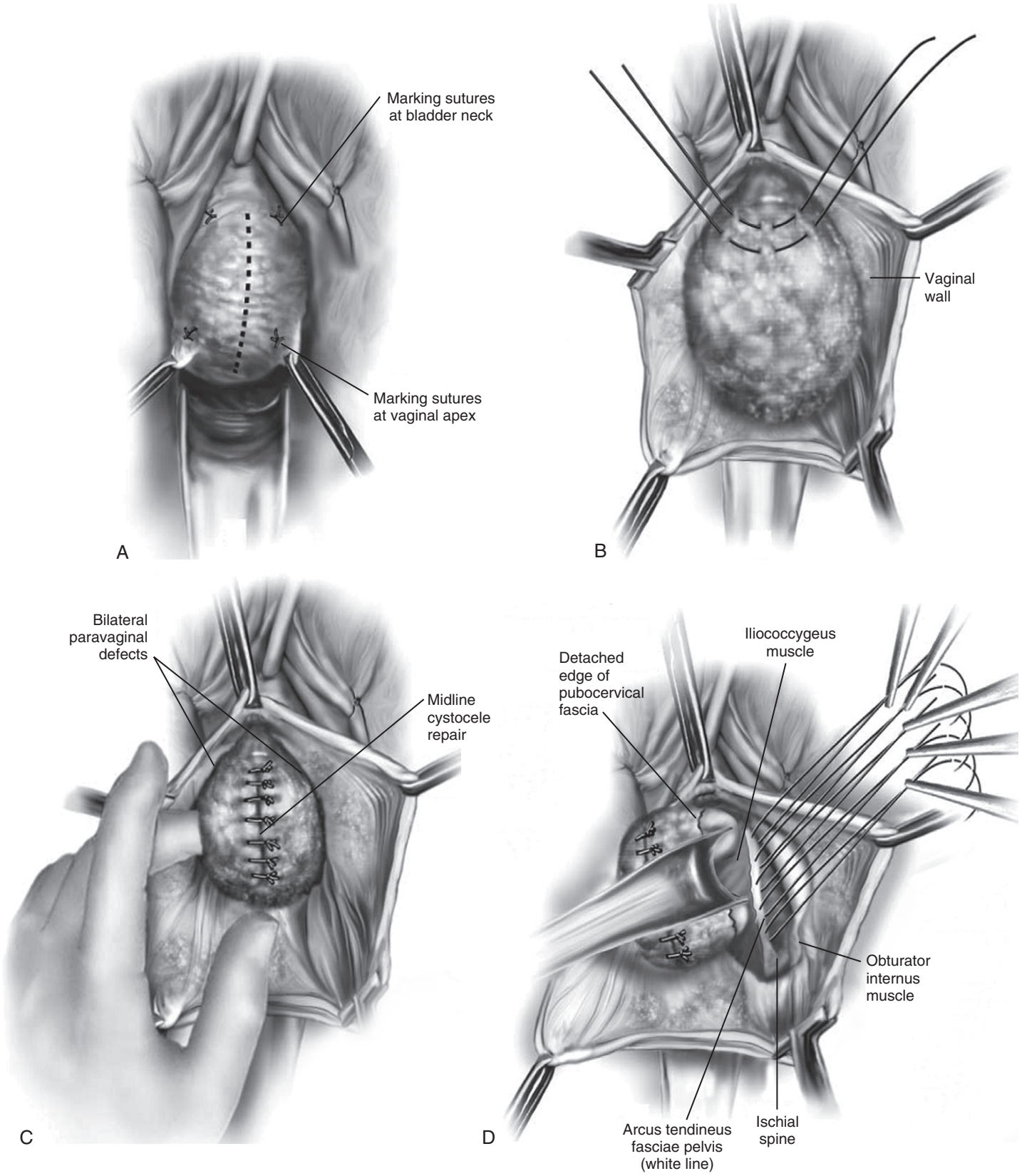


Figure 72–16. Vaginal paravaginal repair. **A,** Unopened anterior vaginal wall with marking sutures placed at anatomic level of bladder neck and vaginal apex. **B,** Anterior vaginal wall opened via a midline incision. Sutures placed for midline cystocele repair. **C,** Midline cystocele repair completed. Bilateral paravaginal defects identified. **D,** Bladder retracted medially to expose lateral pelvic sidewall. Permanent sutures have been passed through the white line.

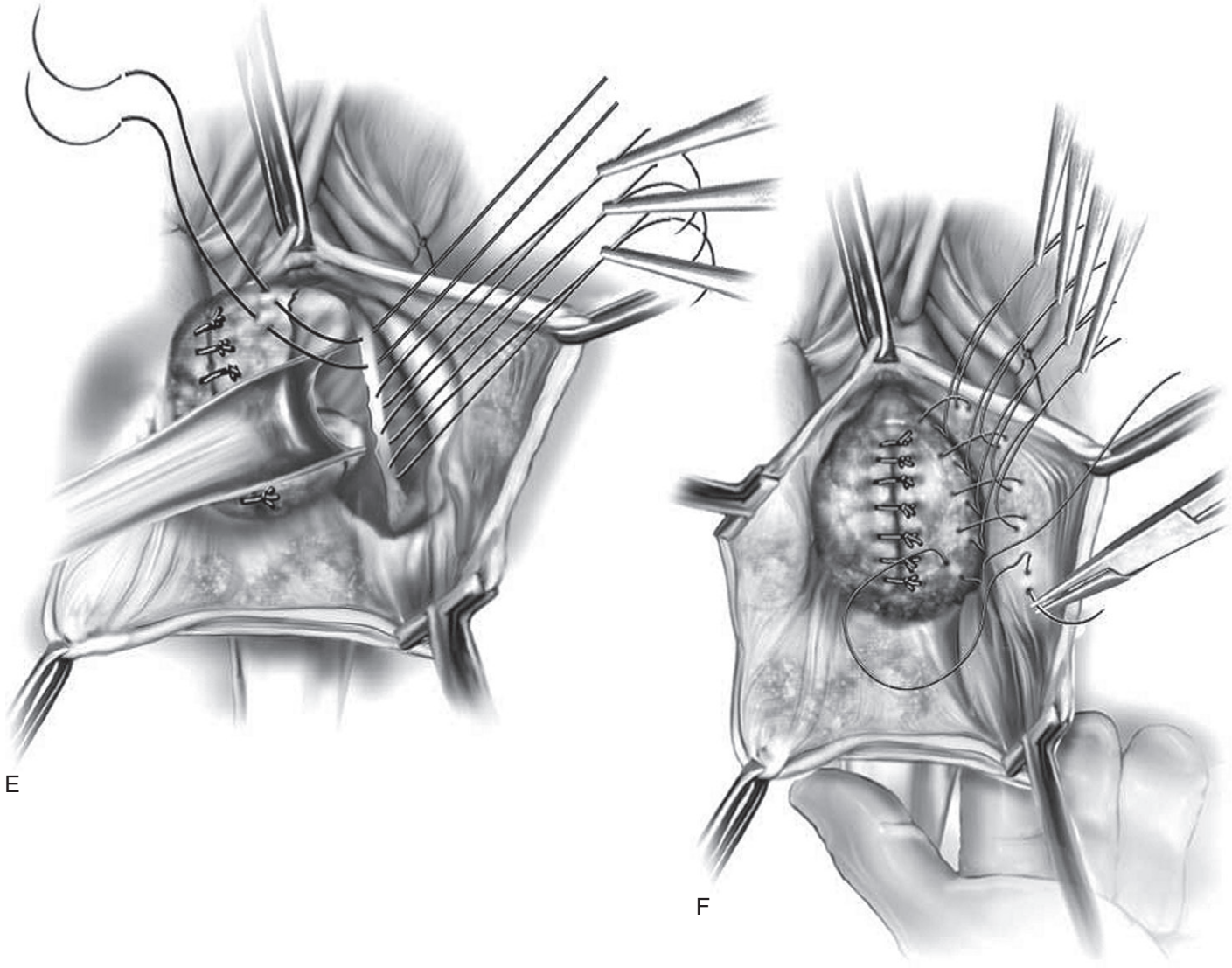


Figure 72–16, cont'd. **E,** Top two sutures have been passed through detached edge of pubocervical fascia. **F,** Three-point closure is completed with all sutures passed through the pubocervical fascia and inside wall of the vagina. (From Mallipeddi PK, Steele AC, Kohli N, et al. Anatomic and functional outcome of vaginal paravaginal repair in the correction of anterior vaginal wall prolapse. Int Urogynecol J 2001;12: 83–88, with permission.)

Importantly, 18 patients in the mesh group (17.3%) had vaginal extrusion of the mesh, although only 4 of the 18 patients were symptomatic and none required total removal of the mesh.

In a prospective study of 98 patients with stage 3 and 4 cystoceles using the POP-Q, Rodriguez and associates (2005) attached a 5 × 5-cm piece of polypropylene mesh to the obturator internus fascia using 2-0 polyglactin suture to repair the paravaginal defect (Fig. 72–18). This mesh was placed after repair of the central defect with horizontal mattress sutures of 3-0 polyglactin. All patients underwent a distal urethral polypropylene sling regardless of any SUI symptoms. They reported an 85% anatomic success rate, defined as stage 0 or 1. No patient experienced urinary retention. Three patients who did not report SUI before the procedure developed mild de novo SUI after the procedure. Overall quality of life due to genitourinary symptoms improved from 4.7 (unhappy) to 1 (pleased) ($P < .005$).

CADAVERIC FASCIA (see Table 72–4). Groutz and colleagues (2001) prospectively enrolled 21 women with grade 3 or 4 anterior vaginal wall prolapse to cystocele repair using solvent dehydrated cadaveric fascia lata (Fig. 72–19). The graft was anchored transversally between the bilateral arcus tendineus and the cardinal and uterosacral ligaments. Also, 19 of the 21 women underwent concomitant pubovaginal sling for either symptomatic or occult SUI. After a mean follow-up 20 months, none of the patients developed a recurrent cystocele. In addition, no patient developed new-onset dyspareunia, pelvic pain, or postoperative vaginal stenosis.

Gandhi and colleagues (2005) published a prospective randomized controlled trial comparing ultralateral anterior colporrhaphy with 0 polyglactin suture (n = 78) to the same colporrhaphy reinforced with cadaveric fascia lata (n = 76) in women with grade 2 or greater anterior vaginal wall prolapse. Previous surgery did not preclude participation. Although there was a trend toward improved anatomic outcome with graft use, the addition of the

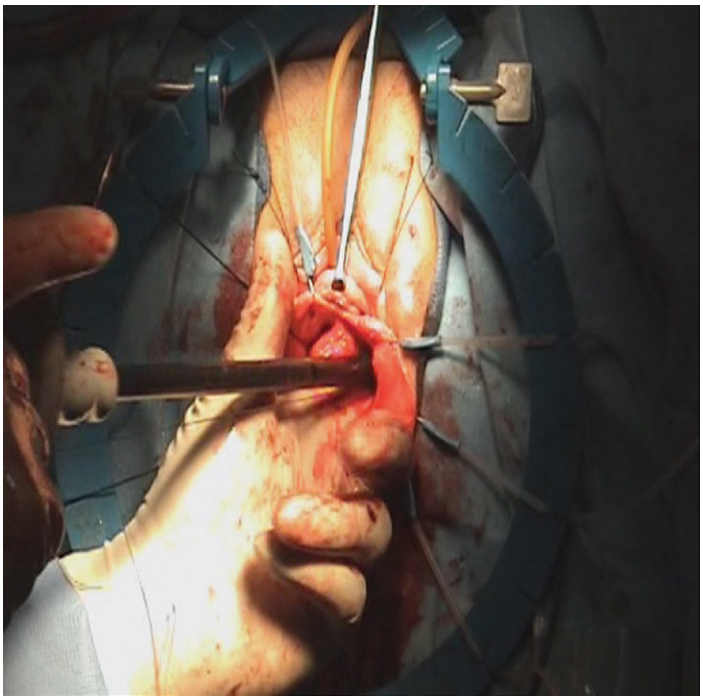


Figure 72–17. Capio needle driver utilized to facilitate suture placement in the arcus tendineus fascia pelvis. (Photograph courtesy of Victor Nitti.)



Figure 72–18. Anterior compartment repair with polypropylene mesh graft. Polypropylene mesh is anchored to the uterosacral ligament at the bladder base, laterally to the obturator fascia and distally to the bladder neck using 2-0 polyglactin suture. (From Rogriguez LR, Bukkapatnam R, Shah SM, et al. Transvaginal paravaginal repair of high-grade cystocele central and lateral defects with concomitant suburethral sling: report of early results, outcomes, and patient satisfaction with a new technique. Urology 2005;66[Suppl. 5A]:57–65.)

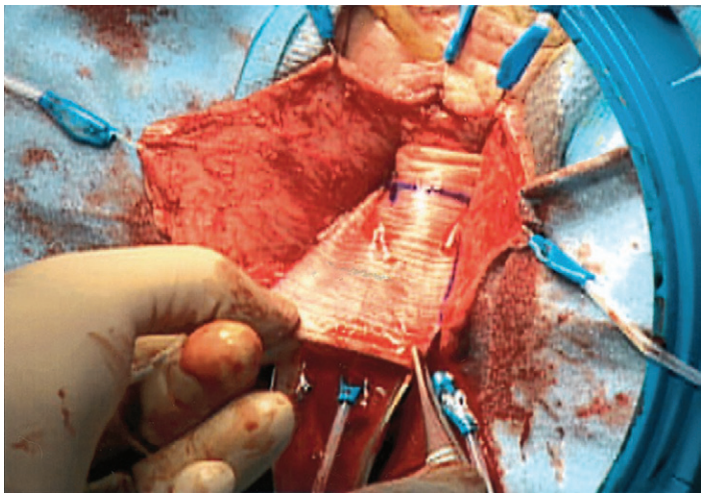


Figure 72–19. Anterior compartment repair with cadaveric fascia graft. Cadaveric fascia patch was tailored appropriately. Typically a 5- × 7-cm patch is more than adequate. (From Groutz A, Chaikin DC, Theusen E, et al. Use of cadaveric solvent-dehydrated fascia lata for cystocele repair—preliminary results. Urology 2001:58:179–83.)

fascia lata patch to the anterior repair did not statistically decrease the risk of recurrent grade 2 or greater anterior vaginal wall prolapse ($P = .23$). Of the 39 total patients with recurrent prolapse, 26 (67%) were asymptomatic. Interestingly, concomitant transvaginal Cooper ligament sling procedures were associated with a decrease in recurrent grade 2 anterior vaginal wall prolapse ($P < .0001$).

Kobashi and coworkers (2000) first described the cadaveric prolapse repair and sling procedure (CaPS) as combined treatment of both symptomatic cystocele and SUI. The procedure is performed transvaginally using a 6 × 8-cm piece of cadaveric fascia lata and bone anchors. In a noncomparative study of 251 patients with a mean follow-up of 2 years after CaPS, Frederick and Leach (2005) noted a symptomatic cystocele recurrence rate of 7%. Because the cured/dry rate for SUI was 56%, with most of the failures occurring beyond 1 year, the authors questioned the long-term efficacy of the sling portion of the CaPS.

Cadaveric dermis was evaluated by Chung and colleagues (2002) in 19 patients with combined SUI and symptomatic grade 3 cystocele. The proximal portion of the 3 × 7-cm graft was sutured to the uterosacral/cardinal ligament complex to repair the central cystocele defect, and the distal portion of the allograft was used as the sling. Patients with lateral and paravaginal defects were excluded. The mean follow-up was 28 months. One patient developed a graft infection and underwent graft removal. Of the remaining 18 patients, 16 patients had no cystocele recurrence. Seventeen of the 18 patients (94%) were cured of their SUI, including 10 patients who had prior incontinence surgery. Clemons and coworkers (2003) described a vaginal paravaginal repair using cadaveric dermis in 33 women with recurrent stage 2 or with primary or recurrent POP-Q stage 3 or 4 cystoceles. The 3 × 7-cm graft was positioned over the bladder base and secured to the ATFP with four sutures of 2-0 braided permanent polyester bilaterally. The mean follow-up was 18 months. Objectively, 13 patients (41%) had recurrent stage 2 cystoceles; however, only 1 patient (3%) had a symptomatic recurrence. All of the objective failures were failures of point Aa on the POP-Q, implying that the anterior vaginal wall was well supported proximally but not distally. Eight

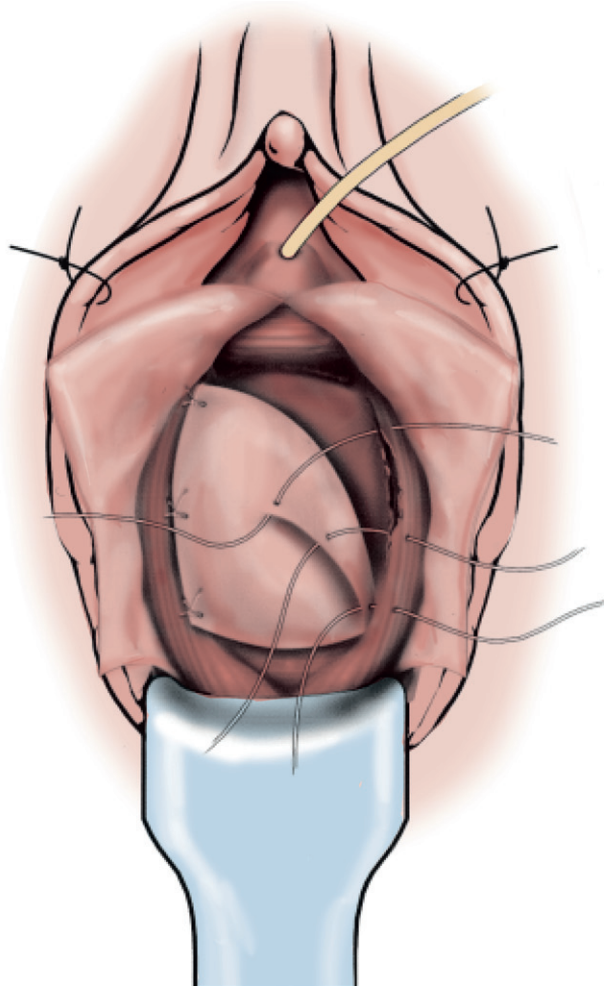


Figure 72–20. Anterior compartment repair with porcine dermis graft. Three pairs of delayed absorbable sutures are inserted into the arcus tendineus fasciae pelvis and into the porcine dermis patch. (From Gomelsky A, Rudy DC, Dmochowski RR. Porcine dermis interposition graft for repair of high grade anterior compartment defects with or without concomitant pelvic organ procedures. J Urol 2004;171:1581–4.)

women underwent a concurrent TVT sling, and the TVT sling did not prevent objective failure.

PORCINE DERMIS (see Table 72–4). The majority of clinical experience in the use of xenografts for pelvic organ prolapse has been with porcine dermis. Pelvicol (CR Bard, Murray Hill, NJ) is acellular cross-linked porcine dermis (Chen et al, 2007). Gomelsky and associates (2004) reported favorable, durable outcomes using a 6 × 8-cm piece of porcine dermis sutured laterally to the ATFP to correct high-grade cystoceles (Fig. 72–20). In a retrospective review of 70 patients, 61 patients (87%) had no cystocele recurrence after a mean follow-up of 24 months. Of the 9 patients (13%) with recurrent cystoceles, none was symptomatic. One patient had superficial vaginal wound separation, which was treated with conservative measures.

Meschia and colleagues (2007) published a prospective randomized controlled trial comparing anterior colporrhaphy with 0 polyglactin suture (n = 103) to the same colporrhaphy reinforced with a 4 × 7-cm piece of Pelvicol (n = 98) in women with stage 2 or greater anterior vaginal wall prolapse as defined on the POP-Q. After 1 year of follow-up, the women randomized to receive the Pelvicol graft experience graft failure 7% of the time, compared with the 19% failure rate in those women who underwent the anterior colporrhaphy with suture plication alone (P = .019). One patient who received the Pelvicol graft had vaginal extrusion of the mesh 1 month after surgery. Finally, there were no differences between the two groups in the incidence of postoperative dyspareunia.

In a recent retrospective study, Handel and associates (2007) compared two different grafts (polypropylene mesh and porcine dermis) to traditional anterior colporrhaphy with suture alone. In a nonrandomized comparison, 119 patients underwent cystocele repair using one of the three techniques. Traditional anterior colporrhaphy was performed in 18 patients, colporrhaphy reinforced with a 3 × 7-cm piece of polypropylene mesh was performed in 25 patients, and colporrhaphy reinforced with a 3 × 7-cm piece of porcine dermis was performed in 56 patients. For patients undergoing repair with a graft, it was anchored to the levator fascia bilaterally and to the uterosacral/cardinal ligament complex. With a mean follow-up of 13.5 months there was no significant difference in failure rate (defined as grade 2 or greater on the Baden-Walker classification) between the three groups. Unfortunately, the study was not powered adequately because there was no sample size justification among the groups.

Complications. **Vaginal exposure (extrusion) has been reported in anterior compartment prolapse repair with most materials.** Rates from 0% to 13% have been reported in recent series with synthetic grafts (Sand et al, 2001; Weber et al, 2001; Dwyer and O'Reilly, 2004; de Tayrac et al, 2005; Milani et al, 2005; Rodriguez et al, 2005) and are less common with biologic grafts. Dyspareunia has been reported by 3.1% to 19% of patients with anterior colporrhaphy (Dwyer and O'Reilly, 2004; Yan et al, 2004; Milani et al, 2005).

Other Procedures to Correct Anterior Compartment Defects

Six-Corner Needle Suspension. Raz and colleagues (1989) originally described the four-corner needle suspension in 1989 for women with SUI due to urethral hypermobility and mild to moderate lateral cystocele defect. With a mean follow-up of 24 months, they reported a 94% subjective correction of SUI and a 98% correction of cystocele on physical examination. The procedure did not include anterior colporrhaphy. The technique was modified to a six-corner suspension in 1996 by Albo and associates to treat larger-grade cystoceles.

Technique (Fig. 72–21)**.** The technique begins by making two parallel, oblique incisions from the bladder neck to the proximal vagina. Alternatively, this can also be accomplished through a midline incision. The dissection is then carried lateral to expose the pubocervical fascia. The endopelvic fascia is perforated, and the retropubic space is entered. Three sets of size 1 polypropylene suture are placed on each side. Each suture incorporates multiple passes through the tissue. The proximal sutures are placed through the cardinal ligament and vaginal wall to support the bladder base. The middle and distal sutures are placed to support the bladder neck and proximal urethra, respectively. Next, a small suprapubic incision is made, and the double-pronged ligature carrier is passed under direct fingertip control through the retropubic space, exiting in the vaginal incision. All six sutures are transferred individually to the suprapubic incision. After the administration of intravenous indigo carmine, cystoscopy is performed to confirm both ureteral patency and the absence of suture in either the bladder or urethra. The polypropylene sutures are then lifted to ensure anatomic reduction of the cystocele. The vaginal incision is closed with a running 2-0 polyglactin suture. Finally, the polypropylene

suspension sutures are tied sequentially to themselves and to the corresponding one from the opposite side. **It is important to tie the polypropylene suspension sutures without tension to avoid postoperative urinary retention.** The suprapubic site is irrigated with povidone-iodine solution, and the wound is closed with 4-0 polyglactin.

Results (see Table 72–4)**.** For larger cystoceles with a central defect, Raz and colleagues (1991) combined anterior colporrhaphy with his four-corner needle suspension. Of the 46 patients who underwent the repair, 5 (11%) had prolapse recurrence with a mean follow-up of 2.8 years. Miyazaki and colleagues (1994) noted a prolapse recurrence rate of 59% in the 22 patients they followed for 3.5 to 4 years after four-corner needle suspension. In a prospective study of 47 patients, Dmochowski and associates (1997) noted that 27 patients (57%) had grade 1 or 2 cystoceles after a four-corner needle suspension with a mean follow-up of 37 months. Recurrent prolapse symptoms were noted in 12 of these 27 patients. Safir and associates (1999) described the four-defect repair of grade 4 cystoceles, whereby a vaginal wall sling and anterior colporrhaphy reinforced with polyglactin mesh are added to the traditional Raz four-corner needle suspension. With a mean follow-up of 21 months, 92% of the 112 patients had excellent objective and subjective results for cystocele repair. Of the patients with preoperative SUI, 90% had excellent or good subjective results.

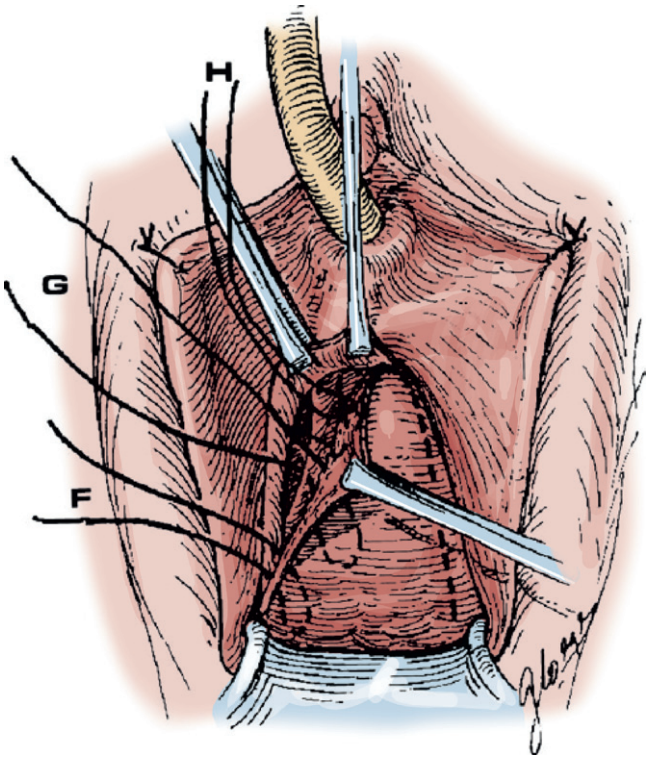


Figure 72–21. Six-corner bladder neck suspension with size 1 polypropylene sutures placed at the level of the vaginal cuff (F), bladder neck (G), and distal urethra (H). (From Albo M, Dupont MC, Raz S. Transvaginal correction of pelvic prolapse. J Endourol 1996;10:231–9.)

Complications. Complications of four- and six-corner suspensions include bladder or urethral injury with suture passage, ureteral obstruction, and injury or entrapment of the genital branch of the genitofemoral or ilioinguinal nerve.

A number of needle suspension reports have demonstrated high failure rates utilizing the six-corner repair in the treatment of anterior compartment defects. Perhaps, suture displacement through weakened tissue contributes to these failures. Although not commonly utilized at present, these procedures were influential in exposing urologists to the technique of endopelvic fascia perforation and access into the retropubic space, which is a useful adjunct to many commonly performed procedures utilized today in the correction of POP.

Abdominal Paravaginal Repair. ***Technique*** (Fig. 72–22)**.** Positioning and preparation of the patient to allow abdominal and vaginal access initiate the repair. The bladder is drained. The retropubic space is entered through either a low midline or transverse incision. Additionally, this may be accomplished laparoscopically. The bladder neck, symphysis pubis, endopelvic fascia, ATFP, and obturator fascia should all be clearly identified. The normal site of normal vaginal attachment on the pelvic side wall from the interior aspect of the superior pubic ramus to the ischial spine is then identified. The surgeon's nondominant hand is placed into the vagina and used to elevate the lateral superior vaginal sulcus to its site of normal attachment along the course of the ATFP. With the bladder retracted medially, four to six interrupted nonabsorbable sutures are placed at 1-cm intervals through the ATFP extending from the ischial spine to the pubic bone. These sutures are then placed in the appropriate location in the lateral wall of the vagina. Care is taken to avoid paravaginal veins, which commonly course through this area. Elevating the vagina to its normal

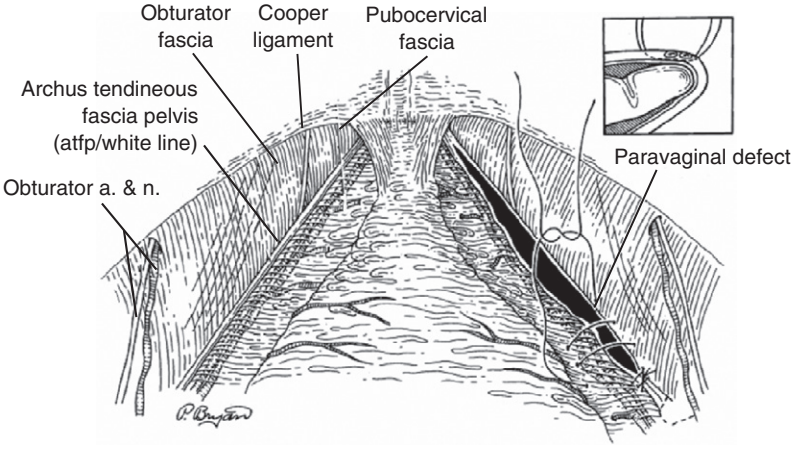


Figure 72–22. Abdominal paravaginal repair. Paravaginal defect repair as viewed from the retropubic space: approximation of the pubocervical fascia medially to the arcus tendineus fasciae pelvis laterally with 2-0 braided nonabsorbable suture. Note the vertical orientation of the vaginal vessels in relation to the transverse orientation of the bladder vessels. *Inset* shows suture being passed beneath the vaginal vessels to ensure generous purchase of pubocervical fascia and control of hemostasis. (From Bruce RG, El-Galley R, Galloway NT. Paravaginal defect repair in the treatment of female stress urinary incontinence and cystocele. Urology 1999;54:647–51.)

anatomic position to localize suture placement site may facilitate vaginal suture placement. After the sutures are tied, cystoscopy must be performed to confirm ureteral patency and the absence of intravesical sutures. The incision is closed and the catheter is left indwelling.

Results (see Table 72–4)**.** Richardson and coworkers (1976) popularized the abdominal paravaginal defect repair. In a retrospective study of 233 patients with follow-up spanning 2 to 8 years, they reported an anatomic cure of 95%. Of these patients, 53 (23%) had previously undergone one or more successful anterior vaginal wall prolapse repairs. No patient required transfusion. Eighty-eight percent of the women with preoperative SUI were cured after abdominal paravaginal repair (Richardson et al, 1981).

Other authors published the results of case series that demonstrated similar encouraging results with SUI cure rates of 85% to 97% after abdominal paravaginal repair (Baden and Walker, 1987; Shull and Baden, 1989). **However, recent evidence over the past 15 years suggests that abdominal paravaginal defect repair is not as effective as either the Burch colposuspension or suburethral sling for the treatment of SUI.** In 1996, Colombo and coworkers (2000) published the results of a randomized trial comparing paravaginal defect repair to Burch colposuspension for the treatment of SUI in 18 patients. With a mean follow-up of 2.2 years, the objective (urodynamic) cure rates were 100% for Burch colposuspension and 61% for abdominal paravaginal defect repair. Colombo and coworkers found that the Burch colposuspension increased the functional urethral length and pressure transmission ratio in the proximal urethra whereas the abdominal paravaginal repair did not. Bruce and associates (1999) examined the abdominal paravaginal defect repair (PVdR) in the treatment of women with both lateral cystocele and symptomatic SUI. In this retrospective cohort of 52 patients, half underwent abdominal PVdR and half underwent abdominal PVdR with pubovaginal sling using rectus muscle. All the patients who underwent concomitant sling had intrinsic sphincter deficiency. With a mean follow-up of 17 months, 4 patients (8%) had recurrent cystocele, 3 patients developed vault prolapse, and 1 patient developed an enterocele. Thus, the overall prolapse cure rate was 85%. Finally, the overall cure rate for SUI was 72% in the group that underwent PVdR alone and 85% in the group that underwent PVdR and pubovaginal sling.

Anterior Compartment Repair with Sling. In patients with high-grade anterior compartment prolapse the descent may create urethral kinking and urethral compression (Gallentine and Cespades, 2001) (Fig. 72–23). This may predispose a patient to develop SUI after prolapse correction. Documenting the presence of SUI in patients with the prolapse reduced is helpful in the preoperative management of women with high-grade anterior compartment prolapse. **SUI occurring in presumably continent women after prolapse correction is known as occult SUI. It is essential for women with high-grade prolapse to undergo an evaluation with the prolapse reduced to identify if they are at risk for occult SUI.** In two prospective studies POP repair in clinically continent women was shown to result in postoperative SUI in 11% to 22% (Stanton et al, 1982; Borstad and Rud, 1989).

To diagnose occult SUI, the prolapse may be reduced with vaginal packing, rectal swabs, a speculum blade, or pessary. Ghoniem and coworkers (1994) used a vaginal pack (formed from two rolled 4 × 4-inch gauze pads) to reduce large cystoceles and found occult SUI in 69% of the women. They found that the vaginal pack provided superior visualization of the vesicourethral angle during fluoroscopic urodynamics. Gallentine and Cespades (2001) used gauze packing and a speculum blade to reduce high-stage POP and found occult SUI in at least 50% of the women with high-grade anterior compartment prolapse. Using a fitted vaginal pessary, Chaikin and coworkers (2000) detected occult SUI in 58% of the women. They also noted that none of the women had urethral obstruction after pessary placement.

There are multiple techniques used to reduce prolapse, and these methods are not standardized. This has led to variance in the reported incidence of occult SUI (Haessler et al, 2005). Veronikis and associates (1997) compared prolapse reduction with rectal swabs, Gellhorn pessary, and a Graves speculum blade. Because prolapse reduction with rectal swabs revealed a significantly lower midurethral closure pressure, these authors concluded that the rectal swabs were superior. **Sensitivity and specificity data are lacking with all of the methods used to reduce POP. As such, no method for prolapse reduction has been proven to be superior.**

Performing a concomitant sling at the time of anterior vaginal wall prolapse repair in women without symptoms of SUI or occult SUI remains controversial. Twiss and colleagues (2007) recommended a simultaneous anti-incontinence procedure at the time of high-grade POP repair because they contend there is no correlation between the preoperative position of the urethra utilizing any

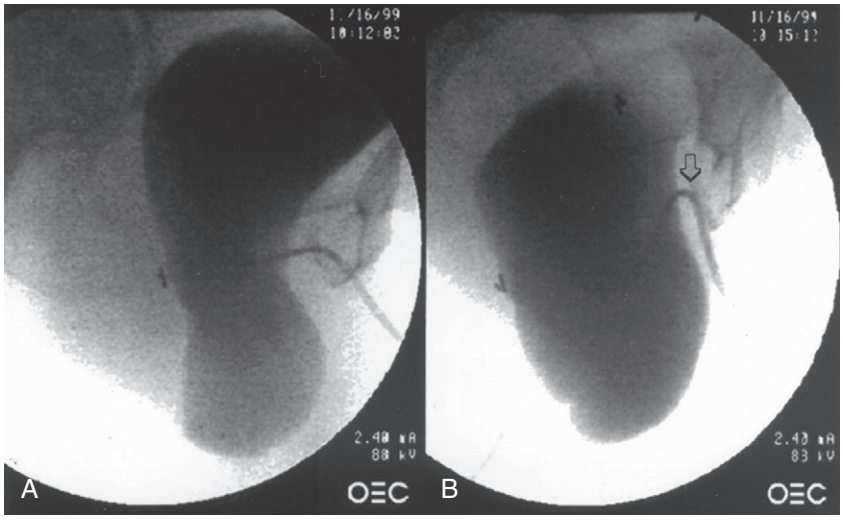


Figure 72–23. Urethral kinking caused by large cystocele. Fluorourodynamic study shows a large cystocele before **(A)** and after **(B)** Valsalva maneuver was performed. The urethra *(arrow)* clearly can be seen to "kink off" during the Valsalva maneuver. The patient did demonstrate severe SUI after prolapse reduction. (From Gallentine ML, Cespedes RD. Occult stress urinary incontinence and the effect of vaginal vault prolapsed on abdominal leak point pressures. Urology 2001;57:40–4.)

method of cystocele reduction and the ultimate position of the urethra after surgery. Thus they believe that the diagnosis of occult SUI is inconsistent and not reproducible. Consequently, occult SUI could be missed. It has also been reported that a concomitant suburethral sling may contribute to the long-term success of anterior compartment repairs. Goldberg and associates (2001) demonstrated a 55% reduction in postoperative cystocele recurrence in patients who underwent suburethral sling at the time of prolapse repair. Also, Cross and coworkers (1997) reported that the support created by the simultaneous placement of a pubovaginal sling in grade 3 and 4 cystoceles was improved. It remains an important distinction that the protection from recurrent anterior compartment defects has only been described for bladder neck slings, which are not the most commonly performed midurethral sling procedures.

Liang and associates (2004) prospectively evaluated 49 patients with severe POP and occult urinary incontinence. POP repair alone was performed in 17 patients with occult SUI, and POP repair with simultaneous TVT was performed in 32 patients. They found that the addition of a prophylactic TVT to the prolapse repair significantly decreased postoperative objective and subjective SUI rates. Yet, in this series some patients with occult SUI did not undergo sling. Of the 30 patients without occult SUI preoperatively, none had SUI postoperatively. Also, complication rates were higher in the group undergoing concomitant sling.

The Colpopexy and Urinary Reduction Efforts trial is the only large, randomized, controlled trial evaluating a simultaneous anti-incontinence procedure with POP repair (Brubaker et al, 2006). The investigators evaluated 322 patients with stage 2 to 4 POP who underwent abdominal sacrocolpopexy, of whom 157 were randomized to concomitant Burch colposuspension and 165 were randomized to abdominal sacrocolpopexy alone. The addition of a Burch colposuspension to abdominal sacrocolpopexy decreased postoperative SUI from 44.1% to 23.6% at 3 months postoperatively. In a subsequent study examining 2-year outcomes in the same group of patients, the authors found that 32% of patients who underwent concomitant Burch colposuspension were incontinent versus 45% of patients who underwent abdominal sacrocolpopexy alone (Brubaker et al, 2008). Approximately a third of the women after a Burch colposuspension still had SUI. Thus the major implication of this work is that women undergoing colpopexy should have an anti-incontinence procedure. However, these data cannot be generalized to women who undergo transvaginal POP repair or anti-incontinence procedures other than Burch colposuspension.

Most authors who have examined this issue have reported that the majority of women without occult SUI or symptoms of SUI do not leak after prolapse surgery. Chaikin and colleagues (2000) reported that all (100%) of their patients without occult SUI did not leak after prolapse. They concluded that the decision to perform a concomitant prophylactic anti-incontinence procedure should be tailored to individual urodynamic findings. Ballert and associates (2009) reported that 22 of 24 women (91.7%) without symptomatic or occult SUI did not leak after repair of stage 2 to 4 POP. They also found that the risk of intervention due to obstruction after receiving a midurethral sling was 8.5%. Therefore, the risk of intervention due to sling obstruction was equal to the risk of intervention due to SUI when no clinical, urodynamic, or occult SUI was present and no midurethral sling was placed. Because the need to intervene for complications resulting from a midurethral sling equaled the risk of having to perform a secondary sling, the necessity for secondary surgery in women without SUI after repair of anterior vaginal wall prolapse is not decreased.

In summary, there is no standardized terminology or accurate testing for occult SUI. In addition, there are no controlled studies proving that continent women (no clinical, urodynamic, or occult SUI) develop postoperative SUI. **However, it is clear that all women with advanced stage anterior compartment prolapse should be screened for the presence of SUI with the prolapse reduced and consideration should be given to a concomitant anti-incontinence procedure. All women with preoperative symptoms of SUI, occult SUI, or urodynamically proven SUI should undergo a simultaneous anti-incontinence procedure. The risks and benefits of a prophylactic anti-incontinence procedure on continent women should be reviewed with each patient because the current literature supports selective use of an anti-incontinence procedure at the time of POP repair.**

Apical Vaginal Compartment

Middle compartment defects involve the vaginal apex. The organs involved in defects of the middle compartment include the uterus, bowel or omentum, and, depending on the size, bladder and rectum. **The apex remains the cornerstone of vaginal support, and failure to ensure apical support at the time of prolapse correction will undoubtedly increase the risk of recurrence exponentially.**

McCall (1957) highlighted this importance when he described his technique of posterior culdoplasty. This technique closed the peritoneal cul-de-sac posteriorly, thereby preventing enterocele formation, and emphasized the importance of apical fixation. In this landmark paper, he described the following technique:

> The posterior culdoplasty is a simple procedure which obliterates the redundant cul-de-sac of Douglas by a series of continuous sutures so as to suspend it by the uterosacral ligaments which then are brought together in the midline…The first suture picks up the left uterosacral ligament about 2 cm above its cut edge. Several bites of redundant sac are then taken at 1-2 cm intervals until the right uterosacral ligament is reached and picked up…Three external through-and-through sutures of this type are usually inserted, each one higher than the last, so as to be placed through the uterosacral ligaments at intervals between the internal sutures. The highest of these is placed just at the top of the newly supported vagina. It is this suture, which brings the new vaginal vault to the highest possible level thus insuring that the vagina will be as long as possible in each instance. The internal sutures are now tied and the previously herniated cul-de-sac obliterated into a firm, shelflike structure. The external sutures are then tied and the vaginal mucosa snugged against this shelf.

Apical Vaginal Prolapse Repairs

The uterosacral vault suspension preserves the orientation of the vaginal axis in its natural position, thus potentially preventing recurrence of prolapse in other segments (Silva et al, 2006). Several authors have reported that the uterosacral ligaments break at specific points rather than an attenuation of the uterosacral/cardinal ligament complex, thus allowing for a more site-specific repair (Jenkins, 1997; Barber et al, 2000; Shull et al, 2000). These findings are in contrast to a histologic assessment of the uterosacral ligaments, which calls into question the integrity of this structure for long-term apical support (Cole et al, 2006).

Surgical Anatomy of the Uterosacral Ligaments. The ligament is attached broadly to S1 to S3 and variably to S4 (Buller et al, 2001) (Figs. 72–24 and 72–25). It proceeds in a fanlike manner anterolaterally to the cervical os and also onto the proximal portion of the posterior vagina. The ligament can be divided into sacral, intermediate, and cervical portions. Beneath the sacral portion of the ligament runs the superior gluteal vein. Although there is great variability in the location of the ureter relative to the spine (Karram

et al, 2001), the ureter has been reported to be near the anterior margin of the uterosacral ligament near the cervix. As the ureter courses distally, the distance between the uterosacral ligament and ureter decreases from 4 cm near the sacrum to 0.9 cm near the cervix (Buller et al, 2001). Because of the fibrous tissues of the ureteral sheath, the ureter is subject to kinking from traction caused by sutures placed in the adjacent tissue (Dwyer and Fatton, 2008). If sutures are placed close to the sacrum there is a risk of entrapping fibers of the sacral plexus trunk of S1 to S4 (Siddique et al, 2006; Wieslander et al, 2007). This can result in buttock pain, which radiates to the posterior thigh and popliteal fossa. **Placing sutures in the intermediate portion of the uterosacral ligament appears to be the optimal site because there are fewer structures to be potentially affected and it provides a stable point of fixation. There is a decreased chance of traction affecting the ureter at this point, because it is further away from the ureter and its sheath.**

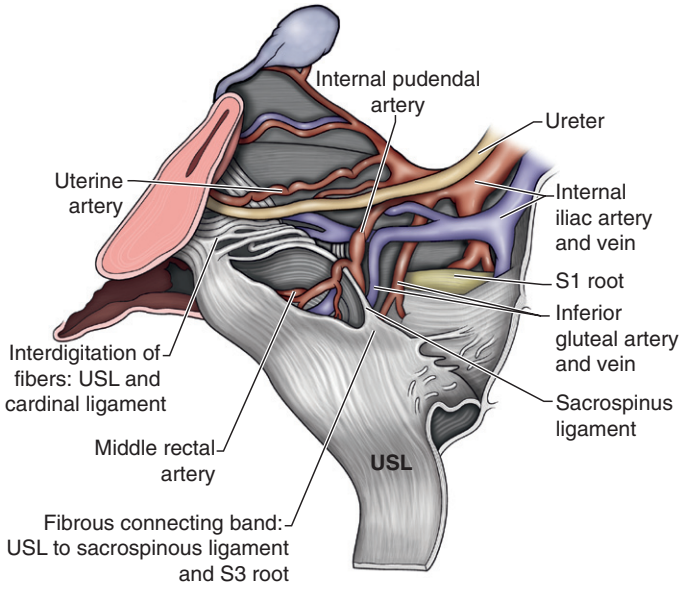


Figure 72–24. Right hemipelvis: sagittal view. The uterosacral ligament (USL) has been reflected to show subjacent anatomy. (From Buller JL, Thompson JR, Cundiff GW, et al. Uterosacral ligament: description of anatomic relationships to optimize surgical safety. Obstet Gynecol 2001;97:873–9.)

Placing the sutures from lateral to medial will also minimize accidentally catching either the ureter or its attachments in the stitch (Shull et al, 2000). The intermediate segment can be located 1 cm posterior along the palpable uterosacral ligament at the level of the ischial spine with the uterosacral ligament placed on tension (Buller et al, 2001). An advantage of suspension to the uterosacral ligament is that it minimizes injury to the pudendal and gluteal vessels relative to sacrospinous ligament fixation (Barber et al, 2000).

Technique

HIGH UTEROSACRAL VAGINAL VAULT SUSPENSION. This procedure starts intraperitoneally (Karram et al, 2001). After hysterectomy the apex is identified on the vaginal cuff at the 3- and 9-o'clock positions, which represent the attachments of the cardinal and uterosacral ligaments (Shull et al, 1993). It is useful to place stay sutures at these dimples before incision. The vaginal epithelium is dissected away from the peritoneum of the hernia sac. Once the dissection has mobilized the hernia sac from the epithelium to the neck of the sac, it is entered and the sac excised (Fig. 72–26). Laparotomy pads are placed to pack the bowel away. Ischial spines can then be palpated transperitoneally. The uterosacral ligaments will be located posteriorly and medially to the ischial spines. By placing traction to the stay sutures or by placing an Allis clamp at the 5- and 7-o'clock positions of the apex the uterosacral ligament will tent and two to four nonabsorbable sutures can be placed through the uterosacral/cardinal ligament complex (Fig. 72–27). The ureters should be located lateral to the uterosacral ligaments; however, it should be noted that depending on the degree of the prolapse there can be significant variability in their location relative to the edge of the uterosacral ligament (Silva and Karram, 2006). If there is any question as to their location, temporary stents may be placed to facilitate their palpation. In placing the needles through the uterosacral ligaments it is important to pass them lateral to medial, exiting away from the ureter to avoid inadvertent inclusion into the tie (Shull et al, 2000). To ensure the proper depth, the suture should be passed at the level of the ischial spines. Subsequent sutures are placed proximal to the last. If an anterior colporrhaphy or sling is planned it may be done at this point. Suspensory sutures in the uterosacral ligaments are then placed in the most apical portions of the pubocervical and rectovaginal fascia. The highest sutures are then sewn to the most medial portions of the pubocervical and rectovaginal fascia. The more distal sutures are placed most laterally in the pubocervical and rectovaginal fascia and passed out of the vaginal epithelium on each side

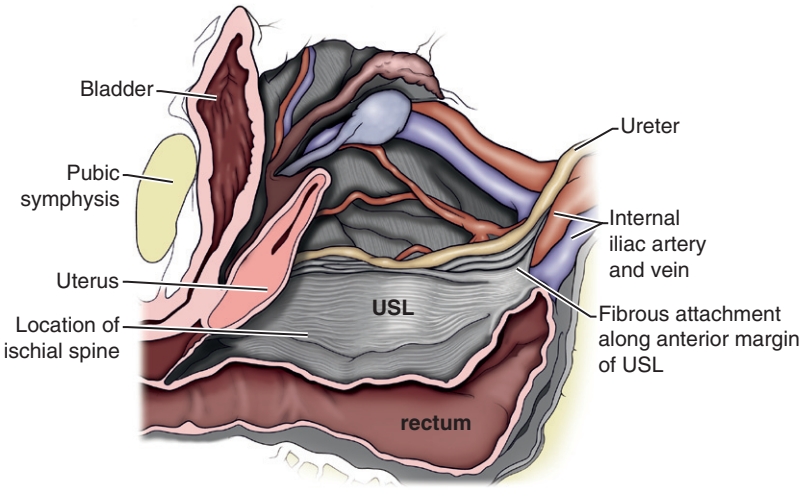


Figure 72–25. Right hemipelvis sagittal view. The peritoneum has been removed and the uterosacral ligament (USL) was left intact to show the proximity of the ureter in this specimen. (From Buller JL, Thompson JR, Cundiff GW, et al. Uterosacral ligament: description of anatomic relationships to optimize surgical safety. Obstet Gynecol 2001;97:873–9, with permission.)

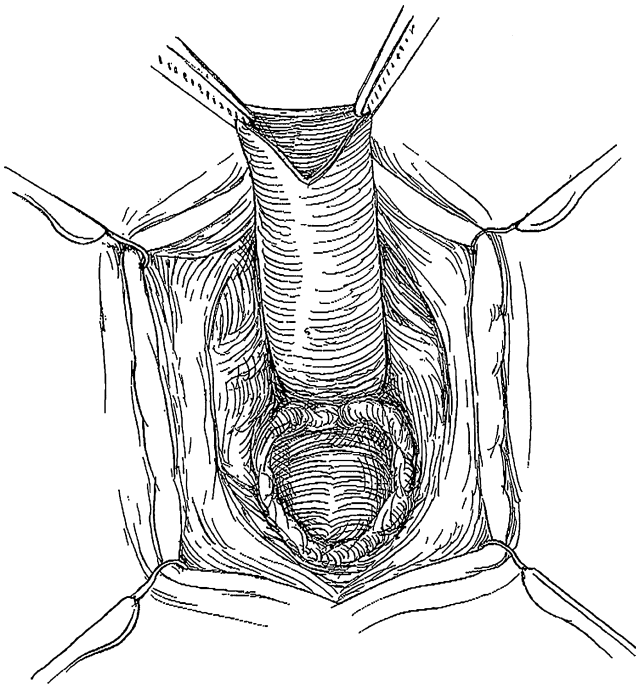


Figure 72–26. Vaginal enterocele repair. Enterocele sac is identified and opened to reduce its contents. It is then tied in a purse-string suture and the excess is excised. Before closure of the enterocele sac the peritoneal cavity is entered to access the uterosacral ligament. (From Cespedes RD, Winters CW. Colpocleisis for the treatment of severe vaginal vault prolapse. In: Vasavada SP, Appell RA, Sand PK, Raz S, editors. Female urology, urogynecology, and voiding dysfunction. Boca Raton [FL]: Taylor & Francis; 2005.)

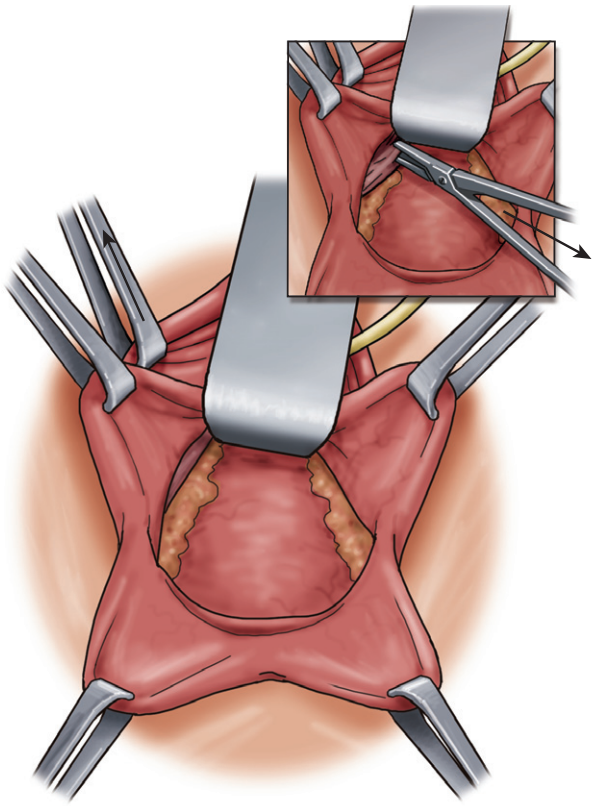


Figure 72–27. To identify the uterosacral ligament, an Allis clamp is placed on the vaginal epithelium at the right apex and pulled straight upward. Placing the right uterosacral ligament on tension aids in visualizing this structure within the pelvis. *Inset,* A long Allis clamp is used to grasp the right uterosacral ligament. (From Walters M, Muir T. Surgical treatment of vaginal apex prolapse. In: Vasavada SP, Appell RA, Sand PK, Raz S, editors. Female urology, urogynecology, and voiding dysfunction. Boca Raton [FL]: Taylor & Francis; 2005.)

(Fig. 72–28). Cystoscopy with indigo carmine is an essential step after this procedure to confirm ureteral patency and should be performed before trimming the suture because this will facilitate identification of the sutures if they need to be removed due to obstruction. If no efflux of urine is seen the sutures should be removed starting with the most lateral suture of the ipsilateral side. In addition, it is important to perform the cystoscopy after the suture is tied, not just placed (Yazdany and Bhatia, 2008). After ureteral patency is ensured, it is useful to close the vaginal cuff at least one third of the length of the incision before tying down the uterosacral sutures to avoid the difficulty of placing the closing sutures high in the vagina once it is suspended. As one ties these suspending sutures, the rectovaginal fascia and pubocervical fascia are brought together at the uterosacral/cardinal ligament complex, thus resuspending the apex of the vagina and closing the cul-de-sac (Fig. 72–29).

An extraperitoneal approach has also been described (Dwyer and Fatton, 2008). A midline incision is made, depending on concomitant prolapse. The vaginal epithelium is then dissected away from the endopelvic fascia, and the enterocele sac is identified and dissected free of the vault. Dissection is continued laterally until the uterosacral/cardinal ligament complex is identified posterior and medial to the ischial spine. Palpation to tent the uterosacral/cardinal ligament complex is facilitated by placing tension on the vagina. Use of the Breisky-Navratil retractor to retract the bladder and ureters anteriorly has prevented ureteral obstruction through traction or injury (Fatton et al, 2009). Once the ligaments are identified, the sutures are placed in a similar fashion to the intraperitoneal approach. Cystoscopy and vaginal closure are performed as described previously.

ABDOMINAL APPROACH TO THE UTEROSACRAL LIGAMENTS. The uterosacral ligaments may be accessed transabdominally (Lowenstein et al, 2009). This technique begins by elevating the uterus at the time of abdominal hysterectomy. Three permanent sutures are placed in each of the uterosacral ligaments proximal and medial to the ischial spine. They are numbered in the manner described by Shull and colleagues (2000) (Fig. 72–30). Once the hysterectomy has been performed and the cuff has been closed, the sutures are placed sequentially through the anterior and posterior leaves of the endopelvic fascia. By reapproximating the anterior and posterior muscularis of the vagina, any potential enterocele defects are closed and the cuff is elevated toward the sacrum, re-creating the normal vaginal axis. Cystoscopy is performed after tying the sutures, which are left uncut until efflux of urine is demonstrated. If no urine is seen, the most lateral ipsilateral suture is removed and subsequent sutures are taken down in sequence.

Results (Table 72–5)**.** Jenkins (1997) reported his experience in 50 patients who underwent vaginal vault suspension to the uterosacral ligaments, 33 of whom underwent concomitant vaginal hysterectomy. There was no recurrence of vault prolapse; however, 2 patients had asymptomatic cystoceles. Three had erosion of the suture (monofilament) into the vagina. Although not sexually active, 1 patient who had vaginal narrowing complained of tightness of the bladder and vagina. Three had de novo dyspareunia, with resolution in 2 by 6 months. Barber and associates (2000)

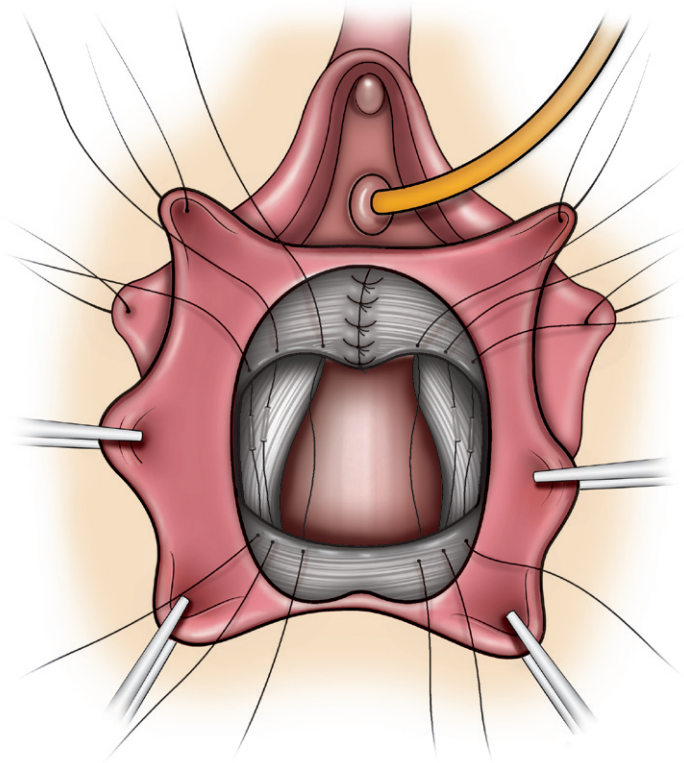


Figure 72–28. High uterosacral ligament vaginal vault suspension. Three sutures are placed from lateral to medial in each uterosacral ligament. The sutures are brought through the vaginal muscularis anteriorly (pubocervical fascia) and posteriorly (rectovaginal fascia). (From Walters M, Muir T. Surgical treatment of vaginal apex prolapse. In: Vasavada SP, Appell RA, Sand PK, Raz S, editors. Female urology, urogynecology, and voiding dysfunction. Boca Raton [FL]: Taylor & Francis; 2005, with permission.)

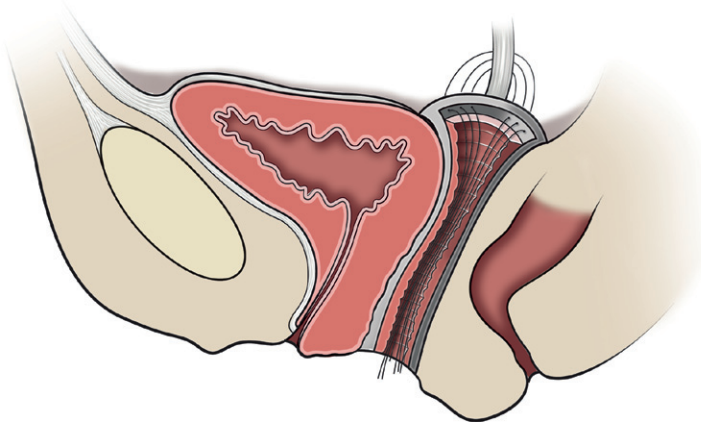


Figure 72–29. Completed uterosacral vaginal vault suspension with anterior colporrhaphy. (From Walters M, Muir T. Surgical treatment of vaginal apex prolapse. In: Vasavada SP, Appell RA, Sand PK, Raz S, editors. Female urology, urogynecology, and voiding dysfunction. Boca Raton [FL]: Taylor & Francis; 2005, with permission.)

reported on 46 women who underwent site-specific repair of the endopelvic fascia defects with suspension of the vaginal cuff to the proximal uterosacral ligaments. At a median follow-up of 15.5 months, 67% had POP-Q stage 1 or less prolapse of any compartment, and 95% had correction of apical prolapse. Voiding dysfunction was noted to improve from 59% to 7%. Eleven percent of patients were noted to have entrapment of the ureter, which was recognized intraoperatively. Two had to undergo ureteral reimplantation, which was performed at the time of the original surgery. This emphasizes the need for intraoperative cystoscopy to identify ureteral injury. Shull and colleagues (2000) reported a large series of patients who underwent uterosacral ligament suspension. Of 289 patients who were observed over time, a majority (87%) had no recurrence of support defect at any site on any postoperative examination. Only 5% of the patients had grade 2 prolapse or greater. The most common site was the anterior compartment in which 10 patients had grade 2 or 3 defects. One patient required ureteroneocystostomy. Two patients required removal of suspensory sutures. Karram and coworkers (2001) reported on 202 patients who underwent vaginal vault suspension. Of interest, uterosacral ligament suspension could not be performed in six patients because the enterocele sac could not be identified or exposure of the cul-de-sac could not be carried out. These patients underwent sacrospinous ligament fixation. Ninety-nine percent had a successful vaginal vault suspension. Ten women had recurrent grade 2 prolapse at other sites. Wheeler and associates (2007) reported patient satisfaction of 89% in 35 patients. No ureteral injuries were noted, and none of the patients required operation for recurrent prolapse, urinary incontinence, or urinary tract injury. Amundsen and associates (2003) reported on a retrospective analysis of 33 patients who underwent bilateral uterosacral ligament suspension with concomitant pubovaginal sling and site-specific endopelvic fascial repair. Vaginal prolapse symptoms resolved in 82%, and SUI improved in 82%. No dyspareunia was reported postoperatively. Eighty-three percent of women who needed to perform vaginal or perineal splinting ceased to do so postoperatively. POP-Q measurements improved significantly ($P < .05$) for all sites. Although these investigators noted a decrease in total vaginal length of 0.9 cm there was no corresponding loss of sexual function. Silva and Karram (2006) evaluated 5-year anatomic and functional outcomes of high uterosacral vaginal vault suspension. Apical recurrence occurred in 2 of 78 patients. Seven patients had de novo postoperative dyspareunia. Short-form Incontinence Impact Questionnaire/Urinary Distress Inventory scores indicated improvement in all three domains of irritative, obstructive, stress, and overall symptoms compared with preoperative scores. Rare complications such as blood transfusion (1% to 3%), bowel injury (0% to 0.6%), and pelvic infection (0.6%) have all been reported after the uterosacral ligament suspension (Shull et al, 2000; Karram et al, 2001; Amundsen et al, 2003).

Fatton and colleagues (2009) examined their results performing an extraperitoneal bilateral uterosacral vaginal vault suspension over 2 years. Some of the patients in this series also had mesh reinforcement both anteriorly (47.1%) and posteriorly (53.7%). Recurrence at the apex was noted in 4.6% of patients. Mesh exposure occurred and was diagnosed within 6 months in the majority of the patients. Their results are similar to that reported for an intraperitoneal approach.

Sacrospinous Ligament Fixation

The sacrospinous ligament fixation was first described by Richter in 1942 but was not widely utilized until Nichols reported on the technique forty years later (Nichols, 1982). The sacrospinous ligament fixation has been shown to be an effective method to correct apical prolapsed (Cruikshank and Muniz, 2003). This technique is appealing because of its retroperitoneal approach and consistency as a strong structure on which to anchor the apex. Access to the spine was originally achieved from the posterior approach, although dissection from the anterior approach may also be

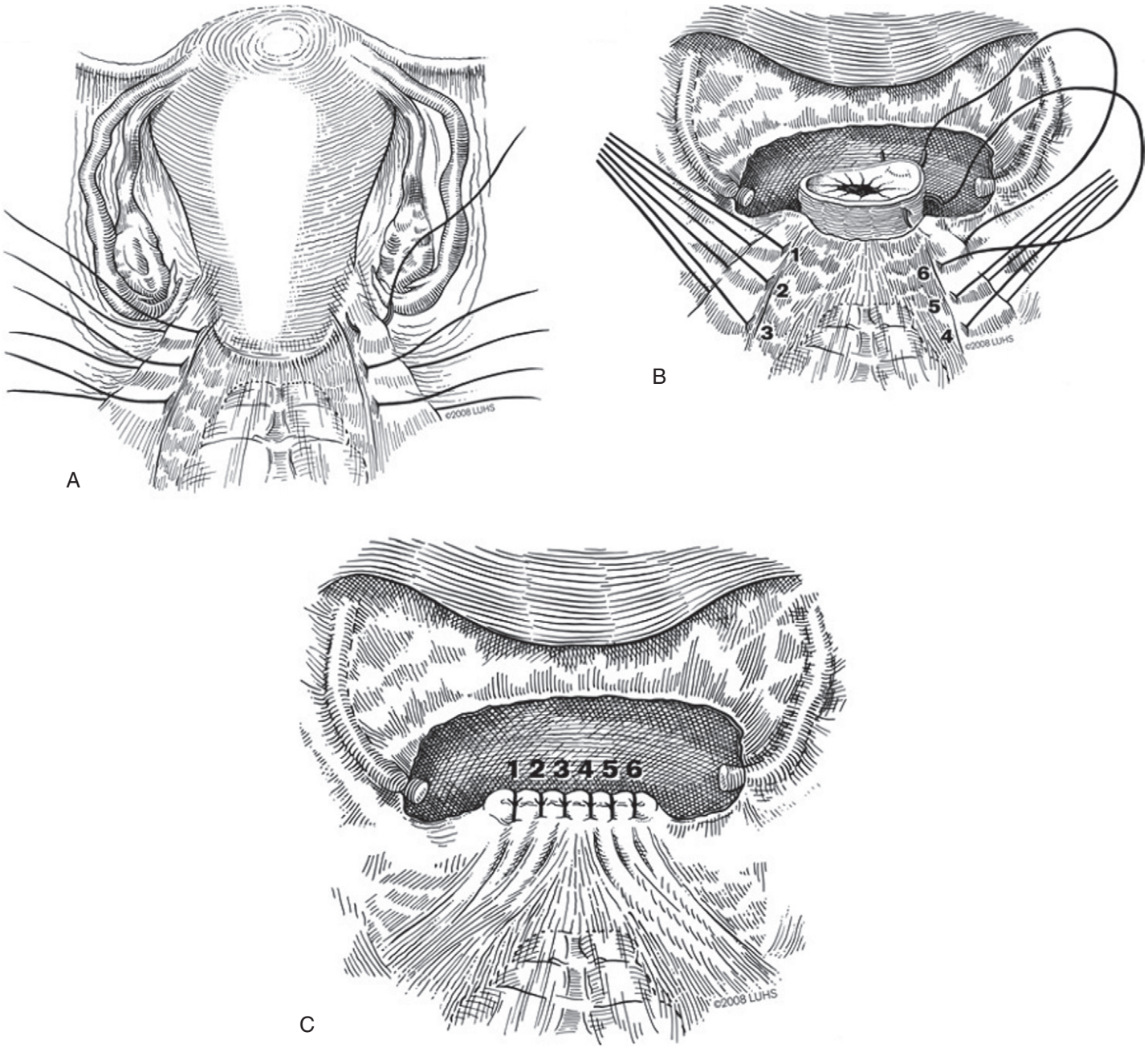


Figure 72–30. **A,** Three permanent sutures are placed in each of the uterosacral ligaments medial to the ischial spine. **B,** One end of each of the six sutures is placed serially across vaginal apex through the anterior endopelvic fascia and the other end is placed through the posterior endopelvic fascia. **C,** All sutures are tied to reapproximate the anterior and posterior vaginal muscularis, to close any potential enterocele defect, and to elevate the vaginal apex toward the sacrum. (© 2008 Loyola University Health System. Used with permission from Mary Pat Fitzgerald, MD.)

performed via the paravaginal space (Cespedes, 2000; Winkler et al, 2000). The advantages of sacrospinous ligament suspension are success rates comparable to abdominal procedures (Brown et al, 1989; Imparato et al, 1992), ability to repair concomitant pelvic floor defects, absence of a laparotomy (Morley and DeLancey, 1988), shorter hospital stay (Brown et al, 1989), preservation of vaginal length and function (Morley and DeLancey, 1988; Brown et al, 1989), and cost effectiveness (Brown et al, 1989). The structures at risk with this technique include the pudendal or inferior gluteal vessels and the sciatic or pudendal nerves. Pudendal nerve entrapment results in posterior buttocks pain, which may radiate down the back of the thigh. **A disadvantage of this approach is the alteration in vaginal axis, which results in apical displacement posteriorly and to the right side when unilateral fixation is used. This posterior displacement can result in anterior compartment recurrence even when an anterior repair is performed** (Morley and DeLancey, 1988; Shull et al, 1992; Sauer and Klutke, 1995).

Sacrospinous fixation may be performed unilaterally or bilaterally (Pohl and Frattarelli, 1997). With the unilateral suspension, right-sided placement is generally preferred. Technically, it is easier to place the sutures on the right ligament for a right-handed surgeon (Sauer and Klutke, 1995). Cespedes (2000) reported success using the bilateral anterior support and noted the advantage of

Table 72–5.

Results of Uterosacral Ligament Repairs

AUTHOR	NO. PATIENTS	FOLLOW-UP (mo)	SUCCESS RATE %	METHOD OF EVALUATION	COMPLICATIONS
Jenkins et al, 1997	50 Uterine 33 Vaginal vault 17	 33 (6-48) 20 (6-38)	100 apex 3 cystoceles	Examination	Bladder perforation, blood loss >500 mL, fever, atelectasis, cuff cellulitis, pneumonia, UTI, voiding difficulty
Barber et al, 2000	46	15.5 (3.5-40.8)	95	POP-Q symptom assessment	Ureteral occlusion 11%, ureteral injury, excessive blood loss, UTI, vaginal cuff cellulitis
Shull et al, 2000	302 (289)	2-38	87	Baden-Walker classification	Bleeding, ureteral injury, removal and replacement of suture due to ureteral obstruction, death presumed to be from PE, arrhythmia
Karram et al, 2001	202 (168)	6-36	94	Baden-Walker classification IIQ-7, UDI-6	Ureteral occlusion, ureterotomy, small bowel injury, pelvic abscess
Wheeler et al, 2007	35	24.3 (9-46)	100 examination 88.9 questionnaire	POP-Q, IIQ-7, UDI-6, PFDI-46	One ureteral kinking
Amundsen et al, 2003	33	6-43	94 apex	POP-Q	Blood transfusion in one patient
Silva et al, 2006	72	42-90	97.2 apex 84.7 global	POP-Q, IIQ-7, UDI-6, Female Sexual Function Index	Long-term study, intraoperative complications were not reported
Fatton et al, 2009 (extraperitoneal)	123	6-60	95.4 apex 85.5 global	POP-Q	Bladder injury, rectal laceration, ureteral obstruction, blood transfusion, de novo dyspareunia

IIQ-7, Incontinence Impact Questionnaire; PE, pulmonary embolism; PFDI-46 Pelvic Floor Distress Inventory; POP-Q, Pelvic Organ Prolapse Quantification System; UDI-6, Urogenital Distress Inventory, Short Form; UTI, urinary tract infection.

more midline location of the vaginal apex. Although bilateral placement has been advocated (Nichols, 1996), there is little to support the advantage of bilateral fixation over unilateral fixation when examining outcomes (Morley and DeLancey, 1988).

Surgical Anatomy of the Sacrospinous Ligament Fixation. The sacrospinous ligament is 7 to 8 cm in length (Morley and DeLancey, 1988). It extends from the ischial spine laterally, courses medially under the coccygeus muscle, and inserts into the sacrum. The pudendal nerves and vessels are in close proximity to the ligament just proximal to their course around the ischial spine (Fig. 72–31). Additionally, the hypogastric plexus of veins are located superiorly and the hemorrhoidal vessels are located medially to the sacrospinous ligament (Morley and DeLancey, 1988); thus retraction should be carried out carefully in these respective areas. To avoid the gluteal vessels, the suture should be placed into the ligament and not behind it (Kettel and Herbertson, 1989). Pudendal nerve entrapment may result in pain, which localizes to the buttocks or perineum. This may be avoided by placing sutures more medially about 1.5 cm from the ischial spine (Sauer and Klutke, 1995; Alevizon and Finan, 1996). **Thus, the optimal position of the suture placement is 1.5 to 2.0 cm medial to the ischial spine, directly into the sacrospinous ligament.** Placing it too far medially may risk failure of the repair because the sacrospinous ligament fans and thins as it inserts into the sacrum (Sauer and Klutke, 1995). In addition, there is a higher concentration of sacral nerves in this medial location. Barksdale and associates (1997) performed a cadaveric study to assess the histology of the sacrospinous ligament. Segments were taken near the ischial spine, including middle and sacral portions of the ligament. The highest concentration of nerves was found in the sacral portion of the ligament, with the lowest being near the spine. Although it was postulated that the nerves embedded in the sacrospinous ligament were a potential source of neuropathic pain, no clinical correlation could be made in this cadaveric study. Lantzsch and coworkers (2001) concluded that localization and depth of the suture can also influence the occurrence and intensity of sciatic neuralgia.

Technique. The procedure starts by marking the apex of the vagina. The vaginal apex is then reduced to the sacrospinous ligament(s) intended to be used. This site of attachment is then tagged for later fixation. A midline vaginal incision is fashioned, the location of which is largely dependent on the need for other compartmental repairs. The vaginal epithelium is separated from the rectovaginal septum posteriorly and/or pubocervical fascia anteriorly. If an anterior compartment repair will be performed, the sacrospinous ligament may be approached anteriorly, exposing the paravesical space. The tissue attachments overlying the spine and ligament are swept medially. Alternatively, if the posterior approach is used, one must enter the perirectal space by bluntly mobilizing the rectum medially. On entering the perirectal space the ischial spine is identified. With further dorsal and medial blunt dissection, the sacrospinous ligament is palpated. Blunt dissection is continued to ensure that the rectum is retracted medially, and the ligament is adequately exposed. At this point Heaney or Breisky-Navratil retractors are very useful to visualize the ligament and facilitate suture placement. Additionally, long lighted retractors can provide added visualization. The sacrospinous ligament is then palpated. The suture is placed approximately one to two fingerbreadths medial from the spine, to avoid damage to the structures in the Alcock canal. Several different methods have been used to fix the suture to the sacrospinous ligament. The Capio Suture Capturing Device (Boston Scientific, Natick, MA)

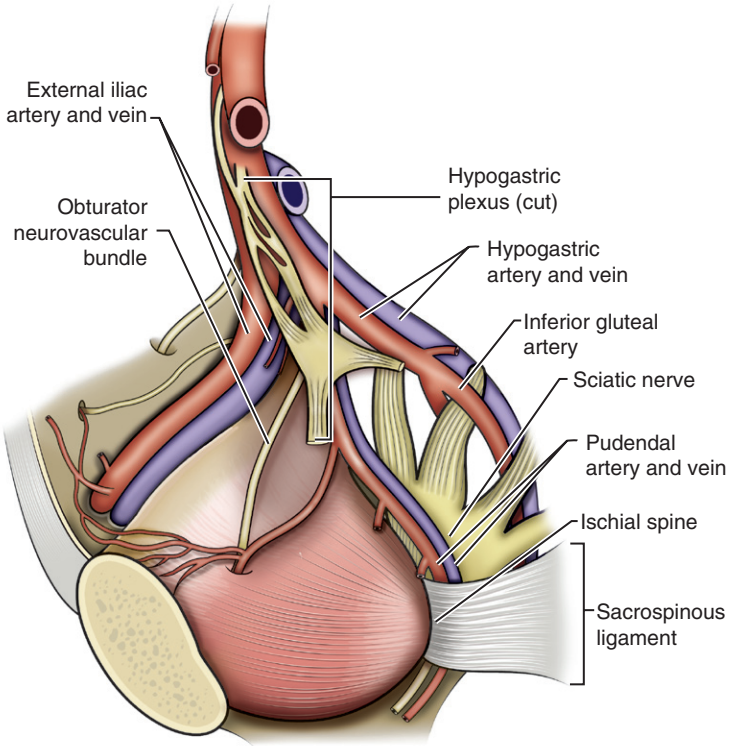


Figure 72–31. Anatomy of the sacral spinous ligament and surrounding structures. Note the close proximity of the pudendal vessels, hypogastric plexus, inferior gluteal vessels, and sciatic nerve. (From Walters M, Muir T. Surgical treatment of vaginal apex prolapse. In: Vasavada SP, Appell RA, Sand PK, Raz S, editors. Female urology, urogynecology, and voiding dysfunction. Boca Raton [FL]: Taylor & Francis; 2005, with permission.)

enables the suture to be placed by palpation. Alternatively, the Miya Hook (Cooper Surgical, Trumbull, CT) (Miyazaki, 1987), the Autosuture Endo Stitch Suturing Device (Covidien, Norwalk, CT) (Schlesinger, 1997), and Deschamps Ligature Carrier may be utilized to place the sutures under direct vision. Two sutures are most commonly placed. In cases of bilateral sacrospinous ligament fixation, one suture may be placed on each ligament. In the case of unilateral sacrospinous ligament fixation the placement of the sutures on the ligament 2 cm apart will prevent constriction of the vaginal apex. Additional repairs may be performed at this point. Following this, the previously placed sacrospinous ligament sutures are brought out of the vagina to the previously marked vaginal apex (Fig. 72–32). If a permanent suture is utilized for sacrospinous ligament fixation, a (pulley stitch) configuration, which ensures that the knot of the suture will remain internal, is needed. To create a pulley stitch, tying a knot onto the fibromuscular portion on the visceral side of the vagina creates a fixed point. The free end of the suture is then pulled, thus suspending the apex to the sacrospinous ligament, and this is then secured by tying a secure knot. Importantly, this resultant knot remains internal and is not within the vaginal canal. Closure of the vaginal wall halfway before tying down the sutures is useful because the suspended apex may be quite difficult to reach. The sutures should be tied such that the vaginal apex is firmly attached to the coccygeal/sacrospinous ligament complex with no intervening suture material bridging a gap (Morley and DeLancey, 1988; Sze and Karram, 1997). Palpation of the suture behind the vaginal cuff will ensure that the suture is tied securely. It is useful to leave the suture untrimmed until the cystoscopy is performed in case the suture needs to be removed. Once efflux has been ensured, the suture is trimmed and the remainder of the vaginal wall is closed.

Results (Table 72–6). Nichols (1982) reported outcomes of sacrospinous ligament fixation in 163 patients, some with "massive" vaginal eversion and procidentia, and had no recurrences of

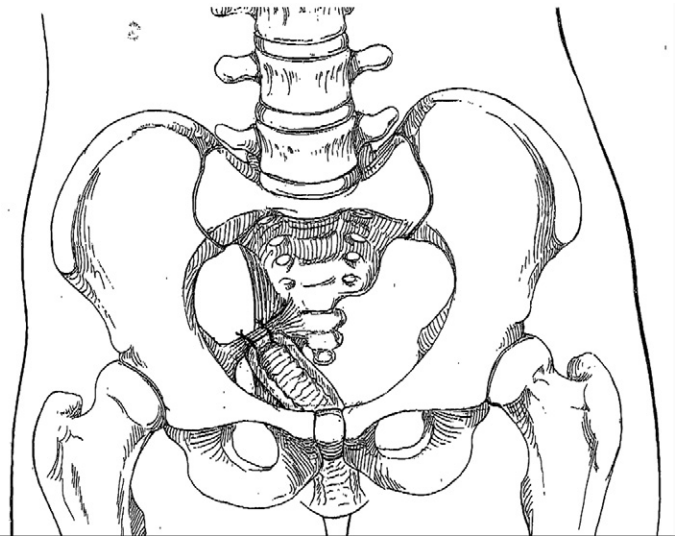


Figure 72–32. Sacral spinous ligament fixation. With a unilateral suspension, the vagina is deflected to the right side and caudally. (From Richter K, Albright W. Long-term results following fixation of the vagina on the sacrospinous ligament by the vaginal route [vaginaefixatio sacrospinalis vaginalis]. Am J Obstet Gynecol 1981;141:811–6, with permission.)

vaginal vault prolapse. Nine patients reported that the vagina was too narrow postoperatively. Richter and Albrich (1981) reported excellent patient satisfaction, although eight patients were reluctant to resume sexual relations because of a perceived narrowed vagina. Morley and DeLancey (1988) reported on 100 patients who underwent sacrospinous ligament fixation, 33 of whom underwent isolated apical treatment. Sixty-seven had concomitant prolapse repairs. Apical success was noted in 95.7%, 90.1%

Table 72–6.

Results of Sacrospinous Ligament Fixation

AUTHOR	NO. PATIENTS	FOLLOW-UP (mo)	SUCCESS RATE %	METHOD OF EVALUATION	COMPLICATIONS
Richter and Albrich, 1981	81	Not reported, range 1-10 years	100 apex	Examination*	Bladder laceration superficial rectal injury, suture abscess, dyspareunia
Nichols, 1982	163	≥24	97	Examination*	Vaginal foreshortening, nerve damage, rectal injury, death from MI
Morley and DeLancey, 1988	100 (71 available ≥1 yr	≥12 (12-132)	96 apex 90 global	Examination* and questionnaire*	Transfusion, cystotomy, UTI, wound infection, voiding difficulty, vaginal
Shull et al, 1992	81follow-up) 41 ≥24 mo	≥24 (24-60)	98 apex 88 global	Examination	Not reported
Sauer and Klutke, 1995	24	13.8 mean (4-26)	87.5 apex 79.2 global	Examination	Rectal laceration, mild buttock pain, bladder instability
Paraiso et al, 1996	243	73.6	1 yr (5 yr): apex 96.9 (95.1); global 88.3 (79.7)	Examination (Baden-Walker classification halfway) Questionnaire	Bleeding, fever, urinary retention, UTI, cardiac complication, PE, pneumonia, wound infection, buttock pain
Meschia et al, 1999	103 (91 available for exam)	43 (12-81)	94 apex 61.5 global	Examination (Baden-Walker halfway)	Fever, hematoma, buttock pain, de novo stress incontinence, voiding dysfunction, fecal incontinence
Winkler et al, 2000	75	8.5 (1.5-105)	93 apex 73 global	Examination	Recurrent prolapse
Cespedes, 2000	28	17 (5-35)	96.4 apex 89.3 global	Examination	Transient buttock pain, recurrent cystocele, urinary retention, transfusion, residual urgency incontinence
Lantzsch et al, 2001	200 (123)	57 (6-108)	96.7 apex 90.4 global	Examination and evaluation for SUI	UTI, sciatic neuralgia, voiding dysfunction, partial ureteral obstruction, bleeding, thrombosis

*Not standardized.

MI, myocardial infarction; PE, pulmonary embolism; SUI, stress urinary incontinence; UTI, urinary tract infection.

globally, with four patients having prolapse in the anterior compartment. They noted that the long-term results were acceptable with minimal adverse effects.

Bilateral sacrospinous ligament suspension was compared with abdominal sacrocolpopexy in a prospective randomized study (Benson et al, 1996). Time to failure was shorter in the sacrospinous ligament suspension group compared with the abdominal sacrocolpopexy group (11 vs. 22 months) with the vaginal group having 12 cystoceles requiring reoperation versus 4 cystoceles in the abdominal group. Sauer and Klutke (1995) reported on 24 patients with a mean follow-up of 13.8 months. They had very little blood loss, and no transfusions were needed. Mild buttock pain was noted that resolved by 3 months. In 21 of 24 patients there was no recurrence of prolapse at the apex. One patient underwent repeat operation for a significant cystocele. Meschia and associates (1999) reported on 103 patients who underwent sacrospinous ligament fixation and found excellent results for the posterior and apical compartments but disappointing results for the anterior compartment, with 16% having grade 2 or greater prolapse.

The anterior compartment has been reported as a particularly vulnerable site for developing a defect after sacrospinous vaginal vault suspension. Recurrent cystoceles have been reported in 7.6% to 92% of patients postoperatively (Richter and Albrich, 1981; Morley and DeLancey, 1988; Pasley, 1995). This has been attributed to vaginal retroversion. This is noted not only postoperatively but intraoperatively, although many who develop anterior defects remain asymptomatic and do not undergo subsequent surgery to correct the anterior compartment defect (Paraiso et al, 1996).

Several authors have demonstrated the feasibility and efficacy of an anterior approach to the sacrospinous ligament vaginal vault suspension (Cespedes, 2000; Winkler et al, 2000). Winkler and coworkers (2000) reported that the anterior compartment recurrence rate after an anterior sacrospinous ligament fixation and anterior repair was 9%, in contrast to a 24% after sacrospinous ligament fixation with posterior repair. Cespedes (2000) reported on the bilateral anterior approach and noted no recurrences. Some of the theoretical advantages of the anterior approach include improved ability of the vagina to withstand increased intra-abdominal pressures (Pohl and Frattarelli, 1997) and less likelihood of rectal injury (Sauer and Klutke, 1995). Again, a low incidence of anterior compartment recurrence was noted (7%) (Cespedes, 2000).

Successful healing in the short term may predict long-term success of the sacrospinous ligament suspension. Shull and colleagues (1992) reported on 81 women undergoing sacrospinous ligament suspension, 72% of whom had undergone previous pelvic surgery. Those who showed absence of any compartment defect at the 6-week follow-up visit had a 3% likelihood of requiring additional reconstructive surgery within 2 to 5 years.

Complications. Cruikshank and Muniz (2003) reported 15% of patients experienced gluteal pain after sacrospinous ligament fixation on the ipsilateral side. Generally this pain resolves

spontaneously within 2 to 3 months when delayed absorbable sutures are used (Maher et al, 2001). Postoperative neuropathic pain can be managed with observation, and patients should be counseled that duration may be as long as 3 months (Sauer and Klutke, 1995). Injection of the nerve with local anesthetic has also been reported (Lantzsch et al, 2001). Rectal perforation has been reported, recognized at the time of surgery, and repaired primarily with no sequelae (Richter and Albrich, 1981; Sauer and Klutke, 1995). In addition, injury to the pudendal nerve and internal pudendal vessels may occur with medially placed sutures near the ischial spine.

Iliococcygeus Suspension

The iliococcygeus suspension has the advantage of maintaining the vagina in the normal axis and is useful in cases in which the uterosacral ligaments are insufficient for attachment or cannot be identified. In this technique the vaginal vault is attached to the fascia of the iliococcygeus muscle as the anchoring site in contrast to the uterosacral or sacrospinous ligaments.

Technique and Results. The approach is similar to the uterosacral and sacrospinous ligament fixation and is usually approached extraperitoneally. The fascia of the iliococcygeus muscle is identified lateral to the rectum and anterior to the ischial spine (Shull et al, 1993). The point of suture fixation is placed 1 cm distal to the ischial spine, near the insertion of the ATFP. This suture is then passed through the condensation of connective tissue at the apex of the vagina anteriorly through the pubocervical fascia and posteriorly through the rectovaginal fascia (Fig. 72–33). Another suture is placed on the contralateral side in a similar manner. It is recommended that bilateral suture fixation be performed to achieve optimal results. Once the sutures are tied securely the vagina will be suspended bilaterally. As in sacrospinous ligament fixation the sutures may be placed through an anterior or posterior approach. Special needle drivers and lighted retraction are useful to facilitate suture placement. In cases utilizing permanent suture a pulley stitch technique is applied tying the knot internally.

Shull and colleagues (1993) reported on bilateral attachment of the vaginal cuff to the iliococcygeus fascia in 42 patients. Eight patients experienced pelvic support loss postoperatively, 3 in the middle compartment, 2 in the posterior compartment, and 4 in the anterior compartment. Six patients had additional surgery. Meeks and associates (1994) reported an anatomic cure of 96% in 110 patients. Intraoperative complications included rectal and bladder laceration and hemorrhage requiring transfusion. Postoperative complications included vaginal cuff abscess, fever, and transient femoral neuropathy. Maher and coworkers (2001) reported a 53% cure rate in 50 patients, and 19% of the patients experienced buttock pain.

Abdominal Sacrocolpopexy

The abdominal sacrocolpopexy should be considered a treatment option in the following clinical scenarios: in a patient with a failed previous vaginal repair, in a patient with isolated apical prolapse and/or enterocele, and in a younger woman with an active lifestyle who desires to continue sexual intercourse. In these patients, **abdominal sacrocolpopexy is an excellent choice because it maximizes functional vaginal length and a near-normal vaginal axis.** As discussed earlier, other pelvic floor defects and occult SUI can be addressed at the same time. In addition to open surgery, robotic-assisted laparoscopic and pure laparoscopic approaches have all been described (Sundaram et al, 2004; Rozet et al, 2005; Daneshgari et al, 2006; Elliott et al, 2006). The principles of the operation remain the same regardless of the approach.

Technique. The critical elements of the operation include the use of permanent mesh (type I macroporous, monofilament) as graft material, secure fixation of the graft to the sacral promontory and vaginal cuff, and complete enterocele reduction and culdoplasty.

The patient is positioned in the low lithotomy position, providing both transvaginal and transabdominal access. A Pfannenstiel or low midline abdominal incision may be used. On entry into the peritoneal cavity it is important to achieve exposure of true

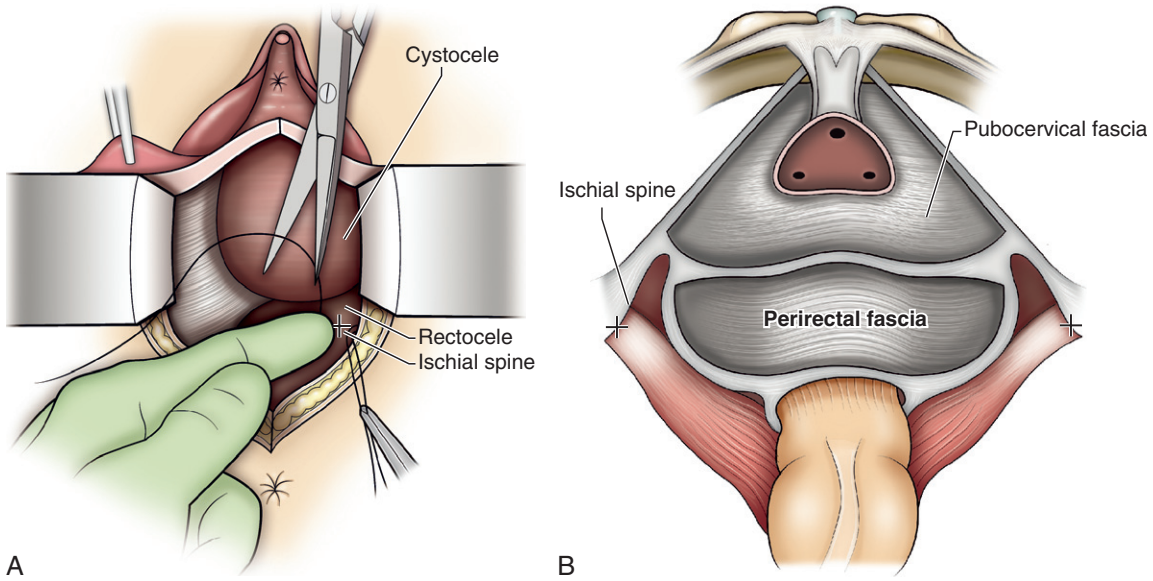


Figure 72–33. Iliococcygeus fascia suspension. **A,** With the surgeon's finger deflecting the rectum downward, the right iliococcygeus fascia sutures are placed. *Inset,* View of the dissected vagina. **B,** Abdominal view of the endopelvic fascia. Approximate location of the sutures is delineated by the + sign. (From Walters M, Muir T. Surgical treatment of vaginal apex prolapse. In: Vasavada SP, Appell RA, Sand PK, Raz S, editors. Female urology, urogynecology, and voiding dysfunction. Boca Raton [FL]: Taylor & Francis; 2005, with permission.)

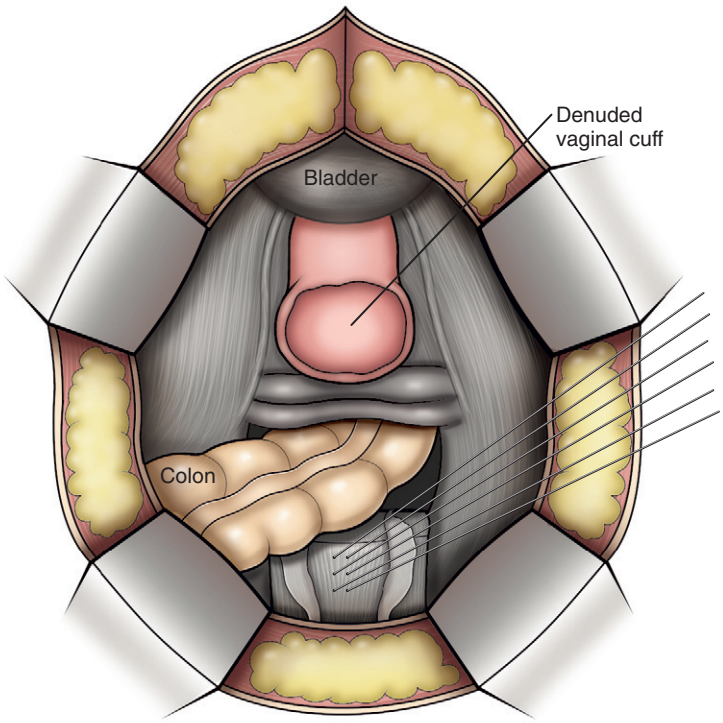


Figure 72–34. Abdominal sacral colpopexy. *A,* Incision in peritoneal cuff overlying the vagina, exposing the vaginal cuff. *B,* Two permanent sutures are placed in the sacral promontory to secure the graft material. (From Delacroix S, Winters J. Abdominal sacral colpopexy. In: Graham SD, Keane TE, editors. Glenn's atlas of urologic surgery. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2009, with permission.)

pelvis by careful packing of the small intestine and sigmoid colon. This is accomplished by releasing all adhesions in the pelvis and packing the bowel above the level of the sacral promontory. An incision is made in the posterior peritoneum over the sacral promontory, extending inferiorly along the right lateral aspect of the rectum. Electrocautery is used when dividing the fatty tissue over the promontory. Careful dissection in this area is essential to avoid shearing of presacral veins because severe bleeding may occur. The middle sacral vein traverses over the promontory and should also be avoided. As the fatty tissue is dissected free, the anterior surface of the sacral promontory is visualized, usually by identification of the anterior longitudinal ligament. Two or three permanent sutures are placed into the sacral promontory. These sutures are safely tagged for later placement into the graft. Alternatively, commercially available tacking devices may be used for securing the graft to the sacral promontory (Fig. 72–34).

After placing an obturator in the vagina (large end-to-end anastomosis sizers are useful) the enterocele sac is identified and secured with an Allis clamp. If the enterocele is large, a Halban culdoplasty is performed by placing linear permanent (or delayed absorbable) sutures through the posterior peritoneum and on the outer surface of rectum up to the vaginal cuff (Geomini et al, 2001). Upward retraction of the sizer will assist in exposing the cul-de-sac. Usually four to six sutures are used to complete adequate cul-de-sac closure. This technique of closure (Fig. 72–35) is in contrast to that of the Moschowitz procedure, which involves purse-string closure and may predispose to ureteral angulation and obstruction.

The peritoneum over the vaginal cuff is incised, and the peritoneum is dissected off of the cuff of the vagina (see Fig. 72–35). A 2.0-cm wide segment of graft is sutured to the exposed vaginal cuff using six to eight sutures of permanent suture material (Fig. 72–36). Care is taken to identify the border of the bladder to avoid suturing the graft to the bladder. An obturator in the vagina is useful to facilitate suture placement and secure the mesh to the vagina. A polypropylene, macroporous, monofilament, nonabsorbable mesh is recommended. The graft is secured to the vagina by folding over the cuff of the vagina and allowing the long end of the graft to exit posteriorly and extend to the sacrum. (Alternatively, a T-shaped configuration of the graft may be created. The short arm of the T is placed on the top of the vagina, and the long arm of the T is secured to the lower end of the vagina.) Additionally, a long segment of posterior mesh may be attached to the perineal body, a procedure termed *colpoperineopexy* (Cundiff et al, 1997). At this step the central sutures from the culdoplasty are placed through the long arm of the mesh if desired.

The graft is then secured to the promontory. Care must be taken to avoid excessive tension. Placing the obturator all the way into the vagina but not pushing the vagina upward establishes the proper length of the graft. The graft is placed around the right lateral aspect of the rectum. A space of 2 fingerbreadths between the graft and the rectum prevents compression of the rectum over the graft (Fig. 72–37). The excessive length of the graft is trimmed after fixation to the sacrum. Lastly, the graft is positioned in the retroperitoneal space by closing the presacral peritoneum over the graft and covering the graft on the vagina with the superior edge of the peritoneum over the vagina. Procedures for SUI (if indicated) are then performed. The patient is then examined to determine if any ancillary prolapse repairs are needed.

Abdominal sacrocolpopexy maintains a functional vagina and restores maximum vaginal length and support. In a comparative study, vaginal length was longer after abdominal sacrocolpopexy compared with sacrospinous fixation (Given et al, 1993). A nonabsorbable monofilament synthetic mesh should be used during abdominal sacrocolpopexy. In a study by Culligan and coworkers (2005), patients undergoing abdominal sacrocolpopexy using either absorbable cadaveric fascia lata graft (Tutoplast) or nonabsorbable monofilament polypropylene were randomized. The objective failure rate for recurrence at any other vaginal site was 14 of 44 in the fascial group and 4 of 45 in the mesh group.

There are numerous reports by multiple authors that confirm the success of abdominal sacrocolpopexy.

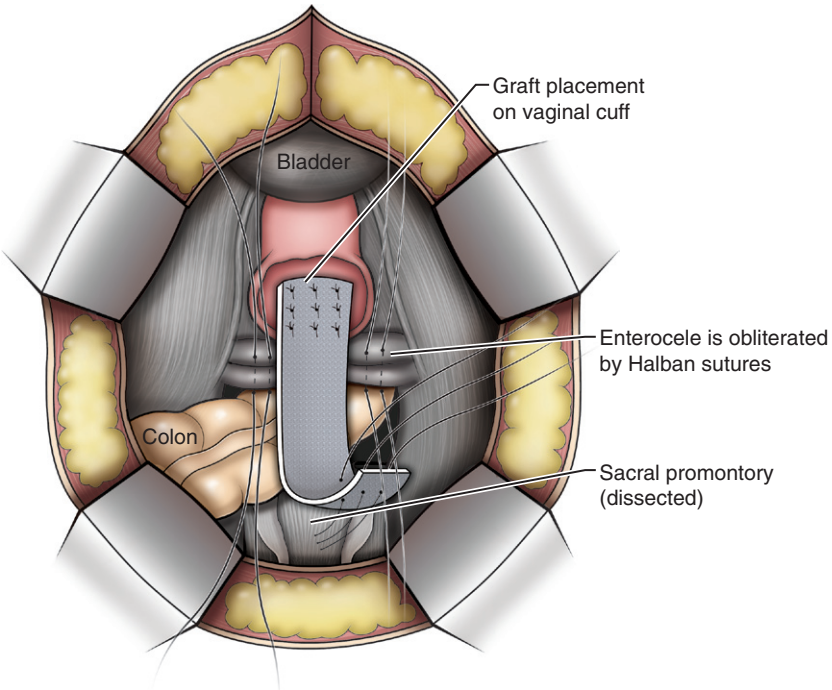


Figure 72–35. Abdominal sacral colpopexy: Synthetic graft material is sutured securely to vaginal cuff using multiple interrupted permanent sutures. The peritoneal cul-de-sac is closed using linearly placed sutures to obliterate this potential space. (From Winters J, Cespedes R, Vanlangendonck R. Abdominal sacrocolpopexy and abdominal enterocele repair in the treatment of vaginal vault prolapse. Urology 2000;56:55–63, with permission.)

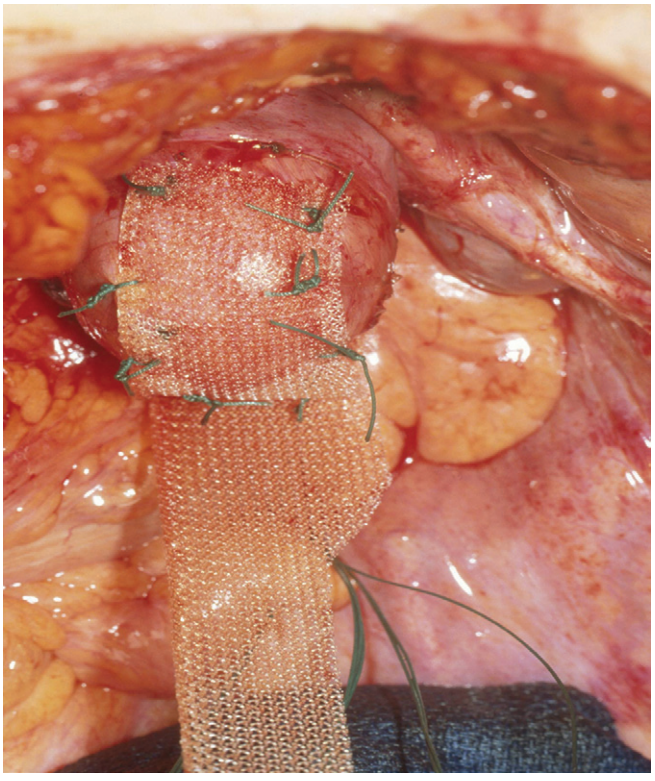


Figure 72–36. Abdominal sacral colpopexy: intraoperative view. Permanent mesh material sutured to vaginal cuff. End-to end anastomosis sizer was utilized to provide exposure of vaginal cuff. (From Scarpero H, Cespedes R, Winters J. Abdominal approach to the repair of vaginal vault prolapse. Tech Urol 2001;7:139–45, with permission.)

Multiple authors have reported success rates greater than 90% (Snyder and Krantz, 1991; Addison and Timmons, 1993; Webb et al, 1998; Menefee et al, 1999). There are several randomized, prospective trials comparing sacrospinous ligament fixation with abdominal sacrocolpopexy. In a comparative study between abdominal sacrocolpopexy versus vaginal repair, Benson and colleagues (1996) reported a lower success rate with vaginal repair, and an equivalent hospital stay between the two groups. Lo and Wang (1998) reported on their results of abdominal sacrocolpopexy versus sacrospinous ligament fixation at a duration of 2.1 years: 94.2% success in abdominal sacrocolpopexy compared with 80% in sacrospinous ligament fixation. Maher and coworkers (2001) reported on a comparative study between abdominal sacrocolpopexy and sacrospinous ligament fixation. At 2 years follow-up, symptoms and anatomic success were equivalent but asymptomatic failures to introitus and recurrent cystoceles were less after abdominal sacrocolpopexy. **Overall, vaginal (sacrospinous ligament fixation) procedures have a higher rate of recurrent anterior defects even when performed in the setting of a concomitant anterior repair (colporrhaphy)** (Holley et al, 1995). After an isolated abdominal repair of vaginal vault prolapse without addressing concomitant pelvic floor defects, recurrent distal defects such as cystocele and rectocele may occur up to a third of the time. This may predispose to decreased patient satisfaction and the possibility of secondary vaginal repair (Blanchard et al, 2006). Although most patients remain asymptomatic, secondary repair of these defects may be required (Blanchard et al, 2006). **It is important to counsel patients preoperatively about the possibility of distal anterior or posterior defects after abdominal sacrocolpopexy and the need for secondary vaginal repair, which can occur up to 20% of the time** (Blanchard et al, 2006).

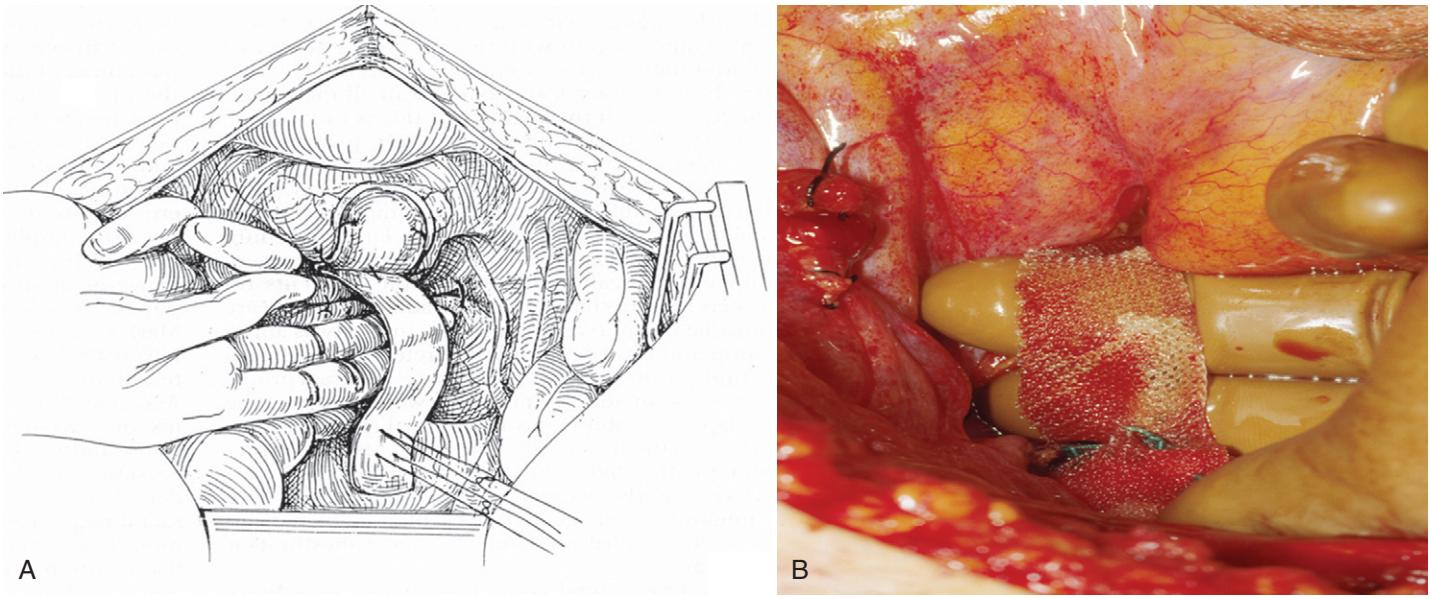


Figure 72–37. Abdominal sacral colpopexy. **A,** Graft is secured without tension to sacral promontory. **B,** Intraoperative view. (**A,** From Winters J, Cespedes R, Vanlangendonck R. Abdominal sacrocolpopexy and abdominal enterocele repair in the treatment of vaginal vault prolapse. Urology 2000;56:55–63, with permission; **B,** from Scarpero H, Cespedes R, Winters J. Abdominal approach to the repair of vaginal vault prolapse. Tech Urol 2001;7[2]:139–45.)

In a comprehensive review by Nygaard and coworkers (2004), intraoperative complications of sacrocolpopexy included hemorrhage or transfusion in 4.4%, cystotomy in 3.1%, enterotomy in 1.6%, and ureteral injury in 1.0%. Postoperative complications included urinary tract infection in 10.9%, wound infection in 4.6%, ileus in 3.6%, deep venous thrombosis or pulmonary embolism in 3.3%, and small bowel obstruction in 1.1%. The risk of significant bleeding has been reported from 1.6% to 4.4% and may be controlled with the use of stainless steel thumbtacks (Timmons et al, 1991). **Significant hemorrhage may occur from disruption of the presacral vessels, and the occurrence of this complication may be reduced when fixation of the graft is performed high on the sacral promontory.** The rate of reoperation for gastrointestinal complications is 1.2% (Whitehead et al, 2007). Vaginal exposure of mesh is heralded by persistent pain, discharge, or infections, and clinicians must be vigilant in follow-up (Karlovsky et al, 2005). In a recently reported meta-analysis, mesh erosion into the vagina is reported at 3.4% to 5.4% and may vary on the type of mesh used (Brizzolara and Pillai-Allen, 2003; Nygaard et al, 2004). **Erosions are more prevalent with Teflon or Gore-Tex materials and rare with macroporous, monofilament meshes.** Several authors have suggested that hysterectomy at the time of colpopexy increases the rate of mesh extrusion, although these findings are not uniform (Nygaard et al, 2004; Marinkovic, 2008) and no randomized trials address this issue (Nygaard et al, 2004). In 60 patients undergoing concomitant hysterectomy using a two-layer closure of the vaginal cuff followed by abdominal sacrocolpopexy with synthetic nonabsorbable monofilament mesh, the erosion rate was 0.8% compared with 0% in the 64 patients with a prior hysterectomy (Wu et al, 2006). In patients undergoing a combined operation, supracervical hysterectomy or a meticulous two-layer closure of the cuff should be performed to decrease the incidence of mesh erosion. **Surgeons must be aware that the concerns of mesh erosion after abdominal sacrocolpopexy are higher after hysterectomy.** Options in the management of eroded mesh after colpopexy may also include mesh excision with partial colpocleisis (Quiroz et al, 2008) and abdominal mesh excision.

Colpocleisis

Colpocleisis is an obliterative procedure used in the treatment of posthysterectomy vaginal vault prolapse or significant uterovaginal prolapse. In properly counseled, older patients who do not desire functional vaginal anatomy for sexual activity, colpocleisis may be an appropriate procedure. The total colpocleisis refers to removal of the vaginal epithelium to 0.5 to 2 cm from the urethral meatus with complete closure. A partial colpocleisis is used in cases of uterovaginal prolapse, and this procedure involves creating lateral channels to allow uterine drainage. Advantages of the colpocleisis procedures are shorter operative time, ability to use regional anesthesia or local anesthesia with sedation, minimal complications, and decreased recuperative time (Cespedes et al, 2001; FitzGerald et al, 2008). In those whose uterus is to be left in situ, preoperative evaluation should include a Papanicolaou smear, pelvic ultrasonography, and endometrial biopsy if indicated. Performance of hysterectomy at the time of colpocleisis eliminates the risk of developing cervical or endometrial cancer and eliminates the risk of developing pyometra, which is a serious complication of partial colpocleisis when the channels become obstructed (Shayya et al, 2009). However, most patients selected for colpocleisis are older with significant comorbidities that make a concomitant hysterectomy undesirable.

Technique

PARTIAL COLPOCLEISIS. The patient is placed in the standard lithotomy position. A Foley catheter is placed into the bladder. If an anti-incontinence procedure is needed, it may be performed first. The cervix is grasped with a tenaculum, and a rectangular segment of vaginal epithelium is marked anteriorly and posteriorly. The excision of the vaginal epithelium will extend 3 cm from the urethral meatus to 3 cm from the cervix (Cespedes et al, 2001).

It is important to leave sufficient vaginal epithelium laterally to allow creation of the lateral channels to facilitate drainage. The epithelium is then excised. It is optional to place a 14-Fr red Robinson catheter along the vaginal sidewalls to assist in forming the channels. Then, starting at the leading edge of the prolapse, one places successive layers of 2-0 delayed absorbable sutures, which plicate and reduce the prolapse until the prolapsed tissues are above the levator plate (Fig. 72-38A). The sutures are placed in transverse rows consisting of linear sutures through the pubocervical fascia anteriorly and rectovaginal fascia posteriorly. As these sutures are tied, the apical prolapse is reduced proximally (see Fig. 72-38B). Successive rows of sutures are placed until the apical prolapse is completely reduced. A high perineorrhaphy is performed by removing a triangular segment of the vaginal epithelium. The fibromuscular tissues of the perineal body are approximated in the midline with absorbable sutures to narrow the introitus. The completed procedures are shown in Figure 72–39. Indigo carmine is administered and a cystoscopy is carried out to confirm ureteral patency.

TOTAL COLPOCLEISIS (Fig. 72–40). The technique differs from partial colpocleisis in that the lateral channels are not left in place, but, rather, the entire prolapsed vagina is denuded of its epithelium from the apex to 3 cm proximal to the urethral meatus. The dissection is carried laterally and continued to the posterior lateral sulcus. The prolapse sac is dissected away from the vaginal epithelium. Usually the enterocele reduces easily and no further treatment is necessary (Cespedes et al, 2001). At this point the colpocleisis is carried out starting at the leading edge of the prolapse. Purse-string sutures of 2-0 absorbable sutures are placed circumferentially around the prolapse (see Fig. 72–37A). As each progressive suture is tied, the prolapse is reduced proximally (see Fig. 72-37B). These progressive purse-string sutures are tied until the prolapse is adequately reduced. Alternatively, the prolapse may be reduced as described for the partial colpocleisis by placing transverse rows of interrupted sutures. As these rows are tied the prolapse is reduced proximally. Successive rows of sutures are placed until the prolapse is fully reduced. The remainder of the procedure is performed as described for the partial colpocleisis. After the prolapse is reduced the posterior vaginal wall and perineum are repaired. A high perineorrhaphy is important to narrow the introitus. Cystoscopy to ensure patency of the ureters is recommended. For both techniques, success depends on the amount of vaginal tissue sutured together. This creates a septum of support, which is enhanced by bringing the levator muscles together along with the perineorrhaphy.

Several authors have reported that it is unnecessary to open the enterocele sac if one is present, because the repair will close the potential space in which the bowel might protrude (DeLancey, 1997; Glavind and Kempf, 2005). If the enterocele sac cannot be reduced, then purse-string absorbable sutures incorporating the sac and the uterosacral remnants can be used to reduce the sac (Cespedes et al, 2001).

Results (Table 72–7)

TOTAL COLPOCLEISIS. DeLancey (1997) reported on 33 women who underwent colpocleisis over a 20-year period. In this study, opening of the enterocele sac was avoided. One patient had recurrence of a vaginal eversion and was treated with repeat colpocleisis and had a good response 1 year after the second colpocleisis. All but one patient expressly denied regret over the decision to have an operation that precludes the ability to have intercourse; however, one "accepted" her sexual inactivity. Many indicated relief of the discomfort associated with the prolapse and were positive about the outcome of the operation. Cespedes and

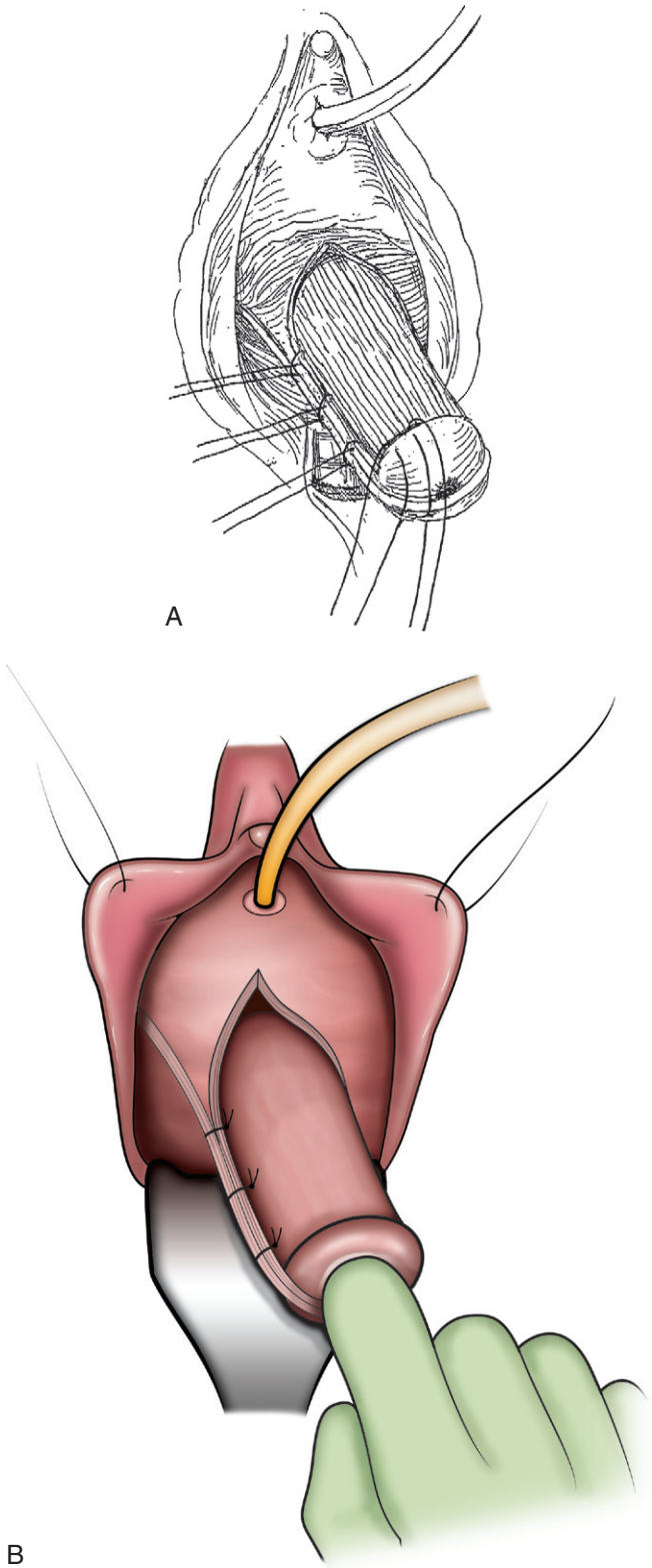


Figure 72–38. **A,** Partial colpocleisis is started by excising rectangular portions of the vaginal epithelium, leaving lateral channels. The cervix is then everted over a red Robinson catheter. **B,** The cervix is everted as the prolapse is reduced. (From Cespedes RD, Winters CW. Colpocleisis for the treatment of severe vaginal vault prolapse. In: Vasavada SP, Appell RA, Sand PK, Raz S, editors. Female urology, urogynecology, and voiding dysfunction. Boca Raton [FL]: Taylor & Francis; 2005, with permission.)

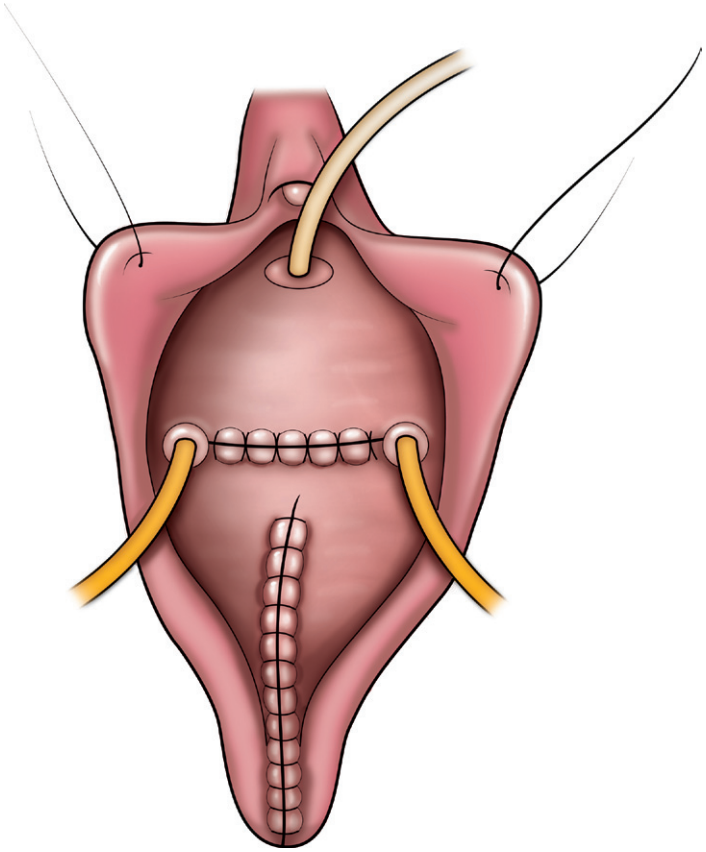


Figure 72–39. The partial colpocleisis is completed along with perineorrhaphy. (From Cespedes RD, Winters CW. Colpocleisis for the treatment of severe vaginal vault prolapse. In: Vasavada SP, Appell RA, Sand PK, Raz S, editors. Female urology, urogynecology, and voiding dysfunction. Boca Raton [FL]: Taylor & Francis; 2005, with permission.)

coworkers (2001) reported on 38 patients who underwent a mean of 24 months follow-up. There was no recurrent prolapse. Three patients who had a Kelly plication for incontinence had mild SUI, and two were treated successfully with collagen. All were satisfied with the procedure, and no complications were noted. von Pechmann and colleagues (2003) reported on a large study (92 patients) who underwent colpocleisis. Patients were followed by examination and telephone survey, which appraised satisfaction and regret. Regret over the loss of coital ability was expressed in 12.9% (eight patients). In a multicenter, prospective study designed to study the effect of colpocleisis on pelvic support, symptoms, quality of life, morbidity, and postoperative satisfaction, FitzGerald and associates (2006) reported on 152 patients with 1-year follow-up. Eighty-four percent stated they were either very satisfied or satisfied about the decision for vaginal closure. One patient was dissatisfied, and one was very dissatisfied. One patient underwent repeat colpocleisis for recurrence. Most patients did not experience worsening of their body image. Hoffman and coworkers (2003) reported favorably on vaginectomy or hysterovaginectomy in which the denuded tissues are brought together with serial purse-string sutures. They preferred this approach because of optimal exposure to the cul-de-sac and the ability to perform multicompartmental repair.

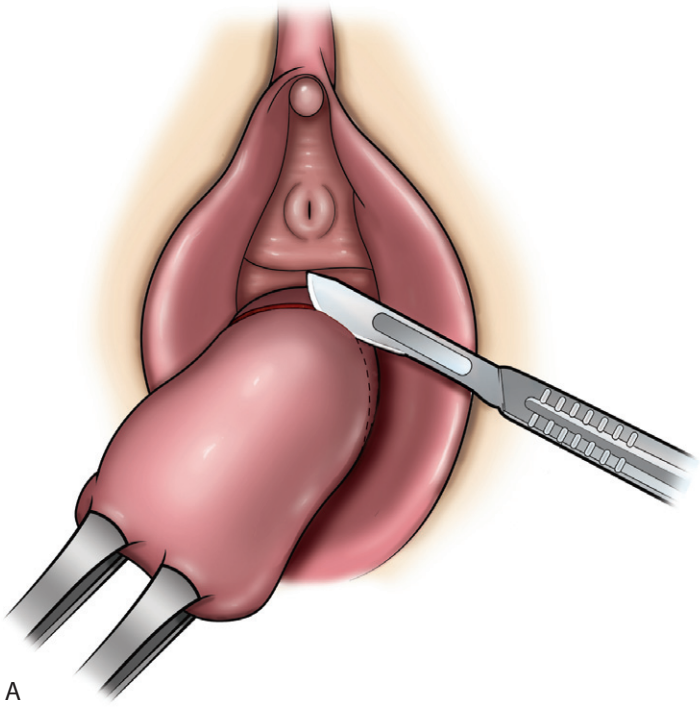
PARTIAL COLPOCLEISIS (see Table 72–7). Goldman and coworkers (1981) reported on 118 patients who underwent Le Fort colpocleisis. Good anatomic results were noted in 107 patients, with 101 reporting relief of symptoms. There were three recurrences but no patient underwent further operative therapy. Immediate postoperative complications were one pulmonary embolism, fever, and urinary tract infection. Langmade and Oliver (1986) reported on 102 patients. There were no recurrences and no de novo stress incontinence. Sixteen patients had transient postoperative urinary retention. No patient changed her mind regarding the ability to engage in sexual intercourse.

Table 72–7.

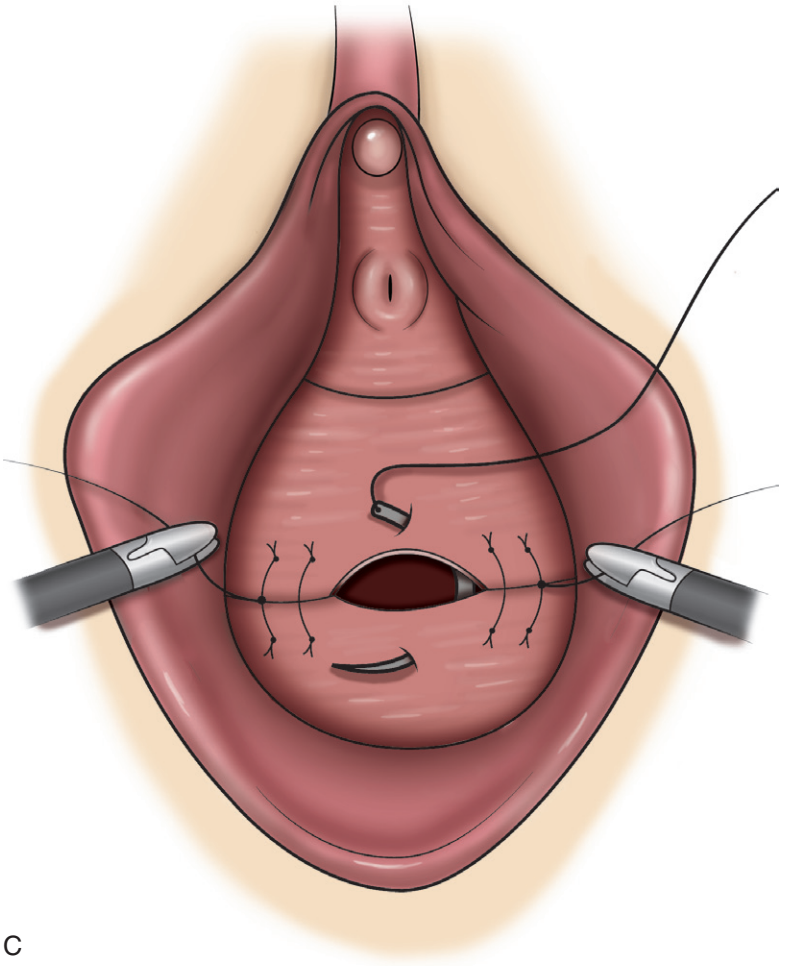
Results of Partial and Total Colpocleisis

AUTHOR	NO. PATIENTS	FOLLOW-UP (mo)	SUCCESS RATE	METHOD OF EVALUATION	COMPLICATIONS
Total Colpocleisis					
DeLancey, 1997	33	1-18 (examination) 36-88 (phone)	97% anatomic 97% did not regret loss of coital ability	Examination Structured telephone questionnaire	Postoperative pneumonia, UTI, worsening of CHF
Cespedes et al, 2001	38	3-52 mean 24	100%	Examination	None
von Pechmann et al, 2003	92	0-64 (examination) 13-161 (phone)	98% anatomic 90% phone survey	Examination Phone survey	One death (lung cancer) rectal prolapse, transfusion, ureteral occlusion, proctotomy, prolapse recurrence
Hoffman et al, 2003 (vaginectomy)	54	6-56	100%	Examination Phone survey	CVA, pulmonary edema, atrial fibrillation
Harmanli et al, 2003	41	5-65	100%	Examination Phone survey	Vesical injury, late rectal bleeding
Deval, 2005	30	7.7 (1-21 examination) 35 (13-161 phone)	100% anatomic 88% answered very satisfied or satisfied	Examination Phone survey	CHF, PE, UTI, 6.6% de novo stress incontinence
Partial Colpocleisis					
Goldman et al, 1981	118	12-180	91%	Examination	Fever, UTI, thrombophlebitis, PE, wound infection
Langmade and Oliver, 1986	102	35 (12-168)	100%	Examination	Urinary urgency, renal toxic reaction to the tobramycin, fever

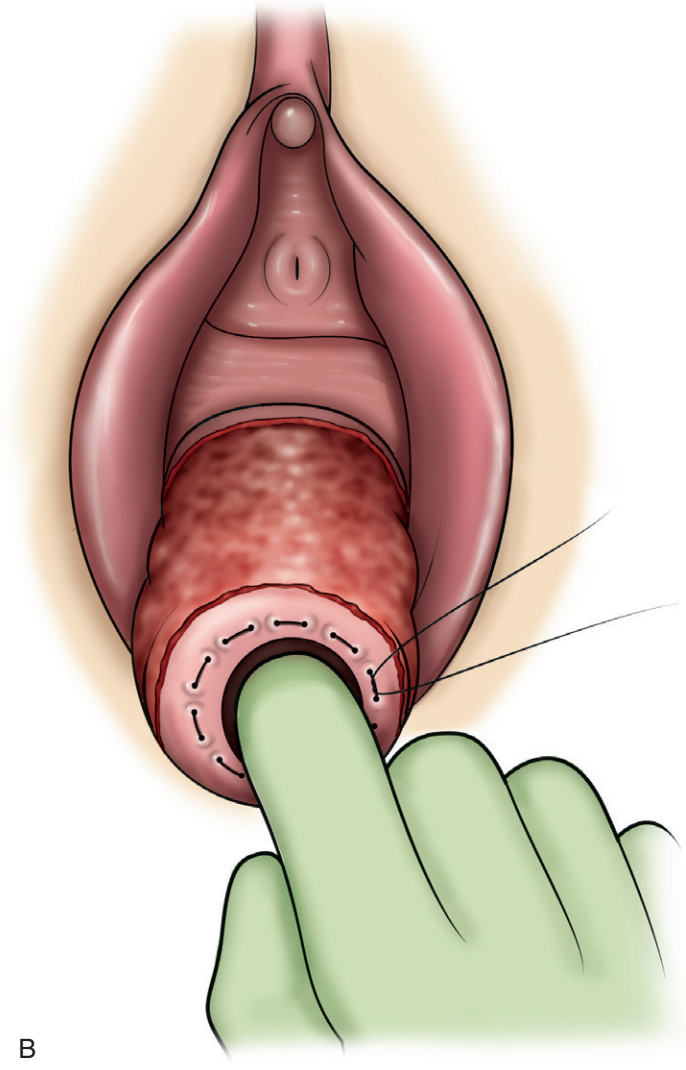
CHF, congestive heart failure; CVA, cerebrovascular accident; PE, pulmonary embolism; UTI, urinary tract infection.



A



C



B

Figure 72–40. Total colpocleisis. **A,** A circumferential incision is created at the base of the prolapse. **B,** Purse-string sutures are placed in the prolapsed tissues to reduce it. **C,** The vaginal epithelium is closed transversely. (From Delancey JO, Morley GW. Total colpocleisis for vaginal eversion. Am J Obstet Gynecol 1997;176:1228–35, with permission.)

Urinary incontinence after colpectomy may occur and has been attributed to several mechanisms. The first, occult stress incontinence, is when correction of the urethral angulation will unmask preexisting stress incontinence. The other is from traction of the urethra when it is approximated with the posterior vaginal muscularis (FitzGerald et al, 2006). Thus it is recommended to modify the procedure so that the distal edge of the colpocleisis is at least 1.5 cm from the urethral meatus (FitzGerald et al, 2006). As with other prolapse cases, the recommendation of a concomitant anti-incontinence procedure in an asymptomatic patient is controversial and remains to be substantiated by prospective studies. **However, it is clear that these women may develop SUI postoperatively. Thus all women before undergoing colpocleisis should be screened for the presence of occult SUI, and anti-incontinence procedures should be done concomitantly in women with symptoms of SUI or occult SUI.** Additionally, in these frail, elderly patients there is a concern of urinary retention, which frequently is the result of impaired contractility and other perioperative factors. This may be more difficult to manage because these patients are more likely to be unable to perform intermittent catheterization. Thus these possibilities must be discussed with the patients in advance of surgery. Patients considered at significant risk for retention should be offered a suprapubic tube to assist in bladder management postoperatively.

Uterine Prolapse

Pelvic organ prolapse was the indication for 16.3% of all hysterectomies performed between 1988 and 1990. Although the majority of hysterectomies are performed transabdominally, the vaginal approach offers the advantages of less invasive surgery and the ability to repair concomitant pelvic floor defects (ACOG, 2009; Eilber et al, 2004).

The uterus is suspended in the pelvis by the cardinal/uterosacral ligament complex. The body of the uterus is enveloped between the two leaves of the broad ligament, which also surrounds the fallopian tube, round ligament, and ovarian ligament along with the uterine and ovarian vessels. The broad ligament does not provide significant support (Eilber et al, 2004). Therefore the defect prompting uterine prolapse is in the form of attenuated ligaments or specific breaks in the continuity of the cardinal/uterosacral ligament complex. Contraindications for the vaginal approach are endometriosis of unknown extent, obliteration of the cul-de-sac, large fibroids (size disproportion to the introitus), pelvic tumor, adnexal tumor, and malignancy of the uterus or ovaries (Eilber et al, 2005).

Transvaginal Hysterectomy

Technique. The patient is placed in the dorsal lithotomy position. A catheter is placed to drain the bladder. Retraction of the labia with a ring retractor and stays is useful. Two Lahey clamps are placed on the cervix. Care must be taken to place it on the most distal portion because the bladder may descend fairly low on the anterior vaginal wall. The incision is made full thickness through the vaginal epithelium around the cervix approximately 1 cm from the cervical os (Fig. 72–41). Because the posterior cul-de-sac is entered first, a U-shaped incision is made initially from the 3-o'clock position to the 6-o'clock position to the 9-o'clock position. The posterior peritoneal fold is exposed (Fig. 72–42). Applying traction to the tenaculum and using a right angle retractor to apply countertraction to the vagina facilitate this exposure. This maneuver will help to identify the correct plane, because the vagina will retract when the correct depth is reached. Once the posterior peritoneal fold is identified, it is opened sharply to enter



Figure 72–41. Circumferential incision through the vaginal epithelium is made at the level of the cervix. (From Rooney CM, Karram MM. Vaginal hysterectomy in the treatment of vaginal prolapse. In Raz S, Rodriguez LV, editors. Female urology. 3rd ed. Philadelphia: Elsevier Saunders; 2008.)

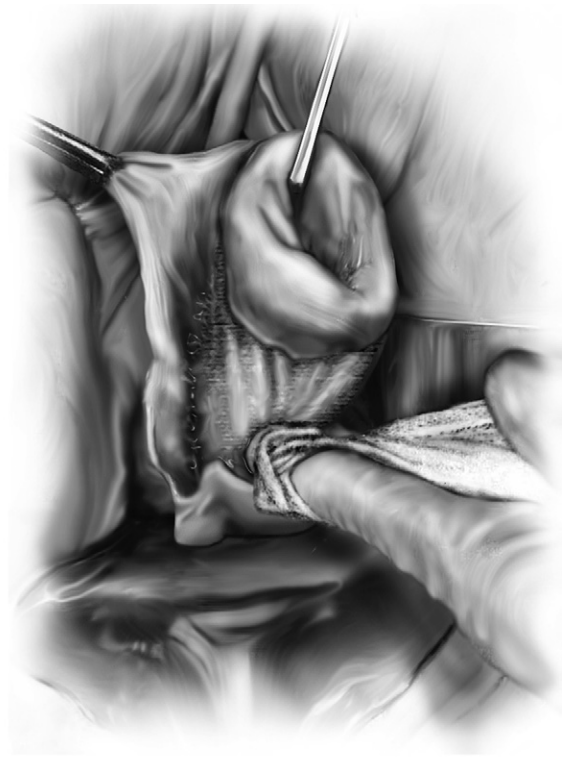


Figure 72–42. The vaginal epithelium is sharply dissected from the cervix revealing the posterior peritoneal fold. (From Rooney CM, Karram MM. Vaginal hysterectomy in the treatment of vaginal prolapse. In: Raz S, Rodriguez LV, editors. Female urology. 3rd ed. Philadelphia: Elsevier Saunders; 2008.)

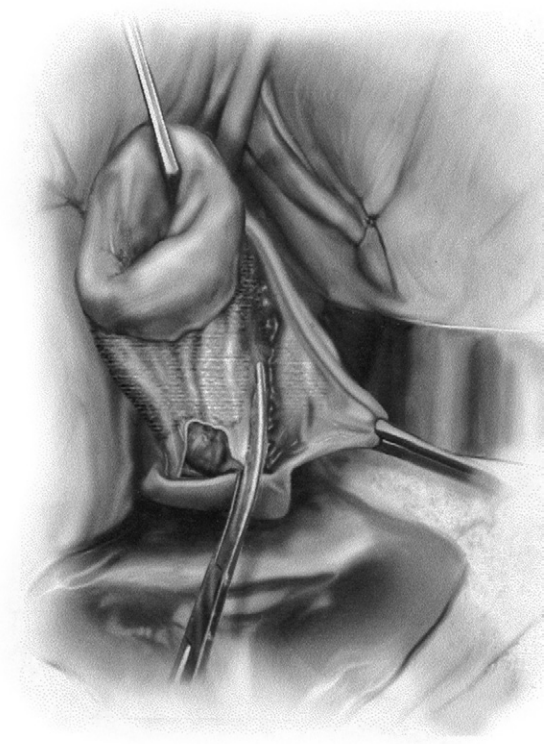


Figure 72–43. Clamping of the uterosacral ligaments. (From Rooney CM, Karram MM. Vaginal hysterectomy in the treatment of vaginal prolapse. In: Raz S, Rodriguez LV. Female urology. 3rd ed. Philadelphia: Elsevier Saunders; 2008.)

the cul-de-sac. Visualization of bowel and omentum will confirm correct entry into the peritoneal cavity. By entering the peritoneal cavity posteriorly, control of the uterosacral ligaments can be attained before the anterior dissection (Fig. 72–43). This prevents potential anterior bleeding from obscuring the posterior portion of the dissection and facilitates mobilization of the uterus when the uterosacral ligaments are divided. Countertraction and use of gauze will aid with separation of the peritoneum off of the posterior aspect of the uterus. Once the cul-de-sac is entered, the uterus and adnexa may be palpated to check for further pathology. A long, weighted vaginal speculum is placed with the beak into the abdominal cavity. The anterior dissection is now started. The circumferential incision is completed anteriorly. It is imperative to keep the dissection close to the uterus by placing the tips of the curved Metzenbaum scissors toward the cervix. The glistening white surface of the uterus confirms the correct plane of dissection. Traction on the cervix with countertraction applied with a right angle (Heaney) retractor will facilitate with the dissection of the vesicouterine space. The peritoneum is identified anteriorly and entered. Visualization of the bowel or omentum will confirm the location in the peritoneal cavity. Once the peritoneum has been entered anteriorly and posteriorly the ureters can be palpated to verify the location. The uterosacral ligament can then be shortened to facilitate suspension into the pelvis to restore the vaginal cuff once the uterus has been removed.

The cardinal and uterosacral ligaments are isolated with a large right-angle clamp and Phaneuf clamp, divided, and then suture ligated with delayed absorbable suture. First, the uterosacral ligament is identified. A small stump of tissue should be left rather than cutting flush with the clamp to facilitate later identification. This is done bilaterally. The pedicles should be tagged with a curved hemostat. The uterus will then descend. The cardinal ligament is then grasped by swinging the clamp laterally, which shortens the pedicle. It is not unusual to have an elongated cervix with prolapse, which will make visualization of the fundus of the uterus challenging. The uterine arteries are cross clamped, suture ligated, and then divided, being careful to leave enough of a stump so that the suture does not slip (Fig. 72–44). Including the peritoneum anteriorly and posteriorly will ensure the complete inclusion of the artery in the clamp. Next comes the broad ligament. If the ovaries and adnexa are to be left, the utero-ovarian ligament, fallopian tube, and round ligaments are visualized from anterior to posterior and are divided and ligated. The broad ligament is then clamped and divided bilaterally. All the pedicles are examined for hemostasis.

Vaginal vault suspension is crucial because the hysterectomy alone will not restore the anatomy of the vaginal vault. Two maneuvers are important to perform. The pubocervical fascia and the rectovaginal fascia are approximated to close the cul-de-sac and a culdoplasty is done. The culdoplasty should be performed first. This is started by placing a suture into the uterosacral ligaments and a suture at the corners of the vaginal cuff. These are not tied down until after the cuff is closed, because doing so will suspend the vaginal vault. Two purse-string sutures of 0 polyglactin are placed to close the cul-de-sac. These sutures will incorporate the pubocervical fascia, rectovaginal septum, cardinal/uterosacral ligament complex, broad ligaments, and perivesical fascia. The sutures are not placed too laterally on the pubocervical fascia because this can cause ureteral injury. The purse-string sutures are tagged and not tied down at this point. The vaginal cuff can then be closed in a continuous locking or interrupted fashion. The sutures from the uterosacral ligaments are brought to the midline, and then the purse-string sutures are tied. The suspension sutures are then tied, thus suspending the vaginal vault and restoring vaginal depth. At this point any other repair is performed, but extending the anterior or posterior incisions to the previously incised vaginal cuff (T colpotomy) should be avoided because this inherently weakens the repair (Fine and DeLancey, 2005). A cystoscopy is then performed before cutting the excess suture material.

Posterior Compartment Repair

Symptoms attributable to posterior compartment prolapse can be divided conceptually as herniation symptoms, defecatory dysfunction, and sexual dysfunction (Cundiff and Fenner, 2004). Herniation symptoms include vaginal bulging and bleeding of the epithelium from excoriation. Defecatory dysfunction includes stool trapping requiring vaginal splinting or manual digitations, defecatory urgency, and constipation. It is important to differentiate between outlet obstruction (including defects in the support of the posterior compartment, perineum, and rectum), motility disorders, and anismus (Cundiff and Fenner, 2004). Anismus is the failure of the puborectalis to relax during defecation. Motility disorders, which usually involve impaired transit of the rectum and anus, are treated with dietary modifications and medication. Anismus responds to biofeedback, and pelvic floor support defects are treated surgically. In combined disorders it is recommended that nonsurgical treatment for anismus or slow transit constipation (the most common disorder of motility) be treated before embarking on surgical intervention. Sexual dysfunction is thought to be secondary to dyspareunia, although decreased desire and



Figure 72–44. The uterine vessels are clamped and the vascular pedicle suture ligated. Care should be taken to leave enough of a stump to prevent the suture from slipping off the pedicle. (From Rooney CM, Karram MM. Vaginal hysterectomy in the treatment of vaginal prolapse. In Raz S, Rodriguez LV. Female urology. 3rd ed. Philadelphia: Elsevier Saunders; 2008.)

anorgasmia may also be contributing factors (Handa et al, 2004). There is conflicting evidence between the correlation both in sexual dysfunction and defecatory dysfunction and the degree of POP (Weber et al, 1998; Ellerkman et al, 2001; Fialkow et al, 2002; Jelovsek et al, 2005; Bradley et al, 2006).

Several authors have sought to identify patient factors that would predict who might benefit most from rectocele repair (Murthy et al, 1996; Watson et al, 1996). These include sensation of vaginal mass or bulge, need for digitalization to complete rectal evacuation, nonemptying or partial emptying on defecography, and presence of a large rectocele. Sensation of incomplete emptying and constipation are not specific to rectoceles and may be associated with other disorders, including irritable rectum and slow transit constipation. **Patients should be counseled that surgery may reduce the vaginal protrusion and decrease or eliminate the need for vaginal splinting; however, some patients may have persistence of constipation because motility disorders and anismus can coexist with prolapse.**

Rectoceles can be approached transanally or transvaginally. Nieminen and coworkers (2004) randomized 30 patients to rectovaginal fascia plication or transanal repair. Both approaches resulted in a high rate of symptom resolution (93% for the vaginal approach vs. 73% for the transanal approach). However, the vaginal approach had better objective findings and a lower rate of prolapse recurrence (7% vs. 66%). The traditional posterior colporrhaphy was devised in the 19th century to treat perineal tears, which occurred during vaginal delivery. The original description involved plicating the pubococcygeus muscles and the posterior vaginal wall and reconstruction of the perineal body, which was termed *posterior colpoperineorrhaphy* (Cundiff and Fenner, 2004). This creates a rigid inferior shelf, which reduced the herniation of the posterior wall and prevented descensus of the vaginal vault or uterus. In 1961, Francis and Jeffcoate (1961) reported a high incidence of dyspareunia after colporrhaphy with levator plication. In their series of 243 women, 50% developed postoperative dyspareunia. In addition, there is evidence to suggest that the traditional posterior colporrhaphy with levator plication may worsen defecatory symptoms. Khan and Stanton (1997) reported increased symptoms of fecal incontinence, constipation, incomplete evacuation, and dyspareunia postoperatively. **Because of the increase in dyspareunia postoperatively, plication of the levator ani muscles has largely been abandoned. Site-specific repairs and midline fascial plication without levator ani plication have emerged as the predominant surgical treatments of rectocele.**

Posterior Colporrhaphy

Technique (Fig. 72–45). The patient is placed in the dorsal lithotomy position. If a patient requires an anterior or middle compartment repair, it is performed first (Rovner and Ginsberg, 2001). The anterior wall can be retracted with a Heaney retractor to improve visualization. Hydrodissection may be accomplished by injecting saline or a local anesthetic. A midline incision is made on the posterior vaginal epithelium. For a high rectocele the incision may be as high as the vaginal vault; for smaller rectoceles the incision is started at the most caudal position. The rectovaginal fascia is separated from the vaginal epithelium with Metzenbaum scissors. The tips of the scissors should be pointed toward the vagina to avoid rectal injury. The dissection proceeds laterally until the pararectal attachments to the pelvic sidewall are visualized. In cases of large posterior defects, a purse-string suture of 2-0 or 3-0 absorbable suture may be placed at the base of the rectal herniation to reduce it. Additionally, this acts to bring the attenuated rectovaginal tissue together to aid in its reapproximation. The rectovaginal tissue is then plicated in the midline with either interrupted or continuous 2-0 absorbable suture. Care is taken to avoid excessively lateral placement of these sutures, because this may result in a painful "ridge" along the posterior vaginal wall. This is extended distally and incorporated into a perineal body reapproximation. The excess vaginal epithelium is trimmed, and the vaginal epithelium is closed with an absorbable suture. A perineorrhaphy may also be performed before the vaginal epithelium is closed.

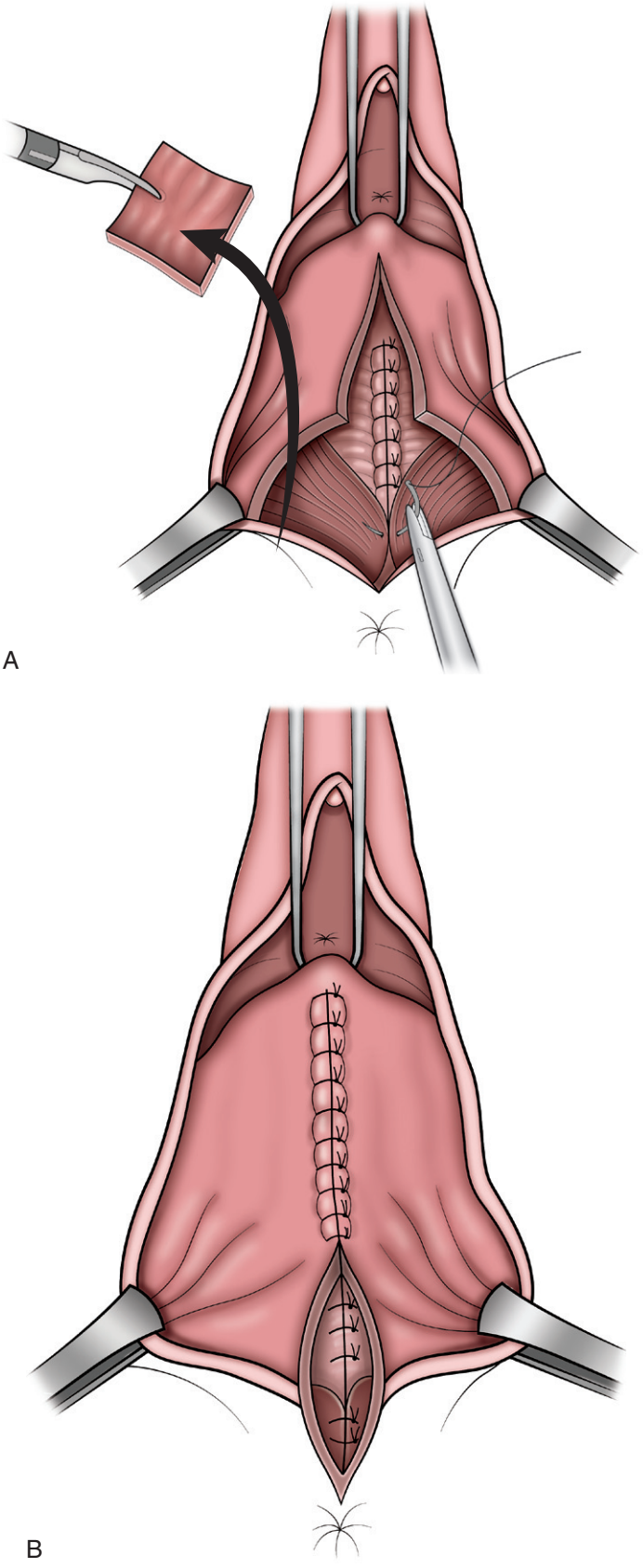


Figure 72–45. **A** and **B,** Technique of posterior colporrhaphy with rectovaginal tissue plication. From Ginsberg D. Treatment of vaginal wall prolapse. In: Goldman H, Vasabada S, editors. Female urology: a practical clinical guide. Totowa [NJ]: Humana Press; 2007. p. 281–96, with permission.)

SITE-SPECIFIC REPAIR. To minimize complications associated with posterior colporrhaphy, a site-specific defect repair was described. Richardson (1993) described discrete defects in the rectovaginal fascia found in both patients undergoing posterior colporrhaphy and cadaveric dissections. He found that the most common defect was the transverse configuration, separating the vaginal septum from the perineal body (Fig. 72–46). This essentially results in a separation of the rectovaginal tissues from the perineal body. The goal of the site-specific repair is to restore the anatomy by closing these discrete defects.

A midline incision is made on the posterior vaginal epithelium. For a high rectocele the incision may be as high as the vaginal vault; for smaller rectoceles the incision is started at the most caudal position. The rectovaginal fascia is separated through a virtually bloodless plane from the vaginal epithelium. The index finger of the nondominant hand is then inserted into the rectum to facilitate identification of the fascial defect. The defect is closed with absorbable interrupted sutures. The excess vaginal epithelium is trimmed, and the vaginal epithelium is closed with interrupted sutures.

PERINEORRHAPHY. A triangular incision at the mucocutaneous junction is removed (Rovner and Ginsberg, 2001). The triangular island of posterior vaginal wall is sharply removed from the pre-rectal levator fascia. Horizontal mattress sutures are used to approximate the attenuated perineal body fibromuscular tissue. Once these are brought together, the muscles of the urogenital diaphragm are reconstituted and support is restored to the central tendon. It is important that a smooth contour be created along the suture line, because ridges may cause dyspareunia. A vaginal packing soaked with the antibiotic solution or metronidazole gel is then placed.

Results (Table 72–8). Khan and Stanton (1997) reported on the anatomic and functional results of posterior repair utilizing levator plication. Both reported anatomic success; however, many patients complained of bowel symptoms and dyspareunia postoperatively. Because of these adverse events associated with levator plication, this technique has been largely abandoned.

Paraiso and associates (2006) randomized patients prospectively to posterior colporrhaphy (rectovaginal fascial plication), site-specific repair, or site-specific repair with porcine small intestinal submucosa graft. They found that posterior colporrhaphy and site-specific rectocele repair had similar functional and anatomic outcomes. The addition of the porcine-derived graft did not improve anatomic outcomes. Rates of dyspareunia did not differ when comparing all three groups. In a follow-up study of these same patients specifically looking at bowel symptoms, Gustilo-Ashby and coworkers (2007) found that anatomic cure was associated with a reduced risk of postoperative straining and sensation of incomplete bowel evacuation but not with other bowel symptoms. They found that bowel symptoms, including feeling of incomplete emptying, straining to defecate, splinting to defecate, and fecal incontinence improved significantly after rectocele repair. Abramov and associates (2005) retrospectively studied patients with advanced posterior vaginal prolapse and compared patients who underwent posterior repair to those who had site-specific repair. They found that the recurrence of posterior defects was higher in the site-specific group compared with the midline plication of the rectovaginal fascia (33% vs. 14% for second-degree repair and 11% vs. 4% for third-degree repair). In addition, recurrence of symptomatic rectocele was greater in the site-specific group (11% vs. 4%). Rates of de novo dyspareunia and postoperative bowel symptoms were the same in both groups. Maher and colleagues (2004) prospectively studied the efficacy of posterior

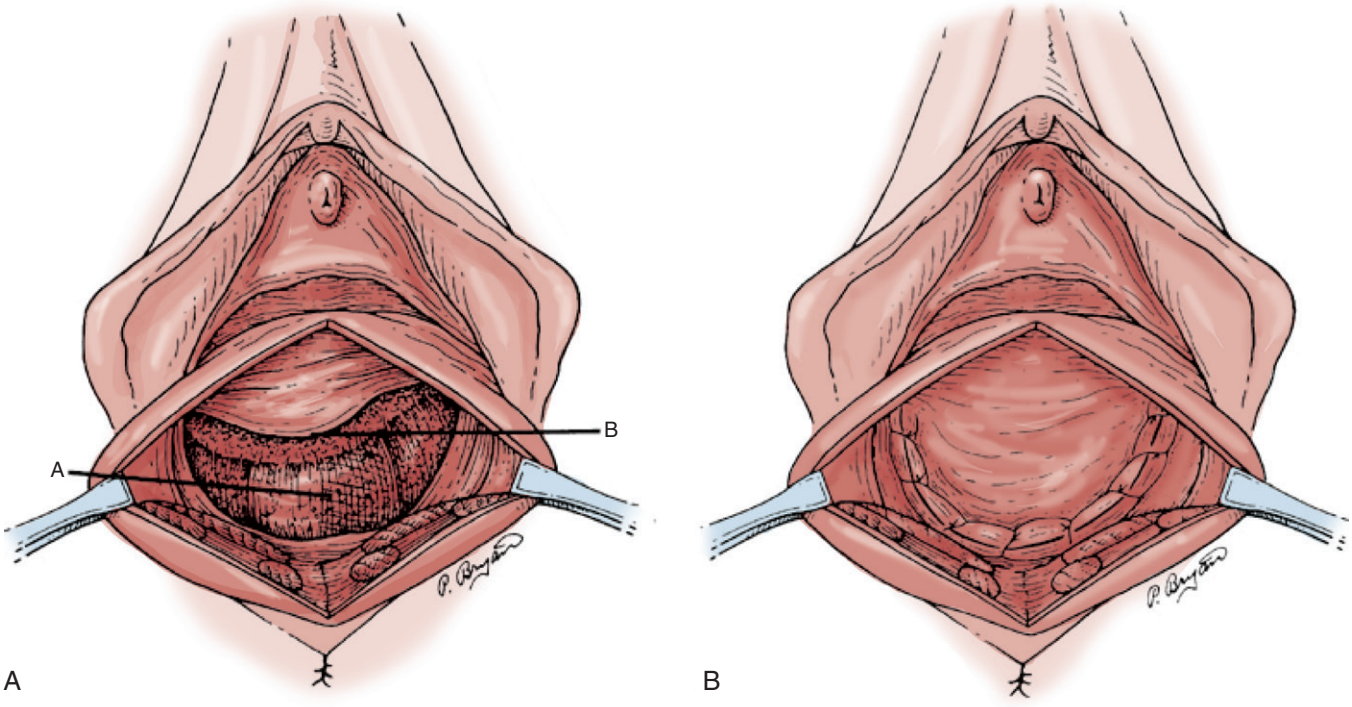


Figure 72–46. Site-specific rectocele repair. A low transverse defect is identified and repaired primarily. (From Richardson AC. The rectovaginal septum revisited: its relationship to rectocele and its importance in rectocele repair. Clin Obstet Gynecol 1993;36:976–83.)

Table 72–8.

Results of Posterior Compartment Repair

TECHNIQUE	STUDY	NO. PATIENTS	FOLLOW-UP (mo)	SUCCESS RATE	EVALUATION	COMPLICATIONS
Levator ani plication	Lopez et al, 2001	25	61	96% anatomic 91% improved symptoms	Examination, questionnaire, defecography, colonic transit time, manometry	Hematoma, fever, dyspareunia, pelvic heaviness
	Khan and Stanton, 1997	231 (171 evaluated)	42	76% rectocele	Examination, postoperative interview, and phone interview	Incomplete bowel emptying, constipation, fecal incontinence, dyspareunia
	Mellgren et al, 1995	25	12	96% anatomic 88% symptoms	Standardized questionnaire, examination	Not reported
Midline fascial plication	Paraiso et al, 2006	37 (28 evaluated)	24	86%	POP-Q, validated questionnaire	Worsening of prolapse, dyspareunia, defecatory dysfunction
	Abramov et al, 2005	183	>12	82%	Baden-Walker classification, POP-Q, questionnaire	Hemorrhage, wound infection
	Maher et al, 2004	38	12 (2.5-26 mo)	79% objective 89% subjective	POP-Q, validated questionnaire, visual analog scale	UTI, proctotomy, rectovaginal hematoma
	Singh et al, 2003	42	18	92%	POP-Q, questionnaire	Wound infection
Site-specific repair	Paraiso et al, 2006	37 (27 evaluated)	24	78%	POP-Q, validated questionnaire	Worsening of prolapse, dyspareunia, defecatory dysfunction
	Abramov, 2005	124	>12	56%	Baden-Walker classification, POP-Q, questionnaire	Hemorrhage, wound infection
	Glavind and Madsen, 2000	67	3	100%	Examination, nonstandardized questions	Not reported
	Porter et al, 1999	125	18 (6-36)	82%	Standardized questionnaires, Baden-Walker classification,	Not reported
	Kenton et al, 1999	66	12	77%	POP-Q, questionnaire	Not reported
	Cundiff et al, 1998	69	12 (3-48)	86%	POP-Q, questionnaire	Not reported

POP-Q, Pelvic Organ Prolapse Quantification System; UTI, urinary tract infection.

repair with plication of the rectovaginal fascia and found that improved anatomic outcome correlated with improved functional outcomes. Eighty-seven percent of patients no longer experienced obstructed defecation postoperatively. Significant improvements were seen in awareness of prolapse, obstructed defecation, straining to defecate, hard stools, dyspareunia, and digitations. Dyspareunia decreased from 37% to 5%. Singh and associates (2003) reported a prospective study of 42 women evaluated for bowel, sexual, urinary, and prolapse symptoms as well as anatomic outcomes after fascial plication technique. At 6-week follow-up, 87% noted an improvement of bowel symptoms. At 18 months they estimated the relief of vaginal symptoms to be between 73% and 92%. Sixty-five percent had improvement of the defecatory symptoms and 38% had improvement of sexual discomfort. None of the patients reported de novo dyspareunia or bowel symptoms.

In contrast to the generalized repair of midline plication of the rectovaginal fascia, several authors have reported their experience with site-specific repair. Glavind and Madsen (2000) prospectively studied 67 patients who underwent a discrete repair. Of the 67 patients, 64 were found to have a discrete defect, which was repaired; and in 3 there was an attenuation of the tissue. At 3-month follow-up, 85% of those who reported bowel symptoms preoperatively reported resolution of symptoms. Two patients (3%) had de novo dyspareunia. Porter and colleagues (1999) examined anatomic, functional, and quality of life aspects of posterior colporrhaphy in a retrospective study. Improvement or cure was noted for pain or pressure, vaginal mass, splinting, and difficulty with defecation. Constipation did not significantly change. Preoperative dyspareunia improved in 73% patients, worsened in 19%, and occurred de novo in three patients. Emotional health improved, specifically thoughts of embarrassment and frustration. Kenton and coworkers (2007) reported on 66 patients who underwent site-specific repair; all patients had reattachment of the rectovaginal septum to the perineal body. Statistically significant symptom relief was noted in protrusion, manual evacuation, difficult defecation, and dyspareunia. Constipation was unchanged. Three patients developed de novo dyspareunia, and one had de novo constipation. At 1 year, 7 of 11 patients who used manual evacuation preoperatively returned to doing so. The authors commented that this may be due to a functional decompensation of the rectum that is not corrected surgically. Finally, Cundiff and colleagues (1998) reported on the anatomic and functional aspects of discrete fascial defect repair of the posterior compartment. At 12-month follow-up, 86% were noted to have stage 1 or less. Splinting was eliminated in 63% of patients who reported this symptom preoperatively. The mean satisfaction score was 8.6 (10 highest). **The mean improvement did not correlate to the anatomic correction but did correlate with alleviation of defecatory symptoms, stressing the importance of symptom relief being of priority to the patient over anatomic correction.**

Interposition Graft Repairs of the Posterior Compartment (Table 72–9)

Both synthetic mesh and biologic grafts have been used in posterior repairs, although data are lacking regarding routine use. Also, several authors caution against the use of synthetic materials in the posterior compartment, owing to the potential for dyspareunia and visceral erosion, and favor using biologic grafts (Chen et al, 2007). Kohli and Miklos (2003) reported anatomic outcomes on 43 patients who underwent a site-specific repair with cadaveric dermis: 30 were available for evaluation at an average of 12.9 months. The graft was fixed proximally to the vaginal apex, laterally to the levator ani muscles, and distally to the perineal body. They reported a 93% success rate using the POP-Q system. Kobashi and associates (2005) reported using cadaveric fascia lata in 73 patients. With a mean follow-up of 13.7 months, there was an 83% to 89% improvement in symptoms. Ninety percent of those examined had a grade 0 rectocele by the Baden-Walker classification. Dell and O'Kelley (2005) used Pelvisoft, a fenestrated, porcine dermal acellular matrix, and reported no wound complications. Despite these encouraging results, Altman and associates (2005) reported on 29 patients using collagen mesh for symptomatic rectocele. Twenty-three were available at 3-year follow up: 41% had recurrence of stage 2 or greater, and 12 of 23 patients reported incomplete rectal evacuation. They advocated further study before recommending the routine use of graft-augmented tissue repair.

A number of authors are utilizing permanent mesh materials via a posterior approach. By using permanent materials, multicompartmental repairs are more commonly performed extending from the sacrospinous ligament to the perineal body. de Tayrac and associates (2006) reported on 26 patients with 2-year follow up. Objective and subjective cure rates of 92.3% and 88%, respectively, were observed. Dwyer and O'Reilly (2004) used a technique attaching Atrium mesh to the sacrospinous ligament bilaterally to the perineal body. Fifty patients underwent posterior repair, 17 of whom had both anterior and posterior repair. No rectocele recurrence was seen at 13 months. Lim and associates (2005) reported using a composite polyglactin/polypropylene mesh (Vypro II, Ethicon, Somerville, NJ). In a descriptive study, 90 patients underwent interposition graft placement with no primary repair. Mesh was placed loosely. Success was noted in 27 of 31 (84%) at minimum 6-month follow-up. The 5 patients with recurrence of the rectocele did not have prolapse in other compartments. Mercer-Jones and coworkers (2004) reported 22 patients who underwent transperineal placement of either polyglactin/polypropylene or just polypropylene mesh: 77% reported moderate, good, or excellent results after mesh repair.

In the posterior compartment, graft extrusion rates of 1.3% to 12% have been reported (Kobashi et al, 2005; Lim et al, 2005; de Tayrac et al, 2006, 2007). Dyspareunia has also been reported with rates as high as 60% when using mesh posteriorly (Milani et al, 2005).

Vaginal Kits

There has been a rapid expansion of the use of vaginal kits in the treatment of pelvic organ prolapse. With the popularity of the transobturator approach of the midurethral sling it was not long before techniques involving the blind passage of trocars to the level of the sacrospinous ligament via the paravaginal space were developed. Although some have been marketed as single-compartment repairs, in actuality the presence of the mesh at the level of the vaginal apex with fixation turns a single-compartment repair into a multicompartmental repair, thus making comparisons to traditional prolapse repairs challenging. Lo and Wang (1998) reported on their results of abdominal sacrocolpopexy versus sacrospinous ligament fixation at a duration of 2.1 years. Success was noted in 94.2% of patients after abdominal sacrocolpopexy compared with 80% success after the sacrospinous ligament fixation.

Transvaginal Kits

Tension-free vaginal kits have been introduced to provide a graft augmented durable repair. The proposed advantages of kits are

Table 72–9.

Vaginal Approach—Posterior

STUDY	GRAFT MATERIAL (NO. PATIENTS)	ATTACHMENT SITE	FOLLOW-UP (mo)	ANATOMIC SUCCESS RATE	SUBJECTIVE SUCCESS RATE	RECURRENT PROLAPSE	COMPLICATIONS
Single Compartment							
Kohli and Miklos, 2003	Cadaveric dermis (43)	Levator ani	12.9	0.93	NR	2 rectocele	None
Kobashi et al, 2005	Cadaveric fascia lata (73)	Levator ani	13.7	0.9	Stool trapping (83%) Splinting (89.5%) Dyspareunia (64.3%)	5 rectocele 10%) 1 enterocele (2%)	8 exposed suture (16%) 3 wound separation (6%) 1 fecal urgency (2%) 2 prolonged pain (4%)
Lim et al, 2005	Polyglactin/ polypropylene (90)	Levator ani	3 (90 pts) 6 (31 pts)	0.84	Vaginal bulge (80%) Constipation (64%) Defecation difficulty (65%) Dyspareunia (83%)	5 rectocele (16%)	9 vaginal erosion (10%) 2 de novo dyspareunia (3.4%)
Multicompartmental							
Dell and O'Kelley, 2005	Porcine dermis (35)	Levator ani	12	NR	NR	NR	None
Altman et al, 2005, 2006	Porcine dermis (29)	Levator ani	38	0.59	≤50% (various bowel emptying difficulties)	11 rectocele (41%)	None
de Tayrac et al, 2006	Polypropylene (25)	Sacral spinous ligament, levator ani, perineal body	22.7	0.923	22/25 (88%) based on PFDI and PFIQ	1 rectocele (3.8%)	3 vaginal erosion (12%) 1 de novo dyspareunia (7.7%)
Milani et al, 2005	Polypropylene (31)	Levator ani, perineal body	17	0.94	Improved constipation (15%) Improved anal incontinence (4%)	1 rectocele (6%)	2 mesh extrusion (6.5%) 1 pelvic abscess (3.2%) 19 de novo dyspareunia (61%)

NR, not reported; PFDI, Pelvic Floor Distress Inventory; PFIQ, Pelvic Floor Impact Questionnaire.

"less invasive," standardization of technique, standardization of mesh, and the ability to repair multiple compartments through a vaginal approach. Currently, there are a number of vaginal prolapse repair kits on the market (Table 72–10), with Prolift (Ethicon, Johnson and Johnson, Somerville, NJ) and Apogee/Perigee (American Medical Systems, Minnetonka, MN) being most commonly utilized. Short-term cure rates of approximately 90% have been reported in several series (de Tayrac et al, 2007; Fatton et al, 2007; Gauruder-Burmester et al, 2007). These transvaginal kit procedures have gained widespread acceptance in light of little controlled, quality data that strongly support their use. Implanting surgeons must realize that these procedures are utilizing a significantly higher volume of mesh than conventional midurethral slings and that the trocars are passed deeply into the pelvic musculature. The potential for organ injury and hemorrhage are greater with these procedures. In addition, functional implications regarding these mesh procedures remain largely unknown. **Thus, pelvic surgeons must make an informed decision with the patient, which weighs the apparent advantage in anatomic efficacy, decreased invasiveness, and potential durability against the potential morbidity associated with mesh erosion and the possibility of more significant complications unique to these procedures.**

Technique. The anterior prolapse repair follows many of the same basic steps for all of the kit procedures. A midline incision is created in the anterior vaginal wall. Hydrodissection may facilitate a deep, full-thickness vaginal dissection. The full-thickness dissection is important to minimize the occurrence of vaginal exposure of mesh. The dissection progresses laterally to the level of the endopelvic fascia, which is entered by sharp or blunt dissection. The pelvic sidewalls are developed until the ischial spines and the ATFP are palpated. Stab incisions are made overlying the obturator foramen. The distal incisions are placed in the anteromedial edge of the obturator foramen at the level of the clitoris, and the proximal incisions are placed 2 cm below and 1 cm lateral to the distal incision. The trocars are utilized to position the arms of the mesh patch along the ATFP. The distal trocars are placed approximately 2 cm from the distal aspect of the pubic bone, and the proximal trocars are advanced along the ATFP, exiting 1 cm distal to the ischial spine. The proximal trocars in the Perigee system are different than the distal needles, which facilitate a deep passage of the proximal devices to the ischial spine. The mesh arms are utilized to position the mesh appropriately without tension. Sutures are used to fix the mesh both proximally at the level of the vaginal cuff (preferably with delayed absorbable or permanent sutures) and distally proximal to the bladder neck with

Table 72–10.

Vaginal Prolapse Repair Kits

	COVIDIEN POSTERIOR IVS	AMS APOGEE (POSTERIOR) PERIGEE (ANTERIOR)	BARD AVAULTA	GYNECARE PROLIFT	AMS ELEVATE	BOSTON SCIENTIFIC PINNACLE
Mesh type	Tightly woven multifilament polypropylene	Porcine dermis (InteXen) or large-pore monofilament polypropylene (IntePro)	Large-pore polypropylene with or without hydrophilic porcine collagen coating (Pelvitex)	Large-pore monofilament polypropylene (Gynemesh PS)	Porcine dermis (InteXen) or large-pore monofilament polypropylene (IntePro)	Large pore monofilament polypropylene (Polyform)
Mesh arms	Same as above	Large-pore monofilament polypropylene	Knit polypropylene without collagen coating	Large-pore monofilament polypropylene	None (self-fixating tips)	None (Capio device)
Fixation point	Single system	Anterior and posterior systems	Anterior and posterior systems	Single system	Anterior and posterior systems	Anterior and posterior systems

absorbable sutures. Prior to mesh placement, anterior colporrhaphy may be performed to correct a central defect if present. Cystoscopy is performed to confirm lower urinary tract integrity. Care is taken to confirm the absence of excessive tension on each of the mesh arms (Fig. 72–47). The vagina is then closed without trimming the vaginal wall to minimize the occurrence of vaginal mesh extrusion. A loosely interrupted vertical mattress closure may be used to create a virtual two-layer closure of the vaginal epithelium.

The posterior and apical approach to kit placement does vary between kit devices. The Prolift device utilizes proximal attachment through the sacrospinous ligament, whereas the Apogee device is fixed proximally 1 cm distal to the ischial spine. For all procedures, the dissection begins with a posterior vaginal incision, which is full thickness. The dissection proceeds laterally and proximally to expose the ischial spine (Apogee) and the sacrospinous ligament (Prolift). Two stab incisions are made 3 cm lateral and below the anus. With the surgeon's hand in the vagina retracting the rectum, the trocars are advanced through the ischiorectal fossa. The Prolift is brought through the sacrospinous ligament 3 cm medial to the ischial spine. The Apogee trocars exit 1 cm distal to the ischial spine. The mesh is trimmed so that it does not extend to within 1 cm of the perineal body. This avoids mesh complications in the perineum. The mesh is fixed laterally with absorbable sutures. The mesh is fixed with permanent or delayed absorbable suture proximally to the vaginal apex or posterior lip of the cervix. As with the anterior compartment, no trimming of the epithelium is recommended and closure is completed with absorbable suture.

There are new kits, which do not utilize trocars for mesh placement. The Pinnacle device (Boston Scientific, Nantucket, MA) uses a Capio Needle Driver System to pass the arms of the mesh through the sacrospinous ligament proximally and the ATFP and obturator internus fascia distally to provide anterior support. The mesh may also be deployed posteriorly using the Capio device as well. The Elevate (American Medical Systems, Minnetonka, MN) has a unique "tacking" device, which anchors the graft in the sacrospinous ligament as well as ATFP. There is a special tool that facilitates adjustment of mesh tension after the tacking mechanism is deployed. Both of these devices have not been in use very long and there are little meaningful data at this time.

Results. When evaluating the results of the vaginal kit procedures in the treatment of prolapse there are a paucity of peer review data to guide most appropriate usage. Much of the literature regarding kits include preliminary data in abstract form. The multicenter preliminary results of Prolift have been published by Fatton and associates (2007): 110 patients were observed for 3 months, and a 94.3% success rate was reported. Gauruder-Burmester and colleagues (2007) reported on a retrospective analysis of 121 women utilizing Apogee/Perigee. Success rates of 93% were achieved. Sanses and colleagues (2009) compared the outcomes of Prolift, uterosacral ligament suspension and abdominal sacrocolpopexy for the treatment of apical prolapse. Prolift, uterosacral ligament suspension, and abdominal sacrocolpopexy were performed for 206, 231, and 305 subjects, respectively. There was no difference in apical success after Prolift (98.8%) compared with uterosacral ligament suspension (99.1%) or abdominal sacrocolpopexy (99.3%) (both $P = 1.00$) 3 to 6 months after surgery. The average elevation of the vaginal apex was lower after Prolift

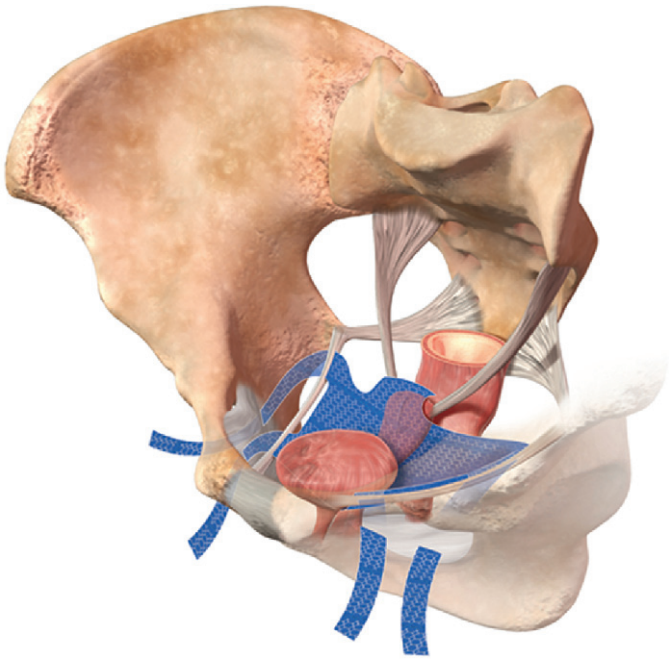


Figure 72–47. Transvaginal kit. Total Prolift device in place. (Courtesy of Ethicon, Inc.)

(–6.9 cm) than uterosacral ligament suspension (–8.05 cm) and abdominal sacrocolpopexy (–8.5 cm) (both $P < .001$) (Sanses et al, 2009). Feiner and associates (2009) performed a meta-analysis of the peer-reviewed literature and select peer-reviewed gynecologic abstracts to evaluate outcomes and complications after transvaginal synthetic apical suspension procedures. After the Apogee procedure, 525 women had a mean follow-up of 26 weeks (range 10 to 56 weeks). Mean objective success was 95% (range 81 to100). In the same meta-analysis, a posterior or total Prolift procedure was performed in 1295 women with mean follow-up time of 30 weeks (range 12 to 52 weeks), and the mean objective success rate was 87% (range 75% to 94%). Although these early data demonstrate successful outcomes, it is important to note that serious complications, some unique to these procedures, are being reported. These concerns have prompted comments regarding new procedures and materials for the treatment of incontinence and prolapse, warning that there are insufficient data supporting the routine use of these devices (Ostergaard, 2007). In light of this, it is incumbent on physicians to openly discuss these issues with patients.

Complications. Mesh complications are most commonly in the form of mesh exposure or "extrusion." Extrusion rates of approximately 10% can be expected (Gauruder-Burmester et al, 2007; Feiner et al, 2009). The exposures seem to occur more frequently on the anterior wall, and a concomitant hysterectomy significantly increases the risk (de Tayrac et al, 2007; Gauruder-Burmester et al, 2007). **Measures to minimize the occurrence of vaginal mesh exposure are minimizing excessive vaginal wall trimming and closing without tension. Some advocate closing with a vertical mattress technique to separate the graft from the wound** (de Tayrac et al, 2006). Symptoms of mesh extrusion include vaginal discharge, persistent bleeding, pain, dyspareunia, partner pain, dysuria, and recurrent urinary tract infections. Examination by palpation as well as visualization is important to detect this complication. While some patients can be managed with either observation or local treatment, many will require excision with primary vaginal closure (de Tayrac et al, 2006). Infected vaginal mesh can lead to sinus formation, abscess, and enterovaginal fistula formation. One case of necrotizing fasciitis with *Staphylococcus aureus* requiring extensive perineal debridement and colostomy has been reported after a kit procedure (Abdel-Fattah et al, 2008). Persistent groin pain has been reported after transobturator grafts and may signify an erosion or abscess of a transobturator graft (Mahajan et al, 2005; Rafii et al, 2006).

Unfortunately, significant lower urinary tract erosion into the bladder or urethra have also been reported, with significant consequences (Yamada et al, 2006). Altman and Falconer (2007) found the overall risk of serious complications of the Prolift procedure is 4.4%. The majority of serious complications were visceral perforations. Including transvaginal kits systems, the incidences of visceral (including urethra) injuries have been reported from 2.7% to 4.4% (Altman and Falconer, 2007; de Tayrac et al, 2007). The rates of bladder perforation vary between 0.9% and 2.8% (Altman and Falconer, 2007; de Tayrac et al, 2007; Fatton et al, 2007). Bladder perforation after retropubic midurethral slings is not uncommon and appears to be a benign event in the presence of adequate bladder drainage (Kuuva and Nilsson, 2002). The fate of bladder injury at the time of mesh prolapse repairs is much less certain. Two studies have reported on placement of mesh with single, small, uncomplicated bladder injuries (Fatton et al, 2007; Popovic et al, 2007). **If the bladder is injured, it is the opinion of the authors that the procedure should be completed without a mesh interposition of the anterior compartment, because placing mesh in the setting of a bladder laceration would prohibitively increase the risk of erosion.** Extensive erosions into the bladder requiring partial cystectomy have been reported (Abdel-Fattah et al, 2008). With urethral injury, the defect should be repaired primarily, and, again, mesh/graft placement should not be done.

Rectal perforation is reported in 0.7% to 2.8% of cases (Altman and Falconer, 2007; de Tayrac et al, 2007). If rectal injury is recognized intraoperatively, synthetic mesh should not be placed (Mercer-Jones et al, 2004; de Tayrac et al, 2006). Rectal erosion of synthetic mesh may require both rectal and vaginal excision (Hurtado et al, 2007). From these outcomes it is clear that **if the rectum is perforated a multilayer closure should be performed, povidone-iodine distention of the rectum should follow to ensure the integrity of the repair, and the procedure should be abandoned.**

The trocars are passed through the pelvic muscular complex both for anterior and posterior kit repairs. The trocars pass near the ischial spine, and significant intraoperative bleeding may occur. This would usually emanate from the pudendal neurovascular bundle, and embolization of the source of bleeding has been reported (Mokrzycki and Hampton, 2007). Also multiple authors have reported pelvic hematomas after transvaginal kit procedures (Ignjatovic and Stosic, 2007; LaSala and Schimpf, 2007; Abdel-Fattah et al, 2008). Abdel-Fattah and colleagues described vascular complications after Prolift and Apogee/Perigee procedures, including arterial injury requiring embolization. Perhaps blind passage of the trocars through the levator musculature poses a risk for these hemorrhagic complications. Hematomas have also been reported after these procedures (Ignjatovic and Stosic, 2007). Commonly, patients will present with unusually more pelvic pain than typically encountered. Computed tomography is an excellent method to detect hematomas. Thus, if excessive postoperative pain occurs after the procedure, one should consider an evaluation with computed tomography to detect a hematoma. If a hematoma is present, observation with serial hematocrit levels is the appropriate initial evaluation; however, surgical drainage may be required for expanding hematomas, decreasing hematocrits, refractory pain, or infection.

Local complications such as pelvic pain, defecatory pain, and dyspareunia have been reported after kit procedures (Altman and Falconer, 2007; de Tayrac et al, 2007). When examining these patients, one must carefully look for areas of impaired healing, banding or tenting of the mesh, "trigger points" that elicit pain, and signs of focal inflammation. If these abnormal areas are identified, release of the arms or site of mesh tension may alleviate these areas of discomfort. When performing the mesh release, one should excise as much offending mesh material as possible before vaginal closure. In cases of infection, granulomas, or persistent draining sinuses, all mesh involved in the infected areas must be removed. If no local incriminating factors are found, a period of conservative therapy consisting of physical therapy, trigger point injections, and other adjunctive techniques should be attempted first.

U.S. Food and Drug Administration Public Health Notification

A public health notification is an important message from the FDA for devices and radiologic health to the health care community (Schultz, 2008). This message describes a risk associated with the use of a medical device and provides recommendations to avoid or reduce the risk. In October 2008 the FDA released a public

health statement that "Serious Complications are Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence." This report was designed to alert health care practitioners of complications associated with transvaginal placement of surgical mesh to treat POP and SUI. This report cited that over 3 years the FDA received more than 1000 reports from nine surgical mesh manufacturers of complications that were associated with surgical mesh devices used to repair POP and SUI. These potential complications are outlined previously and in some cases lead to a significant decrease in quality of life due to discomfort and pain, including dyspareunia. As a result, a number of recommendations were made to physicians that include obtaining specialized training for each mesh placement technique and to inform patients that implantation of surgical mesh is permanent. As a result, some complications associated with the implanted mesh may require additional surgery that may or may not correct the complication. In addition it is recommended to inform patients about the potential for serious complications and their adverse effect on quality of life. Also, it is recommended that the physicians provide patients with a written copy of the patient labeling from the surgical mesh manufacturer, if available.

The impact of these recommendations or the evidence that these recommendations will improve outcomes is unknown. However, it is important for pelvic surgeons to be aware of the growing concerns regarding the potential for serious complications associated with the use of these materials. Patients must be informed of the indications for and benefits and risks of mesh placement before any surgical intervention, and surgeons must remain vigilant in assessing their own outcomes. It is only through well-designed and sufficiently powered randomized controlled trials that these questions will be answered.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter 73

Slings: Autologous, Biologic, Synthetic, and Midurethral

Roger R. Dmochowski, MD, FACS • Priya Padmanabhan, MD, MPH • Harriette Miles Scarpero, MD

Pubovaginal Slings

Midurethral Slings

Urethral slings are currently the procedure of choice for the surgical correction of female stress urinary incontinence (SUI). A variety of materials (autologous, allograft, and synthetic) and techniques have been pursued for sling placement. The concept of slings for urethral support was first introduced in 1907 by Von Giordano as a gracilis muscle graft wrapping around the urethra (Blaivas, 1994). German surgeons were using slings fashioned from muscle and fascia for slings in children at the turn of the century (Goebell, 1910). The rectus abdominis muscle and fascia were first used by Frangenheim in 1914 and then adapted by Millin for use in recurrent SUI (Frangenheim, 1914; Millin, 1948). It was Aldridge who first understood the abdominal relationship between muscles and urethra and showed that an increase in abdominal pressure caused simultaneous compression of the urethra. He used rectus fascial slings in conjunction with vaginal plastic operations (Aldridge, 1942). Jeffcoate (1953) used the Aldridge technique on 40 women and reported an 86% cure rate. It was **McGuire's use of the pubovaginal sling** (PVS) in patients who failed prior retropubic suspension and anterior colporrhaphy, with a cure rate of 91% that reintroduced this procedure (McGuire, 1978). **This is the modern description of the PVS, with placement at the bladder neck, in an effort to correct urethral hypermobility and modify the pressure transmission invoked by intra-abdominal pressure changes** (Blaivas and Olsson, 1988).

PUBOVAGINAL SLING

In addition to the correction of urethral hypermobility, the PVS (a sling at the bladder neck as distinct from a midurethral sling) is also **indicated for intrinsic sphincter deficiency (ISD) associated with urethral hypermobility, SUI presenting with concomitant cystoceles** (Cross et al, 1997; Serels et al, 1999), **and SUI associated with urethral diverticulum or urethral defects (e.g., urethrovaginal fistula) in which urethral reconstruction is required and in women with SUI and associated neurogenic conditions** (Austin et al, 2001). In neurogenic patients, such as those with myelodysplasia, a PVS is indicated for SUI that occurs between clean intermittent catheterizations (once a thorough urodynamic study [UDS] of compliance and bladder capacity is completed). A PVS is used during **reconstruction of proximal urethral loss secondary to trauma, or erosion (synthetic material or prolonged Foley catheter), or for interposition in repairs of urethrovaginal fistulae or urethral diverticula** (Gormley et al, 1994; McGuire and O'Connell, 1995; Blaivas and Heritz, 1996; Leng and McGuire, 1998). A PVS is also indicated for **recurrent SUI**, especially **after failed retropubic suspensions or prior midurethral sling placement** (Beck et al, 1988; Petrou and Frank, 2001). **The definition of ISD has evolved from a strict urodynamic criterion to a clinical diagnosis. In understanding surgical treatment it is essential to appreciate that all women with SUI have some component of ISD. The PVS is the gold standard for management of *all* forms of SUI.** The PVS has less morbidity than older retropubic suspensions and a better long-term outcome than needle suspensions and urethral collagen injections. Using female Medicare beneficiary records, Anger and colleagues (2009) identified patterns in the surgical treatment of women with SUI in the United States from 1992 to 2001. By 2001, the PVS became the dominant anti-incontinence procedure, corresponding with a steady decline in needle suspensions and anterior urethropexies (Anger et al, 2009).

Assessment of Intrinsic Sphincter Deficiency

The immobile urethra with poor intrinsic function has been classified as type III incontinence (Blaivas and Olsson, 1988) **but is more commonly referred to as ISD.** ISD is a complex condition with an imprecise definition and a large variability in measurement. The earliest measurements were by radiographic or endoscopic procedures, confirming an open proximal urethra and urethrovesical junction at rest (Blaivas and Olsson, 1988). Earlier methods for diagnosing ISD included the use of the supine stress test (empty and at capacity) (Lobel and Sand, 1996; Hsu et al, 1999), easy removal of inflated 8-Fr pediatric Foley balloon catheters as a positive office screening tool (Arya et al, 2001), color translabial sagittal ultrasonography for urethral vascularization measurement (Siracusano et al, 2002), ultrasound assessment of bladder neck funneling during straining (Huang and Yang, 2003), and translabial ultrasonography for measurement of the diameter of the urethra (Oliveira et al, 2006). In 2008, Oliveira and colleagues retrospectively reported lower opening detrusor pressure in stress incontinent women with ISD. Smith and Appell

(2008) tried to determine whether voiding flow rates in women with symptomatic vaginal prolapse could predict ISD. Flow rates did not predict ISD (Hosker, 2009).

ISD continues to be defined imprecisely by a low-pressure urethra based on urethral closure pressures and abdominal leak point pressures. **A maximum urethral closure pressure (MUCP) of 20 cm H_2O or less has been a determinant of ISD since McGuire's (1981) research on failed SUI procedures.** Although patients who experienced treatment failure were more likely to have an MUCP of 20 cm H_2O or less, McGuire was unable to determine whether closure pressure was the cause or effect of the failures. Therefore, Sand and associates (1987) performed UDS on 86 women undergoing modified Burch colposuspensions. The women were divided into two groups: one with an MUCP of 20 cm H_2O or less and one with an MUCP of more than 20 cm H_2O. The group with lower urethral closure pressures had a 54% failure rate, compared with 18% in the group with higher urethral closure pressures. Sand and associates concluded that a modified Burch colposuspension was not appropriate in patients younger than age 50 years with an MUCP of 20 cm H_2O or less. Also other authors have not used an MUCP of less than or equal to 20 cm H_2O to define ISD (Clemons and La Sala, 2007; Fritel et al, 2008). **Abdominal leak point pressure (ALPP) less than or equal to 60 cm H_2O has been used as a determinant of ISD since videourodynamic analysis by McGuire and colleagues** (1993). They found that women who leaked with low abdominal pressures (5 to 60 cm H_2O) were most seriously incontinent and 75% had ISD on videourodynamics (proximal urethral pressure <10 cm H_2O at 0.5 cm from the bladder neck or a nonfunctioning open sphincter with leakage). There was no correlation between ALPP and MUCP (Hosker, 2009). ISD is clinically relevant, but until the imprecision of diagnosis is addressed it cannot be utilized completely.

Anatomy and Mechanics

Female SUI is due to a combination of urethral hypermobility and ISD. The female urethra lies under the pubic symphysis, and the pubourethral ligaments suspend the anterior urethral wall to the pubic arch. **During Valsalva or other stress maneuvers the posterior wall of the urethra slides away from the anterior urethral wall and causes the bladder neck to open in cases of urethral hypermobility. The uneven pressure transmission combined with opening of the bladder neck (funneling) causes a loss of urine with stress maneuvers. ISD arises from defects within the urethra proper, so that the urethral sphincter is unable to coapt and generate enough resting urethral closing pressure to store urine in the bladder.** The female urethra is composed of four separate tissue layers that assist in keeping it closed. It is compression from the middle muscular coat that helps to maintain the resting urethral closure mechanism and the outer seromuscular layer that augments this closing pressure. In normal circumstances the resting urethral closing pressure of the internal sphincter exceeds the resting or Valsalva pressure exerted by the bladder. Additionally, the fast-twitch fibers of the external sphincter allow for the sudden voluntary guarding reflex and the slow-twitch fibers provide continuous passive control by the involuntary guarding reflex. In addition to these structures the integrity of the pelvic diaphragm is dependent on the levator ani for continence control. The urethropelvic ligament and pubocervical fascia also provide needed support to the bladder neck and undersurface of the bladder, respectively, to prevent SUI (Vasavada and Rackley, 2011).

The PVS is positioned at the bladder neck to provide urethral compression without obstruction during times of increased intra-abdominal pressure. The ultimate goal is to provide adequate urethral coaptation to increase urethral responsiveness to abdominal pressure. This must be balanced with the risks of ischemia, retention, and erosion from unnecessary tension. Aldridge's (1942) earliest anatomic descriptions had fascia attached at the medial aspect of the rectus limiting sling mobility and provided no method for avoiding excess tension, resulting in outlet obstruction. The sling was often too short to pass under the urethra. McGuire (1978) modified this technique with a strip of rectus fascia 1 × 12 cm in length, which remained attached laterally on one side. In this technique there was also no way to adjust the tension with one side attached. The modifications by Blaivas and Jacobs (1991) with a free graft of rectus fascia whose tension could be adjusted (by pulling up and tying the sutures at each end of the free graft) are the present concept of the PVS. This allows for a shorter fascial sling. The key to the length of the fascial sling is its method of providing support. It is the incorporation of the sling into the endopelvic fascia and subsequent fibrosis, and not entry into the retropubic space, that prevents SUI. The width (2 to 3 cm) of the PVS ensures that there is sufficient support to provide the needed urethral compression and a cross-sectional area adequate to avoid the formation of a narrow constricting band. The choice of material in PVS requires material longevity and durability to allow for a strong sling scaffolding. The material should be incorporated and remain intact, with limited tissue reaction.

Sling Materials

Various substances have been utilized for construction of a PVS—**autologous, allograft, xenograft, or synthetic materials.** The ideal material provides long-lasting suburethral support with minimal complications. Ideally, implanted material should be incorporated into the host with minimal tissue reaction. In reality, most materials promote organized fibrosis, reinforcing the sphincteric mechanism through improved suburethral support. Theoretically, a greater degree of fibrosis leads to better clinical results (Bidmead and Cardozo, 2000; Woodruff et al, 2008). Yet, inflammatory infiltration leads to rapid sling material degradation and possible tissue destruction with erosion (Bidmead and Cardozo, 2000). Although there is complete biocompatibility of the autologous sling and negligible urethral erosion, biologic and synthetic graft materials have been increasingly used to decrease operative time, morbidity, pain, and hospital stay (Niknejad et al, 2002). Outcomes of these materials are discussed later.

Autologous Materials

The most commonly used autologous materials include **rectus fascia and fascia lata.** Rectus fascia is harvested through a suprapubic Pfannenstiel incision. FitzGerald and associates (2000) reported that after sling placement, rectus fascial grafts undergo extensive remodeling with increased fibroblasts and connective tissue on biopsy specimens. Yet, histologic comparison of PVS grafts noted the **greatest degree of host fibroblast infiltration and neovascularization in autologous materials with minimal inflammatory or foreign body reaction.** The fascial graft changes were consistently intact with a small

amount of sling degradation at explantation up to 65 months after placement (Woodruff et al, 2008). The rectus fascia harvest site may be scarred and thickened after prior operations, but this does not compromise its utility for PVS placement. **The benefits of autologous tissue include the lack of tissue reaction and negligible urethral erosion** (Webster and Gerridzen, 2003). **Disadvantages include increased operative time and hospital stay, relative increase in postoperative pain, and suprapubic tissue seroma formation and hernia formation in a rectus fascial PVS** (Gomelsky et al, 2003).

Fascia lata is the other commonly utilized autologous material for a PVS. It is harvested from the thigh and has similar properties to rectus fascia (Beck et al, 1988; Latini et al, 2004). Methods for harvest are discussed in the section on operative procedure. Like rectus fascia, fascia lata is completely biocompatibility and is associated with minimal tissue reaction. The **recovery time may be less, and there is no risk of future abdominal hernia formation,** unlike rectus fascia. Yet, fascia lata **requires repositioning of the patient, increased operative time, and operating in an area unfamiliar to urologists** (Govier et al, 1997). Wheatcroft and colleagues (1997) reported 67% of their patients had pain on walking for 1 week after surgery. Latini and coworkers (2004) only reported 7% of patients with pain at incision site 1 week postoperatively after using a Crawford fascial stripper. Debility from a thigh hernia has also been reported.

Another autologous material, vaginal wall, has also been used. Raz and associates (1989) described use of in-situ vaginal wall for autologous sling material. This tissue may lack sufficient tensile strength, and there is a risk of epithelial inclusion cyst formation and possible vaginal shortening. Lack of retropubic space dissection may militate against overall efficacy of this procedural variety (Raz et al, 1989; Ghoniem and Hassouna, 1998; Loughlin, 1998; Appell, 2000).

Allograft Materials

Biologic and synthetic graft materials have been increasingly used to decrease operative time, morbidity, pain, and hospital stay. Cadaveric allografts have been used in many nonurologic surgical arenas (e.g., orthopedics, neurosurgery) and eventually adopted for SUI. Allograft slings are currently derived from either **cadaveric fascia lata or acellular human dermis.** After harvest the allografts are processed by solvent dehydration or by lyophilization (freeze-drying) to remove genetic material and to prevent the transmission of infectious agents. Secondary sterilization may also be achieved by gamma radiation (Gomelsky et al, 2003). Histologic analysis reveals cadaveric dermis to **have little host fibroblast infiltration and little neovascularity, particularly in central aspects of the graft.** Additionally, inconsistencies were found within the materials grossly, with specimens exhibiting **significant thinning and degradation of the graft, disrupting the sling scaffold** (Woodruff et al, 2008). **No specific allograft has shown a clinical advantage in use.** Acellular dermis rehydrates in 0.9% saline quicker than does cadaveric fascia lata (5 minutes vs. 15 to 30 minutes), but each type is pliable, easy to use, and available in a variety of sizes (Gomelsky et al, 2003).

Biomechanical studies have shown that solvent-dehydrated cadaveric fascia lata and acellular dermis have a higher maximal load failure compared with freeze-dried cadaveric fascia lata (Hinton et al, 1992; Lemer et al, 1999). Lemer and associates (1999) prospectively studied the maximum load failure and stiffness of rectus fascia versus freeze-dried fascia versus solvent-dehydrated fascia and cadaveric dermal grafts. The mean values for maximum load to failure, maximum load-graft width, and stiffness were all significantly lower for the freeze-dried fascia lata group compared with the autologous, solvent-dehydrated, and dermal graft groups. The authors believed that ice crystal formation characteristics of tissue freezing may disrupt the collagen matrices, yielding poor strength properties. Dermal grafts differ from fascial allografts because they are derived from skin that is processed to eliminate the epidermis and all immunogenic cellular elements. Dermal grafts provide a protein matrix that serves as a collagen scaffold for the host's own cellular matrix (Lemer et al, 1999).

Although biomaterials were thought to be a good choice for increased biocompatibility, lower risk of erosion, and lack of response to hormonal stimuli, allografts raise the concern of potential transfer of disease, including human immunodeficiency virus (HIV), hepatitis, and Creutzfeldt-Jacob prion infection. There has been one documented case of HIV transmission from a tissue transplant since the onset of screening in 1985. **The estimated risk of acquiring tissue from a properly screened donor infected with HIV is 1 in 1,667,600** (Gallantine and Cespedes, 2002). A few cases of Creutzfeld-Jakob disease (CJD) have been reported after transplantation of cadaveric dura or corneas; however, skin obtained from animals infected with prions has demonstrated no detectable infectious particles. Currently, **the theoretical risk of developing CJD from a non-neural allograft is 1 in 3.5 million.** No cases of hepatitis or CJD have ever been attributed to the use of processed cadaveric fascia or dermis (Amundsen et al, 2000b; Gallantine and Cespedes, 2002). Within the musculoskeletal tissue transplantation literature, two cases of hepatitis transmission have been reported. The first refers to one tissue donor (cancellous chips) who transmitted HIV, hepatitis B virus, and human T-lymphotrophic virus. These transmissions all occurred before the implementation of extensive donor screening for viruses and bacteria or the availability of validate serologic tests (or both) (Shutkin, 1954). In June 2002, the Centers for Disease Control and Prevention (CDC) reported a case of hepatitis C transmission from minimally processed, cryopreserved patellar tendon allograft. Donor screening was performed during the window period for hepatitis C virus (HCV). Retest of the donor sample with HCV RNA testing confirmed the donor as the source once the recipient reported HCV infection 1 year after transplantation (CDC, 2003; Vangsness, 2006). Despite the low risk of disease transmission, human DNA has been detected in various allograft materials (Choe and Bell, 2001; Hathaway and Choe, 2002). The clinical significance of this is unknown. The theoretical risk of developing hepatitis from allograft graft material is unknown.

Xenograft Materials

Xenografts have been utilized since the 1980s (Descurtins and Buchmann, 1982; Iosif, 1987) owing to their immediate accessibility and use without morbidity. Porcine and bovine xenografts have been used as sling material with decreasing popularity in recent years. The forms of xenograft available for use are **porcine dermis or small intestinal submucosa (SIS) and bovine pericardium.** Modern processing techniques using diisocyanate to remove genetic material have made porcine safer and more pliable, yet there is significant loss of tensile strength after implantation in a 12-week rabbit model (Dora et al, 2004). Histopathologic analysis has shown porcine SIS to contain growth factors that may reduce significant host-graft immunologic reaction and result

in less tissue scarring (Wiedemann and Otto, 2004). Although a majority of data support SIS as nonimmunogenic, animal studies by Thiel and colleagues (2005) suggest that an intense inflammatory reaction 30 to 90 days after subcutaneous implantation occurs. In a report by Kalota (2004), 6 of 18 (33%) patients experienced postoperative inflammation after a PVS procedure. Konig and coworkers (2004) reported a single case of postoperative inflammation with abscess formation. Ho and colleagues (2004) reported a similar reaction in 6 of 10 patients. All of the patients presented with pain and erythema at the abdominal incision, and 2 developed abscesses. Five of the 6 patients with inflammatory responses are currently dry. All were treated conservatively, except 1 patient who required abscess drainage. The etiology is unknown but is likely due to a foreign body reaction from the multilayered (8-ply) SIS material, a reactive manufacturing ingredient, or a tendency for suprapubic fat to produce an inflammatory reaction (John et al, 2008). Kubricht and colleagues (2001) have shown that **porcine SIS has less tensile strength than cadaveric fascia lata** (Kubricht et al, 2001). Bovine pericardium is available in a preparation either cross-linked with glutaraldehyde or as a non–cross-linked acellular matrix (Gomelsky et al, 2003). Histopathologic comparison of sling materials revealed xenograft (porcine dermis) to have **no host fibroblast infiltration, no inflammatory reaction, and no foreign body reaction. Xenograft had the highest propensity to encapsulate.** A capsule formed around the porcine dermis, isolating the graft from the periurethral tissue. The graft was described as appearing similar to its original appearance at time of implantation (Woodruff et al, 2008).

Synthetic Materials

In 1959, Francis Usher introduced the first synthetic biomaterial—polyethylene mesh—for use in hernia surgery. In the decades since there has been a transition to polypropylene and the introduction of additional synthetic materials (Amid, 1997). The first synthetic sling, made of nylon, was introduced in 1953 (Kraatz, 1953). The addition of synthetic material for use in PVS surgery brought **obvious advantages: unlimited supply of artificial graft material in endless sizes and shapes, consistency in quality, and elimination of harvest site and decreased associated operative time.** As compared with absorbable biomaterials, synthetic materials are **more uniform, more consistent, and more durable.** Additionally, **artificial graft materials are sterile, biocompatible, noncarcinogenic, and free of biomaterials** (Niknejad et al, 2002). On histopathologic comparison, **synthetic materials demonstrated the greatest amount of fibroblast ingrowth and tissue ingrowth into the specimen. There is no degradation or disruption of the graft, and the mesh is completely infiltrated by the viable host tissue.** Microscopically, the synthetic material **has large amounts of fibroblasts and foreign body reaction characterized by giant cells and occasional microcalcification.** This foreign body reaction is not visible grossly by graft disruption, and the graft was completely infiltrated by host tissue (Woodruff et al, 2008).

Artificial graft materials do have **potential drawbacks, including graft infection, genitourinary erosion, or vaginal extrusion.** The chemical and physical properties of each artificial material and patient characteristics determine how the sling is incorporated into the surrounding tissue and its susceptibility to infection, rejection, erosion, or extrusion. **The susceptibility to infection in multifilament fibers is proportional to the porosity and the pore size of the materials** (Amid, 1997; Niknejad et al, 2002). **Tightly woven mesh provides a safe harbor for small bacteria, excluding macrophages and polymorphonuclear leukocytes. Loosely woven mesh allows tissue ingrowth and neovascularization, without limiting cellular access.** Tissue bonding to the mesh strengthens and supports the repair. **A tightly woven and large-diameter filament mesh will tend to exhibit increased stiffness or decreased pliability, contributing to migration, extrusion, or erosion.** The classification by Amid (1997) used for synthetic materials in hernia surgery may be practically applied to urology as well (Table 73-1). The most frequently used materials are grouped into four types. Type I are totally macroporous prostheses (Atrium, Trelex, Marlex, Prolene) containing pores larger than 75 μm, which is the pore size for admission of macrophages, fibroblasts, blood vessels, and collagen fibers (White et al, 1981; Bobyn et al, 1982; White, 1988). Type II includes totally microporous prostheses (polytetrafluoroethylene [PTFE]: GORE-TEX, Surgical Membrane, and Dualmesh) containing pores less than 10 μm in at least one of their dimensions. Type III includes a macroporous prosthesis with multifilamentous or microporous components (PTFE: Teflon; braided Dacron mesh: Mersilene; braided polypropylene mesh: Surgipro; and perforate PTFE patch: MycroMesh). Lastly, type IV includes biomaterials with submicronic pore size (Silastic, Cellgard (polypropylene sheeting). Type IV is not appropriate for hernia surgery unless used in combination with type I (Amid, 1992). **The most commonly utilized synthetic material for a PVS is polypropylene mesh** (Table 73–2). **It is composed of loosely woven strands of synthetic material, with a pore size greater than 80 μm, permitting passage of macrophages that may allow better host tissue ingrowth compared with the smoother, more tightly woven counterparts** (Kobashi et al, 2005). This represents type I among the Amid classification. In fact, Amid (1997) concluded that the risk of infection and seroma formation was avoided by utilization of type I prostheses.

Historically, sling techniques have changed to limit the associated morbid complications. **Synthetic material is no longer utilized in a PVS graft to pull the bladder neck into a high retropubic position owing to high erosion rates** (see section on complications). **Instead, newer approaches position a sling at the midurethra** (see later) (Niknejad et al, 2002).

Table 73–1.

Amid Classification for Synthetic Materials

TYPE	DESCRIPTION	BRANDS
I	Pores >75 μm; macroporous	Atrium, Trelex, Marlex, Prolene
II	Pores <10 μm; microporous	PTFE: GORE-TEX, Surgical Membrane, Dualmesh
III	Macroporous with multifilamentous or microporous components	PTFE: Teflon, braided Dacron mesh (Mersilene), braided polypropylene mesh (Surgipro), perforated PTFE patch (MicroMesh)
IV	Submicronic pore size	Silastic, Cellcard (polypropylene sheeting)

PTFE, polytetrafluoroethylene.

Adapted from Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia 1997;1:15–21.

Table 73–2.

Synthetic Sling Materials

TRADE NAME	COMPOSITION	DETAILS
Mersilene	Polyethylene terephthalatae	Multifilament fibers Very porous, becomes firmly embedded in native tissues
Teflon	Polytetrafluoroethylene (PTFE)	Multifilament
GORE-TEX	Expanded PTFE	Very flexible
Silastic	Silicone plus woven polyethylene terephthalate	Minimal tissue reaction, which facilitates removal or revision if necessary
ProteGen	Synthetic mesh impregnated with collagen matrix	Removed from market secondary to high rate of vaginal extrusion
Marlex, Prolene	Polypropylene	Monofilament with open-weave pattern

Adapted from Niknejad K, Plzak LS, Staskin DR, Loughlin KR. Autologous and synthetic urethral slings for female incontinence. Urol Clin North Am 2002; 29:597–611.

Key Points: Pubovaginal Sling Materials

- The construction of a PVS has utilized various materials: autologous (rectus fascia or fascia lata), allograft, xenograft, and synthetic.
- The ideal material is sterile, biocompatible, noncarcinogenic, and consistent in quality. The implanted material should be incorporated into the host with minimal tissue reaction and provide long-lasting suburethral support with minimal complications.
- Autologous materials remain the gold standard, associated with no tissue reaction and negligible urethral erosion.
- To decrease operative time, hospital stay, and postoperative stay, other biomaterials are utilized.
- Allografts raise concern for transfer of infection, whereas reportable cases are extremely rare. Additionally, the type of processing technique may disrupt the microstructure and affect strength properties.
- Xenografts have less tensile strength than allograft in situ and have the highest propensity to encapsulate.
- Synthetic materials have large inflammatory and foreign body reactions and are associated with high rates of graft infection and erosion, owing to their placement at the bladder neck. Synthetic materials are no longer used for a bladder neck PVS.

Operative Procedure

Preoperative and Preliminary Steps

Before performing a PVS, a thorough history and physical examination is performed. Key points in the history should include preoperative voiding status and symptoms. Specifically, the relationship between stress maneuvers (i.e., cough, sneeze, laugh, weight bearing, exercise) and related incontinence should be elucidated. It is important to identify preoperative storage symptoms, such as frequency, urgency, and urinary urgency incontinence (UUI), because these symptoms may not resolve after a sling procedure. A complete history of all prior vaginal and abdominal operations should include graft material placement, prior urethrolysis, and/or prolapse surgery. A history of prior irradiation is useful because this may compromise the quality of a rectus fascial graft. Physical examination should include an abdominal examination and complete pelvic examination to assess urethral hypermobility, quality of vaginal epithelium, extrusion of previously placed graft material, and prolapse. Cystocele and other forms of prolapse should be assessed, because they may lead to symptomatology and be a source of future obstruction. Special attention should be paid to the anterior vaginal compartment to determine if coexistent prolapse is present. The authors recommend UDS on all women undergoing surgical intervention for SUI, with or without simultaneous prolapse correction. UDS is recommended by the International Consultation on Incontinence (ICI) before undergoing surgical procedures to obtain a more accurate preoperative diagnosis (Griffiths et al, 2005). Knowing the urodynamic abnormalities responsible for urinary manifestations is essential to directing treatment at the underlying pathophysiology. The American Urological Association (AUA) recognizes uroflow, cystometry, leak point pressures, sphincter electromyography, and radiographic visualization as five modalities useful in understanding bladder storage and emptying. Implicitly, diagnosing impaired detrusor contractility or obstruction requires Pdet/uroflow, and cystometry is necessary for identifying detrusor overactivity (DO) (Rutman and Blaivas, 2007). A cough stress test may demonstrate SUI, but it provides no information regarding a patient's bladder storage and emptying characteristics. This information is essential for tailoring the appropriate treatment plan. "The bladder is an unreliable witness," because symptoms are not predictive of diagnosis. UDS may aid the clinician in detection of preoperative DO, preoperative abnormal voiding patterns (high postmicturition residual, obstructed flow), and de novo DO (Digesu et al, 2009). Cundiff and colleagues (1997) studied 535 incontinent women and concluded that pure symptoms identified less than half of the patients with urodynamic SUI, recommending UDS for all patients considering surgical intervention. UDS should be performed with and without a pessary if prolapse is present.

This procedure may be performed with the patient under spinal or general anesthesia, based on preference determined between the surgeon and anesthesiologist. A single perioperative dose of cefazolin or fluoroquinolone is given intravenously (as per Centers for Medicare and Medicaid Services recommendations). Bilateral lower extremity sequential compression devices (SCDs) are placed before administration of anesthesia. The patient is placed in the dorsal lithotomy position, and the abdomen (from umbilicus down) and vagina are prepped and draped in sterile fashion. A weighted speculum is placed in the vagina, and an 18-Fr Foley catheter is placed into the urethra and left in place with the bladder left to straight drainage. The patient should be placed in moderate Trendelenburg position, and the surgeon would benefit from a headlight for optimal visualization during vaginal dissection. A vaginal ring retractor is utilized initially for retracting the labia majora for ease with dissection and visualization.

In the case of fascia lata harvesting, the SCDs are placed below the patient's patella on the harvest side. The knee is elevated and supported with a 1-L bag of intravenous fluid or an appropriate cushion or pad. The involved extremity is internally rotated at the hip and secured to the table using 3-inch tape, below the operative site. The thigh is prepped and draped to expose the anterolateral aspect of the thigh from the greater trochanter to distal to the patella. The greater trochanter and lateral femoral condyle of the femur are identified and marked. These landmarks mark the

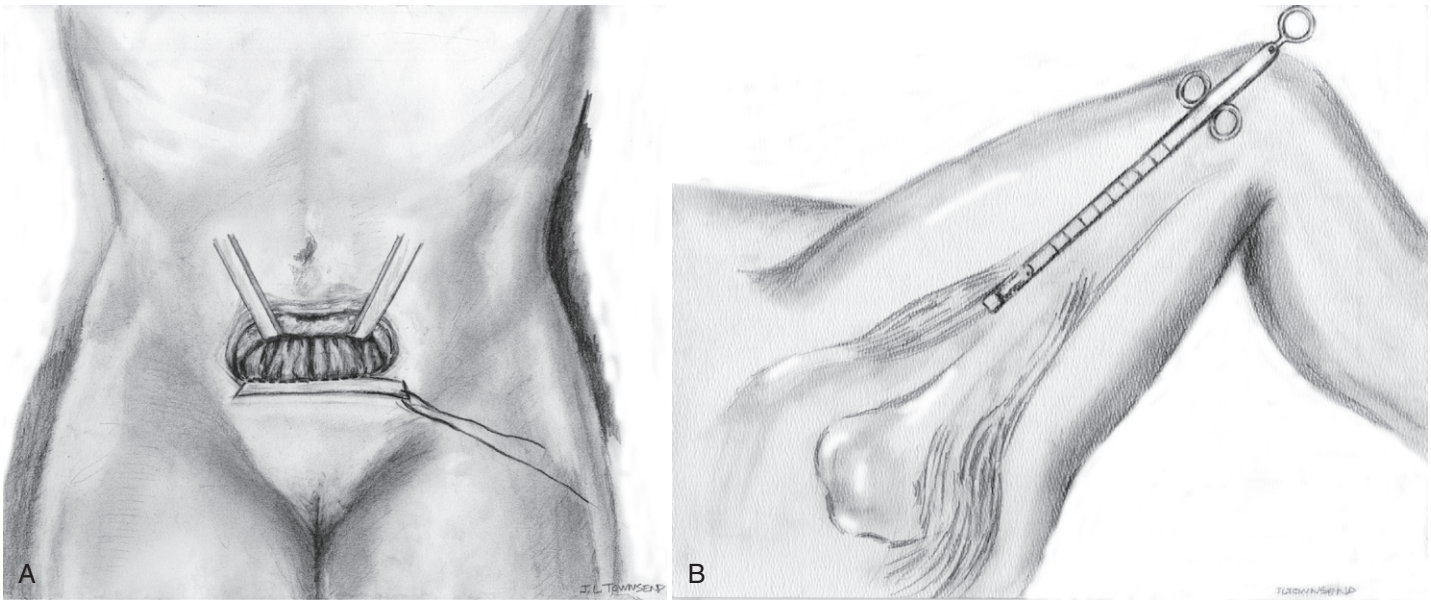


Figure 73–1. **A,** Rectus fascial graft harvest. **B,** Autologous fascia lata harvest.

proximal and distal attachments of the fascia lata (Dwyer and Kreder, 2008).

Graft Harvest

A 6- to 7-cm Pfannenstiel incision is made approximately 2 cm above the pubic symphysis and carried down to the rectus fascia. A 2-cm wide by 8-cm long graft is marked out in the rectus fascia. The premarked graft is harvested out of the rectus fascia. With the use of Allis clamps the edges of the free fascia are freed from the underlying rectus muscle with bovie cautery to aid in a tension-free closure (Fig. 73–1A). The fascia is closed with a running 1 polydioxanone (PDS) suture or other alternative suture. The graft is placed in 0.9% normal saline solution after harvest. On a sterile side table, the overlying fat and perifascial tissue are cleaned off of the graft. A size 1 polydioxanone suture is utilized (perpendicular to sling fibers) at each end of the sling to run across the full width of the sling and tied down. Sutures are left long, and the graft is placed in the 0.9% normal saline until needed.

For fascia lata harvest, a 3-cm longitudinal incision is marked beginning just above the patella over the iliotibial band (see Fig. 73-1B). Dissection is carried down to the level of the fascia lata, where two parallel incisions are made longitudinally in the fascia lata, 2 cm apart. The autologous fascia is bluntly lifted off the underlying muscle and clamped as far distally as possible with a right-angle clamp (3 to 4 cm) and transected, allowing one free end. The free end is secured with a 1-0 polypropylene, polydioxanone, or polyglactin suture, and the proximal fascia lata is lifted off the muscle belly with a thin, malleable retractor. The fascia lata is separated from both the adipose tissue and the muscle fibers by passing the retractor superficial and deep to the fascia lata. With the free distal end under tension, a Crawford fascial stripper is used to extend the fascial incision proximally and divide it before removal. Classically, the fascial strip was 20 × 2 cm in dimension; however, now shorter lengths (8 cm) are used (Karram and Bhatia, 1990). Another 1-0 polypropylene monofilament suture is secured to the other free end of the graft, and the graft is placed in 0.9% normal saline until needed. Immediate compression is applied to the thigh to constrict perforating vessels. The wound is irrigated and closed in three layers without closing the fascia lata. The area is carefully evaluated for bleeding arteries before closure. Once the thigh closure is complete, a compressive wrap is applied to the thigh and the SCD is replaced (to remain in place for the duration of the hospital stay). The compressive bandage should remain in place for 8 hours postoperatively, and the patient should be encouraged to ambulate early postoperatively (Dwyer and Kreder, 2008).

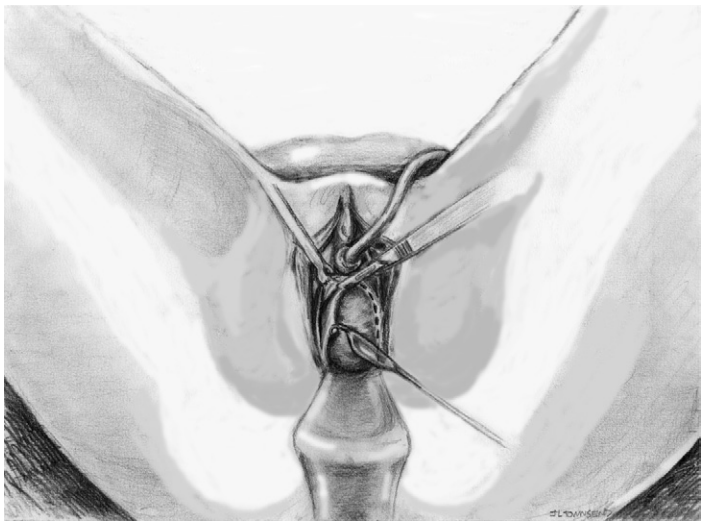


Figure 73–2. Inverted-U incision.

Vaginal Approach

Sterile 0.9% normal saline is injected into the vaginal epithelium, surrounding the urethra to provide hydrodistention and aid in tissue dissection. The authors prefer an inverted-U–shaped incision because it enables adequate exposure to the urethra and bladder and access to the endopelvic fascia and subsequent retropubic space (Fig. 73–2). The top of the incision is approximately 2 cm below the urethral meatus (easily visualized with assistance

of an Allis clamp placed immediately below the meatus), and the arms of U should extend to the level of the bladder neck (determined by Foley balloon location). A No. 15 blade knife is used to carry this incision down through the vaginal epithelium, with care to stay above the periurethral and pubocervical fascia (to avoid bleeding and injury to the urethra and bladder). With an Allis clamp and Metzenbaum scissors, thick vaginal epithelial flaps are created. The flaps are retracted with the help of the vaginal ring retractor. Once adequate lateral flaps have been created and the ischiopubic rami are easily palpated, it is appropriate to perforate the endopelvic fascia. It is imperative that the bladder is adequately drained before this maneuver and before later passage of Stamey needles or larger clamps to prevent inadvertent bladder perforation. With the tips of the Metzenbaum scissors pointed upward and to the ipsilateral shoulder, the endopelvic fascia is perforated by remaining directly medial and immediately under the ischiopubic ramus at the superior margin of dissection (Fig. 73–3). Perforation occurs in a superolateral direction, and the dissecting scissors are spread widely to aid in dissection. With the use of blunt finger dissection, the retropubic space is dissected bilaterally (Fig. 73–4). This dissection leads to the connection between the infrapubic and retropubic dissection planes. Simultaneous finger palpation from abdominal and vaginal incisions should be possible, while gently palpating the bladder medially. Aggressive medial mobilization should not be attempted because it may result in bladder injury. Hemostasis should be achieved with bipolar cautery. In the case of women who have undergone prior urethral suspension or sling, more aggressive dissection may be required. The dissection plane into the retropubic space should be immediately adjacent to the periosteum of the pubis, and the dissection should be performed only sharply to minimize risk of injury to the pelvic viscera.

Sling Placement and Fixation

Stamey needles or large clamps are passed from above, through the abdominal incision by careful guidance behind the pubis, and passage is in contact with the pubis throughout until brought out lateral to the bladder and through the vagina (Fig. 73–5). Alternatively, large surgical instruments such as Tonsil clamps may also be used (McGuire, 1978; Blaivas and Olsson, 1988). The bladder must be completely drained before passage of the Stamey needles to avoid inadvertent bladder injury. Cystoscopy should be performed with a 70-degree lens after passage of the needles to confirm the integrity of the bladder, by following the course of the needles (while an assistant moves them). Cystoscopy is not practiced consistently by all urologists after needle passage except when there is visible hematuria or another cause for suspicion (Niknejad et al, 2002; Seung-June et al, 2007). It is the authors' belief that this step eliminates the morbidity and reoperation required for passage of the sling through the bladder and that **cystoscopy is an essential step.** In the case of a small bladder injury or inadvertent passage of Stamey needles through the bladder, the needles are removed and passed again and the procedure is completed. Extravesical passage is confirmed. One ampule of indigo carmine is given at this point to confirm ureteral efflux during final cystoscopy for tensioning of sling. The Foley catheter is replaced. The ends of graft suture are passed through the Stamey needle eyelets. After marking the center of the graft with a clamp, the Stamey needles are removed and the ends of the suture are brought out through the abdominal incision and tagged with hemostat clamps (Figs. 73–6 and 73–7). The distal aspect of the graft is sutured to the periurethral tissue with two simple 4-0 polyglactin sutures. The vaginal incision is closed with a watertight, running 2-0 polyglactin suture after complete hemostasis is



Figure 73–4. Blunt dissection of retropubic space.

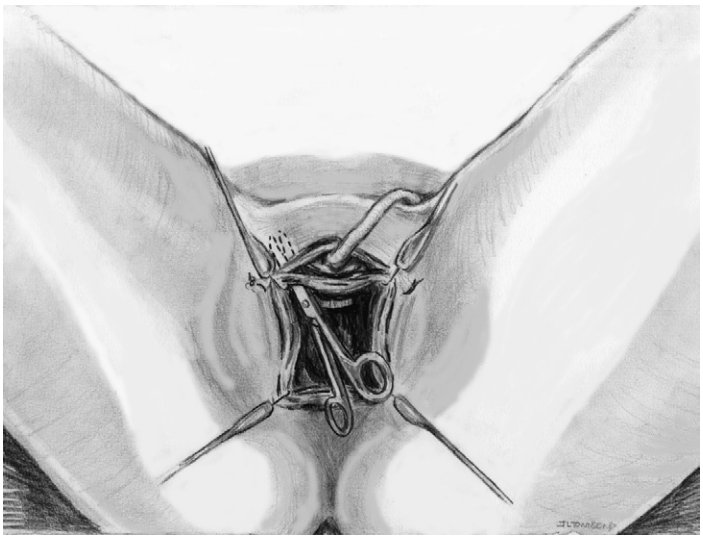


Figure 73–3. Perforation of endopelvic fascia.

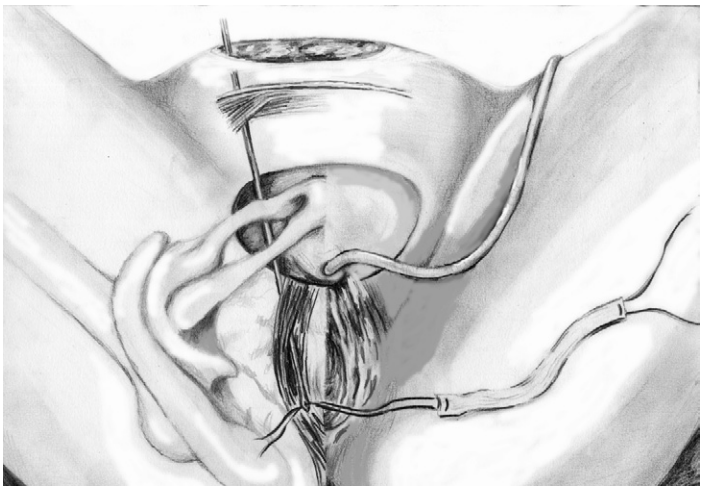


Figure 73–5. Passage of Stamey needles behind pubis.

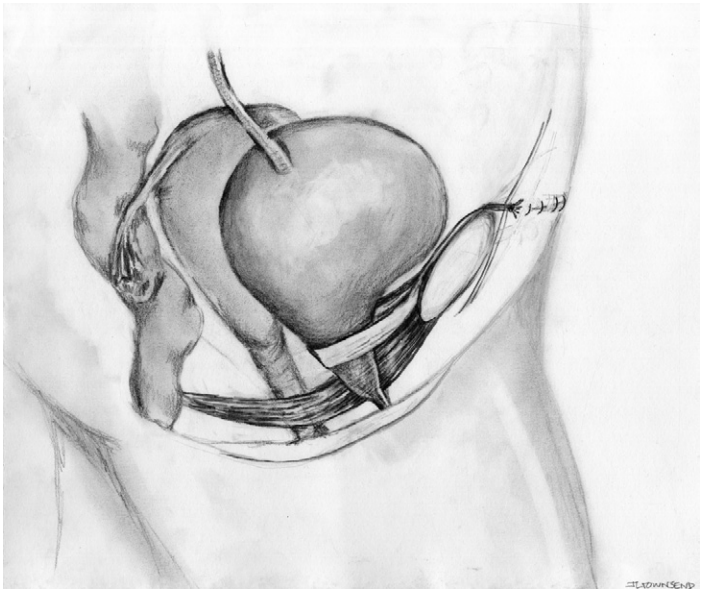


Figure 73–6. Sagittal view of pubovaginal sling position at bladder neck in retropubic position.

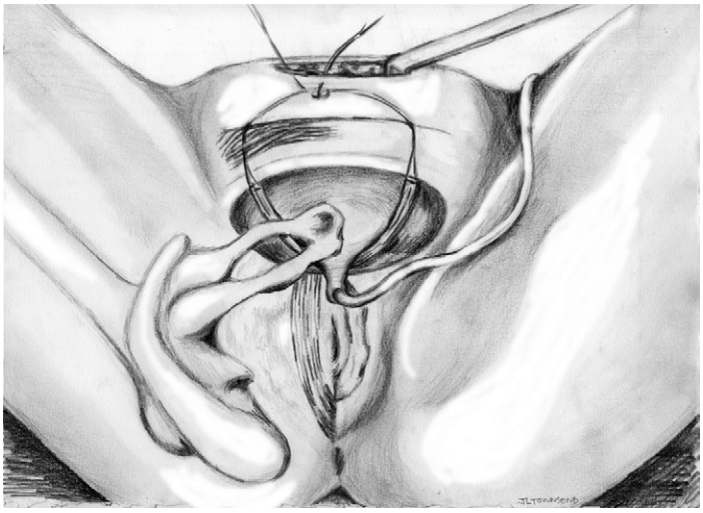


Figure 73–7. Tying and tensioning of sling.

achieved. Before final tensioning of the sling (see Fig. 73-7) the vagina should be closed and the weighted speculum removed to eliminate factors that can affect the final tension. The polydioxanone sutures are tied down above the rectus fascia (see Fig. 73–7) while cystoscopy with a 30-degree lens is performed to visualize adequate coaptation of the proximal urethra. There is approximately a two-fingerbreadth width between the rectus fascia and the sutures once tied down. The amount of tension may vary owing to the mobility of the urethra or desire to create permanent retention in an individual who will have permanent catheterization. The abdominal incision is closed with a subcuticular 4-0 polyglactin suture. The Foley catheter is left to straight drainage, and a vaginal pack moistened with conjugated estrogens is placed.

Postoperative Care

The vaginal packing is removed on postoperative day 1, and the patient is given a voiding trial once she is ambulating. If the patient voids adequately (after postvoid residual urine confirmation), she is discharged. If she is unable to urinate or has an elevated postvoid residual urine volume, she is discharged with a Foley catheter. She will return within 5 days for a repeat trial of voiding. Patients are instructed to avoid heavy lifting (>5 lb) and sexual intercourse for 6 weeks postoperatively. Sexual intercourse should be resumed only after a physical examination by the surgeon.

Outcomes

Autologous Pubovaginal Sling

Since McGuire's reintroduction of the autologous PVS in 1978 with 80% overall success rate, continence rates have been reproducibly satisfactory, even at long-term follow-up (Table 73–3). Earliest series (McGuire, 1987; Blaivas and Jacobs, 1991) with rectus fascial slings include a diverse and complex patient population, with patients having a history of pelvic irradiation, diabetes, spinal cord injury, and pelvic trauma. Poor or no urethral function was associated with 35% of cases (McGuire, 1987). Cure rates among these earliest series were similar (82%). A main cause of failure was urgency and UUI. A majority of the patients who required clean intermittent catheterization postoperatively had a neurogenic bladder and were counseled to expect urinary retention. Harvesting of rectus fascia appears a favored option over fascia lata for autologous material, likely owing to the urologist's greater comfort with abdominal anatomy. Yet, intermediate and long-term results of fascia lata PVS procedures (Beck et al, 1988; Govier et al, 1997) are comparable to those that use rectus fascia. Beck and colleagues (1988) noted that all three sling failures occurred within the first 22 cases performed and that 10 of the 13 overall failures were due to UUI. Five (3%) of the patients in this study population were extremely bothered by delayed voiding (mean interval of 59.6 days) and underwent a urethrolysis. Govier and associates (1997) administered an independent survey to assess outcomes, yielding worse outcomes than cure rates reported based on their chart review (70% vs. 87.5%, respectively). The vast majority of incontinence reported postoperatively was related to urgency. This patient satisfaction rate was similar to that noted by Brown and associates (2000) with questionnaire-based outcomes. In this group, all of the patients had thigh pain at 1 to 2 weeks and 11% described persistent thigh pain at 6 weeks. Latini and colleagues (2004) used the Crawford fascial stripper to obtain fascia lata. They reported 20% localized numbness at harvest site, 7% with harvest site pain 1 week postoperatively, 5% tendonitis in the harvest site leg, and 1 case of a harvest site hematoma requiring physical therapy. Yet, 83% of respondents indicated that the procedure had a positive effect on their life, 82% would recommend the surgery to a friend, and 83% would undergo the procedure again (Latini et al, 2004).

The rectus fascial autologous sling has been effective up to 7 years (Howden et al, 2006) postoperatively with low morbidity when performed by experienced surgeons. **Cure rates have ranged from 46% to 97%, although the measurement of outcomes is varied. Patient-derived cure rates are lower than physician-based or chart review–based outcomes.** There is no direct correlation between universally accepted objective and subjective measures of improvement or cure for antiincontinence procedures (Padmanabhan and Nitti, 2006). The most commonly cited reason for failure relates to urgency symptoms. UUI at follow-up is a common reason for patient dissatisfaction. **Reported de novo or UUI rates are 2.0% to 20.8%** (Mason and Roach, 1996; Zaragoza, 1996; Haab et al, 1997;

Table 73–3.

Outcomes with Autologous Pubovaginal Sling

STUDY	NO. PATIENTS	TYPE	AGE	PURE SUI	FOLLOW-UP (mo)	CURED/IMPROVED/ FAILED	ASSESSMENT OF OUTCOME	DE NOVO URGENCY OR UUI	PERSISTENT URINARY RETENTION
Blaivas and Jacobs, 1991	67	R	54 (27-80)	34 (50%)	3.5 yr (1-8)	82%/9%/9%	Questionnaire	1	6*
McGuire et al, 1987	81†	R	14-83	NA	3 yr	82% cured 18% failure	Not reported	NA	2
Beck et al, 1988	170	FL	56.7 (23-84)	NA	6 wk-10 yr	92.4% cured 7.6% failure	Cough test	1	5
Zaragoza et al, 1996	60	R	56.6 (34-78)	25 (42%)	25 mo (11-34)	95% cured 5% failure	Subjective	12%	0
Mason et al, 1996	63	R	56 (39-83)	NA	11.7 mo (3-27)	85.7%/14.3% (2 AUR, 4 SUI, 3 DO)	Questionnaire	NA	2
Govier et al, 1997	32	FL	61 (44-79)	21 (65.6%)	14 mo (3-33)	Subjective: 87.5%/9.4%/3.1% Objective: 70%/20%/10%	Subjective/chart review; telephone survey	3	0
Haab et al, 1997	40	R	65.7 (45 -79)	12 (33%)	48.2 mo (24-60)	46% dry 24% 1 pad per day 30% >1 pad per day 86% improvement	Questionnaire	4	3
Cross et al, 1998	150	R	57 (24-79)	102 (68%)	22 mo (6-42)	93% cure rate	Subjective; telephone interview	19%	2.8%
Chaikin et al, 1998	251	R	56 (19-80)	63 (25%)	3 yr (1-15)	Overall: 73%/19%/8% Patient: 67%/26%/7% Physician: 46%/49%/5% Pad test: 74%/20%/6% Voiding diary: 72%/7%/21%	Questionnaire, cough test, voiding diary, pad test	3%	4
Wright et al, 1998	33	NA	56 (36-82)	18 (54.5%)	16 (15-28) mo	94% success	SEAPI scoring system based on chart review	1	1
Hassouna and Ghoniem, 1999	112	R	55.5 (37-82)	49%	3.4 yr (0.5-8)	80.8% success 19.2% failure; Pad test: 60.6% dry/15.5% 1 pad per day/23.9% 2 or more pads per day	Quality of life questionnaire; subjective; pad test	20.8%	0
Brown et al, 2000	46	FL	62	35%	44 mo	73% cured 27% improved 0% failure	Mailed questionnaire	NA	3
Morgan et al, 2000	247	R	54.5 (10-84)	138 (56%)	51 mo (22-68)	85% cured	Questionnaire; subjective	5	7%
Groutz et al, 2001	67	R	55-58 ± 11	NA	33.9 mo (12-60)	67% cured (74% primary, 59% secondary) 33% improved	Subjective, cough test, voiding diary, pad test	10%	0
Richter et al, 2001	57	R or FL	18-84	NA	42 mo (0.5-134)	97% cured	Telephone interviews; UDS	0	4
Flynn et al, 2002	71	R or FL	53 (33-76)	26 (36.6%)	44 ± 7 mo	77%/13%/10%	Subjective; questionnaire	5%	1
Chou et al, 2003	131	R	66 (45-84)	46 (48.5%)	3 yr (1-7)	97% cure rate (for SUI) and 93% (for MUI)	Voiding diary; pad test; questionnaire	NA	1
Latini et al, 2004	100	FL	NA	NA	4.4 yr (0.8-9.3)	85% dry or improved Pad test: 84% 0-3 pads weekly	Questionnaire; subjective	NA	0

Continued

Table 73–3.

Outcomes with Autologous Pubovaginal Sling—cont'd

STUDY	NO. PATIENTS	TYPE	AGE	PURE SUI	FOLLOW-UP (mo)	CURED/IMPROVED/ FAILED	ASSESSMENT OF OUTCOME	DE NOVO URGENCY OR UUI	PERSISTENT URINARY RETENTION
Almeida et al, 2004	30	R	53.4 (37-73)	NA	33 (24-41) mo	70% cured 20% improved 10% failed	Subjective	NA	NA
Howden et al, 2006	153	R	62.7 ± 10.4	NA	7.1 yr	71.7% cured 28.3% failed 3.3% reoperation rate	Subjective; questionnaire; cough test	NA	NA
Albo et al, 2007	326	R	51.6 ± 10.1	247 (76%)	24 mo	66% success	Pad test; cough test; voiding diary	3%	6%
Mitsui et al, 2007	29	R	64 (43-79)	6 (21%)	25 mo (5-91)	80% cured 10% improved 10% failed	Questionnaire; subjective; UDS	1	8 (28%)
Onur et al, 2008	25	R	57 (39-85)	NA	18 mo (5-28)	84% cured/improved	Questionnaire	2	0

*4 of 6 patients had neurogenic bladders planned on clean intermittent catheterization postoperatively.
†1 of 82 was a male patient and excluded.
AUR, acute urinary retention; DO, detrusor overactivity; FL, fascia lata; MUI, mixed urinary incontinence; NA, not available; R, rectus; SUI, stress urinary incontinence; UDS, urodynamic study; UUI, urgency urinary incontinence.

Chaikin et al, 1998; Cross et al, 1998; Hassouna an Ghoniem, 1999; Morgan et al, 2000; Groutz et al, 2001; Flynn and Yap, 2002; Albo et al, 2007; Mitsui et al, 2007; Onur et al, 2008). Zaragoza and colleagues (1996) report that their three failures had persistent leakage due to UUI (present preoperatively). One of these patients had previous pelvic irradiation and radiation cystitis, and 1 had additional UDS, confirming bladder instability and lack of urethral obstruction. The short-term complication of postoperative retention that occurred in 60% immediately postoperatively is highlighted. Urinary retention persisted in this group for a median of 6.5 days (1 day to 5 weeks) and resolved in 70% within 10 days. Mason and Roach (1996) confirmed the success of a modified rectus fascial sling (smaller graft, 4 × 2 cm) with intermediate follow-up. Twelve (19%) patients had urgency, and 10 (15.9%) had frank UUI. By 6 months these symptoms had resolved in all but 3 (4.8%), who remained on anticholinergic medication. Haab and associates (1997) provided results of long-term follow-up using a self-administered questionnaire to assess success rates and overall patient satisfaction. Among the 3 patients (7.5%) requiring permanent clean intermittent catheterization, 2 had known sacral arc denervation and were expected to have urinary retention. These investigators cited the main reason for failure as urgency symptoms in 62% of patients at follow-up, with 10% reporting de novo urgency. The low reported dry rate (46%) relates to the large preoperative mixed urinary incontinence (MUI) group (67%) as compared with their cure rate for SUI only (73%).

Cross and colleagues (1998) advocated the use of a PVS in conjunction with anterior colporrhaphy for repair of cystocele to treat both conditions effectively. Thirty-six patients (63%) had a PVS due to a grade III or IV broad-based cystocele and SUI. Thirty-three (92%) of these cystoceles were cured. These authors reported a 28% postoperative urgency/UUI rate with 19% de novo urgency/UUI. Yet only 3% had persistent UUI requiring treatment; 2.8% underwent further urethrolysis to resolve voiding difficulties. Hassouna and colleagues (1999) reported long-term outcomes of a modified rectus fascial PVS. The modified PVS is a modification of the free rectus fascial strip technique popularized by McGuire that includes fixation of the sling to the pubocervical and periurethral ligaments in a four-quadrant manner (Ghoniem, 1991). After the initial reported 95% success rate by Ghoniem, this study confirms a lower overall rate of 80.8%, when including assessment by a patient quality of life questionnaire. All 15 of the patients with documented failures had UUI or severe irritative symptoms. The additional quality of life assessment highlights the impact of UUI, frequency, nocturia, and pain on patient satisfaction.

Chaikin and Blaivas (1998) and Morgan and associates (2000) provide a long-term analysis of the efficacy and quality of life impact of an autologous PVS. Chaikin and Blaivas (1998) reported an SUI cure or improved rate of 92% but also compared instruments for measurement of incontinence (patient assessment, chart review, pad testing, and voiding diary entries). Seventy-five percent of the patients have "complex" SUI, which included "pipe stem urethra," urethral or vesicovaginal fistula, urethral diverticulum, grade 3 or 4 cystocele, or neurogenic bladder. Concern is raised over the PVS converting an incompetent bladder neck into an obstructing system, with the finding of 23% incidence of DO at 1 year, which increased to 41% at 10 years. The failure rate due to UUI (de novo plus persistent) is similar to that reported by Cross and coworkers (1998) of 22%. Morgan and associates (2000) reported an 85% cure rate at 5 years, yet to achieve this level of cure 14 patients (5.7%) had secondary procedures. This included six collagen injections, three repeat PVS procedures, and five urethrolyses. Eighty percent of these 5 patients had a subsequent return to normal voiding. Chaikin and Blaivas (1998) and Morgan and associates (2000) together demonstrate that when SUI is resolved for more than 1 year after an autologous PVS procedure, the long-term (5 to 10 year) risk of recurrent SUI is low.

Groutz and associates (2001) reported outcomes based on whether the PVS was the primary (57%) or secondary anti-incontinence procedure (43%). The latter group had undergone 1 to 3 prior unsuccessful anti-incontinence procedures for recurrent incontinence. The cure rate was significantly higher in patients with primary incontinence than those with recurrent incontinence (74% vs. 59%, $P = .006$). Yet there were no surgical failures

in either group. All of the patients were either cured or improved based on their outcome score, incorporating 24-hour voiding diary, 24-hour pad test, and patient satisfaction. Richter and associates (2001) assessed long-term effects based on a telephone quality of life survey. This study reports high patient satisfaction, whereas 11.8% of the subjects required regular intermittent self-catheterization; 5.8% had to adopt adaptive positions to facilitate voiding. All of the obstructed patients were satisfied due to freedom from urinary incontinence and did not elect urethrolysis. This may relate to an emphasis of preoperative counseling in conveying the possibility of long-term voiding dysfunction after a PVS procedure. Chou and colleagues (2003) provided long-term outcomes for the effectiveness of an autologous PVS in management of MUI. The population included 48.5% with simple SUI and 51.5% with MUI. On univariate analysis of MUI, the higher number of urgency or UUI episodes preoperatively, the more likely it was that the PVS would fail. Yet, women with SUI and concurrent UUI or DO have a successful PVS outcome at a rate comparable to that in women with simple SUI (97% vs. 93%, respectively, $P = .33$). DO in 26% of those with MUI did not predict a poor outcome. This is contrary to their earlier observations (Chaikin and Blaivas, 1998).

The SiSTER trial (Albo et al, 2007), **a multicenter, randomized clinical trial, compared the rectus fascial autologous sling to the Burch colposuspension. The two primary outcomes were composite measures of success in terms of overall urinary incontinence measures (no self-reported symptoms of incontinence, increase of less than 15 g in pad weight during a 24-hour pad test, and no medical or surgical treatment for incontinence) and of SUI measures (no self-reported symptoms of SUI and negative stress test), specifically. Whereas success rates were higher for the PVS (47% vs. 38%, $P = .01$), voiding symptoms were also higher: urinary tract infections (UTIs) (48% vs. 32%), difficulty voiding (14% vs. 2%, $P < .001$), and postoperative UUI (27% vs. 20%, $P = .04$). All of the surgical procedures for bladder outlet obstruction (19 of 20) were performed in the sling group.**

Mitsui and associates (2007) analyzed the risk factors for postoperative voiding difficulty. Patients with a postvoid residual urine volume greater than 100 mL ($P = .05$) or $\dot{Q}max$ of less than or equal to 20 mL/s ($P = .09$) in preoperative urodynamics were more likely to require prolonged intermittent self-catheterization. In this group, 28% needed prolonged intermittent self-catheterization (range 4 to 40 months). There have been heterogeneous outcomes in regard to risk factors for postoperative voiding difficulty. This may relate to differences in surgeon skill or surgical method. **Although postoperative urgency and UUI are strongly related to failure, there are no preoperative risk factors that consistently predict outcomes after a PVS operation** (Mitsui et al, 2007).

Petrou and Frank (2001) **retrospectively reviewed the safety and efficacy of a repeat PVS for recurrent SUI among 14 women and concluded that repeat PVS is a reasonable treatment option.** The original surgeries included autologous PVS (3 patients), cadaveric bone–anchored PVS (3 patients), cadaveric bone–anchored suburethral sling (5 patients), and a vaginal patch sling (3 patients). Postoperative complications included a pelvic abscess related to a prior cadaveric sling and osteomyelitis pubis related to the prior bone anchored sling. One (7%) of the patients developed long-term urinary retention and is on intermittent bladder catheterization; 86% of the patients considered themselves cured or improved.

Value of Autologous Pubovaginal Sling in Urethral Reconstruction. Urethral and bladder neck reconstruction for fistulae and diverticula requires restoration of both anatomy and function. An autologous PVS serves an important role in these reconstructions. Anatomic damage refers to tissue loss and can range from a urethrovaginal fistula to absence of the urethra or vesical neck. The causes of damage include protracted obstetric delivery, antiincontinence procedures, urethral diverticulectomy or other sequelae of urethral diverticulum, aggressive transurethral resection of the bladder neck, long-term indwelling urethral catheter, pelvic trauma, tumors, and irradiation (Blaivas and Jacobs, 1991). The goals of surgical repair are to restore function and anatomy while fashioning an unobstructed urethra and maintaining continence (Blaivas and Heritz, 1996).

Swiertzewski and McGuire (1993) reviewed the records of 14 women who underwent urethral diverticulectomy during a 3-year period. Only 8 (57%) had symptoms of SUI, confirmed on urodynamics in 7. All 7 women were cured with a diverticulectomy and autologous PVS. One patient demonstrated DO. These investigators concluded that the presence of a urethral diverticulum did not compromise the outcomes of the PVS. Chancellor and coworkers (1994) performed a PVS procedure in 14 women with destroyed urethras secondary to long-term indwelling Foley catheter management of neurogenic bladder dysfunction. Greater tension was applied to the sling suspension to achieve urethral closure. Ten patients had simultaneous intestinal augmentations or diversions, 2 had concurrent suprapubic tube placement, and 2 had adequate bladder capacity and compliance and only had PVS performed. All of the patients achieved continence. The PVS is a simpler addition and avoids the risk of fistula formation associated with bladder neck closure, which has historically been used in this population. Blaivas and Heritz (1996) performed a retrospective study of 49 women who underwent a one-stage urethral reconstruction at up to 11-year follow-up. Forty-one of these women had a concomitant PVS placed for management of preoperative SUI. Only 1 patient experienced obstruction and DO after PVS placement, requiring incision and subsequently is continent. Three of 5 women who had Pereyra repairs for SUI required secondary PVS and are also now continent.

Faerber (1998) reported on 16 women who had simultaneous PVS and diverticulum repairs after UDS. All were either significantly improved (12%) or cured (88%), and only 2 patients developed de novo urgency. The average time for achieving adequate bladder emptying after repair was 5 weeks. For the initial 2 weeks, a Foley catheter is usually in place for urethral healing. Rovner and Wein (2003) reported on the circumferential urethral diverticulum repair among 9 patients who received either end-to-end urethroplasties or dorsal urethroplasties. Based on preoperative SUI status or evidence of open bladder neck on preoperative cystography, 8 patients were recommended to have a concurrent PVS procedure performed. All patients had a rectus fascial PVS sling placed, except 1 who requested a porcine PVS and 1 who refused to have PVS repair. All patients were continent postoperatively, except the patient who refused the PVS procedure and developed de novo SUI. Flisser and Blaivas (2003) evaluated the results of 74 women with urethral pathologic processes that required vaginal flap reconstructions. A majority of the women had required reconstruction for a diverticulum or urethral fistula secondary to iatrogenic causes. Fifty-six of these women had a concomitant PVS placed. Eighty-seven percent (54 women) considered themselves cured postoperatively. Three of 4 patients who had persistent SUI had failed a modified Pereyra procedure but were cured at reoperation. One patient was

continent after operative revision of the PVS for obstruction and significant UUI.

Allograft

The autologous fascial PVS remains a gold standard with efficacious and durable outcomes, but, owing to the morbidity of graft procurement, cadaveric allograft slings were introduced. This was to provide decreased morbidity, reduce operative time, and minimize pain (Table 73–4). There are limited outcome data owing to questions surrounding efficacy and durability. Early literature used cadaveric frozen or freeze-dried fascia lata with a variety of fixation methods, including suture fixation and bone anchors (Handa et al, 1996; Wright et al, 1998; FitzGerald et al, 1999; Brown and Govier, 2000; Carbone et al, 2001; Flynn and Yap, 2002; O'Reilly and Govier, 2002; Walsh et al, 2002; Amundsen et al, 2003; Richter et al, 2003; Almeida et al, 2004; Howden et al, 2006). Experience has shown that tissue processing techniques can have deleterious effects on cadaveric sling outcome (Nazemi et al, 2008). Lemer and associates (1999) found differences in both tissue integrity and durability between freeze-dried fascia and solvent-dehydrated fascia. They theorized that ice crystal formation characteristics of tissue freezing may disrupt the collagen matrices, yielding poor strength properties. **Failure rates for frozen or freeze-dried grafts range from 6.0% to 37.6%** (Handa et al, 1996; Wright et al, 1998; FitzGerald et al, 1999; Brown and Govier, 2000; Carbone et al, 2001; Flynn and Yap, 2002; O'Reilly and Govier, 2002; Walsh et al, 2002; Amundsen et al, 2003; Richter et al, 2003; Almeida et al, 2004; Howden et al, 2006).

Handa and associates (1996) reported on some of the earliest short-term outcomes for cadaveric fascia lata, with promising cure rates. Two of their patients (12%) developed abdominal wound infections, which resolved with local care, including drainage.

Table 73–4.

Outcomes with Allograft Pubovaginal Sling

STUDY	NO. PATIENTS	TISSUE PROCESSING TECHNIQUE	AGE (yr)	PURE SUI	FOLLOW-UP	CURED/ IMPROVED/ FAILED	ASSESSMENT OF OUTCOME	DE NOVO URGENCY OR UUI	PERSISTENT URINARY RETENTION
Handa et al, 1996	16	Fresh-frozen or freeze-dried	52-83	NA	187-354 days	86% (subjective) 79% (objective)	Subjective; UDS	36%	1
Wright et al, 1998	59	Freeze-dried	60 (16-82)	32 (52%)	9.6 mo (1-20)	98% cure rate	SEAPI scoring system based on chart review	2	1
FitzGerald et al, 1999	35	Freeze-dried	NA	NA	1 wk-9 mo	82.8% cure rate	Subjective; cough and Valsalva test	NA	NA
Amundsen et al, 2000	104	Freeze-dried	61.7 ± 11.6	35%	19.4 ± 10.3 (3-37) mo	54%/21%/25%	Questionnaire, pad test	15%	1
Brown et al, 2000	121	Freeze-dried	62	50%	12 mo	74% cured 19% 1-3 pads per day 7% >3 pads per day	Mailed questionnaire	NA	2
Huang et al, 2001	18	Solvent dehydrated	51.7 (37-76)	11 (61%)	9.2 (6.9-11.6) mo	72.2% successful 27.8% failed	Mailed questionnaire	NA	NA
Carbone et al, 2001	154	Freeze-dried	60 (38-85)	NA	10.6 (6-16) mo	62.4% success 37.6% failure	Questionnaire; telephone survey	03.2%	0
Flynn et al, 2002	63	Freeze-dried	54 (21-77)	3 (4.8%)	29 ± 3 months	71%/13%/16%	Subjective; questionnaire	28%	0
O'Reilly et al, 2002	121	120 fresh frozen 1 solvent dehydrated	62	100%	6.5 (4-13) mo	86.4% cure rate 13.6% failure rate	Mailed questionnaire	NA	NA
Walsh et al, 2002	31	Freeze-dried	63 (40-75)	26%	13.5 (12-14) mo	94% cure rate 6% failure rate	Voiding diary; questionnaire	NA	1
Richter et al, 2003	102	Freeze-dried	63.1 (29-87)	NA	35 ± 12.5	75% better or much better 25% failed 64.3% satisfied 21.4% partially satisfied 14.3% not satisfied	Questionnaire	NA	NA

Table 73–4.

Outcomes with Allograft Pubovaginal Sling—cont'd

STUDY	NO. PATIENTS	TISSUE PROCESSING TECHNIQUE	AGE (yr)	PURE SUI	FOLLOW-UP	CURED/ IMPROVED/ FAILED	ASSESSMENT OF OUTCOME	DE NOVO URGENCY OR UUI	PERSISTENT URINARY RETENTION
Carey et al, 2004	265	Solvent-dehydrated	<80 yr: 61.2 (33-79) >80 yr: 82.8 (80-93)	<80 yr: 103 (44%) >80 yr: 10 (32%)	<80 yr: 24.3 (12-51) mo >80 yr: 21.4 (12-50) mo	<80 yr: 61% (>70% improved)/24% (<50% improved); overall failure rate: 23% >80 yr: 55% (>70% improved)/32% (<50% improved); overall failure rate: 32%	Questionnaire	<80 yr: 13% >80 yr: 10%	0
Almeida et al, 2004	30	Freeze-dried	53.4 (37-73)	NA	36 (22-44) mo	40% cured 28% improved 22% failure	Subjective	NA	NA
Owens and Winters, 2004	25	Dermal graft	62 (30-83)	18 (72%)	14.8 (8-23) mo	32% dry 36% improved 32% failed	Chart review; telephone questionnaire	NA	3
Crivellaro et al, 2004	253	Dermal graft	58.3	97 (38.3%)	18 (5-54) mo	53% cured 25% improved 22% failure	Subjective; questionnaire	5%	2
Onur et al, 2005	25	Solvent-dehydrated	62 (39-77)	15 (60%)	12 (8-22) mo	80% cured 20% failed	Questionnaire	12%	0
Frederick et al, 2005	251	Solvent-dehydrated	66 (31-90)	153 (61%)	24 (6-61) mo	76% cured or improved 24% failed For only SUI: 82% cured or improved 18% failed (for only SUI)	Questionnaire; SEAPI scores	8.5%	1
Howden et al, 2006	150	Freeze-dried	63 ± 10.3	NA	3.5 yr	60.4% success 39.6% failure 12.7% reoperation rate	Subjective; questionnaire; cough test	NA	NA
Pianezza et al, 2007	37	NA	60.2 (38-78)	54%	3.8 (2-6.2) yr	UDI and IIQ-7 scores greater for preoperative MUI than SUI patients (96.7 vs. 58.0; 32.5 vs. 11.9)*	Questionnaire	NA	2
Nazemi et al, 2008	358	Solvent-dehydrated	CAPS 68 (43-97); CATS 72 (38-97)	NA	24-60 mo	Dry rate: 34% (24 mo) 27% (48 mo) 22% (60 mo) Success rate: 82% (24 mo) 78% (48 mo) 75% (60 mo)	Questionnaire	10	4
Onur et al, 2008	25	Solvent-dehydrated	61 (39-77)	NA	13 (8-20) mo	79% cured or improved 20% failed†	Questionnaire	3	0

*Questionnaire results are significant ($P = .04$ and $P = .03$), indicating patients with preoperative MUI have increased risk of postoperative dissatisfaction.
†Represents 5/25 allograft suburethral slings.
CAPS, cadaveric sling placement and prolapsed repair; CATS, cadaveric sling placement; MUI, mixed urinary incontinence; NA, not available; SUI, stress urinary incontinence; UDS, urodynamic study; UUI, urgency urinary incontinence.

They reported de novo urgency in 36% of the cases, whereas DO resolved in one of four cases. Two of the 3 patients who had SUI recurrence were continent after a synthetic midurethral sling. FitzGerald and associates (1999) reported on 35 patients undergoing cadaveric fascia lata sling placement with a high failure rate of 17%. Symptom recurrence was seen very early (1 week to 5 months). Histopathologic analyses of the retrieved material indicated ongoing processes in the failed graft: disorganized remodeling, areas of graft degeneration, and evidence of immune reaction. These findings led them to conclude that freeze-dried, irradiated donor fascia lata grafts should not be used for urogynecologic procedures due to the high material failure rate.

Three studies (Amundsen et al, 2000b; Walsh et al; 2002; Richter et al, 2003) documented good results without significant adverse outcomes using freeze-dried fascia lata. Amundsen and associates (2000b) utilized questionnaires and pad testing to assess incontinence outcomes in a complex population (80% having had prior pelvic surgery and 49% having had at least 1 prior anti-incontinence procedure). Sixty-five percent of the group had MUI preoperatively, with 41% of them having resolution of UUI; 15% developed de novo UUI, and no erosions were present. In 1 patient who underwent reoperation for a failed sling the fascia lata was found completely intact. The sling was torn from its nonabsorbable suture material, similar to a previously reported case (Chaikin and Blaivas, 1998; Amundsen et al, 2000b). Walsh and colleagues (2002) prospectively evaluated 31 women with promising short-term follow-up. There was complete resolution of SUI in 94% at both 4 months and 1 year. There was also a reduction in the incidence and severity of urgency and UUI after surgery, reflected in the declining use of anticholinergic surgery from before to 4 months and 1 year postoperatively (55% to 32% to 26%). Richter and colleagues (2003) conducted a prospective long-term study using validated questionnaires for a follow-up of 48 months. Difficulty emptying the bladder was described by 58.2% of patients at 12 month follow-up, with 34.2% describing it as slight. By 48 months, 50% of patients continue to have difficulty emptying their bladders. Patients reported a 90.2% satisfaction rate at 12-month follow-up and continued to be satisfied at 48-month follow-up (85.7%).

Two groups documented high failure rates with freeze-dried allograft (Carbone et al, 2001; O'Reilly and Govier, 2002). Carbone and associates (2001) used cadaveric fascia with titanium bone anchors for placement bilaterally in pubic bones. They reported a 38% failure rate and 17% reoperation rate at short-term follow-up of 11 months. Average time to reoperation was 9 months (3 to 15 months). Intraoperative findings at reoperation revealed the titanium anchors to be in position, the polypropylene sutures to be intact, and retropubic fibrosis and scarring of the urethropelvic ligament suggesting appropriate placement of the sling. All of the allogenic fascia appeared to be fragmented, attenuated, or simply absent. These authors have subsequently abandoned the use of cadaveric fascia allografts in all the PVS procedures at their institution. O'Reilly and Govier (2002) reported high intermediate failure rates in 121 women. Eight patients had recurrent SUI at a mean of 6.5 months (4 to 13 months); 7 of the 8 women had previous incontinence surgery and had multiple comorbidities, including neurologic disease, diabetes, previous pelvic irradiation, and previous pelvic surgery. Based on these results and findings by Lemer and associates (1999), this group discontinued use of fresh frozen grafts and switched to solvent dehydrated cadaveric fascia and dermal grafts.

Some studies support the efficacy of solvent-dehydrated fascial slings (Frederick and Leach, 2005; Onur and Singla, 2005; Pianezza et al, 2007; Nazemi et al, 2008), yet previous reported failures coupled with the consistent success and rapid adoption of synthetic midurethral slings has led to abandonment of all types of cadaveric allograft at most centers. Thus there are few data to assess long-term outcomes and define sling outcomes after solvent dehydration techniques (Nazemi et al, 2008).

Huang and colleagues (2001) were the earliest to report unfavorable experiences using solvent-dehydrated allograft in 18 women at short-term follow-up. They reported a 27.8% failure rate with full recurrence of incontinence and subsequently stopped using all allograft as a sling material. On reoperation with an autologous PVS for recurrent SUI the allograft remained only rudimentary and was very friable. Histologic examination of the retrieved allograft revealed wavy collagen fibers with loosely packed fibroblasts and focal areas of degeneration. Carey and Leach (2004) prospectively compared octogenarians and younger women undergoing treatment for incontinence with bone-anchored solvent-dehydrated cadaveric fascia lata. No statistically significant difference in outcome parameters was identified. The rates of de novo urgency were similar between the two groups, yet persistent urgency was greater among the octogenarians. Onur and associates (2005) reported 80% cure rates at 12-month follow-up. In 5 patients (20%) complete recrudescence of symptoms occurred within 6 months of surgery. Frederick and associates (2005) reported on prospective, intermediate-term results for cadaveric prolapse repair with bone-anchored sling (CaPS), with dry/cure rate and improvement rate of 56% and 82%, respectively. There was one case of osteitis pubis related to use of transvaginal bone anchor fixation that resolved with conservative management. Fifty-six percent of the failures occurred after 12 months of follow-up: 80% of these women were satisfied and 77% stated that they would undergo the CaPS procedure again. Using validated questionnaires (i.e., Urogenital Distress Inventory, Short Form [UDI-6]; Incontinent Impact Questionnaire [IIQ-7]), Pianezza and associates (2007) reported on similar levels of long-term patient satisfaction. Patients with preoperative MUI were at the greatest risk for postoperative dissatisfaction. Nazemi and associates (2008) described durable improvements in incontinence episodes, patient satisfaction, and validated quality of life end points when comparing a CaPS and CaTS (cadaveric sling placement alone) cohort. Yet there was a reduction in dry rates with extended follow-up (24 months, 48 months, and 60 months), especially in the CaTS group (23%, 18%, and 9% respectively); 4% of patients presented with sling extrusion and 4% required sling incision and urethrolysis.

Because of early and intermediate graft failure with cadaveric fascia lata, surgeons were prompted to use alternative materials: cadaveric dermal grafts. Crivellaro and associates (2004) presented their prospective series of patients treated with bone-anchored Repliform cadaveric human dermal allograft (LifeCell Corp., The Woodlands, TX) PVS. There was a 22% failure rate, yet based on patient report there was average incontinence improvement at 9 months of 85% and at 18 months of 80%. The 2 patients requiring long-term intermittent catheterization had neurogenic bladders. Owens and Winters (2004) assessed outcome and patient satisfaction with Duraderm allograft (C.R. Bard, Covington, GA). Initial results were promising, with a dry rate of 68% and improved rate of 24%. At intermediate follow-up only 32% of the patients were dry and 36% noted improvement. Two of the 8 patients who experienced graft failure underwent periurethral injections with significant improvement, and 1 is dry after an autologous sling procedure. Surgical reexploration revealed almost complete absence of graft material, without evidence of infection or excessive inflammatory response.

Six studies have compared the outcomes of women undergoing a PVS procedure using either autologous or cadaveric allograft fascia (Wright et al, 1998; Brown and Govier, 2000; Flynn and Yap, 2002; Almeida et al, 2004; Howden et al, 2006; Onur and Singla, 2008). Four groups found the outcomes comparable with equally high success rates and no negligible difference in complications. They concluded that allograft fascia lata may be used as an alternative to autologous fascia for PVS, to reduce operative time and decrease postoperative pain and disability (Wright et al, 1998; Brown and Govier, 2000, Flynn and Yap, 2002; Onur and Singla, 2008). With long-term follow-up, two groups noted superior continence outcomes in the autologous group (Almeida et al, 2004; Howden et al, 2006). Almeida and associates (2004) did not report adverse outcomes in either group. Howden and colleagues (2006) found recurrent symptoms occurred in a higher proportion in the cadaveric group (39.6%) compared with the autologous group (28.3%; P = .04). The reoperation rate was also higher for the allograft group (12.7% vs. 3.3%, P = .003).

Xenograft

A number of different sling materials are available and have been discussed. Because of the morbidity of autologous fascial harvest, high failure rates of allograft materials, and high erosion rate with synthetic PVS materials, xenografts are an attractive option. **They are associated with a low rate of infection, rejection, or extrusion, owing to their incorporation into host tissue** (Rutner et al, 2003). **Studies present in the literature utilize porcine dermis (Pelvicol), porcine SIS, and bovine dermis as xenografts for use in PVS surgery** (Arunkalaivanan and Barrington, 2003; Rutner et al, 2003; Abdel-Fattah et al, 2004;Wiedemann and Otto, 2004; Giri et al, 2006; Wilson et al, 2008) (Table 73–5). Rutner and colleagues (2003) were the first to describe the use of porcine SIS as a bone-anchored PVS in 152 patients with long-term follow-up. They reported cure rates comparable to those with the autologous sling. Among the 7 patients who experienced graft failure (4.6%), 5 had recurrent SUI within 3 months of surgery and the other 2 had recurrences at 9 and 11 months postoperatively. Two of the failures were related to the bone anchors. One patient had repeat porcine SIS PVS, with continued failure to relieve incontinence and 1 patient became dry after carbon bead bulking injections. One patient achieved continence after a urethrolysis 2 years postoperatively. At reoperation, grossly no evidence of the implanted SIS material was found. Biopsy specimens of the periurethral tissue revealed fibrous and muscular tissues with a few remnants of SIS. Wiedemann and Otto (2004) performed the first histopathologic examination of porcine SIS in a series of 15 women with SIS PVS. Three reoperations (20%) were necessary owing to recurrent SUI at a mean of 12.7 months. All 3 patients underwent reoperation with implantation of a polypropylene mesh and achieved immediate continence. Biopsy specimens from the SIS band under the vaginal mucosa revealed only focal residues of SIS without any evidence of tissue reaction. There was also no evidence of a significant immunologic or chronic inflammatory reaction. These authors concluded that the advanced incorporation of the implant would lend to good biocompatibility.

Arunkalaivanan and Barrington (2003) first reported on Pelvicol in a randomized, short-term trial comparing Pelvicol PVS with the tension-free vaginal tape (TVT) procedure. Questionnaire-based cure rates were comparable between the two: 85% in the TVT group and 89% in the Pelvicol implant group. Abdel-Fattah and associates (2004) presented the 3-year follow-up data for this prospective trial. Cure rates remained high and comparable between the two groups: 79.1% for the TVT group and 77.8% for the Pelvicol group. There was no statistical difference in regard to complication rates or postoperative pad score. Giri and colleagues (2006) compared the 3-year efficacy of Pelvicol with autologous rectus fascia in 101 consecutive, nonrandomized patients. Although porcine dermis reduced the associated surgical morbidity, there were significantly inferior long-term cure rates as compared with the autologous PVS. Treatment failure occurred by 9 months in the autologous group and by 24 months after the Pelvicol sling. Repeat UDS indicated SUI as the cause of treatment failure in 18 of 20 (90%) women treated with porcine dermis but only in 3 of 8 (6.5%) women after a rectus fascial sling. These authors concluded that Pelvicol should not be used as a substitute for rectus fascia.

Bovine dermis is the most recently reported material used for a xenograft PVS (Wilson et al, 2008). Women at high risk for sling failure (with advanced age, previous surgical failure, intrinsic sphincter deficiency) underwent either a bovine dermis or autologous rectus fascia PVS procedure with short-term follow-up. Global

Table 73–5.

Outcomes with Xenograft Pubovaginal Sling

STUDY	NO. PATIENTS	TYPE	AGE	PURE SUI	FOLLOW-UP (mo)	CURED/ IMPROVED/ FAILED	ASSESSMENT OF OUTCOME	DE NOVO URGENCY	PERSISTENT URINARY RETENTION
Rutner et al, 2003	152	Porcine SIS*	NA	75 (49%)	2.3 yr (4-48 mo)	93.4%/2%/4.6%	Subjective	5	0
Abdel-Fattah et al, 2004	74	Pelvicol†	53 (34-75)	NA	36 mo	77.8% (dry)/9.7%/12.5%)	Subjective; mail questionnaire	17.6%	0
Giri et al, 2006	51	Pelvicol	46 (34-52)	NA	36 mo	31%/23%/46%	Subjective; mail and telephone questionnaire	1	1
Wilson et al, 2008	37	Xenform Matrix‡	67.7	NA	19.5 mo	83.8% SUI cure rate; 54.1 global cure rate	Cough test; questionnaire	NA	NA

*Porcine SIS is an acellular, collagen matrix of processed small intestine submucosa.
†Pelvicol is gamma sterilized, cross-linked porcine skin.
‡Xenform Matrix is acellular bovine dermis.
NA, not available; SUI, stress urinary incontinence.

cure rates and SUI cure rates were not statistically different between the two groups. Four women (8.3%) in the autologous group were reoperated with injections, repeat autologous PVS placement, and anterior colporrhaphy with interposition graft. Two women (5.4%) in the bovine dermis group underwent additional interventions: injections and a repeat autologous PVS placement. Biopsy specimens of the bovine dermis sling material during reoperation (for SUI recurrence at 3 months) revealed the sling was replaced by fibrosis, hemorrhage, and mild chronic inflammatory infiltrate, with no acellular component. Tissue breakdown, represented by intermittent areas of myxoid degeneration, was present and may indicate evidence of early graft failure.

Key Points: Pubovaginal Sling Outcomes and Urethral Reconstruction

- The autologous PVS is associated with cure rates of 46% to 97% with variable measurements of outcome utilized.
- De novo urgency and UUI rates are 2.0% to 20.8%.
- There are no risk factors that consistently predict the outcomes after a PVS. Only one study reports on the rate of cure with PVS for recurrent SUI (86%), and the PVS appears to be a valid and useful treatment option.
- Autologous PVS serves an important role for providing continence and robust tissue coverage in urethral reconstruction (urethral fistula, urethral diverticulum, destroyed urethra).
- Freeze-dried allograft is associated with higher failure rates (6.0% to 37.6%) and has been predominately replaced by solvent-dehydrated fascia.
- Pelvicol, SIS, and bovine dermis are the xenografts used in PVS surgery, with cure rates of 31% to 93.4%. In randomized trials, porcine dermis was associated with significantly inferior long-term cure rates compared with the autologous PVS (Arunkalaivanan and Barrington, 2003).

Complications

Erosion and Extrusion

The incidence of sling erosion is dependent on the composition of sling material. Synthetic slings erode 15 times more often into the urethra and extrude 14 times more often into the vagina than autologous, allograft and xenograft slings (Blaivas and Sandhu, 2004). This is based on a meta-analysis of peer-reviewed literature in 1997, citing a urethral erosion incidence of 0.02% and vaginal extrusion of 0.007% in 1515 patients who underwent synthetic slings. This is compared with a urethral erosion incidence of 0.003% and vaginal extrusion of 0.0001% in 1715 patients undergoing autologous and allograft slings (Leach et al, 1997). In subsequent studies, most erosions have been associated with synthetic slings, particularly woven polyester slings (Summit et al, 1992; Bent et al, 1993; Weinberger and Ostergard, 1995; Myers and LaSala, 1998; Kobashi et al, 1999; Duckett and Constantine, 2000; Clemens et al, 2000; Amundsen et al, 2003; Chen et al, 2010), but recently there are a few reported cases of autologous and allograft slings (Handa and Stone, 1999; Golomb et al, 2001; Amundsen et al, 2003; Bradley et al, 2003; Blaivas and Sandhu, 2004) (Table 73–6).

Most urethral erosions are diagnosed 1 to 18 months after the original surgery, with a mean presentation of approximately 9 months. **Presenting symptoms often include urinary retention, UUI, and MUI. Synthetic sling erosions are often also associated with vaginal discharge, vaginal pain/pressure, suprapubic pain, and recurrent UTIs. The etiology is multifactorial, including local tissue factors (i.e., postsurgical scarring, urethral atrophy, estrogen deficiency, and radiation-induced ischemia) or surgical techniques (i.e., excessive tension, dissection too near urethra, or perforation of urethra or bladder)** (Blaivas and Sandhu, 2004). Golomb and colleagues (2001) reported a rare case of autologous sling erosion into the midurethra after traumatic urethral catheterization for prolonged urinary retention.

Erosion of an autologous PVS is rare. There are only four cases of erosions documented in peer-reviewed literature. Handa and Stone (1999) and Golomb and colleagues (2001) reported on an individual case of an autologous sling eroding through the midurethra. Possible causative factors include misplacement or incorrect technique in sling passage or positioning, excessive tension, or traumatic urethral instrumentation after placement of a PVS (i.e., for retention, hematuria clot evacuation, surveillance cystoscopy). In both cases the eroded portion of the sling was excised and the urethra was closed (Handa and Stone, 1999; Golomb et al, 2001). Clemens and colleagues (2000) described two cases of bladder dome erosion by an autologous rectus fascial sling that presented as recurrent UTI, dysuria, and UUI. One of these patients presented with a bladder calculus on sling material that was visible on cystoscopy. The other woman presented with edema and suture at the dome. In both cases adequate cystoscopy with 30- and 70-degree lenses after Stamey needle passage may have avoided this. Both cases were successfully managed with endoscopic removal of stitches and treatment of the bladder stone. No further treatments were necessary (Clemens et al, 2000).

Eight cases of allograft erosion and extrusion were found within the literature between three groups (Clemens et al, 2000; Amundsen et al, 2003; Bradley et al, 2003). Among the three cases of vaginal extrusion (Clemens et al, 2000; Bradley et al, 2003) of an allograft PVS, patients commonly presented with vaginal bleeding, persistent SUI, and irritative voiding symptoms. All three cases were managed successfully with transvaginal exploration, partial sling removal, and closure of the vagina. The patients did not require reoperation or further treatment. **Management of autologous and allograft sling urethral erosion is usually done with incision or excision of that part of the sling that has eroded and simple closure of the urethra** (Blaivas and Sandhu, 2004). Rarely are additional coverage measures (i.e., Martius flap) required. **No cases of xenograft erosion or extrusion are present in the literature.**

Erosions and extrusion of a synthetic PVS were very common and associated with significant morbidity. Synthetic material is no longer utilized for bladder neck slings. In fact, the ProteGen sling (Boston Scientific, Natick, MA) was recalled in January 1999 because of the high erosion rates (Clemens et al, 2000). The other 60 cases of erosion and extrusion found within the literature are cases of synthetic PVS: ProteGen, Mersilene, silicone, GORE-TEX or polypropylene (Myers and LaSala, 1998; Kobashi et al, 1999; Clemens et al, 2000; Duckett and Constantine, 2000; Amundsen et al, 2003). Rates of rejection or erosion, usually requiring removal of the synthetic material historically, vary from 2.7% to 22% (Summit et al, 1992; Bent et al, 1993; Weinberger and Ostergard, 1995). **Most authors agree that erosions from synthetic slings require complete removal of the sling and all other foreign materials (sutures, bone anchors, screws) whenever present** (Blaivas and

Table 73–6.

Pubovaginal Sling (PVS) Erosion and Extrusion

STUDY	NO. AND TYPE	LOCATION	TIME TO PRESENTATION (mean mo)	MANAGEMENT	RATE OF SUI	SUBSEQUENT TREATMENT
Myers and LaSala, 1998	7 Mersilene	7 vaginal*	4.1 (1-3)	7 transvaginal partial excision and/or cauterization	0%	NA
Kobashi et al, 1999	34 ProteGen	17 vaginal 7 urethral 4 vaginal + urethral 6 urethrovaginal fistula	7.9 (1-22)	31 transvaginal 3 transurethral complete excision and bone anchor removal	74%	4 rectus fascial PVS, 2 cadaveric PVS, 2 collagen
Handa and Stone, 1999	1 autologous	Vaginal	2.5	Transvaginal revision	0%	NA
Duckett and Constantine, 2000	5 silicone	5 abdominal sinus 1 abdominal + vaginal sinus	8.6 (3-16)	Transvaginal Complete removal	1	NA
Clemens et al, 2000	10 ProteGen 1 GORE-TEX 2 autologous, 1 allograft	6 vaginal 2 bladder (dome) 6 vaginal + urethral	11.2 (4-31)	11 transvaginal 1 transvaginal + urethral 2 retropubic Complete excision	50%†	1 rectus fascial PVS, 2 rectus fascial PVS + collagen
Golomb et al, 2001	1 autologous	urethral	4 yr	Transvaginal Partial symmetric lateral excision	none	NA
Amundsen et al, 2003	2 ProteGen 1 polypropylene 5 allograft 1 autologous	9 urethral	9 (3-18)	All transvaginal Complete excision	22.2%	1 allograft PVS, 1 collagen
Bradley et al, 2003	2 allograft	2 vaginal	2.5 and 5	1 partial and 1 complete transvaginal excision	1	NA

*1 of 7 patients re-presented 3 months after excision with further vaginal erosion.
†7 of 12 patients (58%) with urethral or vaginal erosions experienced recurrent SUI after sling removal.
SUI, stress urinary incontinence.

Sandhu, 2004). Myers and LaSala (1998) reported on 7 patients with vaginal extrusion among 116 women with bladder neck Mersilene mesh slings. All of the cases presented within 4 to 12 weeks of initial operation and were managed with trimming of visible mesh, excision of granulation tissue, and re-covering of erosion. One of these 7 women presented with recurrent extrusion (Myers and LaSala, 1998). Of note, whereas follow-up of these 7 women was up to 37 months, many of the other 109 patients were likely also to have had subsequent erosions or extrusions. Kobashi and colleagues (1999) published the multi-institutional results of ProteGen sling (bovine collagen with bone anchors) erosions and extrusions in 34 women. The most common presenting complaints were delayed vaginal discharge in 21 (32%), vaginal pain or pressure in 21 (62%), suprapubic pain in 11 (32%), and recurrent UTI in 5 (15%). The synthetic sling was entirely removed. Attempt was additionally made to remove all bone anchors. One patient with residual pain after sling removal had a "hot area" at the bone anchor site revealed on bone scintigraphy (Kobashi et al, 1999). Duckett and Constantine (2000) came to a similar conclusion about silicone as sling material as other groups reported with the ProteGen sling. Among the initial 7 women who had a silicone PVS placed, 5 experienced silicone erosion and sinus formation. The study was terminated due to the high complication rates. Clemens and colleagues (2000) reported on complications associated with 10 cases of ProteGen and 1 case of GORE-TEX. This included four ProteGen extrusions, six ProteGen erosions with extrusions, and one GORE-TEX extrusion. All of the cases were managed with transvaginal removal of sling sutures and bone anchors wherever possible. Five of these 14 women had recurrent SUI, including 1 who opted to have an autologous sling placed at the time of ProteGen sling removal owing to persistent SUI after the initial surgery. Other symptoms resolved among all of the patients (Clemens et al, 2000). Amundsen and colleagues (2003) performed complete sling removal, urethral repair, and additional placement of a Martius flap in patients with two of the three synthetic erosions that occurred. They noted an intense inflammatory reaction with superimposed infection, leading to extensive urethral loss. This was thought to contribute to the significant recurrent SUI (ISD), requiring a PVS and collagen (Amundsen et al, 2003). **The incidence of recurrent SUI in contemporary series of urethral erosions after synthetic PVS placement is 74% to 100%, often necessitating a secondary PVS** (Kobashi et al, 1999; Clemens et al, 2000).

There are few studies concerning treatment of urethral erosions after a PVS procedure, success rates, and rates of continence. **Urethral reconstruction is successful a majority of the time, yet continence is achieved in only 17% to 56% of patients** (Clemens et al, 2000; Amundsen et al, 2003) **who had erosions secondary to a synthetic sling. When erosions were managed with concurrent placement of a new PVS, Flisser and Blaivas** (2003) **reported an 87% continence rate. Secondary procedures such as bulking agents and PVS surgery are successful in a majority of patients** (Blaivas and Sandhu, 2004). **However, if the bladder neck is involved with the erosion the authors have noted much lower overall continence rates, even with the use of concomitant autologous slings at the time of reconstruction.**

Key Points: Erosion and Extrusion

- The incidence of erosion is dependent on the sling material, with synthetic slings eroding 15 times more often into the urethra and 14 times more often into the vagina than other materials. For this reason the synthetic PVS is no longer used for support at the bladder neck.
- Synthetic sling erosion presents as vaginal discharge, pain, suprapubic pain, and recurrent UTIs and requires complete removal of the PVS.
- The incidence of recurrent SUI after synthetic PVS urethral erosion is 74% to 100%, often requiring a secondary PVS.
- Erosion with other materials has more association with urgency, UUI, and irritative voiding symptoms and requires excision of eroded portion of sling. Erosion of autologous PVS is rare.

Voiding Dysfunction Secondary to Bladder Outlet Obstruction

The voiding dysfunction that develops from iatrogenic outlet obstruction by a PVS is related to **obstruction, DO, or impaired detrusor contractility.** The incidence of voiding dysfunction after continence surgery varies widely in the literature, from 2.5% to 35% (Foster and McGuire, 1993; Carr and Webster, 1997; Cross et al, 1998; Chaliha and Stanton, 1999). The traditional PVS is known to have higher rates of voiding dysfunction than the Burch colposuspension (Stanton et al, 1983). A multi-institutional, randomized clinical trial (SiSTER) compared the autologous rectus fascia PVS procedure and the Burch colposuspension. Although success rates were higher for women who underwent the sling procedure there was significantly greater voiding dysfunction (63% vs. 47%, $P < .001$): UTIs, difficulty voiding, and postoperative UUI (Albo et al, 2007). A meta-analysis by the **AUA Stress Urinary Incontinence Clinical Guidelines Panel reported that the incidence of urinary retention more than 4 weeks after PVS placement was 8% and the risk of permanent retention "generally does not exceed 5%"** (Leach et al, 1997). In a series of 252 women at 4-year follow-up, Morgan and colleagues (2000) reported a prolonged **urinary retention rate of only 2.4%. Patients may present with complete urinary retention or obstructive voiding symptoms and less obvious irritative symptoms, including UUI** (Carr and Webster, 1997). **Obstruction may present as recurrent UTIs, prolonged suprapubic pain, and painful voiding,** even if emptying is completed. Nitti and colleagues (2002) found that 16% of patients who required PVS lysis did not have obstructive symptoms or retention. Some studies report **persistent postoperative UUI and urgency as presenting more commonly (8% to 25%) than frank retention** after a PVS (Cross et al, 1998). The risk of iatrogenic obstruction usually relates to technical factors (i.e., placement and tension of sutures or sling material). When there is an inadequately supported bladder neck/proximal urethra there is potential for continued SUI. When the sling is tied too tightly there is excessive elevation of the bladder neck toward the pubic bone, causing "hypersuspension" or overcorrection of the urethrovesical angle.

Preoperative voiding dysfunction affects a patient's ability to empty after anti-incontinence surgery. **Detrusor hypocontractility, a condition that is present preoperatively, may manifest symptomatically with even a "relative obstruction" when urethral resistance is increased by an anti-incontinence surgery.** During preoperative counseling these patients should be warned of the possibility of postoperative voiding dysfunction. Dysfunctional voiding or failure of relaxation of the external (striated) urethral sphincter may affect emptying after surgery (FitzGerald and Brubaker, 2001). A patient who habitually voids by abdominal straining may have difficulty emptying after incontinence surgery. Because of the variability of presenting symptoms after a PVS procedure it is important to ascertain the predominant symptom through a focused history. **The temporal relationship between anti-incontinence surgery and onset of persistent voiding symptoms is key.** For example, de novo urgency may actually exist as a result of urethral obstruction. On physical examination an abnormal urethral angulation, a foreshortened nonpliable vagina, or a nonmobile urethra may be noted. Hypersuspension is usually not evident on physical examination. The postvoid residual urine volume is very important in the evaluation of voiding dysfunction, although no clear cut-off values exist (Siddighi and Karram, 2007). **Cystoscopy is useful to rule out a bladder pathologic process, sling erosion, and a hypersuspended urethra. Videourodynamics are useful in selected cases at the physician's discretion. Most important remain the temporal relationship between the symptoms and the surgical procedure and the main criterion for a sling incision or urethrolysis.**

There are no well-established risk factors for patients who are likely to experience obstruction after anti-incontinence surgery. UDS has been used to investigate multiple factors to determine which may be predictive. Miller and associates (2003) noted that women undergoing an allograft PVS who voided with no or minimal detrusor pressure (19%) had a significantly increased risk of postoperative retention. In contrast, no patient with a detrusor contraction developed retention postoperatively. Weinberger and Ostergard (1995) studied 108 women undergoing synthetic PVS procedures and found that the absence of detrusor contractions predicted delayed returns to normal voiding. Valsalva voiding had no affect on the incidence of postoperative retention or voiding dysfunction in either of these studies. The association between low voiding detrusor pressures and Valsalva voiding with subsequent voiding dysfunction was not seen by others (McLennan et al, 1998). **UDS is useful in understanding voiding dynamics of incontinent women, yet low detrusor pressure or Valsalva voiding preoperatively should not exclude patients from having an anti-incontinence procedure.** Lemack and colleagues (2008) examined the preoperative and postoperative urodynamic data for patients enrolled in the SiSTER trial (prospective, randomized clinical trial comparing the PVS procedure with Burch colposuspension) to predict voiding dysfunction after surgery. UDS findings did not predict postoperative voiding dysfunction or the risk of surgical revision in the PVS group. Recently, there have been anecdotal data on correlation between preoperative postvoid residual urine volume and urodynamic $\dot{Q}max$ with postoperative retention (Mitsui et al, 2007). **No study to date has shown a definitive relationship between preoperative urodynamic findings and risk of postoperative retention.**

A key factor in assessing voiding dysfunction is prolapse that was either uncorrected at the time of surgery or occurred postoperatively. **Prolapse of sufficient size may kink or angulate and externally compress the urethra.** Apical, anterior, and posterior prolapse must be ruled out as a cause of the urethral obstruction. Kobashi and colleagues reported on a technique of combined cystocele repair and PVS using a single piece of

cadaveric fascia. Although no patients required surgery for obstruction the follow-up was only 6 months and long-term data are lacking (Kobashi et al, 2000). There is a paucity of literature on the affects of concurrent PVS and prolapse repair on postoperative emptying and voiding symptoms. Barnes and associates (2002) reported on 38 women with grade 3 to 4 pelvic prolapse and occult SUI who underwent concurrent PVS with prolapse repair. No patient developed permanent urinary retention. Two (9.5%) of the women developed de novo UUI. Existing UUI resolved in 45%. These investigators concluded that concurrent surgery had little negative effect on postoperative bladder emptying. **Data are lacking on risk factors for voiding dysfunction after an anti-incontinence procedure performed with surgery for pelvic organ prolapse.**

Whereas transient urinary retention is common, most patients return to spontaneous voiding within the first 10 days (Zaragoza, 1996; Cross et al, 1998). **Obstruction after a PVS procedure may improve or resolve with time, which is the reason most physicians historically prefer waiting 3 months before considering surgical intervention.** Persistent voiding dysfunction is initially treated conservatively. This includes temporary catheter drainage, clean intermittent catheterization, timed voiding, double voiding, biofeedback, pelvic floor muscle training, and antimuscarinic agents, which are extremely effective in specific cases. Anecdotal evidence shows improvement in urethral obstruction with urethral dilation and downward traction. These results may vary from temporary relief to worsening of the urethral rigidity secondary to periurethral fibrosis (Zimmern et al, 1987; Beck et al, 1988). This, like resection or incision of the bladder neck, is likely to fail because the sling is extraluminal. Additionally, these procedures may be associated with damage to the sphincter or bladder neck, leading to worsened incontinence, in addition to postoperative fibrosis and bladder neck contracture (Ghoniem and Elgamasy, 1995). It is not the authors' practice to perform urethral dilation. When conservative measures fail, surgical intervention is indicated.

Surgical management of bladder outlet obstruction after a PVS procedure traditionally involves complete urethrolysis by a retropubic, transvaginal, or suprameatal approach, with success rates of 65% to 93% (Foster and McGuire, 1993; Carr and Webster, 1997; Cross et al, 1998; Goldman, 1999; Petrou et al, 1999). Most of these series include patients with obstruction after many different anti-incontinence procedures. Only two groups have stratified their results specifically for the PVS (Foster and McGuire, 1993; Petrou et al, 1999). Foster and McGuire (1993) reported that transvaginal urethrolysis was successful in 50% of PVS obstructions, which was less than both needle suspensions (75%) or retropubic urethropexy (63%). Their conclusion was that transvaginal lateral dissection is insufficient in relieving the direct suburethral compressive force of the sling. Petrou and coworkers (1999) reported on the suprameatal approach as superior to the transvaginal approach, allowing access and division of the lateral wings of the sling. Eight of 12 patients had successful results. In a series of 12 women, Petrou and Young (2002) reported resolution of obstruction in 10 patients with new-onset SUI (18% of women) after retropubic urethrolysis. Carr and Webster (1997) reported complete or significant resolution of symptoms in 86% of patients with retropubic urethrolysis. **Recurrent SUI after formal urethrolysis is reported as 0% to 19%** (Table 73–7).

Table 73–7.

Results of Therapy for Bladder Outlet Obstruction after Pubovaginal Sling (PVS) Surgery

STUDY	NO. PATIENTS	MANAGEMENT	TIME TO TREATMENT (MEAN)	SUCCESS RATE	RECURRENT SUI	REPEAT SURGERIES
Foster and McGuire, 1993	10	Transvaginal urethrolysis	25.9 mo (2-35)	50%	None	NA
Carr and Webster, 1997	51	Retropubic, vaginal, or infrapubic urethrolysis	15 mo (4-268)	86% (retropubic), 73% (vaginal), 25% (infrapubic)	13.7%	NA
Cross et al, 1998	15	Transvaginal urethrolysis	16 mo (3-36)	72%	1 patient	PVS 1 year after urethrolysis
Goldman et al, 1999	11	Transvaginal urethrolysis	14 mo (2-36)	84%	19%	NA
Petrou et al, 1999	12	Suprameatal transvaginal urethrolysis	1.5 yr (3 mo-6 yr	66.7%	None	NA
Defreitas and Herschorn, 2000	16	Lateral sling lysis	NA	94%	34%	NA
Amundsen et al, 2000	32	22 transvaginal urethrolysis 10 sling lysis	39 wk (5-150)	84% (not stratified by procedure)	12.5%	1 patient received collagen injections
Kusuda, 2001	5	Sling lysis	6 wk-2 yr	100%	None	NA
Nitti et al, 2002	19	Sling lysis	10.6 mo (3-72)	84%	17%	2 patients received collagen injections; 1 patient had repeat PVS
Goldman, 2003	14	Sling lysis	8.6 mo (3-26)	93%	21%	1 patient received polypropylene sling
Thiel et al, 2005	13 (2 lost to follow-up)	Sling lysis	65 days (36-235)	45% improved; 45% cured	7.7%	No repeat surgery

SUI, stress urinary incontinence.

Ghoniem and Elgamasy (1995) were the first to report on the successful use of sling incision and interposition of a free graft of vaginal wall for obstruction. **Sling incision has comparable success rates (84% to 100%) without the longer operative time and potential morbidity of a formal urethrolysis** (McLennan and Bent, 1997; Defreitas and Herschorn, 2000; Shenassa et al, 2000; Amundsen et al, 2000a; Kusuda, 2001; Nitti et al, 2002; Goldman, 2003; Thiel et al, 2005). Theoretically the interposition of autologous graft material between cut ends of the sling was to prevent recurrent incontinence. Others have found that this technique did not live up to this expectation. Shenassa and associates (2000) and McLennan and Bent (1997) used vaginal wall interposition in 12 and 4 women, respectively. The success rate was 92% and 100%, but SUI recurred in 25% in each series. Several small series have reported on successful sling incision without graft interposition. Kusuda and colleagues (2001) reported successful outcomes for 5 patients who underwent lateral sling incision. Defreitas and Herschorn (2000) had a 94% success rate in 16 women after lateral sling incision, with a 34% rate of recurrent SUI. Lateral incision is beneficial to avoid urethral injury in cases in which the sling is identified but the dissection plane between the urethra and sling is difficult. Amundsen and associates (2000a) used midline incision of a PVS in 10 of 32 patients, in whom the sling was easily identified. In the rest, a formal urethrolysis with entrance into the retropubic space was performed. The overall success rate was 84%, but the results were not stratified between sling incision and formal urethrolysis. In 9 of 12 of the obstructing autologous slings in this series the sling material could not be identified and was replaced by dense fibrosis. Nitti and colleagues (2002) reported on 19 women who underwent a PVS lysis for obstruction. The success rate was 84% and the recurrent SUI rate was 17%. Two of the 3 women who experienced failure of their procedures underwent subsequent successful retropubic urethrolysis. This allowed for complete release of all retropubic space scarring, which likely contributed to the failure of the suburethral sling release. Goldman (2003) performed simple sling incision in 14 women with iatrogenic urethral obstruction. This included 3 patients with a midurethral polypropylene mesh sling. Thirteen of 14 (93%) patients had complete or significant improvement of presenting complaints, and 1 (7%) required subsequent urethrolysis. Twenty-one percent (3 patients) developed recurrent SUI, with only 1 patient requiring treatment (repeat mesh midurethral sling). Long-term results after simple sling incision were reported on 13 women with catheter-dependent urinary retention after PVS surgery by Thiel and colleagues (2005). At 5-year follow-up, patients reported 45% cure and 45% improvement; 7.7% of the women noted recurrent SUI but chose to not pursue further therapy.

There are no preoperative or urodynamic parameters that predict success or failure of urethrolysis. Foster and McGuire (1993) found that patients with DO had a higher rate of failure but later studies contradicted this. Carr and Webster (1997) found the only parameter predictive of success was no prior urethrolysis. Nitti and Raz (1994) found that as the postvoid residual urine volume increased so did the failure. This has not been confirmed by others. Four of these women who failed to generate a contraction during UDS testing had successful urethrolysis. They also reported that UDS findings in patients whose procedures were considered failures after transvaginal urethrolysis failed to elucidate the reason for their continued voiding dysfunction. Because of the limitation of UDS in evaluation of these patients the temporal relationship of urethrolysis to the onset of symptoms is relied on as an indicator of obstruction. If a patient fails to resume voiding or improve significantly, then continued obstruction is suspected.

Failure of urethrolysis may be due to persistent or recurrent obstruction, DO, impaired detrusor contractility, or learned voiding dysfunction. Recurrent obstruction may result from periurethral fibrosis and scarring or intrinsic damage to the urethra that has occurred from the prior urethrolysis surgery. The most common reason is likely due to insufficient dissection and lysis of the urethra. Scarpero and colleagues (2003) reported on the value of repeat urethrolysis after failed urethrolysis in 24 women. Both transvaginal and retropubic approaches were chosen depending on the clinical situation. Obstruction was cured in 92%, but storage symptoms only resolved in 12%. Sixty-nine percent were improved and continued to require antimuscarinic therapy. SUI recurred in 18% of the women. This supports the use of repeat urethrolysis in the presence of initial failure or in cases in which the aggressiveness of the initial dissection is unknown. After an aggressive transvaginal urethrolysis, a retropubic urethrolysis may be considered (Scarpero et al, 2003).

Refractory storage symptoms after a urethrolysis are a challenging problem to treat. Overactive bladder symptoms are refractory in more than 50%, affecting patient satisfaction and quality of life. There are no predictors of outcome after urethrolysis, yet DO preoperatively may suggest an increased likelihood of refractory overactive bladder (Starkman et al, 2008b). **There are no established guidelines for management.** Twenty-five women with UUI after urogynecologic surgery (19 PVS, 3 retropubic suspension, and 3 transperitoneal vesicovaginal fistula repair; 4 required further urethrolysis) were retrospectively analyzed after sacral neuromodulation stimulation (SNS) therapy (Starkman et al, 2007). SNS was effective (80% reported > 50% improvement and 6 were continent), and there were no significant differences in response based on age, duration of symptoms, type of surgery, or urodynamic parameters. Starkman and associates (2007, 2008b) evaluated SNS in the management of 8 women who had at least one urethrolysis. Six patients had a favorable response during test stimulation and underwent implantation of a pulse generator. All 6 of the patients significantly improved, and the 2 who failed test stimulation perceived no change (Starkman et al, 2008b). In addition to antimuscarinic agents, SNS should be considered as an option for de novo or refractory urgency and UUI after urethrolysis.

Mixed Urinary Incontinence

The treatment of patients with mixed urgency and SUI is complicated and often involves a combination of anticholinergic therapy and surgery. Medical therapy for MUI is associated with significant resolution of the urgency component in only two thirds of patients (Nordling et al, 1979; Stephenson and Mundy, 1994). This therapy does not address the bladder outlet and would not be expected to achieve complete dryness. **Anti-incontinence surgery may cure or aggravate the urgency symptoms and lead to de novo urgency. This aspect of anti-incontinence surgery is unpredictable and a major cause of patient dissatisfaction.** Osman and associates (2003) evaluated outcomes of patients with stress and sensory UUI (no DO on UDS) compared with a control group of patients with pure SUI. Patients were divided between a Burch colposuspension study arm (Valsalva leak point pressure [VLPP] >90 cm H_2O) with 24 patients and a PVS study arm (VLPP < 90 cm H_2O) with 26 patients. Twelve PVS procedures and 8 Burch colposuspensions were performed among the SUI-only control subjects, using the same leak point parameters. The

Key Points: Voiding Dysfunction after a Pubovaginal Sling Procedure

- Obstruction, DO, and impaired detrusor contractility are the manifestations of voiding dysfunction from iatrogenic outlet obstruction by a PVS.
- The incidence of permanent retention is usually 5% or less (Leach et al, 1997). Persistent urgency incontinence and urgency (8% to 25%) are more common presenting symptoms in bladder outlet obstruction after a PVS than frank retention (Cross et al, 1998).
- The key to diagnosis is the temporal relationship between the anti-incontinence surgery and onset of voiding symptom. UDS is essential in these cases to diagnose and make an appropriate treatment plan.
- Transient urinary retention usually resolves within 10 days, and obstruction from a PVS may improve or resolve with time; therefore most surgical intervention is avoided until 3 months postoperatively.
- Reported success rates of surgical management of bladder outlet obstruction after a PVS procedure are 65% to 93%. There is a 0% to 19% recurrent SUI rate after urethrolysis. There are no preoperative variables that predict success or failure of urethrolysis. Overactive bladder symptoms are refractory in 50% of affected patients after urethrolysis and account for a significant portion of the reported failures.

incidence of persistent UUI was 12% among the PVS patients with MUI. Twenty percent of controls with PVS had de novo UUI. The incidence of residual urgency was not significantly higher than that of de novo urgency in those with genuine SUI. Chou and colleagues (2003) used a validated questionnaire, voiding diary, and pad testing to report outcomes of the PVS for MUI, compared with pure SUI. Among 98 patients, 46 (48.5%) had pure SUI and 52 (51.5%) had MUI (26% with DO). The cure/improved rates were 97% among the SUI group and 93% in the MUI cases ($P = .33$). Increasing episodes of urgency and UUI on preoperative voiding diary correlated directly with surgical failure, whereas voiding frequency was associated with cure. This frequent voiding may have been adapted by patients preoperatively to avoid incontinence. Stress-induced DO is unique and difficult to treat. It is thought that traction on the pelvic nerves when increased abdominal pressure is applied to weakened pelvic supportive tissue causes this form of DO (Serels et al, 2000). Records of 36 patients with Valsalva-induced DO were reviewed by Serels and associates. Seventy-five percent of patients had resolution of UUI, and 92% achieved cure. Leak point pressures did not correlate with outcome. **The presence of residual urgency is similar to de novo urgency after a PVS procedure. Increasing episodes of urgency and UUI may correlate with surgical failure. The PVS is an effective treatment option for stress-induced DO with cure rates similar to those of simple SUI.**

Fulford and colleagues (1999) were the first group to utilize videourodynamics in the assessment of how a PVS affects the urgency syndrome. Ninety-seven percent (83 of 85 women) were symptomatically cured of SUI but only 66 (78%) were satisfied with the surgical result, owing to persistence of urgency symptoms in 27. Among these 27 women, 9 (41%) had an open bladder neck at rest compared with 4 of 50 (8%) women without UUI ($P < .01$) postoperatively. The storage symptoms resolved in 69% (32 patients), almost all of whom had a closed bladder neck at rest. Yet the postoperative urgency symptoms were not significantly associated with any preoperative clinical or urodynamic variables. Schrepferman and associates (2000) attempted to predict urinary urgency resolution after a PVS procedure with preoperative videourodynamics. Seventy women with MUI were divided into two groups of sensory urgency (one or more episodes of subjective symptoms without DO) and motor urgency (one or more episodes of subjective urgency symptoms correlating with DO). DO was documented in 41 patients. They concluded that there was a significantly greater resolution of urinary urgency symptoms in those with low-pressure motor urgency than high-pressure motor urgency or sensory urgency. Overall, urgency resolution rate in patients with MUI was 51% in this study (Schrepferman et al, 2000). Stoffel and colleagues (2008) found no difference in preoperative videourodynamics between women with MUI and urodynamic DO and those without DO. MUI patients with DO had less improvement in UDI-6 scores than MUI patients without DO, despite similar reduction in pad use/day. **The presence of preoperative DO on UDS may relate to decreased quality of life and decreased urgency resolution rates after a PVS procedure. There are no data on consistent videourodynamic parameters that relate to outcomes of MUI after a PVS.**

Key Points: Pubovaginal Sling for Mixed Urinary Incontinence

- Treatment of these patients is complicated and involves a combination of anticholinergic therapy and surgery.
- The PVS is an effective treatment option for stress-induced DO with cure rates similar to those of PVS done for SUI only.
- The presence of preoperative DO may relate to decreased quality of life and decreased urgency resolution rates after a PVS procedure.
- There is no preoperative variable relating to outcomes of MUI after a PVS procedure.

Nonurologic Complications

Beyond discussion of voiding dysfunction and erosions after PVS placement, the AUA Female Stress Urinary Incontinence Clinical Guidelines Panel (1997) reported on surgical management of female SUI, which included summary data of published outcomes data on complications (Table 73-8). Although an extensive literature review was performed there was insufficient information to estimate the following complications: large bowel injury, peripheral nerve injury, and vascular injury. The literature available for UTI had variable definitions and bias. Due to death being a rare complication, the panel estimated a death rate of approximately 5 per 10,000 procedures, combining all SUI procedures (retropubic suspension, transvaginal suspensions, anterior repairs, and PVS surgeries).

Anger and associates (2007a) analyzed Medicare claims data and determined short-term complications after sling surgery among female beneficiaries aged 65 years and older. A total of 1356 sling procedures were performed between 1999 and 2001. In 3 months after the procedure, 12.5% women developed surgical or urologic complications and 33.6% were diagnosed with UTIs. At 1 year after the operation the following nonurologic complications were

Table 73–8.

American Urological Association Female Stress Urinary Incontinence Clinical Guidelines Panel Complication Summary

COMPLICATION	%
Postoperative urgency	
For patients with urgency and DO preoperatively	46 (24-68)
For patients with urgency and no DO preoperatively	34 (13-61)
For patients with no urgency but with DO preoperatively	20 (5-45)
For patients with no urgency and no DO preoperatively	7 (3-11)
Retention	
Longer than 4 weeks	8 (6-11)
Permanent	<5
Transfusion	4 (2-7)
General medical complications (significant/nonsignificant)	4 (2-5)/6 (3-10)
Subjective complications	6 (2-13)
Complications requiring surgery	3 (2-5)

DO, detrusor overactivity.

reported: bowel injury or obstruction (6.6%), cardiac (9.1%), thromboembolic (2.6%), pulmonary (15.3%), and other (22.1%). Multivariate analysis revealed that race, age, and comorbidity did significantly impact on both urologic and nonurologic complications. Nonwhite subjects were more likely to experience urologic and nonurologic postoperative complications. Women 65 to 69 years were significantly less likely to experience nonurologic complications or undergo treatment for outlet obstruction or re-treatment for incontinence than women older than 75 years.

MIDURETHRAL SLINGS

Since the inception of the PVS approximately a century ago, experimentation has continued with multiple types of slings composed of different materials using different suspension techniques. Materials used as sling constituents have included autografts, allografts, xenografts, and, more recently, synthetic variants. Methods of anchoring these slings have also undergone development and advancement; however, the ideal method of suspension remains to be completely defined. **Sling placement was classically described at the level of the bladder neck in an effort to correct urethral hypermobility and enhance pressure transmission invoked by intra-abdominal straining.**

However, competing theories arose initially as espoused by Zaccharin in the 1960s and DeLancey in the 1990s (Zaccharin, 1968; DeLancey, 1994). In these theories the importance of the pubourethral ligaments and their function in maintaining the integrity of urinary control **furthered the concept of the importance of the midurethral mechanism for preservation of urinary incontinence under stress circumstances. These findings further demonstrate the fact that hypermobility is a secondary finding noted in association with incontinence but not causative of the condition of effort-related urinary loss (SUI).** Studies performed by Asmussen and Ulmsten (1983) demonstrated the importance of the distal components of the urethra for preserving urethral closure during stress events. They demonstrated that **MUCP occurs at the level of the midurethra and this closure mechanism is associated with intrinsic urethral function in continent women.** Ingelman-Sundberg (1953) noted that the pubococcygeal muscles also played a role in the midurethral mechanism, inserting at the level of the midurethra just outside the vaginal epithelial wall, and propounded this anatomic finding as being important when considering methods to correct urinary incontinence. Westby and colleagues (1982) demonstrated that in continent women, midurethral closure is associated with the area of MUCPs on pressure evaluation of the urethra and considered this phenomenon to be due to the confluence of anatomic structures in that area.

Petros and Ulmsten (1993), **using these theories, proposed a unifying concept now known as the midurethra theory (previously the integral theory). They postulated that injury arising from surgery, parturition, aging, or hormonal deprivation led to weakening or damage of the pubourethral ligaments, impairing midurethral function and anterior urethral wall support, thus resulting in urinary incontinence. They theorized that this damage was not only a ligamentous injury but also a representation of weakening of the pubococcygeal muscles at the level of the midurethra.** It has been shown that weakness of soft tissue in this area and specifically connective tissue can contribute to urinary incontinence (Ulmsten et al, 1987). Ultrasound techniques provide greater understanding of the vesicourethral dynamics by giving a detailed view of the exact anatomic location of the midurethral sling. Lo and associates (2003) conducted early ultrasound studies to describe dynamic urethral kinking (or rotational urethral descent) as the morphologic feature (92% of the time) contributing to continence after a TVT procedure. Preoperative real-time imaging demonstrates the motion of anterior and posterior urethral walls in the same axis and vector, regardless of the urethral descent. Midurethral tape binding impedes the movement of the posterior urethra above the tape, directing its motion away from an inferior course in an anteroinferior or anterior direction. Inward movement of the posterior urethral wall results in urethral narrowing. Width, position, and appearance of slings on ultrasonography are similar: a V at rest, round angulation on Valsalva maneuver, and closed angulation at maximum retaining. It is closer angulation during a Valsalva maneuver that may be associated with postoperative voiding dysfunction (Dietz and Wilson, 2004; Masata et al, 2006; Chene et al, 2008; Kociszewski et al, 2008).

The Tension-Free Vaginal Tape Procedure

The TVT procedure was developed using the concepts of the integral theory. The provisions of this operation include **a minimally invasive approach, which would supplement the diminished midurethral mechanism and produce the ingrowth of new host tissues after implantation for purposes of further supplementing support introduced by the procedure.** As initially described, the procedure was performed with the patient under local anesthesia to allow ambulatory delivery of the intervention and enable intraoperative testing of the urethral compression.

Initially, several types of material were evaluated until the final material was chosen, **a synthetic polypropylene monofilament mesh with pore size under 150 μm. Also, this material allowed optimal migration of host inflammatory components (leukocytes and macrophages) into the**

mesh for purposes of infectious surveillance and host wound healing (imbibition and inosculation). It was found that this material was optimal for inciting fibrous tissue ingrowth. This type of mesh is known as a type 1 mesh and has previously been described in the general surgical literature as being favorable from the standpoints of its mechanical properties (stretch and elasticity) (Dietz et al, 2001, 2003). Efforts have been made to standardize the procedure by incorporating certain technical approaches and safety features for purposes of avoiding injury to surrounding structures. To date, more than 400,000 of these procedures have been performed worldwide.

The Procedure

The device consists of two specially curved 5-mm-diameter insertion needles that are attached to a 40-cm segment of polypropylene tape that is 11 mm wide. The tape is covered with a clear plastic sheath, which protects the tape from contamination and allows easy passage through host tissues. A rigid catheter guide is placed in the bladder with an 18-Fr Foley catheter to help deflect the bladder away from the locale of needle path insertion. An ergonomic handle is attached to the insertion needles for actual placement of the needles during the procedure. This handle is reusable and sterilizable.

The midurethra sling procedure (transvaginal tape) is performed with the patient in the dorsal lithotomy position with a significant degree of flexion (70 degrees or more) of the thighs. The patient has received parenteral sedation and then local anesthetics are placed in the region of insertion of the device (vaginal wall and retropubic space). Approximately 5 mL of local anesthetic is injected into the vaginal area as well as into the planned suprapubic insertion skin sites. For placement of retropubic local anesthesia, another 20 mL of local anesthetic agent is injected into the area along the posterior aspect of the pubic bone to the level of the urogenital diaphragm. Additional vaginal infiltration includes approximately 10 mL injected on either side of the urethra to the level of the urogenital diaphragm.

After appropriate anesthesia, two small suprapubic stab incisions are created just above the level of the symphysis pubis, approximately 2 cm lateral to the midline. A third midline vaginal incision approximately 1.5 cm wide is created approximately 1.5 cm from the external meatus of the urethra, between that structure and the bladder neck. After the vaginal incision is created, minimal dissection is performed using Metzenbaum scissors under the vaginal flaps on either side to elevate the vaginal epithelium from the underlying periurethral tissue to the level of the pubocervical fascia, which is not perforated. The TVT needle is then placed in the dissection tunnel immediately beneath the vaginal epithelium on one side of the urethra with the needle tip situated in close proximity to the lower rim of the pubic ramus. With the use of controlled pressure, the needle is elevated through the endopelvic fascia, into the space of Retzius, through the rectus muscles, and through the previously created suprapubic skin incision. During this maneuver the needle is kept in close contact with the intrapelvic surface of the pubic bone to avoid perforation of the lower urinary tract and also to avoid intraperitoneal entry. Tactile contact ensures direct apposition of metal to bone, as does slow graded pressure during needle advancement.

Simultaneous deflection of the lower urinary tract is accomplished during insertion using the catheter guide and catheter with the pelvic viscera deflected away from the side of needle insertion. The same maneuver is performed contralaterally so that each needle exits through the appropriate skin incision. Cystoscopy is performed to exclude needle penetration of the lower urinary tract. The use of a 70-degree lens is essential, as is complete distention of the bladder with irrigant to exclude subtle tangential injury. If perforation is noted, the needle is withdrawn and passed once more in the same area in an effort to avoid further perforation. Once cystoscopy has demonstrated no evidence of bladder injury, the tape is brought through the incisions and tension adjustment of the tape is performed. Tension adjustment is most commonly performed by inserting either a surgical instrument (clamp) or a metallic sound between the tape and urethra while the covering plastic sheath is removed from the field. The tape is set to tension such that with the bladder full to 300 mL of saline and the patient now aroused and asked to cough, no incontinence occurs during the stress maneuver. Redundant tape is then excised at the level of the suprapubic skin incisions, and all incisions are closed (Fig. 73–8).

The procedure may also be performed with the use of regional or general anesthesia according to the surgeon's preference. Outcome data support the incorporation of midurethral sling techniques with concomitant vaginal prolapse repairs.

Results

In reviewing the extensive results reporting for the midurethral sling, several caveats must be entertained. Outcomes are reported in varying fashions using different tools, lengths of follow-up, and overall definitions of success and failure. These factors should be kept in mind when attempting to cross-compare different groups and procedural nuances.

Initial results with the midurethral sling technique approximated 80% (author-defined) success rates (Ulmsten et al, 1996). A subsequent prospective multicenter trial that included 130 women with genuine SUI who were observed for 1 year revealed success rates of 91% (Ulmsten et al, 1998). Seven percent were considered improved, and only 2% were deemed failures. Complication rates were low, including one bladder perforation and one wound infection. Voiding dysfunction was also relatively low, with 1 patient experiencing retention for 12 days, which resolved spontaneously, and 3 patients with less than 3 days of voiding dysfunction (regarding catheterization), which the authors defined as a short-term voiding problem.

On the basis of these findings, further studies were then embarked upon. Nilsson and Kuuva (2001) evaluated 161 consecutive TVT operations in cases of which 28% had failed prior incontinence surgery, 11% had ISD, and 37% had MUI. At 16 months mean follow-up, the overall objective cure rate was 87%, with 7% significantly improved and another 5% considered failures. Bladder injury rate at the time of insertion was 3.7%, and 4.3% of women experienced short-term de novo voiding dysfunction. Urgency symptoms arising after surgery occurred in 3% of women, yet 80% of the women who had preoperative urgency symptoms had relief of those symptoms at their 16-month visit. No serious complications were noted.

Long-term results mirror the short-term experience with this procedure. Success rates ranging from 81% to 90% have been reported at more than 3 years. Ulmsten and associates (1999) reported an 86% success rate in 50 women at 3 years. Olsson and Kroon (1999) reported 90% success in 51 women at 3 years. Doo and colleagues (2006) evaluated long-term efficacy and safety of this procedure among 134 Korean women. The overall 5-year success rate was 94.9%, with an 86.6% patient satisfaction rate. Although success rates between 1 and 5 years were similar (97.7% and 94.9%), the cure rate decreased from 90.1% to 76.9%. Nilsson and coworkers reported success rates of 84.7% at 5 years (Nilsson

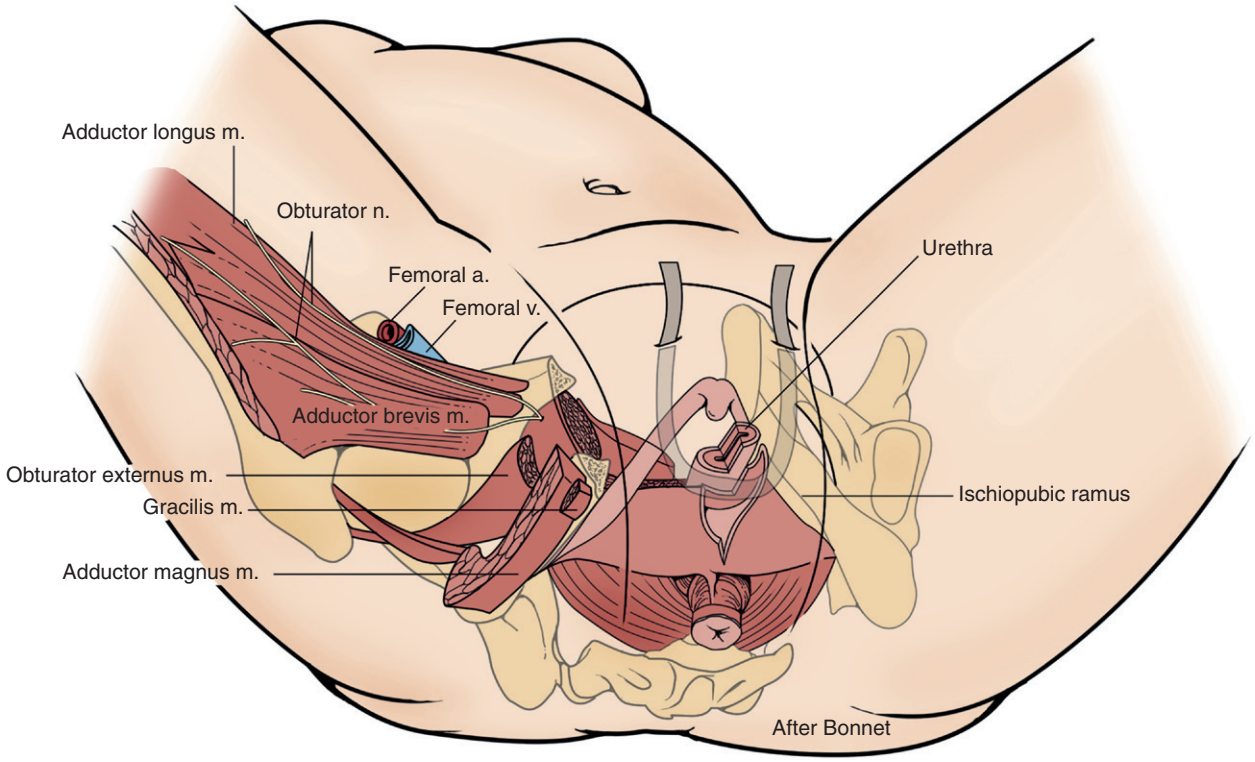


Figure 73–8. Midurethral sling as placed by the suprapubic approach (any technique).

et al, 2001) and 81.3% at 7 years (Nilsson et al, 2004) in a consistent cohort of 90 women. Liapis and colleagues (2008) prospectively assessed the efficacy of the TVT in 65 women: at 5-year follow-up the objective cure rate was 53% and failure rate was 9.4%, whereas at 7-year follow-up the objective cure rate was 80% and the failure rate 13.5%. Song and associates (2009) reported on the second longest follow-up (≥7 years) in 306 women with a cure rate of 84.6%; they reported on 6 patients who had complications from mesh exposure. As a continuation of their earlier work, Nilsson and coworkers (2008) provide the longest (11 years) prospective observational cohort study of 90 women with primary SUI. Ninety percent of these women were objectively cured, and 77% reported subjective cure. No late onset adverse effects or cases of tape erosion were seen. The Austrian Urogynecology Working Group published their data compiled within the Austrian central registry beginning in 1998 (Table 73–9). There were no serious complications and no mortality within the registry; 363 (45%) of those in the registry had a TVT in combination with other procedures (Tamussino et al, 2001). These long-term studies have all attempted to evaluate risk factors for declining effectiveness. **There does appear to be a tendency for higher failure rates to be associated with advancing age at the time of procedure and also with diminished urethral function (ISD).**

Twelve randomized clinical trials have compared the TVT with traditional incontinence procedures in published peer-reviewed journals. This includes five that compared TVT with open colposuspension (Ward and Hilton, 2002, 2004, 2008; Bai et al, 2005; El-Barky et al, 2005), four comparing TVT with laparoscopic colposuspension (Persson et al, 2002; Ustun et al, 2003; Paraiso et al, 2004; Valpas et al, 2004), two comparing TVT with a fascial sling (Bai et al, 2005; Wadie et al, 2005), and one that compared TVT with no treatment (Campeau et al, 2007) (Table 73–10).

Table 73–9.

Austrian Tension-Free Tape (TVT) Central Registry Database

	TVT IN COMBINATION (%) (n = 363)	TVT ALONE (%) (n = 443)	OVERALL (n = 806)
Operating time (min)	85 (20-390)	30 (10-120)	
Anesthesisa			
Local	15 (4%)	189 (46%)	204 (27%)
Regional	215 (60%)	189 (43%)	404 (5%)
General	132 (36%)	57 (13%)	189 (23%)
Bladder drainage			
Intermittent	24 (8%)	65 (20%)	89 (12%)
Urethral Foley	225 (62%)	306 (69%)	531 (68%)
Suprapubic	109 (30%)	49 (11%)	158 (20%)
Intraoperative complications			
None	332 (91%)	399 (91%)	731 (92%)
Bleeding	8 (2%)	11 (2%)	19 (2%)
Bladder perforation	15 (4%)	20 (4%)	35 (4%)
Postoperative stay (days)	7 (2-13)	4 (0-37)	6 (0-37)

From Tamussino K, Hanzal E, Kolle D, et al. The Austrian Tension-Free Vaginal Tape Registry. Int Urogynecol 2001;Suppl. 2:S28–9.

Among the TVT versus Burch comparisons, the trials by Ward and Hilton (2002, 2004, 2008) and Valpas and associates (2004) enrolled the greatest number of patients. The United Kingdom/Ireland cooperative group compared TVT with open colposuspension published data at short (Ward and Hilton, 2002), intermediate (Ward and Hilton, 2004), and long-term (Ward and Hilton, 2008) follow-up. At 6-month follow-up, 344 women were

Table 73–10.

Comparison of Cure Rates between the Tension-Free Vaginal Tape (TVT) and Traditional Incontinence Management

STUDY	NO. PATIENTS	FOLLOW-UP	CURE RATES
Ward and Hilton, 2002	175 TVT 169 Burch	6 mo	66% TVT 57% Burch
Ward and Hilton, 2004	175 TVT 169 Burch	24 mo	63% TVT 51% Burch
Ward and Hilton, 2008	175 TVT 169 Burch	5 yr	75% TVT 69% Burch
El-Barky et al, 2005	25 TVT 25 Burch	6 mo	92% cured or improved TVT 88% cured or improved Burch
Bai et al, 2005	31 TVT 33 Burch 28 PVS	12 mo	87% TVT 87.8% Burch 92.8% PVS
Wadie et al, 2005	28 TVT/ 25 PVS	6 mo	92.9% TVT 92% PVS
Persson et al, 2002	37 TVT/ 31 lap colposuspension	12 mo	94% TVT 100% laparoscopic colposuspension
Ustun et al, 2003	23 TVT/ 23 lap colposuspension	24 mo	82.6% TVT 82.6% lap colposuspension
Paraiso et al, 2004	36 TVT/ 36 lap colposuspension	18 mo	97% TVT 81% laparoscopic colposuspension
Valpas et al, 2004	70 TVT/ 51 lap colposuspension	18 mo	86% TVT 57% laparoscopic colposuspension

PVS, pubovaginal sling.

randomized to TVT and Burch colposuspension study arms, with no significant difference in cure rates. Surgery with TVT was associated with more operative complications (i.e., bladder injury), yet colposuspension was associated with more postoperative complications and longer recovery (Ward and Hilton, 2002). At 2-year follow-up, 175 and 169 women were randomized to TVT and Burch colposuspension, respectively. A variety of outcome measures, including subjective and objective measures, were utilized. Overall cure rates noted in the study were lower than other reported cure rates, with 63% of TVT patients and 51% of colposuspension patients being cured. This is likely due to their strict definition of cure (1-hour pad test with change in weight <1 g) and failures including both dropouts and those lost to follow-up. There were significantly more patients in the colposuspension group needing intermittent self-catheterization (<0.0045) and surgery for pelvic organ prolapse (<0.0042) than in the TVT group (Ward and Hilton, 2004). At long-term follow-up (5 years) there were no difference in cure rates. Consistent with earlier studies, prolapse was seen more commonly in the Burch colposuspension group. Two tape extrusions (only one symptomatic) were found in the TVT group. Unlike reports of 27% de novo urgency and UUI in the literature (Jarvis, 1994) after colposuspension, this group reported less than 2% after TVT and less than 5% after colposuspension (Ward and Hilton, 2008). Ward and Hilton (2002) and El-Barky and colleagues (2005) found operation time, hospital stay, and time until return to normal activity significantly shorter in the TVT group. El-Barky and colleagues (2005) reported two bladder perforations in the TVT group (<0.05), whereas wound infections (<0.05) were more common among the Burch colposuspension patients. Bai and associates (2005) compared TVT with open colposuspension and fascial sling: at 3- and 6-month follow-up there were no differences in cure rates between the operations, but at 12 months the patients with a PVS had significantly higher cure rates (92.8%) than those who had the colposuspension (87.8%) or the TVT procedure (87.0%). Wadie and associates (2005) found PVS and TVT procedures to be equally effective. The TVT procedure is cost effective and superior in terms of impact on health care spending compared with open colposuspension (Manca et al, 2003).

Four randomized trials (Persson et al, 2002; Ustun et al, 2003; Paraiso et al, 2004; Valpas et al, 2004) have been performed comparing TVT with laparoscopic colposuspension. Valpas and associates (2004) and Persson and coworkers (2002) reported results at 12 months, and Paraiso and colleagues (2004) reported outcomes at 18 months. The results of the laparoscopic comparator trials revealed TVT cure rates in the range of 86% to 97%, with colposuspension rates ranging from 57% to 100%, depending on the reporting method. There was no apparent difference between procedures in the Persson and coworkers' trial, but Paraiso and colleagues and Valpas and associates noted significant differences in success in the two study groups. These trials noted no other apparent differences between techniques other than that the TVT group recovered more rapidly and had a lower need for subsequent urogenital prolapse procedures than the colposuspension group. Dean and colleagues (2006) reviewed seven randomized trials comparing TVT and laparoscopic colposuspension and found no statistically significant difference in reported subjective cure rates within 18 months. Yet the overall objective cure rate was significantly higher for TVT. Novara and colleagues (2008) performed a meta-analysis of 33 randomized controlled trials comparing tension-free midurethral slings with other anti-incontinence procedures. Complications were similar between TVT and Burch colposuspension, with the exception of bladder perforation (higher in TVT group) and reoperation rate (higher in the Burch colposuspension study arm). TVT and PVS procedures were found to be equally effective, with better cure rates than the Burch colposuspension (Novara et al, 2008).

Because of the success of the TVT operation, several modifications to the retropubic procedure and use of different tape materials arose. These retropubic modifications have not been evaluated

extensively. Only seven randomized studies exist comparing the TVT with different retropubic slings. Three trials compared the TVT with the suprapubic arc sling (SPARC), a polypropylene tape material approaching the midurethra from the abdominal incision (Tseng et al, 2005; Andonian et al, 2005; Lord et al, 2006). Tseng and associates (2005) found the TVT and SPARC to be equally effective. The SPARC group had a greater (12.9%) number of bladder perforations than the TVT group (0%). This was not statistically significant, but the authors believed it was clinically significant. Andonian and associates (2005) randomized 84 patients to either study arm and found no statistically significant difference between SPARC and TVT, in terms of objective cure rates at 12-month follow-up. Tape erosion, infected pelvic hematoma, and UTI were only found postoperatively in the SPARC group, yet there were no differences in other perioperative complications (bladder perforation, blood loss, hospital stay, urinary retention, postoperative analgesia). Lord and colleagues (2006) found the TVT group to have a lower rate of vaginal erosion (4.8% vs. 10.5%) and a statistically significantly higher subjective cure rate (87.1% vs. 76.5%) than the SPARC group. The SPARC was found to be more difficult to adjust correctly, and a statistically significant number of patients required loosening of the tape (P =.002). Campeau and colleagues (2007) compared elderly women who either had a TVT or had to wait 6 months for surgery, using quality of life questionnaires. The women who had the TVT procedure had a significantly higher quality of life (P < .0001), yet 22.6% experienced bladder perforation and 12.9% had urinary retention.

Arunkalaivanan and Barrington (2003) compared the TVT procedure with the use of allogenic acellular porcine collagen (Pelvicol) in a questionnaire-based study. They reported on both 12-month and 36-month results and found no difference in subjective cure rates. TVT was compared in three studies to the intravaginal sling (IVS), a multifilament, miniporous polypropylene tape material produced by Tyco that is passed similar to a SPARC. Rechberger and associates (2009) reported no differences in cure rates at 13-month follow-up of 50 patients per group. Complications were similar with the exception of postoperative acute urinary retention occurring significantly more commonly among the patients having the TVT procedure. Meschia and colleagues (2006) compared the TVT and IVS with intermediate follow-up and reported subjective cure rates of 80% (TVT) and 78% (IVS) and objective cure rates of 85% (TVT) and 72% (IVS). Eight (9%) of the IVS patients experienced vaginal erosion, with none found in the TVT group. The TVT was compared with the IVS and SPARC by Lim and associates (2005) in the SUSPEND trial. There was no significant difference between the cure rates: 87.9% (TVT) versus 81.5% (IVS) and 71.4% (SPARC). There was a significantly greater rate of tape extrusion in the SPARC group. Balakrishnan and coworkers (2007) followed a subgroup of IVS patients from the Lim and associates' (2005) group up to 30 months and found 13% with sling erosions, requiring removal of the sling. Of the 29 patients (47%) from this initial IVS group seen 12 to 34 months postoperatively, 24% experienced sling erosion with associated sinus formation, requiring sling removal. In Novara and colleagues' (2007) meta-analysis the TVT was found to be more efficacious than the IVS and SPARC.

Special Groups of Patients

Elderly. Although there is a large body of literature that demonstrates the efficacy and low morbidity associated with midurethral slings for SUI **there are few data evaluating the effect of advanced age on outcomes.** Aging affects the lower urinary tract both anatomically and functionally. The aging lower urinary tract has a higher rate of DO, UUI, and ISD. Emptying abnormalities related to impaired contractility are also more common in elderly persons. Older women are more likely to have had prior procedures for incontinence and therefore may have higher rates of urethral fixation. More severe vaginal atrophy related to long-standing lack of salubrious estrogen support of the vaginal tissues in the older woman could pose a greater risk of poor healing and erosion after vaginal incontinence surgery. Older patients are generally considered poorer surgical candidates because of medical comorbidities that could complicate the surgery, the surgical outcome, or the postoperative course. Prior studies and prevailing attitudes maintain that retropubic suspensions and vaginal procedures for SUI in elderly patients have variable rates of success (Gillon and Stanton, 1984; Schmidbauer et al, 1986; Couillard et al, 1994; Chilaka et al, 2002).

Few studies of relatively small numbers of patients examine the safety and efficacy of midurethral slings in older women. In all these studies, "old" is defined as 70 years of age and older. The most robust of the studies is a prospective comparison of 460 consecutive women who underwent TVT surgery (Gordon et al, 2005); 157 (34%) were elderly, and all women underwent UDS preoperatively and 3 months postoperatively. Outcome measures were compared between elderly and younger patients with follow-up of at least 12 months, and mean follow-up was 26 months. Preoperatively, a statistically significant greater prevalence of MUI was noted in the older (31%) versus younger (23%) patients. Concomitant pelvic organ prolapse surgery was undertaken in 84% of older patients and 67% of younger patients. The main outcome measures evaluated were perioperative morbidity, postoperative SUI, persistent or de novo UUI, and voiding dysfunction. Intraoperative complications were infrequent. The rates of blood loss were equal, and there were significantly fewer bladder perforations in the elderly patients. The incidence of postoperative fever, UTI, wound infection, and hematoma formation was similar in the two groups. Older patients did experience some age-related morbidities such as pulmonary embolism (2 patients), cardiac arrhythmia (2 patients), deep vein thrombosis (1 patient), and pneumonia (1 patient), whereas of the younger patients only 1 had a cardiac arrhythmia. Older women experienced no increased risk of urethral erosion or vaginal extrusion. The rates of postoperative voiding dysfunction necessitating catheterization for more than 1 week were low and similar between groups. Only 1 patient, an older woman, required urethrolysis. Rates of persistent SUI were uniformly low and no higher in the older women. Rates of UUI were similar between groups, but the **rate of de novo UUI was greater to a statistically significant degree in the older patients** (18% vs. 4%).

A similar rate of postoperative de novo urgency in elderly women undergoing TVT was documented in a smaller study of 76 women (Sevestre et al, 2003). One strength of this study is that a description of the degree of urethral hypermobility is given. Of these women, 53% had urethral hypermobility defined by a Q-tip test greater than 30 degrees, 28.9% had undergone prior incontinence procedures, and 4 (5.2%) showed UDS evidence of DO. At a mean follow-up of 24.6 months, 67% of the patients were cured, as determined by questionnaire and examination. Ten (13.7%) had persistent SUI, and all of these had negative Q-tip tests preoperatively; and 14 (18.4%) had UUI. Satisfaction with the procedure was 82%, and rates of dissatisfaction were higher in those with de novo UUI. For the older women with a negative Q-tip test, the cure rate was 71%, compared with 100% in women with a positive test. The rate of immediate urinary retention was 26.3%,

but only 1 patient had urinary retention for more than 1 week. One case of bladder perforation and one case of vaginal erosion were reported. Liapis and associates (2006) similarly correlated the degree of urethral hypermobility and outcomes after a TVT procedure among women aged 65 to 85 years. An overall cure rate of 76% was reported, with positive correlation to bladder neck mobility. Of patients in whom the angle of displacement on the Q-tip test was less than 30 degrees, 42% became continent, whereas 90% were continent among those with an angle greater than 30 degrees. Among those in whom the angle was less than 10 degrees, 80% remained incontinent.

The success rates and complications after colposuspension and TVT procedure were compared between women older than age 70 years and younger women (Pugsley et al, 2005). The cure rates were similar between the age groups. There was an increased incidence of UTI among the elderly women with Burch colposuspensions and the TVT patients. After the Burch colposuspension, women older than age 70 required more long-term self-catheterization. Among the elderly group with the TVT procedure, postoperative UDS was required more often for voiding dysfunction and eventual need for sling lysis was higher. Touloupidis and coworkers (2007) reported a cure rate of 96% among women with mean age 72.3 years; however, these authors were concerned by the rate of bladder perforation (5.8%) and de novo urgency (9.8%).

Overall, **cure rates at least in older women with urethral hypermobility are comparable to those in younger women.** Complication rates vary, with some studies citing a higher rate of age-related morbidities but no apparent increase in intraoperative complications. Jha and colleagues (2009) evaluated factors influencing outcome with the TVT procedure and found that age did not impact significantly on outcomes for SUI reduction or improvement in quality of life. **Postoperative voiding dysfunction or increased de novo urgency does seem to be a complication of greater incidence and significant impact in older women.** Postoperative urgency symptoms in as many as 60% of women older than 70 years have been reported (Allahdin et al, 2004), and 44% developed the symptom de novo. Bafghi and associates (2005) noted cure rates among patients younger than 70 years of 97.5% versus 78.5% among patients older than 70 years ($P = .001$). The satisfaction among the younger group was also higher, 92.6% and 66.7%, respectively. This difference was attributed to higher rates of de novo and persistent UUI in those older than age 75 years.

A sensation of impaired emptying postoperatively has also been reported (Sevestre et al, 2003). Furthermore, one study documented a 4-fold increase in the need for repeated UDS in older women after TVT surgery and an approximately 30-fold higher risk of further surgery to divide the tape.

Another important measure of the success of a TVT procedure in elderly patients is quality of life assessments. The outcome of TVT surgery was assessed prospectively in older women at a mean follow-up of 22 months by a validated health-related quality of life instrument, the King's Health Questionnaire (Walsh et al, 2004). The improvement in SUI was greater in the age group younger than 70, which is not clearly attributed to any preoperative factor. Rates of preoperative DO were 24% versus 9% in older and younger women, respectively. Older women had a history of prior surgery more often than younger women (67% vs. 28%) and lower leak point pressures, but no specific comment on their physical examination and degree of urethral hypermobility was made. Although the outcome for the TVT procedure was successful, the hospital course may be longer, as found by Walsh and colleagues (2004). The mean hospital stay in their series was 6 days, indicating that the postoperative morbidity in this age group was significant. The reasons for the longer hospital stays were not given in this study.

Hellberg and colleagues (2007) used a mailed questionnaire for 970 consecutive TVT procedures performed between 1995 and 2001 to compare outcomes between women older than 75 years and younger women at a mean follow-up of 5.7 years. The older women were significantly more often on hormone replacement therapy, had lower education, and had history of recurrent UTIs, previous vaginal repair, and previous incontinence surgery. The elderly patients more commonly had MUI and required longer hospitalization postoperative care. The unfavorable cure rates among the older women (55.7% vs. 79.7%, $P = .0001$) were due to higher failure rate for SUI, rather than for urgency symptoms.

Most recently, a multicenter, prospective randomized clinical trial was performed to compare TVT surgery versus no treatment in elderly women with SUI. Campeau and colleagues (2007) studied 69 women older than the age of 70 years who consented to be randomized to undergo immediate TVT surgery or wait for 6 months before submitting to the same surgery (control group). The main outcomes measured included the Incontinence-Quality of Life (I-QOL) Questionnaire, the Patient Satisfaction Questionnaire, and the Urinary Problems Self-Assessment Questionnaire. At 6 months after randomization the group of elderly women who underwent immediate TVT surgery had significant improvement in quality of life and patient satisfaction and fewer urinary complaints compared with the group of women waiting for the same surgery. Importantly, no age-related morbidity was observed in the immediate surgery group.

Obesity. **Whether obesity affects surgical outcome with the TVT procedure is controversial.** A few small studies have examined the safety and efficacy of TVT surgery in this population. In a prospective study of 242 women with genuine SUI, women were stratified into three groups on the basis of body mass index (BMI) (Mukherjee and Constantine, 2001). The cure rate in obese women was 90% versus 95% in women with a BMI of 25 to 29 and 85% in those with a BMI less than 25. No women experienced a wound infection, and there was no higher rate of retropubic hematoma in obese women. In addition, obese patients undergoing TVT surgery did not demonstrate a statistically significant difference in the incidence of voiding dysfunction: de novo urgency symptoms, UUI, or voiding disorders. Although few in number, studies with 6- to 12-month follow-up support equal efficacy and no difference in intraoperative or postoperative complication rate. No relation between obesity and the occurrence of bladder injury has been found (Lovatsis et al, 2003; Rafii et al, 2003). Skriapas and associates (2006) matched 31 women with BMI greater than 40 with 52 women with BMI less than 30 and reported on their 18.5 month follow-up after a TVT procedure. The continence rates among the morbidly obese group were not significantly different from those of the control group, 87% and 92% ($P = .103$), respectively. The early postoperative complications were significantly higher among the morbidly obese patients. Killingsworth and coworkers (2009) reported on 127 overweight to obese women and concluded that success rates, patient satisfaction, and complications were not significantly different with increasing BMI. Meschia and colleagues (2007) had similar findings to those of Mukherjee and Constantine (2001) and Killingsworth and coworkers (2009) with no differences in BMI of successes and failure, suggesting that the TVT procedure could be confidently used in overweight women. Muller and associates (2007) reviewed randomized and retrospective clinical trials in the

English TVT surgical literature from 1998 to 2006. Neither age older than 70 years nor morbid obesity was a risk factor for failure of the TVT procedure; however, there was an increase of de novo urgency among the elderly women and those with a BMI greater than 35.

Hellberg and colleagues (2007) conducted a questionnaire-based study, including 970 consecutive TVT procedures performed between 1995 and 2001 to compare outcomes between women with a BMI greater than 35 (n = 61) and those who had normal weight at a mean follow-up of 5.7 years. There was a sharp decline in long-term cure rates between women with a BMI less than 25 and those with a BMI greater than or equal to 35: 81.2% and 52.1%, respectively (P = .0005). The obese women were significantly older, had a higher parity, were less educated, and more often had diabetes and chronic bronchitis. The women with normal weight had higher mean postvoid residual urine volumes after surgery and required more adjustments of tape. The increased failure rate among the obese population was due to low cure rates of both stress and urgency components.

Despite the success of the TVT procedure in obese women there is a reported case of necrotizing surgical site infection after TVT placement in a 53-year-old obese woman (Connolly, 2004). Morbidly obese patients have a 44% increased risk of postoperative infectious morbidity (Forse et al, 1989). Obesity poses a greater risk for necrotizing fasciitis than diabetes in obstetric and gynecologic procedures (Gallup et al, 2002). Standard antibiotic prophylaxis and the time of surgery may need to be altered for the morbidly obese to provide adequate tissue levels, and infected tapes require complete removal. Obese women, like all women undergoing midurethral sling, should be counseled about the risk of infection.

Concomitant Pelvic Organ Prolapse. A large proportion of women with SUI have associated pelvic organ prolapse that requires concurrent treatment. Many studies have explored the outcomes of TVT with concomitant surgery. **The advantage of using a synthetic sling with concomitant surgery is that operative time is reduced sizably and blood loss from the TVT portion is usually minimal compared with autologous slings or retropubic suspensions. Some of the theoretical risks of midurethral slings with concomitant transvaginal surgery are that the increased dissection will increase exposure of the graft, leading to greater rates of infection, erosion, or vaginal extrusion, or that increased blood loss or anatomic distortion from the concomitant procedures could increase the rate of sling migration and postoperative voiding dysfunction or obstruction. These studies tend to be small and have short follow-up, but results suggest that the TVT procedure can be added to prolapse surgery with minimal morbidity.** Success rates in combined TVT and prolapse repair vary from 88% to 93% (Jomaa, 2001; Huang et al, 2003; Meltomaa et al, 2004). Even in questionnaire-based assessments 3 years after surgery the data do not show a statistical difference in the cure rate of SUI and incidence of urgency symptoms after TVT alone or in combination with other vaginal surgery (Meltomaa et al, 2004). Transient urinary retention occurred more often in patients undergoing concomitant vaginal surgery, but urethrolysis rates were low and not statistically different between groups. Interpretations of rates of postoperative urinary retention are limited by variation in the definition of retention, and therefore caution must be exercised when reviewing outcomes.

Gordon and colleagues (2005) examined TVT surgery as a prophylactic procedure for SUI in prolapse repairs. None of the patients had undergone prior incontinence surgery. With a mean follow-up of 14 months, no patient developed symptomatic SUI but 3 had a positive stress test urodynamically. Six of 9 patients with preoperative urgency had persistent symptoms, and 4 (13.3%) developed de novo urgency without evidence of obstruction. No woman had urinary retention lasting more than 2 weeks. Subsequent 5-year data from a prospective analysis of a large group of women undergoing TVT for occult SUI combined with transvaginal repair of second- or third-degree prolapse showed a low incidence of complications (Groutz et al, 2004). The authors reported that one case of bladder perforation was managed conservatively without consequence. Two patients experienced extended voiding difficulty requiring catheterization for more than 7 days, but urethrolysis was not necessary in any case. Three cases of vaginal erosion were documented. Two patients developed recurrent symptomatic SUI, and another 15 patients were found to have asymptomatic urodynamically confirmed SUI. Eight patients developed de novo UUI, and 72% of the 18 patients with preoperative UUI had postoperative persistent incontinence. Yuan and associates (2008) retrospectively reviewed results of 12 patients who underwent concurrent TVT and Prolift repair of prolapse. Thirty percent of the patients initially presenting with SUI had moderate to severe anterior prolapse. All patients had satisfactory results. The Cochrane Incontinence Group reviewed 22 randomized trials of surgical prolapse repair that included 2368 women. It was concluded that the addition of a TVT procedure to endopelvic fascial plication, Burch colposuspension, and abdominal sacrocolpopexy may reduce the incidence of postoperative SUI, but issues of cost and associated adverse effects were unclear (Maher et al, 2008).

Although **concurrent surgery does not appear to alter success of a TVT procedure,** whether concurrent surgery alters the time to efficient voiding or incidence of urinary retention has been examined separately in a retrospective study of 267 women (66% having concurrent prolapse repair) (Sokol et al, 2005). Without standard definitions of urinary retention, results are not comparable between studies. Sokol and associates (2005) noted that there was no significant difference in median days to voiding and rate of urinary retention based on prolapse repair status. Yet, increasing age, decreasing BMI, and postoperative UTI were independent predictors of time to adequate voiding. Only previous history of incontinence surgery was an independent predictor of urinary retention. No statistically significant difference in the rate of urethrolysis between TVT surgery alone and TVT with prolapse repair was found.

Unlike most other authors, Partoll (2002) claimed that urinary retention is far more common after combined procedures than with a TVT procedure alone. Results showed a 94% cure rate at 11 months and an alarming 43% rate of urinary retention after concurrent anterior or posterior repair. However, in her study, "urinary retention" was defined as not meeting the criteria for catheter removal on postoperative day 2. The expectation of voiding efficiently within 48 hours of surgery, rather than the more lenient expectations in other studies, probably accounts for the higher rate of retention found in her study. Using Medicare claims data on a 5% national random sample of female beneficiaries who underwent sling procedures, Anger reviewed 1356 cases. Of 1356 sling cases, 467 (34.4%) had concomitant prolapse repairs. Women who underwent prolapse repair at the time of the sling surgery were significantly more likely to be diagnosed with postoperative outlet obstruction (9.4% vs. 5.5%, $P < .007$) but less likely to undergo a repeat procedure for SUI or reoperation for prolapse within 1 year after sling surgery (Anger et al, 2008).

When TVT procedures are placed for only urodynamic or occult SUI at the time of prolapse repair, the risk of intervention due to obstruction is equal to the risk of intervention due to SUI when no clinical, urodynamic, or occult SUI is present and no TVT was placed (8.5% and 8.3%, respectively) (Ballert et al, 2009). Ballert and colleagues (2009) did report that the risk of intervention for SUI in patients with clinical SUI but no urodynamic or occult SUI and no midurethral sling was 30%.

TVT surgery performed with either transvaginal or laparoscopic-assisted vaginal hysterectomy and anterior/posterior colporrhaphy has been shown to have success rates similar to those in published series of a TVT procedure alone (Huang et al, 2005). Complication rates were also in accordance with other TVT surgical series, with 2% bladder perforation, 11% postoperative urgency, and 11% postoperative voiding difficulty. A study specifically looking at the complications and cure rates of TVT procedures performed with or without vaginal hysterectomy found that there was no overall difference (Darai et al, 2002). The TVT-hysterectomy group did have a trend toward more bladder perforation and lower postoperative urinary flow rates, but it was not statistically significant. Objective and subjective cures for this group were 92.5% and 75%, respectively, which was not significantly different from the TVT-alone group.

Anger and associates (2007b) evaluated the relationship between provider specialty and outcomes of sling surgery specifically related to concurrent prolapse management. Utilizing 1999 to 2000 Medicare data, they reported on 1063 slings performed by urologists and 246 by gynecologists. Urologists performed concomitant prolapse repairs in 29.1% of cases versus 55.7% among gynecologists ($P < .0001$). After a year, urologists were more likely to perform a repeat incontinence procedure (9.3% vs. 4.9%, $P = .024$) and prolapse repair (26.0% vs. 12.2%, $P < .0001$). Their findings suggest that urologists should identify and manage prolapse at the time of evaluation of urinary incontinence, to avoid the morbidity and cost of repeat surgery.

The design and methodology for the OPUS trial is presently being finalized. This will attempt to determine whether the use of a concomitant prophylactic anti-incontinence procedure may prevent development of SUI symptoms in women undergoing prolapse surgery and to evaluate the cost-effectiveness of this prophylactic approach. Ethical issues may arise because the protocol includes a sham incision in the control arm and patients may be reluctant to accept random assignment for invasive randomization (Wei et al, 2009).

Mixed Incontinence. **Evidence suggests that the TVT procedure has successful outcomes for women with MUI symptoms.** However, interpretation of these studies should be judicious because many outcomes were reported on the basis of symptoms only, with no UDS substantiation. **There are presently no randomized control trials evaluating the TVT placement for MUI symptoms.**

In a retrospective analysis of 112 consecutive women with genuine SUI and MUI the objective cure rate as measured by clinical and urodynamic examination was 89.3% at a mean follow-up of 25 months. Objective cure was defined as no evidence of SUI, a negative stress provocation test, and any urinary retention or residual volume greater than 150 mL. No difference was found in the objective cure rate between patients with genuine SUI and those with MUI. The overall subjective cure rate determined by the Contilife questionnaire was 66%. Subjective cure was lower than objective cure in both patients with genuine SUI and patients with MUI, 69.3% and 54.2%, respectively. The type of incontinence did not alter the incidence of postoperative voiding difficulty. Ten of the 24 patients with MUI had persistence of the urgency component (Jeffry et al, 2002).

Holmgren and colleagues (2005) evaluated the outcome of TVT surgery in women with SUI and MUI with mailed questionnaires 2 to 8 years postoperatively. This was a large cohort of 970 women, and the 78% response rate was remarkable. Five hundred eighty women with SUI and 112 women with UUI were eligible for analysis. However, UDS was not performed in these women preoperatively or postoperatively, and therefore categorization of their incontinence was based only on a positive stress test and a history of leakage immediately preceded by urgency. The questionnaire itself is not fully described in this article; therefore, it is not clear whether a validated instrument was used. Specific questions regarding SUI and UUI were posed, and respondents selected options including worsened, unchanged, improved, almost cured, and cured. For analysis, the women were grouped into cohorts by the number of years since they had undergone TVT surgery. The mean age of women with MUI was greater than the age of women with SUI (67 vs. 61.2), and this was a statistically significant difference. Adjustment for age was made in the analysis. In addition, women with MUI had a statistically significant higher BMI, rate of cesarean delivery, and prevalence of urinary frequency than those with SUI. More women with MUI had a history of irradiation for gynecologic malignancy. Although the numbers were small, irradiation may have had repercussions for bladder function that cannot be fully elucidated by questionnaire and could skew results. Sixty percent of women with MUI were cured up to 3 years after surgery, but outcome declined steadily thereafter. By 6 to 8 years postoperatively the cure rate in women with MUI was only 30%. Urgency and episodes of UUI increased with time after the TVT procedure. In the final analysis the lower rate of cure in the patients with MUI may be due to the other variables in this population, such as age, cesarean section, irradiation, and higher BMI. These differences in the populations confound the ability to assess outcome and highlight the limitations of this study design. Overall, despite the population variables, early outcomes of TVT surgery are good and equal in women with SUI and those with UUI. The diminishment of results over time needs to be confirmed by a prospective study (Holmgren et al, 2005).

In a similar Finnish study, 191 women who underwent TVT procedures were evaluated by examination or telephone interview for outcome at a mean follow-up of 17 months. Sixty-four (34%) of these women had preoperative stress-predominant MUI. None of the women had preoperative UDS; instead, the preoperative diagnosis was based on symptoms. Cure after the TVT surgery was judged as self-report of completely dry in any stress situation. At latest follow-up, 164 of the 187 patients were completely cured, for a cure rate of 87.7%. The cure rate in women with MUI was 69% compared with a cure rate of 97% in the women with pure SUI. This outcome difference was statistically significant. No difference in cure rate was found between women who had concomitant surgery or TVT surgery alone. Sixty percent of the women with MUI considered themselves improved from an UUI perspective as well. The lower cure rate in the MUI patients is not fully known. No description of the preoperative physical examination is given, and it is not known how many of them were among the 149 (78%) who had urethral hypermobility. The authors suggested that, on the basis of these results, preoperative UDS should be performed in women with MUI before anti-incontinence surgery (Laurikainen and Killholma, 2003).

Segal and colleagues (2004) evaluated 98 women after TVT placement explicitly to answer the question of what happens to

the UUI. The outcome of TVT surgery in women with mixed incontinence or significant SUI with associated frequency and urgency was assessed retrospectively by a variety of methods: subjectively by patients' symptoms, by the rate of anticholinergic use before and after TVT, and by before and after quality of life questionnaires. One strength of this study is that patients with concomitant surgery were excluded to minimize the confounding effect of other causes on UUI or frequency and urgency. Sixty-five women were identified as having UUI, and follow-up occurred at 3 months and 1 year. Several preoperative factors were looked at for risk of postoperative frequency, urgency, or UUI requiring anticholinergic agents. On the basis of preoperative subjective symptoms, the urgency component was found to be resolved in 63.1% after the TVT procedure. Two patients with complaints of UUI only but SUI identified on UDS had persistent UUI requiring anticholinergic drug treatment. Seventy-five patients had preoperative urinary frequency and urgency, which resolved in 57.3% after TVT surgery. Thirty (57.7%) of the 52 patients requiring anticholinergic agents preoperatively no longer needed medication after surgery. Only 4 (8.7%) patients needed anticholinergic agents for the first time after TVT surgery. Of all the variables assessed as possible risk factors for postoperative OAB requiring an anticholinergic agent, only a history of prior anti-incontinence surgery was statistically significant. Patients with prior surgery were eight times more likely to have postoperative OAB requiring anticholinergic therapy. Overall, the resolution of preoperative UUI was 63% and the resolution of preoperative urinary frequency and urgency was 57.3%. Resolution based on no longer needing anticholinergic medication postoperatively was 57.7%. TVT surgery resulted in statistically significant improvement in quality of life scores postoperatively in women with stress-predominant MUI and with SUI with urinary frequency and urgency (Segal et al, 2004).

Rezapour and Ulmsten (2001) reported their 5-year data on the efficacy and safety of TVT in women with MUI. In all of these women the urgency component was sensory, and no woman had urodynamic evidence of DO. Eighty women were evaluated, and results were reported in a retrospective fashion. All had undergone UDS preoperatively, and all were found to have SUI as well as motor detrusor contractions during filling. At follow-up, 85% were reported as cured and an additional 4% had improved symptoms on the basis of pad testing and symptom questionnaire. These investigators concluded that UDS was essential before surgery to analyze presenting symptoms. Only 1 patient had prolonged retention (6 weeks), but 8% were found to have small hematomas and 1 patient required exploration for bleeding.

Basu and Duckett (2007) reported on two case reports of women with DO and clinical SUI but no evidence of urodynamic SUI. In both cases the SUI and DO resolved with TVT placement and postoperative anticholinergic treatment. Yet, both women continued to have persistent urgency requiring prolonged anticholinergic therapy.

The short-term outcomes of TVT surgery and use of outside-in transobturator tape (TOT) and SPARC in women with MUI were reported by Paick and colleagues (2008). There was no significant difference in cure rates for SUI. Preoperative DO was an independent risk factor for treatment failure of the UUI component. Athanasiou and associates (2009) compared the efficacy of the TVT procedure and inside-out transobturator tape (TVT-O) for treatment of urinary incontinence in women with MUI and idiopathic DO. There were no subjective differences in outcome, yet women undergoing the TVT procedure were less likely to have persistent DO postoperatively.

Kulseng-Hanssen and colleagues (2008) evaluated results of TVT placement in 1113 women with MUI based on the patient's predominant bother, that is, SUI, UUI, or SUI and UUI equally. There were no differences in cure rates between the three groups. Patients with predominant SUI bother had significantly better results at 7 and 38 months than the other two groups, especially those complaining mainly of UUI. Eleven percent of women had an increase in UUI 38 months after the TVT procedure. The authors concluded that patients with predominant UUI have poorer results than those with predominant SUI. In a retrospective evaluation of long-term effects of TVT surgery on OAB and urodynamic SUI, Leron and colleagues (2009) noted 88.7% cure and 9% improvement with 62.2% improvement in OAB symptoms. There was no change in severity of symptoms in a third of the patients. De novo OAB symptoms developed in 6.2%. Using the AUA Symptom Index for measurement of outcomes, Ballert and coworkers (2008) found no difference in storage, voiding, or total score between patients with SUI and MUI or those undergoing TVT versus TVT-O placement. Sinha and associates (2008) used the Medical Epidemiology and Social Aspects of Ageing (MESA) and other outcome measures used by the British Society of Urogynaecology (BSUG) database for short-term evaluation of TVT in women with MUI. SUI and UUI were either cured or improved in 78% and 75% of women, respectively. The postoperative global impression of outcome noted great or moderate improvement in 75% of cases and reduction in mean MESA scores of 69% ($P < .001$).

Duckett and associates (2008) used perineal ultrasonography in 77 women with DO and urodynamic SUI to determine whether the position of a TVT has any effect on the resolution of irritative symptoms. They found that placement of the TVT on any part of the urethra is not more likely to resolve irritative bladder symptoms. Three studies have attempted to correlate preoperative variables with outcomes of TVT in women with MUI (Basu and Duckett, 2007; Gamble et al, 2008; Panayi et al, 2009). Duckett and Basu (2007) reported on correlation between preoperative pressure-flow studies and resolution of DO and OAB symptoms after a TVT procedure. Pressure-flow studies were compared before and after TVT surgery. Women whose $\dot{Q}max$ decreased significantly after the TVT placement were more likely to have persistent OAB symptoms. The flow rate was significantly higher in women before the TVT placement, with an objective cure of DO after TVT placement than in those with persistent DO. Basu and Duckett believed that this supported an obstructive cause in women with persistent DO. Gamble and associates (2008) found that age, nocturia, maximum capacity, and choice of sling procedure (lowest rate of DO with TVT-O, followed by TVT, SPARC, and then bladder neck sling) impacted on the persistence of DO and UUI. Panayi and coworkers (2009) found higher median preoperative opening detrusor pressure in women with DO postoperatively (33 cm H_2O vs. 26 cm H_2O, $P < .05$).

Intrinsic Sphincteric Deficiency. In most evidence sources, ISD is defined urodynamically as a leak point pressure less than 60 cm H_2O or MUCPs less than 20 cm H_2O. However, several of these articles fail to describe the patients' physical examination or reveal whether any urethral hypermobility existed. **What is clear from the current literature is that success of midurethral slings is less in the patient with a fixed urethra and that low leak point pressures seem to portend a poorer outcome, but this may be due to lack of urethral mobility in the same patient.** Rezapour and associates (2001) published a prospective 4-year follow-up study of 49 women with ISD who underwent TVT surgery. Forty-one of these women had hypermobility of the urethra; the other 8 had immobile urethras.

Postoperatively, 36 (74%) of patients were cured, 12% were improved, and 7 patients (14%) experienced failure of the procedure. None of the women with fixed urethras was cured: 3 improved and in 5 the procedure failed. Other studies support lower cure rates of TVT surgery in women with low leak point pressures when rates of urethral hypermobility are not statistically different (Paick et al, 2004). **Urethral mobility before midurethral sling procedures has been shown to be predictive of success.** The more the proximal urethra moves during Valsalva maneuvers, the better the cure rate for incontinence (Fritel et al, 2002). Leak point pressures alone have not been shown to predict outcome after a midurethral sling (Gutierrez Banos et al, 2004; Rodriguez et al, 2004); therefore, low leak point pressures are not necessarily a contraindication to TVT surgery. Leak point pressures in the era of the midurethral sling should be correlated with the patient's physical examination and used to counsel patients about their risk for a reduced chance of success.

A deficient sphincter mechanism is an important risk factor for failure of conventional anti-incontinence procedures. It is difficult to evaluate the efficacy of surgical treatment for ISD because no universally accepted definition presently exists. A few studies have been performed to assess the clinical effectiveness of the TVT procedure in women with ISD (Ghezzi et al, 2006; O'Connor et al, 2006; Sang et al, 2007; Rechberger et al, 2009). In all of these studies, patients were included with urodynamic SUI from ISD, based on a VLPP less than 60 cm H_2O. Ghezzi and coworkers (2006) prospectively studied 35 patients and noted a 93.7% cure rate at 12.5 month follow-up. Two of the 3 patients who failed the procedure were noted to have a fixed urethra preoperatively. In a retrospective study, Song and colleagues (2009) compared the treatment outcome of the TVT procedure in patients with ISD (31 patients) and non-ISD (80 patients) SUI after 1-year follow-up. Whereas at the 1-month follow-up there was significant difference in cure rates between the ISD (87%) and non-ISD patients (100%), by 1 year after surgery there was no significant difference. Rechberger and associates (2009) conducted a prospective, randomized trial with a follow-up of 18 months comparing the clinical effectiveness of retropubic and transobturator midurethral slings. Although the efficacy of both techniques was comparable, the retropubic route was more efficient in the ISD group.

Mode of Anesthesia

In the original description of the midurethral sling, anesthesia was local so that the patient would be able to perform a cough as a method of adjusting sling tension intraoperatively. It was believed that this would minimize the incidence of obstruction; however there is conflicting information in the literature regarding whether the mode of anesthesia affects the incidence of intraoperative and postoperative complication. Two studies have failed to show a difference in the efficacy or safety of the TVT procedure performed with the use of local or spinal anesthesia (Wang and Chen, 2001; Adamiak et al, 2002). In a study of 103 women who underwent TVT procedures, a comparison of local and spinal anesthesia was made; 67 women underwent the procedure with local anesthesia and 36 underwent TVT with spinal anesthesia (Adamiak et al, 2002). In the postoperative evaluation there was no difference in the success rate of the TVT surgery performed; there was also no difference in the rate of complications between the groups. There was a difference in the patients' ability to perform a cough test effectively during the procedure because of spinal anesthesia, but this did not result in an increase in the rate of postoperative obstruction. It appears that tensioning the sling by cough stress test is not necessary. Lo and colleagues (2002b) demonstrated that vigorous manual pressure against the abdominal wall and intraoperative introital ultrasonography to set tension resulted in no obstruction in 45 patients at 1 year. No comparisons of tensioning techniques have been performed to the authors' knowledge, and many different methods are used. Outcomes in women who undergo TVT surgery in combination with a prolapse repair under general or spinal anesthesia are similar to those in women who undergo TVT surgery alone.

Key Points: Tension-Free Vaginal Tape Surgical Results in Special Populations

- The literature supports the use of midurethral slings in a variety of special populations of patients.
- Efficacy and safety of the TVT procedure are not compromised in the elderly, obese, those with recurrent incontinence, or those undergoing concomitant vaginal surgery.
- A few small studies suggest that concomitant vaginal surgery places a patient at higher risk for delayed return to normal voiding and urinary retention. However, limitations in the studies prevent comparison of the data.
- It is difficult to analyze the current sling data because of the lack of standard definitions of cure and improvement and lack of standard outcome measures. Absolute conclusions about the use of the TVT procedure in special populations should not be made until larger prospective multicenter studies can be performed.

Complications

Complications associated with the TVT procedure appear to be within the acceptable range for incontinence procedures. **Quality of life is affected not only by the outcome of the incontinence surgery from the standpoint of cure or improvement but also by the appearance of voiding difficulties, UTIs, and other adverse consequences of the surgical procedure itself.** The evidence appears to suggest that a minimally invasive procedure that is standardized can decrease rates of complications. **The Finnish TVT registry demonstrates a pronounced learning curve** for surgeons adopting this new technology (Kuuva and Nilsson, 2003). This registry is unique in that all TVT procedures are recorded in this database, and therefore the data are reflective of an entire national experience with a new procedure. A second registry is currently maintained in Austria and includes more than 3000 cases but it does not involve all surgeons in the country (Tamussino et al, 2001). Overall, the rate of complications associated with the TVT procedure is relatively low. **Bladder injury in the two national registries ranges from 2.7% to 3.8%. Voiding dysfunction is reported as approximately 7.6%, and wound healing problems are less than 1%.** Other studies have also reported complication rates in smaller but still significant groups of patients (Table 73–11).

The definition of voiding dysfunction in these studies varies; however, the common definition is the need for catheterization, with short-term catheterization usually being defined as 2 days. The highest voiding dysfunction rate (19.7%) was reported by Abouassaly and colleagues (2004) at 48 hours. The highest UTI rates were reported in the Austrian National Registry (17%) (Tamussino et al, 2001). However, in this registry the infection rate may be reflective of the operative tendency to leave indwelling catheters in the majority of cases. Bodelsson and associates (2002)

Table 73–11.

Complications as Reported by Recent Large Series (Two of Which Represent National Registries)*

STUDY	NO. PATIENTS	BLADDER INJURY	BLEEDING/ DEFECT HEALING	DE NOVO URGE HEMATOMA	UTI	VOIDING DIFFICULTY	WOUND INFECTION
Abouassaly et al, 2004	241	5.8	2.5/1.9	0.4	15 NR	19.7	0.4
Karram et al, 2003	350	4.9	0.9/1.7 0.9	12.0	10	4.9	NR
Kuuva and Nilson, 2002	1455	3.8	1.9/2.4 0.7	0.2	4.1	7.6	0.8
Levin et al, 2004	313	5.1	NR/NR 1.3	8.3	NR	2.5	NR
Nilsson and Kuuva, 2001	161	3.7	1.8/1.2 NR	3.1	6.2	4.3	1.8
Tamussino et al, 2001	2795	2.7	2.3/NR NR	NR	17	NR	NR
Doo et al, 2006	134	3.7	0/0 NR	3.8	2.2	8.2	NR
Song et al, 2009	306	5.9	0.3/0 2.0	0.7	NR	1.3	NR

*Definitions of some entities vary, and voiding dysfunction specifically is defined differently between trials.
NR, not reported; UTI, urinary tract infection.

found that the risk of bladder perforation was three times higher in patients undergoing regional versus local anesthesia.

When UUI and urgency symptoms are evaluated, patients with MUI experienced cure rates of approximately 80% with resolution in patients with urgency in 50% to 80% of cases. The appearance of de novo urgency occurs in 0.2% to 15% of patients without an apparent escalation of risk over time from the initial procedure. Long-term follow-up suggests approximately 6% of patients with de novo urgency postoperatively (Nilsson et al, 2001).

Intraoperative and postoperative bleeding are also variably defined, often by estimation of volume of blood loss. **Hemorrhage, however, is relatively rare.** Hemorrhage, defined as greater than 200 mL or postoperative hematoma, occurs in approximately 2% of patients and can usually be managed by observation or local compression. Flock and colleagues (2004) reported a rate of 4.1% of 249 patients experiencing hemorrhage of 300 mL or more and requiring surgical intervention.

Although rare, vaginal, urethral, and intravesical erosion of the midurethral sling polypropylene mesh is a particularly feared complication of the technique, largely because of advances in materials science. Tape erosion has been reported in the literature with an incidence of 0.3% to 23%, and currently there is no clear consensus on the management of this particular complication. Given the extensive experience with the TVT device, the majority of reported complications have been associated with this device; however, given the similarity between the various devices, it is reasonable to assume that these results will be noted with other types of midurethral slings (Clemens et al, 2000; Volkmer et al, 2003).

The incidence of TVT erosion in the reported literature is extremely low. Many attribute this phenomenon to the macroporous characteristics of the polypropylene mesh. These characteristics allow excellent incorporation of fibroblasts, macrophages, white blood cells, collagen, and neovascular tissue within the interstices of the tape. The excellent tissue ingrowth facilitates integration of the mesh with the surrounding host tissues and decreases tape encapsulation, all of which minimize the risk of an erosion complication. **The erosion rate reported in the literature for polypropylene mesh is 0.5% to 1.3%** (Meschia et al, 2001; Kuuva and Nilsson, 2002; Karram et al, 2003; Levin et al, 2004).

Voiding dysfunction after genitourinary erosion of synthetic midurethral slings has been reported. Starkman and associates retrospectively reviewed the voiding dysfunction in 19 patients with genitourinary erosion of polypropylene mesh slings after mesh excision. They reported on a total of 11 vaginal, 7 intravesical, and 5 urethral erosions. After surgery, only 4 patients (21%) achieved complete resolution of symptoms. Persistent voiding dysfunction was present in 15 patients (79%), including persistent or de novo pelvic pain, storage symptoms, and SUI. Ten patients were incontinent after surgery (4 had SUI, 2 had UUI, and 4 had MUI) (Starkman et al, 2006).

The Austrian Urogynecology Working Group reported no serious complications and no mortality within their registry (Tamussino et al, 2001) (see Table 73–9). Two percent were noted to have intraoperative bleeding, and 4% had bladder perforation. Among those reported to have bleeding, most were treated conservatively and only 0.8% required conversion or reoperation (Kolle et al, 2005).

Terminology. **The term *erosion* implies that the mesh has either entered the lower genitourinary tract (urethra or bladder) or has penetrated through the vaginal epithelium.** The latter circumstance may better be termed *exposure* or *extrusion* (*exposure* may be preferable because the underlying causative mechanism may not be identifiable) and may arise from either mechanical or wound-related variables. The actual mechanism of erosion is still poorly understood. There are a number of theoretical possibilities, including subclinical infection, poor tissue ingrowth into the sling, disturbed wound healing, rolling or twisting of the tape, and excessive friction between host tissue and the tape. Also, iatrogenic injury and surgeon technical error should be considered as factors in the etiology of erosive complications (Kobashi and Govier, 2003a, 2003b; Domingo et al, 2005). Biomechanical properties of the sling material play a major role in the incidence of complications related to tape erosion. Although various materials have been historically utilized for sling implants there has been a trend in the contemporary literature toward the use of macroporous polypropylene slings. The increased pore size allows excellent tissue ingrowth, promotes integration with the surrounding host tissues, and decreases encapsulation and infection (Dietz et al, 2001, 2003; Slack et al, 2005). Adherence to meticulous surgical technique and utilization of polypropylene tapes with favorable biomechanical properties may help the surgeon minimize this particular complication.

Vaginal Erosion. Vaginal tape erosion or extrusion is a rare complication after the TVT procedure (Fig. 73–9). **In three large studies the incidence was reported to be 1.1%, 1.3%, and 0.5%** (Meschia et al, 2001; Levin et al, 2004; Huang et al, 2005). Most cases present within a few weeks to a few months after the

midurethral sling procedure. One case of delayed vaginal erosion at 18 months has been reported (Sharma and Oligbo, 2004). **Symptoms of vaginal erosion include vaginal discharge (with variable constituents and different amounts of blood and inflammatory components), a palpable rough surface in the vagina, sexual discomfort (including partner related), pelvic pain, inguinal discomfort, and lower urinary tract symptoms** (LUTS) (urgency, frequency, persistent incontinence, hematuria). Symptoms are often nonspecific, and therefore a high index of suspicion is required. Careful vaginal examination usually identifies an area on the anterior vaginal wall with separated epithelial edges and exposed mesh. **The management of this complication is not standardized, and there are various reports claiming successful outcomes with observation, partial tape excision, complete tape excision, and reapproximation of the vaginal mucosa over the exposed tape** (Table 73–12).

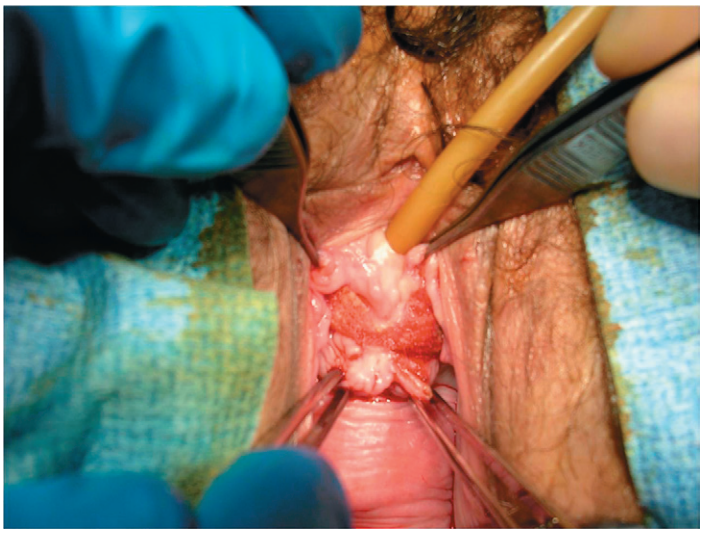


Figure 73–9. Vaginal mesh extrusion.

Historically, most authors have advocated removal of the exposed tape when a vaginal erosion occurs. Reports of conservative management in the literature are sparse. Kobashi and Govier (2003a) reported their experience managing 4 patients (3 SPARC and 1 TVT) with vaginal erosion in a conservative fashion. Two patients presented with persistent vaginal discharge and 2 were completely asymptomatic. All patients were observed with serial physical examinations, and all patients had spontaneous reepithelialization of the mesh at 3 months, which they attributed to the macroporous characteristics of the polypropylene mesh facilitating excellent tissue ingrowth. This is less likely with other synthetic materials such as GORE-TEX, polyester, and silicone, because epithelialization is not likely to occur (Leach et al, 1997; Kobashi et al, 1999).

In a review by Huang and associates (2005), six vaginal erosions and one bladder erosion after creation of polypropylene synthetic slings were initially expectantly managed. In 4 patients with vaginal mesh erosion of less than 1 cm, conservative management was initiated for a 3-month period. One of these patients was observed for 24 months without adverse sequelae. In contrast to the results seen by Kobashi and Govier (2003b), none of the patients in their series had vaginal epithelialization over the area of erosion. Therefore, all 6 patients underwent TVT excision in conjunction with excision of all fibrotic vaginal tissues. Symptoms resolved in all patients, and all patients were continent at their last follow-up. Although all patients ultimately required surgical intervention, the authors believed that a trial of conservative management in appropriately selected patients (i.e., erosion <1 cm) was reasonable; and if no epithelialization occurs at 3 months of follow-up the tape should be surgically removed. In a review of tape-related complications in a series of 200 patients, Tsivian and coworkers (2004) observed five vaginal tape erosions.

Table 73–12.

Vaginal Erosion and Management

STUDY	NO. PATIENTS	LOCATION OF EROSION	MANAGEMENT	REMOVAL	SYMPTOM RESOLUTION	CONTINENCE
Huang et al, 2005	6	6 vaginal	6 transvaginal	Partial	6 asymptomatic	6 dry
Tsivian et al, 2004	5	5 vaginal	4 vaginal; 1 observation	Partial	5 asymptomatic	4 dry; 1 dry repeat TVT
Karram et al, 2003	3	3 vaginal	1 vaginal excision; 1 vaginal advancement flap; 1 antibiotics	Partial	3 asymptomatic	2 dry; 1 SUI
Levin et al, 2004	4	4 vaginal	4 vaginal excision		NR	NR
Kuuva and Nilsson, 2002	10	10 vaginal	4 resutured; 2 tape partially removed; 3 observation; 1 unknown	Partial		10 dry
Meschia et al, 2001	2	2 vaginal	Resuture vaginal mucosa		Yes	2 dry
Volkmer et al, 2003	1	1 vaginal	Transvaginal tape excision	Partial	Yes	Recurrent SUI
Sharma and Oligbo, 2004	1	1 vaginal—delayed 18 mo	3 transvaginal tape excisions (same patient)	Partial	Yes	NA
Kobashi and Govier, 2003a	4	4 vaginal	Observation	NA	Yes	All 4 dry
Hammad et al, 2005	17	17 vaginal	Transvaginal tape excision	Partial	11 yes	NR
Starkman et al, 2006	11	11 vaginal	Transvaginal tape excision	Partial	Yes	
Giri et al, 2007	5	5 vaginal	Resuture vaginal mucosa	NA	Yes	NR
Ordorica et al, 2008	11	11 vaginal	Transvaginal tape excision	Complete	Yes	2 SUI
Lapouge et al, 2009	12	12 vaginal	Transvaginal tape excision	Partial	10 yes	4 dry
Al-Wadi et al, 2009	1	1 vaginal	Martius flap	NA	Yes	Dry

NA, not available; NR, not reported; SUI, stress urinary incontinence; TVT, tension-free vaginal tape.

Four patients required surgical excision of the exposed tape, and 1 asymptomatic patient was being observed conservatively without adverse outcomes. Four of the 5 patients were dry, and 1 with recurrent SUI was dry with repeated TVT surgery. Symptoms resolved in all patients after partial tape excision and judicious vaginal debridement. Furthermore, in a large series of 350 TVT procedures reported by Karram and colleagues (2003), three vaginal erosions were noted with 1 patient managed with local estrogen cream and antibiotics. This patient had done well without recurrence of symptoms or additional morbidity at last follow-up. In the same series, another patient underwent careful excision of the vaginal tissues with coverage of the tape with a vaginal advancement flap with satisfactory results. The third patient required partial excision of the exposed tape and redeveloped SUI. In all patients, symptoms related to the tape erosion resolved after management.

In the Finish nationwide review of 1455 TVT procedures, 10 patients were identified with vaginal polypropylene tape exposure. Three of these patients were managed without surgical intervention with good results and maintenance of continence (Kuuva and Nilsson, 2002). Four patients had the vaginal mucosa resutured over the exposed tape, and 2 patients required partial tape excision. One patient was lost to follow-up, and management was unknown at the time of their report. According to this national registry, continence was maintained in all patients, regardless of the management. Australasian data on erosions was presented by Hammad and associates (2005) that included 17 vaginal erosions. Thirty-five percent of the erosions were asymptomatic and identified by vaginal examination. Symptomatic patients complained of palpable tape and vaginal discharge, local pain, UTI, and dyspareunia. All vaginal erosions were managed with either partial or complete sling removal. Five (29%) of these patient with erosions had simultaneous anti-incontinence procedures. Data are unavailable on the other 12 patients.

Among 166 patients in whom TVT procedures performed, 5 (3%) developed vaginal extrusion between 4 and 40 months postoperatively (Giri et al, 2007). Patients complained of vaginal discharge, pain, bleeding, and dyspareunia. The eroded margin of vaginal mucosa was trimmed and closed over the tape. All of the patients were subsequently symptom free at 12-month follow-up. Ordorica and colleagues (2008) reported on 11 vaginal erosions after nonautologous sling (33 retropubic, 2 bone anchors, 3 TOT) placement. Involved sling and suture were excised. The bone anchors were unable to be removed. An autologous sling was placed in the same setting if the patient complained of SUI at presentation. Two patients had recurrent or persistent SUI, 2 had de novo urgency/frequency, and 1 developed osteitis pubis. Lapouge and colleagues (2009) described their management of 12 patients with vaginal erosions. Initially all patients were managed with partial transvaginal excision. Eight (67%) had no complaints after excision, and 50% of these were continent. Al-Wadi and associates (2009) presented a case report of a women with vaginal extrusion of mesh after a TVT procedure that was managed without excision of the exposed sling. After failure of conservative treatment, a Martius graft was used for coverage, with preservation of the exposed mesh and closure of the vagina. These authors believed that removal of sling material increased the patient's chance of recurrent incontinence. At 5-month follow-up the woman is asymptomatic and dry.

Chen and associates (2008) analyzed risk factors associated with vaginal erosion (6/239, 2.5%) after synthetic sling placement. Women with diabetes were 8.3 time more at risk of developing vaginal erosion after synthetic sling placement. The vaginal erosion-free rate during the 24-month follow-up decreased significantly in women with diabetes. There was also a 10.7% more vaginal erosion rate associated with type III multifilamentous polypropylene sling (intravaginal slingplasty) than with type I monofilament polypropylene sling (TVT and TVT-O, $P = .054$). These authors encourage counseling women with diabetes of the risk of erosion.

The sexual function of women after correction of erosion from a midurethral sling was determined using a validated questionnaire (Female Sexual Function Index [FSFI]) by Kuhn and coworkers (2009a, 2009b). Among 21 erosions, 3 healed with topical estrogen; and 18 larger defects required operative intervention. Initially, vaginal closure was attempted, but 2 patients had recurrent erosion. One patient had repeat vaginal closure, and the other had partial sling excision and vaginal closure. The results for the domains of desire, arousal, lubrication, satisfaction, and pain improved significantly. The results pertaining to orgasm remained unchanged.

Key Points: Tension-Free Vaginal Tape Procedure—Vaginal Erosion

- Conservative management seems to be a plausible option in well-selected patients who are relatively asymptomatic and have small-caliber erosions.
- Good results have also been observed in selected patients with vaginal advancement flaps and suture approximation of the debrided vaginal mucosa over the exposed tape (Meschia et al, 2001; Kuuva and Nilsson, 2002, 2003; Karram et al, 2003).
- Even with partial excision of the tape, continence is maintained in the majority of patients.
- Observation should never be considered when there is foreign body involvement of the urinary tract, as with urethral or intravesical erosion.
- Obviously, more data supporting specific management strategies are necessary before a given approach can be advocated for patients with this complication.
- The authors recommend initial judicious observation for small vaginal erosions (with use of topical estrogen cream when appropriate). Excision should be reserved for failure of conservative therapy or when local symptoms militate against observational management (i.e., bothersome dyspareunia).

Urethral Erosion. *Urethral erosion* is defined as presence of sling material within the urethral lumen (Fig. 73–10). **A review of the published literature by the AUA Stress Urinary Incontinence Clinical Guidelines Panel found 5 cases of urethral erosion after 1715 autologous fascial slings (0.003%) and 27 cases of urethral erosion after 1515 synthetic PVS procedures (0.02%)** (Leach et al, 1997). **The exact incidence of urethral erosion after the newer tension-free midurethral sling procedures is, as yet, undetermined. Factors thought to contribute to urethral erosion include compromised urethral blood supply** (i.e., radiation therapy or estrogen deficiency), **excessive sling tension, extensive dissection too close to the urethra with subsequent urethral devascularization, iatrogenic urethral injury (at time of device insertion), and traumatic catheterization/dilation. Furthermore, twisting or rolling of the tape**

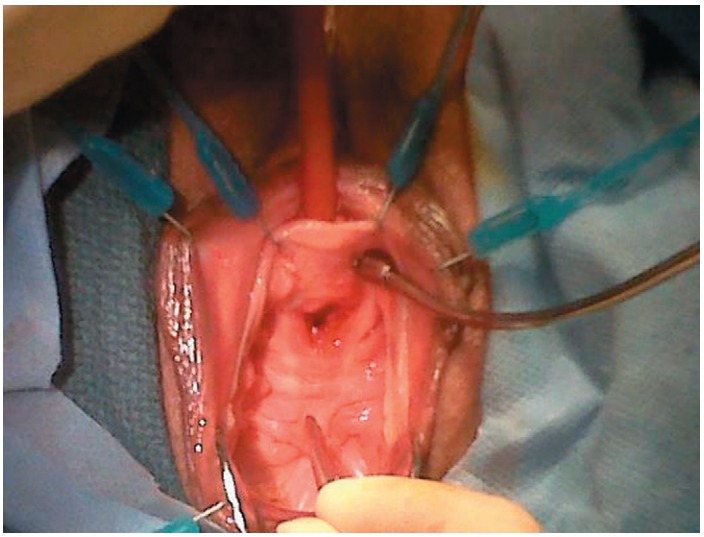


Figure 73–10. Urethral mesh erosion and urethrovaginal fistula.

can create a ridge that leads to pressure necrosis and erosion through the urethra (Dell and O'Kelley, 2005). Management of this complication is extremely challenging with the possibility of significant morbidity, because access to the tape is traditionally gained by incising the urethra, although endoscopic management has been attempted.

Presenting symptoms are varied. In almost all published cases, voiding dysfunction is predominant, with **typical symptoms including urgency, UUI, obstructive voiding, urinary retention, history of self-catheterization, urethral dilations, recurrent UTI, and persistent urinary incontinence** (Haferkamp et al, 2002; Madjar et al, 2002; Pit, 2002; Sweat et al, 2002; Lieb and Das, 2003; Vassallo et al, 2003; Glavind and Sander, 2004; McLennan, 2004; Tsivian et al, 2004; Wai et al, 2004). Diagnosis is often delayed in these patients for an extended period of time. In a review by Amundsen and associates (2003), the average time from placement of the initial PVS to diagnosis of urethral erosion was 9 months.

Diagnosis is made by confirming the presence of the tape within the urethral lumen during cystoscopy. Voiding cystourethrography has also been useful adjunctively by documenting a dilated proximal urethra related to high-grade obstruction caused by the eroded tape (Lieb and Das, 2003).

Management of urethral tape erosion has typically involved transvaginal urethrotomy and excision of the exposed tape. In selected cases an autologous fascial sling and Martius labial fat pad graft can be utilized at the discretion of the surgeon. Pit (2002) described two cases of urethral erosion. The urethra was incised, and the tape was cut at the level of the mucosa. The tape was then dissected on its medial edge toward the inferior ischiopubic ramus and cut bilaterally, which allowed the tape to be removed from the periurethral fascia. A Martius graft was placed over the urethra in one case, and a cadaveric fascia lata graft was used in the second case. A second TVT was then placed over the tissue bolsters without complication. In a review by Sweat and colleagues (2002), transvaginal tape excision was accomplished by identifying and dividing the tape in the midline, followed by sharp lateral dissection along the medial border of the tape, freeing the mesh from the urethra and bladder neck. The endopelvic fascia was perforated and the tape cut in the retropubic space. A Martius fat pad graft was interposed over the urethral closure in one case and an autologous fascial sling placed over the graft in both cases. Both patients improved symptomatically and were continent during postoperative follow-up. Glavind and coworkers (2004) reported a urethrovaginal fistula caused by urethral erosion of the polypropylene tape. Transvaginal tape excision failed to resolve the fistula, and the patient required two transabdominal fistula repairs until closure was achieved and symptom resolution occurred. Persistent SUI was managed by conservative means with satisfactory results. Sokol and Urban (2008) reported use of the internal urinary sphincter for covering the defect after sling resection. They believe this may reduce the risk of fistula formation and be a less morbid option than a Martius flap. Four other additional case reports reported excellent results utilizing a midline transvaginal approach with partial tape excision and closure of the urethra (Haferkamp et al, 2002; Madjar et al, 2002; Lieb and Das, 2003; Wai et al, 2004). The postoperative results reported by each of these investigators were excellent, with all patients achieving symptom resolution after surgical intervention. In 2 patients mild recurrent SUI was successfully managed with biofeedback (Glavind and Sander, 2004; Wai et al, 2004). In 2 patients continence was achieved by intraoperative fascial sling, and in 1 patient a postoperative fascial sling resulted in satisfactory continence (Vassallo et al, 2003; Wai et al, 2004).

Three cases without ideal outcomes utilizing transvaginal excision have been reported. Mesens and associates (2007) described a patient who had recurrence of her erosion paraurethrally 3 months after the initial transvaginal excision. Powers and colleagues (2006) describe two women who presented 1 and 3 years after TVT surgery with urethral erosion. Both patients had UUI and pain at presentation and underwent transvaginal excision. Both women had recurrence of SUI and 1 had persistence of her UUI.

In 2004, McLennan successfully managed a TVT urethral erosion endoscopically. Hysteroscopic scissors were used to transect the tape flush with the urethral mucosa. Catheter drainage was continued postoperatively for 72 hours. The patient remained symptom free and continent at 10 months of follow-up. In a case report by Wai and associates (2004), a combined endoscopic and transvaginal approach was used successfully to manage a difficult urethral erosion. Initially, the tape was cut in the midline transurethrally. Transvaginal periurethral dissection was performed, and the tape was identified and removed from the dense fibrous attachments. An accidental urethrotomy was noted and closed without difficulty. The theoretical advantage of this technique is that, with endoscopic transection of the tape, entry into the urethral lumen is unnecessary. Wijffels and coworkers (2009) utilized an endoscopic transurethral approach successfully in three cases of urethral erosion. The visible tape is grasped with forceps and cut while on traction with scissors. This is performed on both sides of the urethra. One patient had recurrent SUI and another had a TVT placed. Otherwise there were no complaints. A similar approach was used by Baracat and coworkers (2005) successfully for five urethral erosions.

Nine urethral erosions (0.6%) were reported in the Australasian data presented by Hammad and associates (2005). Thirty percent of these erosions presented more than 1 year after surgery, and 89% were symptomatic. Presenting symptoms included urinary retention, bleeding, and local pain. One case was discovered incidentally on cystoscopy. Unlike the reported vaginal erosions, 33% of the urethral erosions occurred when the polypropylene sling followed another anti-incontinence procedure. Four (44%) were managed conservatively (2 patients were too frail to undergo operative intervention). Five patients (56%) had transvaginal excision:

all were cured and dry. Velemir and colleagues (2008) presented a retrospective analysis of eight cases of urethral erosion that were managed with a combination of transvaginal and endoscopic approaches. One patient refused intervention. Two had transvaginal excision of mesh, with 1 developing recurrent SUI, although continent with Zuidex bulking injections followed by laparoscopic Burch colposuspension. One underwent a combined endoscopic and transvaginal excision of mesh but required later endoscopic removal of residual mesh; the patient was dry and asymptomatic following her second endoscopic mesh excision. Four patients were managed endoscopically. Three of the 4patients required repeat endoscopic attempts at mesh removal and urethral stone removal. Two patients had recurrent SUI and were treated with Zuidex bulking injections and a TVT-O procedure.

Key Points: Tension-Free Vaginal Tape Procedure—Urethral Erosion

- Overall, the incidence of urethral erosion is extremely low in the reported literature.
- As the number of synthetic midurethral slings continues to increase, physicians need to be aware of the potential complications, have a high index of suspicion, and be aware of the management options available to treat the patient.
- Conservative observational treatment is not an option for urethral tape erosion.
- The success of endoscopic tape transection needs to be duplicated by others before it can be considered first-line management of urethral erosion.
- Currently, transvaginal excision of the polypropylene mesh with closure of the urethrotomy should be considered the first line of management and is the authors' preferred method if significant surface area of the sling is present within the urethral lumen.
- If the repair is tenuous, a vascularized Martius fat pad graft can bolster the repair. Furthermore, an autologous fascial sling can be placed at the time of surgery or in a delayed fashion to treat recurrent SUI.

Intravesical Tape Erosion. The finding of synthetic mesh within the lumen of the urinary bladder is another particularly distressing complication (Fig. 73-11). This complication is also **exceedingly rare after the TVT procedure** with only case reports in the published literature. Bladder injury recognized at the time of cystoscopy is much more common, occurring with a frequency between 2% and 11% of cases (Nilsson et al, 2001). Recognition of this complication allows the surgeon to remove and reintroduce the trocar in a controlled fashion, with placement of the tape in the correct anatomic plane. The **vast majority of intravesical tape erosions are most likely due to unrecognized cystotomy and placement of the tape within the urinary bladder at the time of surgery. True erosion of the tape across the seromuscular wall of the bladder into the lumen is much less likely.** Thus, performing complete and thorough cystoscopic examination of the bladder with adequate hydrodistention is critical to minimize this complication. Occasionally the insertion trocar may telescope the vesical wall during insertion and may obscure intravesical entry.

Patients typically present after their TVT procedure with a variety of symptoms. A review of seven reported cases in the literature was included in a case report by Negoro and colleagues (2005). **Typical symptoms can include lower abdominal pain, intermittent gross hematuria, recurrent UTI, urgency, frequency, dysuria, and urinary incontinence.**

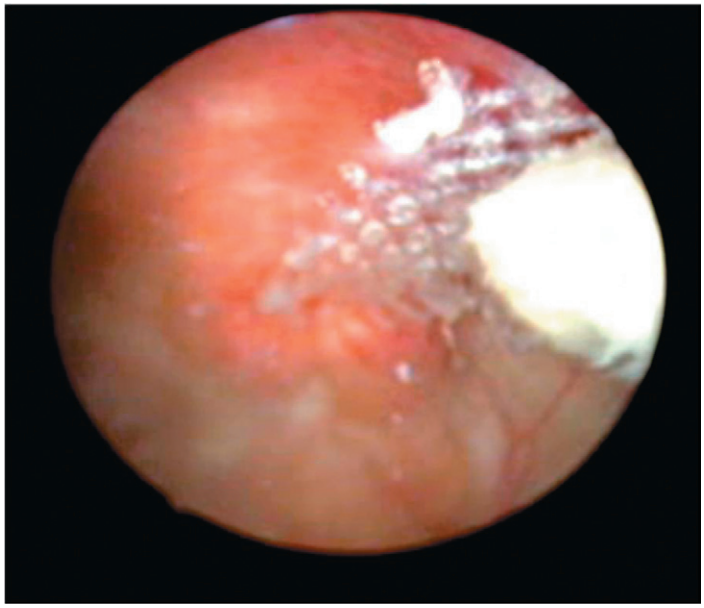


Figure 73–11. Cystoscopic view of intravesical retropubic sling erosion.

Diagnosis is made with a high index of suspicion by the clinician and cystoscopic examination confirming the presence of the tape within the lumen of the urinary bladder. Imaging including computed tomography and cystography may help in difficult cases but is not a substitute for cystoscopic examination. A review of intravesical polypropylene tape erosions is presented in Tables 73–13 and 73–14.

Management goals are aimed at removing the portion of polypropylene tape from the urinary tract and reconstructing the lower urinary tract. Observational treatment is not recommended because the tape often becomes encrusted, leading to stone formation, persistent lower urinary tract storage/voiding symptoms, recurrent UTI, and intermittent gross hematuria. Different techniques and surgical approaches have been advocated with varying levels of invasiveness, complexity, and success.

In a report by Negoro and colleagues (2005) a retropubic approach was used to resect the intravesical portion of the tape. The bladder was closed with absorbable suture, and catheter drainage was maintained postoperatively. The patient was symptom free and continent at 10-month follow-up. Volkmer and coworkers (2003), Sweat and associates (2002), and Huang and colleagues (2003) used a combined transvaginal and abdominal approach to remove the tape in its entirety. One patient had residual urgency and frequency treated with anticholinergic agents; the other patients had resolution of symptoms but recurrent SUI managed with collagen in one patient and pelvic floor muscle training and estrogen in the remaining two patients.

Ordorica and associates (2008) reported two vesical erosions after nonautologous sling placement. These were managed with either transvesical removal of mesh or a suprapubic extravesical approach. Lapouge and colleagues (2009) retrospectively reviewed five bladder erosions after TVT placement that were initially managed endoscopically. Two patients went on to need open

Table 73–13.

Urethral Erosion and Management

STUDY	NO. PATIENTS	LOCATION OF EROSION	MANAGEMENT	REMOVAL	SYMPTOM RESOLUTION	CONTINENCE
McLennan, 2004	1	1 urethral	Endoscopic resection	Partial	Yes	Dry
Pit, 2002	2	2 urethral	TV resection, Martius with TVT; TV with dermis with TVT	Partial	Yes	Dry
Haferkamp et al, 2002	1	1 urethral	TV resection, urethral reconstruction	Partial	Yes	Dry
Lieb and Das, 2003	1	1 urethral	TV resection, urethral reconstruction	Partial	NR	NR
Vassallo et al, 2003	1	1 urethral	TV revision, urethrotomy closure	Partial	Yes	Dry with fascial PVS
Wai et al, 2004	1	1 urethral	Endoscopic and TV	Partial	Yes	SUI treatment with biofeedback
Madjar et al, 2002	1	1 urethral	TV partial resection, closure of urethra	Partial	Yes	Dry
Glavind and Sander, 2004	1	1 urethral vaginal fistula TVT	Partial tape removal, two transabdominal repairs	Partial	Yes	SUI treatment with biofeedback
Sweat et al, 2002	3	2 urethral	TV excision, PVS, Martius; TV/retropubic	Near complete	NR	3 dry (1 with collagen)
Hammad et al, 2005	9	Urethral	4 conservative/5 TV excision	Partial	Yes	4 unknown/5 dry
Baracat et al, 2005	5	Urethral	Endoscopic	Partial	Yes	Dry
Starkman et al, 2006	5	Urethral	TV/retropubic/PVS	Partial	2 complete resolution	2 dry
Powers et al, 2006	2	Urethral	TV excision	Partial	Partial	1 MUI/1 SUI
Mesens et al, 2007	1	Urethral	TV excision	Partial	Yes	Dry (recurrent erosion)
Sokol et al, 2008	1	Urethral	TV excision, internal urethral sphincter for coverage	Partial	yes	Dry
Velemir et al, 2008	8	Urethral	2 TV excision, 4 endoscopic, 1 combined TV and endoscopic, 1 conservative	Partial	Yes	4 dry/1 unknown
Wijffels et al, 2009	3	Urethral	Endoscopic transurethral	Partial	Yes	2 dry

MUI, mixed urinary incontinence; NR, not reported; PVS, pubovaginal sling; SUI, stress urinary incontinence; TV, transvaginal; TVT, tension-free vaginal tape.

transvesical removal of residual sling material, owing to insufficient removal on endoscopy or recurrent symptoms. All 5 patients were dry after the last treatment. Oh and Ryu (2009) evaluated the efficacy of transurethral resection in 14 patients with intravesical mesh. The intravesical mesh was resected deep into the perivesical fat. The patients presented with dysuria, hematuria, pelvic pain, and urgency. Six patients presented with stone encasing the mesh. Thirteen (92.9%) had mesh completely removed during a mean follow-up of 18 months. One patient had recurrent bladder stones. One patient had mild SUI and UUI, which was controlled with anticholinergic agents; no further treatment for SUI was performed.

Jorion (2002) excised the tape endoscopically using an offset nephroscope transurethrally and a 5-mm laparoscopic trocar placed suprapubically. Laparoscopic grasping forceps were used to grasp the tape, and endoscopic shears excised the mesh flush with the bladder mucosa, allowing the tape to be easily removed. Cystoscopy at 1 month revealed healed mucosa, and the patient was continent and symptom free. In a separate report by Tsivian and coworkers (2004), the tape was cut endoscopically. Because of dense adhesions and adherent calculus the tape could not be extracted endoscopically. Therefore, a suprapubic approach was required to remove the stone and intravesical tape. Wyczolkowski and associates (2001) attempted to cut the tape endoscopically without success. Transabdominal exploration allowed the tape to be excised, and the cut ends were secured to the inguinal ligaments bilaterally. Holmum:yttrium-aluminum-garnet (YAG) laser excision of encrusted intravesical TVT has been successful in 15 cases (Baracat et al, 2005; Giri et al, 2005; Huwyler et al, 2008; Shrotri et al, 2010). Holmium laser destruction (vaporization) of visible tape has also been performed successfully in two cases (Hodroff et al, 2004; Lane et al, 2005). In two cases, patients presented with bladder stones that had formed on intravesical portions of TVT. Endoscopic lithotripsy of the calculi and transurethral resection of the TVT material was performed. Both patients demonstrated complete mucosal healing and remain asymptomatic and dry (Irer et al, 2005; Mahmoud and Wadie, 2007). There are three reported cases of successful laparoscopic removal of intravesical mesh after retropubic sling placement. In one of these cases a three-port intraperitoneal approach was used (Siow et al, 2005), and in the other two a three-port extraperitoneal approach was used (Rehman et al, 2008). All of the patients were free of symptoms and dry after the mesh removal.

It is unclear from the literature whether complete or partial tape excision is preferred. The authors routinely use the open cystotomy approach for complete tape

Table 73–14.

Intravesical Erosion and Management

STUDY	NO. PATIENTS	LOCATION	MANAGEMENT	REMOVAL	SYMPTOMS	SYMPTOM RESOLUTION	CONTINENCE
Huang et al, 2005	1	1 bladder	Combined transvaginal/ retropubic	Complete	F/U/UUI/ hematuria/pain	1 urge/UUI	UUI treatment anticholinergic
Tsivian et al, 2004	1	1 bladder	Combined endoscopic/ suprapubic	Partial	UTI, perineal pain	Yes	1 dry
Levin et al, 2004	2	2 bladder	2 endoscopic excision	Partial	UTI, F/U/UUI	NR	NR
Sweat et al, 2002	1	1 bladder	Combined transvaginal/ retropubic	Complete	UTI, hematuria	NR	SUI (dry with collagen)
Wyczolkowski et al, 2001	1	1 bladder	Failed endoscopic; retropubic with inguinal fixation	Partial	Abdominal pain	Yes	Dry
Volkmer et al, 2003	1	2 bladder	TV tape excision; suprapubic tape resection	Complete	UTI	Yes	2 SUI, PFMT, estrogen
Jorion, 2002	1	1 bladder	Endoscopic	Partial	UTI	Yes	Dry
Negoro et al, 2005	1	1 bladder	Retropubic	Partial	UTI	Yes	Dry
Irer et al, 2005	1	1 bladder	Endoscopic	Partial	Dysuria, hematuria	Yes	Dry
Giri et al, 2005	3	3 bladder	Endoscopic	Partial	Hematuria, UTI, UUI	Yes	Dry
Baracat et al, 2005	6	6 bladder	Endoscopic	Partial	UTI	Yes	Dry
Siow et al, 2005	1	1 bladder	Intraperitoneal laparoscopic	Partial	UTI, discharge; dyspareunia	Yes	Dry
Starkman et al, 2006	7	7 bladder	Combined TV/retropubic	Partial	UTI/F/U/UUI, hematuria, pain	None	UI
Mustafa and Wadie, 2007	1	1 bladder	Endoscopic	Partial	Dysuria, hematuria	Yes	Dry
Ordorica et al, 2008	2	2 bladder	Transvesical or suprapubic extravesical	Complete	UTI, pelvic pain, dysuria	Yes	NR
Huwyler et al, 2008	5	5 bladder	Endoscopic	Partial	UTI, dysuria, urgency	Yes	Dry
Rehman et al, 2008	2	2 bladder	Extraperitoneal laparoscopic	Complete	UTI, pelvic pressure	Yes	Dry
Shrotri et al, 2009	1	1 bladder	Endoscopic	Partial	Urgency, dysuria	Yes	Dry
Oh et al, 2009	14	14 bladder	Endoscopic	Partial	Dysuria, hematuria, UUI, stones	Yes	13 dry

F, frequency; NR, not reported; PFMT, pelvic floor muscle training; SUI, stress urinary incontinence; TV, transvaginal; U, urgency; UTI, urinary tract infection; UUI, urgency urinary incontinence.

excision. This approach is necessitated by a large surface area of tape present in the vesical lumen or in the case of tape collocation near the bladder neck, trigone, or ureteral orifices. Only patients with complete tape removal had recurrent SUI; the patients with partial excision maintained continence postoperatively. The significance of this, given the small number of cases, is unclear, but it may imply that suburethral support is maintained when the midurethral portion of tape is left in situ. The endoscopic approach is intriguing because it is minimally invasive and with the addition of the laparoscopic trocar achieved a satisfactory outcome. This should be duplicated by others before it is universally adopted to treat patients with this particular complication.

Voiding Dysfunction. Voiding dysfunction is a well-recognized complication of suburethral sling procedures for SUI. Although it is difficult to quantify objectively, a review by the AUA guidelines panel concluded that the incidence of permanent urinary retention after suburethral slings does not exceed 5% (Leach et al, 1997). **Anti-incontinence surgery, regardless of the technique, has some effect on outlet resistance. As a result, clinical symptoms of urethral obstruction have not been eliminated by the TVT procedure with an incidence in the literature of 1.9% to 9.9%** (Klutke et al, 2001; Meschia et al, 2001; Kuuva and Nilsson, 2002, 2003; Volkmer et al, 2003; Levin et al, 2004; Long et al, 2004).

Despite the fact that TVT is described as a tension-free procedure there is controversy about whether tension or resistance is directed at the bladder outlet. In one study of 404 TVT procedures, UDS before and after surgery showed an increase in voiding time but no difference in flow rate, urethral closure pressure, or urethral functional length (Meschia et al, 2001). A study by Lo and colleagues (2001) showed no statistical difference in several UDS parameters ($\dot{Q}avg$, $\dot{Q}max$, postvoid residual urine volume, MUCP, and functional urethral length) in 82 patients before and after TVT. In another study, Wang and Chen (2001) looked at filling cystometry, uroflowmetry, and urethral pressure profile data before and after TVT and found the only statistically significant difference to be in resting MUCP. Several other studies have also shown

no statistical difference in UDS pressure flow variables after the TVT procedure (Wang, 2000; Wang and Chen, 2003a, 2003b; Lin et al, 2004).

In contrast, Gateau and associates (2003) analyzed UDS findings before and after TVT surgery in 112 patients and reported consistent decreases in $\dot{Q}max$, increased mean Pdet $\dot{Q}max$, increased mean urethral resistance, and elevated postvoid residual urine volume. They concluded from their data that TVT surgery leads to obstructive changes in the bladder outlet. Sander and colleagues (2002) evaluated the voiding phase before and 1 year after the TVT procedure. They found both subjective and objective changes in the voiding phase, with 78% of patients experiencing more difficult voiding and significant decreases in $\dot{Q}max$, corrected $\dot{Q}max$, and $\dot{Q}avg$. Postvoid residual urine volume was also significantly increased, although not greater than 25% capacity. Furthermore, in another study comparing the TVT procedure and Burch colposuspension, a significant decrease in the flow rate was observed after surgery (Atherton and Staton, 2000).

There are contemporary UDS data both supporting and refuting bladder outlet obstructive changes after the TVT procedure. The physician must therefore consider these issues when counseling patients with SUI before surgical intervention with TVT. It would be most helpful when selecting patients for the TVT procedure to identify preoperative factors predictive of voiding dysfunction and urinary retention after surgery. One study assessed differences in surgical outcome after TVT by subgrouping patients into two groups, those with dysfunctional voiding and those with normal voiding (Wang and Chen, 2003b). Dysfunctional voiding in this study was defined as having both a free $\dot{Q}max$ of less than 12 mL/sec and a Pdet $\dot{Q}max$ of greater than 20 cm H_2O as defined by Blaivas and Groutz (2000). Statistically significant differences in pressure-flow variables of free $\dot{Q}max$ and Pdet $\dot{Q}max$ between the two groups were observed, as well as a higher objective cure rate in the normal voiding group. In a separate study by Hong and colleagues (2003), 375 patients were analyzed to see which factors predicted urinary retention after the TVT procedure. Urinary retention, defined as the need to catheterize for 72 hours or longer after surgery, was identified in 32 patients. Twenty-eight patients resumed normal voiding within 3 months, and 4 patients required a TVT release procedure. Patients' age, parity, peak flow rate, and history of hysterectomy predicted urinary retention on univariate analysis, and only peak flow rate predicted urinary retention on multivariate analysis. Finally, a small study of 14 patients showed that low Pdet $\dot{Q}max$ on the preoperative pressure-flow study correlated with elevated postvoid residual urine volume in 3 patients after a TVT procedure (Kawashima et al, 2004).

Urethral obstruction after suburethral sling surgery can arise in variety of ways. **Patients may complain of straining to void, incomplete emptying, urgency and frequency, hesitancy, UUI, elevated postvoid residual urine volume, recurrent UTI, and total urinary retention.** These symptoms usually cause patients bother and prompt evaluation and treatment after the initial surgical procedure.

The optimal evaluation for patients with postoperative voiding dysfunction is poorly defined in the literature. In a study by Carr and Webster (1997) there were no parameters (urodynamic, previous surgery, time from suspension to urethrolysis, and surgical approach) that predicted which patients would benefit from urethrolysis. The decision to perform urethrolysis was based on a clear temporal relationship between onset of symptoms and the surgical procedure. In a study by Petrou and coworkers (1999) there was no difference in urethrolysis outcomes with respect to patients with urodynamic obstruction versus those who had surgery based on clinical criteria. Under ideal circumstances, videourodynamics would differentiate patients with high-pressure, low-flow voiding consistent with obstruction and patients with detrusor hypocontractility. **At this time there does not appear to be enough evidence correlating urodynamic parameters with surgical outcomes. Therefore, UDS can be useful in selected cases at the physician's discretion; however, it appears that the temporal relationship correlating symptoms with an antecedent surgical procedure should be the primary criterion in selecting patients for urethrolysis and tape release procedures. Cystoscopy is useful to rule out bladder pathology, urethral tape erosion, and a hypersuspended bladder neck.**

In most cases, persistent postoperative voiding dysfunction is initially treated conservatively. Temporary catheter drainage, clean intermittent catheterization, timed voiding, biofeedback, pelvic floor muscle training, and selective medical therapy have all been successful to some degree in managing postoperative voiding dysfunction. Several reports have shown some benefit with urethral dilation (Hong et al, 2003; Mishra et al, 2005). **However, when these conservative measures fail, surgical intervention is usually indicated.** The urethrolysis literature is more mature and robust in the management of urethral obstruction secondary to traditional PVS surgery. A discussion of the results of surgical management of urethral obstruction after a TVT procedure follows (Table 73–15).

In a large review of 1175 TVT procedures, Rardin and colleagues (2002) found 23 (1.9%) women with persistent voiding dysfunction. Twenty patients had urinary retention or incomplete emptying, 3 patients had symptoms of refractory urgency and UUI, and 7 had both. Symptoms of incomplete bladder emptying usually arose in the immediate postoperative period, and LUTS arose in delayed fashion some weeks later. All patients were refractory to conservative regimens and underwent TVT release at a mean time of 17.3 weeks after the TVT procedure. Tape release was performed in the majority (17 patients), with mild urethrolysis in 2 patients and segmental tape excision (2 to 11 mm) in 4 patients. Relief of impaired bladder emptying was complete in 100%, and relief of urgency/UUI was complete in 30% and partial in 70%. Fourteen patients (61%) maintained their baseline continence, 6 (26%) were improved over baseline, and 3 (13%) had recurrent SUI.

Kuuva and Nilsson (2002, 2003) reviewed complications associated with the TVT procedure from the nationwide database in Finland. In their analysis of 1455 TVT procedures, 34 cases (2.3%) of urinary retention were reported and duration was recorded for 23 patients. A normal voiding pattern was resumed in 14 patients (2 days to 2 weeks), 2 patients (5 to 6 weeks), and 6 patients (within 24 hours) after surgery. One patient required that the tape be released by cutting it in the midline, and normal voiding resumed. In 111 cases the authors noted "minor" postoperative voiding difficulty (e.g., urgency, frequency) that resolved without intervention in the majority of patients. Thirteen cases were identified that lasted up to 4 months, and 2 of these patients required surgical transection of the tape to achieve a normal voiding pattern.

In another large review by Klutke and colleagues (2001), 17 of 600 patients (2.8%) required reoperation secondary to urinary retention and persistent obstructive symptoms. In their series, tape release was performed at a mean of 64 days after the TVT procedure. The tape was identified and either released with downward traction for 1 cm or cut in the midline. There was one urethral injury, which was repaired without sequelae. Symptoms resolved in all patients after tape release, all patients voided to

Table 73–15.

Results of Therapy for Urethral Obstruction after Midurethral Sling Surgery

STUDY	NO. PATIENTS	TIME TO SURGERY	MANAGEMENT	SYMPTOM IMPROVEMENT	CONTINENCE
Rardin et al, 2002	23/1175 (1.9%)	17.3 wk (2-69)	Midline transection (17); urethrolysis (2); segmental excision (4)	Retention (100%); LUTS (30% complete, 70% partial)	14 dry; 6 improved; 3 SUI
Klutke et al, 2001	17/600 (2.8%)	64 days (6-228)	Midline transection or 1 cm downward traction	All patients symptom free	16 dry; 1 SUI
Long et al, 2004	7/71 (9.9%)	28 days (4-108)	Right-sided lateral transection (J sling)	6/7 symptom free	5/7 dry; 2 SUI
Meschia et al, 2001	17/404 (4%)	NR	2 patients required midline tape release	17 patients resumed normal voiding	NR
Volkmer et al, 2003	3	14 mo, 6 mo, 6 wk	1 segmental tape excision; 2 tape cut in midline	All patients symptom free	2 dry; 1 SUI
Levin et al, 2004	8/313 (2.5%)	2 mo	1 patient required transvaginal excision and urethrolysis	All patients symptom free	All dry
Kuuva and Nilsson, 2002	34/1455 (2.3%) 111/1455	3 mo	1 patient tape cut in midline	Symptom free	All dry
	Subset with "minor" voiding dysfunction (7.6%)	1 mo and 4 mo	2 patients with persistent urgency/frequency tape cut midline	Symptom free	All dry
Tsivian et al, 2004	8	14 mo (5-46)	5 midline transection, 3 lateral segmental excision	Symptom free	6 dry; 2 SUI
Karram et al, 2003	17/350 (4.9%)	6 wk	6 tape takedown and midline transection	Symptom free	4 dry; 2 SUI
Hong et al, 2003	32/375 (8.5%)	3 mo	4 transvaginal midline incision of tape	Symptom free	4 dry
Zubke et al, 2004	3	NR	3 transvaginal midline incision polypropylene mesh lengthening	Symptom free	3 dry
Abouassaly et al, 2004	15/241 (6.2%)		7 transvaginal tape release, 3 segmental tape excision	Symptom free	6 dry; 4 SUI
Hammad et al, 2005	95/1459 (6.5%)	NR	7 transvaginal loosening, 19 transvaginal midline incision, 7 urethrolysis	NR	NR
Sokol et al, 2005	18/80 (11.2%) TVT only; 41/187 (11.3%) TVT with prolapse	6 wk	4.1% prolonged catheter, 1.9% urethral dilation, 4.9% urethrolysis	NR	NR
Nguyen, 2005	10/163 (6%)	3-10 days	10 transvaginal loosening	Symptom free	All dry
Laurikainen et al, 2006	50/9040 (0.6%)	197 days	50 transvaginal midline incision, or bilateral lateral incisions (tape not removed)	49% cured, 39% improved	49% dry, 12% retention
Gamé et al, 2006	30	12.7 ± 14.7 mo	Transvaginal single lateral incision	70% cured	21 dry, 2 SUI
Glavind and Galvind, 2007	10/143 (7%)	1- 3 wk 5-7 mo 5 wk-9 mo	5 sling loosening 2 transvaginal sling lysis Clean intermittent catheterization	100% cure SUI Urgency, prolonged voiding	All dry 2 SUI

LUTS, lower urinary tract symptoms; NR, not reported; SUI, stress urinary incontinence; TVT, tension-free tape.

completion, and 16 patients remained continent. In a review by Long and associates (2004), 7 of 71 patients (9.9%) underwent lateral tape excision to treat patients with evidence of urethral obstruction. All patients had irritative symptoms or elevated amounts of residual urine and 6 patients voided with significant straining. Six of the patients had urodynamic obstruction (Pdet > 20 cm H_2O and $\dot{Q}max$ < 12 mL/sec) and 1 patient had low-pressure, low-flow voiding. Long and associates described a technique transecting the tape lateral to the midline on the right side of the periurethral fascia, leaving the tape in the shape of a J underneath the urethra. Symptoms resolved in 6 patients, and 5 patients were continent. Of note, in the 2 patients who had

recurrent SUI after transection of the tape, the tape was cut on postoperative day 4 in both cases. In the other cases the tape was cut after a minimum of 14 days after TVT. Therefore, on the basis of their experience, the authors recommended a minimum waiting period of 2 weeks before surgical intervention.

In a study reviewing outcomes and complications of 404 TVT procedures, Meschia and coworkers (2001) found 17 patients (4%) who had voiding difficulties defined as residual urine greater than 100 mL. At 1-month follow-up, 15 patients resumed normal voiding patterns and the remaining 2 patients required the tape to be cut in the midline to release tension; normal voiding was observed thereafter. A review by Volkmer and coworkers (2003) found 3 patients with permanent urinary retention after the TVT procedure. UDS revealed high-grade obstruction in each patient utilizing the Abrams-Griffiths nomogram. Two patients had the tape cut in the midline transvaginally, and 1 patient had segmental excision of the entire suburethral portion of the tape. All 3 patients were able to resume normal voiding without significant residual urine, and 2 of the 3 patients remained continent. In the patient with recurrent SUI the suburethral portion of the tape was excised and she underwent repeated TVT surgery to restore continence.

Levin and colleagues (2004) reviewed a series of 313 patients who underwent the TVT procedure. They identified 8 patients (2.5%) who had urinary retention with incomplete bladder emptying. Seven patients required temporary catheterization for a short period of time before resumption of normal voiding at a follow-up of 1 month. The remaining patient had persistent urinary retention 2 months after TVT surgery, and UDS showed obstruction on the pressure-flow study. Transvaginal urethrolysis with tape excision was performed, and the patient thereafter resumed complete bladder emptying with complete continence. Tsivian and associates (2004) found 8 of 12 patients who required repeated surgery after a TVT procedure to have urethral obstruction, with complaints ranging from severe urgency symptoms to straining to void. All patients had incomplete bladder emptying, and 5 patients had objective evidence of obstruction on pressure-flow UDS. All 8 women underwent corrective surgery with resolution of symptoms, and only 2 women suffered from recurrent SUI symptoms.

Karram and coworkers (2003) reviewed their series of TVT procedures looking at the incidence of postoperative complications. Seventeen women (4.9%) were performing clean intermittent self-catheterization beyond 7 days. Another 42 women with irritative LUTS were taking anticholinergic medications more than 6 weeks after surgery. Twenty-eight patients underwent urethral dilation, which provided symptom relief in 23; and 6 patients with persistent urinary retention had transvaginal takedown and incision of the tape. Normal voiding resumed in all 6 of these patients, although 2 experienced recurrent SUI.

Zubke and colleagues (2004) managed 3 patients with urethral obstruction after TVT with a novel surgical technique. They cut the tape in the midline with a transvaginal approach and sutured the edges of the tape to a Prolene mesh, thus lengthening the tape. All 3 patients were continent and resumed normal voiding after intervention. Mishra and colleagues performed urethral dilation on 3 of 52 cases who had retention 3 months after TVT. Two of the three patients voided effectively after urethral dilation. In this series the postoperative retention rate is significantly higher (23%) than published data. Although many practitioners report anecdotal success, no randomized trials exist in peer-reviewed literature. It is the authors' opinion that urethral dilation is of limited utility and if used too aggressively may be detrimental. There are concerns about the potentially traumatic nature of dilation, which could induce scarring of the urethra. Hammad and associates (2005) reported on their incidence and management of urinary retention in an Australasian cohort after 1459 midurethral slings (993 TVT, 466 SPARC). Postoperative retention occurred in 95 patients, but surgical intervention was only required in 33 patients. This included sling loosening, lysis, and urethrolysis. This study does not provide information on time to presentation of obstruction or of results after treatment of obstruction.

Sokol and coworkers (2005) described the management of obstruction after a TVT procedure with and without concurrent prolapsed repair. The median days to voiding (8 vs. 5 days) and rate of urinary retention were similar between patients with and without prolapse repair. Increasing age, decreasing BMI, and postoperative UTI were independent predictors of time to adequate voiding, whereas previous history of incontinence surgery was the only independent variable predictive of urinary retention. Sling loosening was reported by Nguyen (2005) within approximately 1 week after TVT placement. All patients had a suprapubic tube placed at time of initial TVT, which was removed once the patient was able to void at least 75% of total bladder volume on two consecutive occasions. All patients were continent after mobilization, and quality of life scores of the nonvoiders did not differ from those of voiders 1 year after surgery.

A nationwide analysis of obstruction after TVT surgery was performed by Finnish authors (Laurikainen and Killholma, 2006). A retrospective review of 9040 patients who received a TVT procedure was reviewed. Approximately 50% were cured with sling lysis and remained continent. Four (12%) continued to have retention after lysis. There was no difference in continence rate among patients based on interval between a TVT procedure and sling lysis. Repeat sling lysis and urethrolysis were options used in managing the refractory retention.

Gamé and colleagues (2006) presented results of 30 women requiring sling lysis with a single lateral incision over a 4-year period. Seventy percent were continent after intervention, and 2 women developed recurrent SUI. Glavind and Glavind (2007) evaluated different treatment options for managing prolonged voiding dysfunction after TVT placement (clean intermittent catheterization, sling loosening, and lysis). Seven percent of their initial cohort developed prolonged voiding difficulties. Five patients experienced loosening at between 1 and 3 weeks; 2 underwent sling lysis between 5 and 7 months, and 3 patients chose to perform extended clean intermittent catheterization. The sling loosening study arm was the only group who was subsequently continent. The authors concluded that voiding issues should be followed closely for the first 1 to 2 weeks and intervention should not be delayed if symptoms persist. The value of this study is limited by the large variability in time between presentation of symptoms after TVT and intervention. It clearly supports timely evaluation and intervention for obstruction or related symptoms.

Three studies attempted to relate preoperative or intraoperative variables to postoperative voiding dysfunction. Takacs and colleagues (2007) found that a poor quality intraoperative cough test predicted immediate postoperative retention. The quality of the cough test was determined by whether every cough produced urinary incontinence. This study is limited by subjective measurements of the cough test. The cough test is no longer commonly performed intraoperatively for setting sling tension. Shukla and colleagues (2007) found no significant predictive factors but described a trend toward long-term voiding difficulty after concurrent posterior vaginal repairs and in women with low preoperative flow rates. Vervest and colleagues (2007) performed a prospective

cohorts study in 703 women with a TVT procedure and reported the need for postoperative catheterization for more than 24 hours in 11% and sling lysis in 1.3% of patients. Using validated questionnaires, these authors found that the negative impact of abnormal voiding on TVT outcomes is greater than in those without voiding dysfunction. Yet, this impact decreased significantly after a TVT procedure, implying a considerable improvement in quality of life.

Key Points: Tension-Free Vaginal Tape Procedure—Voiding Dysfunction

- It appears that long-term urinary retention and obstructive voiding dysfunction are extremely rare after the TVT procedure.
- Although definitions of urinary retention and indications for management vary in the reported literature, most patients are initially managed conservatively. Anecdotal cases have shown modest benefit from urethral dilation.
- For patients with persistently elevated residual urine and bothersome symptoms refractory to conservative management, TVT release procedures consistently provide resolution of symptoms with maintenance of continence in the majority of patients.
- The authors recommend a waiting period of at least 4 weeks before any consideration of sling release. Sling release should be attempted through a small midline vaginal incision using minimal dissection.

Other Complications. A diverse group of complications have been reported with the midurethral sling, aside from those mentioned previously. These include vascular injury, bowel perforation, dyspareunia, pain (inguinal, suprapubic, pelvic), and infection-related complications. Death has also occurred after sling implant and been directly attributable to the procedure.

Wound-related complications include minor superficial cutaneous infections, pelvic abscesses, and UTI. A case of necrotizing fasciitis was reported in an obese, diabetic patient. This resolved after intensive resuscitation (Connolly, 2004). Interestingly, a review of necrotizing fasciitis in gynecologic surgery found that obesity (88%), hypertension (65%), and diabetes (47%) were all strong factors in the development of this infection after surgery (Gallup et al, 2002).

Serious complications such as vascular perforation or intestinal perforation remain relatively low. The rate of serious vascular complications in the Finnish registry was 0.07% (Kuuva and Nilson, 2002), and the Austrian registry reported a bowel perforation rate of 0.04% (Tamussino et al, 2001). In a systemic evaluation of the occurrence of postoperative retropubic hematoma formation, Flock and colleagues (2004) reported a rate of 4.1% among 249 consecutive cases, with only 4 patients with hematomas exceeding 300 mL and requiring surgical intervention.

Groin and suprapubic pain are potential problems after TVT placement. Thigh pain is usually associated with the transobturator approach (see later). A randomized controlled study from Finland (Laurikainen and Killhoma, 2006) reveals 16% of women in the transobturator (inside-to-outside) group had groin pain compared with only 1.5% of those in the TVT study arm. This groin pain persisted longer after the TVT-O than after the TVT (Daneshgari et al, 2008). Long and associates (2009) and Wang and colleagues (2009) both also found the TVT-O group to have significantly more postoperative groin and thigh pain. Duckett and Jain (2005) reviewed different strategies for managing groin pain after a TVT procedure or other similar midurethral slings in five women (1%). Initial conservative management was successful in most patients. Those with persistent or severe pain (four women) were given combination of corticosteroid and local anesthetic injections. Two women developed recurrent pain and had the TVT excised, with significant pain relief. Doo and associates (2006) noted persistent suprapubic pain in three (2.2%) women at 5-year follow-up after a TVT procedure.

Varying degrees of sexual impairment after TVT insertion (0% to 15%) have been associated with dyspareunia (Kuhn et al, 2009a). Among 20% prospectively evaluated who reported sexual impairment after TVT placement, 14.5% related this to dyspareunia (none preoperatively vs. eight postoperatively, $P < 0.01$) (Mazouni et al, 2004). Marszalek and colleagues (2007) performed a cross-sectional analysis and noted that the 14.3% deterioration in sexual function was significantly associated with de novo urgency, dyspareunia, and a sensation of incomplete emptying. The sexual satisfaction of the TVT and Burch colposuspension were compared (Demirkesen, 2008). Fifty-four percent expressed a negative change, of which the majority suffered from dyspareunia. The TVT procedure appeared to more adversely affect sexual satisfaction, but the difference was not significant. Kuhn and coworkers (2009a) reviewed the impact of sling removal for postoperative female de novo dyspareunia and found that pain improved significantly.

Review of the U.S. Food and Drug Administration safety database for complications reported to that agency is noted in Table 73–16. Catastrophic complications are rare but do occur and may result in mortality: 11 reported deaths exist in the database from 1998 to July 2009.

Key Points: Tension-Free Vaginal Tape Procedure—Voiding Dysfunction

- Clinical experience with the TVT operation suggests that it is beneficial in the management of SUI.
- In prospective trials, significant percentages of patients have been found to be cured or significantly improved compared with standard operations for the indication of SUI.
- There appears to be a relatively robust outcome expected from this procedure in patients with all types of incontinence, whether it be primary SUI or MUI, or in patients who have prior failed procedures or who are undergoing simultaneous pelvic prolapse surgery.
- Patients with ISD appear to have worse outcomes, although the absolute reported rates of cure and improvement are within the range of reported results experienced with other types of procedures.
- The risks of intraoperative and short-term postoperative complications are low, especially with trained physicians. There does appear to be a learning curve, which must be taken into account with new adopters and trainees. There do not appear to be any long-term adverse events.

Table 73–16.

Summary of All Significant Complications Reported to the U.S. Food and Drug Administration with the Midurethral Sling TVT: 1998-2009

Bladder erosion	50
Urethral erosion	51
Vaginal erosion	239
Bowel perforation	48
Major vascular	26
Blood loss >200 mL	36
Plastic sheath malfunction	51
Leg pain	44
Needle broken from mesh	154

This analysis is limited by reporting inaccuracies and the incomplete nature of adverse event reporting in common practice.

Transobturator Slings

Subsequent to the development of TVT it was recognized that transobturator tape (TOT) was a viable method for correction of SUI. Since Ulmsten's initial article in 1996 there has been extensive acceptance of the various midurethral sling technologies. In Europe, as of 2005, approximately 83.9% of all procedures are midurethral-type synthetic slings, of which 26.9% are with TOT (de Tayrac and Medelenat, 2004). Since the initial description of the TOT approach, numerous other similar TOT approaches have been noted.

The goal of the minimally invasive surgical procedure should be to provide acceptable long-term efficacy comparable to that of more standard methods as well as a relatively low incidence of long-term complications, again compared with these "gold standard" procedures. Retropubic midurethral slings have demonstrated robust outcomes in both primary and recurrent SUI as well as in women with MUI and in those with ISD. Delorme (2001) initially described the placement of synthetic polypropylene mesh using the TOT approach. The technique was described as being relatively facile and associated with fewer complications than retropubic approaches. It was also thought that the procedure did not require cystoscopy.

Much of the understanding of the function of the TOT slings arises from that which has evolved from TVT-type procedures. Perineal ultrasonography has been used to assess the function of the TVT in patients who undergo successful incontinence procedures. In those individuals, a functional kinking of the urethra during stress events is noted to occur when the tape is placed at the midurethra (Lo et al, 2004). In relatively long-term follow-up (3 years), 92% of patients had ultrasonic demonstration of tape at the midurethra and evidence of urethra kinking that caused the "urethral knee angle." Of these patients, 92% were continent. Of the patients who had tape location either at the posterior urethra or bladder neck, only three of five (60%) were continent, presumably because of lack of a fulcrum-like effect at the midurethra. These ultrasound studies appear to underscore the importance of the midurethral location and also the ability of the TOT to accomplish this localization (Lo et al, 2001, 2004).

Similarly, Minaglia and colleagues (2004), using a variant of the TOT (ObTape), showed no difference in resting urethral angulation after tape insertion. These authors, however, did notice that there was a statically significant difference preoperatively and postoperatively in urethral angle with straining. They also noted that most women had persistent urethral hypermobility after the procedure, and they concluded that correction of hypermobility was not necessary to achieve continence. Their results documented that 90.4% of patients with documented hypermobility were continent, whereas only 50% of the patients without hypermobility were continent. They concluded that a persistently positive Q-tip test was predictive of a successful outcome. They found that concomitant prolapse surgery or previous incontinence surgery had no effect on outcome.

Surgical Anatomy

For successful implantation of the TOT, an understanding of the surgical anatomy of the pelvic floor, including the surrounding neurovascular structures, pelvic and perineal anatomy, and the obturator foramen, is crucial to provide surgical success and minimize morbidity. Three reviews have demonstrated with cadaveric dissection the importance of landmarks and implantation technique for the success of the TOT procedure.

Bonnet and colleagues (2005) performed the "inside-out" TOT technique as described by de Leval (2003) in 13 cadavers to determine tape path and proximity to surrounding structures. Cadaveric dissection was extended from the femoral triangle medially through the obturator externus muscle and adductor longus to the inferior pubic ramus. The perineal space was then entered, and the pubic bone was sectioned to evaluate the relationship of the tape to various structures. Finally, the subfascial anterior perineum and pelvis were dissected to analyze the tape path fully. These authors demonstrated several significant points in their cadaveric dissection. They noted that the tape never penetrated the adductor longus muscle, thus being a safe distance from neurovascular structures. In approximately 70% of studied cases the implanted material did traverse the adductor magnus, adductor brevis, and gracilis muscles during its path into the pelvis.

At the level of the obturator foramen the tape was noted to traverse both the obturator externus and internus muscles as well as the obturator membrane. The relationship between the inserted tape and the obturator nerve showed that the closest proximity of the two was 22 mm with a distance as great as 30 mm (mean 26.2 ± 2 mm) at the level of the obturator foramen. The authors emphasized that an individual's thighs in hyperflexion and the rotational trajectory of the helical passer associated with this positioning ensured the separation of the insertion tool from the nerve during the actual implantation of the material. They also noted that regional vascular anatomy (anterior branch of the obturator) was protected from injury by the bony architecture of the inferior pubic ramus.

More medially, the tape entered the anterior compartment of the ischiorectal fascia, in the area of the levator ani membrane and obturator internus muscle. The tape remained outside the pelvic space and did not penetrate the levator ani muscular group. The tape remained above the perineal membrane at all times. The dorsal nerve of the clitoris was found to be consistently caudal to the perineal membrane and thus protected from injury during needle passage. These relationships were found to be consistently confirmed in each cadaveric specimen, and thus Bonnet and colleagues believed that these observations represented highly reproducible anatomic positioning and therefore concluded that the TOT technique is safe.

Delmas and associates (2003) utilized the "outside-in" approach on 10 female cadavers, again detailing the relevant pelvic anatomy in relationship to the tape insertion path. In this study, dissection demonstrated that the tape always consistently passed 4 cm opposite and caudal to the obturator canal, again confirming the

relative safety of neurovascular structures. They also demonstrated that the tape traverses a plane between the perineal and levator antimusculature but above the neurovascular pedicle of the pudendum. They also noted that in the pelvic component of their dissections, the tape courses medial to the obturator plexus. They concluded that tunneling passage anteriorly risks injury to the bladder and passage in the posterior dissection demonstrated a risk of vaginal perforation.

A third study by Whiteside and Walters (2004) further evaluated the obturator anatomy in relationship to tape insertion in six female cadavers. These authors found that the mesh, on average, passed 2.4 cm inferior and medial to the obturator canal and that both divisions of the obturator (anterior and posterior) were 3.4 and 2.8 cm, respectively, separated from the path of the insertion tool. They also noted that the insertion tool passed within, on average, 1.1 cm proximity to the medial branch of the obturator vessels. These authors concluded that a risk of injury does exist and that appropriate caution should be exercised.

Operative Technique

Operative technique varies with insertion method. Various procedures using similar insertion methods represent relatively similar technique (Fig. 73–12). Not only does implantation technique affect overall success of the sling, but also the type of mesh or tape implanted has a substantive effect on overall results. Mesh properties have been shown to have a significant effect on local inflammatory response and ingrowth of local fibrous tissues (collagen, neovascularity) and subsequent integration of these tapes into host tissues. These differences in properties are believed to affect the risk of erosion and subsequent infection and other vaginal and local complications. There are intrinsic differences between the various meshes that have been used for the TOT approach. The ObTape and UraTape meshes are polypropylene material but are small pore, knitted, and thermally bonded with an approximately 15-mm silicone component that is immediately suburethral in location after implantation. A second-generation obturator tape developed by the Mentor Corporation is known as the Aris TOT; it has a larger 200-μm pore size that allows improved tissue ingrowth with less encapsulation. The ObTryx, TVT-O, Monarc, I STOP, and Urotex-TO are large-pore open knit polypropylene meshes. A unique obturator mesh is the BioArc, which, like the suprapubic variety, has a biologic graft material that is sutured on either end to the polypropylene tape. The biologic material actually occupies a suburethral position (de Leval, 2003; Delorme et al, 2003) (Table 73–17; Fig. 73–13).

Transobturator Outside-In. The patient is placed in the dorsal lithotomy position with legs in hyperflexion (120 degrees). A small vertical vaginal incision is created as with the TVT procedure over the midurethra, and dissection is carried out laterally to the ischiopubic ramus. A puncture incision is made in the obturator foramen at the level of the clitoris in the leg using the tunneler; the obturator membrane is perforated, at which point resistance is noted by the operative surgeon. Using the nondominant index finger and identifying the landmarks of ramus and the obturator internus muscle, the surgeon turns the tunneler in a medial orientation and advances it on the tip of the index finger and brings it out through the vaginal incision. Inspection is carried out at this point to exclude inadvertent penetration of the vaginal fornix or associated urinary structures. The synthetic material is then attached to the tunneler and brought out through the inner thigh stab wound. The procedure is then repeated on the contralateral side. Tension is set on the tape by passing a clamp between the tape and urethra such that a surgical clamp can be passed easily between these two structures. Excess material is then cut at the

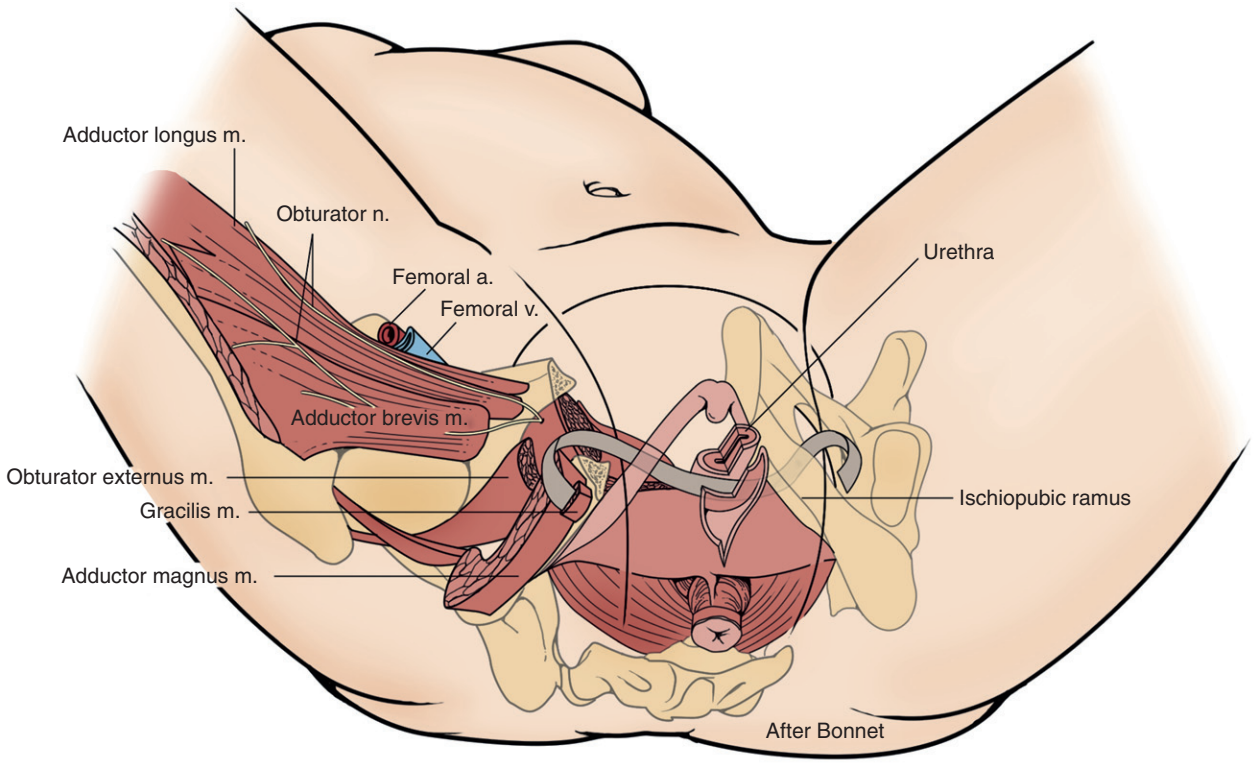


Figure 73–12. Midurethral sling as placed by the transobturator approach (any technique).

Table 73–17.

Devices and Descriptions (see Fig. 73–13)

COMPANY	BRAND NAME	MESH MATERIAL	PORE SIZE (μm)
Mentor	ObTape	Prolene, 15-mm silicone	50
	UraTape	Prolene, 15-mm silicone	50
	Aris	Polypropylene	200
AMS	Monarc	Knitted polypropylene	Large, open knit
	BioArc	Polypropylene with biologic suburethral component	Large, open knit
	SPARC	Polypropylene	Large, open knit
	In-Fast Ultra	Polypropylene	Large, open knit
	MiniArc	Polypropylene	Large, open knit
GyneCare	TVT-Obturator	Polypropylene	Large, open knit
	TVT Secur	Polypropylene	Large, open knit
C.R. Bard	Uretex-TO	Polypropylene	Large pore
	Align	Polypropylene	Large, open knit
Boston Scientific	ObTryx	Polypropylene with detangled suburethral segment	Large pore, >100 >75, low weight/ area
	Advantage	Polypropylene with detangled suburethral segment	Large pore, >100
	Lynx	Polypropylene with detangled suburethral segment	Large pore, >100
	Prefyx	Polypropylene with detangled suburethral segment	Large pore, >100
	Solyx	Polypropylene with detangled suburethral segment	Large pore, >100
CL Medical, France	I STOP	Monofilament prolene	Macropore weave

skin puncture site, and the incisions are closed according to the surgeon's preference.

This approach is used for the following devices: ObTape, UraTape, Aris TOT, Monarc, BioArc TO, Uretex-TO, ObTryx, I STOP.

Transobturator Inside-Out. The vaginal component of the procedure is essentially the same as in the outside-in technique. Stab incisions are created approximately 2 cm superior to the horizontal line level with the urethra and 2 cm lateral to the labial folds, which will be the exit point for the helical passer. Once the device is inserted through the urethra and the upper part of the ischiopubic ramus is reached with the device, the obturator membrane is perforated sharply with scissors. The introducer is then passed at a 45-degree angle relative to the midline sagittal plane until it reaches and perforates the obturator membrane. The open side of the introducer is passed out facing the surgeon. The more distal end of the tubing is then mounted on the spiral segment of the helical passer and slipped along the open gutter of the introducer. The passer is aligned parallel to the sagittal axis and rotated so that the tip of the tubing exits the inner thigh stab incision. The tubing is then removed from the passer until the first few centimeters of the tape become externalized, and the procedure is repeated on the contralateral side. All plastic covering sheaths are then removed simultaneously from the tape while maintaining no tension on the sling itself using the technique previously described.

Only one technique currently uses this method: TVT-O.

Results

Since the initial description by Delorme in 2001, continence rates have been reproducibly satisfactory although follow-up has, in general, been short (Table 73–18). Reported continence rates range from 80.5% to 96% on the basis of a variety of subjective (questionnaire and quality of life single-item assessment) and objective (cough stress test, uroflowmetry, physical examination) measures.

Efficacy

Efficacy analyses have included heterogeneous groups of patients, including those in whom prior procedures failed, those who had concomitant prolapse, and those with MUI. Delorme (2001) noted that 15.6% of his patients had ISD, and Mellier and colleagues (2004) diagnosed 28% of their patients with ISD. Despite these diverse populations of patients, relatively similar results were obtained. O'Connor was the first group to examine the early outcomes of the transobturator approach for SUI in women with a variable VLPP. Patients were divided into high (>60 cm H_2O) or low (<60 cm H_2O) VLPP groups. The odds of continued SUI after TVT-O were 12 times greater for women with VLPP less than 60 cm H_2O compared with those with VLPP greater than 60 cm H_2O (O'Connor et al, 2006). However, no preoperative predictors of outcomes using either clinical or urodynamic parameters were established to determine overall results of these procedures. Therefore, the effect of MUI and concomitant prolapse on surgical outcomes for this intervention are unknown. Prospective studies are needed to answer these questions.

Two nonrandomized studies have compared TOT with TVT procedures and have found no significant difference in postoperative voiding dysfunction, complications, or overall continence. There was a tendency toward more bladder injuries (10% vs. 0%) and hemorrhage (10% vs. 2%) with the suprapubic as compared with the TOT approach, but this did not reach statistical significance (de Tayrac et al, 2004; Mellier et al, 2004). Five prospective randomized studies have compared TOT with TVT procedures, ranging in follow-up from 6 to 31 months (Lee et al, 2007b; Porena et al; 2007; Zullo et al, 2007; Rinne et al, 2008; Schierlitz et al, 2008; Rechberger et al, 2009). Among two groups there were a significantly greater number of bladder perforations in patients with the retropubic approach over the TOT approach: 6.5% vs. 0% (Rechberger et al, 2009) and 7.3% vs. 0% (Schierlitz et al, 2008). Both of these groups also found the TVT to be more effective than the TOT in patients with ISD. Schierlitz and colleagues (2008) observed that at 6-month follow-up, 13% of the TOT procedure patients with ISD required further surgery whereas 0% of the TVT patients with ISD required reoperation for SUI (Schierlitz et al, 2008). Porena and associates noted that storage symptoms were significantly improved in the TOT group (still present in 24%) while persisting in 44% of the TVT group (Porena et al, 2007). **A few key points are consistent between these studies: these techniques were safe, there were no long-term complications in either group, cure rates were equal (with exception of ISD group), and patients were equally satisfied.**

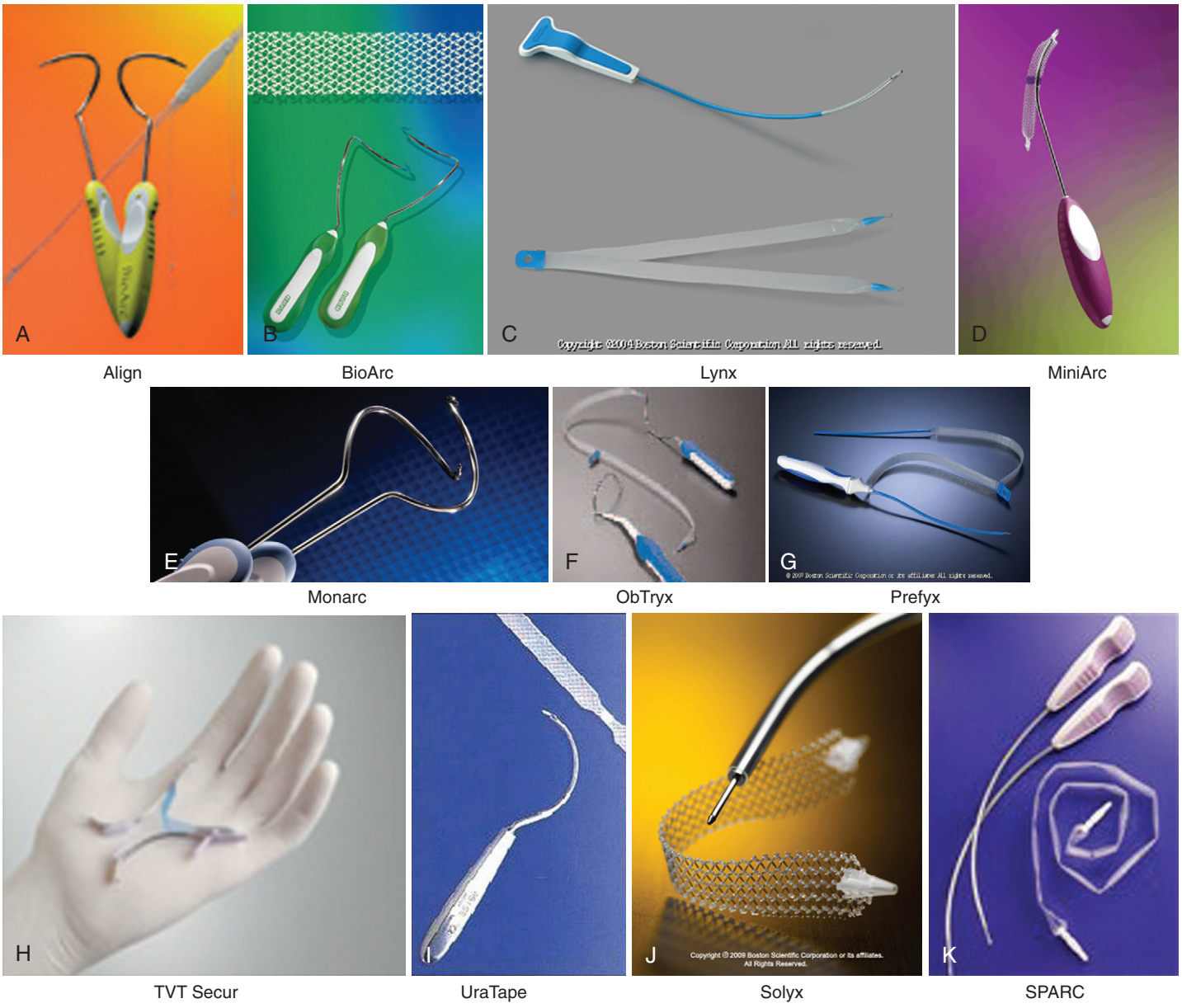


Figure 73–13. Midurethral devices.

Complications of the Transobturator Approach

Despite the minimally invasive nature of these procedures, perioperative and postoperative complications have been reported with a variety of techniques.

Bladder Injury. The anatomic variation between the inside-out (TVT-O) and outside-in (TOT) approaches has been compared, especially in regard to their association with adverse outcomes. Cadaver dissections after a TVT-O procedure noted the mean distance from the vaginal incision to the obturator membrane is 4.0 cm, and from the vaginal incision to the obturator neurovascular bundle is 6.75 cm. At the obturator membrane the closest point of the passer is only a mean distance of 2 cm from the obturator neurovascular bundle. This is the reason the curved passer is directed away from these structures and advanced. Also, an anterior branch of the obturator artery coursed medially along the exterior edge of the obturator foreman in 60% of the cadavers. They believed that this artery was protected by the exterior bony rim of the obturator foramen during an inside-out pass but could be potentially injured in an outside-in approach (Rogers et al, 2005).

Conflicting results have been reported by Zahn and associates (2007), who found that the inside-out method was significantly closer to the obturator canal. The greater proximity and distance from the ischiopubic ramus of the inside-out method was noted in all of their cadaveric dissections. Additional dissections revealed the deep external pudendal vascular structures coursing from superolateral to inferomedial over the obturator foramen, putting it at risk during the exit of an inside-out approach. No clinical correlations exist to date, suggesting that one approach is associated with a higher incidence of tunneler-related complications.

Bladder perforation appears to be the most common complication associated with any midurethral sling, with a 2% to 11% risk with the suprapubic approach. Although initial reports described the risk with the TOT approach as being negligible, the risk of bladder injury

Table 73–18.

Outcomes with Transobturator Techniques

STUDY	N	FOLLOW-UP	CURED/ IMPROVED/ FAILED	ASSESSMENT OF OUTCOME	PATIENTS' AGE	PURE SUI	MUI	ISD	PREVIOUS ANTI-INCONTINENCE SURGERY	PREHYSTERECTOMY
Delorme et al, 2003	150 (32 wk/1-yr follow-up)	17 mo (13-29)	90.6%/9.4%/0%	Cough stress test; uroflow	64 (50-81)	14 (44%)	18 (56%)	5 (15.6%)	5 (15.6%)	5 (15.6%)
Costa et al, 2004	183	7 mo (1-21)	80.5%/7.5%/12%	Cough stress test/ questionnaire	56 yr (29-87)	53%	27.30%	10 (MUCP < 20 cm H_2O); 5.4%	14.20%	25.70%
de Tayrac et al, 2004	30	12 mo	90%; 3.3%; 6.7% 92% objective cure 97% subjective;	Cough stress test/ questionnaire	54.7	27	3	4	4	2 (4 previous prolapse surgery)
Cindolo et al, 2004	80	4 mo (1-8)	96% overall satisfaction	Questionnaire/ quality of life instrument	56 (39-79)	62 with Q-tip test (78%)	22 (28%)	NA	16 (20%)	NA
Mellier et al, 2004	94	12.8 mo (2-20)	95% cured; 4%; 1%	Telephone questionnaire	58.1 (±9.3)	94 (100%) defined on three-grade scale	12 (13%) preoperative urgency	26 (28%) MUCP < 30 cm H_2O	28 (30%)	17 (18%)
Queimadelos et al, 2004	47	18 mo	45/47 (96%)	Questionnaire	55 (40-69)	47	0	3	NA	NA
Krauth et al, 2005	604 (140 wk/1-yr follow-up)	1-3 mo in 572; 1 yr in 140	85.5% satisfied at 1 yr	Subjective questioning	57	47.30%	52.70%	NR	NR	NR
Lim et al, 2006	59 (59%)	18.5 mo	95% cure	Questionnaire, cough stress test	55.5 (SD 9.43)	41%	59%			
Kocjancic et al, 2008	70	32 (12-48)	90%	Questionnaire	59 (35-78)	85%	15%	0		
Juma and Brito, 2007	117	16.9 mo (12-24)	88.8% improved	Subjective/ questionnaire	58 (27-87)	33.30%	66.70%	64		
Neuman, 2007	300	15 mo (4-24)	97.3% cure	Questionnaire	55 (29-83)	69%	31%		15 (5%)	
Al-Singary et al, 2007	24	36 mo	79.2% improved 20.8% failed	Questionnaire	63 (40-83)	62.50%	37.50%		3 (12.5%)	
Waltregny et al, 2006	102	40 mo (36-49)	87.9% cure 8.8% improved	Questionnaire	25-85	62.70%	37.30%			

ISD, intrinsic sphincter deficiency; MUCP, maximum urethral closure pressure; MUI, mixed urinary incontinence; NA, not available; NR, not reported; SUI, stress urinary incontinence.

is now identified as associated with this sling insertion technique (Table 73–19) (Olsson and Kroon, 1999; Kobashi and Govier, 2003b; de Tayrac et al, 2004).

Minaglia and colleagues (2004) reported three cases of intraoperative bladder injury while performing the TOT insertion method. They identified all injuries intraoperatively because of their utilization of cystoscopy as an adjunct to all insertion procedures. All injuries were managed with catheter placement for 1 week postoperatively, and these authors noted no complications after sling removal and reinsertion at that same setting. Parekh and associates (2006) reported a case of intravesical mesh erosion after TOT placement and cystocele repair. The patient did not have cystoscopy intraoperatively. She initially presented with mesh on the left side of the bladder and then 6 months later with sling material in the right side of the bladder. She had a successful transurethral, transvaginal, and suprapubic mesh resection.

A single case of bladder laceration was reported by Cindolo and Costa that was also managed intraoperatively (Cindolo et al, 2004; Costa et al, 2004). This apparently was a more extensive injury than just trocar perforation. The tunneler passage of the outside-in obturator approach has been shown to be associated with lower urinary tract injury. To date, no case of bladder injury when performing the TOT procedure by the inside-out approach has been reported using the TVT-O (Hermieu et al, 2003; Whiteside and Walters, 2004).

Table 73–19.

Complications Associated with Transobturator Tape Techniques

STUDY	NO. PATIENTS	ADVERSE EVENTS
Delorme et al, 2003	32	None reported
de Leval, 2003	107	One superficial vein thrombosis with abscess; ?(27/107) 15.9% transient thigh pain
Domingo et al, 2005	65	Nine vaginal mesh erosion
Costa et al, 2004	183	Three vaginal erosion; two urethral erosion; one bladder perforation; one vaginal perforation; two urethral perforation
de Tayrac et al, 2004	30	Six uncomplicated UTI; one obturator hematoma
Cindolo et al, 2004	80	One vaginal erosion with inguinal abscess
Mellier et al, 2004	94	2% intraoperative hemorrhage (300 mL); one urethral perforation
Queimadelos et al, 2004	47	None reported
Krauth et al, 2005	604 (140 with 1-yr follow-up)	0.3% vaginal erosion; 2.5%UTI; 0.5% bladder perforation; 0.33% vaginal perforation; 2.3% perineal pain
Giberti et al, 2007	118	6.4% vaginal erosion; one vaginal hematoma
Juma and Brito, 2007	117	3.84% vaginal erosion; 1.52% bladder perforation
Neuman, 2007	300	0.7% vaginal erosion; 1.3% dyspareunia
Al-Singary et al, 2007	24	1% perforated vaginal fornix; 12.5% vaginal erosion
Waltregny et al, 2008	102	1 vaginal laceration
Rechberger et al, 2009	197	2.5% vaginal erosion; 5.5% UTI; 5% urinary retention
Lee et al, 2009	105	4% dyspareunia

UTI, urinary tract infection.

Erosions, Extrusions, and Infectious Complications. Domingo and coworkers (2005) reported a relatively high incidence of vaginal erosion in their series using either the ObTape or UraTape. They attributed their erosion rate to the characteristics of the particular mesh that they utilized, with the reduced pore size and other mechanical properties of that particular material. They noted a slightly increased risk of erosion with the ObTape (15-mm silicone-coated portion)—19% versus 12% compared with the UraTape—and they believed that this was most likely due to reduction in pore size and higher degree of encapsulation. They also concluded that synthetic mesh with larger pore sizes facilitates vascular and tissue ingrowth, optimizing mesh incorporation. Tape erosion was usually managed by removal by the transvaginal approach alone or combined with the transobturator approach. They noted continence rates of 78% (despite tape removal in their series) (Domingo et al, 2005). Vaginal extrusions and erosions of up to 15% have been reported, often accompanied by obturator and ischiorectal abscesses, sinus formation, and voiding difficulty using the ObTape or UraTape (Babalola et al, 2005; Domingo et al, 2005; Deval et al, 2006; Robert et al, 2006; Al-Singary et al, 2007; Dobson et al, 2007; Giberti et al, 2007; Juma and Brito, 2007; Karsenty et al, 2007). Abscess and adductor myositis have been reported, manifesting as leg pain, difficulty ambulating, and cellulitis (Goldman, 2006; DeSouza et al, 2007; Karsenty et al, 2007; Leanza et al, 2008; Zumbé et al, 2008). Gamé and colleagues (2004) reported an infected obturator hematoma also requiring exploration and drainage. Tamussino and associates (2007) published data from the Austrian database, including 2543 transobturator cases, using 11 different tape systems. They reported greater number of complications than reported earlier in their TVT database. This included 120 intraoperative complications (4.7%), 85 cases of bleeding (3.3%), 10 vaginal perforations (0.4%), 10 bladder perforations (0.4%), and 2 urethral perforations. Bladder perforations occurred more frequently with the outside-in tape systems than the inside-out tape systems in their database. The ObTape is no longer available for construction due to the high erosion rates.

Newer, knitted polypropylene slings and many of the reports using the inside-out approach have lower incidence of erosions, extrusions, and infectious complications (Neuman, 2007; Waltregny et al, 2008; Lee et al, 2009; Rechberger et al, 2009). Neuman (2007) reported two patients with vaginal extrusion, which were repaired by covering the exposed mesh with surrounding vaginal mucosa successfully. Of the 197 women who had multifilament transobturator slings by Rechberger and associates (2009), 2.5% developed vaginal extrusions. These were all managed successfully with sling excision and closure of the vagina. Two groups reported no evidence of extrusion or erosion at 1 year (Lee et al, 2009) and 3-year (Waltregny et al, 2008) follow-up. Waltregny and associates (2008) experienced one intraoperative vaginal sulcus laceration, which was closed uneventfully. Lee and colleagues (2009) presents a modified canal TOT approach, creating a suburethral tunnel between two oblique lateral incisions in the anterior vaginal wall to decrease the incidence of vaginal extrusion through the classic single midline incision. The value of this needs to confirmed by a randomized control trial.

Voiding Dysfunction. Postoperative voiding dysfunction has been noted to occur in 0% to 20.6% of patients after

a TVT procedure (Pesschers et al, 2000). **The incidence after TOT procedures varies between 2.1% and 6.7%.** Although clinically there seems greater voiding dysfunction associated with a TVT than the TOT there is no significant difference in postoperative voiding dysfunction between the TVT and TOT in nonrandomized studies (Mansoor et al, 2003; de Tayrac et al, 2004). Urinary retention also appears to not be significantly different. **The rate of obstructive symptoms after the TOT midurethral sling varies between 1.5% and 15.6% of patients.** Tsivian and colleagues (2009) assessed the effect of concomitant vagina surgery on the outcomes of TOT placement. The group without concurrent vaginal surgery had no voiding dysfunction postoperatively, whereas 7 (11%) of the group who had additional pelvic surgery experienced voiding dysfunction. Three went on to require sling lysis for obstruction. After lysis, the continence rates were similar: 82.86% and 85.2%. Yang and associates (2009) identified morphologic features associated with functional impairment after a transobturator procedure. Among 98 women at a median follow-up of 22 months, 11 women had recurrent SUI, 22 had voiding dysfunction, and 12 had worsening or de novo urgency. A resting tape distance of less than 12 mm and urethral encroachment at rest were the variables predictive of postoperative voiding dysfunction. Bladder neck funneling was associated with postoperative urgency symptoms.

Urinary obstruction is usually transient and managed with short-term intermittent catheterization, although occasionally symptoms mandate tape release. Long-term retention after TVT is a rare complication (0.6% to 3.8%) and can be expected in the TOT population as well (deTayrac et al, 2004). Removal of the tape, in most cases, improves the patient's symptoms. There has been some anecdotal experience with downward displacement of the tape under local anesthesia to provide symptomatic relief in patients with persistent voiding dysfunction (Ozel et al, 2004). Nonetheless, the overall risk of postoperative voiding dysfunction after the TOT is relatively low.

Management of MUI by a TOT sling has been discussed by three groups (Botros et al, 2007; Paick et al, 2008; Tahseen and Reed, 2009). Botros and coworkers (2007) compared the resolution of DO, UUI, and de novo urgency between the Monarc (125), TVT (99), and SPARC (52) procedures. De novo urgency was significantly lower in the Monarc group (8% vs. 33% TVT and 17% SPARC, $P = .04$), yet rates of resolution of DO, UUI, and de novo DO did not differ between the three groups. Paick and associates (2008) performed 72 TVT, 22 SPARC, and 50 TOT procedures in women with MUI. There were no significant differences in SUI cure rates or general urinary incontinence cure rates between the three slings. The presence of DO during preoperative UDS was associated with a high treatment failure of UUI in all three groups. Tahseen and associates (2009) performed a TOT procedure in 58 women and found a 77% SUI cure rate and 19% SUI improvement rate. UUI was additionally cured in 43% and improved in 36% of women suffering from MUI. Twenty-one percent had persistent UUI.

Pain. Another bothersome complication, unique to the TOT approach, is that of postoperative leg pain. de Leval (2003) described 15.9% of patients with temporary groin pain that resolved after the second postoperative day. Similarly, Krauth and associates (2005) reported 14 cases (2.3%) of patients with postoperative perineal groin pain. They also noted it to be transient and responding to nonsteroidal anti-inflammatory agents in all but 1 case. They hypothesized that the cause of the pain was either subclinical hematoma or a transient neuropathic phenomenon. They recommended that persistent leg pain that does not respond to conservative measures should prompt an investigation to exclude the possibility of erosion. Roth (2007) managed three women with persistent groin pain 3 months postoperatively in a similar fashion. Combined corticosteroids and local anesthetic was effective for pain relief, and no side effects were noted from the treatment. One case of failed sling and vaginal extrusion was reported by Mahajan and associates (2006). This patient additionally reported severe groin pain, fevers, and chills 10 days postoperatively. The tape was easily removed through the vaginal erosion, and mesh cultures were positive for *Bacteroides fragilis*. Complete symptom resolution occurred within 1 week of tape removal. Wolter and colleagues published a case report on recalcitrant medial thigh pain after TOT midurethral sling placement; the patient ultimately required medial thigh/TOT exploration by orthopedic surgery and sling excision (Wolter et al, 2008).

Key Points: Transobturator Midurethral Slings

- The transobturator sling appears to have reproducible short-term continence results similar to those seen with the TVT procedure, yet seemingly less voiding dysfunction.
- It does appear to mimic the suprapubic approach by stabilizing the midurethra, recapitulating the "hammock" support that is thought to be responsible for continence. Major vascular and bowel complications have not been reported, but lower urinary tract injury does occur, and this experience underscores the necessity of cystoscopy as an adjunct to this technique.
- Initial retrospective comparisons with the TVT show no significant difference in efficacy outcomes between these techniques. Longer-term follow-up is necessary prospectively to evaluate these procedures.

Secondary or Salvage Procedure

There are limited data regarding the efficacy of midurethral slings as secondary surgery in women with recurrent incontinence. Five small studies with relatively short follow-up could be found addressing the issue (Azam et al, 2001; Rezapour and Ulmsten, 2001; Kuuva and Nilsson, 2002, 2003; Lo et al, 2002a; Rardin et al, 2002). Comparison of the studies is hampered by differences in the definitions used for *cure, improved,* and *failed*. The population of patients may be considered skewed by the inclusion of women in whom bulking agents failed. It is debatable whether women in whom bulking agents fail are the same as those in whom a surgical anti-incontinence procedure has failed. The methods of evaluating outcomes (objective, subjective, or both) also differ between studies. Despite these limitations between studies, cure rates of a midurethral sling after prior failed anti-incontinence surgery vary from 81% to 89.6%. Failure rates vary from 4.2% to 13%. In a review of these articles, several trends emerge: **the procedure can be performed in the same way as it is performed for primary genuine SUI. The complication rate is similar to that of TVT done for primary SUI, but risk of bladder perforation appears to be higher in women who have had one or more prior retropubic suspensions. The failure rate is higher in women with immobile urethras, as is the case in primary surgery.**

The longest follow-up of women who underwent TVT for recurrent incontinence is 4 years in a study by Rezapour and Ulmsten (2001). The 34 women studied had undergone 64 different

anti-incontinence surgeries. Any patient with significant prolapse, DO, or ISD defined as a MUCP of less than 20 cm H_2O was excluded. By physical examination, 24 women had a hypermobile urethra. Ten had a less mobile urethra, but none had a fixed urethra. The procedure was performed using the standard TVT technique, and only one bladder perforation occurred in a patient with a prior Marshall-Marchetti-Krantz urethroplasty. No significant complications were encountered. Twenty-eight (82%) were cured by objective and subjective parameters, 3 (9%) were improved based on failure to achieve more than 90% improvement in quality of life, and in 3 the procedure failed. Postoperative voiding dysfunction was negligible with no change in postvoid residual urine volume after 8 weeks. Long-term catheterization was not necessary in any patient. These results were durable up to 5 years.

The mechanism of failure in midurethral slings is typically misplacement of the suburethral tape or inadequate tension on the tape. There are a few reports of small numbers concerning recurrent incontinence after a midurethral sling in patients being treated with a repeat midurethral sling (Riachi et al, 2002; Villet et al, 2002; Lee et al, 2007a; Tsivian et al, 2007; Biggs et al, 2009). Reported cure rates of a midurethral sling after prior failed anti-incontinence surgery vary from 62.5% to 92.3%. **Cure rates are higher for retropubic slings than for the TOT approach for recurrent SUI.** Tsivian and associates (2007) found that in 12 patients with repeat midurethral sling the only procedure that failed was the TOT. Similarly, Lee and colleagues (2007a) found that the cure rate for the repeat TOT approach was 62.5% as compared with 92.3% for the repeat retropubic sling procedure. A possible explanation for this difference is the angle of the tape; specifically the retropubic sling has a U shape, which may be more supportive and obstructive than the TOT. Additionally, the outside-in approach to the TOT procedure may need wider dissection of the periurethral area, leading to future migration of the tape. Salvage procedures are performed on a portion of women who failed the initial midurethral sling due to underlying ISD or now have a fixed urethra from the initial surgery. This is consistent with the evidence of high success in retropubic slings for patients with a component of ISD.

Key Points: Midurethral Slings for Refractory Stress Urinary Incontinence

- A repeat midurethral synthetic sling for persistent or recurrent SUI is a viable option for select patients in whom the initial procedure has failed.
- Cure rates are higher for redo retropubic slings than the TOT approach, in a great part due to the higher number of patients with ISD.

New Technology: Single-Incision Transvaginal Slings

Surgical treatment of SUI has expanded to include a single-incision sling (TVT-S). This technology was first approved (Gynecare, TVT Secur) by the U.S. Food and Drug Administration in 2006 and has since included the AMS and MiniArc. There are little data available regarding the safety and efficacy of this new generation of slings. The ideal midurethral sling requires a short hospital stay, has rare and mild complications, provides a quick return to active life, and has high success rates.

Procedure

The device consists of a short 8 × 1.1-cm polypropylene laser-cut tape, the same material as a standard TVT, which is coated on both ends with an absorbable fleece material (Ethisorb). The absorbable material is made of polyglactin and polydioxanone. It is usually absorbable within 90 days, with polypropylene remaining intact to provide long-term fixation. A curved stainless steel inserter instrument and "release wire" is attached on both ends of the mesh. The implant may be placed under the midurethra and can be fixed in the "hammock" position (Fig. 73–14A) into the obturator internus muscle or in the U-shaped position (see Fig. 73–14B) into the connective tissue of the urogenital diaphragm behind the pubic bone (Meschia et al, 2009).

The procedure is performed with the patient in the dorsal lithotomy position (with sequential compression devices in place) with a significant degree of flexion (70 degrees or more) of the thighs. A Foley catheter is placed before the repair to ensure the bladder is fully decompressed before passage of the device. As heretofore described, the patient has received parenteral sedation, and approximately 5 mL of 0.9% normal saline is used to hydrodistend the anterior vagina. After the vaginal incision is created, minimal dissection is performed using Metzenbaum scissors under the vaginal flaps on either side to elevate the vaginal epithelium from the underlying periurethral tissue to the level of the pubocervical fascia, which is not perforated. One inserter of the device is placed in the right dissection tunnel immediately beneath the vaginal epithelium and advanced up to the ischiopubic bone and into the internal obturator muscle, where the tape edges are anchored by the needle holder. The left side is introduced in the same way, creating a hammock-shaped sling. The definitive sling tension is achieved when the tip of a hemostat is easily passed between the urethra and the sling. Before engaging the sling by pulling the release wire, the patient is given indigo carmine and undergoes cystoscopy with a 30-degree rigid cystoscope. This step is essential to avoid the future morbidity of repeat surgery for intravesical or urethral mesh. Efflux of both ureteral orifices is confirmed. At this point the release wires are pulled with an empty needle driver and the inserters are removed on each side with a twisting motion of the hand. The authors' experience suggests that the tension of the mini-slings should be tighter than in the classic TVT or TVT-O procedures to achieve the same result.

Anatomic Considerations

Like the TVT procedure, early attempts are being made at describing the anatomic localization and function of the TVT-S with cadaveric dissection and through ultrasound. Using 14 embalmed and 5 fresh frozen female bodies, Hubka and colleagues (2009) placed TVT-S inserters bilaterally. After dissection, they measured the distances from the obturator bundle (obturator nerve and vessels) and found that the mean distance of the TVT-S from the obturator bundle was 3.05 to 3.07 cm. Perforation of the fascia of obturator internus muscle occurred in 4.4% and they believed that injury to variable vessels could occur. The position of the TVT-S was not found to change with repositioning the legs. Ultrasound studies attempt to identify the dynamics behind the curative effects of the TVT-S. Martan and associates (2009) analyzed 85 patients after a TVT-S with perineal ultrasonography. Efficacy of the TVT-S was evaluated with cough test and validated questionnaire. Objectively, 62% had a negative cough test and 38% had persistent leakage. The TVT-S was noted to restrict urethral mobility, with a higher degree of obstruction associated with a higher

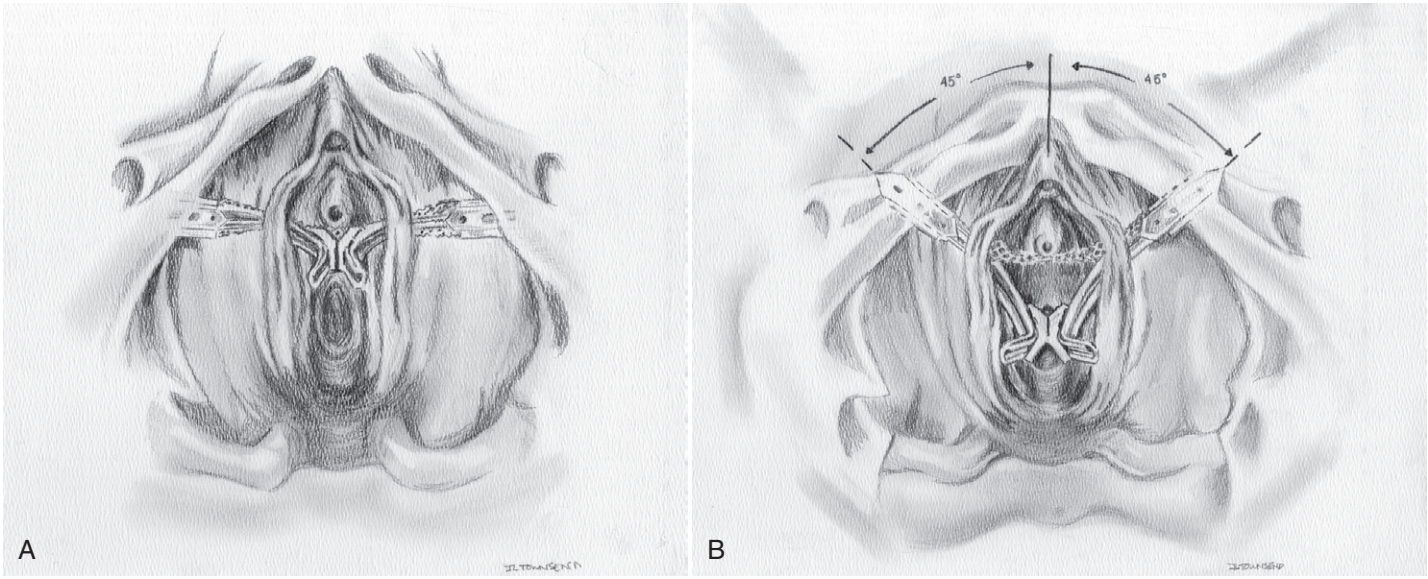


Figure 73–14. Midurethral sling as placed with single-incision approach. **A,** "Hammock." **B,** "U" position.

likelihood of cure. This restrictive effect was noted to weaken within the first 3 months after surgery.

Results

There are nine prospective, often multi-institutional trials with minimum of 1-year follow-up reviewing the results of TVT-S and MiniArc slings. Dmochowski and colleagues (2009) report on the largest ongoing registry at 29 sites in eight countries. Effectiveness was measured by standing cough test and Incontinence Quality of Life (I-QOL) instrument. Six hundred forty-two women were studied, with 64.5% having a hammock placement and 35.5% having the U placement of the TVT-S. Of these women, 65.3% had pure SUI and 34.7% had MUI, with predominately stress symptoms. Intraoperative complications noted included one bladder perforation (0.2%) and 3 cases of bleeding more than 200 mL (0.5%). Postoperatively, there was one reported case of retention (0.2%), 10 UTIs (1.6%), 6 cases of voiding dysfunction (0.9%), and 15 cases of de novo urgency (2.3%). There were 5 cases of mesh erosion (0.8%). Improvements in quality of life at 3 months were sustained at 12 months. Objective incontinence with cough test was 11% at 6 months and 12.5% at 12 months, giving an objective cure rate of 87.5%.

Pickens and colleagues (2009) presented their initial experience with 120 MiniArc cases at 13 month follow-up. Success was defined as using no pads, with subjective outcomes assessed with the IIQ-7 and UDI-6 questionnaires. Thirty-five percent had concurrent UUI. At 13 months, 94% had complete resolution of SUI whereas 6 patients reported significant improvement and 1 patient experienced a treatment failure. Twenty-four percent reported resolution of their UUI. Three patients (0.4%) had intraoperative bladder perforations. Two patients experienced retention postoperatively: in 1 it resolved, and the other patient had a urethrolysis due to persistent retention.

Krofta and coworkers (2009) analyzed the efficacy and complications among 73 women using a cough stress test and validated questionnaires. There were no major perioperative complications or cases of urinary retention reported. Two patients had UTIs (2.9%) and 4 had wound infections (5.8%) within the first week after surgery. Mesh erosion occurred in 4 patients (6%). Subjective outcomes were cure of 58.2%, 23.9% improvement, and 17.9% failure. Objective cure rate was 51.5%. A second anti-incontinence procedure was performed in 8 patients (six TVT procedures, two Burch colposuspensions). These authors believe that the TVT-S was less effective than the TVT or TVT-O.

In a prospective, multicenter study of 154 women with TVT-S, Debodinance and associates (2009) reported cure rates of 70.3%, improvement in 11%, and failure in 18.7% at 1 year follow-up. MUI occurred in 31.8%. Perioperative complications included five hemorrhages, one bladder injury, one vaginal wound, 21 cases of elevated postvoid residual urine volume, and 1 woman with persistent groin pain. Two patients returned with vaginal extrusion of mesh and 1 with a granuloma. Cure of urgency was reported by 61.1%, whereas 12.3% reported de novo urgency. The overall cure rate did not change between 2 months and 1 year.

Neuman and associates (2008) performed a prospective observational study of 100 consecutive women with "hammock-style" TVT-S. The perioperative and 12-month postoperative data were compared between the first 50 patients and the last 50 patients. The objective failure rate went down from 20% to 8% between the two groups with the tape being placed closer to the urethra. Four (8%) patients in the first group had vaginal perforation with the inserter. This was avoided in the second group by widening the submucosal tunnel. The tape extrusion rate decreased from 12% to 8% by making deeper submucosal tunnels. There was one case of a paravesical self-remitting hematoma. Otherwise, the authors reported no cases of bladder or urethral perforation, UTI, wound infection, or intraoperative bleeding. At 12-month follow-up the objective cure rates between the two groups were 88.6% and 93.5%. Oliveira and colleagues (2009) provide 15-month follow-up of 107 patients with TVT-S. Fifteen percent had MUI, with predominant SUI symptoms. Seventy-one percent reported being dry, and 14% improved. Six (5.6%) patients presented with de novo urgency, and one case of vaginal mesh extrusion was reported. There were no cases of bowel injury, bladder perforation, hematuria, excessive bleeding, or hematoma formation. Meschia and coworkers (2009) used multiple validated questionnaires and cough test to assess 91 women after placement of TVT-S at 1-year follow-up. Fifty-five patients had a TVT-S in the hammock position, and 40 patients had it in the U position. These researchers reported subjective and objective cure rates of 78% and 81%,

respectively. No bladder perforations were encountered. Two patients had intraoperative hemorrhage greater than 500 mL. Postoperative complications included 7 women with voiding difficulty (8%), 9 with recurrent UTIs (10%), 9 with de novo urgency (10%), and 2 with vaginal extrusions. Among the 20 with failed procedures, 8 patients went on to have a second anti-incontinence procedure (5 with retropubic TVT surgery, 2 with transobturator slings, 1 with a Reemex implant). Tartaglia and colleagues (2009) provide up to 18-month follow-up on 32 hammock-shaped TVT-S tapes. There were no surgical complications or reports of postoperative pain. One case of vaginal extrusion occurred. All 32 patients achieved continence based on quality of life assessment and physical examination. Jimenez and associates (2008) reported on their experience with both TVT-S and MiniArc slings in 41 patients with 1-year follow-up. The median follow-up in the TVT-S group was longer than the MiniArc group (328 days vs. 101 days). Only one bladder perforation was experienced in the TVT-S group. The reported cure rates were 80.4% in the TVT-S group and 90.2% in the MiniArc group. Ninety percent of the patients reported being satisfied at 3 months.

Four studies have compared mini-slings to standard midurethral slings (TVT or TVT-O). Using the TVT-WORLD observational registry, Tincello and colleagues (2009) compared 12-month outcomes of the TVT, TVT-O, and TVT-S procedures. The primary outcome measures are cough stress test and incontinence quality of life. The baseline characteristics, including proportions of MUI, were similar. TVT-S procedure patients returned to normal activities quicker than those who received either the TVT or TVT-O. Satisfaction rates were similar between the three groups. Objective cure rates were as follows: 90.6% TVT-S, 87.7% TVT, and 97.2% TVT-O. In regard to complications, all three techniques were similar.

Basu and Duckett (2009) performed a prospective, randomized control trial of the TVT versus the MiniArc in 70 women with 6-month follow-up. The MiniArc group had statistically lower subjective cure rates and urodynamic SUI cure rates than the TVT group: 63.3% vs. 100% and 45% vs. 93%, respectively. At 6-month follow-up, 50% of the MiniArc population had urodynamic SUI versus 7% of the TVT group. Two groups reported on randomized control trials of the TVT-O versus the TVT-S (Hinoul et al, 2009; Jarmi-Di et al, 2009). Jarmy-Di and associates (2009) observed the early postoperative results at 30 days. Two patients in the TVT-S group had temporary urinary retention, and 1 patient in the TVT-O group had leg pain. There were no UTIs or evidence of de novo urgency within this month period. No early mesh erosions were reported. Hinoul and associates (2009) performed a 12-month study of 135 randomized women (70 TVT-O and 65 TVT-S). Quality of life and subjective outcomes were reported using validated questionnaires. One bladder perforation occurred in the TVT-O group. The self-reported cure rates for the TVT-O were significantly higher than for the TVT-S (91.5% vs. 78.5%, $P = .02$), yet the TVT-S procedure was associated with less pain in the first week postoperatively. This pain difference disappeared within 2 weeks. Based on short-term follow-up, the single incision slings are a valuable addition, providing short hospital stays, quicker return to active life, and success rates equal to the TVT and TVT-O procedures. Their appeal is the single incision, avoidance of the retropubic space, and prevention of thigh pain. Most importantly, patients thus far appear to have reduced discomfort in the postoperative period. Long-term, comparative data collection is necessary to establish the efficacy and durability of these procedures.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter
74

Injection Therapy for Urinary Incontinence

Sender Herschorn, MDCM, FRCSC

History of Injectable Agents

Use of Injectable Agents in Female Stress Urinary Incontinence

Pathophysiology of Incontinence After Prostatectomy and Use of Injectable Agents for Male Stress Urinary Incontinence

Use of Injectable Agents for Incontinence After Urinary Diversion

HISTORY OF INJECTABLE AGENTS

The quest for injectable agents for stress urinary incontinence (SUI) started at the end of the 19th century when Gersuny (1900) from Vienna suggested periurethral paraffin injection for urethral compression. In 1914, Kelly and Dumm warned about the dangers of embolism after injection and pointed out that this treatment showed only temporary improvement of symptoms. In 1938, Murless first reported the injection of sodium morrhuate, a sclerosing agent synthesized from cod liver oil, into the anterior vaginal wall for treatment of SUI. Of the 20 patients treated, 17 were cured or improved for at least 12 months. Sloughing of a segment of the anterior vaginal wall was seen in 12 patients, and of these 75% were cured. Murless postulated that success was due to contraction of the resulting scar of the anterior vaginal wall. Quackels (1955) reported on the injection of paraffin for incontinence after prostatectomy in 1955; and Sachse (1963), based on previous reports, injected a mineral oil preparation, granugenol oil (Dondren), another sclerosing agent. He reported cures in 12 of 24 men after prostatectomy and 4 of 7 women. However, significant complications of pulmonary emboli and urethral sloughing were seen. With the last case report of distal ureteral stenosis after periurethral injection it was recommended not to use sclerosing agents for incontinence (Bubanz et al, 1980).

Polytetrafluoroethylene (Teflon) paste was first introduced by Berg (1973) and then popularized by Politano and colleagues (1973) in the 1970s. Shortliffe and coworkers (1989) published the first report on glutaraldehyde cross-linked collagen, and Cervigni and colleagues (1994) described the use of autologous fat in woman with SUI. More recently, newer synthetic materials have been described that theoretically should improve efficacy, durability, and safety.

The ideal injectable agent should be easily injectable and conserve its volume over time. It should also be biocompatible, nonantigenic, noncarcinogenic, and nonmigratory and cause little or no inflammatory reaction (Kershen and Atala, 1999) **or fibrotic ingrowth** (Dmochowski and Appell, 2000). **The components of the bulking agent should not separate or dissociate on injection, and if the agent contains microcrystalline or micropolymeric components they should be reasonably uniform spheres of particle sizes above 110 μm that are nonfragile and adhere to host tissue** (Dmochowski and Appell, 2000). **If the substance used is not successful it should not interfere with subsequent surgical intervention. To date, no substance has met all of these requirements.**

Over the past 15 years there has been an evolution of injectable agents and diverse types have been tested. Table 74–1 is a list of the agents that are discussed here. Most of the agents are bulking agents, but recently injection of autologous muscle stem cells for sphincter enhancement and implantable balloons that compress the urethra have been introduced.

USE OF INJECTABLE AGENTS IN FEMALE STRESS URINARY INCONTINENCE

Pathophysiology of Stress Urinary Incontinence and the Role of Injectable Agents

Please see the online edition of this chapter on the Expert Consult website for a discussion of this topic, along with Figures 74–1 and 74–2.

The goal of injectable agents is to augment or restore urethral mucosal coaptation and its "hermetic seal effect" contribution to the continence mechanism (Appell and Winters, 2007). It is generally thought that these agents improve intrinsic sphincter function, although the exact mechanism has not been defined (Smith et al, 2009). Bulking agents such as collagen have been reported (McGuire and Appell, 1994; Monga et al, 1995) to augment urethral mucosa and improve coaptation and intrinsic sphincter function, as evidenced by an increase in post-treatment abdominal leak point pressure (ALPP) (Herschorn et al, 1992; Richardson et al, 1995; Winters and Appell, 1995). Bulking agents do not generally obstruct voiding after the initial post-treatment period.

Table 74–1.

Types of Injectable Agents for Stress Urinary Incontinence

Biologic
BULKING
Currently used: Homologous: bovine collagen (Contigen), porcine collagen (Permacol)
No longer used: Autologous fat
FUNCTIONAL
Autologous muscle stem cells
Synthetic
Currently used: Carbon-coated zirconium beads (Durasphere), polydimethylsiloxane (Macroplastique), hyaluronic acid dextranomer (Deflux), polyacrylamide hydrogel (Bulkamid), calcium hydroxyapatite (Coaptite)
No longer used: Polytetrafluoroethylene (Teflon), ethylene vinyl alcohol (Tegress)
Balloons
Currently used: Adjustable balloons (ACT, ProACT)
No longer used: Microballoons (UroVive)

Monga and coworkers (1995) showed that successfully treated patients have an increased area and pressure transmission ratio in the first fourth of the urethra. They suggested that placement of the injectable agent at the bladder neck or proximal urethra prevents bladder neck opening under stress, although this is controversial. Proper placement of the injectable agent, possibly just below the bladder neck, rather than actual quantity (Khullar et al, 1997) of the agent improves intrinsic sphincter deficiency (ISD).

Patient Selection, Indications, and Contraindications

Injectable agents are one of the many treatment options for SUI. **Although initially it was thought that these agents would be most effective in patients with ISD alone, multiple reports have shown clinical efficacy in patients with hypermobility** (Herschorn et al, 1996; Steele et al, 2000; Bent et al, 2001). **Injectable agents may provide a rapid response for some patients and are an option for those who do not wish to undergo more invasive procedures. However, these patients must understand that efficacy and duration of these agents are inferior to surgery and follow-up injections may be required. Other possible indications include elderly patients, those with high anesthetic risk, or those willing to accept an improvement rather than cure of their SUI symptoms** (Appell et al, 2009).

Detrusor overactivity should be treated before injection because results may be compromised (Herschorn et al, 1996). Severe urethral scarring from radiation or surgery may affect mucosal pliability by preventing bulking and retention of the injectable agent in the urethra.

Contraindications include active urinary tract infection and hypersensitivity to the injectable material.

Patient History

Patients who may be candidates for injectable agents should undergo a diagnostic evaluation to confirm the diagnosis in a similar fashion to other SUI patients. A focused history to characterize the chief complaint including the frequency, severity, and degree of bother should be done. An assessment of other urinary symptoms should be completed, and the desire for treatment should be ascertained. Helpful tools include various validated Symptom and Quality of Life questionnaires and frequency-volume charts (Appell et al, 2009; Abrams et al, 2010).

Physical Examination

The physical examination should provide information about the cause of the lower urinary tract symptoms and suggest additional management options. The general examination should include an abdominal examination to evaluate the skin, surgical incisions, and the presence of any hernias or abdominal masses, including a full bladder.

Pelvic Examination

The patient is placed in the lithotomy position. The external genitalia should be examined for dermatologic lesions and inflammatory conditions. The internal genitalia should be examined for estrogen deficiency, urine or abnormal vaginal discharge, pelvic organ prolapse, and abnormal pelvic masses. The poorly estrogenized vaginal wall has a thinned epithelium with loss of transverse rugae, which are normally present in its lower two thirds (Fantl et al, 1994). The patient should be examined with a comfortably full bladder to assess stress leakage and, if necessary, with an empty bladder to assess other pelvic organ prolapse and masses.

Because incontinence (or pelvic organ prolapse) may not be evident, or its full extent demonstrated, in the dorsal lithotomy position, it has been recommended that the patient be examined in the semi-upright or even upright position (Walters and Karram, 1992). A systematic examination of the vaginal walls and perineum should also be done. (For details, see Chapter 64.)

Urethral mobility can be observed with the patient straining or by the Q-tip test (Crystle et al, 1971). The angles of deflection of the Q-tip at rest and with straining are measured with a goniometer. *Hypermobility* is defined as a maximum strain axis of more than 30 degrees from the horizontal. Urethral axis testing does not diagnose any form of incontinence because continent women may demonstrate rotational descent of the urethra (Fantl et al, 1986) and incontinent women may have no descent. Although urethral axis testing has been shown to be reproducible (Fantl et al, 1986), it has not been compared with other radiologic methods. However, it may be helpful in assessing the degree of hypermobility.

If the patient has a fixed nonmobile urethra, especially if there has been previous SUI surgery, and leaks with coughing and/or straining, most likely that patient has ISD as the predominant cause of the SUI. However, if hypermobility is present the relative contribution of the causes (ISD vs. anatomic support) cannot be ascertained clinically.

Additional Testing

The initial evaluation of urinary incontinence in women includes a history, physical examination, urinalysis, and measurement of postvoid residual urine (Abrams et al, 2010). The basic evaluation may be satisfactory for proceeding with treatment, including surgery, for patients with straightforward SUI associated with hypermobility with normal postvoid residual volume (Fantl et al,

1996). The indications for additional testing include an inability to make a definitive diagnosis based on symptoms and the initial evaluation, concomitant overactive bladder symptoms, prior lower urinary tract surgery (including failed anti-incontinence procedures), known or suspected neurologic disease affecting the bladder, a negative stress test, abnormal findings of urinalysis such as hematuria or pyuria, abnormal levels of postvoid residual urine, beyond hymen and symptomatic pelvic prolapse, and dysfunctional voiding (Appell et al, 2009). Additional testing can include pad testing and/or use of a voiding diary, urodynamic studies, cystoscopy, and imaging. The evaluation can be tailored to elucidate the patient's problem.

Urodynamic Studies. In the evaluation of the patient with SUI, urodynamic studies before interventional treatment are helpful in specific circumstances. These are to confirm the diagnosis if the symptoms are confusing or complex and other problems are suspected, such as detrusor overactivity, urethral obstruction or voiding dysfunction, low bladder compliance, and/or impaired or absent detrusor contractility (National Institute for Health and Clinical Excellence, 2006; Appell et al, 2009). Urodynamic studies have also been recommended if there has been previous surgery for SUI or anterior compartment prolapse (National Institute for Health and Clinical Excellence, 2006). There is controversy as to whether urodynamic studies are warranted in the straightforward or pure SUI patient with no previous surgery. The National Institute for Health and Clinical Excellence guidelines (2006), similar to the updated American Urological Association guidelines (Appell et al, 2009), did not recommend testing, whereas testing was recommended by the recent 4th International Consultation on Incontinence (Hosker et al, 2009). This was based largely on a report from Agur and coworkers (2009) that showed that only 5.2% of 6276 women in a urodynamic patient database had pure SUI and of those a fourth had other findings that could impact clinical decision making, such as detrusor overactivity, voiding dysfunction, and absence of SUI on testing.

Because injectable agents are indicated for the ISD component of SUI, can urodynamic studies assess ISD? Two measures of urethral function have been used: maximum urethral closure pressure (MUCP) and ALPP. An MUCP of less than or equal to 20 cm H_2O has been suggested as indicating clinically significant urethral weakness, but there is controversy regarding the diagnostic and predictive value of urethral pressure profilometry in characterizing ISD (Weber, 2001). **Similarly, an ALPP of less than or equal to 60 cm H_2O was identified as an indicator of severe ISD** (McGuire et al, 1993) **but many studies have not confirmed the test's value in quantifying the degree of ISD** (Koelbl et al, 2009). **Previously, ALPP measurements of initially less than or equal to 65 cm H_2O and then less than or equal to 100 cm H_2O were used as indicators of ISD to justify the use of injectable agents** (Appell and Winters, 2007). **However, because ISD may be present in many patients with SUI with or without urethral hypermobility** (Koelbl et al, 2009), **the specific value of either the MUCP or ALPP may be of little importance in the clinical decision about the use of injectable agents.** As with other patients with SUI who opt for interventional therapy, urodynamic studies are helpful for the reasons mentioned earlier.

Cystoscopy. Routine cystoscopy is not recommended for the evaluation of SUI. However, it is indicated for the evaluation of incontinent patients who have sterile hematuria or pyuria; urgency incontinence to rule out other pathologic processes (e.g., bladder tumor, interstitial cystitis); recurrent or iatrogenic incontinence when surgery is indicated or planned; vesicovaginal fistula or extraurethral incontinence (Tubaro et al, 2009); and when urodynamic studies fail to duplicate symptoms of incontinence (Fantl et al, 1996). Furthermore, **preinjection cystoscopy is helpful to make sure that there are no adverse factors or unexpected findings that may prevent or compromise the injection procedure such as extensive urethral scarring from previous surgery, irradiation, or trauma, foreign bodies, or urethral diverticula.**

Injection Techniques

The materials can be administered under local anesthesia with cystoscopic control as an outpatient procedure. Both the **periurethral** and **transurethral** methods have been done to implant the agent within the urethral wall, preferably into the submucosa or lamina propria. It is thought that the implant should be positioned at the bladder neck or proximal urethra. Different sites can be chosen such as the 3- and 9-o'clock or 4- and 8-o'clock positions. The needle size depends on the viscosity of the agent. Preoperative and postoperative antibiotics are frequently administered. The technique of injection is seen in Figures 74–3 and 74–4. Additional bilateral periurethral infiltration of 2 to 3 mL of 1% or 2% aqueous lidocaine injected lateral to the urethra may improve patient comfort. The goal with current injectable agents is to create mucosal apposition at the end of treatment.

Periurethral Technique

The patient is placed in the lithotomy position and prepared and draped in the usual sterile fashion. Topical 2% urethral lidocaine jelly is instilled into the meatus. Perimeatal blebs are raised with 1% or 2% aqueous lidocaine at the 3- and 9-o'clock or 4- and 8-o'clock positions 3 to 4 mm lateral to the urethral meatus with a 25-gauge needle. A 20-Fr urethroscope with a 30-degree telescope is inserted into the urethra. The periurethral needle is introduced and advanced parallel to the endoscope sheath until its position can be seen cystoscopically just below the bladder neck within the mucosa. The surgeon can hold the cystoscope in one hand and advance the needle with the other. Care must be taken to prevent the needle from getting too close to or entering the urethral lumen because rupture of the mucosa and extravasation will occur. Rocking the needle will confirm the position of the tip. If penetration of the mucosa occurs, the needle should be removed and repositioned. The substance is injected either unilaterally or bilaterally to create the appearance of "prostatic" lobes (Fig. 74–5). Transvaginal injection with the needle placed through the biopsy port of an ultrasound probe has also been described (Appell, 1996).

An 18-gauge "bent tip needle" has been designed for the periurethral approach for placement of carbon-coated zirconium spheres (Durasphere; Boston Scientific, Natick, MA) within the proper plane (Appell and Winters, 2007).

Transurethral Techniques

With Cystoscopic Monitoring. The implant can also be injected transurethrally through the cystoscope with specially designed injection needles or with other devices that do not necessitate cystoscopy. In this approach a 0-, 12-, or 30-degree lens may be used. Various cystoscope sheaths are available, but one with a flat rather than beaked end will prevent the needle from penetrating the urethra proximal to the view from the lens. Endoscopic instrument companies have an array of equipment designed for transurethral injections. The material can be injected through a

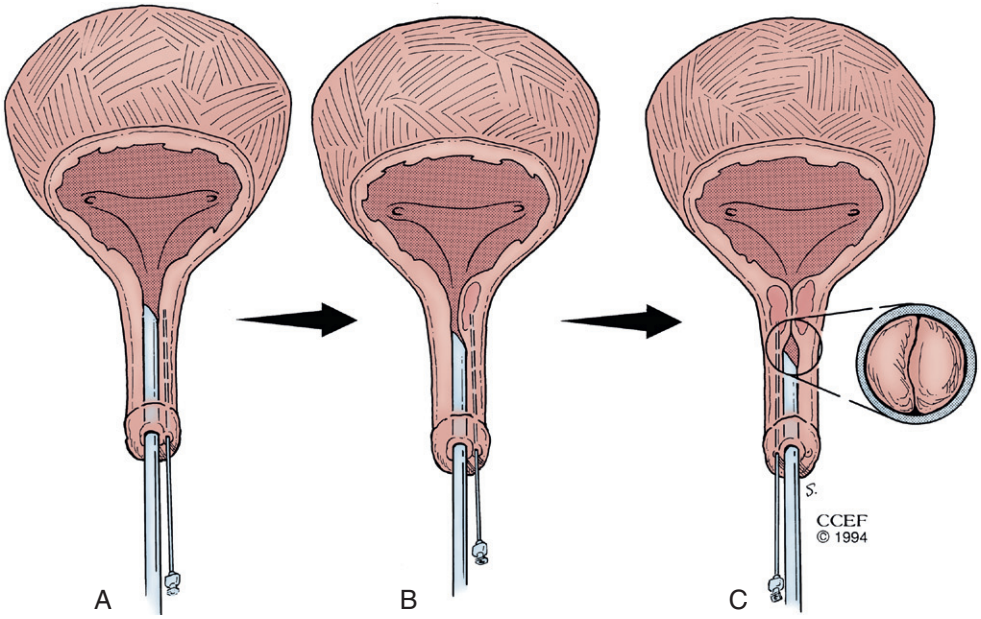


Figure 74–3. Periurethral collagen injection. The 20-Fr cystoscope with a 30-degree lens is positioned in the urethra while the substance is injected into the bladder neck region. **A,** Appearance of the urethra before treatment. **B,** Periurethral needle positioned in the proximal urethra below the bladder neck. **C,** Appearance of the urethra after injection. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1994-2011. All Rights Reserved.)

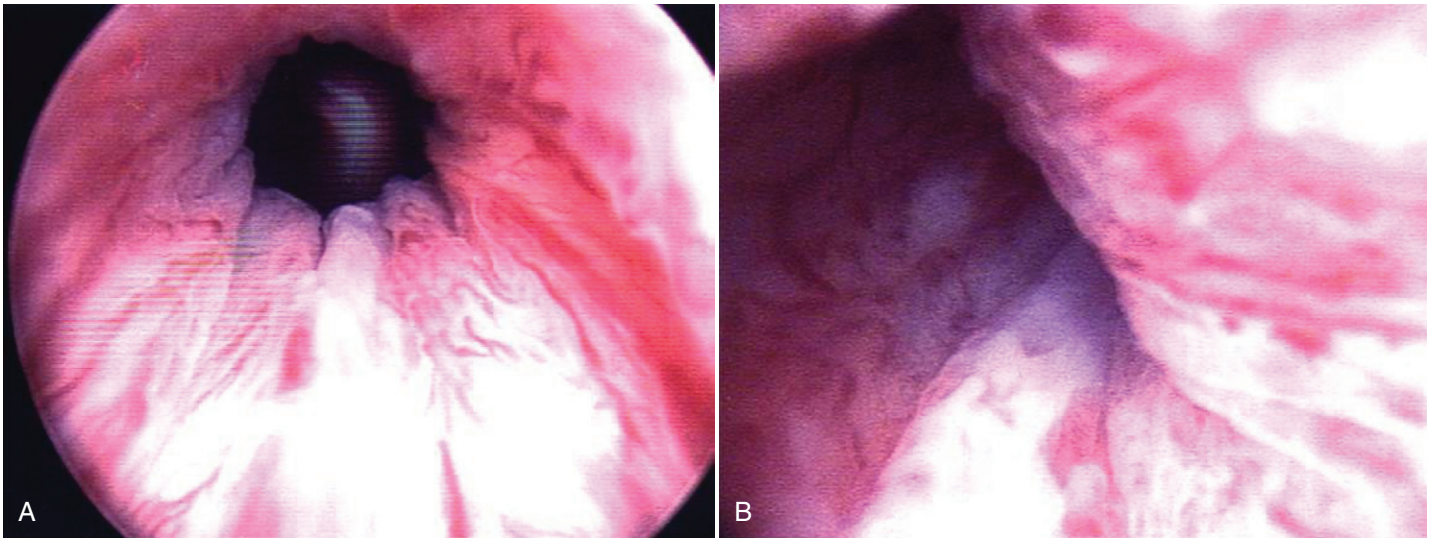


Figure 74–4. **A,** Cystoscopic view of the open bladder neck region before injection. **B,** Collagen has been injected via the periurethral route on the patient's left side. Note the intraluminal bulking effect of the bulking agent.

semi-rigid needle that is advanced through a working element or a flexible needle that is advanced by the surgeon. Both have 22-gauge tips that are about 1 cm long.

The patient is prepared in the same fashion as with the periurethral approach. Topical urethral lidocaine jelly as well as aqueous lidocaine injected periurethrally can be used. The injection needle is inserted into the urethra at a 30- to 45-degree angle and advanced proximally in the submucosal region under the surface of the mucosa. The point of penetration of the urethra has to be at a distance below the bladder neck of more than the length of the needle to prevent extravasation of the substance into the bladder. Injections can be given at the 3-, 6-, and 9-o'clock positions until mucosal apposition is achieved. The cystoscope should not be advanced through the bulked-up urethra and bladder neck to avoid compressing or causing extravasation of the injected material.

Because of its high viscosity, silicone microimplant (Macroplastique; Uroplasty, Inc, Minnetonka, MN) injections require the use of a ratcheted injection gun (Fig. 74–6A). The injection needle is 7 Fr with a 10-mm, 18-gauge needle tip.

The periurethral and transurethral approaches for collagen were compared first by Faerber and colleagues (1998), **who reported no significant difference in success rates and numbers of injections required in 24 patients with transurethral treatment versus 21 with a periurethral approach. However, significantly more collagen**

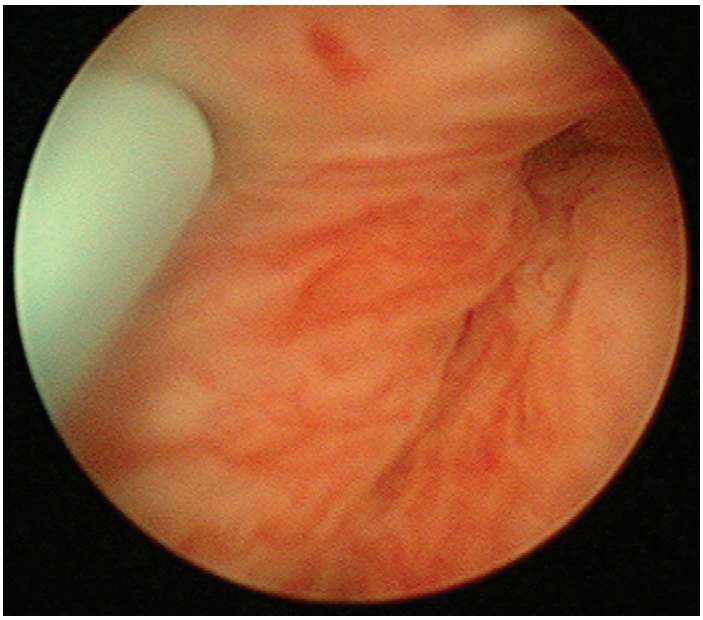


Figure 74–5. Appearance of urethra after injection of collagen with a transurethral needle that is seen on the left. Both sides of the urethra have been injected, giving the appearance of an occlusive prostate.

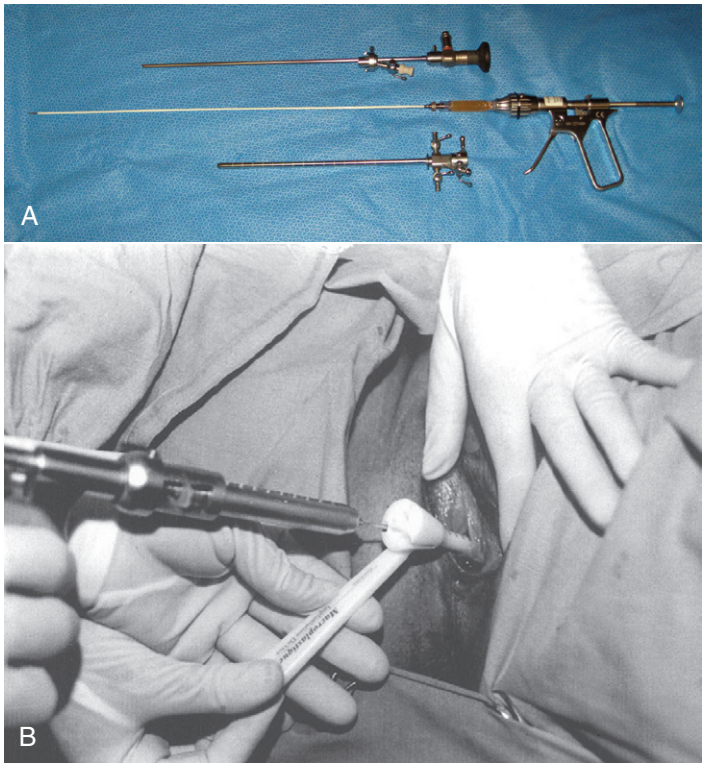


Figure 74–6. **A,** Silicone macroparticle injection gun. The injection needle is 7 Fr with a 10-mm, 18-gauge needle tip. **B,** The implantation procedure. The bulking agent is injected through the device using the injection gun and a rigid needle. (From Tamanini JT, D'Ancona CA, Netto NR Jr. Treatment of intrinsic sphincter deficiency using the Macroplastique Implantation System: two-year follow-up. J Endourol 2004;18[9]:906–11.)

was required for the periurethral approach. Schulz and coworkers (2004) **reported similar findings in 40 women randomly assigned to either technique. There was no difference in short-term success rate, but the 20 women assigned to the periurethral approach required more collagen than those assigned to the transurethral approach. The transurethral approach is now much more commonly reported than the periurethral approach.**

Without Cystoscopic Monitoring. A handheld device that allows the operator to inject Macroplastique transurethrally without cystoscopy was introduced by Henalla and colleagues (2000) in a multicenter trial of 40 patients (see Fig. 74–6B). Device efficacy and acceptability were rated highly by the surgeons at 92.5% and 95%, respectively, and at 3 months 74.3% of patients had a good outcome. Twelve-month outcomes in a cohort of 21 patients who had Macroplastique injections administered with this device were reported by Tamanini and coworkers (2003): 57.1% of patients considered themselves cured, 19% were improved, and 23.8% experienced failure. Outcomes at 2 years showed some deterioration in results, with 47% considered cured, 14.3% improved, and 38.1% failed (Tamanini et al, 2004).

A handheld Implacer device was designed to administer hyaluronic acid dextranomer (Zuidex), but it was withdrawn from the market with failure of the North American multicenter randomized trial to demonstrate noninferiority of Zuidex compared with collagen (Lightner et al, 2009).

Periprocedural Care

Although randomized trials have not been done, prophylactic antibiotics with a fluoroquinolone or trimethoprim-sulfamethoxazole (TMP-SMX) for 24 hours or less can be recommended (Wolf et al, 2008). An additional 2 to 3 days has also been suggested (Appell and Winters, 2007).

After the injection the patient is asked to cough or strain in the supine and then upright positions. If leakage still occurs, more agent may be given. If no leakage is seen the procedure may be terminated. The patient then voids and can be discharged. Urinary retention can be treated by insertion of a fine Foley catheter (12 to 14 Fr or smaller) overnight or intermittent catheterization. Although not specifically reported, an indwelling Foley catheter may cause molding of the agent and lead to early failure, so long-term catheterization should be avoided.

Reinjections

The minimum timing for reinjections varies and depends on the agent. Although collagen can be reinjected within 7 days, most clinicians wait 4 weeks or longer to assess response of the urethra and the need for reinjection (Appell and Winters, 2007). Macroplastique injections can be repeated after 12 weeks. Durasphere can be reinjected after a minimum of 7 days (Lightner et al, 2001) and calcium hydroxyapatite (Coaptite; Bioform Medical, San Mateo, CA) can be reinjected after 1 month or less (Mayer et al, 2007). Reinjection timing with other new agents, if known, is mentioned later in the chapter.

Pitfalls in Reported Study Results of Durability

A number of pitfalls in reporting of injectable studies can lead to inflated success rates. Because injectable agents

can be repeated if the patient is not a success or fails, authors should specify whether that time point is after all treatments have been completed or whether it is from baseline. If durability is reported after all injections are administered, then an accurate picture of duration of efficacy can be conveyed. A Kaplan-Meier curve of efficacy has been useful in showing what happens to patients' continence outcome over time (Herschorn and Radomski, 1997; Lightner et al, 2001). **Nevertheless, some studies report duration of results from initial treatment** (Richardson et al, 1995) **or do not specify it** (Monga et al, 1995). **This may overestimate success because failures are re-treated and can be counted as successes within the follow-up period. Another pitfall is reporting success rates on cohorts of patients followed for the long term rather than on all patients treated from the start** (Stenberg et al, 2003). **If the patients in whom the procedure failed or those lost to follow-up are not included in the denominator the success rate is higher.**

Outcome Assessment in Bulking Agent Clinical Trials by the U.S. Food and Drug Administration

The Stamey 0 to 3 Grading System (Stamey, 1979) (Table 74–2) for SUI has been recommended as the primary outcome measure by the FDA since the original U.S. collagen trial (McGuire and Appell, 1994). Although the scale is extensively used there is little evidence that it is as valid or reliable as other measures, such as voiding diaries, pad tests, and leak point measurements (Payne et al, 2009).

Systematic Reviews of Injectable Agents for Women with SUI

The *Cochrane Database of Systematic Reviews* published an update review of injectable agents in women in 2009 (Keegan et al, 2007). The authors reviewed 12 trials with 1318 women. They concluded that the trials were small and generally of moderate quality. Pending further evidence, injection therapy may represent a useful option for short-term symptomatic relief for women with comorbidity that precludes anesthesia. Two or three injections are likely to be required to achieve a satisfactory result.

Injection therapy was also reviewed at the Fourth International Consultation on Urinary Incontinence (Smith et al, 2009). **Evidence for the benefit of injectable agents was also considered to be limited and of short term. Greater symptomatic improvement was observed after surgery, which is of higher risk. There is no evidence for the superiority of any bulking agent over another (although new data on silicone microimplant injections may challenge this** [Ghoniem et al, 2009]**). There are also no available data comparing bulking agents with nonsurgical or minimal access surgical techniques. It was recommended that, if bulking agents are to be used, women should be made aware that repeat injections are likely to be required, that efficacy diminishes with time, and that this therapy is inferior to that of conventional surgical techniques. Women should also be aware of alternative minimally invasive procedures.**

Table 74–2.

Stamey Incontinence Grading System

Grade 0	Continent
Grade 1	Patient loses urine with sudden increases in abdominal pressure but not while supine
Grade 2	Patient loses urine with physical stress (walking; changing from a reclining to a standing position; sitting up in bed)
Grade 3	Patient with total incontinence; urine loss unrelated to physical activity and/or position

Key Points: Use of Injectable Agents in Female Stress Urinary Incontinence

- The ideal injectable agent that is biocompatible, nonantigenic, noncarcinogenic, and nonmigratory, causes little or no inflammatory reaction or fibrotic ingrowth, and retains efficacy over time has not yet been found.
- The goal of injectable agents is to augment or restore urethral mucosal coaptation and its "hermetic seal effect" contribution to the continence mechanism.
- Although initially it was thought that these agents would be most effective in patients with ISD alone, multiple reports have shown clinical efficacy in patients with hypermobility.
- Injectable agents may provide a rapid response for some patients and are an option for those who do not wish to undergo more invasive procedures. The efficacy and duration are inferior to surgery, and follow-up injections may be required. Other possible indications include elderly patients, those with high anesthetic risk, or those willing to accept an improvement rather than cure of their SUI symptoms.
- The workup includes history and physical examination. Urodynamic studies are helpful. Cystoscopy is helpful to rule out adverse factors such as scarring, foreign bodies, and diverticula that may prevent or compromise injections.
- Injectable agents are indicated for the ISD component of SUI. However, because ISD may be present in many patients with SUI with or without urethral hypermobility the specific value of either the MUCP or the ALPP may be of little importance in the clinical decision about the use of injectable agents.
- The results of periurethral and transurethral techniques are similar. Most reports are now about the transurethral technique.
- Periprocedural antibiotics for 24 hours or less can be recommended.

Currently Used Injectable Agents

Glutaraldehyde Cross-linked Bovine Collagen (Contigen)

Glutaraldehyde cross-linked collagen (Contigen; C.R. Bard, Covington, GA) is a highly purified suspension of bovine collagen in normal saline containing at least 95% type I collagen and 1% to 5% type III collagen (Remacle et al, 1990). This cross-linking makes the collagen resistant to the fibroblast-secreted collagenase. As a result of this, the collagen is only very slightly resorbed. The implant causes little inflammatory reaction or granuloma formation and is colonized by host fibroblasts and blood vessels. It is not known to migrate; however, it does degrade over time with

volume loss via absorption of the carrier medium (Kershen and Atala, 1999) and may be replaced by host collagen, to explain its persistence (Keefe et al, 1992). To decrease its antigenicity the collagen is prepared by selective hydrolysis of the nonhelicoidal amino- and carboxy-terminal groups (telopeptides) of the collagen molecule that are the antigenic parts of the molecule (Remacle and Declaye, 1988).

All patients must undergo a skin test into the volar aspect of the forearm 30 days before treatment. Approximately 3% of patients will have a positive skin test reaction, with 70% showing the reaction within 3 days, indicating a preexisting sensitivity to bovine dermal collagen through dietary exposure. The remaining 30% do not respond until later so a 4-week period is required (Keefe et al, 1992). A negative skin test does not preclude development of a hypersensitivity reaction to subsequent treatment and, although infrequently used, a second skin test has been recommended (Elson, 1989; Stothers and Goldenberg, 1998). Positive responders should be excluded.

Collagen can be injected transurethrally or periurethrally through a 22-gauge needle. It is supplied in syringes that contain about 3 mL of collagen. Ordinarily one to three syringes are used during each treatment.

Collagen is the standard against which all new injectable agents have been compared. The results of these trials are outlined in the following sections. C.R. Bard, Inc., has announced that Contigen will not be available after 2011.

Results. The most extensively reported injectable agent has been collagen (Table 74–3). It was first reported by Shortliffe and colleagues in 1989, and since then numerous reports of its efficacy, safety, ease of administration, and relative lack of morbidity have appeared. The author's original report, with short-term follow-up of 32 patients for 6 months (Herschorn et al, 1992), showed a cured and improved rate of 90.3%. Longer-term results of more than 1 to 2 years vary from 57%, cure and improved (Khullar et al, 1997), to 94% (Cross et al, 1998). Most patients need one to two treatment sessions with means of 5.6 to 15 mL of collagen. Winters

Table 74–3.

Comparison of Collagen Parameters and Results

STUDY	NO. PATIENTS	TYPE OF INCONTINENCE	FOLLOW-UP (mo)	Results		
				No. Dry (%)	No. Improved (%)	No. Failed (%)
Eckford and Abrams, 1991	25	Not specified	3	16 (64)	4 (16)	5 (20)
Kieswetter et al, 1992	16	Not specified	9	7 (44)	7 (44)	2 (12)
Stricker and Haylen, 1993	50	ISD	Mean: 11 Range: 1-21	21 (42)	20 (40)	7 (14)
McGuire and Appell, 1994	17	Mobile	>12	8 (47)	3 (17)	6 (35)
	137	ISD	>12	63 (46)	47 (34)	29 (19)
O'Connell et al, 1995	44	42 with ISD 2 hypermobile	1-2 (longest 7)	20 (45)	8 (18)	16 (37)
Moore et al, 1995	11	Types 1 and 3	2	1 (9)	7 (63)	2 (18)
Winters and Appell, 1995	50	ISD	>12	48 (96) dry or socially continent	2 (4)	
Monga et al, 1995	60	Some hypermobile	3 (n = 59)	27 (46)	24 (40)	
			12 (n = 54)	22 (40)	20 (37)	
			24 (n = 29)	14 (48)	6 (20)	
Richardson et al, 1995	42	ISD	46 (10-66 after 1st injection)	17 (40)	18 (43)	7 (17)
Homma et al, 1996	60	Hypermobile	24	4 (7)	39 (65)	17 (28)
Faerber, 1996	12	Type 1	10.3 Range: 3-24	10 (83)	2 (17)	0
Herschorn et al, 1996	181	Type 1: 54	Mean: 22 Range: 4-69	42 (23)	94 (52)	45 (25)
		Type 2: 67	≥24 (n = 62)	27 (43.5)	29 (46.8)	6 (9.7)
		Type 3: 60	≥36 (n = 25)	13 (52)	8 (32)	4 (16)
Smith et al, 1997	94	Type 3	Median: 14	36 (38.3)	27 (28.7)	31 (33)
Khullar et al, 1997	21	Not specified	24 (minimum)	10 (48)	2 (9)	9 (43)
Swami et al, 1997	107	Some hypermobile	24 (minimum)	27 (25)	43 (40)	37 (35)
Cross et al, 1998	103	Type 3	Median: 18 Range: 6-36	Substantially improved 103 (74)	29 (20)	7 (6)
Corcos and Fournier, 1999	40	Type 1(8) Type 2 (20) Type 3 (12)	Average: 52 Range: 47-55	12 (30%)	16 (40%)	12 (30%)
Gorton et al, 1999	53	Hypermobile	60 (minimum)	1 (2)	13 (25)	39 (73)
Groutz et al, 2000	63	Type 3	Mean: 6.4 ± 4.9	13%	10% good 17% fair 42% poor	18%
Steele et al, 2000	40	9 hypermobile	8.4	71%	29%	
		31 without	8.2	32%	68%	
Bent et al, 2001	90	Types 1 and 2	12	19 (21%)	19 (21%)	62 (58%)

ISD, intrinsic sphincter deficiency.

and Appell (1995) reported a 50% rate of complete continence in a multicenter trial after 2 years. Corcos and Fournier (1999) reported 4-year follow-up with 40% improvement and 30% cure. The longest follow-up reported to date is from Gorton and coworkers (1999), who reported on 53 patients with at least 5 years after their last collagen injection: only 14 (26%) had persistent improvement, and of these 1 (2%) was completely dry. Because patients in any series are treated at different times and durations of follow-up vary, a Kaplan-Meier curve is useful to display the persistence of a good result (Herschorn and Radomski, 1997). Figure 74–7 shows that the probability of remaining dry after the last collagen injection was 72% at 1 year, 57% at 2 years, and 45% at 3 years. A similar deterioration over time was reported by Gorton and coworkers (1999).

Multiple factors that may influence outcome have been reported. Previous incontinence surgery was identified by Eckford and Abrams (1991) as a favorable factor but was not supported by others (Herschorn et al, 1996). Preoperative detrusor overactivity may be an adverse factor (Herschorn et al, 1996; Smith et al, 1997). The degree of mucosal coaptation after injection as judged on cystoscopy was not found to correlate with long-term improvement (Kim et al, 1997). Elia and Bergman (1996) used perineal ultrasonography to measure the location of the collagen deposit 3 months after the procedure. They reported that a positive outcome was more likely if collagen was located at a distance of 6 mm or less from the bladder neck. Defreitas and coworkers (2003) correlated a good outcome to circumferential distribution of collagen around the urethra. They did three-dimensional transvaginal ultrasonography in 46 patients at a median follow-up of 14 months and found that the 21 satisfied patients had a higher rate of circumferential distribution compared with the 25 unsatisfied patients. Kuhn and colleagues (2008) compared the site of injection (i.e., bladder neck versus midurethra) in a small randomized study. They found no difference in outcome between the two sites.

Collagen and Hypermobility. The use of collagen for patients with hypermobility has been reported extensively. Moore and colleagues (1995) included patients with hypermobility. Faerber (1996) treated elderly patients with type 1 abnormality. In the report by McGuire and Appell (1994) the results at more than 1 year in women with ISD were similar to those in women with hypermobility, although there were far more women with ISD. Monga and coworkers (1995) included patients with hypermobility and found that cure rates were not reduced for women with up to 2.5 cm of movement. In the author's series of 181 patients there was no significant difference in outcome in patients with or without hypermobility (Herschorn and Radomski, 1997). Corcos and Fournier (1999) found no difference between patients with and without bladder neck hypermobility in their 4-year follow-up on 40 patients. Steele and colleagues (2000) found that urethral mobility did not significantly affect the success rate. Furthermore, 4 of 6 patients with urethral hypermobility were dry at the 6-month follow-up examination, whereas among the 19 women without hypermobility only a 32% remained dry. Bent and colleagues (2001) reported a 44% cure/improvement rate for 12 months in a cohort of 90 women with SUI and hypermobility. **They concluded, as have others, that collagen injection therapy is appropriate for women with hypermobility.**

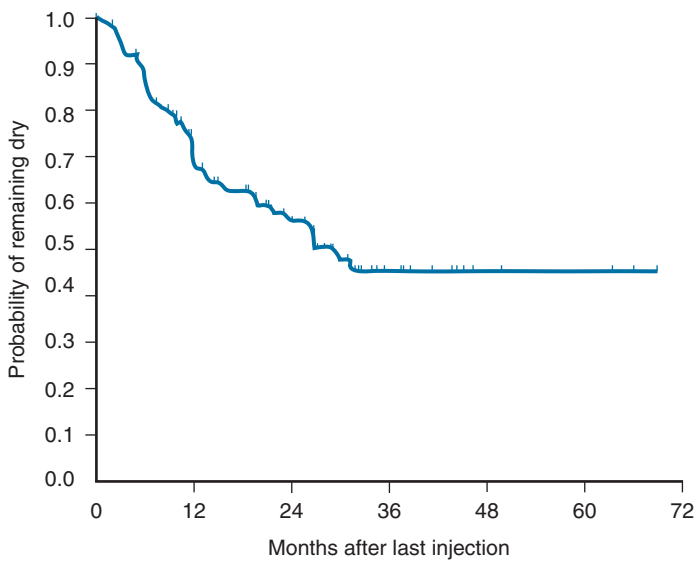


Figure 74–7. Durability: Kaplan-Meier curve showing durability of cure of incontinence after the last collagen injection in 78 patients. (From Herschorn S, Radomski SB. Collagen injections for genuine stress urinary incontinence: patient selection and durability. Int Urogynecol J Pelvic Floor Dysfunct 1997;8[1]:18–24.)

Collagen versus Surgery. Berman and Kreder (1997) found that after an average follow-up of 14.9 months after sling cystourethropexy 71.4% of the patients were continent versus 26.7% of patients with collagen after 21.3 months. They analyzed associated costs and concluded that surgery was more cost effective than collagen. In a multicenter prospective randomized trial, Corcos and colleagues (2005) reported a lower success rate of 53.1% in the collagen-treated patients versus 72.2% in the surgery group. However, general and disease-specific quality of life scores were similar, satisfaction was slightly higher in the surgery group, but complications were less frequent and severe with collagen. Corcos and colleagues concluded that collagen was a reasonable alternative to surgery. The follow-up was relatively short, and the study was done before the era of midurethral slings.

Complications. **Treatment-related morbidity has been minimal. Common complications include transient urinary retention, which ranges from 1% to 21%** (Herschorn et al, 1992; Winters and Appell, 1995; Appell and Winters, 2007) **and can be managed with intermittent catheterization or short-term use of a Foley catheter. Urinary tract infection occurs in 1% to 25% of patients** (Herschorn et al, 1992; Winters and Appell, 1995; Appell and Winters, 2007). **De novo detrusor overactivity was reported in 11 of 28 elderly women (39%) treated by** Khullar and coworkers (1997). Stothers and colleagues (1998) **reported de novo urgency with urgency incontinence in 43 of 337 patients (12.6%), 21% of whom did not respond to anticholinergic agents. Hematuria can occur in 2% of patients** (Appell and Winters, 2007). Extravasation resolves quickly with flushing away of the dilute collagen suspension and sealing over of the small needle site.

A rare complication is periurethral abscess formation (Sweat and Lightner, 1999). Another is a reaction in the previously negative skin test site after a urethral collagen injection (Stothers and Goldenberg, 1998). This occurred in 3 patients (1.9%) and was associated with arthralgias in 2. This reaction has been reported before in dermatology (Elson, 1989), and two negative pretreatment skin tests have been suggested to prevent it. The potential for hypersensitivity reactions is present because antibody production is stimulated by collagen injection (McClelland and Delustro, 1996).

Vesicovaginal fistula occurring after collagen injections for SUI in 2 women after cystectomy and neobladder was described by

Pruthi and colleagues (2000). Carlin and Klutke (2000) reported a urethrovaginal fistula in a woman whose warfarin was not completely reversed. She had a postinjection hematoma that ultimately fistulized to the vagina.

Carbon-Coated Zirconium Beads (Durasphere)

Durasphere consists of nonabsorbable pyrolytic carbon-coated zirconium beads suspended in a water-based polysaccharide carrier gel of 2.8% β-glucan (Lightner et al, 2001). Pyrolytic carbon has been used in medical devices such as heart valves. The bead size ranges from 212 to 500 μm, which is larger than the threshold for particle size migration of 80 μm (Malizia et al, 1984). It is nonantigenic, and no skin testing is required. The agent can be delivered through an 18-gauge needle via the transurethral or periurethral approach with cystoscopic monitoring. It is more viscous than collagen, so greater pressure is required for delivery into the tissues.

As a result of reported difficulty in injecting the agent the beads were modified and made smaller. The bead sizes of Durasphere EXP now range from 90 to 212 μm, still larger than 80 μm threshold for migration.

Results. Published results with Durasphere are shown in Table 74–4. In the original multicenter randomized 235-patient clinical trial of Durasphere versus collagen, Lightner and colleagues (2001) reported a 12-month continence grade improvement rate of 76/115 (66.1%) in the Durasphere group versus 79/120 (65.8%) in the collagen group ($P = 1.000$). They also reported that at 1 year after their last treatment 49 of 61 (80.3%) in the Durasphere group versus 47 of 68 (69.1%) in the collagen group had a continence grade improvement ($P = .162$). Both injectable agents performed similarly. There was also no difference in number of injections or in results of a pad weight test. However, the injected initial and repeat injection volume of Durasphere was significantly less than those of collagen. It is notable that in the 12-month result after the last injection 45% (106/235) of the study patients were not accounted for.

In another randomized prospective trial of Durasphere versus collagen, Andersen (2002) reported 80% (20/25) of Durasphere patients versus 61.9% (13/21) of collagen patients had a continence grade improvement ($P = .205$) after a mean of 2.6 and 2.8 years, respectively, after initial treatment. This is similar to the study of Lightner and colleagues (2001).

In a series of 13 women, Pannek and colleagues (2001) reported a decline in success from 76.9% at 6 months to 33% at 12 months. In contrast to the study of Lightner and colleagues (2001) they demonstrated particle migration locally and to distant sites on follow-up plain radiographs. As a result of reported injection difficulties, Madjar and coworkers (2003) modified the technique by injecting local anesthetic into the mucosa to raise a circumferential bleb into which the Durasphere is injected. They reported results on 46/70 (65.7%) of patients. At a mean of 9.4 months, 65.2% of patients considered themselves to be cured or improved.

In a longer-term follow-up matched-cohort study, Chrouser and colleagues (2004) reported initial success of 63% in both groups. With longer follow-up of 24 and 36 months, Durasphere was effective in 33% and 21% whereas collagen was effective in 19% and 9%, respectively. The results were not significantly different. Sokol and coworkers (2008) tried to improve on the results of transurethral collagen by injecting additional periurethral Durasphere. However, they failed to show any benefit. After 6 months there was no difference in cure rates: 33.3% in the combined group versus 29.4% in the collagen alone group.

Overall, no study has shown a benefit over collagen.

Complications. In the multicenter randomized trial of Durasphere versus collagen the adverse event profiles were similar (Lightner et al, 2001). However, more women had significantly more post-treatment urgency and acute retention with Durasphere versus collagen: 24.7% and 16.9% versus 11.9% and 3.4%, respectively. Pelvic radiographs taken at 1 and 2 years after injection showed stability of the bulking agents at the injection site. Pannek and associates (2001) reported particle migration. This was attributed to the high pressure necessary to inject the viscous material with large particles, resulting in material displacement into vascular or lymphatic spaces (Appell et al, 2006). Durasphere EXP with its smaller particles may be less likely to lead to this.

Other reported adverse events include urethral mucosal prolapse (Ghoniem and Khater, 2006) and periurethral sterile abscess formation in 2.9% of a series of 135 patients (Madjar et al, 2006).

Silicone Microimplants (Macroplastique)

Silicone microimplants (Harriss et al, 1996) are solid polydimethylsiloxane (silicone rubber) particles suspended in a nonsilicone carrier gel that is absorbed by the reticuloendothelial system and excreted unchanged in the urine. Because 99% of the particles are between 100 μm and 450 μm in diameter, the likelihood of migration is low. Henly and coworkers (1995) demonstrated distant migration of small particles, less than 70 μm, but no migration of particles greater than 100 μm in diameter. Although there was a typical histiocytic and giant cell reaction within the injection site there was no granuloma formation in response to the larger particles. Because the substance is quite viscous it must be injected with an injection gun and a 16-gauge tip transurethral needle. The vials contain 2.5 mL of silicone microimplants.

Results. The results for silicone microimplants are shown in Table 74–5. Harriss and colleagues (1996) reported on 40 patients

Table 74–4.

Carbon-Coated Zirconium Beads (Durasphere): Results for Female Stress Incontinence

STUDY	NO. PATIENTS	FOLLOW-UP (mo)	Results		
			No. Dry (%)	No. Improved (%)	No. Failed (%)
Lightner et al, 2001	61 (Durasphere)	12	49 (80.3)		12 (19.7)
	68 (collagen)		47 (69.1)		21 (30.9)
Andersen, 2002	26 (Durasphere)	31.2 (25 pts.)	10 (40)	10 (40)	5 (20)
	26 (collagen)	33.6 (21 pts.)	3 (14)	10 (48)	8 (38)
Pannek et al, 2001	9	12		3 (33.3)	6 (66.7)
Madjar et al, 2003	46	9.4	6 (13)	24 (52.2)	16 (34.7)
Chrouser et al, 2004	43 (Durasphere)	24, 36	(33), (21)		(67), (79)
	43 (collagen)	24, 36	(19), (9)		(81), (91)

Table 74–5.

Results of Silicone Microimplant injections for Female Stress Urinary Incontinence

STUDY	NO. PATIENTS	FOLLOW-UP (yr)	Results		
			No. Dry (%)	No. Improved (%)	No. Failed (%)
Harriss et al, 1996	40	3	16 (40)	7 (18)	17 (42)
Sheriff et al, 1997	34	2	16 (48)		18 (52)
Koelbl et al, 1998	32	1	19 (60)		13 (40)
Usman and Henalla, 1998	102	0.25	69 (68)		
Radley et al, 2001	60	1.5	12 (20)	25 (41)	23 (39)
Barranger et al, 2000	21	2.5	4 (19)	8 (38)	9 (43)
Soliman and Evans, 2001	68	1.6	24 (35)	18 (26.5)	26 (38.2)
Peeker et al, 2002	22	≥2	14 (63.6)	3 (13.7)	5 (22.7)
Grdal et al, 2002	29	2	13 (45)	4 (17)	12 (41)
Tamanini et al, 2003	21	1	12 (57)	4 (19)	5 (24)
Tamanini et al, 2004	21	2	10 (47)	3 (14.3)	8 (38.1)
Plotti et al, 2009	24	1	10 (42)	10 (42)	4 (16)
Ghoniem et al, 2009	122 (Macroplastique)	1	45 (36.9)	30 (24.6)	47 (38.5)
	125 (collagen)		31 (24.8)	29 (23.2)	65 (52)

followed for a minimum of 3 years, at which time 16 (40%) were dry, 7 (18%) were improved, and 17 (42%) reported failure of the treatment. Twelve of the 16 required one injection, and 4 needed two injections to become dry. Sheriff and coworkers (1997) reported an overall success of 48% in 34 patients after unsuccessful surgery for SUI, and Koelbl and colleagues (1998) reported a 60% success rate in 32 women after 12 months but noted a time-dependent decrease in success. Radley and coworkers (2001) reported a success rate of 61% (19.6% cured and 41.1% improved) in 60 women after a mean of 19 months. Barranger and coworkers (2000) in a group of 21 patients reported a dry rate of 19%, an improved rate of 38%, and a failure rate of 52% at a median follow-up of 31 months; interestingly, they did not observe a time-dependent decrease in results. Tamanini and coworkers (2003, 2004) reported 1- and 2-year results in 21 patients with the use of a handheld noncystoscopic injector system (see Fig. 74–6B). There was a decrease in continence outcome after 2 years. Plotti and colleagues (2009) reported 84% cure/improvement rates in a series of 24 women with de novo SUI after radical hysterectomy.

Recently Ghoniem and colleagues reported the results of a North American multicenter randomized trial of Macroplastique versus collagen (Ghoniem et al, 2009). **After 1 year, 61.5% (75/122) with Macroplastique and 48% (60/125) with collagen had an improvement of at least 1 Stamey grade. This indicated that Macroplastique was noninferior to collagen ($P < .001$). The proportion of the patients who were dry was higher in the Macroplastique group at 36.9% versus 24.8% ($P < .05$). However, there were no significant differences in pad weight testing, quality of life scale, or adverse events.** The same authors subsequently reported the 2-year results in the Macroplastique group (Ghoniem et al, 2010). Eighty-four percent of those who had a benefit at 12 months maintained that level of cure or improvement to 24 months. That means that of the original 122 patients 51.7% had a good outcome at 2 years.

Complications. Self-limited side effects of urinary tract infection, hematuria, dysuria, urgency, frequency, voiding difficulty, and urinary retention have been reported (Ghoniem et al, 2009). Rarely erosion of the injectable occurs. The lack of a granulomatous reaction and migration of the large silicone particles may provide some benefit over smaller-particle injectable agents such as polytetrafluoroethylene, although long-term data are not yet available. Despite the laboratory and clinical evidence of safety with the large particles, concerns still exist about the small silicone particle migration and long-term tissue response to the injection (Henly et al, 1995).

Calcium Hydroxyapatite (Coaptite)

Calcium hydroxyapatite (Coaptite; Bioform Medical, San Mateo, CA), which is a normal constituent of bone, can be manufactured into particles of a spherical mean diameter of 100 μm (75 to 125 μm) suspended in a carboxymethylcellulose gel carrier. This exogenous substance has been used in orthopedic and dental applications (Bucholz, 2002), as well as soft tissue augmentation of vocal cords (Belafsky and Postma, 2004), face (Tzikas, 2004), and the ureteral orifice for reflux (Mevorach et al, 2006). Animal experiments have demonstrated the safety and biocompatibility of this substance. It stimulates fibroblast infiltration when placed into soft tissue, which may explain its long-term bulking effect after degradation of the carrier gel (Mayer et al, 2007).

The implant is currently supplied in 1-mL syringes and can be injected via a transurethral approach though a 21-gauge needle.

Results. Mayer and colleagues (2001) reported initial results in 10 women with ISD and limited hypermobility. After 1 year, 7 reported substantial improvement, 2 improved, and 1 had no change. No significant complications were reported. In a randomized prospective trial of calcium hydroxyapatite compared with collagen, Mayer and coworkers (2007) reported results in 231 women. Up to 5 injections were performed in the first 6 months of the trial. At 12 months, 83 (63.4%) of 131 patients who had injections of calcium hydroxyapatite showed improvement of one Stamey grade or more versus 57 (57%) of 100 collagen patients ($P = .34$). There was no difference in cure (39% calcium hydroxyapatite vs. 37% collagen) and improvement (50% calcium hydroxyapatite vs. 46% collagen) rates. More patients who had had calcium hydroxyapatite injections required only one injection, and the total average injected volume was lower (4.0 mL vs. 6.6 mL, respectively; $P < .0001$).

Complications. Minor adverse events such as transient retention (41%), urinary tract infection, and urgency incontinence (5.7%) were reported (Mayer et al, 2007). Serious adverse events were vaginal wall erosion of the implant and dissection of the material

beneath the trigone. Because this agent has a greater particle density than collagen it is thought to have the potential to cause more local tissue pressure effects.

Autologous Fat

Autologous fat has been used for aesthetic and defect reconstruction since the 1980s (Billings and May, 1989). Although fat is biocompatible and readily available, 50% to 90% of the transferred adipose tissue graft may not survive (Horl et al, 1991). Graft survival depends on minimal handling, low suction pressure during liposuction, and the use of large-bore needles. Smaller grafts survive better than larger ones (Bircoll and Novack, 1987).

The procedure involves harvesting abdominal wall fat by liposuction either under local (Trockman and Leach, 1995) or general anesthesia (Su et al, 1998). The injection is usually carried out via the periurethral route with a 16- or 18-gauge needle. Postprocedural care may involve intermittent catheterization or even a suprapubic tube (Su et al, 1998).

Results. A number of reports of urethral fat injections have been published and appear in Table 74–6. Most of the series report short-term results with success apparently lower than that of other injectable agents, apart from the study of Su and colleagues (1998) with a follow-up of more than 12 months. Palma and coworkers (1997) showed that repeat injections improved the cure rate from 31% to 64%. Haab and colleagues (1997) reported a comparative study with collagen. After a mean of 7 months, 13% of the women with fat injection were cured versus 24% of the women with collagen injections. The subjective improvement rate was also higher with the collagen. Lee and colleagues (2001) reported a randomized double-blind study of autologous fat versus saline injection. At 3 months, 6 of 27 (22.2%) and 6 of 29 (20.7%) women were cured or improved in the fat and saline groups, respectively. In this study, periurethral fat injection did not appear to be more efficacious than placebo in treating SUI.

Since the publication of the randomized trial of Lee and colleagues (2001) **showing that fat was no more efficacious than saline, no further publications have appeared in the literature. Furthermore, the report of a death from fat embolism** (Currie et al, 1997) **most likely discouraged additional studies.** However, experimental work on the use of adipose-derived stem cells to help improve function after urethral injury has progressed in the rat model (Lin et al, 2010).

Complications. Reported complications are similar to other injectable agents with urinary infection, retention, hematuria, and extravasation. Additional problems with donor site, the abdominal wall, such as pain, hematomas, and infection may also be seen. Other noteworthy complications are urethral pseudolipoma (Palma et al, 1996) and fat embolism (Sweat and Lightner, 1999), one of which was fatal (Currie et al, 1997).

Key Points: Currently Used Injectable Agents for Female Stress Urinary Incontinence

- All patients must undergo a skin test into the volar aspect of the forearm 30 days before treatment with collagen.
- Results of collagen may be optimized if there is circumferential distribution of the injections in the proximal urethra.
- Complications of collagen are usually mild and may be self-limited. Common ones include transient retention, urinary infection, de novo urgency and urgency incontinence, and hematuria.
- In two separate randomized clinical trials versus collagen, both carbon-coated zirconium beads (Durasphere) and calcium hydroxyapatite (Coaptite) showed similar results to collagen after a 1-year follow-up.
- In a randomized clinical trial comparing silicone microimplants (Macroplastique) to collagen, silicone microimplants were shown to be noninferior to collagen after 1-year follow-up.

New Agents Undergoing Development

Polyacrylamide Hydrogel (Bulkamid)

Polyacrylamide hydrogel (PAHG) is a nontoxic, nonresorbable sterile aqueous gel consisting of 2.5% cross-linked polyacrylamide and 97.5% nonpyrogenic water. It is homogeneous, stable, and nonbiodegradable and has tissue-like viscosity and elasticity. It is being used in plastic surgery (Breiting et al, 2004) and ophthalmology (Lloyd et al, 2001).

Lose and coworkers (2006) reported 12-month results in a study with 25 women. The injection was delivered transurethrally with a 23-gauge needle. Four women were lost to follow-up. Eleven women (44%) underwent a second injection after 3 months because of lack of effect. Overall, 8 (32%) were dry and 9 (36%) experienced improvement. Minor adverse events included urinary tract infections (40%), transient retention (10%), urgency (8%), urgency incontinence (8%), and nocturia (4%). Multicenter randomized trials are underway in North America and Europe.

Table 74–6.
Results of Autologous Fat Injection

STUDY	NO. PATIENTS	FOLLOW-UP (mo)	Results		
			No. Dry (%)	No. Improved (%)	No. Failed (%)
Cervigni et al, 1994	11	22.6	6 (54.5)	2 (18)	3 (27.3)
Santarosa and Blaivas, 1994	12	11	7 (58)		5 (42)
Trockman and Leach, 1995	32	6	4 (12)	14 (44)	14 (44)
Haab et al, 1997	45	7	6 (13)	13 (29)	26 (58)
Su et al, 1998	26	Mean: 17.4 Range: 12-30	13 (50)	4 (15)	9 (35)
Palma et al, 1997	30	12	1 injection: 4/13 (34) 2 injections: 11/17 (67)		

Porcine Dermal Collagen

Porcine dermal collagen implants have been used in hernia repairs and pelvic floor reconstruction (Harper, 2001; Dench et al, 2006). This substance is maintained in its original three-dimensional form and is close to human dermis in architecture (Meyer et al, 1978). It is biocompatible, and patients do not have to be skin tested as for bovine collagen.

Bano and colleagues (2005) reported early results of a randomized trial of porcine dermal collagen versus Macroplastique. There were 25 patients in each arm. The porcine collagen was injected periurethrally in 21 patients. At 6 months, 15 (60%) of 25 in the collagen group were dry and 10 were unchanged or worse (40%). In the Macroplastique group, 9 (36%) were dry, 1 was improved (4%), and 14 (56%) were unchanged or worse. There were no significant differences between the groups. Minor complications of transient retention and urgency incontinence were seen in both groups and were similar.

Autologous Chondrocytes

A bulking agent composed of autologous chondrocytes has been used to treat children with vesicoureteral reflux (Diamond and Caldamone, 1999). Animal studies of the implant demonstrated stability and lack of migration over time (Atala et al, 1994; Cozzolino et al, 1999). The injectable material consists of autologous chondrocytes in a calcium alginate gel administered endoscopically through a 22-gauge needle. The chondrocytes obtained from biopsy of the external pinna of the patient's ear are expanded in tissue culture and combined with a carrier gel that degrades after injection.

Bent and coworkers (2001) reported 12-month results in 32 women after a single outpatient injection in a multicenter trial. Incontinence grading indicated 16 patients dry and 10 improved, for a total of 26 (81.3%). Side effects were minimal.

Implantable Balloons

To obviate the degradation and movement of injectable materials Yoo and coworkers (1997) developed a self-detachable implantable balloon system. The balloon is a silicone elastomer with a check valve that prevents escape of the solution that is injected at the time of implant. The filling solution is a biocompatible cross-linked hydrogel that maintains its volume within the silicone shell. The balloons are inserted into the submucosal area, usually periurethrally, with cystoscopic control.

Pycha and coworkers (1998) reported that 8 (42%) of 19 women were dry and 7 (36.8%) were improved after a mean of 14.4 months. The patients with hypermobility had a poor outcome. Mazouni and colleagues (2004) reported results in 45 women who were observed for a mean of 3 months. The overall success rate was 65%, with 24 dry and 2 improved. Complications included detrusor overactivity, balloon rupture on insertion, and balloon extrusion.

There have been no recent developments in the technology.

Adjustable Continence Therapy (ACT)

The Adjustable Continence Therapy (ACT) device (Uromedica, Plymouth, MN) consists of two inflatable silicone balloons attached to silicone tubing with a titanium and silicone port (Fig. 74–8). The procedure can be done under local, regional, or general anesthesia. The balloons are placed into the periurethral space at the bladder neck with introducer devices inserted through two 1-cm incisions in the labial sulci at the level of the vaginal introitus. The procedure is carried out under fluoroscopic guidance with a contrast-filled Foley balloon positioned at the bladder neck. After the correct position is ascertained the device balloons are inflated with 1.0 to 1.5 mL of an isotonic solution (sterile water and contrast material).The aim is to increase urethral resistance and support the bladder neck with the inflated balloons (Stecco et al, 2006). The ports are buried in the subcutaneous tissue of the labia to enable postoperative reinjection of the balloons if necessary (Kocjancic et al, 2008). Beginning at 6 weeks, additional fluid, usually with volumes of 2 mL, can be added to the balloons by injecting percutaneously through the port sites, if necessary. The technology was developed as an alternative to bulking agents that would not migrate (Kocjancic et al, 2008).

Kocjancic and coworkers (2008) implanted 49 patients, of whom 38 were observed for more than 1 year. Of these, 26 of 38 (68%) were dry, 6 of 38 (16%) were improved, and 6 of 38 (16%)

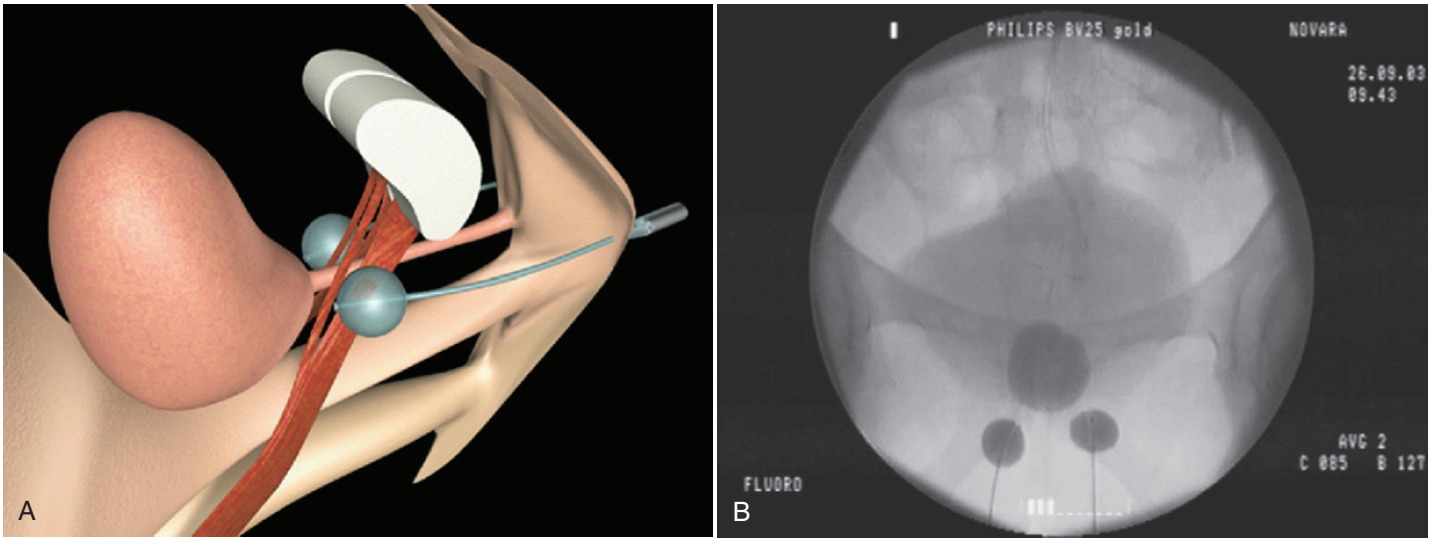


Figure 74–8. Illustration of Adjustable Continence Therapy balloon device for women. **A,** Schematic diagram showing percutaneous placement of the balloons on both sides of the bladder neck. **B,** Fluoroscopic picture showing contrast agent in the bladder, Foley catheter, and balloons. (From Aboseif SR, Franke EI, Nash SD, et al. The adjustable continence therapy system for recurrent female stress urinary incontinence: 1-year results of the North America Clinical Study Group. J Urol 2009;181[5]:2187–91.)

experienced failure. In 62%, one to five fluid additions were necessary throughout the follow-up period. Wachter and coworkers (2008) reported a series of 41 women: the dry rate was 44%, marked improvement was 15%, and 41% had slight improvement or no change; device adjustment was need in 70% of patients. Aboseif and coworkers (2009) reported a North American study consisting of 162 patients of whom 84% had undergone at least one unsuccessful surgical procedure for SUI. Of those observed for 1 year or more, 107 of 140 (76.4%) improved by one or more Stamey grades, 67 of 130 (52%) had less than 2 g of urine on pad weight testing, and 102 of 126 (81%) had a greater than 50% reduction in provocative pad weight. Within 9 months of implantation a mean of 2.3 balloon readjustments were required. Because volume adjustments were done during the follow-up periods in all series there were no data available on continence outcome long after cessation of fluid addition.

Complications. Complications have occurred in 24% (Aboseif et al, 2009) to 39% (Wachter et al, 2008) of patients, with most classified as mild to moderate. Common ones include port or balloon erosion (13%), balloon or port migration (8%), urinary retention (8%), and balloon failure (4%). Kocjancic and coworkers (2008) removed the device in 11 (22%) and then reimplanted it in all of them. Aboseif and coworkers (2009) reimplanted the device in half of the 28 (20% of the total) patients who required its removal, and Wachter and coworkers (2008) explanted 6 devices (15%) owing to nonresponse.

Overall, the procedure may be more suited to patients after surgical failures. Long-term durability still has to be established.

Autologous Myoblasts

Myoblasts, the mononuclear precursor cells of skeletal muscle, can differentiate into multinucleated muscle fibers capable of muscle contraction. They fuse to form myotubes, which stop dividing with maturation and can express protein for a prolonged period (Yokoyama et al, 2000). These cells can be harvested from skeletal muscle outside the urinary tract. The aim is to improve urinary sphincter function with urethral sphincter injections of these cells.

In a short-term feasibility animal study, Chancellor and coworkers (2000) injected mouse myoblasts into rat urethras and bladders. After 3 to 4 days the harvested organs showed viable cells with fusion of injected cells to form myotubes. The same group subsequently used adult rat muscle–derived allografts containing satellite cells and myoblasts and injected it into autologous animals and compared it with injected collagen. After 30 days there was almost no collagen but there was a large cell mass bulging into the urethral lumen (Yokoyama et al, 2001). Mitterberger and coworkers (2007) injected allograft myoblasts in a porcine model and demonstrated a 300% increase in urethral pressure values and survival of the injected cells with formation of myofibers.

Mitterberger and coworkers (2008) reported on 20 women with SUI who underwent transurethral ultrasound-guided injection of autologous fibroblast injection into the urethral submucosal and myoblast injection into the rhabdosphincter. The cells were cultured from skeletal muscle forearm biopsy specimens. Two years after therapy, 16 were cured, 2 were improved, and 2 were lost to follow-up. Apart from 1 patient with transient retention, no complications were encountered. Strasser and associates (2007), **from the same group in Innsbruck, Austria, published results of a randomized trial of autologous myoblast versus collagen injection, but the article was subsequently retracted by the *Lancet*** (Kleinert and Horton, 2008).

Carr and colleagues (2008) reported results in 8 women followed for a mean of 16 months after transurethral or periurethral injection of autologous skeletal thigh muscle–derived stem cells. Five of 8 improved with one reporting being dry. No serious adverse events were reported.

This technology looks promising and may provide advantages over bulking agents. No long-term data are available at present, and further studies are underway.

Agents That Are No Longer Used

The reader is referred to the electronic version of this edition on the Expert Consult website.

Key Points: New Agents Undergoing Development for Female Stress Urinary Incontinence

- Both biologic and synthetic agents are undergoing development.
- Adjustable volume silicone balloons are technically feasible, but no comparative studies have been done or long-term durability demonstrated.

PATHOPHYSIOLOGY OF INCONTINENCE AFTER PROSTATECTOMY AND USE OF INJECTABLE AGENTS FOR MALE STRESS URINARY INCONTINENCE

Incontinence after prostatectomy may be caused by bladder dysfunction, sphincter dysfunction, or a combination of the two. Urodynamic investigations are helpful to rule out bladder outlet obstruction or significant bladder dysfunction. In addition to incontinence symptoms, storage and voiding symptoms may be associated (Gray et al, 1999; Hollenbeck et al, 2002). **Urodynamic studies have demonstrated that sphincter incompetence occurs as the sole cause in more than two thirds of patients whereas isolated bladder dysfunction (detrusor overactivity, poor compliance, detrusor underactivity during voiding) is uncommon, occurring in less than 10% of patients** (Ficazzola and Nitti, 1998; Groutz et al, 2000). **However, sphincter and bladder dysfunction can coexist in at least one third of incontinent patients.** Decreased sphincter resistance may be due to tissue scarring in some cases and is reflected by a low urethral compliance; however, this parameter is difficult to measure (Groutz et al, 2000). Scarring may lead to an anastomotic stricture evidenced by endoscopy or urethrography and is clinically suspected when incontinence and decreased force of stream coexist.

The preoperative length of the membranous urethra determined on magnetic resonance imaging has been shown to be related to time to postoperative continence (Coakley et al, 2002). Urodynamic studies have revealed that a reduced functional urethral length was predictive of incontinence (Hammerer and Huland, 1997; Van Kampen et al, 1998; Wei et al, 2000). The state of a patient's pelvic floor may also influence continence or return to continence after radical prostatectomy. Physiotherapy and

pelvic floor rehabilitation have been shown to improve or enhance continence (decreased time to final continence level) in the postoperative period in two randomized studies, but only if such measures are instituted before or immediately after catheter removal (Van Kampen et al, 2000; Parekh et al, 2003). Maximum difference between physiotherapy and no treatment is achieved at 3 months, with almost no difference at 12 months. A randomized study in which randomization occurred 6 weeks after surgery showed no difference in continence at 6 months (Wille et al, 2003).

Bulking agents are the most minimally invasive treatment for incontinence after prostatectomy after conservative measures have been tried. They work theoretically by adding bulk and increasing coaptation at the level of the bladder neck and proximal urethra. Several agents have been used, including bovine collagen (Contigen) and silicone microimplants (Macroplastique). All agents share the similar problems, including the need for multiple injections and treatment sessions, deterioration of effect over time, and low cure rates. It remains to be seen if improvements in outcomes can be achieved with alternative agents or if the concept of urethral bulking has achieved its maximum benefit with currently available agents (Herschorn et al, 2010). An alternative technology with implanted adjustable volume balloons (ProACT) will be discussed.

Workup

Basic evaluation includes history, physical examination, urinalysis, and measurement of postvoid residual urine. A frequency-volume chart (Griffiths et al, 1993) or bladder diary is also helpful. A pad test quantifies the severity of incontinence. The 24-hour home test is the most accurate pad test for quantification and diagnosis and the most reproducible (Mouritsen et al, 1989). The 1-hour pad test is widely used because it is more easily done and standardized. The amount of postvoid residual urine is a good estimation of voiding efficiency (Diokno et al, 1988; Starer and Libow, 1988).

Blood tests (blood urea nitrogen, creatinine, glucose) are recommended if compromised renal function is suspected or documented (Fantl et al, 1996).

Uroflowmetry is also helpful to assess voiding function.

Cystourethroscopy is done to verify integrity of the urethral wall, bladder neck, and the status of the bladder (e.g., trabeculation, stones, diverticula). Injectable agents are not effective with scarred supramembranous urethras because the tissues cannot expand with the agent. The status of the urethra should be assessed preoperatively.

Invasive urodynamic studies are useful to assess bladder and urethral function before interventional therapy (Herschorn et al, 2010). Detrusor overactivity or decreased bladder compliance demonstrated on multichannel testing may be contributing to symptoms and may merit alternative treatment. Sphincter weakness can be documented by the Valsalva (McGuire et al, 1993) or cough (Schick, 1985) abdominal leak point pressure, but its reproducibility has been studied in women and not men. **Although ALPP may be helpful, it has been shown to be a poor predictor of incontinence severity after radical prostatectomy** (Twiss et al, 2005). **Furthermore, in male patients, ALPP measurement may be better via a rectal catheter because a urethral catheter may occlude a scarred urethra** (Flood et al, 1996). **Although definite evidence supporting the predictive value of urodynamic studies is lacking, they are still recommended before interventional treatment** (Hosker et al, 2009).

Injection Techniques

Retrograde Injection

The patient is placed in the lithotomy position, and the surgical field is prepared in the usual sterile fashion (Fig. 74–9A). The procedure can be performed with local, regional, or general anesthesia. If local anesthesia is employed, 2% topical urethral lidocaine jelly can be inserted 10 minutes before instrumentation. In some patients, preoperative sedation may also be of benefit. A 20- or 22-Fr cystoscopic sheath is employed using a 0- or 30-degree lens. Collagen is provided in a 3.0-mL Luer-Lok syringe containing 2.5 mL of injectable material. The syringe attaches to a 5-Fr injection catheter containing a 1.5-cm 20-gauge needle at the tip. Most injections are done transurethrally under cystoscopic vision.

After a prostatectomy the urethra is frequently scarred and not very pliable; thus, several needle insertions are frequently needed to deposit sufficient material to produce urethral coaptation. The injection is completed in up to four quadrants after localization of the appropriate level in the proximal urethra. The needle is advanced under the urethral mucosa with the beveled portion of the needle facing the urethral lumen to allow for layering of the material. The injectable material is then delivered, creating a bleb under the urethral mucosa that protrudes into the urethral lumen. This is performed in a circumferential manner in four quadrants, creating a bleb in each quadrant. After completion, the urethral mucosa should be completely coapted and creates the appearance of an obstructed urethra. Extrusion of the injectable agent into the urethral lumen as the needle is withdrawn may occur. This may be prevented in most cases by leaving the needle in place for at least 30 seconds after the injection is completed or by flushing the material with saline. The loss of additional material is diminished by preventing advancement of the cystoscope proximal to the injection sites. If material extravasation occurs in all quadrants during injection, the procedure should be terminated and rescheduled (Appell and Winters, 2007).

Antegrade Injection

Because of less than optimal results an alternative method of injecting collagen in men was introduced using a suprapubic antegrade approach. The antegrade approach has the advantage of direct visualization of the bladder neck and the injection of material into more supple, less scarred urethra (see Fig. 74–9B). The patient is placed in the lithotomy position, and flexible cystoscopy is carried out, simultaneously filling the bladder. A percutaneous suprapubic puncture allows placement of two guide wires into the bladder. The site is dilated to 16 Fr with Amplatz dilators. A sheath may be used, but commonly the cystoscope (flexible or rigid pediatric) can be advanced over one of the guide wires into the bladder. A small red rubber catheter or the flexible cystoscope can be used to assist in localization of the bladder neck. The needle is placed just under the urethral mucosa at the level of the bladder neck and advanced proximally, meaning it is pulled back toward the bladder. The bladder neck closes off completely as the material is injected. Injection stops after the bladder neck closes off, the two sides meeting in apposition near the midline. A small suprapubic tube can be placed to avoid the possible necessity of urethral catheterization.

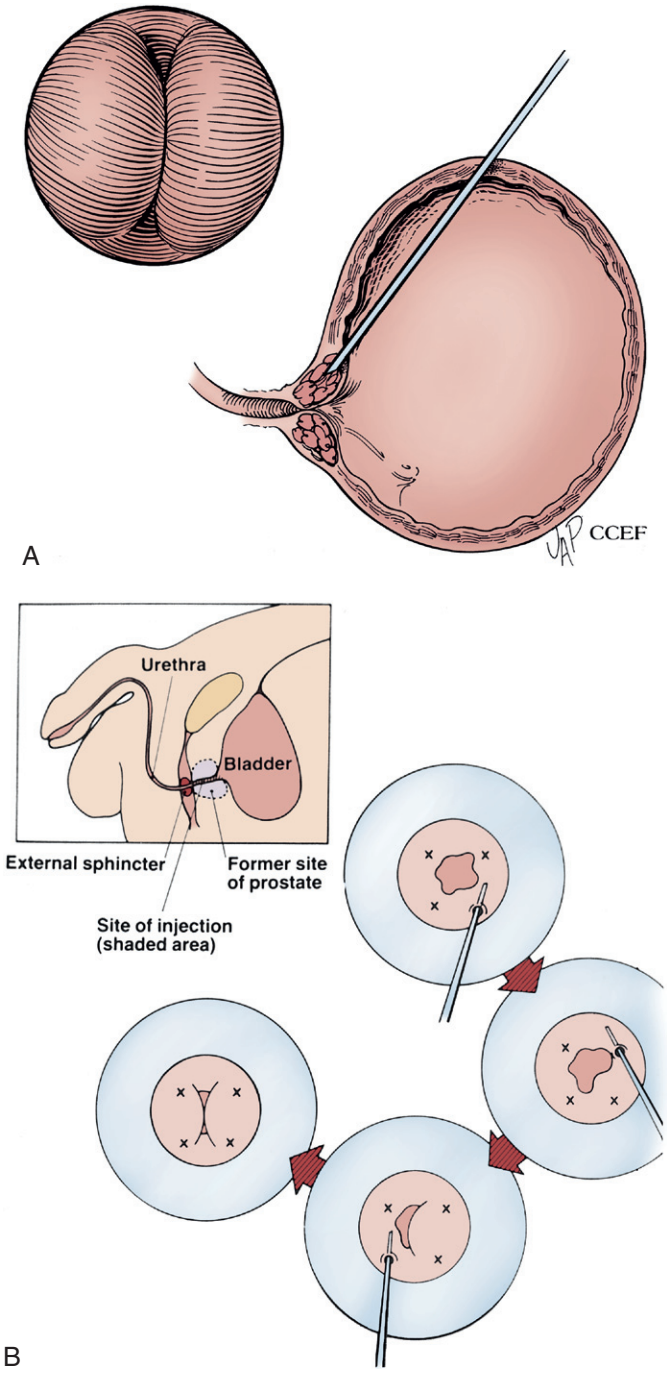


Figure 74–9. **A,** Retrograde urethral injection technique in men. Schematic representation of transurethral circumferential injection in a male after prostatectomy. **B,** Antegrade urethral technique injection in the male after radical prostatectomy. (**A,** Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1994-2011. All Rights Reserved.)

Periprocedural Care

Prophylactic antibiotics with a fluoroquinolone or trimethoprim-sulfamethoxazole for 24 hours or less can be recommended (Wolf et al, 2008). Therapy for an additional 2 to 3 days also has been suggested (Appell and Winters, 2007).

The patient then voids and can be discharged. Urinary retention can be treated by insertion of a fine Foley catheter (12 to 14 Fr or smaller) overnight or intermittent catheterization. Although not specifically reported, an indwelling Foley catheter may cause molding of the agent and lead to early failure; thus long-term catheterization should be avoided.

Reinjections

The same schedule applies as in female patients.

Currently Used Injectable Agents

Glutaraldehyde Cross-linked Bovine Collagen (Contigen)

Collagen has been injected transurethrally with cystoscopic monitoring into the supramembranous urethra. It has also been injected percutaneously through a suprapubic approach in an antegrade manner. The published results for both techniques are in Tables 74–7 and 74–8.

For collagen, "success rates" for incontinence after prostatectomy range from 36% to 69%, with 4% to 20% of patients reporting being dry (McGuire and Appell, 1994; Aboseif et al, 1996; Cummings et al, 1996; Sanchez-Ortiz et al, 1997; Smith et al, 1998; Cespedes et al, 1999; Klutke et al, 1999; Tiguert et al, 1999). Unfortunately, the end points in most of these studies are subjectively based, making comparisons difficult; however, it is clear that cure rates (total dryness) are low, and multiple injections are required to achieve modest rates of subjective improvement. There is no advantage of delivery technique (retrograde vs. antegrade). Several authors have identified factors that negatively affect results, including extensive scarring or stricture formation, previous irradiation, and high-grade SUI and low ALPP (Aboseif et al, 1996; Sanchez-Ortiz et al, 1997; Smith et al, 1998; Cespedes et al, 1999). One study reported more favorable results for collagen in treating incontinence after transurethral prostatectomy as opposed to radical prostatectomy (35.2% "social continence" vs. 62.5%) (Smith et al, 1998). Westney and coworkers (2005) reported long-term results in 322 men observed for a mean of 40.1 months. Overall, 55 patients (17%) were dry for a mean of 11.1 months and required 3.8 injections with a total volume of 29.3 mL. In those who experienced any improvement the mean duration of response was 6.3 months. They concluded that collagen was of some benefit but that the duration of response was limited.

Collagen injection does not adversely affect outcomes of artificial sphincter implantation and does not increase the complication rate (Gomes et al, 2000), nor does collagen injection adversely affect the outcome of the bone-anchored male sling (Comiter, 2002; Onur and Singla, 2006). The cost efficacy of injections remains to be determined.

Complications. In addition to those reported in the section in females, worsening of incontinence symptoms may occur in 1.5% of patients (Westney et al, 2005).

Silicone Microimplants (Macroplastique)

Initial success has been demonstrated with silicone microimplants, but results deteriorate over time. Bugel and coworkers (1999) treated 15 patients. They noted rapid deterioration after initial improvements with success rates of 40%, 71%, 33%, and 26% at 1, 3, 6, and 12 months, respectively. They also noted that a urethral closure pressure of at least 30 cm H_2O was essential for success. Kylmala and colleagues (2003) studied 50 patients with mild to moderate SUI (average 48 mL on 1-hour pad test), with 12% achieving short-term continence after one injection and an additional 20%, 18%, and 10% achieving continence with two,

Table 74–7.

Results of Retrograde Transurethral Collagen Injection Therapy for Incontinence after Prostatectomy

STUDY	NO. PATIENTS	MEAN FOLLOW-UP (mo)	MEAN NO. INJECTIONS	MEAN VOLUME (mL)	Results		
					No. Cured (%)	No. Improved (%)	No. Failed (%)
Shortliffe et al, 1989	14	19-23	1.6	28.4	3 (21)	5 (36)	6 (43)
Herschorn et al, 1992	10	6	4.7	51.8	2 (20)	5 (50)	3 (30)
Bevan-Thomas et al, 1999	257	28	4.4	36.6	52 (20)	101 (39)	104 (41)
Smith et al, 1998	54	29	4	20		19 (38)	35 (62)
Cespedes et al, 1999	110	7	4.2	28.4	58 (53)	10 (9)	42 (38)
Aboseif et al, 1996	88	10	2.8	31	42 (48)	33 (37)	13 (15)
Martins et al, 1997	46	26	2.8	31	11 (24)	21 (46)	14 (30)
Faerber and Richardson, 1997	68	38	5	36	7 (10)	7 (10)	54 (80)
Griebling, 1997	25	13.3	2.6	35.5	0 (0)	10 (40)	15 (60)
Cummings et al, 1996	19	10.4	1.8	13.8	4 (21)	7 (37)	8 (42)
Elsergany and Ghoneim, 1998)	35	17.6	2	10	7 (20)	11 (31)	17 (48)
Tiguert et al, 1999	21	12.5	2.9	18.2	1 (5)	12 (57)	8 (38)
Westney et al, 2005	322	40.1	4.37	36	55 (17)	87 (27)	180 (56)

Table 74–8.

Results of Antegrade Injection Collagen Injection Therapy for Incontinence after Prostatectomy

STUDY	NO. PATIENTS	MEAN FOLLOW-UP (mo)	MEAN NO. INJECTIONS	MEAN VOLUME (mL)	Results		
					No. Cured (%)	No. Improved (%)	No. Failed (%)
Wainstein and Klutke, 1997	48	8.5		14.5	12 (25)	22 (45)	14 (30)
Appell et al, 1996	24	12	1	7.1	9 (37.5)	15 (62.5)	
Klutke et al, 1999	20	28	1	14.5	2 (10)	7 (35)	11 (55)

three, and four injections, respectively. Follow-up, however, was limited to 3 months. In a series of 14 men with spinal injuries and SUI, Hamid and associates (2003) reported that 5 (36%) were dry, 3 (21%) improved, and 6 (43%) experienced failure after a mean follow-up of 35 months.

In a randomized trial of the Artificial Urinary Sphincter (AUS) versus Macroplastique injection in patients with minimal SUI (the vast majority had SUI after surgery for benign prostatic hyperplasia, with greater than a third of the cohort suffering from SUI after radical retropubic prostatectomy), Imamoglu and colleagues (2005) demonstrated no difference in success with AUS versus Macroplastique in men with mild incontinence. However, in patients with more severe incontinence, the AUS was superior and minimal improvement was seen after transurethral implantation of Macroplastique.

Complications. Side effects in men are similar to those reported in women.

Adjustable Balloons (ProACT)

The adjustable balloon procedure is based on the concept of passive compression utilizing balloons located on either side of the urethra. Balloons may be progressively inflated until there is optimal coaptation, thereby achieving continence. The biomaterial name ACT (Adjustable Continence Therapy) was originally developed for female SUI and subsequently was applied to male incontinence. The male ProACT device (Uromedica, Plymouth, MN) was first reported in 2000 (Hubner, 2000).

The device consists of a silicone elastomer balloon attached to an injectable titanium port with a silicone tube (Fig. 74–10). A balloon is implanted on either side of the urethra, either under the bladder neck for post–radical prostatectomy incontinence or under the verumontanum for incontinence after transurethral resection of the prostate. The ports are positioned subcutaneously in the scrotum, allowing simple access for percutaneous adjustment of the balloon volume. The implantation is performed under general or spinal anesthesia through a short perineal incision. A trocar covered with a U-shaped sheath is inserted up to the site of implantation and then the balloon is pushed along inside the sheath. Fluoroscopic and urethroscopic guidance is used for the procedure. Transrectal ultrasound-guided implantation (Gregori et al, 2006, 2010) is a possible option. The balloons are filled with 2 mL of isotonic sterile water and contrast medium during the initial procedure. After approximately 1 month, the balloons are refilled with 1 mL of this solution at each period (maximum filling is 8 mL) until continence is achieved. The adjustments of the filling are volume limited and are carried out step by step to obtain a pseudocapsule surrounding the balloons to minimize the risk of urethral erosion or migration.

Results from seven studies are shown in Table 74–9. Of 170 patients reported by Hubner and Schlarp (2005) and Lebret and colleagues (2008), one third became pad free. In other studies 70% of patients utilized no pad or just 1 pad daily (Hubner and Schlarp, 2005; Trigo-Rocha et al, 2006; Cansino Alcaide et al, 2007; Lebret et al, 2008). Mean procedure time of 35 minutes was reported. Along with this improvement in pad use there were parallel improvements in Incontinence-Quality of Life questionnaire (I-QOL) score (Hubner and Schlarp, 2005; Trigo-Rocha et al, 2006; Lebret et al, 2008). The mean number of postoperative adjustments of the balloon was 3 to 5, with some patients requiring up to 15.

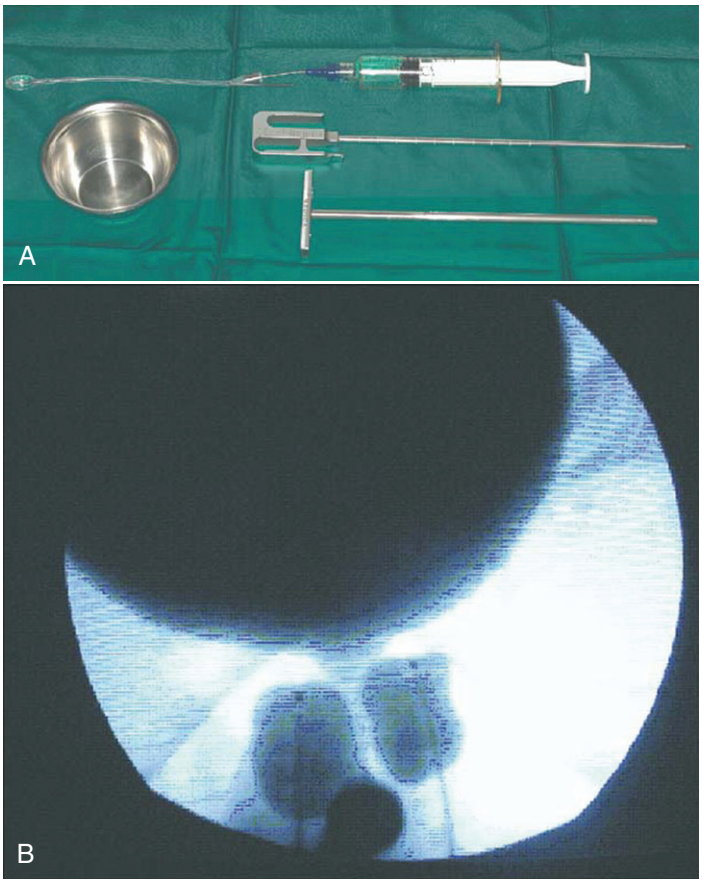


Figure 74–10. Illustration of Adjustable Continence Therapy balloon device for men. **A,** Balloon, trocar, and U-shaped insertion device are shown. Syringe with contrast agent is connected to balloon port. **B,** Fluoroscopic picture showing contrast agent in the bladder and urethra with balloons near the bladder neck. (From Trigo-Rocha F, Gomes CM, Pompeo AC, et al. Prospective study evaluating efficacy and safety of Adjustable Continence Therapy [ProACT] for post radical prostatectomy urinary incontinence. Urology 2006;67[5]:965–69.)

In a simultaneously treated cohort study from two centers, Crivellaro and colleagues (2008) reported no difference in outcome of the adjustable balloons versus the bone-anchored male sling. At a mean follow-up of 19 months after use of adjustable balloons, 30 of 44 men (68%) were dry and 7 (16%) were improved versus 23 of 36 (64%) and 8 (22%) after a bone-anchored male sling procedure, respectively, after a mean of 33 months ($P > .05$).

Complications. The most common perioperative complication is urethral or bladder perforation, necessitating termination of the implant on the perforated side. However, contralateral implantation was not adversely affected, and repeat ipsilateral implantation was invariably achieved after healing of the urethral or bladder wall. Lebret and colleagues (2008) reported a perforation rate of 10% and Hubner and Schlarp (2007) reported a rate of 18% early in their series but a lower urethral perforation rate in more recent cases, illustrating a relatively short learning curve for optimal balloon placement near the urethral/bladder wall. Temporary urinary retention was reported at 5% (Hubner and Schlarp, 2007). Voiding was restored by removing fluid from the balloon.

Device explantation is related to balloon failure, infection, erosion, or migration. The explantation rate ranged from 11% to 58% (Hubner and Schlarp, 2005, 2007; Trigo-Rocha et al, 2006; Cansino Alcaide et al, 2007; Lebret et al, 2008) but decreased with experience (Hubner and Schlarp, 2007). Device removal is straightforward, because a deflated balloon can be explanted transperineally. Reported risk factors for failure and complications were prior external beam radiation therapy (Lebret et al, 2008; Gregori et al, 2010) and severe preoperative incontinence (Gregori et al, 2010). Kocjancic and colleagues (2007) reported a continence rate of 67% in nonirradiated patients compared with 36% in irradiated patients.

Conclusion. The adjustable balloon (ProACT) technique appears to be a feasible procedure to improve continence in the short and medium term. Appropriate candidates include those with mild to moderate leakage and no previous radiation. **The benefit of an adjustable system should be weighed against the need for multiple sessions to refill the balloons and with reported rate of perioperative and postoperative complications necessitating removal.**

The technology appears to have better results than injectable agents in men. Longer follow-up is needed before definitive comparison to male sling or artificial sphincter can be made (Herschorn et al, 2010). The device is not commercially available in the United States.

Table 74–9.

Results and Complications of Adjustable Balloons (ProACT) in Urinary Incontinence after Prostatectomy

STUDY	NO. PATIENTS	MEAN FOLLOW-UP (mo)	NO. OF ADJUSTMENTS (BALLOON REFILLING)	POSTOPERATIVE COMPLICATIONS WITH EXPLANTATION (UNILATERAL OR BILATERAL)	CONTINENCE 0-1 PAD/DAY	COMPLETE CONTINENCE
Hubner and Schlarp, 2005	117	13	3 (1-15)	46%	68% (46/63)	35% (22/63) (same at 1 and 2 yrs)
Trigo-Rocha et al, 2006	23	22	5 (1-6)	17%	65% (15:23)	
Hubner and Schlarp, 2007	50 first	20	5	58%	52%	
	50 last	23	4	24%	60%	
Cansino Alcaide et al, 2007	69	22	2	12%	70%	14%
Kocjancic et al, 2007	64	20	3 (0-8)	17%		67%
Lebret et al, 2008	62	6	4	31%	71%	30%
Gregori et al, 2010	62	25	3.6 (0-14)	11%		61%

Key Points: Use of Injectable Agents in Male Stress Urinary Incontinence

- The workup includes history and physical examination, urinalysis, uroflowmetry, and assessment of postvoid residual urine. Urodynamic studies are helpful. Cystoscopy is done to verify the status of the urethra because scarring may prevent the tissues from expanding with the bulking agent.
- Both transurethral retrograde and percutaneous antegrade techniques are feasible with no differences in outcome reported.
- Commonly reported injectable agents have included collagen and silicone microimplants. All agents show initial good results, the need for multiple treatment sessions, and deterioration of outcome over time.
- Implanted adjustable silicone balloons appear to be a feasible technique. However, randomized trials have yet to be done and long-term durability is still to be demonstrated.

USE OF INJECTABLE AGENTS FOR INCONTINENCE AFTER URINARY DIVERSION

There are very few reports in the literature about the use of injectable agents after urinary diversion. Izes and colleagues (1997) demonstrated in a canine study that collagen injected circumferentially into the lumen of the ileocecal valve can increase the leak point pressure for up to 1 month after injection. Subsequently, Smith and colleagues (1998) reported results of collagen in four women and two men with leaking Indiana pouches. They injected a mean of 16 mL circumferentially into the ileocecal junction to obtain visual closure of the bowel lumen. After a mean follow-up of 26 months 5 of the 6 patients remained dry.

Use of injectable agents has been reported in women after construction of a neobladder. Tchetgen and colleagues (2001) reported on 3 patients with SUI after cystectomy and orthotopic neobladder. An average of two injections was given with a cure in 1, improvement in 1, and no change in 1. Wilson and colleagues (2004) administered transurethral collagen to 11 patients and pyrolytic carbon-coated zirconium beads to 1 patient with SUI after cystectomy and construction of a neobladder. After a mean of 22.5 months 2 patients (16.7%) were dry although continued to have urinary frequency. Four patients (33.3%) were improved, and 6 were unchanged. These researchers concluded that the treatment response was not optimal nor durable.

New-onset vesicovaginal fistula has been reported in 2 patients after collagen injection for SUI after cystectomy and construction of a neobladder (Pruthi et al, 2000). Both patients underwent transvaginal fistula repair with pubovaginal sling procedures.

To date, the success of injectable agents for these clinical circumstances is limited.

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The complete reference list is available online at www.expertconsult.com.

chapter
75

Other Therapies for Storage and Emptying Failure

R. Duane Cespedes, MD ● Jason L. Gerboc, DO

Methods to Improve Bladder Filling/Urine Storage
Decreasing Spasticity and Increasing Cystometric Capacity
Increasing Outlet Resistance
Lower Urinary Tract Reconstruction, Diversion, and Bladder Substitution
Catheterization
Urinary Collection Devices and Continence Products
Methods to Improve Bladder Emptying
Decreasing Outlet Resistance at a Site of Anatomic Obstruction
Decreasing Outlet Resistance at the Level of the Striated Sphincter
Summary

The etiologies of voiding dysfunction are diverse and may occur as a result of neurologic, inflammatory, or infectious disorders. Other factors such as surgical or nonsurgical trauma and aging are also important causes. Obstruction continues to occupy a central role in the development of emptying failure and, when present chronically, may lead to poor bladder compliance and the failure to store. For both filling/storage and emptying disorders, dysfunction may originate primarily from the bladder, sphincter, or a combination of both. The majority of patients with voiding dysfunction will respond favorably to standard therapy (discussed elsewhere in this book). The treatment of complex cases should be individually tailored and may entail a combination of techniques, especially if approached through different mechanisms. Tables 61–3 and 61–4, list the numerous strategies devised to meet this goal, a testament to the complex management of voiding dysfunction. Additional treatments that have been developed for the management of storage and emptying failure are discussed in this chapter. Some of the topics are covered in other areas of this text but require special mention, while other topics are covered nowhere else in this edition. While some of these approaches offer promising results and are deserving of continued follow-up, others have been mentioned for historic reference only.

METHODS TO IMPROVE BLADDER FILLING/URINE STORAGE

Symptoms of urinary frequency, urgency, and/or incontinence are among the most common manifestations of storage failure. These symptoms can be tremendously bothersome and significantly decrease the patient's quality of life. When severe, many patients will limit their activities and social functions in order to avoid embarrassment from their disorders. **Volume accommodation with low pressure, continence, and the absence of involuntary bladder contractions are the goals of management.** Treatment is often targeted at decreasing sensory input during filling, inhibition of bladder contractility, and increasing outlet resistance. The following sections discuss methods to facilitate urine storage and promote bladder filling by different means.

DECREASING SPASTICITY AND INCREASING CYSTOMETRIC CAPACITY

Lower Urinary Tract Denervation, Decentralization, and Neuromodulation

Altering the innervation of the urinary tract is the focus of several strategies for the management of storage failure and is the central mechanism for procedures that vary from sacral rhizotomy to intravesical botulinum toxin. In addition, interventions may involve different levels of the nervous system, such as the spinal cord, nerve roots, or peripheral nerves. Of note, noncentral denervation proximal to the postganglionic neuron is properly termed "decentralization" and because the bladder is innervated by a short-neuron system, almost all denervation procedures outside the central nervous system that we will describe are properly referred to as decentralization. **In general, more central procedures would appear more suitable for patients with spinal cord injury (SCI) or neurogenic detrusor overactivity, and although central denervation is theoretically very effective, it may also have a potentially wider range**

of unintended consequences. Peripheral decentralization is more selective for the bladder and more suitable for idiopathic detrusor overactivity, as other structures innervated by the sacral nerves remain neurologically intact (Madersbacher, 2000). There would seem to be only a small role for most of the procedures discussed in this section, because conservative measures are often sufficient in significantly improving or alleviating storage symptoms in most patients. Although favorable results have been reported with denervation techniques, some of these procedures have been accompanied by significant adverse outcomes that have limited their usefulness. **One significant problem with central denervation and decentralization is that neuroplasticity often results in a variable restoration of neurologic function, with an even less desirable result than was present originally in many cases** (Madersbacher, 2000). This section will focus on surgical techniques of bladder denervation, both central and peripheral. Sacral neuromodulation is covered in Chapter 70.

Central (Subarachnoid) Block

These procedures, comprise chemical rhizolysis, sacral rhizotomy, and conusectomy, selective anterior sacral rhizotomy, and dorsal rhizotomy are seldom used today and are discussed fully on the Expert Consult website.

Peripheral, Perivesical, and Intravesical Bladder Denervation

Transvaginal Denervation

A number of procedures fall into the category of attempts to achieve a peripheral denervation. The exact nature of these denervations is unclear and may involve interruption of sensory, motor, or both types of innervation. **As evident from neuroanatomic considerations, at best, such attempts achieve primarily neurologic decentralization and, at most, partial peripheral denervation.** Although many authors report relatively high success rates for these procedures, it is unclear why they are not used more frequently. Because they are primarily used for detrusor overactivity, it is likely that many clinicians use nonsurgical methods first and are often successful in managing detrusor overactivity with fewer side effects. Also, because these procedures are uncommonly performed, many clinicians are unfamiliar with how to perform the procedure, and the success rate is likely much lower than when performed by clinicians who commonly perform these procedures. Lastly, many clinicians have begun to use neuromodulation or botulinum toxin injections to treat refractory overactive bladder, leaving the role of transvaginal denervation in question.

Regarding the literature on transvaginal denervation, in many articles, there is little description of what "success" actually means. In addition, there are few studies with long-term follow-up, and "postoperative assessment" often means a few months of follow-up. A comprehensive summary of the surgical treatment of detrusor overactivity by peripheral denervation was reported by Mundy in 1985; however, many reports have been published since that time.

Transvaginal partial denervation of the bladder was originally described by Ingelman-Sunberg in 1959. The original procedure, which was an extensive denervation, was used mostly for the treatment of refractory urge-urinary incontinence, and in the originator's hands, success rates of up to 80% were achieved. Mundy (1985) reported that other investigators found success in 50% to 65% of cases, and Torrens (1985) noted that "the technique has not found favor with other workers."

More recently, Cespedes and associates (1996) described McGuire's modification (limited lateral vaginal dissections) of the Ingelman-Sundberg procedure in 25 women with urinary urgency incontinence and detrusor overactivity who had failed behavioral and medical therapy (Fig. 75–1). Transvaginal local anesthesia was used as a test to determine which patients would benefit from the procedure, with significant improvement of urgency symptoms considered a positive test. Twenty-five patients were found to have a positive test; the number of patients unsuccessfully tested was not reported. Sixteen (64%) of these patients were cured of urgency incontinence at a mean follow-up of 14.8 months. Of the 16 patients cured, 9 patients required one medication, and 2 required two medications. Madersbacher (2000) comments that a follow-up period of 15 months is too short to determine long-term effects.

Long-term follow-up was reported by Westney and associates (2002), who retrospectively reviewed 28 patients with refractory urgency incontinence, having undergone the modified procedure with a mean follow-up of 44.1 months. Of these, 68% were cured (54%) or improved (14%). Based on these results and the prior series, the authors concluded that the modified Ingelman-Sundberg procedure is an efficacious, minimally invasive option for this difficult-to-treat patient population.

Bladder Transection and Peripheral Chemical Neurolysis

These procedures are seldom used today and are fully discussed on the Expert Consult website.

Acupuncture

The use of acupuncture as a therapeutic treatment modality is described in Chinese medical texts as early as 300 BC. Acupuncture is a form of somatic sensory stimulation using a variety of procedures that involve stimulation of specific anatomical locations by insertion of thin, solid, metallic needles into the skin. In the classic forms of acupuncture, needles are stimulated manually to achieve the desired effects. In more modern forms of acupuncture, heat or electrical stimulation may be provided by the addition of an energy source or be performed needleless, as in laser acupuncture. Indeed, McGuire and coworkers' (1983) developed transcutaneous posterior tibial nerve stimulation for bladder inhibition that was based on the acupuncture points. The use of acupuncture has been described for a number of urologic symptoms, including urinary urgency, frequency, incontinence, nonobstructive urinary retention, enuresis, and neurogenic detrusor overactivity. Acupuncture is generally a well-tolerated procedure, and although side effects are generally uncommon and minimal in nature, treatment may occasionally result in localized pain, hematoma, infection, and even organ puncture. Several treatment sessions are usually required.

There has been much interest in determining the mechanism by which acupuncture exerts its beneficial effects. According to traditional Chinese medicine, concepts such as the meridian system, circulation of Qi, and other related theories remain difficult to define and characterize. Sato (1997) has shown somatovisceral reflexes evoked from somatic afferent stimulation may induce either excitatory or inhibitory changes in bladder function and sphincter activity**. Bergström and associates** (2000)

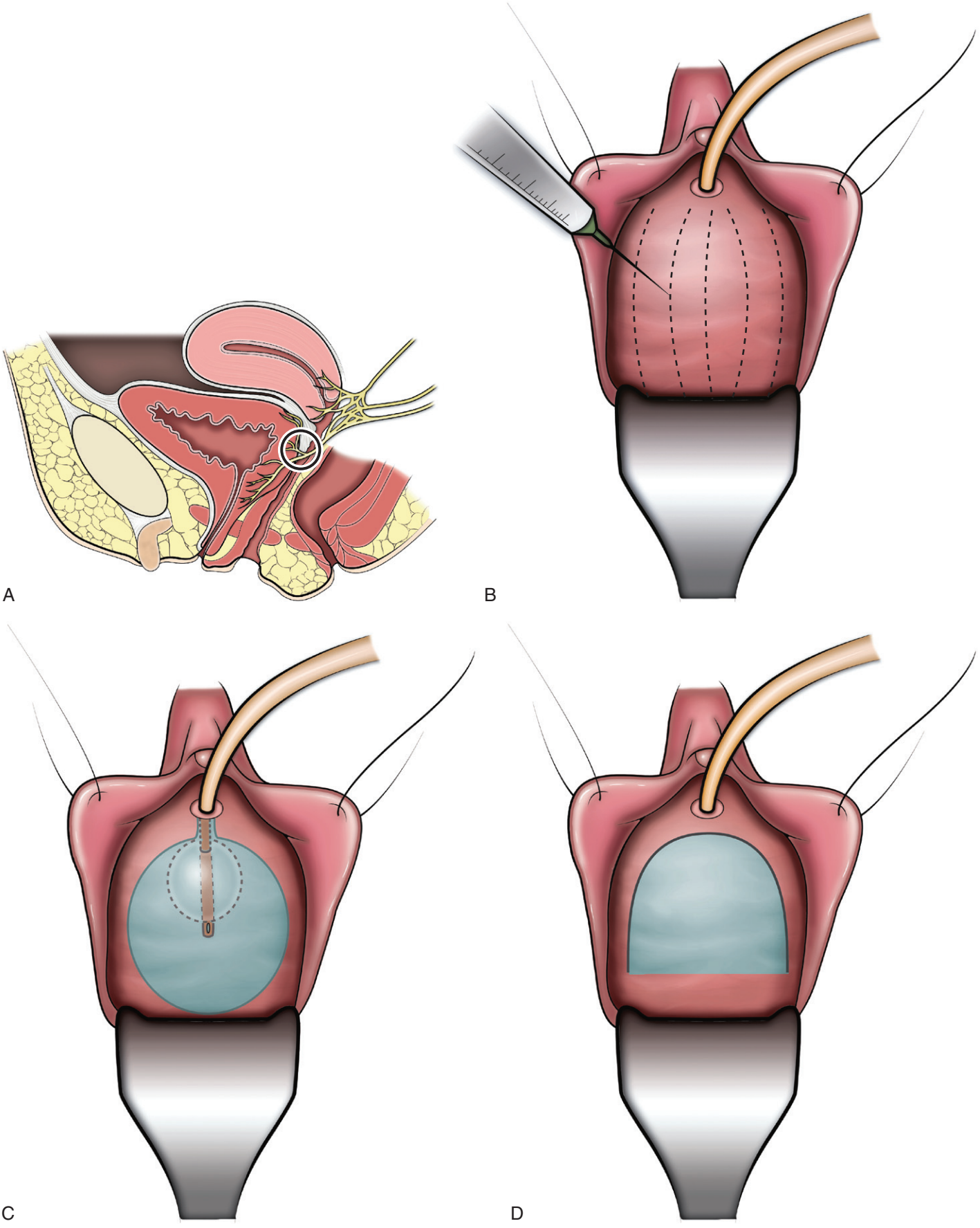


Figure 75–1. Terminal pelvic nerve branches enter the bladder near the trigone. **A**, To assess preoperatively in clinic whether the patient would benefit from the procedure, local anesthetic (0.25% bupivacaine) is injected subtrigonally to block the nerves which would be denervated by the operative procedure. **B**, Normal saline is injected submucosally to facilitate dissection of the vaginal mucosa off the bladder. **C**, Position of the trigone outlined by a catheter balloon inflated to 30 mL. **D**, Inverted-"U" vaginal incision is made.

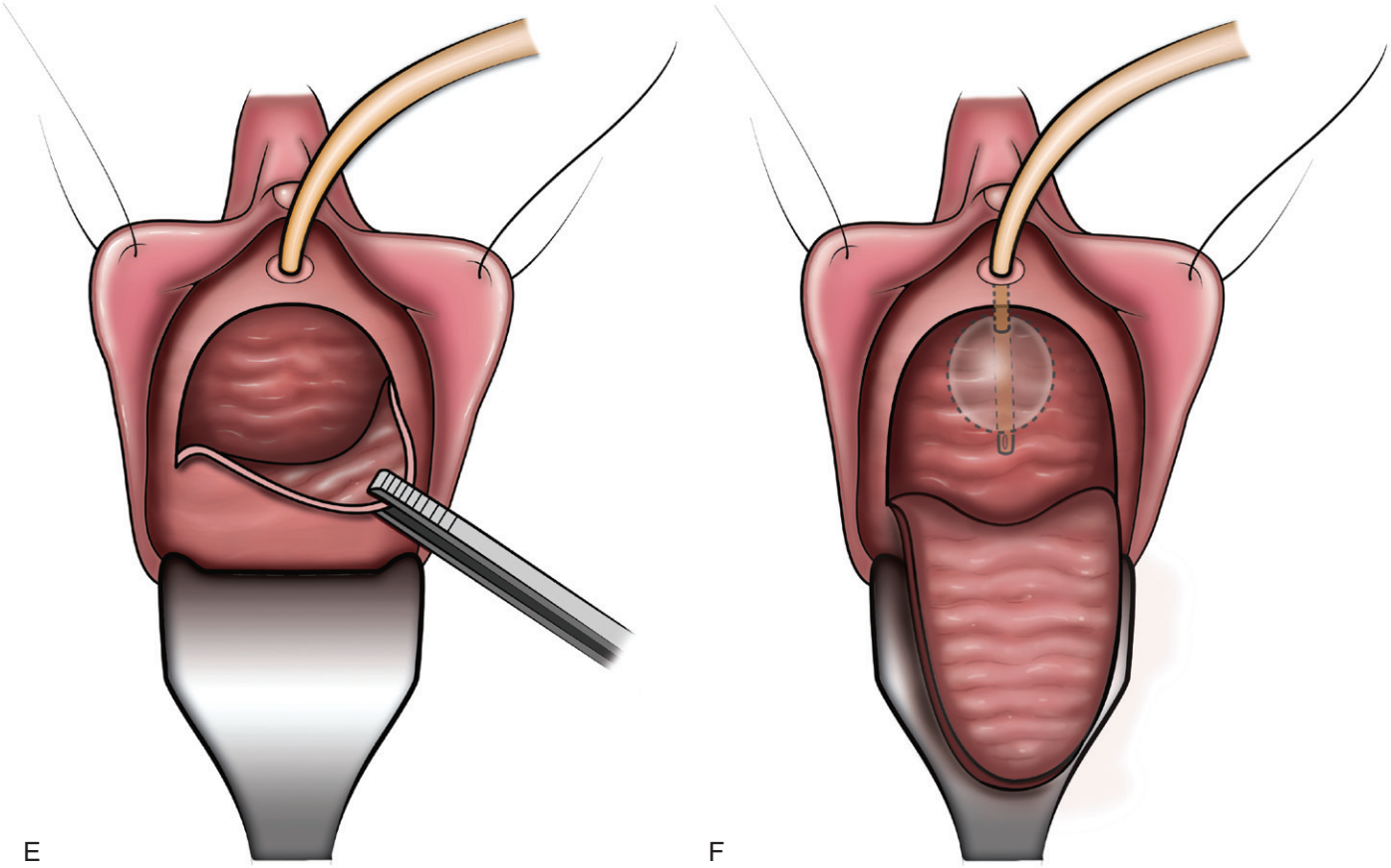


Figure 75–1, cont'd. **E**, Dissection of the vaginal mucosa and deeper tissues off the underlying bladder. **F**, Completed dissection.

hypothesized any one or a combination of (1) endorphinergic effects at the sacral spinal cord level or above, (2) inhibitory somatovisceral reflexes, and (3) increase in peripheral circulation as possible mechanisms of action. The true nature of how acupuncture exerts its beneficial effects remains incompletely understood.

Bergström and associates (2000) reported on the results of classic acupuncture performed twice weekly in a group of 15 elderly women with urgency or mixed incontinence. In this open, uncontrolled study, subjective assessments of improvement and objective measurements in the form of grams of leakage over 48 hours were encouraging, not only at the end of the study but also after 1 and 3 months. More recently, Emmons and Otto (2005) compared acupuncture versus placebo acupuncture in the treatment of women with overactive bladder and urinary urgency incontinence. The number of incontinent episodes decreased by 59% in the treatment group compared with 40% in the placebo group. The treatment group had a significant improvement in bladder capacity, urgency, frequency, and quality-of-life scores compared with the placebo group.

Many studies have been performed to determine the efficacy of acupuncture; however, the level of evidence continues to be limited secondary to difficulties in performing adequate placebo controlled, double-blind studies. In addition, acupuncture requires extensive training, is performed by few clinicians, and few teachers exist. Overall, the importance of acupuncture may not just be in learning or performing the procedure; it may be more important to learn the mechanisms by which it achieves these results, in order to develop easier and less invasive methods of achieving the same (or better) clinical results.

Bladder Distention Therapy

Initially described by Helmstein in 1972 for the treatment of patients with bladder carcinoma, this treatment modality has undergone several modifications. Bladder overdistention, most familiar for its use in the treatment of interstitial cystitis (see Chapter 12), has also been used for other diverse indications, including nocturnal enuresis, irritative symptoms following radiation or BCG, and for patients with overactive bladder.

No standard technique has been clearly defined for this procedure and, as such, several variations exist. Bladder distention may be performed under regional or general anesthesia. The bladder is then distended by either a balloon catheter or more commonly by saline infused cystoscopically or through a urethral catheter. **The ideal pressure and duration needed to distend the bladder has not been well defined. Dunn and colleagues** (1974) **described prolonged bladder distention of several hours at a pressure equal to the patients' systolic blood pressure.** At this pressure, therapeutic benefit is thought to derive from ischemic changes induced in submucosal afferent nerve endings and stretch receptors (Dunn et al, 1977). In a primarily interstitial cystitis population, Hanno and Wein (1991) described distending the bladder to 80 cm H_2O for several minutes with good results. **Bladder rupture, historically as high as 5%**

to 10%, is the most significant complication after bladder distention therapy. Other possible complications include hematuria, back pain, and urinary retention.

Ramsden and colleagues (1976) reported good to excellent results in the treatment of patients with detrusor overactivity, while most others have reported inferior results with this treatment modality. In this same patient population, Jorgensen and coworkers (1985) reported a success rate of only 1 in 15 (6%) patients. In a retrospective review by Taub and Stein (1994), 8 of 22 (36%) of patients with frequency and urgency of various etiologies had subjective improvement, while no patient with detrusor overactivity improved. They also demonstrated that short duration distention therapy (15 to 30 minutes) was as efficacious as prolonged therapy (6 hours). Lloyd and colleagues (1992) reported that only 6 of 29 women with severe irritative symptoms, including 6 patients with interstitial cystitis and none with neurogenic detrusor overactivity, had a good response to treatment. In a study of 26 women with frequency and urgency, Liapis and associates (2001) found a statistically significant increase in bladder capacity after treatment; however, only 4 (15%) had any improvement in symptoms beyond 9 months. **Although largely regarded as an ineffective procedure in patients with storage failure secondary to neurogenic detrusor overactivity, bladder overdistention may provide substantial, but usually temporary, improvement to some patients with non-neurogenic storage symptoms who have failed medical therapy.**

Key Points: Storage Failure Due to Bladder Overactivity, Decreased Compliance, or Hypersensitivity

- Adequate capacity, low detrusor storage pressures, continence, and the absence of involuntary bladder contractions are the goals of managing storage failure.
- To obtain optimal results, complex cases of voiding dysfunction may best be managed by a combination of techniques approached through different mechanisms.
- Central denervation appears to be more suitable for patients with SCI or neurogenic detrusor overactivity but may cause a wide range of unintended side effects.
- Peripheral denervation is relatively bladder selective and more suitable for detrusor instability, with fewer neurologic side effects than more centrally based procedures.
- Denervation may be achieved by sectioning anterior (motor), posterior (sensory) or both sacral roots, converting an overactive bladder into an areflexic one.
- Significant side effects may develop following rhizotomy and may affect bladder, bowel, sphincter, sexual, and motor/sensory elements of the lower extremities.
- To enhance clinical efficacy, differential sacral rhizotomy is typically preceded by stimulation and blockade of the individual sacral roots with cystometric and sphincterometric control.
- The anterior S3 nerve root is the dominant motor innervation of the human bladder.
- Afferent stimulation from dorsal nerve roots is important in generating detrusor contractions. Interruption of the afferent reflex arc by complete transection of all dorsal roots (sacral or sensory deafferentation) abolishes detrusor overactivity.
- Complete dorsal rhizotomy of the S2 through S5 nerve roots abolishes reflex erections, reflex ejaculation, and sacral sensation, and it can reduce reflex defecation.
- The Ingelman-Sundberg procedure and its modifications involve transvaginal partial denervation of the bladder and may benefit patients with refractory urge urinary incontinence.
- It is unclear whether bladder transection, encompassing complete circumferential division of the full thickness of the bladder wall just above the ureteric orifices, is a viable procedure.
- The use of acupuncture has been described for a number of urologic symptoms, including urinary urgency, frequency, incontinence, nonobstructive urinary retention, enuresis, and neurogenic detrusor overactivity.
- The somatic afferent stimulation generated by acupuncture is believed to evoke somatovisceral reflexes that may induce an either excitatory or inhibitory change in bladder function and sphincter activity. Other theories regarding the mechanism of action of acupuncture include endorphinergic effects at the sacral spinal cord level or above and an increase in peripheral circulation.
- Bladder overdistention has been used to treat irritative lower urinary tract symptoms of various etiologies. The most significant complication of bladder distention therapy is bladder rupture. Generally regarded as ineffective for neurogenic detrusor overactivity, distention therapy may provide substantial, albeit temporary, improvements in patients with non-neurogenic–related storage symptoms.

INCREASING OUTLET RESISTANCE

See the Expert Consult website for a discussion of this topic, as well as Figures 75–2 and 75–3.

Key Points: Storage Failure Due to Sphincter Underactivity

- Urethral compression devices are primarily used to treat patients with pure sphincteric incontinence, most commonly postprostatectomy incontinence (PPI). Normal bladder capacity and storage pressures are a relative requirement. Pressure-related injuries may occur with these devices and may be more prevalent in patients with impaired sensation or cognition.
- Injectables treat stress incontinence by increasing the abdominal leak point pressure. Patients with intrinsic sphincter deficiency (ISD) are the best candidates for injectables.
- Most male patients undergoing injection therapy for mild PPI require four to five injections with reinjections every 6 to 12 months to maintain dryness.
- Severe vaginal vault prolapse may cause occult urinary incontinence, defined as stress incontinence, which only occurs with reduction of the prolapse.
- The artificial urinary sphincter (AUS) is very effective in preventing incontinence and may be used in adults or children of both sexes. Caution should be exercised in patients with neurogenic bladder, because renal deterioration may occur if high bladder pressures develop due to poor compliance.

- The main indication for bladder outlet closure is urethral destruction secondary to prolonged catheter drainage in patients with neurogenic bladder.
- Bladder outlet reconstruction may involve tightening, lengthening, or reconstructing the urethral segment to improve the sphincteric mechanism and continence.
- Skeletal muscle transposition and injection of allogenic muscle-derived progenitor cells represent two methods by which functional sphincteric reconstruction may be performed. Further study is required to determine the role of these treatment modalities.
- These topics, many of which are covered elsewhere in the text, are fully discussed on the Expert Consult website.

LOWER URINARY TRACT RECONSTRUCTION, DIVERSION, AND BLADDER SUBSTITUTION

See the Expert Consult website for a discussion of the topic.

Key Points: Lower Urinary Tract Reconstruction, Diversion, and Bladder Substitution

- Bladder augmentation offers the best chance to construct a "normal" urinary system, but the ability to void without catheterization is not guaranteed; therefore, only patients who have the ability and motivation to perform CIC should be considered for this procedure.
- Although bladder augmentation is invasive, it is generally very effective, with significant improvement reported in up to 90% of patients with neurogenic lower urinary tract dysfunction or limited-capacity bladders due to other causes.
- Results are less favorable and of shorter duration following the autoaugmentation procedure than with conventional enterocystoplasty. Autoaugmentation is less morbid and may benefit patients who require avoidance of intestinal segments.
- Supravesical diversion may serve as treatment for both storage and emptying disorders. Indications for diversion may include progressive, medically refractory hydronephrosis; recurrent urosepsis; or intractable storage or emptying failure when CIC is impossible.
- The incontinent ileovesicostomy is an excellent method for managing patients with neurogenic bladder who are unable to perform CIC independently. Complications of long-term indwelling catheters are avoided, and the native antireflux and urethral sphincteric mechanisms are maintained.
- The ileal conduit is the most recognized and commonly performed form of urinary diversion.
- Despite advances in the development of the tissue-engineered and artificial bladder, we are still far from achieving an adequate bladder replacement.
- A more extensive discussion of these topics can be found on the Expert Consult website.

CATHETERIZATION

Catheterization, in its many forms, is an effective method of bladder emptying, and is a useful adjunct when efforts to increase intravesical pressure and/or decrease outlet resistance have been unsuccessful. In addition, for those patients who have filling/storage failure caused by bladder overactivity and/or sphincteric incontinence, catheterization may also be used if the dysfunction can be converted solely or primarily to one of emptying by nonsurgical or surgical means (Wein and Barrett, 1988). The common goals, irrespective of the mode of catheterization, are to provide low-pressure storage, preserve continence, avoid renal deterioration, minimize complications, and maintain quality of life.

Indwelling urethral catheters are generally used for short-term bladder drainage, and careful use of a small-bore catheter for a short time is unlikely to adversely affect the ultimate outcome, especially if used in the initial bladder management in SCI (Lloyd et al, 1986). Long-term bladder drainage may be obtained by intermittent catheterization, or by an indwelling suprapubic or urethral catheter. Historically, the most appropriate form of bladder drainage in patients requiring prolonged bladder management has been debated. Most studies evaluating the different forms of long-term bladder management have been retrospective and in patients with SCI, because they represent the majority of patients requiring long-term catheterization. **The main area of controversy concerns whether long-term indwelling catheterization in neurologically impaired patients is associated with an inferior outcome compared to clean intermittent catheterization, specifically regarding urinary tract complications or quality of life.**

Although CIC is currently the preferred management for patients requiring prolonged bladder drainage, it is a recent innovation. Intermittent catheterization was first introduced as a sterile procedure in 1949 by Guttman and, at the time, challenged the beliefs of most urologists (Guttman, 1949; Guttman and Frankel, 1966). It was not until Lapides and colleagues (1972) introduced the concept of clean intermittent catheterization that widespread usage became more common. **As the popularity of CIC grew, long-term indwelling catheterization was condemned, based on both infectious risks and a perceived increased risk of other urologic complications.** Jacobs and Kaufman (1978) reported that there were more renal and other urologic complications with long-term (>10 years) catheterization use than with short-term use. Hackler (1982) also reported accelerated renal deterioration in patients with SCI managed with long-term suprapubic catheterization. McGuire and Savastano (1984) reported a poorer outcome in women with an indwelling urethral catheter than in those on CIC after 2 to 12 years. Of 13 in the catheter group, 54% had adverse changes on intravenous pyelography, as opposed to 0% in the CIC group. Other urologic complications were also more frequent and severe in the catheter group.

Conversely, more recent investigations have suggested the complications from chronic indwelling catheters may be lower than previously thought. Sekar and coworkers (1997) reported on the effect of different bladder management methods in 1114 patients with SCI using total and individual kidney-effective renal plasma flow as the primary outcome measure. Follow-up was relatively long with 51.3% followed 0 to 3 years, 40% at least 5 years, and 20% for at least 10 years. Unfortunately, many issues, such as unclear methods of urinary management at discharge, incomplete data on approximately 200 patients, and the fact that most men who were discharged using CIC later changed to condom catheter drainage, weaken the authors' conclusions that there was very little change in renal function over time in patients using different bladder management methods. Dewire and associates (1992)

reviewed the course of 32 quadriplegic patients managed with, and 25 without, an indwelling catheter. The groups were roughly comparable, and follow-up was for 10 years or longer. The incidences of upper and lower urinary tract complications and renal deterioration were not significantly different. Chao and coworkers (1993) did a similar review on 32 patients with SCI with an indwelling urethral (14 patients) or suprapubic catheter (18 patients) versus 41 patients without. Follow-up was 20 years or longer. Although the catheterized group had a higher prevalence of upper tract scarring and caliectasis, no significant differences were found in other indices of renal function or in the prevalence of other urologic complications. Jackson and DeVivo (1992) reported on the results of indwelling catheterization in 108 women (with SCI) followed for 2 to 5 years (56 women), 6 to 9 years (31 women), and 10 or more years (21 women) after injury. Compared with the male population, the majority being managed by condom drainage, there was no difference in upper or lower tract complications. MacDiarmid and colleagues (1995) reported on suprapubic catheterization in 44 patients with SCI, with follow-up ranging from 12 to 150 months (mean, 58 months). They reported that no patient had renal deterioration or vesicoureteral reflux and that the incidences of incontinence, infection, and calculi were acceptable. Eleven percent of the patients had leakage, 100% had bacteriuria, 41% developed bladder calculi, and 7% developed renal calculi. Thirty-six percent of patients developed episodes of catheter blockage, and gross hematuria resulting in hospitalization occurred in 5%.

Upper tract and infectious complications often occur regardless of whether intermittent or indwelling catheterization is used. Although bacteruria is common in all forms of bladder catheterization, symptomatic infection is not. **The presence of asymptomatic bacteruria does not usually require treatment and should be distinguished from an invasive, symptomatic urinary tract infection (UTI). Treatment of asymptomatic bacteruria has not proven beneficial, and the use of continuous prophylactic antibiotics is rarely indicated (Gribble and Puterman, 1993).** Nevertheless, infectious complications are the most common complications associated with prolonged catheterization, and procedures such as frequent catheter changes should be considered to reduce these complications (Weld and Dmochowski, 2000; Wyndaele, 2002). Much interest has recently been generated with catheter-associated infections in hospitalized patients. Under new rules by the Centers of Medicare and Medicaid Services, hospitals will not be compensated for catheter-associated UTIs, causing many hospitals to intensify their efforts in implementing preventive measures (Saint et al, 2009). For more information regarding bacteruria and catheter-associated UTI see Chapter 10.

More recent studies have shown the superiority of CIC over long-term indwelling catheter drainage. Weld and Dmochowski (2000) reported a retrospective review of 316 patients with SCI with a mean follow-up of 18.3 years. Bladder management methods included chronic urethral catheterization in 114 patients, CIC in 92, spontaneous voiding in 74, and suprapubic catheterization in 36. Complications were recorded in terms of infectious complications (epididymitis and pyelonephritis), renal and bladder calculi, urethral complications (stricture and periurethral abscess), and radiographic abnormalities (vesicoureteral reflux and abnormal urographic findings). Overall, there were 398 complications recorded, of which 236 developed in 61 patients (53.5%) on chronic urethral catheterization, 48 in 16 patients (44.4%) on suprapubic catheterization, 57 in 24 patients (32.4%) who voided spontaneously, and 57 in 25 patients (27.2%) on CIC. Separate bar graphs for each type of complication seem to confirm the overall superiority of CIC as the least problematic long-term form of bladder management (Fig. 75–4).

The exact etiology of upper tract deterioration in patients with long-term indwelling catheters is unclear, because the bladder should be well drained by a catheter; however, it is likely related to chronic "occult" or subclinical detrusor overactivity in the face of sphincteric dyssynergy providing a functional obstruction. Regardless of the etiology, it is clinically heralded by the development of poor detrusor compliance demonstrated on urodynamic studies. Weld and colleagues (2000) reported the effects of CIC versus indwelling urethral catheterization on bladder compliance in patients with SCI. Logistical regression analysis of compliance versus bladder management and interval because injury revealed that CIC and spontaneous voiding were associated more with normal compliance than indwelling urethral catheterization. **Poor compliance was statistically associated with vesicoureteral reflux, radiographic upper tract abnormalities, clinical pyelonephritis, and upper tract calculi** (Fig. 75–5). Jamil and associates (1999) reported on ambulatory urodynamics in 30 patients with SCI whose bladders were managed with an indwelling urethral catheter. They found that freely draining indwelling catheters did not guarantee consistently low intravesical pressure. Eleven of 30 patients demonstrated intermittent detrusor contractions causing intravesical pressure increases greater than 40 cm H_2O for up to 4.5 minutes. These patients had used an indwelling catheter for a mean of 14.3 years (range, 4 to 36 years). Renal scarring was observed in 9 patients, and, of these, 6 were in the group with the abnormal bladder contractions, whereas only 5 of 21 patients with normal kidneys had such pressure rises. **The clinical correlate emphasized by the authors was their belief that maintenance of a compliant bladder and suppression of high-pressure contractions in chronically catheterized patients may play a role in the prevention of renal deterioration.** Kim (1997) demonstrated in a retrospective analysis that anticholinergic medications can reduce the incidence of hydronephrosis, improve bladder compliance, as well as decrease leak point pressures in patients with chronic catheters. The role of anticholinergics with various forms of prolonged bladder management and in the prevention of upper tract complications has not yet been clarified (Feifer, 2008).

There is certainly some controversy about the classic teaching that long-term continuous bladder catheterization in patients with neurogenic bladder dysfunction should be avoided at all costs. There are clearly some situations in which such management is desirable and necessary. Most of the studies that purport to compare methods of management regarding lower and upper tract complications are often flawed and prevent total acceptance of their conclusions. In the absence of a prospective, randomized study or acceptable retrospective data, patient and family comfort, convenience, and quality of life must be strongly considered in the decision of which method of catheterization will be employed. Regardless of which method is used, **periodic upper and lower tract evaluation using renal ultrasonography and cystoscopy should be considered in all patients who require prolonged bladder management.** Lastly, the use of urodynamics to monitor the bladder in neurologically impaired individuals is controversial. **At a minimum, we believe that urodynamics should be**

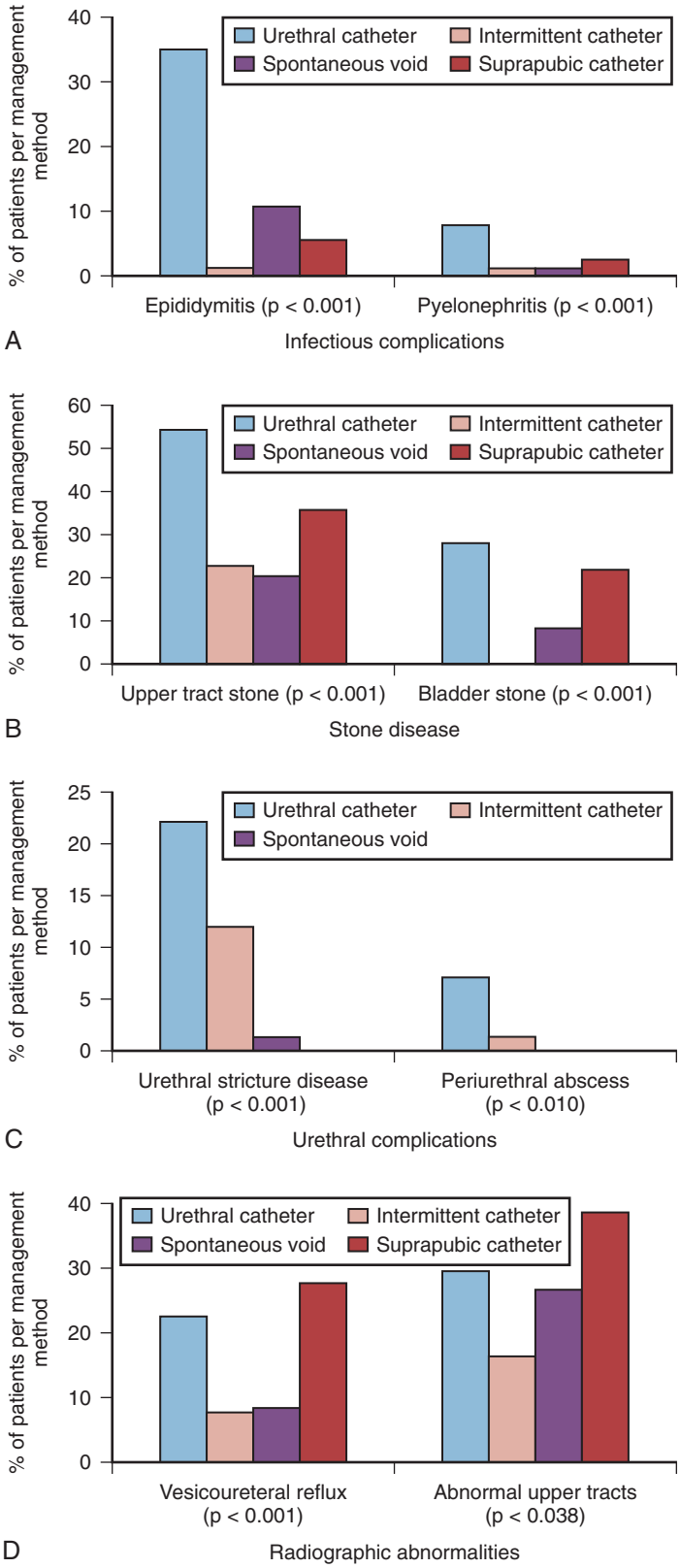


Figure 75–4. Complications related to specific bladder management methods: infectious **(A);** stone disease **(B);** urethral **(C);** radiographic abnormalities **(D).** (Modified from Weld KJ, Dmochowski RR. Effect of bladder management on urological complications in spinal cord injured patients. J Urol 2000;163:768–72.)

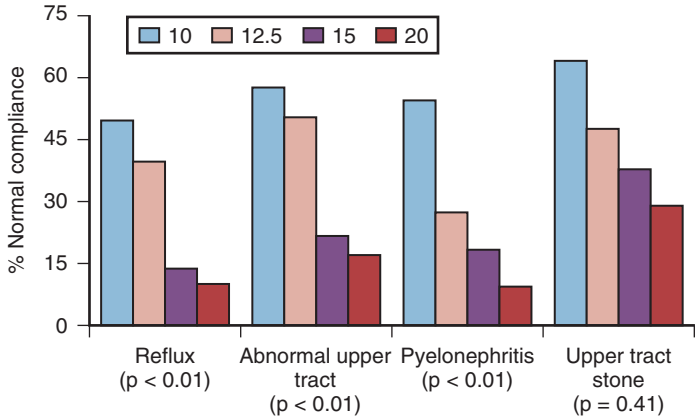


Figure 75–5. Incidence of patients with upper tract complications who had normal bladder compliance at various threshold values. (From Weld KJ, Graney MJ, Dmochowski RR. Differences in bladder compliance with time and associations of bladder management with compliance in spinal cord injured patients. J Urol 2000;163:1228–33.)

performed after the initial neurologic injury is stable and whenever any significant changes in continence or voiding function occur. The initial urodynamics is useful to direct early bladder management, while subsequent urodynamics evaluations are performed to determine if lower urinary tract changes, such as the development of dyssynergia, have occurred.

Clean Intermittent Catheterization (CIC)

CIC has proved to be the most effective and practical means of attaining a catheter-free state in the majority of patients with acute spinal cord lesions. CIC has revolutionized the treatment of difficult cases of neuromuscular dysfunction of the lower urinary tract by providing a safe and effective method that preserves the independence of the patient to empty the lower urinary tract in cases in which continence has been achieved pharmacologically or surgically, producing total or partial urinary retention. **For example, without CIC, the successful outcomes achieved using augmentation cystoplasty or continent urinary diversion would have never been achieved. CIC is based on a theory proposed by Lapides that high intravesical pressure or bladder overdistention is primarily responsible for the development of UTI, not the bacteruria itself.** Theoretically, reduced blood flow to the bladder can lead to increased host susceptibility to bacterial invasion and UTI. Bacteria introduced by CIC would be neutralized by the host, and relatively sterile urine would be maintained as long as bladder distention and high intraluminal pressures were avoided. The long-term efficacy and safety of such a program has been demonstrated by Lapides and others (Weld and Dmochowski, 2000).

Whereas indwelling catheter drainage requires little input from the patient, **a cooperative, well-motivated patient or family is a requirement for CIC.** The patient must have adequate hand control, or a family member must be willing to perform the catheterization. In addition, **there must be adequate urethral exposure.** Graham (1989) reported on the factors required to successfully develop a catheterization program

for patients with functional limitations, which commonly exists in patients with neurogenic bladder dysfunction. It is advantageous to have a dedicated nurse who instructs the patients and families in the catheterization regimen; provides them with understandable written instructions to refresh their memory regarding technique, precautions, and danger signals; and provides continuing support for patients and families who call with questions or problems regarding their regimen. Many patients are initially reluctant to perform any procedure on their own genitalia. Patients need a thorough explanation of the advantages of CIC along with assurances that it is simple and that it will not tie them to their houses or to an absolute time schedule. Additionally, proper selection of equipment for the patient's intelligence and financial level will increase patient acceptance of and compliance with a self-catheterization program. Patients who are reticent initially are continually amazed by the ease with which such a regimen is established. Successful CIC is intimately associated with patient compliance, and therefore patients should be monitored periodically to ensure catheterization is performed properly. Of note, **CIC should be used cautiously in patients known to have autonomic dysreflexia.**

Intermittent catheterization may be performed by clean, aseptic, or sterile techniques (Hudson and Murahata, 2005). Clean intermittent catheterization often includes reusing a catheter several times before disposal. It is washed, generally with soap and water, and allowed to air dry prior to storage. When reusing catheters, some have advocated boiling or microwaving for sterilization (Douglas et al, 1990). **In April 2008, in an attempt to decrease the incidence of UTIs in patients performing intermittent catheterization, Medicare policy regarding intermittent catheterization changed. Any patient requiring intermittent catheterization may obtain up to 200 sterile catheters per month for one-time use.** This change in policy has negated the need for reusing catheters in most patients, but it still may be necessary in patients without insurance coverage or other financial limitations. **For adult patients, catheterization is typically performed at a minimum of every 4 to 6 hours to minimize bacterial dwell time. CIC may need to be more frequent if large volumes of fluid are ingested. In most cases, catheterizations should be timed to maintain bladder volumes below the normal 400- to 500-mL capacity** to minimize bladder wall pressure. Even smaller volumes may be required if they have poor detrusor compliance. Catheter choice is variable, but a 12- to 16-Fr soft catheter may be used for males and short (6-inch "female") 12- to 16-Fr catheters for females. Note that rigid catheters have the potential to injure the urethra in insensate males because they may not "make the bend" at the prostate, causing a false passage such that CIC may be quite difficult or impossible. Larger catheters may be required in patients with a prior bowel augmentation or those who require bladder irrigation. In men, hydrophilic coated catheters have been found to reduce the incidence of UTI and hematuria and have higher patient satisfaction rates than conventional plastic catheters (Vapnek et al, 2003; De Ridder et al, 2005). Patients with recurrent UTIs, despite the use of single-use sterile catheters, may obtain sterile catheter kits for sterile intermittent catheterization (IC). Anticholinergic medication should be considered when urine leakage occurs between catheterization intervals or if high storage pressures develop. Wyndaele (2002) reported that trauma from catheterization occurs frequently, but effects are usually not long standing, and urethral stricture and false passages are more common the longer that CIC is employed.

Continuous Catheterization

Long-term indwelling catheters should be considered when anatomical, functional, or familial limitations prohibit performance of intermittent catheterization. Continuous catheterization may also be indicated in patients with complications from persistent incontinence or autonomic dysreflexia, despite therapy or when a small bladder capacity prohibits effective CIC. Long-term catheterization may be accomplished by either a urethral or suprapubic catheter. The basics of urethral catheterization, including the technique of suprapubic tube (SPT) insertion are covered in Chapter 7.

In males, the benefits of an indwelling SPT over urethral catheterization include a lower incidence of epididymitis and urethral stricture disease (Weld and Dmochowski, 2000) **and preserved sexual function** (Rutkowski et al, 1995) (see Fig. 75–4). Overall, suprapubic catheters have been associated with high rates of patient satisfaction. Barnes and associates (1993) concluded that long-term suprapubic catheters were well tolerated by patients with neuropathic bladders. Based on the replies of 32 patients who expressed an opinion, 84% were satisfied; however, the follow-up was short (mean 23 months), and in 2 of 12 patients assessable at over 2 years, creatinine levels increased. Other problems occurred, including recurrent catheter blockage in 38%, recurrent symptomatic urinary infections in 23%, and displaced catheters requiring reinsertion in the operating room in 15%. Urethral leakage occurred in 8 of 14 females with a suprapubic catheter alone and in 6 of 16 males. **Patients using a suprapubic catheter must be warned that urinary incontinence may commence or worsen in the setting of sphincteric incontinence or reflex detrusor overactivity, because active opening of the sphincteric unit will occur in the absence of dyssynergia.** Sheriff and associates (1998) discussed the clinical outcome in a satisfaction survey of 185 patients with neuropathic bladder dysfunction treated with long-term suprapubic catheterization (follow-up, 3 to 68 months; mean, 24 months). The authors reported an 82% satisfaction rate; however, the main reason for this procedure was failed CIC from poor hand function. In addition, only 103 of the 185 patients filled out the satisfaction questionnaire, and only 8 patients had a suprapubic catheter for longer than 2 years. Complications in this group included 5 patients with a small-bowel injury during insertion, 2 developing significant hemorrhage, 2 requiring catheter repositioning, 1 requiring reinsertion because of dislodgement, 8 with persistent incontinence, and 18% with recurrent catheter blockage. Bacteriuria existed in 98% of the patients, but recurrent symptomatic infection occurred in only 4%. More recently, Ahluwalia and colleagues (2006) reported a satisfaction rating of 71% among 219 patients having indwelling suprapubic catheters for greater than 50 months.

A controversial issue, common to all long-term indwelling catheters, is the development of bladder cancer. **The long-term risk of carcinoma in the SCI patient with a chronic catheter has been estimated to be 8% to 10%** (Locke et al, 1985; Delnay et al, 1999). Kaufman and colleagues (1977) were among the first to recognize that patients with SCI and chronic indwelling catheters had an increased incidence of bladder cancer, particularly squamous cell carcinoma (SCC). Several others have reported similar findings (Chao et al, 1993; Stonehill et al, 1996). Since this report, the association between chronic indwelling catheterization and the development of bladder carcinoma has been debated. **No associations with intermittent**

catheterization have been identified. Chronic inflammation is the most likely causative factor and may be caused by the indwelling catheter itself, bladder calculi, and/or recurrent infections. It is not clear whether earlier treatment of these conditions or better follow-up will lessen the risk for bladder carcinoma. A mechanism for the development of bladder carcinoma secondary to long-term inflammation was described by Wall and colleagues (2001). **According to their report, inducible nitric oxide synthase expressed by inflammatory macrophages in areas of chronic inflammation may lead to the formation of potentially carcinogenic nitrosamines in the bladder.** For more on the development of carcinoma and the associations with spinal cord injury and chronic catheterization, see Chapter 65.

When SCC is identified in SCI patients, it is often advanced and commonly fatal; however, routine screening cystoscopy for SCI patients at risk is controversial. **Although some authors suggest that screening cystoscopy conveys a survival advantage by identifying bladder cancer at an earlier stage** (Navon et al, 1997), **others have found no advantage for screening** (Yang and Clowers, 1999; Hamid et al, 2003). Cytology, although commonly obtained, is not useful for detecting squamous cell carcinoma (Bejany et al, 1987). Additionally, SCC may not always be cystoscopically detectable (Kaufman et al, 1977). For this reason, routine random biopsies have been advocated by some (Stonehill et al, 1996). **Despite the lack of data in non-SCI patients, most urologists recommend all patients with chronic catheters undergo annual screening, generally starting after 8 years** (Stonehill et al, 1996). **Gross hematuria has been reported by several investigators as the most common presenting symptom for patients eventually diagnosed with bladder cancer** (Hess et al, 2003). Despite the disparate opinions regarding screening, certainly all would agree that patients with new-onset gross hematuria should be evaluated with upper tract imaging, urinary cytology, cystoscopy, and perhaps random biopsies. **Other patients to consider for close surveillance should include patients with known risk factors for the development of carcinoma, such as recurrent UTIs or recurrent bladder stones.**

Key Points: Catheterization

- Catheterization is an effective tool in promoting bladder emptying and may also assist patients with filling/storage failure due to overactivity and/or sphincteric incontinence, especially if the bladder can be converted solely or primarily into a storage organ using either medical or surgical means.
- Whether long-term indwelling catheterization is inferior to clean intermittent catheterization remains a main area of controversy, specifically regarding urinary tract complications and quality of life.
- Asymptomatic bacteruria is common in catheterized patients and does not require treatment unless the patient becomes symptomatic.
- Periodic surveillance should be considered in patients with chronic catheters, because elevated bladder pressures, poor bladder compliance, and upper tract deterioration may develop despite seemingly adequate bladder drainage by CIC or an indwelling catheter.
- Maintenance of low intravesical pressure and avoidance of bladder overdistention is essential to successful CIC.
- The most common complications associated with catheter use include infectious (epididymitis, periurethral abscess, pyelonephritis), renal and bladder calculi, urethral stricture, and vesicoureteral reflux.
- The exact etiology of upper tract deterioration in patients with long-term indwelling catheters is unclear; however, it is likely related to chronic "occult" or subclinical detrusor overactivity in the face of sphincteric dyssynergy providing a functional obstruction.
- Poor compliance is associated with vesicoureteral reflux, radiographic upper tract abnormalities, clinical pyelonephritis, and upper tract calculi.
- In patients with SCI, urodynamics should be performed after the initial neurologic injury is stable and whenever any significant changes in continence or voiding function occur. Periodic upper and lower tract evaluation using renal ultrasonography and cystoscopy should also be considered in all patients who require prolonged bladder management.
- CIC should be used cautiously in patients known to have autonomic dysreflexia.
- Intermittent catheterization may be performed by clean, aseptic, or sterile techniques.
- Any patient requiring intermittent catheterization may obtain up to 200 sterile catheters per month for one-time use.
- In most patients, catheterizations should be timed to maintain bladder volumes below the normal 400- to 500-mL capacity.
- Long-term indwelling catheters should be considered when anatomical, functional, or familial limitations prohibit performance on intermittent catheterization.
- In males, the benefits of an indwelling SPT over urethral catheterization include a lower incidence of epididymitis and urethral stricture disease with preservation of sexual function.
- The long-term risk of carcinoma in the SCI patient with a chronic catheter has been estimated to be 8% to 10%. This association has not been identified in patients performing intermittent catheterization.
- The development of gross hematuria in patients with a chronic indwelling catheter should prompt further evaluation, including upper tract imaging, urine cytology, cystoscopy, and consideration of bladder biopsy.

URINARY COLLECTION DEVICES AND CONTINENCE PRODUCTS

See the Expert Consult website for a discussion of the topic.

Key Points: Urinary Collection Devices and Continence Products

- There currently is no external collection device that performs effectively or reliably for female patients.
- The most common male external collection device is the condom catheter. Patients often perceive condom catheters as more comfortable than indwelling catheters; however, many find the device unacceptable due to its visibility and potential for foul odors.
- Condom catheters may be associated with pressure-related injuries, especially when used by patients with impaired sensation or cognition.
- Condom catheters and absorbent products are associated with a lower incidence of complications than indwelling catheters, but higher complication rates than if no devices or products are used at all.
- A patient's satisfaction with absorbent products may be influenced by several factors, such as the shape or contour of the pad, their capacity and speed of absorbency, amount of core fluff, fit, and comfort when dry or wet.
- Selection of an absorbent product is often a matter of trial and error and often based on personal opinion, manufacturer's claims, convenience of the caregiver, or cost of the product, rather than any evidence-based guidance.
- Incontinence-associated dermatitis (IAD) is defined as inflammation of the surface of the skin with redness, edema, and in some cases bullae. IAD predominately occurs in skin folds and may promote candidiasis or bacterial skin infections.
- A complete discussion of these topics can be found on the Expert Consult website.

METHODS TO IMPROVE BLADDER EMPTYING

Low flow rates and elevated residual volumes are often signs of a bladder that fails to empty. Symptoms are less specific in identifying the underlying abnormality but may include incomplete emptying, straining to urinate, and decreased force of stream. Patients with emptying failure are prone to bladder stones, UTI, and urinary retention and, if not addressed, may lead to renal deterioration. **Methods to improve bladder emptying consist of two main strategies: increasing intravesical pressure and decreasing outlet resistance. Unfortunately, management of poor detrusor contractility is limited and has not been overwhelmingly successful,** obliging most patients to rely on chronic catheterization. Attempts to alter the contractility of the bladder through pharmacotherapy or electrical stimulation have also been described and are detailed in Chapters 68 and 70, respectively.

Conversely, **methods of decreasing outlet resistance due to obstruction are more straightforward, more successful,** and are thoroughly discussed in several chapters. Pharmacologic measures have been used to decrease outlet resistance both at sites of anatomic and sphincteric obstruction and are reviewed in Chapters 92 and 68. Chapter 36 outlines the management of urethral stricture disease; prostatic obstruction is discussed in Chapters 93 and 94. For patients with intractable emptying failure and inability to catheterize, urinary diversion may be considered (see earlier discussion in this chapter). In the following sections, we discuss further management options to improve bladder emptying. Some of these modalities are well known and established, while others are less familiar.

Increasing Intravesical Pressure or Facilitating Bladder Contractility

External Compression (Credé) and Valsalva Maneuver

The Credé maneuver (manual compression of the bladder) is most effective in patients with decreased bladder tone who can generate an intravesical pressure greater than 50 cm H_2O and have decreased bladder outlet resistance (Wein and Barrett, 1988). The technique of voiding by the openhanded Credé method involves placement of the thumbs of each hand over the area of the anterior superior iliac spines and the digits over the suprapubic area, with slight overlap at the fingertips. The slightly overlapped digits are pressed into the lower abdomen and when they are located behind the symphysis, are pressed downward to compress the fundus of the bladder. For some patients, this maneuver can be accomplished more efficiently by using a closed fist of one hand or using a rolled-up towel. Straining as the Credé maneuver is applied is generally counterproductive because this increases intra-abdominal pressure and causes bulging of the abdominal wall, which then tends to lift the compressing hands off the fundus of the bladder. If the guarding reflex arc is intact, this may also produce a striated sphincter contraction. The Credé maneuver is much easier in a patient with a lax, lean abdominal wall than in one with a taut or obese one, and it is more readily performed in a child than an adult.

A similar increase in intravesical pressure may be achieved by abdominal straining (Valsalva maneuver). The proper technique involves sitting and letting the abdomen protrude forward on the thighs. During straining in this position, hugging of the knees and legs may be advantageous to prevent any bulging of the abdomen. To increase intravesical pressure in this manner requires voluntary control of the abdominal wall and diaphragmatic muscles.

"Voiding" by the Credé or Valsalva maneuver is generally discouraged, because it is nonphysiologic and is resisted by the same forces that normally resist stress incontinence. Reflex sphincteric opening of the bladder outlet does not occur with external compression maneuvers of any kind, and, in many cases, an increase in outlet resistance may occur reflexively. If adequate emptying does not occur in the properly selected patient, other types of therapy to decrease outlet resistance may be considered; however, these treatments may adversely affect urinary continence.

The best chance of success with this mode of therapy (some would say it should never be used) is in the patient with an areflexic bladder and some degree of outlet denervation. This is most commonly seen in the patient with an autonomous neurogenic bladder (Lapides classification), T11 through L2 spinal cord injury where the sympathetic nervous supply is damaged, or after outlet resistance is decreased surgically or by botulinum toxin injection. Most of these patients already

have stress incontinence, and the Credé or Valsalva maneuver simply helps the patient overcome outlet resistance to empty the bladder at a convenient time. These techniques may also be useful to decompress a neobladder when the outlet resistance is low either by volitional sphincteric relaxation or when surgically induced.

Vesicoureteral reflux is a relative contraindication to external compression or the Valsalva maneuver, especially in patients capable of generating a high intravesical pressure. The most flagrant misuse of this form of management is in the patient with a neurogenic bladder and poor detrusor compliance, because the increased storage pressures can cause upper tract deterioration with minimal filling. External compression or Valsalva maneuvers will only further aggravate this already dangerous situation.

Even when the patient has a flaccid bladder and/or low detrusor leak point pressures, close follow-up and periodic evaluation are necessary to avoid upper tract deterioration. Chang and colleagues (2000) reported the long-term urologic complications and residual volumes of 74 SCI patients with flaccid bladders who routinely performed the Credé maneuver as their primary form of bladder management for more than 20 years. Residual urine volume was greater than 100 ml in 93% of patients, and 50% were greater than 300 ml. The authors also reported that 59.5% developed ureteral dilation, 35.1% developed hydronephrosis, and 16.2% suffered renal deterioration. Males were significantly more likely to develop these complications than females, probably due to increased outlet resistance. Other complications included recurrent UTIs, pyuria, urinary lithiasis, epididymo-orchitis, genital-rectal prolapse, and hemorrhoids (Chang et al, 2000; Wyndaele, 2008).

Promotion or Initiation of Reflex Contractions

In patients with SCI and an intact sacral spinal cord, voiding can be elicited by exploiting existing spinal reflexes. The sacral micturition reflex occurs when tension receptors within the bladder wall are stimulated by bladder filling and activate sensory afferent neurons. Motor efferents from the spinal cord respond by generating a reflexive bladder contraction and, when of adequate magnitude, will result in voiding. Bladder contractions obtained in this manner are often involuntary and sporadic. In some cases, patients with SCI may be able to trigger this reflex voluntarily by manual stimulation of areas within the sacral or lumbar dermatomes**. According to the classic reference by Glahn** (1974), **the most effective method of initiating a reflex contraction is rhythmic suprapubic manual pressure (seven or eight pushes every 3 seconds). Quick repetitive stimulation in this manner is thought to produce a summation effect on the tension receptors in the bladder wall, resulting in activation of the bladder reflex arc.** Ideally, the elicited contraction would be of sufficient magnitude and duration to empty the bladder. **Other commonly used maneuvers to induce reflex detrusor contractions include pulling the skin or hair of the pubis, scrotum, or thigh; squeezing the clitoris; or by digital rectal stimulation** (Wein and Barrett, 1988). Patients able to void in such a way are encouraged to find their own optimal trigger points and position for urination. If induced emptying can be carried out frequently enough to keep bladder volume and pressure below the threshold for activation of the involuntary micturition reflex, and below pressures that might cause upper tract deterioration, incontinence can be controlled, similar to timed voiding in normal individuals. Reflex voiding is dependent on the ability to stimulate detrusor contractions and may be most suitable for patients with SCI or conditions characterized by detrusor overactivity. To void reflexively, patients require manual dexterity and the ability to transfer to a commode, or at least the ability to use and maintain an external collecting device. For this reason, reflex voiding may not be suitable for many female patients. Surgical procedures to reduce outlet resistance should be considered if significant obstruction or sphincter dyssynergia are present. Complications with this voiding technique are most often related to the use of external collection devices or from the development of high-pressure storage resulting in upper tract deterioration. To ensure compliance, periodic surveillance should be performed with consideration of regular urodynamic evaluation.

Some clinicians believe that the micturition reflex can be "trained" by maintaining a copious fluid intake and periodically clamping and unclamping an indwelling catheter or by CIC at regular intervals. This cyclic pattern of filling and emptying may promote storage and emptying in a more physiologic manner, focuses attention on the urinary tract, and ensures an adequate fluid intake. It is true that balanced lower urinary tract function can be achieved using this program (Opitz, 1984; Menon and Tan, 1992), but whether this is a cause-and-effect relationship is unknown and difficult to prove.

One fascinating set of experiments that relates to the concept of establishing or promoting a reflex pathway for micturition is that reported by Xiao and de Groat (1999). They created a skin-to–central nervous system to bladder reflex pathway in cats by intradural microanastomosis of the left L7 ventral root to the S1 ventral root, leaving the L7 dorsal root intact to conduct cutaneous afferent signals. A detrusor contraction, without striated sphincter dyssynergia, could be initiated by scratching the skin or by percutaneous electrical stimulation in the L7 dermatome. The pathway was found to be mediated by cholinergic transmission at both ganglionic and peripheral levels. **The importance of this experimental model is that somatic motor axons were able to innervate parasympathetic bladder ganglion cells and therefore transfer somatic reflex activity to the lower urinary tract**. Xiao and colleagues (2003) reported on the first human clinical trial, in which 15 males with neurogenic overactivity and detrusor–external sphincter dyssynergia (DESD) secondary to complete suprasacral SCI underwent a ventral root microanastomosis between the L5 and the S2 and/or S3 ventral root. With a mean follow-up of 3 years, recovery in bladder storage and emptying function was reported in 10 (67%) patients. Average residual urine decreased from 332 cc to 31 cc with resolution of UTIs and overflow incontinence. Postoperative urodynamics demonstrated the resolution of detrusor overactivity and DESD to near-normal storage pressures, with synergic voiding and without DESD. Improvement in bowel function was also noted. Xiao and colleagues (2005) subsequently reported on 20 children with neurogenic bladder from spina bifida, among whom 17 of 20 (71.4%) demonstrated urodynamic improvements after surgery. Partial loss of L4 or L5 motor function, ranging from slight muscular weakness to visible foot drop, was reported in 5 of 20 patients. Xiao (2006) recently reviewed the initial human trials to date, and although encouraging results have been reported, experiences from other centers are needed to confirm these findings.

Reduction Cystoplasty

Myogenic decompensation of the bladder with excessive urinary capacity and chronic urinary retention may be idiopathic, of neurologic origin, the result of an infravesical obstruction, or exist as one of the components of the prune belly syndrome (Eagle-Barrett

syndrome). **The simplicity of partial cystectomy to reduce bladder capacity and, theoretically, restore contractility has often enticed surgeons to perform this procedure; however, if urodynamic evaluation after prolonged Foley catheter drainage shows no spontaneous detrusor contractions, this procedure is unlikely to be successful. If contractility is proven, surgical reduction is certainly an option in the appropriate patient.** Some of the techniques that have been used in the past include fundus invagination (Stewart, 1966), transection and removal of the upper "free" part of the bladder (Klarskov et al, 1988), a detrusor wrap (Hanna, 1982), or detrusor duplication (Zoedler, 1964). Kinn (1985) reported on 10 patients with various etiologies and was successful in reducing the bladder capacity, reducing residual urine volume, and reducing frequency of urinary infection, but found no improvement of detrusor contractility after reduction cystoplasty. Similar results were obtained by Klarskov and colleagues (1988), who reported on 11 patients, with only 3 being subjectively cured, one proceeding to supravesical diversion, and 5 using CIC. **Although patients with acontractile bladders generally do poorly, encouraging results have been attained in patients with hypocontractile detrusor function** (Kinn, 1985; Klarskov et al, 1988). Kinn (1985) recommended that a radical incision of the bladder neck also be performed in men undergoing these procedures to reduce outlet resistance. Bukowski and Perlmutter (1994) reported on the long-term outcome of reduction cystoplasty in 11 boys with prune belly syndrome. They found that short-term reductions in bladder volume may have initially contributed to the decreased incidence of urinary infections, but bladder capacity and residual volumes tended to increase over time. **Overall, reduction cystoplasty has not been definitively proven to yield long-term success in most patients, and its use remains debatable.** When compared to properly performed CIC alone, reduction cystoplasty is unlikely to add much to the patient's quality of life and should be used in only select patients.

Bladder Myoplasty

Patients with impaired or absent detrusor contractility have few dependable treatment options, except for continuous or clean intermittent catheterization. **Although neurostimulator implantation has achieved modest success in patients with idiopathic detrusor hypotonicity, it has not shown significant benefit in neurogenic conditions where the bladder is unable to generate a contraction.** To address this particularly difficult situation, several investigators have focused on attempting to restore bladder contractility through correction of the myogenic component of the disorder. Restoration of myogenic deficits by the transfer of an innervated, striated free muscle flap has been used successfully in reconstructive efforts involving other areas of the body, such as the heart (Blanc et al, 1993; Ninkovic et al, 2003). The augmentation of detrusor function with a skeletal muscle flap and cellular tissue engineering using injectable myoblasts represent the two current methodologies that have evolved.

In an animal feasibility study, Chancellor and associates (1994c) were among the first to report successful restoration of voluntary emptying of the bladder using a wrap of skeletal muscle. To augment the noncontractile detrusor, a segment of neurovascularly intact rectus muscle was wrapped around the bladder. Further experience was reported by Stenzl and colleagues (1998), when three patients managed with chronic catheterization for bladder acontractility were treated with a microneurovascular free transfer of autologous latissimus dorsi muscle. Short-term follow-up revealed peak flow rates of 18 to 26 mL/sec and residual urine volumes of 0 to 90 mL. In this procedure, the main neural and vascular supply to the latissimus dorsi was anastomosed to the lowermost motor branch of the intercostal nerve and to the inferior epigastric vessels supplying the rectus abdominis muscle. The transferred muscle was wrapped around the bladder with longitudinal tension and a slightly spiral configuration, ultimately covering about 75% of the mobilized bladder and leaving only the area of the trigone and the lateral pedicles uncovered. Patients were instructed to empty their bladders by actively contracting the lower abdominal musculature. Similarly, Stenzl and colleagues (2003) reported on 20 patients with bladder acontractility, with a mean follow-up of 44 months, and found that 14 of 20 (70%) were able to void spontaneously within 4 months, 4 more were able to void spontaneously after a bladder neck incision, while 2 had minimal improvement. Available urodynamic parameters revealed mean voided volumes of 447 mL (range, 250 to 728 mL), mean postvoid residual volumes of 38 mL (range, 0 to 100 mL), and mean maximum detrusor pressures of 72 cm H_2O (range, 5 to 218 cm H_2O). **Recently, equally impressive results were reported in a multicenter trial of latissimus dorsi detrusor myoplasty by Gakis and associates** (2009). **In 24 patients with a mean follow-up of 46 months, 16 of 24 (67%) regained spontaneous micturition without the need for CIC, while 3 were able to reduce the frequency of CIC.**

Key Points: Increasing Intravesical Pressure or Facilitating Detrusor Contractility

- Methods to improve bladder emptying consist of two main strategies: increasing intravesical pressure and/or decreasing outlet resistance.
- Management of poor detrusor contractility is limited and has few dependable treatment options other than continuous or clean intermittent catheterization.
- The Credé maneuver is most effective in patients with decreased bladder tone who can generate an intravesical pressure greater than 50 cm H_2O and have decreased bladder outlet resistance.
- Both the Credé and Valsalva maneuvers may elevate intravesical pressure sufficiently to cause upper tract deterioration, especially if performed in the setting of poor detrusor compliance.
- In SCI patients with an intact sacral spinal cord, reflex voiding can be initiated through activation of the sacral micturition reflex. Voiding can be elicited by pulling the skin or hair of the pubis, scrotum, or thigh; squeezing the clitoris; or by digital rectal stimulation.
- Reflex voiding is dependent on the ability to stimulate detrusor contractions and may be most suitable for patients with SCI or conditions characterized by neurogenic detrusor overactivity.
- Reduction cystoplasty has not been definitively proven to yield long-term success, and its use remains debatable.
- Bladder myoplasty including augmentation of detrusor function with a skeletal muscle flap or injectable myoblasts has been successfully performed in a few specialized centers but requires further study.

Both Von Heyden and colleagues (1998) and Van Savage and associates (2000) reported early studies with electrically stimulated detrusor myoplasty in dogs. Von Heyden and colleagues described anastomosing the thoracodorsal nerve to the obturator nerve and the vascular supply to the external iliac vessels. The graft was then stimulated by electrodes connected to the anastomosed neural supply and with direct muscle stimulation. Van Savage and associates described detrusor myoplasty with rectus muscle with the addition of stimulation being achieved with electrodes inserted into the muscle near the nerve entrance. Good results were reported initially with acute stimulation generating bladder pressures adequate for bladder emptying. Unfortunately, in a study of chronic contractile dysfunction, although detrusor compliance and flap viability were maintained, bladder emptying was not (Van Savage et al, 2002).

Yokoyama and coworkers (2000) reported on myoblast-mediated ex-vivo gene transfer to improve contractility. **The authors demonstrated successful long-term survival of the injected myoblasts in the bladder, with preliminary histochemical evidence that these skeletal myoblasts can differentiate to smooth muscle.** Further research in this area will be needed to determine whether tissue engineering using cellular myoplasty can improve impaired bladder contractility. For further discussion of the role of myoblast injection therapy for urologic disorders, including treatment of detrusor failure and stress urinary incontinence, see Chapter 19.

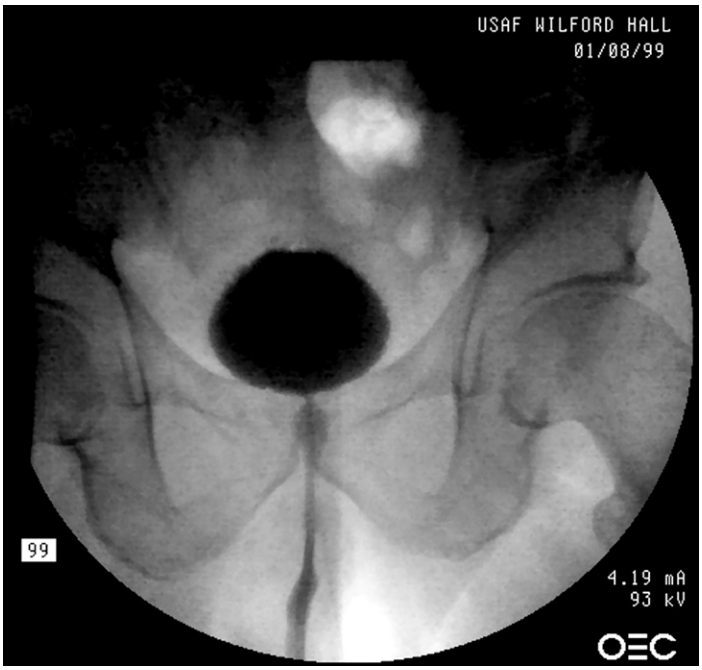


Figure 75–6. During urodynamics in a young male with severe lower urinary tract symptoms, a primary bladder neck obstruction was found. The bladder neck obstruction was accentuated by having the patient tighten his voluntary sphincter during voiding.

DECREASING OUTLET RESISTANCE AT A SITE OF ANATOMIC OBSTRUCTION

Transurethral Resection or Incision of the Bladder Neck

The first transurethral bladder neck resection for neurogenic lower urinary tract dysfunction was performed by Emmett in 1937 (Wein and Barrett, 1988). Originally, the procedure had two main indications: a hypocontractile (or atonic bladder) and anatomic (or functional) obstruction at the level of the bladder neck and/or proximal urethra that prevented emptying despite abdominal straining or a sustained detrusor contraction. It was also used in areflexic bladder patients with sacral spinal cord lesions who could not adequately empty by straining or Credé maneuver; however, this simply created progressively severe stress incontinence. In these instances, other alternatives for improving bladder emptying should be sought first (Wein et al, 1976).

The most common modern indication for transurethral resection (TURBN) or incision (TUIBN) of the bladder neck is a urodynamic-confirmed anatomic or functional obstruction at the bladder neck or proximal urethra. **Primary bladder neck obstruction (PBNO) is a videourodynamically diagnosed condition, characterized by high-pressure, low-flow voiding, with radiographic evidence of obstruction at the bladder neck, without striated sphincter contraction or distal obstruction** (Padmanabhan and Nitti, 2007) (Fig. 75–6). Alternatively, the diagnosis can be made by a micturitional urethral profile (McGuire et al, 1984). The true prevalence and etiology of PBNO is unknown. The highest reported incidence is in younger males with severe lower urinary tract symptoms (LUTS) and ranges from 33% to 54% in this population (Huckabay and Nitti, 2005). Much lower incidences have been reported for females (4.6% to 8.7%). For more on bladder neck dysfunction refer to Chapter 65.

Currently, the preferred technique is incision of the bladder neck at the 5-o'clock and/or 7-o'clock positions. A single full-thickness incision is extended from 1 cm distal to each ureteral orifice and continued through the bladder neck and prostatic fossa to just proximal to the verumontanum. The incision is deepened until no ridge is visible at the bladder neck, and fat is visualized through the capsular fibers (Huckabay and Nitti, 2005). Other techniques include a limited resection of the dorsal tissue from the 3-o'clock to the 9-o'clock position and a resection limited to the posterior lip. In women, incisions may be performed at the same anatomic location as in men and extended from just inside the vesical neck through the proximal third of the urethra (Blaivas et al, 2004). Overly aggressive technique should be avoided in females, because of the risk of stress incontinence.

In this predominately young male population, one of the most significant concerns with bladder neck incision or resection is the development of retrograde ejaculation. A reduction in the incidence of retrograde ejaculation has been reported with the performance of a unilateral TUIBN (Kaplan et al, 1994; Kochakarn et al, 2003). Earlier studies reported the incidence of diminished ejaculate volume ranging from 10% (Turner-Warwick, 1984) to as high as 50% (Norlen and Blaivas, 1986). More recently, a 27% incidence was reported with bilateral incisions (Trockman et al, 1996), while antegrade ejaculation was preserved in all patients who underwent a unilateral incision (Kaplan et al, 1994).

Significant improvements in symptom relief and maximum flow rate have been reported with these techniques (Huckabay and Nitti, 2005). Norlen and Blaivis (1986) reported subjective improvement in 18 men with PBNO, with an increase in Q_{max} from 9.1 mL/sec to 26.1 mL/sec. Kaplan and colleagues (1994) performed a unilateral incision in 31 men, 30 of 31 had subjective improvement and a mean increase in Q_{max} from 9.2 to 15.6 mL/sec. Peng

and Kuo (2005) reported their experience with TUIBN in 11 women with urodynamically confirmed bladder neck obstruction. After a mean follow-up of 10 months, significant urodynamic improvements were reported in Q_{max} (3.8 to 12.0 mL/sec), residual urine (355.5 to 84.5 mL), and voiding pressure (86.5 to 59.1 cm H_2O). A similar study of 11 women with PBNO was reported by Goldman and Zimmern (2006). Ten had improvement or resolution of symptoms, and one developed mild SUI postoperatively.

YV-Plasty of the Bladder Neck

The objective of the YV-plasty is to reduce bladder outlet resistance by revision of the anterior bladder neck; however, this technique is now rarely performed. Bladder neck resection or incision performed endoscopically is now the preferred procedure and is capable of achieving the same objectives as the YV-plasty but with less morbidity. It would only seem appropriate to consider this method when a concurrent open procedure is already required for a concomitant urologic disorder. Significant incontinence may result following this procedure and, at times, was the intended consequence, especially when it was performed radically or in the setting of a refractory, poorly emptying bladder. Due to the infrequency and short-lived use of this procedure, the efficacy of YV-plasty and incidence of postoperative complications have not been reported.

DECREASING OUTLET RESISTANCE AT THE LEVEL OF THE STRIATED SPHINCTER

Detrusor sphincter dyssynergia (DSD) is the most common cause of neurogenic sphincteric obstruction and is most often managed by intermittent catheterization. Avoidance of high intravesical pressure through appropriate bladder drainage protects the upper tracts, decreases provocation of autonomic dysreflexia, and lessens the risk for other complications such as UTI and stones. **If improperly treated, complications from DSD will occur in greater than 50% of men** (Chancellor and Rivas, 1995; Ku, 2006). For patients who are unwilling or unable to self-catheterize, the most effective treatment option is controversial. Historically, external sphincterotomy served as the primary surgical intervention for DSD, resulting in significant short-term improvement in bladder emptying in 70% to 90% of cases (Wein et al, 1976). Failure rates as high as 40% to 50%, however, have left the long-term efficacy of sphincterotomy in question (Santiago, 1993; Vapnek et al, 1994; Yang and Mayo, 1995). With favorable results being reported for less invasive alternatives such as laser sphincterotomy and urethral stenting, the role of traditional sphincterotomy continues to be debated. Sphincteric injection of botulinum toxin has also gained interest as an alternative to sphincterotomy. Other pharmacologic alternatives, including the use of Botox are discussed in Chapter 68.

Surgical Sphincterotomy

Therapeutic destruction of the external urethral sphincter was initially performed in 1936, but the first large clinical series was not reported until 1958 by Ross and colleagues (Wein and Barrett, 1988). **Several techniques have been described; however, the 12-o'clock sphincterotomy, as originally proposed by Madersbacher and Scott** (1975), **remains the procedure of choice for a number of reasons.** The anatomy of the striated sphincter is such that its main bulk is anteromedial. With the blood supply primarily lateral, a 12-o'clock incision is least likely to cause hemorrhage, with reported rates of 5% to 20%. The rate of postoperative erectile dysfunction with this incision is approximately 5% compared with a 5% to 30% incidence with a 3-o'clock and 9-o'clock technique. Significant urinary extravasation has also been reported. Sphincterotomy can be performed using a knife electrode, resection with a loop electrode, or laser ablation. The incision must extend from the level of the verumontanum at least to the bulbomembranous junction. Gradual deepening of the incision allows good visual control and minimizes the chance of significant hemorrhage and extravasation. An external collecting device is usually necessary postoperatively, precluding usage in females. Vapnek and associates (1994) reported that conversion to suprapubic bladder drainage was most commonly attributed to difficulty with the collection device. Continuous sphincteric incontinence or severe stress incontinence is uncommon, unless the urethra or bladder neck has been compromised by prior surgery or preexisting pathology. Noll and colleagues (1995) reported that laser sphincterotomy seems to have an advantage over conventional diathermy procedures, after finding that only 15.1% of laser-treated patients required resphincterotomy compared with 30% of those treated with a conventional procedure. Further advantages of laser sphincterotomy were reported by Perkash (1996) with the finding of less bleeding following procedures performed in this manner.

When early failure occurs, it is generally attributable to an inadequate surgical procedure (either not deep enough or not extensive enough), inadequate detrusor function, and bladder neck or prostatic obstruction. Late failure may occur because of fibrosis somewhere along the extent of the sphincterotomy, a change in detrusor function, the development of prostatic obstruction, or a change in neurologic status such that smooth sphincter dyssynergia develops (Lockhart and Pow-Sang, 1989). **Yang and Mayo** (1995) **defined failure as (1) the presence of large postvoid residual urine volumes associated with urinary tract infections, (2) autonomic hyperreflexia symptomatology associated with bladder overdistention or high voiding pressures, and/or (3) progressive upper tract deterioration from persistent reflux or poor bladder emptying.**

Failure rates following sphincterotomy have been reported to be as high as 40% to 50% in some series (Santiago, 1993; Vapnek et al, 1994; Yang and Mayo, 1995). In addition, the incidence of failure increases with time from the initial procedure (Vapnek et al, 1994; Yang and Mayo, 1995). In a more recently reported series, Pan and colleagues (2009) reported only a 32% primary success rate following external sphincterotomy, with eventual failure occurring in 57 of 84 (68%) patients at a mean of 42.7 months from the initial procedure. Of the 57 patients that failed, 30 underwent a repeat sphincterotomy with a mean response of 56 additional months. Kim and colleagues (1998) reported a significantly higher incidence of upper tract damage and persistent sphincter dyssynergia with detrusor leak point pressures of greater than 40 cm H_2O. Juma and associates (1995) considered detrusor leak point pressure as the most reliable urodynamic parameter to predict the risk of upper tract complications after sphincterotomy. The authors reported a 30% incidence of significant upper tract complications (half of which developed more than 2 years after sphincterotomy), in their series of 63 patients with a mean follow-up of 11 years. Lower urinary tract complications (recurrent infection, calculi, urethral diverticula, stricture,

bladder neck stenosis, and recurrent epididymitis) occurred in 48% of patients.

Urethral Stenting

The use of a urethral stent to bypass the striated sphincter was suggested by Shah and associates (1990). Chancellor and Rivas (1995) reported the initial multicenter North American data using the UroLume stent (American Medical Systems, Minnetonka, MN) in 153 patients at 15 centers. A significant decrease in detrusor leak pressure and residual urine volume was seen; however, 18% of patients required more than one procedure to adequately open the sphincter, hyperplasia within the lumen was seen in 42 patients (33.3%) at 3 months, and 10 devices were removed (7 for migration) and 7 were replaced. Bladder neck obstruction requiring treatment was seen in 13 patients (4 with α blockers, 7 with incision, 2 with CIC), and when removal was required (in 4) this was not a problem up to 12 months. Rivas and coworkers (1994) concluded that a stent prosthesis is as effective, easier, less morbid, and less expensive than a sphincterotomy.

Chancellor and colleagues (1999b) reported the long-term follow-up of the UroLume stent in for striated sphincter dyssynergia in a group of 160 men with SCI at 15 centers in North America. **Mean voiding pressure decreased from 75.1 cm H_2O to 37.4 cm H_2O at year 1 and was maintained for up to 5 years. Residual urine volume also decreased and was maintained for 5 years; however, the residual urine volume was not less than 105 mL in any group, and mean cystometric bladder capacity did not change. Symptoms of autonomic hyperreflexia after stent placement were reduced in 53 of 89 patients at 1 year and 37 of 72 at 2 years.** De novo detrusor overactivity developed in only 1 of 36 patients in the 1-year follow-up group and only 3 of 30 in the 2-year group. **One obvious advantage using a sphincteric stent is that it is potentially reversible.** Fifteen percent of patients (24 patients) required stent removal; another stent was implanted in 4 of these. Stent migration occurred in 12.4% of patients at 3 months after implantation and in 5% at 6 months, with correspondingly decreased percentages up to 4 and 5 years. Forty-seven patients (26.3%) were diagnosed with bladder neck obstruction after stent placement, and were managed by bladder neck incision in 20, α blockade in 10, CIC in 8, and watchful waiting in 9. The authors commented that in those patients who required stent removal, the procedure could be accomplished despite epithelialization but that a learning curve certainly exists before one becomes comfortable removing the stent.

Chancellor and colleagues reported a prospective, randomized, multicenter trial of sphincteric stent placement versus external sphincterotomy (Chancellor et al, 1999a). Fifty-seven men were randomized; the primary outcome indicator was maximum detrusor pressure. At 12 months, there was no significant difference; however, at 24 months, maximum detrusor pressure had decreased from 90.6 cm H_2O to 41.6 cm H_2O in the sphincterotomy group and from 101.9 cm H_2O to 71.6 cm H_2O in the stent group. Whether this is meaningful is uncertain. At 24 months, residual urine volume had decreased from 218 to 112 mL in the sphincterotomy group and from 164 to 132 mL in the stent group. Cystometric capacities did not appear to change up to 24 months. Bladder neck obstruction requiring treatment developed in 6 patients in each group. Six of the 31 stent patients required stent removal, all without difficulty.

The use of temporary urethral stents in 147 men with DSD was reported by Gamé and colleagues (2008). Patient satisfaction and treatment efficacy was assessed every 3 months postoperatively until a mean of 10 months after insertion. After the initial period of temporary stenting, patients who were subjectively satisfied with this treatment modality, who also had a significant decrease in urinary complications and in postvoid residual, went on to permanent urethral stenting, 70.7% in this case. Seven (4.7%) recovered enough neurologically to perform CIC upon removal of the temporary stent. The authors state that the use of temporary urethral stents allows identification of patients who are unlikely to benefit from permanent stent insertion.

The ideal patient and therapeutic role for urethral stenting remains controversial (Boone, 2009; Perkash, 2009). **The reversibility of this procedure is attractive to some; however, stent removal, when necessary, may be difficult. Complications include obstruction by urothelial ingrowth, stent encrustation, stricture, stent migration, and UTI.** Similar to sphincterotomy, a collection device is required with urethral stenting, precluding use in females.

An intraurethral sphincter prosthesis with a self-contained urinary pump has been developed for use in women with a hypocontractile or acontractile bladder ("inflow" intraurethral insert). Schurch and associates (1999) reported on the use of this device in 18 women with neurogenic voiding dysfunction and a hypocontractile bladder. Sixteen months after placement, only 6 of the women were still using the implant and were satisfied. In 10 patients, severe incontinence around the catheter or irritation necessitated removal. In 2 patients, the device was removed because the patients could not transfer to the toilet to empty their bladder. Fourteen of the devices had to be replaced early because of device dysfunction, and three external remote control units malfunctioned. At that time, the authors considered the device unsuitable for long-term use.

Madjar and colleagues (2000) reported on 92 women, having the device, who were followed for periods of longer than 1 year. Early removal of the device (<14 days) was required in 56.5% of patients, mostly because of local discomfort and urinary leakage. In an additional 20.6% of patients, the device was removed between 2 and 16 months after placement. Only 21 patients (22.8% of the original group) with the device still in place after more than 1 year (mean, 24.6 months) were being followed. In these patients, six device removals in 4 patients were required because of migration into the bladder, asymptomatic bacteriuria developed in 15 patients, and symptomatic urinary tract infections developed in 4 patients. The authors' conclusion that further studies are necessary to compare this treatment with CIC and other modalities seems justified.

Pharmacologic Sphincterotomy

Botulinum toxin is a protein neurotoxin produced by the bacterium *Clostridium botulinum*. Urologic use of botulinum toxin for the treatment of detrusor striated sphincter dyssynergia was first reported by Dykstra and colleagues (Dykstra and Sidi, 1990; Dykstra et al, 1998). Further experiences followed, with several reports of botulinum toxin usage in diverse groups with voiding dysfunction (Schurch et al 1996; Gallien et al, 1998; Petit et al, 1998). Fowler and coworkers (1992) injected botulinum toxin into six women with difficult voiding/urinary retention secondary to what is now called the Fowler syndrome (manifested by abnormal myotonus-like electromyographic activity in the striated urethral sphincter). Kuo (2003) reported periurethral injections of botulinum A toxin in 103 patients with lower urinary tract dysfunction

due to a number of different causes, including detrusor sphincter dyssynergia, dysfunctional voiding, nonrelaxing urethral sphincter, cauda equina lesion, peripheral neuropathy, and idiopathic detrusor underactivity. As the role of botulinum toxin in the treatment of sphincteric obstruction continues to evolve, its use remains uncommon and unclear. A more detailed discussion of the role of botulinum toxin in urologic practice is covered in Chapter 68.

Theoretically, any agent that promotes striated sphincter relaxation in a uroselective manner could be used to decrease outlet resistance and facilitate voiding dysfunction. Yoshiyama and associates (2000) reported improved voiding in rats with SCI by using intravenously administered α-bungarotoxin. This compound is a toxin, extracted from the venom of a Formosan snake, that selectively blocks nicotinic receptors without influencing transmission in autonomic ganglia. The nicotinic receptors in the striated sphincter have been shown to be a potential target for drug therapy for striated sphincter dyssynergia.

Urethral Overdilatation

Urethral overdilatation to 40 to 50 Fr in females can achieve the same objective as external sphincterotomy in males (see Wein and Barrett, 1988) but is rarely performed because of the lack of a suitable external collecting device. In young boys, a similar stretching of the posterior urethra can be performed using a perineal urethrostomy, obviating or postponing the need for a surgical sphincterotomy. Wang and associates (1989) reported the results of urethral dilatation, using sounds or balloon procedures, to 22 to 28 Fr in 11 myelodysplastic children with high intravesical pressures refractory to traditional forms of treatment. **After dilatation, the intravesical pressures decreased, and upper tract function and bladder compliance improved. There was no discernible effect on continence. These observations demonstrated that urethral dilation can decrease outlet resistance and improve compliance without deterioration in urinary control beyond preoperative conditions.**

Balloon dilatation of the external urethral sphincter was reported by Werbrouck and associates (1990). Using balloon dilatation to 90 Fr at 3 atm, Chancellor and colleagues (1994b) compared balloon dilatation (20 patients), sphincterotomy (15 patients), and stent placement (26 patients) in the treatment of striated sphincter dyssynergia. A significant decrease in detrusor leak point pressure and residual urine occurred in all three groups. Bladder capacity remained constant, renal function stabilized or improved, and autonomic hyperreflexia improved. Balloon dilatation and stent placement were associated with a significantly shorter surgery and hospitalization times and less blood loss. In the dilatation group, 3 patients developed recurrent obstruction (at 3, 8, and 12 months), 1 required transfusion, and 1 developed a 1-cm bulbar stricture. In the surgical sphincterotomy group, 2 patients required transfusion, 2 developed a stricture with obstruction, and 1 developed erectile dysfunction. In the stent group, 3 patients had migration requiring adjustment (1 had the stent replaced, 2 had a second overlapping stent), and 2 developed bladder neck obstruction requiring transurethral incision. McFarlane and colleagues (1997) reported on the use of balloon dilatation of the striated sphincter as an alternative to sphincterotomy in 14 patients followed for a mean of 55.5 months (8 to 68 months). Sphincter activity was initially abolished in all patients, and reflux, which was present in 1 patient, resolved. Long term, however, 62% failed within 1 year, and overall 85% failed. The authors concluded that this is an ineffective long-term treatment for striated sphincter dyssynergia in the majority of patients, thus recommending either surgical sphincterotomy or stenting as the surgical treatments of choice for this condition.

Pudendal Nerve Interruption

Relief of obstruction at the level of the striated sphincter can also be achieved by pudendal neurectomy, first described in 1899 by Rocket (see Wein and Barrett, 1988). This method is seldom used today due to potential undesirable effects, even after a unilateral nerve section. Bilateral nerve section results in an extremely high rate of impotence and may result in significant fecal and stress urinary incontinence. If this procedure is contemplated, the results

Key Points: Decreasing Outlet Resistance

- The most common indication for transurethral resection or incision of the bladder neck is a urodynamically confirmed anatomic or functional obstruction at the bladder neck or proximal urethra.
- Primary bladder neck obstruction (PBNO) is diagnosed videourodynamically and characterized by high-pressure, low-flow voiding, with radiographic evidence of obstruction at the bladder neck, without striated sphincter contraction or distal obstruction. Alternatively, PBNO may be diagnosed by micturitional urethral profiles.
- One of the most significant concerns with bladder neck incision or resection is the development of retrograde ejaculation, especially given the predominately younger-aged patient affected with this disorder.
- Given the less morbid and often successful use of endoscopic procedures, open YV-plasty of the bladder neck is only rarely performed and would only seem appropriate to consider when a concurrent open urologic procedure is already required.
- If improperly treated, complications from DSD will occur in greater than 50% of men.
- Early failure after sphincterotomy is often due to inadequate surgical technique, inadequate detrusor function, or obstruction at the level of the bladder neck or prostate.
- Late failure after sphincterotomy typically occurs when fibrosis develops at site of sphincterotomy, prostatic obstruction develops, or following changes in detrusor function or neurologic status.
- Urethral stenting offers a less invasive alternative to traditional sphincterotomy with the added advantage of being a reversible procedure. The ideal patient for this procedure continues to be debated. Complications of urethral stenting include stent migration, recurrent obstruction, stent encrustation, stricture, and UTI.
- Although successfully used, the role of botulinum toxin in the treatment of sphincteric obstruction still remains to be defined.
- Urethral overdilatation through the use of urethral sounds or balloon procedures may improve compliance and decrease outlet resistance; however, long-term success is unlikely.
- Pudendal nerve interruption is seldom performed today due to potential complications, including impotence and significant fecal and stress urinary incontinence.

of a block should precede the formal procedure, which should be performed only unilaterally. More recently, Changfeng and colleagues (2004) reported on the use of high-frequency electrical stimulation to provide a reversible pudendal nerve block in cats. The authors stated that the goal of this approach is to relax the external urethral sphincter only at the time of voiding, allowing normal function between voids to maintain continence. No human studies have been reported at this time.

SUMMARY

The possible etiologies of voiding and storage dysfunction are numerous and varied. Some conditions will require a complex treatment strategy including a combination of medications and diverse surgical procedures. It is important that we continue to advance our understanding of the complex pathophysiology of storage and voiding dysfunction to improve the quality of life of the patients under our care.

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chapter
76

Geriatric Incontinence and Voiding Dysfunction

Neil M. Resnick, MD ● Stasa D. Tadic, MD, MS ● Subbarao V. Yalla, MD

The Impact of Age on Incontinence
Causes of Transient Incontinence
Established Incontinence
Diagnostic Approach
Therapy
Summary

Urinary incontinence is a major problem for the elderly (Chang et al, 2008). **It afflicts 15% to 30% of older people living at home, one third of those in acute-care settings, and half of those in nursing homes** (Fantl et al, 1996; McGrother, 1998). It predisposes to perineal rashes, pressure ulcers, urinary tract infections, urosepsis, falls, and fractures (Fantl et al, 1996; Tromp et al, 1998; Brown et al, 2000; Parsons et al, 2009). It is associated with embarrassment, stigmatization, isolation, depression, anxiety, sexual dysfunction, and risk of institutionalization (Fantl et al, 1996; Farage et al, 2008; Angner et al, 2009). Also, it cost more than $26 billion to manage incontinence in America's elderly in 1995, the last time primary data was collected (Wagner and Hu, 1998). This amount exceeded the amount devoted to dialysis and coronary bypass surgery combined. Despite these considerations, geriatric incontinence remains neglected by patients and physicians alike.

Providers and older patients alike often neglect incontinence or dismiss it as a normal part of growing old (Branch et al, 1994; Mann et al, 2000; Chang et al, 2008; Lawhorne et al, 2008), but **it is abnormal at any age** (Resnick, 1988; Herzog and Fultz, 1990; Fantl et al, 1996). Although its prevalence increases, at no age does incontinence affect the majority of individuals**,** even over age 85 (Wetle et al, 1995). Moreover, its increased prevalence relates more to age-associated diseases and functional impairments than to age itself (Resnick et al, 1988; Herzog and Fultz, 1990; Resnick et al, 1995; Wetle et al, 1995). Regardless, **incontinence is usually treatable and often curable at all ages, even in frail elderly** (Ouslander and Schnelle, 1995; Resnick, 1995; Wagg and Malone-Lee, 1998; Weinberger et al, 1999)**, but the approach must differ significantly from that used in younger patients**.

THE IMPACT OF AGE ON INCONTINENCE

At any age, continence depends on not only the integrity of lower urinary tract function but also the presence of adequate mentation, mobility, motivation, and manual dexterity. Although incontinence in younger patients is rarely associated with deficits outside the urinary tract, such deficits occur commonly in older patients. It is crucial to detect them, both because they exacerbate and, occasionally, even cause incontinence in the elderly, and because design of an efficacious intervention requires that they be addressed.

In addition, **the lower urinary tract changes with age,** even in the absence of disease. Data from continent elderly are sparse and longitudinal data virtually nonexistent. However, it appears that although **bladder capacity does not change with age** (Pfisterer et al, 2006b), **bladder sensation, contractility, and the ability to postpone voiding decline in both sexes, while urethral length and maximum closure pressure, as well as striated muscle cells in the rhabdosphincter and urogenital diaphragm, probably decline with age in women** (Diokno et al, 1988; Resnick, 1988; Resnick et al, 1995; Strasser et al, 1999; Perucchini et al, 2002; Pfisterer et al, 2006a, 2006b; Trowbridge et al, 2007; Betschart et al, 2008). The prostate enlarges in most men, and appears to cause urodynamic obstruction in half (Resnick et al, 1995). **In both sexes, the prevalence of involuntary detrusor contractions increases, whereas the postvoid residual (PVR) volume probably increases but to no more than 50 to 100 mL** (Diokno et al, 1988; Resnick, 1988; Resnick et al, 1995; Bonde et al, 1996). In addition, **the elderly often excrete most of their fluid intake at night,** even in the absence of venous insufficiency, renal disease, heart failure, or prostatism (Miller, 2000; Morgan et al, 2000). **This fact, coupled with an age-associated increase in sleep disorders, leads to one to two episodes of nocturia in the majority of healthy elderly** (Miller, 2000; Morgan et al, 2000). Finally, **at the cellular level, detrusor smooth muscle develops a "dense band pattern" characterized by dense sarcolemmal bands with depleted caveolae** (Elbadawi et al, 1993a, 1993b, 1997a). This depletion may mediate the age-related decline in bladder contractility. **In addition, an "incomplete dysjunction pattern" develops,** characterized by scattered protrusion junctions, albeit not in chains; these changes may underlie the high prevalence of involuntary detrusor contractions (vide infra) (Resnick et al, 1995; Hailemariam et al, 1997; Elbadawi et al, 1997a).

None of these age-related changes causes incontinence, but they do predispose to it. This predisposition, coupled with the increased likelihood that an older person will encounter an

additional pathologic, physiologic, or pharmacologic insult, explains why the elderly are so likely to become incontinent. The implications are equally important. **The onset or exacerbation of incontinence in an older person is probably due to precipitant(s) *outside* the lower urinary tract that are amenable to medical intervention. Furthermore, *treatment of the precipitant(s) alone may be sufficient to restore continence, even if there is coexistent urinary tract dysfunction***. For instance, flare of hip arthritis in a woman with age-related detrusor overactivity may be sufficient to convert her urinary urgency into incontinence. Treatment of the arthritis, rather than the involuntary detrusor contractions, will not only restore continence but also lessen pain and improve mobility. These principles, depicted in Figures 76–1 and 76–2 (Resnick, 1996; Resnick and Marcantonio, 1997), provide the rationale in the older patient for adding a set of transient causes to the established lower urinary tract causes of incontinence. Because of their frequency, ready reversibility, and association with morbidity beyond incontinence, the transient causes are discussed first.

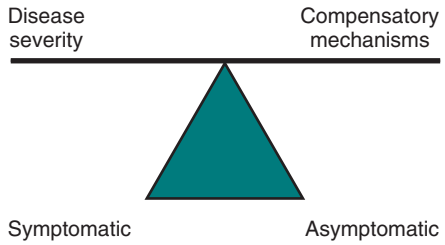


Figure 76–1. Incontinence results when the ability to compensate for bladder dysfunction is inadequate. For instance, in the intact older person, detrusor overactivity or sphincter weakness may not cause leakage if the patient is more attuned to bladder fullness, drinks less, voids more often, eliminates precipitants such as coughing, and stays close to a toilet. This explains how older patients may remain continent despite such abnormalities, and also suggests alternative therapeutic approaches independent of the urinary tract. (From Resnick NM. An 89-year-old woman with urinary incontinence. JAMA 1996;276:1832–40.)

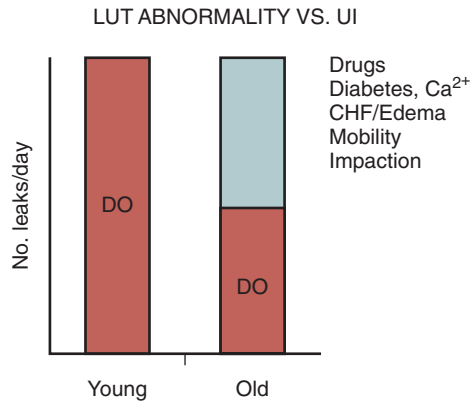


Figure 76–2. This graph shows why treatment of urinary incontinence (UI) in older adults has to differ and is often easier than in younger adults. Both of these patients with detrusor overactivity (DO) have the same frequency of leakage. However, in the younger patient with intact compensatory mechanisms, such leakage reflects solely the contribution of the DO. In the older adult, other comorbid conditions make it more difficult to appreciate bladder fullness, adjust fluid output, and reach the bathroom. Such conditions magnify the impact of DO and will be unaffected by bladder relaxant therapy. But addressing them will result in a marked improvement in the UI even without treatment of the DO and will make DO therapy, if still required, more effective. LUT, lower urinary tract. (From Resnick NM, Marcantonio ER. How should clinical care of the aged differ? Lancet 1997;350:1157–58.)

CAUSES OF TRANSIENT INCONTINENCE

Incontinence is transient in up to one third of community-dwelling elderly and in up to half of acutely hospitalized patients (Resnick, 1988; Herzog and Fultz, 1990). Although most of the transient causes lie outside the lower urinary tract, **three points warrant emphasis. First, the risk of transient incontinence is increased if, in addition to physiologic changes of the lower urinary tract, the older person also suffers from pathologic changes.** Anticholinergic agents are more likely to cause overflow incontinence in persons with a weak or obstructed bladder, while excess urine output is more likely to cause urge incontinence in persons with detrusor overactivity and/or impaired mobility (Fantl et al, 1990; Diokno et al, 1991). **Second, although termed "transient," these causes of incontinence may persist if left untreated and cannot be dismissed merely because incontinence is longstanding.** Third, similar to the situation for established causes (vide infra), identification of "the most common cause" is of little value. The likelihood of each cause depends on the individual, the clinical setting (community, acute hospital, nursing home), and referral pattern. Moreover, **geriatric incontinence is rarely due to just one of these causes.** Trying to disentangle which of the multiple abnormalities is "the" cause is more useful for metaphysics than for clinical practice.

The causes of transient incontinence can be recalled easily using the mnemonic "DIAPERS" (Table 76–1). In the setting of ***delirium*** (an acute and fluctuating confusional state due to virtually any drug or acute illness), incontinence is merely an associated symptom that abates once the underlying cause of confusion is identified and treated. The patient needs medical rather than bladder management (Resnick, 1988).

Symptomatic urinary tract ***infection*** causes transient incontinence when dysuria and urgency are so prominent that the older person is unable to reach the toilet before voiding. **Asymptomatic bacteriuria**, which is much more common in the elderly, **does not cause incontinence** (Brocklehurst et al, 1968; Resnick, 1988; Baldassare and Kaye, 1991; Ouslander et al, 1995). Because illness can present atypically in older patients, however, incontinence is occasionally the only atypical symptom of a urinary tract infection (UTI). Thus, if otherwise asymptomatic bacteriuria is found on initial evaluation, it should be treated and the result recorded in the patient's record to prevent future futile therapy.

Atrophic urethritis/vaginitis frequently causes lower urinary tract symptoms, including incontinence. Up to 80% of elderly women attending an incontinence clinic have atrophic vaginitis, characterized by vaginal mucosal atrophy, friability, erosions, and punctate hemorrhages (Robinson and Brocklehurst, 1984). Incontinence associated with this entity usually is associated with urgency and, occasionally, a sense of "scalding" dysuria that mimics a urinary tract infection, but both symptoms may be unimpressive. In demented individuals, atrophic vaginitis may present as agitation. Atrophic vaginitis also can exacerbate stress incontinence.

The importance of recognizing atrophic vaginitis is that it may respond to low-dose estrogen (Fantl et al, 1996;

Table 76–1.

Causes of Transient Incontinence

CAUSE	NOTES
Delirium/confusional state	Results from almost any underlying illness or medication; incontinence is secondary and abates once the cause of confusion has been corrected
Infection—Urinary (only *symptomatic*)	Causes incontinence, but the more common asymptomatic bacteriuria does not
Atrophic urethritis/ vaginitis	Characterized by vaginal erosions, telangiectasia, petechiae, and friability; may cause or contribute to incontinence. Now controversial but may be worth a 3- to 6-month trial of estrogen, especially topical application (if not contraindicated by breast or uterine cancer)
Pharmaceuticals	Includes many prescribed and nonprescribed agents, because incontinence can be caused by diverse mechanisms (see Table 76–2)
Excess urine output	Results from large fluid intake, diuretic agents (including theophylline, caffeinated beverages, and alcohol), and metabolic disorders (e.g., hyperglycemia or hypercalcemia); nocturnal incontinence also may result from mobilization of peripheral edema (e.g., congestive heart failure [CHF], venous insufficiency, drug side effect)
Restricted mobility	Often results from overlooked, correctable conditions such as arthritis, pain, foot problem, postprandial hypotension, or fear of falling
Stool impaction	May cause both fecal and urinary incontinence that remit with disimpaction

Adapted from Resnick NM. Urinary incontinence in the elderly. Med Grand Rounds 1984;3:281–90.

Cardozo et al, 2004). Moreover, as for other causes of transient incontinence, treatment has additional benefits; in the case of atrophic urethritis, treatment ameliorates dyspareunia and reduces the frequency of recurrent cystitis (Resnick, 1988; Raz and Stamm, 1993; Cardozo et al, 1998; Eriksen, 1999).

Reports from two large-scale randomized prospective trials, however, have recently challenged long-standing assumptions about the benefits and risks of hormone therapy. The **Women's Health Initiative (WHI)** randomized more than 27,000 women, aged 50 to 79 years, to oral conjugated equine estrogen (CEE) 0.625 mg, with or without medroxyprogesterone (MPA) 2.5 mg (Hendrix et al, 2005). The **Heart and Estrogen/Progestin Replacement Study (HERS)** randomized nearly 2800 postmenopausal women of the same age to the same regimen (Grady et al, 2001). **Both studies found that hormone therapy was associated with worsening of pre-existing incontinence. WHI investigators also found that hormone therapy,** whether prescribed as CEE alone or with MPA, **was associated with increased incidence of new incontinence.** Because both studies also found that hormone therapy did not protect against heart disease, they advised against using hormone therapy for urinary incontinence.

In trying to apply the results of the WHI and HERS trials, several caveats should be noted. Postmenopausal hormone levels differ substantially, and in some individuals they are similar to levels seen in the follicular phase of premenopausal women (Kuchel et al, 2001). Tissue sensitivity also varies. Thus it is surprising that neither WHI nor HERS randomized or stratified results by the presence or absence of atrophic vaginitis, nor did investigators examine patients to determine whether the dose administered was sufficient to treat the condition if it was present. Dropout rates in WHI were also high: 42% in the combined hormone therapy group and 54% in the estrogen-alone group. In addition, incontinence data were based on self-report, which can be problematic in older adults, both for reproducibility and for determining the type of incontinence (Resnick et al, 1994; Kirschner-Hermanns et al, 1998). Urodynamic testing was not performed. Moreover, although drugs used to treat heart disease in such patients can cause or exacerbate incontinence (e.g., diuretics, α blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors (ACEI), their impact was not reported. Finally, other hormone doses, types, and routes of administration were not evaluated. For example, a recent randomized placebo-controlled study with ultralow-dose transdermal estrogen (0.014 mg) revealed no substantial effect on either the frequency of incontinence or the risk of developing at least weekly incontinence (Waetjen et al, 2005).

There is less evidence available from recent studies of nursing home patients, but limitations of sample size; selection bias; route, dose adequacy, and type of hormone used; and characterization and stratification by type of urinary infection (UI) all similarly preclude meaningful conclusions (DuBeau, 2001; Ouslander et al, 2001a).

The apparent lack of efficacy for conjugated equine estrogen demonstrated in these two studies, as well as the risks associated with long-term use of higher doses, must be balanced against the other benefits cited above—the lower doses and shorter duration of treatment advised for treatment of atrophic vaginitis, and the shorter life expectancy of many older women in whom the prevalence and severity of atrophic vaginitis are highest. Moreover, data from other randomized double-blind trials, which employed different estrogen preparations (estriol, estradiol, or quinestradol), demonstrated significant reduction in incontinence among nursing home residents (Judge, 1969) and postmenopausal women with sensory urge incontinence (Walter et al, 1978; Moehrer et al, 2003). Thus clinical judgment is warranted, and local administration of other types of estrogen may be best. Unfortunately, the use of vaginal estrogen has not yet been well-studied.

With adequate treatment, symptoms of atrophic vaginitis remit in a few days to several weeks, but the intracellular response takes longer (Semmens et al, 1985). The duration of therapy has not been well established (Pandit and Ouslander, 1997). One approach is to insert a ring containing estradiol. The advantage is that it is small and delivers the dose locally. Because it does not increase systemic estrogen concentrations, it is often considered for women with a past history of breast cancer. The disadvantage is that, despite its small size, it is not always feasible or well tolerated by frail older women, especially those with pronounced vaginal stenosis. Another option is to administer a low dose of estradiol orally or vaginally for 1 to 2 months and then taper it. Most patients probably can be weaned to a dose given as infrequently as 2 to 4 times per month. After 6 months, estrogen can be discontinued entirely in some patients, but recrudescence is common. Because the dose is low and given briefly, the carcinogenic effect is likely slight, if any. However, if long-term treatment is selected,

a progestin probably should be added if the patient has a uterus. **Hormone treatment (except for administration by a vaginal ring) is contraindicated for women with a history of breast cancer. For those without such a history, mammography should be performed prior to initiating hormone therapy.** There appears to be a slightly increased risk of breast cancer among women using oral estrogen daily for more than 5 years, but fortunately, such high-dose, frequent, and long-term therapy is rarely required.

Pharmaceuticals are one of the most common causes of geriatric incontinence, precipitating leakage by a variety of mechanisms (Table 76–2 and Tsakiris et al, 2008). Experts often cite dosages and serum levels below which side effects are uncommon. Unfortunately, such rules are of limited use in the elderly, because they are generally derived from studies of healthy younger persons who have no other diseases and take no other medications. Of note, many of these agents also are used in the treatment of incontinence, underscoring the fact that most medications are "double-edged swords" for the elderly.

Long-acting sedative/hypnotics, whose half-life can exceed 100 hours, are associated not only with incontinence (Landi et al, 2002) but also with falling, hip fractures, driving accidents, depression, and confusion. Alcohol causes similar problems, but, for a variety of reasons, physicians frequently fail to identify alcohol use by older people as a source of symptoms, including incontinence. Sequelae of alcohol abuse are often absent or attributed to other causes. In addition, because of age-related alterations in the pharmacokinetics and pharmacodynamics of alcohol disposal, as well as interactions with other commonly used drugs, as few as one or two drinks can pose a problem for older individuals.

Because **anticholinergic agents** are prescribed so often for the elderly, and are used even without prescription (e.g., sedating antihistamines used for allergies, coryza, and insomnia), it is important to ask about them. They cause or contribute to incontinence in several ways. In addition to provoking overt urinary retention, these agents often induce subclinical retention. The resultant decrease in available bladder capacity (i.e., total capacity minus residual) allows it to be reached more quickly, exacerbating incontinence due to DO, as well as that due to functional impairment. By increasing bladder capacity (and often residual volume), anticholinergic agents also may aggravate leakage due to stress incontinence by further increasing the challenge to the sphincter mechanism. Additionally, many of these drugs decrease mobility (e.g., antipsychotics that induce extrapyramidal stiffness) and precipitate confusion. Finally, several agents intensify the dry mouth that many elderly already suffer owing to an age-related decrease in salivary gland function; the resultant increased fluid intake contributes to incontinence. Attempts should be made to discontinue anticholinergic agents, or to substitute with ones having less anticholinergic effect (e.g., a selective serotonin uptake inhibitor [SSRI] for a tricyclic antidepressant; risperidone for chlorpromazine). Limited data suggest that bethanechol may be useful for nonobstructed patients whose urinary retention is associated with use of an anticholinergic that cannot be discontinued (Everett, 1975).

In men with asymptomatic prostatic obstruction, **α-adrenergic agonists** can provoke acute retention. Particularly problematic are **nonprescribed decongestants.** They often contain an (anticholinergic) antihistamine and are frequently taken with a nonprescribed hypnotic, all of which are also sedating antihistamines. Because older individuals often fail to mention nonprescribed agents to a physician, urinary retention due to use of a decongestant, nose drops, and a hypnotic may result in premature or even unnecessary prostatectomy.

By blocking receptors at the bladder neck, **α-adrenergic antagonists** (many antihypertensives) may induce stress

Table 76–2.

Commonly Used Medications That May Affect Continence

TYPE OF MEDICATION	EXAMPLES	POTENTIAL EFFECTS ON CONTINENCE
Sedatives/hypnotics	Long-acting benzodiazepines (e.g., diazepam, flurazepam)	Sedation, delirium, immobility
Alcohol		Polyuria, frequency, urgency, sedation, delirium, immobility
Anticholinergics	Dicyclomine, disopyramide, antihistamines (sedating ones only, e.g., Benadryl)	Urinary retention, overflow incontinence, delirium, impaction
Antipsychotics	Thioridazine, haloperidol	Anticholinergic actions, sedation, rigidity, immobility
Antidepressants *(tricyclics)*	Amitriptyline, desipramine; *not* SSRIs	Anticholinergic actions, sedation
Anti-Parkinsonians	Trihexyphenidyl, benztropine mesylate (*not* L-dopa or selegiline)	Anticholinergic actions, sedation
Narcotic analgesics	Opiates	Urinary retention, fecal impaction, sedation, delirium
α-Adrenergic antagonists	Prazosin, terazosin, doxazosin	Urethral relaxation may precipitate stress incontinence in women
α-Adrenergic agonists	Nasal decongestants	Urinary retention in men
Calcium channel blockers	All dihydropyridines*	Urinary retention; nocturnal diuresis due to fluid retention
Potent diuretics	Furosemide, bumetanide (***not*** thiazides)	Polyuria, frequency, urgency
NSAIDs	Indomethacin, COX-2 inhibitors	Nocturnal diuresis due to fluid retention
Thiazolidinediones	Rosiglitazone, pioglitazone	Nocturnal diuresis due to fluid retention
Anticonvulsants/analgesics	Gabapentin, pregabalin	Nocturnal diuresis due to fluid retention
Parkinson agents (some)	Pramipexole, ropinirole, amantadine	Nocturnal diuresis due to fluid retention
Angiotensin converting enzyme (ACE) inhibitors	Captopril, enalapril, lisinopril	Drug-induced cough can precipitate stress incontinence in women and in some men with prior prostatectomy
Vincristine		Urinary retention owing to neuropathy

*Examples include amlodipine (Norvasc), nifedipine, nicardipine, isradipine, felodipine, nimodipine.

COX-2, cyclooxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

Adapted from Resnick NM. Geriatric medicine. In: Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DJ, editors. Harrison's principles of internal medicine. New York: McGraw-Hill; 2004. p. 34.

incontinence in older women (Mathew et al, 1988; Marshall and Beevers, 1996) in whom urethral length and closure pressure decline with age. Because hypertension affects half of the elderly, use of these agents may increase. Before considering interventions for stress incontinence in such women, one should substitute an alternative agent and reevaluate the incontinence.

Calcium channel blockers also can cause incontinence. As smooth muscle relaxants, they may increase residual volume and may occasionally lead to overflow incontinence, particularly in obstructed men with coexisting detrusor weakness. The dihydropyridine class of these agents (e.g., nifedipine, amlodipine, nicardipine, isradipine, nimodipine) also can cause peripheral edema, which can exacerbate nocturnal polyuria and nocturnal incontinence.

Angiotensin-converting enzyme inhibitors (ACEI) are prescribed increasingly for age-associated conditions such as myocardial infarction, congestive heart failure, and hypertension. Because the risk of developing an ACEI-induced cough increases with age, these agents may exacerbate what otherwise would be minimal stress incontinence in older women.

A few reports impugn **cholinesterase inhibitors,** such as donepezil (Aricept) or rivastigmine, as a cause of urinary incontinence (Hashimoto et al, 2000; Starr, 2007). The association is plausible, because these agents block the breakdown of acetylcholine within the neuroeffector junctional cleft. However, the incontinence often ceases even if the drug is continued, the number of cases is small, and the descriptions and evaluations of these cases are sparse. In addition, prospective trials in which these agents were evaluated for their cognitive impact did not note an increase in incontinence. Nonetheless, the association has not been well-evaluated to date, and because incontinence may improve or resolve on decreasing the drug dose or discontinuation, such an association is worth keeping in mind.

Excess urine output commonly contributes to or even causes geriatric incontinence. Causes include excessive fluid intake; diuretics (including theophylline-containing fluids, lithium, and alcohol); metabolic abnormalities (e.g., hyperglycemia and hypercalcemia); and disorders associated with fluid overload, including congestive heart failure, peripheral venous insufficiency, hypoalbuminemia (especially in malnourished debilitated elderly), and drug-induced peripheral edema associated with an increasing array of medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), dihydropyridine calcium channel blockers, thiazolidinediones ("glitazones"), pramipexole and ropinirol (for Parkinson disease), amantadine (for Parkinson disease and influenza), and β blockers. Fluid overload is a likely contributor when incontinence is associated with nocturia.

Restricted mobility commonly contributes to geriatric incontinence. It can result from numerous treatable conditions, including arthritis, hip deformity, deconditioning, postural or postprandial hypotension, claudication, spinal stenosis, heart failure, poor eyesight, fear of falling, stroke, foot problems, drug-induced disequilibrium or confusion, or being restrained in a bed or chair (Resnick, 2004). A careful search will often identify these or other correctable causes. If not, a urinal or bedside commode may still improve or resolve the incontinence.

Finally, **stool impaction** is implicated as a cause of urinary incontinence in up to 10% of older patients admitted to acute hospitals or referred to incontinence clinics (Resnick, 1988); the mechanism may involve stimulation of opioid receptors (Hellstrom and Sjoqvist, 1988). Patients present with urge or overflow incontinence and typically have associated fecal incontinence as well. Disimpaction restores continence.

These seven reversible causes of incontinence should be assiduously sought in every elderly patient. In one series of hospitalized elderly patients, when these causes were identified, continence was regained by most of those who became incontinent in the context of acute illness (Resnick, 1988). Regardless of their frequency, their identification is important in all settings because they are easily treatable and contribute to morbidity beyond incontinence.

Key Points: Transient Incontinence

- In the elderly, continence generally results *not* from normal lower urinary tract (LUT) function but *despite* abnormal LUT function. Thus the compensatory role of factors beyond the urinary tract is more important in older incontinent patients than in younger individuals.
- Because such compensatory factors are often impaired in older patients, owing to comorbidity and medication use, these factors should be identified and addressed in all incontinent older adults.
- Reversal of such factors can resolve or improve incontinence in many older patients and improve the efficacy of lower urinary tract therapy in the remainder.

ESTABLISHED INCONTINENCE

Lower Urinary Tract Causes

If incontinence persists after transient causes have been addressed, the lower urinary tract causes should be considered. These are similar to the causes in younger individuals, but there are several significant differences.

***Detrusor overactivity (DO) is* the most common type of lower urinary tract dysfunction in incontinent elderly of either sex** (Resnick, 1988; Resnick et al, 1989). DO has been associated with increased spontaneous activity of detrusor smooth muscle and with specific changes at the cellular level. Termed the "complete dysjunction pattern," these changes include widening of the intercellular space, reduction of normal (intermediate) muscle cell junctions, and emergence of novel "protrusion" junctions and "ultraclose abutments" connecting cells together in chains. These junctions and abutments may mediate a change in cell coupling from a mechanical to an electrical mechanism, which could facilitate propagation of heightened smooth muscle activity and provide the "final common pathway" by which such spontaneous cellular contractions result in involuntary contraction of the entire bladder (Elbadawi et al, 1993c, 1997a, 1997b; Hailemariam et al, 1997; Tse et al, 2000). However, this remains speculative to date. Other potential mechanisms are also being investigated, including, among others, the role of ischemia (Azadzoi et al, 2007), suburothelial myofibroblasts (Fry et al, 2007), and changes in central nervous system (CNS) structural and functional control mechanisms (Griffiths et al, 2007, 2009; Poggesi et al, 2008; Tadic et al, 2008; Kuchel et al, 2009).

A distinction is generally made between detrusor overactivity that is associated with a CNS lesion and that which is not. In older patients, the distinction is often unclear, because involuntary detrusor contractions may be due to normal aging, a past stroke (even if clinically unapparent), or urethral incompetence or

obstruction—even in a patient with Alzheimer disease. There is still no reliable way to determine the source of such contractions (Elbadawi et al, 2003). This obviously complicates treatment decisions. It also suggests that DO coexisting with urethral obstruction or stress incontinence is less likely to resolve postoperatively than in younger individuals without other reasons for detrusor overactivity (Resnick, 1988; Gormley et al, 1993).

Traditionally, detrusor overactivity has been thought to be the primary urinary tract cause of incontinence in demented patients. Although this is true, DO is also the most common cause in nondemented older patients; the three studies that examined it failed to find an association between cognitive status and DO (Castleden et al, 1981; Resnick et al, 1989; Dennis et al, 1991). This lack of association likely reflects the fact that, in the elderly, there are multiple causes of DO unrelated to dementia, including cervical disk disease or spondylosis, Parkinson disease, stroke, subclinical urethral obstruction or sphincter incompetence, and age itself. Moreover, demented patients also may be incontinent due to the transient causes discussed above. Thus it is no longer tenable to ascribe incontinence in demented individuals a priori to detrusor overactivity (Resnick, 1995).

Detrusor overactivity in the elderly exists as two physiologic subsets: one in which contractile function is preserved and one in which it is impaired (Resnick and Yalla, 1987; Yalla et al, 2007). **The latter condition is termed detrusor hyperactivity with impaired contractility (DHIC) and is likely the most common form of DO in the elderly** (Resnick et al, 1989; Elbadawi et al, 1993c). DHIC appears to represent the coexistence of DO and bladder weakness rather than a separate entity (Elbadawi et al, 1993c). Regardless of the cause, DHIC has several implications. First, because the bladder is weak, urinary retention develops commonly in these patients, and DHIC must be added to outlet obstruction and detrusor underactivity as a cause of retention. Second, even in the absence of retention, DHIC mimics virtually every other lower urinary tract cause of incontinence. For instance, if the involuntary detrusor contraction is triggered by or occurs coincident with a stress maneuver, and the weak contraction (often only 2 to 6 cm water) is not detected, DHIC will be misdiagnosed as stress incontinence or urethral instability (Resnick et al, 1996a); alternatively, because DHIC may be associated with urinary urgency, frequency, weak flow rate, elevated residual urine, and bladder trabeculation, in men it may mimic urethral obstruction (Resnick et al, 1996a). Third, bladder weakness often frustrates anticholinergic therapy of DHIC because urinary retention is induced so easily. Thus alternative therapeutic approaches are often required (see Therapy section).

Stress incontinence is the second most common cause of incontinence in older women. As in younger women, it is **usually associated with urethral hypermobility. A less common cause is intrinsic sphincter deficiency (ISD)** or type 3 stress incontinence (McGuire, 1981; Blaivas and Olsson, 1988). The prevalence of ISD may be lower than thought, however, because the diagnosis is often based solely on documenting a very low leak point or urethral closure pressure. Because urethral pressure decreases with age, even a closure pressure of less than 20 cm water does not establish the presence of ISD. Moreover, because urethral pressure normally decreases with detrusor contraction, leakage coinciding with low urethral pressure can be observed in patients with DHIC in whom the low pressure contraction is missed (Resnick et al, 1996a).

When it occurs, ISD is usually due to operative trauma. But a milder form also occurs in older women, resulting only from urethral atrophy superimposed on the age-related decline in urethral pressure. Instead of leaking, with any bladder volume, such women leak at higher amounts (e.g., >200 mL). ***Many become dry if bladder volume is kept below this level.***

A rare cause of stress incontinence in older women is "urethral instability," in which the sphincter paradoxically relaxes in the absence of apparent detrusor contraction (McGuire, 1978). However, most older women thought to have this condition actually have DHIC (Resnick et al, 1996a).

In men, stress incontinence is usually due to sphincter damage following radical prostatectomy. In both sexes, stress-associated leakage also can occur in association with urinary retention, but in this situation leakage is not due to outlet incompetence.

Incontinence in the setting of ***outlet obstruction*** is the second most common cause of incontinence in older men, although most obstructed men are not incontinent. When obstruction is associated with incontinence, it generally presents as urge incontinence owing to the associated DO; overflow incontinence owing to obstruction is uncommon. Especially in older adults, it is difficult to determine whether DO that occurs with obstruction is related to the obstruction or is simply coexistent owing to its increased prevalence with age, even in non-obstructed individuals. Nonetheless, DO is more common among obstructed patients, even older ones, (Resnick et al, 1995) and can cause incontinence. In most women, urethral elasticity decreases with age. In a small proportion of older women, this reduced elasticity may be compounded by fibrotic changes associated with atrophic vaginitis and can result in moderate urethral stenosis. Frank outlet obstruction, however, is as rare in older women as in younger women. When present, it is usually due to kinking associated with a large cystocele or to obstruction following bladder neck suspension. Rarely, bladder neck obstruction or a bladder calculus is the cause.

Detrusor underactivity is **usually idiopathic,** but more information on this condition is emerging (Taylor and Kuchel, 2006). In the absence of obstruction or overt neuropathy, detrusor underactivity is characterized at the cellular level by widespread degenerative changes of both muscle cells and axons, without accompanying regenerative changes (Elbadawi et al, 1993b; Hindley et al, 2002). **When it causes incontinence, detrusor underactivity is associated with overflow incontinence** (<10% of geriatric incontinence) (Diokno et al, 1988; Resnick, 1988; Resnick et al, 1989). Owing to the age-related decline in sphincter strength, however, the postvoid residual (PVR) volume in women with overflow incontinence is often lower than in younger women. **A mild degree of bladder weakness occurs quite commonly in older individuals. Although insufficient to cause incontinence, it can complicate treatment of other causes** (see Therapy section).

Causes Unrelated to the Lower Urinary Tract ("Functional" Incontinence)

"Functional" incontinence is often cited as a distinct type of geriatric incontinence and attributed to deficits of cognition and mobility. This concept is problematic for several reasons (Resnick and Marcantonio, 1997). First, "functional incontinence" implies that urinary tract function is normal, but studies of both institutionalized and ambulatory elderly reveal that normal urinary tract function is the exception even in continent subjects, and is rarely observed in the

incontinent elderly (Ouslander et al, 1986; Resnick, 1988; Resnick et al, 1989; Resnick et al, 1995). **Second, incontinence is not inevitable with either dementia or immobility.** We found that 17% of the most severely demented institutionalized residents (mean age 89) were continent and, if they could merely transfer from a bed to a chair, nearly *half* were *continent* (Resnick et al, 1988). **Third,** because functionally-impaired individuals are the most likely to suffer from factors causing transient incontinence (Resnick et al, 1988; DuBeau and Resnick, 1995; Skelly and Flint, 1995; Brandeis et al, 1997), **a diagnosis of functional incontinence may result in failure to detect reversible causes of incontinence. Finally, functionally-impaired individuals may still have obstruction or stress incontinence and benefit from targeted therapy** (Resnick, 1988; Resnick et al, 1989; Gormley et al, 1993; DuBeau and Resnick, 1995).

Nonetheless, the importance of functional impairment as a factor *contributing* to incontinence should not be underestimated, because incontinence is also affected by environmental demands, mentation, mobility, manual dexterity, medical factors, and motivation (Jenkins and Fultz, 2005; Cigolle et al, 2007; Kikuchi et al, 2007) Although lower urinary tract function is rarely normal in such individuals, these factors are important to keep in mind because small improvements in each may markedly ameliorate both incontinence and functional status. In fact, once one has excluded causes of transient incontinence and serious underlying lesions, addressing causes of functional impairment may obviate the need for further investigation.

Key Points: Established Incontinence

- Established causes of geriatric incontinence comprise those in the lower urinary tract and also those beyond it.
- Detrusor overactivity (DO) is the most common lower urinary tract cause of incontinence in older adults, even in the absence of cognitive impairment. Differentiating a neurogenic from a non-neurogenic etiology is generally not possible in older patients, nor is differentiating DO that is due to urethral obstruction or incompetence from DO that simply coexists with these abnormalities.
- In older patients, DO commonly coexists with detrusor weakness, a condition known as DHIC. Without careful evaluation, such patients may be misdiagnosed as having urethral incompetence or, especially in the setting of urinary retention, urethral obstruction. Urethral surgery may exacerbate the problem.
- Stress incontinence is the second most common cause of incontinence in older women. Although urethral hypermobility is the most common cause, it often coexists with an age-related impairment of sphincter function.
- Urethral obstruction can contribute to incontinence in many men but is as uncommon in older women as in younger women.
- Isolated detrusor weakness is a very uncommon cause of overflow incontinence.
- In addition to abnormalities of lower urinary tract function, impairment of cognitive and/or physical function can also contribute to established geriatric incontinence and occasionally even cause it.

DIAGNOSTIC APPROACH

Evaluation

The evaluation should **identify transient and established causes of incontinence, assess the patient's environment and available support, and detect uncommon but serious conditions that may underlie incontinence,** including lesions of the brain and spinal cord, carcinoma of the bladder or prostate, hydronephrosis, bladder calculi, detrusor-sphincter dyssynergia, and decreased bladder compliance. **Assessment must be tailored** to the patient's clinical status and goals, and **tempered by the realization that not all detected conditions can be cured, that simple interventions may be effective even in the absence of a diagnosis, and that for many elderly patients, diagnostic tests are themselves often interventions.** Because the evaluation generally requires a comprehensive approach, it should be conducted over more than one visit to ease the burden and obviate further evaluation in those who respond to simple measures.

History

In addition to the assessment outlined in Chapter 64, evaluation of the older patient should search for transient causes of incontinence (including nonprescribed medications) and functional impairment. It should be augmented by medical records, as well as input from caregivers. Functional assessment focuses on both basic activities of daily living (ADLs: i.e., transferring from a bed, walking, bathing, toileting, eating, and dressing) and more advanced "instrumental" activities of daily living (IADLs: i.e., shopping, cooking, driving, managing finances, using the telephone). The assessment is accomplished by using a questionnaire, which can be completed by the patient or caregiver prior to the evaluation, and by objective evaluation of the patient from the beginning of the encounter, noting affect, mobility, ability to sit and rise from a chair, ability to provide a coherent history, and amount of time and assistance required to dress and undress.

Of course, as for younger individuals, it also is important to characterize the voiding pattern and the type of incontinence. Although the clinical type of incontinence most often associated with detrusor overactivity (DO) is urge incontinence, **"urge" is neither a sensitive nor specific symptom; it is absent in 20% of older patients with detrusor overactivity, and the figure is higher in demented patients** (Resnick et al, 1989). **"Urge" is also reported commonly by patients with stress incontinence, outlet obstruction, and overflow incontinence.**

A better term for the symptom associated with DO is **"precipitancy,"** which can be defined in two ways. For patients with no warning of imminent urination ("reflex" or "unconscious" incontinence), the abrupt gush of urine in the absence of a stress maneuver can be termed **precipitant leakage,** and it is **almost invariably due to DO.** For those who do sense a warning, it is of less value to focus on the leakage, because the presence and volume of leakage in this situation depend on bladder volume, amount of warning, toilet accessibility, the patient's mobility, and whether the patient can overcome the relative sphincter relaxation accompanying detrusor contraction (Dyro and Yalla, 1986). Instead, **precipitancy** should be defined as the *abrupt sensation* that urination is imminent, *whatever the interval or amount of leakage that follows*; defined in these two ways, precipitancy is both a sensitive and specific symptom (Resnick, 1990).

Table 76–3.

Causes of Nocturia

Volume Related
Age-related
Excess intake/alcohol
Diuretic, caffeine, theophylline, lithium
Endocrine/metabolic
Diabetes mellitus/insipidus
Hypercalcemia
Peripheral edema
Congestive heart failure
Low albumin states
Peripheral vascular disease
Venous insufficiency
Drugs (e.g., NSAIDs [indomethacin, COX-2 inhibitors], nifedipine)
Sleep Related
Insomnia
Obstructive sleep apnea (causes polyuria as well)
Restless legs syndrome
Pain
Dyspnea
Depression
Drugs
Lower Urinary Tract–Related
Small bladder capacity
Detrusor overactivity
Prostate related
Overflow incontinence
Decreased bladder compliance
Sensory urgency

COX-2, cyclooxygenase; NSAIDs, nonsteroidal anti-inflammatory drugs.
Adapted from Resnick NM. Noninvasive diagnosis of the patient with complex incontinence. Gerontology 1990;36(Suppl. 2):8–18.

Date	Time	Volume Voided (mL)	Are You Wet or Dry?	Approximate Volume of Incontinence	Comments
4/5	3:50 pm	240	Wet	Slight	
	6:05 pm	210	Dry		
	8:15 pm	150	Dry		
	10:20 pm	150	Wet	15 mL	Running water
	10:30 pm	30	Dry		Bowel movement
4/6	3:15 am	270	Wet	Slight	
	6:05 am	300	Wet	Slight	
	7:40 am	200	Dry		
	9:50 am	?	Dry		
	11:20 am	200	Dry		
	12:50 pm	180	Dry		
	1:40 pm	240	Dry		
	3:35 pm	160	Dry		
	6:00 pm	170	Dry		
	8:20 pm	215	Wet	Slight	Running water
	10:25 pm	130	Dry		

Figure 76–3. Voiding diary of an incontinent 75-year-old man. Urodynamic evaluation excluded urethral obstruction and confirmed a diagnosis of detrusor hyperactivity with impaired contractility (DHIC). Note the 24-hour urine output of nearly 3 L, due to the belief that drinking 10 glasses of fluid/day was "good for my health." (He did not mention this until queried about the voiding record). Given the typical voided volume of 150 to 250 mL and a measured postvoid residual (PVR) of 150 mL, excess fluid intake was overwhelming his usual bladder capacity of 400 mL (150 + 250 mL). Although involuntary bladder contractions were present, the easily reversible volume component of the problem—combined with the risk of precipitating urinary retention with an anticholinergic agent—prompted treatment with volume restriction alone. After daily urinary output dropped to 1500 mL, frequency abated and incontinence resolved. (Adapted from DuBeau CE, Resnick NM. Evaluation of the causes and severity of geriatric incontinence: a critical appraisal. Urol Clin North Am 1991;18:243–56.)

Similar to the situation for urgency, other symptoms ascribed to DO also can be misleading in the older person unless explored carefully. **Urinary frequency (greater than seven diurnal voids) is common** (Brocklehurst et al, 1968; Diokno et al, 1986; Resnick, 1988), and may be due to voiding habit, preemptive urination to avoid leakage, overflow incontinence, sensory urgency, a stable but poorly compliant bladder, excessive urine production, depression, anxiety, or social reasons (Resnick, 1990). **Conversely, incontinent individuals may severely restrict their fluid intake so that even in the presence of DO they do not void frequently.** Thus the significance of urinary frequency, or its absence, can be determined only in the context of more information.

Nocturia also can be misleading unless it is first defined (e.g., two episodes may be normal for the individual who sleeps 10 hours but not for one who sleeps 4 hours) and then approached systematically (Table 76–3). The **three general reasons for nocturia—excessive urine output, sleep-related difficulties, and urinary tract dysfunction—can be differentiated by careful questioning and a voiding diary that includes voided volumes** (Fig. 76–3). The record of voided volumes is inspected to determine the available bladder capacity (the largest single voided volume) and then compares this capacity to the volume of each nighttime void. For instance, if the available bladder capacity is 400 mL and each of three nightly voids is approximately 400 mL, the nocturia is due to excessive production of urine at night. If the volume of most nightly voids is much smaller than bladder capacity, nocturia reflects either: (1) a sleep-related problem (the patient voids because she is awake anyway), or (2) a problem with the lower urinary tract. Similar to excess urine output, sleep-related nocturia may also be due to treatable causes, including age-related sleep disorders, pain (e.g., bursitis, arthritis), dyspnea, depression, caffeine, or a short-acting hypnotic (e.g., triazolam). Bladder-related causes of nocturia are displayed in the table. Whatever the cause, the nocturnal component of incontinence can generally be ameliorated.

The symptoms of "prostatism" also warrant comment. Owing to the high prevalence of medication use, nocturnal polyuria (Reynard et al, 1998), constipation, and DHIC, as well as the impairment of bladder contractility that accompanies aging, "prostatic" symptoms are even less specific in older men than in younger men (DuBeau and Resnick, 1991).

When asking about leakage with stress maneuvers, it is important to ensure that the absence of such leakage is not due to simply the lack of coughing or sneezing. For those without such precipitants, it is useful to inquire about instantaneous leakage with lifting or bending over to put on a shoe or stockings.

Finally, **patients or their caregivers should be asked which voiding symptom is most bothersome.** For example, although a woman may have both stress and urge incontinence,

the urge component may be her worst problem and should become the focus of evaluation and treatment. A man with "prostatism" may be most bothered by nocturia (DuBeau et al, 1995), which may be remedied without any consideration of his prostate (see Fig. 76–3). Failure to address symptom bother can lead to frustration for patient and provider alike.

Voiding Diary

One of the most helpful components of the history is the voiding diary. Kept by the patient or caregiver for 48 to 72 hours, the diary records the time of each void and incontinent episode. No attempt is made to alter voiding pattern or fluid intake. Many formats have been proposed; a sample is shown in Figure 76–3.

To record voided volumes at home, individuals use a measuring cup, coffee can, pickle jar, or other large-mouth container. **Information regarding the volume voided provides an index of functional bladder capacity and, together with the pattern of voiding and leakage, can suggest the cause of leakage.** For example, incontinence occurring only between 8 AM and noon may be caused by a morning diuretic. Incontinence that occurs at night in a demented man with congestive heart failure, but not during a 4-hour nap in his wheelchair, is likely due to neither dementia nor prostatic obstruction but to postural diuresis associated with his heart failure. A woman with volume-dependent stress incontinence may leak only on the way to void after a full night's sleep, when her bladder contains greater than 400 mL—more than it ever does during her continent waking hours. A patient with impaired mobility may become incontinent if polyuria develops.

The voiding diary should also guide therapy. For instance, in a patient with DO or prostatic obstruction, excess nocturnal excretion may result in nocturnal incontinence, which is more severe and troublesome than daytime leakage; successful therapy must address the excess excretion. By contrast, another patient with the same urinary tract dysfunction and excretion—but with the ability to hold more urine when asleep—might be bothered more by daytime leakage. Shifting nocturnal excretion to the daytime will *exacerbate* his problem.

Targeted Physical Examination

Similar to the history, the physical examination is essential to detect transient causes, comorbid disease, and functional impairment. In addition to the standard neurourologic examination, one should check for signs of neurologic diseases that are more common in older people, such as delirium, dementia, stroke, Parkinson disease, cord compression, and neuropathy (autonomic or peripheral), as well as for atrophic vaginitis and general medical illnesses, such as heart failure and peripheral edema. The rectal exam checks for fecal impaction, masses, sacral reflexes, symmetry of the gluteal creases, and prostate consistency and nodularity; as noted in Chapter 92, the palpated size of the prostate is unhelpful. Many neurologically unimpaired elderly patients are unable to volitionally contract the anal sphincter, but, if they can, it is evidence against a spinal cord lesion. The absence of the anal wink is not necessarily pathologic in the elderly, nor does its presence exclude an underactive detrusor (due to diabetic neuropathy, for example).

Stress Testing and PVR Measurement

Several caveats apply to performing the stress test and measuring the PVR in older patients. Stress testing is performed optimally when the bladder is full, and the patient is relaxed (check the gluteal folds to corroborate) and in as close to the upright position as possible. The cough or strain should be vigorous and *single*, so one can determine whether leakage coincides with the increase in abdominal pressure or follows it. Stress-related leakage may be missed if any of these conditions is not met. Delayed leakage typical of stress-induced DO should be differentiated from leakage typical of stress incontinence, which is instantaneous and ceases as soon as abdominal pressure declines. **To be useful diagnostically, leakage must replicate the symptom for which help is sought,** because many older women have incidental but not bothersome leakage of a few drops. The test should not be performed if the patient has an abrupt urge to void because this is usually due to an involuntary detrusor contraction that will lead to a falsely positive stress test. Falsely negative tests occur when the patient fails to cough vigorously or to relax the perineal muscles, the bladder is not full, or the test is performed in the upright position in a woman with a large cystocele (that kinks the urethra). If performed correctly, the stress test is reasonably sensitive and quite specific (>90%) (Hilton and Stanton, 1981; Diokno, 1990; Kong et al, 1990).

Following the stress test, the patient is asked to void into a receptacle, and the PVR is measured. If the stress test was negative, the history suggests stress incontinence, *and* the combined volume of the void and PVR is less than 200 mL, the bladder should be filled with sterile fluid so that the stress test can be repeated at an adequate volume. There is no need to repeat a correctly performed positive stress test. Neither is there a need to repeat it in a woman whose history is negative for stress-related leakage; the sensitivity of the history for stress incontinence, unlike its specificity, exceeds 90% (Diokno et al, 1987; Jensen et al, 1994), making the likelihood of stress incontinence rare in this situation.

Optimally, the PVR is measured by portable ultrasonography, and within 5 minutes of voiding. Measuring it after an intentional void is better than after an incontinent episode, because many patients are able to partially suppress the involuntary contraction during the episode, and more than the true PVR remains. In cognitively impaired patients this may not be possible. Nonetheless, because the resulting artifact will lead to a falsely elevated PVR, a low value is still useful. The PVR will also be spuriously high if measurement is delayed (especially if the patient's fluid intake was high or included caffeine), the patient was inhibited during voiding, or there is discomfort due to urethral inflammation or bladder infection. It will be spuriously low if the patient augmented voiding by straining (most important in women). If a catheter is used, the PVR will be spuriously low if the catheter is withdrawn too quickly or if the woman has a cystocele that allows urine to "puddle" beneath the reach of the catheter. Of note, relying on the ease of catheterization to establish the presence of obstruction can be misleading, because difficult catheter passage may be caused by urethral tortuosity, a "false passage," or catheter-induced spasm of the distal sphincter, although catheter passage may be easy even in obstructed men (Klarskov et al, 1987).

Two other tests should be mentioned. The Q-tip (cotton swab) test for pelvic floor laxity is of little value in determining the cause of a patient's leakage, and has a high false-negative rate in elderly women (DuBeau and Resnick, 1991). The Bonney (or Marshall) test is also of limited usefulness in the elderly, because vaginal stenosis is common and may lead to a false-positive result by precluding accurate finger placement. Furthermore, even if the test is performed correctly, a false positive result may occur if the first episode of leakage was due to a cough-induced detrusor contraction that, having emptied the bladder, does not recur during bladder base elevation.

Laboratory Investigation

(Resnick and Ouslander, 1990; DuBeau and Resnick, 1991; Fantl et al, 1996). **BUN, creatinine, urinalysis, urine culture, and PVR should be checked in all older patients. Serum sodium, calcium, and glucose should be measured in patients with confusion.** If the voiding record suggests polyuria, serum glucose and calcium (and albumin, to allow calculation of free calcium levels in sick or malnourished patients) should be determined. Sterile hematuria suggests partially/recently treated bacteriuria, malignancy, or calculus; tuberculosis should also be considered, because the elderly, particularly institutionalized residents, are an unappreciated reservoir of this infection (Stead, 1985). Finally, it is important to recognize when evaluating renal function that the **age-related decline in glomerular flow rate (GFR)—30% by the 8th decade—is not associated with an increase in creatinine because of a concomitant decrease in muscle mass; thus *normal creatinine levels do not imply a normal GFR*.**

Empiric Diagnostic Categorization

After transient and serious causes have been addressed, the optimal diagnostic strategy for persistent incontinence is unknown (Resnick and Ouslander, 1990; Fantl et al, 1996; Abrams et al, 2005; Fonda et al, 2005). "Bedside" cystometry has been proposed, but its utility is limited because it misses low-pressure contractions of DHIC; its feasibility and accuracy are low in frail elderly (Ouslander and Colling, 1992); and detected DO may be either incidental and unrelated to leakage, or due to urethral obstruction or incompetence and warrant different therapy. The following approach (Resnick, 1995), although still unproven, is relatively noninvasive, accurate, cost effective, and easily tolerated. A similar approach forms the basis for the Agency for Health Care Policy Research (AHCPR) Clinical Practice Guideline (Fantl et al, 1996), the International Consultation on Incontinence (Fonda et al, 2005), as well as the Minimum Data Set/Resident Assessment Instrument, which we designed and validated for use in all American nursing homes (Resnick et al, 1996b).

The **first step is to identify individuals with overflow incontinence** (e.g., PVR > 450 mL). **Because obstruction and underactive detrusor cannot be differentiated clinically** (Resnick et al, 1996b; DuBeau et al, 1998; Sonke et al, 2000), **further assessment is warranted for those in whom it would affect therapy, while catheterization should be used for the rest. For the remaining 90% to 95% of patients, the next step depends on their sex. In women, the differential diagnosis is generally between stress incontinence and DO, because obstruction is rare in the absence of previous bladder neck suspension or prolapsing cystocele.** If the contemplated intervention is nonoperative, the diagnosis usually can be established on clinical grounds alone, informed by the caveats mentioned earlier.

In men, stress incontinence is uncommon and, when present, results in a characteristic drip (similar to a "leaky faucet") that is exacerbated by standing or straining. Thus **the usual problem in men is differentiating unobstructed DO from obstruction. Uroflowmetry is helpful, but only if peak flow is normal (e.g., >12 mL/sec for voided volume of 200 mL); the age-related decrease in bladder contractility means that a normal *unstrained* flow rate, together with PVR <100 mL, effectively excludes clinically significant obstruction in an older man** (DuBeau et al, 1998). **The next step is to search for hydronephrosis in men whose PVR exceeds 200 mL and to decompress those in whom it is found** (DuBeau and Resnick, 1992). Further evaluation is also reasonable for men without hydronephrosis who are appropriate candidates and would be amenable to surgery if obstructed. For the rest, **it seems sensible to treat those with urge incontinence for presumed DO, provided they are compliant and can be taught signs of incipient urinary retention;** bladder relaxants probably should be avoided in those with significantly elevated PVR (e.g., ≥ 150 mL). A similar approach is advocated for cognitively impaired men who can be closely observed (e.g., institutionalized residents) (Resnick et al, 1996b). **Men without urge incontinence, those who fail empiric therapy, and those who are cognitively impaired and less supervised should be evaluated further if findings would affect therapy.**

Urodynamic Testing

Although its precise role in the elderly is unclear, **multichannel urodynamic evaluation is probably warranted when diagnostic uncertainty may affect therapy and when empiric therapy has failed and other approaches would be tried.** Because conditions that closely mimic obstruction and stress incontinence are so common in the elderly, including altered fluid excretion (Reynard et al, 1998), medication use, DH, and DHIC (Resnick et al, 1996a), urodynamic corroboration of the diagnosis is strongly recommended if surgery will be performed (Resnick et al, 1991; Fantl et al, 1996; Resnick and Baumann, 1997). Whatever its role, however, urodynamic evaluation of even frail elderly patients is reproducible, safe, and feasible (Resnick et al, 1987; Resnick et al, 1989).

Key Points: Diagnostic Approach

- The evaluation should identify contributing factors both within and beyond the lower urinary tract and determine their impact on the patient's symptoms.
- Because the range of contributing causes is broader in older adults, and because fluid excretion changes with age, the voiding diary is of particular importance in evaluating older incontinent patients.
- Laboratory testing should often include more than serum measures of renal function. In addition, it is important to recall that serum creatinine underestimates creatinine clearance owing to the age-related decline in muscle mass and creatine production.
- DHIC can mimic both urethral obstruction and stress incontinence.
- Urodynamic testing should be strongly considered if surgery is contemplated since DHIC can mimic both urethral obstruction and stress incontinence.

THERAPY

Similar to the diagnostic approach, treatment must be individualized, because factors outside the lower urinary tract so often affect therapeutic feasibility and efficacy. For instance, although both may have detrusor overactivity that can be managed successfully, a severely demented and bedfast woman must be treated differently from one who is ambulatory and cognitively intact. This

section and Table 76–4 outline several treatments for each condition and provide guidance for their use. It is assumed that serious underlying conditions, transient causes of incontinence, and functional impairments have already been addressed.

It cannot be overemphasized that **successful treatment of established incontinence, especially in the elderly, is usually multifactorial and requires addressing factors beyond the urinary tract.** Figure 76–4, based on empiric data, illustrates the many factors that determine whether DO in an older adult will be associated with incontinence and, if so, the frequency of the related leakage (Miller et al, 2002; Rosenberg et al, 2005).

Detrusor Overactivity

The initial approach to detrusor overactivity is to identify and treat its reversible causes. Unfortunately, many of its causes are not amenable to specific therapy or a cause may not be found, so treatment usually must be symptomatic. **Simple measures, such as adjusting the timing or amount of fluid**

Table 76–4.

Stepwise Approach to Treatment of Urinary Incontinence*

CONDITION	CLINICAL TYPE OF INCONTINENCE†	TREATMENT
Detrusor overactivity with normal contractility (DO)	Urge	1. Bladder retraining or prompted voiding regimens 2. ± Bladder relaxant medication, if needed and not contraindicated (see drug list below) 3. Indwelling catheterization alone is often unhelpful because detrusor "spasms" often increase, leading to leakage around the catheter 4. In selected cases, induce urinary retention pharmacologically and add intermittent or indwelling catheterization‡
Detrusor hyperactivity with impaired contractility (DHIC)	Urge§	1. If bladder empties adequately, behavioral methods (as above) ± bladder relaxant medication (low doses; especially feasible if sphincter incompetence coexists) 2. If residual urine ≥150 mL, augmented voiding techniques‖ or intermittent catheterization (± bladder relaxant medication). If neither feasible, undergarment or indwelling catheter‡ 3. In selected cases, induce urinary retention pharmacologically and add intermittent or indwelling catheterization‡
Stress incontinence	Stress	1. Conservative methods (weight loss if obese; treatment of cough or atrophic vaginitis; physical maneuvers to prevent leakage [e.g., tighten pelvic muscles before cough, cross legs]; occasionally, use of tampon or pessary is useful) 2. If leakage threshold ≥150 mL identified, adjust fluid excretion and voiding intervals appropriately 3. Pelvic muscle exercises ± biofeedback/weighted intravaginal "cones"; must continue indefinitely 4. Surgery (sling, artificial sphincter, periurethral bulking injections)
Urethral obstruction	Urge/overflow¶	1. Conservative methods (including adjustment of fluid excretion, bladder retraining/prompted voiding) if hydronephrosis, recurrent symptomatic UTI, and gross hematuria have been excluded 2. α-Adrenergic antagonist 3. Also consider adding a bladder relaxant if DO coexists, PVR is small, and surgery not desired/feasible; *monitor PVR!* 4. Finasteride, if not contraindicated and the patient either prefers it or is not a surgical candidate 5. Surgery (incision, prostatectomy) is an effective alternative before or after these steps
Underactive detrusor	Overflow	1. Decompress for at least several days (the larger the PVR, the longer should be the decompression [up to a month]) and then perform a voiding trial 2. Exclude urethral obstruction if this has not already been done 3. If cannot void or PVR remains large, try augmented voiding techniques‖ 4. ± α-Adrenergic antagonist, but only if some voiding possible; bethanechol *rarely* useful 5. If fails, or voiding is not possible, intermittent or indwelling catheterization‡

*These treatments should be initiated only after adequate toilet access has been ensured, contributing conditions have been treated (e.g., atrophic vaginitis, UTI, fecal impaction, heart failure), fluid management has been optimized, and unnecessary or exacerbating medications have been addressed. For additional details, see text.

†*Urge:* Leakage in the absence of stress maneuvers and urinary retention, usually preceded by *abrupt* onset of desire to void.
Stress: Leakage that coincides *instantaneously* with stress maneuvers, in the absence of urinary retention or detrusor contraction.
Overflow: Frequent leakage of small amounts associated with urinary retention.

‡UTI prophylaxis can be used for recurrent symptomatic UTIs, but only if catheter is not indwelling.

§May also mimic stress or overflow incontinence.

‖Augmented voiding techniques include Credé (application of suprapubic pressure) and Valsalva (straining) maneuvers, and "double" voiding. They should be performed only *after* voiding has begun.

¶Also can cause postvoid "dribbling" alone, which is treated conservatively (e.g., by sitting to void and allowing more time, "double voiding," and in men by gently "milking" the urethra after voiding).

PVR, Postvoid residual; UTI, urinary tract infection.

Adapted and updated in 2010 from Resnick NM. Voiding dysfunction and urinary incontinence. In: Beck JC, editor. Geriatric review syllabus. New York: American Geriatrics Society; 1991. p. 141–54.

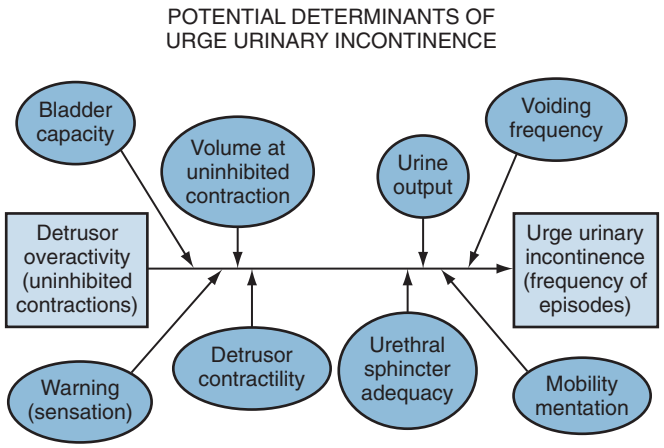


Figure 76–4. Factors that determine whether detrusor overactivity, found in nearly half of *continent* older adults, will be associated with urge incontinence and, if so, the frequency of the related leakage. (Data from Miller KL, DuBeau CE, Bergmann M, et al. Quest for a detrusor overactivity index. J Urol 2002;167:578–85; Rosenberg LJ, Griffiths DJ, Resnick NM. Factors that distinguish continent from incontinent older adults with detrusor overactivity. J Urol 2005;174:1868–72.)

excretion (see Fig. 76–3) **or providing a bedside commode or urinal are often successful. If not, the cornerstone of treatment is behavioral therapy, which can be effective and avoids drug side effects.** Some evidence suggests that it also may be more durable than drug therapy (Kafri et al, 2008). If the patient can cooperate, bladder training regimens will extend the voiding interval (Fantl et al, 1991; Burgio et al, 1998; Berghmans et al, 2000; Payne, 2000; Burgio et al, 2002). For instance, if the voiding record documents incontinence when the interval exceeds 3 hours, the patient is instructed to void every 2 hours and suppress urgency in between. Once dry, the patient can extend the interval by half an hour, and repeat the process until a satisfactory result or continence is achieved. Patients need not follow this regimen at night, because nighttime improvement parallels daytime success (Johnson et al, 2005). Biofeedback may be added (Berghmans et al, 2000), but its marginal benefit is unclear (Resnick, 1998; Burgio et al, 2002; Wilson et al, 2005; Shamliyan et al, 2008; Hartmann et al, 2009).

For cognitively impaired patients, "prompted voiding" is used (Fantl et al, 1996; Tannenbaum and DuBeau, 2004). Asked every 2 hours whether they need to void, patients are escorted to the toilet if the response is affirmative. Positive verbal reinforcement is employed, and negative comments are avoided. Prompted voiding reduces incontinence frequency in nursing homes by roughly 50%, and leakage can be virtually eliminated during daytime hours in one third of residents (Hu et al, 1989; Engel et al, 1990; Schnelle, 1990; Fink et al, 2008). The latter group can be identified within three days. When prompted *hourly* to void, they urinate into a toilet or commode more than two thirds of the time that they indicate the need to do so, or they become continent on more than 80% of checks. Response is maintained when the prompting interval is increased to two hours. Half of the remaining patients also improve with prompting, but they are still wet more than once during the daytime. For the quarter of patients who do not respond to prompting at baseline, little benefit is obtained by further prompting. Importantly, response does not correlate with the degree of dementia. In addition, these results were obtained without drugs, and urodynamic evaluations were not performed (Schnelle, 1990; Ouslander et al, 1995). Two additional studies found that adding oxybutynin or tolterodine improved results still further (Ouslander et al, 2001b; Fink et al, 2008).

The voiding record also can be helpful if it reveals that nocturnal incontinence correlates with nocturnal diuresis. If due to systolic congestive heart failure, it should improve with diuretic therapy. If due to obstructive sleep apnea, it may respond to continuous positive airway pressure (Guilleminault et al, 2004). If due to peripheral edema in the absence of heart failure and hypoalbuminemia (i.e., venous insufficiency), it should respond to pressure gradient stockings. If not associated with peripheral edema, it may respond to alteration of the pattern of fluid intake or to administration of a rapidly acting diuretic in the late afternoon or early evening (Pedersen and Johansen, 1988; Reynard et al, 1998). For patients with DHIC, whose voiding record and PVR suggest that involuntary detrusor contractions are provoked only at high bladder volume, augmented voiding techniques or catheterization at bedtime will remove the residual urine, thereby increasing functional bladder capacity and restoring both continence and sleep.

Drugs may augment behavioral intervention but do not supplant it, because they generally do not abolish involuntary detrusor contractions. Moreover, combining the two interventions generally improves outcome (Burgio et al, 2000; Mattiasson et al, 2003; Alhasso et al, 2006; Burgio et al, 2008). Timed toileting or bladder retraining in conjunction with a bladder relaxant is especially useful for older adults who have little warning before detrusor contraction (Wagg and Malone-Lee, 1998).

There are few data on comparative efficacy or toxicity of standard incontinence drugs in the elderly, but available **studies show similar efficacy for most agents,** except flavoxate, which fares poorly in controlled trials; (Fantl et al, 1996; Andersson et al, 2009a; Hartmann et al, 2009) no controlled data are available for hyoscyamine in any adult age group.

Data regarding use in the elderly are most extensive for oxybutynin and tolterodine. This includes dozens of trials that have included the elderly, several that have stratified results by age, and several that have focused exclusively on older adults, including patients who were frail and/or reside in nursing homes (Zinner et al, 2002; Ouslander, 2004; Sand et al, 2004; Sand et al, 2006; Lackner et al, 2008; Andersson et al, 2009a; DuBeau et al, 2009; Griebling et al, 2009; Hartmann et al, 2009). Such trials have established that these agents are likely as effective for improving incontinence and quality of life in older adults as they are in younger individuals and, especially in lower doses, as tolerable. **Thus oxybutynin and tolterodine should be considered first-line pharmacotherapy in this population.** As for any drug used in older adults, **therapy should start with a low dose that is increased slowly,** consistent with the agent's pharmacokinetics and pharmacodynamics in older patients. **Given the marked variability, however, dose escalation should continue until either a successful end point is reached or an intolerable side effect is encountered.** Experience suggests that for oxybutynin IR, most older adults will respond best to 2.5 mg 3 to 4 times daily; for oxybutynin ER, 5 to 15 mg is optimal. At larger doses, side effects increase much more than therapeutic response. Immediate release oxybutynin, which has a short half-life, can be employed prophylactically if incontinence occurs at predictable times. Intravesical instillation of these agents is also effective in younger patients, but the need for self-catheterization makes this strategy less useful in the elderly.

The only currently used agents that have been evaluated in the nursing home setting are the immediate release formulations of tolterodine (1 to 2 mg twice daily) and oxybutynin (2.5 mg 3 to 4 times daily). Both have been evaluated during daytime hours when staff is available (7 AM to 7 PM). Overall, the reported reduction in leakage frequency is roughly 25%; roughly one third of such patients experience a decrease of at least 33%, and about 10% become continent during that time period (Ouslander et al, 2001b; DuBeau et al, 2009).

Antimuscarinic agents used to treat UI can induce confusion in older adults, but the incidence is rare, both in trials and in practice, and the very small risk should not preclude prescribing them for older adults, even those who are frail and/or cognitively impaired. There is justifiable concern about prescribing anticholinergic drugs in the elderly. CNS levels of acetylcholine decline with age and decline still further in the presence of many diseases. Many drugs prescribed for the elderly have anticholinergic properties, and anticholinergic agents are one of the most common causes of delirium in this age group, especially among individuals with preexisting cognitive, sensory, affective, or functional impairment. In addition, all currently-available agents used for incontinence either require metabolism by the hepatic cytochrome P450 system and/or renal excretion. Each of these functions declines with age and can be further impaired by other drugs and diseases.

Theoretical arguments have been marshaled for using one antimuscarinic over another. These are largely based on the drug's characteristics, including muscarinic subtype affinity, lipophilicity, polarity, molecular size, protein binding, drug half-life, and active and passive transport across the blood-brain barrier. Also cited are experimental studies that observed a short-term impact on some components of detailed neuropsychological testing (Klausner and Steers, 2007; Kay and Ebinger, 2008), when continent volunteers were given doses of oxybutynin that are likely too high for older adults.

Yet understanding of the role and importance of CNS muscarinic subtypes in humans is still limited, and the blood brain barrier can be compromised by age and other drugs, as well as by a host of diseases that are common in the elderly, including diabetes, Alzheimer disease, stroke, Parkinson disease, and trauma (Klausner and Steers, 2007; Kay and Ebinger, 2008). The resulting permeability changes may dwarf the differences observed in experiments that involved younger and healthier elderly subjects. In addition, neuropsychologic impairments observed in older volunteers have generally been mild, and the subjects have been unaware of them, making it difficult to assess their relevance. Because the studies to date also have been short term, have been conducted in artificial conditions, and have used high doses of oxybutynin, it is impossible to know whether such effects would persist with chronic treatment. It is also worth noting that even darifenacin, which is widely marketed as being free of such effects, has been associated with significantly slowed reaction times in the Divided Attention Test (Kay et al, 2006), which could potentially predispose to problems in tasks that require such attention, such as driving and walking without falling.

Moreover, after decades of widespread use, evidence of clinical cognitive impairment still comprises only a handful of case reports, and clinical trials—which have involved relatively large numbers of older individuals—have observed only rare instances of drug-associated cognitive impairment (Tsao and Heilman, 2003; Andersson, 2004; Ouslander, 2004). For instance, analysis of the OPERA trial, which included approximately 120 patients over age 75 years, disclosed only 1 of 390 patients on oxybutynin 10 mg/day ER who reported confusion, and it was judged "mild" because it did not interfere with activities or require intervention; none of the 399 patients on tolterodine 4 mg LA reported confusion (Chu et al, 2005). Another study randomized 50 cognitively impaired nursing home residents, average age 89 years, to receive extended release oxybutynin 5 mg or placebo for 4 weeks. No changes were found in cognitive test performance, nor were there any cases of delirium. Another group of 48 nursing home residents responded well to tolterodine 1 to 2 mg administered twice daily in an 8-week trial. Side effects were minimal, and only 1 patient experienced worsening of baseline confusion (Ouslander et al, 2001b). In summary, the risk of drug-induced cognitive impairment appears to be real but small.

There is also a theoretical concern about prescribing an anticholinergic bladder relaxant to a patient taking a cholinesterase inhibitor. Fortunately, this has not proved to be a problem in clinical practice. Although a few case reports have appeared (Siegler and Reidenberg, 2004), neither a large observational nursing home study (Sink et al, 2008) nor a recent case series of 26 demented patients (Sakakibara et al, 2005) noted a deterioration in mental status when patients were also prescribed an antimuscarinic drug for incontinence. Furthermore, in some situations, the clinician and caregiver will decide that the positive impact on the incontinence warrants continuation of both agents regardless.

Finally, there is concern that an antimuscarinic-induced increase in heart rate may be dangerous. Apart from terodiline (which was withdrawn), however, there are no data to substantiate this concern at present, although the risk cannot yet be completely excluded. Among patients with established heart disease (who are generally not taking an anticholinergic agent), increased heart rates are associated with increased mortality. However, the risk in such patients likely reflects the extent of intrinsic heart disease and/or the drugs used to treat it. Heart rate increases induced by antimuscarinics are generally less than or equal to 5 beats/minute. An increase of this magnitude is of unknown significance and, to date, has not been associated with an increased mortality rate in antimuscarinic trials. Studies have also revealed little impact on the electrocardiogram (ECG) or Q-T interval (other than with terodiline). Moreover, because vagal influence on heart rate is substantially less in older adults than in younger adults, the likelihood of inducing an increased heart rate is less, especially because the appropriate dose of an antimuscarinic is also lower in the elderly.

Newer agents include darifenacin, solifenacin, trospium, and fesoterodine. Similar to the extended-release preparations of oxybutynin and tolterodine, and the newer preparations of oxybutynin (patch and gel), each is more convenient and better tolerated than the immediate release versions of oxybutynin and tolterodine. Not surprisingly, however, data for older people taking these drugs are still limited. To date, the only controlled trial of darifenacin in older adults focused on a relatively young (mean age 72 years) and fit group. Although the group randomized to placebo was younger than the darifenacin group (31% >75 years vs. 43%), urge incontinence improved similarly in both (Chapple et al, 2007). The only controlled data of solifenacin in older adults comprises a secondary analysis of pooled Phase 3 data, which revealed efficacy and safety similar to that seen among younger enrollees (Wagg et al, 2006); however, a higher rate of adverse effects was documented in a 12-week postmarketing surveillance study, especially among patients over age 80 years who were also taking multiple other medications (Michel et al, 2008). No controlled studies of fesoterodine or trospium have yet stratified the

results by age, despite marketing for the latter agent that emphasizes its theoretical advantage in older adults as being less likely to cross the blood-brain barrier. Regardless, each agent has theoretical benefits and drawbacks for older adults; Table 76–5 notes some of the relevant caveats.

Table 76–5.

Bladder Relaxant Medications Used to Treat Urge Incontinence*

MEDICATION CLASS, NAME, AND DOSAGE	COMMENTS
Anticholinergic Agents	These agents are now the drugs of choice for older adults. Both oxybutynin and tolterodine have proved effective for older patients in controlled trials when used continuously; less controlled data are yet available for the other agents and still less for their efficacy, side effects, and drug interactions in frail older adults. Benefits of M3 selectivity remain theoretical. Concerns re: CNS side effects of oxybutynin and tolterodine emanate primarily from rare case reports and short-term, artificial experiments and likely are overstated. Immediate release oxybutynin has a rapid onset of action and can be tried prophylactically if incontinence occurs at predictable times.
Oxybutynin IR 7.5-20 mg daily (2.5-5 mg PO tid-qid)†	
Oxybutynin XL 5-30 mg daily (given once daily)	
Oxybutynin patch twice weekly	
Oxybutynin gel	
Tolterodine 2 mg twice daily	
Tolterodine LA 4 mg daily	
Darifenacin (7.5-15 mg qd)‡	
Solifenacin (5-10 mg qd)‡§	
Trospium (20 mg daily to twice daily; XL now available)§‖	
Fesoterodine	
Smooth Muscle Relaxant	Obsolete; has not proved effective in placebo-controlled trials
Flavoxate 300-800 mg daily (100-200 mg PO tid-qid)	
Tricyclic Antidepressants¶	Older controlled trial data support their use, but they are not first choice. May be helpful in women with coexistent stress incontinence. Orthostatic hypotension often precludes their use, but a tricyclic antidepressant may be preferred for a depressed incontinent patient without risk for orthostatic hypotension. Doxepin has more anticholinergic side effects than imipramine and can cause confusion.
Imipramine 25-100 mg daily (10-25 mg PO qd-qid)	
(Doxepin 25-75 mg daily [10-25 mg PO qd-tid])	

*Each drug should be started at the lowest dose and increased slowly until encountering maximum benefit or intolerable side effects. The highest doses are generally not required and can cause problematic side effects for older patients.

†May also be applied intravesically in patients who can use intermittent catheterization.

‡Toxicity can occur with concurrent use of potent cytochrome P450 3A4 inhibitors (e.g., amiodarone).

§Dose reduction required for creatinine clearance ≤30 mL/min (e.g., in an 85-year-old woman with serum creatinine of 1.2 who weighs 50 kg).

‖Levels may be affected by other commonly used drugs in the elderly such as digoxin or metformin, which compete for renal tubular secretion.

¶May give as single daily dose of 25-100 mg after determining the optimal dose.

CNS, central nervous system; IR, immediate release; XL and LA, extended release.

Adapted and updated in 2005 from Resnick NM. Urinary incontinence. Lancet 1995;346:94–9.

Other agents, formerly advocated for older incontinent adults, are no longer advised. Specifically, there are no appropriate trials for hyoscyamine (Roxburgh et al, 2007; Andersson et al, 2009a) and, as the active ingredient in atropine, hyoscyamine has a substantial risk of inducing confusion in older adults. Flavoxate has been not been found effective despite several controlled trials (Roxburgh et al, 2007). Calcium channel blockers, drugs long thought to be theoretically preferable for the elderly, were finally studied in a controlled trial and found to be ineffective (Naglie et al, 2002). For the incontinent and depressed older patient, nortriptyline or imipramine may be considered (amitriptyline and doxepin should not be given to older patients) (Fantl et al, 1996), but because evidence of their efficacy falls short of modern standards, they should be used only if depression has not already responded to an SSRI, there is no evidence of orthostatic hypotension, and the patient can be monitored for orthostasis and falls.

Regardless of which antimuscarinic is used, urinary retention may develop. The PVR and urine output should be monitored, especially with DHIC, in which the detrusor is already weak. Subclinical urinary retention also may develop, reducing available bladder capacity and attenuating, or even reversing, the drug's benefit. Thus if incontinence worsens as the dose is increased, the PVR should be remeasured. **Another reason for drug failure is excess fluid ingestion engendered by anticholinergic-induced xerostomia.** For patients whose incontinence defies other remedies (such as those with DHIC), inducing urinary retention and using intermittent catheterization may be viable if catheterization is feasible.

Other remedies for urge incontinence, including electrical stimulation (see Chapter 70) **and selective nerve blocks, are successful in selected situations.** However, they have not been studied adequately in the elderly, and the limited preliminary data suggest that older patients may not fare as well (Amundsen and Webster, 2002; Amundsen et al, 2005; South et al, 2007; White et al, 2009). Trials of botulinum A toxin (BoNT) intradetrusor injection have included some older adults, but only a single study has focused on older patients (White et al, 2008). In that series, symptoms in 16 of the 21 patients over age 75 improved by at least 50%. However, incontinence was not specifically reported, and patients with PVR greater than 150 mL were excluded, as were those whose bladder failed to empty completely with a detrusor contraction on urodynamic testing. Moreover, a recent randomized clinical trial (RCT) of middle-aged women (Brubaker et al, 2008), mean age 65 years, found a much higher incidence of urinary retention and UTIs than previously reported. In 2009, the Food and Drug Administration (FDA) required a black-box warning for BoNT, owing to the risk of injected toxin migrating and causing paralysis, and even death. **Thus BoNT appears promising, but given the very limited experience in older adults, the significant number who have impaired detrusor contractility, the non-feasibility of intermittent catheterization in many older patients, the risk, and the numerous remaining questions regarding optimal patient selection, dose, dilution, and injection site, BoNT is still best viewed as investigational** (Brubaker et al, 2008; DuBeau et al, 2009; Hartmann et al, 2009).

Recent studies have suggested that desmopressin is relatively safe for older adults. However, these studies have generally been short term, have included very few subjects older than age 75, have included still fewer with comorbidity or diuretic use, and have sedulously screened and monitored all subjects. Moreover, they also have enrolled *only* patients who, during a prestudy

run-in period, tolerated treatment with desmopressin, responded well to it, and did not lower their serum sodium (Weatherall, 2004). Despite these precautions, hyponatremia still developed in up to 22% of patients. Serum sodium levels decreased to less than 130 mMol/L in one fifth of these patients, almost all of whom were more than 65 years old (Abrams et al, 2002; Weatherall, 2004; Rembratt et al, 2006). More recently, a longer-term study documented the risk of hyponatremia at 6 months, even among patients who did not develop it earlier (Bae et al, 2007). Additional concerns include the fact that many older persons do not develop warning symptoms of hyponatremia, as well as recent data suggesting that even short-term desmopressin therapy can increase calcium excretion and decrease potassium excretion (Chang et al, 2007). If substantiated in longer-term studies, this effect would be problematic for older patients in whom the prevalence of both osteoporosis and renal insufficiency is considerable. Moreover, **there is little evidence that vasopressin is effective for geriatric incontinence** (Dequecker, 1965; Asplund and Aberg, 1993; Cannon et al, 1999). Thus **the high prevalence of contraindications to its use (e.g., hyponatremia, renal insufficiency, heart failure [even subclinical]), the risk of inducing serious hyponatremia with fluid retention** (Cannon et al, 1999), **the potentially adverse impact on calcium and potassium excretion** (Chang et al, 2007), **and its lack of demonstrated efficacy all suggest that desmopressin should be used to treat urge incontinence in older adults with extreme caution, if at all.**

Adjunctive measures, such as pads and special undergarments, are invaluable if incontinence proves refractory. Many types are now available, allowing the recommendation to be tailored to the individual's problem (Fader et al, 2007; Fader et al, 2008; Cottenden et al, 2009). Most are included in an illustrated catalog (National Association for Continence (NAFC), PO Box 1019, Charleston, SC 29402; www.nafc.org). For bedridden individuals, a launderable bed pad may be preferable, while for those with a stroke, a diaper or pant that can be opened using the good hand may be preferred. For ambulatory patients with large gushes of incontinence, wood pulp–containing products can be superior to ones containing polymer gel, because the gel generally cannot absorb the large amount and rapid flow, while the wood-pulp product can be doubled up if necessary. Optimal products for men and women differ because of the location of the "target zone" of the urinary loss. Finally, the choice will be influenced by patient preference, cost, and the presence of fecal incontinence.

Condom catheters are helpful for men, but they are associated with skin breakdown, bacteriuria, and decreased motivation to become dry (Ouslander and Schnelle, 1995; Cottenden et al, 2009), and they are not feasible for the older man with a small or retracted penis. External collecting devices have been devised for institutionalized women, but whether they will adhere adequately in more active women remains to be determined. **Indwelling urethral catheters are not recommended for detrusor overactivity because they usually exacerbate it.** If they must be used (e.g., to allow healing of a pressure sore), a small catheter with a small balloon is preferable to avoid leakage around the catheter; such leakage almost invariably results from bladder contractions rather than from a catheter that is too small. Increasing catheter and balloon size only aggravates the problem and may result in urethral erosion and sphincter incompetence. If spasms persist, drugs such as oxybutynin can be tried. **More potent anticholinergic agents, such as belladonna suppositories, should be avoided in the elderly.**

Stress Incontinence

Urethral hypermobility, the most common cause of stress incontinence in older women, may be improved by **weight loss** if the patient is obese, (Brown et al, 2006; Hunskaar, 2008; Subak et al, 2009) **by postural maneuvers** (Norton and Baker, 1994), **by therapy of precipitating conditions such as atrophic vaginitis or cough** (e.g., due to an ACE inhibitor), **and by insertion of a pessary** (Suarez et al, 1991; Zeitlin and Lebherz, 1992; Donnelly et al, 2004; Cottenden et al, 2009). If the voiding diary reveals that leakage is volume dependent, it also may be improved by adjusting fluid excretion and voiding intervals to keep bladder volume below this threshold. However, if the threshold is less than 150 to 200 mL, this strategy, alone, is generally not sufficient.

Pelvic muscle exercises can decrease incontinence substantially in older women who are motivated, cognitively intact, and trained to perform them 30 to 200 times daily (Wells et al, 1991; Burns et al, 1993; Fantl et al, 1996; Goode et al, 2003; Choi et al, 2007; Hay-Smith et al, 2009). Unfortunately, such exercises must be pursued indefinitely, efficacy is limited for severe incontinence, only 10% to 25% of women become fully continent, and many older women are unable or unmotivated to follow such regimens. Adding vaginal cones, biofeedback, or electrical stimulation may enhance efficacy, but their marginal benefit remains unclear (Burns et al, 1993; Fantl et al, 1996; Burgio et al, 2002; Goode et al, 2003; Resnick and Griffiths, 2003; Neumann et al, 2006; Hay-Smith et al, 2009).

Effective pharmacotherapy for stress incontinence in older women remains elusive. Studies document, at best, modest efficacy for any of the available agents, and it is of unknown durability and often associated with significant side effects (Mariappan et al, 2007; Shamliyan et al, 2008; Andersson et al, 2009a). Phenylpropanolamine, the agent for which the most data are available, was withdrawn from the American market owing to reports of a small risk of hemorrhagic stroke (Haller and Benowitz, 2000). The FDA has added a "black-box" warning for duloxetine, and neither the FDA nor the United Kingdom's National Institute for Clinical Excellence (NICE) agency have approved it to treat stress incontinence (Andersson et al, 2009a). However, for mild to moderate stress incontinence, pseudoephedrine is inexpensive and remains available without prescription. Because it is also contained in nonprescribed remedies for coryza and allergy, and some capsules also contain agents such as chlorpheniramine in doses that can be troublesome for elderly patients, the physician should prescribe the dose and guide the choice of preparation. The physician should also closely supervise its use in patients with hypertension, if it is used at all. Imipramine, which inhibits reuptake of both norepinephrine and serotonin, can also be useful for mild stress incontinence (Lin et al, 1999), but it should be considered only if symptoms and signs of postural hypotension have been excluded. Estrogen monotherapy has not proved effective for stress incontinence (Al-Badr et al, 2003), and although the addition of estrogen to α-adrenergic therapy may improve the latter's efficacy, the magnitude of the effect is modest at best (Andersson et al, 2009a). Fewer and less promising data are available for pharmacotherapy of stress incontinence in older men.

If these methods fail or are unacceptable, surgical options should be considered. As recent data have challenged the long-term durability of bladder neck suspensions, suburethral slings and midurethral tape slings have become increasingly employed

(Anger et al, 2009). **Older women generally can tolerate a suburethral sling** (Carey and Leach, 2004; Anger et al, 2007), **but the ability to perform the midurethral procedures under regional, or even local, anesthesia on an outpatient basis makes them more feasible.** In the few studies published to date, success rates for tension-free vaginal tape (TVT) procedures have been lower for older patients than for younger individuals, likely reflecting the higher prevalence of comorbidity, detrusor overactivity, intrinsic sphincter deficiency, decreased detrusor contractility, and prior operations in the elderly (Lo et al, 2002; Gordon et al, 2005; Sharp et al, 2006; Hellberg et al, 2007; Richter et al, 2009; Smith et al, 2009). Nonetheless, reported cure rates in older women have been 80% to 96% within the first year, declining to 60% to 70% at 2 to 3 years. Longer-term data are also available; to date, the lowest reported long-term cure rate is still 55% after a mean of 5 years in a group of 113 women at least age 75 (75 to 91 years) at the time of their TVT (Hellberg et al, 2007). In addition, investigators who have measured both cure and satisfaction have generally found that the level of satisfaction among older patients generally exceeds their cure rate (Sevestre et al, 2003; Tannenbaum et al, 2008; Richter et al, 2009). **Complications, such as prolonged urinary retention and obstructive symptoms have generally ranged from 2% to 15%, while reported de novo urgency/DO has tended to be somewhat more common.** Whether such results will be mirrored in routine practice remains to be seen, but long-term success rates for procedures available prior to the popularity of these procedures revealed "real-world" success rates of approximately 70% at 2 years and 40% at 10 years for women older than age 70 years (Diokno et al, 2003).

Other treatments for sphincter incompetence include periurethral bulking injections and insertion of an artificial sphincter (Shamliyan et al, 2008). Experience with these approaches has proved less auspicious than originally thought, but older women appear to benefit as much as younger women, although factors predicting success or failure in this group are still not entirely clear, and short-term and long-term data in women older than age 75 are still limited (Winters et al, 2000; Keegan et al, 2007; Smith et al, 2009). Yet, injections have several potential advantages over slings for older women. Injections are less invasive, can be performed in an office under local anesthesia, and are associated with fewer perioperative and postoperative complications. The ideal candidate appears to be an older woman whose mild to moderate stress incontinence is associated with intrinsic sphincter deficiency, absent or minimal detrusor overactivity/urgency, normal to moderately impaired detrusor contractility, and minimal urethral hypermobility; the last factor may be particularly important because it may substantially diminish the likelihood of success with TVT (Liapis et al, 2006). The woman should also understand that repeated injections will likely be required over time and that these may not be as effective as they were initially (Winters et al, 2000).

For men in whom these interventions fail, an artificial urinary sphincter (AUS) and "male sling" are potential options. Unfortunately, there are still little data regarding their use in older men (especially for the sling), for which techniques are still evolving and long-term data are lacking (Herschorn et al, 2009). For those who have mild postprostatectomy incontinence, have a strong detrusor, and have not had prior radiation, the sling is theoretically appealing because it is less invasive than the AUS, avoids a mechanical device, and is less expensive (Comiter, 2006). However, its theoretical advantages must be weighed against the known risks of sepsis, persistent perineal pain, and the need for explantation, as well as the risk of persistent urinary retention in older men whose detrusor contractility is more apt to be impaired. Although the same AUS model has been used successfully for many years, few studies have focused on its use in older patients or have examined the impact of age on outcome. In those few studies, carefully selected older patients seemed to do as well as younger ones, even up to 10 years (O'Connor et al, 2007, Kim et al, 2008). In addition, a sphincter can be used in older men with impaired detrusor contractility. Drawbacks include the higher complication and revision rates and the need for the patient to have adequate cognitive capacity and manual dexterity.

Prostheses such as condom catheters or penile clamps may be useful, but most of these require substantial cognitive capacity, and manual dexterity as well, and are often poorly tolerated. Penile sheaths (e.g., McGuire prosthesis or adhesive underwear liners) are an alternative. As discussed above, pads and undergarments are used as adjunctive measures. However, in these cases, polymer gel pads are frequently successful because the gel can more readily absorb the smaller amount of leakage. Some products can be flushed down the toilet, a convenient feature for ambulatory individuals.

Outlet Obstruction

For older men, **conservative management of outlet obstruction often suffices.** In the absence of urinary retention or upper tract damage, modification of fluid excretion and voiding habits may be effective. If not, **α-adrenergic antagonists** are useful and generally well-tolerated; they are actually beneficial for men with systolic (not diastolic) congestive heart failure. However, their use requires caution. With age, cardiac output depends less on cardioacceleration than on adequate ventricular filling. Unfortunately, the left ventricle also becomes stiffer, necessitating higher filling pressure. Thus, α blockers, which decrease preload as well as afterload, can result in symptomatic hypotension in older men, particularly those whose age-related left ventricular hypertrophy is exacerbated by hypertension or aortic stenosis. Medical consultation should be sought before prescribing an α blocker to such individuals. Although the **newer agents, tamsulosin and alfuzosin, are more selective and appear to be less likely to cause orthostasis than terazosin and doxazosin in older patients** (Mann et al, 2000; AUA Practice Guidelines Committee, 2003), further data are required. **Because doxazosin was associated with an increased risk of heart failure when used to treat older men with hypertension in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) Trial, it probably should be avoided.** Recent studies also show that **alpha 1α blockers, especially tamsulosin, increase the risk of serious ophthalmic events following iridectomy** (Bell et al, 2009). Unfortunately, other α blockers are not free of such risk, and it is **not yet clear how long these agents should be discontinued prior to surgery** (Friedman, 2009). Fortunately, the risk is low, and new ophthalmologic strategies are under development.

Recent studies (Abrams, 2002; Lee et al, 2004; Kaplan et al, 2006; Blake-James et al, 2007; Rovner et al, 2008) have shown that **anticholinergic therapy can be both effective and safe** for obstructed men with concomitant DO who have not responded well to treatment with an α blocker, although the impact on incontinence has generally not been reported. Notably, all of these studies excluded men with severe obstruction, postvoid residual

volume greater than 150 to 200 mL, and renal disease. **Particular caution should be exercised for men who take other agents that have anticholinergic properties, for men with any degree of cognitive impairment, for men with PVR greater than 150 mL, and for men in whom close follow-up is questionable.** Preliminary data on botulinum toxin A suggest that it too may have a role as further data become available (Maria et al, 2003; Kuo, 2005).

The 5α-reductase inhibitors (finasteride or dutasteride) have also proved effective as monotherapy, but fewer men appear to benefit, the effect is more modest, and the response occurs over months (Gormley et al, 1992). By contrast, and **particularly for men with larger glands, combined therapy with an α blocker for several years is more efficacious than therapy with either drug alone. It also reduces the risk of urinary retention, although this appears to take at least a year.** Devices and surgical approaches, as well as the approach to obstruction in women, are discussed elsewhere (see Chapters 69, 93, and 94). Of note, DO may resolve less often following removal of obstruction in older patients than in younger ones, but incontinence may still improve, even in cognitively impaired patients (Eastwood and Smart, 1985; Gormley et al, 1993; Mitterberger et al, 2007). In addition, less extensive resection or ablation often suffices for frail elderly men, in whom recurrence of symptoms with adenoma re-growth years later is often not an issue. This fact, coupled with surgical techniques that now permit resection under local anesthesia, has made surgery increasingly feasible for this population.

Underactive Detrusor

Management of detrusor underactivity is directed at reducing the residual volume, eliminating hydronephrosis (if present), and preventing urosepsis (Taylor and Kuchel, 2006; Yalla et al, 2007). **The first step is to use indwelling or intermittent catheterization** to decompress the bladder for up to a month (at least 7 to 14 days), while reversing potential contributors to impaired detrusor function (fecal impaction and medications). **For patients presenting with acute retention, an α blocker should be used as well.** Recent data suggest that such therapy increases the chances of success in men without another obvious cause of retention, even among men older than age 65 years and those with retained volume of 1000 to 1500 mL (Lucas et al, 2005; McNeill et al, 2005; Fitzpatrick and Kirby, 2006). Given the long-term success of combined therapy with an α blocker and a 5α-reductase inhibitor, addition of the latter should also be considered if the patient's life expectancy is estimated to exceed one year.

If an indwelling catheter has been inserted, it should then be removed (Table 76–6). **If decompression does not fully restore bladder function, augmented voiding techniques (such as double voiding and implementation of the Credé** [application of suprapubic pressure during voiding] or Valsalva maneuver) **may help** if the patient is able to initiate a detrusor contraction or if there is coexistent stress incontinence, especially in women. **Bethanechol** (40 to 200 mg/day in divided doses) **is occasionally useful in a patient whose bladder contracts poorly because of treatment with anticholinergic agents that cannot be discontinued** (e.g., tricyclic antidepressant). **In other patients,** bethanechol may decrease the PVR if sphincter function and local innervation are normal, but **evidence for its efficacy is equivocal at best** (Barendrecht et al, 2007; Andersson et al, 2009a), and residual volume should be monitored to assess its effect.

Table 76–6.

Removing an Indwelling Urethral Catheter*

Ensure that the bladder has been decompressed for at least several days, and 7 to 21 days if possible; the higher the residual volume, the longer the bladder should be decompressed.

Correct reversible causes of urinary retention: fecal impaction; pelvic/perineal pain; and use of anticholinergic, alpha adrenergic agonist, or calcium channel blocker medications. If an anticholinergic antidepressant/antipsychotic agent cannot be stopped, consider switching to one with fewer or no anticholinergic side effects.

Treat delirium, depression, atrophic vaginitis, impaction, or urinary tract infection, if present.

An α blocker (e.g., alfuzosin or tamsulosin) increases the chances of success in men but is still unproven in women. It should be initiated several days before the catheter is removed. If life expectancy is estimated to exceed a year, initiation of finasteride should be considered as well.

Record output at 6- to 8-hour intervals for 2 days to establish a pattern of baseline urine excretion.

Remove the catheter at a time that permits accurate recording of urine output and allows for postvoiding recatheterization; clamping the catheter before removal is unnecessary and can be dangerous.

Reinsert the catheter *only:*

- After the patient voids, to determine PVR volume; or
- After the expected bladder *volume* (based on records of urine output)—not the time since the catheter was removed—exceeds a preset limit (e.g., 600-800 mL); or
- If the patient is uncomfortable and unable to void despite ensured privacy and maneuvers to encourage voiding (e.g., running water, tapping suprapubic area, or stroking inner thigh).

If the patient voids and the PVR volume is:

- Greater than 400 mL—reinsert the catheter and evaluate further, if appropriate*
- 100-400 mL—watch for delayed retention and evaluate further, if appropriate*
- Less than 100 mL—watch for delayed retention.

If the patient is unable to void, evaluate further if appropriate.* If not, resident requires permanent catheterization.

*Further evaluation is appropriate when the patient and physician feel that if a surgically correctable condition was found (e.g., urethral obstruction), an operation would be preferable to chronic catheterization or the other options described in the text.

PVR, postvoiding residual.

Modified from Resnick NM. Incontinence. In: Beck JC, editor. Geriatric review syllabus. New York: American Geriatrics Society; 1991. p. 141–54.

On the other hand, if after decompression the detrusor is acontractile, these interventions are apt to be fruitless, and the patient should be started on intermittent catheterization or an indwelling urethral catheter. For individuals at home, intermittent self-catheterization is preferable and requires only clean, rather than sterile, catheter insertion. The patient can purchase two or three of these catheters inexpensively. One or two are used during the day and another is kept at home. The catheters are cleaned daily, allowed to air dry at night, sterilized periodically, and may be reused repeatedly. Antibiotic or methenamine prophylaxis against urinary tract infection is probably warranted if the individual gets more than an occasional symptomatic infection or has an abnormal heart valve (Chawla et al, 1988; Warren, 1990; Cottenden et al, 2005). Intermittent catheterization in this setting is generally painless, safe, inexpensive, and effective, and allows individuals to carry on with their

Table 76–7.

Principles of Indwelling Catheter Care

Maintain sterile, closed gravity drainage system:
- Secure the catheter to upper thigh or abdomen to avoid urethral irritation and contamination. Rotate the site of attachment every few days.
- Empty the bag every 8 hours.
- Do not routinely irrigate the catheter.
- Do not clamp or kink the drainage tubing, and keep the collection bag below bladder level at all times.
- Avoid frequent cleaning of the urethral meatus; washing with soap and water once daily is sufficient; periurethral application of antimicrobial creams is ineffective.
- Adding disinfectants to the catheter bag is ineffective.

If "bypassing" occurs in the absence of obstruction, it is likely due to a bladder spasm, which can be minimized by using the smallest balloon that will keep the catheter in place and by treating with a bladder relaxant medication if necessary.

Infection prophylaxis, as well as treatment of asymptomatic bacteriuria, is fruitless and usually leads to the emergence of resistant organisms.

Surveillance cultures are unnecessary and potentially misleading because bacteriuria is universal, frequently changing, and often polymicrobial.

If symptomatic urinary tract infection (UTI) develops, change the catheter before obtaining a culture specimen, because cultures obtained through the old catheter may reflect organisms colonizing encrustations rather than the infecting organism. Pending culture results, antibiotic treatment should include coverage of common uropathogens, as well as uncommon ones such as *Providencia stuartii* and *Morganella morganii*.

If catheter obstruction occurs frequently, and urine cultures reveal *Providencia stuartii* or *Proteus mirabilis*, antibiotic treatment may reduce the frequency of obstruction but induces emergence of resistant organisms. In the absence of urea-splitting organisms, consider urine acidification if urine output is normal (at low output, acidification may increase blockage due to uric acid crystals). If frequent blockage persists, consider using a silicon catheter.

In the absence of obstruction and symptomatic UTI, there is no consensus on the best time to change the catheter. Some persons form material that frequently clogs the lumen; their catheter probably should be changed often enough to reduce such obstruction. Other individuals can use the same catheter for years, but it is customary to change it every 1 to 2 months. For patients who are difficult to catheterize, the catheter can be changed less frequently, if it remains patent, and complication free.

For long-term need, a silicone or silicone hydrogel–coated catheter should be considered.

Adapted from Resnick NM. Voiding dysfunction and urinary incontinence. In: Beck JC, editor. Geriatric review syllabus. New York: American Geriatrics Society; 1991. p. 141–54.

usual daily activities. For debilitated patients, however, intermittent catheterization is usually less feasible, although sometimes possible (Hunt and Whitaker, 1990). If used in an institutional setting, sterile rather than clean technique should be employed until studies document the safety of the latter (Gammack, 2003).

Unfortunately, despite the benefits and proven feasibility of intermittent catheterization (Bennett and Diokno, 1984; Hunt and Whitaker, 1990; Bakke et al, 1992), most elderly patients choose indwelling catheterization instead. As in younger individuals, complications of chronic indwelling catheterization include renal inflammation and chronic pyelonephritis (Warren et al, 1994), bladder and urethral erosions, bladder stones and cancer, as well as urosepsis (Warren, 1990; Gammack, 2003; Cottenden et al, 2005). Principles of catheter care are summarized in Table 76–7.

When indicated, indwelling catheters can be extremely effective, but their use should be restricted, especially in nursing home settings (Johnson and Ouslander, 2006) (Center for Medicare and Medicaid Services: Surveyor Guidance for Urinary Incontinence and Catheters; available at: www.cms.hhs.gov/medicaid/survey-cert/sc0523.pdf). Catheters are indicated in acutely ill patients to monitor fluid balance, in the patient with a nonhealing pressure ulcer, for temporary bladder decompression in patients with acute urinary retention, and in the patient with overflow incontinence refractory to other measures. Even in long-term care facilities, they are probably indicated for only 1% to 2% of patients.

Key Points: Therapy

- Successful treatment of geriatric UI is generally feasible, but it usually requires a stepwise approach.
- Addressing contributing medications, fluid excretion, and diseases beyond the LUT will often restore continence or will improve incontinence enough that no further treatment is necessary. Even when this approach is not sufficient, it will enhance the efficacy of other therapeutic interventions.
- Behavioral therapy often works as well or better than medications. When drugs are prescribed, dosing should be adjusted to account for age-related factors and for potential drug–drug and drug–disease interactions.
- Anticholinergic agents remain the mainstay of pharmacotherapy for detrusor overactivity. Neuromodulation and intradetrusor botulinum toxin injections are still considered investigational for older adults.
- Age-related factors also affect the choice of therapy and outcome of interventions for stress incontinence, urethral obstruction, and underactive detrusor.
- If surgery is contemplated, urodynamic testing should be considered owing to the common presence of DHIC in older adults and its ability to cause urinary retention and to mimic urethral obstruction and incompetence.

SUMMARY

Regardless of age, mobility, mentation, or institutionalization, incontinence is never normal. By attenuating physiologic reserve, aging increases the likelihood of becoming incontinent in the setting of additional physiologic, pharmacologic, or pathologic insults. Because many of these problems lie outside the urinary tract, so too must the diagnostic and therapeutic focus. However, such a strategy, coupled with a multifactorial, creative, persistent, and optimistic approach, will increase the chances of a successful outcome and generally reward patient and physician alike.

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chapter 77

Urinary Tract Fistulae

Eric S. Rovner, MD

General Considerations
Urogynecologic Fistulae
Uroenteric Fistulae
Urovascular Fistulae
Other Urinary Fistulae

A fistula represents an extra-anatomic communication between two or more epithelial or mesothelial-lined body cavities or the skin surface. **Although most fistulae in the industrialized world are iatrogenic, they may also occur as a result of congenital anomalies, malignancy, inflammation and infection, radiation therapy, iatrogenic (surgical) or external tissue trauma, ischemia, parturition, and a variety of other processes. The potential exists for fistula formation between a portion of the urinary tract (i.e., kidney, ureters, bladder, and urethra) and virtually any other body cavity,** including the chest (pleural cavity), gastrointestinal (GI) tract, lymphatics, vascular system, genitalia, skin, and reproductive organs. **Classification is generally based on the organ of origin in the urinary tract and the termination point of the fistula (e.g., vagina, skin, GI tract).** The presenting symptoms and signs are variable and depend to a large degree on the involved organs, the presence of underlying urinary obstruction or infection, the size of the fistula, and associated medical conditions such as malignancy.

GENERAL CONSIDERATIONS

Acquired urinary fistulae in the industrialized world are almost universally unexpected and may result in a great deal of inconvenience, discomfort, and physical disability for the affected individual. They are most often acquired as a result of a medical or surgical intervention for an unrelated problem, and, consequently, considerable emotional and psychologic distress often accompanies the diagnosis and subsequent treatment. This may be expressed as anger, resentment, and disappointment on the part of the patient toward the physician. As a result, not infrequently, the medicolegal aspects of these cases can be very disturbing to the treating health care practitioner, with an increasing proportion of these cases being adjudicated in court (Thomas and Williams, 2000). Only the most naive surgeon would fail to recognize that many of these fascinating reconstructive cases often have significant medicolegal implications, especially in the setting of iatrogenic fistula creation. Nevertheless, minimizing patient discomfort, maintaining a positive and honest patient–physician relationship while providing constant reassurance, and, finally and perhaps most importantly, pursuing expeditious and successful treatment of the fistula will most often result in a satisfactory, non-confrontational, mutually satisfying long-term outcome.

Notably, after the initial diagnosis of a urinary fistula, which results in external urinary leakage, immediate management or control of the urinary leakage is vital. Addressing this quickly will reduce skin breakdown and related complications, as well as alleviate much of the psychologic distress on the part of the affected individual. The judicious use of catheters, pads, and appliances can be very helpful in this regard. Skin care and odor control products are also adjunctive measures in minimizing patient-related distress until definitive therapy and repair of the fistula can be undertaken. The importance of these types of interventions on the patient's behalf should not be underestimated by the surgeon. These simple measures can often deflect or assuage the anger of an otherwise very disaffected sufferer, thereby reducing the potential for further aggravating an already difficult medical and, possibly, litigious situation.

The principles of repair of urinary fistulae are outlined in Table 77–1 and can be applied to virtually any type of fistula involving the urinary tract (see Table 77–1). **Prevention of urinary fistulae is, of course, paramount; however, nutrition, infection, and malignancy are important considerations not only when assessing a patient for the risk of creation of a fistula during any given intervention, but also during an evaluation for the repair of an existing urinary fistula.** Although the vast majority of urinary fistulae in the industrialized world occur in healthy, well-nourished individuals, a nutritional assessment may be an important factor in some patients with fistulae, such as those patients with malignancies. Ensuring adequate nutrition is integral to surgical healing in general, but is especially important in the setting of a urinary fistula. Not uncommonly, the catabolic processes contributing to the lack of healing, which may have been a contributing factor in the initial fistula formation, are often ongoing. This is especially relevant in fistulae related to radiation therapy or in debilitated patients.

Although some types of urinary fistulae will heal with conservative management, surgery often assumes a role in the definitive repair. Repair and reconstruction of urinary fistulae are sometimes complex. **These should be approached on a case by case basis, because repair may involve some innovative and even improvisational maneuvers in the operating room.**

Table 77–1.

Principles of Urinary Fistula Management

Adequate nutrition
Elimination of infection
Unobstructed urinary drainage and/or stenting
Removal or bypass of distal urinary obstruction
Beware of malignant etiology of fistula

Table 77–2.

Principles of Surgical Repair of Urinary Fistula

Adequate exposure of the fistula tract with debridement of devitalized and ischemic tissue.
Removal of involved foreign bodies or synthetic materials from region of fistula, if applicable
Careful dissection and/or anatomic separation of the involved organ cavities
Watertight closure
Use of well-vascularized, healthy tissue flaps for repair (atraumatic handling of tissue)
Multiple-layer closure
Tension-free, nonoverlapping suture lines
Adequate urinary tract drainage and/or stenting after repair
Treatment and prevention of infection (appropriate use of antimicrobials)
Maintenance of hemostasis

The surgeon should be familiar with a variety of approaches and techniques, because **one approach will not be optimal for all patients with a given type of urinary fistulae.** Principles of surgical management of urinary fistulae are outlined in Table 77–2. **The finding of a persistent fistula after presumably definitive treatment may suggest the existence of other contributing host factors, such as malignancy, nutritional issues, the possibility of an unrecognized foreign body, tissue ischemia, or surgical factors, such as inadequate postoperative urinary drainage, persistent distal urinary obstruction, or technical problems with the surgery.**

Key Points: Presentation

- Urinary fistulae are often associated with considerable physical and psychologic distress for the patient.
- Nutrition, infection, malignancy, urinary obstruction, and the presence of a foreign body are all important factors to consider in the initial approach to urinary fistula, and in those patients who have failed primary therapy.

UROGYNECOLOGIC FISTULAE

Vesicovaginal Fistulae

Vesicovaginal fistulae (VVF) are the most common acquired fistula of the urinary tract (Gerber and Schoenberg, 1993) **and have been known since ancient times** (Fig. 77–1). However, it was not until 1663 that Hendrik von Roonhuyse first described surgical repair of VVF by denuding the fistula margins and then reapproximating them with sharpened stiff swan quills (Margolis and Mercer, 1994). Johann Fatio is generally credited with the first successful VVF repair, in 1675, using von Roonhuyse's technique (Falk and Tancer, 1954). In 1838, using leaden suture, John Peter Mettauer was the first U.S. surgeon to claim a successful VVF closure (Kight, 1967). In 1852, James Marion Sims published his now famous surgical series describing his method of surgical treatment of VVF using silver wire in a transvaginal approach (Sims, 1852). Of note, it was not until his 30th attempt at closure of VVF that he achieved success. However, Sims remains the subject of considerable debate regarding his ethics (Richardson, 1994; Sartin, 2004), because it is unknown whether the patients in his surgical series were willing and consenting participants (all were African-American slaves in pre–Civil War America). He was later to become one of the great figures in the history of operative gynecology. The first successful transabdominal approach to VVF repair was reported by Trendelenburg in 1888, and the concept of an interpositional flap was first proposed and reported in 1928 by Martius, who used a labial fat pad.

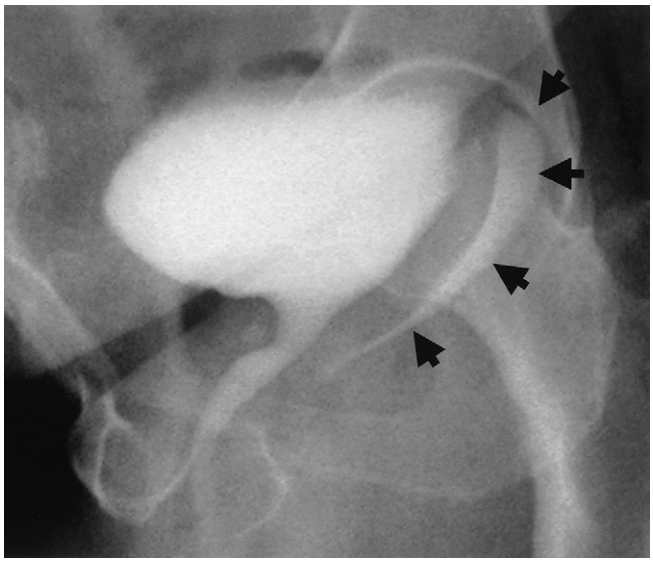


Figure 77–1. Voiding cystourethrogram demonstrates filling of the vagina with voiding due to a post-hysterectomy vesicovaginal fistula.

Etiology and Prevalence

The etiology of VVF differs in various parts of the world. In the industrialized world, the most common cause (>75%) of VVF is injury to the bladder at the time of gynecologic, urologic, or other pelvic surgery (Symmonds, 1984; Lee et al, 1988; Tancer, 1992). **Surgical injury to the lower urinary tract most commonly occurs in the setting of hysterectomy** (Fig. 77–2), **whereas most of the remainder are related to general surgery procedures in the pelvis, anterior colporrhaphy or cystocele repair, antiincontinence surgery, or other urologic procedures** (Armenakas et al, 2004). Of 207 VVF repaired at the University of Caliornia–Los Angeles (UCLA) over a 10-year period ending in 2001, Eilber and colleagues (2003) reported the cause as abdominal hysterectomy in 83%, vaginal hysterectomy in 8%, radiation in 4%, and miscellaneous in 5%. In 1964, Massee and colleagues from the Mayo Clinic reviewed the cause of urogenital fistulae in 262 patients and cited uterine operations as a proximate cause in 73.7%, vaginal wall operations in 6.5%, urinary tract operations in 6.9%, and obstetric operations in 6.5%, with the remainder

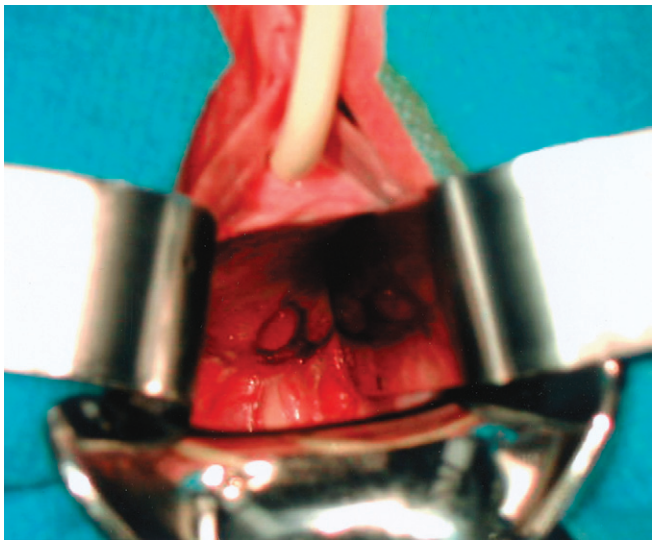


Figure 77–2. Posthysterectomy vesicovaginal fistula (VVF). Retraction with a weighted speculum and Heaney right-angled retractors to provide lateral retraction are needed to visualize this posthysterectomy VVF in a nulliparous woman.

being due to miscellaneous causes. A later series of greater than 300 fistulae from the same institution cited gynecologic surgery as the cause of VVF in 82%, obstetric procedures in 8%, radiation in 6%, and trauma or fulguration in 4% (Lee et al, 1988). **Other causes of VVF in the industrialized world include malignancy, pelvic radiation, and obstetrical trauma (including forceps lacerations and uterine rupture)** (Everett and Mattingly, 1956; Gerber and Schoenberg, 1993). The use of vaginal mesh for prolapse repair may also result in VVF (Margulies et al, 2008; Ridgeway et al, 2008). Although fortunately uncommon during labor, approximately 22% of uterine ruptures are associated with a bladder injury (Raghavaiah and Devi, 1975). Prior to 1900, the most common cause of VVF in the United States was obstructed labor (Stothers et al, 1996). However, obstructed labor and obstetric trauma, in general, now account for very few VVF in the United States and other industrialized nations, probably due to the widespread availability of excellent prenatal and perinatal obstetric care.

The rate of iatrogenic bladder injury during abdominal hysterectomy is estimated to be between 0.5% and 1.0% (Keettel et al, 1978). Mathevet and colleagues (2001) reported the incidence of bladder injury during vaginal hysterectomy to be 1.7% in 3076 cases, with all injuries being recognized and repaired intraoperatively. Despite the immediate intraoperative repair reported in this series, there were four VVF noted, giving a crude VVF rate during vaginal hysterectomy of 0.13%. The reported incidence of intraoperative bladder injury varies considerably in the literature, depending on whether routine cystoscopy was performed. In series where cystoscopy was not performed, the overall rate of bladder injury was reported to be approximately 2.6 per 1000 cases, whereas in series where cystoscopy was routinely performed, the overall rate of bladder injury was approximately 10.4 per 1000 cases (Gilmour et al, 1999). **The incidence of fistula after hysterectomy is estimated to be approximately 0.1% to 0.2%** (Harris, 1995). There are approximately 140 to 150 VVF repairs annually in England and Wales (Hilton, 1997).

Posthysterectomy VVF are thought to result most commonly from an incidental unrecognized iatrogenic cystotomy near the vaginal cuff (Kursh et al, 1988). If unrecognized intraoperatively, a pelvic urinoma may develop and ultimately drain out through the vaginal cuff. Ongoing urinary drainage along this tract results in a fistula. **Other potential mechanisms for posthysterectomy VVF include tissue necrosis from cautery, a suture placed through both the bladder and vaginal wall during closure of the vaginal cuff, or an attempt to control pelvic bleeding by suture ligature.** Tissue ischemia and then necrosis promotes fibrosis and induration, finally resulting in an epithelial or mucosal lining of the tract and the development of a fistula tract. Possibly, factors other than an isolated suture placed through the bladder and vagina are necessary for posthysterectomy VVF formation because, at least, in an animal model, deliberate suture fixation of the bladder to the vagina does not invariably result in VVF in the absence of infection, urinary extravasation, or other complicating factors (Meeks et al, 1997).

In the developing world where routine perinatal obstetrical care may be limited, VVF most commonly occur as a result of prolonged obstructed labor due to cephalopelvic disproportion, with resulting pressure necrosis to the anterior vaginal wall, bladder, bladder neck, and proximal urethra from the baby (Arrowsmith et al, 1996) (Fig. 77–3). **The constellation of problems resulting from obstructed labor is not limited to VVF and has been termed the "obstructed labor injury complex" and includes varying degrees of each of the following: urethral loss, stress incontinence, hydroureteronephrosis, renal failure, rectovaginal fistula, rectal atresia, anal sphincter incompetence, cervical destruction, amenorrhea, pelvic inflammatory disease, secondary infertility, vaginal stenosis, osteitis pubis, and foot drop** (Arrowsmith et al, 1996). The obstructed labor injury complex occurs largely in developing countries in certain cultures due to several factors, including (1) marriage and conception at a very young age, which results in childbearing in a relatively small and immature pelvis, (2) poor nutrition resulting in stunted skeletal (e.g., pelvic) growth in the mother, and (3) relative absence of qualified prenatal and obstetrical care (Margolis and Mercer, 1994). Patients may suffer with obstructed labor for days in a rural environment, eventually traveling to a distant health care facility only to have a stillborn fetus and a VVF. In direct contradistinction to the epidemiology of VVF in the industrialized world, 96.5% of 932 VVF seen at a single hospital in Nigeria over a 7-year period were temporally associated with labor and delivery (Wall et al, 2004). The incidence of obstetric fistula in developing countries has been estimated at approximately 0.3% to 0.4% of deliveries (Margolis et al, 1994), or between 1 and 4 per 1000 vaginal deliveries (Margolis et al, 1994; Danso et al, 1996). In sub-Saharan Africa the incidence rate has been estimated at 10.3 per 100,000 deliveries (Vangeenderhuysen et al, 2001). An estimate of up to 500,000 new cases of obstetric fistula occur throughout the world annually (Hilton, 2003), although the total morbidity from obstructed maternal labor has been estimated to be in excess of 5 million individuals annually (Kelly, 1991). Risk factors include young or old maternal age, and primigravids (Danso et al, 1996).

Obstetric fistulae tend to be larger, located distally in the vagina, and may involve large portions of the bladder neck and proximal urethra. Even in experienced hands, these are often very difficult to repair due to the extensive soft tissue loss, as well as the ischemia and fibrosis of adjacent tissues (Arrowsmith, 1994; Elkins, 1994). Obstetric fistulae are devastating injuries in the developing world, with significant socioeconomic

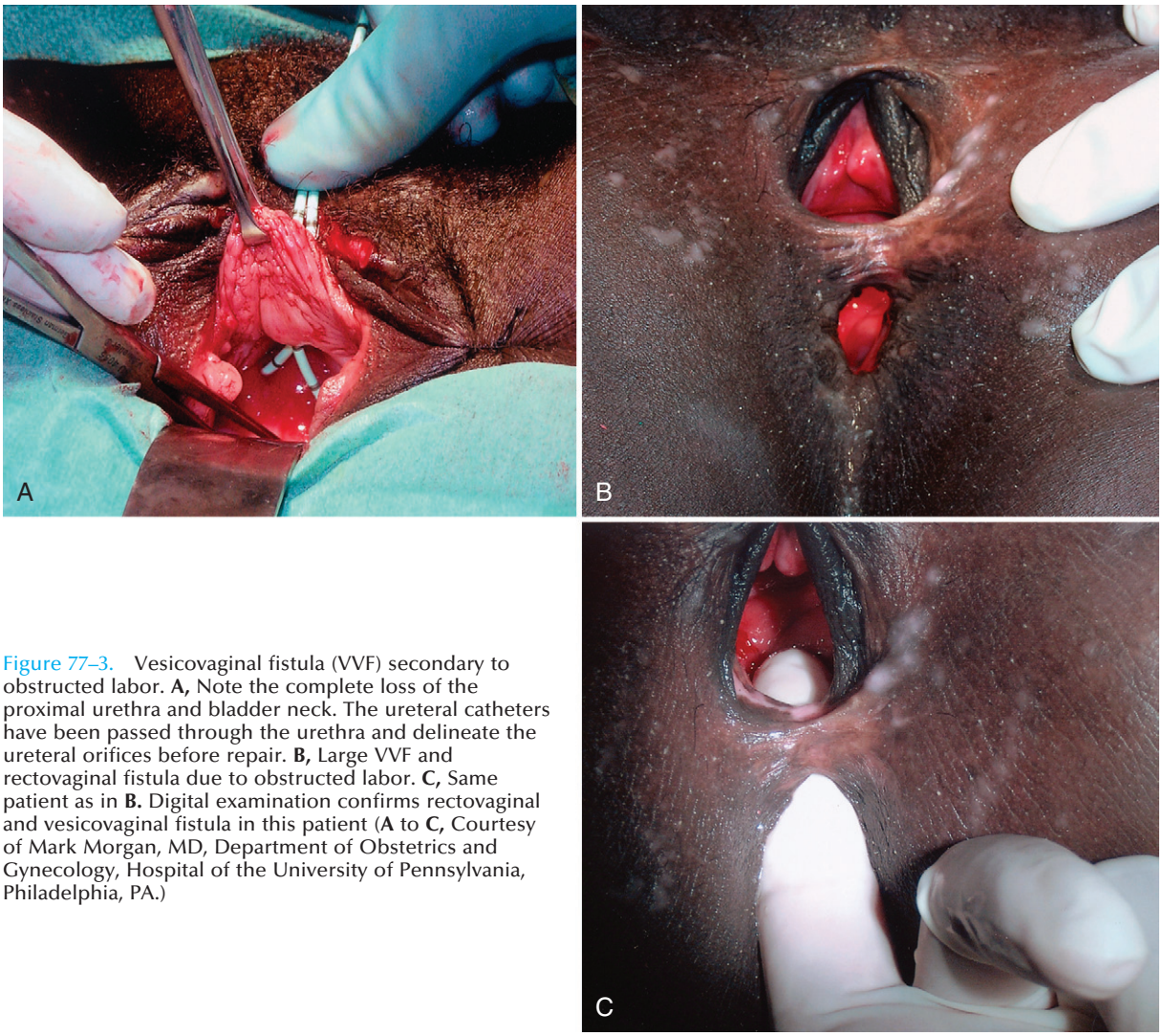


Figure 77–3. Vesicovaginal fistula (VVF) secondary to obstructed labor. **A,** Note the complete loss of the proximal urethra and bladder neck. The ureteral catheters have been passed through the urethra and delineate the ureteral orifices before repair. **B,** Large VVF and rectovaginal fistula due to obstructed labor. **C,** Same patient as in **B.** Digital examination confirms rectovaginal and vesicovaginal fistula in this patient (**A** to **C,** Courtesy of Mark Morgan, MD, Department of Obstetrics and Gynecology, Hospital of the University of Pennsylvania, Philadelphia, PA.)

ramifications (Donnay and Weil, 2004; Wall et al, 2004). The affected individuals, commonly young teens, are often ostracized and shunned from family and friends and become permanent outcasts in society. Only rarely are these individuals able to get adequate care and repair due to the lack of organized health care in many countries in the developing world. Major efforts are underway to improve education, the socioeconomic status of women, and access to health care in these regions (Tahzib, 1983; Tahzib, 1989; Kelly, 1991; Wall, 1996; Donnay and Weil, 2004; Kelly, 2004). With improvements in the delivery of prenatal care in some areas of the developing world, it appears that the incidence of VVF due to obstetric causes may be decreasing as a subset of all VVF, with a proportional increase in the rate of iatrogenic gynecologic fistulae approaching that in industrialized nations (Ayhan et al, 1995; Obi et al, 2008). Another important cause of VVF in some parts of the world is traditional folk treatments such as "gishiri cutting," which may account for up to 13% of VVF in some series (Tahzib, 1983). This ritual practice involves using a knife to incise the anterior vagina as a treatment for a variety of conditions, including infertility, dyspareunia, dysuria, and back pain.

Other causes of VVF include urologic or gynecologic instrumentation, including percutaneous procedures (Ramsay et al, 1992; Pruthi et al, 2000), **retroperitoneal, vascular or pelvic surgery, infectious and inflammatory diseases** (Borjas and Rodriguez Diaz 1949; Bland and Gelfand, 1970; Ba-Thike et al, 1992; Monteiro et al, 1995), **foreign bodies (including neglected pessaries)** (Binstock et al, 1990; Goldstein et al, 1990; Grody et al, 1999), **congenital VVF** (Rousseau et al, 1996), **sexual trauma** (Roy et al, 2002), **vaginal laser procedures** (Colombel et al, 1995), **and external violence** (see Table 77–3). **The three most common locally advanced malignancies that result in VVF include cervical, vaginal, and endometrial carcinoma, which in aggregate account for approximately 3% to 5% of VVF in the industrialized world.**

VVF due to radiation therapy deserve special mention. **These VVF may occur several decades after completion of the radiation** (Zoubek et al, 1989). **The incidence of urinary fistula following radiation therapy varies with the type, dose, and location of the radiation.** Both external beam and interstitial (Aristizabal et al, 1983) radiation therapy may result in VVF. **An incidence of 1.6% of any type of urinary fistula was noted in one series of greater than 2200 patients treated with a variety of different radiation modalities for cervical carcinoma** (Alert et al, 1980). Perez reported a

Table 77–3.

Etiology of Vesicovaginal Fistula

Traumatic
Postsurgical
Abdominal hysterectomy
Vaginal hysterectomy
Anti-incontinence surgery
Anterior vaginal wall prolapse surgery (e.g., colporrhaphy)
Vaginal biopsy
Bladder biopsy/endoscopic resection/laser
Other pelvic surgery (e.g., vascular, rectal)
External trauma (e.g., penetrating, pelvic fracture, sexual)
Radiation therapy
Advanced pelvic malignancy
Infectious/inflammatory
Foreign body
Obstetric
Obstructed labor
Forceps laceration
Uterine rupture
Caesarean section injury to bladder
Congenital

0.6% to 2.0% incidence of VVF formation in 1456 patients undergoing combined external beam radiotherapy and brachytherapy for stages I to III cervical cancer (Perez et al, 1999). In a series of 2096 patients undergoing therapy for cervical cancer, there was an overall genital fistula rate of 1.8%, including rectovaginal fistulae. All patients diagnosed with fistula had received radiation therapy, and the median interval from completion of radiation to presentation of VVF was 8.7 months (Emmert and Kohler, 1996). Higher radiation doses seem to correlate with a greater risk for overall morbidity, as well as fistula formation (Perez et al, 1984; Perez et al, 1999). The endarteritis as a result of the radiation therapy may involve the surrounding tissues, limiting reconstructive options. **An important consideration in any fistula following radiation therapy for malignancy is the possibility that the fistula represents a recurrence of the malignancy. Therefore biopsy of fistula tract should be strongly considered prior to considering definitive repair in these patients.**

Intraoperative Risk Factors for Iatrogenic VVF

Clearly, intraoperative injury to the urinary bladder is a primary risk factor for subsequent development of a postoperative VVF. Other risk factors for postoperative VVF formation include prior uterine surgery (cesarean section), endometriosis, infection, diabetes, arteriosclerosis, pelvic inflammatory disease, and prior radiation therapy (Blandy et al, 1991; Likic et al, 2008). In a large series of VVF, Tancer and colleagues (1992) described several factors that increased the risk for VVF following hysterectomy, including prior uterine operation (especially cesarean section), endometriosis, recent cold-knife cervical conization, and prior radiation therapy. Nevertheless, almost 30% of the patients in this series had no identifiable risk factor. **The operative approach to hysterectomy is an important factor, because bladder injuries are at least three times more common during abdominal hysterectomy compared with vaginal hysterectomy.** Intraoperative recognition and repair of bladder injury is paramount in prevention of VVF; however, despite intraoperative repair, VVF may still result in a substantial number of patients. In 1969, Hutch emphasized five factors in the prevention of VVF during gynecologic surgery: (1) immediate detection of bladder injury using vital dyes if necessary; (2) watertight closure of the bladder; (3) satisfactory extravesical drain placement; (4) avoidance of a vaginal incision, if possible, following recognition of the bladder injury; and (5) prolonged, uninterrupted postoperative bladder drainage (Hutch and Noll, 1970).

Clinical Features

Evaluation and Diagnosis. VVF must be distinguished from urinary incontinence due to other causes, including stress (urethral) incontinence, urge (bladder) incontinence, and overflow incontinence.

Presentation. **The most common complaint in patients with VVF is constant urinary drainage per vagina.** The amount of urinary leakage can vary considerably from patient to patient and may be proportional to the size of the fistula tract. Patients may void a variable amount, depending on the size of the fistula and the volume of urinary leakage. For example, when a large VVF is present, patients may not void at all and simply have continuous leakage of urine into the vagina. Small, pinpoint fistulae may present with intermittent wetness, which is positional in nature. In the supine position, when sleeping, the amount of leakage reported by the patient may be minimal, but upon rising to a seated or standing position, the amount of leakage may increase precipitously. Patients may also complain of recurrent cystitis, perineal skin irritation due to constant wetness, vaginal fungal infections, or rarely pelvic pain. In fact, **pain is an uncommon finding in patients with VVF, unless there is considerable skin irritation or the VVF occurred as a result of radiation therapy.**

VVF following hysterectomy or other surgical procedures may present upon removal of the urethral catheter, or VVF may present 1 to 3 weeks later with urinary drainage per vagina. It may be possible to identify some patients at high risk for VVF in the immediate postoperative period. Kursh and colleagues (1988) noted that patients who developed VVF following hysterectomy more commonly had postoperative ileus, hematuria, bladder irritability, and elevated white blood cell count compared with a cohort of patients who did not develop VVF. Occasionally, posthysterectomy VVF may go undiagnosed for an extended period of time, because postoperative clear or serosanguinous vaginal discharge is often attributed to the surgery itself.

As noted previously, VVF resulting from radiation therapy may not present for months to years following completion of radiation. These tend to be very challenging reconstructive cases due to the size and complexity of the fistula, the poor quality of the surrounding tissues, and the associated voiding dysfunction due to the radiation effects on the urinary bladder.

Physical Examination. **A pelvic exam with a speculum should always be performed in the evaluation of VVF. The bivalved speculum examination usually provides a precise assessment of VVF including the location, size, and number of fistulae.** Vaginoscopy has been suggested as an adjunct measure, in some cases, using a modified endoscope to precisely visualize the fistula tract (Redman, 1990). **Most commonly, VVF following hysterectomy are located along the anterior vaginal wall at the level of the vaginal cuff** (Fig. 77–4). **A visual and manual assessment of inflammation surrounding the fistula is necessary, because it may affect timing of the repair.** Significant inflammation, infection, or induration around the fistula may mitigate against

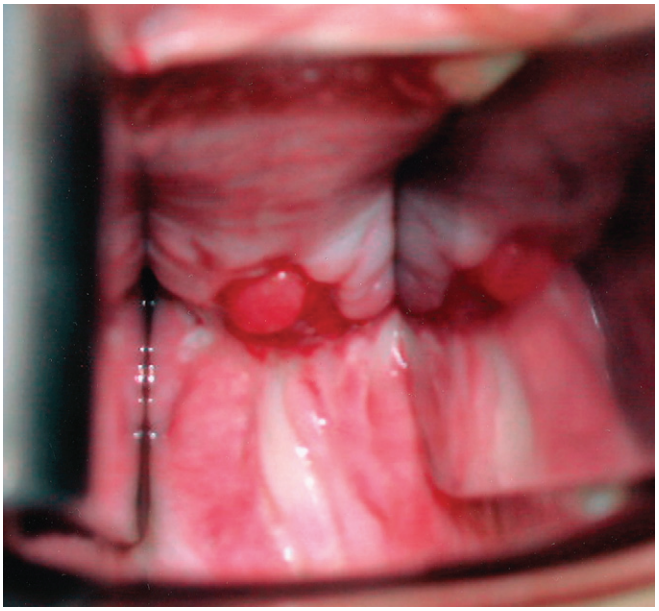


Figure 77–4. Vesicovaginal fistula (VVF) on physical examination. A large VVF is seen at the apex of the vagina after hysterectomy. The VVF in this image is seen as reddish pink bladder mucosa prolapsing into the vagina. Hand-held Heaney right-angled retractors provide lateral retraction in this image.

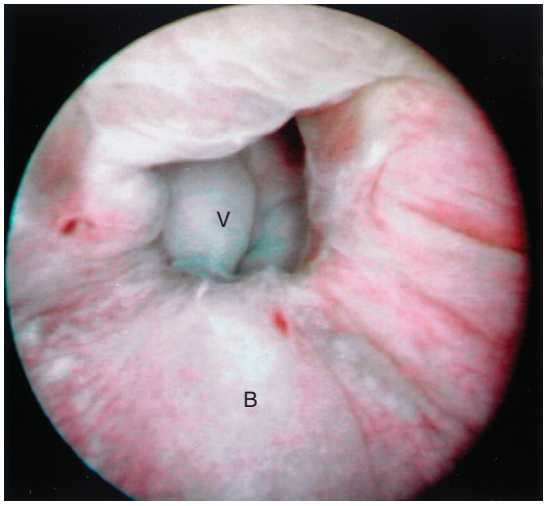


Figure 77–5. Endoscopic view of vesicovaginal fistula (VVF). This is the same patient as in Figure 77–4. The fistula is now seen from the bladder side. This VVF is large enough to see directly into the vagina (V) through the bladder (B).

immediate repair. **Relevant vaginal anatomy, including depth, associated prolapse, atrophy, and introital size are carefully recorded, because these may affect the surgical approach to repair.** Anatomically, fistulae located high in the vagina, at the level of the hysterectomy cuff in a deep narrow vagina, may be best approached by some surgeons abdominally because a vaginal approach in these patients can be challenging. This may be especially relevant in nulliparous females in whom there is usually very limited pelvic floor laxity or vaginal prolapse. Postmenopausal vaginal atrophy may be treated with preoperative topical estrogen replacement, thereby optimizing the health and vascularity of potential reconstructive flaps. Palpation for masses or other pelvic pathology, which may require attention at the time of fistula repair, is also performed. Notation of prior incisions in the perineum, lower abdomen, and thigh is necessary because these tissues may be required for flap reconstruction when definitive repair is undertaken.

The presence of a VVF may be confirmed by instilling a vital blue dye into the bladder per urethra and observing whether vaginal drainage is discolored. Small or occult fistulae may be identified in this fashion (Drutz and Mainprize, 1988). A colored solution, such as methylene blue or indigo carmine, is mixed into solution and infused into the bladder. The vagina may be packed with gauze or directly inspected for blue-tinged leakage. If blue-tinged leakage is not apparent and the diagnosis of VVF is in doubt, the sensitivity of this test may be improved by placing a vaginal packing and ambulating the patient for a short period of time. Staining at the introital (distal) end of the packing suggests urinary incontinence or a urethrovaginal fistula, whereas proximal staining suggests a VVF. **If the vaginal packing remains dye-free with this maneuver, then the possibility of a ureterovaginal fistula can be investigated with the use of a clean vaginal packing, intravenous indigo carmine (or other vital dye), and a repeat pad test. Blue staining at the proximal end of the pad, following this maneuver, suggests the presence of a ureterovaginal fistula.**

A double dye or tampon test may confirm the diagnosis of urinary fistula, as well as suggest the possibility of an associated ureterovaginal or urethrovaginal fistula (Moir, 1973; Raghavaiah, 1974). In one variation of the double dye test, a tampon is placed per vagina. Oral phenazopyridine is administered, and vital blue dye is instilled into the bladder. If the tampon is discolored yellow-orange at the top, it is suggestive of a ureterovaginal fistula. Blue discoloration in the midportion of the tampon suggests VVF, whereas blue staining at the bottom suggests a urethrovaginal fistula.

Clear vaginal discharge following hysterectomy does not invariably represent a urinary fistula or incontinence. Other than normal vaginal secretions, less common causes include a peritoneovaginal fistula (Ginsberg, 1998), lymphatic fistula (Lau and Wong, 1994), vaginitis, and fallopian tube fluid (Leach, 1987). Incontinence following caesarian section, in which a VVF has been excluded, may suggest the possibility of a ureterovaginal or vesicouterine fistula.

Cystoscopy. **An endoscopic examination should be performed in patients with a suspicion of VVF** (Fig. 77–5). Immature fistulae may appear as an area of localized bullous edema without distinct ostia. Mature fistulae may have smooth margins with variably sized ostia. In some cases, multiple pits and cavities along an area of the traumatized posterior bladder wall, in the setting of a small VVF, may make it difficult to identify the exact fistula tract. In these cases, a guidewire or ureteral catheter may be placed through the working channel of the cystoscope and into the fistula tract (Fig. 77–6). Visualization of the wire in the vagina confirms the exact location of the VVF on both the bladder and genital sides. Cystourethroscopy can confirm the presence of the fistula, but also may assess the size of the tract, the presence of collateral fistulae, and the location of the ureteral orifices in relation to the fistula. Small fistulae, usually less than 3 to 4 mm in diameter may be amenable to simple fulguration, which can be performed at the time of cystoscopy (see later discussion) (Stovsky et al, 1994). **Importantly, in the setting of a prior history of pelvic malignancy, a biopsy of the fistula is often done to evaluate for the possibility of a recurrent malignancy.**

Fistulae located near or at the ureteral orifice may require ureteral reimplantation at the time of VVF repair. This type of requirement would usually mitigate against a completely transvaginal attempt at repair.

Imaging. **A cystogram and/or voiding cystourethrogram (VCUG) and an upper tract study should be performed in patients being evaluated for a VVF. The cystogram may objectively determine the presence and location of the fistula.** Upon filling of the bladder, contrast often begins to opacify the vagina, almost immediately confirming the presence of a VVF. VVF are often best seen in the lateral projection (Fig. 77–7) in which the bladder and vagina are not superimposed. Often, the actual VVF tract may be visible in the lateral projection (Fig. 77–8). **However, voiding images may be necessary in some patients with small fistulae, to demonstrate the VVF.** The slight increase in intravesical pressure that accompanies micturition is usually adequate to demonstrate even very small fistulae. **Importantly, a cystogram that fails to demonstrate a suspected VVF, but lacks voiding images or postvoid images, should be considered nondiagnostic.** During voiding, care should be taken to exclude vaginal voiding or reflux of contrast from the introital region cephalad into the vagina, which would produce a falsely positive image. An involuntary bladder contraction can be provoked with rapid filling during cystography, and if the intravesical pressure rises sufficiently, this may also be sufficient to demonstrate a VVF when the filling images of the cystogram failed to demonstrate it. In some instances, a cystogram can also make an assessment of bladder capacity (important in the setting of prior radiotherapy), cystocele, bladder neck competence, and vesicoureteral reflux, any of which may have an impact on operative repair.

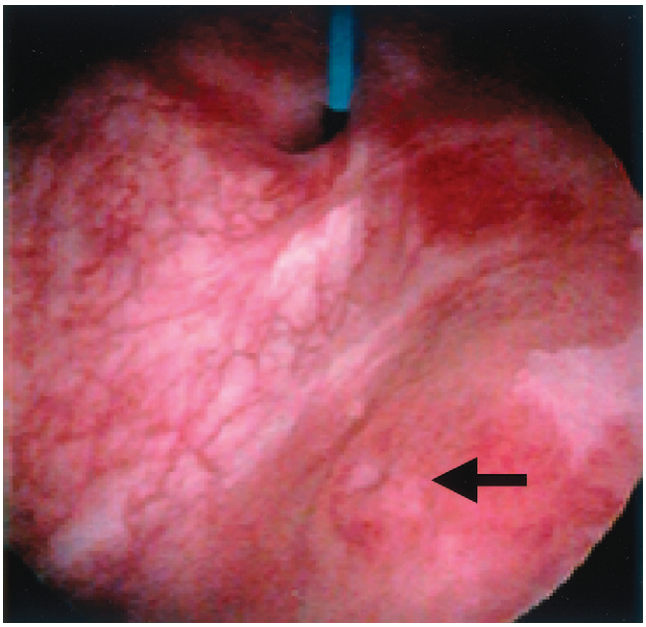


Figure 77–6. Confirmation of a vesicovaginal fistula (VVF). A 4-Fr ureteral catheter traverses the fistula tract in this endoscopic photograph. The VVF is high on the posterior bladder wall, the typical location for a post-hysterectomy VVF. The right ureter is seen *(arrow)*.

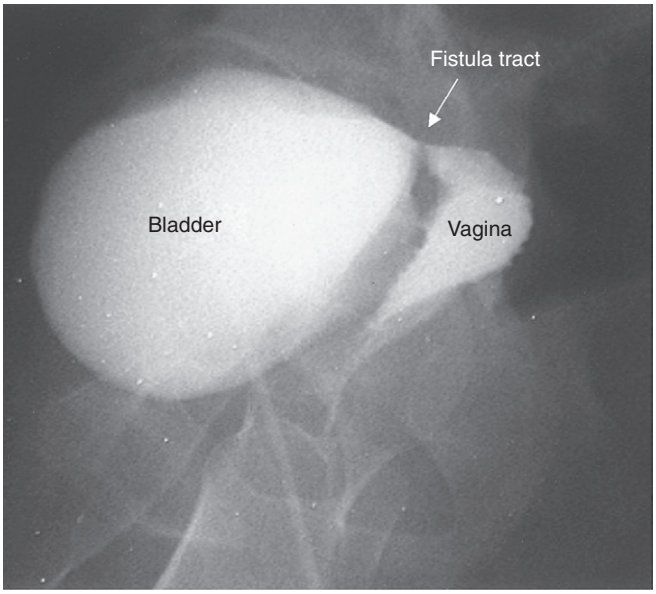


Figure 77–8. Lateral image during cystography demonstrates the vesicovaginal fistula tract.

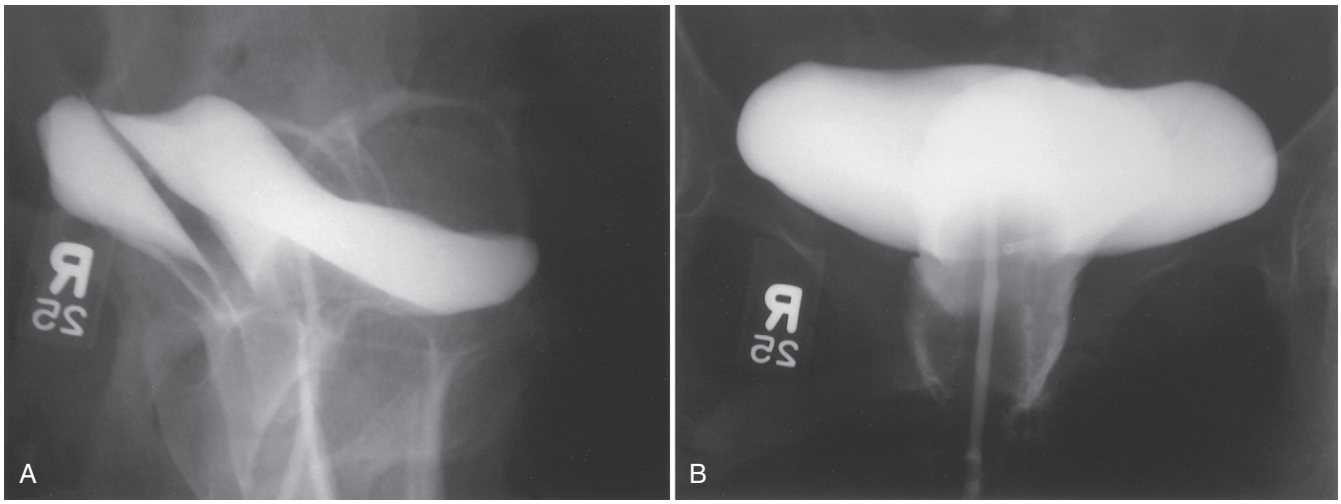


Figure 77–7. Cystogram demonstrating a vesicovaginal fistula (VVF). **A,** Lateral image demonstrates a posthysterectomy VVF. **B,** Anteroposterior view. The contrast agent is seen opacifying and outlining the vagina superimposed on the bladder.

Up to 12% of postsurgical VVF have an associated ureteral injury or ureterovaginal fistula (Goodwin and Scardino, 1980); **thus, upper urinary tract evaluation is important.** Intravenous urography (IVU) (Gerber and Schoenberg, 1993), or, more recently, computed tomography (CT) urography is usually sufficient for this purpose. In one series of 216 consecutive patients with VVF due to obstructed labor, almost 50% of patients were diagnosed with an upper tract abnormality on IVU; caliectasis was found in 71% of those affected; however, almost 10% were found to have a nonfunctioning renal unit (Lagundoye et al, 1976). If there is a suspicion for a ureterovaginal fistula, or if the distal ureter is not well seen IVU, retrograde pyelography may be performed (Blandy et al, 1991) (Fig. 77–9).

In addition to contrast cystography and VCUG, CT, ultrasonography, and magnetic resonance imaging (MRI) have been used in the evaluation of VVF (Kuhlman and Fishman, 1990; Outwater and Schiebler, 1993; Yang et al, 1994). Delayed CT visualization of contrast within the vagina is considered highly suspicious for VVF in the majority of cases (Kuhlman and Fishman, 1990) (Fig. 77–10). In cases of suspected VVF, CT should be performed with only intravenous contrast, or, alternatively, a CT cystogram can be performed to isolate the bladder. A vaginal tampon placed per vagina during IVU or CT scan may improve the sensitivity for finding small or occult VVF in patients with an otherwise negative evaluation (Wesolowski and Meaney, 1977). **Cross-sectional imaging may also be helpful in assessing for recurrent malignant disease in those with such a history.**

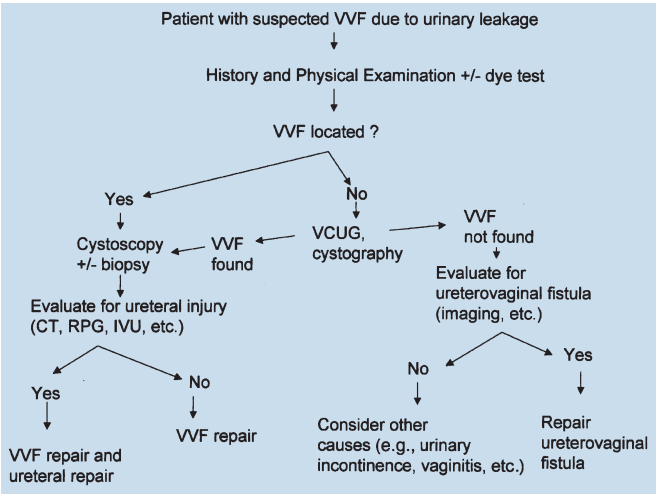


Figure 77–9. Algorithm for the diagnosis of vesicovaginal fistula (VVF). CT, computed tomography; IVU, intravenous urography; RPG, retrograde pyelography; VCUG, voiding cystourethrography.

Other Studies. **Appropriate urine studies including culture, and cytology when indicated, are performed.** When infection is detected, appropriate antibiotic coverage is initiated. Urodynamics, including videourodynamics, are generally not necessary in the evaluation of routine posthysterectomy VVF. However, in the setting of a prior history of radiation, radical pelvic surgery (e.g, radical hysterectomy), or in those with preexisting neurogenic vesicourethral dysfunction, a urodynamic evaluation can be used to evaluate for significant detrusor dysfunction, including impaired bladder compliance. In patients with a history of significant symptoms of voiding dysfunction and incontinence preceding the VVF, urodynamic evaluation may help to define these symptoms prior to repair of the VVF (Hilton, 1998), an important element in preoperative counseling regarding potential outcomes and preparation for the optimal operative plan.

Treatment

Conservative and Minimally Invasive Therapy. **The goal of treatment of VVF is the rapid cessation of urinary leakage with return of normal and complete urinary and genital function.** As noted previously, the physical and psychologic impact of constant urinary incontinence from a VVF can be overwhelming due to the burden of continual wetness, undesirable odor, vaginal and bladder infections and their related discomfort. Bladder catheterization may temporize some of these effects until definitive repair is undertaken but often will not completely eradicate leakage, especially in those with large fistula

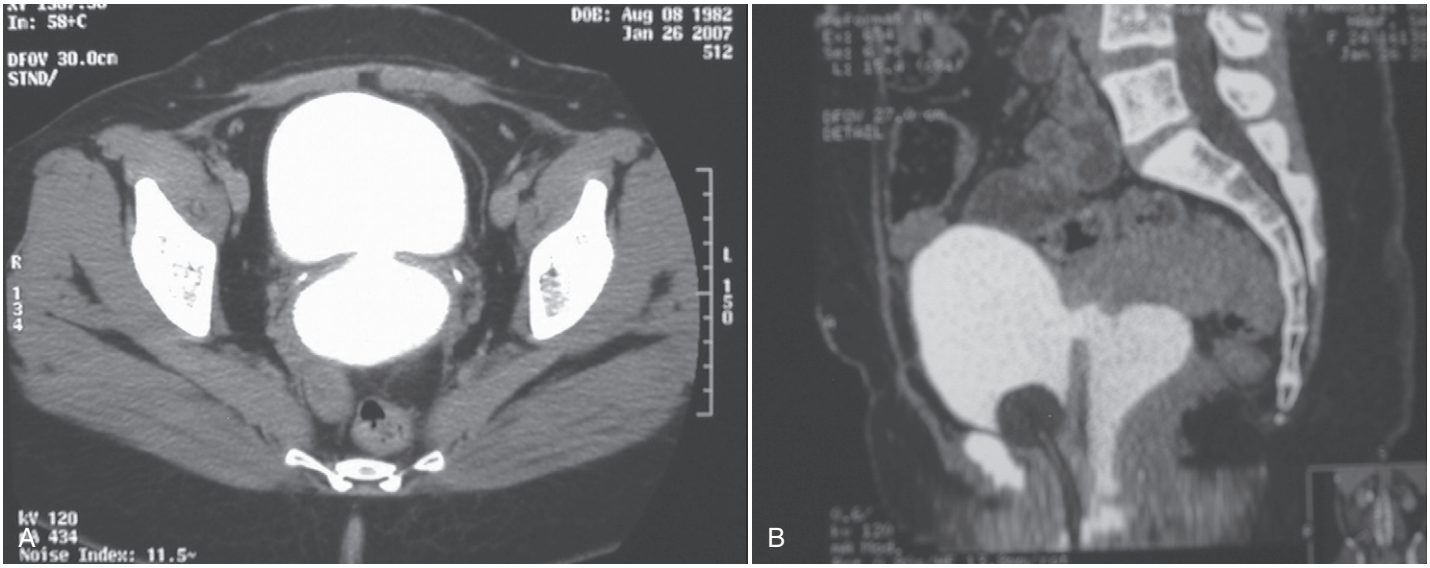


Figure 77–10. CT scan of vesicovaginal fistula (VVF). **A,** After intravenous administration of the contrast agent, there is high-density material in both the bladder and vagina consistent with a VVF. The fistulous connection between the bladder anteriorly and the vagina posteriorly. **B,** Sagittal CT reconstruction demonstrating VVF.

or those with significant detrusor overactivity. Furthermore, catheterization may provoke additional irritation and pelvic pain and is a constant reminder to the patient of an iatrogenic insult.

Regardless of the aforementioned limitations and drawbacks, a trial of indwelling catheterization and anticholinergic medication for at least 2 to 3 weeks may be warranted in selected patients with newly diagnosed VVF, because spontaneous healing may result (Davits and Miranda, 1991). This is especially applicable in those patients in whom the initial placement of the catheter immediately resolves the vaginal leakage. Tancer (1992) reported three patients with immature VVF tracts who were successfully treated expectantly with indwelling catheterization. All three patients were seen within 3 weeks of the initial surgery and were found to have non-epithelialized VVF tracts on physical examination. **Fistulous tracts that remain open 3 or more weeks after adequate Foley drainage are unlikely to resolve without further intervention, especially those which appear completely epithelialized on examination.**

Patients with small epithelialized fistulae may benefit from a minimally invasive treatment involving disruption of the epithelial layer of the fistula tract (Fig. 77–11). **Catheterization may be combined with minimally invasive electrocoagulation of the fistula tract.** In this approach, a small cautery electrode is passed into the fistula tract endoscopically as far as possible. The electrode is slowly withdrawn from the tract with the electrode set on coagulation. The edges of the fistula tract should blanche. Care is taken not to overcoagulate, because this can cause widespread tissue necrosis, sloughing, and enlargement of the fistula. This approach was advocated by O'Conor, as far back as 1938, for small, highly-situated fistulae (O'Conor and Sokol, 1951). Stovsky and colleagues (1994) demonstrated success with endoscopic electrocoagulation and bladder drainage in 11 of 15 cases. All patients had VVF less than 3.5 mm in diameter and were drained for a minimum of 2 weeks post-treatment. It was suggested that disruption of the epithelial component of the VVF tract with subsequent fibrosis, scarring, and closure of the tract is the mechanism by which electrocoagulation exerted its favorable effects. Falk and Orkin (1957) successfully treated eight patients with electrocoagulation and catheter drainage for 10 days. All successfully treated patients had VVF less than 3 mm in diameter; two patients with 6-mm VVF failed this approach. **Importantly, in patients with a thin vesicovaginal septum, large VVF, a nonoblique fistula tract, or those with significant inflammation around the fistula tract, fulguration risks failure and the possibility of enlarging the size of the fistula.** This approach may also devitalize adjacent tissues, thereby compromising their future utility as flaps. Fibrin sealant has been used as an adjunctive measure to treat VVF (Pettersson et al, 1979; Hedelin et al, 1982). The fibrin sealant may be injected directly into the fistula tract following fulguration as described above. The bladder is then drained for several weeks. Presumably, the gel-like nature of the fibrin sealant plugs the hole until tissue ingrowth occurs from the edges of the fistula. Fibrin sealant has been used successfully in combination with (Morita and Tokue, 1999) and without (Evans et al, 2003b) bovine collagen as an additional "plug." **In general, these conservative measures are useful for small, oblique fistulae (usually less than 2 to 3 mm in diameter), in patients who are agreeable to this course of therapy.**

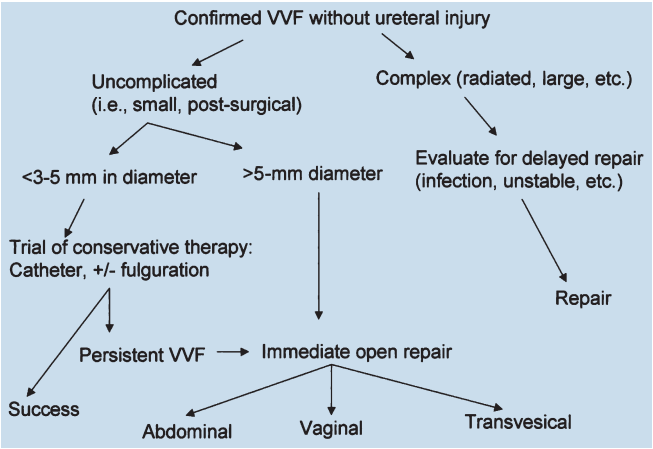


Figure 77–11. Algorithm for management of vesicovaginal fistula (VVF).

Case reports of other minimally invasive VVF repair techniques have been reported, including laser tissue welding with a Nd-YAG laser (Dogra and Nabi, 2001), as well as transurethral endoscopic suturing (Okamura et al, 1997; McKay, 2001).

Surgical Repair. It has been stated that the best opportunity to achieve successful repair of VVF is with the initial operation (Weed, 1978; Elkins 1994). Previous failed attempts at repair produce scarring, anatomical distortion, and may compromise potential reconstructive flaps. Therefore careful preoperative planning is essential to maximize the chances for a successful result. **There is no "best" approach for all patients with VVF.**

Timing: Immediate versus Delayed Repair. The timing of VVF repair is somewhat controversial. **Repair of VVF should be as expeditious as possible to minimize patient suffering; however, optimal timing for repair should allow consideration of certain medical and surgical factors as well.** It is generally accepted that VVF resulting from obstructed labor should be associated with a 3- to 6-month delay prior to definitive repair (Wein et al, 1980a, Arrowsmith, 1994; Waaldijk, 1994) to allow maximum demarcation of ischemic tissue and resolution of the associated edema and inflammatory reaction. Longer periods of time, up to 6 to 12 months, have been advocated for radiation-induced fistulae (Wein et al, 1980a), which are often associated with severe obliterative endarteritis and reduced tissue vascularity.

In the classical teaching of VVF, a minimal waiting period of several months is suggested—from the inciting event prior to the definitive repair attempt—to allow reduced tissue edema and inflammation, and optimal pliability of the tissues (Persky and Rabin 1973; Lawson, 1978; O'Conor, 1980; Wein et al, 1980a). O'Conor recommended a waiting period of 3 to 6 months for suprapubic VVF repairs (O'Conor et al, 1973). In this setting, reduced inflammation and edema permit easier identification of tissue planes (and therefore flap development), less bleeding, and less tension on the reapproximated suture lines. **However, over the ensuing decades, the enthusiasm for delayed management has waned and, in general, uncomplicated post-gynecological urinary fistulae may be repaired as soon as they are identified and confirmed, thereby minimizing patient discomfort and anguish** (Collins et al, 1971; Persky et al, 1979; Fourie, 1983; Badenoch et al, 1987a; Cruikshank, 1988; Wang and Hadley 1990; Blandy et al, 1991; Blaivas et al, 1995; Kostakopoulos et al, 1998b). This is especially true when they occur as a result of clean surgical trauma (Wang and Hadley, 1990). Nondelayed closure has also been applied to

obstetric fistulae with good results (Waaldijk, 1994; Waaldijk, 2004). Nevertheless, in some cases, the timing of a VVF repair is best tailored to the individual patient (Blaivas et al, 1995). Raz and colleagues (1993) suggested that uncomplicated VVF following abdominal hysterectomy could and should be repaired as expediently as possible transvaginally; however, a 2- to 3-month waiting period may be warranted for some VVF following vaginal hysterectomy. Conversely, if an abdominal approach is being considered following a particularly difficult or complicated abdominal surgery that resulted in the VVF (i.e, complicated by abscess, urinoma), then a delay may be warranted to allow resolution of active inflammation. Another potential reason to delay repair is to treat ongoing infection or inflammation at the level of the vaginal cuff. Periodic reexamination of the vaginal tissues can be performed every 1 to 2 weeks and definitive repair scheduled when suitable pliability is noted (Carr and Webster, 1996).

A vaginal approach can be attempted as soon as 2 to 3 weeks after the initial injury, if conservative therapy fails (i.e., the patient remains wet when a Foley catheter is in place to provide adequate drainage of the bladder) and the patient is in good general health. The vaginal tissues are usually relatively undisturbed from the prior causative surgery, especially if the surgery was transabdominal. Wide healthy vaginal flaps can usually be obtained. In the rare circumstance when a VVF presents within the first 24 to 48 hours postoperatively, an immediate repair can be attempted (Margolis and Mercer, 1994); however, it is possible that these VVF, especially if small in diameter, may heal spontaneously with catheterization over the course of several weeks. It is well documented that similar outcomes can be achieved with early versus delayed abdominal and vaginal repair (Collins et al, 1960; Persky et al, 1979; Zimmern et al, 1985; Badenoch et al, 1987a; Wang and Hadley, 1990; Blandy et al, 1991) with success rates in excess of 90% for uncomplicated VVF.

Approach: Abdominal versus Vaginal. Vesicovaginal fistulae may be repaired through a transvaginal or transabdominal (transvesical) approach. Each approach has merits depending on the particular circumstances of the fistula, and excellent outcomes can be expected with both approaches (Table 77–4). **Although factors such as size, location, and the need for adjunctive procedures often influence the choice of approach, the most important factor is the experience of the operating surgeon. Thus there is no preferred approach for all fistulae, and the "optimal" approach to the uncomplicated postgynecological VVF is usually the one that is most successful in the individual surgeon's hands** (Gerber and Schoenberg, 1993; Akman et al, 1999). Although it has been a long-held belief that gynecologists prefer to fix VVF transvaginally, and urologists prefer a transabdominal approach due to their respective training and experience, (Edwards, 1982; Gerber and Schoenberg, 1993), this difference is becoming increasingly blurred as urologists gain more experience and comfort operating transvaginally for a variety of disparate indications.

The vast majority of VVF in the industrialized world are amenable to a transvaginal repair (Turner-Warwick, 1972; Margolis and Mercer, 1994). **The relative advantages of a transvaginal approach** compared with an abdominal approach are outlined in Table 77–5 and include **shorter operative times, briefer hospital stay, and less blood loss** (Goodwin and Scardino, 1979). **The principal disadvantages of the transvaginal approach include the relative lack of familiarity of the vaginal cuff anatomy to many urologists; the potential for vaginal shortening, especially with the Latzko approach; and, finally, the difficulty in**

Table 77–4.

Abdominal versus Transvaginal Repair of Vesicovaginal Fistula

	ABDOMINAL	TRANSVAGINAL
Incision	Abdominal incision	Vaginal incision(s)
Timing of repair (elapsed time from fistula creation)	Often delayed 3-6 months	can be done immediately in the absence of infection or other complications
Exposure	Fistula located low on the trigone or near the bladder neck may be difficult to expose transabdominally	Fistula located high at the vaginal cuff may be difficult to expose transvaginally
Location of ureters relative to fistula tract	Fistula located near ureteral orifice may necessitate reimplantation	Reimplantation may not be necessary even if fistula tract located near ureteral orifice
Sexual function	No change in vaginal depth	Risk of vaginal shortening (e.g., Latzko technique)
Use of adjunctive flaps	Omentum, peritoneal flap, rectus abdominus flap	Labial fat pad (Martius fat pad), peritoneal flap, gluteal skin or gracilis myocutaneous flap
Relative indications	Large fistulae, location high in a deep narrow vagina, radiation fistulae, failed transvaginal approach, small-capacity bladder requiring augmentation, need for ureteral reimplantation, inability to place patient in the lithotomy position	Uncomplicated fistulae, low fistulae

Table 77–5.

Potential Advantages of a Transvaginal Approach for Posthysterectomy Vesicovaginal Fistula

Avoidance of a laparotomy and its associated morbidity
Short operative time
Brief inpatient stay
Quick convalescence and return to normal activities
Minimal postoperative pain
Minimal blood loss
Absence of the need for wide opening or bivalving of the bladder
Approach is not compromised by multiple prior abdominal and/or pelvic surgeries
Concomitant anti-incontinence or prolapse surgery may be performed
Local interpositional flaps are adjacent (e.g., Martius, peritoneal)
A three- or four-layer closure is possible
If failure occurs, a subsequent abdominal approach is not compromised

exposing high or retracted fistulae located near the vaginal cuff, especially in deep, narrow vaginas, or in those without any apical prolapse, such as that found in nulliparous females (see Fig. 77–2). Patients who are unable to get into the high-lithotomy position due to musculoskeletal conditions are not candidates for a transvaginal approach.

The abdominal approach to VVF repair is advantageous in several circumstances. If the VVF is associated with **other intra-abdominal pathology requiring repair—** including an associated ureteral injury (i.e., ureterovaginal fistula), or a complex fistula, including those involving another intra-abdominal organ—then a transabdominal approach is indicated to address the problems simultaneously. If the VVF is located adjacent to the ureteral orifice, some authors have suggested that this is an indication for an abdominal approach (Carr and Webster, 1996), whereas others have not so advocated (Dupont and Raz, 1996). In patients with **a small capacity or poorly compliant bladder (often secondary to radiation) requiring augmentation cystoplasty,** an abdominal approach is indicated, because both procedures can be performed using the same incision. **Complicated fistulae,** including those associated with multiple prior failed attempts at repair (Kristensen and Lose, 1994) or those which are quite large (>5 cm), **might be best approached abdominally as well.** Nevertheless, a prior failed attempt at repair is not necessarily a contraindication to a transvaginal approach because excellent results can be achieved in this setting (Eilber et al, 2003).

Combined transabdominal-transvaginal approaches to VVF have been described (Clark and Holland, 1975; Taylor et al, 1980; Henriksson et al, 1982a). This approach may be applicable selectively in the setting of large, complex, or recurrent VVF after prior attempts at repair.

Handling of Fistula Tract: Excision versus No Excision. A long-held tenet for successful fistula closure, dating back to Sims' original description in 1852, involves complete excision of the fistulous scar tissue and tract (Fearl and Keizur, 1969; Persky et al, 1979; Wein et al, 1980a; Fourie, 1983). This approach ensures clean, well-vascularized viable edges to be approximated for the initial layer of repair. Simple excision of the scar in an inverted "funnel" shape with careful reapproximation of the defective edges has been shown to be an effective repair of VVF (Iselin et al, 1998; Flynn et al, 2004). **However, excision of the fistula tract itself is not always necessary and may even compromise the repair in some patients** (Zimmern et al, 1985; Cruikshank, 1988; Tancer, 1992; Raz et al, 1993; Margolis and Mercer, 1994). There are several potential disadvantages of excision of the fistula tract. Firstly, this creates a larger soft tissue defect to be repaired. Excision of the fibrous tract may lead to bleeding, which, if cautery is used, may result in tissue necrosis and impede healing (Eilber et al, 2003). If the VVF is adjacent to the ureter, then excision of the tract may mandate reimplantation of the ureter. Alternatively, if the tract is left in situ, the ureter may be catheterized for the repair and then left undisturbed during a transvaginal operation, obviating the need for reimplantation. In addition, in chronic fistulae, a strong fibrous ring forms outside the epithelialized tract, which maintains some strength through the repair if this layer is incorporated into the closure. This can be an important consideration in those patients with significant detrusor overactivity postoperatively from either the repair itself or the indwelling drainage catheters.

Use of Adjuvant Flaps or Grafts: Type and Application. Prior to embarking on surgical repair, the surgeon should be familiar with a variety of adjuvant flaps and grafts that allow for the interposition of healthy tissue during VVF repair. It is often not possible to predict which patients will require these procedures ahead of time. **The indications for tissue interposition are not well defined, but these measures are most commonly used in the setting of radiated tissues, obstetrical fistulae, failed prior repairs, large fistulae, and those with tenuous repairs.** The various types of flaps will be discussed in more detail later in the chapter.

Other Considerations. **Preoperative estrogen supplementation may be beneficial in the postmenopausal patient with vaginal atrophy and VVF** (Massee et al, 1964). **There exists little data in the literature, beyond expert opinion, to support their use. However, topical estrogen preparations may improve vascularity** (Margolis and Mercer, 1994) **and local tissue quality** (Carr and Webster, 1996). Therefore a trial of topical estrogens in individuals with postmenopausal vaginal atrophy and a posthysterectomy VVF may be warranted provided that there are no contraindications to their use.

Perioperative intravenous antibiotics are often administered, although their utility in the posthysterectomy VVF repair is questionable in the absence of infection. Whether antibiotics should be administered prophylactically prior to surgical repair is controversial, but at least one study suggests that preoperative antibiotics do not improve outcomes when administered prior to the repair of obstetric fistula (Tomlinson and Thornton, 1998). Treatment of existing infection based on preoperative urine culture is potentially beneficial in preventing bacteremia during surgery. However, prolonged use of broad-spectrum antibiotics postoperatively following repair may result in bacterial resistance and possibly fungal vaginal infections that may compromise suture lines.

Sexual activity should be documented preoperatively. Patients should be specifically queried regarding sexual function and dyspareunia occurring prior to the onset of the event that resulted in the fistula. Although this data is subject to recall bias**, it may play an important role in the choice of surgical approach, as well as having medicolegal implications postoperatively.** Some types of vaginal procedures for the repair of VVF, including the Latzko partial colpocleisis, may result in vaginal shortening and postoperative dyspareunia. Preoperative documentation of this preexisting condition can be invaluable. Furthermore, adjuvant procedures that may alter vaginal appearance or function, such as the harvesting of a Martius fibrofatty labial flap or an episiotomy, should be carefully discussed with the patient in advance, especially regarding sexual function.

Finally, postoperative drainage following VVF repair can be maintained by single or dual catheters. Some authors suggest that a urethral catheter, alone, provides satisfactory drainage (Collins et al, 1960; Fearl and Keizur, 1968; Tancer, 1980; Leng et al, 1998). Others advocate a suprapubic catheter (Blaivas et al, 1995; Carr and Webster, 1996; Iselin et al, 1998), alone, to minimize bladder spasms and trauma to the surgical repair. Most commonly, both urethral and suprapubic drainage catheters (O'Conor et al, 1973; Wein et al, 1980a; Dupont and Raz, 1996; Eilber et al, 2003) are left postoperatively. The disadvantage to single catheter drainage is principally that the catheter will malfunction, clog, or kink, resulting in bladder filling, eventual overdistention, and disruption of the suture line.

Preoperative Counseling and Indications for Surgery. Surgical repair of a VVF is indicated following confirmation of the diagnosis. As noted previously, a trial of conservative management may be warranted in selected cases, especially in those with a newly diagnosed, small, uncomplicated fistula in which the vaginal leakage significantly improves or resolves with catheter drainage.

When conservative measures fail or, if after adequate counseling, the patient requests repair prior to a trial of conservative management, surgical treatment is pursued. Prior to surgery patients should be counseled that most VVF in the industrialized world are repaired on the first attempt in greater than 90% of cases; however, prolonged postoperative urinary catheter drainage is necessary following surgery. Postoperative urinary urgency and frequency are common for a period of time after removal of the catheter but are usually self limited. Finally, the patient should be aware that it may be necessary to alter the surgical plan intraoperatively due to a variety of factors encountered during the operation, and that interpositional flaps or grafts may be used.

Vaginal Techniques. Common vaginal approaches to the repair of uncomplicated VVF are described. The merits of the vaginal approach are reviewed in Tables 77–4 and 77–5.

Vaginal Flap or Flap-Splitting Technique. This approach popularized by Raz and colleagues (Zimmern et al, 1985; Raz et al, 1993; Stothers et al, 1996; Eilber et al, 2003) results in a three-layer closure without the use of an adjuvant flap, and a four-layer closure if a flap is used (Fig. 77–12). It can be performed as an outpatient procedure and is applicable to most simple, uncomplicated VVF.

Step 1 (positioning, preparation, and retraction): The patient is placed in the dorsal lithotomy position, a rectal packing is placed (to aid in identification of the rectum) and the lower abdomen

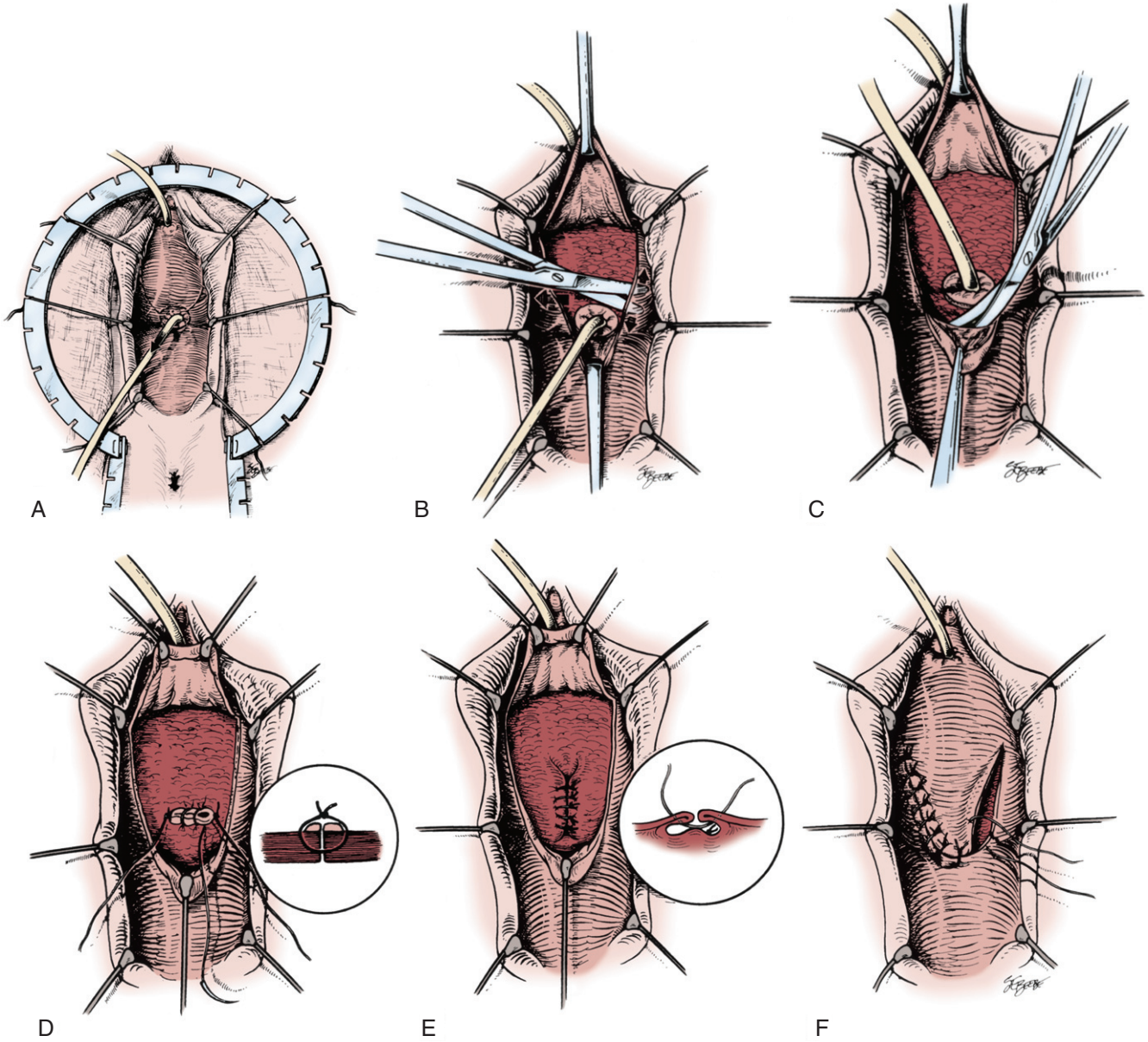


Figure 77–12. Technique of vaginal repair of a posthysterectomy vesicovaginal fistula (VVF). **A,** Retraction including ring retractor, vaginal speculum, and Foley catheter in the VVF tract. A Foley catheter is seen in the VVF tract providing traction on the vaginal cuff. **B,** Mobilization of anterior vaginal wall flap. Lateral flaps are developed as well, thereby isolating the VVF tract. **C,** Mobilization of posterior vaginal wall flap. **D,** Initial layer of closure is performed without excising the edges of the fistula tract. **E,** The perivesical fascia is closed with Lembert-type sutures. This line of closure is perpendicular to the initial suture line. **F,** The vaginal wall flaps are advanced to avoid overlapping suture lines. (From Ganabathi K, Sirls L, Zimmern P, Leach GE. Vesicovaginal fistulae: reconstructive techniques. In: McAninch J, editor. Traumatic and reconstructive urology. Philadelphia: WB Saunders; 1996. p. 317.)

and perineum is prepared with a standard surgical preparation solution. Appropriate exposure is maintained with use of a vaginal weighted speculum, silk labial retraction sutures, and a ring retractor with hooks. A suprapubic tube is placed, cystoscopy with reassessment of the VVF location is performed, and ureteral catheters are placed if the fistula tract is adjacent to or involves the ureteral orifices. A posterolateral episiotomy may be performed to improve exposure in patients with a narrow introitus. A urethral catheter is placed in addition to the suprapubic tube maximizing postoperative urinary drainage (Fig. 77–13A). **Any concomitant anti-incontinence or other vaginal surgery that is to be done simultaneous with VVF repair should be done prior to reconstruction to avoid disturbing the repair once completed.**

Step 2 (incision): The fistula tract is cannulated with a small Foley catheter (10 to 12 Fr) and, after inflation of the balloon, gentle downward traction is placed on the Foley catheter, pulling the VVF towards the introitus. Occasionally, a small VVF requires

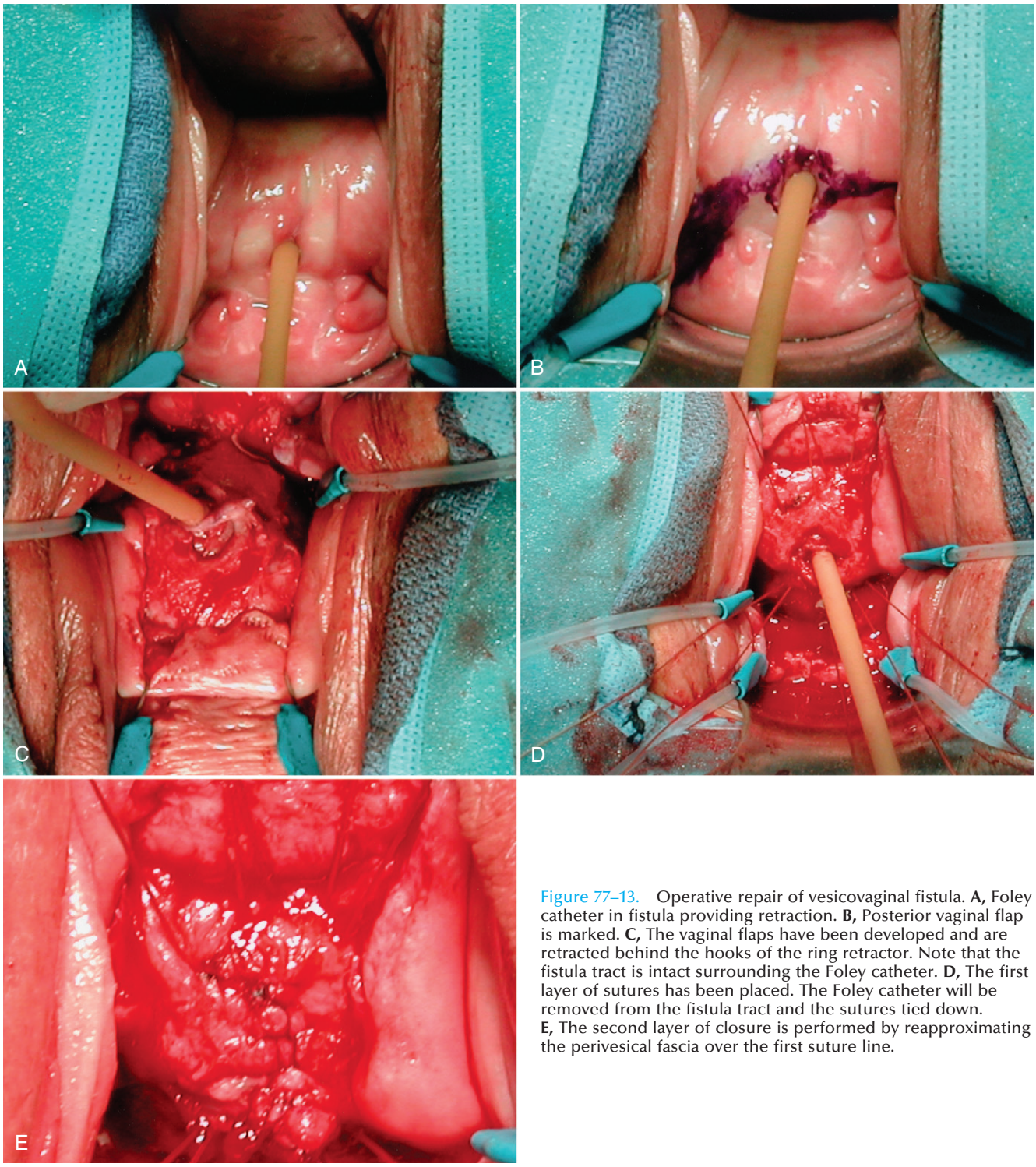


Figure 77–13. Operative repair of vesicovaginal fistula. **A,** Foley catheter in fistula providing retraction. **B,** Posterior vaginal flap is marked. **C,** The vaginal flaps have been developed and are retracted behind the hooks of the ring retractor. Note that the fistula tract is intact surrounding the Foley catheter. **D,** The first layer of sutures has been placed. The Foley catheter will be removed from the fistula tract and the sutures tied down. **E,** The second layer of closure is performed by reapproximating the perivesical fascia over the first suture line.

dilation with metal sounds to place the Foley catheter. To facilitate dilation of the fistula tract in these cases, a guidewire may be placed through the fistula tract endoscopically and sequential dilation performed using Goodwin sounds. The gentle traction on the VVF provided by the Foley catheter greatly enhances exposure (see Fig. 77–8). The vaginal flaps are marked (Fig. 77–13B). Saline is then injected into the anterior vaginal wall surrounding the fistula tract and along the lines of the vaginal flaps. The fistula tract is carefully circumscribed. An inverted J-shaped or U-shaped incision that circumscribes the fistula tract is made with the limbs of the J or U extending to the apex of the vagina. The circumscribed fistula is incorporated into the curved portion of the incision. The nature of this incision allows creation of a vaginal wall flap that can be advanced and rotated over the fistula repair. This helps avoid vaginal shortening and overlapping of suture lines during reconstruction. However, some surgeons have recommended that the long end of the incision be extended along the anterior vaginal wall toward the introitus (Wang and Hadley, 1990).

Step 3 (creation of vaginal wall flaps): The vaginal wall flaps are created by dissecting in a proximal, distal, and lateral direction away from the fistula tract (Fig. 77–13C). Initially, dissection may be difficult due to scarring from the insult that resulted in the VVF. It is important to remain in the correct surgical plane while developing the vaginal wall flaps, so not to compromise their vascularity. Adequate mobilization of the vaginal wall distal to the VVF is especially important, because it will be necessary to advance the proximal vaginal wall flap beyond the fistula as the final layer of closure. Each flap is mobilized 2 to 4 cm from the fistula tract, exposing the underlying perivesical fascia. The ring of vaginal wall tissue, where the initial incision circumscribed the fistula opening, is left intact; thus, flap creation is done in healthy tissue, avoiding dissection of the actual fistula tract. This technique facilitates dissection in proper tissue planes, avoids bleeding edges at the resected fistula tract, ensures that closure of the fistula is done with healthy tissue (vaginal wall flaps), and decreases the risk of potential bladder perforation. Wide mobilization of the vagina off the perivesical fascia for a distance of several centimeters bladder allows creation of a tension-free closure.

Step 4 (fistula closure): Closure of the fistulous opening is now done. The catheter in the fistula tract is removed, and the first layer of the repair is performed. Interrupted 3-0 or 4-0 absorbable sutures are placed in a transverse or vertical fashion across the fistula. These sutures incorporate bladder wall and the fistulous tract itself, starting in healthy tissue approximately 0.5 cm away from the margin of the fistula (Fig. 77–13D). Inclusion of the fistula tract in the repair (and not resecting the fistula) provides a strong anchor of supporting tissue for the first layer of the repair. The use of a double-armed suture, with both sides thrown from within the fistula tract outward, facilitates incorporation of good-quality tissue. The Foley catheter can be taken off traction while these sutures are placed to avoid puncturing the balloon. The second layer of the repair is placed with interrupted 2-0 or 3-0 absorbable sutures. These sutures are placed to invert the previous layer by imbricating the perivesical fascia and the deep musculature of the bladder over the first layer/fistula tract (Fig. 77–13E). The sutures should be applied at least 3 to 5 mm from the prior suture line, free of tension, and at a 90-degree angle from the first suture line to minimize overlapping of the two lines of repair. The integrity of the repair is confirmed by filling the bladder with 200 to 300 cc of saline mixed with indigo carmine and observing for vaginal staining. At this point, if desired, an interpositional peritoneal or Martius flap may be mobilized and secured over the existing suture line (Raz et al, 1993; Eilber et al, 2003).

Step 5 (advancement and closure of vaginal wall flap): The final and third layer of closure is done with the vaginal wall flaps that were previously created. The redundant, excess anterior (distal) vaginal flap is excised, and the posterior (proximal) vaginal flap is advanced beyond the fistula closure. This covers the fistula site with fresh, healthy vaginal tissue, which helps avoid overlapping of suture lines.

Step 6: (closure of the vaginal wall): The flap is advanced at least 2 to 3 cm beyond the fistula closure, and the vaginal wall is closed with a running, locking, absorbable 2-0 suture. An antibiotic-impregnated vaginal packing is placed for 24 hours postoperatively. The urethral Foley and suprapubic catheters are left to drain for 10 to 14 days.

Postoperative urinary drainage is essential, and the draining catheter(s) are left in all patients postoperatively until cystography confirms successful repair of the fistula. Generally, imaging is obtained at between 10 and 21 days from the time of repair. If a persistent leak is noted, ongoing catheterization and repeat imaging at a 2- to 3-week interval may demonstrate eventual resolution (Schwab and Rovner, 2003). Anticholinergic agents are given to decrease bladder irritability. A cystogram is done prior to catheter removal to document integrity of the repair. Sexual intercourse is avoided for 2 to 3 months postoperatively.

Complications. Proper surgical technique is critical in avoiding complications. Dissection in the proper surgical planes assures minimal bleeding. When significant bleeding is encountered during the dissection, it is possible that an improper plane of dissection was entered. Careful intraoperative inspection and reevaluation of the surgical planes are warranted. Furthermore, excessive use of cautery may compromise the vascular supply of the tissue flaps used for repair. This may only become evident in the postoperative period with ischemic flaps and recurrence of the fistula. Intraoperative bleeding should be controlled with fine absorbable suture whenever possible. **The possibility of ureteral injury is a concern, if the VVF is located adjacent to the insertion of the ureter.** If there is doubt regarding a ureteral injury, then cystoscopy should be performed following the intravenous administration of indigo carmine. Blue efflux from the ureteral orifice confirms ureteral patency.

Long-term complications from transvaginal VVF repair include vaginal shortening and stenosis. Careful attention to flap mobilization and reconstruction will minimize this complication. In addition, excessive resection of the vaginal wall should be avoided during reconstruction to avoid vaginal shortening or scarring.

The most important complication of VVF repair is recurrence of the fistula. A repeat transvaginal approach can be attempted with satisfactory success. A careful review of potential factors leading to failure of the initial repair is undertaken, and any remediable factors (i.e., inadequate nutrition, vaginal atrophy, excessive postoperative bladder spasms) are addressed. Strong consideration should be given toward the use of adjuvant flaps in repeat VVF repairs where tissue quality may be suboptimal.

Other Transvaginal Techniques. There are multiple variations to transvaginal fistula repair, including those originally described by Latzko in 1914. The Latzko high-partial colpocleisis is a very popular approach among some reconstructive surgeons, with reported success rates in excess of 90% (Kaser, 1977; Tancer, 1980). This approach may not be as successful as the vaginal flap

technique for large obstetric fistulae (Elkins et al, 1988). In this procedure, the fistula tract is isolated, and the tissue surrounding the VVF tract is denuded of vaginal "epithelium" circumferentially for a distance of 1 to 2 cm. Care is taken to avoid deeply "denuding" the vaginal tissues to avoid entry into the bladder or perivesical fascia. The denuded areas are then reapproximated over the fistula tract with a series of interrupted absorbable sutures. Sutures are not placed into the bladder wall or vesical mucosa. The edges of the vaginal wall are then reapproximated as a second layer, creating a partial colpocleisis in some patients. Advantages of the Latzko procedure include minimal blood loss, no need for ureteral reimplantation (even for a fistula adjacent to the ureter, because sutures are not placed through the bladder), and a short convalescence. Potential disadvantages include the possibility for vaginal shortening (Enzelsberger and Gitsch, 1991), as well as the creation of directly overlapping suture lines.

Webster and colleagues reported excellent results with a transvaginal approach to VVF by vaginal cuff excision (Iselin et al, 1998; Flynn et al, 2004). In this approach, the fistula tract is isolated, and the entire epithelialized portion of the tract is excised in the fashion of a wide inverted cone, leaving a funnel-shaped defect from the vesical to the vaginal side of the fistula. The defect is then closed in 3 or 4 layers using absorbable suture. The principal advantages of this technique are that mobilization of vaginal flaps is not required, and vaginal shortening is minimal.

Abdominal Techniques. **VVF may be repaired transabdominally, and this is the preferred approach in those cases requiring augmention cystoplasty or ureteral reimplantation.** Compared with the vaginal approach, the abdominal approach to VVF repair is associated with a longer recovery time and in-patient hospitalization, greater blood loss, more cosmetic deformity, and, in general, greater morbidity. Abdominal repair of VVF may be performed intraperitoneally or extraperitoneally, as well as transvesically.

Suprapubic Intraperitoneal/Extraperitoneal Approach. The patient is positioned in a low-lithotomy position with access to the vagina in the sterile operative field. Ureteral catheters may be placed preoperatively or intraoperatively to assist in identification of the ureters, especially if the VVF is in close proximity to the ureteral orifices. A lower midline incision is carried out. As classically described by O'Conor and colleagues (O'Conor and Sokol, 1951; O'Conor et al, 1973), the bladder is approached extraperitoneally; however, in some cases, the peritoneum will be entered. The bladder is opened vertically, and the cystotomy is extended down to the opening of the VVF (Fig. 77–14). As the dissection proceeds distally, stay sutures placed on the bladder edges greatly assist in retraction. In addition, a curved sponge stick placed per vagina with gentle upward traction can provide excellent exposure of the VVF. Having bivalved the bladder down to the level of the VVF, the VVF tract is excised, and the dissection is continued beyond the fistula tract to develop the vesicovaginal space (Fig. 77–15A to D). The vagina is carefully dissected and separated from the bladder for a distance of 2 to 3 cm beyond the VVF. **The key to the operation is the mobilization of the bladder from the vagina caudal to (beyond) the VVF tract.** Following wide mobilization from the bladder, the vagina is closed with a running absorbable suture. At this point, if an interpositional flap of greater omentum is to be used, it is mobilized and then secured 1 to 2 cm distally beyond the excised VVF tract (see later discussion) (Wein et al, 1980a). The bladder is then closed in several layers. A suprapubic tube and urethral catheter are usually left for postoperative drainage. Anticholinergic agents are used liberally in the postoperative period to minimize bladder irritability, which may be problematic.

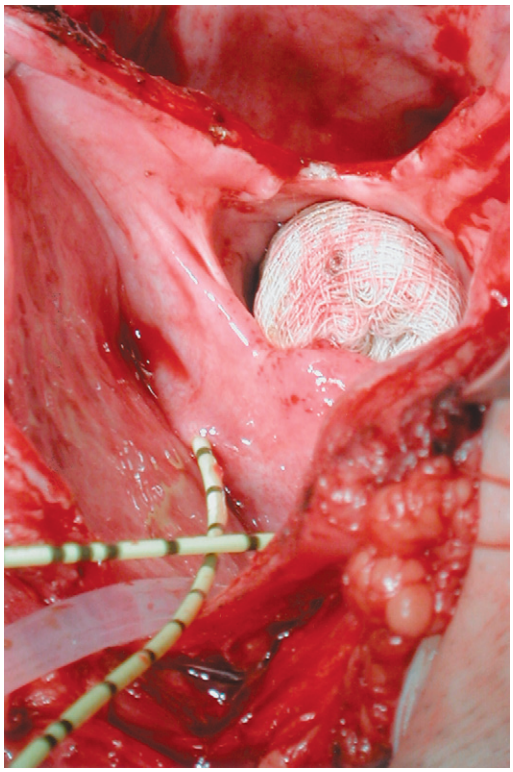


Figure 77–14. Intraoperative photograph from a suprapubic vesicovaginal fistula (VVF) repair. The bladder has been opened anteriorly and bivalved in the midline down to the level of a very large VVF. The gauze packing lies in the vagina. The ureteral catheters were placed to identify the ureters intraoperatively.

Bladder augmentation or ureteral reimplantation, if necessary, can be incorporated into the suprapubic approach prior to closure of the bladder. Large or small bowel may be used for augmentation cystoplasty, depending on the clinical circumstances.

Transvesical. A suprapubic transvesical approach to VVF repair has also been described (Landes, 1979; Cetin et al, 1988; Gil-Vernet et al, 1989). In this approach, the bladder is opened through a vertical cystotomy but is not bivalved down to the VVF tract. From a transvesical approach, the VVF tract is circumscribed and excised transvesically. The vaginal edges are then carefully mobilized from the bladder. The vagina and bladder are closed sequentially. A V-shaped flap of adjacent posterior bladder wall may be brought down as a flap to close a large gap or to minimize overlapping suture lines (Gil-Vernet et al, 1989). This approach has been successful in both simple and complex fistula (Gil-Vernet et al, 1989; Leng et al, 1998), and modifications have been described incorporating an omental flap (Hellenthal et al, 2007).

Laparoscopic/Robotic Approaches. Laparoscopic VVF repair is an alternative to the classical open approach described previously. Compared with the O'Conor transabdominal approach, laparoscopic repair is reported to be associated with less surgical trauma, shorter convalescence, and lower morbidity (Nezhat et al, 1994; von Theobald et al, 1998; Miklos et al, 1999; Ou et al, 2004). Laparoscopic VVF repair is most useful in the same scenarios as the transabdominal repair, such as in the setting of a high VVF in which a vaginal operation would be anatomically challenging.

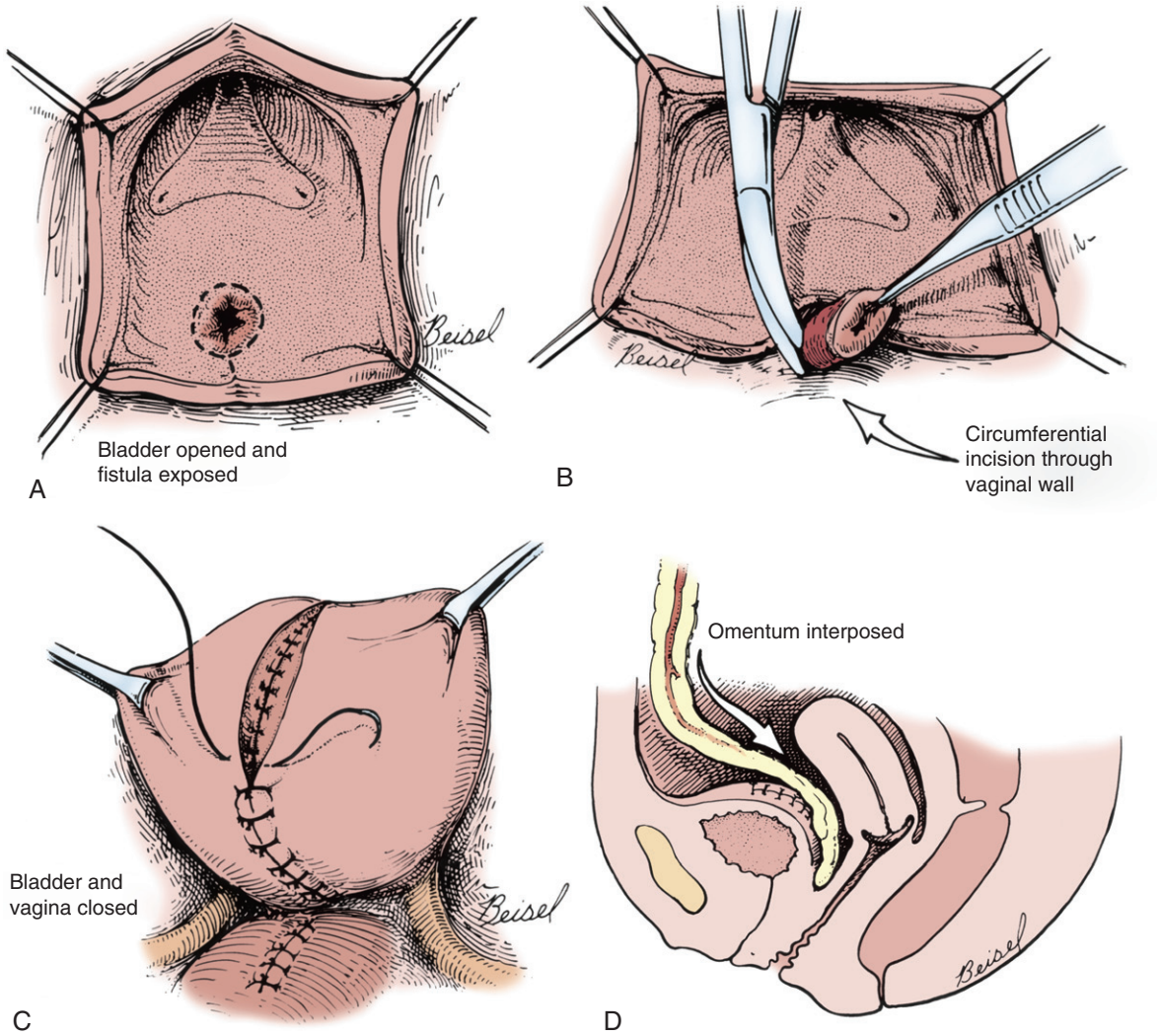


Figure 77–15. Diagrams of suprapubic repair of vesicovaginal fistula (VVF). **A,** The bladder opened and bivalved down to the level of the VVF. **B,** The VVF tract is excised. **C,** After closure of the vagina, the bladder is closed in multiple layers. **D,** Omentum is interposed between the bladder and vaginal closures. (From Ganabathi K, Sirls L, Zimmern P, Leach GE. Vesicovaginal fistulae: reconstructive techniques. In: McAninch J, editor. Traumatic and reconstructive urology. Philadelphia: WB Saunders; 1996. p. 315.)

Dense pelvic adhesions and/or inflammation from prior abdominal surgery can make this approach less desirable in some patients. Furthermore, intracorporeal laparoscopic suturing, a requirement for VVF repair, is an advanced skill many surgeons lack. Because of these limitations, the laparoscopic VVF repair has not been widely adopted.

Successful robotic VVF repair was first reported in 2005 (Melamud et al, 2005), and several small case series have been subsequently reported (Sundaram et al, 2006; Hemal et al, 2008). A five-port technique has been described using a vaginal pack to maintain pneumoperitoneum throughout the case (Sundaram et al, 2006; Hemal et al, 2008). Removal of the vaginal packing without loss of pneumoperitoneum confirms successful closure. Advantages to the robotic technique include three-dimensional visualization, wristed instrumentation reducing the severe angulation required for laparoscopic VVF repair, and technically simpler intracorporeal knot tying.

Although there have been no direct comparisons between the classical transabdominal VVF repair, transvaginal VVF repair, and the minimally invasive robotic/laparoscopic techniques, **it is doubtful that a single procedure will emerge as the optimal surgery for all patients with VVF, given the variability in the nature of the condition, the patients in whom it occurs, and the expertise of the individual surgeon.**

Adjuvant Procedures in the Repair of VVF: Tissue Interposition. The interposition of a healthy, well-vascularized tissue flap during VVF repair may be beneficial under certain circumstances. **Tissue flaps are especially helpful in the setting of a complex fistulae, such as those which have recurred after a prior attempt at repair, those related to previous radiotherapy, ischemic or obstetrical fistulae, large fistulae, and, finally, those associated with a difficult or tenuous closure due to poor tissue quality.** For those VVF repaired transvaginally, a labial fat pad (Martius flap) or a peritoneal flap are most commonly used. From a transabdominal approach, omentum or peritoneum is often used as an interpositional flap (Eisen et al, 1974).

Martius Flap. For low or distal fistulae, a Martius fibrofatty labial flap is a reliable source of tissue. The fibrofatty labial flap was first described by Heinrich Martius in 1928. **This flap consists of adipose tissue and connective tissue and is the**

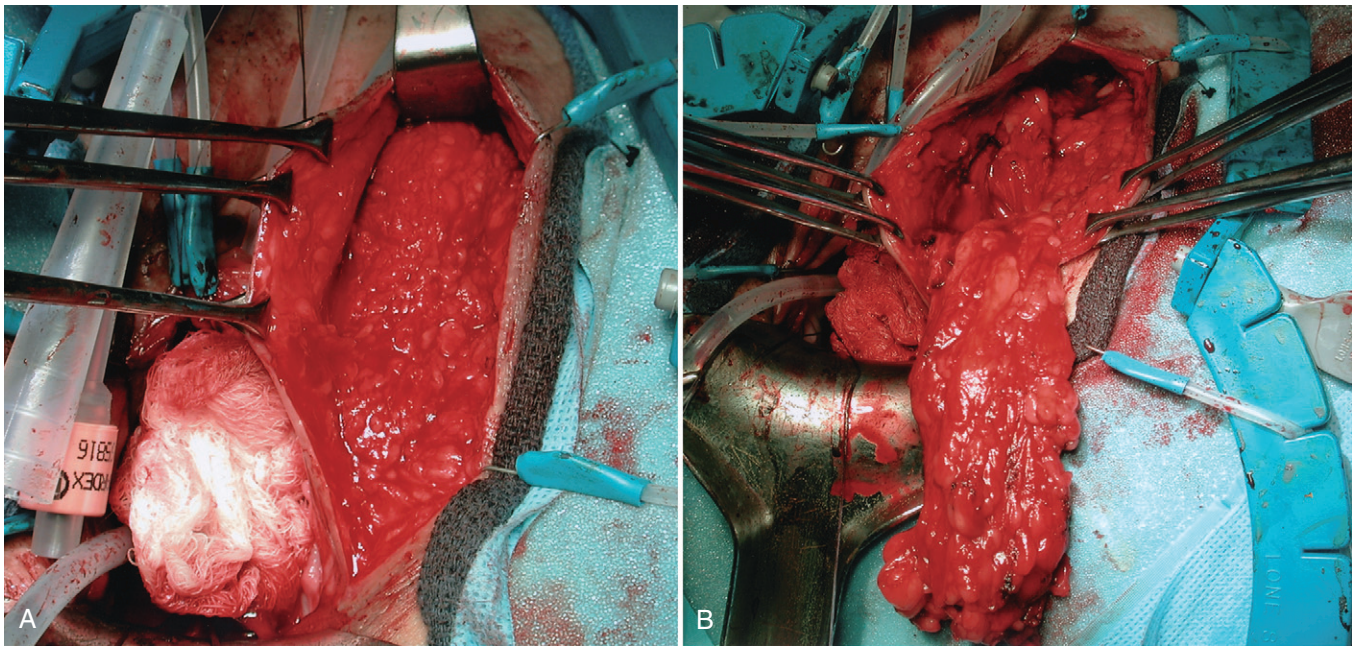


Figure 77–16. Harvesting of a Martius flap. **A,** The incision is made in the labia. **B,** A large flap may be obtained.

preferential tissue for fistulae involving the trigone, bladder neck, and urethra (Zimmern et al, 1986; Rangnekar et al, 2000a). **The blood supply to the flap derives inferiorly from the posterior labial vessels (off the internal pudendal artery), superiorly from the external pudendal artery, and laterally from the obturator artery.** The lateral blood supply is sacrificed during mobilization of the flap; the flap may be divided at either its most superior or inferior margin (basing the blood supply on the inferior or superior vascular pedicle, respectively), depending on where the flap will be transferred.

The flap is harvested after the first two layers of closure of the VVF but before advancing the final vaginal wall flap over the repair (see discussion above). To harvest the flap, a vertical incision is made over the labia majora. The borders of dissection include the labiocrural fold laterally, the labia minora and the bulbocavernosus muscle medially, and Colles fascia covering the urogenital diaphragm posteriorly. Flap harvest is accomplished in a lateral to medial fashion. Dissecting down to the adductor muscles laterally before coming around the width of the Martius flap facilitates the harvest of a thick, fatty segment for flap placement. Before final division of the flap inferiorly or superiorly, mobilization may be facilitated by gentle downward traction using a Penrose drain, incorporating the entire thickness of the fibrofatty flap. For a posterior-based flap, the main vascular supply to the flap is located at the base of the labia majora. The anterior segment is clamped and transected anterior to the pubic symphysis (Fig. 77–16).

Having mobilized the flap, a tunnel is created from the labial incision to the site of the fistula repair (Fig. 77–17). A hemostat is used to transfer the fibrofatty flap from the harvest site, through the tunnel, to the level of the fistula repair. The flap is placed over the fistula repair and secured with interrupted absorbable sutures in a tension-free manner. The vaginal wall flap is advanced over the Martius flap and closed as previously described. A small Jackson-Pratt or Penrose drain may be left in the labial incision in the operative bed. The labial incision is closed, and a pressure dressing may be applied to the labial skin incision.

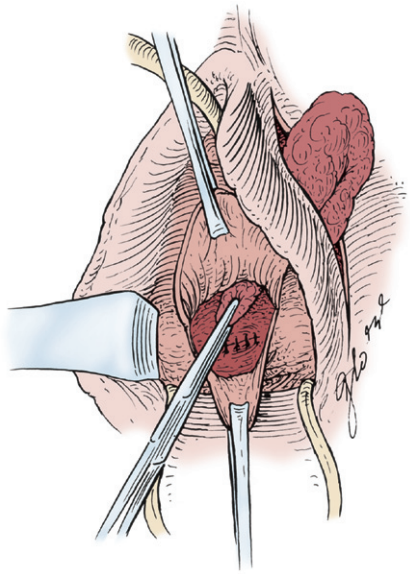


Figure 77–17. Tunneling of the Martius flap. (From Raz S. Vesicovaginal fistulae. In: Raz S, editor. Atlas of transvaginal surgery. Philadelphia: WB Saunders; 1992. p. 158.)

Rangnekar and colleagues (2000a) reported on the utility of the Martius flap in both urethrovaginal and vesicovaginal fistulae, the majority of which (32 of 46) were due to obstetric trauma. Of the patients undergoing VVF repair, 4 of 21 repairs without a Martius flap failed, compared with none of the 13 patients who underwent an adjuvant Martius flap. Eilber and colleagues (2003) reported that 33 of 34 (97%) of patients undergoing repair of a distal VVF with a Martius flap were cured following the first operation.

For posthysterectomy fistulae, the distance from the labial harvesting site of the Martius flap to the fistula at the apex of the vagina may be considerable. Mobilizing and then tunneling the Martius flap to reach this

location may compromise its blood supply and viability. In these cases, a peritoneal flap is preferred (Raz et al, 1993).

Peritoneal Flap. The use of a peritoneal flap during transvaginal repair of a complex VVF is a simple procedure that does not require extravaginal harvesting of the flap. **This technique is primarily used in conjunction with repair of a high-lying posthysterectomy VVF** (Raz et al, 1993; Eilber et al, 2003). Notably, peritoneal flaps may also be used as an adjunctive measure during transabdominal repair of VVF, although the approach and technique are vastly different (Eisen et al, 1974).

Following a two-layer closure as described previously, the peritoneum is identified posteriorly. The peritoneum and preperitoneal fat is identified, isolated, and mobilized from the caudal origin of the vaginal wall flap using sharp dissection. Usually, dissection just beyond the posterior wall of the bladder will expose the edge of the peritoneum in the anterior cul-de-sac (Raz et al, 1993). The peritoneum is identified as a distinct layer from the bladder. The peritoneum is not opened but is mobilized and then advanced over the fistula repair and secured with interrupted absorbable sutures in a tension-free manner (Fig. 77–18). If a peritoneotomy is made during dissection or mobilization, the peritoneal defect can be closed as the flap is secured to the perivesical fascia over the fistula repair. The vaginal flap is then advanced and closed as previously described.

Raz initially reported success in 9 of 11 patients with high VVF undergoing peritoneal flap placement (Raz et al, 1993). A later study from the same institution reported on the use of peritoneal flaps in 83 patients, of whom 80 were cured following the first operation (Eilber et al, 2003). Two of the 3 failed patients were successfully repaired with a repeat transvaginal repair and peritoneal flap, whereas the 1 patient required a transabdominal repair with omental interposition.

Greater Omentum. The omentum is a particularly useful structure in the repair of VVF. **Although most commonly used as an adjunct during transabdominal VVF repair (an interpositional layer between the bladder and vagina),** it has occasional utility in transvaginal VVF repair, if it had been brought down into the pelvis during a prior surgical procedure. **Favorable properties of the omentum include its ability to be mobilized on a well-vascularized pedicle into the deep pelvis without tension, its inherent lymphatic properties, its ability to contribute to healing even in the presence of infection, and the ease with which epithelialization occurs on its surface** (Turner-Warwick, 1976; Wein et al, 1980b).

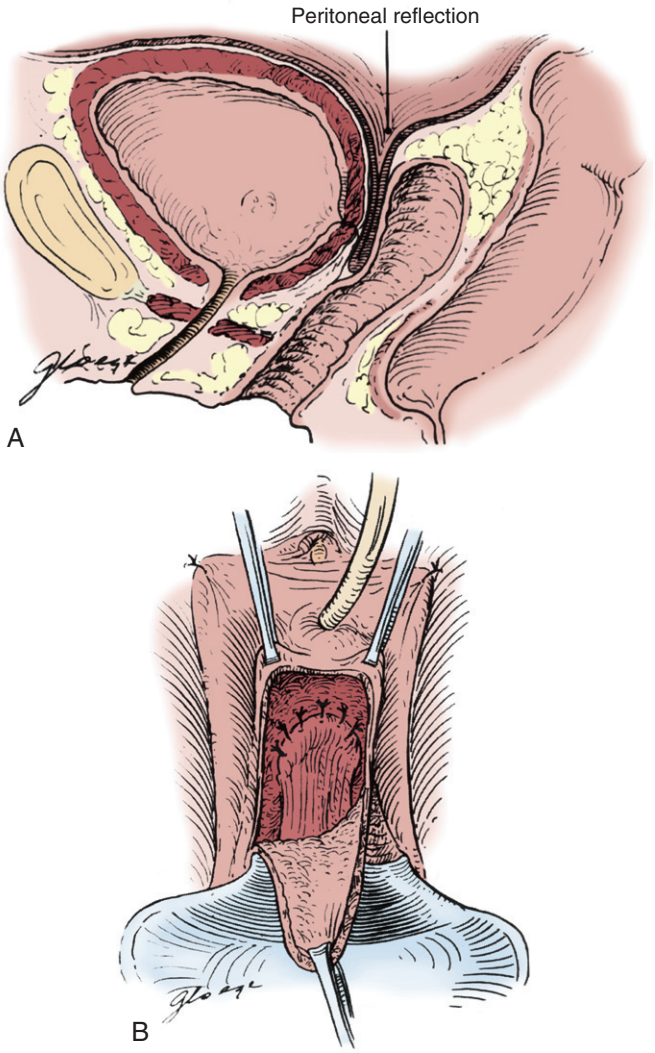


Figure 77–18. Peritoneal flap. **A,** Diagrammatic representation of the location of the peritoneal flap during vesicovaginal fistula repair. **B,** Diagram of peritoneal flap advanced over fistula repair. (**A** and **B,** From Raz S. Fistulae: transvaginal repair of vesicovaginal and urethrovaginal fistulae. In: Raz S, editor. Atlas of transvaginal surgery. 2nd ed. Philadelphia, WB Saunders; 2002. p. 242.)

The blood supply of the greater omentum derives principally from the right and left gastroepiploic arteries, as well as the distal branches of the gastroduodenal and splenic arteries, respectively. The right and left gastroepiploic arteries join along the greater curvature of the stomach to form the gastroepiploic arch. The arterial anatomy within the greater omentum is variable but usually consists of a right and left omental artery, and occasionally a middle omental artery, all of which run perpendicular to their origin off the gastroepiploic arch. **The caliber of the right gastroepiploic artery is usually larger than the left one, which generally favors a pedicle based on this artery; however, in practice, a pedicle based on either artery may be used** (Kiricuta and Goldstein, 1972; Bissada and Bissada, 1992). In addition, anatomically, the origin of the right gastroepiploic artery is somewhat caudal compared with the left one, allowing a slight advantage in reaching into the deep pelvis. In some cases, the free distal end of the greater omentum is long enough to reach into the deep pelvis tension-free without any further mobilization. In either situation, the omental flap is secured with absorbable suture to healthy tissue at a location distal to and beyond the closed VVF tract, between the vagina and bladder. Securing the omental flap beyond and between the suture lines of the closed viscera prevents overlying or apposed suture lines. Evans and colleagues (2001) reported retrospectively on the utility of an omental interpositional flap in 37 patients undergoing transabdominal VVF. Of the 29 patients with a benign etiology of VVF, all 10 patients in whom an omental flap was used were cured, compared with only 12 of 19 (63%) in whom an omental flap was not used. Orford and Theron (1985) reported a 93% cure rate with the use of an omental pedicle graft in 52 patients undergoing VVF repair. In addition to its utility in routine posthysterectomy VVF, the omentum is reported to be a useful adjunct in complicated or complex cases, such as those associated with large VVF (Kiricuta and Goldstein, 1972; Bissada and McDonald, 1983), obstetric VVF (Baines et al, 1976; Sharma et al, 1980),

and those associated with radiation therapy (Bissada and Bissada, 1992; Evans et al, 2001).

Other Flap and Graft Techniques. A variety of flaps including gracilis muscle flaps (Izes et al, 1992), labial myocutaneous flaps (Symmonds and Hill, 1978), seromuscular intestinal flaps (Mraz and Sutory, 1994), and rectus abdominis flaps (Menchaca et al, 1990; Viennas et al, 1995; Reynolds et al, 2008) have been used as adjunctive measures in the repair of complex VVF. Obstetric fistulae associated with significant urethral loss may be repaired, in part, with the use of anterior or posterior bladder flaps (Hanash and Sieck, 1983; Elkins et al, 1992; Khanna, 1992). The gracilis muscle in the medial thigh is a convenient adjunct to repair large soft tissue defects, especially those associated with radiation therapy (Obrink and Bunne, 1978; Heckler, 1980). The gracilis muscle is in close proximity to the vagina and has a reliable blood supply. The muscle is mobilized through a thigh incision from its distal attachment on the tibial condyle, with care to preserve its blood supply. It is tunneled cephalad into the vagina subcutaneously and secured over the fistula. Bilateral gracilis muscle flaps can be used for total vaginal reconstruction.

Bladder mucosa as a free graft has been used for repair of VVF (Brandt et al, 1998; Ostad et al, 1998; Sharifi-Aghdas et al, 2002). The bladder is approached extraperitoneally and a small cystotomy is performed. The fistula tract is identified and denuded of mucosa circumferentially for approximately 1 cm. A free graft of bladder mucosa is harvested from the edge of the cystotomy and placed over the denuded VVF tract and secured in place with absorbable suture. Brandt and colleagues (1998) reported a 96.3% success rate in 80 patients. Ostad and colleagues (1998) reported on 6 patients with complex, high, radiated, large or recurrent VVF, all of whom were cured by this technique.

Outcomes of VVF Repair. The success rate reported for a simple VVF repair in the modern era, whether through an abdominal or vaginal approach, is in excess of 90% (Table 77–6). Long-term follow-up suggests that the majority of patients are greatly improved, although minimally bothersome symptoms may persist in a minority of patients over the long term, causing little impact on quality of life (Dolan et al, 2008). Complicated VVF, including those resulting from obstetric causes (Elkins et al, 1988; Arrowsmith, 1994), larger fistulae, as well as those associated with radiation therapy, generally have lower success rates (Massee et al, 1964; Hedlund and Lindstedt, 1987; Langkilde et al, 1999; Ockrim et al, 2009). Massee and colleagues (1964) reported a 93.8% cure rate of urinary vaginal fistulae due to surgical trauma, but only a 66.7% cure rate with those due to radiation therapy. Some authors have suggested that urinary diversion should be strongly considered as primary therapy (Murray et al, 2002) for radiation-induced fistulae, because the results with surgical repair in this group is less than optimal (Langkilde et al, 1999). **In patients with obstetric fistulae associated with loss of the bladder neck and**

Table 77–6.

Outcomes for Vesicovaginal Fistula Repair

AUTHOR (DATE)	NO. PATIENTS	SUCCESS (%)	APPROACH	COMMENTS
Eisen et al (1974)	29	90	Abdominal	Peritoneal flap
Kaser (1977)	38	92	Vaginal	Latzko
Persky et al (1979)	7	86	6 abdominal 1 vaginal	
Tancer (1980)	45	93	43 vaginal 1 abdominal 1 spontaneous closure	Latzko vaginal approach
O'Conor (1980)	42	88	Abdominal	
Wein et al (1980)	34	88	Abdominal	
Keettel et al (1978)	168	94	156 vaginal 6 abdominal 6 combined	
Lee et al (1988)	182	98	145 vaginal 37 abdominal	100% success with abdomimal approach
Gil-Vernet et al (1989)	42	100	Abdominal	Transvesical
Wang et al (1990)	16	94	Vaginal	
Blandy et al (1991)	25	100	Abdominal	
Motiwala et al (1991)	68	94	Abdominal	58 transvesical 10 transabdominal with omental flap
Raz et al (1993)	11	82	Vaginal	Peritoneal flap
Arrowsmith (1994)	98	96 (81% success after 1st attempt)	Multiple	All obstetric fistulae
Elkins et al (1994)	82	95 (88% success after 1st attempt at VVF)		All obstetric fistulae
Kristensen et al (1994)	18	94	Abdominal	5 ureteral reimplants required
Blaivas et al (1995)	24	96	15 vaginal 8 abdominal 1 spontaneous closure	
Ayhan et al (1995)	70	93	66 vaginal 4 abdominal	
Brandt et al (1998)	80	96	Abdominal	Bladder mucosa autograft
Iselin et al (1998)	20	100	Vaginal	Vaginal cuff excision
Evans et al (2001)	37	76	Abdominal	Includes 8 malignant fistulae
Eilber et al (2003)	207	97	Vaginal	

proximal urethra, relatively high rates of persistent severe sphincteric incontinence are noted despite successful repair of the VVF (Murray et al, 2002; Browning, 2004), **and this type of fistula is involved in the majority of treatment failures** (Kelly, 1992). Thus despite a technically successful VVF repair, functionally, from the patient's perspective, some of these individuals may not be significantly improved following the repair due to severe stress urinary incontinence. Pubovaginal slings and periurethral injectable agents are often beneficial in these patients, once the VVF has been surgically closed (Arrowsmith, 1994). In the developing world, access to synthetic midurethral slings is limited. Futhermore, the safety of using such materials in the setting of extensive reconstruction, such as that after repair of an obstetric fistula, is not established.

VVF and Urinary Diversion. **In some patients, repair of VVF is not possible or multiple surgical attempts have failed.** This is probably most commonly associated with existing pelvic malignancy, severe radiation damage, and/or large soft tissue loss, especially in the setting of obstetric fistula. However, some patients may simply not be candidates for repair due to coexistent medical morbidities, making them a prohibitive surgical risk. **In the former group, urinary diversion, either in the form of a urinary conduit** (Kisner and Kesner, 1987), **or a continent reservoir can be considered. Fistulae in patients who are not candidates for surgical intervention may be managed by percutaneous ureteral occlusion and permanent nephrostomy** (Kinn et al, 1986; Stern et al, 1987; Hubner et al, 1992; Farrell et al, 1997; Amsellem-Ouazana et al, 2006; Natarajan et al, 2007; Shindel et al, 2007).

In the developing world, where catheters and ostomy appliances are either too expensive or completely unavailable, continent urinary diversion or incontinent urostomies are often not practical, which presents ethical issues with the alternative treatments (Wall et al, 2008). In these situations, internal urinary diversion with ureterosigmoidostomy has some application in patients with unreconstructable lower urinary tracts (Attah and Ozumba, 1993). It should be recognized that this is clearly a last-resort operation due to its significant metabolic and neoplastic potential.

Key Points: Vesicovaginal Fistulae

- VVF is the most common acquired fistula of the urinary tract.
- In the industrialized world, surgical injury to the bladder is the most common cause of VVF; most commonly seen following hysterectomy. In the developing world, VVF is most commonly related to complications from obstructed labor.
- VVF due to radiation therapy are usually complex.
- VVF occurring in the setting of a history of pelvic malignancy should undergo biopsy prior to repair to exclude recurrent malignancy as a cause of the fistula.
- Diagnosis of VVF can be confirmed on VCUG. Voiding images should be obtained if the fistula was not demonstrated on the filling images of the cystogram.
- Upper tract imaging is obtained following a diagnosis of VVF to exclude injury to the ureter(s).
- Small, oblique fistulae may respond to conservative therapy, including prolonged urinary catheterization with or without fulguration of the fistula tract.
- There is no optimal method for the surgical repair of all VVF. In the properly selected patient, transabdominal and transvaginal approaches to fistula repair have similar success rates.
- Adjuvant tissue flaps may be useful to prevent surgical failure in the setting of complex or recurrent fistula, radiation fistula, obstetrical fistula, and those with tenuous repairs.

Ureterovaginal Fistulae

Ureteral fistulae to the genital tract in the female most often connect with the vagina but have also been reported to connect with other genital structures, including the fallopian tube (Crochet et al, 2008) or uterus (Billmeyer et al, 2001). **Risk factors for the development of ureterovaginal fistulae include endometriosis, obesity, pelvic inflammatory disease** (Symmonds, 1976), **as well as radiation therapy and pelvic malignancy.** Nevertheless, Symmonds has noted that the patient with a ureteral injury following gynecologic surgery is typically one who had an uncomplicated, technically easy hysterectomy for minimal disease (Symmonds, 1976). Thus, except for those oncologic cases where a segment of ureter is deliberately excised, many ureteral injuries are likely due to technical or iatrogenic factors.

Etiology and Presentation

The most common etiology for ureterovaginal fistulae is surgical injury to the distal ureter, with gynecologic procedures being by far the most common cause (Symmonds, 1976; Dowling et al, 1986; Badenoch et al, 1987b; Lee et al, 1988; Blandy et al, 1991). **The vast majority of ureterovaginal fistulae occur during procedures for benign rather than malignant indications** (Mandal et al, 1990), **including hysterectomy most commonly, but also caesarean section, cystocele repair, and other pelvic surgery** such as infertility procedures (von Eye et al, 2008; Mongiu et al, 2009) (Table 77–7). Regarding the approach for hysterectomy, the risk of ureteral injury appears to be greatest during laparoscopic hysterectomy, followed by abdominal and then vaginal hysterectomy (Harkki-Siren et al, 1998). **The incidence of iatrogenic ureteral injury during major gynecologic surgery is estimated to be about 0.5% to 2.5%** (Symmonds, 1976; Payne, 1996; Gilmour et al, 1999).

Table 77–7.

Etiology of Ureterovaginal Fistula

Gynecologic Surgery
Abdominal hysterectomy
Vaginal hysterectomy
Radical hysterectomy
Caesarian section
Anterior colporrhaphy (cystocele repair)
Other Pelvic Surgical Procedures
Vascular surgery
Urologic surgery including retropubic bladder neck suspensions
Colon surgery
Other
Locally advanced malignancy
Radiation therapy
Pelvic trauma
Chronic inflammatory diseases: actinomycosis, etc.

The mechanism of injury resulting in iatrogenic postoperative ureterovaginal fistulae includes ureteral laceration or transection, blunt avulsion, crush injury, partial or complete suture ligation, and, finally, ischemia due to operative devitalization of the ureteral vascular supply and/or cautery injury. Overall, the ureter is most commonly injured during gynecologic surgery in the distal one third or pelvic portion, which is, accordingly, the only location at which a ureteral injury may result in a ureterovaginal fistula. Not uncommonly this occurs inadvertently during an attempt by the surgeon to control active bleeding using clamps or suture ligation of large tissue segments in the deep pelvis.

The pelvic ureter is intimately related to the female genital tract throughout its course. **In the deep pelvis, the ureter passes at the lateral edge of the uterosacral ligament and ventral to the uterine artery, and then passes just lateral to the cervix and fornix of the vagina.** In close apposition to these structures, the ureter must be carefully avoided during any gynecologic procedure in the deep pelvis. **Any injury to the ureter that exposes the ureteral lumen (i.e., laceration), or results in delayed necrosis of a portion of the ureter (i.e., suture ligation) and subsequent urinary extravasation, may lead to a fistula.** A ureterovaginal fistula may result from a sequence of events, including urinary extravasation from the ureteral injury, urinoma formation, subsequent extension along nonanatomic planes created during surgery, and eventual drainage through the vaginal incision or an ischemic area of the vaginal cuff. Infection, prior radiation therapy, or other factors that may impede healing probably promote the development of ureterovaginal fistulae under these circumstances.

The most common presenting symptom is the onset of constant urinary incontinence 1 to 4 weeks following surgery (Mandal et al, 1990). This may have been preceded by several days of flank or abdominal pain, nausea, and low-grade fever, presumably as a result of urinoma and/or obstruction of the kidney (Lee et al, 1988). Flank pain will often be masked in the postoperative period due to the use of postoperative narcotic analgesics. **Importantly, and in direct contrast to VVF, in the setting of continuous urine leakage from a ureterovaginal fistula, patients will continue to report normal voiding habits as bladder filling is maintained from the contralateral, presumably undamaged, upper urinary tract.**

Diagnosis and Management

Diagnosis and confirmation of a ureterovaginal fistula can usually be accomplished with a combination of a relevant history, physical examination, and appropriate radiologic studies, including cross-sectional imaging (such as a CT urogram), intravenous urography (IVU), and retrograde pyelography (Mandal et al, 1990) (Fig. 77–19). **A double dye test may be of some value in differentiating between a ureterovaginal and vesicovaginal fistula as a cause of ongoing urinary leakage** (Raghavaiah, 1974). Suspicion of a ureterovaginal fistula should prompt upper tract imaging (Badenoch et al, 1987a). **The IVU or CT urogram most commonly will demonstrate some degree of ureteral obstruction and associated caliectasis or ureteral dilation** (Selzman et al, 1995). **These findings in the presence of constant vaginal drainage strongly suggest a ureterovaginal fistula.** Alternatively, if the fistula is mature and large, the upper urinary tract may appear completely unremarkable; however, urine will be seen opacifying the vagina prior to the postvoid image (Fig. 77–20). Antegrade pyelography following nephrostomy tube decompression of a partially obstructed ureter may be associated with similar findings (Fig. 77–21). **A**

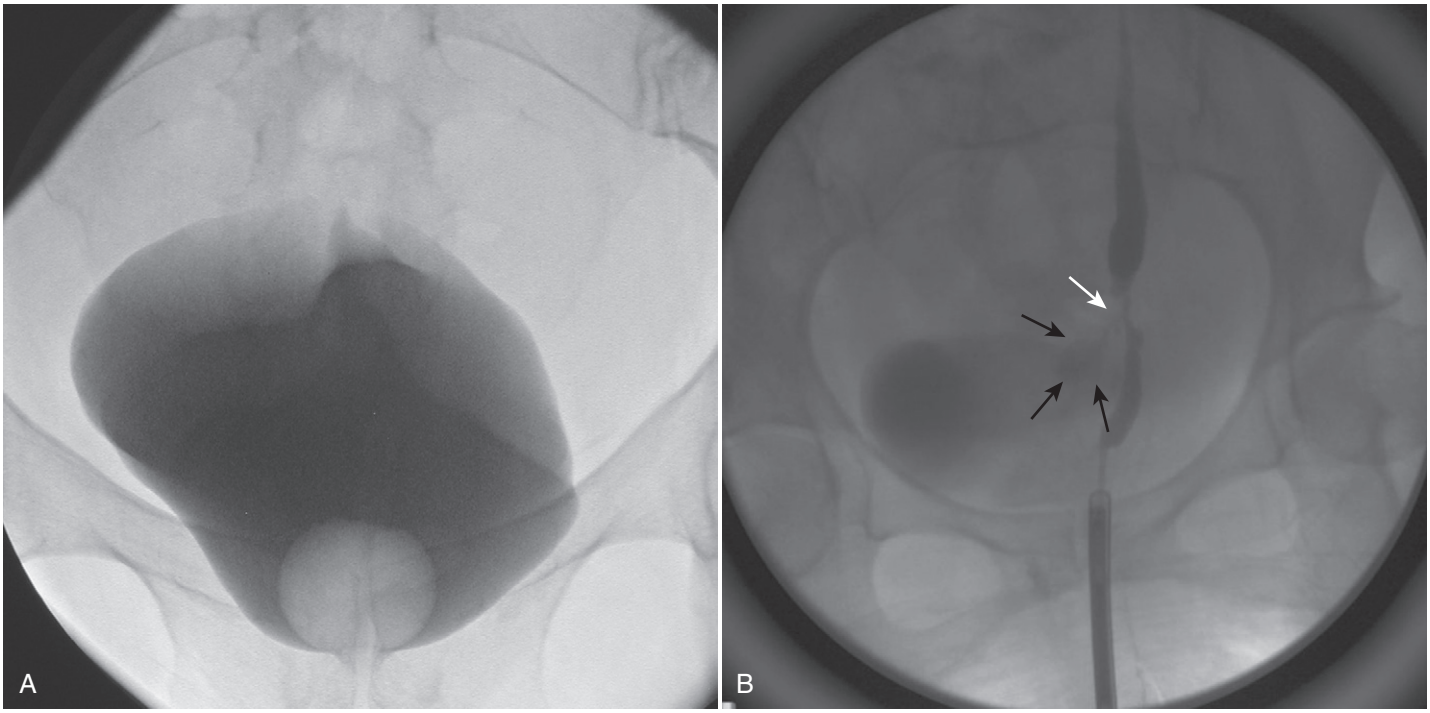


Figure 77–19. Diagnosis of ureterovaginal fistula. **A,** Normal cystogram in a woman complaining of constant urinary drainage since undergoing an abdominal hysterectomy. **B,** Retrograde pyelogram demonstrates a distal ureteric stricture with a small fistula tract *(white arrow)* with contrast in the vagina *(black arrows)* superimposed on contrast in the bladder from the contralateral retrograde ureterogram.

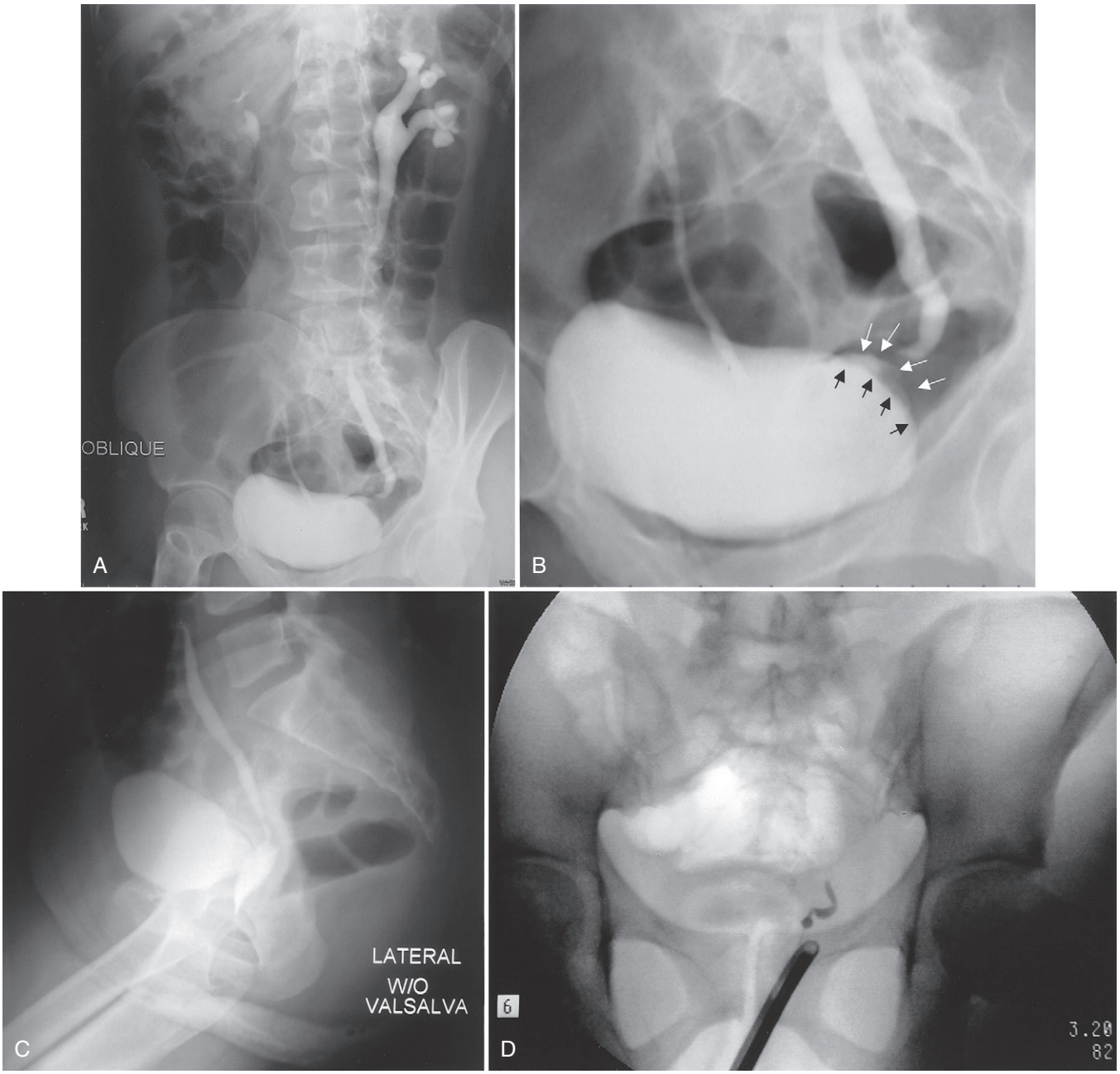


Figure 77–20. Ureterovaginal fistula. **A,** Oblique view on intravenous urography shows mild left-sided hydroureteronephrosis associated with a distal tapering of the ureter. **B,** Faint and subtle opacification of the vagina *(white arrows)* is somewhat obscured by bladder filling (bladder edge indicated by *black arrows*) on this oblique image. **C,** Lateral view demonstrates the ureter clearly entering the vagina. **D,** Retrograde pyelogram demonstrates abrupt termination of the distal ureter.

high oblique or lateral film may be necessary to differentiate the contrast in the bladder from that in the vagina. A retrograde pyelogram may show the ureter and fistula well, or may demonstrate an abrupt termination of the ureter 2 to 4 cm from the ureteral orifice. **Retrograde pyelography may be the single best test to diagnose a ureteral injury** (Payne, 1996). **If retrograde pyelography demonstrates the fistula, as well as ureteral continuity, then an attempt at stenting is warranted. Cystography is performed primarily to exclude a coexistent VVF.** A cystogram will not demonstrate the ureterovaginal fistula unless there is preexisting vesicoureteral reflux. Ureterovaginal fistulae may be seen on CT urography (Fig. 77–22); however, an additional role for such cross-sectional imaging is to evaluate for an associated pelvic abscess or undrained urinoma.

The goal of therapy is the expeditious resolution of urinary leakage, avoidance of urosepsis, and preservation of renal function. Once the diagnosis is made, prompt drainage of the affected upper urinary tract is essential (Gerber and Schoenberg, 1993), **because partial ureteral obstruction is often present.** An attempt at ureteral stenting or percutaneous nephrostomy tube decompression is warranted as soon as possible (Dowling et al, 1986; Kostakopoulos et al, 1998a) if direct open surgical repair is not immediately considered. Occasionally, conservative, nonoperative management, alone, will result in fistula closure in patients with ureteral

continuity and a normal-appearing ureter beyond the fistula (Alonso et al, 1986), although this is unusual. Endoscopic management, including ureteral stenting, may be sufficient to promote closure of the fistula in some cases. Dowling and colleagues (1986) reported that 11 of 23 patients with ureteral injuries recognized postoperatively were successfully managed with nephrostomy tube drainage and/or ureteral stenting. Selzman and coworkers (1995) reported successful management of 7 of 20 ureterovaginal fistulae with internal ureteral stenting alone. None of the 7 patients in whom a ureteral stent was successfully placed required open surgery. In general, if ureteral continuity can be demonstrated on imaging, retrograde placement of a stent is often possible. In some cases, an antegrade stent placement will be successful where a retrograde attempt had failed.

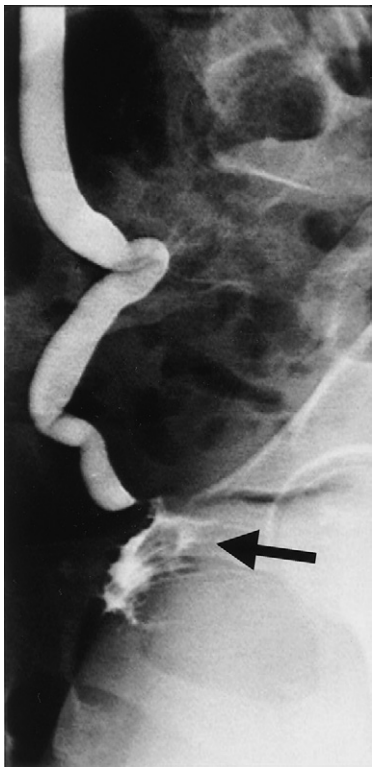


Figure 77–21. Ureterovaginal fistula. Antegrade nephrostogram demonstrates mild ureterectasis with opacification of the vagina *(arrow)*.

If ureteral stenting is unsuccessful due to complete ureteral occlusion, or prolonged leakage persists despite stenting, then formal surgical repair is indicated (Fig. 77–23). **Timing of the repair of ureterovaginal fistulae is controversial.** Some authors advocate early repair (Talbert et al, 1965; Flynn et al, 1979; Badenoch et al, 1987b; Blandy et al, 1991; Selzman et al, 1995), while others recommend a delay of 4 to 8 weeks (Hulse et al, 1968; Lee and Symmonds, 1971). More recent literature suggests that early repair is preferred and is not associated with an increase in morbidity or higher failure rates (Payne, 1996).

As noted previously, ureterovaginal fistulae most commonly result from injury to the distal one third of the ureter below the level of the iliac vessels. **The usual site of the injury in the very distal ureter and the surrounding fibrosis and inflammation usually precludes primary repair of the fistula. Therefore open surgical repair most commonly involves ureteroneocystostomy.** The ureter is located and dissected as distally as possible in the pelvis. Care is taken to preserve the periureteral adventitial layer to prevent ureteral ischemia. The ureter is divided distally, and a ureteroneocystostomy is performed with or without a psoas hitch. Occasionally, a Boari flap may be necessary due to extensive ureteral injury. **Robotic and laparoscopic repairs have been reported using the same principles as open repair** (Modi et al, 2005; Laungani et al, 2008; Modi et al, 2008; Patil et al, 2008), **with the potential benefits of shorter hospitalization and quicker convalescence.** Rarely, transureteroureterostomy, ileal substitution of the ureter, or renal autotransplantation are required. In patients with a normal contralateral kidney in whom there is extensive renal damage due to obstruction or infection, nephrectomy may be the most expeditious method of management.

Successful repair of ureterovaginal fistulae is expected in greater than 90% of cases. Blandy and colleagues reported on early repair of iatrogenic injury to the ureter in 43 cases including 30 ureterovaginal fistulae. All patients were cured using a combination of techniques including the Boari flap (Blandy et al, 1991). Others have reported similar results (Lee and Symmonds, 1971; Flynn et al, 1979; Mandal et al, 1990).

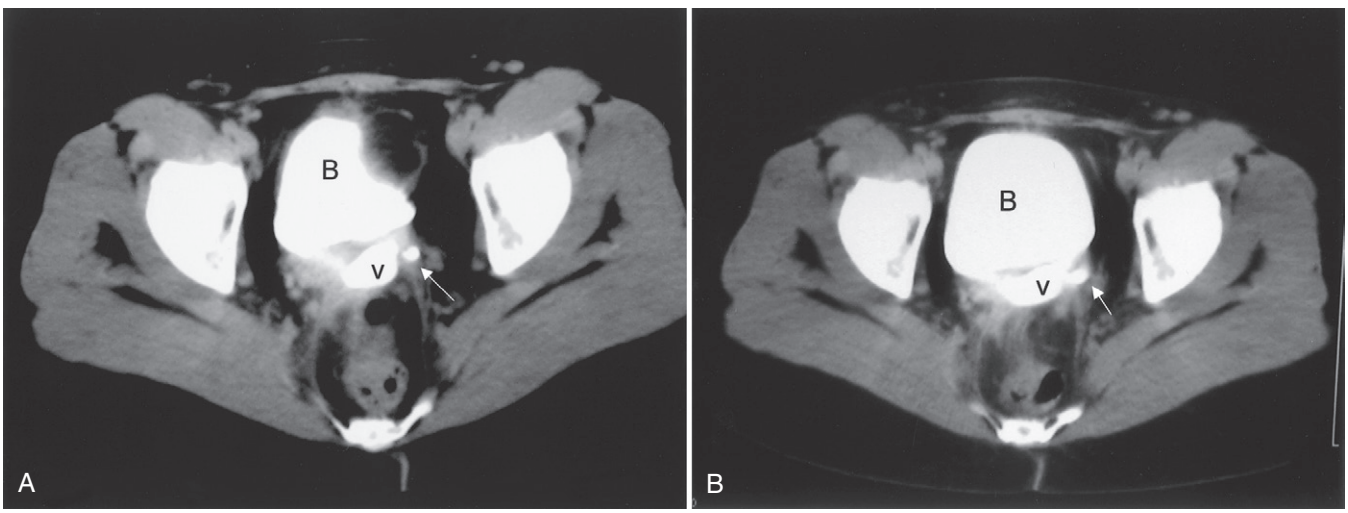


Figure 77–22. CT scan of ureterovaginal fistula. **A,** CT scan demonstrates contrast material within the bladder (B) and vagina (v). The ureter is seen *(arrow)* adjacent to the vagina. **B,** This image shows the ureter *(arrow)* entering the vagina.

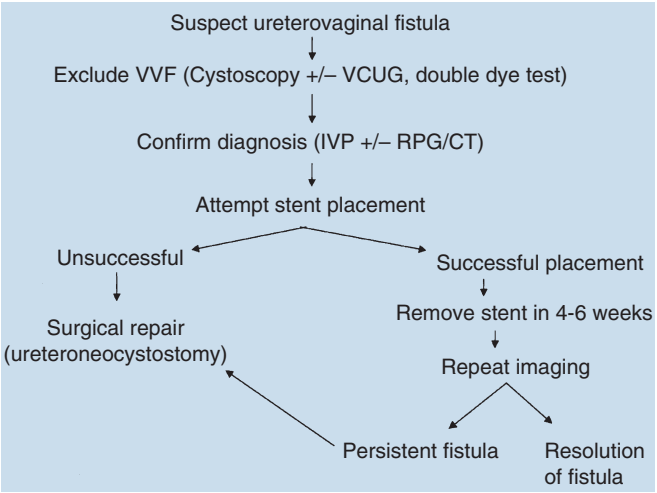


Figure 77–23. Algorithm for diagnosis and management of ureterovaginal fistula. CT, computed tomography; IVP, intravenous pyelography; RPG, retrograde pyelography; VCUG, voiding cystourethrography; VVF, vesicovaginal fistula.

Ureteral fistulae to other gynecologic organs have been reported. Ureterouterine fistulae may occur as a result of caesarean section, uterine malignancy and elective abortion (Keegan and Forkowitz, 1982; Lazarevski and Badiev, 1996; Wang and Hung, 1997; Sheen et al, 1998). Ureterofallopian tube fistulae have also been reported as a consequence of laparoscopic fulguration of endometriosis (Steckel et al, 1993).

Key Points: Ureterovaginal Fistulae

- Ureterovaginal fistulae occur more commonly following benign hysterectomy compared with radical hysterectomy.
- Patients present with constant urinary leakage but usually a normal voiding pattern.
- In the setting of ureteral patency, a trial of an indwelling ureteral stent may result in resolution of the fistula.
- If conservative management fails, or there is complete obstruction of the distal ureter, then ureteral reimplantation with or without a psoas hitch is usually curative.

Vesicouterine Fistulae

Etiology and Presentation

Vesicouterine fistulae are among the least common urogynecologic fistulae. Less than 100 cases were reported in the world literature between 1908 and 1986, with no series having greater than four patients (Tancer, 1986). However, the incidence of this condition is increasing in parallel with the rising numbers of low-segment caesarean sections being done worldwide (Porcaro et al, 2002). **Caesarean section is by far the most common cause of this unusual fistula** (Tancer, 1986; Miklos et al, 1995; Vu et al, 1995). Tancer related that of the 74 cases of vesicouterine fistulae reported from 1947 to 1986, 57 followed low-segment caesarean section, 7 followed vaginal operative delivery, while the remaining cases were related to a variety of disparate scenarios, including induced abortion, hysterectomy, and dilation and curettage (D&C) (Tancer, 1986). Jozwik and colleagues (1997) reported that 21 of 24 vesicouterine fistulae treated over a 12-year period occurred following caesarean section, the majority of which were repeat caesarean sections. Those undergoing vaginal birth after a prior caesarean section (VBAC) are also at risk for vesicouterine fistula (Gil and Sultana, 2001). Vesicouterine fistulae may occur spontaneously as a result of a ruptured uterus during obstructed labor. In these cases, the posterior bladder wall may tear along the uterine rupture line creating the potential for a fistula. Bladder wall invasion by chorionic villi penetrating beyond the uterine serosa, placenta percreta, may also create a vesicouterine fistula (Krysiewicz et al, 1988). A foreign body such as an intrauterine device (IUD) (Schwartzwald et al, 1986), uterine artery embolization (Sultana et al, 2002), brachytherapy (Memon et al, 1998), and traumatic bladder catheterization (Futter and Baker, 1995) have all been reported to cause vesicouterine fistula. **In most cases, simultaneous injury to the bladder and uterus is the inciting event.** An unrecognized and unrepaired (occult) bladder injury, or incorporation of a portion of the bladder during closure of the uterus following any number of operations, may result in a vesicouterine fistula. **Anatomically, the most common location of the fistula is along the posterior bladder wall in the midline, or from the genital side, just cephalad to the internal cervical os.**

Unlike other types of urogynecologic fistulae, vesicouterine fistulae may or may not present with constant urinary incontinence due to the sphincter-like activity of the cervix; the exception is in the setting of an incompetent cervix where urinary leakage is constant. In this clinical setting, which typically occurs following vaginal delivery, urine flows from the bladder through the fistula into the uterine cavity and then into the vagina through an incompetent cervical os. Tancer (1986) described 12 such patients, with urinary incontinence as the presenting symptom, out of 15 patients with vesicouterine fistulae following vaginal operative delivery. However, in the setting of a relevant clinical history, vesicouterine fistulae will also present with menouria and cyclical hematuria in the setting of urinary continence. **Youssef syndrome describes the presenting symptom complex of vesicouterine fistula: menouria, cyclic hematuria with associated apparent amenorrhea, infertility, and urinary *continence*** (Youssef, 1957; Tancer, 1986) **in a patient who has undergone prior low-segment caesarean section.** Endometriosis of the bladder, in which cyclical hematuria may be present, must be differentiated from this condition.

Diagnosis and Management

Diagnosis of vesicouterine fistula can be made by a combination of cystoscopy and radiographic studies, although a high degree of suspicion is necessary to pursue the diagnosis if initial radiographic studies prove negative (Smayra et al, 2005). Cystoscopy may demonstrate a midline lesion along the posterior bladder wall (Fig. 77–24). Urine cytology may reveal endothelial cells. Instillation of contrast material into the bladder (cystogram) will outline the uterine cavity (Fig. 77–25), whereas a hysterosalpingogram will demonstrate filling of the bladder. MRI, CT (Fig. 77–26), and ultrasonography have been used in the diagnosis and evaluation of vesicouterine fistulae as well (Mercader et al, 1995; Huang and Yao, 1996; Murphy et al, 1999). An IVU or contrast-enhanced CT scan can be used to exclude concomitant ureteral injury.

Several different approaches have been advocated for the treatment of vesicouterine fistulae. Spontaneous resolution may occur, and Graziotti and colleagues (1978) noted that only five such cases, including theirs, had previously been reported in the

literature. Therefore these authors recommend against a "precocious" surgical repair of these lesions as time may allow some fistulae to resolve without surgery. **Prolonged indwelling bladder catheterization or fulguration of the fistula tract followed by bladder drainage may be successful in select cases, especially those with small, immature fistulae** (Graziotti et al, 1978; Molina et al, 1989; Ravi et al, 2003; Novi et al, 2004). **Hormonal induction of menopause will induce involution of the puerperal uterus, and this principle has been used with some success in treating this condition as well** (Hemal et al, 1994; Jozwik and Jozwik, 1999; Ravi et al, 2003). Jozwik and colleagues (1999) reported successful treatment in 8 of 9 patients using hormonal manipulation.

Surgical therapy for vesicouterine fistulae is often contingent on the specific reproductive wishes of the patient (Smayra et al, 2005), **as well as other surgical factors,** but is considered definitive therapy (DiMarco et al, 2006; Rao et al, 2006)**. If there is no further desire for childbearing, then transabdominal hysterectomy and bladder closure should be considered. Ureteral stents can be placed to facilitate identification of the ureters intraoperatively.** Following performance of the hysterectomy, the fistula tract on the posterior bladder wall is excised and the bladder is closed primarily. An omental flap can be placed into the deep pelvis to buttress the bladder closure and separate the bladder closure from the vaginal closure to reduce the possibility of a postoperative vesicovaginal fistula. **For the patient who desires preservation of fertility, uterine-sparing surgery can be considered.** In a manner similar to an O'Conor transabdominal VVF repair, the bladder is opened and bivalved down to the fistula tract. Careful dissection allows separation of the bladder from the uterus beyond the fistula tract. The fistula tract is excised from both structures, the uterus and bladder are closed individually, and an interpositional flap, usually omentum, is secured between the two organs. Fertility is possible following repair of vesicouterine

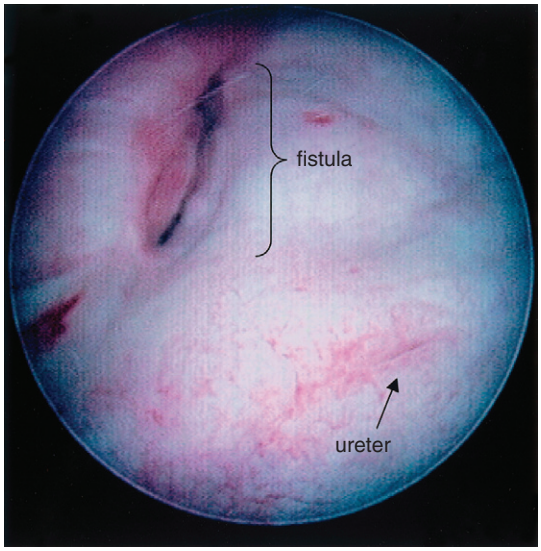


Figure 77–24. Cystoscopic view of vesicouterine fistula before repair.

Key Points: Vesicouterine Fistulae

- The most common cause of vesicouterine fistulae is low-segment caesarean section.
- Vesicouterine fistulae do not always present with urinary incontinence.
- Nonsurgical management of vesicouterine fistulae is possible by hormonally inducing involution of the uterus with maintenance of urinary drainage.
- Management of vesicouterine fistulae is contingent on the reproductive wishes of the patient. Hysterectomy followed by repair of the bladder is indicated for the individual who no longer desires fertility. Uterine-sparing procedures can be used and successful pregnancy is possible following vesicouterine fistula repair.

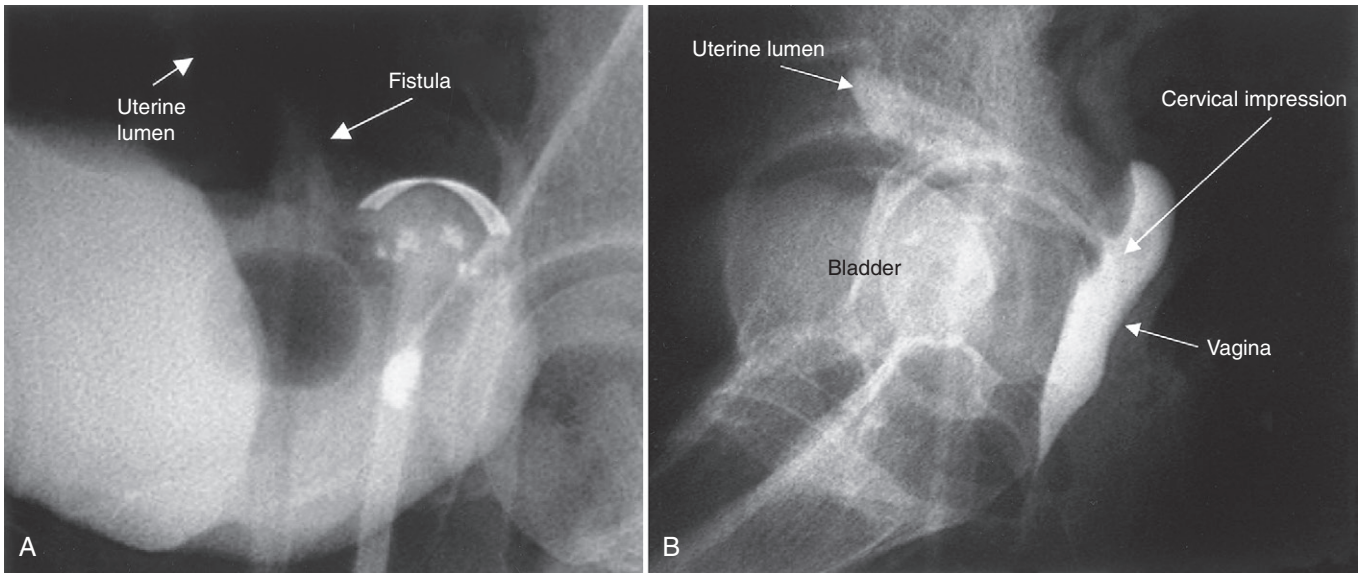


Figure 77–25. Cystogram demonstrating vesicouterine fistula in a postpartum woman. **A,** Filling of the bladder demonstrates a small amount of contrast material cephalad to the tip of the Foley catheter. The uterine cavity is faintly seen. **B,** Postvoid image demonstrates filling of the uterine cavity and cervical canal. The bladder is not well seen. This patient is immediately postpartum. Contrast material in the vagina outlines the incompetent cervical canal and os.

fistula. Lotocki and colleagues (1996) reported five pregnancies with four full-term deliveries in a cohort of 16 patients who had undergone uterine-sparing surgery for vesicouterine fistulae. Minimally invasive laparoscopic and robotic surgical approaches to the repair of vesicouterine fistulae have been reported (Miklos, 1999; Tarhan et al, 2007; Ramalingam et al, 2008).

Urethrovaginal Fistulae

Etiology and Presentation

In the industrialized world, urethrovaginal fistulae most commonly occur as a result of vaginal surgery, including anti-incontinence surgery, anterior vaginal wall prolapse surgery, and urethral diverticulectomy (Henriksson et al, 1982b; Webster et al, 1984; Blaivas, 1989; Glavind and Larsen, 2001). Importantly, with the rising popularity of midurethral synthetic slings for the treatment of stress urinary incontinence, there is the potential for increasing numbers of urethrovaginal fistulae due to iatrogenic urethral injury at the time of sling placement (Reisenauer et al, 2007; Morton and Hilton, 2009) (Fig. 77–27). In the developing world, similar to the etiology of VVF, obstructed labor is the most common cause of urethrovaginal fistulae (Elkins, 1994) (Fig. 77–28). In the setting of obstructed labor, this condition occurs due to extensive ischemic necrosis and often extends beyond the bladder neck, resulting in a combined urethrovesicovaginal fistula. These are extraordinarily challenging cases to repair due to the size of the fistula, ischemia of the surrounding tissues, and implications for continence in those individuals with destruction of the bladder neck and proximal urethra. Fortunately, due to modern obstetrical care in the industrialized world, these are rarely seen. **Other causes of urethrovaginal fistulae include radiation therapy for pelvic malignancy, trauma (including pelvic fracture), and vaginal neoplasms.** Another important cause in the long-term–care setting is urethral catheter erosion (Trop and Bennett, 1992; Andrews and Shah, 1998). In patients with poor sensation, especially the cognitively or otherwise neurologically impaired patient, pressure necrosis from a chronically indwelling catheter may result in a traumatic hypospadius and urethrovaginal fistula. If not recognized, over time the catheter may erode to the level of the bladder neck and beyond, effectively creating a bivalved urethra and a urethrovesicovaginal fistula (Fig. 77–29).

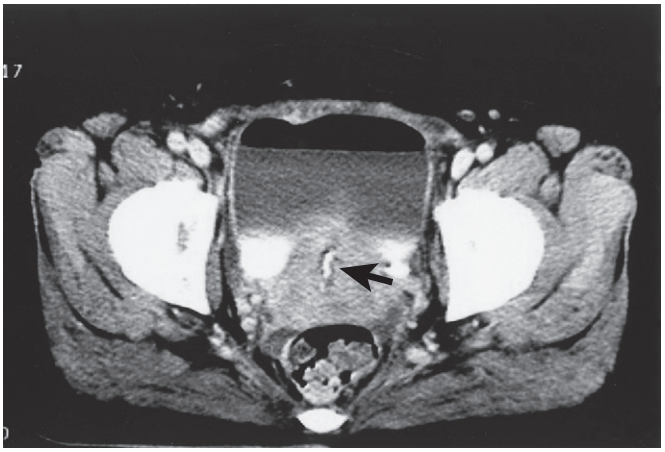


Figure 77–26. CT scan with contrast enhancement demonstrating a vesicouterine fistula. Contrast material is seen layering in the partially filled urinary bladder; contrast opacification of the uterine canal *(arrow)* suggests a vesicouterine fistula.

Symptoms of urethrovaginal fistulae are largely dependent on the size and location of the fistula along the urethral lumen. A small fistula may produce only minimal leakage, whereas a large urethrovaginal fistula can present with continuous urine drainage. **Proximal fistulae can be associated with stress incontinence, or, if they are located at the bladder neck, continuous incontinence may result, similar to that associated with vesicovaginal fistulae. Distal fistulae beyond the sphincteric mechanism may be completely asymptomatic or may be associated with a splayed urinary stream.** Occasionally, distal fistulae are associated with vaginal voiding and pseudoincontinence, so called because the patient only complains of urinary incontinence when rising from a seated position after voiding. This occurs as a result of urine accumulation in the vagina during voiding, with

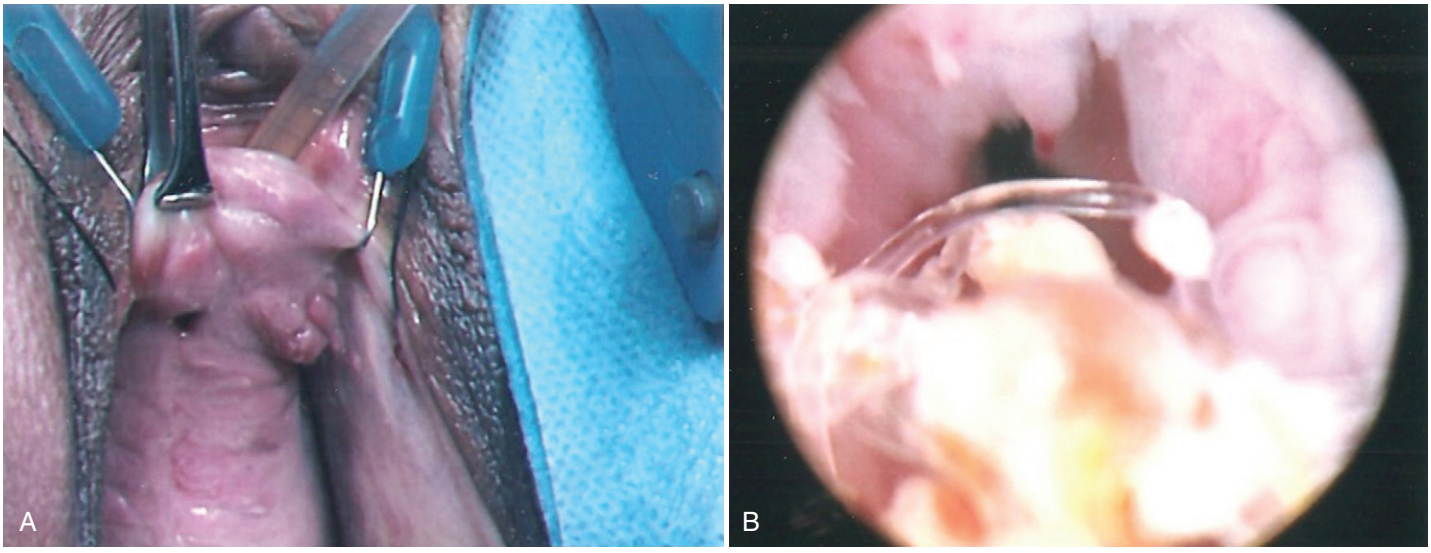


Figure 77–27. Urethrovaginal fistula following midurethral synthetic sling. **A,** Intraoperative view demonstrating a urethrovaginal fistula at the bladder neck following a midurethral sling. **B,** Cystoscopy demonstrates intraurethral sling material with calcified material.



Figure 77–28. Urethrovaginal fistula at the bladder neck from obstructed labor. A hemostat is seen entering the urethral meatus. (Courtesy of Mark Morgan, MD, Department of Obstetrics and Gynecology, Hospital of the University of Pennsylvania, Philadelphia, PA.)

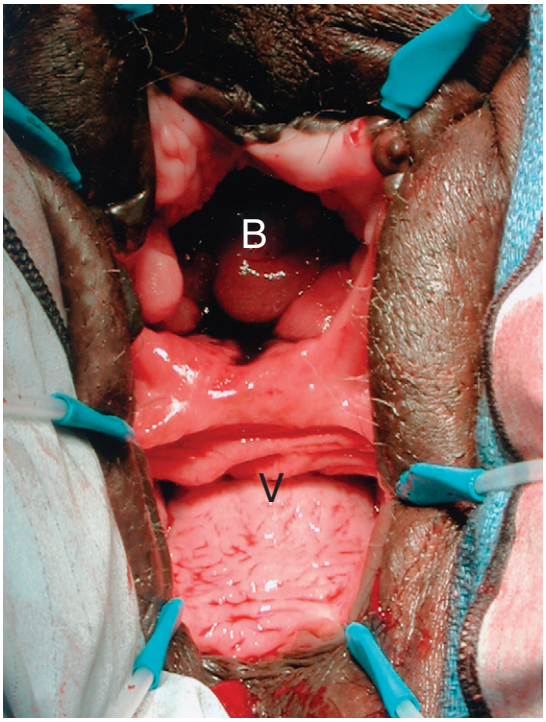


Figure 77–29. Severe complete erosion of the urethra secondary to chronic indwelling urinary catheter. This patient with advanced multiple sclerosis underwent surgical bladder neck closure and ileovesicostomy (ileal chimney). B, bladder; V, vagina.

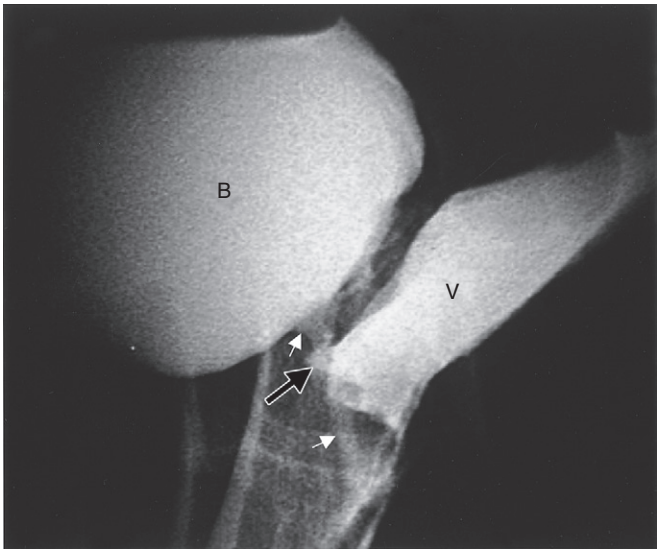


Figure 77–30. Urethrovaginal fistula on lateral voiding image from voiding cystourethrography demonstrates fistula *(black arrow)* in this patient with a primary symptom of vaginal voiding. The urethra proximal and distal to the fistula is well opacified *(white arrows)*. B, bladder; V, vagina.

emptying occurring upon standing—so-called vaginal voiding (Fig. 77–30).

Diagnosis and Management

The diagnosis of urethrovaginal fistula can often be made on physical examination and cystourethroscopy; however, voiding cystourethrography is most useful (Fig. 77–31), especially in complex cases. Small fistulae may be very difficult to locate on physical examination, even with a speculum, due to the surrounding vaginal rugation (Fig. 77–32). It is important to note that an **associated vesicovaginal fistula will be found in up to 20% of cases,** and therefore a thorough evaluation of the entire lower urinary tract is warranted (Lee et al, 1988).

Endoscopic examination of the urethra should be performed. However, due to its short length, the female urethra may be difficult to fully examine with a standard rigid cystoscope, because the irrigation fluid is discharged 1 to 2 cm proximal to the lens. A flexible cystoscope or a specially designed female cystoscope with a short beak is very helpful in visualizing the entire urethral lumen, because the irrigation fluid is discharged next to the lens, distending the adjacent urethral lumen (Fig. 77–33). Once the diagnosis is made on cystoscopy, the bladder is examined for additional fistulae. **Videourodynamics may accurately characterize any associated incontinence, including that associated with detrusor dysfunction. This study also assesses the anatomic relationship of the fistula to the bladder neck and urethra, as well as examines associated VVF.**

The surgical repair of urethrovaginal fistulae is challenging and can often be more difficult than repair of VVF. This is due to several factors, including extensive soft tissue defects as well as the lack of local viable tissue for a multilayer repair (Keettel et al, 1978). Repair of urethrovaginal fistulae usually involves the use of rotational vaginal wall flaps, but anterior- (Elkins et al, 1992) and posterior-based (Khanna, 1992) bladder flap tubes have been used as well.

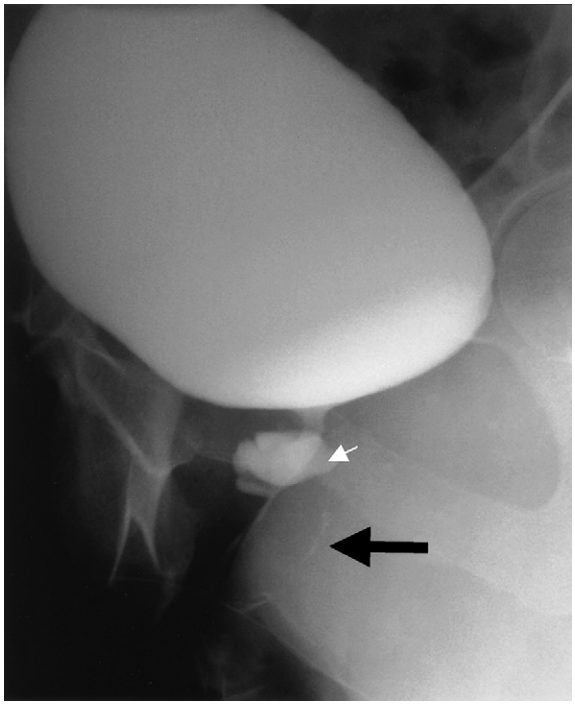


Figure 77–31. This patient was referred for the evaluation of persistent incontinence after urethral diverticulectomy. A voiding cystourethrogram demonstrates incomplete resection of the urethral diverticulum *(white arrow)* with a pinpoint postoperative urethrovaginal fistula (*black arrow* shows a small amount of contrast material faintly outlining the anterior vaginal wall). Resection of the residual diverticulum with repair of the fistula by a Martius flap was curative.

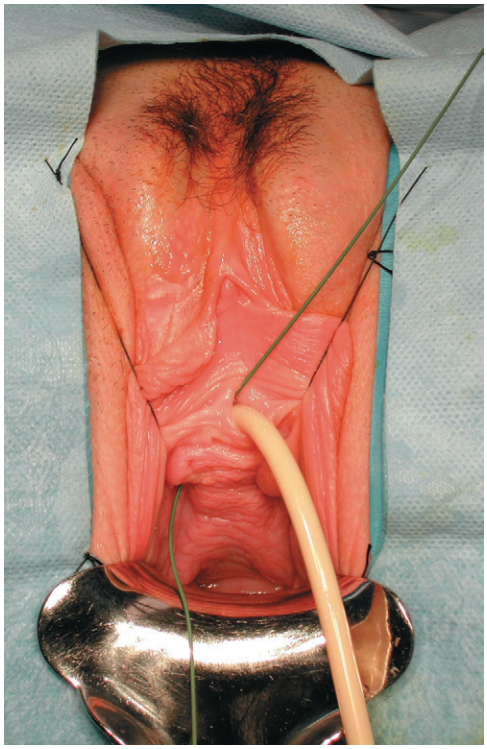


Figure 77–32. Urethrovaginal fistula. Identification of the exact fistula tract can be difficult in redo cases. Passage of a flexible wire endoscopically from the urethral lumen into the vagina can aid in locating the fistula tract.

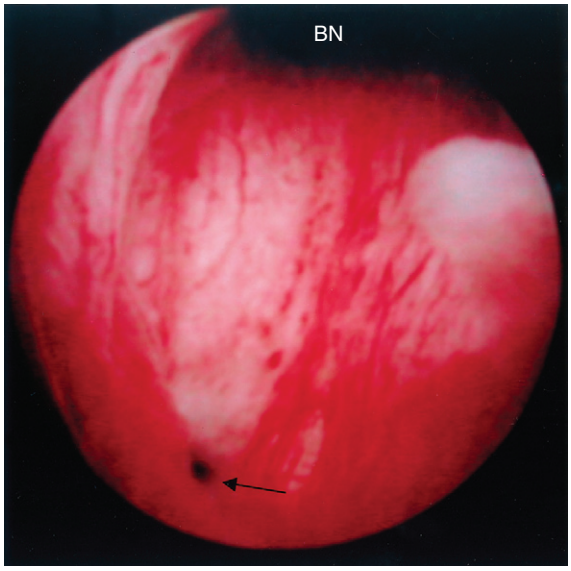


Figure 77–33. Endoscopic view of a urethrovaginal fistula *(arrow)*. This patient complained of ongoing urinary incontinence for 10 years after an endoscopic bladder neck suspension. BN, bladder neck.

A number of factors should be considered prior to repair. If the fistula is due to a foreign body, such as a synthetic sling (Reisenauer et al, 2007), the foreign material should be excised as widely as possible from the margins of the fistula, debridement performed on the associated devitalized or inflamed tissue and then the fistula closed with healthy tissues and flaps, if necessary. Small fistulae may be managed by a multilayered closure, usually with an interpositional graft such as a Martius flap (Webster et al, 1984; Leach, 1991). Larger fistulae, including those resulting from obstructed labor, may require extensive surgery, including urethral reconstruction (Tehan et al, 1980; Elkins et al, 1992; Wang and Hadley, 1993). **Distal fistulae without associated voiding symptoms or incontinence may be observed or, alternatively, can be managed with an extended meatotomy** (Lamensdorf et al, 1977). The quality of the vaginal tissues should be optimized prior to operative repair, which may include the use of antibiotics to treat associated infection, or topical estrogen treatment in those patients with significant atrophic vaginitis. Similar to VVF, timing of repair is controversial. Some authors have suggested that a waiting time of 2 to 6 months is advisable in most patients, with a waiting period of up to 1 year in those with radiation fistulae (Webster et al, 1984; Zimmern et al, 1986). Other authors have advocated immediate repair as soon as the vaginal tissues are free of infection and inflammation (Blaivas, 1989; Blaivas et al, 1995).

Operative Technique. The repair of urethrovaginal fistulae is conceptually very similar to the vaginal flap repair of VVF described previously. The patient is positioned in the dorsal lithotomy position, and urethral and suprapubic catheters are placed. A ring retractor is helpful for exposure. Allis clamps are used to reflect the vaginal wall cephalad exposing the fistula. In some patients, an episiotomy may facilitate exposure to the fistula improving visualization for repair (Webster et al, 1984). However, due to the distal (with respect to the vagina) location of these lesions, this is not usually necessary.

After infiltrating the fistula margins with injectable saline, the fistula tract is circumscribed through the vaginal wall (Fig. 77–34). The fistula tract and immediate surrounding epithelium is not

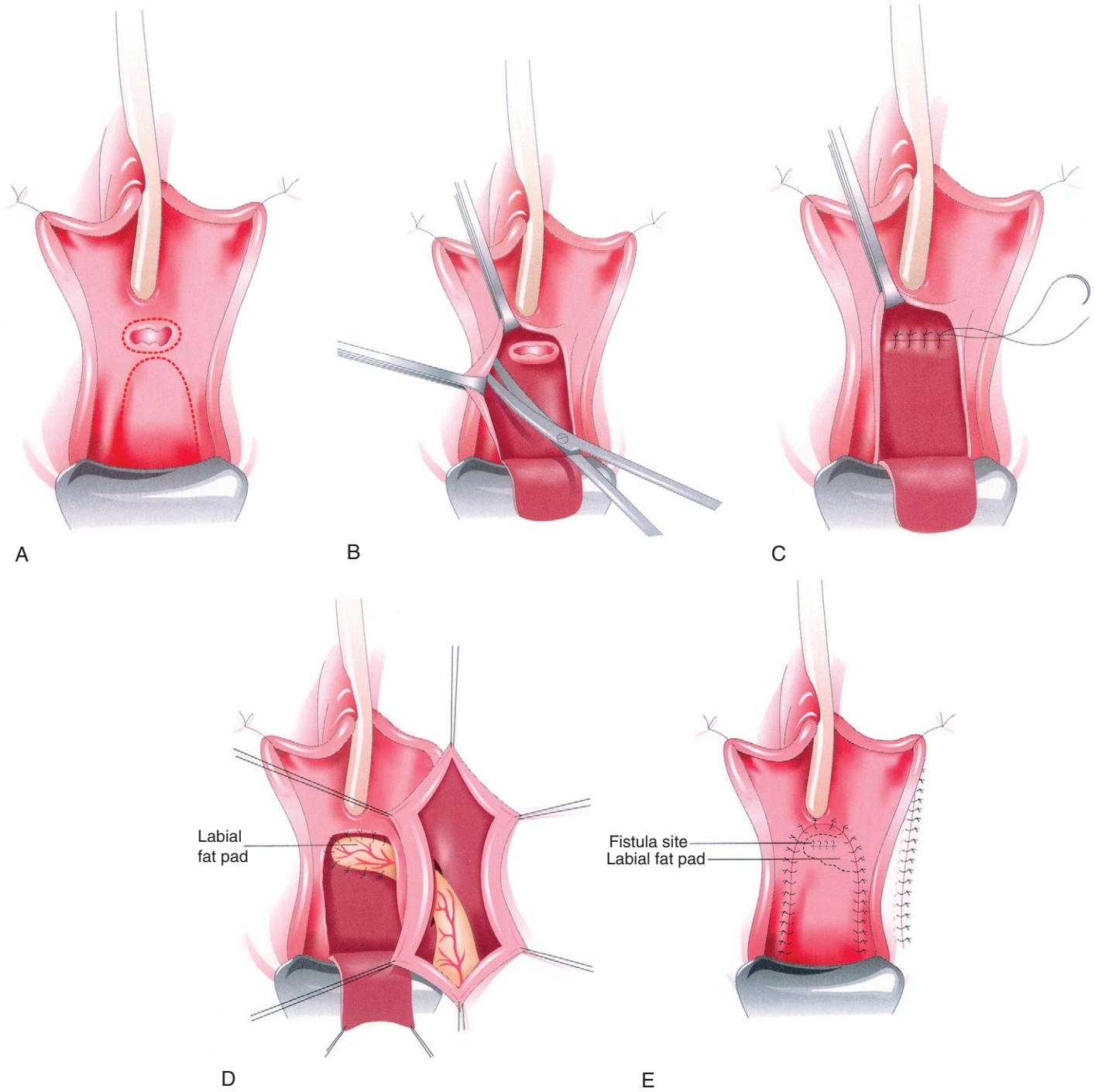


Figure 77–34. Operative diagram of urethrovaginal fistula repair. **A,** Inverted U incision is made in the anterior vaginal wall with the base of the U at the proximal margin of the fistula. The fistula is circumscribed. **B,** The anterior vaginal wall flap is mobilized, exposing the periurethral fascia. Dissection is also carried out laterally and distally from the margins of the fistula. The edges of the fistula tract are not excised. **C,** The epithelialized margins of the fistula tract are reapproximated with absorbable suture for the initial layer of closure. The periurethral fascia may be closed as a second layer, imbricating the initial layer of closure (not shown). **D,** A Martius flap may be harvested from the labia majora and tunneled as an additional layer of closure. **E,** The anterior vaginal wall flap is advanced over the closure and secured with absorbable suture. (From Leach GE, Kobashi KC. Urethral diverticulum and fistula. In: Cardozo L, Staskin D, editors. Textbook of female urology and urogynecology. London: Isis Medical Media; 2001. p. 721–45.)

typically excised, because this will create a larger defect in the urethra that will be more difficult to close without undue tension. However, the vaginal wall is dissected several millimeters from the edge of the circumscribed fistula tract in a radial orientation. An inverted U- or J-shaped incision is marked along the anterior vaginal wall, with the base of the U or J at the margin of the circumscribed fistula tract. This is infiltrated with injectable saline and the anterior vaginal wall flap is developed exposing the underlying periurethral fascia to the level of the bladder neck or beyond, depending on the size and location of the fistula. If a concomitant

anti-incontinence procedure is planned, dissection may be carried laterally from the edges of the flap at the level of the bladder neck and the retropubic space entered.

The edges of the circumscribed tract are reflected over the fistula and apposed with absorbable suture to create the first layer of closure. The periurethral fascia is then reapproximated in a perpendicular suture to the first layer of closure, thereby minimizing overlap. At this point, a Martius flap or other adjuvant flap can be secured over the periurethral fascia. Finally, the anterior vaginal wall flap is brought over the repair, including a Martius flap if used, and secured beyond the original fistula tract.

Adjuvant Flaps and Procedures in the Repair of Urethrovaginal Fistula. **Various types of soft tissue flaps are often an important component of a successful urethrovaginal fistula repair because fistula excision and vaginal flap advancement has been historically associated with a high rate of failure** (Birkhoff et al, 1977; Keettel et al, 1978; Davis et al, 1980; Patil et al, 1980; Leach, 1991; Fall, 1995; Bruce et al, 2000; Rangnekar et al, 2000b). A variety of adjuvant procedures have been used in the repair of urethrovaginal fistulae, including, most commonly, a Martius labial fat flap, but also gracilis and rectus abdominis muscle, myocutaneous flaps, vaginal wall flaps, fibrin glue, and free labial skin grafts (Keettel et al, 1978; McKinney, 1979; Tolle et al, 1981; Webster et al, 1984; Krogh et al, 1989; Leach, 1991; Izes et al, 1992; Candiani et al, 1993; Fall, 1995; Rangnekar et al, 2000b).

Webster and colleagues (1984) reported on 11 patients with urethrovaginal fistulae, of which 10 underwent surgical repair. Three of the 10 had recurrence of the fistula, all of whom were salvaged with a subsequent repair combined with a Martius labial fat pad interposition. Two patients had primary repair with a Martius flap (see prior discussion under VVF for a more complete discussion of the Martius flap), and both were cured. These authors recommended a Martius flap for all patients undergoing urethrovaginal fistula repair. Bruce and colleagues (2000) reported on the use of a pedicled rectus abdominis muscle flap based on the inferior epigastric artery for complex and refractory urethrovaginal fistulae in 6 patients. All patients had failed at least one attempt at repair with a Martius flap. Six of 6 patients remained successfully closed at a mean follow-up of 23 months. One of 6 patients had persistent urge incontinence postoperatively. The authors concluded that the rectus abdominis flap is a useful adjunct in the repair of complex or refractory urethrovaginal fistulae.

Suprapubic, as opposed to urethral catheterization, has been suggested postoperatively for at least 14 days to allow adequate healing (Tehan et al, 1980; Webster et al, 1984), although the use of only a single drainage catheter postoperatively is not universally agreed upon; other authors use both a suprapubic and urethral catheter (Leach, 1991). Anticholinergics are administered liberally to reduce bladder irritability. Usually, a VCUG with contrast administered through the suprapubic tube is obtained to document resolution of the fistula.

Stress incontinence (SUI) may persist following repair of urethrovaginal fistulae. Whether repair of SUI should be done concomitantly with the fistula surgery, or should be deferred until after repair of the fistula, is controversial. Blaivas and colleagues (1989) argued that sphincteric incontinence should be repaired at the time of fistula surgery with a Martius flap interposed between the fistula repair and a pubovaginal fascial sling. Webster and colleagues (1984) suggested that stress incontinence (SUI) associated with a proximal or mid-urethral urethrovaginal fistula should not be corrected until the fistula is closed and the patient reassessed for persistent incontinence. These authors suggest, however, that SUI associated with distal urethrovaginal fistula can be repaired concomitantly.

Overall, the success rate of urethrovaginal fistula repair is variable but is not generally considered to be as high as that for VVF repair (Gerber and Schoenberg, 1993). Not uncommonly, two or more procedures may be necessary to gain a satisfactory result (Webster et al, 1984).

Key Points: Urethrovaginal Fistulae

- Distal urethrovaginal fistulae are often asymptomatic, whereas proximal fistulae may present with intermittent or constant urinary leakage.
- Urethrovaginal fistulae due to surgical trauma may be difficult to visualize on physical examination or cystoscopy.
- Diagnosis of a urethrovaginal fistula is best made with VCUG.
- Repair of urethrovaginal fistulae can be challenging and often involve an interpositional tissue flap due to the relative lack of surrounding connective tissue in the mid and distal urethra.

UROENTERIC FISTULAE

Vesicoenteric Fistulae

Etiology and Presentation

Vesicoenteric fistulae commonly occur in the setting of bowel disease, such as diverticulitis, colorectal carcinoma, and Crohn disease. Less common causes include radiation, infection, and trauma—external penetrating trauma, as well as that due to iatrogenic surgical trauma. Diverticulitis is the most common cause of colovesical fistulae in most series, accounting for approximately 70% of cases (Mileski et al, 1987; Pollard et al, 1987; Walker et al, 2002; Najjar et al, 2004) (Table 77–8). **The second most common cause of vesicoenteric fistulae is cancer, followed by Crohn disease.** The peak incidence of vesicoenteric fisula is between 55 and 65 years of age, although fistulae due to Crohn disease present much earlier (Badlani et al, 1980). Approximately 2% of patients with diverticulitis may experience a colovesical fistula as a complication of their disease (Hafner et al, 1962). In a multi-institutional retrospective review of 400 patients with Crohn disease over a 10-year period, 8 patients (2%) were found to have enterovesical fistulae (Gruner et al, 2002). The underlying GI tract disease strongly influences the type of fistula**; ileovesical fistulae are more common in Crohn disease than in cancer, and colovesical fistulae are usually due to diverticulitis.**

Table 77–8.

Causes of Vesicoenteric Fistulae*

Diverticulitis	65%-75%
Malignancy	10%-15%
Crohn disease	5%-6%
Other (trauma, appendiceal abscess, foreign body)	<5%

*See Morse and Dretler, 1974; Amendola et al, 1984; Pollard et al, 1987; Schofield, 1988; Walker et al, 2002.

Table 77–9.

Presenting Symptoms of Vesicoenteric Fistula*

Pneumaturia	52%-77%
Fecaluria	36%-51%
Urinary tract infection symptoms (frequency, urgency, dysuria)	44%-45%
Fever and chills	41%
Abdominal pain	25%
Nonspecific gastrointestinal symptoms	25%
Hematuria	5%-22%
Orchitis	10%
Urine per rectum	5%

*Morse and Dretler, 1974; Pontari et al, 1992; Najjar et al, 2004.

Symptoms of vesicoenteric fistulae may originate from the urinary or gastrointestinal tract; however, in general, lower urinary tract symptoms are more common at presentation (Morse and Dretler, 1974; Ray et al, 1976). In the early stages, symptoms are nonspecific and relate to lower urinary tract dysfunction. Lower urinary tract symptoms include pneumaturia, frequency, urgency, suprapubic pain, recurrent urinary tract infections (UTIs), and hematuria (Table 77–9). **Pneumaturia is considered the most common presenting symptom noted in 50% to 70% of cases** (Morse and Dretler, 1974; Pontari et al, 1992; Jarrett and Vaughan, 1995; Solem et al, 2002). GI symptoms may include fecaluria and tenesmus. **The classic presentation of vesicoenteric fistula is described as Gouverneur syndrome and consists of suprapubic pain, urinary frequency, dysuria, and tenesmus** (Sans et al, 1986). Recurrent UTIs or cystitis refractory to antibiotic therapy may suggest a colovesical fistula (Rao et al, 1987). Although it is rare for enterovesical fistulae to present with sepsis (Woods et al, 1988), patients presenting with such signs are found to have urinary obstruction in approximately 70% of cases (Mileski et al, 1987).

Diagnosis

Many studies exist for the diagnosis of enterovesical fistulae; however, there are significant problems with both false negatives and false positives among the diagnostic modalities, and thus the diagnosis is often made on clinical grounds. **Cystoscopy has the highest yield in identifying a potential lesion, with some type of abnormality noted on endoscopic exam in greater than 90% of cases** (Morse and Dretler, 1974) (Fig. 77–35). **However, the findings on cystoscopy are often nonspecific and include localized erythema, papillary, or bullous change; a definitive diagnosis using cystoscopy can be made in only 35% to 46% of cases** (Woods et al, 1988; Pontari et al, 1992). Cystoscopy and biopsy of abnormal-appearing tissue, or an established fistula tract in the setting of a history of malignancy is indicated to evaluate for the possibility of a malignant fistula.

Cross-sectional imaging, especially CT scanning has become the imaging modality of choice (Goldman et al, 1984; Goldman et al, 1985; Jarrett and Vaughan, 1995; Gruner et al, 2002). CT or MRI (Haggett et al, 1995) may localize the fistula tract, as well as the involved segment of bowel. **The triad of findings on CT that are suspicious for colovesical fistulae consist of (1) bladder wall thickening adjacent to a loop of thickened colon, (2) air in the bladder (in the absence of previous lower urinary manipulation), and (3) the presence of colonic diverticula** (Labs et al, 1988).



Figure 77–35. Cystoscopic view of a chronic long-standing colovesical fistula. Unlike the majority of these fistulae, there is minimal inflammation around the fistula tract.



Figure 77–36. CT scan of colovesical fistula. Note the air in the bladder with the thickened posterior bladder wall.

Labs and colleagues (1988) correctly diagnosed colovesical fistulae on CT in 11 of 12 patients with surgically confirmed lesions. **CT is now generally considered to be the most sensitive and specific modality for the diagnosis of colovesical fistulae in suspect patients** (Najjar et al, 2004), **with diagnostic accuracy as high as 90% to 100%** (Goldman et al, 1985; Jarrett and Vaughan, 1995). **The high diagnostic accuracy of CT in detecting enterovesical fistulae relates to its ability to detect even a very small amount of air in the bladder** (Fig. 77–36). Although air in the bladder on diagnostic imaging is

very suggestive of colovesical fistulae, **false positives may be created by recent instrumentation (catheterization, cystoscopy) or an active UTI with a gas-forming organism. CT scanning should be done after the administration of oral contrast but prior to the administration of intravenous contrast to permit detection of barium within the bladder.** Ultrasonagraphy has also been reported to be useful in the diagnosis of colovesical fistulae. A characteristic "beak" sign may be noted; however, this study is not usually performed in the routine evaluation of the patient with a suspected enterovesical fistula (Chen et al, 1990).

Although commonly used, cystography and transrectal contrast studies (e.g., barium enema) are generally less likely to demonstrate the fistula. Rao and colleagues (1987) reported that 14 of 24 barium enemas either demonstrated or were suspicious for colovesical fistulae in a series of surgically treated patients. Barium enemas and/or colonoscopy may be valuable adjunctive studies in evaluating for colonic disease, such as malignancy, as a cause of the fistula; the preoperative knowledge of such a condition can considerably alter management decisions. Nevertheless, barium enemas have limited utility in the diagnosis of enterovesical fistulae due to low sensitivity (Amendola et al, 1984). **The Bourne test, however, can be a useful adjunctive study in the evaluation of colovesical fistulae** (Bourne, 1964). **As described, the Bourne test is performed following a nondiagnostic barium enema. The first voided urine following the barium enema is immediately centrifuged and then examined radiographically. Radiodense particles in the urine are considered a positive test and evidence for a vesicoenteric fistula.** Amendola and colleagues (1984) reported a positive Bourne test in 9 of 10 patients with colovesical fistulae; the Bourne test was the only evidence for a colovesical fistula in 7 such patients who had an otherwise negative evaluation with a combination of other diagnostic studies.

The diagnosis of vesicoenteric fistulae may be confirmed by the oral administration of activated charcoal which, in the setting of a fistula, will appear in the urine as black particles (Geier et al, 1972). This test provides no anatomic information regarding the location of the fistula but is useful in confirming the diagnosis in suspect cases. Intrarectal administration of vital dyes has been advocated for the diagnosis of occult colovesical fistula; however, the dye may be absorbed and then excreted in the urine, giving a false positive test (Deshmukh et al, 1977).

Management

Nonoperative management is a viable option in selected patients with vesicoenteric fistula. Amin and colleagues (1984) reported on 4 of 30 patients with colovesical fistulae secondary to diverticulitis who were observed without active intervention for 3 to 14 years. There were no significant long-term sequelae in this select patient population. **In nontoxic, minimally symptomatic patients with nonmalignant causes of enterovesical fistulae, a trial of medical therapy including intravenous total parenteral nutrition** (Dudrick et al, 1999), **bowel rest, and antibiotics may be warranted. This may be the preferred initial approach, especially in patients with Crohn disease, in whom the notion of immediate exploratory laparotomy and bowel resection is often discouraged due to the chronic relapsing nature of the disease** (Evans et al, 2003a). **There is also the potential for successful medical management of other fistulae resulting from inflammatory bowel disease** (Mahadevan et al, 2003; Parsi et al, 2004).

The goal of operative management is to separate and close the involved organs with minimal anatomic disruption and normal long-term function of both systems. Unfortunately, enterovesical fistulae may be complicated by intense pelvic inflammation, pelvic abscess, and phlegmon formation (in some cases), requiring complex staged reconstructions (Shackley et al, 2000). Bowel resection and/or partial cystectomy may be necessary to obtain viable tissue margins to ensure adequate, watertight closure of the involved viscera. An interpositional flap of greater omentum is often placed between the repaired bowel and urinary bladder to prevent overlapping suture lines and provide a well-vascularized surface for healing.

Both single and multistage procedures have been advocated, depending on the clinical circumstances (Morse and Dretler, 1974; Castro, 1975; Ray et al, 1976; Morrison and Addison, 1983; Mileski et al, 1987; Pollard et al, 1987; Rao et al, 1987; Shackley et al, 2000; Walker et al, 2002; Najjar et al, 2004). A one-stage procedure involves removal of the fistula, closure of the involved organs, and primary reanastomosis of the bowel following resection of the involved bowel segment. A two-stage approach advocates removal of the fistula, closure of the involved organs, and creation of a temporary proximal diverting colostomy, with a later return to the operating room for colostomy takedown once the fistula tract is demonstrated to be closed. **The choice of whether to proceed with a one-stage or two-stage repair is influenced by the location and cause of the fistula, the patient's general condition, the presence of a pelvic abscess, and the presence of colonic obstruction** (McConnell et al, 1980). **Patients with an inflammatory cause of the fistula, but without gross contamination, can be treated with a one-stage procedure, whereas those with an unprepared bowel, gross contamination, or abscess may require a multistage procedure** (Mileski et al, 1987; Shackley et al, 2000). As noted previously, most patients with colovesical fistulae present electively with lower urinary tract symptoms, not emergently in extremis with sepsis (Mileski et al, 1987). Therefore adequate preoperative support, including bowel preparation, nutritional supplementation, and appropriate antibiotics can be used in the majority of cases allowing an elective one-stage approach.

Laparoscopic management of colovesical fistulae has been reported, albeit with a relatively high rate of conversion to open repair (Joo et al, 1997).

Key Points: Vesicoenteric Fistulae

- The most common cause of vesicoenteric fistulae is diverticulitis.
- Presenting symptoms are usually urinary, most commonly pneumaturia.
- Diagnosis is generally made with a combination of cystoscopy and cross-sectional imaging, including a CT scan.
- Repair of colovesical fistulae involves a single- or multistage procedure, depending on a number of clinical factors, including the presence of gross fecal contamination and infection.

Ureteroenteric Fistulae

Fistulae between the ureter and the bowel are most likely to occur in the setting of inflammatory bowel

disease such as Crohn disease. The segment of bowel most likely to be involved is the terminal ileum (Banner, 1987), **and thus the vast majority cases of ureteroenteric fistulae are unilateral and right sided** (Sigel et al, 1977). Rarely, diverticulitis (Ney et al, 1986; Cirocco et al, 1994; Maeda et al, 1998) or ulcerative colitis will lead to a left- sided ureteroenteric fistula (Sigel et al, 1977). Involvement of the ureter is usually at the level of the sacral promontory (Sigel et al, 1977). Other causes of ureteroenteric fistulae include calculous disease, tuberculosis (TB), external and iatrogenic (surgical) trauma, radiation therapy, and transitional cell carcinoma (Javadpour et al, 1973; Sankaran et al, 1974; McElwee et al, 1983; Sumiya et al, 1985; Flood et al, 1992; Goetz et al, 1992; Toporoff et al, 1992; Oh et al, 2002). Unlike vesicoenteric fistulae, ureteroenteric fistulae are more likely to present with bowel rather than urinary symptoms. Pain may also be reported in the hip, flank, or anterior thigh.

The diagnosis is most often made by retrograde pyelography, although CT and IVU are useful as well. Barium contrast studies of the small bowel will often show a diseased segment of bowel but will only rarely demonstrate the fistula. **Treatment involves ureterolysis and possible bowel resection. Ureteral resection is not necessary if it can be separated from the involved bowel segment and stented.** Unfortunately, in many of these cases, significant renal damage has occurred prior to the definitive diagnosis, and thus nephrectomy may be necessary for definitive management (Sigel et al, 1977).

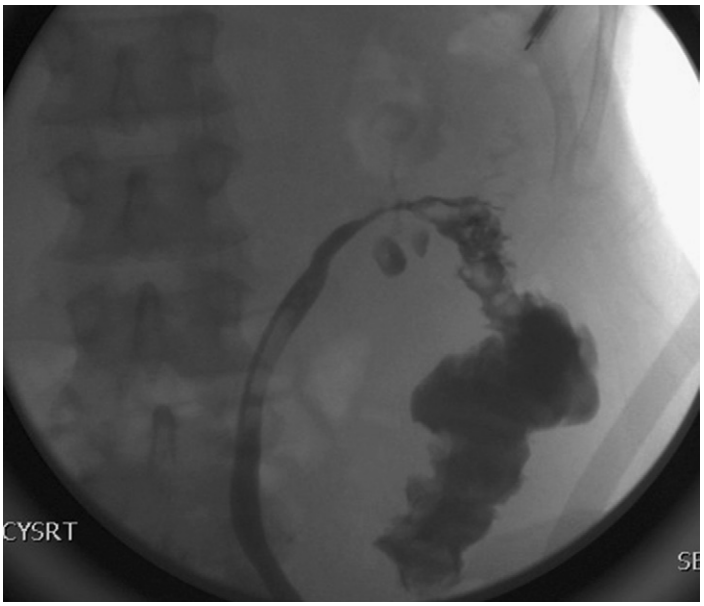


Figure 77–37. Pyelocolonic fistula following cryosurgical ablation of a renal tumor. Retrograde pyeloureterogram demonstrates contrast extravasation into the colon.

Pyeloenteric Fistulae

Pyelointestinal fistulae represent an epithelialized connection between the renal pelvis or collecting system of the kidney and the GI tract. **Chronic inflammatory disease, such as xanthogranulomatous pyelonephritis or other infectious diseases involving the kidney or bowel, historically has been the most common cause of this condition** (Schwartz et al, 1970; Greene et al, 1975; Bhargava et al, 1982; Cheatle et al, 1985; Desmond et al, 1989; Yildiz et al, 1993; Majeed et al, 1997). **However, iatrogenic surgical trauma, especially that related to percutaneous renal surgery and percutaneous nephrolithotomy (PCNL), has been associated with an increasing number of such fistulae** (LeRoy et al, 1985; Culkin et al, 1990) (Fig. 77–37). Penetrating external trauma, malignancy, ulcer disease, ingested foreign bodies, and complex calculous disease may also result in pyeloenteric fistulae (Brust and Morgan 1974; Mooreville et al, 1988; Blatstein and Ginsberg, 1996; Ginsberg et al, 1996; Chen et al, 2002). **Right-sided pyeloenteric fistulae most often involve the duodenum due to their close anatomical relationship, whereas left-sided pyeloenteric fistulae most commonly involve the descending colon.**

The majority of patients present with nonspecific symptoms, including malaise, nonspecific GI symptoms, urinary frequency, flank mass, or tenderness. Approximately 60% to 70% of patients present with flank pain, fever, and pyuria (Desmond et al, 1989). **Iatrogenic fistulae as a result of endourologic procedures may present with minimal symptoms.** In some cases, they are only noted incidentally on postoperative nephostogram (Culkin et al, 1990). Diagnosis can be made with a combination of urography, retrograde pyelography, and nephrostogram. The GI tract may be studied with a barium swallow or enema.

Historically, pyeloenteric fistulae were treated by nephrectomy and closure of the GI tract (Greene et al, 1975); however, given the changing nature of the cause of these lesions, in many cases the fistula may be initially treated conservatively, especially if associated with a normally functioning kidney. **A large nephrostomy tube, enteric suction or bowel rest, antibiotics, and removal of any foreign body (e.g., a stone) may be attempted. Internal stenting of the urinary tract may be pursued for maximal drainage** (Desmond et al, 1989). **Fistulae associated with a poorly functioning kidney are best treated by primary closure of the bowel and nephrectomy.**

Urethrorectal (Rectourethral or Prostatorectal) Fistulae

Acquired rectourethral fistulae (RUF) may occur in the male under a variety of clinical circumstances, including that related to prostatectomy for benign or malignant disease, cryotherapy, pelvic radiotherapy, anorectal surgery, external penetrating trauma (Bukowski et al, 1995; al-Ali and Kashmoula, 1997), **urethral instrumentation** (Thompson and Marx, 1990), **locally advanced prostatic or rectal malignancy, infection (e.g., TB)** (Okaneya et al, 1988), **ruptured prostatic abscess, or inflammatory disease (e.g., Crohn disease)** (Stamler et al, 1985; Fazio et al, 1987). Congenital rectourethral fistula associated with imperforate anus is covered in Chapter 128.

Etiology and Presentation

The incidence of rectourethral fistulae following radical retropubic prostatectomy (RRP) is low, but due to the frequency with which the operation is performed, it is the most common etiology of RUF in most modern series (Stephenson and Middleton, 1996; Nyam and Pemberton 1999; Renschler and Middleton, 2003). **Rectal injury during radical prostatectomy occurs in less than 1% to 2% of patients** (Igel et al, 1987; Borland and Walsh, 1992; McLaren et al, 1993;

Guillonneau et al, 2003). In a Mayo RRP series, there were 27 documented rectal injuries in 2212 patients (McLaren et al, 1993). In this series, 26 of 27 injuries were recognized intraoperatively and repaired. Six patients underwent temporary colostomy and 4 patients developed RUF. In a community-based practice, Harpster and colleagues (1995) reported rectal injuries in 7 of 516 patients undergoing RRP (1.4%) and in 1 of 17 patients undergoing radical perineal prostatectomy (Harpster et al, 1995). Five rectal injuries were recognized and repaired intraoperatively. There were three RUF reported in this series; none closed with conservative management and all required formal repair. In 2003, Rassweiler and colleagues reported one RUF in a series of 219 patients undergoing RRP but seven RUF in 538 patients undergoing laparoscopic radical prostatectomy. All operations were performed by the same surgical team. Guillonneau and colleagues (2003) reported a 1.3% incidence of rectal injury in 1000 consecutive patients undergoing laparoscopic radical prostatectomy. Eleven of 13 injuries were recognized and repaired intraoperatively with a two-layer closure. One of these patients subsequently underwent temporary colostomy for complications related to the injury. Both patients with rectal injuries that were recognized postoperatively underwent colostomy. One of the 2 patients presenting late with a rectal injury developed a RUF requiring a primary surgical closure.

In the setting of radical prostatectomy, a prior history of pelvic radiation therapy, rectal surgery, or TURP is associated with an increased risk of RUF (Thompson and Marx, 1990; McLaren et al, 1993). RUF that occur following radical prostatectomy are usually seen at the vesicourethral anastomosis and are often due to an unrecognized rectal injury at the time of surgery. However, when a rectal injury is recognized and repaired intraoperatively, RUF is extremely uncommon. Borland and Walsh reported 10 rectal injuries in 1000 nonirradiated patients undergoing radical prostatectomy at Johns Hopkins Hospital; however, no patient developed a rectourethral fistula (Borland and Walsh, 1992). Nine of 10 patients had a two-layer closure performed with an omental interpositional flap at the time of injury. One patient underwent a temporary diverting colostomy as the rectal injury was diagnosed and repaired postoperative day 2. Anal sphincter dilation performed on all patients, and they received 7 to 14 days of postoperative antibiotics.

The reported incidence of RUF following cryosurgical ablation as primary therapy for localized carcinoma of the prostate is between 0.5% and 2% (Zippe, 1996; Long et al, 2001), **whereas the rate of RUF following cryotherapy as salvage therapy for prostate cancer is somewhat higher at approximately 3.3%** (Chin et al, 2001). **The incidence of RUF following brachytherapy for prostate cancer, reported by Theodorescu and colleagues** (2000), **is 0.4%.** Rectourethral fistulae have also been reported following high-intensity focused ultrasound treatment (HIFU) (Uchida et al, 2002; Blana et al, 2004), HIFU combined with external beam radiotherapy (6% incidence) (Gelet et al, 2004), laparoscopic radical prostatectomy (Guillonneau et al, 2003; Katz et al, 2003; Rassweiler et al, 2003; Dafnis et al, 2004), and transurethral thermotherapy for benign prostatic hyperplasia (BPH) (Norby and Frimodt-Moller, 2000). The incidence of RUF in Crohn disease is estimated to be approximately 0.3% (Stamler et al, 1985) (Fig. 77–38). Fistulae due to Crohn disease are complex, and management should be individualized (Stamler et al, 1985; Fazio et al, 1987; Santoro et al, 1995; Cools et al, 1996; Rius et al, 2000).

The presentation of rectourethral fistula is variable. **Symptoms may include fecaluria, hematuria, UTI, nausea, vomiting, and fever.** Peritonitis and sepsis may occur as well. Digital rectal examination often permits palpation of the fistula tract along the anterior rectal wall. **Cystoscopy and sigmoidoscopy** (Shin et al, 2000) **visualize the fistula tract in the vast majority of cases and provide a mechanism for biopsy. In patients with a history of pelvic malignancy, biopsy of the fistula is suggested to evaluate for a local recurrence of the tumor** (Shin et al, 2000). Voiding cystourethrography (VCUG) or retrograde urethrography (RUG) usually provide a definitive diagnosis of RUF (Fig. 77–39). The exact anatomic location and size of the fistula is also usually well delineated on VCUG or RUG, providing important information in surgical planning. Lateral projections may be necessary to visualize small fistulae, because contrast in the rectum or urethra can sometimes obscure extremely thin fistulous tracts. **Upper tract imaging should be performed in patients with rectourethral fistulae to exclude a related ureteral injury. It is important to make an assessment of continence and sphincteric function in patients with RUF following radical prostatectomy. Given the location of most RUF at or near the vesicourethral anastomosis and the membranous urethra, there is a risk for persistent severe stress incontinence postoperatively following RUF repair** (Ghoniem et al, 2008). In patients with RUF and severe stress incontinence, closure of the RUF may not be sufficient to bring about continence in many patients. Additional procedures may be needed to bring about a satisfactory result in these patients; this is an important issue to discuss in preoperative patient counseling.

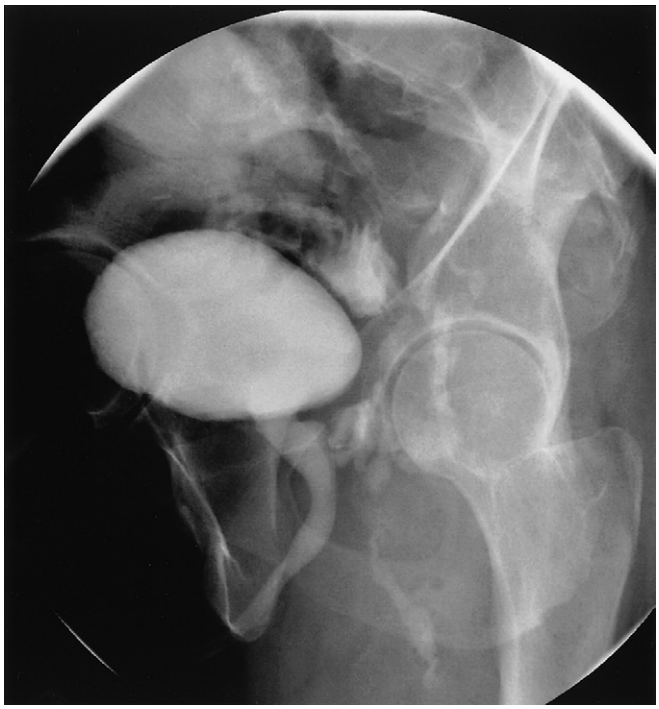


Figure 77–38. Rectourethral fistula due to Crohn disease. Contrast material is seen posterior to the bladder on this voiding image from voiding cystourethrography. (Courtesy of Nancy Curry, MD, Department of Radiology, Medical University of South Carolina, Charleston, SC.)

Management

Most RUF will require surgical repair (Bukowski et al, 1995; Stephenson and Middleton, 1996) although it is clear that some will



Figure 77–39. Rectourethral fistula after brachytherapy for carcinoma of the prostate. A retrograde urethrogram demonstrates filling of the rectum in this patient who presented several years after brachytherapy with fecaluria. The bladder is not opacified. The brachytherapy seeds are seen in the area of the prostate.

close with conservative management. **RUF following open or laparoscopic prostatectomy may heal spontaneously with catheter drainage, bowel rest, and intravenous hyperalimentation. In some cases, fecal diversion is necessary.** Rassweiler and colleagues (2003) reported that 6 of 8 RUF patients were treated successfully in such a manner. Two patients required a temporary colostomy. Noldus and colleagues (1999) reported closure with conservative management in 7 of 13 patients with RUF following radical prostatectomy or cystoprostatectomy. Six patients eventually were successfully closed with a transanal Latzko procedure (see below). Successful minimally invasive management has been reported, as well, using endoscopic suturing, fulguration of the fistula tract, and the application of fibrin glue (Wilbert et al, 1996).

Surgical repair of RUF can be challenging, and the basic tenets of operative fistula repair are especially relevant in these cases (see Table 77–2). Several surgical approaches have been advocated and are outlined below. **Single and staged repairs have been described for the repair of RUF.** The controversy surrounding the staged repair centers on the issue of whether or not to perform fecal diversion at all, or to perform it prior to or at the time of repair of the urinary tract. Some authors have advocated fecal diversion and staged repair of all RUF (Shin et al, 2000). This is considered the standard conservative approach and, in combination with an indwelling urethral catheter, permits a trial of spontaneous healing of the fistula without open manipulation of the urinary tract. In support of the single-stage repair, a successful one-stage approach limits the potential morbidity and cost of multiple procedures that, by design, accompanies the staged repair. **Suggested guidelines for cases in which a one-stage approach might be appropriate include surgically induced, small RUF not associated with infection, an abscess, or a poor bowel preparation** (Wood and Middleton, 1990; Nunoo-Mensah et al, 2008). **Staged repairs might be considered in cases of large fistulae, those associated with radiation therapy, uncontrolled local or systemic infection, immunocompromised states, or inadequate bowel preparation at the time of definitive repair** (Stephenson and Middleton, 1996; Nunoo-Mensah et al, 2008).

Transrectal approaches with and without division of the anal sphincter have been described for the operative repair of RUF. **The York-Mason procedure is a transrectal, transsphincteric approach that has been found to be effective and with low morbidity** (Henderson et al, 1981; Prasad et al, 1983; Wood and Middleton, 1990; Stephenson and Middleton, 1996; Fengler and Abcarian, 1997; Renschler and Middleton, 2003). **Classically, this is a staged repair with fecal diversion performed prior to repair of the RUF. However, in patients with small, nonirradiated fistulae, a single-stage approach can be used, provided that a vigorous bowel prepapration and broad-spectrum antibiotics are used** (Renschler and Middleton, 2003). For repair of the urinary tract, the patient is placed prone on the operating room table in the jack-knife position. A full-thickness incision through the posterior anus and dorsal rectal wall is performed and deepened down to the level of the coccyx through the external anal sphincter (Fig. 77–40). Care is taken to mark or tag each layer of the anal sphincter as it is divided. Later in the procedure during closure, careful anatomical reapproximation of the layers of the external anal sphincter is necessary to avoid the devastating complication of anal incontinence postoperatively. The anorectal incision as described provides excellent exposure of the fistula in the anterior rectal wall. The fistula tract is excised, and the anterior rectal wall is mobilized circumferentially around the fistula margins. The urethra is closed, and then the anterior rectal wall is closed. Finally, the rectal mucosa is reapproximated, providing a three-layer closure. Alternatively, following excision of the RUF, an anterior rectal wall flap can be developed and advanced over the fistula (al-Ali and Kashmoula, 1997), similar to the transvaginal repair of VVF using the vaginal wall (see previous discussion under VVF repair). Closure of the incision is performed by reapproximating the posterior rectal wall and then sequentially closing the layers of the anal sphincter in an anatomic fashion. Results with the York-Mason procedure have been excellent. In the largest series of patients undergoing the York-Mason procedure, Renschler and Middleton (2003) reported a successful repair in 22 of 24 patients. One of the two failures was subsequently repaired with another York-Mason procedure. No serious complications were reported, and no patient developed anal incontinence or anal stenosis. Similar excellent results have been noted by other authors (Prasad et al, 1983; Bukowski et al, 1995; Fengler and Abcarian, 1997).

In contrast to the transrectal, transsphincteric approach, the **transanal approach** to RUF repair does not involve division of the anal sphincter. Exposure of the fistula is provided by dilation of the anus and fixed retraction. The Latzko procedure is one such approach (Noldus et al, 1999; Hata et al, 2002). Similar to the Latzko method described previously for transvaginal VVF repair (see prior discussion), the fistula tract and surrounding rectal mucosa is denuded in all four quadrants. The fistula is then closed in three layers. The major disadvantage to this approach is the relatively poor exposure and lack of maneuverability within the operative field. Rectal advancement flaps have also been used to successfully treat RUF through a transanal approach (Fazio et al, 1987; Dreznik et al, 2003; Garofalo et al, 2003).

A **perineal approach** to RUF has been advocated by some authors in selected cases of RUF (Bukowski et al, 1995; Nyam and

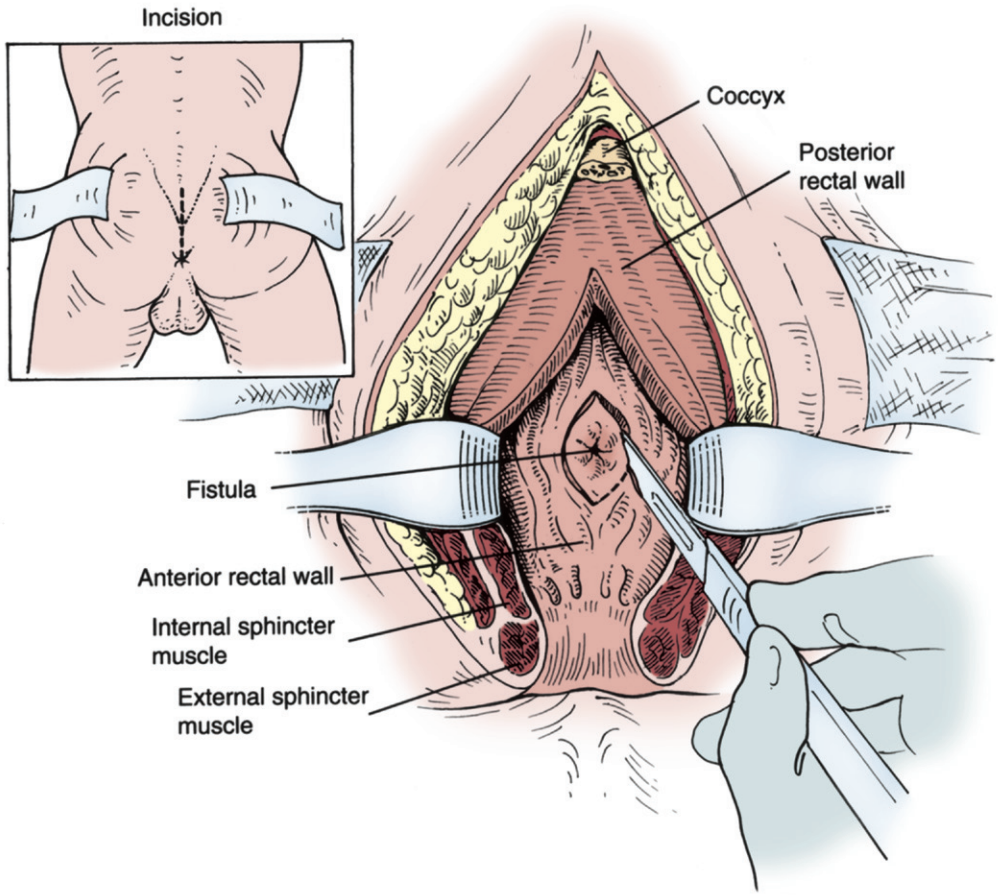


Figure 77–40. Diagram of York-Mason approach to the repair of rectourethral fistula. (From Middleton RG. Rectourethral fistula repair. In: Krane RJ, Siroky MB, Fitzpatrick JM, editors. Operative urology. Philadelphia: Churchill Livingstone; 2000. p. 286.)

Pemberton, 1999; Youssef et al, 1999; Zmora et al, 2003). Anatomically, this is a familiar approach for many urologists and has the added advantage of local access to a variety of potential interpositional flaps. Excellent results have been obtained with the perineal approach in combination with an interpositional flap, including gracilis muscle (Ryan et al, 1979; Rius et al, 2000; Zmora et al, 2003; Ghoniem et al, 2008; Gupta et al, 2008), pedicled Dartos muscle (Venable, 1989; Youssef et al, 1999; Yamazaki et al, 2001; Varma et al, 2007), penile skin (Morgan, 1975), levator muscle (Goodwin et al, 1958), and bladder (Kokotas and Kontogeorgos, 1983). Transabdominal approaches to RUF have been described with limited success (Bukowski et al, 1995; Nyam and Pemberton, 1999; Shin et al, 2000). The principal advantage of this technique is the availability of greater omentum for an interpositional flap. Potential disadvantages include the morbidity and prolonged postoperative convalescence associated with a laparotomy incision, poor exposure of the operative field (with limited maneuverability in the deep pelvis), and the risk of urinary and fecal incontinence.

The repair of rectourethral fistulae following external beam radiotherapy, (Chrouser et al, 2005), **combined radiotherapy** (Marguet et al, 2007), **brachytherapy** (Lane et al, 2006), **or cryosurgical ablation of the prostate can be especially difficult** (Izawa et al, 2000a; Elliott et al, 2006). These fistulae may be large and are associated with considerable induration, fibrosis, and ischemia for a variable distance around the fistula limiting reconstructive options. Urinary reconstruction may not be possible in some of these cases, necessitating urinary diversion. Moreira and colleagues (2004) reported on 11 cases of RUF following brachytherapy for the treatment of prostate cancer, all of whom underwent diverting colostomy. Three patients with satisfactory baseline continence underwent primary repair by a York-Mason approach with a gracilis flap; 7 patients underwent urinary diversion combined with radical pelvic surgery (6 cystoprostatectomy, 1 prostatectomy); and 1 refused repair. Izawa and colleagues (2000b) reported on the management of severe complications of cryosurgical ablation of the prostate, including two cases of prostatopubic fistulae and one rectourethral fistula. Two of these patients underwent cystoprostatectomy, and one had a bladder neck closure and continent reconstruction.

Key Points: Rectourethral Fistulae

- Rectourethral fistulae are an uncommon outcome that results most commonly from the surgical treatment of localized prostate cancer.
- Diagnosis of rectourethral fistulae can be confirmed with VCUG.
- Treatment of rectourethral fistulae most commonly involves surgical repair; however, select patients may respond to conservative therapy, including Foley catheter drainage.

UROVASCULAR FISTULAE

Fistulae between the urinary tract and the vascular system are rare but have increased in frequency with the rapid integration of minimally invasive interventions in the upper urinary tract, such as percutaneous access procedures (Clayman et al, 1984; Segura et al, 1985), **and indwelling ureteral stents** (Kar et al, 1984; Smith, 1984; Teuton et al, 1987; Sacks and Miller, 1988; Cass and Odland, 1990). These fistulae include communications between the upper urinary tract, including the collecting system or ureter and an artery or vein.

Renovascular and Pyelovascular Fistulae

The most common causes of renovascular or pyelovascular fistulae are procedures in which percutaneous renal access is required, such as percutaneous nephrolithotomy (PCNL) (Clayman et al, 1984; Segura et al, 1985; Lang, 1987; Lee et al, 1987). Typically, these fistulae are created upon puncture of an intrarenal vascular structure while creating or dilating the nephrostomy tract. The damaged vessel may bleed on puncture, or may not hemorrhage immediately due to external compression and tamponade from the catheter in the nephrostomy tract. However, upon removal of the catheter, brisk bleeding may be noted into the relatively lower-pressure renal collecting system (Patterson et al, 1985). Alternatively, a long-term indwelling nephrostomy tube may lead to pyelovascular fistula formation. In this setting, a chronic indwelling, large-bore nephrostomy tube may result in erosion into an adjacent renal vessel, with resulting hemorrhage following removal of the tube. Lee and colleagues (1987) reported an 11.2% incidence of bleeding requiring transfusion and 1.2% incidence of bleeding requiring surgical or angiographic intervention following PCNL in 582 patients. Patterson and colleagues (1985) reported a vascular injury in 0.9% of 1032 patients undergoing percutaneous renal stone surgery. Segura and colleagues (1985) reported a 3% transfusion rate in 1000 patients undergoing PCNL. Other causes of renovascular fistula include external penetrating and blunt (Stower et al, 1989) trauma, infection, and open renal surgery, including partial nephrectomy.

Renovascular fistulae may present with life-threatening hemorrhage and hypovolemic shock, or intermittent gross hematuria. Following PCNL, these fistulae may appear upon removal of the nephrostomy tube with brisk bleeding out of the flank from the nephrostomy tube tract in combination with brisk hematuria, or they may present several days to weeks later with only hematuria (Clayman et al, 1984; Patterson et al, 1985).

Treatment of renovascular fistulae is contingent on the presentation, etiology, and hemodynamic stability of the patient. Patients with severe hemorrhage upon removal of the nephrostomy tube can be temporized in some instances by replacing the tube, or, in large mature tracts, by placing a Foley catheter to tamponade the bleeding. In patients with ongoing bleeding, transcatheter angiographic embolization of the lacerated vessel is recommended (Clayman et al, 1984; Patterson et al, 1985). Occasionally, flank exploration is necessary with partial or simple nephrectomy to control hemorrhage.

Ureterovascular Fistulae

Rarely reported prior to the advent of indwelling ureteral stents, ureterovascular fistulae are becoming increasingly common. **Most reported ureterovascular fistulae are ureteroiliac artery fistulae, although ureteroiliac vein fistulae have been reported as well** (Teuton et al, 1987). Ureteroaortic fistulae are extremely rare, with few cases reported in the literature (Holmes et al, 1998; Georgopoulos et al, 2003).

Most cases of ureteroarterial fistulae are reported in patients with a prior history of vascular disease, radiation therapy, and/or pelvic surgery, especially in the setting of indwelling ureteral stents. In fact, ureteroarterial fistulae are highly associated with indwelling stents (Nelson and Fried, 1981; Kar et al, 1984; Smith, 1984; Bhargava and Yusuf, 1987; Sacks and Miller, 1988; Cass and Odland, 1990; Batter et al, 1996; Bergqvist et al, 2001). Of the 37 cases of ureteroarterial fistula reported in the literature by Batter and colleagues (1996) prior to 1996, 24 were associated with a ureteral stent (Table 77–10). All patients in this review had at least one of the risk factors listed in Table 77–10. Pressure necrosis from a chronic, relatively inflexible indwelling stent against a pulsatile iliac artery may be an important factor in the development of ureteroarterial fistulae in some cases (Batter et al, 1996). Fistula formation occurs between the high-pressure vascular lumen and the low-pressure ureter with the development of gross hematuria. A history of radiation therapy or prior pelvic surgery may exacerbate the already compromised and stented ureter, thus increasing the risk of fistula formation (Toolin et al, 1984). Ureteroarterial fistulae are also highly associated with vascular pathology such as iliac artery aneurysms. Atherosclerotic aneurysms may produce perivascular inflammation and fibrosis that entraps the overlying ureter, especially in the region of the iliac vessels. The ureter may become fixed and obstructed and, in such a position, may be subject to chronic pulsations from the underlying abnormal vessel. Placement of a ureteral stent to relieve the obstruction may further compromise the ureteral wall where it crosses over the vessel, resulting in pressure necrosis and eventual fistula formation (Sacks and Miller, 1988; Cass and Odland, 1990). Ureteroarterial fistulae have been reported following balloon dilation of ureteral strictures (Sacks and Miller, 1988; Quillin et al, 1994). Ureteroarterial fistulae may also present in the setting of ileal conduit reconstruction, pelvic malignancy, prior ureterolithotomy, external penetrating trauma, and pregnancy (Reiner et al, 1975; Cass and Odland, 1990; Dervanian et al, 1992; Puppo et al, 1992; Wampler et al, 1992; Batter et al, 1996; DePasquale et al, 2001; Siablis et al, 2002; Takahashi et al, 2004).

Ureterovascular fistulae may present with microscopic hematuria, intermittent gross hematuria, or life-threatening exsanguinating hemorrhage. The key to the diagnosis of ureteroarterial fistulae is a high index of suspicion in an at-risk patient presenting with gross hematuria (Smith, 1984; Dervanian et al, 1992; Batter et al, 1996). These fistulae are rarely considered in the initial differential

Table 77–10.

Predisposing Risk Factors in 37 Patients with Ureteroarterial Fistulae

Prior genitourinary/pelvic surgery	68%
Ureteral stenting	65%
Radiation therapy	46%
Prior vascular surgery	19%
Vascular pathology	19%

From Batter SJ, McGovern FJ, Cambria RP. Ureteroarterial fistula: case report and review of the literature. Urology 1996;48:481–9.

diagnosis of gross hematuria. **Intermittent gross hematuria or the sudden onset of massive hematuria in a patient with an indwelling stent and a history of previous iliac artery surgery or radiation should raise the suspicion of a ureteroarterial fistula** (Cass and Odland, 1990).

The routine urologic and radiologic evaluation of hematuria will not generally provide evidence of ureterovascular fistula (Quillin et al, 1994). **Even in suspected or proven cases, preoperative radiologic investigations, including nonselective arteriography and pyelography, are often nondiagnostic** (Cass and Odland, 1990; Batter et al, 1996). This is especially true in patients with intermittent hematuria in whom there is no active bleeding at the time of the radiographic investigation, presumably due to thrombus over the site of the fistula. Selective or subselective arteriography of the iliac vessels may be more revealing in suspected cases, and provocative maneuvers, such as stent removal, or mechanical friction of the ureteral lumen by manipulation of the stent may be necessary to demonstrate the fistulous connection in patients without active bleeding who are undergoing angiography (Keller et al, 1990; Quillin et al, 1994). **However, these adjuvant maneuvers should only be performed with extreme caution in an appropriate setting where immediate angiographic or surgical intervention is possible.** In the review by Batter and colleagues (1996) retrograde pyelography was diagnostic for only 6 of 10 patients in whom it was performed, and arteriography was diagnostic for a ureterovascular fistula in only 4 of 14 cases. Indirect evidence of a ureteroarterial fistula can be found on CT, but findings are usually nonspecific and only suspicious in retrospect following a confirmed diagnosis by other means (Baum et al, 1987; Jafri et al, 1987). **Nevertheless, in a stable patient with a suspected ureterovascular fistula, a full radiographic evaluation may be pursued, not only for diagnostic purposes but also to evaluate potential reconstructive options** (Batter et al, 1996), **and, in select cases, to perform therapeutic angiographic embolization procedures.**

Because these patients may present in extremis with hypotension and severe hemorrhage, surgical intervention must be considered early, especially because radiographic evaluation may be nondiagnostic (Dervanian et al, 1992). **In cases where angiography is pursued for diagnosis, an endovascular stent graft may be placed** (Bergqvist et al, 2001; Sherif et al, 2002; Krambeck et al, 2005; Meester et al, 2006; Muraoka et al, 2006; Ishibashi et al, 2007; Araki et al, 2008).

Eventual management of these fistulae must address both the vascular and urinary sides of the fistula. Successful management of the vascular side may involve embolization, endovascular stent graft placement, primary repair (Kar et al, 1984), or even ligation with or without extra-anatomic vascular bypass. Limb salvage is an important consideration in iliac artery fistulae, and therefore vascular surgery consultation is necessary in most cases. Ultimate management of the vascular side of the fistula is dependent on several factors, including the presence of infection or abscess, presence of aneurysm or occlusive disease in the iliac artery, and the availability of collateral circulation to the ipsilateral lower extremity (Batter et al, 1996). Often, vascular occlusion, either angiographically or surgically, is followed by vascular bypass procedures in these cases.

Repair and reconstruction of the urinary tract is complicated in these patients who often have a history of pelvic radiation, malignancy, vascular disease, and/or prior surgery. Preservation of nephrons is a priority in functioning renal units. Urinary reconstruction can be performed by ureteroureterostomy, transureteroureterostomy, cutaneous ureterostomy, or percutaneous nephrostomy with ureteral ligation (Nelson and Fried 1981; Kar et al, 1984; Smith 1984; Batter et al, 1996; Gibbons et al, 1998). Nephrectomy is usually reserved for poorly functioning kidneys, or those patients unfit for urinary reconstruction.

General recommendations to prevent ureteroarterial fistulae include the use of the smallest, softest, and most flexible ureteral stents for the shortest time interval possible in patients at risk for ureterovascular fistula (Cass and Odland, 1990; Puppo et al, 1992).

Key Points: Urovascular Fistulae

- Pyelovascular fistulae most commonly result from percutaneous interventional procedures to the upper urinary tract.
- Patients with suspected ureteroarterial fistulae usually have one or more risk factors including a history of pelvic radiotherapy, indwelling ureteral stents, prior pelvic surgery, and/or vascular disease.
- Ureteroarterial fistulae are difficult to diagnose radiographically with standard imaging, including CT scan and retrograde pyelography.
- Patients suspected of having a ureteroarterial fistula based on history and the presence of significant risk factors should be treated expeditiously and aggressively upon presentation.

OTHER URINARY FISTULAE

Urinary fistulae have been reported between the kidneys and thoracic cavity due to a number of causes, including infection, trauma, and stone disease. Infectious causes include xanthogranulomatous pyelonephritis, TB, and renal abscess (Arida and Verderame, 1977; Blight, 1980; Kyriakopoulos et al, 1991; Haney et al, 1992; Alifano et al, 1999). Fortunately, nephropleural and nephrobronchial fistulae are uncommon. **Importantly, percutaneous access to the kidney for endourologic procedures may be complicated by nephropleural fistula.** Lallas and colleagues (2004) reported a 1% incidence of nephropleural fistulae in 375 patients undergoing percutaneous access procedures. All of the affected patients had a supracostal access tract performed; none of the patients with a subcostal access tract developed this complication. Presenting symptoms may include cough, a urine-like taste in the mouth, fever, and flank pain. Rarely, recurrent lung abscess may be a manifestation of an occult nephropleural fistula (Caberwal et al, 1977; O'Brien and Ettinger, 1995).

Treatment of nephropleural or nephrobronchial fistulae generally involves percutaneous drainage of any associated abscess (if present), treatment of associated infection, and/or urinary obstruction, and surgical exploration with interposition of healthy tissue. **Iatrogenic fistulae due to percutaneous access procedures can be managed nonoperatively in some cases** (Lallas et al, 2004). For patients undergoing surgical exploration, a double-lumen endotracheal tube may be useful during surgery to isolate the affected lung and pleural cavity and prevent contamination of the contralateral side (Rao et al, 1981). **Nephrectomy is indicated in poorly functioning renal units.**

Cutaneous fistulae from the urinary tract may arise from the kidney, ureter, bladder, or urethra. Renocutaneous fistulae may occur as a result of chronic infection, especially in the setting of calculous disease (Haney et al, 1992). Often the associated renal unit is poorly functioning, and thus definitive treatment is provided by nephrectomy. External trauma or iatrogenic surgical trauma, such as percutaneous renal surgery or partial nephrectomy, may also result in a renocutaneous fistula. Prompt treatment with internal ureteric stenting is generally successful by providing unobstructed antegrade urinary drainage. Most ureterocutaneous and vesicocutaneous fistulae are iatrogenic or otherwise purposefully surgically created to facilitate urinary drainage. Other uncommon causes include external penetrating trauma, malignancy, and chronic infection.

For newly diagnosed urocutaneous fistulae, it is imperative to evaluate for distal urinary obstruction. If present, the obstruction should be treated, if possible, or bypassed. **Individuals with nonhealing urocutaneous fistulae due to chronic infection should be evaluated for not only an occult source of the infection, but also undergo a nutritional evaluation because these individuals may be catabolic, immunosuppressed, and unable to mobilize adequate metabolic reserves to initiate wound closure.** Other considerations in individuals with non-healing urocutaneous fistulae include occult malignancy or an undiscovered foreign body.

Urethrocutaneous fistulae in the male most commonly present as sequelae of hypospadias repair and are covered in Chapter 130.

Key Points: Other Fistulae

- Nephropleural or nephrobronchial fistulae are uncommon and may occur secondary to percutaneous access procedures to the upper urinary tract.
- Urocutaneous fistulae may originate from multiple locations within the urinary tract.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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Bladder and Female Urethral Diverticula

Eric S. Rovner, MD

BLADDER DIVERTICULA

Bladder diverticula represent a herniation of the bladder urothelium through the muscularis propria of the bladder wall. This results in the typical finding of a variably sized, thin-walled, urine-filled structure adjacent to and connecting with the bladder lumen through a narrow neck, or ostium. **Histologically, the diverticulum wall is composed of mucosa, subepithelial connective tissue or lamina propria, scattered thin muscle fibers, and an adventitial layer** (Fig. 78–1) (Peterson et al, 1973; Gil-Vernet, 1998). **A fibrous capsule or pseudocapsule outer shell is often present and may be a useful surgical plane for excision** (see later discussion). The outside wall of the bladder diverticulum may contain some residual scattered strands or bundles of smooth muscle; however, these are disorganized and nonfunctional. Therefore bladder diverticula generally empty poorly during micturition, leaving a large postvoid residual urine volume that results in the characteristic findings on presentation and imaging.

Classification, Pathophysiology, and Etiology

Bladder diverticula may be classified as either congenital or acquired. Pathophysiology, presentation, and imaging may differentiate these two types. **Congenital diverticula usually present during childhood, with a peak incidence in those less than 10 years old** (Boechat and Lebowitz, 1978). **These are usually solitary, occur most commonly in males** (Stage and Tank, 1992; Sarihan and Abes, 1998; Evangelidis et al, 2005; Garat et al, 2007), **and are located lateral and posterior to the ureteral orifice, often in association with vesicoureteral reflux** (Evangelidis et al, 2005; Garat et al, 2007). **The primary causation in those without coexisting lower urinary tract conditions appears to be a congenital weakness at the level of the ureterovesical junction and not bladder outlet obstruction** (Johnston, 1960; Hutch, 1961; Hutch et al, 1961; Stephens, 1979). Blane and colleagues (1994) reported the incidence of bladder diverticula in children to be approximately 1.7% in a pediatric genitourinary database of more than 5000 cases. Congenital bladder diverticula are usually solitary but larger in comparison with those associated with obstruction or neurogenic bladder dysfunction (Gearhart, 2002). The most common presentation of congenital bladder diverticula is urinary tract infection (Bauer and Retik, 1974; Pieretti and Pieretti-Vanmarcke, 1999; Evangelidis et al, 2005; Garat et al, 2007). Congenital bladder diverticula may occur in the presence of normal voiding dynamics in the absence of bladder outlet obstruction (Cendron and Alain, 1972; Barrett et al, 1976), but secondary bladder outlet obstruction may occur when the diverticulum extends distally toward the bladder neck (Taylor et al, 1979; Epstein et al, 1982; Verghese and Belman, 1984; Oge et al, 2002). **Typically, congenital bladder diverticula are found in smooth-walled bladders and are not associated with significant trabeculation on cystoscopic examination** (Hutch, 1961). However, in patients with prune-belly syndrome or posterior urethral valves, bladder diverticula may be located at the dome and be associated with aberrant voiding dynamics and/or anatomy. These are to be distinguished from the urachal diverticula seen in some pediatric urologic conditions. Congenital bladder diverticula have been noted in association with a number of congenital syndromes, including Menkes syndrome (kinky hair or copper deficiency syndrome) (Harcke et al, 1977; Daly and Rabinovitch, 1981), Williams syndrome (Babbitt et al, 1979; Blane et al, 1994; Schulman et al, 1996), Ehlers-Danlos syndrome (Breivik et al, 1985; Levard et al, 1989; Schippers and Dittler, 1989; Rabin et al, 1991; Bade et al, 1994; Cuckow et al, 1994; Burrows et al, 1998), and fetal alcohol syndrome (Lewis and Woods, 1994). Whether there is a genetic predisposition to the formation of bladder diverticula in individuals without congenital syndromes is unclear, although congenital bladder diverticula have been reported in twins (Beall and Berger, 1978) and possibly as an autosomal-dominant trait in a family (Hofmann et al, 1984).

Acquired (also termed "secondary") diverticula occur most commonly in the setting of bladder outlet obstruction or neurogenic vesicourethral dysfunction. Similar to the congenital type, these diverticula are also located most commonly at the ureterovesical hiatus (Van Arsdalen and Wein, 1992) but also occur elsewhere in the bladder. **Acquired diverticula in males usually occur after age 60, which corresponds to the age of the development of prostatic enlargement** (Fig. 78–2). Bladder outlet obstructions, including those due to benign and malignant disease of the prostate or urethral stricture, are commonly associated factors in adults, although obstruction is not considered to be present in all cases (Blacklock et al, 1983). **Acquired diverticula are often multiple, typically found in association with significant bladder trabeculation** (Wesselhoeft et al, 1963), **and much more common in males than females** (Senger et al, 1952; Pool and Hacker, 1966). Bladder

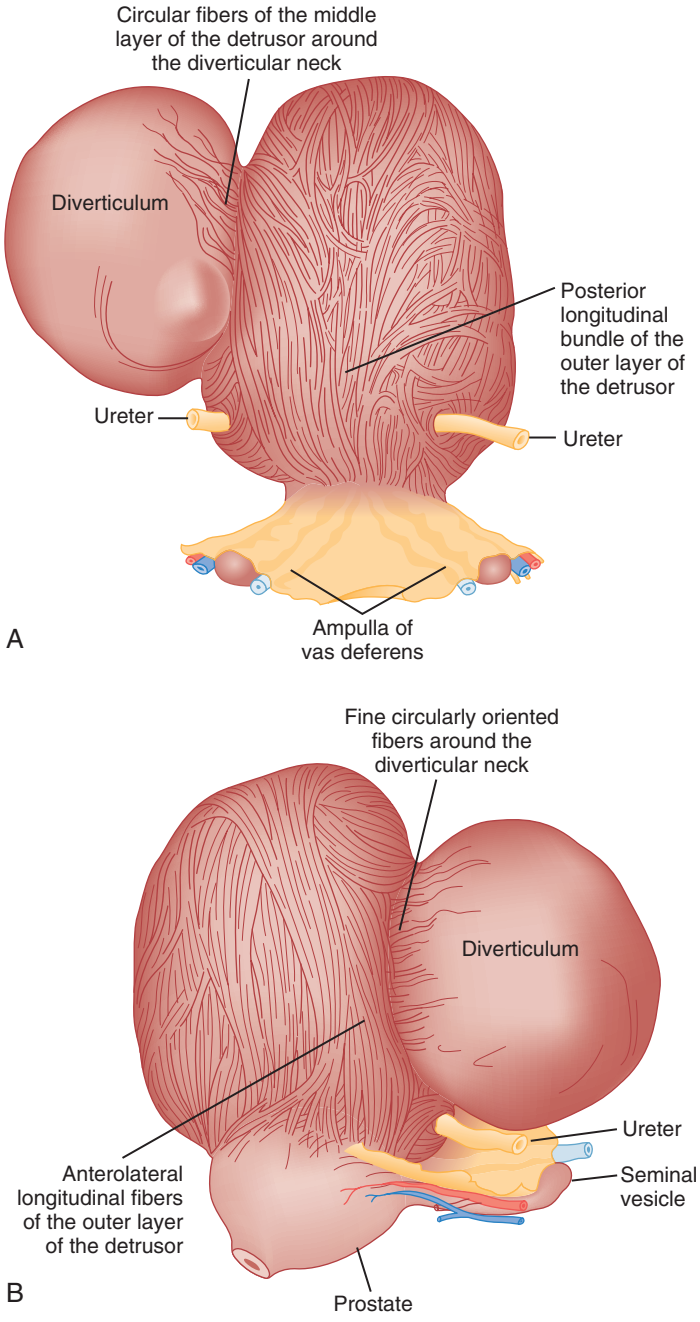


Figure 78–1. Drawing of bladder diverticulum. **A,** Posterior view. **B,** Lateral view.

diverticula in females are uncommon (Gillon et al, 1988) and quite rare in the absence of obstruction (Safir et al, 1998) (Fig. 78–3). Historically, the reported prevalence of moderate- to large-sized bladder diverticula in association with "prostatism" is approximately 1% to 6% (Burns, 1944). It is important to note that an acquired bladder diverticulum may also be found in children and young adults secondary to a number of conditions, including bladder neck dysfunction, posterior urethral valves, and neurogenic vesicourethral dysfunction. **If the diverticulum encompasses the ureteral orifice in the setting of a neurogenic bladder and vesicoureteral reflux, it is termed a "Hutch" diverticulum** (Hutch, 1952). These diverticula may also occur in the setting of dysfunctional voiding.

Bladder diverticula may also be iatrogenic (Hernandez et al, 1997; Suzuki et al, 2002; Chertin and Prat, 2008). Inadequate closure of the muscular layers of the bladder wall following a cystotomy for any indication may result in formation of a bladder diverticulum at a weak point of the suture line. Bladder diverticula may also occur following ureteral reimplantation surgery at the ureteroneocystostomy site (Ahmed and Tan, 1982; Sheu et al, 1998).

Diagnosis and Evaluation

Presentation

Acquired bladder diverticula do not typically produce specific symptoms. Because large bladder diverticula empty poorly or incompletely during voiding, symptoms and signs, if present, are usually attributed to urinary stasis within the diverticulum or, alternatively, to its mass effect in the lower abdomen and pelvis. Retrospectively, when queried, patient symptoms such as incomplete bladder emptying, lower abdominal fullness, and double voiding may be attributed to some large bladder diverticula. These symptoms, however, are nonspecific and can be due to prostatic enlargement, obstruction, or a number of other lower urinary tract conditions. **Most bladder diverticula are found during the investigation of nonspecific lower urinary symptoms, hematuria, or infection—or, alternatively, noted incidentally during radiographic or endoscopic investigation of these conditions.** As noted previously, congenital bladder diverticula most often present with urinary tract infection (Bauer and Retik, 1974; Pieretti and Pieretti-Vanmarcke, 1999; Evangelidis et al, 2005; Garat et al, 2007), but hematuria, abdominal pain, or an abdominal mass may be present as well. Inguinal hernias containing bladder diverticula have also been reported (Scardino and Upson, 1953; Bolton and Joyce, 1994; Buchholz et al, 1998; Schewe et al, 2000).

Urinary tract infection (UTI) in the male has been associated with bladder diverticula, because it is often an infection in a male that provides the impetus for further clinical investigation uncovering a diverticulum. A bladder diverticulum and subsequent urinary stasis may result in a predisposition for UTI and may also confer an increased difficulty in eradicating an existing infection (Shah, 1979; Taylor et al, 1979). Nevertheless, urine analysis and urine culture are important in the evaluation of bladder diverticula. Abnormalities of the urine sediment are common in patients with bladder diverticula. Pyuria and hematuria are often present. In fact, relapsing or persistent pyuria unresponsive to antibiotic therapy may be an indication for bladder diverticulectomy. **Urine cytology should be considered in most patients with bladder diverticula, especially when nonoperative management is being considered.**

Imaging

The diagnosis of bladder diverticula relies on radiographic and endoscopic findings. Bladder diverticula are part of the radiologic continuum that includes cellules and saccules. Cellules, saccules, and bladder diverticula are felt to represent increasingly larger, therefore more severe manifestations of the same pathologic process involving elevated intravesical voiding pressure (Talner et al, 2000). **Cellules and saccules represent small outpouchings between hypertrophied bands of bladder muscle, with saccules generally being larger than cellules. However, there are no universally agreed upon minimum size requirements between cellules, saccules,**

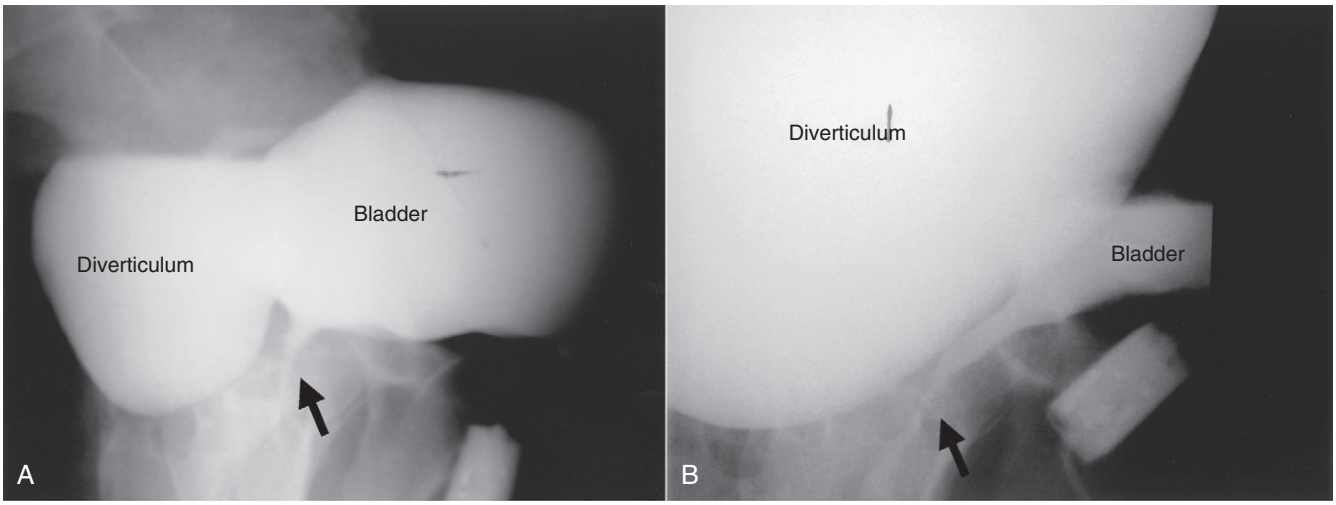


Figure 78–2. Voiding cystourethrogram (VCUG) demonstrating a bladder diverticulum in a male. **A,** The diverticulum is seen posterior to the bladder on this lateral voiding image (*arrow* points to urethra). There is a fluid-fluid level within the diverticulum representing the relatively denser contrast media settling below the urine. **B,** Later image from the VCUG demonstrates near emptying of the bladder with enlargement of the diverticulum.

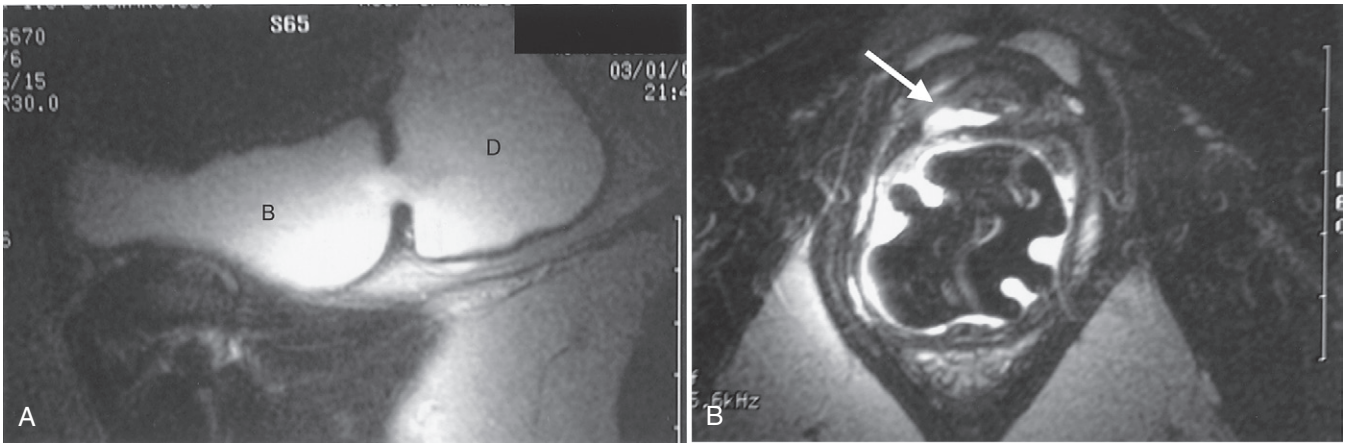


Figure 78–3. Bladder and urethral diverticula in a female. **A,** MRI of a bladder diverticulum. **B,** Endoluminal MRI demonstrating urethral diverticulum (*arrow* points to urethral diverticulum). B, bladder; D, bladder diverticulum.

and bladder diverticula, and the differentiation between these three entities is often subjective and arbitrary (Talner et al, 2000).

As noted previously, bladder diverticula are often found incidentally in the radiographic investigation of recurrent urinary tract infections or other nonspecific lower urinary tract symptoms or signs. Fluoroscopically monitored voiding cystourethrography is an excellent study to detect bladder diverticula; however, false negatives are possible (Hernanz-Schulman and Lebowitz, 1985). **A voiding urethrocystogram (VCUG) with anterior-posterior, oblique, and lateral images provides information regarding anatomy, location, and size and also associated vesicoureteric reflux and, importantly, emptying of the bladder diverticulum with voiding.** Anomalous voiding into the diverticulum during a detrusor contraction may result in paradoxical enlargement of the bladder diverticulum during micturition (Wesselhoeft et al, 1963) (see Fig. 78–2). Presumably, this occurs as the contrast flows from an area of relatively high pressure in the bladder, during the detrusor contraction, to the diverticulum, which represents an area of low pressure. In some instances, the bladder may empty partly into the diverticulum and partly through the urethra. The amount of postvoid residual urine in the bladder diverticulum and bladder should be noted. Incomplete bladder emptying suggests that a urodynamic abnormality may be present, requiring further study.

If the neck of the diverticulum is obstructed from a tumor or otherwise not patent, cross-sectional imaging may be required for diagnosis (Dondalski et al, 1993). Cross-sectional imaging, including computed tomography (CT) and magnetic resonance imaging (MRI) may also be useful for the evaluation of masses within the diverticulum (see under Associated Conditions). **Review of the radiographic films should accurately characterize the number, anatomy, and location of the diverticula.** Filling defects within the diverticula or other bladder abnormalities should prompt further investigation (Fig. 78–4).

Imaging of the upper urinary tract may include intravenous pyelography (IVP), ultrasonography, CT, or MRI. **In the absence of hematuria or a known or suspected urinary tract malignancy, the goal of upper tract imaging is to evaluate for asymptomatic or silent hydroureteronephrosis related to the diverticulum** (Lebowitz et al, 1979; Sharma et al, 1997). Hydronephrosis may be related to obstruction of the

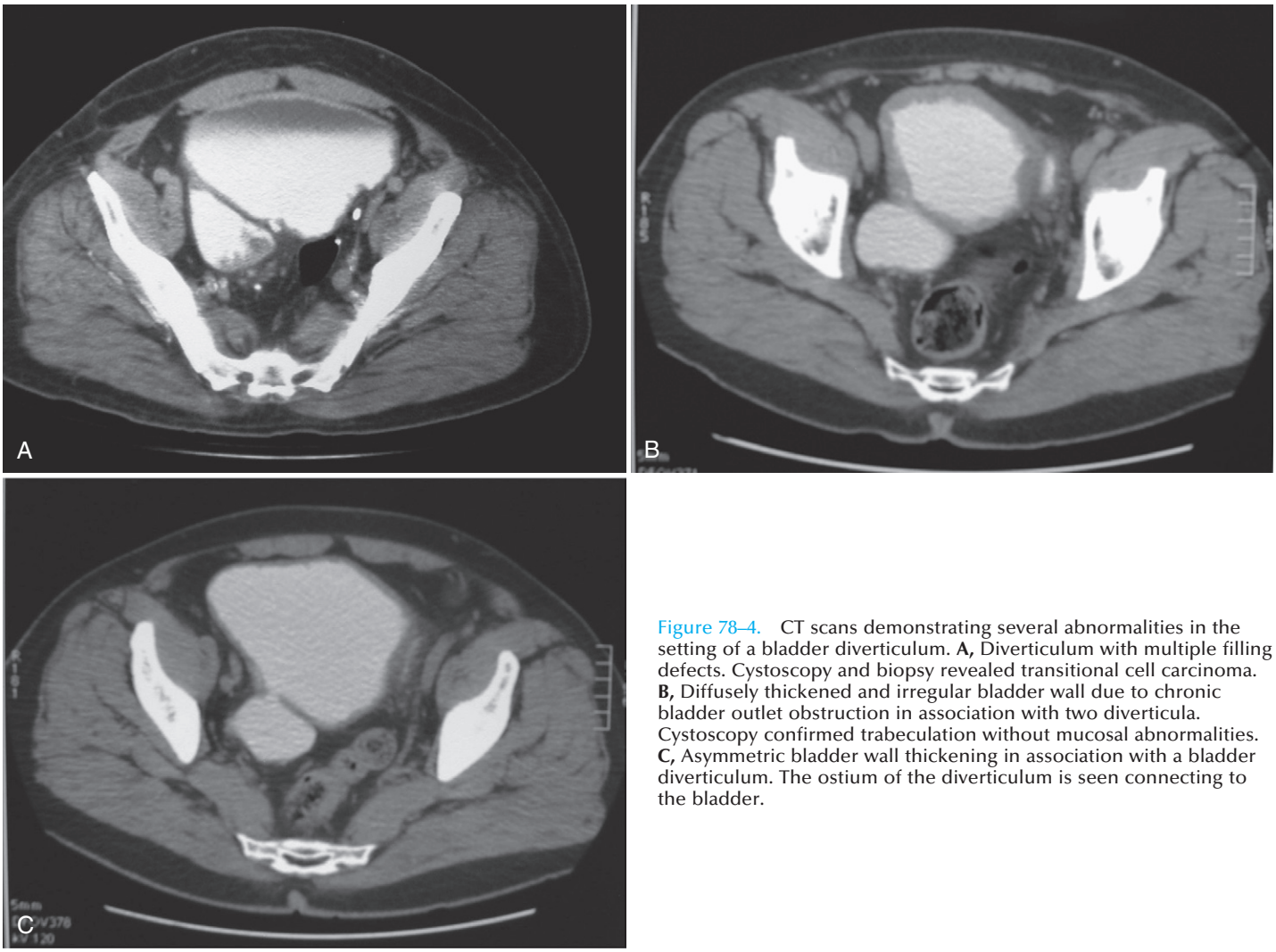


Figure 78–4. CT scans demonstrating several abnormalities in the setting of a bladder diverticulum. **A,** Diverticulum with multiple filling defects. Cystoscopy and biopsy revealed transitional cell carcinoma. **B,** Diffusely thickened and irregular bladder wall due to chronic bladder outlet obstruction in association with two diverticula. Cystoscopy confirmed trabeculation without mucosal abnormalities. **C,** Asymmetric bladder wall thickening in association with a bladder diverticulum. The ostium of the diverticulum is seen connecting to the bladder.

ureter (Kwan and Lowe, 1992; Livne and Gonzales, 1985), an underlying urodynamic abnormality that resulted in the formation of the diverticulum, vesicoureteral reflux in association with the diverticulum, inflammation (Bellinger et al, 1985), or may be completely unrelated to the bladder diverticulum. A multichannel urodynamic study in combination with a voiding cystourethrogram (VCUG) or, alternatively, a videourodynamic study is useful in this setting to differentiate upper from lower urinary tract causes of the hydronephrosis.

A bladder diverticulum may cause deviation with or without compression of the ipsilateral ureter. **On intravenous urography, medial deviation of the pelvic ureter is most commonly seen; however, lateral deviation may also occur** (Talner et al, 2000) (Fig. 78–5). Furthermore, a bladder diverticulum that encompasses the ureteral orifice may create a functionally shortened intramural ureteral segment and result in vesicoureteric reflux (see later discussion). In these patients, excision of the bladder diverticulum with ureteroneocystotomy may be necessary.

Urodynamics

Bladder outlet obstruction, impaired compliance, and/or neurogenic voiding dysfunction may result in the formation of bladder diverticula. Therefore a urodynamic study can be very helpful in the investigation of these patients. **Failure to identify and treat an existing underlying urodynamic abnormality prior to or, concomitantly, with definitive surgical therapy for bladder diverticula may result in a high risk of recurrent diverticula or other problems following surgery.** Successful treatment of the urodynamic abnormality may improve bladder emptying and may potentially result in resolution of the symptoms and/or complications. Importantly, **bladder contractility may appear to be diminished on urodynamics due to the "pressure sink" effect of the bladder diverticulum.** This artifact occurs as the detrusor contracts and the intravesical contents are decompressed through the path of least resistance into the bladder diverticulum as opposed to the urethra (Wilson and Klufio, 1985). Nevertheless, when carefully measured, bladder contractility is not significantly different from those individuals with benign prostatic hyperplasia (BPH) without bladder diverticula (Adot Zurbano et al, 2005).

Endoscopic Examination

Endoscopically, the entire interior of each bladder diverticulum should be thoroughly inspected for stones or abnormal-appearing epithelium. Flexible cystoscopy is often required to examine the entire interior of some diverticula. The location of the diverticula relative to the ureters and bladder outlet is noted, and the size of

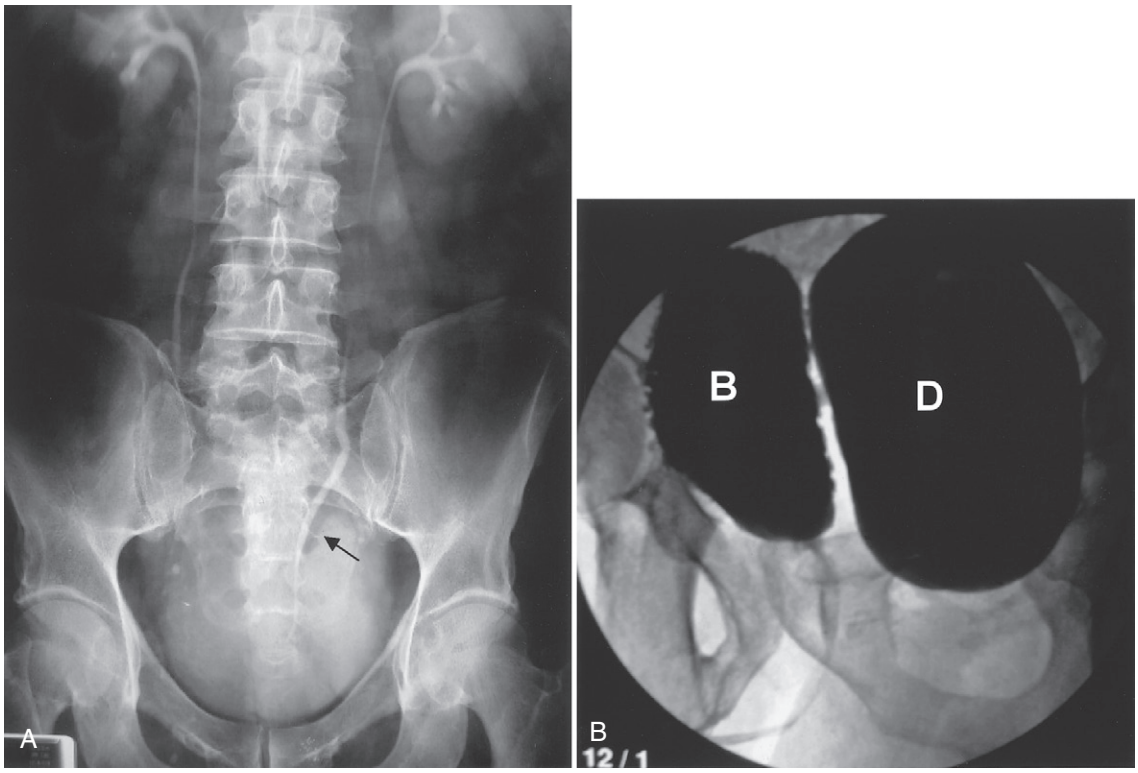


Figure 78–5. Bladder diverticulum with deviation of the ureter. This patient had a long history of recurrent urinary tract infections due to presumed prostatitis. **A,** 10-min film from the intravenous urogram demonstrating medial deviation of the pelvic ureter *(arrow)*. **B,** Voiding image from the voiding cystourethrogram revealed a large, smooth-walled bladder diverticulum (D) emanating from the trabeculated bladder (B).

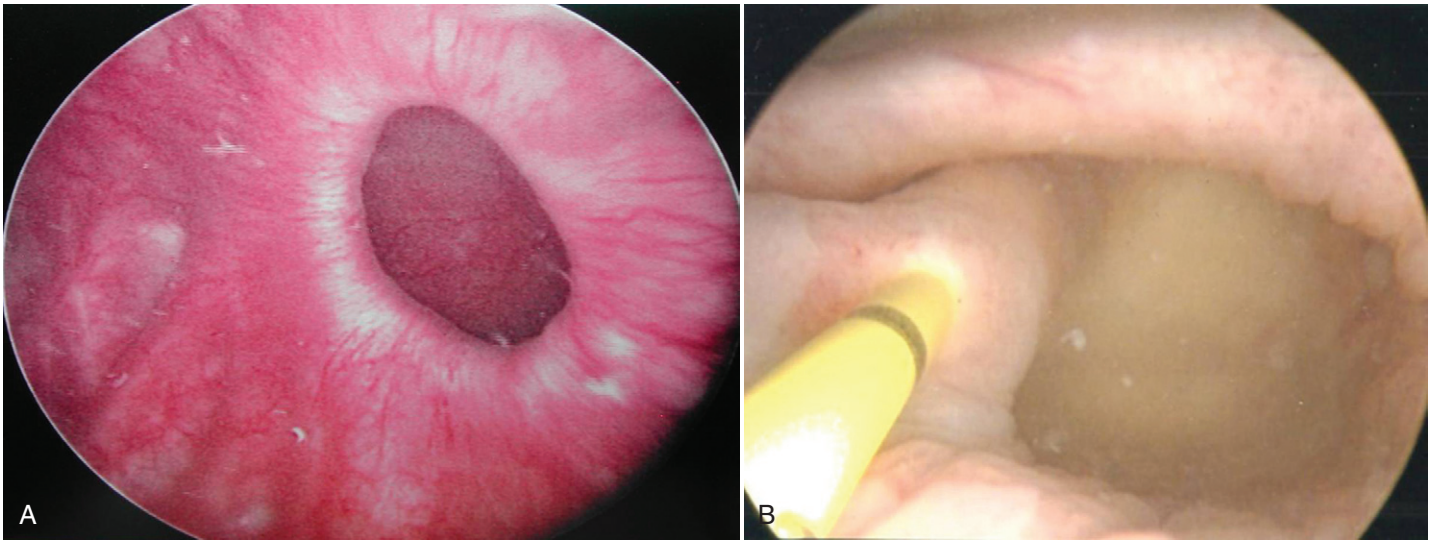


Figure 78–6. Endoscopic views bladder diverticula. **A,** Lateral wall diverticulum in a male with bladder outlet obstruction. **B,** Paraureteral diverticulum in an adult female with vesicoureteral reflux and urinary tract infections. The right ureter is intubated with a catheter.

the diverticulum is carefully recorded (Fig. 78–6). Ideally, urine cytology should be obtained from the diverticulum during endoscopic examination. **Any abnormal-appearing epithelium or lesions within the diverticulum are carefully biopsied. Extreme care must be taken during the biopsy to prevent perforation, because the wall of the diverticulum is very thin due to the lack of a muscularis propria layer. Patients who elect nonoperative management of bladder diverticula are usually followed closely with periodic endoscopic examinations and cytology.** The natural history of untreated bladder diverticula is unknown, but the possibility of malignant transformation over time due to urinary stasis within the diverticulum should be considered.

Associated Conditions

Acquired bladder diverticula are commonly found to exist in the setting of bladder outlet obstruction. Common causes of bladder

outlet obstruction in the male include benign and malignant disease of the prostate, and urethral stricture disease. Less common causes include bladder neck hypertrophy (primary bladder neck obstruction), vesicourethral anastomotic stricture following prostatectomy, and functional obstruction as a result of neurogenic vesicourethral dysfunction (bladder neck and/or striated sphincter dyssynergia). Strong consideration should be given toward management of bladder outlet obstruction prior to or concomitant with treatment of the bladder diverticulum. **In some patients, treatment of bladder outlet obstruction alone may subsequently allow low pressure and complete emptying of the bladder diverticulum with micturition, thus reducing the potential for complications associated with these lesions and possibly avoiding the need for future operative intervention in the form of diverticulectomy.**

The finding of a neoplasm within a bladder diverticulum has particularly important diagnostic and therapeutic considerations. The overall prevalence of malignant tumors within a bladder diverticulum has been reported as ranging from 0.8% to 10% (Montague and Boltuch, 1976; Micic and Ilic, 1983; Melekos et al, 1987; Baniel and Vishna, 1997; Golijanin et al, 2003). However, it is likely that the prevalence of bladder diverticula overall is underreported and, as such, the prevalence of tumors within diverticula is probably considerably smaller than that reported above. **Nevertheless, the most common histologic type of malignancy seen within bladder diverticula is transitional cell carcinoma in approximately 70% to 80% of cases, followed by squamous cell carcinoma in 20% to 25% of cases** (Montague and Boltuch, 1976; Redman et al, 1976; Micic and Ilic, 1983; Van Arsdalen and Wein, 1992; Yu et al, 1993; Baniel and Vishna, 1997; Golijanin et al, 2003). Tumors in bladder diverticula occur almost exclusively in adults with a peak occurrence between ages 65 and 75 (Ostroff et al, 1973). The prognosis for patients with these tumors has been historically reported as poor (Faysal and Freiha, 1981; Micic and Ilic, 1983; Das and Amar, 1986; Melekos et al, 1987), although some reports may suggest otherwise in selected patients (Montague and Boltuch, 1976; Baniel and Vishna, 1997). The reason for the poor prognosis has been attributed to delayed diagnosis and advanced stage at presentation (Ostroff et al, 1973; Fellows, 1978; Faysal and Freiha, 1981; Micic and Ilic, 1983) in some patients. The lack of a well-defined muscularis layer of bladder diverticula is likely to be a very important factor. **Because bladder diverticula lack a muscular layer beyond the urothelium, there is a theoretically greater risk for early transmural involvement with local extension to the perivesical fat through the comparatively thinner diverticular wall as compared with the normal bladder wall.** In addition, the lack of a defined muscular wall risks early dissemination of tumor cells into an extravesical location during transurethral resection of these lesions and makes precise pathologic staging difficult. Accurate identification of tumors within bladder diverticula has been demonstrated using a variety of radiographic techniques, including CT, MRI, and ultrasonography (Dragsted and Nilsson, 1985; Saez et al, 1985; Williams and Gooding; 1985; Lowe et al, 1989; Dondalski et al, 1993; Durfee et al, 1997; Mallampati and Siegelman, 2004) (see Fig. 78–4). Whether these modalities can reliably predict extravesical invasion and therefore affect staging and prognosis is not clear. It has been suggested that clinical stage at presentation is the most important prognostic factor for patients with tumors in bladder diverticula, with 5-year actuarial survival ranging from 83 ± 9% in patients with superficial disease to 45 ± 14% in those presenting with extradiverticular disease (Golijanin et al, 2003). One small series suggests that aggressive individualized multimodal therapy in these patients, including surgery, chemotherapy, and radiation therapy may improve prognosis (Garzotto et al, 1996). Because pathologic staging following transurethral resection is difficult and often inaccurate, some authors have suggested a very aggressive approach to these tumors. This surgical staging approach involves an open exploration and partial or radical cystectomy without a prior transurethral resection (Redman et al, 1976). Others have advocated a selective individualized approach, taking into account the clinical stage and pathologic grade of the tumor (Golijanin et al, 2003). Low-grade, low-stage tumors may be successfully treated with diverticulectomy alone (Baniel and Vishna, 1997; Sulaiman et al, 1998); however, it is important to recognize that the ability to reliably predict stage and grade preoperatively is limited, and therefore this approach should be undertaken only with caution in select cases, with adequate counseling and follow-up. In any case, close surveillance of these patients is warranted whether or not aggressive therapy is undertaken.

The location of many bladder diverticula at the level of the ureterovesical junction may explain the high incidence of associated ipsilateral ureteral abnormalities. For a ureter found within a diverticulum, the lack of a muscular backing to the diverticulum results in a functionally shortened intramural tunnel (see Fig. 78–6B). **A very high prevalence of ipsilateral vesicoureteral reflux has been noted in association with congenital bladder diverticula** (Amar, 1972). One study noted reflux in 83 of 89 diverticulum associated ureteric units (Barrett et al, 1976). Other considerations in the evaluation and management of bladder diverticula include the potential development of stones within the diverticulum, ureteral obstruction (Lebowitz et al, 1979; Bellinger et al, 1985; Kwan and Lowe, 1992; Khan et al, 1994; Sharma et al, 1997), and even the potential for the rare but life-threatening complication of perforation and/or rupture of the bladder diverticulum (Mitchell and Hamilton, 1971; Keeler and Sant, 1990; Itoh and Kounami, 1994; Jorion and Michel, 1999).

Key Points: Bladder Diverticula—Diagnosis

- Bladder diverticula do not contain a defined functional muscularis propria layer and therefore empty poorly with micturition.
- In the adult, bladder diverticula are often associated with bladder outlet obstruction or neurogenic vesicourethral dysfunction. Congenital bladder diverticula are usually solitary, associated with a smooth-walled bladder, and occur in the absence of bladder outlet obstruction.
- Presenting symptoms of bladder diverticula are legion; bladder diverticula are most often diagnosed incidentally in the evaluation of nonspecific lower urinary tract symptoms or infection.
- Patients with bladder diverticula should be evaluated for bladder outlet obstruction, and if this is present, it should be addressed in advance of or concomitantly with definitive treatment of the bladder diverticulum.
- Malignancy can occur within a bladder diverticulum, and consideration should be given to the possibility of early extravesical disease extension due to the lack of a defined muscularis propria.

Management

In general, if the etiology of the bladder diverticulum is felt to be consistent with bladder outlet obstruction, definitive treatment of the bladder outlet is indicated prior to formal diverticulectomy. This approach allows reassessment of the diverticulum following relief of outlet obstruction and, if bladder emptying is satisfactory, then the diverticulum may not require excision. However, simultaneous open bladder diverticulectomy/open prostatectomy, as well as simultaneous laparoscopic bladder diverticulectomy/transurethral prostatectomy (TURP) can be performed (Porpiglia et al, 2004). If treatment of the obstruction is pursued initially and results in satisfactory emptying of the diverticulum postoperatively, and complicating factors such as reflux, infection, malignancy, or stones are absent, then ongoing surveillance of the diverticulum may be all that is required. Emptying of the diverticulum following relief of outlet obstruction may be assessed on ultrasonography, VCUG, or by videourodynamics.

Management options in the treatment of bladder diverticula include observation, endoscopic management, and surgical excision; however, there are many factors to consider during the evaluation of these lesions prior to deciding on appropriate therapy (Fig. 78–7).

Observation/Expectant Management

Patients who have poor bladder emptying following relief of obstruction, or who are unable or unwilling to undergo surgical excision of the bladder diverticulum, may be effectively treated with clean intermittent catheterization (CIC) or an indwelling catheter. In this setting, and in the absence of future complicating factors, surveillance of the bladder diverticulum may be all that is required. Patients who demonstrate significantly impaired bladder contractility on preoperative urodynamics, or who fail to empty their bladder (independent of the emptying of the diverticulum) on preoperative VCUG or videourodynamics following relief of obstruction, may have persistent failure to empty their bladder even following successful diverticulectomy. Therefore long-term CIC may be a viable option in these patients.

Indications for Intervention

Incidentally found congenital or acquired bladder diverticula may require no further therapy unless associated with persistent symptoms, recurrent infections, obstruction, stones, malignancy, or other complicating factors such as ipsilateral vesicoureteral reflux. Symptoms or complications related to bladder diverticula are most often due to poor emptying of the diverticulum and urinary stasis. Therefore excision of the diverticula would be expected to improve emptying of the lower urinary tract, provided that the primary problem that resulted in the formation of the bladder diverticulum (i.e., obstruction) has been adequately addressed. **Therefore bladder diverticulectomy is indicated for the treatment of symptoms related to the diverticulum, or for the major complications directly related to it, including chronic relapsing urinary tract infection, stones within the diverticulum, carcinoma or premalignant change, and, finally, upper urinary tract deterioration as a result of obstruction or reflux.**

Bladder diverticula can vary tremendously in size and, in some instances, are larger than the bladder itself. The size of the diverticulum does not appear to correlate with symptoms or complications and therefore cannot be used as an absolute indication to proceed with surgery. Asymptomatic patients without complicating factors may be followed closely with endoscopic examination, urine cytology, and cultures. **Controversy exists as to whether prophylactic excision of asymptomatic bladder diverticula should be carried out to prevent malignant transformation or whether close observation is sufficient.** Cytologic techniques and endoscopic equipment allow excellent follow-up, but patients should be counseled that the treatment and prognosis of malignant lesions, should they develop in follow-up, remain variable and unpredictable.

Excision of bladder diverticula is most commonly elective. The relative merits of surgical excision versus surveillance should be carefully considered and discussed with each patient individually. The patient should be in relatively good health and be a reasonable surgical risk prior to considering the procedure. Preoperative medical status should be assessed and reversible risk factors corrected and/or optimized (nutritional, renal, cardiac, pulmonary, etc.). Preoperative urinary tract infection should be treated. Patients who are prohibitive surgical risks due to concurrent medical illness or other factors should not undergo surgical excision but may be candidates for CIC or endoscopic treatment.

Endoscopic Management

Endoscopic management of bladder diverticulum may be considered in patients who are aged or somewhat debilitated, those who are not good candidates for an open operative approach, or for those undergoing transurethral resection of prostate in whom there exists an associated poorly draining diverticulum (Orandi, 1977; Vitale and Woodside, 1979). Transurethral resection of the diverticular neck has been reported to be successful in select cases (Vitale and Woodside, 1979). This technique is performed with a standard resectoscope. The neck of the diverticulum is incised using the resectoscope loop or Collins knife. Incisions are carried down to the muscular fibers of the bladder at the level of the ostium of the diverticulum. Circumferential resection of the entire neck may be performed. When successful, this procedure enlarges the neck of the diverticulum, disrupting the narrow sphincteric-like properties of its connection to the bladder lumen, thereby permitting improved emptying of the diverticulum during micturition. Although generally safe and well tolerated, this technique has resulted in urinary retention due to a reversal of flow during micturition and "venting" of the bladder contents into the diverticulum postoperatively (Schulze and Hald, 1983). Transurethral resection of the diverticular neck may be combined with fulguration of the entire urothelial lining of the diverticulum (Clayman et al, 1984; Adachi et al, 1991a, 1991b; Yamaguchi et al, 1992). Fulguration of the lining of the diverticulum should result in obliteration of the diverticulum or a considerable reduction in its size.

Open Surgical Management

Open excision is usually performed through a transvesical approach, although extravesical and combined approaches have been described. In cases of marked prostatic enlargement and obstruction, open suprapubic prostatectomy and transvesical bladder diverticulectomy may be performed concomitantly. Adequate preoperative imaging and endoscopic evaluation should provide information regarding the size, number, and location of all bladder diverticula. Furthermore, the relationship of the adjacent anatomic structures, including the major pelvic vessels, ureters, and bowel, should be noted. Surgically, the bladder is most commonly approached extraperitoneally through a low midline

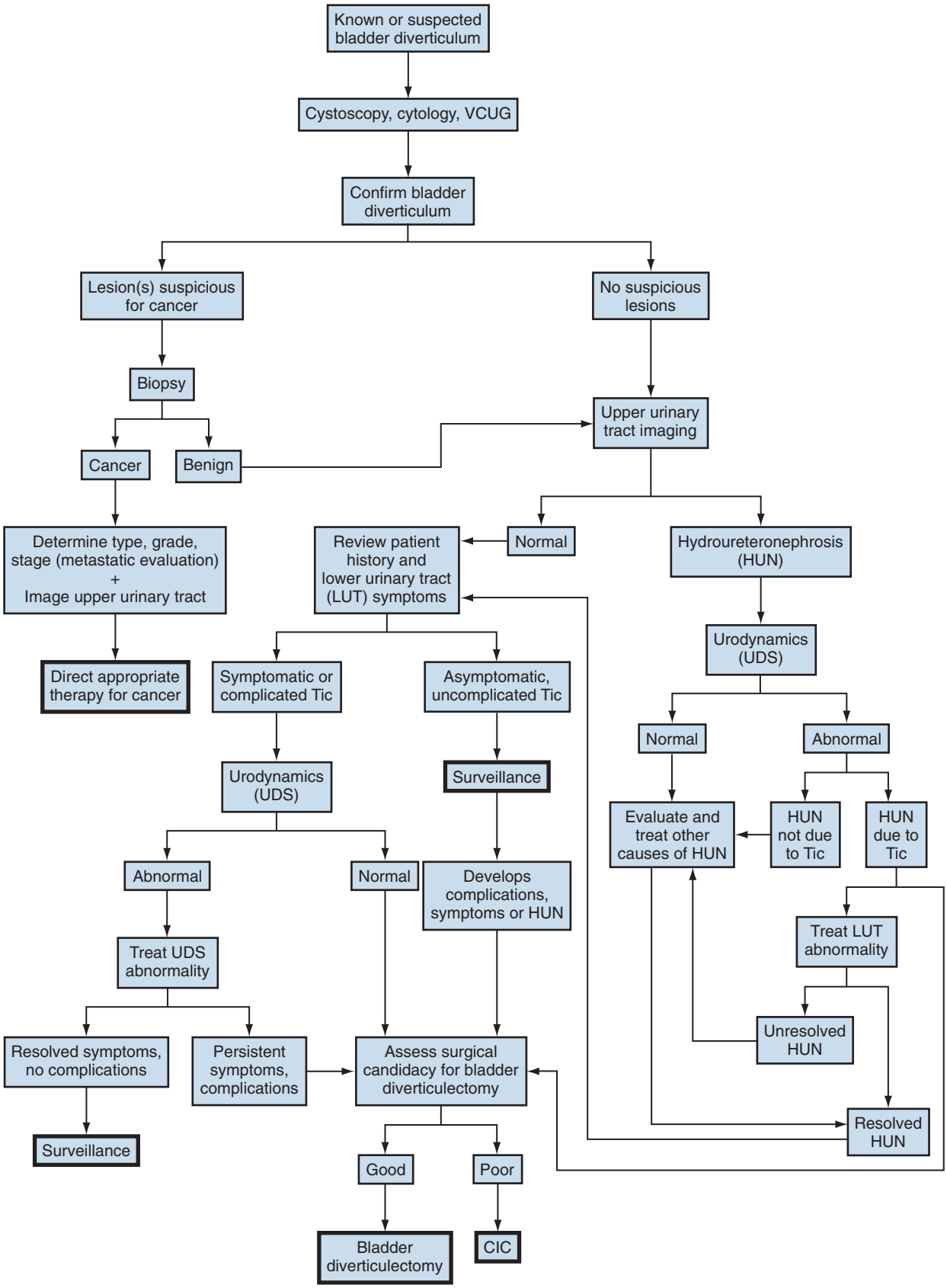


Figure 78–7. Algorithm for the evaluation and therapy of bladder diverticula. CIC, clean intermittent catheterization; VCUG, voiding cystourethrogram. (Adapted from Rovner ES, Wein AJ. Bladder diverticula in adults. In: Resnick M, Elder JA, Spirnak JP, editors. Decision making in urology. 3rd ed. Hamilton [Ontario]: B.C. Decker; 2004. p. 260–3.)

or transverse incision. The retropubic space is entered and developed. Regardless of the technique used, careful dissection is required during excision of the diverticulum to avoid ureteral injury, because many bladder diverticula are located adjacent to the ureter or may be adherent to it. Ureteral stents are often placed preoperatively or intraoperatively to facilitate dissection and avoid ureteric injury. Often, several bladder diverticula are noted preoperatively. Simultaneous resection of all existing bladder diverticula should be performed to optimize postoperative bladder emptying (Gil-Vernet, 1998).

Transvesical Bladder Diverticulectomy. The transvesical approach to bladder diverticulectomy was first reported by Hugh Hampton Young in 1906 (Gil-Vernet, 1998). The bladder is opened along the anterior wall and suitable retraction is placed in order to visualize the neck of the diverticulum. For the excision of small diverticula, saccules or cellules, a locking instrument such as an Allis-type clamp is passed through the neck of the diverticulum, and the base or bottom of the diverticulum is grasped, pulled, and everted back into the bladder. **In the absence of extravesical adhesions or inflammation, a small diverticulum can be completely everted into the bladder and exposed in this manner.** The urothelium of the diverticulum at the level of the neck is incised circumferentially, and the diverticulum is removed. The defect in the bladder wall is closed with absorbable suture in two layers. **Care must be taken when performing this technique to avoid injuring structures adherent or adjacent to external surface of the diverticulum, because they may be blindly pulled into the bladder with the diverticulum wall and inadvertently injured during resection.**

If eversion of the diverticulum is not possible due to adhesions or inflammation, or the diverticulum is too large to permit complete exposure during eversion, submucosal excision of the diverticulum may be performed. An anterior cystotomy is performed, the bladder is opened and suitable retraction is placed to visualize the neck of the diverticulum within the bladder. The neck of diverticulum is then identified and mobilized initially, similar to the technique used for the first part of the dissection of the ureter during ureteroneocystostomy. The diverticular neck is circumscribed sharply with scissors or electrocautery, and the plane between the wall of the diverticulum and the surrounding fibrous capsule is defined (Fig. 78–8A to D). Traction is placed on the edges of the neck of the diverticulum with Allis clamps circumferentially, and the neck and then the exterior walls of the diverticulum are carefully mobilized from the surrounding tissues and delivered into the bladder lumen. Sharp and blunt dissection on the exterior wall of the diverticulum is performed in a well-defined periadventitial plane between the diverticulum wall and the fibrous pseudocapsule. Packing of the diverticulum with gauze may facilitate dissection and provide some countertraction (Fig. 78–9A to D). The diverticulum is completely freed from its fibrous pseudocapsule and removed. The bladder wall defect is then repaired in two layers with absorbable sutures. Drainage of the potential space left by the pseudocapsule is usually not necessary (Firstater and Farkas, 1977).

Combined Intravesical/Extravesical Approach. **For individuals with large diverticula and/or considerable peridiverticular inflammation, a purely transvesical approach may not be feasible.** In addition, involvement of the ureter within the diverticulum, or severe peridiverticular inflammation encompassing the ureter may have altered the usual course of the ureter and may incur a prohibitive risk of injuring the ureter with a transvesical approach. Therefore a combined intravesical and extravesical approach may be warranted. Ureteral catheters are usually placed to prevent ureteral injury. The bladder is opened as if for a transvesical diverticulectomy. The diverticular neck is incised circumferentially. The surgeon's finger is then inserted into the diverticulum to identify the location of the rest of the diverticulum (Fig. 78–10). The diverticulum may be packed with gauze as well. If the neck of the diverticulum is sufficiently mobile, the anterior aspect of the neck is brought up into the operative field outside the bladder using the surgeon's finger. The overlying tissue is dissected free, and the anterior portion of the neck of the diverticulum is exposed and incised extravesically. The neck is circumferentially mobilized, and then transected. The diverticular wall is then mobilized and dissected free of its attachments as described previously. In some cases, anterior reflection of the surgeon's finger allows opening of the diverticulum itself, and dissection can be carried out in the plane between the pseudocapsule and the urothelium in a completely extravesical fashion. In some cases, it may be necessary to divide the ipsilateral superior vesical pedicle to facilitate exposure and delivery of the diverticulum. If additional difficulty is encountered in exposing the diverticulum, the original cystotomy incision can be extended or enlarged in a "T" fashion over to the neck of the diverticulum. This procedure generally removes the entire diverticulum, including the mucosa and fibrous pseudocapsule. In cases where considerable inflammation is encountered and the diverticulum is closely adhering to adjacent vital structures, it may be necessary to leave portions of the fibrous pseudocapsule in situ. The bladder is closed as described previously.

Laparoscopic and Robotic Diverticulectomy. Minimally invasive techniques, such as laparoscopy and robotics (Myer and Wagner, 2007), have been applied to surgical diverticulectomy using a similar surgical approach (Das, 1992; Parra et al, 1992; Jarrett et al, 1995; Faramarzi-Roques et al, 2004; Abdel-Hakim et al, 2007; Macejko et al, 2008). Intra- and extraperitoneal approaches have been reported. Approaching the diverticulum extravesically using such a minimally invasive approach can be challenging; however, simultaneous intraoperative cystoscopic transillumination may aid in locating the diverticulum within the retroperitoneal tissues (Macejko et al, 2008). Small, non-randomized case series suggest that outcomes are similar to established open techniques (Porpiglia et al, 2004; Myer and Wagner, 2007).

Complications

The most devastating complication during bladder diverticulectomy is ureteral injury. Fortunately, this is rare and can be avoided by careful attention to technique. Placement of a ureteral catheter can be very helpful in identifying the ureter during surgery. If identified intraoperatively, a partial transaction may be repaired primarily and stented. Complete transection usually mandates ureteral reimplantation into the bladder with or

Key Points: Bladder Diverticula—Management

- Bladder diverticulectomy is not indicated in all cases. Surgical treatment should be reserved for the treatment of symptoms related to the diverticulum, chronic relapsing urinary tract infection, stones within the diverticulum, carcinoma or premalignant change, and, finally, upper urinary tract deterioration as a result of obstruction or reflux.
- Surgical diverticulectomy can be performed with a variety of approaches and is often curative.

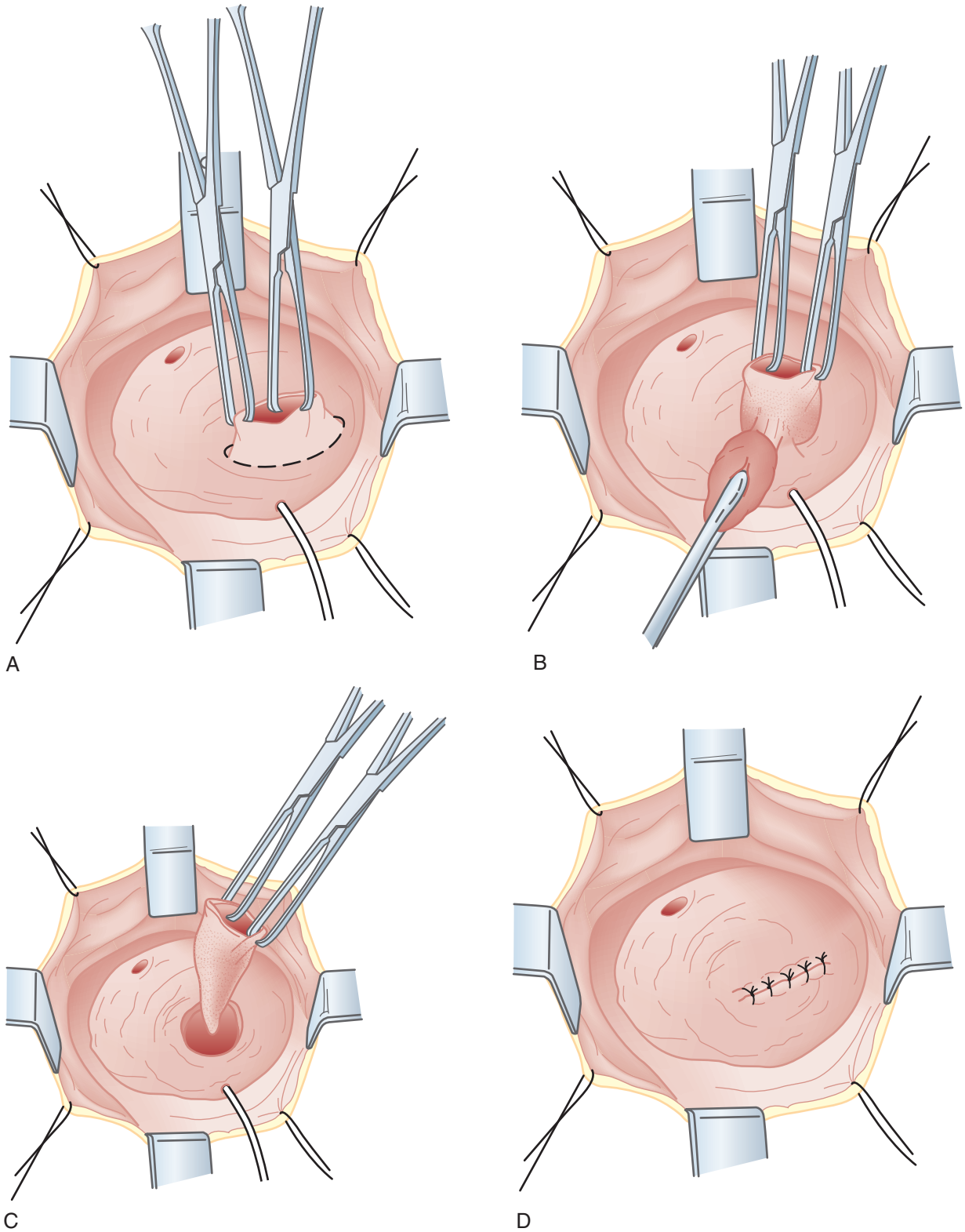


Figure 78–8. Intravesical submucosal bladder diverticulectomy. **A,** The neck of the diverticulum is grasped and circumscribed sharply. **B,** The adventitial tissue is dissected free from the diverticulum wall. **C,** The diverticulum is completely removed. **D,** The bladder is repaired.

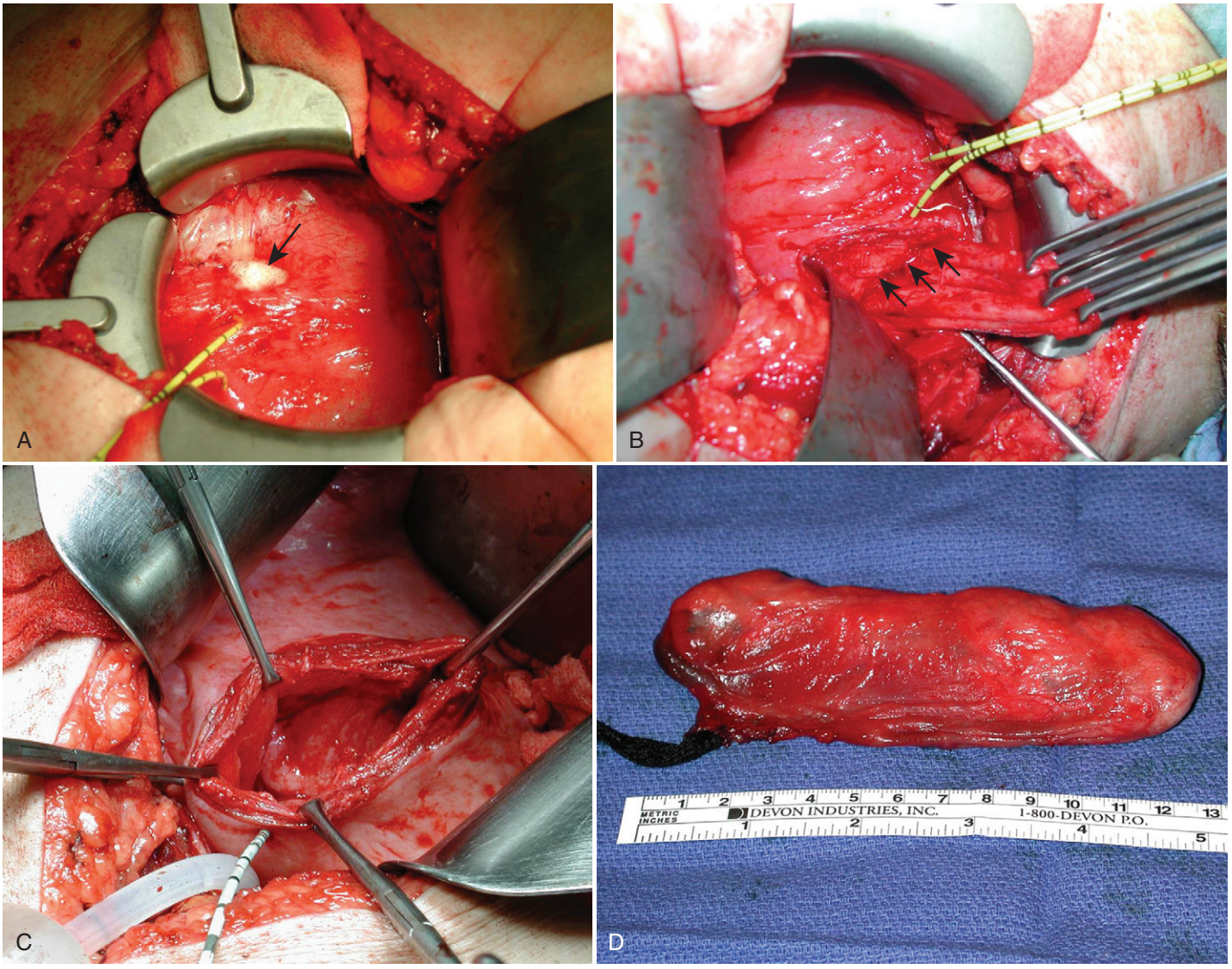


Figure 78–9. Transvesical submucosal bladder diverticulectomy. **A,** Intraoperative packing of the diverticulum *(arrow)* with gauze may facilitate dissection. Ureteric catheters demonstrate the proximity of the diverticulum to the right ureter. **B,** Allis clamps are seen on the edge of the neck of the diverticulum providing traction. The *arrows* show the plane of dissection along the pseudocapsule of the diverticulum as it is dissected free from the retroperitoneal tissues. **C,** View into the retroperitoneal space through the bladder wall defect created by removal of the diverticulum. **D,** Intact diverticulum specimen packed with gauze.

without a psoas hitch. Other complications include urinary tract infection, bleeding, prolonged urinary extravasation postoperatively, urinary fistula, and bowel injury.

FEMALE URETHRAL DIVERTICULA (UD)

A urethral diverticulum in the female can be generally described as a periurethral cystic structure adjacent to the urethra. Diverticula of the female urethra present some of the most challenging diagnostic and reconstructive problems in female urology. UD are notable for a bewildering variety of clinical presentations ranging from completely asymptomatic, incidentally noted lesions on physical examination or radiographs, to very debilitating, painful vaginal masses associated with incontinence, stones, and/or tumors. Anatomical variations between patients and in the location, size, and complexity of these lesions, ensure that each case is unique.

Although described as early as the 19th century (Hey, 1805), the modern era of female urethral diverticula (UD) began in 1956 with the advent of positive-pressure urethrography by Davis and Cian (1952). Over the next several years, there was a dramatic increase in number of cases of UD reported in the literature. A published series of 121 cases by Davis and Telinde (1958) approximately doubled the number of cases reported during the previous 60 years. Development of adjuvant imaging techniques, such as ultrasonography and surface coil/endoluminal MRI, in the past 2 to 3 decades have contributed greatly to further understanding of UD (Fig. 78–11).

Anatomy of the Female Urethra

The normal female urethra is a musculofascial tube approximately 3 to 4 cm in length, extending from the bladder neck to the external urethral meatus, suspended to the pelvic sidewall and pelvic

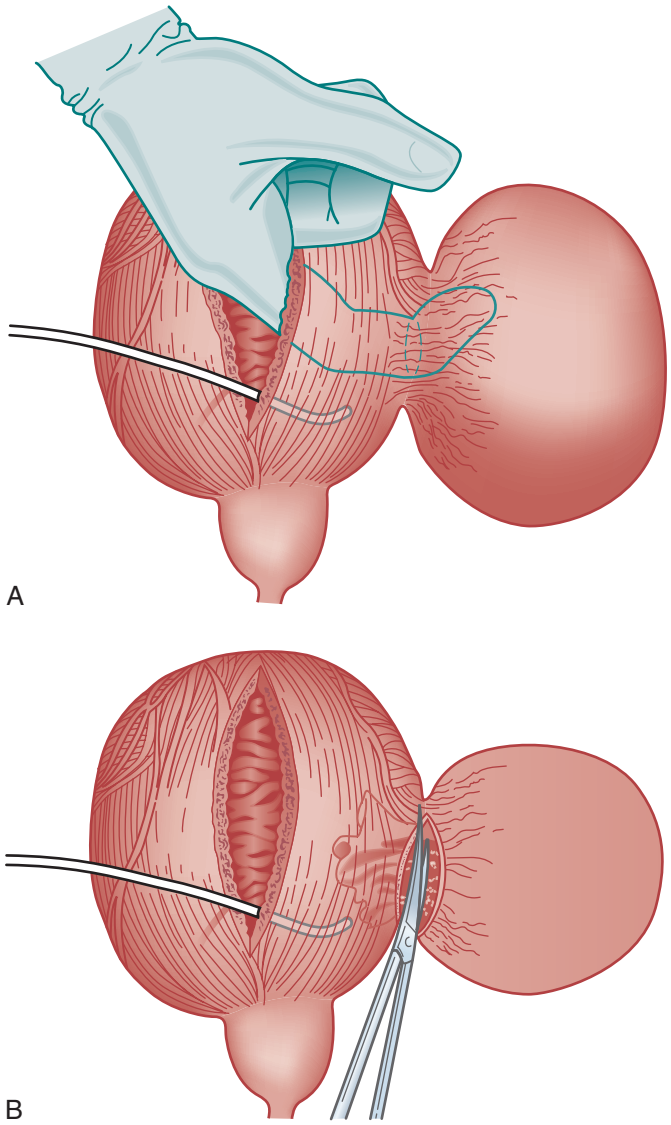


Figure 78–10. Combined intravesical-extravesical bladder diverticulectomy. **A,** The surgeon's finger is inserted into the diverticulum through a cystotomy allowing identification of the diverticular neck. **B,** The diverticular neck is divided and the remaining portion of the diverticulum is dissected free from the surrounding tissues.

fascia (tendinous arc of the obturator muscle) by a sheet of connective tissue termed the urethropelvic ligament. The urethropelvic ligament is composed of two layers of fused pelvic fascia that extend toward the pelvic sidewall bilaterally (Fig. 78–12). This structure can be considered to have an abdominal side (the endopelvic fascia) and a vaginal side (periurethral fascia). **Within and between these two leaves of fascia lies the urethra and the location of most urethral diverticula.**

The urethral lumen is lined by an epithelial layer that is a transitional cell type proximally and nonkeratinized stratified squamous cell type distally. The urethra may be conceptualized as a rich, vascular, spongy cylinder surrounded by an envelope consisting of smooth and skeletal muscle and fibroelastic tissue (Young et al, 1996). Within the thick, vascular lamina propria/submucosal layer are the periurethral glands (Fig. 78–13). These tubuloalveolar glands exist over the entire length of the urethra posterolaterally; however, they are most prominent over the distal two thirds, with the majority of the glands draining into the distal one third of the urethra. Skene glands are the largest and most distal of these glands. These glands drain outside the urethral lumen, lateral to the urethral meatus. **It is from pathologic processes involving the periurethral glands that most acquired female urethral diverticula are thought to originate.**

The urethra has several muscular layers: an internal longitudinal smooth muscle layer, an outer circular smooth muscle layer, and a skeletal muscle layer. The skeletal muscle component spans much of the length of the urethra but is more prominent in the middle third. It has a U-shaped configuration, being deficient dorsally. Ventral to the urethra, but separated from it by the periurethral fascia, lies the anterior vaginal wall (see Fig. 78–12). **The location and competence of the urethral sphincters have important implications when considering surgical repair of urethral diverticula due to the anatomic overlap of these two entities.**

Arterial inflow to the urethra derives from two sources. The proximal urethra has a blood supply similar to the adjacent bladder, whereas the distal urethra derives its blood supply from the terminal branches of the inferior vesical artery through the vaginal artery that runs along the superior lateral aspect of the vagina (Hinman, 1993). Lymphatic drainage of the female urethra is to the external and internal iliac nodes from the proximal urethra, and to the superficial and deep inguinal lymph nodes from the distal urethra. Innervation to the female urethra is from the pudendal nerve (S2-S4), and afferents from the urethra travel through the pelvic splanchnic nerves.

Urethral Diverticula

Pathophysiology and Etiology

As conceptualized by Young and colleagues (1996), urethral diverticula represent a cavity dissecting within the confines of the fascia of the urethropelvic ligament. This defect is often an isolated cyst-like appendage with a single discreet connection to the urethral lumen termed the neck, or ostium (Fig. 78–14). **However, complicated anatomic patterns may exist, and in certain cases the UD may extend partially ("saddlebag" UD) around the urethra, anterior to the urethra** (Vakili et al, 2003), **or circumferentially around the entire urethra** (Rovner and Wein, 2003) (Fig. 78–15).

The exact origin of UD is still unproven. A major debate in the earlier part of the 20th century focused on whether UD were congenital or acquired lesions (Johnson, 1938; Gilbert and Rivera-Cintron, 1954; Pinkerton, 1963). Although this condition exists in children, the diagnosis may represent a different clinical entity from adult female UD. Scattered reports of congenital UD in female infants have been described (Glassman et al, 1975). Marshall (1981) reported five cases of UD in young females, of whom three underwent spontaneous regression. Congenital anterior urethral diverticulum is a well-described entity in boys (Kirks and Grossman, 1981; Lau and Ong, 1981; Kaneti et al, 1984), but this is considered to be an entirely different clinical entity from UD in the female. Congenital Skene gland cysts have been reported (Kimbrough and Vaughan, 1977; Lee and Kim, 1992) but are considered extremely rare. Diverticula in the pediatric population have been attributed to a number of congenital anomalies, including an ectopic ureter draining into a Gartner duct cyst and a form fruste of urethral duplication (Silk and Lebowitz, 1969; Vanhoutte, 1970; Boyd and Raz, 1993). **The vast majority of UD, however, are likely to be acquired and are diagnosed in adult females.**

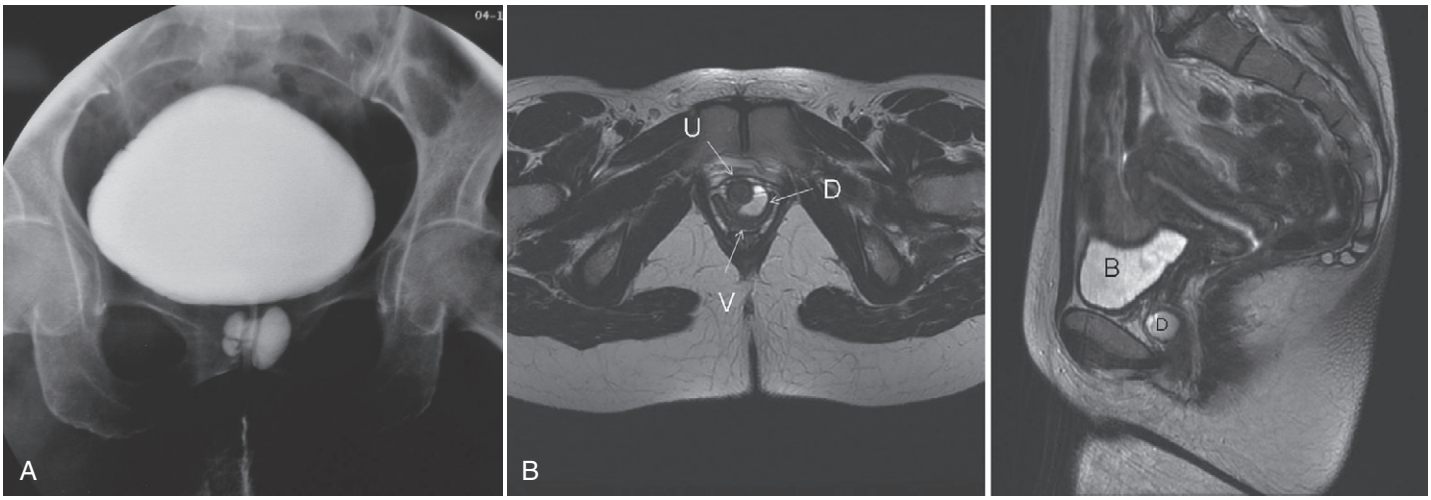


Figure 78–11. Imaging of urethral diverticula. **A,** Anterior-posterior view from a voiding cystourethrogram demonstrating a collection of contrast below the bladder, suggesting a urethral diverticulum. **B,** Surface coil MRI with both sagittal and axial T2 images demonstrating the relevant anatomy of a patient with a urethral diverticulum. B, bladder; D, urethral diverticulum; U, urethra; V, vagina.

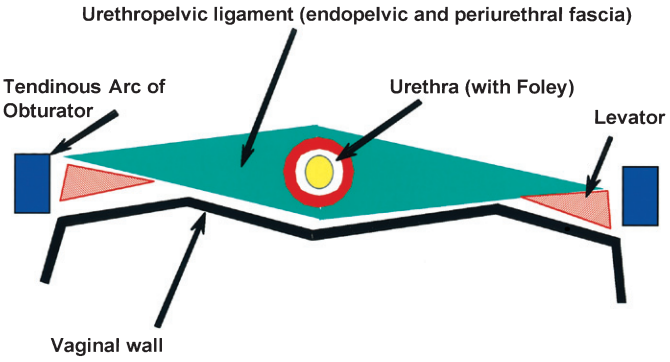


Figure 78–12. Schematic diagram of the anatomy of the midurethra in a coronal plane.

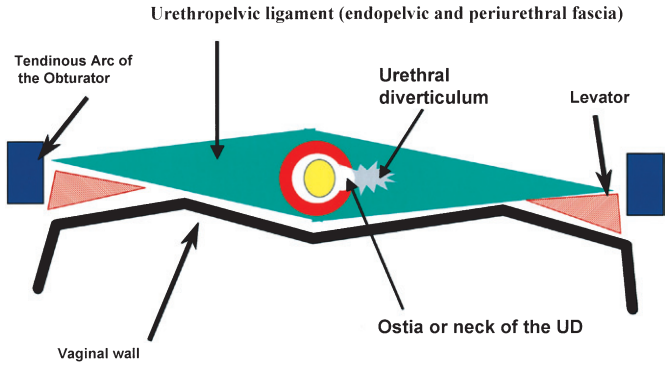


Figure 78–14. Diagram of urethral diverticulum. The urethral diverticulum forms within and between the layers of the urethropelvic ligament.

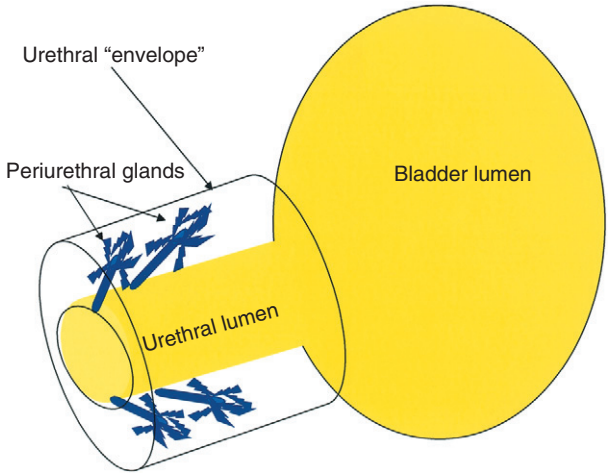


Figure 78–13. Periurethral glands are located within submucosa of urethra deep to the muscular envelope draining distally but arborizing proximally.

In two large series of UD, there were no patients reported who were younger than 10 years of age (Davis and Robinson, 1970; Davis and TeLinde, 1958), arguing against a congenital etiology for these lesions. Although it is possible that there exists a congenital defect in patients that results in or represents a precursor to UD, which then only becomes symptomatic later in life, it is still unproven.

There are multiple theories regarding the formation of acquired UD. For many years, acquired UD were felt to be most likely due to trauma from vaginal childbirth (McNally, 1935). It was postulated that mechanical trauma during vaginal delivery resulted in herniation of the urethral mucosa through the muscular layers of the urethra with the subsequent development of a UD. However, up to 20% to 30% of patients in some UD series are nulliparous (Lee, 1984; Ganabathi et al, 1994), which may significantly discount parity as a risk factor. Trauma with forceps delivery, however, has been reported to cause UD (Klyszejko et al, 1985), and the radiographic appearance of periurethral injectable agents, including collagen (Clemens and Bushman, 2001; Bridges et al, 2005) and other injectable agents (Castillo-Vico et al, 2007), can simulate a urethral diverticulum.

The periurethral glands are felt to be the probable site of origin of acquired UD (Young et al, 1996). Huffman's anatomic work with wax models of the female urethra was critical to the early theories regarding the pathophysiology of UD and the involvement of the periurethral glands (Huffman, 1948). By reviewing 10-μm transverse sections, he refuted earlier anatomic descriptions of the glandular anatomy of the female. He characterized the periurethral glands as located primarily dorsolateral to the

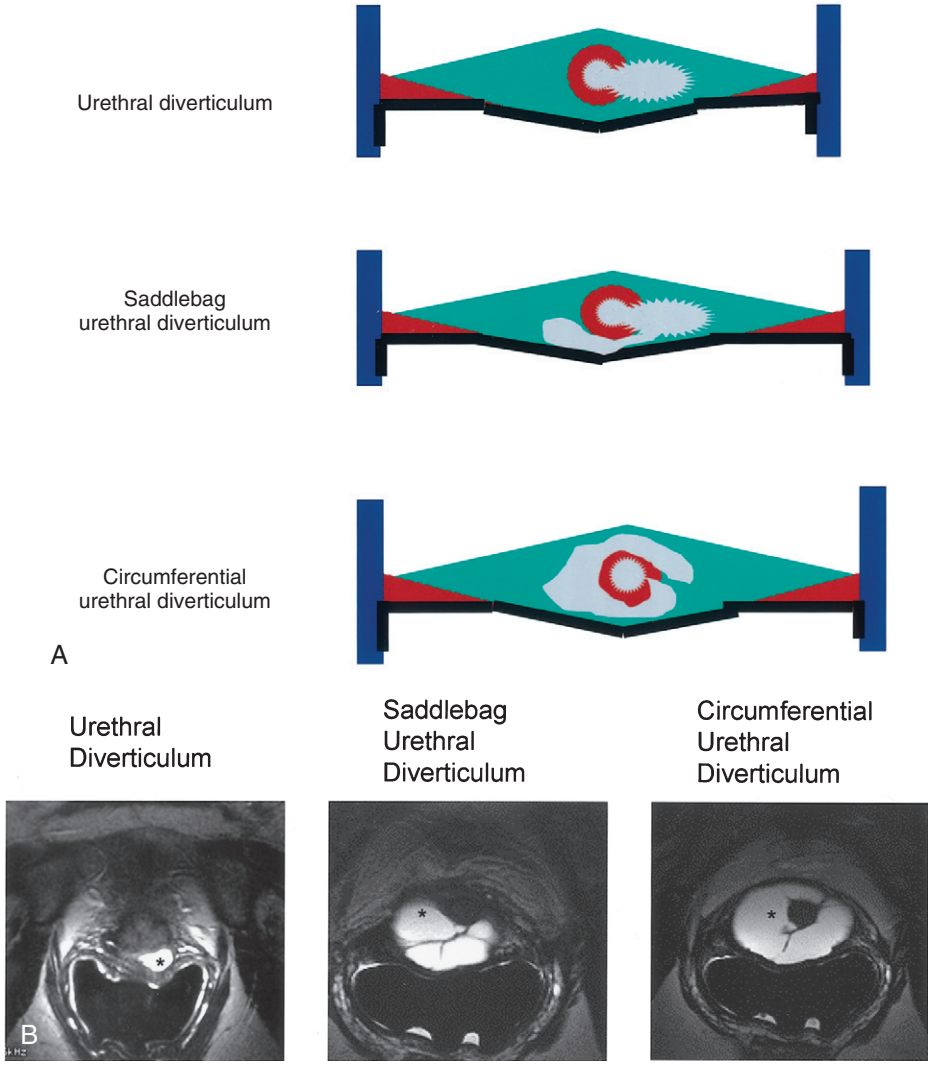


Figure 78–15. Multiple different morphologies of urethral diverticulum (UD) may exist. **A,** Schematic diagrams representing three different morphologies of UD. **B,** Endoluminal MR images corresponding to each of the configurations in three different patients (*asterisk* indicates urethral diverticulum).

urethra, arborizing proximally along the urethra, and yet draining into ducts located in the distal one third of the urethra (see Fig. 78–13). Furthermore, he noted that periductal and interductal inflammation was found commonly. **In support of these observations and an infectious (acquired) etiology of UD, in over 90% of UD cases, the ostium is located posterolaterally in the mid- or distal urethra, which corresponds to the anatomic location of the periurethral glands** (Lang and Davis, 1959; MacKinnon et al, 1959).

Although there are probably other unknown factors that may facilitate the initiation, formation or propagation of UD, infection of the periurethral glands seems to the most generally accepted common etiologic factor in most cases. Peters and Vaughan (1976) found a strong association with concurrent or previous infection with *Neisseria gonorrhea* and UD. However, the initial infection and, especially, subsequent reinfections may originate from a variety of sources, including *E. coli* and other coliform bacteria as well as vaginal flora. **Nevertheless, UD have been attributed historically to recurrent infection of the periurethral glands, with obstruction, suburethral abscess formation, and subsequent rupture of these infected glands into the urethral lumen.** Continual filling and pooling of urine in the resultant cavity may lead to stasis, recurrent infection, and eventual epithelialization of the cavity, forming a permanent urethral diverticulum. This concept was first popularized by Routh (1890) over a century ago and has now become the most widely accepted theory regarding the formation of female UD. Reinfection, inflammation, and recurrent obstruction of the neck of the cavity are theorized to result in patient symptoms and enlargement of the diverticulum. This proposed pathophysiology appears to adequately explain the anatomic location and configuration of most UD and is supported by the work of Huffman noted previously. However, it should be noted that Daneshgari and colleagues (1999) have reported noncommunicating urethral diverticula diagnosed by MRI. Whether this lesion represents a forme fruste of UD or simply a UD with an obstructed ostium is unclear.

Young and colleagues (1996) have formulated a modern hypothesis regarding the pathogenesis of UD through extensive clinical experience with this entity, including the diagnosis, imaging, and surgical repair of UD. These authors have proposed that acquired UD results from infection and obstruction of the periurethral glands. These glands are normally found in the submucosal layer of the spongy tissue of the distal two thirds of the urethra. Repeated infection and abscess formation in these obstructed glands eventually result in enlargement and expansion. Initially the expanding

mass displaces the spongy tissue of the urethral wall and then enlarges to disrupt the muscular envelope of the urethra. This results in herniation into the periurethral fascia. The enlarging cavity can then expand and dissect within the leaves of the periurethral fascia and urethropelvic ligament. This expansion occurs most commonly ventrally, resulting in the classic anterior vaginal wall mass palpated on physical examination in some patients with UD. However, it is important to note that these may also expand laterally, or even dorsally, about the urethra. Eventually, the abscess cavity ruptures into the urethral lumen, resulting in the communication between the UD and the urethral lumen.

Prevalence

Moore (1952) **stated that UD as an entity is "...found in direct proportion to the avidity with which it is sought."** Although it is not considered a rare lesion today, less than 100 cases of UD had been reported in the literature prior to 1950. With the development of sophisticated imaging techniques, including positive-pressure urethrography in the 1950s, the diagnosis of UD became increasingly common.

The true prevalence of female UD, however, is not known; it is reported to occur in up to 1% to 6% of adult females in some series. Determining the true prevalence of UD would require appropriate screening and imaging of a large number of symptomatic and asymptomatic adult female subjects in a primary care setting, which, to date, has not been done. Bruning (1959) found UD in 3 of 500 female autopsy specimens. In 1967, Andersen reported the results of positive-pressure urethrography done for 300 women with cervical cancer but without lower urinary tract symptoms (LUTS) and found UD in 3%. Aldridge (1978) reported a prevalence of UD in 1.4% of women presenting with incontinence and related symptoms. Stewart (1981) found UD in 16 of 40 highly symptomatic females investigated with positive-pressure urethrography. Endorectal coil MRI was performed on 140 consecutive female patients *with* LUTS, and the incidence of UD was approximately 10% (Lorenzo et al, 2003). However, this represented a series of *symptomatic* females at a tertiary referral center and therefore probably is not reflective of general population. More recently, Burrows and colleagues (2004) reviewed U.S. hospital and ambulatory surgery databases and concluded that the rate of urethral diverticulectomy surgery from 1994 to 1996 was approximately 6.7 per 1 million females. However, this is well below the historical prevalence figures cited previously.

Some series have suggested a definite racial predilection, with African-Americans being as much as six times as likely to develop UD as their white counterparts (Davis and Robinson, 1970). The reasons for this racial distribution are not well understood. Recent data suggests that inpatient surgery for urethral diverticulum occurs threefold more commonly in African-Americans than in whites (Burrows et al, 2004).

Diverticular Anatomy

Most commonly, UD represent an epithelialized cavity with a single connection to the urethral lumen. The size of the lesion may vary from only a few millimeters to several centimeters. In addition, the size may vary over time due to inflammation, intermittent obstruction of the ostium, and subsequent drainage into the urethral lumen.

The epithelium of UD may be columnar, cubiodal, stratified squamous, or transitional. In some cases, the epithelium is absent, and the wall of the UD consists of only fibrous tissue. UD are found within the periurethral fascia bordered by the anterior vaginal wall ventrally. In the sagittal plane, UD are most often located and centered at the level of the middle third of the urethra, with the luminal connection, or ostium, located posterolaterally. They may extend distally along the vaginal wall, almost to the urethral meatus or proximally up to and beyond the bladder neck underneath the trigone of the bladder (Fig. 78–16). A bewildering array of configurations can be noted on imaging and at surgical exploration (Table 78–1). In the axial plane, the UD cavity may extend laterally along the urethral wall and, in some cases, around to the dorsal side of the urethra or wrap circumferentially around the entire urethra. UD may be bilobed (dumbbell shaped), extending across the midline in a so-called "saddle bag" configuration (see Fig. 78–15). Multiple loculations are not uncommon, and at least 10% of patients have

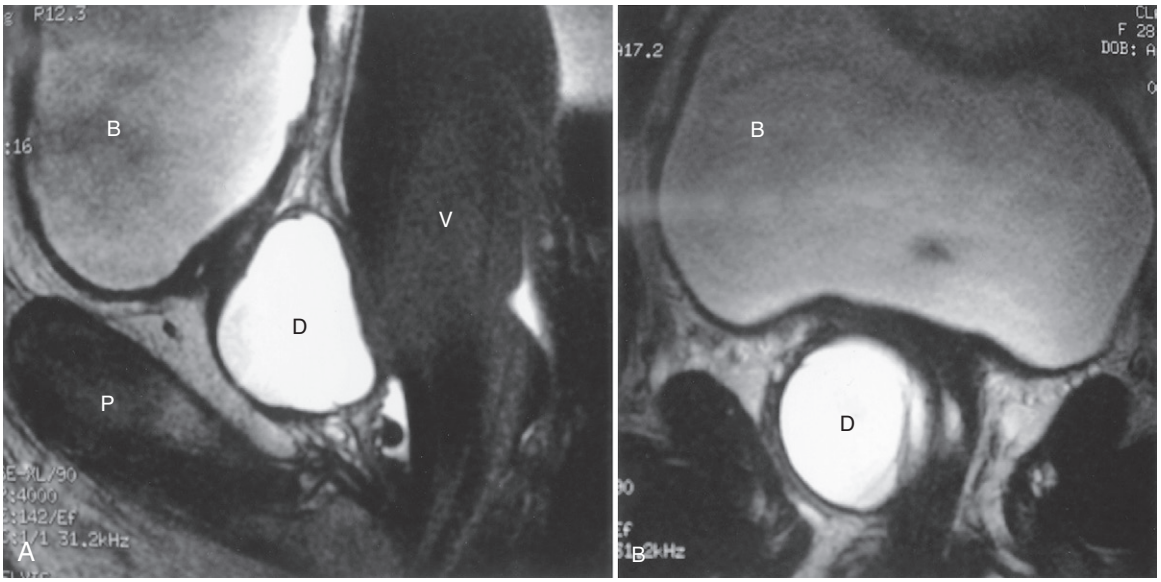


Figure 78–16. T2 MRI images demonstrating a large urethral diverticulum extending to the trigone of the bladder in the (**A**) sagittal, (**B**) coronal planes. B, bladder; D, urethral diverticulum; P, symphysis pubis; V, vagina.

Table 78–1.

Diverticular Morphology and Characteristics

			AXIAL LOCATION (%)			NUMBER (%)		CORONAL LOCATION (%)		
Series	Number of Patients	Size Range (cm)	Anterior	Lateral	Posterior	Single	Multiple	Proximal	Mid	Distal
Lang/Davis[1]	108	N/A	N/A	N/A	N/A	N/A	N/A	11(10)	50(46)	47(44)
Hoffman[2]	60	0.5-5.0	N/A	N/A	N/A	N/A	N/A	4(7)	29(48)	23(38)
Pavlica[3]	47	0.5-6.0	3(6)	6(13)	38(81)	41(87)	6(13)	3(6)	39(83)	5(11)
Kim[4]	16	0.9-4.5	5(31)*	N/A	11(69)	N/A	N/A	4(25)	10(63)	2(12)
Leach[5]	61	0.02-5.0	N/A	N/A	N/A	55(90)	6(10)	15(25)	37(60)	9(15)

*Anterior and lateral.
[1]Lang and Davis, 1959.
[2]Hoffman and Adams, 1965.
[3]Pavlica et al, 1988.
[4]Kim et al, 1993.
[5]Leach et al, 1993.
Adapted from Westney OL, Leng WW, McGuire EJ. The diagnosis and treatment of female urethral diverticulum. American Urological Association Update Series (Houston, TX), 2001;20:Lesson 37, p. 291.

multiple UD at presentation. Varying degrees of sphincteric compromise may exist due to the location of diverticulum relative to the proximal and distal urinary sphincter mechanisms, or sphincteric compromise may coexist with UD due to other factors. This is important to note when considering surgical repair as discussed later.

Presentation

The majority of patients with UD present between the third and seventh decade of life (Johnson, 1938; Moore, 1952; Pathak and House, 1970; Ginsburg and Genadry, 1983; Ganabathi et al, 1994). The presenting symptoms and signs in patients with UD are protean (Table 78–2). **The classic presentation of UD has been described historically as the "three Ds": dysuria, dyspareunia, and dribbling (postvoid).** However, individually or collectively, these symptoms are neither sensitive nor specific for UD. **Although presentation is highly variable, the most common symptoms are irritative (frequency, urgency, etc.) lower urinary tract symptoms (LUTS), pain, and infection** (Davis and TeLinde, 1958; Davis and Robinson, 1970; Peters and Vaughan, 1976; Leach et al, 1986). **Dyspareunia will be noted by 12% to 24% of patients** (Davis and TeLinde, 1958; Davis and Robinson, 1970). **Approximately 5% to 32% of patients will complain of postvoid dribbling** (Davis and Robinson, 1970; Ganabathi et al, 1994). **Recurrent cystitis or urinary tract infection is also a frequent presentation in one third of subjects** (Davis and Robinson, 1970; Ganabathi et al, 1994), **probably due to urinary stasis in the UD. Multiple bouts of recurrent cystitis should alert the clinician to the possibility of a UD. Other complaints include pain, a vaginal mass, hematuria, vaginal discharge, obstructive symptoms or urinary retention, and incontinence (stress or urge).** Patients may present with complaints of a tender or nontender anterior vaginal wall mass, which upon gentle compression may reveal retained urine or purulent discharge per the urethral meatus. Although spontaneous rupture of these lesions is extremely rare, urethrovaginal fistula may result under these circumstances (Nielsen et al, 1987). **Notably, up to 20% of patients diagnosed with UD may be completely asymptomatic, having the lesions diagnosed incidentally on imaging or physical examination.**

Table 78–2.

Signs and Symptoms of Urethral Diverticula

Symptoms
Vaginal or pelvic mass
Pelvic pain
Urethral pain
Dysuria
Urinary frequency
Postvoid dribbling
Dyspareunia
Urinary urgency
Incontinence
Urinary hesitancy
Vaginal or urethral discharge
Double voiding
Sense of incomplete emptying
Signs
Recurrent urinary tract infection
Hematuria
Vaginal or perineal tenderness
Urinary retention
Vaginal mass
Urethral discharge with stripping of anterior vaginal wall

It is important to note that the size of the UD does not correlate with symptoms. In some cases, very large UD may result in minimal symptoms, and, conversely, some UD that are non-palpable may result in considerable patient discomfort and distress. Finally, symptoms may wax and wane and even resolve for long periods of time. The reasons for these exacerbations and remissions are poorly understood but may be related to periodic and repeated episodes of infection and inflammation.

Because many of the symptoms associated with UD are nonspecific, patients may often be misdiagnosed and treated for years for a number of unrelated conditions before the diagnosis of UD is made. This may include therapies for interstitial cystitis, recurrent cystitis, vulvodynia, endometriosis, vulvovestibulitis, and other conditions. In one series of 46 consecutively examined women eventually diagnosed with UD, the mean interval from onset of symptoms to diagnosis was 5.2

years (Romanzi et al, 2000). In this series, women consulted with an average of nine physicians prior to the definitive diagnosis being made, despite the fact that 52% of women had a palpable mass on exam. This underscores the importance of a baseline level of suspicion and a thorough pelvic exam in female patients complaining of LUTS or other symptoms that may be associated with UD.

Evaluation and Diagnosis

The diagnosis and complete evaluation of UD can be made with a combination of a thorough history, physical examination, appropriate urine studies (including urine culture and analysis), endoscopic examination of the bladder and urethra, and selected radiologic imaging. A urodynamic study may also be helpful in selected cases.

Physical Examination. During physical examination, the anterior vaginal wall should be carefully palpated for masses and tenderness. The location, size, and consistency of any suspected UD should be recorded. **Most UD are located ventrally over the middle and proximal portions of the urethra, corresponding to the area of the anterior vaginal wall 1 to 3 cm inside the introitus** (Fig.78–17). However, UD may also be located anterior to the urethra or extend partially or completely around the urethral lumen. These particular configurations may have significant implications when undertaking surgical excision and reconstruction. UD may also extend proximally toward the bladder neck. These UD may produce distortion of the bladder outlet and trigone of the bladder on cystoscopy or on radiographic imaging. Special care should be taken during surgical excision and reconstruction due to concerns for intraoperative bladder and ureteral injury, as well as the potential development of postoperative voiding dysfunction and urinary incontinence. Distal vaginal masses or perimeatal masses may represent other lesions, including abnormalities of Skene glands (see later discussion). The differentiation between these lesions sometimes cannot be made on the basis of a physical examination alone and may require additional radiologic imaging. **A particularly hard anterior vaginal wall mass may indicate a calculus or malignancy within the UD and mandates further investigation. During physical examination, the urethra may be gently "stripped" or "milked" distally in an attempt to express purulent material or urine from within the UD cavity.** Although often described for the evaluation of UD, this maneuver is not successful in producing the characteristic discharge per urethral meatus in the majority of patients (Leach and Bavendam, 1987).

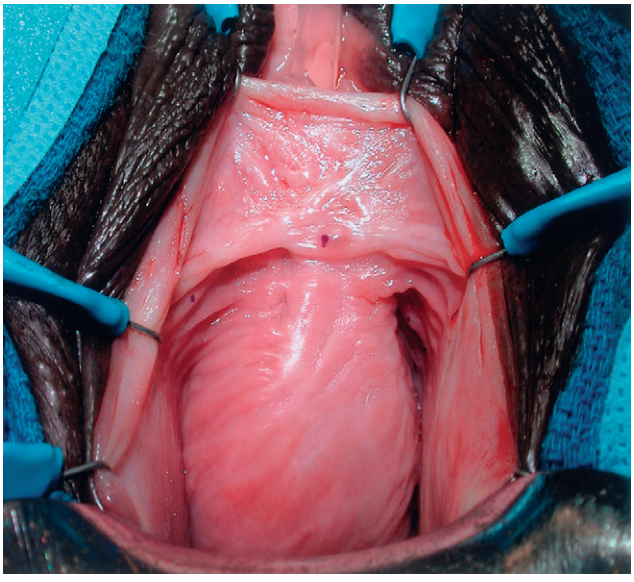


Figure 78–17. Large anterior vaginal wall mass. The urethral catheter is seen superiorly, and a weighted vaginal speculum is seen inferiorly. Scott retractor hooks are seen exposing the anterior vaginal wall in this intraoperative photograph.

The vaginal walls are assessed for atrophy, rugation, and elasticity. Poorly estrogenized, atrophic tissues are important to note if surgery is being considered for definitive treatment. These tissues are mobilized intraoperatively and may be used for flaps during excision and reconstruction. The distal vagina and vaginal introitus are also assessed for capacity. These factors may impact on surgical planning, because a narrow introitus can make surgical exposure difficult and may mandate an episiotomy or other measures. Finally, during physical examination, a provocative maneuver to elicit stress incontinence should be performed, as well as an assessment of the presence or absence of any vaginal prolapse.

Urine Studies. Urine analysis and culture should be performed. The most common organisms isolated in patients with UD is *E. coli*. However, other gram-negative enteric flora, as well as *N. gonorrhea, Chlamydia,* streptococci, and staphylococci, are often present (Davis and TeLinde, 1958; Hoffman and Adams, 1965). A sterile urine culture does not exclude infection, because these patients are often on antibiotic therapy at presentation. In patients with irritative symptoms or where a malignancy is suspected, urine cytology can be performed.

Cystourethroscopy. Cystourethroscopy is performed both in an attempt to visualize the UD ostium as well as to rule out other causes for the patient's LUTS. A flexible fiberoptic cystoscope or specially designed rigid female cystoscope can be extremely helpful in evaluating the female urethra. The short beak of the female cystoscope and the lack of a beak on a flexible cystoscope maintains the discharge of the irrigation solution immediately adjacent to the lens and thus aids in distention of the relatively short (as compared to the male) urethra, permitting improved visualization. It may also be advantageous to compress the bladder neck while simultaneously applying pressure to the diverticular sac with an assistant's finger. Luminal discharge of purulent material can often be seen with this maneuver or with simple digital compression of the UD during urethroscopy. **The UD ostium is most often located posterolaterally at the level of the midurethra but can be very difficult to identify in some patients** (Fig. 78–18). The success in identifying a diverticular ostium on cystourethroscopy is highly variable and is reported to be 15% to 89% (Davis and Robinson, 1970; Leach and Bavendam, 1987; Ganabathi et al, 1994). As a note of caution, patients with UD are often highly symptomatic, and endoscopic examination can be very difficult to initiate or complete without anesthesia. Notably, a positive exam may help in surgical planning; however, the failure to locate an ostium on cystourethroscopy should not influence the decision to proceed with further investigations or surgical repair.

Urodynamics. For patients with UD and urinary incontinence or significant voiding dysfunction, a urodynamic study may be helpful in accurately characterizing these symptoms (Bhatia et al, 1981; Reid et al, 1986; Summitt and Stovall, 1992). Urodynamics may document the presence or absence of stress urinary incontinence (SUI) prior to repair. **Approximately 50% of women with UD will demonstrate SUI on urodynamic evaluation**

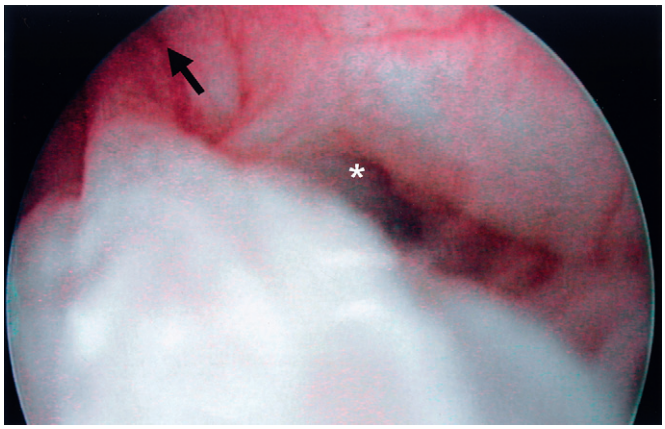


Figure 78–18. Cystoscopic view of the ostium of a urethral diverticulum. The ostium is often difficult to visualize endoscopically. *Asterisk* represents the ostium of the diverticulum; *arrow* shows the orientation of the lumen of the urethra.

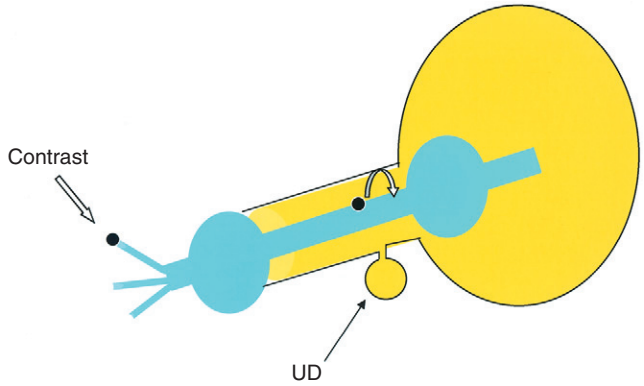


Figure 78–19. Schematic diagram of a double-balloon catheter. The *curved white arrow* represents flow of the contrast as it enters the urethral lumen. UD, urethral diverticulum.

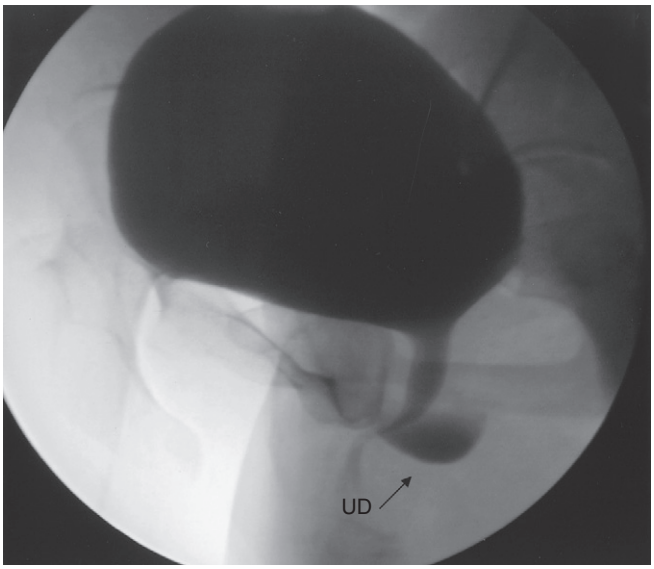


Figure 78–20. Voiding image from a voiding cystourethrogram demonstrating a urethral diverticulum (UD).

(Bass and Leach 1991; Ganabathi et al, 1994). A videourodynamic study combines both a voiding cystourethrogram and a urodynamic study, thus consolidating the diagnostic evaluation and decreasing the number of required urethral catheterizations during the patient's clinical workup. **For patients undergoing surgery for UD—with coexistent symptomatic SUI demonstrated on physical examination, urodynamically demonstrable SUI, or in those found to have an open bladder neck on preoperative evaluation—a concomitant anti-incontinence surgery can be offered.** Multiple authors have described successful repair of urethral diverticula and stress incontinence in the same operative setting (Bass and Leach, 1991; Swierzewski and McGuire, 1993; Ganabathi et al, 1994; Faerber, 1998). Alternatively, a small number of patients may have evidence of bladder outlet obstruction on urodynamic evaluation due to the obstructive or mass effects of the UD on the urethra. It should be noted that SUI may coexist with obstruction (Bradley and Rovner, 2004) but, nevertheless, both conditions can be treated successfully with a carefully planned and executed operation. Urethral pressure profilometry has also been used by some authors to assess and/or diagnose patients with UD, noting a biphasic pattern or pressure drop at the level of the lesion during the study (Bhatia et al, 1981; Wagner et al, 1986; Summitt and Stovall, 1992).

Imaging

High-quality preoperative imaging is important in the diagnosis and therapy of female urethral diverticula. **Aside from its utility as a diagnostic entity, radiologic imaging should also provide an accurate reflection of the relevant anatomy of the UD, including its relationship to the proximal urethra and bladder neck.**

Diagnostic Contrast Radiography: PPU, VCUG, and IVU. A number of imaging techniques have been applied to the study of female UD, and no single study can be considered the gold standard or optimal imaging study for the evaluation of UD. Each technique has relative advantages and disadvantages, and the ultimate choice of diagnostic study in many centers often depends on several factors, including local availability, cost, and the experience and expertise of the radiologist. Currently available techniques for the evaluation of UD include double-balloon positive-pressure urethrography (PPU), voiding cystourethrography (VCUG), intravenous urography (IVU), ultrasonography (US), and magnetic resonance imaging (MRI) with or without an endoluminal coil (eMRI).

Historically, double-balloon PPU had been considered to be the optimal study for the diagnosis and assessment of female UD (Davis and Cian, 1952; Davis and TeLinde, 1958; Greenberg et al, 1981; Ganabathi et al, 1994). In this technique, a highly specialized catheter with two balloons separated by several centimeters is inserted into the female urethra (Fig. 78–19). This catheter contains a channel within the catheter that exits through a side hole between the two balloons. One balloon is positioned adjacent to the external urethral meatus, and the other balloon is situated at the bladder neck. Both balloons are inflated, creating a seal about the urethral lumen. Contrast is then infused through the channel under slight pressure, distending the urethral lumen between the two balloons and forcing contrast into the UD, thereby opacifying the cavity. **This highly specialized study provides outstanding images of the urethra and UD and, importantly unlike VCUG, is not dependent on the patient successfully voiding during the study.** However, PPU is not widely performed clinically.

As an alternative to PPU, VCUG may provide excellent imaging of UD (Fig. 78–20). It is widely available and is a familiar

diagnostic technique to most radiologists. Sensitivity for UD with this technique varies from 44% to 95% (Ganabathi et al, 1994; Jacoby and Rowbotham, 1999). Patients often will have difficulty in initiating micturition in the radiology suite due to the pain associated with urethral catheterization, psychogenic inhibition due to voiding in the presence of others, or other factors. In the absence of voiding, the urethral diverticulum will not be seen. Therefore a VCUG which does not demonstrate a urethral diverticulum but did not contain voiding images or postvoid images is nondiagnostic. If the patient is unable to void under fluoroscopy during the VCUG, an attempt should be made to void in the privacy of an adjacent bathroom. If voiding in private was successful, a postvoid film taken under these circumstances will likely show a collection of contrast inferior to the bladder demonstrating the urethral diverticulum. Unfortunately, an inability to generate an adequate flow rate during the VCUG will result in suboptimal filling of the UD and an underestimation of its size and complexity (Fig. 78–21). Three-dimensional CT VCUG with reconstructions is being investigated as a novel imaging technique for UD but is not yet widely available clinically (Kim et al, 2005).

IVU (intravenous urography) may be considered in patients in whom it is necessary to delineate the upper urinary tract or to evaluate for the possibility of a congenital ectopic ureteral anomaly as the cause of an anterior vaginal wall mass (Blacklock and Shaw, 1982). The post-void film of the urogram can be helpful for the diagnosis of UD in some patients (Stern and Patel, 1976; Goldfarb et al, 1981).

Ultrasonography. This study has been advocated for the preoperative assessment of vaginal masses and UD by multiple authors (Lee and Keller, 1977; Wexler and McGovern, 1980; Baert et al,

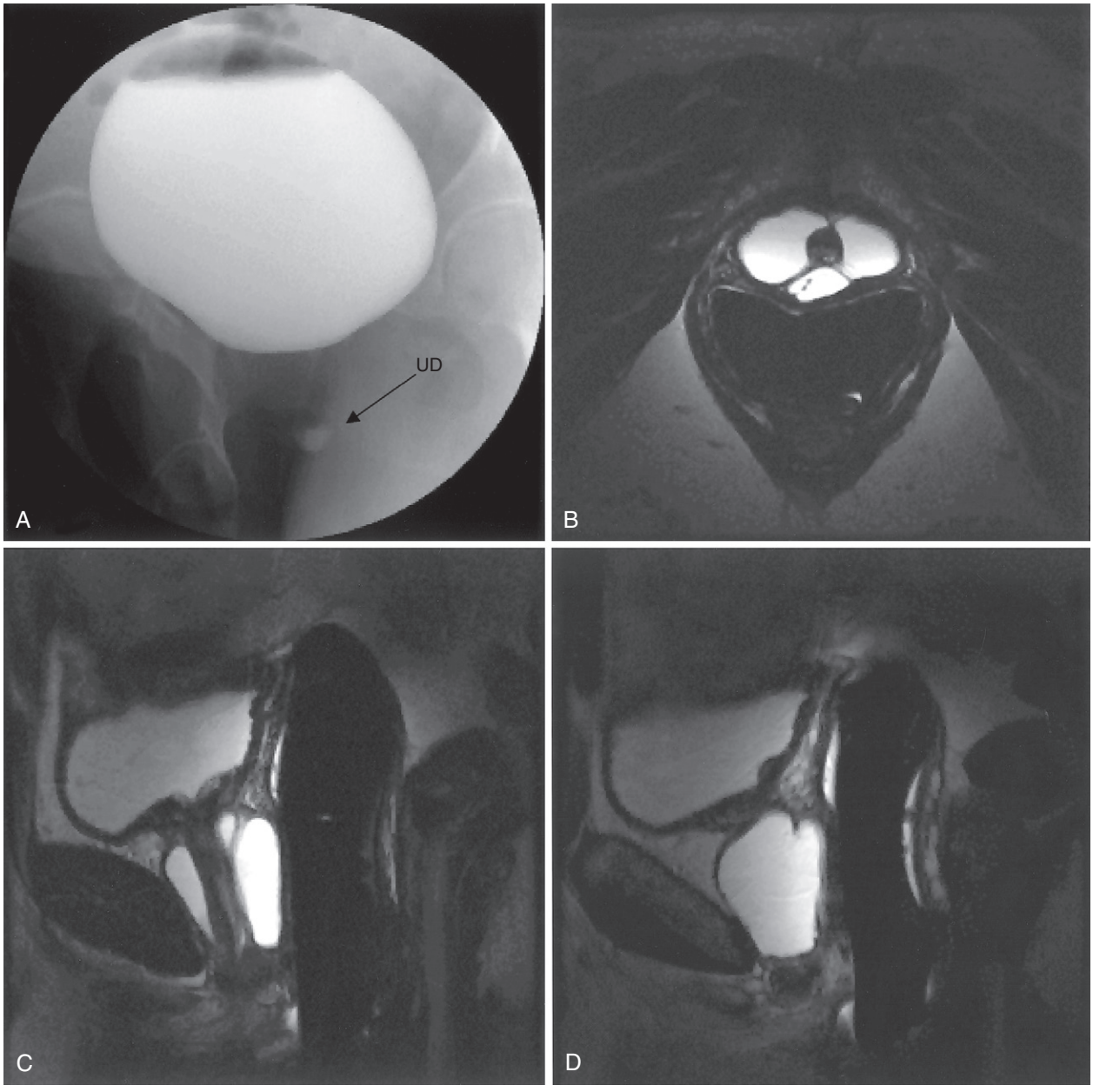


Figure 78–21. Voiding cystourethrogram (VCUG) and MRI from a patient with a large circumferential urethral diverticulum (UD). The voiding image from the VCUG **(A)** shows poor opacification of the proximal urethra with suboptimal distention of the UD due to a poor voiding effort. The endoluminal MRI demonstrates the full extent and complexity of the lesion on the T2 axial **(B),** midline sagittal **(C),** and parasagittal **(D)** images.

1992; Martensson and Duchek, 1994; Chancellor et al, 1995; Vargas-Serrano et al, 1997; Dmochowski, 2001; Fortunato et al, 2001; Lee et al, 2001; Gerrard et al, 2003). Abdominal, transvaginal, translabial, and transurethral techniques have been described. **Transvaginal imaging often provides information regarding the size and location of UD.** On ultrasonographic imaging, the UD appears as an anechoic or hypoechoic area with enhanced through transmission. Ultrasonography (US) is relatively noninvasive and does not expose the patient to radiation. Another significant advantage of US is that successful imaging of UD does not require voiding. However, US may not produce detailed high-resolution images that demonstrate precise surgical anatomy.

MRI. As an alternative to the radiologic investigations noted previously, MRI permits relatively noninvasive, high-resolution, multiplanar imaging of UD. **UD appear as areas of decreased signal intensity on T1 compared with the surrounding soft tissues, and have high signal intensity on T2 images. A distinct advantage of MRI compared with VCUG is that successful imaging of UD is wholly independent of voiding and that it is free from ionizing radiation.** Surface coil (Hricak et al, 1991; Kim et al, 1993) (Fig. 78–22) and endoluminal techniques (Siegelman et al, 1997; Wang and Wang, 2000; Blander et al, 2001; Lorenzo et al, 2003) have been described. Endoluminal imaging (eMRI) places the magnetic coil into a body cavity adjacent to the area of interest. This location produces an improved signal-to-noise ratio and high-resolution imaging of these areas (Siegelman et al, 1997; Blander et al, 2001). For the evaluation of UD, the coil is placed intravaginally or intrarectally. Both surface coil MRI and eMRI appear to be superior to VCUG and/or PPU in the evaluation of UD (Kim et al, 1993; Neitlich et al, 1998; Blander et al, 2001), but the technology is expensive and not widely available. Contraindications to MRI for UD are few; these include metallic foreign body fragments, claustrophobia, and an inability to tolerate the endoluminal probe.

Differential Diagnosis of UD: Periurethral Masses Other Than Urethral Diverticula

Periurethral masses other than UD comprise a wide spectrum of conditions that must be differentiated from each other and UD. It may often be possible to make a definitive diagnosis based on history and physical exam alone; in other cases, judicious use of radiographic and cystoscopic studies will be necessary to exclude UD.

Vaginal Leiomyoma. Vaginal leiomyomata are benign mesenchymal tumors of the vaginal wall that arise from smooth muscle elements. They commonly present as a smooth, firm, round mass on the anterior vaginal wall (Fig. 78–23). It is an uncommon lesion, with approximately 300 cases reported in the literature (Young et al, 1991). In a recent series of 79 patients with periurethral masses, 4 (5%) were found to have vaginal leiomyoma (Blaivas et al, 2004). These masses were all apparent on physical examination as freely mobile, firm, nontender masses on the anterior vaginal wall. They may be misdiagnosed as UD (Shirvani and Winters, 2000). Symptoms, if they exist, are usually related to the size of the lesion and include a mass effect, obstruction, pain, and dyspareunia. They commonly present in the fourth to fifth decade. Similar to uterine leiomyoma, these lesions are usually estrogen dependent and have been demonstrated to regress during menopause (Liu, 1988). Excision or enucleation (Young et al, 1991) through a vaginal approach is often curative and is recommended to confirm the diagnosis, exclude malignant histology, and also to alleviate symptoms.

Skene Gland Abnormalities. Skene gland cysts and abscesses are similar lesions that are differentiated based on clinical findings (Fig. 78–24). Both lesions generally present as small, cystic masses just lateral or inferolateral to the urethral meatus. They may be lined with transitional or stratified squamous epithelium. Abscesses may be extremely tender and inflamed, and, in some

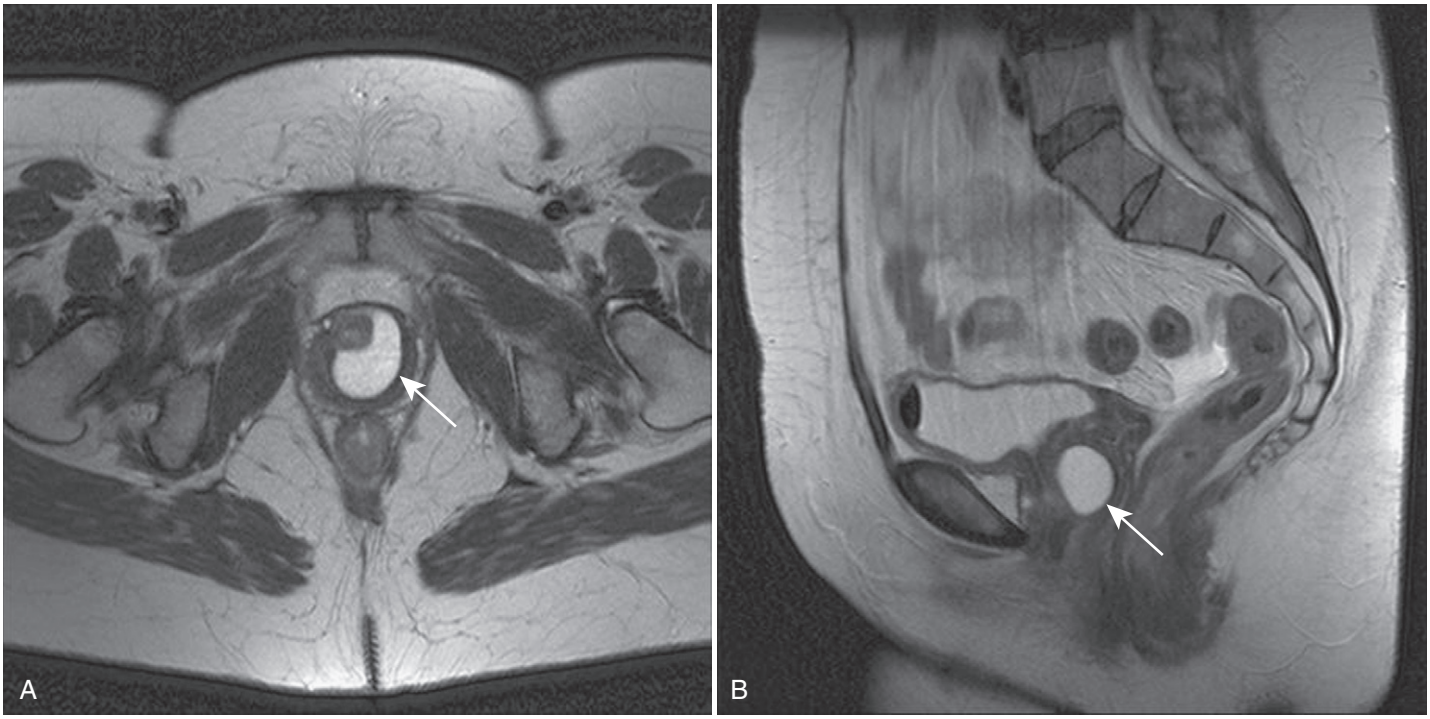


Figure 78–22. Surface coil T2 MRI demonstrating a urethral diverticulum in the sagittal **(A)** and axial **(B)** planes. *Arrow* shows the urethral diverticulum.

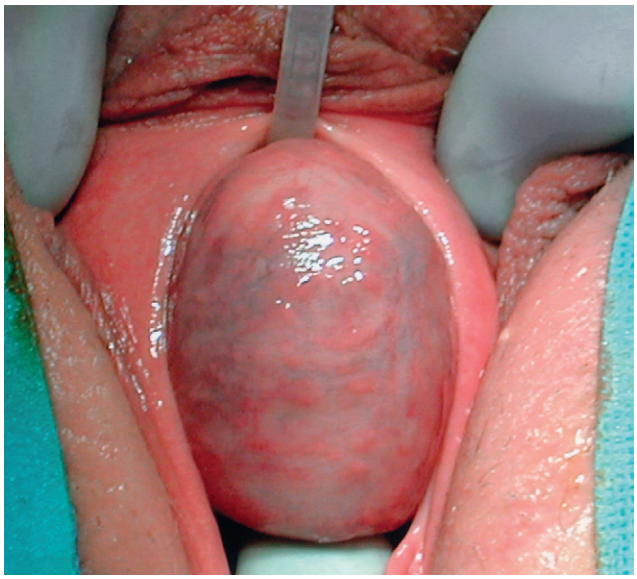


Figure 78–23. Large anterior vaginal wall leiomyoma.

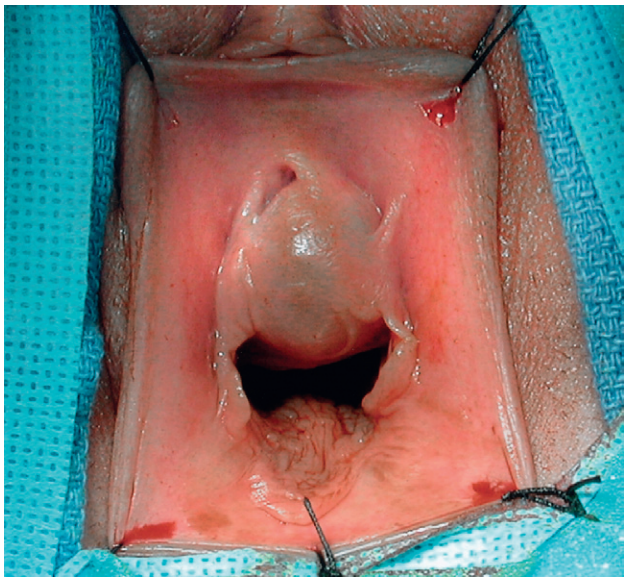


Figure 78–24. Skene gland cyst in a 19-year-old female. Note the large periurethral mass with displacement of the urethral meatus.

cases, purulent fluid can be expressed from the ductular orifice. **Classically, in contrast to UD, these lesions do not communicate with the urethral lumen.** Skene gland cysts are not uncommonly noted in neonatal girls and young to middle-aged female patients (Lee and Kim, 1992). Symptoms may include dysuria, dyspareunia, obstruction, and pain. **Differentiation from UD can often be made on physical examination, because these lesions are located relatively distally on the urethra, often distorting the urethral meatus as compared with UD, which most commonly occur over the mid- and proximal urethra.** Various treatments for abnormalities of Skene gland abnormalities have been described, including aspiration, marsupialization, incision and drainage, and simple excision.

Adenocarcinoma arising in Skene glands has been reported. Because of homology with the prostate, these patients may

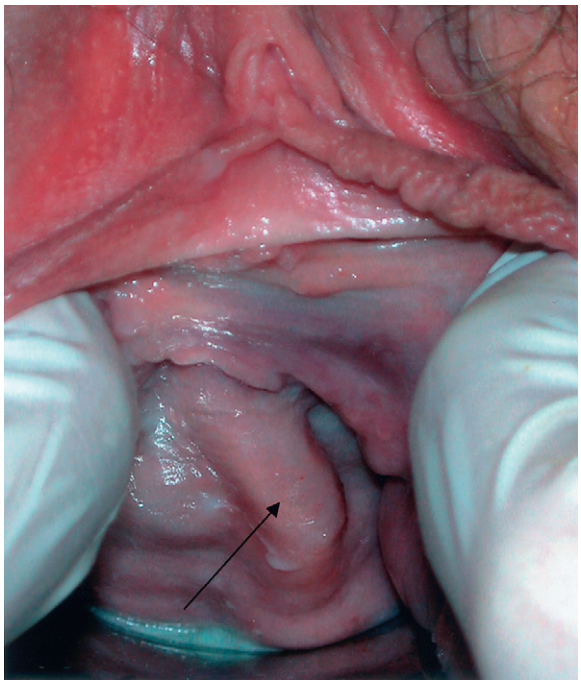


Figure 78–25. Upper pole ectopic ureter in a 39-year-old female being evaluated for lifelong urinary incontinence and recurrent pyelonephritis. A tubelike structure *(arrow)* representing the turgid, debris-filled ectopic ureter is seen on the anterior vaginal wall.

demonstrate elevated PSA levels that normalize with treatment (Dodson et al, 1994).

Gartner Duct Abnormalities. Gartner duct cysts represent mesonephric remnants and are found on the anterolateral vaginal wall from the cervix to the introitus. Because these are mesonephric remnants, they may drain ectopic ureters from poorly functioning or nonfunctioning upper pole moieties in duplicated systems (Fig. 78–25). They have also been reported with single-system ectopia, although this is much less common in females (Gadbois and Duckett, 1974; Currarino, 1982). It is not clear what proportion of patients with Gartner duct cysts will have ipsilateral renal abnormalities, but upper tract evaluation is recommended. In contrast, approximately 6% of subjects with unilateral renal agenesis will have a Gartner duct cyst (Eilber and Raz, 2003). Up to 50% of patients with Gartner duct cysts and renal dysplasia may also have ipsilateral müllerian duct obstruction (Sheih et al, 1998).

Treatment depends on symptoms and association with ectopic ureters. If the lesions are asymptomatic and are associated with a nonfunctioning renal moiety, they can be observed. Aspiration and sclerotherapy has been successful (Abd-Rabbo and Atta, 1991). Simple excision or marsupialization has also been recommended for symptomatic lesions. If the cyst is associated with a functioning renal moiety, treatment must be individualized.

Vaginal Wall Cysts. Vaginal wall cysts usually present as small asymptomatic masses on the anterior vaginal wall (Deppisch, 1975) but may enlarge to cause lower urinary tract symptoms or dyspareunia (Fig. 78–26). They may arise from multiple cell types: mesonephric (Gartner duct cysts), paramesonephric (müllerian), endometriotic, urothelial, or epidermoid (inclusion cyst). A specific diagnosis cannot be reliably made until the specimen is removed and examined by a pathologist. The histologic subtype is usually of little consequence, although epidermoid cysts are usually associated with previous trauma or vaginal surgery.



Figure 78–26. Anterior vaginal wall cyst prior to planned excision. This anterior vaginal wall mass was misdiagnosed as a cystocele and followed for many years in this patient with considerable lower urinary tract symptoms.

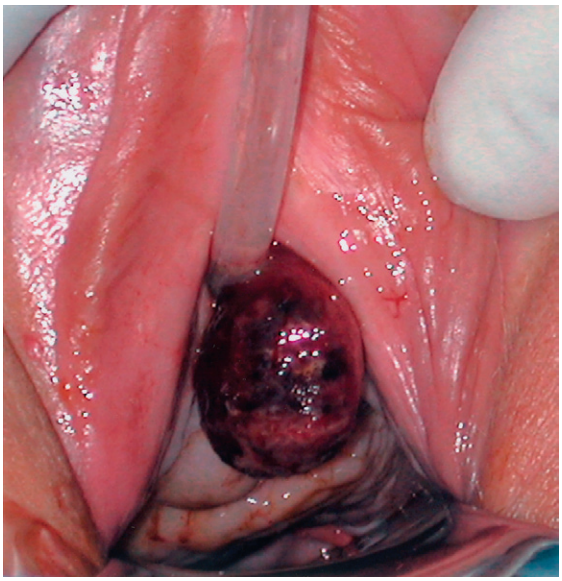


Figure 78–27. Thrombosed urethral caruncle in a postmenopausal female. The Foley catheter is seen in the urethra. Simple excision was curative.

Pradhan and Tobon (1986) described the pathologic characteristics of 43 vaginal cysts removed over a 10-year period from 41 women. The derivation of the cyst was müllerian in 44%, epidermoid in 23%, and mesonephric in 11%. The remainder were a Bartholin gland type, endometriotic and indeterminate. As with other periurethral masses, they must be differentiated from UD. Treatment is usually by simple excision in symptomatic patients.

Urethral Mucosal Prolapse. Urethral prolapse presents as a circumferential herniation or eversion of the urethral mucosa at the urethral meatus. The prolapsed mucosa commonly appears as a beefy red "doughnut"-shaped lesion that completely surrounds the urethral meatus. It may be asymptomatic or present with bleeding, spotting, pain, or urinary symptoms. It is commonly noted in two separate populations: postmenopausal women and prepubertal girls. Although thought to be more common in young African-American girls, more recent series do not confirm this predilection (Fernandes et al, 1993; Rudin et al, 1997). In children, it is often causally related to Valsalva or constipation. Eversion of the mucosa may then occur due to a pathologically loose attachment between smooth muscle layers of the urethra (Lowe et al, 1986). Etiology is much less clear for postmenopausal women, although it has been epidemiologically linked to estrogen deficiency. Treatment may be medical or surgical. Medical treatment involves topical creams (estrogen, anti-inflammatory) and/or sitz baths. Various surgical techniques have been described, including cauterization, ligation around a Foley catheter, and complete circumferential excision. Circumferential excision with suture reapproximation of the remaining urethral mucosa to the vaginal wall can be performed with few complications. Rudin and colleagues (1997) reported outcomes in 58 girls with urethral prolapse. Medical treatment was initially successful in 20 patients among whom there were five recurrences. The remaining 38 patients failed initial conservative management and underwent surgical excision with four complications, including urethral stenosis in 2 patients. Jerkins and colleagues (1984) found superior results in surgically treated patients when compared with medical management or catheter ligation.

Urethral Caruncle. Urethral caruncle is an inflammatory lesion of the distal urethra that is most commonly diagnosed in postmenopausal women. It usually appears as a reddish exophytic mass at the urethral meatus, which is covered with mucosa. These lesions are often symptomatic and noted incidentally on gynecologic examination. When irritated, they may cause underwear spotting or become painful. Less commonly they may cause voiding symptoms. Rarely, these lesions may thrombose, resulting in a discolored periurethral mass (Fig. 78–27). Etiologically, they are related to mucosal prolapse. Chronic irritation contributes to hemorrhage, necrosis, and inflammatory growth of the tissue that corresponds to the histology of excised lesions. If the lesion is atypical in appearance or behavior, excision may be warranted to exclude other entities. Intestinal metaplasia, tuberculosis, melanoma, and lymphoma have all been reported to either coexist with or mimic urethral caruncles (Willett and Lack, 1990; Indudhara et al, 1992; Khatib et al, 1993; Lopez et al, 1993; Atalay et al, 1998).

There is a paucity of literature regarding optimal treatment of urethral caruncle. Most authors recommend initial conservative management with topical estrogen or anti-inflammatory creams and sitz baths. Large or refractory lesions may be managed with simple excision. The tip of the lesions should be grasped and traction employed to fully expose the base of the caruncle. The lesion can then easily be excised. If a large defect remains, the mucosa may be reapproximated with absorbable suture. In most instances, the urethral mucosa will heal around a Foley catheter, which may be left in place for several days.

Periurethral Bulking Agents. The transurethral or periurethral injection of bulking agents for the treatment of stress incontinence may result in an anterior vaginal wall mass that appears cystic on imaging, consistent with a urethral diverticulum (Bridges et al, 2005). A careful history will elicit this possibility. Typically, these lesions do not communicate with the urethra and are largely asymptomatic. In the absence of symptoms or complications, many bulking agents will reabsorb with time, and thus observation is all that is required.

Classification of Urethral Diverticula

Although not yet widely adopted, a classification system for UD has been proposed by Leach and colleagues (1993). This staging system for UD, termed the L/N/S/C3 classification system, is similar to that used for cancer staging and is based on several characteristics of UD, including location, number, size, anatomic configuration, site of communication to the urethral lumen, and continence status of the patient. This system attempts to standardize description of UD, but currently it has not been prospectively applied or validated by other authors. Another proposed classification scheme uses the location of the UD as the primary determinant of surgical approach, with distal lesions undergoing marsupialization and more proximal lesions undergoing excision and reconstruction (Ginsburg and Genadry, 1983).

Finally, a classification system proposed by Leng and McGuire (1998) divides UD into two categories based on the presence or absence of a preserved periurethral fascial layer. In some patients with UD who have undergone prior vaginal or urethral surgery, the periurethral fascial layer may be deficient, resulting in a pseudodiverticulum. These authors suggest that the recognition of this anatomic configuration has important implications for surgical reconstruction. These patients may require additional reconstruction or interposition of a tissue flap or graft for reconstruction.

Key Points: Female Urethral Diverticula—Diagnosis

- Female urethral diverticula are often diagnosed in the evaluation of nonspecific lower urinary tract symptoms, including dysuria, pelvic pain, vaginal mass, dyspareunia, and recurrent UTIs.
- Multiple imaging modalities may be used in the diagnosis and evaluation of female urethral diverticula, including positive-pressure urethrography, VCUG, ultrasonography, and MRI; each of these techniques has inherent advantages and disadvantages.
- The differential diagnosis of periurethral vaginal masses is extensive. A careful history, physical examination, and appropriate diagnostic studies will usually be adequate to provide a definitive preoperative diagnosis.

Surgical Repair of Female Urethral Diverticula

Indications for Repair

Although often highly symptomatic, not all urethral diverticula mandate surgical excision. Some patients may be asymptomatic at presentation, with the lesion incidentally diagnosed on imaging for another condition or, perhaps, incidentally noted on routine physical examination. Other patients may be unwilling or medically unable to undergo surgical removal. **Very little is known regarding the natural history of untreated urethral diverticula. Whether these lesions will progress in size, symptomatology, or complexity with time is unknown.** For these reasons, and due to the lack of symptoms in selected cases, some patients may not desire surgical therapy. However, it should be noted that there are multiple reports in the literature of carcinomas arising in UD (Marshall and Hirsch 1977; Prudente et al, 1978; Tesluk, 1981; Tines et al, 1982; Patanaphan et al, 1983; Gonzalez et al, 1985; Thomas and Maguire, 1991; Rajan et al, 1993; Seballos and Rich, 1995; Hickey et al, 2000), and it is possible that certain carcinomas arising in UD are asymptomatic and may not be prospectively identified on radiologic imaging. Thus patient counseling is necessary in patients who elect primary nonoperative management. Patients electing nonoperative management can be treated with low-dose antibacterial suppressants and digital stripping of the anterior vaginal wall following micturition to prevent postvoid dribbling and reduce the risk of UTI due to stasis in the UD. Whether long-term surveillance is required in these patients, with periodic physical examinations, radiographic imaging, or endoscopic examination, is unknown.

Symptomatic patients may be offered surgical excision, including those with dysuria, refractory bothersome postvoid dribbling, recurrent UTIs, dyspareunia, and pelvic pain, in whom the symptoms can be attributed to the UD. Those with UD and symptomatic stress urinary incontinence can be considered for a concomitant anti-incontinence procedure at the time of UD excision (see later discussion) (Fig. 78–28).

Techniques for Repair

Alternative Techniques. A variety of surgical interventions for urethral diverticula have been reported since 1805 when Hey described transvaginal incision of the UD and packing the resulting cavity with lint. Approaches have included transurethral (Davis and Robinson, 1970) and open (Spence and Duckett, 1970; Roehrborn, 1988) marsupialization, endoscopic unroofing (Lapides, 1978; Spencer and Streem, 1987), fulguration (Saito, 2000), incision and obliteration with oxidized cellulose (Ellick, 1957) or polytetrafluoroethylene (Mizrahi and Bitterman, 1988), coagulation (Mizrahi and Bitterman, 1988), and excision with reconstruction. Most commonly, a complete excision and reconstruction is performed as described below. However, for distal lesions, a transvaginal marsupialization as described by Spence and Duckett may reduce operative time, blood loss, and recurrence rate (Spence and Duckett, 1969, 1970; Roehrborn, 1988). **During this procedure, care must be taken to avoid aggressively extending the incision proximally, which could result in vaginal voiding or potentially damage the proximal and distal sphincteric mechanism, resulting in stress urinary incontinence.** Another potentially significant complication with the Spence-Duckett procedure is that in sexually active women, a pseudoseptum may be created by the marsupialization of the urethra with respect to the anterior vaginal wall, which may result in dyspareunia. Therefore this approach is probably only applicable to UD in very select cases involving the distal one third of the urethra. It is not commonly performed.

Excision and Reconstruction. **Excision and reconstruction is probably the most common surgical approach to UD in the modern era.** The principles of the urethral diverticulectomy operation have been well described (Table 78–3). There are only a few minor issues about which some surgeons may disagree, including the type of vaginal incision (inverted "U" vs. inverted "T"), whether it is necessary to remove the entire mucosalized portion of the lesion, and, finally, the optimal type of postoperative catheter drainage (urethra only vs. urethra and suprapubic).

Complex urethral reconstructive techniques for the repair of UD have been described. Fall (1995) described the use of a bipedicled vaginal wall flap for urethral reconstruction in patients with UD and urethrovaginal fistula. Laterally based vaginal flaps have also been used as an initial approach to UD (Woodhouse et al,

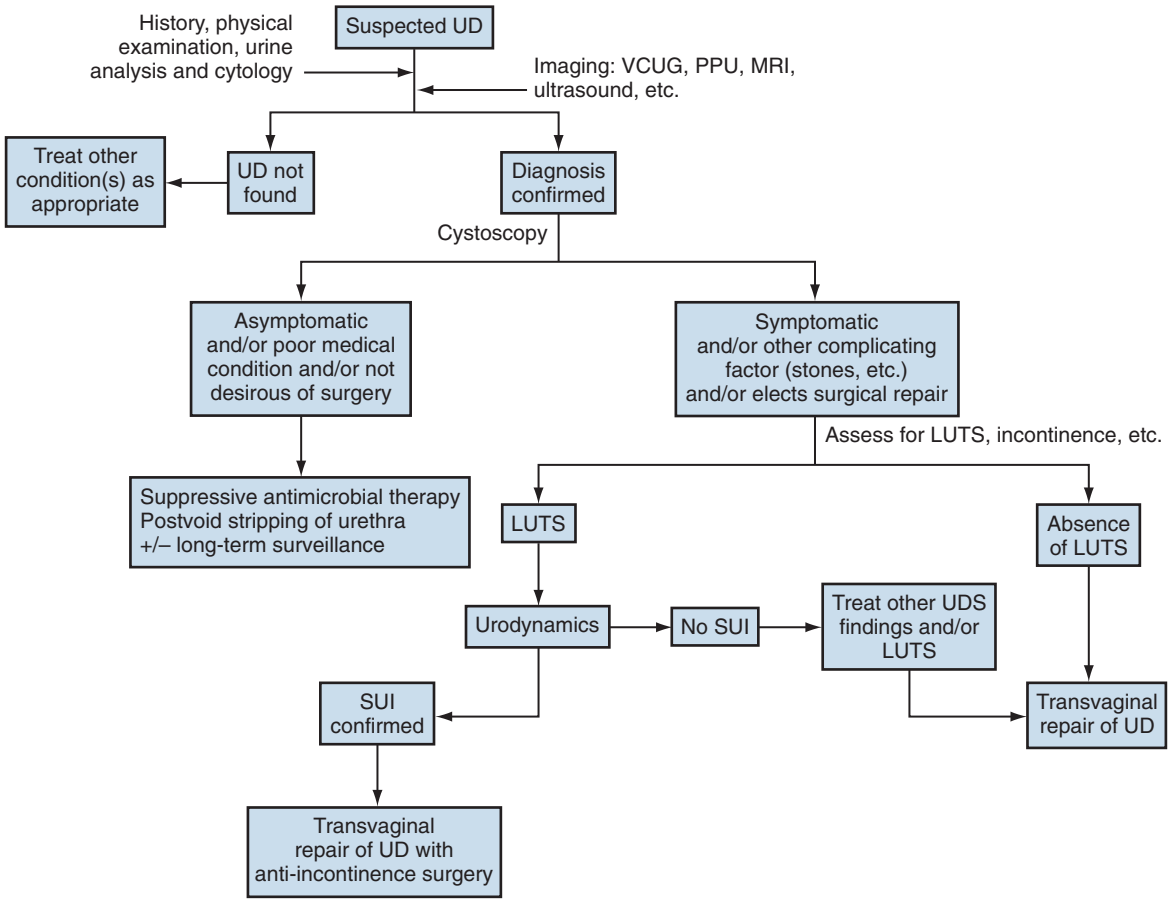


Figure 78–28. Algorithm for treatment of urethral diverticula. LUTS, lower urinary tract symptoms; MRI, magnetic resonance imaging; PPU, positive-pressure urethrography; SUI, stress urinary incontinence; UD, urethral diverticulum; UDS, urodynamics; VCUG, voiding cystourethrography.

Table 78–3.

Principles of Transvaginal Urethral Diverticulectomy (UD)

Mobilization of a well-vascularized anterior vaginal wall flap(s)
Preservation of the periurethral fascia
Identification and excision of the neck of the UD, or ostium
Removal of entire UD wall or sac (mucosa)
Watertight urethral closure
Multilayered, nonoverlapping closure with absorbable suture
Closure of dead space
Preservation or creation of continence

1980; Appell and Suarez, 1982). Complex anatomic configurations may exist, and many novel approaches have been described for complicated anteriorly located or circumferential lesions (Clyne and Flood, 2002; Rovner and Wein, 2003; Vakili et al, 2003).

The technique described herein is similar to that described by Leach and Raz (Leach et al, 1986), based on earlier work by Benjamin and colleagues (1974) and Busch and Carter (1973).

Preoperative Preparation. Prophylactic antibiotics are often used preoperatively to ensure sterile urine at the time of surgery. Patients can also be encouraged to strip the anterior vaginal wall following voiding, thereby consistently emptying the UD and preventing urinary stasis and recurrent UTIs. This may not be possible in those with noncommunicating UD or in those who have significant pain related to the UD. In some patients with postmenopausal atrophic vaginitis, application of topical estrogen creams for several weeks prior to surgery may be beneficial in improving the overall quality of the tissues with respect to planned operative dissection and mobilization. Preoperative parenteral antibiotics are often administered especially for those with recurrent or persistent UTIs.

Urethral diverticulectomy surgery is complex and sometimes quite technically challenging. Further complicating these cases are the associated preoperative symptoms, such as pain, dyspareunia, voiding dysfunction, urinary tract infections, and urinary incontinence. These associated symptoms are often, but not always, improved or eliminated with surgical repair despite even a technically successful surgery. Therefore the importance of appropriate preoperative patient counseling regarding surgery and postoperative expectations of cure cannot be overemphasized.

Patients with symptomatic stress urinary incontinence can be offered simultaneous anti-incontinence surgery. Preoperative videourodynamics may be helpful in evaluating the anatomy of the UD, assessing the competence of the bladder neck, and confirming the diagnosis of stress urinary incontinence. In patients with SUI and UD, Ganabathi and others have described excellent results with concomitant needle bladder neck suspension in these complex patients (Lockhart et al, 1990; Ganabathi et al, 1994). More recently, pubovaginal fascial slings have been used in patients with UD and stress urinary incontinence with satisfactory outcomes (Swierzewski and McGuire,

1993; Faerber, 1998; Romanzi et al, 2000). **The role of synthetic midurethral slings, however, has not been well defined in this population.** Placement of synthetic material adjacent to a fresh suture line following diverticulectomy in the setting of potentially infected urine may increase the risk of complications, such as urethral erosion and vaginal extrusion of the sling material, as well as urethrovaginal fistula formation.

Procedure. The patient is placed in the lithotomy position with all pressure points well padded. The use of padded adjustable stirrups for the lower extremities greatly enhances operative access to the female perineum. A standard vaginal antiseptic preparation is applied. A weighted vaginal speculum and Scott retractor with hooks aid in exposure. **A posterolateral episiotomy may be beneficial in some patients for additional exposure, although the midurethral (and therefore somewhat distal in the vaginal canal) location of most UD usually precludes the need for this type of adjunctive procedure.** A Foley catheter is placed per urethra. If desired, a suprapubic tube is placed at the start of the procedure, either using the Lowsley retractor or proceeding percutaneously under direct transurethral cystoscopic visual guidance. Placement of the suprapubic tube at the end of the case is not advisable because this will require traversing the fresh urethral suture line and risk disruption of the repair.

An inverted U is marked along the anterior vaginal wall with the base of the U at the level of the distal urethra and the limbs extending to the bladder neck or beyond (Fig. 78–29A). Care is taken to ensure that the limbs of the U are progressively wider proximally (toward the bladder neck) to ensure adequate vascularity at the distal lateral margins of the anterior vaginal wall flap. Compared with the inverted T incision, the inverted U incision provides excellent exposure laterally at the level of the midvagina and can be extended proximally as needed for lesions that extend beyond the bladder neck. Injectable saline can be infused along the lines of the incision to facilitate dissection. An anterior vaginal wall flap is created by careful dissection in the potential space between the vaginal wall and the periurethral fascia. **The use of sufficient counter-traction during this portion of the procedure is important in maintaining the proper plane of dissection. Care is taken to preserve the periurethral fascia and avoid inadvertent entry into the UD.**

A distinct layer of periurethral fascia is usually interposed between the vaginal wall and the UD. Preservation and later reconstruction of this layer is of paramount

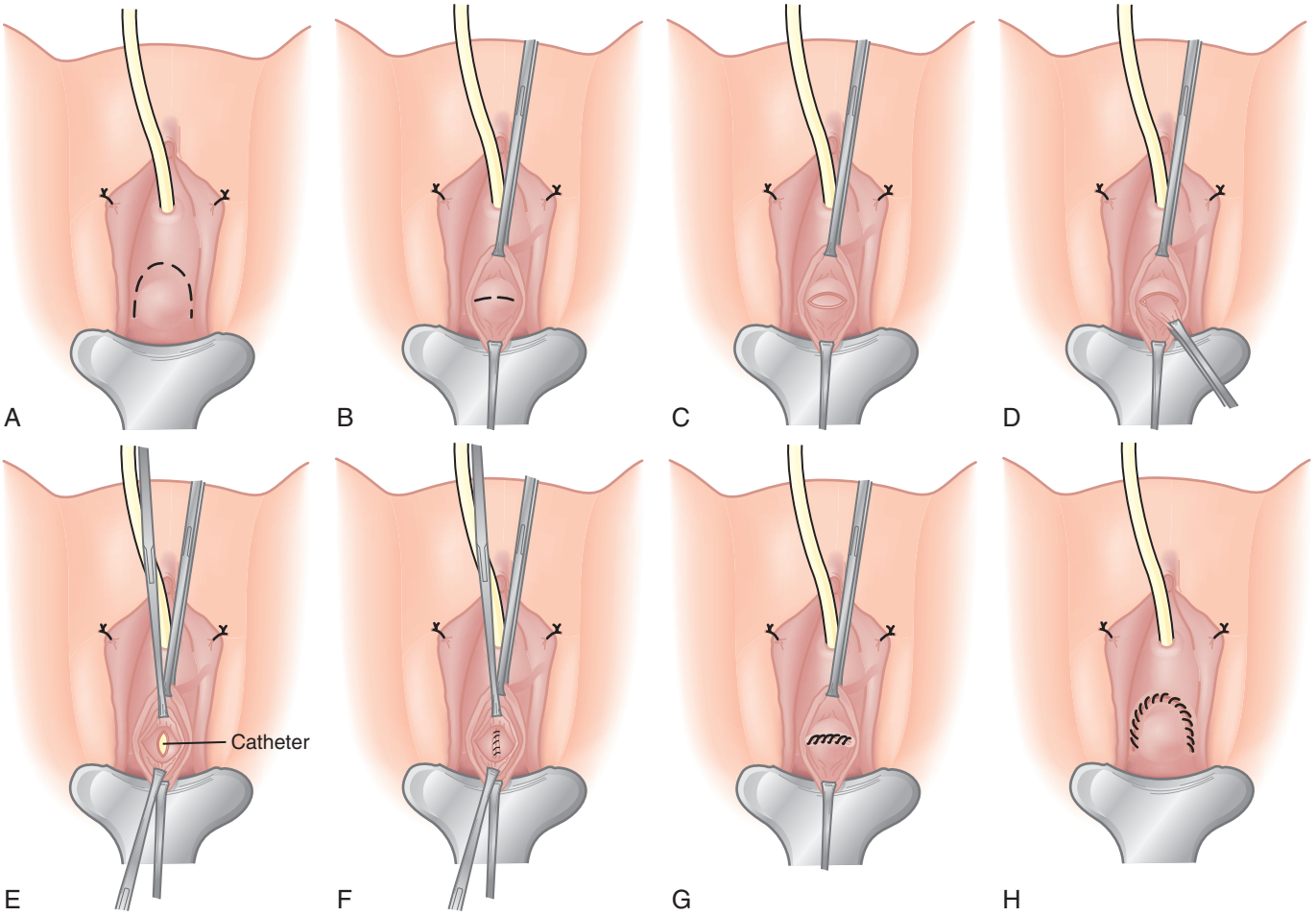


Figure 78–29. **A,** An inverted U incision is marked on the anterior vaginal wall. Retraction is aided by the use of Allis clamps and a ring retractor with hooks. **B,** After reflection of the anterior vaginal wall, a transverse incision is made in the periurethral fascia. The *dotted line* represents the intended incision line. **C,** The periurethral fascia is incised and dissected from the underlying urethral diverticulum. **D,** The diverticular sac is freed from the periurethral fascia. **E,** The urethral catheter is seen after complete excision of the diverticular sac. **F,** The urethra is closed with absorbable suture. **G,** The periurethral fascia is closed with care to obliterate any dead space. **H,** The anterior vaginal wall flap is advanced over the periurethral suture line and secured with running interlocking absorbable suture.

importance to prevent recurrence, close dead space, and avoid urethrovaginal fistula formation postoperatively. Pseudodiverticula have been described where this layer of tissue is considerably attenuated or even absent (Leng and McGuire, 1998). In these patients, an interpositional flap or graft, such as a pubovaginal sling, may be used for reconstruction.

The periurethral fascia is incised transversely (Fig. 78–29B). Proximal and distal layers of periurethral fascia are carefully developed, avoiding entrance into the UD. The UD is then grasped and dissected back to its origin on the urethra within the leaves of the periurethral fascia (Fig. 78–29C). In many cases, it is necessary to open the UD to facilitate dissection from the surrounding tissues. The ostium or connection to the urethra is identified and the walls of UD are completely removed. Every effort should be made to remove the entire mucosalized surface of the UD to prevent recurrence (Ganabathi et al, 1994; Fortunato et al, 2001). This may involve removing small adherent or inflamed portions of the urethral wall, especially in the area of the ostium (Fig. 78–29D). All abnormal tissue in the area of the ostium should be removed, if possible, to ensure that no mucosal elements of the UD wall remain, which could result in postoperative urine leakage and recurrence. Elaborate methods of identifying the full extent of the UD cavity have been described, including catheterization of the UD with urinary (Moore, 1952; Kohorn and Glickman, 1992) and Fogarty (Wear, 1976) catheters, packing the UD with gauze (Hyams and Hyams, 1939), infusing and staining the UD with methylene blue (Gilbert and Rivera Cintron, 1954), and the use of silicone (Hirschhorn, 1964) or cryoprecipitate (Feldstein, 1981) to create a solid mass and ease dissection. However, these measures are mostly of historical interest only and are usually not necessary in modern UD surgery (Leach and Bavendam, 1987; Ganabathi et al, 1994).

The Foley catheter is usually seen following complete excision of UD (Fig. 78–29E). The urethra can be reconstructed over as small as a 12-Fr Foley catheter without long-term risk of urethral stricture (Young et al, 1996) and should be closed in a watertight fashion with absorbable suture (Fig. 78–29F). The closure should be tension-free. Uncommonly, a UD may extend circumferentially around the urethra and require segmental resection of the involved portion of the urethra and complex reconstruction (Tamada et al, 2000; Rovner and Wein, 2003).

The periurethral fascial flaps are reapproximated with absorbable suture in a perpendicular orientation to the urethral closure line to minimize overlap and the risk of postoperative urethrovaginal fistula formation (Fig. 78–29G). Care is taken to secure the periurethral fascial flaps so that all dead space is closed.

If desired, a fibrofatty labial (Martius) flap can be harvested at this point and placed over the periurethral fascia as an additional layer of closure (Dmochowski, 2001). **Indications for such a flap are not universally agreed upon. However, in those patients with poor-quality tissues, attenuated periurethral fascia, or in whom significant inflammation is encountered intraoperatively, a well-vascularized adjuvant flap, such as a Martius flap, may reduce the risk of wound breakdown and subsequent complications, such as urethrovaginal fistula.**

The anterior vaginal wall flap is then repositioned and reapproximated with absorbable suture (Fig. 78–29H). This completes a three-layer closure (four layers if a Martius flap is used). An antibiotic-impregnated vaginal pack is placed.

Postoperative Care. Antibiotics are continued for 24 hours postoperatively. The vaginal packing is removed and the patient discharged home with closed urinary drainage. Antispasmodics are used liberally to reduce bladder spasms. A pericatheter VCUG is obtained at 14 to 21 days postoperatively. If there is no extravasation, the catheters are removed. If extravasation is seen, then repeat pericatheter VCUGs are performed weekly until resolution is noted. In the vast majority of cases, extravasation will resolve in several weeks with this type of conservative management (Schwab and Rovner, 2003).

Complications. Careful adherence to the principles of transvaginal urethral diverticulectomy should minimize postoperative complications. Nevertheless, complications may arise (Table 78–4). One small series suggested that large diverticula (>4 cm) or those associated with a lateral or horseshoe configuration may be associated with a greater likelihood of postoperative complications (Porpiglia et al, 2002). **Common complications include recurrent UTIs, urinary incontinence, or recurrent UD. Urethrovaginal fistula is a devastating complication of urethral diverticulectomy and deserves special mention.** A urethrovaginal fistula located beyond the sphincteric mechanism should not be associated with symptoms other than perhaps a split urinary stream and/or vaginal voiding. As such, an asymptomatic distal urethrovaginal fistula may not require repair, although some patients may request repair. Conversely, a proximal fistula located at the bladder neck or at the midurethra in patients with an incompetent bladder neck will likely result in considerable symptomatic urinary leakage. These patients should undergo repair with consideration for the use of an adjuvant tissue flap, such as a Martius flap, to provide a well-vascularized additional tissue layer. The actual timing of the repair relative to the initial procedure is controversial. Meticulous attention to surgical technique, good hemostasis, avoidance of infection, preservation of the periurethral fascia (Fig. 78–30A and B) and a well-vascularized anterior vaginal wall flap, and a multilayered closure with nonoverlapping suture lines should minimize the potential for postoperative urethrovaginal fistula formation.

Significant postoperative de novo stress urinary incontinence may occur in 7% to 16% of individuals undergoing urethral diverticulectomy surgery without a concomitant anti-incontinence surgery (Han et al, 2007; Ljungqvist and Fall, 2007; Stav et al, 2008). However, Lee and colleagues (2008) noted at least minor de novo SUI in 49% of patients following urethral diverticulectomy, the majority of which was minor and did not require additional therapy. Only 10% of these individuals underwent a subsequent SUI operation. Risk factors for de novo SUI may include the size of the diverticulum (>30 mm) and more proximal location (Stav et al, 2008).

Table 78–4.

Complications of Transvaginal Urethral Diverticulectomy (UD)

Complication (% Range of Reported Incidence)
Urinary incontinence (1.7%-16.1%)
Urethrovaginal fistula (0.9%-8.3%)
Urethral stricture (0%-5.2%)
Recurrent UD (1%-25%)
Recurrent urinary tract infection (0%-31.3%)
Other:
Hypospadias/distal urethral necrosis
Bladder or ureteral injury
Vaginal scarring or narrowing: dyspareunia, etc.

Adapted from Dmochowski R. Surgery for vesicovaginal fistula, urethrovaginal fistula, and urethral diverticulum. In: Walsh PC, Retik AB, Vaughan ED Jr, et al, editors. Campbell's urology. 8th ed. Philadelphia: WB Saunders; 2002.

Persistence of Symptoms Following Urethral Diverticulectomy. Some patients will have persistence or recurrence of their preoperative symptoms postoperatively. The finding of a UD following a presumably successful urethral diverticulectomy may occur as a result of a new medical problem (e.g., UTI, etc.), a new UD, or, alternatively, as a result of recurrence of the original lesion. Recurrence of UD may be due to incomplete removal of the UD, inadequate closure of the urethra or residual dead space, or other technical factors. Lee (1983) noted recurrent urethral diverticulum in 8 of 85 patients at follow-up of 2 to 15 years from the initial UD resection, while Ljungqvist and colleagues (2007) reported recurrence in 11 of 68 patients during a 26-year follow-up (Ljungqvist and Fall, 2007). The risk of recurrence of UD following transvaginal excision may be related to the complexity of the anatomic configuration. Han and colleagues (2007) reported no recurrent UD in 17 patients with simple UD, but of the 10 patients with circumferential UD, recurrence was noted in 6 (60%). Notably in this series, secondary procedures were not as successful in completely removing the UD. Ockrim and colleagues (2009) similarly cured all 19 patients presenting with simple urethral diverticula on the first attempt, but the 11 patients with complex anatomic configurations required a total of 17 procedures for success. **Repeat urethral diverticulectomy surgery can be challenging due to altered anatomy, scarring, and the difficulty in identifying the proper anatomic planes.** Complications such as fistula and recurrence of the UD are more common in reoperative cases (Ljungqvist and Fall, 2007).

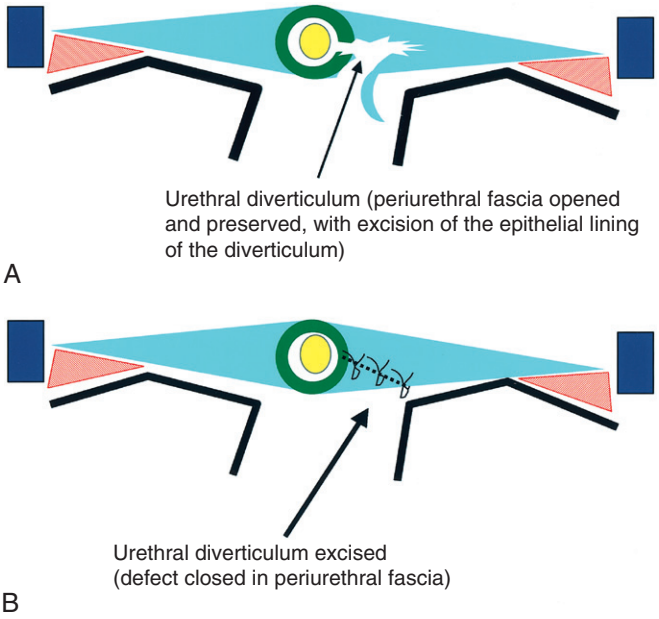


Figure 78–30. Diagrams demonstrating the importance of preserving and reconstructing the periurethral fascia. **A,** The periurethral fascia has been opened and the urethral diverticulum has been excised. **B,** The periurethral fascia has been closed.

Female Urethral Diverticula and Associated Conditions

Malignant and benign tumors may be found in urethral diverticula. **Approximately 10% of urethral diverticulectomy specimens may demonstrate significant histopathologic abnormalities, including metaplasia, dysplasia, or frank carcinoma that require long-term follow-up or additional therapy** (Thomas et al, 2008). **Less than 100 cases of carcinoma within UD have been reported in the English-language literature** (Rajan et al, 1993). **The most common malignant pathology in UD is adenocarcinoma, followed by transitional cell and squamous cell carcinomas** (Rajan et al, 1993; Thomas et al, 2008). This is in direct contrast to primary urethral carcinoma, in which the primary histologic type is squamous cell carcinoma. Some authors have suggested that UD is associated with the development of urethral adenocarcinoma in the female (Oliva and Young, 1996). If this is true, then nonexcisional therapy of UD, such as marsupialization or endoscopic incision, should always be combined with a biopsy to rule out malignancy (McLoughlin, 1975). **There is no consensus on proper treatment in these cases, and recurrence rates are high with local treatment alone** (Rajan et al, 1993). The incidental finding of malignancy in these cases can be particularly

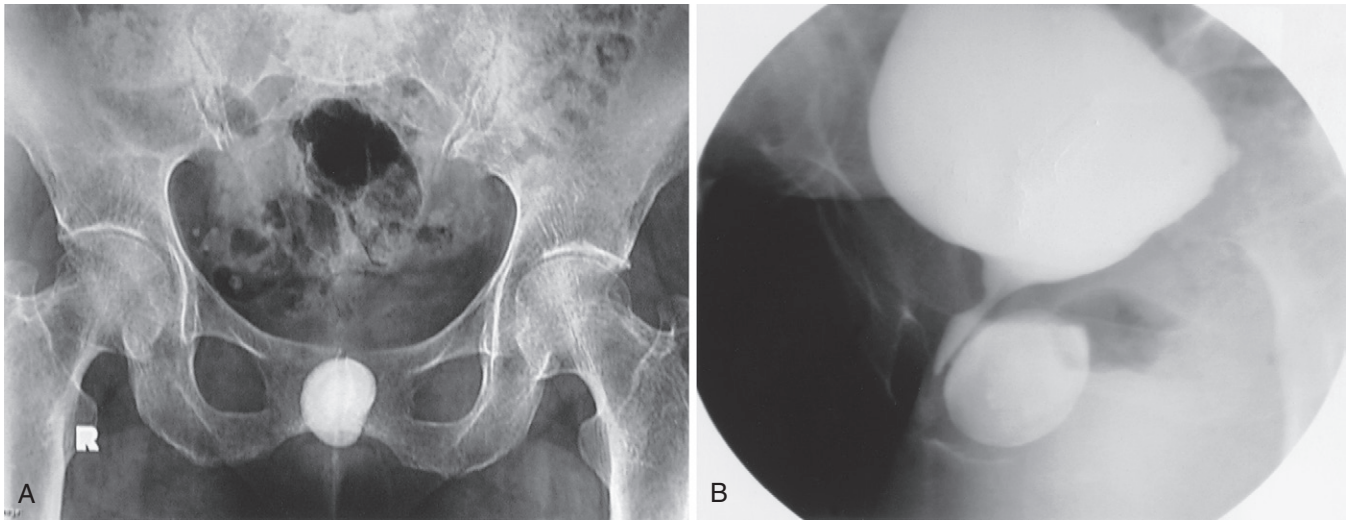


Figure 78–31. Calculi within a urethral diverticulum. **A,** Scout film shows a calcified density overlying the symphysis pubis. **B,** Voiding images from a voiding cystourethrogram demonstrates that the density seen on the scout film represents a stone within a urethral diverticulum.

troubling when found intraoperatively, or even more disturbing on the postoperative pathology report. Although it is interesting to speculate, it has not been conclusively demonstrated that any particular preoperative imaging modality, such as ultrasonography or MRI can reliably and prospectively diagnose a small malignancy arising in a UD. When considering curative therapy, it is unclear whether extensive surgery, including cystourethrectomy with or without adjuvant external beam radiotherapy, is superior to local excision followed by radiotherapy (Patanaphan et al, 1983).

Multiple benign lesions, including both nephrogenic adenoma and endometriosis, have been described within urethral diverticula (Palagiri, 1978; Peterson and Matsumoto, 1978; Piazza et al, 1987; Paik and Lee, 1997). Pathologically, nephrogenic adenoma can be difficult to differentiate from adenocarcinoma.

Calculi within UD are not uncommon and may be diagnosed in 4% to 10% of cases (Ward et al, 1967; Ginesin et al, 1988; Romanzi et al, 2000) and is most likely due to urinary stasis and/or infection (Fig. 78–31). This may be suspected by physical exam findings or noted incidentally on imaging evaluation. The presence of a stone will not significantly alter the evaluation or surgical approach and can be considered an incidental finding. The stone is removed with the UD specimen at the time of surgery.

Key Points: Female Urethral Diverticula—Management

- Concomitant urinary incontinence symptoms should be thoroughly investigated preoperatively, and strong consideration should be given toward surgical treatment of stress urinary incontinence at the time of urethral diverticulectomy.
- Transvaginal excision and urethral reconstruction is the most common approach to the treatment of urethral diverticula in the female.

UD has also been reported to present during pregnancy. Moran reported four cases of UD diagnosed during pregnancy (Moran et al, 1998). Conservative treatment included antibiotics and aspiration or incision and drainage. Two women delivered vaginally and the other two delivered by cesarean section for unrelated reasons. In one patient, drainage was performed during labor to facilitate delivery. Three of the four women had definitive repair performed after delivery. It is not known if pregnancy is associated with formation of UD, although patients may be more likely to become symptomatic during this period. Usually, conservative management with antibiotics may be desirable until after delivery to avoid precipitating premature labor, although successful surgical treatment during pregnancy has been reported (Wittich, 1997).

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter
79

Surgical Procedures for Sphincteric Incontinence in the Male: The Artificial Genitourinary Sphincter and Perineal Sling Procedures

Hunter Wessells, MD, FACS ● Andrew C. Peterson, MD, FACS

Classification, Pathophysiology, and Etiology
History and Development of Devices
Evaluation and Diagnosis
Indications for Surgery
Technique of Implantation
AUS Complications
Sling Complications
Long-Term Results of AUS and Slings
Summary

Urinary incontinence (UI), the complaint of any involuntary leakage of urine (Abrams et al, 2002), may be the result of congenital anomalies, injury, genitourinary surgery, and other conditions. The most common etiology of sphincteric UI in men is radical prostatectomy (RP), with the primary mechanism being failure to store urine secondary to inadequate resistance of the outlet sphincter. Despite improvements in surgical technique that have reduced the rate of post-prostatectomy UI, the burden of disease in the United States remains high and is expected to rise because of increasing numbers of RP performed annually (Stanford et al, 1999).

UI significantly compromises heath-related quality of life in men (Coyne et al, 2003) and can be improved by surgical treatment, including transurethral bulking agents, bulbar urethral slings, and the artificial urinary sphincter (AUS). These procedures prevent involuntary urinary loss by increasing outlet resistance. **Although bulking agents have been used in the past as first-line treatment for male sphincteric UI, the severity of incontinence and postsurgical scarring in the vesicourethral region postprostatectomy have made surgical correction first-line treatment for the majority of cases.**

After a number of generations, several bulbar urethral slings have emerged as viable treatment options for male UI, although the relative paucity of long-term follow-up and unsure reproducibility limits recommendations about the efficacy and broad applicability of sling procedures. The AUS remains the gold standard for the treatment of UI in males due to its long-term durability and effectiveness across the spectrum of moderate and severe degrees of urinary loss.

CLASSIFICATION, PATHOPHYSIOLOGY, AND ETIOLOGY

Urinary continence in the male depends on a compliant and contractile bladder body, functional posterior urethra, including the bladder neck and prostate (internal sphincter) and an intact rhabdosphincter (external sphincter). Thus stress urinary incontinence develops only in men with concomitant internal and external sphincter impairment. Internal sphincter incompetence results from pelvic surgery, bladder neck injury, specific sympathetic neuropathic dysfunction, or embryologic disruption. **Incompetence of the external sphincter, known as intrinsic sphincter deficiency (ISD), occurs most frequently after radical prostatectomy,** but also can result from prostatomembranous urethral distraction injuries, traumatic and acquired myelopathy, and congenital disorders, such as spinal dysraphism, sacral agenesis, and the exstrophy/epispadias complex. Table 79–1 shows conditions in which the bladder neck and rhabdosphincter may be dysfunctional or compromised. **Associated bladder dysfunction, including decreased compliance or detrusor overactivity, may complicate or confound the diagnosis and management of male UI and requires careful evaluation (see below).**

Male incontinence is rare in the general population, affecting only 5% of older men (Bortolotti, 2000). The incidence of UI in men parallels the rate of various surgical procedures and urologic conditions listed in Table 79–1. **Incontinence after transurethral prostatectomy (TURP) may reflect persistent**

Table 79–1.

Common Causes and Mechanisms of Male Sphincteric Urinary Incontinence

CONDITION	BN/PU DYSFUNCTION	RHABDOSPHINCTER DYSFUNCTION	OVERALL RISK OF SUI
RP	Present	Significant risk	Moderate
TURP	Present	Minimal risk	Low
Pelvic fracture/urethral injury	Rare	Significant risk	Low
Myelomeningocele	At risk	At risk	Moderate
Exstrophy/epispadias	At risk	At risk	Moderate

BN, bladder neck; PU, posterior urethra; SUI, stress urinary incontinence; RP, radical prostatectomy; TURP, transurethral prostatectomy.

bladder overactivity but rarely results from damage to the external sphincter during transurethral resection. In a large Veterans Affairs Cooperative Study (Wasson et al, 1995), the rate of de novo UI after TURP was no different than in the watchful waiting group. **The historical incidence of incontinence after radical prostatectomy varies from 2.5% to 87%** (Foote et al, 1991). Progressive improvement in urinary control has been reported to occur for as long as 2 years after surgery; in one study the percentage of men who used one pad or less after RP was 71%, 87%, 92%, and 98.5% at 3, 6, 12, and 24 months, respectively (Lepor and Kaci, 2004). Nerve-sparing techniques pioneered by Walsh (Eggleston and Walsh, 1985) have been associated with a reduced incidence of postoperative UI (Wei et al, 2000a). Although the mechanism of this effect remains debatable, sensory and motor pudendal innervation of the rhabdosphincter is generally preserved post-RP; in contrast, autonomic afferent denervation and impaired membranous urethral sensitivity seems to be associated with post-RP UI (Catarin et al, 2008). Bladder neck contracture is also associated with a reduced continence rate after RP, probably due to secondary surgical intervention (Park et al, 2001).

Contemporary series demonstrate improved continence after prostatectomy when compared with historical rates, but wide variation in reported outcomes reflect patient- and surgeon-specific factors as well as methodology of data collection (Flynn and Webster, 2004). Validated disease-specific questionnaires, such as the University of California–Los Angeles (UCLA) Prostate Cancer Index (Litwin et al, 1998) or the Expanded Prostate Cancer Index Composite (Wei et al, 2000b), that capture symptoms of stress and urgency incontinence are recommended. Rates of incontinence are higher when calculated from such self-report instruments as compared with chart review or physician-recorded outcomes (Carlson and Nitti, 2001; Flynn and Webster, 2004). For example, Litwin and colleagues (1995) reported that up to 40% of patients in a large cohort study complained of persistent long-term urinary incontinence after RP. Although most patients reported mild UI, 4% complained of significant lifestyle-compromising leakage.

HISTORY AND DEVELOPMENT OF DEVICES

Devices to control urinary incontinence in men have been described since antiquity (Schultheiss et al, 2000). One of the first modern prosthetic devices to treat incontinence in men was reported by Berry and associates in 1961 (Engel and Wade, 1969). This acrylic prosthesis was designed to kink and compress the bulbar urethra, but poor results, pain, and fistula formation led to its abandonment (Engel and Wade, 1969). In 1970, Kaufman reported the first of several procedures to provide continence by compressing the urethra with the Kaufman I procedure. This was modified by incorporating a tetrafluoroethylene mesh tape in the Kaufman II procedure and a silicone-gel–filled hemispherical prosthesis in the Kaufman III procedure, giving a success rate of 70%.

Slings to treat stress urinary incontinence (SUI) in men were introduced in 1975 by Kishev, who described the placement of a pliable prosthetic "wad" under the bulbar urethra. Schaeffer then described a bulbourethral sling that used bolsters suspended from the rectus fascia (Schaeffer et al, 1998; Clemens et al, 1999). Another report documented results with a composite graft of polypropylene and porcine skin collagen placed suburethrally (John, 2004). Male bulbourethral slings have continued to evolve with the development of bone screws for synthetic mesh fixation (InVance; American Medical Systems, Minnetonka, MN), transobturator fixation (AdVance; American Medical Systems), and a newly announced combined prepubic and transobturator sling (Virtue; Coloplast, Minneapolis, MN) (Comiter and Rhee, 2008).

In 1976, Rosen designed the first model of an AUS, but hydraulic failure and fistula formation approached 100%, and this device was abandoned (Fowler and Auld, 1985). Scott presented his initial report with the AMS 721 (American Medical Systems, Minnetonka, MN), noting a 79% success rate (Timm et al, 1976; Scott, 1978). Over the next 10 years, further developments in design of the AUS were made. The AMS 742 allowed automatic cuff closure after cuff decompression. The AMS 791 and 792 used a silicone rubber cuff and a deactivation button (Scott, 1989). The AMS 800 included the deactivation button within the control pump; and, in 1987, the narrow-backed cuff was introduced (Fig. 79–1), which, by improving pressure transmission from the cuff pressure to the underlying tissue, has greatly decreased the incidence of urethral erosion and tissue atrophy (Light and Reynolds, 1992).

EVALUATION AND DIAGNOSIS

The initial evaluation of a man with UI requires a detailed history, physical examination, and urinalysis. Many cases of sphincteric UI will also require cystoscopy and pressure flow urodynamics to evaluate potential bladder neck contracture and bladder storage function respectively. Figure 79–2 shows the overall management algorithm.

History

The medical history should focus on the type, degree, and severity of UI; previous surgical procedures; and symptoms of neurologic disease. Specific evaluation of the failed AUS will be considered at the end of this section. **Differentiation between stress and urge UI is important and can be aided by the voiding diary and pad test, simple inexpensive assessments of urinary incontinence that are recommended before proceeding with invasive testing** (Flynn and Webster, 2004). The

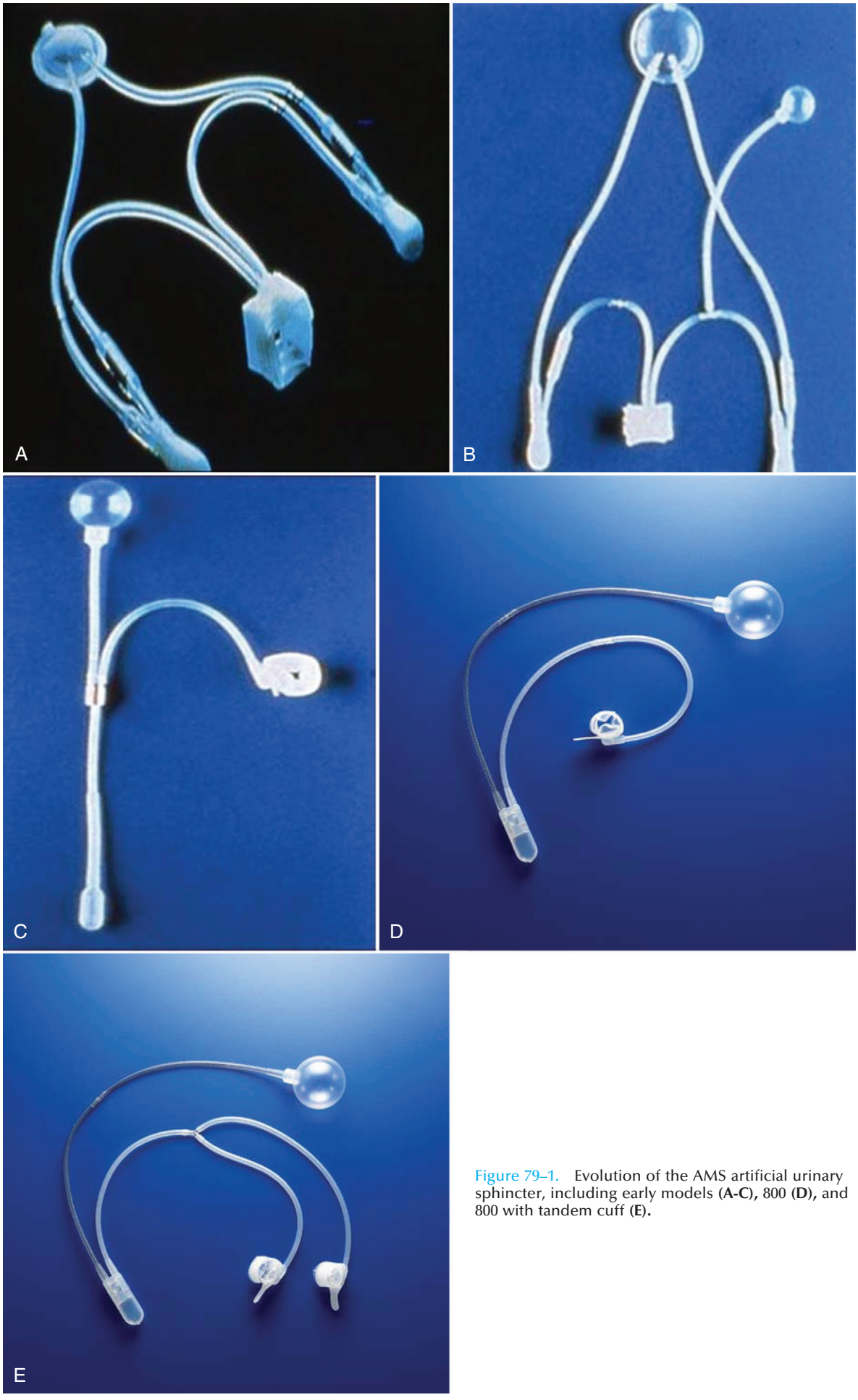


Figure 79–1. Evolution of the AMS artificial urinary sphincter, including early models **(A-C)**, 800 **(D)**, and 800 with tandem cuff **(E)**.

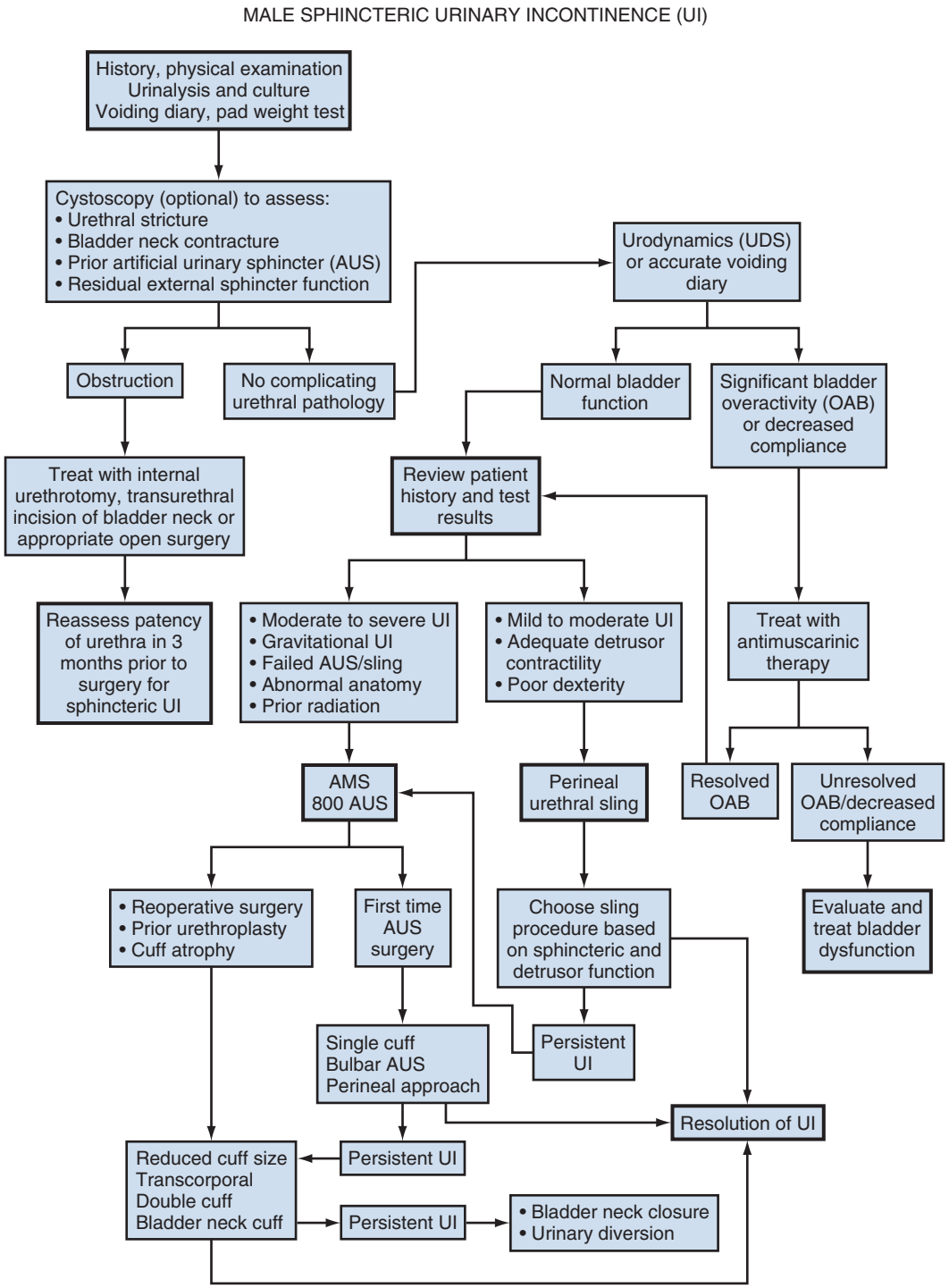


Figure 79–2. Algorithm for the evaluation and management of sphincteric urinary incontinence (UI).

voiding diary reliably assesses the number of incontinent episodes and may uncover significant urgency and urge incontinence (Groutz et al, 2000). Self-reported daily pad usage varies considerably, with only moderate concordance with urinary incontinence volume (Dylewski et al, 2007). Thus the 24-hour pad weight test, which objectively measures the magnitude of the incontinence, may be helpful in directing appropriate therapy. However, because the effectiveness of current surgical therapies has not been stratified according to severity of UI, the most important current use for the pad test may be as an outcome measure postoperatively.

Physical Examination

A complete examination of the abdomen, back, genitalia, perineum, rectum, and neurologic system is essential to identify conditions associated with specific causes of UI. The skin should be inspected for signs of breakdown or secondary fungal or bacterial infection, which need to be treated prior to surgery. **Previous surgical incisions should be noted when planning AUS pressure-regulating balloon (PRB) placement. Likewise, inguinal hernias should be identified and, if**

contralateral PRB placement is not possible, concomitant repair is advisable. Scrotal examination will detect pathology that may influence pump placement, such as hydrocele, hernias, and scrotal masses.

Laboratory

Urine analysis and culture are required prior to surgical correction of male UI, and all abnormalities need complete investigation. UTI must be appropriately evaluated and eradicated. Serum creatinine and prostate-specific antigen (PSA) assays should be obtained to assess renal function and cancer status post-RP. Renal insufficiency requires careful evaluation prior to proceeding with surgical intervention.

Cystoscopy

Detection of vesicourethral anastomotic stricture, bladder neck contracture, and bulbar urethral stricture prior to planned surgery may be achieved by history or uroflowmetry in most cases (Yurkanin et al, 2001). **Because unrecognized urethral pathology can significantly complicate all surgical approaches, endoscopic evaluation is recommended prior to surgical correction of UI post-RP or -TURP even though bladder neck contracture is rare** (Wasson et al, 1995; Erickson et al, 2009; Krambeck et al, 2009). Cystoscopic evaluation of the degree of residual function of the external sphincter may help identify appropriate candidates for transobturator sling procedures (see section on Transobturator Bulbourethral Sling and Fig. 79–3). Furthermore, in patients with recurrent incontinence after AUS implantation, cystoscopy may aid in differentiating mechanical failure from other causes such as urethral atrophy. Finally, when an AUS or sling (Harris et al, 2009) has been removed due to infection or erosion, repeat evaluation of the urethra prior to reimplantation is essential to identify stricture, diverticulum, and other urethral complications.

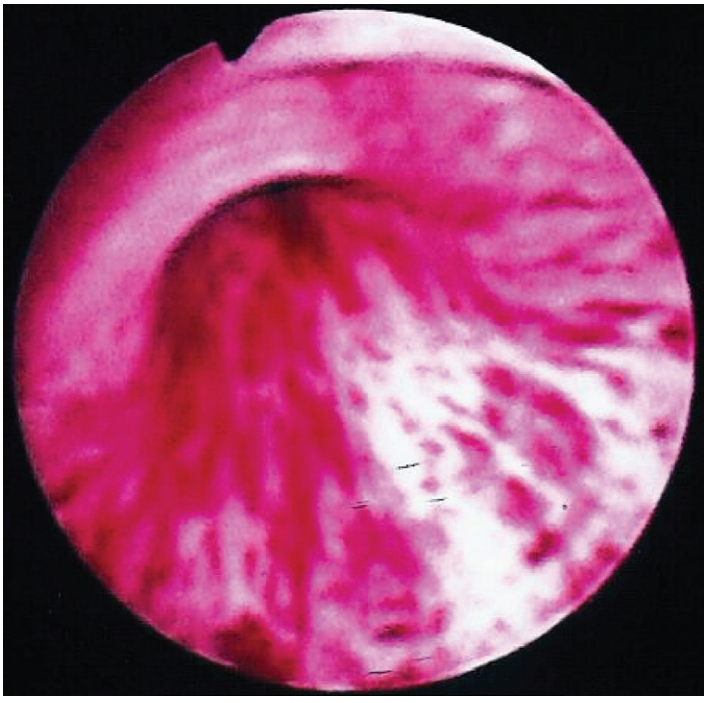


Figure 79–3. Appearance of external sphincter of a man with postprostatectomy urinary incontinence showing incomplete circumferential coaptation. Such a patient would not be a candidate for the transobturator sling, which relies on repositioning of a functional external sphincter unit.

Urodynamics

Assessment of bladder capacity, compliance, and contractility is required prior to considering surgical correction of UI. A careful history and voiding diary may be sufficient to confirm the adequacy of bladder function; however, pressure-flow urodynamics permits an accurate assessment of bladder function, incontinence type, and severity. ISD will be identified in almost all cases. **Although 40% to 45% of men with UI post-RP have bladder dysfunction, it is the sole cause of incontinence in a very small percentage** (Leach et al, 1996; Ficazzola and Nitti, 1998). Filling cystometry can be difficult in men with severe incontinence, and occlusion of the bladder neck with a balloon catheter may be required to assess compliance and overactivity. **Detrusor overactivity, although not a contraindication to surgery for UI if discovered, requires realistic counseling regarding the likelihood of a successful outcome.** Reduced bladder compliance presents a more serious concern, because prolonged storage at high pressures may lead to deteriorating renal function. Notably, such urodynamic findings do not reliably predict worse post-AUS continence (Trigo-Rocha et al, 2008; Lai et al, 2009). This effectiveness, in spite of adverse urodynamic findings, could portend silent upper tract deterioration. Conversely, **detrusor hypocontractility on pressure-flow urodynamics may indicate the need for AUS, if adequate detrusor function does not exist to overcome the fixed resistance of a compressive sling** (Comiter, 2007).

Evaluation of Persistent Incontinence after AUS

The diagnostic evaluation of recurrent UI after AUS must differentiate between inadvertent deactivation, insufficient urethral compression (oversizing of cuff), mechanical failure with fluid loss, cuff erosion, bladder storage failure, urethral or bladder neck atrophy under the cuff, as well as rare causes such as a plugged delay-fill resistor or kinked tubing (Montague and Angermeier, 2001). The evaluation includes the same general approach described for de novo UI in Figure 79–2. A history of sudden loss of continence suggests deactivation or mechanical failure. Active cycling of the device excludes inadvertent deactivation. If the pump is deactivated with inadequate fluid to cycle, passive filling can be achieved by squeezing the pump on its lateral edges or by pushing on the pump with a cotton-tipped applicator opposite the deactivation button. Fluid loss from the device implies mechanical failure and leak. Plain radiography (for contrast-filled systems) or ultrasonography (for saline-filled systems) of the PRB during cycling can help differentiate fluid loss from cuff atrophy. If the PRB size changes with cycling and refills passively, mechanical failure is less likely, thus suggesting cuff atrophy (Taylor and Lebowitz, 1985; Lorentzen et al, 1987). Cystoscopy, in addition to excluding erosion, can be used to visualize the cuff during cycling and give insight into the likelihood of atrophy. Urodynamics should be performed when bladder storage failure is suspected.

Key Points: Initial Evaluation

- A careful history and voiding diary characterizes the type and severity of urinary incontinence in most men.
- Urinalysis and culture are required prior to surgical treatment.
- Suspected outlet obstruction, bladder overactivity, or impaired bladder contractility require cystoscopy and urodynamics.

INDICATIONS FOR SURGERY

Surgical correction of UI is indicated in male patients with irreversible intrinsic sphincter deficiency and bothersome involuntary leakage of urine. After prostatectomy, all men should undergo a course of pelvic floor muscle exercise. Because progressive improvement in continence occurs after RP, some authors recommend a 1-year observation period (Peyromaure et al, 2002; Flynn and Webster, 2004). However, it is unnecessary to delay intervention for patients with severe or gravitational UI who show no improvement beyond 6 months, particularly if cystoscopy shows a significant external sphincter defect. **Because of limited efficacy, submucosal bulking agents are no longer part of the treatment algorithm for post-RP UI** (Kuznetsov et al, 2000; Montague and Angermeier, 2000; Abrams et al, 2009). **Thus AUS and slings should be recommended as first-line surgical therapy for sphincteric incontinence in most men, although a trial of bulking agent may be appropriate in cases of neurogenic male stress UI.**

Once the diagnostic evaluation has been completed (see Fig. 79–2), the best option for a given patient can be selected. **Factors to consider include the severity of UI and associated bother; patient characteristics, including prior surgical procedures, bladder function, and cystoscopic findings; manual dexterity and cognitive function; efficacy of the various implants; long-term risk of complications and reoperation; and patient preference. Absolute contraindications to surgical correction of male UI are few, and include bladder disorders that jeopardize renal function, such as diminished vesical compliance and vesicoureteral reflux at low intravesical pressure. Inadequate tissue integrity at the bladder neck or urethra to accommodate a sling or AUS may require bladder neck closure or urinary diversion. Additionally, urinary tract abnormalities that require future transurethral management, such as bladder cancer or refractory vesicourethral anastomotic strictures, should be considered relative contraindications to surgery.** In such cases, an AUS or sling procedure could impair transurethral access, and repeated instrumentation may put the devices at risk for infection or erosion. Although metastatic prostate cancer is not a contraindication to surgical correction of UI, improvements in quality of life must be balanced against performance status and life expectancy.

The AUS remains the established device for treatment of moderate to severe UI, supported by numerous publications documenting its benefits (Table 79–2). Advantages include reproducible and reliable implantation, ability of patients to empty the bladder without detrusor contraction, and proven efficacy after pelvic irradiation. A national study using validated questions from the University of California–Los Angeles Prostate Cancer Index (UCLA PCI) provides useful data on AUS results (Dalkin et al, 2003) (Table 79–3). Few men post-AUS have severe degrees of incontinence (9%), but many continue to use pads and report a moderately high urinary bother. There is accumulating data that men who are completely dry after radical prostatectomy have significantly better health-related quality of life compared with those who wear one pad daily (Cooperberg et al, 2003). Whether this is also the case after AUS remains unknown. **Long-term durability of the AUS is well established, although a revision rate of 16% and 28% at 2 and 5 years, respectively highlights the limitations of the devices** (Dalkin et al, 2003) and is consistent with a large single institution series in which 72% had the original sphincter in place and functioning at a mean follow-up of 69 months (Elliott and Barrett, 1998).

Table 79–2.

Outcomes and Complication Rates of Surgical Therapy for Male Sphincteric Urinary Incontinence

DEVICE	OUTCOMES (%) Cured or Improved	Cured	Improved	Failed	Infection/ Erosion
AUS	88-89	73-76*	13-16	18-25	11-41
Bone-anchored sling	67-92	37-67†	12-37	8-33	2-15
Transobturator sling	70-84	40-55	27-30	16-30	11

*Defined as 0 to 1 pads.

†Defined as no pads. Not included are results from one series that included a higher proportion of men with moderate to severe UI. Of these men, only 15.8% were dry, and no successes were reported in the severely incontinent group. Adapted from Castle EP, Andrews PE, Itano N, et al: The male sling for post-prostatectomy incontinence: mean followup of 18 months. J Urol 2005;173:1657–60.

AUS, artificial urinary sphincter; UI, urinary incontinence.

Data other than that from Castle et al. (2005) based on the following references: Hajivassiliou, 1999; Montague and Angermeier, 2000; Ullrich and Comiter, 2004; Rajpurkar et al, 2005; Rehder and Gozzi, 2007; Bauer et al, 2009; Davies et al, 2009; Giberti et al, 2009; Guimaraes et al, 2009.

Table 79–3.

National Questionnaire-Based Assessment of AUS Outcomes 2 and 5 Years after Implantation

	2 YEARS POST-AUS	5 YEARS POST-AUS
Category		
Urinary function*	53 (25)	40 (22)
Urinary bother*	59 (24)	48 (32)
Degree of Incontinence (%)		
Mild	59	38
Moderate	32	37
Severe	9	24
Revision Rate (%)	16	28
N	289	292

Age-adjusted urinary function and bother scores derived from the UCLA PCI.

*Results are expressed as a numerical score (mean and SD) ranging from 0 to 100, with 100 being the highest possible response.

AUS, artificial urinary sphincter; UCLA PCI, University of California–Los Angeles Prostate Cancer Index.

Adapted from Dalkin BL, Wessells H, Cui H: A national survey of urinary and health related quality of life outcomes in men with an artificial urinary sphincter for post-radical prostatectomy incontinence. J Urol 2003;169:237–9.

Male sling procedures represent a significant addition to the surgical armamentarium for UI by providing an alternative to AUS. They impart outlet resistance without occlusion of the urethra with a cuff, potentially reducing the risk of erosion and mechanical failure (Comiter, 2007). The bone-anchored sling is performed through a single perineal incision that results in short operative times and low erosion rates (Madjar, 2001a; Comiter, 2002). Titanium screws provide stable fixation of the sling to the inferior pubic ramus, avoiding the need for retropubic passage of suspension sutures. **The mechanism of continence with the bone-anchored sling relies on compression of the urethra, as demonstrated by an increase in fixed resistance of the urethra** (Ullrich and Comiter, 2004). However, no urodynamic evidence of increased detrusor pressure during voiding was seen. The results with this technique have been generally positive, although longer-term follow-up has revealed cases of persistent pain, infection and erosion (see Table 79–2) (Giberti et al, 2009).

A transobturator sling introduced by AMS (AdVance) has been shown to be effective in short-term follow up of well-characterized case series (see Table 79–2) (Rehder and Gozzi, 2007; Davies et al, 2009). In these highly selected populations, approximately 75% of patients are cured or significantly improved, with results persisting at 12 months. Unlike the bone-anchored sling, in which continence is improved by compression, it appears that the transobturator sling augments sphincteric function by repositioning and lengthening the membranous urethra (Firrozi and Vasavada, 2009). Although the absence of increased detrusor pressure during voiding was interpreted as a noncompressive mechanism (Davies et al, 2009), the significant tensioning required during sling placement suggests that compression may play a role in the function of the transobturator sling as well (Latini, 2009).

Bulbar urethral slings can be seen as alternatives for those who refuse AUS from fear of infection, erosion, or mechanical failure, as well as those with limited physical or cognitive capacity. Comiter (2007) notes that the techniques differ in their indications, relative success rates, and complication rates for patients with varying degrees of incontinence. **The trade-off between risk and efficacy most be considered, with most authors recommending AUS for more severe UI. For mild UI, bulbar sling procedures become viable alternatives, whereas AUS may represent therapeutic overkill. Thus the bone-anchored and transobturator slings should be primarily used in cases with mild incontinence, which can be defined as a 24-hour pad weight of less than 150 grams** (Flynn and Webster, 2004). **A sling procedure should not be offered to those with prior radiation therapy or urethral erosion, because the degree of urine loss that exists in this group usually exceeds the limits of the procedure** (Schaeffer et al, 1998; Dikranian et al, 2004; Castle et al, 2005; Giberti et al, 2009).

Key Points: Implant Selection

- Surgical intervention is indicated for stress urinary incontinence due to ISD that fails to improve with conservative management.
- Implant selection depends on the severity of UI, prior surgical procedures, bladder function, cystoscopic findings, manual dexterity and cognitive function, long-term risk of complications and reoperation, and patient preference.
- Slings should not be used in cases of radiation, bladder acontractility, and severe urinary incontinence.
- AUS should not be used in cases of poor manual dexterity, cognitive disability, poor urethral tissue integrity, or reduced bladder compliance.

TECHNIQUES OF IMPLANTATION

Operative Preparation

The entire operative site is shaved, and an antiseptic skin preparation is performed, including the lower abdomen, genitals, and perineum. Surgery is conducted under general or spinal anesthesia with the patient in the low lithotomy position. **Intravenous antibiotics, including an aminoglycoside and a first- or second-generation cephalosporin or vancomycin, are administered within 60 minutes prior to skin incision according to American Urological Association (AUA) Guidelines on antimicrobial prophylaxis** (Wolf et al, 2008). The patient is then carefully draped, and a urethral catheter is placed to drain the bladder and facilitate identification and dissection of the urethra.

Artificial Urinary Sphincter

The AUS (AMS 800) consists of a fluid-filled cuff placed around the bladder neck or bulbar urethra, a control pump placed in the scrotum, and a pressure-regulating balloon (PRB) placed in a preperitoneal or intraperitoneal location. Fluid transfer from the cuff to the PRB is accomplished by active "pumping" while refilling occurs passively by a pressure gradient from the PRB that traverses a resistor implanted in the pump. This valve prevents acute pressure transmission from the reservoir to the cuff.

The AUS cuff is most commonly placed around the bulbar urethra through a perineal incision, although a transscrotal approach popularized by Wilson and associates (Wilson et al, 2003) **also may be selected** (see below). The aim is to place the cuff as proximal on the bulbar urethra as possible—proximal to the fusion of the two corporeal bodies (Fig. 79–4A and B). This location allows safe circumferential dissection of the urethra, provides protection of the cuff from activation while sitting, and exposes the largest diameter of corpus spongiosum for placement of the cuff.

After incising the skin, Colles fascia, and bulbospongiosus muscle, Buck fascia is incised as it reflects off the bulbar urethra onto the diverging corporeal bodies (Fig. 79–4C). A 2-cm wide tunnel is created under direct vision using sharp dissection, dorsal to Buck fascia over the roof of the urethra. A right-angle clamp is then passed through this tunnel (Fig. 79–4D). Blunt spreading dissection is discouraged in this area, because it risks injury to the urethra, especially in reoperative cases. **The circumference of the urethra is measured around the corpus spongiosum to guide selection of cuff size, most commonly 4.0 or 4.5 cm.** The urethral catheter should be removed prior to measurement. Although some authors advocate selecting a cuff size 0.5 to 1 cm smaller than the measured circumference of the urethra to compensate for postoperative subcuff atrophy of the spongiosum, the best test of cuff fit is the visual and endoscopic appearance after it has been placed around the urethra (Fig. 79–5A and B). If the cuff size is obviously incorrect, the next appropriate size should be selected. The tubing from the AUS cuff is then

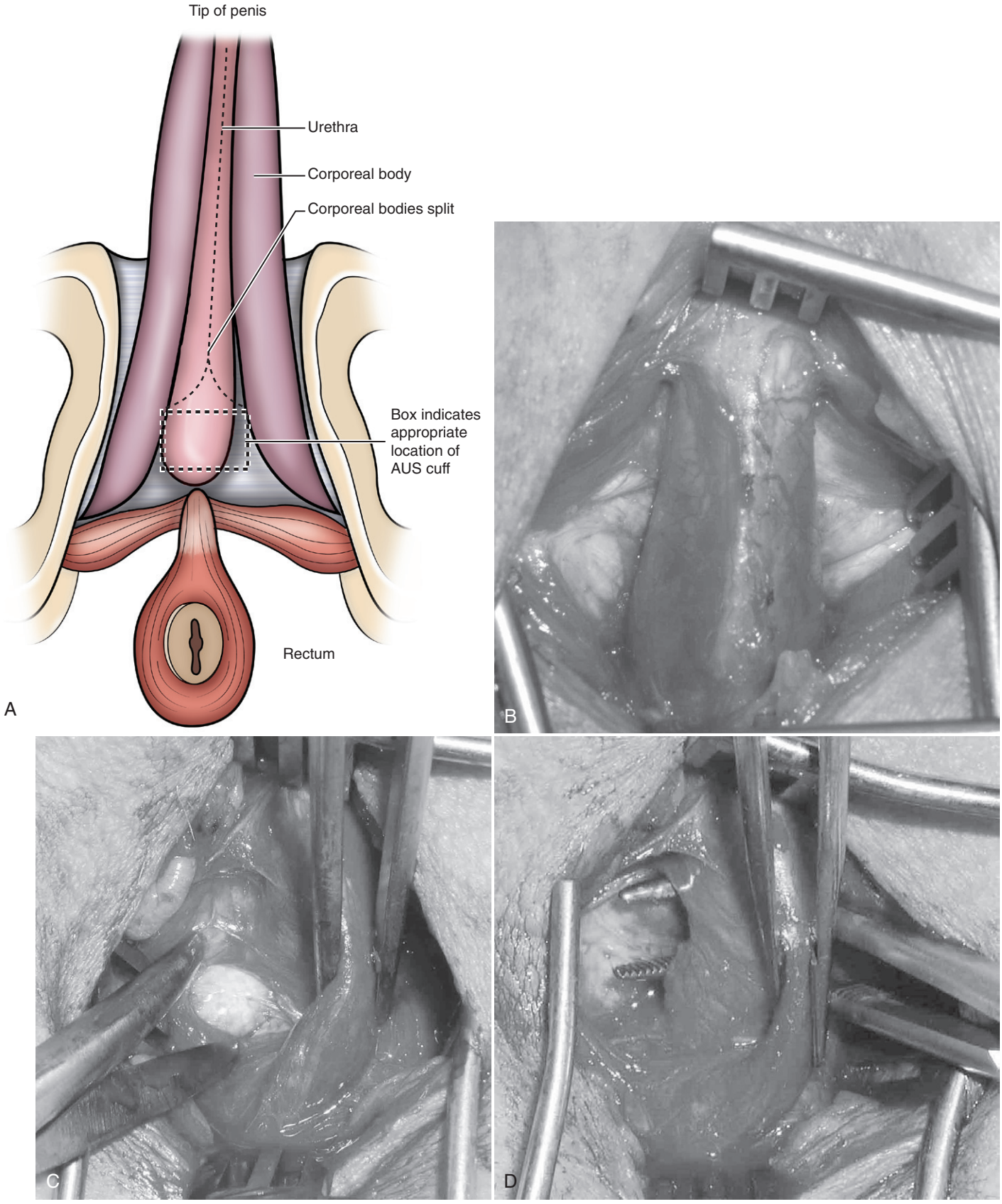


Figure 79–4. Perineal anatomy and bulbar urethral dissection. **A,** Preferred location for first-time bulbar cuff proximal to convergence of corpora cavernosa. Note box indicating ideal cuff placement. **B,** Exposure of the corpus spongiosum after division of the bulbospongiosus muscle. **C,** Dissection at interface between spongiosum and right crus of the cavernosum. **D,** Right-angle clamp behind corpus spongiosum after circumferential dissection. AUS, artificial urinary sphincter.

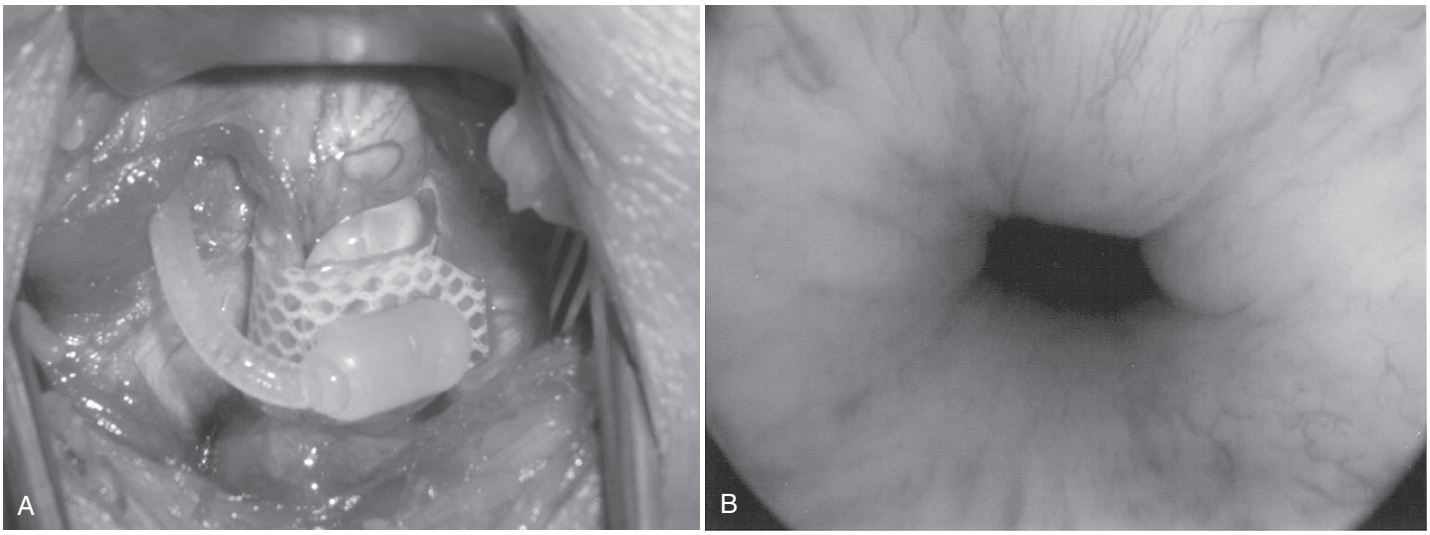


Figure 79–5. Appropriate appearance of cuff. **A,** Perineal placement encircling the bulbar urethra. **B,** Endoscopic appearance with cuff activated.

passed through the overlying bulbospongiosus muscle into the deep perineal space beneath Colles fascia.

Pressure-Regulating Balloon (PRB). The placement of the PRB may be achieved through a scrotal, perineal, or abdominal incision, depending on prior surgical incisions, body habitus, and surgeon preference. Implanters should be familiar with each approach. For abdominal placement, a horizontal lower-quadrant incision is made in the abdomen ipsilateral to pump placement. The rectus or external oblique fascia is incised, allowing the surgeon to split the underlying muscle and access the preperitoneal or intraperitoneal space. Digital dissection creates the space required for the PRB, which is small. **We place a 61- to 70-cm H_2O PRB in all bulbar AUS and reserve the 71- to 80-cm H_2O PRB for bladder neck cuff placement.** The abdominal wall fascia is closed around the tubing.

Alternatively, the PRB can be placed through the external inguinal ring, using techniques adapted from penile implant surgery. Using either a transverse scrotal or perineal incision, the external ring is identified and used to provide access to the retropubic space by penetrating through the floor of the inguinal canal with a fingertip or instrument. No sutures are required, because the transversalis fascia provides a natural barrier to PRB extrusion. Contraindications to this approach include mesh hernia repairs, radical cystectomy, and other extensive abdominal surgery. In such cases, the abdominal approach reduces the risk of bladder or intestinal injury.

The PRB is filled with 23 mL of sterile normal saline or contrast material, unless a bladder neck cuff is used, which requires additional fluid volume. Filling solutions include 0.9% normal saline, Cysto-Conray (Covidien Pharmaceuticals, Hazelwood, MO) 60 cc of contrast diluted with 15 cc of sterile water, or Hypaque (Amersham Health, Princeton, NJ) 25% 50 cc contrast diluted with 60 cc of sterile water. To provide an isotonic solution, contrast solutions should always be diluted with sterile water. Contrast media are contraindicated if the patient has an iodine or contrast allergy.

Control Pump Placement. The pump assembly is placed into the anterior scrotum from the inguinal, scrotal, or perineal incision. When the PRB has been placed abdominally, dissection proceeds inferiorly to the scrotum above the abdominal wall fascia, accessing the anterior scrotum deep to Scarpa fascia. A finger placed outside the dependent portion of the scrotum then invaginates this skin upward into the inguinal incision, allowing the fascial layers to be stripped off the dartos layer with an instrument, creating a small pocket for the pump (Fig. 79–6). The pump is then placed into that position with the tubing held loosely with a Babcock clamp. For the single-incision approaches, a small subdartos pouch is created directly from the scrotal or perineal incision, orienting the pump accordingly toward the foot (scrotal) or head (perineal).



Figure 79–6. Placement of the pump beneath the skin in a subdartos pocket.

Making the Connections. Connections are typically made in the abdominal incision, when used, thus protecting the connections from excess wear and allowing easy exploration at a later date. **The quick connectors supplied by the manufacturer provide excellent, secure, and watertight connections for newly implanted devices. However, they cannot be used for revision surgeries, because a biofilm on the tubing interferes with watertight connection.** Therefore one must use hand-tie connectors in revision cases where the entire device is not being replaced. After completing

the connections, the device is cycled several times through the activation and deactivation states. We verify adequate coaptation of the urethra using urethroscopy. The closed cuff should cause slight blanching of the urethral tissue, indicating adequate urethral coaptation, filling, and connection of the device (see Fig. 79–5B).

Tandem-Cuff AUS

Up to 11% of men may have significant incontinence after single-cuff AUS placement, despite significant improvements in AMS 800 design and implantation techniques (Montague and Angermeier, 2000). In such patients, **when the cause of persistent UI is incomplete urethral occlusion, the addition of a second cuff around the bulbar urethra** (Fig. 79–7A and B) **can yield satisfactory continence** (Brito et al, 1993; Kabalin, 1996; DiMarco and Elliott, 2003; O'Connor et al, 2003). Indiscriminate use of the tandem-cuff approach as first-line surgical treatment should be tempered by higher rates of erosion associated with the distal cuff in several series (Kowalczyk et al, 1996b; Bell and Mulcahy, 2000).

Placement of the second cuff can be accomplished through the perineal incision. After circumferentially dissection around the distal bulbar urethra, at least 1.5 to 2 cm distal to the primary cuff, a new cuff, usually 4.0 cm, is placed. Connection to the existing device requires division of the existing cuff tubing and use of a metal Y-connector. An additional 3 mL of fluid must be added to the system. When adding a new cuff to an existing system, the tubing must be connected with hand ties as described above. The entire device is left deactivated for 6 weeks postoperatively.

Transcorporal AUS Cuff

The transcorporal placement of the AUS provides another approach to difficult initial or revision surgery (Guralnick et al, 2002). Rather than dissecting between the corpus spongiosum and the ventral cavernosa, parallel longitudinal incisions in the tunica albuginea of the corpora cavernosa, near the interface with the corpus spongiosum, allow the plane of dissection to pass through the septum of the corpora from one side to the other. This technique leaves the ventral tunica albuginea attached to the dorsum of the spongiosum (Fig. 79–7D). The lateral edges of the tunica albuginea may need to be imbricated behind the cuff; preplacement of sutures to accomplish this is advisable. **Advantages of the transcorporal approach include reduced risk of urethral injury during reoperation after prior erosion or urethra injury, better cuff fit because of the increased bulk of the urethra, and potential reduction in erosion risk.** The technique is particularly useful when proximal cuff atrophy occurs under a 4.0-cm cuff. Transcorporal placement, 2 to 3 cm distally, leaves an intervening segment of normal urethra that may yield AUS continence results similar to those given in Table 79–2. Webster and associates reported a cure and improvement rate of 84% without intraoperative urethral injuries or postoperative urethral erosions at a mean follow-up of 17 months (Guralnick et al, 2002). An operative video in the AUA video series details the technique.

Transscrotal AUS

Wilson and associates (2003) described a technique in which all components of the AUS are placed through a transverse scrotal incision. Originally developed for reoperative surgery due to urethral atrophy, it allowed placement of a more distal cuff in tandem or with the transcorporal technique (Fig. 79–7C). Although the initial report was favorable in terms of continence outcomes, several reports suggested that the transscrotal technique yields inferior continence results (Stone et al, 2003; Henry et al, 2008). One possible explanation is that it does not allow equivalent placement of the cuff around the proximal, larger-diameter bulbar urethra when compared with the perineal approach. Corroborative evidence comes from data on implanted cuff size. In the Mayo clinic experience, 267 of the 272 perineal cuffs measured 4.5 cm while the remaining cuffs were 5.0 cm (Elliott and Barrett, 1998). Conversely, in the transscrotal series, 32 of the 37 cuffs measured 4.0 cm, and the remaining cuffs were 4.5 cm (Wilson et al, 2003). A modified version of the transscrotal approach, using enhanced exposure (personal communication: SK Wilson, August 7, 2009), has allowed the use of larger cuff sizes around the proximal bulbar urethra and may address the concerns raised in the literature.

Bladder Neck AUS

Bladder neck AUS remains an attractive, although more invasive, method of cuff placement in those men with sphincteric UI in whom the prostate is without external surgical or traumatic disruption. Thus for etiologies of exstrophy/epispadias, myelomeningocele, and other neuropathic disorders, it should be considered before bulbar AUS (Herndon et al, 2003). **Its use is contraindicated after RP.** Advantages include a lower likelihood of erosion and cuff atrophy. Placement of the cuff requires a lower abdominal incision, exposure of the bladder base, and circumferential dissection of the vesicoprostatic junction. Opening the endopelvic fascia helps to develop of the plane of dissection; a catheter placed in the urethra and another in the rectum helps in identifying these structures. If necessary, cystotomy with placement of a finger in the lumen of the bladder neck may also assist the dissection. The bladder neck in adults requires a much larger cuff implant (usually 8 cm or greater), higher PRB pressure (usually 71 to 80 cm H_2O), and a larger fluid volume in the system. Manufacturer packaging includes details relevant to implantation. In children, cuff and PRB characteristics may need to be altered significantly (Ruiz et al, 2006).

Key Points: Implantation of AUS

- Standard implantation of the bulbar AUS places the cuff around the corpus spongiosum proximal to the convergence of the corporeal bodies.
- A pressure-regulating balloon of 61 to 70 cm H_2O is advised for all bulbar urethral cuffs; placement may be by the abdominal, scrotal, or perineal approach.
- Postoperative deactivation of the cuff for 4 to 6 weeks is essential for proper healing without erosion.
- Prolonged urinary retention requires suprapubic cystostomy drainage.
- Revision surgery for nonmechanical causes may require modified cuff placement using tandem-cuff or transcorporal placement.

Bone-Anchored Bulbourethral Sling

The bone-anchored perineal sling popularized using the AMS InVance implant is a synthetic mesh device placed outside the bulbospongiosus muscle and attached to the

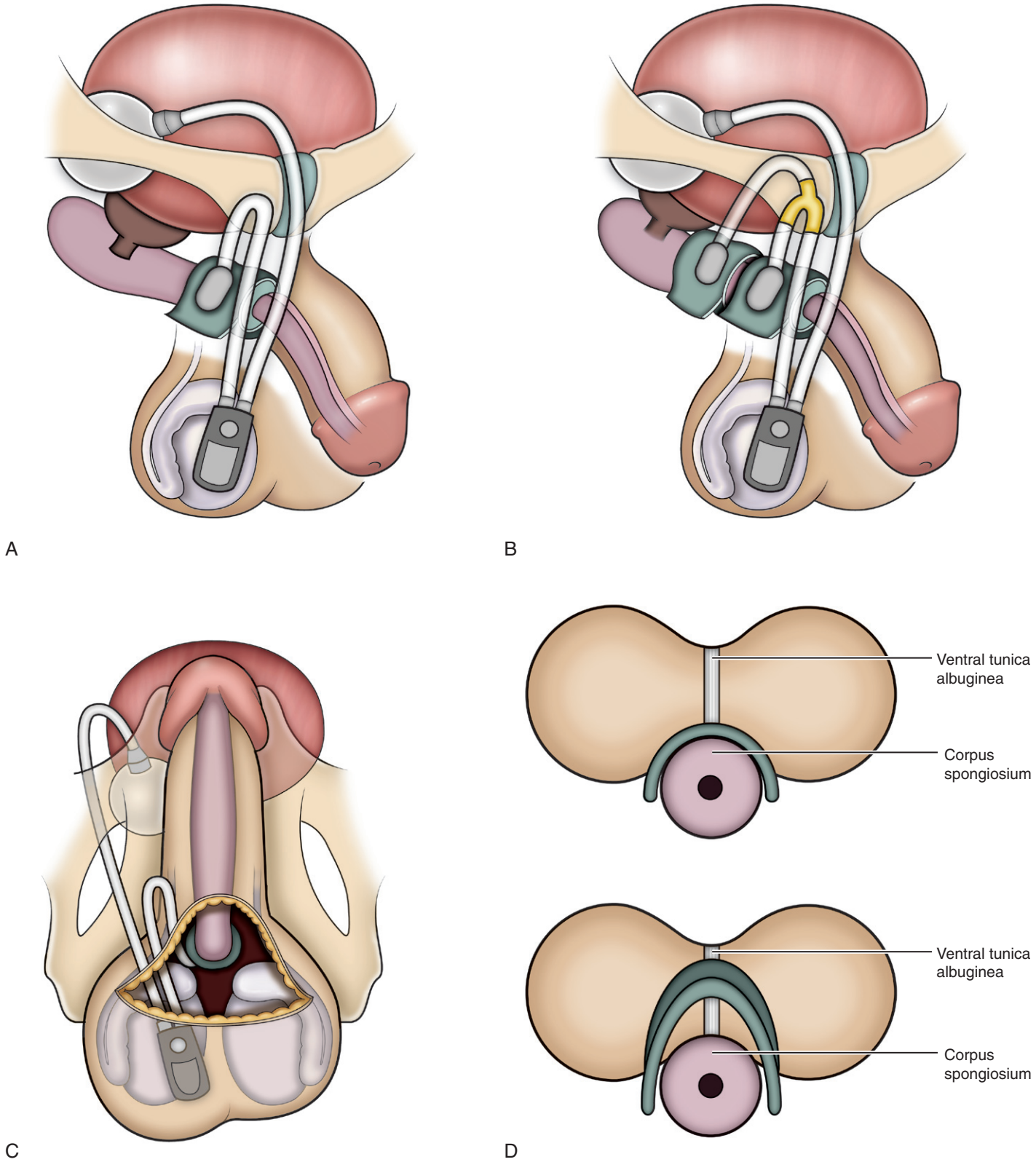


Figure 79–7. Diagram of the AUS including perineal **(A)**, tandem **(B)**, scrotal **(C)**, and transcorporal **(D)** approaches. Note the incorporation of the ventral tunica albuginea with the corpus spongiosum in the transcorporal approach.

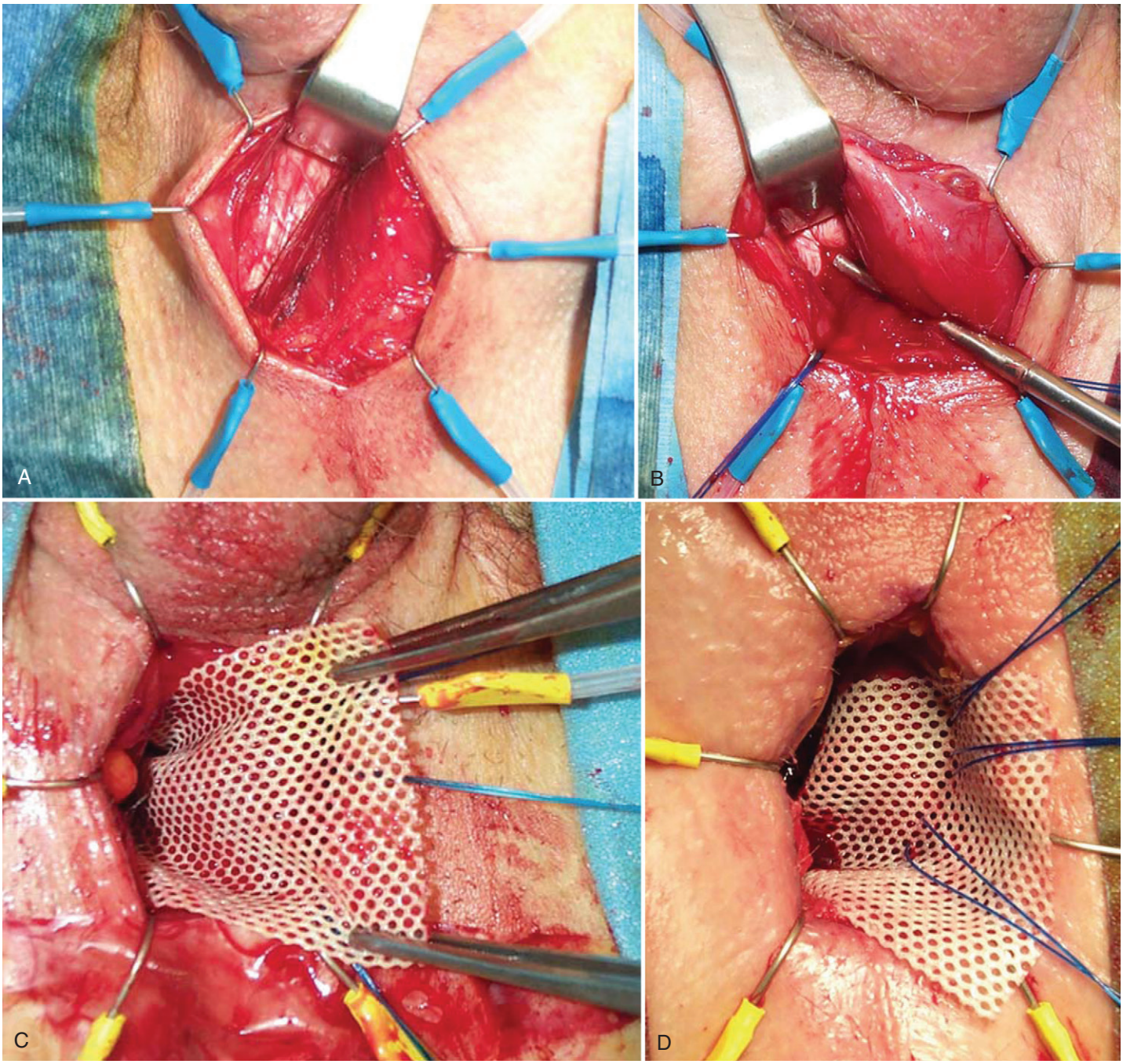


Figure 79–8. Bone-anchored sling insertion. **A,** Exposure of the right crus of the corpus cavernosum with bulbospongiosus muscle retracted medially. **B,** Screw insertion into inferior pubic ramus. **C,** Placement of the right side of the synthetic mesh device. **D,** Initial tensioning with sutures on the left side of the sling.

pubic rami. A vertical perineal incision centered over the bulbar urethra exposes the bulbospongiosus muscle and the medial aspect of each inferior pubic ramus (Fig. 79–8A). Three titanium bone screws preloaded with a pair of 1-0 polypropylene sutures are inserted in the anteromedial aspect of each descending pubic ramus using a bone drill (Fig. 79–8B). The proximal bone screws are placed just beneath the junction of the descending ramus and pubic symphysis, and the distal screws are inserted approximately 3 cm caudally at the level of the bulbar urethra. **Comiter and colleagues** (1997) **described retrograde leak point pressure (RLPP) to tension the device** (Comiter et al, 1997). The basic technique uses a 14-Fr catheter with the balloon inflated with 1 mL H_2O in the distal penile urethra. Prior to tensioning the sling, perfusion sphincterometry is performed by connecting a bag of saline to the catheter through sterile tubing. The bag is elevated until fluid flows from the bag, through the drip chamber, and into the urethra (Comiter et al, 1997). The RLPP is recorded as the height of the fluid column above the symphysis at which fluid flow begins.

A 4- × 7-cm sling composed of synthetic or organic material is secured to the bone-anchored sutures by passing the sutures through the sling with the aid of an 18-gauge needle, 0.5 cm from the right edge, equally spaced along the width of the sling. The right-sided sutures are then tied down to the bone (Fig. 79-8C).

With the sling positioned over the bulbospongiosus muscle, the contralateral sutures are passed through the left side of the sling and secured with a single throw of the suture over a silk safety tie. RLPP is repeated, allowing sling tension to be adjusted by moving the left-sided sutures more medially (tighter) or laterally (looser) until an RLPP of 60 cm H_2O is achieved (Fig. 79-8D). The wound is irrigated and closed in two layers. The catheter is removed in the recovery room or the following morning for a trial of voiding.

Determining the appropriate tension of the sling is the most critical portion of the operation. Although the original choice of 60 cm H_2O was based on the pressure range of the AUS PRB, subsequent studies have also demonstrated that patients who achieve a RLPP of 60 cm have better outcomes than those who demonstrate a lower compression pressure (Ullrich and Comiter, 2004). **Alternative methods of sling tensioning have been described, such as an intraoperative cough test to determine sling tensioning** (Madjar et al, 2001a; Rajpurkar et al, 2005).

Transobturator Bulbourethral Sling

Rehder and Gozzi (2007) described a male transobturator sling that provides an alternative surgical technique for suburethral placement. **In contrast to the bone-anchored approach, the AdVance sling is designed to reposition and lengthen the membranous urethra.** After exposing the corpus spongiosum in a manner identical to the AUS described above, the space between the corpus spongiosum and corpora cavernosa is developed on each side. The corpus spongiosum is dissected along its ventral surface proximally to the level of the perineal body, which is marked to facilitate later sling positioning. Using the inferior margin of the adductor longus muscle as a landmark, a small stab wound is made approximately one fingerbreadth below the muscle on each side. A spinal needle locates the obturator foramen immediately lateral to the pubic ramus. Then, using an outside-inside direction, the appropriate left- or right-sided helical passing device is inserted from the thigh through the obturator foramen and out of the perineal wound medial to the ipsilateral corporeal body. This needle should be brought out as close as possible to the superior aspect of the triangle formed by the corpus spongiosum and the pubic ramus. Once this has been completed bilaterally, the polypropylene mesh is loosely positioned in the perineum, attached to the passing devices, and pulled out of the obturator foramen to the medial thigh without tension. The midportion is placed on the corpus spongiosum, and the arms of the sling are pulled up to tension the device (Fig. 79–9). **With tensioning, the perineal body and proximal bulbar urethra should move proximally and cephalad, 3 to 4 cm.** The maneuver is repeated with cystoscopic visualization of the external sphincter region to confirm the repositioning of the urethra (Rehder and Gozzi, 2007). Once in position, the sling is flattened out again, attached with absorbable suture, and final tensioning is performed. The tail ends of the sling are trimmed and buried under the skin. The perineal incision is closed in layers, including the bulbospongiosus muscle, Colles fascia, and skin. Overnight catheter drainage is usually sufficient for decompression of the bladder.

Other Devices

The Prostate Adjustable Continence Therapy device (ProACT; Uromedica, Plymouth, MN) consists of two balloons placed on both sides of the bladder neck and is designed to increase resistance. Percutaneous adjustment of the pressure applied to the bladder neck is performed through titanium ports within the scrotum. Hübner and Schlarp showed significantly improved continence as they used this device over time, which stimulated the use of the ProACT device in centers in Europe (Hübner and Schlarp, 2005; Trigo-Rocha et al, 2006).

Another transobturator sling with limited clinical data has lateral strips for urethral transobturator elevation in addition to prepubic arms designed to provide concomitant compression. Early results have been published (Comiter, 2007), and the device in being commercialized.

Key Points: Sling Indications and Mechanisms

- Male bulbar urethral slings are indicated in men with mild to moderate sphincteric UI, intact bladder contractility, and well-vascularized nonradiated urethral anatomy.
- Bone-anchored slings provide compressive mechanism of continence and require specific protocols for tensioning.
- Transobturator slings reposition and elongate the membranous urethra and depend on the intact external sphincter.

AUS COMPLICATIONS

Urinary Retention

Urinary retention in the immediate postoperative period should be managed by transurethral bladder drainage with a small (10-Fr or 12-Fr) catheter for 24 to 48 hours. Cuff deactivation must be confirmed before catheterization. **If the patient fails a voiding trial at 48 hours, suprapubic drainage is recommended to reduce the risk of urethral erosion.** Ultrasound or fluoroscopic guidance is recommended to prevent puncture or potential contamination of the PRB. Retention persisting beyond several weeks implies undersizing of the cuff; in such cases, reoperation and cuff replacement may be required. Correlation with preoperative urodynamic findings is advised in such cases. Late-onset urinary retention mandates endoscopic and urodynamic evaluation to rule out proximal urethral obstruction, erosion, or detrusor failure.

AUS Infection

Infection remains a serious and devastating complication of any implant surgery. The rate of infection with initial AUS surgery is 1% to 3% (Gundian et al, 1989; Marks and Light, 1989; Litwiller et al, 1996; Montague and Angermeier, 2000) but may be as high as 10% in patients after pelvic radiation and in reoperations (Montague, 1992). **Skin pathogens are the most commonly cultured organisms, usually *Staphylococcus epidermidis* and *S. aureus*** (Licht et al, 1995). The introduction of the InhibiZone Surface Treatment (American Medical Systems), combining rifampin and minocycline hydrochloride to the AUS cuff and pump, is likely to lead to a reduction in postoperative infection rates, although the results seen in the penile implant literature (Carson, 2004) have not yet been replicated in the AUS literature. Late infections (>4 months) may represent indolent organisms introduced at the time of infection or by hematogenous spread. Therefore **in men with AUS, antibiotics should be considered before urinary tract manipulation in accordance with AUA Guidelines** (Wolf et al, 2008).

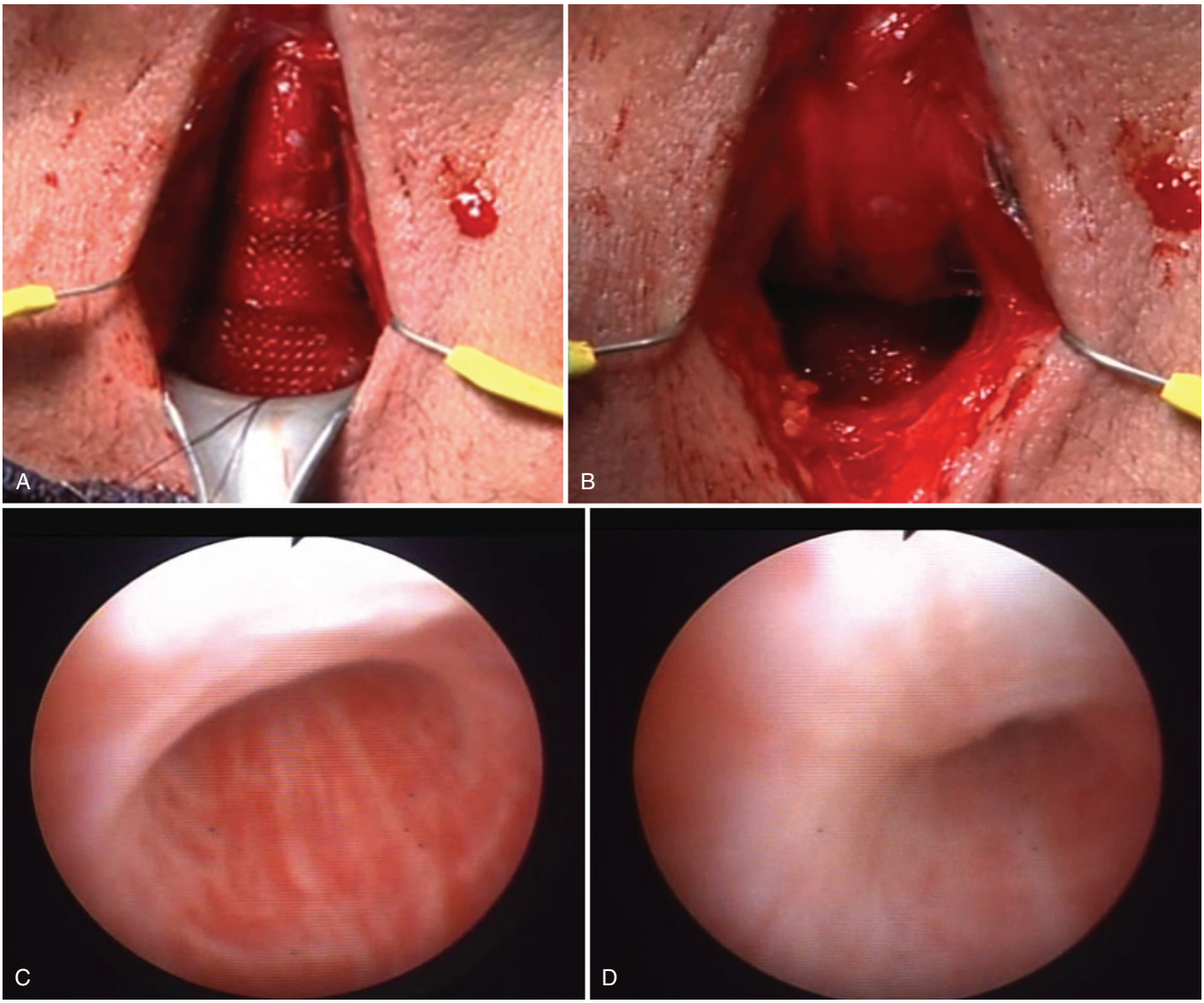


Figure 79–9. Transobturator sling. **A,** Sling in place loosely. **B,** Sling on tension. **C,** Endoscopic appearance before tensioning. **D,** Endoscopic appearance after tensioning.

The initial presentation of an early postoperative AUS infection is usually scrotal pain, although erythema, edema, and frank purulence will commonly accompany this symptom. **Because implant infections are not amenable to antibiotic therapy, AUS infection will almost always require explantation.** Traditional management includes device removal followed by a waiting period of several months with delayed reimplantation.

Immediate salvage of infected noneroded AUS can be accomplished with complete device removal, antiseptic irrigation, and immediate reimplantation (Kowalczyk et al, 1996a; Bell and Mulcahy, 2000; Bryan et al, 2002). This procedure includes an irrigation regimen used in penile prosthesis salvage protocols (Mulcahy et al, 1995). Mulcahy and associates used this approach to salvage seven of eight patients with infected noneroded AUS in a total of nine operations (Bryan et al, 2002). In all cases, the entire AUS was removed, and the wounds were copiously irrigated according to a seven-solution protocol prior to a new system being implanted. Contraindications to prosthesis salvage include sepsis, ketoacidosis, necrotizing infection, immunosuppression, and the finding of gross purulent material at the time of explantation.

Urethral Erosion

Urethral erosion is reported in up to 5% of AUS implantations (Gundian et al, 1989; Marks and Light, 1989; Litwiller et al, 1996; Singh and Thomas, 1996; Montague and Angermeier, 2000). Furlow and Barrett (1985) introduced the concept of postoperative deactivation during the healing process to decrease pressure-induced ischemia and necrosis. **Delayed deactivation has lowered the risk of urethral erosion, especially in cases of reimplantation.** Motley and Barrett (1990) saw a decrease in secondary urethral erosion from 18% to 1.3% with this technique. In an analysis of their 13-year experience in patients with urethral erosions, Webster and associates (Raj et al, 2006) determined that

patients with hypertension, coronary artery disease, prior radiation therapy, and prior AUS revisions were more than twice as likely to suffer secondary urethral erosions.

Immediate removal of all the components of the AUS is imperative in cases of erosion, because they are assumed to be infected. The urethral injury is managed with urethral catheter drainage and or suprapubic cystostomy (Kowalczyk et al, 1996a; Flynn and Webster, 2004). Perineal wounds are considered infected and loosely approximated or allowed to close by secondary intention. Reimplantation is considered only after urethral healing is confirmed by urethrography and a delay of 3 to 6 months is observed.

Urethral patency must be confirmed by cystoscopy or retrograde urethrogram before attempted device replacement (Motley and Barrett, 1990; Kowalczyk et al, 1996a; Frank et al, 2000). A new cuff should be placed either proximal or distal to the previous site. Significant scarring, as well as a compromised vascular supply, makes replacement of the cuff at the erosion site difficult and risky (Motley and Barrett, 1990; Kowalczyk et al, 1996a). Frank and colleagues (2000) reported a successful outcome in 87% of de novo reimplantation after erosion or infection, with recurrent urethral erosion in 8.7%. **The authors recommended nightly deactivation of the AUS in cases of reimplantation for prior erosion.** More recently, in a series of 46 patients with prior AUS erosion who underwent reimplantation, 35% suffered another erosion within an average of 6.7 months (Raj et al, 2006). Use of the transcorporal approach in such cases may reduce the risk of urethral injury during the secondary surgery, as well as potentially provide greater protection against subsequent erosion.

Urethral Atrophy

Urethral atrophy results from the chronic compression of the spongy tissue under the occlusive cuff. This is the most common reason for revision of the AUS. Treatment options include cuff downsizing, movement of the cuff to a more proximal or distal location where the urethra may be thicker, or placement of a second cuff in tandem. Simple replacement of the PRB with a higher-pressure reservoir to overcome urethral atrophy is no longer recommended due to risk of erosion (Raj et al, 2005).

Our approach is to downsize the cuff in the same location when possible. If the existing cuff is already 4.0 cm, we place the cuff more proximally when feasible, or distally using the transcorporal technique if necessary. Saffarian and colleagues (2003) reported a significant improvement in daily pad usage from 3.9 to 0.5 in 17 patients with urethral atrophy. In a large series of secondary AUS surgery, the cuff was replaced in 142 cases, of which 33% of cuffs were placed distal to the original location, 11% were placed proximal, and 52% were placed at the original cuff location (Raj et al, 2005). The cuffs were downsized in 56% of cases, unchanged in 30%, and upsized in 13%, reflecting the new locations. In cases of urethral atrophy, several prominent centers have successfully added a second cuff in tandem to salvage continence (Brito et al, 1993; DiMarco and Elliott, 2003).

Mechanical Failure

The historical incidence of mechanical failure has diminished substantially after introduction of the narrow-backed cuff. Elliott and Barrett (1998) reviewed the long-term durability of the AMS 800 in 323 patients who were implanted at the Mayo clinic between 1983 and 1994. The change in design resulted in a decrease in nonmechanical failure from 17% to 9%, primarily due to a reduction in urethral atrophy. A decrease in mechanical failure from 21% to 7.6% was primarily due to a reduction in cuff leak along with improvements in the synthetic material, which lessened the risk of fracture or kinking of the device. **Patients can generally expect a 7- to 10-year life expectancy for the AUS. In the absence of infection or erosion, replacement of an isolated malfunctioning component may be feasible if the revision occurs within 3 years of implantation. However, a slow leak from the PRB may be difficult to diagnose intraoperatively, and, if in doubt, total device replacement is prudent. Devices greater than 3 years old should be replaced *in toto*.**

Special Circumstances

The management of **urethral and vesicourethral anastomotic stricture** encountered after AUS implantation proposes a unique challenge. Stricture at the site of the AUS cuff may result from compression or ischemia and may indicate impending urethral erosion. One such bulbar urethral stricture was successfully managed with periodic filiform and follower dilation (Debell and Wessells, 2001). Others have successfully treated strictures proximal to an AUS with balloon dilation (Westney et al, 1992) or holmium laser through a flexible ureteroscope (Anger et al, 2005). In the event significant endoscopic manipulation is required proximal to the cuff site, our practice is to surgically uncouple the cuff for the duration of the endoscopic procedure.

SLING COMPLICATIONS

The most commonly reported complications of male slings include perineal pain, urinary retention, infection, anchoring complications from bone anchors, and rare cases of erosion. **Perineal pain may be reported in up to 74% of patients** (Giberti et al, 2009) **after bone-anchored sling procedures, but, for the majority, pain resolves within 3 months** (Comiter, 2005). Retention is short lived and resolves within several weeks. Isolated cases have required release of the sling. The infection/erosion rate for both types of slings ranges from 2% to 15%, and the need for revision (secondary to bone-anchor dislodgement) has been reported for 2% to 4.2% of patients. Patients should be counseled about the possibility of persistent pain and osteitis pubis after a bone-anchored sling procedure.

LONG-TERM RESULTS OF AUS AND SLINGS

Montague and Angermeier, in 2000, reviewed the results of the AUS in 286 patients from five centers. They noted that on average 76% of patients were dry (dry: 0 to 1 pads/day) and 13% were improved, for an overall success rate of 89% at a mean follow-up of 18 to 44 months. Revision of the device occurred due to urethral erosion (5%), AUS infection (3%), and mechanical failure (15%). Other studies have confirmed these results (Hajivassiliou, 1999; Venn et al, 2000). Although many patients still need minor protection with urinary pads, most are satisfied with the long-term outcome of the AUS (Haab et al, 1997; Montague et al, 2001; Dalkin et al, 2003). Success rates for revision surgery compare favorably with initial surgery, although infection and erosion rates are higher (Raj et al, 2005). Differences among centers may be

related to surgical volume, inclusion of secondary implants, as well as the sensitivity and accuracy of outcome measures.

Initial results with the bone-anchored and transobturator sling appear similar to those with AUS (see Table 79–2). Results obtained by Ullrich and Comiter (2004) with the InVance sling showed a cured/improved rate of 92% at 25 months without significant morbidity. However, not all subsequent series have replicated these findings, with failure rates being as high as 33% (Giberti et al, 2009; Guimaraes et al, 2009). The place of the AdVance sling in the armamentarium remains unclear; early results are promising (Bauer et al, 2009), but patient selection criteria, particularly regarding assessment of external sphincter function and reproducibility of results requires further validation in other series.

Key Points: Complications

- Device infection requires total explantation and salvage antibiotic regimens.
- Device erosion requires total explantation and catheter drainage.
- Troubleshooting of recurrent UI post-AUS requires a systematic and exhaustive evaluation.
- Cuff atrophy requires downsizing, repositioning, tandem-cuff, or transcorporal surgery.

SUMMARY

The expanding use of PSA testing and surgery for localized prostate cancer predict that male sphincteric UI will remain prevalent and require surgical treatment to improve symptoms and quality of life. The initial evaluation must include a focused history and physical examination, voiding diary, pad weight test, and, in many cases, cystoscopy and pressure-flow urodynamics. The AUS remains the gold standard treatment for moderate to severe male UI, especially in complex cases, with excellent overall success and acceptable complication rates. For mild to moderate UI in the absence of prior urethral surgery, radiation therapy, or detrusor acontractility, male slings provide efficacious alternatives. The outcomes after AUS and male sling procedures cannot be fully compared due to differences in endpoints, follow-up, and patient numbers. Nevertheless, **regardless of incontinence severity, nearly 90% of men with sphincteric UI will have minimal leakage and an acceptable quality of life related to urinary symptoms after surgical treatment.** Similar cured and improved rates have been reported with both the bone-anchored and transobturator slings. However, several caveats exist. Neither device has been compared to AUS in a controlled clinical trial. It is likely that selection bias regarding UI severity and other factors exists in choosing a sling versus AUS at most institutions. Furthermore, the **bone-anchored and transobturator slings depend on subtle technical maneuvers relating to positioning and tensioning. Conversely, once the urethra has been circumferentially mobilized and measured, the effectiveness of AUS is largely independent of technique.** Thus the occasional implanter will be more likely to achieve success with AUS versus either of the sling procedures, although the potential for erosion and mechanical failure will continue to drive the need for alternative solutions.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

SUGGESTED READINGS

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chapter 80

Urothelial Tumors of the Bladder

David P. Wood, Jr., MD

Benign Tumors of the Bladder

Urothelial Cancer

Nonurothelial Malignancies

The urothelium of the bladder is traditionally considered to be lined by transitional cells, which, as suggested by the name, can transform into a variety of benign and malignant tumors. Therefore the list of bladder tumors is long and includes those derived from the urothelium and mesenchyme. In this chapter we will discuss the epidemiology, etiology, pathology, staging, origin, recurrence, dissemination, molecular biology, detection, and prevention of the more common benign and malignant tumors of the bladder, with an emphasis on urothelial cancer.

BENIGN TUMORS OF THE BLADDER

There are numerous benign tumors of the bladder, but the more common ones include epithelial metaplasia, leukoplakia, inverted papilloma, nephrogenic adenoma, leiomyoma, cystitis cystica, and cystitis glandularis.

Epithelial Metaplasia

Epithelial metaplasia is focal areas of transformed urothelium with normal nuclear and cellular architecture surrounded by normal urothelium usually located on the trigone and composed of squamous (squamous metaplasia) or glandular (glandular metaplasia) cells. Squamous metaplasia often has a knobby appearance and is covered by white, flaky, easily disrupted material lying on the trigone. Glandular metaplasia appears as clumps of raised red areas that appear inflammatory and are often confused for cancer. **Approximately 40% of women and 5% of men have squamous metaplasia of the bladder, which is usually related to infection, trauma, and surgery** (Ozbey et al, 1999). There are no racial differences, and squamous metaplasia is more common in women of childbearing age. Spinal cord injury is associated with squamous metaplasia most likely from catheter trauma and urinary tract infections (Vaidyanathan et al, 2003). Glandular metaplasia can extensively involve the bladder, particularly the trigone, but biopsy is not required. Treatment is unnecessary, and a preventive agent has not been identified.

Leukoplakia

Leukoplakia of the bladder is similar to squamous metaplasia with the addition of keratin deposition that appears as a white flaky substance floating in the bladder (Staack et al, 2006). Leukoplakia occurs in other organs that are covered by squamous epithelium and is often premalignant (Zhang et al, 2009). However, cytogenetic studies on bladder leukoplakia are consistent with a benign lesion, and no treatment is necessary (Staack et al, 2006).

Inverted Papilloma

An inverted papilloma is a benign proliferative lesion that is associated with chronic inflammation or bladder outlet obstruction and can be located throughout the bladder but most commonly on the trigone, comprising less than 1% of all bladder tumors (Sung et al, 2006; Jones et al, 2007; Kilciler et al, 2008). Inverted papillomas demonstrate an inverted growth pattern composed of anastomosing islands of histologically and cytologically normal urothelial cells invaginating from the surface urothelium into the lamina propria but not into the muscularis propria (Fig. 80–1) (Sung et al, 2006). **When diagnosed according to strictly defined criteria (e.g., lack of cytologic atypia), inverted papillomas behave in a benign fashion with only a 1% incidence of tumor recurrence** (Sung et al, 2006; Kilciler et al, 2008). Occasionally, inverted papillomas are present with coexistent urothelial cancer elsewhere in the urinary system, occurring more commonly in the upper tract than the bladder (Asano et al, 2003). The use of fluorescent in-situ hybridization (FISH) to evaluate chromosomal changes can distinguish between an inverted papilloma and a urothelial cancer with an inverted growth pattern (Jones et al, 2007). Transurethral resection is the treatment of choice.

Papilloma

Urothelial papilloma is a benign proliferative growth in the bladder that is composed of delicate stalks lined by normal-appearing urothelium (Fig. 80–2) (Montironi and Lopez-Beltran, 2005). **Papillomas had previously been categorized as grade 1 Ta tumors of the bladder until the World Health Organization (WHO) changed the classification of noninvasive bladder cancer in 1998** (Epstein et al, 1998). Papillomas rarely have mitotic figures and lack markers of aggressive growth such as *TP53* or *RB* mutations, but 75% of these tumors will have mutations in the fibroblast growth factor receptor-3 *(FGFR-3)* (van Rhijn et al, 2004). Papillomas may recur, but they do not progress or invade.

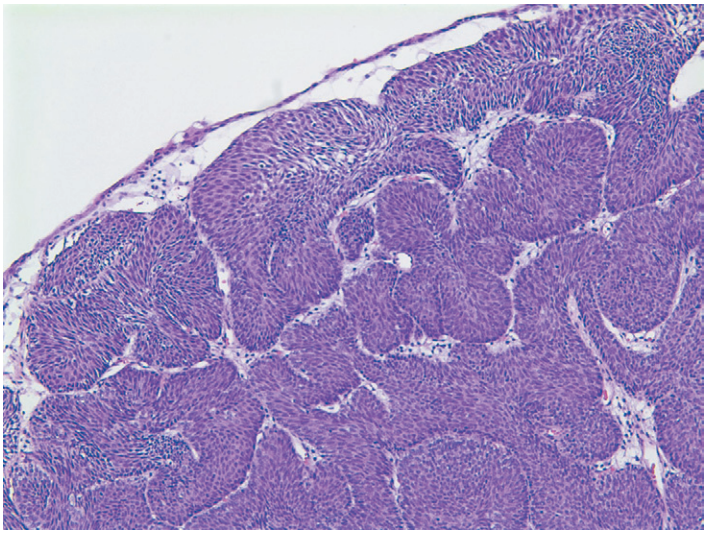


Figure 80–1. Inverted papilloma.

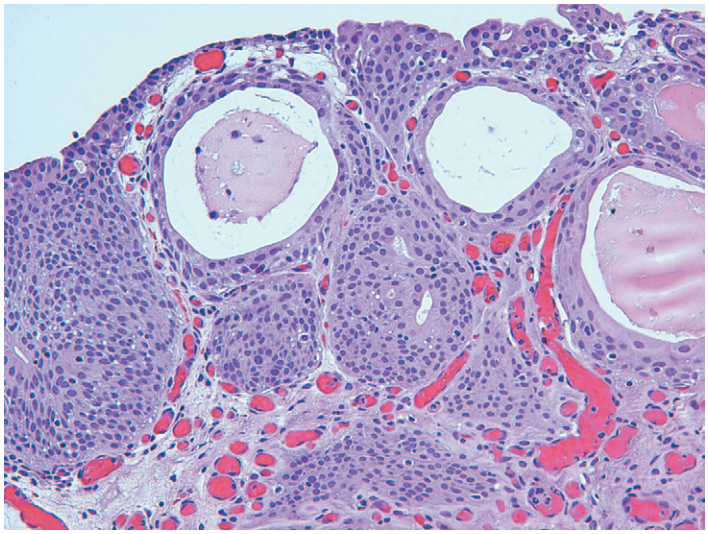


Figure 80–3. Von Brunn nest with cystitis cystica.

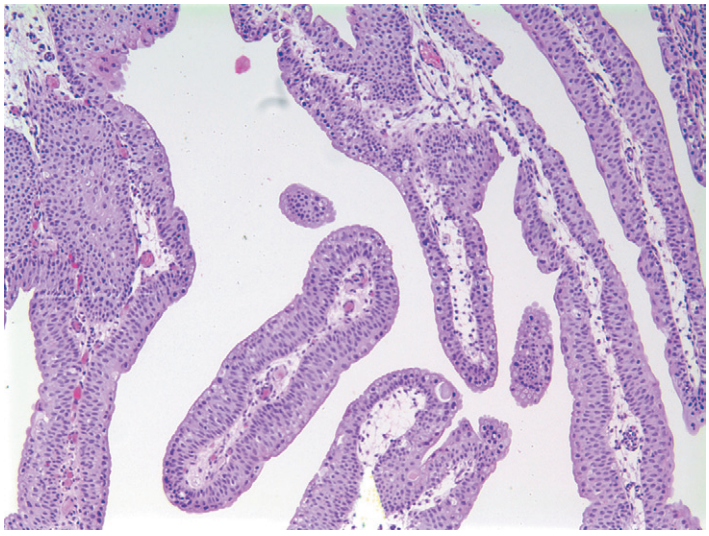


Figure 80–2. Papilloma.

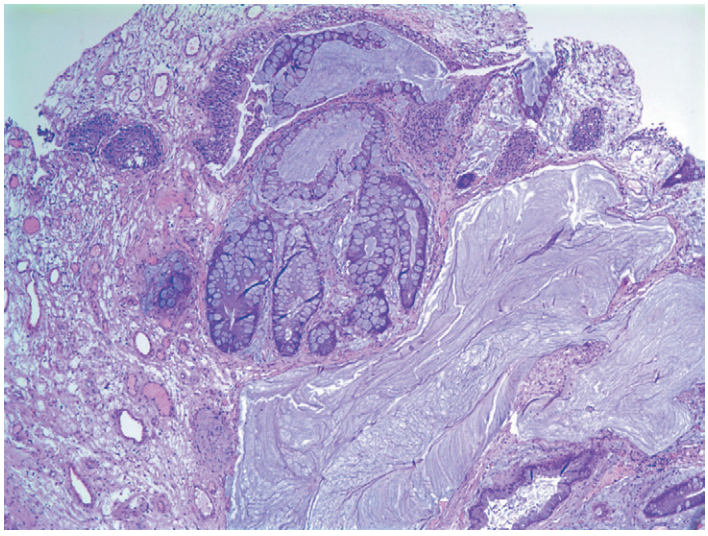


Figure 80–4. Cystitis glandularis.

Nephrogenic Adenoma

Nephrogenic adenoma is a rare tumor caused by chronic irritation of the urothelium; it arises from a variety of sources, including trauma, previous surgery, renal transplantation, intravesical chemotherapy, stones, catheters, and infection (Wood et al, 1988; Tse et al, 1997). Nephrogenic adenoma is composed of glandular-appearing tubules similar to renal tubules that involve the mucosa and submucosa of the bladder. These structures are covered by cuboidal cells with clear or eosinophilic cytoplasm with cytologically normal nuclei. The lesion may be vascular, which explains the presence of gross hematuria in most cases (Porcaro et al, 2001). There is no racial or gender association with the entity. **The constant theme of chronic inflammation suggests metaplastic changes to the urothelium lead to nephrogenic adenoma, though some authors have proposed a theory that nephrogenic adenoma arises from nests of displaced mesonephric tissue in the urothelium that is activated with mucosal injury** (Porcaro et al, 2001). The most frequent presenting symptom is gross hematuria, often in conjunction with a urinary tract infection. Treatment consists of transurethral resection and elimination of the chronic irritation.

Cystitis Cystica and Glandularis

Cystitis cystica and/or glandularis is a common finding in normal bladders, usually associated with inflammation or chronic obstruction (Semins and Schoenberg, 2007). These benign tumors represent cystic nests that are lined by columnar or cuboidal cells and are generally associated with proliferation of Von Brunn nests (Figs. 80–3 and 80–4). Cystitis glandularis can be associated with pelvic lipomatosis and may occupy the majority of the bladder (Buckley et al, 2007). Cystitis glandularis may develop into or coexist with intestinal metaplasia, which are benign tumors characterized by goblet cells that are histologically similar to colonic epithelium. There have been a few case reports of cystitis cystica

or glandularis transforming into adenocarcinoma, and therefore regular endoscopic evaluation of patients with these entities is recommended (Smith et al, 2008). The most common presenting feature of cystitis cystica or glandularis is irritative voiding symptoms and hematuria. Treatment is transurethral resection and relief of the obstruction or inflammatory condition.

Leiomyoma

Leiomyomas are the most common nonepithelial benign tumor of the bladder composed of benign smooth muscle. Several hundred cases have been reported, but this may under-represent the true prevalence. These tumors occur most commonly in women of childbearing age and are histologically similar to leiomyomas of the uterus (Castillo et al, 2008). Leiomyomas appear as smooth indentations of the bladder and can be confused with a bladder tumor except for the normal urothelium overlying the tumor (Fasih et al, 2008). Imaging, especially with magnetic resonance imaging (MRI), can confirm the diagnosis and spare invasive procedures (Fasih et al, 2008). Surgical resection is required if the leiomyoma is large or painful.

UROTHELIAL CANCER

Epidemiology

The incidence rate of a cancer is defined as the number of new cancers diagnosed per 100,000 persons per year. The prevalence rate is the total number of cancers per 100,000 persons per year, not just new cases. **Because urothelial cancer is a cancer of the environment and age, the incidence and prevalence rates increase with age, peaking in the 8th decade of life, and there is a strong association between environmental toxins and urothelial cancer formation** (Jemal et al, 2008; Parkin, 2008). The incidence rate of urothelial cancer has been rising over the last 60 to 70 years, but the rate of rise has recently decreased significantly and in some geographic areas has leveled off (Parkin, 2008). Unfortunately, the incidence rate is rising the fastest in underdeveloped countries where industrialization has led to carcinogenic exposure.

According to the latest American Cancer Society statistics, there were 68,810 total cases diagnosed in the United States in 2007, comprising 51,230 men and 17,580 women and accounting for 7% of all cancers (Jemal et al, 2008). Bladder cancer is a lethal disease with 14,100 deaths recorded in 2007, comprising 9950 men and 4150 women and accounting for 3% of all cancer deaths. **Importantly, there has been a 5% decrease in bladder cancer mortality from 1990 to 2004 despite a continued rise in the incidence of the disease.** Bladder cancer contributes to 0.7% of the absolute decrease in the cancer death rate seen during this time, when all cancers are considered (Jemal et al, 2008). Globally, the incidence rate of bladder cancer has been increasing, but due to smoking cessation programs, at a slower rate over the last decade (Parkin, 2008). The mortality rate from bladder cancer has decreased significantly from 1990 to 2004 with both men and women recording a 18.4% decrease in mortality rate (Fig. 80–5). This decrease in mortality rate is more striking in men than women because of the earlier peak when men begin to smoke, which occurred approximately 20 years before women. Because of the latency period with urothelial cancer–causing agents in tobacco, we should see a commensurate decrease in the mortality rate in women in 15 to 20 years as their smoking cessation programs become more widespread.

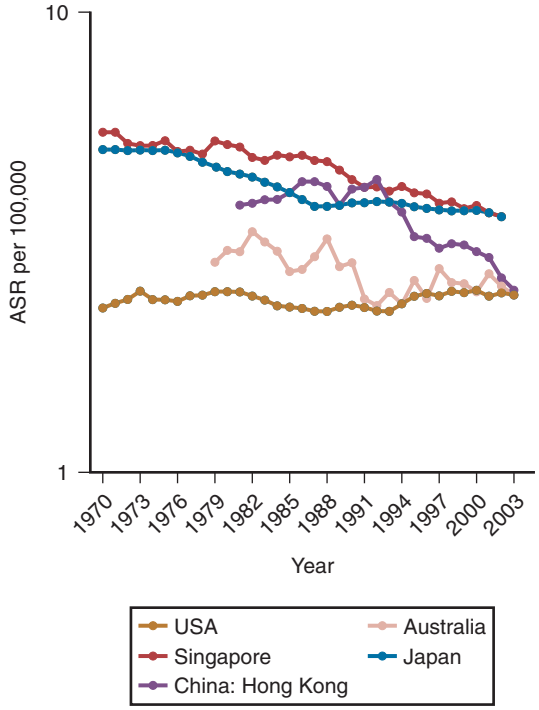


Figure 80–5. Age-Standardized Rates (ASR) of global mortality from bladder cancer. (From Parkin DM. The global burden of urinary bladder cancer. Scand J Urol Nephrol Suppl 2008;218: 12–20.)

Gender/Racial/Age Differences

Males are 3 to 4 times more likely to develop bladder cancer than females, presumably because of an increased prevalence of smoking and exposure to environmental toxins (Jemal et al, 2008; Parkin, 2008). African-American males have a 19% higher incidence rate than white males for all cancers and a 37% higher death rate. However, for urothelial cancer, white males have a higher incidence and death rate than African-Americans (Jemal et al, 2008; Parkin, 2008). African-American women have a 6% lower incidence but a 17% higher death rate than white women in all cancers (Jemal et al, 2008). However, bladder cancer is roughly 1½ times more common in white women than in African-American women. **A white male has a 3.7% chance of developing urothelial cancer in his lifetime, which is roughly 3 times the probability for white females or African-American males and more than 4½ times the probability for African-American females** (Hayat et al, 2007; Jemal et al, 2008). The risk of developing invasive bladder cancer is age dependant (Jemal et al, 2008). For men from birth to age 39 years, the incidence rate of invasive bladder cancer is 0.02%; ages 40 to 59 years, 0.41%; ages 60 to 69 years, 0.96%; ages 70 years and older, 3.5%; and from birth to death, 3.7%. The bladder cancer incidence for women from birth to age 39 years is 0.1%; ages 40 to 59 years, 0.13%; ages 60 to 69 years, 0.26%; ages 70 years and older, 0.99%; and from birth to death, 1.17%. **In general, adolescents and young adults (less than age 40 years) tend to develop well-differentiated noninvasive, rather than invasive, bladder cancer** (Linn et al, 1998). Unlike many other cancers where younger patients tend to

develop more aggressive disease, the opposite appears to be true in bladder cancer, because they present more frequently with noninvasive low-grade tumors. However, the death rate, stage for stage, from bladder cancer is the same across all age groups (Wan and Grossman, 1989).

Global Burden of Bladder Cancer

There is a geographic difference in bladder cancer incidence rates across the world with the highest occurring in Southern and Eastern Europe parts of Africa, the Middle East, and North America and the lowest occurring in Asia and underdeveloped areas in Africa (Ferlay et al, 2007). **Bladder cancer is the 9th most common cancer worldwide, with 357,000 cases recorded in 2002** (Parkin, 2008). Bladder cancer is the 13th most common cause of death, accounting for 145,000 deaths worldwide (Ferlay et al, 2007; Parkin, 2008). The incidence rate of bladder cancer has been rising in Asia and Russia because of an increased prevalence of smoking. Sixty-three percent of all bladder cancer cases occur in developed countries, with 55% from North America and Europe. In the United States, the highest bladder cancer incidence rate is in Rhode Island and the lowest is in the District of Columbia (Jemal et al, 2008). The histologic cell type of bladder cancer is very geographically dependent, but urothelial cancer is the most common. **In North America and Europe, 95% to 97% of cases are urothelial carcinoma; in Africa 60% to 90% are urothelial and 10% to 40% are squamous cell; and Egypt has the highest rate of squamous cell carcinoma because of the endemic infections with *Schistosoma* species** (Parkin, 2008).

Mortality

The mortality rate from bladder cancer in Egypt is 3 times higher than in Europe and 8 times greater than in North America because of the aggressive nature of squamous cell carcinoma that is highly prevalent in Egypt (Parekh et al, 2002). In the United States, death rates for all cancer sites combined decreased by 2.6% per year in males and by 1.8% in females from 2002 to 2004 compared with 1.5% and 0.8% per year in males and females, respectively, from 1992 to 2002 (Jemal et al, 2008). The mortality rate for bladder cancer has decreased by 5% during this period primarily because of smoking cessation, changes in environmental carcinogens, and healthier lifestyles. Mortality from bladder cancer is highest in elderly persons, particularly those over the age of 80 years, accounting for the third most common cause of cancer deaths in men older than age 80 years (Jemal et al, 2008). Whether this increase in mortality rate is related to tumor biology or changes in physician practices with the elderly is unclear. Recent evidence suggests that physician practices may be related to bladder cancer deaths in the elderly (Morris et al, 2009). **These authors estimated that 31% of all bladder cancer deaths were avoidable, more commonly in noninvasive rather than invasive disease.** Better chemotherapy has improved the survival rate in patients with metastatic bladder cancer, but changes in physician practices related to more timely care and more aggressive treatment in healthy patients could well lead to improvement in overall survival. Lee and colleagues (2006) reported that a delay of more than 12 weeks from the diagnosis of bladder cancer to cystectomy treatment was associated with a decrease in overall and cancer-specific survival. However, more intensive treatment (intravesical chemotherapy and cystoscopy) for patients with noninvasive bladder cancer did not correlate with the better survival or less need for invasive treatment (Hollenbeck et al, 2009; Morris et al, 2009).

Key Points: Epidemiology

- Bladder cancer is related to age and exposure to environmental carcinogens, primarily smoking.
- Bladder cancer is 3 times more common in men than in women.
- Bladder cancer is rare in persons less than the age of 40 years and typically nonaggressive and well differentiated.
- The median age of bladder cancer diagnosis is 70 years of age for men and women, and the incidence and mortality from the disease increases with age.
- Bladder cancer is less common in African-Americans than in whites; however, the death rate from bladder cancer is higher in African-Americans than in whites.
- The incidence rate of bladder cancer is decreasing faster in men than in women because of the recent decrease in the percent of men smoking compared with women.

Etiology

Bladder cancer is caused by genetic abnormalities and external risk factors, including carcinogen exposure, nutritional factors, fluid intake, alcohol, inflammation, infection, chemotherapy, radiation, and possibly artificial sweeteners.

Genetic

The higher incidence of bladder cancer in white compared with African-American males is probably not genetic but environmental, or it may be related to differential susceptibility to carcinogens (Bouchardy et al, 1995, 1996; Wanner et al, 1995). There are several polymorphisms that seem to be related to the formation of bladder cancer, in particular the susceptibility to environmental carcinogens. *N*-acetyl transferase (NAT) detoxifies nitrosamines, a known bladder carcinogen. Specifically, NAT-2 regulates the rate of acetylation of compounds such as caffeine, which are related to bladder cancer formation. The slow NAT-2 polymorphism is related to bladder cancer with an odds ratio of 1.4 compared with the fast polymorphism (Garcia-Closas et al, 2005). Glutathione-*S*-transferase (GSTM1) conjugates several reactive chemicals, including arylamines and nitrosamines. The null GSTM1 polymorphism is associated with an increased bladder risk with a relative risk of 1.5 (Garcia-Closas et al, 2005). **The null GSTM1 and slow NAT-2 lead to high levels of 3-aminobiphenyl and higher risk of bladder cancer.** These polymorphisms are present in 27% of white, 15% of African-American, and 3% of Asian males, thus partially explaining the different bladder cancer incidence rates across ethnic groups.

External Risk Factors

In addition to the skin and lungs, the bladder is the main internal organ affected by occupational carcinogens. **The primary culprits are the aromatic amines that bind to DNA** (Delclos and Lerner, 2008; Reulen et al, 2008). Twenty percent to 27% of all bladder cancers are associated with industrial exposure of some

type, primarily in areas with a heavy concentration of chemical industries (Case and Hosker, 1954; Blot and Fraumeni, 1978; Reulen et al, 2008). Among the first chemical agents implicated in the formation of bladder cancer in dye and rubber workers were benzidine and β-naphthylamine (Case and Hosker, 1954). Activation of these amines to allow DNA binding occurs with enzymes that are selectively expressed in the population, making some subjects more susceptible to cancer formation as described above for the NAT-2 and GSTM1 polymorphisms. There are 11 specific aromatic amines implicated in bladder cancer formation; they are broken into three groups—definite, probable, and possible—as seen in Table 80–1. Other industrial agents implicated in bladder cancer formation include polycyclic aromatic hydrocarbons (PAH), diesel exhaust, and paint substances (Zeegers et al, 2001a).

Environmental carcinogens can enter the system and cause bladder cancer from inhalation or through skin absorption. In general, there is a long latency period of 10 to 20 years between the industrial exposure and the formation of the bladder cancer, thus proving definitive causative relationships is difficult (Dryson et al, 2008). However, there are a variety of occupations statistically associated with bladder cancer formation, and all are industrial in nature (Table 80–2) (Reulen et al, 2008). The overall increased risk of bladder cancer formation in industrial workers is 30%, with agriculture workers having the lowest and rubber workers the highest risk of bladder cancer formation.

Smoking

Tobacco is the main known cause for urothelial cancer formation, particularly cigarette smoking, accounts for 60% and 30% of all urothelial cancers in males and females, respectively (Brennan

Table 80–1.

Aromatic Amines Associated with Urothelial Cancer Formation

DEFINITE	PROBABLE	POSSIBLE
4-Aminobiphenyl	4-Chloro-ortho-toluidine	4,4′-Methylene bis(2-methylaniline)
Arsenic		Perchloroethylene
Benzopyrene		Trichloroethylene
Benzidine		Tetrachloroethylene
β-Naphthylamine		4,4′-Methylene bis(2-methylaniline)
N,N-Bis(2-chloroethyl)-2-naphthylamine		Perchloroethylene
4,4′-Methylene bis(2-chloroaniline)		Trichloroethylene

Data from Delclos GL, Lerner SP. Occupational risk factors. Scand J Urol Nephrol Suppl 2008;218:58–63; and IARC. Tobacco smoke and involuntary smoking. Lyon (France): IARC Press; 2004.

Table 80–2.

Relative Risk of Occupations Associated with Urothelial Cancer Formation

OCCUPATION	RR (95% CI)	OCCUPATION	RR (95% CI)
Armed forces	1.09 (0.94-1.26)	Mechanics	1.21 (1.12-1.31)
Managers	1.17 (0.96-1.44)	Motor mechanics	1.27 (1.10-1.46)
Architects and engineers	1.07 (0.91-1.25)	Glassmakers	1.31 (0.94-1.81)
Health professionals	1.02 (0.92-1.13)	Printers	1.13 (0.96-1.33)
Nurses	1.07 (0.91-1.26)	Food processors	1.02 (0.93-1.11)
Teaching professionals	0.90 (0.74-0.09)	Butchers	0.99 (0.78-1.26)
Writers and artists	1.20 (1.05-1.36)	Bakers	1.05 (0.87-1.26)
Clerks	1.01 (0.92-1.10)	Cabinetmakers	1.10 (0.94-1.27)
Cooks	1.14 (0.86-1.50)	Textile workers	1.12 (0.97-1.29)
Hairdressers	1.23 (1.11-1.37)	Tailors	1.28 (0.99-1.65)
Protective service occupations	1.07 (0.96-1.19)	Leather workers	1.27 (1.07-1.49)
Firefighters	1.17 (0.92-1.49)	Machinist	1.18 (1.06-1.30)
Police officers and guards	1.10 (0.95-1.29)	Metal processors	1.18 (1.06-1.32)
Agricultural workers	0.86 (0.79-0.93)	Furnace operators	1.17 (0.96-1.42)
Gardeners	1.04 (0.78-1.40)	Paper-pulp workers	1.08 (0.90-1.29)
Forestry workers	0.93 (0.73-1.17)	Petroleum workers	1.15 (0.97-1.36)
Fishery workers	0.95 (0.83-1.07)	Rubber workers	1.29 (1.06-1.58)
Miners	1.31 (1.09-1.57)	Motor vehicle drivers	1.11 (1.06-1.17)
Building-frame workers	1.06 (0.97-1.16)	Car, taxi, and van drivers	1.20 (1.03-1.39)
Bricklayers	1.03 (0.97-1.10)	Bus drivers	1.29 (1.08-1.53)
Carpenters	1.04 (0.90-1.21)	Truck drivers	1.18 (1.06-1.33)
Building finishers	1.10 (1.05-1.15)	Domestic helpers	1.19 (1.01-1.42)
Plumbers	1.14 (1.03-1.25)	Cleaners	1.06 (0.80-1.41)
Electricians	1.07 (1.02-1.13)	Launderers	1.27 (0.95-1.71)
Painters	1.17 (1.10-1.23)	Building caretakers	1.17 (0.92-1.49)
Metalworkers	1.10 (1.02-1.20)	Hand packers	1.07 (0.93-1.23)
Welders	1.09 (0.98-1.20)	Freight handlers	1.03 (0.96-1.11)
Sheet-metal workers	1.14 (0.98-1.33)	Dye makers	1.10 (1.06-1.13)
Blacksmiths and toolmakers	1.16 (1.06-1.26)	Sales workers	1.05 (0.98-1.13)
Blacksmiths	1.27 (1.02-1.58)	Woodworkers	1.05 (0.89-1.24)
Toolmakers	1.10 (0.90-1.34)	Chemical workers	1.19 (0.98-1.43)
Machine-tool setters	1.24 (1.09-1.42)		

CI, confidence interval; RR, relative risk.
From Reulen RC, Kellen E, Buntinx F, et al. A meta-analysis on the association between bladder cancer and occupation. Scand J Urol Nephrol Suppl 2008;218:64–78.

et al, 2000, 2001; Boffetta, 2008; Gandini et al, 2008). The relative risk of developing urothelial cancer from smoking is 2.8 and 2.73 in men and women, respectively (Gandini et al, 2008). **Overall there is a 2- to 6-times greater chance of developing urothelial cancer with smoking, and the intensity and duration of smoking is linearly related to the increased risk, with no clear plateau level** (Brennan et al, 2000; Smoke, 2004; Boffetta, 2008). If a person smokes 1 to 9 cigarettes versus more than 21 cigarettes per day, the relative risk of bladder cancer is 1.5 versus 5.4, respectively (Weir and Dunn, 1970). If a person smokes 1 to 10 years versus more than 40 years, the relative risk of bladder cancer is 1.2 versus 3.0, respectively (Burns and Swanson, 1991). If a person smokes more than 60 years, they have a sixfold increased risk of developing urothelial cancer compared with a nonsmoker (Burch et al, 1989). The type of tobacco smoked appears to be associated with bladder cancer formation because of different carcinogens present within the tobacco. Black tobacco appears to be worse than blonde tobacco because of a greater amount of aromatic amines in the former (Boffetta, 2008). Cigars and pipes are probably associated with bladder cancer formation, but there are too few studies evaluating only cigar and pipe smokers because of the high probability that these subjects also smoke cigarettes. The risk of bladder cancer formation in those who chew tobacco is unclear. Again, most studies did not restrict their subjects to just chewing tobacco, but in general, there is an increased risk of bladder cancer formation associated with chewing tobacco. **The risk of secondhand smoke in bladder cancer formation is low and not statistically different than that for nonsmokers** (Zeegers et al, 2002). Importantly, smoking cessation does make a difference in urothelial cancer formation. Smokers who have stopped for 1 to 3 years have a 2.6 relative risk, and those stopping for more than 15 years have a 1.1 relative risk of bladder cancer formation (Wynder and Goldsmith, 1977; Smoke, 2004). Smoking is responsible for 30% of all deaths from bladder cancer in males and accounts for 46% of all bladder cancer deaths in high-income countries and 28% in low- to middle-income countries (Brennan et al, 2000; Parkin, 2008). The impact of smoking on mortality is more startling in women, in whom smoking is responsible for 13% of bladder cancer deaths, with 29% in high-income countries compared with only 3% in low- to middle-income countries.

Nutritional Factors

Most nutrients or other metabolites are excreted in the urine and have prolonged contact with the urothelium, particularly in the bladder; therefore nutrition plays a role in urothelial cancer formation (Steinmaus et al, 2000; Brinkman and Zeegers, 2008). However, there are inconsistent reports regarding the exact fruits and vegetables that are beneficial in preventing urothelial cancer, suggesting that epidemiologic factors are at play. **In general, a Mediterranean diet leads to the lowest urothelial cancer risk.** In a case-controlled study, there were fewer cases of urothelial cancer in the group given a Mediterranean diet versus a standard Western diet, probably because of the increased ingestion of fruits and vegetables (de Lorgeril et al, 1998). **Both fruits and vegetables—specifically citrus, apples, berries, tomatoes, carrots, and cruciferous vegetables—contain several active compounds that are important in detoxification.** These compounds include polyphenols, antioxidants, and enzymes that modulate the detoxification of nitrous amines and can prevent DNA adduct formation and oxidative damage (Boffetta, 2008; De Stefani et al, 2008; Lumbreras et al, 2008). Micronutrients associated with a preventive effect on urothelial cancer formation are mainly antioxidants, including vitamins A, C, and E; selenium; and zinc (Michaud et al, 2000; Zeegers et al, 2002; Schabath et al, 2005; Brinkman and Zeegers, 2008). Fish, rice, and cereal do not seem to have a protective or detrimental effect on urothelial cancer formation (Radosavljevic et al, 2005). Foods that have an indeterminate effect on bladder cancer formation include beef, eggs, and processed meats (Balbi et al, 2001; Wakai et al, 2004; Brinkman and Zeegers, 2008). Nutritional factors that have been associated with causing or promoting the formation of urothelial cancer include salted and barbequed meat, pork, total fat, pickled vegetables, soy, and spices (Balbi et al, 2001).

Occurrence of urothelial cancer is moderately higher in coffee and tea drinkers, but this may be compounded by smoking or other dietary factors associated with people who drink coffee or tea (Pelucchi et al, 2008). There is no apparent intensity or duration association of coffee and tea ingestion, suggesting an indirect causative effect, unlike for smoking. Coffee and tea do not appear to have any carcinogenic effect in animals; however, one study did show a twofold increase in urothelial cancer formation in nonsmokers who drank large amounts of coffee in western New York (Vena et al, 1993a). Conversely, a pooled analysis of 10 studies of nonsmokers related to coffee or tea ingestion showed no increased risk of cancer formation in coffee or tea drinkers (Sala et al, 2000). In conclusion, there are inconsistencies regarding nutritional factors related to urothelial cancer formation, in part because of confounding effects and associations, including coffee ingestion and smoking, ingestion of fruits and vegetables without involvement of smoking, and epidemiologic factors. **However, even if not directly causative, there is a very clear association between a healthy diet and a decreased risk of urothelial cancer formation.**

Fluid Intake

Urogenesis theory prescribes that decreased fluid intake leads to less micturition and higher concentrations of potential carcinogens in the urine and thus an increased risk of bladder cancer (Braver et al, 1987). A meta-analysis concluded that approximately 50% of the studies on fluid intake and bladder cancer risk showed an association and 50% did not find an association (Brinkman and Zeegers, 2008). Adding to the controversy, Vena and colleagues (1993b) reported a decreased risk of bladder cancer with increased fluid intake in women, but the opposite was true in men. In conclusion, although it makes sense that increased fluid intake would decrease the concentration of potential carcinogens and thus decrease the risk of bladder cancer, the scientific data supporting this theory is inconclusive.

Alcohol

Alcohol intake is related to several cancers, including those of the oral cavity, esophagus, liver, larynx, and breast, accounting for 3.6% of all cancers (Boffetta and Hashibe, 2006; Pelucchi et al, 2008). However, a meta-analysis of available literature from the last 20 years did not show an association between alcohol intake and bladder cancer, with a relative risk of 1.2 overall—1.3 in men and 1.0 in women (Zeegers et al, 2001b).

Artificial Sweeteners

Some animal studies have shown that large doses of saccharine or cyclamates may influence the development of bladder cancer (Allen et al, 1957; Sontag, 1980). These studies are controversial because of the high doses of saccharine and cyclamates provided

to the animals and the altered composition of these compounds, which may have influenced the carcinogenic activity found in animal studies (Cohen et al, 1995). **Epidemiologic studies in humans have shown no evidence of an increased risk of bladder cancer in consumers of artificial sweeteners** (Armstrong and Doll, 1975; Morrison et al, 1982).

Analgesic Abuse

Acetaminophen is the active metabolite of phenacetin, a commonly used antipyretic and analgesic. Consumptions of large quantities of acetaminophen or phenacetin (5 to 15 kg during a 10-year period) have been associated with an increased risk of renal cancer and, perhaps, bladder cancer (Piper et al, 1985). However, these studies relied on interviews and questionnaires to ascertain drug exposure rather than actual determination of analgesic use. Kaye and colleagues (2001) performed a nested match case–controlled study and found no association between acetaminophen or other nonsteroidal anti-inflammatory drug ingestion and bladder cancer.

Inflammation/Infection

Infection is clearly a contributor to the formation of squamous cell carcinoma in patients chronically infected with *Schistosoma hematobium* and will be covered in the section on squamous cell carcinoma of the bladder (Abol-Enein, 2008). There is a possible link between human papillomavirus (HPV) and urothelial cancer formation. HPV encodes two oncoproteins, E6 and E7. E6 interacts with TP53, which has a role in bladder cancer progression and formation (Westenend et al, 2001). A meta-analysis supports a possible association between HPV infection and bladder cancer, reporting a 2.3 relative risk with confidence intervals of 1.3 to 4.1 (Gutierrez et al, 2006). However, the association between HPV and bladder cancer depends significantly on the method of analysis, the statistical evaluation of the data, proving infection status, and recall bias by the individual. The BK virus is oncogenic in newborn hamsters and can immortalize mammalian cells in vitro (Newton et al, 2005). BK virus can cause severe hemorrhagic cystitis in bone marrow transplant recipients; however, there is no consistent link between BK virus infection and urothelial carcinoma.

Bacterial. Several investigators have suggested that chronic bacterial infections may play a role in bladder cancer formation (Davis et al, 1991). Clinically, chronic catheter use, stones, and infections are associated with bladder carcinoma, but the mechanism of neoplastic formation is not well understood (Abol-Enein, 2008). The mechanism of action may be related to the production of carcinogens like nitrosamines that can be produced with chronic urinary tract infections (Radomski et al, 1978). In an animal model, rats with a urinary tract infection produce increased urinary levels of N1 *N*-dimethylnitrosamine over a 24-week period, and this was associated with urothelial hyperplasia and early neoplastic changes in the urothelium. The potential carcinogens were produced primarily with infections caused by *Escherichia coli* and *Pseudomonas*. **A retrospective review of published literature suggests that chronic urinary tract infections are associated with bladder cancer, reporting a 14 to 16 relative risk of developing bladder cancer for any history of urinary tract infection versus none** (Abol-Enein, 2008). However, there has been no prospective study examining the association between urinary tract infections and bladder cancer risk. It remains possible that the positive association between infection and urothelial cancer is driven by detection bias or preferential recall between cases and controls. Finally, a large case control study from the United States based on data from the National Bladder Cancer Study Group reported a 4.8 relative risk (CI, 1.9 to 11.5) of bladder cancer formation for subjects with greater than or equal to three urinary tract infections versus none (Kantor et al, 1984).

Previous gonorrhea infections have been associated with urothelial cancer formation. In a case-controlled study adjusting for age, gender, smoking, and other confounders, the relative risk of urothelial cancer formation was 2.1 to 2.4 (La Vecchia et al, 1991). A prospective study found a 1.92 relative risk (CI, 1.0 to 3.3) of bladder cancer formation in men with a history of gonorrhea (Michaud et al, 2007). Previous gonorrhea infection was most associated with invasive rather than noninvasive cancers. These studies suggest that gonorrhea infection may be associated with bladder cancer formation, and further prospective studies would be warranted.

Radiation

The potential association between radiation exposure and bladder cancer formation is primarily based on atomic bomb survivors during World War II (Ron et al, 1994; Thompson et al, 1994; Pierce et al, 1996; Hall, 2008). Since 1950, 86,572 people who were exposed to atomic bomb radiation have been followed. Seventy-three percent had a low dose of exposure (less than 50 mSv), and 6% had exposure to very high doses of radiation (more than 500 mSv). There is a significant increased risk of dying from any cancer if a person is exposed to greater than 50 mSv. For urothelial cancer, the relative risk of urothelial cancer formation is 1.63 in men and 1.74 in women. **Interestingly, urothelial cancer formation after radiation is not age related, but the latency period is 15 to 30 years. Further support that radiation can cause bladder cancer is an increased risk of urothelial cancer in those patients with prostate or cervical cancer who were treated with radiation therapy** (Boice et al, 1988; Neugut et al, 1997; Brenner et al, 2000). Even the radiation from more than six CT scans in a given year is associated with second malignancies (Hansen and Jurik, 2009). However, there is no association with low-dose or industrial exposure of radiation therapy and bladder cancer formation. Importantly, urologic technicians or nuclear radiation workers do not have an increased risk of urothelial cancer formation (Sont et al, 2001; Mohan et al, 2003; Sigurdson et al, 2003).

Chemotherapy

Chemotherapy destroys malignant cells by causing significant DNA and cellular damage, but can also have a profound effect on rapidly dividing normal epithelium such as in the bladder. **The only chemotherapeutic agent that has been proven to cause bladder cancer is cyclophosphamide** (Travis et al, 1995; Nilsson and Ullen, 2008). The risk of bladder cancer formation is linearly related to the duration and intensity of cyclophosphamide treatment, supporting a causative role. Phosphoramide mustard is the primary mutagenic metabolite that causes bladder cancer in patients exposed to cyclophosphamide.

Heredity

First-degree relatives of patients with bladder cancer have a twofold increased risk of developing urothelial cancer themselves, but high-risk of urothelial cancer families are relatively rare (Aben et al, 2002; Murta-Nascimento et al, 2007; Kiemeney, 2008). The hereditary risk seems to be higher for women and nonsmokers, but it is not related to secondhand exposure to smoking in families. The inherited risk of bladder cancer formation appears to affect all stages of

urothelial carcinoma and is not associated with bladder cancer formation at an earlier age. Unfortunately, there are no clear mendelian inheritance patterns, making classic linkage studies impossible. Most likely, there are a variety of low-penetrance genes that can be inherited to make a person more susceptible to carcinogenic exposure, thus increasing the risk of bladder cancer formation. There are two high-penetrance genes that are associated with urothelial carcinoma: *RB1* and *CDC91L1* (Fletcher et al, 2004; Guo et al, 2004). In a recent study, there were five bladder cancer cases from 144 patients with known retinoblastoma, resulting in a relative risk of 26.3 compared with those without retinoblastoma (Fletcher et al, 2004). *CDC91L1* was discovered in 1996 and is a germline translocation of t(5;20) (p15;q11) that is located on 20q11 (Guo et al, 2004). This gene encodes phosphatidylinositol glycan class U and is amplified in one third of urothelial carcinomas. The role of the gene is unclear, and the protein expressed is unknown at this time. Thelen and Schaeuble were the first to report familial clustering of urothelial carcinomas in 1957 by identifying identical twins with urothelial papillomas. This finding has led to further evaluations of looking for an inherited form of urothelial cancer, which to date has proven elusive.

Key Points: External Risk Factors

- Bladder cancer is caused by genetic abnormalities and external risk factors.
- Smoking is the most common cause of urothelial cancer.
- A diet rich in fruits and vegetables is protective against bladder cancer formation.
- There is a hereditary component to bladder cancer formation, probably through low-penetrance genes (*NAT-2* and the *GSTM1* polymorphisms) that increase the susceptibility of carcinogens.

Pathology

Histologically, 90% of bladder cancers are of urothelial origin, 5% are squamous cell carcinomas, and less than 2% are adenocarcinoma or other variants (Lopez-Beltran, 2008). **Urothelial carcinoma is the most common malignancy of the urinary tract and is the second most common cause of death among genitourinary tumors.** At initial presentation, 80% of urothelial tumors are non–muscle invasive. There are multiple growth patterns of urothelial cancer, including flat carcinoma in situ (CIS), papillary tumors that can be low or high grade, and sessile tumors with a solid growth pattern. Non–muscle-invasive cancers can be very large because of lack of genetic alterations required for invasion. Likewise, invasive tumors can be quite small if early genetic changes occur within the tumor cell, allowing for an invasive phenotype.

The World Health Organization (WHO) first determined nomenclature for the histologic classification of urothelial cancer in 1973. In 1998, the International Society of Urological Pathology (ISUP) developed a new nomenclature to better reflect the recurrence and progression rates of urothelial cancer (Epstein et al, 1998). **The two main changes were recognition that papillary Ta grade 1 urothelial cancers should not be considered cancers because of their indolent growth and lack of invasion, and the second was elimination of "grade 2" cancers, which became a grey zone encompassing grade 1 and grade 3 cancers causing interobserver variation.** In 2004, the WHO adopted the ISUP recommended staging system and is the standard histologic nomenclature for urothelial carcinoma (Sauter et al, 2004). The clinical pattern of presentation is related to the cytologic and architectural alterations that occur within the tumor. Table 80–3 lists the histologic changes that occur from normal epithelium to high-grade muscle-invasive disease. Table 80–4 lists the neoplasms that can occur in the

Table 80–3.

Histologic Characteristics of Noninvasive Papillary Urothelial Tumors of the Bladder According to the WHO 2004 Classification

	PAPILLOMA	PAPILLARY NEOPLASM OF LOW MALIGNANT POTENTIAL (PUNLMP)	LOW-GRADE PAPILLARY CARCINOMA	HIGH-GRADE PAPILLARY CARCINOMA
Architectural Features				
Papillae	Delicate	Delicate. Occasionally fused, not branching.	Fused, branching	Fused, branching
Organization of cells	Identical to normal urothelium	Ordered. Polarity identical to normal urothelium, any thickness, cohesive.	Predominately ordered, minimal crowding, and minimal loss of polarity; any thickness, cohesive	Predominately disordered with frequent loss of polarity, variable thickness, discohesive
Cytologic Features				
Nuclear size	Identical to normal urothelium	May be enlarged but uniform	Enlarged with variation in size	Enlarged with variation in size readily visible
Nuclear shape	Identical to normal urothelium	Elongated, round to oval, uniform	Round to oval, slight variation in shape and contour	Moderate to marked pleomorphism
Nuclear chromatin	Fine	Fine	Mild variation	Moderate to marked variation. Hyperchromasia.
Nucleoli	Absent	Absent to inconspicuous	Usually inconspicuous	Multiple prominent nucleoli may be present
Mitoses	Absent	Rare, basal	Occasionally at any level	Usually frequent, at any level
Umbrella cells	Uniformly present	Present	Usually present	Usually absent

From Montironi R, Lopez-Beltran A. The 2004 WHO classification of bladder tumors: a summary and commentary. Int J Surg Pathol 2005;13(2):143–53.

Table 80–4.

Histologic Type of Tumors of the Urinary Bladder (World Health Organization, 2004)

Urothelial neoplasia
Benign
Urothelial papilloma
Inverted papilloma
Papillary urothelial neoplasia of low malignant potential
Malignant papillary
Papillary carcinoma, low-grade
Papillary carcinoma, high-grade
Papillary carcinoma with squamous or glandular differentiation
Malignant nonpapillary
Flat carcinoma in situ
Invasive carcinoma
Variants of invasive carcinoma
Nested pattern
Small tubular pattern
Microcystic pattern
Inverted pattern
Squamous differentiation
Glandular differentiation
Micropapillary
Sarcomatoid carcinoma
Clear cell urothelial carcinoma
Plasmacytoid
With syncytiotrophoblasts
With unusual stromal reactions
Pseudosarcomatous stroma
Stromal osseous or cartilaginous metaplasia
Osteoclast-type giant cells
With prominent lymphoid infiltrate
Squamous cell carcinoma
Usual type
Variant
Verrucous
Basaloid
With sarcomatoid features
Adenocarcinoma (from bladder mucosa, urachal, with extrophy)
Usual intestinal type
Mucinous (including colloid)
Signet ring cell
Clear cell
Hepatoid
Mixture of above patterns
Adenocarcinoma NOS
Tumors of mixed cell types
Undifferentiated carcinomas*
Small cell carcinoma
Large cell neuroendocrine carcinoma
Lymphoepithelioma-like carcinoma
Giant cell carcinoma
Undifferentiated carcinoma NOS
Metastatic carcinoma

*Refers to tumors that are undifferentiated by light microscopy.
NOS, not otherwise specified.
Lopez-Beltran A. Bladder cancer: clinical and pathological profile. Scand J Urol Nephrol Suppl 2008;218:95–109.

Table 80–5.

2004 World Health Organization Classification of Noninvasive and Invasive Urothelial Neoplasia

Noninvasive Urothelial Neoplasia
Hyperplasia (flat and papillary)
Reactive atypia
Atypia of unknown significance
Urothelial dysplasia (low-grade intraurothelial neoplasia)
Urothelial carcinoma in situ (high-grade intraurothelial neoplasia)
Urothelial papilloma
Urothelial papilloma, inverted type
Papillary urothelial neoplasm of low malignant potential
Noninvasive low-grade papillary urothelial carcinoma
Noninvasive high-grade papillary urothelial carcinoma
Invasive Urothelial Neoplasia
Lamina propria invasion
Muscularis propria (detrusor muscle) invasion

From Montironi R, Lopez-Beltran A. The 2004 WHO classification of bladder tumors: a summary and commentary. Int J Surg Pathol 2005;13(2):143–53.

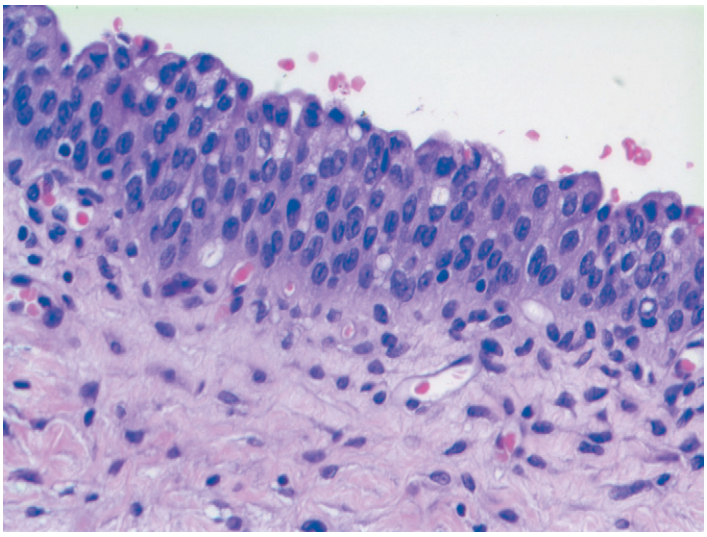


Figure 80–6. Normal urothelium.

bladder, and Table 80–5 lists the WHO 2004 classification of urothelial neoplasms (Sauter et al, 2004; Montironi and Lopez-Beltran, 2005).

Precursor Lesions to Urothelial Cancer

Normal bladder urothelium is multilayered and less than seven cells thick (Epstein et al, 1998; Montironi and Lopez-Beltran, 2005) (Fig. 80–6). The cells mature from the basement membrane to the surface cells in an orderly fashion. The surface has large umbrella cells that may have nuclear atypia and form asymmetrical units. Their membrane is composed of uroplakin proteins and is rigid. These umbrella cells are part of the urine bladder barrier preventing toxins within the urine from transforming urothelial cells. Previously, normal urothelium was called "transitional cells" because of their ability to transition into other cell types, including squamous cells and adenocolumnar cells.

Precursor lesions are a continuum from hyperplasia to atypia to dysplasia and finally cancer. Different pathologists have their own interpretation of important cellular or structural changes that separate these histologic changes into different categories. Hyperplasia is characterized by markedly thicker mucosa with or without atypia (Fig. 80–7). The urothelium is more than seven cells thick, and there is some disorganization of the cellular architecture. Hyperplasia is often adjacent to low-grade tumors and thought to

Table 80–6.

Clinical Significance of Different Non–Muscle-Invasive Urothelial Cancer Categories in WHO 2004 Grading System

	PAPILLOMA	PAPILLARY NEOPLASM OF LOW MALIGNANT POTENTIAL	LOW-GRADE PAPILLARY CARCINOMA	HIGH-GRADE CARCINOMA (PAPILLARY AND CIS)
Recurrence (%)	0-8	27-47	48-71	55-58
Grade progression (%)	2	11	7	N/A
Stage progression (%)	0	0-4	2-12	27-61
Survival (%)	100	93-100	82-96	74-90

CIS, carcinoma in situ; N/A, not applicable; WHO, World Health Organization.
From Montironi R, Lopez-Beltran A. The 2004 WHO classification of bladder tumors: a summary and commentary. Int J Surg Pathol 2005;13(2):143–53.

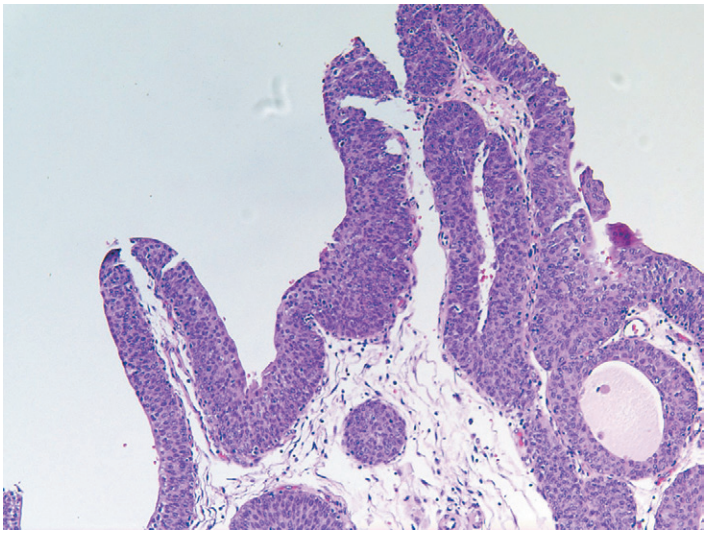


Figure 80–7. Papillary urothelial hyperplasia.

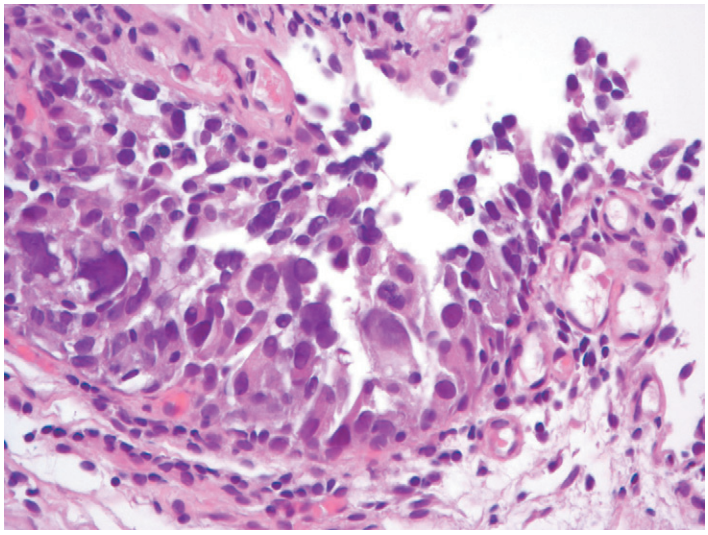


Figure 80–8. Carcinoma in situ.

be a precursor lesion (Epstein et al, 1998). **Loss of parts of chromosome 9 can occur in hyperplasia, particularly if adjacent to low-grade tumors** (Hartmann et al, 1999). Urothelial hyperplasia appears as undulating or papillary growths that are best seen on flexible cystoscopy (Sauter et al, 2004). The presence of hyperplasia does not increase the risk of developing cancer; however, if present in someone with a history of urothelial carcinoma, it may herald a recurrence in the future (Montironi and Lopez-Beltran, 2005; Lopez-Beltran, 2008).

Reactive atypia can have nuclear changes associated with inflammation, regeneration, or reaction from noxious stimuli and is characterized by large cells with prominent nucleoli (Lopez-Beltran et al, 2002). Mitotic activity without abnormal forms can be present. Endoscopically, reactive atypia is edematous, especially in the lamina propria and associated with previous urinary instrumentation, stones, infection, or intravesical therapy (Lopez-Beltran, 2008).

Urothelial dysplasia has abnormal cytologic and nuclear changes that are preneoplastic but are not sufficient to be characterized as CIS (Sauter et al, 2004). Dysplasia is characterized by cohesive cells with mildly abnormal nuclear changes. There is nuclear crowding, prominent nucleoli, and abnormal mitotic figures may be present. Umbrella cells can be present with dysplasia, but not with CIS. Most cellular abnormalities are in the basal or early cell layers, with appropriate maturation toward the luminal surface. The urothelium is more than seven cells thick at times, but there can be sloughing of the more mature urothelium, exposing the less mature early cell layers. There is allelic loss of chromosome 9 and occasional *TP53* abnormalities (Harnden et al, 1996; Hartmann et al, 1999). It is difficult to quantitate the clinical significance of dysplasia secondary to the interobserver reproducibility of this entity (Montironi and Lopez-Beltran, 2005). **However, dysplasia is a good indication of urothelial instability and a marker of recurrence and progression in those with known urothelial cancer.** Isolated dysplasia progressing to CIS occurs in approximately 19% of cases, but dysplasia in the face of previous history of urothelial cancer will form CIS in approximately 60% of cases (Cheng et al, 1999a).

Urothelial Cancer Histology

Non–muscle-invasive bladder cancer (NMIBC) includes CIS, papillary urothelial neoplasia of low-malignant potential (PUNLMP), and low- and high-grade urothelial cancer that previously had been called "superficial bladder cancer," which is a misnomer. The clinical significance of the WHO grading classification is shown in Table 80–6. The grade distribution of NMIBC is 25% PUNLMP, 50% low grade, and 25% high grade (including CIS) (Holmang et al, 2001; Samaratunga et al, 2002). CIS is characterized as nonpapillary, flat, high-grade tumors in which the surface epithelium contains cancer cells (Fig. 80–8) (Sauter et al, 2004). There is severe nuclear atypia, loss of cellular polarity, and a noncohesive cellular structure. The cells are large, pleomorphic, chromatin clumping, and abnormal mitotic figures are common. Loss of umbrella cells is a characteristic, separating CIS from dysplasia. All CIS is high grade by definition. **The genetic abnormalities associated with CIS include alterations to the *RB, TP53,* and *PTEN***

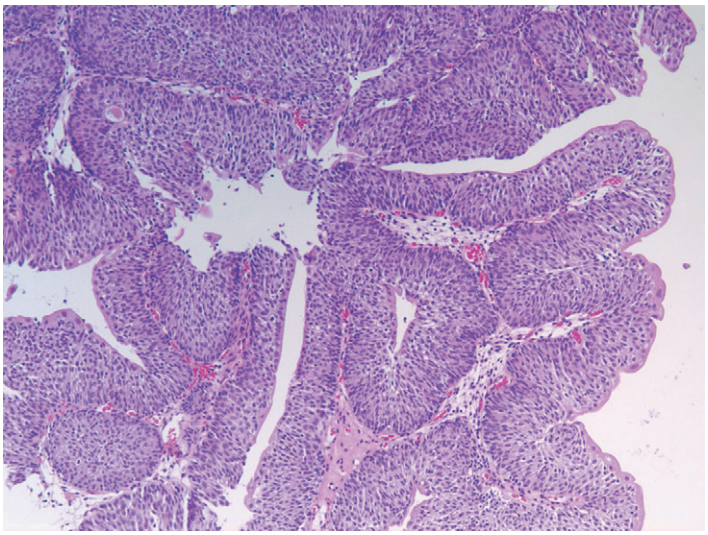


Figure 80–9. Papillary urothelial neoplasm of low malignant potential.

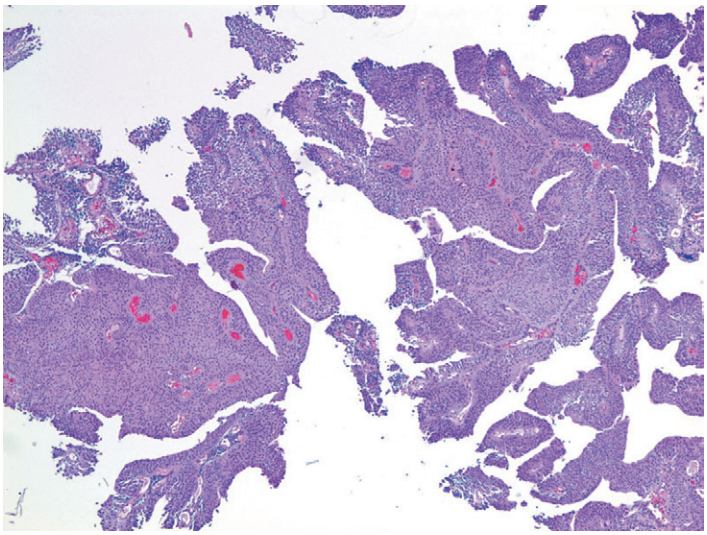


Figure 80–10. Low-grade papillary urothelial neoplasm.

genes (Cordon-Cardo et al, 2000; Lopez-Beltran et al, 2002; Cordon-Cardo, 2008). CIS is immunoreactive for cytokeratin 20, and NMP22 is present in the cells. CIS is a precursor lesion for invasive cancer and can spread to the distal ureters and prostatic urethra on the surface or in a pagetoid manner, undermining normal adjacent urothelium (Montironi et al, 2002). Endoscopically, CIS is reddish with heaped-up mucosa and can be mistaken for inflammatory changes or radiation cystitis. CIS in association with invasive tumors have a worse prognosis, with a 45% to 65% 5-year death rate (Lopez-Beltran et al, 2002).

PUNLMP is a papillary growth with minimal cytological atypia that is more than seven cells thick and is generally solitary and located on the trigone (Fig. 80–9) (Holmang et al, 2001; Sauter et al, 2004). PUNLMP is composed of thin papillary stalks, where the polarity of the cells is maintained and the nuclei are minimally enlarged. PUNLMP has a low proliferation rate and is not associated with invasion or metastases, but almost 80% will have loss of chromosome 9 (Cheng et al, 2004). PUNLMP is different from a benign papilloma in that a PUNLMP has a thicker cell layer and large nuclei with occasionally mitotic figures. The male to female ratio for PUNLMP is 5:1, and the mean age is 65 (Holmang et al, 2001). PUNLMP can recur within the bladder in 35% of cases, but progression is rare, occurring in less than 4% (Oosterhuis et al, 2002).

Low-grade urothelial carcinoma is typically papillary in nature with a fibrovascular stalk and frequent papillary branching with increased cellular size, some nuclear atypia (more than in PUNLMP), and occasional mitotic figures (Fig. 80–10) (Epstein et al, 1998). Genetic abnormalities associated with low-grade cancer include deletion of 9q and alterations of *FGFR-3, HRAS,* and *PI3K* (Holmang et al, 2001; Cordon-Cardo, 2008). Low-grade carcinomas are immunoreactive for cytokeratin-20 and CD-44. The architectural and histologic changes that separate low-grade urothelial carcinoma from a PUNLMP include multiple stalks, more cytologic atypia, and the multifocal nature of low-grade carcinomas compared with the solitary PUNLMP.

High-grade papillary urothelial cancer is composed of fused papillary stalks with high-grade cancer in the urothelial layer. There is a disordered growth pattern, numerous mitotic figures present, and there are pleomorphic cells with exaggerated nuclei. Over 80% of high-grade cancers will invade the underlying stroma

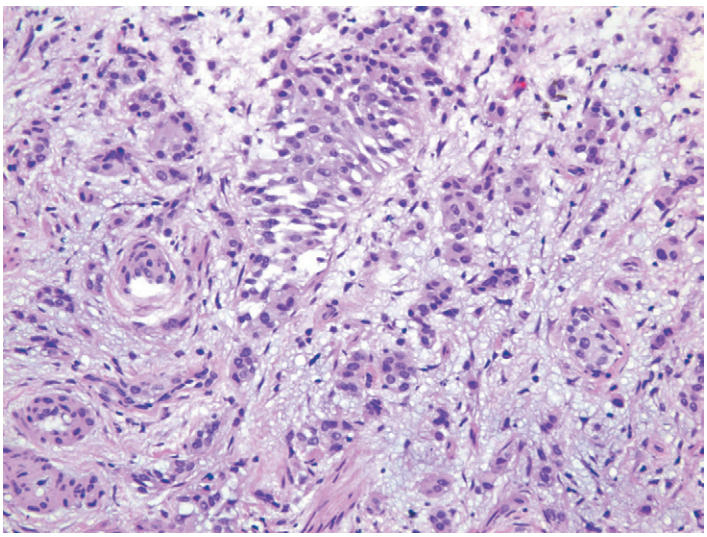


Figure 80–11. High-grade urothelial cancer invading the lamina propria.

if left untreated. Genetic abnormalities associated with high-grade papillary urothelial cancer include similar abnormalities seen in the low-grade type plus alterations in the *INK4A* gene (Cordon-Cardo, 2008). In addition, there can be deletions of 2q, 5q, 10q, 18q, and gains of 5q and 20q (Knowles, 2008b). Alterations of *TP21* and *TP27* along with *TP53* have been reported (Simon et al, 2004). High-grade urothelial carcinoma stains are immunoreactive for cytokeratin-20 and are likely aneuploid.

There are key genetic and phenotypic changes that occur in cancer cells, thus providing the ability to invade the underlying stroma. Invasive urothelial carcinoma is divided into two groups: lamina propria and deep muscle invasion. Lamina propria invasive tumors are high-grade cancers that can be in clusters or in single cells, with single-cell invasion having a worse prognosis (Fig. 80–11). Rarely, low-grade cancers can invade the lamina propria. Vascular invasion can occur within the lamina propria because of the large vascular network within this tissue layer; however, it is frequently overcalled because of retraction artifact around tumor

nests. There is a subdivision of lamina propria invasion into T1a (invasion above muscularis mucosa) and T1b (invasion below the muscularis mucosa). This subject will be dealt with more extensively in the Staging section.

Muscle-invasive urothelial carcinoma is by definition high grade and is composed of cancerous cells extending through the lamina propria into the deep muscle bundles. There are rare cases of metastases to the deep muscle, but the overwhelming majority of cases are a direct extension from a surface urothelial carcinoma through the lamina propria into the deep muscle.

Staging

The American Joint Commission on Cancer in combination with the International Union Cancer Consortium meets on a regular basis to determine the tumor, nodes, and metastases (TNM) staging classifications. The 2009 staging system is shown in Table 80–7 (Edge et al, 2010). Ta and CIS disease have no invasion of the basement membrane, but endophytic growth of low-grade tumors into the lamina propria is possible, and cancer can occur in Von Brunn nests (Sung et al, 2006, Jones et al, 2007). T1 disease, as mentioned earlier, can be divided into T1a and T1b disease (Smits et al, 1998). The subdivision is based on the muscularis mucosa, which comprises thin wavy vesicles of muscle within the lamina propria that are associated with large vessels and lymphatics (Fig. 80–12). Some investigators substitute the presence of this large-vessel lymphatic layer for the muscularis mucosa when dividing T1a and T1b disease (Lopez-Beltran and Cheng, 2003). Unfortunately, muscularis mucosa is only identified in 15% to 80% of bladder biopsy specimens and in 90% of radical cystectomy specimens (Cheng et al, 1999; Sozen et al, 2002; Lopez-Beltran and Cheng, 2003; Lopez-Beltran, 2008). **The prognostic significance of T1a and T1b disease is inconsistent because of the lack of muscularis mucosa in many bladder biopsy specimens. Essentially, the T1a and T1b stratifications suggest that the deeper the tumor invades in the lamina propria, the worse the survival.**

Muscle-invasive disease is subdivided into T2a and T2b. T2a includes invasion into the inner half of the muscularis propria, while T2b is deeper into the outer half. Analysis of the American Joint Committee on Cancer (AJCC) data would suggest that there is a disease-free survival difference between T2a and T2b disease (Edge et al, 2010). On the contrary, Cheng and colleagues (1999b) showed that depth of muscle invasion was not predictive of disease-free survival, but the size of the tumor was the key element. T3 disease constitutes invasion outside the bladder proper into the periadipose tissue. T3a disease involves microscopic extension, while T3b involves macroscopic extension. Clinically, T3a disease is identified by a palpable mass at the time of examination under anesthesia during the initial transurethral resection and subsequently is nonpalpable after the tumor is resected. T3b disease has a persistent palpable mass after transurethral resection of the tumor. Pathologically, T3a disease is microscopic extension into the periadipose tissue, while T3b disease is macroscopic extension. T4a disease is invasion of the prostatic stroma, uterus, or vagina, and T4b disease is invasion of the pelvic wall or abdominal wall. **Extension of the tumor into the prostatic urethra without stromal invasion is currently classified under the prostatic urethral section and does not carry an adverse prognosis for patients with known bladder cancer** (Pagano et al, 1996; Edge et al, 2010). Prostatic stromal invasion, however, particularly if it is a direct extension from the bladder through the muscle into the prostate, does have a poor

Table 80–7.

Definition of TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumor"
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscularis propria
pT2a	Tumor invades superficial muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue:
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostatic stroma, uterus, vagina
T4b	Tumor invades pelvic wall, abdominal wall

Regional Lymph Nodes (N)

Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are considered distant lymph nodes.

NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Anatomic Stage/Prognostic Groups

Group	T	N	M
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1-3	M0
	Any T	Any N	M1

Prognostic Factors (Site-Specific Factors)

Required for staging	None
Clinically significant	Presence or absence of extranodal extension
	Size of the largest tumor deposit in the lymph nodes
	World Health Organization/International Society of Urologic Pathology (WHO/ISUP) grade

From Edge SB, Byrd DR, Compton CC, et al, editors. AJCC cancer staging manual. 7th edition. New York: Springer; 2010.

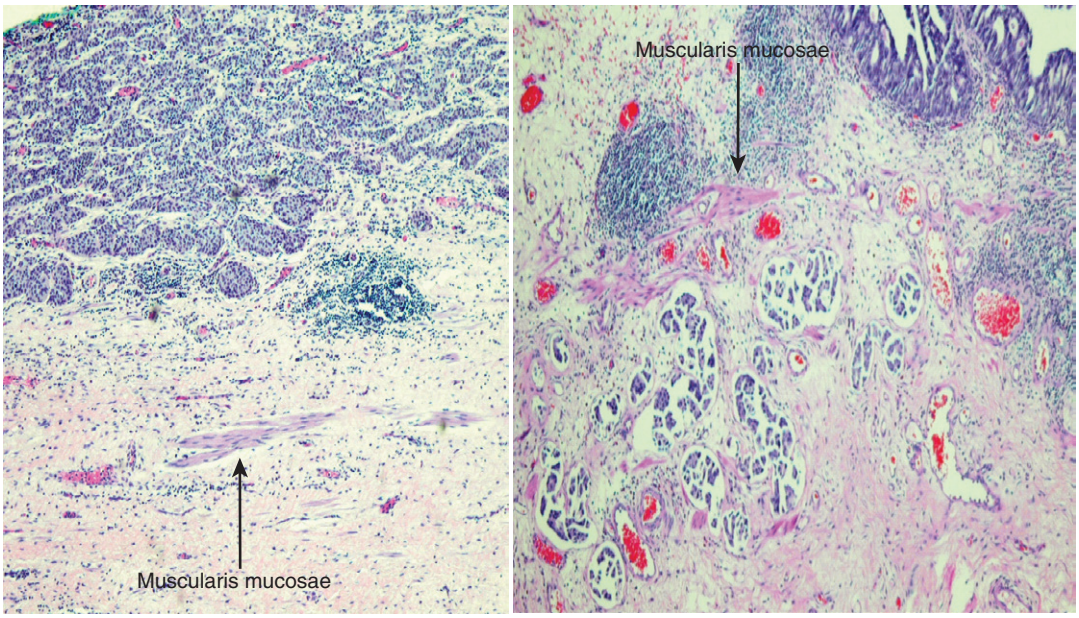


Figure 80–12. High-grade T1a (*left*) and T1b (*right*) urothelial cancer.

prognostic factor, with a 5-year overall survival of less than 25% (Esrig et al, 1996; Pagano et al, 1996).

A major problem in bladder cancer is understaging, occurring in 34% to 64% of cases. Chang and colleagues (2001) reported that 27% of T1 tumors were upstaged after radical cystectomy, and 49% of T2 tumors were upstaged to T3. **Because of this understaging, the American Urological Association (AUA) guidelines call for a repeat transurethral resection in patients with T1 tumors to assess for muscle invasive disease even if muscle was present in the specimen** (Hall et al, 2007). The significance of this restaging is shown in an article by Herr and colleagues (2007). Of 701 patients with T1 disease on the first transurethral resection, a second transurethral resection found 22% had no residual tumor, 23% had Ta or TIs disease, 25% had T1 disease, and 30% had muscle-invasive T2 cancer. If muscle was present in the original specimen, only 15% were upstaged to muscle-invasive disease, but if there was no muscle in the specimen, 40% were upstaged to T2 disease. This suggests that even if muscle is present in the initial specimen, an additional transurethral resection will detect muscle-invasive disease in up to 15% of cases.

Key Points: History and Staging

- The WHO 2004 grading scheme should be used routinely and replaces the 1973 and 1998 WHO classification system.
- The delineation of PUNLMP is important and describes bladder lesions that can recur but rarely invade.
- The elimination of the grade 1, grade 2, and grade 3 1973 WHO system is collapsed into low grade or high grade in the 2004 WHO classification.
- Low-grade papillary lesions are likely to recur in up to 60% of patients but invade in less than 10% of cases. High-grade lesions also recur; however, invasion and subsequent stage progression can occur in 50% of tumors. This is particularly true if CIS is associated with a high-grade papillary lesion.
- Stratification of T1 disease is desirable, but there is a lack of a reliable system to accurately identify the muscularis mucosa and therefore stratify tumors accurately.
- Superficial bladder cancer is a misnomer and should be replaced by non–muscle-invasive bladder cancer that includes PUNLMP, CIS, Ta, and T1 tumors.
- Muscle-invasive bladder cancer leads to death in a significant proportion of patients despite aggressive therapy.

Origin, Recurrence, and Dissemination of Urothelial Cancer

Primary Tumors

The formation of primary urothelial carcinoma is a combination of environmental, genetic, and epigenetic causes. The main environmental factor associated with primary urothelial cancer is cigarette smoking, occurring in one third to one half of all bladder cancers in men and in 30% in women (Brennan et al, 2001; Boffetta, 2008). Smokers have a 2.77 relative risk of developing bladder cancer compared to nonsmokers (Gandini et al, 2008). Other external risk factors are listed above in the Etiology section. These external environmental factors then cause genetic and epigenetic instability that ultimately result in the formation of urothelial carcinoma**. The deletion of parts or all of chromosome 9 is most likely the earliest mutation seen in low-malignant potential, non–muscle-invasive bladder cancer** (Obermann et al, 2003). **There is a known tumor suppressor gene at 9p21 that is a negative regulator of *RB*** (Berggren et al, 2003). **Another genetic abnormality mutated in 75% of low–malignant potential, non–muscle-invasive bladder cancer is FGFR-3** (Billerey et al, 2001; Gomez-Roman et al, 2005). High–malignant potential, non–muscle-invasive bladder cancer is more likely associated with deletions of tumor suppressor genes such as *TP53* and *RB* (Chatterjee et al, 2004a;

George et al, 2007; Sanchez-Carbayo et al, 2007). There are a large number of genes associated with stage progression because of the general genetic instability seen in high-grade tumors. Deletions of 3p, 5q, 6q, 11p, 16q, 18q, and *TP53* with *RB* are all important for stage progression (Cordon-Cardo et al, 2000). It is the accumulation of these multiple genetic alterations, most often caused by external risk factors, that leads to the formation of urothelial cancer.

Recurrent Tumors

A hallmark of urothelial cancer is the high recurrence rate that approaches 80% for high–malignant potential, non–muscle-invasive bladder cancer. The two primary theories for recurrent tumor formation are field change effects within the bladder and tumor implantation. **Using a cDNA expression library, genetic abnormalities seen in CIS can be found in endoscopically appearing normal urothelium away from the primary tumor** (Dyrskjot et al, 2007). Similarly, alterations in certain urine markers that are associated with bladder cancer can be found in biopsy-negative bladders from patients with a history of urothelial carcinoma, suggesting that normal-appearing urothelium has the capacity to produce these various tumor markers (Keesee et al, 1996; Black et al, 2006). Because of these field-change genetic and epigenetic alterations, random bladder biopsies taken from patients after intravesical therapies for non–muscle-invasive bladder cancer or in those with positive urine cytology and yet endoscopically negative bladders are useful to detect incipient disease. Mufti and Singh (1992) evaluated the utility of random mucosal biopsies in the management of noninvasive bladder cancer and found 23% of normal-appearing bladder mucosa biopsies had dysplasia, CIS, or low–malignant potential papillary tumors (Mufti and Singh, 1992). **Multifocality and rapidly recurring tumors are strong prognostic factors associated with finding histologically abnormal urothelium in endoscopically normal-appearing bladder tissue.** In addition, the effectiveness of maintenance bacillus Calmette-Guérin (BCG) therapy in preventing tumor recurrence compared with an induction course only is supportive of field-change effects in the normal-appearing urothelium (Lamm et al, 2000). This suggests that treating the "nonvisible" tumors can prevent or delay the formation of visible cancer.

Tumor implantation during a transurethral resection of the bladder tumor has been suggested as a possible cause for recurrent tumor formation (Soloway and Masters, 1980; Pode et al, 1986). **In experimental mouse models, 54% of transurethrally placed inoculates of tumor cells implanted successfully and grew in mice that underwent simultaneous bladder cauterization, in contrast with 12% of mice with an intact urothelial surface** (Soloway and Masters, 1980). The immediate introduction of intravesical therapy, after the tumor inoculation and cauterization, significantly reduced the implantation rate. **This finding has been confirmed by phase III clinical trials, showing that the immediate instillation of intravesical agents after transurethral resection of the bladder tumor can significantly decrease the risk of subsequent tumor recurrence** (Kurth et al, 2000; Sylvester et al, 2004). However, for patients with a normal random bladder biopsy, the risk of subsequent tumor recurrence was significantly lower than those presenting with multiple tumors or single tumors with an abnormal random bladder biopsy (Mufti and Singh, 1992). The authors suggest that performing random bladder biopsies do not lead to an increased risk of bladder cancer formation; however, a strict control group was not used. Data from studies combining a transurethral resection of the prostate with a simultaneous transurethral resection of the bladder tumor did not find an increase risk of tumor implantation in the bladder neck or prostatic fossa (Ugurlu et al, 2007; Ham et al, 2009). Interestingly, Ham and colleagues (2009) showed a decreased risk of tumor recurrence in patients who had a simultaneous transurethral resection of the prostate and bladder tumor presumably because of a lower postvoid residual volume and, consequently, less urothelial exposure to carcinogens. It is unclear whether this was a cause and effect, and further studies are required to confirm this result.

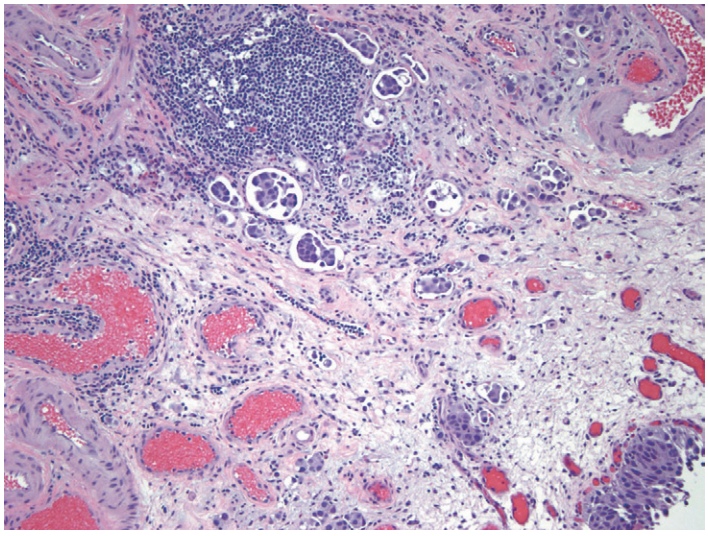


Figure 80–13. Angiolymphatic invasion by high-grade urothelial cancer.

Angiolymphatic Invasion

The key phenotypic change that occurs in urothelial cancer that is destined to metastasize is the ability to invade the angiolymphatic system, which is seen in approximately 25% of invasive urothelial carcinoma (Fig. 80–13) (Kunju et al, 2008). **Angiolymphatic invasion is a poor prognostic sign with a 40% risk of nodal disease and is an independent predictor of overall and cancer specific survival** (Abdel-Latif et al, 2004; Lotan et al, 2005). A transurethral resection of the bladder tumor can detect angiolymphatic invasion that is subsequently found in the radical cystectomy specimen 65% of the time. It is critical to use CD-31 and CD-34 monoclonal antibodies with immunohistochemistry to accurately identify the blood vessels in contrast to tumor retraction artifacts (Lotan et al, 2005; Kunju et al, 2008).

Pagetoid Spread

Pagetoid spread occurs when cancer cells grow underneath a layer of normal-appearing surface urothelium (Montironi et al, 2002). Pagetoid spread is primarily seen in urothelial CIS and was first described by Melicow and Hollowell in 1952. Detection of pagetoid spread is difficult because it occurs in approximately 15% of bladders that contain CIS and decreases to 11% in patients with papillary high–malignant potential, non–muscle-invasive bladder cancer (Orozco et al, 1993; McKenney et al, 2001). Pagetoid spread of urothelial cancer can occur into the prostatic urethra and distal ureters. This is more common after repeated doses of intravesical therapies, and therefore biopsies of normal-appearing prostatic urothelium are needed in the evaluation of patients with positive urine cytology and yet endoscopically normal bladder (Wood et al, 1989a, 1989b).

Direct Extension

Direct extension of tumors into the basal lamina, connective tissue, and, ultimately, the angiolymphatic system is caused by genetic and epigenetic changes that produce substances capable of invading these tissues. These substances include collagenases, motility and growth factors, and cell adhesion molecules. There are several collagenases associated with tumor invasion, primarily collagenase type IV (Bianco et al, 1998). Several members of the metalloproteinase (MMP) family are also associated with the invasive phenotype. MMPs are a family of proteases that chelate zinc and calcium. They are inhibited by tissue inhibitors of metalloproteinase called TIMPS. The ratio of MMP to TIMP is increased in invasive bladder cancer and associated with a poor clinical outcome (Bianco et al, 1998; Ozdemir et al, 1999). Urokinase plasminogen activator (UPA) is a serum protease that cleaves plasminogen to plasmin (Hanke et al, 2007). Plasmin degrades laminin, which is a major component of the basal lamina layer. High expression of UPA is seen invasive urothelial cancer and is an independent predictor of survival (Hasui and Osada, 1997).

There are numerous motility and growth factors present within the extracellular matrix that increase tumor growth. Proepithelin may play a critical role as an autocrine growth factor in the establishment and progression of bladder cancer, and studies suggest that proepithelin may be a novel biomarker for the diagnosis and prognosis of bladder neoplasms (Lovat et al, 2009). The ability of cancer cells to migrate and invade through the extracellular matrix is a critical step for tumor metastasis. Other growth factors associated with bladder cancer invasion include epidermal growth factors (EGF), transforming growth factor-α, heparin-binding growth factor, and insulin-like growth factor (Brown et al, 1993; Theodorescu et al, 1998). Cell adhesion molecules are critical for integrity of cell–cell junctions and the inhibition of cell growth. Cell adhesion molecules associated with invasive urothelial carcinoma include E-cadherin, integrins, CD-44 and NCD-44 (Kashibuchi et al, 2007). Decreased levels of these cell adhesion molecules are seen in invasive tumors and are related to cancer specific survival. A combination of genetic and epigenetic changes causing increased production of substances to invade underlying stromal tissue in combination with a lack of cell–cell binding and increased cellular growth all lead to the invasive phenotype and subsequent metastasis.

Prognostic Factors

There are genetic, pathologic, and phenotypic changes in bladder cancer that are characteristic of poor cancer-specific survival. **Overall genetic instability is the hallmark of invasive urothelial cancer, but specifically alterations of *TP53, RB,* and *PTEN* carry a very poor prognosis** (Chatterjee et al, 2004a). Wang and colleagues (2009) developed a gene expression signature that could accurately segregate poor- and good-risk noninvasive and invasive bladder cancers. They were able to make the segregation even within similar pathologically staged tumors. However, despite the major advances in understanding the genetics of urothelial carcinoma, the stage and grade of the primary tumor is still the strongest predictor of survival. Grade is indicative of the growth potential of the cell and stage describes the extent of the cancer and the ability to invade. The ability of high-grade tumors to invade and thus metastasize is due to micrometastatic disease from angiolymphatic invasion. As mentioned above, there are numerous genetic and epigenetic causes for the invasive phenotype, but because of genetic instability, it is difficult to determine a true cause and effect for any given genetic change. New markers of proliferation and invasion are being developed that can better define the invasive phenotype. Proliferation markers, such as MIB-1 and PCNA, are found in high-grade tumors and are associated with worse prognosis (Lopez-Beltran et al, 2004). Alteration in cell cycle regulators, such as cyclins, TP53, and TP27, leads to increased proliferation as seen by MIB-1 staining. Ultimately, it will be the integration of stage, grade, and molecular markers that will greatly improve the prognostic determination of urothelial carcinomas and hopefully provide new therapeutic targets.

Key Points: Origin, Recurrence, and Invasion

- Primary urothelial cancer is an environmentally caused tumor that recurs because of persistent genetic changes within the normal-appearing urothelium.
- Recurrent urothelial tumors occur by activation of nascent normal cells that have some genetic instability by environmental factors and tumor seeding during transurethral tumor resection.
- Accumulation of genetic changes leads to cellular proliferation, loss of cell–cell adhesion, and invasion.
- The depth of invasion and grade of the tumor are the best prognostic determinants of urothelial cancer, but molecular assays are likely to be incorporated into future staging schemas.

Molecular Biology

Cancer is abnormal, unregulated, and excessive cell growth occurring after an initial transforming event that eventually results in cellular changes that, in turn, allow widespread dissemination. The abnormal inciting events are a combination of somatic and hereditary genetic changes that result in genetic instability characteristic of cancer formation (Vogelstein and Kinzler, 2004). **Somatic mutations are more common than germline mutations, and if germline mutations occur, they are associated with a specific type of cancer such as von Hippel-Lindau disease.** These somatic and germline genetic changes result in an altered phenotype that can be enhanced or, at times, be caused by epigenetic alterations, such as promoter methylation or protein degradation, that suppress gene function involved in bladder cancer formation (Wolff et al, 2005).

Genes associated with cancer formation are divided into two groups: proto-oncogenes and tumor suppressor genes. **Proto-oncogenes are generally activated by point mutations in the genetic code, gene amplification, and gene translocation. The activated proto-oncogenes become oncogenes that can cause cancer and are considered a positive or dominant growth effect** (Lengauer et al, 1998; Wolff et al, 2005; Cordon-Cardo, 2008). **Tumor suppressor genes are mainly activated by allelic deletions followed by point mutations of the remaining allele. Tumor suppressor genes are recessive or have a negative effect resulting in unregulated cellular growth.** Both oncogene and tumor suppressor gene activation occur with the same frequency. The key to cancer formation is the accumulation of the genetic events that ultimately cause enough phenotypic changes to result in unregulated cell growth and invasion (Lengauer et al, 1998; Vogelstein and Kinzler, 2004).

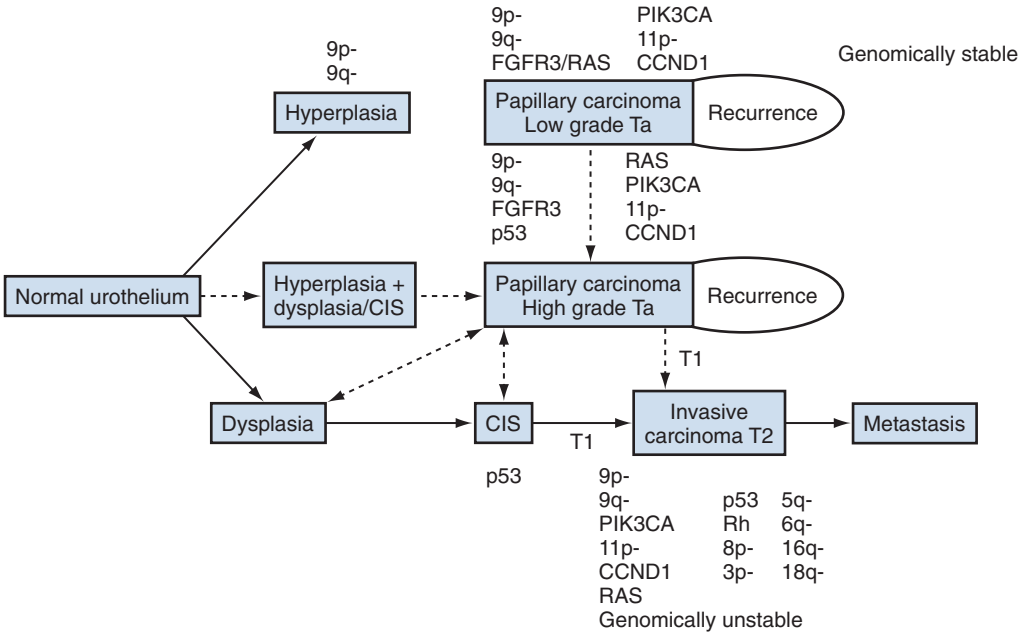


Figure 80–14. Pathogenesis of urothelial cancer formation. (From Knowles MA. Bladder cancer subtypes defined by genomic alterations. Scand J Urol Nephrol Suppl 2008;218:116–30.)

There are specific genetic changes that occur between each stage of urothelial tumor development (Cordon-Cardo et al, 2000; Simon et al, 2004; Cordon-Cardo, 2008). **Traditionally, there are two pathways in urothelial cancer formation: normal urothelium to low-grade noninvasive disease and normal urothelium to CIS and subsequent muscle-invasive disease. A proposed third pathway involves normal urothelium to hyperplasia/dysplasia to high-grade papillary carcinoma and subsequent muscle-invasive disease** (Fig. 80–14). Low-grade papillary carcinoma with additional genetic alterations can develop into high-grade papillary disease and subsequent muscle-invasive disease, but it is rare for high-grade tumors to mutate into low-grade cancers. In general, low-grade papillary tumors have genomic stability that allows tumor recurrence but rarely progression. High-grade papillary cancer and CIS have unstable genomes that more readily allow additional genetic alterations needed for muscle-invasive or metastatic disease (Spruck et al, 1994; Knowles, 2006; Lindgren et al, 2006).

The genetic alterations that are the hallmark of low-grade non–muscle-invasive disease are alterations in the fibroblast growth factor receptor–3 *(FGFR-3)* and deletions of chromosome regions 9p and 9q. High-grade invasive disease has infrequent *FGFR-3* mutations but a high rate of *TP53* mutations that approaches 60%. Noninvasive tumors that have both *FGFR-3* and *TP53* mutations are rare and constitute the third pathway to the formation of invasive disease by forming papillary rather than sessile T1 cancer that is derived from CIS (Knowles, 2006; van der Kwast, 2008). Genetic changes that occur in noninvasive and invasive bladder cancers are listed in Tables 80–8 and 80–9, respectively.

Normal urothelium transforms into low-grade papillary cancer through activation of proto-oncogenes, resulting in phenotypic changes that are histologically named papilloma, papillary urothelial neoplasia of low-malignant potential (PUNLMP), hyperplasia, and low-grade urothelial cancer. Papillomas lack genetic alterations and have no *FGFR-3* mutations, thus distinguishing this growth pattern from low-grade urothelial carcinoma and therefore are probably not a precursor lesion to cancer (Knowles, 2006). Conversely, PUNLMP does contain the same genetic abnormalities seen in low-grade urothelial carcinoma, has a proliferation rate similar to low-grade carcinoma, and is likely to be a precursor to low-grade bladder cancer. Thus there are no clear DNA markers that can distinguish PUNLMP from low-grade cancer (Dyrskjot et al, 2007). Urothelial hyperplasia is considered a precursor of low-grade carcinoma, and the most frequent genetic deletion is of chromosome 9 and is most likely the earliest mutation seen in low-grade urothelial cancer formation (Obermann et al, 2003). There are a variety of tumor suppressor genes present on both regions 9p and 9q. At 9p21, *CDKN2A* codes for TP16 (INK4A), which is a negative regulator of *RB,* and *TP14ARF*, which is a negative regulator of *TP53* (Berggren et al, 2003). In addition, *CDKN2B* is located at 9p21 and codes for TP15. It is less clear which genes located on 9q are deleted. *PTCH* is located at 9q22, and *DBC1* and *TSC1* are located on 9q33-34 (Aboulkassim et al, 2003; Adachi et al, 2003). The multiple gene losses on chromosome 9 cumulatively lead to the formation of low-grade urothelial neoplasia. It is rare in low-grade papillary cancers to have markers of aggressiveness, such as loss of chromosome 17p, 2q, 4, or 11p (Cordon-Cardo, 2008). Urothelial hyperplastic lesions associated with papillary low-grade urothelial carcinoma in the same bladder have the same alterations in the majority of cases (Obermann et al, 2003; van Oers et al, 2005). This suggests that some papillary hyperplastic lesions have the genetic abnormalities to form low-grade carcinomas, while others that are histologically similar do not and instead stay as hyperplastic lesions even if they are near a papillary tumor.

FGFR-3 is related to EGFR, which is not mutated in low-grade cancers but can be overexpressed in low- or high-grade urothelial cancer. FGFR-3 is a tyrosine kinase that causes enhanced growth of bladder cells and is altered in up to 75% of noninvasive low-grade tumors (Gomez-Roman et al, 2005). Altered FGFR-3 can be found in CIS and muscle-invasive disease, although to a much lesser extent, supporting the overlapping nature of tumor formation with multiple genetic changes destined to make either

Table 80–8.

Genetic Changes Identified in Ta Bladder Tumors

GENE (CYTOGENETIC LOCATION)	ALTERATION	FREQUENCY
	Oncogenes	
HRAS (11p15)/*NRAS* (1p13)/*KRAS2* (12p12)	Activating mutations	15%
FGFR-3 (4p16)	Activating mutations	60%-80%
CCND1 (11q13)	Amplification/ overexpression	10%-20%
PIK3CA (3q26)	Activating mutations	25% PUNLMP; 16% Ta
MDM2 (12q13)	Overexpression	≈30% overexpression
	Tumor Suppressor Genes	
CDKN2A (9P21)	Homozygous deletion/ methylation/ mutation	HD 20%-30%; LOH ≈60%
PTCH (9q22)	Deletion/mutation	LOH ≈60%; mutation frequency low
DBCI (9q32-33)	Deletion/methylation	LOH ≈60%
TSCI (9q34)	Deletion/mutation	LOH ≈60%; mutation ≈12%
	DNA Copy Number Changes; Target Gene(S) Unkown*	
2q	Deletion	10%
8p	Deletion	16%
9p	Deletion	36%-47%
9q	Deletion	44%-66%
10p	Deletion	20%
10q	Deletion	20%
11p	Deletion/LOH	10%-24%
13q	Deletion	17%
17q	Deletion	15%
18q	Deletion	13%
Y	Deletion	24%-28%
1q	Gain	11%-14%
17q	Gain	14%
20q	Gain	13%-17%
8p12	Amplification	Occasional
11q13 (including *CCND1*)	Amplification	Occasional

*Comparative genomic hybridization analyses.

HD, homozygously deleted; LOH, loss of heterozygosity; PUNLMP, papillary urothelial neoplasm of low malignant potential.

From Knowles MA. Bladder cancer subtypes defined by genomic alterations. Scand J Urol Nephrol Suppl 2008;218:116–30.

noninvasive or invasive disease. Interestingly, *FGFR-3* mutations are also found in seborrheic keratosis, which is a benign papillary skin wart that can be multiple, recur, but does not invade (Logie et al, 2005). FGFR-3 mRNA is overexpressed eightfold in noninvasive disease and up to fourfold in muscle-invasive disease. Normal urothelium does not produce the FGFR-3 protein, but over 71% of noninvasive bladder cancer will be immunopositive for the FGFR-3 receptor (Billerey et al, 2001). Because of the differential FGFR-3 expression between normal and cancerous tissue, it could be a therapeutic target (Knowles, 2008c). *FGRF-3* and *HRAS* mutations are mutually exclusive, because they are in the same *RAS-MEK-ERK* pathway. Mutations of *FGFR-3* cause constitutive activation of the FGFR-3 receptor and thus signaling through the *MAPK* pathway (Cordon-Cardo, 2008; Knowles, 2008c). *FGFR-3* and *TP53* mutations are virtually mutually exclusive as well, but not because of a common signaling pathway. It is unclear why these two mutations are mutually exclusive, but it does highlight the different pathways in the formation of urothelial carcinoma (Bakkar et al, 2003).

RAS genes are from a family of transforming oncogenes that were originally identified in T24 bladder cancer cell lines (McBride et al, 1982). The most frequent site of *HRAS* activations are mutations in codons 12, 13, 59, and 61 that result in increased enzymatic activity. ***HRAS* mutations occur in 40% of urothelial carcinoma, and mutations in codon 12 are the most common** (Czerniak et al, 1992). Point mutations in *PIK3CA* are found in 10% of noninvasive bladder cancer and are critical in the *PTEN* pathway (Cairns et al, 1998). *FGFR-3* and *PIK3CA* work together in a similar pathway, and thus both mutations are often seen in the same tumor. Deletions on 9q activate the tumor suppressor genes *TSCI, PTCH,* and *DBC1* (Hornigold et al, 1999; Louhelainen et al, 2006). *TSCI* is a major negative regulator of the *PTEN* signaling pathway, encodes hamartian, is located on 9q34, and is mutated in 10% of noninvasive bladder cancer. *TSCI* controls the activity of *RHEB*, which in turn regulates *MTOR* and the downstream events of the pathway. Deletion of *TSC1* activates the oncogenic potential of the signaling network. Deletions of *PTCH* located on 9q22 and loss of heterozygosity is seen in 40% of noninvasive tumors and cause increased cellular proliferation (McGarvey et al, 1998). *EBC1* is located on 9q33 and is mutated in 50% of noninvasive bladder cancer and also causes increased cellular proliferation (Louhelainen et al, 2006).

The transformation of normal urothelium to high-grade invasive bladder cancer is a continuum from dysplasia to CIS and then invasive disease. **The conversion of normal urothelium to dysplasia is associated with chromosome 9 deletions in 75% of cases, abnormal TP53 accumulation in 50%, and increased cellular growth in all cases** (Mallofre et al, 2003). The subsequent genetic changes to CIS are most likely deletions of tumor suppressor genes rather than activation of oncogenes, and alterations of *TP53* are the main hallmark of high-grade disease (George et al, 2007; Sanchez-Carbayo et al, 2007). *TP53* is located on chromosome 17p and controls the expression of multiple apoptosis-related genes. The presence of TP53 nuclear protein overexpression and *TP53* gene mutations occur in approximately 80% of high-grade tumors, including CIS. **Primary CIS, which is defined as CIS not associated with a papillary or invasive lesion, has TP53 overexpression but lacks deletion of chromosome 9. This is in contrast to secondary CIS, which is associated with papillary lesions, can display alterations in chromosome 9, and has molecular expression profiles similar to the adjacent papillary tumor, thus highlighting the overlapping pathways to invasive disease from flat CIS or the hyperplasia to papillary high-grade disease, and then subsequent muscle-invasive disease** (Hopman et al, 2002). Also, the same expression signature that exists for secondary CIS can be found in biopsies of morphologically normal urothelium in the same bladder (Dyrskjot et al, 2004). The retinoblastoma gene *(RB)* encodes for a 110 kD nuclear phosphoprotein that functions as a negative cell cycle regulator (Chatterjee et al, 2004a, 2004b). Undetectable levels of the RB protein are associated with poor prognoses and increased tumor growth, presumably by affecting the *E2F* gene pathway. Decreased PTEN expression is seen in advanced urothelial cancers and CIS. *PTEN* genetic alterations are an independent predictor of survival

Table 80–9.

Genetic Changes Found in Invasive (≥T2) Bladder Tumors

GENE (CYTOGENETIC LOCATION)	ALTERATION	FREQUENCY
	Oncogenes	
HRAS (11p15)/*NRAS* (1p13)/*KRAS2* (12p12)	Activating mutations	10%-15%
FGFR-3 (4p16)	Activating mutations	0%-34%
ERBB2 (17q)	Amplification/ overexpression	10%-14% amplification
CCND1 (11q13)	Amplification/ overexpression	10%-20%
MDM2 (12q13)	Amplification/ overexpression	4% amplification
E2F3 (6p22)	Amplification/ overexpression	9%-11% amplification in ≥T1
	Tumor Suppressor Genes	
CDKN2A (9P21)	Homozygous deletion/ methylation/ mutation	HD 20%-30%; LOH ≈60%
PTCH (9q22)	Deletion/ mutation	LOH ≈60%; mutation frequency low
DBCI (9q32-33)	Deletion/ methylation	LOH ≈60%
TSCI (9q34)	Deletion/ mutation	LOH ≈60%; mutation ≈12%
PTEN (10q23)	Homozygous deletion/ mutation	LOH 30%-35%; mutation 17%
RB1 (13q14)	Deletion	37%
TP53 (17p13)	Deletion/ mutation	70%

GENE (CYTOGENETIC LOCATION)	ALTERATION	FREQUENCY
	DNA Copy Number Changes; Target Gene(S) Unkown*	
2q	Deletion	12%
5q	Deletion	15%-24%
6q	Deletion	15%-28%
8p	Deletion	29%-34%
9p	Deletion	21%-30%
9q	Deletion	17%
10q	Deletion	16%-21%
11p	Deletion	18%-24%
11q	Deletion	22%
13q	Deletion	19%
15q	Deletion	13%
16q	Deletion	15%
17q	Deletion	17%-24%
18q	Deletion	16%-17%
Y	Deletion	21%
1q	Gain	17%-33%
3q	Gain	18%
5p	Gain	24%-37%
7p	Gain	20%
8q	Gain	23%-34%
10p	Gain	12%
17q	Gain	30%
20p	Gain	21%
20q	Gain	26%-28%
1q22	Amplification	<5%
3p24	Amplification	<5%
6p22	Amplification	5%-10%
8p12	Amplification	<5%
8q21-22 and q24	Amplification	<5%
10p13-14	Amplification	<5%
12q15	Amplification	<5%
17q21	Amplification	<5%
20q13	Amplification	<5%

*Comparative genomic hybridization analyses.
HD, homozygously deleted; LOH, loss of heterozygosity.
From Knowles MA. Bladder cancer subtypes defined by genomic alterations. Scand J Urol Nephrol Suppl 2008;218:116–30.

in advanced cancer, and altered *PTEN* and *TP53* mutations are associated with aggressive tumor growth (Puzio-Kuter et al, 2009).

The genetic changes that occur between noninvasive and invasive high-grade lesions are essentially genes needed to invade rather than to grow. The earliest changes seen in T1 disease are deletions of 3p, 5q, 6q, 11p, 16q, and 18q (Cordon-Cardo, 2008). Alterations in the *TP53, RB,* and *PTEN* pathways are hallmarks of invasive disease, and the combined alterations of all three pathways carries a much worse prognosis (Chatterjee et al, 2004a, 2004b). Finally, the general genetic instability seen in muscle-invasive disease to metastatic disease makes identification of specific genes associated with this progression difficult to clearly delineate (Knowles, 2008a).

Many investigators are using the genetic changes identified in urothelial cancer to determine the malignant potential of small noninvasive cancers by using molecular staging (van der Kwast, 2008). Through the formation of cDNA expression libraries, 80% of Ta urothelial cancers are correctly staged by their genetic profile. Of the 20% of Ta tumors that were wrongly classified as T1 or T2 by genetic profiling, most had a significantly worse prognosis than the correctly staged Ta tumors (Dyrskjot et al, 2003, 2007; Blaveri et al, 2005). **A 16-gene expression chip of CIS has been developed to discriminate CIS from normal bladder urothelium, with an 80% sensitivity and a 68% specificity.** Unfortunately, gene abnormalities for CIS can be found in normal urothelium, confirming the field-chain effect seen in bladder cancer (Dyrskjot et al, 2007). **The main genetic changes that separate noninvasive from invasive disease, as mentioned above, include high *FGFR-3* and low *TP53* mutation rates and general genetic stability.** T1 disease has low *FGFR3* and high *TP53* mutation rates and loss of 17p, 13q, and 8p (Knowles, 2008a). Many of these genetic changes are not necessarily related to invasive potential but, instead, reflect the different grade of tumor seen in Ta and T1 disease. The separation of T1 and T2 disease by genetic analysis is more difficult because of the overall worsening genetic instability and because both are high-grade

tumors. However, T2 tumors have more frequent allelic imbalance of chromosomes 6, 10p, and 22 (Koed et al, 2005). Finally, response to chemotherapy in T2 tumors may be predicted by cDNA profiling of the emmprin and survivin genes, although further prospective studies are required (Als et al, 2007). The accumulation of genetic changes in cell cycle regulation *(TP53),* angiogenesis *(NRP2),* and metastases suppressors *(RhoGDI2)* eventually leads to the highly malignant phenotype of high-grade urothelial cancer (Aaboe et al, 2006). On the horizon, these genetic signatures of aggressive disease will be used for prognostic and therapeutic intent. **Wang and colleagues** (2009) **developed a multiplex quantitative polymerase chain reaction (PCR) assay that accurately segregated Ta, T1, and T2 bladder cancer into high- and low-risk groups. Using a 57-gene mRNA expression profile, at 2 years, the high-risk groups had greater stage progression in each pathologic group.** A prospective multi-institutional study is needed to confirm these results but may herald a new staging method.

Detection of Urothelial Carcinoma

Gross, painless hematuria is the primary symptom in 85% of patients with a newly diagnosed bladder tumor, and microscopic hematuria occurs in virtually all patients (Khadra et al, 2000; Alishahi et al, 2002; Edwards et al, 2006). The hematuria is usually intermittent and can be related to Valsalva maneuvers; therefore any episode of gross hematuria should be evaluated even if subsequent urinalysis is negative. **Fifty percent of patients with gross hematuria will have a demonstrable cause, 20% will have a urologic malignancy, and 12% will have a bladder tumor** (Khadra et al, 2000). The risk of malignancy in patients with recurrent gross or microscopic hematuria who had a full, negative evaluation is nearly zero within the first 6 years (Khadra et al, 2000). This should be considered when recommending repeat evaluations for patients with recurrent hematuria.

A full hematuria evaluation for bladder cancer includes cystoscopy, urine cytology, upper-tract imaging (primarily a CT scan of the abdomen and pelvis), and a prostate-specific antigen (PSA) blood test. A PSA blood test is recommended, because 10% of patients with recurrent gross hematuria will have prostate cancer (Mishriki et al, 2009). Microscopic hematuria is typically asymptomatic and carries a 5.4% risk of urologic malignancy and a 4.1% risk of bladder cancer (Mishriki et al, 2008). For patients with a negative microscopic hematuria evaluation, 84.5% never had a recurrence, and of those with repeat microscopic hematuria, none had a urologic malignancy with a 13-year follow-up (Mishriki et al, 2008). **The AUA guidelines for microscopic hematuria evaluation include a cystoscopy, upper tract imaging, and urine cytology** (Grossfeld et al, 2001). The guidelines recommend consideration for re-evaluation of low-risk patients with microscopic hematuria, but repeat evaluation every 6 months with urinalysis, cytology, and blood pressure (to detect renal disease) is recommended for high-risk patients (Table 80–10).

The main diagnostic test for bladder cancer is cystoscopy and biopsy. White light cystoscopy (WLC) is the gold standard, and flexible office cystoscopy is as reliable as a rigid endoscopy (Grossfeld et al, 2001). White light cystoscopy has an excellent sensitivity and specificity for papillary tumors but is relatively poor for CIS. Cystoscopy with porphyrin dye (commonly referred to as blue light cystoscopy) may be more sensitive in the detection of CIS (Fradet et al, 2007; Grossman et al, 2007). **Porphyrin-induced fluorescence cystoscopy uses photoactive porphyrins, such as hexaminolevulinate, that accumulate preferentially in neoplastic tissue and emit red fluorescence under blue-wavelength light. This may improve the detection of small papillary lesions and CIS.** A phase III trial evaluating white and blue light cystoscopy in patients with known or suspected tumors was recently completed (Grossman et al, 2007). Blue light cystoscopy detected 58% of CIS compared with 15% using white light. However, at the patient level, the sensitivity of blue light was 87% and 83% for white light. Blue light cystoscopy has a false-positive rate of 39% (Fradet et al, 2007). The true impact of blue light cystoscopy on the detection of bladder cancer is unclear and further studies are required to determine its exact clinical role.

Narrow-band imaging (NBI) is an endoscopic optical image enhancement technique that enhances the contrast between mucosal surfaces and microvascular structures without the use of dyes. The depth of light penetration into the bladder wall increases with increasing wavelength. NBI illuminates the mucosal surface with light of a narrow bandwidth in the blue (415 nm) and green (540 nm) light spectrum, which are strongly absorbed by hemoglobin. Consequently, the vascular structures appear dark brown or green against a pink or white mucosal background. Commercially available systems have integrated NBI and WLC, allowing activation of the NBI wavelengths with the push of a button. Herr et al. performed white light cystoscopy with subsequent NBI cystoscopy in 427 consecutive patients with a history of NMIBC (Herr and Donat, 2008). **Of the 103 patients with a tumor recurrence, 56% had additional tumors identified with NBI compared with use of white light cystoscopy, and in 12% of patients, the recurrent tumor was only found with NBI. For white light and NBI cystoscopy, the overall sensitivity was 87% and 100% and the overall specificity 85% and 82%, respectively.** A recent study suggests that NBI more accurately detects tumor recurrence after BCG therapy than do urine cytology or white light cystoscopy, and NBI can obviate the need for random bladder biopsies in post-BCG bladders (Herr, 2008). NBI detected tumor recurrence in 21 of 22 patients with tumor recurrence after BCG, but another 10 patients had a false-positive NBI resulting in unnecessary biopsies. Because the NBI and white light cystoscopy is performed by the same urologist, observation bias may skew these results.

Random bladder biopsies are recommended to detect unsuspected CIS or small papillary tumors in endoscopically normal urothelium. Overall, there is a 2.5% detection rate of CIS or small papillary tumors in random biopsies of patients with known or

Table 80–10.

High-Risk Characteristics of Patients with Microscopic Hematuria

Smoking history
Occupational exposure
History of gross hematuria
Greater than age 40 years
Previous urologic surgery
Irritating voiding symptoms
History of urinary tract infections
Analgesic abuse
History of pelvic radiation
Previous cyclophosphamide therapy

From Grossfeld GD, Litwin MS, Wolf JS Jr, et al. Evaluation of asymptomatic microscopic hematuria in adults: the American Urological Association best practice policy—part II: patient evaluation, cytology, voided markers, imaging, cystoscopy, nephrology evaluation, and follow-up. Urology 2001;57(4):604–10.

suspected bladder tumors (Fradet et al, 2007). For patients with concurrent bladder tumors, a random biopsy will detect dysplasia or CIS in up to 23% of cases (Mufti and Singh, 1992). **It is reasonable to perform random biopsies in high-risk individuals, such as for those given postintravesical therapy or for those with a positive cytology and an endoscopically negative bladder.** Urine cytology, first introduced by Papanicolaou in 1945, evaluates the morphologic changes associated with bladder cancer and is the gold standard urinary marker against which other markers are held (Papanicolaou and Marshall, 1945). Overall, the sensitivity and specificity for cytology in detecting bladder cancer is 40% to 62% and 94% to 100%, respectively (van Rhijn et al, 2005; Volpe et al, 2008). Positive urine cytology is virtually diagnostic of a bladder tumor, though there are cases in which the tumor is not endoscopically visible. The sensitivity and specificity of urine cytology is dependent on the cytopathologist, number of samples evaluated, and the stage and grade of the tumor (Volpe et al, 2008). Instrumented urine during cystoscopy has improved sensitivity and specificity, but an invasive procedure is required (Badalament et al, 1987). Fifteen percent of patients with atypical cytology that is not diagnostic of cancer will have an underlying malignancy (Novicki et al, 1998). Thus patients with an atypical cytology need more frequent evaluation or repeat random bladder biopsies.

Urine Markers for Urothelial Cancer

Van Rhijn and colleagues (2005) did a systematic literature review evaluating urine marker studies for surveillance only and included those markers that had at least two studies published from two separate institutions (Table 80–11). We will discuss the markers that had at least 70% sensitivity and specificity plus novel markers that may be important in the future. The sensitivity and specificity of these tests are lower in patients undergoing surveillance evaluations with no active tumor or those with low-grade cancers (van Rhijn et al, 2005; Zwarthoff, 2008).

NMP-22 is a nuclear matrix protein that is used to form the cell nuclei. NMP-22 is shed into the urine and has a 20-times higher concentration in the urine of bladder cancer patients than in noncancer controls (Keesee et al, 1996). There are a variety of NMP-22 cutoff levels for bladder cancer detection, but typically 10 units/mL is used to identify patients with or without cancer (Soloway et al, 1996; Grossman et al, 2006). A lower cutoff level of 5 units/mL improves the sensitivity but significantly worsens the specificity. The cutoff level does not appear to be related to stage or grade of the disease. False positives with NMP-22 can occur from patients with an active urinary tract infection or significant hematuria (Atsu et al, 2002). Grossman and colleagues (2006) reported a large multi-institutional study evaluating the efficacy of using NMP-22 (Grossman et al, 2006) as a marker. **Using a cutoff level of 10 units/mL, the overall sensitivity and specificity for detecting urothelial cancer was 49% and 87%, respectively.** The sensitivity for Ta, T1, and T2 tumors was 36%, 65%, and 88%, respectively. A combination of cystoscopy and NMP-22 detected all but one of the 103 tumors seen in this study. NMP-22 picked up eight of the nine tumors missed by white light cystoscopy. NMP-22 appears to be an adjunct to white light cystoscopy in approximately 10% of patients.

The Lewis blood group antigen X is usually absent from urothelial cells in adults except for occasional umbrella cells (Sheinfeld et al, 1990). There is increased Lewis X expression in bladder cancers, and it is independent of secretor status, grade, and stage. The sensitivity and specificity for the detection of bladder cancer is 75% and 85%, respectively. There is no commercially available test to date. CK 20 and CYFRA 21.1 are fragments of cytoskeletal proteins that can be detected in the urine of bladder cancer patients by either protein or mRNA detection (Ramos et al, 2003). CK 20 has a sensitivity and specificity of 85% and 76%, respectively. A recent multicenter study of 446 patients evaluating the role of CYFRA 21.1, with a cutoff value of 4 ng/mL, found a sensitivity and specificity of 43% and 68%, respectively (Fernandez-Gomez et al, 2007). Unfortunately, none of the Ta tumors were identified at the 4 ng/mL cutoff. Decreasing the CYFRA 21.1 cutoff to 1.5 ng/mL increased Ta detection to 33%, but the specificity dropped to an unacceptable 43%. Therefore it is not felt to be a useful marker in the current form, or at least for low-grade disease.

Fluorescence in-situ hybridization (FISH) identifies fluorescently labeled DNA probes that bind to intranuclear chromosomes. **The current commercially available probes evaluate**

Table 80–11.

Sensitivity and Specificity of Urinary Markers in the Detection of Urothelial Cancer

MARKER	MEDIAN SENSITIVITY (%)	RANGE (MINIMUM %–MAXIMUM %)	MEDIAN SPECIFICITY (%)	RANGE (MINIMUM %–MAXIMUM %)
BTA stat	70	24-89	75	52-93
BTAtrak	69	57-79	65	48-95
NMP22	73	47-100	80	56-95
FDP	61	52-81	79	75-96
ImmunoCyt	83	50-100	80	69-90
Cytometry	60	45-83	80	36-87
Quanticyt	59	45-69	79	70-93
Hb-dipstick	52	41-95	82	68-93
Lewis X	83	80-89	85	80-86
FISH	84	73-92	95	92-100
Telomerase	75	7-100	86	24-93
Microsatellite	91	83-95	94	89-100
CYFRA21-1	94	74-99	86	67-100
UBC	78	66-87	91	80-97
Cytokeratin 20	91	82-96	84	67-97
BTA	50	28-80	86	66-95
TPS	72	64-88	78	55-95
Cytology	48	31-100	94	62-100

From van Rhijn BW, van der Poel HG, van der Kwast TH. Urine markers for bladder cancer surveillance: a systematic review. Eur Urol 2005;47(6):736–48.

aneuploidy for chromosomes 3, 7, and 17 and homozygous loss of 9p 21 (Zwarthoff, 2008). The median sensitivity and specificity of FISH analysis is 79% and 70%, respectively (van Rhijn et al, 2005). A recent prospective study of 250 patients evaluated the role of FISH analysis for identifying recurrent urothelial cancer (Yoder et al, 2007). FISH detected 25 of 39 concurrent tumors, and 35 tumors occurred later in 56 patients who initially had a positive FISH test. The authors suggested that this was an anticipatory finding. Another study by Moonen and colleagues (2007) evaluated 105 patients with urothelial cancer. The sensitivity for Ta, T1, and T2 tumors was 26.7%, 60%, and 50%, respectively. These lower sensitivity findings were confirmed (Gudjonsson et al, 2008). **It appears FISH analysis is moderately useful for high-grade disease and may be anticipatory of new tumor formation; however, because of the recurrent nature of noninvasive bladder cancer, it is difficult to tell if the FISH test was identifying chromosomal abnormalities present in normal-appearing urothelium or if it was false-positive test.** There are multiple markers available to identify short DNA repeats present throughout the chromosomes that are lost in some tumor cells. **Microsatellite analysis amplifies these repeats in the genome that are highly polymorphic, and PCR amplification can detect tumor-associated loss of heterozygosity by comparing the peak ratio of the two alleles in tumor DNA in the urine sample with the presence of the alleles in a blood sample from the same individual** (Steiner et al, 1997, Wang et al, 1997). The sensitivity and specificity of microsatellite analysis for the detection of urothelial carcinoma range from 72% to 97% and 80% to 100%, respectively (Steiner et al, 1997; Wang et al, 1997). A recent European study evaluated microsatellite analysis in voided urine samples for the detection of low–malignant potential non–muscle-invasive urothelial carcinoma (van der Aa et al, 2009). They report sensitivity and specificity of 58% and 72%, respectively. Microsatellite analysis missed only one T1 high-grade urothelial cancer. **Interestingly, if the microsatellite analysis is persistently positive, there was an 83% 2-year recurrence rate, but if the analysis was persistently negative, only 22% of patients had recurrent tumors.** Hopefully, standardization of the test will allow analysis without a blood sample, and this will significantly improve the patient's acceptance.

CpG dinucleotide islands cluster around promoters in an unmethylated state to allow gene expression (Knowles, 2007). **Methylation of the CpG islands shuts down the promoter, and if the promoter in question is part of a tumor suppressor gene then cancer can form.** Examples of promoter methylation of CpG islands causing epigenetic changes in urothelial cancer include the *P16/CDKN2A* gene (Gonzalez-Zulueta et al, 1995). The sensitivity of gene methylation for the detection of bladder cancer is 75%; however, methylated CpG islands can be found in the normal urothelial cells of older patients (Yates et al, 2006). *FGFR-3* point mutations are found in 75% of non–muscle-invasive bladder cancer, particularly in Ta tumors (van Rhijn et al, 2004; Wolff et al, 2005). Unfortunately, there are over 11 different point mutation sites within this gene, and therefore identification of all possible mutations is difficult in a single urine sample. Single-strand conformational polymorphism can detect these point mutations, and a snapshot assay has been produced that holds the possibility for rapid identification of *FGFR-3* mutations (van Oers et al, 2005). Surface-enhanced laser desorption ionization (SELDI) mass spectroscopy of urine samples has a sensitivity and specificity for detecting bladder cancer of 50% to 90% and 60% to 90%, respectively (Vlahou et al, 2001). Tumor grade, patient age, and type of analysis are confounders of SELDI analysis, and a multi-institutional trial is needed to determine its effectiveness in identifying urothelial carcinoma. Survivin is an antiapoptotic protein that has a high expression in urothelial cancer (Smith et al, 2001). Survivin is found in 10% to 30% of bladder cancers and is readily shed into the urine. The sensitivity and specificity of survivin in the detection of urothelial tumors is 64% to 100% and 87% to 93%, respectively (Smith et al, 2001; Shariat et al, 2004). This test may be useful in predicting which patients will respond to intravesical therapy (Hausladen et al, 2003). Survivin was relatively poor at detecting advanced-stage or high-grade tumors, with a sensitivity of 71% for stage T2 tumors and 80% for high-grade cancers (Shariat et al, 2004). Hylauronic acid controls intercellular communications and cell replication. Urothelial cancer induces hylauronic acid production from fibroblasts, and the amount correlates with the stage of the disease. The sensitivity and specificity of hylauronic acid for detection of bladder cancer is 91% to 100% and 84% to 90%, respectively (Pham et al, 1997; Lokeshwar et al, 2002). The sensitivity and specificity for discriminating between low-grade and high-grade lesions is unclear. Telomerase resides at the terminal ends of the chromosomes and duplicates random DNA repeats to prevent cell death (Rhyu, 1995). Telomerase activity is measured in telomeric repeat application protocol (TRAP) and is detected in 80% of urine from patients with bladder cancer with no grade differential. The sensitivity and specificity is 90% and 88%, respectively (Sanchini et al, 2005). The ImmunoCyt test (Diagnocure, Québec, Canada) detects mucin-based antigens that are present on most bladder cancer cells. The sensitivity and specificity is 61% to 92% and 71% to 90%, respectively (Halling et al, 2000; Pfister et al, 2003).

Virtually all patients complain of pain and discomfort with an office cystoscopy. **Urine markers studies could forgo this pain in select situations as described above. However, patients reported that a urine marker study would need 90% sensitivity in order to replace office cystoscopy** (Vriesema et al, 2000). The primary concern is missing tumor cells by relying on the urinary marker. None of the currently available urinary markers meet this 90% sensitivity on a reliable basis, and therefore a combination of cystoscopy with urine markers, in select situations, is appropriate for surveillance of patients with non–muscle-invasive bladder cancer.

Key Points: Detection of Urothelial Cancer

- Painless gross hematuria occurs in 85% of patients with bladder cancer and requires a complete evaluation that includes cystoscopy, urine cytology, CT scan, and a PSA blood test.
- Patients with microscopic hematuria require a full evaluation, but low-risk patients do not require repeat evaluations. High-risk individuals primarily are those with a smoking history and should be evaluated every 6 months.
- White light cystoscopy with random bladder biopsies is the gold standard for tumor detection, but blue light cystoscopy may be an adjunct.
- There are various urine markers that evaluate secreted proteins or shed cells in the hope of noninvasively detecting bladder cancer. To date, none of these markers have a high enough sensitivity or specificity to replace office cystoscopy.

Prevention/Complementary Medicine Treatments for Urothelial Cancer

Bladder cancer is primarily caused by urothelial exposure to carcinogens in the environment. The long lag time between carcinogenic exposure and subsequent bladder cancer formation makes testing of preventive measures difficult. Prevention of urothelial cancer is a high priority because it is the most expensive cancer to treat for several reasons, including that most urothelial cancer patients do not die from the disease, there is a high recurrence rate, and the primary mode of cancer control is repeated surgical procedures (Botteman et al, 2003; Jemal et al, 2008). There are three avenues to cancer prevention: primary/avoidance, prevention of malignant transformation of premalignant lesions, and prevention of tumor recurrence. Because there are no well-defined premalignant lesions in bladder cancer formation, most research has centered on primary tumor prevention and prevention of recurrent tumor.

Smoking cessation is the primary mode to prevent urothelial carcinoma. **Smoking is responsible for 30% to 50% of all bladder cancers in males, and smokers have a two- to sixfold greater chance of getting bladder cancer than nonsmokers** (Brennan et al, 2000; Boffetta, 2008). Smoking cessation will decrease the risk of eventual urothelial cancer formation in a linear fashion. After 15 years of not smoking, the risk of cancer formation is the same as for someone who never smoked (Smoke IAfRoCT, 2004). The strong influence of smoking in bladder cancer formation prevents accurate determination of other less significant dietary, micronutrient, or lifestyle changes that may alter bladder cancer formation. There have been several animal studies that show calorie restriction prolongs life and prevents cancer (Kuska, 2000). The mechanism is unclear but may be mediated through insulin-like growth factor-1 (IGF-1), because calorie-restricted mice given IGF-1 had cancer formation similar to normal-calorie mice but more than calorie-restricted mice without IGF-1 supplementation (Dunn et al, 1997). However, it is difficult to translate these calorie-restriction animal studies to the human setting, because exercise level cannot be controlled. The key seems to be less caloric intake rather than total body weight, although the two are indirectly related. **A randomized breast cancer study evaluated low- versus normal-fat diets in women with recently resected breast cancer. Women on the low-fat diet with aggressive breast cancer had a significantly lower risk of recurrence.** This could be due to a variety of factors, including weight loss, lower caloric intake, and lower insulin levels (Chlebowski et al, 2006). Fruit and vegetable ingestion has been postulated to prevent a variety of cancers, including urothelial cancer. There have been many prospective and case-control studies evaluating fruit and vegetable intake. Most show equivocal results, although one showed a statistically significant difference in bladder cancer rates only in male subjects (Michaud et al, 2000). **Citrus, apples, berries, and tomatoes have been shown in some, but not all studies, to result in a lower risk of urothelial cancer** (Brinkman and Zeegers, 2008). **Carrots and cruciferous vegetables, particularly cabbage, cauliflower, and kale, have also been implicated to have an inverse relationship with bladder cancer formation.** None of these studies have been a randomized trial, therefore whether ingestion of fruits and vegetables leads to a healthier lifestyle that is associated with lower urothelial cancer formation, or if these particular agents have a direct effect on urothelial cancer formation, is unclear.

There have been several studies evaluating the role of vitamin ingestion in bladder cancer formation. None of the large vitamin trials have shown a decreased risk in primary urothelial cancer prevention (Grossman et al, 2008). A randomized trial of patients with urothelial cancer did show that BCG plus high-dose vitamins significantly prolonged the time of recurrence (Lamm et al, 1994). **In this randomized trial of active urothelial cancer patients, all received intravesical BCG plus the recommended dietary-allowed vitamin doses, and half were randomly assigned to high-dose vitamins that included 4000 units of vitamin A, 100 mg vitamin B6, 2000 mg of vitamin C, 400 international units of vitamin E, and 90 mg of zinc daily. The high-dose vitamin group had a significantly prolonged time to urothelial cancer recurrence, with a 5-year disease survival rate of 91% compared with 41% in the standard-dose vitamin group ($P = .0014$).** To date, follow-up trials have not been conducted to corroborate these results. Micronutrient ingestion has been suggested to decrease the bladder cancer risk. There is one ongoing randomized placebo-controlled trial of 200 μg of selenium plus 154 mg of α-tocopherol daily that should be completed by 2011.

The urogenesis theory suggests that high fluid intake leads to more micturition and lower concentrations of potential carcinogens in the urine and thus a lower risk of urothelial cancer (Braver et al, 1987). There are conflicting results showing an inverse relationship between fluid intake and urothelial cancer formation, but it is strongest in women (Vena et al, 1993b). The health professional follow-up study of 48,000 participants found that total fluid intake was inversely related to urothelial cancer formation but only when comparing the highest quintile (>2500 mL) and lowest quintile (<1300 mL) groups (Michaud et al, 2007). **Green tea contains polyphenolic compounds that are potent antioxidants—specifically, epigallocatechin-3 gallate, which inhibits urothelial cell growth in vitro** (Qin et al, 2007). A large Japanese study of 49,566 men and 54,874 women evaluated the effect of smoking, caffeine, and green tea on urothelial cancer formation during a 15-year period (Kurahashi et al, 2008). As expected, smoking was strongly associated with urothelial cancer formation. Caffeine, either in the form of coffee or green tea, may be associated with urothelial cancer formation, and this effect was strongest in women. Caffeine is a known risk factor for urothelial cancer formation, and the carcinogenic affect of caffeine on urothelial cancer cells may be stronger than the antioxidant affect found in green tea (Pelucchi et al, 2008).

Key Points: Prevention

- Stopping or never starting smoking is the best prevention for bladder cancer.
- There are no clear dietary or micronutrient programs to prevent primary bladder cancer.
- BCG plus high-dose vitamins may prevent recurrent bladder cancer.

Histologic Variants of Urothelial Cancer

Urothelial carcinoma of the bladder had previously been labeled transitional cell carcinoma of the bladder because of its known propensity for cellular differentiation into other tumor types, such

Table 80–12.

Variants of Invasive Urothelial Carcinoma

Nested pattern
Small tubular pattern
Microcystic pattern
Inverted pattern
With squamous differentiation
With glandular differentiation
Micropapillary
Sarcomatoid carcinoma
Clear cell urothelial carcinoma
Plasmacytoid
With syncytiotrophoblasts
With unusual stromal reactions

Lopez-Beltran A, Cheng L. Histologic variants of urothelial carcinoma: differential diagnosis and clinical implications. Hum Pathol 2006;37(11):1371–88.

as squamous cell carcinoma, adenocarcinoma, and clear cell carcinoma. Recently the wider spectrum of histologic variance of urothelial cancer has been identified to include distinct growth patterns of urothelial carcinoma, altered cellular differentiation of urothelial carcinoma, mixed cellular growth patterns, and unusual stromal reactions combined with urothelial cancer growth (Table 80–12) (Lopez-Beltran and Cheng, 2006). The more common histologic variants will be discussed.

Micropapillary Urothelial Carcinoma

Micropapillary urothelial carcinoma was first described in the early 1990s as a tumor growth pattern that occurs in many organs, including bladder, breast, lung, and ovary, usually presenting at an advanced stage (Amin et al, 1994; Samaratunga and Khoo, 2004). The incidence of micropapillary urothelial carcinoma is 0.7% to 2.2% of all urothelial tumors, with a male to female ratio of 10:1 and an average age at diagnosis of 65 years (Amin et al, 1994). Because of the advanced stage at diagnosis, the 5- and 10-year overall survival rate of patients with micropapillary urothelial carcinoma is 51% and 24%, respectively (Kamat et al, 2007). The cancer-specific and overall survival rates are similar, suggesting that most patients died from their cancer (Johansson et al, 1999). The histologic characteristics of micropapillary urothelial carcinoma are similar to papillary serous carcinoma of the ovary that develops delicate filiform processes with infiltrating clusters of micropapillary tumors lacking vascular stalks (Fig. 80–15). Micropapillary urothelial carcinoma is associated with conventional urothelial carcinoma in 80% of cases (Lopez-Beltran and Cheng, 2006). **Angiolymphatic invasion is common even in non–muscle-invasive disease, highlighting the aggressive nature of this cancer. There is a high progression rate from non–muscle-invasive to muscle-invasive bladder cancer approaching 70%, with a high subsequent metastatic rate despite treatment** (Johansson et al, 1999; Kamat et al, 2007). The most effective treatment for all stages of micropapillary urothelial carcinoma is surgical resection. Treatment with transurethral resection and BCG therapy is ineffective unless the tumor is completely resected (Kamat et al, 2007). **Similar to ovarian cancer, neoadjuvant chemotherapy does not appear effective in micropapillary urothelial carcinoma** (Bristow et al, 2002; Kamat et al, 2007). Neoadjuvant chemotherapy may actually worsen survival by delaying therapy when compared with immediate cystectomy. Even in the best of situations, immediate cystectomy for non–muscle-invasive micropapillary bladder cancer has a cancer-specific survival rate of 72%

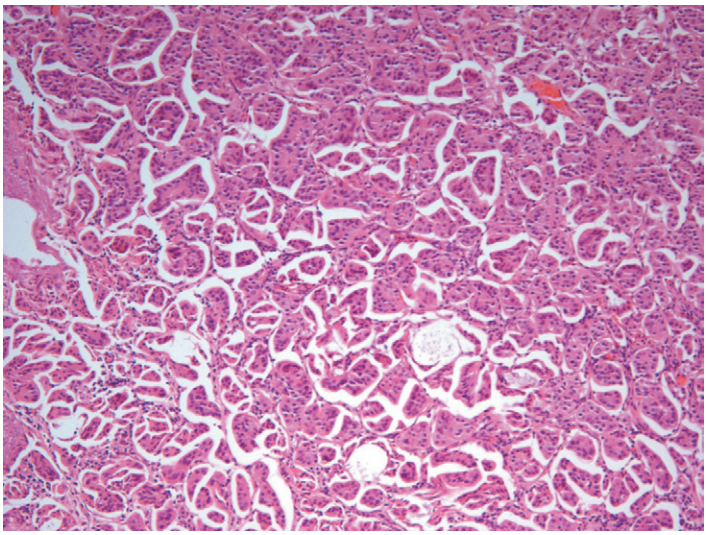


Figure 80–15. Micropapillary urothelial cancer.

compared with 60% for those treated with transurethral resection of the bladder tumor and BCG followed by cystectomy at the time of progression (Kamat et al, 2007). The best outcomes were in those patients who had no residual micropapillary tumor at the time of cystectomy, suggesting that complete resection of the tumor is the key procedure. Patients with locally advanced disease do poorly despite aggressive chemotherapy and surgical resection, with a cancer-specific survival rate of less than 22% at 4 years. There are no specific molecular markers associated with micropapillary urothelial carcinoma; however, these tumors are immunoreactive for epithelial membrane antigen and cytokeratins 7, 20, and 34 (Samaratunga and Khoo, 2004). Micropapillary urothelial carcinoma presents at an advanced stage, with less than 9% having noninvasive disease and more than 50% presenting as muscle-invasive, nodal, or metastatic disease (Johansson et al, 1999).

Nested Variant of Urothelial Carcinoma

This is a rare but aggressive cancer that has a male to female ratio of 6:1 and can be confused with benign lesions such as Von Brunn nests that are in the lamina propria, cystitis cystica, and inverted papillomas (Holmang and Johansson, 2001). There is little nuclear atypia in nested variant urothelial carcinoma, but the tumor cells will often contain areas with large nuclei and mitotic figures (Fig. 80–16). Despite aggressive therapy, the mortality rate from nested variant urothelial carcinoma is significant, with 70% dying of their disease within three years (Paik and Park, 1996).

Clear Cell Variant of Urothelial Carcinoma

Seventy percent of urothelial cancer will have foci of clear cells within the tumor (Lopez-Beltran and Cheng, 2006). These clear cells contain glycogen-rich vacuoles and may be confused with metastatic clear cell carcinoma of the kidney; however, the clear cell variant does not portent a significantly worse prognosis for urothelial cancers.

Glandular/Adeno Differentiation

Mixed tumor differentiation is most common with squamous cell cancer, but glandular differentiation only occurs in 6% of urothelial cancer cases (Lopez-Beltran and Cheng, 2006). Glandular differentiation is defined as the presence of two glandular spaces

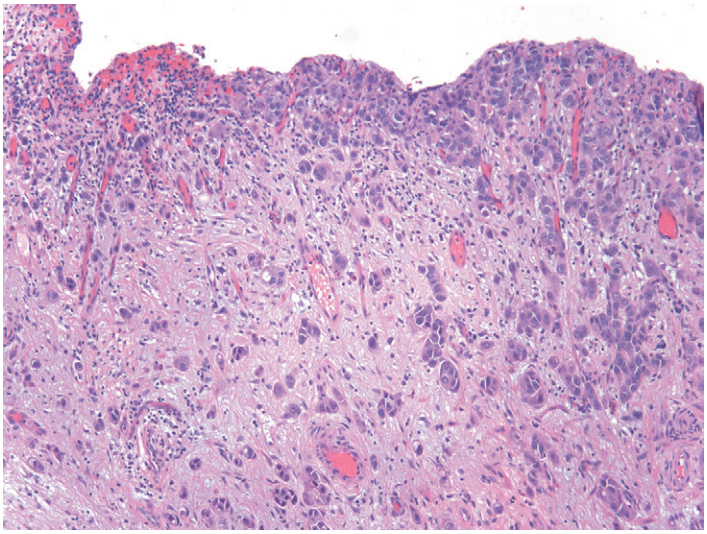


Figure 80–16. Nested variant of urothelial cancer.

within the tumor. It is important that these glandular spaces are not confused with lymphatic invasion or with processing artifacts. Mucin production can occur, and tumor cells seem to be floating in the mucin. Adjuvant chemotherapy plus radical cystectomy is the best method of treatment for glandular-differentiated urothelial cancer. Previous data has suggested that neoadjuvant chemotherapy was relatively ineffective against glandular and squamous differentiation for muscle-invasive disease. **A recent secondary analysis of the Southwest Oncology Group Trial 8710 of neoadjuvant muscle methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) followed by cystectomy versus cystectomy alone for muscle-invasive bladder cancer evaluated the effect of neoadjuvant therapy on mixed cellular differentiation of urothelial cancer. Among the patients with mixed tumors, the survival benefit from chemotherapy appeared to be greater in magnitude (hazard ratio [HR] = 0.46, *P* = .02) than among patients with pure urothelial carcinoma (HR = 0.9, *P* = .48) compared with immediate cystectomy** (Scosyrev et al, 2010). This suggests that neoadjuvant chemotherapy is an appropriate treatment prior to radical cystectomy for patients with invasive mixed differentiation urothelial cancer.

NONUROTHELIAL MALIGNANCIES

Sarcomas

Sarcomas are the most common mesenchymal tumor of the bladder but comprise less than 1% of all bladder cancers (Berkmen and Celebioglu, 1997; Parekh et al, 2002; Dotan et al, 2006). Subclassification of sarcoma is based on histologic variations, depending on the specific malignant cell type (Parekh et al, 2002; Spiess et al, 2007). **Leiomyosarcoma is the most common histologic subtype, followed by rhabdomyosarcoma and then, rarely, angiosarcoma, osteosarcoma, and carcinosarcoma.** The male to female ratio is 2:1, and the average age at presentation is in the 6th decade of life. There are no clear agents that cause bladder sarcomas, although there is an association with pelvic radiation and systemic chemotherapy for other malignancies (Spiess et al, 2007). Importantly, bladder sarcomas are not smoking related. Genetic abnormalities of leiomyosarcoma are inconsistent and not used in staging or identification. The majority of sarcomas are high-grade, and greater than 75% will be confined to bladder muscle (Rosser et al, 2003; Dotan et al, 2006). The most common presenting symptom is gross painless hematuria in 79%, followed by local irritative symptoms in 16%. Transurethral resection of the tumor, which may appear to have normal overlying urothelium, is necessary for diagnosis along with abdominal and chest imaging. The grade of the sarcoma is the primary prognostic factor and incorporated into the overall sarcoma staging system (Dotan et al, 2006). Treatment for localized disease includes radical cystectomy, with a premium on obtaining negative surgical margins because the local recurrence rate is 2.4 times higher in patients with a positive surgical margin (Dotan et al, 2006). The overall 5-year disease-free survival rate for leiomyosarcoma of the bladder is 52% to 62% (Rosser et al, 2003). Other poor prognostic factors associated with sarcomas include angiolymphatic invasion and metastatic disease at the time of presentation**. Active chemotherapeutic regimens are lacking for bladder sarcomas, but doxorubicin, ifosphamide, and cisplatin are the most effective agents** (Dotan et al, 2006; Spiess et al, 2007). The most common site for metastatic disease is lung, followed by bone, liver, and, rarely, soft tissue organs. Rhabdomyosarcomas may occur at any age, but in young children, they produce polyploid lesions at the base of the bladder, described as botryoides tumors. Multi-modality therapy combining chemotherapy with surgical resection and radiation are used in the treatment of pediatric rhabdomyosarcomas (Zanetta et al, 1999).

Signet Ring Cell Carcinoma

Primary signet ring cell carcinoma of the bladder is extremely rare, occupying less than 1% of all epithelial bladder neoplasms (Morelli et al, 2006). Signet ring cell carcinoma can be of urachal origin and directly extend into the bladder. **These tumors generally present as high-grade, high-stage tumors and have a uniformly poor prognosis.** The primary treatment is radical cystectomy; however, in the majority of cases there are regional or distant metastases at the time of presentation, and the mean survival time is less than 20 months (Torenbeek et al, 1996). There are reports of elevated carcinoembryonic antigen (CEA) in patients with signet ring cell carcinoma. The prognostic significance of this elevated serum marker is unclear (Morelli et al, 2006). Understaging is very common in signet ring cell carcinoma, with peritoneal studding common at the time of surgical exploration.

Small Cell Carcinoma

Small cell carcinoma primarily arises in the lung, but can occur in extrapulmonary sites, including the bladder, prostate, and colon (Blomjous et al, 1989). **Small cell carcinoma of the bladder should be considered and treated as metastatic disease, even if there is no radiologic evidence of disease outside the bladder.** Small cell carcinoma of the bladder accounts for much less than 1% of all primary bladder tumors. In general, small cell carcinoma of the bladder is very chemosensitive, and the primary mode of therapy is chemoradiation therapy. The tumor affects men older than 70 years, and there is a slightly higher prevalence in smokers (Choong et al, 2005). The origin of extrapulmonary small cell carcinoma is unclear, but may be related to multipotential stem cells that can develop into small cell carcinoma within extrapulmonary organs (Blomjous et al, 1989). The most common presenting symptom is painless gross hematuria; however, local irritation and pain are relatively frequent. At transurethral resection the mass is indistinguishable from urothelial

carcinoma, and resection is required to make a histologic diagnosis. Histologically, the common cellular pattern is diffuse sheets of dark blue cells with necrosis and mitosis. Chromogranin A staining is the primary method to distinguish high-grade urothelial carcinoma from small cell cancer of the bladder (Iczkowski et al, 1999). A variety of chemotherapeutic regimens have been used, but carboplatin or cisplatin and etoposide is the current treatment of choice (Choong et al, 2005). It is common to have a complete response from initial chemotherapy; however, clinical relapse occurs in greater than 80% of cases. It is not uncommon to see small cell carcinoma admixed with other histologic types of bladder cancer, including urothelial, adenocarcinoma, and squamous cell cancer (Choong et al, 2005). This supports the stem cell theory of histogenesis with multipotential undifferentiated stem cells producing small cell carcinoma and other histologic types of bladder cancer. Identical patterns of allelic loss in small cell carcinoma and coexisting urothelial cancers suggest a common clonal origin. Small cell carcinoma of the bladder exhibits both epithelial and neuroendocrine differentiation. Neuron-specific enolase, chromagranin A, and synaptophysin markers help differentiate from urothelial carcinoma (Mukesh et al, 2009). Although chemoradiation therapy is the primary treatment for small cell carcinoma of the bladder, experience combining chemotherapy with radical cystectomy for primary small cell cancers of the bladder has shown equal, or perhaps better, local control and disease-free survival than found with chemoradiation (Quek et al, 2005). However, with 5-year cancer-specific survival rates of 16% to 18% with chemoradiation or chemotherapy and radical cystectomy, respectively, the primary method to improve survival will be more effective systemic therapy.

Squamous Cell Cancer

Chronic infection with *Schistosoma hematobium* or other bacteria, to a lesser degree, leads to squamous cell formation of the bladder (Abol-Enein, 2008). The *Schistosoma* ova are deposited in the wall of the bladder and produce chronic inflammation that converts the urothelium to a squamous cell epithelium. Squamous cell epithelium has a much greater proliferation rate, and, with the presence of chronic inflammation, over time this greater proliferation rate leads to cancer formation. The exact mechanism by which *Schistosoma* ova can cause squamous cell carcinoma is unclear, but two factors are suspected. One is the increased proliferation rate, and the second is the chronic inflammation and exposure to environmental agents. The increased proliferation of the squamous epithelium leads to a higher risk of spontaneous genetic alterations that can cause cancer (Cohen and Ellwein, 1990). A chronic inflammatory process and exposure to environmental agents can combine to generate genotoxic substances in the urine, such as *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine. This substance is generated in very high levels in the urine of patients chronically infected with *Schistosoma* organisms and is a known bladder cancer carcinogen in bladder cancer models (Abol-Enein, 2008). In addition, chronic infection with *Schistosoma hematobium* converts nitrates to nitrites and subsequently to nitrosamines, which are known bladder carcinogens. Chronic schistosomiasis leads predominantly to squamous cell carcinoma rather than urothelial carcinoma, with 70% of infected patients who develop bladder cancer having squamous cell carcinoma, although many will have both urothelial and squamous cell cancer (Cohen and Johansson, 1992) (Fig. 80–17). Spinal cord–injured patients are also at risk for developing squamous cell carcinoma, most likely because of chronic catheter irritation and infection. **Older studies have suggested a 2.5% to 10% incidence of squamous cell carcinoma in the spinal cord–injured population, with a mean delay of 17 years after the spinal cord injury** (Kaufman et al, 1977). **More recent analysis of the association of spinal cord injury and bladder cancer formation has shown a remarkably lower risk of bladder cancer formation of 0.38%, most likely because of better catheter care** (Bickel et al, 1991). This supports the concept that chronic infection and foreign bodies can lead to bladder cancer formation.

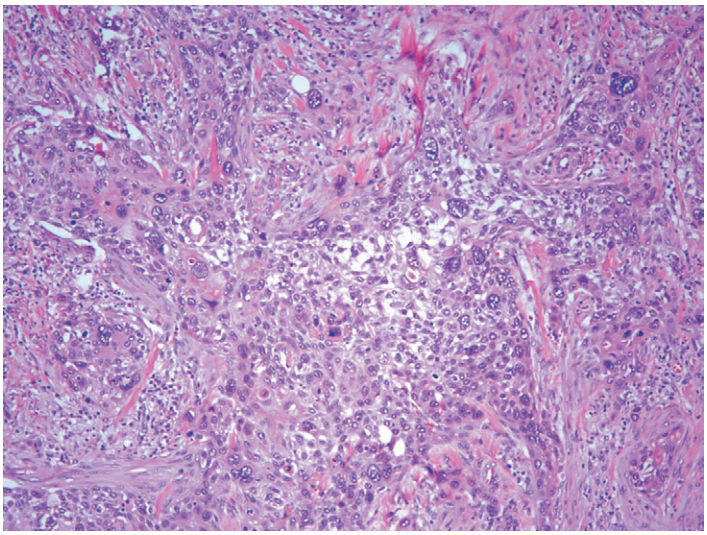


Figure 80–17. Squamous cell cancer with associated urothelial cancer.

Key Points: Histologic Variants

- Eighty percent of urothelial carcinomas will contain some mixed differentiation, most commonly squamous cell.
- Altered growth patterns, particularly micropapillary and nested variants, carry poor prognosis, even for non–muscle-invasive disease.
- Neoadjuvant chemotherapy appears to be active in mixed tumors containing adenocarcinoma or squamous cell cancer but not against altered growth patterns such as in micropapillary and nested urothelial cancer.
- Small cell carcinoma of the bladder should be treated as metastatic disease with institution of chemotherapy followed by either radiation therapy or surgery for elimination of the local disease.
- Signet ring carcinoma is uniformly understaged and invariably presents as local, regional, or metastatic stages.

Prostatic Urethral Cancer

Ortega was the first to describe urothelial carcinoma involving the prostatic urethra (Ortega et al, 1953). Prostatic urethral cancer is associated with urothelial cancer in 90% of cases, primarily CIS, and most will have multifocal bladder tumors. However, the incidence of prostatic urethral disease in patients with primary urothelial cancer is only 3% (Rikken et al, 1987; Millan-Rodriguez

et al, 2000). **Secondary prostatic urethral involvement in patients with a history of urothelial cancer is approximately 15% at 5 years and 30% at 15 years, almost uniformly associated with extensive intravesical therapy** (Herr and Donat, 1999). For patients undergoing radical cystectomy for urothelial cancer, the risk of identifying prostatic urethral disease is 40%. Risk factors for prostatic urethral involvement are CIS of the bladder neck and a history of intravesical chemotherapy (Wood et al, 1989a). Most patients with prostatic urethral disease will have direct extension of their bladder cancer into the prostatic urethra; however, some patients will have pagetoid spread underneath normal-appearing urothelium at the bladder neck.

Transurethral resection of the prostatic urethra is the primary method for detecting prostatic urethral carcinoma, with a sensitivity and specificity of greater than 90% (Wood et al, 1989; Sakamoto et al, 1993; Donat et al, 2001a, 2001b). A transurethral resection of the prostatic urethra should be performed on all patients with positive urine cytology but a negative bladder biopsy, or on those with recurrent bladder cancer after multiple courses of intravesical chemotherapy. **For patients with noninvasive prostatic urethral cancer, transurethral resection of the prostate with BCG therapy is appropriate** (Palou et al, 2007). **For patients with prostatic ductal disease, a complete transurethral prostatectomy (TURP) is warranted, plus BCG therapy.** The current 2009 bladder cancer staging system now excludes noninvasive prostatic urethral disease from the T4 category. These tumors have a relatively good prognosis not consistent with T4 staging status. Prostatic urethral cancer is now staged in a prostatic urethral category in the AJCC staging manual (Edge et al, 2010). Only patients with prostatic stromal invasion, either direct or indirect, are considered to have T4a-staged disease. Prostatic stromal invasion occurs in 7.6% to 25% of patients with prostatic urethral cancer (Wood et al, 1989b; Herr and Donat, 1999). Ninety percent of these cases are associated with previous bladder tumors, and almost all have had previous BCG therapy. Transurethral biopsy of the prostate is recommended, however, if patients have direct extension of the tumor through the bladder wall into the prostate, a prostate needle biopsy may be warranted (Donat et al, 2001). Patients with prostatic stromal disease are staged at T4a, and a better prognosis is associated with those who have stromal invasion through the prostatic urethra compared with invasion directly through the bladder wall into the prostate (Esrig et al, 1996). Multimodal therapy combining chemotherapy with radical cystectomy is the appropriate treatment (Palou et al, 2007).

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The complete reference list is available online at www.expertconsult.com.

chapter 81

Non–Muscle-Invasive Bladder Cancer (Ta, T1, and CIS)

J. Stephen Jones, MD, MBA ● William A. Larchian, MD

Staging
Endoscopic Surgical Management
Immunotherapy
Intravesical Chemotherapy
Management of Refractory High-Grade Disease
Surveillance and Prevention

Traditionally known as *superficial bladder cancer,* **malignant urothelial tumors that have not invaded the detrusor are more appropriately termed *non–muscle invasive*** (Epstein et al, 1998; Smith et al, 1999). The former term suggested that all such tumors shared the relatively benign course of low-grade papillary tumors, giving misleading reassurance to patients with the highly malignant subcategories of carcinoma in situ (CIS) and high-grade Ta and T1 lesions. **Approximately 70% are non–muscle invasive at presentation. Of these, 70% present as stage Ta, 20% as T1, and 10% as CIS** (Fig. 81–1) (Ro et al, 1992).

The presence of bladder cancer is usually suspected by hematuria. Patients with macroscopic (gross) hematuria have reported rates of bladder cancer of 13% to 34.5% (Lee and Davis, 1953; Varkarakis et al, 1974). **Microscopic hematuria is associated with a 0.5% to 10.5% rate of bladder cancer** (Golin and Howard, 1980; Mohr et al, 1986; Sultana et al, 1996; Khadra et al, 2000). The **presence of irritative voiding symptoms may double the risk, especially for CIS** (5% vs. 10.5%) (Mohr et al, 1986). The Mayo Clinic reported that 80% of patients with CIS presented with irritative symptoms (Zincke et al, 1985). In a review of 600 patients diagnosed with interstitial cystitis, 1% of the patients had a missed diagnosis of urothelial carcinoma. Of note, two thirds of these patients did not have hematuria (Tissot et al, 2004). Thus **cystoscopy and upper tract imaging are indicated in patients with hematuria and/or unexplained irritative symptoms** (Grossfeld et al, 2001).

Recurrence is common in all patients with non–muscle-invasive urothelial cancer but can often be controlled successfully with transurethral surgery, intravesical therapy, or a combination. In contrast to recurrence, **patients can be divided into low or high risk for progression, which is the true concern. Low-grade Ta lesions are low risk, whereas all high-grade lesions (including CIS) have a high risk of progressing.** The frequency of progression and death is shown in Table 81–1.

STAGING

Pathology: Staging and Grading

Although the World Health Organization (WHO) has determined that **the term *urothelial cancer* (UC) is preferable to the term *transitional cell cancer* (TCC),** the latter remains in widespread use. However, their recommendation to move away from the traditional grading system (1 to 3, from low grade to high grade) is now accepted by many urologists and pathologists. They recommend that **malignant tumors be classified as low grade or high grade, regardless of invasion status.**

In contrast, essentially benign **papillary tumors with orderly cellular arrangement, minimal architectural abnormalities, and minimal nuclear atypia are distinct from those two grades and are designated Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP).** Such tumors would have been labeled either papillomas or grade 1 TCC in older systems but are now regarded as so unlikely to progress that they are considered benign. However, on the basis of this low risk, the WHO recommends that such pathology reports contain the note, "Patients with these tumors are at risk of developing new bladder tumors ("recurrence"), usually of similar histology. However, occasionally these subsequent lesions manifest as UC, such that follow-up of the patient is warranted" (Epstein et al, 1998). Papillomas are truly benign and not associated with risk of progression (Figs. 81–1 through 81–5).

Pathologic Staging

The bladder has three main histologic layers: (1) urothelium, (2) suburothelial loose connective tissue called *lamina propria,* and (3) detrusor or muscularis propria (which is absent beneath the urothelium of diverticulae). Stage Ta denotes a papillary tumor confined to the urothelium. CIS (also termed *Tis*) is a flat, high-grade

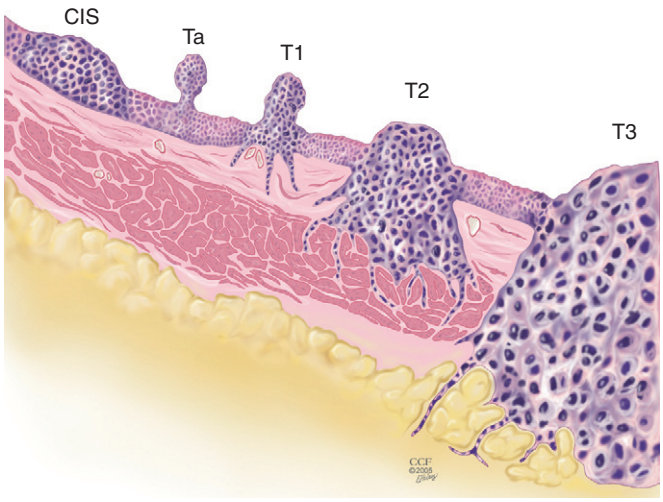


Figure 81–1. Carcinoma in situ is a high-grade, flat malignancy confined to the urothelium. Papillary tumors confined to the urothelium are Ta, whereas papillary tumors invading lamina propria are T1. The T1 tumor here intertwines with the wispy fibers of the muscularis propria but by definition does not invade the smooth muscle fibers of the detrusor. T2 tumors invade the detrusor muscle, and T3 tumors are in extravesical fat as shown.

Table 81–1.

Estimates of Disease Progression in Non–Muscle-Invasive Bladder Cancer: World Health Organization/International Society of Urologic Pathology Consensus Classification

TUMOR TYPE	% RELATIVE FREQUENCY	% PROGRESSION	% DEATHS
Noninvasive			
Papilloma	10	0-1	0
Papillary urothelial neoplasm of low malignant potential	20	3	0-1
Papillary cancer low grade (TaG1)	20	5-10	1-5
Papillary cancer high grade (TaG3)	30	15-40	10-25
Invasive			
Papillary cancer (T1G3)	20	30-50	33
Carcinoma in Situ			
Primary	10	>50	—
Secondary	90		

From Donat SM. Evaluation and follow-up strategies for superficial bladder cancer. Urol Clin North Am 2003;30:765–6.

lesion confined to the same layer, and T1 is a tumor invading lamina propria. The TNM grading system for non–muscle-invasive tumors is demonstrated in Figure 81–1.

The demarcation between "superficial" and "invasive" has sometimes been errantly considered between T1 and T2. However, **T1 tumors invade the lamina propria by definition, so they cannot be accurately characterized as "noninvasive."** Unlike the urothelium, which is devoid of vessels or lymphatics, the lamina propria is rich in both, providing opportunity for metastasis. These tumors sometimes invade the wispy and

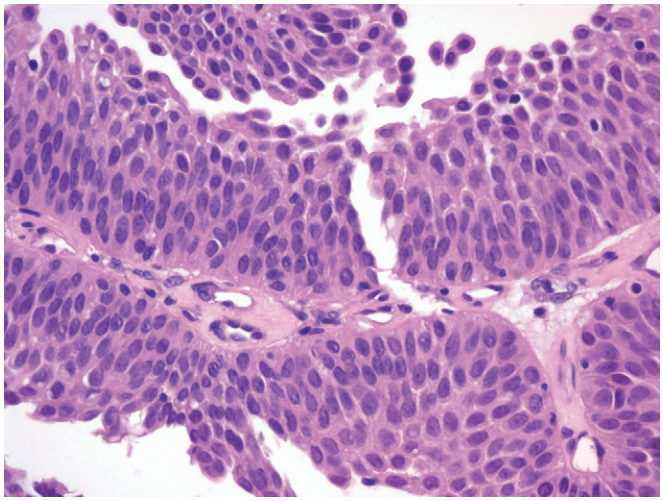


Figure 81–2. The urothelium is thickened, but cells and nuclei are normal in papillary urothelial neoplasm of low malignant potential (×40).

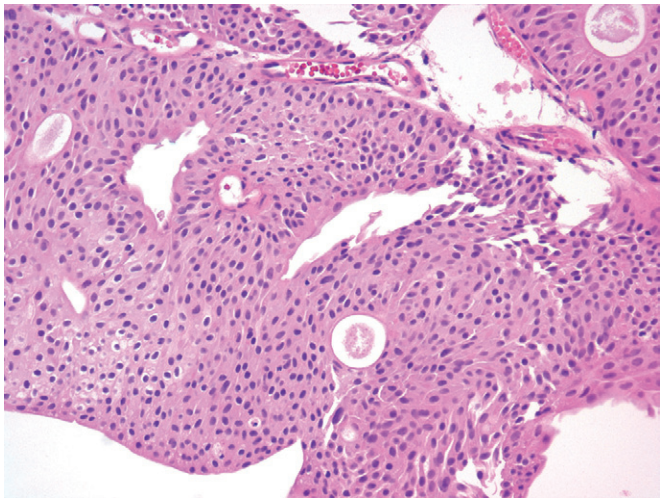


Figure 81–3. Ta low-grade tumor (×40). Cells are relatively normal but exhibit irregularity and some nuclear differentiation.

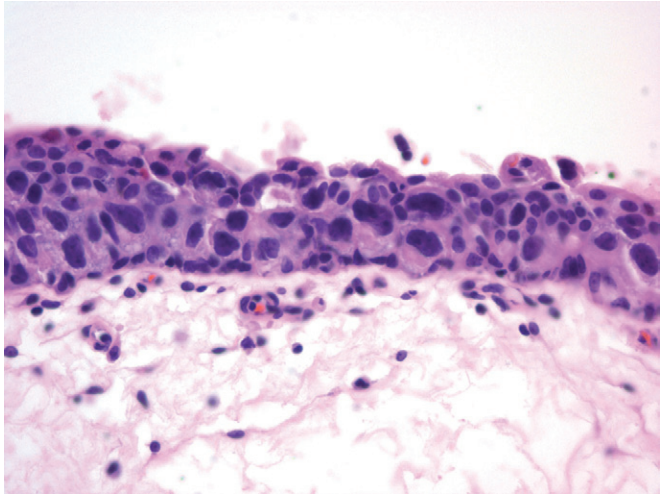


Figure 81–4. Carcinoma in situ (×40) exhibits severe irregularity of cellular structure and nuclear pleomorphism, but there is no invasion of lamina propria.

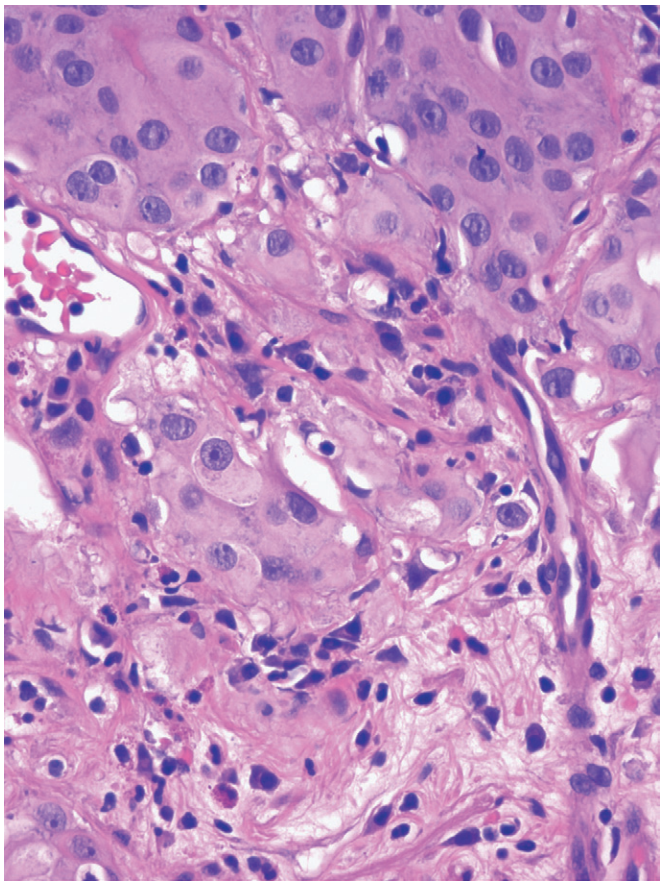


Figure 81–5. T1 (×40) high-grade tumor exhibits nesting of abnormal cells and mitotic figures. Tumor cells can be seen invading the lamina propria in the lower one third of the photomicrograph.

discontinuous muscularis mucosae of the lamina propria, which can be confused for muscularis propria (detrusor) during pathologic interpretation. **Imprecise verbiage on the pathology report can lead the urologist to misinterpret invasion of muscularis mucosae to be "muscle invasive,"** risking overstaging error. Direct communication between urologist and pathologist when this occurs is essential.

Deep lamina propria invasion carries a substantially more serious prognosis in some reports, and some have proposed these be subcategorized as T1b (Younes et al, 1990). However, the value of substaging has not been validated in other studies, so the 1998 Bladder Cancer Consensus Conference Committee rejected the concept (Platz et al, 1996; Epstein et al, 1998).

Tumor Biology

Low-grade tumors rarely invade the lamina propria or detrusor, so invasive tumors may be almost equated with high-grade histology. However, tumors of all grades and degrees of potential aggressiveness can be identified before invasion of the muscularis propria, so no such grading assumption can be made about these lesions.

Low-grade Ta lesions recur at a rate of 50% to 70% and progress in approximately 5% of cases. In contrast, high-grade T1 lesions recur in more than 80% of cases and progress in 50% of patients within 3 years. This behavior is primarily grade, rather than stage, dependent, because patients with high-grade tumors progressed with similar frequency regardless of whether they were invasive (T1) or noninvasive (Ta) (Herr, 2000a). **Prognosis also correlates with tumor size, multiplicity, papillary versus sessile configuration, presence or absence of lymphovascular invasion, and status of the remaining urothelium** (Althausen et al, 1976; Lutzeyer et al, 1982; Heney et al, 1983a, 1983b; Kunju et al, 2008).

The variance in biologic behavior for low-grade versus high-grade lesions correlates with the known dual molecular lines of genetic development for these two pathways and supports the concept that **high-grade and low-grade cancers may be considered as essentially different diseases** (Hasui et al, 1994; Droller, 2005). **Chromosomal alterations caused by oxidative DNA damage create two separate genetic pathways to the development of UC** (Spruck et al, 1994; Richter et al, 1997; Cote and Chatterjee, 1999). The first and more common (low grade) leads to noninvasive, papillary tumors. These usually follow an indolent course unless they convert to or are associated with a tumor of the second pathway (Kiemeney et al, 1993).

The second pathway leads to the development of high-grade cancer including CIS, T1, and, ultimately, muscle-invasive carcinoma. Such genetic alterations can be evaluated using karyotyping, microsatellite analysis for allelic imbalance (Mao et al, 1996), comparative genomic hybridization (Kallioniemi et al, 1995), DNA ploidy analysis by flow cytometry (Bittard et al, 1996), and fluorescence in-situ hybridization (FISH) (Degtyar et al, 2004). These evaluations can show that **low-grade papillary tumors tend to exhibit relatively few chromosomal abnormalities, primarily involving loss of all or part of chromosome 9 (particularly the q arm). In contrast, high-grade tumors tend to have numerous and greatly variable chromosomal gains and losses. In addition to their relatively predictable aneuploidy, high-grade tumors can also lose all or part of chromosome 9** (Richter et al, 1997). Although almost any chromosome can be affected, aneuploidy of chromosomes 7, 9, and 17 is associated with especially aggressive tumors (Olumi et al, 1990; Waldman et al, 1991; Degtyar et al, 2004).

Because of these differing genetic imprints, it has been suggested that papillary pTa tumors could almost be considered benign and might be a completely separate disease entity in contrast to high-grade tumors (Sauter and Mihatsch, 1998; Harnden, 2007). Nevertheless, high-grade and low-grade lesions are known to coexist. UC is traditionally considered a field change disease, with tumors arising at different times and sites. Rarely, patients who initially have low-grade tumors will subsequently develop high-grade tumors, often years after the original tumors, so long-term surveillance is usually reasonable (Prout and Barton, 1992).

Pathologic Characteristics by Stage and Implications for Clinical Staging Errors

Stage Ta tumors are usually low grade. Although recurrence is common, especially in the setting of multiplicity, progression is rare. However, **2.9% to 18% of Ta tumors are high grade, with an average of 6.9%** (Sylvester et al, 2005). **The most important risk factor for progression is grade, not stage** (Norming et al, 1992; Millan-Rodriguez et al, 2000). Stein and colleagues (2001) found little difference in survival comparing noninvasive and muscle-invasive tumors as long as the cancer was organ confined (Stein et al, 2001; Sylvester et al, 2005).

CIS is occasionally mischaracterized as "premalignant" (Sylvester et al, 2005), **but it is actually a flat, noninvasive UC that is high grade by definition.** Although confined to the urothelium in the same manner as stage Ta, **CIS is regarded as a precursor for the development of invasive high-grade cancer.**

CIS lesions are composed of severely dysplastic urothelium. Microscopically, the slide will demonstrate disorderly histology with nuclear atypia characteristic of high-grade malignancy; denudement of some or all of the mucosa due to loss of cellular cohesion sometimes complicates interpretation. A pathology report read as dysplasia or atypia can create confusion. Most pathologists consider mild examples of these entities to be benign. However, **lesions interpreted as severe dysplasia or severe atypia are regarded as being the same entity as CIS** (Epstein et al, 1998). Again, unambiguous communication between pathologist and urologist can minimize the risk for misinterpretation.

Between 40% and 83% of patients with CIS will develop muscle invasion if untreated, especially if associated with papillary tumors (Althausen et al, 1976). Among patients thought to have CIS alone, up to 20% who are treated with cystectomy are found to contain invasion on final pathology (Farrow et al, 1976). The presence of CIS in cystectomy specimens performed for presumed T1 tumors was associated with upstaging in 55% of patients in a recent series, compared with 6% upstaging in patients without CIS (Masood et al, 2004). **In a series of 1500 patients, CIS was the second most important prognostic factor after grade** (Millan-Rodriguez et al, 2000). Multicentricity presents another ominous characteristic of CIS (Koch and Smith, 1996). The presence of irritative voiding symptoms has been associated with diffuse disease, invasion, and a compromised prognosis, but there is no consensus on this finding in the literature (Smith et al, 1999; Sylvester et al, 2005).

T1 tumors are usually papillary; a nodular or sessile appearance suggests deeper invasion. Deep penetration into the lamina propria, especially if involving muscularis mucosae, increases the risk of recurrence and progression in some reports. Lymphovascular invasion increases the risk as well (Lotan et al, 2005). **Hydronephrosis usually indicates muscle invasion.**

There is significant potential for understaging in patients with high-grade, apparently non–muscle-invasive tumors, especially for those that appear to be stage T1. Many tumors are found to be more extensive than the transurethral resection (TUR) specimen indicated when patients undergo cystectomy. **Stein** (Freeman et al, 1995) **reported that one third of patients believed to have non–muscle-invasive disease at the time of cystectomy were found to actually have muscle invasion, only half of which were organ confined.** Metastases were already present in 8% of these patients (Freeman et al, 1995). Stein's subsequent review noted that understaging errors from 34% to 62% have been reported (Stein, 2001), and a study from the Mayo Clinic before widespread use of intravesical therapy showed that 78% of patients with clinical T1 disease that underwent cystectomy had muscle invasion, with 62% having extravesical disease. Studies from the past decade addressing the risk of understaging of T1 tumors are shown in Table 81–2.

Although it is likely that the patients who underwent cystectomy had more serious risk factors than those who did not, these data offer compelling evidence that the term *superficial* to describe all such lesions is misleading.

Table 81–2.

Risk of Understaging When Cystectomy Is Performed for Presumed Non–Muscle-Invasive Disease

STUDY	INSTITUTION	RISK (%) OF UNDERSTAGING
Stein et al, 2001	Southern California	39
Dutta et al, 2001	Vanderbilt University	40
Bianco et al, 2004	Wayne State University	27
Bayraktar et al, 2004	Vakif Gureba Hospital Aksaray-Istanbul, Turkey	50
Huguet et al, 2005	Servicio de Urologia, Fundacion Puigvert, Barcelona	27
Ficarra et al, 2005	University of Verona, Italy	43

Key Points: Pathology

- Malignant tumors are now classified as low grade or high grade, regardless of invasion.
- High-grade and low-grade cancers may be regarded as essentially separate diseases from genetic development, biologic behavior, and management standpoints.
- The most important risk factor for progression is grade, not stage.
- Papillary tumors with orderly cellular arrangement, minimal architectural abnormalities, and minimal nuclear atypia are designated papillary urothelial neoplasm of low malignant potential (PUNLMP).

ENDOSCOPIC SURGICAL MANAGEMENT

When bladder cancer is identified during office-based cystoscopy, the location, number, and nature of tumors are recorded, as is involvement of areas likely to reflect extravesical extension such as the ureteral orifices and bladder neck/prostatic urethra. Urinary cytology is obtained as a baseline and to establish the likelihood of high-grade disease. Positivity will encourage random bladder biopsy at the time of TUR as discussed later.

Upper tract imaging is usually performed both to identify other sources of hematuria and to assess the extravesical urothelium due to the "field change" nature of UC that can affect such cells throughout the urinary tract. **Expert consensus is that patients with solitary or limited low-grade Ta lesions do not need imaging, owing to the very low risk of extravesical disease** (Goessl et al, 1997).

TUR of bladder tumor (TURBT) under regional or general anesthesia is the initial treatment for visible lesions and is performed to (1) remove all visible tumors and (2) provide specimens for pathologic examination to determine stage and grade. Bimanual examination of the bladder should be performed under anesthesia before prepping and draping unless the tumor is clearly small and noninvasive, and it should be repeated after resection. Fixation or persistence of a palpable mass after resection suggests locally advanced disease. An increase in abdominal girth or fullness after resection indicates intraperitoneal perforation.

Complete visualization to plan the resection is facilitated by either the flexible cystoscope or preferably the 70-degree rod lens, which allows maintenance of the anatomic relationships. Resection is performed using a 30-degree lens placed through a resectoscope sheath because this deflection allows visualization of the loop placed at this location. **Continuous irrigation with the bladder filled only enough to visualize its contents minimizes bladder wall movement and lessens thinning of the detrusor through overdistention** (Koch and Smith, 1996). **Video TUR allows magnification, facilitates resident teaching, allows documentation of findings, and reduces the risk of body fluid exposure to the surgeon** (Manoharan and Soloway, 2005; Nieder et al, 2005). Resection is performed piecemeal, delaying transection of any stalk until most tumor is resected in order to maintain countertraction. **Friable, low-grade tumors can often be removed without the use of electrical energy** because the nonpowered cutting loop will break off most segments. This minimizes the chance of bladder perforation. Higher-grade, more solid tumors and the base of all tumors require the use of cutting current; cautery yields hemostasis once all of the tumor is resected. **Lifting the tumor edge away from detrusor lessens the chance of perforation** (Holzbeierlein and Smith, 2000). Repeated slow fulguration may complicate the ability of the pathologist to determine grade or invasion status.

After all visible tumor is resected, an additional pass of the cutting loop or a cold cup biopsy can be obtained to send to pathology separately to determine the presence of muscle invasion of the tumor base. A chip evacuator gathers the specimen. Final confirmation of hemostasis in the presence of minimal irrigation after all chips are removed through vigorous irrigation is helpful.

Traditionally, TUR has been performed in sterile water because saline solutions conduct electricity and disperse energy from the monopolar cautery cutting loop. Glycine is more expensive, and there is no evidence of its benefit compared with water (Holzbeierlein and Smith, 2000). Introduction of **bipolar electroresection is reported to allow transurethral resection in saline (TURIS) and to minimize the risk of the obturator reflex that can predispose to bladder perforation** (Shiozawa et al, 2002; Miki et al, 2003). **The use of general anesthesia with muscle-paralyzing agents also prevents obturator reflex.** This can also be accomplished by direct injection of 20 to 30 mL of local anesthetic (lidocaine) into the obturator nerve and its canal, but few centers have experience with this.

Resection of diverticular tumors presents significant risk of bladder wall perforation, and accurate staging is difficult to achieve in this circumstance because the underlying detrusor is absent. Invasion beyond the lamina propria immediately involves perivesical fat or stage T3a. Resection in diverticula almost inevitably leads to perforation. Low-grade diverticular tumors are best treated with a combination of resection and fulguration of the base. Conservative resection can be followed with subsequent repeat resection if the final pathologic interpretation is high grade. High-grade tumors require adequate sampling of the tumor base, often including perivesical fat, despite the near-certainty of bladder perforation. An indwelling catheter allows healing. **Partial or radical cystectomy should be strongly considered for high-grade diverticular lesions.**

Anterior wall tumors and tumors at the dome in patients with large bladders can be difficult to reach. Minimal bladder filling combined with manual compression of the lower abdominal wall to bring the tumor toward the resectoscope facilitates removal. Modern resectoscopes are long enough to reach the entirety of most bladders; creation of a temporary perineal urethrostomy offers deeper access but is rarely necessary except in the obese patient with an inaccessible tumor. Digital manipulation through the rectum or vagina can occasionally facilitate resection.

Care must be taken during resection near the ureteral orifice to prevent obstruction from scarring after fulguration. **Pure cutting current causes minimal scarring and may be safely performed including resection of the orifice if necessary.** Resection of the intramural ureter can lead to complete eradication of the tumor but risks reflux of malignant cells. The clinical implications of this are unclear (Palou et al, 1992).

Alternatively, **small tumors may be resected using the cold cup biopsy forceps** alone. This is especially helpful in the thin-walled bladder of elderly women, who are predisposed to perforation due to their thin-walled bladder. If perforation occurs, the cup causes a smaller hole than does the cutting loop. A Bugbee electrode facilitates hemostasis. **A successful cauterization method involves placing the Bugbee electrode inside the biopsy site with the bladder under minimal distention. Touching the cut surface of the biopsy crater, the electrical energy will cause the mucosa to contract around the electrode unless the bladder is full.** Light irrigation clears the area of blood and vaporization bubbles created during fulguration. **Visualizing a small (1 to 2 mm) ring of white coagulation confirms hemostasis and yields less damage to the bladder than that occurring when the biopsy area is "painted" with cautery.** Removing the electrode from the site before discontinuing the energy current lessens the chance of pulling the fresh clot off as the Bugbee electrode separates from the urothelium.

If a tumor appears to be muscle invasive, biopsies of the borders and base in order to establish invasion may be performed in lieu of complete resection, because cystectomy will likely follow based on confirmatory biopsies. Failure to demonstrate invasion necessitates repeat resection unless the decision is made to proceed to cystectomy-based factors other than muscle invasion.

Complications of Transurethral Resection of Bladder Tumor

Minor bleeding and irritative symptoms are common side effects in the immediate postoperative period. The major complications of uncontrolled hematuria and clinical bladder perforation occur in less than 5% of cases, although a majority of patients will exhibit contrast agent extravasation indicative of minor perforation if cystography is performed. The **incidence of perforation can be reduced by attention to technical details, avoiding overdistention of the bladder, and using anesthetic paralysis during the resection of significant lateral wall lesions to lessen an obturator reflex response. Moreover, large, bulky tumors and those that appear to be muscle invasive are often best resected in a staged manner** because it is believed that repeat resection can more safely remove residual tumor if indicated.

The vast majority of perforations are extraperitoneal, but intraperitoneal rupture is possible when resecting tumors at the dome (Collado et al, 2000). The risk of tumor seeding due to perforation appears to be low (Balbay et al, 2005). Anecdotal reports have identified extravesical recurrences after perforation, theoretically

due to seeding (Mydlo et al, 1999). It has been suggested that the risk of tumor seeding is higher in patients who undergo surgical repair, but this may be related to patient selection because only serious intraperitoneal perforations are likely to be managed in this manner (Mydlo et al, 1999; Skolarikos et al, 2005).

Management of extraperitoneal perforation is usually possible by prolonged urethral catheter drainage. Intraperitoneal perforation is less likely to close spontaneously and often requires open or laparoscopic surgical repair. Decisions for surgical correction should be made on the basis of the extent of the perforation and the clinical status of the patient.

TUR syndrome from fluid absorption is uncommon and managed in the same manner as during TURP. As long as resection of the ureteral orifice is done with pure cutting current, scarring is minimal and obstruction unlikely. Cystoscopy to visualize efflux, which is occasionally aided by intravenous administration of indigo carmine or methylene blue or retrograde ureteropyelography, can determine presence or absence of obstruction. Balloon dilation of the orifice or endoscopic incision can relieve obstruction, but failure to respond may require reimplantation (Chang et al, 1989).

Repeat Transurethral Resection of Bladder Tumor

Complete tumor removal is not always possible, whether due to excessive tumor volume, anatomic inaccessibility, medical instability requiring premature cessation, or risk of perforation. However, even in the absence of these circumstances repeat TUR is often indicated. When repeat TUR is performed within several days to several weeks of the original resection, residual tumor is identified at the site of the initial resection at least 40% of the time (Klan et al, 1991; Mersdorf et al, 1998; Vogeli et al, 1998). In a review, Miladi and coworkers (2003) found that a second TURBT performed within 6 weeks of the initial resection detected residual tumor in 26% to 83% of cases and corrected clinical staging errors in half of those cases. The potential for understaging high-risk disease ranged from 18% to 37% (Amling et al, 1994).

Repeat TURBT is usually appropriate in the evaluation of T1 tumors because a repeat TUR can demonstrate worse prognostic findings in up to 25% of specimens (Schwaibold et al, 2000). **This is especially likely if no muscle is identified on initial pathology, which can occur in almost half of cases. The Vanderbilt University group reported a 64% risk of understaging T1 lesions when muscle was absent, compared with 30% when muscle was present in the specimen** (Dutta et al, 2001). Herr (1999) reported that a second resection changed treatment in one third of cases. Importantly, survival was 63% in patients who underwent a second TURBT versus 40% for those who did not in a German observational study (Grimm et al, 2003). The efficacy of bacillus Calmette-Guérin (BCG) in preventing progression appears to be higher in patients with high-grade papillary tumors and CIS if a restaging TURBT was performed before instillation of BCG (Herr, 2005).

There appears to be variability in completeness of resection among surgeons. In patients with multiple tumors who had adjuvant treatment, recurrence rates varied between 7.4% and 45.8% depending on the surgeon (Brausi et al, 2002). **Repeat resection is helpful in the setting of a second opinion unless clear evidence of muscle invasion is identified on the initial resection,** especially if the outside pathology slides are not available for review.

Consensus is that patients with pT1 and high-grade Ta tumors merit repeat resection. There is no consensus on timing of repeat TURBT, but most authors recommend 1 to 6 weeks after the initial resection (Nieder et al, 2005).

Role of "Random" or Additional Biopsies

Biopsies of any suspicious areas are an important part of a complete evaluation. Cold-cup biopsies may not provide as much information regarding muscular invasion but provide tissue sampling without cautery artifact that can interfere with pathologic interpretation (Soloway et al, 1978; Smith, 1986a, 1986b).

On the basis of the understanding that CIS can exist in normal-appearing urothelium, some authors advocate the use of random biopsies to identify CIS in otherwise normal-appearing mucosa. This remains controversial. May and colleagues (2003) performed random biopsies in high-risk patients and found that the results were positive in 12.4% and altered treatment in 7% including 14 of 1033 patients in whom the only positive tissue was in the random biopsy, not the primary resected tumor. However, even when velvety red patches were sampled, only 11.9% of biopsies were positive in one report (Swinn et al, 2004). A European Organisation for Research and Treatment of Cancer (EORTC) retrospective review found that 10% of random biopsies were positive (3.5% CIS) and concluded such biopsies were not warranted (van der Meijden et al, 1999). Fujimoto and colleagues (2003) prospectively evaluated the role of random biopsies of normal-appearing urothelium and found cancer in only 8 of 100 biopsy samples, 5 of which were CIS. They concluded that random biopsies are indicated only in the setting of multiple tumors or positive cytology. **The current consensus is that random biopsies are not indicated in low-risk patients** (i.e., those with low-grade papillary tumors and negative cytology).

Prostatic urethral biopsy using the cutting loop may be performed, especially if neobladder creation is anticipated for high-risk disease, but bleeding may be more common (Holzbeierlein and Smith, 2000). The additional value of the information obtained from cold cup and urethral biopsies must be weighed against the theoretical risk that biopsies provide an exposed bed to aid tumor implantation (Mufti and Singh, 1992; Kiemeney et al, 1994; Yamada et al, 1996). Traditional teaching is that TUR of the prostate (TURP) and TURBT of a low-grade bladder tumor may be performed at the same setting but that resection of a high-grade bladder tumor should not be resected coincident to TURP to avoid tumor seeding and possible intravasation of tumor cells likely to metastasize. Despite anecdotal reports of low-grade tumors implanting in the prostatic urethra after simultaneous resection, this risk appears to be small and the literature does not adequately address the risk of metastasis in this setting (Tsivian et al, 2003).

Perioperative Intravesical Therapy to Prevent Tumor Implantation

It is believed that tumor cell implantation immediately after resection is responsible for many early recurrences and this has been used to explain the observation that initial tumors are most

commonly found on the floor and lower side walls of the bladder, whereas recurrences are often located near the dome (Heney et al, 1981). Thus intravesical chemotherapy to kill such cells before implantation has been used (Zincke et al, 1983; Klan et al, 1991).

Mitomycin C (MMC) appears to be the most effective adjuvant intravesical chemotherapeutic agent perioperatively, although epirubicin is used in Europe and direct comparative studies are lacking (Witjes and Hendricksen, 2008). **Consistent with its proposed mechanism of action to prevent tumor cell implantation, a single dose administered within 6 hours lessens recurrence rates, whereas a dose 24 hours later does not** (Isaka et al, 1992; Oosterlinck et al, 1993; Sekine et al, 1994; Solsona et al, 1999; Duque and Loughlin, 2000), and maintenance therapy does not reduce the risk further (Bouffioux et al, 1995; Tolley et al, 1996). **Nevertheless, the level 1 data in support of single-dose MMC immediately after resection to reduce tumor recurrence are compelling** (Table 81–3).

A meta-analysis found that low-risk patients at a median follow-up of 3.4 years experience an approximate 39% drop in the odds of recurrence (i.e., from 48.4% to 36.7%). Patients with multiple tumors experience a 56% reduction in the odds of recurrence. MMC, epirubicin, and pirarubicin all significantly lessened the recurrence of both single and multiple tumors. Thiotepa did not show the same benefit, but data were limited and some studies used dilute strengths (Sylvester et al, 2004). The number needed to treat (NNT) to prevent one recurrence in the meta-analysis was 8.5, so some authors suggest that intravesical chemotherapy reduces overall cost of care by reducing the need for secondary resections. However, subsequent studies have shown that the tumors prevented are primarily smaller tumors that are often treated in the office or ambulatory surgery setting (Berrum-Svennung et al, 2008). In addition, the benefit appears limited to patients with low risk of recurrence (Gudjónsson et al, 2009), so the economic benefit regarding recurrences appears limited if treated in any manner other than inpatient care (Rao and Jones, 2009).

Although local irritative symptoms are the most common complications of postoperative instillation, serious sequelae and rare deaths have occurred, especially in patients with perforation during resection (Oddens et al, 2004). **Chemotherapy should be withheld in patients with extensive resection or when there is concern about perforation.**

BCG can never be safely administered immediately after TUR because the risk of bacterial sepsis and death is high.

Table 81–3.

Successful Perioperative Administration of Intravesical Chemotherapy

1. Include intent to administer perioperative chemotherapy (and agent) on actual operative schedule.
2. Contact pharmacy before case to have medication available. A written prescription may be required.
3. After resection, confirm absence of clinical perforation. Place 3-way catheter into bladder while patient is still in operating room. Attach inflow port to saline infusion bag and clamp inflow.
4. Administer chemotherapeutic agent through catheter outflow port in recovery room within 6 hours of operation and clamp outflow tubing with hemostat to allow retention.
5. Give order for outflow tubing to be opened 1 hour after administration and for irrigation, to be opened to gravity drainage for next 30 to 60 minutes.
6. Remove Foley catheter and discard in biohazard container.
7. Wear gloves.

Modified from O'Donnell MA. Practical applications of intravesical chemotherapy and immunotherapy in high-risk patients with superficial bladder cancer. Urol Clin North Am 2005;32:121–31.

Laser Therapy

Laser coagulation allows minimally invasive ablation of tumors up to 2.5 cm in size. The neodymium:yttrium-aluminum-garnet (Nd:YAG) laser has the best properties for use in bladder cancer. Lesions can be coagulated until nonviable through protein denaturation using a straight or 90-degree noncontact "free beam" laser using power output of up to 60 W. **The most significant complication of laser therapy is forward scatter of laser energy to adjacent structures, resulting in perforation of a hollow, viscous organ such as overlying bowel.** This is rare but most commonly occurs with the neodymium:YAG laser because of its deeper tissue penetration than with holmium:YAG and KTP lasers (Smith, 1986a, 1986b). Unless higher energy is necessary for a very large tumor, **limiting energy to 35 W precludes exceeding 60° C on the outer bladder wall, minimizing the risk of perforation** (Hofstetter et al, 1994). **The most efficient delivery appears to be an end-fire noncontact fiber with a 5- to 15-degree angle of divergence, which allows variable penetration depth up to 5 mm** (Smith and Landau, 1989; Holzbeierlein and Smith, 2000). Treatment should be under direct visualization and should discontinue as soon as protein denaturation is evident by the white appearance of the treated tissue. Persistence after this occurs risks extravesical injury.

Laser therapy can be more expensive than resection due to the cost of laser fibers, but bleeding is negligible and there is no risk of obturator reflex. Small lesions can be treated easily using intravesical anesthesia. Because there is no tissue available for pathologic inspection, the optimal candidate for laser therapy is the patient with recurrent, low-grade lesions whose biology is already known. Additional information regarding tumor grade may be obtained with a cold cup biopsy if necessary. Some reports suggest lower recurrence rates using laser compared with TURBT, but this remains inconclusive (Smith et al, 1983; Malloy et al, 1984; Beisland and Seland, 1986; Smith, 1986a, 1986b; Beer et al, 1989).

Holmium:yttrium-aluminum-garnet (YAG), argon, and potassium titanyl phosphate (KTP) lasers ablate tissues by cutting (vaporization) and thus have limited applicability due to lack of deep coagulation (Johnson et al, 1991; Benson, 1992; Holzbeierlein and Smith, 2000). The carbon dioxide laser is completely absorbed by fluid, so it is not appropriate for use in the treatment of bladder cancer (Benson, 1992).

Office-Based Endoscopic Management

Many patients with small (<0.5 mL) low-grade recurrences can be managed safely in the office setting using diathermy or laser ablation under intravesical local anesthetic (Donat et al, 2004). Instillation of viscous or injectable 1% to 2% lidocaine through a catheter and a dwelling time of 15 to 30 minutes yield satisfactory mucosal analgesia. Pain with fulguration of 1- to 2-mm tumors is often acceptable with no analgesia. **A tissue diagnosis and a negative cytology for the initial tumor occurrence are mandatory** to determine whether the tumor is of high or low grade.

Additionally, **many small, low-grade tumors can be safely observed until they exhibit significant growth due to the minimal risk of progression** (Soloway et al, 2003: Pruthi et al, 2008). These conservative approaches can obviate the need for anesthesia and use of hospital-based resources for selected small, low-grade recurrences.

Fluorescence Cystoscopy

Endoscopically, urologists can suspect malignancy only on the basis of the presence of visible changes such as tumors or "red spots." As noted, random biopsy of normal-appearing areas sometimes detects unsuspected malignancy, usually CIS. Moreover, a multicenter study found that 37% of the biopsies performed on the basis of suspicious endoscopic findings resulted in false-negative biopsy, emphasizing the subjectivity and attendant false-positive and false-negative rates of cystoscopy (Riedl et al, 2001; Sarosdy et al, 2002). **The imperfect sensitivity of cystoscopy potentially explains the high rate of cancer recurrence soon after complete removal of all visible tumors** (tumor cell implantation also contributing, as described earlier). It is likely that cancer was already present but not visible at the time of resection and simply became visible in follow-up when it became morphologically abnormal enough to differentiate from adjacent normal urothelium.

Photoactive porphyrins accumulate preferentially in neoplastic tissue. Under blue light they emit red fluorescence, which can help in the diagnosis of indiscernible malignant lesions. Hematoporphyrin derivatives must be administered systemically and can cause lengthy, residual cutaneous photosensitization. Intravesical application of 5-aminolevulinic acid (5-ALA), a precursor of photoactive porphyrin, avoids residual systemic photosensitization and has improved the detection of bladder tumors. Modifications of 5-ALA may allow deeper tissue penetration and improved accumulation in neoplastic cells (Lange et al, 1999). A more lipophilic ester, hexaminolevulinate (HAL), is the most studied agent.

When using this technology, both small papillary tumors and almost one-third more cases of CIS overlooked by cystoscopy are identified (Jichlinski et al, 2003; Schmidbauer et al, 2004; Fradet et al, 2007). Of all tumors, 96% were detected with HAL imaging compared with 77% using standard cystoscopy. Detection was improved for dysplasia (93% vs. 48%), CIS (95% vs. 68%), and papillary tumors (96% vs. 85%) (Jocham et al, 2005). The clinical impact of improved tumor detection seems intuitive, and prospective evidence shows that this decreases recurrence rates in patients who undergo HAL fluorescence cystoscopy compared with controls (Filbeck et al, 2003; Denzinger et al, 2007).

Intravesical HAL for use with fluorescence cystoscopy received approval for use in Europe in 2004. A multinational study to determine the actual impact on recurrence rates before approval in North America showed similar findings (unpublished data) (Figs. 81–6 and 81–7).

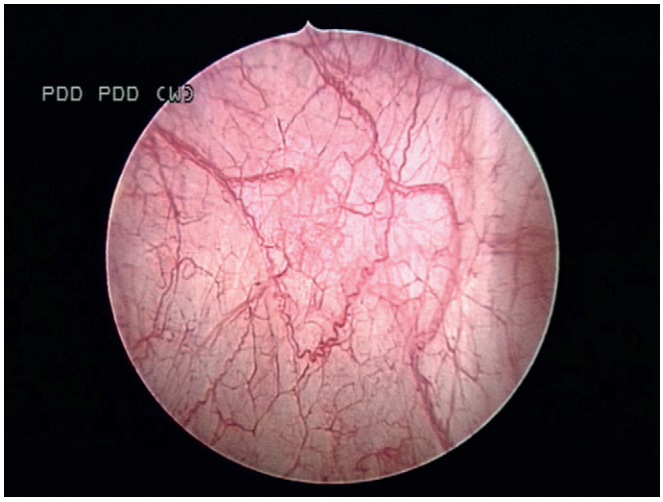


Figure 81–6. White light microscopy reveals normal appearing mucosa. (Courtesy of H. Barton Grossman, MD.)



Figure 81–7. Blue light microscopy reveals accumulation of hexaminolevulinate in an area proven subsequently to contain a small focus of carcinoma in situ. (Courtesy of H. Barton Grossman, MD.)

IMMUNOTHERAPY

Intravesical immunotherapy results in a massive local immune response characterized by induced expression of cytokines in the urine and bladder wall and by an influx of granulocytes, mononuclear, and dendritic cells (Shen et al, 2008). The mechanism of action has been intensively investigated. **The initial step appears to be direct binding**

Key Points: Endoscopic Surgical Management

- TURBT is performed both to remove all visible tumors and to provide specimens for pathologic examination to determine stage and grade.
- Repeat resection within 1 to 6 weeks is usually indicated in patients with high-grade disease, especially if no muscle was present in the initial TURBT.
- Single-dose intravesical chemotherapy administered within 6 hours of resection reduces recurrence of low-risk tumors.
- All suspicious lesions should be sampled, but "random" biopsies are not required in low-risk patients.
- Office-based fulguration and observation may be applied to certain low-risk patients.
- Fluorescence cystoscopy with 5-ALA derivatives improves the ability to visualize inconspicuous tumors and appears to reduce recurrence rates following TUR.

to fibronectin within the bladder wall, subsequently leading to direct stimulation of cell-based immunologic response and an antiangiogenic state. Numerous cytokines involved in the initiation or maintenance of inflammatory processes including tumor necrosis factor (TNF)-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, and interleukin (IL)-1, IL-2, IL-5, IL-6, IL-8, IL-10, IL-12, and IL-18 have been detected in the urine of patients treated with intravesical BCG and other immunostimulatory agents. **The observed pattern of cytokine induction with preferential upregulation of interferon-γ, IL-2, and IL-12 reflects induction of a T-helper type-1 (Th1) response.** This immunologic response activates cell-mediated cytotoxic mechanisms that are believed to underlie the efficacy of BCG and other agents in the prevention of recurrence and progression (Bohle and Brandau, 2003). In addition, BCG may concomitantly stimulate IL-10, resulting in the suppressive T-helper type-2 (Th2) response. Increasing the predominance of the Th1 response versus the Th2 response is an area of continued research (Lou, 2003). Overall, response to intravesical immunotherapy may be limited if a patient has an immunosuppressive disease or by advanced age (Joudi, 2006a, 2006b).

Bacillus Calmette-Guérin

BCG is an attenuated mycobacterium developed as a vaccine for tuberculosis that has demonstrated antitumor activity in several different cancers including UC (Morales et al, 1976). The original regimen described by Morales included a percutaneous dose, which was discontinued after success using a similar intravesical regimen by Brosman (1982).

BCG is stored in refrigeration and reconstituted from a lyophilized powder. Connaught, Tice, Armand Frappier, Pasteur, Tokyo, and RIVM strains all arise from a common original strain developed at the Pasteur Institute. The vaccine is reconstituted with 50 mL of saline and should be administered through a urethral catheter under gravity drainage soon thereafter to avoid aggregation (Ratliff et al, 1994). **Treatments are generally begun 2 to 4 weeks after tumor resection, allowing time for re-epithelialization, which minimizes the potential for intravasation of live bacteria** (Lamm et al, 1992b). **For the same reason, a urinalysis is usually performed immediately before instillation to further ensure a diminished probability of systemic uptake of BCG. In the event of a traumatic catheterization, the treatment should be delayed for several days to 1 week, depending on the extent of injury. After instillation, the patient should retain the solution for at least 2 hours.** Some clinicians have advocated the patient turn from side to side to bathe the entire urothelium, but there is no scientific support for this practice. Fluid, diuretic, and caffeine restriction before instillation is essential to limit dilution of the agent with urine and to facilitate retention of the agent for 2 hours (Lamm et al, 2000a). Patients are instructed to clean the toilet with bleach, although there is no demonstrable risk of close contact infection.

BCG Treatment of Carcinoma in Situ

American urologists use BCG by a 2:1 margin compared with intravesical adjuvant or maintenance chemotherapy (e.g., doxorubicin hydrochloride [Adriamycin], gemcitabine, thiotepa), whereas European urologists favor chemotherapy. BCG is approved for this indication by the U.S. Food and Drug Administration (FDA). Before the adoption of BCG intravesical therapy, CIS reportedly progressed at an average rate of 7% per year (Zinke, 1985).**The initial tumor-free response rate is as high as 84%** (Brosman, 1982; DeJager et al, 1991; Hudson and Herr, 1995; Lamm et al, 2000a, 2000b, 2000c). **Approximately 50% of patients experience a durable response for a median period of 4 years. Over a 10-year period, approximately 30% of patients remain free of tumor progression or recurrence, so close follow-up is mandatory. The majority of these occur within the first 5 years** (Herr et al, 1992). Herr and coworkers (1989) **reported progression in 19% of initial responders at 5 years but found the rate to be 95% in nonresponders—findings confirmed by other investigators** (Coplen et al, 1990; Harland et al, 1992). **The American Urological Association (AUA) Guidelines Panel supported BCG as the preferred initial treatment option for CIS** (Hall et al, 2007).

BCG has gained a pre-eminent role in North America on the basis of higher efficacy reports compared with intravesical chemotherapy, despite greater morbidity than chemotherapy (O'Donnell, 2007). In more than 600 patients, there was a 68% complete response rate to BCG and a 49% complete response rate to chemotherapy. In responders, 68% of patients treated with BCG remained free of disease as compared with 47% of patients receiving chemotherapy, on the basis of a median follow-up of 3.75 years. The overall disease-free rates were 51% and 27%, respectively (Sylvester et al, 2005).

BCG Treatment of Residual Tumor

Intravesical **BCG can effectively treat residual papillary lesions but should not be used as a substitute for surgical resection.** Investigators have demonstrated a nearly 60% response by residual tumor with intravesical BCG alone (Brosman, 1982; Schellhammer et al, 1986; Coplen et al, 1990).

Carcinoma of the mucosa or the superficial ducts of the prostate can be adequately treated by BCG with a 50% tumor-free rate. A limited TURP can be effective in decreasing tumor burden and facilitating exposure of the prostate surface to BCG administration (Bretton et al, 1990; Schellhammer et al, 1995).

BCG Prophylaxis to Prevent Recurrence

Early single-center studies demonstrated an advantage in decreased tumor recurrence of approximately 30% when a 6-week course of BCG was administered after recovery from TURBT (Brosman, 1982; Morales et al, 1992). In several larger series, tumor recurrence after TURBT was reduced by 20% to 65%, for an average of approximately 40% (Pagano et al, 1991a, 1991b; Herr et al, 1992; Melekos et al, 1993; Krege et al, 1996). Han and Pan published a meta-analysis in 2006 evaluating 2000 patients with Ta, T1, and/or CIS disease. Patients receiving maintenance BCG had a statistically decreased rate of recurrence compared with those receiving induction therapy alone (Han and Pan, 2006).

The efficacy of BCG after TURBT for high-risk papillary disease has been demonstrated in several series of T1 lesions, with recurrence rates of 16% to 40% and progression rates of 4.4% to 40%, a substantial improvement compared with TUR alone (Cookson and Sarosdy, 1992; Pansadoro et al, 1995; Herr, 1997; Jimenez-Cruz et al, 1997; Gohji et al, 1999; Hurle et al, 1999a, 1999b). Tumor multiplicity and associated CIS were associated with increased risk of progression. Substaging lesions on the basis of the presence or absence of muscularis mucosae invasion in a series of 49 patients did not improve

prediction of recurrence (69% vs. 65%) or progression (22% vs. 29%) after BCG therapy (Kondylis et al, 2000).

Impact of BCG on Progression

Although reports of the impact of BCG on tumor recurrence are compelling, the greater need is the potential for impact on progression. In 403 patients with CIS, BCG reduced the risk of progression by 35% compared with intravesical chemotherapy (Sylvester, 2002).

In a randomized trial of 86 patients with high-risk superficial disease, Herr and colleagues (1988) demonstrated a greater delay in interval progression for BCG patients versus TUR controls. Additionally, the cystectomy rate was significantly decreased for CIS patients treated with BCG (11% vs. 55% for controls), as was the time to cystectomy. However, only 27% of patients were alive with an intact functioning bladder after follow-up over 10 to 15 years, so this apparent advantage is temporary in many cases (Cookson et al, 1997). Available data suggest that BCG can delay progression of high-risk bladder cancer, yet the long-term survival advantage is hypothetical.

Nevertheless, two meta-analyses have concluded that BCG reduces the risk of progression. Progression at 2.5 years' median follow-up was reduced by 27% (9.8% for BCG vs. 13.8% for non-BCG) in one (Sylvester, 2002) and by 23% (7.7% for BCG vs. 9.4% for MMC) at 26-month median follow-up in another analysis (Bohle and Bock, 2004). In both cases the **superior results with BCG were only seen in trials using BCG maintenance therapy. In contrast, no chemotherapy trials have achieved a significant reduction in progression** (Grossman et al, 2008).

Nuclear P53 overexpression before BCG therapy has not been shown to predict response to therapy, but post-therapy P53 overexpression is an independent marker of disease progression (Lacome et al, 1996; Lebret et al, 1998). The AUA Guidelines panel concluded that BCG appeared likely to reduce progression (Hall et al, 2007).

Determining Optimum BCG Treatment Schedule

The optimal treatment schedule and dose for BCG have not been established. Morales wrote in the reply to an editorial comment to his landmark article (see box), "This regimen is arbitrary, and may be modified in the future as additional data become available" (Morales et al, 1976). In reality, **several studies suggest that a 6-week induction course alone is insufficient to obtain an optimal response in many patients and that maintenance therapy is requisite** (Lamm et al, 2000a, 2000b, 2000c; Palou et al, 2001).

One of the enduring urban myths in urology is the story of Dr. Alvaro Morales' initial work with BCG. Although the rumor is usually stated that he chose the dosing regimen based on the fact the drug is shipped in a "6-pack," he relates that there is more to the story:

"A contemporary abstract had indicated that BCG was ineffective for bladder cancer. However, from our experience and that of others, we knew that at least a 3-week period of immunizations was needed for mounting a delayed hypersensitivity reaction. The intradermal administration provided not only assurance of an enhanced systemic recognition, but also an inexpensive and readily available marker of immune competence. To this day, I remain convinced that eliminating the simultaneous transdermal administration is very convenient for patients and physicians but is not as effective. It was our impression that the skin reactions reached by weeks 4 to 5 were not further enhanced by more BCG. The Frappier labs provided us with boxes of six vials. We thus—for better or worse—decided to stop treatment at 6 weeks, assuming that what was seen on the skin was occurring on the bladder mucosa. Fortunately, that turned out to be true. Bohle and others reported years later that 6 weeks were ideal for maximum response to BCG, although we now know that maintenance dosing enhances response even further."

The average additional response to a second induction course is 25% in those patients treated for prophylaxis and 30% in CIS patients (Haaff et al, 1986a, 1986b; Kavoussi et al, 1988; Bretton et al, 1990; Coplen et al, 1990; Sylvester, 2002; Bohle and Bock, 2004). However, **additional courses of BCG to treat refractory patients after a second 6-week course are accompanied by a significant risk of tumor progression in 20% to 50% of patients** (Nadler et al, 1994). Catalona and colleagues (1987) reported roughly a 7% actuarial risk of progression with every additional course of BCG therapy. Response to BCG at 6 months can be used as a predictor of prognosis, with the number of patients developing progressive disease being significantly higher among nonresponders (Orsola et al, 1998).

The Southwest Oncology Group (SWOG) reported the most significant impact of maintenance therapy. Patients received a 6-week induction course followed by three weekly instillations at 3 and 6 months and every 6 months thereafter for 3 years. **Estimated median recurrence-free survival was 76.8 months in the maintenance arm and 35.7 months in the control arm (P = .0001).** Average recurrence-free survival was 111.5 months in the control arm and not able to be estimated in the maintenance arm (P = .04). Overall 5-year survival was 78% in the control arm and 83% in the maintenance arm. No toxicities above grade 3 were observed, yet **only 16% of patients tolerated the full dose-schedule regimen.** Two thirds of the patients who stopped BCG due to side effects did so in the first 6 months, suggesting that the side effects do not increase appreciably with additional time on therapy. An interpretation that the intended full course of maintenance therapy cannot be accomplished in most patients due to side effects is misleading. **Due to the fact that the treatment group fared better despite most patients failing to complete the full course of therapy, the maximum benefit may have been achieved earlier. Shorter maintenance schedules and reduced dosages may accomplish the same results with less toxicity** (Lamm et al, 2000b).

Although some older studies failed to identify a benefit to maintenance therapy (Badalament et al, 1987), most authorities believe that at least 1 year of maintenance therapy is appropriate. Clearly for high-grade T1 lesions or CIS, maintenance therapy has proven superior in multiple studies (Palou et al, 2001). **The determination of whether the optimal treatment schedule should be as described in the SWOG study or monthly remains unclear, and optimal duration of a monthly maintenance schedule, if chosen, is unknown** (Lamm et al, 2000a, 2000b, 2000c; O'Donnell, 2005). The authors routinely administer

Table 81–4.

Contraindications to Bacillus Calmette-Guérin (BCG) Therapy

Absolute Contraindications

Immunosuppressed and immunocompromised patients
Immediately after transurethral resection on the basis of the risk of intravasation and septic death
Personal history of BCG sepsis
Gross hematuria (intravasation risk)
Traumatic catheterization (intravasation risk)
Total incontinence (patient will not retain agent)

Relative Contraindications

Urinary tract infection (intravasation risk)
Liver disease (precludes treatment with isoniazid if sepsis occurs)
Personal history of tuberculosis (risk theorized but unknown)
Poor overall performance status
Advanced age

No or Insufficient Data on Potential Need for Contraindications

Patients with prosthetic materials
Ureteral reflux
Anti–tumor necrosis factor medications (theoretically predispose to BCG sepsis)

From Ehlers S. Why does tumor necrosis factor targeted therapy reactivate tuberculosis? J Rheumatol (Suppl.) 2005;74:35–9.

Table 81–5.

Cleveland Clinic Approach to Management of Bacillus Calmette-Guérin (BCG) Toxicity

Grade 1: Moderate Symptoms <48 Hr

Mild/moderate irritative voiding symptoms, mild hematuria, fever <38.5° C

ASSESSMENT

Possible urine culture to rule out bacterial urinary tract infection

SYMPTOM MANAGEMENT

Anticholinergics, topical antispasmodics (phenazopyridine), analgesics, nonsteroidal anti-inflammatory drugs

Grade 2: Severe Symptoms and/or >48 Hr

Severe irritative voiding symptoms, hematuria, or symptoms lasting >48 hr
All maneuvers for grade 1, plus the following:

ASSESSMENT

Urine culture, chest radiograph, liver function tests

MANAGEMENT

Consult immediately with physician experienced in management of mycobacterial infections/complications.
Consider dose reduction to one half to one third of dose when instillations resume.
Treat culture results as appropriate.

ANTIMICROBIAL AGENTS

Administer isoniazid and rifampins, 300 mg/day and 600 mg/day, orally until symptom resolution.
Do not use monotherapy.
Observe for rifampin drug-drug interactions (e.g., warfarin).

Grade 3: Serious Complications (Hemodynamic Changes, Persistent High-Grade Fever)

ALLERGIC REACTIONS (JOINT PAIN, RASH)

Perform all maneuvers described for grades 1 and 2, plus the following:
Isoniazid, 300 mg/day, and rifampin, 600 mg/day, for 3-6 months depending on response

SOLID ORGAN INVOLVEMENT (EPIDIDYMITIS, LIVER, LUNG, KIDNEY, OSTEOMYELITIS, PROSTATE)

Isoniazid, 300 mg/day, rifampin, 600 mg/day, ethambutol, 15 mg/kg/day single daily dose for 3-6 months
Cycloserine often causes severe psychiatric symptoms and is to be strongly discouraged.
BCG is almost uniformly resistant to pyrazinamide, so this drug has no role.
Consider prednisone, 40 mg/day, when response is inadequate or for septic shock (never given without effective antibacterial therapy).

From Walton Tomford, MD, Cleveland Clinic.

the first of three maintenance doses immediately after the scheduled cystoscopy confirms absence of recurrence, with the two following doses weekly thereafter.

Several investigators have evaluated the potential for BCG dose reduction (Morales et al, 1992; Melekos et al, 1993; Martinez-Pineiro et al, 1995; Pagano et al, 1995). In general, a decrease in toxicity with no statistical difference in efficacy has been noted in small series (Pagano et al, 1991b; Mack and Frick, 1995; Hurle et al, 1996), although multifocal and high-grade tumors may respond better to full dosing (Martinez-Pineiro et al, 2002). Some studies have shown an upregulation of the Th1 response with a lower-dose BCG. Lengthening of the instillation interval may decrease side effects without loss of efficacy (Bassi et al, 2000). European studies, where BCG inoculation for tuberculosis is more common than in North America, suggest the dose may be safely reduced by half (Martinez-Pineiro et al, 2002). The difference in response to doing so in immunologically naive North Americans is unknown, but Morales and colleagues (1992) found a significant decrease in response rates (67% vs. 37%), especially for patients with CIS in combination with papillary tumors treated with the reduced dose.

Antibiotic therapy may have a beneficial effect in treating or preventing systemic side effects of BCG therapy, yet it may also inhibit the effectiveness of BCG therapy if it is given routinely for urinary tract prophylaxis during a course of BCG therapy (Durek et al, 1999a, 1999b). **Quinolones in particular may affect the viability of BCG and should be avoided if possible during the course of BCG treatments** (Durek et al, 1999b). In contrast, in vitro data suggest that quinolone antibiotic therapy may augment intravesical chemotherapy with agents such as doxorubicin because both agents affect topoisomerase II inhibitors (Kamat et al, 1999) (Tables 81–4 and 81–5).

Interferon

Interferons are glycoproteins produced in response to antigenic stimuli. Interferons have multiple antitumor activities including inhibition of nucleotide synthesis; upregulation of tumor antigens, antiangiogenic properties; and stimulation of cytokine release with enhanced T and B cell activation, as well as enhanced natural killer cell activity (Naitoh et al, 1999). Among several subtypes, interferon-α has been the most extensively studied. It is most active in doses of at least 100 million units, although optimal dose and administration schedule have yet to be determined (Torti et al, 1988; Belldegrun et al, 1998).

Interferon as a solitary agent is more expensive and less effective than BCG or intravesical chemotherapy in eradicating residual disease, preventing recurrence of papillary disease, and treating CIS (20% to 43% complete response). Its long-term efficacy for CIS

is less than 15% (Belldegrun et al, 1998). A randomized trial demonstrated CIS responses from 5% at low doses (10 million units) to as high as 43% at high doses (100 million units) (Torti et al, 1988). As a prophylactic agent, interferon alone demonstrated recurrence rates that were generally inferior to those of BCG alone (from 60% to 16%) (Glashan, 1990; Kalble et al, 1994). It has demonstrated limited activity against T1 tumors (Malmstrom, 2001). However, it can occasionally be effective in patients who have failed BCG (15% to 20% complete response, see later).

Interferon-α has also been studied in a combination treatment regimen with either chemotherapy or BCG (Bercovich et al, 1995; Stricker et al, 1996). There appeared to be additive effects with either epirubicin or MMC. **Several trials investigated the combination of BCG and interferon and suggested the potential superiority of the combination or the possibility of decreasing the dosage of BCG, which may reduce side effects. Initial pioneering work by O'Donnell and colleagues in 2001 reported a 63% disease-free rate at 12 months and 53% at 24 months using combination therapy.** In a larger trial of 1000 overall patients, 231 patients with CIS were evaluated. In those CIS patients who failed an induction course of BCG, the combination of low-dose BCG and interferon produced a 45% durable response at 2 years. However, in those patients who had CIS and were BCG naïve, the BCG/interferon combination treatment resulted in 59% disease-free status at 24 months (Joudi, 2006a). Overall, patients who failed BCG alone within 12 months had a poor response to combination therapy. Of the nonresponders to combination BCG/interferon, the majority of patients who failed with recurrence did so **within 4 months of initial treatment** (Grossman et al, 2008).

Investigational Immunotherapeutic Agents

A number of novel agents have shown potential, but none has reached clinical practice. Keyhole-limpet hemocyanin (KLH) from the hemolymph of the mollusk *Megathura crenulata* is a nonspecific immune stimulant whose potential effectiveness in UC was identified serendipitously (Olsson et al, 1974; Jurincic et al, 1989). Bropirimine is an oral arylpyridinone that is an inducer of host interferon and induces natural killer cell and tumor necrosis factor, demonstrating a 23% to 55% complete response in patients with CIS (Sarosdy et al, 1992). Mycobacterial cell wall DNA extract contains a mixture of immunostimulatory DNA attached to antigenic cell wall. Phase 2 trial results indicate success rates less than that achieved with BCG, but with good tolerability (Morales et al, 2001). Thiosulfinate extracts of garlic were demonstrated to inhibit tumor growth in older studies and may have an immunostimulatory role (Riggs et al, 1997; Lamm and Riggs, 2001). Several reports have suggested immunostimulatory activity of mistletoe extract (Elsasser-Biele et al, 2005).

Interleukin-12 (IL-2) is highly expressed after BCG stimulation and is a key component of the Th1 immune response. Preclinical data suggest a potential benefit and little toxicity (Horinaga et al, 2005). Multiple studies have documented the potential use of either intravesical IL-2 alone, with BCG, or with BCG and interferon (Shapiro et al, 2007). Preclinical data identifying the efficacy of liposome-mediated intravesical IL-2 with biologic response modifiers have elucidated long-term T-cell memory against muscle-invasive and non–muscle-invasive bladder cancer (NMIBC) (Horiguchi et al, 2000; Larchian et al, 2000). Recent work at MD Anderson has led to a clinical trial employing adenoviral-delivered GM-CSF for BCG refractory bladder cancer.

Clinical studies evaluating the use of antiangiogenic agents for the treatment of refractory bladder cancer have begun at multiple institutions. The evaluation of these agents in concert with intravesical immunotherapy is now being reported (Patel et al, 2009).

INTRAVESICAL CHEMOTHERAPY

Induction therapy using chemotherapeutic agents instilled within 6 hours of TURBT has demonstrated a clear impact on recurrence rates, as described earlier. However, the role of chemotherapy in the adjuvant setting is less clear compared with the efficacy of BCG. A **SWOG comparison of doxorubicin and BCG showed a 15% progression rate in BCG patients compared with a 37% progression rate in chemotherapy patients** (Lamm et al, 1991). Nevertheless, the risk of BCG infectious complications is nonexistent with chemotherapy, leading many in the European community to favor this approach.

The agents are summarized in Table 81–6.

Table 81–6.

Comparisons between Intravesical Agents

AGENT	MW	PERIOPERATIVE USE	RISK GROUP	CYSTITIS (%)	OTHER TOXICITY	DROPOUT (%)	CONCENTRATION/ DOSAGE	COST*
Doxorubicin (Adriamycin)	580	Yes	Low-Intermediate	20-40	Fever, allergy, contracted bladder, 5%	2-16	50 mg/50 mL	$36
Epirubicin	580	Yes	Low-Intermediate	10-30	Contracted bladder rare	3-6	50 mg/50 mL	$595
Thiotepa	189	Yes	Low-Intermediate	10-30	Myelosuppression 8%-19%	2-11	30 mg/30 mL	$80
Mitomycin	334	Yes	Low-Intermediate	30-40	Rash 8%-19%, contracted bladder 5%	2-14	40 mg/20-40 mL	$130
BCG	N/A	No	Intermediate-High	60-80	Serious infection, 5%	5-10	1 vial/50 mL	$150
Interferon	23,000	No	Salvage	<5	Flulike symptoms 20%	Rare	50-100 MU/50 mL	$670-$1340
Gemcitabine	300	Yes	Salvage	Mild	Occasional nausea	<10	1-2 g/50-100 mL	$540-$1080

*Based on 2005 discount acquisition costs from oncology supply distributors.

Modified from O'Donnell MA. Practical applications of intravesical chemotherapy and immunotherapy in high-risk patients with superficial bladder cancer. Urol Clin North Am 2005;32:121–31.

Key Points: Immunotherapy

- Intravesical BCG has higher efficacy than intravesical chemotherapy.
- BCG should be used cautiously for patients with low-risk disease because of concern about side effects.
- BCG is the only agent shown to delay or reduce high-grade tumor progression.
- The optimum dosage and the treatment schedule for BCG are undetermined, but results are better with maintenance therapy, if tolerated.
- BCG is contraindicated in the setting of a disrupted urothelium because of the risk of intravasation and septic death.
- Interferon-α has not been shown to have benefit compared with BCG for primary treatment but appears to work well in combination with low-dose BCG, especially for salvage.

Mitomycin C

Mitomycin C is an alkylating agent that inhibits DNA synthesis. The drug is usually instilled weekly for 6 to 8 weeks at dose ranges from 20 to 60 mg. A meta-analysis of nine clinical trials compared its efficacy on progression with that of BCG. Within median follow-up of 26 months, **7.67% of the patients in the BCG group and 9.44% of the patients in the MMC group developed tumor progression** (Bohle and Bock, 2004). **Another review found a 38% reduction in tumor recurrence with MMC. This was not as effective as BCG but was considered in most studies to make MMC a viable option in light of its lesser side effects, particularly the low but real risk of sepsis** (Huncharek et al, 2001).

Optimization of MMC delivery can result in halving of the recurrence rate in some studies. This can be achieved by eliminating residual urine volume, overnight fasting, using sodium bicarbonate to reduce drug degradation, and increasing concentration to 40 mg in 20 mL (Au et al, 2001). The use of local microwave therapy in conjunction with MMC, 20 mg/50 mL, reduced recurrence rates from 57.5% to 17.1% in a multicenter trial. A study using microwave with higher doses of 40 to 80 mg for 6 to 8 weeks in high-grade bladder cancer found a recurrence-free rate of 75% at 2 years (Gofrit et al, 2004; van der Heijden et al, 2004).

Electromotive intravesical MMC appears to improve drug delivery into bladder tissue (Di Stasi and Riedl, 2009). This treatment reported reduction in recurrence rates with MMC from 58% to 31%, whereas patients in the BCG control arm had a 64% recurrence rate (Di Stasi et al, 2003). Peak plasma MMC was significantly higher in the electromotive group, supporting its reputed mechanism of action.

Doxorubicin and Its Derivatives

Doxorubicin (Adriamycin) is anthracycline antibiotic that acts by binding DNA base pairs, inhibiting topoisomerase II, and inhibiting protein synthesis. In a review, **doxorubicin demonstrated a 13% to 17% improvement over TUR in preventing recurrence but no advantage in preventing tumor progression (15.2% vs. 12.6%)** (Kurth et al, 1997). The principal side effect of intravesical doxorubicin is chemical cystitis, which can occur in up to half of patients. Reduced bladder capacity has been reported in several series (Thrasher and Crawford, 1992).

The **doxorubicin derivative epirubicin decreases recurrence compared with TUR alone by 12% to 15%** (Oosterlinck et al, 1993). This was demonstrated when epirubicin was given in a single, immediate, perioperative dose, as well as in full 8-week courses of intravesical therapy. Epirubicin is available for UC in Europe and FDA approved but is unavailable for treatment of UC in the United States.

Valrubicin is a semisynthetic analog of doxorubicin that was approved by the FDA for treatment of BCG refractory CIS in patients who cannot tolerate cystectomy and became available in 2009 in the United States (Sweatman et al, 1991; Greenberg et al, 1997; Grossman et al, 2008). In a cohort of 90 patients with BCG-refractory CIS, 21% demonstrated a complete response (Steinberg et al, 2000).

Thiotepa

Thiotepa (triethylenethiophosphoramide) is the only chemotherapeutic agent approved by the FDA specifically for the intravesical treatment of papillary bladder cancer. It is an alkylating agent and is not cell cycle specific. In controlled clinical trials ($N = 950$ patients), it has been shown to significantly **decrease tumor recurrence in 6 of 11 studies by up to 41% (mean decrease, 16%).** Systemic side effects can be seen owing to its low molecular weight, resulting in up to half of administered doses being absorbed and risking hematopoietic toxicity (Thrasher and Crawford, 1992). Nevertheless, most centers have substituted its use with BCG or the above chemotherapeutic agents.

Novel Agents

Gemcitabine and the taxanes paclitaxel and docetaxel have demonstrated activity against metastatic bladder cancer (Calabro and Sternberg, 2002). Intravesical gemcitabine can be safely administered either weekly or twice weekly for six to eight treatments. Minimal systemic absorption occurs through the bladder. Several small phase 1 and phase 2 studies have demonstrated reduction of recurrence of 39% to 70% including modest efficacy in heavily pretreated BCG-refractory patients (Maymi et al, 2004; O'Donnell, 2005). Taxanes have been formulated into an active intravesical treatment, but current published data are limited to preclinical studies (Le Visage et al, 2004).

Combination Therapy

Combining mechanisms of different agents is a logical and often successful approach to improve response rates for systemic therapy. However, studies have not identified clear benefit to doing so in intravesical therapy. For instance, in the study by Fukui and coworkers (1992), MMC (20 mg) was administered on day 1 and doxorubicin (40 mg) on day 2 once a week for 5 weeks in 101 patients. Fifty-one patients demonstrated a complete response and were further randomized to maintenance or no maintenance. Local side effects were significant in 50% of patients. Patients with CIS had fewer recurrences with maintenance therapy. Other studies demonstrated similar outcomes, with a **general theme of increased local side effects with modest outcome improvement** (Isaka et al, 1992; Sekine et al, 1994).

Combination chemotherapy and BCG was evaluated in prospective trials by several investigators. The EORTC reported a 46% complete response rate when a solitary marker tumor was intentionally not resected and patients were subsequently given sequential MMC and BCG (van der Meijden et al, 1996). In a study of

Key Points: Intravesical Chemotherapy

- Intravesical chemotherapy has a clear impact on tumor recurrence when immediately instilled after TURBT and in the adjuvant setting. There is no clear evidence of an impact on progression.
- Combinations of various chemotherapeutic agents and chemotherapy combined with BCG have not demonstrated major benefit combined with single-agent treatment, with the exception of interferon.
- In general, side effects of chemotherapy tend to be less common and less severe than those for BCG, but BCG is more efficacious.

188 patients with Ta and T1 lesions, no difference was seen with regard to recurrence, progression, or side effects in those patients treated with BCG and MMC compared with those treated with MMC alone. There was actually a significantly longer disease-free interval in the BCG monotherapy arm (55%) compared with the same combination arm (45%) in another study of 314 patients (Malmstrom et al, 1999; Solsona et al, 2002). Thus **no clear advantage is obtained with sequential therapy, combination chemotherapy, or chemotherapy and BCG regimens using any of the combinations explored to date** (Rintala et al, 1995, 1996; Witjes et al, 1998; Nieder et al, 2005).

MANAGEMENT OF REFRACTORY HIGH-GRADE DISEASE

Recurrent or persistent disease after an initial 6-week course of BCG has been traditionally referred to as *BCG failure,* although this term has been poorly defined in the past. Current consensus is that **persistent disease after BCG therapy can be categorized as BCG refractory (nonimproving or worsening disease despite BCG), BCG resistant (recurrence or persistence of lesser degree, stage, or grade after an initial course, which then resolves with further BCG), or BCG relapsing (recurrence after initial resolution with BCG). BCG-refractory patients in particular are an especially high-risk group and should be strongly considered for immediate cystectomy if young and in generally good health** (Herr and Dalbagni, 2003). Intravesical treatment should be reserved for patients refusing or too ill to undergo cystectomy, or on defined investigational protocols.

The necessity of biopsy to determine BCG response is unclear, although it should be strongly considered in high-risk patients to determine disease status at this key point in time. Urine cytology can be useful in this setting. Dalbagni and colleagues (1999) reported minimal utility in routine biopsy after BCG if cystoscopy and urinary cytology were both negative. Whereas 5 of 11 patients with erythematous bladder mucosa and positive cytology had positive bladder biopsies, none of 37 with erythematous lesions and negative cytology was positive, and only 1 in 13 patients with a normal mucosa had positive biopsies (Dalbagni et al, 1999). Other studies have suggested that the value of routine post-BCG biopsy is limited (Dalbagni et al, 1999). UroVysion FISH (Abbott Molecular, Chicago) conversion from positive to negative has been shown to correlate with BCG response in single-center studies (Kipp et al, 2005; Whitson et al, 2009).

Declaring failure may take up to 6 months because the response rate for patients with high-grade bladder cancer treated with BCG rose from 57% to 80% between 3 and 6 months after therapy. Clearly, the tumoricidal activity continued for some period after cessation of therapy. This has obvious implications not only for declaring BCG failure and the need for subsequent therapy but also for interpretation of success rates of salvage protocols if administered soon after therapy (Herr and Dalbagni, 2003).

Although most urologists will administer an initial 6-week course of intravesical therapy for high-risk patients (most likely involving BCG in North America and chemotherapy in Europe), **management of patients with persistent disease after the first course is more complex. Such patients are at increased risk of progression, which is particularly likely in the event of early recurrence, progression while on therapy, or multiple recurrences.**

If the initial treatment was chemotherapy, a course of BCG should be considered. BCG has demonstrated superiority to repeat courses of chemotherapy in this setting because the latter will lead to only an approximately 20% disease-free survival (Malmstrom et al, 1999; Steinberg et al, 2000). For patients who have failed BCG, a second course still gives a 30% to 50% response (Pansadoro and De Paula, 1987; Brake et al, 2000). Patients who cannot tolerate BCG for any reason may be considered for salvage chemotherapy, but the risk of failure and progression is high.

Further courses of BCG or chemotherapy beyond two are not recommended because they will fail 80% of the time. Rapid disease progression is common in such patients, so salvage chemotherapy, investigational protocols, and interferons alone or in combination with reduced doses of BCG may only be appropriate for patients who are unwilling or unable to undergo surgery even after being informed of their risks (Catalona et al, 1987).

The combination of IFN-α with BCG is expensive and has not been shown superior to BCG alone in primary therapy, so it has been used mostly for BCG failures. Small single-institution studies using low-dose BCG (typically one-third dose) plus 50 to 100 million units of IFN-α have demonstrated 1- to 2-year success rates of 50% to 60%, with better results with a second reinduction option and three sets of 3-week miniseries maintenance treatments 3, 9, and 15 months later (O'Donnell et al, 2001; Lam et al, 2003; Punnen et al, 2003). A large national multicenter phase 2 trial of combination BCG plus IFN-α in BCG-naïve and BCG-failure patients revealed similar findings (O'Donnell et al, 2004). Estimates for freedom from disease at 2 years were 57% for BCG-naïve patients and 42% for BCG-failure patients. Progression was seen in only 8% of patients in each group, suggesting this combination has a potential role regardless of prior BCG response.

Role of "Early" Cystectomy

Despite local therapy, **many cases of high-grade non–muscle-invasive bladder cancer will progress to invasion and risk of cancer death.** Although the initial response rate to BCG therapy in CIS patients can be above 80%, those patients who fail have a 50% chance of disease progression and potential for disease-specific mortality (Catalona et al, 1987; Nadler et al, 1994). Early (3-month) failure for T1 tumors after BCG is associated with an 82% progression rate, compared with a 25% progression rate in patients who do not fail at 3 months (Herr et al, 1997, 2000b). Up to 20% of patients with CIS will die of UC within 10 years (Herr et al, 1989), and each occurrence of T1 tumors is associated with a 5% to 10% chance of metastasis (Herr and Sogani, 2001), and

residual tumor found on repeat resection in these patients is associated with an 82% chance of developing muscle invasion (Herr et al, 1997). **These data offer compelling evidence of the potential to underestimate disease status in high-risk patients.**

Cookson and coworkers (1997) reported that 27% of high-risk patients treated initially with aggressive intravesical therapy did well and died of other causes, and the same low number survived with an intact, functioning bladder 15 years after diagnosis. However, approximately half of patients experienced progression, and one third died of their disease. In contrast, **patients who undergo immediate cystectomy for clinical T1 tumors benefit from more accurate pathologic staging in addition to a 10-year disease-free survival of 92%, compared with 64% with those with clinical T1 tumors who were found to actually have muscle invasion at the time of cystectomy** (Bianco et al, 2004).

Despite the benign connotation of the term *superficial* formerly applied, up to 50% of patients with presumed non–muscle-invasive high-grade disease who undergo cystectomy will actually be found to have muscle-invasive disease. Such procedures have traditionally been termed *early cystectomy* on the basis of the fact that they are performed before the traditional surgical indication of documented detrusor muscle invasion. Considering that up to 15% will already have micrometastases (Chang and Cookson, 2005) and that a delay in cystectomy of even 12 weeks is associated with poorer survival, some of these procedures do not seem to be "early" enough (Sanchez-Ortiz et al, 2003).

The risk of progression must be weighed against the risk, morbidity, and impact on quality of life for cystectomy. Thus **a reasonable goal might be, as termed by Chang and Cookson** (2005), **"timely" cystectomy for patients at risk.**

Ten-year survival after cystectomy for non–muscle-invasive cancer can range from 67% to 92% (Amling et al, 1994; Freeman et al, 1995). **However, despite the bias that substantial progression can be averted with the benefit of early detection and close surveillance in patients whose tumors are identified before muscle invasion, it appears that such patients who progress to muscle invasion have a poorer prognosis than do those who initially present with muscle-invasive disease** (Schrier, 2004; Lee et al, 2007). **Thus overconfidence in disease control status with high-risk patients on surveillance creates a false sense of security.**

The AUA Guidelines Panel listed cystectomy as the first option for patients with refractory disease after an initial course of intravesical therapy (see later). Nevertheless, **fewer than one in five American urologists surveyed stated that they would recommend cystectomy for their patients with CIS refractory to two courses of intravesical BCG, a group with an 80% risk of failure or progression** (Joudi, 2006). **Cystectomy in that setting, or for persistent high-grade papillary disease after two courses of intravesical therapy, is the standard of care and should not be considered "early."**

Retrospective data in most series suggest that tumor markers such as P53 and RB may be useful for stratifying high-risk patients in the future. High-risk P53 lesions have a 75% progression rate, compared with 25% in P53-negative lesions. Survival is 60% at 10 years in patients with P53-positive lesions, whereas it is 88% in patients with P53-negative lesions (Sarkis et al, 1993). Grossman and colleagues (1998) found that for T1 lesions evaluated for P53 and RB, progression at 5 years was 30% if either marker was positive and 47% if both markers were positive. No progression was noted in lesions that were wild type for both markers (Grossman et al, 1998). Although P53 positivity did not predict response for BCG-treated patients in another study, post-BCG P53-positive expression was a marker of tumor progression (P53 positive, 82% progression and 41% mortality; P53 negative, 13% progression and 7% mortality) (Lacome et al, 1996). Other studies have refuted these findings, so **the role of P53 for the prediction of tumor behavior and response to therapy remains under debate** (Peyromaure et al, 2002).

The role of surgical approaches involving potential oncologic concessions such as seminal and nerve-sparing cystectomy in such patients theoretically at lower risk of recurrence compared with patients with muscle invasion remains unknown (Hautmann and Stein, 2005). The availability of neobladder for less disfiguring urinary diversion has been reported to decrease the delay in treatment of such patients, potentially leading to significantly improved disease-free survival (Hautmann, 1998).

Critical evaluation of partial cystectomy for non–muscle-invasive bladder cancer is limited, although the practice is common (up to 20% of patients treated with extirpative therapy in the United States) in patients with muscle invasion (Hollenbeck et al, 2005). Holzbeierlein and colleagues (2004) reported that 6.9% of the patients presenting to Memorial Sloan-Kettering Cancer Center for surgical management of bladder cancer underwent partial cystectomy (29% of whom did so for clinical non–muscle-invasive disease). Five-year survival was 69%, and two thirds of patients were alive with an intact, functioning bladder. CIS was the most significant predictor of progression.

Partial cystectomy provides more accurate pathologic staging than does TURBT and allows lymphadenectomy. Appropriate candidates with non–muscle-invasive tumors would logically be the same as those for invasive cancer—those with solitary non-recurring tumors at the dome or well away from the trigone and no CIS.

Cystectomy should also be considered in patients whose cancer cannot be reasonably controlled through resection: bulky tumors, inaccessible due to a large bladder or urethral stricture disease, or otherwise not amenable to safe removal endoscopically.

In summary, **radical cystectomy offers the most accurate pathologic staging option and should be strongly considered for patients with non–muscle-invasive bladder cancers that are high grade and invading deeply into lamina propria, exhibit lymphovascular invasion, are associated with diffuse CIS, are in diverticula, substantially involve the distal ureters or prostatic urethra, are refractory to initial therapy, or are too large or anatomically inaccessible to remove in their entirety endoscopically. It can also be used in patients who understand the risks and benefits of bladder preservation versus cystectomy and request definitive therapy** (Stein, 2003). Partial cystectomy suffers from limited data but might be a promising bladder preservation option situated between the extremes of TURBT combined with intravesical therapy and radical cystectomy.

Role of Alternative Options for Refractory Disease

Photodynamic therapy (PDT) is performed by administering a photosensitizing agent such as porfimer sodium (Photofrin) systemically or hexaminolevulinate (HAL) intravesically. Two to 3

days after the substance has cleared from the normal tissue (for Photofrin), the patient is given an intravesical treatment with red laser light (630 nm) for 12 to 20 minutes. Intravesical intralipid allows for more uniform distribution of laser light (Manyak et al, 1990). After excitation by light the photosensitizer reacts with molecular oxygen to form free radicals and reactive singlet oxygen, which are cytotoxic.

The response rate in CIS patients from combined series is 66%, with a duration of 37 to 84 months (Jocham et al, 1989; Nseyo et al, 1997, 1998; Walther, 2000). For patients with papillary disease, an overall response rate of 51% has been achieved with a median time to recurrence of 24 to 48 months (Naito et al, 1991; Nseyo et al, 1997, 1998; Walther, 2000). PDT has been limited by significant side effects such as bladder contracture or irritability (50%) and dermal sensitivity (19%) (Naito et al, 1991; Uchibayashi et al, 1995; Nseyo et al, 1997, 1998).

Research efforts have been directed at development of improved photosensitizers and modifications in laser dosimetry (Kriegmair et al, 1996a; Nseyo et al, 1997, 1998). A leading candidate for photosensitization is HAL, a more lipophilic ester of 5-ALA, which generates a sensitizer called protoporphyrin IX that appears more tumor specific, although clinical data are limited (Datta et al, 1998). Preclinical studies using hypericin show promise (Kamuhabwa, 2004).

Radiation therapy in the treatment of non–muscle-invasive bladder cancer is generally restricted to those individuals who refuse cystectomy after the failure of intravesical therapy or who are unsuitable for major surgery (Kim, 2000). A complete response to radiation therapy and TUR is attainable in 50% to 75% of patients, but the additional benefit of radiation to TUR remains unclear (DeNeve et al, 1992; Rozan et al, 1992; Jansson et al, 1998). Five-year response rates are 44% to 60%. There is no significant effect on CIS. **Due to reports that up to 50% of patients will develop progression and a high likelihood of death** (Rödel, 2001), **there is a limited role for radiation therapy other than for palliative purposes in this population.**

Key Points: Management of Refractory Disease

- Patients who fail to respond to an initial course of intravesical therapy after TURBT are at high risk of recurrence or progression.
- Failure after initial chemotherapy or BCG is most appropriately treated with a subsequent course of BCG because its efficacy in this setting is significantly greater than that of chemotherapy.
- Patients at high risk for progression should be considered for cystectomy.
- Failure to respond to an initial course of intravesical therapy is occasion to reconsider cystectomy. Failure to respond to a second course is an indication for immediate cystectomy unless contraindicated or the patient chooses to pursue clinical trials.

SURVEILLANCE AND PREVENTION

Although bladder cancer is less common than prostate cancer, expenditures are almost twice as high for bladder cancer due to its chronic nature and the need for long-term surveillance. According to the Agency for Health Care Policy and Research, annual expenditures are $2.2 billion for bladder cancer versus $1.4 billion for prostate cancer (Donat, 2003). A significant portion of this cost is due to surveillance (Hedelin et al, 2002).

Surveillance strategies for UC recurrence have historically relied on the diagnostic combination of cystoscopy and urinary cytology. In clinical practice, only 40% of patients actually comply with a standard surveillance protocol (Schrag et al, 2003). Most protocols include this combination every 3 months for 18 to 24 months after the initial diagnosis, then every 6 months for the following 2 years, and then annually, resetting the clock with each newly identified tumor (Fitzpatrick, 1993). Although the accuracy of both tests relies on subjective and operator-dependent interpretation of visible findings, their traditional presumed status as the "gold standard" has been widely accepted (Brown, 2000).

Cystoscopic Surveillance

Office-based cystoscopy offers rapid, relatively painless visual access to the urothelium. Papillary tumors are readily identified arising from the smooth bladder surface. CIS is classically described as a velvety red mucosal patch, although the reliability of such findings has been called into question.

The role of cystoscopy as a "gold standard" in cancer detection has come under scrutiny with the emergence of tumor markers and the development of newer endoscopic technology including fluorescence cystoscopy as described previously (Kriegmair et al, 1996a, 1996b, 1999; Filbeck et al, 1999). Nevertheless, for office-based diagnosis it allows identification of the site and characteristics of most tumors. **There is a high positive predictive value with cystoscopy because most lesions believed to be malignant are proven so pathologically. The endoscopic appearance cannot reliably predict tumor stage or grade, although sessile morphology and/or the presence of necrosis suggest high-grade disease likely to be invasive.**

Cystoscopy is usually performed in the outpatient setting. Rigid rod lens systems offer accurate visualization of the bladder. Flexible fiberoptic cystoscopes are almost as sensitive and are markedly more comfortable for men, although there is no clear advantage to their use in women because of the short, straight female urethra. Newer digital chip cystoscopes offer similar tolerability but better visualization due to clarity and magnification on video monitors. Complete visualization of the bladder mucosa is possible in a matter of seconds in most patients. Their high-resolution imaging obviates the only potential advantage of rigid cystoscopy (slightly better optics than fiberoptic flexible scopes). Thus **flexible cystoscopy has essentially replaced rigid cystoscopy for surveillance in men in North America and may do so in women.**

Using the same technology for flexible cystoscopy as described earlier for HAL fluorescence rigid cystoscopy, phase 2 studies have had mixed results but suggest that office-based fluorescence cystoscopy can improve the detection of CIS and papillary tumors (Witjes, 2004; Loidl, 2005).

The vast majority of both men and women tolerate office-based cystoscopy with minimal discomfort. **Intraurethral injection of local anesthetics is almost universal among urologists despite a paucity of data to support the practice. Most studies and a meta-analysis** (Patel et al, 2008b) **have failed to identify benefit** (Palit et al, 2003; Rodriguez-Rubio et al, 2004), and two recent studies actually found that pain experience was higher with the use of local anesthetics than in patients cystoscoped using aqueous lubricant alone (Ho et al, 2003; Chen et al, 2005). **Considering the fact that anesthetic agents**

can partially cloud visualization, this ubiquitous practice should be reconsidered. Use of a video monitor allows the patient to see and understand the findings, theoretically distracting them from any discomfort. Men who are able to do so tolerate the procedure with approximately 50% less pain (VAS 2.21 vs. 1.31, $P < .01$) than those who cannot see their findings on the monitor (Patel et al, 2007). This has not been found to be of significant benefit in women for unclear reasons (Patel et al, 2008).

The **bladder should be evacuated before cystoscopy. This removes concentrated amorphous detritus and radiographic contrast** if studies were performed earlier in the day. Aspiration is occasionally necessary during the procedure using a 60-mL syringe attached to the irrigant port. This can further lessen clouding. A systematic approach is mandatory to ensure all urothelium is visualized.

Attempts to modify the previously described surveillance schedule have been made using decision analysis tools (Kent et al, 1989; Abel, 1993). Several authors recommend termination of surveillance at 5 or more years for low-risk patients (Haukaas et al, 1999). However, the actual cost of surveillance cystoscopy is responsible for only 13% of the expenditures for bladder cancer care in one study, so the financial opportunity may be limited for such efforts (Schoenberg et al, 2000; Hedelin et al, 2002). In addition, the risk of recurrence and potential for progression exists beyond this period. Reports of late recurrences of high-grade cancer years after the original tumor temper some authors' enthusiasm with terminating surveillance at any point (Thompson et al, 1993; Morris et al, 1995; LeBlanc et al, 1999; Zieger et al, 2000). Thus there is no consensus on such programs.

Other investigators have examined the predictive impact of early or multiple recurrences and how this might affect surveillance (Parmar et al, 1989; Holmang et al, 1995; Reading et al, 1995). **Tumor recurrence on initial 3-month cystoscopy and number of tumors on initial resection (single or multiple) provide the most predictive information with regard to recurrence in several studies. Absence of recurrence on the 3-month surveillance cystoscopy in patients with TaG1 tumors is associated with recurrence rates so low that annual cystoscopy appears safe even at that point (beginning 12 months after the initial resection** (Fitzpatrick et al, 1986; Olsen and Genster, 1995; Frydenberg et al, 2005). Finally, patients with a negative cystoscopy and a negative UroVysion assay (see later) are at low risk of recurrence in the following 6 to 12 months, creating opportunity to individualize the surveillance schedule (Sarosdy et al, 2002).

Urine Cytology

Cytology involves microscopic evaluation of stained cellular smears from the urine. Unlike tumor markers, urinary cytology is not a laboratory test—it is a pathologist's interpretation of the morphologic features of shed urothelial cells. Poor cellular cohesion in high-grade tumors, especially CIS, enhances the yield.

Its high specificity is the most important feature of cytology because a **positive reading regardless of cystoscopic or radiographic findings suggests the existence of malignancy in the vast majority of patients.** Even in the setting of UC patients with a negative workup (cystoscopy and upper tract imaging) with a persistently positive cytology, 40% were found to have genitourinary cancer within 24 months, with a mean time to diagnosis of 5.6 months (Nabi, 2004).

Bladder irrigation or barbotage increases the cellularity available for evaluation compared with voided urine. Nevertheless, Murphy (1981) showed that urine collected cystoscopically before obtaining a bladder wash provided additional diagnostic information in their study of 313 patients. Bladder washings had a higher yield, but 13.1% of cancers would have been missed in bladder washings alone. Moreover, mechanical trauma has the potential to create cellular alterations that might interfere with interpretation. Radiographic contrast media have also been implicated in creating cellular shrinkage, nuclear pyknosis, fragmentation, and cytoplasmic vacuolization that might lead to a false-positive reading, especially when injected for retrograde ureteropyelography (McClennan et al, 1978). This may not be a concern when low osmolar, ionic and nonionic, contrast media are used (Andriole et al, 1989).

Although cytology has traditionally been believed to have high sensitivity for high-grade cancer, recent studies do not support this. When Mayo Clinic researchers reviewed laboratory findings, they observed that only 58% of bladder tumors were identified using cytology. Its sensitivity was not limited to low-grade tumors because only 71% of high-grade cancers were identified. Because this was lower than expected, they subsequently reviewed the literature and found that **cumulative data from series published after 1990 reported that cytology actually identified (using the older grading system) 11% of grade 1, 31% of grade 2, and only 60% of grade 3 tumors** (Halling et al, 2000). In contrast, they observed that these recent findings were well below those reported before 1990, when the sensitivity of cytology was 94% for grade 3 tumors, but could find no explanation for this deterioration. These findings are supported by numerous other studies and emphasized by a recent multicenter study involving several institutions noted for bladder cancer expertise that found cytology had an overall sensitivity of 15.8% (Grossman, 2005).

Thus cytology has high specificity but low sensitivity for both high-grade and low-grade tumors including CIS in recently published reports.

Tumor Markers

Many attempts have been made to develop a UC biomarker test to complement or replace urinary cytology (Table 81–7). Most of these have had adequate sensitivity but poor specificity, resulting in substantial false-positive readings, creating the need for further diagnostic testing. Current urinary markers have been developed to detect tumor-associated antigens, blood group antigens, growth factors, cell cycle/apoptosis, and extracellular matrix proteins. **The most significant issue limiting widespread adoption of tumor markers is the lack of prospective data to support their impact on prognosis or disease management** (Lokeshwar et al, 2005). They are considered alphabetically as follows.

The qualitative point-of-care test BTA stat (Polymedco, Inc., Cortlandt Manor, NY) and the quantitative BTA TRAK (Polymedco) assays detect human complement factor H–related protein. The overall sensitivity of these tests ranges from 50% to 80%, whereas the specificity is between 50% and 75%. These tests are more sensitive than cytology but can be falsely positive in patients with inflammation, infection, or hematuria (Liou, 2006).

ImmunoCyt (DiagnoCure, Inc., Saint Foy, Canada) is a hybrid of cytology and an immunofluorescent assay. Three fluorescent-labeled monoclonal antibodies are targeted at a UC variant of carcinoembryonic antigen and two bladder mucins. Sensitivity and specificity are reported to be 86% and 79%, respectively. It has not been shown to be affected by benign conditions, but

Table 81–7.

Commercially Available Markers

Commercially Available Marker	Reagent Cost*	Reimbursement	SENSITIVITY		SPECIFICITY	
			Mean (%)	Range (%)	Mean (%)	Range (%)
Cytology	$2.00	$25.00	48	16-89	96	81-100
Hematuria dipstick	$0.60	$3.00	68	40-93	68	51-97
NMP22	$25.00	$35.00	75	32-92	75	51-94
NMP22 BladderChek	$25.00	$35.00	55.7	85.7		
BTA stat	$14.00	$24.00	68	53-89	74	54-93
BTA TRAK	$7.00	$24.00	61	17-78	71	51-89
ImmunoCyt	$80.00	$109.00-$230.00	74	39-100	80	73-84
UroVysion	$102.47	$407.00	77	73-81	98	96-100

*Reagent only; labor costs vary.

Modified from Andriole G, Koney B: In office urinary markers for bladder Ca: what's new. Urol Times [serial online]. July 1, 2004; Liou LS: Urothelial cancer biomarkers for detection and surveillance. Urology 2006;67(3 Suppl. 1):25–33.

interpretation is complex and operator dependent (Toma, 2004; Tetu, 2005).

The NMP22 BladderChek Test (Matritech, Inc., Newton, MA) is based on the detection of nuclear matrix protein 22, part of the mitotic apparatus released from urothelial nuclei upon cellular apoptosis. The protein is elevated in UC, but it is also released from dead and dying urothelial cells. Benign conditions of the urinary tract such as stones, infection, inflammation, hematuria, and cystoscopy can cause a false-positive reading. Both a laboratory-based, quantitative immunoassay and a qualitative point-of-care test are available. The sensitivities and specificities range from 68.5% to 88.5% for sensitivity and from 65.2% to 91.3% for specificity (Liou, 2006). A multi-institutional trial involving 1331 patients showed that, overall, the NMP22 was more sensitive than cytology but less specific. Sensitivities were 50% and 90% for noninvasive and invasive cancer, respectively, with an overall sensitivity of 55.7%. Overall specificity was higher for cytology at 99.2% compared with NMP22 at 85.7%. The sensitivity of cystoscopy in this study was 88.6%, but when combined with NMP22 this increased to 93.7% (Grossman, 2005).

UroVysion (Abbott Molecular, Chicago) is a cytology-based test that uses FISH of DNA probes or "labels" specifically chosen to identify certain chromosomal foci. Probes to identify aneuploidy of chromosomes 3, 7, and 17 are combined with a probe to the 9p21 locus. Probes can be developed to identify essentially any locus, but this combination has the best sensitivity and specificity (Halling et al, 2000). Cumulative data from comparative studies show sensitivity for cytology compared with FISH of 19% versus 58% for grade 1, 50% versus 77% for grade 2, and 71% versus 96% for grade 3. Similar findings occurred by stage where cytology compared with FISH sensitivity was 35% versus 64% for Ta, 66% versus 83% for T1, and 76% versus 94% for muscle-invasive carcinoma (Jones, 2006).

Notably, cytology detected only 67% of cases with CIS versus 100% detection by FISH in comparative studies. UroVysion has the highest specificity of the available tumor markers. It will, however, detect chromosomal changes before the development of phenotypic expression of malignancy, so it leads to an "anticipatory positive" reading in some patients. Such readings are often not false positives and will lead to identification of clinical tumors within 3 to 15 months in the majority of cases (Sarosdy et al, 2002). Moreover, patients testing negative are unlikely to experience tumor recurrence in less than 1 year (Yoder et al, 2007). This may allow identification of patients at risk of recurrence versus those unlikely to recur in order to individualize surveillance protocols.

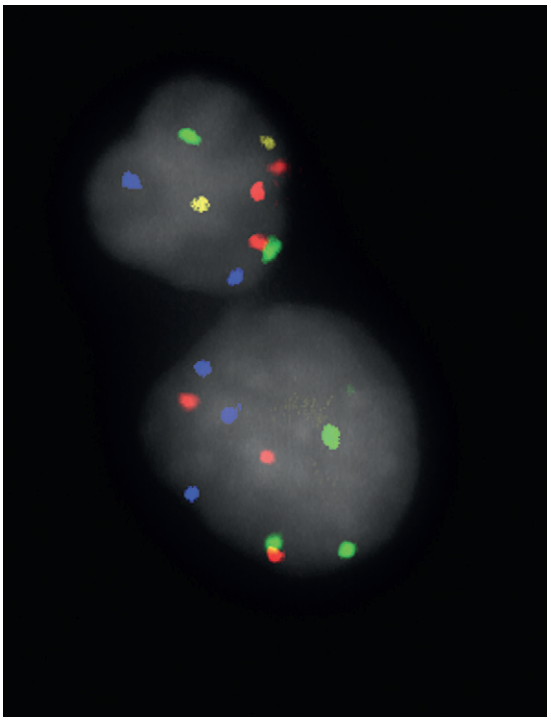


Figure 81–8. An abnormal enlarged cell *(lower right)* demonstrates three copies of chromosome 3 *(red),* chromosome 7 *(green),* and chromosome 17 *(aqua)* using fluorescence in situ hybridization. Homozygous deletion of band 9p21 locus *(yellow)* is also present. (Courtesy of Raymond Tubbs, MD; Department of Laboratory Pathology, Cleveland Clinic Foundation.)

UroVysion has also been shown to clarify equivocal findings in patients with atypical or negative cytology (Skacel, 2003). It is not affected by hematuria, inflammation, or other factors that can cause false-positive readings with some tumor markers, so it appears to be useful as a marker of BCG response (Kipp et al, 2005; Whitson et al, 2009).

Determining the utility of tumor markers and the choice of which one to use is not clear at this time. For example, if indication for biopsy in the operating room is the end point, then high specificity is desired to limit the number of negative biopsies. On the other hand, if increasing the interval of cystoscopic surveillance is the end point, then high sensitivity, particularly for high-grade tumors, is desired. Defining that a patient has a low likelihood of recurrence within the following year can allow individualization of surveillance protocols (Fig. 81–8) (Grossman et al, 2006).

Extravesical Surveillance

The proportion of patients developing upper tract UC after treatment of non–muscle-invasive disease has been reported as 0.002% to 2.4% over intervals of 5 to 13 years (Shinka et al, 1988; Oldbring et al, 1989; Holmang et al, 1995; Sadek et al, 1999), although the risk increases substantially over time to as high as 18% in very high-risk populations (Herr et al, 1997). Synchronous tumors were detected in none of 78 patients (0%) with grade 1 (using the prior grading system) tumors, 4 of 361 (1.1%) with grade 2, and 5 of 360 (1.3%) with grade 3, as well as 0% for low-grade Ta and 7% for T1 (Herranz-Amo et al, 1999). Most patients will require upper tract imaging specifically for the indication of hematuria. **A recent report from the Surveillance Epidemiology and End Results (SEER) database showed that only 0.8% of bladder cancer patients develop subsequent upper tract tumors, so surveillance is of limited value unless the patient has hematuria or a high-grade tumor near the ureteral orifice** (Wright et al, 2009). In a review of 591 patients with median follow-up of 86 months, upper tract recurrence was 0.9% in low-risk patients (solitary, low-grade, low-stage Ta/T1), 2.2% in patients at intermediate risk (recurrent or multifocal disease), and 9.8% in high-risk patients including intravesical chemotherapy failures (Hurle et al, 1998). **Most reviews have concluded that patients who have high-grade or multiple tumors should undergo upper tract imaging on the basis of the risk of upper tract disease, but those with low-grade tumors probably do not benefit from imaging at the time of bladder cancer diagnosis.**

The proper study to evaluate the upper tract is debatable. Excretory urography is the traditional choice but gives limited information about renal parenchyma and can miss small tumors. Retrograde ureteropyelography requires instrumentation, but this is often not a problem because these patients require removal of the primary bladder tumor, so the procedures can be combined. Computed tomography (CT) urography is a promising technology for the evaluation of hematuria, but its role in the evaluation of patients with non–muscle-invasive bladder cancer has not been extensively reported (Herts, 2003).

Although infrequent, the appearance of upper tract disease is associated with mortality rates of 40% to 70%. Patients with high-risk disease treated with BCG experience upper tract recurrence risk of 13% to 18% (Miller et al, 1993; Herr et al, 1997). The risk for recurrence in this population appears greatest over the first 5 years after treatment (median time to detection, 56 months) yet persists at least 15 years.

Selective cytology of the upper tract may increase the yield of upper tract lesions detected, but, in the presence of a bladder tumor, selective upper tract cytology may be falsely positive and is not recommended for most patients (Zincke et al, 1983; Sadek et al, 1999).

Secondary tumor involvement of the prostatic urethra and ducts by UC may be detected in 10% to 15% of patients with high-risk non–muscle-invasive disease within 5 years and in 20% to 40% within 10 years (Donat, 2003). Patients who have refractory disease are at risk for extravesical recurrence in the prostatic fossa in approximately one third of cases, 44% of which are fatal (Herr et al, 1988).

In summary, surveillance strategies should be individualized on the basis of the risk of recurrence in the bladder and extravesical sites (Table 81–8).

Secondary Prevention Strategies

Both lifestyle changes and chemoprevention could potentially reduce the risk of recurrence and should be considered in the comprehensive management of patients with non–muscle-invasive disease. **Unlike primary prevention, secondary prevention seeks to prevent recurrent tumors in patients who already carry a diagnosis of a specific cancer.** Although this may also involve minimizing exposure to carcinogens, it relies more heavily on optimizing host responses and creating an environment that can retard tumor growth.

Lifestyle changes are particularly important because UC is directly linked to environmental factors in the majority of cases. **Smoking cessation, increased fluid intake, and a low-fat diet may all reduce the risk of recurrence,** with the former being of paramount importance. **Increased hydration reduces the concentration and dwell time of carcinogens** and thereby reduces the risk of malignant transformation within the urothelium (Jiang, 2008). The Physician Health Study showed an inverse correlation between fluid intake and the incidence of UC on longitudinal follow-up, but this simple measure may also be of benefit for secondary prevention for patients who already have a history of UC (Michaud et al, 1999). **High fat and cholesterol intake are now firmly established as risk factors** for many cancers and UC is no exception, although the mechanisms are not as well defined as for other malignancies (Steineck et al, 1990).

Table 81–8.

Suggested Surveillance Strategies

RISK	TUMOR STATUS	CYSTOSCOPY SCHEDULE	UPPER TRACT IMAGING
Low	Solitary TaG1	3 mo following initial resection Annually beginning 9 mo after initial surveillance if no recurrence Consider cessation at 5 or more yr Consider cytology or tumor markers	Not necessary unless hematuria present
Intermediate	Multiple TaG1 Large tumor Recurrence at 3 mo	Q 3 months for 1-2 yr Semiannual or annual after 2 yr Consider cytology or tumor markers Restart clock with each recurrence	Consider imaging, especially for recurrence Imaging for hematuria
High	Any high grade (including CIS)	Q 3 months for 2 yr Semiannual for 2 yr Annually for lifetime Cytology at same schedule Consider tumor markers Restart clock with each recurrence	Imaging annually for 2 yr, then consider lengthening interval

Table 81–9.

American Urological Association 2007 Guidelines for Non–Muscle-Invasive Bladder Cancer

Index Patient #1: Abnormal Urothelial "Growth" but Not Proven Cancer

Standard: Obtain biopsy to confirm grade for all index patients
If possible, eradicate all visible tumors
If cancer, periodic cystoscopy
Option: Single dose of postoperative intravesical chemotherapy

Index Patient #2: Small-Volume, Low-Grade Ta

Recommendation: Single dose of postoperative intravesical chemotherapy

Index Patient #3: Multifocal or Large Low-Grade Ta, or Recurrent Low-Grade Ta

Recommendation: Intravesical BCG or MMC—goal to prevent/delay recurrence
Option: Maintenance BCG or MMC

Index Patient #4: High-Grade Ta, T1, or CIS

Standard: If T1 disease, but no muscularis in specimen, repeat resection
Recommendation: Intravesical BCG with maintenance therapy
Option: Consider cystectomy for select patients

Index Patient #5: High-Grade Ta, T1, and/or CIS Following Prior Intravesical Therapy

Standard: T1 disease but no muscularis in specimen, repeat resection
Recommendation: Consider cystectomy as therapeutic alternative
Option: Further intravesical therapy may be considered

BCG, bacillus Calmette-Guérin; CIS, carcinoma in situ; MMC, mitomycin C.
From Hall MC, Chang SS, Dalbagni G, et al. Guideline for the management of non-muscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. J Urol 2007;178:2314.

A variety of agents have been investigated for chemoprevention strategies for patients with UC and, although not clinically fruitful to date, this remains an active area of investigation. Retinoids including vitamin A and its analogs have been studied most intensively. These agents enhance differentiation of normal and neoplastic cells and appear to have antioxidant and immunostimulatory properties. Whereas animal studies for preventing UC were promising, studies looking at primary prevention in humans were conflicting and the side effects of these agents were problematic in this long-term prophylactic setting (Sporn et al, 1977; Becci et al, 1978; Eichholzer et al, 1996; Steinmaus et al, 2000). Synthetic retinoids with the potential for reduced toxicity have been tested in patients with known UC. However, fenretinide failed to reduce recurrence rates when compared with placebo, and 3 patients (12%) in the etretinate arm of another randomized study were found to have myocardial infarctions, although this may have been coincidental (Studer et al, 1995; Decensi et al, 2000; Lerner et al, 2005). Etretinate delayed the time to second recurrence but had no effect on time to first recurrence, and potential cardiac risk was of concern.

Pyridoxine (vitamin B_6) breaks down tryptophan metabolites in the urine that may induce UC, but clinical studies have been conflicting (Byar and Blackard, 1977; Newling et al, 1995). Difluoromethylornithine (DFMO), which inhibits the enzyme ornithine decarboxylase that contributes to malignant transformation, was also studied recently in patients with non–muscle-invasive UC (Messing et al, 2005). However, recurrence rates for this agent were not reduced when compared with placebo and enthusiasm has thus waned.

The most promising data for secondary chemoprevention of UC relate to the use of high doses of multivitamins. One small but important study randomized 65 patients with noninvasive UC to either a recommended daily allowance (RDA) multivitamin or megadose vitamins with augmented levels of vitamins A, B_6, C, and E (Lamm et al, 1994). Comparison of the two regimens revealed no difference in recurrence rates in the first year; however, there was a statistically significant advantage for the megadose group when the 5-year recurrence rates were calculated. At this point, 80% of patients in the RDA group had experienced recurrence compared with only 40% in the megadose group. These findings suggest that the beneficial effect of megadose vitamins is related to its suppressive effect on partially transformed cells within the urothelium rather than inhibiting early recurrences, which are typically caused by tumor cell implantation or incomplete resection. Confirmation of these findings by larger prospective trials is necessary.

Ongoing phase 3 trials for patients with noninvasive UC are evaluating the potential chemopreventive roles of celecoxib (a cyclooxygenase-2 inhibitor), erlotinib (an epidermal growth factor receptor inhibitor), and green tea extracts.

Key Points: Surveillance and Prevention

- Cystoscopy is the hallmark of surveillance. The optimum schedule is undefined but may be individualized on the basis of risk.
- Table 81–8 demonstrates reasonable surveillance protocols based on clinical scenarios. Guidelines for management are shown in Table 81–9.
- A number of tumor markers have shown the ability to improve upon the sensitivity of cytology, but specificity is lower for most.
- Increased fluids, smoking cessation, and a low-fat diet are recommended.

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The complete reference list is available online at www.expertconsult.com.

chapter 82

Management of Metastatic and Invasive Bladder Cancer

Seth P. Lerner, MD, FACS ● Cora N. Sternberg, MD, FACP

Clinical Presentation, Diagnosis, and Evaluation
Treatment: Surgical
Neoadjuvant Chemotherapy
Adjuvant Chemotherapy
Bladder Preservation and Combined Modality Approaches
Molecular Markers in Invasive and Advanced Bladder Cancer
Nomograms in the Management of Patients with Invasive Bladder Cancer
Management of Metastatic Bladder Cancer
Neoadjuvant Therapy to Develop Novel Agents
Conclusions

CLINICAL PRESENTATION, DIAGNOSIS, AND EVALUATION

Significant progress has been made in the management of invasive cancer, and, along with our increased knowledge of multimodal therapy, a multidisciplinary approach to the evaluation and management has become increasingly imperative. The urologist, medical oncologist, and radiation oncologist play a central role in integrating the disciplines of surgery, chemotherapy, and radiation therapy in order to achieve the goal of long-term cancer control. This chapter focuses on the evaluation and treatment of patients with muscle-invasive and metastatic bladder cancer.

Natural History

The majority (80%) of patients with bladder cancer present de novo with muscle-invasive disease as its first manifestation. The remaining 15% to 20% progress from non–muscle-invasive cancer after treatment with intravesical therapy. **Deaths due to bladder cancer invariably occur as a result of distant metastases present at the time of loco-regional therapy.** Progression of cancer after definitive loco-regional therapy commonly occurs within the first 2 years after treatment. Late recurrences are more common after perioperative systemic chemotherapy and often occur in unusual sites including the central nervous system, bowel serosa, and peritoneum. Muscle-invasive bladder cancer must be considered as a systemic disease and therapeutic strategies must be designed around the integration of treatment targeting the loco-regional disease (bladder and pelvic lymph nodes) and occult visceral metastatic disease according to pathologic risk factors.

Histology

Primary cancers of the bladder arise from the urothelium, and by far the most common cell type is transitional cell. Squamous cell predominates in Middle Eastern countries where bilharziasis is endemic. It occurs more frequently in Western countries in women and in the setting of chronic indwelling catheters and recurrent infection. As the prevalence of bilharziasis has diminished significantly, transitional cell carcinoma (TCC) now accounts for more than one half of bladder cancer diagnosed in Egypt (el-Mekresh et al, 2009). Adenocarcinomas of the bladder are uncommon but occur in the bladder base/trigone area. Patients with exstrophy are at increased risk. Surgical treatment of urachal adenocarcinoma is partial cystectomy, and the biology is similar to that of colorectal adenocarcinoma. Small cell neuroendocrine cancer is also a rare variant and may be the predominant histology or may be mixed with TCC (Mazzucchelli et al, 2009). This phenotype is easily distinguished by immunohistochemistry expressing synaptophysin and chromogranin. Treatment requires neoadjuvant chemotherapy (cisplatin and etoposide) followed by radical cystectomy or radiation therapy (Siefker-Radtke et al, 2004). Small cell tumors may also be associated with paraneoplastic syndromes including ectopic adrenocorticotropic hormone (ACTH) production, hypercalcemia, and hypophosphatemia. Other neuroendocrine tumors occur in the bladder and include carcinoid tumors, which may originate in the bladder or invade the bladder from the gastrointestinal tract, most commonly from the appendix. Large cell neuroendocrine tumors are rare with few cases reported in the literature and are believed to behave in a manner similar to that of small cell tumors (Akamatsu et al, 2008).

Other unusual variants reported have included lymphoepithelioma-like cancers, which have a better prognosis than high-grade invasive TCCs, although treatment is similar stage for stage. The micropapillary variant resembles ovarian papillary serous cancer and is aggressive. It tends toward high grade and high stage and is frequently associated with lymphatic and vascular invasion (Kamat et al, 2006). Radical cystectomy is the treatment of choice because this phenotype typically does not respond to chemotherapy directed at TCC. Rhabdomyosarcoma is seen in both children and adults, and leiomyosarcoma is seen in adults. Primary lymphoma of the bladder is rare, but the bladder may be involved in up to 10% of cases of systemic lymphoma.

Clinical and Pathologic Staging

The T stage denotes the clinical stage, which is determined before definitive therapy. The depth of invasion determined on the transurethral resection of the bladder tumor (TURBT) specimen and the bimanual examination under anesthesia determine the clinical stage. Pathologic stage is derived from the cystectomy specimen. Clinical understaging is more common than overstaging (which does occur, however).

The 1997 TNM staging schema introduced a modification of prior staging schemes. Before 1997, T2 described disease in the inner half of muscle and T3a described disease in the outer half. T3b was used to identify all levels of perivesical fat invasion. In the current system T2a and T2b are used to designate the inner and outer half of the muscle, respectively, and the T3 category is split into T3a (microscopic) and T3b (macroscopic, or visible on gross inspection of the cystectomy specimen). The T4a prostate designation requires established stromal invasion, which can occur via the urethra or as direct extension via the bladder neck or posteriorly into the seminal vesicles or periprostatic tissue. Finding carcinoma in situ (CIS) in the prostatic urethra or ducts does not lead to upstaging because outcome is determined by the primary bladder cancer stage (Esrig et al, 1996; Pagano et al; 1996). Staging of nodes and metastases is similar to that for other genitourinary malignancies. Positive nodes above the common iliac bifurcation are classified as N+M1 disease. The UICC and AJCC staging systems were uniform in the sixth edition of the American Joint Committee on Cancer (AJCC) Staging Manual (Greene et al, 2002). An updated seventh edition includes the number of nodes removed as a quality measure of radical cystectomy. In addition, node metastases above the common iliac bifurcation are classified as N3 rather than M1 (Table 82–1) (Edge et al, 2010).

Table 82–1.

Tumor Node Metastasis Staging System for Bladder Cancer

Primary Tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Ta	Noninvasive papillary carcinoma		
Tis	Carcinoma in situ: "flat tumor"		
T1	Tumor invades subepithelial connective tissue		
T2	Tumor invades muscularis propria		
pT2a	Tumor invades superficial muscularis propria (inner half)		
pT2b	Tumor invades deep muscularis propria (outer half)		
T3	Tumor invades perivesical tissue		
pT3a	Microscopically		
pT3b	Macroscopically (extravesical mass)		
T4	Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall		
T4a	Tumor invades prostatic stroma, uterus, vagina		
T4b	Tumor invades pelvic wall, abdominal wall		
Regional Lymph Nodes (N)*			
NX	Lymph nodes cannot be assessed		
N0	No lymph node metastasis		
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)		
N2	Multiple regional lymph node metastasis in the true pelvic (hypogastric, obturator, external iliac, or presacral lymph node metastasis)		
N3	Lymph node metastasis to the common iliac lymph nodes		
Distant Metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic Stage/Prognostic Groups			
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1-3	M0
	Any T	Any N	M1

Note: cTNM is the clinical classification, and pTNM is the pathologic classification.
*Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are considered distant lymph nodes.
From Edge SB, Byrd DR, Compton CC, et al, editors. AJCC cancer staging manual. 7th ed. New York: Springer; 2010.

Staging Pitfalls

T1 versus T2. European Association of Urology (EAU) Guidelines require muscularis propria in the TURBT specimen for accurate staging of invasive cancers. In the absence of muscularis propria, understaging of T1 disease is common, and, unfortunately, this leads to worse outcomes for patients with T1 cancer (Dutta et al, 2001). True, T1 is often mistaken for T2 because there are fine muscle bundles called *muscularis mucosa* present within the lamina propria (Fig. 82–1A and B). There are blood vessels in this area as well. These muscle bundles may be confused with the muscularis propria and lead to overstaging of a T1 tumor as T2. In addition, recent data suggest that **up to 40% of patients initially diagnosed with T1 who undergo cystectomy have pathologic T2 disease** (Dutta et al, 2001). Because the management of patients with high-grade T1 tumors is challenging, it is imperative to stage these patients accurately before embarking on intravesical therapy. We therefore routinely re-resect T1G3 tumors before determining appropriate therapy even when we performed the original resection. Presence of persistent T1 cancer on re-resection is a highly significant predictor of poor outcome in patients treated with bacillus Calmette-Guérin (BCG) and is an indication for early cystectomy (Herr et al, 2007). Additional indications for initial

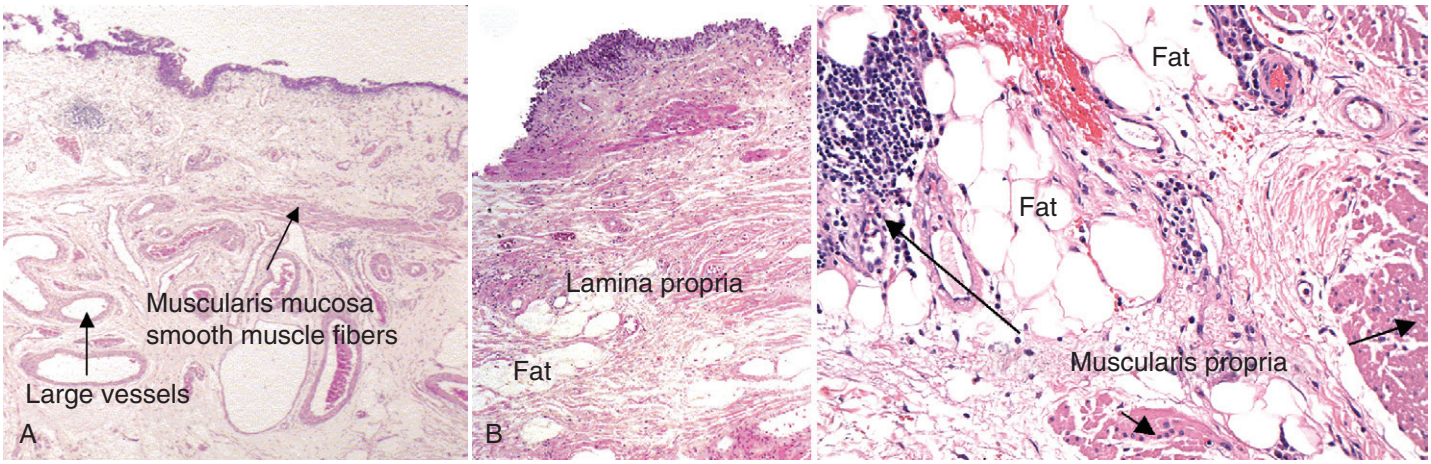


Figure 82–1. **A,** Smooth muscle fibers can be observed in the superficial and deep portion of the lamina propria and are not to be confused with muscularis propria invasion. Large vessels may be found throughout the lamina propria as well. **B,** Fat can be observed in lamina propria and deep portions of the muscularis propria and should not be confused with perivesical fat invasion.

cystectomy in patients with T1 disease include size greater than 3 cm, micropapillary histology, and lymphovascular invasion.

T2 versus T3. Fat can be observed in the lamina propria and deep portions of the muscularis propria and should not be confused with perivesical fat invasion (see Fig. 82–1B). In stage T3, cancer appears in fat in the absence of muscle bundles.

Staging Tumors of the Bladder and Urethra

The goals in staging the primary tumor are to establish histology; look for lymphatic/vascular invasion, which is a risk factor for metastasis; and determine the depth of penetration through a combination of biopsy and bimanual examination. When cystectomy is anticipated, complete resection is not necessary and the risk of bladder perforation is avoided. Downstaging, however, may provide some benefit because retrospective studies and secondary analysis of randomized neoadjuvant chemotherapy trials suggest that survival may be improved when the pathologic tumor stage is less than the precystectomy clinical stage for clinical stage T2 patients (Grossman et al, 2003a; Sonpavde et al, 2009). Patients who are P0 at cystectomy may progress, but at a lower rate than patients with residual invasive cancer (Grossman et al, 2003a).

One must also determine whether the local tumor is causing upper tract obstruction and whether there is a concomitant upper tract tumor that also needs treatment. This is accomplished by imaging with computed tomography, magnetic resonance imaging (MRI), and/or retrograde ureteropyelography. **With the patient anesthetized, the T stage of the tumor is identified with a combination of transurethral resection and bimanual examination. Findings described originally by Marshall in 1952 are T2a—nonpalpable; T2b—induration but no three-dimensional mass; T3—a three-dimensional mass that is mobile; T4a—invading adjacent structures such as the prostate, vagina, or rectum; T4b—fixed to pelvic sidewall and not mobile** (Marshall, 1952). Because tumors of the trigone or those encroaching on the bladder neck in men may directly invade the prostatic stroma, additional tissue should be obtained at resection for accurate staging because this may affect decisions regarding neoadjuvant chemotherapy. The utility of site-directed biopsies or biopsy of normal-appearing, remote mucosa is controversial in non–muscle-invasive cancer (Kiemeney et al, 1994; van der Meijden et al, 1999). However, with high-grade muscle-invasive cancers, at least one half of patients have associated CIS that may affect treatment decisions and outcome if remote from the index tumor (Shariat et al, 2007). The last piece of information needed is the status of the bladder neck (female) or prostatic urethra (male) to serve as a basis for planning appropriate management of the urethra and urinary diversion.

Biopsies of the prostatic urethra may provide useful information before radical cystectomy (Lerner et al, 2008a). Using a resectoscope, the surgeon takes a full loop from the midprostate (or bladder neck in shorter prostates) to the mid to distal verumontanum and 5 and 7 o'clock adjacent to the verumontanum. This is the site of the highest concentration of prostatic ducts and the place where CIS is most likely to be found (Sakamoto et al, 1993). The full-thickness chip allows the pathologist to see the interface between the urethral mucosa, prostatic ducts, and stroma. This method is the most accurate means of staging the prostatic urethra (Wood et al, 1989). Negative prostatic urethra biopsies are associated with a negative apical urethral margin and obviate the need for intraoperative frozen section (Lerner and Shen, 2008b). In women, bladder neck biopsies are an accurate surrogate for urethral biopsy when removal of the distal two thirds of the urethra and orthotopic diversion is being considered.

Staging Evaluation: Regional and Metastatic Disease

Laboratory tests and radiographic imaging are directed at determining the effect of the local tumor on the upper urinary tract and the presence or absence of synchronous urothelial cancer of the ureter, renal pelvis, or urethra, and for evaluating the status of potential sites of metastatic disease. Laboratory testing at a minimum should include blood urea nitrogen (BUN), creatinine, electrolytes, complete blood count, and liver function tests. Imaging studies are directed to the most common sites of visceral metastasis, which include lung, liver, and bone. Following chemotherapy, metastasis may occur in unusual sites including the central nervous system and the peritoneum (with late presentation of bowel obstruction), but these sites are generally not a focus of staging at initial presentation.

Table 82–2.

Incidence of Pathologic Pelvic Node Metastasis (%) at Radical Cystectomy in Selected Contemporary Series (2000-2009)

	NO. OF PATIENTS	P1	P2a	*P2*	P2b	P3a	*P3*	P3b	P4a	*P4*	P4b
Stein et al (2001)	1054	*7*		*18*		26		46	42		
Leissner et al (2004)	290	2	11		22	46		40	40		80
Vazina et al (2004)	176	4		*16*			*40*			*50*	
Steven et al (2007)	263	5	14		24	40		33	42		
Ghoneim et al (2008)	2720	2	8		19		*39*			*36*	

Computed tomography (CT) has largely replaced intravenous urography for upper tract imaging. CT provides the added benefit of cross-sectional imaging of the pelvic, iliac, and retroperitoneal lymph nodes, as well as the liver. The incidence of pelvic node metastases is directly related to the depth of invasion of the primary tumor (Table 82–2) (Stein et al, 2001; Leissner et al, 2004; Vazina et al, 2004; Steven and Poulsen, 2007; Ghoneim et al, 2008) and the presence of lymphovascular invasion (Quek et al, 2005).

Histologic confirmation of metastatic disease is desirable because its presence has a significant effect on treatment decisions and evaluating response to subsequent therapy. A chest radiograph is important for evaluating the lungs and mediastinum. A chest CT is obtained to further define abnormalities and should be obtained routinely in patients with muscle-invasive disease or N+ disease in whom the risk of visceral metastasis is greatest. Similarly, bone scintigraphy is obtained in these highest-risk patients and in patients with an elevated alkaline phosphatase or new-onset bone pain. An MRI may be useful for patients with an allergy to iodinated contrast or to resolve questions about an equivocal bone scan. The introduction of novel contrast agents with MRI may provide a more sensitive means for detecting nodal metastases. Ferromagnetic nanoparticles, for example, are taken up by macrophages, and dark areas represented by metastatic deposits can be detected with foci as small as 3 mm (Deserno et al, 2004). These studies, which require a 3 Tesla magnet, need further study and validation.

Positron emission tomography (PET) is used increasingly in oncology. Combination with CT is now standard and thus provides more accurate localization of abnormalities. Although there is as yet no defined role for routine staging of nodal or visceral metastases in invasive bladder cancer, PET/CT can be particularly helpful in discerning nodal or visceral metastatic disease when these findings will determine the use of chemotherapy or surgery (Kibel et al, 2009).

Several commercially available serum biomarkers (CEA, CA-125, CA-19.9) have been reported to be elevated in patients with advanced disease and may provide a marker that correlates with disease activity and response to therapy, but they are not standard (Margel et al, 2006; Kouba et al, 2009).

TREATMENT: SURGICAL

Radical Cystectomy and Bilateral Pelvic and Iliac Lymphadenectomy

The goal of therapy is complete eradication of the loco-regional disease including the primary tumor and regional lymph nodes. Neoadjuvant or adjuvant chemotherapy targeting occult regional node and/or visceral metastases should be integrated with loco-regional therapy when the risk of this occurrence is sufficiently high. Patients should have volitional control of urination via the retained urethra or by a continent catheterizable stoma in properly selected patients, and treatment-related morbidity should be minimized wherever possible.

Radical cystectomy provides excellent local control of the primary tumor and should include the bladder and surrounding perivesical soft tissue, prostate, and seminal vesicles in men and the ovaries, uterus/cervix, and anterior vagina in women. In sexually active women, vaginal preservation and/or reconstruction must be discussed and planned preoperatively. Recent reports challenge the dogma of removal of the internal female organs because involvement of the uterus, cervix, and ovaries is uncommon (Chang et al, 2002). Preservation of the vagina and uterus provides better support for a neobladder and the pelvic floor when the extent of the cancer or the age and general health status of the patient does not warrant anterior pelvic exenteration (Ali-El-Dein et al, 2002). Involvement of the urethra or bladder neck is an absolute contraindication to sparing the urethra in women, and a posterior-based invasive cancer is a relative contraindication.

Extent of Pelvic and Iliac Node Dissection. **Lymph node (LN) metastasis is found in 20% to 25% of patients who undergo radical cystectomy (RC) and pelvic lymphadenectomy for bladder cancer, and it is the most important prognostic factor in these patients, predicting significantly decreased recurrence-free survival and overall survival compared with that for patients without nodal metastases** (Lerner et al, 1993; Poulsen et al, 1998; Stein et al, 2001). In node-negative patients, the total number of LNs removed and the anatomic extent of the node dissection are both useful measures in evaluating the proper extent of surgery and predicting outcome. In patients with nodal metastasis, the number of nodes removed and the number and percent of positive nodes may both be independent predictors of recurrence and survival (Leissner et al, 2000; Herr et al, 2002; Herr, 2003; Stein et al, 2003b).

What Constitutes an Adequate Lymph Node Dissection? The extent of the lymph node dissection as it relates to cancer control and detection of lymph node metastases is an important area for research. The minimum number of lymph nodes to be removed for accurate staging and therapeutic value in bladder cancer has yet to be defined (Mills et al, 2001; Vazina et al, 2004). The unfortunate reality revealed in the Surveillance, Epidemiology and End Results (SEER) database in 2003 was that the majority of patients in a population-based analysis had four or fewer nodes removed with cystectomy (Konety et al, 2003; Hollenbeck et al, 2008). Some improvement had occurred by 2004 with an increase in the

number of nodes removed and fewer patients undergoing no node dissection at all (Hellenthal et al, 2009).

The wide range of total lymph node dissections reported may reflect a lack of standardization of the extent of node dissection, different sampling techniques, and differences in processing of tissue by the pathologist (en bloc removal vs. presentation in packets). Bochner and colleagues (2001, 2004) demonstrated that simply presenting the nodes to the pathologist in packets rather than en bloc with the cystectomy specimen increased the node count. This has been corroborated by others and should be considered the standard of care (Stein et al, 2007; Ather et al, 2008). Node dissection that includes the common iliac, presacral, and precaval/preaortic nodes may result in a higher number of lymph nodes removed (Vazina et al, 2004).

Patient's age and comorbidities are factors that may affect a surgeon's decision about the extent of LN dissection, thus influencing the number of LNs retrieved (Bochner et al, 2004; Vazina et al, 2004). A recent study, although small, suggested that in a single institution an individual surgeon had an independent impact on number of nodes removed (Kulkarni et al, 2008). This is not surprising because significant variability in the extent of the node dissection and node counts has been observed in prospective studies requiring a predefined anatomic extent of lymphadenectomy (Leissner et al, 2004; Lerner et al, 2009). Hospital and patient mix affecting comorbidities may affect node counts and mortality associated with cystectomy (Hollenbeck et al, 2008).

Staging. The current TNM staging system distinguishes between number of nodes with metastases, the size of nodal metastases, and the anatomic location, with nodal metastasis above the common iliac bifurcation denoting M1 disease and thus equivalence to visceral metastasis. The seventh edition of the American Joint Committee on Cancer (AJCC) Staging Manual (released October 2009) notes that at least 12 nodes should be removed. Most studies comparing extended and "standard" nodal dissection or packet presentation of the lymph nodes suggest that the overall incidence of node positivity is not altered, but, in fact, the number of nodes examined may be increased by extending the anatomic extent of the dissection (Poulsen et al, 1998; Vazina et al, 2004; Lerner et al, 2009; Edge et al, 2010).

With the focus on number of nodes removed and number of positive nodes as prognostic factors, investigators have developed a combined variable of lymph node density (LND), which takes both of these variables into account. Separate reports from the University of Southern California (USC) and Memorial Sloan-Kettering Cancer Center (MSKCC) published in 2003 described this and determined that LND (positive nodes/total nodes removed) had prognostic significance independent of the prognostic value of the number of positive nodes, pathologic tumor stage, and history of adjuvant chemotherapy (Herr, 2003; Stein et al, 2003b). The prognostic importance of LND has been corroborated in several retrospectively evaluated series (Kassouf et al, 2008; Osawa et al, 2009). An important caveat is that LND is affected by all of the factors described earlier that potentially affect the quality of the node dissection and interpretation by the pathologist (Svatek and Shariat, 2008). Quek and Flanigan wrote an excellent review of this subject and concluded that the body of evidence, based largely on retrospective review, suggests that LN density is an important pathologic prognostic variable (Quek and Flanigan, 2009). As indicated later, prospective validation is important and results lead to improved prognostic models.

Is There a Threshold of Number of Nodes Removed in Order to Identify the Majority of N+ Patients? Koppie and colleagues (2006) reported a study designed to determine if there is a minimum number of lymph nodes analyzed above which there is no improvement in survival. The cohort included 1121 patients from MSKCC accrued over a 14-year period, and the investigators determined that there was no plateau in the dose-response curve with increasing number of nodes up to 23 nodes because few had 24 or more nodes removed. The authors did not indicate the percent of patients who underwent an extended node dissection, and, in fact, 13% had no nodes identified in the pathology report. The median number of nodes removed was 9. Capitanio and colleagues (2009) reported a similar analysis from the Bladder Cancer Research Consortium (BCRC), a three-center database including Baylor College of Medicine, University of Texas Southwestern, and Johns Hopkins University. The median number of nodes removed was 19, and all patients underwent at least a bilateral pelvic node dissection. Using receiver operator curve analysis, the authors determined that analysis of 45 nodes resulted in detection of 90% of patients with nodal metastasis. Removal of 25 nodes resulted in detection of 75% (Fig. 82–2). The largest gain in sensitivity was between 15 and 30 nodes, and there was only modest improvement in sensitivity with examination of more than 30 nodes. They suggested that 25 nodes be the minimum number analyzed, and these findings provide some insight as to why a threshold was not observed in the MSKCC series.

Outcome Related to Nodal Status. **With so many factors contributing to the variability in node counts, one could argue that the anatomic extent and completeness of the node dissection deserve the most emphasis.** It is clear that the more tissue removed, the more nodes a diligent pathologist will identify, and this should increase sensitivity in detecting nodal metastases. It is also clear that small-volume nodal disease is compatible with long-term survival, especially when the primary bladder cancer is organ confined. The integration of systemic

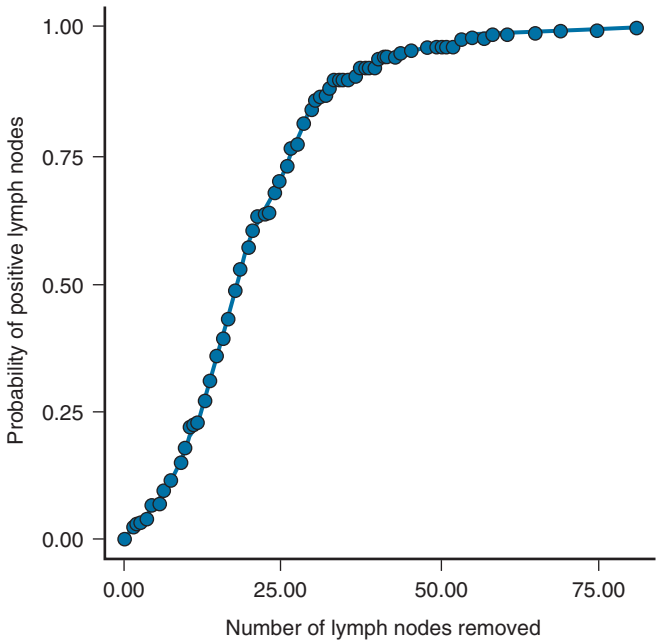


Figure 82–2. A plot describing the relationship between the number of lymph nodes removed and the probability of detecting lymph node metastasis. (Reprinted with permission from Capitanio U, Suardi N, Shariat SF, et al. Assessing the minimum number of lymph nodes needed at radical cystectomy in patients with bladder cancer. BJU Int 2009;103:1359–62, Fig. 1, p. 1360.)

chemotherapy either before or after radical cystectomy provides an incremental survival benefit, and a thorough node dissection is an integral component of this strategy (Herr et al, 2004). If there is a survival advantage associated with a more extensive node dissection, it is most likely due to the complete removal of all potential node-bearing tissue in the primary and secondary landing zones. This would lead to improved local and regional cancer control and to a more precise identification of patients with nodal metastasis who might benefit from adjuvant chemotherapy. Despite level 1 evidence supporting the use of neoadjuvant chemotherapy for muscle-invasive bladder cancer and a meta-analysis of adjuvant chemotherapy also supporting use of perioperative chemotherapy, recent estimates suggest that only 12% of patients are treated with an integrated treatment strategy of cystectomy and systemic chemotherapy (David et al, 2007). This reality requires that urologic surgeons performing radical cystectomy optimize the anatomic extent and completeness of the lymph node dissection.

Skinner and colleagues suggested in 1982 that "a meticulous pelvic node dissection can make a difference," reporting 5-year survival of 36% in patients with node-positive disease (Skinner, 1982). In addition, they noted excellent local control and no increase in morbidity. These data were further supported in a larger series that also introduced the concept of lymph node density (Stein et al, 2003b). Poulsen and colleagues (1998) suggested that the extended node dissection as described by Skinner and colleagues was associated with better survival for patients with organ-confined cancers and patients with negative nodes than for patients with a pelvic dissection that included only the external and internal iliac and obturator nodes. Recently, Steven and Poulsen confirmed their earlier observation in a consecutive series of 336 patients who had an extended node dissection (Steven and Poulsen, 2007). Patients with lymph node metastases above the common iliac bifurcation had a survival probability similar to that of patients with nodal metastases confined to the pelvis (37% vs. 42%, respectively). An editorial commented that stage migration might account for some of the improvement in survival associated with an extended node dissection, particularly for patients with negative nodes with a more complete node dissection and meticulous pathologic evaluation (Poulsen et al, 1998). The question of whether an extended node dissection improves overall survival or whether that benefit applies only to particular subgroups should be addressed in the context of a randomized clinical trial.

Intraoperative Decision Making

Grossly Positive Nodes and T4b Disease. The management of patients with grossly involved lymph nodes includes treatment of systemic micrometastatic and loco-regional disease. If disease is recognized on preoperative imaging and outside the true pelvis, a CT-guided biopsy is performed to establish histology. If it is positive, then chemotherapy is initiated and followed by cystectomy. When adenopathy is encountered at the time of a cystectomy, a frozen section biopsy is undertaken to confirm the presence of metastasis, and extended lymph node dissection and radical cystectomy are performed. Cystectomy is not performed when (1) lymph node metastases are unresectable because of bulk or proximal extent above the common iliac vessels; (2) there is evidence of extensive periureteral disease; (3) the bladder is fixed to the pelvic sidewall; or (4) tumor is invading the rectosigmoid colon.

Carcinoma in Situ of the Ureter. Much has been written regarding the utility of intraoperative frozen section (FS) biopsy to identify CIS at the ureteral margin (Schoenberg et al, 1996; Silver et al, 1997; Balaji et al, 1999; Sved et al, 2004; Lee et al, 2006; Raj et al, 2006; Osman et al, 2007). Although previous retrospective studies suggested that FS lacked sufficient correlation with final margin status, contemporary studies both retrospective and prospective found high sensitivity and specificity and positive and negative predictive values for final margin status (Raj et al, 2006; Osman et al, 2007). There is little disagreement about whether every effort should be made to obtain a negative proximal margin before reimplantation when frank tumor is encountered at the margin. It is clear, moreover, that atypia and dysplasia do not require any action. In the case of CIS, an attempt is made to achieve a negative margin without compromising ureteral length because nephrectomy is not indicated for CIS of the ureter. Raj and colleagues, however, question the value of achieving a negative margin because this did not alter the risk of development of subsequent upper tract tumor (Raj et al, 2006). CIS of the ureter is not independently associated with a worse outcome following cystectomy (Lee et al, 2006). Cancer recurrence at the anastomosis is rare even with a positive margin showing CIS, but a positive margin is a risk factor for developing a second primary tumor of the ureter or renal pelvis (Lee et al, 2006; Raj et al, 2006). Upper tract tumors found after cystectomy are often at a more advanced stage and, particularly when symptomatic, may be associated with a worse prognosis (Balaji et al, 1999; Sved et al, 2004; Sanderson et al, 2007). Surveillance ureteroscopy is the most sensitive means for following patients with a positive ureteral margin, and long-term follow-up is required. The median time to occurrence in one recent series was 53 months (Wagner et al, 2008).

Prostatic Transitional Cell Carcinoma and Managing the Apical Urethral Margin. The risk of developing a second primary tumor of the retained urethra following cystectomy is influenced by the presence and extent of involvement of the prostatic urethra and prostatic stroma, with stromal invasion carrying the highest risk of approximately 30% (none < focal CIS < diffuse CIS < ductal/acinar involvement < stromal invasion) (Hardeman and Soloway, 1990). Urethrectomy should be considered in men if CIS is diffuse within the prostatic urethra or ducts or if there is invasion of prostatic stroma. One method for assessing the risk to the retained urethra and determining the appropriate choice of urinary diversion is to perform transurethral resection biopsies of the prostatic urethra (see "Staging the Bladder and Urethra" earlier) (Wood et al, 1989; Lerner and Shen, 2008b). **Some experts, however, believe that the only absolute indication for consideration of urethrectomy is cancer at the apical urethral margin** (Donat et al, 2001; Stein et al, 2005). **Small low-grade papillary tumors of the urethra can be resected before cystectomy and the urethra retained if there is no other indication for urethrectomy.** The probability of developing a second primary TCC of the retained urethra is lower with orthotopic diversion than with cutaneous diversion (Stein et al, 2005).

Managing the Female Urethra. Cystectomy in women has historically included the urethra. New data indicate that the distal two thirds of the urethra serves as an adequate sphincter mechanism innervated by the pudendal nerve and is infrequently involved with transitional cell cancer (Stenzl et al, 1995; Stein et al, 1998). Limiting dissection only to the soft tissue above the endopelvic fascia will preserve the innervation crucial to maintaining the sphincter function of the urethra. **Cancer at the bladder neck or urethra or a T4 tumor involving the anterior vagina is a contraindication to urethral preservation and creation of an orthotopic neobladder.** Posterior T3 tumors are a relative contraindication, particularly if the tumor involves the trigone, because achieving an adequate margin is difficult.

Urethral cancer is always associated with bladder neck cancer, so findings of a biopsy of the bladder neck are an excellent surrogate for preoperative staging of the female urethra (Fig. 82–3). The proximal one third of the urethra is resected en bloc with the cystectomy specimen in order to reduce the risk of urinary retention, leaving the distal two thirds to provide adequate sphincter function.

Survival and Treated Natural History. Pathologic tumor stage and nodal status are the primary variables affecting the risk of progression and survival probability following cystectomy (Table 82–3) (Stein et al, 2001; Madersbacher et al, 2003; Hautmann et al, 2006; Shariat et al, 2006b; Ghoneim et al, 2008; Manoharan et al, 2009). The incidence of nodal metastasis increases with depth of invasion, and lymphovascular invasion increases the risk of nodal metastasis and is an independent predictor of outcome (Quek et al, 2005; Algaba, 2006; Herrmann et al, 2008). Positive surgical margins have an adverse impact on outcome as well (Dotan et al, 2007; Sonpavde et al, 2009). Recent studies suggest that improved outcomes are associated with high-volume surgeons and hospitals and that patient's age and body mass index (BMI) may also affect morbidity and survival (Konety et al, 2005; Nielsen et al, 2007; Bagrodia et al, 2009).

Up to 50% of patients with infiltrating disease develop metastases and ultimately succumb to their disease. Failure is usually due to occult metastatic disease present at the time of initial diagnosis. Long-term survival remains low and chemotherapy currently provides the potential for cure only in selected patients.

After metastases develop, there are few long-term survivors, although some 70% of patients have disease that is sensitive to chemotherapy. The suggestion is that systemic treatment in addition to radical cystectomy is required. Extensive lymph node dissection has both prognostic and therapeutic significance, and effective systemic therapies that eliminate micrometastases may improve outcome.

Perioperative chemotherapy is administered before (neoadjuvant) or after (adjuvant) cystectomy (bimodality therapy) to eradicate subclinical disease and primarily to improve survival. Concomitant chemotherapy and radiation therapy with thorough transurethral resection of the bladder (TURB) (trimodality therapy) is another method of treating patients with invasive bladder cancer and is particularly aimed at bladder preservation.

The majority of randomized clinical trials evaluating perioperative chemotherapy has been underpowered, used ineffective chemotherapy, or have had methodological flaws (Sylvester and Sternberg, 2000). However, more sufficiently powered neoadjuvant studies and meta-analyses provide further recommendations (Hall, 2002; Grossman et al, 2003b; Advanced Bladder Cancer Meta-analysis Collaboration, 2005b).

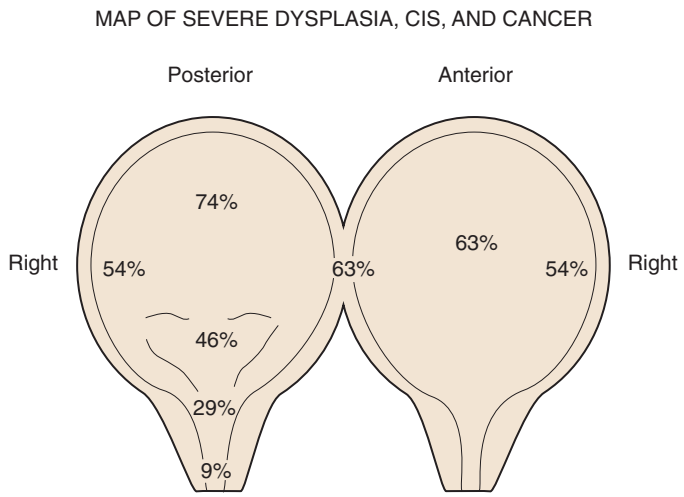


Figure 82–3. Location of cancer in 65 female radical cystectomy specimens. Bladder neck involvement is a surrogate for urethra involvement (SPL, personal series). Biopsies of the bladder neck should be performed in order to determine the suitability of urethra preservation in women and orthotopic diversion. CIS, carcinoma in situ.

NEOADJUVANT CHEMOTHERAPY

Neoadjuvant chemotherapy has been used for patients with operable clinical stage T2 to T4a muscle-invasive disease. The rationale for chemotherapy before cystectomy or, in some cases, full-dose radiation therapy (RT), is based on the intent to treat micrometastatic disease present at diagnosis.

Chemotherapy before surgery has several advantages. Therapy is better tolerated before surgery or radiation. Chemotherapy-related toxicities are considerably less in patients with localized disease than in those with metastatic disease on the basis of performance status. Patients are often able to tolerate a greater dose intensity and more cycles of chemotherapy preoperatively than postoperatively. Neoadjuvant chemotherapy allows in vivo drug sensitivity testing that may provide useful information for later therapy. The primary tumor can be evaluated for response, which also has major prognostic significance. In addition, preoperative chemotherapy may down-stage tumors, potentially allowing for technically easier surgery (Calabrò and Sternberg, 2009b).

Evaluating response to neoadjuvant chemotherapy can be complicated by discrepancies between clinical and pathologic staging, which have been reported in some 30% of cases (Herr and Scher, 1990; Sternberg et al, 2003). The major disadvantage of neoadjuvant chemotherapy is a delay in definitive local therapy in patients who do not respond or whose disease progresses. An interval

Table 82–3.

Percentage 5-Year Disease-Specific Survival (DSS) by Pathologic Stage after Radical Cystectomy with and without Pelvic Lymph Node Metastasis: Selected Series Reporting DSS (2000-2009)

SELECTED SERIES	NO. OF PATIENTS	≤P1	P2A	*P2*	P2B	P3A	*P3*	P3B	P4A,B	N NEG	N+
Stein et al (2001)	1054	88		*81*		68		47	44	78	35
Madersbacher et al (2003)	507	76		*74*			*52*		36	—	33
Hautmann et al (2006)	788	90		*72*			*43*		28	75	21
Shariat et al (2006b)	888	81		*72*			*44*		28	80	35
Ghoneim et al (2008)	2720	82	75		53		*40*		29	62	27
Manoharan et al (2009)	432	81		*70*			*44*		16	72	29

longer than 12 weeks between the diagnosis of muscle invasion and cystectomy has even been associated with a poorer outcome (Sanchez-Ortiz et al, 2003; Stein, 2003a).

Another theoretic disadvantage of neoadjuvant chemotherapy is the possible increase in the incidence of perioperative morbidity. Few reports have studied this (Hall et al, 1996; Millikan et al, 2001). In a comparative study of neoadjuvant and adjuvant chemotherapy, neoadjuvant chemotherapy did not increase perioperative morbidity (Millikan et al, 2001). In the United States and in most of Europe, radical cystectomy is the preferred treatment for fit patients who have a good performance status.

Randomized Trials of Neoadjuvant Chemotherapy

Many randomized trials have evaluated the impact of neoadjuvant chemotherapy on survival. These trials have shown either a trend toward a benefit or no survival advantage. The majority of these trials have, however, been underpowered. Randomized neoadjuvant chemotherapy trials are summarized in Table 82–4 (Sternberg et al, 2007).

The largest trial of neoadjuvant chemotherapy was performed by the European Organization for Research and Treatment of Cancer and the Medical Research Council (EORTC and MRC). A total of 976 patients who were accrued over 5½ years from 106 institutions were randomized to receive cisplatin, methotrexate, and vinblastine (CMV) neoadjuvant chemotherapy or no chemotherapy. Cystectomy and/or radiation therapy was permitted as definitive management of the primary tumor. The study was designed to detect an absolute improvement in survival of 10% (from 50% to 60%) with a power of 90% and a type 1 error of 5%.

When results were first published, there was a nonsignificant trend toward improvement in survival in patients treated with neoadjuvant CMV chemotherapy (International Collaboration of Trialists, 1999). In an update presented at the American Society of Clinical Oncology (ASCO) meeting in 2002, with longer follow-up of 7.4 years, the data have barely reached statistical significance ($P = .048$). There was a 5.5% benefit in favor of patients treated with CMV (Hall, 2002). Survival at 5 years was 50% compared with 44%, and at 8 years was 43% versus 37%. Following neoadjuvant chemotherapy, no residual tumor or pathologic complete response (pCR) was found in 32.5% of cystectomy specimens. Chemotherapy-related mortality was 1%. Chemotherapy did not increase the rate of postoperative complications. Although patients treated with CMV had a survival benefit that was maintained over time, it was concluded that there was no change in absolute benefit.

This study demonstrated an improvement with CMV chemotherapy, but the improvement was slightly less than the magnitude originally sought in the trial. Several factors may explain why the experimental arm in this study achieved somewhat lower survival than anticipated. The chemotherapeutic regimen used in this study is not considered standard of care, although CMV has never been compared with methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) in a randomized trial. Local therapy included cystectomy or radiation or both, with 42% and 43% of patients receiving radiation alone as local therapy in the neoadjuvant chemotherapy group and the no-chemotherapy group, respectively. Although in Europe radiation therapy is believed to be equivalent to cystectomy, no prospective randomized trial has ever proven this.

In the Southwest Oncology Group (SWOG) Intergroup trial, 317 patients with clinical T2 to T4a bladder cancer were randomized to receive cystectomy or three cycles of neoadjuvant M-VAC chemotherapy followed by cystectomy (Grossman et al, 2003a). Enrollment took place at 126 institutions over 11 years. Patients were stratified according to age (younger than 65 years old or 65 years and older) and stage (cT2 vs. cT3 or cT4a). The aim of the study was to detect an increase in survival with M-VAC chemotherapy. The original study was planned for one-sided testing, which means that the investigators were planning to test not for a difference but only for improvement because the hypothesis was that medical practice would change only if there was an improvement with chemotherapy.

Median survival among patients randomized to surgery alone was 46 months, as compared with 77 months for patients who received neoadjuvant M-VAC chemotherapy ($P = .06$; two-sided stratified log rank test). In part because of the very long accrual period and follow-up, these results have achieved borderline statistical significance. The estimated risk of death was decreased by 25% (HR = 1.33) in patients treated with neoadjuvant M-VAC (Grossman et al, 2003b). The neoadjuvant chemotherapy group had a significantly higher proportion of patients with pCR than the cystectomy-alone group (38% vs. 15%, $P < .001$). Patients

Table 82–4.

Randomized Phase III Trials of Neoadjuvant Chemotherapy

STUDY GROUP	NEOADJUVANT ARM	STANDARD ARM	PATIENTS	SURVIVAL
Aust/UK (Wallace et al, 1991)	DDP/RT	RT	255	No difference
Canada/NCI (Coppin et al, 1996)	DDP/RT or preop RT + Cyst	RT or preop RT + Cyst	99	No difference
Spain (CUETO) (Martinez Pineiro et al, 1995)	DDP/Cyst	Cyst	121	No difference
EORTC/MRC (International Collaboration of Trialists, 1999)	CMV/RT or Cyst	RT or Cyst	976	5.5% difference in favor of CMV
SWOG Intergroup (Natale et al, 2001)	M-VAC/Cyst	Cyst	298	Trend in benefit with M-VAC ($P = .06$)
Italy (GUONE) (Bassi et al, 1998)	M-VAC/Cyst	Cyst	206	No difference
Italy (GISTV, 1996)	M-VEC/Cyst	Cyst	171	No difference
Genoa (Orsatti et al, 1995)	DDP/5FU/RT/Cyst	Cyst	104	No difference
Nordic 1 (Malmstrom et al, 1996)	ADM/DDP/RT/Cyst	RT/Cyst	311	No difference, 15% benefit with ADM + DDP in T3-T4a
Nordic 2 (Sherif et al, 2002)	MTX/DDP/Cyst	Cyst	317	No difference
Abol-Enein (1997)	CarboMV/Cyst	Cyst	194	Benefit with CarboMV

ADM, doxorubicin; Carbo, carboplatin; Cyst, cystectomy; DDP or C, cisplatin; E, epirubicin; MTX, methotrexate; RT, radiation therapy; V, vinblastine.

with locally advanced (cT3 or T4a) disease had the greatest survival benefit from neoadjuvant chemotherapy (65 vs. 24 months). Other randomized trials of neoadjuvant chemotherapy are found in Table 82–4 (Malmstrom et al, 1996; Bassi et al, 1998; Sherif et al, 2002).

Meta-Analyses of Randomized Neoadjuvant Chemotherapy Trials

The majority of neoadjuvant randomized trials have failed to show an unequivocal survival benefit in favor of chemotherapy. However, the majority of the studies have been hampered by inadequate sample sizes, suboptimal chemotherapy, premature closure, or inadequate follow-up (Sylvester and Sternberg, 2000). For this reason, meta-analyses have attempted to explain and interpret these data (International Collaboration of Trialists, 1999; Winquist et al, 2004).

The Advanced Bladder Cancer (ABC) Meta-analysis included data on 3005 patients from 11 randomized neoadjuvant chemotherapy trials (Advanced Bladder Cancer Meta-analysis Collaboration, 2005b).The overall analysis was in favor of chemotherapy (HR = .89, 95% CI .81 to .98, P = .022). In patients who received single-agent cisplatin chemotherapy, neoadjuvant chemotherapy appeared detrimental, but the numbers were too small to support definitive conclusions (P = .264). However, in the subset of patients who received cisplatin-based combination neoadjuvant chemotherapy, the meta-analysis showed a reduction in the risk of death of 14% (HR = .86, 95% CI .77 to .95, P = .003), translating into a 5% absolute survival benefit at 5 years (95% CI: +2% to +9%). The results are similar to the results obtained in the EORTC and MRC trial, which was the largest trial in the analysis (Hall, 2002). The authors noted no difference in the relative risk reduction either in relation to the type of local treatment (cystectomy, radiotherapy or the combination) or in relation to patient characteristics. However, apart from this study, neoadjuvant chemotherapy before radiation therapy has not been shown to improve survival (Zietman et al, 1997).

Despite the 5% survival benefit, the neoadjuvant approach before cystectomy has not been widely accepted. In an analysis of stage III bladder cancer from the National Bladder Cancer Database (n = 11,328), only 0.7% of patients received neoadjuvant chemotherapy (David et al, 2007). Part of the reason may be that physicians feel that it is not worthwhile to give chemotherapy to all patients to achieve a 5% benefit (Sternberg and Collette, 2006a). The studies on which recommendations have been made do not contain information on toxicity and quality of life. In most of the trials elderly patients (median age 63 to 65 years in EORTC, SWOG, Nordic) or those with poor renal function or performance status have not been included, making it difficult to generalize the results to all of the elderly patients who are affected with bladder cancer (Droz, 2005). Information is lacking on subgroups of patients to indicate who would derive the most benefit from treatment. In some studies (Nordic) both neoadjuvant and adjuvant chemotherapy were used. And of perhaps most importance, the impact of cystectomy and the quality of surgery have been shown to be as important as whether or not chemotherapy was administered (Herr, 2004). The delay in definitive surgery in patients who do not respond to treatment raises concerns regarding compromise of curability, and many urologists simply believe that a potential 5% advantage in overall survival is not great enough to justify giving toxic chemotherapy to all patients before surgery.

Many oncologists prefer to use newer agents such as gemcitabine or the taxanes, which have not been evaluated in randomized studies. A single-institution retrospective report of neoadjuvant gemcitabine and cisplatin before cystectomy reported that 26% of patients achieved a pathologic complete response to chemotherapy, which may be comparable with other combination cisplatin-based regimens (Dash et al, 2008).

In conclusion, cystectomy is the "gold standard" of treatment for patients with localized muscle-invasive bladder cancer. Neoadjuvant chemotherapy is intended for patients with operable clinical stage T2 to T4a muscle-invasive disease. The rationale for chemotherapy before cystectomy is based on the intent to treat micrometastatic disease present at diagnosis. Although the data available support the use of M-VAC or CMV as neoadjuvant chemotherapy, these regimens are less frequently used today because the regimen of gemcitabine and cisplatin has been widely used for metastatic disease. However, the efficacy of the gemcitabine and cisplatin combination in the neoadjuvant setting has not been proven, suggesting that M-VAC or CMV should still be used on the basis of level 1 evidence. Toxicity and mortality associated with neoadjuvant chemotherapy are acceptable because these patients are generally less debilitated than patients with metastatic disease.

Discrepancies between clinical and pathologic staging can be expected. Available data suggest that for "average-risk" patients with cT2 cancer, the benefit of adding chemotherapy to local therapy is at best modest. Studies suggest a more substantial benefit for patients with cT3b disease. The quality of the surgery is an important factor that cannot be underestimated. Meta-analysis of cisplatin-containing combination neoadjuvant chemotherapy trials reveals a 5% difference in favor of neoadjuvant chemotherapy. Unfortunately, however, quality of life data are not available.

ADJUVANT CHEMOTHERAPY

In patients with pT3-4 and/or N+M0 disease, 5-year survival after radical cystectomy is only 25% to 35% at best. As a result, adjuvant chemotherapy has been advocated for high-risk patients in an effort to delay recurrence and prolong survival. Delivery of chemotherapy postoperatively has potential advantages. An adjuvant approach allows selection of patients at highest risk of metastatic or recurrent disease on the basis of an accurate pathologic evaluation (Calabrò and Sternberg, 2009b). Surgery is performed without delay, and the advent of orthotopic neobladders and continent urinary diversions has improved quality of life in patients after cystectomy, favoring immediate cystectomy. There is evidence that delaying cystectomy can be detrimental (Chang et al, 2003; Sanchez-Ortiz et al, 2003), and no time is wasted in those patients who do not respond to chemotherapy. The availability of sufficient tissue for increasingly sophisticated analysis of molecular prognostic and predictive markers is also a potential advantage. If micrometastases are present, they can be treated with chemotherapy when at a low volume, rather than after there is overt metastatic disease.

The major disadvantages are that the bladder is not preserved and that there is a delay in starting systemic therapy for occult metastases while the focus is first on the primary tumor. Response cannot be easily evaluated, and the only clinical end point that can be assessed is the time to tumor recurrence.

Several factors contribute to the difficulty in accrual to bladder cancer trials. Patients are often elderly with significant comorbidities that are related to smoking and/or compromised

renal function (Jin et al, 2006). An additional disadvantage is the difficulty in administering chemotherapy to those with surgical morbidities following cystectomy. A prospective standardized reporting methodology was used to quantify and characterize the risk of perioperative morbidity following cystectomy at MSKCC, a center with high-volume, fellowship-trained urologists. Staggering rates of postoperative complications were observed within 90 days of surgery (Donat et al, 2009; Shabsigh et al, 2009), further confirming prior observations at another high-volume center in California (Stein and Skinner, 2006). These often underreported postoperative morbidities can lead to long delays and difficulties in administering adjuvant chemotherapy.

Randomized Trials of Adjuvant Chemotherapy

Despite its appeal, there have been few randomized trials evaluating adjuvant chemotherapy. Table 82–5 shows the results of randomized trials of adjuvant chemotherapy after cystectomy (Logothetis et al, 1988; Skinner et al, 1991; Stockle et al, 1992; Studer et al, 1994; Stockle et al, 1995; Freiha F et al, 1996; Bono et al, 1997; Otto et al, 2001; Cognetti et al, 2008). All of these trials were relatively small, enrolling only 49 to 108 patients. Nonetheless, two trials suggest a survival benefit with adjuvant chemotherapy.

In the USC trial, 91 patients with pT3-4a or node-positive bladder cancer were randomized to adjuvant chemotherapy for 4 cycles or no further treatment after cystectomy (Skinner et al, 1991). The chemotherapy given was heterogeneous and included a cisplatin, cyclophosphamide, and doxorubicin hydrochloride (Adriamycin) (CISCA)-like regimen, single-agent cisplatin, and chemotherapy regimens selected by clonal assays. Three-year time to progression was significantly delayed ($P = .01$) with adjuvant chemotherapy (70%) compared with time to progression with observation only (46%). Median survival was also significantly improved ($P = .0062$) in the chemotherapy arm (4.3 years) compared with results in the observation arm (2.4 years). However, 3-year survival with adjuvant chemotherapy (66%) was not statistically superior ($P = .09$) to survival after surgery alone (50%).

This trial has been criticized both for its statistical design and for its treatment plan. Its small size resulted in a lack of statistical power, limiting its ability to detect a clinically meaningful survival difference.

Another adjuvant chemotherapy trial was conducted in Germany (Stockle et al, 1992; Stockle et al, 1995). High-risk patients were randomized to M-VAC/M-VEC (methotrexate, vinblastine, epirubicin, and cisplatinum) or to no further therapy after cystectomy. The study was terminated early with only 49 patients enrolled when an interim analysis showed significant improvement in 3-year disease-free survival (63% vs. 13%, $P = .002$). Ten-year survival data from this trial still favored adjuvant chemotherapy over surgery alone for progression-free survival (44% vs. 13%, $P = .002$), tumor-specific survival (42% vs. 17%, $P = .007$), and a trend in overall survival (27% vs. 17%, $P = .07$). Significant benefit was noted in patients with positive lymph nodes who received adjuvant chemotherapy. Only 27% of patients who received chemotherapy had evidence of tumor progression compared with 92% of those treated with cystectomy alone.

This trial has also been heavily criticized. The study took 3.5 years to accrue 49 patients and was stopped early when an interim analysis revealed a significant advantage in favor of chemotherapy. Many patients in the cystectomy alone group were not offered chemotherapy when disease progressed, and some patients randomized to the chemotherapy group never received chemotherapy.

Other randomized trials have not shown a survival benefit with adjuvant chemotherapy. A systematic review of randomized trials of adjuvant cisplatin-containing combination chemotherapy in locally advanced bladder cancer revealed that adjuvant trials have been hampered by serious methodological flaws. Major deficiencies have been observed with small sample sizes, early closure of trials, and limitations of statistical analyses, reporting of results, and poorly substantiated conclusions (Sylvester and Sternberg, 2000). These trials provide insufficient evidence to support the routine use of adjuvant chemotherapy.

The ABC Meta-analysis Collaboration (2005a) identified 11 randomized trials of adjuvant chemotherapy, but individual patient survival data from only 6 adjuvant trials comprising 283 events in 491 patients were eventually included, and 4 of these 6 trials were stopped early. Although the results suggest a 9% improvement in absolute survival at 3 years (HR = .75, 95% CI .60 to .96, $P = .019$), the analysis was severely compromised by underpowered survival curves. In publishing their results, the authors clearly acknowledged the problems with interpretation of these data (Sternberg and Collette, 2006a).

A randomized adjuvant trial from Italy failed to reach its planned accrual (Cognetti et al, 2008). In this trial patients with G3T2 were also eligible; however, the trial was closed with only 190 patients accrued. The study was underpowered, and no difference in survival for either pN0 or pN+ patients was observed in patients treated with two different regimens of gemcitabine and

Table 82–5.

Adjuvant Chemotherapy Trials Following Cystectomy

INVESTIGATOR	YR	REGIMEN	CHEMO	NO CHEMO	RESULTS
Logothetis (1988)	1988	CISCA	62	71	Benefit but not randomized
Skinner (1991)	1991	CAP	47	44	Benefit; few patients received therapy
Stockle (1992, 1995)	1992	M-VAC/ M-VEC	23	26	Benefit; no treatment at relapse
Studer (1994)	1994	DDP	40	37	No benefit
Bono (1997)	1995	CM	48	35	No benefit for N0
Freiha (1996)	1996	CMV	25	25	Benefit in relapse-free survival
Otto (2001)	2001	M-VEC	55	53	No benefit
Cognetti (2008)	2008	GC	97	86	No benefit for N0 or N+

CAP, cisplatin, cyclophosphamide, and doxorubicin; CISCA, cisplatin, cyclophosphamide, and doxorubicin; CMV, cisplatin, methotrexate, and vinblastine; DDP or C, cisplatin; GC, gemcitabine and cisplatin; M-VAC, methotrexate, vinblastine, doxorubicin and cisplatin; M-VEC, methotrexate, vinblastine, epirubicin, and cisplatin.

cisplatin (GC). The Spanish Oncology Genitourinary Group (SOGUG) accrued 146 of the 340 patients planned and in July 2007 closed a phase III study comparing surgery followed by four cycles of GCP (gemcitabine, cisplatin, and paclitaxel) or observation.

The role of adjuvant chemotherapy continues to be unresolved; yet it is widely administered in the United States and Europe. The EORTC evaluated early versus delayed chemotherapy using M-VAC, high-density M-VAC, or the gemcitabine-cisplatin combination. The trial was closed with only 278 patients of a planned 660 patients accrued as of June 2008, making it unlikely that there will ever be a definitive answer to this important question.

Finally, the USC/SWOG International trial has completed accrual to a study evaluating adjuvant M-VAC in patients with organ-confined (pT1-pT2) high-risk bladder cancer as defined by altered p53 status (Stadler et al, 2009). With 511 patients registered and 110 randomized, the data safety monitoring committee recommended study closure on the basis of a futility analysis, suggesting that the probability of detecting a significant difference in time to relapse would be highly unlikely. The study was unable to confirm the prognostic or predictive value of p53 as measured by immunohistochemistry (IHC).

Unfortunately, the question of the true benefit of adjuvant chemotherapy in high-risk patients with pT3, pT4, and N+ disease is likely to remain unanswered. Perhaps a meta-analysis of the EORTC, Spanish, and Italian studies may someday be of interest. Defining optimal therapy in all patients with muscle-invasive bladder cancer is a difficult task. Neoadjuvant and adjuvant chemotherapy probably have similar efficacy, although only one randomized trial has looked at this comparison (Logothetis et al, 1996).

Some patients have been cured by TURB or radiation alone, and selection of optimal therapy for a given patient should be individualized. Current data appear to favor neoadjuvant chemotherapy followed by radical cystectomy with adequate complete pelvic lymph node dissection (PLND). More patients are likely to receive effective chemotherapy before rather than after surgery. All clinical stages of invasive bladder cancer may benefit from this combined strategy. However, a 5% absolute survival benefit for chemotherapy-treated patients is only a small improvement, and development of more effective regimens is necessary.

BLADDER PRESERVATION AND COMBINED MODALITY APPROACHES

Radical Transurethral Resection of Bladder Tumor (TURBT)

For selection of candidates, strict criteria are required and include (1) initial occurrence of bladder cancer; (2) no CIS; (3) size less than or equal to 3 cm; (4) stage T2 (no palpable mass); and (5) not in the dome or high posterior wall because of the risk of bowel injury. Patients with T3b tumors are not candidates for complete TUR, and those with T4 tumors are not eligible because, by definition, the tumors are invading surrounding structures. When these criteria are used, long-term survival is comparable with that of radical cystectomy for the small fraction of potentially eligible patients. Herr (2001) and Solsona and colleagues (1998) reported 10-year survival probabilities for 99 and 130 patients, respectively, with disease-progression rates ranging from 30% to 34%, disease-specific survival 76% to 80%, and cystectomy rates of 9% to 34%.

All patients must undergo re-resection 3 months after radical TURBT, and if tumor persists at this time, radical cystectomy or radiation is considered. Leibovici and colleagues (2007) reported the experience from the M.D. Anderson Cancer Center, where they adopted a policy of re-resecting tumors in all patients with muscle-invasive cancer and offered bladder preservation to those patients whose cancer was stage T0. Of the 35 eligible patients, 27 opted for preservation. Of these, 15 had recurrence and 8 of these patients underwent radical cystectomy. Overall and cancer-specific survival rates exceeded 80% in this highly selected group of patients.

The advantage of this approach is that at least a small portion of patients with invasive bladder cancer preserve their native bladder and optimum quality of life. The disadvantages are the absence of pathologic staging of the pelvic and iliac lymph nodes and the requirement for lifelong surveillance because up to 25% ultimately require cystectomy.

Partial Cystectomy

The indications for partial cystectomy are similar to those for radical TURBT with one exception—the location. **Tumors must be in a location suitable for bladder preservation—usually on the dome and away from the ureteral orifices.** Bilateral pelvic lymphadenectomy is performed at the time of surgery for pathologic staging of the nodes. Although early series reported a high rate of progression and mortality, contemporary series report long-term relapse rates that are comparable with those for radical cystectomy when strict selection criteria are applied (Holzbeierlein et al, 2004; Kassouf et al, 2006). Smaldone and colleagues (2008) recently reported on a series of 25 patients accrued over 11 years in whom partial cystectomy was performed for patients with primary solitary T2 or high-grade T1 tumors and no CIS. All patients received preoperative radiation for 5 days and a single dose of intraoperative intravesical chemotherapy followed by partial cystectomy. Follow-up included intravesical BCG, and the 5-year cancer-specific survival probability was 84%. These authors emphasize the need for lifelong cystoscopic surveillance and abdominal imaging.

This surgical option also has a definite role in patients who have had an objective response to neoadjuvant chemotherapy, with or without radiation therapy (Herr et al, 1998; Koga et al, 2009; Sternberg et al, 2003). The tumor site can be resected in patients with a clinical complete response (CR) in order to ensure pathologically that the tumor has been completely removed. This may also be an option for patients with a partial response (PR) if the tumor location is amenable and there is no CIS. However, radical cystectomy remains the gold standard in patients who experience a PR. **In the unique situation of urachal adenocarcinoma, partial cystectomy with en bloc resection of the urachus is the preferred surgical method for local control** (Siefker-Radtke, 2006; Gopalan et al, 2009). This is undertaken using a closed technique in order to avoid tumor spill of this highly implantable tumor, with en bloc resection of the posterior rectus sheath, urachus, and dome of the bladder.

Neoadjuvant or Concomitant Chemotherapy and Bladder Preservation

Advantages of bladder preservation are that there is less surgery, there is no need for a urinary diversion, sexual function

is preserved, and a better quality of life results. Neoadjuvant chemotherapy or concomitant chemotherapy with radiation therapy has been given to patients with muscle-invasive bladder cancer as a bladder-preserving strategy. The common theme has been to select patients with a complete pathologic response to treatment for bladder preservation. Appropriate candidates for bladder preservation include those with solitary T2 or early T2 tumors less than 6 cm in size, no tumor-associated hydronephrosis, tumors allowing a visibly complete TURB, invasive tumors not associated with CIS, and renal function adequate to allow use of cisplatin concurrent with radiation.

Although this strategy appears promising, bladder preservation protocols have never been compared with radical cystectomy in randomized studies. Therefore these techniques are often applied in highly selected patients with low-volume disease or in those who refuse or who are poor candidates for radical cystectomy.

Can we save the bladder and obtain the same survival as with radical cystectomy? Up to 15% of patients with muscle-invasive tumors have no residual disease at the time of cystectomy, indicating that TURB alone can potentially cure some patients (Herr, 2009; Solsona et al, 2009). However, the absence of residual disease at TURB does not mean that patients are necessarily cured. Understaging with TURB occurs in approximately 30% of cases (Herr and Scher, 1990; Frazier et al, 1993; Amling et al, 1994; Stein, 2000; Sternberg et al, 2003). The limited efficacy of surgery alone and the introduction of effective combination chemotherapy have led increasingly to a multidisciplinary approach to bladder preservation. However, bladder preservation is usually achieved with trimodality (chemoradiation and thorough TURB) and occasionally with bimodality protocols.

Bimodality Therapy

In Italy, three cycles of neoadjuvant M-VAC chemotherapy, with extensive TURB before chemotherapy, were used in 104 cT2-T4 N0M0 bladder tumor patients with the intent of bladder preservation (Sternberg et al, 2003). At the TURB following M-VAC, 49 (49%) patients were T0. Responding patients underwent TURB or partial cystectomy. Median survival was 7.5 years (95% CI, 4.9 to 10 years); 60% of the patients treated with M-VAC and TURB alone were alive at a median follow-up of 56 months (10 to 160+), and 44% in the TURB alone group maintained an intact bladder. Patients who were down-staged to pathologic CR or superficial disease after chemotherapy had a 5-year survival of 69%, whereas those with persistent muscle-invasive disease after chemotherapy had a 5-year survival of only 26%. Bladder sparing was possible in selected patients on the basis of response to neoadjuvant chemotherapy.

Likewise, investigators at MSKCC have used neoadjuvant M-VAC in 111 T2-T3N0M0 bladder cancer patients followed by transurethral bladder-sparing surgery (Herr et al, 1998). Of these patients, 60 (54%) achieved pCR (pT0). The majority of patients who achieved pCR after TURB and neoadjuvant chemotherapy benefitted from long-term survival with the bladder preserved.

From these single-institution studies, one could conclude that patients with cT0 status after chemotherapy who forego cystectomy have a survival rate similar to that of patients undergoing immediate cystectomy. However, because these data are from highly specialized single institutions, this practice must be considered investigational and this approach cannot be considered as standard methodology.

In an intergroup SWOG study, neoadjuvant paclitaxel, carboplatin, and gemcitabine produced a promising 46% cT0 rate in 77 patients with histologically confirmed T2 to T4a muscle-invasive disease. There was, however, an unacceptably high rate (60%) of persistent cancer at cystectomy in patients presumed to have pT0 status. The authors recommended that patients completing neoadjuvant chemotherapy should strongly consider definitive local therapy rather than cystoscopic surveillance regardless of post-chemotherapy cT0 status (DeVere White et al, 2009).

Neoadjuvant chemotherapy can be given safely, and patients who respond to chemotherapy have a favorable outcome. However, in a multi-institutional setting after neoadjuvant chemotherapy, TURB cannot be safely relied on to determine which patients require cystectomy. Definitive local therapy should be a mandatory component of the treatment paradigm. Perioperative chemotherapy has a role in treating this disease, but the exact timing of delivery and the appropriate patient population require further definition.

Trimodality Therapy

Combining systemic chemotherapy with RT can permit bladder preservation while sensitizing the tumor to RT and perhaps also treating occult metastases. The optimal combined-modality bladder-sparing regimen is not well defined. The majority of modern series have used single-agent cisplatin as the radiosensitizing agent. Trimodality therapy for clinical stages T2 to T4a includes maximal TURB of the bladder tumor, modern external beam XRT with radiosensitizing chemotherapy given concurrently, and a careful urology-based surveillance program with prompt cystectomy for persistent or recurrent invasive tumors. This approach is best illustrated by the Radiation Therapy Oncology Group (RTOG) series of trials, in which complete responses in the bladder were observed in 59% to 87% of patients (Fernando and Sandler, 2007).

Trials of concomitant neoadjuvant chemotherapy and RT are shown in Table 82–6 (Kaufman et al, 1993; Housset et al, 1997; Kachnic et al, 1997; Shipley et al, 1998; Rodel et al, 2002). In a study at the Massachusetts General Hospital, 106 patients with muscle-invasive stage T2 to T4a bladder cancer underwent

Table 82–6.

Trials of Chemoradiation and Bladder Preservation

STUDY GROUP	*N*	CHEMOTHERAPY	5-YR SURVIVAL (%)	5-YR SURVIVAL WITH INTACT BLADDER (%)
RTOG-8903 (Shipley et al, 1998)	123	MCV + RT and DDP	48	36
Erlangen (Rodel et al, 2002)	289	CDDP/CBDCA ± 5FU	51	42
Paris (Housset et al, 1997)	120	CDDP/5FU	63	
MGH (Kaufman et al, 1993; Kachnic et al, 1997)	106	MCV + RT and DDP	52	43

CBDCA, carboplatin; DDP or C, cisplatin; 5FU, fluorouracil; RT, radiation therapy; V, vinblastine.

chemoradiation following TURB (Kaufman et al, 1993; Kachnic et al, 1997). Patients received two cycles of CMV followed by radiotherapy (4000 cGy) with two cycles of concurrent cisplatin every 3 weeks. Those with persistent disease underwent radical cystectomy, and those who attained CR were selected for additional radiation (2480 cGy) and one additional cycle of cisplatin. After a median follow-up of 48 months, the 5-year overall survival (OS) and disease-specific survivals were 52% and 60%, respectively. The 5-year OS rate with an intact functioning bladder was 43%. These investigators contend that TURB plus chemoradiation can be considered as an alternative to radical cystectomy.

However, RTOG investigators reported a randomized study of 123 patients treated with two cycles of neoadjuvant CMV before concomitant cisplatin and RT (39.6 Gy) (Shipley et al, 1998). Those who achieved a CR received an additional 25.2 Gy plus one concurrent cycle of cisplatin. Patients with persistent disease underwent cystectomy. Neoadjuvant CMV did not improve 5-year survival (48% vs. 49%) or survival rate with preserved bladders (36% vs. 40%). An unfavorable toxicity profile was observed, and the study did not complete accrual.

Paclitaxel as a radiosensitizer has also been evaluated, as well as adjuvant chemotherapy with GC. The results of RTOG protocol 99-06 were reported with more than 4 years of median follow-up in 80 patients, showing an 81% complete response rate and actuarial 5-year overall and disease-specific survival rates of 56% and 71%, respectively (Kaufman et al, 2009b). The RTOG has also performed a randomized phase II trial to identify the optimum concurrent chemotherapy regimen in conjunction with radiation. Patients were randomized to radiation twice daily with either concurrent paclitaxel and cisplatin or concurrent infusional fluorouracil and cisplatin during the induction and consolidation phases. Additionally, the adjuvant chemotherapy triplet regimen of gemcitabine, paclitaxel, and cisplatin was investigated (Kaufman et al, 2009a).

What appears to emerge from these studies is that neoadjuvant chemotherapy before radiation therapy is not beneficial in terms of survival (Zietman et al, 1997). Concomitant chemoradiation therapy with chemotherapy as a sensitizing agent is an alternative to cystectomy. It is difficult to interpret the contribution to survival of each component of these multimodality bladder-sparing approaches. Because restaging TURB has not been performed as standard practice in all series, it is difficult to know the true impact of TURB alone. One expects patients who have been rendered clinical p0, either by TURB alone or by chemoradiation before TURB or cystectomy, to have improved long-term survival (Herr, 1996; Herr et al, 1998; Sternberg, 2005).

Cystectomy series do not report by "intention to treat" and exclude those patients for whom cystectomy is found to be inappropriate. Additionally, many patients in cystectomy series do not have preoperative proof of muscle invasion by tumor. Most cystectomy reports include 25% to 40% of the patients having less than P2-stage tumors. Although survival may be similar to that in contemporary cystectomy series, it is extremely difficult to compare methodologies (Shipley et al, 2001).

The combined morbidities of chemotherapy and radiation must also be considered. Evaluation of quality of life is important because patients are often candidates for immediate cystectomy with continent diversions. Late adverse effects of trimodality chemoradiation therapy may include poor bladder function (6%), occasional rectal bleeding (2% to 5%), rectal urgency (19%), impotence (20% to 50%), vaginal dryness (rare), and temporary neuropathy (common) (Heney et al, 2009). Available data regarding quality of life indicate that urinary, bowel, and sexual function after bladder preservation seem acceptable. Patients who undergo chemoradiation and bladder preservation should be carefully selected and well informed, willing to undergo frequent follow-up and multiple cystoscopies, and understand the possibility that cystectomy may become necessary.

Current protocols incorporate newer chemotherapeutic agents such as paclitaxel and gemcitabine in an attempt to improve efficacy. Various radiation schedules such as hypofractionation and twice-daily treatments are under evaluation. Carefully selected patients with small T2 tumors who undergo complete TURB, have no evidence of urethral obstruction, and have complete response to induction chemoradiation are the most suitable candidates.

No prospective randomized trials have compared survival with chemotherapy and TURB alone or with concomitant chemoradiation and radical cystectomy in muscle-invasive disease. Factors associated with maintaining the bladder include (1) clinical stage (organ-confined), (2) tumor size less than 3 to 5 cm, (3) absence of hydronephrosis, (4) absence of a palpable mass, and (5) unifocal disease. Patients with residual disease at first cystoscopy (within 3 months) after TURB alone or neoadjuvant chemotherapy plus TURB are at risk and should undergo cystectomy.

MOLECULAR MARKERS IN INVASIVE AND ADVANCED BLADDER CANCER

Peripheral Blood

Despite accurate pathologic staging and tissue biomarkers, pretreatment markers that reflect the overall biology of the patient's cancer are lacking. Because 40% to 50% of patients die within 5 years despite aggressive surgery and perioperative chemotherapy, clinically useful markers that are associated with risk of progression and response to treatment are necessary.

Early studies, perhaps the earliest, evaluated carbohydrate-based cell surface markers including CEA, CA19-9, and CA-125. Several reports indicate that these may be elevated in locally advanced and/or metastatic disease and may correlate with response to therapy (Cook et al, 2000; Izes et al, 2001; Margel et al, 2006). Margel and colleagues (2006, 2007) prospectively evaluated these three markers and found that CEA elevations were modest and not associated with pathologic stage but that CA19-9 and CA-125 were associated with non-organ-confined disease and with overall and/or disease-specific survival. Cook and colleagues (2000) evaluated 74 patients with metastatic disease and found that 58% had at least one elevated marker and that marker response correlated with clinical response to treatment. Margel and colleagues (2009) incorporated these three peripheral biomarkers into a predictive model that included four clinical parameters—hydronephrosis, clinical stage, presence of CIS, and tumor size greater than 3 cm—for predicting non-organ-confined cancer and demonstrated 85% accuracy.

Recent studies suggest that several growth factors and cytokines that are measurable in peripheral blood are elevated in invasive bladder cancer and are associated with metastatic disease and increased risk of progression. These include growth factors such as transforming growth factor beta-1 (TGF-β_1), insulin growth factor-1 (IGF-1) and IGF binding protein-3, and the cytokine receptor interleukin 6 (IL-6) and its soluble receptor (IL6-sR) (Shariat et al, 2001; Andrews et al, 2002; Shariat et al, 2003a). Other classes include the soluble proteolytic cleavage product of the cell adhesion molecule E-cadherin. Loss of expression of E-cadherin in bladder cancer is associated with a higher risk of

progression, and high blood levels of the soluble fraction are associated with a high risk of progression after cystectomy (Byrne et al, 2001; Matsumoto et al, 2003). Still other markers include urokinase type plasminogen activator (UPA) (Shariat et al, 2003b). Several of these biomarkers are associated with lymphovascular invasion and nodal metastases. When analyzed in a COX proportional hazards analysis, IL6-sR and UPA were independently associated with progression after cystectomy (Sanderson et al, 2004). Clearly, before incorporation into clinical practice, more research with prospective validation is necessary.

Proteomic profiling using mass spectrometry is beginning to be explored as an alternative to tissue-based genomic profiling. Schiffer and colleagues (2009) identified a panel of urinary polypeptide bladder cancer biomarkers in 127 patients with bladder cancer and then evaluated the panel prospectively in 130 patients in order to discriminate between noninvasive and muscle-invasive cancers. Multivariate analysis revealed that the proteomic panel and tumor grade, but not cytology, were associated with muscle invasion. This work may also serve as a basis for discovery of novel proteins associated with bladder cancer progression.

With the first FDA approval of techniques to detect rare circulating tumor cells (CTCs) in breast, colorectal, and prostate cancer, several investigators are conducting studies to determine if CTCs can be detected in various stages of invasive bladder cancer (Cristofanilli et al, 2004; Goodman et al, 2009). Preliminary data suggest that the presence and number of CTCs are associated with metastatic disease and are measurable using a variety of platforms (Naoe et al, 2007; Gallagher et al, 2009; Nezos et al, 2009).

Tissue Markers

A substantial volume of research has examined molecular alterations in bladder cancer. The initial focus was on the cell cycle regulatory gene p53 and the retinoblastoma tumor suppressor gene (Rb), both of which are altered in about 50% of high-grade transitional cell cancers (Chatterjee et al, 2004a; Shariat et al, 2004). In addition, genes downstream from p53 and Rb including p21, p27, and p16 are known to be altered frequently and to contribute prognostic information in combination with p53 and Rb (Benedict et al, 1999; Chatterjee et al, 2004b; Shariat et al, 2008). A clinical trial, initiated by investigators at USC who were later joined by SWOG, was the first multicenter multinational trial designed to validate p53 alterations as a prognostic marker and to use it to define a high-risk group of patients with organ-confined disease after radical cystectomy (see "Adjuvant Chemotherapy" earlier) (Lerner et al, 2009). Patients with altered p53 IHC were offered randomization to M-VAC adjuvant chemotherapy or observation. Recently reported results of the trial were negative because adjuvant chemotherapy appeared to offer no benefit, at least in part because of a lower than predicted progression rate in p53 positive (altered) patients (Stadler et al, 2009). The study does, however, contribute a rich repository of biologic tissues and long-term clinical follow-up to aid in determining the influence of a variety of immunohistochemical markers on progression after radical cystectomy. A more contemporary study analyzed both p53 IHC and gene mutation status and found that each was predictive of outcome after cystectomy but that the two techniques combined provided the most accurate determination of outcome (George et al, 2007).

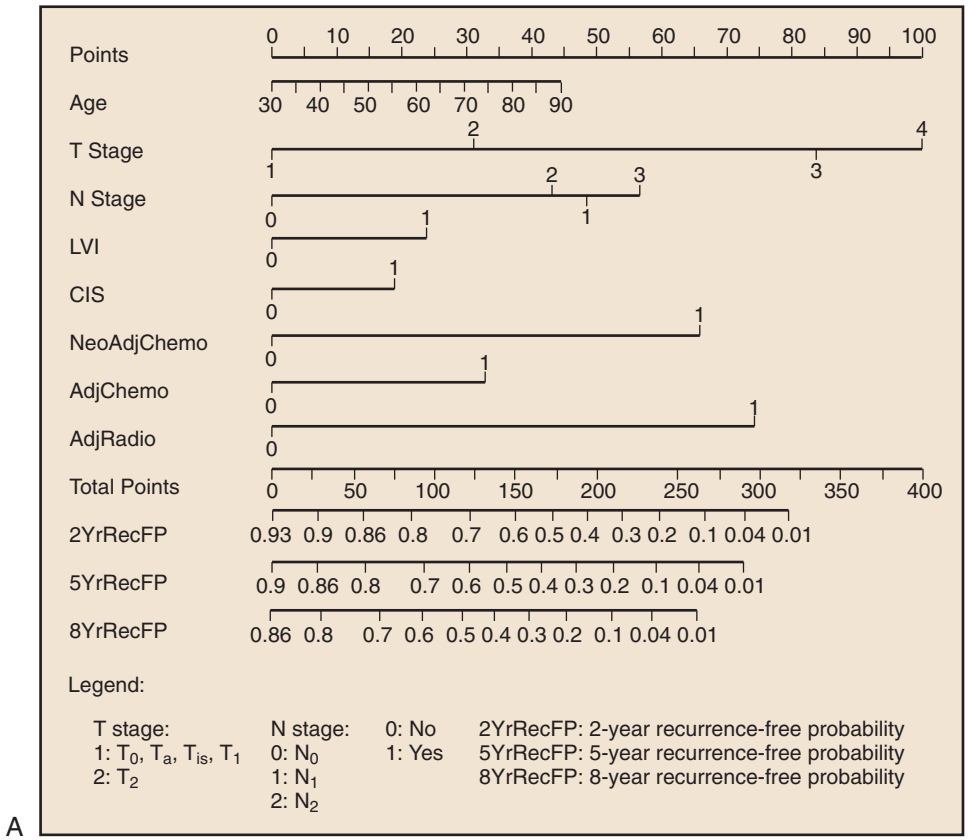
Other tissue markers that are associated with outcome after cystectomy include the calcium-dependent cell adhesion marker E-cadherin (Byrne et al, 2001). Loss of expression is associated with a higher probability of advanced pathologic stage and worse outcome following radical cystectomy. Proliferation markers such as Ki-67 (Margulis et al, 2009), markers of angiogenesis (vascular endothelial growth factor [VEGF], thrombospondin, microvessel density) (Bochner et al, 1997; Grossfeld et al, 1997; Slaton et al, 2004), and markers involved in apoptosis (Caspase 3, survivin, bcl-2) (Karam et al, 2007) have been analyzed primarily in cystectomy specimens and demonstrate that increased proliferation rates, increased angiogenesis, and loss of expression of apoptosis markers or inhibitors are associated with worse outcomes. A multicenter group has recently reported a nomogram incorporating several of these tissue markers with better predictive accuracy than TNM staging (see "Nomograms" later) (Shariat et al, 2008). To date, however, no marker or combination of markers has been validated as a predictive biomarker for progression or survival.

Advances in high-throughput genomic profiling have delivered results in identifying gene expression profiles associated with invasive bladder cancer. Mitra and colleagues (2009) evaluated 69 genes involved in known cancer pathways and identified a 4-gene panel including JUN, MAP2K6, STAT3, and ICAM 1 that predicted recurrence and survival in patients with Ta-T4 bladder cancer. A group of investigators in Denmark pioneered applications of single nucleotide polymorphism (SNP) array analysis to identify patterns of allelic imbalance associated with invasive cancer (Zieger et al, 2009). Several studies using microarray analysis analyzed gene expression profiles, and Wang and colleagues (2009) recently reported a meta-analysis of 12 studies designed to identify a 59-gene signature that distinguished invasive from noninvasive cancers. These techniques, which can be applied to predict progression and response to chemotherapy or radiotherapy, herald the age of personalized genomic medicine.

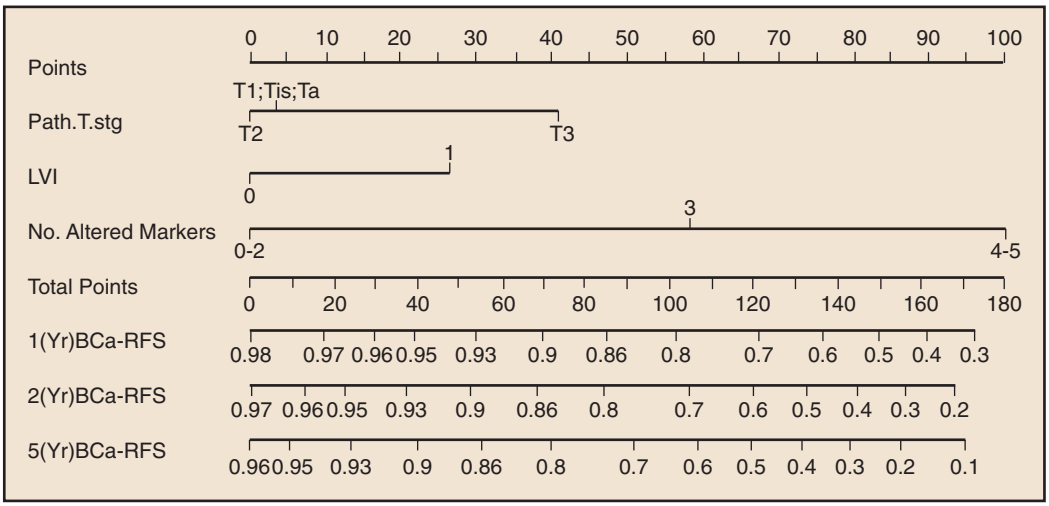
NOMOGRAMS IN THE MANAGEMENT OF PATIENTS WITH INVASIVE BLADDER CANCER

Clinical decision making has evolved over time from physician judgment, to use of overall average outcome prediction, to risk group stratification, and to use of prediction models using Cox multivariate or logistic regression, to use of nomograms, which graphically represent a prediction model for individualized prediction of an end point (Kattan, 2005). The most accurate prediction of outcomes after radical cystectomy (RC) has been based on pathologic staging of the primary tumor and regional lymph node status. Several large, contemporary radical cystectomy studies have documented risks of recurrence and death based on either TNM staging or pathologic groupings that separate organ-confined, extravesical, and node-positive tumors (Stein et al, 2001; Shariat et al, 2006b). Although these traditional prognostic groupings have provided useful estimates for recurrence risk and survival outcomes, significant variation has been observed within each prognostic group. The observed variation in outcomes is related to the heterogeneity of tumor biology and patient characteristics within each pathologic subgroup. Other factors that may affect outcome after stratification by stage and nodal status include lymphovascular invasion, patient age and gender, and histology. Patient comorbidities may also influence outcome. Alternative prognostic models capable of simultaneous evaluation of multiple relevant variables have been shown to provide improved estimates of outcome that can be applied more accurately to an individual patient (Kattan, 2003; Lerner et al, 2007).

Two consortia first reported nomograms for predicting recurrence after radical cystectomy (Fig. 82–4) (Bochner et al, 2006;



A



B

Figure 82–4. To obtain nomogram-predicted probability of recurrence, locate patient values at each axis. Draw a vertical line to the "Point" axis to determine how many points are attributed for each variable value. Sum the points for all variables. Locate the sum on the "Total Points" line. Draw a vertical line toward the 2YrRecFP, 5YrRecFP, and 8YrRecFP axes to respectively determine the 2-year recurrence-free probability, 5-year recurrence-free probability, and 8-year recurrence-free probability. **A,** Postoperative nomogram for predicting recurrence after radical cystectomy. **B,** Postoperative nomogram for predicting recurrence after radical cystectomy incorporating tissue biomarkers. CIS, carcinoma in situ; LVI, lymphovascular invasion. (**A,** Reprinted with permission from Karakiewicz PI, Shariat SF, Palapattu GS, et al. Nomogram for predicting disease recurrence after radical cystectomy for transitional cell carcinoma of the bladder. J Urol 2006;176:1354–62, Fig. 3, p. 1359. **B,** Reprinted with permission from Shariat SF, Karakiewicz PI, Ashfaq R, et al. Multiple biomarkers improve prediction of bladder cancer recurrence and mortality in patients undergoing cystectomy. Cancer 2008;112:315–25, Fig. 2A, p. 321.)

Karakiewicz et al, 2006a). The Bladder Cancer Research Consortium (BCRC), a collaboration among Baylor College of Medicine, University of Texas Southwestern Medical Center, Johns Hopkins University, and the University of Montreal, studied outcomes following radical cystectomy. The resulting data set was composed of 958 patients from three institutions with 728 evaluable for recurrence. The BCRC group has also developed a suite of nomograms for predicting overall and cancer-specific survival for patients with advanced pathologic T and N stage disease (available online at www.nomogram.org) (Karakiewicz et al, 2006a; Karakiewicz et al, 2006b; Shariat et al, 2006a). The International Bladder Cancer Nomogram was developed by a team from MSKCC and

based on data from 4840 evaluable patients (available online at www.mskcc.org/mskcc/html/73854.cfm) (Bochner et al, 2006). The accuracy for predicting recurrence was remarkably similar between groups with concordance indices of 0.78 and 0.75, respectively. Both were significantly more accurate than AJCC TNM and standard pathologic stage groupings.

In order to improve on the accuracy of these "first-generation" nomograms, Shariat and colleagues (2008) incorporated several tissue biomarkers. This work, built on research described earlier in the "Molecular Markers in Invasive and Advanced Bladder Cancer" section, demonstrated that altered expression of multiple cell cycle regulatory gene products was independently associated with outcome following radical cystectomy. This "second-generation" nomogram incorporated p53, pRB, p21, p27, and cyclin E1 measured by immunohistochemistry into a nomogram that predicted recurrence and survival for patents with pTa-3N0M0 disease at cystectomy. With the addition of the biomarkers, the accuracy for predicting recurrence and cancer-specific survival compared with accuracy of a nomogram based on TNM stage was increased by 10.9% (83.4% vs. 72.5%, $P < .001$) and 8.6% (86.9% vs. 78.3, $P < .001$), respectively. These instruments are based on data acquired retrospectively and must be validated prospectively in order for their utility in clinical practice to be determined.

MANAGEMENT OF METASTATIC BLADDER CANCER

Systemic combination chemotherapy is the primary treatment modality for patients with metastatic urothelial cancer. Cisplatin-based first-line chemotherapy regimens for urothelial or transitional cell carcinoma include M-VAC or high-density (HD) M-VAC and GC (Sternberg et al, 1989; Loehrer et al, 1992; Saxman et al, 1997; von der Maase et al, 2005; Sternberg et al, 2006b). Despite initial high response rates (RRs) of 40% to 70% in advanced disease, chemotherapy is usually not curative and overall 5-year survival is only approximately 5% to 20% (Table 82–7) (Saxman et al, 1997; von der Maase et al, 2005; Sternberg et al, 2006b; Bellmunt et al, 2007b). A contemporary EORTC/Intergroup randomized trial failed to demonstrate an OS benefit with the addition of paclitaxel to GC (Bellmunt et al, 2007b).

Renal dysfunction (usually defined as a creatinine clearance of <60 mL/min), poor performance status, and advanced age are relatively common and often preclude cisplatin chemotherapy. Carboplatin-based combination regimens are feasible for such patients but appear to be suboptimal compared with cisplatin-based regimens (Petrioli et al, 1996; Bellmunt et al, 1997; Dogliotti et al, 2007).

Ongoing randomized trials specifically evaluate regimens for elderly patients or poor performance status or patients with poor renal function. These studies include comparisons of carboplatin and gemcitabine with methotrexate, vinblastine, and carboplatin (De Santis et al, 2008) and studies of gemcitabine compared with gemcitabine and vinflunine (Culine et al, 2006).

Salvage chemotherapy for advanced TCC with conventional chemotherapeutic agents (taxanes, gemcitabine) usually yields suboptimal response rates and variable median survivals (Table 82–8) (Dreicer et al, 1996; McCaffrey et al, 1997; Lorusso et al, 1998; Sternberg et al, 2001; Albers et al, 2002; Vaughn et al, 2002). However, a nonplatinum taxane-gemcitabine regimen may in some cases be a reasonable alternative for such patients (Dreicer et al, 2003; Calabrò et al, 2009a).

The development of novel and tolerable agents for TCC is clearly warranted, coupled with utilization of factors that may be predictive of response such as ERCC1 (Bellmunt et al, 2007a).

Prognostic Factors

Comparisons among phase II and III studies of metastatic TCC require that prognostic factors be well balanced. Two key factors have been shown to be predictors of a poor prognosis for patients treated with first-line cisplatin-based chemotherapy. A poor performance status (PS) (KPS <80) and the presence of visceral metastases adversely affect survival in patients with locally advanced or metastatic TCC (Bajorin et al, 1999).

In the analysis of patients treated at MSKCC with M-VAC, median survival of patients with zero, one, or two risk factors ranged from 33 to 13.4 to 9.3 months, respectively (Bajorin et al, 1999). In a recent presentation from MSKCC, a nomogram was constructed incorporating four parameters: hemoglobin, serum albumin, KPS, and visceral metastasis (Bajorin et al, 2007). This nomogram needs further validation.

Table 82–7.

Randomized Trials of Frontline Chemotherapy for Metastatic Urothelial Cancer

GROUP	TREATMENT	*N*	RR (%)	MEDIAN OS (MO)	5-YR OS	BEST ARM
Intergroup (Loehrer et al, 1992)	M-VAC	126	39	12.5	3.7%	M-VAC
	Cisplatin	120	12	8.2	0.6%	
MDAH (Logothetis et al, 1990)	M-VAC	65	65	12.6		M-VAC
	CISCA	55	46	10.0		
EORTC (Sternberg et al, 2006b)	M-VAC	129	58	14.9	13.5%	HD-M-VAC ≈ M-VAC
	HD-M-VAC	134	72	15.1	21.8%	
Lilly (von der Maase et al, 2005)	M-VAC	202	46	15.2	13%	M-VAC ≈ GC
	GC	203	49	14.0	15.3%	
Greece (Bamias et al, 2004)	M-VAC	109	37	14.2	2-yr OS 18.9%	M-VAC
	DC	111	54	9.3	28.6%	
EORTC (Bellmunt et al, 2007b)	GC	315	46	12.8	NR	PCG ≈ GC
	PCG	312	57	15.7		

CISCA, cisplatin, cyclophosphamide, doxorubicin; DC, docetaxel, cisplatin; GC, gemcitabine, cisplatin; HD-M-VAC, high-dose M-VAC; M-VAC, methotrexate, vinblastine, doxorubicin, cisplatin; N, number of patients; NR, not reported; OS, overall survival; PCG, paclitaxel, cisplatin, gemcitabine; RR, response rate.

Table 82–8.

Salvage Chemotherapy for Metastatic Urothelial Cancer

DRUG	AUTHOR (REFERENCE)	*N*	ELIGIBILITY	RR (%)	MEDIAN PFS (MO)	MEDIAN OS (MO)
Paclitaxel (24-hr)	Dreicer (1996)	9	1 prior regimen	56	—	—
Paclitaxel (Weekly)	Vaughn (2002)	31	1 prior regimen for advanced disease, prior adjuvant chemotherapy and taxanes allowed	10	2.2	7.2
Docetaxel (Every 3 wk)	McCaffrey (1997)	30	1 prior cisplatin regimen, prior taxanes not allowed	13	—	9.0
Gemcitabine	Lorusso (1998)	35	1 prior platinum regimen	22.5	—	5.0
Gemcitabine	Albers (2002)	30	1 prior cisplatin regimen	11	4.9	8.7
Gemcitabine-Paclitaxel	Sternberg (2001)	41	1 prior cisplatin regimen including perioperative therapy	60	—	14.4

N, number of patients; OS, overall survival; PFS, progression-free survival; RR, response rate.

Table 82–9.

Salvage Trials with Novel Chemotherapeutic Regimens for Metastatic Urothelial Cancer

Vinflunine	Culine (2006)	51	1 prior platinum regimen	18	3.0	6.6
Pemetrexed	Sweeney (2006)	47	1 prior regimen including perioperative therapy within 12 mo	27.7	2.9	9.6
Pemetrexed	Galsky (2007)	12	1 prior regimen	8	—	—
Ixabepilone	Dreicer (2007)	42	1 prior platinum regimen, prior taxane allowed	11.9	2.7	8.0
Oxaliplatin	Winquist (2005)	18	1 prior regimen for advanced disease, prior adjuvant chemotherapy >6 mo earlier not counted	6	—	—

N, number of patients; OS, overall survival; PFS, progression-free survival; RR, response rate.

Novel Agents for Advanced Transitional Cell Carcinoma

Several novel agents that are discussed later have been evaluated in patients with advanced and metastatic TCC (Sonpavde and Sternberg, 2008b).

Vinflunine. Vinflunine ditartrate is a novel antitubulin agent obtained from a vinca alkaloid. Salvage therapy with vinflunine plus BSC (best supportive care) was compared with BSC in a multinational randomized trial. Unfortunately, no improvement in survival was demonstrated (Bellmunt Molins et al, 2008). After subset analyses, this agent was approved in the second-line setting by the EMEA. Another ongoing randomized trial compares the combination of frontline vinflunine and gemcitabine with gemcitabine alone in patients ineligible for cisplatin.

Pemetrexed. Pemetrexed is a multitargeted antifolate agent approved for pleural mesothelioma and non–small cell lung cancer. Supplementation of vitamin B_{12} and folate attenuate its toxicities. Although initial phase II reports with this agent were promising (Paz-Ares et al, 1998; Sweeney et al, 2006) (Table 82–9), enthusiasm has waned after a trial from MSKCC revealed an overall RR of 8% (Galsky et al, 2007). Combined frontline treatment of pemetrexed and gemcitabine also failed to reveal results that were better than those achieved with gemcitabine alone (von der Maase et al, 2006). A phase II trial is evaluating the combination of cisplatin and pemetrexed as frontline therapy for advanced TCC (Table 82–10).

Ixabepilone. The epothilones are novel nontaxane tubulin polymerization agents, and aza-epothilone B is a semisynthetic analog of the natural product, epothilone B. Ixabepilone has been evaluated as second-line therapy of metastatic TCC in a phase II trial in patients who previously had received taxanes (Dreicer et al, 2007) (see Table 82–9).

Table 82–10.

Ongoing and Planned Trials of Chemotherapeutic Regimens for Urothelial Cancer

DRUG/REGIMEN	INSTITUTION	ELIGIBILITY	TRIAL PHASE/ DESIGN
Larotaxel	Randomized trial	First-line	Phase III Larotaxel + C vs GC
E7389	USC	Frontline, salvage	Phase II
Irinotecan	SWOG	Salvage	Phase II
Nab-paclitaxel	Canadian	Second-line	Phase II
Ifosfamide-cisplatin-Nab paclitaxel	MSKCC	Neoadjuvant	Phase I/II
CaG-Nab-paclitaxel	U Minnesota	Neoadjuvant	Phase I/II
Cisplatin-pemetrexed	Spanish	Frontline	Phase I/II
Oxaliplatin-docetaxel	Stanford	Frontline, Cr <1.8 mg/dL	Phase II
AG-paclitaxel	MDACC	Frontline, renal dys	Phase II
HD-M-VAC	DFCI	Neoadjuvant	Phase II

AG, doxorubicin, gemcitabine; BSC, best supportive care; CaG, carboplatin, gemcitabine; Cr, creatinine; GC, gemcitabine, cisplatin; HD-M-VAC, high-dose M-VAC; Nab-paclitaxel, nanoparticle albumin-bound paclitaxel; renal dys, renal dysfunction.

Larotaxel. Larotaxel is a novel, semisynthetic taxoid with several advantages over docetaxel and paclitaxel. It is active in tumor cells sensitive to docetaxel but also in tumor cells expressing P-glycoprotein, which plays a key role in taxane resistance. Several specific toxicities related to taxanes (nail changes, fluid retention,

and allergic reaction) appear to be less frequent with larotaxel. In addition, larotaxel has the potential to cross the blood-brain barrier (Investigator's Brochure Edition 12, dated April 3, 2006). A randomized study of larotaxel and cisplatin (LC) versus GC in the firstline treatment of locally advanced/metastatic urothelial tract or bladder cancer is under way. The primary end point is overall survival.

Nanoparticle Albumin-Bound (Nab) Paclitaxel. Nab-paclitaxel is a novel solvent-free, albumin-bound formulation of paclitaxel designed to avoid solvent-related toxicities and to deliver paclitaxel to tumors via molecular pathways involving an endothelial cell-surface albumin receptor and an albumin-binding protein expressed by tumor cells and secreted into the tumor interstitium (secreted protein acid rich in cysteine [SPARC]) (Nyman et al, 2005). Nab-paclitaxel is being evaluated both for the salvage therapy of progressive TCC and as a component of combination regimens in the neoadjuvant setting (see Table 82–10).

Oxaliplatin. Oxaliplatin is a non-nephrotoxic third-generation platinum analogue that has been studied in previously-treated metastatic TCC in a phase II trial (Winquist et al, 2005) (see Table 82–9). Combinations of oxaliplatin and gemcitabine and of docetaxel and oxaliplatin may be of some interest (see Table 82–10).

Monoclonal Antibodies

Trastuzumab. HER2/neu expression in urothelial cancers is variable and may be associated with a more aggressive clinical course (Lonn et al, 1995). In a phase II trial, patients with metastatic TCC or squamous cell carcinoma that expressed HER2/neu (by immunohistochemistry f, serology, or fluorescence in situ hybridization [FISH]) were treated with trastuzumab in combination with paclitaxel, carboplatin, and gemcitabine (Hussain et al, 2007). Thirty-one (70%) of 44 HER2/neu-positive patients responded (5 CRs and 26 PRs), with 25 (57%) confirmed responses. These outcomes are promising, and a randomized trial of gemcitabine and cisplatin with or without trastuzumab has been conducted in France. One thousand patients have been screened, and 60 have actually been included in this trial with an HER2 positivity of only around 5% to 10%. Trastuzumab is also being evaluated in combination with paclitaxel and radiotherapy in a bladder preservation strategy (Table 82–11).

Bevacizumab. VEGF (vascular endothelial growth factor) receptors are expressed in TCC, and preclinical evidence supports the antitumor efficacy of targeting this pathway in combination with chemotherapy (Inoue et al, 2000). A phase II trial by the Hoosier Oncology Group (HOG) has evaluated frontline GC plus

Table 82–11.

Ongoing and Planned Trials of Biologic Agents Alone or with Chemotherapy for Urothelial Cancer

DRUG/REGIMEN	INSTITUTION	ELIGIBILITY	TRIAL PHASE/DESIGN
GC-Bevacizumab	HOG	Frontline	Phase II
GC ± Bevacizumab	CALGB	Frontline	Phase III
GC-Bevacizumab	MUSC	Neoadjuvant	Phase II
CaG-Bevacizumab	MSKCC	Frontline, renal dys	Phase II
HD-M-VAC-Bevacizumab	MDACC	Neoadjuvant	Phase II
AG-Bortezomib	MDACC	Frontline	Phase I/II
VEGF-Trap	NCI	Salvage, frontline	Phase II
Docetaxel ± Vandetanib	DFCI	Salvage	Randomized phase II
Lapatinib	U.S. Oncology	Salvage	Randomized discontinuation
Lapatinib	EORTC	Frontline	Phase I
GC ± Gefitinib	European	Frontline	Randomized phase II
Docetaxel ± Gefitinib	MDACC	Salvage consolidation	Randomized phase II
Erlotinib	UNC	Neoadjuvant	Phase II with correlative studies
Docetaxel ± Gefitinib	MDACC	Second-line consolidation	Randomized phase II
Cetuximab ± Paclitaxel	Fox Chase	Second-line	Randomized phase II
GC ± Cetuximab	U Michigan	Frontline	Randomized phase II
Trastuzumab-Paclitaxel-RT	RTOG	Frontline	Phase II bladder conserving
Sorafenib	ECOG	Salvage	Phase II
GC-Sorafenib	MSKCC	Frontline	Phase II
CaG-Sorafenib	Yale	Frontline	Phase II
Sunitinib	MSKCC	Second-line	Phase II
Sunitinib	U Michigan	Second-line consolidation	Randomized phase II
Sunitinib	Cleveland Clin	Neoadjuvant	Phase II with correlative studies
Gemcitabine-Sunitinib	DFCI	Frontline, renal dys	Phase II
GC-Sunitinib	Baylor-HOG	Neoadjuvant	Phase II
Pazopanib	NCI	Salvage, frontline	Phase II
Dasatinib	Baylor-HOG	Neoadjuvant	Phase II with correlative studies
Ipilimumab	MDACC	Neoadjuvant	Phase I with correlative studies
Tamoxifen	Baylor	Salvage	Phase II
Vorinostat	California	Salvage	Phase II

AG, doxorubicin, gemcitabine; CaG, carboplatin, gemcitabine; GC, gemcitabine, cisplatin; HD-M-VAC, high-dose M-VAC (methotrexate, vinblastine, doxorubicin, cisplatin); HOG, Hoosier Oncology Group; renal dys, renal dysfunction; VEGF-Trap, vascular endothelial growth factor trap.

Modified with permission from Sonpavde G, Ross R, Powles T, et al. Novel agents for muscle-invasive and advanced urothelial cancer. BJU Int 2008;101:937–43, Table 2, p. 939.

bevacizumab for metastatic TCC (Hahn et al, 2009). Gemcitabine was reduced to 1000 mg/m^2 intravenous days 1 and 8 after the first 17 patients were entered because of 7 thrombotic DVT or PE events. The Cancer and Leukemia Group B (CALGB) is nonetheless planning a frontline randomized phase III trial of GC versus GC and bevacizumab (see Table 82–11).

Cetuximab. Human TCCs overexpress epidermal growth factor receptor (EGFR), which confers a poor prognosis (Sriplakich et al, 1999). Cetuximab is an intravenously administered EGFR monoclonal antibody commonly used in colorectal cancer and in head and neck cancers. A trial is planned to evaluate the combination of cetuximab with frontline GC, as well as with salvage paclitaxel (see Table 82–11).

Small-Molecule Biologic Agents

EGFR and HER2 Receptor Tyrosine Kinase Inhibitors (TKIs). The CALGB reported a phase II trial of frontline GC and gefitinib (an orally bioavailable EGFR TKI) in metastatic urothelial cancer, with an RR of 51% and median survival of 14.4 months (Philips et al, 2006). This is now under evaluation in a randomized study of GC with or without gefitinib (see Table 82–9). Erlotinib, another oral EGFR TKI, used commonly in the treatment of non–small cell lung cancer, is being studied in the neoadjuvant setting before cystectomy with primarily correlative and pharmacodynamic end points (see Table 82–11).

Lapatinib is an oral TKI that targets EGFR and HER2 and has been successful in combination with capecitabine chemotherapy in breast cancer. In a preliminary report of a phase II trial of 59 patients with EGFR and/or HER2 expression (1+ to 3+ by IHC), lapatinib was active as salvage therapy for advanced TCC with PRs in 3% and clinical benefit (response + stability ≥ 16 weeks) in 12% of patients (Wuelfing et al, 2005). The median time to progression was 8.6 weeks, and there was a trend toward clinical benefit in those with EGFR or HER2 2+/3+ by IHC. A randomized discontinuation trial being conducted by the U.S. Oncology Research network is evaluating salvage therapy with lapatinib in HER2 expressing (by FISH) metastatic TCC. The EORTC is evaluating the combination of GC and lapatinib in a phase I dose escalation study (see Table 82–11).

VEGF Receptor TKIs. Sorafenib was the first orally bioavailable multitargeted receptor TKI to be approved for use as second-line therapy in advanced renal cancer. It was designed as a c- and b-raf kinase inhibitor since the ras/raf signaling pathway mediates tumor cell proliferation and angiogenesis. Sorafenib also inhibits several receptor tyrosine kinases, among them VEGF receptor (R)-2, PDGFR-β, Flt-3, and c-KIT. Sorafenib as a single agent was ineffective as second-line therapy for advanced TCC (Dreicer, 2008). However, the combination of sorafenib with carboplatin/cisplatin and gemcitabine is being evaluated for frontline therapy (see Table 82–11).

Sunitinib, another small-molecule, multitargeted receptor TKI taken orally, is also approved for the therapy of renal cell cancer. It targets VEGFR-2, PDGFR-β, KIT, and Flt-3 receptors. A preclinical study recently demonstrated significant activity of sunitinib both as a single agent and in combination with cisplatin (Sonpavde et al, 2007). In addition, activity has been demonstrated in a phase II trial of sunitinib as salvage therapy for TCC (Gallagher et al, 2007). Another trial compares sunitinib with placebo in patients who are stable or responding to frontline chemotherapy (see Table 82–9). The Cleveland Clinic is evaluating neoadjuvant sunitinib alone with primarily correlative studies, and another neoadjuvant phase II trial of sunitinib in combination with GC is planned by the HOG.

Axitinib, a perhaps more potent VEGFR TKI, caused regression of subcutaneous human TCC xenografts and inhibited angiogenesis and VEGFR-2 and PDGFR-β phosphorylation (Zhu et al, 2006). This molecule is clearly of interest for future studies. Another randomized phase II trial led by the Dana Farber Cancer Institute is evaluating salvage docetaxel alone or with vandetanib, a dual EGFR and VEGFR-TKI in the second-line setting (see Table 82–9).

Other Novel Agents

On the basis of ER-β expression in urothelial cancers, which increases with increasing stage and grade, and the inhibitory effect of selective estrogen receptor modulators in preclinical models, salvage therapy with oral tamoxifen is being evaluated in a multiinstitutional phase II trial of advanced UC at Baylor College of Medicine in collaboration with colleagues in Los Angeles and Rome (see Table 82–9).

NEOADJUVANT THERAPY TO DEVELOP NOVEL AGENTS

Among novel therapies, neoadjuvant therapy before cystectomy is an interesting model. Pathologic complete remission (pCR) is used as a surrogate for the efficacy of neoadjuvant chemotherapy and long-term outcomes (Grossman et al, 2003b). Neoadjuvant therapy with cisplatin-based regimens (M-VAC, GC) has been shown to be safe and does not increase the risk of postoperative complications (Grossman et al, 2003b; Dash et al, 2008). Therefore the neoadjuvant paradigm may accelerate the development of novel agents. Owing to the availability of tissue before and after chemotherapy, it may be possible to determine molecular and biologic characteristics that predict chemosensitivity.

The choice of novel agents should be based on the knowledge of potential molecular targets emerging from studies examining urothelial cancer biology. If biologic activity can be demonstrated in initial small pilot trials (e.g., 15 to 25 patients with an appropriate statistical design to detect a biologic effect), additional larger phase II and randomized phase II studies of novel agents alone or in combination may be planned with more rigorous efficacy end points (pCR). Additional goals may be discovering markers predictive for efficacy including global gene expression assays. Before initiation of trials that require large sample sizes, careful consideration of potential activity may be achieved using a neoadjuvant strategy.

Predictive Factors

In order to guide optimal patient selection, the discovery of predictive factors should proceed with the development of novel agents. Levels of DNA-repair genes including ERCC1, RRM1, BRCA1, and caveolin-1 have been evaluated in 57 patients with advanced bladder cancer treated with either GC or PCG (Bellmunt et al, 2007a). Median survival was significantly higher in patients with low ERCC1 levels (25.4 vs. 15.4 months; $P = .03$). A trend toward longer time to progression was observed in patients with tumors, expressing low levels of all markers. On multivariate analysis of pretreatment prognostic factors, ERCC1 emerged as an independent predictive factor for survival. The results indicate that ERCC1 may predict survival in urothelial cancer treated with platinum-based therapy.

CONCLUSIONS

Invasive bladder cancer should be viewed as diseases with both loco-regional and systemic implications requiring an integrated multidisciplinary treatment approach. Attention to accurate staging and surgical quality including the extent and completeness of the node dissection are significant determinants of long-term survival. Quality of life can be maintained with appropriate sexual function–preserving surgical techniques and continent urinary diversion in motivated patients. Both neoadjuvant and adjuvant chemotherapy continue to play a role in treatment of locally advanced bladder cancer, although meta-analyses reported in currently available studies lean more toward the use of neoadjuvant chemotherapy. Concomitant chemoradiation is an excellent strategy for selected patients in whom bladder preservation can be considered. Future investigation will focus on optimizing radiation techniques including the possibility of radiosensitization. Progress in the treatment of muscle-invasive and advanced TCC hopefully will be made with the addition and rational use of novel biologic agents to current cisplatin-based combination chemotherapeutic strategies.

Thorough understanding of biology is necessary in order to improve outcomes. Employment of the neoadjuvant paradigm may be a powerful tool to accelerate drug development and discovery of factors predictive of efficacy. Factors predictive of response to specific agents need to be better defined in order to facilitate more personalized strategies. Close coordination among all disciplines is required to achieve optimal results, incorporating more effective systemic chemotherapy and the proper selection of patients based on predictive molecular markers.

Key Points

- Understand staging and natural history of urothelial cancer of the urinary bladder.
- Know the indications for partial versus radical cystectomy.
- Understand the anatomic extent of pelvic lymphadenectomy and impact on outcomes.
- Know the indications for neoadjuvant and adjuvant chemotherapy.
- Know the role of bladder-preserving strategies in patients with invasive bladder cancer.
- Know the role for systemic therapy in the management of patients with advanced disease.
- Understand the common molecular alterations associated with bladder cancer.

SUGGESTED READINGS

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The complete reference list is available online at www.expertconsult.com.

chapter 83

Surgery for Bladder Cancer

Ryan Kent Berglund, MD ● Harry W. Herr, MD

Transurethral Resection of Bladder Tumors
Surgical Technique
Radical Cystectomy in the Male
Radical Cystectomy in the Female
Partial Cystectomy
Postoperative Management

According to the American Cancer Society, cancers of the urinary bladder accounted for an estimated 70,980 new cases and 14,330 deaths in the United States in 2009 (Jemal et al, 2009). These cancers are the sixth leading cause of cancer death among Americans, and they are a significant source of health care costs.

Surgery of bladder cancer consists of transurethral resection for diagnosis and cure of noninvasive or minimally invasive neoplasms and radical cystectomy and pelvic lymph node dissection for invasive cancers. Radical cystectomy for transitional cell carcinoma (TCC) of the bladder serves as the gold standard for local control and survival of muscle-invasive tumors. The aim of the procedure is to remove all cancer in the bladder, pelvis, and regional lymph nodes with a wide soft tissue margin. The plane of dissection is the musculoskeletal boundaries of the pelvis.

Early attempts at cystectomy met with poor survival outcomes. **In 1887 Bardenheuer of Cologne, Germany performed the first cystectomy.** The procedure was one in which only the bladder was removed and neither ureter was diverted. The patient died a few days after surgery from sepsis, and other contemporary attempts often met with a similar outcome.

The first publication of long-term outcomes using the techniques of radical surgery with wide local excision and removal of regional lymph nodes with urinary diversion came from Whitmore and Marshall (1962). **In their landmark publication, they observed 5-year survival rates of 21% to 49% in their series of 230 patients.** Since then, advances in endoscopic and open surgical technique, as well as perioperative care, have reduced the surgical mortality from more than 10% to less than 5% and improved results. Additionally, the use of neoadjuvant chemotherapy treatment before surgery has led to increased long-term survival. **Recent large series have shown 10-year cancer-specific survival rates in patients with pathologic T2 cancers of 65% to 78%** (Stein et al, 2001; Shariat et al, 2006).

TRANSURETHRAL RESECTION OF BLADDER TUMORS

Since the introduction of the cystoscope by Nitze in 1877, endoscopic diagnosis and treatment have been the initial steps in the management of bladder tumors. Flexible office cystoscopy and sometimes biopsy are performed to establish presence of a bladder tumor in patients presenting with gross hematuria, persistent microscopic hematuria, or irritative voiding symptoms such as dysuria. An examination under anesthesia and endoscopic resection are performed under spinal or general anesthesia to remove the tumor completely, if possible, and to obtain sufficient pathologic material for staging. **In the case of noninvasive (superficial) disease, and in some cases muscle-invasive disease, resection alone can be curative.**

Initial presentation to the urologist is often through a referral for microscopic or macroscopic hematuria, although other presenting symptoms can include irritative voiding, bladder outlet obstruction, abdominal mass, or flank pain. Occasionally, patients present with a tumor found incidentally either through imaging or an unrelated cystoscopy. At presentation, a history and physical examination are performed, with special attention paid to environmental exposures. Current or past tobacco use, exposure to aromatic amines in the rubber and dye industry, cyclophosphamide-based chemotherapy, and radiation exposure (particularly for prostate cancer) are all known risk factors for developing bladder cancer. Physical examination includes palpation of lymph nodes, flank, and abdomen. Men undergo a digital rectal examination to assess possible prostate involvement, and women have a bimanual examination to palpate size, location, and extent of the bladder tumor.

Laboratory studies comprise a complete blood count including white blood cell count, hemoglobin, hematocrit, and platelet count because many patients have underlying infection and anemia. A basic metabolic panel including serum electrolytes and creatinine with a calculated glomerular filtration rate demonstrate any underlying metabolic or renal dysfunction. Prothrombin time (with calculated international normalized ratio) and partial thromboplastin time are included as well, with any abnormalities addressed preoperatively. A urinalysis and urine culture should be sent before resection because many patients are colonized with bacteria and yeast before resection and require appropriate preoperative antibiotic treatment or prophylaxis.

Before the endoscopic treatment of a bladder tumor, **the patient should undergo upper tract imaging to rule out the presence of an upper tract TCC.** For patients with a glomerular filtration rate greater than 60 mL/min and no allergies to intravenous (IV) iodinated contrast, the standard modality in most centers is a computed tomography (CT) urogram, which can combine abdominal imaging for local spread or metastasis with delayed images that can detect intraluminal defects of the upper

tract. Where unavailable, intravenous pyelography is a reasonable alternative for the detection of intraluminal filling defects. For a patient with a glomerular filtration rate (GFR) of 30 to 60 mL/min or an IV contrast allergy, magnetic resonance urography provides a safer alternative to CT urogram and provides the combined benefits of abdominal imaging with effective upper tract imaging. For patients with chronic kidney disease and a GFR less than 30 mL/min, upper tract imaging should include renal ultrasound and a retrograde pyelogram to image the ureter and renal pelvis.

In the operating room, the patient is placed in the dorsal lithotomy position after a local or general anesthetic induction. An appropriate antibiotic is given within 1 hour of initiation of the procedure, with either a second-generation cephalosporin or a quinolone given in the event of a preoperatively negative urine culture. Initially a bimanual examination of the pelvis is performed to determine clinical staging of the tumor. Then a complete endoscopic evaluation of the urethra, prostate (in males), and bladder are performed using both a 30- and 70-degree angled lens. Both ureteral orifices are examined for proximity to a tumor and involvement in the disease process. The bladder is filled with either water or 1.5% glycine irrigant (in the case of monopolar electrocautery being used) or 0.9% sodium chloride solution (if bipolar electrocautery is used).

Once the tumor or tumors are identified, **resection is performed using a cutting current on the loop resection device down to the level of the detrusor muscle.** It is essential to resect to this depth to obtain sufficient tissue for pathologic staging and for completeness of resection (Fig. 83–1). The margin of resection should include a 2- to 3-cm visually negative margin as deep muscle spread of tumor can occur in either a broad-based or tentacular fashion (Fig. 83–2). Resection of tumors involving the lateral bladder wall risk stimulation of the obturator nerves, leading to rapid thigh adduction and possible perforation of the bladder. This can be minimized by reducing the cautery current and rapidly tapping the foot pedal. Smaller and multiple lesions can be treated with cold cup biopsy and fulguration or fulguration alone on a coagulation current, or with another energy source such as a neodynium-yttrium-aluminum garnet laser (Nd:YAG).

Bladder perforation is a complication that occurs in resections carried to the optimal depth of resection into the detrusor muscle. On the basis of the location of the perforation, these result in either an extravesical or intravesical extravasation of irrigant. Perforations that occur at the trigone, bladder base, and laterally typically result in an extravesical perforation with irrigant extravasation and can often be managed conservatively with Foley catheter drainage (Fig. 83–3A). Perforations at the bladder dome can result in intraperitoneal perforation and extravasation and often require operative repair and drainage of irrigant (Fig. 83–3B). Intraperitoneal ruptures are often diagnosed intraoperatively with palpation of the abdomen confirming distension from irrigant. An intraoperative cystogram can confirm rupture of either type.

Following resection without bladder perforation, instillation of intravesical chemotherapy with agents

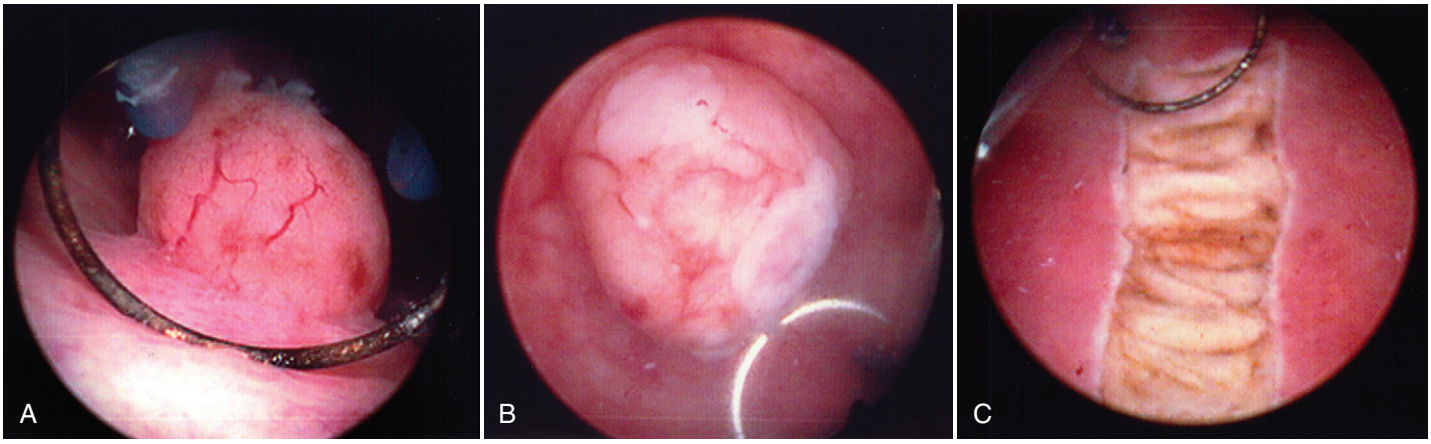


Figure 83–1. **A,** Broad-based papillary lesion. **B,** Resection of lesion with loop electrocautery. **C,** Depth of resection to detrusor muscle.

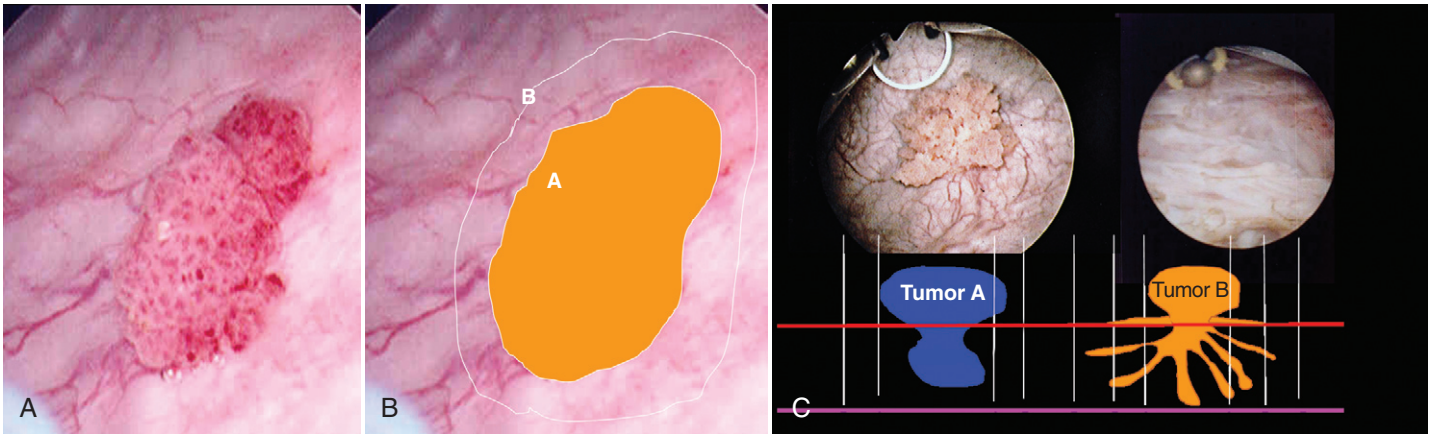


Figure 83–2. **A,** Papillary bladder lesion. **B,** *A* demonstrates visual boundary of tumor and *B* demonstrates margin of resection to optimize tumor destruction. **C,** Deep invasion of tumor in broad-based and tentacular pattern.

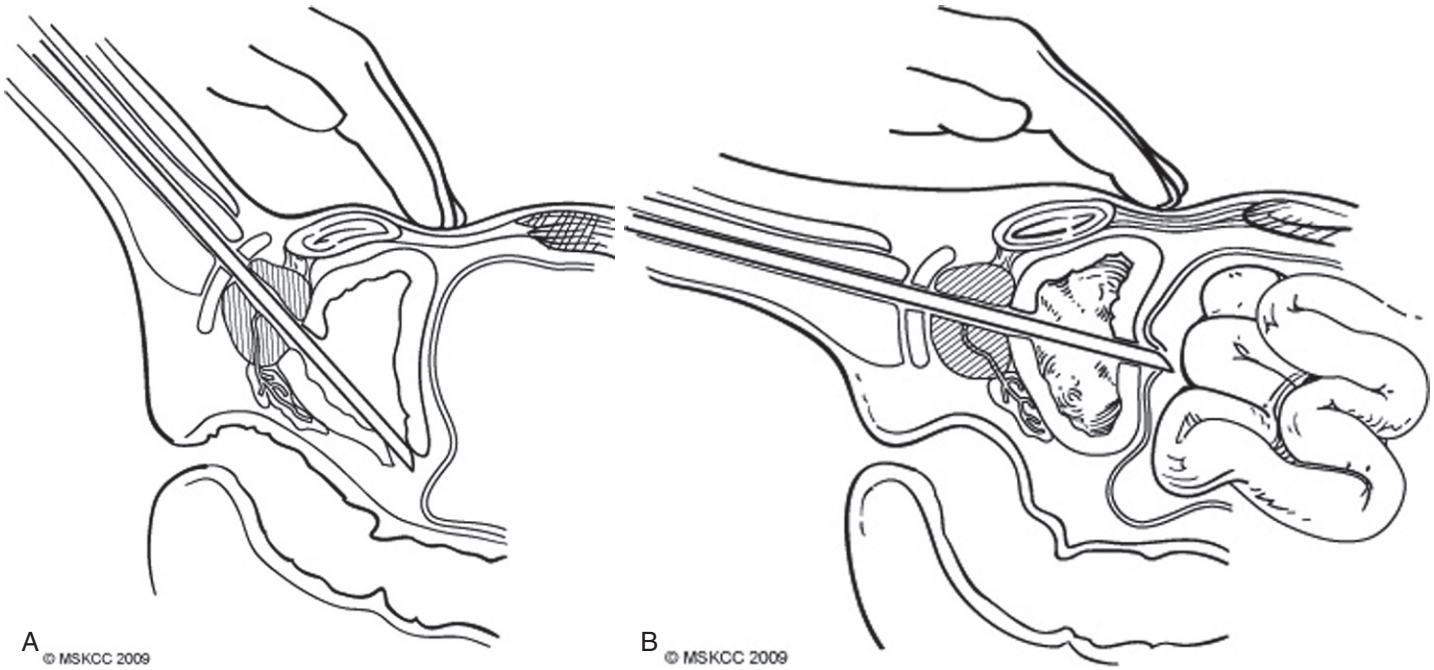


Figure 83–3. **A,** Extraperitoneal bladder rupture during transurethral resection (TUR) of a bladder tumor. **B,** Intraperitoneal bladder rupture during TUR of a bladder tumor with subsequent intraperitoneal leakage of irrigant and urine.

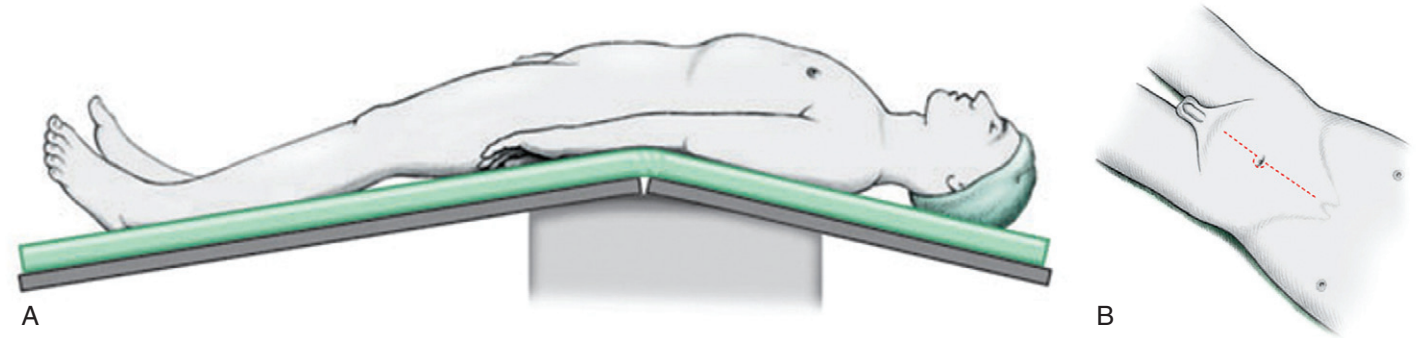


Figure 83–4. Positioning of the patient in the supine position with the bed flexed to 15 degrees **(A).** An incision is made in the midline from 2 cm above the umbilicus to just above the level of the pubis **(B).**

such as doxorubicin or mitomycin-c can modestly reduce recurrence rates from 15% to 38% but have little effect on progression (Kurth et al, 1997; Huncharek et al, 2001). Instillation of BCG, which is reserved for superficial high-grade disease, has shown superior efficacy in both recurrence rates and progression but should be instilled 2 to 4 weeks after resection due to the potential risks of "BCG-osis" with a disrupted urothelium (Lamm et al, 1991).

SURGICAL TECHNIQUE

Surgery on the bladder first involves preoperative evaluation with staging through CT scan of the chest, abdomen, and pelvis to rule out metastatic spread of disease. Patients should be medically optimized before surgery because many of the patients have preexisting comorbidities such as chronic obstructive pulmonary disease, coronary artery disease, and anemia. Also, the site of a diverting urinary stoma should be marked with an enterostomal therapist in the preoperative setting to locate an appropriate placement for the patient in a standing and seated position. Of note, even in patients who have selected to undergo orthotopic neobladder construction, a stomal site should be selected in the event that a neobladder cannot be performed.

The patient should have a clear liquid diet the day before surgery and nothing by mouth after midnight. A mechanical bowel prep with 4 L of polyethylene glycol 3350 and electrolytes should be administered starting at 12 PM the day before surgery. Many patients are dehydrated the morning of surgery, and intravenous hydration with iso-osmolar crystalloid should be initiated. Intravenous antibiotics should be initiated within 1 hour of incision with a third-generation cephalosporin and metronidazole.

The patient is positioned in the supine position with the table flexed at the level of the anterior superior iliac spine of 15 degrees (Fig. 83–4). Spreader bars or low-lying stirrups are helpful, especially to facilitate access to the perineum in males or vaginal vault in females. The abdomen is prepared with a 10% povidone-iodine solution from below the xiphoid process to the upper thighs, with the perineum and inner thigh prepped as well. A vaginal prep should be done in the female patient. An incision is made in the midline from 2 cm above the umbilicus to the pubis, although in many cases the operation can be performed only through an infraumbilical incision, facilitating a faster recovery. The

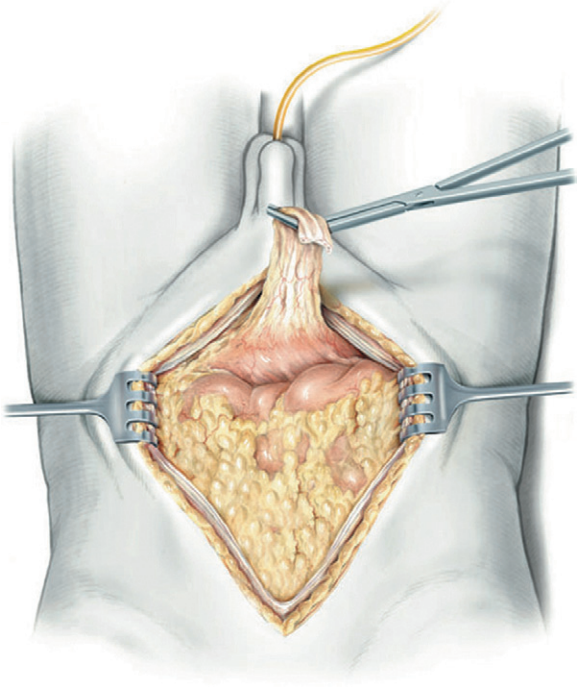


Figure 83–5. Mobilization and division of the umbilicus.

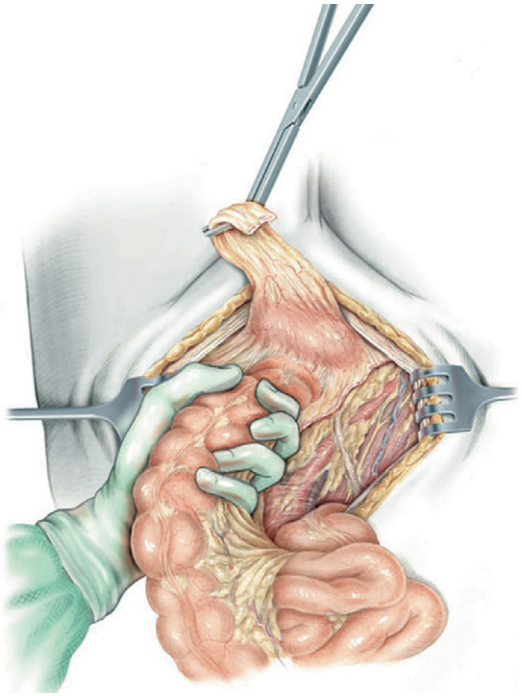


Figure 83–6. Mobilization of the root of the small bowel mesentery and the left colon.

underlying anterior and posterior layers of the fascia are divided, and the extraperitoneal space is entered. The bladder is then mobilized to the pelvic side walls on both sides. Once this space is developed, a peritoneotomy is made and the peritoneum is entered. **The urachal remnant is then encircled and divided near the level of the umbilicus** (Fig. 83–5). The peritoneum is incised lateral to the medial umbilical ligaments to the internal inguinal rings bilaterally. The peritoneum overlying the bladder should always be removed with the specimen. The vas deferens is encountered and divided.

At this time, the root of the small bowel mesentery is mobilized from the right lower quadrant to ensure appropriate exposure of the right ureter, gonadal vessels, and great vessels in preparation of the lymph node dissection, while the descending colon is mobilized laterally at the white line of Toldt (Fig. 83–6). A large peritoneal window is developed with the sigmoid colon to allow a sufficient gap through which the left ureter can pass for the urinary diversion.

A self-retaining retractor such as a Bookwalter retractor system is placed into position, and the bowels are packed out of the surgical field. The right and left ureters are identified at the crossing of the iliac arteries bilaterally, and they are carefully dissected proximally for approximately 5 cm and distally to below the level of the superior vesical artery, where they are distally ligated (to prevent tumor spillage) and transected. **A distal ureteral margin can be sent for frozen section to ensure that the ureteral margin is free of neoplasm; however, routine use of frozen sections is controversial. Schumacher and colleagues** (2006) **demonstrated that upper tract recurrences occur in 3% to 5% of patients, and they are usually at sites distant from the anastomosis.** Furthermore, they found no correlation between frozen and permanent section findings in their cohort (Schumacher et al, 2006). The ureters are then packed out of the surgical field.

Attention is then turned toward a standard lymph node dissection. The boundaries of dissection are the genitofemoral nerve laterally, the internal iliac artery medially, Cooper ligament caudally, and the crossing of the ureter at the common iliac artery cranially (Fig. 83–7A). In some cases, an extended template pelvic lymph node dissection is indicated. The margins of resection include the proximal common iliac artery cranially, the genitofemoral nerves laterally, Cooper ligament inferiorly, and the obturator canal and hypogastric vessels, laterally and medially, caudally. Individual node packets include the common iliac, presacral, external iliac, and obturator and hypogastric nodes (Fig. 83–7B). Attention to meticulous dissection with ligation of nodal packets both proximally and distally and removal of all nodal tissue are essential (Fig. 83–7C and D). On occasion, an extended dissection up to the bifurcation of the aorta or even the inferior mesenteric artery is necessary, especially after chemotherapy for regional disease. Whether routine extended lymph node dissection improves survival remains unproved. **Wright and colleagues (2008) demonstrated in a cohort from the Surveillance, Epidemiology, and End Results registry (SEER) that removal of greater than 10 lymph nodes at the time of cystectomy in patients with at least one positive node was associated with improved overall survival (hazard ratio 0.52; 95% confidence interval, 0.43 to 0.64).** This is confirmed by a multicenter prospective cooperative group study of radical cystectomy, in which standard pelvic node dissection removing more than 10 nodes improved overall survival after radical cystectomy (Herr et al, 2004).

With the completion of pelvic lymph node dissection, attention is then turned to the ligation of the anterior and lateral vascular pedicles on either side of the bladder. With the bladder retracted medially, the branches of the hypogastric artery and vein are skeletonized and ligated either using metal clips (Fig. 83–8A), an endovascular stapler (Fig. 83–8B), or a radiofrequency or electrocautery vascular sealing device (such as a LigaSure [Valley Lab, Boulder, CO] or a Harmonic Scalpel [Ethicon Endo-Surgery, Blue Ash, OH]). These branches include the superior, middle, and inferior vesical arteries and veins, as well as branches from the obturator and pudendal vessels.

RADICAL CYSTECTOMY IN THE MALE

In the male patient, with the division of the lateral vascular pedicles, the peritoneum overlying the seminal vesicles is opened sharply to expose the plane between the bladder and rectum (Fig. 83–9A and B). This plane is dissected with both sharp and blunt dissection to separate the rectum in the midline below the posterior wall of the bladder and prostate and out laterally where the shared vascular supply of the bladder and rectum are encountered. These vessels make up the posterior vascular pedicle of the bladder, and they can be divided using clips, staples, or sealing devices as well (Fig. 83–10). Ultimately, this leads to Denonvilliers fascia and to the space below the level of the prostate. Denonvilliers fascia is incised, and the space is developed using sharp or blunt dissection.

From here, the remainder of the case is performed anteriorly, with the opening of the endopelvic fascia lateral to the prostate and the division of the dorsal venous complex over the anterior urethra distal to the apex of the prostate (Fig. 83–11). The use of a 2-0 polyglactin braided suture with suturing to the periosteum of the pubis helps secure this fragile tissue when tied.

Nerve-sparing or non–nerve-sparing technique is then used to release the prostate laterally. **Nerve-sparing technique is the same as that used in radical retropubic prostatectomy, with the neurovascular bundle of the prostate released sharply on both sides of the prostate with incision of its**

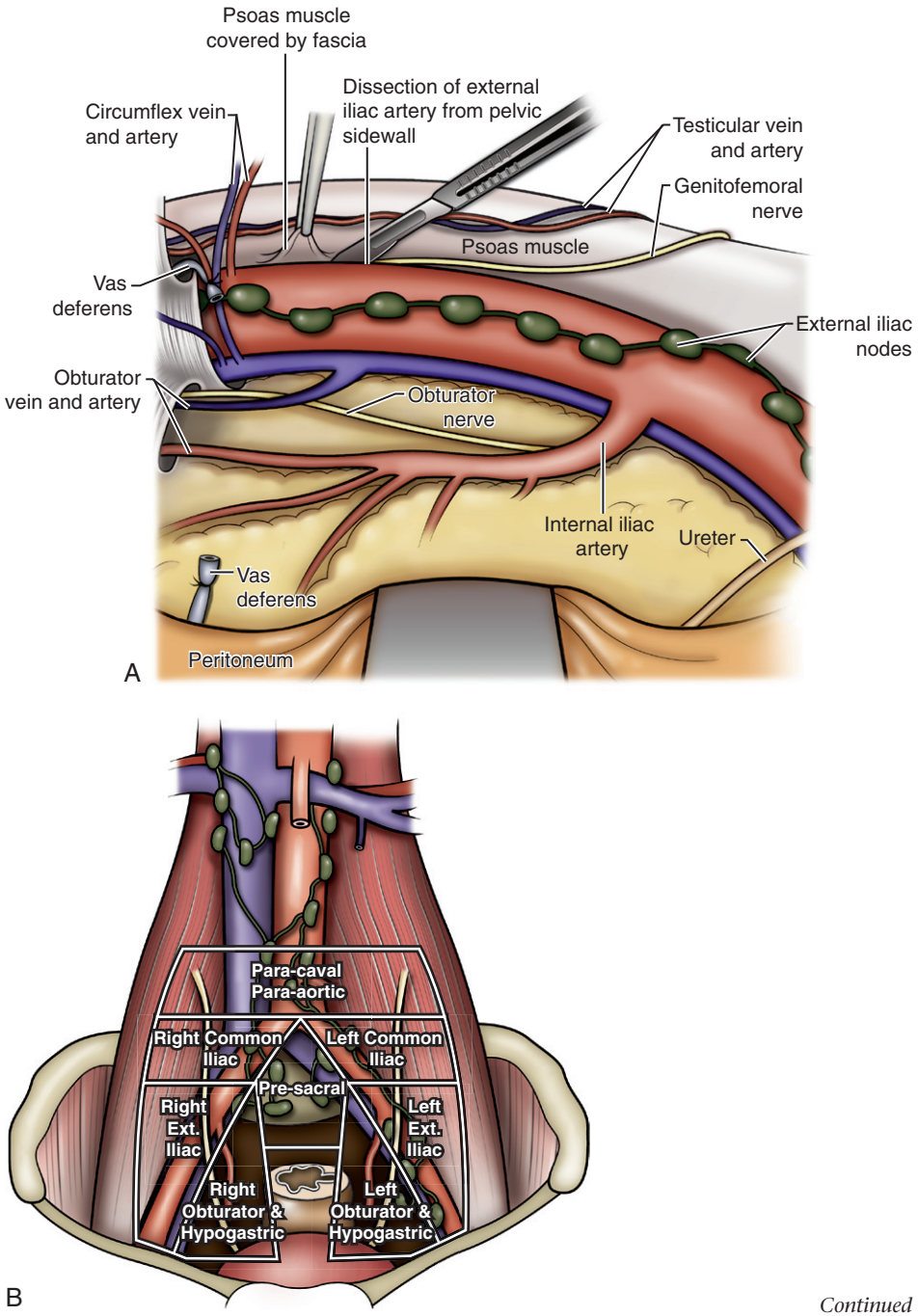


Figure 83–7. **A,** Standard pelvic lymph node dissection. **B,** Distributions of the eight node packets from an extended pelvic and retroperitoneal lymph node dissection.

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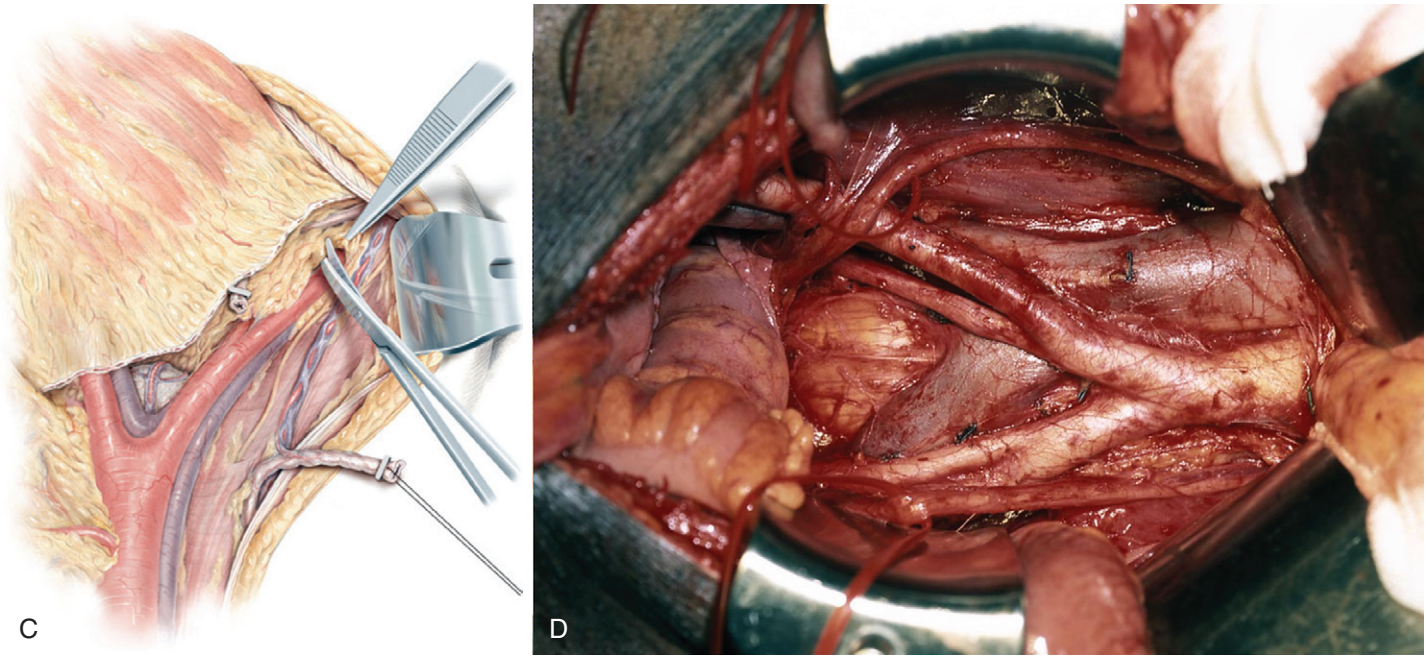


Figure 83–7, cont'd. **C,** Meticulous pelvic lymph node dissection. **D,** Completed extended pelvic lymph node dissection.

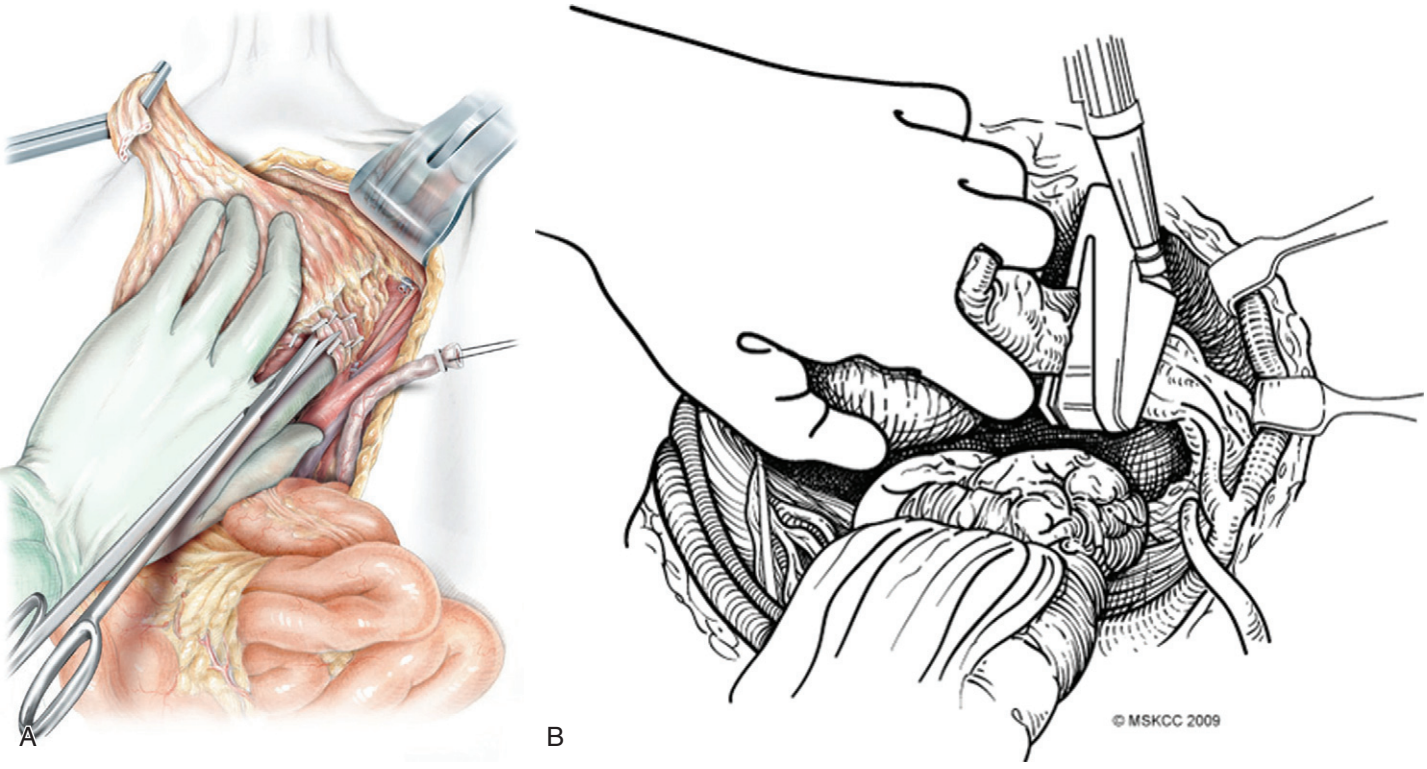


Figure 83–8. **A,** Application of clips to the lateral vascular pedicle of the bladder. **B,** Application of an endovascular stapler to the lateral vascular pedicle of the bladder.

thin fascia while remaining outside the capsule of the prostate (Fig. 83–12A and B). This is done from the apex of the prostate to the tip of the seminal vesicles, and the concepts of limited traction and cautery apply as with the radical prostatectomy procedure. **Using this technique, Schoenberg and colleagues** (1996) **report an age-dependent preservation of erectile function in 62% of patients younger than 50, 47% for those aged 50 to 60, and 20% for those aged older than 60 years.** In patients with preexisting impotence or concurrent locally advanced bladder or prostate cancer, a non–nerve-sparing technique can be performed, with wide excision of the neurovascular bundles (Fig. 83–13).

Some groups advocate the use of prostate- or prostate capsule–sparing techniques to improve potency and continence preservation. In a number of series looking at this question, improved continence and potency was achieved through sparing some portion of the prostate and/or capsule while leaving some prostate tissue behind. The advantage of this approach is avoidance of the

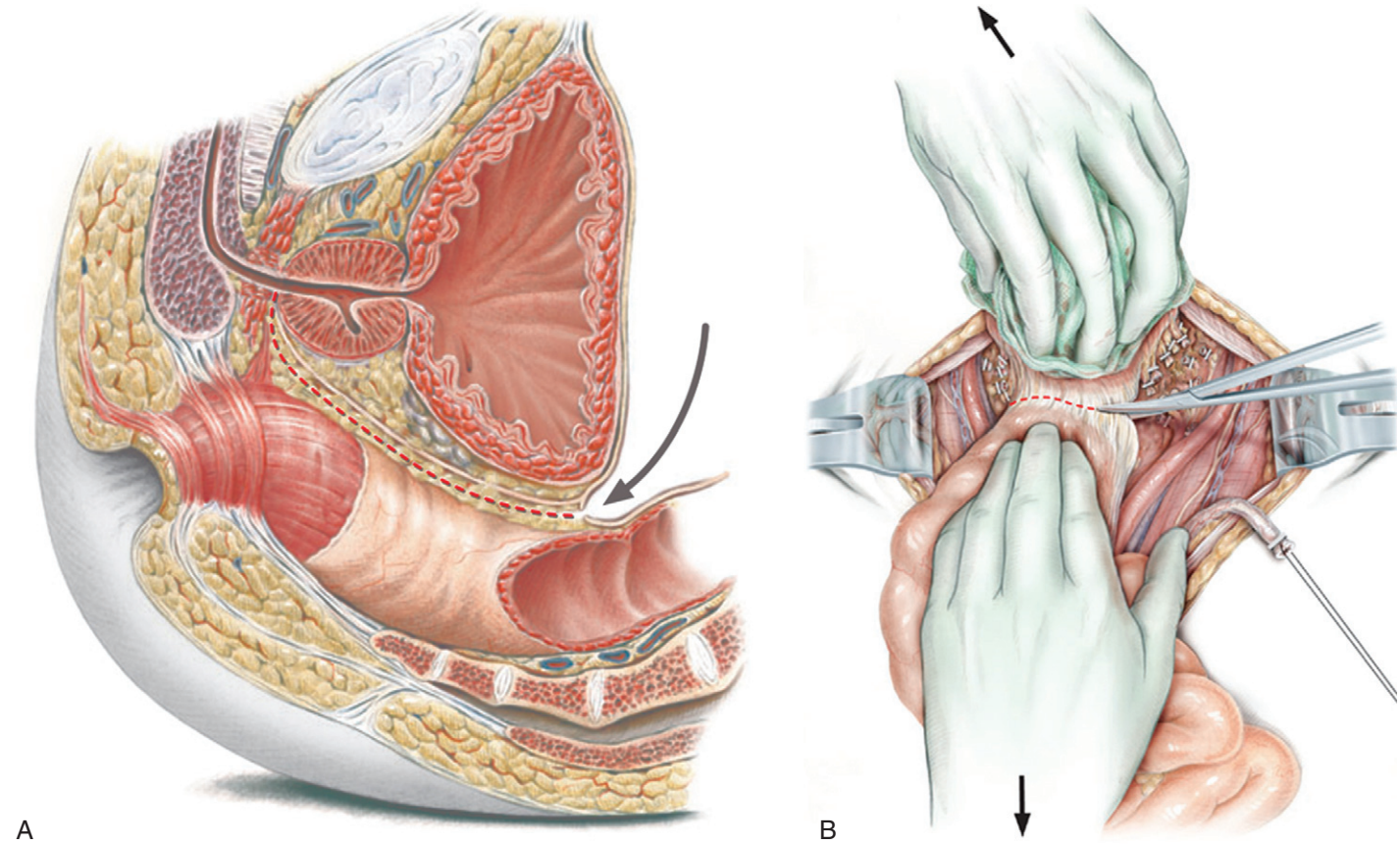


Figure 83–9. **A,** The posterior plane beyond the cul-de-sac, which separates the bladder and prostate from the rectum. **B,** Division of the peritoneum overlying the rectum in the cul-de-sac.

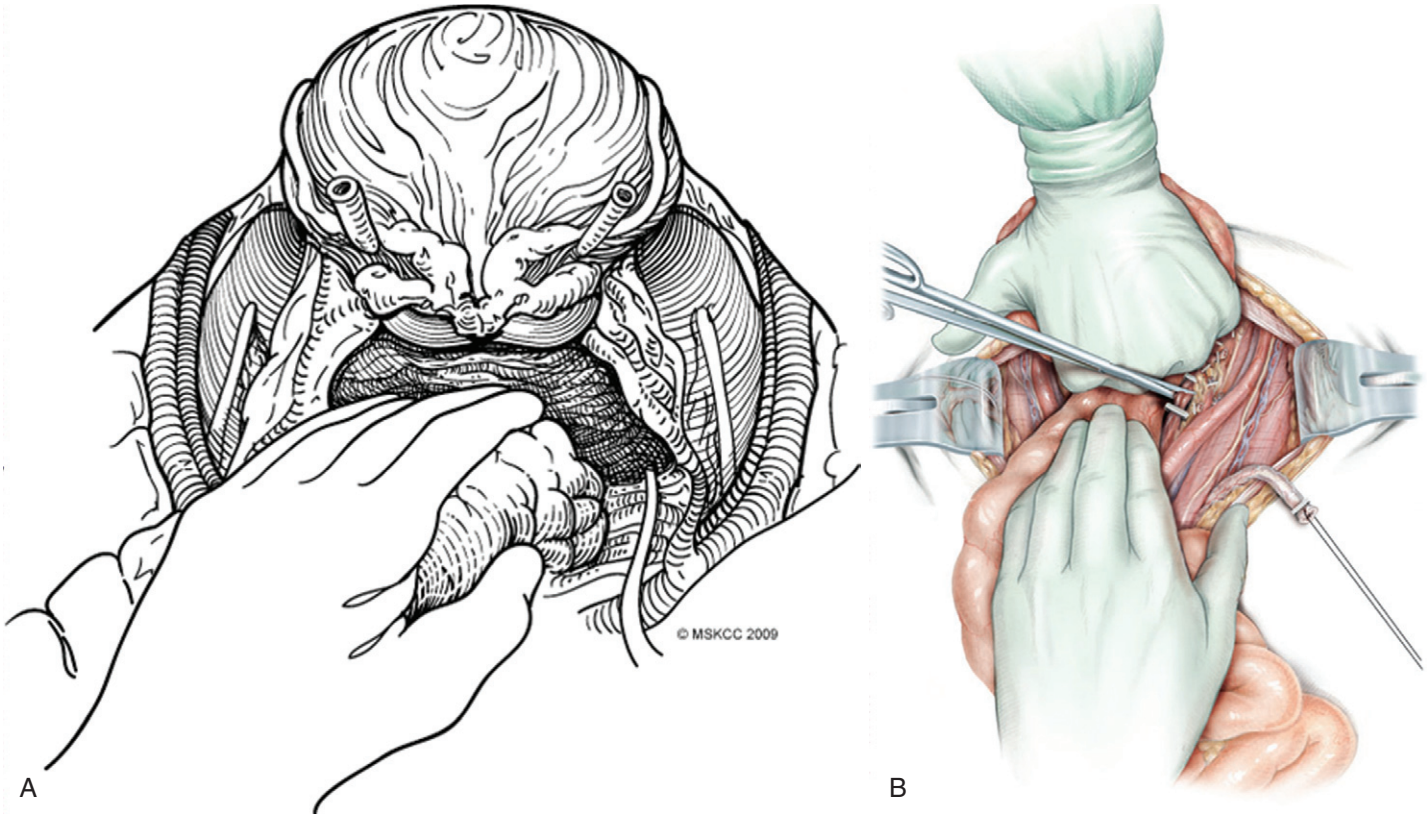


Figure 83–10. **A,** Exposure of the posterior vascular pedicle of the bladder for ligation. **B,** Ligation and division of the posterior pedicle.

neurovascular bundles laterally and the striated sphincter at the apex. In patients undergoing orthotopic neobladder, six groups have reported on preservation of daytime continence in 90% to 100% of patients and preservation of nighttime continence in 31% to 95%. Of patients who were initially potent, potency was preserved in 80% to 100% of patients. With the concern being residual occult TCC or prostate cancer being left in the field, the studies found a 0% to 4% incidence of prostate cancer and there was a local recurrence rate of 0% to 24% and distant metastasis of 0% to 30% (Vallancien et al, 2002; Botto et al, 2004; Colombo et al, 2004; Muto et al, 2004; Saidi et al, 2004; Nieuwenhuijzen et al, 2005; Terrone et al, 2006). This is in contrast to the findings of Pettus and colleagues, who found that 48% of patients undergoing radical cystoprostatectomy had an occult prostate cancer and a third had undisclosed urothelial carcinoma involving the prostate (Pettus et al, 2008). Furthermore, Revelo and colleagues (2008) found that 41% of patients harbored an unsuspected prostate cancer, while 48% harbored TCC in the prostate. Overall, 74% of patients had an occult cancer in the prostate at final pathology (Revelo et al, 2008). **Caution should be used in treating patients with prostate-sparing techniques and should be done in a setting in which a preoperative evaluation has minimized the risk of occult cancer.** This requires digital rectal examination, serum prostate-specific antigen (PSA), and transrectal biopsy of the prostate or transurethral resection of the prostate.

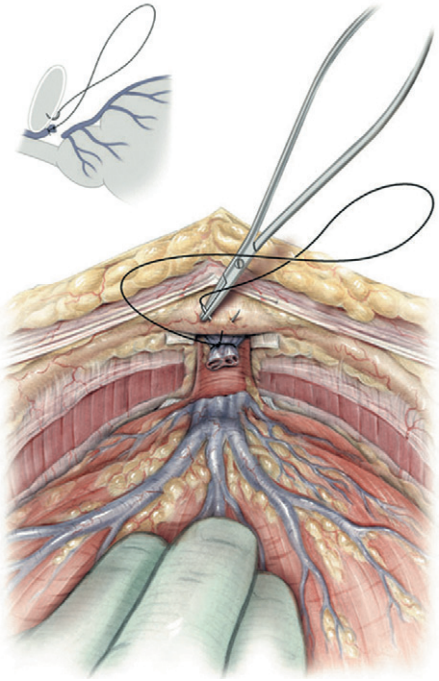


Figure 83–11. Division of the dorsal venous complex.

RADICAL CYSTECTOMY IN THE FEMALE

The traditional cystectomy in the female patient involves anterior pelvic exenteration with removal of the bladder, as well as the adjoining cervix, uterus, and anterior vaginal wall. This procedure ensures a sufficient soft tissue margin, even for most stage-T3 and stage-T4 lesions originating in the bladder.

Initially, the tissues of the anterior pelvis are isolated and the vagina posterior to the cervix is identified (Fig. 83–14A). The posterior vaginal cuff is then incised and the vault is entered (Fig. 83–14B). This allows for simple identification of the posterior and lateral pedicles of the bladder because they are opposed to the lateral surface of the vaginal wall. With this landmark identified, endovascular staples, titanium clips, or an electrocautery vascular sealing device can be applied to safely control the lateral vascular supply. The anterior vaginal wall, uterus and cervix, and bladder are then taken en bloc to the level of the apex. The complete urethra including the meatus is excised, and the specimen is removed from the field.

Careful attention should be paid to hemostasis at this stage of the operation because the vaginal wall consists of a rich vascular plexus that can be a source of intraoperative and postoperative hemorrhage. The remaining field consists of the posterior vaginal

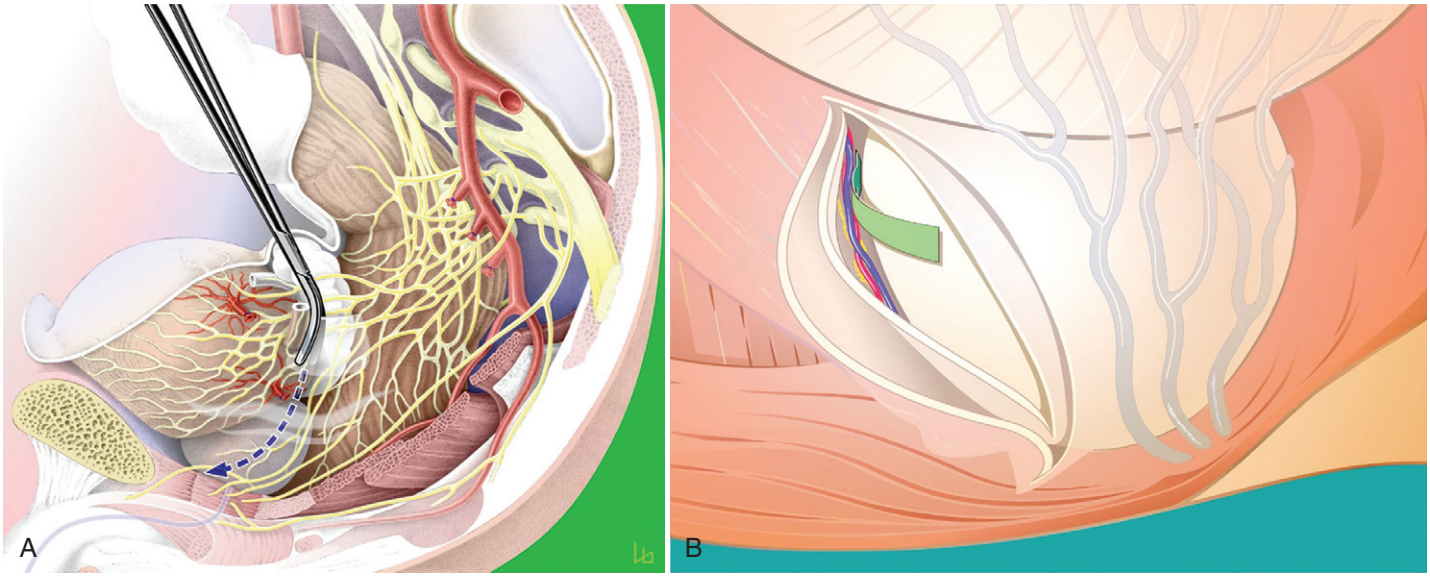


Figure 83–12. **A,** Nerve-sparing radical cystectomy in the male patient. **B,** Separation of the plane between the prostatic capsule and the neurovascular bundle.

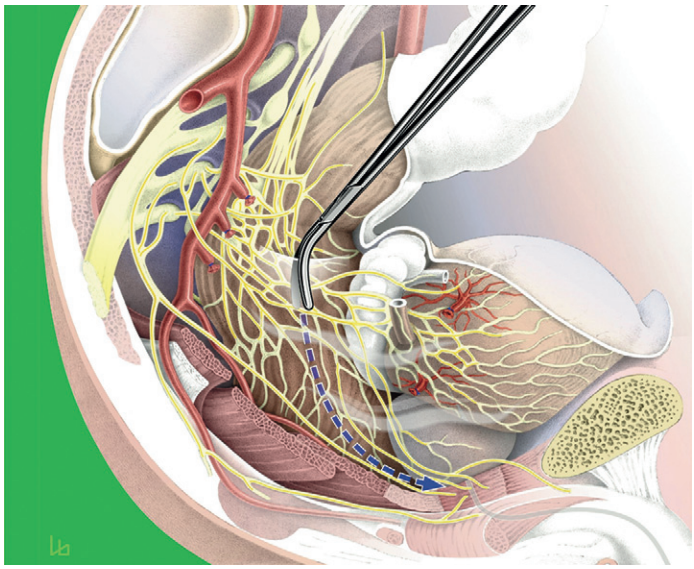


Figure 83–13. Non–nerve-sparing radical cystectomy in the male.

wall and an opening at the level of the introitus between the labia minora (Fig. 83–15A and B). The posterior vaginal wall is then incised in a semicircular fashion, and a plane developed between the vagina and the anterior rectal wall such that a sufficient flap of vagina can be produced to allow for coverage of the defect. This flap is then sutured to the defect using a running or interrupted 0 polyglactin braided suture (Fig. 83–15C).

Female patients with stage T1 or T2 bladder tumors that are distal to the bladder trigone are candidates for orthotopic neobladder construction. In order to achieve proper placement and support of a neobladder, an anterior pelvic exenteration would not allow for preservation of the vaginal and urethra, which is necessary to maintain continence. In this circumstance, a urethra- and vaginal-sparing technique is used. The lateral vascular pedicles of the bladder are separated from the vaginal wall laterally, and they are taken separately. The vaginal cuff is opened posteriorly and then circumferentially excised from its attachment to the cervix. A plane is then entered between the bladder and anterior vaginal wall, and the bladder is detached from the urethra (Fig. 83–16A). This allows for placement of the anastomotic sutures to be used with the orthotopic neobladder

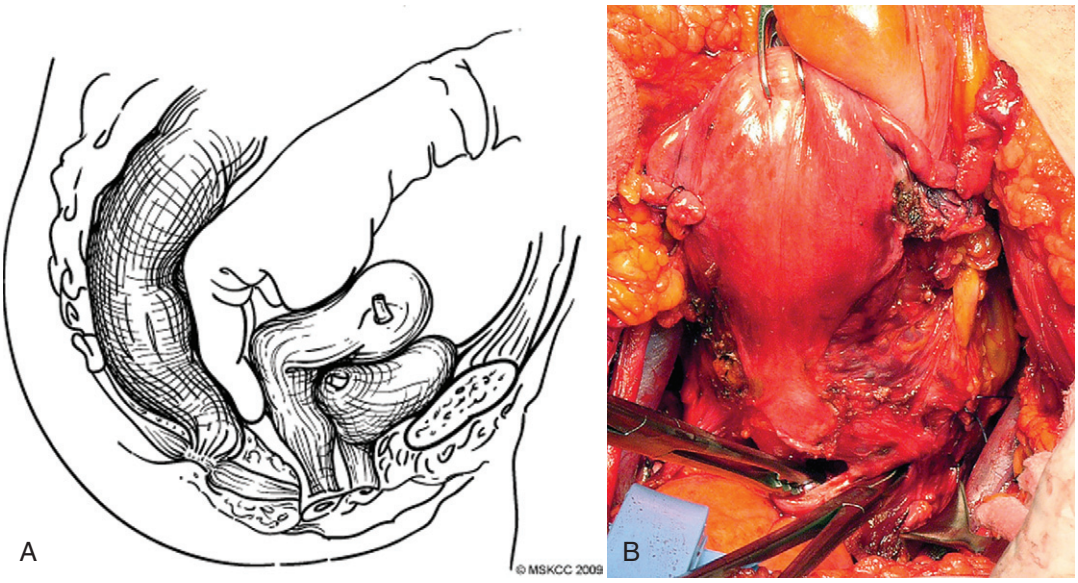


Figure 83–14. **A,** Identification of the vaginal cuff posterior to the cervix. **B,** Incision of the posterior vaginal cuff.

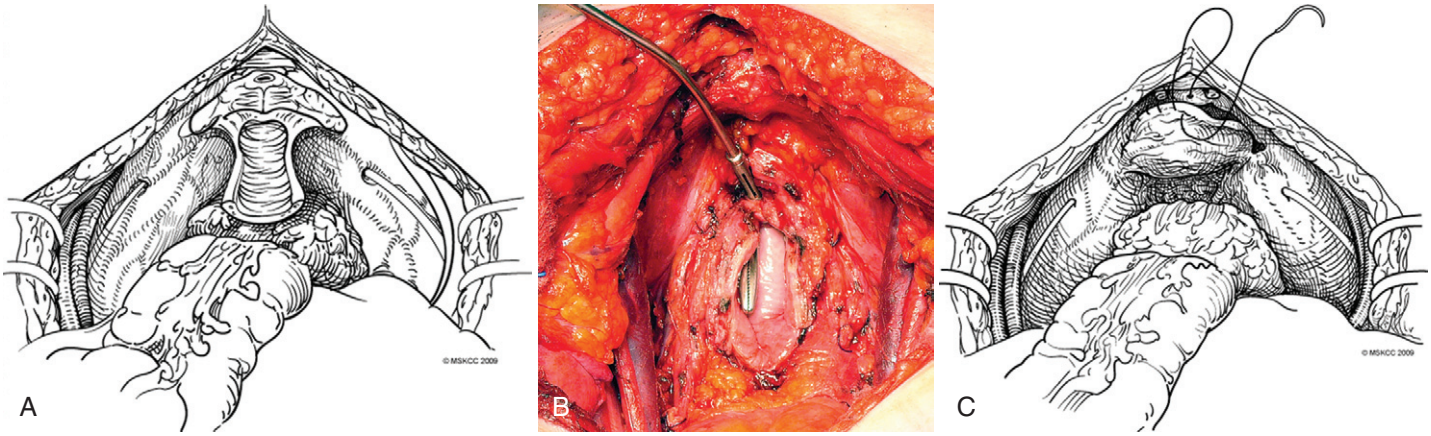


Figure 83–15. **A,** Posterior vaginal wall and defect at the level of the introitus after en bloc removal of the bladder in an anterior pelvic exenteration in the female patient. **B,** Intraoperative photograph of the introital defect. **C,** Coverage of the introital defect with a flap made from the posterior vaginal wall.

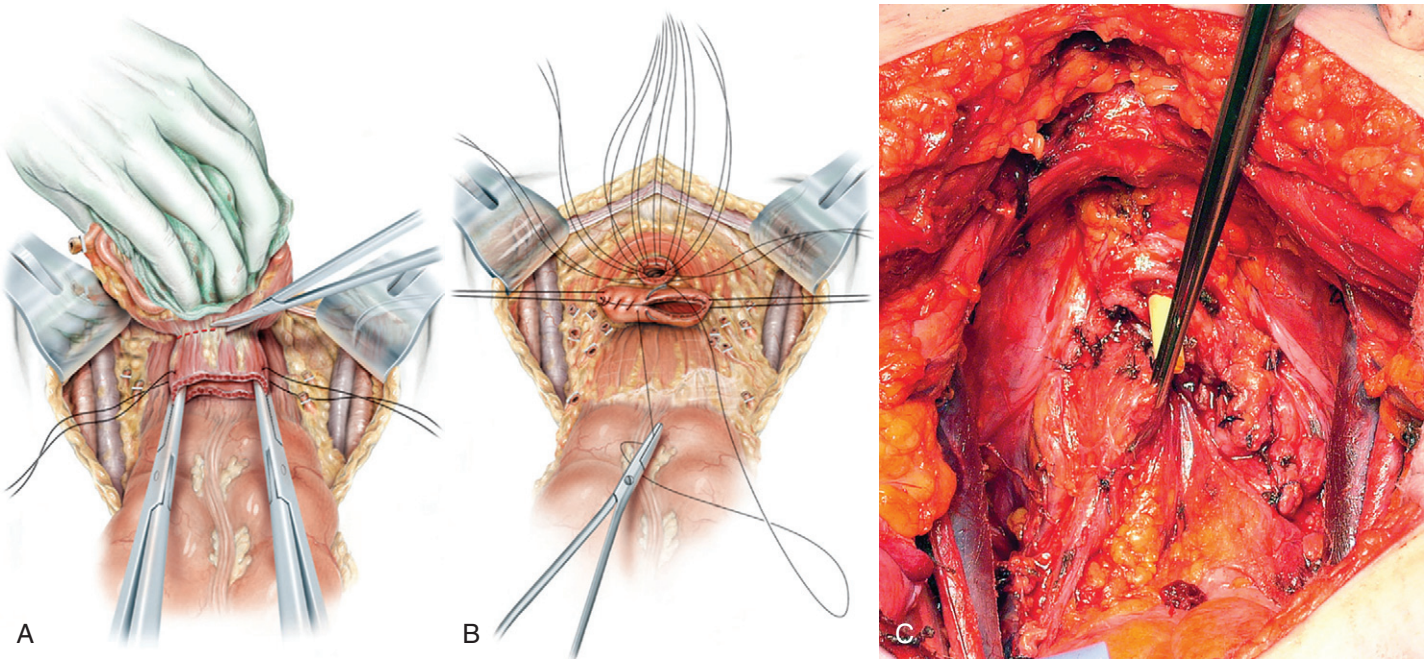


Figure 83–16. **A,** Circumferential division of the vaginal cuff from the attachments to the cervix. **B,** Closure of the vaginal cuff and placement of the urethral anastomotic sutures. **C,** Intraoperative photograph of the completed repair.

(Fig. 83–16B). The vaginal cuff is then closed with a running 0 polyglactin braided suture. Frozen section pathology taken at the time of surgery of the bladder neck should be performed at this step to ensure a free margin at the anastomosis. **Presence of residual cancer at the bladder neck is a contraindication to orthotopic neobladder.**

PARTIAL CYSTECTOMY

The role for partial cystectomy in the patient with TCC should be limited to patients with a solitary lesion in which radical cystectomy is otherwise contraindicated and a sufficient margin can be obtained. In the series by Holzbeierlein and colleagues (2004) at Memorial Sloan-Kettering Cancer Center, in select patients undergoing partial cystectomy for TCC, with 33 months' follow-up, 74% of patients preserved their bladders and there was an overall 5-year survival of 69%. Although superficial recurrences occurred in some patients, only the presence of carcinoma in situ and lymph node–positive disease were associated with advanced progression. Partial cystectomy can be curative in other tumor types including squamous cell carcinoma and adenocarcinoma.

Partial cystectomy involves full template lymph node dissection, mobilization of the bladder, and cystotomy. The lesion is identified within the bladder, and the tumor is resected with at least a 1- to 2-cm visual margin, with intraoperative frozen section sent to confirm the absence of microscopic disease at the margin. Frequently the tumor will abut or involve one or both of the ureteral orifices, and this may require ureteral reimplantation with a psoas hitch. Closure of the bladder is performed in three layers, which include a mucosal, seromuscular, and adventitial layer with 2-0 polyglactin braided suture.

A special circumstance involves the presence of an adenocarcinoma of the urachus, an embryologic remnant of the allantois. Tumors of this structure involve the dome of the bladder, and they follow the course of the urachus to the umbilicus. In performing a partial cystectomy to remove this structure, an incision is made in the midline below the umbilicus and the umbilicus itself is resected along with the urachus and dome of the bladder because the umbilicus is continuous with this structure. A wide margin of soft tissue around the urachus is taken, as is a cuff of the dome of the bladder, leaving a 2-cm visual margin from the tumor (Fig. 83–17). Frozen section may then be used to confirm the absence of microscopic disease at the resection margin.

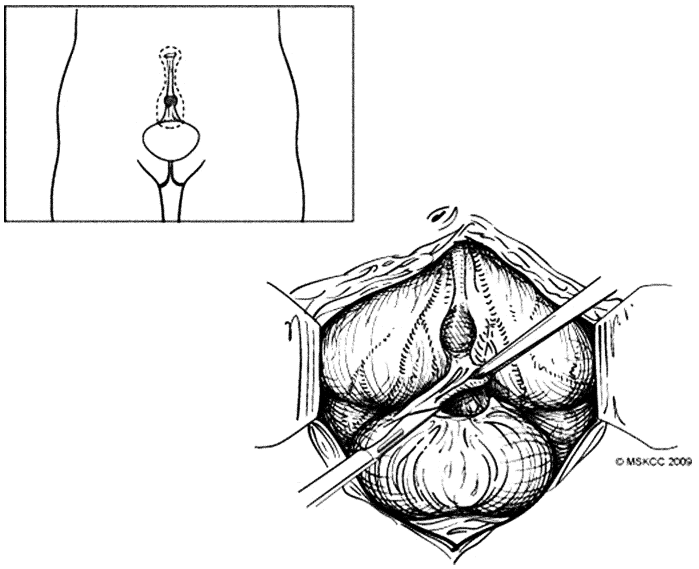


Figure 83–17. Resection of an adenocarcinoma of the urachus.

POSTOPERATIVE MANAGEMENT

After the procedure is complete, the placement of a closed suction drain (Jackson-Pratt type) in the vicinity of the urinary diversion is advisable to limit complications from urinary leakage

postoperatively. The patient is admitted to the recovery room or stepdown unit for a 24-hour period to allow close monitoring of fluids and urine output. Postoperative laboratory studies should include complete blood count with transfusion of blood and platelets as needed. A complete metabolic panel should be ordered, as well with replacement of electrolyte derangements, paying close attention to hypokalemia and hypomagnesemia. An electrocardiogram should be checked, and cardiac monitoring should be followed in the postoperative setting. A chest radiograph can confirm central venous line placement while also assessing for pulmonary congestion suggestive of fluid overload.

Bowel complications are a frequent source of problems in the recovery period, and diet should be advanced with the passage of flatus. Use of a perioperative epidural analgesic can reduce overall narcotic usage in this setting, and this reduces the incidence of paralytic ileus. Early ambulation can also help to prevent this, as well as contribute to deep venous thrombosis prophylaxis.

Deep venous thrombosis and pulmonary embolism are a serious complication in the recovery period, and prophylaxis with intermittent compression stockings can help decrease their incidence. In the patient with a stable hemoglobin and hematocrit, subcutaneous administration of low-molecular-weight heparin can assist with this as well. Incentive spirometry is used throughout the hospitalization to prevent atelectasis and fever, as well as pneumonia.

In a recent prospective series from Memorial Sloan-Kettering Cancer Center, 64% of patients undergoing radical cystectomy experienced at least one perioperative complication within 90 days of surgery, and 13% experienced a high-grade complication (grade 3 or higher) (Shabsigh et al, 2009). The majority of complications were gastrointestinal (29%), with infectious (25%) and wound-related complications (15%) being the next most common. The 30-day mortality rate was 1.5%. In the elderly patient (70 years or older), the complication rate goes up to 72%, with 17% high-grade complications and a 3.4% 30-day mortality rate (Froehner et al, 2009). Attention to detail in the perioperative care of the cystectomy patient is necessary to limit the morbidity and mortality of this complex procedure.

Key Points

- Cancers of the urinary bladder are the sixth leading cause of cancer death among Americans, and they are a significant source of health care costs.
- Recent large series have shown 10-year cancer-specific survival rates in patients with pathologic T2 cancers treated with radical cystectomy of 65% to 78%.
- Before the endoscopic treatment of a bladder tumor, the patient should undergo upper tract imaging to rule out the presence of an upper tract TCC.
- Bladder perforation is a complication that occurs in resections carried to the optimal depth of resection into the detrusor muscle.
- A distal ureteral margin can be sent for frozen section to ensure that the ureteral margin is free of neoplasm, but routine use of frozen sections is controversial.
- The boundaries of dissection of a standard pelvic lymph node dissection are the genitofemoral nerve laterally, the internal iliac artery medially, Cooper ligament caudally, and the crossing of the ureter at the common iliac artery cranially.
- Nerve-sparing technique is the same as that used in radical retropubic prostatectomy, with the neurovascular bundle of the prostate released sharply on both sides of the prostate with incision of its thin fascia while remaining outside the capsule of the prostate.
- Caution should be used in treating patients with prostate-sparing techniques and should be done in a setting in which a preoperative evaluation has minimized the risk of occult cancer. This requires digital rectal examination, serum PSA, and transrectal biopsy of the prostate or transurethral resection of the prostate.
- Female patients with stage T1 or T2 bladder tumors that are distal to the bladder trigone are candidates for orthotopic neobladder construction.
- The role for partial cystectomy in the patient with TCC should be limited to patients with a solitary lesion in which radical cystectomy is otherwise contraindicated and a sufficient margin can be obtained.
- Partial cystectomy can be curative in other tumor types including squamous cell carcinoma and adenocarcinoma.
- A special circumstance involves the presence of an adenocarcinoma of the urachus, an embryologic remnant of the allantois.
- In a recent prospective series from Memorial Sloan-Kettering Cancer Center, 64% of patients undergoing radical cystectomy experienced at least one perioperative complication within 90 days of surgery and 13% experienced a high-grade complication (grade 3 or higher).

Acknowledgments

The authors would like to acknowledge Dr. John Stein of the University of Southern California in Los Angeles for Figures 83–5, 83–6, and 83–7B and C, 83–8A, 83–9A and B, 83–10B, 83–11, and 83–16A and B and Dr. Urs Studer of the University of Bern, Switzerland for Figures 83–12A and B and 83–13.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

SUGGESTED READINGS

Herr HW, Faulkner JR, Grossman HB, et al. Surgical factors influence bladder cancer outcomes: a cooperative group report. J Clin Oncol 2004;22(14):2781–9.

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chapter
84

Robotic and Laparoscopic Bladder Surgery

Lee Richstone, MD ● Douglas S. Scherr, MD

Bladder Diverticulectomy
Ureteral Reimplantation
Nonrefluxing Ureteral Reimplantation
Refluxing Ureteral Reimplantation
Psoas Hitch and Bladder Advancement Flaps
Enterocystoplasty
Vesicovaginal and Ureterovaginal Fistula
Urachal Surgery and Partial Cystectomy
Radical Cystoprostatectomy

Surgery of the urinary bladder and distal ureter is indicated for a wide variety of benign and malignant disease. Major extirpative and complex reconstructive techniques are often required, demanding skill and experience from the urologic surgeon. Perhaps as a result of these technical challenges, bladder surgery is associated with some of the highest rates of complications reported in the urologic literature.

In an attempt to minimize the morbidity of open surgery, minimally invasive techniques for surgery of the urinary bladder have been introduced and refined. Operative procedures that once required large open incisions and extensive dissection can now be performed through a limited number of keyhole incisions, representing a revolution in urologic pelvic surgery. Laparoscopic techniques can be used for essentially every bladder operation. In most cases, improved cosmetic results are matched by reductions in associated pain, duration of hospitalization, and recovery times. With experience, operative times, complication rates, and outcome measures have equaled or exceeded open surgical counterparts.

No sooner were laparoscopic techniques established that the field witnessed the rise of a new minimally invasive technique: robotic-assisted laparoscopic surgery. Robotic surgical approaches have been employed for nearly all types of bladder surgery, becoming an accepted alternative for the operative management of lower tract pathology of benign and malignant etiology. Technology continues to drive the field forward, and natural orifice transendoluminal surgery (NOTES) and laparoendoscopic single-site (LESS) surgical techniques have been employed to further reduce the incisions and morbidity associated with surgery of the urinary bladder. In this chapter we describe conventional laparoscopic, LESS, and robotic approaches to surgery of the distal ureter and the bladder, focusing on indications, technique, complications, and outcomes (Table 84–1).

BLADDER DIVERTICULECTOMY

Diverticula of the urinary bladder represent a herniation of the urinary mucosa through a weakness of absence of the detrusor muscle. Bladder diverticula have scattered and/or nonfunctional residual muscle fibers, impairing emptying and contributing to urinary stasis. Diverticula can be congenital, acquired, or, rarely, iatrogenic in nature. Congenital bladder diverticula include periureteral diverticula, also referred to as *Hutch diverticula,* which can be associated with vesicoureteral reflux (VUR). Posterior urethral valves and neurogenic bladder are also commonly associated with diverticula. Various syndromes including Williams, Menkes, and prune belly can include multiple diverticula in the absence of outlet obstruction. Acquired diverticula are most commonly associated with bladder outlet obstruction (BOO), with resultant high-pressure voiding and subsequent diverticula formation. Traditionally, diverticulectomy has been approached through a low midline incision. However, with the evolution of minimally invasive technology and skill, even complex and multiple bladder diverticula can be managed with minimally invasive surgical techniques (Fig. 84–1). In combination with endoscopic management of bladder outlet obstruction and bladder calculi, these techniques often result in reduced morbidity to the patient.

Evaluation and Surgical Indications

The first step in evaluation of a bladder diverticulum involves the determination of the underlying etiology responsible for the diverticulum. Most often, this involves confirmation of BOO and may involve determination of urinary flow rate, postvoid residual urine volume, and urodynamic studies. Underlying BOO must be identified and addressed, typically at the time of diverticulectomy. Cystoscopy is an essential component of the evaluation of bladder diverticula. Diverticula size, number, and location are recorded, and proximity to the ureteral orifices is noted. The bladder outlet is evaluated for evidence of prostatic hypertrophy, bladder neck contracture, or stricture. In conjunction with urinary cytology, thorough inspection of all diverticula is mandatory to rule out malignancy. Small diverticula can be managed with cystoscopic fulguration. Voiding cystourethrography (VCUG) defines the location, size, and number of diverticula and can diagnose concomitant reflux or urinary stasis. Upper tract imaging with intravenous urography (IVU) or computed tomography (CT) urogram is useful

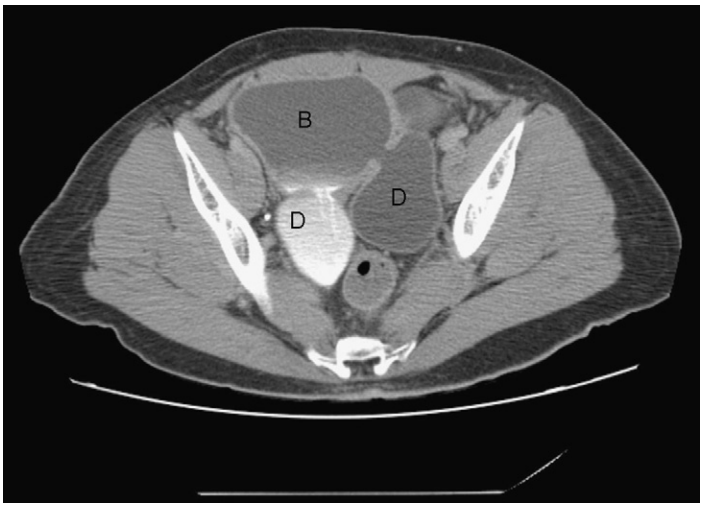


Figure 84–1. Computed tomography urogram of abdomen/pelvis of patient with Williams syndrome and four bladder diverticula. Laparoscopic bladder diverticulectomy of all diverticula can be performed in a single setting in experienced hands. Contiguity between true bladder (*B*) and two posterior bladder diverticula (*D*) is demonstrated.

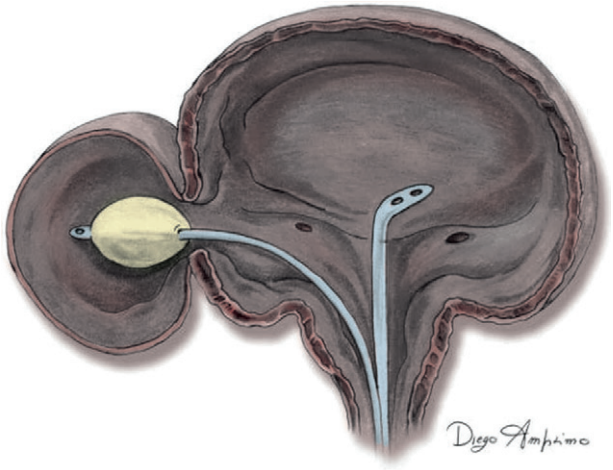


Figure 84–2. Selective catheterization of the bladder diverticulum with a Councill tip catheter. A Foley catheter in the bladder permits selective distention of the diverticulum to aid in diverticular identification and dissection. Ureteral catheterization aids in ureteral identification to avoid injury. (From Porpiglia F, Tarabuzzi R, Cossu M, et al: Sequential transurethral resection of the prostate and laparoscopic bladder diverticulectomy: comparison with open surgery. Urology 2002;60:1045.)

Table 84–1.

Minimally Invasive Surgery of the Bladder and Distal

Bladder diverticulectomy
Ureteral reimplantation
Boari and bladder advancement flaps
Enterocystoplasty
Vesicovaginal and ureterovaginal fistula
Partial cystectomy
Radical cystectomy and extended lymphadenectomy
Urinary diversion

to evaluate the relationship of the ureter to the diverticulum to prevent injury during surgery, as well as identify any hydronephrosis due to obstruction. Urinalysis and culture is essential before surgical intervention.

Small, asymptomatic bladder diverticula without associated complications can be observed. Diverticulectomy is indicated for large diverticula with incomplete emptying, chronic or repeated urinary tract infection, bladder calculi, or pain. Occasionally, a bladder diverticulum can result in ureteral reflux or obstruction, requiring diverticulectomy and ureteral reimplantation. High-grade or bulky tumor within a bladder diverticulum is an indication for partial or radical cystectomy. Any bladder outlet obstruction must be addressed before or at the time of diverticulectomy.

Surgical Approach

Since Czerny's first description of diverticulectomy in 1897 (Knappenberger et al, 1960), the surgical treatment of bladder diverticula has evolved from open surgery, to endoscopic procedures, to laparoscopic and robotic techniques. Transperitoneal laparoscopic bladder diverticulectomy (LBD) was first introduced in 1992 (Das et al, 1992; Parra et al, 1992) and later in the pediatric setting (Kok et al, 2000). Numerous subsequent reports demonstrate the reproducibility of the technique via transvesical and extravesical approaches (Nadler et al, 1995). Extraperitoneal laparoscopy may limit the risk of visceral injury and intra-abdominal urine leak. The transperitoneal approach provides a wide and generous working space, as well as superior access for posterior diverticula. Laparoscopic bladder diverticulectomy has also been described for tumor within a diverticulum (Tai et al, 2007; Wang et al, 2007; Thwaini et al, 2008) and is described in more detail in a subsequent section on laparoscopic and robotic partial cystectomy.

Similarly, robotic bladder diverticulectomy (RBD) has been described in adults and children as an effective minimally invasive alternative providing similar benefits (Myer et al, 2007; Rao et al, 2007; Macejko et al, 2008; Tareen et al, 2008; Meeks et al, 2009). The robotic approach mimics the laparoscopic technique, while aiding the surgeon without extensive laparoscopic experience, especially for complex diverticula and the need for concomitant ureteral reimplantation. Neither approach is likely to be superior to one another in efficacy. Choosing a surgical approach to bladder diverticulectomy is dependent on numerous factors including the number and location of diverticula, proximity of the diverticulum to the ureter(s), and the need for concomitant ureteral or bladder outlet surgery. Even complex and multiple diverticula requiring concomitant ureteral reimplantation can be handled via a laparoscopic or robotic approach provided sufficient surgeon experience and skill.

Technique

Before port placement, flexible cystoscopy can be performed for ureteral catheterization if necessary. Selective catheterization of the diverticulum can be performed by placing a Councill tip catheter over a guidewire into the diverticulum and a separate Foley catheter into the bladder proper, for selective filling and intraoperative identification of bladder diverticula (Nadler et al, 1995; Porpiglia et al, 2002; Khonsari et al, 2004), as seen in Figure 84–2.

Alternatively, real-time illumination of the diverticulum with the flexible cystoscope is a useful aid in identifying the diverticulum (Parra et al, 1992; Jarrett et al, 1995; Nadler et al, 1995). In

the authors' experience, this is particularly valuable in patients with multiple diverticula, in which separate catheterization of each diverticulum is not practical (Cinman et al, in press). After pneumoperitoneum is established by closed or open technique, trocars for robotic and laparoscopic bladder diverticulectomy are positioned as depicted in Figure 84–3.

If approached transperitoneally, LBD or RBD begins with incision of the peritoneum overlying the diverticulum. For complex, large, or multiple diverticula, the bladder can be mobilized: The peritoneum is incised medial to the obliterated umbilical ligament bilaterally, the urachus is divided, and the bladder is "dropped" posteriorly, allowing for entry into the space of Retzius. The 10-mm LigaSure (Valleylab, Boulder, CO) can be used during LBD, and a combination of monopolar and bipolar cautery instrumentation is employed during RBD. With the aid of either selective catheterization and filling or cystoscopic transillumination, the diverticulum is identified. Peridiverticular adhesions are transected, and the mouth of the diverticulum is then circumscribed and excised. Constant vigilance is required to prevent injury to the ureter or ureteral orifice. If necessary, a transvesical approach can be employed. The bladder is opened and the diverticulum pulled into the bladder, circumscribed, and excised. In either approach, the bladder is then closed anatomically in two layers with 2-0 polyglactin suture. During LBD, free-hand intracorporeal suturing can be employed. Alternatively, an Endo Stitch device (Covidien, Mansfield, MA) can be used as a suturing aid. An Endo GIA (Covidien, Mansfield, MA) stapling device can also be used for excision, yet this carries with it the theoretical risk of bladder stone formation (Kerbl et al, 1993; Wang et al, 2007). The bladder is then filled to ensure water-tight closure. A Jackson-Pratt drain is placed via one of the trocar sites to avoid an unnecessary additional incision. If needed, ureteral reimplantation secondary to reflux, obstruction, or iatrogenic injury is performed as described in the following section.

Surgical management for bladder outlet obstruction can be performed concomitantly, either immediately before or after bladder diverticulectomy (BD). This includes TURP, KTP laser vaporization, or holmium laser enucleation (Iselin et al, 1996; Grønlund et al, 1998; Porpiglia et al, 2002; Faramarzi-Roques et al, 2004; Shah et al, 2006; Cinman et al, in press). If performed after diverticulectomy, a suprapubic catheter should be placed to avoid perforation at the bladder-closure suture lines. Similarly, laparoscopic or robotic simple prostatectomy can be performed at the time of LBD or RBD (Magera et al, 2008).

Postoperative care involves Jackson-Pratt drain removal, typically 48 hours postoperatively. Cystography is performed to rule out a bladder leak before Foley catheter removal, at approximately 1 week following surgery.

Outcomes and Complications

Minimally invasive techniques have been demonstrated to be effective in treating BD. For example, in 2009 Cinman and colleagues (in press) demonstrated that LBD was effective in reducing PVR (preoperative mean 475 mL) to normal values less than 50 mL (Fig. 84–4). LBD has been demonstrated effective even for patients with complex pathology including giant diverticula up to 30 cm, multiple diverticula (Khonsari et al, 2004; Cinman et al, in press), and those needing concomitant ureteral reimplantation or laparoscopic pyeloplasty (Cinman et al, in press).

Minimally invasive management of a bladder diverticulum and BOO with concomitant LBD and TURP has been demonstrated to be superior when compared with open BD and transvesical

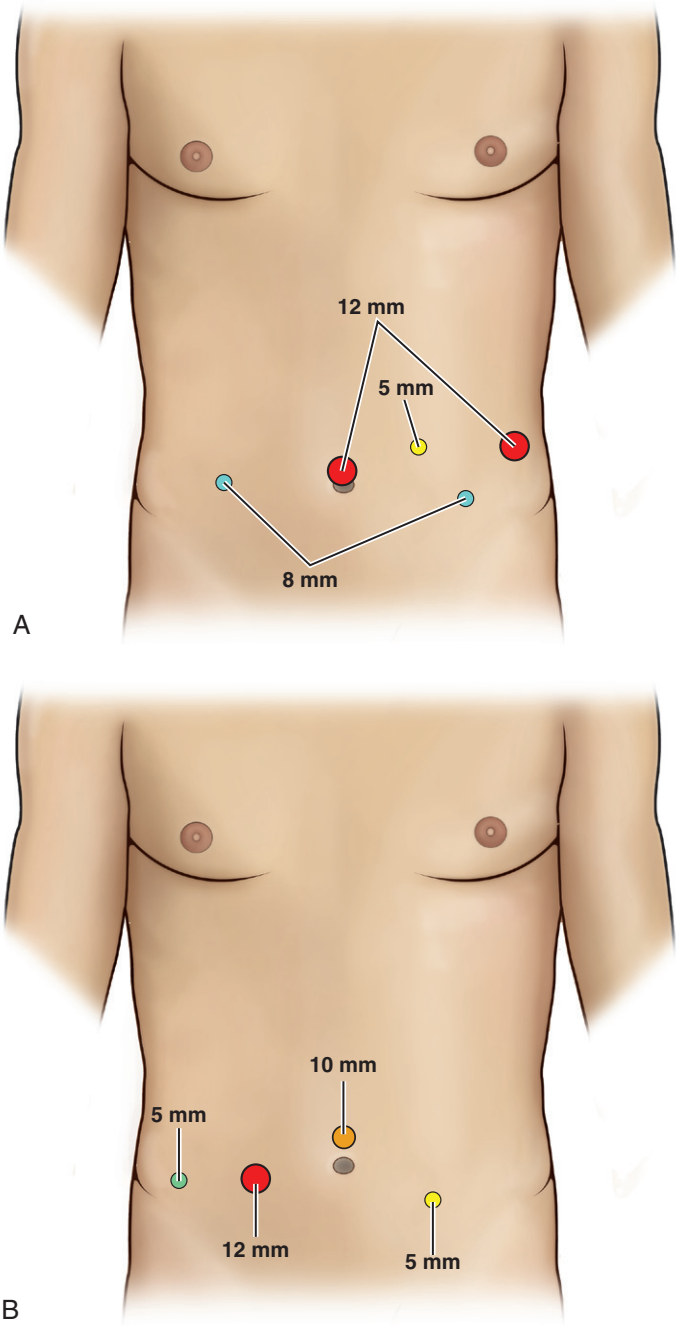


Figure 84–3. **A,** Robotic bladder diverticulectomy. A 12-mm port at the umbilicus is employed for the endoscope. Two 8-mm robotic trocars are placed 10 cm inferolaterally at the pararectus location. At the surgeon's discretion, assistant ports are placed as needed; options include a 5-mm trocar (placed halfway in between the camera and robotic trocar) and/or a 12-mm trocar (two fingerbreadths above the anterior superior iliac spine [ASIS]). If needed, an additional 8-mm trocar can be used for the fourth arm of the robot two fingerbreadths above the contralateral ASIS. **B,** Laparoscopic bladder diverticulectomy. A 10-mm port at the umbilicus is employed for the endoscope. For the right-handed surgeon, working ports include 12-mm and 5-mm trocars, at the right and left pararectus location, respectively. An optional 5-mm trocar can be placed approximately 2 cm cephalad and medial to ASIS (depicted in *green*).

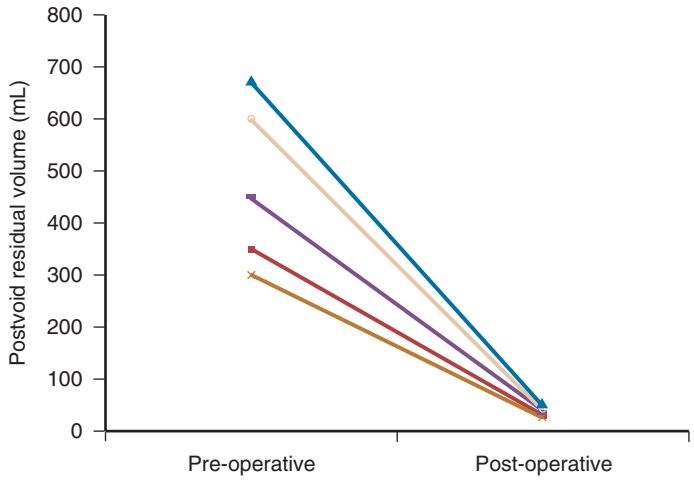


Figure 84–4. Significant reduction in postvoid residual urinary volumes document the efficacy of laparoscopic bladder diverticulectomy for complex bladder diverticula. (Richstone and Kavoussi, unpublished data.)

prostatectomy. LBD and TURP is associated with reduced blood loss, analgesic requirements, and shorter hospital stay but longer operating room times (Porpiglia et al, 2002; Porpiglia et al, 2004). No complications were noted with either approach, and postoperative urinary flow rates were equivalent. In a series of 13 patients undergoing extravesical LBD without concurrent management of BOO, Abdel-Hakim and colleagues (2007) experienced only one complication in the form of extravasation from the suture line that resolved with conservative management.

One limitation of LBD and RBD is longer operative times compared with open surgery. However, operative times are dependent on surgeon experience, as well as the need for concomitant outlet or ureteral surgery. Complications of minimally invasive surgery (MIS) for BD are similar to those encountered during open BD and include ureteral injury, infection, urinary extravasation, urinary fistula, wound infection, and bowel injury.

Key Points: Diverticulectomy

- Laparoscopic and robotic bladder diverticulectomy is an effective approach for even complex diverticula.
- Bladder outlet or ureteral surgery can be managed in the same setting using endoscopic and/or laparoscopic techniques.

URETERAL REIMPLANTATION

Ureteral reimplantation is traditionally performed via an open low midline or Pfannenstiel incision. Laparoscopic ureteroneocystostomy is now a well-described and effective alternative but requires significant laparoscopic experience and intracorporeal suturing skills. In a drive to limit scar number and size, LESS ureteral reimplantation may offer cosmetic benefits, albeit with even greater technical demands on the surgeon. In contrast, the robotic-assisted laparoscopic approach offers simplified suturing and reconstructive aspects of this procedure, while offering the cosmetic and recovery benefits of minimally invasive surgery.

Evaluation and Surgical Indications

Indications for ureteroneocystostomy include VUR, ureteral obstruction, and transection. The specific indication for ureteral reimplantation in the setting of VUR is beyond the scope of this chapter and is discussed elsewhere in this text. Ureteral obstruction can be secondary to stone disease, inflammatory, infectious, iatrogenic, and traumatic etiology, as well as benign or malignant mass lesions. When medical and/or endoscopic approaches fail or are deemed insufficient for the given pathology, ureteral reimplantation is indicated.

Vesicoureteral reflux is evaluated and graded with voiding cystourethrography. In the setting of ureteral obstruction, stricture length can be evaluated with a combination of excretory and retrograde urography. An estimation of the length of the diseased segment is critical in determining whether ureteral length will allow for a ureteroneocystostomy or warrant more complex reconstruction. Nuclear renography is useful to document obstruction and, when necessary, to evaluate function when there is a history of long-standing or severe obstruction or reflux. In appropriate patients, it is critical to consider and rule out malignancy with urinary cytology, endoscopy, and appropriate imaging.

Technique

Laparoscopic and robotic ureteral reimplantation can be performed via an extravesical or intravesical approach. Refluxing or nonrefluxing reimplantation techniques have been described. The approach should be tailored to patient age, pathology, anatomy, and surgeon preference.

NONREFLUXING URETERAL REIMPLANTATION

Several investigators demonstrated the feasibility of laparoscopic correction of VUR in animal studies (Atala et al, 1993; Schimberg et al, 1994; McDougall et al, 1995). Laparoscopic extravesical Lich-Gregoir ureteral reimplantation in humans followed shortly thereafter (Ehrlich et al, 1994; Reddy et al, 1994; Janetschek et al, 1995). Typical port-site placement is similar to that employed for bladder diverticulectomy (see Fig. 84–3).

The extravesical Lich-Gregoir technique can be performed via a conventional laparoscopic or robotic-assisted approach. The ureter is identified medial to the obliterated umbilical ligament, and the overlying peritoneum is incised. The ureter is mobilized to the ureterovesical junction, preserving periureteric tissue to ensure adequate vascular supply. The location of the proposed tunnel is then determined with the bladder filled with saline, and care is taken to avoid creating a "kinking" tunnel. A 5:1 tunnel-to-ureteral diameter is maintained. Taking care to avoid perforation of the bladder mucosa, the detrusor muscle is incised to create a sufficient trough. The ureter is placed within the trough and the detrusor closed over it, using a series of interrupted 3-0 absorbable sutures (Fig. 84–5) (Reddy et al, 1994; Lakshmanan et al, 2000).

The transvesical Cohen cross-trigonal approach has been employed by several authors, by both the pure laparoscopic and

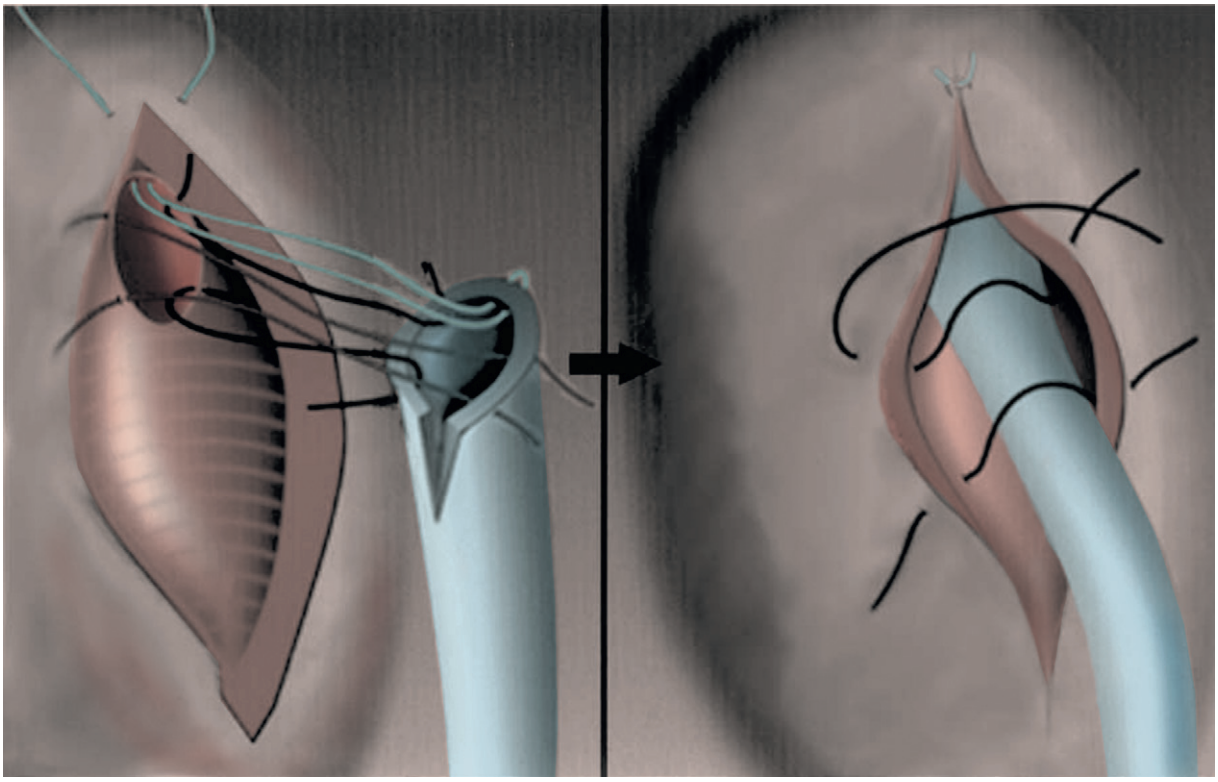


Figure 84–5. Extravesical ureteral reimplantation. A tunnel is made in the detrusor muscle for the ureter, completing the antirefluxing mechanism. (From Andou M, Yoshioka T, Ikuma K. Laparoscopic ureteroneocystostomy. Obstet Gynecol 2003;102:1183.)

robotic technique (Gill et al, 2001; Peters et al, 2005; Yeung et al, 2005; Kutikov et al, 2006). By avoiding the peritoneal cavity, this transvesical approach has the potential to limit complications associated with the transabdominal approach. A three-trocar configuration accommodates either the pure laparoscopic or robotic technique.

As originally described by Gill and colleagues, the procedure is performed with two 5-mm transvesical trocars, glycine irrigation within the bladder, and visualization throughout the procedure with a transurethral 24-Fr resectoscope (Gill et al, 2001). An electrosurgical Collins knife is used to incise the bladder mucosa and create the cross-trigonal trough. Then the detrusor is sewn over the ureter laparoscopically. This procedure was modified by Yeung and colleagues using carbon dioxide insufflation of the bladder and the use of a midline trocar for laparoscopic, rather than cystoscopic visualization of the procedure. In pediatric patients, two 3-mm trocars can be used for working ports, a 5-mm midline trocar can be used for a camera, and an 8-Fr pediatric feeding tube can be placed via urethra for intermittent suctioning (Kutikov et al, 2006). Similarly, a three-trocar robotic transvesical approach to cross-trigonal reimplantation has been described (Peters et al, 2005). After circumferential incision around the ureteral orifice, the ureter is mobilized by incising periureteral attachments. The native hiatus is reduced with 4-0 absorbable suture, and a cross-trigonal submucosal tunnel and new mucosa hiatus are created. The ureter is advanced and anchored with several interrupted 4-0 absorbable sutures, and the periureteral mucosa is sutured to the bladder mucosa with 5-0 absorbable stitches (Fig. 84–6).

REFLUXING URETERAL REIMPLANTATION

Laparoscopic or robotic ureteral reimplantation for benign ureteral stricture disease or select cases of ureteral malignancy is commonly performed in a refluxing manner (Seideman et al, 2009). The authors routinely perform laparoscopic ureteral reimplantation using a three-trocar approach (Fig. 84–7).

The distal ureter is dissected, and the diseased segment is excised. In cases of transitional cell carcinoma, a flexible cystoscope can be placed in the bladder to ensure adequate bladder cuff resection and protection of the contralateral ureteral orifice. The ureteral hiatus is closed in two layers with absorbable sutures. A new ureteral hiatus is created at the dome of the bladder, and the spatulated ureter is reimplanted with 4-0 absorbable sutures in a running or interrupted fashion (Reddy et al, 1994; Fugita et al, 2001). Minimally invasive management of longer ureteral defects is discussed in the next section on psoas hitch and bladder advancement flaps.

Outcomes and Complications

Clinical experience with laparoscopic and robotic ureteroneocystostomy continues to evolve. Small feasibility studies prevail; however, a few larger studies with intermediate follow-up data support the efficacy of the approach.

Lakshmanan and colleagues (2000) describe 71 extravesical ureteral reimplantations in 47 patients for management of VUR. No

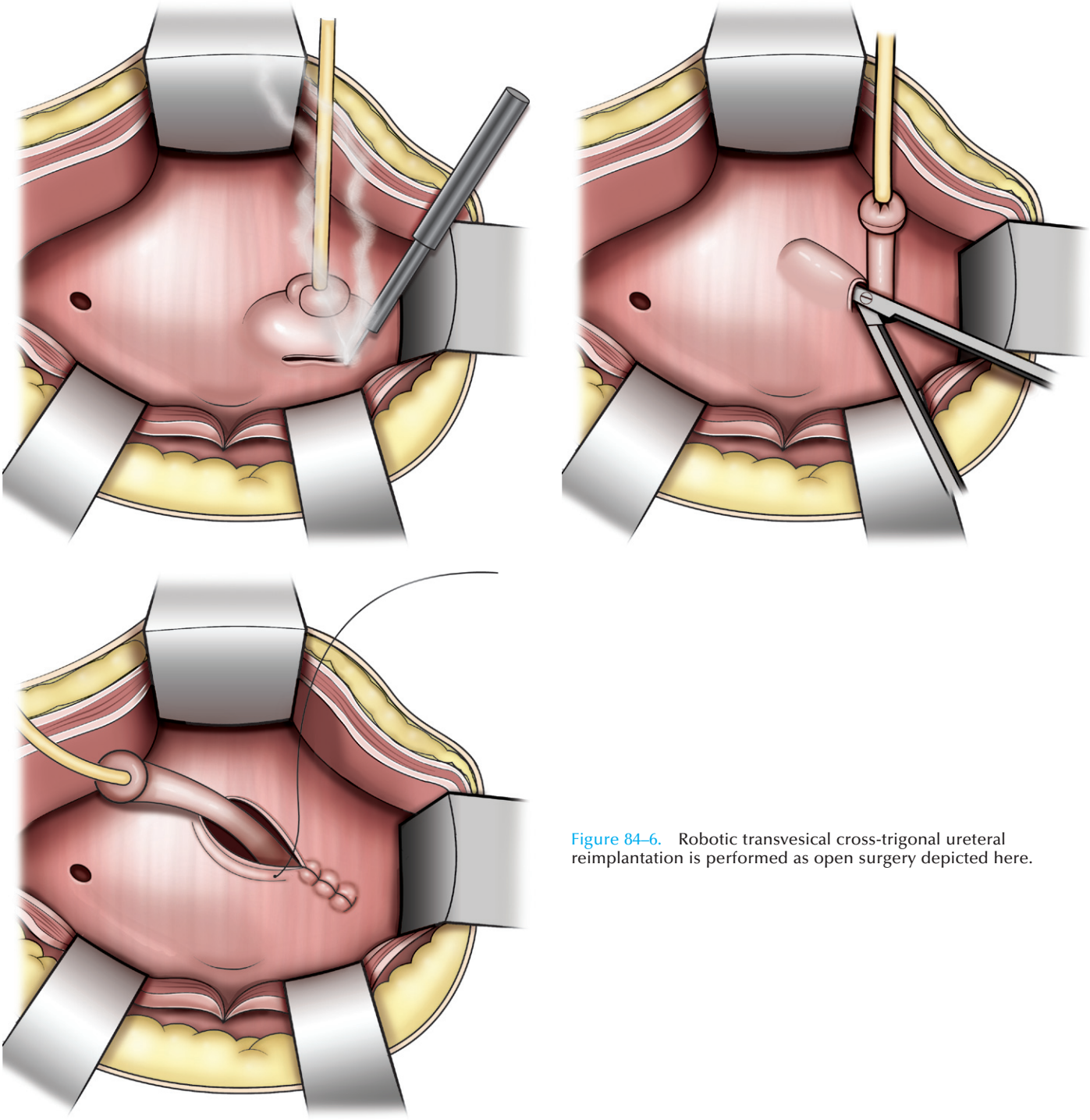


Figure 84–6. Robotic transvesical cross-trigonal ureteral reimplantation is performed as open surgery depicted here.

patients experienced subsequent obstruction or recurrent reflux. Complications were minimal and included three ureteral injuries, two of which required open reimplantation. Yeung and colleagues (2005) performed 30 laparoscopic transvesical cross-trigonal reimplantations in 16 patients. The mean operative team was 112 minutes for unilateral and 178 minutes for bilateral cases. Two patients had subcutaneous and scrotal emphysema that resolved spontaneously. The radiographic success rate was 96%.

In the largest reported series in the adult population, Seideman and colleagues (2009) reported on 45 patients undergoing laparoscopic ureteral reimplantation for benign and malignant pathology. The median hospital stay was 3 days and estimated blood loss (EBL) of 150 mL. Minimal complications were experienced including three patients with urinary extravasation at the anastomotic site, conservatively managed in all cases. With a mean follow-up of 2 years, the authors reported a 96% success rate.

Rassweiler (2007) compared 10 patients undergoing laparoscopic ureteral reimplantation to 10 patients treated by open techniques. In this small series, the laparoscopic approach was associated with less blood loss, analgesic requirements, time to

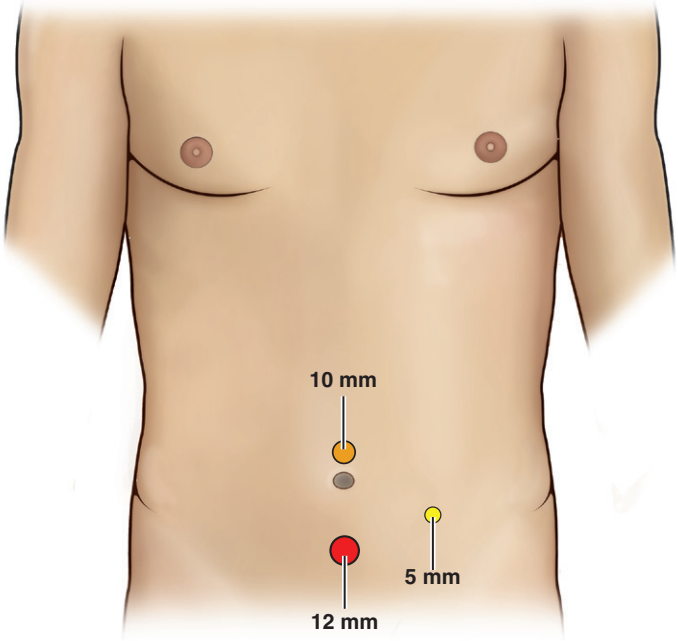


Figure 84–7. Ureteral reimplantation: Trocar placement for left ureteral reimplantation includes a 10-mm umbilical camera port and a 12-mm working port placed halfway between the umbilicus and symphysis pubis. A 5-mm working port is placed at the lateral edge of the rectus muscle at the level of the umbilicus on the ipsilateral side of the procedure.

oral intake, hospital stay, and convalescence time. Similarly, Simmons and colleagues (2007) retrospectively compared 12 laparoscopic versus 34 open ureteral reimplantation procedures, demonstrating a reduced blood loss and shorter hospitalization associated with laparoscopy. Complication rates and ureteral patency rates were equivalent at a mean follow-up of nearly 2 years. Several authors have documented the feasibility of robotic-assisted ureteral reimplantation (Yohannes et al, 2003; Uberoi et al, 2007; Patil et al, 2008). The robotic technique recapitulates the laparoscopic technique and may facilitate the learning curve for reconstructive procedures requiring intracorporeal suturing.

More recently, LESS surgery has emerged as a technique with the potential for improved cosmetic outcomes and perhaps reduced pain and convalescence. LESS ureteroneocystostomy has been reported, but larger series are necessary to validate the efficacy and safety of the approach (Desai et al, 2009).

Key Points: Ureteral Reimplantation

- Laparoscopic and robotic ureteroneocystostomy are viable alternatives to open surgery.
- Extravesical and transvesical approaches can be employed to perform refluxing or nonrefluxing ureteral reimplantation.
- Evolving data support the efficacy of this approach for VUR, as well as ureteral obstruction or transection.
- In the future, LESS surgery may provide an even less invasive approach to ureteroneocystostomy, possibly reducing disfigurement and morbidity.

PSOAS HITCH AND BLADDER ADVANCEMENT FLAPS

When faced with minimal distal ureteral loss, simple ureteroneocystostomy is sufficient to re-establish urinary continuity. However, more extensive gaps require more complex reconstructive techniques. The Boari bladder flap was introduced for bridging larger gaps between the ureter and bladder in 1894 in the canine model and in humans in 1947 (Fugita et al, 2001). Laparoscopic Boari flap was first performed in the porcine model and in humans in 2001 (Fergany et al, 2001; Fugita et al, 2001). This can be performed with or without a psoas hitch, to anchor the bladder in order to gain additional length and avoid anastomotic tension. Defects of the distal third ureter are routinely bridged with this technique, and in select cases the mid or proximal ureter can be reached. When this approach is not sufficient, transureteroureterostomy, autotransplantation, or ileal ureteral substitution can be considered.

Evaluation and Surgical Indications

Laparoscopic or robotic Boari flap with or without psoas hitch is indicated when the degree of ureteral loss precludes simple ureteroureterostomy or ureteroneocystostomy. Preoperative evaluation of ureteral obstruction includes antegrade and/or retrograde urography in order to estimate the extent of disease and aid in planning for the surgical approach. Ultimately, intraoperative findings dictate the need for Boari flap and/or psoas hitch. Nuclear renography is indicated if impaired renal function is suspected. Cystoscopy, urinalysis, and urinary cytology are performed to rule out malignancy.

Technique

Laparoscopic or Robotic Boari Flap

Laparoscopic Boari flap was first described in humans in by Fugita and colleagues (2001) in a series of three patients with distal ureteral obstruction. The robotic-assisted laparoscopic approach was first reported several years later (Schimpf et al, 2008). Trocar placement for robotic and laparoscopic reimplantation and Boari flap is depicted in Figures 84–3 and 84–7, respectively. The procedure begins by incising the ipsilateral white line of Toldt and the ureter identified as it crosses the iliac vessels. The ureter is mobilized distally, and the diseased segment excised, ensuring that the distal margin is well vascularized and healthy. If indicated, a distal margin is sent for frozen section, and the ureter is spatulated. The bladder is filled with 200 mL of normal saline and mobilized by incising the peritoneum medial to the obliterated umbilical ligaments bilaterally and transecting the urachus. Blunt dissection allows the bladder to "drop" posteriorly, and the space of Retzius is entered. Ligation of the contralateral bladder pedicle with an Endo GIA stapling device (Covidien, Mansfield, MA) and psoas hitch using 2-0 absorbable suture can often provide enough mobilization to perform a ureteroneocystostomy (Modi et al, 2005; Schimpf et al, 2008). If this maneuver does not suffice, a Boari flap or bladder advancement flap is performed. Using electrosurgical scissors or a 10-mm LigaSure (Valleylab, Boulder, CO) device, an anterior bladder flap is created beginning approximately 2 cm from the bladder neck, extending to the ipsilateral bladder dome; the apex and base of the flap are approximately 2 cm and 4 cm, respectively (Fugita et al, 2001) (Fig. 84–8). Care should be taken to ensure that the base of the flap is wide enough to ensure

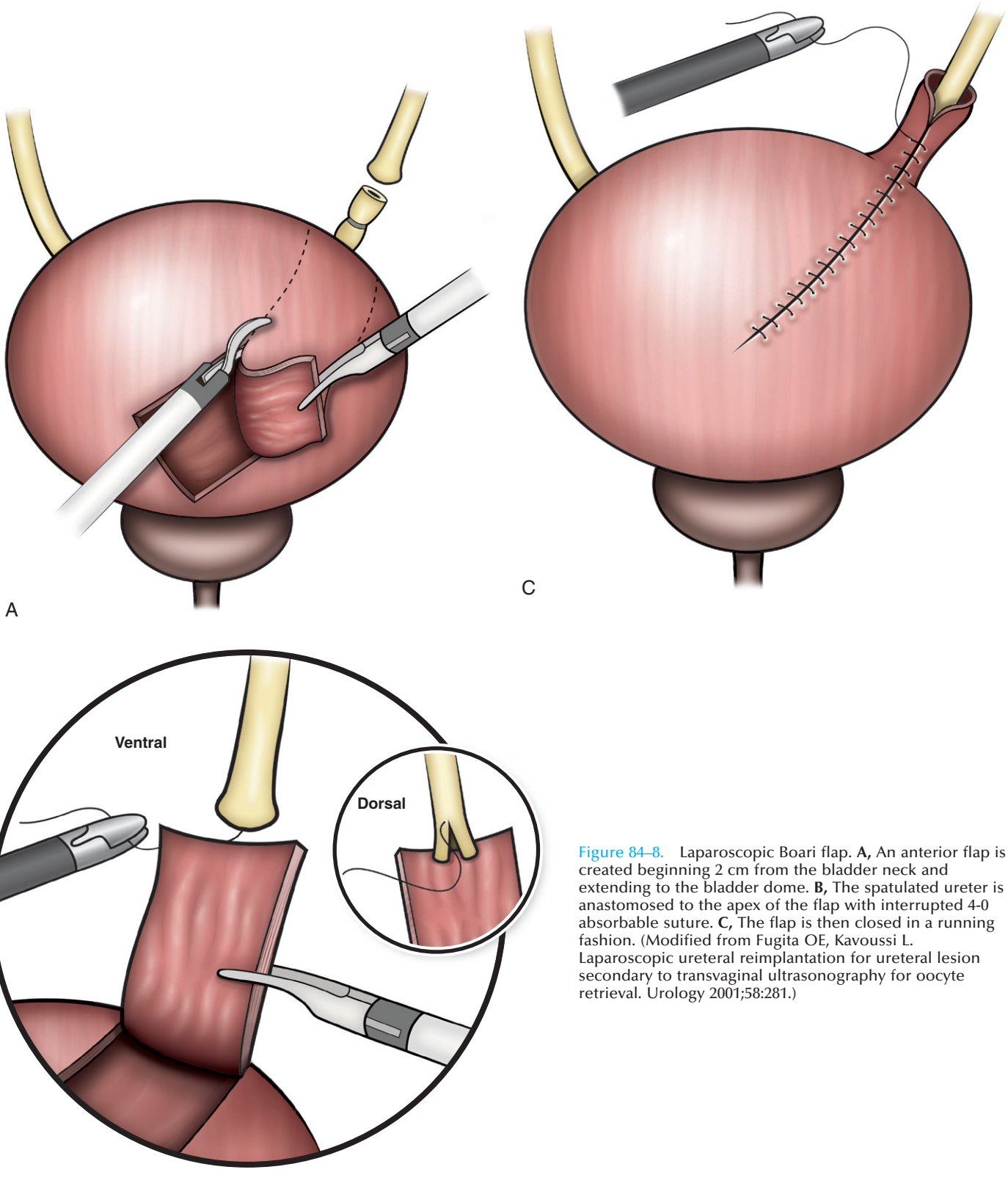


Figure 84–8. Laparoscopic Boari flap. **A,** An anterior flap is created beginning 2 cm from the bladder neck and extending to the bladder dome. **B,** The spatulated ureter is anastomosed to the apex of the flap with interrupted 4-0 absorbable suture. **C,** The flap is then closed in a running fashion. (Modified from Fugita OE, Kavoussi L. Laparoscopic ureteral reimplantation for ureteral lesion secondary to transvaginal ultrasonography for oocyte retrieval. Urology 2001;58:281.)

adequate vascularity. The spatulated ureter is anastomosed to the apex of the flap with interrupted 4-0 absorbable suture. After placement of a 7-Fr double pigtail catheter over a guidewire, the flap is then closed in a running fashion in two layers with 4-0 and 2-0 absorbable suture or with the assistance of an EndoStitch device (Covidien, Mansfield, MA). The bladder is filled to 300 mL to identify any sites of anastomotic leakage, and a Jackson-Pratt drain is placed through the 5-mm trocar site. The Jackson-Pratt drain is typically removed in 48 hours, and the Foley catheter is removed in 1 week following a cystogram to confirm no urinary leakage. The ureteral stent is removed in 4 weeks.

Laparoscopic Bladder Advancement Flap

Laparoscopic bladder advancement flap was first described by Lima and colleagues (2005) as a simplified alternative to a Boari flap. The bladder is opened with a transverse incision, placed one third of the distance from the dome to the bladder neck (Fig. 84–9). The spatulated ureter is anastomosed to the bladder flap in a fashion similar to a Boari flap, described previously.

Outcomes and Complications

The first clinical series of laparoscopic ureteral reimplantation with Boari flap was reported in 2001, involving three patients (Fugita et al, 2001). The approach was demonstrated to be feasible with a mean operative time of 220 minutes and EBL ranging from 400 to 600 mL. With a mean follow-up of 11 months, all patients had resolution of obstruction. Castillo and colleagues (2005) reported a slightly larger series of laparoscopic Boari flap in eight patients. Operative times (mean 157 minutes), blood loss (mean 124 mL), and hospital stay (mean 3 days) further validated the feasibility of the technique. Two complications occurred including one pulmonary embolism and one patient with urinary leakage at the anastomosis requiring laparoscopic repair. With a mean follow-up of 18 months, all patients had resolution of obstruction. Seideman and colleagues (2009) reported laparoscopic Boari flap in 21 out of 45 patients undergoing laparoscopic ureteral reimplantation, representing the largest published series to date, with the longest reported follow-up (mean 24 months). Two patients underwent distal ureterectomy for transitional cell carcinoma. Median length of stay and EBL was 3 days and 150 mL, respectively. Complications included one patient with small bowel obstruction, one patient with *Clostridium difficile* colitis and respiratory distress, and two patients with urinary leakage that was managed conservatively in both cases.

Key Points: Psoas Hitch and Advancement Flaps

- Laparoscopic and robotic approaches to psoas hitch, Boari flap, and bladder advancement flap for patients with moderate distal ureter loss have been demonstrated to be an effective alternative to open surgical techniques.
- Outcomes appear favorable when compared with open series.

ENTEROCYSTOPLASTY

Augmentation cystoplasty is a well-established surgical option for the patient with a small capacity, poorly compliant bladder who has failed conservative management. Docimo and colleagues (1995) were the first to perform a purely laparoscopic gastrocystoplasty in a single patient. Although the procedure took almost 11 hours and involved a 13-day hospital course, the feasibility of the technique was demonstrated. Subsequently, Gill and colleagues (2000) described the laparoscopic ileocystoplasty, sigmoidocystoplasty, and cecocoloplasty with the bowel anastomosis done extracorporeally. Over the past decade, ileocystoplasty has emerged as the most widely employed technique. Reports of laparoscopic, robotic, and even LESS bladder augmentation have documented the reproducibility of these techniques by both purely intracorporeal and partly extracorporeal approaches.

Evaluation and Surgical Indications

Candidates for augmentation cystoplasty include patients with small-volume, poorly compliant bladders who are capable of self-catheterization (Elliott et al, 2002). Most commonly, these patients have neurogenic bladder secondary to spinal dysraphism or other anatomic abnormalities. All patients should undergo video urodynamics before augmentation. An ultrasound should be performed to rule out hydronephrosis, which should then be evaluated before surgery. All patients must be physically and psychologically competent and willing to perform self-catheterization. Contraindications to either open or MIS augmentation include renal insufficiency, renal tubular acidosis, and gastrointestinal disease including short gut syndrome, inflammatory bowel disease, and liver failure (Elliot et al, 2002).

Technique

The procedure begins with cystoscopic evaluation and placement of bilateral open-ended, or single-J, ureteral catheters, which are then secured to a urethral catheter. Pneumoperitoneum is established. Laparoscopic or robotic enterocystoplasty is performed via three to five trocars depending on surgeon experience and preference. The bladder is fully mobilized by incising the peritoneum medial to the obliterated umbilical ligament bilaterally, and the urachus is divided to "drop" the bladder posteriorly and enter the space of Retzius. An appropriate 15- to 20-cm segment of bowel is chosen, taking care to ensure an adequate vascular pedicle and that the segment will reach to the bladder neck. The bowel work can be completed via a purely laparoscopic approach (Meng et al, 2002) or extracorporeally by extending the length of the umbilical incision (Gill et al, 2000) as described later. In either approach, the segment is harvested using an Endo GIA (Covidien, Mansfield, MA) stapler. The mesentery can be divided with additional reloads of the Endo GIA or with a 10-mm LigaSure device (Valleylab, Boulder, CO). Bowel continuity is re-established with a side-to-side anastomosis using the Endo GIA device. The anastomosis is completed using a TA stapler (Covidien, Mansfield, MA) if performed extracorporeally and with a series of Lembert sutures if performed via intracorporeal suturing (Fig. 84–10). The mesenteric window, or "trap," is then closed.

The bowel segment is then irrigated copiously, the staple lines are excised on each end, and the bowel segment is opened along the antimesenteric border. During ileal augmentation, the sides of the bowel segment are approximated to form a U-shaped segment with running 2-0 polyglactin suture. At this time the bladder is filled with saline and bivalved at the midsagittal line. The segment is brought down to the pelvis without tension or torsion of the mesenteric pedicle. With the bowel segment oriented so that the apex of the U is positioned anteriorly at the bladder neck, the patch is sutured to the bladder in a running continuous fashion with 2-0 polyglactin suture, beginning posteriorly and ending

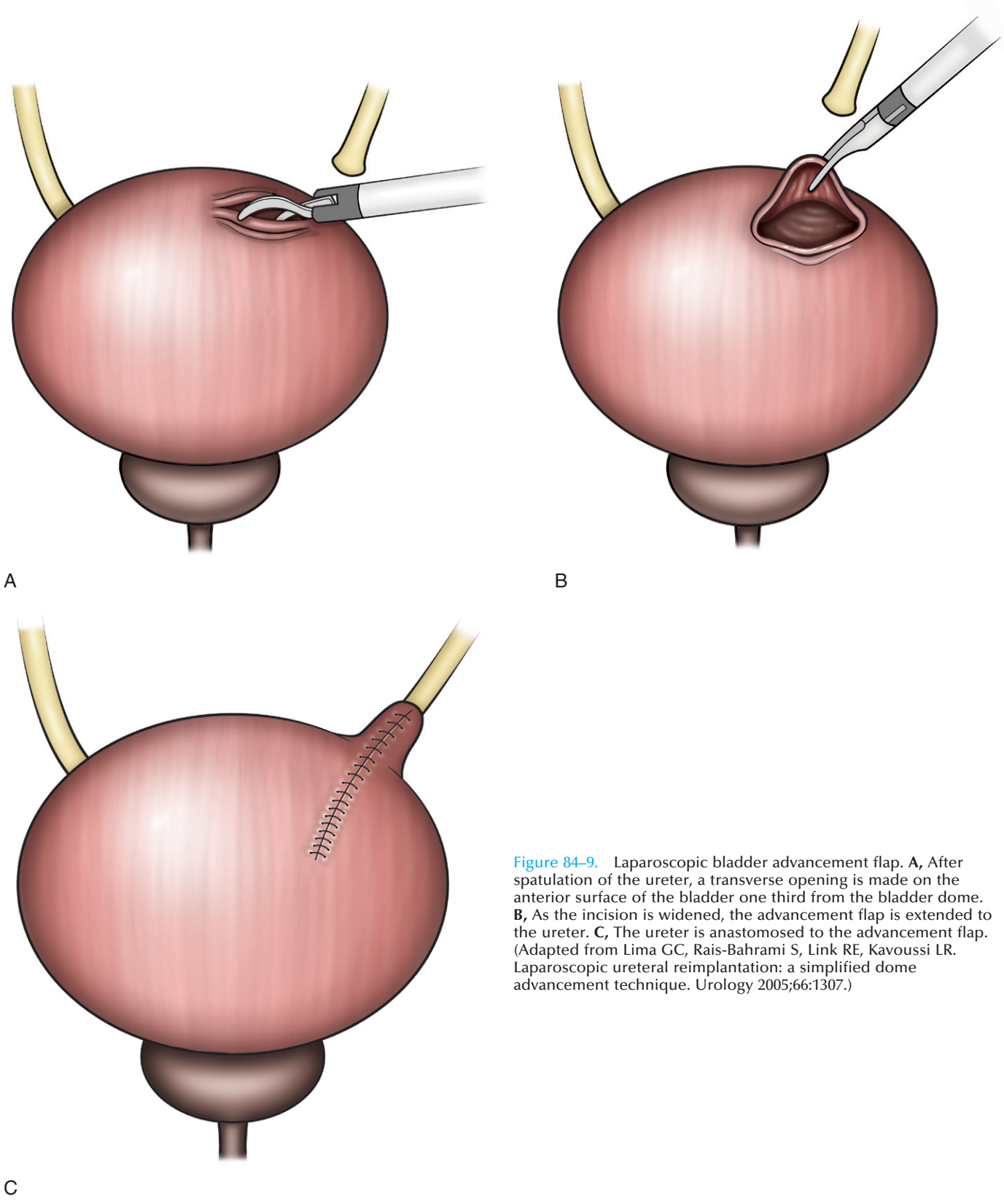


Figure 84–9. Laparoscopic bladder advancement flap. **A,** After spatulation of the ureter, a transverse opening is made on the anterior surface of the bladder one third from the bladder dome. **B,** As the incision is widened, the advancement flap is extended to the ureter. **C,** The ureter is anastomosed to the advancement flap. (Adapted from Lima GC, Rais-Bahrami S, Link RE, Kavoussi LR. Laparoscopic ureteral reimplantation: a simplified dome advancement technique. Urology 2005;66:1307.)

anteriorly (Gill et al, 2000; Elliot et al, 2002; Meng et al, 2002). The integrity of the completed augment is confirmed by irrigating the bladder via the Foley catheter, and finally a pelvic drain is positioned. Laparoscopic and robotic ileocystoplasty and cecocoloplasty with catheterizable stoma creation have also been described (Gill et al, 2000; Gundeti et al, 2008). For patients with concomitant refractory constipation, the Malone antegrade continence enema (ACE) procedure can be performed concurrently (Shadpour et al, 2005). As an alternative to vesicoplasty for select patients, appendicovesicostomy has also been reported both

laparoscopically (Hsu et al, 2004; Lorenzo et al, 2007) and with a robot-assisted laparoscopic approach (Lendvay et al, 2008).

More recently, LESS enterocystoplasty has been reported (but larger series are necessary to validate the efficacy and safety of the approach) (Desai et al, 2009).

Outcomes and Complications

Complications of laparoscopic and robotic bladder augmentation are similar to those encountered during open surgery and include infection, metabolic derangements, stones, perforation, mucus production, and malignancy. Intracorporeal bowel segment irrigation and detubularization may increase the risk of infectious complications.

Docimo and colleagues (1995) performed the first pure laparoscopic gastrocystoplasty in a single patient with a five-port technique. The procedure involved almost 11 hours of operating time and a 13-day hospitalization. A laparoscopic-assisted approach, in which the laparoscopic work was largely limited to bowel mobilization, followed (Hedican et al, 1999; Chung et al, 2004). Gill and colleagues (2000) reported the first laparoscopic ileocystoplasty, sigmoidocystoplasty, and cecocoloplasty. Bowel harvest and anastomotic work were done extracorporeally with a four-port approach. In this small series of three patients, operative times of 5 to 8 hours and blood loss of 50 to 200 mL were reported. A single complication in the form of a rectus sheath hematoma occurred. The first purely laparoscopic ileocystoplasty in a human was reported in 2002 (Elliot et al, 2002; Meng et al, 2002). The patient underwent a 9-hour procedure and required a 13-day hospitalization secondary to prolonged ileus. The largest published series of MIS cystoplasty involves six patients who underwent pure laparoscopic ileocystoplasty and ACE procedure (Shadpour et al, 2005). Operative times were 5 to 8.5 hours, with a median hospitalization of 5 days. Complications included one ileal anastomotic leak that resolved conservatively and one appendiceal stomal stenosis requiring revision. With intermediate length follow-up (13 to 16 months), all patients were continent of urine between catheterizations and nearly all had perfect fecal continence. Purely intracorporeal robotic augmentation ileocystoplasty with and without Mitrofanoff appendicovesicostomy has also been described (Al Othman et al, 2008; Gundeti et al, 2008). The technique is essentially identical to the laparoscopic approach, however, the use of the robotic system may facilitate the learning curve for intracorporeal suturing.

In a continuing attempt to improve cosmesis, and possibly other outcome measures, LESS enterocystoplasty has recently been reported (Noguera et al, 2009). This technique is an exact replication of the technique described by Gill and colleagues (2000) with extracorporeal bowel work. The operating time was 300 minutes, and EBL was less than 100 mL, with no intraoperative or postoperative complications.

VESICOVAGINAL AND URETEROVAGINAL FISTULA

Vesicovaginal fistula (VVF) is a distressing condition that often leads to significant psychologic and medical morbidity. In the underdeveloped world, birth trauma remains the most common

Key Points: Enterocystoplasty

- Small feasibility studies document that bladder augmentation cystoplasty can be performed laparoscopically, robotically, and more recently with a LESS approach.
- The principles of open cystoplasty can be replicated by experienced laparoscopic and robotic surgeons, despite the technical rigors associated with bowel work and extensive reconstruction.
- Although cosmetic outcomes are likely improved, further study is necessary to determine what additional benefits these approaches may confer to this patient population.

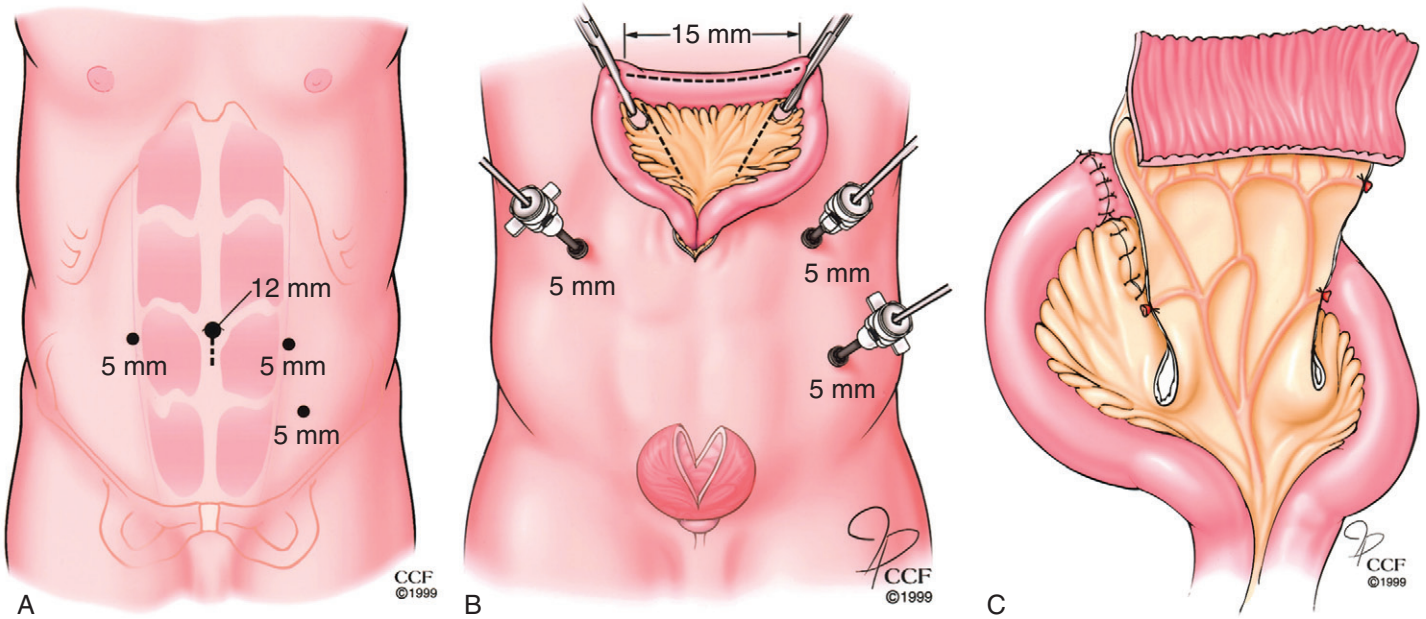


Figure 84–10. **A,** Port placement for laparoscopic enterocystoplasty. Four-port transperitoneal technique is employed including an umbilical port, one port at each lateral border of the rectus muscle at the level of the umbilicus, and a port in the iliac fossa at the level of the anterior superior iliac spine. **B,** The selected bowel segment (15 cm) is exteriorized through an extension of the umbilical port incision. Alternatively, the bowel work can be performed intracorporeally. The anteroposteriorly bivalved bladder is shown.

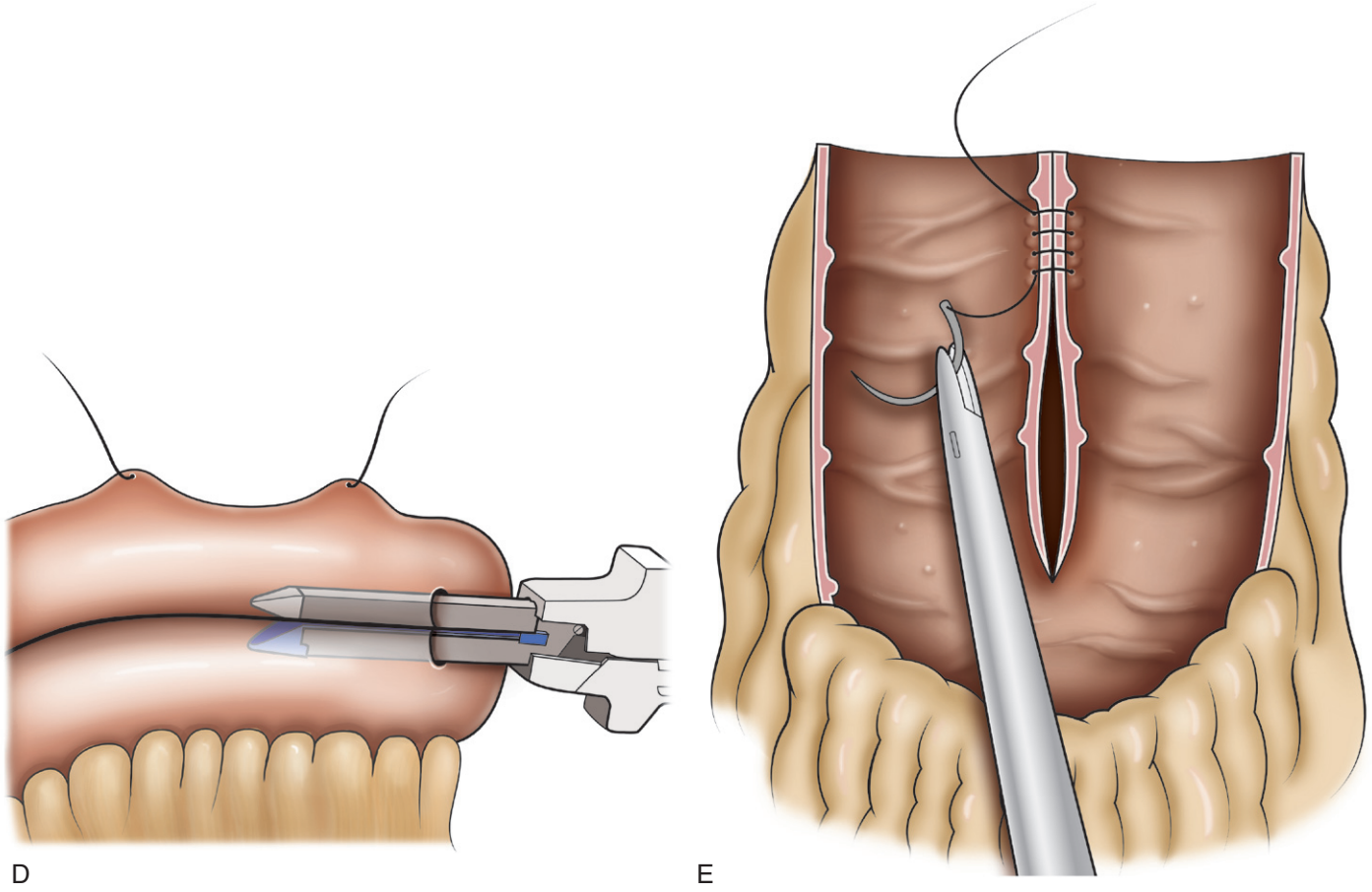


Figure 84–10, cont'd. **C,** Ileoileal reanastomosis is performed cephalad (anterior) to the isolated bowel segment, which can be performed with a GIA stapling device **(D),** which is then detubularized and cleaned. Proper orientation of bowel mesentery must be maintained. **E,** The ileal segment is fashioned into a U-shaped patch with intra- or extracorporeal suturing. **F,** Ileovesical anastomosis is performed in a circumferential manner with continuous, full-thickness, freehand laparoscopic suturing with 2-0 Vicryl suture on a CT-1 needle. The completed augmentation ileocystoplasty is shown in the *inset*. (**A, B, C,** and **F,** Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1991-2011. All Rights Reserved. **D** and **E,** based on Elliott SP, Meng MV, Anwar HP, Stoller ML. Complete laparoscopic ileal cystoplasty. Urology 2002;59:939; and on Gill IS, Rackley RR, Meraney AM, et al. Laparoscopic enterocystoplasty. Urology 2000;55:178.)

etiology of VVF. Prolonged, obstructed labor leads to bladder ischemia and subsequent VVF formation (Miller et al, 2001). In developed nations, urogynecologic surgery is the most common cause of VVF, particularly as a complication of abdominal hysterectomy. In fact, VVF is estimated to occur after 1 in 1800 abdominal hysterectomies (Miller et al, 2001). Less common etiologies of VVF include trauma, foreign body erosion, pelvic irradiation, and other urogynecologic operations (Miller et al, 2001). Ureterovaginal fistulas (UVFs) are also typically the result of ureteral injury during urogynecologic surgery, most often hysterectomy.

Evaluation and Surgical Indications

Patients with VVF/UVF following hysterectomy classically present with continuous urinary incontinence 10 to 14 days following surgery (Miller et al, 2001). A complete evaluation of the upper

and lower tract is necessary to identify the source of leakage as a vesicovaginal, urethrovaginal, and/or ureterovaginal fistula. Vesicouterine fistulas can also occur. All patients should undergo a thorough pelvic examination, cystoscopy, and vaginoscopy. A "double dye" tampon test with oral phenazopyridine and intravesical methylene blue can be a useful office-based test. Appropriate imaging includes cystography and intravenous urography (IVU) to identify VVF and UVF, respectively. Retrograde ureterograms are indicated if IVU is inconclusive for ureteral fistula (Miller et al, 2001).

Conservative management of VVF includes bladder drainage with Foley catheter and/or endoscopic fulguration; however, success rates are low ranging from 7% to 12.5% (Sotelo et al, 2005). Most fistulas ultimately require surgical repair, which can be approached via an abdominal, vaginal, or combined approach. Controversy exists as to the ideal approach for fistula repair, and surgeon preference and experience most often dictates the approach (Miller et al, 2001). Some argue that large fistulas, fistulas in close proximity to the ureteral orifices, and recurrent fistulas after failed transvaginal repair are particularly well-suited for an abdominal approach (Hemal et al, 2008). Similarly, controversy exists over the ideal timing of fistula repair. Although traditional management has favored delayed intervention, literature supports early repair in select cases (Blandy et al, 1991; Blaivas et al, 1995; Langkilde et al, 1999; Miller et al, 2001).

Technique

Transabdominal VVF and UVF repair has been demonstrated to be feasible and effective via a pure laparoscopic, or robotic-assisted laparoscopic approach. Core principles of open surgical fistula repair can and must be followed via minimally invasive approaches: (1) wide exposure and complete excision of the fistulous tract; (2) optimal tissue health (adequate vascularity, freedom from infection, inflammation, and malignancy); (3) a tension-free, watertight, multilayered closure with nonoverlapping suture lines; (4) interposition of omentum, a peritoneal or bladder flap, or sigmoid epiploicae in between the bladder and vaginal suture lines; and (5) adequate postoperative bladder drainage (Sotelo et al, 2005; Wong et al, 2006).

After the induction of anesthesia, cystoscopy is performed and bilateral ureteral catheters are placed for ureteral identification and protection. In order to aid in identification and dissection of the fistulous tract, an additional ureteral catheter is passed from the bladder through the fistula and out the vaginal introitus. A Foley catheter can be used in lieu of a catheter for a large fistula. A sponge stick is placed in the vaginal vault to manipulate the vagina.

Pneumoperitoneum is established, and four or five trocars are placed. A transperitoneal approach is commonly employed. The patient is placed into the steep Trendelenburg position, and the robot is docked if a robotic-assisted approach is used. Cystoscopic illumination of the bladder allows for ready identification of the fistula location. Replicating the open technique described by O'Conor, a vertical cystotomy incision is made from the dome to the fistula (O'Conor et al, 1980; Chibber et al, 2005). Sotelo and colleagues (2005) describe a limited cystotomy in the vicinity of the fistulous tract to limit bladder dissection. Using this approach, dissection of the prevesical and extensive bivalving of the bladder is avoided. Dissection is continued posteriorly until the catheter in the fistulous tract is identified. Alternatively, direct dissection in the vesicovaginal space can be performed. In order to prevent loss of pneumoperitoneum, a clamped Foley catheter with an inflated balloon and moist sponge pack can be placed in the bladder and vagina, respectively. The vesicovaginal space is dissected to separate the bladder from the vagina. The fistulous tract is excised completely, ensuring viable edges of both bladder and vagina (Fig. 84–11).

The surgeon must remain cognizant of the ureteral orifices at all times to avoid injury. The bladder is closed vertically using 2-0 or 3-0 polyglactin suture in two layers. The vagina is closed transversely to allow for nonoverlapping suture lines. Omental tissue can be interposed between the suture lines and anchored to the anterior vaginal wall with interrupted absorbable sutures (Sotelo et al, 2005). Alternatively, a peritoneal flap (Hemal et al, 2008; Gozen et al, 2009) or pericolic or mesenteric fat (Chibber et al, 2005) can be used for interposition. The bladder is filled with sterile saline to ensure a water-tight closure. The ureteral catheters are removed. A Foley catheter in the bladder and closed suction pelvic drain are placed. The drain is removed within 24 to 48 hours. A cystogram is performed 10 to 14 days after surgery, and the Foley catheter is removed.

Outcomes and Complications

Laparoscopic and robotic VVF repair were first performed in 1994 and 2005, respectively (Nezhat et al, 1994; Melamud et al, 2005). The reproducibility of laparoscopic VVF repair has since been demonstrated, with 49 patients reported in 12 published series (Sotelo et al, 2005; Gozen et al, 2009). In the largest reported series, Sotelo and colleagues (2005) reported success in 14 out of 15 patients with a mean follow-up of 26.2 months. Two complications occurred including one enterotomy and subsequent fistula and one epigastric arterial bleed requiring a return to the operating room. In a series of 11 patients with VVF and 1 with vesicouterine fistula, Das Mahapatra and colleagues (2007) had one failure with 12 to 36 months of follow-up. Chibber and colleagues (2005) reported on eight patients undergoing VVF or vesicouterine fistula repair with 100% success rate at 3 to 40 months, with no complications. Otsuka and colleagues (2008) successfully performed laparoscopic VVF on seven patients with no recurrences and two complications including one urinary tract infection and an inferior limb compartment syndrome in another. Several authors have also documented the feasibility and success of laparoscopic VVF for recurrent fistulas (Miklos et al, 1999; Nabi et al, 2001; Otsuka et al, 2008).

Similarly, robotic-assisted laparoscopic VVF repair has been demonstrated as feasible in small series, with 15 patients reported in the literature (Melamud et al, 2005; Sundaram et al, 2006; Schimpf et al, 2007; Sears et al, 2007; Hemal et al, 2008). With short-term follow-up, no failures and no complications have been

Key Points: Vesicovaginal and Ureterovaginal Fistula

- Laparoscopic and robotic-assisted laparoscopic repair of vesicovaginal fistula has been demonstrated to be reproducible and effective in small series.
- Larger series and randomized studies are necessary to determine what advantages may be conferred to patients compared with transabdominal and transvaginal approaches.
- In the future, LESS VVF repair may confer advantages of laparoscopy with optimal cosmetic outcomes.

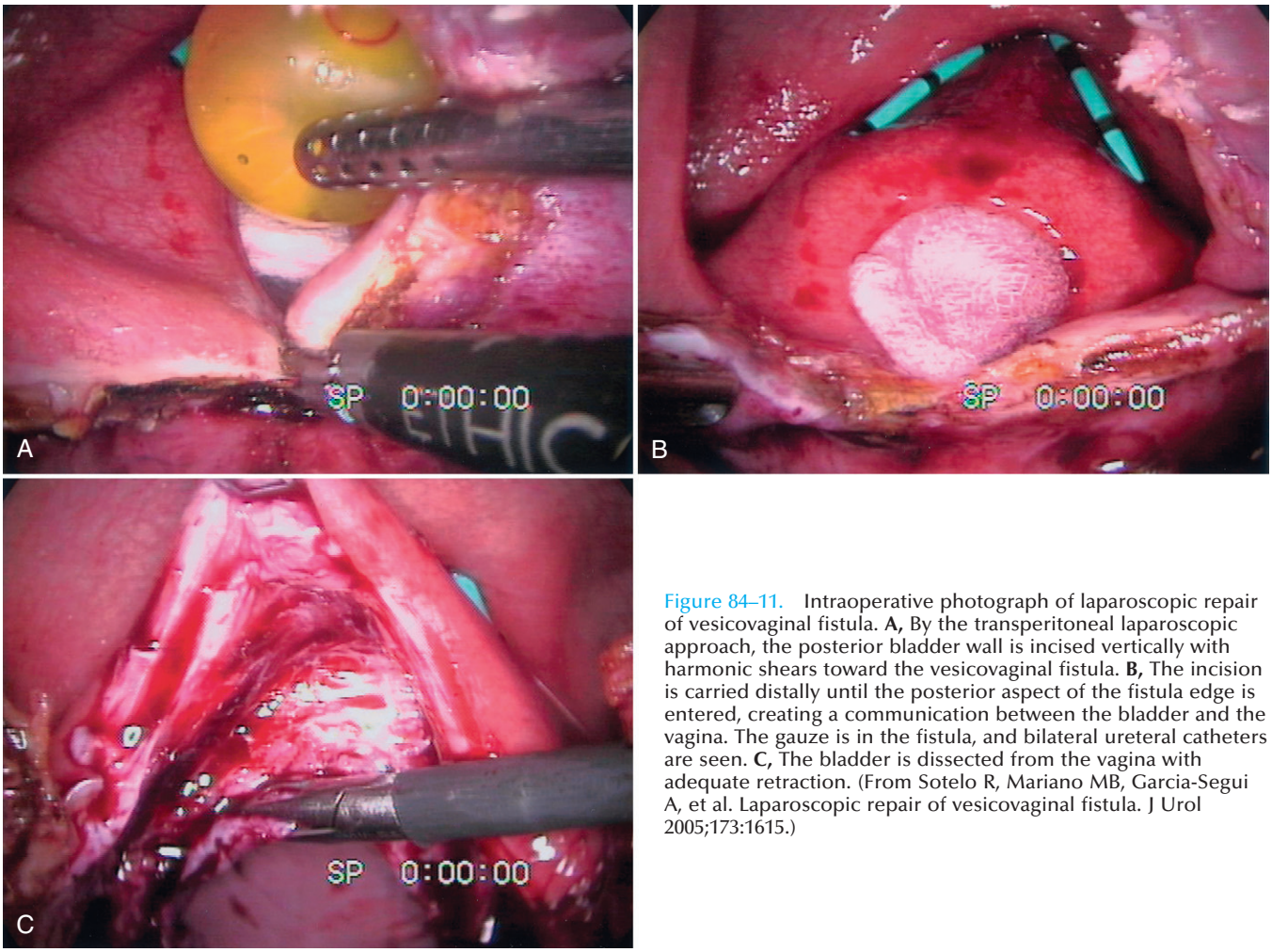


Figure 84–11. Intraoperative photograph of laparoscopic repair of vesicovaginal fistula. **A,** By the transperitoneal laparoscopic approach, the posterior bladder wall is incised vertically with harmonic shears toward the vesicovaginal fistula. **B,** The incision is carried distally until the posterior aspect of the fistula edge is entered, creating a communication between the bladder and the vagina. The gauze is in the fistula, and bilateral ureteral catheters are seen. **C,** The bladder is dissected from the vagina with adequate retraction. (From Sotelo R, Mariano MB, Garcia-Segui A, et al. Laparoscopic repair of vesicovaginal fistula. J Urol 2005;173:1615.)

reported to date. Successful laparoscopic and robotic-assisted laparoscopic UVF repair has also been reported (Ramalingam et al, 2005; Laungani et al, 2008). Similarly, laparoscopic and robotic rectourethral fistula repair and laparoscopic cervicovesical fistula repair have been reported (Hemal et al, 2001; Sotelo et al, 2007, 2008). More recently, transvesical LESS VVF repair with a 10-mm urethral port has been reported (Rao, personal communication). Further experience is necessary to explore the possible benefits of this approach.

URACHAL SURGERY AND PARTIAL CYSTECTOMY

The urachus is the embryologic remnant of the allantois. It provides ligamentous support from the dome of the bladder to the umbilicus. Urologic diseases affecting the urachus include both benign and malignant processes. Benign conditions include urachal cysts and inflammatory and infectious processes. Urachal adenocarcinoma is rare and typically presents as a tumor at the dome of the bladder, but it has been reported in the urachus alone without any bladder manifestations. Partial cystectomy can be employed for urachal adenocarcinoma, as well as select cases of transitional cell carcinoma.

Evaluation and Surgical Indications

Most patients with urachal adenocarcinoma present with microscopic or gross hematuria. On occasion, a mucinous adenocarcinoma may present with mucoid discharge or pyuria. Infected or inflamed urachal cysts may present with bloody discharge from the umbilicus or an indurated and fluctuant umbilicus. Diagnostic evaluation includes cystoscopy and CT imaging. Cystoscopically, a lesion at the dome of the bladder is the hallmark finding. Imaging will reveal a dome lesion in the bladder. Staging is critical to rule out lymphadenopathy or distant metastatic disease. For benign or infectious lesions of the urachus, CT imaging may reveal a periumbilical cyst or abscess.

Treatment is indicated for symptomatic or infected urachal cysts. Although studies are limited, there is no clear evidence to suggest that urachal cysts will transform into urachal malignancies. Therefore treatment should be limited to the symptomatic patient. In the setting of inflammation or infection, patients should be treated with oral or intravenous antibiotics. Swab culture of the umbilicus and urine cultures should be sent before the onset of antibiotics. Anti-inflammatory medications may be used for symptomatic relief. In the setting of a fluctuant umbilicus, a local incision and drainage can be performed. If the infection resolves with full symptomatic relief, no further intervention is

required. In the setting of the recurrent infected urachal cyst, surgical excision is indicated. In this setting, the entire urachus should be excised including a small area on the dome of the bladder. It is not necessary to remove the umbilicus in absence of malignancy, so long as a proper incision and drainage of any subcutaneous fluid has been performed.

Urachal carcinoma mandates a formal excision of the entire urachus including a partial or radical cystectomy, depending on the extent of bladder involvement. Because these lesions often involve only the dome of the bladder, a partial cystectomy may be sufficient and has been demonstrated to provide equal oncologic efficacy (Herr et al, 2007). In this setting, the entire urachus is removed en bloc with the dome of the bladder inferiorly and the umbilicus superiorly. In addition, wide peritoneal wings are taken to ensure adequate margins. An extended pelvic lymphadenectomy is performed for adequate staging.

Patients with solitary transitional cell carcinomas at the bladder dome or within a bladder diverticulum are potential candidates for partial cystectomy. Patients with multifocal disease are not candidates, mandating thorough cystoscopic evaluation with random bladder and prostatic urethral biopsies.

Technique

Patient Positioning/Port Site Placement

Patients undergoing laparoscopic or robotic partial cystectomy are positioned in the dorsal lithotomy position. The patient is placed into the steep Trendelenburg position to allow the small bowel contents to fall out of the pelvis for better visualization. Port configurations for laparoscopic and robotic partial cystectomy are similar to those used for diverticulectomy (see Fig. 84–3). When performing partial cystectomy for urachal carcinoma and the umbilicus is to be removed, the 12-mm camera port is inserted approximately 5 cm above and 2 cm to the left of the umbilicus.

Cystoscopic Evaluation

Once the patient is positioned and the ports are placed, the operating surgeon should begin with a flexible or rigid cystoscopy. This is done with the robotic/laparoscopic intraperitoneal light turned down so that the surgeon can see the cystoscopic light within the bladder from inside the abdominal cavity. This will allow the surgeon to delineate the involved area of the bladder from an intraperitoneal perspective and ensure adequate margins of resection. The electrocautery can be used to outline the area of resection on the outside of the bladder. Once this is complete, the cystoscope is removed and a Foley catheter is placed.

Surgical Technique

In contrast to conventional open surgery, the urachus is dissected out last. The laparoscopic/robotic surgeon should leave the bladder attached to the anterior abdominal wall during the initial dissection to maximize visualization and exposure. The bladder can be filled with approximately 200 to 300 mL of sterile water to better define the anatomy. Using an electrocautery, the bladder segment to be resected is scored and dissection proceeds through all layers of the bladder with the exception of the bladder mucosa. Before dividing the bladder mucosa, the bladder should be emptied to avoid any spillage of bladder contents into the abdominal cavity. Before dividing the bladder mucosa, the entire urachus with wide peritoneal wings is dissected all the way to the level of the umbilicus. The urachus is divided at this level, and the umbilicus can be removed at the end of the case if necessary. Once the entire urachus is dissected free, the bladder is opened and the entire bladder lesion is excised circumferentially. The specimen is immediately placed in a 10- or 15-cm Endo Catch bag (Covidien, Mansfield, MA). A frozen section analysis is performed on the bladder margin to ensure complete resection. If negative margins cannot be obtained, then a radical cystoprostatectomy is performed. If margins are adequate, the bladder is closed in two layers using a polyglactin suture. A Foley catheter is left in place for 7 days and removed after a negative cystogram. An extended pelvic lymph node dissection is then carried out as described later. The specimen bag is retrieved at the time of umbilical resection through the resultant defect. All port sites are closed, and a pelvic drain is left in place for 24 hours.

Outcomes and Complications

Small series have demonstrated the feasibility of laparoscopic and robotic partial cystectomy for urachal carcinoma. Hospital stay ranges from 2.5 to 4 days in reported series (Wadhwa et al, 2006; Colombo et al, 2008; Park et al, 2008); however, in the authors' experience patients can often be discharged on postoperative day 1 with the Foley catheter in place. With no recurrences at a mean follow-up of up to 28.5 months, preliminary data suggest these techniques to be oncologically sound with minimal complications reported (Wadhwa et al, 2006; Colombo et al, 2008; Park et al, 2008).

Key Points: Partial Cystectomy

- Laparoscopic/robotic partial cystectomy is technically feasible.
- Morbidity is limited.
- The urologic literature is scant in reported series, and oncologic follow-up is short.
- This remains an untested technology in the treatment of urachal or transitional cell carcinoma.
- With the growing popularity of robotic surgery, reported cohorts in the literature will likely grow and confidence in the procedure will increase.

RADICAL CYSTOPROSTATECTOMY

In recent years, minimally invasive techniques have been employed in an attempt to reduce the morbidity of what has traditionally been one of the most invasive of urologic operations: radical cystoprostatectomy. A number of institutions have begun to assess robotic and laparoscopic cystoprostatectomy for the treatment of bladder cancer (Table 84–2). Although emerging data suggest that one can lower the morbidity associated with this procedure, long-term follow-up regarding oncologic outcomes is still lacking. Conventional open radical cystoprostatectomy, therefore, remains the gold standard for invasive bladder cancer, providing for cure in a significant proportion of patients with recurrent superficial bladder cancer and invasive disease alike. The benchmark for oncologic efficacy remains justly high, and any acceptance of new technology must keep this in mind. Sutures and instruments needed for robotic radical prostatectomy are presented in Tables 84–3 and 84–4.

Table 84–2.

Minimally Invasive Cystoprostatectomy

INSTITUTION	AUTHOR	AGE	NO. PTS.	TECHNIQUE	% + MARGIN	MEAN NO. NODES	% ORGAN CONFINED	% ≥ PT3	FOLLOW-UP (mo)	% RECURRENCE RATE	OR TIME (hr)	% PRIOR ABD. SURGERY	COMP. RATE	EBL	MEDIAN LOS	% ILEAL CONDUIT	% EXTRA CORP. DIVERSION
Cornell University	1,2	71	83	Robotic	7.2	17.9	13.3	38.5			6.25	36	41%	460	5.5	49	All
Cleveland Clinic	3			Laparoscopic				28						363			
University of North Carolina	4,5	63.7	50	Robotic	0	19	66	14	13.2	14	5.1			271	4.5	58	All
Rochester General Hospital	6,7	67	54	Robotic	13	17.5	43	55.5			6.1	63	27%	546	9.4	94	All
Guy's Hospital, UK	8,9	64.8	23	Robotic	0	16	74	17.4	17	8.7	6.6		26%	278	11.6	82	All
Henry Ford Hospital	10		17	Robotic							4.3			150		17	All

EBL, estimated blood loss; LOS, length of stay.

From Ng et al (2010), Wang et al (2007), Stephenson and Gill (2008), Pruthi and Wallen (2007), Pruthi et al (2008), Yuh et al (2008), Butt et al (2008), Khan et al (2008), Murphy et al (2008), Menon et al (2003). See references for details.

Table 84–3.

Instrumentation List

SURGEON INSTRUMENTATION		RIGHT ASSISTANT INSTRUMENTATION	LEFT ASSISTANT INSTRUMENTATION
Right Arm (Yellow)	Left Arm (Green)		
Curved monopolar scissors Needle driver	Precise bipolar grasper Needle driver	MicroFrance grasper Laparoscopic scissors Valleylab 10-mm LigaSure Atlas Large Hem-o-Lok clip applier Small Hem-o-Lok clip applier Autosuture Endo Clip 10-mm clip applier 15-mm Autosuture Endo Catch retrieval device 10-mm Autosuture Endo Catch retrieval device (2) Laparoscopic needle driver Laparoscopic Maryland grasper Suction-irrigator	MicroFrance grasper Suction-irrigator (for transposition of left ureter behind sigmoid mesentery)

Table 84–4.

Sutures

SUTURE	LENGTH	NEEDLE	PROCEDURE	NOTE
0-Vicryl tie (secured to large Hem-o-Lok clip)	Full length (24 in)		Used to tag the ureter once it is transected	Dyed and undyed
0-Vicryl	8 in	GS-21	Dorsal vein complex	
2-0 Biosyn (undyed)	10 in	GU-46	Urethral neobladder anastomosis	
2-0 Monocryl (dyed)	10 in	UR-6	Urethral neobladder anastomosis	Sutures are tied together to create a double-armed suture
0-Maxon	Full length	GS-21	Fascial closure of periumbilical incision	
4-0 Biosyn	Full length	P-12	Skin closure	

Technique

Surgical Positioning and Port Placement

Operative setup will, in many cases, be dictated by the specific characteristics of each surgeon's operating room and number of available assistants. When two bedside assistants can be used, our preferred operative setup for robotic radical cystectomy is depicted in Figure 84–12. At least three monitors are required in this setting. The scrub nurse should be positioned on the side of the assistant using the 15-mm port in order to facilitate exchange of clip appliers, sutures, and Endo Catch retrieval bags (Covidien, Mansfield, MA). The console surgeon must have easy access to the operative table to scrub into the procedure at a moment's notice.

The patient is placed in the dorsal lithotomy position using standard operative stirrups (Fig. 84–13). With the table flat, plastic sleds are used to tuck the patient's arms. All pressure points are protected using standard egg-crate foam padding. The patient is secured to the operating table using a cross-shoulder harness made by four strips of egg-crate foam padding. Each strip is 6 × 24 inches, and two strips are used on each side of the patient, creating an X configuration across the patient's chest. The pads are secured to the operating table using cloth tape. Care must be taken not to secure the lower portion of the pads below the costal margin because this may interfere with subsequent lateral port placement. Once the patient is secured to the table, the leg attachment is lowered and the patient is placed in a 30-degree steep Trendelenburg position. The anesthesia team places an orogastric tube to low wall suction for the duration of the case, and foam padding is placed over the patient's face to prevent injury from the camera, particularly when the 30-degree down lens is being used. A Foley catheter is placed on the operative field.

A laparotomy incision for specimen extraction and extracorporeal bowel work is marked. For ileal conduit construction this incision can be periumbilical, whereas a low midline incision can be employed for orthotopic neobladder if the urethral anastomosis is preferred to be created via an open approach. For extended lymphadenectomy and the ability to adequately visualize the aortic bifurcation, as well as maximal cranial dissection of the ureter, the camera trocar is best positioned approximately 25 cm from the pubic symphysis or 5 cm cephalad to the umbilicus. Insufflation of the abdominal cavity is performed using a Veress needle to 15 mm Hg. In particularly obese patients, communication with the anesthesia team is imperative because pneumoperitoneum can result in unacceptably high inspiratory pressure, necessitating a lower abdominal insufflation pressure. A six-trocar approach is employed, as seen in Figure 84–14.

Ureteral Identification and Transection

Technique for robotic cystectomy is described as follows; laparoscopic cystectomy follows essentially the same procedure with differing instrumentation. Dissection is initiated by incising the avascular white line of Toldt on the patient's left. This allows the descending colon to be reflected medially, exposing the retroperitoneal space beneath. This should be carried out as cranially as possible to allow for maximal left ureteral mobilization. The ureter is identified and dissected proximally and distally. An identical dissection is performed on the right side (Fig. 84–15).

Division of the Anterior Pedicle

Once each ureter is dissected as caudally as possible, the identification of the anterior pedicle to the bladder including the superior

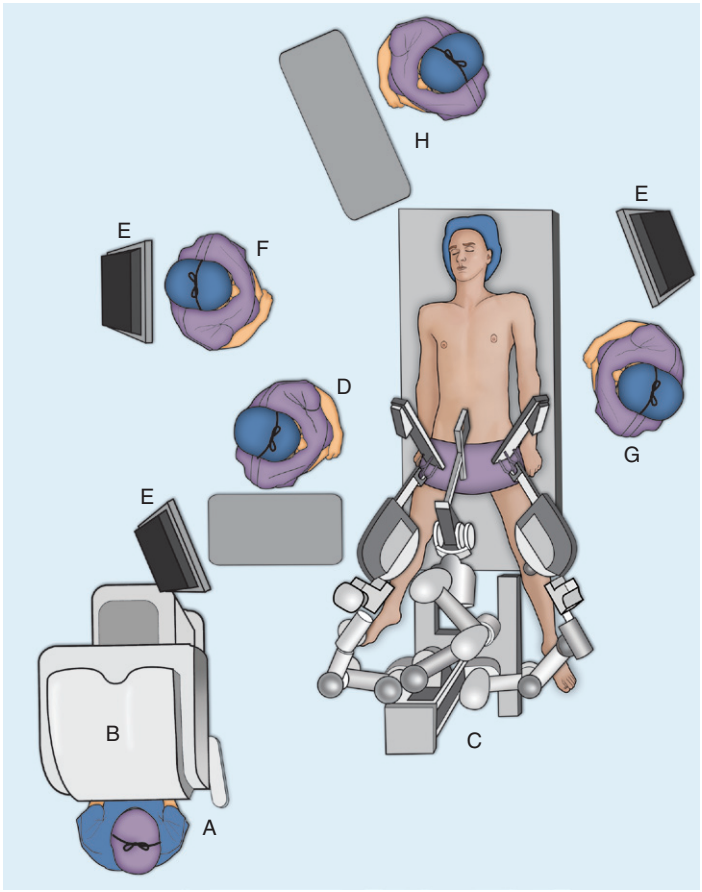


Figure 84–12. Operating room setup for robotic cystoprostatectomy. *A,* Surgeon, *B,* console, *C,* da Vinci system, *D,* scrub nurse, *E,* high-definition monitors, *F,* right assistant, *G,* left assistant, *H,* anesthesia. If using a robotic fourth arm, the authors prefer the solitary bedside assistant to be positioned on the patient's left, with a grasper employed via the fourth robotic arm positioned two fingerbreadths above the right anterior superior iliac spine. When the fourth arm grasper is employed, it can be used opposite the grasper typically in the surgeon's left hand to aim in two-handed grasping and manipulation.

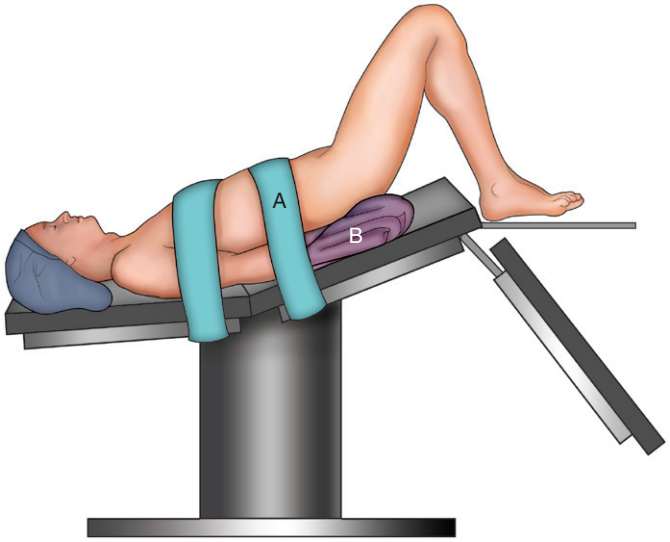


Figure 84–13. Patient is placed in the dorsal lithotomy position using standard operative stirrups. All pressure points are protected using standard egg-crate foam padding. *A,* Cross-shoulder harness made by four strips of egg-crate foam padding. Each strip is 6 × 24 inches, and two strips are used on each side of the patient, creating an X configuration across the patient's chest. The pads are secured to the operating table using cloth tape. *B,* Plastic sleds are used to tuck the patient's arms.

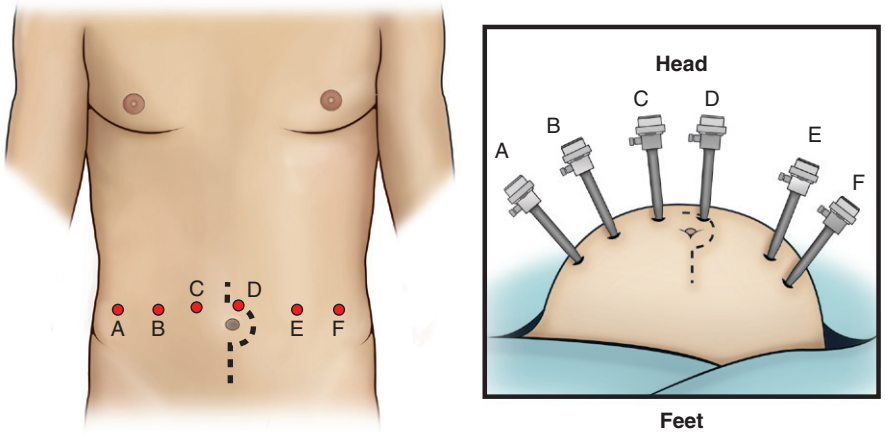


Figure 84–14. Port site placement for cystoprostatectomy. A standard laparotomy incision at the beginning of the case. Insufflation of the abdominal cavity is performed using a Veress needle to 15 mm Hg. Once the abdomen has been insufflated, a 10- to 12-mm, bladed disposable trocar is placed in the periumbilical incision, or 5 cm cephalad when performing extended lymphadectomy *(D)*. All remaining trocars are placed under direct vision. Left and right 8-mm robotic ports *(B, E)* are placed 10 cm lateral to, and 4 cm inferior to, the camera port. A 12-mm trocar is then placed for the bedside assistant port *(A)* in the midaxillary line two fingerbreadths above the anterior superior iliac spine (ASIS); when employing a fourth robotic arm, an 8-mm robotic trocar is placed here, and the 12-mm assistant trocar placed above the left ASIS. A 5-mm disposable or reusable screw-in port, used primarily for suction-irrigation *(C),* is then placed midway between the camera port and the 8-mm robotic port on the ipsilateral side as the primary bedside assistant. This suction port should be placed at the level of the umbilical trocar, or above, to avoid clashing and space limitation between the camera and robotic arm. An extra-long suction adapter aids in reaching the most dependent portions of the pelvis. A 5-mm disposable port can be placed for the second assistant *(F)* in the midaxillary line two fingerbreadths superior to the ASIS.

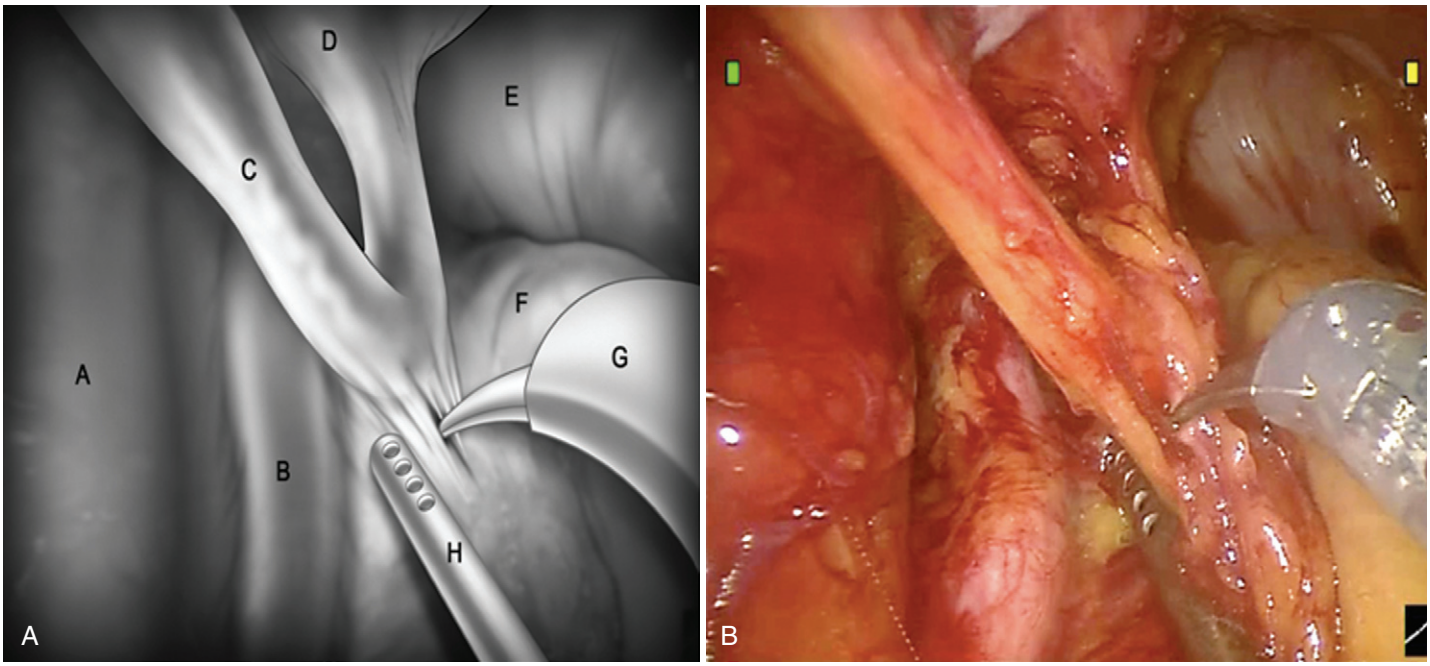


Figure 84–15. **A** and **B,** Dissection of the ureter identification of the ureter, shown here on the patient's left side, begins with retraction of the sigmoid colon by the right bedside assistant (using a MicroFrance grasper) or robotic fourth arm (using a ProGrasp, Intuitive Surgical, Sunnyvale, CA). *A,* Pelvic sidewall and external iliac artery. *B,* Hypogastric artery. *C,* Ureter, retracted anteriorly by left robotic arm. *D,* Bladder and ureteral hiatus. *E,* Rectum. *F,* Sigmoid colon. *G,* Right robotic arm. *H,* Suction-irrigator. The surgeon incises the posterior peritoneum overlying the external iliac artery, where the ureter is most easily identified. The ureter should not be directly grasped by the surgeon or the assistants, and effective ureteral retraction can be accomplished by placing the left robotic grasper beneath the ureter. The ureter is then dissected proximally as high as possible to the level of the upper common iliac artery. Distal dissection is performed to the level of the ureteral hiatus.

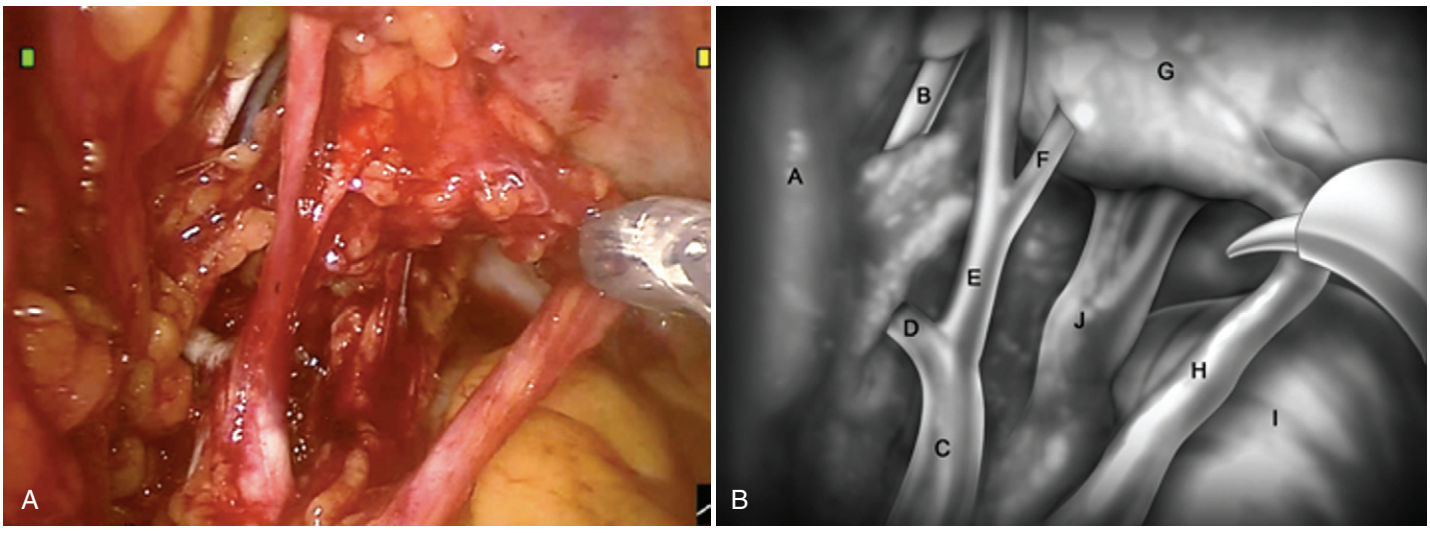


Figure 84–16. **A** and **B,** Development of the anterior pedicle on the patient's left side begins with identifying the avascular plane located between the pelvic side wall and the bladder. *A,* Pelvic side wall; *B,* obturator nerve; *C,* internal iliac (hypogastric) artery; *D,* obturator artery; *E,* superior vesicle artery; *F,* branch off of superior vesicle artery; *G,* bladder; *H,* ureter; *I,* rectum; *J,* posterior pedicle to bladder.

vesicle artery is carried out (Fig. 84–16). This is facilitated by developing the avascular plane between the external iliac vessels and the lateral aspect of the bladder. At the most posterior aspect of this plane is the superior vesicle artery. This vessel can be clipped and divided. In a non–nerve-sparing operation, the remaining anterior pedicle is divided using a 10-mm LigaSure (Valleylab, Boulder, CO) device. In a nerve-sparing operation, surgical clips are employed to avoid the use of electrocautery near the neurovascular bundles. Once the anterior pedicle is divided, this allows for identification of the ureteral hiatus into the bladder. At this point, each ureter is clipped and divided. The proximal clip has a long suture attached to it for identification at a later point in the case. At this point, both vas deferens can be divided as well.

Development of the Posterior Plane

Once both ureters are divided, attention is then paid to separating the bladder off of the rectum (Fig. 84–17). From left to right the posterior peritoneal reflection between the bladder and the rectum

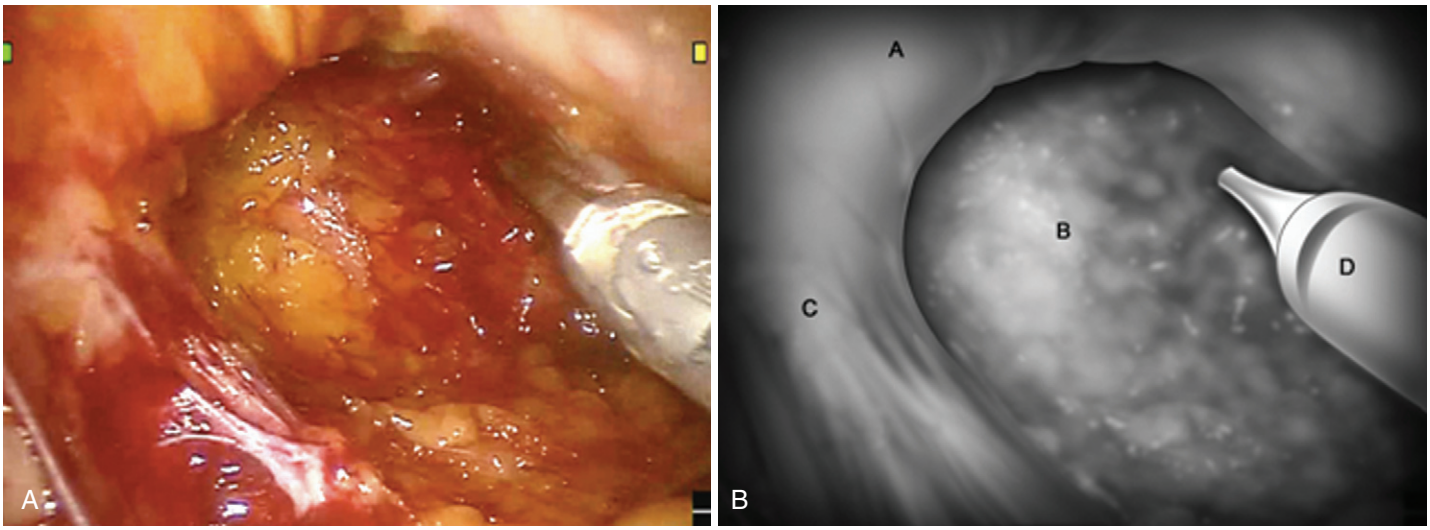


Figure 84–17. **A** and **B,** Once the anterior pedicles are divided, the posterior peritoneal reflection is incised separating the bladder and rectum in the midline. *A,* Bladder. *B,* Rectum. *C,* Left posterior pedicle. *D,* Right robotic arm with monopolar scissors. The left assistant lifts the bladder anteriorly, and the right assistant retracts the posterior peritoneal edge. Using a combination of broad, sweeping motions and electrocautery with the monopolar scissors, one can develop the posterior plane between the bladder and rectum beneath the posterior leaflet of Denonvilliers fascia. This dissection is carried as distally as possible and well beyond the vasa deferentia and seminal vesicles toward the prostatic apex.

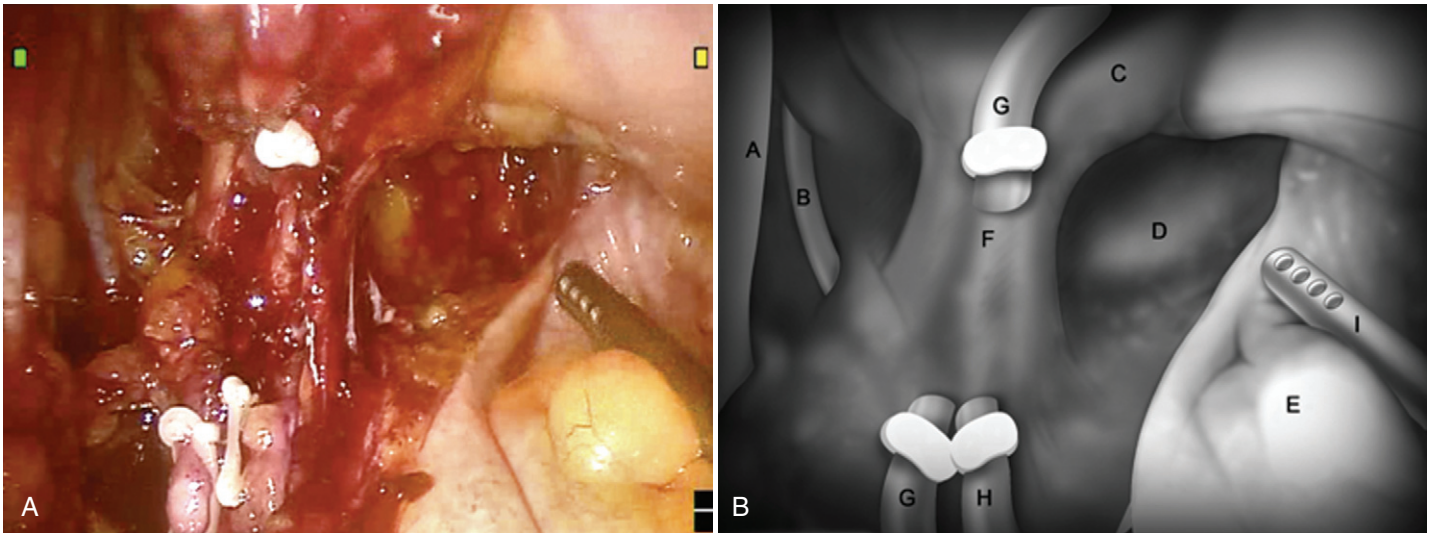


Figure 84–18. **A** and **B,** Development of the plane between the bladder and rectum reveals the posterior pedicle, shown here on the patient's left side. *A,* External iliac vein. *B,* Obturator vein. *C,* Bladder. *D,* Rectum. *E,* Sigmoid colon. *F,* Posterior pedicle. *G,* Superior vesicle artery, cut. *H,* Branch of superior vesicle artery, cut. *I,* Suction-irrigator. The posterior pedicle is located just distal to the previously divided anterior pedicle. Exposure of the left posterior pedicle is facilitated by the bedside assistant (or fourth robotic arm) providing superior and medial traction on the bladder while the remaining assistant provides posterior retraction of the rectum. Division of the posterior pedicle is complete when the endopelvic fascia is encountered.

is divided. The surgeon should be certain to get beneath the posterior leaflet of Denonvilliers fascia in order to ensure an adequate posterior margin. This plan of dissection is carried out as distally as possible, preferably to the level of the prostatic apex. This maneuver will then allow for identification of the posterior pedicles of the bladder. At this point the bladder has *not yet been released* from its attachments on the anterior abdominal wall.

Division of the Posterior Bladder and Prostatic Pedicles

Using a 10-mm LigaSure (Valleylab, Boulder, CO) device or reticulating laparoscopic stapler with 2.5-mm vascular staple loads, the bedside assistant divides the posterior pedicles of the bladder bilaterally (Fig. 84–18). This is carried out as distally as possible. In a nerve-sparing operation, clips and staples are used instead of thermal energy. Once the bladder pedicles are completely divided, the endopelvic fascia is divided on each side. This allows for identification of the prostatic pedicles, which are then divided in a similar fashion (Fig. 84–19). This should proceed as caudally as possible because the posterior plane will be difficult to visualize once the bladder is "dropped" posteriorly.

Dropping of the Bladder

Once the pedicles are completely divided, the bladder can then be released from its anterior abdominal wall attachments (Fig. 84–20). The urachus is first divided just below the level of the

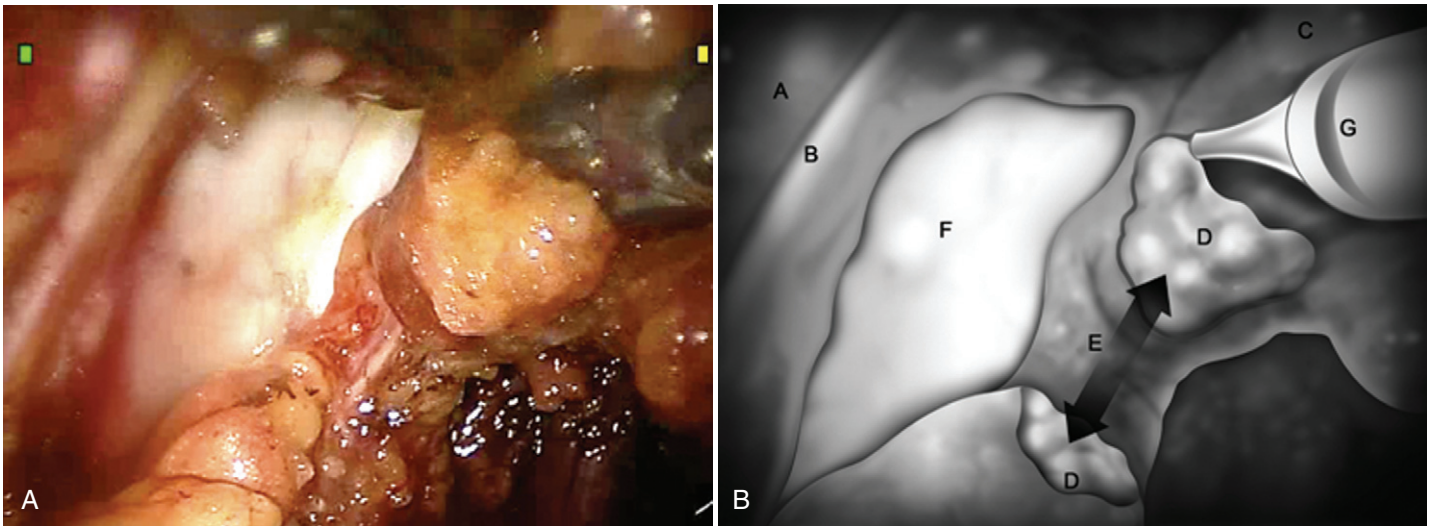


Figure 84–19. **A** and **B,** Adipose tissue overlying the endopelvic fascia, shown here on the patient's left side, is removed by the robotic instruments using sweeping motions. *A,* Pubic bone. *B,* Pectineal line. *C,* Bladder. *D,* Posterior pedicle, cut. *E,* Beginning of prostate pedicle. *F,* Endopelvic fascia. *G,* Right robotic arm. The endopelvic fascia is sharply incised using the robotic scissors. This exposes the prostate pedicles, which are then secured and divided using the LigaSure device in a non–nerve-sparing operation or Hem-o-Lok clips in a nerve-sparing procedure. To avoid injury to the rectum, the right assistant should retract the rectum posteriorly using either the suction or grasper. It is important to carry this dissection as distally as possible because once the bladder is released from its anterior attachments, visualization of the posterior prostatic apex is quite limited.

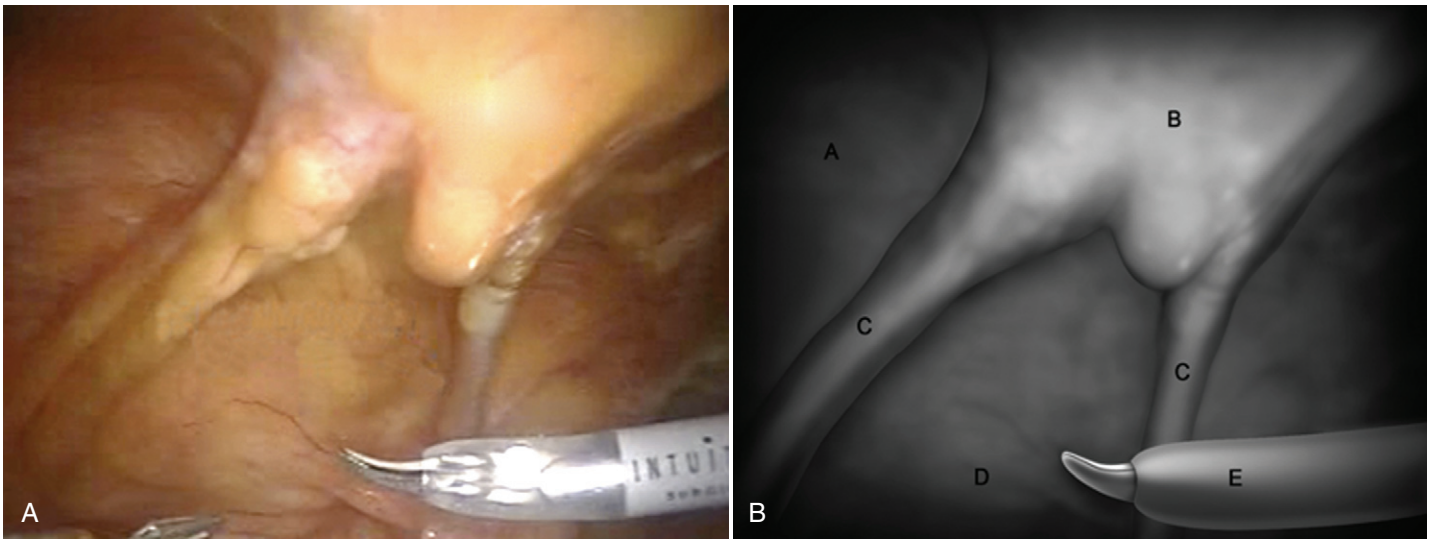


Figure 84–20. **A** and **B,** Dropping the bladder from the anterior abdominal wall. Oncologic principles dictate removal of the urachus with the bladder en bloc with wide peritoneal wings. *A,* Anterior abdominal wall. *B,* Urachus. *C,* Medial umbilical ligaments. *D,* Bladder. *E,* Right robotic arm. The importance of placing the camera port several centimeters superior to the umbilicus at the beginning of the procedure is revealed. If the camera port is not placed superiorly enough, then complete excision of the urachus will be compromised, as will the proximal extent of the subsequent pelvic lymphadenectomy. The medial umbilical ligament on each side is grasped by the contralateral assistant and/or robotic fourth arm. Providing medial retraction, the monopolar scissors are then used to incise the anterior peritoneum. The peritoneum is incised widely in an inferior direction until the pubic bone is exposed.

umbilicus. Wide peritoneal wings are then taken downward, and the median umbilical ligaments are divided as well. The space of Retzius is completely dissected. Any remaining endopelvic fascia is opened at this point. If a nonorthotopic urinary diversion is going to be performed, then the puboprostatic ligaments are divided. In an orthotopic urinary diversion, the puboprostatic ligaments are preserved.

Division of Dorsal Vein Complex

A 0-0 polyglactin suture on a CT-1 needle is passed underneath the dorsal vein complex (DVC), distal to the apex of the prostate (Fig. 84–21). Because urothelial cell carcinoma can involve the prostatic urethra, the entire prostate is removed en bloc with the bladder and prostate-sparing cystectomy is not recommended. Once the DVC is secured, it is then divided. This exposes the underlying urethra. The urethra is then divided distal to the prostatic apex. The Foley catheter is then lifted upward, and a Hem-o-Lok clip is placed over it to prevent any urinary spillage into the operative field. The catheter is then divided distal to the clip, and the assistant pulls the cut catheter in a cranial direction. The posterior urethra is then divided, and any remaining attachments are released. The bladder, prostate, and seminal vesicles are then

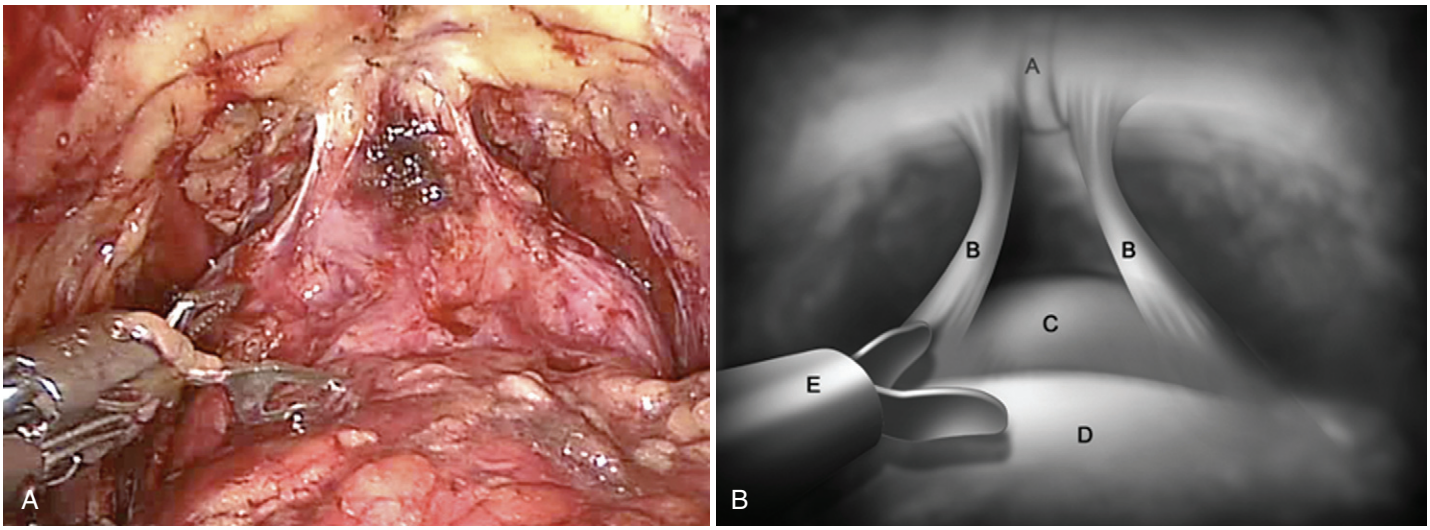


Figure 84–21. **A** and **B,** Transection of the dorsal vein complex (DVC). *A,* Pubic bone. *B,* Puboprostatic ligaments. *C,* Prostate. *D,* Bladder. *E,* Left robotic arm. The puboprostatic ligaments are preserved for orthotopic urinary diversion. For nonorthotopic diversion, the urethra is not preserved and therefore the puboprostatic ligaments are divided for optimal distal dissection. A 0-0 polyglactin suture is placed to secure the DVC. In a non–nerve-sparing cystoprostatectomy, the DVC can be divided with thermal modalities; in nerve-sparing procedures electrocautery is avoided. The urethra is also divided without electrocautery for patients undergoing orthotopic neobladder. With superior traction on the bladder, the anterior half of the urethra is divided and the Foley catheter is pulled into the patient. The catheter is secured with a large Hem-o-Lok clip and then divided, preventing possible tumor spillage. The left assistant provides superior retraction on the prostate and bladder by grasping the cut end of the Foley catheter. Remaining apical attachments are divided, and the bladder, prostate, and seminal vesicles are placed in a 15-mm Endo Catch bag (Covidien, Mansfield, MA).

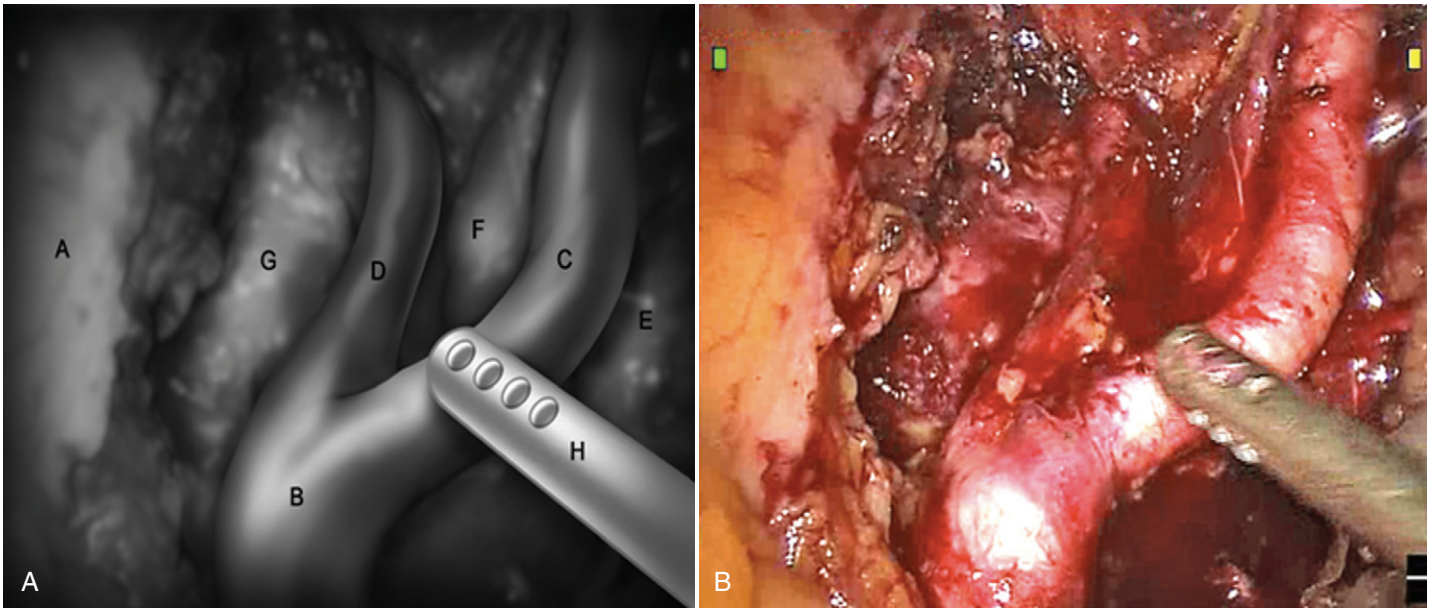


Figure 84–22. **A** and **B,** Extended pelvic lymphadenectomy. Dissection includes a complete removal of lymphatic tissue from the aortic bifurcation to Cooper ligament. Distal dissection shown on patient's right side. *A,* Posterior peritoneum, cut. *B,* Common iliac artery. *C,* External iliac artery. *D,* Hypogastric artery. *E,* External iliac lymph node packet. *F,* Hypogastric lymph node packet. *G,* Presacral lymph node packet. *H,* Suction-irrigator. The contralateral assistant or robotic fourth arm grasper retracts the node packet medially, and the packet is developed proximally. The borders of the pelvic lymphadenectomy include the aortic bifurcation proximally, Cooper ligament inferiorly, the genitofemoral nerve laterally, and the sacral promontory medially. All presacral, hypogastric, external iliac, obturator, and common iliac lymph node packets are removed en bloc and placed in a 10-mm Endo Catch retrieval device (Covidien, Mansfield, MA). The left and right pelvic lymph node packets are placed in separate bags and can be distinguished by placing a Hem-o-Lok clip on one of the retrieval bags.

placed into a 15-cm Endo Catch bag. At this point an extended pelvic lymphadenectomy is performed.

Extended Pelvic Lymph Node Dissection

Dissection is begun on the external iliac artery (Fig. 84–22). All lymphatic tissue is removed between the genitofemoral nerve laterally and the external iliac artery medially. This is carried out from the common iliac bifurcation down to Cooper ligament distally. This is then sent as the "external iliac node package." At this point the internal iliac and obturator nodes are dissected and sent as a separate package. The left colon and right colon are then reflected medially, and the presacral nodes are removed en bloc

and sent to pathology as a separate specimen. Finally, the upper nodes from the aortic bifurcation down to the takeoff of the external iliac artery are removed and sent as the most cephalad node package. This can be performed completely robotically or via a conventional laparoscopic approach. All lymphatic packages are placed in Endo Catch bags and extracted at the end of the case (Woods et al, 2008).

Transposition of Left Ureter to Right Side

A separate plane is developed just anterior to the great vessels underneath the sigmoid colon (Figs. 84–23 and 84–24). A grasping instrument is placed from the right side under the sigmoid mesentery to the left side. The suture on the end of the left ureter is then grasped, and the left ureter is then brought under the sigmoid colon to the right side. At this point, a small 7-cm periumbilical or low midline incision is made and all specimens are retrieved and sent off to pathology for analysis.

Ileal Conduit Urinary Diversion. For an ileal conduit urinary diversion, all surgery from this point forward is performed in a conventional open fashion through the 7-cm periumbilical incision. A Jackson-Pratt drain is left in the pelvis, and bilateral ureteral stents are placed. In addition, a 24-Fr multieyed catheter is placed through the stoma and passed beyond the abdominal wall fascia. This serves to prevent any transient stomal obstruction that may occur with postoperative edema. The stents and stoma catheter are removed before discharge.

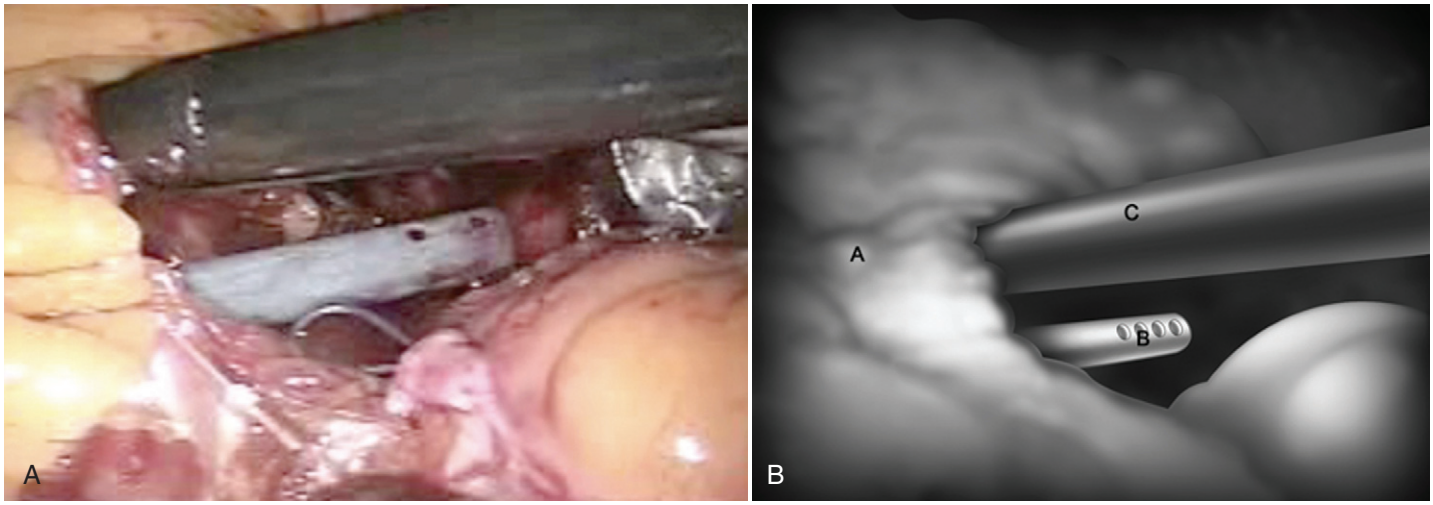


Figure 84–23. **A** and **B,** Transposition of the left ureter under sigmoid colon. The left assistant places the suction-irrigator device through the left 5-mm port. With the right assistant retracting the sigmoid colon with a grasper, the surgeon defines a plane posterior to the sigmoid mesentery and superior to the aortic bifurcation just anterior to the great vessels. The suction device is then passed from left to right along this plane. Further dissection is often necessary on the right side of the sigmoid mesentery to identify the tip of the suction device. *A,* Sigmoid colon. *B,* Suction-irrigator, passed posterior to the sigmoid mesentery from the patient's left to right side. *C,* Right robotic arm, elevating sigmoid colon. The right assistant then passes a laparoscopic Maryland dissector through the 5- to 15-mm port, and the tips of the Maryland are placed firmly into the suction device. The right assistant then directs his or her instrument toward the patient's left side such that the tips of the Maryland dissector can now be found posterior to the sigmoid mesentery on the patient's left side. The 0-0 tie attached to the left ureter is placed in the Maryland grasper, and the left ureter is then brought behind the sigmoid mesentery to the patient's right side.

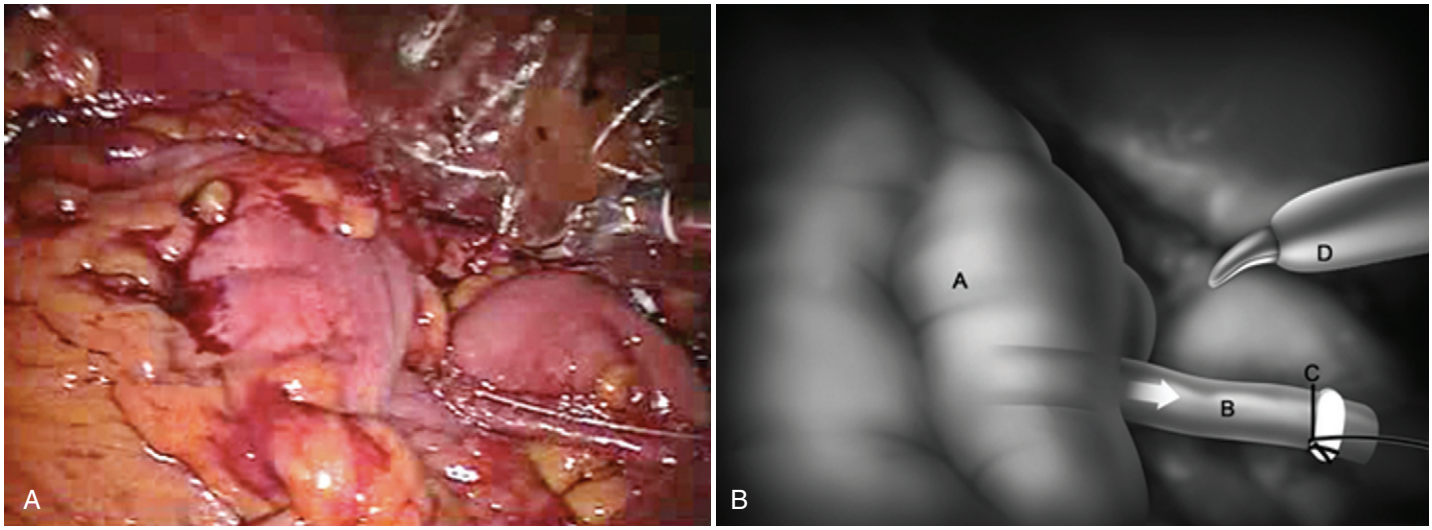


Figure 84–24. **A** and **B,** Completed transposition of the left ureter. *A,* Sigmoid colon. *B,* Left ureter, passed posterior to the sigmoid mesentery and delivered to the patient's right side. *C,* Hem-o-Lok clip with 0-Vicryl tie attached to the cut end of the left ureter. *D,* Right robotic arm.

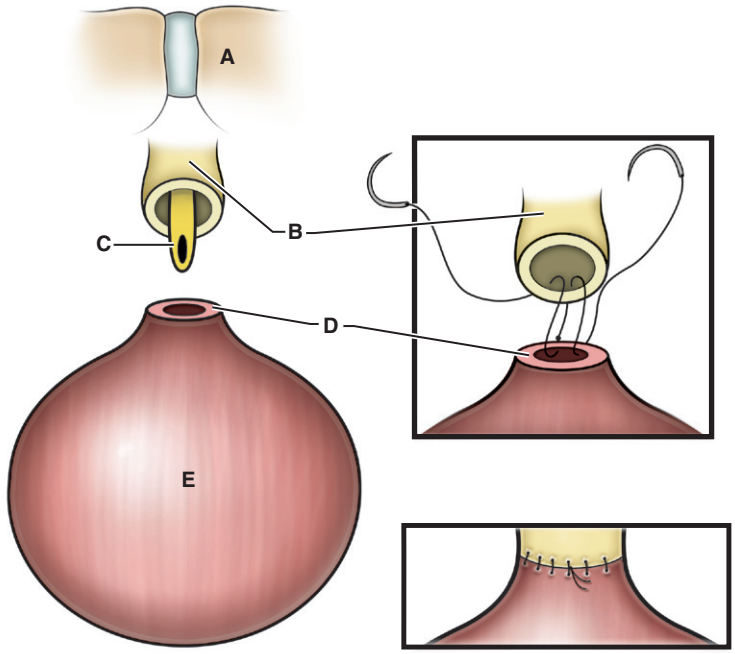


Figure 84–25. For patients undergoing orthotopic neobladder, robotic anastomosis formation can be performed. A Foley catheter is placed per the urethra, and once the catheter is within the neobladder the balloon is inflated with 15 mL of sterile water and placed on mild traction to bring the neobladder in closer proximity to the urethra. The periumbilical anterior rectus fascia incision is then closed in a running fashion, leaving a 1-cm opening at the superior aspect of the wound for replacement of the 10- to 12-mm robotic camera port. The robot is then redocked, and the anastomosis is performed. *A,* Pubic bone. *B,* Urethra. *C,* Foley catheter. *D,* Everted mucosa of neobladder. *E,* Neobladder. A double-armed suture consisting of an undyed 2-0 Biosyn on a GU-46 needle is cut to 10 inches, which is then tied to a 10-inch segment of dyed 2-0 Monocryl on a UR-6 needle. Anastomosis begins at the 6 o'clock position with the dyed 2-0 Monocryl suture. This suture is placed "outside to in" on the neobladder, then "inside to out" on the urethra. After five throws have been placed in a clockwise direction, the suture will be on the inside of the neobladder and the neobladder is brought down to the urethra. The left assistant then grasps the dyed suture and places it on gentle traction to prevent the posterior anastomosis from distracting. The undyed 2-0 Biosyn suture is then placed "outside to in" on the urethra at the 5 o'clock position. This suture is run in a counterclockwise direction until the undyed 2-0 Biosyn is outside the bladder at the 2 o'clock position. The right assistant is then handed the undyed suture, which is placed on gentle traction. The dyed 2-0 Monocryl suture is then run in a clockwise fashion until the suture is outside the urethra at the 12 o'clock position. Both GU needles are then removed, and the anastomosis is secured. At this time, a 15-Fr round Jackson-Pratt drain is placed through the 5-mm left side port. The robot is undocked and the camera port is removed to complete fascial closure of the periumbilical incision. All wounds are copiously irrigated with sterile water and injected with 0.25% bupivacaine. Skin closure is performed in a running subcuticular fashion using 4-0 Biosyn suture on a P-12 needle.

Continent Cutaneous Urinary Diversion (Right Colon Pouch)

At the beginning of the case, conventional laparoscopic instrumentation is used to reflect the entire right colon, ileocecal valve, and transverse colon. This is done early so that the entire continent cutaneous diversion can be performed through the small 7-cm periumbilical incision.

Orthotopic Urinary Diversion

A small 7-cm periumbilical incision is made and the neobladder is created *ex vivo*. All ureteral anastamoses are completed *ex vivo* as well. Once complete, a Foley catheter is placed through the urethra and passed through the neobladder neck (Fig. 84–25). The neobladder is then pulled down inside the abdominal cavity toward the urethra. Following this maneuver, the periumbilical incision is closed and the robot is redocked into position with the patient in steep Trendelenburg position. The urethrovesical anastomosis is then performed robotically using a double-armed 2-0 polyglactin suture in a running fashion. The suprapubic tube and stents are brought out through separate stab wounds in the right lower quadrant. Alternatively, in what some consider to be a time-saving approach that avoids redocking of the robot, a lower midline incision can be employed for specimen extraction and neobladder and ureteral anastomosis formation. Urethrovesical anastomosis can be performed in a traditional open fashion.

Outcomes and Complications

As evidenced in Table 84–1, robotic cystectomy series are relatively few in number. Yet there is a considerable and growing experience at the time of this publication to warrant discussion on outcomes and complications. It is apparent that robotic cystectomy can significantly reduce the morbidity associated with radical cystectomy. Evidence suggests that at least the number of lymph nodes retrieved is comparable with open surgical series, but it remains to be seen as to the quality of the node dissections (Woods et al,

Key Points: Radical Cystoprostatectomy

- Robotic-assisted radical cystectomy represents an evolving field in urology.
- It is certainly one tool that can be used in the treatment of invasive bladder cancer.
- Morbidity is limited, operative time is comparable, and long-term oncologic outcomes are awaited.

2008). Oncologic follow-up is limited with the longest of any series being less than 2 years. Margin status also appears similar to other published open series, and case selection has become less of an issue in interpreting the robotic data.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter 85

Use of Intestinal Segments in Urinary Diversion

Douglas M. Dahl, MD ● W. Scott McDougal, MD, MA (Hon)

Surgical Anatomy
Selecting the Segment of Intestine
Bowel Preparation
Intestinal Anastomoses
Ureterointestinal Anastomoses
Renal Deterioration
Urinary Diversion
Metabolic and Neuromechanical Problems of Urinary Intestinal Diversion
Summary

Reconstructive urologic surgery frequently requires use of bowel for ureteral substitutes, bladder augmentation, or bladder replacement. In rare cases, gastrointestinal segments may also function as urethral or vaginal substitutes. The stomach, jejunum, ileum, and colon each have a potential use in these various procedures. The appropriate use of these intestinal segments requires a thorough knowledge of their surgical anatomy, the methods of preparing the intestine for an operative event, and the techniques for isolating segments of intestine and reconstituting continuity of the enteric tract. Also crucial to success is an understanding of the technical procedures and potential complications of incorporating the intestine into the urinary tract. With this knowledge, reconstruction of the urinary tract may be performed with the proper segment of intestine in the least morbid way. This chapter reviews the technical aspects involved in the use of intestinal segments in urologic surgery that are germane to all types of reconstructive procedures. We review the potential acute and long-term difficulties and complications of the use of intestinal segments in reconstructing the genitourinary tract.

SURGICAL ANATOMY

Please see the Expert Consult website for this section, including Figures 85–1 and 85–2.

SELECTING THE SEGMENT OF INTESTINE

Please see the Expert Consult website for this section.

BOWEL PREPARATION

It has been a long-held tenet of elective intestinal surgery that bowel preparation is appropriate. The bacterial population in the stomach is relatively low, but in the remaining segments of the bowel including the jejunum, ileum, and colon, there are high bacterial counts. Early studies had suggested that bowel anastomoses in the patients whose intestinal tract had not been prepared before surgery had increased wound infection rates, increased intraperitoneal abscesses, and an anastomotic dehiscence rate greater than in those patients who have had proper bowel preparation before surgery (Irvin and Goligher, 1973; Dion et al, 1980). Other studies showed that mechanical preparation resulted in collapsed bowel at the time of surgery, which was shown to reduce the incidence of anastomotic leaks (Christensen and Kronborg, 1981). Studies have recently begun to question the widely held belief that bowel preparation is mandatory. In meta-analyses of randomized clinical trials of anastomotic leakage during colon and rectal surgery, researchers found that there was no support for the conclusion that bowel preparation reduces anastomotic leak rates and other complications (Guenaga et al, 2003; Slim, 2009). There are suggestions that mechanical bowel preparation may actually increase the rate of anastomotic leakage and wound complications (Guenaga et al, 2005).

In experimental animals, it has been shown that an anastomosis with vascular compromise at the anastomotic line, which would normally result in perforation, heals if the bowel has been properly prepared with antibiotics. Also, solid feces may place strain on the anastomosis in the early phase of healing and result in ischemia with subsequent perforation. **Complications that result from bacterial contamination are a major cause of morbidity and mortality in patients undergoing urologic procedures.** Infectious complications after radical cystectomy that are a direct result of fecal contamination may occur in 18% to 20% of patients who undergo radical cystectomy and include wound infections, peritonitis, intra-abdominal abscesses, wound dehiscence, anastomotic dehiscence, and systemic sepsis (Bracken et al, 1981). More recent series suggest that current management practices appear to have made a substantial improvement with perioperative infectious complications of 7% (Stein et al, 2004). In another contemporary series of radical cystectomy with continent or ileal loop urinary diversion in 167 patients, there was an infection complication rate of 7.2% (Mansson et al, 2003). A 5.2% rate of infectious complications was reported in another contemporary series (Cookson et al, 2003).

There are two aspects to bowel preparation, mechanical and antibiotic. Both methods attempt to reduce the complication rate from intestinal surgery. **The mechanical preparation reduces the amount of feces, whereas the antibiotic preparation reduces the bacterial count.** The bacterial flora in the bowel consists of aerobic organisms, the most common of which are *Escherichia coli* and *Enterococcus faecalis,* and anaerobic organisms, the most common of which are *Bacteroides* species and *Clostridium* species. **The bacterial concentration ranges from 10 to 10^5 organisms per gram of fecal content in the jejunum, 10^5 to 10^7 in the distal ileum, 10^6 to 10^8 in the ascending colon, and 10^{10} to 10^{12} in the descending colon.**

Mechanical Bowel Preparation

A mechanical bowel preparation reduces the total number of bacteria but not their concentration. Thus the same number of organisms is present per gram of fecal content (Nichols et al, 1972). Therefore spilling enteric contents during the procedure may be less likely with the mechanically prepared bowel because there is less of it to spill; however, once spilled, cubic centimeter for cubic centimeter, the inoculum is the same as if the bowel had not been prepared. Recent analysis has suggested, however, that there may in fact be an increase in bacterial contamination in patients who have undergone bowel preparation (Fa-Si-Oen et al, 2005).

Conventional bowel preparations commonly used in the past tended to exhaust the patient and exacerbate nutritional depletion because they generally required a 3-day preparation period of insufficient calorie intake (Table 85–1). The use of elemental diets has been advocated to clean the colon of feces while not compromising the nutritional status of the patient. Unfortunately, they have not proved useful because the elemental diets do not empty the colon of feces, and they do not reduce the bacterial flora (Arabi et al, 1978). In an attempt to reduce the time required for intestinal preparation and to obviate low-calorie intakes, whole-gut irrigation has been used. Originally, whole-gut irrigation was performed by placement of a nasogastric tube (NGT) into the stomach and infusion of 9 to 12 L of lactated Ringer solution or normal saline during a several-hour period. These fluids were subsequently replaced with 10% mannitol, which was equally successful in ridding the bowel of its fecal content; however, the mannitol served as a bacterial nutrient and thereby facilitated microbial growth (Hares and Alexander-Williams, 1982). These solutions have largely been replaced by a polyethylene glycol–electrolyte solution. Whole-gut irrigation may be exhausting to the patient and may, in fact, result in a fluid gain, particularly when either saline or mannitol is used. **Whole-gut irrigation is contraindicated in patients with an unstable cardiovascular system, patients with cirrhosis, patients with severe renal disease, patients with congestive heart failure, or those with an obstructed bowel.** Whole-gut irrigation has been found to be no more effective than conventional preparations in reducing wound infections and septic complications (Christensen and Kronborg, 1981), even though there is a reduction of aerobic flora compared with the conventional preparations (van den Bogaard et al, 1981). **The advantages of the whole-gut irrigation are that it gives the patient dietary freedom, there is a short preparation time, and it eliminates the enema. Its disadvantages are that it may result in the patient's exhaustion, it is rather rigorous, and it does result on occasion in fluid overload.**

The polyethylene glycol–electrolyte lavage solution (GoLYTELY or the more palatable NuLYTELY) is an effective lavage agent in preparing the gut for elective colon and rectal surgery, as well as for urologic surgery in which bowel is used. For the adult, 20 to 30 mL/min or approximately 1 to 1.5 L/hr for 3 hours is given either orally or through a small-caliber NGT placed into the stomach. If it is taken by mouth, it is better tolerated if the solution is chilled. The administration of GoLYTELY is stopped when the rectal effluent is clear and there is no particulate matter in it or when 4 L of fluid has been given. This preparation in the adult has been as effective as conventional preparations. The septic complications with its use are approximately 4%. An inadequate preparation occurs in 5% of the patients using this modality (Wolff et al, 1988). For children, even those younger than 1 year, GoLYTELY may be used at a rate of 20 to 40 mL/kg/hour and given until the rectal effluent is clear and free of particulate matter (Tuggle et al, 1987). Metoclopramide (Reglan), 10 mg, in adults is often given simultaneously to control nausea.

Bowel preparation can increase metabolic complications and cause electrolyte disturbances, which could affect surgical care. **Caution must be exercised in elderly and debilitated patients receiving sodium phosphate preparation; the sodium phosphate preparation has been shown to cause significant derangements in potassium, calcium, and phosphorus levels in frail individuals** (Beloosesky et al, 2003). **Phosphate nephropathy has recently been recognized as a serious complication of oral sodium phosphate (OSP) bowel preparation** (Markowitz, 2005). **Caution should be used in prescribing OSP to patients with underlying renal insufficiency or treated with nephrotoxic medications.** The only study in postsurgical complications comparing sodium phosphate with polyethylene glycol found no significant difference in complication rates (Oliveira et al, 1997). One study suggested that polyethylene glycol is better tolerated by elderly patients and causes less disruption in potassium and sodium levels (Seinela et al, 2003). **Oral electrolyte solution rehydration**

Table 85–1.

Mechanical Bowel Preparation

PREOPERATIVE		CONVENTIONAL	POLYETHYLENE GLYCOL–ELECTROLYTE SOLUTIONS	
Day	Diet	Cathartic	Diet	Polyethylene Glycol
3	Low residue plus supplements		Regular plus supplements	
2	Low residue plus supplements		Low residue plus supplements	
1	Clear liquids	250 mL citrate of magnesia at 7 AM and 1 PM	Clear liquids	2 to 4 L (adults) or 25 mL/kg/hr × 2 (children)

may prevent some of the complications of bowel preparation (Tjandra and Tagkalidis, 2004).

A number of studies have questioned the efficacy of mechanical bowel preparation. Some have suggested that a limited mechanical bowel preparation is all that is necessary; others have questioned even the need for a mechanical bowel preparation. In one study, 2 L of polyethylene glycol plus metoclopramide was compared with the administration of 4 L of polyethylene glycol solution. There was no difference in surgical complication rate or the extent to which the bowel was clean (Grundel et al, 1997). In another study, when 4 L of polyethylene glycol was compared with 90 mL of sodium phosphate, there was no significant difference in surgical complication rate (Oliveira et al, 1997). Two meta-analyses have found that there is an increased anastomotic dehiscence rate with preoperative mechanical bowel preparation (Wille-Jorgensen et al, 2003; Bucher et al, 2005). Polyethylene glycol may be the agent responsible for the increased rate of complications, but other preparation strategies have not been adequately analyzed (Slim et al, 2004). A recent meta-analysis of randomized trials comparing mechanical bowel prep to no bowel prep before elective colorectal surgery found no difference between the groups for anastomotic leakage, abdominal abscess, or wound sepsis (Slim, 2009). No study has adequately addressed the issue of the need for debulking of the intestine before laparoscopic approaches to intestinal surgery. It is extremely important to note that in these studies, the administration of intravenous antibiotics was crucial in keeping the complication rate low. Moreover, it is important to note that in these studies there was limited exposure of the intestine as the patients underwent elective bowel resections, unlike urologic procedures in which long segments of the intestine are opened or interposed in a urinary tract that is normally free of fecal contents.

Antibiotic Bowel Preparation

There has been considerable recent controversy as to whether the addition of antibiotics in elective colon and small bowel surgery reduces mortality and morbidity significantly. **The long-held practice of mechanical and oral antibiotic bowel preparation dates to the 1970s.** In one study, the septic complication rate was reduced from 68% in the control group to 8% in the antibiotic group (Washington et al, 1974). Most series, however, report a lesser incidence of reduction in wound infection, generally from 35% without antibiotics to 9% with their use (Clarke et al, 1977). Others have suggested that the mortality rate drops from 9% to 3% with the use of antibiotics (Baum et al, 1981). It is clear that the use of antibiotics protects vulnerable bowel in that it may allow the tenuous anastomosis to survive. Other studies, however, have shown that without the use of oral antibiotics in mechanically prepared bowel in elective surgery, the septic complication rate is comparable with those studies using antibiotics and the rate of *Clostridium difficile* colitis was lower without oral antibiotics (Wren, 2005). In the presence of a bowel obstruction, however, oral antibiotics are of little value because they do little good in sterilizing the bowel. **The disadvantages of antibiotics include postoperative increase in the incidence of diarrhea; pseudomembranous enterocolitis; theoretical increased incidence of tumor implantation at the suture line that is not germane to urologic surgery; monilial overgrowth resulting in stomatitis, thrush, and diarrhea; and, with prolonged use, malabsorption of protein, carbohydrate, and fat.** The antibiotics most commonly used for bowel preparation include kanamycin, which is the best single agent; neomycin and erythromycin base; and neomycin and metronidazole (Table 85–2). With an appropriate antibiotic preparation, enteric organisms are reduced to 10^2 per gram of feces (Nichols et al, 1972). **A contemporary randomized trial of patients undergoing elective colonic surgery found the lowest fecal bacterial concentrations when patients had preoperative mechanical bowel preparation, oral neomycin, and supplemental "synbiotic" treatment (to provide benign flora to the intestine). No difference in clinical infections was seen between patients prepared with or without oral antibiotic bowel preparation** (Reddy, 2007).

Perioperative intravenous antibiotics appear to be the most important means of preventing infectious complications of intestinal surgery. Systemic antibiotics must be given before the operative event if they are to be effective. Ideally, antibiotics should be given between 1 and 2 hours before the start of surgery (Classen et al, 1992). They appear to be most effective against the anaerobic flora and apparently reduce the complications caused by these organisms (Dion et al, 1980). Perioperative systemic antibiotics, when added to the oral regimen, reduced the septic complication rate from 15% to 20% to half that rate in several series (Hares and Alexander-Williams, 1982; Gottrup et al, 1985). Other studies, however, have shown no effect of systemic cephalosporin, for example, in reducing septic complications (Wolff et al, 1988). **If perioperative antibiotics are given, they should be effective against anaerobes because it is complications from these organisms against which perioperative antibiotics appear to be particularly effective.** Third-generation cephalosporins have been advocated as an appropriate systemic antibiotic. Other recent studies support the use of both oral and systemic antibiotic prophylaxis before intestinal surgery (Lewis, 2002). It is clear that preoperative antibiotics reduce postoperative complications. Most agree that preoperative intravenous antibiotics are important, and many advocate discontinuing the use of oral antibiotics as the incidence of *C. difficile* diarrhea is increased and there appears to be no advantage

Table 85–2.
Antibiotic Bowel Preparation

PREOPERATIVE DAY	KANAMYCIN	NEOMYCIN PLUS ERYTHROMYCIN BASE	NEOMYCIN PLUS METRONIDAZOLE
3	1 g kanamycin orally every 1 hr × 4, then 4 times/day	—	—
2	1 g kanamycin orally 4 times/day	—	1 g neomycin 4 times/day plus 750 mg metronidazole 4 times/day
1	1 g kanamycin orally 4 times/day	1 g erythromycin base plus 1 g neomycin at 1 PM, 2 PM, and 11 PM	1 g neomycin 4 times/day plus 750 mg metronidazole 4 times/day

provided preoperative intravenous antibiotics are given within an hour of the operative event (Wren et al, 2005).

It is the authors' preference not to perform a vigorous mechanical bowel preparation allowing the patient a normal diet until one day preoperatively, at which time a clear liquid diet is begun and citrate of magnesia is taken as a cathartic. No oral antibiotic bowel preparation is performed; however, the patient is given intravenous antibiotics 1 hour before the incision.

Diarrhea and Pseudomembranous Enterocolitis

Antibiotic bowel preparations may result in diarrhea and pseudomembranous enterocolitis. Pseudomembranous enterocolitis is the more severe form of a spectrum of diarrhea. Clinically, this occurs after a bowel preparation in the postoperative period and is heralded by abdominal pain and diarrhea usually in the absence of fever or chills. As the symptoms and infection become more severe, systemic toxicity supervenes. **These patients can develop a toxic megacolon, and if this occurs, the mortality may exceed 15% to 20%.** Historically, pseudomembranous enterocolitis was thought to be due to staphylococcus, but there was, in fact, little evidence to support that organism as the etiologic agent. It is now clear that ***C. difficile* plays a significant role in the majority of cases.** *C. difficile* elaborates at least two toxins that cause diarrhea and enterocolitis. *C. difficile* does not invade the bowel, and it is not normally a significant inhabitant of the fecal flora. It is held in check by other bacteria that inhibit its growth. Thus antibiotics destroy the bacteria that inhibit the growth of *C. difficile* and thereby allow it to flourish. The toxin produces a diffuse inflammatory response with cream-colored plaque formation, erythema, and edema of the bowel wall. On microscopic examination, the villi appear to be intact and there is a polymorphonuclear leukocyte infiltrate of the submucosa (Bartlett, 2002).

As the disease progresses, large areas of mucosa may slough and areas of the bowel are denuded of their mucosa. The lesions may involve the colon, in which case it is called *pseudomembranous enterocolitis,* or the small bowel, in which case it is called *pseudomembranous enteritis,* or they may involve both. **The diagnosis is suspected by the symptoms or endoscopy and confirmed by culture of the organism or identification of its toxin. Because culture takes a prolonged time, it is more expeditious and therefore clinically useful to confirm the diagnosis by identifying the toxin produced by *C. difficile*.** Once the diagnosis has been made, **treatment involves the administration of vancomycin or metronidazole and discontinuance of other antibiotics that the patient is receiving.** Vancomycin or metronidazole is effective in most cases. **Rarely, toxic megacolon supervenes, requiring subtotal colectomy as a lifesaving procedure** (Chang, 1985).

INTESTINAL ANASTOMOSES

Regardless of the type of anastomosis or the methods used to perform it, certain fundamental principles must be observed to minimize morbidity and mortality from intestinal surgery. **In urologic procedures in which gut is used, the most common cause of mortality and morbidity within the immediate postoperative period relates to complications involving the bowel,** either with the enteroenterostomy or with the segment interposed in the urinary tract. Therefore it cannot be overemphasized that great care must be taken and proper techniques used in handling bowel in urologic procedures. Unfortunately, the portion of the procedure that involves mobilization of the intestine and reanastomosis often follows a rather lengthy urologic endeavor and is performed when the surgical team is not fresh. Therefore the following principles should be so firmly ingrained in the surgeon that they are performed without the need to recall each one specifically.

The first principle of proper technique for intestinal anastomoses is adequate exposure. The intestine should be mobilized sufficiently so that the anastomosis may be performed without struggling for exposure. If possible, it is preferable to mobilize the intestine sufficiently so that the anastomosis can be performed on the anterior abdominal wall. The area of the anastomosis should be walled off from the rest of the abdominal cavity with Mikulicz pads. This is important so that any inadvertent enteric spills are not distributed throughout the abdominal cavity. The mesentery must be cleared from the bowel segments to be anastomosed for a suitable distance (usually 0.5 cm) from the intestinal clamps or staple line at the severed ends so that good serosal apposition may be achieved without interposed mesentery. Sufficient serosa must be exposed so that the seromuscular sutures or staples can be placed directly in the serosa without traversing the mesentery.

The second principle of performing a proper anastomosis is to maintain a good blood supply to the severed ends of the bowel. The blood supply may be compromised by construction of an anastomosis under tension, excessive dissection or mobilization of the bowel, excessive use of the electrocautery, and tying of the sutures so tight that the intervening tissue is strangulated. A cut margin of bowel that is pink and bleeds freely suggests that the blood supply has not been compromised; however, hemostasis must be ensured before beginning the anastomosis. The site of transection is selected at a point where the blood supply is adequate to both segments. The mesentery should be transilluminated so that the blood supply may be defined before transection of the bowel segment. In urologic surgery, the location of the transection is elective so that an area may be selected in which excellent arcades supply both sections of the transected segment. The area must be selected with an eye to how deep the mesenteric transection must be for proper segment mobility. After location of the appropriate area where the mesentery is to be transected, it is cleaned from the serosa, severed between mosquito clamps, and tied with 4-0 silk sutures. Alternatively, the mesentery may be transected with the LDS staple device (Covidien Surgical, Mansfield, MA), a bipolar cautery device, or ultrasonic shears.

The third principle involves prevention of local spillage of enteric contents. The best way of preventing spills is to operate on bowel properly prepared (i.e., devoid of feces and collapsed). Stripping of the enteric contents between the fingers both cephalad and caudad from the proposed transection site and application of a noncrushing occlusive clamp across the bowel make a spill even less likely. The clamp should prevent enteric contents from exiting the cut ends of the bowel without interference with the mesenteric blood supply. After linen-shod clamps are applied and the area is walled off, Allen clamps are applied to the bowel and the bowel is transected between the Allen clamps. An anastomotic staple device may be used to transect the bowel at this point in place of Allen clamps (see later). Local spills and local sepsis have an adverse effect on the healing anastomosis, and it is for this reason that noncrushing occlusion clamps, in addition to an adequate bowel preparation, are advisable. If a spill does occur, it should be caught in the Mikulicz pads if the bowel has been

properly walled off as described previously. The isolated segment that is to be used in the reconstructive procedure should be irrigated thoroughly with copious amounts of normal saline. The segment should be walled off. The irrigant is placed in one end of the segment and caught in a kidney basin as it exits the other end. This should be continued until the efflux is clear. This procedure prevents local spills during the ureterointestinal anastomosis and other aspects of reconstruction.

The fourth principle, germane to all intestinal anastomoses, is that **there should be an accurate apposition of serosa to serosa of the two segments of bowel to be anastomosed.** The anastomosis should be watertight and performed without tension. The bowel must be handled gently with the use of noncrushing forceps. The anastomotic line should be inverted and not everted. There is considerable controversy about this issue in that an everted anastomosis has been shown to heal with few complications. It is clear that when marginal conditions occur, an inverted anastomosis is more likely to remain intact than is the everted anastomosis.

The fifth principle is not to tie the sutures so tight that the tissue is strangulated. Obviously, the sutures must bring the serosa of the two segments firmly together. Nonabsorbable sutures used for the anastomosis result in a stronger anastomotic line in the early healing phase compared with absorbable sutures, but the difference is minimal and probably not particularly significant.

The final principle involves realignment of the mesentery of the two segments of bowel to be joined. These should be parallel to each other and ensure that there is no twist on completion of the anastomosis.

Factors that significantly contribute to anastomotic breakdown include poor blood supply, local sepsis induced by fecal spillage, drains placed on an intra-abdominal anastomosis, and anastomosis performed in irradiated bowel. Poor blood supply and local sepsis cause ischemia. Drains placed on the anastomosis increase the likelihood of an anastomotic leak, and an anastomosis performed in irradiated bowel is more likely to result in an anastomotic failure than one performed in nonirradiated tissue. The importance of careful technique and adherence to these principles is emphasized by the fact that in one series of urinary intestinal diversion, **75% of the lethal complications that occurred in the postoperative period were related to the bowel. Eighty percent of these patients had received radiation before the intestinal surgery** (Mansson et al, 1979).

Types of Anastomoses

Intestinal anastomoses may be performed with use of sutures or staples. Properly performed, both have similar complication rates (Catena, 2004). In selected circumstances, however, one method may have advantages over the other. **Because there is a high rate of stones that form on surgical staples** (Woodhouse, 2004), **absorbable suture should be used for intestinal segments that are exposed to urine** (e.g., suturing intestine to renal pelvis or bladder, closing the proximal end of a conduit [Costello and Johnson, 1984], and forming an intestinal pouch for urine).

Enteroenterostomy by a Two-Layer Suture Anastomosis

A 3-0 silk holding suture is placed on the mesenteric border just beneath the Allen clamps traversing both segments to be anastomosed, and a second suture is placed on the antimesenteric border similarly just beneath the Allen clamps (Fig. 85–3). It is important that the mesentery is cleaned sufficiently so that these sutures are placed in the serosa under direct vision. A row of silk sutures is placed 2 mm apart between the two holding sutures. This is accomplished by rotating the two Allen clamps away from each other, thus apposing the serosal surfaces. Sutures must traverse the muscularis but should not traverse the full thickness of the bowel. After all sutures have been placed, each is tied and the tails of all the sutures are cut, except those at each end; these are used as holding sutures. The Allen clamps are removed, and hemostasis is achieved, if necessary, with the light application of electrocautery. A 3-0 double-ended chromic intestinal suture is placed in the posterior suture line through all layers and tied to itself. Each end of the suture is then run in a locking fashion away from the midpoint until the mesenteric and antimesenteric borders are approached. As the lateral aspects of the bowel are approached, the suture is converted to a Connell suture (Fig. 85–4), which proceeds onto the anterior bowel wall. The sutures meet anteriorly in the midline and are tied together. The anterior serosa is then apposed with interrupted 3-0 silk sutures. The noncrushing

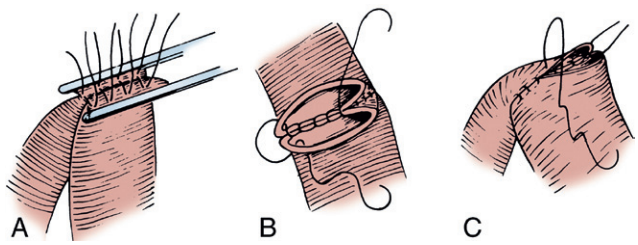


Figure 85–3. Two-layer suture anastomosis. **A,** Two holding sutures of 3-0 silk have been placed at the mesenteric and antimesenteric border, and the posterior wall is approximated with seromuscular sutures of 3-0 silk. **B,** A 3-0 intestinal chromic suture is placed through the full thickness of the bowel posteriorly, tied to itself, and run to the lateral borders with a continuous locking suture. At the lateral borders, it is converted to a Connell suture. **C,** The Connell suture brings the anterior margins together, inverting the suture line. The anastomosis is completed by placement of horizontal mattress seromuscular sutures of 3-0 silk over the anterior suture line (not depicted).

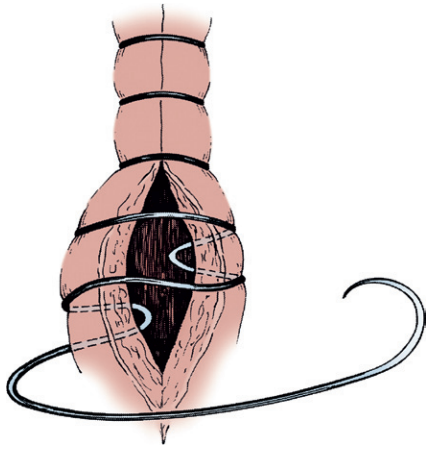


Figure 85–4. Connell suture. The suture traverses the bowel from serosa to mucosa and then from mucosa to serosa on the same side of the anastomosis. The suture is then placed on the opposite side of the anastomosis "outside in-inside out." The sequence is repeated until the two segments are approximated.

occlusive clamps are removed, and the mesentery is closed with interrupted 3-0 silk sutures.

Patency of the anastomosis is ensured by palpating the anastomosis with the thumb and forefinger and feeling an annulus of tissue around the fingers. This anastomotic technique is employed when the antrum pylorus is removed and intestinal continuity is restored by a Billroth I procedure. It is also the most secure of all the anastomoses and should be used when one is forced to do an anastomosis under less than ideal circumstances.

Enteroenterostomy by a Single-Layer Suture Anastomosis

The single-layer anastomosis for reapproximating bowel is an excellent technique with a low complication rate, that is, a 0.2% anastomotic leakage rate compared with an 8.4% anastomotic leakage rate for a stapled anastomosis in one large series (Leslie and Steele, 2003).

The mesenteries of the two segments of bowel to be anastomosed are aligned, and a 3-0 silk suture is passed through the seromuscular layers of both segments on the mesenteric side; a second suture is similarly placed on the antimesenteric side. The mesenteric suture is tied, and the antimesenteric suture is left untied. The Allen clamps are removed, and hemostasis is achieved with light electrocautery. The critical point of the anastomosis, where most leaks occur, is at the mesenteric border. Leaking generally occurs because the sutures are placed carelessly or the serosa has not been cleaned of mesentery sufficiently so that the sutures are placed through it under direct vision. Because this mesenteric border is the critical area, it is approached first. Two 3-0 silk sutures are placed through the full thickness of the bowel on either side of the mesenteric holding suture. These sutures are placed in such a way as to include more serosa than mucosa, thus causing inversion of the suture line (Fig. 85–5A). Some prefer to use a Gambee stitch at this point, which involves placing the suture through the full thickness of the bowel followed by traversing a small segment of mucosa of each segment of bowel before exiting through the full thickness of the bowel of the other segment (Fig. 85–5B). The two bowel sutures on the mesenteric border are tied, with care taken to invert the suture line, thus apposing serosa. Then 3-0 silk sutures are placed 2 mm apart, both on the anterior and posterior walls, inverting the suture line, thus apposing the serosa of the two bowel segments to each other. On approaching the antimesenteric holding suture, several sutures are placed before all are tied. A patent anastomosis is confirmed by feeling the annulus with the thumb and forefinger as described previously.

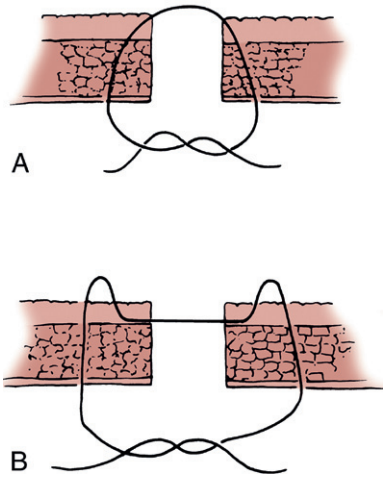


Figure 85–5. **A,** When it is properly placed, the suture through the intestine should include more serosa than mucosa. **B,** The Gambee stitch. The suture is placed through the full thickness of the bowel, the mucosa is traversed, and then the mirror image procedure is performed on the segment to be anastomosed.

End-to-Side Ileocolic Sutured Anastomosis

The transected end of the colon is closed in the following manner (Fig. 85–6). A 3-0 silk suture is placed beneath the Allen clamp on the mesenteric border, and a second suture is placed on the antimesenteric border. These are tied. A 3-0 chromic suture is placed beneath the clamp in a horizontal mattress fashion. Beginning at the mesenteric border, it is tied to itself and the horizontal mattress suture is placed until the antimesenteric border is reached, at which point the suture is again tied to itself. The clamp is removed, and an over-and-over suture is performed with the same chromic suture throughout the full thickness of the bowel until returning to the point of origin (i.e., the mesenteric border is approached). At this point, the suture is again tied to itself. The suture line is buried by approximating the serosa on each side with interrupted 3-0 silk sutures placed 2 mm apart. Our preference is to close the end of the colon similarly to the way one closes the proximal end of a conduit. After a 3-0 silk suture is placed through the serosa on the antimesenteric and mesenteric sides, the clamp is removed and a 3-0 chromic suture is placed through all layers at the mesenteric and antimesenteric end. A Connell suture is used—the two chromic sutures meet in the middle and are tied together. Seromuscular sutures of 3-0 silk are placed to appose the serosal margins.

The mesenteries are aligned, and the ileal serosa is sutured with interrupted 3-0 silk sutures to the colonic serosa 2 mm below a taenia (Fig. 85–7). The taenia is incised the length of the diameter of the ileum adjacent to it. As described earlier for the two-layer anastomosis, a 3-0 double-ended intestinal chromic suture is placed through all layers of the colon and ileum in the midpoint of the posterior wall and run in a locking fashion laterally to either side of the incision in the taenia. At the most lateral border, the suture is converted to a Connell suture and the anterior wall is closed. Seromuscular sutures of 3-0 silk placed from ileum to colon bury the anterior suture line. The mesentery is reapproximated.

Ileocolonic End-to-End Sutured Anastomosis with Discrepant Bowel Sizes

A 3-0 silk suture is placed on the mesenteric border of the ileum and colon (Fig. 85–8). A second 3-0 silk suture is placed on the

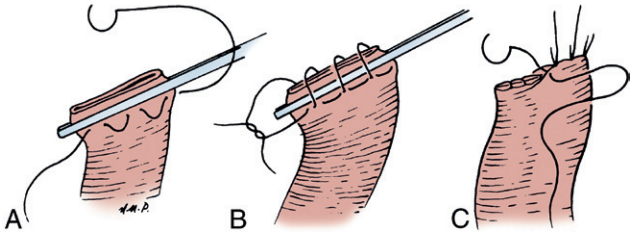


Figure 85–6. Closure of the proximal end of the intestine. **A,** A 3-0 chromic suture is tied to itself at the antimesenteric border and placed beyond the intestinal clamp in a horizontal mattress fashion until the mesenteric border is reached. The suture is then tied to itself at this point. **B,** The intestinal clamp is removed, and an over-and-over suture through the full thickness of the bowel returns the chromic suture to its point of origin, where it is again tied to itself. **C,** Interrupted horizontal mattress seromuscular sutures of 3-0 silk invert the chromic suture line.

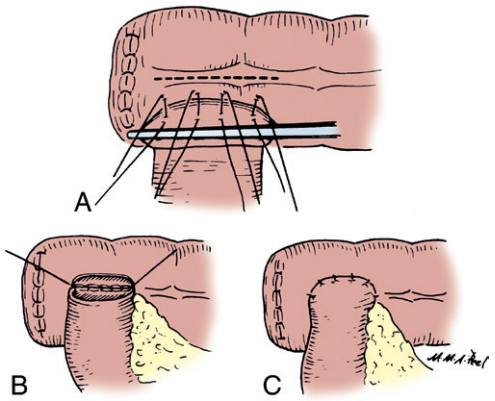


Figure 85–7. End-to-side anastomosis. **A,** The serosa of the ileum is sutured to the serosa of the colon 2 to 3 mm below a taenia. **B,** The taenia is opened for a distance sufficient to accommodate the diameter of the ileum. A 3-0 chromic suture is placed through all layers on the posterior wall, tied to itself, run in a locking fashion to both borders, and converted to a Connell suture laterally, thus completing the inversion anteriorly. **C,** The anterior margin of serosa is reapproximated with interrupted horizontal mattress sutures of 3-0 silk.

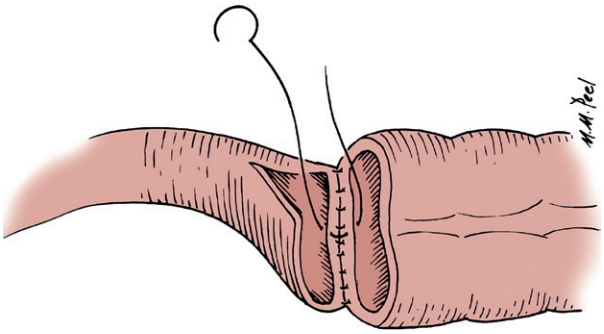


Figure 85–8. Anastomosis of discrepant-sized bowel. A seromuscular suture of 3-0 silk is placed adjacent to each end of the lumen on the mesenteric side. A second 3-0 silk seromuscular suture is placed adjacent to the lumen on the colon and on the antimesenteric border proximal to the cut end of the small bowel at a distance sufficient that when the antimesenteric border is incised, the lumens are the same size. Interrupted seromuscular sutures of 3-0 silk are then placed at 2-mm intervals between the two holding sutures. The small bowel is opened on its antimesenteric border until the opening in the small bowel is the same size as the opening in the colon. A 3-0 chromic suture is placed through all layers, tied to itself, and run laterally in a running locking fashion. At the borders, it is converted to a Connell suture, thus inverting the anterior margin. The anastomosis is completed with interrupted horizontal mattress 3-0 silk sutures that bring the seromuscular layers together anteriorly. This is similar to the closure depicted in Figure 85–3.

antimesenteric border of the colon immediately beneath the Allen clamp. The other end of the suture is placed on the antimesenteric border of the ileum at a distance proximal to the Allen clamp so that the serosal lengths between the two sutures of both ileal and colon segment are equal. Thus an equal amount of ileal serosa is applied to the length of colonic serosa bordering the severed end of bowel. In the seromuscular layers of ileum and colon, 3-0 silk sutures are placed 2 mm apart, thus apposing the serosa of the ileum to the colon. The Allen clamps are removed. Hemostasis is achieved, and the antimesenteric border of the ileum is incised to the level of the most proximal suture in the ileum. Thus the bowel lumens are now of identical size. With a 3-0 chromic double-ended intestinal suture, the posterior row is run in a locking fashion, laterally converting to a Connell suture, and the anterior row is completed. Seromuscular sutures of 3-0 silk bury the anterior suture line.

Stapled Anastomoses

The theoretical benefits of a stapled anastomosis are that it provides for a better blood supply to the healing margin, there is reduced tissue manipulation, there is minimal edema with uniformity of suture placement, a wider lumen is constructed, there is greater ease and less time involved in performing the anastomosis, and the length of postoperative paralytic ileus is reduced. When they are placed in intestine through which urine traverses, however, stapled anastomoses employing nonabsorbable staples frequently cause stone formation and should be avoided (Costello and Johnson, 1984; Woodhouse, 2004).

The TA (transverse anastomosis) stapled anastomosis everts the suture line. Because staples close in a B and do not crush the tissue, theoretically they prevent ischemia at the suture line. This may be obvious when a staple line is used to transect the bowel and bleeding continues to occur. The bleeding points may be lightly electrocoagulated or tied off with fine absorbable suture. Stapled bowel anastomoses have been shown to be as efficacious as hand-sewn anastomoses because both have similar complication rates. **They usually require less time to perform when the techniques are properly learned, but for prolonged procedures, they save little if any time when the length of time for the whole procedure is taken into account.** In a large prospective, randomized trial in which a two-layer closure was compared with a staple closure, it was found that the complication rate was the same, but the time required to complete the stapled anastomosis was 10 minutes less than that for the hand-sewn anastomosis; when the total operative time was compared between the two, it was the same (Didolkar et al, 1986). **A comparison of complications between sutured and stapled anastomoses reveals a leak and fistula rate of 2.8% for stapled and 3% for sutured anastomoses** (Chassin et al, 1978). The clinically significant leak rate, however, is only 0.9% (Fazio et al, 1985). A 4.5% incidence of stapled anastomotic leakage has been reported during ileal conduit construction (Costello and Johnson, 1984).

Thus the use of staples or sutured anastomosis is at the discretion of the surgeon. A stapled anastomosis appears to be superior to a hand-sewn anastomosis in an esophageal-intestinal anastomosis and a low rectal anastomosis. In these two areas, the circular stapler allows a more precise anastomosis than is often possible with hand-sewn techniques. Because these are not problems of urologic surgery, staples are used if that is the preference of the surgeon. The one area in urology where the authors believe the stapling device is superior is in the ileocolonic end-to-side anastomosis. With use of the circular stapling device, a widely patent anastomosis can be achieved expeditiously.

Three staple instruments are commonly employed in intestinal reconstruction: the linear stapler, the anastomotic stapler, and the circular stapler. The linear stapler places a double or triple row of staggered staples in a straight line. Depending on the cartridge and instrument chosen, various lengths of staple lines and heights of the closed staples may be chosen. The length is selected according to how long one wants the staple line to be. **The height of staple is selected according to the tissue to be stapled.** Vascular and pulmonary tissues

require staples with a closed height of 1 mm (open height of 2.5 mm). Most intestinal anastomoses are performed with medium staples, which have a closed height of approximately 1.5 mm (open height of 3.5 mm). On occasion, for thick tissues, large staples are required that have a closed height of 2 mm (open height of 4.8 mm). If there is any doubt in selecting the staple size, the tissue thickness may be measured with a special instrument used for this purpose. In general, **tissues less than 1 mm or more than 3 mm in thickness are not amenable to the use of staples.**

The anastomotic stapler places two linear double rows of staggered staples. When the knife is advanced, the staple line is divided. The height of the staples is also chosen according to the tissue to be transected.

The circular stapler places two concentric, staggered circular staple rows and cuts the tissue within the circle completely from the surrounding tissue. It may be selected in various diameters and with various heights of staples. The diameter and height are selected according to the tissue to be anastomosed. The diameter to be selected is determined by sizing the diameter of the tissue to be stapled. Special sizers are available for this maneuver. In most intestinal anastomoses in urology, the height of the closed staple is 1.5 to 2 mm. The following is a description of various types of stapled anastomoses.

Ileocolonic Anastomosis with the Circular Stapling Device

The mesenteric borders are cleared for a distance of 1.5 cm from the cut end of both the colon and the ileum (Fig. 85–9). Holding sutures of 3-0 silk are placed on the mesenteric and antimesenteric border of the colon. Two other holding sutures are placed on the medial and lateral walls of the colon, midway between the mesenteric and antimesenteric sutures. A purse-string suture of 2-0 polypropylene (Prolene) is placed around the ileum no more than 2 mm from the cut end. It is important to take small bites of mucosa to avoid bunching of tissue. Sutures must be placed evenly to avoid a gap. A purse-string instrument can be used for this step, if preferred. The ileal diameter is determined with sizers so that the correct circular stapler diameter instrument may be chosen—usually 25 mm. A purse-string suture is also placed in a circle, 1 cm in diameter, through which a taenia traverses on the medial aspect of the colon. A stab wound is made in the center of the colonic purse-string suture. The distal anvil of the circular stapler is removed, and the instrument is placed through the open end of the colon with its post passed out the stab wound made in the center of the purse-string on the medial wall of the colon. The purse-string is tied tight. The top anvil is then secured to the post, and the ileum is placed over it. The ileal purse-string is tied.

Care must be taken to align the mesenteries at this point. The instrument is approximated with a staple gap of 1.5 to 2 mm. Care must be taken not to catch fat or mesentery in the gap. The instrument is fired and removed by rotatory movement from the colon. Two doughnuts of tissue should be identified on the instrument, and they should have their complete circumference intact with no gaps. With a finger in the open end of the colon and through the anastomosis, seromuscular sutures of 3-0 silk are placed 3 to 4 mm apart around the circumference of the anastomotic line.

The transected end of the colon may be closed by the suture technique or by the use of staples. If the end is to be closed with sutures, one 3-0 chromic suture is brought out the mesenteric border and another out the antimesenteric border, and both are tied to themselves with the knots on the inside of the bowel. The two sutures are run toward each other with a Connell stitch until they meet, and then they are tied to each other. The suture line is inverted by placement of a second row of 3-0 silk seromuscular sutures. If staples are preferred, the holding sutures are held up and a linear stapler is applied across the open end. Excess tissue is trimmed and the stapler removed. By holding the holding sutures up, one is secure in applying the staple line to the serosa and mucosa circumferentially around the bowel. Some invert the staple line with seromuscular sutures of 3-0 silk. This is not necessary, however. The mesentery between the two segments is now approximated with interrupted 3-0 silk sutures.

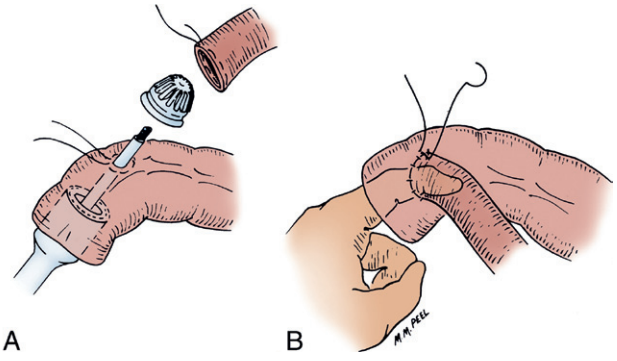


Figure 85–9. Stapled circular anastomosis. **A,** A purse-string suture of 2-0 polypropylene (Prolene) is placed around the circumference of the small bowel, and a second purse-string suture 1 cm in diameter is placed on a medial taenia 5 to 6 cm from the open end of the colon. The anvil is removed. A stab wound is made in the center of the purse-string suture in the colon, and the circular stapler is introduced through the end of the colon, with its post thrust through the stab wound. **B,** The anvil is placed on the post and introduced into the end of the small bowel, the purse-string sutures in the small bowel and colon are tied snugly around the post, and the circular stapler is approximated with a gap of 1.5 to 2 mm, with care taken not to include any mesentery in the gap. The anastomosis is completed by placement of interrupted silk sutures around the circumference of the anastomosis.

End-to-End Stapled Anastomosis: Ileal-Ileal or Ileocolonic Anastomosis

The antimesenteric border of the two bowel segments to be joined is approximated with a 3-0 silk suture 5 to 6 cm from the cut ends of the bowel (Fig. 85–10). A holding suture is placed through both segments of bowel at their cut ends at the midpoint of the antimesenteric borders. Stay sutures are placed at the mesenteric border of each bowel segment, and two other sutures midway between the mesenteric and antimesenteric border on the lateral aspects of the bowel are also placed. The anastomotic stapler is positioned in the lumens of both segments of bowel along the antimesenteric border. The antimesenteric holding suture is pulled up adjacent to the stapler. The anastomotic stapler is locked in place, the staples are fired, and the knife is advanced. The staple lines are inspected for bleeders, which if persistent should be suture ligated with an absorbable suture. It is important for several 3-0 silk sutures to be placed at the apex of the stapled and cut antimesenteric incision. At this point, slight tension on the anastomotic line can place undue stress on the staple margin and cause a leak. The holding sutures are held up, and a linear stapler is placed across the open end of bowel and fired. Care must be taken so that the staples include the serosa in its entire circumference. Excess bowel tissue is excised flush with the instrument before it is disengaged. The mesentery is then reapproximated.

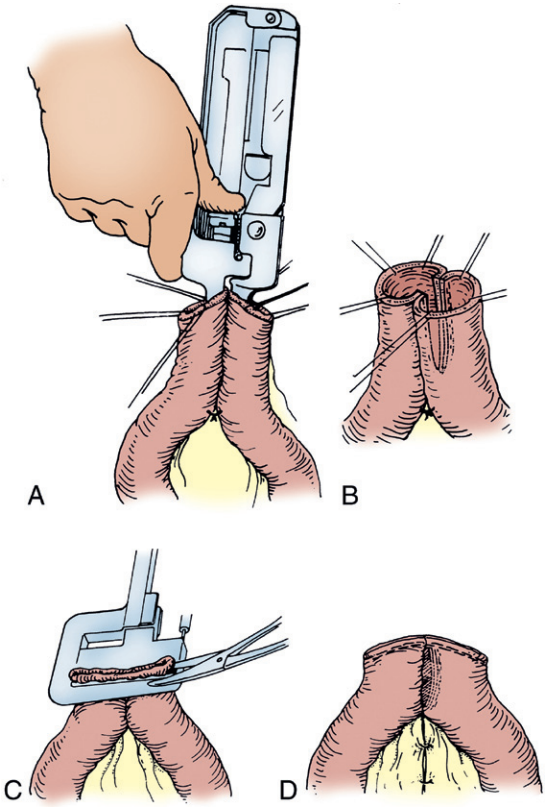


Figure 85–10. Stapled end-to-end anastomosis. **A,** A 3-0 silk suture is placed 5 to 6 cm from the cut ends of the intestine on the antimesenteric borders of both intestinal segments and tied. Holding sutures are placed around the circumference of both intestinal lumens, one suture securing together the antimesenteric borders of both intestinal segments. The linear anastomotic stapler is placed into the lumens, secured and locked in place, and fired. The knife is advanced. **B,** The appearance of the intestinal anastomosis after firing of the staple device. **C,** The open end of the two intestinal segments is closed with a linear stapler by elevation of the holding sutures while the linear stapler is applied so that the circumferences of the mucosa and serosa are incorporated in the staple margin. **D,** The anastomosis is completed by closure of the mesentery with interrupted 3-0 silk sutures.

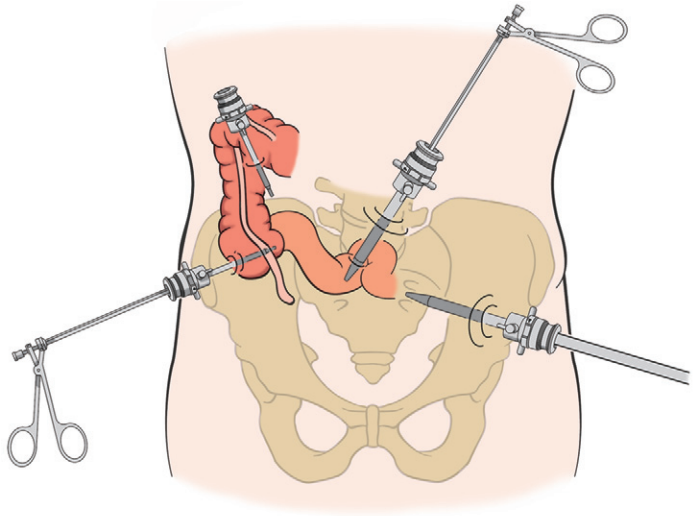


Figure 85–11. Trocar placement for laparoscopic mobilization of the distal ileum.

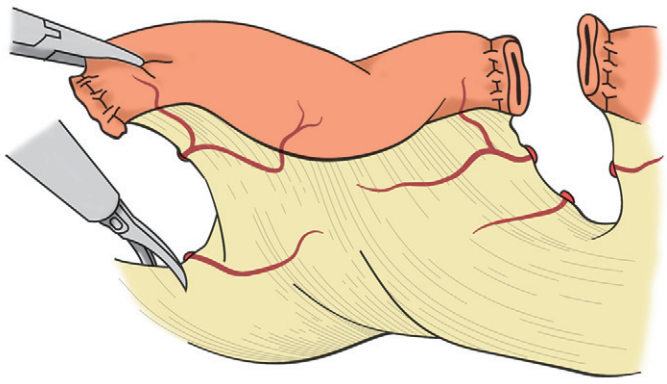


Figure 85–12. Laparoscopic mobilization of a small bowel segment for use in reconstruction. The visceral peritoneum is divided sharply; then the mesenteric vessels are ligated and divided. Staplers, ultrasonic shears, or bipolar cautery devices may be used to divide the mesenteric vessels.

Laparoscopic Anastomoses

Laparoscopic approaches to cystectomy and augmentation cystoplasty have been reported (Gill et al, 2000a, 2002; Guilliotreau, 2009). In these procedures of urinary diversion with continent neobladder or ileal ureter substitution, a purely laparoscopic technique is possible for bowel resection with the use of endoscopic stapling devices. Proper placement of the trocars is dependent on the need to mobilize the bowel and the procedure for which the bowel is to be used. Trocar placement for mobilization of the distal ileum is illustrated in Figure 85–11. The technique primarily involves the use of endoscopic linear cutting and stapling devices, which can be used to divide small bowel and its mesentery (Figs. 85–12 and 85–13). Reanastomosis purely intracorporeally can be accomplished with the same endo-GIA stapler to reconstitute bowel continuity with a side-to-side functional end-to-end anastomosis (Gill et al, 2000b; Potter et al, 2000). An endoscopic TA stapler may be used to complete the bowel closure.

A laparoscopic ileal conduit can be performed with these techniques. The ureterointestinal anastomosis is performed with freehand laparoscopic suturing. One of the abdominal trocar sites is used to draw the bowel segment through the abdominal wall for stoma construction. Completely laparoscopic orthotopic ileal neobladder has been reported (Gill et al, 2002). The neobladder is constructed by freehand running suture with use of laparoscopic techniques (Fig. 85–14). The results of laparoscopic bowel anastomoses suggest that these anastomoses are safe, but no large series that compares open with laparoscopic approaches for bowel anastomosis has been published (Canin-Endres et al, 1999; Rothenberg, 2002).

Other approaches to laparoscopic intestinal surgery include laparoscopic mobilization of the bowel segment and exteriorization of the segment; the anastomosis of the bowel and ureteral anastomoses are then performed in an open fashion through a small laparotomy incision (Fig. 85–15). This is now the preferred approach for many performing laparoscopic cystoprostatectomy. **Purely laparoscopic intestinal anastomoses in radical cystectomy are associated with a much higher complication rate from intestinal and ureteral anastomotic leaks than an exteriorized approach** (Stephenson, 2008). In radical cystectomy, a small incision is already required for intact specimen

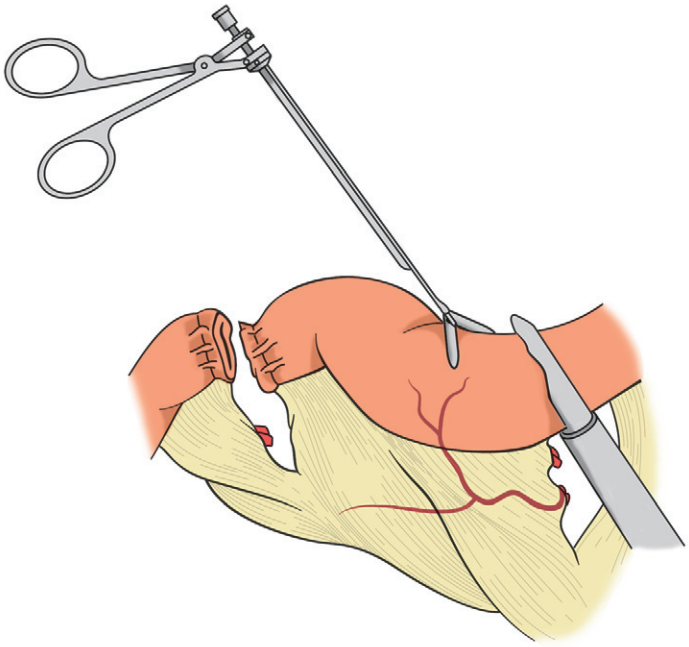


Figure 85–13. The endoscopic gastrointestinal stapler divides the intestinal segment. The staple line must be excised from the segment intended for use in the urinary reconstruction.

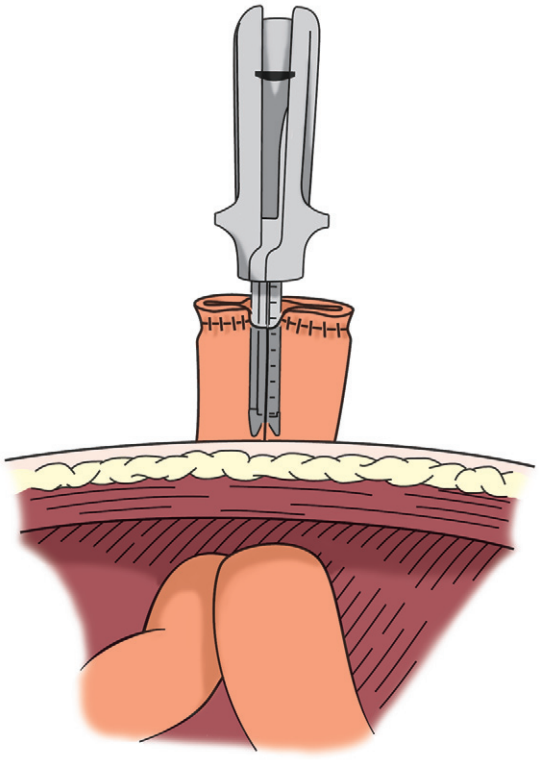


Figure 85–14. Many urologic procedures in which intestinal segments are used for reconstruction involve extirpative surgery in which a small laparotomy is employed for specimen removal. In this case the small laparotomy is used to deliver the bowel segment outside the abdomen. Any form of anastomosis may be employed by this technique, which also reduces the chance of spillage of intestinal contents.

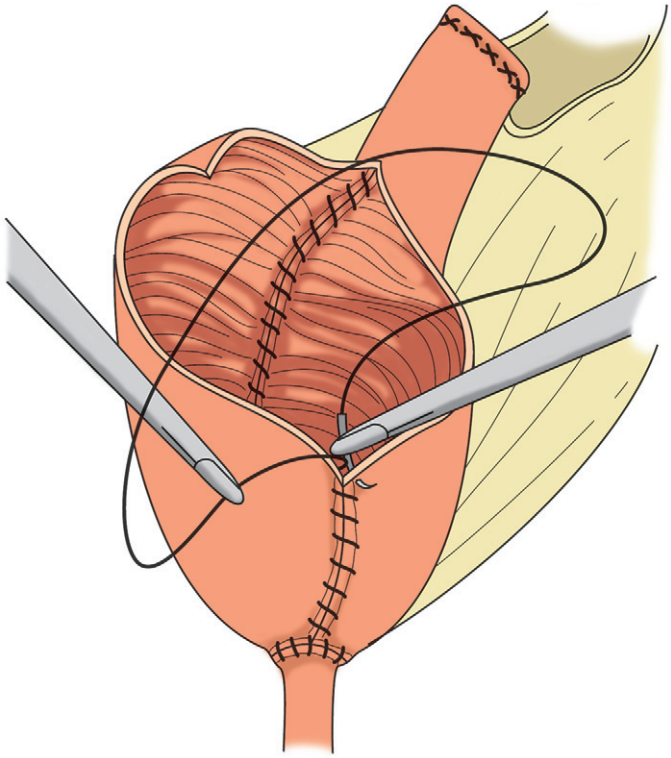


Figure 85–15. Completely intracorporeal laparoscopic construction of a small intestinal neobladder; 2-0 polyglycolic acid suture is employed in a running closure of the pouch.

removal. An open approach therefore allows direct tactile assessment of the anastomoses.

Compression Anastomoses and the Biofragmentable Ring

There is a long history of experimental work on compression anastomoses. These technologies may facilitate natural orifice and minimally invasive surgery. With the most clinical evidence, the biofragmentable ring has proven safe, effective, and time efficient. Several studies have shown that these intestinal anastomoses are as safe as hand-sewn or stapled anastomoses (Ghitulescu et al, 2003). Other compression devices have been devised but have not gained in popularity (Kaidar-Persno, 2008).

Postoperative Care

The patient should not be allowed to begin oral alimentation until bowel function returns after surgery. Coordinated small bowel activity begins within hours after the operative event, and stomach activity may return as early as 24 hours postoperatively. Clear liquids may be begun when the paralytic ileus resolves and bowel activity resumes. If clear liquids are tolerated, the diet may be advanced. This sequence of events generally takes 1 to 4 days. **If the nutritional condition of the patient is impaired preoperatively, a postoperative complication delays oral feeding, or the paralytic ileus is still present on the fifth postoperative day, the patient should receive intravenous nutrition that supplies the total calorie requirement (hyperalimentation). It is preferable to begin the hyperalimentation the day after surgery if any of these**

complications are anticipated. Once started, it is discontinued only when oral intake is sufficient to satisfy the body's calorie requirements. Some have advocated the use of a jejunal feeding tube for the early institution of intestinal feeding (Maffezzini et al, 2008).

The use of nasogastric or gastrostomy decompression during the postoperative period of ileus is somewhat controversial. In a prospective study of elective intestinal anastomoses in which 274 patients had postoperative gastric decompression and 261 patients were given nothing by mouth until bowel activity resumed, **there was no significant difference in major intestinal complications between the two groups; however, those who did not have gastric decompression showed a much greater incidence of abdominal distention, nausea, and vomiting.** It must be understood that only healthy patients with no complications were entered into the study. Sixty percent of the patients initially entered were excluded. Specific exclusion criteria included emergency surgery with peritonitis, extensive fibrous adhesions, enterotomies, previous pelvic irradiation, intra-abdominal infection, pancreatitis, chronic obstruction, prolonged operating time, and difficult endotracheal intubation (Wolff et al, 1988). Meta-analysis of randomized studies of postoperative nasogastric decompression suggests that bowel function returns earlier without a tube. In this study, nonsignificant trends were seen toward fewer pulmonary complications but more wound complications when an NGT was not used (Nelson et al, 2005).

Because of the limitations in the available studies, it is still recommended to use nasogastric decompression in all but the most medically fit patients. Vomiting in the postoperative period increases the risk of aspiration and morbidity in the compromised patient. Moreover, tube decompression allows the administration of ice chips by mouth before enteric activity resumes, thus enhancing the patient's comfort. **If the patient has severe pulmonary disease, decompression by placement of a gastrostomy tube at the time of surgery facilitates pulmonary toilet and enhances comfort. In patients who have significant comorbid conditions such as sepsis, consideration should be given to administration of a histamine (H_2) blocker and an antacid via the stomach tube every 2 hours as needed to keep the gastric pH above 5 during the period of ileus.** By keeping the gastric contents alkaline in these critically ill patients in the postoperative period, the incidence of gastric stress ulceration is markedly reduced.

Because many studies have shown that the absence of an NGT in the postoperative period after intestinal surgery does not increase intestinal anastomotic complications compared with patients in whom NGTs are used, there is a trend to reduce the length of time the NGT is in place. In patients who underwent a radical cystectomy and who were given metoclopramide 10 mg intravenously every 6 hours, until taking fluids orally, the authors found that three quarters of the NGTs could be removed in less than a day. Compared with the standard regimen of NGT drainage, the group given metoclopramide had a much earlier return of bowel function (Donat et al, 1999). More recent studies also support the safety of early NGT removal (Park, 2005).

Complications of Intestinal Anastomoses

The complications that follow anastomoses include leakage of fecal contents, sepsis, wound infections, abdominal abscesses, hemorrhage, anastomotic stenosis, pseudo-obstruction of the colon (Ogilvie syndrome), and intestinal obstruction. These untoward events increase morbidity and are frequently major contributors to mortality. The complication rates for elective colocolonic and ileocolonic anastomoses performed in prepared bowel with contemporary technique are intestinal leak, 2%; hemorrhage, 1%; and stenosis or obstruction, 4%. These complications require reoperations in 1% of the patients and result in death in 0.2% of patients (Jex et al, 1987).

Fistulas

Fistulas in the postoperative period are of two types, fecal and urinary. **These generally occur within the first several weeks after the operative event.** They frequently result in sepsis and markedly increase morbidity and mortality. Fecal fistulas occur in 4% to 5% of patients (Sullivan et al, 1980; Beckley et al, 1982). **Sepsis is a common complication of these untoward events and carries with it a mortality of 2%** (1 of 47 patients) (Hill and Ransley, 1983).

Sepsis and Other Infectious Complications

Wound infections, pelvic abscesses, and wound dehiscences may complicate the immediate postoperative period. Although wound dehiscences and pelvic abscesses are rare complications, morbid wound infections occur with an incidence of 5% (3 of 62 patients) (Loening et al, 1982). Many of these complications may be averted by operating on a properly prepared bowel, by walling off the intestine with Mikulicz pads while the anastomosis is being completed, and by irrigating the intestinal segment to be used in the reconstruction until it is free of any residual enteric contents before it is manipulated and its contents are spilled in the abdomen and pelvis. The overall septicemia rate after radical cystectomy is currently 3.6% with a 17% mortality rate (Davies, 2009).

Bowel Obstruction

The incidence of intestinal obstruction after abdominal procedures for urinary intestinal diversion differs according to whether the stomach, ileum, or colon is used for the diversion. In patients who have had a **segment of stomach or ileum removed for the diversion, there is a 10% incidence of postoperative bowel obstruction requiring treatment.** When the colon is used, the incidence of postoperative obstruction requiring an operation is 5% (Table 85–3). Half of the bowel obstructions occur in the early postoperative period. In one series, after radical cystectomy and ileal conduit, 15% of the patients had a mild obstruction in the first 6 months that responded to conservative management, whereas 3% required an operation to relieve the obstruction during this period. The occurrence of obstruction after this 6-month period was much less frequent (Sullivan et al, 1980). More recently, a 10.5% incidence of reoperation for bowel obstruction was noted in a large series of radical cystectomy patients (Varkarakis, 2006). **Bowel obstruction can be a morbid event: A significant number of patients who develop obstruction after an ileal conduit and require an operation die. The most common cause of the obstruction is adhesions, followed by recurrent cancer.** These two causes account for the great majority of the cases. Volvulus and internal hernia account for far fewer cases (Jaffe et al, 1968). Rarely, severe stenosis or obstruction at the anastomotic suture line occurs. Stenosis is a result of edema, poor technique, or performing the anastomosis on ischemic bowel (Fig. 85–16); obstruction is a result of improper technique.

Table 85–3.

Complications of Urinary Intestinal Diversion*

COMPLICATION	TYPE OF DIVERSION	NO. OF PATIENTS (COMPLICATION/TOTAL NO.)	INCIDENCE (%)
Bowel obstruction	Ileal conduit	124/1289	10
	Colon conduit	9/230	4
	Gastric conduit	2/21	10
	Continent diversion	2/250	4
Ureteral-intestinal obstruction	Ileal conduit	90/1142	8
	Antireflux colon conduit	25/122	20
	Colon conduit	8/92	9
	Continent diversion	16/461	4
Urine leak	Ileal conduit	23/886	3
	Colon conduit	6/130	5
	Continent diversion		
	Ileum	104/629	17
	Colon	5/123	4
Stomal stenosis, hernia	Ileal conduit	196/806	24
	Colon conduit	45/227	20
	Continent diversion	28/310	9
Renal calculi	Ileal conduit	70/964	7
	Antireflux colon conduit	5/94	5
Pouch calculi	Continent diversion	42/317	13
Acidosis requiring treatment	Ileal conduit	46/296	16
	Antireflux colon conduit	5/94	5
	Gastric conduit	0/21	0
	Continent diversion		
	Ileum	21/263	8
	Colon/colon-ileum	17/63	27
Pyelonephritis	Ileal conduit	132/1142	20
	Antireflux colon conduit	13/96	13
	Continent diversion	15/296	5
Renal deterioration	Ileal conduit	146/808	18
	Antireflux colon conduit	15/103	15

*Composite from the literature. Follow-up averages 5 years for ileal conduits, 3 years for colon conduits, 2 years for gastric conduits, and 2 years for continent diversions. From the following sources, which can be found in *Campbell-Walsh Urology, 10th Edition,* on the Expert Consult website: Jaffe et al, 1968; Castro and Ram, 1970; Malek et al, 1971; Smith, 1972; Schmidt et al, 1973; Richie, 1974; Flanigan et al, 1975; Schwarz and Jeffs, 1975; Shapiro et al, 1975; Middleton and Hendren, 1976; Althausen et al, 1978; Elder et al, 1979; Hagen-Cook and Althausen, 1979; Pitts and Muecke, 1979; Sullivan et al, 1980; Beckley et al, 1982; Loening et al, 1982; Adams et al, 1988; Boyd et al, 1989; Madersbacher et al, 2003; Studer 2006; Nieuwenhuijzen, 2008.

The incidence of postoperative bowel obstruction may be reduced by using nonirradiated bowel, performing the anastomosis on well-vascularized bowel, closing all apertures, reperitonealizing the isolated segment, decompressing the gastrointestinal tract for an adequate time, placing omentum over the anastomosis, and reconstituting the pelvic floor after exenterative surgery. The isolated segment is reperitonealized by tacking its antimesenteric border to the lateral abdominal sidewall peritoneum. The proximal mesenteric border should be tacked to the posterior parietal peritoneum because failure to obliterate this potential space has resulted in entrapment of bowel, causing a bowel obstruction. Placing the sigmoid colon in the area may close the pelvic space left after an anterior exenteration. This effectively prevents small bowel from herniating into the raw pelvis. Omentum may also be mobilized and used to fill any space the sigmoid colon does not fill. In a total exenteration, sufficient sigmoid colon is not available and the omentum is often not bulky enough to fill the pelvis and thus prevent small bowel from filling the denuded pelvis. This situation is of particular concern in patients who must receive postoperative pelvic irradiation. The bowel may be kept out of the pelvis in these patients by reconstructing the pelvic floor with polyglactin mesh. The mesh is sutured along the posterior pelvic brim to the sacral promontory and presacral fascia and laterally to the adventitia of the iliac vessels. Laterally and anteriorly, it is sewn to the peritoneum two thirds of the distance between the pubis and umbilicus. Omentum is then brought down, placed over the mesh, and sutured in position. This effectively excludes the bowel from the pelvis for 4 to 6 weeks while postoperative irradiation is being administered (Sener et al, 1989).

Hemorrhage

Hemorrhage is a rare complication of intestinal anastomoses. It is much more likely to occur when stomach is used and a Billroth I anastomosis is constructed. **It is usually due to failure to secure bleeding at the time of anastomosis or anastomotic ulcers that develop on the suture line.**

Intestinal Stenosis

Intestinal stenosis occurs at two distinct times: in the immediate postoperative period and during the long term. Intestinal stenosis in the immediate postoperative period is due to technical mishaps or edema. Edema resolves by continuing the intestinal decompression, whereas technical mishap requires a reoperation. During the



Figure 85–16. Upper gastrointestinal tract series illustrates a small bowel stricture *(arrow)* at the ileoileostomy after ileal conduit urinary diversion. At the time of the initial ileoileostomy, the anastomotic suture line appeared bluish. At subsequent exploration, a bowel lumen of only 2 mm was found. The serosa at the anastomotic site was fibrotic.

long term, it is likely due to ischemia or perienteric infection. Figure 85–16 shows an upper gastrointestinal tract series of a severe intestinal stenosis caused by ischemia. At the time of the ileoileostomy, the suture line was blue. Chronic symptoms of partial small bowel obstruction occurred in the postoperative period.

Pseudo-obstruction

Pseudo-obstruction of the colon, or Ogilvie syndrome, on rare occasion may complicate the early postoperative period. Its cause is not understood. **Pseudo-obstruction usually occurs within the first 3 days postoperatively in patients with multiple medical illnesses.** The patient complains of severe abdominal pain, and a radiograph of the abdomen reveals a dilated cecum. A gentle water-soluble contrast enema eliminates the possibility of a mechanical obstruction. In the presence of a rising leukocyte count or cecum that is increasing in size and exceeds 12 to 15 cm in diameter, rupture may be imminent. Under these circumstances, an emergency cecostomy should be performed (Clayman et al, 1981). In less acute circumstances, endoscopic decompression may be attempted (DeGiorgio, 2009).

Complications of the Isolated Intestinal Segment

Intestinal Stricture

Strictures of intestinal segments are usually late complications primarily occurring in conduits, although they have been described in ileal ureters as well. **The stricture is thought to be a consequence of lymphoid depletion of the intestine exposed to urine.** The lymphoid depletion contributes to persistent infection, which may result in midloop stricture, bacterial seeding of the upper tracts, and renal deterioration (Tapper and Folkman, 1976). Because of the persistent infection and lack of intestinal resistance to the detrimental action of bacteria, submucosal edema with fibrosis and stricture formation occurs. The intestinal segment may also be blocked by encroachment of hypertrophied mesenteric lymph nodes. **Hypertrophied mesenteric lymph nodes, submucosal lymphoid depletion, edema, and fibrosis are commonly found when intestinal segments that have been chronically exposed to urine are examined pathologically.**

Elongation of the Segment

Another complication of the intestinal segment is elongation, occasionally resulting in massive enlargement. When this occurs in conduits or ureteral substitutes, there is usually a distal obstruction. In continent diversions, it may signal failure to catheterize the pouch frequently enough. If allowed to persist, the increased pressure may result in deterioration of renal function. Enlargement and elongation of the intestine may also result in a volvulus of the segment (Fig. 85–17).

Abdominal Stomas

Two types of stomas may be made on the anterior abdominal wall: those that are flush with the skin and those that protrude. The flush stoma is preferable for the continent type of diversion in which intermittent catheterization is carried out and over which a small dressing is placed. The stoma that protrudes is preferable when a collection device is worn. **A properly protruding stoma worn with an appliance results in a lesser incidence of stomal stenosis and a better appliance fit with fewer peristomal skin problems. There are two types of protruding stomas: the end stoma and the loop end ileostomy. Most complications of stomas are the result of technical errors in their construction.** Therefore to minimize such complications, specific technical points must be rigidly followed.

The site of the stoma should be selected preoperatively. This is done by marking the stomal site with the patient in the sitting position, as well as in the supine position; care is taken to place it over the rectus muscle at least 5 cm away from the planned incision line. The point chosen should be well away from skin creases, scars, the umbilicus, belt lines, and bone prominences. A site in which radiotherapy has previously injured the area should be avoided. **All stomas should be placed through the belly of the rectus muscle and be located at the peak of the infraumbilical fat roll.** If the stoma is placed lateral to the rectus sheath, a parastomal hernia is likely to occur. The bowel should traverse the abdominal wall perpendicular to the peritoneal lining (i.e., it should come straight out). One should avoid trimming fat or epiploic appendages from around the margin of

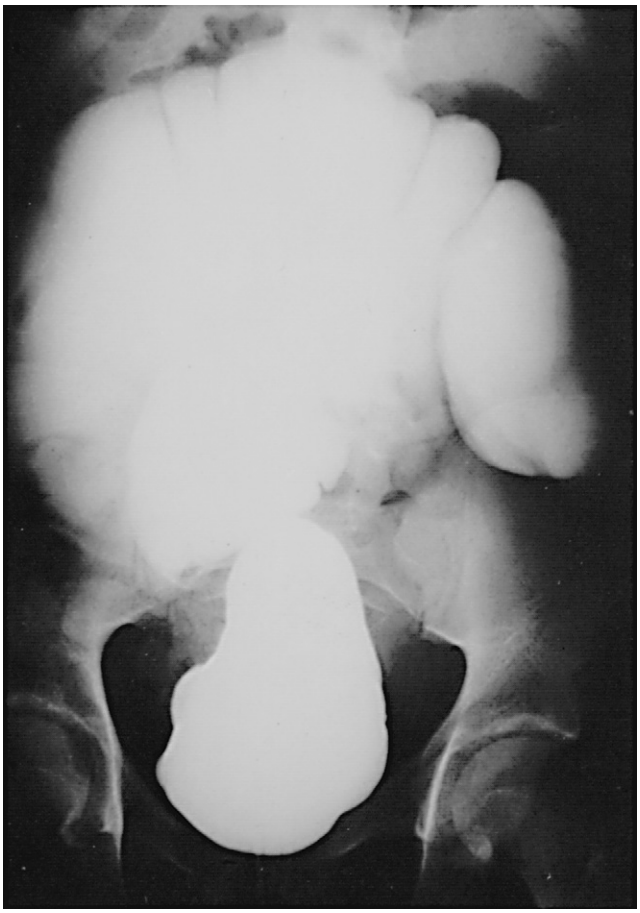


Figure 85–17. Volvulus of an orthotopic right colon bladder. This segment enlarged markedly because of the patient's lack of adherence to a regimen of frequent intermittent catheterization.

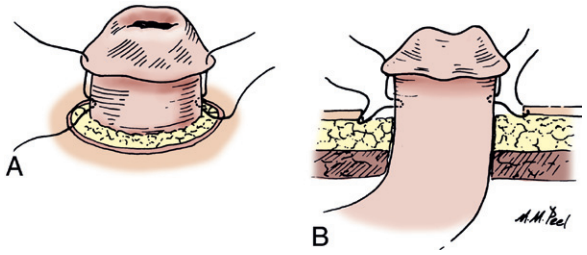


Figure 85–18. **A** and **B,** Nipple stoma. Five to 6 cm of intestine are brought through the abdominal wall. The serosa is scarified, and quadrant 3-0 chromic sutures are placed through the full thickness of the distal end of the intestine. Each suture is placed in the seromuscular layer 3 cm proximal and then secured to the dermis before it is tied.

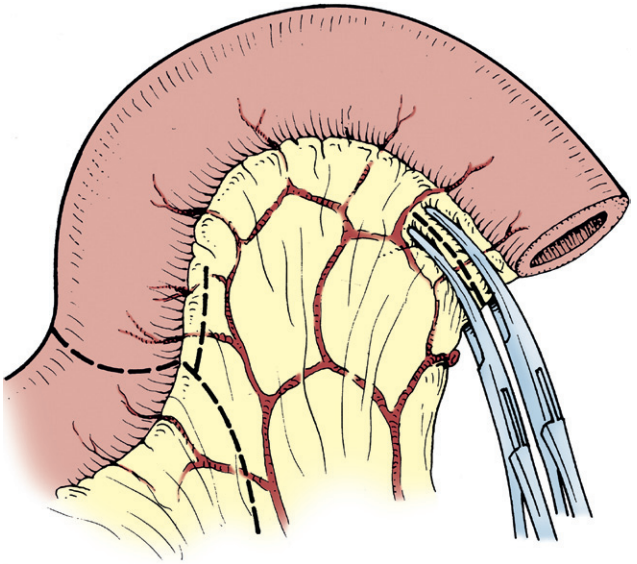


Figure 85–19. If it is tethered by the mesentery, the bowel may be straightened by incising the mesentery several centimeters away from the serosa and parallel to the bowel.

the stoma, and the appliances should be applied in the operating room.

The stoma should be brought through a circular incision made at the predetermined site. A perfectly circular opening in the skin may be made by placing the finger hole of a Kelly clamp at the desired point and grasping the skin in the center of the hole with a Kocher clamp. Pulling up on the Kocher and pushing the handle of the Kelly against the abdominal wall allows for a small button of skin to be removed with a single pass of the knife. This makes a perfectly circular opening in the skin. However, the tendency to remove too much skin is great, resulting in a circular opening that is too large. To avoid this complication, one should not cut the skin flush with the Kelly clamp but rather immediately beneath the Kocher clamp. The subcutaneous tissue is left intact. This is spread, not excising any fat, because the fat falls back adjacent to the bowel and eliminates any dead space. Kocher clamps are placed on the fascia in the incision and pulled medial so that when the fascia and peritoneum are incised, they are incised directly over the skin line and thus do not result in angulation of the gut when the abdominal incision is closed. The fascia is incised in a cruciate manner, and the rectus muscles are spread. The peritoneum is incised. The opening should accommodate two fingers snugly.

Nipple Stoma: "Rosebud"

A Babcock clamp is placed through the opening, and the bowel is grasped and brought out for a distance of 5 to 6 cm to make a nipple of about 2 to 3 cm in length (Fig. 85–18). Two 3-0 chromic sutures are placed through the seromuscular layer of the bowel and the peritoneum on the anterior abdominal wall. Alternatively, the serosa may be sutured to the fascia with two 2-0 chromic sutures. The mesentery is aligned in its normal anatomic direction before the serosa is sutured to the peritoneal wall. The ileum is usually curved concave toward the mesentery. If this is severe, the mesentery may be partially incised 1 cm from the bowel wall (Fig. 85–19). Thus a portion of mesentery is preserved along the entire length of the bowel. This should straighten the curve in the bowel significantly if not completely. Four 3-0 chromic sutures are placed in quadrants through the full thickness of the bowel edge and through the seromuscular layer of the bowel 3 to 4 cm from the cut edge and then through the subcuticular skin layer. Sutures should not traverse the full thickness of the skin but should be placed through the subcuticular and subdermal layers only.

When the sutures are tied, the bowel is everted and forms a nipple. A more secure nipple may be made by performing multiple myotomies through the seromuscular layer of the bowel above the skin line before construction of the nipple. The myotomies adhere serosa to serosa and reduce the risk of stomal retraction. This is particularly appropriate for patients who are obese.

Flush Stoma

Quadrant sutures of 3-0 chromic are placed through the full thickness of the bowel and subsequently passed through the subdermal layer of the skin and tied. Several sutures are placed between the quadrant sutures from bowel to subdermal skin. This constructs a flush stoma that has a 1-mm raised margin.

Loop End Ileostomy

Obese patients have a thick abdominal wall and often a thick, short ileal mesentery. This makes construction of an end ileal stoma extremely difficult. **The loop end ileostomy obviates some of these problems and is usually easier to perform than the ileal end stoma in the patient who is obese** (Fig. 85–20). To construct this type of stoma, the distal end of the ileum is closed as described previously for closing the proximal end of an intestinal segment and a loop is brought up through the belly of the rectus muscle and onto the anterior abdominal wall. This avoids bringing the mesenteric border onto the abdominal wall and prevents one side of the ileostomy from being involved with mesentery. A slightly larger skin opening is required than for the end stoma. A 3-cm disk of skin is removed. The subcutaneous tissue is spread, the fascia incised, the rectus spread, and the peritoneum incised as described earlier. The opening should admit two fingers comfortably. The loop may be pulled through the opening in the abdominal wall by passing an umbilical tape through a small opening in the mesentery at a distance from the distal end that is sufficient to leave that end in the abdomen when the loop has been pulled through the abdominal wall. By gentle traction on the umbilical tape, the loop is brought onto the abdomen.

The distal portion of the bowel is brought through the opening such that the closed end lies cephalad to the body of the segment.

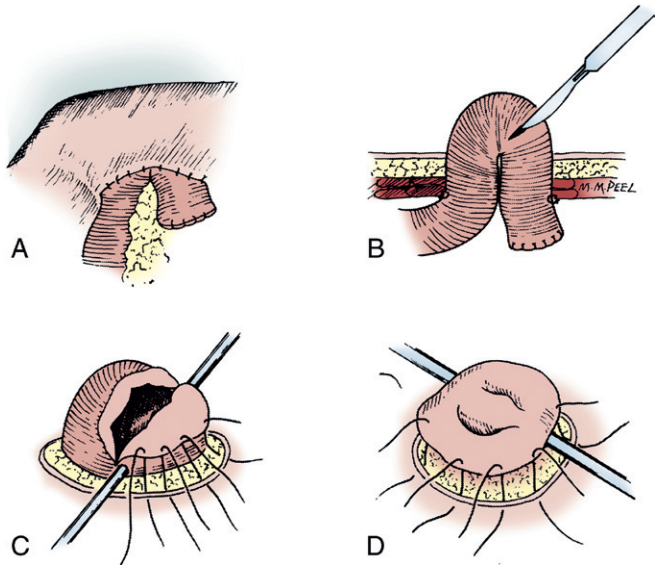


Figure 85–20. Loop end ileostomy. **A,** After the distal end of the loop is closed and the bowel is drawn through the rent in the abdominal wall, the bowel is held in place by a rod passed through the mesentery. The mesentery is realigned, and the peritoneum is sutured to the serosa of the bowel circumferentially. **B,** A transverse incision is made in the bowel four fifths of the loop distance cephalad. **C,** The cephalad portion of the stoma is simply sutured to the dermal layer of skin with interrupted 3-0 chromic sutures. **D,** On the inferior aspect of the incision, 3-0 chromic sutures are placed through the full thickness of the cut edge, then through the seromuscular layer, and then through the dermis. This everts the caudal portion of the stoma.

When a sufficient amount of loop protrudes beyond the skin edge, a small rod is placed through the hole in the mesentery at the apex of the loop and holds the bowel on the anterior abdominal wall during suturing. If the rent in the rectus muscle is too large, it may be closed with interrupted 0 chromic sutures from within the abdomen. The serosa is sutured to the peritoneum on the anterior abdominal wall. The bowel wall is opened in a transverse direction at a point four fifths of the distance cephalad to the most caudal portion of the loop. With 3-0 chromic sutures, the full thickness of the caudal incision in the bowel is sutured back to itself (serosa) and then to the dermis as in the rosebud technique. The cephalad nonfunctional opening is sutured directly to the dermis. The rod is sutured to the skin and left in place for 7 days.

The Turnbull loop stoma results in a lesser incidence of stomal stenosis but a higher incidence of parastomal hernias (Emmott et al, 1985). Overall, the two types of stoma are functionally equivalent over time (Chechile, 1992). Stomas for the colon may be constructed in much the same way as end stomas for the ileum. Their suturing, however, is usually more flush than everted.

Complications of Intestinal Stomas

Complications of the abdominal stoma are the single-most common problem encountered in the postoperative period after urinary intestinal diversion. Early complications of abdominal stomas include bowel necrosis, bleeding, dermatitis, parastomal hernia, prolapse, obstruction, stomal retraction, and stomal stenosis. At some point, virtually every patient has one of these complications. Many of these complications can be reduced by proper construction of the stoma. If periodic visits with the enterostomal therapist are made, products for skin care are appropriately used, nonirritative stomal adhesives are employed, the urine in the collection device is maintained acidic, and properly fitting collection devices are used, most stomal complications can be significantly reduced and many eliminated.

Parastomal skin lesions may be classified as irritative, which are manifested by hypopigmentation, hyperpigmentation, and skin atrophy; erythematous erosive lesions, which appear as macular lesions, scaling of the skin, and loss of the epidermis; and pseudoverrucous, which are wartlike lesions (Borglund et al, 1988).

Stomal stenosis has been reported, on average, in 20% to 24% of patients with ileal conduits and 10% to 20% of patients with colon conduits (see Table 85–3). This incidence has been considerably reduced by better attention to stomal care and better-fitting appliances. Stomal stenosis is less for loop stomas than for end stomas. Parastomal hernias occur rarely (1% to 4%) with end stomas but are more likely to occur with loop stomas, with reported incidences ranging from 4% to 20%. Stenosis of catheterizable stomas is high, reaching to more than 50% in children (Barqawi et al, 2004). Stoma-related complications appear to be more common in an umbilically placed stoma versus one in the abdominal wall (De Ganck et al, 2002). Others have reported excellent long-term results with few complications in the concealed umbilical stoma (Glassman and Docimo, 2001).

Bleeding, stomal stenosis, and dermatitis can be markedly reduced by attention to parastomal skin care and by the use of a properly fitting appliance around a protruding stoma. The other complications are minimized by proper surgical technique.

Parastomal hernia occurs frequently after ileal loop urinary diversion, with an incidence of 2% to 6.6%. It can be effectively treated with open repair (Franks and Hrebinko, 2001; Ho and Fawcett, 2004). Laparoscopic approaches have also been reported

with mixed results. One series reported a 56% failure rate within 6 months of laparoscopic parastomal hernia repair with Gore-Tex mesh (Safadi, 2004). This contrasts with the high success rate reported in another small series (Kozlowski et al, 2001).

Massive bleeding from the conduit occasionally occurs, usually as a result of varices. There have been several interesting reports of patients who have developed ileal conduit varices generally as a result of hepatic dysfunction and portal hypertension. Treatment by transhepatic portal-systemic shunt and transhepatic angiography and embolization is a relatively minimally invasive technique that has promise and is worthwhile using in these difficult patients (Lashley et al, 1997; Medina et al, 1998).

URETEROINTESTINAL ANASTOMOSES

The ureter may be anastomosed to the colon or small bowel in a refluxing or nonrefluxing anastomosis. There is considerable controversy as to whether a nonrefluxing or refluxing anastomosis is desirable in urinary tract reconstruction. Deterioration of the upper tracts for ileal and colon conduits has been reported in 10% to 60% of the patients (Koch et al, 1992; Samuel, 2006). In one series, 49% of the upper tracts showed changes after conduit diversion, 16% of which had an increase of the blood urea nitrogen of 10 mg/dL or more (Schwarz and Jeffs, 1975). **Deterioration of the upper tracts is usually a consequence of lack of ureteral motility, infection, or stones and less commonly due to obstruction at the ureteral-intestinal anastomosis.** Because bacteriuria occurs in almost all conduits and because the intestine certainly does not inhibit and may, in fact, promote bacterial colonization, many have suggested that a nonrefluxing anastomosis would minimize the incidence of renal deterioration.

The evidence that suggests a nonrefluxing system in urinary intestinal diversions is desirable comes from several observations. **In a group of patients who had nonrefluxing colon conduits constructed, those whose anastomoses remained nonrefluxing had a lesser incidence of renal deterioration than did those in whom the antireflux anastomosis failed.** Follow-up for 9 to 20 years revealed that 79% (22 of 28 patients) of the refluxing renal units deteriorated, whereas only 22% (11 of 51 patients) of the nonrefluxing units deteriorated (Elder et al, 1979; Husmann et al, 1989). Others have reported that in continent diversions, the majority of patients who experience reflux show upper tract dilation and deterioration, whereas few show upper tract deterioration when a nonrefluxing anastomosis is present (Kock et al, 1978). Similar findings have been reported in experimental animals.

If a nonrefluxing ureteral-colonic conduit diversion is constructed, only 7% of the renal units show evidence of pyelonephritic scarring after 3 months. If a refluxing anastomosis is constructed, 83% of the renal units show scarring. Half of the conduits in both groups have significant bacteriuria (Richie and Skinner, 1975). **Others have not found the same high incidence of renal deterioration associated with ureteral-intestinal reflux.** One group of investigators studying colon conduits noted no difference in the incidence of renal deterioration regardless of whether the colon conduit demonstrated reflux; 17% (5 of 29) of nonrefluxing renal units showed deterioration compared with 18% (5 of 27) of refluxing units (Hill and Ransley, 1983). In another series, only 3 of 135 renal units with refluxing ureteral-intestinal anastomoses that were unobstructed showed evidence of renal deterioration (Shapiro et al, 1975). A more recent study compared refluxing and nonrefluxing ureteral-intestinal anastomoses in 58 patients with conduit diversions; 56 renal units were refluxing and 60 renal units were nonrefluxing. There was no difference in renal deterioration or in pyelonephritis between the two groups. Ureteral-intestinal stricture formation occurred in 2% of refluxing units as opposed to 13% of nonrefluxing units (Pantuck et al, 2000). A high-capacity, low-pressure reservoir may not require antirefluxing anastomoses (Hohenfellner, 2002).

It does not appear that conduit pressures are transmitted to the renal pelvis. The pressure within the renal pelvis in refluxing conduit diversions is not elevated above normal, and it is not dependent on the segment of bowel used (i.e., ileum or colon) (Magnus, 1977; Kamizaki and Cass, 1978; Hayashi et al, 1986). Peristaltic ureteral contractions apparently dampen pressure transmission from intestine to renal pelvis, attesting to the importance of normal ureters. **When bowel is substituted for the ureter, it does not appear that it makes any difference whether there is reflux at the bladder.** The voiding pressure is blunted by the distensible bowel segment. Indeed, in one study of continent diversions in which a segment of ileum formed the pouch to which the ureters were anastomosed, radionuclide voiding cystography failed to detect reflux to the kidneys (Waidelich et al, 1998). Moreover, there is no difference in ileal and colon conduits between those who experience reflux and those who do not in renal function measured 2 to 5 years postoperatively (Mansson et al, 1984). **Also, the successful construction of an antirefluxing anastomosis does not prevent bacterial colonization of the renal pelvis.** In six of eight patients with nonrefluxing enterocystoplasties and one patient with a nonrefluxing colon conduit in whom the absence of reflux was documented by loopogram, percutaneous renal pelvic aspiration revealed positive cultures (Gonzalez and Reinberg, 1987). **One stated advantage of a refluxing anastomosis in patients who have urothelia and are prone to malignant change is that the upper tracts may be observed by periodic introduction of contrast material into the conduit. From these studies, it appears that reflux associated with impaired ureteral peristalsis in the presence of bacteriuria or obstruction results in renal deterioration, but it has not been established for either conduit or continent diversions that reflux associated with the normal ureter in the absence of obstruction is detrimental to the adult kidney.**

Although many techniques have been described to make the various types of ureterointestinal anastomoses, certain **basic surgical principles are germane to all the anastomoses** regardless of type. **Only as much ureter as needed should be mobilized** so that there is no redundancy or tension on the anastomosis. **Mobilization should not strip the ureter of its periadventitial tissue** because it is in this tissue that the ureter's blood supply courses. The ureter should be cleaned of its adventitial tissue only for 2 to 3 mm at its most distal portion where the ureter-intestinal mucosa anastomosis is to be performed. **The ureterointestinal anastomosis must be performed with fine absorbable sutures, which are placed so that a watertight mucosa-to-mucosa apposition is constructed. The bowel should be brought to the ureter and not vice versa** (i.e., the ureter should not be extensively mobilized so that it can be brought into the wound to the bowel lying on the anterior abdominal wall). **At the completion of the anastomosis, the bowel should be fixed to the abdominal cavity, preferably adjacent to the site of the ureterointestinal anastomosis.** If possible, **the anastomosis should be**

retroperitonealized or a pedicle flap of peritoneum should be placed over the anastomosis.

In those diversions in which the intestinal stoma is brought to the abdomen and the proximal end of the bowel fixed to the retroperitoneum, there are two places where the bowel may be conveniently fixed to the retroperitoneum without jeopardizing mesenteric blood supply. The most convenient point of fixation is below the root of the small bowel mesentery at the level of the pelvic brim. The ureterointestinal anastomosis may be retroperitonealized at the level of the pelvic brim, thus fixing the bowel segment to the posterior body wall. In those situations in which the ureters are short, a more cephalad fixation to the posterior peritoneum may be accomplished by placing the proximal end in the right upper quadrant cephalad to the takeoff of the right colic artery and immediately below the duodenum. This is a relatively avascular area and places the intestine fairly close to the right and left kidneys, thus reducing the length of ureter required to reach the intestinal segment.

Perhaps one of the most difficult complications of ureterointestinal anastomoses to manage is a **stricture. Strictures are generally caused by ischemia, a urine leak, radiation, or infection.** The incidence of urine leak for all types of ureterointestinal anastomoses is 3% to 5% (see Table 85–3). **This incidence of leak can be reduced nearly to zero if soft Silastic stents are used.** In one series of ureterointestinal anastomoses done at the same institution, the nonstented group had a 2% anastomotic leak and a 4% stricture rate. When non-Silastic rigid stents were used, there was a 10% incidence of stricture. When a soft Silastic stent was used, however, there were no strictures or leaks (Regan and Barrett, 1985). In a similar series in which colon conduits were constructed after gynecologic exenterative operations, the nonstented group had an 18% leak rate and an 18% stricture rate, whereas those who had been stented had a 3% leak rate and an 8% stricture rate (Beddoe et al, 1987). Early postoperative metabolic complications were reduced in a randomized study of stented versus nonstented anastomoses (Mattei, 2008). **Thus the evidence indicates that modern soft Silastic stents are effective in reducing the leak rate, subsequent stricture formation, and postoperative complications.** Better technique and better suture materials have also reduced the incidence of stricture in nonrefluxing anastomoses. A series of nonrefluxing ureter-colon anastomoses reported an 8% incidence of stricture formation (Stein et al, 1996).

In constructing a submucosal tunnel in those procedures in which a nonrefluxing anastomosis is made, it is often helpful to inject saline with a 25-gauge needle submucosally to raise the mucosa away from the seromuscular layer. This makes dissection considerably easier (Menon et al, 1982).

These principles of surgical technique are common to all ureterointestinal anastomoses. Each type of ureterointestinal anastomosis, however, has specific technical points unique to its construction. Techniques involving ureter-colon anastomoses are discussed first, followed by ureter–small bowel anastomoses.

Ureterocolonic Anastomoses

Combined Technique of Leadbetter and Clarke

This method establishes a nonrefluxing ureterocolonic anastomosis by employing a submucosal tunnel. The technique combines the ureterocolonic anastomosis of Nesbit, which is a refluxing elliptical anastomosis to the intestine, with the tunneled technique of Coffey (Fig. 85–21) (Leadbetter and Clarke, 1954).

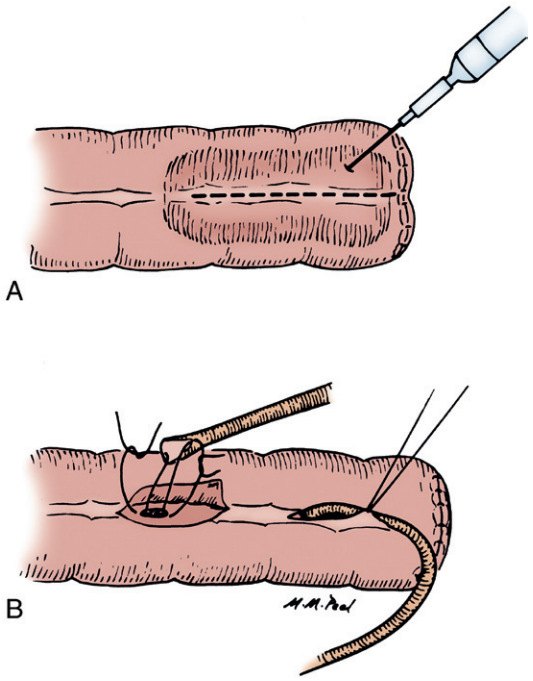


Figure 85–21. Leadbetter-Clarke ureterointestinal anastomosis. **A,** Injection of the submucosal tissues with saline facilitates the dissection. **B,** A linear incision is made in the taenia, the taenia is raised, and the mucosa is identified. A small button of mucosa is removed, and the ureter is spatulated and then sutured to the mucosa with 5-0 PDS. The seromuscular layer is sutured over the ureter, with care taken not to compromise or occlude the ureter.

The anterior taenia is incised obliquely for 2.5 to 3 cm as close to the mesenteric border as possible. The mucosa is dissected off the muscularis for the entire length of the incision. At the distal end of the incision in the taenia, the mucosa is picked up with a fine Adson forceps and a small button is excised. The ureter is spatulated for 5 to 7 mm such that an elliptical anastomosis may be made. The ureter is sewn mucosa to mucosa with 5-0 polydioxanone sutures (PDS) by either interrupted sutures with the knots tied on the outside or a running suture. If the suture line is to be run, it is wise to begin the anastomosis at the apex of the ureter. This suture is tied, and the posterior row is run to the most distal portion of the ureter, which is subsequently tied. A second running suture completes the anterior aspect. The seromuscular layer is then reapproximated loosely over the ureter in such a way as to allow "the ureter [to] lie in the bowel as a hammock without being compressed" (Leadbetter and Clarke, 1954). The bowel should be fixed to the peritoneum so that there is no tension on the ureters.

The complications reported with this procedure include a leak rate of 2.5%; deterioration of the upper tracts, which varies between 4.3% and 25%; and a stricture rate that varies between 8% and 14% (Table 85–4).

Transcolonic Technique of Goodwin

This method establishes a nonrefluxing ureterocolonic anastomosis by construction of a submucosal tunnel (Fig. 85–22). By this technique, the anastomosis is performed from within the bowel (Goodwin et al, 1953). If it is performed in bowel in continuity with the gastrointestinal tract, a noncrushing occlusive clamp is applied across the bowel cephalad to the desired point of the ureterointestinal anastomosis. This clamp is placed loosely about

Table 85–4.

Complications of Ureterointestinal Anastomoses

PROCEDURE	NO. OF PATIENTS	STRICTURE (%)	LEAKAGE (%)	REFLUX (%)
Colon				
Leadbetter-Clarke[1-4]	127	14	3	4
Strickler[5]	28	14	—	—
Pagano[6]	63	7	—	6
Small Bowel				
Bricker[7,8,18,19]	1809	7	4	—
Wallace-Y[9-11,17,19]	129	3	2	—
Nipple[8]	37	8	—	17
Serosal tunnel[12]	10	10	—	0
Le Duc[13-17]	82	18	2	13

The following sources can be found in *Campbell-Walsh Urology, 10th Edition,* on the Expert Consult website:
[1]Hagen-Cook and Althausen, 1979; [2]Leadbetter and Clarke, 1954; [3]Hill and Ransley, 1983; [4]King, 1987; [5]Jacobs and Young, 1980; [6]Pagano et al, 1984; [7]Clark, 1979; [8]Patil et al, 1976; [9]Clark, 1979; [10]Beckley et al, 1982; [11]Wendel et al, 1969; [12]Starr et al, 1975; [13]Hautmann et al, 1988; [14]Le Duc et al, 1987; [15]Klein et al, 1986; [16]Lockhart and Bejany, 1987; [17]Palascak et al, 2001; [18]Studer, 2006; [19]Kouba et al, 2007.

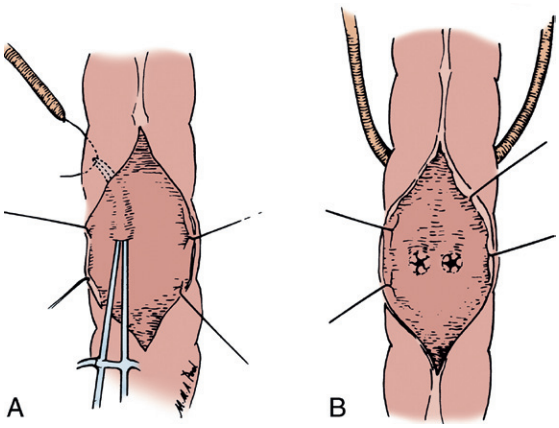


Figure 85–22. Transcolonic technique of Goodwin. **A,** The bowel is opened on its anterior surface; a small rent in the mucosa is made; and with a mosquito hemostat, the mucosa is raised from the submucosa extending laterally. A 3- to 4-cm tunnel is made before the clamp exits the serosal wall. The ureter is grasped and pulled into the submucosal tunnel. **B,** Both ureters have been drawn into the bowel through their submucosal tunnels before each is spatulated and circumferentially sutured to the mucosa. These sutures should also incorporate a portion of the muscularis for security. Where the ureter enters the colonic sidewall adjacent to the mesentery, the adventitia of the ureter is secured to the colonic serosa with interrupted 5-0 polydioxanone sutures.

the bowel so as not to occlude the arterial supply in the mesentery.

A vertical incision is made in the bowel anteriorly, and the desired point of entrance of the ureter into the bowel is identified. A 0.5-cm incision is made in the posterior mucosa, and with use of a curved hemostat the mucosa is dissected from the submucosal layer in an oblique fashion coursing from medial to lateral. The hemostat is passed beneath the mucosa for a distance of

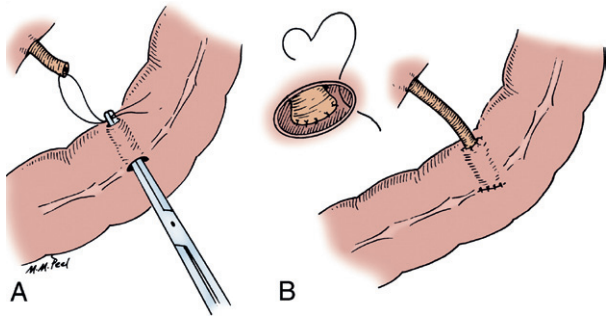


Figure 85–23. Strickler ureterointestinal anastomosis. **A,** A small linear incision is made in the taenia, and the submucosa is dissected from the mucosa laterally. After a distance of 3 to 4 cm is achieved, a small hole is made in the serosa and the ureter is drawn through. **B,** A button of mucosa is excised, and the ureter is spatulated and sutured to the mucosa with 5-0 polydioxanone sutures. The rent in the taenia is closed with interrupted sutures, and an adventitial suture at the ureter's entrance point into the colon secures it to the serosa of the colon.

approximately 3 to 4 cm and then brought through the serosa. A traction suture that has been placed on the ureter is then grasped with the hemostat, and the ureter brought into the colon. Both ureters should be brought into the bowel before they are sutured to the mucosa. The ureters should lie without tension or angulation. A No. 5 feeding tube is passed through the ureter to be sure that there is no kinking as it passes through the bowel wall. The redundant ureter is excised, and its end is spatulated and sewn with interrupted 5-0 PDS to the mucosa, with care taken to include with the mucosa some muscularis so that the ureter is securely fixed in place. A Silastic stent is placed up both ureters. As the ureters come through the serosa from without the bowel, the adventitia of the ureter is sutured to the serosa of the colon with two 4-0 PDS sutures. The anterior bowel wall is closed in two layers.

The reported results with this technique appear to be satisfactory. However, specific reliable data on the complication rate are not available.

Strickler Technique

This method establishes a nonrefluxing ureterocolonic anastomosis by construction of a submucosal tunnel (Fig. 85–23) (Strickler, 1965; Jacobs and Young, 1980). A 1-cm incision is made on the margin of the taenia. The technique originally described removal of a 2-mm button of seromuscular tissue. A 2-cm tunnel is formed laterally beneath the seromuscular layer with a hemostat. The seromuscular layer is incised, with care taken not to tent up the mucosa and inadvertently incise it. The holding suture in the ureter is grasped and drawn throughout the submucosal tunnel. The ureter is spatulated for 0.5 cm. A button of mucosa is removed, and the full thickness of the ureter is sewn to the mucosa of the bowel with either interrupted or running 5-0 PDS. The serosa is reapproximated over the ureter with 4-0 silk sutures. The serosal suture line is perpendicular to the course of the ureter. Where the ureters enter the serosa, they are also fixed with interrupted 4-0 PDS sutures. A lateral peritoneal flap is placed over the anastomosis.

The advantage of this anastomosis is that because the taeniae do not need to be aligned, one can form the tunnel according to the normal course of the ureter and avoid angulation. This technique reliably prevents reflux but results in a stricture rate of approximately 14% (see Table 85–4).

Pagano Technique

This method establishes a nonrefluxing ureterointestinal anastomosis by construction of a submucosal tunnel (Fig. 85–24) (Pagano, 1980). The taenia is incised for a length of 4 to 5 cm, and the seromuscular layer is separated from the mucosa on both sides of the taenia laterally as far as the mesenteric border. The ureter is brought in one end (i.e., the distal end) laterally and laid in the 4- to 5-cm tunnel paralleling the mesenteric border. A button of mucosa is excised, and the ureters are spatulated and sutured to the mucosa with either interrupted or running 5-0 PDS. The seromuscular layer is then closed loosely with silk sutures in the midline. Each suture includes the seromuscular layer of the taenia and the mucosa in the midline.

This technique has a reported low complication rate. The leakage rate is approximately 3%, the stricture rate is 6%, and the reflux rate is approximately 6% (see Table 85–4) (Pagano et al, 1984).

Cordonnier and Nesbit Technique

These techniques use no tunnel and are direct refluxing anastomoses of the ureter to the colon (Nesbit, 1949; Cordonnier, 1950). They are not desirable for ureterosigmoidostomies. They are performed in much the same way a Bricker anastomosis would be performed for the small bowel (see later).

Small Bowel Anastomoses

There is a variety of ureter–small bowel anastomoses, which are of two basic types: end-to-side or end-to-end. The end-to-side anastomoses may be constructed in a refluxing or nonrefluxing manner.

Bricker Anastomosis

The Bricker anastomosis is a refluxing end-to-side ureter–small bowel anastomosis that is simple to perform and has a low complication rate (Fig. 85–25) (Bricker, 1950). Although originally described for the small bowel, it may be employed in any suitable intestinal segment.

In the original description, the adventitia of the ureter was sutured with interrupted silk sutures to the serosa of the bowel. The mucosa and serosa were incised; a small mucosa plug was removed; and with fine absorbable chromic sutures, the full thickness of the ureter was sewn to the mucosa of the bowel. The anterior layer of ureteral adventitia was then sewn with interrupted silk sutures to the serosa of the bowel. A less cumbersome method of performing this anastomosis is to excise a small button of seromuscular tissue and mucosa, spatulate the ureter for 0.5 cm, and suture the full thickness of the ureter to the full thickness of the bowel (i.e., mucosa and seromuscular layer to ureteral wall) with either interrupted or running 5-0 PDS. The anastomosis is stented with a soft Silastic catheter.

The stricture rate for this anastomosis varies between 4% and 22% (average of 6%). The leak rate is approximately 3% in the absence of stents (see Table 85–4).

Wallace Technique

A frequently employed anastomotic technique is that of Wallace, in which the end of the intestine is sutured to the end of the ureter (Fig. 85–26) (Wallace, 1970; Albert and Persky, 1971). This is a refluxing anastomosis. The intestinal segment employed may be either small bowel or colon. There are three basic types of anastomoses:

1. The end of one ureter is sutured to the end of the other ureter, and this composite anastomosis is sutured to the end of the bowel.
2. A Y anastomosis of the ureters is constructed and sutured to the end of the bowel.
3. A head-to-tail ureteroureteral anastomosis is formed, which is then sutured to the end of the bowel.

The ureters are spatulated for 1.5 to 2 cm, and fine 5-0 PDS sutures are used for each anastomosis.

For the first anastomosis, a fine suture is placed at the apex of each ureter with the knot tied to the outside. The posterior medial ureteral walls are sutured together, and the anterior lateral walls are sutured directly to the bowel with interrupted 5-0 PDS. Where the suture line of the end of the ureters comes to the bowel, a horizontal mattress suture is placed to make the anastomosis watertight. If a Y type of anastomosis is desired, after the posterior ureteral walls are sutured together as described previously, the anterior walls of the ureters are sutured together, and the end of

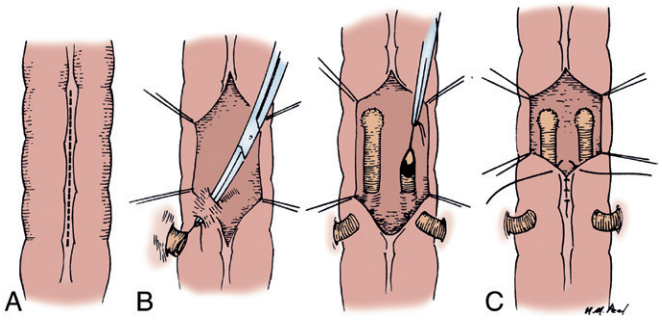


Figure 85–24. Pagano ureterointestinal anastomosis. **A,** A linear incision is made in the taenia between 4 and 5 cm in length. **B,** The submucosa is dissected from the mucosa laterally on both sides to the level of the mesentery. The ureters are drawn into the submucosal tunnel distally and sutured to the mucosa with 5-0 polydioxanone sutures proximally. **C,** The serosa is reapproximated, with incorporation of the mucosa in the midline.

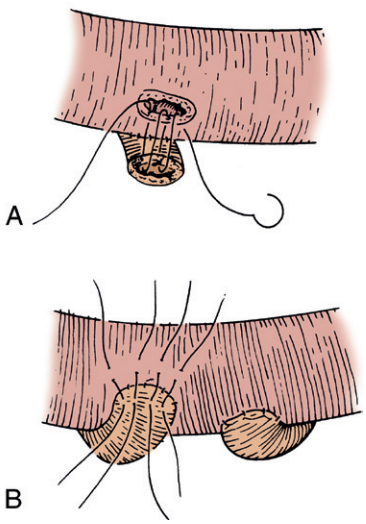


Figure 85–25. Bricker ureterointestinal anastomosis. **A,** The adventitia of the ureter is sutured to the serosa of the bowel. A small full-thickness serosal and mucosal plug is removed. Interrupted 5-0 polydioxanone sutures approximate the ureter to the full thickness of the mucosa and serosa. **B,** The anterior layer is completed by interrupted sutures placed through the adventitia of the ureter and the serosa of the small bowel.

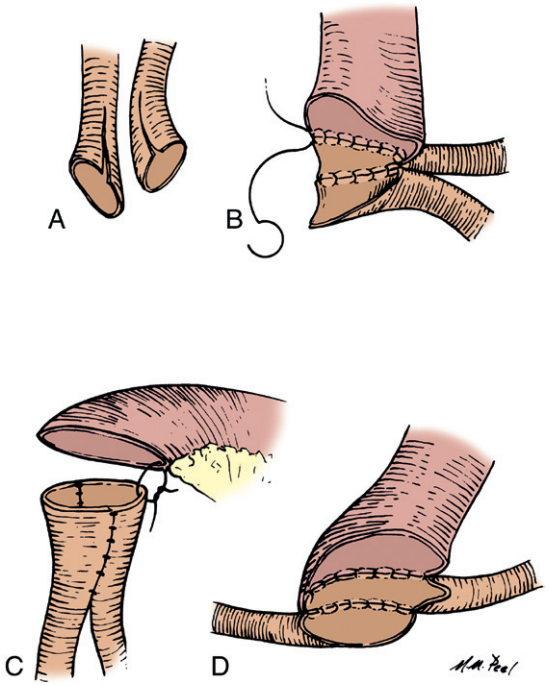


Figure 85–26. Wallace ureterointestinal anastomosis. **A,** Both ureters are spatulated and laid adjacent to each other. **B,** The apex of one ureter is sutured to the apex of the other ureter with 5-0 polydioxanone sutures (PDS). The posterior medial walls of both ureters are then sutured together with interrupted or running 5-0 PDS, the knots tied to the outside. The lateral ureteral walls are then sutured to the intestine. **C,** A Y-type anastomosis is formed by completing the anterior row of the anterior lateral ureteral walls of the ureters as shown in **B** and then suturing the ends of the ureters directly to the intestine. **D,** The head-to-tail anastomosis involves suturing the apex of one ureter to the end of the other. The posterior medial walls are sewn together, and then the ends and lateral walls are sewn to the intestine.

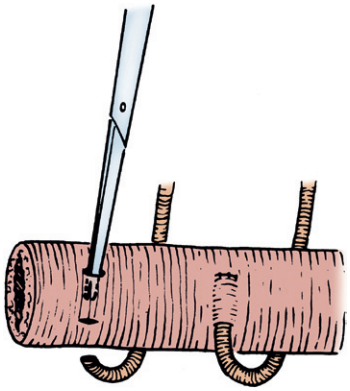


Figure 85–27. Tunneled small bowel anastomosis. A small transverse incision is made in the small bowel, and a second transverse incision 3 cm lateral to it is also made. The submucosal tunnel is made, a button of mucosa is removed, and the ureter is drawn through the tunnel and sutured directly to the mucosa. The rent in the serosa is closed, and an adventitial ureteral suture is placed and secured to the serosa at the ureter's entrance to the small bowel.

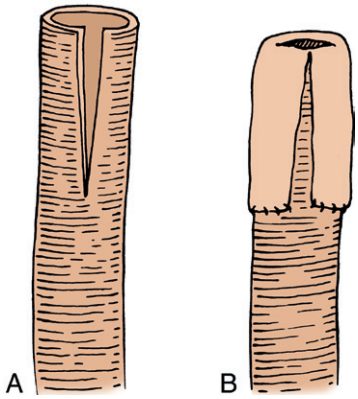


Figure 85–28. **A** and **B,** Split-nipple technique. The ureter is spatulated and turned back on itself, and the end of the ureter is secured to the adventitia of the ureter with interrupted 5-0 polydioxanone sutures.

the composite anastomosis is sutured to the bowel. Again, where the suture lines meet the bowel, a horizontal mattress suture is placed so that the anastomosis is watertight. The head-to-tail anastomosis involves suturing the end of one ureter to the apex of the other. The posterior medial walls of the two ureters are approximated. The anterior lateral walls are sutured to the bowel.

The Wallace anastomosis has the lowest complication rate of any of the ureterointestinal anastomotic techniques. Stricture formation is approximately 3%, deterioration of the upper tracts is about 4%, and leakage is about 2% (see Table 85–4). The Wallace technique is not recommended for patients who have extensive carcinoma in situ or who have a high likelihood of recurrent tumor in the ureter. A recurrence of tumor at the anastomotic line in one ureter would block both ureters, causing uremia from bilateral obstruction.

Tunneled Small Bowel Anastomosis

This method attempts to establish a nonrefluxing anastomosis by construction of a submucosal tunnel (Fig. 85–27) (Starr et al, 1975). Two 0.5-cm incisions are made in the serosa on the antimesenteric border 2.5 cm apart at right angles to the long axis of the bowel. The seromuscular layer is then gently separated from the mucosa with a blunt hemostat. The ureter is pulled through one incision, a button of mucosa is removed over the other incision, and the ureter is spatulated and sutured to the mucosa with interrupted 5-0 PDS. The serosa is then closed with interrupted 4-0 silk, and the adventitia of the ureter is sutured at its entrance through the serosa of the bowel to the serosa.

Good results have been reported, but this technique has not been widely used. Therefore long-term follow-up is not available.

Split-Nipple Technique

This method attempts to establish a nonrefluxing anastomosis by employing a nipple mechanism. It may be applied to either the small or large bowel. This technique was described by Griffiths and involves formation of a nipple in the ureter and implantation into the small bowel (Fig. 85–28) (Turner-Warwick and Ashken, 1967). A 0.5-cm longitudinal incision in the ureter is made, and the ureteral wall is turned back on itself, constructing a nipple at least twice as long as its width. The cuff is stabilized at the corners with sutures. A button of seromuscular and mucosal tissue is removed, and the ureter is then placed into the bowel such that it protrudes through the mucosa. The adventitia just proximal to the point where the ureter has been sewn to itself is sutured to the full thickness of the bowel wall with interrupted 5-0 PDS. The anastomosis is stented.

In one series, this type of anastomosis prevented reflux in more than 50% of the patients. In other subsequent series, approximately 80% of patients had a nonrefluxing anastomosis with an acceptably low incidence of stenosis (see Table 85–4). There is a stricture rate of about 7% (De Carli et al, 1997).

Le Duc Technique

This method establishes a nonrefluxing anastomosis by laying the ureter onto the interior of the bowel wall, eventually resulting in a submucosal tunnel when it is re-epithelialized (Fig. 85–29) (Le Duc et al, 1987). This technique has been used to prevent reflux in the ureter–small intestine anastomosis. Excellent exposure is required, and therefore the small bowel needs to be opened along its antimesenteric border for a length of approximately 5 cm. The mucosa is incised for a length of 3 cm beginning 2 cm proximal to the cut edge of the bowel. It is important to begin the mucosal tunnel away from the cut edge of the bowel to allow enough distal bowel for closure without jeopardizing the entrance point of the ureter. The ureter is then brought through the serosa at the most distal portion of the mucosal sulcus, laid in the trough, spatulated, and sutured to the proximal end of the sulcus with interrupted 5-0 PDS using the full thickness of ureteral wall and anchored to the muscularis and mucosal layers of the bowel. The mucosa of the sulcus of the bowel is then sutured to the adventitia of the ureter. The mucosa of the bowel should not be sutured over the ureter but rather to its lateral aspect. The idea is that the mucosa eventually grows over the top of the ureter. Where the ureter enters the small bowel, its adventitia is sutured to the bowel serosa with 4-0 silk sutures. Stents are placed in the ureter, and their passage must be unimpeded to ensure that there is no angulation. The bowel should be fixed to the body wall near the site of the ureteral implantation so that the ureters do not angulate.

The complication rate for this technique is relatively low, although the follow-up is also relatively short. Initial reports suggested that it carried with it an 87% incidence of maintaining an antireflux valve with a 5% incidence of stricture and a 2% incidence of leak (Schwaibold et al, 1998). A modification of the Le Duc technique was prompted by a 15% incidence of stricture when longer follow-up was available. With the modified technique, the stricture rate was 3% with 2½ years of follow-up. The technique involves construction of a 3-cm mucosal sulcus to the submucosa. The ureter is brought in the proximal sulcus transmurally and anchored to the serosa externally. The ureter is spatulated for 1.5 cm, and only the spatulated portion is sewn to the muscularis of the bowel. The proximal intraluminal ureter is not fixed to the bowel (see Table 85–4).

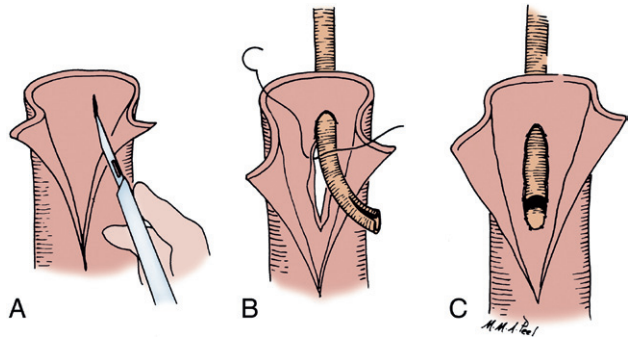


Figure 85–29. Le Duc ureterointestinal anastomosis. **A,** The small bowel is opened for approximately 4 to 5 cm. A longitudinal rent in the mucosa is made and the mucosa raised. **B,** At the distal end of the mucosal rent, a hole is made in the serosa, and the ureter is then drawn through. The entrance of the ureter through the serosa should be at least 2 cm proximal to the cut end of the bowel to allow sufficient bowel length to close the end. **C,** The ureter is spatulated and sutured to the mucosa and muscle layers. The mucosa is not reapproximated over the top of the ureter but rather sutured to the side of it.

Hammock Anastomosis

This type of anastomosis involves conjoining the ureters and implanting them into the small bowel in a nonrefluxing manner. The small bowel is closed at its proximal end, and three 10-cm longitudinal incisions separated by 1 to 2 mm are made through the seromuscular layer to the mucosa. These incisions are cross-hatched by multiple incisions. This serves as a hammock. The ureters are conjoined as in the Wallace technique and sutured to the intestinal mucosa. The ureters are buried by closing the intestinal wall over the top of them with seromuscular sutures of 3-0 polyglycolic acid suture (Hirdes et al, 1988).

With this technique, there is a 6% incidence of ureteroileal stenosis and approximately a 20% incidence of reflux. Follow-up, however, is relatively short.

Ureter–Small Bowel Anastomosis Employing Serosal Compression of the Extramural Ureter as an Antireflux Mechanism

This technique is primarily applicable to a continent diversion in which detubularized small bowel is employed and an antireflux ureterointestinal anastomosis is desired. It requires two segments of small bowel to be juxtaposed to each other. The ureter is laid between the two small bowel serosal surfaces, which are sutured posterior and anterior to the extramural portion of the ureter. The technique is as follows.

The posterior wall of the extramural tunnel is composed of the two segments of small bowel sutured together with 3-0 silk (Fig. 85–30A and B). The two segments of small bowel are opened along their antimesenteric borders. The ureter is spatulated and sutured to the mucosal-seromuscular layer with 5-0 absorbable sutures. The edges of the opened small bowel are then reapproximated over the anterior ureter with absorbable sutures (Fig. 85–30C), thus making a serosal tunnel of 4 cm in length. When the bowel is distended, it then applies pressure to the extramural ureter, thus preventing reflux (Abol-Enein and Ghoneim, 1994).

With an average of 3 years of follow-up, the anastomotic stricture rate is 4% and the failure of the antireflux mechanism is 3% (Abol-Enein and Ghoneim, 2001; Turkolmez et al, 2004).

Intestinal Antireflux Valves

Another technique of preventing reflux into the ureter involves construction of an antireflux mechanism with bowel distal to the ureterointestinal anastomosis. The ureter is sutured by the technique of either Bricker or Wallace (as described earlier) to the end of the bowel, and the bowel is used to make a one-way valve. Unlike with individual ureterointestinal antirefluxing anastomosis, when these valves fail or stenose, both kidneys are affected. Three basic types of antireflux mechanisms commonly employed with use of the bowel are ileocecal intussusception, ileoileal intussusception, and ileal nipple valve placed into colon.

Intussuscepted Ileocecal Valve

The mesentery is cleaned from the ileum for a length of 8 cm beginning at the cecum and coursing proximal (Fig. 85–31). At least 5 cm of ileum proximal to the detached mesentery must be

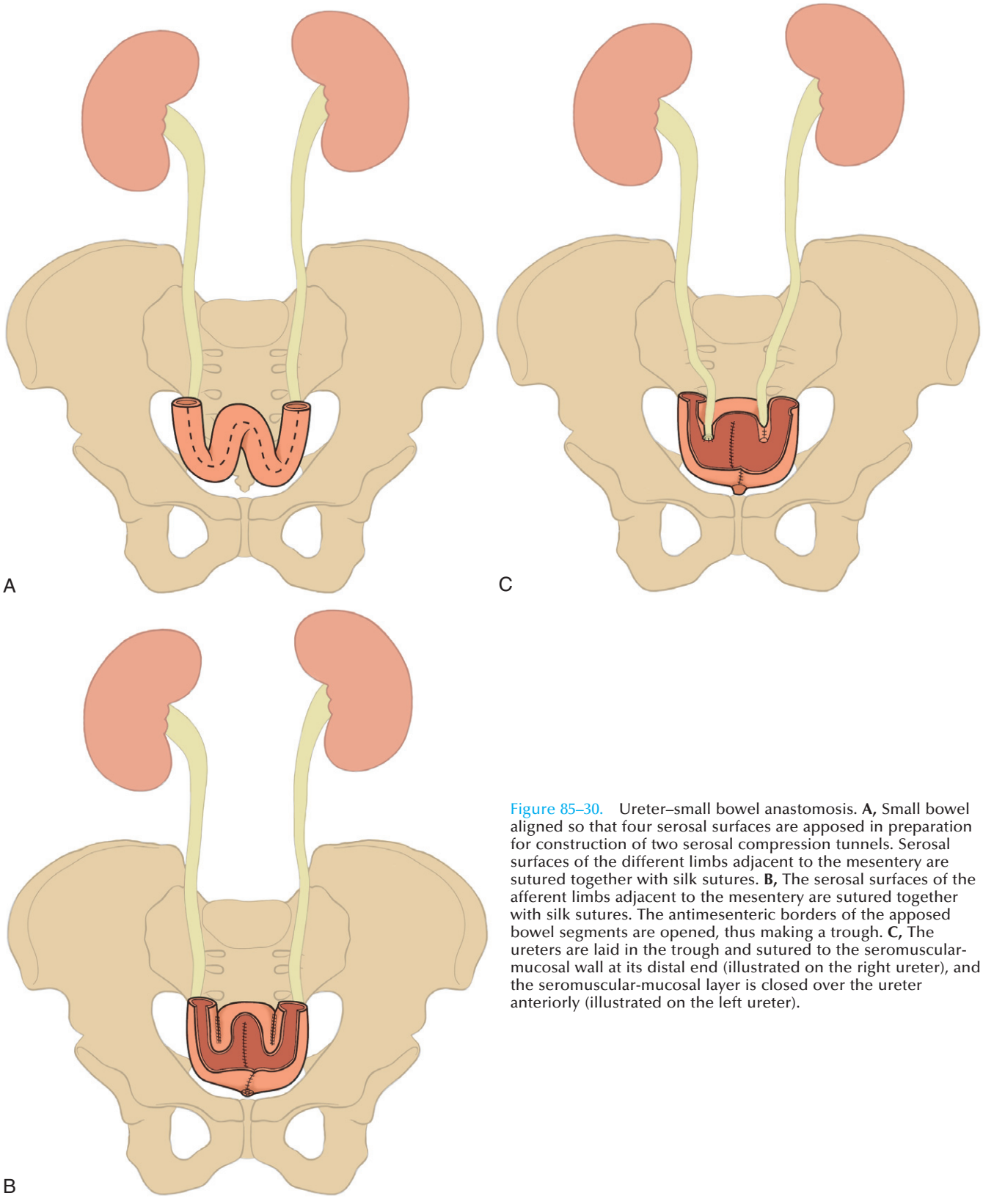


Figure 85–30. Ureter–small bowel anastomosis. **A,** Small bowel aligned so that four serosal surfaces are apposed in preparation for construction of two serosal compression tunnels. Serosal surfaces of the different limbs adjacent to the mesentery are sutured together with silk sutures. **B,** The serosal surfaces of the afferent limbs adjacent to the mesentery are sutured together with silk sutures. The antimesenteric borders of the apposed bowel segments are opened, thus making a trough. **C,** The ureters are laid in the trough and sutured to the seromuscular-mucosal wall at its distal end (illustrated on the right ureter), and the seromuscular-mucosal layer is closed over the ureter anteriorly (illustrated on the left ureter).

intact to ensure intestinal viability. Thus the ileum should not be transected less than 13 cm from the ileocecal junction. A No. 22 catheter is placed through the ileum into the cecum. The ileal serosa is scarified either by multiple cross-incisions with a knife or with the electrocautery unit. The 8-cm segment is intussuscepted over the catheter into the cecum. The intussuscepted ileum is secured to the cecal wall with 3-0 silk sutures placed circumferentially 2 mm apart.

The valve has a moderate tendency to fail because the intussusception has a significant chance of reduction. In one series, the

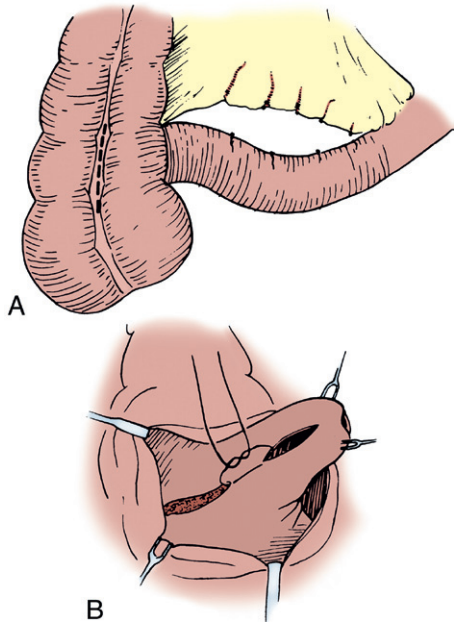


Figure 85–31. Ileocecal intussusception. **A,** An 8-cm segment of ileal mesentery is cleaned from the serosa beginning at the ileocecal junction. At least 5 cm of mesentery remains attached to the proximal ileum. An incision is made along a taenia at the level of the ileocecal valve. **B,** The ileum is intussuscepted over a No. 22 French catheter into the cecum under direct vision. The mucosa of the intussuscepted segment is incised, and the mucosa of the cecum adjacent to it is also incised. The muscle coats of both segments are sutured together. The serosa of the ileum is secured to the serosa of the cecum with interrupted 3-0 silk sutures placed circumferentially (not depicted).

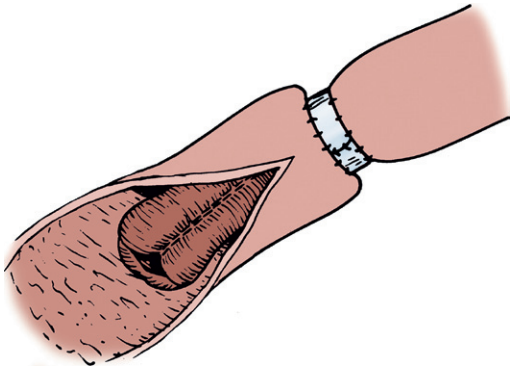


Figure 85–32. Intussuscepted ileal nipple valve. Eight centimeters of ileal mesentery are cleaned from the serosa. The ileum distally is opened within 2 to 3 cm of the rent in the mesentery. Five centimeters of ileum are intussuscepted and secured by placement of staples in quadrants. The ileal mucosa is incised adjacent to an incision in the intussuscepted segment, and the two muscle coats are sutured together with interrupted 3-0 chromic suture. The serosa of the intussuscepted segment is sutured circumferentially to the base of the ileum, into which the proximal segment is intussuscepted with interrupted silk suture.

antireflux mechanism remained intact in 55% of the patients during the long term (Hensle and Burbige, 1985). The intussusception may be made more secure by employing a modification described by King. The mesentery is cleaned as described before. The cecum is opened along a taenia, and the ileum is intussuscepted over the catheter under direct vision. Where the intussusception lies adjacent to the cecal wall, mucosa of the intussuscepted ileum and the cecal mucosa adjacent to it are incised down to muscle. The muscles are sewn together with interrupted 3-0 chromic suture. Long-term follow-up in eight patients reveals maintenance of the antireflux valve in seven with the modified technique (King, 1987; Friedman et al, 1992). The Mainz group advocates stapling the intussuscepted ileum to the ileocecal valve to prevent reduction. In their series 82% of patients maintain valve competence; however, there is a 20% incidence of stone formation (Wiesner et al, 2006).

Intussuscepted Ileal Valve

The mesentery is cleaned from an 8-cm segment of ileal serosa (Fig. 85–32). There must be 5 cm of ileal mesentery proximal and distal to the cleared segment to ensure proper blood supply. The ureters are sewn to the proximal end of ileum. The distal end of ileum is opened along its antimesenteric border to within 2 to 3 cm of the cleared mesentery to provide adequate exposure and direct visualization of the intussuscepted segment. A Babcock clamp is placed into the lumen of the bowel, and a portion of bowel wall is grasped by invaginating it into the clamp with a finger. The ileal segment is intussuscepted by pulling on the Babcock clamp with gentle constant traction. If there is resistance, the mesentery is generally too bulky and it must be defatted carefully before trying again to intussuscept the segment. A 5-cm intussuscepted segment should protrude. The gastrointestinal stapler without the knife or the linear stapler, from which the distal five to eight staples have been removed, is used to secure the intussusception in place; three rows with the gastrointestinal stapler or four rows with the linear stapler are placed in quadrants. The staple size should be 4.8 mm. The proximal staples are important in securing the intussusception and preventing its reduction, whereas the distal staples are less effective and more likely to be exposed to urine and thus facilitate stone formation. It is for this reason that the distal staples are removed from the staple cartridge before it is placed in the stapler and before the intussusception is stapled. With the cautery unit, the mucosa of the intussusception is incised along its length. Adjacent to this incision, another is made in the mucosa of the ileum. The muscularis of both is exposed and sewn together with interrupted 3-0 chromic suture. The distal serosa is then sutured proximally to the serosa of the intussuscepted segment circumferentially with 3-0 nonabsorbable sutures. This is meant to secure the intussusception and to prevent its reduction with failure of the antireflux mechanism. The valve is successful in preventing reflux 90% of the time (Kock et al, 1982; Skinner et al, 1989).

Because the intussuscepted nipple valve as an antireflux mechanism has resulted in a 10% complication rate (5% stone formation on the exposed staples, 4% stenosis, and 1% prolapse [Stein et al, 1996]), modifications have been developed in an attempt to reduce these untoward outcomes. One such modification has been described by the University of Southern California group. An 8- to 10-cm isolated segment of ileum is tapered distally and laid between two segments of small bowel in which their serosal walls adjacent to the mesentery are sutured together. This serves as the posterior support for the isolated segment. The apposed bowel is opened along its antimesenteric border; lateral flaps are constructed adjacent to the segment and closed over its anterior aspect, thus making a serosal trough in which 4 cm of the segment of tapered ileum is positioned (Stein and Skinner, 2003). When the pouch is closed, a nipple valve is constructed. The concept is that as pressure in the pouch increases, the walls of the tapered nipple valve are compressed, thus preventing reflux. The authors

call their modification a T pouch. At the time of this writing, long-term outcomes are not available.

Nipple Valve

The simplest intestinal antireflux valve to make is the nipple valve with use of ileum (Fig. 85–33). The mesentery is cleared from the last 8 cm of the cut end of the ileum. The distal 6 cm of serosa is scarified by multiple cross-striations and then turned back on itself to form a nipple. The nipple should be at least 4 to 4.5 cm in length. The end of the inverted ileum is then sutured to itself with interrupted 4-0 PDS. An incision on the taenia large enough to accommodate the segment is made. A No. 22 catheter is placed through the segment, and its serosa is sutured to the colon serosa circumferentially with interrupted 3-0 silk sutures placed 2 mm apart. The long-term success rate for this type of valve is unknown but would appear to be less than with the other two methods.

Complications of Ureterointestinal Anastomoses

The complications that occur with ureterointestinal anastomoses include leakage, stricture, reflux in those anastomoses that were performed to prevent reflux, and pyelonephritis. In a review of the various types of procedures, it appears that of the colonic antirefluxing procedures, the Pagano technique offers the lowest incidence of stricture with an acceptable incidence of reflux. With respect to small bowel antireflux procedures, the Le Duc procedure and the ureterointestinal serosal apposition procedure seem to offer the lowest incidence of stricture with the highest success rates in preventing reflux. With respect to stricture formation and leakage, it appears the Wallace technique has the best results. In a comparison of the Bricker, the Wallace, and the nipple valve, however, in one series there was no difference in complication rate among any of the procedures. In another contemporary series the Wallace technique had the lowest incidence of stricture (Kouba et al, 2007). All had an incidence of approximately 29% of some form of obstruction in the long term (Mansson et al, 1979). In a more recent study, there appeared to be no difference between rate of reflux and stricture when a Bricker anastomosis was compared with a split-cuff nipple. The incidence of stricture was 7% for both types (De Carli et al, 1997).

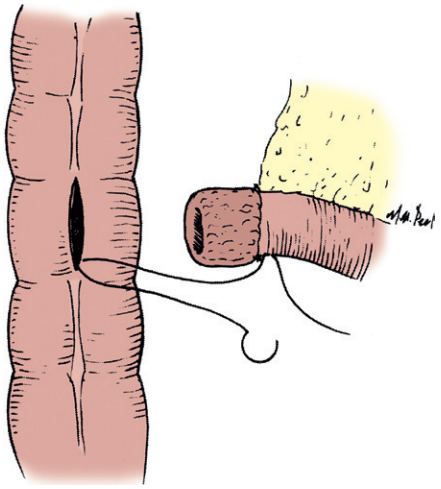


Figure 85–33. Nipple valve. Approximately 8 cm of mesentery are cleaned from the distal end of the ileum, and the serosa is scarified and then turned back on itself to form a nipple of approximately 4 cm in length. The end of the ileum is sutured to itself with interrupted 4-0 PDS. A rent is made in the colon through a taenia, and the nipple valve is placed through the rent and secured with circumferential interrupted 4-0 PDS through the full thickness of the colon and the seromuscular layer of the ileum.

Urinary Fistula

Urinary fistulas invariably occur within the first 7 to 10 days postoperatively with an incidence of 3% to 9% (see Table 85–4) (Beckley et al, 1982; Loening et al, 1982). **The incidence of urinary intestinal leak is markedly reduced by the use of soft Silastic stents** (Mattei et al, 2008). A urinary intestinal leak may cause periureteral fibrosis and scarring with subsequent stricture formation.

Stricture

In general, **the antirefluxing techniques have a higher incidence of stricture.** Patients are at risk for ureterointestinal strictures for the life of the anastomosis and must be observed on a scheduled periodic basis. A stricture has been reported to develop 13 years after the procedure (Shapiro et al, 1975). **Ureteral strictures also occur away from the ureterointestinal anastomosis. This stricture is most common in the left ureter and is usually found as the ureter crosses over the aorta beneath the inferior mesenteric artery.** It has been suggested that this is due to too-aggressive stripping of adventitia and angulation of the ureter at the inferior mesenteric artery.

Once a stricture has developed, various techniques may be used to rectify the situation. The most successful is re-exploration, with removal of the stenotic segment and reanastomosis of the ureter to the bowel by one of the aforementioned techniques. A number of studies have compared open surgical correction of ureterointestinal anastomotic strictures with endourologic methods. In general, **open repair has a success rate of approximately 75% at 3 years versus 15% for balloon dilation** with similar follow-up (DiMarco et al, 2001). Open surgical methods may be morbid and difficult procedures. Endourologic procedures employing balloon dilation have not proved to be durable, and therefore many have employed either cold knife incisions or laser incisions. **When several series employing endourologic methods are combined, there is a 50% to 60% success rate** with 2 years of follow-up. Strictures occurring in less than 1 year from the original procedure, strictures 1.5 cm or longer, and left-sided strictures have less favorable outcomes from endourologic methods (Kramolowsky et al, 1987, 1988; Cornud et al, 1996; Laven et al, 2001; Poulakis et al, 2003). These data must be viewed with caution because longer follow-up generally results in additional recurrences. In selected cases, metallic stents have been employed, which might be a reasonable approach in a patient with a limited life expectancy, thus avoiding a major open operation (Barbalias et al, 1998). A study in which nonmalignant ureterointestinal strictures were stented reported that all patients were successfully treated with 2 years of follow-up; one patient developed a stone on the stent (Palascak et al, 2001).

Pyelonephritis

Acute pyelonephritis occurs both in the early postoperative period and during the long term. Its incidence is approximately 10% to 20% in patients diverted with ileal conduits and 9% in those diverted with antirefluxing colon conduits (see Table 85–3). **These complications cause considerable morbidity and in fact are associated with significant**

mortality. In one series of intestinal segments in the urinary tract, 8 of 178 patients died of sepsis (Schmidt et al, 1973). **That these complications may result in delayed mortality is indicated by the fact that 2 of 115 children and 3 of 127 adults died of septic complications 5 to 14 years after intestinal diversion** (Pitts and Muecke, 1979). **When sepsis is associated with decreasing renal function and uremia, the morbidity and mortality are markedly increased.**

Table 85–4 summarizes the complications and success rates for the various types of anastomoses. The table is derived from composite reports in the literature in which specific anastomoses were described and from which the data could be accurately analyzed. Because of these two requirements, it is not possible to comment, for example, on the incidences of reflux or leakage among various anastomotic types inclusively. These complications can be minimized by adherence to the principles of ureterointestinal surgery discussed earlier.

RENAL DETERIORATION

The incidence of renal deterioration after conduit urinary intestinal diversion has varied from 10% to 60% (Koch et al, 1992; Madersbacher et al, 2003). This variance is perhaps due to the fact that many reports include both renal units that were abnormal and those that were normal before diversion. **In analyzing abnormal renal units before diversion and documenting progressive disease, it is difficult to be sure whether the urinary diversion caused the progression or whether progression is due to the intrinsic abnormality for which the diversion was constructed. When the incidence of renal deterioration is determined by comparing renal units that were normal before diversion and then deteriorated postoperatively, 18% of patients who have ileal conduits show progressive deterioration versus 13% who have nonrefluxing colon conduits** (see Table 85–3). Twenty percent of patients with nonrefluxing continent ileocecal bladders show some evidence of deterioration of the upper tracts when they are observed during the long term (Benchekroun, 1987). This deterioration leads to a 10% incidence of azotemia in children with ileal conduits (Schwarz and Jeffs, 1975) and a 12% (5 of 41 patients) incidence of renal failure in patients with colon conduits constructed for benign disease (Elder et al, 1979).

The incidence of both sepsis and renal failure is greater in patients with ureterosigmoidostomy than in those with conduits. Sepsis and renal failure may occur either in the immediate postoperative period or many years later. **The most common cause of death in patients who have had a ureterosigmoidostomy for more than 15 years is acquired renal disease (i.e., sepsis or renal failure).** In this group of patients, approximately 10% to 22% die of these disorders (Zabbo and Kay, 1986), some as late as 27 years after diversion (Mesrobian et al, 1988). **In patients with ileal conduits, about 6% ultimately die of renal failure** (Richie, 1974).

Renal Function Necessary for Urinary Intestinal Diversion

The amount of renal function required to effectively blunt the reabsorption of urinary solutes by the intestinal segment and to prevent serious metabolic side effects depends on the type of urinary intestinal diversion constructed (i.e., the amount of bowel to be used and the length of time the urine is exposed to the intestinal mucosa). Thus **a greater degree of renal function is necessary for retentive (continent) diversions than for short conduit diversions.** Patients who have a glomerular filtration rate (GFR) on average above 40 mL/min generally tolerate a continent diversion reasonably well. Indeed, in one study, two groups of patients were analyzed: those with GFRs around 100 mL/min (range, 91 to 112) and those with GFRs around 55 mL/min (range, 36 to 69). Both seemed to tolerate the metabolic load well with a minimal development of metabolic acidosis. There was a slightly increased incidence of metabolic acidosis in the group with low GFR, as would be expected; however, in this group, distal tubule function was excellently maintained as demonstrated by ammonium chloride loading. This observation points out that GFR is not the sole determining factor that allows the body to manage intestinal diversion. Indeed, GFR is but one factor. Just as important is distal tubule function. This article confirms that when distal tubule function is normal and the GFR is above 40 mL/min, patients do extremely well (Kristjansson et al, 1997).

There are five components of renal function: renal blood flow, glomerular filtration, tubule transport, concentration and dilution, and glomerular permeability. Aspects of renal function that must be specifically addressed are GFR, best measured by inulin clearance; ability of the tubule to acidify, determined by ammonium chloride loading; concentrating ability, determined by water deprivation; and glomerular permeability, reflected by urine protein concentrations. **In general, patients with normal urine protein content who have a serum creatinine concentration below 2.0 mg/dL do well with intestine interposed in the urinary tract.** Serum cytostatin C is a promising serum protein that reflects GFR more accurately than creatinine; however, its usefulness in urinary intestinal diversion has not yet been determined (Herget-Rosenthal et al, 2004). At a level of serum creatinine below 2 mg/dL, renal blood flow, GFR, tubule transport, and concentrating and diluting ability are relatively well preserved. **In patients whose serum creatinine concentration exceeds 2 mg/dL and who are being considered for retentive diversion or in whom long segments of intestine will be used, a more detailed analysis of renal function is necessary. If the patient can achieve a urine pH of 5.8 or less after an ammonium chloride load, has a urine osmolality of 600 mOsm/kg or greater in response to water deprivation, has a GFR that exceeds 35 mL/min, and has minimal protein in the urine, the patient may be considered for a retentive diversion.**

URINARY DIVERSION

This section deals with specific types of conduit urinary diversions. Fundamentally, there are two types of conduits: (1) those using the small bowel, which includes the jejunum or ileum, and (2) those in which a portion of large bowel is used. Conduits made of stomach have been described but are rarely indicated and may carry with them difficult problems of stomal maintenance. Their construction is not discussed here. Each type of conduit has specific indications and advantages, and for each there are specific complications. Some complications, however, are similar among all types. **The indications for a conduit are the need for urinary diversion: after a cystectomy; because of a diseased bladder; before transplantation in a patient who has a bladder that cannot adequately receive the transplant ureter; and for dysfunctional bladders that result in persistent bleeding, obstructed ureters, poor**

compliance with upper tract deterioration, and inadequate storage with total urinary incontinence.

Preparation

Regardless of whether small or large bowel is used for the conduit, although subject to debate as noted previously, it is the authors' preference that **all patients have a bowel preparation** as outlined earlier.The reason for this is that large segments of bowel are exposed to the urinary tract and in some cases require detubularization, thus exposing the abdominal cavity to a large amount of solid fecal material if the bowel is unprepared. The specific types of ureterointestinal anastomosis and stomal construction and their complications are also described in previous sections. This section describes features that are unique to the construction of the conduit. The complications cited for each conduit also depend on the length of follow-up and the concomitant procedure performed.

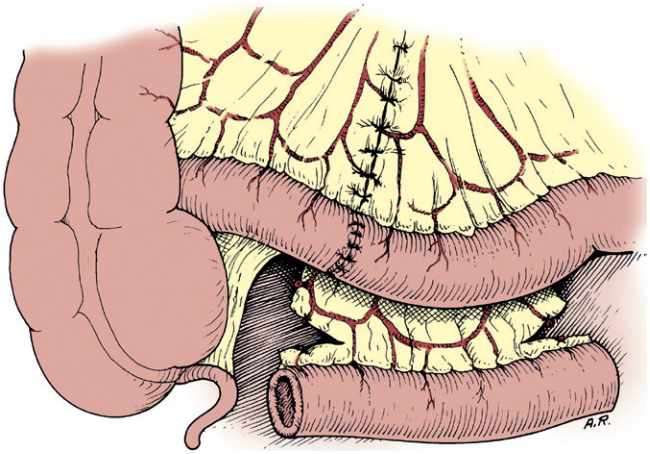


Figure 85–34. The isolated segment of ileum is placed caudal to the ileoileostomy. An incision on the mesentery of the isolated segment 1 cm from the bowel wall straightens the end. This is generally not necessary unless the mesentery is excessively bulky.

Ileal Conduit

In this procedure, a portion of distal ileum is chosen. **It is the simplest type of conduit diversion to perform and is associated with the fewest intraoperative and immediate postoperative complications. It is not advisable to use ileum for a conduit in patients with a short bowel syndrome, in patients with inflammatory small bowel disease, and in those whose ileum has received extensive irradiation, often as a consequence of prior radiation therapy for a pelvic malignant neoplasm.**

Procedure

A segment 10 to 15 cm in length is selected 10 to 15 cm from the ileocecal valve. The cecum and ileal appendage (i.e., that portion of the distal ileum fixed to the retroperitoneum) are mobilized. The ileal mesentery is transilluminated, and a major arcade identified to the segment selected. With a mosquito clamp, the mesentery immediately beneath the bowel is penetrated, and the bowel is encircled with a vessel loop. An area at the base of the mesentery that is to one side of the feeding vessel is selected, and a second vessel loop is placed through the mesentery. At this juncture, the peritoneum overlying both sides of the mesentery is incised from bowel vessel loop to the base of mesentery vessel loop. With mosquito clamps, the tissue is clamped, severed, and tied with 4-0 silk. A portion of mesentery 2 cm in length is cleaned away from the bowel beneath the mesenteric incision. This procedure is repeated at the other end of the selected segment. The base of the mesentery should be as wide as possible and the mesenteric windows not excessive (generally about 5 cm in length) to prevent ischemia of the segment. Allen clamps are placed across the bowel in an angled fashion such that the antimesenteric portion is shorter than the mesenteric portion. (Some prefer to transect the bowel with an anastomotic stapler.) Thus a triangular piece of bowel is removed and discarded.

The isolated ileal segment is placed caudad, and an ileoileostomy is performed as described earlier (Fig. 85–34). The mesenteric window of the ileoileostomy is closed with interrupted 3-0 silk sutures. The isolated segment is then flushed with copious amounts of saline until the irrigant is clear, at which point the ureters are brought out the retroperitoneum in the right lower quadrant. To accomplish this, the left ureter must be brought over the great vessels and posterior to the sigmoid mesentery to the rent in the posterior peritoneum. This may be done by mobilizing the cecum cephalad to identify the right ureter. The left ureter may be identified by incising the line of Toldt of the left descending colon (Fig. 85–35). This dissection allows anastomosis of the ileal segment as proximal as needed to the ureter. Indeed, the ileum may be anastomosed directly to the renal pelvis on both sides if necessary (Fig. 85–35C). After a cystectomy, the ureters are identified caudad to the iliac vessels and may be conveniently traced cephalad similar to the previous description. The ureteral-ileal anastomoses are performed as described previously. These anastomoses are stented.

A convenient method of introducing the stent through the loop to the opening in the bowel is illustrated in Figure 85–36. The base of the conduit is fixed to the retroperitoneum in the right lower quadrant by suturing the posterior peritoneum to the conduit, thus effectively retroperitonealizing the ureterointestinal anastomosis. The stoma is made as described previously. The authors prefer to suture the loop segment to the lateral peritoneal wall, thus obviating any chance of herniating small bowel lateral to the conduit. Many prefer to bring the segment directly to the anterior abdominal wall, however, thus allowing bowel to descend caudad on either side of the loop.

Complications

Early and late postoperative complications are listed in Table 85–5. It is difficult to clearly ascribe these complications solely to construction of the conduit because many are reported in patients undergoing a cystectomy as well. These incidences in Table 85–5 are therefore expected to reflect the high end of the spectrum. **Bleeding may occur from either the stoma or the conduit itself. Approximately 10% of patients have stomal bleeding. In 4%, it originates from the loop beneath the fascia** (Delgado and Muecke, 1973). Bleeding that is extremely difficult to manage may be due to cirrhosis and varices. In this situation, life-threatening bleeding from the conduit may occur. To stop the bleeding, portal decompression may be required (Chavez et al, 1994). A less morbid method involves percutaneous transhepatic portal shunt or transhepatic angiography with embolization (Lashley et al, 1997; Medina et al, 1998). Indeed, this has been successful in several reported cases. **Complications not listed include hypertension, renal failure, decreased renal function, and death.** These complications in large part depend on the concomitant procedure performed, the length of follow-up,

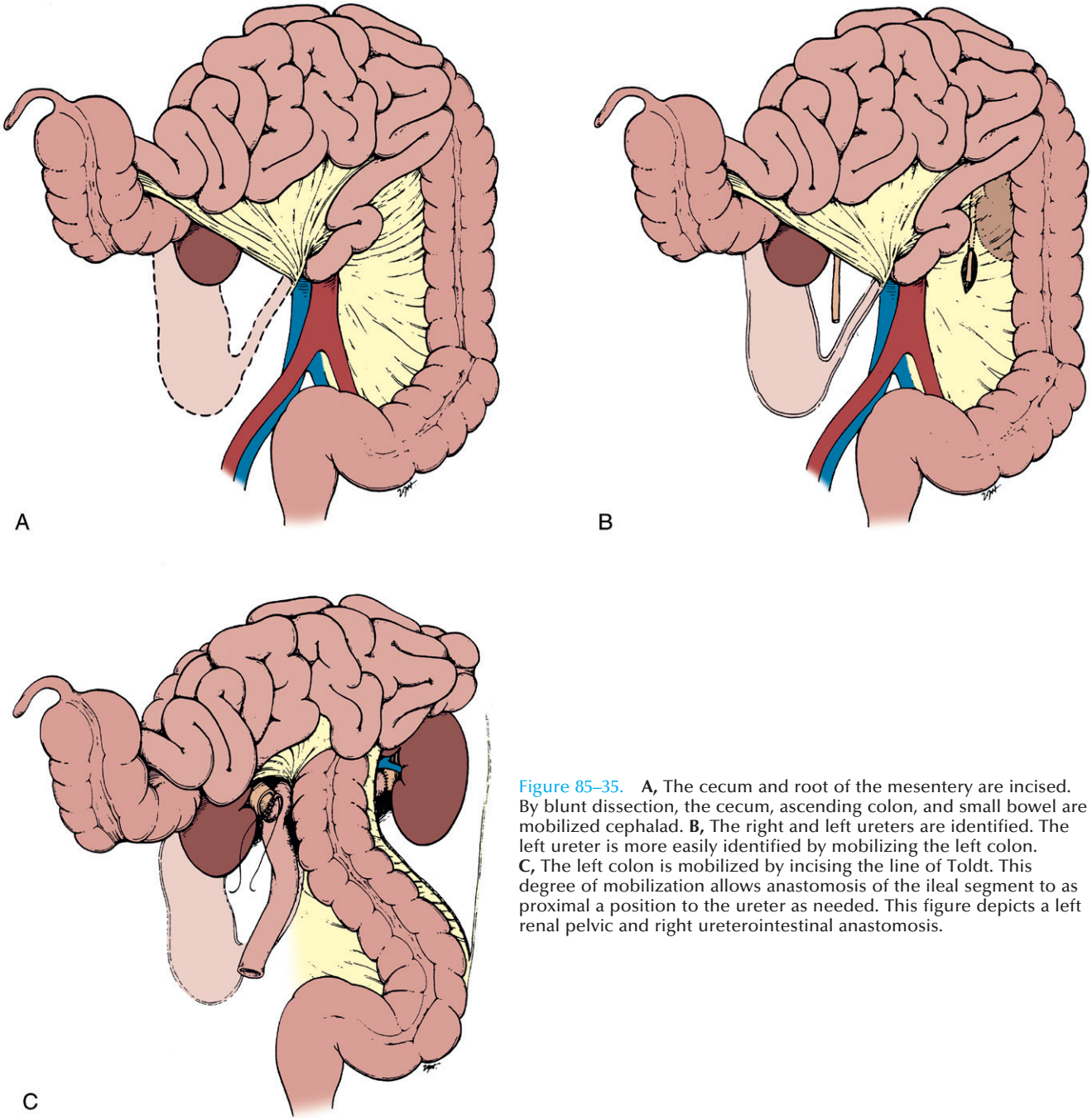


Figure 85–35. **A,** The cecum and root of the mesentery are incised. By blunt dissection, the cecum, ascending colon, and small bowel are mobilized cephalad. **B,** The right and left ureters are identified. The left ureter is more easily identified by mobilizing the left colon. **C,** The left colon is mobilized by incising the line of Toldt. This degree of mobilization allows anastomosis of the ileal segment to as proximal a position to the ureter as needed. This figure depicts a left renal pelvic and right ureterointestinal anastomosis.

and the status of the kidneys before diversion. **During the long term (20 years), 7% of patients have renal failure requiring dialysis, and 60% show deterioration of the upper tracts** (Koch et al, 1992). **After salvage cystectomy, complications are increased so that approximately one third of patients have one of the early complications** (Abratt et al, 1993). Also, the complication rate is increased in patients in whom an intestinal segment is used in those requiring renal transplantation (Nguyen et al, 1990).

One should be cautious in identifying duplex ureters. A failure to identify a second ureter on one side results in intraperitoneal urine leak and can cause excessive morbidity (Evans et al, 1994). The duplex ureters may be dealt with by implanting them separately if they are of sufficient caliber, or they may be spatulated, sewn together, and then implanted into the ileal conduit as a single unit (Fig. 85–37).

Jejunal Conduit

The jejunum has the largest diameter of the small bowel and the longest mesentery. Jejunal conduits generally have not had a high rate of acceptance because of perceived electrolyte abnormalities. A more recent report of patients, most of whom have been observed for more than 5 years, has shown that the bulk of electrolyte problems are minor—only about 4% in this series had severe hyponatremic metabolic acidosis. Renal calculi (12%), parastomal hernia (6%), and pyelonephritis (4%) constituted the majority of the remaining complications (Fontaine et al, 1997).

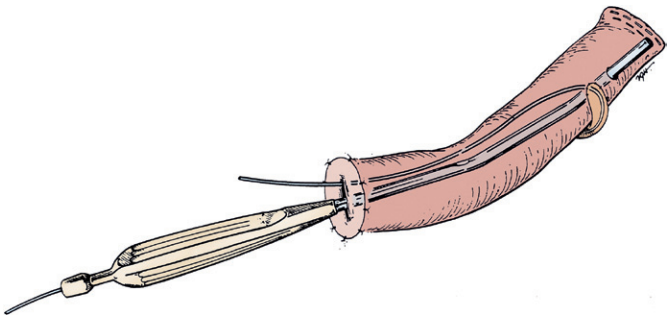


Figure 85–36. The ureterointestinal anastomoses should be stented with soft Silastic stents. These stents may be conveniently introduced with a Yankauer suction instrument from which the tip has been removed. The suction instrument is introduced by way of the distal end of the segment to the desired location of the ureteral anastomosis. When one cuts down on the Yankauer tip, its end protrudes through the bowel at the desired site. The stent is threaded through the suction instrument and the instrument removed.

Table 85–5.

Complications: Ileal Conduit*

	EARLY	LATE
Urine leak	2% (9/356)	
Bowel leak		
Sepsis	3% (7/230)	3% (4/142)
Acute pyelonephritis	3% (21/700)	18% (133/726)
Wound infection	7% (17/230)	2% (4/178)
Wound dehiscence	3% (11/326)	
Gastrointestinal bleed	2% (2/90)	
Abscess	2% (3/168)	
Prolonged ileus	6% (14/230)	
Conduit bleed	2% (3/178)	10% (18/178)
Intestinal obstruction	3% (18/610)	5% (42/878)
Ureteral obstruction	2% (14/610)	6% (56/878)
Parastomal hernia		2% (9/454)
Stomal stenosis		3% (143/486)
Stone formation		7% (59/822)
Excessive conduit length		9% (26/276)
Metabolic acidosis		13% (27/206)
Conduit infarction		2% (2/90)
Volvulus		7% (2/268)
Conduit stenosis		3% (11/320)
Conduit-enteric fistula		<1%

*Incidence as a percentage of the total number of reported cases from the literature. Numbers in parentheses represent the number of cases from which the percentage is derived.

The advantage of using the jejunum is that it avoids irradiated bowel and ureter. It is difficult to make a case for the jejunal conduit except in circumstances in which it is inadvisable to use either colon or ileum. However, this series does point out that when necessary, one can successfully use jejunum as a conduit. This might occur in patients who have extensive irradiation that involves the ileum, those with severe adhesions of the ileum and absence of the large bowel, and those who have an absent colon with inflammatory disease of the distal small bowel. **The contraindications to its use are severe bowel nutritional disorders and the presence of another acceptable segment.**

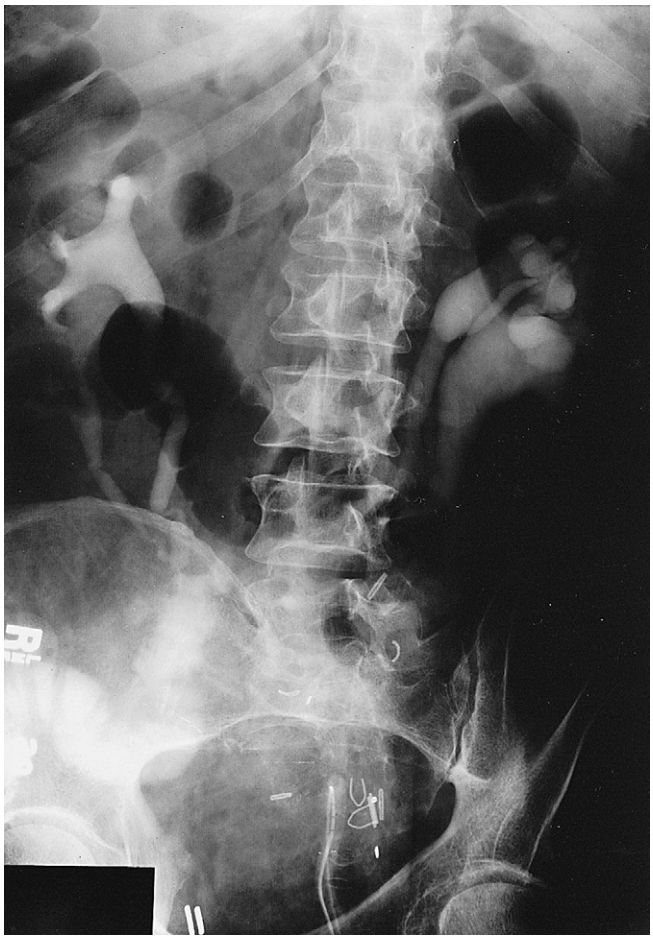


Figure 85–37. Intravenous urogram 6 days postoperatively in a patient who had bilateral duplex ureters. The ureters on each side were spatulated, sewn together, and anastomosed to the ileum.

Procedure

The procedure is similar to that for an ileal conduit. A 10- to 15-cm segment of jejunum is isolated 15 to 25 cm from the ligament of Treitz as described for the ileal conduit. One should plan for the stoma to be in the upper quadrant, generally the left upper quadrant. The remainder of the technique is as described for the ileal conduit.

Complications

The early and long-term complications are similar to those listed for ileal conduit except that the electrolyte abnormality is a hyperkalemic, hyponatremic metabolic acidosis instead of the hyperchloremic metabolic acidosis of ileal diversion (Table 85–6). The treatment of the jejunal syndrome consists of administration of sodium chloride and sodium bicarbonate. Thiazides may also be used and are helpful in allaying the hyperkalemia (Hasan et al, 1994).

Colon Conduit

Three types of colon conduits are commonly used: transverse, sigmoid, and ileocecal. Each has specific indications with advantages and disadvantages.

The transverse colon is used when one wants to be sure that the segment of conduit employed has not been

Table 85–6.

Complications: Jejunal Conduit*

	EARLY	LATE
Urine leak	14% (3/21)	
Wound dehiscence	5% (1/21)	
Acute pyelonephritis		10% (2/21)
Gastrointestinal bleed	4% (1/27)	
Electrolyte abnormalities		27% (17/62)
Stomal stenosis		7% (2/27)
Bowel obstruction		7% (2/27)
Ureteral stricture		12% (5/41)
Enteric fistula	2% (4/140)	

*Incidence as a percentage of the total number of reported cases from the literature. Numbers in parentheses represent the number of cases from which the percentage is derived.

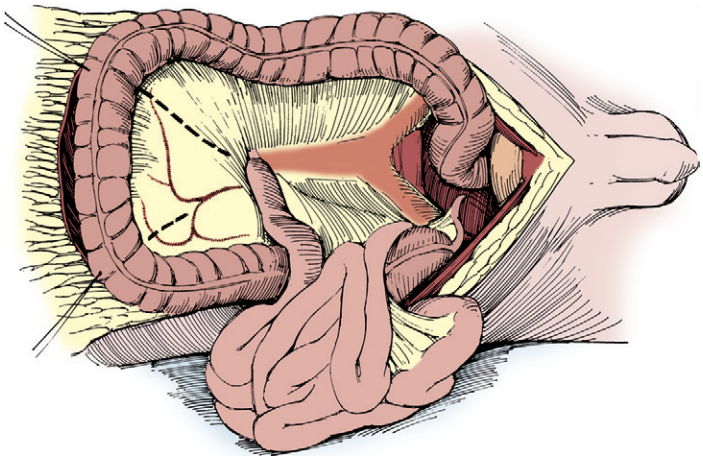


Figure 85–38. Transverse colon conduit may be based on right colic or middle colic arteries (depicted). (From Hinman F Jr. Atlas of urologic surgery. Philadelphia: WB Saunders; 1989.)

irradiated in individuals who have received extensive pelvic irradiation. It is also an excellent segment when an intestinal pyelostomy needs to be performed. The sigmoid conduit is a good choice in patients undergoing a pelvic exenteration who will have a colostomy. Thus no bowel anastomosis needs to be made. It also allows nonrefluxing submucosal reimplantation and provides for an easily placed left-sided stoma when that is desirable.

The use of sigmoid colon is contraindicated with disease of this segment or when the hypogastric arteries have been ligated and the rectum has been left in situ. The latter circumstance may result in sloughing of the rectum or its mucosa because its blood supply of necessity is interrupted. **It is also unwise to use this segment in individuals with extensive pelvic irradiation** because it has probably been included in the radiation fields.

An ileocecal conduit has the advantage of providing a long segment of ileum when long segments of ureter need replacement, as well as the advantage of providing colon for the stoma. It is also used in situations in which free reflux of urine from the conduit to the upper tracts is thought to be undesirable. **Contraindications to the use of transverse, sigmoid, and ileocecal conduits include the presence of inflammatory large bowel disease and severe chronic diarrhea.**

Procedure

Transverse Colon. The segment may be isolated on the right or middle colic arteries, most commonly the latter (Fig. 85–38). The gastrocolic ligament is taken down, and the omentum is dissected from the portion of colon that is to be isolated. The splenic and hepatic flexures should be mobilized next. The proper length of segment is determined by taking into consideration the desired location of the stoma and the length of available ureters. In general, a length of 15 cm is sufficient. It is important not to isolate a segment that is too short and therefore incapable of reaching the retroperitoneum in such a position that a tension-free ureterocolonic anastomosis may be performed and retroperitonealized. The segment is isolated between bowel clamps, and a two-layer colocolostomy or stapled anastomosis is performed as outlined earlier. The segment is placed caudad to the anastomosis. If a colopyelostomy is to be performed, the segment should be placed cephalad to the bowel anastomosis. The isolated segment is irrigated with copious amounts of saline until the effluent is clear. The proximal end is closed with a running Connell suture of 3-0 chromic and a second layer of Lembert sutures of 3-0 silk. The ureterocolic anastomoses are then performed (see earlier), and the end is anchored to the retroperitoneum close to the midline. The stoma is usually placed in the right upper quadrant but may be placed anywhere in the abdomen if indicated.

Sigmoid Colon. The sigmoid colon is mobilized by incising its peritoneal attachments and the line of Toldt along the descending colon. The segment is isolated on the sigmoid vessels and placed lateral to the sigmoid colon (Fig. 85–39). The anastomosis of the sigmoid colon and ureterocolic anastomosis are as described for the transverse colon.

Ileocecal Conduit. The ileocecal conduit is based on the terminal branches of the superior mesenteric artery (i.e., ileocecal artery). The segment is placed caudad, and an ileum-ascending colon anastomosis is performed as described previously. The stoma is placed in the right lower quadrant. The ileocecal valve may be reinforced to ensure prevention of reflux. This is described earlier (see Fig. 85–31). For the ureterointestinal anastomoses, see previously as well.

Complications

Early and late complications after a transverse colon (Beckley et al, 1982; Ravi et al, 1994; Schmidt et al, 1985), sigmoid, or ileocecal conduit are listed in Tables 85–7 to 85–9. As is true for the small bowel, complications not listed including death, renal failure, and renal deterioration depend on the concomitant procedure performed and the length of follow-up. Interestingly, early reports suggested a lower incidence of renal deterioration with colon conduits, but some recent series suggest that the incidence of these complications is about the same. However, there continue to be proponents of the colon conduit in that during the long term, there appears to be a 7.6% incidence of pyelonephritis and a 78% incidence of preservation of the upper tracts (Stein et al, 1996).

Complications of the ileocecal conduit in one reported series occurred in 21% of patients (Matsuura et al, 1991). In this series, complications of the ileal conduit were compared with those of the ileocecal conduit, and there appeared to be no difference in the frequency of early and late postoperative complications. Early complications included urinary leakage, bowel obstruction, fecal leakage, acute renal failure, fulminant hepatitis, pneumonia, gastrointestinal bleeding, hemorrhage, perforation of ileum, heart failure, and wound dehiscence. Late complications included

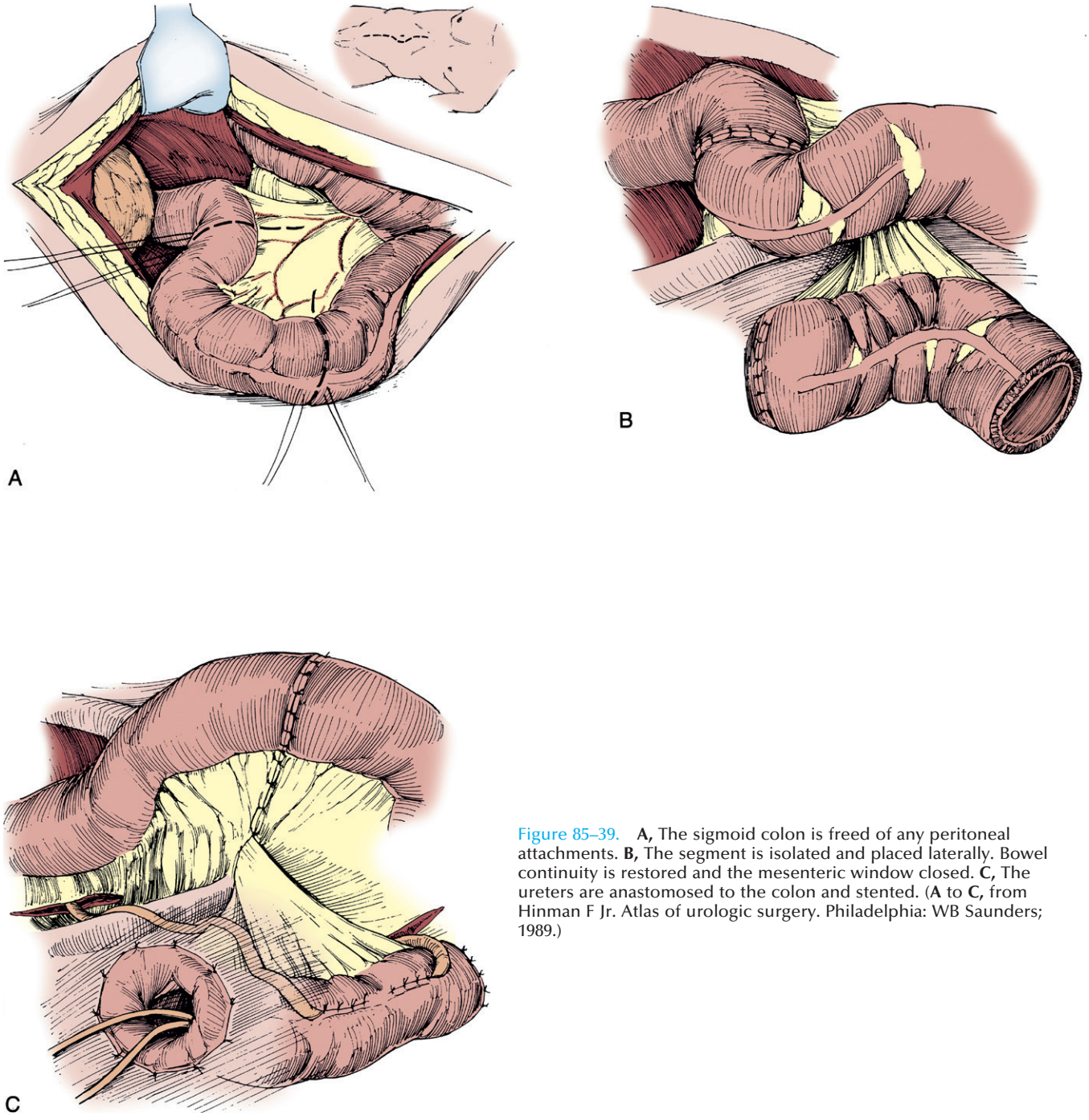


Figure 85–39. **A,** The sigmoid colon is freed of any peritoneal attachments. **B,** The segment is isolated and placed laterally. Bowel continuity is restored and the mesenteric window closed. **C,** The ureters are anastomosed to the colon and stented. (**A** to **C,** from Hinman F Jr. Atlas of urologic surgery. Philadelphia: WB Saunders; 1989.)

stomal prolapse, acute pyelonephritis, bowel obstruction, urinary stones, parastomal hernia, incisional hernia, stomal stenosis, and fecal leakage. There was no difference in the incidence of deterioration of the upper tracts with either form of diversion. Of some note is that at high pressures, a large portion of the ileocecal conduits experienced reflux. At low pressures, however, there was minimal or no reflux. Whenever a portion of colon is used for a conduit, chronic diarrhea may be a consequence.

Ileal Vesicostomy

An ileal vesicostomy uses spatulated ileum and a generous transverse cystotomy to decompress the bladder and to allow an appliance to be used on the abdomen. This procedure is particularly well suited to spinal cord injury patients or those with significant neurologic disease. The concept is that patients with a neurogenic bladder have an easier job of caring for themselves with an abdominal stoma. Patients who are particularly good candidates are those with significant detrusor-external sphincter dyssynergia. Those who have detrusor hyperreflexia, particularly women, may have an increased incidence of incontinence. The complications of the procedure include urethral incontinence requiring closure of the urethra in 20% of patients, stomal stenosis, and bladder and renal calculi.

The procedure is performed by spatulating an ileal segment and performing a generous transverse cystotomy. The spatulated ileum

Table 85–7.

Complications: Transverse Colon Conduit*

	EARLY	LATE
Urine leak	8% (11/137)	8% (2/25)
Acute pyelonephritis		11% (8/75)
Wound infection	5% (5/92)	
Wound dehiscence	7% (8/109)	
Abscess		5% (3/62)
Prolonged ileus	6% (2/30)	
Ureteral stricture	6% (5/84)	17% (37/215)
Bowel obstruction	3% (1/30)	2% (2/109)
Parastomal hernia		4% (5/114)
Stones		11% (11/98)
Enterocutaneous fistula		2% (1/62)
Stomal stenosis		2% (1/62)
Stomal prolapse		11% (6/56)
Metabolic acidosis		12% (3/26)

*Incidence as a percentage of the total number of reported cases from the literature. Numbers in parentheses represent the number of cases from which the percentage is derived.

Table 85–8.

Complications: Sigmoid Conduit*

	EARLY	LATE
Urine leak	1% (1/70)	
Wound infection	1% (1/70)	
Wound dehiscence	1% (1/70)	
Acute pyelonephritis		7% (5/70)
Bowel obstruction		6% (4/70)
Ureteral stricture		9% (6/70)
Stones		4% (3/70)
Parastomal hernia		3% (2/70)
Stomal stenosis		3% (2/70)

*Incidence as a percentage of the total number of reported cases from the literature. Numbers in parentheses represent the number of cases from which the percentage is derived.

Table 85–9.

Complications: Ileocecal Conduit*

	EARLY	LATE
Urine leak	6% (9/147)	
Bowel leak	3% (5/147)	
Gastrointestinal bleed	1% (1/147)	
Wound dehiscence	7% (11/147)	
Acute pyelonephritis		14% (20/147)
Bowel obstruction	3% (5/147)	10% (14/147)
Stomal prolapse		16% (24/147)
Parastomal hernia		5% (7/147)
Stomal stenosis		2% (3/147)
Stones		5% (8/147)
Fecal fistula		2% (3/147)

*Incidence as a percentage of the total number of reported cases from the literature. Numbers in parentheses represent the number of cases from which the percentage is derived.

is sutured to the bladder with absorbable suture, and the distal segment is brought to the abdominal wall by fashioning a rosebud stoma. This results theoretically in a low-pressure reservoir. Its appeal is that if indicated at a later date, the patient's anatomy can be converted back to normal (Mutchnik et al, 1997; Atan et al, 1999).

Management Common to All Conduits

All anastomoses are stented with Silastic stents. A convenient method for introducing the stents through the conduit and into the ureter is illustrated in Figure 85–36. They are removed individually on the fourth to sixth postoperative days. If there is no increase in drainage, the Jackson-Pratt closed-suction drain is removed. **All conduits are retroperitonealized,** with the ureterointestinal anastomosis being placed in the retroperitoneum. This may be accomplished by suturing the posterior peritoneum to the serosa of the conduit above the ureterointestinal anastomosis. A drain may then be laid into the retroperitoneum. The authors prefer to drain the ureterointestinal anastomosis with a Jackson-Pratt closed-suction drain laid in the retroperitoneum 3 to 4 cm away from the anastomosis. The peritoneal cavity should not be drained.

All patients are given nothing by mouth until bowel function returns. A progressive diet is instituted after confirmation of bowel activity. It has been the authors' practice to use NGT decompression in all patients having a bowel anastomosis. In reported surgical series, it is clear that there are advantages and disadvantages of NGT decompression after intestinal surgery. Without its use, vomiting is more common. With its use, pulmonary complications are more frequent. For those individuals with severe respiratory disease, consideration should be given to performing a gastrostomy. All patients have compression boots applied as prophylaxis for pulmonary embolus. The authors have not employed heparin or warfarin (Coumadin) prophylaxis in this group of patients.

METABOLIC AND NEUROMECHANICAL PROBLEMS OF URINARY INTESTINAL DIVERSION

Problems that result from interposition of intestine in the urinary tract may be conveniently divided into three areas for the purposes of discussion: metabolic, neuromechanical, and technical-surgical. Metabolic complications are the result of altered solute reabsorption by the intestine of the urine that it contains. Neuromechanical aspects involve the configuration of the gut, which affects storage volume and contraction of the intestine that may lead to difficulties in storage. Finally, technical-surgical complications involve aspects of the procedure that result in surgical morbidity; these have been discussed after each section on the technical aspects of urinary intestinal diversion. The following is a discussion of metabolic and neuromechanical problems.

Metabolic Complications

Metabolic complications include electrolyte abnormalities, altered sensorium, abnormal drug metabolism, osteomalacia, growth retardation, persistent and recurrent infections, formation of renal and reservoir calculi, problems ensuing from removal of portions of the gut from the intestinal tract, and development of urothelial or intestinal cancer. Many of these complications are a consequence of altered solute absorption across the intestinal segment. **The factors that influence the amount of solute and type of absorption are the segment of bowel used, the surface area of the bowel, the amount of time the urine is exposed to the bowel, the concentration of solutes in the urine, the renal function, and the pH of the fluid.**

Electrolyte Abnormalities

Serum electrolyte complications and the type of electrolyte abnormalities that occur are different, depending on the segment of bowel used. If stomach is employed, a hypochloremic metabolic alkalosis may occur. If jejunum is the segment used, hyponatremia, hyperkalemia, and metabolic acidosis occur. If the ileum or colon is used, a hyperchloremic metabolic acidosis ensues. Other electrolyte abnormalities that have been described include hypokalemia, hypomagnesemia, hypocalcemia, hyperammonemia, and elevated blood urea nitrogen and creatinine. Specific abnormalities for each segment of intestine are detailed.

When stomach is used, a hypochloremic, hypokalemic metabolic alkalosis may ensue. This is generally not a significant problem unless the patient has concomitant renal failure, in which case there is a significant impairment of bicarbonate excretion or the patient is significantly dehydrated (Kurzrock et al, 1998). The metabolic alkalosis on occasion can be severe and life threatening (syndrome of severe metabolic alkalosis) (Table 85–10). This syndrome has been reported in patients with normal renal function. **When it is fully manifested, lethargy, respiratory insufficiency, seizures, and ventricular arrhythmias may occur** (Gosalbez et al, 1993). These symptoms are usually preceded by vomiting resulting in dehydration. A pronounced hypochloremic, hypokalemic metabolic alkalosis ensues. Patients are generally successfully treated with an H_2 blocker to reduce proton secretion by the gastric segment and rehydration. In life-threatening circumstances, arginine hydrochloride infusion has been employed to rapidly restore acid-base balance. On occasion, when the H_2 blockers are ineffective, the proton pump blocker omeprazole has been successfully employed. Rarely, omeprazole is ineffective and if the life-threatening metabolic alkalosis persists, the gastric segment must be removed (Gosalbez et al, 1993).

The role the serum concentration of gastrin plays appears pivotal in the syndrome. In the severe cases that have been reported, there is generally an elevated serum gastrin level. We have shown that **serum gastrin levels are significantly correlated with systemic bicarbonate concentration in gastrocystoplasty patients;** the greater the gastrin level, the more severe the metabolic alkalosis (Tanrikut and McDougal, 2004). When volume depletion, hypochloremia, and hypokalemia result from vomiting in those who normally have elevated circulating gastrin levels and a persisting long-standing metabolic alkalosis, the patient is at greater risk for development of the syndrome of severe metabolic alkalosis and manifestation of the symptoms outlined before. Thus persistent loss of protons from the gastric-augmented bladder with net addition of bicarbonate to the systemic circulation, alteration of normal homeostatic mechanisms for acute changes in acid-base balance, and impaired ability of even a normal kidney to excrete bicarbonate in the face of hypochloremia, hypokalemia, and increased circulating aldosterone levels (due to the dehydration) create a vicious circle in which normal homeostatic mechanisms are circumvented. Indeed, elevated aldosterone levels have been reported in this syndrome (Gosalbez et al, 1993). Hypokalemia, hypochloremia, and increased aldosterone levels impair the kidney's ability to excrete excess bicarbonate. These perturbations coupled with a continued addition of bicarbonate from the gastric segment produce the extreme electrolyte abnormalities noted in the patients described. In view of the **sigmoid correlation of serum bicarbonate to gastrin levels in patients with gastric segments in the urinary tract, patients at most risk for development of the syndrome of severe metabolic alkalosis are those whose serum gastrin concentrations exceed 120 ng/L because on this portion of the curve, small additional increments in gastrin concentration result in large increases in serum bicarbonate** (Fig. 85–40). On the other hand, patients with serum gastrin concentrations below 100 ng/L can have significant increases in gastrin levels with little change in serum bicarbonate. **Failure to properly empty the diversion with overdistention of the gastric segment would be expected to increase the serum gastrin level because stretch is a stimulus for gastrin release. For those who have either an elevated resting gastrin level in excess of 120 ng/L or impaired renal function, both patient and physician should be made aware of the consequences of dehydration and distention of the segment.**

Electrolyte disorders that occur when jejunum is used for urinary intestinal diversion, particularly when proximal jejunum is used, **include hyponatremia, hypochloremia, hyperkalemia, azotemia, and acidosis** (see Table 85–10). These disorders result from an increased secretion of sodium and chloride with an increased reabsorption of potassium and hydrogen ions. This excessive loss of sodium chloride carries with it water, and thus the patient becomes dehydrated. The dehydration results in hypovolemia, which increases renin secretion and thereby aldosterone production (Golimbu and Morales, 1975). Aldosterone production may also be stimulated by hyperkalemia. The high levels of renin-aldosterone facilitate sodium reabsorption by the kidney and potassium loss, which produces a urine low in sodium content and high in potassium. This, when presented to the jejunum, results in a favorable concentration gradient for loss of sodium by the jejunum and increased reabsorption of potassium, thus perpetuating the abnormalities.

These electrolyte abnormalities result in lethargy, nausea, vomiting, dehydration, muscle weakness, and elevated temperature. If the abnormalities are allowed to persist, the patient may become moribund and finally die. **This syndrome may be exacerbated by administration of hyperalimentation solutions.** The mechanism by which

Table 85–10.

Syndromes of Electrolyte Disturbances in Patients in Whom Bowel Is Interposed in the Urinary Tract

SYNDROME	SEGMENT	SYMPTOMS	ASSOCIATED ABNORMALITIES
Syndrome of severe metabolic alkalosis	Stomach	Lethargy, muscle weakness, respiratory insufficiency, seizures, ventricular arrhythmia	Elevated aldosterone, hypochloremia, hypokalemia
Syndrome of hyperkalemia, hypochloremia, metabolic acidosis	Jejunum	Lethargy, nausea, vomiting, dehydration, muscle weakness	Elevated renin, angiotensin
Syndrome of hyperchloremia, metabolic acidosis	Ileum, colon	Fatigue, anorexia, lethargy, weakness	Total-body potassium depletion, hypocalcemia

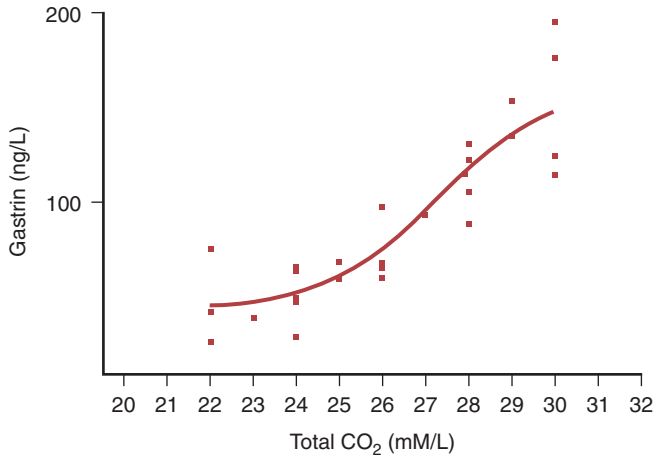


Figure 85–40. Sigmoid relationship of serum gastrin level to serum bicarbonate. Notice that over the physiologic range of normal gastrin levels, 10 to 120 ng/L, there is little change in serum bicarbonate. However, at levels of serum gastrin in excess of 120 ng/L, small changes in serum gastrin levels result in large changes in serum bicarbonate.

hyperalimentation solutions exacerbate this syndrome in patients with jejunal intestine interposed in the urinary tract is unclear (Bonnheim et al, 1984). **The severity of the syndrome depends on the location of the segment of jejunum that is used. The more proximal the segment, the more likely the syndrome is to develop.** Its incidence varies from a low of 25% (Klein et al, 1986) to the majority of patients demonstrating significant abnormalities. Severe abnormalities may occur in as little as 4% when short segments are employed (Fontaine et al, 1997). Treatment of the disorder is rehydration with sodium chloride and correction of the acidosis with sodium bicarbonate. Provided that renal function is normal, the hyperkalemia is corrected by renal secretion. On occasion, a diuretic may be helpful to correct the hyperkalemia. After restoration of normal electrolyte balance, long-term therapy involves oral supplements with sodium chloride. A thiazide diuretic has also been useful in selected cases to control hyperkalemia during the long term (Hasan et al, 1994).

The electrolyte abnormality that occurs with the ileum and colon is hyperchloremic metabolic acidosis (see Table 85–10). This acidosis occurs to some degree in most patients who have ileum or colon interposed in the urinary tract but is generally of a minor degree. Its clinical significance when it is of a minor degree at this time is unknown. Hyperchloremic acidosis has been reported with a frequency of 68% of patients (19 of 28 patients; 10 of the 19 cases were severe enough to require treatment) with ileal conduits (Castro and Ram, 1970). In another study, 70% of patients with ileal conduits observed for 4 years or more had a decreased serum bicarbonate concentration (Malek et al, 1971). A more current study places the incidence at about 25% (Nieuwenhuijzen et al, 2008) with about 4% requiring hospitalization for correction (Studer et al, 2006). Severe electrolyte disturbances occur to a much lesser degree. It has been reported to be a major problem in 18% of patients (8 of 45) with intestinal cystoplasties (Whitmore and Gittes, 1983), in 10% of patients (17 of 178) with ileal conduits (Schmidt et al, 1973), and in 80% of patients (112 of 141) with ureterosigmoidostomies (Ferris and Odel, 1950). In continent diversions involving either ileum and cecum or cecum alone, most patients have an elevated serum chloride and depressed serum bicarbonate (Ashken, 1987; McDougal et al, 1989). Sixty-five percent of patients with Mainz pouches require alkali therapy to maintain a normal acid-base balance (Thuroff et al, 1987). Early reports of patients with continent diversions made of ileum have a much lower incidence of electrolyte problems, in the range of 10% to 15% (see Table 85–3) (Allen et al, 1985; Boyd et al, 1989). **Symptoms in those in whom the syndrome is severe include easy fatigability, anorexia, weight loss, polydipsia, and lethargy.** Those with ureterosigmoidostomies also have an exacerbation of diarrhea.

These electrolyte abnormalities, if significant and allowed to persist, result in major metabolic abnormalities, to be discussed subsequently. In and of themselves, however, they may be lethal because severe electrolyte abnormalities have contributed to death of patients (Heidler et al, 1979).

The mechanism of hyperchloremic metabolic acidosis is due to the ionized transport of ammonium. Ammonium substitutes for sodium in the Na^+-H^+ antiport. The exchange of the weak acid NH_4 for a proton is coupled with the exchange of bicarbonate for chloride. **Thus ammonium chloride is absorbed across the lumen into the blood in exchange for carbonic acid (i.e., CO_2 and water).** Ammonium may also gain entry to the blood from bowel lumen through potassium channels (McDougal et al, 1995).

The treatment of hyperchloremic metabolic acidosis involves administration of alkalizing agents or blockers of chloride transport. Alkalinization with oral sodium bicarbonate is effective in restoring normal acid-base balance. Oral administration of bicarbonate may not be tolerated particularly well, however, because it can produce considerable intestinal gas. An effective alternative is sodium citrate and citric acid solution (Bicitra or Shohl solution) used together; however, many patients do not care for the taste. Potassium citrate, sodium citrate, and citric acid solution (Polycitra) may be used instead if excessive sodium administration is a problem because of cardiac or renal disease and if potassium supplementation is desirable or at least not harmful. In those patients in whom persistent hyperchloremic metabolic acidosis occurs and in whom excessive sodium loads are undesirable, chlorpromazine or nicotinic acid may be used to limit the degree of the acidosis. These agents used alone do not correct the acidosis in humans, but they limit its development and thus reduce the need for alkalinizing agents. Chlorpromazine and nicotinic acid inhibit cyclic adenosine monophosphate and thereby impede chloride transport. Chlorpromazine may be given in a dose of 25 mg three times a day. On occasion, as much as 50 mg three times a day may be necessary, but at such doses, side effects are not uncommon. Chlorpromazine should be used with care in adults because there are many untoward side effects including tardive dyskinesia. Nicotinic acid may be given in a dose of 400 mg three or four times a day. The drug should not be used in patients with peptic ulcer disease or significant hepatic insufficiency. Side effects that may be observed include exacerbation of liver dysfunction, exacerbation of peptic ulcer disease, headaches, and double vision. Flushing and dermatitis are not uncommon and generally disappear as the patient becomes adapted to the drug.

Hypokalemia and total-body depletion of potassium may occur in patients with urinary intestinal diversion. This is more common in patients with ureterosigmoidostomies than it is in patients who have other types of urinary intestinal diversion (Geist and Ansell, 1961). In one study, patients with ureterocolonic diversions had a 30% reduction in total-body potassium, whereas those with ileal conduits had, as a group, no significant alteration in total-body potassium;

individually, however, some had as much as a 14% reduction in total-body potassium (Williams et al, 1967). Patients with continent diversions have also been noted to have a decrease in total-body potassium. The patients most susceptible to total-body potassium depletion are those with long-standing uncorrected metabolic acidosis (Stein et al, 1998). **The potassium depletion is probably due to renal potassium wasting as a consequence of renal damage, osmotic diuresis, and gut loss through intestinal secretion.** The last-mentioned (probably quantitatively) plays a relatively minor role. Indeed, it has been shown that ileal segments exposed to high concentrations of potassium in the urine reabsorb some of the potassium, whereas colon is less likely to do so (Koch et al, 1990). Thus **those with ileum interposed in the urinary tract likely blunt the potassium loss by the kidney, whereas those with colon do not, thus explaining why patients with ureterosigmoidostomies and ureterocolonic diversions are more likely to have total-body potassium depletion.** When the depletion is severe, the patient may develop a flaccid paralysis. **In treating these patients, one must remember that if the hypokalemia is associated with severe hyperchloremic metabolic acidosis, treatment must involve both replacement of potassium and correction of the acidosis with bicarbonate.** If the acidosis is corrected without attention to potassium replacement, severe hypokalemia may occur, marked flaccid paralysis may develop, and significant morbidity may ensue (Koff, 1975).

Because the bowel transports solutes and because its membrane is not particularly watertight, osmolality generally re-equilibrates across the bowel wall. Thus **attempts to deprive a patient of water and determine osmolality as a reflection of renal function are inappropriate because the bowel alters the osmotic content. The bowel also makes the contents more alkaline, and therefore it is impossible to determine the ability of the kidney to acidify simply by measuring urinary pH in patients with urinary intestinal diversion. Finally, because urea and creatinine are reabsorbed by both the ileum and the colon, serum concentrations of urea and creatinine do not necessarily accurately reflect renal function** (Koch and McDougal, 1985; McDougal and Koch, 1986).

Histologic alterations of the intestine may occur over time when urine is chronically exposed to the mucosa. Villous atrophy and the formation of pseudocrypts may occur, particularly in the ileum. These changes are patchy because there is normal ileal mucosa interspersed between these abnormalities. Submucosal inflammatory infiltrates may also be observed. There appear to be fewer changes in the colonic mucosa during the long term. In the colon, a decrease in the size of goblet cells has been described. In time, some transport processes may be altered, with some solutes less actively transported, whereas other processes of solute transport remain active (Philipson et al, 1983). **The ability to establish a hyperchloremic metabolic acidosis, however, appears to be retained by most segments of ileum and colon over time.** In an experimental study, chronic exposure of intestine to urine resulted in a decreased number of transporters, but those that remained were perfectly functional (Grocela and McDougal, 1999).

Altered Sensorium

Alteration of the sensorium may occur as a consequence of magnesium deficiency, drug intoxication, or abnormalities in ammonia metabolism. Patients who develop magnesium deficiency do so either secondary to nutritional depletion or in relation to magnesium wasting by the kidney in much the same way that calcium wasting occurs (see later). Alterations in the sensorium have also occurred because of diabetic hyperglycemia; however, this is not a consequence of the intestinal diversion. In such patients, reabsorption of urinary glucose can result in hyperglycemia without demonstrable glucosuria (Onwubalili, 1982). Perhaps the more common cause of an altered sensorium is a consequence of altered ammonia metabolism. **Ammoniagenic coma in patients with urinary intestinal diversion has been reported in those with cirrhosis** (Silberman, 1958), **those with altered liver function without underlying chronic liver disease** (McDermott, 1957), and those with normal hepatic function as determined by serum enzyme activities (Mounger and Branson, 1972; Kaufman, 1984; Perez-Fidalgo, 2007). The syndrome is most commonly associated with decreased liver function, however, and even in those cases in which normal liver function has been reported, the crude methods by which it was assessed in these reports have been unable to confirm the absence of subtle alterations in liver function. The syndrome is most commonly found in patients with ureterosigmoidostomies but has been reported for those with ileal conduits as well (McDermott, 1957).

The treatment of ammoniagenic coma involves draining the urinary intestinal diversion, either with a rectal tube in the case of ureterosigmoidostomy or with a Foley catheter in those with a continent diversion so that the urine does not remain exposed to the intestine for extended periods. **Neomycin is administered orally to reduce the ammonia load from the enteric tract, and protein consumption is curtailed,** thus limiting the nitrogen load to the patient until serum ammonium levels return to normal. In severe circumstances, arginine glutamate, 50 g in 1000 mL of 5% dextrose in water, may be given intravenously. This complexes the ammonia by providing substrate for the formation of glutamine (Silberman, 1958). Lactulose may be given orally or by rectum (Edwards, 1984). This complexes the ammonia in the gut and prevents its absorption.

Abnormal Drug Absorption

Drug intoxication has been reported in patients with urinary intestinal diversion. **Drugs more likely to be problematic are those absorbed by the gastrointestinal tract and excreted unchanged by the kidney.** Thus the excreted drug is re-exposed to the intestinal segment, which then reabsorbs it, and toxic serum levels develop. This has been reported for phenytoin (Dilantin) (Savarirayan and Dixey, 1969) and has been seen for certain antibiotics that are excreted unchanged. Although chemotherapy is generally well tolerated by patients with conduits, methotrexate toxicity has been documented in a patient with an ileal conduit (Bowyer and Davies, 1986).

A more recent study suggests that in patients with normal renal function, both those with and without continent diversions tolerate chemotherapy well. The authors studied 23 patients with continent diversions and 19 with ileal conduits who received cisplatin, methotrexate, and vinblastine. The authors concluded that there was no difference in toxicity in patients without diversions, those with ileal conduits, and those with continent diversions. Indeed, the patients with continent diversions did not have a Foley catheter placed during the chemotherapy infusion. However, if one looks carefully at the data, it is clear that there is in fact an increased toxicity in the continent diversion group, although it did not achieve statistical significance (Srinivas et al, 1998). In those patients receiving antimetabolites, it is prudent to carefully

monitor the patient for toxic products that are excreted in the urine and capable of intestinal absorption lest lethal toxic serum levels develop. Moreover, **in patients with continent diversions who are receiving chemotherapy, consideration should be given to draining the pouch during the time the toxic drugs are being administered.**

Osteomalacia

Osteomalacia or renal rickets occurs when mineralized bone is reduced and the osteoid component becomes excessive. Osteomalacia has been reported in patients with colocystoplasty (Hassain, 1970), ileal ureters (Salahudeen et al, 1984), colon and ileal conduits, and, most commonly, ureterosigmoidostomies (Harrison, 1958; Specht, 1967). **The cause of osteomalacia may be multifactorial but commonly involves acidosis.** With persistent acidosis, the excess protons are buffered by the bone with release of bone calcium. With its release, it is excreted by the kidney. Support for the theory that chronic acidosis is causative in osteomalacia comes from those patients in whom correction of the acidosis results in remineralization of the bone (Richards et al, 1972; Siklos et al, 1980). It has also been shown, however, that major alterations in serum bicarbonate are not necessary for the development of the syndrome (Koch and McDougal, 1988; McDougal et al, 1988). Moreover, some patients with osteomalacia secondary to urinary intestinal diversion do not have bone demineralization corrected with restoration of normal acid-base balance. **These patients have been found to manifest vitamin D resistance that is independent of the acidosis.** It is likely that this resistance is of renal origin. Resistance can be overcome by supplying 1-α-hydroxycholecalciferol, a vitamin D metabolite that is much more potent than vitamin D_2. By providing this substrate in excess amount, remineralization of bone occurs (Perry et al, 1977). Also, it has been shown that reabsorption of urinary solutes may play a role in increasing calcium excretion by the kidney. Sulfate filtered by the kidney inhibits calcium reabsorption and results in both calcium and magnesium loss by the kidney. Thus if the gut increases its sulfate reabsorption and requires the kidney to increase sulfate excretion, this results in hypercalciuria and hypermagnesuria (McDougal and Koch, 1989). Finally, there is some evidence to indicate that the calcium-to-parathormone ratio is altered, suggesting that a resistance to parathormones develops during the long term (Tanrikut and McDougal, 2004). **Osteomalacia in urinary intestinal diversion may be due to persistent acidosis, vitamin D resistance, and excessive calcium loss by the kidney. It appears that the degree to which each of these contributes to the syndrome may vary from patient to patient.**

It is clear that a number of metabolic problems have been obviated when meticulous attention is paid to correction of the abnormalities prospectively. If a base deficit of more than 2.5 mEq/L is corrected, some investigators have found no evidence of bone mineral density abnormalities (Stein et al, 1998). Indeed, the type of diversion does not seem to make a difference when the acidosis is taken into account and corrected (Kawakita et al, 1996). Others suggest that there is no difference in continent diversions and ileal conduits (Campanello et al, 1996); however, in such selected series, the distribution of acidosis across both groups is generally identical. It is clear that if the groups are large enough and not preselected, there is an increased incidence of acidosis in continent diversion patients. Indeed, if patients are followed long enough some will develop bone mineral density abnormalities, particularly in those who are acidotic over the long term (Incel et al, 2006). The take-home message is that if one pays meticulous attention to correction of the acidosis, bone mineral density abnormalities will probably not become a problem.

Patients who develop osteomalacia generally complain of lethargy; joint pain, especially in the weight-bearing joints; and proximal myopathy. Analysis of serum chemistries reveals that the calcium concentration is either low or normal. The alkaline phosphatase level is elevated, and the phosphate level is low or normal (Harrison, 1958). The treatment as indicated earlier involves correction of the acidosis and dietary supplementation of calcium. If this does not result in remineralization of the bone, the active form of vitamin D may be administered. If this is not successful, the more active metabolite of vitamin D_3, 1-α-hydroxycholecalciferol, should be administered.

Growth and Development

Considerable evidence suggests that urinary intestinal diversion has a detrimental effect on growth and development. In a study of 93 myelodysplasia patients observed for 17 to 23 years, significant aberrations in growth were noted when morphometric parameters were analyzed. Anthropometric measurements in those with urinary intestinal diversion showed a decrease in linear growth in all indices measured, with a statistically significant decrease in biacromial span and elbow-hand length (Koch et al, 1992).

Patients with long-term urinary diversions are more susceptible to fractures and to complications after orthopedic procedures. When myelodysplastic patients with ileal conduits were compared with a similar group of patients who retained their bladder and were on intermittent catheterization, the patients with an ileal conduit had an increased number of fractures, as well as malunions and nonunions after orthopedic procedures (Koch et al, 1992). It was found that more patients with urinary intestinal diversion fell below the tenth percentile than did patients who were treated with intermittent catheterization. There was, in fact, no difference in height and weight between the two groups studied (Koch et al, 1992; McDougal, 1992).

There is also experimental evidence for impaired linear growth in urinary intestinal diversion. Rats with unilateral ureterosigmoidostomies observed long term demonstrated significantly decreased femoral bone length compared with nondiverted controls (Koch and McDougal, 1988). Thus it appears clear that although obvious alterations in growth and development do not occur, when carefully studied, patients who have urinary intestinal diversions constructed in childhood and who maintain these diversions for more than 10 years have significant changes in linear growth.

Infection

An increased incidence of bacteriuria, bacteremia, and septic episodes occurs in patients with bowel interposition. A significant number of patients with intestinal cystoplasty develop pyelonephritis, and 13% have septic and major infectious complications (Kuss et al, 1970). The episodes are more frequent after colocystoplasty than ileocystoplasty (Kuss et al, 1970). In a contemporary series 4% of patients were admitted to a hospital for sepsis (Studer et al, 2006). Acute pyelonephritis occurs in 10% to 17% of patients with colon and ileal conduits (Schmidt et al, 1973; Schwarz and Jeffs, 1975; Hagen-Cook and Althausen, 1979). Approximately 4% of patients (8 of 178) with ileal conduits die of sepsis (Schmidt et al, 1973).

Patients with conduits have a high incidence of bacteriuria. Indeed, **approximately three quarters of ileal conduit**

urine specimens are infected (Guinan et al, 1972; Middleton and Hendren, 1976; Elder et al, 1979). It is clear that some patients are merely colonized at the distal end of the conduit because the incidence of positive cultures can be markedly diminished by culture of the proximal portion of the loop by a double-catheter technique (Smith, 1972). Many of these patients, however, show no untoward effects and seem to do well with chronic bacteriuria. **Deterioration of the upper tracts is more likely when the culture becomes dominant for *Proteus* or *Pseudomonas*. Thus patients with relatively pure cultures of *Proteus* or *Pseudomonas* should be treated, whereas those with mixed cultures may generally be observed, provided they are not symptomatic. Patients with continent diversions also have a significant incidence of bacteriuria and septic episodes** (McDougal, 1986). Indeed, two thirds of patients with Kock continent diversions have positive cultures (Kock, 1987). The reasons for the increased incidence of bacteriuria and sepsis are unclear, but it is likely that the intestine is incapable of inhibiting bacterial proliferation, in contrast to the urothelium. Thus intestine that normally lives symbiotically with bacteria when interposed in the urinary tract serves as a source for ascending infection and septic complications. Moreover, the intestine may make the urine less bacteriostatic and thereby promote the growth of bacteria. Distention of the intestinal segment may aid in translocation of bacteria across the intestine and into the blood. Studies have shown some changes in intestinal mucosal immunologic bacterial defense mechanisms; however, for the most part, they seem to be preserved (Wullt et al, 2004).

Stones

One of the consequences of persistent infection is the development of magnesium ammonium phosphate stones. Indeed, **the great majority of stones formed in patients with urinary intestinal diversions are composed of calcium, magnesium, and ammonium phosphate. Those most susceptible to development of renal calculi are patients who have hyperchloremic metabolic acidosis, pre-existing pyelonephritis, and urinary tract infection with a urea-splitting organism** (Dretler, 1973). The incidence of renal stones is 3% to 4% in patients with colon conduits (Althausen et al, 1978; Hagen-Cook and Althausen, 1979) and 10% to 12% in those with ileal conduits (Schmidt et al, 1973). In those with continent cecal reservoirs, there is a 20% incidence of calculi within the reservoir (Ashken, 1987). The stones may be due to persistent infection with alkalinization of the urine, persistent hypercalciuria for reasons described previously, and alterations of urinary excretion products by the intestine. A major cause of calculus formation in conduits and pouches is a foreign body such as a staple or nonabsorbable suture, on which concretions form. In intestinal reservoirs, alterations in bowel mucosa may also serve as a nidus for stone formation. Finally, alterations in intestinal mucus, particularly in the presence of infection or obstruction, may serve as a nidus or more importantly may interfere with emptying and thereby exacerbate infection and stone formation (N'Dow et al, 2004).

Intestinal Motility, Short Bowel, and Nutritional Problems

Many nutritional problems may occur from the loss of significant intestinal absorptive surface resulting from removal of substantial portions of the gut for construction of a urinary intestinal diversion. **In patients with a significant loss of ileum, vitamin B_{12} malabsorption has been reported and results in anemia and neurologic abnormalities.** Vitamin B_{12} deficiency has been shown to occur in 10 of 41 patients who received preoperative radiotherapy before radical cystectomy and ileal ureterostomy (Kinn and Lantz, 1984) and 21% of children following ileocystoplasty have low serum levels of B_{12} (Rosenbaum et al, 2008). **Loss of significant portions of ileum also results in malabsorption of bile salts.** Because the ileum is the major site of bile salt reabsorption, the lack of reabsorption allows bile salts entry into the colon, which causes mucosal irritation and diarrhea. Also, loss of the ileum results in the loss of the "ileal break." The ileal break is a mechanism whereby gut motility is reduced when lipids come in contact with the ileal mucosa so that increased absorption can occur. With the loss of ileum, the lipid does not result in decreased motility and is presented unmetabolized to the colon, which may result in fatty diarrhea.

It has been difficult to demonstrate untoward effects of low serum B_{12} levels in these patients. The liver stores enough B_{12} to supply the body's requirement for 3 to 5 years without oral intake. Thus pathologic problems would not be expected to manifest themselves for many years and have rarely been reported. Moreover, low serum levels of Vitamin B_{12} do not necessarily correlate with metabolic deficiency. To assess whether or not there is a metabolic impact it is necessary to measure serum levels of homocysteine and/or methylmalonic acid. Because vitamin B_{12} serves as a coenzyme in the metabolic pathways of homocysteine and methylmalonic acid, their measurement is a sensitive indicator of whether the low vitamin B_{12} level is significant. These measurements have not been done in this group of patients, and thus it is unclear at this time as to the importance of vitamin B_{12} measurements in these patients. Many physicians, however, empirically give patients who have had intestinal diversions of ileum in place for more than 5 to 7 years parenteral vitamin B_{12} as a precaution.

Loss of the ileocecal valve may have a number of untoward effects. Because of the loss of the valve, reflux of large concentrations of bacteria into the ileum may occur, resulting in small intestinal bacterial overgrowth. This may result in nutritional abnormalities that involve interference with fatty acid reabsorption and bile salt interaction. With the lack of absorption of fats and bile salts, these are presented to the colon and result in diarrhea. Moreover, reflux of bacteria into the small bowel may result in bile salt deficiency. Also, the lack of fat absorption may result in deficiencies of the fat-soluble vitamin A, osteomalacia due to lack of vitamin D, and complexing of calcium with the fats to form soaps and thus lack of its absorption. The ileocecal valve also serves as a break, and an intact valve prolongs transit time of the small bowel and enhances absorption. Thus its loss may contribute to nutritional abnormalities. Some have advocated reconstruction of the valve mechanism between ileum and colon when the ileocecal segment is used for reconstruction.

Loss of a significant portion of jejunum may result in malabsorption of fat, calcium, and folic acid; however, significant portions of jejunum are rarely used for urologic reconstructive procedures. Loss of the colon may result in diarrhea because of lack of fluid and electrolyte absorption, loss of bicarbonate because of its increased secretion in the ileum and lack of reabsorption, and dehydration because of the loss of fluids.

Of concern when intestinal segments are used in urinary reconstruction is the effect removal of a segment of intestine from the alimentary tract might have on intrinsic bowel function. Indeed, removal of major segments from the alimentary tract may cause nocturnal bowel movements, fecal urgency, fecal incontinence, diarrhea, and nutritional deficiencies (Riddick et al, 2004). A study compared patients with ileal conduits with those who had

segments used for clam cystoplasty and not surprisingly found that those with clam cystoplasty had a 40% incidence of significant bowel problems. It is known that there is an association between detrusor instability and irritable bowel, perhaps accounting for the incidence of untoward disorders of bowel function in this series (N'Dow et al, 1998). Thus there is a need for heightened awareness of bowel dysfunction in patients with detrusor instability in whom bowel segments are to be used. A recent report of patients who had an ileocystoplasty noted that 7% had significant diarrhea (Blaivas et al, 2005). One should warn patients who will have major portions of the intestinal tract used in the reconstruction that bowel problems may ensue.

Cancer

The incidence of cancer development in patients with ureterosigmoidostomy varies between 6% and 29%, with a mean of 11% (Schipper and Decter, 1981; Stewart et al, 1982; Zabbo and Kay, 1986). There is generally a 10- to 20-year delay before the cancer becomes manifest. **On histologic examination, the tumors include adenocarcinoma, adenomatous polyps, sarcomas, and transitional cell carcinoma.** Case reports of tumors developing in patients with ileal conduits, colon conduits, bladder augmentations, rectal bladder, neobladders, and ileal ureters have been described (Austen and Kalble, 2004). Anaplastic carcinomas and adenomatous polyps have been reported in patients with ileal conduits. Adenocarcinoma has developed in patients with colon conduits; adenocarcinoma, undifferentiated carcinoma, sarcomas, and transitional cell carcinomas have developed in patients with bladder augmentations with both ileum and colon (Filmer, 1986).

The etiologic mechanism of the development of the carcinoma is not understood. Whether the tumor arises from transitional epithelium or colonic epithelium is unclear. Because most of the tumors are adenocarcinomas, it has been assumed that the tumor arises from the intestinal epithelium. Adenocarcinomas have been shown to arise from transitional cell epithelium exposed to the fecal stream in experimental animals (Aaronson et al, 1989). Furthermore, studies show that the ureters in ureterosigmoidostomy patients have an exceedingly high incidence of dysplasia (Aaronson and Sinclair-Smith, 1984). Moreover, if the transitional epithelium is removed from the enteric tract, adenocarcinomas do not develop. **If the urothelium is left in contact with the intestinal mucosa, however, even though the diversion is defunctionalized and the area is not bathed in urine, adenocarcinoma may still develop.** This is illustrated by a case report in which a patient who had a ureterosigmoidostomy that was defunctionalized with a conduit subsequently developed cancer 9 months later. The distal ureters at the sigmoid were left in situ. Twenty-two years later, the patient developed cancer at the site of the ureterointestinal anastomosis (Schipper and Decter, 1981). This suggests that **when ureterointestinal anastomoses are defunctionalized, they should be excised rather than merely ligated and left in situ.** Other evidence including cell staining techniques suggests that the colon is the primary organ of origin (Mundy, personal communication, 1991). Whether the urothelium or intestine is the primary site of origin, it seems likely that tumors can arise from both tissues.

The highest incidence of cancer occurs when the transitional epithelium is juxtaposed to the colonic epithelium and both are bathed by feces (Shands et al, 1989). Nitrosamines, known mutagens, are produced in rats with ureterosigmoidostomy (Cohen et al, 1987), but there appears at least at this juncture no convincing evidence to support a primary role for them in the genesis of the tumor. An abnormal pattern of colonic mucin secretion has been demonstrated in patients with ureterosigmoidostomy, but its significance is unclear (Iannoni et al, 1986). Induction of specific enzymes associated with carcinoma has also been demonstrated. Ornithine decarboxylase, an enzyme that has been found to be elevated in malignant colonic mucosa, is also elevated in experimental animals with vesicosigmoidostomy (Weber et al, 1988). The role of epidermal growth factor and other growth factors is currently being investigated. Evidence suggests that these may at least play a role in development, if not in induction. At this time, the cause of the genesis of cancer in urinary intestinal diversion is not known. **Because its incidence is significant in patients with ureterosigmoidostomies, they should have routine colonoscopies on a scheduled periodic basis.**

Neuromechanical Aspects of Intestinal Segments

Both small bowel and colon contract to propel luminal contents in an aboral direction. The ability to propel luminal contents is a consequence of muscle activity, as well as coordinated nerve activity. Both the small bowel and the colon have an outer longitudinal layer of muscle and an inner circular layer. There is also a muscularis mucosa, which is immediately beneath the mucosa and may extend into the villi. The outer and inner layers of muscle, however, play the major role in peristalsis. In the colon, the outer longitudinal layer of muscle condenses to form three taeniae coli. The bowel receives its parasympathetic innervation from the vagus. It is also innervated by the sympathetic nervous system. The nerves lie between the circular and longitudinal layers of muscle. The enteral nervous system operates autonomously, and therefore one can denervate the intestine and not affect the coordinated contractions. These contractions are termed *activity fronts* and may be stimulated by feeding, or they may be inhibited by exposure of the lumen to various substances (i.e., lipid in the ileum decreases ileal motility). Two aspects of neuromechanical properties are particularly germane to urinary intestinal diversion: volume-pressure relationships and motor activity.

Volume-Pressure Considerations

The volume-pressure relationships depend on the configuration of the bowel. If one splits the bowel segment and turns it back on itself, the volume may be doubled if the ends are not closed (Fig. 85–41). In reconstruction of intestinal segments for the urinary tract, however, one must close the ends. Thus the limit of doubling the volume is never quite reached. Indeed, **the greater the ratio of length to diameter, the greater the volume change when the ends are closed. If the ends are closed when a ratio of 1:3.5 diameter to length is reached, splitting the segment no longer increases the volume. By splitting most segments, one is, in fact, increasing the volume by about 50%. The goal in reconfiguring the bowel is to achieve a spherical storage vessel. This configuration has the most volume for the least surface area.** By increasing the volume, it has been suggested that pressure relationships within the confines of the intestine are reduced. This is based on Laplace's law, which states that for a sphere, the tension of its wall is proportional to the product of the radius and pressure. Thus theoretically, for a given wall tension, the greater the radius, the smaller the generated pressure. This is desirable in an attempt to prevent deterioration of the upper tracts or incontinence. **This relationship (Laplace's law), however,**

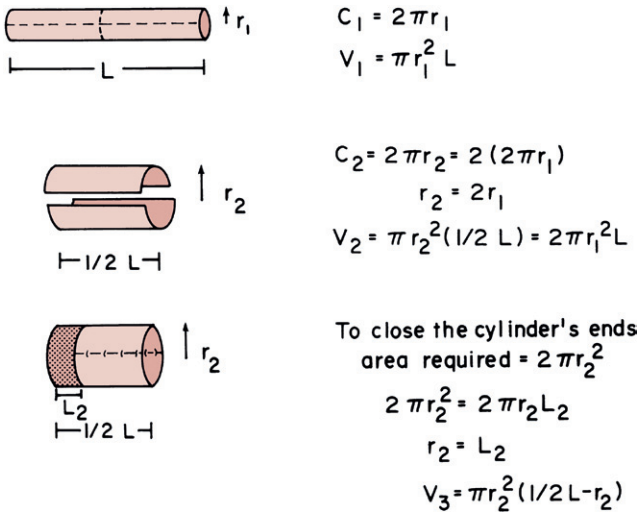


Figure 85–41. Effect of "detubularization." The bowel is split on its antimesenteric border and divided in two. When the two segments are placed together, the circumference is doubled, thus doubling the volume. Closing the ends of the cylinder requires a reduction in its length equal to the radius of the end. This limits the increase in volume that occurs by reconfiguration.

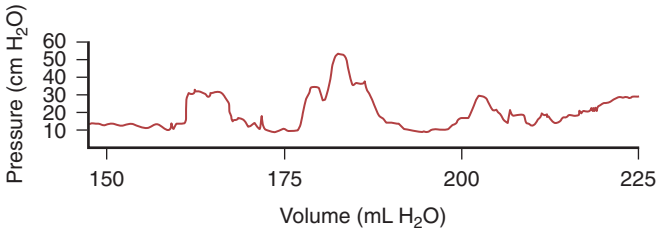


Figure 85–42. Pressure waves recorded 1 year postoperatively in a patient with a continent diversion constructed from detubularized ileum and right colon. Notice that the coordinated pressure waves are of magnitude and frequency similar to those found in a normal colonic or ileal segment.

may not be accurately reflected for intestinal segments because they are not perfectly spherical, and the intestinal wall does not conform to Hooke's law but rather demonstrates viscoelastic properties, which tend to distort the relationship between pressure applied at the wall and tension generated in it. In any event, it seems desirable to attempt to construct as spherical a container as possible if one is attempting to make a reservoir.

Over time, the volume capacity of segments increases. This occurs only if they are frequently filled. Their volume decreases with time if they are nonfunctional (Kock et al, 1978). Over time, it can be demonstrated that there is a marked accommodation in volume of pouches made from intestine. For ileal pouches, it has been shown that the capacity increases sevenfold after 1 year (Berglund et al, 1987). As the reservoirs increase in volume, there is a significant increase in smooth muscle thickness of the bowel wall (Philipson et al, 1983).

Motor Activity

It has been suggested that splitting the bowel on its antimesenteric border discoordinates motor activity and thereby causes a lesser intraluminal pressure. Clearly, the ideal situation is to provide the patient with a spherical vessel that has few or ineffective contractions of its walls. It can be demonstrated in experimental animals that by **splitting the bowel wall on its antimesenteric border and reconfiguring it, acutely there is a marked interruption of coordinated activity fronts, which during a period of 3 months return to their normal coordinated state** (Concepcion et al, 1988). This has also been demonstrated clinically: Initially after reconfiguration of the bowel (detubularization), coordinated activity fronts have been shown to decrease. During extended periods, however, many of the peristaltic waves (activity fronts) reappear and can be readily demonstrated (Fig. 85–42).

The literature is contradictory with respect to the effect of detubularization on segments of ileum and colon used to construct storage vessels for continent diversions. Pressure within the lumen of bowel that has both ends closed may be increased by adding volume or reducing the size of the bowel through contractions of its wall. Because the bowel wall is freely permeable to water, the higher osmotic content of urine obligates movement of water into the bowel lumen. Most patients with continent diversions excrete 2 to 4 L/day (McDougal, 1986). In evaluating whether motor activity is the primary determinant of intravesical pressure, one must be cognizant of fluid volume changes. Also, as indicated previously, early reports of detubularized segments would be expected to differ from later reports when coordinated activity fronts in these segments return.

These facts are often forgotten, and because pressure measurements are used to infer motor activity, rather than its direct measurement as reflected by changes in bowel wall tension, it is not difficult to understand why there are so many contradictions reported in the literature. Detubularization of ileal segments has been reported by some to decrease motor activity at a year compared with immediately postoperatively (Berglund et al, 1987), whereas others have noted increased motor activity at 1 year. Involuntary pressure waves occur in 25% of patients with Kock pouches. Maximum intravesical pressures average 41 cm H_2O in these pouches (Chen et al, 1989). Ileum has also been shown to have fewer activity fronts per unit of time than cecum (Berglund et al, 1986). Cecum has been observed to have the same number of activity fronts 1 year postoperatively, but the amplitude of the pressure waves has been observed to decrease over time (Hedlund et al, 1984). Maximum pressures in normal cecum have been shown to range from 18 to 100 cm H_2O (Jakobsen et al, 1987), whereas detubularized cecum has been shown to have pressures that range between 5 and 25 cm H_2O 1 year postoperatively (Hedlund et al, 1984). Others, comparing ileum to cecum, find no difference in pressure generated after a year (Hedlund et al, 1984). The Mainz pouch, which employs both ileum and cecum, has an average pressure at capacity of 39 cm H_2O with a maximum pressure of 63 cm H_2O (Thuroff et al, 1987). **Thus reconfiguring bowel usually increases the volume, but its long-term effect on motor activity and wall tension is unclear at this time. It has been the authors' observation that some patients with orthotopic bladders after a number of years of spontaneous voiding require intermittent catheterization. In these patients the bowel segment has become flaccid, and the ability of the patient to generate intraluminal pressure by a Valsalva maneuver is limited.**

SUMMARY

This chapter has addressed complications both independent of and dependent on the specific type of urinary intestinal diversion. Each unique type of diversion has its own set of individual

Key Points: Urinary Intestinal Diversion

- Although 15 cm of small bowel can survive beyond the last vessel, it is unwise to assume that more than 8 cm of small bowel will survive beyond a straight vessel.
- The bacterial concentration ranges from 10 to 10^5 in the jejunum, 10^5 to 10^7 in the distal ileum, 10^6 to 10^8 in the ascending colon, and 10^{10} to 10^{12} in the descending colon.
- A mechanical bowel preparation reduces the total number of bacteria, not their concentration.
- The guiding principles of a proper intestinal anastomosis include adequate exposure, good blood supply, prevention of spillage of enteric contents, accurate apposition of the serosa of the two segments of bowel, proper tension of the sutures, and realignment of the mesentery of the two segments.
- After a ureteral anastomosis, deterioration of the upper tracts during the long term is usually due to a lack of ureteral motility, infection, or stones and less commonly due to a stricture at the anastomotic site.
- Antirefluxing ureteral-intestinal anastomoses have a higher rate of stricture than refluxing anastomoses.
- Limited segments of bowel should be used in patients who have an inability to acidify the urine to less than 5.8, an inability to concentrate greater than 600 mOsm/kg, or a GFR less than 35 mL/min.
- Metabolic complications of intestine interposed in the urinary tract include electrolyte abnormalities, altered sensorium, abnormal drug metabolism, osteomalacia, growth retardation, persistent and recurrent urinary tract infection, formation of calculi, short gut, and development of urothelial or intestinal cancers.
- Those gastrocystoplasty patients most at risk for the development of the syndrome of severe metabolic alkalosis are those with high resting levels of serum gastrin who overdistend their pouches and are dehydrated.
- The electrolyte abnormality that occurs with ileum and colon is a hyperchloremic metabolic acidosis.
- Patients receiving chemotherapy who have intestine interposed in the urinary tract have increased toxic effects of chemotherapeutic agents compared with patients with normal urinary tracts.

complications. Moreover, the procedure preceding the urinary intestinal diversion also has a set of complications that must be added to those described previously. It is clear that with current modalities of urinary intestinal diversion, long-term complications significantly contribute to mortality and morbidity. Many patients who have intestinal diversion after an extirpative procedure for cancer, however, die of the cancer rather than of these long-term complications. Those for whom a urinary intestinal diversion has been constructed for benign disease and those who are cured of cancer are most likely to experience long-term morbid complications. The knowledge of the frequency of these complications and the correct performance of preoperative preparation, surgical technique, and postoperative care, as outlined in this chapter, should provide the best chance for the least mortality and morbidity in patients undergoing urinary intestinal diversion.

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The complete reference list is available online at www.expertconsult.com.

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Cutaneous Continent Urinary Diversion

James M. McKiernan, MD ● G. Joel DeCastro, MD, MPH ● Mitchell C. Benson, MD

General Considerations
Continent Urinary Diversion
Quality of Life Assessments
Variations in Operative Technique
Summary

GENERAL CONSIDERATIONS

Continent urinary diversion is widely accepted by both urologist and patient alike as an acceptable form of urinary reconstruction after cystectomy. Orthotopic urethral anastomotic procedures and continent catheterizable stomal reservoirs have stood the test of time, and both procedures should always be considered for all appropriate patients. Orthotopic continent diversion and the metabolic consequences of continent urinary diversion are covered in separate chapters. In this chapter the focus is on the continent cutaneous diversion surgeries associated with the highest success rates. Over the past 25 years the design of the reservoir has not substantially changed. However, an evolution has occurred in the techniques used to create antireflux and continence mechanisms in order to make them more effective and reliable. In addition, attention is given to the long-term quality of life outcomes of continent cutaneous reservoirs, as well as to the newer laparoscopic approaches used to create such reservoirs.

Despite the considerable enthusiasm for continent urinary diversion operations, those procedures requiring the use of external urinary collecting appliances remain more common. Although continent urinary diversion is certainly appropriate in selected patients, the procedures are technically more challenging and associated with higher short-term and long-term complication rates than those that use external collecting devices. However, the operating time associated with these more complex procedures has been significantly reduced by the widespread use of absorbable and metal staples in the construction of the reservoirs and limbs. These techniques are discussed in detail later. Also, as experience with continent urinary diversion has grown, complication rates have decreased dramatically. As a result, in some centers continent diversions are now more commonly employed than conduit diversions.

Patient Selection

Because the ability to self-catheterize is essential to the patient undergoing continent diversion, the patient must be assessed for the ability to care for himself or herself. Consultation between an enterostomal therapist and the patient is extremely helpful in this regard because the patient may be at greater ease with the therapist and more willing to express any concerns. Certain patients may not be able to comprehend the strict flushing and catheterization regimens that must be followed after continent urinary diversion or may lack the motor skills to independently perform self-care. **Patients with multiple sclerosis, quadriplegic individuals, and frail or mentally impaired patients will at some point in their lives require family or visiting nurses for basic care and are therefore viewed as poor candidates for any form of continent diversion.** Indeed, these patients may also require assistance with external appliances, but the degree of time and expertise required is much less burdensome on the care provider and the health care system. On the contrary, continent catheterizable diversion requires continuous attention and may limit patient and family options when determining long-term care needs.

Patient Preparation

All patients undergoing anticipated continent urinary diversion should be prepared for the possibility that a traditional ileal conduit might be performed. Although it is rare to abandon a continent diversion owing to unanticipated problems, this always remains a possibility. Therefore before starting the operation, the site for an external stoma should be selected with extreme care. In general, the location must be free from fat creases in both the standing and sitting position and it should not be close to prior abdominal scars that may interfere with proper adherence of an external appliance. Here, again, the aid of an enterostomal therapist is helpful. In general, the stoma should be brought through the right (or left) lower quadrant of the abdomen on a line extending from the umbilicus to the anterior superior iliac spine. The stoma should be as far lateral from the midline as possible, but the site selected should ensure that the bowel segment comprising the stoma traverses the rectus muscle. Failure to adhere to this rule increases the risk of parastomal hernias. The selected site for the stoma should be marked with an X scratched onto the anterior abdominal wall. Marking the stoma site with ink should be avoided because it may be washed away during the antiseptic preparation of the skin.

The surgeon undertaking continent urinary diversion should be familiar with more than one type of continent diversion

technique. Although it is uncommon to have to abandon a given bowel segment for the reservoir, it is not uncommon to have to modify the antireflux or continence mechanism. In these circumstances, it is essential that the surgeon be able to select an alternate form of continent diversion from what was originally intended.

Renal and hepatic function must be reviewed carefully in the patient selected for continent diversion (Mills and Studer, 1999). The reabsorption and recirculation of urinary constituents and other metabolites require that liver function be normal and that serum creatinine levels be within normal range, or certainly below the level of 1.8 mg/dL. In cases in which renal function is borderline, creatinine clearance should be measured. A minimal level of 60 mL/min should be documented before deeming the patient an appropriate candidate for continent diversion. In patients with bilateral hydronephrosis in whom renal functional improvement might be anticipated on relief of the ureteral obstruction, the upper urinary tract should first be decompressed with either ureteral stenting or percutaneous nephrostomy(ies). Subsequent reevaluation of renal function should be performed before undertaking a continent diversion.

Procedures that will require use of the colon should always be preceded by a colonoscopic assessment of the entire large intestine. Performing only a sigmoidoscopy for a procedure that will use only this segment of the large bowel is insufficient because disease proximal to the resected segment may leave the patient with short colon syndrome. The preoperative assessment of the colon is not necessary if continent urinary diversion using small intestine is planned.

Healthy patients undergoing radical cystectomy can be admitted to the hospital on the day of surgery. A mechanical bowel preparation is administered after a liquid dinner on the night before surgery. The patient is instructed to drink copious amounts of water, and at 8 PM and 10 PM the patient is administered oral metronidazole (500 mg). In addition, the patient should receive cefoxitin (1 gm) intravenously 1 hour before the skin incision.

Cystectomy

All operations described require a midline incision, skirting the umbilicus to the side opposite the selected stoma site. The incision for a right colon pouch usually extends from the pubis to a point midway between the umbilicus and the xiphoid. The cranial extent of the incision is governed by the hepatic flexure, which must be divided to obtain sufficient colonic length and to allow for the right colon to easily fold on itself. On some occasions, the incision will be extended to the xiphoid. The incision for procedures using only the ileum should extend to just below the umbilicus. The cystectomy procedure is covered elsewhere in this text, and only those points germane to continent diversion are covered here.

After abdominal exploration, the ureters are isolated, transected, and transposed to an appropriate place for subsequent diversion. The right retroperitoneum is first opened over the iliac artery to expose the right ureter. In the typical circumstance of conduit diversion, the right ureter is transected below the common iliac artery. For all continent diversions, both ureters are transected as low as possible and shortened to the appropriate length once the final anatomy is determined. The sigmoid colon is freed from its lateral peritoneal attachments by incising along the line of Toldt. A wide tunnel is created by blunt finger dissection ventral to the aorta and common iliac arteries and caudal to the inferior mesenteric artery. This affords left ureteral access to the previously exposed right retroperitoneum. In cases of uroepithelial malignancy it is prudent to evaluate the margin status of the most distal portion of both ureters using frozen section analysis. In situations where substantial ureteral length is removed to obtain negative surgical margins, extension of the afferent limb mechanism may be necessary to allow tension-free ureteral intestinal anastomoses.

All sutures used in the urinary tract should be absorbable. The individual surgeon's preference will dictate the caliber and type of suture material used. When carrying out bowel surgery for continent urinary diversions, stapling is the preferred method for division of the bowel segment, as well as for reconstruction of bowel continuity. This technique shortens operative times greatly and affords safe and reliable bowel anastomosis. Suturing is not necessary with the exception of placing two silk Lembert sutures at the apex of side-to-side stapled bowel anastomoses in order to prevent tension on the staple line. To avoid stone formation on the stapled proximal bowel segments, oversewing the stapled end of the conduit with absorbable material isolates the metal staple line from urinary contact within the lumen.

In constructing a nonappendiceal continent urinary diversion stoma, a skin button matching the diameter of the structure to be used in the diversion is resected. Cutaneous tissues are separated down to the level of the anterior rectus fascia, where a circle of similar diameter is excised from this fascia or, alternatively, the fascia is incised in a cruciate fashion. In carrying out this maneuver, it is essential that the fascia and skin are properly aligned in order to avoid angulation. Rectus muscle fibers are separated bluntly and an instrument passed through the posterior fascia and peritoneum. For appendiceal stomas, we prefer to perform a Y-shaped cutaneous incision that allows for a YV-type plasty incision between the appendiceal limb and the skin (Fig. 86–1). This will decrease the likelihood of subsequent stomal stenosis. Alternatively, the appendix lends itself to an umbilical stoma (Bissada, 1993; Gerharz et al, 1997). Favorable results with this appendiceal YV plasty technique to the umbilical site have been reported (Bissada, 1998).

It is standard procedure to use long, end-hole single J–type diverting stents in all continent cutaneous urinary diversions. These stents drain urine externally, ensuring that urine is safely diverted beyond any anastomotic site during the early healing period. They can also be safely manipulated or exchanged if necessary. The end hole allows for the passage of a straight wire through the stent, which decreases the likelihood of anastomotic trauma at the time of stent removal.

The authors advocate the use of closed suction drains in all cases of urinary diversion. Soft silicone Jackson-Pratt closed suction drains are preferred because they have less potential for tissue damage or migration into pouches.

Abdominal closure is performed according to the surgeon's preference. In general a single-layer closure, using No. 2 nylon, Surgilene, or Prolene taken through all layers of fascia and muscle provides a rapid and secure abdominal closure in the majority of patients. In obese patients, those with tissues of poor quality, or nutritionally depleted patients, through-and-through stay sutures are also used. Ureteral stents are always brought through separate abdominal stab wounds, sutured to the anterior abdominal wall, and directed into separate drainage bags to monitor urine output. Even at this early stage it is important to ensure adequate drainage of the reservoir in order to prevent pouch rupture should the ureteral stents be displaced. In the case of limited pouch access such as with an appendiceal stoma, a Malecot tube should be placed directly into the reservoir and secured to the skin. The reservoir is sutured to the abdominal wall to prevent urine leakage

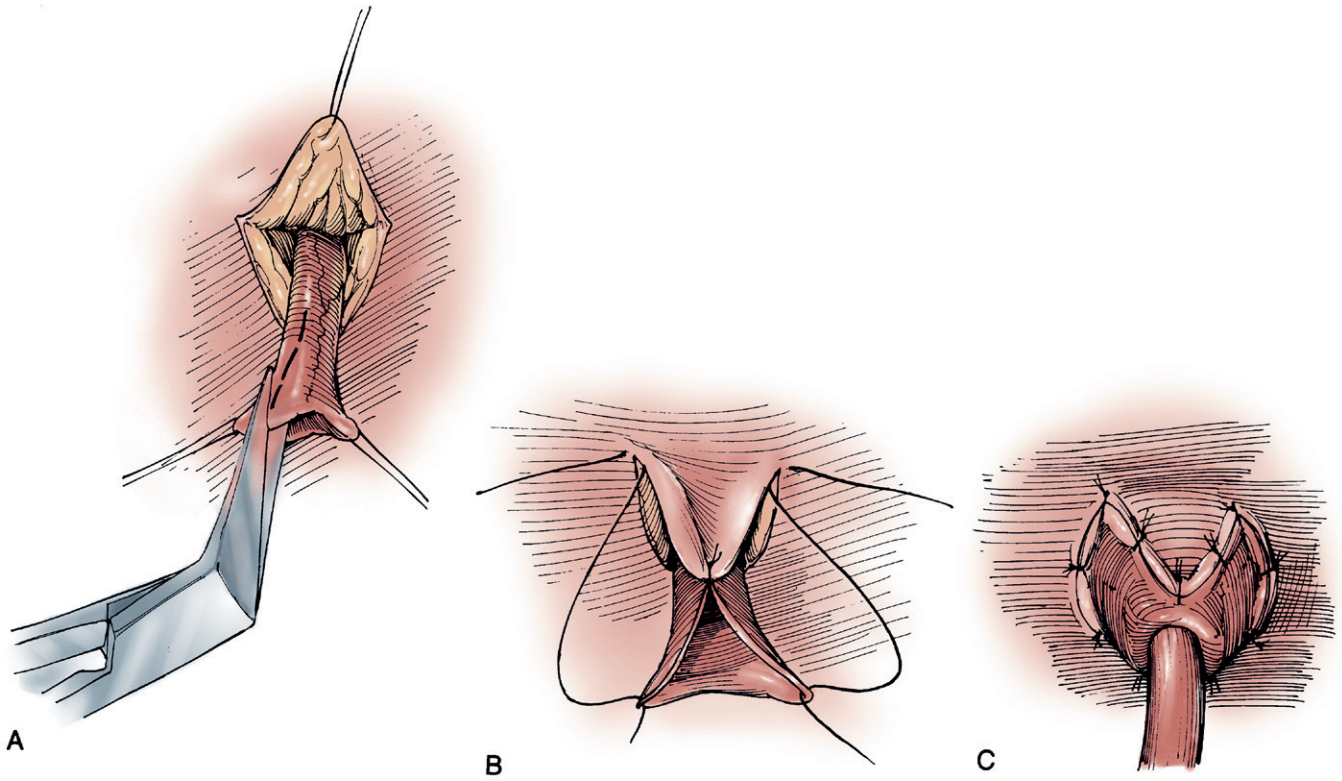


Figure 86–1. **A** to **C,** A V-flap is incised in the skin and a similar length incision made on the adjacent appendiceal surface. This is similar to the technique used to mature a cutaneous ureterostomy. For an appendiceal stoma, no eversion is required. (From Hinman F Jr. Atlas of urologic surgery. Philadelphia: WB Saunders; 1989.)

into the peritoneal cavity when the tube is removed. This maneuver also helps to prevent migration and angulation of the reservoir, which could result in incontinence or catheterization difficulties.

Postoperative Care and Comments

Paralytic ileus is a common complication following urinary diversion procedures. Gastric decompression should be maintained until extubation. This can be achieved in the majority of patients by means of nasogastric intubation. However, certain patients may be managed best by formal gastrostomy decompression inserted intraoperatively. These individuals include those with multiple prior abdominal procedures in whom prolonged ileus is more likely. **If the patient is nutritionally depleted preoperatively, hyperalimentation has been suggested to be of value if initiated during the preoperative interval** (Hensle, 1983; Askanazi et al, 1985).

Ureteral stents are usually removed 1 week after surgery. Before any manipulation, a urine sample from each stent should be sent for culture and sensitivity testing. Before stent removal, radiographs of the pouch are obtained to ensure that the pouch is intact. Radiologic contrast studies are performed to ensure against ureteral anastomotic leakage. Each stent is injected with contrast agent in a search for extravasation; if none is seen, guidewires are advanced to each kidney and the stents removed. If there is any question of extravasation, stents can be advanced over the wires, positioned fluoroscopically, and left in situ for re-evaluation after additional healing has taken place.

Late malignancy has been reported in all bowel segments exposed to the urinary stream, whether or not there is a commingling with feces (Filmer and Spencer, 1990; Shokeir et al, 1995). A study by Gitlin and colleagues (1999) suggests that the malignancy may develop from the urothelial component and not as a result of urine affecting intestinal mucosa. **As a result, urinary cytology should be performed in all patients undergoing a continent urinary diversion whether or not the diversion was performed secondary to a urothelial malignancy. When the ureters are directed into the fecal stream, routine colonoscopy should also be performed. Latency periods have been reported as short as 5 years, so all patients developing gross or microscopic hematuria should be fully evaluated** (Golomb et al, 1989). If an anastomotic transitional cell cancer is discovered, the patient should be fully evaluated with upper tract imaging and ureteroscopy if possible. Antegrade ureteropyeloscopy can be employed if necessary. For an isolated anastomotic recurrence, distal ureterectomy and reimplantation may be appropriate. If nephroureterectomy is necessary, some patients may require removal of their continent diversion due to resulting renal insufficiency.

CONTINENT URINARY DIVERSION

Continent, nonorthotopic urinary diversion can be divided into two major categories. First, the variations of ureterosigmoidostomy such as ileocecal sigmoidostomy, rectal bladder, and the sigmoid hemi-Kock operation with proximal colonic intussusception are discussed. These techniques allow for excretion of urine by means of evacuation. Second is the large category of continent diversions requiring clean intermittent catheterization of the constructed pouch for urine drainage at standard intervals.

The concept of refashioning bowel so that it serves as a urinary reservoir rather than a conduit has become universally accepted. This concept is based on original pioneering observations by Goodwin and colleagues in the development of the cystoplasty augmentation procedure (Goodwin et al, 1958). The destruction of peristaltic integrity and refashioning of bowel has led to the development of many innovative urinary reservoirs constructed from bowel. Several antireflux procedures have evolved to avoid upper tract urinary damage by sepsis or reflux, while other surgical techniques have been devised to achieve urinary continence.

Because there are numerous variants of continent urinary diversion used worldwide, a complete review of all operative techniques is beyond the scope of this or any chapter. However, many of these procedures are simple modifications of parent operations. In this chapter we describe in detail each parent operation, as well as major modifications. The fact that there are many continent urinary diversion procedures described reveals an obvious corresponding fact: the "best" continent diversion has yet to be devised. There is, to date, no consensus that would indicate one continent cutaneous diversion is superior to another, but it is becoming apparent that certain procedures are associated with lower early and late complication rates. Points of controversy include which bowel segment is most appropriate for fashioning into a urinary reservoir, the best techniques to use for achieving urinary continence, and the best technique for prevention of urine reflux into the upper tracts. There are now various continence mechanisms that appear reliable. In the authors' experience, procedures using a right colon reservoir with some form of appendiceal continence mechanism are the fastest and easiest to perform.

It should be re-emphasized that all continent diversions will allow for substantial reabsorption of urinary constituents that will place an increased workload on the kidneys (Mills and Studer, 1999). No patient with substantial renal impairment should be considered for any of these procedures. The long-term sequelae of continent urinary diversion are well understood and, unfortunately, commonly involve significant renal damage. Although it has been suggested that the absence of reflux into the upper urinary tracts in catheterizable pouches may reduce the long-term impact of continent diversion procedures on renal function, it should be cautioned that long-term 15-year data are now available and, in some instances, antireflux procedures are associated with a higher risk of obstruction due to anastomotic stricture (Kristjansson et al, 1995). In addition to increased stricture rates, it is not clear whether antirefluxing mechanisms actually result in improved preservation of the upper tracts (Pantuck et al, 2000).

Multiple international studies have suggested an improved psychosocial adjustment of patients undergoing continent urinary and fecal diversion compared with those patients with diversions requiring collecting appliances (Gerber, 1980; McLeod and Fazio, 1984; Boyd et al, 1987; Salter, 1992a, 1992b; Bjerre et al, 1995; Filipas et al, 1997; Hart et al, 1999; McGuire et al, 2000). Although this is indeed true and is best exemplified by the individual with a conduit who desires conversion to a continent procedure, it is also true that many individuals seem to adjust well to wearing external appliances. The sense of body image is a remarkably personal and subjective parameter that varies greatly from patient to patient. In fact, the majority of patients are satisfied with their choice of urinary diversion, whether it is continent or not.

The process of patient counseling that we employ always refers to ileal conduit diversion as the gold standard against which the newer, more complex operations must be compared. The patient should be advised that continent diversion is, all other considerations being equal, associated with a longer hospital stay, higher complication rates, and greater potential for requiring reoperative surgery. However, it should be noted that an extensive review from our institution has demonstrated no statistically significant difference in reoperations, mortality, or hospital stay in patients undergoing continent diversion versus conduit diversion by the same three surgeons over a 3-year period (Benson et al, 1992). Analysis of the two patient groups, on the other hand, showed that, in general, those selected for continent diversion were 12 years younger and four times less likely to have significant concurrent illness. What this review suggests is that, with proper patient selection, continent diversion operations can be safely conducted with results similar to those for conduit diversion. To determine if continent diversion could be safely performed in selected elderly patients, Navon and colleagues (1995) compared the clinical course of 25 patients older than the age of 75 years undergoing a modified Indiana reservoir to a cohort of 25 randomly selected patients younger than 75. The mean age of the first group was 78.5 years, and the mean age of the second was 59.3 years. The complication rates between the two groups were acceptably low and surprisingly similar. Navon and colleagues concluded that age alone should not be a contraindication to continent diversion and that the Indiana reservoir can be successfully performed in elderly patients.

Rectal Bladder Urinary Diversion

Various innovative surgical techniques have been advocated for separating the fecal and urinary streams, while still employing the principles of ureterosigmoidostomy. These operations can generally be discussed together as rectal bladder urinary diversions. In each of these operations the ureters are transplanted into the rectal stump. The proximal sigmoid colon is managed by terminal sigmoid colostomy or, more commonly, by bringing the sigmoid to the perineum, thereby using the anal sphincter to achieve both bowel and urinary control. Although these operations continue to be commonly performed, they have never been well accepted in the United States. The principal reason is the potential for the calamitous complication of combined urinary and fecal incontinence, presumably occurring as a consequence of damage to the anal sphincter mechanism during the dissection processes (Culp, 1984).

If the urologist selects one of these procedures, the preoperative evaluation should include all of the caveats of ureterosigmoidostomy. Dilated ureters are not acceptable. Patients with extensive pelvic irradiation are not candidates, and neither are those with existing renal insufficiency. Anal sphincteric tone must be judged competent before electing these operations. **Our preference has been to use a 400- to 500-mL thin mixture of oatmeal and water that the patient is asked to retain for 1 hour in the upright position** (Spirnak and Caldamone, 1986). **Finally, colonoscopy must be carried out before the procedure to rule out pre-existing colorectal disease, as well as after the procedure to guard against the potential development of colonic cancer.** Procedures that separate the fecal and urinary streams but drain both through the rectal sphincter are not described here. Those wishing a detailed description of these procedures can find them in prior editions of this chapter. The following is a brief description of more modern surgical procedures that use the intact anal sphincter for urinary and fecal continence. However, the surgical techniques for these procedures will likewise not be discussed in this edition.

Folded Rectosigmoid Bladder

A modification of the ureterointestinal anastomosis was described by a group from Mansoura, Egypt (Hafez et al, 1995; El-Mekresh et al, 1997). This procedure creates a folded rectosigmoid bladder with anastomosis of the ureters via serosa-lined tunnels rather than into the taenia coli. This procedure has the advantage of a larger sigmoid reservoir, as well as the prevention of reflux by creating the above serous-lined tunnel for the anastomosis. This reimplantation technique was first described by Abol-Enein and Ghoneim (1993) and appears to have a lower complication rate than direct taenial implantation (Hafez et al, 1995).

Postoperative Care and Comments. Patients undergoing this procedure must be closely monitored for the development of hyperchloremic acidosis. This will occur in the majority of cases, and it is wise to initiate a bicarbonate replacement program following the operation. Because hypokalemia is also a feature of ureterosigmoidostomy, replacement of potassium along with bicarbonate may be achieved with oral potassium citrate. Routine nightly insertion of a rectal tube is advocated in the long-term care of the patient. However, many patients will reject this practice as uncomfortable and unappealing. Nighttime urinary drainage should be mandated in any patient who cannot maintain electrolyte homeostasis with oral medication. Bissada and colleagues (1995) reported that 30 of 61 patients were able to stay dry during the night without awakening. The other 31 required two or more awakenings to remain dry overnight. Hyperchloremic acidosis was reported in 4 of 61 noncompliant patients.

In 1997 El-Mekresh and colleagues (1997) reported on 64 patients (32 women, 20 men, and 12 children) who underwent their rectosigmoid bladder procedure between 1992 and 1995. Follow-up ranged from 6 to 36 months. Functional results were assessable in 57 patients: 1 died of a postoperative pulmonary embolism and 6 died from their disease. All patients were continent during the day with two to four emptyings, whereas all but four remained dry at night with zero to two emptyings. Four children experienced enuresis that responded to 25 mg of imipramine at bedtime. Importantly, upper urinary tract function was maintained or improved in 95% of patients. However, six renal units (5.3%) developed obstructive hydronephrosis secondary to ureterocolic anastomotic strictures. Two were remedied by antegrade dilation, one was repaired by open revision, and one nonfunctioning renal unit was removed. The fate of the remaining two units was not specified. No patient in this series developed a postoperative metabolic acidosis. However, all patients were maintained on prophylactic oral alkalinization.

Obviously, all patients undergoing these procedures have exposure of the urinary tract to fecal flora. Most authors would advocate chronic administration of an antibacterial agent in all patients (Duckett and Gazak, 1983; Spirnak and Caldamone, 1986). Ureteral strictures require reoperative surgery and are experienced in 26% to 35% of cases over time (Williams et al, 1969; Duckett and Gazak, 1983).

Because of the concern for development of rectal cancer anywhere between 5 and 50 years (average 21 years) after ureterosigmoidostomy (Ambrose, 1983), it is suggested that patients with long-term ureterosigmoidostomy undergo annual colonoscopy (Filmer and Spencer, 1990). Barium enemas are relatively contraindicated because reflux of this material into the kidneys (if the antireflux procedure fails) can result in dire consequences (Williams, 1984). Additional methods for colon carcinoma screening in this population are the evaluation of stool for blood, and the attempted cytologic examination of the mixed urine and feces specimen (Filmer and Spencer, 1990).

Augmented Valved Rectum

Kock developed this technique to be used in locales where stoma appliances were not readily available (Kock et al, 1988). This operation is similar to standard ureterosigmoidostomy except that a proximal intussusception of the sigmoid colon confines the urine to a smaller surface area, thus minimizing the problems of electrolyte imbalance. Additionally the rectum is patched with ileum to improve the urodynamic properties of the rectum as a urinary reservoir. Preoperative evaluation is similar to that used in ureterosigmoidostomy. The large bowel must be studied for pre-existing disease, and anal sphincteric integrity must be tested before surgery.

Hemi-Kock and T Pouch Procedures with Valved Rectum

In his description of the augmented valved rectum procedure, Kock described the use of a foreshortened hemi-Kock pouch to be used as a rectal patch when the ureters were too dilated to bring down between the leaves of the intussuscepted sigmoid (Kock et al, 1988). Skinner then modified this procedure by using an entire hemi-Kock segment to augment the rectum after sigmoid intussusception (Skinner et al, 1989).

After extensive experience with the Kock ileal reservoir, the group at the University of Southern California has attempted to improve on the intussuscepted Kock continence mechanism. The result has been the modification of the T pouch to serve as an ileal anal reservoir (Stein et al, 1999a). The technique consists of the construction of a hemi-Kock or T pouch employing doubly folded, marsupialized ileum and a proximal continence mechanism to prevent pouch-ureteral reflux. This pouch is then anastomosed to the rectum directly as a patch. Contact of urine with the proximal colon can be avoided by the intussusception of the sigmoid colon proximal to the anastomotic site (Fig. 86–2).

Postoperative Care and Comments. Postoperative management and complications associated with this operation are similar to those that might be experienced after any procedure that directs the urinary stream into the rectum. Radiologic studies of the stents are carried out on the seventh postoperative day. Before conducting stent studies, a Gastrografin enema may be performed through the rectal tube to ensure that the region of ureterocolonic anastomosis is intact. Follow-up films are taken to ensure prompt drainage of the upper urinary tracts into the rectosigmoid region. The rectal tube may be removed at this point, but some believe that it is advisable to have it reinserted for evening drainage over the forthcoming week. The patient is instructed to empty the colon at intervals of no more than every 2 hours, particularly in the early postoperative period.

When the rectal tube is removed, as in other situations when the urinary tract is diverted to the rectum, the patient must be closely monitored for the development of hyperchloremic acidosis. Because hypokalemic metabolic acidosis often occurs after ureterosigmoidostomy, bicarbonate replacement with oral potassium citrate should begin in the immediate postoperative setting. Long-term care should include nightly insertion of a rectal tube despite the uncomfortable and unappealing nature of the process. In addition, nighttime urinary drainage is necessary in patients who cannot maintain electrolyte homeostasis with oral medication.

The hemi-T procedure with valved rectum has one theoretical advantage over the valved rectum operation itself: Because

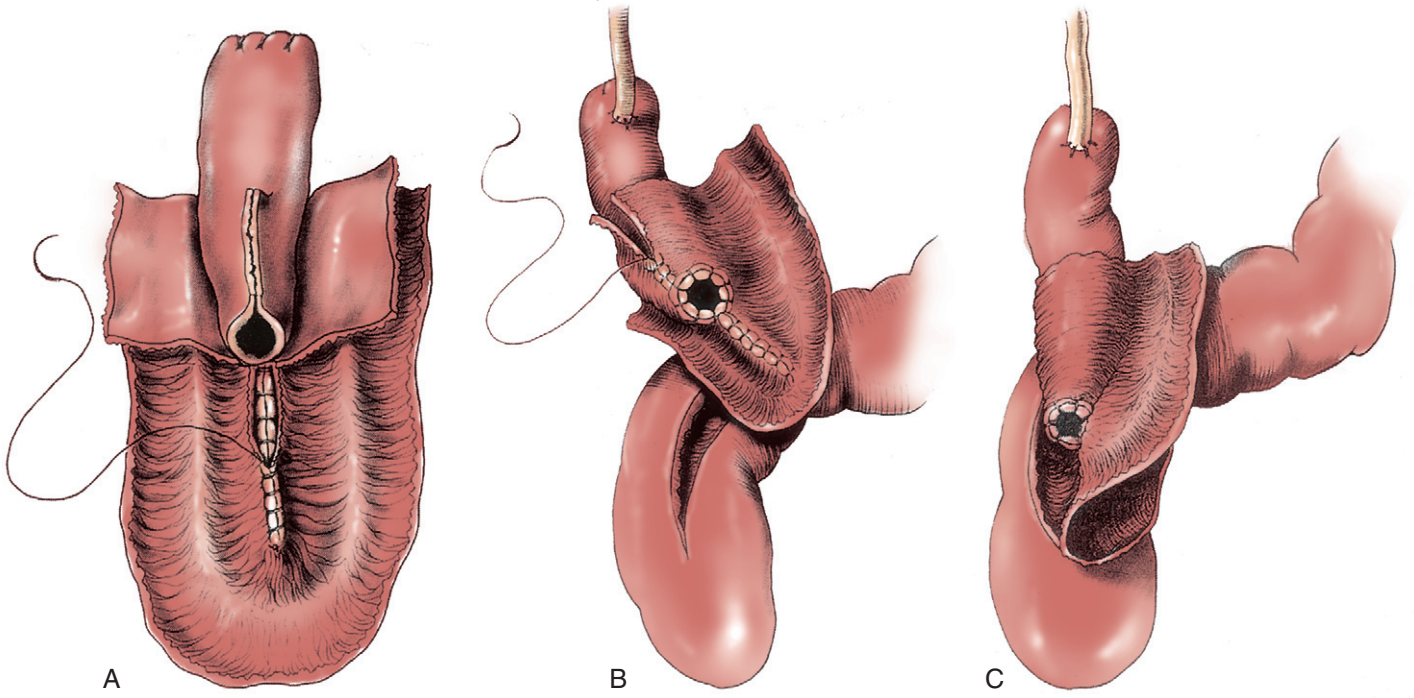


Figure 86–2. **A,** A 30-cm segment of ileum is selected, the first 10 cm for the T implant and the distal 20 cm for the patch. The 20-cm segment is folded into a U and opened as shown. The medial borders are closed with running absorbable sutures. **B,** The ostium of the T is secured to the walls of the ileum with interrupted absorbable sutures. The wall of the ileum is closed over the T mechanism with a running absorbable suture. **C,** The ureters are anastomosed to the top of the T in the usual end-to-side fashion. The T patch is then secured to the 15-cm proctotomy with a two-layer closure. (From Stein JP, Buscarini M, DeFilippo RE, Skinner DG. Application of the T pouch as an ileo-anal reservoir. J Urol 1999;162:2052–3.)

transitional ureteral epithelium is not in contact with colonic epithelium, there may be a reduced risk of developing colonic malignancy. As in the augmented valved rectum, the proximal colonic intussusception used in this procedure decreases the contact between urine and colonic epithelium, thereby potentially decreasing the risk of hyperchloremic acidosis. Nevertheless, attention should be paid to electrolyte levels after removal of stents and rectal tubes.

Skinner and colleagues reported on the results of the hemi-Kock procedure in 15 patients between 1987 and 1991 (Simoneau and Skinner, 1995). Four patients had prior bladder exstrophy and were converted to an ileoanal reservoir, and 11 patients underwent the procedure as a form of primary diversion after cystectomy. At the time of the report 10 patients were still alive and could be evaluated. Early postoperative complications occurred in three patients (20%): a colocutaneous fistula in two patients, urine leak in one, and deep venous thrombosis in another. Late complications included partial small bowel obstruction in four patients (with two requiring surgery), urinary retention requiring surgery in two patients, and metabolic acidosis in five patients. Two of the 11 patients undergoing primary construction never achieved continence; both were older than 68 years. The authors summarized their experience by concluding that the operation is best suited for the younger exstrophy patient and that it is essential to avoid colonic redundancy distal to the reservoir. The use of the T pouch as an ileoanal reservoir has been reported in one former exstrophy patient (Stein et al, 1999a), with no reported postoperative complications.

Sigma-Rectum Pouch, Mainz II

A variation of ureterosigmoidostomy was described by Fisch and Hohenfellner in 1991 and updated in 1996 (Fisch and Hohenfellner, 1991; Fisch et al, 1996). This operation, which they termed the *sigma rectum* or the *Mainz II pouch,* creates a low-pressure rectosigmoid reservoir of increased capacity. They viewed the simplicity and reproducibility of the operation as one of its major advantages.

Postoperative Care and Comments. The rectal tube is removed on the third to fifth postoperative day, and the ureteral stents are removed around the eighth day. On the 15th postoperative day the Mainz group performs an intravenous pyelogram to assess the upper tracts and the sigma rectum pouch construction. Radiography of the pouch is performed on the 17th postoperative day.

The results of the Mainz II pouch were reported by Fisch and colleagues in 1997. Between 1990 and 1993, 73 patients (59 adults and 14 children) underwent the Mainz II pouch procedure. Early complications were encountered in 5 of 73 patients (6.8%). These included single examples of a dislodged ureteral stent, pneumonia, pulmonary embolism, wound dehiscence, and ileus necessitating surgical intervention. There were eight (10.9%) late complications that required surgery: ureteral stenosis occurred in five patients (6.8%); one patient with nephrolithiasis was treated with extracorporeal shockwave lithotripsy; one patient with rupture of the anterior suture line required temporary colostomy; and one patient experienced perianal bleeding after chemotherapy that required endoscopic coagulation. Six patients presented with

pyelonephritis (8.2%) and were treated with antibiotics. Daytime and nighttime continence were reported as 94.5% and 98.6%, respectively. Oral alkalinization to prevent metabolic acidosis was used in 49 of 73 patients (67.1%). Two patients who refused any oral medication developed metabolic acidosis. The Mainz group concluded that the overall complication rate was low and comparable with other techniques of continent urinary diversion.

Woodhouse and Christofides (1998) reported on their experience with the Mainz II pouch in 15 primary cystectomy patients and 4 patients with prior standard ureterosigmoidostomy who were incontinent. They reported excellent results: 14 of 15 (93.3%) of the primary patients achieved documented daytime and nighttime urinary control, while the remaining patient refused follow-up but reported continence. The four patients undergoing a salvage procedure fared less well. Only two patients became continent, while the remaining two were found to be in chronic retention. Their failed continence was believed to be secondary to inadequate pouch emptying. Similarly, excellent results have been achieved by Venn and Mundy (1999). They reported full daytime and nighttime urinary continence in 14 of 14 patients and no major postoperative complications.

Bastian and colleagues (2004) have reported on the health-related quality of life in 83 patients undergoing Mainz II urinary diversion. They found that quality of life was similar to that of age-matched controls except for diarrhea symptoms, with 100% daytime continence.

There appears to be no metabolic advantage to this procedure because the need for oral alkalinization is similar to standard ureterosigmoidostomy. In fact, the only difference between this operation and standard ureterosigmoidostomy is the partial reconfiguration of the rectosigmoid junction. It does appear that the reduced intracolonic pressures that result from the partial reconfiguration increases the sigmoid capacity and results in better daytime and nighttime continence. Whether the increased capacity and lower pressure of this pouch will decrease the incidence of upper tract complications remains to be determined by longer follow-up.

Continent Catheterizing Pouches

Numerous operative techniques have been developed for continent diversion wherein urine is emptied at intervals by clean intermittent self-catheterization. Many of these operations are described in this chapter, although certain pioneering procedures that used intact bowel (e.g., those of Gilchrist and colleagues [1950], Ashken [1987], Mansson and colleagues [1984, 1987], Benchekroun [1987]) are not. This is not to discredit the pioneers in the field but simply to allow this chapter to focus on those pouches that incorporate modern principles that attempt to achieve a spherical configuration and disruption of peristalsis.

In continent urinary diversion, the two favorite sites for stomal location are (1) at the umbilicus and (2) in the lower quadrant of the abdomen, through the rectus bulge and below the "bikini" line. This location is often preferred because it affords both men and women the opportunity to conceal the stoma. The umbilicus is a preferred location for the individual confined to a wheelchair and has been reported to have a lower incidence of stomal stenosis, especially when fashioning an appendiceal stoma. The umbilical location is also far easier for the paraplegic individual to catheterize without the need for chair transfer and disrobing. In individuals with a recessed umbilicus, the umbilical location of a stoma is barely perceptible from a normal umbilical dimple. Generally, the stoma site is covered with a gauze pad or square bandage to avoid mucous soiling of clothing. Patients undergoing continent urinary diversion to an umbilical location should be advised to wear a medical alert bracelet that informs the examiner of the umbilical stoma.

Before the extension of orthotopic neobladder construction to women, there was some enthusiasm for the orthotopic placement of a catheterizing portal. This procedure has been carried out in certain female patients with success. The construction of a neourethra to the introitus is attractive, provided there is no substantial difficulty in the catheterizing process. Because it can be difficult to direct a catheter through the "chimney" of an intussuscepted nipple valve, those continent diversions employing nipple valves are not particularly adaptable to orthotopic location, although they have been performed with success in a small number of patients (Olsson, 1987). In contrast, the imbricated and tapered ileal segment leading to an Indiana pouch is relatively easier to catheterize and can be used for orthotopic catheterizing diversion (Rowland et al, 1987). However, it may be difficult to obtain sufficient mesenteric length in some patients. The appendix can also be used as a neourethra, in which case mesenteric length should become less of a problem (Hubner and Pfluger, 1995).

Four general techniques have been employed to create a dependable, catheterizable continence zone. For right colon pouches, appendiceal techniques, pseudoappendiceal tubes fashioned from ileum or right colon, and the ileocecal valve plication are applicable. Appendiceal tunneling procedures are the simplest of all to perform because they use established surgical techniques already present in the urologic armamentarium. The in situ or transposed appendix is tunneled into the cecal taenia in a fashion similar to ureterocolonic anastomosis. Appendiceal continence mechanisms have been criticized for three general reasons. First, the appendix may be unavailable in some patients because of prior appendectomy. For those individuals, techniques have been developed that allow for the construction of a similar tube fashioned from ileum (Woodhouse and MacNeily, 1994) or from the wall of the right colon (Lampel et al, 1995a). Second, the appendiceal stump may be too short to reach the anterior abdominal wall or umbilicus while still maintaining sufficient length for tunneling. This criticism has been addressed by an operative variation described by Mitchell, in which the appendiceal stump can be lengthened by the inclusion of a tubular portion of proximal cecum (Burns and Mitchell, 1990) (Fig. 86–3). This lengthening procedure has the added advantage of allowing for a slightly larger stoma made of cecum that is less prone to stomal stenosis. Appendiceal continence mechanisms share the feature of allowing only small-diameter (14- to 16-Fr) catheters to be used for intermittent catheterization, whereas the large amount of mucus produced by an intestinal reservoir is more easily emptied or irrigated using a 20- to 22-Fr catheter. We believe that these criticisms are more theoretical and that the appendiceal or pseudoappendiceal continence mechanism remains an attractive and reliable continence mechanism.

The second major type of continence mechanism used in right colon pouches is the tapered and/or imbricated terminal ileum and ileocecal valve. Here again the technology is rather simple, with imbrication or plication of the ileocecal valve region along with tapering of the more proximal ileum in the fashion of a neourethra (Rowland et al, 1985; Lockhart, 1987; Bejany and Politano, 1988). These techniques afford a reliable continence mechanism.

One feature of right colon pouches that has been criticized is the loss of the ileocecal valve. Although this does result in an

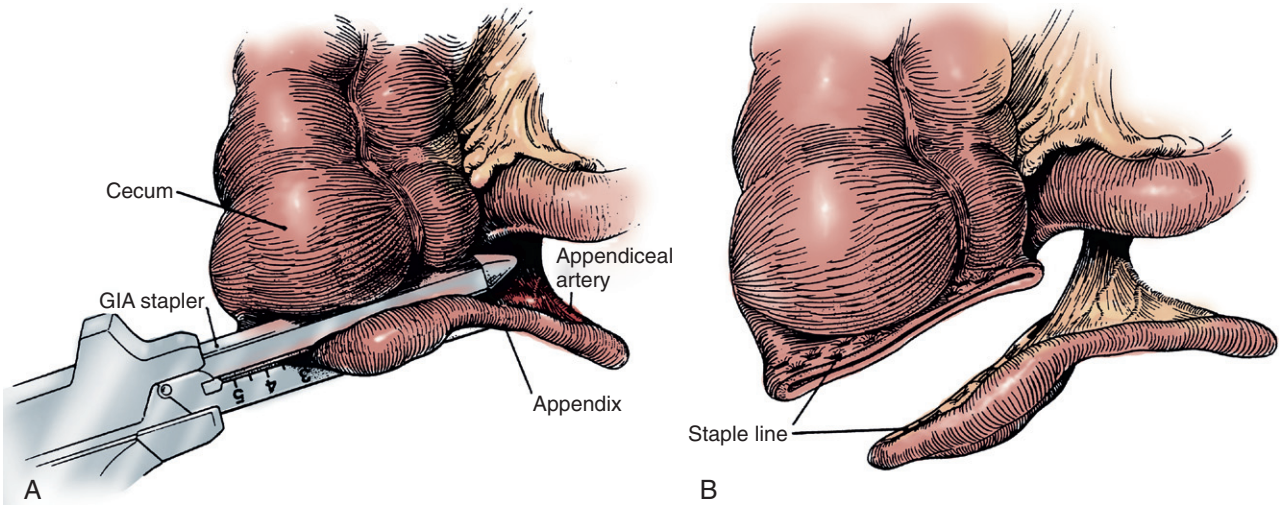


Figure 86–3. **A,** The appendiceal stump is lengthened by the inclusion of a tubular portion of proximal cecum by the application of the gastrointestinal anastomosis (GIA) stapler to the terminal cecum. A window is made in the mesoappendix, and the blade of the GIA stapler is advanced through the window. This maneuver ensures that the blood supply is not inadvertently damaged. **B,** The added length is demonstrated. The appendix is rotated and implanted into the taenia; the cecal tube serves as the stoma. (From Burns MW, Mitchell ME. Tips on constructing the Mitrofanoff appendiceal stoma. Contemp Urol 1990;May:10–2.)

increased frequency of bowel movements for some patients in the short term, the majority will experience bowel regularity either through intestinal adaptation or with the use of pharmacologic therapy. However, some patients have developed rather striking diarrhea/steatorrhea after the loss of the ileocecal valve. This may be particularly true in pediatric patients in whom there is neurogenic bowel dysfunction (e.g., myelomeningocele).

The third surgical principle used in constructing the continence mechanism is the use of the intussuscepted nipple valve or, more recently, the flap valve, which avoids the need for intussusception. The creation of nipple valves is by far the most technologically demanding of all the continence mechanisms, and it is associated with the highest complication and reoperation rates. There exists a significant learning curve before the surgeon achieves reproducible and dependable results. For this reason, nipple valve construction should probably not be chosen by the surgeon carrying out occasional construction of continent pouches. Furthermore, it should be noted that in the past 2 decades we have seen the introduction of numerous modifications of the original technique of Kock for construction of a stable nipple valve. The singular reason for all of these modifications is the rather disappointing long-term stability of the nipple valve in some patients. As a result, the group at the University of Southern California has developed the T pouch, which uses a flap valve (Stein et al, 1998). This procedure, which appears much simpler than the intussuscepted nipple valve, has been used to create both a continence and an antireflux mechanism. Nipple valve failure from slippage or valve effacement can be anticipated in 10% to 15% of cases even in the hands of the best and experienced surgeons. In addition to slippage, nipple valves are subject to ischemic atrophy. When this occurs, a new nipple valve must be fashioned from a new bowel segment.

A final feature of stapled nipple valves is the potential for stone formation on exposed staples. This was greatly lessened by the omission of staples at the tip of the intussuscepted nipple valve, as suggested by Skinner and colleagues (1984). However, more proximal staples occasionally erode into the pouch and serve as a nidus for stone formation. These stones are usually manageable endoscopically with forceps extraction or else with electrohydraulic or ultrasonic disintegration of the stone with subsequent forceps extraction of the staple. Although exposed staples may serve as a nidus for stone formation, continent urinary diversion in and of itself results in more urinary excretion of calcium, magnesium, and phosphate as compared with ileal conduit diversion (Terai et al, 1995). Thus all patients undergoing continent diversion are at an increased risk for the formation of reservoir stones.

The fourth major technique of continence mechanism construction is the provision of a hydraulic valve, as in the Benchekroun nipple (1987). In this procedure a small bowel segment is isolated, with subsequent reversed intussusception that effectively apposes the mucosal surfaces of the segment. Tacking sutures are placed on a portion of the circumference of the intussuscepted segment in order to stabilize the nipple valve while allowing urine to flow freely between the leaves of apposed ileal mucosa. As the pouch fills, hydraulic pressure closes the leaves, thereby ensuring continence. The premise of this technique is that as the reservoir fills, the pressure within the valve would also increase, resulting in continence. Concerns regarding stomal stenosis, especially in children, and nipple destabilization have resulted in this procedure being largely abandoned (Sanda et al, 1995). As a result, it is not discussed in this chapter.

General Procedural Methodology

During construction of the pouch, intraoperative testing for pouch integrity should always be performed. The continence mechanism is also tested for ease of catheterization, as well as continence after the pouch construction has been completed. The pouch is filled with saline, the continence mechanism catheter is removed, and the pouch is compressed lightly to look for points of leakage and to test the continence mechanism for its ability to contain urine. **Thereafter, the continence mechanism is catheterized to ensure ease of catheter passage. This is an extremely important and crucial maneuver because the inability to catheterize is a serious complication that will often result in the**

need for reoperation. In general, all redundancy should be removed from the continence mechanism. It is often useful to secure the reservoir to the anterior abdominal wall in a manner that prevents the reservoir from migrating. This can prevent the development of a false passage or a kink, thereby facilitating catheterization.

Postoperatively, the larger-bore catheter used for drainage of the pouch should be irrigated at frequent intervals to prevent mucous obstruction. This can be performed at 4-hour intervals by simple irrigation with 45 to 50 mL of saline. Less frequent intervals of irrigation can be employed when the urine is totally diverted from the kidneys by means of long indwelling stents. It is essential that as soon as possible the patient be taught how to self-irrigate and what kind of regimen is required. This is performed to familiarize the patients with the catheterization process, to reduce the work burden on the nursing staff, and to allow for earlier discharge.

On the seventh postoperative day, a contrast study is performed to ensure pouch integrity. Thereafter, ureteral stents may be removed if no leaks are demonstrated by imaging studies. When it has been ascertained that the ureteral anastomoses and pouch are intact, the suction drain is removed. The suprapubic tube (if employed) can also be removed at this time, or it can be left in place until the patient is confident with self-catheterization. The patient is taught to irrigate the tube traversing the continence mechanism at 4-hour intervals and whenever any episode of intra-abdominal pressure or discomfort is experienced. Once these procedures are mastered and the patient is tolerating a regular diet, the patient can be discharged. This usually occurs between hospital days 6 and 8.

The following represents a summary of common patient questions and everyday solutions:

- *What kind of catheter do I use?* For nipple valves, a straight-ended 22- to 24-Fr tube; for ileocecal plication, a 20- to 22-Fr coudé tip catheter; and for appendiceal sphincters, a 14- to 16-Fr coudé tip catheter.
- *How do I carry my catheter?* In a zipper-locked bag that can be placed in a women's purse or a man's coat pocket.
- *How do I clean the stoma before catheterizing in a public facility?* With a benzalkonium chloride wipe, which can be purchased in individual foil-wrapped packets.
- *How do I lubricate the catheter?* By tearing off the end of an individual-use foil pack of water-soluble lubricant and inserting the tip of the catheter into the pack.
- *What do I do with the stoma after catheterizing?* Cover it with a bandage.
- *How do I clean my catheter after draining my pouch?* By rinsing ordinary tap water through the inside channel and over the outside surface before replacing it in its zipper-locked bag.

In the case of ileal pouches, pouch capacity will initially be low (150 mL). Therefore the frequency of catheterization will have to be significantly different in these individuals compared with those with right colon pouches in which initial comfortable capacities will be in excess of 300 mL. To ensure restful sleep, the smaller-capacity pouches may be managed best with indwelling catheterization during sleeping hours.

General Care

Because all patients with catheterized pouches will have chronic bacteriuria, the problem of antibiotic management should be discussed. **Most authors would suggest that bacteriuria in the absence of symptomatology does not warrant antibiotic treatment** (Skinner et al, 1987). The construction of an effective antireflux mechanism in these pouches may help protect against clinical episodes of pyelonephritis, in contrast to patients with freely refluxing conduits. Obviously, if clinical pyelonephritis does occur, antibiotic treatment should be instituted. Episodes of recurrent pyelonephritis should be evaluated with radiography of the pouch in order to diagnose failure of the antireflux mechanism or upper tract stone formation.

A condition termed "pouchitis" is manifested by pain in the region of the pouch along with increased pouch contractility. It should be mentioned that this condition, although infrequent, may result in temporary failure of the continence mechanism because of the hypercontractility of the bowel segment employed for construction of the pouch. The patient typically presents with a history of sudden explosive discharge of urine through the continence mechanism (rather than dribbling incontinence), along with discomfort in the region of the pouch. Appropriate antibiotic therapy will usually result in resolution of these symptoms. It has been our experience that short courses of antibiotics are not usually successful when treating pouch infections. This may be due to the larger amount of foreign material in the form of mucus and sediment within intestinal pouches as opposed to the bladder. Intestinal crypts may also serve as bacterial sanctuaries. Therefore whenever a pouch infection is diagnosed, antibiotic therapy should be continued for at least 10 days. Pyelonephritis will, of course, require longer courses of therapy.

Urinary retention is an infrequent but serious occurrence in catheterizable pouches. It is most commonly seen with pouches whose continence mechanism consists of a nipple valve. In these circumstances, when the chimney of the nipple valve is not near the abdominal surface, the catheter may be misdirected into folds of bowel rather than into the nipple valve proper, resulting in urinary retention. **Pouch urinary retention represents a true emergency, and the patient must seek immediate attention so that catheterization and drainage by experienced personnel can be achieved promptly.** The use of a coudé tipped catheter may be helpful. Rarely, a flexible cystoscope will be necessary. After the immediate problem has been resolved by emptying the pouch, a catheter should be left indwelling for 3 to 5 days to allow the edema and trauma to the catheterization portal to resolve. Before discharge, the patient should be observed to successfully self-catheterize on multiple occasions. The appropriate angle of entry should be taught to the patient until he or she is comfortable with the use of the new catheter. In fact, the authors prefer to routinely use coudé catheters with non–nipple valve pouches.

Intraperitoneal rupture of catheterizable pouches has been reported (Kristiansen et al, 1991; Thompson and Kursh, 1992; Watanabe et al, 1994). In general, these episodes are more common in the neurologic patient when sensation of pouch fullness may be less distinct (Hensle, personal communication; Mitchell, personal communication). Ruptures may also be associated with mild abdominal trauma, such as a fall. In general, these patients require immediate pouch decompression and radiographic pouch studies. For patients with large defects, surgical exploration and pouch repair are required. If the amount of urinary extravasation is small, and the patient does not have evidence of peritonitis, catheter drainage and antibiotic administration may suffice in treating an intraperitoneal rupture. Patients managed with this conservative approach require careful monitoring. If there is any sign of progressive peritonitis, surgical exploration and repair is imperative. The authors have successfully employed this nonoperative approach on patients with ruptured right colon pouches.

Continent Ileal Reservoir (Kock Pouch)

This operation was first reported for use in urinary diversion by Kock and colleagues in 1982. This report was singularly responsible for the renewed interest in continent diversion procedures at that time. An outgrowth of the Kock procedure for continent ileostomy (Kock, 1971), the Kock pouch combined reasonably dependable techniques for ensuring urinary continence and preventing reflux to the upper urinary tracts (nipple valves) with carefully refashioned bowel that provided a low-pressure urinary reservoir. This procedure and the similarly constructed T pouch are the only catheterizable continent diversions that preserve the ileocecal valve. **Skinner and his colleagues** (1989, 1992) **have carefully studied and improved the technique over the years while amassing a prodigious experience with the operation and its variants. The high complication rate and the technical difficulties involved with constructing this reservoir have resulted in the procedure being abandoned by most individuals.** As a result, this procedure is not discussed further in this edition. Those interested in a more detailed description should refer to previous editions of this text. However, the construction of a Kock limb remains an important procedure for use in repairing failed continence or reflux mechanisms and, as such, is described in more detail. It is Skinner's operative description that will be followed closely in this chapter.

Procedure. A 15- to 20-cm length of ileum is selected for creating the intussuscepted nipple valve. The proximal 10 cm serve as the valve, and the distal 5 to 10 cm serve as the patch (Fig. 86–4A). The distal length is chosen on the basis of the volume lost after resection of the failed mechanism. Only 5 cm are necessary for the patch, but on some occasions the reservoir itself may require augmentation. The middle 6 to 8 cm of the 10-cm segment are denuded of mesentery by electrocoagulation. An Allis or Babcock clamp is advanced into the ileal terminus, grasping the full thickness of the intussusceptum and inverting the ileum into the pouch (see Fig. 86–4B). Using the TA-55 stapler, three rows of 4.8-mm staples are applied to the intussuscepted nipple valve (see Fig. 86–4C). The distal six staples from each cartridge are removed before staple application to ensure that the tip of the valve is free of staples. Most authors suggest that the pin of the stapling instrument should always be kept in place so that staple misalignment does not occur. This will result in a pinhole puncture site at the base of the nipple valve that should be oversewn with absorbable suture material to prevent fistula formation after staple application is complete. The nipple valve is then fixed to the back wall of the patch by one of two stapling techniques (Skinner et al, 1984). A small buttonhole may be made in the back wall of the ileal plate so that the anvil of the stapler can be passed through the buttonhole and advanced into the nipple valve before application of the fourth row of staples (see Fig. 86–4D). If this is carried out, the buttonhole is oversewn afterward with absorbable material. Alternatively, the anvil of the stapler can be directed between the two leaves of the intussuscipiens and the fourth row of staples used to fix the inner leaf of the nipple valve to the pouch wall (see Fig. 86–4E).

Some authors including Skinner and colleagues (1989) suggest the use of an absorbable mesh collar to anchor the base of the nipple valve. If a collar is used, a 2.5-cm wide strip of absorbable mesh is placed through an additional window of Deaver at the base of the nipple valve. The mesh strip is fashioned into a collar and sewn to the base of the patch with seromuscular sutures of absorbable material (see Fig. 86–4F and G). The patch is then sewn to the reservoir.

Double T Pouch

As indicated earlier, many surgeons have abandoned the Kock pouch largely due to the technical difficulties of creating the continence and antireflux mechanisms, as well as the high complication rates associated with them. This should not be viewed as a condemnation of the pioneering work of Kock and his colleagues. Without their initial efforts, many of the procedures described in this chapter would never have come into being. Rather, this represents the natural evolution of surgical techniques.

The group at the University of Southern California modified a technique described by Abol-Enein and Ghoneim (1993, 1994) to create a novel continence mechanism created entirely from ileum (Bochner et al, 1988). Abol-Einein and Ghoneim described a technique that created an extramural serosal tunnel into which the ureters were implanted. This extramural trough created a pseudotunnel that prevents reflux but in theory is associated with a lower risk of obstruction than either the Goodwin (1958), Leadbetter (1961), or LeDuc and colleagues' (1987) techniques of direct transmural ureteral implantation. Stein and colleagues (1998) first reported on the use in a neobladder of a tapered ileal segment implanted into a serosal trough as the antireflux mechanism. In 1999 they reported on their adaptation of the technique to the ileal-anal reservoir, and in 1999 they presented their early experience with a double T pouch as a replacement for the Kock pouch at the meeting of the American Urological Association (Stein et al, 1999a). It was published elsewhere (Stein and Skinner, 2001) and is the technique presented in this section.

Procedure. A 70-cm segment of terminal ileum is isolated 15 to 20 cm from the ileocecal valve at the line of Treves. The proximal isoperistaltic 10- to 12-cm segment is isolated and will serve as the antireflux mechanism. The distal 12- to 15-cm segment is isolated and rotated in an antiperistaltic fashion and will create the cutaneous continence mechanism (Fig. 86–5A and B). A short 2- to 3-cm mesenteric incision is made to isolate the proximal limb, and a 4-cm incision is made for the distal limb, thereby preserving the major vascular arches. The proximal and distal segments can vary in length, depending on ureteral length and the thickness of the anterior abdominal wall. The middle 44 cm of ileum are folded in a W with each limb measuring 11 cm.

The afferent antireflux mechanism is created by opening the windows of Deaver between the vascular arcades along the distal 3 to 4 cm. The efferent continence mechanism is created by opening the proximal 7 to 8 cm of vascular arcades (antiperistaltic) (see Fig. 86–5C). One-fourth-inch Penrose drains are then placed in each window of Deaver to facilitate passage of the 3-0 silk horizontal mattress sutures that are used to approximate the serosa of the corresponding 11-cm limbs of the W (see Fig. 86–5D). The 3- to 4-cm anchored portion of the proximal limb is then tapered over a 30-Fr catheter, and the 7- to 8-cm anchored portion of the efferent limb is tapered over a 16-Fr catheter. In both instances, tapering is performed with a gastrointestinal anastomosis (GIA) stapler (the staples will not be in contact with urine). Care must be taken in the efferent limb to create a gradual taper so that the catheter does not hit a false cul-de-sac (see Fig. 86–5E). The portions of the 11-cm W limbs not forming the troughs are then sutured together with a running 3-0 polyglycolic acid (PGA). The bowel is now incised along its antimesenteric border in the portion where the serosal trough exists and in close proximity to the medial PGA suture lines when beyond the two limbs

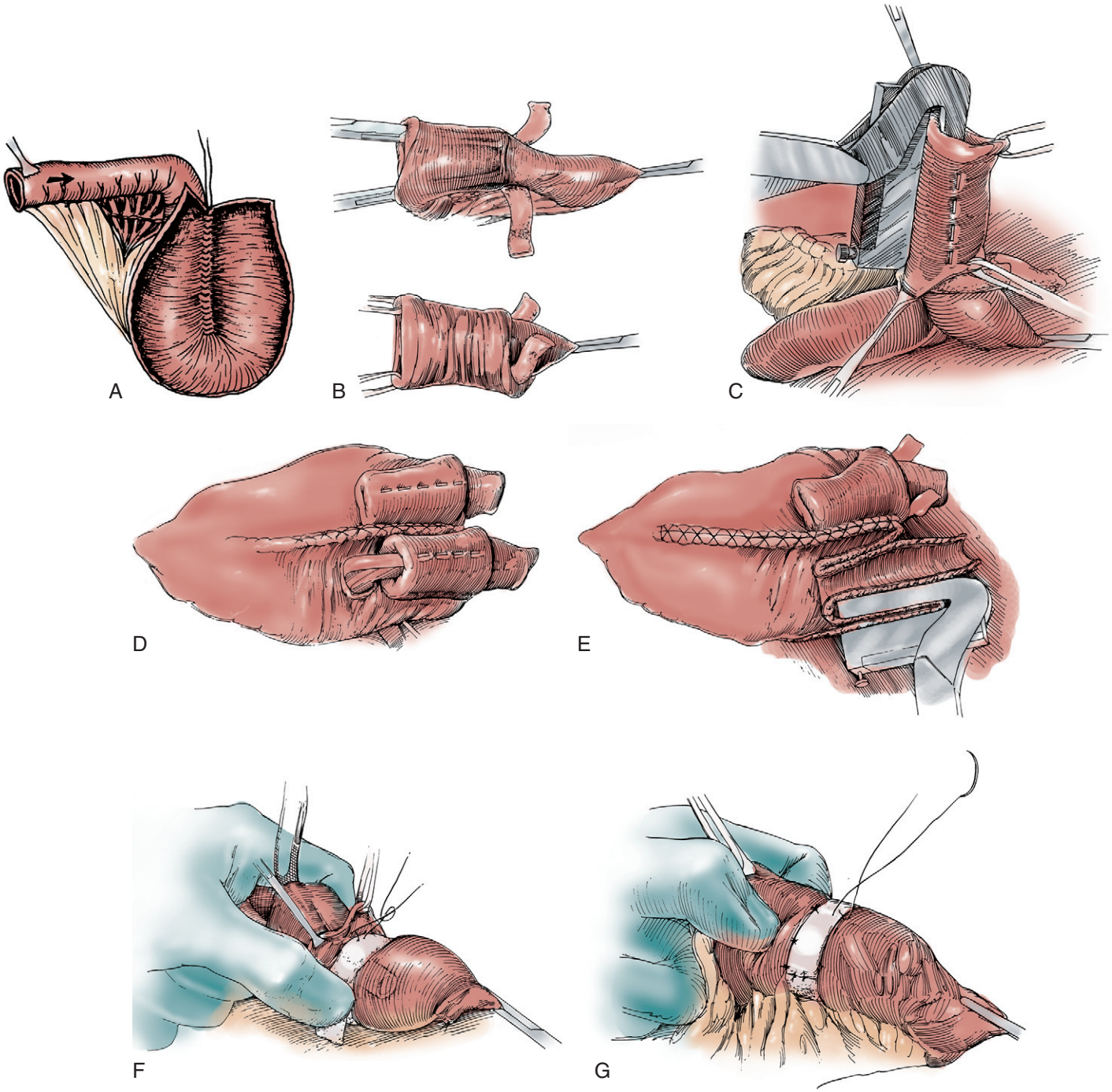


Figure 86–4. **A,** A 15-cm segment of terminal ileum is isolated and opened along its antimesenteric wall. The proximal 10 cm will serve as the continent intussusception and the distal 5 to 10 cm, the patch. The size of the patch will vary according to the size of the excised segment. **B,** An Allis or Babcock clamp is advanced into the ileal terminus, the full thickness of the intussuscipiens is grasped, and it is prolapsed into the pouch. **C,** Three rows of 4.8-mm staples are applied to the intussuscepted nipple valve using the TA-55 stapler. **D,** A small buttonhole is made in the back wall of the ileal plate to allow the anvil of the TA-55 stapler to be passed through and advanced into the nipple valve. A fourth row of staples is applied. The figure shows two valve mechanisms, but in this instance there would be only one. **E,** The anvil of the stapler can be directed between the two leaves of the intussuscipiens and the fourth row of staples applied in this manner. Two valve mechanisms are shown, but in this instance there would be only one. **F,** A 2.5-cm wide strip of absorbable mesh is placed through additional windows of Deaver at the base of each nipple valve. The mesh strips are fashioned into collars. **G,** The collars are sewn to the base of the pouch and the ileal terminus with seromuscular sutures. (**A,** From Ghoneim MA, Lock NG, Lycke G, El-Din AB. An appliance-free, sphincter-controlled bladder substitute. J Urol 1987;138:1150–4; **B** to **G,** from Hinman F Jr. Atlas of urologic surgery. Philadelphia: WB Saunders; 1989.)

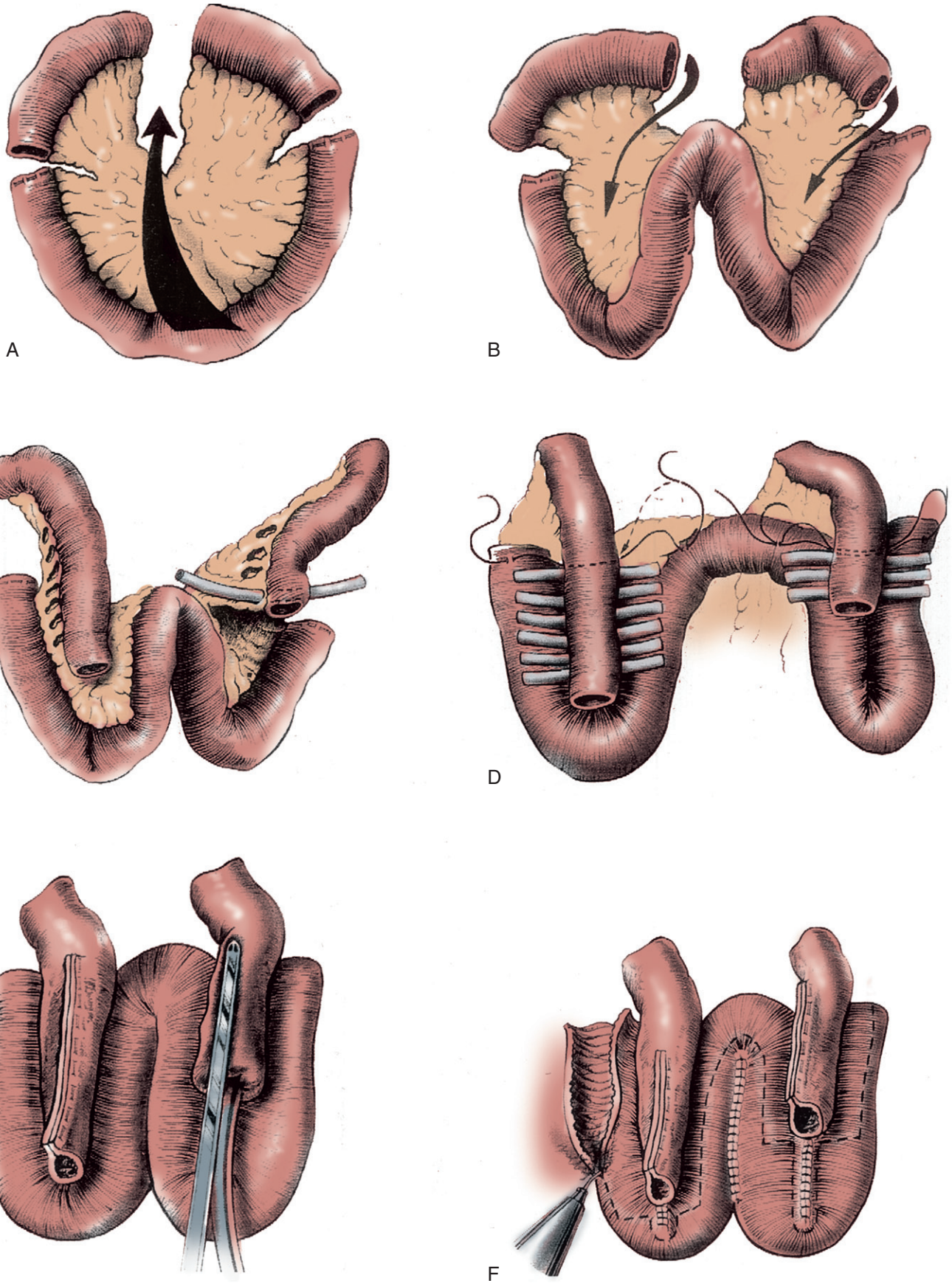
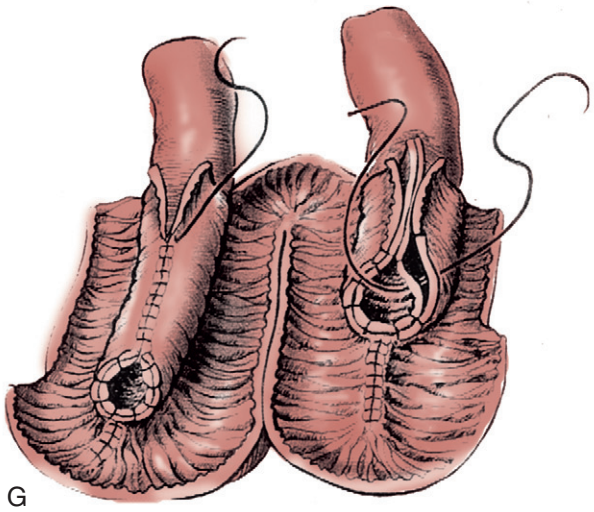
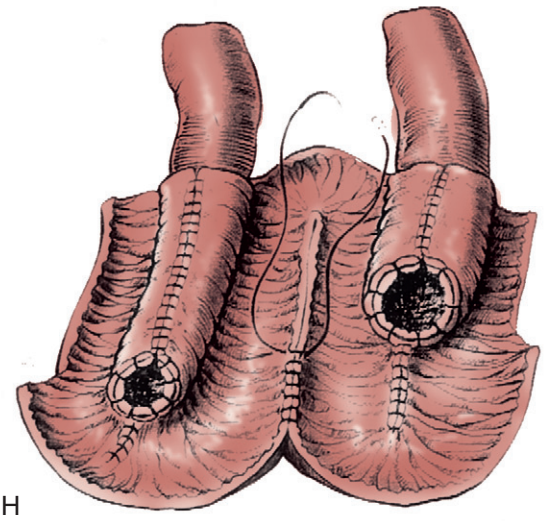


Figure 86–5. **A,** A 70-cm segment of terminal ileum is isolated 15 to 20 cm from the ileal cecal valve. **B,** A proximal 10-cm segment is isolated and rotated toward what will become the reservoir in an isoperistaltic direction. The distal 12 to 15 cm is rotated toward the reservoir in an antiperistaltic direction. **C,** The windows of Deaver are opened to allow the walls of the W reservoir to be apposed behind the valve mechanisms. Penrose drains are passed to guide suture passage. **D,** Horizontal mattress sutures of 3-0 silk are passed through each window. The distal continence mechanism is longer than the proximal antireflux mechanism. **E,** The proximal and distal mechanisms are tapered with a metal gastrointestinal anastomosis stapler. **F,** The bowel is incised along its antimesenteric border, where it will overlie the 2 Ts. Distal to the Ts, the bowel is incised close to the approximated limbs of the reservoir.

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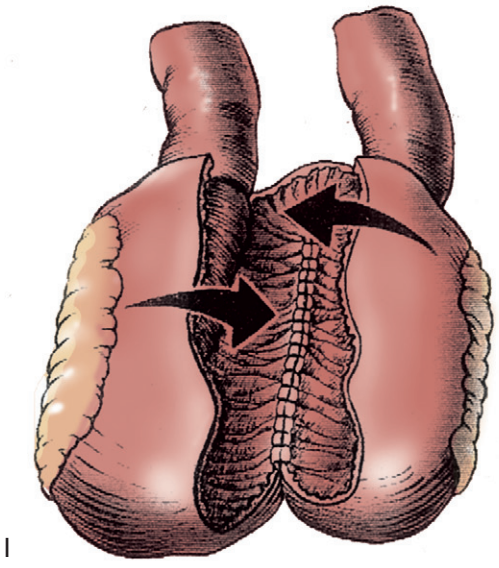


Figure 86–5, cont'd. **G,** The ostia of the valves are secured to the bowel wall with interrupted absorbable sutures. The two flaps of ileum are closed over the Ts with running absorbable sutures. **H,** The back wall of the reservoir is closed with running absorbable sutures. **I,** The lateral walls are folded medially, and the construction is completed with running absorbable sutures. (From Stein JP, Buscarini M, DeFilippo RE, Skinner DG. Application of the T pouch as an ileo-anal reservoir. J Urol 1999;162:2052–3.)

(see Fig. 86–5F). The incised mucosa is then closed in two layers with a running suture of 3-0 PGA. The incised intestinal flaps (antimesenteric incision) are then sutured to each ostium with interrupted sutures of 3-0 PGA, and the two ileal flaps are sutured over each segment with a running suture of 3-0 PGA (see Fig. 86–5G). The reservoir is then closed side to side in two layers with 3-0 PGA, thereby completing its construction (see Fig. 86–5H and I). The ureters are anastomosed end to side over stents to the proximal limb, which has been closed with a running absorbable Parker-Kerr suture. The efferent limb is then brought to the abdominal wall stoma site, and redundant ileum is resected. The stoma is then matured with the reservoir lying immediately adjacent to the anterior abdominal wall.

Postoperative Care and Comments. Postoperative care is similar to that for any continent reservoir. Stein and colleagues (1999b) initially reported on nine patients, seven of whom could be evaluated for continence and long-term complications and two of whom died of disease during follow-up. All seven patients achieved immediate continence on catheter removal. However, two patients later became incontinent, with one requiring surgical revision. None of the nine patients experienced an early postoperative complication. One patient developed a reservoir stone 9 months after surgery that was removed endoscopically without sequelae. Pouch capacity was excellent: 400 to 700 mL (average 500 mL). There was no radiographic evidence of reflux in any patient, and there was no upper tract deterioration. This operative procedure

appears to have many advantages over the Kock pouch, and good long-term continence results have been reported. Marino and colleagues (2002) reported on 18 patients with 1-year follow-up with 100% day and night continence and no delayed complications. Seifert and colleagues (2008) recently published their results on 19 patients who underwent ileal double T pouch construction between 1998 and 2006. Five patients (26%) had complications related to the diversion, some of which required surgical revision. Three patients (16%), all of whom had body mass indices of greater than 30, suffered necrosis of the efferent loop and subsequent cutaneous fistulas. Sixteen (84%) eventually developed both daytime and nighttime continence. Although a mild acidosis was common in this group, no urinary reflux was detected and no patients suffered significant upper tract deterioration or pyelonephritis.

Mainz Pouch I

The catheterizable Mainz pouch has undergone considerable modification over the years (Thuroff et al, 1985; Stein et al, 1995; Lampel et al, 1996; Gerharz et al, 1997). **The main impetus for these changes has been the difficulty encountered with the nipple valve mechanism.** The operative technique has now been modified to use the intact ileocecal valve as a means of further stabilizing the intussusception (Thuroff et al, 1988). This procedure is described here without further reference to earlier prototypes.

Procedure. The catheterizable Mainz pouch varies somewhat from the orthotopic, voiding Mainz pouch. First, a longer segment of bowel is used. A 10- to 15-cm portion of cecum and ascending colon is isolated along with two separate, equally sized limbs of distal ileum and an additional portion of ileum measuring 20 cm (Fig. 86–6A). The entire colon and distal segments of ileum are spatulated, taking care to preserve the ileocecal valve. These three bowel segments are folded in the form of an incomplete W and their posterior aspects sutured to one another to form a broad posterior plate (see Fig. 86–6B). A portion of the intact proximal ileal terminus is freed of its mesentery for a distance of 6 to 8 cm, and intussusception of the segment is achieved. Two rows of staples are applied on the intussusceptum itself (see Fig. 86–6C). Thereafter, the intussusceptum is led through the intact ileocecal

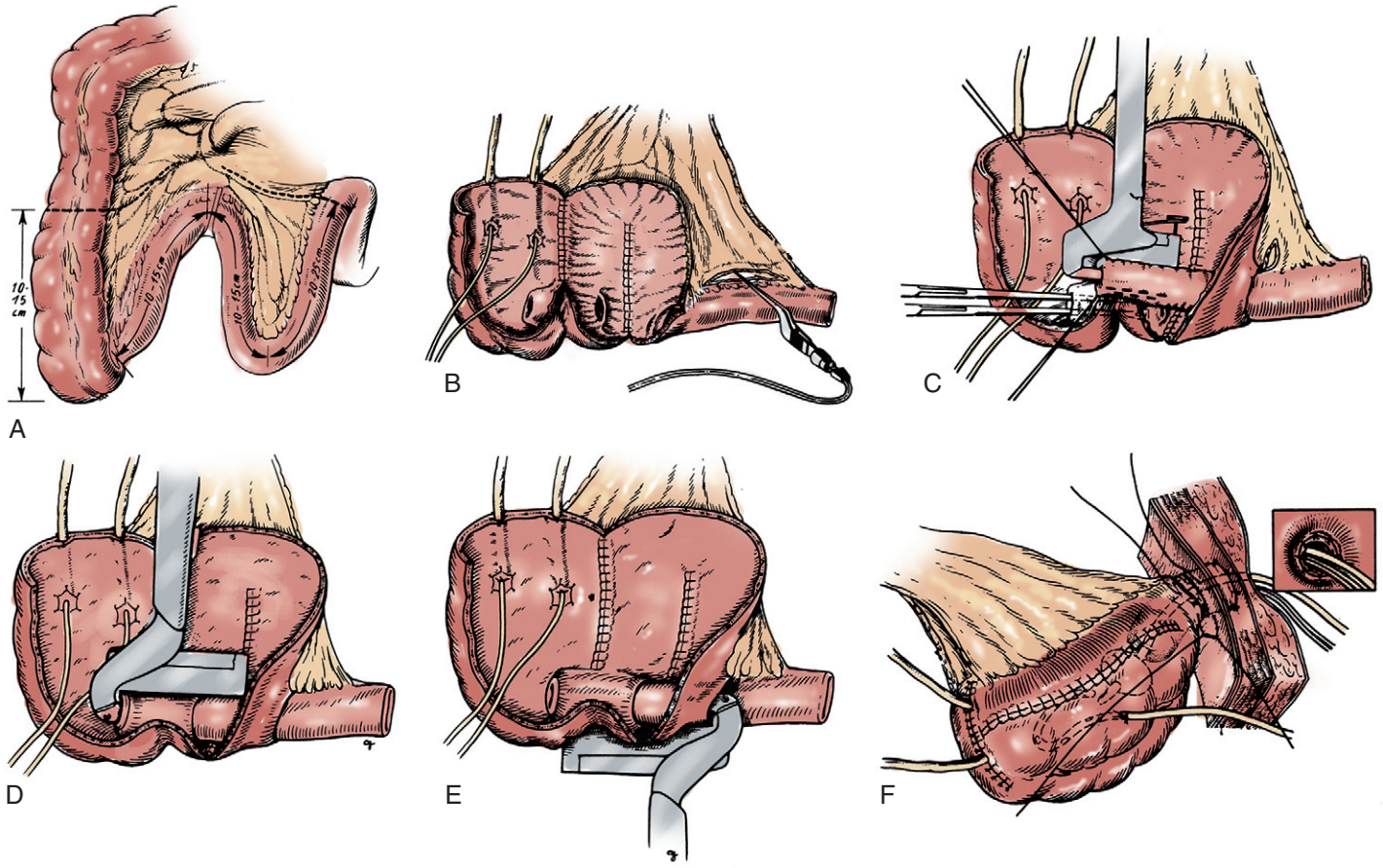


Figure 86–6. **A,** A 10- to 15-cm portion of cecum and ascending colon is isolated along with two separate equal-sized limbs of distal ileum and an additional portion of ileum measuring 20 cm. **B,** A portion of the intact proximal ileal terminus is freed of its mesentery for a distance of 6 to 8 cm. **C,** The intact ileum is intussuscepted, and two rows of staples are taken on the intussuscipiens itself. **D,** The intussuscipiens is led through the intact ileocecal valve, and a third row of staples is taken to stabilize the nipple valve to the ileocecal valve. **E,** A fourth row of staples is taken inferiorly, securing the inner leaf of the intussusception to the ileal wall. **F,** A button of skin is removed from the depth of the umbilical funnel, and the ileal terminus is directed through this buttonhole. Excess ileal length is resected, and the ileum is sutured at the depth of the umbilical funnel. (**A,** From Thuroff JW, Alken P, Hohenfellner R. The MAINZ pouch [mixed augmentation with ileum 'n' cecum] for bladder augmentation and continent diversion. In: King LR, Stone AR, Webster GD, editors. Bladder reconstruction and continent urinary diversion. Chicago: Year Book Medical Publishers; 1987. p. 252; **B** to **F,** from Thuroff JW, Alken P, Riedmiller H, et al. 100 cases of MAINZ pouch: continuing experience and evolution. J Urol 1988;140:283–8.)

valve and a third row of staples is applied to stabilize the nipple valve to the ileocecal valve (see Fig. 86–6D). Finally, a fourth row of staples is applied inferiorly, securing the inner leaf of the intussusception to the ileal wall (see Fig. 86–6E).

Ureterocolonic anastomoses are created at the apex of the reservoir, which is then folded on itself in a side-to-side fashion to complete pouch construction. The entire pouch is rotated cephalad so as to bring the ileal terminus to the region of the umbilicus. A small button of skin is removed from the depth of the umbilical funnel, and the ileal terminus is directed through this buttonhole (see Fig. 86–6F). The pouch is secured to the posterior fascia with interrupted absorbable sutures, and the ileal terminus is sewn similarly to anterior fascia. Excess ileal length is resected, and the ileum is sutured at the depth of the umbilical funnel with interrupted absorbable sutures.

Postoperative Care and Comments. No specific differences in postoperative care or complications associated with the Mainz pouch need to be addressed. Initial pouch capacities are higher than in the Kock or T pouch. Final mean capacity averaging greater than 600 mL has been reported. Pouch pressures are 23 cm H_2O at half capacity and 31 cm H_2O when the pouch is full. Contraction waves beginning at 50% pouch fullness can be recorded at an amplitude of 12 cm H_2O. Thus this pouch seems to produce a reasonably low-pressure urinary reservoir, although the pressures are not as low as those achieved with the use of small bowel alone.

Recently, the 10- and 12-year experiences with the Mainz pouch and the variations created by its developers were presented (Stein et al, 1995; Lampel et al, 1996). Between 1983 and 1994, 440 patients underwent a Mainz I operation in two urology departments, Mainz and Wuppertal. Continence mechanisms varied: in 146 cases the appendix was used as the continence mechanism; in 270 patients the intussuscepted nipple was used as the continent stoma; in 14 patients a submucosal, seromuscular bowel flap was employed; and in 10 patients a submucosal full-thickness bowel flap was used. The early complication rate was 12% and included mechanical ileus requiring open revision in 9 patients (1.6%), pouch leakage requiring revision in 5 patients (0.9%), wound dehiscence in 4 patients (0.7%), and fatal pulmonary emboli in 4 patients (0.7%).

The late complication rate was 37% and was predominantly attributable to the pouch. Stomal failure requiring open revision occurred in 45 patients (8%) and was directly related to the continence mechanism. Only 2 of 146 patients (1.4%) with an appendiceal continence mechanism were incontinent, but stomal stenosis occurred in 21%. The developers of this procedure were innovative in their attempts to bring the incontinence rate down to an acceptable level. To this end they tried multiple techniques, with variable success: an alloplastic stoma (4/4 incontinent); sutured intussusception (8/8 incontinent); stapled intussusception (5/22, 23% incontinent); and stapled ileocecal intussusception (10/204, 4.9% incontinent). The stapled ileocecal intussusception described previously is the current recommendation, and the long-term incontinence rate among the patients undergoing the stapled nipple valves was reduced to 10%. Other late complications included the need for ureteral reimplantation in 28 patients (4.9%) and stomal stenosis in 29 patients with an ileal nipple (11.7%) and in 17 patients with an appendiceal stoma (14.7%).

Calculus formation in the pouch occurred in 38 patients (6.8%), resulting in 36 percutaneous procedures. Despite the loss of the terminal ileum, no significant decrease in serum vitamin B_{12} levels has been reported and no patient has developed a macrocytic anemia or neurologic symptoms. However, 25% of patients are on oral alkalinization to avoid metabolic acidosis.

Since its inception, the overall complication rate for this procedure has been considered high (31%). However, as Stein and colleagues (1995) **pointed out, 50% of the complications were manageable with percutaneous techniques. Additionally, since 1988 the incontinence rate has been only 3.2% and less than 2% in patients with an appendiceal mechanism.**

Gerharz and colleagues (1997) from Marburg, Germany, reported their single-institution experience with the Mainz I ileocecal pouch. From 1990 to 1996, 202 consecutive patients underwent continent diversion, 96 with a submucosally embedded in-situ appendix and 106 with an intussuscepted ileal nipple. All patients had an umbilical stoma. In 172 of 200 patients (85%), no stomal complications occurred. In 17 of 96 patients (18%) with an appendiceal stoma, 23 revisions were performed for stomal stenosis. In contrast, only 13 of 106 patients (12%) with an intussuscepted ileal nipple developed problems with their stoma. However, these patients required more invasive, major procedures for correction, whereas those with an appendiceal stenosis could usually be repaired with a minor procedure. Three patients with an ileal nipple (3%) developed pouch calculi, whereas none of the patients with an appendiceal continence mechanism developed stones. As a result, the authors concluded that the appendix, when available, should be the intestinal continence mechanism of choice.

We share the enthusiasm for the use of the appendix as a continence mechanism. In our experience it has also been a reliable technique that is easy to perform. It has been our tendency in constructing right colon pouches employing an appendiceal continence mechanism to use the entire right colon inclusive of the hepatic flexure to form the reservoir, thereby preserving more terminal ileum. This has the theoretical advantage of fewer metabolic complications, but the Mainz group has not reported significant metabolic problems.

The introduction of the more reliable appendiceal continence mechanism has greatly increased the acceptance of the Mainz I procedure. The Mainz group has also developed two new techniques for construction of a Mitrofanoff, or appendiceal, type tube for use in patients whose appendix is either unsuitable or absent (Lampel et al, 1995a, 1995b; Lampel and Thurhoff, 1998). Both techniques use a small-caliber conduit fashioned from the large intestine in the region of the cecum. One technique uses a full-thickness tube lined by mucosa (Fig. 86–7) and the other a seromuscular tube lined by serosa (Fig. 86–8). Both techniques appear to be successful, although the full-thickness tube was associated with a lower complication rate and a higher success rate in their initial report (Lampel et al, 1995b). With longer follow-up, the authors have observed a similar success rates with both tubes; 93% of the patients (25 of 27) with a seromuscular tube and 92% of the patients (22 of 24) with a bowel wall tube were continent day and night (Lampel and Thurhoff, 1998). The authors believed that either tube was reliable and that each had its own unique advantages and disadvantages. In general, the full-thickness bowel wall tube was more adaptable, owing to the ability to create a longer tube. However, this came at the expense of a more tenuous blood supply. The decreased distal blood supply might be improved by creating a wider base on the tube. This could, however, make taenial implantation more difficult. The seromuscular tube was equally reliable but could only be anastomosed to the umbilicus, owing to the short adit tube. Either tube was believed to be indicated as a continence mechanism in the Mainz I pouch when the appendix was not available or as a continence mechanism for reservoirs created from other large intestinal segments. Either

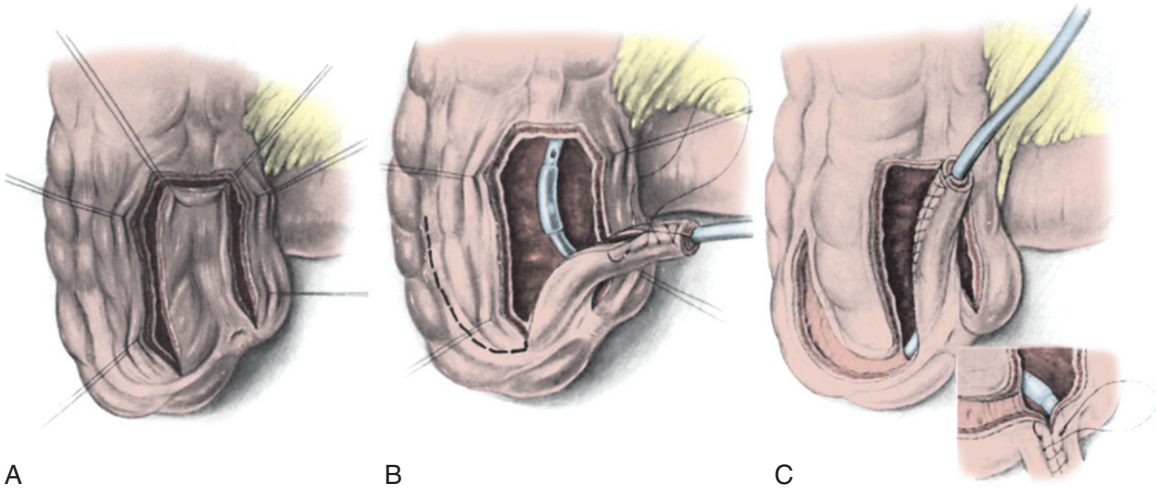


Figure 86–7. **A** to **C,** A full-thickness tube lined by mucosa is fashioned over an 18-Fr Foley catheter for tunneled reimplantation. The tube is closed with a running 3-0 absorbable suture. For longer tubes, the authors advise a wider base to prevent distal ischemia. The continence mechanism is created by placing the tube into the adjacent taenial trough. (From Lampel A, Hohenfellner M, Schultz-Lampel D, Thuroff JW. In-situ tunneled bowel flap tubes: two new techniques of a continent outlet for Mainz pouch cutaneous diversion. J Urol 1995;153:308–15.)

technique could be used as a salvage procedure when another primary continence mechanism had failed.

Another novel Mitrofanoff continence mechanism was described by Montie (1997), who conceived of a procedure in which a 2- to 3-cm segment of terminal ileum is isolated on its blood supply (Fig. 86–9A). The width of the segment was chosen to correspond to the circumference of the tube to be created. Once isolated, the segment is opened near one of its mesenteric junctions to create a longitudinal reconfiguration (see Fig. 86–9B and C). The tube is then closed with a running 3-0 absorbable suture (see Fig. 86–9D). It can now be used for a Mitrofanoff implant. When longer tubes are necessary, two adjacent segments can be isolated, reconfigured, and joined together (see Fig. 86–9E and F). Although originally described in dogs, the authors have used this technique in humans without complication. Montie (1997) reported on a high rate of stomal stenosis in dogs, but this may have been secondary to infrequent catheterizations. Stomal stenosis has not occurred in our limited series of patients. Other groups have used tapered ileum to create a tunneled access into the right colon (Fig. 86–10) (Woodhouse and MacNeily, 1994; Hampel et al, 1995). Using tapered ileum for this purpose has the advantage of a blood supply independent of the reservoir and no length restrictions while having the disadvantage of further limiting intestinal absorptive surface.

Wiesner and colleagues (2007) recently compared their long-term results in 458 patients who underwent Mainz I pouch construction. The anastomosis was made using a submucosal tunnel in 809 renal-ureteric units and using a serosa-lined extramural tunnel in 74 units. At 17 months postoperatively they found a significantly higher occurrence of anastomotic obstruction in the submucosal tunnel group compared with the extramural group (7.3% vs. 4.1%, respectively). Importantly, they found a much higher rate of obstruction in patients with previously dilated upper tracts (14%) or with a history of neurogenic bladder (17%). No significant deterioration of the upper tracts was identified.

In another comparison of patients with a Mainz I pouch, Wiesner and colleagues (2006) reported on 800 patients with almost 8 years of follow-up. Overall continence was approximately 93%. Stomal stenosis occurred in 23.5% of patients with a submucosally embedded in-situ appendix, whereas stenosis was reported in 15.3% of patients with intussuscepted ileal nipple valves. Rates of calculi formation were the reverse: 10.8% incidence in patients with an ileal nipple valve and only in 5.6% of patients with an appendix stoma. Ischemic degeneration of the continence mechanism occurred almost three times more often in the appendiceal group.

Right Colon Pouches with Intussuscepted Terminal Ileum

Additional pouches using nipple valve technology for the continence mechanism include those right colon pouches in which intussusception of the terminal ileum and ileal cecal valve is employed. As such, they are variations on the continent cecal reservoir initially described by Mansson (1987) that employ an intact cecal segment. These three pouches are the Le Bag (Light and Scardino, 1986), Duke pouch (Webster and King, 1987), and UCLA pouch (Raz, personal communication, 1989). These surgeries differ from each other only by a few features mainly related to the technique employed for stabilizing the nipple valve. Unless the appendix is being used as a continence mechanism, appendectomy must be performed in all cases because an in-situ appendix would serve as a nidus for infection and abscess formation.

These operations were described in detail in the prior edition of this text. Since then, no new modifications to these procedures have been reported, and they are not further described here. The reader is referred to the prior edition of this text for an in-depth description of these operations.

Indiana Pouch

The concept of using the buttressed ileocecal valve as a dependable continence mechanism that can withstand the trauma of intermittent catheterization was first reported by Rowland and colleagues (1987) **from Indiana University.** This operation, which involved the partial spatulation of the cecal segment and attachment of an ileal patch, represented major contributions to the original ileocecal reservoir as described by Gilchrist and colleagues (1950), in which the intact bowel reservoir was employed and no attempt was made to strengthen the ileocecal valve. Originally, strengthening the ileocecal valve consisted of a double row of imbricating sutures taken

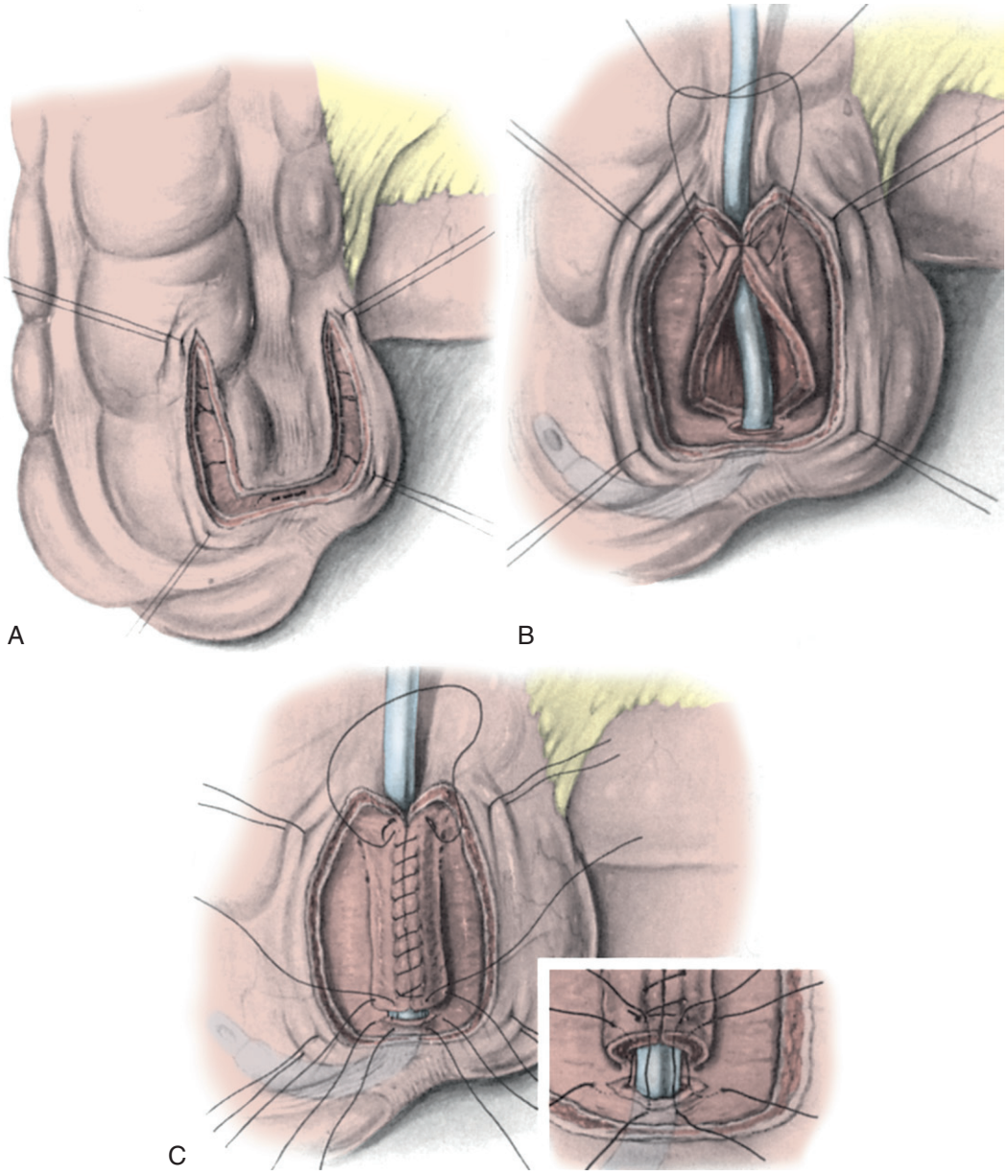


Figure 86–8. **A** to **C,** A 3- to 5-cm seromuscular tube denuded of mucosa and lined by serosa is fashioned for tunneled reimplantation. The tube is rolled over an 18-Fr Foley catheter. A mucosal window is opened at the base of the U, and the tube sutured to the mucosa with interrupted sutures. (From Lampel A, Hohenfellner M, Schultz-Lampel D, Thuroff JW. In situ tunneled bowel flap tubes: two new techniques of a continent outlet for Mainz pouch cutaneous diversion. J Urol 1995;153:308–15.)

to the entire ileal segment (Rowland et al, 1985, 1987). It soon became apparent that this was necessary only in the region of the ileocecal valve. "Neourethral" pressure profiles showed that the continence zone was confined to the region of the reconfigured ileocecal valve (Bejany and Politano, 1988). The remaining "neourethra" could be tapered and brought through an abdominal or perineal stoma. At Indiana University, as well as other institutions, it became clear that the concept of marsupializing only a portion of the ascending colon segment left enough peristaltic integrity in the cecal region to generate pressures sufficiently high to overcome the continence mechanism in some patients. A number of groups contributed to the concept of using the entire right colon or more, marsupializing the entire structure and refashioning it in a Heineke-Mikulicz configuration (Lockhart, 1987; Bejany and Politano, 1988; Benson et al, 1988; Rowland, personal communication, 1989). These variations have been entitled the Florida pouch (Lockhart, 1987) and the University of Miami pouch (Bejany and Politano, 1988). However, they represent relatively minor variations on the theme of the Indiana pouch.

Procedure. The Indiana pouch, in its present form, involves isolating a segment of terminal ileum approximately 10 cm in length along with the entire right colon to the junction of the right and middle colic artery blood supplies (Fig. 86–11A). After bowel continuity is re-established, appendectomy is performed and the appendiceal fat pad obscuring the inferior margin of the ileocecal junction is removed by cautery (see Fig. 86–11B). The entire right colon is opened along its antimesenteric border, and ureteral-taenial implants are fashioned (see Fig. 86–11C). The ileocecal junction is buttressed according to various reported techniques. Using nonabsorbable sutures, interrupted Lembert sutures

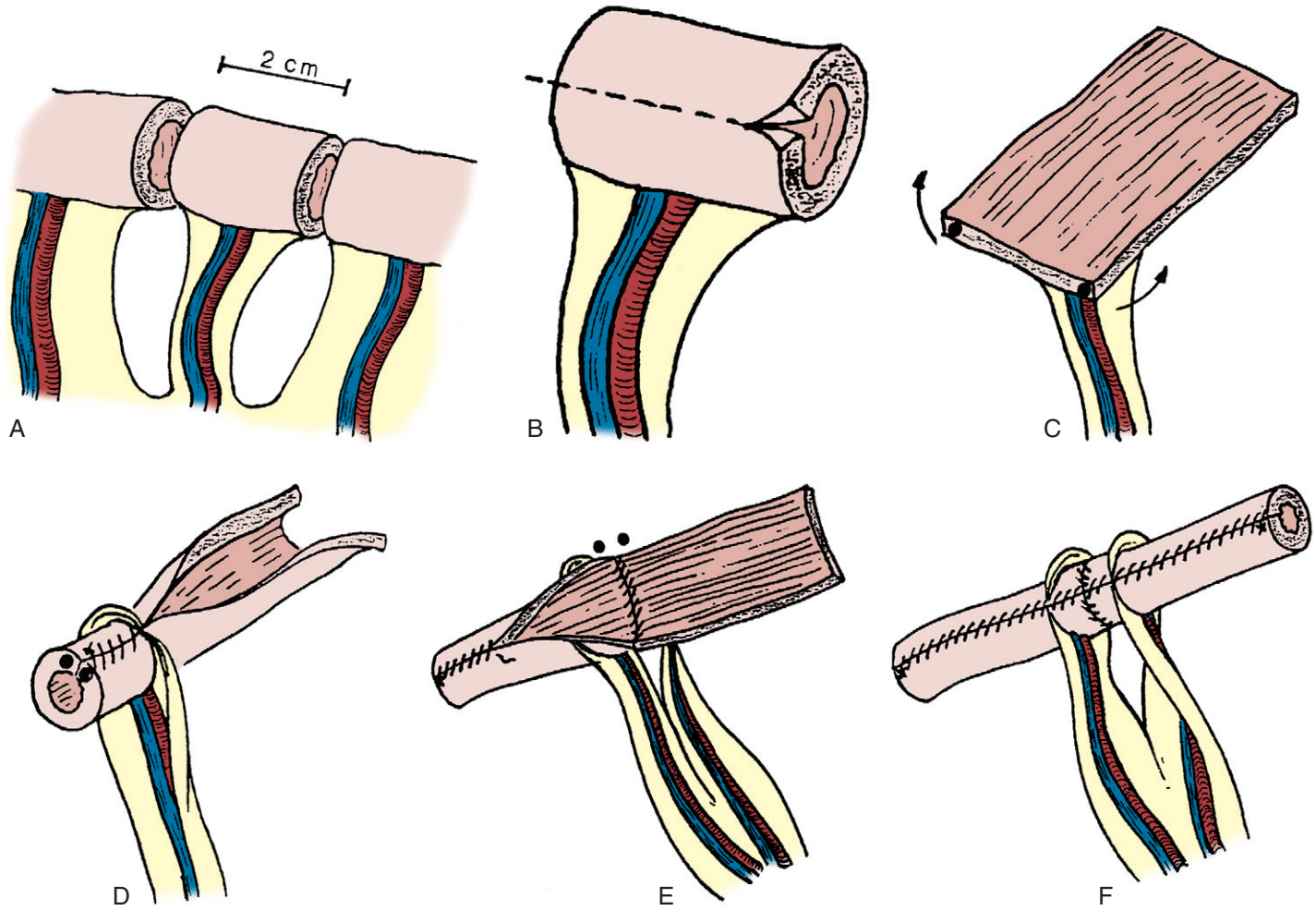


Figure 86–9. **A,** A 2- to 3-cm segment of terminal ileum is isolated on its blood supply. **B** and **C,** The tubular segment is opened approximately one fourth of the way up one side. This results in a well-vascularized rectangular plate. **D,** The rectangular tube is now closed over a catheter with a running absorbable suture. **E** and **F,** Two adjacent segments can be joined together to create one long tube. (From Monti PR, Lara RC, Dutra MA, et al. New techniques for construction of efferent conduits based on the Mitrofanoff principle. Urology 1997;49:112–5.)

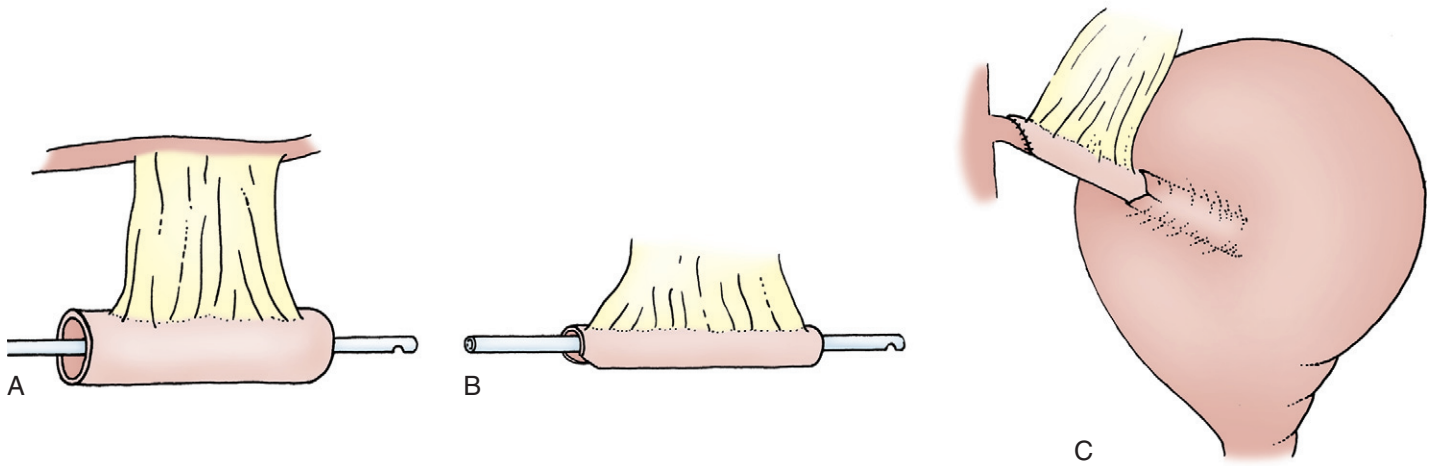


Figure 86–10. **A** to **C,** Woodhouse tapered ileum. (From Woodhouse CR, MacNeily AE. The Mitrofanoff principle: expanding upon a versatile technique. Br J Urol 1994;74:447–53.)

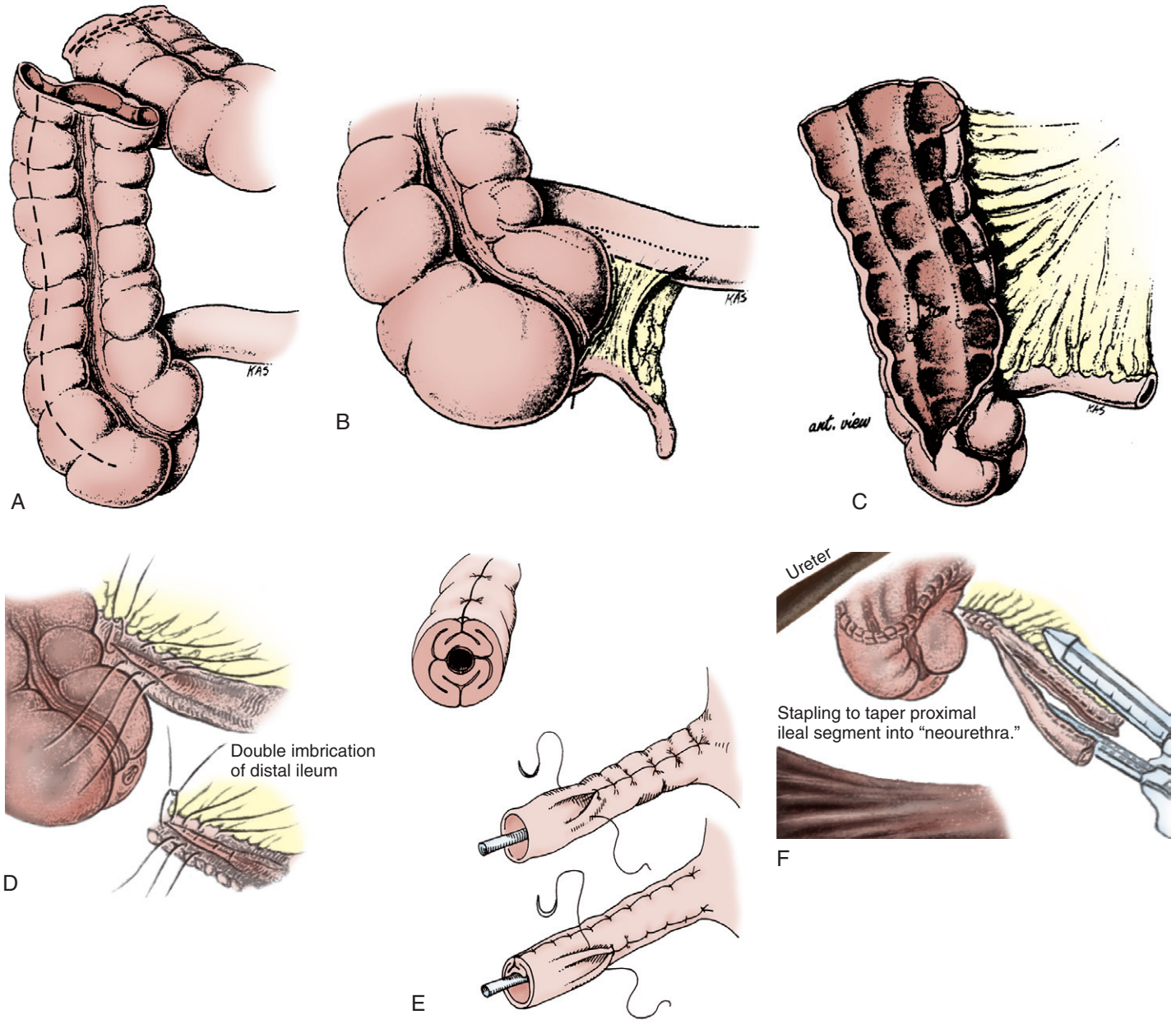


Figure 86–11. **A,** A segment of terminal ileum approximately 10 cm in length along with the entire right colon is isolated. **B,** An appendectomy is performed, and the appendiceal fat pad obscuring the inferior margin of the ileocecal junction is removed by cautery. **C,** The entire right colon is opened along its antimesenteric border. **D,** Interrupted Lembert sutures are taken over a short distance (3 to 4 cm) in two rows for the double imbrication of the ileocecal valve as described at Indiana. **E,** Application of opposing Lembert sutures on each side of the terminal ileum. **F,** Excess ileum can be tapered by stapling technique. (**A** to **C,** From Benson MC, Sawczuk IS, Hensle TW, et al. Modified Indiana University continent diversion. Curr Surg Tech Urol 1988;1:1–8; **D** and **F,** from Olsson CA. Contemp Urol 1989;Sept:62–8; **E,** from Lockhart J. Remodeled right colon: an alternative urinary reservoir. J Urol 1987;138:730–4.)

are taken over a distance of 3 to 4 cm in two rows for the double imbrication of the ileocecal valve as described at Indiana University (see Fig. 86–11D). The second row of sutures should attempt to bring the opposite mesenteric edges of ileum together, usually over a 12- to 14-Fr catheter. These two rows of sutures should be placed approximately 8 mm from one another, and the initial suture in each row may be taken in a purse-string fashion around the cecal margin as well. Alternatively, the University of Miami group suggests placing purse-string sutures in the same ileal region (Bejany and Politano, 1988). Finally, the Tampa group suggests placement of apposing Lembert sutures on each side of the terminal ileum (see Fig. 86–11E). The remaining ileum can be tapered over the catheter and excess ileum removed with a stapling technique (see Fig. 86–11F).

It is important to carry out the imbrication while the cecal reservoir is still open (Rowland, 1996) so that the gradual closure of the ileocecal valve can be closely observed. The pouch is then closed in a Heineke-Mikulicz configuration with a running absorbable suture. Ureteral stents and a suprapubic tube are taken through a stab wound in the pouch and led through the right lower abdominal quadrant. The pouch is rotated so as to bring the ileal neourethra as close as possible to the selected stoma site. A fingerbreadth-width skin button is transected along with a similar button from the anterior and posterior fascia. The ileal neourethra

is advanced between bundles of the rectus muscle through the stoma, and excess ileum is transected. The ileal edges are sewn to skin with interrupted sutures so as to create a flush stoma.

In addition to the differences in the technique of ileocecal valve imbrication, both the University of Miami and the Florida pouches differ in the amount of colon used. The entire ascending colon and the right third or half of the transverse colon is isolated along with 10 to 12 cm of ileum. The entire upper extremity of the large bowel is mobilized laterally in the fashion of an inverted U (Fig. 86–12A). The medial limbs of the U are sutured to one another after the bowel is spatulated (see Fig. 86–12B). The bowel plate is then closed side to side (see Fig. 86–12C). This inverted-U closure, however, is exactly the same as a Heineke-Mikulicz reconfiguration.

Recent modifications to the Indiana reservoir allow for more rapid construction and a lower complication rate (Rowland, 1996). The modifications incorporate the use of metal staples to create the efferent limb and absorbable staples to fashion the reservoir. The concept of using a metal GIA stapler to fashion the efferent limb was first introduced by Bejany and Politano (1988). Carroll and Presti (1992) reported on the urodynamic features of the stapled and plicated terminal ileum and found that the stapled limb performed equally well and was easier to construct. The use of absorbable staples to create this and other types of reservoirs is described later in the chapter.

Postoperative Care and Comments. The postoperative care of the patient with an Indiana pouch or its variants is not substantially different from that used in patients with other right colon catheterizable diversions. In early reports, Rowland recommended discharging the patient with the suprapubic tube in place until readmission to the hospital 3 weeks later for tube removal and instruction in self-catheterization. In the current medical climate, which places a premium on outpatient procedures, tube removal and catheterization instruction is now an ambulatory procedure at most institutions including Indiana University (Bihrle, 1997).

Average pouch capacities of 400 to 500 mL have been reported by the Indiana group (Rowland et al, 1987). Combining the partially and totally spatulated bowel procedures, this group reports a reoperation rate of 26%. Overall continence rates of 93% were achieved. Elegant urodynamic studies were conducted in Indiana pouch variants by Carroll and colleagues (1989). They found only 86% of patients totally continent in a small series. However, their pouch capacities exceeded 650 mL, and peak contractions of 47 cm H_2O were recorded at capacity.

The last 81 patients operated on by Rowland underwent construction of a stapled efferent limb, and, in the last 20, the reservoir was created with absorbable staples (Rowland, 1996). **The results in this group of patients were extremely favorable. Early pouch-related complications occurred in only three patients (3.7%).** Two patients experienced a pouch leak that was managed conservatively, and one patient required open revision of the efferent limb owing to difficulty with catheterization. Early complications not directly attributable to the pouch occurred in seven patients (8.6%). Transient small bowel obstruction was the most common complication, occurring in four patients (4.9%). One patient developed a superficial wound infection, and one patient developed an abdominal abscess requiring surgery (1.2%). Late complications associated with the reservoir occurred in 23 patients (28.4%). Incontinence occurred in six patients (7.4%): In five patients it occurred secondary to high pouch pressures, whereas in the remaining patient it was due to failure of the efferent limb. One of the former and the latter patient underwent reoperation. Three patients (3.7%) developed stomal stenosis, and three had parastomal hernias; all six underwent surgery. Pouch stones occurred in three patients: One underwent open removal, and two had endoscopic extraction. Acute pyelonephritis was seen in four patients (4.9%). The most common late complication not related to the pouch was small bowel obstruction; this was seen in six patients and managed conservatively in five. In summary, the early reoperation rate was 2.5% and the late reoperation rate 14.8%. **At 1 year, daytime and nighttime dry intervals of 4 hours or greater were achieved in 98% of patients.** Eighty-four percent of patients stated they slept through the night without the need to awake for catheterization. Similarly excellent results in the last 150 patients, 50 with at least 2.5-year follow-up, were reported by Birhle (1997).

The Florida pouch has been performed in more than 190 patients (Helal et al, 1993). In 165 patients involving 326 ureters, no attempt was made to create a tunneled reimplantation. This approach was adopted owing to the high incidence of ureteral obstruction encountered in the first 30 ureters that were tunneled into a Florida pouch (4 patients, 13.3%). In the last 165 patients, 16/326 ureters (4.9%) developed primary obstruction and were treated by percutaneous balloon dilation, nephrectomy, or

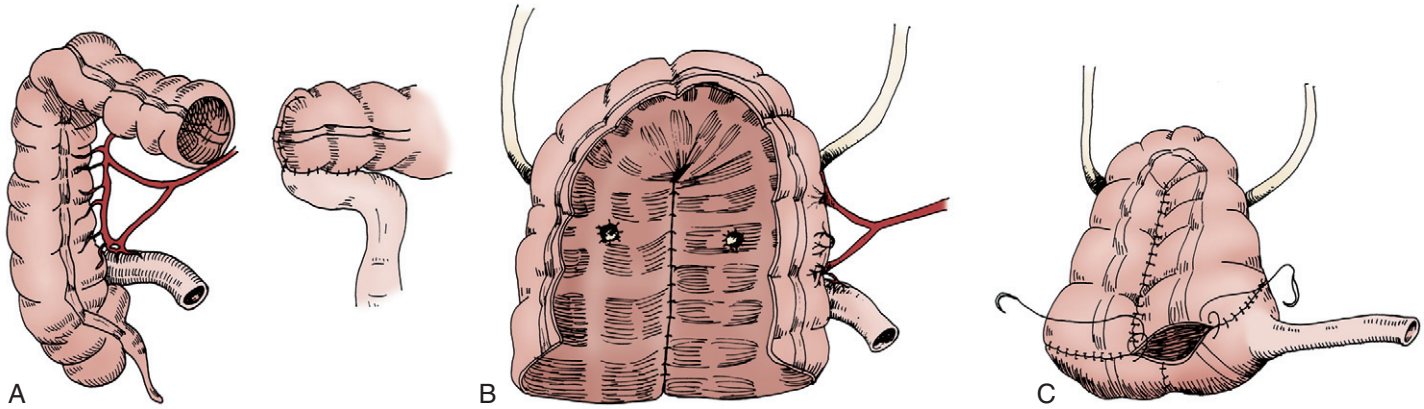


Figure 86–12. **A,** The entire ascending colon and the right third or half of the transverse colon is isolated along with 10 to 12 cm of ileum. **B,** The entire upper extremity of the large bowel is mobilized laterally in the fashion of an inverted U. The medial limbs of the U are sutured after the bowel is spatulated. **C,** The bowel plate is then closed side to side. (From Lockhart J. Remodeled right colon: an alternative urinary reservoir. J Urol 1987;138:730–4.)

observation. Although no attempt is made to create an antirefluxing anastomosis, only 7.1% of the ureters implanted demonstrated reflux. All are being followed conservatively, and no renal deterioration has been demonstrated. In the initial 100 patients, a 7.2% reoperation rate was reported (Lockhart, 1987). Although hyperchloremia was noted in 70% of patients, only four patients (including those who had pre-existing renal disease) required treatment. Reservoir capacities ranged from 400 to 1200 mL, and maximal reservoir pressures at capacity ranged from 18 to 55 cm H_2O (Lockhart, 1987). The reason why these authors experienced such a high incidence of ureteral obstruction with both nontunneled and tunneled ureteral colonic anastomoses is not clear. It is also surprising that only 23 of 326 ureters that were anastomosed end to side had reflux.

The University of Miami group has reported on its results in 75 patients. Early complications occurred in 19 patients (25%). Sixteen patients (21%) experienced late complications. The success rate of the ureterocolonic anastomosis was 90%, and total continence occurred in 98.6% of patients. Average pouch capacities were 750 mL or higher, and end filling pressures of 20 cm H_2O were reported. No patient required alkali therapy.

The Indiana pouch remains one of the most reliable of all catheterizable reservoirs. It is among the easiest to construct and has low short-term and long-term complications.

Penn Pouch

The Penn pouch was the first continent diversion employing the Mitrofanoff (1980) **principle in which the appendix served as the continence mechanism. As mentioned earlier, this operation enjoys the singular feature of affording a catheterizable continent diversion that can be performed using techniques already present in the urologic armamentarium.**

Procedure. Two techniques of appendiceal continence mechanisms have been reported. Mitrofanoff reported excising the appendix with a button of cecum and reversing it on itself before tunneled reimplantation (Mitrofanoff, 1980; Duckett and Snyder, 1986). Alternatively, Riedmiller and colleagues (1990) left the appendix attached to the cecum and buried it into the adjacent taenia by rolling it back onto itself. A wide tunnel is created in the taenia extending 5 to 6 cm from the base of the appendix (Fig. 86–13). Windows are created in the mesoappendix between blood vessels. The appendix is folded cephalad into the tunnel, and seromuscular sutures are placed through the mesoappendix windows to complete the tunneling. The tip of the appendix is amputated and brought to the selected stoma site.

As described by Duckett and Snyder (1986), an ileocecal pouch is created by isolating a segment of cecum up to the junction of the ileocolic and middle colic blood supplies along with a similar length of terminal ileum. These two structures are marsupialized on the antimesenteric borders and sutured to one another in the form of a neotubularized pouch. The superior margin of the pouch is sutured in a transverse fashion (all sutures being of absorbable material). A button of cecum surrounding the origin of the appendix is circumcised, and the resulting cecal aperture is closed with running absorbable suture. The mesentery of the appendix is dissected carefully from the base of the cecum, thereby preserving its blood supply. The appendix is then reversed on itself so that the cecal button can reach the anterior abdominal wall and the tail of the appendix can be directed to the taenia of the colon (Fig. 86–14). The appendiceal tip is obliquely transected and may be spatulated. Then a tunneled appendiceal-taenial implantation is carried out. If additional appendiceal length is required, the variation proposed by Burns and Mitchell (1990) of creating a tube from the base of the cecum can be employed (see Fig. 86–3). Instead of simply removing the appendix with a button of cecum before preparing it for tunneling, the entire base of the cecum leading to the appendix can be resected in continuity with the appendix by the application of the GIA stapler. The authors have found it helpful to spatulate the distal tip of the appendix until it accommodates a catheter at least 12- to 14-Fr in diameter.

Postoperative Care and Comments. Although not shown in Duckett's surgical drawings, the authors would suggest that a large-bore suprapubic tube be used to drain the pouch in the early postoperative interval. The size of the catheter admitted by the appendiceal stump is insufficient to allow for the passage of ureteral stents along with the 12- to 14-Fr catheter. In addition, safe irrigation of mucous debris is best managed by a larger-bore catheter.

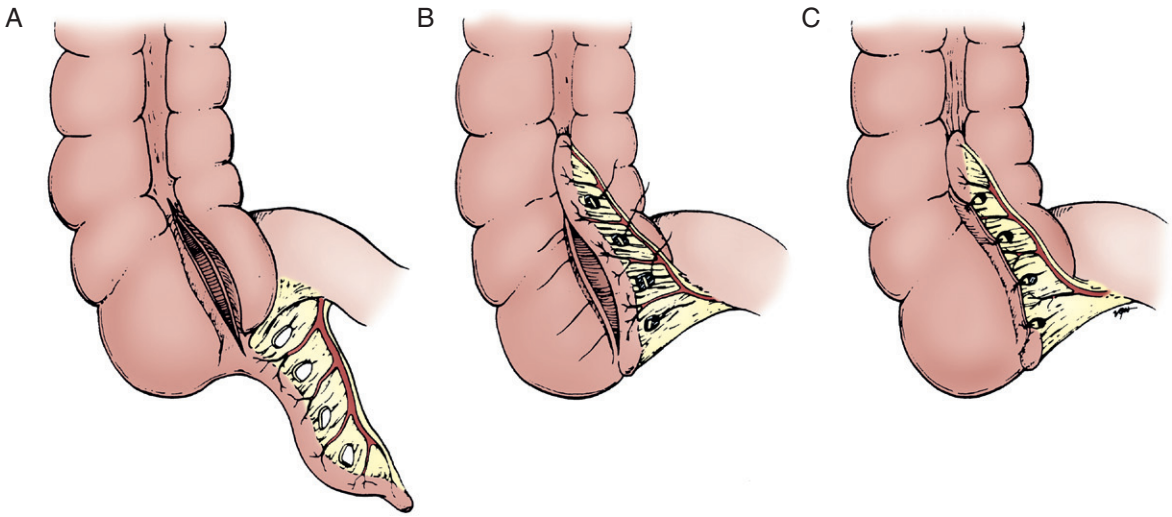


Figure 86–13. **A** to **C,** The appendix is left attached to the cecum and buried into the adjacent cecal taenia by rolling it back onto itself. A wide tunnel is created, extending 5 to 6 cm from the base of the appendix. Windows are created in the mesoappendix between blood vessels. The appendix is folded cephalad into the tunnel, and seromuscular sutures are placed through the mesoappendix.

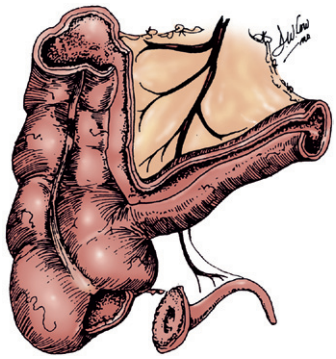


Figure 86–14. A segment of cecum up to the junction of the ileocolic and middle colic blood supplies along with a similar length of terminal ileum is isolated and marsupialized on the antimesenteric borders. A button of cecum surrounding the origin of the appendix is circumcised. The mesentery of the appendix is dissected carefully from the base of the cecum, preserving its blood supply. (From Duckett JW, Snyder HM III. The Mitrofanoff principle in continent urinary reservoirs. Semin Urol 1987;5:55–62.)

Many groups have used the Mitrofanoff principle owing to the simplicity and reliability of the continence mechanism (Burger et al, 1992; Bissada, 1993; Sumfest et al, 1993; Woodhouse and MacNeily, 1994; Hampel et al, 1995). Woodhouse and MacNeily (1994) reported on a series of 100 patients who underwent surgery between 1985 and 1993. They employed seven different catheterizable conduits into six different types of reservoirs. Although they found the Mitrofanoff principle to be versatile and associated with a high success rate (91% continence), the reoperation rate for tube complications was 33%.

Sumfest and colleagues (1993) affirmed the use of the appendix as the Mitrofanoff segment of choice. They reported a continence rate of 96%. In their hands, late complications included difficulty with catheterization in 10.6% and stomal stenosis in 19.1%.

Urodynamic properties and pouch capacities will be a function of the reservoir constructed. Most often, the appendix is used in situ (Burger et al, 1992), and the right colon, either alone or with associated terminal ileum (Mainz), serves as the reservoir. We have used the in-situ appendix with a detubularized right colon reservoir and the native ileocecal valve as an antireflux mechanism (refluxing ureters implanted end to side into terminal ileum). In our hands this has resulted in an excellent success rate with no upper tract problems. The adequacy of the ileocecal valve as an antireflux mechanism was also reported by Alcini and colleagues (1994). In their series, however, the reservoir was not always detubularized and, as expected, upper tract complications ensued owing to high reservoir pressures. This procedure is uniquely capable of affording continent cutaneous diversion to the patient with short ureters because the terminal ileum can be left long enough to reach high into the retroperitoneum.

Gastric Pouches

Pioneering animal experimentation demonstrated the feasibility of employing stomach as a bladder patch or urinary reservoir (Sinaiko, 1956; Rudick et al, 1977; Leong, 1978). **The use of the stomach to create a urinary reservoir has theoretical and real advantages** (Adams et al, 1988). **First, electrolyte reabsorption would be greatly diminished by using this bowel segment in the reservoir. This would potentially make the stomach the selected reservoir for individuals with pre-existing metabolic acidosis or renal insufficiency. Hyperchloremic acidosis would not be an anticipated problem; in fact, in addition to presenting a barrier against the absorption of chloride and ammonium, the gastric mucosa secretes chloride ions** (Piser et al, 1987). **Furthermore, in patients in whom shortening of the bowel may be expected to lead to some degree of malabsorption, the use of stomach is an attractive alternative. The acid pH of the urine may also reduce the risk of bacterial colonization. Finally, when the entire lower bowel has been irradiated, stomach tissue may provide healthy nonirradiated tissue for use in performing continent diversion.** Given these theoretical advantages, a number of groups have initiated trials with gastric pouches and composite reservoirs in both pediatric (Adams et al, 1988) and adult populations (Lockhart et al, 1993; Austin et al, 1997).

Procedure. A wedge-shaped segment of stomach with maximal width of 7 to 10 cm is fashioned from the greater curvature. Care is taken not to extend the wedge through to the lesser curvature to preserve vagal innervation and normal gastric emptying. The left gastroepiploic artery is preferentially used as the blood supply for the isolated gastric wedge, dividing the short gastric vessels from the more proximal artery up to the gastric fundus. Alternatively, if there is a problem with the left artery, the right gastroepiploic vessel may be employed, dividing the short gastric vessels to the level of the pylorus (Fig. 86–15A and B). The stomach is then closed according to the surgeon's preference. Neither gastroduodenostomy nor gastrojejunostomy is mandatory unless the antrum of the stomach has been used. The isolated wedge is refashioned into nearly a sphere by folding it back on itself and suturing the edges together with running absorbable material. Before pouch closure, one ureter is tunneled into the reservoir according to the surgeon's preferred antireflux technique. Contralaterally, proximal transureteroureterostomy is performed. The contralateral distal ureter is used to create the continence mechanism. The distal ureter is tunneled into the reservoir in a fashion similar to an appendiceal implant. The free portion of the ureter can then be brought to the skin or to the introitus (or urethral stump in males) to serve as a catheterization portal (see Fig. 86–15C). Alternatively, the wedge of stomach can be incorporated into a reservoir composed of detubularized ileum (Lockhart et al, 1993). In this procedure, an 11-cm long segment of stomach is isolated on the right gastroepiploic blood supply (Fig. 86–16A). A 22-cm segment of ileum is then isolated, opened along its antimesenteric border, and refashioned in a U shape (see Fig. 86–16B). The edges of the stomach are then sutured to edges of the ileum with a running absorbable suture of 2-0 PGA. This completes the reservoir. The ureters are tunneled into the stomach, and a Mitrofanoff continence mechanism is created according to the preference of the surgeon. For example, the group from the University of South Florida employs a tapered segment of ileum (see Fig. 86–16C).

Postoperative Care and Comments. Adams and colleagues (1988) report mean pouch capacities of 245 mL and end filling pressures averaging 35 cm H_2O in a small patient sample. Combining their experience of gastric continent diversion and gastrocystoplasty, they report minimal mucus production: Only 3 of 13 patients required any irrigations, and the majority maintained sterile urine. Urine pHs have ranged from 4 to 7, but no introital ulceration from acid urine was reported. Three patients had minor elevations of serum gastrin, and none of the continent divisions required reoperation. Leong (1978) has used similar concepts in gastric pouch construction and has alluded to the creation of a voiding pouch created from stomach as well.

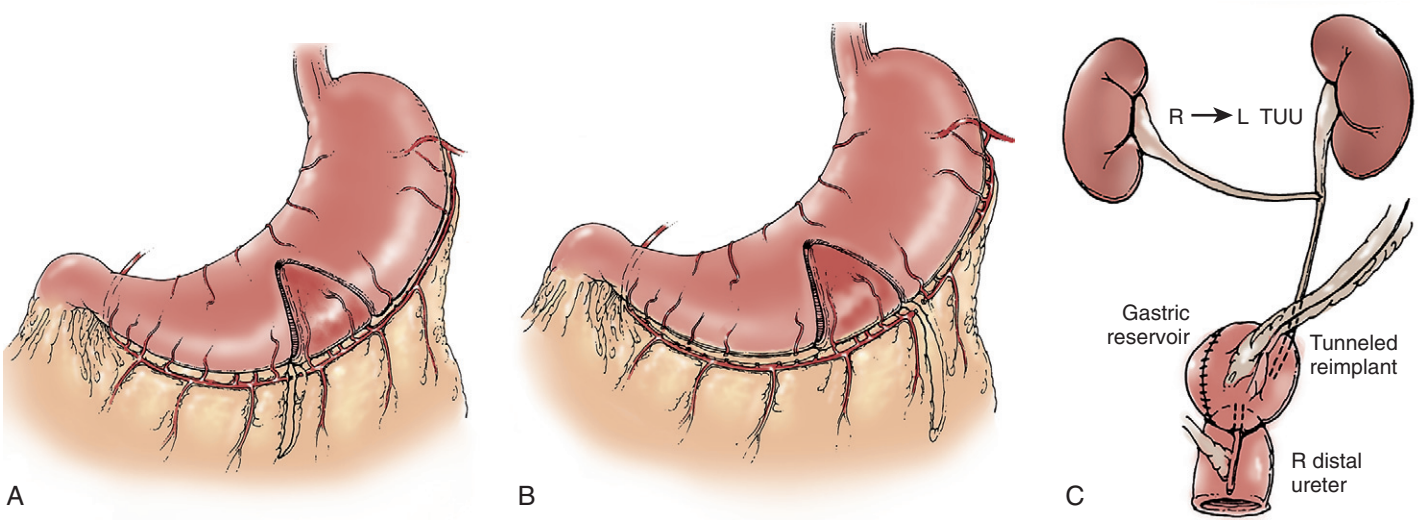


Figure 86–15. **A** and **B,** A wedge-shaped segment of stomach whose greatest width is 7 to 10 cm is fashioned from the greater curvature. The left gastroepiploic artery is preferentially used as the blood supply for the isolated gastric wedge, by dividing the short gastric vessels up to the gastric fundus. Alternatively, if there is a problem with the left artery, the right gastroepiploic vessel may be employed. **C,** The isolated wedge is refashioned into nearly a sphere by folding it back on itself and suturing the edges together with running absorbable material. One ureter is tunneled into the reservoir. A proximal transureteroureterostomy (TUU) is performed. The ipsilateral distal ureter is tunneled into the reservoir with its distal extent brought to the introitus to serve as a catheterization portal. (From Adams MC, Mitchell ME, Rink RC. Gastrocystoplasty: an alternative solution to the problem of urological reconstruction in the severely compromised patient. J Urol 1988;140:1152–6.)

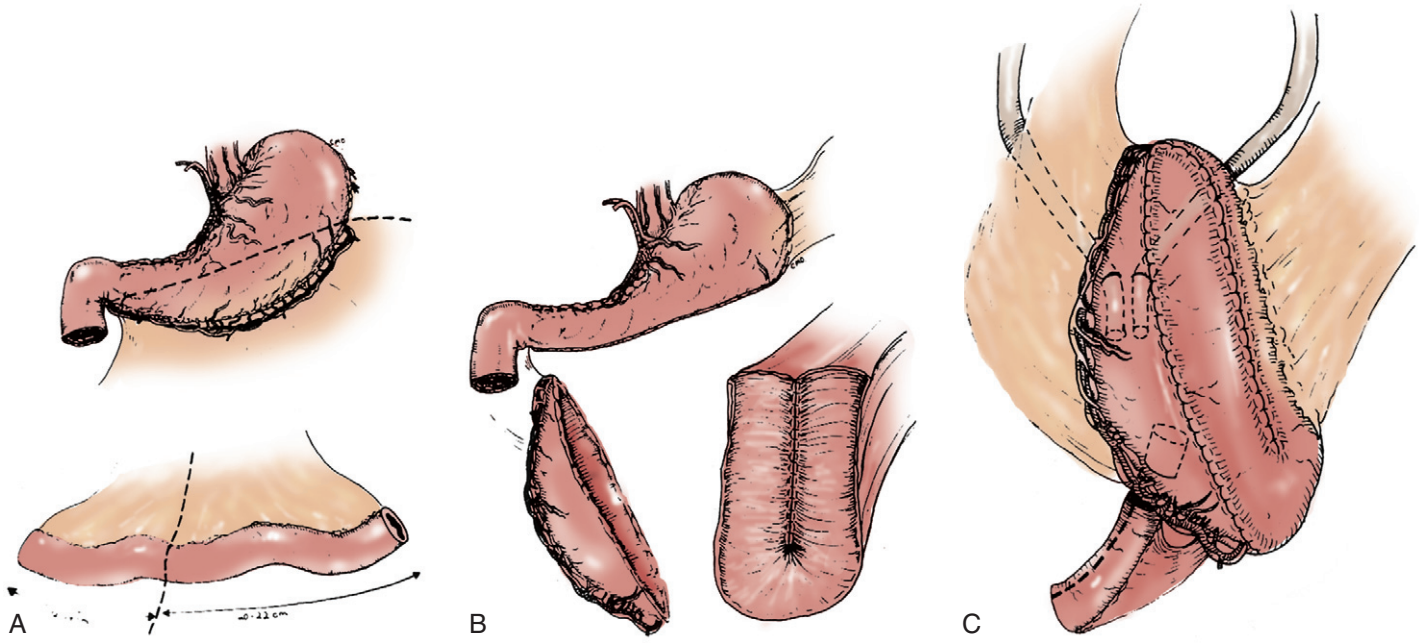


Figure 86–16. **A,** An 11-cm long segment of stomach is isolated on the right gastroepiploic blood supply using a gastrointestinal anastomosis-90 stapler. Usually, two staplers are required. **B,** A 22-cm segment of ileum is then isolated, opened along its antimesenteric border, and refashioned in a U shape. **C,** The edges of the stomach are then sutured to edges of the ileum with a running absorbable suture of 2-0 polyglycolic acid. This completes the reservoir. The ureters are tunneled into the stomach, and a Mitrofanoff continence mechanism is created with a tapered segment of ileum. (From Lockhart JL, Davies R, Cox C, et al. The gastroileal pouch: an alternative continent urinary reservoir for patients with short bowel, acidosis and/or extensive pelvic radiation. J Urol 1993;150:46–51.)

The construction of reservoirs entirely from stomach has not seen widespread acceptance. Rather, there has been greater use of stomach segments either for bladder augmentation or as a portion of a reservoir (composite) either alone or with an in-situ catheterizable tube fashioned from a portion of the stomach (Gosalbez et al, 1994; Carr and Mitchell, 1996).

Goslabez and colleagues (1994) reported on 15 patients who received a gastric tube as part of a composite gastric patch. Complications associated with the gastric patch and in-situ tube included one each of early traumatic perforation of the tube, distal tube stenosis, and mucosal redundancy. Two of these patients required reoperation. Peristomal skin irritation from acid secretion

occurred in two patients but was not considered severe. This is a more frequent complication in other reports and has resulted in skin breakdown in some instances.

Over a 10-year period from January, 1985, to June, 1995, Carr and Mitchell (1996) reported on the use of stomach in 12 patients. Seven had urinary reservoirs totally constructed from stomach, whereas five had composite reservoirs. They report continence in all patients but that the continence mechanisms have often required revision. Average bladder capacity was 309 mL, and average compliance was 12.9 mL/cm H_2O. When stomach is used as a bladder augment or as a portion of a neobladder, a dysuria and hematuria syndrome has been reported (Nguyen et al, 1993).

Austin and colleagues (1997) reported on nine adult patients with a mean follow-up of 54 months who underwent construction of a continent composite reservoir that was gastroileal in seven and gastrocolonic in two. All nine patients had either preexisting metabolic acidosis or a short bowel syndrome. All nine patients achieved electrolyte neutrality, and postoperative serum pH was significantly improved ($P < .01$). Three patients had a short-term serum gastrin elevation, which returned to normal during follow-up. One patient developed skin ulceration at the stoma site.

The use of stomach has particular appeal in the pediatric population in which the stomach's unique acid-base properties can be used to not only reconstruct but also help correct the metabolic problems that are often associated with the need for pediatric urinary reconstruction (Carr and Mitchell, 1996). **Although experience with use of the stomach remains small, its various unique intrinsic properties as a reservoir suggest that its use will continue in selected clinical situations.**

QUALITY OF LIFE ASSESSMENTS

Extraordinarily few well-designed, prospectively conducted studies using validated instruments exist to assess quality of life after continent cutaneous urinary diversion. In fact, no randomized prospective trial has ever been conducted to compare the quality of life after continent cutaneous diversion with either orthotopic continent diversion or incontinent urostomy urinary diversion. Of those studies performed, there appear to be common flaws in the study design and methods used that make any direct comparisons between continent and incontinent diversions difficult (Gerharz et al, 2005).

In general, most quality of life studies show similar results between patients undergoing both ileal conduit and cutaneous continent diversion, with the latter being associated with improvements in stomal and urinary quality of life scores. In one of the few prospective studies to compare quality of life after continent cutaneous and ileal conduit diversion, Hardt and colleagues (2000) followed patients from the preoperative setting until 1 year after surgery. Using validated instruments tested for reliability, they found life satisfaction improved over time in patients with continent cutaneous diversion, whereas it worsened during the first year after ileal conduit construction. Using the Beck Depression Inventory and Profile of Mood States in adults, Boyd and colleagues (1987) found that patients choosing ileal conduit diversion had the lowest expectations of their quality of life. Interestingly, they found the highest overall satisfaction among patients undergoing conversion from ileal conduit to Kock cutaneous pouch diversion.

Mansson and colleagues (2002) found no difference in overall quality of life in men undergoing continent cutaneous diversion when compared with orthotopic neobladder using the FACT-BL and Hospital Anxiety and Depression Scale. In specific questions concerning intestinal, urinary, and sexual function, patients with cutaneous reservoirs experienced less difficulty with incontinence and emptied less frequently. Sexual function appeared better in patients undergoing orthotopic bladder substitution, likely due to urethral preservation.

VARIATIONS IN OPERATIVE TECHNIQUE

Minimally Invasive Continent Cutaneous Diversion

With recent improvements in both laparoscopic and robotic-assisted laparoscopic techniques, radical cystectomy can now be performed in selected centers using these minimally invasive techniques. The vast majority of centers performing minimally invasive cystectomy and continent cutaneous diversion perform the urinary diversion via standard open techniques. Turk has reported on an initial series of five patients who have undergone radical cystectomy with bilateral pelvic lymphadenectomy and continent urinary diversion using a rectosigmoid pouch performed with an intracorporeal laparoscopic technique. A bilateral stented antireflux ureteral reimplantation was used, and laparotomy was not performed. Operative time was 7.4 hours with minimal blood loss and a mean hospital stay of 10 days. No intraoperative or postoperative complications were encountered.

The complex nature of minimally invasive reconstructive surgery necessary in continent cutaneous diversion has limited these procedures to select centers. In addition, because of the prolonged time for return of postoperative bowel function, the benefits in hospital stay routinely encountered after laparoscopic nephrectomy do not seem to exist when urinary diversion is performed.

Conduit Conversion to a Continent Reservoir

The major indication for conversion of a functioning conduit to a continent urinary reservoir is the patient's desire for improved quality of life. Pow-Sang and colleagues (1992) reported on conversion in 20 patients. Fifteen were converted from an ileal conduit, and one each from a cecal conduit, ureterosigmoidostomy, cutaneous ureterostomy, sigmoid conduit, and a suprapubic tube. In 14 of the 20 patients the conduit was discarded or used only as a patch to a colonic reservoir. Renal units that were obstructed preoperatively were associated with a 71% failure rate. Metabolic acidosis was seen in 15 (75%) but was believed to be mild. Pouch-related complications are, in general, a function of the reconstruction selected and should not necessarily be higher in this setting. However, patient selection is important in determining appropriate candidates for conversion.

The authors prefer to use the conduit in some form whenever possible. This strategy was supported in a report on two patients by Oesterling and Gearhart (1990). The use of an existing bowel segment has the potential to diminish metabolic sequelae and may result in a lower complication rate. The form of continent reconstruction chosen will have to depend on intraoperative findings, and no one procedure is more amenable than another. Before undertaking conversion, the patient should be fully evaluated for disease recurrence, renal functional status, urinary anatomy, hydronephrosis, intestinal length, and intestinal health.

Pahernik and colleagues (2004) have described the long-term outcomes of conversion of 39 patients from conduit diversion to Mainz I pouch diversion. With a mean follow-up of 102 months, the most common complications were stomal stenosis and pouch calculi. Long-term continence was achieved in 95% of patients.

Absorbable Stapling Techniques in Continent Urinary Diversion

The principle of bowel detubularization to increase reservoir capacity and diminish the effects of peristalsis is a fundamental principle of all contemporary continent urinary diversions. The process of detubularization and refashioning of the spatulated bowel segment consumes at least 1 hour of operating time and is by far the most time-consuming and tedious aspect of pouch construction. **The use of absorbable staples has substantially reduced the time required to fashion bowel reservoirs and has demonstrated short-term and long-term reliability with respect to reservoir integrity and volume.**

Bonney and Robinson (1990) first demonstrated the potential use of absorbable staplers to substitute for conventional suturing of bowel reservoirs. These authors used a bulky absorbable stapler (Polysorb staples in a TA Premium 55 stapler [US Surgical, Norwalk, CT]) to construct an S pouch configuration in a canine ileal urinary pouch model. Although the same stapler was used in humans by the authors in 1992 and by Cummings in 1995, its clinical use was never widely adopted because the bulky staple configuration destroyed a significant portion of the bowel diameter, particularly when applied to the small intestine. The fact that up to 20 costly staple cartridges were required to complete the closure of a bowel reservoir further reduced the potential benefits of absorbable pouch construction.

A 75-mm GIA instrument (PolyGIA [US Surgical, Norwalk, CT]) that incorporates substantially smaller absorbable staples was made available for clinical use in 1992. The stapler delivers four rows of absorbable polylactic acid and PGA blend copolymer staples, dividing the bowel between the second and third rows. Thus each staple line of the pouch has a double, staggered, stapled closure. This device has enabled both the refashioning and closure of bowel pouches to be performed with fewer staple applications and is strong and watertight. Finally, the width of bowel sacrificed with the new instrument is appreciably less than that with the older staple device. Several investigators have subsequently used the new "absorbable" GIA stapler to construct catheterizable pouches and neobladders (Olsson et al, 1993; Montie et al, 1994, 1995; Olsson and Kirsch, 1995). **However, it is important to note that the absorbable PolyGIA staples must not overlap because this will result in the failure of the staples to lock together. This is in direct contrast to metal staples, which are meant to overlap to create anastomotic integrity.** As a result of the need to prevent overlap of absorbable staples, the reservoir construction procedures must be varied when using such staples, as described next.

Surgical Techniques

Right Colon Pouch

In 1993 the authors described a technique using the absorbable GIA staplers to fully detubularize and refashion large bowel (Olsson et al, 1993). The technique of colon pouch construction described here incorporates the principles of bowel detubularization and refashioning using absorbable staplers in a simple "one-step" process.

The right colon and 10 cm of terminal ileum are mobilized by incising the peritoneum along the white line of Toldt and along the base of the mesentery and are isolated using metal GIA staplers (Fig. 86–17A). After bowel continuity is restored with standard metal GIA and TA staplers, the distal staple line of the right colon is excised and the bowel lumen is irrigated to remove residual enteric contents. Using electrocautery, a small opening (2 cm) is created on the antimesenteric border of the cecum to fit the absorbable stapler. The distal open end of the colon is aligned with the cecostomy by folding the right colon on itself, as depicted in Figure 86–17B. The limbs of the absorbable GIA stapler are inserted into the distal open end and into the cecostomy, and the stapler is fired along the antimesenteric line of the apposed folded bowel (see Fig. 86–17C). It is necessary to evert the bowel to continue subsequent staple applications. This may be achieved by placing Babcock clamps on each side of the distal staple line (see Fig. 86–17D). A small incision at the junction of each staple line is made to prevent overlap of the absorbable staple rows and to allow for the next staple application. Because of this incision, there is often a short unstapled area at the junction between each application of the stapler, requiring one or two simple figure-of-eight sutures of 2-0 absorbable material at each of these points. The last staple application traverses the apex of the fold of bowel. In adults, three to four applications of the stapling device have been required to construct the right colon pouch, whereas in children two to three staples suffice. The appearance of the nearly completed pouch is illustrated in Figure 86–17E.

Once the generic right pouch has been fashioned, several options exist for ureteral anastomosis and formation of a sphincter mechanism. These maneuvers may be approached through the coalesced distal colon opening and cecostomy, which accesses the interior of the pouch (see Fig. 86–17E). The opening permits appropriate stent placement or inspection of a buttressed ileocecal valve. Any of the Mitrofanoff techniques described in conjunction with the Mainz I procedure can be employed. Likewise, the terminal ileum can be either stapled or plicated to create a continence mechanism. Once construction of a continence mechanism and ureteral anastomoses has been performed, the opening can be closed with a running 2-0 absorbable suture or the application of an absorbable TA stapler of appropriate length.

Continent diversion procedures commonly employ the right colon or the cecum and terminal ileum. The array of right colon pouches that can be facilitated by this technique include all of the reservoirs described previously. Reservoirs using terminal ileum and cecum such as the Penn Pouch and the Mainz Pouch can also be fashioned in this manner.

Stapled Sigmoid Reservoir

The same stapling maneuvers can be applied to create a reservoir constructed from the sigmoid colon (Olsson and Kirsch, 1995). A portion of the sigmoid and descending colon measuring approximately 35 cm is mobilized by incising the peritoneum along the white line of Toldt. Once mesenteric windows have been created, the segment of colon is isolated using metal GIA staplers (Fig. 86–18A). Restoration of bowel continuity is achieved with either GIA, TA, or EEA staple devices.

Each of the metal stapled ends of the isolated colon are excised, and the bowel lumen is irrigated. The isolated sigmoid is folded on itself in a U configuration, aligning both open ends (see Fig. 86–18B). The absorbable GIA stapler is inserted into the open bowel ends and fired along the antimesenteric line of the folded

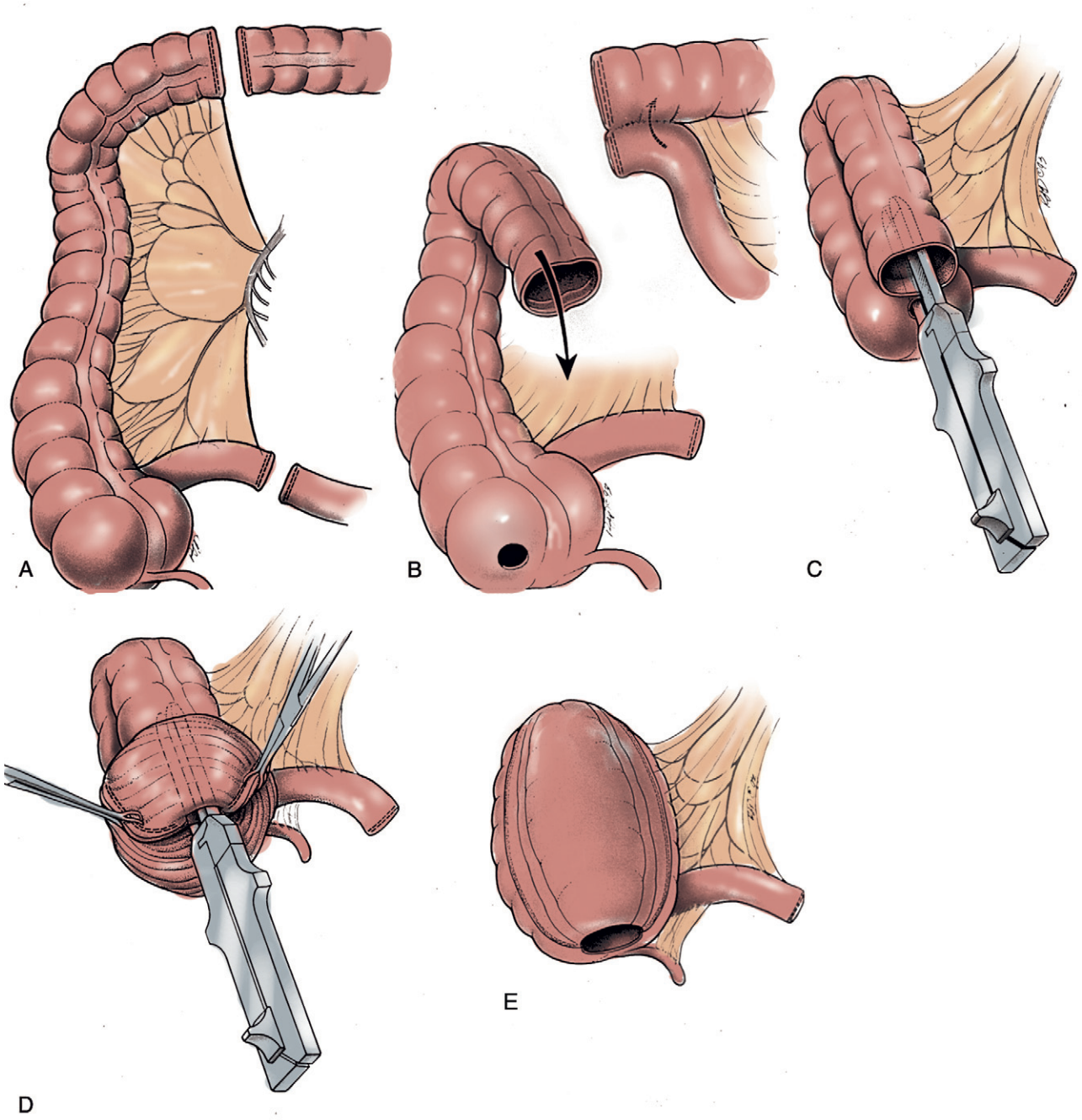


Figure 86–17. **A,** Isolation of colon and blood supply using metal gastrointestinal anastomosis staplers. **B,** Opening created in cecum and open end of colon to fit absorbable stapler. Bowel continuity restored between colon and ileum. **C,** Stapler activated along antimesenteric line and folded bowel. **D,** Inversion of bowel required to continue staple applications. **E,** Pouch inversion is complete. (From Olsson CA, Kirsch AJ, Whang MI-S. Rapid construction of right colon pouch. Curr Surg Tech Urol 1993;6:1–8.)

bowel (see Fig. 86–18C). Following the procedure for bowel eversion as described earlier completes the reservoir. Again, usually two or three applications of the stapler are required to complete the pouch, cutting each staple line tip to avoid staple overlap.

After bowel reinversion, ureteral implants into the taenia can be carried out, using the residual colon opening to assist stent passage. These stents and a suprapubic tube are led through a separate stab wound in the pouch and brought through a lower abdominal wall stab incision. A continence mechanism employing one of the Mitrofanoff variations is then performed.

W-Stapled Reservoir

Montie and colleagues (1994) used the absorbable GIA stapler to construct ileal neobladders in patients undergoing cystoprostatectomy. A segment of ileum measuring 50 cm is divided with a standard metal GIA stapler 20 cm from the ileocecal valve. The terminal ends of each limb of the isolated ileal segment are closed with an absorbable TA-55 stapler, and the metal staple line is resected. The bowel is aligned in a W configuration, and an enterotomy is made 10 cm from each end (Fig. 86–19A). To assist

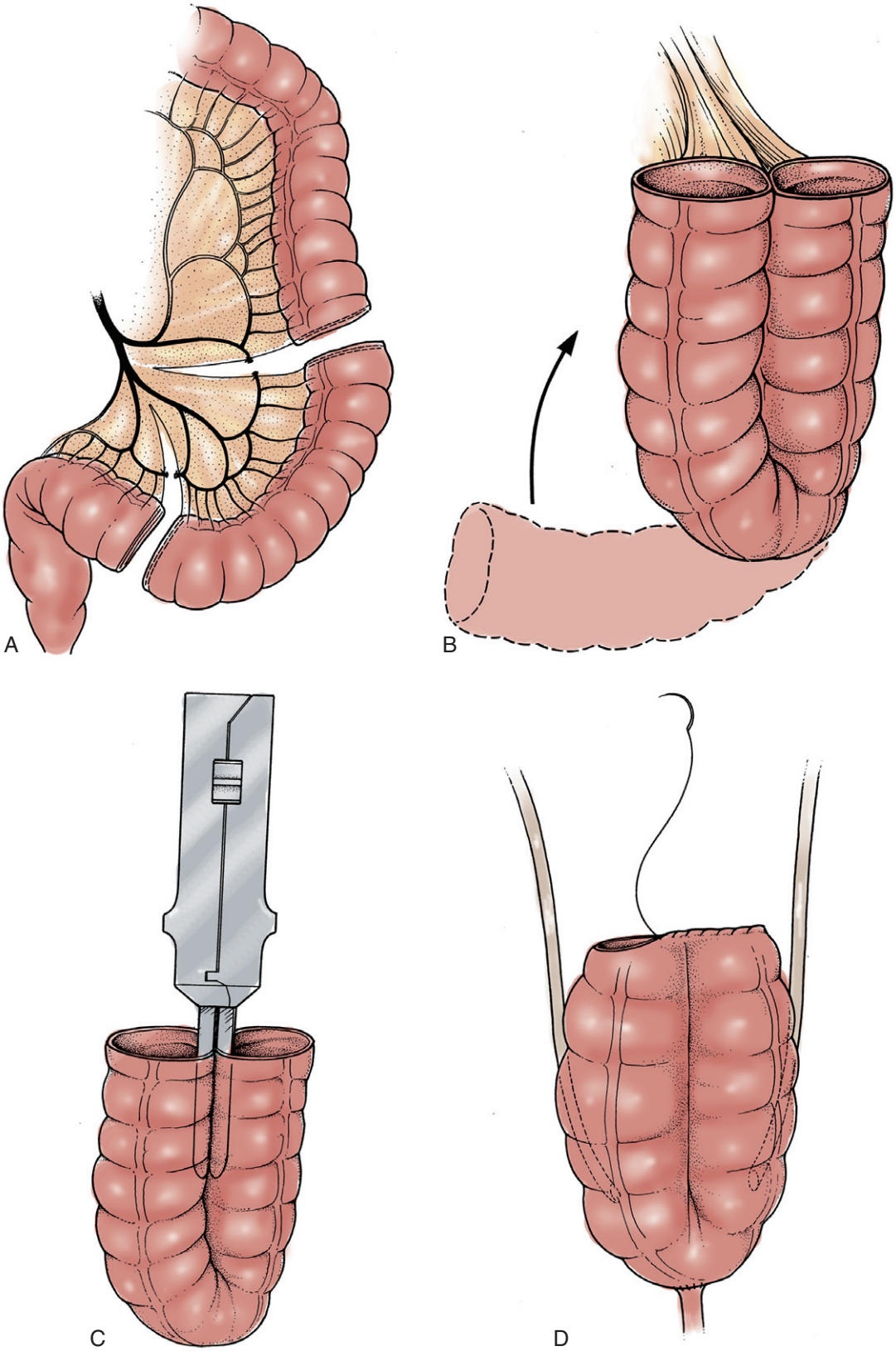


Figure 86–18. **A,** Isolation of colon and blood supply using metal gastrointestinal anastomosis staplers. **B,** Sigmoid bowel folded in a U shape. **C,** Stapler fired along antimesenteric border of folded sigmoid. **D,** Oversewing of superior open end completes pouch construction. (From Olsson CA, Kirsch AJ, Whang MI-S. Rapid construction of right colon pouch. Curr Surg Tech Urol 1993;6:1–8.)

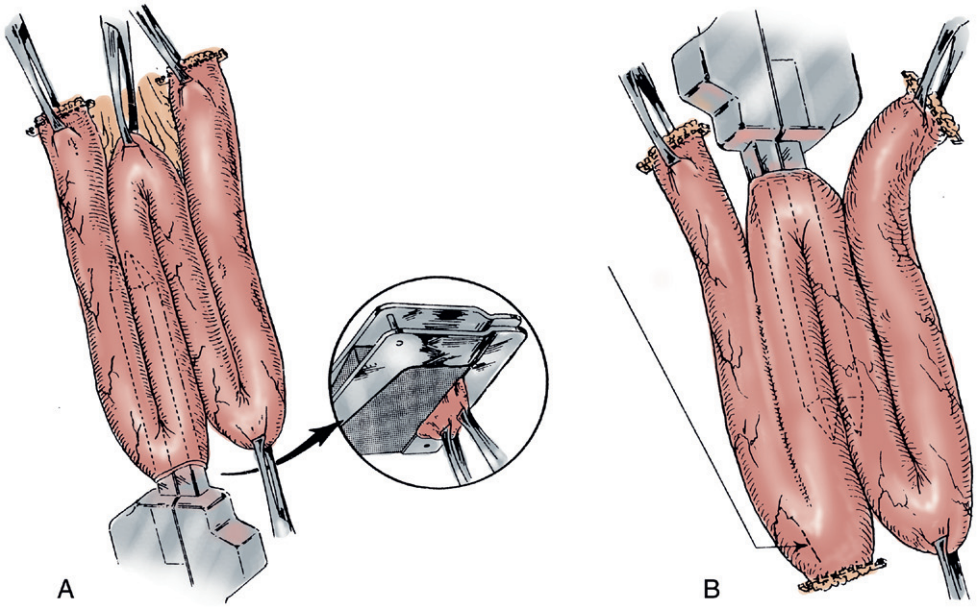


Figure 86–19. **A,** After closure of butt ends of reservoir with TA-55 stapler, enterotomy is made in dependent portion of first limb of the W. Absorbable stapler is inserted through enterotomy and fired, creating common lumen between two adjacent limbs. *Arrow* indicates close-up of closure of enterotomy with TA-55 stapler. **B,** In middle limb of W, stapler is placed through enterotomy at apex, and again common lumen is created. Staple lines are not directly opposing for their entire distance to avoid ischemia between adjacent staple lines. *Arrow* indicates site of enterotomy where urethro-ileal anastomosis will be performed. (From Pontes JE. Genitourinary oncologic pelvic surgery. New York: John Wiley & Sons; 1993.)

closure of the enterotomy with a TA instrument (see Fig. 86–19, inset), the enterotomy must be made midway between the mesentery and antimesenteric border. The absorbable GIA device is inserted through the enterotomy and is activated. This maneuver adjoins the two adjacent bowel segments. The enterotomy may be closed with the absorbable TA-55 instrument or running absorbable suture, completing the distal segment of the W. The middle and proximal segments are constructed similarly (see Fig. 86–19B). Montie stresses that the segments of the W must be offset to avoid staple lines that overlap each other. Exceeding a 3 to 6 cm overlap may result in bowel ischemia.

Postoperative Care and Comments

In the first 50 adult patients to undergo our absorbable stapling technique in right colon pouch construction, with at least 7 years of follow-up, there have been no complications attributable to absorbable staples. Similar results have been reported by Rowland (1996). In the pediatric population, we have applied the absorbable stapler to continent urinary diversion, as well as to bladder augmentation (Hensle et al, 1995). In the first 18 children observed for up to 3 years, there have been no instances of pouch perforation or inadequate pouch capacity and, to date, only one of the patients has developed a reservoir calculus.

Montie and colleagues (1994) used absorbable staplers to create W-stapled ileal neobladders in 25 patients. Ileal pouch construction was performed in approximately 20 minutes, and functional aspects were comparable with bowel reservoirs constructed by conventional suturing. Urodynamic evaluation at 6 months, however, documented a small-capacity reservoir requiring augmentation enterocystoplasty in 3 of 25 patients (12%). Montie and colleagues attributed this complication to either the size of the staples or reservoir fibrosis secondary to foreign body reaction. It is conceivable that a similar situation would arise when constructing a W-stapled T pouch.

The authors have used the absorbable stapler to construct both large and small bowel reservoirs. In our experience, colonic pouches appear better suited for construction with the absorbable stapler because of their relatively larger lumen. **The introduction of stapling devices delivering still smaller staples and automatic staple line sealing devices may prevent the problems presently seen when ileal pouches are constructed with current technology.**

SUMMARY

In summary, continent urinary diversion is now an accepted part of the urologic surgical armamentarium. A wide array of surgical techniques exists to accomplish the desired goal of creating a continent, stomal-free, nonrefluxing pouch. A paucity of long-term quality of life studies exists to compare outcomes between continent cutaneous urinary diversion and ileal conduit urinary diversion. Surgeons contemplating these forms of urinary diversion should familiarize themselves with several of the techniques and the management of the most common complications.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

Key Points

- Because the ability to self-catheterize is essential to the patient undergoing continent diversion, the patient must be assessed for the ability to care for himself or herself.
- Patients with multiple sclerosis, quadriplegic individuals, and frail or mentally impaired patients will at some point in their lives require the care of family members or a visiting nurse, and such patients are viewed as poor candidates for any form of continent diversion.
- Renal and hepatic function must be reviewed carefully in the patient selected for continent diversion. The reabsorption and recirculation of urinary constituents and other metabolites require that liver function be normal and that serum creatinine levels are in the normal range, certainly below the level of 1.8 mg/dL.
- When the ureters are directed into the fecal stream, routine colonoscopy should also be performed. There have been isolated reports of malignancy developing earlier, and all patients developing gross or microscopic hematuria should be fully evaluated.
- Many studies from throughout the world have suggested an improved psychosocial adjustment of the patient undergoing continent urinary and fecal diversion compared with those patients with diversions requiring collecting appliances.
- Four general techniques have been employed to create a dependable, catheterizable continence zone. For right colon pouches, appendiceal techniques, pseudoappendiceal tubes fashioned from ileum or right colon, and the ileocecal valve plication are adaptable. Appendiceal tunneling techniques are the simplest of all to perform in that they use established surgical techniques that are already in the urologic armamentarium.
- The second major type of continence mechanism used in right colon pouches is the tapered and/or imbricated terminal ileum and ileocecal valve. However, some patients have developed rather striking diarrhea/steatorrhea after the loss of the ileocecal valve. This may be particularly true in the pediatric patient.
- The third surgical principle used in constructing the continence mechanism is the use of the intussuscepted nipple valve or, more recently, the flap valve, which avoids the need for intussusception. The creation of nipple valves is the most technologically demanding of all the continence mechanisms and is associated with the highest complication rate.
- The fourth major technique of continence mechanism construction is the provision of a hydraulic valve, as in the Benchekroun nipple. In this procedure, a small bowel segment is isolated and a reversed intussusception is used to appose the surfaces of the small bowel.
- Pouch urinary retention represents a true emergency, and the patient must seek immediate attention so that catheterization and drainage by experienced personnel can be achieved promptly.
- Because all patients with catheterized pouches will have chronic bacteriuria, the problem of antibiotic management should be discussed. Most authors would suggest that bacteriuria in the absence of symptomatology does not warrant antibiotic treatment.
- The concept of using the buttressed ileocecal valve as a dependable continence mechanism that can withstand the trauma of intermittent catheterization was first reported from Indiana University by Rowland and Mitchell (1987).
- The Indiana pouch remains one of the most reliable of all catheterizable reservoirs. It is among the easiest to construct, and it has few short-term and long-term complications.
- The use of absorbable staplers has substantially reduced the time required to fashion bowel reservoirs and has demonstrated short-term and long-term reliability with respect to reservoir integrity and volume.
- It is anticipated that in the near future technologic advances in minimally invasive surgery will allow for the laparoscopic (robotic) construction of these reservoirs. These technologic advances will likely include automated suturing devices and biosealants.

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chapter 87

Orthotopic Urinary Diversion

Eila C. Skinner, MD ● Donald G. Skinner, MD ● John P. Stein, MD

Evolution of Orthotopic Urinary Diversion

Basic Principles of Continent Orthotopic Urinary Diversion

Patient Selection

Continence Mechanism in Patients Undergoing Orthotopic Diversion

Surgical Techniques for Continence Preservation during Radical Cystectomy

Techniques for Orthotopic Bladder Substitution

Results and Complications of Orthotopic Neobladders

EVOLUTION OF ORTHOTOPIC URINARY DIVERSION

Since the early 1900s, innovative surgeons have investigated how best to replace the original bladder when it must be removed for either benign or malignant disease. Contemporary objectives of lower urinary tract reconstruction have had an ultimate goal of finding a system that allows volitional voiding through the native urethra while eliminating the need for a cutaneous urinary stoma or intermittent catheterization. If continued progress is to be made in the field of urinary diversion, a thorough understanding and appreciation of previous techniques and accomplishments must be achieved.

Ureterosigmoidostomy is the oldest form of clinically applied urinary diversion. The first reported urinary diversion into a segment of bowel was by Simon in 1852. He attempted a ureterosigmoidostomy in an exstrophy patient by drawing the ureters into the rectum with the use of needles and suture to create a fistula. Although the patient died of sepsis 12 months later, this marked the first reported attempt at some form of urinary diversion (Simon, 1852). Over the following 100 years the evolution of urinary diversion was marked by a continued search for better methods and techniques to reconstruct the lower urinary tract. A number of technical modifications of the ureterosigmoidostomy ensued, particularly related to the ureteral implantation technique (Hinman, 1936). The rates of obstruction and ascending pyelonephritis in patients with ureterosigmoidostomy were significantly reduced after a direct anastomosis of the ureter into the sigmoid colon, incorporating an antireflux submucosal tunnel (Leadbetter, 1951; Goodwin et al, 1953).

Ureterosigmoidostomy remained the diversion of choice until the late 1950s, but long-term electrolyte imbalance, upper tract obstruction and infection, and secondary malignant neoplasms arising at the ureteral implantation site were observed (Leadbetter and Clarke, 1954; Clarke and Leadbetter, 1955; Ridlon, 1963; Wear and Barquin, 1973). These significant complications inspired surgeons to develop better forms of urinary diversion. **In 1950 Bricker refined and popularized the ileal conduit form of urinary diversion, building on an original description by Zaayer in 1911** (Zaayer, 1911; Bricker, 1950). The ileal conduit is a technically simple urinary diversion. This form of reconstruction was a reliable technique for urinary diversion and became widely accepted. It has remained the "gold standard" to which other types of urinary diversion are compared. It continues to be the most common form of urinary diversion performed throughout the world today.

Since the 1950s, the further evolution of lower urinary tract reconstruction has developed along three distinct paths: (1) variations of cutaneous conduit forms of urinary diversion (ileal or colon conduit); (2) continent cutaneous forms of urinary diversion to the skin (such as the cutaneous Kock pouch and Indiana pouch); and (3) most recently, the orthotopic form of diversion to the native, intact urethra (neobladder).

Long-term complications with the Bricker ileal conduit started to come to light in the 1970s. Although problems with hyperchloremic metabolic acidosis and pyelonephritis were substantially less common than in patients with ureterosigmoidostomy, **late complications with the ileal conduit such as stomal stenosis, pyelonephritis, calculus formation, ureteral obstruction, and renal deterioration became more apparent with longer follow-up** (Butcher et al, 1962; Shapiro et al, 1975; Middleton, 1976; Johnson and Lamy, 1977; Pitts and Muecke, 1979; Sullivan et al, 1980). These clinical sequelae were thought to be related to the reflux of infected urinary or obstruction of the upper urinary tract. It was postulated that the addition of an antireflux technique to a conduit form of diversion could help diminish the problems of reflux and renal deterioration in these patients. In fact, well-performed laboratory experiments provided evidence to support the advantage of nonrefluxing colonic conduits over ileal conduits (Richie et al, 1974; Claesson et al, 1985). Unfortunately, with longer follow-up, similar complications with colon conduits including upper urinary tract damage developed, again dampening enthusiasm for this form of urinary diversion (Morales and Golimbu, 1975; Althausen et al, 1978; Elder et al, 1979).

The first continent diversion was described by Gilchrist and colleagues. This form of urinary reconstruction incorporated a cecal reservoir with the ileocecal valve as the continence mechanism and the distal ileum as a catheterizable stomam (Gilchrist et al, 1950). However, this innovation attracted little attention at the time. The concept of a continent cutaneous diversion was subsequently reintroduced by Kock and colleagues (1982). This diversion was originally designed for a continent terminal ileostomy and used an intussuscepted nipple valve to maintain continence and avoid reflux. In animal experiments and then in humans, **Kock demonstrated the importance of complete detubularization of the bowel segment and the double-folding technique that creates the most spherical shape possible** (Eckman et al, 1964; Kock et al, 1982). These concepts are the cornerstone of current cutaneous and orthotopic reservoirs. After Kock described his results in his initial 12 patients, Donald Skinner began performing this diversion in adults undergoing cystectomy for bladder cancer. Although this form of urinary diversion required catheterization of an abdominal stoma, it eliminated the need for and associated problems with an external urostomy appliance. It was a popular concept for patients and referring physicians alike, and Skinner quickly amassed a large clinical experience with this type of diversion (Skinner et al, 1984, 1987).

The "Achilles' heel" of continent cutaneous reservoirs is the design of a reliable, durable, efferent continence mechanism that is easily catheterizable. A number of techniques have been described using large and small bowel and even stomach, with many ingenious continence mechanisms. However, stones, difficulty catheterizing, peristomal hernias, and the development of leakage are potential problems with all of them, often requiring open surgical revision to resolve (Lieskovsky et al, 1987; Rowland, 1995).

The concept of orthotopic diversion began even before Gilchrist's continent cutaneous diversion. Tizzoni and Poggi (1988) were the first to experiment in a dog transplanting the ureters into an isolated loop of ileum interposed between the ureters and the urethra. The dog was reportedly continent and subsequently underwent three successful pregnancies before expiring 30 months postoperatively (Tizzoni and Poggi, 1988). Lemoine is credited with performing the first orthotopic reconstruction in a human subject. This patient initially underwent a cystectomy with ureterosigmoidostomy. Complications related to recurrent pyelonephritis led to undiversion in this patient; the rectal segment was isolated, transected, and anastomosed to the urethra, and the sigmoid colon was brought down and anastomosed to the anus (Lemoine, 1913).

In 1979 Camey and Le Duc reported their pioneering and extensive clinical experience with orthotopic substitution to the native urethra in male bladder cancer patients (Camey and Le Duc, 1979). This was a substantial accomplishment that demonstrated the feasibility of lower urinary tract reconstruction to the native urethra. The initial Camey diversion used an intact segment of ileum, resulting in a high-pressure reservoir. Subsequently the Camey II detubularized reservoir (Camey, 1990); the Hautmann W-neobladder (Hautmann et al, 1988); the Studer pouch (Studer et al, 1989); the T pouch (Stein et al, 1998b); stomach neobladder (Hauri, 1998); cecal and ileocecal neobladders (Light and Englemann, 1986; Mansson and Colleen, 1990); and sigmoid reservoir (Reddy and Lange, 1987) have been described. Many of these now have a large clinical experience with long-term follow-up demonstrating good renal preservation and continence results (discussed further later). Initially these techniques were only applied to male patients because continence in the female was believed to be dependent on an intact bladder neck. In the mid-1990s it was discovered through anatomic dissections and initial clinical experience that women could remain continent with a low-pressure reservoir and preservation of only the urethra itself (Borirakchanyavat et al, 1997; Colleselli, 1998). In addition **there were several careful pathologic studies of female cystectomy specimens showing that preservation of the urethra was safe in the majority of women with bladder cancer without compromising the oncologic efficacy of the operation** (Stein et al, 1995, 1998a; Stenzl, 1995b; Maralani, 1997).

Although the ideal bladder substitute remains to be developed, the orthotopic neobladder most closely resembles the original bladder in both location and function. This form of lower urinary tract reconstruction relies on the intact external rhabdosphincter continence mechanism, usually does not require intermittent catheterization, and avoids the difficulties associated with the efferent continence mechanism of continent cutaneous reservoirs. Voiding is accomplished by concomitantly increasing intra-abdominal pressure (Valsalva maneuver) with relaxation of the pelvic floor musculature. The majority of patients undergoing orthotopic reconstruction are continent and void to completion without the need for intermittent catheterization. The pioneering work of Camey and Le Duc with orthotopic reconstruction in carefully selected male patients has subsequently evolved into a common form of lower urinary tract reconstruction potentially applicable to most patients requiring urinary diversion (Camey and Le Duc, 1979).

In many centers worldwide orthotopic reconstruction has replaced the ileal conduit as the standard form of reconstruction. The experience of urinary diversion at the Keck University of Southern California School of Medicine demonstrates this evolution (Fig. 87–1). Beginning in 1986, the number of orthotopic bladder substitutes performed dramatically increased while the number of conduits dramatically declined. Currently the authors perform continent orthotopic diversion in approximately 90% of male and 75% of female patients undergoing radical cystectomy. It is, however, incumbent on the surgeon who is actively involved in lower urinary tract reconstruction to understand the indications for and contraindications to orthotopic diversion, as

Key Points: Historic Evolution of Orthotopic Urinary Diversion

- Historically, urinary diversion has developed along three paths: a conduit form of diversion, continent cutaneous diversions, and most recently orthotopic diversion.
- Long-term complications of the ileal and colon conduits include stomal stenosis, peristomal hernia, pyelonephritis, calculus formation, ureteral obstruction, and renal deterioration.
- The major long-term problems with continent cutaneous diversion are caused by malfunction of the efferent continence mechanism and often require open surgical revision to resolve.
- The orthotopic neobladder relies on the rhabdosphincter for continence; most patients are continent and able to void to completion without the need for intermittent catheterization.

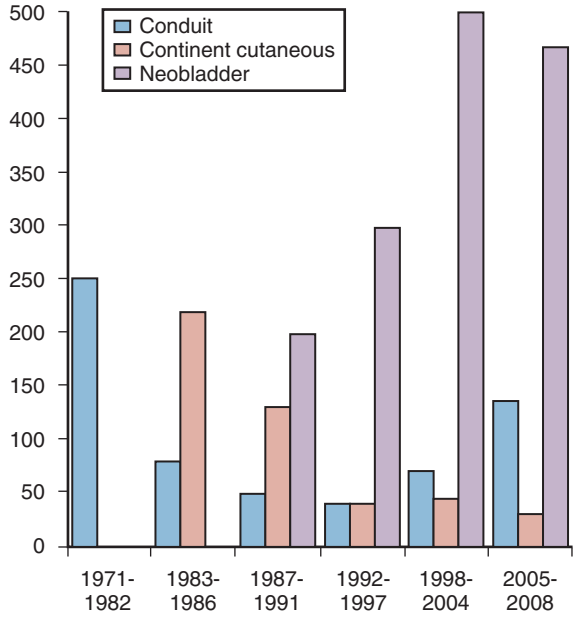


Figure 87–1. Evolution of urinary diversion at the University of Southern California from 1971 to 2008. Orthotopic reconstruction was first applied to men in 1986 and to women in 1990, with a steady increase in the number of bladder substitutes since that time and a decline in the number of conduit forms of diversion during the same period. Recent increases in the percentage of older patients undergoing this surgery have resulted in a slight increase in ileal conduit diversion in the past few years.

well as to be familiar with the various reconstructive options. This will help ensure optimal clinical outcomes and improved satisfaction of patients.

BASIC PRINCIPLES OF CONTINENT ORTHOTOPIC URINARY DIVERSION

Many methods for construction of an orthotopic neobladder using intestinal segments exist, but three basic principles must be satisfied for a successful outcome. **First, the patient must have an adequate external sphincter mechanism and nonobstructed urethra.** This aspect is discussed in more detail later in the sections on patient selection and description of the anatomy of the external sphincter and surgical techniques for continence preservation.

Secondly, the reservoir must be sufficiently compliant to maintain a low pressure throughout the filling phase. This is best achieved by splitting the bowel segment open longitudinally to completely detubularize it and folding it to create a spherical shape. This concept was described by Goodwin and colleagues (1959) and further developed by Kock in elegant animal experiments (Eckman et al, 1964). The sphere has the greatest internal volume for a given surface area and thus the greatest capacity. By Laplace's law (T = PR) for a given wall tension (T), the internal pressure (P) decreases as the radius (R) of the sphere increases. The compliance of the wall relates to the physical characteristics of the bowel wall itself and is greater in small bowel compared with large bowel. The double-folded technique of Kock, or S- or W-shaped reservoirs all effectively ablate the coordinated high-pressure contractions of the bowel wall, allowing the reservoir to maintain low internal pressure throughout the filling phase (Kock et al, 1982; Hinman, 1988). Early techniques for bladder augmentation using an intact cecal segment and the early Camey orthotopic ileal neobladder failed to incorporate the important step of detubularization and thus resulted in unacceptable incontinence and upper tract deterioration (Camey and Le Duc, 1979; Lilien and Camey, 1984). All current techniques use detubularized bowel to construct the reservoir portion of the orthotopic diversion.

Thirdly, the reservoir must have adequate volume to allow for reasonable voiding intervals. This generally should be at least 300 to 500 mL. All bowel segments effectively stretch over time if there is adequate outflow resistance. The standard 44-cm length of ileum formed into a double-folding reservoir by the Kock technique (also used for both the Studer and T pouch neobladders) holds less than 200 mL initially. When used for a cutaneous pouch with high outflow resistance, this segment routinely stretches up over time to hold more than 1000 mL at low pressure. Such high volumes are not ideal for orthotopic diversion because of the difficulty emptying such large reservoirs, so patients are encouraged to empty more frequently. Nevertheless, this emphasizes that larger initial volumes are not necessary to ultimately achieve an adequate voiding volume. However, colonic segments do not stretch up as easily and a larger initial volume may be necessary for pouches constructed out of colon. In general small bowel, when available, has advantages over colon in terms of wall compliance and ability to stretch, as well as reduced mucous formation (Khafagy, 2006).

Key Points: Three Basic Principles of Orthotopic Neobladder Construction

- Patient must have adequate external sphincter function to maintain continence.
- Bowel segment should be detubularized and reconstructed into a spherical shape.
- Ultimate storage volume should be at least 400 to 500 mL at low pressure.

PATIENT SELECTION

Nearly all patients who undergo radical cystectomy should be considered at least potential candidates for orthotopic urinary diversion. There are few absolute contraindications. However, a number of factors should be considered in counseling the individual patient as to the best diversion for him or her, and these can be divided into cancer-related factors and patient factors.

Cancer-Related Factors

Risk of Urethral Recurrence in Men

The primary cancer-related contraindication for orthotopic diversion is presence of urothelial carcinoma in the urethral stump to which the neobladder is to be connected. **In the male patient involvement of the prostatic urethra is associated with a higher risk of subsequent urethral recurrence.** Ashworth first reported that patients with prostatic urethral involvement are at increased risk for urethral tumor involvement after cystectomy and ileal conduit. Prostatic urethral tumor involvement was found in five of seven patients (71%) who later developed anterior urethral tumors (Ashworth, 1956). Other series have subsequently

confirmed this finding (Raz et al, 1978; Faysal, 1980; Hardeman, 1990; Levinson et al, 1990; Tobisu et al, 1991; Nieder et al, 2004). Freeman and colleagues (1994) reviewed six studies, in which 31 of 122 patients (25%) with some form of prostatic urethral involvement developed an anterior urethral tumor after radical cystectomy for bladder cancer. These findings have subsequently been confirmed in our cystectomy series in which the overall probability of urethral recurrence was estimated to be approximately 7% at 5 years and 9% at 10 years. Recurrences were observed at a median of 2 years after cystectomy (range 0.2 to 13 years). **The risk was only 5% at 5 years in the 639 patients without any prostate tumor involvement compared with 11% for the 129 men with any prostate involvement** (Stein et al, 2005). In a large, comprehensive, pooled analysis of 25 series, Stenzl and colleagues (1995b) reported a total of 256 anterior urethral tumor recurrences in 3165 patients (8.1%) undergoing cystectomy for bladder cancer.

Specific characteristics of the primary bladder cancer have been analyzed to determine if any particular histopathologic parameters can identify patients at increased risk for urethral recurrence after cystectomy. Various pathologic risk factors have been implicated including the presence of papillary tumors, tumor multifocality, trigone or bladder neck tumor involvement, associated carcinoma in situ in the bladder or upper tracts, and various degrees of involvement of the prostate (Freeman et al, 1996). Several investigators have evaluated the presence of carcinoma in situ in the bladder as a risk factor for urethral recurrence with variable results (Hardeman and Soloway, 1990; Levinson et al, 1990; Tobisu et al, 1991; Stein et al, 2005). Tobisu and colleagues (1991) combined these pathologic risk factors and showed in a multivariate analysis that the risk of urethral recurrence more than doubled each time the number of risk factors was increased by one.

Of all the risk factors, the degree of prostatic tumor involvement is most useful in predicting the risk of subsequent urethral recurrence. **In general, prostatic involvement can be divided into urethral mucosa only (including carcinoma in situ), ductal involvement with carcinoma in situ, and prostatic stromal invasion.** Hardeman and Soloway (1990) evaluated 30 patients with some involvement of the prostate and found anterior urethral recurrence in 11 (37%). No patient with only mucosal involvement developed a recurrence, whereas 25% of men with prostatic ductal involvement and 64% of men with prostatic stromal involvement developed urethral recurrence. In the same series, only 2 of 56 patients (4%) without prostatic urethral tumor involvement in the primary tumor suffered subsequent urethral recurrence (Hardeman and Soloway, 1990). In another study, Levinson and colleagues (1990) found similar results, with urethral recurrences rates of 0% for mucosa only, 10% for ductal involvement, and 30% with stromal invasion. Overall, 67% of their patients with urethral recurrences had a history of prostatic urethral involvement in their primary tumor (Levinson et al, 1990). Hassan and colleagues (2004) reported an even lower risk of urethral recurrence, with only one recurrence observed in more than 400 patients, though with relatively short follow-up.

These observations were confirmed in our series of 768 men undergoing cystectomy without urethrectomy with long-term follow-up (median 13 years) (Stein et al, 2005). The extent of prostatic tumor involvement was the most significant predictor for urethral tumor recurrence. Of the 129 patients with pathologic transitional cell carcinoma involving the prostate at cystectomy, 14 (11%) developed urethral recurrence. The 5-year estimated probability of urethral recurrence for superficial (mucosa and ductal, without stroma) involvement was 12%, compared with 18% with prostatic stroma invasion. **In a multivariate analysis, any prostate tumor involvement (superficial or invasive) remained an independent and significant predictor of a urethral tumor recurrence. Carcinoma in situ and tumor multifocality were not individually associated with a significant risk for anterior urethral recurrence** (Stein et al, 2005). Collectively, these studies confirm that **prostatic stromal invasion is the single strongest pathologic predictor of subsequent recurrence in the anterior urethra after cystectomy for bladder cancer. It does not appear that the presence of carcinoma in situ in the bladder alone is a clear risk factor for subsequent urethral recurrence.**

Some evidence indicates that orthotopic diversion itself may provide some protection against urethral recurrence. In the University of Southern California experience, the type of diversion was an independent variable predicting urethral recurrence. In patients without prostatic involvement, the risk of urethral recurrence at 5 years was 3% versus 8% in patients with orthotopic versus cutaneous diversion, respectively. Interestingly, there was no benefit seen if patients with any prostatic involvement were taken as a whole. However, in patients with the highest-risk disease (prostatic stromal invasion) there did seem to be some protection for those undergoing orthotopic diversion, with a 5-year risk of recurrence of 11% versus 24% for those with cutaneous diversion. The reason for this observation is unclear, though there has been speculation that continued flow of urine, perhaps with changes in urinary characteristics due to the interposed bowel, might be responsible (Stein et al, 2005).

There is some controversy about the importance of attempting to identify prostatic urethral involvement preoperatively, as well as what to recommend for those patients in whom prostatic involvement is identified. At the time of transurethral resection of the primary bladder tumor, the surgeon may take deep transurethral resection biopsies of the prostate, preferably at the 5- and 7-o'clock positions lateral to the verumontanum. This should certainly be done if the mucosa of the prostate looks suspicious or in cases with obvious tumor at the bladder neck. Some authors have recommended that this should be done routinely and have advocated repeat transurethral resection (TUR) before cystectomy in cases where it was omitted (Wood et al, 1989; Sakamoto et al, 1993). However, the reliability of preoperative transurethral prostatic biopsies has been challenged by others (Lebret et al, 1998; Donat et al, 2001). In a prospective series of 118 patients, Lebret and colleagues examined the utility of preoperative prostatic biopsies compared with intraoperative frozen-section analysis of the prostatic urethral margin at the time of cystectomy in predicting urethral recurrence. They found that intraoperative frozen-section analysis was more accurate than any preoperative parameter including preoperative prostate biopsies in predicting urethral recurrence (Lebret et al, 1998). In another series of 246 men who underwent preoperative transurethral loop biopsy of the prostate, Donat and colleagues (2001) reported that this preoperative pathologic evaluation did not accurately determine prostatic tumor involvement—both false-negative and false-positive results were observed. Forty-three percent of patients with prostatic involvement on final pathology were missed on the TUR biopsy, and 12 of 36 patients with prostatic stromal invasion identified on TUR specimen had no residual prostatic involvement on the final cystectomy specimen (Donat et al, 2001). In light of this it is questionable whether the risk of the additional anesthetic and the potential delay to definitive surgery warrants the

additional information garnered by a repeat TUR with prostatic urethral biopsy. The authors have not routinely recommended repeat TUR before cystectomy in the majority of patients. Other centers have adopted a similar philosophy with comparable clinical outcomes (Iselin et al, 1997; Hautmann, 2003).

It has been the authors' practice to counsel patients with documented prostatic mucosal, ductal, or stromal invasion about the increased risk of urethral recurrence if the urethra is left in situ and to help them weigh that risk against any perceived advantage of an orthotopic diversion. If an orthotopic diversion is still preferred, the authors will depend on the intraoperative frozen section of the urethral margin to make the final decision. Patients with extensive prostatic stroma invasion, similar to those with clinical extravesical disease, should also be strongly considered for neoadjuvant chemotherapy before cystectomy (Grossman et al, 2003). If the patient opts for a cutaneous diversion, the authors will perform an en bloc urethrectomy at the time of cystectomy.

Risk of Urethral Recurrence in Women

In the past, urethrectomy was routinely performed at the time of radical cystectomy in women. With the acceptance of continent neobladder in men a number of investigators began evaluating the feasibility of preservation of the urethra in women. This was initially attempted in women with nontransitional cell carcinoma in whom there was little concern about possible urethral recurrence with excellent functional results (Stein et al, 1996). At the time it was generally believed that the bladder neck was the primary continence mechanism in women, so it was somewhat surprising that one could achieve excellent continence dividing distal to the bladder neck (Tanagho et al, 1966).

Two important pathologic studies were critical to the ultimate decision to expand urethral-preserving cystectomy to women with urothelial carcinoma. Stein and colleagues (1995) retrospectively evaluated a series of archival cystectomy specimens from female patients undergoing cystectomy for bladder cancer. Sixty-seven consecutive female cystectomy specimens removed for transitional cell carcinoma of the bladder were pathologically re-evaluated. Histologic evidence of tumor involving the urethra was found in 9 women (13%), whereas 17 patients (25%) demonstrated bladder neck tumors. All female patients with an uninvolved bladder neck also had an uninvolved urethra (no skip lesions), whereas approximately 50% of patients with a bladder neck tumor had concomitant urethral tumor involvement. **Risk factors for urethral involvement in this study included increased grade, stage, and lymph node involvement, but the presence of carcinoma in situ did not predict urethral involvement. Vaginal wall involvement was also a major risk factor for urethral involvement.** Although vaginal wall invasion was a relatively rare event (1%), all of these patients also had bladder neck involvement and 50% had urethral extention (Stein et al, 1995).

Stenzl and colleagues (1995b) also studied the risk of synchronous or secondary urethral tumors with long-term follow-up in women with bladder cancer. The charts of women treated for various stages of bladder cancer during a 19-year period were reviewed. They evaluated 356 women with a mean follow-up of 5.5 years. Overall, 7 of 356 patients (2%) had a urethral tumor at presentation (Stenzl et al, 1995b). This is a similar incidence as had been observed by Ashworth in his earlier endoscopic analysis. Of the women with clinical stages T2 to T3b, N0, M0 (potential candidates for radical cystectomy with preservation of the urethra), only 1% had urethral tumor (Ashworth, 1956). The authors' evaluation of the impact of tumor localization revealed that bladder neck involvement was most significantly associated with secondary urethral tumor in these women (Stenzl et al, 1995b). Furthermore, no patient in this analysis had an isolated urethral tumor without concomitant bladder neck tumor involvement. The authors emphasized that the only consistent risk factor for urethral tumor involvement was concurrent tumor at the bladder neck. No correlation between urethral tumors and other pathologic factors such as carcinoma in situ or tumor multifocality was found. **They concluded that the urethra can be safely preserved in selected female cystectomy patients provided that neither preoperative biopsy specimens of the bladder neck nor intraoperative frozen-section specimens of the proximal urethra demonstrate any tumor or atypia** (Stenzl, 1995b). It has been suggested that the apparent lower incidence of urethral tumors in women (compared with men) may be related to the fact that transitional cell mucosa in women covers a smaller urethral segment, with the remainder being normal or metaplastic squamous cell mucosa. The area at risk in the female urethra is therefore smaller and probably diminishes with increasing age as the demarcation line between squamous and transitional cell mucosa migrates cranially during menopause. In the sixth and seventh decades of life, when most bladder tumors occur, metaplastic squamous cell mucosa may cover the entire urethra, the bladder neck, and even a portion of the trigone (Peckhman, 1971).

This pathologic finding was confirmed by Maralani and colleagues (1997), who retrospectively evaluated 43 female cystectomy specimens removed for bladder cancer. They reported a 16% incidence of urethral tumor involvement, and vaginal involvement in this study was the most significant risk factor for urethral tumor involvement (Maralani et al, 1997). Similarly, Chen and colleagues also retrospectively reviewed the risk of secondary urethral, vaginal, and cervical involvement by transitional cell carcinoma in women undergoing radical cystectomy. They found an overall 8% incidence of tumor of the urethra, and approximately 50% of patients with vaginal or cervical invasion also demonstrated urethral tumor involvement. They similarly confirmed previous reports that the most significant risk factor for urethral tumor involvement is tumor at the bladder neck (Chen et al, 1997). Similar conclusions had been previously reached by Coloby and da Paepe (De Paepe et al, 1990; Coloby et al, 1994).

Stein and colleagues (1998a) embarked on a prospective study to evaluate and confirm the previously established pathologic risk factors in women undergoing cystectomy for bladder cancer to determine if these criteria safely identify appropriate female candidates for orthotopic diversion. Final pathologic analysis of the bladder neck and proximal urethra was performed and compared with the intraoperative frozen-section analysis of the distal surgical margin (proximal urethra). Tumor involvement at the bladder neck and proximal urethra was found in 14 (19%) and 5 (7%) cystectomy specimens, respectively. All patients with urethral tumors also demonstrated concomitant bladder neck tumors. **Bladder neck tumor involvement was again found to be the most significant risk factor for tumor involving the urethra, confirming the findings from retrospective series** (Stein et al, 1995). **However, approximately half of patients with bladder neck tumors had a normal (tumor-free) proximal urethra.** Furthermore, no patient with a normal bladder neck demonstrated tumor involvement of the urethra. **In all cases, intraoperative frozen-section analysis of the proximal urethra correlated with and was correctly confirmed by final permanent section** (Stein et al, 1998a). These

results were virtually identical to the results from previous retrospective study (Stein et al, 1995) and suggest that preoperative biopsy of the bladder neck or urethra is not necessary, but rather one may depend on the intraoperative frozen section to determine the feasibility of orthotopic diversion. Clinical follow-up data of the first 88 women undergoing orthotopic diversion at that institution showed that no urethral recurrences were observed with a median follow-up of 30 months in this group (Stein et al, 2002). More recently Al el Dein and colleagues (2004) prospectively evaluated 145 women undergoing cystectomy and orthotopic diversion. Two patients developed urethral recurrence. One had a primary squamous cell cancer of the bladder, and the other had urothelial carcinoma with carcinoma in situ of the trigone (Al el Dein et al, 2004).

Under no circumstance should the adequacy of the cancer operation be compromised by the type of reconstruction. The authors continue to recommend the intraoperative frozen-section analysis of the proximal urethral margin in both female and male patients as an appropriate mechanism to determine who is an appropriate candidate for orthotopic diversion from a cancer perspective.

Locally Advanced Tumor Stage

Many urologists are hesitant to perform continent orthotopic diversion in patients with locally extensive disease. This is based on two factors: (1) concern about the possible impact of local recurrence on the neobladder itself and (2) a belief that these patients are doomed to suffer distant recurrence and have a shortened life expectancy and will not benefit from the neobladder.

Radical cystectomy with bilateral pelvic iliac lymphadenectomy provides excellent local (pelvic) control for the treatment of invasive bladder cancer. Stein and colleagues (2001a) reported the clinical outcomes for 1054 patients who underwent radical cystectomy for bladder cancer with a median follow-up of more than 10 years. In this series, an overall local pelvic recurrence rate of 7% was observed for the entire group of patients. The risk of recurrence ranged from 6% with organ-confined, node-negative disease to 13% for patients with extravesical or node-positive disease (Stein et al, 2001a). These results suggest that local recurrence even for patients demonstrating locally advanced or lymph node–positive disease is relatively infrequent and should not necessarily preclude an orthotopic form of urinary diversion. In addition, **the results of this study show that a significant percentage of patients with locally advanced disease will be long-term survivors and may benefit from a continent form of urinary diversion.** Nearly 50% of patients with extravesical tumor extension and 30% of patients with lymph node–positive disease were still alive without evidence of disease 5 years following cystectomy (Stein et al, 2001a).

If local tumor recurrence does develop in patients with an orthotopic diversion, only a minority will develop problems related to the urinary diversion itself. Hautmann and colleagues evaluated this question in 43 of 357 men who underwent radical cystectomy and ileal neobladder and developed local recurrence. Most of them (84 %) had advanced disease (≥pT3a) on final pathology at the time of cystectomy. A total of 17 patients (43%) had concomitant distant metastasis at the time of diagnosis of the local recurrence. Local recurrence interfered with the upper urinary tract in 24 cases, the neobladder in 10 (23%), and the intestinal tract in 7; only 1 patient required removal of the neobladder because of an intestinal fistula. The authors concluded that **most patients can anticipate normal neobladder function even in the presence of locally recurrent disease** (Hautmann and Simon, 1999).

Similar results have been reported by others. Tefilli and colleagues (1999) found that 1 of 11 patients with orthotopic diversion required conversion to an ileal conduit after local recurrence. To evaluate the impact of orthotopic diversion on the quality of the cystectomy and ensuring appropriate cancer control, Yossepowitch and colleagues retrospectively evaluated 214 patients who underwent radical cystectomy and orthotopic reconstruction and compared them with 269 patients similarly treated with an ileal conduit diversion. Adjusting for pathologic stage, there was no cancer-specific survival difference between the two diversion groups. Patterns of relapse in 62 of the 214 patients (29%) with an orthotopic neobladder included local recurrence in 11%, distant recurrence in 9%, and combined local and distant recurrence in 18%. Only one patient in this series required the neobladder to be converted to an ileal conduit secondary to a relapse at the ureteroenteric anastomosis and expanding into the pouch. **The authors concluded that the low risk of local recurrence showed that in this cohort of patients the oncologic efficacy of the operation was not compromised** (Yossepowitch et al, 2003).

Key Points: Cancer-Related Factors in Patient Selection

- The presence of carcinoma in situ, multifocal tumor, or extravesical disease should not preclude orthotopic diversion if the urethral margin is negative.
- The most important risk factor for a urethral tumor recurrence in men after orthotopic diversion is the presence of prostatic stromal invasion on final pathology.
- Orthotopic diversion may provide some protection from urethral recurrence in men compared with cutaneous diversion without urethrectomy.
- The most important risk factor in women for urethral tumor recurrence is bladder neck or anterior vaginal wall involvement with tumor. The latter is best evaluated on bimanual examination under anesthesia at the time of cystectomy.
- Intraoperative frozen-section analysis of the urethral margin in men and women provides an accurate assessment of the urethra and appropriately determines candidacy for orthotopic diversion. Preoperative biopsy of the prostatic urethra or bladder neck is not mandatory.
- Local pelvic recurrence should occur in less than 10% of patients undergoing a proper cystectomy and pelvic lymphadenectomy for bladder cancer and rarely interferes with the function of the neobladder.

Patient-Related Factors

The type of urinary diversion to be performed depends on a combination of the cancer-related factors and patient-related factors. The latter includes the patient's general health and social circumstances, baseline renal function, presence of a functional urethra, manual dexterity, and previous treatments including pelvic radiation, prostate surgery, or bowel resection. Perhaps equally important is the patient's personal preference and attitudes about the risk of incontinence, need to self-catheterize, and management of an external appliance. The relative importance of each of these factors in determining how to counsel an individual patient must

be decided on a case-by-case basis. The patient and his or her family must have a realistic understanding of the pros and cons of each type of diversion before making a decision. There is a natural inclination for most patients to opt for an orthotopic reconstruction because it is the most "natural." They must gain the understanding that problems can occur with each type of diversion, although the specific types of problems differ. An honest, informed discussion, carefully explaining the various options along with the short- and long-term risks and benefits of each form of urinary diversion, must be performed. It may also be helpful to have the patient talk with other patients who have undergone the various forms of urinary reconstruction.

Patients with poor general health, difficult social circumstances, or poor cognitive function are probably best managed with an ileal conduit. **Severe urethral stricture disease in men is a contraindication for orthotopic diversion. Poor external sphincter function in a man highly motivated to undergo orthotopic diversion may be managed with a concomitant artificial urinary sphincter device. Similarly a female with significant stress incontinence might undergo a concomitant pubourethral sling procedure, though she would most likely be dependent on intermittent catheterization to drain properly.**

Age

Many authors have evaluated the success of continent diversion in elderly patients (Lance et al, 2001; Clark et al, 2005; Sogni et al, 2008). Although elderly patients undergoing orthotopic diversion may regain continence more slowly and have a higher rate of mild stress incontinence, ultimately older patients achieve daytime and nighttime continence rates similar to those for younger patients (Elmajian et al, 1996). The clear consensus is that **age alone is not a contraindication for continent diversion and options should be considered for each patient on the basis of other factors.** Medical comorbidities; renal, cardiac, pulmonary, and cognitive function; and manual dexterity are all important factors that should be considered, along with the patient's social support situation. A frail, sedentary, elderly person is probably best served with an expeditious conduit. Similarly, a conduit may be easier for a caregiver to manage than an orthotopic diversion with the risk of incontinence. However, an active, generally healthy, elderly patient may certainly be considered a reasonable candidate for orthotopic diversion depending on his or her wishes.

Renal Function

One of the most important contraindications for continent neobladder reconstruction is compromised renal function. Urinary electrolytes including urea, potassium, and bicarbonate are reabsorbed from the small bowel mucosa, resulting in an increased acid load that must be handled by the kidneys. In patients with compromised renal function, hyperchloremic metabolic acidosis can develop along with worsening dehydration, uremia, nausea, and bone loss. The exact level of acceptable renal function for consideration for continent diversion is somewhat controversial. As a general rule, a serum creatinine level of less than 1.7 to 2.2 mg/dL (150 to 200 μmol/L) or an estimated creatinine clearance of greater than 35 to 40 mL/min is recommended (Hautmann, 2003; Hautmann et al, 2007). However, decision making in individual patients can at times be less clear-cut. Acute upper tract obstruction caused by the tumor often results in a transient rise in creatinine, which would be expected to improve after cystectomy.

Body Habitus

Obesity is not a contraindication for orthotopic diversion, although working with the thickened bowel mesentery may be challenging. **In fact, obese patients may be better served with orthotopic diversion because of the difficulty constructing functional conduit stomas on their abdomens.**

Manual Dexterity and Willingness to Do Self-Catheterization

The need to do occasional or routine self-catheterization is reported in 10% to 50% of men and in up to 30% to 50% of women (Hautmann et al, 2007). It is generally impossible to predict which patients will require catheterization to empty, and retention can occur many years after the initial surgery. Thus **all patients considered for continent diversion should be willing and able to do self-catheterization.** The authors have each patient meet with a specially trained enterostomal therapist before surgery to go over this technique in addition to other perioperative issues. It has been rare for a patient to decide against a continent orthotopic diversion because of this requirement.

Prior Pelvic Radiation

It is not uncommon for patients to present for surgical management of invasive bladder cancer after previous failed radiation therapy or after radiation treatment of a previous pelvic malignancy. Stein and colleagues (2001a) found that 8.5% of 1471 patients had some prior pelvic radiation. This exposure can significantly increase the difficulty of the surgery and can affect wound healing and postoperative complications. Many surgeons are hesitant to offer orthotopic diversion in this setting.

Ahlering and colleagues (1988) retrospectively evaluated patients undergoing cystectomy and cutaneous continent diversion comparing 44 patients who had a history of prior radiation with 42 matched patients who did not. They found no significant difference between irradiated and nonirradiated patients in operative time, blood loss, transfusion requirements, and wound or ureteral complications (Ahlering et al, 1988). Kim and Steinberg found an increased risk of surgical complications, especially those that required percutaneous or surgical intervention, in 23 patients undergoing cystectomy and conduit following radiation compared with 23 matched controls (Kim and Steinberg, 2001). Chang and colleagues (2004) evaluated outcomes of ileal conduits in 36 patients with prior radiation. They found ureteroileal complications occurred in 9% of patients by 5 years and concluded that it was appropriate to use ileum for diversion rather than a colon conduit.

The complications and ultimate functional outcome of orthotopic neobladders in patients with prior pelvic radiation have been evaluated by a number of authors. Gschwend and colleagues reported on 11 such patients. The postoperative course in this group including duration of hospital stay, perioperative complications, and early functional results did not differ from that of a control group of nonirradiated patients. They concluded that high-dose pelvic irradiation should not be a primary contraindication for orthotopic urinary diversion with segments of small intestine (Gschwend et al, 1996).

Gheiler and colleagues (1997) evaluated their clinical outcomes in three patients undergoing orthotopic substitution after cystoprostatectomy for radiorecurrent prostate cancer. Postoperative complications included pyelonephritis in one patient and prolonged ileus in another. All patients with an orthotopic

neobladder were continent during the day; one patient required a single pad at night. This group concluded from their small series that orthotopic urinary diversion is a valid option for well-selected patients with radiorecurrent prostate cancer who require salvage cystoprostatectomy and that it can be performed with minimal complications, resulting in good continence and quality of life (Gheiler et al, 1997).

Bochner and colleagues (1998) described their experience with salvage surgery and orthotopic bladder substitution after failed radical radiation therapy. A total of 18 patients who had failed definitive radiation therapy (total minimum dose, ≥60 Gy) for bladder or prostate cancer and had undergone a salvage procedure with construction of an orthotopic neobladder were evaluated. Operative characteristics, postoperative outcomes, and complications (related or unrelated to the urinary diversion) were found to be similar in irradiated and nonirradiated patients. Good daytime and nighttime continence after surgery was reported by 67% and 56% of irradiated patients, respectively. Patients with poor postoperative continence (22%) were successfully treated with the placement of an artificial urinary sphincter. **These authors concluded that salvage surgery and orthotopic urinary reconstruction appear to be safe, effective procedures that provide a functional lower urinary tract in patients in whom definitive pelvic radiation therapy has failed** (Bochner et al, 1998). Nieuwenhuijzen and colleagues (2004) reported on 27 patients who underwent salvage cystectomy, 9 of whom had an orthotopic diversion. Eight of them achieved complete daytime continence, similar to results expected in nonirradiated patients (Nieuwenhuijzen et al, 2004).

It is clear that in carefully selected patients, orthotopic lower urinary tract reconstruction can be performed after definitive, full-dose pelvic irradiation. Even selected women with a history of pelvic irradiation may be appropriate candidates for orthotopic reconstruction with good clinical outcomes (Stein et al, 2002; Lee et al, 2004). However, **these are challenging procedures that clearly require technical expertise and keen intraoperative judgment.** Previous high-dose prostate radiation (external beam or brachytherapy) or a vaginal implant for cervical cancer cause more scarring around the rhabdosphincter area than does radiation for either bladder cancer or previous colon cancer. Similarly, interstitial seed implants for prostate cancer may result in severe scarring around the area of the external sphincter, depending on the placement of the seeds. Preoperative evaluation including cystoscopy is mandatory to evaluate the integrity of the mucosa around the area of the sphincter. However, it may not be possible to accurately predict the degree of radiation damage found at surgery, **so careful intraoperative tissue assessment and determination of the condition of the urethra, ureters, and bowel must be performed to make a final decision about the feasibility of orthotopic diversion** (Abbas et al, 2001). These patients should always be counseled preoperatively that the orthotopic diversion may not be possible.

Prior Prostate Surgery or Bowel Resection

Prior abdominal or pelvic surgery may also present challenges for the surgeon performing orthotopic diversion. Patients who have had a prior radical prostatectomy may have a particularly difficult dissection around the proximal urethra at the prior vesicourethral anastomosis. Nevertheless, this is often feasible with careful dissection. The health of the proximal urethra can be assessed at surgery and acceptable continence can be obtained in selected patients (Schuster et al, 2003). In general, with careful dissection a patient who was continent following the first surgery can be expected to have an acceptable result with a neobladder.

A patient with multiple prior bowel resections may be at risk of developing chronic diarrhea or even short bowel syndrome after an additional 45 to 60 cm of small bowel is resected. In these patients alternatives for orthotopic diversion such as a sigmoid neobladder might be entertained. Generally prior bowel resections can be managed by carefully dissecting out all of the small bowel, taking down any adhesions before performing the diversion. **It is critical to identify the old bowel anastomosis and, whenever possible, take that down and use that site as one end of the continent reservoir.** This avoids potential devascularization of the bowel segment between the old and new bowel anastomoses.

Key Points: Previous Pelvic Radiation or Pelvic Surgery

- Orthotopic lower urinary tract reconstruction can be performed after definitive, full-dose pelvic irradiation in carefully selected male and female patients.
- Incontinence rates after salvage cystectomy and orthotopic reconstruction are higher and may require an artificial urinary sphincter in men or a sling procedure in women.
- In patients with prior bowel resection the prior anastomosis should be taken down and that segment used for the orthotopic diversion rather than chosing a new site to avoid devascularization of the bowel.

CONTINENCE MECHANISM IN PATIENTS UNDERGOING ORTHOTOPIC DIVERSION

An understanding of the anatomy of the urethral continence mechanism in men and women is crucial to preserving this function at the time of radical cystectomy. The surgical dissection at the prostatic apex in men and bladder neck in women must be carefully and precisely performed to achieve optimum continence while taking care not to compromise the oncologic effectiveness of the surgery.

Much of what has been learned of the rhabdosphincter complex comes from elegant neuroanatomic studies of the female urethra. Colleselli and colleagues (1998) performed extensive microneuroanatomic dissections, histologic examination, and three-dimensional reconstructive imaging to better define the urethral sphincteric and rhabdosphincteric anatomy in women. The female urethral sphincter system consists of smooth muscle innervated by the autonomic nervous system and striated muscle supplied by somatic nerves. There is general agreement that the autonomic nerves that serve the smooth muscle sphincter originate in the pelvic plexus. These autonomic fibers emerge from the the pelvic plexus and course along the lateral aspect of the rectum and vagina toward the bladder neck and very proximal urethra. Some of these fibers branch off from a thick fiber at the lower margin of the lateral vaginal wall and enter the bladder neck and cranial portion of the urethra from the dorsolateral aspect. These autonomic nerves do not appear to play a significant role in the innervation of the rhabdosphincter or the continence mechanism and are essentially sacrificed during the exenterative portion

of the operation without compromising continence (Colleselli et al, 1998).

Innervation of the voluntary urinary sphincter system, however, is a matter of some controversy. Most interested investigators agree that the rhabdosphincter is probably supplied primarily by the branches of the pudendal nerve (Borirakchanyavat et al, 1997; Stenzl et al, 1997; Colleselli et al, 1998). Although these dissections were performed on female cadavers, the observations and findings have been similarly described in men (Strasser, 2000). Collectively, these findings have allowed a more precise and anatomic approach to maintain the continence mechanism in all patients undergoing cystectomy and orthotopic substitution.

In the same study, Colleselli and colleagues (1998) found that the major portion of the striated muscle that corresponds to the striated rhabdosphincter is located on the ventral and lateral aspects (omega shaped) of the urethra. No clear, defined line could be identified between the transverse smooth muscle cranially and the striated muscle caudally. Rather, a gradual transition was noted in the middle third of the urethra, with intermingling fibers of both types of muscle (Colleselli et al, 1998). This area has been found to correspond to the area of continence region on fluorourodynamic studies performed on women who had undergone orthotopic reconstruction after cystectomy (Grossfeld, 1996). Branches off the pudendal nerve coursing beneath the levator muscle can be traced to the rhabdosphincter. Delicate fibers from the perineal portion of the pudendal nerve course underneath the urogenital diaphragm, entering the caudal portion of the urethra laterally.

In a neuroanatomic study performed in male human cadaveric pelves, similar anatomic findings and innervation were described. Strasser and Bartsch (2000) described the male rhabdosphincter as an independent muscle unit that is not in direct contact with the fibers of the levator ani muscle. These dissections demonstrated that the male sphincter does not form a horizontal muscular ring around the membranous urethra. Rather, the male rhabdosphincter is a muscular coat situated ventral and lateral to the membranous urethra and prostate, the core of which is an omega-shaped loop that surrounds the membranous urethra. The innervation of the male rhabdosphincter was also found to originate from fine branches that arise off the pudendal nerve. These authors suggested that injury to either the rhabdosphincter or the pudendal innervation may impair the sphincter mechanism in men (Strasser and Bartsch, 2000).

SURGICAL TECHNIQUES FOR CONTINENCE PRESERVATION DURING RADICAL CYSTECTOMY

Attention to anatomic and surgical detail is important to optimize functional and clinical outcomes in patients undergoing orthotopic diversion after radical pelvic surgery. **Minimal manipulation of the muscle fibers of the rhabdosphincter, fascial attachments, and corresponding innervation is essential in providing optimal urinary continence** (Stein et al, 1997, 2001b; Colleselli et al, 1998; Stenzl et al, 1998; Strasser, 2000).

Anterior Apical Dissection in the Male Patient

The technique of an extended bilateral pelvic lymphadenectomy with radical cystoprostatectomy is well established (Stein and Skinner, 2004). **Urethral preparation with preservation of the continence mechanism is critical when orthotopic diversion is anticipated. The continence mechanism in men may be maximized if dissection in the region of the pelvic floor and anterior urethra is minimized.** Attention to surgical technique is important and is described in detail elsewhere (Stein et al, 2001b). Several fundamental key surgical issues in the preparation of the urethra in patients undergoing orthotopic diversion deserve special mention.

In a standard cystectomy the bladder and prostate are completely freed off of the rectum and mobile posteriorly before the urethral dissection. Posterior dissection should not extend distal to the apex of the prostate. If a nerve-sparing approach is planned, the urethra may be divided after taking down the lateral pedicles to the bladder (anterior branches of the internal iliac vessels) before performing the posterior dissection. The prostate is then dissected in a retrograde fashion off of the rectum and bilateral neurovascular bundles, and the posterior pedicles are divided last.

In either approach, all fibroareolar connections along the anterior bladder wall, prostate, and undersurface of the pubic symphysis are divided. The endopelvic fascia is incised adjacent to the prostate, and the levator muscles are carefully swept off the lateral and apical portions of the prostate. The superficial branch of the deep dorsal vein is identified, ligated, and divided. With tension placed posteriorly on the prostate, the puboprostatic ligaments are identified and slightly divided just beneath the pubis and lateral to the deep dorsal venous complex, which courses between these ligaments. Care should be taken to avoid any extensive dissection in this region. The puboprostatic ligaments need to be incised only enough to allow proper apical dissection of the prostate.

Several methods can be performed to properly control the dorsal venous complex (DVC) (Stein et al, 2001b; Stein and Skinner, 2006). One may carefully pass an angled clamp beneath the dorsal venous complex, anterior to the urethra to pass a suture to ligate the complex. Alternatively, a suture on a long curved needle may be directly passed just anterior to the urethra, posterior to the venous complex, and tied as a simple or figure-of-eight stitch. A third alternative is to gather the complex in a long Allis clamp before passing the suture. The suture is best placed with the surgeon facing the head of the table and with the needle holder perpendicular to the patient. These latter maneuvers avoid passage of any instruments between the dorsal venous complex and the rhabdosphincter, which could potentially injure these structures and compromise the continence mechanism. Alternatively, especially in a patient with a broad, short DVC, the complex can simply be sharply divided and oversewn as needed to obtain adequate hemostasis. Absorbable suture should be used to avoid any risk of subsequent suture erosion into the urethral anastomosis.

Once the venous complex is ligated, it may be divided close to the apex of the prostate. Any bleeding from the transected venous complex can be controlled with an absorbable 2-0 polyglycolic acid suture. However, only suturing that is absolutely necessary should be performed and **care should be taken to avoid deep suture bites into the complex or levator muscles, which could injure the continence mechanism.** The DVC suture can then be used to suspend the venous complex anteriorly to the periosteum of the symphysis pubis to re-establish anterior fixation of the dorsal venous complex and puboprostatic ligaments, which may enhance continence recovery.

The anterior urethra is now exposed. Before division of the urethra, the authors prefer to place a heavy suture around the apex of the prostate encircling the catheter to decrease the risk of urine

spill when the urethra is divided. The anterior urethra is then incised just beyond the apex of the prostate. Six 2-0 absorbable monofilament or woven polyglycolic acid sutures are placed in the urethra circumferentially, carefully incorporating only the mucosa and submucosa of the urethra without incorporating the levator muscles. The urethral catheter is clamped and divided distally. Two additional sutures are then placed, incorporating the recto-urethral muscle posteriorly and the caudal extent of Denonvillier fascia. After this, the posterior urethra is divided and the specimen removed. The urethral sutures are appropriately tagged to identify their location and are placed under a towel until the urethroenteric anastomosis is performed.

Regardless of the technique, frozen-section analysis of the distal urethral margin (prostatic apex) on the cystectomy specimen is performed to exclude tumor involvement. The decision to perform an orthotopic bladder substitute is ultimately made at this time. If there is no evidence of tumor, orthotopic reconstruction may be performed.

Urethral Dissection in the Female Patient

When orthotopic diversion is considered in female patients, several technical issues should be noted to optimize the continence mechanism (Stein et al, 2001b; Stein and Skinner, 2004). A standard female cystectomy includes removal of the uterus, cervix, and ovaries (anterior exenteration). However, in selected females with clinically lower-stage disease some authors have advocated preservation of the uterus and ovaries (Chang et al, 2002; Zippe et al, 2005). **In either case, whenever possible the bladder is dissected completely off of the vagina, but a tumor on the posterior bladder wall may necessitate excision of a portion of the anterior vaginal wall.** This does increase the risk of subsequent pouch-vagina fistula but is not an absolute contraindication to orthotopic reconstruction. However, a patient with a significant tumor at the bladder neck or with palpable extention into the vaginal wall is a poor candidate for neobladder and should undergo en bloc urethrectomy and cutaneous diversion.

In developing the posterior pedicles, the posterior vagina is incised at the posterior fornix posterior to the cervix. If the patient has undergone prior hysterectomy, a sponge stick in the vagina facilitates identification of the vaginal apex. In that case the vagina is generally not entered. Before dissecting off the bladder, the posterior vascular pedicles are developed and divided. The vaginal apex may be grasped with a curved Kocher clamp to provide countertraction, and scissors are used to dissect right along the lateral vaginal wall. This develops the posterior pedicle coming around the rectum and vagina toward the bladder, which can be controlled with hemoclips, vascular staples, or a LigaSure (Covidien Ltd., Mansfield, MA) or similar device. Care is taken to dissect along the midlateral vaginal border, rather than dissecting back along the rectum or anterior into the bladder.

The issue of nerve-sparing cystectomy in women is controversial. Some authors have suggested that a sympathetic nerve-sparing cystectomy may be important in maintaining continence in women undergoing orthotopic diversion (Stenzl et al, 1995a; Hautmann, 1997; Turner et al, 1997; Bhatta et al, 2007). Others have routinely sacrificed the autonomic nerves coursing along the lateral aspect of the uterus and vagina and have successfully relied on the pudendal innervation of the rhabdosphincter complex for continence (Stein et al, 1997, 2004; Ali-El-Dein et al, 2002). In fact, the authors have observed good continence results in women undergoing complete bowel and urinary tract reconstruction after total pelvic exenteration with removal of all pelvic autonomic innervation. This, again, supports the concept that autonomic innervation is not critical to the continence mechanism.

Once the posterior pedicles are divided, careful dissection of the bladder off of the anterior vaginal wall is performed sharply. Care must be taken to dissect in the proper plane to prevent entry into the posterior bladder and reduce the amount of bleeding in this vessel-rich area. Dissection is carried just distal to the vesicourethral junction. Palpation of the Foley catheter balloon assists in identifying this region.

Once the posterior dissection is completed, the fatty tissue overlying the anterior urethra is swept off and the vesico-urethral junction is carefully identified using the Foley catheter balloon. **The endopelvic fascia and periurethral tissue anteriorly should not be disturbed.** A pedicle clamp is placed across the bladder neck, which prevents any tumor spill from the bladder when the urethra is transected. With gentle traction, the proximal urethra and Foley catheter are sharply divided just distal to the bladder neck. It is not necessary to place the urethral sutures as the urethra is divided because it does not retract away as it does in the male. Frozen-section analysis is performed on the distal surgical margin of the cystectomy specimen to exclude any tumor. Once the decision is made to perform the orthotopic diversion, 8 to 10 sutures of 2-0 absorbable suture are placed circumferentially through the urethra, tagged, and set aside.

In the case of a deeply invasive posterior bladder, the anterior vaginal wall may be removed en bloc with the cystectomy specimen by incision along the long axis of the lateral vaginal wall. This leaves the anterior vaginal wall attached to the posterior bladder specimen. Again, the Foley catheter balloon facilitates identification of the vesicourethral junction. A rim of anterior vaginal wall must be preserved proximal to the urethra to close the vagina. The vagina may be closed in a clamshell or horizontal manner. Other reconstructions to increase vaginal volume are feasible, but it may be difficult to perform a complex vaginal reconstruction along with a neobladder simply because of a lack of adequate room in the pelvis.

If the anterior vaginal wall has been preserved, the vagina is closed at the apex with absorbable suture and then suspended. One may suspend the vagina to the Cooper ligament or to preserved cut ends of the round ligaments to prevent postoperative vaginal prolapse. However, the authors routinely perform a colposacroplexy incorporating a short strip of permanent mesh to fix the vagina to the sacral promontory at a more natural angle

Key Points: Continence Mechanism and Surgical Techniques for Continence Preservation

- The innervation of the striated urethral rhabdosphincter arises from the branches of the pudendal nerve and is most important to maintain continence in patients with an orthotopic neobladder.
- The striated rhabdosphincter muscle fibers are concentrated in the area anterior and lateral to the proximal urethra.
- In males one should obtain careful control of the dorsal venous complex and avoidance of deep suture bites into the pelvic floor muscles.
- In females the endopelvic fascia and levator muscles should not be disturbed.

without any tension. This may be important to support the neobladder and avoid a possible cause of late voiding difficulty. **Regardless of the form of vaginal reconstruction, a well-vascularized omental pedicle graft must be placed between the reconstructed vagina and the neobladder and properly secured to the levator ani muscles to separate the suture lines and prevent fistula formation between the vaginal and urethral anastomosis to the neobladder**.

TECHNIQUES FOR ORTHOTOPIC BLADDER SUBSTITUTION

Choice of Bowel Segment

A number of different procedures for orthotopic reconstruction incorporating different segments of bowel have been described. There are clearly some physiologic indications to use various segments of intestine, but the surgeon's preference may be even more influential. It has been suggested that **excellent functional and clinical outcomes with voiding can be achieved regardless of the segment of bowel chosen as long as the principles of preservation of the rhabdosphincter as a continence mechanism and construction of an adequate capacity, low-pressure reservoir are maintained** (Parekh et al, 2000b; Lee et al, 2003). Ideally the surgeon performing orthotopic urinary diversion should be comfortable using a variety of the techniques described later so that he or she can adapt the technique to the needs of the individual patient.

Reservoirs made of detubularized ileum or ileum and colon together appear to have the greatest compliance and lowest likelihood of generating intermittent high pressure contractions. Hohenfellner and colleagues elegantly evaluated the properties of gut smooth muscle layers (circular and longitudinal) of ileal and cecal segments in a canine model. The circular muscle layer of ileum was found to be most distensible, followed by the colonic circular and longitudinal ileal layers. The longitudinal layer of the colonic segment was relatively nondistensible (Hohenfellner et al, 1993).

Several clinical studies have demonstrated that the urodynamic characteristics of the ileum appear to be superior to those of the colon (Berglund et al, 1987; Lytton and Green, 1989; Davidsson et al, 1992; Schrier et al, 2005). Stomach and sigmoid colon have been found to have particularly poor compliance and high pressures (Santucci et al, 1999). Davidsson and colleagues (1992) evaluated the urodynamic profiles of neobladders constructed from the ileum and the right colon and found that although the volume capacity was similar, the pressure at maximum capacity was much lower with the ileal reservoir. Schrier and colleagues (2005) found that neobladders made of ileum had larger capacity, lower filling pressures, lower maximum capacity pressures, and better compliance. The distal small bowel mesentery also tends to have the greatest mobility and generally reaches to the urethra without much difficulty. In patients with short ureteral length due to malignancy or other pathology of the ureters, an ileal pouch with a "tail" (such as the Studer) can be extended to reach all the way to the renal pelvis. A final advantage of ileum is the atrophy of the intestinal mucosa as it is exposed to urine over time. This results in decreased mucous production and decreased reabsorption of urinary electrolytes in the mature reservoir. Mucosal atrophy appears to be more reliable in small bowel than in large bowel reservoirs (Norlen and Trasti, 1978; Mills and Studer, 1999).

The primary disadvantage of using distal ileum lies in the potential loss of absorption of vitamin B_{12}. This segment may also be unacceptably damaged by prior pelvic radiation or may be unavailable due to multiple prior bowel resections or to inflammatory conditions like Crohn disease. Ideally the surgeon performing orthotopic urinary diversion should be comfortable using a variety of the techniques described later so that he or she can adapt the technique to the needs of the individual patient. Whenever available, the authors preferentially use ileum for orthotopic diversion.

Bladder replacement using stomach has also been described, although it has not been a popular technique (Adams et al, 1988; Nguyen, 1991; Hauri, 1998; Lin, 2000). The primary advantage of gastric segments is that the gastric mucosa excretes chloride and hydrogen ions, effectively reversing the acidosis of renal insufficiency. The latter is worsened with a pouch made of small or large bowel. The excreted acid from a stomach segment can also reduce the risk of bacterial colonization, and there is less mucous production. However, the disadvantage of using stomach is that some patients will suffer from dysuria or hematuria from the excreted acid (Nguyen, 1991). Lin and colleagues (2000) reported their clinical outcomes in eight patients undergoing gastric neobladder construction and found that pouch capacity and compliance were worse compared with ileal or ileocecal neobladders. Combining gastric and small or large intestinal segments can counteract some of these side effects and may be ideal from a purely metabolic standpoint (Lockhart et al, 1993). **This construction can theoretically be performed in a patient with compromised renal function when continent diversion is generally contraindicated. It may also provide another option in a patient with prior high-dose pelvic radiation or multiple previous bowel resections.** Few urologists have been trained in the surgical anatomy of the stomach, and most who perform a significant number of cystectomies currently rarely, if ever, using this type of diversion.

Isolation of the segment of bowel to be used for the diversion must be performed carefully in order to preserve blood supply to the pouch, as well as to the bowel anastomosis. If using ileum one should avoid deep incision into the mesentery at the proximal bowel division to avoid compromising the blood supply to the reservoir. In addition, in patients who have had previous bowel resection it is important to take down the old anastomosis rather than choosing another site nearby because that may result in a poorly vascularized segment between the new and old bowel anastomoses. Gastrointestinal complications are a common consequence of cystectomy and diversion, and care must be taken in ensuring a secure bowel anastomosis.

Need to Prevent Reflux

The deleterious effect of vesicoureteral reflux in children is well accepted, especially in the face of infection. In the context of urinary diversion the importance of preventing reflux was first identified in patients undergoing ureterosigmoidostomy (Clarke and Leadbetter, 1955; Wear and Barquin, 1973) and, subsequently, ileal conduit urinary diversion (Middleton and Hendren, 1976; Shapiro et al, 1975). It has been believed that the frequent long-term deterioration of renal function and upper tract changes seen in up to 50% of patients with ileal conduit urinary diversions by 15 years are due to high-pressure reflux of infected urine (Clark et al, 1999; Madersbacher et al, 2003). Mean time to development of kidney problems in conduit patients is 5 years, and the

incidence of such complications seems to increase steadily with time (Clark et al, 1999).

However, studies that have compared refluxing versus nonrefluxing urinary diversion have generally been limited by short follow-up, patient selection bias, retrospective design, or relatively small patient numbers. Richie and colleagues (1974) showed a protective effect of nonrefluxing anastomoses in a dog model. Kristjansson and colleagues (1995a, 1995b) found no difference in colon conduits with nonrefluxing anastomoses versus ileal conduits with refluxing anastomoses. However, continent diversions with antireflux techniques appeared to have less upper tract scarring and bacteruria. Studies by both Elder and Hill showed upper tract deterioration was common in both colonic and ileal conduits, although each had high rates of stomal stenosis and ureteroenteric stenosis (Elder et al, 1979; Hill and Ransley, 1983). Althausen showed better results using nonrefluxing colon conduits, but the follow-up in this study was only 3 years (Althausen, 1978). Song and Hautmann each found no differences in renal function or hydronephrosis in refluxing or nonrefluxing orthotopic neobladders in nonrandomized retrospective studies (Song et al, 2006; Hautmann et al, 2006). All of these studies were retrospective and nonrandomized and generally included relatively small numbers of patients.

With orthotopic diversion, most patients void by Valsalva maneuver with relaxation of the external sphincter. The resulting increase in pressure in the reservoir should be transmitted equally to the rest of the system, limiting any resulting back pressure even without an antireflux mechanism (Thoeny et al, 2002; Studer et al, 2006). However, free reflux into the upper tracts of the Studer pouch is often visible on cystogram with as little as 300 mL of filling, well within the typical voided volume of these patients. It is likely that there is some retrograde flow of urine in these patients at some times. In patients who require intermittent catheterization to empty, such reflux could potentially occur at relatively high pressures when the reservoir is full. Finally, although symptomatic infections are uncommon, it is not unusual for these patients to have asymptomatic bacteruria, especially if they are on self-catheterization. Steven reported 34% 3-year and 24% 5-year prevalence of bacteriuria in 166 men undergoing orthotopic reconstruction (Steven and Poulsen, 2000). Whether any of this is physiologically important is still unclear (Suriano et al, 2008). Wood and colleagues (2003) looked at 66 patients undergoing orthotopic refluxing ileal neobladder. Of these patients, 17% required clean intermittent catheterization, 67% had positive urinalyses, and 39% had a documented positive urine culture. For those who voided without the need for catheterization, they reported an estimated 5-year probability of urinary tract infection of 58% and urosepsis of 18% (Wood et al, 2003).

Medium to long-term results in ileal neobladders without antireflux valves have generally been good. Normal renal function and preserved upper tract anatomy are possible in the majority of patients (Thoeny et al, 2002; Perimenis et al, 2004; Minervini, 2005). Thoeny and colleagues examined long-term results in 76 patients with 5 or more years follow-up with a Studer pouch and found preserved renal function and anatomy in 95% of the patients (Thoeny et al, 2002).

It is clear as well that **any mechanism introduced to prevent reflux may also potentially cause upper tract obstruction.** Initial experience with the intussuscepted Kock nipple valve showed that it provided reliable protection against reflux and seemed to have few drawbacks. However, as surviving patients were followed out to 10 years and beyond it became clear that approximately 5% of patients experienced obstruction from stenosis of the afferent nipple valve, and an additional 5% developed stone on or extussussception of the afferent nipple valve (Stein et al, 1996). Afferent valve problems were often clinically silent: Patients who were not followed carefully occasionally presented with acute renal failure and bilateral hydroureteronephrosis with significant renal damage. Similarly, ureteroileal obstruction with the antireflux Camey–Le Duc ureteral implantation technique has been reported to occur in 7% to 29%, compared with less than 3% for a direct ureteroileal anastomosis (Le Duc et al, 1987; Shaaban et al, 1992; Pitts and Muecke, 1979; Roth, 1997; Pantuck et al, 2000).

Shaaban and colleagues (2006) performed one of the few prospective randomized clinical trials evaluating this question. They studied 60 patients who all had normal renal function preoperatively and no hydronephrosis. In each patient one randomly chosen ureter was implanted in an antireflux manner (using an extraserosal tunnel), and the other was implanted directly into a small tabularized chimney on a standard W ileal neobladder. At 2 years median follow-up they found more deterioration in the renal units drained with the antireflux technique, which resulted in five cases of documented obstruction than in those with a direct refluxing anastomosis (Shaaban et al, 2006). However, longer-term follow-up may be necessary to see any cumulative damage from the reflux itself.

Abol-Enein and Ghoneim (2001) developed a serous-lined ureteral implantation technique with an ileal neobladder and reported their intermediate experience (mean follow-up of 38 months) in 450 patients. In this large series, 96% of upper tracts remained unchanged or improved; reflux was observed in only 3% of patients. They reported that in their series an anastomotic ureteral stricture occurred in 3.8% of patients, an incidence similar to that of most refluxing ureteroileal anastomoses (Pantuck et al, 2000). The T pouch was designed building on this technique to provide protection from reflux while avoiding some of these complications of the Kock nipple valve. This is accomplished by preserving optimum blood supply to the tunneled ileal afferent limb segment while allowing the ureters to be directly implanted into the ileum, allowing for ureters that are dilated or must be divided high (Stein et al, 1998b; Stein and Skinner, 2006). Stein and colleagues (2004) reported results with this type of diversion with 33 months median follow-up showing that renal function and anatomy were preserved in 90% of patients, with only 2% developing stenosis related to the afferent T limb during this time. In recent years the technique has been modified to avoid tapering the afferent limb to attempt to limit further the development of late stenosis (see later).

As the overall therapy (medical and surgical) for pelvic malignant neoplasms improves and patients live longer after cystectomy and urinary diversion (placing them at further long-term risk for renal deterioration), reflux prevention may become a more important issue. The basic question remains whether any benefit in upper tract protection afforded by the antireflux technique outweighs the potential risk of upper tract obstruction due to the antireflux technique itself in patients with bladder cancer. Further clarification of this question awaits the results of prospective randomized studies currently under way (Skinner and Skinner, 2010).

General Perioperative Management

Perioperative management of patients undergoing cystectomy and orthotopic diversion is not materially different than for patients undergoing other types of diversion. A careful history and physical

Key Points: Choice of Bowel Segment and the Need to Prevent Reflux

- Reservoirs made from ileum or combined ileum and colon appear to have the best physiologic properties for orthotopic diversion.
- Isolation of the segment of bowel to be used for the diversion must be performed carefully in order to preserve blood supply to the pouch and bowel anastomosis.
- The absolute necessity to include an antireflux mechanism in orthotopic diversion is still controversial.
- Long-term results with both refluxing and nonrefluxing systems have shown good upper tract preservation.

examination should focus on prior abdominal or pelvic surgery or radiation, current voiding patterns and continence, and general medical problems. If colon may be used for the diversion, a colonoscopy is recommended to rule out polyps or tumors. A contrast study demonstrating the patient's upper tract anatomy is helpful in planning management of the ureters.

There is no consensus on the ideal management of ureteral stents or catheters in patients undergoing orthotopic diversion. Most authors do recommend the use of ureteral stents in the early postoperative period (Mattei et al, 2008). The authors routinely use 8-Fr plastic feeding tubes that are tied to the urethral catheter so that they can be removed at the same time and the patient has fewer external bags to manage. They also use a 24-Fr stiff hematuria catheter, which facilitates routine irrigation of the pouch. The disadvantage of this system is the need to irrigate the catheter several times daily to ensure that the catheter does not plug up with mucus. Many surgeons use externalized ureteral stents brought through the skin and drained separately. The latter allows for less urine to pass through the pouch while it is healing and may decrease dependence on attentive nursing. A pelvic drain should be placed in every patient. The authors routinely use a soft plastic Penrose drain. This type of drain promotes passive drainage without drawing urine out of the pouch by the suction used and can be safely left in for long periods of time.

Although no strict guidelines are available regarding optimal timing of reservoir catheter removal, it has been the authors' practice for patients undergoing orthotopic and continent cutaneous forms of diversion to wait until 3 weeks postoperatively to remove the Foley catheter. When patients return at the 3-week postoperative mark, if there is minimal drainage from the Penrose drain (<100 mL during 24 hours), the catheter is removed, followed by the drain. Routine pouchograms or radiographic studies of the neobladder are not routinely performed unless a significant output from the drain is observed (Ankem et al, 2004). Patients receive education throughout the perioperative period regarding catheter management and proper voiding technique.

Surgical Techniques

A large number of modifications of the techniques presented next have been described in a small number of patients, and this is by no means an exhaustive list.

Ileal Reservoirs

Most ileal reservoirs use from 60 to 75 cm of terminal ileum, which is detubularized and folded in a variety of ways to attempt to create a spherical shape. Modifications primarily include variations in the exact folding technique and variations in management of the ureters, with or without an antireflux mechanism. All reservoirs are generally closed with continuous absorbable suture. The use of nonabsorbable suture and metal staples should be avoided because of the potential for stone formation (Stein et al, 1994b). Absorbable staples have been developed, and some authors have found them useful, though they tend to be somewhat bulky (Bonney and Robinson, 1990; Olsson et al, 1995; Kirsch et al, 1996, Montie et al, 1996).

Camey II

The Camey II orthotopic substitute (Camey, 1990) is a modification of the original Camey bladder substitute (Camey I) (Lilien and Camey, 1984), which was a simple segment of ileum anastomosed to the ureters and urethra. The modification includes detubularization and folding to eliminate peristaltic activity.

A total of 65 cm of ileum is isolated, with an area of the ileum identified to reach to the region of the urethra in a tension-free manner. After the integrity of the bowel is restored, the mesenteric trap is closed and the isolated portion of ileum is opened along the antimesenteric border for the entire length, except the area previously identified for the urethral anastomosis. In this region, the ileal incision is directed toward the mesenteric border. The ileum is then placed in a transverse U orientation. The medial borders of the U are sutured together with a running absorbable suture. A fingertip opening is made in the preselected area for the ileourethral anastomosis, the entire ileal plate is brought down to the pelvis, and the urethral anastomosis is performed. The ureteroileal anastomosis is then performed by a Le Duc technique (Le Duc et al, 1987). The reservoir is completed by folding the ileal plate and suturing with a running absorbable suture. The ends of the U are anchored to the pelvic floor to reduce tension (Fig. 87–2). A modification of the Camey II has been described by Barre and colleagues (1996). This places the ileum in a Z configuration and reportedly has the advantages of shorter length requirements, improved reservoir capacity, and potentially improved functional (continence) results (Barre et al, 1996).

Ileal Neobladder (Hautmann Pouch)

This ileal neobladder was developed by Hautmann and colleagues (1988). This neobladder is an intentionally large-capacity, spherical (W configuration) ileal reservoir that is constructed in an attempt to optimize initial volume and potentially reduce nighttime incontinence.

A segment of terminal ileum of approximately 70 cm is selected. The bowel is reconstituted, and the mesenteric trap is closed. The ileal section that reaches the urethra most easily is identified and marked with a traction suture along the antimesenteric border. The isolated bowel segment is then arranged in either an M or W shape and is opened along the antimesenteric border except for a 5-cm section along the traction suture where the incision is curved to make a U-shaped flap.

The four limbs of the M or W are then sutured to one another with a running absorbable suture. A small full-thickness segment of bowel is excised in the site for the urethral anastomosis, which is then performed with the sutures tied from inside the neobladder. Once the ileal neobladder is situated in the pelvis and the urethral sutures are tied, the ureters are implanted from inside the neobladder through a small incision in the ileum at a convenient site. The remaining portion of the anterior wall is then closed with a running absorbable suture (Fig. 87–3).

Initially Hautmann and colleagues (1988) used an antireflux anastomosis similar to that described by Le Duc and colleagues

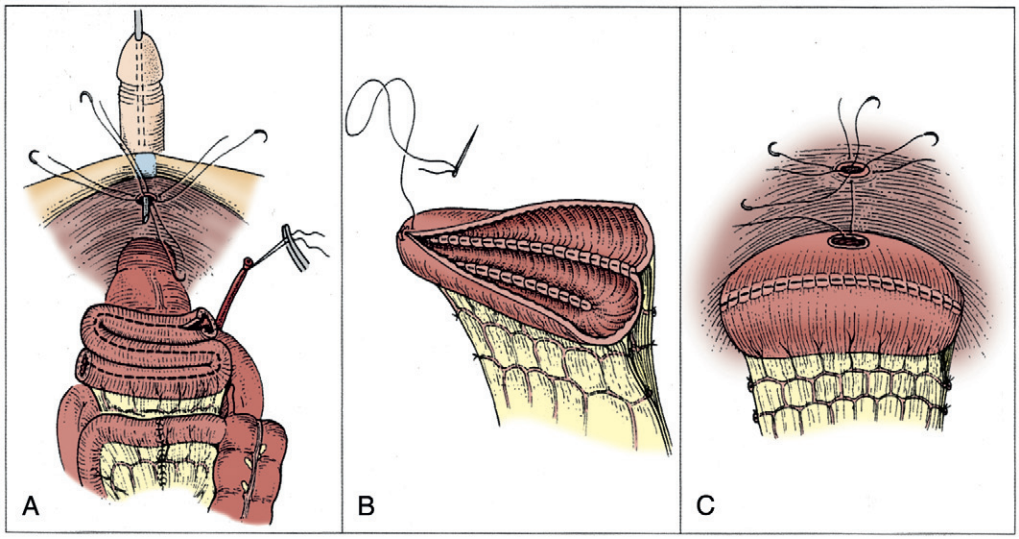


Figure 87–2. Construction of the modified Camey II. **A,** The ileal loop is folded three times (Z shaped) and incised on the antimesenteric border. **B,** The reservoir is closed with a running suture to approximate the incised ileum. **C,** The urethral anastomosis is performed, and the ureters are implanted using a Le Duc antireflux technique.

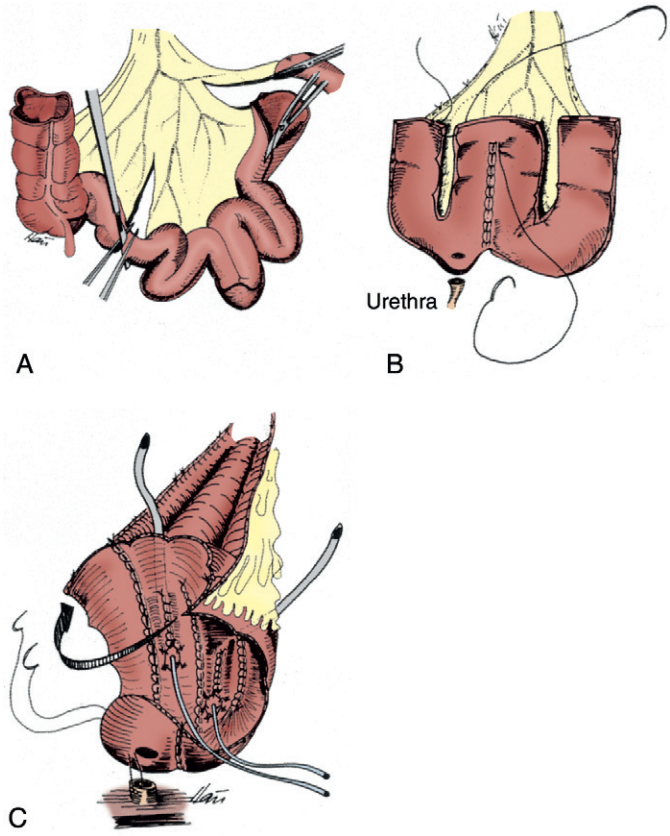


Figure 87–3. Construction of the Hautmann ileal neobladder. **A,** A 70-cm portion of terminal ileum is selected. The isolated segment of ileum is incised on the antimesenteric border. **B,** The ileum is arranged into an M or W configuration with the four limbs sutured to one another. **C,** After a buttonhole of ileum is removed on an antimesenteric portion of the ileum, the urethral anastomosis is performed. The ureteral anastomoses are performed using a Le Duc technique or direct implantation, are stented, and the reservoir is then closed in a side-to-side manner. As an alternative, the two ends of the W may be left slightly longer as a short chimney on either side for implantation of the ureters.

(1987). However, ureteroileal strictures were fairly common and beginning in 1997, the author modified this technique and now employs a freely refluxing, open end-to-side anastomosis implanted into short tabularized segments at each end of the W. This resulted in a decrease in the risk of ureteroileal stenosis from 9.5% to 1% (Hautmann, 2001; Hautmann et al, 1999, 2006; Volkmer et al, 2009).

The potential downside of this reservoir is the large initial capacity, which may result in an increased incidence of late urinary retention and increased electrolyte reabsorption from the pouch. Sevin has reported a modified Hautmann ileal neobladder using only 40 cm of ileum to reduce these potential issues with acceptable clinical outcomes (Sevin et al, 2004). The classic configuration of the pouch also could not accommodate short ureters, but in a popular revised technique one or both ends of the W could be left long to anastomoses to one or both shortened ureters (Hollowell et al, 2000).

Orthotopic Kock Ileal Reservoir ("Hemi-Kock")

The Kock ileal reservoir was first employed as a continent cutaneous ileal reservoir incorporating intussuscepted nipple valves for both the afferent (antireflux) and efferent (continence) limbs (Kock et al, 1982; Skinner et al, 1984). This subsequently evolved into an orthotopic form of diversion in which the afferent intussuscepted limb was maintained to prevent urinary reflux (Fig. 87–4) (Ghoneim et al, 1987; Skinner et al, 1991). Skinner and colleagues (1998) performed more than 500 of these procedures from 1982 to 1995, with excellent continence and a low ureteroileal stricture rate of less than 3% (Elmajian et al, 1996). However, the technique required the use of metal surgical staples to fix the intussuscepted nipple valve, which was a source of potential stone formation. In addition, many surgeons found the technique difficult to master. Schreiter and Deliveliotis each described ileal S bladder modifications of the of the orthotopic Kock ileal reservoir (Schreiter and Noll, 1989; Deliveliotis et al, 2001). Both involve forming the detubularized reservoir into an S shape instead of the double-folded U configuration.

With long-term follow-up, late complications associated with the afferent intussuscepted antireflux nipple developed in a small

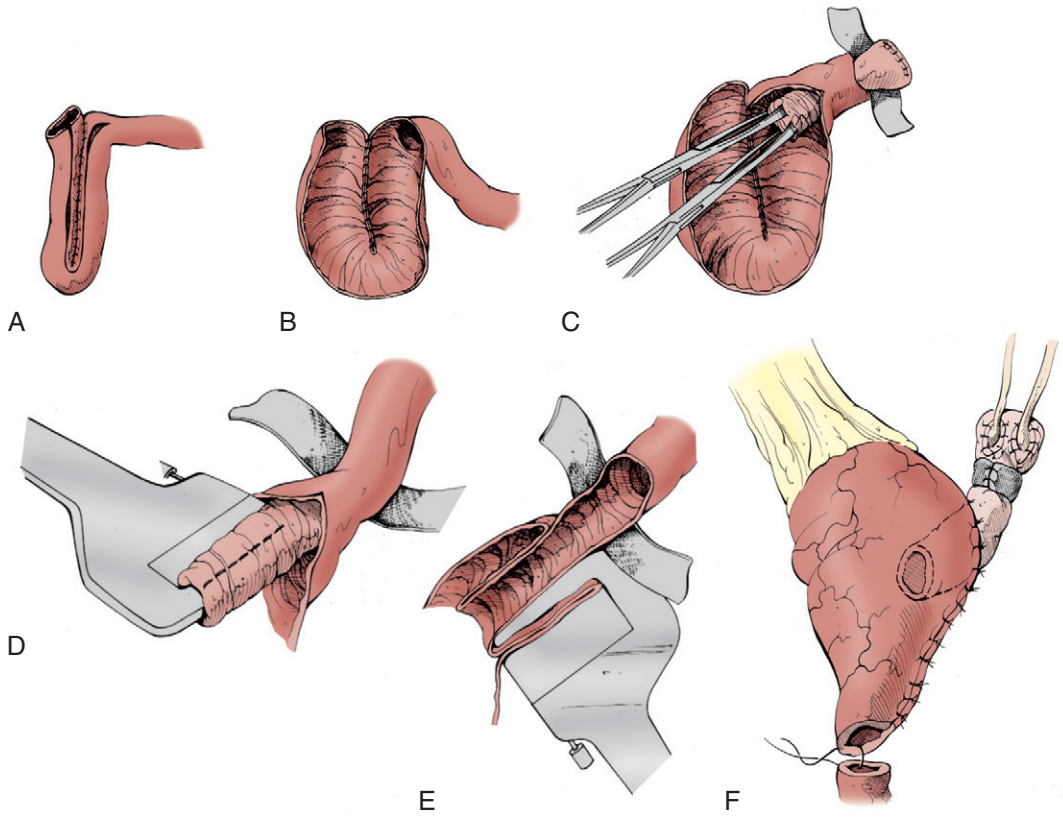


Figure 87–4. Construction of the Kock ileal reservoir. **A,** A total of 61 cm of terminal ileum is isolated. Two 22-cm segments are placed in a U configuration and opened adjacent to the mesentery. The more proximal 17-cm segment of ileum will be used to make the afferent intussuscepted nipple valve. **B,** The posterior wall of the reservoir is then formed by joining the medial portions of the U with a continuous running suture. **C,** A 5- to 7-cm antireflux valve is made by removing the mesentery under that segment and then intussuscepting the afferent limb with the use of Allis forceps clamps. **D,** The afferent limb is fixed with two rows of staples placed within the leaves of the valve. **E,** The valve is then fixed to the back wall from outside the reservoir with additional surgical staples. **F,** After completion of the nipple valve, the reservoir is completed by folding the ileum on itself and closing it, leaving the most dependent end of the suture line open for the urethral anastomosis.

but significant number of patients (Stein et al, 1994, 1996). The primary late complications include stone formation on exposed staples (5%), stenosis of the afferent nipple ostium thought to be secondary to a compromised blood supply (4%), and extussusception or prolapse of the afferent limb (1%). These complications occasionally presented more than 10 years after construction of the reservoir and were clinically silent until the patient developed bilateral hydronephrosis or even renal failure. The technical difficulty of the intussuscepted nipple valve and the associated complications, along with the development of effective alternative antireflux techniques, has made the Kock afferent intussuscepted nipple valve a technique primarily of historic interest today.

Studer Ileal Bladder

This ileal bladder substitute initially described by Studer and colleagues (1989) uses a long, afferent, isoperistaltic, tubular ileal segment. It is believed that the long segment functionally prevents vesicoureteral reflux when the patient voids by Valsalva maneuver (Studer et al, 1989). It is straightforward to construct and has become the most popular form of orthotopic diversion in the United States. The advantages of this bladder substitute include the simplicity of construction, no requirement for surgical staples, and the ability to accommodate short ureters. The reservoir portion uses the double-folded U configuration originally described by Kock (1989). Studer's group reported on 480 of these procedures performed from 1985 through 2005 with excellent long-term results in terms of continence, preservation of renal function, and less than 3% ureteroileal stricture rate (Studer et al, 2006). The original description used a 20-cm afferent segment, with 40 cm used for the reservoir. In more recent years Studer has advocated using a somewhat shorter afferent ileal segment, with similar results (Studer et al, 2006).

A portion of terminal ileum 54 to 56 cm long is isolated approximately 25 cm proximal to the ileocecal valve. Bowel continuity is restored, and the ends of the isolated segment are closed with a running absorbable suture. The distal 40- to 44-cm segment of ileum is placed in a U shape and opened along the antimesenteric border. The ureters are spatulated and anastomosed in an end-to-side fashion to the proximal 14- to 16-cm afferent tubular portion of ileum. The two medial borders of the U-shaped ileum are then oversewn with a running absorbable suture. The bottom of the U is folded over between the two ends of the U. After the lower half of the anterior wall and part of the upper half are closed, a finger is introduced through the remaining reservoir opening to determine the most caudal part of the neobladder. A hole is cut out in this dependent portion of ileum, away from the suture line, which allows urethral anastomosis. The urethral anastomosis is performed, and the remaining portion of the reservoir is then closed (Fig. 87–5).

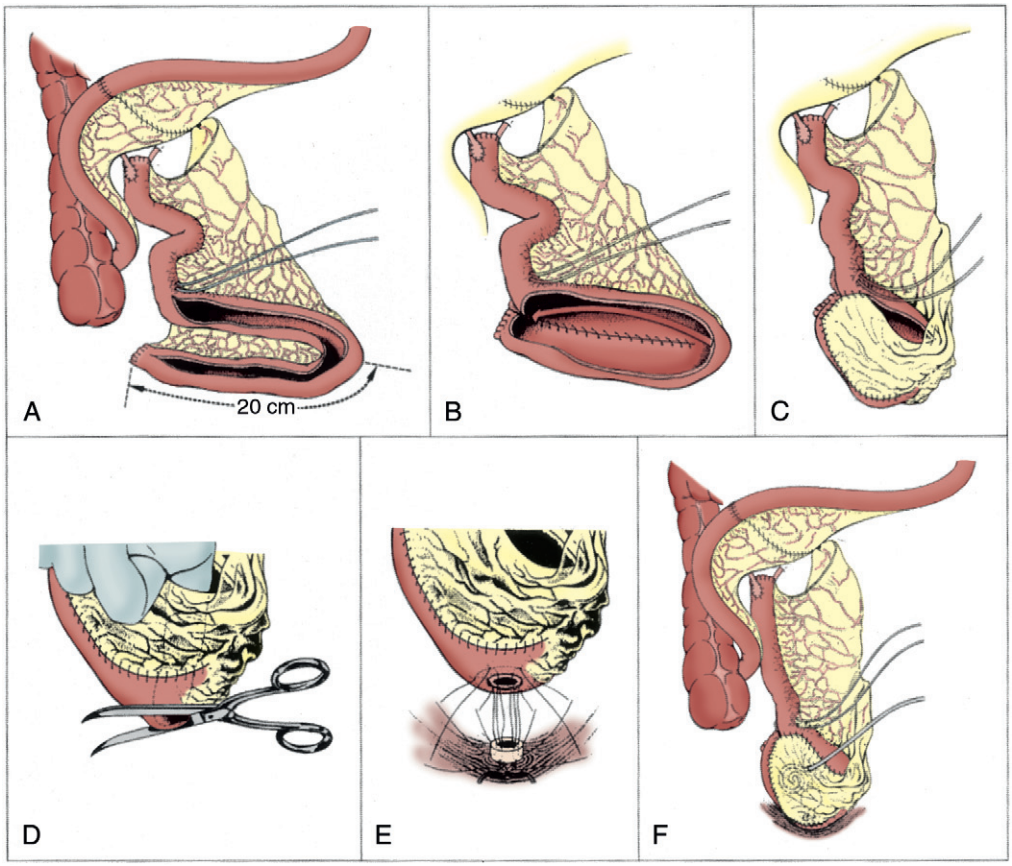


Figure 87–5. Construction of Studer pouch ileal neobladder with an isoperistaltic afferent ileal limb. **A,** A 60- to 65-cm distal ileal segment is isolated, and the distal 40 to 45 cm are folded into a U configuration. It is opened on the antimesenteric border while the more proximal 20 to 25 cm of ileum remain intact (afferent limb). **B,** The posterior wall of the reservoir is closed with a continuous running suture. The ureteroileal anastomoses are performed in a standard end-to-side technique to the proximal portion (afferent limb) of the ileum. Ureteral stents are used and brought out anteriorly through separate stab wounds. **C,** The reservoir is folded and oversewn (anterior wall). **D,** Before complete closure, a buttonhole opening is made in the most dependent (caudal) portion of the reservoir. **E,** The urethral anastomosis is performed. **F,** A cystostomy tube is placed, and the reservoir is closed completely.

Serous-Lined Extramural Tunnel

On the basis of experimental studies, Abol-Enein and Ghoneim demonstrated that an effective reflux mechanism could be made by bringing the ureters into a reservoir through extramural serous-lined tunnels. The authors believed that the construction of an extramural serous-lined tunnel provides several advantages. Metallic staples or synthetic materials are not required. The serous-lined tunnel protects the implanted portion of the ureter from exposure to urine so that sound healing without scarring is ensured. Moreover, a relatively short segment of bowel is used, and the procedure is versatile and not technically difficult (Abol-Enein and Ghoneim, 1993, 1994). The authors updated their excellent results in 450 patients with this technique and demonstrated that the serous-lined extramural tunnel is an effective and durable antireflux technique, with more than 93% of patients with unidirectional, unobstructed urinary flow (Abol-Enein and Ghoneim, 2001).

A 40-cm ileal segment is isolated from the distal ileum and arranged in a W configuration. The antimesenteric border of the isolated intestine is opened, and the edges of the medial flaps are joined with a running absorbable suture. On either side, the two lateral flaps are joined by a seromuscular continuous suture of silk (3-0). This forms two serous-lined intestinal troughs. Each ureter is laid down in its corresponding trough. A mucosa-to-mucosa anastomosis is performed with the spatulated ureter and the intestinal mucosa at the distal end of the trough. The mucosal edges on each side are then approximated over the reimplanted ureter. The anterior wall of the pouch is then closed in a side-to-side fashion. The suture line of the most dependent portion of the pouch close to the urethral stump is reopened to make a hole that will be anastomosed to the urethra (Fig. 87–6).

Good results with this technique have been reported by others (Papadopoulos and Jacobsen, 2001). A modification of this orthotopic substitute with a serous-lined extramural ureteral reimplantation technique has also been reported by Kato and colleagues (2001) with similar results. The primary disadvantage of this technique is the requirement for long ureteral length, inability to accommodate dilated ureters, and a possibly increased risk of ureteral strictures.

T Pouch Ileal Neobladder

In an effort to preserve an antireflux mechanism but avoid the potential long-term complications seen with the Kock nipple valve, as well as allow for more flexibility in managing the ureters, Stein and Skinner developed the T pouch as a modification of Ghoneim and Abol-Enein's ureteral serous-lined tunnel and updated their results with intermediate follow-up of 209 patients (Abol-Enein and Ghoneim, 1994; Stein et al, 2004). The evolution of this technique is detailed elsewhere (Stein et al, 2005).

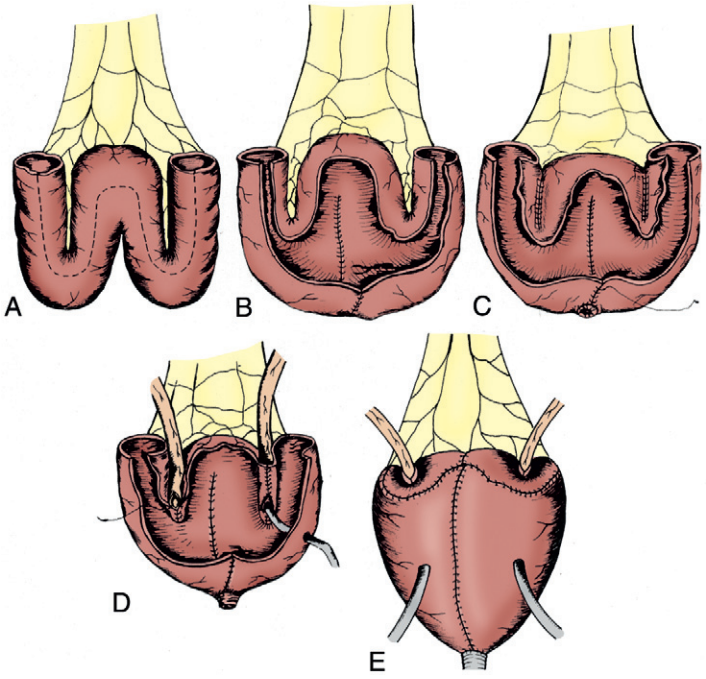


Figure 87–6. Construction of the serous-lined, extramural ileal neobladder (Ghoneim). **A,** A 40-cm segment of ileum is isolated and fashioned into a W configuration. **B,** The ileum is opened along the antimesenteric border for the entire length. **C,** The incised mucosa is joined in the middle with a running suture. The two lateral ileal flaps are joined by a seromuscular continuous suture to make the backing for the serous-lined ureteral tunnels. **D,** The spatulated ureters are laid into each trough, anastomosed to the intestinal mucosa, and stented. The tunnel is then closed over the implanted ureter. **E,** The anterior wall of the reservoir is formed by folding the ileum side to side. The reservoir is then anastomosed to the urethra.

The orthotopic T pouch uses the Kock double-folded U configuration. The afferent antireflux mechanism uses a short segment of ileum, which is fixed in an extraserosal tunnel that functions as a flap valve. If necessary, the afferent limb may be made longer to accommodate short ureters. It has the advantage of a classic Leadbetter ureteroileal anastomosis with its low ureteral stricture rate, and the antireflux mechanism functions regardless of the degree of dilation of the ureters. Maintenance of the vascular arcades of the distal afferent limb preserves the blood supply and should reduce the risk of late stenosis.

The T pouch is constructed from 44 cm of distal ileum placed in a U configuration; a proximal 8- to 10-cm segment of ileum is used to form the afferent antireflux mechanism. If ureteral length is short or compromised, a longer afferent ileal segment may be used. The ileum is divided between the proximal afferent ileal segment and the reservoir segment. The proximal end of the isolated afferent ileal segment is closed with a running absorbable suture. Both ends of the reservoir portion are also closed with absorbable suture.

Windows in the mesentery adjacent to the bowel wall at the distal end of the afferent segment are made ("windows of Deaver"), and the places held with small pieces of Penrose drain. A series of 3-0 silk sutures are then used to approximate the serosa of the two adjacent 22-cm ileal segments at the base of the U, with the sutures passed through the previously opened windows of Deaver. Two or three individual stitches are placed in each window to secure the tunnel. This process is repeated through each individual window until the distal 3 to 4 cm of the afferent segment are permanently fixed in the serous-lined ileal trough (Fig. 87–7).

Initial descriptions of the T pouch included tapering the distal portion of the afferent segment after it had been fixed into the tunnel to decrease its diameter and decrease the risk of reflux. However, these efforts appeared to be associated with occasional late stenosis of the end of the afferent valve. In 2004 the authors stopped tapering the distal afferent limb and have not observed any increase in reflux, but they have seen a decrease in stenosis. Therefore the authors no longer recommend tapering the afferent limb.

The reservoir portions are then opened along the medial mesentery, swinging wide on either side of the fixed afferent segment to construct flaps to close over the top of that segment. The suture lines are all closed with running absorbable suture. The flaps are brought over the top of the afferent limb, and it is matured into the reservoir. Finally, the pouch is folded in the opposite direction and that suture line closed, leaving a fingerbreadth opening at the far right corner for the urethral anastomosis. The ureters are anastomosed to the afferent limb in a direct end-to-side fashion, and the urethral anstomosis is performed last.

Colon and Iliocolonic Pouches

Orthotopic neobladders constructed completely of colon are a good option for patients with multiple previous small bowel resections or who have diseased ileum. Colon segments are less distensible than ileal segments and may be more likely to produce higher pressure waves causing incontinence (Khafagy et al, 2006). As a consequence initial volume should be larger than for an ileal pouch. Combined colon and ileal segments can mitigate this risk.

Orthotopic Mainz Pouch (Mainz III)

The Mainz ("mixed augmented ileum and zecum") pouch was initially described as a continent catheterizable reservoir that was subsequently modified into an orthotopic neobladder (Thuroff et al, 1986; Eisenberger et al, 1999). A 10- to 15-cm segment of cecum, in continuity with a 20- to 30-cm segment of ileum, is isolated. An ascending ileocolostomy is performed. The entire segment of bowel is opened along the antimesenteric border, sacrificing the ileocecal valve. The bowel is placed in a W configuration, with the first limb of the W represented by cecum and the middle two limbs represented by ileum. The adjacent three limbs are sutured together with an absorbable suture, forming the posterior plate of the reservoir.

At the cephalad portion of the cecum, tunneled ureterocolonic anastomosis is performed. A buttonhole incision is made in the cecum at the base of the reservoir, and a ureterocolonic anastomosis is performed. After this, the reservoir is closed side to side with absorbable suture (Fig. 87–8).

Ileocolonic (Le Bag) Pouch

The Le Bag ileocolonic bladder substitute was initially described by Light and Engelmann (1986). A 20-cm segment of ascending colon and a corresponding length of terminal ileum are isolated, and bowel continuity is restored. The antimesenteric border is incised for the entire length of the colon and ileum to make two flat sheets (one small and one large bowel). These sheets are then sewn to one another to form the posterior plate. Initially, in the early experience with this neobladder, the incision in the small bowel commenced 2 inches from the cut end so that this intact tube of ileum could be anastomosed end to end to the urethra. This technique was subsequently modified because the small

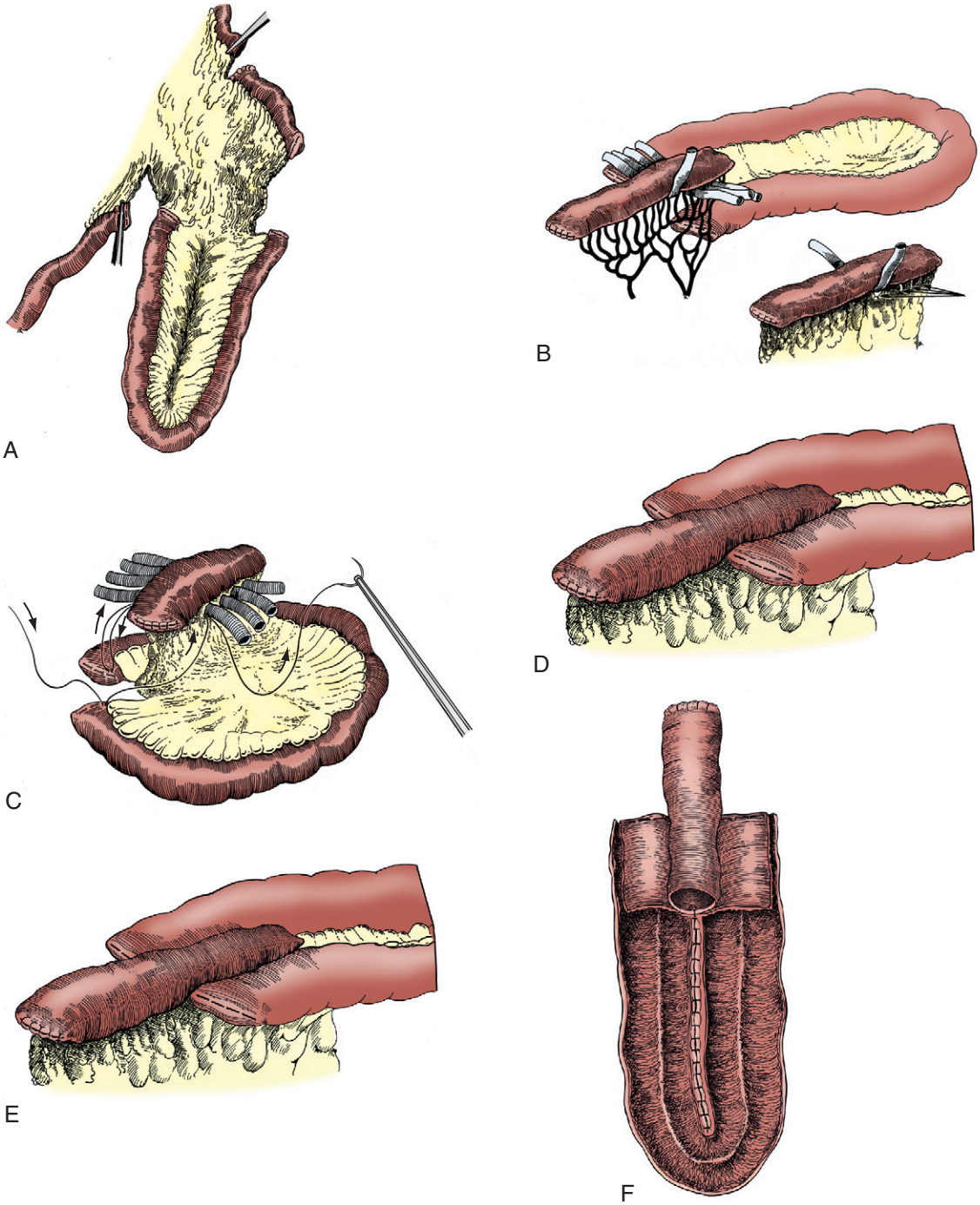


Figure 87–7. Construction of the T pouch orthotopic ileal neobladder. **A,** A total of 62 to 64 cm of distal ileum is isolated. The proximal 8- to 10-cm section is separated from the rest, and the two ends of the 44-cm segment are closed. The long segment is folded in a U shape. **B,** The antireflux mechanism is constructed. Windows in the mesentery of the distal 3 to 4 cm of the short segment are opened just outside of the bowel wall ("windows of Deaver") and held in place with short pieces of small Penrose drains in each window. Note that the blood supply remains intact to this afferent ileal segment. **C,** A series of interrupted silk sutures are used to bring together the serosa of the adjacent 22-cm limbs (cephalad portion) through these windows. Then three to four silk sutures are placed through each window to make a secure backing for the extraserosal tunnel. **D,** the anchored afferent limb in place. **E,** The ileal segments are opened along the medial mesentery. Once the incision reaches the level of the ostium of the afferent limb, it swings wide to create two flaps to close over the top of the anchored afferent limb. **F,** The incised ileal mucosa is oversewn with absorbable running suture.

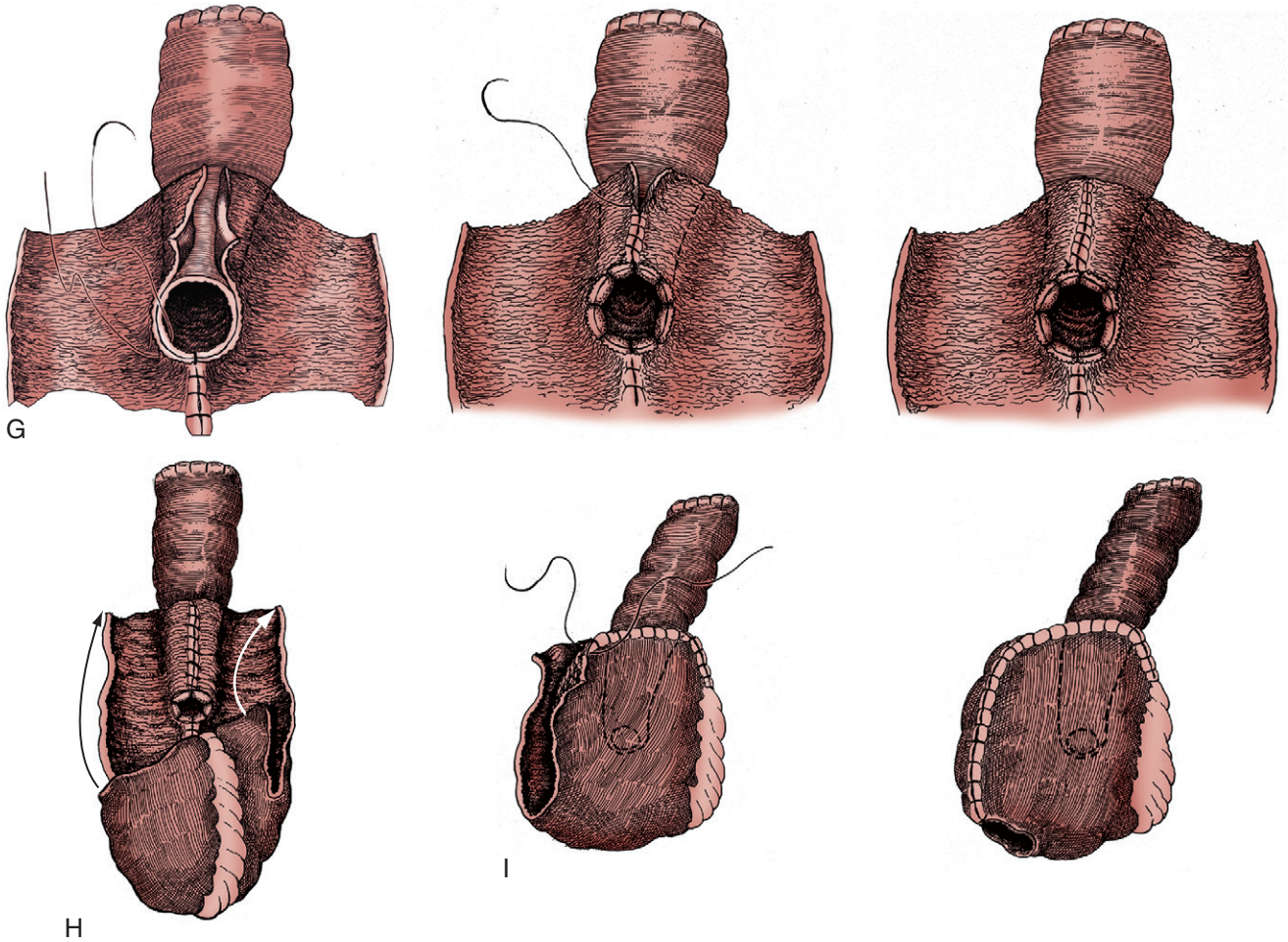


Figure 87–7, cont'd. **G,** The ostium of the afferent segment is sutured to the ileal flaps. The ileal flaps are then brought over and oversewn to cover the tapered afferent ileal segment. This completes the posterior wall of the reservoir and forms the antireflux flap-valve mechanism. **H,** The reservoir is folded in the opposite direction from which it was opened. The ureteral anastomoses are performed in an end-to-side Leadbetter fashion to the afferent limb. **I,** The suture line is left open to accommodate one fingerbreadth on the far right corner for the urethral anastomosis. This becomes the most dependent portion of the reservoir when it is positioned in the pelvis. The urethral anastomosis is the last step of the pouch.

peristaltic ileal segment (intact) was thought to promote urinary incontinence. After this, the entire length of small bowel was incised (Light and Marks, 1990; Kolettis et al, 1996), and the urethra was anastomosed, end to side, to the cecum. The ureters are then brought into the colonic segment and implanted within the reservoir, and the neobladder is closed anteriorly (Fig. 87–9).

A modified version of the Le Bag ileocolonic neobladder has been reported by Baniel and Tal in which a Studer-like ileal chimney is incorporated as the afferent limb (Baniel and Tal, 2004).

Right Colon Pouch

An orthotopic substitute employing the right colon without ileum has been reported (Goldwasser et al, 1986; Mansson and Colleen, 1990; Goldwasser, 1995; Mansson et al, 2003). The entire right colon and cecum are isolated, and a transverse ileocolonic anastomosis is performed to provide bowel continuity. The ileal stump at the ileocecal valve is closed with a running absorbable suture. The colonic segment is then opened along the anterior tenia, leaving the proximal 2 to 3 inches of cecum intact. An appendectomy is performed, and the ureters are implanted in an antireflux fashion within the reservoir. The colon is then folded in a Heineke-Mikulicz manner and closed with a running absorbable suture. The ureterocolonic anastomosis is then performed.

Sigmoid Pouch

Patients who are candidates for radical cystectomy often have a redundant sigmoid colon, which is readily available for use. The only concern is the potential compromise of the vasculature of the distal colon segment due to interruption of branches of the internal iliac artery during the cystectomy. It is important therefore to maintain as much of the vascular supply to both ends of the bowel anastomosis as possible. Some patients will complain of frequent stools or rectal urgency for a period of time after sigmoid colectomy.

The use of the sigmoid in construction of an orthotopic substitute was initially described by Reddy and Lange (1987) (Fig. 87–10). A 35-cm portion of descending colon and sigmoid is isolated and arranged in a U configuration on the basis of the inferior mesenteric artery. The medial taenia of the U is incised down to an area just short of the urethral anastomosis. The incised medial limbs of the U are then brought together with an absorbable suture. Ureteral implantation is performed in a tunnel antireflux fashion. A small button of colon is removed from the most

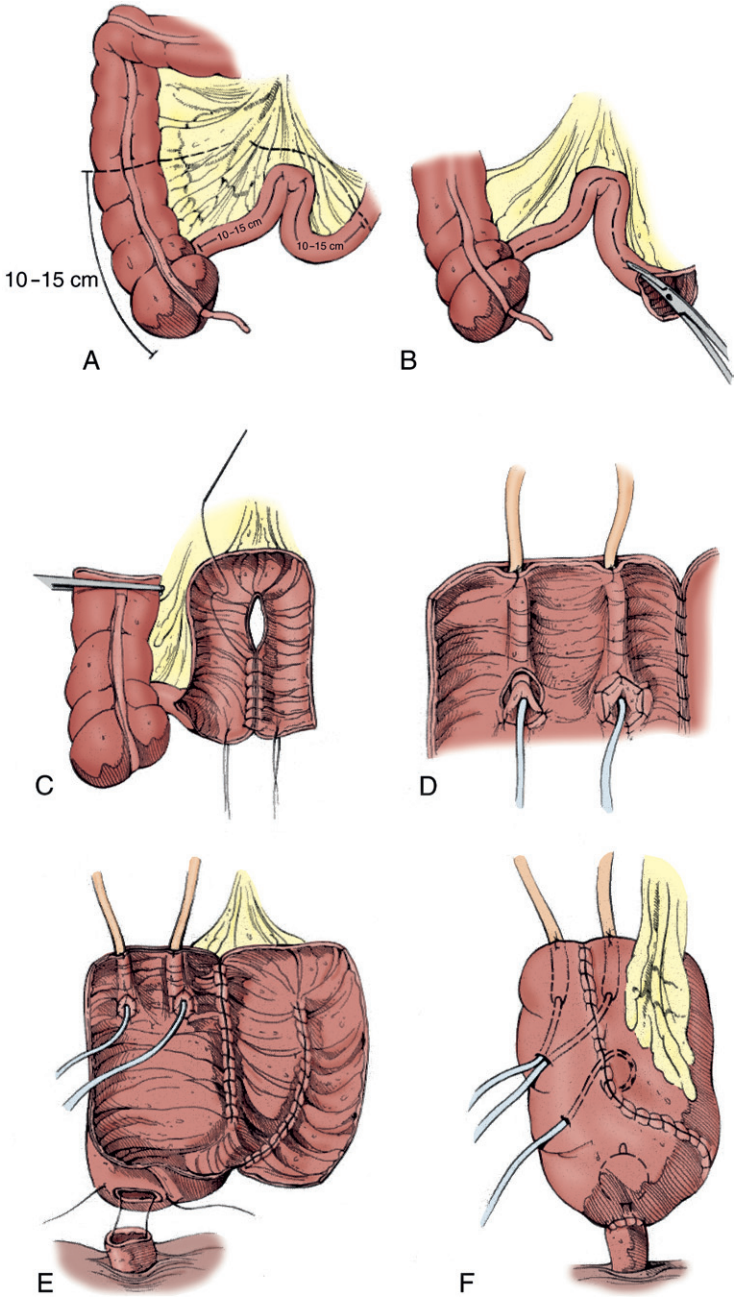


Figure 87–8. Construction of the Mainz ileocolonic orthotopic reservoir. **A,** An isolated 10 to 15 cm of cecum in continuity with 20 to 30 cm of ileum are isolated. **B,** The entire bowel segment is opened along the antimesenteric border. An appendectomy is performed. **C,** The posterior reservoir is closed by joining the opposing three limbs together with a continuous running suture. **D,** An antireflux implantation of the ureters through a submucosal tunnel is performed and stented. **E,** A buttonhole incision in the dependent portion of the cecum is made to provide for the urethral anastomosis. **F,** The reservoir is closed side to side with a cystostomy tube and the stents exiting.

dependent portion of the reservoir, and the urethroenteric anastomosis is performed. The reservoir is then closed side to side.

A modification of this technique was reported by DaPozzo and colleagues in which the entire bowel is detubularized and then folded in a Heineke-Mikulicz fashion to provide a more spherical reservoir (DaPozzo et al, 1994).

Adaptation of Orthotopic Diversion to Minimally Invasive Techniques

Over the past 10 years a number of innovators have begun to perform cystectomy using laparoscopic or robotic-assisted techniques (Gill et al, 2002; Stephenson and Gill, 2008; Huang et al, 2008; Pruthi and Wallen, 2008; Wang et al, 2008; Yuh et al, 2008). Initial attempts to perform the diversion completely intracorporeally were fraught with difficulty and were gradually abandoned by most groups. Currently most reports describe completing the cystectomy and lymph node dissection with the laparoscopic or robotic techniques, then delivering the bowel through a small incision to construct the diversion extracorporeally (Haber et al, 2008). This has allowed construction of continent diversions, both cutaneous and orthotopic. Ileal neobladders using the Studer technique have been the most popular because of ease of mobilization of the segment and simpler bowel anastomosis with a low abdominal incision. In the case of orthotopic neobladders, some authors then reestablish the pneumoperitoneum and use robotic assistance to complete the urethral anastomosis. Others perform the anastomosis in an open fashion (Pruthi and Wallen, 2008).

Although most reports to date contain relatively few patients and relatively short follow-up, there are a few groups with extensive experience and oncologic results

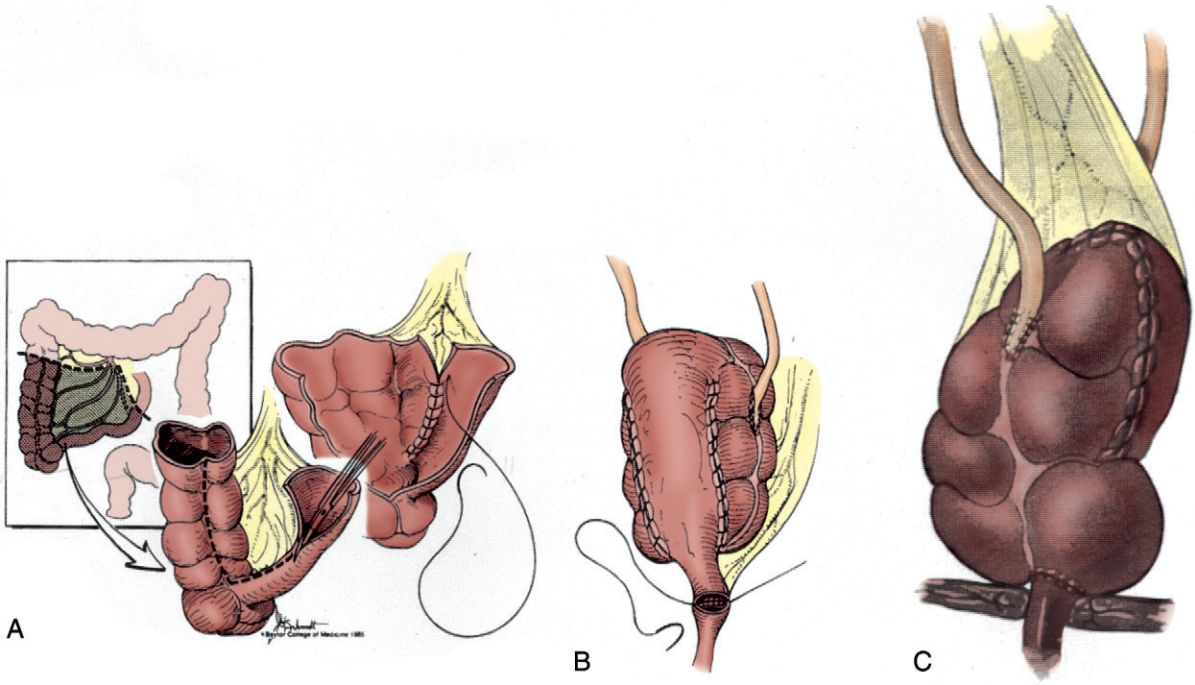


Figure 87–9. Construction of Le Bag (ileocolonic) orthotopic reservoir. **A,** A total of 20 cm of ascending cecum and colon, with a corresponding length of adjacent terminal ileum, is isolated. The bowel is opened along the entire antimesenteric border, and the two incised segments are then sewn to one another. This forms the posterior plate of the reservoir. **B,** This reservoir is folded and rotated 180 degrees into the pelvis with the most proximal portion of the ileum (2 cm nondetubularized) anastomosed to the urethra. **C,** Modification is performed with complete detubularization of the bowel segment, which is then anastomosed to the urethra. (© Baylor College of Medicine.)

to date appear to be comparable to open surgical approaches (Haber et al, 2008, Guillotreau et al, 2009). **Postoperative complications and length of stay in most series have only been modestly decreased, with longer operative times but decreased blood loss and in some cases reduced ileus and shorter hospital stay.** These techniques continue to evolve and may ultimately be applied more widely. **As with other cancer surgeries, it is mandatory that the oncologic efficacy of the operation not be compromised in the use of minimally invasive techniques. Most importantly in treating invasive bladder cancer, the surgeon must attempt to achieve negative surgical margins and there are clear oncologic advantages to a more extensive lymphadenectomy** (Skinner et al, 2007).

RESULTS AND COMPLICATIONS OF ORTHOTOPIC NEOBLADDERS

Continence

In evaluating the continence results and clinical outcomes of various series of cystectomy and orthotopic neobladders, several considerations must be kept in mind. The prevalence and severity of urinary incontinence may be confounded by many variables including age and gender of the patients, surgical indications, prior treatments (such as radiation or prior transurethral resection of the prostate), and technique of urinary diversion. In addition, the definitions of incontinence, the techniques used to collect the information (i.e., chart review, telephone interview, or anonymous validated questionnaire), and the length and diligence of follow-up are all crucial when trying to compare results from different reported series (Thuroff et al, 1996) (Table 87–1).

Common observations from nearly all series of patients undergoing orthotopic diversion include a gradual period of improvement in daytime continence over the first 6 to 12 months and a higher incidence of persistent nighttime incontinence seen in 20% to 50% of patients. In a pooled analysis of 2238 patients with various forms of orthotopic neobladder, daytime incontinence was reported in an average of 13% of patients. Risk factors in this study for daytime incontinence included advanced age of the patient (older than 65 years), use of colonic segments, and in some series lack of nerve-sparing techniques (Steers, 2000).

Kessler and colleagues (2004) assessed various factors influencing urinary continence after radical cystectomy and ileal orthotopic bladder substitution in 331 male patients. In a multivariate analysis, the time to achieve daytime continence and the ultimate rate of success were significantly higher in patients younger than 65 and in those with attempted nerve-sparing techniques (Kessler et al, 2004). These findings strengthen the relationship of nerve-sparing techniques and continence in these cystectomy patients with an orthotopic substitute. It is the authors' conviction that in patients with bulkier tumors (>T2), especially on the posterior bladder, trigone, or bladder neck, and in most patients older than age 70, that the advantage of nerve-sparing techniques is outweighed by a potential increased risk of incomplete tumor excision. Positive surgical margins in this disease are almost always ultimately fatal, so appropriate selection of patients for nerve-sparing is crucial.

Nighttime incontinence remains one of the most bothersome sequelae of neobladders, seen in 7% to 70% of patients with an average of 28% (Steers, 2000). Nocturnal incontinence after orthotopic reconstruction results in part from the absence of neurologic feedback and sphincter detrusor reflex, as well as decreased sphincter tonus at night. Similar to daytime incontinence, nighttime incontinence generally improves as functional capacity increases

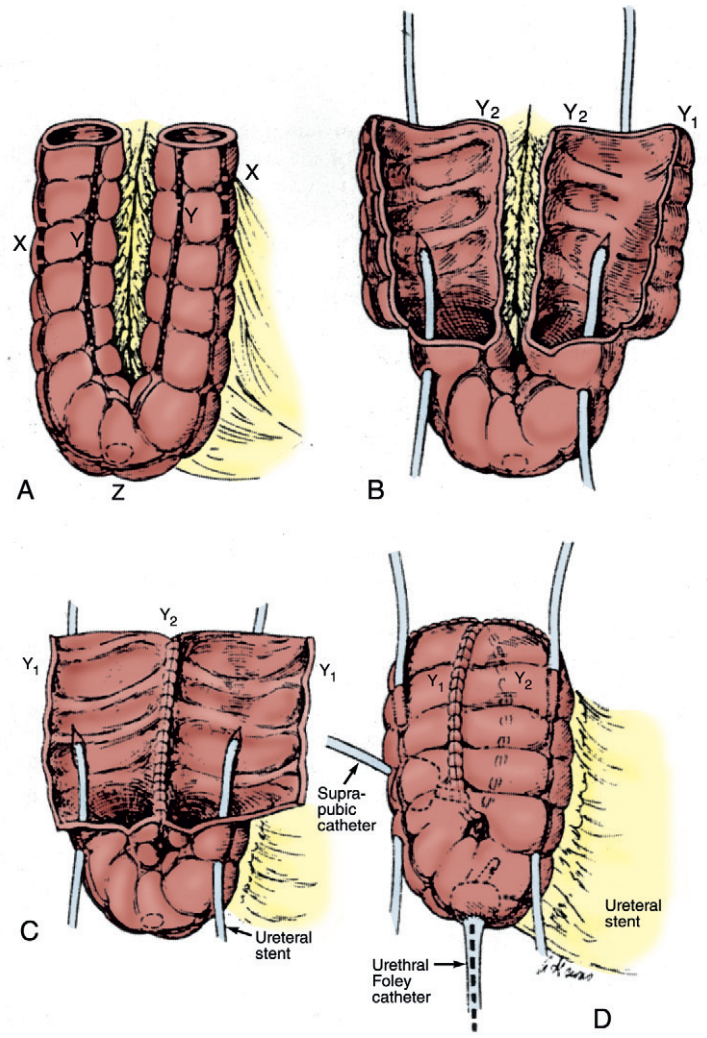


Figure 87–10. Construction of the sigmoid (Reddy) neobladder. **A,** A 35-cm segment of descending and sigmoid colon is isolated and folded into a U shape. **B,** The colon is incised along the medial tenia down to a point a few centimeters short of the entire colon. A buttonhole is made in the caudal portion of the colon that is later anastomosed to the urethra. **C,** The medial portions of the U are sewn together, and a tunneled ureterocolonic anastomosis is performed. **D,** The colonic pouch is closed by folding the reservoir side to side, and it is anastomosed to the urethra.

and as the absorptive capacity of the mucosa decreases over time (El Bahnasawy et al, 2000). The latter results in a reversal of the normal antiduiretic effect of nighttime dehydration. In elderly patients there is also a physiologic diuresis associated with increasing age. Instructing the patient to completely empty immediately before bedtime and to awaken two or three times with the assistance of an alarm clock may help reduce some of the issues of nighttime incontinence. The authors and others have observed that nighttime incontinence may improve as late as 24 months after surgery (Elmajian et al, 1996; Granberg et al, 2008).

Decreased urethral sensitivity has been proposed as a potential factor contributing to urinary incontinence after radical cystectomy and orthotopic diversion. It has been suggested that conscious or unconscious sensation of urine leakage in the membranous urethra may normally produce either a reflex or voluntary contraction with increased tone of the external urethra (Kessler et al, 2007). This may be impaired in some patients with an orthotopic diversion. This reflex may also diminish with age and contribute to gradually decreasing continence in some individuals after orthotopic reconstruction (Hugonnet et al, 1999; Madersbacher et al, 2002). To some degree this worsening continence with age might be offset by the lack of problems related to prostatic enlargement, detrusor hypertrophy, and overactive bladder, all of which are common in elderly patients.

The evaluation and management of urinary incontinence after orthotopic diversion should be delayed until the neobladder has had time to enlarge. This may take 6 months to a year after surgery (Grossfeld, 1996; Granberg et al, 2008). Physical therapy with biofeedback focused on the pelvic floor muscles may help some patients attain initial continence (Parekh et al, 2003). Urodynamic investigation may be indicated to ensure adequate capacity, without pressure waves. If reduction in maximal urethral closure or low Valsalva leak pressure is demonstrated, transurethral injection of bulking agents may be considered but it has had only marginal results in the authors' experience. Alternatively, in men an artificial urinary sphincter can be considered and may provide a more definitive treatment. In women, although injection of urethral bulking agents provides a minimally invasive approach with some positive results (Tchetgen et al, 2000), it is best employed for women with minimal symptoms of incontinence, with overall success rates below 50% and with less than optimal durable responses (Wilson et al, 2004). Pubovaginal sling procedures for incontinence may be more effective in women with incontinence after orthotopic reconstruction (Quek et al, 2004). Female patients undergoing a sling, however, must be informed of the high likelihood of urinary retention and the need to perform intermittent catheterization. Importantly, one should avoid blind passage of needles or sling material into the pelvis in these patients because of a high risk of injury to the pouch or a loop of bowel stuck to the pubic symphysis. Use of infrapubic bone anchors or a prepubic approach may provide the safest surgical options (Quek et al, 2004).

Urinary Retention

Failure to empty or urinary retention has been reported in 4% to 25% of patients undergoing orthotopic reconstruction and is more common in women than in men (Steers, 2000; Nagele et al, 2006). Stein and colleagues (2004) reported that 25% of 209 patients with an orthotopic T pouch required at least occasional intermittent catheterization (20% of men and 43% of women).

Patients with incomplete emptying may present with acute retention but more often present with recurrent infections or the new onset of overflow incontinence. They may also be discovered on routine follow-up with a palpable suprapubic mass or distended reservoir on imaging. The development of retention is often a late event, so the reported rates are heavily influenced by the length of follow-up of the series. Risk factors for urinary retention in patients with an orthotopic reservoir include the use of excessive intestinal length for the reservoir (>60 cm of ileum) and the use of prostate-sparing or nerve-sparing surgical procedures (Steers, 2000; Steven and Poulsen, 2000; Stein et al, 2004). Some authors have suggested that the location of the urethral anastomosis in the neobladder may contribute to retention in men (Thurairaja and Studer, 2008), but the chapter authors' experience using the end of the suture line for the anastomosis has resulted in a low incidence of retention (Elmajian et al, 1996; Stein et al, 2004).

Rectal or vaginal examination and cystoscopy should be performed in patients who develop retention to rule out a urethral

Table 87–1.

Results with Orthotopic Diversion

Author	Type of Reservoir	No. of Patients	Follow-up (mo)	Mean Age (yr)	Mortality (%)	Complications*		Continence		IC(%)†	Antireflux Mechanism
						Early (%)	Late (%)	Day (%)	Night (%)		
Barre et al (1996)	Camey II, ileum	110	32	62	1	—	—	93	74	1	Le Duc
Elmajian et al (1996)	Kock, ileum	295	42	66	1	7	12	87	86	8	Nipple valve
Steven and Poulsen (2000)	Kock, ileum	166	32	62	0	12	23	98	80	32	Nipple valve
Hautmann (1999)	W, ileum	363	57	63	3	15	23	96	95	6	Le Duc
Hollowell et al (2000)	W, ileum	50	20	62	2	10	20	93	86	4	Isoperistaltic "chimney"
Stein et al (2004)	T pouch, ileum	209	33	69	1.4	5	14	87	72	25	T limb mechanism
Studer et al (1996a)	Studer, ileum	200	30	64	2	—	—	90	80	0.5	Isoperistaltic limb
Cancrini et al (1996)	Studer, ileum	96	28	60	6	6	24	98	83	—	Isoperistaltic limb
Thuroff et al (1986)	Mainz, ileocecal	61	46	—	—	5	18	95	86	13	Submucosal tunnel
Kolettis et al (1996)	Ileocecal (Le Bag)	38	14	61	0	8	8	91	80	3	Le Duc and Bricker
Abol-Enein and Ghoneim (2001)	Serous-lined extramural, ileum	450	38	47	0.8	9	8	93	80	2	Serous-lined extramural ureter
Mansson and Colleen (1990)	Right colon	67	70	61	3	4	29	—	—	37	Le Duc
Laguna et al (2005)	Sigmoid	49	38	63	0	—	55	89	10	0	Submucosal tunnel
Granberg et al (2008)	Studer, ileum	59‡	29	62	0	22	5	90	57	35	Isoperistaltic limb
Ali-el-Dein et al (2008)	Ileum, serous lined extramural tunnel	192‡	51	54	2	16	35	92	72	16	Serous-lined extramural ureter

*Complications reported related to urinary diversion.
†Some form of intermittent catheterization to empty neobladder.
‡Females only.

anastomotic stricture or tumor recurrence. Urinary retention is best managed by intermittent self-catheterization (Steers, 2000). Pharmacologic intervention for patients with urinary retention does not appear to be an effective measure to improve this voiding dysfunction. Biofeedback training in pelvic floor relaxation may be helpful, and some authors have suggested that many of these patients have a flap of mucosa causing the obstruction that may be incised endoscopically with good effect (Thurairaja and Studer, 2008). Others have not found this to be a common cause of retention (Simon et al, 2006). Patients should be advised during the first few years of follow-up of the importance of adequate emptying and the need to consciously relax the external sphincter along with using Valsalva pressure during voiding.

A significant number of patients with orthotopic reservoirs will develop abdominal wall or incisional hernias postoperatively. These fascial defects will reduce the efficiency in completely evacuating the neobladder by reducing the ability to effectively increase intra-abdominal pressure. These hernias should be identified and surgically repaired.

In women it appears that posterior prolapse of the pouch may contribute to late retention, and posterior support by means of omental flaps and sacroculpopexy has been advocated (Ali-el-Dein et al, 2002; Stenzl and Höltl, 2003; Lee et al, 2004; Stein and Skinner, 2004). Ali-el-Dein and colleagues elegantly studied the possible causes of chronic retention after radical cystectomy and orthotopic bladder substitution in women. A total of 136 women underwent a standard radical cystectomy and orthotopic substitution, with 100 patients evaluable at a mean follow-up of 36 months. Overall, 95% of the women were continent in the day, 86% were continent at night, 2% were completely incontinent, and 16% were in chronic retention. Video-urodynamics showed that retention appeared to be mechanical in nature due to the pouch's falling back in the wide pelvic cavity, resulting in acute angulation of the posterior pouch-urethral junction. In addition, herniation of the pouch wall through the prolapsed vaginal stump was observed in most cases. Pelvic floor electromyography demonstrated complete pelvic floor silence during voiding, suggesting that urinary retention was not related to a neurogenic cause. The authors suggested that omental packing behind the reservoir, suturing of the peritoneum on the rectal wall to the vaginal stump, suspension of the vaginal stump by the preserved round ligaments, and suspension of the pouch near the dome to the back of the rectus muscle at cystectomy will help reduce the incidence of chronic retention (Ali-El-Dein et al, 2002). The proposed technical modifications to increase back support of the pouch with ventral suspension near its dome and support of the vaginal stump should help reduce the incidence of urinary retention in these patients.

Key Points: Continence and Urinary Retention

- Daytime continence develops gradually over 3 to 6 months in most patients and is ultimately achieved in 80% to 90% of both male and female patients.
- Persistent nocturnal incontinence is common, observed in 20% to 50% of patients. Nocturnal continence may continue to improve beyond 12 months from surgery.
- Factors influencing continence rates include age, intestinal segment used, and possibly the application of a nerve-sparing technique.
- Failure to empty or urinary retention has been reported in 4% to 25% of patients and tends to be more common in females.

Complications of Orthotopic Diversion

Complications of radical cystectomy and diversion are common, and many are severe and potentially life threatening (Konety et al, 2006; Quek et al, 2006; Ali El Dein et al, 2008). Most early complications include bleeding, thrombotic events, infection, and cardiovascular and pulmonary complications are not directly related to the urinary diversion and do not appear to be different in patients undergoing different types of diversion. Gastrointestinal complications are also common after cystectomy and are at least partially related to the need for a bowel anastomosis, which is common to all types of diversion. Similarly, urine leak and ureteral complications are possible with any type of diversion (Jensen et al, 2006). The overall rates of diversion-related early and late complications reported in some recent published series of patients undergoing orthotopic diversion are listed in Table 87–2. **A number of authors have shown that the overall rate of complications, hospital stay, and reoperation rates are not increased by using continent diversion compared with ileal conduit diversion** (Benson et al, 1992; Gburek et al, 1998; Parekh et al, 2000a).

Urine leaks may be more common in continent diversion than in conduits because of the long suture lines, but with properly managed stents and drains these generally resolve with observation alone. **If a patient has an undrained leak, an attempt at percutaneous drainage and/or bilateral nephrostomy tube placement is preferable to open surgical repair.** The latter is extremely difficult during the first few weeks after the initial surgery and is likely to be complicated by enterotomies and a risk of fistula formation. In the authors' experience approximately 5% of patients require some sort of percutaneous drain or nephrostomy tube placement during the early postoperative period to manage these problems.

Late complications, however, are often influenced by the type of urinary diversion. Complications may also be influenced by other factors including tumor recurrence and the use of adjuvant

Table 87–2.

Suggested Follow-up Protocol for Bladder Cancer Patients following Cystectomy and Orthotopic Diversion

Every 4 Months First Year, Then Every 6 Months to 3 Years, Then Annually
Physical examination including pelvic/rectal examination
Blood chemistries and complete blood count
Annual Visits Only
Voided urine cytology
Urethral wash (if carcinoma in situ on pathology)
Vitamin B_{12} level
Prostate-specific antigen (if prostate cancer on pathology)
Imaging Depending on Cystectomy Pathology
>pT2 or N+: computed tomography abdomen and pelvis with intravenous contrast and chest radiograph each visit
≤pT2: computed tomography or intravenous urography and chest radiograph at 4 and 12 months, then annually to 5 years, then every 2 years thereafter (may replace with ultrasound after 3 years)

or salvage systemic chemotherapy or radiation, and these causes may be difficult to separate out from causes related to the surgery. Complications not directly related to the diversion include late bowel obstruction, ventral hernia, late thrombotic events, and cardiovascular problems common to patients in this age group. **The primary late complications of orthotopic diversion that may be related to the diversion itself include urinary tract infection, ureteroileal or afferent limb obstruction, urethral stricture, upper tract and pouch stones, and incontinence. Most of these complications can be managed by endoscopic procedures and rarely require open surgical revision** (Jensen et al, 2006). This is in contradistinction to cutaneous continent diversion, in which open revision is often required for stomal problems such as difficulty catheterizing or leakage (Rowland, 1995).

Pouch perforation is rare in continent diversion in general, especially in orthotopic diversion because outlet resistance is usually low. The risk may be increased in patients who have had previous radiation therapy. It is a potentially life-threatening complication when it occurs. The authors have seen at least two deaths due to pouch perforation of an orthotopic diversion that was unrecognized when our patients were admitted to an outside hospital. Patients generally present with acute abdominal pain and distention, often with signs of sepsis. Computed tomography (CT) cystogram is usually diagnostic. These patients should be generally managed with exploration and repair, though conservative management with percutaneous drains has been described (Mansson et al, 1997; Singh and Choon, 2004).

Obstruction from an antireflux valve has been seen in both hemi-Kock pouches and in the extraserosal tunneled afferent limb of the T pouch (Stein et al, 1996, 2004). **These may be clinically silent until the patient presents with bilateral hydronephrosis or even renal failure. Diagnosis may be suspected on CT or ultrasound and can be confirmed on retrograde pyelography.** In both types of diversion these may be managed by endoscopic incision of the valve mechanism. It can be technically challenging to find the afferent limb in some cases, and special techniques may be necessary to catheterize and incise it (Dunn et al, 2007).

Pouch-vaginal fistula is a unique complication of orthotopic neobladder in women that can be quite difficult to resolve. The reported incidence in larger series is 5% to 10%, and the risk is increased if a portion of the anterior vaginal wall must be excised along with the cystectomy specimen and in irradiated patients (Al el Dein et al, 2008; Granberg et al, 2008). **Prevention methods are crucial including careful watertight closure of the vaginal cuff and placement of an omental flap** between the vagina and neobladder, tacked to the perivaginal tissue on either side of the urethral anastomosis (Stein and Skinner, 2006). In the early postoperative period any concern about vaginal urinary leakage should be evaluated with a lateral cystogram before removal of the catheter. Fistula should also be ruled out in any woman with persistent incontinence after the first few months of recovery.

Beyond the initial few weeks a pouch-vaginal fistula is unlikely to heal spontaneously or with urinary diversion with a catheter or percutaneous nephrostomy tubes alone. Repair may be attempted transvaginally, though reported success varies (Rapp et al, 2004; Smith, 2005; Al el Dein et al, 2008). Repair may ultimately require transabdominal exploration or even conversion to a cutanous form of diversion.

Follow-up for Patients with Orthotopic Diversion

There is no consensus on the ideal follow-up regimen for patients with orthotopic diversion. Imaging techniques include intravenous urography, CT, magnetic resonance imaging, and ultrasound. Physicians in the United States tend to depend more on radiographic imaging, whereas those in Europe often rely more on ultrasound evaluation. Regardless of the type of imaging, the follow-up regimen can be divided into three time segments:

- Early evaluation (first 4 months) to identify early ureteroileal anastomotic strictures due to technical difficulties or poorly vascularized distal ureters.
- Middle period (4 months to 5 years) primarily focused on detecting cancer recurrence. This is best managed with CT or other cross-sectional imaging, which also allows evaluation of the upper tracts and reservoir for stones or obstruction. The frequency of the follow-up can be risk-adapted according to the pathologic findings at the time of cystectomy and the risk of subsequent recurrence.
- Long-term follow-up (beyond 5 years) to detect pouch stones, late upper tract obstruction, and urothelial carcinoma arising in the urethra or upper tracts.

Our current follow-up scheme is shown in Table 87–2, but others have been described (Thurairaja and Studer, 2008). Positron emission tomography–CT imaging is a promising new tool for follow-up of higher-risk patients (Bouchelouche and Oehr, 2008). The authors routinely perform cytology on both voided urine and urethral wash in male patients, especially those with carcinoma in situ in their primary pathology. It does require a cytologist with experience looking at urine specimens from neobladder patients to be adept at evaluating them. Women can be evaluated with bimanual examination and voided cytology or a urethral swab processed as a thin prep smear.

Monitoring the retained urethra for all patients after radical cystectomy for bladder cancer is particularly important in patients undergoing an orthotopic form of urinary diversion. At a minimum, this should include annual voided cytology and full evaluation including urethroscopy in patients who develop symptoms related to the urethra or a change in voiding pattern or hematuria. Symptomatic patients with a urethral tumor recurrence usually present with bloody urethral discharge or gross hematuria but may also present with new-onset urinary retention or change in voiding pattern.

Clark and colleagues (2004) evaluated 47 men who developed urethral recurrence after cystectomy. Although this study was not specific for orthotopic diversion, the majority of patients were symptomatic on presentation for a urethral tumor recurrence. Among the 37 patients in whom urethral tumor recurrence was detected during the long-term follow-up period, cytologic screening alone diagnosed 13 of 37 patients (35%). Among the patients with cytology data available in this study, 94% had a positive cytology result. However, 4 of the 14 patients with an orthotopic neobladder who developed a urethral recurrence presented with a change in voiding habits, which in one case was the patient's only complaint (Clark et al, 2004). It is therefore important to consider a urethral recurrence in the differential diagnosis whenever a patient who has undergone lower urinary tract reconstruction with an orthotopic neobladder presents with any change in voiding habits.

Key Points: Complications from Orthotopic Neobladders and Recommended Follow-Up

- Early morbidity and mortality of cystectomy and orthotopic diversion are not increased compared with ileal conduit.
- Undrained urine leak is best managed using percutaneous drains and bilateral nephrostomy tubes when necessary. Early open surgical revision should be avoided.
- The majority of late urologic complications related to the neobladder can be managed using endoscopic techniques.
- Patients require regular follow-up imaging to identify upper tract obstruction and stones, which may be clinically silent.
- Follow-up should include rectal/pelvic examination and urethral cytology to identify urethral recurrence, which occurs in approximately 10% of males and rarely in females.

Quality of Life after Urinary Diversion

During the past decade, there has been an increasing focus on quality of life issues and outcomes in various urologic diseases. This has been aided by the development of new, health-related quality of life instruments for use specifically in urology. Health-related quality of life can be defined as a patient's evaluation of the impact of a health condition and its treatment on relevant aspects of his or her life. Quality of life issues are becoming increasingly important in selection of the type of urinary diversion and are likely to play a larger role in future management of patients undergoing lower urinary tract reconstruction after cystectomy. One of the perceived advantages of the various forms of continent urinary diversion (particularly orthotopic diversion) is a presumed improvement in quality of life compared with a conduit form of diversion. However, these more "complicated" forms of urinary diversion may have some disadvantages as well. Continent diversions are technically more challenging and time consuming. Postoperatively, patients leave the hospital with indwelling catheters and may have a longer convalescence. Once the catheters are removed, patients generally require a period of education in the techniques required to properly care for the reservoir or neobladder. In addition, patients with continent diversions may be at slightly higher risk for bowel dysfunction (diarrhea and vitamin B_{12} malabsorption).

A number of studies have been undertaken to try to measure the impact of cystectomy and diversion on quality of life and to try to measure differences between the various types of diversion. These studies have been limited by the fact that there has never been a randomized study of conduits compared with continent diversion. In addition, there are often major differences in the baseline characteristics of patients undergoing the different types of diversion, making it difficult to compare them. Patients with different diversion also experience different types of difficulties, and it is difficult to write a questionnaire that captures them all equally.

Initial studies by Boyd, Mansson, and their colleagues in the 1980s pioneered comparative evaluation regarding quality of life issues in patients with different forms of urinary diversion after cystectomy. Boyd and colleagues (1987) compared quality of life in patients with an ileal conduit and in patients with a continent cutaneous Kock ileal reservoir. They found that all patients surveyed in the study were generally satisfied with their diversion and adapted reasonably well socially, physically, and psychologically. The key to adaptation seemed to be a detailed and realistic preoperative education or discussion about the type of diversion. Patients with ileal conduit diversions, however, had the lowest expectations of the form of diversion, as defined by preoperative awareness of the need to wear an external ostomy appliance along with the associated inconveniences and changes in external body image. Postoperatively, ileal conduit patients also had the poorest self-images as defined by a decrease in sexual desire and in all forms of physical contact (sexual and nonsexual). Interestingly, a subset of patients who underwent conversion from conduit diversions to continent cutaneous pouches were statistically the most satisfied and the most physically and sexually active. Although not directly related to orthotopic diversion, this early study suggested that from a quality of life perspective, a continent diversion may provide an important alternative to noncontinent forms of urinary diversion (Boyd et al, 1987). Mansson and colleagues (1988) also evaluated quality of life issues in patients undergoing cystectomy and urinary diversion. They demonstrated that urinary diversion affects most aspects of life in all patients. Although problems related to the diversion procedure tend to be fewer in patients with continent cutaneous reservoirs than in patients with conduits, both forms of diversion could be associated with serious social, sexual, mental, and emotional problems (Mansson et al, 1988).

Hobisch and colleagues (2000) compared 69 patients with orthotopic diversion to 33 patients who underwent an ileal conduit using both standardized and institutionally developed questionnaires. Patients with the continent diversion were more likely to recommend the procedure to friends, more likely to describe themselves as feeling "completely safe" with their diversion (74.6% vs. 33.3%), and more likely to feel "not handicapped at all" (92.8% vs. 66.7%). However, the groups were not totally comparable. The ileal conduit patients were significantly older, more likely to be female and unmarried, and less likely to be working (Hobisch et al, 2000). All of these factors can affect quality of life.

These initial quality of life studies in patients with urinary diversion paved the way to evaluate and compare patients undergoing an orthotopic form of diversion. Bjerre and colleagues (1995) compared health-related quality of life in patients undergoing an orthotopic neobladder (38 patients) or an ileal conduit (29 patients) form of diversion. Despite higher daytime and nighttime urine leakage in the bladder substitute group, the urine leakage affected conduit patients more severely, and they scored higher on a leakage distress scale. The ileal conduit group was also found not to retain healthy body image as well as patients with a bladder substitute (Bjerre et al, 1995).

In one of the first studies to compare long-term quality of life outcomes, Hart and colleagues (1999) reported on a total of 224 participating patients who completed four self-reporting questionnaires including a profile of mood states and adapted versions of the sexual history form, body image dissatisfaction scale, and quality of life questionnaire. This study compared self-reports of emotional distress; global quality of life; sexuality; body image dissatisfaction; urinary diversion problems; and problems with social, physical, and functional activities. The diversions included an ileal conduit in 25, a cutaneous Kock pouch in 93, and an orthotopic neobladder in 103 patients. Men who had or had not received an inflatable penile prosthesis after cystectomy were also compared with regard to quality of life variables. Regardless of the form of urinary diversion, the majority of patients reported good overall quality of life, little emotional distress, and few problems with social, physical, or functional activities. Problems with urinary diversion and sexual function were identified as most

common. **After controlling for age, no significant differences in any quality of life area were found among the urinary diversion subgroups.** However, controlling for age in men indicated that penile prosthesis placement was significantly associated with better sexual function and satisfaction. Quality of life also appeared good in those patients who were long-term survivors of bladder cancer. The type of urinary diversion, at least in this study, did not appear to be associated with significant differences in quality of life. Furthermore, the authors suggested that the option of erectile aids in men after cystectomy should be considered (Hart et al, 1999).

Weijerman and colleagues (1998) compared quality of life issues in patients undergoing either an orthotopic or a cutaneous continent urinary diversion. Quality of life assessment in this study revealed only a minor advantage for an orthotopic placement. Importantly, quality of life assessment was found to be favorable for both types of urinary diversion (Weijerman et al, 1998). Similar results have been reported by others (Sullivan et al, 1998).

Most of the studies that evaluated and compared quality of life issues in patients undergoing various forms of urinary diversion have been criticized for methodologic problems that limit their conclusions (Gerharz et al, 2005; Gerharz, 2007). Most of the early studies were retrospective and failed to employ a well-validated measure of assessing quality of life that compared different groups. In one of the better studies, McGuire and colleagues (2000) used a well-validated survey to assess the impact of different forms of urinary diversion on overall quality of life in patients with locoregional bladder cancer after cystectomy. This study evaluated a total of 92 patients without evidence of disease recurrence who had undergone one of three different forms of urinary diversion. Patients completed a validated quality of life survey by mail. A total of 38 men with an orthotopic substitute had a mean physical score of 48.4 and a mean mental score of 51; 16 men and women with an Indiana pouch had a mean physical score of 48.4 and a mean mental score of 55.7. These results were not statistically different from published age-based and sex-based population norms. Thirty-eight men with an ileal conduit diversion had a mean physical score of 41.4 and a mean mental score of 48.2. The physical score was not statistically different from the population-based norm; however, the mental score was significantly decreased from the published norm. These authors concluded that patients with ileal conduits have significantly decreased mental health quality of life, whereas patients with continent urinary diversions do not. Furthermore, they suggested that when it is not medically contraindicated, patients should be offered a continent form of diversion after cystectomy. Although not specific for an orthotopic substitute, these data again provide further support for a continent form of urinary diversion (McGuire et al, 2000).

Hautmann and Paiss (1998) attempted to determine if the option of a neobladder substitute stimulates the decisions of patient and physician toward an earlier cystectomy in patients with bladder cancer. They reported on a total of 213 men undergoing cystectomy for bladder malignant neoplasm, 135 patients with an ileal neobladder and 78 with an ileal conduit diversion. The interval from the primary diagnosis was 11.8 months in the neobladder and 16.7 months in the conduit group. Five-year survival rate was significantly higher for all disease stages in the neobladder group than in the conduit group. The authors concluded that the availability of ileal neobladder may decrease the physician's reluctance to perform cystectomy early in the disease process, thus increasing the survival rate. They also implied that orthotopic urinary diversion positively influenced patients and physicians to choose radical surgery earlier in the course of disease (Hautmann and Paiss, 1998).

Critical analyses of the current quality of life literature suggest that there is not enough evidence to conclude that there is a clear quality of life advantage for patients undergoing continent diversion. Porter and Penson (2005) performed a systematic review to determine if any differences exist in health-related quality of life outcomes among different types of urinary diversion after radical cystectomy. They performed a detailed MEDLINE search of appropriate studies inclusive of the dates 1966 to January 2004. Inclusion criteria included adult patients, patients with bladder cancer, comparative studies, original research, primary study outcome related to quality of life, and use of a quality of life instrument to measure outcomes. Only studies comparing neobladder, continent reservoir, or conduit diversion were included. Of 378 initial articles, only 15 studies met all the inclusion criteria. None of the studies were randomized trials, and only one was prospective. Common limitations included unvalidated health-related quality of life outcomes instruments, use of general health-related quality of life outcomes instruments only, lack of baseline data, cross-sectional analysis, and retrospective study design. The authors found that the current body of published literature is insufficient for it to be concluded that any form of urinary diversion is superior to another on the basis of health-related quality of life outcomes (Porter and Penson, 2005). Gerharz came to similar conclusions (Gerharz et al, 2005; Gerharz, 2007).

Clearly, to better understand and evaluate these quality of life issues in patients undergoing various forms of urinary diversion, future studies in this area must incorporate prospective data collection, provide longer-term follow-up, and incorporate validated disease-specific health-related quality of life outcomes instruments.

In summary, although there are not clear data showing an overall quality of life advantage for patients undergoing neobladder reconstruction, in fact many patients will chose this option simply because it seems the most natural. Patients must, however, have realistic expectations about the risk of incontinence and the possible need for self-catheterization. However, the majority of patients who undergo continent orthotopic diversion are happy with the results and would recommend it to a friend who was having a cystectomy.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

Key Points: Quality of Life after Urinary Diversion

- Most quality of life studies that have evaluated and compared patients undergoing various forms of urinary diversion have been criticized for methodologic problems that limit their conclusions.
- The current body of published literature is insufficient to conclude that any form of urinary diversion is superior to another on the basis of health-related quality of life outcomes.

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The complete reference list is available online at www.expertconsult.com.

chapter 88

Genital and Lower Urinary Tract Trauma

Allen F. Morey, MD, FACS ● Daniel D. Dugi III, MD

Injuries of the External Genitalia
Bladder Injuries
Urethral Injuries

INJURIES OF THE EXTERNAL GENITALIA

Penis

Traumatic injuries to the genitalia are uncommon, in part because of the mobility of the penis and scrotum. Blunt phallic traumatic injury is usually of concern only with an erect penis, when fracture of the tunica albuginea may result. In general, prompt surgical reconstruction of most penile injuries usually leads to adequate and acceptable cosmetic and functional results.

Fracture

Etiology. Penile fracture is the disruption of the tunica albuginea with rupture of the corpus cavernosum. Fracture typically occurs during vigorous sexual intercourse, when the rigid penis slips out of the vagina and strikes the perineum or pubic bone, producing a buckling injury.

The tunica albuginea is a bilaminar structure (inner circular, outer longitudinal) composed of collagen and elastin. The outer layer determines the strength and thickness of the tunica, which varies in different locations along the shaft and is thinnest ventrolaterally (Hsu et al, 1994; Brock et al, 1997). The tensile strength of the tunica albuginea is remarkable, resisting rupture until intracavernous pressures rise to more than 1500 mm Hg (Bitsch et al, 1990). When the erect penis bends abnormally, the abrupt increase in intracavernosal pressure exceeds the tensile strength of the tunica albuginea, and a transverse laceration of the proximal shaft usually results.

Whereas penile fracture has been reported most commonly with sexual intercourse, it has also been described with masturbation, rolling over or falling onto the erect penis, and myriad other scenarios. In the Middle East, self-inflicted fractures predominate; the erect penis is forcibly bent during masturbation or as a means to achieve rapid detumescence, the practice of *taghaandan* (Zargooshi, 2000).

Mydlo (2001) reported that 94% of fractures in Philadelphia, Pennsylvania, were a result of sexual intercourse; Zargooshi (2000) described 69% of fractures in Kermanshah, Iran, as being due to self-manipulation. The tunical tear is usually transverse and 1 to 2 cm in length (Asgari et al, 1996; Mydlo, 2001). The injury is usually unilateral, although tears in both corporeal bodies have been reported (Mydlo, 2001; El-Taher et al, 2004). **Although the site of rupture can occur anywhere along the penile shaft, most fractures are distal to the suspensory ligament. Injuries associated with coitus are usually ventral or lateral** (Mydlo, 2001; Lee et al, 2007), **where the tunica albuginea is the thinnest** (Hsu et al, 1994).

Diagnosis and Imaging. **The diagnosis of penile fracture is often straightforward and can be made reliably by history and physical examination.** Patients usually describe a cracking or popping sound as the tunica tears, followed by pain, rapid detumescence, and discoloration and swelling of the penile shaft. If the Buck fascia remains intact, the penile hematoma remains contained between the skin and tunica, resulting in a typical eggplant deformity. If the Buck fascia is disrupted, hematoma can extend to the scrotum, perineum, and suprapubic regions (Fig. 88–1 on the Expert Consult website). The swollen, ecchymotic phallus often deviates to the side opposite the tunical tear because of hematoma and mass effect. The fracture line in the tunica albuginea may be palpable. Because fear and embarrassment are commonly associated, the patient's presentation to the emergency department or clinic is sometimes significantly delayed.

The incidence of urethral injury is significantly higher in the United States and Europe (20%) than in Asia, the Middle East, and the Mediterranean region (3%), probably owing to the different etiology—intercourse trauma versus self-inflicted injury (Eke, 2002; Zargooshi, 2002; Jack et al, 2004; Derouiche et al, 2008). Most urethral injuries are associated with gross hematuria, blood at the meatus (Fig. 88–2), or inability to void, although the absence of these findings does not definitively rule out urethral injury (Tsang and Demby, 1992; Mydlo, 2001; Jack et al, 2004). **Given that urethral injury occurs not infrequently, preoperative urethrography should be considered when urethral injury is suspected. However, because urethrography can be time consuming and inaccurate** (Kamdar et al, 2008), **intraoperative flexible cystoscopy is now performed routinely just before catheter placement at the time of penile exploration when urethral injury is suspected.**

The typical history and clinical presentation of fractured penis usually make adjunctive imaging studies unnecessary. Although cavernosography has been advocated to assist in diagnosis, false-negative studies have been reported (Mydlo, 2001); false-positive studies can result from inadequate filling of one corporeal body and misinterpretation of complex venous drainage (Pliskow and Ohme, 1979; Beysel et al, 2002). **Cavernosography is discouraged in the evaluation of a**

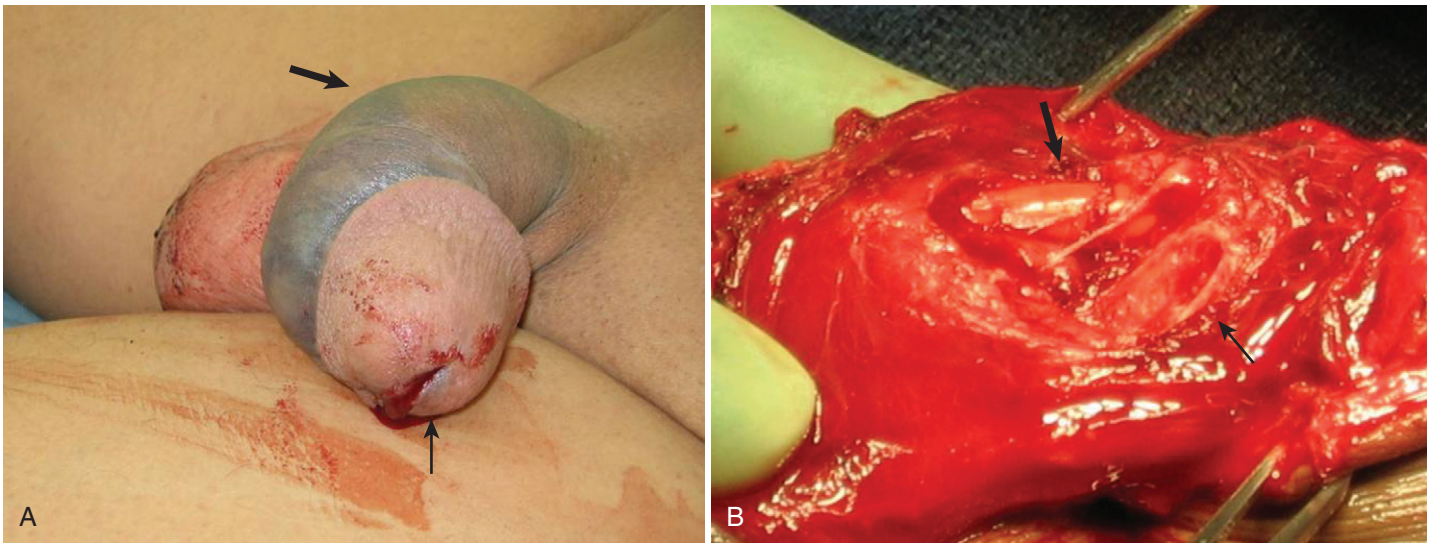


Figure 88–2. **A,** *Large arrow* indicates pronounced ecchymosis and swelling in this patient with a penile fracture sustained during intercourse. *Small arrow* indicates blood at urethral meatus. **B,** During surgical exploration and repair, urethral laceration with exposed Foley catheter is noted *(large arrow)*. *Small arrow* indicates laceration of corpus cavernosum.

suspected penile fracture because it is time consuming and unfamiliar to most urologists and radiologists (Morey et al, 2004). Ultrasonography, although noninvasive and easy to perform, has also been associated with significant false-negative studies (Koga et al, 1993; Fedel et al, 1996).

Magnetic resonance imaging (MRI) is a noninvasive and accurate means of demonstrating disruption of the tunica albuginea (Fedel et al, 1996; Uder et al, 2002). Arguments against the routine use of MRI are the expense, limited availability, and time requirements involved with the study. **MRI is reasonable in the evaluation of patients without the typical presentation and physical findings of penile fracture.**

False fracture has been reported in patients who present with penile swelling and ecchymosis, and some even describe the classic "snap-pop" or rapid detumescence typically associated with fracture (Feki et al, 2007). Physical examination may not be adequate for definitive diagnosis of a corporeal tear in these circumstances (Shah et al, 2003). Surgical exploration (Fig. 88–3 on the Expert Consult website) or evaluation with MRI should be considered. Another condition that may mimic penile fracture is rupture of the dorsal penile artery or vein during sexual intercourse (Armenakas et al, 2001; Bar-Yosef et al, 2007).

Management. **Multiple contemporary publications indicate that suspected penile fractures should be promptly explored and surgically repaired. Although small lateral incisions may be used for localized hematomas or palpable tunical defects** (El Bahnasawy and Gomha, 2000; Nasser and Mostafa, 2008), **a distal circumcising incision is appropriate in most cases, thus providing exposure to all three penile compartments. Closure of the tunical defect with interrupted 2-0 or 3-0 absorbable sutures is recommended; deep corporeal vascular ligation or excessive debridement of the delicate underlying erectile tissue must be avoided.** Induction of an artificial erection with saline or colored dye may aid in locating the corporeal laceration (Shaeer, 2006). Partial urethral injuries should be oversewn with fine absorbable suture over a urethral catheter. Complete urethral injuries should be debrided, mobilized, and repaired in a tension-free fashion over a catheter. Therapy with broad-spectrum antibiotics and 1 month of sexual abstinence are recommended. In uncircumcised patients, strong consideration should be given to performing limited circumcision at the conclusion of the repair because wide mobilization of the foreskin may place the distal prepuce at risk for ischemia.

Outcome and Complications. Immediate surgical reconstruction results in faster recovery, decreased morbidity, lower complication rates, and lower incidence of long-term penile curvature (Nicolaisen et al, 1983; Orvis and McAninch, 1989; Hinev, 2002; El-Taher et al, 2004; Muentener et al, 2004). Although immediate repair results in penile curvature in less than 5% of patients (El Atat et al, 2008), conservative management of penile fracture has been associated with penile curvature in more than 10% of patients, abscess or debilitating plaques in 25% to 30%, and significantly longer hospitalization times and recovery (Meares, 1971; Nicolaisen et al, 1983; Kalash and Young, 1984; Orvis and McAninch, 1989). Zargooshi (2002) reported in a personal surgical series of 170 patients that surgical management of penile fractures resulted in erectile function comparable to that of a control population. Timing of surgery may also influence long-term success—those undergoing repair within 8 hours of injury had significantly better long-term results than did those having surgery delayed 36 hours after the fracture occurred (Asgari et al, 1996; Karadeniz et al, 1996).

Gunshot and Penetrating Injuries

Gunshot Wounds. The majority of penetrating wounds to the genitalia are due to gunshots (Mohr et al, 2003), and most require surgical exploration. **Treatment principles include immediate exploration, copious irrigation, excision of foreign matter, antibiotic prophylaxis, and surgical closure.** Gunshot injuries to the phallus are rarely isolated wounds—nearly all victims have significant associated injuries, including abdominal, pelvic, lower extremity, vascular, or additional genitourinary injuries (Bandi and Santucci, 2004; Kunkle et al, 2008). Excellent cosmetic and functional outcomes can be expected with immediate reconstruction (Gomez et al, 1993; Cavalcanti et al, 2006). An artificial erection may be induced to ensure penile straightness,

and plication techniques may be used to correct any curvature resulting from closure of a large corporeal injury (Kunkle et al, 2008).

Urethral injuries have been reported in 15% to 50% of penile gunshot wounds (Miles et al, 1990; Goldman et al, 1996; Mohr et al, 2003). **Retrograde urethrography should be strongly considered in any patient with penetrating injury to the penis, especially with high-velocity missile injuries, blood at the meatus, or difficulty voiding and when the trajectory of the bullet was near the urethra** (Goldman et al, 1996; Mohr et al, 2003; Bandi and Santucci, 2004, Phonsombat et al, 2008). Alternatively, intraoperative retrograde urethral injection of methylene blue or indigo carmine may identify the site of injury and the adequacy of closure. If a catheter has already been placed, pericatheter injection may help to ascertain urethral integrity.

Urethral injuries due to penetrating trauma should be closed primarily by use of standard urethroplasty principles whenever possible—excellent results have been reported (Miles et al, 1990; Bandi and Santucci, 2004). Patients with urethral injury and extensive tissue damage from high-velocity weapons or close-range shotgun blasts may require staged repair and suprapubic urinary diversion (Bandi and Santucci, 2004), especially those located in the penile urethra (Cavalcanti et al, 2006).

Animal and Human Bites. The morbidity of animal bites is directly related to the severity of the initial wound. Most victims are boys, and dog bites are the most common injury (Gomes et al, 2001; Van der Horst et al, 2004). Infectious complications are unusual because treatment is sought early. **Initial management of dog bites includes copious irrigation, debridement, and immediate primary closure along with prophylactic use of broad-spectrum antibiotic** (Cummings and Boullier, 2000). Tetanus and rabies immunizations should be used as appropriate. Because of the risk of polymicrobial infection and the antimicrobial susceptibilities of typical organisms, recommended empiric antimicrobial therapy choices include beta lactam antibiotic with a beta lactamase inhibitor (i.e., amoxicillin-clavulinic acid); a second-generation cephalosporin with anaerobic efficacy (i.e., cefoxitin, cefotetan); or clindamycin with a fluoroquinolone (Talan et al, 1999).

Human bites produce contaminated wounds that often should not be closed primarily. Most human bite victims seek medical attention after a substantial delay and thus are more likely to present with gross infection. Empirical antibiotic administration is warranted with amoxicillin/clavulanic acid or moxifloxacin (Talan et al, 2003).

Amputation

Traumatic amputation of the penis, although rare, is usually the result of genital self-mutilation. Sixty-five to 87 percent of patients performing genital self-mutilation are psychotic (Greilsheimer and Groves, 1979; Aboseif et al, 1993; Romilly and Isaac, 1996). Psychiatric consultation should be sought in all such cases.

Reconstruction of the urethra and reanastomosis of the corporeal bodies with microsurgical repair of dorsal penile vessels and nerves achieves remarkably good results. Patients should be transferred to a facility with microsurgical capabilities; however, if this is unavailable, macroscopic anastomosis of the urethra and corporeal bodies can be performed with good erectile results, albeit with potential compromise of sensation and skin loss. Every attempt should be made to locate, clean, and preserve the severed portion in a "double bag" technique. The distal penis should be rinsed in saline solution, wrapped in saline-soaked gauze, and sealed in a sterile plastic bag. The bag should then be placed into an outer bag with ice or slush (Jezior et al, 2001). **Hypothermic injury to the amputated segment can occur if it is in direct contact with ice for a prolonged period.** Successful reimplantation is possible after 16 hours of cold ischemia time or 6 hours of warm ischemia (Lowe et al, 1991). If the severed part is not available, the penile stump should be formalized by closing the corpora and spatulating the urethral neomeatus, similar to a partial penectomy procedure for malignant disease.

Microvascular reconstruction of the dorsal arteries, vein, and nerves is the preferred method of repair for the amputated penis. Adequate erectile function is possible with both microvascular reanastomosis and macroscopic replantation, with more than 50% of men able to achieve erection with either technique (Bhanganada et al, 1983; Lowe et al, 1991; Aboseif et al, 1993). However, **complications such as urethral strictures, skin loss, and sensory abnormalities are all less common with microvascular repair** (Jezior et al, 2001).

Normal penile sensation returns in 0% to 10% of patients after macroscopic replantation (Bhanganada et al, 1983; Lowe et al, 1991), whereas sensation is present in more than 80% of microscopic replantations (Jordan and Gilbert, 1989; Lowe et al, 1991; Jezior et al, 2001). Penile skin necrosis, sometimes complete, is often a troublesome problem, although less common with microsurgical repair. This is because the blood supply of the skin is independent of the corporeal bodies and because without repair of the superficial vascular structures the penile skin is essentially a free graft (Jezior et al, 2001) Split-thickness skin grafts are applied when the native skin becomes necrotic (Ozturk et al, 2009). An alternative strategy is to denude the phallus of all skin and bury it in the scrotum, leaving the glans exposed, followed by separation of the structures after 2 months (Bhanganada et al, 1983; Jordan and Gilbert, 1989). Adjuvant techniques after penile replant include the use of hyperbaric oxygen to promote healing (Landström et al, 2004; Zhong et al, 2007) or medical leeches on the penis after macroreplantation to augment venous outflow and decrease edema (Mineo et al, 2004).

Key Points: Step-by-Step Approach to Penile Reattachment

- Suprapubic cystostomy
- Two-layer urethral closure over a catheter with 5-0 absorbable suture
- Minimal dissection along the neurovascular bundle to identify severed vessels and nerves
- Closure of the tunica albuginea with 3-0 absorbable suture
- Microscopic anastomosis of the dorsal artery with 11-0 nylon
- Microscopic dorsal vein repair with 9-0 nylon
- Microscopic epineural repair of dorsal nerve with 10-0 nylon
- Skin coverage

Zipper Injuries

Zipper injuries to the penis usually happen more often to impatient boys or intoxicated adults. Multiple maneuvers are available

to free the entrapped skin and to remove the mechanism. After a penile block the zipper slider and adjacent skin can be lubricated with mineral oil, followed by a single attempt to unzip and untangle the skin (Kanegaye and Schonfeld, 1993; Mydlo, 2000). The cloth material connected to the zipper can be incised with perpendicular cuts in between each zipper tooth to release the lateral support of the zipper, allowing the device to fall apart and release the trapped skin (Oosterlinck, 1981). A bone cutter or similar tool can be used to cut the median bar (diamond-shaped connection) of the slider. This maneuver allows separation of the upper and lower shields of the slider, and the entire zipper falls apart (Flowerdew et al, 1977; Saraf and Rabinowitz, 1982). Some children may require more than local anesthesia or sedation; circumcision or an elliptical skin excision can be performed in the operating room under anesthesia (Yip et al, 1989; Mydlo, 2000).

Strangulation Injuries

Accidental injuries with thread, hair, or rubber bands occur in children, but child abuse must be considered in such cases. Any child with unexplained penile swelling, erythema, or difficulty voiding should be examined closely for a hidden strangulating hair or string. Adults may place objects around the shaft as a means of sexual pleasure or to prolong an erection. The constricting device can reduce blood flow, cause edema, and induce ischemia; gangrene and urethral injury may develop in delayed presentations. Emergent treatment requires decompression of the constricted penis to allow blood flow and micturition. Depending on the constricting device, significant resourcefulness may be required of the physician.

String, hair, and rubber bands can be incised. Initial attempts to remove a solid constricting device causing penile strangulation involve lubrication of the shaft and foreign body and attempted direct removal. Edema distal to the strangulation often makes removal difficult. A string or latex tourniquet can be wrapped around the distal shaft to decrease swelling and to improve the odds of removing the device with lubrication. If the constricting object cannot be severed or removed, a string technique should be considered (Browning and Reed, 1969; Vahasarja et al, 1993; Noh et al, 2004). A thick silk suture or umbilical tape is passed proximally under the strangulation object and wound tightly around the penis distally toward the glans. The tag of suture or tape proximal to the ring is grasped; unwinding from the proximal end will push the object distally. Glanular puncture with a needle or blade will allow escape of dark trapped blood and improve the odds of removing the object with the string method (Browning and Reed, 1969; Noh et al, 2004).

Plastic constricting devices can be incised with a scalpel or an oscillating cast saw (Pannek and Martin, 2003), but metal objects present a more difficult challenge. Readily available hospital equipment (ring cutters, bolt cutters, dental drills, commercially available rotary tools, orthopedic and neurosurgical operative drills) may not be adequate to cut through heavy iron or steel items. The use of industrial drills, steel saws, hacksaws, saber saws, and high-speed electric drills has been reported (Perabo et al, 2002; Santucci et al, 2004). On occasion, fire department and emergency medical services equipment may be required to cut through iron and steel rings. The phallus should be protected from thermal injury, sparks, and the cutting blade by use of tongue depressors, sponges, or malleable retractors; continuous saline irrigation may be used for cooling. Such elaborate undertakings are best accomplished in the operating room under anesthesia. If decompression is delayed and the patient is distended and unable to void, a suprapubic bladder catheter should be placed. Outcomes are generally good with device removal alone, although the surgeon should be prepared to consider reconstructive techniques such as skin grafting if the strangulation injury causes skin necrosis (Ivanovski et al, 2007).

Testis

Etiology. Although the testis is relatively protected by the mobility of the scrotum, reflexive cremasteric muscle contraction, and its tough fibrous tunica albuginea, blunt injury (usually the result of assault, sports-related events, and motor vehicle accidents) can result in rupture of the tunica albuginea, contusion, hematoma, dislocation, or torsion of the testis. Testicular injury results from blunt trauma in about 75% of cases (McAninch et al, 1984; Cass and Luxenberg, 1991), whereas penetrating injuries due to firearms, explosions, or impalement make up the remainder.

Whereas only 1.5% of blunt testis injury involves both gonads, about 30% of penetrating scrotal trauma results in bilateral injury (Cass and Luxenberg, 1988, 1991). Like penetrating urethral injuries, penetrating scrotal trauma (roughly 80%) usually involves neighboring structures, including the thigh, penis, perineum, bladder, urethra, and/or femoral vessels (Gomez et al, 1993; Cline et al, 1998). In contemporary military conflicts, genital wounds account for a larger percentage of urologic injuries because of the powerful explosive weapons involved and absence of protective body armor over the genitalia (Thompson et al, 1998). Blast injuries are typically associated with extensive scrotal skin loss, multiple projectile injuries of both testes, and concomitant extensive destruction of the lower extremities and abdomen.

Diagnosis. Rupture of the testis must be considered in all cases of blunt scrotal trauma. Most patients complain of exquisite scrotal pain and nausea. **Swelling and ecchymosis are variable, and the degree of hematoma may not correlate with the severity of testicular injury; absence does not entirely rule out testicular rupture, and contusion without fracture can present as significant bleeding.** Scrotal hemorrhage and hematocele along with tenderness to palpation often limit a complete physical examination. Concomitant urethral injury should be suspected and evaluated when examination reveals blood at the meatus or if the mechanism of injury or hematuria suggests this possibility. Penetrating injuries mandate careful examination of surrounding structures, especially the femoral vessels.

Ultrasonography can be helpful to assess the integrity and vascularity of the testis in equivocal cases. Ultrasonography is rapid, readily available, and noninvasive. Because it may be operator dependent, false-positive and false-negative studies range from 56% to 94% (Fournier et al, 1989; Corrales et al, 1993; Herbener, 1996; Dreitlein et al, 2001). **Ultrasound findings suggestive of testicular fracture include a heterogeneous echo pattern of the testicular parenchyma and disruption of the tunica albuginea** (Micallef et al, 2001; Buckley and McAninch, 2006) (Fig. 88–4). **Although ultrasonography may assist in detection of testicular fracture or hematoma** (Guichard et al, 2008), **a normal or equivocal ultrasound study should not delay surgical exploration when physical examination findings suggest testicular damage; definitive diagnosis is often made in the operating room.** Although MRI may effectively demonstrate testicular integrity, its widespread use is not the norm because of expense, limited availability, and potential delay in definitive surgical care of the patient (Serra et al, 1998; Muglia et al, 2002; Kim et al, 2009).

Differential diagnosis of testicular fracture includes hematocele without rupture, torsion of the testis or an appendage, reactive hydrocele, hematoma of the epididymis or spermatic cord, and intratesticular hematoma. A nonpalpable testis in a trauma patient should raise the possibility of dislocation outside the scrotum. This entity usually occurs after motorcycle crashes when extreme forces on the scrotum expel the testis into surrounding tissues such as the superficial inguinal pouch (50%) or to a pubic, penile, pelvic, abdominal, or perineal location (Schwartz and Faerber, 1994; Bromberg, 2003). Bilateral dislocation after trauma has been reported (Bromberg et al, 2003; O'Brien et al, 2004). Manual or surgical reduction of the displaced testis is indicated. Finally, approximately 5% of spermatic cord torsions are believed to be precipitated by trauma; torsion should be considered in all cases of significant scrotal pain without signs or symptoms of major scrotal trauma (Elsaharty et al, 1984; Manson, 1989; Lrhorfi et al, 2002).

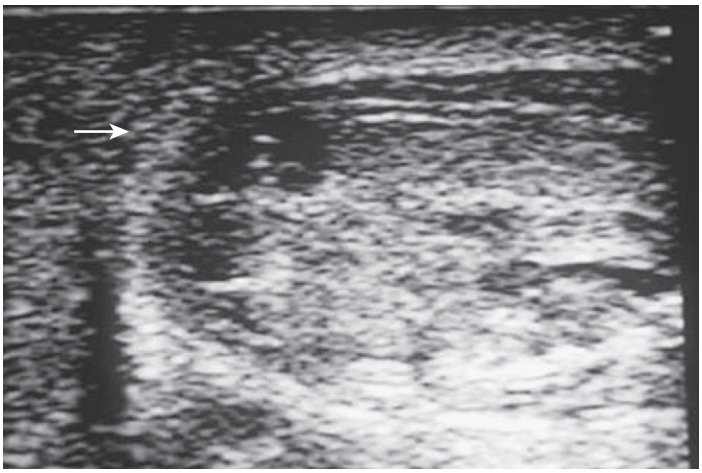


Figure 88–4. Ultrasound examination demonstrates hypoechoic intratesticular areas *(arrow)* consistent with testicular rupture sustained by blunt trauma. Scrotal exploration revealed large hematocele and exposed seminiferous tubules.

Management. **Early exploration and repair of testicular injury is associated with increased testicular salvage, reduced convalescence and disability, faster return to normal activities, and preservation of fertility and hormonal function** (Kukadia et al, 1996). Minor scrotal injuries without testicular damage can be managed with ice, elevation, analgesics, and irrigation and closure in some circumstances.

The objectives of surgical exploration and repair are testicular salvage, prevention of infection, control of bleeding, and reduced convalescence. Transverse scrotal incision is preferable in most cases. **The tunica albuginea should be closed with small absorbable sutures after removal of necrotic and extruded seminiferous tubules.** Even small defects in the tunica albuginea should be closed, because progressive swelling and intratesticular pressure can continue to extrude seminiferous tubules. Every attempt to salvage the testis should be performed; loss of capsule tissue may require removal of additional parenchyma to allow closure of the remaining tunica albuginea. A flap or graft of tunica vaginalis may be used to cover a large defect in the tunica albuginea in an otherwise salvageable testis (Fig. 88–5); synthetic grafts are not recommended for this purpose (Ferguson and Brandes, 2007). Significant intratesticular hematomas should be explored and drained even in the absence of testicular rupture to prevent progressive pressure necrosis and atrophy, delayed exploration (40%), and orchiectomy (15%) (Cass and Luxenberg, 1988). Significant hematoceles should also be explored, regardless of imaging studies, because up to 80% are caused by testicular rupture (Vaccaro et al, 1986).

Penetrating scrotal injuries should be surgically explored to inspect for vascular and vasal injury; as in blunt trauma the same principles of salvage, hemostasis, and reconstruction apply. The vas deferens is injured in 7% to 9% of scrotal gunshot wounds (Gomez et al, 1993; Brandes et al, 1995). The injured vas should be ligated with nonabsorbable suture and delayed reconstruction performed if necessary. Approximately

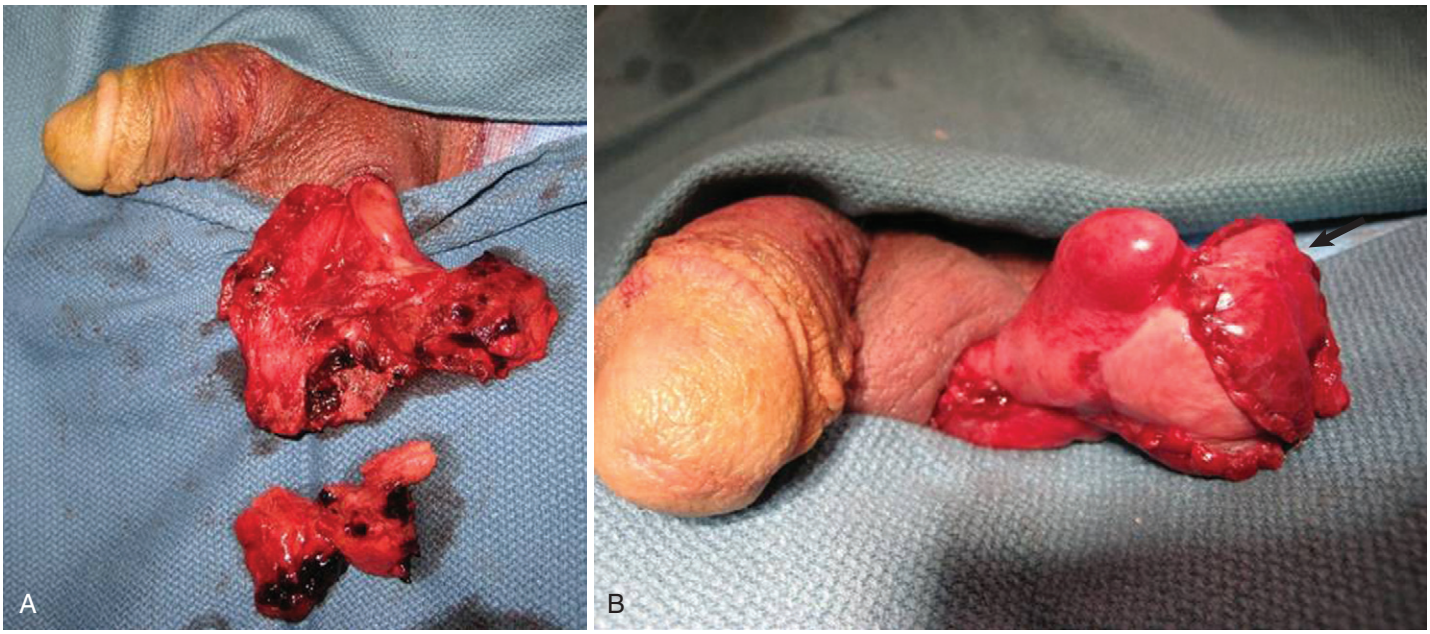


Figure 88–5. **A,** Testicular rupture after blunt trauma. **B,** Reconstructed testis after debridement and closure. *Arrow* indicates placement of tunica vaginalis graft.

30% of gunshot wounds injure both testes—exploration of the contralateral testis should be considered, depending on the findings of physical examination and the path of the projectile.

Outcome and Complications. Nonoperative management of testicular rupture is frequently complicated by infection, atrophy, necrosis, chronic unrelenting pain, and delayed orchiectomy. **Testicular salvage rates exceed 90% with exploration and repair within 3 days of injury** (Del Villar et al, 1973; Schuster, 1982; Fournier et al, 1989; Cass and Luxenberg, 1991) **versus orchiectomy rates threefold to eightfold higher with conservative management and delayed surgery** (Cass and Luxenberg, 1991). Testicular salvage rates with conservative management are as low as 33%, with delayed orchiectomy rates between 21% and 55% (Schuster, 1982; Cass and Luxenberg, 1991; McAleer and Kaplan, 1995). Approximately 45% of patients initially managed conservatively will ultimately undergo surgical exploration for pain, infection, and persistent hematoma (Del Villar et al, 1973; Cass and Luxenberg, 1991). Convalescence and time of return to normal activities are significantly reduced after early surgical repair.

Unlike blunt testis rupture, for which salvage rates are very high, penetrating testicular trauma has historically been associated with gonad salvage in only 32% to 65% of cases (Bickel et al, 1990; Gomez et al, 1993; Brandes et al, 1995; Cline et al, 1998). Improved salvage rates as high as 75% have been reported both in recent civilian (Phonsombat et al, 2008) and combat series (Waxman et al, 2009). The overwhelming majority of surgical patients have adequate preservation of hormonal and fertility function (Kukadia et al, 1996). Sperm production has been documented in men with appropriately repaired bilateral testis rupture and bilateral penetrating injuries (Pohl et al, 1968; Brandes et al, 1995).

Urologists may be consulted for opinion and guidance with regard to boys with a solitary testis who play a contact sport. Fortunately, testicular injuries are exceedingly rare in boys involved in individual or team contact sports and recreational activities (McAleer et al, 2002; Wan 2003a, 2003b). Parents should be appropriately counseled and a protective cup device recommended. The American Academy of Pediatrics Committee on Sports Medicine and Fitness (2001) recommended that many factors be considered regarding whether to allow a child with a solitary testis to play sports; their recommendation was an unqualified yes in this circumstance.

Genital Skin Loss

Etiology. Necrotizing gangrene due to polymicrobial infection in the genital area, or Fournier gangrene, is the most common cause of extensive genital skin loss (McAninch et al, 1984). Skin loss is iatrogenic, caused by the necessity for acute debridement of necrotic genital skin when the patient is seen initially.

Penile skin loss can result from traction by mechanical devices, such as farm or industrial machinery, or by suction devices, such as vacuum cleaners. Because the superficial penile tissue is loose areolar tissue, it is often torn free without damage to the underlying structures. Significant scrotal skin loss resulting from penetrating trauma is uncommon, but it has been seen more recently in battlefield explosive injuries (Fig. 88–6).

Penile burns, although rare, are often full thickness because the penile skin is so thin (Horton, 1990). Constricting bands placed on the penis can result in significant skin loss, although a more common injury involves direct pressure necrosis under the band, which usually heals well with device removal alone.



Figure 88–6. Extensive loss of scrotal skin from explosive blast injury. Note numerous concomitant shrapnel injuries to thigh.

Diagnosis and Initial Management. **Although both cellulitis and Fournier gangrene are commonly associated with significant genital edema and erythema, skin ischemia is the hallmark of Fournier gangrene.** The finding of loss of scrotal rugae is highly suggestive of tissue necrosis. Scrotal ultrasonography (Kane et al, 1996) and computed tomography (CT) may reveal subcutaneous air, a helpful indicator of necrotizing infection (Fig. 88–7).

In most cases of Fournier gangrene, multiple debridements of ischemic or frankly necrotic skin are required over a period of several days until active infection is controlled. Wounds are treated with frequent wet-to-dry dressing changes or with vacuum-assisted closure therapy (Cyzmek et al, 2009) until primary coverage is planned. Inspection at least daily by the surgical team is mandatory. **Suprapubic urinary diversion should be strongly considered for extensive injuries to simplify wound care and to prevent urethral complications related to prolonged catheterization.** Hyperbaric oxygen treatment has been advocated as an adjunctive measure to promote wound healing, although the authors do not recommend this owing to the considerable increase in expense and logistical complexity in the absence of proven benefit (Mindrup et al, 2005).

Genital burns are largely treated like other burns, with early resection of burn eschar and coverage with split-thickness skin grafts when possible. Partial-thickness skin loss or genital burns may be treated with silver sulfadiazine cream. For deep penile electrical burns, a conservative approach is warranted because the ultimate outcome will usually be autopenectomy and/or death due to extensive concurrent injuries.

Penile Reconstruction

In selected uncircumcised patients, mobilization of redundant foreskin may allow primary closure of middle to distal penile skin

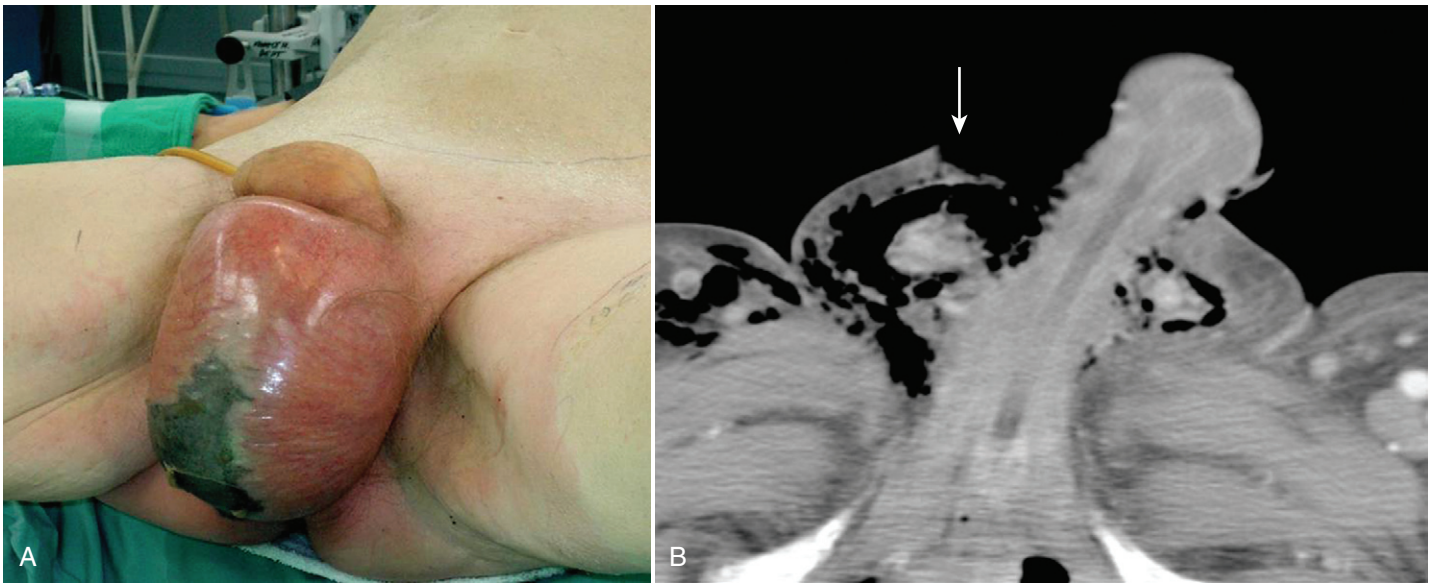


Figure 88–7. **A,** Large erythematous scrotum with central necrosis suggestive of necrotizing infection. **B,** CT reveals subcutaneous air in scrotum *(arrow)* secondary to Fournier gangrene.

loss (Horton, 1990). Scrotal rotation flaps can be used for more proximal defects if skin loss is limited, but the hair-bearing nature of scrotal skin risks an unacceptable cosmetic result. Local flaps, such as from the abdomen and thigh, also can be used but are cosmetically inferior to split-thickness skin grafts. Skin coverage with avulsed skin should be avoided because it often becomes necrotic.

Thick (0.012- to 0.015-inch), nonmeshed, split-thickness skin grafts (McAninch et al, 1984) **are preferred for penile reconstruction.** Meshed grafts can be used but have a tendency to contract and are cosmetically inferior to unmeshed grafts. Grafts are usually harvested from the anterior thigh with a pneumatic dermatome. **If grafts are to be used, care must be taken to remove any subcoronal skin remaining after debridement. Lymphatic obstruction of this distal foreskin, if it is not excised, will result in circumferential lymphedema** (McDougal, 2003). Graft stabilization in the immediate postoperative period may be achieved by either tie-over-bolster technique or with a circumferential vacuum dressing (Weinfeld et al, 2005; Senchenkov et al, 2006). Skin grafts placed on the penile shaft never regain normal sensation (Horton, 1990), although sexual function is often preserved because of intact sensation in the glans.

Scrotal Reconstruction

Scrotal skin loss defects of up to 50% can often be closed directly. For extensive injuries, the testes may be placed in thigh pouches or treated with wet dressings for up to several weeks until reconstruction (Cummings and Boullier, 2000; Gomes et al, 2001). **Thigh pouches are not recommended initially, until the infection is stabilized, because transmission of the infectious process into uninvolved tissues may occur.** During scrotal reconstruction, local skin flaps should be mobilized initially to cover as much of the tissue defect as possible (Fig. 88–8 on the Expert Consult website). Meshed split-thickness skin grafts can then be employed for reconstruction of the remainder. In addition to providing an excellent cosmetic result, meshing allows exudate to escape from the interstices, thus improving graft take. The spermatic cords and testes are sewn together in multiple areas before grafting to prevent a bifid neoscrotum. The neoscrotum may appear unnaturally tight initially, but after 6 to 12 months the testes eventually occupy a more natural dependent position. Thigh flaps can be used to reconstruct the scrotum when the testes have been buried in the thighs after traumatic or surgical scrotal removal (Morey and McAninch, 1999). Fibrin sealant has proved useful as a tissue glue to promote healing and to reduce drainage during complex genital reconstruction cases (Morris et al, 2006).

BLADDER INJURIES

Etiology. The urinary bladder is generally protected from external trauma because of its deep location in the bony pelvis. Most blunt bladder injuries are the result of rapid-deceleration motor vehicle collisions, but many also occur with falls, crush injuries, assault, and blows to the lower abdomen. Disruption of the bony pelvis tends to tear the bladder at its fascial attachments, but bone fragments can also directly lacerate the organ. Other important causes of bladder rupture include penetrating trauma, iatrogenic surgical complications, and spontaneous rupture in patients with a history of neuropathic disease, pre-existing bladder disease, or prior urologic surgery.

Bladder injures that occur with blunt external trauma are rarely isolated injuries—80% to 94% of patients have significant associated nonurologic injuries (Cass, 1984; Volpe et al, 1999; Hsieh et al, 2002; Parry et al, 2003). Mortality in these patients with multiple injuries is usually related to nonurologic injuries and ranges from 8% to 44% (Carroll and McAninch, 1984; Cass and Luxenberg, 1987; Corriere and Sandler, 1989; Volpe et al, 1999; Alli et al, 2003; Parry et al, 2003). **The most common associated injury is pelvic fracture, which is associated with 83% to 95% of bladder injuries** (Cass, 1989; Corriere and Sandler, 1989; Morey et al, 2001; Parry et al, 2003). Conversely, bladder injury has been reported to occur in only 5% to 10% of pelvic fractures (Cass, 1989; Peters, 1989; Aihara et al, 2002). Sudden force applied to a full bladder may result in a rapid rise in intravesical pressures and lead to rupture without pelvic fracture.

Penetrating bladder trauma is also associated with significant nonurologic injuries and mortality rate. Nearly half of all bladder injuries are iatrogenic (Dobrowolski et al, 2002)—**obstetric and gynecologic complications are the most common causes of bladder injuries during open surgery** (Dobrowolski et al, 2002; Gomez et al, 2004).

Diagnosis. Extraperitoneal bladder injury is usually associated with pelvic fracture. Intraperitoneal injuries can be associated with pelvic fracture but are more commonly due to penetrating injuries or burst injuries at the dome by direct blow to a full bladder. Appropriate diagnostic imaging is important because of the marked influence on management.

Clinical Signs and Symptoms. **Bladder rupture does not occur as an isolated, asymptomatic event in normal individuals. Conscious patients present with pronounced nonspecific symptoms such as suprapubic pain combined with inability to void.** Physical signs include suprapubic tenderness, lower abdominal bruising, muscle guarding and rigidity, and diminished bowel sounds. Associated abdominal and pelvic injuries may mask bladder symptoms, and those who are unresponsive due to intoxication or altered sensorium similarly warrant higher suspicion for bladder injury.

Immediate catheterization should be performed when blunt bladder rupture is suspected because **the most reliable indicator is gross hematuria, which is present in nearly all cases** (Iverson and Morey, 2001; Hsieh et al, 2002; Parry et al, 2003; Gomez et al, 2004). If blood is noted at the meatus or the catheter does not pass easily, retrograde urethrography should be performed first because urethral injuries occur concomitantly in 10% to 29% of patients with bladder rupture (Cass, 1989; Dobrowolski et al, 2002).

Radiographic Imaging. Imaging of the bladder is performed on the basis of clinical suspicion. **After blunt external trauma the absolute indication for immediate cystography is gross hematuria associated with pelvic fracture—approximately 29% of patients presenting with this combination of findings have bladder rupture** (Morey et al, 2001). Relative indications for cystography after blunt trauma include gross hematuria without pelvic fracture and microhematuria with pelvic fracture. **The diagnosis of bladder rupture is extremely low in these atypical groups (e.g., 0.6% in patients with pelvic fracture and microhematuria), but the index of suspicion should be raised by associated clinical indicators of bladder injury. Conversely, penetrating injuries of the buttock, pelvis, or lower abdomen with *any* degree of hematuria warrant cystography.**

Key Points: Clinical Indicators of Bladder Injury

- Suprapubic pain or tenderness
- Free intraperitoneal fluid on CT or ultrasound examination
- Inability to void or low urine output
- Clots in urine or clots noted in bladder on CT
- Enlarged scrotum with ecchymosis
- Abdominal distention or ileus

Retrograde or stress cystography is nearly 100% accurate for bladder injury if performed appropriately. The bladder should be filled in cooperative and conscious patients to a sense of discomfort, otherwise to 350 mL. For a plain film technique, three images are obtained: one before administration of a contrast agent, one full-bladder anteroposterior film, and one drainage film. Posterior extravasation of the contrast medium can be missed without a drainage film. Significant bladder distention is required to visualize small tears. False-negative studies have been reported with retrograde instillation of only 250 mL (Peters, 1989; Morey and Carroll, 1997). Although hematuria and mechanism of injury mandate consideration of upper tract imaging studies, upper and lower urinary tract injuries are almost never coincident (0.4%) (Cass and Luxenberg, 1990).

A dense, flame-shaped collection of contrast material in the pelvis is characteristic of extraperitoneal extravasation (Fig. 88–9). Depending on fascial integrity, contrast material may extend beyond the confines of the pelvis and be visualized in the retroperitoneum, scrotum, phallus, thigh, and/or abdominal wall. The amount of extravasation is not always proportional to the extent of bladder injury. **Intraperitoneal extravasation is identified when contrast material outlines loops of bowel and/or the lower lateral portion of the peritoneal cavity.**

Because CT is now routinely used to assess trauma patients, concomitant CT cystography is now frequently selected as a more efficient means to assess the bladder. CT cystography is as accurate and reliable as plain film cystography to evaluate suspected bladder injury (Fig. 88–10), as long as the bladder is filled in retrograde fashion with contrast material diluted to 2% to 4% (6:1 with saline) to a volume of 350 mL (Peng et al, 1999; Hsieh et al, 2002). Drainage films are not required after CT cystography because the retrovesical space can be well visualized with axial images (Morey and Carroll, 1997). Dilution of the contrast material is mandatory because undiluted contrast material is so dense that the CT quality is compromised by scatter artifact. **Clamping the urethral catheter in an attempt to allow antegrade distention of the bladder by intravenous contrast**

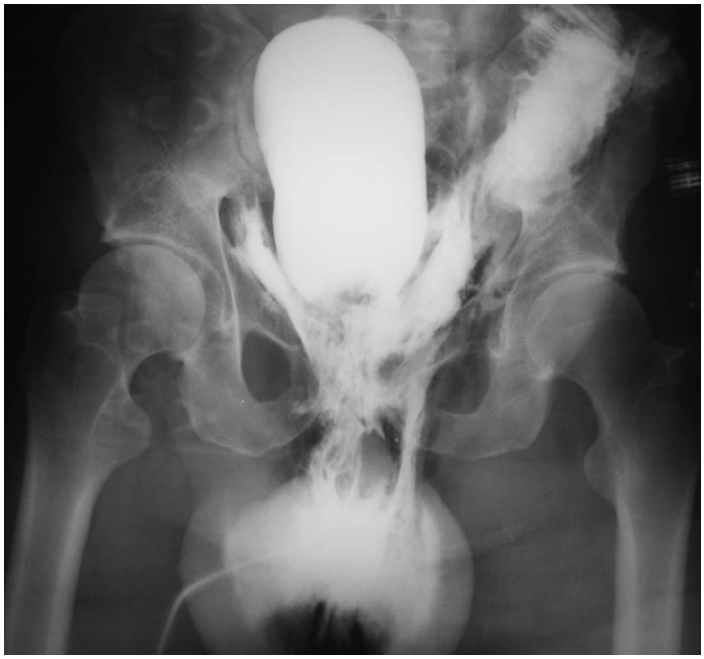


Figure 88–9. Plain film cystogram reveals extraperitoneal bladder rupture with extravasation into scrotum. Surgical exploration revealed anterior bladder neck and prostatic urethral laceration.

medium is inadequate for diagnosis of bladder rupture—retrograde filling is required. Conventional abdominal CT of the trauma patient may show findings suggestive of bladder injury but is not considered to be adequate for bladder evaluation without retrograde contrast distention (Mee et al, 1987; Udekwu et al, 1996; Hsieh et al, 2002).

Management. **The usual treatment of uncomplicated extraperitoneal bladder ruptures, when conditions are ideal, is conservative management with urethral catheter drainage alone** (Fig. 88–11). A large-bore (22 Fr) Foley catheter should be used to promote adequate drainage—if output is poor, fluoroscopic cystography should be considered to ensure proper catheter placement. Cystography is necessary to verify complete healing before catheter removal 14 days after injury; occasionally, extravasation may persist for several additional weeks but will resolve with continuation of urethral catheter drainage, after which radiographic confirmation of healing is essential. Bone spicules within the bladder wall (Fig. 88–12 on the Expert Consult website) may compromise healing. Antimicrobial agents are instituted on the day of injury and continued for at least 1 week to prevent infection of the pelvic hematoma.



Figure 88–10. CT cystogram demonstrates contrast material surrounding loops of bowel consistent with intraperitoneal bladder rupture.

Several authors (Cass, 1989; Kotkin and Koch, 1995) have reported fewer complications, such as fistula, failure to heal, clot retention, and sepsis, with open repair (5% overall) versus conservative management (12% overall). **For this reason, blunt extraperitoneal injuries warrant immediate open repair to prevent complications such as fistula, abscess, and prolonged leak in the presence of any complicating features. If a patient whose condition is stable is undergoing exploratory laparotomy for other associated injuries or internal fixation of pelvic fracture, it is prudent to surgically repair the extraperitoneal rupture at the same setting.** The anterior bladder wall is entered, and the tear is closed intravesically with absorbable suture. The perivesical pelvic hematoma should not be disturbed. When internal fixation of pelvic fractures is performed, concomitant bladder repair is recommended because urine leakage from the injured bladder onto the orthopedic fixative hardware is prevented, thereby reducing the risk of hardware infection. Drainage of the repaired bladder can be safely accomplished with a large-bore Foley catheter alone, and cystography performed 1 week after repair should verify bladder healing.

All penetrating or intraperitoneal injuries resulting from external trauma should be managed by immediate operative repair. These injuries are often larger than suggested on cystography and are unlikely to heal spontaneously, and continued leak of urine causes a chemical peritonitis. Although most injuries are repaired with open surgery, select patients may undergo laparoscopic repair (Kim et al, 2008)—primarily those whose bladder may have been injured during laparoscopic surgical procedures. When bladder injuries are explored after penetrating trauma without preliminary imaging, the ureteral orifices should be inspected for clear efflux; ureteral integrity may also be ensured by intravenous administration of indigo carmine or methylene blue or retrograde passage of a ureteral catheter. Any penetrating

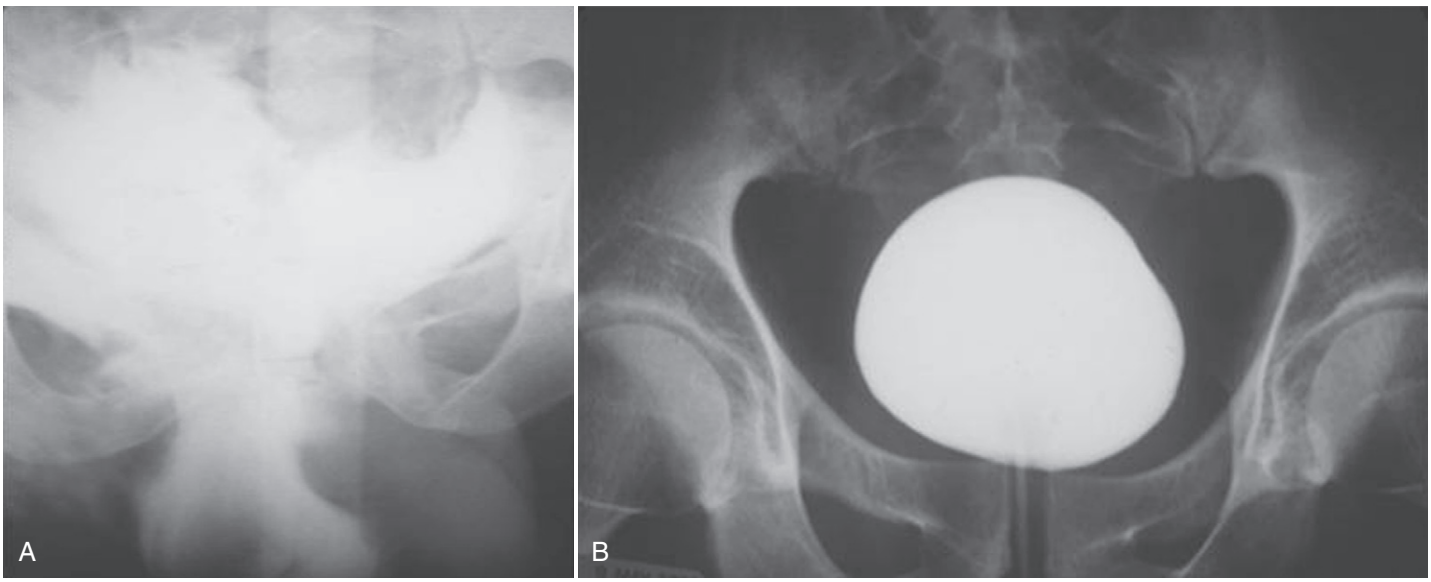


Figure 88–11. **A,** Dense flame-shaped pattern of contrast extravasation in pelvis due to extraperitoneal bladder rupture. **B,** Repeated cystogram in same patient after 2 weeks of catheter drainage shows completely healed bladder.

Key Points: Indications for Immediate Repair of Bladder Injury

- Intraperitoneal injury from external trauma
- Penetrating or iatrogenic nonurologic injury
- Inadequate bladder drainage or clots in urine
- Bladder neck injury
- Rectal or vaginal injury
- Open pelvic fracture
- Pelvic fracture requiring open reduction and internal fixation
- Selected stable patients undergoing laparotomy for other reasons
- Bone fragments projecting into bladder

injury involving the ureteral orifice or intramural ureter warrants primary closure with stented reimplantation of the ureter. A perivesical drain should be employed. In patients with intraperitoneal rupture, antimicrobial agents are administered for 3 days, in the perioperative period only. If the bladder has been repaired, a cystogram is obtained 7 to 10 days after surgery (Corriere and Sandler, 1989). **Several studies have now shown that suprapubic tube drainage provides no benefit over urethral catheter drainage alone** (Volpe et al, 1999; Alli et al, 2003; Parry et al, 2003), although maximal urinary drainage using both is recommended when complex injuries are encountered. When concurrent rectal or vaginal injuries exist, the organ walls should be separated, overlapping suture lines avoided, and every attempt made to interpose viable tissue in between the repaired structures. Fibrin sealant injected over the bladder wall closure may help reduce complications when intervening tissue is unavailable (Evans et al, 2003).

Outcomes and Complications. Prompt diagnosis and appropriate management of bladder injuries promotes excellent results and minimal morbidity. Serious complications are usually associated with delayed diagnosis or treatment due to misdiagnosis, delayed presentation, or complex injuries resulting from devastating pelvic trauma. Unrecognized bladder injuries may manifest as acidosis, azotemia, fever and sepsis, low urine output, peritonitis, ileus, urinary ascites, or respiratory difficulties. Unrecognized bladder neck, vaginal, and rectal injury associated with the bladder rupture can result in incontinence, fistula, stricture, and difficult delayed major reconstruction. Severe pelvic fractures may cause a transient or permanent neurologic injury and result in voiding difficulties despite an adequate bladder repair.

URETHRAL INJURIES

Posterior Urethral Injuries

Etiology. Urethral disruption injuries typically occur in conjunction with multisystem trauma from vehicular accidents, falls, or industrial accidents. Fracture of the anterior pelvic ring or pubic diastasis are almost always present when urethral disruption is encountered, and a greater degree of displacement has been correlated to a higher risk of urethral injury (Basta et al, 2007). **"Straddle fractures"** (Fig. 88–13 on the Expert Consult website) **involving all four pubic rami and fractures resulting in both vertical and rotational pelvic instability are associated with the highest risk of urologic injury** (Mundy, 1996; Koraitim, 1999; Brandes and Borelli, 2001). Urethral injury has been reported to occur in approximately 10% of males and up to 6% of females sustaining pelvic fractures (Koraitim et al, 1999; Black et al, 2006). Girls younger than age 17 years have a higher risk of urethral injury compared with women, perhaps owing to greater compressibility of the pelvic bones (Hemal, 1999).

Because the posterior urethra is densely adherent to the pubis via both the urogenital diaphragm and the puboprostatic ligaments, the bulbomembranous junction is more vulnerable to injury during pelvic fracture than is the prostatomembranous junction (Colapinto and McCallum, 1977; Brandes and Borelli, 2001). **Endoscopic and urodynamic evaluation has confirmed that the membranous urethral sphincter complex tends to remain functionally intact while being avulsed vertically, posteriorly, and/or laterally from the underlying bulb** (Mundy, 1997; Andrich and Mundy, 2001). In children, injuries are more likely to extend proximally to the bladder neck because of the rudimentary nature of the prostate (Devine et al, 1989; Al-Rifaei et al, 1991; Boone et al, 1992).

Diagnosis

Examination. **Urethral disruption is heralded by the triad of blood at the meatus, inability to urinate, and palpably full bladder.** Because these and other classic findings such as a "high-riding" prostate or a "butterfly" perineal hematoma may frequently be absent (Sandler and Corriere, 1989), urethral disruption is often first detected when a urethral catheter cannot be placed by the emergency department trauma team or when it is misplaced into a pelvic hematoma. Pelvic hematoma often obscures the prostatic contour, resulting in a misdiagnosis of impalpable prostate (Koraitim et al, 1996). Females may also develop proximal urethral avulsion injuries, although much more rarely than males; they present with vulvar edema (Fig. 88–14) and blood at the vaginal introitus, thus indicating the need for careful vaginal examination in all female patients with pelvic fracture (Perry and Husmann, 1992).

Urethrography. **When blood at the urethral meatus is discovered, an immediate retrograde urethrogram should be performed to rule out urethral injury**

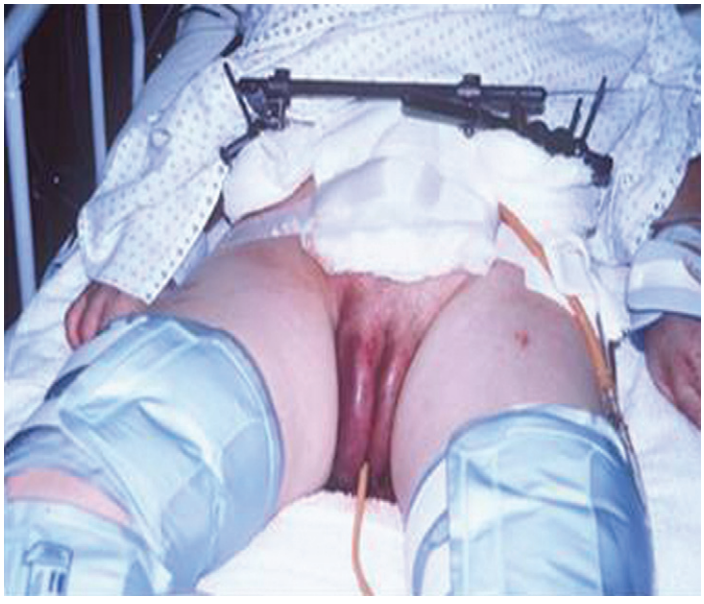


Figure 88–14. Pelvic fracture urethral disruption injury and marked vulvar edema and ecchymosis in a female patient.

(Fig. 88–15). A small-bore urethral catheter (16 Fr) is placed unlubricated 1 cm into the fossa navicularis, and the balloon is filled with 1 cm of water to achieve a snug fit (Sandler and Corriere, 1989). Alternatively, a Brodney clamp or rolled gauze bandage can be used to provide penile traction. Patients should be placed in an oblique or lateral decubitus position, and it is preferable to perform the study under fluorography when it is available; 25 mL of contrast medium is injected gently by a 60-mL catheter-tip syringe, and the film is taken during injection. **Direct inspection by urethroscopy is suggested in lieu of urethrography in females with suspected urethral injury** (Perry and Husmann, 1992; Koraitim, 1999).

Initial Management

Immediate Open Reconstruction. Immediate anastomotic reconstruction of posterior urethral disruption injuries in men has been abandoned because of its association with unsatisfactory outcomes, such as impotence and incontinence, stricture formation, and operative blood loss (Webster et al, 1983; Koraitim, 1996). **In cases of female urethral disruption related to pelvic fracture, most authorities suggest immediate primary repair, or at least urethral realignment over a catheter, to avoid subsequent urethrovaginal fistulas or urethral obliteration** (Fig. 88–16) (Koraitim et al, 1996; Dorairajan et al, 2004, Black et al, 2006). **Concomitant vaginal lacerations also must be closed acutely to prevent vaginal stenosis. Delayed reconstruction is problematic because the female urethra is too short (about 4 cm) to be amenable for mobilization during an anastomotic repair when it becomes embedded in scar** (Podesta, 2001); however, the authors have found that a suprapubic approach with partial pubectomy provides excellent exposure enabling female bladder neck reconstruction.

Suprapubic Cystostomy. **Immediate suprapubic tube placement remains the standard of care in men with posterior urethral injuries.** This may be accomplished through a small infraumbilical incision, which allows inspection and repair of the bladder and proper placement of a large-bore catheter at the bladder dome. Trocar suprapubic tube placement is both safe and expedient when the bladder is obviously distended and no other indications for surgery exist; over the long term, however, smaller "punch" suprapubic tubes are less robust, tending to fracture or become obstructed with debris and often requiring urgent replacement.

Increasingly, patients with pelvic ring fracture undergo early surgical fixation by orthopedists to decrease bleeding, improve healing, and speed ambulation (Connor et al, 2003). **Although orthopedists frequently suggest that a suprapubic tube not be placed if anterior pubic hardware is used in pelvic fracture repair because of concern that the suprapubic tube will lead to hardware infection** (Patterson, 1995), **the authors and others** (Borrelli and Brandes, 2004; Bepple et al, 2007) **have repeatedly found that suprapubic cystostomy can safely be used without complications throughout the course of care** (Fig. 88–17 on the Expert Consult website). The authors use a large-bore (24 Fr) Foley catheter placed high in the bladder and tunneled through the skin as high as possible on the lower abdominal midline to keep the tube away from the plated symphysis.

Primary Realignment. **An attempt at primary realignment of the distraction with a urethral catheter is reasonable in patients whose condition is stable** (Elliott and Barrett, 1997), either acutely or within several days of injury. The authors prefer a simple technique consisting of passage of a coudé catheter antegrade from an anterior cystotomy to the urethral meatus, then tying it to another catheter that is drawn back into the bladder. A variety of more elaborate approaches have been described, frequently with retrograde and anterograde flexible cystoscopes (Follis et al, 1992; Routt et al, 1996; Elliott and Barrett, 1997; Porter et al, 1997; Asci et al, 1999; Mouraviev et al, 2005, Hadjizacharia et al, 2008), although the authors have observed that prolonged endoscopic realignment attempts risk infection of the pelvic hematoma (Morey et al, 1999) and thus cannot be recommended.

When the urethral catheter is removed after 4 to 6 weeks, it is imperative to retain a suprapubic catheter

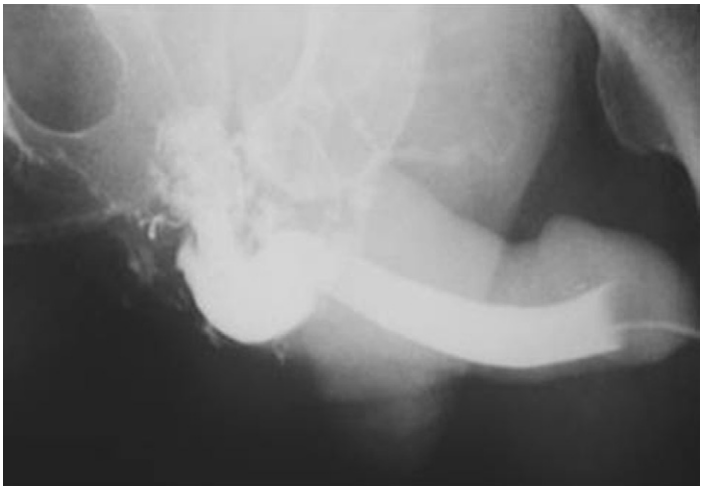


Figure 88–15. Retrograde urethrogram in a patient with a pelvic fracture shows complete disruption of posterior urethra.



Figure 88–16. Initial management of a female urethral disruption injury with suprapubic catheter drainage alone leads to complete urethral obliteration.

because many patients will, despite realignment, develop posterior urethral stenosis. If the patient voids satisfactorily through the urethra, the suprapubic catheter can be removed 7 to 14 days later. Primary realignment may sometimes allow healing without stricture (Elliott and Barrett, 1997), but mild stenosis 1 to 2 cm in length develops in many patients (Kotkin and Koch, 1996; Routt et al, 1996; Asci et al, 1999). Patients managed with suprapubic tubes alone virtually always develop complete stenosis requiring posterior urethroplasty (Kotkin and Koch, 1996; Mouraviev et al, 2005). Although realignment may not always prevent symptomatic stenosis, it may allow resultant strictures to be managed endoscopically or ease the difficulty of open posterior urethroplasty by bringing the prostate and urethra into alignment (Mouraviev et al, 2005; Hadjizacharia et al, 2008).

Incomplete urethral tears are best treated by stenting with a urethral catheter. The authors and others (Al-Ali and Husain, 1983; Mundy, 1991; Kotkin and Koch, 1996) **have not seen any evidence that a gentle attempt to place a urethral catheter can convert an incomplete into a complete transection.** Caution is warranted because misplacement outside the bladder is distinctly possible; radiographic confirmation of adequate positioning is imperative. In no case is traction used after urethral catheter placement; it is unnecessary and may cause incontinence (Asci et al, 1999).

Complex Injuries

Some authors advocate open exploration with realignment in cases of high-riding or "pie-in-the-sky" bladder or associated bladder neck tear in males (Webster et al, 1983). Associated rectal injuries require open exploration, repair, irrigation, and placement of drains.

Delayed Reconstruction

In posterior urethral disruption the rupture defect between the two severed ends fills with scar tissue, resulting in a complete lack of urethral continuity. This separation is not a stricture; it is a true urethral rupture defect filled with fibrosis. **At 3 months, scar tissue at the urethral disruption site is stable enough to allow posterior urethroplasty to be undertaken safely, provided that associated injuries are stabilized and the patient is ambulatory.** Suprapubic cystostomy drainage should be maintained until the associated injuries have healed and the patient can be appropriately positioned for the reconstructive procedure.

Preoperative Evaluation. Before the reconstructive procedure is planned, imaging studies are necessary to delineate the characteristics of the urethral rupture defect. A cystogram and retrograde urethrogram should be obtained simultaneously ("up-and-down-o-gram," Fig. 88–18). The patient is asked to attempt to void with the bladder filled. Ideally, the prostatic urethra should be visualized as the bladder neck opens, enabling measurement of the distance between the severed urethral ends. Should the bladder neck not open, flexible endoscopy should be used to supplement radiographic imaging (Mundy, 1997). The appearance of the bladder neck on preoperative imaging, either open or closed, does not correlate well with bladder neck behavior postoperatively (Mundy, 1997), thus making it difficult to predict bladder neck incompetence or obstruction. MRI has been used successfully to define defect length and to determine the extent and direction of urethral dislocation (Dixon et al, 1992) and the extent of prostatic displacement, and it may help in planning the surgical approach (Koraitim and Reda, 2007).

Endoscopic Treatments. Endoscopic treatments such as direct-vision internal urethrotomy are best reserved for selected short urethral stenoses, such as partial distraction injuries for which early catheterization achieved urethral continuity. In most cases, when preoperative evaluation indicates defects 1 cm or longer, endoscopic procedures such as cutting through the pelvic scar to provide a channel between the two ends of the avulsed urethra ("cut-to-the-light" procedure) are ineffective and have no advantage other than reduced operative time (Levine and Wessels, 2001); moreover, aggressive endoscopic treatments have been associated with complications such as coring of a false passage that inadvertently bypasses the bladder neck (Turner-Warwick, 1989). Cut-to-the-light or similar core-through procedures typically require multiple urethrotomies or long-term dilation by the patient or urologist to keep the channel open. Inevitably, the fibrosis will contract, leading to difficult self-catheterization, false passage, and/or acute urinary retention. In such cases, a 3-month period of "urethral rest" via suprapubic urinary diversion is advised before open reconstruction.

Surgical Reconstruction. Open posterior urethroplasty through a perineal anastomotic approach is the treatment of choice for most urethral distraction injuries because it definitively cures the patient without the need

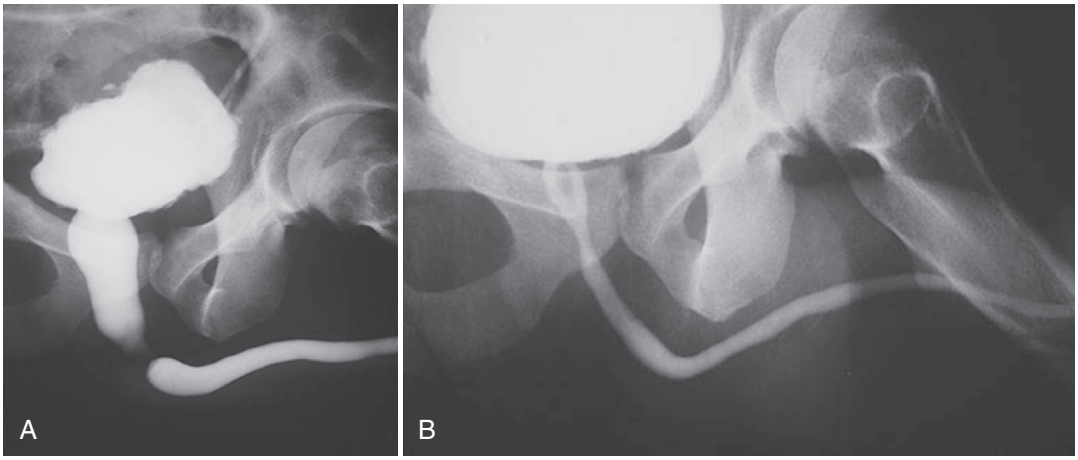


Figure 88–18. **A,** Combined cystogram and urethrogram 4 months after pelvic fracture shows complete posterior urethral disruption injury. **B,** Postoperative appearance reveals normal urethral caliber.

for multiple procedures. Once preoperative studies have determined that the prostatic urethral apex can be reached by a perineal approach, the patient is placed in the high lithotomy position and a midline or lambda-shaped incision is made. The bulbar urethra is freed and mobilized from the site of urethral rupture to the midscrotum. The scar tissue of the urethral rupture defect is excised, and the prostatic urethra is identified at the apex of the prostate. **Care must be taken to carefully and meticulously excise all fibrotic tissue from the proximal urethral margin until at least a 28-Fr bougie passes without resistance** (Fig. 88–19; Turner-Warwick, 1989; Morey and McAninch, 1997). The bulbar urethra is then anastomosed in a tension-free manner to the prostatic urethra.

In 95% of patients, posterior urethral anastomosis will be successfully achieved through a perineal approach alone (Carr and Webster, 1997). Adjunctive maneuvers such as corporeal separation, inferior pubectomy, and corporeal rerouting have been routinely implemented if direct anastomosis proves difficult (Mundy, 1997; Flynn et al, 2003). Others have found these maneuvers, especially supracrural rerouting, to be unnecessary and/or unhelpful (Morey and McAninch, 1997; Rosenstein and Jordan, 2003; Cooperberg et al, 2007; Kizer et al, 2007).

Total removal of the symphysis pubis, first reported by Pierce in 1962, has been recommended when severe injuries result in complicating features such as fistula or marked displacement or retropubic fixation of the prostate (Netto, 1985; McAninch, 1989; Asci et al, 1999). **Alternatively, a combined abdominoperineal approach (with or without partial pubectomy) has proved helpful in cases of severe fibrosis, fistula, previous failed anastomotic urethroplasty, and associated bladder neck injury and in pediatric cases** (Waterhouse, 1976; Al-Rifaei et al, 1991; Koraitim, 2003, 2005; Pratap et al, 2006). It is important to limit the lithotomy time to 5 hours or less to prevent lower extremity complications (Anema et al, 2000) when any complex urethral reconstruction is undertaken.

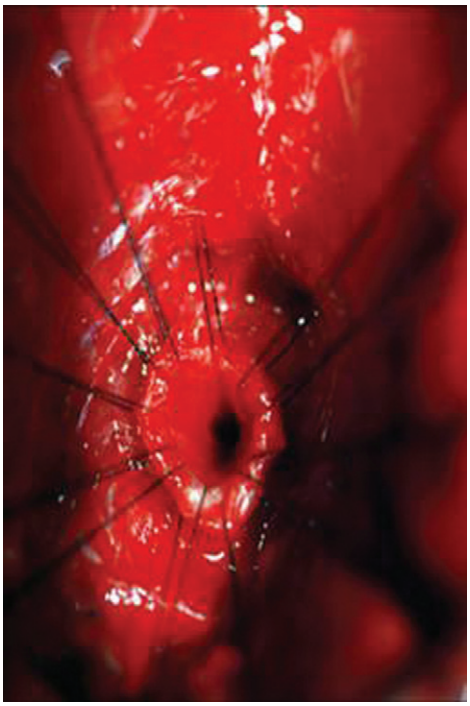


Figure 88–19. Intraoperative view of normal membranous urethra after fibrotic tissue was excised during perineal bulbomembranous urethroplasty.

Complications

Erectile Dysfunction. **Some degree of impotence is noted in up to 82% of patients with pelvic fracture and urethral distraction injury** (Flynn et al, 2003), **although the average reported rate is approximately 50%** (Corriere et al, 1994; Routt et al, 1996; Elliott and Barrett, 1997; Asci et al, 1999; Koraitim, 2005). **The etiology is multifactorial and variably attributed to cavernous nerve injury, arterial insufficiency, venous leak, and direct corporeal injury** (Narumi et al, 1993; Munarriz et al, 1995; Shenfeld et al, 2003).

Some surgical series have shown a small number of patients with new-onset or worsened erectile dysfunction after reconstruction (Tunc et al, 2000); however, the complications of the original pelvic injury are difficult to differentiate from the complications of attempts to repair urethral and bladder injuries. Accounts of greater risk of erectile dysfunction and incontinence with primary realignment are prior to the advent of flexible endoscopes (Koraitim, 1996); Several studies have shown that patients treated with modern techniques of primary endoscopic realignment have rates of impotence and incontinence similar to those of patients who have had either no treatment or delayed open reconstruction (Kotkin and Koch, 1996; Asci et al, 1999; Koraitim, 2005; Mouraviev et al, 2005). **These studies support the conclusion that these complications are usually the result of the injury itself and not of the treatment** (Follis et al, 1992; Elliott and Barrett, 1997; Porter et al, 1997; Corriere, 2001). Some patients who become impotent after injury spontaneously recover erectile function 1 or 2 years later (Turner-Warwick, 1989; Morey and McAninch, 1997; Koraitim, 2005).

Many patients who become impotent as a result of pelvic fracture have some degree of arterial insufficiency (Armenakas, 1993; Matthews, 1995). **Because impotent patients may be more vulnerable to restenosis after posterior urethroplasty as a result of bulbar urethral ischemia, some experts have suggested that "at-risk" patients undergo preoperative penile arterial duplex Doppler studies to identify candidates suitable for initial penile revascularization** (Matthews et al, 1995; Rosenstein and Jordan, 2003). Indications for penile revascularization as a treatment for post-traumatic erectile dysfunction are extremely limited, however (Kawanishi et al, 2004). Overall rates of incontinence, anejaculation, and areflexic bladder are low (2% to 4%) (Corriere et al, 1994; Elliott and Barrett, 1997; Asci et al, 1999; Anger et al, 2008) and also tend to be secondary to the original injury.

Recurrent Stenosis. **After posterior urethroplasty, 5% to 15% of patients have recurrent stenosis at the anastomosis** (Mundy, 1996; Flynn et al, 2003; Koraitim 2005; Cooperberg et al, 2007). Fortunately, endoscopic treatment (e.g., with direct-vision internal urethrotomy) is often successful in this setting because the majority of fibrotic tissue has been eliminated (Netto et al, 1989).

Incontinence. Urinary continence after urethral distraction is the rule rather than the exception, despite destruction of the external sphincter from either the injury itself or the subsequent repair. Incontinence rates after reconstruction are surprisingly low, less than 4% (Koraitim, 2005). The mechanism of continence is thought to be largely attributable to bladder neck function (Iselin and Webster, 1999). Recent urodynamic data show that a significant proportion of patients also have identifiable distal rhabdosphincteric function (Whitson et al, 2008).

Anterior Urethral Injuries

In contrast to posterior urethral distraction, anterior injuries are most often isolated (Kiracofe et al, 1975). The majority occur after straddle injury and involve the bulbar urethra, which is susceptible to compressive injury because of its fixed location beneath the pubis. A smaller percentage of injuries to the anterior urethra are the result of direct penetrating injury to the penis.

As with posterior urethral injury, a high index of suspicion must be maintained in all patients with blunt or penetrating trauma in the urogenital region, and urethrography should be performed in any case of suspected urethral injury (Husmann et al, 1993). Clinical signs of anterior urethral injuries include blood at the meatus, perineal hematoma, gross hematuria, and urinary retention. In severe trauma the Buck fascia may be disrupted, resulting in blood and urinary extravasation into the scrotum (Fig. 88–20 on the Expert Consult website). **The primary morbidity of straddle injury is urethral stricture, which may become symptomatic even years later** (Park and McAninch, 2004).

Initial Management

Armenakas and McAninch (1996) proposed a simple, practical classification scheme dividing anterior urethral injuries on the basis of radiographic findings into contusion, incomplete disruption, and complete disruption. Contusions and incomplete injuries can be treated with urethral catheter diversion alone. **Initial suprapubic cystostomy is the standard of care for major straddle injuries involving the urethra** (Park and McAninch, 2004); however, primary anterior urethral realignment has shown promising results with respect to stricture rate and erectile dysfunction in patients with straddle injuries of lesser magnitude (Ying-Hao et al, 2000; Yu et al, 2007).

Primary surgical repair is recommended for low-velocity urethral gunshot injuries (Kunkle et al, 2008)—catheter alignment alone is associated with a far worse stricture rate (Husmann et al, 1993). Debridement of the corpus spongiosum after trauma should be limited because corporeal blood supply is usually robust, enabling spontaneous healing of most contused areas (Kiracofe et al, 1975; Husmann et al, 1993). Initial suprapubic urinary diversion is recommended after high-velocity gunshot wounds to the urethra, followed by delayed reconstruction.

Delayed Reconstruction

Before any planned procedure, a retrograde urethrogram and voiding cystourethrogram should be obtained to define the site and length of the obliterated urethra clearly. Urethral ultrasound examination may help delineate the length and severity of stricture. Retrograde injection of saline combined with antegrade bladder filling will fill the urethra proximally and distally, and a 10-MHz sonogram will clearly define the nondistensible segment to be excised. Dense fibrous tissue from trauma often demonstrates a fixed, nondistensible appearance sonographically with significant shadowing (Morey and McAninch, 2000). Ultrasound imaging of urethral strictures may be more accurate than retrograde urethrography (Mitterberger et al, 2007), although it is highly operator dependent and currently not widely used.

Anastomotic urethroplasty is the procedure of choice in the totally obliterated bulbar urethra after a straddle injury. The typical scar is 1.5 to 2 cm long and can readily be completely excised. The proximal and distal urethra can be mobilized for a tension-free, end-to-end anastomosis. This is a highly successful procedure in more than 95% of cases (Santucci et al, 2002).

Endoscopic incision through the scar tissue of an obliterated urethra is a hopeless procedure doomed to failure. Partial urethral narrowing can initially be treated by endoscopic incision or dilation with higher success. It is now recognized that repeated endoscopic manipulation is neither clinically effective nor cost effective for the treatment of urethral strictures (Greenwell et al, 2004). Patients who undergo repeated endoscopic procedures are also more likely to require complex reconstructive procedures such as grafts (Park and McAninch, 2004). Open repair should be delayed for several weeks after instrumentation to allow the urethra to stabilize, and a 2-month period of suprapubic urinary diversion may be prudent preoperatively to optimize conditions for repair of complex or recurrent strictures that have been catheter dependent. Finally, UroLume stents are contraindicated in the setting of traumatic urethral strictures (Wilson et al, 2002).

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter 89

Lower Urinary Tract Calculi

Brian M. Benway, MD ● Sam B. Bhayani, MD

Bladder Calculi
Prostatic Calculi
Urethral Calculi
Preputial Calculi

Lower urinary tract lithiasis is among the oldest of known human maladies, with an often dubious and barbaric legacy spanning the full course of recorded human history. Notable sufferers of lower urinary tract lithiasis include Isaac Newton, Benjamin Franklin, Francis Bacon, John Marshall, Peter the Great, Louis XIV, George IV, Boerhaave, Scarpa, and Napoleon Bonaparte and his descendants (Ellis, 1969; Khai-Linh and Segura, 2006).

In 1905, Shattock described what may be the earliest known case of lower urinary tract stone disease, when excavation of gravesites in Egypt revealed a 6.5-cm bladder calculus within the pelvis of the body of a 16-year-old boy, dating back to approximately 4800 BC. Given that the methods of burial diverged from Egyptian tradition, little else about the background of the remains could be surmised (Shattock, 1905).

Although little is known about the understanding and treatment of urinary lithiasis in ancient civilizations, it is apparent that the affliction was so commonplace by the 5th century BC that it warranted specific mention in the works of the prolific Greek physician Hippocrates (Pardalidis et al, 2007; Herr, 2008). Perhaps the most famous instance is his proclamation within the oath bearing his name, stating "I will not cut for stone, even for patients in whom the disease is manifest; I will leave this operation to be performed by practitioners, specialists in this art" (Adams, 1938). Whether this was an early acknowledgment of the emerging field of urology or a caution for physicians to exclude themselves from the lowly butchery perpetrated by early lithotomists remains a matter of debate (Herr, 2008).

Vague descriptions of urinary stone extraction can be found in ancient texts of the Roman, Greek, Persian, and Hindu civilizations; however, the term *lithotomy* was not coined until 276 BC by the Greek Ammonius, and the procedure was not described in detail until the writings of the Roman Cornelius Celsus nearly 300 years later in AD 20 (Pardalidis et al, 2007; Herr, 2008).

Accounts of the Celsian method of cystolithotomy conjure up terrifying images of harrowing, regularly fatal interventions in which the patient, generally a child no older than 14, would be bound or held fast to a table with his legs severely jackknifed and abducted to expose the perineum. One or two fingers would be inserted into the rectum to locate the stone and manually draw it down toward the bladder neck. The perineum was then incised widely with a chisel-like razor, rending the flesh until the bladder was entered, and the stone was then extracted using a forceps or a hook. If the patient were lucky enough to survive the operation before exsanguinating, the surgeon would leave this wound open, applying a dressing of oil-soaked wool or freshly killed and gutted fowl (Moore, 2005; Pardalidis et al, 2007; Trompoukis et al, 2007; Herr, 2008). Recovery was often as agonizing as the initial procedure, when leakage of urine through the wound proved excruciating for the young patient (Trompoukis et al, 2007). Infection, incontinence, impotence, and fistula formation were all-too-common morbidities of the procedure, and nearly half of all patients died soon after the operation (Moore, 2005; Herr, 2008).

The grotesque and morbid nature of the procedure, however, hardly served to dissuade many sufferers of bladder stones from submitting themselves to the procedure. Galen and other notable physicians of the day began performing lithotomy, thereby legitimizing the procedure to some degree. In addition, midwives underwent instruction and education in the technique to offer treatment to female patients. By the Middle Ages the practice of lithotomy was a booming business, performed mostly by roving lithotomists of varying skill and competence who would ply their trade for a fee, performing the procedure on as many patients as possible before being driven out of town as their patients expired en masse (Herr, 2008).

Although small refinements were made to the procedure over the ensuing centuries the practice of lithotomy remained largely unchanged for nearly 1500 years (Herr, 2008). In Paris, during the early 16th century, Jacques de Beaulieu, a poorly trained and uneducated monk known more famously today as the subject of the children's song "Frere Jacques" than as a pioneering surgeon of his time, refined the techniques of Pierre Franco, using a lateralized perineal approach that proved a slightly less morbid operation. Although many surgeons of the time dismissed Frere Jacques as a quack, he became a prolific practitioner of lithotomy, providing his services to over 5000 patients throughout Europe (Kelly, 1909; Bail, 1932; Moore, 2005; Herr, 2008). De Beaulieu's methods were later adopted by William Cheselden, a Briton, who perfected the techniques of his forebears, introducing new instrumentation and an informed anatomic approach that reduced the mortality of lithotomy to less than 10% (Gross and Gross, 1876; Moore, 2005; Herr, 2008).

Fortunately, modern advances in surgical technology and aseptic technique have transformed this once deadly affliction into an eminently manageable and rarely fatal disease process. In addition, changing diets and industrialization have served to significantly reduce the incidence of lower urinary tract calculi, especially in the Western world.

BLADDER CALCULI

Bladder stones are the most common manifestation of lower urinary tract lithiasis, currently accounting for 5% of all urinary stone disease and approximately 1.5% of urologic hospital admissions in industrialized Western nations

(Smith and O'Flynn, 1975; Schwartz and Stoller, 2000; Papatsoris et al, 2006). Bladder calculi in nonendemic areas are typically found in adults and almost always in association with other disease processes resulting in urinary stasis or the introduction of a foreign body (Schwartz and Stoller, 2000). However, in endemic regions, bladder calculi often arise in children in whom a major anatomic abnormality does not coexist; in these regions, dietary intake and socioeconomic factors primarily influence the formation of bladder calculi (Andersen, 1962; Asper, 1984).

Primary Bladder Calculi

Once common in Europe and the United States, primary bladder calculi of childhood have been practically eliminated by the spread of industrialization and the modernization of the Western diet over the past 100 years (Van Reen, 1980; Schwartz and Stoller, 2000). However, childhood bladder lithiasis remains common in endemic regions, throughout a stone belt reaching from northern Africa, through the Middle East and the Balkans, and into India, Japan, Thailand, and Indonesia; they are uncommon in the southern hemisphere (Valyasevi and Van Reen, 1968; Valyasevi and Dhanamitta, 1974; Thalut et al, 1976; Asper, 1984; Teotia and Teotia, 1990; Hesse and Siener, 1997; Kamoun et al, 1999; Rizvi et al, 2003; Ali and Rifat, 2005). It is important to note that the term *primary* in this context refers to the fact that **these stones develop in the absence of any known functional, anatomic, or infectious factors** and does not necessarily imply that stones have formed de novo in the bladder (Andersen, 1962).

Primary bladder calculi are most common in children younger than the age of 10, with a peak incidence at 2 to 4 years of age (Valyasevi and Van Reen, 1968; Thalut et al, 1976; Teotia and Teotia, 1990; Ali and Rifat, 2005). The disease is much more common in boys than in girls, with ratios ranging from 9:1 to as high as 33:1 in areas of India (Andersen, 1962; Thalut et al, 1976; Van Reen, 1980; Kamoun et al, 1999; Rizvi et al, 2003). **Stones are usually solitary and, once removed, rarely recur** (Valyasevi and Van Reen, 1968; Van Reen, 1980; Teotia and Teotia, 1990). Ammonium acid urate, calcium oxalate, uric acid, and calcium phosphate are the most common components of primary bladder calculi (Valyasevi and Van Reen, 1968; Teotia and Teotia, 1990).

Predisposition to the formation of bladder calculi appears to arise from a number of nutritional and socioeconomic factors. **Children in endemic regions often consume a predominantly cereal-based diet that is poor in animal protein and low in phosphate** (Thalut et al, 1976; Van Reen, 1980; Teotia and Teotia, 1990). In some regions, infant diets consist only of predigested rice that is first chewed by the mother, as well as breast milk, both of which are critically low in protein and phosphate (Andersen, 1962; Valyasevi and Van Reen, 1968; Thalut et al, 1976). **Low dietary intake of phosphate not only leads to hypophosphaturia but also to hyperammonuria, promoting the precipitation of both calcium oxalate and ammonium acid urate** (Noe and Stapleton, 1987; Teotia and Teotia, 1990). In addition, in the poor villages of Thailand, tampala and bamboo shoots, both of which are rife with bioavailable oxalate, are a frequent staple for infants (Valyasevi and Dhanamitta, 1974), which when combined with low dietary intake of vitamins B_1, B_6, and magnesium can lead to hyperoxaluria and formation of calcium oxalate stones. Vitamin A deficiency can also lead to urothelial degeneration, which may also promote stone formation (Teotia and Teotia, 1990).

In addition, substandard living conditions and poor sanitation can lead to a paucity of adequate drinking water and an increased prevalence of diarrhea, leading to dehydration and supersaturation of stone-forming compounds in the urine (Valyesevi and Van Reen, 1968; Thalut et al, 1976; Van Reen, 1980; Schwartz and Stoller, 2000).

Children suffering from primary bladder calculi rarely present acutely. There is often a prodrome consisting of the passage of sandy urine or the presence of dusty crystals in dried urine that heralds the precipitation of urinary solutes. Children often complain of vague abdominal discomfort, dysuria, frequency, and hematuria. Pulling of the penis is considered by some to be pathognomonic, because it indicates the child is suffering from stranguria; frank urinary retention, however, is very rare. In some cases, rectal prolapse and conjunctival hemorrhages may develop as the result of intense straining to void (Thalut et al, 1976; Teotia and Teotia, 1990; Ali and Rifat, 2005).

Prevention consists mostly of dietary modification. In Thailand, phosphate supplementation was found to significantly reduce oxalate crystalluria, even without concomitant reduction in oxalate intake (Valyasevi and Dhanamitta, 1974). However, other authors suggest **a transition to a mixed-cereal diet with milk supplementation as the most practicable solution for bladder stone prevention** (Teotia and Teotia, 1990).

Key Points: Primary Bladder Calculi

- Primary bladder calculi are more common in children exposed to low-protein, low-phosphate diets.
- Primary bladder calculi rarely recur after treatment.

Secondary Bladder Calculi

Bladder calculi of the type commonly encountered throughout the Western world are **typically found in men older than the age of 60 and usually in concert with lower urinary tract obstruction,** which prevents complete bladder emptying (Douenias et al, 1991; Takasaki et al, 1995; Hesse and Siener, 1997; Yasui et al, 2008). Over the past 4 decades, the overall incidence of bladder calculi appears to have stabilized or decreased among males and increased slightly for females; these trends are likely due to the increase in the elderly population as life expectancies lengthen, as well as an overall increase in the number of female genitourinary procedures performed annually (Schwartz and Stoller, 2000; Terai et al, 2008; Yasui et al, 2008).

Bladder calculi may arise *de novo* within the bladder or may result from the maturation of stone nidi that migrate from the upper tracts and subsequently fail to be spontaneously voided. The latter appears to be far less common than initially postulated, because **only 3% to 17% of patients will report a history of renal colic to suggest the passage of a calculus from the upper tracts** (Aird, 1957; Smith and O'Flynn, 1975; Douenias et al, 1991). **The frequent absence of calcium oxalate in the nucleus of most bladder stones further suggests against an upper tract origin** (Douenias et al, 1991; Vanwaeyenbergh et al, 1995). The pathogenesis and composition of bladder calculi depend largely on the inciting pathologic process and the presence or absence of infection.

Bladder Outlet Obstruction and Acquired Lower Urinary Tract Pathologic Process

Bladder outlet obstruction resulting in incomplete emptying and the retention of stone fragments is the most common predisposing factor for bladder stone formation in non-neurogenic bladders and is present in 45% to 79% of all patients diagnosed with vesical calculi (Smith and O'Flynn, 1975; Douenias et al, 1991; Takasaki et al, 1995). In men, outlet obstruction is generally related to benign prostatic hyperplasia, whereas urethral kinking from a cystocele or pelvic organ prolapse is often the culprit in females (Smith and O'Flynn, 1975; Douenias et al, 1991; Sarica et al, 1994; Nieder et al, 1998; Schwartz and Stoller, 2000; Papatsoris et al, 2006). Urethral stricture, bladder neck contracture, and bladder diverticula are also secondary causes that may interrupt normal voiding patterns (Smith and O'Flynn, 1975; Douenias et al, 1991).

The composition of stones resulting from anatomic obstruction varies with geography and ethnicity. In Europe, struvite, calcium phosphate, and uric acid predominate, whereas in Japan uric acid calculi are uncommon and calcium stones are increasing in incidence, now representing 72% of all stones in a recent series. Calcium oxalate comprises the majority of bladder stones found in the United States, although uric acid stones predominate among the American Jewish population (Smith and O'Flynn, 1975; Hesse and Siener, 1997; Douenias et al, 1991; Papatsoris et al, 2006; Yasui et al, 2008). Stones are usually solitary, although multiple stones may exist in 25% to 30% of patients (Sarica et al, 1994).

Intravesical Foreign Body

Foreign material within the bladder provides an ideal nidus for stone formation and is responsible for the majority of bladder calculi diagnosed in females (Smith and O'Flynn, 1975; Schwartz and Stoller, 2000; Papatsoris et al, 2006). Often, a foreign body within the bladder will initially encrust with calcium oxalate, as a result of the normal stasis that occurs with the storage of urine. Should infection supersede, rapid coalescence of the stone may occur as struvite is deposited on the nascent stone (Dalton et al, 1975; Khan and Wilkinson, 1990; Vanwaeyenbergh et al, 1995; Schwartz and Stoller, 2000).

The vast majority of intravesical foreign bodies result from iatrogenic interventions, although self-mutilation plays a role in a minority of patients (Dalton et al, 1975; Douenias et al, 1991; Schwartz and Stoller, 2000); complications resulting from urogynecologic interventions predominate. Inadvertent violation of the bladder with suture material during suspension or sling procedures is a common source of an intravesical foreign body. Often this error is not detected intraoperatively, underscoring the importance of thorough cystoscopic inspection before the conclusion of the procedure (Zderic et al, 1988). Along with the rise in popularity of incontinence surgery involving synthetic mesh, such as tension-free vaginal tape procedures, there has been a noted increase in calculi forming on portions of the mesh that have eroded into the bladder (Chamary, 1995; Koelbl et al, 2001; Irer et al, 2005; Mustafa and Wadie, 2007). In addition, erosion of wire suture used for cerclage has been reported (Ehrenpreis et al, 1986). Stone encrustation of migrated intrauterine devices, pessaries, and contraceptive diaphragms have also been reported (Staskin et al, 1985; Khan and Wilkinson, 1990; Mahazan, 1995; Chow et al, 1997; Maskey et al, 1997; Schwartz and Stoller, 2000; Demirci et al, 2003).

In men who have undergone radical retropubic prostatectomy, formation of stone on eroded silk sutures used to ligate the dorsal vein complex have been reported (Scheidler et al, 1990; Miller et al, 1992). In addition, necrotic tissue resulting from chemical ablation of the prostate for benign prostatic hyperplasia has been cited as a nidus for stone formation (Ikari et al, 2005), as has the presence of intraprostatic stents (Chiu et al, 1991; Squires and Gillatt, 1995). Erosion of an inflatable penile prosthesis and artificial urinary sphincters resulting in stone encrustation have also been reported (Dupont and Hochman, 1988; Barroso et al, 2000; Bartoletti et al, 2000).

The development of bladder calculi is an infrequent complication of long-term urinary tract drainage. Encrustation of short-term ureteral stents are a common finding, although significant intravesical stone formation may occur in instances in which the stent is left resident for an extended period of time (Giannakopoulos et al, 2001; Damiano et al, 2002; Hao et al, 2008; Vanderbrink et al, 2008; Waters et al, 2008). Long-term bladder drainage may also result in bladder lithiasis, with a reported **incidence of 0.07% to 2.2% in patients with chronic indwelling catheters** (Kohler-Ockmore and Feneley, 1996). In instances in which Foley balloons burst intravesically, retained fragments frequently lead to subsequent stone formation (Chute, 1962; Smith and O'Flynn, 1975). Even patients who perform clean intermittent catheterization may not be immune, because inadvertent introduction of hair into the bladder with the passage of the catheter may provide a nidus for stone formation (Derry and Nuseibeh, 1997).

On rare occasions, intravesical calculi may also arise as a result of the migration and erosion of foreign bodies unrelated to genitourinary manipulation. These include orthopedic cement, surgical clips, ventriculoperitoneal shunts, and abandoned gallbladder stones resulting from spillage during cholecystectomy (Radford and Thomson, 1989; Chia and Ross, 1995; Maier and Treu, 1996; Eichel et al, 2002).

Neurogenic Bladder and Spinal Cord Injury

Neurogenic bladder resulting from spinal cord injury or myelomeningocele places patients at increased risk of bladder stone formation. **For adults with spinal cord injury the risk for bladder stone formation peaks at 3 months after the initial injury, and within 10 years 15% to 30% of patients will have formed at least one stone** (Chen et al, 2001). Unfortunately, once a patient has formed one stone, **the risk of forming a subsequent stone quadruples** (Ord et al, 2003). The level and severity of the spinal cord injury appears to be closely correlated with the risk of bladder stone formation, especially after the first year (Chen et al, 2001; Sugimura et al, 2008). This is possibly due to the inability of quadriplegics with complete cord lesions to perform intermittent catheterization themselves, relying instead on caretakers or a chronic indwelling catheter for bladder management (Sugimura et al, 2008).

Indeed, the manner in which the bladder is managed in spinal cord injury appears to have a significant impact on the risk of stone formation. One large study of over 450 patients noted that the use of **clean intermittent catheterization was associated with a significant reduction in the risk of bladder stone formation, with an annual risk of 0.2%, compared with 4% in those patients managed by a chronic indwelling catheter** (Ord et al, 2003). This finding has been corroborated by other reports (Mitsui et al, 2000; Chen et al, 2001). In addition, the use of clean intermittent catheterization is associated with a 40-fold decrease in the risk for hospital admissions due to bladder calculi (Ord et al, 2003). As such, clean intermittent catheterization is the recommended form of bladder management in

all patients in whom it is feasible (Feifer and Corcos, 2008). However, for patients who must rely on chronic indwelling catheters, suprapubic cystotomy provides no benefit over urethral catheterization in terms of the development of bladder calculi, although patients often report greater satisfaction with the former (Ord et al, 2003; Sugimura et al, 2008).

The incidence of bladder calculi in children with neurogenic bladder is far lower than in adults, developing in only 5% to 8% of nonaugmented children performing clean intermittent catheterization. The incidence of bladder stones is slightly higher, however, in children who catheterize through a Mitrofanoff conduit than those who catheterize per urethra (Barroso et al, 2000).

Bladder Calculi in Transplant Patients

Bladder calculi are an uncommon complication of solid organ transplantation, **occurring primarily in pancreatic allografts drained via the bladder. In all reported instances, nonabsorbable suture material or surgical clips have been found to serve as the nidus for stone formation** (Hakim et al, 1997; Del Pizzo et al, 1998; Hahnfeld et al, 1998; Rhee et al, 1999; Schwartz and Stoller, 2000). Stone formation may be potentiated by low serum pH due to bicarbonate leak as well as urinary stasis and incomplete bladder emptying due to diabetic uropathy. When combined with an increased coincidence of bacteriuria due to colonization of included duodenal segments and the effects of immunosuppression, the ideal milieu for calculus formation can arise (Rhee et al, 1999). The reported incidence of bladder calculi in pancreatic allograft recipients ranges from 0.5% to 10% (Hakim et al, 1997; Del Pizzo et al, 1998; Hahnfeld et al, 1998).

Bladder calculi may also occur after renal transplantation without simultaneous pancreatic transplant, with incidences ranging from 0% to 5% in the literature. In most instances, suture material serves as the nidus for stone formation; however, although two studies identified the development of calculus material on absorbable polyglactin sutures, another large series found calculus formation only occurred in cases in which nonabsorbable suture material had been used for the ureterovesical anastomosis (Leunissen et al, 1987; Klein and Goldman, 1997; Rhee et al, 1999; Lipke et al, 2004).

Key Points: Secondary Bladder Calculi

- Secondary bladder calculi are generally associated with bladder outlet obstruction.
- Patients with spinal cord injury are at increased risk of bladder stone formation.
- Intermittent catheterization decreases the risk of bladder stone formation over an indwelling catheter.

Augmented Bladders and Urinary Diversion

Bladder and pouch stones are a known complication of augmentation cystoplasty and urinary diversion. They arise from a complex interplay of functional, anatomic, metabolic, and infectious factors.

Bladder Augmentation

The reported incidence of bladder calculus after augmentation cystoplasty ranges from 10% to as high as 52.5% (Edin-Liljegren et al, 1996; Kaefer et al, 1998; Kronner et al, 1998; Bertschy et al, 2000; Mathoera et al, 2000; Madersbacher et al, 2003). Unlike traditional adult urolithiasis, females are more commonly affected than males, likely owing to the high incidence of cloacal abnormality requiring additional procedures beyond augmentation (Mathoera et al, 2000). **Mean time to the formation of first stone ranges from 24.5 to 68 months, and after the first incidence the risk of recurrence is 19% to 44%** (Blyth et al, 1992; Palmer et al, 1993; Kronner et al, 1998; Mathoera et al, 2000; Woodhouse and Lennon, 2001; DeFoor et al, 2004; Hensle et al, 2004).

Because bacteriuria and urinary tract infection are commonplace after augmentation cystoplasty, it is not surprising that the vast majority of associated calculi contain a significant struvite component (Blyth et al, 1992; Palmer et al, 1993; Kaefer et al, 1998; Hensle et al, 2004; Robertson and Woodhouse, 2006). Interestingly, however, struvite is not the predominant component in most infection-related stones found in augmented bladders; rather, one study found a predominance of calcium phosphate in these stones, which is likely due to the comparatively lower pH required for precipitation of calcium phosphate, as compared with struvite. In addition, up to 14% of patients were found to have noninfectious stones, consisting of calcium phosphate and calcium oxalate with no struvite component (Allison et al, 1985; Robertson and Woodhouse, 2006). Uric acid calculi are rare in augmented bladders (Blyth et al, 1992; Palmer et al, 1993; Hensle et al, 2004; Robertson and Woodhouse, 2006). The treatment of recurrent urinary tract infections with antibiotics may have the deleterious effect of eradicating *Oxalobacter formigenes* within the gut, leading to an increase in intestinal oxalate absorption and hyperoxaluria (Robertson and Woodhouse, 2006).

However, infection is just one aspect of the milieu that can lead to stone formation in augmented patients. As in nonaugmented bladders, urinary stasis and incomplete bladder emptying serve to potentiate bladder stone formation. Factors that may contribute to stasis include bladder neck reconstruction, artificial urinary sphincter placement, and urethral sling procedures, all of which are designed to provide hypercontinence (Kronner et al, 1998). In addition, catheterization through nondependent access, such as through Mitrofanoff channels, is associated with a higher risk of stone formation (Kaefer et al, 1998; Kronner et al, 1998; Barroso et al, 2000). Dehydration, hypocitraturia, hypercalciuria, as well as high urinary pH in intestinal augments may also contribute to stone formation (Woodhouse and Robertson, 2004).

The role of intestinal mucus in stone formation remains controversial. Bladder calculi are found almost exclusively in patients who have undergone augmentation cystoplasty with ileum or colon and are rarely encountered after augmentation using stomach or ureter or after autoaugmentation (Kaefer et al, 1998; Kronner et al, 1998; Bertschy et al, 2000; Mathoera et al, 2000; DeFoor et al, 2004; Woodhouse and Robertson, 2004). Although some cite the production of enteric mucus as a predisposing factor in bladder stone formation, both as a nidus for stone formation and as a promoter of bacterial biofilm formation (Bruce et al, 1984; Blyth et al, 1992; Khoury et al, 1997), others have challenged that notion. Two recent studies have evaluated the role of regular bladder irrigation to promote mucus washout; neither found a significant reduction in the incidence of bladder calculi, suggesting that **mucus production has little effect on stone**

formation (Brough et al, 1998; Mathoera et al, 2000). Instead, other authors suggest that it is the low urinary pH associated with gastric segments that inhibit bacterial growth and the precipitation of struvite that explains their decreased propensity for stone formation (Kaefer et al, 1998; Kronner et al, 1998). Indeed, some of the few accounts of vesical stone formation after gastrocystoplasty have resulted in patients on histamine blockade, which raises the urinary pH (Kaefer et al, 1998).

Despite the apparent advantages of gastrocystoplasty in terms of bladder stone formation, the use of stomach carries with it significant comorbidity, such as hypokalemic hypochloremic alkalosis and hematuria-dysuria syndrome that recommend against its routine use (Rink et al, 1995; Kronner et al, 1998).

Urinary Diversion

Similar to augmentation cystoplasty, urinary diversion utilizing intestinal segments is associated with the formation of conduit and reservoir calculi, with incidences largely dependent on the type of diversion created. Calculi in incontinent diversions, such as ileal and colon conduits, are relatively uncommon. Despite early reports of a high rate of stone formation in ileal conduits created using stapler devices in several small series, the incidence in large modern experiences is quite low, ranging from 0% to 7.3% (Brenner and Johnson, 1985; Turk et al, 1999). Urinary stasis from stomal stenosis is believed to be a major predisposing risk factor in these cases; and, despite early concerns, encrustation of stone material on staple lines is not always the rule (Dunn et al, 1979; Brenner and Johnson, 1985; Madersbacher et al, 2003; L'Esperance et al, 2004).

Likewise, the incidence of stone formation in both orthotopic neobladder and Indiana pouch diversion is quite low, ranging from 2.9% to 12.9% in modern series (Terai et al, 1996; Turk et al, 1999; Abol-Enein and Ghoneim, 2001; Deliveliotis et al, 2001; Beiko and Razvi, 2002). However, **patients who undergo continent diversion with a Kock pouch reservoir often do not fare as well, with incidences of pouch stone formation of up to 50%** (Ginsberg et al, 1991; Arai et al, 1993; Terai et al, 1996; Woodhouse and Lennon, 2001). Major contributing factors in the formation of Kock pouch calculi include exposed staple lines used to create the nipple valve, as well as the use of a nonabsorbable mesh collar. Elimination of the collar and the use of absorbable staples is associated with a significant reduction in the incidence of pouch calculi, to as low as 10% (Ginsberg et al, 1991; Arai et al, 1993; Arif et al, 1999; Beiko and Razvi, 2002).

Struvite and calcium phosphate calculi predominate, indicating an infectious component in the development of most calculi in urinary diversions (Kaefer et al, 1998; Arif et al, 1999; Turk et al, 1999). In addition, patients with continent diversions have been noted to have increased levels of urinary calcium, magnesium, and phosphate, as well as low levels of urinary citrate; metabolic acidosis may also occur. These metabolic derangements may further potentiate stone formation (Terai et al, 1995, 1996).

Presentation and Management

The most common presenting symptom of bladder calculi is macroscopic hematuria, which generally is terminal (Smith and O'Flynn, 1975; Papatsoris et al, 2006). **Intermittency, frequency, urgency, dysuria, decreased force of the urinary stream, incontinence, and lower abdominal pain aggravated by brisk movement may also be present** (Ellis et al, 1969; Smith and O'Flynn, 1975; Douenias et al, 1991; Miller et al, 1992; Sarica et al, 1994; Demirci et al, 2004; Irer et al, 2005; Papatsoris et al, 2006). Larger stones tend to cause fewer symptoms, likely owing to restricted movement within the bladder (Douenias et al, 1991). Bladder stones are rarely asymptomatic at the time of discovery (Smith and O'Flynn, 1975; Rhee et al, 1999).

The options for management of vesical calculi are varied. Any planned intervention should also aim to correct the underlying urinary tract pathologic process when appropriate to prevent stone recurrence.

Nonoperative Management

Chemical dissolution is rarely considered a primary form of management, because treatments are protracted and often do not address underlying functional or anatomic pathology. Renacidin is well tolerated and may be employed to dissolve struvite and calcium phosphate calculi. Uric acid calculi may be dissolved with oral administration of potassium citrate or intravesical administration of alkaline solutions (Asper, 1984; Rodman et al, 1984; Blyth et al, 1992; Drach, 1992; Menon and Resnick, 2002; Papatsoris et al, 2006). Irrigations with acetohydroxamic acid have proven effective in reducing the incidence of catheter encrustation in patients requiring chronic indwelling catheters (Burns and Gauthier, 1984).

Open and Percutaneous Cystolithotomy

Once the gold standard for bladder stone treatment, the open approach has fallen into disfavor as newer, less invasive techniques have come to the fore. Open cystolithotomy, while successful, is associated with the need for prolonged catheterization, increased length of hospital stay, and poor cosmesis from the required incision (Bhatia and Biyani, 1994; Demirel et al, 2006). However, one group has reported on the successful implementation of drainless and catheterless open suprapubic cystolithotomy in children after meticulous two-layer closure of the cystotomy. After the procedure most patients were immediately ambulatory and most had no difficulty voiding. However, 7% of patients eventually required catheterization, including one patient who developed a leak and subsequent wound infection (Rattan et al, 2006).

Percutaneous techniques have recently been championed, especially in patients without serviceable urethral access, such as patients who have undergone prior bladder neck reconstruction or closure. This method generally involves the creation and dilation of a suprapubic tract after the bladder is distended. An Amplatz sheath is used in the vast majority of reported techniques, although concern over inadvertent loss of access has compelled some to use a Hasson trocar instead (Ikari et al, 1993; Agrawal et al, 1999; Franzoni and Decter, 1999; Wollin et al, 1999; Segarra et al, 2002; Demirel et al, 2006; Aron et al, 2007). A combination of ultrasonic and pneumatic energy is used to fragment the stone; small fragments may be suctioned while larger fragments are removed using stone forceps. Suprapubic or transurethral catheter drainage is required for 1 to 5 days (Ikari et al, 1993; Wollin et al, 1999; Franzoni and Decter, 1999; Demirel et al, 2006; Aron et al, 2007).

Average operative times for percutaneous cystolithotomy range from 20 to 86 minutes (Wollin et al, 1999; Demirel et al, 2006; Aron et al, 2007), with **successful eradication of stone in 89% to 100% of patients after a single procedure.** Complications, including urine leak and persistent hematuria, are rare, occurring in approximately 1% of patients (Ikari et al, 1993; Franzoni and Decter, 1999; Wollin et al, 1999; Demirel et al, 2006).

Proponents of the percutaneous approach to cystolitholapaxy cite its safety and expedience, as well as the elimination of potential traumatic risk to the urethra from repeated instrument passage (Ikari et al, 1993; Wollin et al, 1999). For patients requiring surgical management for prostatic hyperplasia, transurethral resection of the prostate can be safely performed after percutaneous cystolithotomy (Aron et al, 2007).

Transurethral Cystolitholapaxy and Lithotripsy

The transurethral approach for bladder stone treatment is attractive because it allows for the use of a natural orifice for access. A lithotrite may be used but has fallen into disfavor owing to the high incidence of mucosal injury and bladder perforation as well as the inability to address large calculi and a high rate of stone recurrence (Barnes et al, 1963; Smith and O'Flynn, 1977; Nseyo et al, 1987; Bhatia and Biyani, 1994; Teichman et al, 1997; Schwartz and Stoller, 2000; Lipke et al, 2004). Modern series report the use of the holmium laser, electrohydraulic lithotripter, and lithoclast technology, all with success in both adults and children (Bülow and Frohmüller, 1981; Teichman et al, 1997; Sathaye, 2003; Lipke et al, 2004; Okeke et al, 2004; Isen et al, 2008). However, in addition to the need for multiple probes, **electrohydraulic energy is associated with a higher incidence of complications, including mucosal injury and hematuria** (Teichman et al, 1997; Lipke et al, 2004). One earlier series reported a 1.6% incidence of bladder perforation with electrohydraulic lithotripsy, although this has not been reported in modern series (Bülow and Frohmüller, 1981).

Holmium laser lithotripsy has become the modality of choice, owing to its ability to treat large calculi while incurring a minimum of collateral damage. Most patients undergoing laser lithotripsy will be rendered stone free in one procedure with no major complications (Teichman et al, 1997; Lipke et al, 2004). The use of a side-firing laser is favored by some, owing to increased stability and maneuverability of the fiber as well as shorter operative times (Teichman et al, 1997).

To prevent potential traumatic injury to the urethra from the repeated passage of instruments, one group advocates the use of a transurethral Amplatz sheath after gentle urethral dilation (Okeke et al, 2004). Should a sheath not be used, adequate urethral lubrication and preoperative meatotomy is advocated by others to reduce the incidence of postoperative stricture disease, although the long-term success of this strategy has not been reported (Sathaye, 2003). Concomitant transurethral resection of the prostate can be performed if necessary, although caution is advised owing to associated complication rates as high as 21% (Nseyo et al, 1987; Aron et al, 2007).

Shockwave Lithotripsy

Extracorporeal shockwave lithotripsy has been successfully employed for the treatment of bladder calculi. The patient is placed in a prone position to eliminate obfuscation on fluoroscopy by the pelvis and sacral spine. A Foley catheter is introduced to allow for filling and drainage of the bladder, the latter of which provides for immobility of the stone during fragmentation, although this method is not employed by all authors (Bhatia and Biyani, 1994). Cystoscopic evacuation of stone fragments is necessary for larger calculi (Bosco and Nieh, 1991; Bhatia and Biyani, 1994). Per session 1000 to 4800 shocks are generally required to produce adequate fragmentation, and re-treatment is necessary in 10% to 25% of patients (Bosco and Nieh, 1991; Bhatia and Biyani, 1994; Millán-Rodríguez et al, 2005). Shockwave lithotripsy results in success in 93% to 100% of patients (Bosco and Nieh, 1991; Millán-Rodríguez et al, 2005).

Treatment of Stones in Augmented Bladders and Urinary Diversions

The treatment of calculi in augmented bladders and urinary diversion presents a unique challenge in that **intra-abdominal spillage of urine and irrigation can lead to peritonitis** (Palmer et al, 1993; Kronner et al, 1998; Khai-Linh and Segura, 2006). However, treatment principles remain largely unchanged from the treatment of calculi in intact bladders.

Calculi within conduit diversions are perhaps the most simple to manage, because the majority of calculi will pass spontaneously. For those that do not readily pass, looposcopy with lithotripsy and stone extraction is easily performed (Shapiro et al, 1975; Middleton and Hendren, 1976; Brenner and Johnson, 1985; Ginsberg et al, 1991; L'Esperance et al, 2004). However, if stomal stenosis is diagnosed at the time of presentation, stoma revision is advised (L'Esperance et al, 2004).

Orthotopic diversions and augmented bladders may be safely treated through a transurethral approach (Kronner et al, 1998; DeFoor et al, 2004; L'Esperance et al, 2004). In patients who have undergone bladder neck reconstruction or anti-incontinence procedures, great care must be exercised to prevent disruption of the continence mechanism (Woodhouse and Robertson, 2004). The use of instrumentation up to 21 Fr with and without dilation in these instances has been reported, with no ill effects on continence (Palmer et al, 1993). **Endoscopic management through a Mitrofanoff catheterizable conduit is not advised,** because disruption of the continence mechanism can occur (DeFoor et al, 2004; L'Esperance et al, 2004). Visualization of stone fragments embedded in redundant folds of the augmented bladder may render complete eradication of stone through a transurethral approach difficult (Woodhouse and Robertson, 2004).

Success with percutaneous access of augmented bladders has been reported, although the risk of extravasation of irrigant material can occur if the bladder is not adherent to the abdominal wall. Inadvertent bowel injury and bladder perforation may occur, although the incidence is rare (Palmer et al, 1993; Docimo et al, 1998; Kaefer et al, 1998; Woodhouse and Lennon, 2001; Cain et al, 2002; Woodhouse and Robertson, 2004). In skilled hands, **the percutaneous approach can prove as efficacious as open cystolithotomy** (Docimo et al, 1998). Open cystolithotomy is often the preferred approach for large stone burdens or multiple calculi (Blyth et al, 1992; Palmer et al, 1993; Kaefer et al, 1998; Kronner et al, 1998; Woodhouse and Lennon, 2001; DeFoor et al, 2004; Woodhouse and Robertson, 2004).

The management of pouch calculi depends largely on the pouch type. **Transstomal endoscopic management of Indiana and Penn pouch stones is not recommended owing to concerns over injury to the catheterizable limb or disruption of the continence mechanism** (Patel and Bellman, 1995; L'Esperance et al, 2004; Lam et al, 2007). In such cases, percutaneous access is advocated (Arai et al, 1993; Hollensbe et al, 1993; Patel and Bellman, 1995; Beiko and Razvi, 2002; L'Esperance et al, 2004). However, the larger caliber and intussuscepted nipple of the Kock pouch allows for safe transstomal endoscopic access (Ginsberg et al, 1991; Cohen and Streem, 1994; Patel and Bellman, 1995; Woodhouse and Lennon, 2001). Extracorporeal shockwave lithotripsy has been attempted in a limited number of patients with good initial success (Boyd et al, 1988; Cohen and Streem, 1994).

One novel approach to the percutaneous management of pouch calculi consists of the introduction of a flexible cystoscope through the catheterizable stoma, followed by distention of the pouch. Percutaneous access is obtained under direct vision, and a laparoscopic entrapment sac is passed through the percutaneous tract. The stones are then loaded into the sac and then the sac is partially extruded through the access tract. An Amplatz sheath is introduced into the sac, and ultrasonic lithotripsy is performed to reduce the stones, allowing for extraction through the percutaneous site (Lam et al, 2007).

Key Points: Presentation and Management

- Hematuria is the most common sign of bladder stones.
- Percutaneous cystolithotomy is highly successful in clearing bladder stones and may be less traumatic than transurethral approaches.

Bladder Calculi and Bladder Cancer

Bladder calculi may be associated with urothelial malignancy, certainly as a byproduct of malignancy in terms of encrustation of bladder tumor or necrotic areas of tissue after transurethral resection of bladder tumor (Smith and O'Flynn, 1975). In addition, some authors suggest that the presence of bladder stones may also promote malignant change through chronic irritation of the bladder mucosa, similar to the link previously noted between mucosal irritation and inflammation from long-term indwelling catheters and squamous cell bladder cancer (Groah et al, 2002; Papatsoris et al, 2006). However, of the few focused studies examining this relationship, in none were the researchers able to find a causal link between bladder stones and subsequent malignancy (La Vecchia et al, 1991; Jhamb et al, 2007).

PROSTATIC CALCULI

Prostatic calculi are overwhelmingly common, with **99% of asymptomatic adult men noted to have some degree of prostatic calcification at the time of autopsy, regardless of age** (Søndergaard et al, 1987). Although small areas of microcalcification are generally noted during the second and third decades of life, a sharp increase in the size and overall calculus load occurs during the fifth decade of life, a trend that appears to continue with further aging (Klimas et al, 1985; Søndergaard et al, 1987; Bock et al, 1989; Geramoutsos et al, 2004). Prostate-specific antigen levels are unaffected by the presence of prostatic calculi (Lee et al, 2003).

Pathogenesis and Associated Anatomic Data

Prostatic calculi are believed to arise as a result of inspissation of prostatic secretions within the prostatic ducts. Subsequently, concentric layers of stone material, generally composed of calcium phosphate and calcium carbonate, are deposited on this inspissated core, resulting in gradual growth of the calculus (Sutor and Wooley, 1974; Torres et al, 1979; Kamai et al, 1999). Typically, these calculi remain asymptomatic throughout an individual's lifetime; however, rare cases of exceptionally large calculi causing urinary tract obstruction have been reported (Kamai et al, 1999; Bedir et al, 2005).

The majority of calculi, up to 93%, are found in the posterior and posterolateral zones of the prostate, along the course of large prostatic ducts (Young, 1934; Huggins and Bear, 1944; Fox, 1963; Hassler, 1968; Søndergaard et al, 1987). The second most common area of incidence appears to be centrally located within the anterior aspect of the prostate, found in approximately 23% of patients (Hassler, 1968; Søndergaard et al, 1987). Although scattered microcalcifications are noted within the central zone, the presence of large calculi abutting the urethra is rare, perhaps explaining the infrequency of associated obstructive urinary symptomatology (Søndergaard et al, 1987; Kamai et al, 1999; Bedir et al, 2005). In the elderly, prostatic calculi are more commonly encountered in hyperplastic prostates with areas of nodularity; however, anatomic studies fail to reveal a correlation between areas of nodularity and areas of stone formation (Søndergaard et al, 1987). Prostatic calcification may occur as a rare complication of external-beam irradiation for prostate cancer (Jones et al, 1979).

Implications for Chronic Pelvic Pain Syndrome, Prostatitis, and Prostate Cancer

Given the high incidence of chronic pelvic pain in the male population (McNaughton Collins et al, 1998, 2002; Roberts et al, 1998; Benway and Moon, 2008), recent interest has been focused on evaluation of the potential role of prostatic calculi in the natural history of chronic pelvic pain syndromes. It is estimated that 25% to 47% of men with chronic pelvic pain syndrome are found to harbor significant areas of calcification within the prostate (Evans et al, 2007; Shokses et al, 2007), although the significance of these calculi remain unclear.

One recent study of males between the ages of 21 and 50 found that patients with at least one symptom of prostatitis are 3.2 times more likely to harbor large, coarse prostatic calculi than asymptomatic age-matched cohorts, whereas diffuse areas of microcalcification do not appear to be correlated with prostatitis symptoms. Moreover, the authors noted that it is the size, and not the number of stones, that appears to correlate with the risk of pelvic pain syndromes (Geramoutsos et al, 2004).

Another recent study found that the presence of calculi does not correlate with the severity of prostatitis symptoms on validated questionnaires; however, the duration of reported symptoms is positively correlated with the presence of prostatic stones. Interestingly, patients with prostatic stones were less likely to demonstrate pelvic floor tenderness on examination than those patients whose imaging did not demonstrate significant prostatic calcification. In addition, patients with prostatic calculi were more likely to have positive localized cultures for pathogens such as *Escherichia coli*, enterococci, *Klebsiella* species, and gram-positive pathogens, as well as higher white blood cell counts in expressed prostatic secretions (Shokses et al, 2007). However, other investigators have found no concrete association between prostatic inflammation and infection and the presence of calculi (Hassler, 1968; Søndergaard et al, 1987).

Although some reports have proposed an association between inflammation of the prostate and an increased risk of prostate cancer (Roberts et al, 2004; Sutcliffe and Platz, 2007, 2008), the lack of reliable association between prostatic calculi and

inflammation casts doubt on the role of prostatic calculi in the pathogenesis of prostate cancer. Indeed, a focused pathologic evaluation of patients with prostate cancer found no association between areas of calcification and the location of adenocarcinoma (Muezzinoglu and Gurbuz, 2001).

Evaluation and Management

Because most prostatic calculi are asymptomatic, few patients will ever require specific evaluation for intraprostatic stone disease. However, imaging tests performed for other indications may reveal the presence of prostatic calcification. On plain film, prostatic calculi are noted in up to 14% of patients (Fox, 1963). Because computed tomography and magnetic resonance imaging are not advocated for the evaluation of patients with benign prostatic disease (Scheckowitz and Resnick, 1995), reports on the incidence of prostatic calculi with cross-sectional imaging have not been reliably reported. Transrectal ultrasonography is highly sensitive for the detection of large prostatic calculi, although it does not appear to accurately resolve areas of diffuse calcification, as evidenced by the more than twofold increase in discovery of calcifications on pathologic sectioning (Søndergaard et al, 1987; Shokses et al, 2007).

For rare patients who experience significant morbidity from prostatic calculi, removal of the affected tissue through open prostatolithotomy or transurethral resection should prove curative (Kamai et al, 1999; Bedir et al, 2005; Shah et al, 2007).

URETHRAL CALCULI

Urethral calculi are among the least common manifestations of lower urinary tract lithiasis, **representing only 0.3% of all urinary stone disease** in an endemic region (Aegukkatajit, 1999). Urethral calculi are exceedingly uncommon throughout industrialized Western societies but are more commonly encountered in underdeveloped nations, as well as in endemic regions throughout Asia and the Middle East (Amin, 1973; Koga et al, 1990; Seltzer et al, 1993; Aegukkatajit, 1999; Menon and Martin, 2002; Verit et al, 2006).

Urethral calculi have a bimodal age distribution, with peak incidences in early childhood, as well as in the fourth decade of life (Kamal et al, 2004; Verit et al, 2006). Increased urinary peak flow rates may exert a protective effect in the second and third decades of life by allowing for increased clearance of calculi that migrate into the urethra, which may in part account for the relative paucity of urethral stone disease noted in this demographic group (Jørgensen and Jensen, 1996; Kamal et al, 2004; Verit et al, 2006).

Pathogenesis and Composition

Urethral calculi may result from migration from the bladder or upper tracts or may arise de novo, generally in association with an anatomic abnormality such as a stricture or diverticulum or from condensation on a foreign body. They occur very rarely in females, owing to the comparatively shorter urethral length (Menon et al, 1998; Menon and Martin, 2002; Kamal et al, 2004; Verit et al, 2006; Rivilla et al, 2008).

Migratory Calculi

Migratory calculi account for a large proportion of urethral calculi in children and adults living in underdeveloped nations, where cereal-based diets predominate (Menon and Martin, 2002; Verit et al, 2006). A lower urinary tract pathologic process, such as benign prostatic hyperplasia, urethral stricture, or meatal stenosis, is often present and may serve as a predisposing factor that inhibits the ability to clear migratory calculi (Hegele et al, 2002; Kamal et al, 2004; Verit et al, 2006). Patients may also have a history of prior instrumentation or self-mutilation, which may contribute to urethral anomalies such as strictures (Subbarao et al, 1998).

Although the bladder has long believed to be the primary source of migratory urethral calculi (Shanmugam et al, 2000), recent evidence is challenging that supposition. Calcium oxalate is the predominant component in 86% to 100% of modern migratory urethral calculi, a component associated primarily with upper tract calculi and found rarely in native bladder calculi, where struvite and uric acid components predominate (Douenias et al, 1991; Menon et al, 1998; Kamal et al, 2004; Verit et al, 2006). Furthermore, one recent study found that only 2% of patients with migratory urethral calculi had associated bladder stones, whereas 18% were found to have concurrent upper tract calculus disease (Kamal et al, 2004). In addition, in endemic areas where cereal-based diets have been abandoned in favor of more protein-rich foods there has been a precipitous drop in the incidence of bladder calculi yet little decrease in that of urethral calculi (Aegukkatajit, 1999; Verit et al, 2006) or upper tract stone disease (Kamal et al, 2004).

Primary Urethral Calculi

Calculi that arise de novo in the urethra do so primarily through condensation of stone material on urethral foreign bodies or from stasis of urine in urethral diverticula. Struvite stones predominate, although calcium phosphate and uric acid calculi have also been reported (Singh and Neogi, 2006). Concomitant urinary tract infection with *E. coli, Proteus,* or enterococci is often diagnosed at the time of presentation (Subbarao et al, 1998; Gokce et al, 2004; Gallo et al, 2007; Rivilla et al, 2008; Susco et al, 2008).

When incorporating hair-bearing grafts, urethroplasty and hypospadias repair can lead to urethral stone formation. Despite attempts at thorough epilation of the graft, hair-bearing follicles may persist, leading to symptomatic hairball formation in 3% to 8% of patients undergoing the procedure (Rogers et al, 1992; Singh and Hemal, 2001). Stone encrustation of the hairball may occur, leading to symptomatic urethral calculi that remain adherent to the graft (Singh and Hemal, 2001; Walker and Hamilton, 2001; Rodriguez-Villalba et al, 2003; Hayashi et al, 2007). In addition, exposed suture material from urethral reconstruction may serve as a nidus for stone formation (Frydenberg and Love, 1988).

For patients afflicted with maladies of the prostate, including benign prostatic hyperplasia and prostate cancer, minimally invasive alternatives to simple and radical prostatectomy are becoming more commonplace. However, despite the success of these techniques, unanticipated outcomes of these techniques may lead to urethral lithiasis. For patients who have undergone transurethral resection or ablation of the prostate for benign disease, devitalized and necrotic residual tissue, along with associated inflammation, may serve as a nidus for stone formation within the prostatic urethra (Gawande, 1986; Aus et al, 1997); stone composition in these rare cases often consists of brushite, as well as apatite and calcium oxalate (Magura et al, 1980; Gawande, 1986). In addition, proteinaceous secretions from the residual tissue may also serve as a nidus for stone accumulation; in such instances, apatite and

calcium phosphate may comprise a larger proportion of stone material (Sutor and Wooley, 1974; Gawande, 1986).

Urethral calculi are also a rare long-term complication of patients undergoing brachytherapy and cryoablation of the prostate for carcinoma. Radioactive seeds left in situ after administration of brachytherapy may be prone to migration. Seeds that migrate into the urethra can serve as a nidus for calcification. Often, these patients present with a primary complaint of intermittent gross hematuria, instead of the obstructive symptoms more commonly encountered in other forms of urethral lithiasis (Steinmetz and Barrett, 2006). Urethral calculi are also reported as a rare complication of prostate cryotherapy for carcinoma, again with necrotic residual tissue serving as a nidus for stone formation. Prior treatment with external-beam irradiation and inadequate urethral warming appear to contribute to an increased risk of postoperative urethral lithiasis (Aus et al, 1997).

Finally, urethral lithiasis may arise as a secondary complication from self-mutilation. For instance, one report describes encrustation of two safety pins that had been inserted by a mentally handicapped patient. The stone was discovered after an indolent course with only mild lower urinary tract symptomatology (Gokce et al, 2004).

Calculi within Urethral Diverticula

Calculi found in association with a urethral diverticulum either may represent a primary calculus resulting from stasis of urine or may represent collection of migratory stone material (Dorairajan, 1963; Subbarao et al, 1998; Shanmugam et al, 2000; Walker and Hamilton, 2001). Stones will form in 1% to 10% of all urethral diverticula (Beatrice and Strebel, 2008); and with only one documented exception in the literature a **urethral diverticulum is present in nearly all reported cases of urethral calculi in females** (Martínez-Maestre et al, 2000; Gallo et al, 2007; Beatrice and Strebel, 2008; Rivilla et al, 2008; Susco et al, 2008). Diverticula may arise from congenital malformation or from traumatic or iatrogenic injury to the urethra, including straddle injuries, vaginal delivery, periurethral gland abscess, pelvic fracture, endoscopic and open surgical misadventure, and long-term urethral catheterization (Mohan et al, 1980; Parker et al, 2007; Beatrice and Strebel, 2008; Lin et al, 2008). However, antecedent urethral injury is absent in 50% to 90% of reported cases of male urethral diverticula (Marya et al, 1977; Bazeed et al, 1981). Stone composition of these calculi has not been reliably reported in the literature, although diverticular calculi are often associated with urinary tract infection (Subbarao et al, 1998; Gallo et al, 2007; Susco et al, 2008).

Presentation and Evaluation

The presentation of urethral calculus largely depends on pathogenesis and location of the stone within the urethra. **Patients with migratory calculi often present with acute lower urinary tract symptoms from sudden impaction of the stone, including stranguria, urinary retention, gross hematuria, and dysuria, whereas those with de novo urethral calculi and those residing in diverticula often present with more insidious symptoms.** Urinary tract infection is frequently diagnosed at the time of presentation (Hassan and Mahammed, 1993; Subbarao et al, 1998; Shanmugam et al, 2000; Kamal et al, 2004).

In one large contemporary series, acute urinary retention was the presenting complaint in 78% of all patients with urethral calculi while an additional 22% reported decrease of the urinary stream with dribbling of urine (Kamal et al, 2004). However, older reports vary widely in terms of presentation, with urinary retention rates as low as 0% and as high as 89% (Amin, 1973; Selli et al, 1984; Sharfi, 1991).

Migratory urethral calculi are typically solitary, although multiple calculi have been reported as urethral steinstrasse after shockwave lithotripsy and in one child with a proximal urethral stricture resulting from self-mutilation (Subbarao et al, 1998; Biyani et al, 1993; Atikeler et al, 2005; Verit et al, 2006). Thirty-two to 88 percent reside in the posterior urethra, whereas 8% to 58% are located in the bulbous and penile urethra and 4% to 11% are found at the fossa navicularis (Shanmugam et al, 2000; Kamal et al, 2004).

Calculi within urethral diverticula may be either singular or multiple. Their natural history is often insidious, with minimal obstructive symptoms. Rather, a protracted course of increasing lower abdominal, pelvic, and perineal discomfort as well as hematuria, dysuria, and dyspareunia is often the norm (Subbarao et al, 1998; Koh et al, 1999; Martínez-Maestre et al, 2000; Gallo et al, 2007; Beatrice and Strebel, 2008; Susco et al, 2008). In females, urinary frequency and stress urinary continence also have been reported (Susco et al, 2008).

Patients do not often seek treatment immediately, with delays ranging from several months to up to 10 years (Koh et al, 1999; Gallo et al, 2007; Beatrice and Strebel, 2008; Rivilla et al, 2008; Susco et al, 2008). In instances of prolonged delays in diagnosis, urethrocutaneous or urethrorectal fistulae may develop and may serve as the presenting complaint, especially in patients unable to report lower urinary tract discomfort, such as infants and patients with spinal cord injuries (Kaplan et al, 2006; Shamsa et al, 2008).

In most cases of penile and female urethral calculi the stone is readily palpable on examination, often recognized as a hard mass along the expected course of the male urethra or as a firm mass in the anterior vaginal wall (Subbarao et al, 1998; Martínez-Maestre et al, 2000; Gokce et al, 2004; Kaplan et al, 2006; Gallo et al, 2007; Beatrice and Strebel, 2008; Susco et al, 2008). Prostatic calculi are less commonly palpable and often require imaging or cystoscopic visualization to confirm the diagnosis (Gawande, 1986; Aus et al, 1997; Steinmetz and Barrett, 2006).

Despite early reports indicating that 60% of urethral calculi were radiolucent, in the modern era **98% to 100% of urethral calculi are radiopaque** and can be visualized on plain radiographs (Kamal et al, 2004; Verit et al, 2006). In addition, prostatic calculi are easily visualized on transrectal ultrasonography, as evidenced by significant shadowing around an area of increased signal density (Aus et al, 1997). However, given the potential for associated anatomic abnormality, many authors now advocate the use of urethrography or cross-sectional imaging to aid in diagnosis (Koh et al, 1999; Singh and Hemal, 2001; Hayashi et al, 2007; Rivilla et al, 2008; Susco et al, 2008).

Treatment

Treatment of urethral calculi is largely determined by their location within the urethra, as well as the presence of an associated anatomic pathologic process, such as a diverticulum. Stones located in the posterior urethra may be pushed back into the bladder for subsequent fragmentation with electrohydraulic or laser lithotripsy, a procedure that carries a success rate of 66% to 86% (Aus et al, 1997; Kamal et al, 2004; Verit et al, 2006). If subsequent fragmentation in the bladder is unsuccessful, open cystolithotomy may be required (Kamal et al, 2004). Shockwave lithotripsy after pushback into the bladder has been reported, although success rates were only 60% (El-Sharif and Prasad, 1995).

For stones in the anterior urethra, retrograde relocation to the bladder is rarely feasible and should therefore not be attempted. However, extraction of the stone by "milking" may be successful, provided the stone is smooth; the risk of urethral injury related to this method of extraction is unknown, and thus caution should be exercised (Rodriguez Martinez et al, 2000; Kamal et al, 2004; Maheshwari and Shah, 2005). In addition, milking of the calculus is not advocated if the stone is large or irregular or if it has a spiked surface (Kamal et al, 2004). Some authors have noted success with spontaneous expulsion of small distal stones after the intraurethral administration of lidocaine jelly (El-Sharif and El-Hafi, 1991; Kamal et al, 2004). Success with simple cystoscopic extraction has also been reported (Atikeler et al, 2005).

For calculi not amenable to simple manipulation, urethrotomy with stone extraction has long been the norm and is still advocated when concurrent urethroplasty or urethrocutaneous fistula repair is required (Singh and Hemal, 2001; Gokce et al, 2004). However, recent reports suggest **that in-situ lithotripsy of urethral calculi may be feasible, with reported success rates of up to 80%** (Kamal et al, 2004). Electrohydraulic and Swiss lithoclast fragmentation has been reported, although concerns exist regarding the potential for collateral damage to the surrounding urethral tissue (El-Sharif and El-Hafi, 1991; Koh et al, 1999; Kamal et al, 2004; Verit et al, 2006; Hayashi et al, 2007). Holmium laser lithotripsy has therefore been advocated, citing excellent efficacy with minimal trauma to the surrounding urethral tissue (Walker and Hamilton, 2001; Maheshwari and Shah, 2005).

Stones within diverticula may be addressed with incision of the diverticulum and stone extraction, although success with in-situ lithotripsy has been reported in a female patient (Subbarao et al, 1998; Singh and Neogi, 2006; Susco et al, 2008). Diverticulectomy and urethral repair may be performed concurrently or in a staged fashion (Subbarao et al, 1998; Martínez-Maestre et al, 2000; Karanth et al, 2003; Singh and Neogi, 2006).

PREPUTIAL CALCULI

Preputial calculi are a relatively uncommon manifestation of lower tract calculus disease, with only a handful of reported cases in the literature over the past 2 centuries. Preputial calculi may occur at any age but are far more common in adults and the elderly (Sharma and Bapna, 1977).

Virtually all cases of preputial calculi are associated with severe phimosis in uncircumcised males. Additional risk factors include poor hygiene and low socioeconomic status (Ellis et al, 1986).

Preputial calculi are postulated to arise from one of three possible mechanisms, including **inspissated smegma, stasis with precipitation of urinary salts, or a combination of the two,** typically with a nidus of smegma acting as a condensation nucleus for the precipitation of urinary salts (Winsbury-White, 1954; Ellis et al, 1986; Mohapatra and Kumar, 1989). In addition, smegma itself may act as a direct local irritant, leading to inflammation and scarring of the prepuce, which can cause further obstruction and urinary stasis (Parkash et al, 1973; Mohapatra and Kumar, 1989) and in some cases may create phimosis so severe that the prepuce may serve as an expansile urinary reservoir that collects large amounts of voided urine (Williamson, 1932). Other, less common avenues of pathogenesis include the presence of a foreign body, such as suture material (Ellis et al, 1986), as well as trapping of voided bladder calculi in patients with severe phimosis (Williamson, 1932; Nagata et al, 1999).

In nearly all reported cases of preputial calculi, **progressive difficulty with voiding is the most common presenting complaint.** Other symptoms may include dysuria, gross hematuria, foul-smelling discharge, ballooning of the prepuce with voiding, and palpable calculi within the preputial sac (Williamson, 1932; Shahi and Ram, 1962; Sharma and Bapna, 1977; Ellis et al, 1986; Mohapatra and Kumar, 1989; Nagata et al, 1999). In rare cases, presentation may be delayed until urinary retention develops (Shahi and Ram, 1962).

Evaluation includes careful history, noting the duration and nature of symptoms, as well as history of calculus disease. On physical examination, tight phimosis is often encountered, along with inflammation of the prepuce (Williamson, 1932; Shahi and Ram, 1962; Sharma and Bapna, 1977). The stones are often palpable on examination and may be freely mobile within the preputial sac (Williamson, 1932). **Bilateral inguinal lymphadenopathy, if present, should raise the suspicion of concurrent penile carcinoma** (Mohapatra and Kumar, 1989). Imaging with plain radiography may help to confirm the diagnosis of preputial calculi (Mohapatra and Kumar, 1989; Nagata et al, 1999).

Treatment involves removal of the calculi, as well as the primary cause of urinary obstruction and stasis, generally by circumcision or a dorsal slit procedure (Williamson, 1932; Shahi and Ram, 1962; Sharma and Bapna, 1977; Mohapatra and Kumar, 1989; Nagata et al, 1999). All foreign objects, including suture material, should be removed in their entirety (Ellis et al, 1986). The excised preputial tissue should be sent for histopathologic evaluation to rule out carcinoma. In addition, if an underlying ulceration of the glans is noted, a biopsy of the lesion should also be submitted for pathologic evaluation (Sharma and Bapna, 1977; Mohapatra and Kumar, 1989).

Opening of the preputial sac generally reveals multiple smooth, rounded calculi, which are brittle on examination (Williamson, 1932; Shahi and Ram, 1962). Stone composition varies in published reports but stones are most commonly composed of ammonium magnesium phosphate; however, other materials, including urate, calcium phosphate, and calcium oxalate, may be encountered as well (Sharma and Bapna, 1977; Ellis et al, 1986; Mohapatra and Kumar, 1989; Nagata et al, 1999). Culture may reveal growth of various pathogens, including enterococci and *E. coli,* the latter of which may be carcinogenic (Hawksworth and Hill, 1971; Ellis et al, 1986; Mohapatra and Kumar, 1989). Typically, all symptoms completely resolve after circumcision and calculus removal.

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chapter 90

Development, Molecular Biology, and Physiology of the Prostate

David M. Berman, MD, PhD ● Ronald Rodriguez, MD, PhD ● Robert W. Veltri, PhD

Developmental and Cell Biology
Endocrine Control of Prostate Growth
Regulation of Prostate Growth by Steroids and Protein Growth Factors
Regulation of Prostate Growth at the Molecular Level: Steroid Receptors
Prominent, Nonpeptide Components of Prostatic Secretions
Prostatic Secretory Proteins
Coagulation and Liquefaction of Semen
Prostatic Secretions and Drug Transport

The focus of this chapter is on the development, anatomy, histology, and physiology of the prostate and seminal vesicles, the male sex accessory glands that contribute to seminal fluid. It is worth noting that these roles are deduced by anatomic and physiologic observation but that male infertility is infrequently traced to disorders of these organs. Therefore, their physiologic roles in reproduction are either unimportant or, as the authors believe, exceedingly resistant to malfunction. In the specific case of the prostate, its physiologic role is overshadowed by a striking vulnerability toward other types of disease—pathologic prostate growth represents an especially important cause of morbidity and mortality in men. Because pathologic prostate growth in adults involves reactivation of physiologic growth and differentiation pathways that act in embryonic and perinatal development (Marker, 2008; Schaeffer et al, 2008; Pritchard et al, 2009), regulation of these events is a major scientific and clinical question and comprises the main discussion in this chapter. Our understanding of prostate growth control is based on phenotypic evaluation humans with genetic diseases affecting the androgen receptor (AR) signaling axis and on analysis of laboratory animals or cultured cells subjected to genetic, surgical, or pharmacologic manipulation. The experimental data represent the broadest and deepest vein of information on prostate growth control and are the major source for the discussion of this topic. Possible physiologic roles of cellular constituents of the prostate are described in the final section of this chapter, and this discussion may be useful for students of prostate biomarkers.

DEVELOPMENTAL AND CELL BIOLOGY

Seminal Vesicles

The sex accessory tissues include the epididymis, ampullae, seminal vesicles, prostate, Cowper (bulbourethral) gland, and glands of Littre. All of these glands have reproductive roles, but the seminal vesicles work in tandem with the prostate and provide an important counterpoint to its biology and pathologic processes. The seminal vesicles are two saccular glands that pair with the vasa deferentia to form the ejaculatory ducts that empty into the craniodorsal aspects of the prostate. Together with the prostate the seminal vesicles produce seminal fluid that nurtures, protects, and facilitates sperm transport for mammalian reproduction. The division of labor between the two glands is surprisingly variable. At one of end of the spectrum is the dog, a species in which seminal vesicles are absent and the prostate must therefore carry out the functions that are divided between the two glands in other species. Most mammals, including humans, rats, and mice, occupy the other end of the spectrum, in which the seminal vesicles produce most of the seminal fluid, with the prostate playing a minor role. In species with both glands, physiologic cooperation between the two glands is also appreciable at the molecular level. For example, the major secretory protein product of the seminal vesicles is semenogelin, a 52-kD protein that serves as a substrate for proteolytic enzymes produced by the prostate, including prostate-specific antigen (PSA). Proteolysis of semenogelin yields a variety of peptide byproducts that are believed to serve reproductive and antimicrobial functions in humans (Curry and Atherton, 1990). In mice and rats, seminal vesicle and prostate products cooperate to coagulate the ejaculate into a firm copulatory plug in the vagina during mating. The plug serves as a temporary barrier to further mating by the female, potentially blocking impregnation by competing males.

Embryonic Development of the Seminal Vesicles

Seminal vesicles develop from the mesonephric (wolffian) ducts shortly before the onset of prostate development. Seminal vesicle development is strictly dependent on an intact AR signaling pathway, including the ligand testosterone (reviewed in Wilson

et al, 1981). This requirement contrasts to development of the human prostate (see later), which, in addition to an intact AR pathway, requires conversion of testosterone into the more potent 5α-reduced androgen, dihydrotestosterone (DHT) (Andersson et al, 1991; Mahendroo and Russell, 1999).

Thick smooth muscle layers constitute the muscular stroma of the seminal vesicles, which surrounds a short columnar-to-cuboidal epithelium. The epithelium has distinct basal and luminal layers that are notable for unusually variable nuclear size and shape, a feature that is also found in prostate cancer (Epstein and Netto, 2007). Another notable feature of the epithelium of the seminal vesicles, the almost invariable appearance of gold-colored intracytoplasmic pigment, is usually absent in prostate cancer and helps to clarify any confusion between the two entities. Seminal vesical pigment is thought to derive from cellular byproducts of nonviable sperm ingested by the seminal vesical epithelium (spermatophagy).

The seminal vesicles are extremely resistant to disease. Given their proximity, shared functions, and similar endocrine requirements to the prostate, it is striking that diseases of the seminal vesicles in humans are vanishingly rare. In contrast, prostate disease, at least in Western cultures, is a nearly universal rite of passage into old age (see subsequent chapters on benign prostatic hyperplasia and prostate cancer). Accordingly, contrasting gene expression between seminal vesicles and prostate has been used as a strategy to discover the molecular basis of prostate cancer risk (Thompson et al, 2008).

The Prostate

Regional Differentiation of the Lower Urinary Tract

The prostate is a derivative of the primitive endoderm (gut tube). Regional differentiation of the primitive gut tube into foregut, midgut, and hindgut is followed by a swelling at the caudal end that creates the cloaca (see Chapter 111). The *cloaca*, a Latin term meaning "sewer," receives output from both the urinary and intestinal tracts and represents the fully differentiated state in birds, reptiles, amphibians, marsupials, and monotrenes. In placental mammals, however, the cloaca is divided by the urorectal septum during embryogenesis to create separate urinary and digestive outlets. The ventral urinary compartment is called the primitive urogenital sinus, which further segments into the urinary bladder at its cranial end and the urethra at its caudal terminus.

Prostate Budding

In males, the prostate develops just caudal to the bladder neck via the proliferation of epithelial buds extending out from the urogenital sinus epithelium. Prostate buds invade at stereotyped locations that pattern the future development of distinct prostate lobes in the rodent and, potentially, zones in the human. These regions prepare for epithelial bud invasion by "mesenchymal condensation," a process in which urogenital sinus mesenchymal cells (cells constituting loose connective tissue that will differentiate into stromal elements) become closely packed together (reviewed in Thomson, 2008). This condensation occurs in both males and females and is therefore androgen *independent*. In contrast, epithelial budding is strictly androgen-*dependent* and represents the first events in prostate development that are identifiable at the light microscopic level. Prostate budding requires intricate epithelial-mesenchymal interactions (Fig. 90–1). In humans, prostate budding occurs during the 10th week of gestation. In mice, prostate budding occurs on the 17th gestational day, 2 days before birth. Importantly, androgen exposure is not only *necessary* but also *sufficient* to drive prostatic differentiation and growth in the embryo. This fact, along with the ability to easily manipulate androgen levels in experimental animals, makes the prostate a particularly appealing subject for the study of epithelial cell fate determination (Cunha et al, 1987; Schaeffer et al, 2008). Prostate buds initially grow as solid epithelial cords that subsequently (postnatal days 1 to 14 in mice) branch and canalize (Sugimura et al, 1986) as part of a sophisticated branching morphogenesis program.

Cytodifferentiation

In the mouse, the urogenital sinus epithelium begins as a homogeneous cell compartment that differentiates (after birth in mice) into distinct basal (adjacent to stroma) and luminal layers (Wang et al, 2001). Intervening epithelial cells, called "intermediate cells," are present that have features of both basal and luminal cells. A fourth cell type, the neuroendocrine cell, is present in large numbers before prostate epithelial budding and decreases during embryonic development (Aumuller et al, 2001). The development of this cell type during mouse embryogenesis has not been well characterized, and the source of these cells has been variously proposed to be neural crest or urogenital sinus endoderm (Aumuller et al, 2001; Goldstein et al, 2008), illustrating the need to further delineate lineage commitment events in prostate epithelium.

Molecular Features of Prostate Development

Induction of Prostate Budding. Although AR signaling through DHT is the primary motivating force behind prostate development, it specifies only the timing of events not their location. The AR signaling machinery is present diffusely throughout the lower genitourinary tract (Takeda et al, 1985; Berman et al, 1995). Prostate epithelial buds form at precise locations through mechanisms that are not understood. This spatial control may involve paralogous homeobox (*Hox*) genes, which are transcriptional regulators that govern differential gene expression along the craniocaudal (head to tail) and proximodistal (e.g., shoulder to fingertip) axes in a variety of tissues, including the genitourinary tract (reviewed in Beck et al, 2000; Kmita and Duboule, 2003). In vertebrates, the paralogous *Hox* genes exist as four similar clusters (clusters A, B, C, and D), each of which resides on a separate chromosome and encodes genes whose chromosomal position from 3′ to 5′ mirrors their expression pattern in the embryo. The paralogous genes are distinct from other more distantly related transcription factor families that also contain DNA-binding homeobox motifs, such as the NK family whose members are expressed in a more discrete, organ-specific manner (e.g., see Nkx3.1, later). Paralagous *Hox* genes are sequentially numbered from 1 to 13, with the higher numbers in the 5′ position showing the most distal or caudal expression patterns. Accordingly, *Hoxa13, Hoxb13,* and *Hoxd13* are *paralogues* on chromosomes 7, 17, and 2, respectively, that have overlapping expression patterns and functions in distal genitourinary tract development. *Hoxb13* regulatory elements have been characterized that restrict its function to the caudal end of the genitourinary and digestive tracts and can be used to engineer androgen-independent prostatic expression of genes of interest (McMullin et al, 2009). Homozygous mutations in individual *Hox* genes result in subtle changes in prostatic branching patterns (Podlasek et al, 1997) and/or defective epithelial maturation (Economides and Capecchi, 2003). Mutations involving more than one of these genes results in significantly more severe urogenital phenotypes, such as significant prostate hypoplasia in

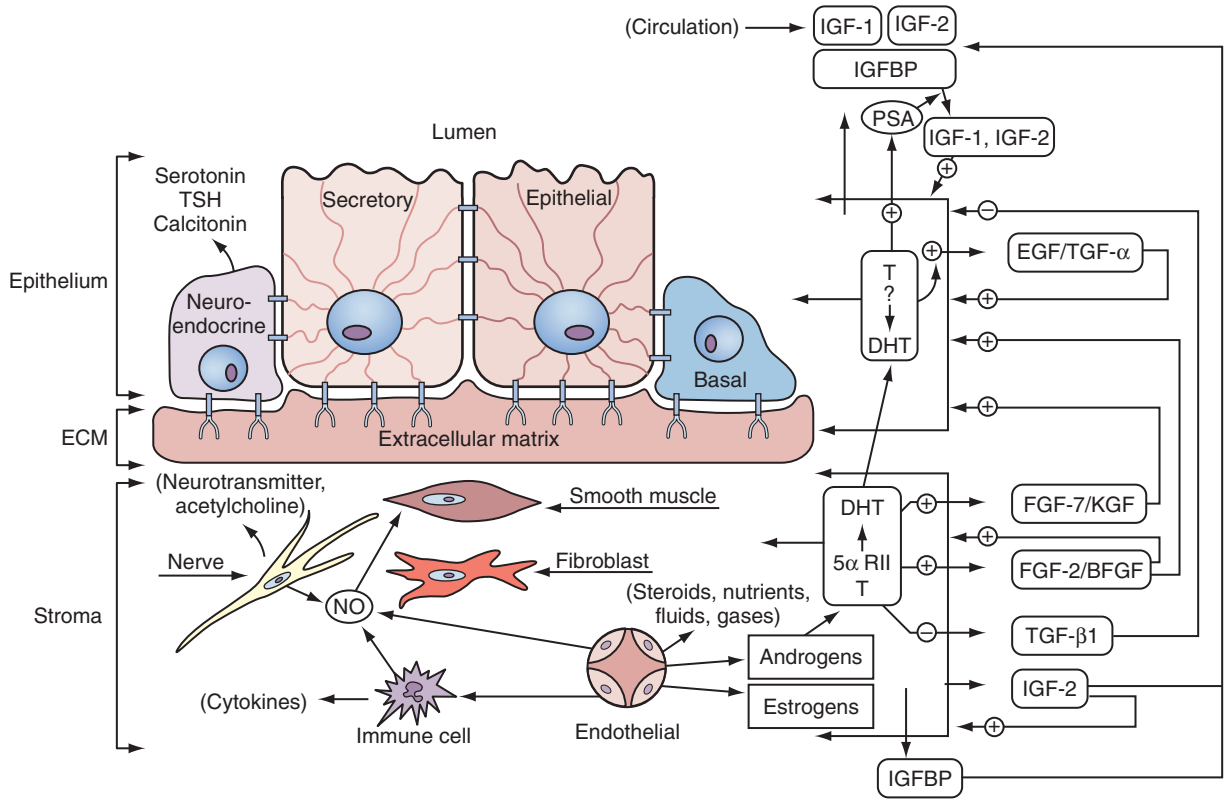


Figure 90–1. Stromal-epithelial interactions. Shown is a schematic of the types of stromal-epithelial interactions in information transfer and regulation within the prostate. Testosterone and growth factors interact on and between stromal and epithelial cells. The production of growth factors is either stimulated or inhibited by androgens. The growth factors can function on the same cell (autocrine) or on distant cells (paracrine). Nitric oxide (NO) is formed from nerve cells, endothelial cells, or macrophages and affects smooth muscle contraction (see text for details). Important features in this schematic are (1) three types of prostate epithelial cells—neuroendocrine, secretory, and basal; (2) five important prostatic stromal cells—smooth muscle, fibroblast, immune cells, endothelial cells, and nerve cells; (3) testosterone converted to dihydrotestosterone (DHT) by 5α-reductase in the stromal compartment; (4) three sources of NO production in the prostate—nerve, immune cells (e.g., macrophages), and endothelial cells; and (5) stromal-epithelial interactions mediated through various growth factors (see text). ECM, extracellular matrix.

Hoxd13/Hoxb13 compound mutant mice or failure of separate urinary and gastrointestinal tract outlets to form in *Hoxa13/Hoxd13* compound mutants (Kondo et al, 1997; Warot et al, 1997). These multigene experiments are technically challenging and have not yet revealed the effects of complete loss of *Hox* gene function in the prostate.

Mesenchymal condensation occurs in both males and females, so it is not sufficient to drive prostate development but may be necessary. Condensation of the ventral mesenchymal pad is defective in mice lacking the gene for Noggin (see TGF-β family section later for further discussion of the roles of Noggin in prostate development), which antagonizes binding of bone morphogenetic protein (BMP) ligands to their receptors (Cook et al, 2007). This observation suggests that BMP signaling enhances mesenchymal condensation, either by direct action on mesenchyme or through regulation of epithelial-derived factors important in this process. Condensed mesenchyme is highly enriched for expression of fibroblast growth factors (FGFs) that are essential for epithelial bud outgrowth. For example, mice with engineered mutations of the mesenchyme-specific growth factor *Fgf10* gene generate small abortive epithelial buds and fail to grow prostates (Donjacour et al, 2003).

Epithelial Budding. Epithelial expression of the NK homeobox transcription family member Nkx3.1 is the earliest indicator of prostate development at the *molecular* level. This transcription factor influences the degree of branching in the mature mouse prostate, where it can act as a tumor suppressor (Bieberich et al, 1996; Bhatia-Gaur et al, 1999; Abate-Shen et al, 2008). Nkx3.1 (Bhatia-Gaur et al, 1999), Sox9 (Lupien et al, 2008; Schaeffer et al, 2008; Thomsen et al, 2008), and sonic hedgehog (Podlasek et al, 1999) are expressed in emerging prostate buds, but prostate buds can emerge in the absence of these factors (see later).

Genes Required for Prostate Epithelial Budding. Mutations in the transcriptional regulator p63 *(TP63)* (Signoretti et al, 2000) or in the AR signaling axis (reviewed in Cunha et al, 1987) can completely abolish prostate induction. Noggin mutations selectively impair budding of the ventral lobes of the prostate, leaving anterior and dorsolateral budding unimpaired (Cook et al, 2007). Overall, however, the process appears to be a very robust one, with evidence of prostate epithelial bud formation persisting in the presence of a variety of genetic mutations that affect future steps in prostate ductal morphogenesis, particularly branching morphogenesis. TP63 has transcriptional repressor and activator activities that balance differentiation and stem/progenitor cell functions in epithelia (McKeon, 2004). The transcriptional targets of TP63 in prostate epithelial cells remain to be elucidated (Grisanzio and Signoretti, 2008).

Andromedins. One of the most striking aspects of the induction of prostate epithelial budding is the finding by Cunha and Lung (1978) that AR signaling is required in the mesenchyme but

dispensable in the epithelium. Thus the action of androgens in this process appears to be indirect. This has led to the hypothesis that mesenchymal cells secrete inductive factors in response to androgens called "andromedins" (Yan et al, 1992). Andromedins have proven to be elusive quarry. Indeed, androgen-regulated mesenchymal factors have been difficult to identify much less characterize functionally (reviewed in Thomson, 2008), leading to alternative hypotheses involving androgen-mediated suppression of soluble factors (Tenniswood, 1986) or of smooth muscle cell barriers (Thomson et al, 2002) that inhibit induction of prostate epithelial budding. Studies to unravel the mechanism by which AR can indirectly induce prostate lineage commitment and growth are ongoing and are likely to yield important insights into the basic underpinnings of both physiologic and pathologic prostate growth.

Molecular Control of Branching Morphogenesis. Once set in motion, prostate growth and homeostasis continues to require androgens throughout life and this requirement appears to continue to be indirect, through mesenchymal or stromal AR signaling. Epithelial branching morphogenesis occurs through signaling cascades that inhibit further outgrowth along the long axis of an extending epithelial bud while stimulating lateral growth at its tip (Hogan, 1999). Through engineered deletion of genes in transgenic mice, several individual genes and components of classic morphogenetic pathways have been shown to be required for branching morphogenesis. Indeed, morphologic aberrations seen on interruption of a cellular pathway may be the most sensitive measure of a role for that pathway in regulation of prostate growth. As such, a wide variety of genes and pathways have been strongly implicated in prostate branching morphogenesis, only a few of which are covered here. For a more comprehensive perspective, including additional pathways such as those centered around Notch and Forkhead proteins, the reader is referred to recent reviews (Leong and Gao, 2008; Matusik et al, 2008).

The transcription factor Nkx3.1 (see earlier) helps determine the branching pattern of the prostate, as demonstrated by the reduced numbers of duct tips seen in mice with engineered *Nkx3.1* deletion (Bhatia-Gaur et al, 1999). This relatively subtle phenotypic change may be important, however, as indicated by a dramatic decrease in the ability of Nkx3.1-mutant prostates to manufacture mature secretory proteins (Bhatia-Gaur et al, 1999). The regulatory machinery that promotes Nkx3.1 expression early in prostate induction has been used to drive expression of Cre recombinase to specifically inactivate other genes in prostate epithelial cells (Lin et al, 2007; Thomsen et al, 2008; Zhang et al, 2008).

Nkx3.1-Cre–mediated deletion was used to show that the sex-determining region Y–box 9 (Sox9) transcription factor is required for the development of the ventral lobe of the mouse prostate. Ventral lobe buds appeared at the normal embryonic age but failed to grow out and branch. The specificity of this proliferative defect for the ventral lobe, rather than other lobes, could be due to either a lobe-specific role for Sox9 or to a delay in Cre-mediated Sox9 excision found in the other prostate lobes. The latter possibility would be consistent with a transient requirement for the protein in ductal outgrowth (Thomsen et al, 2008).

Fibroblast Growth Factors

The fibroblast growth factor (FGF) family of related secreted peptides promote growth in recipient cells by binding to cell surface receptors and activating intracellular second messenger cascades. Epithelial branching morphogenesis, be it in the lung, salivary gland, mammary gland, or prostate, requires such signals to proceed. Of the FGFs, Fgf-7 (keratinocyte growth factor) and Fgf-10 have been studied most extensively in prostate development. Both of these ligands preferentially bind to Fgfr-2 over the three other family members (FGFRs 1, 3, and 4) (reviewed in Thomson, 2001, 2008). Ligand binding activates the intracellular microtubule-associated protein kinase (MAPK) pathway, leading to enhanced activity of growth-promoting transcription factors and increased proliferation.

Fgfr-2 is expressed on developing prostate epithelial cells where it can interact with its coreceptor Frs-2α. Fgf-7 and Fgf-10, in contrast, are secreted by prostate mesenchyme. This arrangement, along with androgen-independent growth of prostate organ cultures exposed to these ligands, have led to the proposal that they act as andromedins (Yan et al, 1992; Lu et al, 1999). However, Thomson and associates (2002) make a compelling argument to the contrary, pointing out that Fgf-7 and Fgf-10 expression patterns are equivalent in male and female rodent embryos and are therefore unlikely to mediate AR signaling from mesenchyme to epithelium. Instead, FGF signaling appears to have a critical role in epithelial outgrowth that is downstream of as yet undetermined prostate-inductive events. This role was demonstrated most dramatically by almost complete failure of prostate development in Fgf-10–deficient mice (Donjacour et al, 2003) and further supported by prostate hypoplasia and decreased epithelial branching in mice with prostate-targeted deletion of the genes encoding Fgfr-2 or Frs-2α.

The Hedgehog (Hh) Signaling Pathway. Across a variety of organs, elaboration of secreted hedgehog ligands (Sonic hedgehog, Indian hedgehog, and Desert hedgehog) by epithelial cells and reception in adjacent mesenchyme coordinates the activities of the Gli family proteins in regulating hedgehog pathway target genes. In the mesenchyme of developing prostate, several Hh target genes have been identified (Yu et al, 2009), including the cytokine Cxcl14, the insulin-like growth factor–binding protein Igfbp3, and the delta/notch-like epidermal growth factor–related receptor Dner. The roles of these particular genes in prostate development have yet to be ascertained, but, as a whole, Hh pathway target genes have been implicated in placement of prostate epithelial buds and in subsequent ductal branching and outgrowth. In particular, buds form in the absence of the dominant Hh ligand in the prostate (Berman et al, 2004) but are mislocalized in prostates of mice bearing mutations of downstream effectors of the pathway, Gli proteins (Doles et al, 2006). Later on in development, Hh ligands enhance epithelial outgrowth and branching (Freestone et al, 2003), which proceed abnormally in prostate organ cultures treated with Hh pathway antagonists (Lamm et al, 2002; Freestone et al, 2003; Berman et al, 2004). In adult animals the pathway may play a role in homeostasis, as indicated in a failure of prostates to regenerate after castration of animals treated with antibodies or small molecules that block Hh signaling (Berman et al, 2004). Taken together, these data indicate a growth-promoting role for the pathway in prostate epithelium, one that may have clinical relevance in pathologic prostate growth (reviewed in Shaw and Bushman, 2007).

The Transforming Growth Factor β (TGF-β) Superfamily. TGF-β superfamily members include TGF-β itself, as well as members of the growth and differentiation factors (GDFs) and the bone morphogenetic proteins (BMPs). These factors act through transmembrane receptors and the SMAD family of intracellular signal transducing proteins (Schmierer and Hill, 2007). Little is known about GDFs in the prostate, but both TGFs and BMPs are likely to play important roles. In organogenesis this superfamily is best known as a mesenchymal mediator of epithelial growth

suppression, but (less frequently) they can also stimulate growth and/or be produced by epithelial cells. TGF-β1 inhibits net growth of the prostate but can stimulate growth in certain regions of the gland, particularly in the distal tips of the ventral prostate (Tomlinson et al, 2004a). Although the mechanism for growth promotion by TGF-β1 is unclear, the growth suppressive effect could quite reasonably relate to its ability to suppress levels of another mesenchymal growth factor FGF-10 (Tomlinson et al, 2004b) (see FGF section, earlier). A similar mechanism could remain in place in mature males, where TGF-β signaling in proximal ducts is believed to help to maintain prostate epithelial stem cells in a quiescent (growth-suppressed) state (Salm et al, 2005). BMP4 and BMP7 exert important and highly localized growth-suppressive activities in prostate development that help guide branching morphogenesis and prevent overproduction and disorganized epithelial growth. Like TGF-β, BMPs are most active during epithelial budding and subsequent prostate branching (Lamm et al, 2001; Tomlinson et al, 2004a; Grishina et al, 2005) (embryonic day 17 through postnatal day 5 in the mouse). Activation of BMP signaling suppresses branching morphogenesis, as indicated by experimental addition of exogenous BMP4 or BMP7 protein to prostate organ cultures (Lamm et al, 2002; Grishina et al, 2005) or by genetic deletion of the BMP inhibitor Noggin (Cook et al, 2007). BMP inactivation can show the opposite effect, as epithelial overgrowth of prostates with genetic deletion of BMP7 (Grishina et al, 2005).

Prostate Zonal and Lobar Anatomy. The rodent prostate is divided into paired anterior, dorsolateral, and ventral lobes. Each empties into to the urethra separately at its proximal extreme, with the distal end floating freely in the pelvic cavity. In contrast, the human prostate, like that of most primates and canine species, grows as a single organ encircling the urethra. In man and in dog, the latter arrangement is coupled with a propensity to grow in old age (benign prostatic hyperplasia), making males vulnerable to urinary obstruction (see Chapter 91). In rodents, the anterior, ventral, and dorsolateral lobes are named for the distinct locations of the urethra from which they originate. Each lobe also has a different branching pattern with a distinctive histologic appearance. These differences reviewed by Timms (2008) have been likened to different zones of the human prostate, histologically (Price, 1963), molecularly (Berquin et al, 2005; Thielen et al, 2007), and in terms of propensities to be affected by disease. In mice, mRNA transcripts for spermine-binding protein, probasin, and renin-1 are specific for ventral, dorsolateral, and anterior lobes, respectively (Cook et al, 2007), whereas human zone specific gene expression has not been as well characterized. Of particular interest, the mouse dorsolateral prostate shares molecular and histologic similarities to the peripheral zone of the human prostate, the zone most prone to the development of cancer.

Prostate Cell Types

The prostatic epithelium in the human is composed of two major cellular compartments: epithelial cells and stromal cells (Table 90–1). The prostate epithelial compartment consists of basal epithelial cells, intermediate cells, neuroendocrine cells, and luminal secretory epithelial cells (reviewed by De Marzo et al, 1998a). The stromal compartment architecturally serves as structural support and consists predominantly of connective tissue, smooth muscle cells, and fibroblasts. Most prostate cell types have been characterized in vitro (Peehl, 2005).

In most glands with renewing cell populations there is a steady-state flow of cells from mostly quiescent stem cells to a more rapidly dividing pool of transient proliferating cells. This proliferating population finally reaches terminal differentiation, characterized by metabolically active secretory epithelium. In the prostate, cell lineage has not been rigorously determined but has been inferred from a variety of sources. A hypothetical differentiation scheme for prostate epithelium is presented in Figure 90–2. As in most multilayered epithelia, stem cells reside in the basal compartment and appear to give rise to all of the other epithelial cell types, as well as neuroendocrine cells. These include fully differentiated secretory cells that line glandular lumina (luminal cells), neuroendocrine cells that secrete bioactive peptides, and intermediate cells that show phenotypic features that are intermediate between basal cells and luminal cells.

Key Points: Embryonic Development

- The wolffian ducts develop into the seminal vesicles, epididymis, vas deferens, ampulla, and ejaculatory duct. The developmental growth of this group of glands is stimulated by fetal testosterone and not dihydrotestosterone.
- Through tissue recombination experiments in mice and rats, the developing urogenital sinus mesenchyme and epithelium have been shown to partner in prostate development. That is, the development, growth, and function of the male and female urogenital tract require stromal-epithelial interaction and action of steroid sex hormones. Androgen acts on the mesenchyme to indirectly induce prostate epithelial outgrowth during development and homeostasis in adulthood.

Luminal Epithelial Cells

The luminal epithelial cell is the "workhorse" of the prostate gland, responsible for epithelial barrier integrity and production of prostatic secretion. Luminal cells constitute most of the prostate epithelium. These tall (10 to 20 μm) columnar secretory epithelial cells are terminally differentiated and have a low proliferative index (De Marzo et al, 1998a); they are easily distinguished by their morphologic features and abundant secretory granules and enzymes. Secretory cells produce a variety of proteins that characterize prostatic differentiation, including PSA, acid phosphatase, AR, leucine amino peptidase, and 15-lipoxygenase-2 (Shappell et al, 1999; Bhatia et al, 2003). They are also rich in keratin filaments (subtypes 8 and 18) (van Leenders and Schalken, 2003). These tall, columnar secretory cells appear in rows like a picket fence with each cell connected to the next by cell adhesion molecules; the apical aspect of these cells projects into the lumen, with the base attached to a basement membrane through integrin receptors (Knox et al, 1994). The nucleus is at the base just below a clear zone (2 to 8 μm) of abundant Golgi apparatus, and the upper cellular periphery is rich in secretory granules and enzymes. The apical plasma membrane facing the lumen possesses microvilli, and secretions move into the open collecting spaces of the acinus. These epithelial cells ring the periphery of the acinus and produce secretions into the acini that drain into ducts connected to the urethra.

Neuroendocrine Cells

Neuroendocrine cells are cells that release hormones in response to neural stimulation. In the prostate, neuroendocrine cells reside among the more abundant secretory epithelial cells in the normal prostate gland as well

Table 90–1.

Summary of the Anatomy and Cell Biology of the Prostate Gland

COMPONENTS	PROPERTIES
Development	
Seminal vesicles	From wolffian ducts through testosterone stimulation
Prostate	From urogenital sinus through dihydrotestosterone stimulation
Prostate Zones	
Anterior fibromuscular	30% of prostate mass, no glandular elements, smooth muscle
Peripheral	Largest zone, 75% of prostate glandular elements, site of carcinomas
Central	25% of prostate glandular elements; surrounds ejaculatory ducts
Transitional	Smallest zone, surrounds upper urethra complex, sphincter
	5% of prostate glandular elements, site of benign prostatic hyperplasia
	15%-30% of prostate volume
Epithelial Cells	
Basal	Small and flattened undifferentiated, nonsecretory cells with a low proliferative index (<1%) that express keratins 5, 14, and 18
Intermediate	Proliferating cell type that has characteristics intermediate between basal and secretory cells, including production of basal and secretory cell keratins
Columnar secretory	Terminally differentiated, nondividing, rich in acid phosphatase and prostate-specific antigen; 20-μm tall, most abundant cell, keratins 5, and 18
Epithelial Cells—cont'd	
Neuroendocrine	Terminally differentiated, nonproliferating cells that express serotonin, chromogranin-A, neuron-specific enolase, and synaptophysin proteins
Stromal Cells	
Smooth muscle	Rich in α-actin, myosin, and desmin
Fibroblast	Vimentin rich and associated with fibronectin
Endothelial	Associated with fibronectin; alkaline phosphatase positive
Tissue Matrix	
Extracellular matrix	
Basement membrane	Type IV and V collagen meshwork that is laminin rich and supports basal cells, stem cells, transit-amplifying cells, and secretory epithelium
Connective tissue	Type I and type III fibrillar collagen; elastin
Glycosaminoglycans	Sulfates of dermatan, chondroitin, and heparin; hyaluronic acid
Cytomatrix	Tubulin, α-actin, and intermediate filaments of keratin
Nuclear matrix	Dynamic structure of the nucleus that directs the functional organization of DNA into loop domains; contains ribonuclear proteins

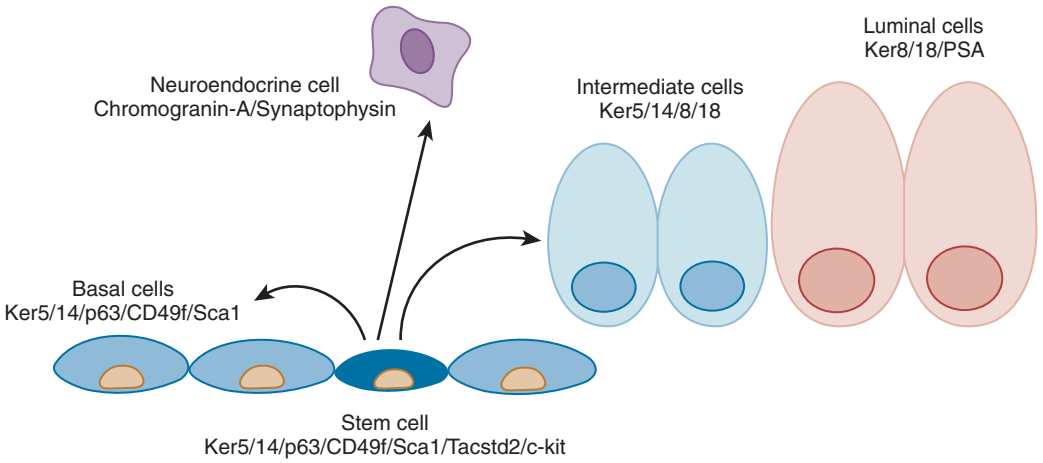


Figure 90–2. Hypothetical cell differentiation in adult prostate. Basal cells *(medium blue)* express basal cell proteins, including cytokeratin (CK) proteins 5, and 14, p63, CD49f, and Sca1. Stem cells within the basal cell compartment *(dark blue)* express basal cell proteins, as well as Tacstd2 and c-kit. Basal stem cells populate the basal cell compartment *(medium blue)* and, eventually, intermediate cells *(light blue)*. Intermediate cells proliferate and differentiate into quiescent luminal cells *(orange)*. Neuroendocrine cells *(purple)* are also believed to derive from epithelial stem cells. Formal lineage tracing has not been performed in all of these cell types, thus the true differentiation pathway remains to be determined. (Modified from Wang Y, Hayward S, et al. Cell differentiation lineage in the prostate. Differentiation 2001;68[4-5]:270–9.)

as in the urothelium of the prostatic urethra (Aumuller et al, 2001). There are two types of neuroendocrine cells: the first is open and possesses specialized microvilli that protrude into the lumen; the second is closed with long dendrite-like processes that extend to nearby epithelial cells and basal cells close to afferent and efferent nerves (diSant-Agnese and deMesy-Jensen, 1984; diSant-Agnese et al, 1985; Abrahamsson, 1999; Vashchenko and Abrahamsson, 2005).

Thinking on the origin of prostatic neuroendocrine cells has evolved. Aumuller and associates (2001) demonstrated that

neuroendocrine cells are readily identified in male and female urogenital sinus epithelium before human prostate development, suggesting that these might represent a separate lineage that is independent of prostate epithelium. More recently, Goldstein and coworkers (2008) showed that neuroendocrine, basal, and secretory luminal cells can all originate from a common pluripotent Trop2-expressing prostate epithelial stem cell precursor.

Current evidence suggests that neuroendocrine cells can influence growth, differentiation, and secretory activity of the prostate epithelium through paracrine and autocrine mechanisms (Abrahamsson, 1999; Vashchenko and Abrahamsson, 2005). Neuroendocrine cells bring about their regulatory activity by the secretion of hormonal polypeptides or biogenic amines such as serotonin. High-pressure liquid chromatography measurements have shown that normal human prostate tissue contains approximately 1400 ng of serotonin per gram of tissue, and this would certainly emphasize the importance of these cells (Davis, 1987). Higgins and Gosling (1989) have studied the structure and intrinsic innervations of the normal human prostate and have observed acetylcholinesterase-containing nerves associated with smooth muscle in both the peripheral and the central parts of the prostate. In addition, they have shown that the majority of the acini in the peripheral and central regions possess a rich plexus of autonomic nerves and that vasoactive intestinal peptide-positive nerve fibers are found in relation to the epithelial lining acini in the central and peripheral regions of the gland. Lepor and Kuhar (1984) characterized and studied the location of the muscarinic cholinergic receptor in human prostate tissue and localized it to the epithelial cells. This is consistent with the neuropharmacology of muscarinic cholinergic agonist, which has a marked effect on increasing prostatic secretion. However, the α_1-adrenergic receptor has its effect in the human prostatic stromal compartment. This is of clinical importance because of the use of selective α_1-adrenergic antagonists to alleviate bladder outlet obstruction secondary to benign prostatic hyperplasia (Lepor, 1993). Recent work has demonstrated three subtypes of the α_1-adrenergic receptor (α_{1A}, α_{1B}, and α_{1D}). Of these, the α_{1A} receptor appears to be linked to smooth muscle contraction of the prostate (Lepor et al, 1993).

Neuroendocrine cells are terminally differentiated (i.e., nonproliferating) and do not express detectable AR, PSA, or Bcl-2. These cells release peptide hormones or prohormones by fusion of intracellular granules with the cell membrane and exocytosis of their contents. In addition to serotonin, neuroendocrine cells produce numerous bioactive macromolecules (bombesin, neuron-specific enolase, calcitonin gene family members, thyroid-stimulating hormone–like peptide, somatostatin, synaptophysin, and parathyroid hormone–like peptide are major examples). Neuroendocrine factors appear likely to influence the growth, differentiation, and secretion of epithelium of the prostate in both normal and malignant conditions (Vashchenko and Abrahamsson, 2005).

Basal Cells

Basal cells (reviewed by De Marzo et al, 1998a) are the smallest of epithelial cells. They have a low mitotic index and are a minor population, accounting for less than 10% of the total cell number. Basal cells express a distinct keratin subtype profile (subtypes 5 and 14) compared with the columnar epithelial cells (subtypes 8 and 18). These cells are typically pyramid shaped with relatively little cytoplasm and condensed chromatin. Basal cells rest on the basement membrane wedged between the bases of adjacent, tall, columnar epithelial cells. The basal cell compartment has long been considered the likely source of the epithelial stem cells of the prostate because they are relatively undifferentiated with a low proliferative index (~1%) and almost devoid of secretory products, such as PSA and prostatic acid phosphatase (see Fig. 90–2).

Prostate Epithelial Stem Cells

Androgen deprivation does not affect stem cells but rather enriches them, because the more fully differentiated cells initiate apoptosis. Experiments in rodents have shown after castration that testosterone supplementation can restore prostate growth by stimulating stem cell proliferation. When mice are castrated after implantation with human prostate primary xenografts and then restimulated with testosterone, the basal cell population is highly overrepresented, consistent with the concept that the human basal compartment also contains prostate epithelial stem cells (Huss et al, 2004).

Recent experimental work in the mouse has provided powerful functional evidence for stem cell populations in the prostate, localizing them to the basal compartment, particularly in the proximal portions of prostatic ducts. These experiments used in vivo grafting assays to demonstrate critical stem cell characteristics including the ability of long-lived cells to proliferate indefinitely and to give rise to more differentiated phenotypes. Tsujimura and colleagues demonstrated DNA label-retaining prostate epithelial cells with long-term proliferative potential that were preferentially localized to the proximal segments of prostatic ducts of adult males (Tsujimura et al, 2002). Further studies have mapped the stem cell properties of proximal duct cells to those expressing the mouse stem cell antigen Sca1, the basal cell integrin α_6 (Itga6 or CD49f), the tumor-associated calcium signal transducer Tacstd2 (also known as Trop2), and the stem cell factor receptor, c-kit (Burger et al, 2005; Xin et al, 2005; Lawson et al, 2007; Goldstein et al, 2008; Leong and Gao, 2008).

Intermediate Cells

Intermediate cells are so named because they possess phenotypic characteristics intermediate between basal and luminal cells. Similarities of these cells to prostate cancer cells have marked them as hypothetical substrates for neoplastic transformation (Verhagen et al, 1992; De Marzo et al, 1998b), although their susceptibility to carcinogenesis is unknown. These investigators proposed that intermediate cells fulfill a transient amplifying function, providing a short-term amplification function for the long-term proliferative capabilities of basal stem cells. Intermediate cells produce basal cell keratins (5 and 14) and the secretory cell keratins 8 and 18 (De Marzo et al, 1998b; Schalken and van Leenders, 2003). Uzgare and colleagues (2004) reported transient amplifying properties of human intermediate cells in culture: a high proliferative fraction with the ability to proliferate for a limited number of generations. Survival of terminally differentiated secretory luminal cells and proliferation of intermediate cells require androgens potentially acting indirectly through the secretion of androgen-regulated growth factors by the stromal compartment (andromedins) (Uzgare et al, 2004).

Key Points: Prostate Epithelial Cell Types

- The prostatic epithelium in the human is composed of two major cell compartments: epithelial cells and stromal cells.
- The epithelial cell types include mature secretory and terminally differentiated cells, neuroendocrine cells, intermediate cells, and basal cells.
- Prostate stem cells reside in the basal compartment and are enriched in the proximal portions of prostatic ducts.

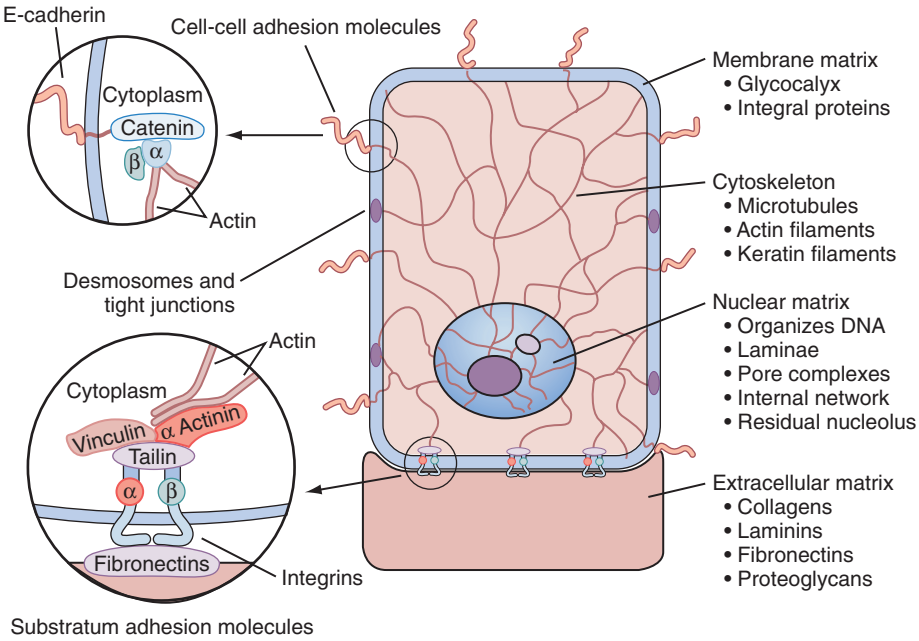


Figure 90–3. The tissue matrix system, a superstructure scaffold network that connects the extracellular matrix components to the cell through interactions with cell adhesion molecules (e.g., integrins). Cell adhesion molecules extend through the plasma membrane and connect directly or indirectly to the cytomatrix structures. The cytomatrix directly couples to the nuclear matrix, which attaches and organizes the cellular DNA. Cell adhesion molecules and desmosomes connect neighboring cells. (From Getzenberg RH, Pienta KJ, Coffey DS. The tissue matrix: cell dynamics and hormone action. Endocr Rev 1990;11:399–416.)

The Stroma and Tissue Matrix

The noncellular stroma and connective tissue of the prostate make up what is termed the *ground substance* and the *extracellular matrix* in what was first suggested by Arcadi (1954) to play an important role in prostate function and disease. The extracellular matrix has long been recognized as one of the important inductive components during normal development of many different types of cells (Cunha, 1976; Hay, 1981; Bissell et al, 1982; Getzenberg et al, 1990; Risbridger et al, 2005). Classic tissue recombination experiments by Cunha and colleagues (1987) have clearly shown the direct importance of the isolated embryonic mesenchyme to the induction of differentiation of normal prostatic epithelial cells (see earlier discussion).

The epithelial cells rest on the basement lamina or membrane, which is a complex structure containing, in part, collagen types IV and V, glycosaminoglycans, complex polysaccharides, and glycolipids. This layer forms an interface to the stromal compartment that provides structural support for the basal cells and their progeny. It consists of an extracellular matrix, ground substance, and a variety of stromal cells, including the fibroblasts, capillary and lymphatic endothelial cells, smooth muscle cells, neuroendocrine cells, and axons (reviewed in Taylor and Risbridger, 2008).

The **cytomatrix** (cytoplasmic skeleton) terminates in the center of the cell by direct attachment to the **nuclear matrix** (Fig. 90–3). The prostatic epithelial cell therefore has direct structural linkage via the matrix system from the DNA to the plasma membrane. The cytomatrix then makes direct contact with the basement membrane, extracellular matrix, and ground substance of the stroma. This entire interlocking tissue scaffolding or superstructure is termed the ***tissue matrix*** and may have dynamic properties in ordering and controlling biologic processes as well as in the transport of secretions from the sex accessory tissues (Getzenberg et al, 1990; Konety and Getzenberg, 1999; Etienne-Manneville, 2004; Miner and Yurchenco, 2004; Hallmann et al, 2005).

Understanding the biologic components of the tissue matrix system within sex accessory tissues is of paramount importance to understanding its physiology. The laminin proteins are glycoproteins of the extracellular matrix that mediate attachment of cells to the type IV collagen of the basement membrane (Miner and Yurchenco, 2004; Yurchenco et al, 2004; Hallmann et al, 2005). Laminin is produced by epithelial cells but not by fibroblasts; it is a large molecule (approximately 800 kD) with molecular domains that interact with the type IV collagen of the basement membrane and with integrin-type receptors within the cell surface glycocalyx of the epithelial cell (Aumailley et al, 2005). Laminins are the major anchor filaments in the basement membranes of epithelial cells that stabilize attachment of hemidesmosomes via $\alpha_6\beta_4$ integrin (Brar et al, 2003; Miner and Yurchenco, 2004). **The key functional properties of the laminins are cell adhesion, proliferation, differentiation, growth, and migration.** Laminin surrounds the basement membrane of prostate acinar epithelial cells, capillaries, smooth muscle, and nerve fibers but not lymphatics, lymphocytes, or fibroblasts; the laminin structure and its distribution are disrupted in BPH and higher-grade prostatic interepithelial neoplasia and higher-grade prostate neoplasms (Sinha et al, 1989; Brar et al, 2003; Miner and Yurchenco, 2004).

In summary, the development and maintenance of the prostate occurs through androgen-dependent and highly regulated tissue morphogenesis in processes involving epithelial cell differentiation, proliferation, and apoptosis (Cunha et al, 2004). **Communication through numerous extracellular interactions is directed to the intracellular cytoskeleton and then to the nuclear matrix, which ultimately regulates a variety of transcriptional cell functions that control such critical phenotypic qualities as cell size and shape, cell motility, epithelial cell turnover, proliferation, and differentiation** (Getzenberg et al, 1990; Pienta, 1993; Miner and Yurchenco, 2004).

ENDOCRINE CONTROL OF PROSTATE GROWTH

The prostate, like other sex accessory tissues, is stimulated in its growth, maintenance, and secretory function by the continued

Key Points: Laminin Proteins

- Laminin surrounds the basement membrane of prostate acinar epithelial cells, capillaries, smooth muscle, and nerve fibers but not lymphatics, lymphocytes, or fibroblasts.
- The laminin structure consists of collagen types IV and V, glycosaminoglycans, complex polysaccharides, and glycolipids and provides structural support for basal, intermediate, and secretory epithelial cells.
- The cytomatrix (i.e., cytoplasmic skeleton) links the plasma cell membrane to the nuclear matrix and also communicates with the extracellular matrix and stroma.

presence of certain hormones and growth factors. Foremost among these is testosterone, which is converted within the prostate into the more active androgen DHT. Testosterone is synthesized in the Leydig cells of the testes from pregnenolone by a series of reversible reactions. However, once testosterone is converted by 5α-reductase into DHT or converted by aromatase into estrogens the process is irreversible: **testosterone can be converted to DHT or estrogens, but estrogens and DHT cannot be converted to testosterone.** Androgens, estrogens, and adrenal steroids are believed to have strong effects on different cells and tissues in the body that can vary with development and age. This varies from embryonic development to puberty and on into adult maintenance and aging. Therefore, androgen ablation or androgen treatments have a wide variety of physiologic effects that merit consideration.

The generalized endocrine physiology of the prostate is depicted in Figure 90–4. The hypothalamus releases a small 10-residue polypeptide (decapeptide) referred to as luteinizing hormone–releasing hormone (LHRH), also called gonadotropin-releasing hormone (GnRH). Under the stimulation of LHRH the pituitary releases luteinizing hormone that is transported to the testes and acts directly on the Leydig cells to stimulate de novo steroid synthesis and release of testosterone, the major serum androgen of the body. Most of the estrogen in the male is derived from peripheral conversion of androgens to estrogens through aromatization. Exogenous estrogens, such as diethylstilbestrol, block androgen action not primarily by direct effects on the prostate but indirectly through blocking pituitary function. The estrogen causes a negative feedback on luteinizing hormone release that reduces the serum signal for testicular testosterone production; therefore, estrogen acts as an effective "chemical castration."

In addition to testosterone, the adrenal secretes a weak androgen, androstenedione; however, this is not a major influence on prostate physiology because castration leads to almost complete involution of the prostate, meaning that insufficient adrenal androgens are present to stimulate any meaningful growth of the normal prostate. Similar to serum testosterone, androstenedione can undergo aromatization to estrone. Overproduction of androstenedione, such as occurs in certain forms of congenital adrenal hyperplasia, may stimulate prostate growth; however, again, the role of adrenal androgens in regulating prostate growth is minor.

Androgen Production by the Testes

Because the testes produce the major serum androgen supporting prostate and sex accessory tissue growth, it is important to briefly review this function. In the normal human male the major circulating serum androgen is testosterone, which is almost exclusively

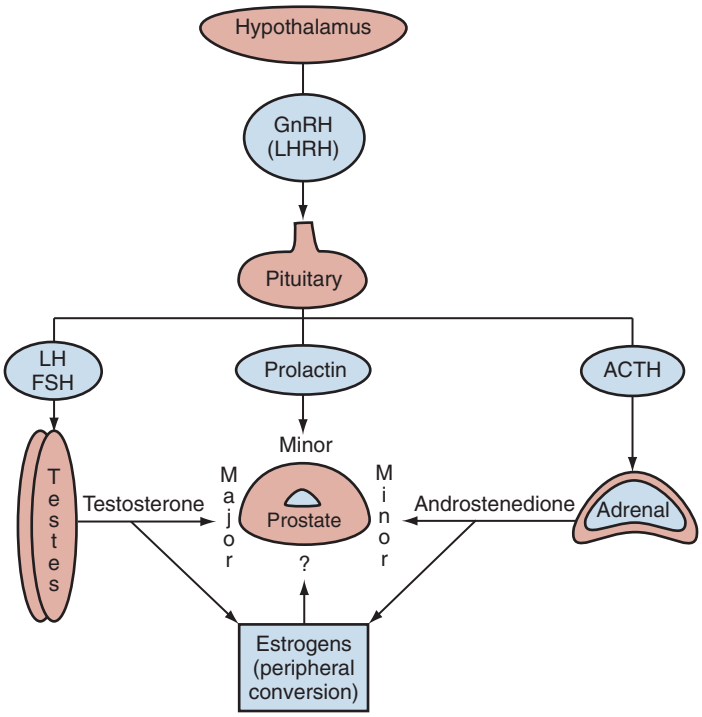


Figure 90–4. Simplified endocrinology of the prostate. Luteinizing hormone–releasing hormone (LHRH), also known as gonadotropin-releasing hormone (GnRH), stimulates the pituitary to release the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which stimulate the Leydig cells of the testes to synthesize testosterone. Testosterone is the major serum androgen stimulating prostate growth. Peripheral conversion of testosterone by aromatization forms the estrogens in the male. The adrenal gland is under stimulation by adrenocorticotropic hormone (ACTH) and releases the minor androgens, such as androstenedione, which is also converted peripherally to estrogens. Prolactin has also been shown to have a minor effect in stimulating androgen-induced prostate growth. The prostate can produce its own growth factors (autocrine or paracrine) or respond to circulating growth factors.

(~95%) of testicular origin. **Under normal physiologic conditions the Leydig cells of the testis are the major source of the testicular androgens.** The Leydig cells are stimulated by the gonadotropins (primarily the luteinizing hormone) to synthesize testosterone from acetate and cholesterol. The spermatic vein concentration of testosterone is 40 to 50 μg/dL, approximately 75 times more concentrated than the level detected in the peripheral venous serum (Hammond, 1978), which is approximately 600 ng/dL. Other androgens also leave the testes by the spermatic vein, and these include androstanediol, androstenedione (3 μg/dL), dehydroepiandrosterone (7 μg/dL), and DHT (0.4 μg/dL). The concentrations of these androgens are much lower in the spermatic vein than the concentration of testosterone, with all being less than 15% of the concentration of testosterone.

The total testosterone that enters the plasma is referred to as the testosterone blood production rate and is 6 to 7 mg/day in the human. Although other steroids, such as androstenedione from the adrenals, can be converted by peripheral metabolism to testosterone they probably account for less than 5% of the overall production of plasma testosterone. The plasma half-life of testosterone is only 10 to 20 minutes, which means that a man undergoing bilateral simple orchiectomy is functionally castrated within 1 to 2 hours of surgery.

Table 90–2.

Average Plasma Levels of Sex Steroids in Healthy Human Males

STEROID (COMMON NAME)	PLASMA CONCENTRATION (ng/dl)	RELATIVE MOLARITY	DAILY BLOOD PRODUCTION RATE (mg/day)	RELATIVE ANDROGENICITY (RAT VP ASSAY)
Testosterone	611 ± 186	100	6.6 ± 0.5	100
Dihydrotestosterone	56 ± 20	9	0.3 ± 0.06	181
5α-Androstane-3α,17β-diol (3β-androstanediol)	14 ± 4	2	0.2 ± 0.03	126
5α-Androstane-3β,17β-diol (3β-androstanediol)		<2	<0.3	18
Androstenediol	161 ± 52	26	0.21	
Androsterone	54 ± 32	9	0.28	53
Androstenedione	150 ± 54	25	1.4	39
Dehydroepiandrosterone	501 ± 98	81	29	15
Dehydroepiandrosterone sulfate	135,925 ± 48,000	17,619		<1
Progesterone		30	4.5	
17β-Estradiol	2.5 ± 0.08		0.4	0.75
Estrone		4.6	0.8	0.04

VP, ventral prostate.

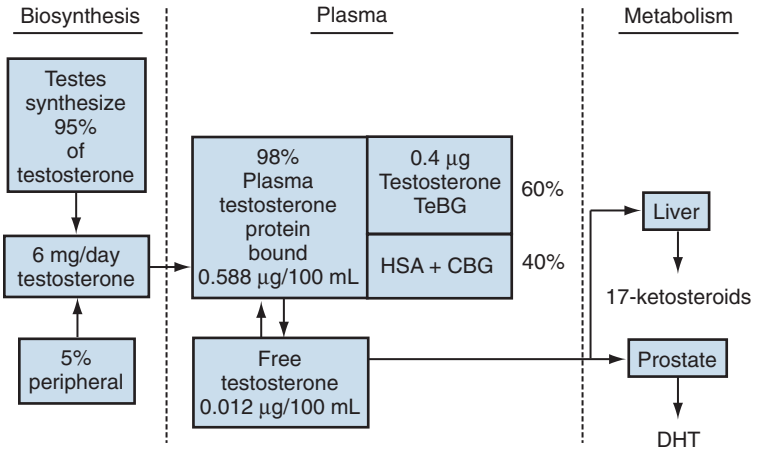


Figure 90–5. Quantitative assessment of the testicular biosynthesis, plasma transport, and metabolism of testosterone. Plasma testosterone is bound to testosterone-binding globulin (TeBG), human serum albumin (HSA), and cortisol-binding globulin (CBG). All numbers are average values for the normal adult male. DHT, dihydrotestosterone.

The average testosterone concentration in the adult human male plasma is approximately 611 ng/dL ± 186 with a normal range of 300 to 1000 that is equal to 10.4 to 34.7 nmol/L in SI units (Table 90–2). Serum testosterone level is not remarkably related to age between 25 and 70 years, although it does decline gradually to approximately 500 ng/dL after 70 years of age. It is recognized that plasma concentrations of testosterone can vary widely in an individual on any one day and may reflect both episodic and diurnal variations in the production rate.

Metabolic androgens such as 17-ketosteroids are then secreted into the urine as water-soluble glucuronide or sulfate conjugates. The total 17-ketosteroid level in the urine in adult men is 4 to 25 mg/24 hr and is not an accurate index of testosterone production, because other steroids from the adrenals as well as nonandrogenic steroids can be metabolized to 17-ketosteroids. Only small (25 to 160 µg/day) amounts of testosterone enter the urine without metabolism, and this urinary testosterone represents less than 2% of the daily testosterone production.

Although testosterone is the primary plasma androgen inducing growth of the prostate gland and other sex accessory tissues, it appears to function as a prohormone in that the most active form of the androgen in the prostate is not testosterone but rather DHT (Farnsworth and Brown, 1963; Anderson and Liao, 1968; Bruchovsky and Wilson, 1968) (Fig. 90–5). The formation of DHT involves the reduction of the double bond in the A ring of testosterone through the enzymatic action of the enzyme 5α-reductase (Fig. 90–6). There are at least two isoforms of this enzyme (type 1 and type 2). Type 2 5α-reductase expression predominates in human accessory sex tissues and is localized to the fibromuscular stromal compartment (Silver et al, 1994). The type 1 isoform predominates in skin, in prostatic epithelia, and to a lesser extent in prostatic fibromuscular stroma. Inhibition of 5α-reductase by finasteride appears to be largely selective for the type 2 isoform (Iehle et al, 1995; Habib et al, 1997); the newer agent dutasteride inhibits both type 1 and type 2 5α-reductase. Both drugs appear to exert similar effects in terms of reduction in prostatic volume and serum PSA concentration, suggesting that the type 2 isoform is the only clinically significant isoform present in the prostate. **DHT concentration in the plasma of normal men is low, 56 ± 20 ng/dL, in comparison to testosterone,** which is 11-fold higher at approximately 611 ng/dL (see Table 90–2). In summary, although DHT is a potent androgen (2 to 10 times as potent as testosterone in many bioassay systems), its low plasma concentration and tight binding to plasma proteins diminishes its direct importance as a circulating androgen affecting prostate and seminal vesicle growth. In contrast, DHT is of paramount importance within the prostate, where it is formed from testosterone. **DHT is the major form of androgen found within the prostate gland (5 ng/g tissue wet weight) and is fivefold higher than**

testosterone. In the prostate, DHT binds to ARs and activates the receptors to regulate a variety of cellular processes. In summary, DHT becomes the major androgen regulating the cellular events of growth, differentiation, and function in the prostate.

The normal adult male plasma levels of some important steroids are summarized in Table 90–2. These values are derived as averages from numerous studies. Individual values can fluctuate with age, time of day, medications, stress, hospitalization, and environmental changes.

Adrenal Androgens

There is evidence that overproduction of adrenal steroids can stimulate growth of the prostate gland. For example, in humans, abnormal virilism has been observed in immature males with a hyperfunctioning adrenal cortex. In rodents, overstimulation of the adrenals can also induce limited prostate growth even in the absence of testicular androgens. For example, administration of exogenous adrenocorticotropic hormone to castrated animals does significantly increase the growth of sex accessory glands (Tullner, 1963; Tisell, 1970; Walsh and Gittes, 1970). However, the effect of normal levels of adrenal androgens on the prostate in noncastrated humans and adult male rats does not appear to be significant because adrenalectomy has little effect on prostate size, DNA, or morphologic characteristics of the sex accessory tissue (Mobbs et al, 1973; Oesterling et al, 1986). Furthermore, after castration in animals, with the adrenals intact, the prostate will finally diminish to a very small size (90% reduction in total cell mass). Finally, the small involuted ventral prostate in the castrated rat cannot be significantly reduced further by additional adrenalectomy or hypophysectomy (Kyprianou, 1987). In castrated rats, the DHT level in the prostatic tissue is approximately 20% of that

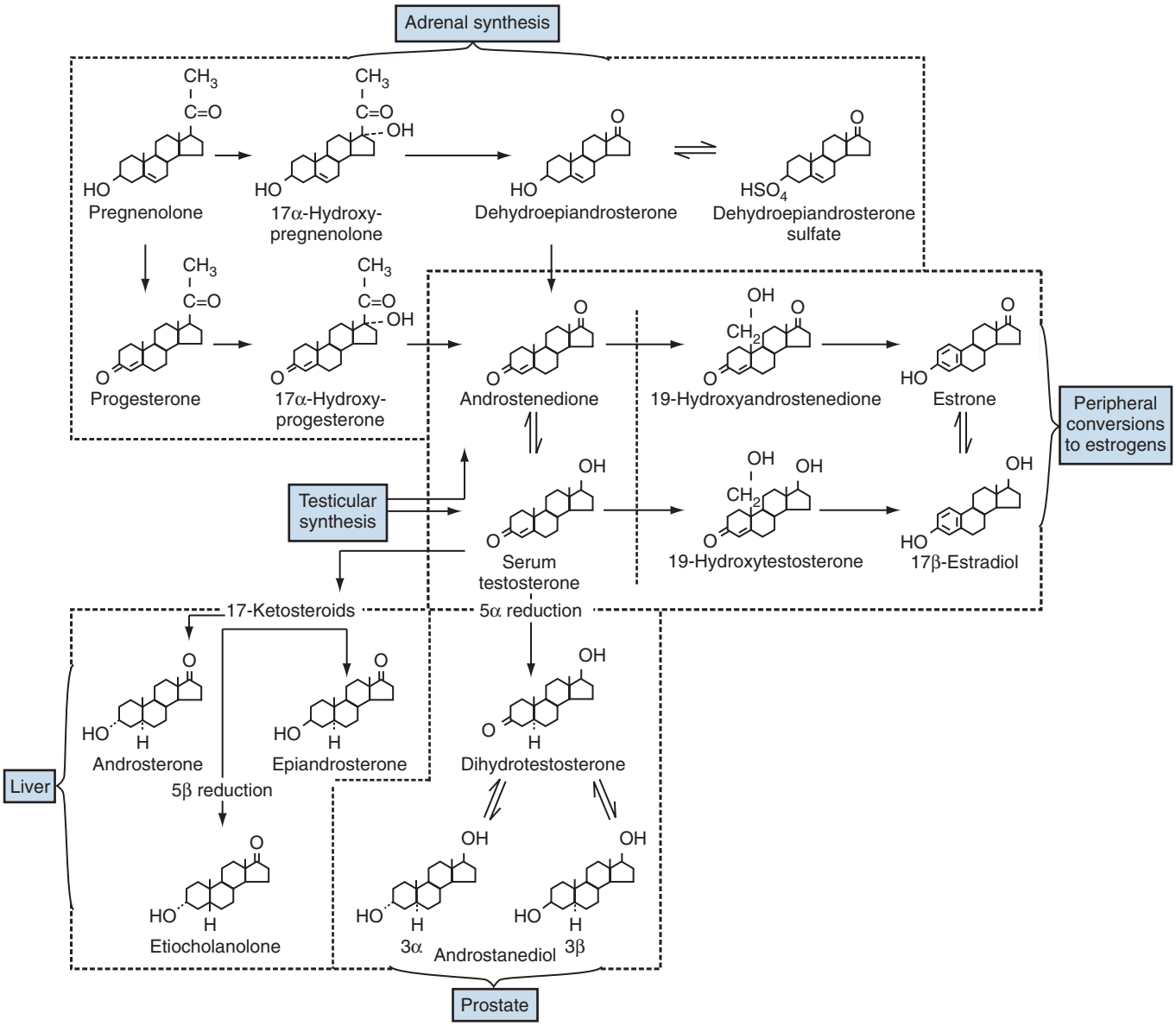


Figure 90–6. Overview of the synthesis and metabolism of testosterone in four main body compartments: adrenal synthesis of androstenedione; peripheral conversion of androgens (androstenedione and testosterone) to estrogens; formation of active androgen (DHT) within the prostate; and inactivation in the liver of testosterone to three types of 17-ketosteroids.

in normal intact animals. Adrenalectomy lowers the DHT to nondetectable levels without further diminution in prostate growth. This indicates that a threshold level of DHT is required in the prostate to stimulate growth and the castrate level is below this threshold. It has also been concluded similarly that the prostate of man does not restore itself after castration, indicating that adrenal androgens are insufficient to compensate for the loss of testicular function. Quantitative morphometry of the human prostate (Oesterling et al, 1986) also confirms that the adrenal gland has little effect on the epithelial cell size of the normal prostate.

The adrenal steroids dehydroepiandrosterone (DHEA) and the conjugate dehydroepiandrosterone sulfate (DHEAS) as well as androstenedione are androgens synthesized from acetate and cholesterol (see Fig. 90–6) that are secreted by the normal human adrenal glands. Essentially all of the DHEA in the male plasma is of adrenal cortex origin, and the production rate in man is 10 to 30 mg/day. **Less than 1% of the total testosterone in the plasma is derived from DHEA** (Horton, 1976; MacDonald, 1976). The prostate and seminal vesicles of the rat and the human prostate can slowly hydrolyze DHEAS to free steroids through a prostate sulfatase enzymatic activity, but the degree of conversion is low; hence, DHEAS is not a potent androgen.

A second adrenal androgen is androstenedione, and the plasma concentration in adult men is approximately 150 ± 54 ng/dL (see Table 90–2). The blood production rate of androstenedione in human males is 2 to 6 mg/day, with approximately 20% of the androstenedione being generated by peripheral metabolism of other steroids. **Androstenedione cannot be converted directly to DHT.** An important role for androstenedione in the male may be its peripheral conversion to estrogens through the aromatase reaction (see Fig. 90–6).

The adrenal gland also produces C21 steroids (e.g., progesterone). The plasma production rate at 0.75 mg/day is low, producing a low plasma progesterone concentration of 30 ng/dL. Although progesterone is weakly androgenic it does not exert a significant effect on the prostate at the low concentrations present in normal male plasma. **In summary, under normal conditions, the adrenals do not support significant growth of prostatic tissue.**

Estrogens in the Male

The estrogen receptors (ERs) are differentially expressed in the prostate. In the mouse, ER-α is expressed early (1 week) in the stroma of the ventral prostate but by 2 weeks is preferentially expressed in the epithelia, and ER-α is absent altogether in the ventral prostate by 4 weeks. In contrast, ER-β exists in the epithelial compartment as the dominant ER by the fourth week. Interestingly, however, knockout mice for ER (both isoforms) are able to form grossly normal prostates, although fertility may be limited in the ER-α (Couse et al, 2001). Only small amounts of estrogen are produced directly by the testes. In the plasma of young healthy human males 75% to 90% of the estrogens are derived from the peripheral conversion of androstenedione and testosterone to estrone and estradiol through the aromatase reaction (see Fig. 90–6) (Horton, 1976; MacDonald, 1976). The androgenic C19 steroids (testosterone and androstenedione) are converted to the estrogenic C18 steroids first by removal of the 19-methyl group and followed by the formation of an aromatic or phenolic steroid A ring (aromatase reaction), present in both estradiol and estrone. Estradiol is formed from testosterone and estrone from androstenedione; these two estrogens are interconvertible. **The daily production of estradiol in the human male is 40 to 50 μg, and only 5 to 10 μg (10% to 25%) can be accounted for by direct testicular secretion** (see Table 90–2).

Androgen-Binding Proteins in the Plasma

Less than 2% of the total testosterone in human plasma is free or unbound; the remaining 98% is bound to several different types of plasma proteins (see Fig. 90–5). The plasma proteins that bind steroids include human serum albumin, sex hormone–binding globulin (SHBG or testosterone-estrogen–binding globulin [TeBG]), corticosteroid-binding globulin (also named transcortin), progesterone-binding globulin, and, to a lesser extent, α_1-acid glycoprotein. Under normal conditions, the total amount of testosterone bound to progesterone-binding globulin and α_1-acid glycoprotein is nominal and is usually ignored.

The regulation of the amount of androgen that is free is an important physiologic variable and varies in different species. **The total amount of steroid bound depends on two factors: (1) the *affinity* of the steroid to bind to a specific protein and (2) the *capacity*, which is the maximal potential binding when all of a binding protein is saturated with bound steroid; the capacity is governed by the amount of binding protein in the plasma.** Serum albumin has a relatively low affinity for testosterone, but, given its abundance, it has a high capacity. In contrast, SHBG has a high affinity for binding steroids but the protein is present in relatively low concentrations; however, the plasma molarity of each binding protein exceeds the plasma molarity for total testosterone concentration. The majority of testosterone bound to plasma protein is associated with SHBG. For example, Vermeulen (1973) has calculated that in the normal human male 57% of testosterone in the plasma is bound to SHBG and 40% is bound to human serum albumin. Less than 1% is bound to corticosteroid-binding globulin, and only 2% of the total testosterone is free (see Fig. 90–5). The normal plasma free testosterone level is therefore 12.1 ± 3.7 ng/dL or 0.42 nM; this non–protein-bound "free testosterone" is bioavailable to diffuse into the sex accessory tissue and into liver cells for metabolism. In addition, a large percentage of the SHBG is saturated whereas only a small fraction of the total capacity of corticosteroid-binding globulin and albumin is used under normal conditions. As testosterone levels increase in the plasma, the order of increasing saturation of the plasma proteins proceeds from SHBG to corticosteroid-binding globulin to albumin. Therefore, the binding of androgen is a dynamic equilibrium between various serum proteins.

The total plasma levels of SHBG can be altered by hormone therapy. **Administration of testosterone decreases SHBG levels in the plasma, whereas estrogen therapy stimulates SHBG levels** (Forest et al, 1968; Vermeulen, 1969; Burton and Westphal, 1972). Estrogen also competes with testosterone for binding to SHBG, but estrogen has only one third the binding affinity of testosterone. **Therefore, administration of small amounts of estrogen increases the total concentration of SHBG, and this effectively increases the binding of testosterone and thus lowers the free testosterone plasma concentration.**

Because only free testosterone is bioavailable, the binding of testosterone to plasma proteins inhibits net testosterone uptake into the prostate (Lasnitzki and Franklin, 1972). It is apparent that androgenic activity is regulated in part by the extent of binding of an androgen to the steroid-binding proteins in the plasma.

Key Points: Endocrine Control of Prostate Growth

- Free testosterone in the plasma is converted in the prostate by 5α-reductase type 2 into dihydrotestosterone, which is 2 to 10 times more active than testosterone.
- Dihydrotestosterone, testosterone, and estrogens are responsible for multiple metabolic actions in the prostate (growth, differentiation, and biologic functions). Free testosterone can be converted to estrogens, but estrogens cannot be converted to testosterone.

REGULATION OF PROSTATE GROWTH BY STEROIDS AND PROTEIN GROWTH FACTORS

There are multiple levels of prostate growth regulation that include steroid hormone action, growth factors, and direct cell-cell communication and interactions with the extracellular matrix. These interactive types of growth control are accomplished by several generalized systems, as depicted in the schematic in Figure 90–7. They include the following:

- *Endocrine factors* or long-range signals arriving at the prostate by serum transport of hormone originating from the secretions of distant organs; this includes serum steroid hormones such as testosterone and estrogens and serum peptide hormones such as prolactin and gonadotropins.
- *Neuroendocrine signals* originating from neural stimulation, such as 5-hydroxytryptamine (serotonin), acetylcholine, and norepinephrine
- *Paracrine factors* or soluble tissue growth factors that stimulate or inhibit growth, which are elaborated over short ranges between neighboring cells within the prostate tissue compartment (fibroblast growth factors, epidermal growth factor)
- *Autocrine factors* that are produced and released by a cell and then fed back on the same cell's external membrane receptors to regulate its own growth or function, such as autocrine motility factor
- *Intracrine factors*, which function like autocrine factors but work inside the cell
- *Extracellular matrix factors,* which are insoluble tissue matrix systems and make direct and coupled contact by being attached through integrins and adhesion molecules of the basal membrane and couple cytoskeleton organization with the extracellular matrix components, which include the glycosaminoglycans, such as heparan sulfate (Getzenberg et al, 1990)
- *Cell-cell interactions* of the epithelial or stromal cells occurring through tight membrane junctions on intramembrane proteins such as the cell adhesion molecules, like E-cadherin, that couple neighboring cells.

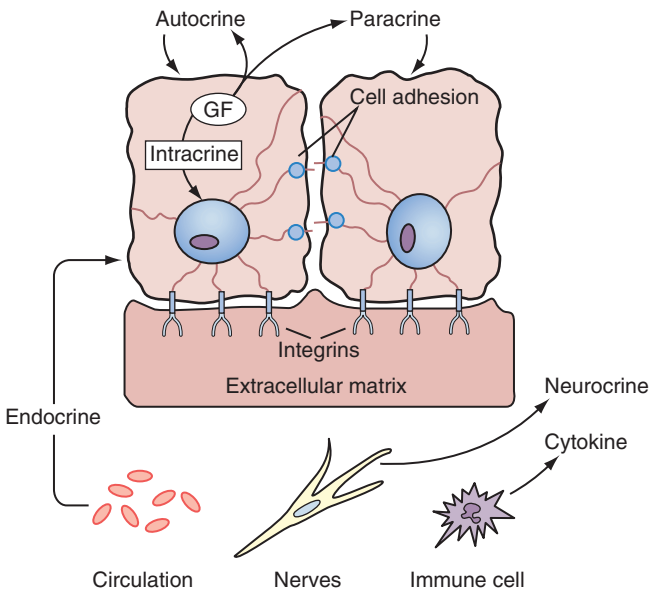


Figure 90–7. Types of growth control. Endocrine signals are carried through the circulation from distant organs. Paracrine signals are produced in proximity by neighboring cells. Autocrine signals feedback on the same cells from which they are produced. Intracrine signals are a special subset of autocrine signals that never leave the cell but rather act locally within that cell. Cytokines are paracrine-like factors (typically) that are made by immune cells. Neurocrine factors are released by nerves. Cell adhesion molecules directly link neighboring cells, often through association with cognate adhesion molecules. Cells are also bound to the extracellular matrix through interactions with other cell adhesion molecules (e.g., integrins). GF, growth factor.

Of these seven growth control systems, the first extensively studied on the prostate was the endocrine effect of androgenic steroids, such as testosterone, in the regulation of prostate growth through changes in serum testosterone levels and conversion to DHT. However, androgens alone are not sufficient for full prostate growth. In the past 2 decades, extensive progress has been made in the understanding of the other systems, particularly the interactive role of growth factors and their receptors. At present, the roles of these receptors in cell signaling to the nucleus and of the structural elements in cellular control involving the tissue matrix are being developed. These mechanisms are reviewed next, starting with androgen action at the cell level beginning with the arrival of testosterone in the serum.

Androgen Action at the Cellular Level

Testosterone in the serum arrives at the prostate bound to albumin and to the steroid-binding globulins. Free testosterone enters the prostate cell by diffusion, where it is then subjected to a variety of steroid metabolic steps that appear to regulate the activity of the steroid hormone and its downstream effectors. A simplified schematic of the temporal sequence of intracellular events is depicted in Figure 90–8 and includes the following:

- Cellular uptake of testosterone
- Testosterone conversion to DHT by metabolism of 5α-reductase
- DHT or testosterone binding to specific ARs in the cytoplasm
- Dimerization and activation of the steroid receptor by a variety of post-translational steps, including, for instance, phosphorylation
- Active nuclear transportation of the activated AR in an adenosine triphosphate (ATP)–dependent fashion
- Chromatin remodeling through interaction with coregulatory molecules
- Transactivation or transrepression, through interactions with other coactivators or corepressors, in a histone acetyltransferase–dependent process
- Binding of the activated receptor/coactivator complex to androgen response elements, which are short, specific sequences of DNA recognized specifically by AR dimers

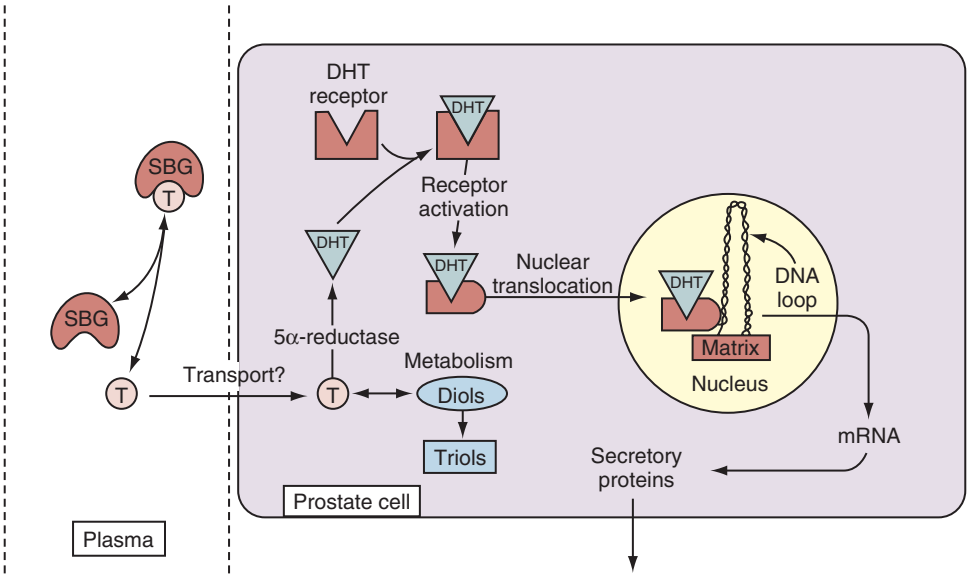


Figure 90–8. Simplified schematic of the effects of testosterone in activating transcriptional targets in an epithelial cell. In the plasma, testosterone (T) is bound to serum-binding globulins (SBG), such as testosterone-binding globulin and albumin. Unbound testosterone is transported by passive diffusion into the prostate, where it is enzymatically converted to dihydrotestosterone (DHT) by 5α-reductase (type 2) and further metabolized to diols (3α or 3β) and irreversibly metabolized into the more water-soluble triols (6α or 7α). DHT binds to a cytoplasmic receptor (androgen receptor) that is activated and translocated to the nucleus. There the androgen receptor localizes in matrix acceptor sites and subsequently activates or represses certain target genes by regulating production of their mRNA. The RNA is then transported to the cytoplasm, where it is translated into a variety of proteins (e.g., secretory proteins such as PSA).

- Gene regulation. The receptor acts as a transcription factor, and when it is bound to the DNA and matrix in proximity to androgen target genes it increases the RNA polymerase II transcription of the DNA into mRNA. The transcribed message (mRNA) is large and contains introns, exons, and a poly-A tail. The intron portion is excised from the initial RNA species, so that only the exon portion is retained in the final message. The trimming and processing of the mRNA are accomplished on the nuclear matrix as it is transported through the nucleus and out through the nuclear pore complex. The stabilized mRNA is transported into the cytoplasmic compartment to be translated at the ribosome into protein, which is then transported to specific cellular sites. Depending on the target gene, some proteins will undergo storage in secretory granules poised for secretion into the lumen on command during the physiologic process of ejaculation.

The epithelial cell is the primary unit in secretion, but specific genes are also activated in the stromal cells, and these events are also regulated by testosterone, estrogens, and growth factors in a similar chain of events. However, not all cells respond the same to androgens or estrogens. For simplicity, these steps are discussed in relation to the epithelial cells. Androgens and estrogens, both together and separately, can affect prostate cells through interaction with receptors, and it appears that estrogens might have their primary effect on the stromal cells.

5α-Reductase and Androgen Metabolism within the Prostate

After the free testosterone in the plasma has entered the prostatic cells through diffusion it is rapidly metabolized to other steroids by a series of prostatic enzymes (Isaacs et al, 1981, 1983; Isaacs and Coffey, 1981; Bruchovsky and Dunstan-Adams, 1985). More than 90% of testosterone is *irreversibly* converted to the main prostatic androgen DHT (Fig. 90–9) through the action of the reduced form of nicotinamide-adenine dinucleotide phosphate (NADP) and the enzyme 5α-reductase located on the endoplasmic reticulum and on the nuclear membrane. The enzyme 5α-reductase reduces the unsaturated bond in testosterone between the 4 and 5 positions to form the 5α-reduced product DHT. The K_m for testosterone is 8.3 nM, and the serum level of testosterone is only in the range of 0.5 to 3.0 nM, indicating that the enzyme cannot be saturated because the testosterone substrate would be less than the K_m value. Bruchovsky and Dunstan-Adams (1985) reported a 10-fold increase in the maximal velocity in the stromal tissue compared with the epithelium. They observed 262 pmol of DHT formed in 30 minutes per milligram of protein from testosterone measured in the stroma and less than 10% of that amount with a maximal velocity of 19 for the epithelium. The stromal K_m was 76 nM and the epithelial K_m was 13 nM. These differences between stromal and epithelial kinetics were used to deduce the existence of two different isoenzymes of the 5α-reductase (Andersson et al, 1991).

In the human, rat, and monkey there are two isozymes of 5α-reductase (Table 90–3). The human and rat 5α-reductase isozymes are composed of 254 to 260 amino acids with a molecular weight of 28 to 29 kD. These enzymes are *N*- and *O*-glycosylated and have a high percentage of hydrophobic amino acids that are distributed throughout the enzyme. The chromosomal localization of the human 5α-reductase isozyme genes has been reported; the type 1 enzyme is at the extreme tip of the short arm of chromosome 5, and the human type 2 gene is on the short arm of chromosome 2. There is a 49% homology between type 1 and 2 enzymes in the human. The properties of these enzymes have been reviewed in detail by Russell and Wilson (1994) and for the effects on prostate growth by McConnell (1995). The effect of finasteride on 5α-reductase activity has been reviewed by Rittmaster (1994). The type 1 enzyme is in the skin and in the adult scalp

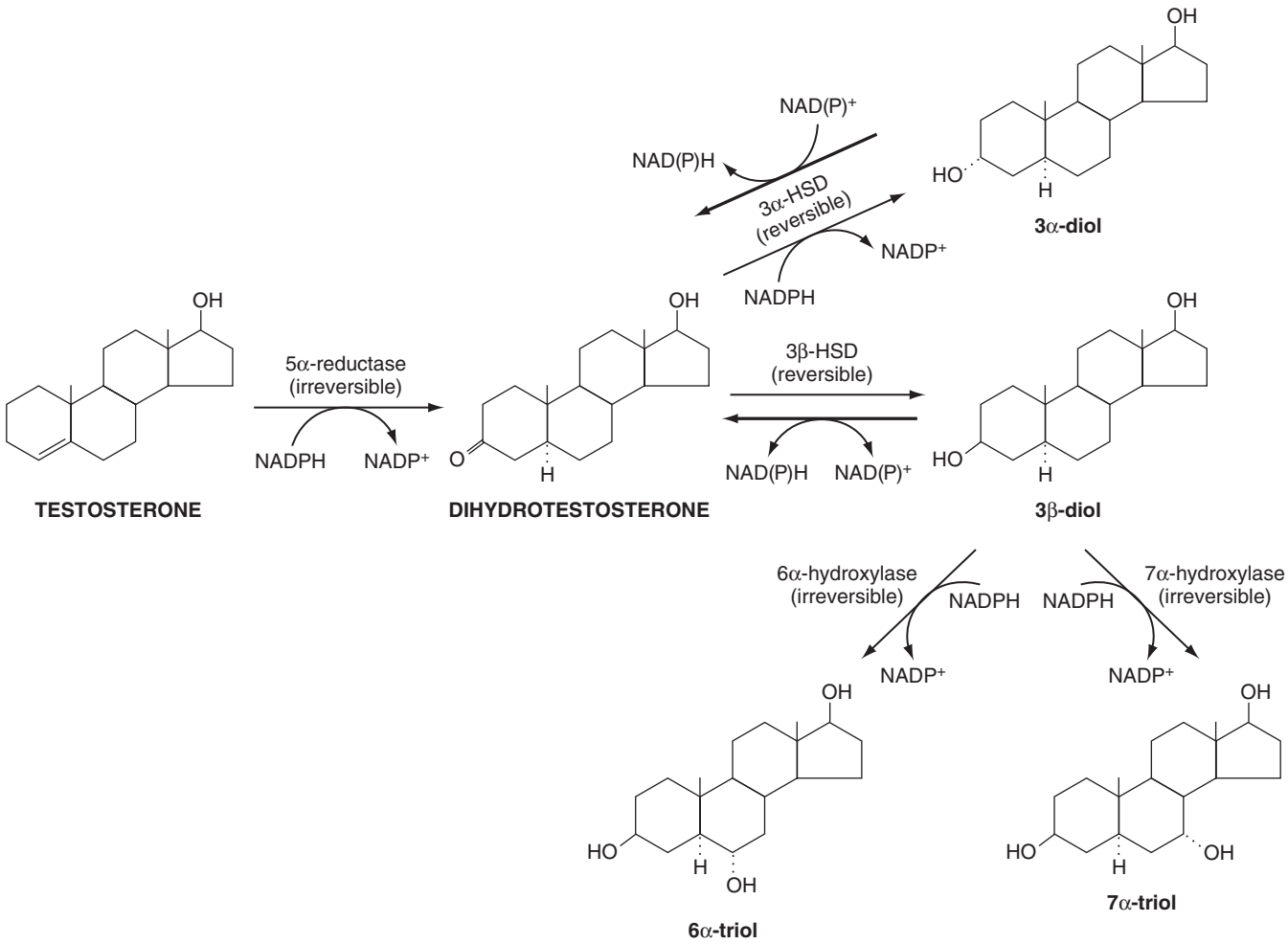


Figure 90–9. Metabolic pathways for testosterone within the prostate. Testosterone is irreversibly metabolized by 5α-reductase to dihydrotestosterone (DHT), which is then reversibly converted into 3α-diol and 3β-diol. The 3β-diol is irreversibly inactivated to the more soluble 6α-triol and 7α-triol. 3α-HSD, 3α-hydroxysteroid dehydrogenase.

and is believed to be involved in hair formation. It is present to lesser degrees in the prostate epithelium and stroma. This isoform is found in normal levels in men with congenital 5α-reductase deficiency. **The type 2 enzyme is mutated in 5α-reductase deficiency and is the dominant isoform present in the prostate gland.** The type 2 enzyme appears in the basal cells of the epithelium and in the stromal cells but is absent in the secretory epithelial cells. This has raised the possibility that DHT stimulation of epithelial cells is derived from DHT converted within the stromal or basal cells. Silver and coworkers (1994) have studied the cell type–specific expression of these reductases as well as their regulation. It appears that the 5α-reductase type 2 in the prostate does not change dramatically in individuals undergoing short-term androgen ablation.

Berman and associates (1995) have studied the distribution of the two 5α-reductase isozymes in the urogenital tract of the fetal rat. At 17 to 21 days of development the expression of type 1 gene predominated in the epithelial cells; the type 2 gene was limited to the mesenchymal cells. This is true in both the testosterone-dependent and DHT-dependent anlagen of the urogenital tract. These investigators observed that androgens could stimulate the expression of the type 2 gene in the urogenital tract but not of the type 1 gene. They suggested that the type 2 5α-reductase gene exhibits positive feedback control in that the product of the enzyme, DHT, can stimulate expression of the gene; however, no evidence for such regulation of either 5α-reductase gene was detected in the fetus.

In summary, 5α-reductase is of great importance because the product DHT is important in the differentiation of the prostate during fetal development and because mutations in 5α-reductase give rise to a rare form of pseudohermaphroditism. In prostate physiology, expression of the 5α-reductase gene is regulated by androgens in both the prostate and liver. It is also believed that 5α-reductase is involved in male pattern baldness, acne, and hirsutism as well as in BPH. **The 5α-reductase inhibitors finasteride (type 2 inhibitor) and dutasteride (type 1 and 2 inhibitor) are clinically useful drugs in the treatment of BPH and male pattern baldness when they are given to appropriate populations of patients.**

After DHT is formed from testosterone in the prostate it is then subjected to a series of reversible metabolic reactions to form 3α-diol (5α-androstane-3α,17β-diol) and 3β-diol (5α-androstane-3β,17β-diol) (see Fig. 90–9). The enzymes that perform this transformation of DHT are 3α- or 3β-hydroxysteroid oxidoreductases. These enzymes use NADP as a cofactor, but in contrast to 5α-reductase they can also use nicotinamide-adenine dinucleotide (NAD). The equilibrium for the metabolism of DHT favors the

Table 90–3.
Properties and Distribution of 5α-Reductase Types 1 and 2

	TYPE 1	TYPE 2
Chromosome	5p15	2p23
Molecular weight	29,000	28,000
Amino acids	259	254
Exons	4	4
Introns	5	5
Homology	49%	49%
pH optima	Alkaline (6-8.5)	Acidic (5.0)
K_m testosterone (μM)	1.5	0.1-1.0
Ki finasteride (nM)	325	12
Half-life (hr)	20-30	20-30
5α-Reductase deficiency	Normal	Mutated
Prostate Cells		
HUMAN		
Luminal epithelial	±	–
Basal epithelial	–	+
Stromal	±	+
Skin	+	–
RAT		
Prostate cells		
Luminal epithelial	–	–
Basal epithelial	+	–
Stromal	–	+

formation of DHT, that is, the 3-hydroxy group of 3α-diol and 3β-diol is oxidized to the 3-ketone that is present in DHT. It is known that administration of 3α-diol to an animal is a strong androgen through its rapid conversion to the effective DHT. On the other hand, 3β-diol is not effective as an androgen because it is rapidly and irreversibly converted to the triol form by hydroxylation in the 6a or 7a position (see Fig. 90–9). The triols are dead-end products of testosterone metabolism but are water soluble and inactive as androgens because they cannot re-form DHT. Steroids also can form glucuronide or sulfate conjugates and be secreted in a more soluble form. **In summary, testosterone is irreversibly metabolized to DHT that is in equilibrium with other reduced steroids primarily through oxidation and reduction at the 3 position. The steroids are inactivated by being irreversibly hydroxylated to the inactive triols.**

Androgen Regulation of Stromal-Epithelial Interactions

It is now apparent that there is a dynamic and reciprocal interaction between the functions of epithelial cells and those of stromal cells (Steiner, 1993; Cunha, 1994; Sikes, 1995; Cunha et al, 2003, 2004). These crosstalk interactions are mediated through the spatial organization of extracellular matrix elements that form the basement membrane linkage. This linkage presents, filters, and organizes the two-way paracrine signals and the flow of information between those two cellular compartments. For example, fluids, gases, nutrients, hormones, and many growth factors arriving in the prostate through the circulation must first pass through the stromal ground substance, the extracellular matrix, and the basement membrane before reaching the base of the secretory epithelial cells. Early in development, the functions of the epithelial and mesenchymal (stromal) elements vary as to their cell types, compositions, properties, and interactions. It is the integrated system biology of these two tissue elements as well as their dynamics during aging that play a vital role in the prostate's functions as a unit and gland. Indeed, it is the breakdown of these tissue interactions that is one of the hallmarks of the abnormal growth of the prostate that starts very early in life and is initiated at some time just after maximum virilization, at approximately 25 years of age. The prostate is extremely susceptible to permanent early alterations in form and structure as a consequence of genetic, environmental, dietary, or metabolic factors with aging (Risbridger et al, 2005). In fact, it is essential to establish the link between hormonal (androgens and estrogens) changes that occur during the fetal or neonatal period that *imprint* and hence may result in onset of late-life disease. With aging, during a period of 50 to 60 years, this organ slowly progresses through the transition from normal zonal histologic anatomy and function to the early signs of BPH, to prostatic inflammatory atrophy, to prostatic interepithelial neoplasia, and finally to various types of prostatic adenocarcinoma. This concept has been thoroughly documented in several rodent models (Rajfer and Coffey, 1978, 1979; Naslund and Coffey, 1986, 1987; Prins and Birch, 1995; Singh et al, 1999; Prins et al, 2001; Risbridger et al, 2005).

Cell Adhesion Molecules

Cell-cell and extracellular matrix interactions are becoming major targets for understanding how the phenotype of a cell is regulated. Transmembrane receptors on the cell surface extend out through the plasma membrane and form a bridge directly connecting the cytoskeleton with proteins and receptors located within the extracellular matrix or on neighboring cells. The cell adhesion molecules (CAMs) are divided into four major types: (1) integrins, which link the cell to the basement membrane and extracellular matrix components through heterodimer interactions; (2) cadherins, which link the cell to neighboring cells through homotypic polymers; (3) selectins, which link the cell to carbohydrate moieties primarily on the vascular system; and (4) immunoglobulin superfamily adhesion molecules. The most extensively studied of these cell adhesion molecules in the prostate in order of interest have been E-cadherins that bind prostate epithelial cells to each other and CD71 that binds to transferrin, as well as several of the integrin molecules. These bindings have been surveyed in prostate tumor cell lines in vitro (Rokhlin and Cohen, 1995), but more extensive work needs to be carried out in vivo in the normal developing prostate and in prostate cancer.

The integrins are made up of two covalently linked heterodimers termed *α* and *β subunits*. These integrins serve externally to contact the extracellular matrix receptors of fibronectin, fibrinogens, collagen, and laminin as well as glycosaminoglycans in the proteoglycans of the extracellular matrix. The integrin receptor domains inside the cell compartment serve as focal points for determining the structure and organization of the cytoskeleton. Approximately eight subunits of α and β can interact in different heterodimers that are tissue specific and can be of several types even on one cell. Different combinations may have varying degrees of binding activity for extracellular matrix components. For example, $\alpha_3\beta_1$ binds to laminin, collagen, and fibronectin and does so by recognizing a triplet of amino acids in those proteins made up of arginine, glycine, and aspartic acid (RGD).

Other types of transmembrane receptors also extend out of the cell to make direct cell-cell contact with the neighboring cell by recognizing similar receptors and forming homodimer bonds.

Certain homophilic dimers that require calcium for interactions to form cell-cell bonds with neighboring cells are termed *cadherins*. Four of the cadherin types have been cloned. They contain between 723 and 748 amino acids that are composed of a single peptide, an extracellular region with three repeated domains, a hydrophobic transmembrane region, and a long cytoplasmic tail. There is approximately 50% homology across species and between integrins. The cadherins are classified into three subtypes: E-cadherins found in adult epithelial cells (also earlier termed *uvomorulin,* cell CAM 120/80, ARC-1, or L-CAM); N-cadherins found in neural tissues of muscle (also termed A-CAM); and P-cadherins found primarily in placenta and epithelium (Albelva, 1994). In the prostate cell, for example, E-cadherins extending out of the surface membrane make contact with the neighboring cell and form a homodimer, and the E-cadherin extending inside the cell by passing through the membrane would form as an organizing center that binds a complex of three cytoplasmic proteins termed *catenins* α, β, and γ. This complex is localized to the zonula adherins of the cell and participates in junction formation and stabilization of the cytoskeleton. These interlocking matrix systems interact to form a structural network extending externally from cell-cell contact and the extracellular matrix interactions and then internally to cytoskeleton organization and centrally, terminating by direct contact with the nuclear matrix that forms tissue-specific DNA organization.

The interactions of the nonhistone tissue matrix regulate many aspects of DNA functions involved in growth and differentiation (Getzenberg et al, 1990; Boccardo et al, 2003). The nonhistone proteins such as high-mobility group (HMG) proteins include HMGI/Y (HMGA) that participate in numerous cellular processes, such as regulation of inducible gene transcription, integration of retroviruses into chromosomes, and induction of malignant transformation (Reeves and Beckerbauer, 2003). Through protein-DNA and protein-protein interactions the members of the HMGA family can influence growth, cell proliferation, differentiation, and cell death; they influence chromosome dynamics by acting as architectural transcription factors affecting several genes that have an impact on tissue structure and organization. This class of genes is often upregulated in cancer (Reeves and Beckerbauer, 2003). These types of tissue matrix interactions are essential to the understanding of stromal-epithelial interactions because they form direct structural linkages and communications between the stroma and the epithelial nuclear DNA. In summary, under the influence of hormones (estrogens and androgens) and diet, it is the regulation of chromatin structure and organization through the histone and nonhistone pathways that replaces and maintains the tissue organization as well as interactions in health and disease.

The discussion, to this point, has concerned primarily insoluble elements in inducing stromal-epithelial interactions, but soluble hormones such as steroids, vitamins, and growth factors are also important (Sikes, 1995). The prostatic stromal cells contain steroid receptors and respond to both androgens and estrogens (see earlier discussion). Androgens and estrogens can alter the formation of collagen (Coffey and Walsh, 1990) and other extracellular matrix components, such as glycosaminoglycans, in the prostate (DeKlerk et al, 1984; DeKlerk and Human, 1985; Kofoed et al, 1990; Horsfall et al, 1994).

In summary, different components of matrix interactions can have either an inhibitory role in negative regulation of normal prostate growth or a positive role in establishing tumor growth. There have been many hypotheses concerning the mechanism of these epithelial-stromal interactions, but they have yet to be fully resolved.

Key Points: Cell Adhesion Molecules

- Transmembrane receptors on the cell surface extend out through the plasma membrane and form a bridge directly connecting the cytoskeleton with proteins and receptors located within the extracellular matrix or on neighboring cells.
- The cell adhesion molecules are divided into four major types: *integrins,* which link the cell to the basement membrane and extracellular matrix components through heterodimer interactions; *cadherins,* which link the cell to neighboring cells through homotypic polymers; *selectins,* which link the cell to carbohydrate moieties primarily on the vascular system; and immunoglobulin superfamily adhesion molecules.

REGULATION OF PROSTATE GROWTH AT THE MOLECULAR LEVEL: STEROID RECEPTORS

In almost all cells in the body, steroids can enter the nucleus, but only a few cells can retain this steroid within the nucleus for any length of time. The cells that retain the steroid have receptors that are steroid specific, which can regulate specific steroid-sensitive genes within the nucleus to alter the expression of certain proteins. The AR's affinity for the nuclear acceptor site to which it binds in the nucleus is probably a compilation of binding to specific sequences on DNA (androgen response elements) as well as tissue-specific binding to coregulatory factors. The uptake and binding of the AR in the nucleus are regulated by the presence of the androgen ligand bound to the receptor, resulting in receptor activation. When androgens are not present, the receptor decreases its affinity for nuclear binding and can easily be removed and, indeed, under castrate conditions, receptors may leak back out into the cytoplasm (Husmann et al, 1990). Immunohistochemical techniques indicate that in the presence of androgen the AR localizes primarily to the nucleus.

The prostate and seminal vesicles contain steroid-specific and high-affinity (10^{-9} to 10^{-10} M K_d) saturable (100 to 1000 fmol of receptor per milligram of DNA equivalents of tissue) ARs that were first described by Liao and Fang in 1969. There are 5,000 to 20,000 molecules of these receptors per cell, far more than can bind to the androgen response element sites, which are probably fewer than 400. Classic AR function has been characterized as a genomic process wherein certain transgenes are regulated by the activated AR. More recently, however, attention has been focusing on the nongenomic mechanisms of androgen action (Benten et al, 1997; Jones et al, 2004). Nongenomic androgen action is characterized by extremely rapid changes in cellular physiology, typically measured in seconds or minutes, as opposed to the longer times required for target gene regulation to be translated into protein changes. Whether nongenomic androgen action occurs through the same ARs involved in genomic regulation still remains to be determined. The properties and hormonal regulation of ARs as well as their uses have been reviewed in detail (Gelmann, 2002; Black and Paschal, 2004).

Key Points: Androgen Receptor

- The androgen receptor, an intracellular steroid-binding protein, is activated by androgens, resulting in both genomic and nongenomic actions, which in turn regulate cellular action.
- This regulation is central to prostate development, growth, and homeostasis and occurs in both the stromal and epithelial compartments.

Androgen Receptor

The cloning of the human AR and its expression was a hallmark in the study of the mechanism of androgen action (Chang et al, 1988b; Lubahn et al, 1988). This led to the study of the sequence of the gene and its protein product—and how this is altered in inherited androgen insensitivity syndromes—as well as receptor function (Chang et al, 1995).

The *AR* gene is on the long arm of the X chromosome at position Xq11.2-q12. Because there is only one X chromosome in a male, it is a single copy gene. The coding sequence on this gene is divided into 8 exons that are transcribed and processed into mRNA and then subsequently translated into protein. The total genomic DNA spans a minimum of 80 kilobases (Marcelli et al, 1990) but forms a final message of only 10.6 kilobases, that is, only 17% of the total gene, with an open reading frame of 2757 base pairs. This is similar to the organization of many other steroid receptors that also contain information from 8 exons, such as the progesterone and estrogen receptors. The AR is a member of the nuclear receptor superfamily, which is a group of ligand-inducible transcription factors. The nuclear receptor superfamily has more than 200 members at present (Escriva et al, 2004). All of these receptors share certain structural features that allow them to regulate gene expression, although the ligands for many of these receptors have yet to be identified (so-called orphan receptors). Such receptors include the glucocorticoid receptor, the retinoic acid receptors (RXR and RAR), the vitamin D receptor, the estrogen and progesterone receptors, the peroxisome proliferator-activated receptor (PPAR-γ), and many orphan receptors. Like other steroid receptors, the AR is divided into three distinct, modular domains: the amino-terminal domain, the DNA-binding domain, and the carboxyl-terminal ligand-binding domain. Despite the similarity in structural organization of all of the nuclear receptors, activation of different receptors results in markedly different cellular responses. Mutational analyses of the human AR have allowed a detailed mapping of a variety of different functions, which are diagrammed schematically in Figure 90–10.

Upstream (5′ direction) of the transcriptional initiation site is the regulatory element of the gene that controls its expression. It is unusual in that it contains the GC box rather than the classic TATA and CCAAT that are commonly found in promoters of polymerase II–dependent genes. Closer to the initiation site located only 70 base pairs upstream is a 50-base pair purine-rich region that is a *cis*-acting element for AR transcription. There are other *cis*-acting elements, including an AP-1 (which is bound by a heterodimer of c-Fos and c-Jun) and a RARE (retinoic acid response element) as well as a cyclic adenosine monophosphate (AMP) response element (AR/CRE1). This suggests that the regulation of expression of the *AR* gene may involve cyclic AMP, activation of c-Fos/c-Jun, or retinoids (Kuiper et al, 1989; Faber et al, 1993; Mizokami et al, 1994; Young et al, 1994). Activation of the AR appears to be a function of multiple steps including initial complex formation with certain chaperonins, binding of ligand, post-translational modifications, dimerization, nuclear localization, and binding of the receptor to certain transcriptional coactivator complexes that remodel chromatin, target the initiation site, and stabilize the RNA polymerase II machinery for repeated rounds of transcription. Each of these features is discussed in the context of known structural features of the receptor as diagrammed in Figure 90–11.

Chaperonin Binding

Immediately after nascent production of the protein in the ribosome, the receptor forms complexes with several other proteins, referred to as chaperonins. These chaperonins form an aggregate complex, which is known as the 8S complex, in reference to the size of the complex on sucrose gradient sedimentation analysis. This chaperonin complex includes at least eight known components (Hsp90, Hsp70, Hip, p60, p23, FKBP51, FKBP52, and Cyp40), which serve to sequester the receptor into an inactive pool (see Fig. 90–11). By analogy to the progesterone receptor, which has had the most detailed scrutiny in regard to the molecular biology of the chaperonin complex (Nair et al, 1996; Pratt and Toft, 1997; Smith, 2000), the AR can dissociate into a monomeric form (4S

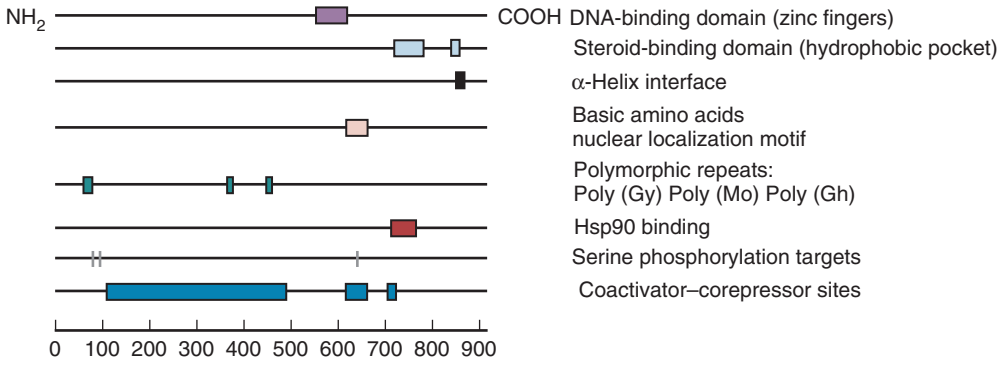


Figure 90–10. Structure of the human androgen receptor protein. The androgen receptor is divided into several functional domains including the DNA-binding domain (consisting of two zinc fingers), a steroid-binding domain (consisting of a hydrophobic pocket), a nuclear localization motif, and several coactivator/corepressor binding sites. There are three polymorphic repeats of glycine, proline, and glutamine, with varying sizes among different populations. The relative positions of the functional elements are shown to scale.

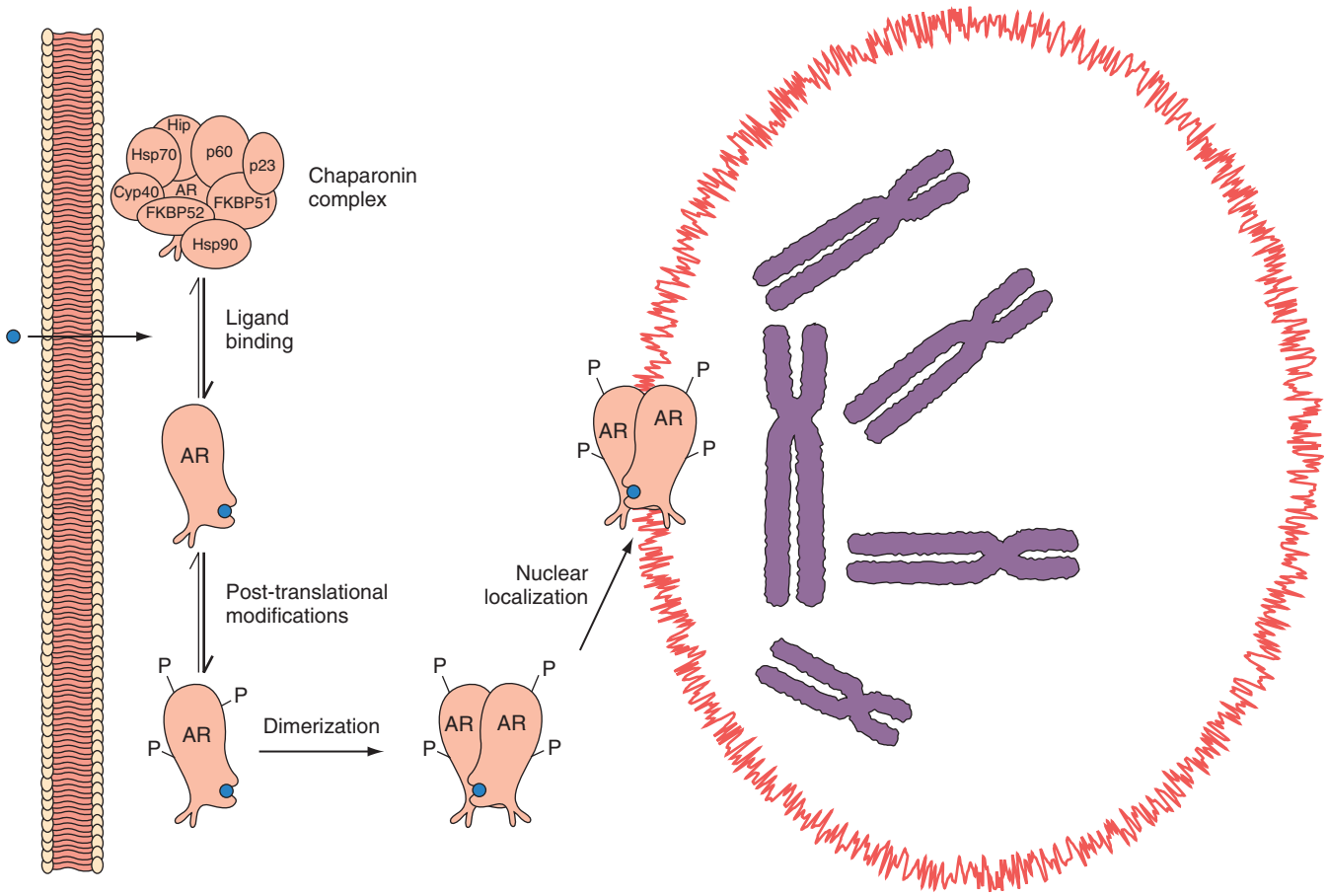


Figure 90–11. Mechanism of androgen receptor (AR) activation by ligand. Androgen enters the cell membrane by passive diffusion and binds the androgen receptor in the cytoplasm. The androgen receptor exists in equilibrium with the chaperonin complex, consisting of at least eight different components, including Hsp90, Hsp70, Hip, p60, p23, FKBP51, FKBP52, and Cyp40. Once activated by binding ligand, post-translational modifications occur, such as phosphorylation. Contemporaneously, dimerization occurs, and the activated modified androgen receptor is translocated to the nucleus by active transport.

on sucrose gradient centrifugation) that is in equilibrium with the 8S form, with the preponderant species existing in the chaperonin complex. This larger complex may be particularly favored by virtue of mass action alone, because the heat shock proteins tend to be among the most abundant proteins in the cell. Although the AR is uncomplexed, it is susceptible to various different post-translational processing steps, including phosphorylation or glycosylation. Such interactions may then inhibit reassociation with the chaperonins, leading to ligand-dependent activation, ligand-independent activation, or receptor inactivation with proteasome-mediated degradation. Evidence for such a mechanism includes a PEST sequence similar to one in the vitamin D receptor that is present in the hinge region of all known mammalian ARs, suggesting that it may function in proteasome-mediated AR turnover. Moreover, proteasome inhibition leads to a significant increase in AR isoforms (Sheflin et al, 2000).

DNA-Binding Domain

Near the end of exon 1 and extending into exon 3 is the coding sequence for the DNA-binding domain. The DNA-binding domain of the AR consists of 72 amino acids rich in cysteine and encoding two zinc finger motifs, which allows specific recognition of certain DNA sequences referred to as androgen response elements. Such elements typically consist of a palindromic repeat separated by a three-nucleotide spacer, for example, GG(A/T)ACAnnnTGTTCT (Roche et al, 1992). X-ray crystallography of certain steroid receptors (glucocorticoid receptor and progesterone receptor) has shown that the first zinc finger directs sequence specificity of binding by directly contacting the DNA bases in the major groove; the second zinc finger functions to stabilize the protein-DNA complex by contacting the sugar-phosphate backbone. Although the protein-DNA interaction appears to be largely limited to the zinc finger motifs, sequences in the amino terminus appear to be important in stabilizing these structures because mutations in this region result in a mildly diminished DNA-binding affinity. This DNA-binding domain of the zinc fingers in the steroid receptor molecule is highly conserved. In this region of exon 2-3, there is a 79% homology with the progesterone receptor, a 76% homology with the glucocorticoid receptor, and a 56% homology with the ER (Chang et al, 1988a, 1988b). The closest homology of the AR is with the progesterone receptor (Lubahn et al, 1988; Marcelli et al, 1990). Mutations of amino acids in this area of the AR can make the receptor unable to activate androgen-sensitive genes (Govindan, 1990), which is the basis of one of the inherited androgen-insensitivity syndromes—testicular feminization.

The DNA-binding domain binds to its cognate DNA-regulatory site, referred to as a hormone response element. Hormone response elements can be divided into different groups on the basis of common structural features for which whole groups of receptors are capable of binding. Class I hormone response elements include the glucocorticoid receptor, the progesterone receptor, and the mineralocorticoid receptor and are characterized by

a half-site consensus sequence of TGTTCT. Class II hormone response elements include the ER, whose prototype half-site sequence is TGACC. The hormone response elements to which ARs have been shown to bind belong to the class I subgroup (Tan, 1990). A consensus sequence for the androgen response element has been determined by an RNA-binding site selection assay with an AR fusion protein to be GG(A/T)ACAnnnTGTTCT (Roche et al, 1992). Such binding sites are characterized by an inverted palindromic repeat with a dyad axis of symmetry, indicating that the receptors are binding in a head-to-head fashion. Recently, however, the androgen response element of the rat probasin promoter has been found to be a direct repeat (Schoenmakers et al, 2000). Surprisingly, x-ray crystallography data reveal that AR dimers bind to direct repeat target sequences in a head-to-head fashion, maintaining the normal orientation of an inverted repeat target sequence (Shaffer et al, 2004). To date, only the AR has been found to bind to a direct repeat target sequence with an orientation normally expected for an inverted repeat. This difference may represent one way ARs maintain specificity of target gene regulation.

Ligand-Binding Domain

Ligand-dependent activation is characterized by ligand-receptor dimerization, post-translational modifications (e.g., phosphorylation), nuclear translocation, and subsequent target gene activation (or repression). It is believed that binding of either DHT or testosterone to the ligand-binding domain can facilitate these processes, although the binding affinity for DHT is significantly higher than for testosterone. Binding of the androgen to the carboxyl-terminal ligand-binding domain is required for activation; however, deletion of the ligand-binding domain can lead to a constitutively active AR. Thus, at least part of the interaction with the chaperonin complex involves the carboxyl portion of the receptor (Marcelli et al, 1990). However, small point mutations in the ligand-binding region can lead to significant changes in the characteristics of AR action. For instance, a single point mutation in the ligand-binding domain of the AR (codon 877, Thr->Ala) identified in the LNCaP cell line of prostate cancer renders it weakly inducible by inappropriate steroids such as progesterone while retaining the ability to be stimulated by androgens. Marcelli and coworkers (1990) reported that mutations in the AR at amino acid 587 or 794 are inactive in the assay for androgen binding and for transcriptional activation. However, the removal of amino acids from 708 to the carboxyl end at 917 (i.e., the entire ligand-binding domain) leads to the synthesis of a receptor protein that does not bind androgens but is still constitutively active in activating transgenes.

Dimerization

The identification of the palindromic structure of certain hormone response elements for all steroid receptors led to the proposal that these transcription factors bind to the DNA as a dimer. Subsequent analysis of the receptor-DNA interactions has confirmed this hypothesis, and dimerization is now thought to represent an important step in the regulation of steroid receptor action. A hydrophobic heptad repeat within the ligand-binding domain at codons 859 to 880 is conserved among all steroid receptors and is thought to be necessary for high-affinity dimerization. Removal of these sequences leads to low-affinity dimerization, presumably through the action of the DNA-binding zinc fingers on the palindromic androgen response elements. Abolishment of the DNA-binding domain does not inhibit the strong affinity dimerization present in the ligand-binding domain. The strong dimerization signal appears to be related to a hydrophobic α-helix interface formed by the conserved heptad (Centenera et al, 2008).

Post-Translational Modifications

Once the AR has been bound to steroid ligand and dissociated from the chaperonin complex, it is susceptible to a variety of post-translational modifications, any one of which may significantly affect the function and turnover of the receptor. For instance, the AR can be acetylated (Fu et al, 2004) or phosphorylated (Goueli et al, 1984). In the rat ventral prostate it has been reported that this occurs through a nuclear cyclic AMP–dependent protein kinase (Kemppainen et al, 1992). Receptor phosphorylation may be an important mechanism in the nuclear translocation of steroid receptors as well as in DNA binding and transcriptional regulation. The stimulation for phosphorylation appears to be optimal with the binding of an androgen agonist, because antagonists such as flutamide appear to favor the dephosphorylated state, suggesting that the phosphorylation status may be associated with the ultimate activity of the receptor (Wang et al, 1999). Both serine and tyrosine residues have been found to be phosphorylated in other steroid receptors (Landers and Spelsberg, 1992; Sadar et al, 1999). In addition to phosphorylation by protein kinase A, ARs also appear to stimulate mitogen-activated protein kinases, which may provide a different level of regulation of gene activity because such kinases often modulate other transcription factors, such as Elk-1 (Peterziel et al, 1999). The prostate is a rich source of acid phosphatases, and some have suggested that these enzymes may be active in regulating the phosphotyrosyl residues of the AR, thus playing a role in dephosphorylation and inactivation of ARs (Goldsteyn, 1989), although this relationship is certainly not causal.

Nuclear Localization

After activation by the binding of steroid ligand the AR is transported to the nucleus across the nuclear pore complex by a process involving at least two nuclear localization signals, one for import and one for nuclear export. Evidence for nuclear localization signal-dependent nuclear translocation is well established and can be found in a variety of nuclear proteins, including the SV40 large T antigen. In most cases it consists of a stretch of basic amino acids. The prototype nuclear localization signal from the SV40 large T antigen is PKKKRKV, although various other basic sequences have also been implicated in nuclear localization signaling. The nuclear localization of the AR appears to involve multiple steps, including the binding of the basic amino acid nuclear localization signal to importins α and β, docking of an importin-cargo complex to the nuclear pore, translocation to the nucleus, and Ran-GTP–mediated release of the cargo (Rao et al, 2002). Two regions of steroid receptors have gained most attention as regulators of receptor trafficking. The first region is the second DNA-binding zinc finger region together with the flanking hinge region (NL1) consisting of a bipartite signal including flanking leucines and the core signal ^{628}RKLKKLGN (Kemppainen et al, 1992; Ylikomi et al, 1992; Poukka et al, 2000). However, this one putative nuclear signal peptide is not sufficient by itself for high-efficiency translocation; and by analogy to other steroid receptors, additional nuclear localization signals may exist in the steroid-binding domain (Kemppainen et al, 1992). NL1 acts constitutively and participates in rapid nuclear import that is facilitated by importin-α binding (Savory et al, 1999). A number of coregulators of steroid receptor–mediated transactivation interact with regions that encompass NL1 (Jackson et al, 1997; Moilanen et al, 1998; Powers et al, 1998; McKenna et al, 1999). Some of these proteins,

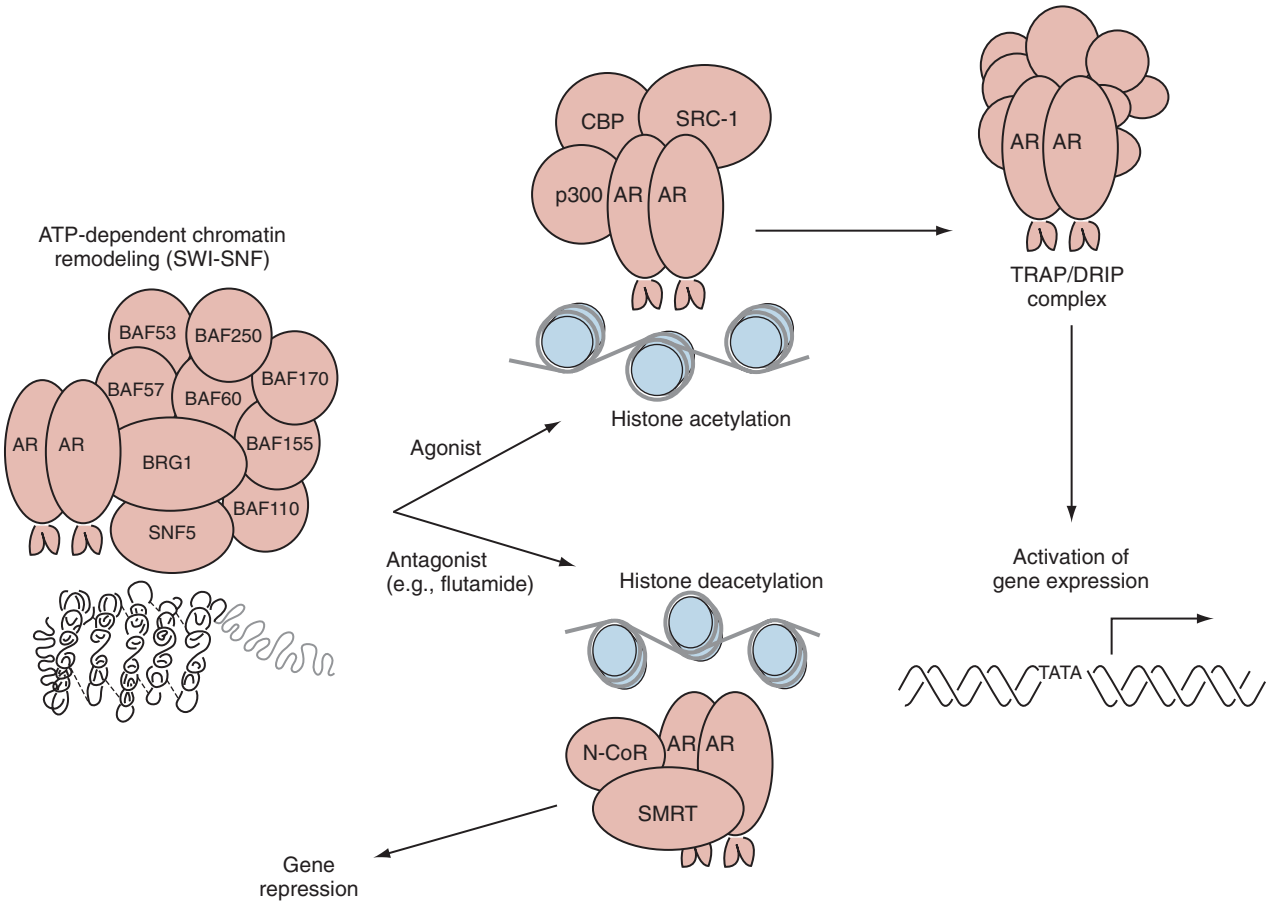


Figure 90–12. Mechanism of action of the nuclear-activated androgen receptor (AR). Once the androgen receptor has been translocated to the nucleus it undergoes several steps (many of which may occur contemporaneously): (1) chromatin remodeling in an ATP-dependent fashion via the SWI-SNF complex; and (2) agonist (i.e., DHT)-mediated histone acetylation in a process involving multiple transmission factors including p300, CBP, and SRC1. In the case of a certain antagonist, histone deacetylation may be favored, and the activated nuclear receptors complex with repressors of gene expression such as N-CoR and SMRT. (3) The activated androgen receptor complexes then associate with other γ-*trans*-acting factors via the TRAP/DRIP complex at sites typically upstream of the target gene known as androgen response elements. This complex then leads to androgen-regulated activation of gene expression.

such as SNURF and Ubc9, lose their ability to interact with AR when the region overlapping with the bipartite NL1 is destroyed (Moilanen et al, 1998; Poukka et al, 2000). A second signal, NES^{AR}, is located in the ligand binding domain (Saporita et al, 2003) and is a nuclear export signal that facilitates export of AR when it is not complexed to ligand. Between the NL1 and NES^{AR}, the AR is actively shuttled between the cytoplasm and nucleus, presumably to tightly regulate its intrinsic ability to activate or repress gene expression.

Transcriptional Activation Domains

Once the AR has achieved active localization into the nucleus it must find and bind to its target sequences in the genomic DNA. The precise mechanism by which receptor localization occurs to target genes is still unknown; however, there is emerging evidence indicating it is a highly orchestrated process (O'Malley, 2008). For instance, it is now known that so-called pioneer factors such as FOXA1 are targeted to specific chromosomal sites by epigenetic signaling, and then the ARs bind to these sites to subsequently regulate the target genes (Lupien et al, 2008). Once the AR has properly localized within the target chromatin sites it must coordinate binding to a number of associated factors referred to as coactivators and corepressors that subsequently regulate gene expression (Fig. 90–12). A list of recently identified coactivators is provided in Table 90–4. Most of these factors interact promiscuously with many steroid receptors, although more AR-specific factors are routinely being discovered. Because the number of potential coregulators clearly exceeds the capacity for direct interaction by a single receptor, the most likely mechanism is that transcriptional activation by AR involves multiple factors that act in both a sequential and combinatorial manner to reorganize chromatin templates (Pollard and Peterson, 1998). The precise timing and sequence of binding of these factors remain to be elucidated; however, one can generally break down the processes empirically into chromatin/nucleosomal remodeling (an energy-dependent process), histone acetyltransferase activity, and subsequent recruitment of TATA-binding protein–associated factors, all of which promote an increased rate of gene transcription by RNA polymerase II. Under certain conditions, such as binding of an AR antagonist (e.g., flutamide), the histone acetyltransferase activity is actually inhibited and transrepression may occur. Such inhibition of gene expression appears to involve the nuclear corepressor proteins N-CoR and SMRT (Glass and Rosenfeld, 2000). Other proteins may play a similar role, such as the *HBO1* gene (Sharma et al, 2000). Amino-terminal deletions in region 46-408 result in dominant negative suppression of hormone-inducible transgene activation, indicating that the coactivator functions require an

Table 90–4.

Abbreviated List of Putative Androgen Receptor Coactivators

ARA24, ARA54, ARA55, ARA70, ARA160
ART-27, ARIP3
β-Catenin
BRCA1, BRCA2
CARM1, CBP, c-Jun, Cdc25B, cyclin E
FHL2 (specific to androgen receptor)
GT198
HBO1
Ku
MAGE 11
Oct-1
p68 helicase, p160, pp32-Rb
pCAF, p300, PGC-1, PNRC, p54nrb
RAC3
RNF-4
SNURF
SRC1, SRC1a, SRC3, SRCAP
TIF2
Tip60
TRAM-1
TRAP/DRIP/GRIP/NRIP
Ubc9, UBCH7
Zac1

interaction within that site and that in the absence of this region the receptor forms dysfunctional complexes in the chromatin (Palvimo et al, 1993).

The transcription domain of the AR is coded in exon 1, which is the largest of the exons, containing 1607 base pairs. Analysis of this region reveals three homopolymeric repeated regions, including a repeat of approximately 20 glutamines, followed by a space containing 8 repetitive prolines and 23 repetitive glycine units (see Fig. 90–12). The glutamine repeats form a β sheet that helps form a polar zipper, which favors certain protein-protein interactions. Fusion of this type of polymeric glutamine repeat with the DNA-binding domain of GAL4 in yeast results in a GAL4-directed increase in transcriptional activity, demonstrating the importance of this region in promoting transgene activation (Gerber et al, 1994).

Studies demonstrate that these polyglutamine repeats appear to interact directly with the carboxyl terminus of the transcription factor p160 (Irvine et al, 2000). In the normal population this repeat varies over a length of 11 to 31 residues, resulting in a true allelic polymorphism. This means that different people have alleles of variant polyglutamine repeat units. This variation is racially defined, and it has been suggested that this may be related to the differences in the incidence rates of prostate cancer in different ethnic groups. The most common CAG repeat length in whites is a modal value of 21; in African-Americans, it is shorter at 18; and in Asians, it is longer at a mean of 23. The longer the glutamine repeats, the lower the activity of the AR in activating target genes. Patients with X-linked spinal and bulbar muscular atrophy, termed *Kennedy disease,* possess a larger glutamine repeat in the range of 40 to 60. The ARs in Kennedy disease exhibit markedly less transactivation activity (Laspada, 1991). Moreover, men with male factor infertility are found to have longer than average polymorphisms of the AR than in normal controls (Tut et al, 1997). Genetic studies of inherited diseases of androgen insensitivity and overvirilization as well as changes in the AR mutation associated with prostate cancer and its biologic properties will be of great help in unraveling the role of the human AR in relation to its structure.

Androgen Receptor–Dependent Chromatin Remodeling

Part of the tissue and gene specificity in the recognition of receptors and DNA may depend on the organization of the DNA within the nucleus (Getzenberg et al, 1990). The steroid-receptor complex can interact only with genes that are in regions that are "open" or in the transcriptionally active form. Studies show that these open regions of chromatin (euchromatin) can extend up to 100,000 base pairs in length, or more than 10-fold the size of a typical gene, which usually ranges from 1000 to 10,000 base pairs. It is unknown how such a large range of DNA is altered in conformation, but it may be through binding to structures like the nuclear matrix, which can order large loop domains in the region of 60,000 to 120,000 base pairs. Nuclear receptors are thought to interact with chromatin remodeling complexes in an ATP-dependent fashion, in a process directed in part by "pioneer factors" including FOXA1 (Lupien et al, 2008), and this may be among the earliest steps in the ultimate regulation of certain target genes (Glass and Rosenfeld, 2000).

During cell division, chromosomal organization is spatially regulated at each of the critical phases of mitosis (Williams and Fisher, 2003). Epigenetic regulation of chromosome structure and function is highly ordered during cell division, differentiation, and development (Lam et al, 2005; Margueron et al, 2005). In fact, chromosomal proteins are required to maintain such ordered structure for euchromatin, heterochromatin, and centromeric chromatin to sustain normal cell and tissue functions. To achieve such coordinate regulation, the protective packaging of DNA is engineered through an elegant system of tightly wound DNA around an eight-component histone core called a nucleosome. This core consists of dimers of H2A, H2B, H3, and H4, whose ability to compact DNA is directly regulated by post-translational modifications. The selective regulation of such post-translational histone modification constitutes a major regulatory mechanism for gene expression and is referred to as the histone code (see Fig. 90–12). Histone modifications include acetylation, phosphorylation, ubiquination, and methylation (Downs and Jackson, 2003; He et al, 2003; Cosgrove et al, 2004; Cosgrove and Wolberger, 2005; Lam et al, 2005).

ARs are known to interact with structural components of the chromatin organizing complexes. Such complexes include the multisubunit human SWI-SNF complex, which has been shown to remodel mononucleosome and polynucleosome templates in an ATP-dependent manner (Peterson and Tamkun, 1995). The isolated hSWI-SNF ATPase subunits BRG1 and hBRM also have these activities (Phelan et al, 2000).

The transcriptional activation of nuclear receptors (neuroendocrine cells) requires multiple factors including SWI-SNF complex, CPB/p300, and SRC family members, which are large and contain numerous subunits, many of which make contact with a variety of nucleosome components and the nuclear matrix (Huang et al, 2003). Such components include BAF53a, BAF57, BAF60, BAF110, BAF155, BAF170, BAF250, BRG1, BRM, and SNF5. Because condensed chromatin renders genes inaccessible for transcription, the combination of a steroid receptor along with the SWI-SNF complex formation appears to be critical for appropriate nucleosomal remodeling to allow appropriate target genes to be accessible for

gene regulation (Sudarsanam and Winston, 2000; Huang et al, 2003). Once the receptor SWI-SNF complex, CPB/p300, and other mediators have successfully "opened" the structure of the chromatin to allow transcriptional regulation, the AR must interact with a distinctly different set of cofactors. Post-translational histone modification clearly appears to be requisite for chromosome remodeling and optimal gene expression (Ewen, 2000; He et al, 2003). In most models tested the rates of gene transcription actually correlate with the degree of modification of histones through acetylation, phosphorylation, ubiquination, and methylation. In other words, hyperacetylated histone regions correspond to the highest gene-transcriptional regions, whereas the hypoacetylated histone regions correspond to the lowest gene-transcriptional regions (Pazin and Kadonaga, 1997). A number of histone acetyltransferase complexes have been found to be associated with nuclear receptors, including the AR. These complexes include p/CAF, a homologue to the yeast GCN5, which participates in the yeast SAGA complex. This complex includes factors that possess HAT activity but also the TATA-binding protein (TBP) and a number of TBP-associated factors. The p/CAF protein has been found to be associated with the retinoic acid receptor and may be involved with multiple nuclear receptors. It is also known to bind to other HAT proteins, including CBP/p300, which is known to acetylate not only histones but other transcription factors as well. The CBP/p300 complex is an essential coactivator for many genes and may actually serve as a molecular scaffold in stimulating gene transcription (McKenna et al, 1999; Huang et al, 2003; Marshall et al, 2003). Such complexes include the SRC1 coactivator, among others. More recently, the modifiers of the histone code have expanded considerably to include sophisticated enzyme-mediated alterations in the histones H2A, H2B, H3, and H4 by phosphorylation, ubiquination, and methylation that open the chromatin, allowing the recruitment of important transcription factors that allow normal cell functions (Lam et al, 2005; Margueron et al, 2005). The list of coactivators associated with nuclear receptors and the AR in particular is extensive and almost certainly incomplete. A short list of factors found to be associated with the receptor at this level of gene regulation is given in Table 90–4. Among the most important factors is SRC1 (steroid receptor coactivator 1), which has mild HAT activity and seems to be required for optimal stimulation of steroid-dependent transcription. Additional factors include SRA, a structural RNA necessary for the coactivator complex to function optimally (McKenna et al, 1999), and p160 coactivator, which appears to be required for hormone-dependent activation and to directly interact with the polyglutamine repeats found in the amino-terminal transactivation domain (Irvine et al, 2000).

Most genes have a regulatory region immediately upstream of the transcriptional start site. The regulatory region is divided into a core *promoter element* that is present in all genes as well as other upstream elements that serve to regulate the overall gene expression pattern. This promoter element specifies the site to which RNA polymerase II will attach to the DNA and will determine the actual point for the initiation of transcription. The RNA polymerase will copy or transcribe the DNA code into mRNA, a process termed *transcription.* This promoter area starts at –16 nucleotides to +32 upstream from the gene initiation site. This region of –32 to +16 was originally referred to as the Goldberg-Hogness box or TATA box and has a consensus sequence of TATAAAAG. The RNA polymerase II enzyme binds to this TATA box as one of the initial steps in transcription. Farther upstream from the TATA box is a second gene control element termed generically the *hormone response element,* which has been identified in many genes regulated by steroid hormones and is one of multiple sites where the receptor binds to the DNA. As stated earlier, in androgen-regulated genes, this area is termed the *androgen response element;* in estrogen, the *estrogen response element;* and in glucocorticoid, the *glucocorticoid response element*. This hormone response element area may contain several discrete sequences, but its overall role is to modulate the frequency of transcription initiation vis-à-vis interactions with transcriptional factors. In independent analysis, thyroid hormone receptors were found to be associated with affinity purified proteins, which were found to markedly enhance ligand-dependent cell-free transcription. This complex was referred to as TRAP, for thyroid receptor-associated proteins (Fondell et al, 1996). In a similar set of experiments, the same type of complex was isolated for the vitamin D receptor and was called DRIP for D receptor–interacting proteins (Rachez et al, 1998). Subsequent analysis revealed that they shared at least nine proteins, and this activator-recruited cofactor complex (TRAP/DRIP/ARC) is part of a large composite coactivator complex used by a variety of transcription factors for the regulation of certain target genes. Such transcription factors include SREBP, NFκB, and VP16 (Sun et al, 1998; Gu et al, 1999; Ito et al, 1999; Naar et al, 1999; Ryu et al, 1999).

In summary, the TATA box tells where RNA polymerase binds and where the initiation of transcription is to start and the hormone response element regulates how frequently it is to be transcribed when it is bound to a hormone receptor. This is accomplished by the presence of certain cofactors in the TRAP/DRIP complex. Because the hormone response element of DNA sequence has been shown to be independent of its position or its orientation, it resembles what has been called the *transcription enhancer element* that has been found in many other types of genes. The hormone response element section can vary in its location upstream from the initiation of the gene from –20 to –6000 for various different types of hormones. With the steroid hormones, it appears to reside about –140 nucleotides upstream from the initiation site. For example, in the glucocorticoid receptor recognition element the site for glucocorticoid receptor recognition is approximately –140 and contains a sequence of nucleotides of AAAATGGAC. Deletion mapping experiments have indicated that the receptor-binding domain located in the hormone response element is indeed required for receptor binding and is necessary for steroid-mediated control of transcription.

Once the DNA is transcribed into mRNA, a series of adenine units are added to the end (called the poly-A tail) and then the mRNA is cut and spliced on small nuclear particles (called splicesomes) located on the nuclear matrix, and this splicing removes the intron portion of the message. The final mRNA is shipped out of the nucleus, believed to occur on the structural components of the nuclear matrix, and passes through the pore complexes of the nucleus and out to the ribosomes where the mRNA is then translated into protein product, a step termed *translation.* The proteins have specific amino acid sequences that instruct the cell where to ship the protein in relation to secretory granules or to the membrane area. The protein can also be modified after translation by the subsequent addition of carbohydrates to become glycoproteins or to be phosphorylated by kinases. Under appropriate signals, such as neurologic control, secretory proteins can then be excreted into the lumen of the prostate. This is a process that occurs when secretory proteins of the prostate and seminal vesicles are formed into the ejaculate. A schematic example of this process is shown in Figure 90–8, and such a system would include PSA and acid phosphatase as well as many other protein products that are regulated in their synthesis by androgens through receptor interactions.

During embryonic development, the AR appears first in the mesenchyme of both the rat ventral prostate and seminal vesicles and a few days later in the epithelial cells, but it is unknown what regulates this timing. **In the development of the seminal vesicles and the wolffian duct, testosterone appears to be the primary androgen in glandular development, and in the ventral prostate that forms from the urogenital sinus the androgen is primarily DHT.** Both testosterone and DHT can bind to the AR; however, on a molar basis, DHT is 3 to 10 times more potent. This decrease in potency of testosterone is believed to be due to the rapid off rates of the testosterone once it is bound so that equilibrium results in less receptor occupancy compared with DHT at similar tissue levels. A report indicates that in some cases, AR-mediated transcriptional regulation can occur even in the absence of direct interaction of the AR with the specific androgen response elements (Kallio et al, 1995). The report stated that the ARs are able to elicit both transrepression and transactivation without interacting directly with the specific DNA elements. This may indicate that the AR can bind to regulatory units within the transcription factors and thus alter their properties even in the absence of direct DNA binding to an androgen response element.

The next part of this discussion is focused on the structure of the nucleus, where the genetic information of the genes, the AR interactions, and the mRNA processing occur and are integrated. This is within a highly ordered structure of the nucleus that is determined by a residual scaffolding framework, called the nuclear matrix, which provides three-dimensional organization to both the nucleus and the DNA.

Role of the Nuclear Matrix in Androgen Action

The DNA may be identical in every cell of different tissues in the body, but it appears to be organized in a different three-dimensional array in different cell types. This spatial organization of DNA appears to be determined in part by nuclear architecture and structure dictated by the scaffolding element termed the *nuclear matrix*. Therefore, more may be required than just a steroid receptor and a DNA sequence with an androgen response element to determine the high tissue specificity of androgen hormone action. It may require regulation of DNA conformation and three-dimensional structure. There is strong evidence to support the belief that structural components of the nucleus may organize the DNA into different topologic constraints that permit specific steroid receptor interactions themselves. It is also believed that these structural modifications of DNA topology may be an integral part of differentiation. The nuclear matrix has been proposed to be an important structural element in this type of DNA organization (Getzenberg et al, 1990; Boccardo et al, 2003). The matrix facilitates the location of target genes and their conformation and facilitates their cointeraction with steroid receptors. Barrack and Coffey first showed that the nuclear matrix is a major target for androgen and ER binding (Barrack and Coffey, 1980; Barrack, 1987). Because the matrix has been implicated in many important nuclear events, it would provide an ideal target for androgen action. The nuclear matrix has been defined as the dynamic structural subcomponent of the nucleus that directs the functional organization of DNA into loop domains and provides sites for the specific control of nucleic acids (Nelson et al, 1986; Getzenberg et al, 1990). Conceptually, it can be viewed as the nuclear equivalent to the cytomatrix or cytoskeleton. The nuclear matrix contains residual nuclear elements, including the pore complex lamina, the residual nucleolus, and an internal ribonucleoprotein particle network attached to a dynamic fibrous protein mesh (Berezney and Coffey, 1977). The nuclear matrix may be isolated by sequential extractions employing nonionic detergent, brief digestion with DNase I, and a hypertonic salt buffer wash. The residual nuclear matrix structures represent only 15% or less of the original total nuclear mass. More than 98% of the DNA, 70% of the RNA, and 90% of the nuclear proteins have been extracted, and the remaining structure is essentially devoid of histones and lipids.

The nuclear matrix has been implicated as an important structural component in a wide variety of biologic functions. There are approximately 50,000 DNA loop domains in a nucleus, each containing about 60 kilobase pairs of DNA, and these loops are attached at their bases to the nuclear matrix (Pardoll et al, 1980; Vogelstein et al, 1980; Luke and Coffey, 1994). This loop organization is maintained during interphase and throughout metaphase (Nelson et al, 1986). Topoisomerase II, an enzyme that modulates DNA twisting and topology, is associated with the nuclear matrix and the mitotic chromosome scaffold. Many studies with a wide variety of systems have demonstrated that active genes are associated with the nuclear matrix, whereas transcriptionally inactive genes are not close to the matrix. This location of active genes on the matrix provides evidence that the matrix plays an important organizing role in differentiation, placing genes in different configuration.

Androgens can activate DNA synthesis and cell replication in target tissues. The nuclear matrix also serves an important role in DNA replication. The matrix contains fixed sites for DNA synthesis (Pardoll et al, 1980) located at the base of the DNA loop. During DNA synthesis the DNA loop domains are reeled down through the attached replicating complex that is fixed on the matrix. Therefore, the DNA replication fork, DNA polymerase, and newly replicated DNA have been shown to be associated with the nuclear matrix. It is easy to visualize how hormone action and alteration in the nuclear matrix structures could impinge on the androgen regulation of DNA synthesis and growth in a prostate cell.

The nuclear matrix is also associated with mRNA synthesis during transcription. Ciejek and colleagues (1982) observed that more than 95% of the unprocessed mRNA precursor for ovalbumin is associated with nuclear matrix of the chick oviduct. When the intron portions of the RNA were spliced out, the mature mRNA was released from the nuclear matrix. This led them to suggest that the nuclear matrix is involved in RNA processing. Marriman and van Venrooij (1985) have reported that all RNA cleavage products and RNA processing intermediates are firmly bound to nuclear matrix. Once again, alterations in nuclear matrix structures with steroid receptor interactions could alter important steps in transcription and RNA processing. The nuclear matrix contains the attachment sites for the small nuclear ribonucleoprotein particles that are part of the nuclear splicesome system central to the nuclear processing of RNA to the final mRNA, which is transported out to the cytoplasm to be translated.

Ahmed and colleagues have carried out an extensive series of studies of the phosphorylation of the nuclear matrix and related proteins in the ventral prostate of the rat after androgen stimulation and withdrawal (Ahmed, 1987; Ahmed et al, 1993; Tawfic et al, 1993, 1994). They have shown that the nuclear matrix can be phosphorylated by casein kinase 2 (CK-2). One of the targets of this phosphorylation is nucleolin, which is an abundant nucleolar phosphoprotein involved in the synthesis of ribosomal DNA and exquisitely regulated by androgens (Tawfic et al, 1994). Another important protein in nucleolar function that is required

for growth is B23, which is also regulated by CK-2 (Tawfic et al, 1993).

In summary, the nuclear matrix is an important structural modulator of nuclear regulation and is an ideal target for hormonal regulation. Indeed, the nuclear matrix is a major site of steroid hormone receptor binding (Barrack and Coffey, 1982; Donnelly et al, 1983; Wilson and Colvard, 1984; Alexander et al, 1987; Barrack, 1987; Metzger and Korach, 1990; Luke and Coffey, 1994). In the prostate, more than 60% of all nuclear ARs are associated with the nuclear matrix (Barrack and Coffey, 1982). The matrix is also a target for many other types of regulatory interactions, including the nuclear products of oncogenes and viral proteins that can also induce growth regulation similar to hormone-induced growth. For example, the nuclear matrix is reported to be a cellular target for the retrovirus Myc oncogene protein and the polyoma large T antigen. All of these transformation proteins that bind to the nucleus are believed to be early molecular events in carcinogenesis or transformation. Therefore, the observation that ARs interact with the matrix has precedence with the matrix as a common target in factors that regulate cell structure and function.

Key Points: Androgen Receptor Structure and Function

- The androgen receptor is a ligand-activated transcriptional regulator that on binding to androgen dissociates from chaperonins, is actively modified by a variety of methods to an active stage, is actively translocated to the nucleus, and associates first with pioneering factors that direct where in the chromatin the receptor will function and then associates with a large number of coactivators and repressors to regulate target gene expression.
- The transport of the AR is reciprocal, which is to say that it is both localized to the nucleus and actively transported out of the nucleus.
- The AR binds to DNA target sequences as a dimer, which can be direct or inverted repeats; however, the receptor always binds with the same orientation.
- The regulation of the AR appears to be one of the most important "gatekeepers" of prostate development and physiology.

PROMINENT, NONPEPTIDE COMPONENTS OF PROSTATIC SECRETIONS

The seminal plasma is formed primarily from the secretions of the sex accessory tissues, which provide a suitable environment for survival and function of spermatozoa. The sex accessory tissues include the epididymis, ampullae, seminal vesicles, prostate, Cowper (bulbourethral) gland, and glands of Littre. **The average volume of the normal human ejaculate is approximately 3 mL, ranging from 2 to 6 mL, and it has two components: spermatozoa and seminal plasma. Spermatozoa, which represent less than 1% of the total ejaculate, are present in the range of 100 million/mL. The major contribution to the volume of seminal plasma (average 3 mL) comes from the seminal vesicles (1.5 to 2 mL), from the prostate (0.5 mL), and from the Cowper gland and glands of Littre (0.1 to 0.2 mL).** During ejaculation the secretions of these glands are released in a sequential manner (Amelar, 1962; Amelar and Hotchkiss, 1965; Tauber and Zaneveld, 1976; Zaneveld, 1981). The first fraction of the human ejaculate is rich in sperm and prostatic secretions, such as citric acid. The level of fructose, which represents a major secretory product of the seminal vesicles, is elevated in the later fraction of ejaculate. More recently, seminal albumin was measured in seminal plasma and the authors demonstrated an association with sperm morphology but not several other semen parameters (Elzanaty et al, 2007). The overall chemical composition of normal human and rodent prostatic secretions and seminal plasma has been widely studied, and the results have been summarized in excellent reviews (Mann, 1981; Zaneveld, 1981; Aumuller and Seitz, 1990; Daniels, 1990; Chow et al, 1993; Gonzalez, 1993; Elzanaty et al, 2007). Recently, an analysis of expressed prostatic secretions (EPS) revealed that citrate, myoinositol, and spermine metabolite measurements could significantly differentiate controls from men with prostate cancer (Serkova et al, 2008). Control levels of citrate were 353.2 (125.9 to 764.5) µmol/mL, those of myoinositol were 21.2 (7.7 to 41.9) µmol/mL, and those of spermine were 58.0 (18.9 to 168.2) µmol/mL. In cancer, citrate levels were significantly reduced whereas those of myoinositol and spermine were significantly increased.

In relation to other body fluids the seminal plasma is unusual because of its high concentrations of potassium, zinc, citric acid, fructose, phosphorylcholine, spermine, free amino acids, prostaglandins, and enzymes (most notably acid phosphatase, diamine oxidase, β-glucuronidase, lactate dehydrogenase, α-amylase, PSA, and seminal proteinase).

Citric Acid

One of the major anions in human seminal plasma is citrate (mean, 376 mg/dL), which is present in the range of 20 mM or 60 mEq/L. This is compared with the chloride ion (155 mg/dL) at 40 mM. Citrate is a potent binder of metal ions, and the seminal plasma concentration of citrate, 20 mM, is comparable to that of the total divalent metals at 13.6 mM (calcium, 7 mM; magnesium, 4.5 mM; zinc, 2.1 mM). Prostatic citrate levels approximate 15.8 mg/mL (Zaneveld, 1981), and the values for seminal vesicle citric acid secretions are almost 100-fold less, being only 0.2 mg/mL. Citric acid is formed in the prostate at 100 times higher concentration than is seen in other soft tissues (e.g., prostate tissue, 30,000 nmol/g; other tissues, range of 150 to 450 nmol/g). **The concentration of citrate in the ejaculate is 500 to 1000 times higher than that in the plasma. Prostate secretory epithelial cells form citrate from aspartic acid and glucose. The high concentrations within the prostate result partly from the inability of the prostate cell mitochondria to oxidize citrate readily once it is formed; therefore, the rate of citrate synthesis far exceeds the rate of citrate oxidation** (Costello and Franklin, 1989, 1994). Kavanagh (1994) measured citrate and isocitrate levels, which are catalyzed by aconitase, and demonstrated ratios of 33:1 in the prostate, whereas other tissues demonstrate ratios of 10:1. This decreased activity of aconitase might explain the high levels of citrate within the prostate.

Diamine oxidase, an enzyme that degrades polyamines within the prostate, has been linked to citric acid concentrations and, indirectly, to sperm motility and fertility (Gonzalez, 1994; Le Calvé et al, 1995). Yacoe and associates (1991) used magnetic resonance spectroscopy to investigate the relationship between citrate

metabolism and prostate cancer and demonstrated small but statistically insignificant differences between normal epithelium and prostate cancer cell lines. The relationship between prostatic inflammatory disease and citric acid has also been investigated (Wolff et al, 1991). In addition, it is now possible to accurately quantify the concentration of citrate within the prostate by proton magnetic resonance spectroscopy (Liney et al, 1996, 1997; Lowry et al, 1996; Lynch and Nicholson, 1997). Most recently, the ratio of citrate to other components of prostatic secretions has been used to diagnose prostate cancer (Costello and Franklin, 1989; Kim et al, 1998; Pucar et al, 2005).

Fructose

The source of fructose in human seminal plasma is the seminal vesicles (Mann, 1981). Patients with congenital absence of the seminal vesicles also have an associated absence of fructose in their ejaculates (Phadke et al, 1973). The seminal vesicle secretion contains smaller amounts of other free sugars such as glucose, sorbitol, ribose, and fructose, and these sugars usually amount to less than 10 mg/dL. In comparison, the concentration of the reducing sugar fructose is approximately 300 mg/dL in human seminal secretion, and it has a level of 200 mg/dL in seminal plasma.

Fructose levels are under androgenic regulation, but many factors, such as storage, frequency of ejaculation, blood glucose levels, and nutritional status, can also affect seminal plasma concentration (Mann, 1981); these considerations may account for the wide variations encountered in different semen samples from the same patient. Furthermore, plasma levels of androgens do not always correlate with seminal plasma fructose levels; therefore these levels are not a reliable index of the androgenic state of the subject. Seminal fructose levels have also been proposed to be under sympathetic control (Lamano-Carvalho et al, 1993; Kempinas et al, 1995). The physiologic role of fructose in seminal vesicle secretion has been indirectly linked to forward sperm motility through prostasome function (Fabiani et al, 1995) and to seminal viscosity (Gonzalez, 1993).

The source of fructose in seminal vesicles appears to proceed from glucose by aldose reduction to sorbitol and a subsequent ketone reduction to form fructose. The fructose of the seminal plasma appears to provide an anaerobic and an aerobic source of energy for the spermatozoa (Mann, 1981). The cervical mucus has high concentrations of glucose and very low levels of fructose, and the sperm are capable of using both types of sugars. In an epidemiologic study conducted among nearly 50,000 participants in the Health Professionals Follow-up Study of Cancer in 1986, fructose consumption (70 vs. 40 g/day) and high fruit intake were identified as protective against the development of advanced prostate cancer (Giovannucci et al, 1998).

Polyamines

Polyamines are the most basic (positively charged) small organic molecules in nature. They occur ubiquitously in tissues at high concentrations and are believed to be involved in diverse physiologic processes that share a relationship to cell proliferation and growth. Indeed, polyamines can serve as growth factors for cultured mammalian cells and bacteria and as inhibitors of enzymes, including protein kinases.

The exact role of polyamines at the molecular level still eludes science, but they represent important biologic compounds and are found at high levels in the ejaculate. Polyamines may affect the gating and transport of substances through membrane channels. From a clinical perspective, polyamines (spermidine and spermine) have been investigated as markers of androgen deprivation therapy among men with advanced-stage prostate cancer by Cipolla and colleagues (Cipolla et al, 1994). Other researchers (Heston, 1991; Kadmon, 1992; Madhubala and Pegg, 1992; Love et al, 1993) have investigated the role of polyamines in the pathophysiology of prostate cancer. The first and rate-limiting step in polyamine synthesis within the prostate is controlled by the enzyme ornithine decarboxylase (ODC). ODC gene expression has been demonstrated to be increased in BPH tissue (Liu et al, 2002). ODC can be inhibited by difluoromethylornithine (DMFO), which in turn inhibits polyamine synthesis. DMFO has been proposed as an agent for chemoprevention of prostate cancer (Kadmon, 1992).

Spermine levels in normal human seminal plasma range from 50 to 350 mg/dL and originate primarily from the prostate gland, which is the richest source of spermine in the body. Spermine [NH_2-$(CH_2)_3$-NH-$(CH_2)_4$-$(CH_2)_4$-NH-$(CH_2)_3$-NH_2] is a basic aliphatic polyamine and, because of its four positive charges, binds strongly to acidic or negatively charged molecules such as phosphate ions, nucleic acid, and phospholipids. When semen is allowed to stand at room temperature, acid phosphatase enzymatically hydrolyzes seminal phosphorylcholine to form free inorganic phosphate ions, which then interact with the positively charged spermine and precipitate as large, translucent salt crystals of spermine phosphate. Polyamines can also form amide bonds and make their covalent addition to protein carboxylic groups (Williams-Ashman, 1975), and this modification may be involved in regulatory function.

There has been much interest in spermine and other related polyamines, such as spermidine and putrescine, because of the rapid and dramatic changes in levels and ratios associated with many types of cells that have been induced into growth. Williams-Ashman and colleagues have investigated in detail the biosynthesis and regulation of polyamines in the male reproductive tract and have characterized the enzymatic reactions that progress from ornithine to putrescine to spermidine to spermine (Williams-Ashman et al, 1969, 1972; Williams-Ashman, 1975). Polyamines are oxidized enzymatically by diamine oxidase (present in the seminal plasma) to form highly reactive aldehyde compounds that can be toxic to both sperm and bacteria (Le Calvé et al, 1995). The formation of these aldehyde products produces the characteristic odor of semen. It is also possible that these aldehydes or polyamines may, themselves, protect the genitourinary tract from infective agents. Relationships between spermine levels in seminal plasma and sperm count and motility have also been suggested (Stamey et al, 1968; Fair et al, 1993; Fair and Parrish, 1981; Le Calvé et al, 1995). Like citrate, spermine can also be quantified within prostate tissue by magnetic resonance spectroscopy (van der Graaf et al, 2000).

Key Points: Polyamines

- Polyamines are the most basic (positively charged) small organic molecules in nature.
- They occur in prostate tissues at high concentrations and are believed to be involved in diverse physiologic processes that share a relationship to cell proliferation and growth.
- Polyamine and citrate can be quantified in a clinical setting by magnetic resonance spectroscopy.

Phosphorylcholine

Other positively charged amines are at high concentrations in the ejaculate, including choline and phosphorylcholine, which are usually found as components of lipid or as lipotropic factors. The semen of mammals is rich in choline [$(CH_3)_3$-N^+-$(CH_2)_2$-OH]. In humans, phosphorylcholine predominates, whereas in most other species much higher levels of α-glycerylphosphorylcholine are present, often exceeding 1 g/dL of seminal plasma. Seligman and associates (1975) have demonstrated that phosphorylcholine is a highly specific substrate for prostatic acid phosphatase, which is also active in seminal plasma. The result of this enzymatic activity is the rapid formation of free choline in the first ejaculate. In contrast, α-glycerylphosphorylcholine is secreted primarily in the epididymis and is not readily hydrolyzed by acid phosphatase. For these reasons, Mann and Mann (1981) have suggested that the level of α-glycerylphosphorylcholine can be used as an index for assessing the contribution of the epididymal secretion to the ejaculate. The secretion from the epididymis is also under androgenic control. The function of these choline compounds is unknown; it appears that they are not metabolized by spermatozoa, nor do they affect the respiration of the sperm (Dawson et al, 1957).

Prostaglandins

The richest sources of prostaglandins in the human are the seminal vesicles (Pourian et al, 1995). Prostaglandins are present in seminal plasma at a total concentration of 100 to 300 μg/mL. Von Euler (1934) proposed the name *prostaglandins* for the active components in seminal plasma in the belief that they originated from the prostate gland, but Eliasson (1959) established that the primary source of prostaglandin is the seminal vesicles not the prostate; however, the original name has survived. Prostaglandins have a wide distribution in mammalian tissues but at much lower concentrations than in the seminal vesicles (Vane and Botting, 1995).

There are more than 90 different prostaglandins present in the human, with 15 prostaglandins present in human semen, and they are all 20-carbon hydroxy fatty acids with a cyclopentane ring having two side chains; as such, they are derivatives of prostanoic acid. The 15 types of prostaglandins within the prostate are divided into four major groups, designated A, B, E, and F according to the structure of the five-membered cyclopentane ring. Each of these groups is further subdivided according to the position and number of double bonds in the side chain (therefore, PGE_3 indicates prostaglandins of E type with three double bonds in the side chain). The E group of prostaglandins is the major component in the male reproductive tract, whereas the F group predominates in the female system. Fuchs and Chantharaski (1976) have summarized the reported levels of human seminal plasma prostaglandins and report the following mean values (μg/mL): PGE_1, 20; PGE_2, 15; ($PGE_1 + E_2$) – 19-OH, 100; $PGA_1 + A_2$, 9; ($PGA_1 + A_2$) – 19-OH1, 31; $PGB_1 + B_2$, 18; ($PGB_1 + B_2$) – 19-OH, 13; $PGF_{1\alpha}$, 3; and $PGF_{2\alpha}$, 4.

These compounds are potent pharmacologic agents that have been implicated in a wide variety of biologic events in the male, including erection, ejaculation, and sperm motility and transport, as well as in testicular and penile contractions. In addition, prostaglandins from seminal fluid deposited in the vagina have been reported to affect cervical mucus, vaginal secretion, and sperm transport in the female genital tract. Chaudry and colleagues (1994) investigated the relationship between prostaglandin metabolism and both benign prostatic tissue and prostate cancer tissue. Prostaglandin E has been related to the immunosuppressive effects of seminal plasma mediated through the extracellular organelles, or "prostasomes" (Kelly et al, 1991). Finally, Olin and associates (1993) have investigated the effect of prostaglandins on fertility.

Cholesterol and Lipids

Scott (1945) reported that human seminal plasma contains 185 mg/dL of total lipids, 103 mg/dL of cholesterol, and 83 mg/dL of phospholipids (Vignon et al, 1992). In comparison, human prostatic secretion contains the following: total lipids, 186 mg/dL; cholesterol, 80 mg/dL; and phospholipids, 180 mg/dL. The lipids of semen have been further described (White, 1976), and the phospholipids of seminal plasma are composed of 44% sphingomyelin, 12.3% ethanolamine plasmalogen, and 11.2% phosphatidylserine (Poulos et al, 1973).

The reported levels of cholesterol in seminal plasma have varied considerably from 11 to 103 mg/dL (Scott, 1945; Eliasson, 1959; Poulos et al, 1973). White (1975) believes that the ratio of cholesterol to phospholipid in seminal plasma stabilizes the sperm against temperature and environmental shock. Thompson and associates (1987), Rohan and coworkers (1995), and Rose and Connolly (1992) have reviewed the role of dietary lipids in the pathogenesis of prostate cancer.

Zinc

The high level of zinc in human seminal plasma (140 μg/mL) appears to originate primarily from secretions of the prostate gland (488 ± 18 μg/mL) (Bedwal and Bahuguna, 1994). The prostate has the highest concentration of zinc (50 mg/100 g dry weight) of any organ. Mackenzie and colleagues (1962) reported that human seminal plasma contained 310 mg of zinc/100 g dry weight and that spermatozoa contained 200 mg/100 g dry weight. In comparison, prostatic secretions from eight normal subjects had 720 mg zinc/100 g dry weight. Byar (1974) has reviewed many of the early experiments and concepts related to zinc in the reproductive tract. Zinc levels are elevated or stable in BPH, whereas there is a marked decrease in zinc content associated with prostatic adenocarcinoma. The localization of zinc-65 in the human prostate by radioautography appears to be within the epithelial cells; however, in the lateral prostate of the rat, large quantities of zinc were also associated with the stroma and particularly with the basal membrane and the elastin protein component (Chandler et al, 1977). Oral intake of zinc does not alter zinc levels in prostatic fluid.

Many physiologic roles have been postulated for zinc since the classic studies of Gunn and associates (1956, 1965), who correlated endocrine effects on zinc uptake and concentration in the prostate of the rodent. There are many important zinc-containing metalloenzymes, but the concentration of zinc in the prostate probably exceeds that present in zinc-associated enzymes. Zinc is known to bind many proteins (Sansone et al, 1991). Johnson and associates (1969) characterized zinc-binding proteins in the prostatic secretion of the dog, on hydrolysis, as containing only eight types of amino acids. Heathcote and Washington (1973) described a zinc-binding protein in human BPH that was rich in histidine and alanine. Jonsson and colleagues (2005) suggested that one possible role of zinc in semen may be to regulate the activity of PSA by binding to semenogelins I and II and fragments thereof. There have been other studies on zinc-binding proteins from the prostate (Reed and Stitch, 1973; Fair et al, 1976), and additional information on these interesting proteins is needed.

An important role for zinc in prostatic secretion has been postulated in the studies of Fair and associates (1976), which suggest the direct role of zinc as a prostatic antibacterial factor. In the study of 36 normal men free from bacterial prostatic infections, the mean value of zinc in the prostatic secretion was approximately 350 µg/mL, with a wide range of 150 to 1000 µg/mL. In comparison, the prostatic fluid obtained from 61 specimens collected from 15 patients with documented chronic bacterial prostatitis had a reduction of more than 80% and averaged only 50 µg/mL, with a range of 0 to 139 µg/mL. The authors proposed a lower limit of normal at 150 µg/mL. In addition, in-vitro studies of free zinc ions at concentrations normally found in prostatic fluid have confirmed the bactericidal activity of zinc against a variety of gram-positive and gram-negative bacteria. However, a considerable portion of the zinc in the prostate appears to be bound to unique proteins, such as metallothionein, and it is not certain how this might alter the biologic properties of zinc (Suzuki et al, 1994, 1995). Yan and colleagues (2008) reported that assessment of decreased zinc in a normal human prostate epithelial cell (PrEC) in vitro resulted in increased single-strand DNA breaks (Comet assay) and differential expression of several genes (Affymetrix HG-U133A gene chips) involved in cell cycle progression, apoptosis, transcription, and DNA damage response and repair. Hence, a zinc deficiency may compromise DNA integrity in the prostate. In prostate cancer the ability of prostate cells to accumulate zinc is lost during disease progression and may be in part due to the genetic and epigenetic alterations produced by zinc depletion.

PROSTATIC SECRETORY PROTEINS

The predominant secretory proteins of the sex accessory tissues have been reviewed (Lilja and Abrahamsson, 1988; Aumuller and Seitz, 1990; Aumuller et al, 1990; Lilja, 1993a, 1993b; Rittenhouse et al, 1998; Saedi et al, 2001; Diamandis and Yousef, 2002; Yousef and Diamandis, 2002). High-resolution, two-dimensional electrophoresis profiles of the major secretory protein markers from human ejaculate, seminal plasma, and prostatic secretions have been reported (Edwards et al, 1981; Carter and Resnick, 1982; Rui et al, 1984; Tsai et al, 1984; Dube et al, 1987; Aumuller and Seitz, 1990); however, several are found in abundance and have clinical significance. These include PSA (human kallikrein 3 [hK3, protein; or *KLK3,* gene]); human kallikrein 2 (hK2 or *KLK2*); prostase/*KLK-L1* (Yousef et al, 1999; Lwaleed et al, 2004; Clements, 2008); prostatic acid phosphatase; and prostate-specific protein (PSP-94), also called β-microseminoprotein (β-MSP). Table 90–5 lists some characteristics of the major secretory proteins in the sex accessory tissues. Table 90–6 illustrates the number of sample, median, and ranges of components of prostatic secretions among normal male reproductive parameters.

Prostate-Specific Antigen

Major changes in the use of PSA have occurred since the 1980s; for a general overview, see the work of Polascik and coworkers (1999). A serine protease, PSA-like molecule was first demonstrated in human prostatic tissue in 1970 (Ablin et al, 1970), found in seminal plasma in 1971 (Hara et al, 1971), purified from prostatic tissue in 1979 (Wang et al, 1979), measured in the serum of men in 1980 (Kuriyama et al, 1980), and widely used as a clinical marker of prostate cancer by 1988 (Seamonds et al, 1986; Chan et al, 1987; Stamey et al, 1987; Oesterling et al, 1988). The historical information, molecular characteristics, physiologic properties, and immunoassay for PSA have been reviewed elsewhere (Oesterling, 1991, 1993; Shellhammer, 1993; Vessella and Lange, 1993;

Table 90–5.

Major Proteins Secreted by the Sex Accessory Tissue

PROTEIN/GENE IDENTIFICATION	MOLECULAR WEIGHT (kd)	SEMINAL PLASMA (mg/nL)	Activity
Prostate-specific antigen (PSA) (hK3 [protein] or *KLK3* [gene])	33-36	0.70	Serine protease; arginine esterase
Human kallikrein 2 (hK2 or *KLK2*)	28.4	0.012 mg/nL	In-vivo activation of proPSA, arginine esterase
Human kallikrein L1 *(KLK-L1)*	Unknown	Unknown	Serine protease, also in testes, breast, adrenal, uterus, thyroid, and salivary glands
Human kallikrein 11	~40	0.002-0.037	Serine protease, also in breast, ovary, and prostate
Prostatic acid phosphatase (PAP)	102-106	0.3-1.0	Phosphotyrosyl protein phosphatase
Prostate-specific transglutaminase	17	Unknown	Involved in the formation of stable, functional peptide-bound glutamine and primary amine groups
Semenogelins I and II	50, 63	2 mM*	Have chymotrypsin-like activity; inhibit PSA activity in the semen
Prostate-specific membrane antigen (PMSA)	~120	Unknown	Has a structure identical to glutamate carboxypeptidase II and folate hydrolase I; found in kidney, testis, ovary, brain, salivary gland, small intestine, colon, liver, spleen, breast, and skeletal muscle
Prostate stem cell antigen (PSCA)	~24	Unknown	A prostate cancer–associated tumor antigen Northern blot and in-situ data show that PSCA is predominantly prostate specific in normal tissues and is overexpressed in greater than 80% of prostate cancers.
Prostate-specific protein (PSP-94) β-micro-seminoprotein (β-MSP)	10.7-16	0.6-0.9	Also found in epithelial cells of antrum of stomach
Immunoglobulins	160	0.007-0.022	Human IgG
C3 complement	~178	0.018	An integral part of the complement cascade (C3 activates alternate pathway)
Transferrin	77	0.18	A plasma protein that transports iron through the blood to the liver, spleen, and bone marrow

*Only given in mM concentrations.

Table 90–6.

Components of Prostatic Secretions

VARIABLES	*N*	MEDIAN	RANGE
Age (yr)	916	34	20-64
Time of sexual abstinence (days)	916	4.0	1.0-60
Semen volume (mL)	916	4.0	1.0-15
Sperm concentration ($\times 106$ mL^{-1})	916	44	0.1-568
Total sperm count ($\times 10^6$ mL^{-1})	916	167	0.4-2400
a (%)	916	14	0-80
b (%)	916	28	0-80
a + *b* (%)	916	50	0-90
c (%)	916	16	0-50
d (%)	916	33	0-100
Total *a* + *b* ($\times 10^6$ per ejaculate)	916	83	0-1200
Normal forms (%)	916	5.0	0-20
Tail defects (%)	916	11	1.0-85
DFI (%)	267	15	3.0-90
HDS (%)	267	7.0	1.0-40
NAG (mU/mL^{-1})	506	6.0	1.0-15
PSA (mg/L^{-1})	900	890	66->3400
Zinc (mmol/L^{-1})	900	2.0	0-7.0
Fructose (mmol/L^{-1})	900	14	0-39
FSH (IU/L^{-1})	351	5.0	1.0-45
LH (IU/L^{-1})	351	3.0	1.0-13
Testosterone (nmol/L^{-1})	351	13	3.0-31
Inhibin B (ng/L^{-1})	351	150	14-450
SHBS (nmol/L$^{-1)}$	351	26	2.0-88

From Elzanaty S, Erenpreiss J, Becker C. Seminal plasma albumin: origin and relation to male reproductive parameters. Andrologia 2007;39:60–5.

Partin and Oesterling, 1994; McCormack et al, 1995; Polascik et al, 1999).

The discovery of PSA resulted from a search of the ejaculate and prostatic fluid by immunoprecipitation to find specific proteins for forensic use. In 1971, Japanese workers isolated, from the seminal plasma, a protein that was proved to be antigenically specific for semen; they reported its chemical and physical characteristics and termed it *γ-seminoprotein* (Hara et al, 1971). Several years later, in an attempt to develop this protein further as a forensic marker for semen identification, γ-seminoprotein was purified from human seminal plasma. These seminal proteins, initially called γ-seminoproteins, have now been shown by sequence to be the same as PSA. Lilja and Abrahamsson (1988) reported the same proteolytic activity and site of glycosylation, the same molecular weight protein and gene sequence, and identical immunohistochemical characteristics and serum characteristics in these proteins.

Wang and coworkers (1979) first reported this human PSA that has now proved to be an important marker of the prostate and prostate disease. **PSA is a glycoprotein acting as a serine protease of molecular weight 33 kD that contains 7% carbohydrate** (Watt et al, 1986) and is found almost exclusively in the epithelial cells of the prostate (Armbruster, 1993; Rittenhouse et al, 1998). PSA was measured in the serum and was demonstrated to be a clinically important assay for monitoring prostate cancer (Kuriyama et al, 1980, 1981). For a detailed description of the use of PSA and its limitations, both clinically and in laboratory medicine analysis, see the work of McCormack and associates (McCormack et al, 1995; Rittenhouse et al, 1998; Polascik et al, 1999).

Watt and coworkers (1986) have studied PSA extensively and were the first to report its complete amino acid sequence. The single polypeptide chain contains 240 amino acids and an O-linked carbohydrate side chain attached to a serine residue. Lundwall and Lilja (1987) cloned the complementary DNA (cDNA) that encodes the PSA gene. Their study indicates that the mRNA of PSA in the prostate is approximately 1.5 kilobases.

PSA acts physiologically like a serine protease and an arginine esterase with both chymotrypsin-like and trypsin-like activity. The sequence of the protein is similar to that of other kallikreins (Rittenhouse et al, 1998) involved in prostatic cell regulatory mechanisms. Lilja (1985) and Watt and coworkers (1986) reported that one of the structural proteins of the seminal fluid, semenogelin, causes the ejaculate to clot. Semenogelin is the predominant seminal vesicle-secreted protein and one of the physiologic substrates for PSA. **One possible biologic role of PSA is to lyse the clot in the ejaculate, but it is at present unknown why this clotting and lysing mechanism is important to reproductive physiology.**

The PSA gene (*hKLK3*) is a member of a human tissue kallikrein gene family that includes *hKLK1, hKLK2, hKLK3,* and *KLK-L1* (Lundwall, 1989; McMullen et al, 1991; Berg et al, 1992; Carbini et al, 1993; Clements, 1994; McCormack et al, 1995; Rittenhouse et al, 1998; Nelson et al, 1999; Yousef and Diamandis, 2003). To date there are more than 15 different human kallikreins, with expression noted in prostate, breast, ovarian, and testicular cancers (Obiezu and Diamandis, 2005). These genes are all located on chromosome 19 (Reigman, 1992; Yousef et al, 1999; Yousef and Diamandis, 2003). The ectopic expression of PSA has been reported in smaller concentrations in the tissue of malignant breast tumors (Yu et al, 1994a, 1994b, 1994c), normal breast tissue, breast milk, female serum, and adrenal and renal carcinomas; however, for practical and clinical purposes, PSA is an organ-specific but not a cancer-specific marker. A limitation of PSA as a tumor marker is demonstrated in the substantial overlap in values between benign and malignant prostate disease (Oesterling et al, 1988; Partin et al, 1990).

Most work regarding the molecular biology and biochemistry of PSA is based on extensive study of purified protein from seminal fluid in which the concentration of PSA is nearly a million-fold higher than that found routinely in serum (McCormack et al, 1995). The concentrations found in seminal plasma range from 0.5 to 5.0 mg/mL, whereas normal serum concentrations in men aged 50 to 80 years without prostatic disease range between 1.0 and 4.0 ng/mL (Catalona et al, 1991). Pre-pro-PSA (261 amino acids) is processed in the endoplasmic reticulum of prostatic epithelial cells, where a 17-peptide pre-region residue is cleaved. Seven more peptides are then cleaved from the propeptide to form the active PSA peptide (Rittenhouse et al, 1998). This pro-PSA represents an inactive (zymogen) precursor of PSA and is secreted and cleaved by hK2 (Lilja, 1985; Villoutreix et al, 1994; Rittenhouse et al, 1998).

The most exciting and clinically useful discovery in this area is the demonstration of different molecular forms of PSA (free [unbound] and complexed [bound]) circulating within the blood (Lilja et al, 1991; Stenman, 1991; Christensson et al, 1993; Lilja, 1993a; McCormack et al, 1995; Partin and Carter, 1996; Polascik et al, 1999). **Complexed PSA is found in the serum irreversibly and covalently bound to α_1-antichymotrypsin** (ACT), an endogenous serine protease inhibitor. This form of complexed PSA (PSA-ACT) is enzymatically inactive yet has immunoreactivity. In addition, an unknown quantity of PSA is also complexed to α_2-macroglobulin (PSA-A2M). Free PSA, found in lower concentrations than complexed PSA (PSA-ACT), is also enzymatically inactive, yet it is also immunoreactive, whereas PSA-A2M is not.

Depending on the monoclonal antibodies used to measure serum PSA, various amounts of free and complexed PSA are recognized and contribute to the total (measurable) amount. Development of new monoclonal antibodies specific for free PSA and complexed PSA has allowed accurate measurement of the different molecular forms of PSA and their ratios. This has the potential of increasing the sensitivity and specificity of PSA for diagnosis of prostate cancer (Catalona et al, 1998).

Human Kallikrein 2

Human kallikrein 2 (hK2 [protein] or *KLK2* [gene]) is a prostate-specific serine protease closely related to PSA and has largely been overlooked thus far (Rittenhouse et al, 1998). hK2 was first demonstrated from a low-stringency hybridization screen of a human liver genomic library in 1992, and the amino acid sequence is predicted to have 80% homology with PSA (hK3, *KLK3*) (Young et al, 1992). The striking homology between these two "prostate-specific" proteins suggested a close physiologic relationship. More recently, recombinant hK2 has been expressed and purified (Kumar et al, 1996; Mikolajczyk et al, 1998). Unlike PSA, hK2 is shown to be trypsin-like with selective cleavage at arginine residues and has a more potent (20,000-fold greater than PSA) protease activity (Mikolajczyk et al, 1998). Monoclonal antibodies to hK2 have been developed and have a low incidence of cross-reacting with PSA (Finlay et al, 1998). An exciting finding has been the independent demonstration that hK2 cleaves pro-PSA to generate the enzymatically active form of PSA (Kumar et al, 1996). Immunohistochemical studies have shown hK2 to be prostate localized and to increase in expression from normal to metastatic, poorly differentiated prostatic epithelium (Darson et al, 1997). Preliminary studies of hK2 in the serum of men with prostate cancer have suggested clinical utility for early detection of prostate cancer (Partin et al, 1999).

Human Kallikrein L1

Attempts to find other novel human kallikrein-like genes on chromosome 19 have identified yet another member of the human kallikrein gene family, *KLK-L1* (Nelson et al, 1999; Yousef et al, 1999). Nelson and associates (1999) constructed a cDNA library enriched through subtraction with the cDNAs from four other normal tissues to yield an expressed sequence tag identifying a gene that they have called prostase. The sequence of prostase exhibits features similar to the other members of the kallikrein family. Yousef and coworkers (1999) also found *KLK-L1* in breast tissue and demonstrated that it is hormonally regulated. Although the clinical utility of the members of the kallikrein gene family has not yet been determined, it is under investigation.

Human Kallikrein 11

Human kallikrein 11 (hK11) is a serine protease that shares similarities to human kallikrein 3 (hK3) or PSA with significant homologies at the levels of nucleotide and protein structure (Diamandis and Yousef, 2002). Localization of hK11 in epithelial cells of various organs has been demonstrated immunohistochemically and hK11 has been further detected in amniotic fluid, milk of lactating women, cerebrospinal fluid, follicular fluid, and breast cancer cytosols. The highest levels of hK11 were observed in prostatic tissue extracts and seminal plasma, in which it was present at 300-fold lower levels than PSA. Elevated serum levels of hK11 were found in 60% of men with prostate cancer; the ratio of hK11 to total PSA was able to reduce the number of biopsies required, and the data were similar to those gleaned from free PSA assays (Diamandis and Yousef, 2002; Nakamura et al, 2003).

Human Kallikrein 14

Human kallikrein 14, a trypsin-like human kallikrein-related peptidase (KLK), has been shown to exert a significant and dose-dependent effect on semen liquefaction (Emami et al, 2008; Emami and Diamandis, 2008). Liquefaction of human semen involves proteolytic degradation of the seminal coagulum and release of motile spermatozoa. Several members of human kallikrein–related peptidases are implicated in semen liquefaction, functioning through highly regulated proteolytic cascades. Among these, *KLK3* (also known as prostate-specific antigen) is the main enzyme responsible for processing of the primary components of semen coagulum. *KLK14* recently has been identified as a potential activator of *KLK3* and other KLKs (Emami et al, 2008; Emami and Diamandis, 2008). Borgono and associates (2003) measured seminal plasma levels of *KLK14* by an enzyme-linked immunosorbent immunoassay (ELISA) in 36 human semen samples and found *KLK14* to be 0.6 to 23.6 µg/L (mean 10.8; median 10.7 µg/L). Semenogelin I and semenogelin II are degraded by PSA to form various biologically active peptides involved in semen liquefaction and release of motile spermatozoa. Semenogelins I and II, through chelation with the excess of free zinc, are also directly cleaved by *KLK14*, in the same manner as PSA. In addition, *KLK14* has also been demonstrated to be a potential biomarker for ovarian and breast cancer (Borgono et al, 2003). ***KLK14* should be considered as another active molecule involved in semen liquefaction.**

Prostate-Specific Transglutaminases

Human prostate-specific transglutaminase 4 belongs to a family of enzymes that irreversibly cross-link peptide-bound glutamine residues through reactions with either lysines or primary amines such as polyamines (Dubbink et al, 1998). Transglutaminases are located throughout the body, but they are highly tissue specific. Dubbink and coworkers (1998) described a new prostate-specific transglutaminase with 35-kilobase genomic DNA and consisting of 13 exons and 12 introns. The main transcription initiation site is located 52 base pairs upstream of the translational start code. At least one splice variant was described, and a transglutaminase 4 gene (*TGM4*) promoter was analyzed by sequencing and transfection experiments and found at –1276 to –563. Subsequently, an Sp1 binding site (promoter) required for basal activity of *TGM4* was identified (Dubbink et al, 1999). The *TGM4* promoter was characterized by deletion mapping and mutational analysis. These researchers determined that positions between –113 and –87 were essential for core activity of the promoter. The sequences identified are binding sites for the Sp1 and Sp3 transcription factors; however, their precise role in *TGM4* regulation was not deduced from experiments described (Dubbink et al, 1999). Of importance is the fact that the major gel-forming proteins in semen, semenogelins I and II, are substrates for transglutaminase 4 (Peter et al, 1998). Esposito and Caputo (2005) reviewed the range of substrates for transglutaminases in detail and characterized the molecular basis of transglutaminase-catalyzed reactions and also assessed possible physiologic function and pathophysiologic processes due to such interactions. The transglutaminase for the prostate is

transglutaminase 4; it weighs 77 kD, is androgen regulated, and is found extracellularly. Transglutaminases catalyze the post-translational modification of proteins by formation of polymerized cross-linkages between the γ-carboxamide group of protein-bound glutamine residues and the ε-amino group of protein-bound lysine residues, which results in a stabilized molecular complex. There is evidence to suggest that the biochemical affinity of transglutaminase 4 for acyl-type substrates such as kinesin proteins in protein secretions of the semen may be important for correct extrusion of transglutaminase 4 from the coagulating gland (Esposito and Caputo, 2005).

An and coworkers (1999) also described cloning of *TGM4* (human prostate-specific transglutaminase) and its promoter in the elements of –1 to –500 and also at –520 to –1400. In addition, this group applied Northern blot hybridization and reverse-transcription polymerase chain reaction (RT-PCR) analysis to confirm prostate specificity and Gleason grade-specific expression by RT-PCR and noted significant downregulation in high Gleason grade as well as in metastatic tissue extracts. From a protein perspective, Birckbichler and colleagues (2000) revealed by quantitative immunofluorescence that prostate cancer was significantly decreased compared with normal prostate and prostatitis cases, but this is in contrast to what was observed with RT-PCR results (An et al, 1999), where the higher Gleason grade tumors tended to be significantly decreased. This discrepancy of results needs to be rectified in larger experiments comparing RT-PCR with protein expression to determine whether this is a technical problem or rather one of translation of transglutaminase 4 mRNA versus protein in the malignant disease process.

Semenogelins I and II

Semenogelin I and semenogelin II are dominant proteins in human semen coagulum that are degraded by PSA to form various biologically active peptides, which in combination with fibronectin give rise to the gel-like coagulum of newly ejaculated semen (Lilja, 1985; Malm et al, 1996; de Lamirande et al, 1997). The genes encoding semenogelins I and II are located in separate regions 11.5 kilobase pairs apart on chromosome 20. The major biologic function of semenogelin involves **capacitation,** which is defined as a series of changes in cell membranes, enzyme activities, and ion fluxes that sperm undergo as they traverse the female urogenital tract to reach the zona pellucida and fertilize the egg (de Lamirande et al, 1997). It has been demonstrated that biologically active peptides from semenogelin I and semenogelin II proteolysis scavenge superoxide anion and may affect sperm oxidase to serve as natural regulators of sperm capacitation (de Lamirande et al, 2001; de Lamirande, 2007). Semenogelins from the seminal vesicles and zinc ions from the prostate play a significant role in semen aggregation at the time of sperm ejaculation and also in sperm motility by binding to the sperm and then interacting with zinc (de Lamirande, 2007; Yoshida et al, 2008). It is of physiologic and possibly pathophysiologic importance that these major gel-forming proteins in semen, semenogelins I and II, are substrates for transglutaminase 4 (Peter et al, 1998). Both of these proteins originate from the glandular epithelium of the seminal vesicles and are produced in high concentrations; however, in the epididymis, only semenogelin I is expressed. There is evidence by immunohistochemistry that other cell types including the vas deferens, prostate, and trachea demonstrate strong signals for semenogelins I and II, and weaker but positive signals were seen in skeletal muscle cells and in the central nervous system (Lundwall et al, 2002).

Key Points: Secretory Proteins

- The prostate has the highest concentration of zinc (50 mg/100 g dry weight) of any organ. Oral intake of zinc does not alter zinc levels in prostatic fluid. Postulated roles of zinc include its importance in the structure in metalloenzymes and in particular its antimicrobial activity.
- Human kallikrein 14, a trypsin-like human kallikrein-related peptidases (KLK), has been shown to exert a significant and dose-dependent effect on semen liquefaction. Liquefaction of human semen involves proteolytic degradation of the seminal coagulum and release of motile spermatozoa.
- Prostate-specific transglutaminases (specifically transglutaminase 4) catalyze the post-translational modification of proteins (semenogelins I and II) by formation of polymerized cross-linkages between the γ-carboxamide group of protein-bound glutamine residues and the ε-amino group of protein-bound lysine residues, which results in a stabilized molecular complex.
- The major biologic function of semenogelin involves **capacitation,** which is defined as a series of changes in cell membranes, enzyme activities, and ion fluxes that sperm undergo as they traverse the female urogenital tract to reach the zona pellucida and fertilize the egg.
- Biochemically, zinc α_2-glycoprotein (ZAG) stimulates lipid degeneration in adipocytes and appears to be involved in cachexia, a wasting syndrome that can affect people with cancer, acquired immunodeficiency syndrome, and other terminal illnesses.
- The human gene for β-microseminoprotein (PSP-94) has been mapped to chromosome 10 (q11.2), and there are three glucocorticoid response elements and one estrogen response element in the promoter region of the first intron. β-Microseminoprotein (PSP-94) and its potential interaction with human spermatozoa may play a possible role in fertility.

Prostate-Specific Membrane Antigen

Recent reviews of the biochemistry and biology of the prostate-specific membrane antigen (PSMA) in human tissues and prostate cancer surveys describe the differential regulation of the molecule, its enzymatic functions, and its potential as a biomarker for in-vivo imaging and immunotherapy (Elgamal et al, 2000; Ghosh and Heston, 2004). The gene encoding PSMA is located on chromosome 11p11-12 and codes for a type II membrane glycoprotein (MW: ~100,000 daltons) with intracellular (1 to 18 amino acids), transmembrane (19 to 43 amino acids), and large extracellular (44 to 750 amino acids) domains (Israeli et al, 1994; Ghosh and Heston, 2004; Davis et al, 2005). The cDNA (2.65 kb GenBank Accession M99487) encoding PSMA was first reported by Israeli and colleagues in 1993 and its deduced amino acid sequence determined (Israeli et al, 1994). It encodes a 750-amino acid protein with a predicted molecular mass of 84 kD (excluding carbohydrates). The hydrophobic amino acids found on amino acid residues 20 to 43 suggested that this protein is a type II integral membrane protein with a small intracellular domain and a large extracellular domain (Fair et al, 1997). The promoter for PSMA has been cloned (Good et al, 1999), and PSMA has been expressed and purified from a baculovirus expression system (Lodge et al, 1999). A portion of the transmembrane domain of this protein (amino

acid residues 1250 to 1700) shares 57% homology with the human transferrin receptor mRNA (Mahadevan and Saldanha, 1999). Alternative splicing variants of PSMA (PSM′-PSA′ extracellular domain protein) are under investigation to better understand the clinical significance of this important membrane protein found within the prostate (Liu et al, 1997; Grauer et al, 1998; Murphy et al, 1998; Ghosh and Heston, 2004; Rajasekaran et al, 2005). PSMA has been crystallized and its structure deduced at 3.5-Å resolution. These analyses reveal a homodimer with structural similarity to the transferrin receptor, a receptor for iron-loaded transferrin that lacks protease activity (Davis et al, 2005). However, unlike the transferrin receptor, the protease domain of PSMA (glutamate carboxypeptidase II) contains a binuclear zinc site, catalytic residues, and a proposed substrate-binding arginine patch.

PSMA in the central nervous system metabolizes the brain neurotransmitter *N*-acetyl-aspartyl-glutamate or NAAG (named NAALADase). In the intestine, PSMA is found in the proximal small intestine, where it removes γ-linked glutamates from poly-γ-glutamated folate (folate hydrolase 1), or as a carboxypeptidase, glutamate carboxypeptidase II. Another interesting potential targeting feature of PSMA expression in the prostate is that it is overexpressed in neovasculature of other tumors (Silver et al, 1997; Chang et al, 1999b, 2001). A PSM-like molecule has been located at 11q14.3, but only PSMA is overexpressed in prostate cancer. In the prostate there are three alternatively spliced variants of PSMA. However, only one of these isoforms (PSM′ located at the 5′ end of PSMA cDNA) is known to be differentially expressed in normal tissue, BPH, and prostate cancer (Elgamal et al, 2000; Rajasekaran et al, 2005). PSMA mRNA expression within prostate cancers is highest in the hormone-deprived state, contrary to PSA mRNA, which often demonstrates lower, even absent expression in the hormone-deprived state (Henttu et al, 1992; Israeli et al, 1994; Wright, 1995; Rajasekaran et al, 2005).

PSMA is hormonally controlled by steroids similar to PSA (Israeli et al, 1994; Elgamal et al, 2000). A study by Su and colleagues (Su et al, 1995) using RT-PCR on peripheral blood demonstrated that the PSMA : PSM′ ratio is threefold to sixfold upregulated in prostate cancer compared with BPH (0.76 to 1.6) and normal (0.075 to 0.45). Also, Elgamal and associates (2000) assessed the overall RT-PCR assay results described for six separate RT-PCR peripheral blood studies; the data yielded a pooled sensitivity of 66% for RT-PCR PSMA versus 62% for RT-PCR PSA, suggesting inadequate sensitivity for routine clinical use.

Today, only a few studies have investigated PSMA protein levels in the blood of patients with prostate disease in spite of numerous publications regarding the production of numerous new monoclonal antibodies made to PSMA (Chang et al, 1999a; Tino et al, 2000). The existing assays can be characterized as research assays only, and the clinical data represent preliminary testing and not validation for a new clinical assay for assessment of diagnostic clinical performance. Reports to date used Western slot blot, a competitive ELISA, and more immuno–surface-enhanced laser desorption/ionization (immuno-SELDI). A competitive ELISA developed by Horoszewicz and colleagues (1987) using 9h10-A4 and 7E11-C5 monoclonal antibodies found an increased PSMA level in 47% of patients (20 of 43) with prostate cancer versus only 5% of patients (3 of 66) without prostate cancer, and the result was negative in 30 normal blood donors. In addition, PSMA expression within cancerous lesions appears to correlate directly with the degree of differentiation and not with tumor stage (Wright, 1995). Other investigators had employed a competitive ELISA and Western blotting and confirmed increasing expression with higher grade and stage, thus implicating PSMA in recurrence and progression (Rochon et al, 1994; Douglas et al, 1997; Murphy et al, 1997). A significant effort has been made to demonstrate tissue expression by quantitative immunoassays in the LNCaP cell line, human prostate cancer, and normal or BPH tissues as well as in metastatic tissue, seminal fluid, and urine (Su et al, 1995; Troyer et al, 1995; Sokoloff et al, 2000; Ross et al, 2003), but none of these assays was developed into serum immunoassays. However, Xiao and colleagues (2001) reported the use of an immuno-SELDI assay for PSMA. The immuno-SELDI assay used the 7E11-C5 immunoglobulin G1 monoclonal antibody developed by Horoszewicz and colleagues (1987) and employed in the clinically available ProstaScint scans. In that study, the ProteinChip array was coated with 1 μg of G protein and then residual active sites were blocked with 1 M ethanolamine, washed, and treated with 1.5 μg 7E11-C5 monoclonal antibody (Xiao et al, 2001). The assay was formatted to create a 96-well array, and the same clinical samples were processed that were run with Western blotting (Beckett et al, 1999; Elgamal et al, 2000). The results of the immuno-SELDI assay clearly revealed that serum PSMA with the 7E11-C5 antibody differentiated prostate cancer (623.1 ng/mL; n = 17) from BPH (117.1 ng/mL; n = 10, $P < .001$). The authors showed considerable age-related overlap in serum activity in normal subjects and patients with BPH older than age 50 years. The knowledge gained from these efforts about PSMA molecular characterization and diagnostics has been very valuable and has set the stage to apply new and innovative methods to manage prostate cancer. The potential use of PSMA as a novel prostate-specific targeting medical device based on PSMA-substrates, PSMA-peptides, PSMA-RNA aptamers, and anti-PSMA antibodies is being tested for targeted drug delivery and medical imaging (Lupold and Rodriguez, 2004; Davis et al, 2005; Chandran et al, 2008).

Finally, a current review of the multifunctional potential of the PSMA molecule by Rajasekaran and colleagues (2005) indicates that **PSMA** (type II membrane glycoprotein) **dimerization is similar to transferrin receptor and may function as a receptor for internalizing a putative ligand. PSMA enzyme activities (NAALADase and folate reductase) are consistent with a role in nutrient uptake. The PSMA peptidase activity may be involved in signal transduction in prostate epithelial cells and may activate cascades that result in cell survival, cell proliferation, and cell migration functions. This multifunctional molecule not only has numerous physiologic benefits but also has several diagnostic and therapeutic potential benefits to manage prostate cancer as well.**

Prostate Stem Cell Antigen

Reiter and coworkers (1998) identified prostate stem cell antigen (PSCA), a cell surface antigen that is expressed in the prostate (among other tissues including bladder). The *PSCA* gene encodes a 123-amino acid glycoprotein, with 30% homology to stem cell antigen 2 (Sca-2). Like Sca-2, PSCA is a member of the Thy-1/Ly-6 family and is anchored by a glycosylphosphatidylinositol linkage. **By use of mRNA in-situ hybridization, PSCA expression was localized in normal prostate to the basal cell epithelium, the putative stem cell compartment of prostatic epithelium; hence, PSCA may be a marker of prostate stem/progenitor cells.** Hara and associates (2002) performed an analysis of PSA, PSMA, and PSCA mRNA level on peripheral blood by RT-PCR in 58 cases of prostate cancer and 71 cases of nonmalignant disorders. The results were 7 of 58 (12.1%) for PSA,

12 of 58 (20.7%) for PSMA, and 8 of 58 (13.8%) for PSCA; zero samples were positive for nonmalignant diseases. A summary of prognostic value for the three biomarkers was a hierarchy of PSCA > PSA > PSMA for RT-PCR of the 58 patients with prostate cancer. Note that in this group of patients, when the RT-PCR result was positive for PSCA the patients had a lower disease progression-free survival than with the other two biomarkers. The PSCA expression increased with higher Gleason score and cancer stage as well as with progression to metastasis and may be a useful biomarker for staging of prostate cancer (Hara et al, 2002). Han and associates (2004) performed immunohistochemistry analysis of PSCA by a 246-patient tissue microarray; the results revealed that a PSCA staining intensity of 3.0 correlated with adverse prognostic features including Gleason score of 7.0 (P = .001), seminal vesicle invasion (P = .005), and capsular involvement (P = .033). However, after multivariate analysis, PSCA did not hold up as an independent predictor of PSA recurrence. Zhigang and Wenlv (2004) studied BPH, low-grade prostatic interepithelial neoplasia (LGPIN), high-grade prostatic interepithelial neoplasia (HGPIN), and prostate cancer at the tissue level by immunohistochemistry and at the mRNA level by in-situ hybridization. In BPH and LGPIN the staining of PSCA protein and mRNA was weak or negative and less intense and uniform than in HGPIN and prostate cancer. There was moderate to strong PSCA protein as well as mRNA expression in 8 of 11 (72.7%) HGPIN and in 40 of 48 (83.4%) prostate cancer specimens that were examined by immunohistochemistry and in-situ hybridization analyses. When the prostate cancer specimens examined by immunohistochemistry and in-situ hybridization analyses were compared with BPH (20%) and LGPIN (22.2%) samples, the results were statistically significant ($P < .05$, respectively). The expression level of PSCA increased with high Gleason grade, advanced stage, and progression to androgen independence ($P < .05$, respectively). In addition, in this study, protein immunostaining and in-situ hybridization mRNA stain showed a high degree of correlation between PSCA protein and mRNA overexpression in prostate cancer, supporting the potential of PSCA as a prognostic biomarker. Clearly, the value of this protein to the biology of prostate epithelial tissue morphogenesis and also as a new biomarker for diagnosis and treatment of prostate cancer is yet to be realized.

The potential use of PSCA, a membrane surface antigen that is highly expressed in the prostate, as a novel prostate targeting medical device for diagnostics (blood immunoassays or medical imaging) and therapy (vaccines or immunotherapy) is currently being actively studied (Olafsen et al, 2007; Raff et al, 2009). Here is another unique opportunity to utilize prostate developmental knowledge as a possible tool to manage prostate cancer because of its amplification during carcinogenesis.

Prostatic Acid Phosphatase

Acid phosphatase activity is more than 200 times more abundant in prostate tissue than in any other tissue and is the source of the high levels of acid phosphatase in ejaculate. Phosphatase enzymes hydrolyze many types of organic monophosphate esters to yield inorganic phosphate and alcohol. Many phosphatase enzymes exhibit optimal activity in vitro in the acid (pH 4 to 6) or alkaline (pH 8 to 11) ranges and are thus classified broadly as either acid or alkaline phosphatase.

Acid phosphatase activity may be further defined by factors that inhibit its enzymatic activity. For example, erythrocyte acid phosphatase is particularly sensitive to inhibition by 0.5% formaldehyde or copper ions (0.2 mM) whereas prostatic acid phosphatase (PAP) activity is far more sensitive to inhibition by fluoride ions (1 mM) or L-tartrate (1 mM).

Osteoclasts are also a rich source of tartrate-insensitive acid phosphatase. Minor elevations in serum acid phosphatase levels can accompany Paget disease, osteoporosis, nonprostatic bone metastasis, and other conditions of increased bone resorption as well as metastatic prostate cancer. All acid phosphatases hydrolyze a wide range of natural and synthetic phosphomonoesters, and this has provided a wide variety of assay systems and the expression of different units of activity, depending on the assay. These synthetic substrates include, in part, phenylphosphate (Gutman, 1938); phenolphthalein phosphate; paranitrophenyl phosphate, also called Sigma 104; and thymolphthalein phosphate (Roy et al, 1971). The specificity of these substrates varies with the type and source of acid phosphatase; it appears that thymolphthalein phosphate may be the most specific substrate for assaying serum levels of prostate-specific acid phosphatase, but specific antibodies are now available for immunoassays. Interest in acid phosphatase assays in serum as a measure of prostatic cancer metastasis before definitive therapy has decreased with the availability of the more sensitive and specific PSA assay (Burnett et al, 1962).

The natural substrate for PAP may be phosphorylcholine phosphate, which is rapidly hydrolyzed in the semen (Seligman et al, 1951). The biologic functions of this enzyme and its reactions are not known, but it is of interest that PAP can hydrolyze protein tyrosine phosphate esters, natural products of many oncogene protein tyrosine kinases (Li et al, 1984; Lin and Clinton, 1986). By magnetic resonance spectroscopic techniques, it has been shown that the ratio of intracellular choline to citrate levels within the prostate can help differentiate normal from cancerous prostate tissue (Scheidler et al, 1999). Further clinical testing is required before this finding will influence clinical practice. It is unknown whether acid phosphatase is a regulatory factor in the tyrosyl protein kinase systems so essential as signaling mechanisms in growth factor function.

Human PAP is a glycoprotein dimer of molecular weight 102,000 and contains about 7% carbohydrate by weight, composed of 15 residues per mole of neutral sugars (fructose, galactose, and mannose), 6 residues per mole of sialic acid, and 13 residues of *N*-acetylglucosamine (Chu et al, 1977). The protein can be dissociated into two subunits of 50 kD. The activity of the purified human enzyme is 723 U/mg with α-naphthyl phosphate, and the seminal plasma contains 0.3 to 1 g/L or 177 to 760 U/mL. The high enzymatic activity of PAP is not characteristic of accessory tissues in many other species; the level is 1000 times higher per gram of tissue in the human prostate than in the rat prostate. The clinical aspects of PAP were reviewed by Romas and Kwan (Lowe and Trauzzi, 1993; Romas and Kwan, 1993).

Prostate-Specific Protein 94 (β-Microseminoprotein and β-Inhibin)

A major, cysteine-rich, nonglycosylated 16-kD protein that contains 94 amino acids has been found in prostatic secretions and named prostate-specific protein 94 (PSP-94); it is one of the three predominant proteins secreted in the prostate glands and found in seminal fluids along with PSA and PAP. This protein had previously been designated β-inhibin and also β-microseminoprotein (Dube et al, 1987; Ulvsback et al, 1989). Transcripts of mRNA for this protein have also been identified in nongenital tissues

(Ulvsback et al, 1989). The human gene for PSP-94 has been mapped to chromosome 10 (q11.2) and there are three glucocorticoid response elements and one estrogen response element in the promoter region of the first intron. Based on these observations the gene is likely regulated by hormones in humans (Nolet et al, 1991; Ochiai et al, 1995) because this also was reported in studies of the rat lateral prostate (Kwong et al, 2000). Also, Valtonen-Andre and associates (2008) demonstrated that in young, healthy males the PSP-94 levels in the serum correlate well with those in the seminal plasma ($r = 0.50$, $P < .001$). An automated immunoassay was performed with an Autodelphia 1235 (Wallac) and produced median values of PSP-94 in 205 young men that were 12 mg/L (2.5 to 97.5 percentile, 4.9 to 26 mg/L) in serum and 0.53 g/L (2.5 to 97.5 percentile, 0.13 to 2.0 g/L) or 1.8 mg (2.5 to 97.5 percentile, 0.32 to 6.6 mg) in seminal plasma. These data provide a solid basis for evaluation of this biomarker both in healthy men and those with prostate cancer.

One of the main biologic functions of PSP-94 is the inhibition of follicle-stimulating hormone (Garde et al, 1999). Whereas follicle-stimulating hormone is made by the pituitary gland, the prostate has been shown to be an extrapituitary source of follicle-stimulating hormone. There are follicle-stimulating hormone receptors in the prostate, and it appears that an autocrine or paracrine regulation of this hormone influences prostate epithelial proliferation (Ben-Josef et al, 1999; Porter et al, 2001). Also, Chan and colleagues (1999) used in-situ hybridization to study expression of PSP-94 in human prostates. They found that fetal prostate at 6 to 7 months synthesizes PSA and PAP but not PSP-94, and this observation appears to relate to the development of the prostate gland. Zonal anatomic distribution of PSP-94 in the adult prostate demonstrated that the protein is expressed mostly in the acini of the peripheral zone rather than the central or transitional zones. Recently, Anahi Franchi and associates (2008) studied the PSP-94 and its potential interaction with human spermatozoa and its possible role in fertility. Using purified PSP-94, they demonstrated a specific interaction at the sperm surface. Also, employing a dual antibody ELISA technology the authors noted that of 62 patients being assessed for fertility fertile men had a lower concentration of the protein than subfertile men (OT, ST, and AS) and suggested that semen quality may be affected by the concentrations of the PSP-94. **Another function of the PSP-94 may be to interact directly with spermatozoa in a manner that can impact the quality of sperm structure and function.**

In the area of cancer, Chan and coworkers (1999) found that PSP-94 expression is markedly downregulated with increasing Gleason grade of prostate cancer. Furthermore, Shukeir and coworkers (2003) demonstrated a significant decrease in growth of the highly metastatic Dunning R3327 subline MatLyLu rat prostate model transfected with parathyroid hormone–related protein by treatment with varying doses of commercial PSP-94 purified from human seminal plasma (0, 0.1, 1.0, and 10 µg/kg/day). Serum levels of parathyroid hormone–related protein and calcium were used to monitor the efficacy of treatment with PSP-94. **Hence, PSP-94 is an effective inhibitor of hormone-independent, late-stage prostate cancer metastasis in this Dunning MatLyLu animal model.** The PSP-94 molecule has not yet been crystallized; however, Joshi and Jyothi (2002), in a computer-simulated molecular model, have predicted its structure and calculated its binding activity and related biologic activity (follicle-stimulating hormone inhibition) and immunogenic properties. Using three-dimensional structure constructed by nuclear magnetic resonance (NMR), Ghasriani and associates (2006, 2009) have shown the PSP-94 molecule to consist of two distinct domains that form a rather extended structure. The two domains are connected to each other by the peptide backbone, one disulfide bond, and interactions between the amino and carboxyl termini and are oriented to give the molecule a rather extended structure. In addition, Ghasriani and associates (2009) have demonstrated the specific molecular interactions of the PSP-94 with cysteine-rich secretory protein 3 (CRISP-3) applying multidimensional NMR. The CRISP proteins are ubiquitous among organisms and snake venoms, and they are reported to be calcium ion channel blockers; however, the relevance of these observations of protein-protein interactions to seminal plasma is yet to be determined.

Protein C Inhibitor

Human semen contains several enzymes and inhibitors of the hemostatic coagulation system (Lwaleed et al, 2004; Fernandez and Heeb, 2007). In human semen PSA exists as a molecular complex with protein C inhibitor (PCI), and the latter provides some inhibitory consequences for actions of PSA. The predominant structural proteins of coagulated semen are those proteins secreted by the seminal vesicle including semenogelins I and II and fibronectin, and these proteins remain stable in the seminal vesicle's secretions for up to 20 hours at 37°C but rapidly cleave into small peptides on mixing with the proteases (e.g., PAP, hKLK2 [PSA], hKLK3, hKLK14) of prostatic secretion (Lwaleed et al, 2004; Fernandez and Heeb, 2007). The human PCI gene is located in chromosome 14q32.1 and is a serine protease inhibitor that corresponds to a region containing the genes of related serpins (SERPINA5) (Suzuki et al, 1987; Fernandez and Heeb, 2007; Suzuki et al, 2007). PCI is a heparin-dependent inhibitor of activated protein C (APC) that is immunologically and functionally identical to a heparin-dependent urokinase inhibitor (plasminogen activator inhibitor type 3). PCI also inhibits several other blood coagulation and fibrinolytic factors (e.g., FXa, FXI, plasma kallikrein) (Lwaleed et al, 2004; Espana et al, 2007; Fernandez and Heeb, 2007; Suzuki et al, 2007). Suzuki and associates (2007) also demonstrated that digestion of human seminal coagula with PSA releases PCI and PSA-PCI complex from the coagula into the soluble phase, suggesting the presence of active PCI within the semen coagula. PCI then forms a "ternary protein complex" with PSA and semenogelin II in the seminal plasma. The binding of semenogelin II to PSA and PCI is influenced by the molecular microenvironment, including pH, ionic strength, heparin, negatively charged dextran sulfate, divalent cations, and particularly by zinc. These observations suggest that binding of PCI to semenogelins in seminal vesicles regulates the PSA-catalyzed degradation of semenogelins in seminal plasma; the complex formation among PCI, PSA, and semenogelins is modulated by several factors in seminal plasma. Espana and colleagues (2007) determined that PCI is secreted at very high levels in the seminal vesicles in an active form and also occurs in high concentrations in the seminal plasma. The concentration of PCI in 40 seminal plasma samples ranged from 2.2 to 3.7 mM (i.e., about 220 mg/L), and 45% of the seminal PCI was functionally active when assayed immediately after ejaculation. Notably, infertile men had significantly decreased seminal PCI levels (0.6 to 3.2 mM). However, the concentration of PSA in seminal plasma far exceeds the capacity of PCI to inhibit this molecule and hence the biologic role of PCI in seminal plasma. Espana and colleagues (2007) utilized purified PCI to assess several functional aspects of PCI, and evidence indicated that PCI is involved in human

reproduction at several key steps, including fertilization. Hence, PCI is abundant in the seminal fluid and it plays a key role in the interaction among semenogelins, PSA, and likely other proteins in semen, resulting in protein-protein interactions critical to semen coagulation and liquefaction. A balance of seminal fluid coagulative proteins, active enzymes, and metabolites is required to effect sperm motility and successful fertilization (Lwaleed et al, 2004; Espana et al, 2007; Fernandez and Heeb, 2007; Suzuki et al, 2007).

Leucine Aminopeptidase

Aminopeptidases hydrolyze the amino-terminal amino acid from small polypeptides. Leucine aminopeptidases are particularly active against the substrate L-leucyl-glycine, and some of these enzymes are referred to as *arylamidases* because the optimal substrate is L-leucyl-β-naphthylamine. The human prostate is rich in the arylamidase type of leucine aminopeptidase, with a presence in prostatic fluid of 30,000 units/mL.

Leucine aminopeptidase is a product of the epithelial cells of the prostate (Niemi et al, 1963) and is secreted into the lumen of the acini (Kirchheim et al, 1964; Vafa et al, 1993). Rackley and associates (1991) demonstrated that extracts from prostatic carcinoma contained less leucine aminopeptidase activity than did tissue obtained from BPH.

Lactate Dehydrogenase

The isoenzyme ratios of lactate dehydrogenase (LDH) in human semen may be altered in a patient with prostate cancer (Oliver et al, 1970; Grayhack et al, 1977). LDH (MW: 150 kD) is composed of four subunits (each of 35 kD) of only two different types of proteins, denoted M and H. The LDH of muscle has four M units, and that of heart has four H units. Five isoenzymes of LDH can be found in tissues with a four-subunit composition as follows: LDH I, MMMM; LDH II, MMMH; LDH III, MMHH; LDH IV, MHHH; and LDH V, HHHH. The M and H subunits appear to be the same in all tissues, but the amounts of LDH I to V can vary. Denis and Prout (1963) observed increased levels of LDH IV and V in prostatic cancer tissue. Several investigators have observed elevated ratios of LDH V/LDH I in human prostatic cancer (Elhilali, 1968; Oliver et al, 1970; Flocks and Schmidt, 1972).

Immunoglobulins, C3 Complement, and Transferrin

There are many reports establishing the presence of immunoglobulins (Igs) in human seminal plasma (Liang et al, 1981; Gahankari and Golhar, 1993). It is possible to measure levels of IgG from 7 to 22 mg/dL and those of IgA from 0 to 6 mg/dL; however, IgM is at low, often undetectable levels (Friberg, 1976). The complete source of these antibodies is not known, although they are found in expressed prostatic fluid (Grayhack et al, 1979) and may be related to infections (Fowler et al, 1982). They are usually found at lower levels in seminal plasma than in blood, but the possibility of diffusion across the "blood–seminal plasma barrier" has not been eliminated (see discussion by Friberg, 1976).

Expressed prostatic fluid contains considerable amounts of the C3 component of complement, present at 1.82 mg/dL, and this increases nearly 10-fold in fluid collected from patients with prostatic adenocarcinoma to levels of 16.9 mg/dL (Grayhack and Lee, 1981). Prostatitis has also been shown to be related to C3 among men with chronic prostatitis (Blenk and Hofstetter, 1991). Prostatitis and BPH increase the level only approximately twofold. In the same manner, transferrin, an iron-carrying protein, is increased, going from levels of 5.3 mg/dL in normal prostatic fluid to 42.4 mg/dL in prostatic carcinoma (Grayhack and Lee, 1981).

John and colleagues (2003) conducted a prospective study of the ejaculate of 88 patients with chronic prostatitis by surveying IgG, IgA, and IgM and interleukin-1α, soluble interleukin-2 receptor, and interleukin-6. The control group consisted of 96 normal ejaculates according to the World Health Organization criteria. Ejaculates of patients with chronic prostatitis increased during symptoms and subsided when clinical symptoms decreased. The authors observed that a combination of the humoral immune (IgA and interleukin-6) changes and T-cell–rich infiltrates is suggestive of an autoimmune component of the disease. Alexander and coworkers (2004) are studying a group of patients with chronic granulomatous prostatitis consisting of histologically diffuse nonspecific inflammatory changes that include epithelioid histiocytes and occasional multinucleate giant cells admixed with lymphocytes and plasma cells. They have identified an association between the major histocompatibility locus antigen HLA-DRB2*1501 and granulomatous prostatitis and have suggested the possibility that it may be an autoimmune disease.

Zinc α_2-Glycoprotein

In the seminal plasma, zinc α_2-glycoprotein (ZAG) is synthesized by prostate epithelial cells and secreted into seminal fluid (Ding et al, 2007), and it constitutes about 30% of the proteins present in the seminal fluid (Poortmans and Schmid, 1968). The ZAG glycoprotein is found in many body fluids with a molecular mass of 41 kD, and the crystal structure is quite similar to that of a class I major histocompatibility complex (Burgi and Schmid, 1961; Burgi et al, 1989; Sanchez et al, 1999; Delker et al, 2004; Hassan et al, 2008a, 2008b). Additionally, ZAG is assigned to the chromosome 7q22.1 based on fluorescent hybridization karyotyping (Hassan et al, 2008a). The crystal structure of ZAG consists of a large groove analogous to class I major histocompatibility complex peptide-binding grooves and the structure and environment of the groove reflect its role in immunoregulation and in lipid catabolism (Sanchez et al, 1999; Hassan et al, 2008b). ZAG appears naturally in blood, sweat, **seminal fluid,** breast cyst fluid, cerebrospinal fluid, and urine and is also found in secretory epithelial cells of the liver and the gastrointestinal tract (Tada et al, 1991; Hassan et al, 2008a, 2008b). Biochemically, ZAG stimulates lipid degeneration in adipocytes and appears to be involved in cachexia, a wasting syndrome that can affect people with cancer, acquired immunodeficiency syndrome, and other terminal illnesses (Hirai et al, 1998; Bing et al, 2004; Russell and Tisdale, 2005; Hassan et al, 2008b). The purification and characterization of ZAG from human seminal plasma revealed that it was bound to prolactin-inducible complex (PIP) (Hassan et al, 2008a). With the use of a ZAG tryptic peptide as a standard and a high-flow liquid chromatography–tandem mass spectrometry assay, serum levels in six healthy men were calculated as 3.65 (0.71) mg/L (Bondar et al, 2007). Furthermore, the concentration of ZAG and PIP has been reported to increase dramatically in carcinomas; therefore it has been considered as a good biomarker for prostate, breast, oral, and epidermal carcinomas (Hassan et al, 2008b). Thus **ZAG is a protein regulated by glucocorticoids and has the ability to impact fertilization and lipid mobilization (adipokine).**

Seminal Vesicle Secretory Proteins

Williams-Ashman (1983) presented a classic review on regulatory features of development and function of the seminal vesicles. The secretory proteins of the seminal vesicles are major proteins and enzymes involved in the rapid clotting of the ejaculate (Cunha et al, 1992). The major clotting protein has been termed *semenogelin* (Lilja and Abrahamsson, 1988). It has been shown to be the seminal vesicle–specific antigen. These clotted proteins from the seminal vesicles serve as substrates for PSA that enzymatically lyse the clot through their protease activity (Lilja, 1985; Aumuller and Seitz, 1990). Beyond the coagulation reaction it is not known what role these seminal vesicle proteins play, but their effects on fertility and uterine sperm motility have been studied in the mouse (Peitz and Olds-Clarke, 1986). Many of the proteins secreted by the seminal vesicles are under androgen regulation (Higgins and Hemingway, 1991; Hagstrom et al, 1992). More recent work (Harvey et al, 1995) has identified an androgen-regulated protease with elastase-like activity within seminal vesicle secretions. The semenogelins I and II are secreted in abundance by the seminal vesicles; and in addition to having coagulum-forming functions and being cleaved by kallikrein-like peptidases to generate biologically active products the semenogelins are assumed to activate sperm hyaluronidase, affect sperm motility, possess antimicrobial activity, serve as substrates for transglutaminase, and have amyloid properties (Jonsson et al, 2006; de Lamirande, 2007; Hassan et al, 2008b).

Additionally, cholesterol and sphingomyelin-rich small, lipid membrane–confined exosome-like vesicles (prostasomes) have been isolated from human semen and these structures provide an additional source of several hundred proteins that are quite important to fully understanding the biology of reproduction as well as improving our knowledge of the semen coagulation and liquefaction system (Ronquist and Brody, 1985; Arienti Saccardi et al, 1999; Poliakov et al, 2009). Prostasomes contain numerous proteins that can affect fertility, promote sperm motility, and stabilize the acrosome reaction (Delves et al, 2007). Sucrose gradient purified prostasomes have been observed by electron microscopy, and their composition has been surveyed after trypsin digestion by liquid chromatography/mass spectroscopy (Poliakov et al, 2009). A diversity of structural and functional proteins involved in fertilization, cell adhesion, apoptosis, immunity, metabolism, signal transduction, transport, angiogenesis, and so on, have been identified in prostasomes and have opened a new source of urologic scientific investigation to pursue new biomarkers of disease and elucidate mechanisms of fertility (Delves et al, 2007; Poliakov et al, 2009).

COAGULATION AND LIQUEFACTION OF SEMEN

Within 5 minutes after ejaculation, human semen coagulates into a semisolid gel. On further standing for a 5- to 20-minute period, the clot spontaneously liquefies to form a viscous liquid (Huggins, 1942; Tauber and Zaneveld, 1976; Mann, 1981). Calcium-binding substances, such as sodium citrate and heparin, do not inhibit the coagulation process, nor are prothrombin, fibrinogen, or factor XII required because they are absent in seminal plasma (Mann, 1981). The seminal clot is formed of fibers 0.15 to 10 nm in width, and its morphologic appearance differs from that of a blood fibrin clot (Huggins, 1942; Tauber and Zaneveld, 1976; Mann, 1981). Factors affecting blood coagulation do not regulate semen viscosity (Amelar, 1962). From these observations, and others, it appears that the coagulation of human semen is different from that of blood.

Examination of split human ejaculates indicates that the first fraction, originating primarily from the Cowper gland and the prostate, contains the liquefaction factors. The final fraction of the ejaculate, enriched in seminal vesicle secretions, is responsible for the coagulation of the ejaculate (Lilja et al, 1987).

It has long been known that prostatic fluid has a dramatic, fibrinolytic-like activity and that 2 mL of this secretion can liquefy 100 mL of clotted blood in 18 hours at 37°C (Huggins, 1942; Mann, 1981). The factors involved in such proteolytic activity in semen have been resolved (Huggins, 1942; Syner et al, 1975; Tauber et al, 1975, 1976; Tauber and Zaneveld, 1976; Mann, 1981; Zaneveld, 1982; Lilja et al, 1987). Two types of seminal plasma proteolytic enzymes appear to be major factors in the liquefaction process: plasminogen activators and PSA. Two plasminogen activators have been isolated from seminal plasma; they have molecular weights of 70 and 74 kD and appear to be related to urokinase (Propping, 1974). It is believed that the plasminogen activators originate from the prostatic secretions.

The seminal plasma contains a variety of other proteolytic enzymes, including pepsinogen, lysozyme, α-amylase, and hyaluronidase. In addition, human semen inhibits the activity of the proteolytic enzyme trypsin, and this is the result of the presence in the seminal plasma of such proteinase inhibitors as α_1-antitrypsin and α_1-antichymotrypsin. Coagulation and liquefaction vary in different species. For example, the semen of the bull or dog does not coagulate whereas rodents, such as the rat and guinea pig, ejaculate a firm pellet that does not appear to liquefy (Tauber et al, 1975, 1976; Tauber and Zaneveld, 1976). In rodents the plugs form through the action of an enzyme called vesiculase, which comes from the anterior lobe of the prostate and reacts with seminal vesicle secretions. Because of this action, the anterior lobe of the rodent prostate is also called the coagulating gland. Vesiculase is not identical to thrombin because it does not coagulate fibrinogen, nor does thrombin clot the secretions of the seminal vesicles. Williams-Ashman and associates (1977) have established that vesiculase has transamidase activity, catalyzing the formation of γ-glutamyl-ε-lysine cross links in a clottable protein derived from the seminal vesicles. This seminal vesicle protein, which serves as a substrate for vesiculase, is a basic substance with a molecular weight of 17.9 kD; it has been characterized as to its physical properties.

In summary, it appears that seminal plasma coagulation and liquefaction are under enzymatic control but the biologic purpose of this process has not been resolved. Several key enzymes (e.g., hKLK2 [PSA], hKLK3, hKLK14, PAP) and proteins (e.g., semenogelins, PSP-94, ZAG) of the seminal vesicles and prostate gland are involved in this coagulation and liquefaction system. There have been reports that some infertile men may have impairment of the liquefaction process (Bunge and Sherman, 1954; Bunge, 1970; Eliasson, 1973; Amelar et al, 1977; Jonsson et al, 2006; de Lamirande, 2007; Anahi Franchi et al, 2008; Hassan et al, 2008b; Poliakov et al, 2009).

PROSTATIC SECRETIONS AND DRUG TRANSPORT

Aumuller and Seitz (1990) have reviewed the secretory mechanism for the sex accessory tissues. Isaacs (1983) also reviewed the concepts related to the fluid and drug transport properties of the prostate and seminal vesicles and has compared the composition

Key Points: Coagulation and Liquefaction of Semen

- PSA is one of several serine proteases secreted by the prostate in high concentrations into the ejaculate. Although its main function may relate to regulation of semen coagulation, it has proved to be a valuable marker of prostate disease states.
- Protein C inhibitor (PCI) is abundant in the seminal fluid and it plays a key role in the interaction among semenogelins, PSA, and likely other proteins in semen, resulting in protein-protein interactions critical to semen coagulation and liquefaction.

and volume of prostatic secretion under basal stimulation and under neurologic stimulation during ejaculation or pilocarpine stimulation. Isaacs calculated that under neurologic stimulation there is a 205-fold increase in the total potassium, chloride, and sodium output over the basal secretory rate, and he has shown that the prostate is capable of secreting five times its total content of sodium and chloride during this active secretion. These findings show the tremendous transport powers of this system. Smith and Hagopian (1981) have studied the transepithelial voltage changes during prostatic secretion in the dog and have concluded that although sodium may move passively through the plasma in the prostatic fluid during ejaculation the movements of potassium and chloride ions involve active transcellular transport. Isaacs and associates (1983) have shown that the androgen-induced secretions can be blocked in the presence of estrogen, although the growth properties and biologic properties of the androgen on the prostate are not markedly altered. This would suggest a direct effect of estrogen in blocking a major transport system in the prostate.

Only a few compounds, including ethanol, iodine, and a few antibiotics, are capable of entering the semen by simple diffusion (Reeves, 1982). Drugs entering prostatic secretions have been of interest because of the prevalence of prostatitis and the need for new modalities of chemotherapy. Earlier, Stamey and colleagues had made extensive studies of the ability of chemotherapeutic agents to concentrate in the prostatic fluid of humans and dogs (Hessl and Stamey, 1971; Stamey et al, 1973), and many other investigators have also contributed to this knowledge (Madsen et al, 1968, 1978; Madsen, 1976; Fowler et al, 1982). Few drugs reach concentrations in the prostatic secretion that approach or surpass their concentrations in blood, but some exceptions are the basic macrolides erythromycin and oleandomycin, sulfonamides, chloramphenicol, tetracycline, clindamycin, trimethoprim, and fluoroquinolones (Reeves, 1982).

In general these drugs are assumed to pass across the membrane by nonionic diffusion, possibly by lipid solubility, through the membrane; when they reach the more acidic prostatic fluid they are protonated and acquire a more positive charge. Thus the charged drugs become relatively trapped within the prostatic secretions. Several factors are critical, including the pKa of the drug and the pH of the prostatic secretions, as well as the drug binding to proteins in each compartment. Basic drugs would be more positively charged in acidic prostatic fluid than in blood. Slight changes in pH can have large effects on this nonionic diffusion. Samples of prostatic secretions from humans varied widely in pH from 6 to 8, with a mean value of 6.6; however, with prostatic inflammation the pH tended to be 7 or higher (White, 1975). Although prostatic secretions are slightly acidic, the pH of freshly ejaculated human semen is slightly alkaline (pH 7.3 to 7.7); on standing, semen first becomes more alkaline with the loss of carbon dioxide and then later acidic owing to accumulation of lactic acid. Drugs may be developed in the future that are transported into the prostate as therapeutic agents, as chemoprotectors, or as a route to the semen to regulate fertility; however, more must be learned about the fundamental transport system in and out of the male reproductive tract before such an approach is feasible.

Key Points: Prostatic Secretions and Drug Transport

- Only a few compounds, including ethanol, iodine, and a few antibiotics, are capable of entering the semen by simple diffusion.
- A few exceptions for drugs are the basic macrolides erythromycin and oleandomycin, sulfonamides, chloramphenicol, tetracycline, clindamycin, trimethoprim, and fluoroquinolones. Perhaps these molecules, because of their lipid solubility, are transported by nonionic diffusion.

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chapter
91

Benign Prostatic Hyperplasia: Etiology, Pathophysiology, Epidemiology, and Natural History

Claus G. Roehrborn, MD

Etiology

Pathophysiology

Epidemiology and Natural History

Benign prostatic hyperplasia (BPH) is a pathologic process that contributes to, but is not the sole cause of, lower urinary tract symptoms (LUTS) in aging men. Despite intense research efforts in the past 5 decades to elucidate the underlying etiology of prostatic growth in older men, cause-and-effect relationships have not been established. For example, androgens are a necessary but not a clearly causative aspect of BPH. **Previously held ideas that the clinical symptoms of BPH (prostatism) are simply due to a mass-related increase in urethral resistance are too simplistic.** It is now clear that **a significant portion of LUTS is due to age-related detrusor dysfunction and other conditions such as polyuria, sleep disorders, and a variety of systemic medical conditions unrelated to the prostate-bladder unit.**

Historically, voiding symptoms have been related to obstruction of the bladder outlet (Chapple et al, 2008). The traditional association in men is with the prostate, the so-called symptoms of "prostatism." However, it is well recognized that voiding symptoms poorly correlate with underlying pathophysiology (de la Rosette et al, 1998). Similar symptoms can also be produced by any other form of obstruction, such as a urethral stricture or, conversely, by poor function of the lower urinary tract in circumstances in which there is impaired detrusor contractility. This has led to the recognition that, although LUTS commonly may be related to bladder outlet obstruction (BOO) as a result of benign prostatic obstruction (BPO), which is often associated with benign prostatic enlargement (BPE) resulting from the histologic condition of BPH, this is not invariably the case. For example, women also commonly present with voiding symptoms (Irwin et al, 2006). Failure to empty can be related to an outlet obstruction or to detrusor underactivity of the bladder or to a combination of both. Postmicturition symptoms, such as postvoid dribbling, occur in both sexes but most often in men, in whom these symptoms are highly common, are very troublesome, and cause significant interference with quality of life (Reynard et al, 1996). Storage symptoms are currently largely encompassed by the term *overactive bladder (OAB) syndrome*, which is defined as urgency, frequency, nocturia, and urgency incontinence and which is believed to be correlated with an underlying detrusor overactivity (Abrams et al, 2003). These symptoms tend to be more bothersome than voiding symptoms, especially if they are associated with incontinence. Storage symptoms in both sexes are commonly associated with urinary infections or, more rarely, with other conditions, such as bladder stones, carcinoma, or carcinoma in-situ in the bladder.

This understanding can be shown as partially overlapping populations (Fig. 91–1). Whereas many men older than the age of 40 will develop histologic hyperplasia (i.e., BPH), not all will have bothersome LUTS. Of those, some will and others will not develop measurable BPE. It is common for men to have BPE without having LUTS and vice versa. BOO may also be present with or without LUTS and with or without BPE; and in some cases BOO exists in men with BPH (e.g., from stricture) (Roehrborn, 2008).

Undoubtedly the constellation of cellular pathologic processes that give rise to the symptoms of LUTS is far more complex than we currently realize. Only by unraveling these complexities, however, will we be able to design alternative strategies to treat successfully and possibly prevent the adverse impact of BPH on lower urinary tract function.

ETIOLOGY

Histopathologically BPH is characterized by an increased number of epithelial and stromal cells in the periurethral area of the prostate and thus correctly referred to as hyperplasia and not hypertrophy, a term often found in the older literature. The observation of new epithelial gland formation is normally seen only in fetal development and gives rise to the concept of embryonic reawakening of the stroma cell's inductive potential (Cunha et al, 1983; Isaacs, 2008). The precise molecular etiology of this hyperplastic process is uncertain. **The observed increase in cell number may be due to epithelial and stromal proliferation or to impaired programmed cell death leading to cellular accumulation.** Androgens, estrogens, stromal-epithelial interactions, growth factors, and neurotransmitters may play a role, either singly or in combination, in the etiology of the hyperplastic process.

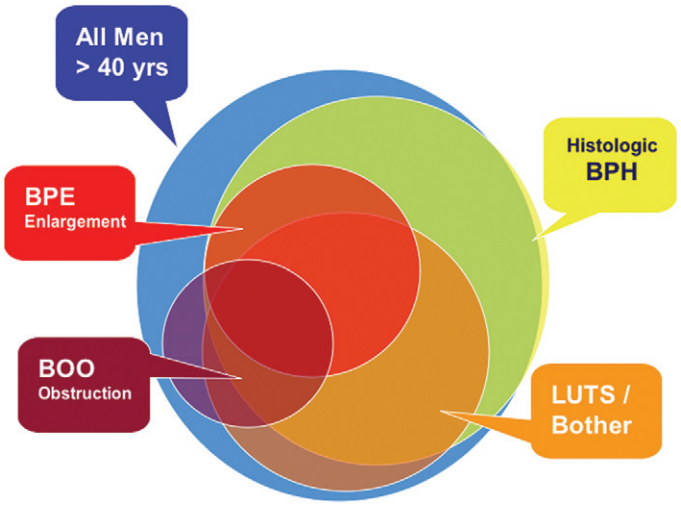


Figure 91–1. Diagram showing the relationship between histologic hyperplasia of the prostate (BPH), lower urinary tract symptoms (LUTS), benign prostate enlargement (BPE), and bladder outlet obstruction (BOO). The size of the circles does not represent actual proportions but rather illustrates the partial overlap between the different disease definitions. (From Roehrborn CG. Pathology of benign prostatic hyperplasia. Int J Impot Res 2008;20[Suppl. 3]:S11–8.)

Hyperplasia

In a given organ, the number of cells, and thus the volume of the organ, is dependent on the equilibrium between cell proliferation and cell death (Isaacs and Coffey, 1987). An organ can enlarge not only by an increase in cell proliferation but also by a decrease in cell death. **Although androgens and growth factors stimulate cell proliferation in experimental models, the relative role of cell proliferation in human BPH is questioned because there is no clear evidence of an active proliferative process.** Although it is possible that the early phases of BPH are associated with a rapid proliferation of cells, the established disease appears to be maintained in the presence of an equal or reduced rate of cell replication. Increased expression of antiapoptotic pathway genes (e.g., *BCL2*) supports this hypothesis (Kyprianou et al, 1996; Colombel et al, 1998) **Androgens not only are required for normal cell proliferation and differentiation in the prostate but also actively inhibit cell death** (Isaacs, 1984). In the dog, experimental BPH can be produced by androgens combined with estradiol (Walsh and Wilson, 1976; DeKlerk et al, 1979; Berry et al, 1986a; Juniewicz et al, 1994). Despite a significant increase in gland size there is actually a reduction in the rate of DNA synthesis compared with untreated controls (Barrack and Berry, 1987), indicating that androgens and estrogens both inhibit the rate of cell death. Neural signaling pathways, especially α-adrenergic pathways, may also play a role in balancing cell death and cell proliferation (Anglin et al, 2002).

The hyperplasia results in a remodeling of the normal prostatic architecture (Untergasser et al, 2005). Epithelial budding from preexisting ducts and the appearance of mesenchymal nodules characterize the early stages of the process, but the tissue phenotype of patients with established disease is highly variable.

BPH may be viewed as a stem cell disease (Barrack and Berry, 1987). Presumably, dormant stem cells in the normal prostate rarely divide, but when they do, they give rise to a second type of transiently proliferating cell capable of undergoing DNA synthesis and proliferation, thus maintaining the number of cells in the prostate. When the proliferating cells mature through a process of terminal differentiation they have a finite life span before undergoing programmed cell death. In this paradigm **the aging process induces a block in this maturation process so that the progression to terminally differentiated cells is reduced, reducing the overall rate of cell death.** Indirect evidence for this hypothesis comes from the observation that secretion, one parameter of epithelial cell differentiation, decreases with age, suggesting that the number of differentiated cells capable of secretory activity may be decreasing (Isaacs and Coffey, 1987). A survey of human BPH specimens for a marker of cellular senescence (senescence-associated β-galactosidase [SA-β-gal]) demonstrated a higher portion of senescent epithelial cells in men with large prostates, suggesting that an accumulation of those cells may play a role in the development of prostate enlargement (Choi et al, 2000). More recent studies support the hypothesis that impaired cell senescence may play a significant role in the etiology of BPH (Castro et al, 2003).

Hormones may exert their influence over the stem cell population not only with advancing age but also during embryonic and neonatal development (Naslund and Coffey, 1986). The size of the prostate may be defined by the absolute number of potential stem cells present in the gland, which in turn may be dictated at the time of embryonic development. Studies in animal models have suggested that **early imprinting of prostatic tissue by postnatal androgen surges is critical to subsequent hormonally induced prostatic growth.** As with the hormonal regulation of adult prostatic tissues, sex steroid hormones may exert their imprinting effect directly or indirectly through a complex series of signaling pathways (Lee and Peehl, 2004).

Role of Androgens

Although androgens do not cause BPH, the development of BPH requires the presence of testicular androgens during prostate development, puberty, and aging (McConnell, 1995; Marcelli and Cunningham, 1999). Patients castrated before puberty or who are affected by a variety of genetic diseases that impair androgen action or production do not develop BPH. It is also known that prostatic levels of dihydrotestosterone (DHT) as well as the androgen receptor (AR) remain high with aging despite the fact that peripheral levels of testosterone are decreasing. Moreover, androgen withdrawal leads to partial involution of established BPH (Peters and Walsh, 1987; Isaacs, 2008).

If normal ranges are assumed, there is no clear relationship between the concentration of circulating androgens and prostate size in aging men. In the Olmsted County Study of Urinary Symptoms and Health Status Among Men cohort (median age 60.9 years) serum bioavailable testosterone levels were found to decline with increasing age while the estradiol/bioavailable testosterone ratio increased (Roberts et al, 2004). Bioavailable testosterone correlated negatively and estradiol/bioavailable testosterone ratio positively with prostate volume, but this association was much less apparent after age adjustment. Baseline data from a large BPH medical therapy study confirmed the absence of a relationship between serum testosterone, serum prostate-specific antigen (PSA), and prostate volume (Marberger et al, 2006) (Table 91–1).

In the brain, skeletal muscle, and seminiferous epithelium, testosterone directly stimulates androgen-dependent processes. **In the prostate, however, the nuclear membrane bound enzyme steroid 5α-reductase converts the hormone testosterone into DHT, the principal androgen in this tissue**

Table 91–1.

Absence of Significant Relationship between Serum Testosterone and Serum PSA and Prostate Volume

BASELINE TESTOSTERONE CATEGORY (ng/mL)*	NO. OF INDIVIDUALS (N = 4254)	AGE (yr)	PSA (ng/mL^{-1})	PROSTATE VOLUME (mL)	BMI (kg/m^2)	BASELINE SFI SCORE
≥300	3092	66.5	4.0	54	27.0	6.8
275-300	291	65.3	3.8	56	28.2	6.6
250-275	269	66.2	3.9	55	28.1	6.4
225-250	225	65.3	4.0	57	29.0	7.2
200-225	143	64.8	3.9	56	30.1	5.9
175-200	115	66.5	4.0	56	29.5	6.8
150-175	67	66.2	3.6	56	29.5	5.8
<150	52	68.7	4.0	61	31.0	5.6

*For nanomoles per liter, divide by 28.8.

BMI, body mass index; PSA, prostate-specific antigen; SFI, Sexual Function Inventory.

Modified from Marberger M, Roehrborn CG, et al. Relationship among serum testosterone, sexual function, and response to treatment in men receiving dutasteride for benign prostatic hyperplasia. J Clin Endocrinol Metab 2006;91(4):1323–8.

(see Fig. 91–1) (McConnell, 1995). Ninety percent of total prostatic androgen is in the form of DHT, principally derived from testicular androgens. Adrenal androgens may constitute 10% of total prostatic androgen, although the importance of this stored hormone source in the etiology of BPH is negligible. Inside the cell, both testosterone and DHT bind to the same high-affinity androgen receptor protein (Chatterjee, 2003). DHT is a more potent androgen than testosterone because of its higher affinity for the AR. Moreover, the DHT-receptor complex may be more stable than the testosterone receptor complex. The hormone receptor then binds to specific DNA binding sites in the nucleus, which results in increased transcription of androgen-dependent genes and ultimately stimulation of protein synthesis (Andriole et al, 2004). Conversely, androgen withdrawal from androgen-sensitive tissue results in a decrease in protein synthesis and tissue involution. **Besides inactivation of key androgen-dependent genes (e.g., PSA), androgen withdrawal leads to the activation of specific genes involved in programmed cell death** (Kyprianou and Isaacs, 1989; Martikainen et al, 1990). Despite the importance of androgens in normal prostatic development and secretory physiology, there is no evidence that either testosterone or DHT serves as the direct mitogen for growth of the prostate in older men. Indeed, neither hormone is mitogenic to cultured prostatic epithelial cells (McKeehan et al, 1984). In the rat ventral prostate, differential gene expression experiments failed to demonstrate direct activation of mitogenic pathways (Wang et al, 1997). However, many growth factors and their receptors are regulated by androgens (see later). Thus the action of testosterone and DHT in the prostate is mediated indirectly through autocrine and paracrine pathways.

Androgen Receptors

The prostate, unlike other androgen-dependent organs, maintains its ability to respond to androgens throughout life. In the penis, AR expression decreases to negligible rates at the completion of puberty (Roehrborn et al, 1987; Takane et al, 1991a, 1991b). Thus, despite high circulating levels of androgen, the adult penis loses its ability for androgen-dependent growth. If the penis maintained high levels of AR throughout life, presumably the organ would grow until the time of death. In contrast, AR levels in the prostate remain high throughout aging (Barrack et al, 1983; Rennie et al, 1988). In fact, there is evidence to suggest that nuclear AR levels may be higher in hyperplastic tissue than in normal controls. Age-related increases in estrogen, as well as other factors, may increase AR expression in the aging prostate, leading to further growth (or to a decrease in cell death), despite decreasing levels of androgen in the peripheral circulation and "normal" levels of DHT in the prostate.

The potential role of AR mutations, polymorphisms, or other alterations in the pathogenesis of BPH is unclear (Chatterjee, 2003). A polymorphism in the number of CAG repeats (short vs. control) in the *AR* gene has been associated with larger prostate size and an increased risk of surgery (Giovannucci et al, 1999a, 1999b). However, another study from the Netherlands showed no relationship between the number of CAG repeats and BPH (Bousema et al, 2000). The later study also found no relationship between BPH and vitamin D receptor polymorphisms, although one Japanese study suggested an association (Habuchi et al, 2000). A more recent study of U.S. men showed a positive correlation between short CAG repeats and prostate volume, but a study of Finnish men found that short CAG repeats were significantly less common in men with BPH compared with control subjects (Mononen et al, 2002). Given the significant variation in reported findings, if short CAG repeats play a role in BPH pathogenesis it is likely to be minor (Hoke and McWilliams, 2008).

Dihydrotestosterone and Steroid 5α-Reductase

Intraprostatic DHT concentrations are maintained but not elevated in BPH. Initial studies of resected prostatic tissue suggested that prostatic DHT levels were higher in the hyperplastic gland than in normal control tissues. However, the controls used for these early studies were largely accident victims. Ongoing metabolism of DHT after death lowers the level of this androgen in cadaveric tissues. This was clearly shown in a study by Walsh and colleagues (1983) in which prostatic surgical specimens from men without BPH were used as the control. These investigators demonstrated that DHT levels are the same in hyperplastic glands as in normal glands. However, the aging prostate maintains a high level of DHT as well as a high level of AR; thus the mechanism for androgen-dependent cell growth is maintained. There is little question that androgens have at least a permissive role in the development of the disease process.

Two types of steroid 5α-reductase have been discovered, each encoded by a separate gene (Russell and Wilson, 1994). Type 1 5α-reductase, the predominant enzyme in extraprostatic tissues, such as skin and liver, is normally expressed in the 5α-reductase deficiency syndrome and is inhibited by dutasteride (Avodart) but not substantially by finasteride (Proscar). Type 2

5α-reductase is the predominant prostatic 5α-reductase, although it is also expressed in extraprostatic tissues. Mutations in the type 2 isoform are responsible for the clinical phenotype observed in the 5α-reductase deficiency syndrome. It is exquisitely sensitive to inhibition by finasteride and dutasteride (Carson and Rittmaster, 2003). Clearly, **the type 2 isoform is critical to normal development of the prostate and hyperplastic growth later in life.** The role of type 1 5α-reductase in normal and abnormal prostate growth remains to be defined. There is growing evidence to suggest that the type 1 isoform may play a more important role in prostate cancer compared with BPH, because increased levels of messenger RNA (mRNA) expression, protein, and functional enzymes have been demonstrated in prostate cancer (Thomas et al, 2008). Given that finasteride produces prostate size reduction identical to that with dual type 1/type 2 inhibitors and roughly equivalent to that with castration, it is unlikely that type 1–derived DHT is critical to hyperplastic growth.

Immunohistochemical studies with type 2 5α-reductase specific antibodies show primarily stromal cell localization of the enzyme (Thigpen et al, 1993; Silver et al, 1994). Epithelial cells uniformly lack type 2 protein, and some basal epithelial cells stain positively. Type 1 5α-reductase protein could not be detected in BPH or prostate cancer using initially available antibodies, although trace levels of type 1 mRNA have been seen in normal prostates, BPH, and cancer (Shirakawa et al, 2004). A study with a selective type 1 antibody demonstrated positive staining in only 7% of BPH cases (Thomas et al, 2003). In the same study, type 1 enzymatic activity was found in only 2 of 29 BPH specimens.

These data demonstrate that the **stromal cell plays a central role in androgen-dependent prostatic growth and that type 2 5α-reductase within the stromal cell is the key androgenic amplification step.** Thus a paracrine model for androgen action in the gland (Fig. 91–2) is evident. In addition, it is possible that **circulating DHT produced in the skin and liver may act on prostate epithelial cells in a true endocrine fashion** (McConnell, 1995). If dual type 1/type 2 5α-reductase inhibition has clinical utility over selective type 2 inhibitors, it is likely to be due to inhibition of peripherally produced DHT.

Immunohistochemical studies in open enucleated BPH specimens show considerable intraprostatic and interprostatic 5α-reductase, making studies of its distribution based on single or one-time biopsy material very difficult (Sherwood et al, 2003).

Polymorphisms in type 2 5α-reductase (SRD5A2) have been reported, but their linkage to BPH is uncertain. The *SRD5A2* gene on chromosome 2p23 frequently encompasses A49T and V89L substitutions and a TA dinucleotide repeat polymorphism. The 89L allele has been associated with lower enzyme activity, whereas the 49T allele has been associated with higher activity. Longer TA repeats are associated with mRNA instability and thus decreased enzyme activity. The number of L alleles, but not testosterone alleles or TA repeats, in one study correlated significantly with the presence of BPH (Salam et al, 2005). In the Olmsted County population, consistent associations between *SRD5A2* genotypes and BPH were not demonstrated, although there was a weak correlation between V89L polymorphisms and prostate volume (Roberts et al, 2005).

Androgen withdrawal may partially exert its effect on the prostate through vascular effects (Buttyan et al, 2000). Castration induces acute and drastic vasoconstriction of blood vessels in the rat prostate (Hayek et al, 1999). This effect does not appear to be mediated through vascular endothelial growth factor (Burchardt et al, 2000). There is indirect evidence to suggest that abnormalities in the prostatic vascular system produced by other disease states (e.g., diabetes) may be a risk factor of BPH (Parsons et al, 2006; Parsons, 2007).

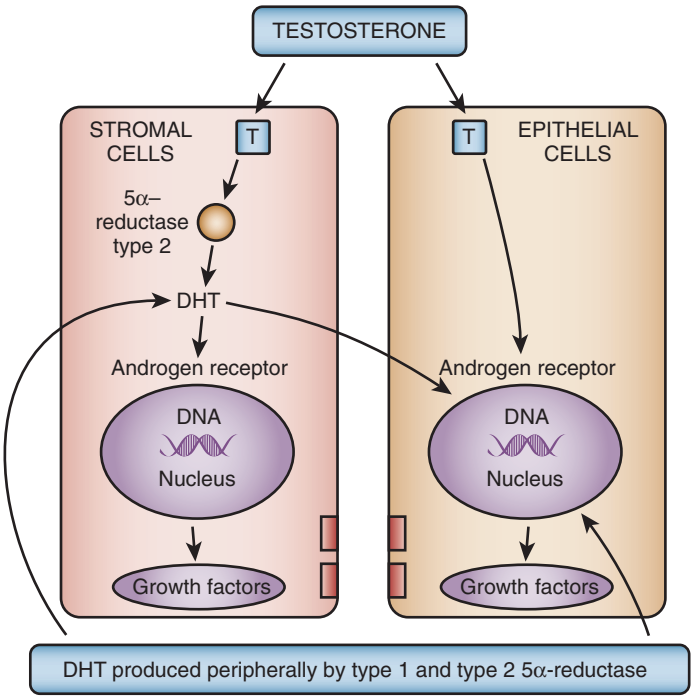


Figure 91–2. Testosterone (T) diffuses into the prostate epithelial and stromal cell. T can interact directly with the androgen (steroid) receptors bound to the promoter region of androgen-regulated genes. In the stromal cell a majority of T is converted into dihydrotestosterone (DHT)—a much more potent androgen—which can act in an autocrine fashion in the stromal cell or in a paracrine fashion by diffusing into epithelial cells in close proximity. DHT produced peripherally, primarily in the skin and liver, can diffuse into the prostate from the circulation and act in a true endocrine fashion. In some cases the basal cell in the prostate may serve as a DHT production site, similar to the stromal cell. Autocrine and paracrine growth factors may also be involved in androgen-dependent processes within the prostate. (From Roehrborn CG. Pathology of benign prostatic hyperplasia. Int J Impot Res 2008;20[Suppl. 3]:S11–8.)

Role of Estrogens

There is animal model evidence to suggest that estrogens play a role in the pathogenesis of BPH; the role of estrogens in the development of human BPH, however, is less clear. In the dog, in which estrogens act synergistically with androgens to produce experimental BPH, estrogen appears to be involved in induction of the AR (Moore et al, 1979). Estrogen may, in fact, "sensitize" the aging dog prostate to the effects of androgen (Barrack and Berry, 1987). The canine prostate contains an abundance of high-affinity estrogen receptor (ER). In the dog, estrogen treatment stimulates the stroma, causing an increase in the total amount of collagen (Berry et al, 1986a, 1986b). There are at least two forms of ER. ER-α is expressed by prostate stromal cells, and ER-β is expressed by prostate epithelial cells (Prins et al, 1998). The estrogenic response of the prostate is determined by the type of ER present within the prostatic cells. Experiments in knockout mice suggest a "constraining influence" of estrogens on the prostate (Krege et al, 1998). In-vitro studies suggest that upregulation

of ER-α in cultured prostate stromal cells is also associated with upregulation of fibroblast growth factor (FGF)-2, FGF-7, and other growth factors; the addition of androgens downregulated the ER and various stroma-derived growth factors (Smith et al, 2000, 2002).

Different actions may be mediated by the stromal ER-α and epithelial ER-β (Prins and Korach, 2008). Evidence also indicates that estrogen action mediated through the separate receptors may contribute to the etiology and progression of multiple prostate-diseased states (Table 91–2). These findings provide new avenues and alternative approaches for the treatment of prostate diseases including prostate cancer with novel therapies directed at ERs or estrogen metabolism. Because the two types of ERs may play distinct and perhaps opposing roles in many diseases of the prostate, including cancer progression, it is possible that receptor-specific agonists and antagonists may prove beneficial in therapeutic strategies in future clinical trials.

Serum estrogen levels increase in men with age, absolutely or relative to testosterone levels. There is also suggestive evidence that intraprostatic levels of estrogen are increased in men with BPH. Patients with larger volumes of BPH tend to have higher levels of estradiol in the peripheral circulation (Partin et al, 1991). In the Olmsted County study cohort, in men with above median levels of bioavailable testosterone, the serum estradiol level correlated positively with prostate volume, even after adjusting for age (Roberts et al, 2004). Data on obesity, serum testosterone, estradiol, and prostate volume are conflicting (Zucchetto et al, 2005). Although there are relatively low concentrations of classic high-affinity ERs in human BPH (Farnsworth, 1996; Sciarra and Toscano, 2000), there may be a sufficient amount for biologic activity.

From experimental studies with aromatase inhibitors it appears that decreases in intraprostatic estrogen in animal models may lead to reduction in drug-induced stromal hyperplasia (Farnsworth, 1996, 1999). At present, however, the role of estrogens in human BPH is not as firmly established as the role of androgens. Species variation and cause-and-effect relationships are problematic.

There are high levels of progesterone receptor in the normal and hyperplastic prostate. However, the role of the progesterone receptor in normal prostatic physiology as well as in BPH remains to be defined.

Table 91–2.

Comparison of ER-α and ER-β Expression and Activities in the Prostate Gland

	ER-α	ER-β
Localization	Stromal	Epithelial
Proliferation	Epithelial squamous metaplasia Stromal proliferation	Antiproliferative
Differentiation	Epithelial dysplasia	Prodifferentiation
Immune response		Anti-inflammatory Antioxidant
Expression	Dysregulated in prostate cancer Silenced in early cancers Re-emergence with progression	Dysregulated in prostate cancer ↓ Organ-confined disease ↑ In metastatic prostate cancer

ER, estrogen receptor.

From Prins GS, Korach KS. The role of estrogens and estrogen receptors in normal prostate growth and disease. Steroids 2008;73(3):233–44.

Regulation of Programmed Cell Death

Programmed cell death (apoptosis) is a physiologic mechanism crucial to the maintenance of normal glandular homeostasis (Kerr and Searle, 1973). Cellular condensation and fragmentation precede phagocytosis and degradation, during which the apoptotic cell is phagocytosed by neighboring cells and degraded by lysosomal enzymes. Apoptosis occurs without activation of the immune system but requires both RNA and protein synthesis (Lee, 1981). In the rat prostate, active cell death occurs naturally in the proximal segment of the prostatic ductal system in the presence of normal concentrations of plasma testosterone (Lee et al, 1990). Androgens (presumably testosterone and DHT) appear to suppress programmed cell death elsewhere in the gland. **After castration, active cell death is increased in the luminal epithelial population as well as in the distal region of each duct.** Tenniswood (1992) suggested that there is regional control over androgen action and epithelial response, with androgens providing a modulating influence over the local production of growth regulatory factors that varies in different parts of the gland. Members of the transforming growth factor-β (TGF-β) family are likely candidates for this regulatory step (Martikainen et al, 1990).

In the rat prostate, at least 25 different genes are induced after castration (Montpetit et al, 1986). Normal glandular homeostasis requires a balance between growth inhibitors and mitogens, which respectively restrain or induce cell proliferation but also prevent or modulate cell death. Abnormal hyperplastic growth patterns, such as BPH, might be induced by local growth factor or growth factor receptor abnormalities, leading to increased proliferation or decreased levels of programmed cell death.

Stromal-Epithelial Interaction

There is abundant experimental evidence to demonstrate that **prostatic stromal and epithelial cells maintain a sophisticated paracrine type of communication.** The growth of canine prostate epithelium can be regulated by cellular interaction with the basement membrane and stromal cells. Isaacs and Coffey (1987), using a marker of canine prostatic epithelial cell function, demonstrated that epithelial cells grown on plastic quickly lose their ability to secrete this protein. In addition, the cells begin to grow rapidly and change their cytoskeletal staining pattern. In contrast, if the cells are grown on prostatic collagen they maintain their normal secretory capacity and cytoskeletal staining pattern and do not grow rapidly. This is strong evidence that **one class of stromal cell excretory protein (i.e., extracellular matrix) partially regulates epithelial cell differentiation. Thus BPH may be due to a defect in a stromal component that normally inhibits cell proliferation, resulting in loss of a normal "braking" mechanism for proliferation.** This abnormality could act in an autocrine fashion to lead to proliferation of stromal cells as well.

Further evidence of the importance of stromal-epithelial interactions in the prostate comes from the elegant developmental studies of Cunha, which demonstrate the importance of embryonic prostatic mesenchyme in dictating differentiation of the urogenital sinus epithelium (Cunha et al, 1980, 1983, 2003; Cunha and Donjacour, 1987; Cunha, 1994, 1996). **The process of new gland formation in the hyperplastic prostate suggests a**

"reawakening" of embryonic processes in which the underlying prostatic stroma induces epithelial cell development (McNeal, 1990). Many of the prostatic stromal-epithelial interactions observed during normal development and in BPH may be mediated by soluble growth factors or by the extracellular matrix (ECM), which itself has growth factor–like properties. This model is even more intriguing, given the cellular localization of 5α-reductase (and thus DHT production) in the prostate stromal cell (Silver et al, 1994).

The complexity of the stromal/ECM/epithelial relationship is revealed in studies of the ECM signaling protein CYR61. CRY61 (an early immediate response gene) is an ECM-associated protein that promotes adhesion, migration, and proliferation of epithelial and stromal cells. A variety of growth factors increase the expression of CYR61 in both cell types, and the suppression of CYR61 expression by an antisense oligonucleotide significantly affects normal cell morphology (Sakamoto et al, 2003, 2004a, 2004b). CRY61 expression is significantly increased in human BPH tissues and is induced by lysophosphatidic acid (an endogenous lipid growth factor).

As our understanding of stromal-epithelial cell relationships in the prostate increases it is possible that therapies may be designed to induce regression of established BPH by modulating these autocrine/paracrine mechanisms.

Growth Factors

Growth factors are small peptide molecules that stimulate, or in some cases inhibit, cell division and differentiation processes (Steiner, 1995; Lee and Peehl, 2004). Cells that respond to growth factors have on their surface receptors specific for that growth factor that in turn are linked to a variety of transmembrane and intracellular signaling mechanisms. **Interactions between growth factors and steroid hormones may alter the balance of cell proliferation versus cell death to produce BPH** (Fig. 91–3). Lawson's group was the first to demonstrate that extracts of BPH stimulate cellular growth. This putative prostatic growth factor was subsequently found on sequence analysis to be basic fibroblastic growth factor (bFGF) (Story et al, 1989). Subsequently, a variety of growth factors have been characterized in normal, hyperplastic, and neoplastic prostatic tissue. In addition to bFGF (FGF-2), acidic FGF (FGF-1), Int-2 (FGF-3), keratinocyte growth factor (KGF, FGF-7), transforming growth factor-β (TGF-β), and epidermal growth factor (EGF) have been implicated in prostate growth. TGF-β is a potent inhibitor of proliferation in normal epithelial cells in a variety of tissues. In models of prostatic cancer there is evidence that malignant cells have escaped the growth inhibitory effect of TGF-β (McKeehan and Adams, 1988). Similar mechanisms may be operational in BPH (Salm et al, 2000), leading to the accumulation of epithelial cells (Kundu et al, 2008). Growth factors may also be important in modulating the phenotype of the prostate smooth muscle cell (Peehl and Sellers, 1998).

There is mounting evidence of interdependence between growth factors, growth factor receptors, and the steroid hormone milieu of the prostate (Rennie et al, 1988; Lee and Peehl, 2004). Although data on the absolute level of growth factor and growth factor receptors in hyperplastic as opposed to normal tissue conflict, it is likely that growth factors play some role in the pathogenesis of BPH. However, further research is necessary to establish the role of growth factors in a disease process in which cellular proliferation is not obvious.

If cellular proliferation is a component of the BPH process, it appears that growth stimulatory factors such as the FGF-1, FGF-2, FGF-7, and FGF-17 families, vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF) may play a role, with DHT augmenting or modulating the growth factor effects. In contrast, TGF-β, which is known to inhibit epithelial cell proliferation, may normally exert a restraining influence over epithelial proliferation that is lost or downregulated in BPH (Wilding et al, 1989; Sporn and Roberts, 1990, 1991; Peehl et al, 1995; Cohen et al, 2000; Lee and Peehl, 2004). TGF-β1 is a potent mitogen for fibroblasts and other mesenchymal cells but is also an important inhibitor of epithelial cell proliferation (Roberts and Sporn, 1993). TGF-β1 also regulates ECM synthesis and degradation and can induce cells to undergo apoptosis. In addition, TGF-β upregulates the production of bFGF-2, which is known to be an autocrine growth factor for prostate stromal cells (Story et al, 1993) and at least on one prostate smooth muscle cell line (PSMC1), TGF functions as an autocrine mitogen (Salm et al, 2000). Thus upregulation of TGF-β1 (which is expressed in prostate stromal cells) during BPH would favor expansion of the stromal compartment.

Indirect evidence to support this view comes from studies of reconstituted mouse prostate (Yang et al, 1997). Interestingly, the observation that TGF-β1 may regulate smooth muscle contractile protein expression suggests that TGF-β isoforms may be physiologic regulators of prostatic smooth muscle function (Orlandi et al, 1994). Cohen and colleagues (2000) found that stromal cells isolated from BPH specimens exhibited a blunted TGF-β growth inhibition relative to normal stromal cells and that the blunted response appeared to be due to a reduction in TGF-mediated increase in IGF binding protein 3 (IGFBP-3) expression. TGF-β may stimulate the overexpression of versican (chondroitin

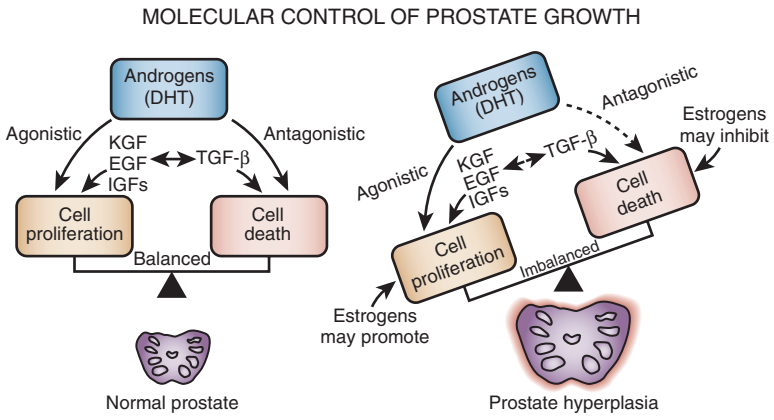


Figure 91–3. Prostate hyperplasia is probably due to an imbalance between cell proliferation and cell death. Androgens play a necessary but probably permissive role. Growth factors are more likely to be sites of primary defects.

sulfate proteoglycan 2) in the ECM through inhibition of key metalloproteases (ADAMTS lineage) that normally degrade versican, leading to accumulation in the ECM (Cross et al, 2006). An increased risk for BPH was described in patients with a codon 10 polymorphism in TGF-β (Li et al, 2004).

The first evidence of increased FGF-2 levels in BPH came from the studies of Begun and coworkers (1995), who demonstrated a twofold to threefold elevation of FGF-2 in BPH compared with histologically normal glands. Further studies have demonstrated that both FGF-2 and FGF-7 are overexpressed in BPH tissues (Ropiquet et al, 1999). The major target of FGF-2 is thought to be the stroma itself (autocrine), although transgenic mice overexpressing FGF-2 develop glandular epithelial hyperplasia (Konno-Takahashi et al, 2004). KGF, a member of the FGF family (FGF-7), is produced in prostatic stromal cells (Yan et al, 1992). However, cell surface receptors for stroma-derived KGF are expressed exclusively in epithelial cells. As a result, **FGF-7 (or a homolog) is the leading candidate for the factor mediating the stromal cell–based hormonal regulation of the prostatic epithelium.** There is direct evidence that FGF-7 plays this role in the androgen-dependent mesenchymal-epithelial interactions involved in development of the seminal vesicle (Alarid et al, 1994). Abnormalities in stromal FGF-7 production or epithelial FGF-7 receptor could promote epithelial cell proliferation. Indirect evidence supporting this hypothesis comes from a study of transgenic mice overexpressing FGF-7 that develop atypical prostatic hyperplasia (Kitsberg and Leder, 1996). McKeehan's laboratory demonstrated that FGF-10, a homolog of FGF-7, is expressed at high levels in the rat prostate, specifically in stromal cells of smooth muscle origin (Lu et al, 1999; Nakano et al, 1999). FGF-10 expression is increased by androgens and may have a mitogenic effect on prostate epithelium. Others studies suggest that cells expressing FGF-7 are localized in the stroma immediately adjacent to the epithelium, suggesting that the epithelial cells may induce FGF-7 expression. The paracrine factor most likely responsible for this effect is cytokine interleukin (IL)-1α (Giri and Ittmann, 2000; Lee and Peehl, 2004).

Some investigators have speculated that local hypoxia in the prostate (perhaps from atherosclerosis or other vascular events) is the initial event that induces FGF production (Lee and Peehl, 2004). Further growth of BPH nodules could impede blood flow, leading to further hypoxia (Parsons et al, 2008; Parsons and Kashefi, 2008). Hypoxia leads to upregulation of hypoxia inducible factor-1, which in turn increases the secretion of FGF-2 and FGF-7 from stromal cells.

Other growth factors implicated in BPH include FGF-17 (Polnaszek et al, 2004), FGF-10, and VEGF (Walsh et al, 2002). It remains difficult to ascertain which of the growth factors and growth factor receptors are key mediators of the BPH disease process and which are bystanders.

A unique animal model provides additional evidence that FGF-like factors may be involved in the etiology of BPH. **A transgenic mouse line expressing the Int-2/FGF-3 growth factor demonstrated androgen-sensitive epithelial hyperplasia in the male mouse prostate histologically similar to human and canine BPH** (Tutrone et al, 1993).

Insulin-like growth factors, binding proteins, and receptors also appear to be important modulators of prostatic growth, at least as it relates to cell growth in culture (Peehl et al, 1995; Lee and Peehl, 2004). A transgenic mouse model with overexpression of IGF-1 demonstrated prostate gland enlargement (Konno-Takahashi et al, 2003). Studies of BPH tissue demonstrate a higher concentration of IGF-2 in the periurethral area than in the peripheral zone (Monti et al, 2001). A study of Chinese men demonstrated a significant correlation between circulating IGF-1 and IGFBP-3 level and BPH (Dahle et al, 2002), but a study of the Olmsted County cohort failed to demonstrate any relationship between serum IGF-1 and prostate volume (Roberts et al, 2003).

Other Signaling Pathways

Sympathetic signaling pathways are important in the pathophysiology of LUTS, as is evident from the use of drugs interfering with the adrenergic nervous system such as α-adrenergic receptor blockers, which are highly effective for the treatment of LUTS (American Urological Association, 2003). In addition, there is increasing evidence that sympathetic pathways may be important in the pathogenesis of the hyperplastic growth process (McVary et al, 1994, 2005). α-Adrenergic blockade, in some model systems, can induce apoptosis (Anglin et al, 2002). α-Adrenergic pathways can also modulate the smooth muscle cell phenotype in the prostate (Lin et al, 2000). All the components of the renin-angiotensin system (RAS) are present in prostatic tissue and may be activated in BPH (Dinh et al, 2001, 2002; Fabiani et al, 2001). Either with or without sympathetic modulation, local RAS pathways may contribute to cell proliferation and smooth muscle contraction.

The early growth response gene-1 (*EGR1*) transcription regulation pathway was found to be active in a BPH cell line (Mora et al, 2005). Also of interest is the finding that α_2-macroglobulin, a large protein that binds PSA and many growth factors, is very highly expressed in human prostate and is upregulated in BPH (Lin et al, 2005). Trapping and inactivation of inhibitory molecules could promote growth pathways.

Potential Role of Inflammatory Pathways and Cytokines in Benign Prostatic Hyperplasia

An additional source of growth factors in human BPH tissue may be the inflammatory cell infiltrates seen in many men with BPH. In the 1990s, descriptive studies suggested a link between inflammation and BPH-related growth. Theyer and associates (1992) reported extensive infiltration of human BPH tissues by activated T cells. Peripheral blood and tumor infiltrating T cells are known to express VEGF, a potent epithelial mitogen (Blotnik et al, 1994; Freeman et al, 1995). T cells are known to produce and secrete a variety of other growth factors, including HB-EGF and bFGF/FGF-2. Thus T cells present in the local prostate environment were thought to be capable of secreting potent epithelial and stromal mitogens that promote stromal and glandular hyperplasia.

In the past 5 years, specific inflammatory mediator pathways have been studied in detail to elucidate the potential role of these pathways in BPH pathogenesis. A large number of cytokines and their receptors are seen in BPH tissue (Konig et al, 2004). Specifically, significant levels of IL-2, IL-4, IL-7, IL-17, interferon-γ (IFN-γ), and their relevant receptors are found in BPH tissue (Kramer et al, 2002; Steiner et al, 2003a, 2003b). IL-2, IL-7, and IFN-γ stimulate the proliferation of prostatic stromal cells in vitro. Prostatic epithelial cell senescence results in increased expression of IL-8, which can promote proliferation of nonsenescent epithelial and stromal cells (Castro et al, 2004). Macrophage inhibitory cytokine-1 is expressed in normal prostate tissue but significantly downregulated in BPH (Kakehi et al, 2004; Taoka et al, 2004). Chronic inflammation in BPH is also associated with focal upregulation of

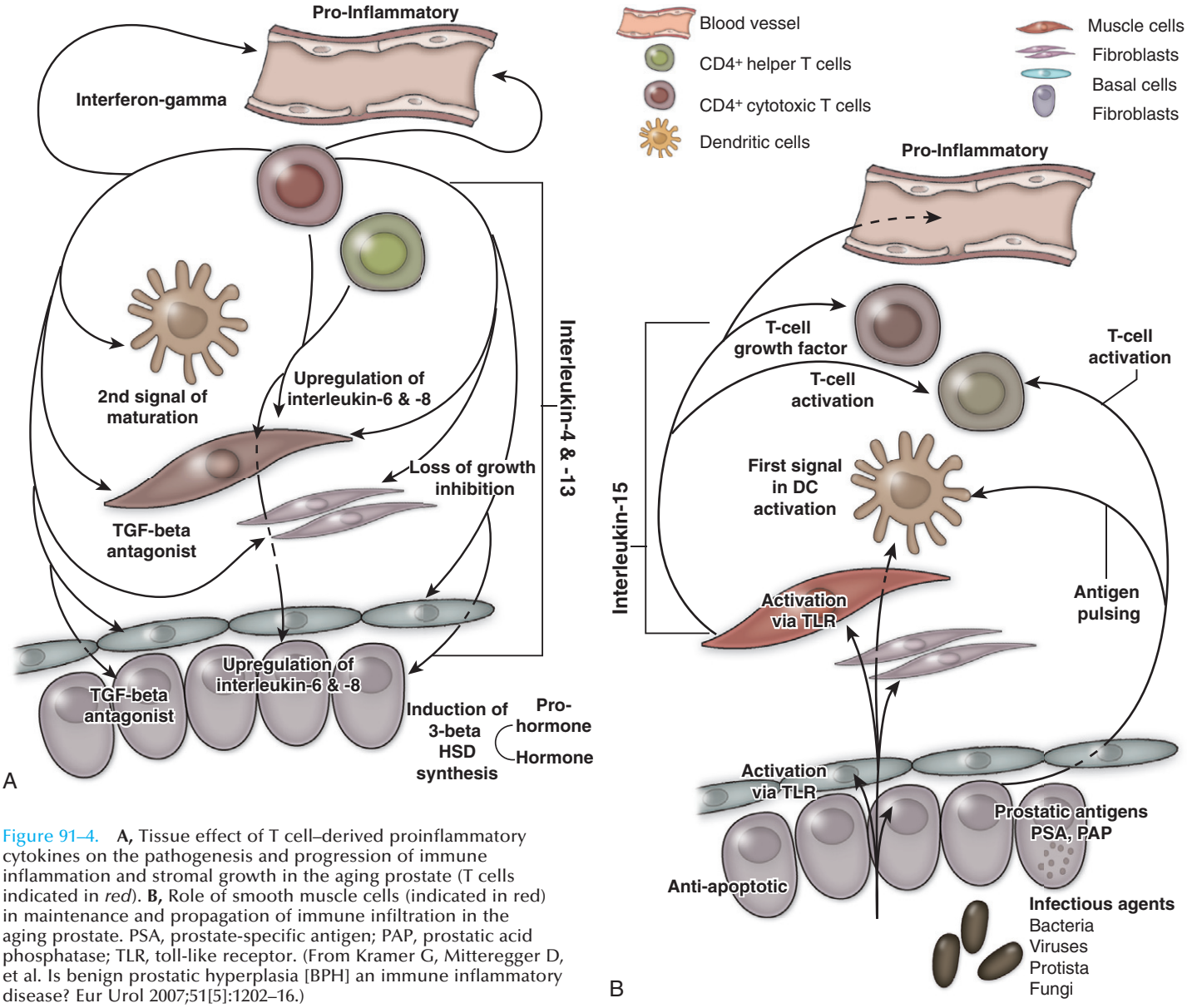


Figure 91–4. **A,** Tissue effect of T cell–derived proinflammatory cytokines on the pathogenesis and progression of immune inflammation and stromal growth in the aging prostate (T cells indicated in *red*). **B,** Role of smooth muscle cells (indicated in red) in maintenance and propagation of immune infiltration in the aging prostate. PSA, prostate-specific antigen; PAP, prostatic acid phosphatase; TLR, toll-like receptor. (From Kramer G, Mitteregger D, et al. Is benign prostatic hyperplasia [BPH] an immune inflammatory disease? Eur Urol 2007;51[5]:1202–16.)

cyclooxygenase 2 (COX-2) in the glandular epithelium (Wang et al, 2004). To date, however, no firm cause-and-effect relationships have been established between prostatic inflammation and related cytokine pathways and stromal-epithelial hyperplasia.

An excellent recent review of BPH as a potentially autoimmune disease was published by Kramer and colleagues (2007), and Figure 91–4 illustrates the immunologic key features of chronic inflammation in BPH and the present interpretation of these changes in the development and progression of BPH.

Genetic and Familial Factors

There is substantial evidence that **BPH has an inheritable genetic component.** Sanda and colleagues conducted a retrospective case-control analysis of surgically treated BPH patients and control subjects at Johns Hopkins Hospital (Partin et al, 1994; Sanda et al, 1994). The BPH patients were men whose resected prostate weights were in the highest quartile (>37 g) and whose age at prostatectomy was in the lowest quartile. **The hazard-function ratio for surgically treated BPH among first-degree male relatives of the BPH cases compared with the first-degree male relatives of the controls was 4.2 (95% confidence interval [CI], 1.7 to 10.2), demonstrating a very strong relationship** (Table 91–3). The results did not appear to be due to differences in health-seeking behavior between the two groups. A segregation analysis showed that the results were most consistent with an **autosomal dominant inheritance pattern.** Utilizing this model, **approximately 50% of men undergoing prostatectomy for BPH when younger than 60 years of age could be attributable to an inheritable form of disease.** In contrast, **only about 9% of men undergoing prostatectomy for BPH when older than 60 years of age would be predicted to have a familial risk.** In addition, monozygotic twins demonstrate a higher concordance rate of BPH than dizygotic twins (Partin et al, 1994).

In a community-based cohort study of more than 2000 men, Roberts and colleagues (1995) found an elevated risk of moderate to severe urologic symptoms in men with a family history of an

Table 91–3.

Family History of Early-Onset BPH Increases Risk of Clinical Significant BPH

BPH (%)* RELATIVES	Frequency of Clinical BPH		Age-Adjusted		Significance‡	
	CASE RELATIVES	CONTROL RELATIVES	ODDS RATIO (UNADJUSTED)†	RELATIVE RISK OF CLINICAL BPH‡	CHI- SQUARE	*P* VALUE
All first-degree male relatives	28.3	8.6	4.2 (1.7-10.2)	4.4 (1.9-9.9)	13.36	.0003
Fathers of proband	33.3	13.2	3.3 (1.1-10.2)	3.5 (1.3-9.5)	5.94	.0148
Brothers of proband	24.2	3.9	8.0 (1.6-40.5)	6.1 (1.3-29.7)	6.85	.0089

*Percent of informative male relatives with history of prostatectomy (open or transurethral) for BPH (60 case relatives and 105 control relatives).
†Chi-square analysis of proportions; Taylor 95% confidence intervals in parentheses.
‡Cox proportional hazards survival model. Censored outcome—prostatectomy. Time variable—age at death or current age. Values in parentheses indicate 95% confidence intervals.
BPH, begin prostatic hyperplasia.
From Sanda MG, Beaty TH, Stutzman RE, et al. Genetic susceptibility of benign prostatic hyperplasia. J Urol 1994;152(1):115–9.

enlarged prostate and a family history of BPH compared with those with no history. Analysis of the subjects who participated in the U.S. finasteride clinical trial identified 69 men who had three or more family members with BPH, including the proband (Sanda et al, 1997). Regression analysis demonstrated that **familial BPH was characterized by large prostate size, with a mean prostate volume of 82.7 mL in men with hereditary BPH compared with 55.5 mL in men with sporadic BPH.** Serum androgen levels and the response to 5α-reductase inhibition were similar in familial and sporadic BPH. A more recent familial aggregation study in the finasteride database confirmed that a strong family history of early-onset and large prostate volume is more likely to be associated with inheritance of risk than symptom severity or other factors (Pearson et al, 2003).

These studies clearly demonstrate the presence of a familial form of BPH and suggest the presence of a gene contributing to the pathogenesis of the disease. The studies of Meikle and coworkers (1997, 1999) also support a genetic basis for BPH. Preliminary studies demonstrate evidence of DNA mutations (White et al, 1990), DNA hypomethylation (Bedford and van Helden, 1987), and abnormalities of nuclear matrix protein expression (Partin et al, 1993), miscellaneous genetic polymorphisms (Werely et al, 1996; Konishi et al, 1997; Habuchi et al, 2000), and abnormal expression of the Wilms tumor gene *(WT1)* (Dong et al, 1997) in human BPH. However, the specific gene or genes involved in familial BPH or that contribute to the risk of significant prostatic enlargement in sporadic disease remain to be elucidated.

Other Etiologic Factors

Androgens and soluble growth factors are clearly not the only important factors for the development of BPH. All mammalian prostates studied have testosterone, DHT, and AR as well as most of the known growth factor signaling pathways; however, only dog and man develop BPH. Interestingly, another glandular organ that remains androgen responsive throughout life, the seminal vesicle, does not develop hyperplasia. Obviously, other mechanisms or cofactors must be present in these two unique species making them susceptible to the disease. Nonandrogenic substances from the testis, perhaps transmitted through the vas deferens or deferential blood vessels, for example, may play some role (Dalton et al, 1990). Rats with intact testes treated with exogenous androgen demonstrate a greater degree of prostatic growth than castrated rats treated with androgen. Sutkowski and coworkers (1993) have demonstrated that human spermatocele fluid is mitogenic to both human prostatic epithelial and stromal cells in culture. Similar results have been seen in castrated versus testes-intact dogs treated with exogenous androgen and exogenous testosterone and estradiol combination (Juniewicz et al, 1994). In addition to increases in prostate weight, the incidence of histologic BPH was significantly higher in the dogs with intact testes. Grayhack and colleagues (1998) have identified a putative substance that may be a candidate for such a factor.

Prolactin has long been speculated to play a role in BPH because of the known effects of this hormone on prostate cells in vitro. Transgenic mice overexpressing the prolactin gene develop significant enlargement of the prostate (Wennbo et al, 1997). However, despite the documented presence of prolactin receptors in the human prostate and low circulating levels of the hormone, the role of prolactin in human prostate disease is unclear.

Molecular profiling, fingerprinting, microarrays, and high-throughput screening tools have uncovered new genes, as well as known genes not previously associated with BPH. Preliminary findings from the Getzenberg laboratory (Prakash et al, 2002; Sakamoto et al, 2004a, 2004b; Shah et al, 2004; Minnery and Getzenberg, 2005) and other groups (Fromont et al, 2004; Dhanasekaran et al, 2005) suggest that new markers for BPH and new therapeutic targets will be found in the next few years.

PATHOPHYSIOLOGY

The pathophysiology of BPH is complex (Fig. 91–5). **Prostatic hyperplasia increases urethral resistance, resulting in compensatory changes in bladder function.** However, the elevated detrusor pressure required to maintain urinary flow in the presence of increased outflow resistance occurs at the expense of normal bladder storage function. **Obstruction-induced changes in detrusor function, compounded by age-related changes in both bladder and nervous system function, lead to urinary frequency, urgency, and nocturia, the most bothersome BPH-related complaints.** Thus, an understanding of BPH pathophysiology requires detailed insight into obstruction-induced bladder dysfunction.

Pathology

Anatomic Features

McNeal (1978) demonstrated that **BPH first develops in the periurethral *transition zone* of the prostate** (Fig. 91–6). The transition zone consists of two separate glands immediately external to the preprostatic sphincter. The main ducts of the transition

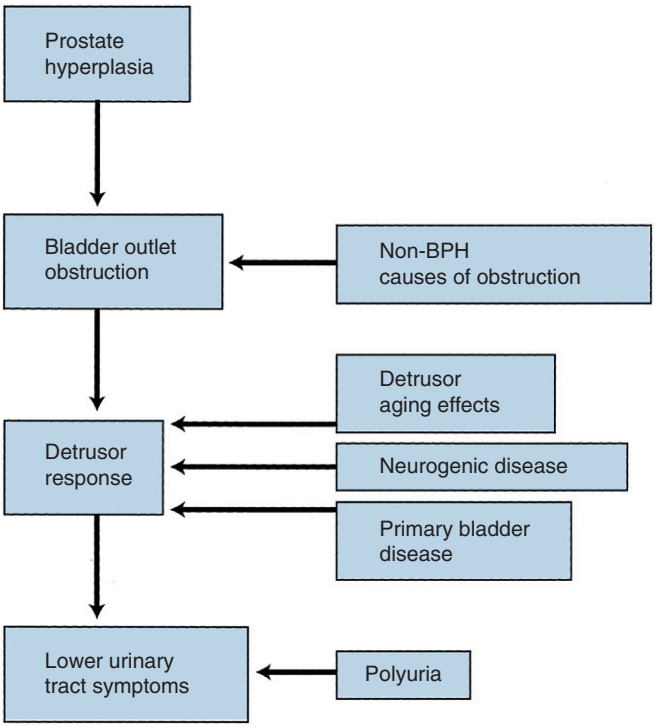


Figure 91–5. The pathophysiology of benign prostatic hyperplasia (BPH) involves complex interactions between urethral obstruction, detrusor function and dysfunction, and urine production.

zone arise on the lateral aspects of the urethral wall at the point of urethral angulation near the verumontanum. Proximal to the origin of the transition zone ducts are the glands of the *periurethral zone* that are confined within the preprostatic sphincter and course parallel to the axis of the urethra. All BPH nodules develop either in the transition zone or in the periurethral region (McNeal, 1978, 1990). Although early transition zone nodules appear to occur either within or immediately adjacent to the preprostatic sphincter, as the disease progresses and the number of small nodules increases they can be found in almost any portion of the transition or periurethral zone. However, **the transition zone also enlarges with age, unrelated to the development of nodules.**

One of the unique features of the human prostate is **the presence of the prostatic capsule, which plays an important role in the development of LUTS** (Caine and Schuger, 1987). In the dog, the only other species known to develop naturally occurring BPH, symptoms of bladder outlet obstruction and urinary symptoms rarely develop because the canine prostate lacks a capsule. Presumably the capsule transmits the "pressure" of tissue expansion to the urethra and leads to an increase in urethral resistance. Thus the clinical symptoms of BPH in man may be due not only to age-related increases in prostatic size but also to the unique anatomic structure of the human gland. **Clinical evidence of the importance of the capsule can be found in series that clearly document that incision of the prostatic capsule (transurethral incision of the prostate) results in a significant improvement in outflow obstruction, despite the fact that the volume of the prostate remains the same.**

The size of the prostate does not correlate with the degree of obstruction. Thus other factors such as dynamic urethral resistance, the prostatic capsule, and anatomic pleomorphism are more important in the production of clinical symptoms than the absolute size of the gland. In some cases, predominant growth of periurethral nodules at the bladder neck gives rise to the "middle lobe" (Fig. 91–7). The middle lobe must be of periurethral origin because there is no transition zone tissue in this area. It is not clear whether middle lobe growth occurs at random in men with BPH or whether there is an underlying genetic susceptibility to this pattern of enlargement.

Histologic Features

BPH is a hyperplastic and not a hypertrophic process, that is, there is a net increase in the number of cells and not in the size of the cells. Histologic studies document an increase in the cell number (McNeal, 1990). In addition, thymidine uptake studies in the dog clearly indicate an increase in DNA synthesis in experimentally induced BPH (Barrack and Berry, 1987). The term *benign prostatic hypertrophy* is pathologically incorrect.

McNeal's studies (1990) demonstrate that the majority of **early periurethral nodules are purely stromal in character.** These small stromal nodules resemble embryonic mesenchyme with an abundance of pale ground substance and minimal collagen. It is unclear whether these early stromal nodules contain mainly fibroblast-like cells or whether differentiation toward a smooth muscle cell type is occurring. In contrast, **the earliest transition zone nodules represent proliferation of glandular tissue** that may be associated with an actual reduction in the relative amount of stroma (Fig. 91–8). The minimal stroma seen initially consists primarily of mature smooth muscle, not unlike that of the uninvolved transition zone tissue. These **glandular nodules are apparently derived from newly formed small duct branches** that bud off from existing ducts, leading to a totally new ductal system within the nodule. This type of **new gland formation is quite rare** outside embryonic development. This proliferative process leads to a tight packing of glands within a given area as well as an increase in the height of the lining epithelium. There appears to be hypertrophy of individual epithelial cells as well. Again, the observed increase in transition zone volume with age appears to be related not only to an increased number of nodules but also to an increase in the overall size of the zone.

During the first 20 years of BPH development, the disease may be predominantly characterized by an increased number of nodules, and the subsequent growth of each new nodule is generally slow. Then a second phase of evolution occurs in which there is a significant increase in large nodules. In the first phase, the glandular nodules tend to be larger than the stromal nodules. In the second phase, when the size of individual nodules is increasing, the size of glandular nodules clearly predominates.

There is significant pleomorphism in stromal-epithelial ratios in resected tissue specimens. Studies from primarily **small resected glands demonstrate a predominance of fibromuscular stroma** (Shapiro et al, 1992). Larger glands, predominantly those removed by enucleation, demonstrate primarily epithelial nodules (Franks, 1976). However, an increase in stromal-epithelial ratios does not necessarily indicate that this is a "stromal disease"; stromal proliferation may well be due to "epithelial disease."

Importance of Prostatic Smooth Muscle

Regardless of the exact proportion of epithelial to stromal cells in the hyperplastic prostate, there is no question that **prostatic smooth muscle represents a significant volume of the**

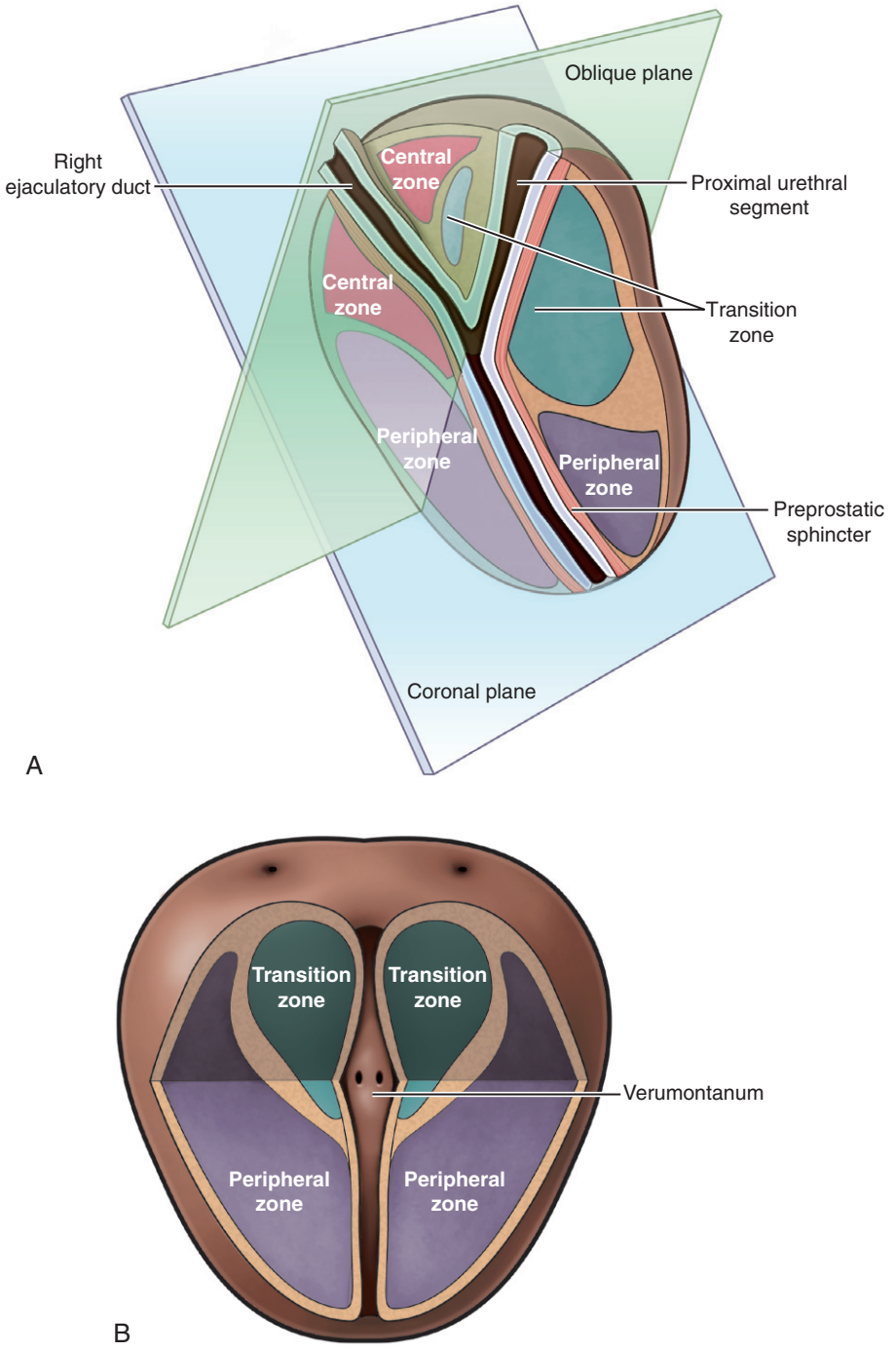


Figure 91–6. Zonal anatomy of the prostate as first described by McNeal (1978). Sagittal **(A)** and coronal **(B)** sections of the prostate showing peripheral zone, transition zone, central zone, the verumontanum, the proximal urethral segment, as well as preprostatic sphincter and ejaculatory duct. (From Roehrborn CG. Pathology of benign prostatic hyperplasia. Int J Impot Res 2008;20[Suppl. 3]:S11–8.)

gland (Shapiro et al, 1992) (Fig. 91–9). Although the smooth muscle cells in the prostate have not been extensively characterized, presumably their contractile properties are similar to those seen in other smooth muscle organs. The spatial arrangement of smooth muscle cells in the prostate is not optimal for force generation; however, there is no question that **both passive and active forces in prostatic tissue play a major role in the pathophysiology of BPH.** The factors that determine passive tone in the prostate remain to be elucidated. The series elastic elements in the stromal and epithelial cells and (most important) the ECM contribute to passive tissue force, independent of active smooth muscle contraction. However, **stimulation of the adrenergic nervous system clearly results in a dynamic increase in prostatic urethral resistance. Blockade of this stimulation by α-receptor blockers clearly diminishes this response.** However, α-adrenergic blockade does not decrease passive tension in the prostate, which may be an equal determinant of urethral resistance.

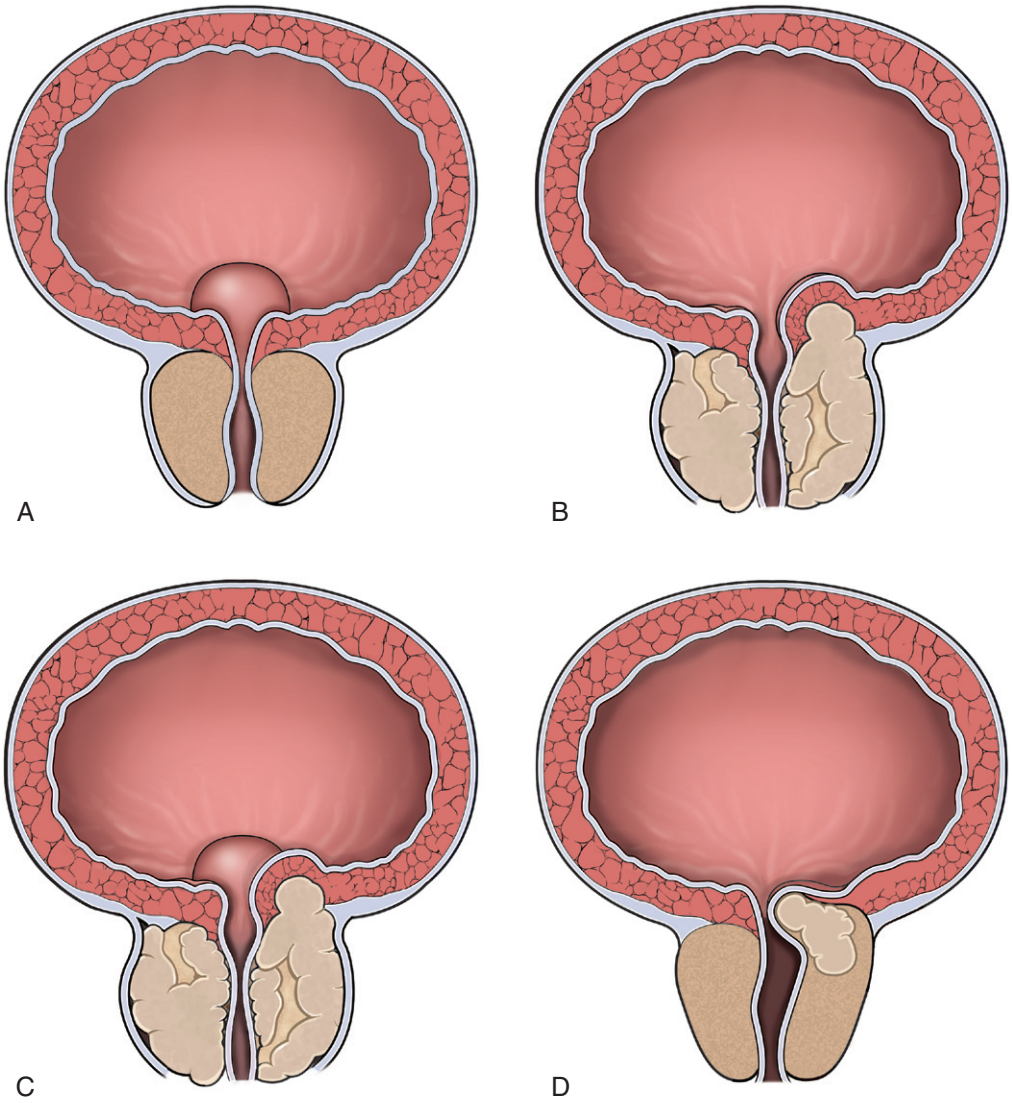


Figure 91–7. Diagrams of hyperplastic prostatic tissue obstructing the prostatic urethra forming "lobes." **A,** Isolated middle lobe enlargement. **B,** Isolated lateral lobe enlargement. **C,** Lateral and middle lobe enlargement. **D,** Posterior commissural hyperplasia (median bar). (After Randall [1931], from Roehrborn CG. Pathology of benign prostatic hyperplasia. Int J Impot Res 2008;20[Suppl. 3]: S11–8.)

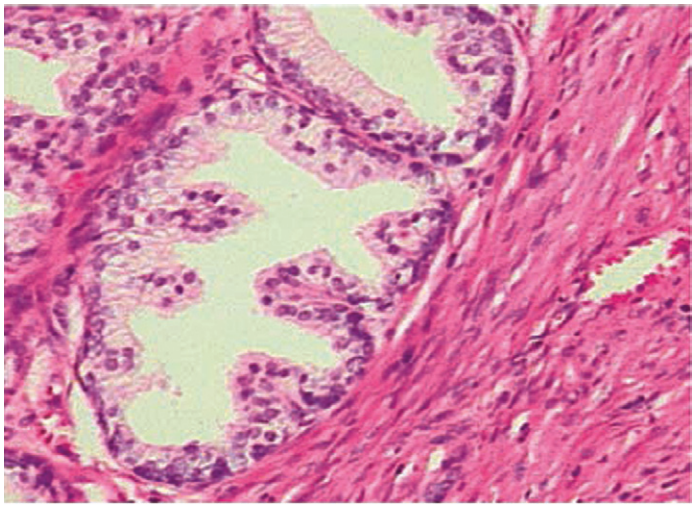


Figure 91–8. Stromoglandular hyperplasia of the prostate showing glandular *(upper left)* and stromal *(lower right)* tissue (hematoxylin and eosin stain). (From Roehrborn CG. Pathology of benign prostatic hyperplasia. Int J Impot Res 2008;20[Suppl. 3]:S11–8.)

Several additional observations on the prostatic stromal/smooth muscle cell are important. It is generally assumed that the stromal cells are resistant to the effects of androgen withdrawal. In short-term studies, androgen ablation appears to affect primarily the epithelial cell population. In general, however, stromal cells have much slower turnover rates than epithelial cells. If the effect of androgen ablation is primarily to increase cell death rates, a decrease in stromal cell numbers may not be appreciated until a year or more of therapy. Thus further study is required to determine whether the stromal cell is really resistant to androgen withdrawal. Likewise, it cannot be assumed that hormonal therapy has no effect on the stroma even if stromal cell volumes are not decreased. In a variety of smooth muscle cell systems (e.g., vascular and myometrial), contractile proteins, neuroreceptors, and ECM proteins are regulated by a variety of hormones and growth factors. In vitro, androgens have been shown to modulate the effects of α-agonists on prostate smooth muscle cells (Smith et al, 2000). Thus a given therapy may affect stromal cell function without decreasing the absolute number or volume of cells.

Studies of human tissue samples by Lin and colleagues (2000) have clearly shown that the smooth muscle cells from men

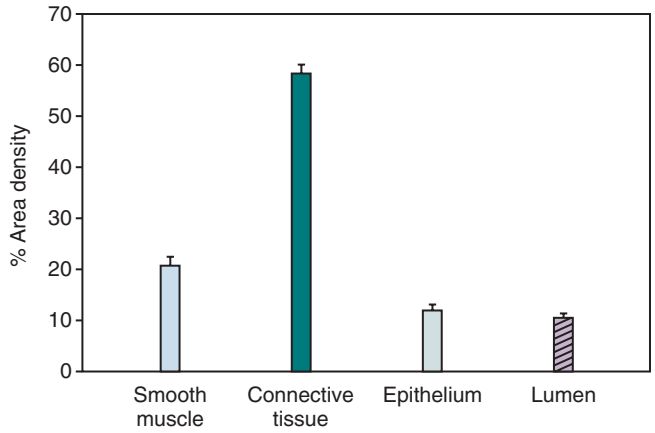


Figure 91–9. Prostate sections obtained from men with symptomatic benign prostatic hyperplasia were analyzed by double immunoenzymatic staining and quantitative image analysis. The percent area density of smooth muscle and connective tissue is significantly greater than glandular epithelium and glandular lumen area density (mean ± SEM). (From Shapiro E, Becich MJ, et al. The relative proportion of stromal and epithelial hyperplasia is related to the development of symptomatic benign prostate hyperplasia. J Urol 1992;147:1293–7.)

with BPH have a significant downregulation of smooth muscle myosin heavy chain and a significant upregulation of nonmuscle myosin heavy chain. This myosin expression pattern is typical of dedifferentiated smooth muscle and indicates either proliferation or loss of normal modulation pathways.

Active smooth muscle tone in the human prostate is regulated by the adrenergic nervous system (Roehrborn and Schwinn, 2004). The α_1-adrenoreceptor nomenclature has been standardized (Hieble et al, 1995) to reconcile differences in nomenclature based on pharmacologic and molecular studies. **Receptor binding studies clearly demonstrate that α_{1A} is the most abundant adrenoreceptor subtype present in the human prostate** (Lepor et al, 1993a, 1993b; Price et al, 1993). **Moreover, the α_{1A} receptor clearly mediates active tension in human prostatic smooth muscle.** It is still unclear whether other factors may regulate smooth muscle contraction. Endothelin and endothelin receptors (Kobayashi et al, 1994a, 1994b; Imajo et al, 1997; Walden et al, 1998) have been reported in human prostate. However, the physiologic role of this potent contractile agent in prostate smooth muscle function remains to be defined. Various components of the kallikrein-kinin system (e.g., bradykinin) may play a role in the regulation of both smooth muscle proliferation and contraction in the prostate (Walden et al, 1999; Srinivasan et al, 2004).

The presence of type 4 and type 5 phosphodiesterase isoenzymes in the prostate and the detrusor muscle of the bladder implies that phosphodiesterase inhibitors may be appropriate candidate therapies for BPH-related LUTS (Uckert et al, 2001, 2008, 2009). In fact, placebo-controlled trials have verified a beneficial effect of commercially available drugs for the treatment of erectile dysfunction in men with LUTS and BPH (McVary et al, 2007; Roehrborn et al, 2008; Stief et al, 2008).

The role of adrenergic stimulation in the prostate may exceed simple smooth muscle contraction. Adrenergic neurotransmitters are known to regulate expression of contractile protein genes in cardiac myocytes (Kariya et al, 1993) and to be involved in the development of cardiac hypertrophy (Matsui et al, 1994). Interestingly, evidence suggests that testosterone may regulate the expression of adrenergic receptors, at least in the kidney (Gong et al, 1995). It is possible that adrenergic neurotransmitters may play a role in prostatic smooth muscle cell *regulation* as well as contraction (Smith et al, 2000). α-Adrenergic blockade in patients with documented BPH leads to a significant downregulation of normal contractile protein gene expression, specifically smooth muscle myosin heavy chain.

Autonomic nervous system overactivity may contribute to LUTS in men with BPH. McVary and coworkers (2005) demonstrated that autonomic nervous system activity, as measured by a standard set of physiologic tests, plasma, and urinary catecholamines, correlates positively with symptom score and other BPH measures. Serum norepinephrine increase after tilt predicted prostate size (transition zone).

The Bladder's Response to Obstruction

Current evidence suggests that the bladder's response to obstruction is largely an adaptive one. However, it is also clear that many lower tract symptoms in men with BPH or prostate enlargement are related to obstruction-induced changes in bladder function rather than to outflow obstruction directly. Approximately one third of men continue to have significant voiding dysfunction and mostly storage symptoms after surgical relief of obstruction (Abrams et al, 1979). Obstruction-induced changes in the bladder are of two basic types. First, the **changes that lead to *detrusor instability* or decreased *compliance* are clinically associated with symptoms of frequency and urgency.** Second, the **changes associated with decreased *detrusor contractility* are associated with further deterioration in the force of the urinary stream, hesitancy, intermittency, increased residual urine,** and (in a minority of cases) detrusor failure. Acute urinary retention should not be viewed as an inevitable result of this process. Many patients presenting with acute urinary retention (AUR) have more than adequate detrusor function, with evidence of a precipitating event leading to the obstruction.

Much of our knowledge of the detrusor's response to obstruction is based on experimental animal studies. Limited information is available on the natural history of the human bladder's response to obstruction. It has been demonstrated that **the major endoscopic detrusor change, trabeculation, is due to an increase in detrusor collagen** (Gosling and Dixon, 1980; Gosling et al, 1986). Severe trabeculation is associated with significant residual urine (Barry et al, 1993), suggesting that incomplete emptying may be due to increased collagen rather than impaired muscle function. Severe trabeculation, however, is seen in fairly advanced disease. In experimental animal models **the initial response of the detrusor to obstruction is the development of smooth muscle hypertrophy** (Levin et al, 1995, 2000). It is likely that this **increase in muscle mass, although an adaptive response to increased intravesical pressure and maintained flow, is associated with significant intracellular and extracellular changes in the smooth muscle cell that lead to detrusor instability and in some cases impaired contractility.** Obstruction also induces changes in smooth muscle cell contractile protein expression, impaired energy production (mitochondrial dysfunction), calcium signaling abnormalities, and impaired cell-to-cell communication (Levin et al, 1995, 2000).

There is considerable evidence that the response of the detrusor smooth muscle cell to stress (increased load related to outlet

obstruction) is not as adaptive as the response of skeletal muscle to stress. In the latter case, a relatively normal repertoire of contractile protein genes are upregulated and an increased number of normally organized contractile units assemble in the muscle cell. In the detrusor smooth muscle cell, load-induced hypertrophy leads to a change in myosin heavy chain isoform expression (Lin and McConnell, 1994; Cher et al, 1996) and to a significant alteration in the expression of a variety of thin filament-associated proteins (Mannikarottu et al, 2005a, 2005b, 2006). Taken together, these observations strongly suggest that smooth muscle cells revert to a secretory phenotype in response to obstruction-induced hypertrophy. One consequence of this phenotypic switch is increased ECM production. The detrusor smooth muscle cell is a key contributor to the complex of symptoms associated with prostatic obstruction. Additional research in this area is required (Christ and Liebert, 2005).

In experimental animal models, unrelieved obstruction is associated with the development of significant increases in detrusor ECM (collagen) (Levin et al, 1995, 2000). This also appears to be the case in the human, although cause-and-effect relationships have not been established (Gosling et al, 1986). In addition to obstruction-induced changes in the smooth muscle cell and ECM of the bladder there is increasing evidence **that obstruction may modulate neural-detrusor responses** as well (Steers et al, 1990, 1999; Clemow et al, 1998, 2000). Altered neural control of micturition has been noted in aging rats, including reduced bladder contractility, impaired central processing, and altered sensation (Chai et al, 2000).

Independent of obstruction, aging produces some of the same changes in bladder function, histology, and cellular function (Nordling, 2002). There is suggestive evidence from animal models that atherosclerosis and the resultant chronic bladder ischemia or hypoxia induced by other mechanisms (e.g., increased bladder wall tension) may contribute to bladder pathology (Tarcan et al, 1998; Azadzoi et al, 1999, 2003, 2008; Azadzoi, 2003).

Key Points: Etiology and Pathophysiology

- The development of BPH requires an intact androgen signaling pathway, but androgens do not cause the disease.
- In the absence of obvious cellular proliferation, the hyperplastic process must be due to an imbalance between cell death and cell proliferation, leading to cell accumulation in both the epithelial and stromal compartments.
- BPH is said to be a "stromal disease," but it remains unclear whether the initiating events occur in the stromal compartment, the epithelial compartment, or both.
- BPH stroma is a complex mixture of smooth muscle cells and extracellular matrix. Much of a given patient's urethral resistance is due to the passive elastic properties of the prostate tissue that cannot be "relaxed" with α-adrenergic blockade.
- Paracrine and autocrine growth factors seem to be the primary factors that stimulate or inhibit stromal and epithelial growth.
- Inflammation, common in BPH specimens, may play a role in the pathogenesis of the disease through cytokines that promote cell growth or lead to smooth muscle contraction.
- BPH can have a familial inheritance, especially if large prostate volumes and surgical intervention as a young age are seen in the pedigree.
- The bladder's response to obstruction is only partially adaptive. Smooth muscle cells subjected to increased load undergo hypertrophy, but the phenotype of the cell changes, ECM production is increased, contractile protein expression is altered, and cell-to-cell signaling is impaired.
- Aging, perhaps through vascular mechanisms, leads to further alteration in bladder biology that in all likelihood amplifies the effects of obstruction. Prostate growth is only one component of LUTS in aging men. Physicians tend to overlook the significant contribution of aging, bladder dysfunction, nervous system changes, and systemic disease that in many cases has more impact on symptoms than the size of the prostate.

EPIDEMIOLOGY AND NATURAL HISTORY

Definitions

The study of epidemiology determines the distribution and determinants of diseases in man. From this evolve the components of descriptive epidemiology, which is the description of disease incidence, mortality and prevalence by person, place, and time, and analytical epidemiology, which is the search for determinants of disease risk that may serve to increase prospects for prevention (Oishi et al, 1989). Epidemiologists assess and compare rates of diseases within one population stratified by sex, age, and other demographic and socioeconomic parameters and between populations of different culture, ethnicity, lifestyles, and diet.

The following definitions of rates are important to understand:

- ***Incidence:*** **number of diseased people per 100,000 population per year**
- ***Prevalence:*** **number of existing cases per 100,000 population at a distinct target date**
- ***Mortality:*** **number of deaths per 100,000 population per year**
- ***Fatality:*** **number of deaths per number of diseased**

Although for highly fatal conditions (those with a high fatality and mortality rate) the incidence rate (i.e., the rate of people developing the condition in a year) is of pre-eminent interest, for conditions such as BPH, which are rather benign in their course, the prevalence rate (i.e., the number of men having the condition at a given point in time) is of greater interest.

There is no globally accepted epidemiologic definition of BPH; thus prevalence and incidence rates must be viewed in the context of the definitions chosen by the investigator reporting the data (Barry, 1990a, 1990b). The prevalence of BPH thus can be calculated based on histologic criteria (autopsy prevalence) or on clinical criteria (clinical prevalence). Because the clinical definitions vary widely, it is easier to compare the autopsy or histologic prevalence of BPH. Despite the low mortality and fatality rates for BPH in modern series a review of these data is interesting and revealing from a historical point of view.

Lastly, descriptive epidemiologic studies can be divided into cross-sectional (a population stratified by baseline parameters is assessed one single time

to determine if and how certain measures change depending on the parameter of interest) and longitudinal (a population is assessed at baseline and in regular intervals to study the changes in parameters of interest stratified by age or other demographic criteria) studies. It is obviously easier to perform cross-sectional studies owing to the cost and logistical difficulties involved with longitudinal follow-up of a cohort over time. The majority of studies addressing LUTS and clinical BPH are cross-sectional. Furthermore, there are by definition no longitudinal autopsy studies of any condition and histologically based longitudinal studies are exceedingly difficult to perform owing to the need for repetitive tissue procurement.

Descriptive Epidemiologic Studies

Histologic or Autopsy Prevalence

The definition of BPH is the presence of stromoglandular hyperplasia on a surgical specimen or in the case of autopsy series in whole prostates removed after death from men not dying of prostate conditions. The 1984 landmark study by Berry and associates (1984) summarized the data from five studies demonstrating that no men younger than the age of 30 had evidence of BPH and that the prevalence rose with each age group, peaking at 88% in men in their 80s. Figure 91–10 demonstrates the age-stratified prevalence based on several rigorously performed autopsy studies in the United States, England, Austria, Norway, Denmark, China, Japan, and India. The prevalence increases rapidly in the fourth decade of life, reaching nearly 100% in the ninth decade. It is striking that the age-specific autopsy prevalence is remarkably similar in all populations studied regardless of ethnic and geographic origin (Moore, 1943; Swyer, 1944; Franks, 1954; Karube, 1961; Harbitz and Haugen, 1972; Haugen and Harbitz, 1972; Pradhan and Chandra, 1975; Holund, 1980; Berry et al, 1984; Carter and Coffey, 1990).

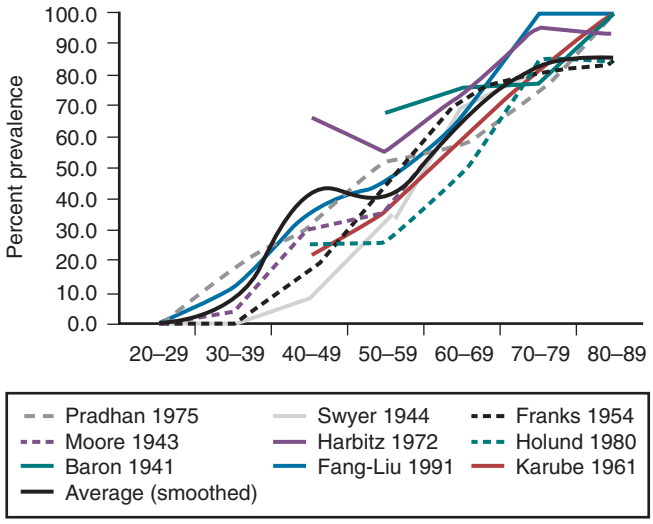


Figure 91–10. Age-stratified autopsy prevalence of histologic benign prostatic hyperplasia from different series and (smoothed) average. (Data from Moore, 1943; Swyer, 1944; Franks, 1954; Karube, 1961; Harbitz and Haugen, 1972; Haugen and Harbitz, 1972; Pradhan and Chandra, 1975; Holund, 1980; Berry et al, 1984; Carter and Coffey, 1990.)

Cross-Sectional Studies of Clinical Prevalence

Descriptive epidemiology relies on the presence of a single universally accepted definition of *disease*. The definitions of *BPH*, however, have undergone several changes in the past decade, and at present no single criterion can be applied. In the past the term *prostatism* was used, incorrectly referring to the prostate as the sole source of the typical LUTS found in aging men. Tage Hald pointed out that there are at least three inter-related phenomena that can be assessed independently, namely, the symptoms (formerly called "prostatism"), enlargement of the prostate gland, and presence of obstruction (Nielsen et al, 1994). In a given patient, all three, two of the three, or only one of the three entities might be present. **Paul Abrams coined the term *lower urinary tract symptoms* to replace the old and inappropriate term *prostatism*** (Chapple et al, 2008). **When evaluating elderly men, one can therefore stratify them by the level of LUTS into mildly, moderately, and severely symptomatic according to a standardized symptom severity and frequency questionnaire** (Barry et al, 1992a). **The same patients then can be further classified based on the degree of prostatic enlargement as measured by digital rectal examination (DRE), transrectal ultrasonography (TRUS), or magnetic resonance imaging (MRI) and lastly by the presence and degree of BOO as measured by flow rate recordings or invasive pressure flow studies.** The diagram in Figure 91–1 attempts to illustrate the difficulties in using different disease definitions. Of all men older than the age of 40, a certain proportion will develop histologic hyperplasia of the prostate, that is, BPH. Of those, some will develop LUTS, while others may have LUTS due to reasons other than BPH (e.g., overactive bladder or other bladder- and detrusor-related conditions, urethral stricture, stones, inflammation). Prostate enlargement occurs in some but again not all men with histologic BPH and LUTS, and some men with enlarged glands may not have any symptoms at all. Lastly, urodynamically proven obstruction may be present in men who have either one or several or all of histologic BPH, LUTS, and enlarged glands, whereas others yet may have obstruction without having any evidence of BPH (e.g., urethral stricture, prostate cancer, primary bladder neck sclerosis). In addition to the mere enumeration of symptoms by frequency of occurrence, the bother associated with the symptoms, interference with activities of daily living, and the impact the symptoms have on quality of life are important distinguishing characteristics.

Accordingly, when studying the prevalence of *clinical BPH* —admittedly an imprecise term describing the just-described constellation of LUTS, bother, interference, quality of life impact, with or without enlargement, obstruction, and so on—disease definitions may be applied that take either one or several of these items into consideration. For the subsequent discussion it is important to recognize that very few clear cutoff points have been established that allow differentiation between whether disease is absent or present (e.g., one might argue that a prostate volume over 30 mL constitutes clinical BPH, but others might argue for a higher or lower cutoff point with similar observations for symptoms or degrees of obstruction). **Thus, rather than describing truly the prevalence of a "disease" in populations, one can describe the distribution of certain attributes of such disease in different populations stratified by age.** Figure 91–11 illustrates the different estimates of prevalence of "disease" when different definitions are applied ranging from autopsy prevalence to a combination of clinical threshold

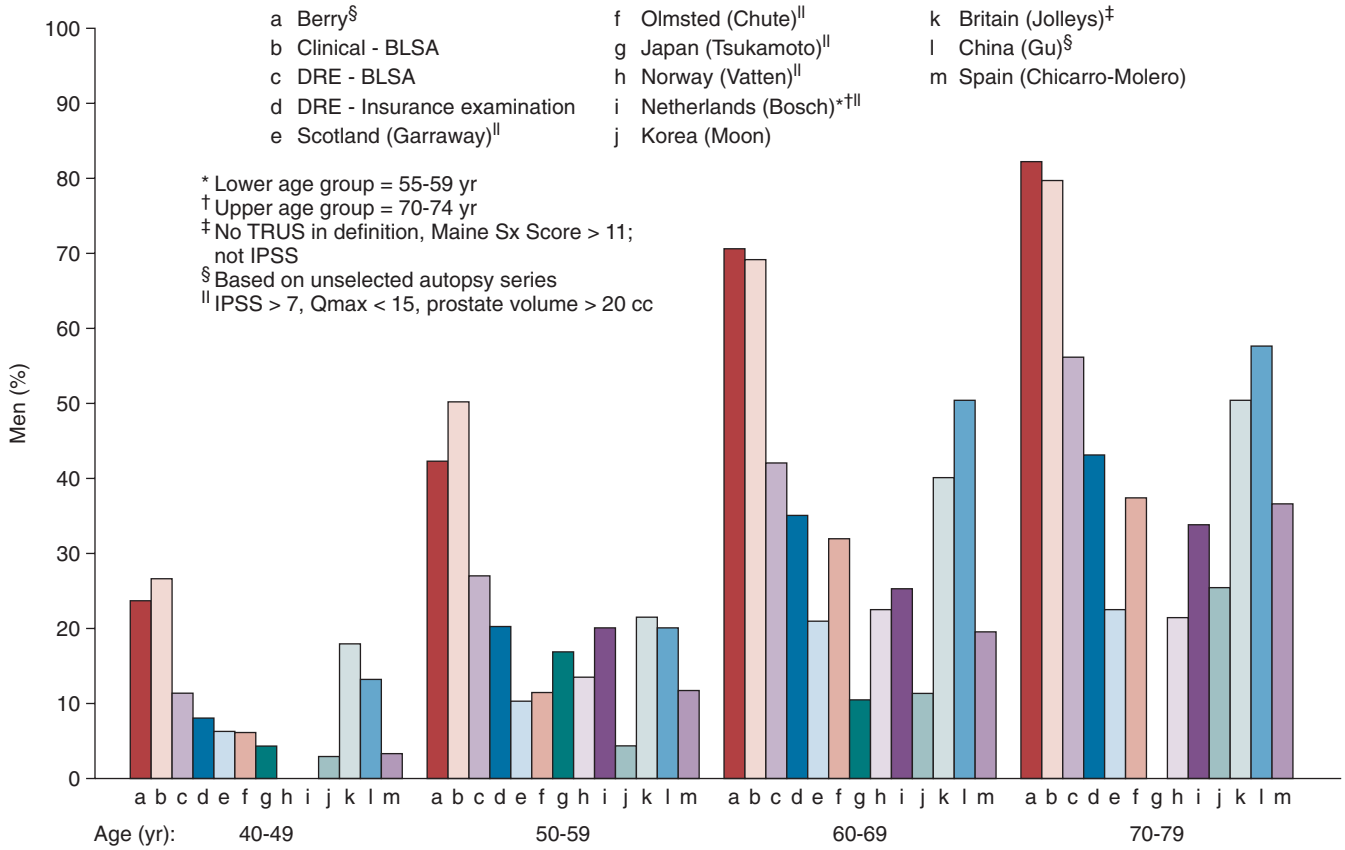


Figure 91–11. Prevalence of disease using autopsy series, clinical diagnosis, low maximum flow rate, palpable prostatic enlargement by digital rectal examination (DRE), and community-based studies. BLSA, Baltimore Longitudinal Study of Aging; IPSS, International Prostate Symptom Score; TRUS, transrectal ultrasonography. (Data from Berry et al, 1984; Garraway et al, 1991; Chute et al, 1993; Gu et al, 1994; Jolleys et al, 1994; Bosch et al, 1995a; Moon et al, 1995; Overland et al, 2001.)

parameters and insurance examination data (Berry et al, 1984; Garraway et al, 1991; Chute et al, 1993; Gu et al, 1994; Jolleys et al, 1994; Bosch et al, 1995a; Guess, 1995; Moon et al, 1995; Overland et al, 2001).

Symptom Severity and Frequency

From a pragmatic point of view, studies of symptom severity and frequency are of greatest importance in a disease that is rarely fatal and is characterized by its effect on the quality of life. The development, validation, translation with cultural and linguistic validation of the standardized, self-administered seven-item American Urological Association (AUA) Symptom Index (AUASI, also known as the International Prostate Symptom Score [IPSS]) has been a pivotal event in the clinical research of LUTS and BPH (Barry et al, 1992a, 1992b; O'Leary et al, 1992). With the total score running from 0 to 35 points, patients scoring 0 to 7 points are classified as mildly symptomatic, those scoring from 8 to 19 points as moderately symptomatic, and those scoring 20 to 35 points as severely symptomatic. The instrument is an integral part of virtually every epidemiologic study as well as treatment studies in the field, and the availability of validated translations in many common languages allows cross-cultural comparisons of unprecedented scope. Socioeconomic factors do not seem to influence responses to the questionnaire (Moon et al, 1994), and fundamentally similar responses are obtained when the questionnaire is self-administered, read to the patient, mailed in or administered in some other way (Barry et al, 1995a), or readministered in a scrambled format (Barnboym et al, 1999). However, there is no question that subtle differences in comprehension of the translated questionnaire as well as different perception of the symptoms, willingness to admit to the symptoms, acceptance of symptoms as a natural sign of aging, and other factors are at least partially the cause for cross-cultural differences in symptom severity reported in the literature. Figure 91–12 shows the prevalence of at least moderate to severe symptoms stratified by decade of life as reported in 11 cross-sectional population-based studies from around the world (Garraway et al, 1991; Chute et al, 1993; Hunter et al, 1994, 1996; Norman et al, 1994; Bosch et al, 1995a; Moon et al, 1995; Tsukamoto et al, 1995; Sagnier et al, 1996; Overland et al, 2001). A very large international investigation of LUTS in Asian men was undertaken by Homma and associates (1997), in which 7588 men from Japan, China, Taiwan, Korea, the Philippines, Thailand, Singapore, Pakistan, India, and Australia were queried. The finding of 18%, 29%, 40%, and 56% of men in their 40s, 50s, 60s, and 70s, respectively, having moderate to severe symptoms is in line with the other studies reported both from Asia and from Europe and North America. In addition to the major community-based studies listed, other studies have been published with similar findings but often done under less stringent conditions (Nacey et al, 1995; Tay et al, 1996). **Despite the significantly different proportion of men admitting to moderate to severe symptoms, a clear trend toward an increase in symptom scores with advancing age is noticeable in all reported studies.**

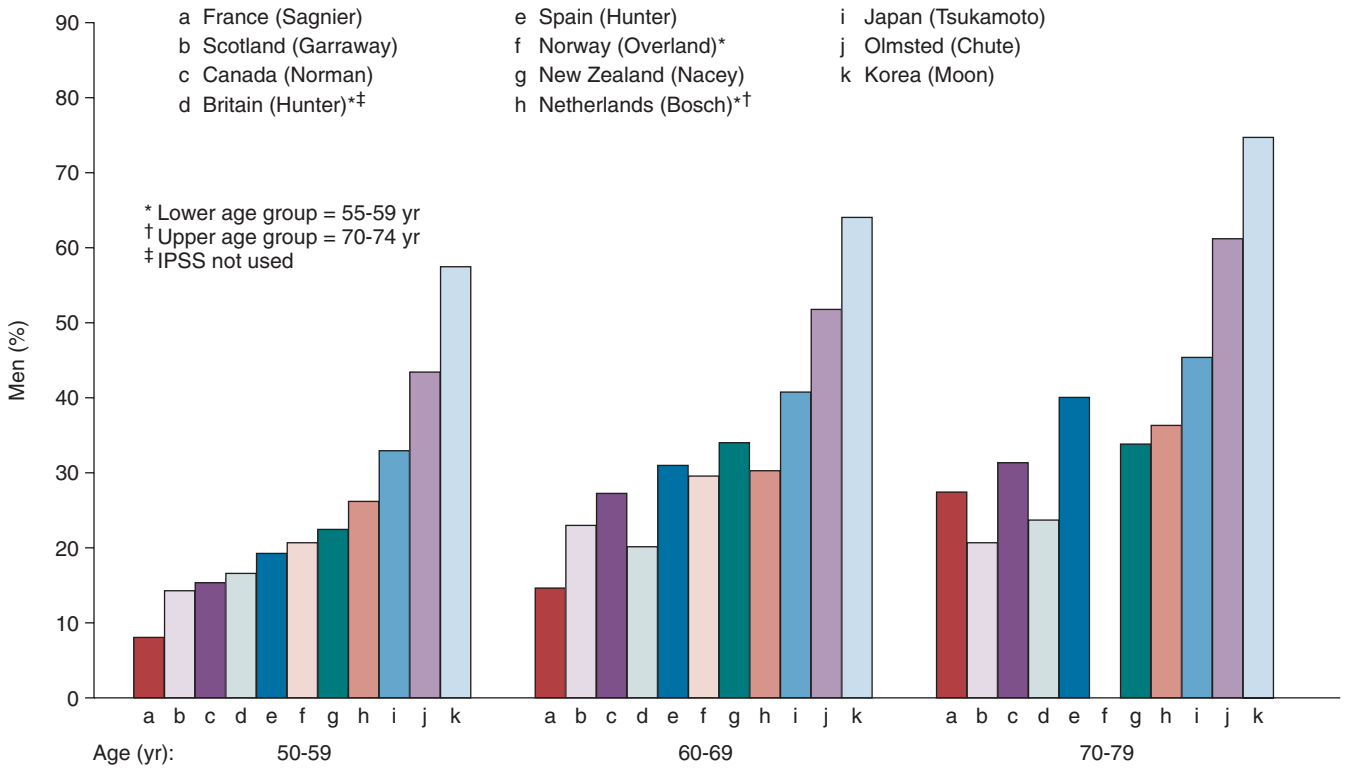


Figure 91–12. Prevalence of at least moderate to severe symptoms stratified by decade of life as reported in cross-sectional population-based studies from around the world. (Data from Garraway et al, 1991; Chute et al, 1993; Hunter et al, 1994; Norman et al, 1994; Bosch et al, 1995a. Moon et al, 1995; Tsukamoto et al, 1995; Hunter et al, 1996; Sagnier et al, 1996; Homma et al, 1997; Overland et al, 2001).

Bother, Interference, and Health-Related Quality of Life (HRQOL)

Bother and interference with activities of daily living due to LUTS are equally if not more important than the enumeration of symptom frequency and severity alone (Garraway et al, 1993b; Roberts et al, 1994b). Embarrassment due to symptoms has been found to be an important determinant in seeking medical care (Roberts et al, 1994b). LUTS and clinical BPH affect overall quality of life as measured, for example, with the Medical Outcomes Trust Short-Form (SF-36) only marginally (Hunter et al, 1995). Accordingly, several instruments were developed and validated to assess bother, interference, and the disease-specific quality of life and sexual function (Epstein et al, 1992; Barry et al, 1995b; Hansen et al, 1995; Lukacs et al, 1995; O'Leary et al, 1995; Donovan et al, 1996).

These instruments have not been as widely applied to cross-sectional descriptive epidemiologic studies as compared with the IPSS. However, as observed for symptom severity and frequency, both bother and interference scores increase with advancing age, and disease-specific HRQOL measures are significantly worse in men with higher symptom frequency and severity ratings in population-based studies done in Olmsted County in the United States, in Forth Valley in Scotland, in France, and in a small fishing village in Japan (Shimamaki-Mura) (Girman et al, 1998).

Prostate Size

Prostate size can be estimated by DRE, although the reliability across observers is in general considered poor (Roehrborn et al, 1997). A recent analysis of the PLCO trial verified the significant errors associated with the DRE-assessed prostate size (Pinsky et al, 2006). In addition, DRE tends to underestimate true prostate size as determined by TRUS or other imaging modalities. The magnitude of the underestimation increases with increasing prostate size from 25% up to 50% or more (Roehrborn et al, 1997). For the purpose of epidemiologic studies TRUS and MRI measurements are preferred, although MRI measurements are somewhat expensive when attempting cross-sectional examinations of populations. **TRUS volume measurements using the prolate ellipsoid volume formula are the most widely accepted measure of prostate volume with reasonable statistical performance characteristics, particularly when performed by a single or several well-trained examiners** (Sech et al, 2001). Three-dimensional TRUS evaluation appears to provide even more accurate measurements, although such technology is not available in urologists' offices for the most part (Giubilei et al, 2005).

In general, in all cross-sectional studies prostate volume as assessed by TRUS has been found to increase slowly but steadily with advancing age. The slight differences in the absolute volume measures and the different slopes of increase with advancing age may be caused by differences in the population examined as follows (Fig. 91–13).

A cohort of 344 men between 40 and 60 years old with no evidence of BPH enrolled in an alopecia study had baseline endorectal coil MRI measurements done (Roehrborn et al, 2000b). Mean total prostate volume (TPV) increased from 31.3, 33.7, 36.1, to 43.1 mL in increments of 5 years. MRI tends to yield prostate volume measurements approximately 10% larger compared with TRUS. A series of 100 men aged 40 to 80 years without BPH or LUTS underwent TRUS measurements of TPV and transition zone volume (TZV). TPV increased from 22.1, 29.1, 41.5, to 43.2 mL by decade, and TZV from 7.2, 9.9, 19.0, to 19.6 mL (Benaim et al, 1998). A cross-sectional study of 611 Norwegian men from 55 to 70 years of age exhibited increases in TPV from 26.5, 31.0, to

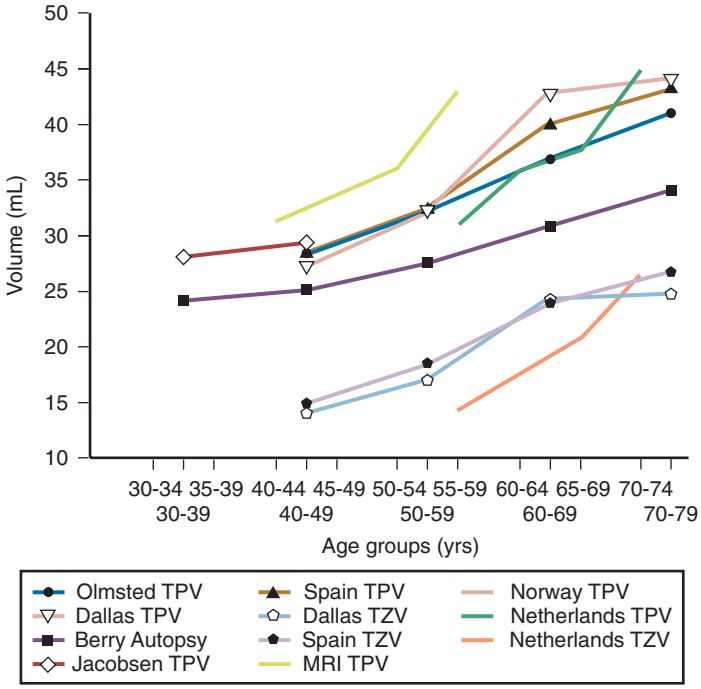


Figure 91–13. Mean estimates for total prostatic volume (TPV) and transitional zone volume (TZV) based on one autopsy series (Berry et al, 1984), one series of baseline MRI measurements in men with alopecia (Roehrborn et al, 2000b), and cross-sectional population-based studies (Torp-Pedersen et al, 1988; Oesterling et al, 1993; Bosch et al, 1994; Benaim et al, 1998; Chicharro-Molero et al, 1998; Overland et al, 2001).

32.0 mL in increments of 5 years (Overland et al, 2001), and Jakobsen and associates (1988) examined patients between 30 and 50 years by TRUS, the mean TPV being 23.9 and 25.7 mL per decade of life. TPV and TZV were assessed in 1104 men older than the age of 40 years in a Spanish cross-sectional study, yielding increases from 23.4 to 41.9 mL for TPV and from 7.9 to 21.9 mL for TZV (Chicharro-Molero et al, 1998). Finally, the baseline data from the Olmsted County study provided data on men from 40 to 79 years of age (Oesterling et al, 1993).

Overall, TPV increases in these cross-sectional studies from approximately 25 mL for men in their 30s to 35 to 45 mL for men in their 70s, whereas TZV increases from 15 mL to 25 mL for similarly aged men. The similarities between the TPV and TZV measurements done in the different studies are striking particularly when considering the different measurement methods used (see Fig. 91–13).

Measures of Obstruction

Subvesical obstruction only can be measured by invasive pressure-flow studies, whereas nonintubated free flow rates provide at best an indirect measure for the probability of obstruction being present (Abrams, 1995). **Unfortunately, no large-scale cross-sectional studies have been done employing pressure-flow studies owing to the invasive and costly nature of the test and it is unlikely that significant datasets will ever become available.**

It is commonly accepted that a maximum flow rate of less than 10 mL/sec indicates a high probability of obstruction, whereas a flow rate of greater than 15 mL/sec indicates a low probability, with the 10- to 15-mL/sec range presenting an intermediate range. The utility of this categorization is reduced by several observations. First, the maximum flow rate is somewhat dependent of the voided volume (Girman et al, 1993). This has prompted some to propose a nomogram to correct for this phenomenon; however, at present no single nomogram is accepted universally (Von Garrelts, 1956, 1957, 1958; Scott and McIlhaney, 1961; Beck and Gaudin, 1969; Susset et al, 1973; Siroky et al, 1979, 1980; Drach and Steinbronn, 1986; Haylen et al, 1998). A high degree of diurnal variability (Golomb et al, 1992) and within-subject day-to-day variability (Barry et al, 1995c) further reduces the utility of flow rate recording in defining disease.

Aging men and women experience a decrease in the maximum urinary flow rate, which is nearly linear. In the Olmsted County study the median flow rate decreased from 20.3 mL/sec for men 40 to 44 years old to 11.3 mL/sec for men 75 to 79 years old (Girman et al, 1993), and similar declines have been reported from other cross-sectional studies. When applying combined thresholds such as at least moderate symptoms of more than 7 points on the IPSS score *and* a maximum flow rate of less than 15 mL/sec, in the Olmsted County study 17% of men in their 50s, 27% of men in their 60s, and 35% of men in their 70s would fall into such category (Jacobsen et al, 1995b) versus 14.4%, 28.6%, and 38.7% of men in the respective age groups in the Spanish population-based study (Chicharro-Molero et al, 1998).

Analytical Epidemiologic Studies

Analytical epidemiologic studies address the search for determinant of a disease. Inasmuch as a clear disease definition is lacking, such a search could attempt to find determinants for LUTS, prostate growth, and/or BOO, consistent with the previously outlined concepts. The presence of functioning testes at time of puberty (hormonal factor) as a required permissive element has long been established and accepted (McConnell, 1991), and age has been shown to be the most critical determinant of all aspect of this complex entity. Numerous other demographic and environmental factors have been suggested as risk factors or contributors to the disease process. When evaluating the associations identified one has to critically ask whether other factors could contribute to the association without their being a cause-and-effect relationship. For example, it seems intuitive that the husbands and family members of nurses are more likely to seek medical care and practice preventive medicine. Therefore the detection rates of prostate cancer in a cohort of nurses' husbands might be higher not due to a truly higher incidence rate of cancer but due to an increased rate of seeking medical attention and an increase in the number of *diagnosed* cases of cancer. Such pitfalls are abundant in epidemiologic studies and have to be suspected and carefully ruled out.

Religion

The case-control study by Morrison (1978), the cohort study by Lytton and colleagues (1968), and the Normative Aging Study (Glynn et al, 1985) all revealed the Jewish religion to be associated with a higher prostatectomy rate (2.2- to 2.6-fold increase). The fact, however, that the Jewish religion is not associated with an increase in the *diagnosis* of BPH allows the speculation that Jewish patients are more likely to see a physician or to be offered surgical therapy.

Socioeconomic Factors

Araki and associates (1983) found higher rates of BPH in higher income groups, whereas, in contrast, Glynn and coworkers (1985) reported higher rates of surgery in lower income groups. One

might argue that higher income groups might have better access to health care whereas lower income groups might submit more readily to the suggestion of a surgical procedure. Education and socioeconomic status do not influence responses to the IPSS (Moon et al, 1994; Badia et al, 2001), but they do appear to influence both expectations from treatment for BPH and perception of improvement, with patients in higher income strata requiring a larger drop in symptom scores after treatment to perceive subjectively similar levels of improvement (Padley et al, 1997). This finding suggests at least some impact of socioeconomic factors if not in the growth of the prostate or measures of obstruction but likely in the perception of symptoms. Data from the Olmsted County study suggest a relationship between care-seeking behavior and physician visit and retirement status. Bivariate analysis suggested significant associations between a propensity to seek care for physical reasons and retirement (odds ratio [OR], 2.0; 95% CI, 1.1 to 2.6), age of 65 years or more (OR, 1.9; 95% CI, 1.5 to 2.4), incomplete high school education (OR, 1.6; 95% CI, 1.1 to 2.2), and an annual income of less than $25,000 (OR, 1.4; 95% CI, 1.1 to 1.9). Multivariable logistic regression analysis demonstrated that retired men were more likely to have a high propensity to seek care (OR, 1.7; 95% CI, 1.2 to 2.4), with the other variables no longer-being significant (Roberts et al, 1997a).

Recently our understanding of the impact of some socioeconomic factors on LUTS and BPH had deepened with the help of two studies, the European Prospective Investigation into Cancer and Nutrition (EPIC) and the Epidemiology of Lower Urinary Tract Symptoms (EpiLUTS), and the Boston Area Community Health (BACH) studies (Rosen et al, 2008; Kaplan et al, 2009) (Table 91–4). It is likely that the longitudinally designed BACH study with a balanced enrollment of men and women stratified by age and race/ethnicity will contribute in the future significantly to our understanding of LUTS in both men and women. A symptom-based cluster analysis was performed in both cohorts, and remarkably similar clusters of symptoms were identified, allowing for an in-depth analysis of their association with comorbidities and other factors (Rosen et al, 2008). In the BACH study, decreasing household income and increasing difficulties in paying for health care were associated with increasingly more severe symptom clusters (Hall et al, 2009).

Sexual Activity and Vasectomy

Ekman (1989) suggested that the increase in the fibromuscular stroma is a result of sexual activity, and many authors since then have attempted to find relevant associations. Morrison (1992) reported a 49% reduction in risk for prostatectomy in widowed versus single men. A similar association could not be verified by other authors. Cross-sectional data from the Olmsted County study suggest that the frequency of ejaculation has no effect on LUTS, peak urinary flow rates, or prostate volume; the apparent protective association appears to be an artifact caused by the confounding effects of age (Jacobsen et al, 2003). The decrease in

Table 91–4.

Overview of the EpiLUTS and BACH Studies

EpiLUTS	BACH
Description	
Cross-sectional, population-representative, Internet-based survey conducted in the United States, the United Kingdom, and Sweden in 30,000 (U.S., 20,000; U.K., 7500; Sweden, 2500) men and women aged 40-99 years (mean age, 56.6 years)	Population-based epidemiologic survey among 5503 randomly selected adults residing in Boston aged 30-79 years in three race/ethnic groups (2301 men, 3202 women; 1767 black, 1877 Hispanic, 1859 white respondents)
LUTS Prevalence	
1 LUTS at least sometimes: 72.3% (men), 76.3% (women) 1 LUTS at least often: 79.99% (men), 52.5% (women)	LUTS (AUASI ≥8): 18.7% (men), 18.6% (women); increased with age (10.5% for 30-39 years to 25.5% for 70-79 years), no difference by race/ethnicity (16.2%-19.3%)
Bother	
Rates of bother were lower for LUTS classified as at least "sometimes" than those classified as at least "often" However, leaking urine during sexual activity, which was reported infrequently, was highly bothersome (82.1% men; 87.2% women), whereas terminal dribble, which was reported frequently, was less bothersome (40.6% men; 40.2% women)	Mean bother scores were higher in those with LUTS (vs. no LUTS) and for women vs. men
Treatment Seeking	
Treatment seeking was low but most common in those in the voiding + storage + postmicturition subgroup: 29.1% men, 27.5% women; prescription medication use was also highest in this subgroup (17.6% and 10.4%, respectively)	Prescription medication use for urinary symptoms was low even among those with AUASI ≥8, at 9.8% (men) and 2.1% (women)
Comorbidities	
Comorbid conditions were most common in the voiding + storage + postmicturition subgroup with significant associations for LUTS with arthritis, asthma, chronic anxiety, depression, diabetes (men only), heart disease, irritable bowel syndrome, neurologic conditions, recurrent UTI, and sleep disorders; childhood nocturnal enuresis was significantly associated with most LUTS subgroups	LUTS (AUASI ≥8) was associated with heart disease, diabetes (men only), and depression

AUASI, American Urological Association Symptom Index; LUTS, lower urinary tract symptoms; UTI, urinary tract infection.

From Kaplan SA, Roehrborn CG, et al. Implications of recent epidemiology studies for the clinical management of lower urinary tract symptoms. BJU Int 2009;103(Suppl. 3):48–57.

sexual ability and frequency of sexual activity with advancing age, exactly when the prevalence of BPH increases, in fact might suggest a reverse relationship, namely, a causative effect of BPH on sexual function (Altwein and Keuler, 1992).

Recent evidence suggests a strong correlation between the severity of LUTS and impairment of sexual function, that is, erectile dysfunction (ED) as well as ejaculatory disturbances (Boyle et al, 2003; Chung et al, 2003; Rosen et al, 2003). Cross-sectional questionnaire-based data from various countries suggest that ED and ejaculatory disturbances increase with advancing age but also within each decade of life with increasing LUTS severity (Fig. 91–14). Although these correlations do not necessarily imply a causative mechanism, it is possible that similar pathophysiologic events underlie the development of both problems in the aging male, the most obvious being ischemia in both the genital and lower urinary tract organs (McVary, 2005). A logistical regression analysis of the EpiLUTS data documented as well a strong relationship between various domains of sexual and ejaculatory dysfunction and LUTS (Wein et al, 2009) (Table 91–5).

Sidney (1987) analyzed the Kaiser Permanente Database and initially found a risk ratio of 1.2 for the diagnosis of BPH among men who had a vasectomy. However, after 5 years of follow-up the risk ratio was 0.97 and not significant. There does not appear to be a relationship between vasectomy and BPH development or prostate size (Jakobsen et al, 1988); and in the Massachusetts Male Aging Study, Meigs and colleagues (2001) did not find that vasectomy increased the risk of being diagnosed with BPH.

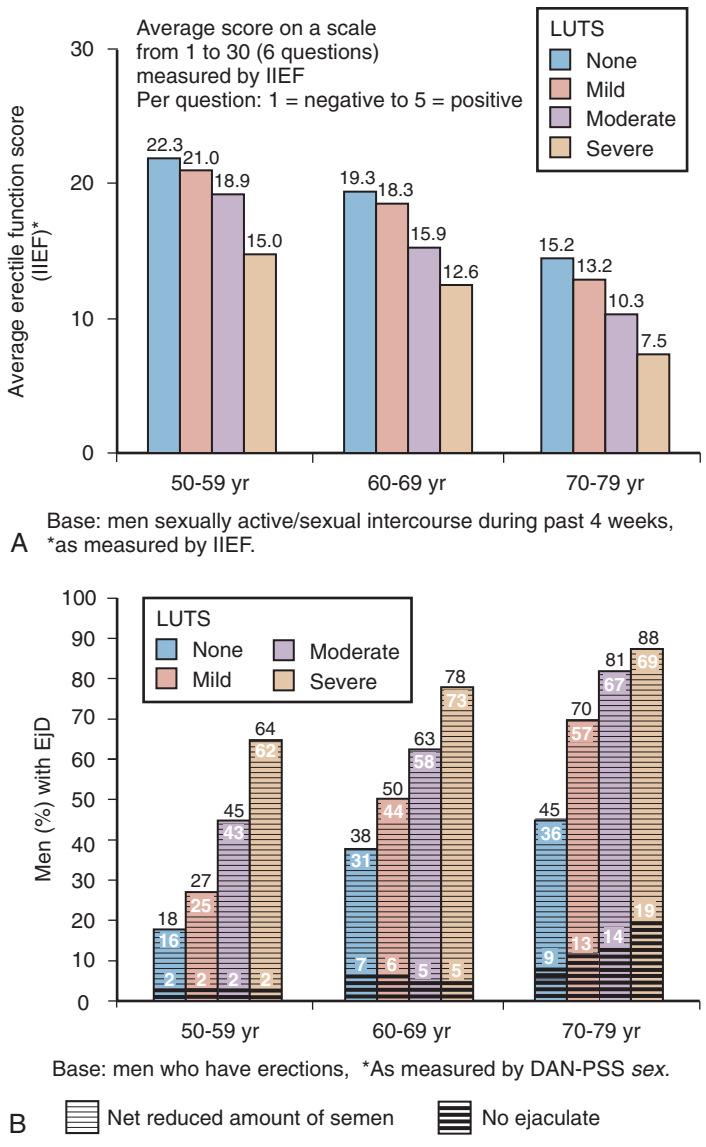


Figure 91–14. Erectile function **(A)** decreases and ejaculatory disturbances **(B)** increase with advancing age, but within each decade of life they also decrease and increase, respectively, with increasing severity in lower urinary tract symptoms (LUTS). DAN-PSS, Danish Prostatic Symptom Score; IIEF, International Index of Erectile Function. (From Rosen R, Altwein J, et al. Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male [MSAM-7]. Eur Urol 2003;44[6]:637–49.)

Alcohol and Liver Cirrhosis

Alcohol may decrease plasma testosterone levels and production and increase clearance of testosterone (Chopra et al, 1973). **Despite this hypothetical reason for a lower incidence of BPH, inverse relationships have been described.** Both Morrison (1992) and Sidney and colleagues (1991b) reported by multivariate analysis an adjusted risk ratio of 0.49 and an age-adjusted risk ratio of 0.75, respectively, for the risk of having surgery for BPH when taking in more than three glasses of alcohol per day. However, one might argue that the poorer health in heavy drinkers might bias the physician against surgery. Glynn and coworkers (1985), in fact, found no increased risk for either the clinical diagnosis or surgical rates. A recent analysis of the Prostate Cancer Prevention Trial (PCPT) showed as well an inverse relationship between a diagnosis of BPH and alcohol intake, that is, a somewhat protective effect (Kristal et al, 2008).

Of five studies examining the relationship between liver cirrhosis and BPH based on autopsy material, four found a lower prevalence of BPH in men with cirrhosis (Bennett et al, 1950; Stumpf and Wilens, 1953; Robson, 1966; Frea et al, 1987) while one study—admittedly with some design flaws—found a higher prevalence (Wu, 1942). Because most cirrhosis cases are alcohol induced, the separation of the effects of alcohol versus cirrhosis is virtually impossible.

Hypertension

The sympathetic nervous system plays via α-adrenergic fibers and receptors an important role in both hypertension and the symptoms of BPH. However, because both hypertension and LUTS/BPH increase with advancing age, it is difficult to prove a causal relationship between these two conditions (Boyle and Napalkov, 1995). The previously cited studies by Glynn and Sidney and their colleagues (Glynn et al, 1985; Sidney et al, 1991b) did not find an association. In a small clinic cohort study with methodologic flaws, Pressler and coworkers (1997) reported an increase in the incidence of hypertension from 15%, to 18% and 31% for men with mild, moderate, and severe symptoms. Autonomic hyperactivity has been implicated in the development of both LUTS and ED in the aging male, but conclusive clinical data are lacking (McVary et al, 2005). In the EpiLUTS study both heart diseases and hypertension were associated with more severe LUTS constellations (Coyne et al, 2009). Further studies are needed to better understand the common underlying pathophysiologic mechanisms and a potential cause-and-effect relationship.

Smoking

Smoking cigarettes appears to increase both testosterone and estrogen levels owing to the nicotine level and thus

Table 91–5.

Logistic Regression of Decreased Sexual Enjoyment and Activity as Well as Predictors of Erectile Dysfunction (ED), Ejaculatory Dysfunction (EJD), and Premature Ejaculation (PE)

COVARIATES	DECREASED SEXUAL ENJOYMENT	SEXUAL ACTIVITY	ED (IIEF-EF < 21)	EJD	PE
Demographic			+†	+†	–†
Age					
BMI					
Hispanic vs. white					
Black vs. white					
Asian vs. white					
Other vs. white		+*			
Sweden vs. U.S.			–†		
U.K. vs. U.S.					
LUTS					
Weak stream	+†	+†	+†		
Split stream	+*		+†		
Intermittency					+*
Hesitancy					
Straining					
Terminal dribble					+*
Perceived frequency	+*	+*			
Nocturia					
Urgency					
Urgency with fear of leaking	+*		+*	+*	
Urgency incontinence					
SUI (laugh/cough)	–*				
SUI (physical activity)					
Leak for no reason		+*			
Other leaking					
Nocturnal enuresis					
Leak during sex	+†	+†	+*	+*	
Incomplete emptying	+†	+*			+*
Postmicturition incontinence					
Dysuria	+*	+†	+*		
Bladder area pain	+†				+*
Pain during sex	+†	+†			
Comorbid conditions					
Heart disease		+†			
Hypertension			+†		
Diabetes			+†		
Prostate cancer	+†	+†		+†	
Bladder cancer	+†	+†			
Prostatitis	+†	+*			-†‡
Depression			+†	+†	
Neurologic conditions					
Concordance index	0.86	0.86	0.77	0.73	0.62

–, negative values for point estimates; +, positive values for point estimates.
BMI, body mass index; LUTS, lower urinary tract symptoms; SUI, stress urinary incontinence.
*$P < .01$
†$P < .001$.
‡Not having a history of prostatitis is associated with premature ejaculation.
From Wein AJ, Coyne KS, et al. The impact of lower urinary tract symptoms on male sexual health: EpiLUTS. BJU Int 2009;103(Suppl. 3):33–41.

should have a positive and inductive effect on the development of BPH. However, because severe smoking causes other health problems, surgery rates are probably a poor indicator for a possible correlation because physicians are biased against surgery in heavy smokers. Seitter and Barrett-Connor (1992) indeed found no correlation between smoking and prostatectomy rates, and Glynn and colleagues (1985) failed to identify a correlation between smoking and the clinical diagnosis of BPH. Sidney and associates (1991b) followed 16,000 men over 15 years and found a negative correlation between being a smoker at baseline and subsequent risk of prostatectomy. Daniell (1993b) examined the records of 345 patients who underwent prostatectomy and found smaller gland volumes in smokers and a lower age-adjusted prevalence of ever-smokers compared with a control group. Roberts and associates (1994a) examined this issue in the Olmsted County study and later (1997b) in a Japanese population. In the Olmsted County study only 16% of the more than 2000 men were current smokers, which appears low but understandable considering the population mix in Rochester, Minnesota. A biphasic association was found, with light to moderate smokers being less likely to have moderate to severe LUTS and heavy smokers at least the same risk as never smokers.

A recent update from the Olmsted County study suggests that smoking is associated with decreased urinary flow rates and moderate to severe symptoms but not with enlarged prostate volume or increasing serum PSA (Rule et al, 2005). This is in contrast to earlier studies suggesting a relationship between smoking and prostate size (Kupeli et al, 1997). In EpiLUTS an ex-smoker had an increased risk of having more severe symptom constellations and a man who had never smoked had a decreased risk, while the risk for a current smoker was not a factor (Coyne et al, 2009).

Any relationships between current or past smoking and LUTS/BPH are likely to be weak and of limited clinical significance.

Physical Activity, Diet, Obesity, Body Mass Index (BMI), and the Metabolic Syndrome

Chyou examined 33 food items in relationship to prostatectomy rates and found only beef intake significantly associated (Chyou et al, 1993). Araki and associates (1983) reported increased clinical diagnosis of BPH in men with higher milk consumption and lower consumption of green and yellow vegetables. **Overall there is no convincing evidence for any individual diet factor to play a major role in the development of LUTS/BPH.**

The relationships between LUTS/BPH and obesity, BMI, and the metabolic syndrome have recently been of great interest (Hammarsten et al, 1998, 1999, 2001; Rohrmann et al, 2005; Gupta et al, 2006; Kasturi et al, 2006). Metabolic syndrome is a clinical constellation of metabolic abnormalities, including obesity, glucose intolerance, dyslipidemia, and hypertension that increases the risk of cardiovascular disease and results primarily from modifiable risk factors, particularly physical inactivity and dietary practices endemic to Westernized societies (Haffner and Taegtmeyer, 2003). **There are plausible biologic considerations: adipose tissue is the main source of aromatization of testosterone to estrogen, and men with lower BMI have higher serum testosterone levels** (Eldrup et al, 1987).

BMI was negatively associated with surgically treated BPH in the Kaiser Permanente cohort study (Sidney et al, 1991b), and with a clinical diagnosis of BPH in the normative aging study (Glynn et al, 1985). In contrast, in a study of 68 men the average prostate weight increased both with age and with increasing obesity together with an increase in serum estradiol levels (Soygur et al, 1996). Daniell (1993a) also found larger adenomas in more obese men undergoing prostatectomy. Both latter studies report a positive correlation between obesity and prostate size, but none between obesity and symptom severity. Several caveats must be mentioned: DRE is less likely to yield a diagnosis of BPH and prostate enlargement in very obese patients owing to anatomic obstacles, and patients with high BMI may be biased against surgical interventions.

Men aged 40 to 75 years who were participants in the Health Professionals Follow-up Study and who were without prior diagnosis of cancer or prostatectomy provided data on weight, height, and waist, and hip circumferences. After adjustment for age, smoking, and BMI, abdominal obesity was related to prostatectomy (OR = 2.38) and with frequent urinary symptoms among those without prostatectomy (OR = 2.00). BMI, hip circumference, and waist-to-hip ratio were not associated with BPH independently of waist circumference. **These results suggest that abdominal obesity in men may increase the frequency and severity of urinary obstructive symptoms and may increase the likelihood that such obese men will undergo a prostatectomy** (Giovannucci et al, 1994).

Hammarsten and Hogstedt (1999) examined 250 patients with LUTS and found non–insulin-dependent diabetes mellitus, hypertension, tallness, obesity, high insulin level, and low high-density lipoprotein cholesterol levels to be risk factors for the development of BPH. They suggest a causal relationship between high insulin levels and the development of BPH and hypothesize increased sympathetic nerve activity in men with BPH. In a hospital-based case-control study being overweight was modestly inversely related to BPH. The hypothesis of reduced testosterone levels in obese individuals may explain the different BPH risk and need to be tested (Zucchetto et al, 2005). Parsons (2007) performed a comprehensive literature review and found factors that potentially increase the risk of BPH and LUTS include obesity and diabetes whereas factors that potentially decrease the risk include increased physical activity and moderate alcohol consumption (Table 91–6). Parsons and Kashefi (2008) performed also a comprehensive literature review and found eight studies (n = 35,675) were eligible for a pooled analysis to study the effect of physical activity levels stratified into light, moderate, and vigorous categories, with a sedentary category for reference. Compared with the sedentary group, the pooled ORs for BPH or LUTS were 0.70, 0.74, and 0.74 for men engaging in light, moderate, and heavy physical activity, respectively. Physical activity thus appears to reduce the risks of BPH and LUTS. Similar findings of increased likelihood of LUTS with increasing BMI and decreasing likelihood with greater physical activity were also reported from the EpiLUTS study (Coyne et al, 2009).

The evidence at present suggests a positive relationship between lack of physical activity, obesity, BMI, and other measures of the metabolic syndrome and both LUTS and BPH (including prostate volume), whereas increased physical activity appears to have a protective effect.

Medications

Very limited information is available. **Cold medications containing α-sympathomimetic drugs exacerbate LUTS by the expected effect on the smooth muscles of the bladder outlet. Recently a careful analysis of the data from the Olmsted County study demonstrated that daily use of antidepressants, antihistamines, or bronchodilators is associated with a 2- to 3-point increase in the IPSS compared with age-matched nonusers and daily use of antidepressants is associated with a decrease in the age-adjusted flow rate** (Su et al, 1996).

Correlations between Parameters

As noted, all relevant parameters such as symptom severity and frequency, bother, interference, disease-specific HRQOL, maximum flow rate, and prostate volume tend to worsen with advancing age. However, reported correlations between these parameters as well as urodynamic pressure-flow studies are in general weak, with some exceptions. Strong correlations exist as one might expect between subjective measures such as symptom severity and frequency (IPSS score), bother, disease-specific HRQOL, and interference scores (Barry et al, 1995b; Girman et al, 1999) (Fig. 91–15).

Weak numerical correlations can arise artifactually, regardless of whether true physiologic relationships exist (Girman, 1998). Correlations are further affected by intraindividual variability of measured parameters, day-to-day variability, measurement errors

Table 91–6.

Cohort Studies of Modifiable Risk Factor Associated with Decreased or Increased Risk of LUTS and/or BPH

Decreased Risk of BPH and LUTS			
STUDY	OUTCOME MEASURE (RISK FACTOR)	REFERENCE CATEGORY	OR (95% CI)
Health Professionals Follow-up Study	Clinical BPH:		
	Alcohol intake 30.1-50 g/day	Alcohol intake 0 g/day	0.59 (0.51-0.70)
	Walking ≥ 2 hr/wk	Walking 0 hr/wk	0.73 (0.63-0.84)
Massachusetts Male Aging Study	Clinical BPH (physical activity 862 kcal/day or greater	Physical activity 140 kcal/day or less	0.50 (0.3-0.9)
PLCO	Clinical BPH (alcohol intake 60 g/day or greater)	Alcohol intake <5 g/day	0.60 (0.5-0.7)
	TURP likelihood (alcohol intake ≥60 g/day)	Alcohol intake <5 g/day	0.40 (0.3-0.7)
	Nocturia (alcohol intake ≥60 g/day)	Alcohol intake <5 g/day	0.80 (0.7-1.0)
NHANES III	LUTS:		
	Alcohol intake ≥1 drink/day	Never	0.59 (0.36-0.97)
	Physical activity >6 times/wk	Physical activity 0 times/wk	0.49 (0.29-0.84)
Increased Risk of BPH and LUTS			
STUDY	OUTCOME MEASURE (RISK FACTOR)	REFERENCE CATEGORY	OR (95% CI)
BLSA	LUTS:		
	Diabetes	No diabetes	2.80 (1.10-7.10)
	Fasting glucose >110 ng/dL	Fasting glucose ≤110 ng/dL	2.60 (1.01-6.70)
	Prostate ≥40 mL:		
	BMI >35 mg/kg^2	BMI <25 kg/m^2	3.52 (1.45-8.56)
	Diabetes	No diabetes	2.25 (1.25-4.11)
	Fasting glucose >110 ng/dL	Fasting glucose ≤110 ng/dL	2.98 (1.70-5.23)
Flint Men's Health Study	LUTS:		
	Diabetes	No diabetes	1.95 (1.49-2.57)
	Hypertension	No hypertension	1.29 (1.04-1.61)
Health Professionals Follow-up Study	BPH surgery (waist circumference >109 cm)	Waist circumference <89 cm	2.38 (1.42-3.99)
	LUTS (waist circumference >109 cm)	Waist circumference <89 cm	2.00 (1.47-2.72)
Hunt-2	LUTS:		
	BMI 40 mg/kg^2 or less	BMI less than 25	1.79 (0.90-3.56)
	Diabetes	No diabetes	1.25 (1.04-1.49)
	Waist/hip ratio 0.94 or less	Waist/hip ratio 0.85 or less	1.32 (1.15-1.50)
NHANES III	LUTS:		
	Diabetes	No diabetes	1.67 (0.72-3.86)
	Hypertension	No hypertension	1.76 (1.20-2.59)
	Increase in BMI between age 25 yr + highest BMI ever	No increase	1.90 (0.89-4.05)
	Waist circumference >102 cm	Waist circumference <94 cm	1.48 (0.87-2.54)

BMI, body mass index; BPH, benign prostatic hyperplasia; CI, confidence interval; LUTS, lower urinary tract symptoms; OR, odds ratio; TURP, transurethral resection of the prostate.

From Parsons JK. Modifiable risk factors for benign prostatic hyperplasia and lower urinary tract symptoms: new approaches to old problems. J Urol 2007;178(2):395–401.

associated with the technique or equipment, or the natural history of the condition itself (Bruskewitz et al, 1982; Diokno et al, 1992; Barry et al, 1995c; Sagnier et al, 1996).

It is furthermore crucial to consider the population utilized to evaluate correlations. A correlation is easier identified if patients exhibiting the full spectrum of the parameters of interest are included. In most LUTS/BPH studies, however, patients are excluded based on thresholds imposed, making it more difficult for a significant correlation to emerge. There are many examples in clinical medicine in which weak numerical correlations exist but strong clinical relationships are well accepted (Wilson and Cleary, 1995).

The absence of meaningful baseline correlations for symptoms, flow rate, and prostate volume in a tightly controlled population of men with LUTS and BPH enrolled in a BPH treatment study is shown in Table 91–7.

An example of how restriction of the full range of parameters affects correlations is shown in Figure 91–16. Volunteers without known prostatic diseases were asked to fill in an AUASI score and perform a flow rate test. When all data are considered a clear relationship exists, with the maximum flow rate decreasing with increasing symptom severity ($r = 0.4$; $P < .05$). However, when only considering those patients typically seen in a BPH study, namely, with a score above 10 points and a maximum flow rate between 5 and 15 mL/sec, the correlation within that cohort exhibiting a limited range of observation on both scales is very weak ($r = 0.08$; not significant [NS]), and the regression line becomes flat.

The correlations observed between symptoms, flow rate and prostate volume in true community-based population studies without artificially imposed entry criteria are consequently somewhat higher than those seen in BPH clinic or trial populations. In the Olmsted County study, after adjusting for age, the odds of moderate to severe symptoms were 3.5 times greater for men with prostatic enlargement (>50 mL) than for men with smaller prostates, whereas the odds were similarly increased (2.4-fold) for men not achieving a peak urinary flow rate of 10 mL/sec (Girman et al, 1995). Men with enlarged prostates were about twice as likely to have bother due to symptoms (OR 2.4) or activity interference (OR

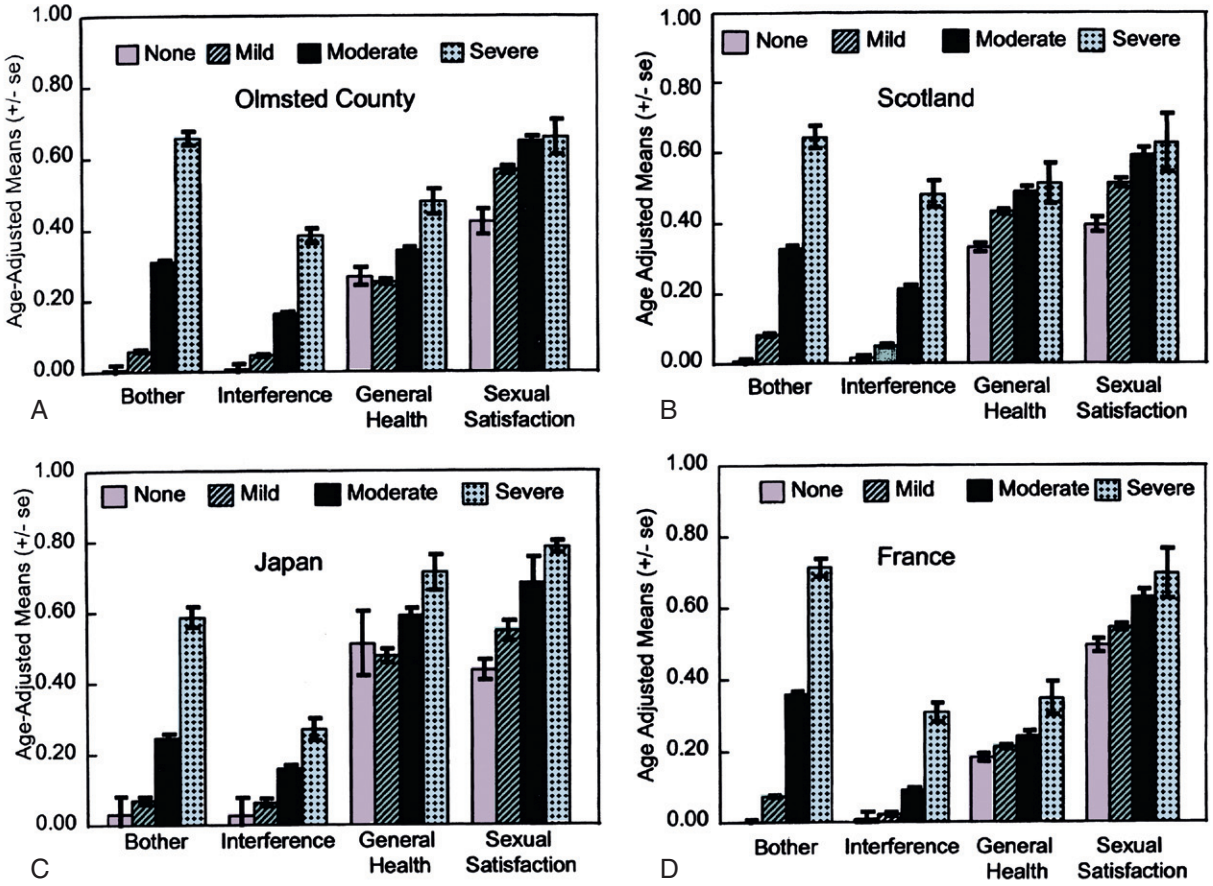


Figure 91–15. **A-D,** Age-adjusted means of disease-specific HRQOL measures after transformation to a 0 to 1 scale stratified by levels of symptom severity and frequency (IPSS score). (From Girman CJ, Jacobsen SJ, et al. Health-related quality of life associated with lower urinary tract symptoms in four countries. Urology 1998;51[3]:428–36.)

Table 91–7.

Correlation Table between Baseline Parameters in a BPH Treatment Study of 2800 Men Older Than Age 50 Years, an IPSS Score >12, Peak Flow Rate (Qmax) <15 mL/sec, Serum PSA between 1.5 and 10 ng/mL, and TPV >30 mL (TZV Not Specified)

	PSA	QMAX	IPSS	TPV	TZV
Age	0.092	–0.078	–0.069	0.152	0.154
	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
PSA		–0.031	–0.016	0.384	0.352
		0.111	0.423	<0.0001	<0.0001
Qmax			–0.117	–0.059	–0.047
			<0.0001	<0.001	<0.05
IPSS				0.020	0.005
				0.293	0.761
TPV					0.775
					<0.0001

BPH, benign prostatic hyperplasia; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen; TPV, total prostate volume; TZV, transition zone volume.

Note the lack of strong correlations except for age and serum PSA versus volume between parameters.

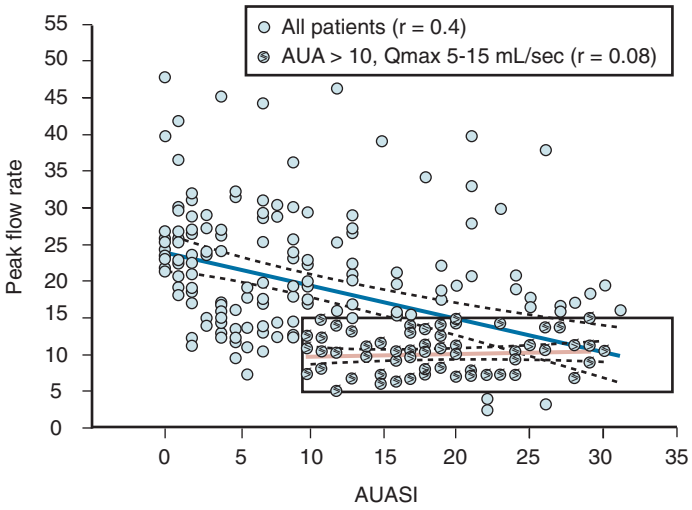


Figure 91–16. Correlation and regression (95% confidence interval) between symptom score and maximum flow rate in volunteers (r = 0.4; $P < .05$). When only those volunteers are considered with a symptom score above 10 points and a flow rate between 5 and 15 mL/sec (Ⓢ), the correlation is virtually absent (r = 0.08; NS) as indicated by a flat regression line *(black)*. AUASI, American Urological Association Symptom Index.

1.8) relative to men with smaller prostates (Girman et al, 1999). In a similar study from the Netherlands, Bosch and colleagues (1995a) reported numerically weak but statistically significant correlations between the IPSS and total prostate volume (r = 0.19, $P < .001$), peak flow rate (r = –0.18, $P < .001$), and postvoid residual urine volume (r = 0.25, $P < .001$).

Although weak correlations between prostate volume and symptoms as well as flow rate have been accepted, recently attention focused on correlations between the transition zone of the prostate and physiologic measures. A stronger correlation between transition zone and symptoms (r = 0.48, $P = .03$), and peak urine flow (r = –0.34, $P = .05$) was reported first by Kaplan and colleagues (1995), who also showed a significant correlation between transition zone index (TZV/TPV) and symptoms (r = 0.75), peak urine flow (r = –0.71), and—somewhat unexpectedly—detrusor pressure at peak urine flow (r = 0.43). These data were generated from a relatively small cohort of 61 men with BPH. Invasive pressure-flow studies are not performed in community-based studies, and thus comparative data from population-based studies cannot be reviewed. However, the finding of a relationship between measures of obstruction and prostate volume is rare, with most authors denying such relationship in series of BPH clinic or trial patients (Bosch et al, 1995c; Yalla et al, 1995; Ezz el Din et al, 1996; Witjes et al, 1997; d'Ancona et al, 1998; Homma et al, 1998; Kuo, 1999; Steele et al, 2000). Data from the Olmsted County study suggest no stronger correlation between symptoms and peak flow rates with transition zone volume (r = 0.17, $P = .001$ and r = –0.20, $P < .001$, respectively) than with total volume (r = 0.16, $P < .001$ and r = –0.16, $P < .001$, respectively). The transition zone index weakly correlated with AUASI score (r = 0.08, $P = .103$) and peak urinary flow rate (r = –0.08, $P = .0823$) (Corica et al, 1999). In a large BPH treatment trial the TZV also did not correlate stronger with other measures compared with the TPV.

The correlation between serum PSA and prostate volume, both total and transition zone, has recently been described in greater detail (Roehrborn et al, 1999b, 1999c). Although the individual variability is significant, precluding an accurate prediction of prostate volume by serum PSA in individual patients, there is a strong log linear relationship between these parameters that can be shown in both population-based as well as clinical studies (Hochberg et al, 2000; Morote et al, 2000; Hedelin et al, 2005). The relationship is further influenced by patients' age, with older patients having a greater increase in prostate volume per unit of serum PSA (Fig. 91–17). In Asian men similar relationships exist; however, in general both prostate volume and serum PSA tend to be smaller/lower (see Fig. 91–17B) (Gupta et al, 2005). Relationships between other PSA-derived parameters have been examined, and certain subforms of PSA (BPSA) have been shown to be stronger related to BPH compared with total serum PSA values (Canto et al, 2004).

With the exception of age, correlations between various measures of LUTS and BPH are modest in community-based population studies and weak in BPH clinic and trial populations. The relationship between serum PSA and prostate volume is moderate and influenced by age and race and ethnic origin. Neither symptoms nor flow rate nor prostate volumes measures can predict presence and degree of obstruction reliably.

Natural History of Untreated Benign Prostatic Hyperplasia

The natural history of a disease process refers to the prognosis of the disease over time. In other words, the measurement of changes in parameters of interest and the incidence rates of significant outcomes constitute what is commonly referred to as the natural history of a disease. It is important for clinicians to gain as good an understanding as possible of the natural history of any illness, because the benefits and risks of any therapeutic interventions should always be balanced with the risks involved in just watching the disease (i.e., the natural history). In fact, the degree to which natural history must be studied depends on the seriousness of the disease, as well as the risks involved with the therapeutic

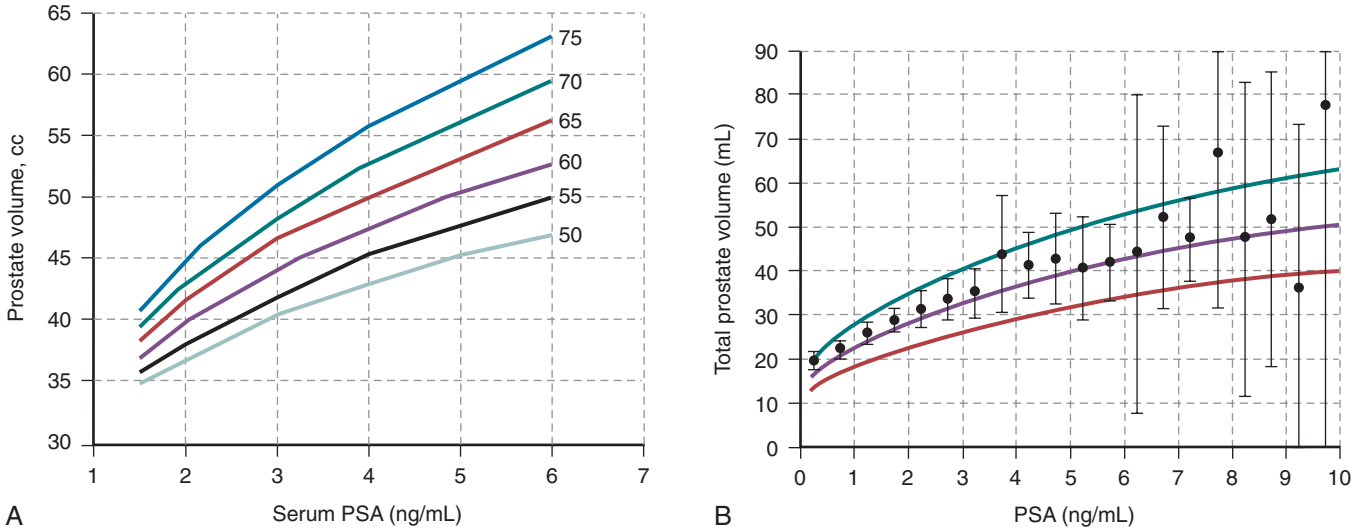


Figure 91–17. Prediction of prostate volume based on serum prostate-specific antigen (PSA) stratified by age in white men **(A)** and in Japanese men **(B)**. **(A,** From Roehrborn CG, Boyle P, Gould AL, Waldstreicher J. Serum prostate-specific antigen as a predicator of prostate volume in men with benign prostatic hyperplasia. Urology 1999;53:581–9. **B,** From Gupta A, Aragaki C, Gotoh M, et al. Relationship between prostate specific antigen and indexes of prostate volume in Japanese men. J Urol 2005;173:503–6.)

intervention. For example, it proves to be crucial to understand the natural history of abdominal aortic aneurysms and how their prognosis is determined by their size, to adequately counsel patients regarding surgical interventions, which have considerable risks in themselves.

Clinical Parameters and Outcomes of Interest

Table 91–8 lists the beneficial and harmful changes in measurable parameters and outcomes, which are of interest in both the natural history and treatment of LUTS and BPH. They may be divided further into direct or biologic and indirect or proxy outcomes (Eddy, 1990, 1992). The biologic or direct outcomes are those that are immediately noticeable by the patients (e.g., symptom changes, infections, death), whereas the indirect or proxy outcomes are not directly noticeable but may predict future changes in direct outcomes (e.g., changes in pressure-flow parameters may predict episode of retention). The parameters and outcomes are dichotomous (yes or no, e.g., retention or no retention), categorical (grades of severity, e.g., grades of obstruction measured by pressure-flow studies), or continuous (scales of severity, e.g., symptom score, maximum flow rate). Accordingly, the most common ways to measure such outcomes are probabilities or rates of occurrences for dichotomous or categorical outcomes and measures of central tendency (mean or median) and variability (standard deviation [SD] or standard error [SE] or confidence intervals [CI]) for outcomes measured by continuous scales.

Table 91–8.

Beneficial and Adverse Changes in Parameters and Outcomes

BENEFICIAL CHANGES		HARMFUL CHANGES	
Probability of symptom improvement	D	D	Probability of symptom worsening
Magnitude of symptom improvement	D	Co	Magnitude of symptom worsening
Magnitude of bother improvement	D	Co	Magnitude of bother worsening
Magnitude of quality of life improvement	D	Co	Magnitude of quality of life worsening
Flow rate improvement	I	Co	Flow rate worsening
Residual urine volume reduction	I	Co	Residual urine volume increase
Prostate size reduction	I	Co	Prostate size increase
Pressure flow parameter improvement	I	Co	Pressure-flow parameter worsening
		Ca	
	D	D or Ca	Urinary incontinence
	D	D or Ca	Erectile dysfunction
	D	D	Acute urinary retention
	D	D	Need for treatment/ surgery
	D	D or Ca	Hematuria
	D	D	Urinary tract infection
	D	D	Bladder stones
	D	D	Bladder diverticula
	D	D or Ca	Detrusor failure
	D	D or Ca	Upper tract obstruction/ deterioration
	D	Co	Azotemia/renal failure
	D	D	Death

Left center column: D, Direct/biologic; I, Indirect/proxy outcome.
Right center column: D, Dichotomous; Ca, Categorical; Co, Continuous outcome.

Methods of Studying Natural History of Benign Prostatic Hyperplasia

The natural history of BPH can theoretically be evaluated by studies of a variety of designs:

- Longitudinal studies of untreated cohorts of men diagnosed with LUTS and clinical BPH by any definition *(watchful waiting cohorts).*
- Studies of the behavior of men diagnosed with LUTS and BPH and enrolled in controlled studies of LUTS and BPH *(control groups)* and receiving:
  no treatment (compared with active intervention)
  placebo treatment (compared with medical treatment)
  sham treatment (compared with device or surgical treatment)
- Longitudinal studies of unselected (i.e., undiagnosed) men living in the community who are less likely to progress and request or require therapy *(longitudinal population-based studies).*

There are problems associated with any of the approaches. Concerning the *watchful waiting cohorts,* the first question to be resolved is whether it is ethical (or feasible) to enroll symptomatic men in such a study even if the disease studied is not fatal. Secondly, the very fact that the patients had an initial contact and presumably subsequent contacts with health care providers in the course of the study will bias them, leading to changes in outcome parameters of interest presumably different from those observed in an age-matched cohort of men similar in all parameters at baseline but who did not choose to participate (a cohort one might call in analogy to genetic language "wild type"). Furthermore, many diagnosed men will in the course of such natural history study become more and more symptomatic and desire and receive treatment, making them ineligible to further participate in the study and thus reducing the number of men available for analysis. Last, a very important bias is introduced by the fact that patients in such cohorts are selected based on thresholds imposed by inclusion and exclusion criteria. In general, patients are selected to participate who are more symptomatic, that is, those with higher symptom scores and lower maximum flow rates. By the principle of trial conduct patients then repeat the symptom and flow rate assessment during follow-up (or after treatment). However, the same inclusion/exclusion criteria are not applied to the follow-up measurements, which leads to a unilateral regression to the mean, suggesting (falsely) an improvement in the parameter of interest.

To determine the effect that the stringency of pretrial screening has on the outcome of placebo treatment, a cohort of 145 volunteers were invited to fill in the IPSS score and perform a flow rate recording twice within a month without receiving any therapy or instructions whatsoever (Sech et al, 1998). Although many patients experienced either an increase or a decrease in both parameters, the mean values did not change significantly (IPSS 12.1 vs. 11.7 points, peak flow rate 17.7 vs. 17.4 mL/sec; NS). However, when typical BPH trial conditions were applied and only those patients considered for analysis who had an IPSS score above (>7, >10, >15) and a flow rate below a certain threshold (<15, <12, <10 mL/sec), a unilateral regression to the mean took place, by which the "more" symptomatic volunteers (i.e., patients) experienced still considerable natural variability on the occasion of the second assessment but the net effect was toward "improvement," that is, lower scores and higher flow rates. For example, when only considering patients with IPSS scores greater than 10 points, the mean difference between first and second assessment was

Table 91–9.

Mean ± Standard Deviation (SD) and Range for American Urological Association Symptom Index for Test No. 1 and Test No. 2, Mean Difference between the Two Tests, and the 95% Confidence Interval (CI) for the Difference, for All Subjects and for Subjects Censored Based on Test No. 1 >7 Points, >10 Points, and >15 Points

SELECTION		MEAN ± SD	RANGE	MEAN DIFFERENCE 95% CI	T-TEST	N
All subjects	No. 1	12.1 ± 8.8	0-32	–0.39	0.133	145
	No. 2	11.7 ± 9.0	0-32	–1.1 to 0.29		
>7 at No. 1	No. 1	17.8 ± 6.5	9-32	–0.97	0.035*	88
	No. 2	16.8 ± 7.7	0-32	–2.0 to 0.08		
>10 at No. 1	No. 1	19.9 ± 5.6	11-32	–1.1	0.036*	70
	No. 2	18.9 ± 6.9	0-32	–2.2 to 0.1		
>15 at No. 1	No. 1	22.0 ± 4.6	16-32	–1.4	0.026*	54
	No. 2	20.6 ± 6.6	0-32	–2.8 to 0.01		

*Statistical comparison between test No. 1 and No. 2 by t-test.
Note the reduction in the number of patients available for follow-up due to censoring that affects the power of the statistical test.
From Sech SM, Montoya JD, et al. The so-called "placebo effect" in benign prostatic hyperplasia treatment trials represents partially a conditional regression to the mean induced by censoring. Urology 1998;51(2):242–50.

between 19.9 versus 18.8 points or –1.1 ($P < .05$). Similarly, when only patients with a peak flow rate less than 12 mL/sec were considered, the mean difference between the first and second assessment was 9.3 versus 10.9 mL/sec or +1.6 mL/sec ($P < .01$) (Table 91–9).

This experiment clearly illustrates that a unilateral regression to the mean induced and controlled by the stringency of the inclusion criteria can result in a significant "improvement" in any parameter for which a threshold is set at the baseline screening. Such purely mathematical effect is likely at work in many if not all studies in which the outcome parameters are measured using a numerical scale of some sort and when baseline screening criteria are applied.

Control groups of men being randomized to receive either no treatment or placebo or sham treatment while being compared with a matched group of men receiving active therapeutic interventions also suffer from a variety of biases. As the *watchful waiting cohorts,* they have initial and constant contact with health care providers, they know from the design of the study that they are randomized to the perceived less effective or ineffective arm, and thus may have a lower threshold than community-dwelling men to cross over to active therapy. On the other hand, owing to a sense of obligation, they may elect to be observed until the trial is over and then choose an active treatment. They are also subject to the regression to the mean bias discussed earlier because they were subjected to inclusion/exclusion criteria.

***Longitudinal population-based studies,* although difficult and expensive to conduct, are likely the best vehicle to understand the natural history of the disease.** The regression to the mean bias does not apply, because the participants are not selected based on inclusion and exclusion thresholds. Because no formal diagnosis is established, the natural history may take place unencumbered by preconceived notions about symptoms, end points of trials, and anything else leading to a bias in a watchful waiting cohort of diagnosed and thus labeled men or in a control group of diagnosed men. One must, however, realize, that the very need to monitor the natural history, that is, the need to ask questions and perform tests and interventions, conflicts with the notion of the "natural history," and thus some biases are likely to be unavoidable even in the most ideal setting.

Watchful Waiting Studies

Observing cohorts of men diagnosed with LUTS and/or BPH conservatively *(watchful waiting cohort)* was attempted by some investigators in the past, but the few published reports are of limited scientific rigor and informational value and have significant shortcomings. Inclusion and exclusion criteria are poorly defined, follow-up and compliance are poor, assessment instruments are either not defined or insufficient, and patient accounting is incomplete. The studies provide answers regarding the probability of symptom changes and the magnitude of flow rate changes.

Five such studies were reported between 1919 and 1988 with a total enrollment of 456 patients and a follow-up ranging from 3 to 6 years (Clarke, 1919; Craigen et al, 1969; Birkhoff et al, 1976; Ball et al, 1981; Kadow et al, 1988). A change in symptom status was reported for all 456 patients, whereas none of the studies utilized a quantitative symptom severity scale. Data on urinary flow rate and residual urine were available for 223 and 197 patients, respectively. The peak urinary flow rate deteriorated in 66% and improved in 20%. Residual urine increased (35%), decreased (37%), and remained unchanged (28%) in about the same number of all patients. The mean change in peak flow rate (in those patients for whom data are available) was +2.2 (from a mean of 9.0 to 11.2) mL/sec or 24%, whereas the mean change in residual urine was +37 (from a mean of 115 to 152) mL or 32%. Data on symptom improvement were reported as a dichotomous outcome (improved vs. not improved). **The mean probability for any improvement in symptom severity in these studies is 42.5% (90% CI 30.8 to 54.8) as calculated by meta-analytical methods** (Eddy and Hasselblad, 1992).

A superior approach, namely, to follow a *no treatment control group* of men diagnosed with LUTS and BPH, was chosen by Wasson and coworkers (1995). **A total of 556 men with moderate symptoms and a Madsen-Iversen symptom score between 10 and 20 points (0-27 point scale) were randomized to either undergo transurethral resection of the prostate (TURP) or be watched conservatively.** There were 47 treatment failures (defined as death, recurrent infection, residual urine volume more than 350 mL,

Table 91-10.

Extended Follow-up Treatment Outcomes by Intention to Treat in the Veterans Affairs Cooperative Study Comparing Watchful Waiting with TURP

OUTCOME	TURP N = 280†	WATCHFUL WAITING N = 276†	RELATIVE RISK‡	*P* VALUE
Treatment failure	28	58	0.476	.0004
Death	16	12	1.311	.562
Urinary retention	1	9	0.110	.011
High residual	5	19	0.259	.003
Azotemia*	3	2	1.479	1.000
Bladder stones	0	1		.496
Incontinence	4	8	0.493	.259
High symptom score	1	13	0.076	.0008
Lost to follow-up	16	18	0.876	.726
Withdrawal of consent	57	36	1.561	.023
Prostate cancer	24	11	2.151	.035

*Azotemia defined as doubling of baseline creatinine value or greater than 3.0 mg/dL.

†High symptom score defined as 21 or greater on two consecutive measurements or 24 or greater on one measurement.

‡Relative risk of TURP to watchful waiting.

TURP, transuretheral resection of the prostate.

From Flanigan RC, Reda DJ, Wasson JH, et al. 5-Year outcome of surgical resection and watchful waiting for men with moderately symptomatic benign prostatic hyperplasia: a Department of Veterans Affairs cooperative study. J Urol 1998;160(1):12–6; discussion 16–7.

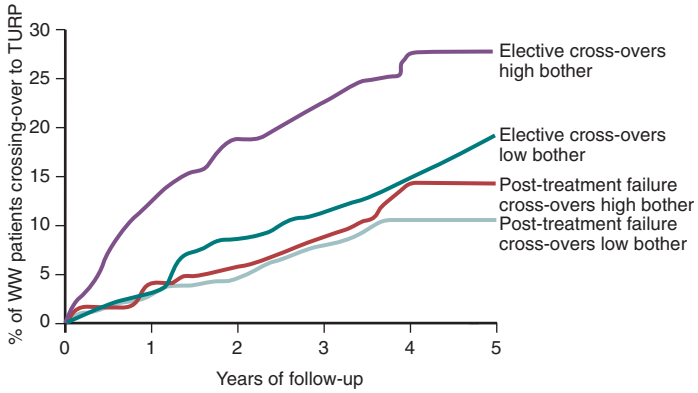


Figure 91–18. Percent of patients crossing over from watchful waiting (WW) to transurethral resection of the prostate (TURP) by baseline bother scores and elective versus post-treatment failure protocol dictated. (From Flanigan RC, Reda DJ, et al. 5-Year outcome of surgical resection and watchful waiting for men with moderately symptomatic benign prostatic hyperplasia: a Department of Veterans Affairs cooperative study. J Urol 1998;160[1]:12–6; discussion 16–7.)

development of bladder calculus, incontinence, a symptom score of 24 or higher, or a doubling of serum creatinine level from baseline) in the watchful waiting study arm (N = 276) versus 23 in the surgery study arm (N = 280) over 3 years of follow-up (relative risk 0.48; 95% CI 0.3 to 0.77). Sixty-five (24%) men assigned to watchful waiting underwent surgery during follow-up, 20 of them for treatment failure. The majority of these men were classified as having more bother at baseline, and about 40% of patients in this category experienced an improvement in the degree of bother from urinary difficulties, a proportion strikingly similar to the overall estimate of 42.5% from the natural history studies. At 3 years of follow-up the patients randomized to watchful waiting who did not fail or cross over to surgery had a small but noticeable improvement in nearly all outcomes measured including a +0.4 mL/sec increase in the maximum flow rate. More recently a 60-month update was reported providing data on 966 patient-years of follow-up on the TURP patients and 990 patient-years on the watchful waiting patients (Flanigan et al, 1998). The treatment failure rate was 21% for the watchful waiting and 10% for the TURP groups, and all outcomes were better for the TURP-treated patients (Table 91–10). During follow-up, 76 (27%) of watchful waiting patients crossed over to TURP, and the 5-year Kaplan-Meier estimate of the crossover rate was 36% and twice as many patients crossed over electively as compared with post-treatment failure protocol dictated crossover. **The most significant factor predicting elective crossover was high baseline bother due to urinary symptoms** (Fig. 91–18). When separately analyzed, the patients crossing over from watchful waiting to TURP had fewer improvements in outcome parameters compared with those randomized to TURP initially (Table 91–11). In many instances the differences between the groups were statistically and clinically significant. A reduction in symptom score by –11 points (high baseline symptom group) and an improvement in maximum flow rate by 8.7 mL/sec (low baseline flow rate group) after TURP is expected; however, in those men undergoing TURP after an unsuccessful trial of watchful waiting the improvements were only –8 points and +4.7 mL/sec. **This allows the speculation that during the period of watchful waiting before crossover some irreversible damage might have occurred preventing symptom and flow rate improvements to the same level as observed in those men initially treated by TURP.**

Djavan and colleagues (2004) followed a group of 397 men presenting to a urology clinic with mild LUTS, defined as scoring less than 8 points on the IPSS. These men were followed for 4 years beginning with a watchful waiting protocol and were re-evaluated every 3 months for 48 months. The cumulative incidence of clinical progression defined as worsening of the IPSS with migration from mild to moderate (IPSS 8 to 18 points) or severe symptoms (IPSS 19 to 35 points) was assessed. The likelihood of migrating or transitioning from one health state to another was 6%, 13%, 15%, 24%, 28%, and 31% at 6, 12, 18, 24, 36, and 48 months, respectively.

Placebo and Sham Control Groups in Randomized Trials

Data from *control groups treated with placebo or sham* and compared with matched groups of patients treated with medications or devices are available to address many of the parameters and outcomes of interest.

Placebo Control Groups

For the Guidelines for the Diagnosis and Treatment of BPH published by the Agency for Health Care Policy and Research in 1994, data on 1417 patients treated in 45 placebo arms of placebo-controlled trials were analyzed (McConnell et al, 1994). **Table 91–12 allows a direct comparison between the watchful waiting studies discussed earlier and these placebo groups, both summarized by meta-analytical techniques.** For none of the examined

Table 91-11.

Changes from Baseline to 60 Months of Follow-up for Patients Initially Randomized to TURP (1), Randomized and Remaining on Watchful Waiting (2), and Those Randomized to Watchful Waiting but Crossing Over to TURP at Some Point during Their Follow-up (3)

	GROUP	HIGH BASELINE	LOW BASELINE
Symptom score	1	–11.0*†	–7.7*†
	3	–8.0‡	–6.2‡
	2	–5.8	–2.2
Maximum flow rate	1	4.6†	8.7*†
	3	2.9‡	4.7‡
	2	–2.2	2.2
Residual urine	1	–100*†	–19
	3	–81‡	–24
	2	–50	–7
Bother score	1	–34.9†	–14.7†
	3	–42.3‡	–7.2
	2	–10.7	1.6

*P value group 1 vs. group 3.
†P value group 1 vs. group 2.
‡P value group 3 vs. group 2.
TURP, transurethral resection of the prostate.
From Flanigan RC, Reda DJ, Wasson JH, et al. 5-Year outcome of surgical resection and watchful waiting for men with moderately symptomatic benign prostatic hyperplasia: a Department of Veterans Affairs cooperative study. J Urol 1998;160(1):12–6; discussion 16–7.

Table 91–12.

Comparison of Outcomes after Watchful Waiting and Placebo Treatment

OUTCOMES	WATCHFUL WAITING	PLACEBO
Total no. of patients	456	1417
Probability for flow rate increase	19.7%	35.8%
Probability for no change in flow rate	14.2%	41.1%
Probability for flow rate decrease	66.1%	23.1%
Mean pre- and post-treatment flow rate (mL/sec)	9.0-11.2	9.1-9.7
Difference (mL/sec) and percent change	+2.2/+24.4%	+0.6/+6.6%
Probability for decrease in residual urine	35.0%	38.0%
Probability for residual urine to remain unchanged	28.0%	26.1%
Probability for increase in residual urine	37.0%	35.9%
Mean pre- and post-treatment residual urine (mL)	115-152	87-76
Difference (mL) and percent change	+37/+32.2%	–11/–12.6%
Probability for symptom improvement	41.7%	41.7%
Probability for symptoms to remain unchanged	25.8%	53.5%
Probability for symptom worsening	32.4%	4.7%
Mean probability for symptom improvement*	41.7%	41.7%
90% CI for symptoms improvement*	30.8-54.8%	26.3-65.1%

*Calculated by confidence profile method using hierarchical Bayes (Eddy and Hasselblad, 1992).
CI, confidence interval.
Modified from McConnell, JD, Barry MJ, et al. Benign prostatic hyperplasia: diagnosis and treatment. Clinical practice guideline no. 8. Rockville (MD): U.S. Department of Health and Human Services, Agency for Health Care Policy and Research, Public Health Service; 1994. p. 1–17.

parameters a significant difference between the two treatment modalities can be identified. However, several points deserve discussion. As opposed to the longer-term follow-up in the watchful waiting studies, the placebo studies are part of short- to mid-term medical treatment trials ranging from 3 days to 52 weeks in duration (mean 13 weeks). In all these studies the patients are blinded as to the treatment arm and thus have in most cases at least a 50:50 (or better in case of 2:1 or 3:1 randomization) chance of receiving an active drug. Dropping out of such studies because of failure does not have the same ramification as it has in watchful waiting studies in which the patients willingly assumed a conservative treatment approach knowing that it might fail (i.e. they might fail and go on to active treatments). In contrast, in some placebo-controlled studies a promise—either tacit or openly—is made stating that after the conclusion of the trial the patient would be eligible for either "free" active treatment or would be "moved up" on the surgical waiting list (this phenomenon is unique to those studies conducted in the United Kingdom). The inactive preparation given should theoretically add to the placebo effect and thus improve the outcome above those noted for watchful waiting studies. The probability for a patient to experience improvement, however, is estimated to be about 40% in the uncontrolled watchful waiting studies, the randomized watchful waiting versus TURP study, and the combined placebo arms. The changes in peak flow rate and residual urine volume are similar and similarly small for these three groups as well. **It becomes evident that 40% of patients report some improvement, and the minimal fluctuation of peak flow rate and residual urine represent the "placebo effect" background against which the more substantial changes in these parameters achieved by active treatment modalities must be seen.**

Sham Control Arms of Device Treatment Trials for Benign Prostatic Hyperplasia

In recent years a multitude of minimally invasive device treatments for BPH have been developed and tested in randomized, sham-controlled, open, single, or even double-blinded trials. Although the majority of these trials compare various types of heat treatments (transrectal or transurethral hyperthermia or thermotherapy) with a sham treatment, one investigator compared balloon dilation with "sham" cystoscopy alone in a randomized, double-blinded trial involving 33 men with BPH (Lepor et al, 1992b).

The outcomes of the balloon dilation versus cystoscopy trial, one multicenter trial using transrectal or transurethral hyperthermia in comparison with a sham control (Abbou et al, 1994), and five transurethral microwave thermotherapy (TUMT) trials and their respective sham control arms can be used for analyses (Blute et al, 1993; Ogden et al, 1993a, 1993b; Bdesha et al, 1994; De la Rosette et al, 1994). Although the mean pretreatment severity score differs from trial to trial, the mean improvements in symptom severity in the sham groups ranged from 5.2% to 15.6% (on a 100% scale) while the active thermotherapy treated patients had improvements ranging from 27.0% to 37.8%, or in most cases twice the improvement as the sham control. The multicenter hyperthermia trial represents the exception, in that the actively

treated cohort has an improvement similar to the sham control, which is well within the range of the other sham control trials. The changes in peak urinary flow rate follow a similar pattern. With few exceptions the changes in peak flow rate are either very modest improvements or deteriorations (0.5, 0.6, –0.2, –1.0 mL/sec), while the active treatment arms report substantial improvements with the exception of the hyperthermia trial.

Placebo/Sham Effect and Baseline Symptom Severity

An area of considerable interest is the question to what degree the placebo/sham effect depends on the baseline status of the patients. This could pertain to baseline symptom severity, baseline bother, quality of life, baseline flow rate, and all other imaginable parameters. Although few investigators have thus far reported data stratified by baseline parameters, results from a multicenter, placebo-controlled, 12-month α-adrenergic blocker trial (terazosin [Hytrin]) can be analyzed (Roehrborn et al, 1996). Although the active drug–treated cohort has almost twice the improvement within each stratum, the placebo-treated patients had improvements ranging from 1.4 points (4.6%) to 7.5 points (21.4%) in order of increasing baseline severity score. The placebo improvement for the placebo cohort overall was 3.3 points (10.6%).

A similar increase in the placebo effect with increasing baseline symptom severity has been reported for patients treated with finasteride in phase 3 trials (Gormley et al, 1992). It might be speculated that the baseline symptom severity may also affect the sham effect seen in device trials. **This phenomenon might be due to increased expectations in patients with more severe baseline symptoms or simply due to a regression to the mean.**

Natural History and Disease Progression in Long-Term Placebo Groups

The distinction between changes in parameters and rates of outcomes observed in *placebo and sham control groups* versus the *longitudinal population-based studies* becomes blurred when the placebo control is carried out over a period of time long enough to allow natural history changes to take place and confound the situation.

The Proscar Long-Term Efficacy and Safety Study (PLESS) followed a cohort of more than 3000 men with moderate symptoms and enlarged prostate glands randomized to treatment with finasteride, 5 mg, daily versus placebo over 4 years (McConnell et al, 1998). In most control arms, both placebo and sham, the combined placebo effect interfering with the natural history of the disease is maintained for the entire duration of the study. In this 4-year trial, however, both the mean symptom score and mean maximum flow rate slowly drifted back to baseline after a typical initial placebo response (McConnell et al, 1998). The changes occurring in measurable parameters after the initial placebo effect has taken place thus can be considered to represent the natural history of the disease. The rates of outcomes such as AUR or surgery, as well as changes in prostate volume, which are less or not at all susceptible to the placebo effect, are also valid measures of the natural history of the disease.

The almost 1500 men in the placebo arm of this trial allowed for a detailed analysis of the placebo response and the subsequent natural history stratified by baseline parameters. It had been shown that in men with BPH there is a relatively strong correlation between prostate volume and serum PSA. In PLESS only 10% of patients underwent baseline and yearly volume measurements by endorectal coil MRI. Based on the assumption that serum PSA would be a good proxy parameter for prostate volume, the analysis was initially performed for serum PSA and based on all 1500 men treated with placebo.

When stratifying the population by serum PSA into tertiles, or thirds, of patients with PSA levels from 0 to 1.3, 1.4 to 3.2, and 3.3 to 10 ng/mL, three distinctly different patterns regarding symptom score and maximum flow rate changes emerge (Fig. 91–19) (Roehrborn et al, 1999a). Whereas the initial placebo response in the lowest PSA tertile for both symptom and flow rate was maintained over the entire 4 years of follow-up, the middle tertile experienced a slow deterioration of symptoms back to baseline and in essence the natural history and progression of disease negated any flow rate gains. In the highest PSA tertile the symptom score increased steadily over time following an initial placebo response by –1.5 points. Over the subsequent years the score increased by 0.5 points/yr, bringing it at the end of the study back to the original baseline level. The initial response in terms of flow rate improvement was completely negated by the progression/natural history after 2 years, and at the end of the study this group of patients registered a net worsening of the flow rate by a mean of –1.0 mL/sec (see Fig. 91–19B). Similar results regarding the changes in symptom and maximum flow rate over time were obtained when the 150 patients for whom prostate volume measurements were available were divided into tertiles (14 to 41 mL,

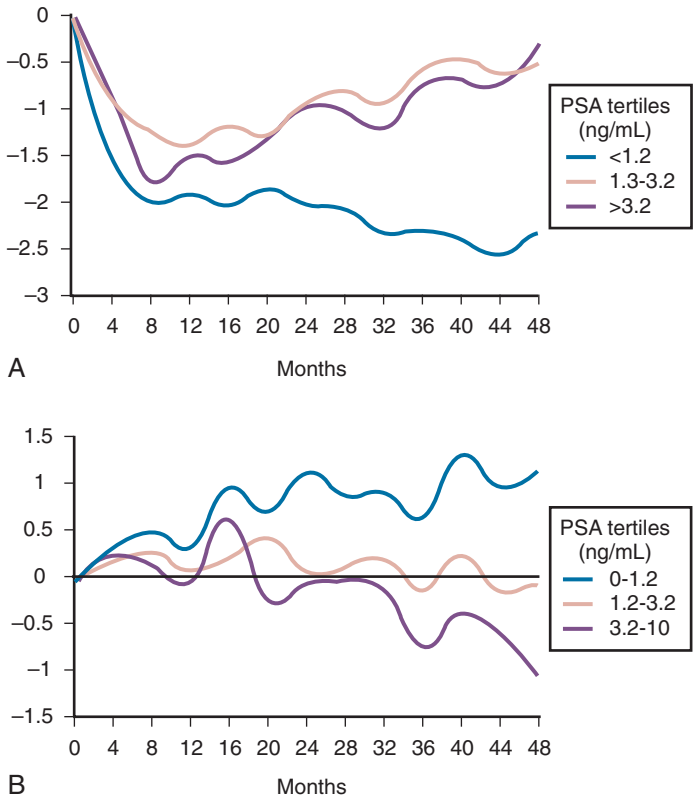


Figure 91–19. Mean changes for symptom **(A)** and peak flow rate **(B)** in placebo-treated patients in Proscar Long-Term Efficacy and Safety Study study stratified by baseline serum prostate-specific antigen (PSA) levels. (From Roehrborn CG, Boyle P, et al. Serum prostate-specific antigen (PSA) is a reliable surrogate for prostate volume. Urology 1999;53:581–9.)

42 to 57 mL, 58 to 150 mL). The PLESS study also assessed periodically bother due to urinary symptoms, disease-specific quality of life, aspects of sexual function, and sense of well-being. Surprisingly, serum PSA at baseline also predicts after an initial placebo response the rate of deterioration of bother, quality of life, and certain aspects of sexual function (Bruskewitz et al, 1999) (Fig. 91–20).

The Medical Therapy of Prostatic Symptoms (MTOPS) study followed 3045 men treated with either placebo versus doxazosin (Cardura) versus finasteride versus combination therapy for 4 to 5 years and was designed as a progression study (Bautista et al, 2003; McConnell et al, 2003). The composite end point captured either a worsening of 4 points or more on the IPSS score verified twice within 4 weeks, AUR, socially unacceptable incontinence, recurrent urinary tract infection, or renal insufficiency due to BPH (Table 91–13). The worsening of 4 points or more was chosen to reflect a clinically meaningful worsening of LUTS symptomatology. Despite an overall numerical improvement in the IPSS by –4.9 points in the placebo group (intention to treat cohort), about 14% of placebo-treated patients experienced a verified worsening by 4 points or more over the course of the study for an incidence of 3.6/100 patient-years.

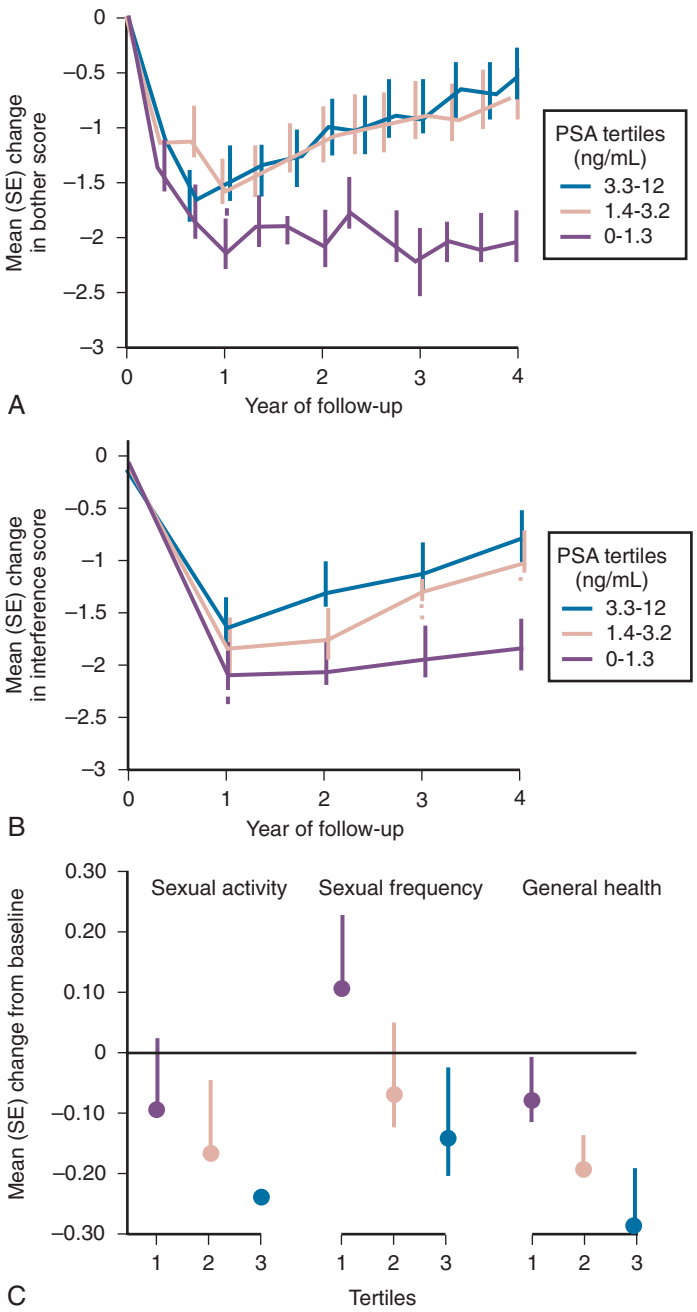


Figure 91–20. Mean changes for bother (**A**), interference with activities of daily living (**B**), and for sexual activity, frequency, and perception of general health (**C**) in placebo-treated patients in Proscar Long-Term Efficacy and Safety Study study stratified by baseline serum prostate-specific antigen (PSA). SE, standard error. (From Bruskewitz R, Girman CJ, et al. Effect of finasteride on bother and other health-related quality of life aspects associated with benign prostatic hyperplasia. PLESS Study Group. Proscar Long-term Efficacy and Safety Study. Urology 1999;54[4]:670–8.)

The PLESS study and its placebo-control group allowed the study of natural history and disease progression in a cohort selected for moderate symptoms and other evidence of disease (in contrast to a population-based study) on the background of the initial combined placebo responses. In MTOPS, approximately 14% of placebo-treated patients experienced a worsening of 4 or more points in the IPSS over 4 years of follow-up.

Relationship between Placebo/Sham Effect and Perception of Improvement

Barry and colleagues (1995d) **reported an important observation by assessing the relationship between changes in the AUASI score and patients' global rating of improvement in over 1200 men treated in a medical treatment trial for BPH. They noted that a mean decrease in AUASI score of 3.1 points was associated with a slight improvement; however, this relationship was strictly dependent of the baseline value. For patients to perceive a slight, moderate, or marked improvement, increasing drops in the AUASI score were required with increasing baseline symptom severity.** For patients starting with a lower

Table 91–13.

Clinical Progression of BPH in Placebo-Treated Patients in MTOPS

EVENT	RATE OVER DURATION OF STUDY	CUMULATIVE NUMBERS OF EVENTS AT 4 YEARS	CUMULATIVE INCIDENCE (95% CI) AT 4 YEARS
Clinical progression overall	4.5	122	17 (14-20)
≥4 points IPSS increase	3.6	97	14 (11-17)
Acute urinary retention	0.6	18	2 (1-4)
Socially unacceptable incontinence	0.3	6	<1 (0-1)
Urinary tract infections	0.1	1	<1 (0-1)
Renal insufficiency due to BPH	0.0	0	0
Invasive therapy due to BPH	1.3	37	5 (3-7)

BPH, benign prostatic hyperplasia; CI, confidence interval; MTOPS, Medical Therapy of Prostatic Symptoms.

From McConnell J, Roehrborn CG, et al. The long-term effects of doxazosin, finasteride and the combination on the clinical progression of benign prostatic hyperplasia. N Engl J Med 2003;349(25):2385–96.

versus higher baseline score, the drop had to be –7.4 versus –15.3 points, respectively, to perceive a marked improvement, –4.0 versus –8.7 for a moderate improvement, –1.9 versus –6.1 for a slight improvement, –0.2 vs –2.0 for no improvement, and +3.3 versus +1.2 for worsening to be perceived.

Longitudinal Population-Based Studies

Diokno and coworkers (1992) **provided estimates of the prevalence, incidence, and remission of LUTS in 803 community-dwelling men 60 years or older.** The annual incidence of prostate surgery was 2.6% and 3.3% during years 1 and 2 of follow-up. The prevalence of at least one symptom was 35%, with annual incidence rates during years 1 and 2 of follow-up as 16.4% and 16.1%. Remission was also noted in that 22.9% of those having severe symptoms at baseline were asymptomatic at follow-up. Table 91–14 details the changes in symptom severity from one survey to the next. **The tendency for fluctuation and spontaneous remission of symptoms as well as the regression to the mean become evident from an analysis of these data.**

Garraway and coworkers conducted a study of LUTS in four villages in the Forth Valley in Scotland in men 40 to 79 years old, defining BPH as a prostate volume of over 20 mL by TRUS and a maximum flow rate of less than 15 mL/sec and applying a lower threshold to the symptom severity (Garraway et al, 1993a, 1993b; Guess CG et al, 1993; Tsang and Garraway, 1993). By this definition the prevalence of BPH increased at baseline from 14% in men in their 40s to 43% in men in their 60s, and about one half of men reported interference with activities of daily living due to LUTS and BPH. One- and 3-year follow-up data have been reported (Lee et al, 1996). **From baseline to 3 years the proportion of men with moderate symptoms increased from 34% to 45% and significant increases in symptom level occurred for 8 of 12 symptoms queried as well as for the AUASI (increase from 6.37 to 7.88 from baseline to year 3, *P* < .0001)** (Lee et al, 1996). **Parallel to symptom frequency and severity, bothersomeness of symptoms increased over time** (Fig. 91–21) **and the proportion of men reporting interference with two or more activities increased from 26% to 41%, with three or more activities from 18% to 27%, and with four or more activities from 15% to 18%. This study clearly demonstrated LUTS and BPH being a progressive disease, albeit with a very flat slope of progression.**

The most informative natural history study to date is the Olmsted County Study of Urinary Symptoms and Health Status Among Men, which has given us much information about prevalence and severity of urinary symptoms, bother, worry and embarrassment, quality of life due to symptoms, and the relationship between symptoms and other parameters such as flow rates, prostate volume, and PSA (Oesterling et al, 1993; Girman et al, 1994, 1995; Guess et al, 1995; Jacobsen et al, 2003; Sarma et al, 2003; Rule et al, 2005).

With continued follow-up of this cohort, data have emerged regarding the longitudinal changes in symptoms and flow rate over time in this population-based study. Of 904 men reporting none to mild symptoms (AUASI, 0 to 7 points) at baseline, 118 reported moderate to severe symptoms (AUASI, > 7 points) at 18 months and 196 did so at 42 months follow-up (Jacobsen et al, 1995a). However, 47 men who had developed moderate to severe symptoms at 18 months had none to mild symptoms at 42 months. At 42 months of follow-up an average increase in the IPSS of 0.18 (95% CI 0.13 to 0.24) points per year of follow-up was recorded. **The average annual symptom score slope and variability in slope increased with patient age at baseline from a mean of 0.05 ± 1.06 (standard deviation) per year among men in their 40s to 0.44 ± 1.35 per year for men in their 60s and decreased to 0.14 ± 1.42 per year for men in their 70s** (Jacobsen et al, 1996). **More recently, 92-month data showed an annual change of 0.34 point/yr, with 31% of all men reporting at least a 3-point increase. The greatest annualized increase was observed in men in their 60s with 0.6 point/yr** (Rhodes et al, 2000).

In addition, 6-year follow-up data on peak flow rate measurements in a subset of about 500 men showed a median peak urinary flow rate slope decrease of –2.1% per year (25th percentile –4.0, 75th percentile –0.6). Peak urinary flow rate declined more rapidly with decreasing baseline rate and increasing baseline age, prostate volume, and symptom severity (all *P* = .001). When the variables were simultaneously adjusted for each other, a rapid decline (negative slope 4.5% or greater per year) was more likely in men 70 years old or older and those with a rate less than 10 mL/sec at baseline compared with those 40 to 49 years old and those with a rate of 15 mL/sec or greater, respectively. Prostate volume and symptom severity were not statistically significant predictors of a rapid decline in peak urinary flow rate when variables were considered simultaneously (Roberts et al, 2000).

Based on TRUS the growth of the prostate in these men 40 to 79 years old was estimated to be about 0.6 mL per year or 6 mL per decade of life. However, prostate growth followed an exponential growth pattern with a slope estimate of 0.4 mL per year for men aged 40 to 59 years at baseline and of 1.2 mL per year for those 60 to 79 years at baseline (Rhodes et al, 1995, 1999). An updated analysis revealed a median growth rate of about 1.9% per year independent of age and symptoms. However, a higher baseline serum PSA and larger prostate volume predicted greater annualized volume increases.

Table 91–14.

Changes in Status of Symptom Severity from One Survey to the Next

SEVERITY	YEAR	NO. PATIENTS	Severity in Following Year (%) NONE	MILD	MODERATE	SEVERE
None	Baseline	293	83.6	12.3	2.7	1.4
	Year 1	223	83.9	9.0	2.2	4.9
Mild	Baseline	88	18.2	55.7	11.4	14.8
	Year 1	84	33.3	52.4	8.3	6.0
Moderate	Baseline	38	7.9	31.6	26.3	34.2
	Year 1	27	3.7	33.3	22.2	40.7
Severe	Baseline	35	22.9	17.1	11.4	48.6
	Year 1	31	9.7	22.6	12.9	54.8

Patients who underwent prostatectomy in preceding year were excluded from next survey.

Modified from Diokno AC, Brown MB, Goldstein N, Herzog AR. Epidemiology of bladder emptying symptoms in elderly men. J Urol 1992;148(6):1817–21.

Complications

Many of the complications of progressive BPH are rare, and much of the knowledge comes from studies of men

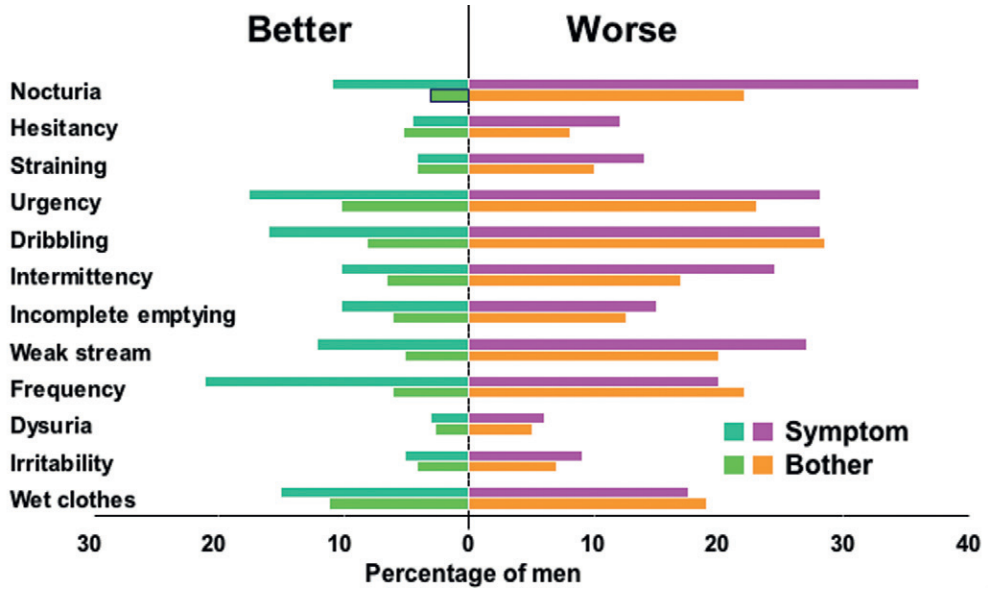


Figure 91–21. Changes in urinary symptoms and bothersomeness status between baseline and 3 years in a Scottish population-based study. (From Lee AJ, Russell EB, et al. Three-year follow-up of a community-based cohort of men with untreated benign prostatic hyperplasia. Eur Urol 1996;30[1]:11–7.)

presenting with such complications for treatment (i.e., cases) rather than observing cohorts of men for the development of complications.

Mortality

Between 1950 and 1954, 17 of 24 countries reported mortality rates of greater than 10 per 100,000, whereas between 1985 and 1989 data were available for 61 countries, only one reporting a greater than 10/100,000 mortality rate (Boyle et al, 1996). **If the mortality rates from 1950 were applied to 1990, 13,681 fewer deaths occurred in the United States alone than expected, a major but unheralded health care achievement.**

Bladder Stones

In a large autopsy study the prevalence of bladder stones was 8 times higher in men with a histologic diagnosis of BPH (3.4%) compared with controls (0.4%) but no increased incidence of ureteral or kidney stones was found (Grosse, 1990). In a study comparing watchful waiting and TURP in men with moderate symptoms, only 1 of 276 patients assigned to watchful waiting developed a bladder stone in 3 years of follow-up (Wasson et al, 1995). The self-reported rate of a bladder stone in a cross-sectional study in 2002 Spanish men was 0.7% (Hunter et al, 1996).

In clinical practice the risk of bladder stone development is small and screening only indicated if clinical circumstances warrant it (e.g., hematuria, stuttering of urination).

Urinary Tract Infections

In older surgical series UTIs constitute the main indication for surgical intervention in about 12% (Holtgrewe et al, 1989; Mebust et al, 1989). **Although one might intuitively assume that increased amounts of residual urine would predispose to the development of UTIs, clear evidence is lacking.** Hunter and colleagues (1996) quoted a rate of 5.2% self-reported episodes of UTI in a cross-sectional survey of 2002 men in Madrid, Spain. The best data to date come from the MTOPS study, in which the incidence of UTIs in the placebo-treated patients was only 0.1/100 patient-years (McConnell et al, 2003).

Bladder Decompensation

Urologists search for a progression from a normal mucosa to advancing trabeculation, development of cellules, and diverticula with ultimate detrusor muscle failure in mind when evaluating the bladder in men with BPH endoscopically. However, when the process starts, whether it really is related to BPH and obstruction, and when an intervention is necessary to prevent decompensation with resultant inability to void is unclear.

Biopsy samples from trabeculated, obstructed bladders show dense connective tissue deposition, a finding similar to that seen in animals experimentally obstructed (Gosling and Dixon, 1980; Levin et al, 1990, 2000; Chapple et al, 1991). However, bladder fibrosis is seen in both sexes with advancing age and may be a normal consequence of aging (Lepor et al, 1992a).

The critical question is whether delayed intervention might lead to progressive irreversible loss of bladder function and misses a window for cure. There is no direct evidence for this from longitudinal population or clinic patient studies. However, in the Veterans Affairs cooperative study comparing watchful waiting with TURP, those patients who crossed over from the conservative arm to TURP later in the trial had not as significant an improvement in symptoms and flow rate compared with those who underwent TURP at the beginning after randomization (Flanigan et al, 1998).

Urinary Incontinence

Incontinence is one of the most feared complications from surgical intervention for BPH. Although it may be the result of BPH secondary to overdistention of the bladder (overflow incontinence) or to detrusor instability estimated to affect up to one half or more of all obstructed patients (urge incontinence) (McConnell et al, 1994), it also is associated with aging; and in a community study an incidence of incontinence of 24% and 49% of incontinence in men and women older than 50 years was reported

(Roberts et al, 1998). In the Veterans Affairs cooperative study a 4% incidence of incontinence in both the surgical and conservative treatment arms was reported (Wasson et al, 1995). The self-reported rate of incontinence in a cross-sectional study in 2002 Spanish men was 6.1% (Hunter et al, 1996). In MTOPS the rate of socially unacceptable incontinence was 0.3/100 patient-years (McConnell et al, 2003).

Upper Urinary Tract Deterioration and Azotemia

The Agency for Health Care Policy and Research BPH guidelines reported a mean of 13.6% (range 0.3% to 30%) of patients presenting for TURP with evidence of renal failure based on predominantly older studies (McConnell et al, 1994). Patients in renal failure have an increased risk for complication after TURP compared with patients with normal renal function (25% vs. 17%) (Holtgrewe et al, 1989; Mebust et al, 1989) whereas the mortality increases up to 6-fold (Holtgrewe and Valk, 1962; Melchior et al, 1974a, 1974b). In the large database of patients who had upper tract imaging before surgery, 7.6% of 6102 patients in 25 series had evidence of hydronephrosis, of whom one third had renal insufficiency (McConnell et al, 1994).

The term *silent obstruction* or *silent prostatism* has been used to describe the constellation of asymptomatic patients who eventually develop renal failure resulting from bladder outlet obstruction, a case both rare and important (Mukamel et al, 1979). In the Veterans Affairs cooperative study, only 3 of 280 surgically treated patients and 1 or 276 patients in the watchful waiting arm developed renal azotemia, defined as a doubling of the serum creatinine concentration from baseline (Wasson et al, 1995). In none of the cohort or population-based studies have cases of renal failure been reported clearly attributable to BPH. However, the self-reported rate of an episode of renal failure in a cross-sectional study in 2002 Spanish men was 2.4% (Hunter et al, 1996).

In MTOPS there was not a single case of renal insufficiency due to BPH in over 3000 men observed for more than 4 years (McConnell et al, 2003). One has to be, however, careful not to overinterpret these findings. Participants in MTOPS were screened at baseline, and one might argue that some at higher risk for developing renal failure were excluded from participation.

Hematuria

It has always been recognized that patients with BPH might develop gross hematuria and form clots with no other cause being identifiable. Recent evidence suggests that in those patients predisposed to hematuria the microvessel density is higher compared with controls. Some renewed interest in the issue of BPH-related hematuria stems from the observation that finasteride appears to be a reasonable first-line therapy apparently influencing the expression of vascular endothelial growth factor (DiPaola et al, 2001). The self-reported rate of hematuria in a cross-sectional study in 2002 Spanish men was 2.5% (Hunter et al, 1996). Precise population estimates and incidence rates are not available, and the clinical management is dictated by the circumstances.

Acute Urinary Retention

AUR is for several reasons one of the most significant complications or long-term outcomes resulting from BPH. It has in the past represented an immediate indication for surgery. Between 25% and 30% of men who underwent TURP had AUR as their main indication in older series (Holtgrewe et al, 1989; Mebust et al, 1989), **and today most patients failing to void after an attempt of catheter removal still undergo surgery. For this reason alone, AUR is both from an economic viewpoint as well as from the viewpoint of the patient an important and feared event.** For the patient it presents as the inability to urinate with increasing pain, eventually a visit to the emergency department, catheterization, follow-up visits to the physicians, an attempt at catheter removal, and either recovery of spontaneous voiding or surgery, both painful and time-consuming processes. In older literature the risk of recurrent AUR was cited as being 56% to 64% within 1 week of the first episode and as occurring in 76% to 83% in men with diagnosed BPH (Breum et al, 1982; Klarskov et al, 1987; Hastie et al, 1990).

The etiology of AUR is poorly understood and obstructive, myogenic, and neurogenic causes all may play a role (Kaplan et al, 2008). **Prostate infection, bladder overdistention** (Powell et al, 1980), **excessive fluid intake, alcohol consumption, sexual activity, debility, and bed rest have all been mentioned** (Stimson and Fihn, 1990). **Prostatic infarction has been suggested as being an underlying event causing AUR** (Graversen et al, 1989). **Spiro and associates** (1976) **found evidence for infarction in 85% of prostates removed for AUR versus 3% in prostates of men having surgery for symptoms only.** In contrast, there was no evidence of infarction in six prostatectomy specimens removed from men who had surgery for AUR (Jacobsen et al, 1997). Anjum and associates (1998) found fundamentally similar rates of infarction in 35 men each in AUR versus no AUR (1.9% vs. 3.0%).

From a clinical and prognostic point of view, spontaneous AUR should be separated from precipitated AUR, although this is by no means consistently done in the literature. Precipitated AUR refers to the inability to urinate after a triggering event such as non–prostate-related surgery, catheterization, anesthesia, ingestion of medications with sympathomimetic or anticholinergic effects or antihistamines, or others. All other AUR episodes are classified as spontaneous (Roehrborn et al, 2000a). The importance of differentiating the two types of AUR becomes clear when evaluating the ultimate outcomes of patients. After spontaneous AUR, 15% of patients had another episode of spontaneous AUR and a total of 75% underwent surgery, whereas after precipitated AUR only 9% had an episode of spontaneous AUR, and 26% underwent surgery (Roehrborn et al, 2000a).

Descriptive Epidemiology

Older estimates of occurrence of AUR range from 4 to 15 to as high as 130 per 1000 patient-years (calculated by Jacobsen et al, 1997, based on studies by Craigen et al, 1969; Birkhoff et al, 1976; Ball et al, 1981), which leads to 10-year cumulative incidence rates ranging from 4% to 73% (Table 91–15). The self-reported rate of AUR in a cross-sectional study in 2002 Spanish men was 5.1% (Hunter et al, 1996).

More recent data from carefully controlled studies in better defined population shed additional light on the incidence rates in community-dwelling men and clinical BPH populations. AUR occurred in the Veterans Affairs cooperative study over 3 years in 1 man after TURP and in 8 of 276 men in the watchful waiting arm for an incidence rate of 9.6/1000 patient-years (Wasson et al, 1995). Barry and associates (1997a) reported outcomes of 500 men diagnosed by urologists with BPH who were candidates for prostatectomy by established criteria but elected to be followed conservatively. In 1574 patient-years 40 episodes of AUR occurred at a constant rate throughout the 4 years of follow-up for an incidence rate of 25/1000 patient-years.

Table 91–15.

Descriptive Studies on the Incidence of Acute Urinary Retention

FIRST AUTHOR/ YEAR	DESCRIPTION OF COHORT	CASES	COHORT	YEARS OF FOLLOW-UP	PERCENT OVERALL	PERCENT/ YEAR	IR/1000 PATIENT-YEARS	95% CI
Ball, 1981	Watchful waiting study	2	107	5	1.9	0.37	3.7	
Craigen, 1969	Watchful waiting study						15.0	
Birkhoff, 1976	Watchful waiting study	10	26	3	39	13	130	
Wasson, 1995	TURP vs. watchful waiting VA Cooperative Study	8	276	3	2.8	0.9	9.6	
Hunter, 1996	Self-reported prior events in Spanish men	102	2002	?	5.1		50.9	
Barry, 1997a	Prostatectomy candidates	40	500	4	8	2.5	25	
Meigs, 1999	Physicians Health Study, self reported	82	6100	3	1.3		4.5	3.1; 6.2
Roberts, 1997a	Community cohort 40-49 years old	57	2115	4			6.8	5.2; 8.9
McConnell, 1998	Placebo group of PLESS	99	1376	4	7.2	1.8	18	
Andersen, 1997	Placebo groups of 2-year BPH studies	57	2109	2	2.7	1.35	13.5	

BPH, benign prostatic hyperplasia; CI, confidence interval; IR, incidence rate; PLESS, Proscar Long-Term Efficacy and Safety Study; TURP, transurethral resection of the prostate.

During 15,851 patient-years of follow-up in the Physicians Health Study 82 men reported an episode of AUR for an incidence rate of 4.5/1000 patient-years (95% CI 3.1 to 6.2) (Meigs et al, 1999). Of the 2115 men aged 40 to 79 years in the Olmsted County study, 57 had a first episode of AUR during 8344 patient-years of follow-up (incidence 6.8/1000 patient-years, 95% CI 5.2, 8.9) (Jacobsen et al, 1997).

The first excellent data from men diagnosed with BPH stem from PLESS (McConnell et al, 1998). **In PLESS, 1,376 placebo-treated men with enlarged prostates and moderate symptoms had complete follow-up over 4 years, of which 99 experienced an episode of AUR for a calculated incidence rate of 1.8/100 patient-years. The placebo treatment groups from three 2-year studies with a similar patient population were meta-analyzed by Boyle and associates** (1998). **Of 2109 patients, 57 experienced AUR over the 2 years with a constant hazard for an incidence rate of 14/1000 patient-years. In the MTOPS placebo group the incidence rate was 0.6/100 patient-years for a cumulative incidence of 2%.**

Analytical Epidemiology

Age. **Several well-controlled studies provided considerable insights into the risk factors for AUR. Perhaps the most significant of these risk factors is age.** Studies from European countries and the United States demonstrate a nearly linear increase in the age-specific incidence of AUR for men ranging in age from 40 to older than 80 years (Jacobsen et al, 1997; Meigs et al, 1999; Verhamme et al, 2005; Cathcart et al, 2006) (Fig. 91–22).

LUTS. **Increased symptom severity is associated with increased risk of AUR in several large population-based or cohort studies** (Table 91–16). In the Physician's Health Study in men with mild symptoms the incidence of AUR increased from 0.4/1000 patient-years for those 45 to 49 years old to 7.9/1000 patient-years for those 70 to 83 years old. In men with an AUASI score of 8 to 35, rates increased from 3.3/1000 patient-years for those 45 to 49 years old to 11.3/1000 patient-years for those 70 to 83 years old. Men with a clinical diagnosis of BPH and an AUASI score of 8 or greater had the highest rates (age-adjusted incidence 13.7/1000 patient-years). All seven LUTS comprising the AUASI individually predicted AUR. The sensation of incomplete bladder emptying, having to void again after less than 2 hours, and a weak urinary stream were the best independent symptom predictors. Use of medications with adrenergic or anticholinergic side effects also predicted AUR (Meigs et al, 1999).

The Olmsted County study focused on age, symptom severity, maximum flow rate, and prostate volume (Jacobsen et al, 1997). **Incidence rates per 1000 patient-years increased from 2.6 to 9.3 for men in their 40s to their 70s if they had mild symptoms and from 3.0 to 34.7 if they had more than mild symptoms** (see Table 91–16).

Urodynamic Parameters. **The relative risk increased for older men, men with moderate to severe symptoms (3.2×), those with a flow rate under 12 mL/sec (3.9 times) and those with a prostate volume greater than 30 mL by TRUS (3.0 times), all compared with a baseline risk of 1.0 time for the corresponding groups** (Fig. 91–23). The highest relative risk by proportional hazard models exists for 60- to 69-year-old men with more than mild symptoms and a flow rate of less than 12 mL/sec (10.3 times), and for 70- to 79-year-old men except if they had mild symptoms and a flow rate over 12 mL/sec. All other stratification of men older than age 70 years had a relative risk ranging from 12.9 to 14.8 times (all compared with men 40 to 49 years old with mild symptoms and a flow rate over 12 mL/sec for which the base risk is 1.0 time).

Prostate Volume and Serum PSA. Although age in community-dwelling men is an important risk factor, in the BPH trial population of men who already are diagnosed with BPH, other factors can be analyzed. In the placebo groups of three 2-year studies (Marberger et al, 2000) and a 4-year study (PLESS) (McConnell et al, 1998; Kaplan et al, 2000; Roehrborn et al, 2000a), prostate volume, serum PSA, and symptom severity all were predictors of AUR episodes.

The incidence increased from 5.6% to 7.7% in men with a serum PSA of less than 1.4 ng/mL from mild to severe symptoms and from 7.8% to 10.2% for those with a serum PSA of more than 1.4 ng/mL over 4 years in PLESS (Kaplan et al, 2000). In the 2-year studies the rate of AUR was 8-fold higher in those with a serum PSA of over 1.4 ng/mL

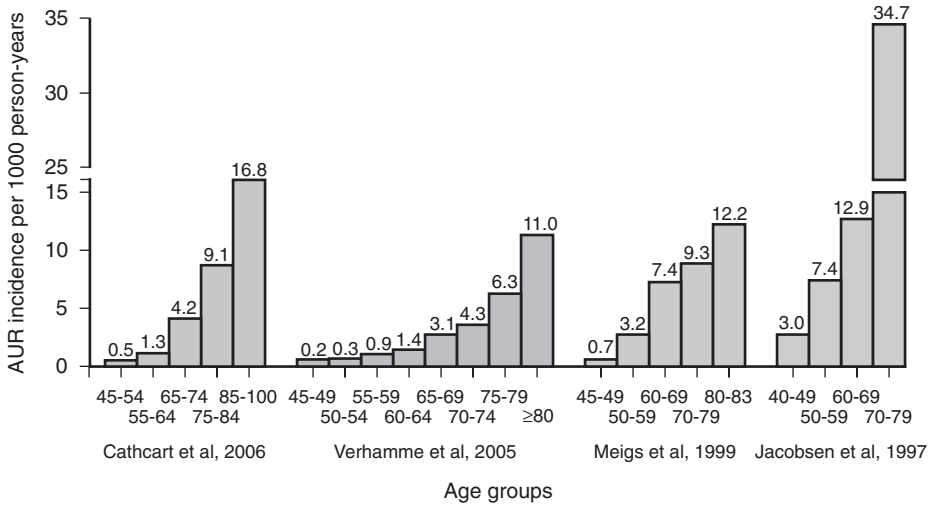


Figure 91–22. Increase in incidence of acute urinary retention (AUR) with age in four large studies. (From Kaplan SA, Wein AJ, et al. Urinary retention and post-void residual urine in men: separating truth from tradition. J Urol 2008;180[1]:47–54.)

Table 91–16.

Incidence of AUR by Patient Age and AUASI Score in Two Population-Based Studies

	No. AUR Events/1000 Men-Years (95% CI)	
AGE GROUP	Health Professionals Follow-up Study*	Olmsted County Study of Urinary Symptoms and Health Status among Men†
AUASI ≤7:		
40-49		2.6 (0.8-6.0)
45-49	0.4 (0.02-1.8)	
50-59	1.2 (0.4-2.6)	1.7 (0.3-4.8)
60-69	3.6 (1.9-6.1)	5.4 (2.0-11.6)
70-79		9.3 (3.4-20.3)
70-83	7.9 (4.1-13.5)	
AUASI >7:		
40-49		3.0 (0.4-10.8)
45-49	3.3 (0.2-14.4)	
50-59	10.0 (5.4-16.8)	7.4 (2.7-16.1)
60-69	14.1 (9.4-20.2)	12.9 (6.2-23.8)
70-79		34.7 (20.2-55.5)
70-83	11.3 (6.4-18.3)	

*Total of 82 AUR episodes in 6100 men with a crude incidence of 5.2/1000 patient-years (95% CI 4.1-6.4) in 15,851 patient-years of follow-up.

†Total of 57 AUR episodes in 2115 men with an overall incidence of 6.8/1000 patient-years (95% CI 5.2-8.9) in 8344 patient-years of follow-up.

AUASI, American Urological Association Symptom Index; AUR, acute urinary retention; CI, confidence interval.

From Kaplan SA, Wein AJ, et al. Urinary retention and post-void residual urine in men: separating truth from tradition. J Urol 2008;180(1):47–54.

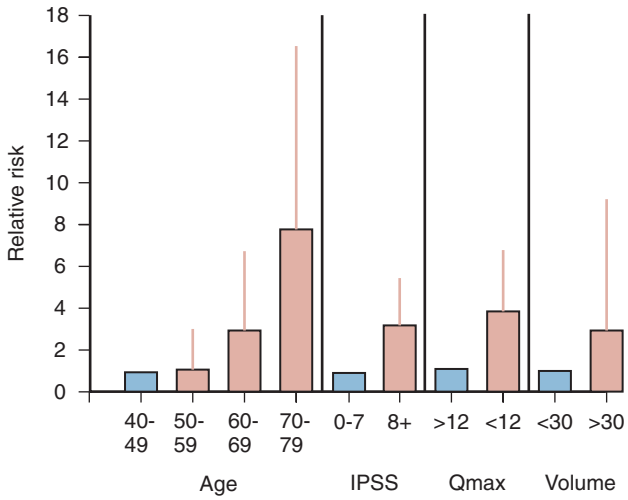


Figure 91–23. Relative risk of acute urinary retention in Olmsted County Study of Urinary Symptoms and Health Status Among Men by age, symptom severity, peak flow rate, and prostate volume. The shaded column represents the baseline and a relative risk of 1.0; the vertical line represents the 95% confidence interval. IPSS, International Prostate Symptom Score. (Data from Jacobsen SJ, Jacobson DJ, et al. Natural history of prostatism: risk factors for acute urinary retention. J Urol 1997;158[2]:481–7.)

(0.4% vs. 3.9%) and threefold higher if the prostate volume was over 40 mL (1.6% vs. 4.2%) (Marberger et al, 2000; Roehrborn et al, 2001). **A detailed analysis showed a near linear increase in risk for AUR with increasing thresholds of serum PSA** (Fig. 91–24) **in PLESS, an observation that applies to both spontaneous and precipitated AUR** (Roehrborn et al, 1999d). **The risk for both types of AUR increases with increasing serum PSA as well as prostate volume stratified by tertiles** (Fig. 91–25). Similar observations were made in MTOPS, in which the risk for AUR increased with increasing prostate volume as well as increasing baseline serum PSA (Fig. 91–26), **as well as in the 2-year phase III studies comparing dutasteride with placebo** (Roehrborn et al, 2002). **An analysis of over 100 possible outcome predictors alone or in combination revealed a combination of serum PSA, urinating more than every 2 hours, symptom problem index, maximum urinary flow rate, and hesitancy as being only slightly superior to PSA alone in predicting AUR episodes** (Roehrborn et al, 2001).

Surgery for Benign Prostatic Hyperplasia

Both surgery and AUR represent distinct end points in the disease progression of BPH. There are, however, distinct differences. AUR is an outcome mandating management, and surgery is one of the commonly employed management styles. AUR is probably one of the clearer indications for surgery, leaving the treating physician little choice in a patient who failed a trial without catheterization. However, most patients undergo surgery not for AUR but for symptoms (Holtgrewe et al, 1989).

Depending on local practice pattern, AUR accounts for 5% to over 30% of the indications for surgery. AUR can be compared with a bone fracture. It is impossible for the physician in his or her interaction with the patient to increase or decrease the probability for that outcome to occur. Furthermore, once it has occurred, no interaction or consultation can undo it. In contrast, it is easy to see how patients can be influenced in their decision to undergo surgery by the consultation with the physician. The interaction style, the quoted probabilities of beneficial and harmful outcomes to occur, and many other factors cause considerable variability in the incidence rates of prostate-related surgery, an observation that caused the Agency for Health Care Policy and Research to develop guidelines for the treatment of BPH (Wennberg et al, 1988). This situation is similar to myocardial infarction and coronary artery bypass grafting (CABG). The analytical epidemiology of myocardial infarctions is well understood, and risk factors are characterized. Not all myocardial infarctions result in CABG, and, in fact, CABG is frequently performed for other indications than a recent infarction. Consequently, there is abundant literature focusing on the geographic variation in the usage of CABG. From this brief discussion it becomes clear that surgery for BPH is a softer end point from an epidemiologic point of view than AUR, and data on rates of prostatectomy need to be interpreted in light of variation in its use, from provider to provider, region to region, health care plan to health care plan, and over time.

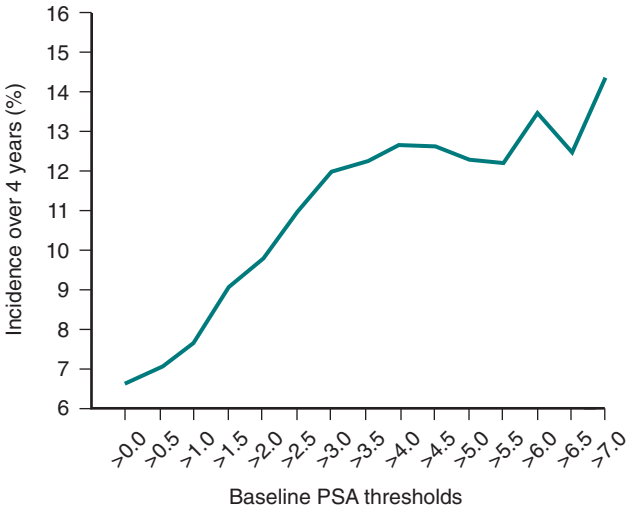


Figure 91–24. Incidence of spontaneous or precipitated acute urinary retention in the Proscar Long-Term Efficacy and Safety Study over 4 years stratified by increasing thresholds of serum prostate-specific antigen (PSA) at baseline. (From Roehrborn CG, McConnell JD, Lieber M, et al. Serum prostate-specific antigen concentration is a powerful predictor of acute urinary retention and need for surgery in men with clinical benign prostatic hyperplasia. PLESS Study Group. Urology 1999;53[3]:473–80.)

Of all prostate surgeries, TURP and laser ablation of the prostate are still clearly the most common procedures and the best studied. Cross-sectional descriptive data on incidence rates are available from the Medicare database. While in 1962 TURP constituted over 50% of all major surgeries performed by American urologists, this number had dropped to 38% by 1986 (Holtgrewe et al, 1989; Mebust et al, 1989). Although the number of TURPs performed on Medicare patients declined from an all time peak of 258,000 in 1987 to 168,000 in 1993—a reduction by 34%—it remains second only to cataract surgery on the list of Medicare's most costly surgical procedures. A 20% sample of Medicare beneficiaries was examined to further specify rates of TURP in the United States. In 1990

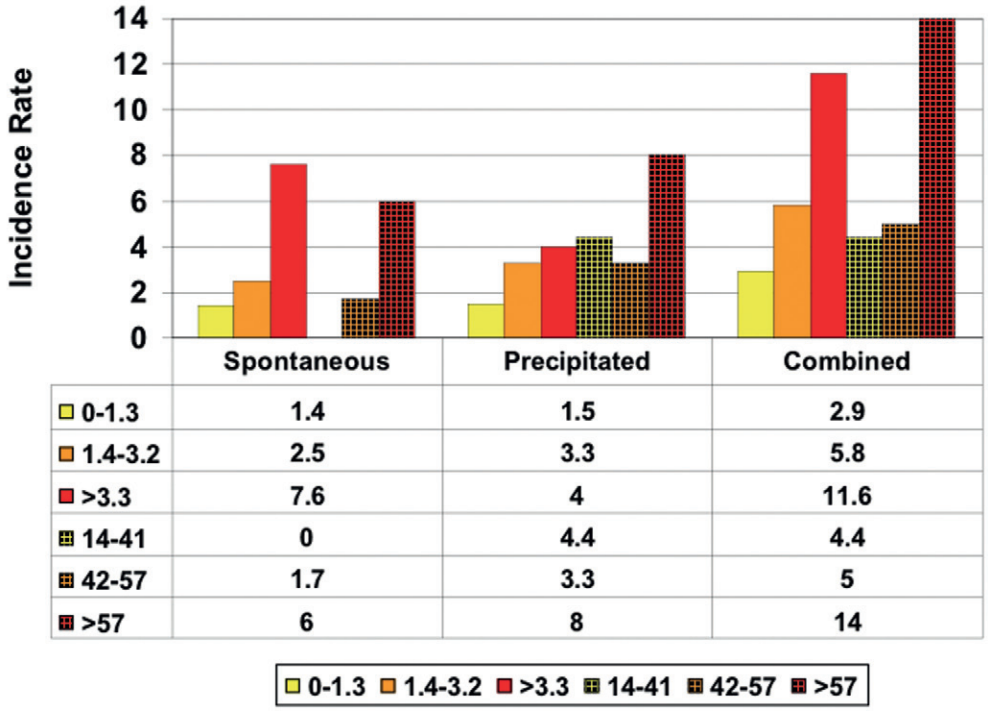


Figure 91–25. Spontaneous, precipitated, or combined acute urinary retention incidence over 4 years in the Proscar Long-Term Efficacy and Safety Study stratified by tertiles of serum prostate-specific antigen or prostate volume at baseline. (From Roehrborn CG, McConnell JD, Lieber M, et al. Serum prostate-specific antigen concentration is a powerful predictor of acute urinary retention and need for surgery in men with clinical benign prostatic hyperplasia. PLESS Study Group. Urology 1999;53[3]:473–80.)

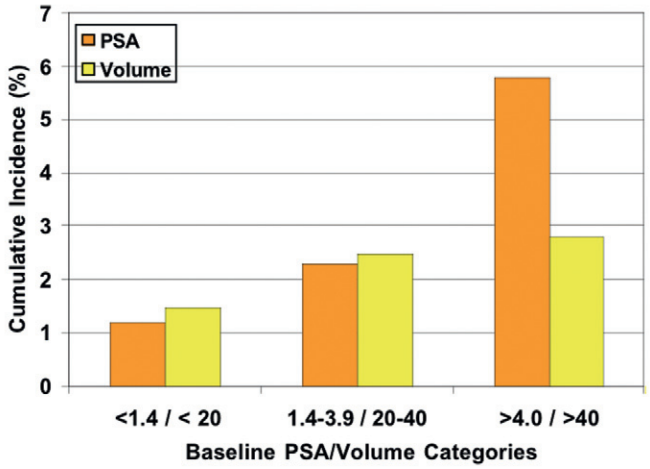


Figure 91–26. Cumulative incidence of acute urinary retention in placebo-treated patients in the Medical Therapy of Prostatic Symptoms study stratified by baseline prostate volume *(yellow)* and baseline serum prostate-specific antigen (PSA) *(orange)*. (From Roehrborn CG, McConnell JD, Lieber M, et al. Serum prostate-specific antigen concentration is a powerful predictor of acute urinary retention and need for surgery in men with clinical benign prostatic hyperplasia. PLESS Study Group. Urology 1999;53[3]:473–80.)

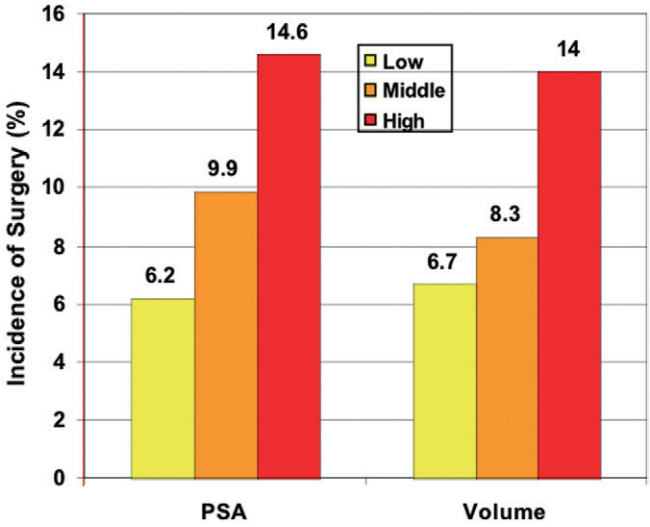


Figure 91–27. Incidence of surgery stratified by tertiles of serum prostate-specific antigen (PSA) and prostate volume in placebo-treated patients in the Proscar Long-Term Efficacy and Safety Study. (From Roehrborn CG, McConnell JD, Lieber M, et al. Serum prostate-specific antigen concentration is a powerful predictor of acute urinary retention and need for surgery in men with clinical benign prostatic hyperplasia. PLESS Study Group. Urology 1999;53[3]:473–80.)

the rates of TURP (including all indications) were approximately 25, 19, and 13 per 1000 for men older than the age of 75, 70 to 74, and 65 to 69, respectively. The 30-day mortality after TURP for the treatment of BPH decreased from 1.20% in 1984 to 0.77% in 1990 (Lu-Yao et al, 1994). **Compared with the period 1984 to 1990, age-adjusted rates of TURP for BPH during 1991 to 1997 declined further by approximately 50% for white (14.6 to 6.72/1000) and 40% for black (11.8 to 6.58/1000) men** (Wasson et al, 2000). Medicare databases are only relevant

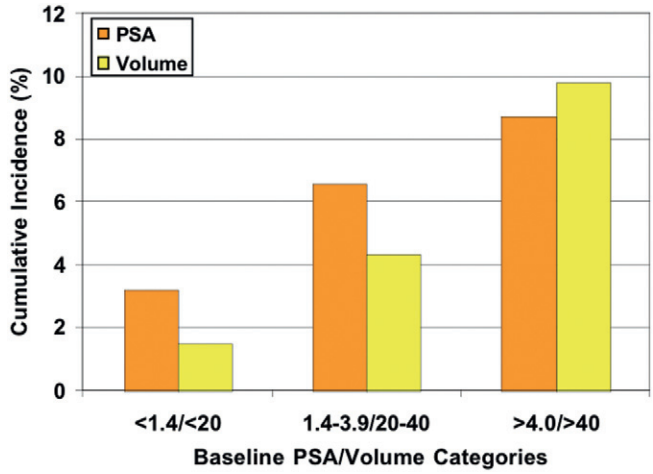


Figure 91–28. Cumulative incidence of invasive therapy (surgery) for benign prostatic hyperplasia in placebo-treated patients in the Medical Therapy of Prostatic Symptoms study stratified by baseline prostate volume *(yellow)* and baseline serum prostate-specific antigen (PSA) *(orange)*. (From Roehrborn CG, McConnell JD, Lieber M, et al. Serum prostate-specific antigen concentration is a powerful predictor of acute urinary retention and need for surgery in men with clinical benign prostatic hyperplasia. PLESS Study Group. Urology 1999;53[3]:473–80.)

to those men older than age 65 years enrolled in Medicare and therefore are less interesting from a longitudinal epidemiologic point of view.

Older series of the natural history of BPH such as the one reported by Craigen and coworkers (1969) projected somewhat unrealistic estimates of 35% incidence of prostatectomy at 1 year and 45% at 7 years. Diokno and colleagues (1992) reported an annual incidence rate of 2.6% and 3.3% for years 1 and 2 in their cohort of men followed longitudinally (1992). Frequency, hesitancy, straining, and an interrupted stream were all associated with an increased risk.

The first study of substantial quality reporting on incidence rates and risk factors of prostate surgery was the Baltimore Longitudinal Study of Aging (BLSA) (Arrighi et al, 1990, 1991; Guess et al, 1990). Over 1000 men were observed for 30 years with yearly symptom assessments, questionnaires, and examinations. **Age, incomplete emptying, change in size, and force of stream were all independently associated with the risk of prostate surgery, as was a reportedly enlarged prostate by DRE.** Of 464 men without risk factors, only 3% required surgery during follow-up. For men with one risk factor the cumulative incidence was 9%, with two risk factors 16%, and with three risk factors even 37%. In a similar study, namely, the Veterans Affairs Normative Aging Study, nocturia and hesitancy emerged as independent predictors of surgery in 1868 men aged 49 to 68 observed for more than 20 years (Hindley et al, 2001). Age and five LUTS (dysuria, incontinence, trouble initiating flow, nocturia, and slow stream) were associated with the risk of surgery in 16,219 men over 40 years enrolled in the Kaiser Permanente Health Plan in California, of whom 1027 men underwent prostatectomy over 12 years of follow-up (Sidney et al, 1991a, 1991b).

In the Veterans Affairs cooperative trial comparing surgery with watchful waiting, 65 of 276 (24%) patients assigned to watchful waiting crossed over to surgery within 3 years of follow-up, of which 20 met predefined end points (azotemia, high residual urine volumes, incontinence, or

Key Points: Epidemiology and Natural History

- There is no globally accepted epidemiologic definition of BPH, and thus prevalence and incidence rates must be viewed in the context of the definitions chosen by the investigator reporting the data.
- Despite the significantly different proportion of men admitting to moderate to severe symptoms, a clear trend toward an increase in symptom scores with advancing age is noticeable in all reported studies.
- In general, in all cross-sectional studies prostate volume as assessed by TRUS has been found to increase slowly but steadily with advancing age.
- Analytical epidemiologic data suggest a limited role of classical determinants of the disease such as religion, socioeconomic factors, sexual activity, alcohol intake, hypertension, dietary factors, and others. There is conflicting evidence regarding smoking and some evidence suggesting dietary factors, obesity, and increased BMI as determinants of disease severity.
- All relevant parameters such as symptom severity and frequency, bother, interference, disease-specific HRQOL, maximum flow rate, and prostate volume tend to worsen with advancing age. However, reported correlations between these parameters as well as urodynamic pressure-flow studies are in general weak, with some exceptions. Strong correlations exist between measures of symptom severity and frequency (IPSS), bother, disease-specific HRQOL, and interference scores.
- The natural history of the disease has been studied in many longitudinal population-based studies as well as in placebo and sham control groups of treatment trials of men diagnosed with the condition. These studies suggest, in general, a worsening of LUTS and BPH with time. There are several key baseline parameters allowing a stratification of patients according to the risk of progression. Age, symptom severity, flow rate, prostate size, and serum PSA are useful predictors of the risk of progression.
- Complications of LUTS and BPH such as mortality, urinary tract infections, bladder decompensation, bladder stones, hematuria, urinary incontinence, upper urinary tract deterioration with renal insufficiency, and others are, in general, rare in properly supervised patients.
- The two most significant progression events are AUR and the need for BPH-related surgery. Although not exceedingly common, there is a significant baseline incidence rate and the risk is cumulative; that is, with increasing time of observation the incidence rate increases linearly.
- The risk of AUR and need for surgery is to some degree predictable from baseline parameters with advancing age, increased prostate size, and higher serum PSA levels representing the most significant risk factors.

high AUASI scores). High baseline bother score was a strong predictor of requiring surgery (Wasson et al, 1995).

The probability of undergoing surgery over 4 years increased from 10% in those men diagnosed with BPH who had mild symptoms to 24% in those with moderate and 39% in those with severe symptoms at baseline as reported in a natural history and observation study by Barry and colleagues (1997a).

The Olmsted County study and the placebo-treated patients from PLESS provide additional insights into the risk factors for undergoing prostate surgery in either community-dwelling men or men enrolled in a BPH treatment trial.

In the Olmsted County study during more than 10,000 patient-years of follow-up 167 men were treated, yielding an overall incidence of 16.0/1000 patient-years. There was a strong age-related increase in risk of any treatment from 3.3/1000 patient-years for men 40 to 49 years old to more than 30/1000 patient-years for those 70 years old or older. Men with moderate to severe symptoms, depressed peak urinary flow rates (<12 mL/sec), enlarged prostate (>30 mL), or elevated serum PSA (≥1.4 ng/mL) had about four times the risk of BPH treatment than those who did not. After adjustment for all measures simultaneously an enlarged prostate (hazard ratio 2.3, 95% CI 1.1 to 4.7), depressed peak flow rate (hazard ratio 2.7, 95% CI 1.4 to 5.3), and moderate to severe symptoms (hazard ratio 5.3, 95% CI 2.5 to 11.1) at baseline each independently predicted subsequent treatment. Overall nearly 1 in 4 men received treatment in the eighth decade of life. **These data suggest that men with moderate to severe LUTS, impaired flow rates, or enlarged prostates are more likely to undergo treatment, with increases in risk of similar magnitude to those associated with adverse outcomes, such as AUR** (Jacobsen et al, 1999).

Over 1500 patients with moderate LUTS and enlarged prostate glands were followed in PLESS on placebo for 4 years. Of these, 10% or 2.5% per year underwent surgery for BPH (McConnell et al, 1998). Whereas the hazard of undergoing surgery was linear, that is, it remained constant throughout the duration of the study, it was different when patients were stratified by either prostate volume or serum PSA in tertiles at the beginning of the study (Fig. 91–27). **Similar to the incidence of AUR, the rates of surgery increased from 6.2% to 14.6% for patients in the lowest to the highest PSA tertile and from 6.7% to 14.0% from the lowest to the highest prostate volume tertile.** In MTOPS the incidence of invasive therapy for BPH in the placebo group increased equally nearly linearly when stratifying by baseline serum PSA or prostate volume (Fig. 91–28) (McConnell et al, 2003).

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chapter
92

Evaluation and Nonsurgical Management of Benign Prostatic Hyperplasia

Thomas Anthony McNicholas, MBBS, FRCS, FEBU ● Roger Sinclair Kirby, MD, MA, FRCS ● Herbert Lepor, MD

Diagnosis

Assessing the Effectiveness and Safety of Medical Therapy

Nonsurgical Therapy

Medical Therapy

Future Strategies

The term ***benign prostatic hyperplasia*** (BPH) has very different connotations to the pathologist, radiologist, urodynamicist, practicing urologist, and patient. BPH to the pathologist is a microscopic diagnosis characterized by cellular proliferation of the stromal and epithelial elements of the prostate. The radiologist confirms the diagnosis of BPH on the basis of an enlarged prostate either with ultrasound or three-dimensional diagnostic imaging studies of the male pelvis (Haas and Resnick, 2000). The hallmark of BPH to the urodynamicist is the synchronous observation of elevated voiding pressure and a low urinary flow rate in the absence of other disease processes that cause bladder outlet obstruction (BOO) (Nitti, 2000). BPH to the practicing urologist represents a constellation of signs and symptoms that develop in the male population in association with aging and prostatic enlargement presumably caused by BOO (Shapiro and Lepor, 1995), together with ultrasound imaging. The patient is typically concerned about the impact of BPH on quality of life rather than about the presence of cellular proliferation, prostatic enlargement, or elevated voiding pressures.

Because of the diverse connotations of the term, it seems sensible to define BPH as microscopic BPH, macroscopic BPH, or clinical BPH. **Microscopic BPH** represents histologic evidence of cellular proliferation of the prostate. **Macroscopic BPH** refers to enlargement of the prostate resulting from microscopic BPH. **Clinical BPH** represents the **lower urinary tract symptoms (LUTS),** bladder dysfunction, hematuria, and urinary tract infection (UTI) resulting from macroscopic BPH. Abrams (1994) has suggested using the more clinically descriptive terms *benign prostatic enlargement* (BPE), *bladder outlet obstruction* (BOO), and *lower urinary tract symptoms* to replace BPH, but the time-honored, although limited, original terminology persists.

Microscopic BPH describes a proliferative process of the stromal and epithelial elements of the prostate (Bartsch et al, 1979). The proliferative process originates in the transition zone and the periurethral glands (McNeal, 1978). It is rarely identified in men younger than 40 years of age (Berry et al, 1984). The autopsy incidence of BPH is age dependent, the proliferative process being present in approximately 70% and 90% of men in their seventh and ninth decades of life, respectively. The development of microscopic BPH requires aging and the testes as the source of androgens (Walsh, 1984). Androgens play a passive role in the proliferative process. The specific molecular events that initiate and promote microscopic BPH have yet to be identified and characterized. Growth factors, such as epidermal growth factor (EGF), are involved through autocrine and paracrine stromal-epithelial interactions (Steiner, 2000).

Macroscopic BPH describes an "enlarged" prostate. Digital rectal examination (DRE) provides a relatively crude estimate of prostate size when compared with measurements using transrectal ultrasonography or magnetic resonance imaging (Roehrborn et al, 1997). Knowledge of prostate size may be clinically relevant in terms of selecting appropriate medical or surgical therapy. A strong correlation exists between serum prostate-specific antigen (PSA) levels and prostate volume (Roehrborn et al, 1999), and, as a consequence, in the absence of adenocarcinoma, the PSA value may be used as a surrogate for prostate volume (Roehrborn et al, 2001). The transition zone (inner gland) accounts for the majority of BPH tissue. The transition zone volume can be quantified using transrectal ultrasonography (Lepor et al, 1994) or magnetic resonance imaging (Tempany et al, 1993). There is no consensus regarding the extent of enlargement required to establish the diagnosis of macroscopic BPH; however, prostate volume of approximately 20 mL may be regarded as normal (Garraway et al, 1991) before BPH develops, and volumes of 100 mL or greater are encountered clinically.

The clinical manifestations of BPH include LUTS, poor bladder emptying, urinary retention, an overactive bladder, UTI, hematuria, and renal insufficiency (Jepsen

and Bruskewitz, 2000). Historically, the pathophysiology of clinical BPH was attributed to BOO secondary to macroscopic enlargement of the prostate gland (Lepor, 2000). This hypothesis was supported by epidemiologic data suggesting that the prevalence of microscopic BPH, macroscopic BPH, and clinical BPH is age dependent and therefore causally related (Isaacs and Coffey, 1989). This rather oversimplistic concept of the pathophysiology of BPH has been challenged by more recent reports demonstrating only weak relationships between prostate size, severity of BOO, and severity of symptoms (Barry et al, 1993; Bosch et al, 1995; Girman et al, 1995; Yalla et al, 1995). However, there are numerous epidemiologic data to confirm that BPH is a slowly progressive disease and that men with a larger prostate (or higher PSA) are at significantly greater risk of LUTS, impaired quality of life, and complications such as acute urinary retention (AUR) (Roehrborn et al, 2001) (see Chapter 91).

DIAGNOSIS

The complex of symptoms now commonly referred to as "LUTS" is not specific for BPH. Aging men with a variety of lower urinary tract pathologic processes may exhibit similar, if not identical, symptoms. The initial diagnostic challenge in these patients is to establish that the symptoms are, in fact, a result of BPH. This is the primary focus of initial evaluation and diagnostic testing. Fortunately, nonprostatic causes of symptoms can be excluded in a significant majority of patients on the basis of history, physical examination, and urinalysis. Additional diagnostic testing is necessary in patients in whom the diagnosis is still unclear after initial evaluation. These tests may also have a modest (but still unproven) value in predicting the response to treatment. The following recommendations concerning the initial evaluation of men presenting with LUTS reflect the consensus opinion for several independent groups. The American Urological Association (AUA) BPH guidelines were presented in 1994 and 2003, were updated in 2010 (McVary et al, 2010), and are available at www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines.cfm?sub=bph. The European Association of Urology (EAU) has published guidelines on "Assessment, Therapy and Follow-Up of Men with Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Obstruction (BPH Guidelines)" (Madersbacher et al, 2004), and in 2009 a Sixth International Consensus document was published (Abrams et al, 2009). Algorithms for the management of LUTS/BPH are shown in Figures 92–1 to 92–3.

Initial Evaluation

Medical History

A detailed medical history should be obtained to identify other causes of voiding dysfunction or cormorbidities that may complicate treatment. Specific additional areas to discuss when taking the history of a man with BPH symptoms include a history of hematuria, UTI, diabetes, nervous system disease (e.g., Parkinson disease or stroke), urethral stricture disease, urinary retention, and aggravation of symptoms by cold or sinus medication. Current use of prescription and over-the-counter medications should be discussed to determine whether the patient is taking drugs that impair bladder contractility (anticholinergic agents) or that increase outflow resistance (α-sympathomimetic agents). A history of prior lower urinary tract surgery raises the possibility of urethral or bladder neck stricture. Use of a voiding diary (recording times and volume) may help identify patients with polyuria or other nonprostatic disorders.

Physical Examination

A DRE and a focused neurologic examination should usually be performed. In addition, examination of the external genitalia is indicated to exclude meatal stenosis or a palpable urethral mass and an abdominal examination is necessary to exclude an overdistended, palpable bladder. The DRE and focused neurologic examination are performed to detect prostate or rectal malignancy, to evaluate anal sphincter tone, and to rule out any neurologic problems that may cause the presenting symptoms. The presence of induration is as important a finding as the presence of a nodule and should be correlated with a serum PSA value so that the need for prostatic biopsy can be assessed and acted upon.

DRE establishes the approximate size of the prostate gland. Estimation of prostate size is important to select the most appropriate pharmacologic or technical approach. DRE provides a sufficiently accurate measurement in most cases. The size of the prostate is not critical in deciding whether active treatment is required. Prostate size does not correlate precisely with symptom severity, degree of urodynamic obstruction, or treatment outcomes (Roehrborn et al, 1986; Simonsen et al, 1987). If a more accurate measurement of prostate volume is needed to determine whether to perform open prostatectomy rather than transurethral resection of the prostate (TURP), or some other procedure such as laser vaporization, ultrasonography (transabdominal or transrectal) is more accurate than cystourethroscopy. It is now established that a larger gland, and consequently a higher PSA, is associated with a greater risk of BPH progression (Roehrborn et al, 2001).

Urinalysis

A urinalysis should be done either by using a dipstick test or microscopic examination of the spun sediment to rule out UTI and hematuria, either of which strongly suggest a non-BPH pathologic process as a cause of symptoms. Because serious urinary tract disorders are relatively uncommon, the positive predictive value of screening for them is low and the effectiveness of early detection and intervention is unproven. **However, in older men with BPH and a higher prevalence of these disorders the benefits of an innocuous test such as urinalysis clearly outweigh the harms involved.** The test permits the selective use of renal imaging and endoscopy for patients with the greatest chance of benefiting from them. More importantly, urinalysis assists in distinguishing UTIs and bladder cancer from BPH. These conditions may produce urinary tract symptoms (e.g., frequency and urgency) that mimic BPH. If a dipstick approach is used, a test that includes leukocyte esterase and nitrite tests for the detection of pyuria and bacteriuria should be used.

The positive predictive value of urinalysis for cancer or other urologic diseases is around 4% to 26%, depending on the patients screened and the rigor of follow-up studies (Mohr et al, 1986, 1987; Messing et al, 1987). **Urine cytology should always be requested in men with severe irritable symptoms and dysuria, especially if they have a smoking history.** Carcinoma in-situ of the bladder is a diagnosis that may have serious consequences if overlooked.

Serum Creatinine Measurement

Although the measurement of the serum creatinine concentration was recommended in the initial evaluation of all patients with

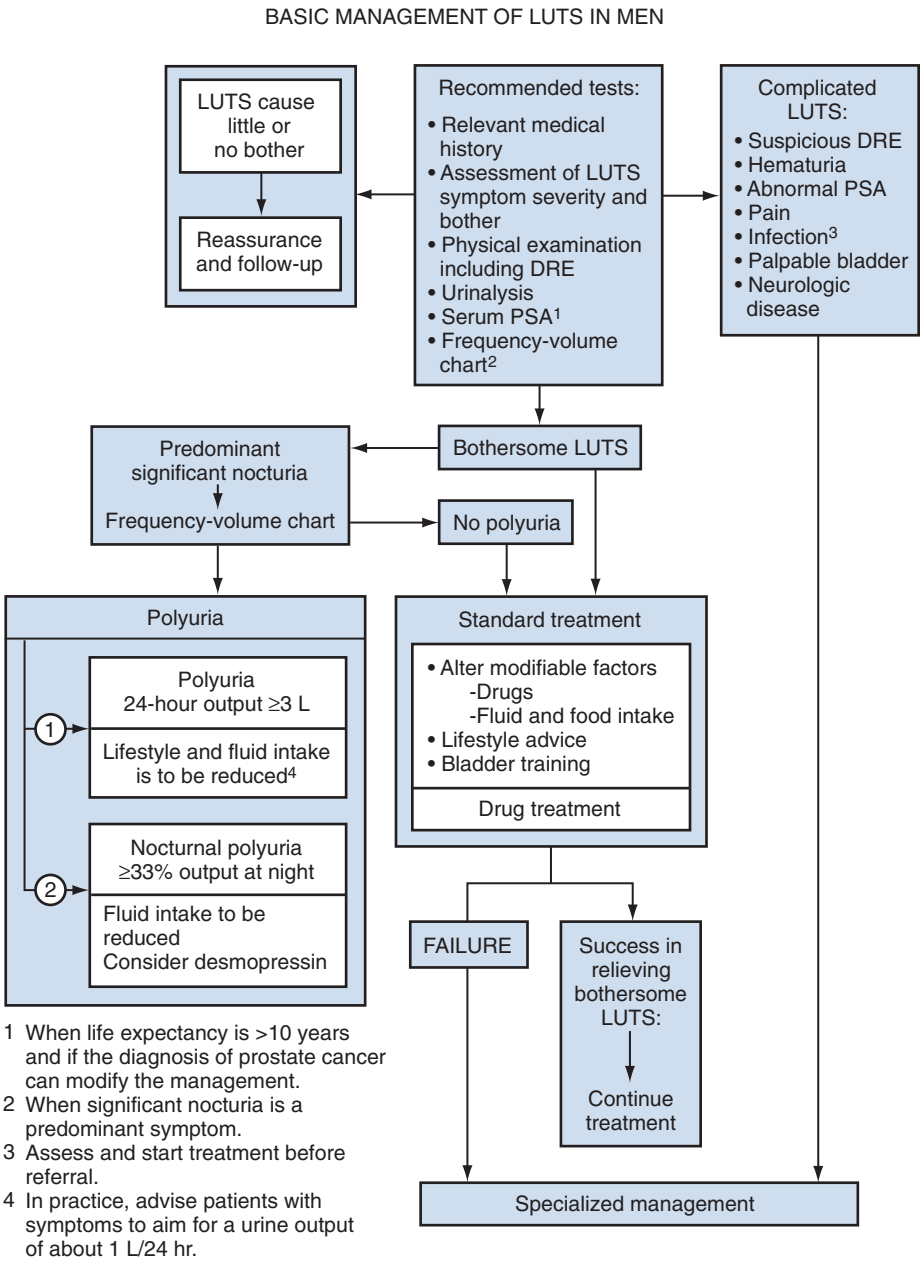


Figure 92–1. International Consensus guideline algorithm for management of lower urinary tract symptoms (2009): Basic management. DRE, digital rectal examination; PSA, prostate-specific antigen. (From Abrams P, Chapple C, Khoury S, et al. Evaluation and treatment of lower urinary tract symptoms in older men. J Urol 2009;181[4]:1779–87.)

symptoms of LUTS to exclude renal insufficiency caused by the presence of obstructive uropathy (McConnell et al, 1994; Denis et al, 1998), at the Fifth International Consultation on BPH it was suggested that serum creatinine determination should be optional or secondary. **The AUA guidelines on BPH and the Sixth International Consensus report no longer recommend routine creatinine measurement in the standard patient.** However, it is well established that BPH patients with renal insufficiency have increased risk for postoperative complications. The risk is 25% for patients with renal insufficiency, compared with 17% for patients without the condition (Mebust et al, 1989). Moreover, the mortality increases up to sixfold for BPH patients treated surgically if they have renal insufficiency (Holtgrewe and Valk, 1962; Melchior et al, 1974). Of 6102 patients evaluated in 25 studies by intravenous urography (IVU) before prostate surgery, 7.6% had evidence of hydronephrosis (McConnell et al, 1994). Of these patients, 33.6% had associated renal insufficiency. **Elevated serum creatinine levels in a patient with BPH is an indication for imaging studies (usually ultrasonography) to evaluate the upper urinary tract.** In a retrospective analysis of 345 patients who had undergone prostatectomy, 1.7% (n = 6) had occult and progressive renal damage (Mukamel et al, 1979). These patients had minimal or no urinary symptoms and presumably fit the category of patients with "silent prostatism." Measurement of the serum creatinine concentration is one means to identify such "at risk" patients.

Serum Prostate-Specific Antigen

Prostate cancer can lead to LUTS by producing bladder outflow obstruction similar to BPH. Moreover, localized prostate cancer commonly coexists with BPH. In most men with a 10-year or longer life span the knowledge of concomitant prostate cancer may well alter management of the BPH component. The detection of a large nodular prostate cancer on DRE would no doubt alter therapy; however, the "early detection" of small volume prostate cancer in an 80-year-old man is unlikely to increase life

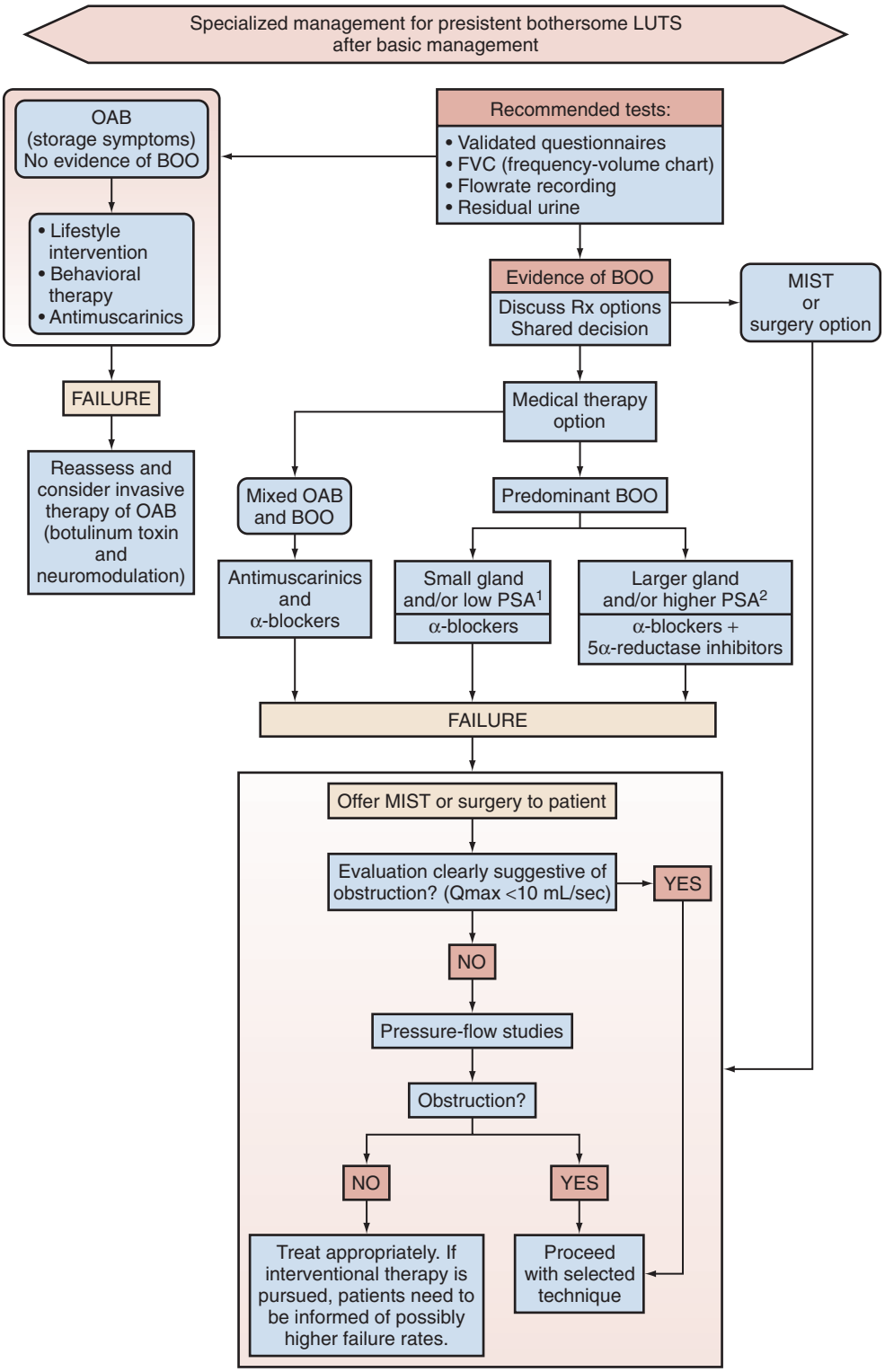


Figure 92–2. International Consensus guideline algorithm for management of lower urinary tract symptoms (LUTS) (2009): Specialized management. [1]PSA <1.5 ng; [2]PSA >1.5 ng; BOO, bladder outlet obstruction; MIST, minimally invasive surgical treatment; OAB, overactive bladder; PSA, prostate-specific antigen. (From Abrams P, Chapple C, Khoury S, et al. Evaluation and treatment of lower urinary tract symptoms in older men. J Urol 2009;181[4]:1779–87.)

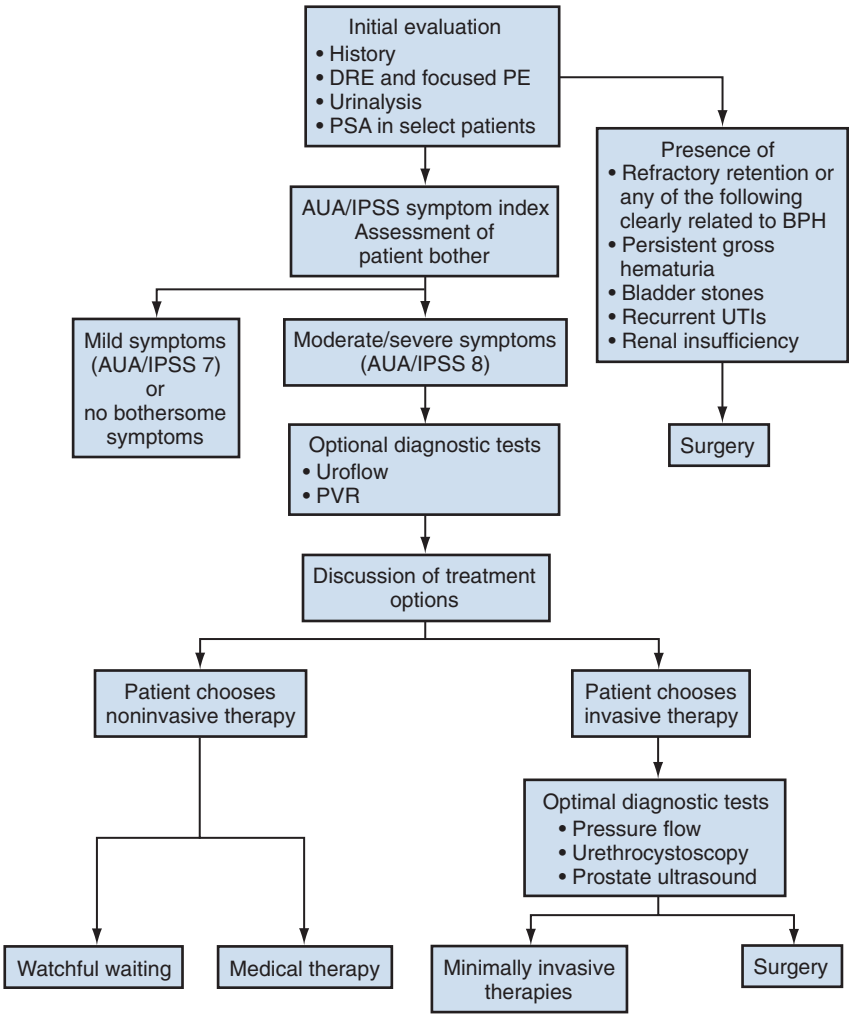


Figure 92–3. American Urological Association (AUA) guideline algorithm for management of benign prostatic hyperplasia (updated 2006). DRE, digital rectal examination; IPSS, International Prostate Symptom Score; PE, physical examination; PSA, prostate-specific antigen; PVR, postvoid residual. (From Kaplan SA. Update on the American Urological Association guidelines for the treatment of benign prostatic hyperplasia. Rev Urol 2006;8[Suppl. 4]:S10–7.)

expectancy. A PSA test and DRE increase the detection rate of prostate cancer over DRE alone. **Therefore measurement of the serum PSA value should be performed in patients in whom the identification of cancer would clearly alter BPH management** (Madersbacher et al, 2004; Kaplan et al, 2006; Abrams et al, 2009). There is significant overlap between the serum PSA values of men with BPH and men with clinically localized prostate cancer. Twenty-eight percent of men with histologically proven BPH have a serum PSA value greater than 4.0 ng/mL (McConnell et al, 1994). Serum PSA trends over time (PSA velocity), measurement of free versus complexed PSA, and PSA density may help to improve the specificity of PSA in men with BPH. Newer markers such as the PCA-3 test can also help to differentiate BPH from prostate cancer.

In the absence of prostate cancer the PSA value provides both a guide to prostate volume and also an indication of the likelihood of response to therapy with 5α-reductase inhibitors. However, in men with BPH already treated with a 5α-reductase inhibitor (e.g., finasteride [Proscar] or dutasteride [Avodart]) serum PSA is reduced 40% to 50% after 6 months of treatment. Failure to establish a baseline (pretreatment) PSA level may therefore complicate interpretation of future PSA values. Men who are taking these agents should have their PSA value doubled to correctly assess their risk of harboring a prostatic adenocarcinoma. Provided that this is done, recent evidence suggests that 5α-reductase therapy actually increases the sensitivity of PSA as a detector of cancer.

Symptom Assessment

The International Prostate Symptom Score (IPSS) is recommended as the symptom scoring instrument to be used for the baseline assessment of symptom severity in men presenting with LUTS (Kaplan et al, 2006; Abrams et al, 2009). When the IPSS system is used, symptoms can be classified as mild (0 to 7), moderate (8 to 19), or severe (20 to 35). The IPSS should also be the primary determinant of treatment response or disease progression in the follow-up period. Although other symptom score questionnaires are used, the IPSS is now the U.S. and international standard.

However, the IPSS cannot be used to establish the diagnosis of BPH. Men (and women) with a variety of lower urinary tract disorders (e.g., infection, tumor, neurogenic bladder disease) will have a high IPSS. Nonetheless, **the IPSS is the ideal instrument to grade baseline symptom severity, assess the response to therapy, and detect symptom progression in those men managed by watchful waiting.** Optimal treatment decisions in individual patients will also need to take into account how a given level of symptoms affects each man's quality of life (degree of bothersomeness).

The IPSS was developed from the AUA Symptom Index (AUASI) developed by the Measurement Committee of the AUA (Barry et al, 1992a, 1992b). Each question on the IPSS can yield 0 to 5 points, producing a total symptom score that can range from 0 to 35. This seven-question set is internally consistent (Cronbach alpha, 0.85) and reliable (test-retest correlation, 0.93). The index correlates strongly with patients' global ratings of their urinary difficulties (r = 0.78) and is sensitive to treatment response.

Johnson and associates (2009) showed that patients with a low education status are more likely to misunderstand the IPSS whether they are managed in public hospital or university practice. They tend to misrepresent their symptoms and therefore may receive inappropriate treatment. Eight percent of university hospital and almost 25% of public hospital patients under-reported their moderate symptoms as mild, and 33% of university hospital and 16% of public hospital patients over-reported their mild symptoms as moderate. When administered by a medical professional, many of the inaccuracies disappear even though the questionnaire is recommended as "self-administered." The use of the additional bother score or quality of life question may be useful in guiding appropriate treatment.

Although the IPSS correlates well with quality of life measures (Sagnier et al, 1995), there is still a need for sensitive BPH-specific quality of life instruments. Furthermore, because storage symptoms often predominate there is a need for better methods of quantifying urgency, frequency, and recording any incontinence. The standardization subcommittee of the International Continence Society has usefully categorized the range of likely symptoms into three groups: storage, voiding, and postmicturition (Abrams et al, 2003). Subdividing the IPSS into the four obstructive and three storage questions may also be useful. Other systems such as the Kings Score may be more sensitive to changes in storage symptoms. A voiding diary with frequency and volume recordings also may be helpful.

Clearly, symptom scores alone do not capture the complete picture of a prostate problem as perceived by the individual patient. Symptom impact on a patient's lifestyle must be considered as well. An intervention may make more sense for a moderately symptomatic patient who finds his symptoms very bothersome than for a severely symptomatic patient who finds his symptoms tolerable.

Additional Diagnostic Tests

Additional testing should be considered after the initial evaluation if there is a significant chance the patient's LUTS may not be due to BPH. Patients with a normal initial evaluation and only mild symptomatology on the IPSS (scores 0 to 7), or even more moderate symptoms but minimal bother, do not need additional diagnostic evaluation and can be considered for an active surveillance program and observed (Kaplan, 2006). Men who have developed serious complications of BPH should be treated surgically in most cases. Urinary flow rate, postvoid residual (PVR) urine volume, and pressure-flow urodynamic studies are appropriate tests to consider in the evaluation of men with moderate to severe symptoms (IPSS 8 to 35). The value of pressure-flow studies is debated, especially in men who elect watchful waiting or medical therapy as their management option. **Cystoscopy should not be done routinely** but is optional during later evaluation if invasive treatment is strongly considered. Urinary flow rate and PVR are generally recommended tests (Madersbacher et al, 2004; Kaplan, 2006; Abrams et al, 2009), and frequency-volume chart recordings are recommended by most clinicians (Madersbacher et al, 2004; Abrams et al, 2009).

It may be appropriate for the physician to offer treatment alternatives to the patient without performing any further diagnostic tests. Especially if the patient chooses watchful waiting or noninvasive therapy, invasive diagnostic tests may not be necessary. Conversely, if the patient elects an invasive treatment option, it may be appropriate for the physician to consider further evaluation.

Diagnostic Tests in Men Who Require Surgery for Benign Prostatic Hyperplasia

Surgery is generally recommended if the patient has refractory urinary retention (failing at least one attempt of catheter removal) or any of the following conditions clearly secondary to BPH: recurrent UTI, recurrent gross hematuria (resistant to 5α-reductase inhibitor therapy), bladder stones, renal insufficiency, or large bladder diverticula (McConnell et al, 1994; Denis et al, 1998; Kaplan et al, 2006; Abrams et al 2009). If there is reason to suspect that the patient's urinary retention may be due to detrusor hypocontractility, then urodynamic studies (e.g., filling cystometry) may be helpful. Pressure-flow urodynamic studies are not informative if the patient cannot urinate. Cystoscopy is appropriate to consider before the operative procedure to help plan the most prudent approach. The presence of infection and hematuria in patients should prompt appropriate evaluation and therapy for these conditions before treatment of BPH.

Uroflowmetry

Uroflowmetry is either generally recommended (by the AUA [Kaplan, 2006]), recommended for specialist investigation (Sixth International Consultation [Abrams et al, 2009]), or recommended generally and required before invasive treatment (EAU [Madersbacher et al, 2004]). Uroflowmetry involves the electronic recording of the urinary flow rate throughout the course of micturition. It is a common, noninvasive urodynamic test used in the diagnostic evaluation of patients presenting with symptoms of BOO. The results of uroflowmetry are nonspecific for causes of the symptoms. For example, an abnormally low flow rate may be caused by an obstruction (e.g., hyperplastic prostate, urethral stricture, meatal stenosis) or by detrusor hypocontractility. **The AHCPR Guideline Panel reached the following conclusions regarding uroflowmetry** (McConnell et al, 1994), which still apply:

- **Flow rate measurements are inaccurate if the voided volume is less than 125 to 150 mL.**
- **Flow rate recording is the single best noninvasive urodynamic test to detect lower urinary tract obstruction. Current evidence, however, is insufficient to recommend a given "cutoff" value to document the appropriateness of therapy.**
- **The peak flow rate (PFR; Qmax) more specifically identifies patients with BPH than does the average flow rate (Qave).**
- **Although PFR decreases with advancing age and decreasing voided volume, no age or volume correction is currently recommended for clinical practice.**

- **Although considerable uncertainty exists, patients with a PFR greater than 15 mL/sec appear to have somewhat poorer treatment outcomes after prostatectomy than patients with a PFR of less than 15 mL/sec.**
- **A PFR of less than 15 mL/sec does not differentiate between obstruction and bladder decompensation.**

The Fourth International Consultation on BPH concluded that flow rate measurement represents a reproducible way to quantify the strength of the urinary stream and, when used in combination with symptom scores for a small subset of patients (20%), has a high probability of correctly characterizing whether there is BOO (Denis et al, 1998).

Despite its limitations, flow rate recording has demonstrated some sensitivity in identifying BOO due to BPH. Scott and coworkers (1967) and Shoukry and associates (1975) found that PFR correlated better than symptoms with the presence or absence of obstruction as determined by pressure-flow studies. Siroky and coworkers (1979) concluded that uroflowmetry was able to separate physiologically unobstructed and obstructed patients. Gleason and colleagues (1982) found that PFR distinguished between normal men and patients with BPH, urethral stricture, or prostatitis. However, they also noted that a subgroup of patients with a decompensated detrusor muscle could not be separated from the obstructed men on the basis of PFR alone.

Chancellor and colleagues (1991) **found that flow rate recording cannot distinguish between BOO and impaired detrusor contractility as the cause for a low PFR.** None of eight measured, noninvasive urodynamic parameters was significantly different for 31 patients with outlet obstruction than for 14 patients with impaired detrusor contractility. Abrams and associates (1977, 1979) studied the value of uroflowmetry before prostatectomy. Failure rates for surgery were found to decrease with the addition of flow rate measurement to symptom assessment in preoperative evaluation.

PFR appears to predict surgical outcome in some studies. In one study reported by Jensen and coworkers (1984), 53 patients underwent prostatectomy based on clinical indication alone. All three groups according to level of PFR experienced improvements in their symptom score after surgery, but the group with a PFR less than 10 mL/sec before treatment had a better overall subjective outcome as assessed by global subjective judgment.

In another study, which included men studied with flow rates before and 6 months after prostatectomy (Jensen et al, 1988a), subjective evaluation revealed an overall symptomatic improvement rate of 80% after surgery. The difference in success rates for men falling above or below the cutoff value of PFR = 10 mL/sec was not significant ($P = .2$). When a PFR cutoff of 15 mL/sec was used, success rates for men above or below the cutoff value differed significantly.

McLoughlin and coworkers (1990), using urodynamic testing and a cutoff value of 12 mL/sec, evaluated 108 men with clinical BPH before and 1 year after surgery and determined that if using a PFR less than 12 mL/sec as an indicator for obstruction then only 3% of patients would have been subjected to an unnecessary TURP. These authors believed that the routine pressure-flow studies or cystometrograms were not indicated but that the screening of flow rates followed by further urodynamic testing in patients with a PFR of greater than 12 mL/sec should be considered. Very low rates do not appear to portend poor treatment outcome. In one study of 84 patients undergoing surgery for symptomatic BPH (Donkervoort et al, 1975), patients with a preoperative PFR less than 7 mL/sec improved symptomatically as much as patients with a PFR greater than 7 mL/sec.

Neither subjectively assessed symptoms nor quantified symptom score analysis correlates strongly with uroflowmetry measurements but each is an independent assessment. Patients with a PFR greater than 15 mL/sec may have somewhat poorer outcomes after surgery than those with a PFR less than 15 mL/sec (although the majority of patients still improve). Other investigators report similar findings for different PFR cutoff values (e.g., 12 mL/sec). Patients with very bothersome symptoms suggestive of clinical BPH but having a PFR greater than 15 mL/sec may benefit from further urodynamic testing (i.e., pressure-flow studies) to reduce the number of surgical treatment failures. A PFR less than 15 mL/sec does not differentiate between outflow obstruction and detrusor impairment. No minimal threshold of PFR reliably diagnoses detrusor failure or predicts a poor surgical outcome.

Postvoid Residual Urine Volume

Postvoid residual urine volume is the amount of fluid remaining in the bladder immediately after the completion of micturition. Studies indicate that PVR urine volume normally ranges from 0.09 to 2.24 mL, with the mean being 0.53 mL (Hinman and Cox, 1967). Seventy-eight percent of normal men have PVR volumes of less than 5 mL, and 100% have volumes of less than 12 mL (DiMare et al, 1963). The Agency for Health Care and Policy Research BPH Guideline Panel reached the following conclusions regarding PVR urine volume (McConnell et al, 1994):

- PVR urine volume measurement has significant intraindividual variability that limits its clinical usefulness.
- PVR urine volume does not correlate well with other signs or symptoms of clinical BPH.
- Large PVR urine volumes may predict a slightly higher failure rate with a strategy of watchful waiting. However, the threshold volume defining a poorer outcome is uncertain.
- It is uncertain whether PVR urine volume predicts the outcome of surgical treatment.
- It is uncertain whether PVR urine volume indicates impending bladder or renal damage.
- PVR urine volume can be measured with sufficient accuracy noninvasively by transabdominal ultrasonography. The measurement variation caused by the method is less than the biologic range of PVR variation.

The Fourth International Consultation initially recommended PVR volume determination in the initial assessment and during monitoring of patients under watchful waiting or other conservative treatment regimens (Denis et al, 1998).

PVR urine volume measurement can be performed by noninvasive (ultrasound) and invasive (catheterization) methods. Invasive techniques are accurate if performed correctly but carry a small, but clinically significant, risk of discomfort, urethral injury, UTI, and transient bacteremia. Small portable and less expensive devices can be used to measure the PVR urine volume with reported accuracy and are comparable to more expensive ultrasound units and catheterization. Birch and coworkers (1988) reported that of 30 men with BPH, 66% had wide variations in PVR urine volume when three measurements were done on the same day. In 34% of patients there was no difference among the three measurements. In 58%, at least two volumes were significantly different. In 8% of patients, all three were different. In most patients, two measurements were statistically similar whereas the third one yielded quite different results. Bruskewitz and colleagues

(1982) found similarly wide variations of the measured amount when they performed repetitive measurements of PVR urine volume (repeated two to five times) by in-and-out catheterization on 47 men before prostatectomy. They also found no correlation between the amount of residual urine and any cystoscopic or urodynamic findings, symptoms, or the presence or absence of a history of UTIs. Most clinical studies demonstrate minimal correlation between PVR urine volume and baseline measurements of symptoms, flow rate, or urodynamic measures of obstruction (Griffiths and Castro, 1970; Shoukry et al, 1975; Abrams and Griffiths, 1979). However, Neal and associates (1987) found a significant association in 253 men between PVR urine volume, age, "below normal" PFR, and high urethral resistance. Low voiding pressure, however, did not correlate well with the PVR amount. The authors concluded that outflow obstruction is related to the development of increasing amounts of PVR urine. In the AUA Outcome Study, Barry and colleagues (1993) found a significant correlation between high PVR urine volumes and low flow rates but no correlation with IPSS.

Traditionally, urologists have assumed that increasing amounts of PVR urine denote BPH progression and are thus an "indication" for surgery. This concept underlies the common inclusion of PVR urine volume in each individual government's appropriateness criteria. Unfortunately, data are lacking to support the predictive value of PVR urine volume. Andersen (1982) studied 104 men with BPH and reported two patterns of BPH progression. The slow course was characterized by the development of high levels of PVR urine that resulted in decompensation of the detrusor muscle and eventually led to urinary retention. The fast course was associated with uninhibited detrusor contractions. The amount of PVR urine, the presence of uninhibited detrusor contractions, and symptoms correlated poorly in the study. Nevertheless, Andersen recommended the PVR urine volume as a safety parameter when measured longitudinally throughout the clinical course of a patient with prostatism.

Data from the Veterans Affairs (VA) cooperative study group randomized trial comparing TURP with watchful waiting demonstrated that PVR urine volume does not predict the outcome of surgery, and there was little evidence to support criteria that require a certain amount of PVR urine before surgery is justified. Additionally, a high PVR urine volume did predict a slightly higher failure rate for watchful waiting. However, the majority of men with large PVR urine volume did not require surgery during the 3-year duration of the trial. In summary, **PVR urine volume is best viewed as a "safety parameter." Men with significant PVR amounts should certainly be monitored more closely if they elect nonsurgical therapy, particularly if antimuscarinic therapy is chosen.**

Pressure-Flow Studies

If the initial evaluation, flow rate, and PVR urine volume are not sufficiently suggestive of BOO, further urodynamic assessment by pressure-flow studies should be considered, especially if an invasive treatment is considered (i.e., surgery) or if surgical treatment has failed (McConnell et al, 1994; Denis et al, 1998; Kaplan et al, 2006; Abrams et al, 2009). **Pressure-flow studies differentiate between patients with a low PFR secondary to obstruction and those whose low PFR is caused by impaired detrusor contractility.** These studies should be performed when the distinction between the two will affect therapeutic decisions. Patients with a history of neurologic diseases known to affect bladder or sphincteric functions, as well as patients with normal flow rates (PFR > 15 mL/sec) but bothersome symptoms, may also benefit from urodynamic evaluation and especially if surgical therapy is contemplated.

The value of pressure-flow measurement in predicting treatment outcome is uncertain. In a study by Abrams and colleagues (1979), the inclusion of pressure-flow data in the preoperative evaluation and indication for surgery reduced the subjective failure rate to 12%, down from 28% when patients were certified as candidates for surgery without the urodynamic data. However, a 28% failure rate is significantly higher than that reported in other TURP series (McConnell et al, 1994). Jensen and Andersen (1990) recommended invasive urodynamic testing for patients with a PFR greater than 15 mL/sec. For the population in their study this would have resulted in an additional 9% of patients being excluded from surgery and a decrease in failure rate to 8.3%. The support for this recommendation has to be questioned, however, in light of an earlier study by Jensen and coworkers (1988b, 1988c) that found most unsatisfied patients are incorrectly classified preoperatively even with urodynamic testing.

Pressure-flow studies do permit more accurate categorization of patients. Abrams and associates (1979) used pressure-flow plots in addition to flow rate measurement. The study found that in about half the cases the patients with LUTS could be correctly classified as obstructed or nonobstructed by PFR alone but that the addition of the detrusor pressure (Pdet) at PFR allowed correct classification in two thirds of the group. The remaining one third of the patients were assessed by pressure-flow plot. In many of these patients, both Pdet and PFR were low, indicating a decompensating detrusor muscle as the source for the low PFR.

Pressure-flow studies provide much more specific insight into detrusor function and the etiology of voiding dysfunction than do flow rate measurements. However, a number of outcome-based investigations demonstrate a modest additional value of pressure-flow studies over symptom and flow rate evaluation. **Discussion of treatment options and the nature of the investigation with the patient is recommended before pressure-flow testing is organized.**

Filling Cystometry (Cystometrography)

Filling cystometry adds limited information to the evaluation of most men with LUTS and is not recommended in routine cases. The test may have value in the evaluation of patients with known or suspected neurologic lesions and LUTS, but pressure-flow studies provide more specific information.

Urethrocystoscopy

Urethrocystoscopy is not recommended to determine the need for treatment. Although the linkage between the endoscopic appearance of the lower urinary tract and the treatment outcome is poorly documented, available information suggests that the relationship is minimal (McConnell et al, 1994). The test is recommended for men with LUTS who have a history of microscopic or gross hematuria, urethral stricture disease (or risk factors such as history of urethritis or urethral injury), bladder cancer or suspicion of carcinoma in-situ, or prior lower urinary tract surgery (especially prior TURP). Urethrocystoscopy may be considered in men with moderate to severe symptoms who have chosen (or require) surgical or other invasive therapy to help the surgeon determine the most appropriate technical approach.

For example, if urethrocystoscopy reveals a large middle lobe, transurethral incision of the prostate (TUIP) is unlikely to be successful. The decision to perform an open prostatectomy or laser vaporization may be appropriately influenced by the shape of the

gland, as well as its size. Urethroscopy is therefore performed to select (or rule out) specific techniques, not to determine the need for treatment.

Imaging of the Upper Urinary Tract

Upper urinary tract imaging is not recommended in the routine evaluation of men with LUTS unless they also have one or more of the following: hematuria, UTI, renal insufficiency (ultrasonography recommended), history of urolithiasis, or history of urinary tract surgery (McConnell et al, 1994; Denis et al, 1998; Kaplan et al, 2006; Abrams et al, 2009). Intravenous urography before BPH treatment was performed by 73.4% of urologists in the United States in the late 1980s (Holtgrewe et al, 1989) and is associated with a 0.1% incidence of significant adverse events. Generally, ultrasound imaging is now preferred but is unnecessary in the uncomplicated case.

The presence or history of hematuria, renal insufficiency, UTI, and/or history of stones or prior urinary tract surgery increases the likelihood that imaging will demonstrate clinically significant findings (Juul et al, 1989; Andrews et al, 2002). Although there are no conclusive data on the combined incidence of the important clinical predictors just listed, approximately one third of all men with BPH have one or another indication for urinary tract imaging.

ASSESSING THE EFFECTIVENESS AND SAFETY OF MEDICAL THERAPY

The role of treatment for any disease process depends on the magnitude of the clinical effect and the incidence and severity of treatment-related morbidity. Assessing the effectiveness of medical therapies for BPH requires defining clinically relevant end points, identifying quantitative and reliable clinical outcome measures, eliminating investigator and patient bias, accounting for the placebo response, and enrolling the proper number of subjects so that only clinically significant changes are statistically significant. Assessing the safety of medical therapies requires a rigorous effort to identify all treatment-related clinical, biochemical, teratogenic, and mutagenic adverse effects associated with drug treatment.

Clinical End Points

The clinical consequences of BPH includes LUTS and associated reduction of quality of life, detrusor dysfunction characterized by detrusor acontractility, detrusor instability, and detrusor fibrosis; incomplete bladder emptying; acute and chronic urinary retention; UTI; renal insufficiency; and hematuria (Shapiro and Lepor, 1995). **The goals of treatment for BPH include relieving LUTS, decreasing BOO, improving bladder emptying, ameliorating detrusor instability, reversing renal insufficiency, and preventing disease progression, which may include a deterioration of symptoms, future episodes of gross hematuria, UTI, AUR, or the need for surgical intervention.**

Quantitative Outcome Measures

Symptoms

The primary objective of the AUASI (now IPSS) was to provide a universally accepted instrument to quantify the impact of BPH therapies on LUTS (Barry et al, 1992a, 1992b). There is no standardized format for reporting changes in the AUASI or other quantitative indices of symptom severity after treatment. Symptom response has been reported as a percentage of patients achieving a threshold response or as group mean changes in a symptom score. The literature typically reports the percentage of men achieving between a 30% and a 50% reduction in the symptom score. Expressing the symptom response as a single threshold response does not discriminate the overall magnitude of the clinical effect. When the baseline symptom scores are mild to moderate, small and clinically insignificant changes correspond to large percentage changes. When baseline symptom scores are severe, relatively large absolute changes may not be clinically significant. Symptom outcome should be expressed both as a percentage of patients achieving a threshold reduction response and as group mean changes in the symptom score.

The clinical significance of changes in the AUASI score were reported by Barry and colleagues (1995). There were 1165 subjects who participated in a randomized double-blind placebo-controlled study of medical therapy and completed the AUASI at baseline and after 3 months of treatment. The absolute and percentage changes in AUASI and BPH Impact Index scores were correlated with five global ratings of symptom improvement. The group mean changes in AUASI for subjects rating their improvement as markedly, moderately, or slightly improved, unchanged, or worse were –8.8, –5.1, –3.0, –0.7, and +2.7, respectively. The relationship between the patients' global ratings of improvement and the AUASI and BPH Impact Index changes were dependent on the baseline AUASI score. This important study provides the data required to determine sample sizes and interpret the clinical significance of symptom improvement in BPH clinical trials. A 3-point change appears perceptible to symptomatic men.

Bladder Outlet Obstruction

Experimental animal models of BOO have demonstrated profound changes in bladder ultrastructure, cellular composition, metabolism, and function resulting from BOO (Levin et al, 2000). These experimental observations must be cautiously extrapolated to man, because the response to BOO depends on the species and the severity and duration of obstruction. Animal studies demonstrate that under experimental conditions BOO causes alterations likely to adversely affect bladder function. The justification for measuring and treating BOO in men with BPH is to reverse or prevent these deleterious consequences of BOO.

Because synchronous pressure-flow urodynamic measurements do not correlate with severity of bladder dysfunction, severity of symptoms, or response to therapy, it is difficult to require these studies when evaluating the effectiveness of medical therapy for BPH. Long-term studies are needed to determine whether urodynamic measurements predict disease progression. At the present time the primary use of urodynamic testing is to discriminate the differential diagnosis of men presenting with multiple potential causes for LUTS.

Uroflowmetry represents a noninvasive and inexpensive but indirect indicator of urinary performances measure of BOO (Siroky, 1990). The reporting of PFR has been standardized (Abrams et al, 2003). At the lower spectrum of PFR a relatively small absolute change (i.e., 4 to 6 mL/sec) corresponds to a relatively high percentage change, whereas at the higher end of PFR a relatively large absolute change (i.e., 12 to 17 mL/sec) corresponds to a relatively modest percent change. The clinical significance of the changes in PFR cannot be defined, owing to

the lack of correlations with relevant clinical, physiologic, or biochemical outcomes.

Bladder Emptying

The clinical significance of PVR urine volume measurement is controversial. Barry and colleagues (1993) reported no correlation between AUASI score and PVR amount. It has been suggested that the PVR urine volume may predispose to UTI and irreversible bladder dysfunction secondary to stasis and overdistention. **There are no data clearly documenting that the incidence of UTI is related to the PVR urine volume.** Another limitation of PVR urine measurements is variability over short intervals of time (Bruskewitz et al, 1982). It is imperative to measure the PVR volume on several occasions if this parameter will influence treatment decisions.

There is no standardization for reporting changes in PVR urine volume. Typically, the data are presented as absolute group mean changes. The majority of BPH clinical trials exclude subjects with high baseline PVR amount (>300 mL) because of the potential risks of randomization to a placebo or ineffective treatment group. **Therefore the majority of subjects enrolled in clinical trials have clinically insignificant baseline PVR urine volumes, potentially undermining the relevance of most trials to "real world" practice.**

Bladder Overactivity

The definition of bladder overactivity (detrusor instability) is the development of a detrusor contraction exceeding 15 cm H_2O at a bladder volume less than 300 mL (Jepsen and Bruskewitz, 2000). The clinical significance of an overactive bladder (OAB) in men with BPH is unresolved. There is no evidence that men with detrusor instability electing watchful waiting are predisposed to develop disease progression. The presence of an OAB does not reliably predict response to medical or surgical treatment. **Therefore improvement of an OAB is not a standard outcome measure in clinical trials.**

Urinary Tract Infection, Renal Insufficiency, and Hematuria

Unlike other manifestations of BPH, the diagnosis of UTI, renal insufficiency, and hematuria is not controversial and the requirements for measurement are noninvasive and inexpensive. Because these events are not disease or gender specific, one must be cautious in assuming a causal relationship to BPH. There is no convincing evidence that UTI in the aging male population is associated with either PVR urine or BOO. It is reasonable to assume that renal insufficiency occurs secondary to urinary retention if renal failure is reversed after catheter drainage. Hematuria may be associated with prostatic vascularity and may sometimes respond to medical therapy with a 5α-reductase inhibitor.

Because the incidences of UTI, renal insufficiency, and hematuria are relatively uncommon and non–disease-specific events in the aging male population, it would be extremely difficult to design a prospective study to determine whether any BPH treatment prevents these events in an unselected cohort of men.

Eliminating Bias

***Bias* may be defined as a systematic error or difference between the true value and that actually attained from all causes other than sampling ability. The only mechanism to ensure that the potential bias of the subject and the investigator does not influence the outcome is a randomized, placebo-controlled, double-blind design.** Because subjects are typically randomized to receive a drug or its matching placebo, any effect of the investigators' bias would occur equally in the intervention and control groups.

The importance of eliminating bias cannot be overemphasized in BPH clinical trials. Some patients are very enthusiastic about receiving the "new" treatment. In the absence of a blinded randomization, these patients may be disproportionately directed into the active treatment groups. A subject receiving a known placebo would be reluctant to report any adverse events or clinical response. An investigator may be inclined to censor various outcomes if treatment group assignment is known. Although subjective outcome measures such as symptoms are more likely to be influenced by the placebo response, quantitative outcome measurements such as the PVR urine volume and PFR are also subject to a placebo response.

The placebo effect can be substantial in trials of drug treatment of BPH. **Trials should therefore include a placebo run-in period before recording baseline values.** Therefore these baseline values have already incorporated the placebo effect before any comparison is made. Ideally a 4-week placebo run-in period before initiation of treatment should be included in any trial design.

Similarly, the statistical concept of "regression toward mean" should also be taken into account in trial design. If measuring urinary symptom scores or PFRs, for instance, then in any population there will be some individuals whose values will be recorded at the extremes of the range for that population. These individuals, when followed up with sequential measurements of the same parameters, will tend to produce values that are less extreme and closer to the mean for the population being studied. Again, incorporating a placebo run-in period will allow this process to occur, at least to a degree, so that subsequent measurements from the baseline values determined after the placebo run-in period are more likely to be in response to a true treatment effect rather than to these two potentially confounding and misleading processes.

Sample Size

It is a general misconception that the validity of a clinical trial is directly proportional to the number of subjects enrolled. One of the objectives of a clinical trial is to determine whether the difference observed between two different treatment groups is clinically relevant. If the sample size of the clinical trial is properly determined in the early planning phase, a statistically significant outcome represents a clinically significant outcome. Calculation of sample size with provisions for adequate levels of significance and power is an essential part of planning a trial. Enrolling an excessive number of subjects may result in an overpowered study; that is, a small and clinically insignificant difference may be statistically significant. Conversely, enrolling insufficient numbers of subjects may result in an underpowered study; that is, a large and clinically significant difference may not be statistically significant. The larger the number of subjects enrolled in a study, the smaller is the change that is required to achieve statistical significance. Therefore the reader must examine the magnitude of the between-group difference and make a judgment about clinical significance.

Adverse Events

For a drug to enter into clinical investigation in humans it must be shown to elicit no significant chemical, behavioral, physiologic, teratogenic, mutagenic, or carcinogenic effects in at least two animal models. **The typical untoward or adverse events captured in a clinical trial include physical findings, laboratory results, and complaints.** A comprehensive physical examination and a battery of general laboratory tests are obtained at baseline and at the completion of the trial to capture any untoward events. The subjects' complaints are typically captured at each study visit. The adverse clinical effects may be expected or unexpected.

Complaints may be elicited by means of a checklist or by the subjects' unsolicited recall of an event. **Adverse clinical events are typically greater with a checklist.** The assessment of adverse events should determine the frequency and severity of the events and whether an event was severe enough to terminate participation in the study. The majority of clinical trials are powered based on outcome measures and not adverse events. **There is a tendency for studies to be underpowered to detect** serious adverse events that may therefore only show up later in postmarketing surveillance studies.

NONSURGICAL THERAPY

Watchful Waiting or "Self-Help"

A significant proportion of men with LUTS will not choose medical or surgical intervention because the symptoms are not bothersome, the complications of treatment are perceived to be greater than the inconvenience of the symptoms, and there is a reluctance to take a daily pill owing to side effects and/or the cost of treatment. Reassured that the symptoms are not caused by cancer or other serious genitourinary pathology, or that the delay in treatment will not have irreversible consequences, watchful waiting is often the patient-driven treatment of choice in the absence of absolute indications for intervention. Of 670 consecutive men with BPH referred to 39 urologists in the Netherlands, 41% elected watchful waiting (Stoevelaar et al, 1999). It is unreasonable to discourage an informed patient with severe symptoms and no other consequences of BPH from pursuing watchful waiting despite the safety and effectiveness of medical therapy. Watchful waiting does not imply the total absence of intervention. The severity and bother due to symptoms may be improved by simple measures such as decreasing total fluid intake especially before bedtime, moderating the intake of alcohol- and caffeine-containing products, and maintaining timed voiding schedules.

The impact of watchful waiting was examined in a study of 556 subjects with moderate symptoms of BPH randomized to TURP versus watchful waiting (Wasson et al, 1995). The changes in all outcome measures were significantly greater in the TURP group. A relevant outcome for patients selecting watchful waiting is disease progression. During 3 years of follow-up, treatment failure was observed in 23 (8.2%) and 47 (17%) of subjects randomized to TURP and watchful waiting, respectively. Treatment failure in the watchful waiting group was most often the result of increasing PVR volume or symptom score. Significant renal impairment was not seen.

Brown and associates (2007) evaluated the effectiveness of self-management as a first-line intervention for men with LUTS in a randomized controlled trial set in a teaching hospital and a district general hospital in London. One hundred forty men were randomized between standard care and "self-management," which comprised three small group sessions of relevant urinary education and lifestyle advice. Self-management significantly reduced the frequency of treatment failure and reduced urinary symptoms. Because of the large observed benefit of self-management, these investigators suggested a large multicenter trial to confirm whether self-management could be considered as first-line treatment for men with LUTS.

MEDICAL THERAPY

Medical therapies extensively investigated for BPH include α-adrenergic blockers, 5α-reductase inhibitors, aromatase inhibitors, and numerous plant extracts. Newer therapies include antimuscarinic drugs and phosphodiesterase inhibitors (PDEIs) and several combinations of these agents. α-Adrenergic blockers and 5α-reductase inhibitors, and the combination of both of these, are emphasized in this chapter because the safety and efficacy of drugs in these classes have been critically examined and these drugs are widely prescribed for the treatment of BPH. Aromatase inhibitors are briefly reviewed for historical interest. Plant extracts are also reviewed, because these agents are widely used in some parts of the world, despite the lack of properly designed clinical trials. Because plant extracts are not classified as drugs, the marketing and claims are not critically scrutinized by regulatory agencies.

The Impact of Medical Therapy

Prior to the 1980s, prostatectomy was the only widely accepted intervention for BPH. **The enthusiasm for medical therapy has been supported in part by the limitations of prostatectomy, which include the morbidity of the surgical procedure, failure to invariably achieve a successful outcome, and a small but significant re-treatment rate** (Lepor, 1993). Although medical therapies do not achieve the same level of efficacy as prostatectomy, the attractive features of medical therapy relative to prostatectomy are that clinically significant outcomes are obtained with fewer, less serious, and reversible side effects (Lepor, 1993). Because the indication for intervention in the overwhelming majority of patients with BPH is to improve quality of life by relieving symptoms (Emberton et al, 2008), the lower morbidity of medical therapy is of paramount importance in patient-driven treatment decisions.

In 1990, TURP was second only to cataract surgery in terms of expenditures paid by the U.S. Medicare program. **Medical therapy is currently considered the preferred treatment alternative for those individuals who lack absolute indications for surgery. Because the overwhelming majority of men undergoing TURP lack absolute indications for intervention** (Mebust et al, 1989) and prefer nonsurgical options (Emberton et al, 2008), the number of prostatectomies performed throughout the world has decreased significantly. A survey of the U.S. Medicare database also revealed that the absolute number of prostatectomies decreased from 250,000 in 1987 to 116,000 in 1996 to 88,000 in 2000 (Wasson, 2000) and stabilized since then. This 55% reduction in TURP has occurred despite the progressively increasing number of men enrolled in the Medicare program and overall increase in U.S. spending on BPH (Wei et al, 2005). Similar

reductions in TURPs have been reported from France, Canada, Denmark, and Germany.

Approximately 30% of American men older than 50 years have moderate to severe symptoms (Chute et al, 1993; Lepor and Machi, 1993). **Based on the demographics of the U.S. population, 6.5 to 8.7 million men are eligible to discuss BPH treatment options** (Wei et al, 2005; Jacobsen et al, 1995). The overwhelming majority of these men would not elect prostatectomy, owing to the risks associated with surgical intervention. These individuals are potential candidates for medical therapy.

Selecting Candidates for Medical Therapy

The ideal candidate for medical therapy should have symptoms that are bothersome and negatively affect quality of life so that the patient is willing to make a lifetime commitment to medical therapy, providing the drug is effective and adverse experiences are either nonexistent or minimal. There are currently no scientific data to support offering medical therapy to individuals presenting with absolute indications for intervention. Individuals presenting with recurrent urinary retention, recurrent UTIs, renal insufficiency, bladder calculi, and recurrent gross hematuria may develop life-threatening consequences from their BPH if it is not managed surgically. **Until properly controlled clinical studies unequivocally demonstrate favorable outcomes, patients presenting with absolute indications for intervention should be discouraged from selecting medical therapy.** If informed patients are willing to accept potential risks, medical therapy may be offered with a proviso for careful follow-up and future prostatectomy if medical therapy proves ineffective.

Preventing Benign Prostatic Hyperplasia with Medical Therapy

A potential role of medical therapy is to prevent the development of BPH or its progression. There are several factors limiting the enthusiasm for preventing the development of BPH. The clinical manifestations of BPH are rarely life threatening. Preventative intervention would have to be initiated before the fifth decade of life coinciding with the development of BPH (Partin, 2000). The long-term exposure to drug-induced adverse events and the prohibitive costs are the primary limitations of prevention therapy. In addition, effective medical and surgical therapy exists when BPH ultimately does becomes clinically evident. Because there are no clinical, biochemical, or genetic predictors of BPH development or progression, every man is potentially at risk. The ability to identify those individuals who are predisposed to develop clinical BPH refractory to medical therapy would provide a more compelling rationale for prophylaxis. There is good evidence that men with very large prostates (and usually higher PSA values) are at greater risk for developing urinary retention (Jacobsen et al, 1997) and that medical therapy (finasteride or dutasteride) can significantly decrease this risk of developing urinary retention (McConnell et al, 1998; Roehrborn et al, 2004). The decision to offer preventative therapy for urinary retention depends on the risk of the events, cost associated with treatment, and patient preferences for intervention.

Therapy with α-Adrenergic Blockers

Rationale

The rationale for α-adrenergic blockers in the treatment of BPH is based on the hypothesis that the pathophysiology of clinical BPH is in part caused by BOO, which is mediated by α_1-adrenergic receptors associated with prostatic smooth muscle (Caine, 1986) (Fig. 92–4). The importance of this dynamic obstruction was supported by morphometric studies demonstrating that smooth muscle is one of the dominant cellular constituents of BPH, accounting for 40% of the area density of the hyperplastic prostate (Shapiro et al, 1992). Caine and coworkers (1975) reported that the human prostate contracts in the presence of the α-adrenergic agonist norepinephrine. Several investigators subsequently demonstrated that the tension of prostate smooth muscle is mediated by the α_1 receptor (Hieble et al, 1985; Lepor et al, 1988; Gup et al, 1989). Lepor and colleagues (1988) were the first investigators to characterize the α_1 receptor in the human prostate using radioligand binding studies. These investigators subsequently reported that 98% of the α_1 receptors are localized to the prostatic stroma (Kobayashi et al, 1994). The importance of the adrenergic innervation of the prostate was further supported by the observation of high levels of norepinephrine in the human prostate (Lepor et al, 1990). Although the finding of high levels of smooth muscle α_1 receptors and norepinephrine in the human prostate suggests an important role of the adrenergic innervation in prostatic function, it cannot be assumed that these factors are directly responsible for clinical BPH. Lepor and associates (1990) reported no significant differences between norepinephrine levels, α_1 receptor density, or isometric contractile responses to phenylephrine (Gup et al, 1989) in BPH tissues obtained from men with symptomatic and asymptomatic BPH. Other investigators have shown α_1 receptor levels are higher in prostatic adenoma relative to prostatic capsule (Yamada et al, 1987; Kawabe et al, 1990). These observations simply show regional differences of α_1 receptors in the prostate and do not prove that clinical BPH is caused by upregulation of the α_1 receptor.

The most definitive evidence that blockade of prostate α_1 receptors relieves BOO was the observed direct relationship between the area density of prostate smooth muscle and the change in the PFR

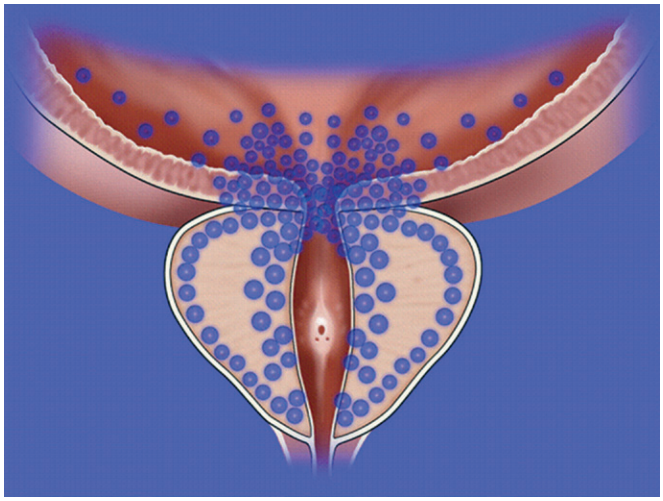


Figure 92–4. Distribution of α_1-adrenergic receptors in the lower urinary tract.

in 26 subjects undergoing prostatic biopsy before initiating α-adrenergic blocker therapy with terazosin (Hytrin) (Shapiro et al, 1992). Although the prostates of those subjects achieving symptom improvement had a significantly greater group mean area density of smooth muscle compared with those of nonresponders, a direct relationship between prostate smooth muscle area density and change in symptom scores was not observed. These observations suggest that nonprostate smooth muscle–mediated α_1 receptor events may also be responsible for the effectiveness of α-adrenergic blockade and that α_1 receptor–mediated symptom improvement and decreases in BOO are mediated by different mechanisms.

Classification of α-Adrenergic Blockers

α-Adrenergic blockers may be classified according to α receptor selectivity and serum elimination half-life (Table 92–1)

Phenoxybenzamine, a nonselective α blocker, was shown to be highly effective for BPH (Caine et al, 1976, 1978). The limitation of phenoxybenzamine was the high incidence and severity of adverse clinical events. Berthelsen and Pettinger (1977) described two subtypes of the α receptor (α_1 and α_2). Prazosin was one of the first α_1 receptor antagonists to be investigated for the treatment of BPH (Hedlund et al, 1983). **The efficacy of phenoxybenzamine and prazosin are comparable; however, prazosin is better tolerated, implying that efficacy and toxicity are mediated primarily by the α_1 and α_2 receptors, respectively** (Lepor, 1989). Prazosin and other α_1 antagonists, including intermediate-release (IR) alfuzosin (Jardin et al, 1991) and indoramin (Ramsay et al, 1985), require at least twice-daily dosing, owing to the relatively short serum elimination half-lives. **The next advance in the development of α-adrenergic blockers was the development of advanced drugs with serum elimination half-lives that allowed for once-a-day dosing.** Terazosin (Hytrin) (Lepor et al, 1992) and doxazosin (Cardura) (Gillenwater et al, 1995), tamsulosin (Flomax) (Chapple et al, 1997; Narayan and Tewari, 1998; Wilt et al, 2002b), and extended-release alfuzosin (UroXatral) (McNeill et al, 2005; van Kerrebroeck et al, 2000) are long-acting α-adrenergic blockers that have been shown to be safe and effective for the treatment of BPH.

Molecular cloning studies have identified three subtypes of the α_1 receptor (Andersson et al, 1997). Price and coworkers (1993) reported that the mRNA encoding the α_{1A} receptor is predominant in the human prostate. The fact that the α_{1A} mRNA is translated does not mean the encoded protein is translated. Lepor and associates reported that using autoradiographic (Kobayashi et al, 1994) and immunohistochemical (Walden et al, 1997) techniques, the α_{1A} and α_{1B} receptors are predominant in the human stroma and epithelium, respectively. Prostate smooth muscle tension has been shown to be mediated by the α_{1A} receptor (Forray et al, 1994).

Tamsulosin is a once-daily administered α_1 antagonist that exhibits some modest degree of selectivity for the α_{1A} versus the α_{1B} receptor and no selectivity for the α_{1A} versus the α_{1D} receptor (Foglar et al, 1995). The pharmaceutical industry has developed α_1 antagonists that are 1000-fold selective for the α_{1A} receptor versus α_{1B}/α_{1D} (Forray et al, 1994). Recently, silodosin (Rapaflo) has been introduced. This agent shows 162:1 selectivity for α_{1A} versus α_{1B} adrenoceptors and is achieving promising results.

Table 92–1.

Classification of α-Adrenergic Blockers and Recommended Doses

CLASS OF α-ADRENERGIC BLOCKER	DOSE
Nonselective	
Phenoxybenzamine	10 mg bid
α_1	
Prazosin	2 mg bid
IR Alfuzosin	2.5 mg tid
Indoramin	20 mg bid
Long-Acting α_1	
Terazosin	5 or 10 mg qd
Doxazosin	4 or 8 mg qd
Alfuzosin SR	10 mg qd
Subtype Selective	
Tamsulosin	0.4 mg qd
Silodosin	8 mg qd

Interpreting the α-Adrenergic Blocker Literature

Meta-analyses derived from the α-adrenergic blocker literature are often misleading because all of the data for a given drug are combined independent of dose and study design.

Study Designs. Four study designs have been used to investigate α-adrenergic blockers for BPH: titration to fixed dose, titration to response, titration to maximal dose, and randomized dose withdrawal.

Subjects enrolled in **titration to fixed dose** studies receive one of several predetermined final doses independent of clinical response unless significant adverse effects are encountered. An advantage of this study design is that dose-dependent efficacy and safety of different doses are determined. A disadvantage is the requirement for a large sample size to identify statistically significant differences between placebo and all of the treatment groups.

Titration to response design allows the investigators to titrate the dose to a threshold response or maximal dose. An advantage of this design is a smaller sample size because all subjects receiving active treatment are analyzed as a composite group independent of final dose. A disadvantage of this design is that the maximal therapeutic effect may be underestimated if the titration is not to maximal response. The data are also misleading if expressed in terms of group mean changes according to final dose because all nonresponders are titrated to the maximal dose in the absence of toxicity.

A randomized dose withdrawal design begins with an open-label dose titration. All responders are randomized to active drug or placebo. An advantage of this design is the enrichment of responders. A disadvantage is that the results are not generalizable to untreated patients.

A titration to maximal dose design, like titration to response, requires a relatively small sample size because there is only one active treatment group. This study design defines maximal clinical response achievable in practice, providing the maximal dose is also the most efficacious tolerable dose.

Dose Response. Multicenter, randomized, placebo-controlled studies have consistently shown that symptom and flow improvement is dependent on the dose of the α_1 blockers. **The differences between the effectiveness of different doses were often not statistically significant because these dose-ranging studies were not adequately powered to show significant differences between dose groups.** MacDiarmid and coworkers (1999) have provided the most compelling evidence for a positive correlation relationship between dose and effectiveness of α_1 blockers in the treatment of BPH. Responders to 4 mg of doxazosin were randomized in a double-blind manner

Table 92–2.

Efficacy of Terazosin in Benign Prostatic Hyperplasia

STUDY	ENROLLED (No.)	RANDOMIZED TREATMENT (mo)	DOSE (mg)	Group Mean Difference from Placebo	
				PFR (mL/sec)	Symptom Score
Lepor et al, 1992	285	3	2	+1.1	−1.0
			5	+0.6	−1.3*
			10	+1.9†	−2.3‡
Brawer et al, 1993	160	6	Titration to response§	+1.4*	−3.5*
Roehrborn et al, 1996	2084	12	Titration to response§	+1.4*	−4.0‡
Elhilali et al, 1996	224	6	Titration to response§	+1.3	−1.8

*$P < .05$.
†$P < .01$.
‡$P < .001$.
§Maximal dose 10 mg.
PFR, peak flow rate.

to receive 4 mg or 8 mg of doxazosin. The improvement observed in the 8-mg group was 3.7 symptom units greater than in the 4-mg group ($P = .03$). In phase 3 trials, the impact of dose observed in the responders is diluted by the lack of effect in the nonresponders. In clinical practice, nonresponders are withdrawn from treatment.

Review of the Literature

Several reviews have summarized the extensive clinical experiences with α-adrenergic blockade in BPH (Chapple, 1998; Djavan and Marberger, 1999; Lowe, 1999; Lepor, 2000; Roehrborn et al, 2004; Kaplan, 2008). Nonselective and short-acting α_1 antagonists are used less commonly in clinical practice, owing to tolerance and the requirement for multiple daily dose. Randomized, double-blind, placebo-controlled studies have reported the safety and efficacy of phenoxybenzamine (Caine et al, 1978; Abrams et al, 1982), prazosin (Hedlund et al, 1983; Kirby et al, 1987; LeDuc et al, 1990; Ruutu et al, 1991; Chapple et al, 1992), indoramin (Iacovou and Dunn, 1987; Chow et al, 1990; Stott and Abrams, 1991), and IR alfuzosin (Ramsay et al, 1985; Carbin et al, 1991; Jardin et al, 1991; Hansen et al, 1994). With the exception of alfuzosin, these studies typically enrolled relatively small numbers of subjects into short-term single-dose studies without quantitative assessment of symptom improvement. **Multicenter, randomized, double-blind, placebo-controlled studies have examined the safety and efficacy of the long-acting α-adrenergic blockers terazosin, doxazosin, tamsulosin, and slow-release (SR) alfuzosin. Subjects enrolled in these studies generally presented with moderate to severe symptoms, PVR less than 300 mL, and no absolute indications for surgical intervention.** Representative studies are reviewed to illustrate the safety, efficacy, and most effective use of α-adrenergic blockers in BPH. The reader is referred to the original articles for more comprehensive outcome assessments.

Terazosin. Randomized, double-blind, multicenter, placebo-controlled studies have consistently demonstrated the efficacy and safety of terazosin for BPH (Di Silverio, 1992; Lepor et al, 1992; Lloyd et al, 1992; Brawer et al, 1993; Elhilali et al, 1996; Lepor et al, 1996; Roehrborn et al, 1996) (Table 92–2). **The multicenter, double-blind, parallel-group, randomized, placebo-controlled study of once-a-day administration of terazosin to patients with symptomatic BPH reported by Lepor and associates** (1992) **is representative of the expectations of terazosin therapy.** Two hundred eighty-five patients entered the double-blind treatment receiving either placebo or 2, 5, or 10 mg of terazosin once daily. Statistically significant decreases from baseline obstructive, irritative, and total symptom scores were observed for all terazosin treatment groups. The level of improvements in the symptom scores were dose dependent. The 10-mg terazosin treatment group exhibited significantly greater decreases in mean irritative and total symptom scores relative to the placebo group. The 5- and 10-mg terazosin treatment groups exhibited a significantly greater mean decrease in obstructive scores relative to the placebo group. The percentages of patients experiencing a greater than 30% improvement in the total symptom scores for the placebo, 2-, 5-, and 10-mg treatment groups were 40%, 51%, 57%, and 69%, respectively (Fig. 92–5).

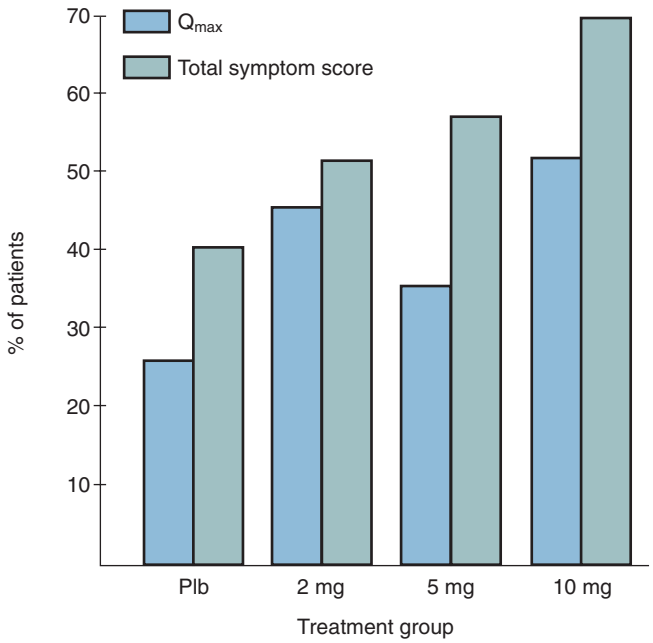


Figure 92–5. Two hundred eighty-five patients were enrolled in a randomized double-blind study comparing placebo (Plb) and 2 mg, 5 mg, and 10 mg terazosin administered once daily. Percentages of patients experiencing more than 30% improvement in total symptom scores and peak urinary flow rates are shown. (From Lepor H. Medical therapy for benign prostatic hyperplasia. Urology 1993;42:483–501.)

The percentage of patients experiencing greater than 30% improvement in total symptom score in the 10-mg treatment groups was significantly greater than that of the placebo group.

A statistically significant improvement from baseline was seen in the peak and mean urinary flow rates for all the treatment groups. The effect of terazosin on PFR was also dose dependent. The 10-mg treatment group exhibited a significantly greater increase from baseline in peak and mean urinary flow rates relative to the placebo group. The percentages of patients experiencing a greater than 30% increase in PFR in the placebo, 2-, 5-, and 10-mg treatment groups were 26%, 40%, 35%, and 52%, respectively. A significantly greater proportion of patients in the 10-mg terazosin treatment group exhibited a greater than 30% improvement in PFR compared with the placebo group. **Overall, the adverse events in the four treatment groups were minor and reversible.** Although a higher incidence of asthenia, flu syndrome, and dizziness were observed in the terazosin treatment groups, the differences from placebo were not statistically significant. There was a significantly greater incidence of postural hypotension in the 5-mg terazosin group than in the placebo group. The incidence of syncope for all terazosin-treated patients was less than 0.5%.

The relationships between percentage change in total symptom score and PFR versus baseline age, prostate size, PFR, PVR, and total symptom score were examined to identify clinical or urodynamic factors that predicted response to terazosin therapy. **No significant association was observed between treatment effect and any of these baseline factors.**

There is legitimate concern whether the results of multicenter studies conducted primarily at tertiary medical centers is generalizable to community practice. Roehrborn and coworkers (1996) **reported the results of the Hytrin Community Assessment Trial (HYCAT), which enrolled 2084 men into a 1-year randomized double-blind study comparing the safety and effectiveness of terazosin versus placebo.** The overwhelming majority of the subjects were enrolled by urologists in community practice. The daily dose of terazosin was titrated up to 10 mg based on the discretion of the principal investigators. The symptom scores in the placebo and terazosin group throughout the study are shown in (Fig. 92–6). The treatment-related improvement (terazosin minus placebo) in the AUASI score and in urinary PFR was 1.4 mL/sec and 3.9 symptom units, respectively. The treatment-related incidences of dizziness, asthenia, and peripheral edema were 5.9%, 4.6%, and 3.1%, respectively.

Lepor (1995) **presented an interim report of 494 patients entered into an open-label extension study demonstrating the durable clinical response of terazosin.** Durations of follow-up ranged from 3 to 42 months. The percentage of patients on final terazosin doses of 1, 2, 5, 10, and 20 mg were 7%, 12%, 26%, 34%, and 21%, respectively. Of the 494 patients, 213 (43.1%) withdrew prematurely: 55 (11%) because of therapeutic failure, 96 (19%) because of adverse events, and 62 (13%) because of administrative reasons.

At all follow-up visits the group mean PFRs were significantly higher than baseline values (Fig. 92–7). At baseline, PFR was 10.0 mL/sec. From 3 to 42 months, improvement ranged from 2.3 to 4.0 mL/sec. Between months 3 and 42, at least a 30% improvement in PFR from baseline was observed in 40% to 59% of the patients. At all follow-up intervals, the group mean Boyarsky symptom scores were significantly lower than at baseline; this was true of obstructive, irritative, and total scores (Fig. 92–8). From 3 months onward, improvement ranged from 4.0 to 5.4 points. Between months 3 and 42, at least a 30% improvement in total symptom score from baseline was observed in 62.4% to 77.1% of the patients.

Kirby (1998b) **has examined the mean changes in blood pressure according to whether subjects were normotensive or hypertensive at baseline** (Table 92–3). In normotensive patients, small, clinically insignificant decreases in blood pressure were generally noted. Untreated hypertensive men had larger and clinically significant decreases in blood pressure. In men with medically controlled hypertension, terazosin had no clinically significant effect on blood pressure, whereas in men with poorly controlled medically treated hypertension, terazosin significantly lowered blood pressure. In all clinical circumstances, terazosin's effect on blood pressure was consistently physiologically desirable. The ability to treat two common coexisting conditions (BPH and hypertension) is a potentially desirable feature of the drug.

Doxazosin. The half-life of doxazosin is longer than that of terazosin (22 vs. 12 hours). The efficacy, safety, and durability of clinical response of doxazosin has been demonstrated in multicenter, randomized, double-blind, placebo-controlled studies (Chapple et al, 1994; Fawzy et al, 1995; Gillenwater et al, 1995) (Table 92–4) and a long-term open-label extension study (Lepor, 1995). **Fawzy and associates** (1995) **reported a 16-week multicenter, randomized, double-blind, placebo-controlled titration to response study in 100 normotensive subjects with BPH.** Of the 41 evaluable subjects receiving doxazosin, 88% underwent titration to the maximal dose (8 mg). The group mean changes in PFR and symptom score were significantly greater in the doxazosin group compared with the placebo group (see Table 92–4). The magnitudes of these treatment-related effects are similar to those of terazosin. The systolic blood pressure changes in normotensive subjects are greater than those with terazosin. The treatment-related incidences of dizziness, fatigue, headache, somnolence, hypotension, and nausea were 20%, 8%, 8%, 6%, 8%, and 8%, respectively. The percentages of subjects withdrawing because of an adverse event were 14% and 2.1% in the doxazosin and placebo groups, respectively. The treatment-related incidence of adverse clinical events in this doxazosin study appears slightly higher than that of terazosin and may be a result of its greater effect on blood pressure.

Gillenwater and coworkers (1995) **reported a multicenter, randomized, double-blind, placebo-controlled titration to fixed dose study comparing placebo versus 2, 4, 8, and 12 mg of doxazosin in 248 men with mild to moderate essential hypertension.** The group mean changes in PFR and Boyarsky symptom score are summarized in Table 92–4 according to treatment groups. Because relatively small numbers

Table 92–3.

Effect of Terazosin on Blood Pressure in Normotensive and Hypertensive Men

	Treatment-Related Changes in Systolic Blood Pressure/Diastolic Blood Pressure (mm Hg)	
	Normotensives	Hypertensives
No antihypertensive treatment	–3.1/–1.7	–13.7/–10.7
Antihypertensive treatment	–2.8/–0.2	–12.6/–11.5

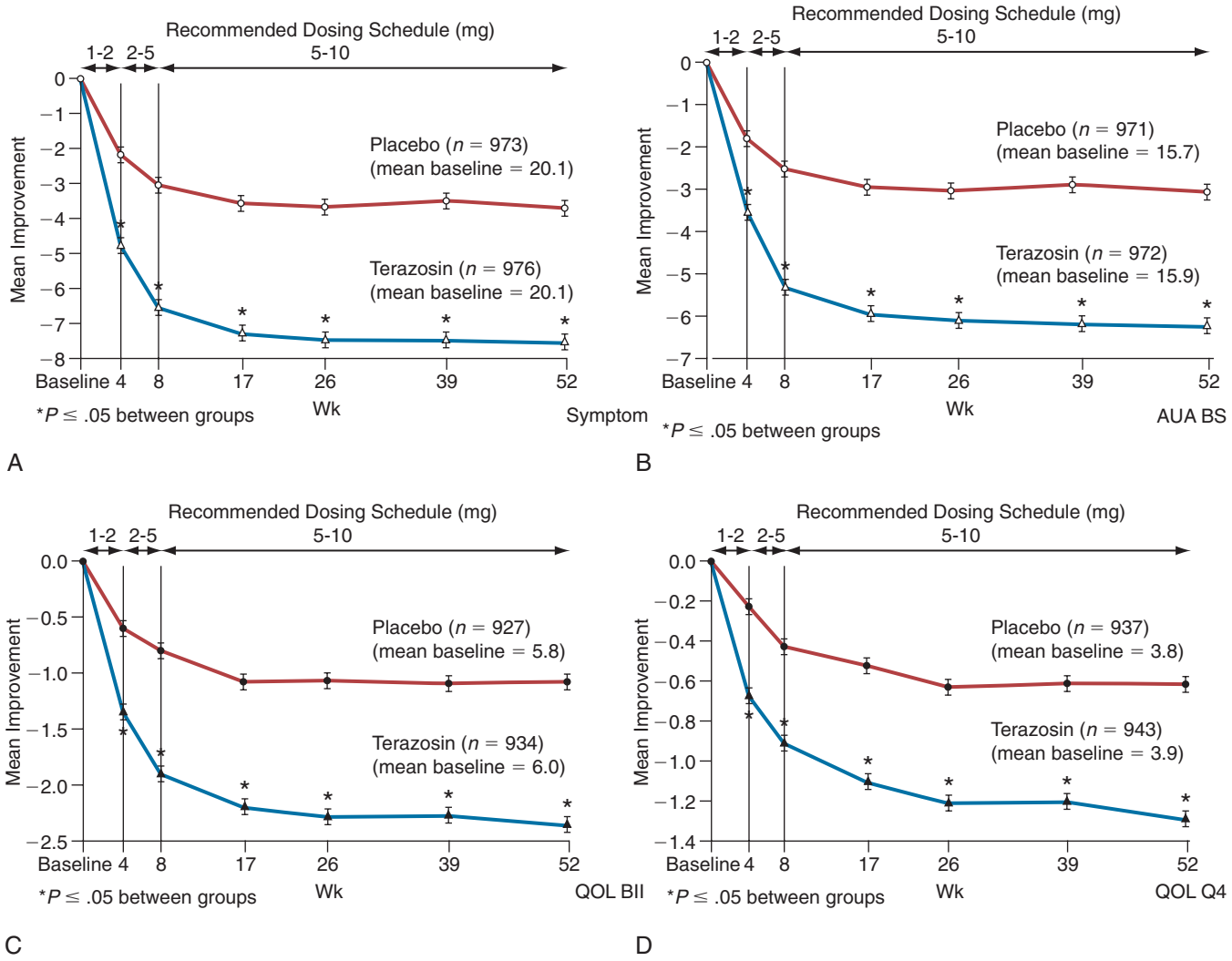


Figure 92–6. Time course of improvements in the American Urological Association (AUA) Symptom Index **(A)**, the AUA Bothersome Score (AUA BS) **(B)**, BPH Impact Index (QOL BII) **(C)**, and Quality of Life question (QOL Q4) **(D)** for placebo and terazosin treatment groups. A lowering of the score represents clinical improvement. Weeks 1 to 2 and 2 to 5 are the mandatory titration periods for 1 and 2 mg of terazosin (and placebo), respectively. (**A** to **D,** redrawn from Roehrborn CG. Effectiveness and safety of terazosin versus placebo in the treatment of men with symptomatic benign prostatic hyperplasia in the HYCAT study. Urology 1996;47:159–68.)

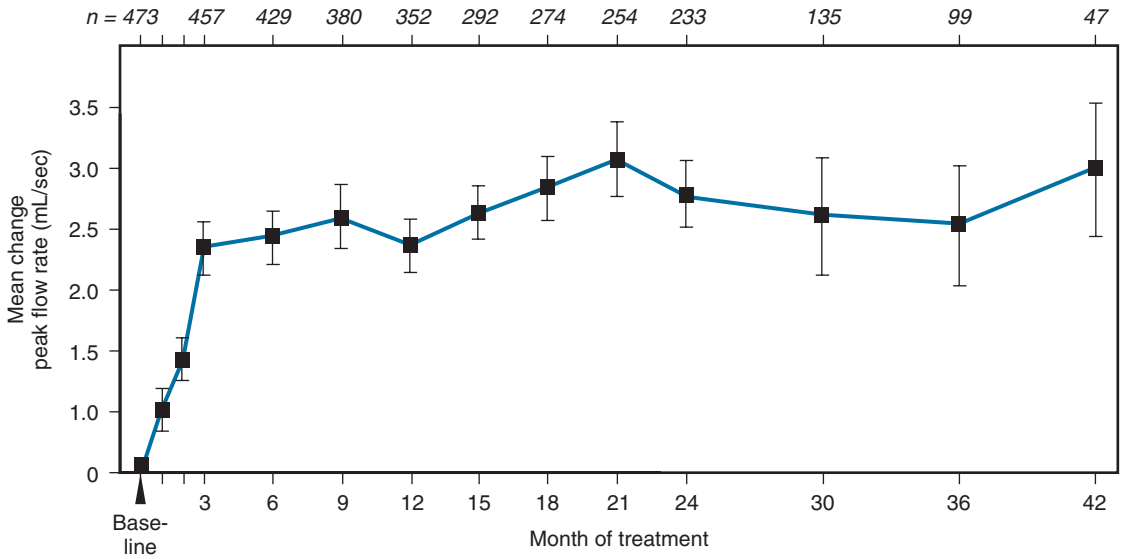


Figure 92–7. Mean change in peak flow rate between baseline and 42 months in terazosin-treated patients. The numbers across the top of the graph indicate the number of patients available at each time interval. All data points were significantly different from baseline at the $P \leq .05$ level. (From Lepor H and the Multicenter Study Group. Long-term efficacy and safety of terazosin in patients with benign prostatic hyperplasia. Urology 1995;45:406–13.)

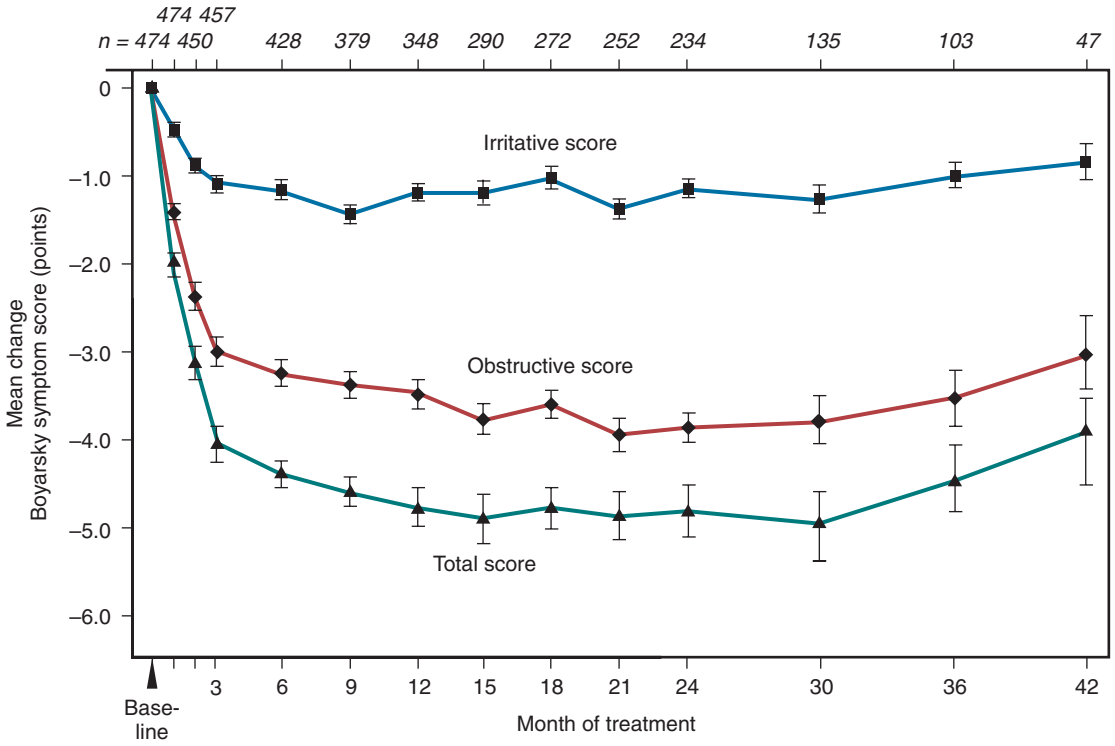


Figure 92–8. Mean change in Boyarsky symptom scores from baseline to 42 months. Baseline scores were 10.5 for total score, 6.2 for obstructive scores, and 4.3 for irritative scores. The numbers across the top of the graph indicate number of patients available at each time interval. All changes were significant at the $P \leq .05$ level. (From Lepor H and the Multicenter Study Group. Long-term efficacy and safety of terazosin in patients with benign prostatic hyperplasia. Urology 1995;45:406–13.)

Table 92–4.

Efficacy of Doxazosin in Benign Prostatic Hyperplasia

STUDY	ENROLLED (No.)	RANDOMIZED TREATMENT (mo)	DOSE (mg)	Group Mean Difference from Placebo	
				PFR (mL/sec)	Symptom Score
Chapple et al, 1994	135	3	4	+1.5	NR
Fawzy et al, 1995	100	4	Titration 2-8 mg	+2.2*	–3.2†
Gillenwater et al, 1995	248	3.5	2	+1.4	–2.5
			4	+2.2‡	–4.7*
			8	+3.2*	–3.9†
			12	+3.5*	–2.1

*$P < .01$.
†$P < .001$.
‡$P < .05$.
NR, not reported; PFR, peak flow rate.

of subjects were randomized into the individual treatment groups the failure to demonstrate statistical significance between placebo and some of the active treatment groups reflects the small sample size. The group mean improvement in PFR was dose dependent and statistically significant relative to placebo for all active treatment groups. The mean improvements in symptom scores relative to placebo for the group were statistically significant for the 4- and 8-mg doxazosin groups. Statistically and clinically significant changes in systolic blood pressure were observed between the placebo and the 4-, 8-, and 12-mg doxazosin groups. Lowering of blood pressure was a desirable outcome in these hypertensive patients. The overall treatment-related incidence of dizziness and fatigue was 15% and 10%, respectively. The percentages of subjects withdrawing because of an adverse event in the doxazosin versus placebo groups were 11.1% and 4.1%, respectively. Statistically significant changes in symptom scores and PFR relative to baseline have been reported in a long-term open-label doxazosin extension study (Lepor, 1995). The initial improvements in symptom scores and PFR in 450 subjects were maintained for up to 42 months. Kirby (1995) summarized the effects of doxazosin on blood pressure in normotensive and hypertensive men enrolled into two double-blind, placebo-controlled trials (Fawzy et al, 1995; Gillenwater et al, 1995). The treatment-related group mean reductions in sitting systolic blood pressure in the normotensive and hypertensive subjects were 3 and 17 mm Hg, respectively. The treatment-related group mean reductions in sitting diastolic blood pressure

in the normotensive and hypertensive subjects were 4 and 3 mm Hg, respectively.

With the standard preparation of doxazosin, multiple titration steps are used to obtain optimal therapeutic response. Often doxazosin standard is started at 1 mg/day and titrated through 2 and 4 mg/day to 8 mg/day to obtain the optimal response. The controlled release gastrointestinal therapeutic system (GITS) formulation of doxazosin reduces the plasma peak-to-trough ratio to minimize the need for titration. To compare the two formulations in 795 men with BPH, doxazosin standard was initiated at 1 mg/day, titrated to 2 mg/day after 1 week to 4 mg/day at 3 weeks and 8 mg/day at 7 weeks if indicated. This regimen was compared with doxazosin GITS initiated at 4 mg once daily and titrated to 8 mg once daily after 7 weeks if indicated and to a placebo group over 13 weeks. The symptoms of BPH were measured with the IPSS, which has seven questions (covering frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying, and urgency) scored 0 (absent) to 5 (severe). On the IPSS there was an improvement of –8.4 and –8.0 with doxazosin standard and GITS, respectively, compared with –6.0 in the placebo group. Doxazosin standard and GITS produced clinically comparable increases in mean PFR, compared with placebo, with a greater improvement observed earlier following treatment with doxazosin GITS than with doxazosin standard. A similar number of patients in both doxazosin groups was titrated to the maximum dose of 8 mg for both formulations. The incidence of adverse effects was slightly higher with doxazosin standard than doxazosin GITS and placebo, which caused a similar incidence.

The previous study and another with 680 men were combined to further analyze the comparison between doxazosin standard and GITS (Kirby et al, 2003). In addition to confirming the results given earlier, in a subgroup reporting sexual dysfunction at baseline there was a modest clinical improvement in sexual function with both preparations of doxazosin.. Treatment-related adverse events occurred in 16.1% of patients on doxazosin GITS, 25.3% of patients on doxazosin standard, and 7.7% of placebo patients. Headache and dizziness occurred in 6.0% and 5.3% of doxazosin GITS patients, compared with 5.1% and 9.1% of doxazosin standard patients, respectively (placebo, 4.5% and 1.9%, respectively). Fewer patients on doxazosin GITS (5.7%) or placebo (2.6%) discontinued treatment because of adverse events than on doxazosin standard (7.2%). The reduction in blood pressure was not clinically significant in the normotensive patients, but there were clinically significant reductions in blood pressure with both preparations of doxazosin (placebo, 3.9/5.0; doxazosin standard, 7.4/6.1; doxazosin GITS, 9.4/6.8). A comparison of the nonconcurrent multicenter, randomized, double-blind, placebo-controlled studies of terazosin (see Table 92–2) and doxazosin (see Table 92–4) shows similar efficacy. Studies of doxazosin versus tamsulosin (Kirby et al, 2003) and doxazosin versus alfuzosin (de Reijke and Klarskov, 2004) revealed only minor differences in safety and efficacy.

α-Adrenergic blockers such as doxazosin may influence smooth muscle growth in the prostate. In BPH patients treated with α_1-adrenoceptor antagonists there is a decreased expression of myosin heavy chain messenger RNA, a functional marker for the smooth muscle phenotype (Lin et al, 2001).

Biopsy and prostatectomy specimens from untreated and doxazosin-treated BPH patients suggest that doxazosin may induce apoptosis in both the epithelial and stromal cells with little effect on cell proliferation. The apoptosis was associated with a decrease in smooth muscle α-actin expression and stromal regression. Another study showed that the mean pretreatment baseline apoptosis was 1.9% and 1.0% for the epithelial and stromal prostate components. The mean apoptotic indexes increased after 3 months of doxazosin treatment for BPH to 6% in the glandular epithelial and 12% in the smooth muscle cells. By 12 months after treatment, epithelial apoptosis had decreased to constitutive levels while the apoptotic index of prostatic stromal cells remained high (Kyprianou et al, 1998).

In primary cultures of human prostate stroma cells, doxazosin increased apoptosis and decreased cell numbers. Transforming growth factor (TGF)-β_1 also decreased cell numbers, and because doxazosin increased the levels of TGF-β_1 in the cells it was suggested that the effect of doxazosin may be mediated through TGF-β_1 (Ilio et al, 2001).

The ability of doxazosin to induce apoptosis may be shared with the other quinazoline-based α_1-adrenergic receptor antagonists terazosin and prazosin, although it seems unlikely that this effect is α_1-adrenergic receptor mediated (Gonzalez-Juanatey et al, 2003). The apoptotic effects of the quinazoline-based α_1 antagonists may be linked to their ability to inhibit HERG potassium channels, which has been demonstrated using cloned channels expressed in *Xenopus* oocytes (Thomas et al, 2004).

Recent data also suggest that doxazosin may have a mildly beneficial impact on sexual function in men suffering from BPH (Kirby et al, 2005). The mechanism for this effect is uncertain but may be the result of a vasodilatory action within the corpora cavernosa.

Tamsulosin. **Tamsulosin is currently the most widely employed α_1 antagonist investigated for BPH** (Foglar et al, 1995). One of the features of tamsulosin is that it exhibits some degree of specificity for the α_{1A}-adrenergic receptor (Foglar et al, 1995). The efficacy and safety of tamsulosin has been investigated in four multicenter, randomized, double-blind, placebo-controlled studies (Kawabe et al, 1990; Abrams et al, 1995, Lepor et al, 1998; Narayan and Tewari, 1998) (Table 92–5).

Lepor and coworkers (1998) reported a multicenter, randomized, double-blind, placebo-controlled study of 756 American men with clinical BPH randomized to receive placebo or 0.4 or 0.8 mg of tamsulosin for 13 weeks. The mean changes in AUASI score, PFR, and adverse events are summarized in Table 92–5. The symptom score improvements were significantly greater in the 0.8-mg tamsulosin group compared with the 0.4-mg group. The treatment-related incidences of dizziness, asthenia, rhinitis, and abnormal ejaculation in the 4-mg group were 5%, 3%, 3%, and 6%, respectively, and in the 0.8-mg group they were 6%, 3%, 9%, and 18%, respectively. The mean changes in systolic and diastolic blood pressure in the placebo and tamsulosin groups were not significantly different for both hypertensive and normotensive subjects. In the subjects who were hypertensive and those whose blood pressure was uncontrolled, the systolic blood pressure changes in the placebo, 0.4-mg, and 0.8-mg groups were –8.4, –7.2, and –10.2 mm Hg, respectively. The advantage of not lowering blood pressure in men who are hypertensive at baseline is controversial.

Of the 618 subjects who completed the 13-week randomized study reported by Lepor and coworkers (1998), 418 (68%) continued into the 40-week extension study on the same double-blind medication and dose. **The symptom and flow rate improvements observed at the end of the 13-week study were maintained throughout the 40-week extension study.**

Narayan and associates (1998) **reported the results of a randomized, double-blind, placebo-controlled trial comparing the safety and effectiveness of 0.4 and 0.8 mg of tamsulosin versus placebo.** Seven hundred thirty-five men were randomized in the study. The active treatment was 13 weeks.

Table 92–5.

Efficacy of Tamsulosin in Benign Prostatic Hyperplasia

STUDY	ENROLLED (No.)	RANDOMIZED TREATMENT (mo)	DOSE (mg)	Group Mean Difference from Placebo	
				PFR (mL/sec)	Symptom Score
Kawabe et al, 1990	270	1	0.1	+0.3	NR
			0.2	+2.6	NR
			0.4	+2.1	NR
Abrams et al, 1995	313	2¼	0.4	+1.7*	–1.3†
Lepor et al, 1998	756	3	0.4	+1.3†	–2.8‡
			0.8	+1.7‡	–3.2‡
Narayan et al, 1998	735	3	0.4	+0.6	–1.5†
			0.8	+0.9†	–2.2†

*$P < .05$.
†$P < .01$.
‡$P < .001$.
NR, not reported; PFR, peak flow rate.

Table 92–6.

Efficacy of Alfuzosin in Benign Prostatic Hyperplasia

STUDY	ENROLLED (No.)	RANDOMIZED TREATMENT (mo)	DOSE (mg)	Group Mean Difference for Placebo	
				PFR (mL/sec)	Symptom Score
Jardin et al, 1994	518	6	7.5-10	1.5*	–1.0†
Buzelin et al, 1997b	390	3	5 bid	1.3†	–1.6‡
Kerrenbroeck et al, 2000	447	3	10 qd	0.9*	–2.0‡
			2.5 tid	1.8†	–1.5‡

*$P < .05$.
†$P < .001$.
‡$P < .01$.
PFR, peak flow rate.

The treatment-related improvements in the AUASI score and PFR were comparable with those reported by Lepor and coworkers (1998). The differences between 0.4 mg and 0.8 mg were not statistically significant; however, the study lacked statistical power to show clinically significant differences between the active treatment groups. The treatment-related incidences of asthenia, dizziness, rhinitis, and abnormal ejaculation observed for the 0.4-mg tamsulosin group were 2%, 5%, 3%, and 11%, respectively; and for the 0.8-mg tamsulosin group they were 3%, 8%, 9%, and 18%, respectively. The incidences of retrograde ejaculation and rhinitis were significantly greater in the 0.8-mg group compared with the 0.4-mg group. No statistically or clinically significant differences were observed for systolic blood pressure between any of the treatment groups.

A systematic review of tamsulosin therapy for BPH has been published (Wilt et al, 2002b). This included 14 studies with a total of 4122 patients. The mean change in symptom score was 12% for the 0.4-mg dosage and 16% with the 0.8-mg dosage. Improvements in flow rate were 1.1 mL/sec for both dosages. Adverse events were generally mild and included dizziness, rhinitis, and abnormal ejaculation. These increased in a dose-dependent manner with discontinuations due to such effects similar to placebo at 0.2 mg but increasing to 16% with the 0.8-mg/day dosage.

Alfuzosin. **Jardin and colleagues** (1991) **reported the first large-scale, multicenter, randomized, placebo-controlled trial demonstrating that alfuzosin was safe and effective for the treatment of BPH** (Table 92–6). A long-term open-label extension study showed that the effectiveness of alfuzosin was durable up to 30 months (Jardin et al, 1994). The primary limitation of alfuzosin was a requirement for multiple daily doses (2.5 mg three times a day or 5 mg twice a day). In the absence of any demonstrable advantage over the once-a-day drugs like terazosin, doxazosin, and tamsulosin there was no compelling reason to prescribe alfuzosin.

Extended-release or slow-release (SR) alfuzosin is a new formulation that allows for a once-daily dosing regimen without dose titration. Buzelin and coworkers (1997b) reported the first randomized, multicenter, placebo-controlled trial evaluating the safety and effectiveness of SR alfuzosin for the treatment of BPH. Three hundred and ninety subjects were randomized to once-daily 5 mg alfuzosin versus placebo for 12 weeks. The treatment-related improvements in the IPSS and PFR were –1.6 symptom unit and 1.3 mL/sec, respectively. The incidence of dropouts because of adverse events was 4.6% and 7.1% in the SR alfuzosin and placebo groups, respectively. The 2-mm Hg change in systolic and diastolic blood pressure was not significantly different from that in the placebo group. The incidences of dizziness and asthenia were similar in the SR alfuzosin and placebo groups.

SR alfuzosin (10 mg once a day) has been compared with IR alfuzosin (2.5 mg three times daily) and placebo (van Kerrebroeck et al, 2000). After a 1-month placebo lead-in, 447 patients were randomly assigned in equal proportions to the three

treatment groups for 3 months. The improvement in the IPSS was 6.9, 6.4, and 4.9 in the alfuzosin 10-mg/day, alfuzosin 2.5-mg three times a day, and placebo groups, respectively. The symptom improvement observed in both active treatment groups was significantly greater than that in the placebo group. The improvements in the filling and voiding subscores and quality of life index were also significantly greater in the active treatment group relative to the placebo group. The improvement in the PFR was 2.3 mL/sec, 3.2 mL/sec, and 1.4 mL/sec in the SR alfuzosin, IR alfuzosin, and placebo groups, respectively. The modest improvements in the PFR were significantly greater in both active treatment groups compared with placebo. The incidences of dizziness were 2.1%, 4.7%, and 1.3%; and those for asthenia were 3.5%, 0.7%, and 2.6% in the SR alfuzosin, IR alfuzosin, and placebo groups, respectively. No sexual dysfunction was reported in the 10-mg/day alfuzosin group. There were no statistically or clinically significant treatment-related effects on blood pressure in normotensive or hypertensive subjects. Of those men who were hypertensive at baseline, the mean reductions in the standing blood pressure were 8.1, 8.6, and 5.8 mm Hg, respectively, in the SR alfuzosin, IR alfuzosin, and placebo groups.

Alfuzosin has been shown to have a beneficial effect on the quality of life of men suffering from BPH. In the ALFUS study (Roehrborn et al, 2001) the quality of life index improved by 18% in both active groups compared with 8% in the placebo study arm ($P = .002$). In an open extension of the ALFORTI trial there was a 35% improvement from baseline of quality of life (van Kerrebroeck et al, 2002). Some part of this effect may be the result of a mildly beneficial impact on sexual function (van Moorselaar et al, 2005).

Because of the lack of adverse effects and blood pressure changes, alfuzosin has been described as a uroselective drug (Kirby, 1998a). SR alfuzosin exhibits no pharmacologic uroselectivity for any of the α_1 subtypes (Andersson et al, 1997). In-vivo studies in the conscious rat have shown that alfuzosin reduces urethral pressure without significantly altering blood pressure (Martin et al, 1995). This experimental observation does not prove clinical uroselectivity because terazosin and doxazosin do not alter blood pressure in normotensive subjects. Another explanation for the lack of adverse events has been the low penetration of alfuzosin into the brain (Rouquier et al, 1994). It is also important to consider that the better tolerance may simply be related to a lower level of α_1 blockade because the treatment-related improvement of the 10 mg of alfuzosin appears to be less than that achieved with 10 mg of terazosin and 8 mg of doxazosin.

The long-term effectiveness of IR alfuzosin 2.5 mg three times a day is supported by an open-label prospective 3-year trial involving 3228 men with clinical BPH (Lukacs et al, 2000). **The improvements in symptom score in BPH-specific health-related quality of life index observed at the 3-month visit were maintained throughout the 36 months of follow-up.** A total of 20.1% of the men withdrew from the study. Only 4.2% of the men discontinued therapy because of an adverse event. The other reasons for withdrawal were death, 7.6%; loss of follow-up, 1.7%; lack of efficacy, 1.8%; study withdrawal owing to personal reasons, 0.8%; concomitant disease, 0.7%; and other reasons, 3.3%. Only 0.3% of men experienced AUR.

Silodosin. In Japan, silodosin, a selective α_1-adrenergic receptor antagonist, is the BPH market leader and received U.S. Food and Drug Administration (FDA) approval in October 2008 (Watson Pharmaceuticals, Inc). In two phase 3 studies, 8 mg once-daily silodosin taken for 12 weeks resulted in significant and rapid improvement of the IPSS compared with placebo. Silodosin was shown to increase urine flow in 2 to 6 hours after the initial dose. Improvement of symptoms was realized in 3 to 4 days, with the majority of patients, including men on concomitant cardiovascular medications, achieving at least a 3-point improvement in IPSS score, regardless of age or severity of symptoms. It was associated with a low incidence of orthostatic hypotension and syncope, fainting, and dizziness. As the newest agent available silodosin has had to satisfy more rigorous cardiovascular requirements by the FDA than other, older agents. Silodosin demonstrated minimal effects on the cardiovascular system, without any meaningful prolongation of the QT interval. The most common drug-related side effect was retrograde ejaculation (better described as anejaculation). Rates of discontinuing therapy due to retrograde ejaculation were low. The second most commonly reported adverse event was dizziness, the rate of which being only slightly higher than in placebo-treated patients. There were no reported events of symptomatic orthostatic hypotension or dizziness when administered with a single dose of medications for erectile dysfunction (ED) in healthy male subjects.

A randomized, double-blind, placebo-controlled study comparing silodosin to tamsulosin or placebo study was conducted at 88 centers in Japan (Kawabe et al, 2006). Men aged 50 years or older with an IPSS of 8 or higher, a quality of life score of 3 or more, a PFR of less than 15 mL/sec, a prostate volume of 20 mL or more, and a PVR urine volume of less than 100 mL were eligible for enrollment. Patients were randomized to receive silodosin 4 mg twice daily, tamsulosin 0.2 mg once daily (i.e., a lower dose than used in the United States or Europe), or placebo, for 12 weeks: 457 men were randomized (silodosin, 176; tamsulosin, 192; and placebo, 89). The change in the total IPSS from baseline in the silodosin, tamsulosin, and placebo groups was –8.3, –6.8, and –5.3, respectively. There was a significant decrease in the IPSS versus placebo in the silodosin group from 1 week. In the early-stage comparison, silodosin showed a significant decrease in IPSS versus tamsulosin at 2 weeks. The change in quality of life score from baseline was –1.7, –1.4, and –1.1 in the silodosin, tamsulosin, and placebo groups, respectively. Silodosin showed a significant improvement in quality of life score versus placebo. In the subgroup of patients with severe symptoms (IPSS ≥ 20) silodosin also gave a significantly better improvement than placebo (–12.4 vs. –8.7). The incidence rates of adverse events and drug-related adverse events were, respectively, 88.6%, 82.3%, and 71.6% and 69.7%, 47.4%, and 36.4%, respectively. The most common adverse event in the silodosin group was abnormal ejaculation, which occurred more often in the silodosin than in the tamsulosin group (22.3% vs. 1.6%). However, only 5 men (2.9%) discontinued treatment for abnormal ejaculation. It is unclear how men in other populations will respond to this effect. Measurement by Noguchi and colleagues (2008) of intraurethral pressure in the prostatic urethra and intraluminal pressure in the vas deferens in anesthetized male dogs given the α_1-adrenergic receptor agonist phenylephrine and then a series of α_1-adrenergic receptor antagonists showed that silodosin had the highest selectivity for the vas deferens (7.5-fold), followed by naftopidil (4.3-fold), alfuzosin (3.8-fold), tamsulosin (2.6-fold), and prazosin (2.5-fold). These results suggest that high tissue selectivity for the vas deferens over the urethra may contribute to the incidence of abnormal ejaculation. These results (and U.S. data presented at the AUA meeting in 2009) do, however, suggest that silodosin is clinically useful for treating LUTS associated with BPH.

Naftopidil. Naftopidil, a relative selective α_{1D}-adrenergic receptor antagonist, seems more effective for patients showing a dominant expression of the α_{1D}-adrenergic receptor subtype. The α_1

adrenergic receptor antagonists tamsulosin and naftopidil were administered to 96 patients with BPH for 8 weeks in a crossover study. With the administration of both drugs, the IPSS significantly decreased and the maximum urinary flow significantly increased. Whereas naftopidil monotherapy decreased the IPSS for storage symptoms, tamsulosin monotherapy decreased the IPSS for voiding symptoms (Ikemoto et al, 2003). It remains to be seen how clinically important this new agent will turn out to be.

Effects of α-Adrenergic Blockers on Bladder Outlet Obstruction

The primary objective of medical therapy is to improve urinary symptoms. The relevance of urodynamic studies for assessing the clinical use of medical therapy for BPH is controversial. A drug that improves urodynamic parameters of BOO without relieving LUTS would be of limited clinical utility. Conversely, a drug that relieves LUTS without improving urodynamic parameters of BOO would be of great clinical importance. There are relatively few randomized, placebo-controlled studies examining the effects of α-adrenergic blockers on pressure-flow parameters. One of the limitations to designing these urodynamic studies is the definition of a clinically significant outcome.

Martorana and colleagues (1997) reported a randomized, double-blind, placebo-controlled study examining the effect of 1 month of alfuzosin, 2.5 mg three times a day, on pressure-flow urodynamic parameters. The changes in Pdet at maximum flow, detrusor opening pressure, and maximum Pdet were significantly greater in the alfuzosin-treatment group compared with the placebo group. There were no significant differences between the effects of alfuzosin and those of placebo on PFR.

α-Adrenergic Blockers and Sexual Function and Sexual Side Effects

Sexual function is complex and includes multiple domains such as sexual desire (libido), erectile function, and ejaculatory function. Erectile and ejaculatory functions are frequently reduced in patients with LUTS/BPH and can impact on their quality of life. Therefore the treatment of BPH should aim to maintain or even restore sexual function. α_1-Adrenergic receptor antagonists lack major effects on sexual desire in placebo-controlled studies (van Dijk et al, 2006). Reports on erectile function are inconsistent, with both beneficial and adverse effects being reported, but ED can occur in some patients without clear differences between drugs. Ejaculatory dysfunction during treatment may represent (relative) anejaculation. It occurs more frequently with tamsulosin and even more so for silodosin than with other drugs of this class.

α-Adrenergic Blockers in the Elderly

The adverse events associated with α-adrenergic blockers that may be particularly problematic in the elderly are dizziness and orthostatic hypertension. Kaplan and colleagues (1997) reviewed a personal series of 36 men with BPH older than age 80 years treated with terazosin or doxazosin. α-Adrenergic blockers were well tolerated, and no serious adverse events were observed. This experience was not of adequate size to address the incidence of falls. Pooled analysis of multicenter, randomized, placebo-controlled studies of terazosin (Zhang and Manski, 1998), doxazosin (Kaplan and D'Alisera, 1998), and tamsulosin (Chapple et al, 1997) have reported that the incidences of adverse events are not age dependent. It is important to emphasize that men enrolled into these studies were highly selected and so the tolerability and safety findings are not generalizable to all elderly men.

Data from population studies such as the 5872 participants in the Osteoporotic Fractures in Men study and a population-based case-control study using data from a managed care organization in southern California with more than 3 million members suggest that **moderate and severe LUTS independently increase the 1-year risk of falls, particularly recurrent falls, in community-dwelling older men** (Parsons et al, 2009) **and that there was a modest increase in risk associated with exposure to α-adrenergic blockers that requires further investigation** (Jacobsen et al, 2008).

α-Adrenergic Blocker Therapy and Coexisting Hypertension

The α-adrenergic blockers terazosin and doxazosin are established agents for the treatment of hypertension. The overwhelming clinical evidence demonstrates that terazosin and doxazosin lower blood pressure primarily in hypertensive men and that the blood pressure lowering is clinically significant (Fawzy et al, 1995; Gillenwater et al, 1995; Kirby, 1995, 1998b; Lepor et al, 1997; Lowe et al, 1999). **Approximately 30% of men treated for BPH have coexisting hypertension** (Boyle and Napalkov, 1995). It is reasonable to advocate the use of α-adrenergic blockers as the treatment of choice for men with hypertension and BPH.

An interim analysis of the Anti-Hypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) questioned the use of doxazosin in men at risk for developing congestive heart failure (ALLHAT Collaborative Research Group, 2000). In this study of 24,335 subjects with hypertension and at least one other coronary risk factor, men were randomized to chlorthalidone, doxazosin, amlodipine, or lisinopril. A significant increased risk of congestive heart failure in the doxazosin group relative to the chlorthalidone group was the basis for the decision to discontinue the doxazosin arm of the antihypertensive trial. There was no significant increase in congestive heart failure between doxazosin and the other antihypertensive agents. It is interesting that comparable levels of blood pressure reduction were achieved by both drugs. **The ALLHAT study questions the role of doxazosin as first-line therapy for the treatment of hypertension. The study does not assess the relative risks and benefits of doxazosin in men with BPH and hypertension, nor does it have any bearing on the use of doxazosin in combination with other antihypertensive agents.** Doxazosin remains an acceptable agent to treat BPH that coexists with hypertension. It should be the discretion of the physician managing the hypertension to add additional agents for treating the hypertension.

Mechanism of Adverse Events Associated with α-Adrenergic Blockade

Dizziness and asthenia are the adverse events most commonly associated with α-adrenergic blocker therapy. Elucidating the mechanism of action for these adverse events is essential for α_1 subtype drug development programs. It has been assumed that dizziness and possibly asthenia were caused by cardiovascular effects. Lepor and colleagues (2000) correlated the incidence of adverse events associated with terazosin relative to blood pressure changes. Men experiencing dizziness and asthenia did not exhibit greater changes in blood pressure while on terazosin therapy. Only postural hypotension was associated with greater changes in blood

pressure. α_1-Adrenergic-mediated dizziness and asthenia are likely due to effects at the level of the central nervous system. Therefore it cannot be assumed that developing an α-adrenergic blocker that eliminates effects on blood pressure will significantly improve the tolerability of α-adrenergic blockers.

α-Adrenergic Blockers and Intraoperative Floppy Iris Syndrome

Intraoperative floppy iris syndrome (IFIS) complicates approximately 2% of cataract surgery cases. The clinical manifestations of IFIS are poor preoperative pupil dilation, iris billowing and prolapse, and progressive intraoperative miosis. Surgical complications are increased when IFIS is not anticipated or recognized by the surgeon. Since IFIS was first described in 2005 (Chang et al, 2005), its association with the α_1-adrenergic antagonist tamsulosin has become well established. It appears that α_{1A} is the predominant receptor subtype in the iris dilator muscle as well. The persistence of IFIS long after the discontinuation of tamsulosin suggests a semipermanent muscular atrophy and loss of tone. It is not clear how long one must take tamsulosin before experiencing these chronic muscular changes. Anecdotal reports suggest that IFIS does not occur until patients have been on tamsulosin therapy for 4 to 6 months. IFIS can also occur up to several years after discontinuation of tamsulosin. IFIS has also been reported but less commonly with non–subtype-specific α_1-adrenergic antagonists, such as terazosin, doxazosin, and alfuzosin. According to an online survey, most members of the American Society of Cataract and Refractive Surgery believe that tamsulosin makes cataract surgery more difficult (95%) and increases the risks of surgery (77%).

Being able to elicit a prior history of tamsulosin use now enables cataract surgeons to anticipate IFIS and to employ alternative methods of managing the complication. Prevention of IFIS by withdrawing tamsulosin preoperatively has not shown consistent benefit. Therefore, in a patient with a known diagnosis of cataract, prescribing physicians may wish to consider involving the patient's cataract surgeon before initiating tamsulosin or α-adrenergic blocker treatment. **Patients should also be encouraged to report any prior or current history of α_1 antagonist use to their ophthalmic surgeon before undergoing any eye surgery.**

Comparison of α-Adrenergic Blockers

Because the therapeutic effect and adverse events associated with α blockers are both dose dependent, the effectiveness and tolerability of two different α blockers can be determined only in a randomized, double-blind, placebo-controlled trial. It is imperative that these studies be appropriately powered to show statistically significant effects for effectiveness and tolerability.

Buzelin and coworkers (1997a) reported a randomized, placebo-controlled study comparing α blockers (IR alfuzosin, 2.5 mg three times a day, vs. tamsulosin, 0.4 mg/day). The improvements in Boyarsky symptom score and PFR and the incidences of dizziness and asthenia were not significantly different between the two treatment groups. The effects of alfuzosin and tamsulosin on systolic and diastolic supine or standing blood pressures in the hypertensive patients were also not significantly different. This study suggests that IR alfuzosin and tamsulosin have equivalent effectiveness and tolerability. The obvious benefit of tamsulosin is that the dose does not have to be titrated.

The recommended daily doses of terazosin, doxazosin, tamsulosin, and SR alfuzosin are 10 mg, 8 mg, 0.4 mg, and 10 mg, respectively. The clinical data suggest that terazosin, 10 mg, and doxazosin, 8 mg, are more effective than tamsulosin, 0.4 mg, and alfuzosin, 10 mg (see Tables 92–2 and 92–4 to 92–6). The incidences of asthenia and dizziness appear to be higher for terazosin and doxazosin. **The apparent better tolerability of tamsulosin and SR alfuzosin may simply be because of degree of α_1 blockade and not uroselectivity.** Assessing the relative efficacy and tolerability of daily terazosin, 10 mg, or doxazosin, 8 mg, versus tamsulosin, 0.4 mg, or SR alfuzosin, 10 mg, would address this issue. In the absence of these studies, nonconcurrent studies can be compared, recognizing the potential impact of differences in study design, patient selection, recording of adverse events, and dosing.

Terazosin and doxazosin exhibit very similar pharmacologic and pharmacokinetic properties. It is therefore not surprising that the effectiveness and tolerability of these two agents are also comparable. The effectiveness of terazosin and doxazosin are both dose dependent, with the greatest recorded improvements in symptom scores observed at the 10-mg and 8-mg daily doses, respectively. These doses have both been shown to be significantly more effective than lower doses. Although the incidence of adverse events is dose dependent, the 10-mg and 8-mg doses of terazosin and doxazosin are generally well tolerated.

Terazosin is unit priced so that there is no financial disincentive to titrate up to the 10-mg dose. There is no significant cost advantage between 10 mg of terazosin and 8 mg of doxazosin. **Thus, until data from randomized, double-blind comparative trials demonstrate the contrary, 10 mg of terazosin and 8 mg of doxazosin should be considered equivalent.** Although the price of doxazosin therapy can be reduced by dividing the 8-mg tablet, this comes at the expense of significant loss of effectiveness.

Tamsulosin and SR alfuzosin have been positioned as uroselective α_1 blockers. Randomized studies have shown that 0.8 mg of tamsulosin is significantly more effective at relieving symptoms than the 0.4-mg dose (Lepor et al, 1998). No dose-ranging studies have been performed with SR alfuzosin. Unfortunately, an 0.8-mg tamsulosin dose has not been manufactured. Whereas the 0.8-mg tamsulosin dose appears to have less asthenia than terazosin and doxazosin, the incidence of dizziness is comparable and rhinitis and abnormal ejaculation are markedly greater. **The most appropriate dose of tamsulosin is 0.4 mg, owing to the cost and adverse events associated with the 0.8-mg dosage.** The advantage of 0.4 mg of tamsulosin is that this clinically effective dose can be administered without dose titration.

The major advantage of 0.4 mg of tamsulosin and SR alfuzosin is the lack of requirement for dose titration. For men presenting in urinary retention, tamsulosin and SR alfuzosin will likely decrease the time to voiding trial because of the lack of titration to an effective dose. The data suggest that tamsulosin and SR alfuzosin exhibit less effect on blood pressure in hypertensive men compared with terazosin and doxazosin.

Summary

Multicenter, randomized, double-blind, placebo-controlled studies have unequivocally demonstrated the safety and efficacy of α-adrenergic blockers for the treatment of BPH. The clinical response is rapid and dose dependent. Long-term open-label studies have demonstrated

that the clinical response is durable. The long-acting α_1 blockers are well tolerated. The blockers are safe in the elderly, diminish BOO, and reduce the risk of urinary retention. Their effect on falling needs further research. Terazosin and doxazosin significantly lower blood pressure only in hypertensive subjects, allowing treatment of coexisting BPH and hypertension. Direct comparison studies of the α-adrenergic blockers are sparse and involve small numbers of patients; therefore any claims of superiority cannot be justified.

Androgen Manipulation

Rationale

The rationale for androgen suppression is based on the observation that the embryonic development of the prostate is dependent on the androgen dihydrotestosterone (DHT) (Shapiro, 1990). Testosterone is converted to DHT by the enzyme 5α-reductase. The genetic deficiency of 5α-reductase in men results in a rudimentary prostate and in feminized external genitalia (Walsh et al, 1974). The development of BPH is also an androgen-dependent process (Coffey and Walsh, 1990). Castration and pharmacologic agents suppressing testosterone and DHT synthesis or action have been shown to reduce prostate volume in men with established BPH (McConnell, 1990). Peters and Walsh (1987) demonstrated that androgen suppression causes regression primarily of the epithelial elements of the prostate. Reducing prostate volume is thought to decrease the static component of BOO resulting from BPH. The primary limitation of the androgen suppression hypothesis is that the pathophysiology of clinical BPH and LUTS are not sufficiently dependent on prostate size.

Classification of Pharmacologic Agents

Surgical castration was reported to be an effective treatment for enlarged prostates in the 1890s (White, 1895; Cabot, 1896). Scott and Wade (1969) reported the first study investigating androgen suppression (medical castration) for BPH. Cyproterone acetate, an antiandrogen, was reported to decrease symptoms and increase PFR in the majority of treated subjects. The pharmacologic strategies of androgen suppression that have been investigated for BPH over the past 3 decades are summarized in Table 92–7.

Caveats Related to Interpreting Androgen Manipulation Studies

The efficacy of androgen suppression in BPH is presumed to be mediated by reduction of prostate volume. **Maximal reduction of prostate volume after initiation of androgen suppression is achieved within 6 months** (Peters and Walsh, 1987; Gormley et al, 1992). Therefore randomized treatment must be at least 6 months to capture maximal therapeutic effect.

Because the mechanism of action is by means of reduction of prostate volume, it is reasonable to assume that subjects with larger prostates achieve the greatest therapeutic benefit. **The majority of randomized, double-blind, placebo-controlled clinical trials evaluating androgen suppression enrolled subjects with larger prostates** (Gormley et al, 1992 [finasteride]; Eri and Tveter, 1993a [Casodex], 1993b [leuprolide]; McConnell et al, 1998 [finasteride], and Roehrborn et al, 2008b [dutasteride]). The results of studies enrolling a disproportionate number of men with large prostates may not be generalizable to the "typical" patient with clinical BPH.

Table 92–7.

Androgen Suppression: Classification of Pharmacologic Agents and Dosages

DRUGS	DOSE	REFERENCE
GnRH Analogues		
Leuprolide	3.75 mg IM qd mo	Schroeder et al, 1986
		Keane et al, 1988
		Eri and Tveter, 1993b
Nafarelin acetate	400 mg SQ qd	Peters and Walsh, 1987
Cetrorelix	1 mg SQ qd ± loading dose	Lepor et al, 1997
	3 dosing regimens	Debruyne et al, 2008
Progestational Agents		
17α-Hydroxycortisone	200 mg IM weekly	Meiraz et al, 1977
Megestrol	250 mg PO tid	Donkervoort et al, 1975
	40 mg PO tid	Geller et al, 1979
Antiandrogens		
Flutamide	100 mg tid	Caine et al, 1975
	250 mg tid	Stone, 1989
Oxandolone	200 mg IM weekly	Ostri et al, 1989
Bicalutamide	50 mg qd	Eri and Tveter, 1993
Zanoterone	100-800 mg qd	Berger et al, 1995
5α-Reductase Inhibitors		
Finasteride	5 mg PO qd	Gormley et al, 1992
	5 mg PO qd	Finasteride Study Group, 1993
	5 mg PO qd	Andersen et al, 1995
	5 mg PO qd	Marberger et al, 1998
	5 mg PO qd	McConnell et al, 1998
Dutasteride	0.5 mg PO qd	Roehrborn et al, 2002
	0.5 mg PO qd	Debruyne et al, 2004
	0.5 mg PO qd	Roehrborn et al, 2004

Review of the Literature

Several excellent reviews of androgen suppression for BPH have been published (Vaughan and Lepor, 1996; McConnell, 1998). The overwhelming majority of drug studies evaluating androgen suppression were not randomized, enrolled small numbers of subjects, and utilized qualitative outcome measures. This section reviews only multicenter, randomized, double-blind, placebo-controlled trials. **Finasteride, a type 2 5α-reductase inhibitor, and dutasteride, a dual inhibitor of both type 1 and type 2 5α-reductase, represent the paradigm for androgen suppression and are emphasized in this section.**

Finasteride. **Finasteride is a competitive inhibitor of the enzyme 5α-reductase** (Vermeulen et al, 1989). Finasteride lowers serum and intraprostatic DHT levels. At least two isozymes (types 1 and 2) of 5α-reductase exist (Jenkins et al, 1992). Finasteride is a selective inhibitor of the type 2 isozyme. Finasteride does not reduce DHT levels to castrate levels because circulating testosterone is converted to DHT by type 1 isozymes that exist in skin and liver (Thigpen et al, 1993). **Gormley and coworkers** (1992) **reported the first multicenter, randomized, double-blind, placebo-controlled trial investigating the safety and efficacy of finasteride in 895 men with BPH.** The subjects were randomized to receive placebo or 1 or 5 mg of finasteride for 1 year. This study is often referred to as the North American Finasteride Trial.

The mean baseline prostate volumes in the placebo and 1- and 5-mg finasteride groups were 61, 61, and 59 cm^3, respectively. The primary outcome measures were group mean changes in a modified Boyarsky symptom score (maximum score, 36) and PFR (Figs. 92–9 and 92–10). The group mean changes in symptom score, PFR, and prostate volume are shown in Table 92–8. The group mean percentage changes in symptom score at 12 months in the placebo and 1- and 5-mg finasteride groups were –2%, 9%, and 21%, respectively. The mean percentage changes in PFR were 8%, 23%, and 22% in the placebo and 1- and 5-mg finasteride groups, respectively. The mean percentage changes in prostate volume were –3%, –18%, and –19% in the placebo and 1- and 5-mg finasteride groups, respectively. The difference between the mean changes in PFR and prostate volume was statistically significant for both the 1- and the 5-mg finasteride groups versus the placebo group. The difference between the mean changes in symptom scores was statistically significant only for placebo versus 5 mg of finasteride. The dose-dependent symptom response was not associated with a dose-dependent prostate volume or PFR response. The changes in prostate volume were not directly related to the magnitude of the clinical response to finasteride. These observations suggest that the efficacy of finasteride may not be mediated exclusively by reduction of prostate volume. The incidences of decreased libido, ejaculatory disorder, and impotence were significantly greater in the finasteride groups compared with the placebo group. The treatment-related incidences of decreased libido, ejaculatory disorder, and impotence in the 1- and 5-mg treatment groups were 4.7%, 2.7%, and 3.7%, respectively, and 3.4%, 2.7%, and 1.7%, respectively. The percentage of subjects withdrawing because of an adverse clinical event was equivalent in the three treatment groups. **Prostate volume regression was maximal at 6 months.** The greatest change in symptom

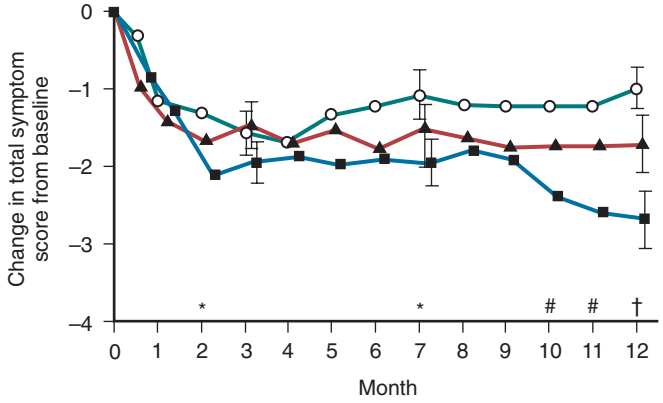


Figure 92–9. Mean (±SE) change in the total symptom score in men with benign prostatic hyperplasia during treatment with placebo *(circles)*, 1 mg of finasteride *(triangles)*, or 5 mg of finasteride *(squares)*. The *asterisks* ($P \leq .05$), the *pound* symbols ($P < .01$), and the *dagger* ($P < .001$) indicate significant differences between the finasteride-treated groups and the placebo group. Month 0 represents the baseline. (From Gormley GJ, Stoner E, Brusekewitz RC, et al. The effect of finasteride in men with benign prostatic hyperplasia. N Engl J Med 1992;327:1185–91. Copyright © 1992 Massachusetts Medical Society.)

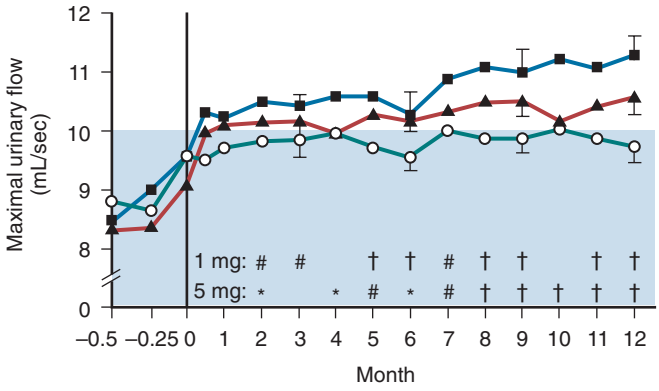


Figure 92–10. Mean (±SE) maximal urinary flow rates in men with benign prostatic hyperplasia during treatment with placebo *(circles)*, 1 mg of finasteride *(triangles)*, or 5 mg of finasteride *(squares)*. The *blue area* indicates the range in which urinary flow was considered to be obstructed. Month 0 represents the baseline. Values before month 0 were obtained during the 2-week placebo run-in period. The *asterisks* ($P < .05$), *pound* symbols ($P < .001$), and *daggers* ($P < .01$) indicate significant differences between the finasteride-treated groups and the placebo group. (From Gormley GJ, Stoner E, Brusekewitz RC, et al. The effect of finasteride in men with benign prostatic hyperplasia. N Engl J Med 1992;327:1185–91. Copyright © 1992 Massachusetts Medical Society.)

Table 92–8.

Efficacy of Finasteride for Benign Prostatic Hyperplasia

STUDY	ENROLLED (No.)	RANDOMIZED TREATMENT (mo)	DOSE (mg)	Group Mean Difference from Placebo		
				PFR (mL/sec)	Symptom Score	Prostate Volume (cm^3)
Gormley et al, 1992	895	12	1	+1.6*	–0.8	–13.0*
			5	+1.8*	–1.7†	–12.3*
Finasteride Study Group, 1993	750	12	1		NR	NR
			5	+1.3†	–1.3‡	NR
Andersen et al, 1995	707	12	5	+1.4‡	–1.2†	NR
		24	5	+1.5‡	–2.2‡	NR
Marberger et al, 1998	3720	12	5	0.6‡	–1.0*	–7.6
		24	5	0.8‡	–1.7*	–9.6
McConnell et al, 1998	3040	48	5	1.7*	–1.6*	NR

*$P < .001$.
†$P < .05$.
‡$P < .01$.
NR, not reported; PFR, peak flow rate.

scores and PFR occurred within the first 2 months of initiating active treatment.

The Finasteride Study Group (1993) **reported another multicenter, randomized, double-blind, placebo-control led clinical trial that is referred to as the International Finasteride Study. The effect of finasteride on symptom scores, PFR, and prostate volume is in agreement with the findings of the North American Finasteride Trial.** Andersen and associates (1995) reported the results of a multicenter, randomized, double-blind, placebo-controlled study investigating the safety and efficiency of finasteride in 707 Scandinavian subjects maintained on randomized treatment for 2 years. The mean baseline prostate volumes in the placebo and finasteride groups were 41.7 and 40.6 cm^3, respectively. A selection bias for enrolling large prostates did not exist in this study. A modified Boyarsky symptom score was used to capture changes in symptom score. The differences in the group mean changes in the symptom score and PFR between finasteride and placebo after 12 and 24 months on active treatment are summarized in Table 92–8. **The difference between the group mean changes in symptom scores and PFR after 1 year of randomized treatment is slightly less than that in the North American Finasteride trial? This may be attributed to the smaller baseline prostate volumes.**

Although the proportion of subjects experiencing any adverse clinical event and the number of withdrawals from adverse clinical events were similar to those in the finasteride and placebo groups there were more patients with sexual dysfunction in the finasteride versus placebo groups (19% vs. 10%). The time-dependent symptom score changes demonstrate that the placebo response returns to baseline between 1 to 2 years whereas the finasteride response remains stable. The authors interpret this to show that finasteride halts or alters the natural history of the disease. The mean differences between the symptom scores at 12 and 24 months in the finasteride and placebo groups were only –0.3 and 0.6 symptom unit, respectively.

Marberger and coworkers (1998) **reported the results of a 2-year randomized, placebo-controlled trial of 3270 men receiving finasteride versus placebo that are comparable with those from the report of Andersen and associates** (1995). The mean baseline prostate volumes in the placebo and finasteride groups were 39.2 and 38.7 cm^3, respectively. The baseline prostate volume is the lowest of all the finasteride trials. The treatment-related improvements in the quasi-AUASI at 1 and 2 years were 1.0 and 1.7 symptom units, respectively. The incidences of AUR were 1.0% and 2.5% in the finasteride and placebo groups, respectively.

Stoner and associates (1994) **reported on the safety and efficacy of 3 years of therapy with finasteride.** Subjects participating in the North American Finasteride Study and International Finasteride Study were offered the opportunity to participate in an open-label extension study after completing 1 year of randomized therapy. The long-term (3 years) efficacy and safety analysis was limited to the 543 subjects randomized to 5 mg. Of the 543 subjects, 297 (55%) completed 3 years of treatment and were evaluable. Of the 246 unevaluable patients, 178 were dropouts and 68 were placed in a category indicating insufficient data. Inspection of the group mean changes in outcome measures reveals that the most precipitous changes in symptom scores, PFR, and prostate volume occurred between the 12- and the 18-month assessment, which coincides with transferring from blinded to unblinded treatment. After 18 months the time-dependent changes were stable, suggesting durability of response. A subsequent report of the open-label extension study demonstrated the durability of finasteride effective up to 5 years (Hudson et al, 1999).

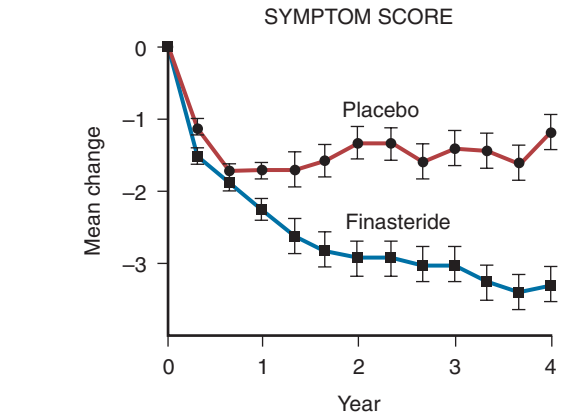
Boyle and coworkers (1996) reported a meta-analysis of six randomized, placebo-controlled clinical trials with finasteride. The mean group changes in symptom scores and PFR correlated with the mean baseline prostate volume. This observation accounts for the variability of treatment effect observed in the different studies.

The Proscar Long-Term Efficacy and Safety Study (PLESS) represented at the time the longest-duration multicenter, randomized, double-blind, placebo-con trolled study reported in the medical therapy of BPH literature (McConnell et al, 1998). The 3040 men with moderate to severe urinary symptoms were randomized to receive daily finasteride, 5 mg, versus placebo for 4 years. A quasi-AUASI was used. The baseline prostate volume in the study population was approximately 55 cm^3, indicating a bias for enrolling men with markedly enlarged prostates. The mean group changes in symptom score, PFR, and prostate volume throughout the study are shown for the finasteride and placebo in Figure 92–11. The treatment-related effects of finasteride on symptom score, PFR, and prostate volume were 2.0 symptom units, 1.7 mL/sec, and 32% size reduction for those subjects on active treatment at the end of the study. The symptom and PFR improvement was modest and consistent with findings of prior finasteride trials. The PLESS demonstrated the durability of symptom and flow improvements by finasteride and very modest progression of these end points in the placebo group.

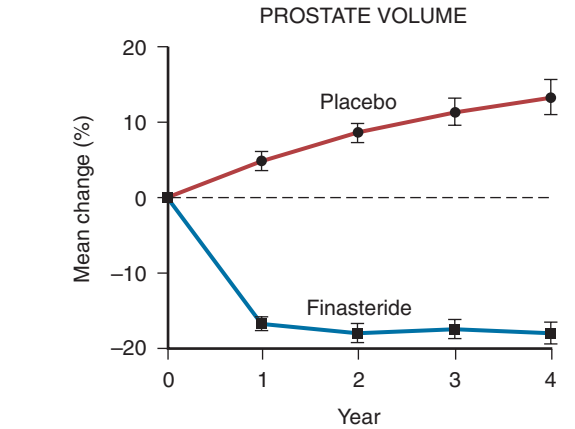
The unique findings of the PLESS were related to incidences of both AUR and surgical intervention for BPH (Fig. 92–12). The cumulative incidences of AUR at 4 years in the finasteride and placebo groups were 7% and 3%, respectively (57% risk reduction). The cumulative risk of undergoing BPH-related surgery was 10% and 5% in the placebo and finasteride groups, respectively (55% risk reduction). In those men with prostate volumes greater than 55 cm^3, the risk reduction of AUR and/or surgical intervention for finasteride was 70%. The risk reduction of AUR and BPH-related surgery was clinically relevant, especially in men with very large prostates. Men with significantly enlarged prostates and LUTS should therefore be advised of their significant risk of urinary retention and the beneficial effects of finasteride.

The PLESS study also provided insights into the impact of finasteride on the detection of prostate cancer. The decision to pursue the diagnosis of prostate cancer in the study was left at the discretion of the principal investigator and therefore represents standard practice. **The detection of prostate cancer was not significantly different in the placebo and finasteride group, suggesting that finasteride does not mask the diagnosis of prostate cancer** (Andriole et al, 1998).

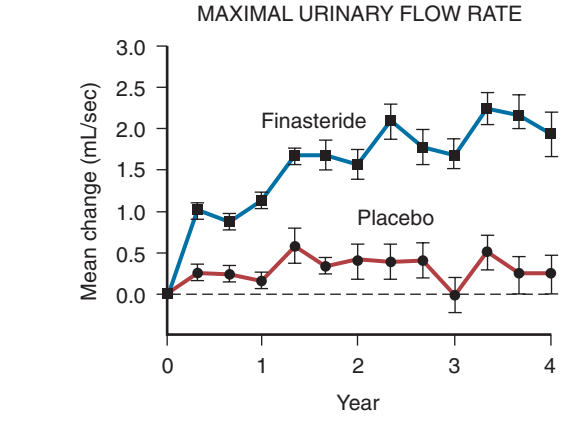
Tammela and Kontturi (1993) **reported a randomized, double-blind, placebo-controlled study examining the effects of finasteride on BOO in 36 men on a routine waiting list for prostatectomy.** The mean prostate volumes in the finasteride and placebo study groups were 50 and 48 cm^3, respectively. The mean baseline Pdet at maximum PFR in the placebo and finasteride groups were 115 and 126 cm H_2O, respectively, indicating that the subjects were severely obstructed. The group mean changes in Pdet at PFR was +3 and –39 cm H_2O in the placebo and finasteride groups, respectively. Although the difference between placebo and finasteride was highly statistically significant, the overwhelming majority of the finasteride-treated subjects remained obstructed after treatment. The marked



Placebo	1438	1296	1101	961	853
Finasteride	1437	1314	1153	1047	965

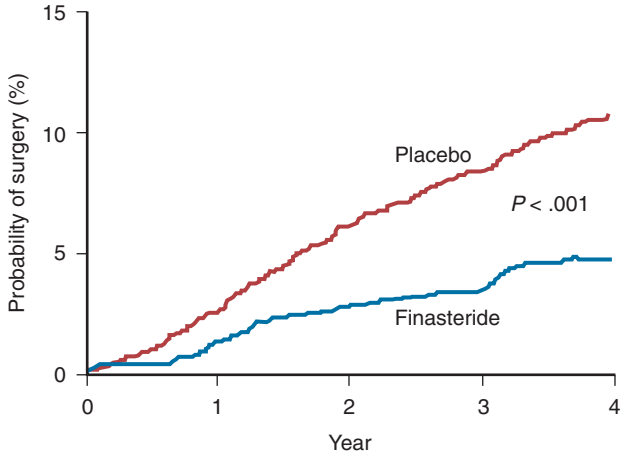


Placebo	155	136	119	98	85
Finasteride	157	144	130	116	102



Placebo	1127	899	720	608	496
Finasteride	1125	928	786	691	588

Figure 92–11. The effect of finasteride or placebo on symptom scores (on the quasi-AUASI), prostate volume, and maximal urinary flow rate over time. Values are mean (±SE) changes from baseline. The numbers below the panels show the numbers of patients with valid data who remained in the study. (From McConnell JD, Bruskewitz R, Walsh P, et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. N Engl J Med 1998;338:557–63.)

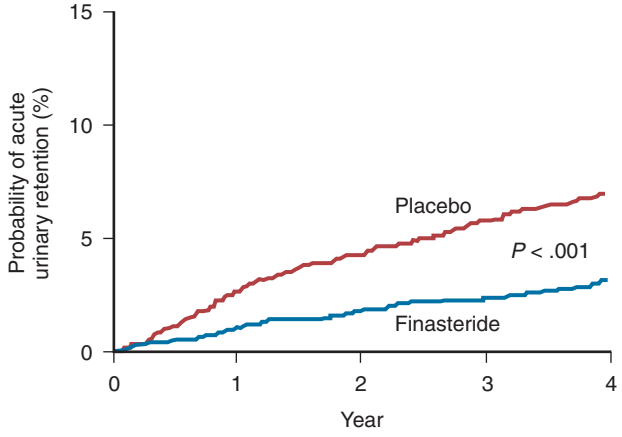


Placebo group

No. of events	37	52	32	31
No. at risk	1503	1454	1374	1314

Finasteride group

No. of events	18	22	9	20
No. at risk	1513	1483	1438	1410



Placebo group

No. of events	36	25	20	18
No. at risk	1503	1454	1398	1347

Finasteride group

No. of events	14	11	7	10
No. at risk	1513	1487	1449	1421

Figure 92–12. Probability of undergoing surgery for benign prostatic hyperplasia or the development of acute urinary retention during the 4-year study period in the placebo and finasteride groups. The figure shows life-table analyses of the proportion of men with each outcome. The numbers of events shown below the graphs are those that occurred during each 1-year interval. The numbers of men at risk are those at the beginning of the respective 1-year intervals. Data on men who died, were given a diagnosis of prostate cancer, or were lost to follow-up were censored at the time of death, diagnosis of prostate cancer, or discontinuation of therapy. (From McConnell JD, Bruskewitz R, Walsh P, et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. N Engl J Med 1998;338:557–63. Copyright © 1998 Massachusetts Medical Society.)

treatment-related changes in Pdet were not associated with statistically significant changes in symptom scores. The authors did not comment on whether the changes in Pdet correlated with changes in prostate volume. Of the subjects participating in the randomized, double-blind study, 27 completed a 4-year open-label extension study (Tammela and Kontturi, 1995). The Pdet at PFR showed further improvements over time.

PSA has become widely accepted as a screening instrument for prostate cancer (Tchetgen and Oesterling, 1995). An elevated or significantly rising PSA value is often an indication for prostatic biopsy. Finasteride reduces group mean serum PSA levels approximately 50% (Guess et al, 1993). The effect of finasteride on individual serum PSA levels is highly variable. **Because of the variable effect on PSA, men who are candidates for early detection of prostate cancer should have their PSA level determined before beginning finasteride therapy.** A biopsy should be performed if the PSA level is elevated. A repeat biopsy should be performed for progressively rising PSA levels after initiation of therapy.

The Prostate Cancer Prevention Trial (PCPT) (Thompson et al, 2003) showed that finasteride reduced the incidence of diagnosed prostate cancer (vs. placebo). There was an increased incidence of high-grade disease, probably owing to technical pathologic reasons.

Gross hematuria is a relatively rare, yet troublesome, manifestation of BPH. Puchner and Miller (1995) reported an uncontrolled personal experience of 18 BPH patients treated with finasteride for refractory gross hematuria secondary to BPH. In the 18 reported cases, 12 of the patients had undergone a prior prostatectomy. Finasteride was very effective in relieving the postprostatectomy-associated gross hematuria. Miller and Puchner (1998) reported a follow-up series that demonstrated the long-term effectiveness of finasteride for the treatment of hematuria from BPH. Carlin and coworkers (1997) reported resolution of gross hematuria in 12 men treated with finasteride. **These preliminary observations have been confirmed by a randomized, double-blind, placebo-controlled study by Foley and associates** (2000) **demonstrating that finasteride prevents recurrent gross hematuria secondary to BPH.** Gross refractory hematuria recurred within 1 year for 63% and 14% of men randomized to placebo and finasteride, respectively.

Dutasteride. **Dutasteride is a dual inhibitor of 5α-reductase types 1 and 2 and therefore has a greater impact on suppressing serum DHT levels** (Clark et al, 2004). In a randomized controlled trial of 4325 men (2951 completed) Roehrborn and colleagues (2002) reported that serum DHT was reduced by 90.2%. The symptom score was improved by 4.5 points (21.4%) ($P < .001$), and the maximal flow rate improved significantly by 2.2 mL/sec ($P < .001$) at 24 months. The risk reduction of AUR was 57% and the risk reduction of BPH-related surgery was 48% compared with placebo. Debruyne and coworkers (2004) reported the pooled results of a 2-year open-label extension study in which both dutasteride- and placebo-treated groups received dutasteride 0.5 mg/day. Significant improvements in symptom scores and PFRs were observed in both study groups. It was concluded that long-term treatment with dutasteride results in continuing improvements in both symptoms and PFR and that the risk reduction of AUR and BPH-related surgery was durable over 4 years. Similar to finasteride, the principal side effects were loss of libido and ED, but these were most frequently seen at the start of therapy and declined over time with treatment. Roehrborn and associates (2004) reported similar results and confirmed 93% suppression of DHT at 4 years. Recently, the results of the REDUCE study of dutasteride versus placebo in terms of their ability to prevent prostate cancer have been reported by Andriole and associates (2009). A 23% reduction in prostate cancer was seen in the dutasteride study arm, with no increase in less well-differentiated cancers in the dutasteride arm. Beneficial effects on symptoms, PFR, and risk of progression were also seen in this group of men at high risk for BPH progression as well as for a prostate cancer diagnosis. Further re-analysis has suggested some risk of high-grade cancers, and in December 2010 the FDA Oncologic Drugs Advisory Committee voted against use of dutasteride for reduction in the risk of prostate cancer. The manufacturer has withdrawn this application.

Zanoterone. **Zanoterone is a steroidal competitive androgen receptor antagonist** (Juniewicz et al, 1993). Berger and coworkers (1995) reported a multicenter, randomized, double-blind, placebo-controlled study in 463 subjects receiving placebo and 100, 200, 400, or 800 mg of zanoterone for 6 months. The group mean changes in AUASI score were not reported; however, the differences between placebo and all of the zanoterone groups were not statistically significant. The mean baseline prostate volumes ranged between 37.7 and 42.2 cm^3 in the five treatment groups. The differences between the percent group mean changes in prostate volume in the placebo (–6%) and active treatment groups (–4% to –8%) were not significantly different. Interestingly, the differences between the percent group mean changes in serum PSA in all of the active treatment groups were significantly greater than those in the placebo group, despite the lack of an apparent drug effect on prostate volume. The difference between the group mean changes in PFR for placebo and the 200-mg dose was 0.7 mL/sec. Fifty-six percent and 22% of all zanoterone subjects reported breast pain and gynecomastia, respectively. The incidence and severity of adverse clinical events and the equivocal efficacy precluded further development of this drug for BPH.

Flutamide. **Flutamide is an orally administered nonsteroidal antiandrogen that inhibits the binding of androgen to its receptor** (Sufrin and Coffey, 1973). The first reported randomized, double-blind, placebo-controlled trial in BPH examined the safety and efficacy of flutamide in 31 men with symptomatic BPH (Caine et al, 1975). Statistically significant differences were not observed between placebo and 300 mg of flutamide for symptoms, prostate size, PVR, and PFR. **Stone** (1989) **reported a multicenter, randomized, double-blind study comparing flutamide and placebo in men with BPH.** Eighty-four patients were randomized to receive 24 weeks of either flutamide, 250 mg three times a day, or placebo. Of the 84 patients, 58 (69%) and 12 (14%) were evaluable 12 and 24 weeks on double-blind treatment. The small sample size at 24 weeks precludes any meaningful conclusions. The between-group comparisons of group mean changes from baseline for placebo versus flutamide were not statistically significant at any time point. The incidences of breast tenderness and diarrhea in the flutamide group were 53% and 11%, respectively. Although the interim analysis was reported in 1989, a subsequent report of the multicenter study has not been published.

Cetrorelix. Cetrorelix is a gonadotropin-releasing hormone antagonist that has been investigated for BPH. **A potential advantage of a gonadotropin-releasing hormone antagonist over the luteinizing hormone–releasing hormone agonists in the treatment of BPH is the ability to titrate the level of androgen suppression.** This would be clinically relevant if different levels of androgen suppression mediate prostate size reduction and adverse events (hot flashes, decreased libido, ED). An open-label study of 11 men demonstrated that

cetrorelix reduced prostate volume and improved LUTS without significant adverse events. Lepor and coworkers (1997) reported a proof of concept randomized, double-blind, placebo-controlled study of cetrorelix in men with BPH. After an 8-day placebo lead in, men received daily subcutaneous injections of placebo or 1 mg of cetrorelix (group C01) for 27 days. One group received loading doses of 10 mg of cetrorelix on the first 4 days of active treatment (group C10). Maximal lowering of testosterone was observed within 24 hours. The testosterone level was reduced to castrate levels in the C10 group and to intermediate testosterone suppression level in the non–loading-dose group (C01) (approximately 20 ng/dL). Men exhibiting a clinical effect were observed for 1 year. In the C10 and C01 groups, the treatment-related improvement in AUASI score was 3.0 and 2.0 symptom units, respectively. In both the C10 and the C01 groups the treatment-related improvement in PFR was 2.0 mL/sec. The treatment-related reductions of prostate volume were 5.5 and 3.0 cm^3, respectively. The treatment-related incidence of hot flashes and sexual dysfunction in the C01 group was negligible. During the open-label extension, prostate volume did not return to baseline, suggesting a prolonged effect on the disease. Because of problems with the drug formulation, phase 3 studies with cetrorelix were not pursued until recently (Debruyne et al, 2008).

In this dose-finding study three dosing regimens were explored: one or two injections weekly for 4 weeks. In all groups a rapid improvement in mean IPSS was obtained, with a peak effect of –5.4 to –5.9 (placebo: –2.8). Changes from baseline and differences to placebo were statistically significant up to week 20. Placebo response was less sustained than usually seen with oral preparations.

The primary disadvantage of cetrorelix and other gonadotropin-releasing hormone antagonists will be the requirement for an injection and the cost. If single-injection therapy provides desirable clinical response (over, for example, 6 months) with minimal adverse events there may exist a role for these antagonists in the treatment of BPH.

Aromatase Inhibitors. **The rationale for aromatase inhibition is that estrogens may be involved in the pathogenesis of BPH.** The estrogenic effect most likely mediates stromal-epithelial interactions that regulate the proliferative activity of the prostate. Several observations support the role of stroma in the development of BPH and the influence of estrogens on prostatic stroma. The inductive potential of prostatic mesenchyme (stroma) is supported by the observation of Cunha and colleagues (1980) in a mouse embryonic animal model. Coffey and Walsh (1990) reported that estrogen treatment of castrated beagles produced a threefold to fourfold increase in the total amount of prostatic stroma. Estrogens also greatly enhanced the ability of androgens to induce BPH in a canine model (Walsh and Wilson, 1976; DeKlerk et al, 1979). This synergistic effect may be mediated by the ability of estrogens to upregulate prostatic androgen receptor content. Stromal hyperplasia can be induced in the prostates of dogs and monkeys treated with aromatizable androgens and prevented by aromatase inhibitors such as atamestane (Habenicht et al, 1987; Habenicht and El Etreby, 1989).

Atamestane is a highly selective aromatase inhibitor that lowers both serum and intraprostatic levels of estradiol and estrone (El Etreby et al, 1991). **Gingell and coworkers** (1995) **reported a multicenter, randomized, double-blind, placebo-controlled study comparing placebo and 400 mg of atamestane** in 160 subjects with clinical BPH. Atamestane resulted in a statistically significant decrease in serum estradiol and estrone levels and a statistically significant increase in serum testosterone. No statistically significant group mean differences were observed for changes in Boyarsky symptom score, PFR, or prostate volume between the atamestane and the placebo groups. One of the explanations contributing to the failure of atamestane to achieve clinical efficacy was the increase in testosterone. The development of atamestane for BPH was suspended because of these negative clinical findings. The failure to demonstrate that atamestane causes regression of established BPH or clinical improvement does not negate the influence of estrogens in the pathogenesis of BPH.

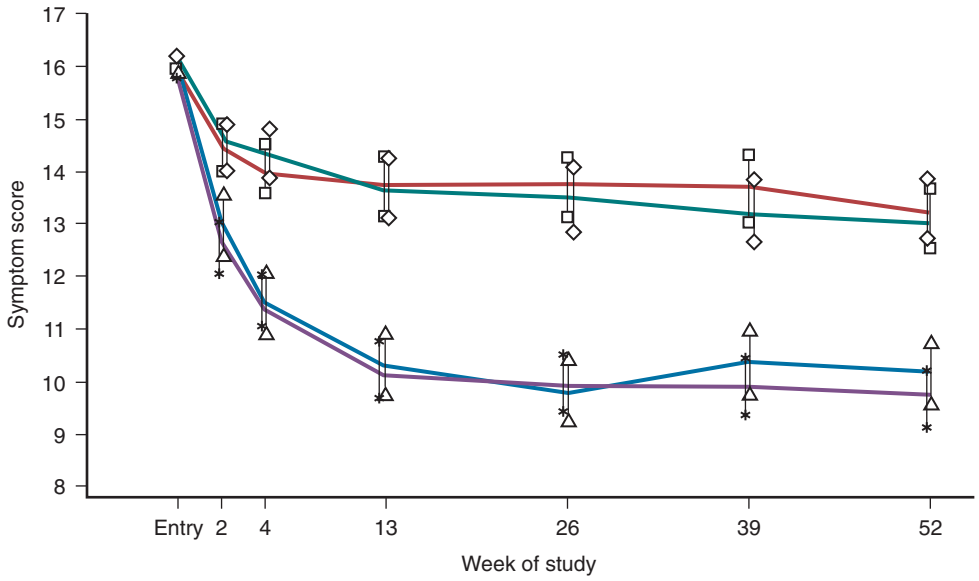
Finasteride and dutasteride are the only drugs available that achieve androgen suppression with acceptable tolerability. Both symptoms and flow rates are improved, especially in men with larger glands. Impotence and decreased ejaculatory volume are the primary treatment-related adverse experiences. The literature also suggests finasteride and dutasteride may be offered to men with hematuria secondary to friable prostatic tissue and in those men with LUTS and enlarged prostates who elect to reduce their risk of developing urinary retention.

Summary

Finasteride represents the androgen suppression drug that has been most extensively characterized in BPH. Multicenter, randomized, double-blind, placebo-control led studies support its role in the treatment of BPH. Finasteride reduces prostate volume approximately 20%. The overall treatment-related improvements in symptom score (approximately 1.0 symptom unit) and PFR (approximately 1.5 mL/sec) relative to placebo are modest. Long-term safety and durability of efficacy has been demonstrated for finasteride. The adverse clinical events associated with finasteride are minimal and are related primarily to sexual function. Finasteride is effective in the management of gross hematuria associated with BPH, especially in the presence of friable prostate tissue. Dutasteride is an inhibitor of both type 1 and type 2 5α-reductase and has similar efficacy and side effects to finasteride. Finasteride and dutasteride alter the natural history of urinary retention in men with LUTS and enlarged prostates. In the recently reported REDUCE study, dutasteride reduced the incidence of prostate cancer by 23%. Antiandrogens have also been investigated for BPH. These studies failed to demonstrate statistically significant treatment-related efficacy. The equivocal efficacy and problematic toxicity of antiandrogens limited the enthusiasm for marketing these drugs for the treatment of BPH. The role of gonadotropin-releasing hormone antagonists requires further study.

Combination Therapy with α-Adrenergic Blockers and 5α-Reductase Inhibitors

Lepor and coworkers (1996) **reported the first multicenter, randomized, double-blind trial comparing placebo, finasteride, terazosin, and combination therapy (finasteride and + terazosin) in 1229 U.S. veterans with clinical BPH.** All subjects randomized to finasteride received a daily dose of 5 mg. The dose of terazosin was titrated in all patients up to 10 mg, providing adverse clinical events were not encountered. The dose of terazosin was reduced at the discretion of the investigators to 5 mg for adverse events. Of the 1229 subjects



No. of men							
Placebo	(□)	305 297 294	290	280	263	265
Finasteride	(◇)	310 304 302	290	279	261	260
Terazosin	(△)	305 301 296	291	288	275	275
Combination	(∗)	309 305 299	292	288	280	278

Figure 92–13. AUA Symptom Index in men with benign prostatic hyperplasia, according to treatment group. Scores are expressed as adjusted means and 95% confidence intervals. The results of primary pairwise comparisons (with Bonferroni's adjustment) are as follows: finasteride and terazosin, $P < .001$; finasteride and combination therapy, $P < .001$; and terazosin and combination therapy, $P = 1.00$. The results of secondary pairwise treatment comparisons are as follows: finasteride and placebo, $P = .63$; terazosin and placebo, $P < .001$; and combination therapy and placebo, $P < .001$. (From Lepor H, Williford WO, Barry MJ, et al. The efficacy of terazosin, finasteride or both in benign prostatic hypertrophy. N Engl J Med 1996;335:533–9. Copyright © 1996 Massachusetts Medical Society.)

randomized, 1007 (81.9%) completed the 1-year randomized treatment on assigned study medication.

The AUASI score (Fig. 92–13) and PFRs (Fig. 92–14) are shown for the four treatment groups throughout the study. The group mean changes between baseline and final study visit for the relevant primary and secondary outcome measures are summarized in Table 92–9. The mean group differences between finasteride and placebo were not statistically significant for AUASI, Symptom Problem Index, and BPH Impact Index scores and PFR. The mean group differences between terazosin versus placebo and terazosin versus finasteride for all of the outcome measures other than prostate volume were highly statistically significant. The group mean differences between combination therapy and terazosin for all of the outcome measures other than prostate volume were not statistically significant, owing to the lack of treatment-related efficacy of finasteride. The Veterans Affairs study demonstrated the superiority of α-adrenergic blockade over androgen suppression for the treatment of clinical BPH over a 1-year interval. Prostate volume decreased approximately 20% in the finasteride and combination groups. The numbers of subjects withdrawing from the study because of adverse clinical events in the finasteride, terazosin, and combination groups were similar.

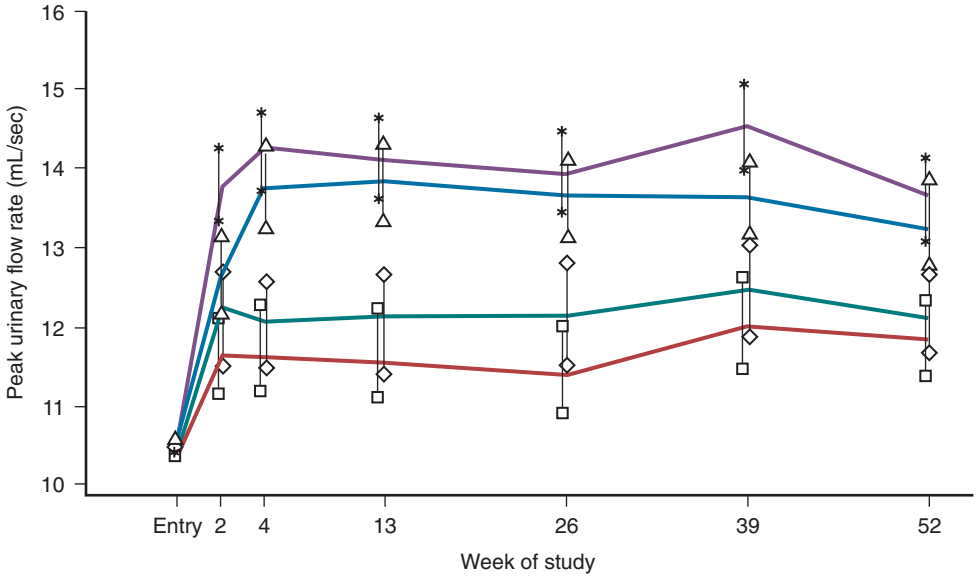
A multicenter, randomized, double-blind, placebo-controlled study comparing placebo, doxazosin, finasteride, and combination therapy confirmed the findings of the Veterans Affairs cooperative study (Kirby et al, 2003). In the Prospective European Doxazosin and Combination Therapy Trial (PREDICT), 1089 men were randomized in equal proportions to one of the just discussed four treatment groups for 1 year. The daily dose of doxazosin was titrated up to 8 mg. The baseline prostate volume was approximately 36 cm^3. The group mean improvement of AUASI score and PFR and change in prostate volume between baseline and final study visit are shown in Table 92–10.

A multicenter, double-blind study compared SR alfuzosin (5 mg), finasteride (5 mg), and combination therapy in 1051 men receiving active treatment for 6 months (Debruyne et al, 1998). The improvement in IPSS was not significantly different in the alfuzosin versus combination groups. At 6 months there were no significant differences between PFR among any of the treatment groups.

Medical Therapy of Prostatic Symptoms (MTOPS) Trial

The results of all three large-scale studies just described appear to suggest that the role of 5α-reductase inhibitors as generalized monotherapy for LUTS may be somewhat limited, a finding at variance with some of the original studies on finasteride. An additional, longer-term trial, which has been progressing in parallel to these studies, has generated important new information on both the clinical potential of 5α-reductase inhibitors as monotherapy and the potential of drug combinations. The MTOPS trial, a prospective, randomized, double-blind, multicenter, placebo-controlled trial, was established to determine whether medical therapy can prevent or delay the progression of BPH in the long term. Further elucidation of the natural history of BPH, determining baseline factors associated with more rapid disease progression, was a secondary aim of the study.

In 18 academic centers across the United States a total of 3047 patients were recruited and randomized to receive doxazosin, finasteride, a combination of both, or placebo. Mean age of



No. of men							
Placebo	(□)	305	296	294	290	279	258	264
Finasteride	(◇)	310	305	301	289	278	259	252
Terazosin	(△)	305	299	296	292	287	271	275
Combination	(∗)	309	304	297	292	284	273	277

Figure 92–14. Peak urinary flow rates in men with benign prostatic hyperplasia, according to treatment group. Rates are expressed as adjusted means and 95% confidence intervals. The results of primary pairwise comparisons (with Bonferroni's adjustment) are as follows: finasteride and terazosin, $P < .001$; finasteride and combination therapy, $P < .001$; and terazosin and combination therapy, $P = .15$. The results of secondary pairwise treatment comparisons are as follows: finasteride and placebo, $P = .07$; terazosin and placebo, $P < .001$; and combination therapy and placebo, $P < .001$. (From Lepor H, Williford WO, Barry MJ, et al. The efficacy of terazosin, finasteride or both in benign prostatic hypertrophy. N Engl J Med 1996;335:533–9. Copyright © 1996 Massachusetts Medical Society.)

Table 92–9.

Comparison of Placebo, Finasteride, Doxazosin, and Combination Therapy: Veterans Affairs Study

OUTCOME MEASURES	Difference between Final and Baseline Study Visits			
	Placebo	Finasteride	Doxazosin	Combination Therapy
AUA Symptom Index	–2.6	–3.2	–6.6*	–6.2*
Symptom Problem Index	–1.4	–1.7	–3.9†	–4.2†
BPH Impact Index	–0.5	–0.5	–1.2†	–1.7†
Prostate volume (cm^3)	+0.5	6.1*	+0.5	+7.2*
PFR (mL/sec)	+1.4	+1.6	+2.7*	+3.2*

*$P < .001$ relative to placebo.
†$P < .01$ relative to placebo.
AUA, American Urological Association; BPH, benign prostatic hyperplasia; PFR, peak flow rate.

Table 92–10.

Comparison of Placebo, Finasteride, Doxazosin, and Combination Therapy in the PREDICT Study

OUTCOME MEASURES	Differences between Final and Baseline Study Visits			
	Placebo	Finasteride	Combination Doxazosin	Therapy
International Prostate Symptom Score	–5.7	–6.6	–8.3*	–8.5*
Peak flow rate (Qmax)	1.4	1.8	3.6*	3.8*
Acute urinary retention	1.5	1.1	0	0.0

*$P < 0.05$ relative to placebo.
PREDICT, Prospective European Doxazasin and Combination Therapy Trial.

participants was 62.6 years, most were white (82.6%), with 8.8% black and 7.2% Hispanic participants. The inclusion/exclusion criteria allowed men with all prostate sizes to be enrolled, as long as the serum PSA value was less than 10 ng/mL. This resulted in a wide distribution of prostate sizes and serum PSA values, allowing for stratified analyses of subsets based on these criteria (McConnell et al, 2003).

Disease progression was defined as a worsening of BPH symptoms according to the AUASI. Progression was deemed to have occurred in the case of one of the following: a 4-point rise in the AUASI score, confirmed by a second visit within 4 weeks; a 50% increase in creatinine relative to baseline levels; AUR; two or more UTIs within 1 year or a single episode of urosepsis due to BOO; and socially unacceptable incontinence. The first occurrence of any of these events indicated BPH progression. Progression as an end point represented a novel concept at the time of the initiation of the MTOPS study, although the PLESS as well as the dutasteride

studies later on utilized AUR and surgery as end points in their study designs (McConnell et al, 1998; Roehrborn et al, 2002). Entirely novel was the concept of utilizing a threshold to define symptom progression. Based on data from the Veterans Affairs cooperative study, in which men perceived general improvement in their symptom status once the AUASI score improved by more than 3 points, a threshold of 4 points was chosen—to be confirmed within 4 weeks—to indicate global subjective worsening of symptom status.

To assess the natural history of BPH, PFR, prostate volume, sexual function, and quality of life were regularly recorded with respect to BPH symptoms. Transrectal ultrasonography and DRE were used to evaluate prostate volume, the Sexual Function Inventory Questionnaire evaluated sexuality, and the Short Form-36 Health Survey instrument recorded quality of life scores. Prostatic biopsies were obtained at baseline and at 5 years (or at primary end point) in 37% of study participants who volunteered to take part in a biopsy substudy. Patients were randomized to receive 5 mg finasteride and doxazosin placebo, 5 mg finasteride and doxazosin titrated to up to 8 mg, titrated doxazosin and finasteride placebo, or two placebo drugs.

The results of the MTOPS trial suggest that the combination of doxazosin and finasteride exerts a clinically relevant, positive effect on rates of disease progression. Men who received combination therapy were significantly less likely to experience BPH progression than those receiving either monotherapy or placebo, with risk reduction rates of 39% for doxazosin, 34% for finasteride, and 67% for combination therapy compared with placebo.

Invasive therapy and AUR risk were significantly reduced by finasteride and combination therapy (by 69% and 64%, and by 79% and 67%, respectively), whereas all treatment regimens (placebo, doxazosin, finasteride, and combination) brought about a significant improvement in AUASI score (4.0, 6.0, 5.0, and 7.0, respectively) and PFR (1.4, 2.5, 2.2, and 3.7 mL/sec, respectively) at 4 years. **AUASI score and PFR improved significantly more in the combination therapy group compared with the monotherapy groups,** whereas adverse events were similar to previously reported studies.

In addition to indicating the potential benefits of combination therapy, MTOPS provided important data regarding the natural history of untreated BPH and the prediction of BPH patients who will respond most effectively to medical treatment. Although the patients receiving finasteride alone or in combination experienced the expected decrease in prostate volume, patients on placebo or doxazosin alone experienced an increase in prostate volume from a baseline of 34.0 mL by 9.3 (30.3%) (placebo) and from 36.4 mL by 9.9 (31.4%) (doxazosin), respectively. Stratified by PSA quartiles**, total prostate volume in both placebo and doxazosin-treated patients increased from 4.9 mL (24.9%) to 16.2 mL (34.5%) from the lowest to the highest quartile for an annualized growth of 1.1 to 3.6 mL/yr.** These findings suggest that doxazosin, despite its apoptotic effect (Glassman et al, 2001), does not interfere with the natural growth tendency of the prostate gland and that baseline **PSA is a useful predictor of future prostate growth in men with LUTS and BPH.**

Examination of baseline measures and the disease outcomes of 737 patients treated with placebo revealed that PSA, PFR, PVR, and prostate volume at baseline correlated with clinical progression of the disease and the need for BPH-related surgery ($P = .03$ to $< .001$). Age was linked to clinical progression ($P < .001$) and AUASI score correlated with need for surgery ($P = .002$). Baseline PSA and prostate volume correlated with risk of AUR ($P = .03$ to $.003$). Risk of progression, BPH-related surgery, and AUR increased alongside levels of serum PSA. In medically treated patients, however, baseline values were variably predictive of BPH outcome. In doxazosin-treated patients, for example, PSA, PFR, and prostate volume were predictive of outcome; however, this was not true of patients treated with finasteride alone or combined therapy.

The number needed to treat (NNT) to prevent a case of BPH progression as defined in MTOPS in the overall population was 8.4 for the combination therapy group and 13.7 and 15.0, respectively, for the doxazosin- and finasteride-treated patients. For those men treated with combination therapy who had a baseline PSA of more than 4.0 ng/mL, however, the NNT was 4.7, and for those with a prostate volume over 40 mL it was 4.9, suggesting that combination therapy becomes an economically stronger option in patients at higher risk for progression.

The link between sexual dysfunction and severity of LUTS was also confirmed by the MTOPS data. A correlation was observed between LUTS and five domains of sexual dysfunction (libido, sexual function, ejaculatory function, the patient's assessment of his sexual problems, and overall satisfaction). In addition, men with larger prostates were more likely to have low libido, low overall sexual functioning, reduced ejaculatory function, and greater sexual problems.

Another study of combination therapy in BPH employing dutasteride and tamsulosin has been reported by Barkin and colleagues (2003). Three hundred twenty-seven patients were treated with both drugs for 24 weeks and then the α-adrenergic blocker was withdrawn for a further 12 weeks; of those patients with an IPSS less than 20, 84% continued without noticeable deterioration of their symptoms. In contrast, in the 27% of patients with more severe symptoms (IPSS > 20), 42.7% reported a worsening of their symptoms compared with 14% of those who remained on combination therapy. It was concluded that a 5α-reductase inhibitor can be used in combination with an α-adrenergic blocker to achieve rapid onset of symptom relief in patients at risk of underlying disease progression and the α-adrenergic blocker can then be discontinued. In patients with severe symptoms, combination therapy should be continued for a longer term.

Combination versus Avodart or Tamsulosin (CombAT) Trial

Recently, Roehrborn and colleagues (2008b) have reported the 2-year results of the CombAT study. In these men with a pretreatment PSA between 1.5 and 10 ng/mL, combination of dutasteride and tamsulosin was more effective than either drug alone. Interestingly, in men with larger prostates, although the tamsulosin effect was rapid, over time dutasteride was the more effective agent. Superiority of combination therapy versus dutasteride was seen from month 3 and versus tamsulosin from month 9 and was maintained for the study duration ($P < .001$).

The full 4-year data will be published soon and are important because longer-term studies are clearly needed to fully evaluate the efficacy of 5α-reductase inhibitor therapy in BPH.

Anticholinergic (Antimuscarinic) Receptor Blockers

There is an overlap between symptoms traditionally regarded as being due to BPH and those ascribed to the syndrome of OAB. OAB

symptoms may coexist with BPH or BOO and may be either secondary to that obstruction or unrelated. Telephone surveys in the United States (Stewart et al, 2003) and in Europe (Milsom et al, 2001) show that 12% to 16% of the adult population admit to OAB symptoms. In Europe 60% of those with symptoms had consulted a medical practitioner about the symptoms and two thirds reported that they had an effect on daily living. Traditionally, in the treatment of OAB symptoms the use of antimuscarinic (commonly called anticholinergic) agents is often employed in women. However, in men there is always anxiety that these antimuscarinic agents decrease detrusor contractility and could, in theory, increase the risk of urinary retention, particularly in a man with significant obstruction. If not leading to AUR, then the risk of increasing PVR might lead to other complications, such as infection.

There have been small studies and anecdotal evidence showing that antimuscarinic agents can be used judiciously with efficacy and with minimal side effects. More recently, newer antimuscarinic agents have been introduced. Tolterodine studies have shown symptomatic benefit without increased AUR in men with OAB with proven BOO (Abrams et al, 2006) and suggest that antimuscarinic agents can be safely administered in men with BOO. Abrams and associates (2006) investigated a total of 222 men older than age 40 years with BOO and detrusor overactivity confirmed by pressure-flow studies who were enrolled and were randomized to tolterodine (2 mg twice daily in 149) or placebo (in 72) for 12 weeks: 87% completed the trial. Primary end points were PFR and Pdet at PFR. Median treatment differences in PFR (–0.7 mL/sec, 95% CI –1.6 to 0.4) and Pdet at PFR (–7 cm H_2O, 95% CI –3 to 11) were comparable. Tolterodine significantly reduced the BOO index versus placebo (–9 vs. 0, $P < .02$), although the urodynamic significance of these changes has been questioned. There were significant treatment differences in volume to first detrusor contraction (+59 mL, 95% CI 19 to 100) and maximum cystometric capacity (+67 mL, 95% CI 35 to 103), favoring tolterodine over placebo ($P < .003$). Change in PVR was significantly greater among patients treated with tolterodine (+25 mL) than placebo (0 mL, $P < .004$). But there were no significant between-group differences in the incidence of adverse events. Urinary retention was reported by 1 patient treated with placebo. Tolterodine did not appear to adversely affect urinary function in men with OAB and BOO. Urinary flow rate was unaltered, and there was no evidence of clinically meaningful changes in voiding pressure and PVR or urinary retention. Tolterodine was also well tolerated. **These results suggest that antimuscarinic agents could be safely administered in men with BOO.**

Blake-James and coworkers (2007) performed a systematic review of the available literature then and, when data were sufficient, performed a meta-analysis to assess the safety and efficacy of antimuscarinic therapy in men with LUTS suggestive of BPH. They analyzed 5 randomized controlled trials and 15 observational studies of good quality (Table 92–11). Minimal changes were reported in PFR or IPSS overall, although storage symptoms scores did appear to improve in 1 trial. PVR did increase, but minimally, and there was no convincing increase in AUR rates. The authors concluded that, although antimuscarinic therapy was safe, more studies were required to define the efficacy of this therapy for men with LUTS/BPH.

Combination Therapy: α-Adrenergic Blockers and Anticholinergic (Antimuscarinic) Receptor Blockers

Response of the OAB symptoms seen in men with LUTS/BPH raises the possibility that a combination with α-adrenergic blocker therapy could both reduce the risk of retention or deteriorating

Table 92–11.

Summary of Outcomes of Randomized Controlled Trials of Antimuscarinic (Anticholinergic) Treatment

	Study				
OUTCOME	Abrams et al, 2006	Lee et al, 2005	Athanasopoulos et al, 2003	Saitoh et al, 1999	Dahm et al, 1995
No. of subjects	221	228	50	134	70
Agent	Tolterodine	Propiverine + doxazosin	Tolterodine + tamsulosin	Propiverine + tamsulosin	Flavoxate
PFR, mL/sec	–0.3 vs. +0.5	+1.0 vs. +1.7	+1.32 vs. +1.16	+0.5 vs. +2.9	–0.1 vs. +0.1
P	NS	NS	NS	NS	NS
PVR, mL/sec	+25 vs. + 0	+20.8 vs. –4.7	–4.2 vs. –8.2	+24 vs. –9.5	–2 vs. –6
Change, *P*	up, .004	up, .002	NS	NS	NS
VFC, mL	+59 vs. –31		+100.4 vs. +30.4		
Change, *P*	up, .003		up, < .001		
MC, mL	+67 vs. –8.0		+36.4 vs. +0.8		
Change, *P*	up, < .001		up, .002		
Frequency episodes		–1.9 vs. –0.9		–1.74 vs. –1.87	
Change, *P*		down, .004		NS	—
Nocturia episodes		–0.7 vs. –0.6		–1.32 vs. –0.65	–0.6 vs. –0.8
Change, *P*		NS		down, 0.004	NS
Urge, IPSS		–1.2 vs. –0.7		–0.62 vs. –0.55	
Change, *P*		down, .02		NS	
IPSS total		–7.4 vs. –7.3		–5.01 vs. –5.51	
P		NS		NS	
IPSS storage		–3.8 vs. –2.9		–2.99 vs. –2.22	
Change, *P*		down, .03			

IPSS, International Prostate Symptom Score; MC, mean capacity; PFR, peak flow rate; PVR, postvoid residual volume; VFC, volume at first contraction.
Change is intervention arm versus change in control; statistical significance between groups $P < .05$; NS, not significant.
From Blake-James BT, Rashidian A, Ikeda Y, Emberton M. The role of anticholinergics in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a systematic review and meta-analysis. BJU Int 2007;99:85–96.

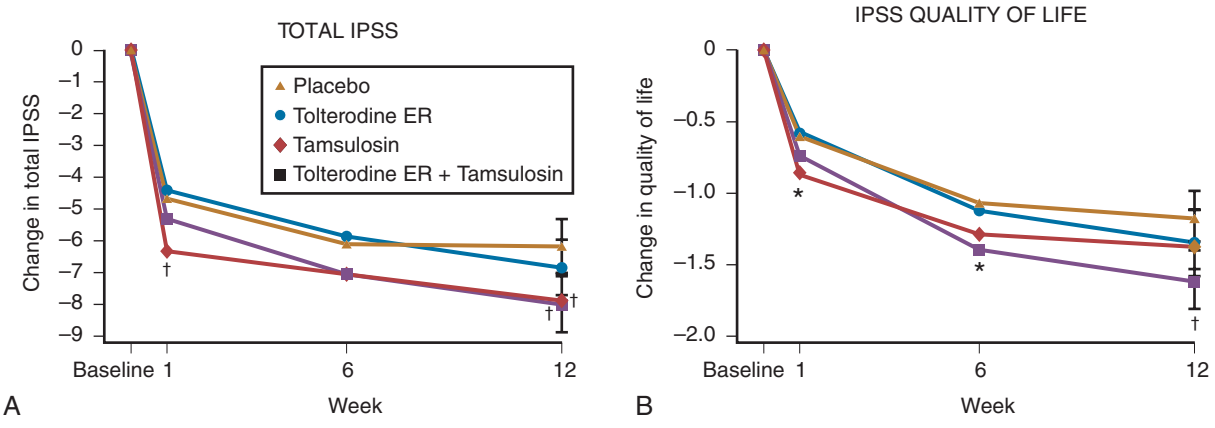
bladder function and also add to the treatment of the remaining obstructive symptoms of LUTS/BPH.

In a Korean randomized study (Lee et al, 2005), 211 men with OAB symptoms and urodynamically proven BOO were randomized (1:2) into two groups; one group was given doxazosin (4 mg once daily) only and the other was given propiverine (20 mg once daily) plus doxazosin for an 8-week trial. Significant improvements were noted in each group after treatment in urinary frequency, maximum flow rate, average micturition volume, and IPSS. Improvement in urinary frequency (23.5% vs. 14.3%, $P = .004$), average micturition volume (32.3% vs. 19.2%, $P = .004$), and storage (41.3% vs. 32.6%, $P = .029$) and urgency ($P = .019$) symptoms were more significant in group 2 given propiverine plus doxazosin. PVR urine was found to be significantly increased only in group 2, but this was not accompanied by urinary retention. Patient satisfaction rates were found to be significantly higher in group 2 than in group 1 ($P = .002$). Overall adverse event rates were higher in group 2 ($P = .002$), although discontinuation rates and discontinuation rates due to adverse events were not different between the two groups, suggesting that combination therapy consisting of α_1-adrenoceptor antagonists with antimuscarinic agents represents an effective and relatively safe treatment modality in select patients with OAB coexisting with benign prostatic obstruction.

Kaplan and coworkers (2006) in a double-blind placebo-controlled trial in 95 centers in the United States enrolled 879 men with the usual LUTS/BPH parameters often found in trials but who also had proven frequency (minimum 8 times a day) and urgency (at least three episodes per 24 hours as recorded in voiding diaries) and randomized them between tolterodine 4 mg daily, tamsulosin 0.4 mg daily, a combination of tolterodine and tamsulosin, and placebo over a 12-week period. The combination group showed a significant benefit over placebo in response to a patient-reported single-item question determining the perception of benefit (80% vs. 62%). This was the primary end point. Data supplied suggest an NNT (number needed to treat) of 5, which is reasonable. Interestingly, neither drug used alone was significantly better than placebo in terms of patient perception of benefit, although the tamsulosin study arm showed IPSS improvement (Fig. 92–15). There were only minor adverse events, which were equally distributed in the groups.

The data suggest that in this population of men with LUTS but enriched by recruiting men with OAB symptoms (24% reported episodes of incontinence at baseline, for instance) that a treatment strategy targeting both the bladder and the prostate was needed to achieve maximal benefit. They postulate that the best candidates for this form of combination therapy might be those men not immediately responding adequately to α-adrenergic blocker therapy alone.

Once again, the added expenses of combination therapy need to be considered, although the NNT rate is encouraging. **There is minimal available evidence on the long-term outcome of medical therapy of mixed OAB and BOO due to BPH. The short-term data suggest that combination of antimuscarinic and α-adrenergic blocker therapy is safe with minimal risk of retention or AUR in carefully selected men.** It would seem advisable to avoid treating men with a substantial residual urine (200 mL or more in the study), and men on this therapy who are reporting increased hesitancy or showing signs of increasing PVR or clinical evidence of retention should be warned to stop the antimuscarinic element of the combination therapy immediately. **Men with significant obstruction and large, persistent residual urine volumes should be considered for surgical therapy rather than the addition of antimuscarinic agents.**



No. of patients						
Placebo	215 208	213	213	215 210	213	213
Tolterodine ER	210 203	206	206	210 206	206	206
Tamsulosin	209 196	197	197	206 198	198	198
Tolterodine ER + Tamsulosin	217 200	203	203	217 204	205	205

Values are adjusted means (i.e., least-squares means). ER indicates extended release; IPSS, International Prostate Symptom Score.
*$P < .05$.
†$P < .01$ vs placebo.

Figure 92–15. **A** and **B,** Response of lower urinary tract symptoms to tolterodine, tamsulosin, or combination vs placebo. (From Kaplan SA, Roehrborn CG, et al. Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. JAMA 2006;296[19]:2319–28.)

Key Points: Antimuscarinic Therapy

- Short-term trial data suggest antimuscarinic agents can be safely given to carefully selected men with OAB/storage symptoms and BPH.
- The combination of antimuscarinic agents and α-adrenergic blocker therapy may improve both storage and voiding symptoms.
- It is advisable to avoid treating men with large PVR urine volumes (≥200 mL) with antimuscarinic agents.
- Men with significant obstruction and large persistent residual urine volumes should be considered for surgical therapy.
- Long-term data are not available.

Phosphodiesterase Inhibitors

The rationale for the use of PDEIs in the treatment of LUTS/BPH was initially based on demographic data showing the frequent occurrence of both ED and LUTS in men as they age (Table 92–12). This raised the possibility of a common underlying mechanism at least contributing to both processes. This, in turn, raised the possibility of new treatment options that might impact on both processes.

After the first clinical report in 2002 of improvement in LUTS in men given sildenafil (Viagra) for their ED (Sairam et al, 2002) there has been an explosion of interest in the role of PDEIs as treatments for LUTS and, in particular, for the management of the many men with both conditions whom we commonly see in clinics. The scientific basis is rapidly becoming stronger and **there is now good level 1 evidence from (currently) four clinical trials clearly showing improvement of LUTS after**

Table 92–12.

Summary of Epidemiologic Studies Associating LUTS with Erectile Dysfunction

STUDY	STUDY DESIGN/NAME	NO.	FINDINGS
Braun et al, 2000	Cologne Male Survey	4000	LUTS in 72.2% of patients with ED vs. 37.7% without ED; prevalence risk highly significant
Blanker et al, 2001	Krimpen Community Cohort	3924	ED RR: 1.8-7.5 for increasing urinary complaints; risk of ED greater with LUTS than with smoking or cardiac symptoms
Moreira et al, 2003	Brazilian Cohort Study	428	ED incidence RR: 3.67 if self-reported BPH—2-yr follow-up; addresses temporality of BPH → ED
Boyle et al, 2003	UrEpik Study	4800	IPSS > 7 showed odds ratio of 1.39 of having ED in a weighted multiple regression model, including age; similar odds ratios: heart attack, hypertension, and smoking
Vallancien et al, 2003	Cross-sectional European Survey	1274	55% of patients with mild LUTS had ED vs. 70% with severe LUTS; significance maintained after multiple regression analyses
Rosen et al, 2003	Multinational Survey of the Aging Male	12815	RR 3.7-7.6; IPSS correlated with IIEF, sexual activity, and ejaculatory parameters; controlled for age and comorbidities; older men still sexually active
Braun et al, 2003	Cologne Male Survey	4489	Prevalence of LUTS in men suffering from ED was about 72.2% (n = 621) vs. 37.7% (n = 1367) in men with normal erections; the odds ratio was 2.11, even after controlling for age
Chung et al, 2004	Cross-sectional Community Survey	2115	LUTS correlated with ED; sexual satisfaction and libido inversely correlated with LUTS
Ponholzer et al, 2004	Austrian Study	2858	RR for ED in men with LUTS (IPSS > 7) was 2.2; controlled for age, vascular risk factors, and predominance of obstructive or irritative symptoms
Hansen et al, 2004	Danish Study	3442	LUTS predicted ED after multiple regression; RR 2.3-3.4; overall LUTS prevalence 39% and ED prevalence 29%
Elliott et al, 2004	U.S. Veterans Affairs Survey	181	ED correlated with obstructive LUTS after controlling for age, depression, hypertension, and coronary artery disease on multivariate analysis
Terai et al, 2004	Japanese Cross-sectional Survey	2084	RR: 1.5; ED correlated with LUTS (IIEF vs. IPSS); correlation remained after controlling for age
McVary et al, 2004	MTOPS Secondary Analysis	3000	AUASI score correlated with ED and other domains; included correlation with maximum flow rate (multivariate analysis controlled for confounders)
Shiri et al, 2005	Finish Cohort Study	1126	RR of ED incidence with DAN-PSS score 7-11 was 2.7, RR was 3.1 for DAN-PSS > 12 over a 5-yr period; addresses temporality of BPH → ED
Paick et al, 2005	PLESS Study and Questionnaire	2981	2% increase in ED risk for unit increase in PLESS LUTS survey, significant after controlling for age
Brookes et al, 2008	BACH Study Subset Analysis	2301	Multivariable regression model of ED found strong association of AUASI score and ED independent of age; nocturia, incontinence, and prostatitis strongest factors; no differences found across race or ethnicity

AUASI, American Urological Association Symptom Index; BACH, Boston Area Community Health Survey; BPH, benign prostatic hyperplasia; DAN-PSS, Danish Prognostic Symptom Score; ED, erectile dysfunction; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms; MTOPS, Medical Therapy of Prostatic Symptoms trial; PLESS, Proscar Long-Term Efficacy and Safety Study; RR, relative risk.

From Kohler T, McVary K. The relationship between erectile dysfunction and lower urinary tract symptoms and the role of phosphodiesterase type 5 inhibitors. Eur Urol 2009;55(1):38–48.

treatment with PDEIs (McVary et al, 2007a, 2007b; Roehrborn et al, 2008b; Stief et al, 2008) (Table 92–13).

However, in the studies so far available to us there are no significant changes in PFR, suggesting that the effects of PDEIs may be either more focused on bladder muscle function than on prostatic tissue or are more profound on storage symptoms than on bladder outflow obstruction itself. The relationship between the management of LUTS and ED has been well reviewed (Kohler and McVary, 2009).

ED is commonly found in the male population who are at risk for LUTS. This association is found throughout the Western world as well as in Asian studies. The pathophysiologic link between these conditions is not yet clear, but several theories have been described with various levels of supporting data (Fig. 92–16). It is likely that there is an overlap between the roles of each of these candidate mechanisms, and an ultimate effect leading to smooth muscle relaxation in prostatic, bladder neck, or erectile tissues appears to be crucial. The candidate mechanisms include the following:

1. Pelvic atherosclerosis
2. Autonomic hyperactivity
3. The calcium-independent Rho-kinase activation pathway
4. Reduced nitric oxide (NO) levels, which is probably the best explored process so far

The pelvic atherosclerosis theory suggests that just as penile ischemia leads to smooth muscle loss in the penis so smooth muscle damage in the bladder would decrease compliance and predispose to replacement of bladder smooth muscle with collagen and fibrosis. Reduced nitric oxide synthase (NOS) expression is seen with ischemia. Furthermore, conditions promoting pelvic atherosclerosis such as hypertension, smoking, hypocholesterolemia, and diabetes mellitus are implicated in both ED and LUTS.

Autonomic hyperactivity and particularly increased sympathetic tone are seen in various components of the metabolic syndrome and have been implicated in the development of LUTS (McVary, 2005).

Abnormal activation of the Rho/Rho-kinase pathway is involved in the pathogenesis of hypertension, vasospasm, and arteriosclerosis and is a potent target of new therapies for these diseases. RhoA/Rho-kinase may suppress endothelial nitric oxide synthase (eNOS). Rho-kinase appears to play a key role in the regulation of force and velocity of actomyosin cross-bridging in smooth muscle by inhibiting myosin phosphatase–mediated dephosphorylation of the regulatory chain of myosin II. This calcium-independent pathway leads to smooth muscle contraction, probably by creating mediators of α-adrenergic (norepinephrine) and endothelin-1 (ET-1) promoted smooth muscle contraction. Abnormal Rho-kinase activation or upregulation contributes to a lack of smooth muscle relaxation in the urinary tract and thus to changes in bladder compliance and to LUTS.

Nitric oxide is a nonadrenergic noncholinergic mediator of smooth muscle activity. Burnett and coworkers (1995) reported NOS activity in the prostate. Takeda and associates (1995) showed that prostate smooth muscle tension is mediated by NO.

NO activates soluble guanylate cyclase of smooth muscle, cells, which in turn increases cyclic guanosine monophosphate (cGMP) levels. That, in turn, is responsible for smooth muscle cell relaxation and penile erection, for instance. This process is most likely to involve activation of potassium channels by cGMP, leading to hyperpolarization and closure of voltage-dependent calcium channels. Intracellular levels of calcium are reduced with an effect on myosin and its detachment from actin and muscle relaxation.

Clinical investigation really began in 2000 with a study of 112 men being investigated for their response to sildenafil but whose urinary symptoms were also prospectively assessed by IPSS and measurement of PFR over a 3-month period (Sairam et al, 2002). This open-label descriptive study was the first study to measure parameters of both ED and urinary symptoms and showed an improvement in LUTS as well as ED in response to sildenafil. Similar smaller studies were followed by four randomized, placebo-controlled studies using sildenafil, tadalafil (Cialis), and vardenafil (Levitra) (McVary et al, 2007a, 2007b; Roehrborn et al, 2008b; Stief et al, 2008). These trials are summarized in Table 92–13.

The first randomized controlled trial published to elucidate the impact of PDEIs on LUTS was by McVary and coworkers (2007a). This was the first proper randomized controlled study and was a 12-week double-blind, placebo-controlled investigation performed in 41 centers in the United States between March 2004 and May 2005. Men with both ED (scoring < 25 on the International Index of Erectile Function [IIEF]) and LUTS (scoring > 12 on IPSS) with no evidence of prostate cancer were enrolled: 369 men in total were randomized between sildenafil (189 men) and placebo (180 men). They were assessed according to a range of other parameters (BPH Impact Index, quality of life score, self-esteem and relationship questionnaire, etc) and, as expected, men's ED improved. However, their IPSS and other urinary symptoms scores improved as well. IPSS improved by 6.32 points compared with 1.93 for placebo. The BPH Impact Index improved by 2 points compared with 0.9 for placebo, and the quality of life score improved by 0.97 compared with 0.29 for placebo. Interestingly, men with more severe LUTS improved more (by 8.6 compared with 2.4 in the less severely symptomatic men). **There was no significant difference in PFR, which led the authors to suggest that possibly other mechanisms were involved than simply smooth muscle relaxation in the bladder and prostate.** They pointed out that other phosphodiesterases were present in the prostate, particularly types 4 and 11, and that these may have a role to play.

In answer to questions raised about their study, more information was subsequently provided regarding baseline IPSS scores. These data showed baseline IPSS scores of 20.76 (±5.6) for those randomized to sildenafil and 20.55 (±5.5) for those randomized to placebo. The sildenafil group improved by 6.32 points compared with 1.93 for the placebo study arm. The subsequent data also indicated that the improvement in IPSS score was greater in those men whose ED also responded, that is, an IPSS improvement of 7 versus 3.2 in those whose ED did not respond ($P < .0001$).

The second randomized controlled trial (McVary et al, 2007b) investigated tadalafil. This was designed to establish a proof of principle prior to larger and more definitive trials. It was a double-blind, placebo-controlled, randomized multicenter study in 21 centers in the United States. It included first a 4-week washout phase but also a 4-week single-blinded placebo run-in period before determination of baseline values and compliance to reduce the placebo effect and the reversion to the mean phenomenon. Then followed the double-blind phase randomizing men between tadalafil and placebo. Men in this study were chosen on the basis of their urinary symptoms (men older than 45 with LUTS by IPSS of 13 and higher and a PFR of 4 to 15 mL/sec, PSA < 10, and PVR of < 200 mL). They were randomized between placebo or tadalafil at 5 mg for 6 weeks, after which the dose was escalated to 20 mg daily for a total of 12 weeks. The study ran between November 2004 and July 2005. As before, a range of parameters were measured. Of 281 men, 138 were randomized to tadalafil and 143 to placebo. There was a moderate response at 6 weeks but a greater

Table 92–13.

Clinical Trials Showing Improvement of LUTS after Treatment with PDEIs: Summary of Level 1 Evidence from Four Randomized Controlled Trials Investigating PDEIs (Sildenafil, Vardenafil, and Tadalafil)

STUDY	AGENT AND DOSE DURATION	NO. TREATED	INCLUSION	EXCLUSION	PLACEBO RUN-IN	IPSS Δ: PDEI vs. PLACEBO (*P* value)	OTHER FINDINGS
McVary et al, 2007	Sildenafil 50-100 mg/day for 12 wk	369 189	Age ≥ 45, history of ED: ≤25 IIEF (EF domain), IPSS ≥12	PCa (or suspected); urinary symptom from causes other than BPH, hypotension, retinitis pigmentosa, hepatic/liver failure, use of 5α-reductase inhibitor within 6 mo; use of α-adrenergic blocker/PDEI within last month	No	6.3 vs. 1.9 ($P < .0001$)	No change in PFR; IIEF, BII, mean IPSS QoL score, and GAQ all significantly improved
Stief et al, 2008	Vardenafil 10 mg bid for 8 wk	222 109	Age 45-64, IPSS ≥12, no history of ED required	Vardenafil contrainidications: spinal cord injury, prostatitis, history of stricture, urinary retention, bladder or prostate cancer, history of cancer with ≤3-yr life expectancy; use of nitrates, androgens, anticoagulants, ED treatments, or α-blocker use during the study	No	5.9 vs. 3.6 ($P = .0013$)	No change in Qmax or PVR; IIEF, QoL, irritative and obstructive IPSS subscores all significantly improved
McVary et al, 2007b	Tadalafil 5 mg → 20 mg/day 4-wk run-in + 12 wk (6 → 6)	281 138	Age ≥45, IPSS ≥12 from BPH for 6 mo, no history of ED required	Elevated PSA, recent 5α-reductase inhibitor use, BPH medication use during the study, history of pelvic surgery, hepatic/liver failure, causes of LUTS other than from BPH, uncontrolled diabetes, nitrate use, chemotherapy	Yes	5 mg 2.8 vs. 1.2 ($P = .003$) **20 mg 3.8 vs. 1.7 ($P < .001$)** 7.1 vs. 4.5 ($P < .001$): includes run-in	No change in PFR; IIEF, irritative and obstructive IPSS subscores, mean IPSS QoL score all significantly improved
Roehrborn et al, 2008	Tadalafil 2.5, 5, 10, 20 mg/day 4-wk run-in +12 wk	1058 ~212/group	Age ≥45, IPSS >12 from BPH for 6 mo, PFR: 4-15 mL/sec	Elevated PSA, recent 5α-reductase inhibitor use, BPH medication use during the study, history of pelvic surgery, hepatic/liver failure, causes of LUTS other than from BPH, uncontrolled diabetes, nitrate use, chemotherapy	Yes	2.5 mg 3.9 vs. 2.3 ($P < .05$) **5 mg 4.9 vs. 1.8 ($P < .05$)** 10 mg 5.2 vs. 4.5 ($P < .05$) 20 mg 5.3 vs. 4.5 ($P < .05$)	No change in Qmax; IIEF, mean IPSS QoL score, BII, LUTS GAQ all significantly improved (≥5 mg); dose > 5 mg minimal Δ improvement but ↑ side effects

BII, BPH Impact Index; BPH, benign prostatic hyperplasia; ED, erectile dysfunction; EF, erectile function; GAQ, Global Assessment Questionnaire; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms; PCa, prostate cancer; PDEI, phosphodiesterase type 5 inhibitor; PFR, peak flow rate; PSA, prostate-specific antigen; QoL, quality of life.

From Kohler T, McVary K. The relationship between erectile dysfunction and lower urinary tract symptoms and the role of phosphodiesterase type 5 inhibitors. Eur Urol 2009;55(1):38–48.

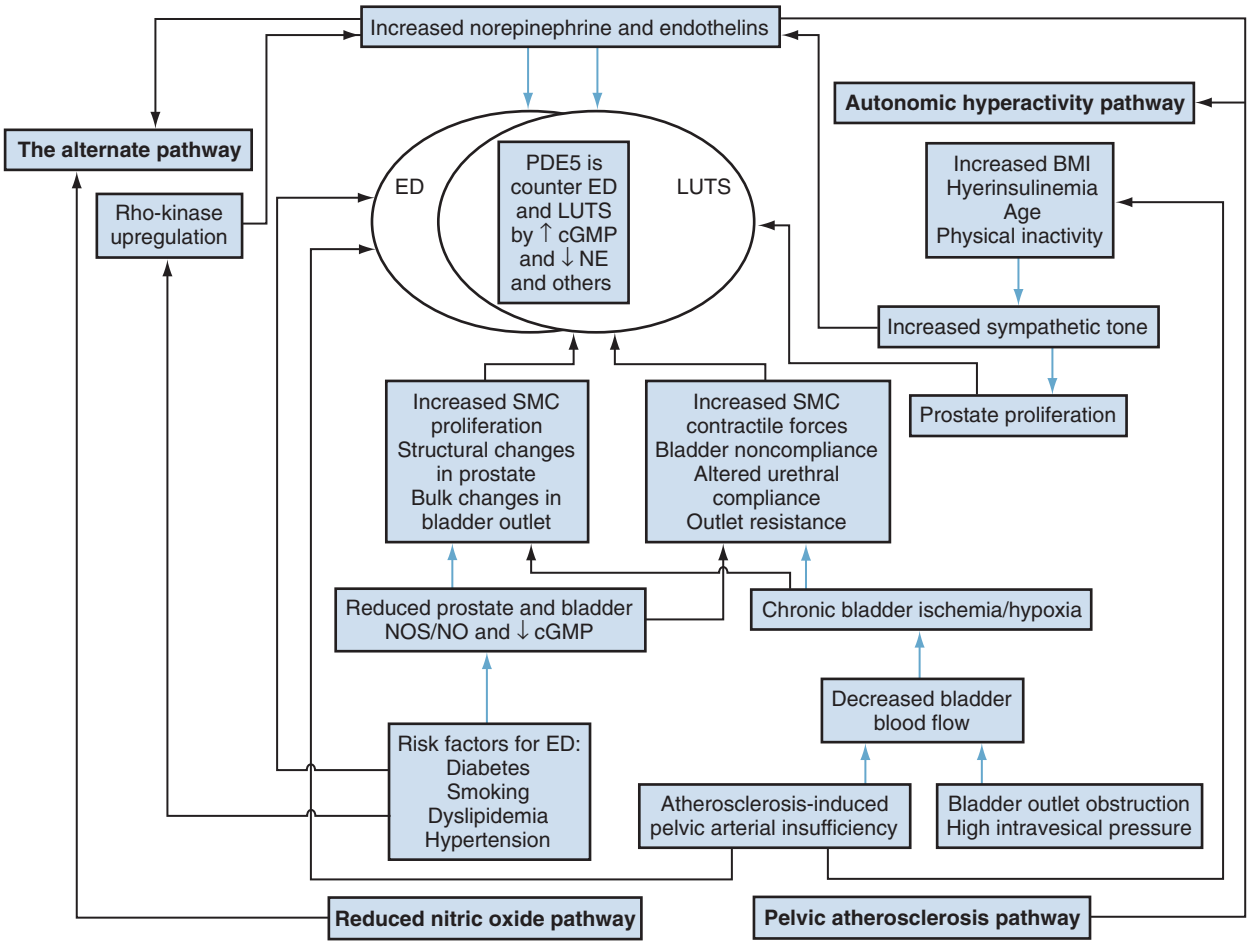


Figure 92–16. Theories linking pathophysiology of erectile dysfunction (ED) and lower urinary tract symptoms (LUTS). BMI, body mass index; cGMP, cyclic guanosine monophosphate; NOS/NO, nitric oxide synthase/nitric oxide; PDE5, phosphodiesterase type 5; SMC, smooth muscle cell. (From Kohler T, McVary K. The relationship between erectile dysfunction and lower urinary tract symptoms and the role of phosphodiesterase type 5 inhibitors. Eur Urol 2009;55[1]:38–48.)

difference between the 2 arms by 12 weeks. Baseline IPSS scores in the tadalafil arm improved from 17.5 to 13.3, that is, by 3.8 points, whereas the placebo arm baseline IPSS of 18.3 improved to 16.1 (or 1.7 points; $P < .001$), thus indicating a net improvement of 2.1 points for the active study arm. Whether a 2-point change is clinically significant or easily perceived by men is uncertain, but it is comparable to the response to α-adrenergic blocker treatment in the meta-analysis performed by the AUA BPH guideline update panel (American Urological Association, 2006). If the placebo run-in period is included, then the active study arm response of 7.1 points on IPSS (±0.6) is similar to that in the sildenafil study (6.32 points). More convincingly, **men in the tadalafil group were more likely to show a 3-point or greater improvement in IPSS by 12 weeks than men in the placebo group (60.9% vs. 42.7%), indicating an NNT of 5.5,** which is seen as reasonable and representing effective therapy (Bandolier, 2011).

Roehrborn and colleagues (2008a) built on this proof of principle experience with a "dose finding study" in a larger study of 1058 men, performed in 92 centers in 10 countries. Men were randomized between placebo and either a 2.5-, 5-, 10-, or 20-mg tadalafil once-daily dose. This randomized, double-blind, placebo-controlled 12-week study also included a 4-week single-blind placebo run-in period (during which period 67 men's IPSS "improved" from the "moderate/severe" range to the "mild" category) and generally similar inclusion criteria and outcome assessments, with the IPSS response to the 5-mg dose of tadalafil being the primary outcome.

Daily dosing with 5 mg of tadalafil led to a statistically significant net improvement of 2.6 points in IPSS compared with placebo (4.87 vs. 2.27), again similar to responses to α-adrenergic blockers. Most of the response was seen by 8 weeks, and there was minimal further improvement at the higher doses (Fig. 92–17). There was no significant change to PFR at any dose, nor changes to PSA or PVR.

Stief and associates (2008) investigated vardenafil in a similar fashion in a randomized, double-blind, placebo-controlled phase 2b study undertaken in 16 centers in Germany between October 2005 and June 2006. Men were randomized between vardenafil 10 mg twice daily (109 men) and placebo (113 men) and assessed at 4 and 8 weeks. This was another proof of concept study and did not include a placebo run-in period. Eventually, 105 men took vardenafil and 110 took a placebo. **Vardenafil was associated with a significant improvement in IPSS versus placebo.** IPSS score improved from 16.8 to 11 (or by approximately 5.9) on vardenafil compared with 16.8 to 13.2 (3.6) on placebo, that is, a mean difference of 2.3 points, again similar to an α-adrenergic blocker response to alfuzosin or tamsulosin. There were small but not significant improvements in PFR (15.9 mL/sec to 17.5). This was a relatively young cohort and had reasonable PFR values at baseline, so a study with older men and lower flow rates might

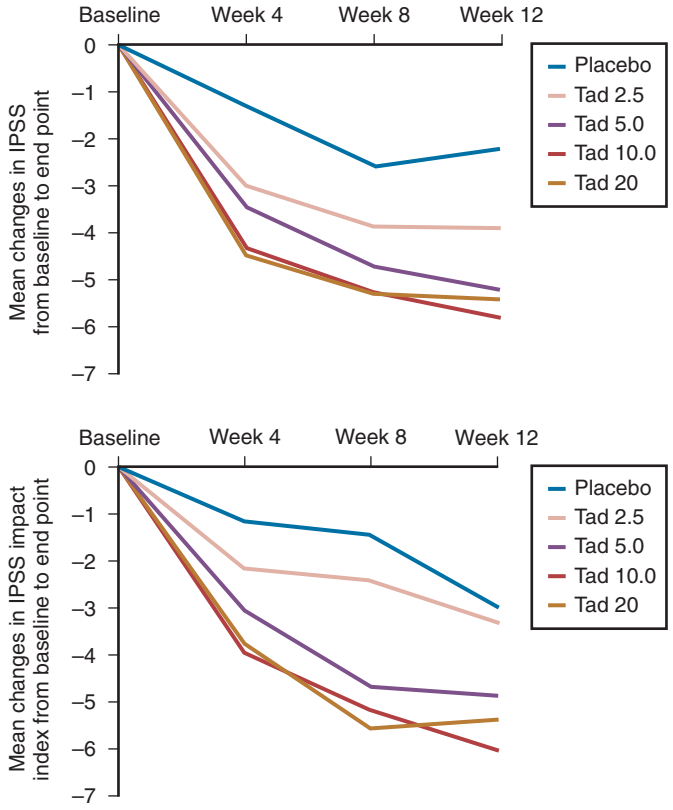


Figure 92–17. Response of lower urinary tract symptoms to tadalafil. Mean change in IPSS and BPH impact index after treatment with placebo or tadalafil (Tad) at 5, 10, and 20 mg/day. (From Roehrborn CG, McVary KT, Elion-Mboussa A, Viktrup L. Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding study. J Urol 2008a;180[4]:1228–34.)

more readily assess whether there is any effect of PDEIs on the flow aspects of BPH/LUTS.

Combination Therapy: α-Adrenergic Blockers and Phosphodiesterase Inhibitors

Most recently there is published evidence that PDEIs and α-adrenergic blockers in combination reduce adrenergic tone in both prostate and cavernosal smooth muscle tissue in organ bath studies (Oger et al, 2009). It is logical to consider combining PDEIs and α-adrenergic blocker medication. α-Adrenergic blockers are established treatments, and from the previous discussion it is likely that PDEIs are effective at reducing LUTS (although not by altering flow rate) and are likely to become more important options for the management of men with BPH/LUTS and ED in future.

So far evidence for combination therapy with α-adrenergic blockers and PDEIs is limited. Kaplan and coworkers (2007) in a 12-week open-label single-center pilot study randomized 62 men between 25 mg of sildenafil (21 men), 10 mg of alfuzosin (20 men), and a combination of both agents (21 men). IPSS improved by 11.8% on sildenafil (i.e., decreased from 16.9 to 14.9), by 15.6% on alfuzosin, and by 24.1% on a combination of sildenafil and alfuzosin, suggesting that there may be a synergistic benefit from the use of both agents.

Improvement in PFR was observed in all groups, but patients receiving combination therapy had greater improvement (29.6%) than patients receiving either only alfuzosin (21.7%) or only tadalafil (9.5%). IPSS was significantly improved in the alfuzosin group (27.2%) and was more marked in the combination therapy group (41.6%). There was a small nonsignificant increase in IPSS in the tadalafil-only group (8.4%).

Liguori and colleagues (2009) in a randomized, open-label, three-arm study gave 66 men complaining of ED and LUTS tadalafil or alfuzosin or tadalafil and alfuzosin and found that the IIEF sexual function scores did improve with alfuzosin alone (+15%). As expected, sexual function scores were more obviously improved with tadalafil alone (+36.3%) but the greatest improvement was experienced with combination therapy (+37.6%).

Improvement in PFR was observed in all groups, but patients receiving combination therapy had greater improvement (29.6%) than patients receiving either only alfuzosin (21.7%) or only tadalafil (9.5%). IPSS was significantly improved in the alfuzosin group (27.2%) and was more marked with the combination therapy (41.6%), and a small increase, although not statistically significant, was also observed with tadalafil (8.4%).

Finally, a new PDEI agent, udenafil (Zydena), has been administered to 120 men with BPH and ED. Men whose conditions were stable on α-adrenergic blocker therapy for their LUTS/BPH were given 100 mg of udenafil for 8 weeks. LUTS and ED improved significantly compared with baseline (IPSS improved from 14.3 to 11.5 and IIEF improved from 11.95 to 18.32). No significant change in blood pressure or heart rate was reported in this study. This is an important issue because **the concomitant use of α-adrenergic blockers and PDEIs may lead to symptomatic hypotension in some patients because both are vasodilators.**

It seems reasonable to suggest that concomitant treatment with PDEIs should only be initiated once the patient's condition has been stabilized on α-adrenergic blocker therapy**. In these patients PDEIs should be initiated at the lowest recommended starting dose. In those men already taking an optimized dose of a PDEI, α-adrenergic blocker therapy should be initiated at the lowest dose.** Any stepwise increase in α-blocker dose may be associated with further lowering of blood pressure in patients taking PDEIs.

Studies so far suggest that vardenafil may be administered at any time with tamsulosin whereas **men given vardenafil and terazosin at the same time were more prone to hypotension.** This effect was minimized by giving vardenafil and terazosin at doses separated by a time interval of 6 hours. **The coadministration of doxazosin (4 and 8 mg daily) and tadalafil (5 mg/day or 20 mg as a single dose intermittently) leads to further lowering of blood pressure, and this combination is not recommended by the manufacturers.**

Summary

PDEIs may well have a role in therapy for BPH/LUTS. There is now good level 1 evidence of a beneficial effect of PDEIs on urinary symptoms. The mechanisms of effect are still unclear but the subject of extensive research because so many other body systems are also affected. **It is likely that PDEI treatment will be of value, especially for men with LUTS and significant ED.** Because recent U.S. data indicate the proportion of men reporting moderate to severe LUTS ranges from 8% in those 30 to 39 years old to 26% in those 70 to 79 years old and the prevalence of ED is also high and increases dramatically with age with 10% of 30- to 39-year-old and 59% of 70- to 79-year-old men reporting mild to moderate or moderate to severe symptoms, this is clearly a substantial number of men who may request treatment (Brookes et al, 2008).

Further data on safety and cost-effectiveness, especially for combination therapy, will be needed. Currently, PDEIs are more expensive than α-adrenergic blockerr or 5α-reductase inhibitors, which are now off patent protection in many countries and health care systems. Studies are needed to determine if costs may be reduced by using combination therapy initially followed by later withdrawal of the more expensive agent.

Key Points: PDEIs

- There is an as yet undetermined link between LUTS/BPH and ED.
- PDEIs improve urinary symptoms scores.
- PDEIs do not improve flow rates.
- The combination of α-adrenergic blockers and PDEIs may lead to a synergistic benefit, thereby improving LUTS.
- The combination of α-adrenergic blockers and PDEIs may lead to symptomatic hypotension.
- PDEIs or a combination of α-adrenergic blockers and PDEIs may be of value in therapy for men with both ED and LUTS.

Phytotherapy

The pharmacologic use of plants and herbs (phytotherapy) for the treatment of LUTS associated with BPH is common. **Phytotherapeutic agents for LUTS/BPH have gained widespread use since about 1990** (Lowe and Fagelman, 1999). These agents are popular in Europe, particularly in France, Austria, and Germany, where they are often prescribed and their costs reimbursed (Lowe et al, 1998). Recent **European data** (Fourcade et al, 2008) **show that although α-adrenergic blocker monotherapy was the most frequently prescribed treatment (62.5% overall, 87.1% in Germany, 46.1% in France), phytotherapy was very popular (23.5%), followed by 5α-reductase inhibitor monotherapy (3.75%).** Combination therapy was rare. Treatment varied according to the severity of the symptoms ($P = .008$), with phytotherapy being given to patients with the lowest IPSS and combination therapy given to those with the highest IPSS. However, use in the United States has escalated. It has been estimated that over $1 billion was spent in the United States alone for these products (Lowe and Fagelman, 1999). These agents have been marketed to "promote prostatic health," and therefore it is not surprising that many men try them. Additional factors that contribute to their widespread use include being "natural" products (not "medications"), presumed safety, ease of accessibility (no prescription necessary), avoidance of prostate surgery, and prevention of prostate cancer (falsely assumed). The widespread availability of these products in health food stores, vitamin shops, traditional pharmacies, and supermarkets, as well as at numerous websites on the Internet, has contributed to their use and reflects the demand for these phytotherapeutic agents.

Origin of Phytotherapeutic Agents

Phytotherapeutic products are not the actual plant but are extracts derived from either the roots, the seeds, the bark, or the fruits of the various plants used (Table 92–14). Although monopreparations (single plant only) are available, many companies manufacture combination products (two or more plant extracts) in an attempt to provide "enhanced" efficacy (never proven), to improve marketability, and to provide their own "unique" product that can be registered because there is no patent protection for these products. However, to determine mechanisms of action and efficacy, only the monopreparations are evaluated and reviewed here.

Table 92–14.
Origin of Plant Extracts

SPECIES	COMMON NAME
Serenoa repens, Sabal serrulata	Saw palmetto berry/American dwarf palm
Hypoxis rooperi	South African star grass
Pygeum africanum	African plum tree
Urtica dioica	Stinging nettle
Secale cereale	Rye pollen
Cucurbita pepo	Pumpkin seed
Opuntia	Cactus flower
Pinus	Pine flower
Picea	Spruce

Table 92–15.
Components of Plant Extracts

PHYTOSTEROLS	PHYTOESTROGENS	TERPENOIDS
β-Sitosterol	Coumestrol	Lectins
Δ5-Sterol	Genistein (isoflavone)	Polysaccharides
Δ7-Sterol	Flavonoids	Aliphatic alcohols
Stigmasterol	Fatty acids	Plant oils
Campesterol	Free	
	Esterified	

Composition of the Phytotherapy Extracts

The composition of plant extracts is very complex. They contain a wide variety of chemical compounds, which include phytosterols, plant oils, fatty acids, and phytoestrogens (Table 92–15). Which of these is the exact "active" component is not definitely known. Both the free fatty acids and the sitosterols have been thought to be the active components.

Most of the plant extracts are unique. First, the plants are not identical, owing to natural variability. Second, the extraction processes used by the various manufacturers are frequently different and use various substrates for the process. Thus, even if the phytotherapeutic compounds produced by two different companies contain the same plant, the exact composition of the final products is probably different and the content of the "active" component in each preparation may also be different. For example, analysis by the National Consumer Lab of free fatty acid content in 27 different saw palmetto products showed variability from 0% to 95%, with only 17 containing more than the presumed standard amount of 85% (http://www.ConsumerLab.com, March 2000).

Mechanism of Action

The mechanisms of action of the phytotherapeutic agents are generally unknown (Lowe et al, 1998). Many in-vitro experimental studies have been undertaken to elucidate this; thus there are numerous proposed mechanisms of action (Table 92–16). Almost all these studies use supraphysiologic doses that are many times higher than the standard doses used clinically. The biologic effects are typically examined in tissue culture, which might not be an accurate reflection of in-vivo effects (Lowe and Ku, 1996). The three mechanisms of action that have received the

Table 92–16.

Suggested Mechanisms of Action of Plant Extracts

Inhibition of 5α-reductase
Anti-inflammatory
Interference with growth factors
Antiandrogenic
Estrogenic
Inhibition of aromatase
Decrease of sex hormone–binding globulin
Alteration of cholesterol metabolism
Action on α-adrenergic receptors
Free radical scavenger
Alteration of lipid peroxidation
Modulation of prolactin-induced prostatic growth
Protection of bladder and detrusor function
Placebo effect

greatest attention are anti-inflammatory effects, 5α-reductase inhibition, and growth factor alteration.

The anti-inflammatory effects are modulated by effects on prostaglandin synthesis. Plant flavonoids are inhibitors of both cyclooxygenase and lipoxygenase enzymes (Bach, 1982; Buck, 1996). Flavone, a phytoestrogen commonly found in plants and herbs, has been shown to be a strong inhibitor of cyclooxygenase (Mower et al, 1984; Alcaraz and Ferrandiz, 1987). *Serenoa repens* (Permixon) has been shown to inhibit phospholipase A_2 activity, thereby decreasing arachidonic acid metabolites and prostaglandin E_2 synthesis (Plosker and Brogden, 1996). Additionally, in two different studies, Paubert-Braquet and colleagues (1994, 1997) demonstrated inhibition of the production of lipoxygenase metabolites and leukotrienes by neutrophils by *S. repens* and *Pygeum africanum* (Tadenan).

The most widely suggested mechanism of action of *S. repens* is as a 5α-reductase inhibitor (Plosker and Brogden, 1996), thus reducing the conversion of testosterone to DHT and potentially leading to reduction of prostate volume (Gormley et al, 1992).

Although inhibition of 5α-reductase activity by *S. repens* was found in experimental models using foreskin fibroblasts (Sultan et al, 1984), transfected Sf9 insect cells (Iehle et al, 1995), DU145 cancer cell line (Delos et al, 1994), primary cultures of human BPH and adenocarcinoma epithelial and fibroblast cells (Delos et al, 1995), and cocultures of human epithelial and fibroblast cells (Scaglione et al 2008), other in-vitro and in-vivo data have not confirmed this effect (Rhodes et al, 1993; Weisser et al, 1996).

Two ex-vivo experiments have demonstrated conflicting results. Pretreatment with *S. repens* for 3 months before suprapubic prostatectomy demonstrated a decrease in prostatic DHT and an increase in prostatic testosterone concentrations compared with controls, which suggests inhibition of 5α-reductase activity (DiSilverio et al, 1998). In a similar pretreatment study using *Sabal serrulata* (IDS-89) for 3 months, prostate tissue levels of 5α-reductase, 3α-hydroxysteroid, and 3β-hydroxysteroid oxidoreductase were not different compared with placebo (Weisser et al, 1996). An in-vivo experiment of healthy male volunteers demonstrated a reduction of serum DHT levels with finasteride but not with *S. repens* (Strauch et al, 1994). Clinically, in a large multicenter trial comparing *S. repens* with finasteride, no effect on PSA levels and only 6% reduction in prostate volume were noted for *S. repens*–treated patients, whereas the finasteride-treated patients had reduction of PSA levels by 41% and prostate volume by 18% (Carraro et al, 1996).

It has been subsequently postulated that *S. repens* inhibits intracellular 5α-reductase while having little or no effect on other androgen-dependent processes (e.g., PSA production) that rely on binding of androgens to their receptor. *S. repens* causes disruption of nuclear membrane in cell culture but has no effect on the integrity of the cell membrane (Bayne et al, 1999); therefore, the intracellular theory has been promulgated. Whether this supraphysiologic cell culture experiment actually reflects what is happening in vivo is uncertain and unproved.

Plant extracts are also thought to act by altering growth factor–induced growth and proliferation. In-vitro studies with *P. africanum* demonstrated an inhibitory effect on both basic fibroblastic growth factor (bFGF)– and epidermal growth factor (EGF)–induced human and rat prostate fibroblast proliferation (Paubert-Braquet et al, 1994; Yablonsky et al, 1997). Subsequent experiments with *S. repens* have also shown inhibition of bFGF- and EGF-induced proliferation of human BPH prostate cells from biopsy specimens (Paubert-Braquet et al, 1998). Additionally, an ex-vivo experiment in men treated with *S. repens* before prostatectomy demonstrated reduced levels of tissue EGF, particularly in periurethral tissue (DiSilverio et al, 1998).

Although experimental data have suggested numerous possible mechanisms of actions for the phytotherapeutic agents it is uncertain which, if any, of these proposed mechanisms is responsible for the clinical responses.

***Serenoa Repens* (Saw Palmetto Berry).** The extract of the berry of the American saw palmetto, or dwarf palm plant, *Serenoa repens* (also known by its botanical name of *Sabal serrulatum*), is the most popular phytotherapeutic agent available for the treatment of BPH. Although numerous clinical trials with saw palmetto berry extracts have been published, many were uncontrolled open-label studies, thus providing little useful information in determining the efficacy of these phytotherapies. Even though placebo-controlled studies have been published (Table 92–17), most of them are flawed and few of them would meet the generally accepted criteria developed by the International Consultation on BPH for assessing treatment results in men with LUTS (McConnell, 1998). The studies are of limited value because of their small numbers of patients, short duration (only 1 to 3 months), and lack of use of standardized symptoms scores.

For example, nocturia was the only symptom available for analysis in all the studies reviewed in two meta-analyses (Wilt et al, 1998; Boyle et al, 2000). In the Wilt and colleagues (1998) meta-analysis of 18 trials involving 2939 patients using various *S. repens* single and combination preparations, the mean weighted difference for nocturia between patients and subjects taking a placebo was –0.76 times per evening (–1.22 to –0.32) for 10 trials. In the Boyle and coworkers (2000) meta-analysis of 13 trials involving 2859 patients using only the Permixon brand of *S. repens,* the attributable reduction of nocturnal urinations was 0.50 (±0.01) times per night. Wilt and coworkers conducted a systematic review, first published in 1998 and updated in 2002 and again in 2009, to evaluate the efficacy and adverse events of *S. repens* (Tacklind et al, 2009). Initially their analysis was mildly supportive of the efficacy of *S. repens*. In this update 9 new trials involving 2053 additional men (a 64.8% increase) were included. For the main comparison—*S. repens* versus placebo—3 trials were added with 419 subjects and three end points (IPSS, peak urine flow, prostate size). Overall, 5222 subjects from 30 randomized trials lasting from 4 to 60 weeks were assessed. Twenty-six trials were double blinded, and treatment allocation concealment was adequate in 18 studies. With these extra data and especially the double-blind, placebo-controlled trial reported by Bent and associates (2006), they

Table 92–17.

Placebo-Controlled Trials of *Serenoa repens* (Permixon)

TRIAL	PATIENTS RANDOMIZED (N)	DURATION (mo)	SIGNIFICANT IMPROVEMENT IN SYMPTOMS VS. PLACEBO	SIGNIFICANT IMPROVEMENT IN PEAK URINARY FLOW RATE
Descotes, 1996	176	1	Yes	$P < .05$
Cukier, 1985	146	2-3	Yes	Not available
Champault, 1984	88	1	Yes	$P < .001$
Reece Smith, 1986	70	3	No	No
Emili, 1983	30	1	No	No
Tasca, 1985	27	2	No	No
Boccafoschi, 1983	22	2	Yes	$P < .05$

Table 92–18.

Inherent Weaknesses of Meta-Analyses

Pooled results incorporate biases of individual studies
New sources of biases created
Selection of studies
Publication bias (only positive trials usually published)
Language bias
Heterogeneity of the studies
Inclusion/exclusion criteria
Study designs
Assessments of efficacy
Variable placebo response rates
Study duration

concluded that *S. repens* was not superior to placebo in improving IPSS or PFR or for reducing prostate size. For nocturia, *S. repens* was significantly better than placebo (weighted mean difference –0.78 nocturnal visits, 95% CI –1.34 to –0.22, $P < 0.05$; 9 trials), but with the caveat of significant heterogeneity within studies. A sensitivity analysis, utilizing higher-quality, larger trials demonstrated no significant difference. *S. repens* was also not superior to finasteride or to tamsulosin. Overall, it was concluded that ***S. repens* was not more effective than placebo for treatment of urinary symptoms consistent with BPH.**

Despite inherent weaknesses in meta-analyses (Table 92–18) these analyses attempt to maximize the information available from clinical trials using *S. repens* in the treatment of symptomatic BPH/LUTS and to provide the best information available until the appropriate placebo-controlled, randomized clinical studies are conducted. However, approximately 35% of the prior meta-analyses performed are not accurately predicted by the subsequent randomized controlled trials (LeLorier et al, 1997). **Therefore, whereas the efficacy of *S. repens* has not been completely determined, current meta-analysis suggests that *S. repens* is not more effective than placebo for treatment of urinary symptoms consistent with BPH.**

***Pygeum africanum* (African Plum).** In addition to the proposed mechanisms of actions previously discussed, *P. africanum* (Tadenan) has been postulated to have additional beneficial effects on LUTS by having a protective effect on the obstructed bladder. Using a rabbit model with partial BOO, Levin and associates (1996) demonstrated that changes in bladder mass, decrease in compliance, and alterations in contractile response to various forms of stimulation could be tempered by pretreatment with *P. africanum*.

A review of the published experience with *P. africanum* identified 2262 patients treated with this extract: 1810 in open-label studies and 452 in comparative trials (Andro and Riffaud, 1995). Twelve double-blind, placebo-controlled studies were completed between 1972 and 1990. Only one study enrolled more than 100 subjects, and none was longer than 12 weeks or used standardized symptom scores. In a 2-month open-label study (Breza et al, 1998) and a 2-month comparison trial of 50 mg twice daily versus 100 mg daily (Chatelain et al, 1999) both trials demonstrated a reduction in IPSS score of approximately 40% (5.7 and 6.4 units) and an improvement in PFRs of approximately 18% (2.1 and 1.7 mL/sec) over baseline. However, without a placebo study arm, the actual magnitude of drug effect cannot be determined. Thus, without at least the data from the Tadenan-IPSS study, the efficacy of *P. africanum* cannot be determined. Additionally, there are few other significant data available with regard to any of the other *P. africanum* extracts.

Thus none of those trials meets the guidelines recommended by the International Consultation Conferences on BPH. Another meta-analysis for the Cochrane collaboration (Wilt et al, 2002a) concluded that an effect was possible but not proven. **Therefore the data concerning the efficacy of *P. africanum* are not conclusive.**

***Hypoxis rooperi* (South African Star Grass).** *Hypoxis rooperi* (Harzol) has been studied in both a 6-month double-blind, placebo-controlled trial of 200 patients (Berges et al, 1995) and, subsequently, an open-label follow-up (Berges et al, 2000). In the initial study, statistically significant improvements were documented for symptom scores (IPSS), quality of life, PFRs, and PVRs (Berges et al, 1995). The placebo group showed appropriate mild improvement in these parameters. The IPSS improved by 7.4 units for β-sitosterol patients and 2.3 units for placebo. Similarly, peak urinary flow rates improved by 5.2 mL/sec for treated patients compared with 1.1 mL/sec for placebo. **This magnitude of improvement has not been observed with any other medical therapy previously evaluated for BPH.**

During the follow-up study, patients were able to remain on or switch over to Harzol therapy. For those 38 patients who continued Harzol therapy, IPSS improvements were maintained. The 27 patients who received placebo initially and were then treated with Harzol demonstrated similar levels of improvement in IPSS scores and PFRs. Surprisingly, the 14 patients who stopped therapy still maintained similar levels of improvement over the next 12 months. This suggests that intermittent therapy could be an option.

Another product (Azuprostat) contains primarily β-sitosterols from *H. rooperi* as well as from *Pinus* (pine) and *Picea* (spruce). Although this is a combination preparation of extracts, its proposed active ingredient β-sitosterol is common to all three. This product (Azuprostat) was evaluated in a 6-month randomized,

placebo-controlled trial with 177 patients (Klippel et al, 1997). Significant improvements in IPSS scores, PFRs, and PVRs were found. IPSS scores improved by 8.2 units for treated patients and 2.8 units for placebo. PFRs improved by 8.9 mL/sec for treated patients and 4.4 mL/sec for placebo. This magnitude of improvement has not been reported for any type of medical therapy for BPH. It is hard to believe these results in which the mean post-treatment PFRs are 19.4 mL/sec, which is a normal value for younger men and not for the typical age of men in the study. If these results are reproducible, they would rival surgical intervention.

Wilt and associates (1999) also produced a meta-analysis for β-sitosterol products. It included four trials (two mentioned earlier and two earlier suboptimal ones) encompassing three different products: Harzol, Azuprostat, and WA184, all of which have different amounts of β-sitosterol. WA184 did not improve PFR (Kadow et al, 1986). Again, this meta-analysis is tempered by the same factors mentioned previously. Their conclusion was that **β-sitosterol does improve urologic symptoms and urinary flow rates, but its long-term effectiveness, safety, and ability to prevent the complications of BPH are unknown** (Wilt et al, 1999).

Other Extracts. The other extracts listed in Table 92–14—*Urtica dioica, Cucurbita pepo, Secale cereale,* and *Opuntia*—have even fewer relevant clinical studies published than the aforementioned ones. Of these extracts, *Secale cereale* (Cernilton) had two placebo-controlled trials published over a decade ago that did not have standardized scores, used different dosages of the preparation, lasted 12 and 24 weeks, and enrolled only 103 and 60 subjects (Buck et al, 1990). Wilt and associates (1999) in a systematic review and meta-analysis of Cernilton concluded that it modestly improves overall urologic symptoms including nocturia, but additional trials are needed to evaluate clinical effectiveness. More recently Zhang and coworkers (2008) have reported a randomized, double-blind, placebo-controlled clinical trial of a flaxseed lignan extract containing 33% secoisolariciresinol diglucoside (SDG). SDG was evaluated for its ability to alleviate LUTS in 87 subjects with BPH with repeated measurements conducted over a 4-month period using treatment dosages of 0 (placebo), 300, or 600 mg/day SDG. After 4 months of treatment, 78 of the 87 subjects completed the study. For the 0, 300, and 600 mg/day SDG groups, respectively, the IPSS decreased –3.67 ± 1.56, –7.33 ± 1.18, and –6.88 ± 1.43 (mean ± SE, $P = .100$, $< .001$, and $< .001$ compared with baseline), the quality of life score improved by –0.71 ± 0.23, –1.48 ± 0.24, and –1.75 ± 0.25 (mean ± SE, $P = .163$ and .012 compared with placebo and $P = .103$, $< .001$, and $< .001$ compared with baseline), and the number of subjects whose LUTS grade changed from "moderate to severe" to "mild" increased by 3, 6, and 10 ($P = .188$, .032, and .012 compared with baseline). PFR insignificantly increased 0.43 ± 1.57, 1.86 ± 1.08, and 2.7 ± 1.93 mL/sec (mean ± SE, no statistical significance reached), and postvoid urine volume decreased insignificantly by –29.4 ± 20.46, –19.2 ± 16.91, and –55.62 ± 36.45 mL (mean ± SE, no statistical significance reached). The observed decreases in IPSS and quality of life score were correlated with the concentrations of plasma total lignans. It was concluded that dietary flaxseed lignan extract appreciably improved LUTS in BPH subjects and that the therapeutic efficacy appeared comparable to that of α_1-adrenergic receptor blockers and 5α-reductase inhibitors.

Summary

Most phytotherapeutic preparations are plant extracts with different components manufactured by different extraction procedures, which prevents comparison of the preparations. Although numerous in-vitro experiments have been conducted to determine their possible mechanisms of pharmaceutical action, it is uncertain which of the actions demonstrated in vitro might be responsible for clinical responses in vivo. **Appropriate randomized placebo-controlled clinical trials monitored by an outside agency are needed to ascertain and to confirm the efficacy of these products. Phytotherapies for BPH should be scrutinized and subjected to trials just as are all regulated drugs.**

Acute Urinary Retention

Acute urinary retention is the most common urologic emergency managed by most urologists worldwide. Furthermore, it will be encountered by most physicians whatever their specialty and is commonly witnessed on surgical and elderly care wards. AUR may be "spontaneous" where it is usually associated with previous LUTS suggestive of BPH. Alternatively, it may be "precipitated" by some other factor, such as the effects of various medications, particularly anticholinergic or sympathicomimetic agents, which are commonly found in cough and cold remedies. Urinary infection, excessive fluid intake, and the consequences of surgery (postoperative pain or the effects of anesthesia or analgesia or loss of mobility) may precipitate AUR. Obviously there can be an overlap between these two rather artificial divisions and AUR in a man with symptomatic or silently progressing BPH may well be precipitated by one of these other factors.

Population-based cohort studies from the United States (Jacobsen et al, 1997; Meigs et al, 1999), from Holland (Verhamme et al, 2005), and also from the United Kingdom (Cathcart et al, 2006) defined the incidence, although it varies among populations. Verhamme and coworkers (2005), in a study based on Dutch general practitioner records covering essentially the whole male population of Holland, reported an incidence of 2.2 AUR events per thousand man-years, of which 40% were precipitated (Fig. 92–18). AUR was the first symptom of BPH in 49% of men designated as suffering from LUTS/BPH, and in this group the risk of AUR was 11 times higher (18.3 per 1000 man-years). They concluded that AUR was of low incidence in the general population but substantial in the LUTS/BPH population. Cathcart and colleagues (2006), reviewing national figures from the United Kingdom, reported 3.1 AUR episodes per 1000 man-years.

These figures are lower than the two U.S. cohort studies. Jacobsen and associates (1997) found an incidence of 6.8 events per 1000 man-years in the Olmsted County Study of Urinary Symptoms and Health Status Among Men, and the Health Professionals Follow-up Study (Meigs et al, 1999) reported a rate of 4.5 per 1000 man-years. There may be selection bias here because the prevalence of BPH/LUTS in these U.S. studies is much higher than in the European studies (33% of the Olmsted County men had an IPSS of greater than 8, 30% of the men in the Health Professionals Follow-up Study had a diagnosis of BPH/LUTS compared with just 8% in the Dutch men. **Analysis of the placebo arms of a series of large studies such as the PLESS evaluation of finasteride, MTOPS, and the CombAT study indicate that increasing age, the presence of LUTS, a low PFR, and prostatic enlargement and/or raised PSA increase the risk of AUR.**

When AUR develops, most men are catheterized for a period or taught intermittent self-catheterization. At some variable point the catheter will usually be removed and a trial without catheter performed (Emberton and Fitzpatrick, 2008). **It is reasonable to**

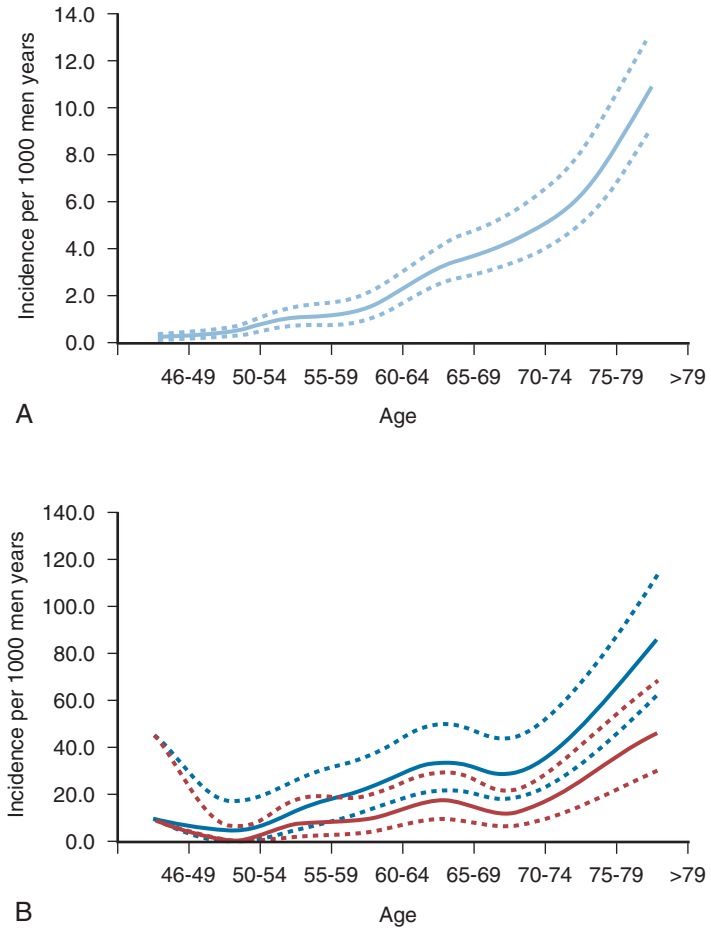


Figure 92–18. Incidence of acute urinary retention in the general population of Dutch men **(A)** and in the lower urinary tract symptom/benign prostatic hyperplasia population **(B)**. (From Verhamme KM, Dieleman JP, van Wijk MA, et al: Low incidence of acute urinary retention in the general male population: the triumph project. Eur Urol 2005;47[4]:494–8.)

speculate that urinary retention is caused in part by dynamic as opposed to static outflow obstruction because a significant proportion of men void spontaneously after catheter placement (Taube and Gajraj, 1989). If urinary retention is caused by increased sympathetic activity at the level of the prostatic smooth muscle, an α-adrenergic blocker should increase the likelihood of spontaneous voiding after catheter removal.

The chance of successful voiding after a period of AUR was improved by the use of alfuzosin (McNeill et al, 2005) and tamsulosin (Lucas et al, 2005). In a multicenter study a total of 360 men with AUR underwent emergency catheterization and were blindly randomized to alfuzosin 10 mg/day or placebo for 3 days (first phase). All patients with successful trial without catheterization, regardless of treatment, were then again blindly randomized to alfuzosin 10 mg/day or placebo for 6 months (second phase). Alfuzosin significantly increased the successful trial without catheterization rate (146 of 236, 61.9%) compared with placebo (58 of 121, 47.9%; $P = .012$). In the second phase, 14 (17.1%) of the 82 alfuzosin-treated patients versus 20 (24.1%) of the 83 placebo-treated patients required BPH surgery, 5 (36%) of 14 versus 13 (65%) of 20 within 1 month, and 8 (57%) of 14 versus 17 (85%) of 20 within 3 months of treatment. Emergency surgery because of AUR relapse was the main cause of failure in both groups (11 [78.6%] of 14 in the alfuzosin group and 16 [80.0%] of 20 in the placebo group). Compared with placebo, alfuzosin improved the Kaplan-Meier survival rates by 9.6% ($P = .04$), 11.4% ($P = .04$), and 8.3% ($P = .20$), with surgical risk reductions of 61%, 52%, and 29% at 1, 3, and 6 months of treatment, respectively. High PSA values and the residual urine volume after the trial without catheterization significantly increased the risk of AUR relapse and BPH surgery (McNeill et al, 2005).

An economic analysis (Annemans et al, 2005) suggests that treatment with alfuzosin before and after a successful trial without catheterization reduces treatment costs in the first 6 months. **Unfortunately, even those who succeed will have a high rate of subsequent failure to void and 80% of those who will experience this failure do so within 6 months** (Cathcart et al, 2006). **At that point surgery and/or pressure-flow studies are indicated.**

Medical Therapy for the Prevention of Acute Urinary Retention

Large-scale, randomized, double-blind, placebo-controlled trials of long-term duration are necessary to determine whether a medical therapy prevents a relatively uncommon event such as AUR. **In the MTOPS trial, finasteride or combination therapy of finasteride with doxazosin, but not doxazosin alone, reduced the incidence of AUR** (McConnell et al, 2003). **Debruyne and associates** (2004) **reported data for dutasteride suggesting similar results.** Because men with large prostates have on average a threefold greater chance of developing urinary retention (Jacobsen et al, 1997), enrolling men with large prostates would enhance the probability of observing an effect on AUR. **The 3-year open-label prospective study of alfuzosin supported a 0.3% risk of retention** (Lukacs et al, 2000). This is markedly lower than the predicted risk of developing urinary retention in an age-matched cohort of men (Jacobsen et al, 1997) but may be more a delay rather than prevention. **The trial data suggest a role for 5α-reductase drugs in the prevention of AUR.**

FUTURE STRATEGIES

Medical therapies provide improvement over watchful waiting for most patients (Hutchison et al 2007). The therapeutic response to medical therapy is less than that of prostatectomy. As Clifford and Farmer (2000) noted in a meta-analysis of α-adrenergic blocker and finasteride studies, "neither finasteride nor α-blockers approach the efficacy of prostatic surgery in terms of improvement in either symptoms or flow rates…." Therefore opportunities exist to develop novel strategies that may be more effective than existing therapies. The development of "pharmacogenetics" and molecular biologic testing may allow "personalized" medication so that α_{1A}-adrenergic receptor–predominant men get tamsulosin and α_{1D}-adrenergic receptor–predominant men get naftopidil, for instance. Developing different classes of drugs to relax smooth muscle and further targeting nonprostatic factors are further potential opportunities.

Endothelins are potent vasoconstrictors. Langenstroer and associates (1993) reported that human prostate contains endogenous endothelin and that **endothelin elicits a very potent contraction in the human prostate.** The contractile response elicited by endothelin in the human prostate is not abolished by pretreatment with selective α_1-adrenergic blockers. These observations suggest that relaxation of prostatic smooth muscle in BPH may also be achieved by endothelin antagonists. The

pharmaceutical industry is actively engaged in efforts to synthesize selective endothelin antagonists. Kobayashi and colleagues (1994) have characterized the binding properties of endothelin receptor subtypes in the human prostate. Both endothelin-A and endothelin-B receptors are present in the human prostate. These receptors are localized primarily in the stroma and glandular epithelium, respectively. Preliminary studies suggest that both types of endothelin receptors mediate the tension of prostate smooth muscle. Endothelin antagonists may emerge as another treatment for BPH.

It is generally assumed that the clinical manifestations of BPH are the result of BOO. Therefore pharmacologic strategies have been directed toward reducing BOO. **Several observations suggest that nonprostatic factors may also contribute to clinical BPH.** The severity of clinical prostatism as captured by symptom scores is poorly correlated with measurement of BOO. In addition, the changes in symptom scores after therapy for BPH are poorly correlated with changes in PFR and obstruction grade. The discordance between symptom severity and measures of obstruction suggests that nonprostatic factors may be contributing to clinical BPH. Clearly several factors including aging, the hormonal milieu, nonurologic diseases, and prostatic growth affect bladder morphometry, neurologic innervation, BOO, and renal function, and these factors collectively contribute to clinical BPH. Our present understanding of the pathophysiology of clinical BPH is rudimentary. It is therefore imperative to develop a more comprehensive understanding of the pathophysiology of symptoms. This knowledge will result in more effective use of existing therapies and will provide the rationale for the next generation of therapeutic modalities.

Key Points: Evaluation and Nonsurgical Management of Benign Prostatic Hyperplasia

- Benign prostatic hyperplasia (BPH) is the most common cause of lower urinary tract symptoms (LUTS) in men beyond middle age.
- Evaluation requires a history and symptom score (IPSS) and a careful physical examination including a digital rectal examination.
- Uroflowmetry and ultrasound estimation of PVR urine volume are often helpful, and determination of the PSA level is requested when a diagnosis of prostate cancer would alter the management of the individual patient.
- Medical therapy is now the usual first-line management of uncomplicated BPH with either an α-adrenergic receptor blocker or (if the prostate is large) a 5α-reductase inhibitor.
- Combination therapy with both an α-adrenergic receptor blocker and a 5α-reductase inhibitor has been demonstrated to be the most effective means of preventing disease progression and seems likely to become the standard of care in appropriate cases.
- Antimuscarinic agents and PDEIs are useful adjuncts for men with "storage" symptoms or ED. Their true importance will become clearer with time.

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chapter 93

Minimally Invasive and Endoscopic Management of Benign Prostatic Hyperplasia

John M. Fitzpatrick, MCh, FRCSI, FC Urol (SA), FRCSGlas, FRCS

Intraprostatic Stents
Transurethral Needle Ablation of the Prostate
Transurethral Microwave Therapy
Lasers
Transurethral Resection of the Prostate
Transurethral Vaporization of the Prostate
Transurethral Incision of the Prostate
Other Technologies
Summary

The prostate continues to be central to urologic practice in terms of the volume of cases that arise involving a disorder of that organ, be it benign, malignant, or inflammatory. Because of this, the amount of money available from grant-giving authorities for research into prostatic diseases is probably the highest for any research on the genitourinary tract, and so inevitably our interest in and understanding of the pathogenesis of problems relating to prostatic conditions have increased greatly. This has led to increasingly effective therapies for some prostatic abnormalities, but after the initial advances in the management of benign prostatic hyperplasia (BPH) of 10 to 12 years ago, how far have things moved forward? And, although groups of patients are continually being identified who would benefit from individual or combined medical treatments, can we say that the same has been happening in our development of minimally invasive therapies?

One thing that is certain is that in our investigation of medical therapy of BPH the identification of groups of patients who would best respond to different drugs has taken many large trials with long-term follow-up and careful statistical powering to demonstrate equivalence or a predefined difference. One always has the feeling that drug trials keep moving forward, leading to a greater understanding of the condition itself and of the ideal treatment for BPH. It can be said with some degree of confidence that the advent of medical management has reduced greatly the indications for and the number of patients undergoing transurethral resection of the prostate (TURP) and has also strongly influenced the wish of patients to have TURP, in that they would now prefer to try most other types of treatment before agreeing to undergo this procedure.

As the pharmacologic management of BPH was flourishing, many new minimally invasive therapies were being introduced. The huge success that greeted the development of technologic innovations in the management of renal calculous disease with percutaneous nephrolithotomy and extracorporeal shockwave lithotripsy prompted most of us to believe that the same could be achieved with BPH.

The yardstick against which the new minimally invasive therapies were measured was, of course, TURP. This was a very significant technologic innovation when it was introduced, and it went through a considerable amount of evolution before it reached the high levels of excellence that it has reached today. We know that it does not seem to produce as good results as the open prostatectomy, but it is not far behind. This statement is made without there having been a randomized trial between the two procedures, and comments on the safety and efficacy of one against the other are not evidence based. However, TURP can be viewed as a highly effective treatment with an acceptable complication rate, so much so that it is now accepted as the "gold standard," that is, the standard against which other minimally invasive therapies must be measured and the standard that it is hoped they can achieve.

One of the slightly disappointing things is that although many of these therapies have been introduced, in spite of the fact that they were originally welcomed as a significant advance in the treatment of BPH, in the longer term they have not turned out to be so. In many cases, the conclusion that they were of value was based on a series of poorly constructed short-term trials in which intention-to-treat analysis of the results may not have been rigidly adhered to. However, the demise of some of the earlier technologies has led to strengthening and evolution of the newer ones, all of which has been beneficial for patients with BPH.

It should also be remembered why it is that the new minimally invasive techniques have been introduced. Ideally, they have been popularized and developed in the hope that they will have less complications than TURP, less requirement for anesthesia, and a shorter hospital stay and if possible will be less expensive. If the treatment is as effective as TURP, it should be ahead on one of these counts, and if it is not as efficacious, a rationale for its use

should be devised, in addition to attempts at the identification of the patients most likely to benefit from it. Its exact therapeutic positioning in the management of BPH should be found.

The discussion presented here focuses on the current approach to the minimally invasive and endoscopic management of BPH. The literature has been critically and fairly reviewed, and the information outlined has relied heavily on evidence-based principles. When level I evidence is available, such as a meta-analysis or systematic literature review, the reader's attention will be drawn to it. The purpose of all of this is to present the data so that readers will be able to make a valued judgment on the various treatment options, thus helping in their urologic practice.

INTRAPROSTATIC STENTS

One of the earliest attempts to find less traumatic methods of treating symptomatic BPH was the introduction of either temporary or permanent intraprostatic stents, and, to a degree, they are still being used. They were first introduced as a method of treating certain cardiovascular conditions; and since the work of Dotter (1969), they have also been part of the treatment for peripheral vascular disease. They have since been used to treat stenosis of the coronary, femoral, and renal arteries (Maass et al, 1982; Dotter et al, 1983; Wright et al, 1985; Palmaz et al, 1987). Other types of obstruction have also been treated by the placement of stents: vena caval obstruction (Furui et al, 1990), bronchial obstruction (Mair et al, 1990), and tracheal stenosis (Skapshay et al, 1989). Even cervical stenosis (Luesley et al, 1990) and lacrimal duct obstruction (Hurwitz, 1989) have been treated in this manner. It is clear that stents have a role to play in treating obstruction in different parts of the body, but the exact role needs to be defined accurately. In the case of coronary artery disease, for example, a trial comparing stents with coronary artery bypass grafting is still awaited. In the case of the prostate, it took some time before it was realized that the role of stents was rather a limited one and that they would not replace TURP in every patient.

One of the few innovations that have occurred has been the introduction of a new temporary prostatic stent, which is based on a modification of the Foley catheter. This is described in detail later.

The idea of using stents for splinting the lobes of the prostate was derived from their original use in the cardiovascular system, where they are used to prevent arterial restenosis after angioplasty. Fabian (1980) first described the use of stents in urology when he suggested their usefulness in the treatment of outlet obstruction secondary to enlargement of the prostate. At some time after this the use of stents was advocated in the treatment of urethral strictures, and, subsequent to this, the use of prostatic stents became widespread, with the introduction of many different types: stents are now available in different lengths, diameters, materials, and designs.

As mentioned earlier, when stents were introduced as a treatment for symptomatic BPH, their exact role was uncertain and tended to be overstated as perhaps something that could be used in virtually every case. **Eventually it became clear that their major role was likely to be found in the management of patients who were unfit for surgery, in either the short or the long term, in which the alternative would have been months or, indeed, a lifetime of indwelling urethral catheterization.**

Along with these changes in the indications for the use of stents have emerged two basic types of stent: that which is put in for a short time and can be removed with ease and that which is placed as a permanent type of treatment and can be removed only with much greater difficulty.

Temporary Stents

Temporary stents are tubular devices that are made of either **a nonabsorbable or a biodegradable material.** They remain in the prostatic urethra for a limited period of time; they neither become covered by the urethral epithelium nor become incorporated into the urethral wall. The nonabsorbable stents need to be removed every 6 to 36 months, depending on which type of material is used. They can usually be removed, and, if necessary, replaced, without difficulty with the patient under topical anesthesia with sedation.

Temporary stents are designed for short-term use, to relieve bladder outlet obstruction (BOO), and to act as an alternative to an indwelling urethral or suprapubic catheter in high-risk patients considered unfit for surgery. In such patients these temporary stents permit normal micturition with an acceptable side effect profile. Success rates have been reported in the range of 50% to 90%. They are easy to reposition or replace, but catheterization or cystoscopy cannot be performed while the stent is in place. Complications such as encrustation, migration, breakage, stress incontinence, and bacteriuria have been reported in varying degrees of frequency.

Spiral Stents

First-Generation Stents. The Urospiral (Porges) and the Prosta Kath (Pharma-Plast) are examples of spiral stents. The former is made of 21-Fr stainless steel and varies between 40 and 80 mm in length. The latter is also made of 21-Fr stainless steel but is gold plated in an attempt to prevent encrustation. It varies in length between 35 and 95 mm. Neither stent should remain in the prostatic urethra for longer than 12 months.

A spiral stent should be inserted with a 21-Fr panendoscope using either a 30-degree or a 0-degree lens under direct vision and with the aid of a grasping forceps. It may also be inserted over a catheter guide under ultrasound visualization (Nordling et al, 1989).

In the original series reported by Nordling and colleagues (1989), the Prosta Kath was inserted under topical anesthesia in 45 patients with acute or chronic retention. Ultrasonography was used in 35 patients and endoscopy in 6 to facilitate stent placement. **Retention was relieved in 41 of the 45 patients, leading the authors to advocate its use in high-risk patients.**

Ozgur and coworkers (1993) reported re-establishment of voiding with the Urospiral with good results after 4 months of follow-up in 31 patients who were unfit for surgery. The Urospiral was also used in 10 patients with advanced prostate cancer (Anson et al, 1993). All had retention or severe obstruction. The patients were started on antiandrogens after stent insertion. The stent was removed 3 months later, and all patients were reported as voiding satisfactorily, although one patient subsequently required a limited TURP. In another report, 18 high-risk patients with BPH had a Urospiral inserted (Karaoglau et al, 1992). **All voided without difficulty and with complete bladder emptying. However, the complications were rather high: hematuria in 2, migration in 1, and infection in 8.**

In 87 patients declared unfit for TURP, Thomas and colleagues (1993) reported an experience extending over 4 years using the Prosta Kath. Sixty-four patients presented with acute urinary retention, and, after treatment, 57 voided successfully whereas 7

failed to void. A further 14 patients presented with chronic urinary retention; 5 of these voided satisfactorily, but 9 required alternative therapy. **Complications included hematuria with clot retention (5%), stent migration (15%), recurrent urinary tract infections (10%), and encrustation (4%).** These findings of relatively high complications are also reported by other authors (Nordling et al, 1989; Harrison and De Souza, 1990). Braf and coworkers (1996) observed 55 men for between 12 and 16 months, 32 of whom were treated with the Prosta Kath and 23 with the Urospiral. Ten patients failed in the Prosta Kath group, and 8 patients failed in the Urospiral group. Complications in both groups include encrustation, urinary tract infection, migration, stricture formation, and failure to void. In the largest number of patients reported from one center Nordling and associates reported on the use of the Prosta Kath in 318 patients. They divided the complications into none, moderate, and severe. In the patients who were described as having severe complications, stress or urgency incontinence occurred in 63, emptying problems in 8, and frequency or nocturia (more than three times per night) or both in 57.

Second-Generation Stents. Other spiral stents have been developed as second-generation models in an attempt to overcome the problems of the first-generation stents just described while maintaining the efficacy and ease of insertion. These are the Memokath and the Prosta Coil.

The Memokath (Engineers and Doctors A/S, Copenhagen, Denmark) is made of nitinol, a nickel-titanium alloy, which has the property of shape memory. It is malleable and heat expandable at a temperature of 45° C to 50° C. Like other temporary stents, it is easy to insert and maintains its expanded position in the prostatic urethra. With the earlier model of the Memokath, epithelial hyperplasia at the apex of the prostate was reported in some cases, but modifications have since been made. The later model ensured close contact of the wires even in the expanded position, thus reducing the possibility of hyperplastic growth of the urethral epithelium through the gaps in the expanded spiral. The Memokath is soft and malleable when cooled, returning to its original shape when heated to the preceding temperatures. Of 22-Fr caliber, it has a length of 35 to 95 mm. It permits the passage of a flexible cystoscope and may be left in place for up to 36 months.

The Prosta Coil is a self-expanding and self-retaining stent made of a nickel-titanium alloy (Instent, Minneapolis, MN). It is inserted by being mounted on a 17-Fr delivery catheter under fluoroscopy; once released from the mounting it takes the form of a wave-shaped tube whose diameter varies from 24 to 30 Fr. Its length is from 40 to 80 mm, and it can be left in position for up to 36 months.

The Memokath was reported as being used in **30 patients who were unfit for surgery or who refused it; the success rate was 80%. Normal voiding is described as having occurred in all patients.** The peak urinary flow rate (PFR, also Qmax) reached a mean of 16 mL/sec immediately after insertion (Poulsen et al, 1993). However, there was a wide range of PFRs, from 4 to 25 mL/sec. Unfortunately, 3 patients later developed urinary retention at 5 days, 2.5 months, and 5 months, respectively, after insertion. Two more stents needed to be removed because of hyperplastic growth of the epithelium. A total of 24 stents were still in place at 3 months. Nordling (1996) updated these authors' experience after inserting 64 of the modified Memokath stents. Similar successful voiding was reported. The complications that patients described as severe were few, with urgency incontinence being the most common (10 patients). However, moderate symptoms were relatively more common.

Results are available from a long-term study conducted in the United Kingdom. The Memokath was inserted in men who were either permanently or temporarily unfit for TURP, in most cases because of severe respiratory or cardiovascular disease. **In this study, 211 men had 217 stents inserted over an 8-year period. In the same time frame, 1511 TURPs were performed. The mean age of patients having stents was 80.2 years, and in the TURP group it was 70.2 years. The patients who had stents fitted experienced an improvement in the mean International Prostate Symptom Score (IPSS) from 20.3 to 8.2 in just 3 months, with results being maintained for 7 years. However, these results must be viewed in the light of the fact that 38% died with stents in place, 34% remain alive with their stents, and 23% had stent removal because of failure. Migration occurred in 13%, and 16% required repositioning. This study suggests that long-term success can be achievable using the Memokath but that failure can also be anticipated in a significant minority** (Perry et al, 2002).

The Prosta Coil has been used in a small series of patients with short follow-up (Yachia et al, 1994). The mean follow-up was 14 months, with a range of 2 to 28 months. There were initial irritative urinary symptoms that were reported as having disappeared within 1 month. **The mean PFR at the most recent follow-up was 21.3 mL/sec (with a range of 15 to 36 mL/sec) and the mean IPSS was 9 (with a range of 6 to 12).**

Thus spiral stents were among the earliest type of temporary stents to be introduced, and they have developed to a large degree from the original designs. New models have reduced such complications as encrustation and urothelial hyperplasia, but stress incontinence and urgency incontinence still occur, as does displacement of the stent. However, they are easy to insert and do not require general anesthesia. Although the follow-up is relatively short term, in most of the reported series, good success rates are reported. The place of spiral stents is clearly that of a nontraumatic therapy for urinary retention in patients unfit for surgery, and they have a reasonable chance of a successful outcome.

It is hard to predict whether further design changes will take place. The earlier type of spiral stents had the advantage of being less expensive. The newer models are made of compounds aimed to reduce complications or prevent stent migration but are all more expensive than the earlier models. With a limited market and with a restricted acceptability, further developments in this type of stent are unlikely.

Polyurethane Stents

Polyurethane stents are also known as intraurethral catheters. There are three types: the intraurethral catheter (Angiomed, Germany), the Barnes stent (CR Bard, Covington, GA), and the trestle stent (Microvasive, Boston Scientific, Natick, MA).

Intraurethral Catheter. The intraurethral catheter, the first to be introduced, was reported initially by Nissenkorn (1991). It is made of a type of polyurethane known as Puroflex and has a fixed 16-Fr caliber. Its length varies from 40 to 60 mm, and it can be left in place for up to 6 months. It has a double device at its proximal end shaped like the head of a de Pezzer or Malecot catheter. It has a nylon string at its distal end and a flared split end proximally, which sits in the bladder. It is inserted under topical anesthesia using a 22-Fr cystoscope. The nylon string is cut after placement, and any positional adjustment required can be performed by the use of a grasping forceps. **Eighty-five devices were inserted into 73 patients, and, of these, 60 patients had an indwelling catheter for 1 week to 3 years before insertion.**

Nissenkorn (1991) described a successful outcome in 63 patients who believed that their quality of life was considerably better than it had been when they had an indwelling catheter. He therefore believed that this was suitable for use in such patients, with a high likelihood of success.

A later study reported the use of the Nissenkorn intraurethral catheter in 43 patients (Sassine and Schulman, 1994). Once again, the patients treated had developed urinary retention and were unfit for surgery but also had a short life expectancy. Thirty-six of the 43 patients were able to void satisfactorily after stent insertion. The intraurethral catheter should not be inserted in the presence of bladder stones or anything else likely to block or have a ball-valve effect on the device.

One of the potential uses of temporary prostatic stents is as an expedient to overcome the early retentive effects of heat treatment to the prostate. Clearly, an objection to this might be that such a therapeutic strategy effectively doubles the cost of the treatment and so makes it less attractive. However, it is an attractive way of overcoming an early complication of heat treatment, which might have been seen by some as a significant limitation of heat treatment. The Barnes stent and the trestle stent may have such an application.

Barnes Stent. What has been called the Barnes stent is made of polyurethane, has a 16-Fr caliber, and is of a single length. It also has a de Pezzer end proximally, but this time a single one. It is thus a modification of the original intraurethral catheter. It was used in 25 patients who underwent endoscopic laser ablation of the prostate (ELAP). Twenty-two of the 25 voided immediately. Early stent migration occurred in 1 patient, but late migration did not occur. The stent was inserted with ease, could be removed with ease at 12 weeks, and was inexpensive. PFRs improved from 8 mL/sec before ELAP to 16.5 mL/sec at 6 weeks with the stent in place (Barnes et al, 1996). The Nissenkorn catheter has also been used safely and with equal success after laser therapy (Nissenkorn et al, 1996).

Trestle Stent. The trestle stent or prostatic bridge catheter has been described and consists of two tubes and an interconnecting thread. The tube that lies in the prostate has a 22-Fr diameter and has a 30-degree angulation. The length is 75 mm, and it has a smooth tip: It is to be used in prostates with a volume of less than 80 mL. The connecting thread is 25 mm, which passes through the distal sphincteric mechanism. The second tube lies in the bulbar urethra and is 35 mm long. It is inserted with the patient under topical anesthesia using a delivery system comprising a positioning stylet, an inflatable balloon with injection cannula, and an outer pusher tube. The technique is described in detail by Djavan and colleagues (1999).

In a report from Devonec and Dahlstrand (1998) the results of its use **in 52 patients after high-energy transurethral microwave therapy (TUMT) were described. Tolerance was good in 32 patients, acceptable in 13, and poor in 6. Retrograde ejaculation occurred in eight. PFRs reached 14.6 mL/sec on the day of removal of the device. The device was left in place for 1 month, but the improvement in PFR was maintained at 1 year.** Djavan and colleagues (1999) also described its use in 54 patients who had received high-energy TUMT. The device was left in place for up to 1 month, and it was found that the incidence of post-treatment retention was prevented, with concurrent early but significantly improved symptom scores and PFRs. Toleration was high, with 48 of 54 devices remaining in place for 1 month. Early removal was required because of urinary retention in 3 and migration in 3.

The intraurethral catheter or its more recent variations are being used in a rather different context than the spiral stents. They have been used successfully, albeit in a small number of nonrandomized short-term studies, with few problems related to tolerance. A further cost-efficacy evaluation is required, in addition to larger multicenter randomized controlled comparative trials.

The Spanner. The spanner has a design very similar to the proximal 4 to 6 cm of a Foley catheter. It includes a balloon to prevent displacement, a port for urine drainage that lies proximal to the balloon, and a reinforced stent of varying length that spans most of the prostatic urethra (Fig. 93–1).

In the first study using this device, the stent was inserted under topical anesthesia in 30 patients (Corica et al, 2004), **of whom 5 had been in urinary retention. The stents remained in place for a mean of 57 days. The mean PFR improved by 42% from 8.2 to 11.6 mL/sec. The overall mean IPSS decreased from 22.3 to 7.1, a 68% difference. The adverse events were few, and the device was found to be stable and patent at the end of the study.**

This article describes an early open study designed to test the efficacy, safety, and stability of the device. It could be criticized in that it was composed of a group of patients whose characteristics were not adequately described, with no entry criteria defined. It is, however, an interesting new device that may well be important for many patients as a temporary method of bypassing prostatic obstruction.

Biodegradable Stents

The concept of stents that can be put in place after a procedure that has a high incidence of secondary and temporary obstruction has been mentioned earlier in the context of stents being inserted after laser or high-energy TUMT. These stents are removed some weeks later. With the biodegradable stent the concept is brought one step further; the stents do not need to be removed, and eventually they disappear by biodegrading. This interesting idea was first introduced in urology when Kemppainen and colleagues (1993) used a biodegradable stent in rabbits after urethrotomy. The idea has now been extended to the ureter (Schlick and Planz, 1998; Lumiaho et al, 1999; Clayman, 2000), after endoscopic urethroplasty (Oosterlinck and Talja, 2000), and in coronary artery disease (Tamai et al, 2000).



Figure 93–1. Pro Vu device used for transurethral needle ablation of the prostate. (Courtesy of Neo Vitalis Ltd, Southport, UK.)

Further experimental studies have shown that biodegradable stents can potentially be used as a bridge across the prostate after minimally invasive procedures, without the necessity of having to remove them later (Petas et al, 1997a, 1998; Laaksovirta et al, 2002; Vaajanen et al, 2003).

In addition, clinical studies have been performed that examine the use of biodegradable stents after various procedures (Talja et al, 1995; Dahlstrand et al, 1997; Petas et al, 1997b). The benefit is that these stents prevent the development of obstruction that can occur after laser procedures; however, the use of the second procedure in association with, for example, laser prostatectomy takes away a great deal from the value of the first procedure, not least in terms of cost-effectiveness. There are three types of biodegradable stents.

A randomized study (Petas et al, 1997b) **compared self-reinforced polyglycolic acid biodegradable spiral stents (group 1), no device (group 2), or an indwelling catheter (group 3) after visual laser ablation of the prostate. The procedure was performed on 72 men, and 27 were in group 1, 23 in group 2, and 22 in group 3. Voiding began at a median of 1 day in group 1 and a median of 6 days in group 2; the indwelling catheter was required for an average of 6.5 days in group 3, and voiding commenced a median of 6 days after this.** The authors found, as they had in previous in-vitro studies, that the stent degraded into small fragments of polymer debris that were passed out in the urine. They commented that voiding became more obstructed at 3 to 4 weeks postoperatively, presumably from degradation and sloughing of the stent, but they found that this was only a transient effect.

In another study, Dahlstrand and colleagues (1997) evaluated the same polyglycolic acid stent after high-energy TUMT with the Prostasoft 2.5. They compared the use of the stent in 15 patients against a further 15 patients in whom a standard 16-Fr urethral catheter was inserted. The mean duration of catheterization was 14.1 days, with a standard deviation of 4.1 days; this was obviously prevented by the stent, which did not cause problems, even when it was degrading.

In a rather innovative way, Knutson and colleagues (2003) described the use of a biodegradable polyglycolic acid stent to assess the risk of post-TURP incontinence in patients with combined BOO and overactive bladder. In 37 patients with severe overactive bladder and moderate to severe BOO this biodegradable stent was inserted into the prostatic urethra; 25 noticed either no leakage or minor leakage and 19 have had TURP with good results. Twelve of the 37 had a major problem with incontinence after the insertion of the stent. There was a small complication rate related to stent insertion.

These stents are definitely of interest for the future, but their exact place in the treatment of BPH needs to be established, with larger and longer-term studies. In addition, the problem related to the overall cost must be defined accurately; otherwise, the value of the primary procedure will be questioned.

Permanent Stents

With permanent stenting of the prostate, the urologist is attempting to treat definitively and permanently patients who present with symptomatic BPH. To be of proven value this type of treatment, like any other, must be shown to be at least comparable to TURP. The initial enthusiasm for permanent stents has been replaced by relative silence in the literature at present. Permanent stents were initially introduced as treatment for recurrent urethral strictures and were subsequently used in patients with lower urinary tract symptoms (LUTS). In urologic terms, permanent stents are being used preferentially for the treatment of detrusor-sphincter dyssynergia (Chancellor et al, 1999; Chartier-Kastler et al, 2000; Gajewski et al, 2000), postbrachytherapy BOO (Konety et al, 2000), anastomotic strictures and urinary incontinence after radical prostatectomy (Meulen et al, 1991), and complex urethral strictures (Tillem et al, 1997). There have been no reports in the recent literature that relate to the long-term follow-up of the patients originally treated with permanent stents, and there has been no indication of new interest in their use.

UroLume

The UroLume endourethral prosthesis (American Medical Systems, Minnetonka, MN) is a woven tubular mesh that maintains its position in the urethra by outward external pressure, thus maintaining the patency of the prostatic urethra. The original 42-Fr device was made of metal superalloy and varied in length from 1.5 to 4.0 cm. It is inserted with a special 21-Fr deployment tool using a 0-degree panendoscope. Gradually, epithelialization occurs, ideally in a smooth manner, covering the individual wires of the mesh. The stent can be removed by securing about 5 mm of the distal aspect in the jaws of a grasping forceps and then pulling the distal end inside a resectoscope sheath to minimize any possibility of urethral trauma while removing it.

The original stent tended to shorten while it expanded outward, leading to its replacement by a stent less likely to do so. However, this stent tended to migrate more easily, and a further modification was required. In addition to these changes the delivery tool was modified, leading to the present, more satisfactory model.

Chapple and colleagues (1990) reported on the initial experience with the UroLume. **Twelve patients who were considered to be a poor risk for surgery presented with LUTS; 9 of the 12 patients presented with urinary retention. The results were encouraging, with 11 of 12 voiding satisfactorily for a mean follow-up of 8.2 months. The mean PFR after the procedure was 13.6 mL/sec.** Further encouragement came from the low complication rate, consisting mainly of short-term irritative voiding symptoms, with only 1 of the 12 being dissatisfied because of severe urgency and frequency (the patient was subsequently found to have detrusor instability). A further study in a similar group of unfit patients was performed by McLoughlin and colleagues (1990). All 19 patients in their study group presented in urinary retention, and all voided satisfactorily after the stent was inserted under local anesthesia.

In a larger, multicenter open trial from the United States, Oesterling and colleagues (1994) reported on 126 men who presented either with moderate or severe LUTS (95 men) or with urinary retention (31 men). There were strict inclusion and exclusion criteria in the trial design, but fitness for surgery was not among them. **In the nonretention group, 80 of 95 were evaluable at 12 months and 52 at 24 months; the Madsen symptom score decreased from 14.0 to 5.9 and 5.4, respectively. In the retention group, 24 of the 31 patients evaluable at 12 months had a mean symptom score of 6.1. In the nonretention group, the PFR increased from 9.1 to 13.0 and 13.1 mL/sec, respectively, with the retention group having a mean PFR of 11.7 mL/sec at 12 months.** Difficulties with insertion were experienced in 16% of cases; irritative voiding symptoms occurred in 10%.

Guazzoni and coworkers (1994) described a European study using the modified UroLume stent (the so-called less shortening variety described earlier). Once again, the strict inclusion and

exclusion criteria did not refer to fitness for surgery, and at this time the stent was being presented as a proposed therapy for prostatic obstruction, not necessarily only for unfit patients. In this multicenter study, 135 healthy patients (91 with LUTS, 44 with urinary retention) were treated. In the nonretention group, 74 of 91 patients were evaluable at 12 months. The mean Madsen-Iversen symptom score had decreased from 14.1 to 6.4, but the tight standard deviations of the mean observed in the U.S. study (0.4) were not seen in this study (5.1); the PFR improved from 9.3 to 15.7 mL/sec at 12 months (with a very wide standard deviation of 6.5, unlike that in the U.S. study). In the retention group, 34 of 44 were evaluable at 12 months; the mean symptom score was 4.5 and the mean PFR was 13.1 mL/sec. The complications were well described but were found to be significant in the long term.

In a British study (Bajoria et al, 1995), 44 men fit for TURP accepted as an alternative a second-generation UroLume stent. The stent was inserted in 44 patients, who either were in urinary retention or had urodynamically proven outflow obstruction. The results achieved were similar to those reported by Guazzoni and colleagues (1994), but there was also a relatively high complication rate. Both sets of authors noted **epithelial hyperplasia and migration of the stent in addition to irritative urinary symptoms and painful ejaculation. The second-generation less shortening stent was not recommended for general use,** and a third-generation stent was then produced. However, Bajoria and colleagues (1995) strongly suggested that permanent stents should still be considered as being under evaluation rather than for general use.

In a multicenter study of 96 men who were unfit for prostatic surgery, 73 presented in acute urinary retention and 11 in chronic retention. **All but 6 were able to void immediately after stent insertion; 2 required a second stent, and 4 required a period of suprapubic catheter drainage. At 12 months, the PFR was 15 mL/sec in the retention group and 18.1 in the nonretention group. Severe irritative symptoms were seen in the majority of patients for up to 3 months, and encrustation was encountered in 15 of 27 patients who underwent cystoscopy** (Williams et al, 1993).

The results of a long-term analysis of the UroLume Wallstent have been published by Masood and coworkers (2004). The stent was inserted in 62 patients with moderate or severe LUTS secondary to BPH. The 5- and 12-year follow-up was completed by 22 and 11 patients, respectively. Death occurred in 21 patients (34%), and the stent was removed in 29 patients (47%), the vast majority of these removals occurring in the first 2 years. The authors concluded that this is a safe treatment but that cases must be carefully selected and that it should be performed only by experienced hands.

The use of the UroLume stent can be seen to have some application in patients with prostatic obstruction, particularly if they are unfit. However, interest in this type of stent seems to have waned somewhat because of the use of other types of less invasive treatments, which appear more satisfactory to patient and urologist alike.

Memotherm

The Memotherm (Angiomed, Germany) is a stent of nickel-titanium alloy that is expandable to 42 Fr with heat. When it is cooled, it can easily be compressed and distorted, but when warmed to body temperature it expands to a flexible cylinder and does not shorten. It is made from a woven single wire, which makes it easy to remove; traction unravels the wire. It is manufactured in lengths varying between 1.5 and 8.0 cm and is available in a prepacked sterile delivery service. It is inserted under direct vision with a 0-degree telescope.

Williams and White (1995) reported on 48 men with LUTS and urodynamic findings suggestive of bladder outflow obstruction. The results were disappointing. **Only 37 patients were able to void immediately after stent insertion, the others requiring a suprapubic catheter for up to 8 weeks. Symptomatic improvement occurred in many, but complications, including stent migration, were relatively high. Thirteen of the 48 patients required removal of their stents.** These authors suggested that the results were not appropriate to encourage marketing of the device.

Gesenberg and Sintermann (1998) used the Memotherm in 123 patients considered to be at high risk for prostatic surgery; 46 of these presented in urinary retention. Of the 123 patients, only 52 were evaluable at 12 months. The mean PFR increased from 7.4 to 13.0 mL/sec (with a standard deviation of 6.2), and the IPSS improved from 24.0 to 8.8 (SD 6.2). **The authors noted a considerable improvement in quality of life. However, the complication rate was relatively high, with recurrent infections and urgency symptoms in 56%, urothelial hyperplasia in 34%, and urethral stricture in 10%. There was a high number of re-treatments,** and the authors suggested that there may be an additional role for medical treatment in some of these patients.

These results have not appeared to be convincing large numbers of urologists to use these stents on patients with symptomatic BPH, but modifications may occur. Heat-expandable stents are widely used in cardiovascular conditions and in biliary stenosis.

Other Permanent Stents

The ASI stent (Advanced Surgical Instruments) was evaluated in several centers (Kirby et al, 1992; Kaplan et al, 1995). It was introduced on a balloon, which was then inflated, thus expanding the stent. The early results suggested an improvement in symptom score (44%) and PFR (22%), but complications also occurred that made it less attractive for general use. It has since been withdrawn from production.

The Ultraflex stent (Boston Scientific, Natick, MA) is made of nickel-titanium alloy that also has a capacity to expand to a caliber of 42 French when exposed to body heat. It is available in lengths varying from 2 to 6 cm. There have been reports of its use in patients with prostatic obstruction, but it has been studied in a group of patients with detrusor-sphincter dyssynergia (Chartier-Kastler et al, 2000), and the incidence of epithelial hyperplasia and migration was encouragingly low.

Summary

Originally, permanent prostatic stents were introduced as a definitive treatment for prostatic obstruction, particularly (but not in every study) for patients unfit for prostatic surgery who presented with urinary retention. Patients were able to void satisfactorily in most cases, but complications were relatively high. One stent has been removed from the market, one has not yet been reported on as a treatment for prostatic problems, variable results have been reported on another, and the most frequently investigated, the UroLume, has not received recent attention in the literature as a specific treatment for BPH.

Temporary stents are receiving widespread attention, but the original idea that they should be used as a temporary expedient to overcome outflow problems in the

medically unfit population is being modified. The newer stents, whether biodegradable or not, are being viewed as possible methods of overcoming the temporary retention that can occur secondary to treatments such as laser therapy or high-energy TUMT.

TRANSURETHRAL NEEDLE ABLATION OF THE PROSTATE

Heat treatment of whatever kind to the prostate is intended to reduce outflow resistance and the volume of the obstruction by increasing the temperature within the prostate and inducing necrosis of prostatic tissue. The aim is to increase prostatic temperature to in excess of 60° C. Transurethral needle ablation of the prostate (TUNA) uses low-level radiofrequency (RF) energy that is delivered by needles into the prostate and that produces localized necrotic lesions in the hyperplastic tissue. It has previously been used to ablate cardiac nerve bundles in the Wolff-Parkinson-White syndrome (Calkins et al, 1992) and to destroy malignant tissue (Rossi et al, 1995; Zlotta et al, 1995). It has also been used to treat chronic cervical zygapophyseal joint pain (Lord et al, 1996). The advantage of TUNA is that it can be delivered under topical anesthesia to patients with symptomatic BPH, causing very precise and reproducible lesions within the prostate.

Delivery of Radiofrequency Energy

The TUNA system (Medtronic, Inc, Minneapolis, MN) consists of a special catheter attached to a generator. At the end of the catheter are two adjustable needles that are withdrawn into two adjustable shields made from Teflon. The needles are advanced into the prostatic tissue and can be placed accurately into the required position.

The generator produces a monopolar RF signal of 490 kHz, which allows excellent penetration and uniform tissue distribution. The patient has a grounding pad placed over the sacrum, and the current passes toward this through the prostatic tissue. In other words, tissue heating is created because of tissue resistance to the current as it flows from the active to the return electrode. The active electrode has a small surface area, with the RF current being concentrated in an area immediately surrounding it. The return electrode is large, and so the diffusion of the RF current is greater. This arrangement allows heat to be concentrated near the active electrode early, thus accurately controlling the tissue effect. The size of the lesion caused by RF relates to the position and depth of insertion of the electrode as well as the power used and the duration of the treatment.

RF produces molecular or ionic agitation with collision of particles that relates to the frequency of the energy, and this results in a central hot core inside the prostate and away from the urethra (Schulman et al, 1993). The limited distance dissipation reinforces the safety of the procedure because RF can be applied to tissue only by direct contact, with heat being generated proportional to one over the fourth power of the radius. If the power generated is too high, the prostate rapidly desiccates with a rise in tissue impedance, preventing the desired heating effect. Therefore the appropriate energy level required to produce the localized necrotic lesion must be found, preventing the increase in tissue impedance resulting in prostatic charring around the needle caused by excessive generation of energy (Schulman et al, 1993). Interestingly, heat is lost by convection, and so increased vascularity can have an effect on the degree of localization of the lesion. RF is very much affected by blood flow and has almost no effect on vessels larger than 2 to 3 mm in diameter (Organ, 1976).

There is a difference in the method of tissue heating brought about by RF and, for example, microwave application. Microwaves treat a broad area and can penetrate tissue more deeply than RF. The central temperature is therefore lower than with RF to maintain safe heat levels at the treatment rim. Therefore treatment with microwaves takes longer than RF to produce coagulative necrosis. **RF, however, has a much hotter central area with a very quick decline in temperature as the distance increases from the treatment needle.** This results in faster generation of the necrotic lesion but of a smaller area (Perlmutter et al, 1993).

Experimental Studies

In a series of preliminary studies on animals and ex-vivo human prostates it has been shown that **the TUNA system can create 1-cm necrotic lesions without difficulty in the prostate with no damage to rectum, bladder base, or distal prostatic urethra** (Goldwasser et al, 1993; Ramon et al, 1993). Other studies showed that the lesions are accurate with sharp delineation from the untreated areas (Schulman et al, 1993). These authors also showed that the lesion appeared first as a hemorrhagic lesion along the needle path, with slight discoloration in the surrounding area. Necrosis was maximal at 7 days, with fibrosis having developed by 15 days.

In an elegant neurohistochemical study, Zlotta and colleagues (1997) removed prostates from patients scheduled for prostatectomy 1 to 46 days after TUNA. Immunohistochemistry was used with anti–S-100 protein and neuron-specific enolase for nerve staining and anti–prostate-specific antigen and antidesmin for glandular and muscle cells. They showed that the maximal lesion size ranged from 10×7 to 20×10 mm^2 and that there was destruction of all tissue components. The lesions were accurately positioned 0.3 to 1.0 cm from the urethra, which remained undamaged. **In the treated area there was an absence of staining for prostate-specific antigen, smooth muscle actin, and α-adrenergic neural tissue. Even in specimens removed 24 hours after TUNA, no positively staining nerve cells were seen in the treated areas.**

It has also been shown (Issa et al, 1996) that there may be sequential damage to different types of nerve endings. **Nitric oxide synthase receptors were found to be most vulnerable to thermal damage, which occurred earliest, with damage to the α-adrenergic receptors maximal at 1 to 2 weeks.**

The temperatures achieved in the largest area have been studied by Rasor and coworkers (1993) using an infrared temperature monitor in an ex-vivo animal model. They showed that the central core of the lesion around the tip of the lesion reached 90° to 100° C. Treatment times of 5 to 7 minutes were required to produce coagulation necrosis in the treatment zone. Dosimetry studies have shown that the temperatures at the edge of the zone were 50° C.

Instruments

The generator produces low-level monopolar RF waves of about 490 kHz, which produce temperatures of about 100° C in the target area. The RF generator is connected to the TUNA catheter, which has changed somewhat in design since it was first manufactured.

The TUNA catheter is, in fact, a specifically designed endoscopic instrument. This has evolved from what was a device through which a panendoscope lens could be inserted. A number of other changes have also been made. The most up-to-date version of the TUNA catheter is called the Pro Vu system, and part of this device is reusable, unlike previous models (Fig. 93–2; see also Fig. 93–1). The new system also contains a markedly improved optical system. Previously, the needles were introduced either blindly or under transrectal ultrasound (TRUS) guidance, which had the advantage in the latter case of seeing how close to the surrounding tissues the needles lay. However, an adequate visualization of the needle entering the prostate tissue gives the urologist a better idea of the treatment area. The final change concerns the angle between the catheter and the needles, which is at present not fixed. This means that a high bladder neck that is hypertrophied or a genuine median lobe enlargement can now be treated easily by this technique.

The configuration of the needles within their protective sheath ensures that the treatment area is deep inside the prostatic lobes, and this ensures that the prostatic urethra is spared. Because there is a limited number of nerve endings in the prostatic glandular tissue and because the higher concentration of nerve endings immediately underlying the urethral epithelium remains undisturbed, topical anesthesia can be used with the patient experiencing only moderate discomfort. In addition, postprocedural irritative urinary symptoms are kept to a minimum.

Treatment

The patient is placed in the lithotomy position and topical anesthesia with 2% intraurethral lidocaine (Xylocaine) is achieved. The best result is attained by applying a penile clamp for 10 minutes and by giving intravenous sedation if required. There is a variation from institution to institution as to the optimum form of anesthesia; for many, what is described previously is satisfactory, but some prefer spinal or even general anesthesia, particularly for their initial experience with the technique. In other cases, a local prostatic block, either transperineally or transrectally, may be the method of choice.

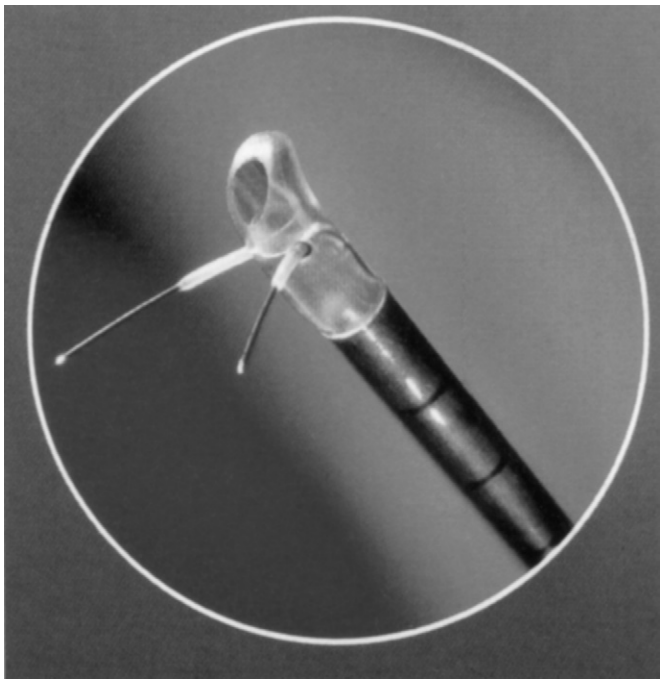


Figure 93–2. Deployment of radiofrequency needles in transurethral needle ablation of the prostate. (Courtesy of Neo Vitalis Ltd, Southport, UK.)

With the new modifications **the TUNA catheter is advanced under vision with the 0-degree fiberoptic telescope, which also allows the urologist to see the needles being advanced accurately into the prostate. The exact position within the prostate of the needle tip can be visualized by TRUS.** Preprocedural assessment of the size of the prostate by this method allows calculation of the length of deployment of the needle within the prostate; this can also be done at the beginning of the procedure, as described earlier, with the ultrasound showing the exact position of the needle tip. It is important to remember that the thermal lesion may extend for up to 5 to 6 mm beyond the position of needle deployment with lesions measuring up to 20 × 10 mm. When the position is deemed satisfactory, the Teflon shield on the proximal part of the needle is advanced to protect the urethral epithelium and the underlying tissue. Therefore the tip of the needle should not lie within 5 to 6 mm of the outer rim of the prostate, and the urethra is protected by the shields that extend from 5 to 6 mm from the TUNA catheter itself.

The number of lesions depends on the size of the prostate, but because there are two needles each time power is switched on in the generator two lesions are produced. It is usually advised that one pair of lesions should be used to treat 20 g of prostate tissue; it can also be expressed in terms of length, with one pair of lesions, or treatment plane, being used for less than 3 cm of prostatic urethral length, two planes for 3 to 4 cm, and one extra plane of treatment for every extra centimeter of urethral length. The procedure is then repeated in the opposite lobe.

The RF power that is delivered is 2 to 15 W for 5 minutes per lesion. In earlier models the treatment was begun at a low power, but now the whole thermal process is automated, with temperature levels at treatment areas preset. The temperature at the tip of the needle varies from 80° C to 100° C. The urethral temperature is kept below 46° C, and the temperature in the lesion is sustained for the treatment period.

At the end of the procedure, some urologists like to leave a urethral catheter in overnight; others do not put in a catheter and allow the patients to go home after they have voided and feel that they are emptying their bladder.

Clinical Results

Table 93–1 shows the results of the total world experience in the use of TUNA. There is a wide variety in the number of patients in each series and in the length of follow-up. Of note is that most are open series, with a minority of randomized studies (Issa and Oesterling, 2000). Although the inclusion and exclusion criteria are the same in most series, they are not exactly the same and are not as strict as those in studies testing α-adrenergic blockers and 5α-reductase inhibitors. The size of the studies varies from 12 to 130 patients, and, in many cases, the number of patients observed for the longest period of time consists of less than 50% of the original sample, which makes it difficult to draw definite conclusions. However, when looking at them all together, a number of points can be considered.

A total of 546 patients have been observed for 12 months, with an increase in the mean PFR by an average of 6 mL/sec, representing an average improvement of

Table 93–1.

Studies of Transurethral Needle Ablation with 12-Month Follow-up

STUDY	NO. PATIENTS	Symptom Score		Peak Urinary Flow	
		Preop.	Postop.	Preop.	Postop.
Roehrborn et al, 1998	130	23.7	11.9	7.8	14.6
Bruskewitz et al, 1998	65	24.7	11.1	8.7	15.0
Schulman et al, 1993	36	21.6	7.8	9.9	16.8
Campo et al, 1997	72	20.8	6.2	8.2	15.9
Ramon et al, 1997	68	22.0	10.0	8.8	11.5
Rosario et al, 1997	58	22.0	10.0	8.8	11.5
Steele and Sleep, 1997	41	22.4	7.0	6.6	10.2
Millard et al, 1996	20	19.0	8.2	3.0	11.4

77%. The mean symptom score decreased by an average of 13.1 symptom units, which is an average improvement of 58%. Although there was consistency of the general improvements, there was a range. The greatest improvement in the mean PFR was 9.2 mL/sec (Giannakopoulos et al, 1996), and in the mean symptom score it was 15.4 symptom units (Steele and Sleep, 1997). The least improvement in mean PFR was 2.7 mL/sec (Rosario et al, 1997) and in symptom score it was 10.8 (Millard et al, 1996). Although the numbers in patients observed for longer are less (176 for 24 months and 88 for 36 months), the mean improvements appear to be maintained (Issa and Oesterling, 2000).

In the U.S. randomized trial comparing TUNA with TURP, 65 patients were treated by TUNA and 56 by TURP (Bruskewitz et al, 1998). At 1 year, 59 of the TUNA group (90%) and 47 of the TURP group (84%) were available for evaluation. **In the TUNA group the symptom score improved from 24.7 to 11.1 (13.6 symptom units) and the PFR from 8.7 to 15.0 mL/sec (6.3 mL/sec). In the TURP group, the symptom score improved from 23.3 to 8.3 (15.0 symptom units) and the PFR improved from 8.4 to 20.8 mL/sec (12.4 mL/sec).** The reasons for patients being lost to follow-up are clearly stated, but it was because of ineffectiveness in only 2 patients (3.1%) of the TUNA group and none of the patients treated by TURP. The treatment was found to be effective and safe. The complication rate of TUNA was low, in both the short and the long term; the most commonly reported adverse events were bleeding (32.3%), urinary tract infection (7.7%), and urethral stricture (1.5%). There was no adverse effect of any kind on sexual function in patients treated by TUNA.

There are some additional long-term studies that are of interest. Zlotta and coworkers (2003) entered 188 consecutive patients into a study; there were 5-year data on 121 of these. At the 5-year assessment, 41 of the 176 patients who were evaluable (2 dead, 10 lost to follow-up) required additional treatment after TUNA (23.3%). Although there were 5-year data on 121 patients, and this was defined as a 5-year follow-up, the 10 patients on whom there were only 4-year data were also included, giving a total of 131 patients**. The mean IPSS decreased from 20.9 to 8.7, with tight standard deviations but a range at long-term follow-up of 2 to 20. The PFR improved from 8.6 to 12.1 mL/sec with a range at long-term follow-up of 6.5 to 19.2 mL/sec, once again giving the impression of quite a wide scatter of results. Although the drop in the mean IPSS is 12.2, which is an impressive decrease, the improvement in PFR is a less impressive decrease, being 3.5 mL/sec and comparable to that achieved by medical management at the same time point.**

In another study from the United States (Hill et al, 2004), 121 men were enrolled in a prospective, randomized, multicenter clinical trial; 65 (54%) were randomly selected to receive TUNA and 56 (46%) were selected to receive TURP. It was reported that 9 of the 65 men (14%) required further intervention in the TUNA cohort, compared with 1 of the 56 men (2%) in the TURP cohort. The requirement for additional medical management in the TUNA cohort was not stated, presumably explaining the difference observed between this study and that described in the previous paragraph. Although this was reported as a 5-year study, only 18 of the 65 men in the TUNA group (28%) and 22 of the 56 (39%) in the TURP were evaluable at 5 years. This makes the 5-year data difficult to interpret despite the highly significant statistical differences described by the authors. At 3 years, the mean IPSS had decreased from 24.0 to 15.2 in the TUNA group and from 24.1 to 10.1 in the TURP group. The mean PFR had improved from 8.8 to 13.0 mL/sec in the TUNA group and from 8.8 to 19.1 mL/sec in the TURP group.

A cost comparison of medical management and TUNA for treating BPH over a 5-year period was performed by Naslund and colleagues (2005). They constructed a cost analysis model using published costs for tamsulosin, finasteride, TUNA, and TURP. They found that over the 5 years tamsulosin was less expensive than TUNA and that finasteride cost the same as TUNA. Combination therapy was more expensive, reaching a break-even point at 2 years and 7 months of treatment. The authors also calculated that TURP is more expensive than TUNA for achieving improvements in IPSS but less expensive for improving PFR.

A meta-analysis of trials of TUNA for treating symptomatic BPH has been reported (Boyle et al, 2004). Meta-analyses are dependent on the data that are put into them. In the case of TUNA, the trials analyzed were often poorly constructed, with inadequate numbers, and not randomized. **In fact, there were 2 randomized trials, 2 nonrandomized observational protocols, and 10 single-aim observational studies. One thing that was consistent, however, was that in all studies the patients had severe LUTS, the mean IPSS at entry being greater than 20. The effect of TUNA was to halve the mean IPSS at 1 year. The shortage of long-term studies makes it difficult to draw specific conclusions, but although there was a tendency for the IPSS to increase in the long term the 50% decrease was maintained. The PFR increased by about 70% from baseline to 1 year. It tended to decline over time, but a 50% or greater improvement was maintained.** One question has not been answered: although the mechanism of action of TUNA is an adequate explanation for the early improvements, how can it explain any positive long-term effect?

Pressure-Flow Studies

There have been six studies that examined relief of urodynamically proven obstruction as an end point, and these are summarized in Table 93–2. The number of patients in each group varies considerably (from 12 to 108), as does the length of follow-up. The largest number of patients are evaluable at 3 months (253), with smaller numbers having been observed to 12 months (140)

Table 93–2.

Pressure-Flow Studies after Transurethral Needle Ablation with 12-Month Follow-up

STUDY	NO. PATIENTS	Detrusor Pressure at Maximum Flow	
		Preop.	Postop.
Campo et al, 1997	72	85.3	63.7
Steele and Sleep, 1997	29	92.4	72.9
Rosario et al, 1997	39	97.0	84.0
Millard et al, 1996	20	70.7	59.9

or even longer. All patients had pressure-flow studies performed before and after treatment by TUNA.

At 3 months the average detrusor pressure (Pdet) at PFR was 85.4 cm H_2O, which 3 months after treatment had decreased to an average of 64.8 cm H_2O (average decrease of 20%). The range at 3 months was 53.2 to 79.0 cm H_2O. It is difficult to draw too many conclusions from these average figures because of the variability in each series, but they do point to the fact that there is a decrease in the Pdet at PFR in most series, if not quite relieving obstruction reliably in every case. At 12 months the average Pdet at PFR was 91.6 before treatment and 73.5 after treatment. In each series there was a small decrease in the difference that had been observed at 3 months.

In another urodynamic study (Minardi et al, 2001), a small number of patients (24) were observed to 24 months. The authors showed that there was initially no change in the prostatic volume or the prostate-specific antigen levels and that pressure-flow studies showed a reduction in the mean opening pressure and Pdet at PFR. **This led them to speculate that the ideal patient for TUNA was a man younger than 70 years with a prostatic volume of less than 6 mL, with a pretreatment Pdet at PFR of less than 60 cm H_2O and residual volume of less than 100 mL.**

Adverse Effects

The adverse effects that occurred in the U.S. randomized study (Bruskewitz et al, 1998) have been alluded to earlier. **By far the most common complication reported, however, is post-treatment urinary retention, occurring at a rate between 13.3% and 41.6%.** It can be expected that within the first 24 hours about 40% of patients experience urinary retention. The second most common adverse event reported is that of irritative voiding symptoms, occurring in about 40% of patients in the early period after treatment. Given the mechanism of the TUNA treatment, this high rate is surprising, but the symptoms are usually mild, lasting between 1 and 7 days.

Urinary tract infection was not commented on in every series, but it was reported in up to 3.1% of patients. It is advisable to give a prophylactic antibiotic to cover the treatment, using whatever regimen the particular urologic department uses for other endoscopic procedures. In this way symptomatic infections leading to epididymo-orchitis or significant sepsis can be completely prevented. Urethral strictures are uncommon, with the highest rate reported as being 1.5%. Hematuria occurs in a large number of treated patients but is almost always mild and short lasting. Patients who are taking aspirin, in whatever dosage, should be advised to refrain from taking it for 7 days before the procedure.

Sexual dysfunction is rare after TUNA. Urinary incontinence has not been reported in any series.

Reoperation

The reoperation rate must be compared with that of TURP. **Although a 14% requirement for reoperation because of lack of efficacy of the primary treatment with TUNA may seem low, it occurred in less than 2 years** (Schulman and Zlotta, 1995). In addition, the 12.7% incidence reported by Steele and Sleep (1997) occurred inside a 2-year period. In the multicenter study reported by Ramon and colleagues (1997), 9 of 76 patients were deemed to have experienced failure of the procedure because of an absence of improvement in PFR. Eight of these patients had no symptomatic improvement, but 5 had an improvement in quality of life.

Indications

The patient most likely to benefit from TUNA would be one who had lateral lobe enlargement and a prostate of 60 g or less (Naslund, 1997). Larger glands can be treated, but more time has to be spent treating each 1-cm segment. Patients with larger prostates, purely bladder neck hypertrophy, or median lobe enlargement are not ideal patients to be treated in this way, but they can be treated; for example, median lobe enlargement can be treated by rotating the TUNA catheter so that the needles point posteriorly, with special care being taken in assessing the depth of their penetration into the prostate.

Summary

The TUNA procedure is simple to perform, and the technology is improving all the time. As long as it is performed carefully, with special emphasis on placement of needles and awareness of the depth of their penetration, complications can be kept to a minimum. With the combination of improved endoscopic visualization of the needles and placement using TRUS, efficacy can be high, with **an average improvement in the mean symptom score of 13.1 symptom units and in the mean PFR of 6 mL/sec to be expected at 12 months. A treatment by some other modality can be expected in 12.7% to 14% of patients within 2 years. TUNA can be given with the patient under topical anesthesia or local prostatic or perineal block, and so it is useful in poor-risk cases also. About 40% of patients have retention within the first 24 hours. The long-term efficacy of the treatment has not been clearly evaluated, with no large series of patients having long-term follow-up.**

TRANSURETHRAL MICROWAVE THERAPY

Transurethral microwave therapy has been much evaluated in the past decade and has been widely used. Many urologists have a high regard for its usefulness in treating patients with LUTS, but, for many others, it has no place in the therapeutic line-up. TUMT has been examined clinically in many centers throughout the world, although the very large number of patients who have been entered into open noncomparative studies may surprise some urologists. The rationale for its effect on symptoms has also been studied carefully by authors from different centers, which is unlike that of many of the other so-called minimally invasive treatment modalities. In addition there has been an evolution in the



Figure 93–3. The Prostatron device. (Courtesy of Urologix, Inc, Minneapolis, MN.)

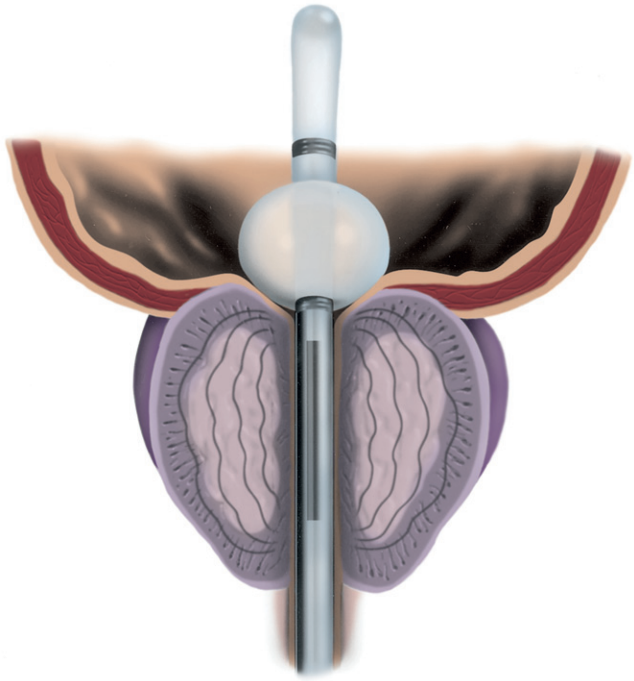


Figure 93–4. The Prostatron antenna, treating the prostatic transition zone. (Courtesy of Urologix, Inc, Minneapolis, MN.)

technology of TUMT (Figs. 93–3 and 93–4), from low-energy to high-energy application, perhaps indicating that this technique has a future in the treatment of LUTS.

The current transurethral method has developed from the early transrectal devices that supplied heat ranging from 42° C to 44° C. The results with this early form of treatment were rather disappointing, and transurethral catheters were developed that would allow higher temperatures to be used while cooling the urethral mucosa. In one of these devices currently used, the Prostatron, the cooling fluid in the catheter maintains the urethral temperature at about 44° C or lower while producing temperatures within the prostate of up to 70° C. The early experimental studies (Magin et al, 1980; Harada et al, 1985; Leib et al, 1986) showed that microwave energy could create high temperatures in the prostate of laboratory animals without damaging the surrounding structures.

Early clinical results using transrectal probes suggested some efficacy (Yerushalmi et al, 1985; Servadio et al, 1987), but overall results were disappointing when tested against sham controls and did not demonstrate that further use of this type of treatment would be beneficial to patients (Zerbib et al, 1992). Later changes resulted in the transurethral method of applying microwave treatment, and this has been further developed, leading ultimately to the sophisticated machines that are being used today. The two most commonly used are the Prostatron and the Targis, but there are several others, all producing similar effects. The Prostatron has three different types of software programs, ranging from relatively low to higher energy: the Prostasoft 2.0, 2.5, and, more recently, 3.5.

Method of Action

The effect of TUMT on prostatic tissue has been studied widely, and a number of different theories, none mutually exclusive, have been presented. These cover heat changes and differential blood flow in the prostate, damage to the sympathetic nerve endings, and induction of apoptosis.

Temperature and Blood Flow

Several studies have been performed that described the interstitial thermal mapping in canine and human subjects (Astrahan et al, 1991; Kaplan et al, 1992; Roehrborn et al, 1992; Devonec et al, 1993). These have all shown that **the temperature varies in the prostatic adenoma, with the area around the urethra being relatively spared from high temperatures and with surrounding tissues such as the rectum also being unaffected.** Some of these studies involved a limited number of measurement sites, the use of periodic rather than continuous temperature monitoring, and difficulties with positioning of the temperature probes.

In an extensive study involving careful and accurate placement of probes, Larson and Collins (1995a) measured temperature gradients within the prostate. Their interstitial thermal mapping method involved the placement of thermosensors using a biplane ultrasound imaging system; this allowed accurate needle

placement in both the anteroposterior and the longitudinal dimensions. In their study they increased the microwave power by 5 W, reaching a maximum of 36 W in 11 minutes and then maintaining an average power of 31.4 W. **In one representative patient, urethral temperature reached a nadir of 21.7° C,** then rose progressively to 40.1° C, and remained between 38.7° C and 41.1° C for the duration of the treatment. Rectal temperature did not show an initial decline but remained at 37.7° C to 39.1° C throughout. Prostatic temperature at a distance of 5 mm radially from the urethra reached 62.4° C about 7 minutes after the initial power maximum and remained between 60.9° C and 68.7° C. At 10 mm radially from the urethra, the average temperature was 50.5° C, whereas at 15 mm it was indistinguishable from urethral or rectal temperature (Larson and Collins, 1995a; Larson et al, 1998b).

Osman and colleagues (2000) performed a study in 13 patients in which they recorded maximum mean peak temperatures of 66.8° ± 13° C at 4 mm from the urethra using the Targis device. No temperature higher than 45° C was recorded beyond 15 mm on either side of the urethra anteroposteriorly or beyond 16 mm on either side of the urethra transversely. **Using gadolinium-enhanced magnetic resonance imaging (MRI), they found postprocedural perfusion defects with means of 28.1% ± 2.1% of the total gland and 63.6% ± 34% of the transition zone volume.**

Histopathologic changes were found to be related to the temperature rises in different parts of the prostate (Larson et al, 1996). **They showed that tissue exposed to a minimum of 45° C** for about 60 minutes suffered hemorrhagic necrosis with uniform extirpation of tissue. The border between viable and necrotic tissue was sharply defined. The histologic changes were related to temperature rises within the prostate, and it was also believed that differences in the thermal sensitivity between stromal and epithelial elements appeared unlikely to account for differences in treatment outcomes. However, there has been some disagreement about these findings. In an evaluation with MRI, Nordenstam and coworkers (1996) did not find that there was significant necrosis in the prostate. Similarly, D'Ancona and colleagues (1999), using the high-energy Prostasoft hardware (Larson and colleagues used the Targis T3), found that histologic parameters were moderately predictive of response; large prostates and prostates with a high epithelium to stroma ratio responded better to high-energy TUMT.

With the use of color Doppler ultrasonography, blood flow changes were estimated during microwave treatment in 2 patients with BPH (Larson and Collins, 1995b). At rest, a comparatively low level of blood flow was seen. **As heat energy was delivered, the blood flow rose in a marked and sustained manner. This increase was seen in the posterior half of the prostate, including the peripheral zone and the posterior half of the transition zone. Marked recruitment of posterior and periurethral vessels was noted. It was also believed that peripheral resistance within the prostatic vessels was reduced.** Therefore these authors in a series of studies linked temperature changes to histologic and blood flow findings. However, the blood flow alterations were performed in only 2 patients, and experimental confirmation with more accurate methods of blood flow estimation is required.

In another study, Larson and coworkers (1998a) **showed that in terms of heating patterns, the Targis antenna (operating at a frequency of 902 to 1928 MHz) gave a more efficient delivery of thermal energy than the Prostatron antenna (operating at a frequency of 1296 MHz).**

Sympathetic Nerve Degeneration

In a histologic study, 10 patients underwent TUMT and some days later had an open prostatectomy (Perachino et al, 1993). Multiple prostatic samples were taken for examination from the periurethral prostatic tissue to a depth of 2.5 cm. The samples were stained with hematoxylin and eosin and with S-100, neuron-specific enolase, and vimentin. The authors found microabscesses, epithelial necrosis, and vasculitis in the prostate. **Compared with controls, it was found that nerve fibers were disrupted, with axons rarely being seen. This study suggested that thermal damage to the adrenergic fibers was behind the improvement in symptoms after TUMT.** The authors did not attempt to quantify their findings. They also believed that the variable response sometimes noted was due to the variable numbers of nerve endings seen in different parts of the prostate.

Support for this theory came from an investigation into human prostatic α_1-adrenergic receptor density after TUMT. Radioligand-binding assays using ^{3}H-prazosin were performed on prostatic tissue from 25 patients, 10 of whom had received TUMT. Binding was saturable, and a single class of high-affinity binding sites was identified in all cases. **In the controls (untreated by TUMT), the mean α_1-adrenergic receptor density** was 96.4 fmol/mg compared with 71.3 fmol/mg in those who had undergone TUMT, a statistically significant difference. The mean dissociation constants were 0.56 in both groups (Bdesha et al, 1996). These results suggested that there was a significant reduction in prostatic α_1-adrenergic receptor density in the region of the prostate that had been subjected to maximal heating.

Another study has been performed to test this hypothesis, but using a different methodology. Ten patients had TUMT 1 week before scheduled TURP. Biopsy samples were taken, 5 to 6 mm deep, and stained with hematoxylin and eosin and with anti–PGP 9.5, which is a nonspecific neural marker gene product that is immunoreactive to all neurons. With this method, nerve fibers were found in the urethral epithelial layer, lamina propria, and smooth muscle layer of controls. **Almost all of the TUMT biopsy samples had nerve fibers in the epithelial layer and the lamina propria, but there were no nerve fibers in the smooth muscle layer in virtually all of the specimens** (Brehmer et al, 2000).

Induction of Apoptosis

Seven patients, all with glands weighing more than 100 g, were selected for open prostatectomy, and all had TUMT with the ECP (Comair, Sweden) 915-MHz equipment 2 hours to 1 week before surgery. Specimens were stained with hematoxylin and eosin, and apoptosis was verified by the terminal deoxynucleotidyl nick-end labeling (TUNEL) technique in sections showing histologic changes suggestive of apoptosis, such as pyknotic nuclei and chromatin segregation. Necrotic areas were frequently seen in the prostate to a depth of 4 to 5 cm. Outside these necrotic areas, normal and apoptotic areas were interspersed, the latter confirmed by TUNEL. The author found that **the area of tissue damage seen after TUMT was relatively small compared with the volume of the prostate** (Brehmer, 1997). The heat was implicated as the cause of the apoptosis, but there was no speculation about the exact mechanism whereby it brought this about.

In another study, Brehmer and Svensson (2000) performed culture of prostatic stromal cells from patients undergoing TURP. These were then stained for several cytoskeletal proteins and assessed for apoptosis by light microscopy of cells stained with the

Giemsa nuclear stain, by transmission electron microscopy, and by measurement of caspase-3–like activity, the latter being one of the main effects of apoptosis. The cell cultures were exposed to moderate hyperthermia (47° C). **Twenty-four hours after heat exposure, 76% of the cells were apoptotic, with only 14% of the cells being necrotic.** The caspase activity (indicating increased apoptosis) had increased to about sixfold by 24 hours after heat treatment. The application of moderate heat for a longer period was found to be the most effective way of inducing apoptosis. Higher temperatures for shorter times resulted in a greater degree of necrosis. It was believed that, in vivo, other factors might modify the apoptotic result, such as stromal-epithelial interactions or heat dissipation by increased blood flow.

Thus these studies have shown that there may be several factors involved in the mode of action of TUMT. High temperatures cause necrosis of prostatic cells, whereas lower temperatures for longer periods of application induce programmed cell death or apoptosis. It is possible that the greater prostatic blood flow that has been found during treatment may be an attempt to dissipate the heat and that this may modify the induction of apoptosis. There is also evidence that TUMT causes disruption of α_1-adrenergic receptor nerves in the smooth muscle of the prostate, another possible cause of the beneficial effect of TUMT, but this effect depends on the number of nerve endings in the treated area of the prostate. A further study investigating the combination of these findings and assessing the relative contribution of many of them was reported by Bolmsjo and coworkers (1996).

Clinical Results

The literature on TUMT is characterized by a large number of open studies, much more than any other technology-based treatment for BPH. In addition, many of them are short-term studies; some of those that purport to be longer term have in fact only a small percentage of patients who have reached what might be called long-term follow-up. However, there are also many carefully performed comparative studies, both against sham treatment and against TURP. The lesson that can be learned from these studies about TUMT is that machines delivering higher power yield better results than those delivering lower power. At the same time it might be said that this use of higher energy makes the procedure more complicated in that there is a greater requirement for sedation or analgesia.

Two of the earliest reports investigated, in a small number of patients, the use of the lower energy Prostatron device. In the first of these, **37 patients were treated and at 3 months had an improvement in Boyarsky symptom score from 12 to 8 and an increase in the PFR from 8.4 to 10.8 mL/sec** (Devonec et al, 1991). These results were statistically significant if perhaps not quite so clinically impressive. In another study, 19 patients with LUTS who were not in retention were treated (Carter et al, 1991), but, at 12 weeks, only 9 of these patients were evaluable. The mean symptom score had improved from 12.0 to 2.8 and the mean PFR from 8.2 to 14.3 mL/sec. However, this study could be criticized for the fact that fewer than half of the patients were evaluable at 12 weeks and that the standard deviations of the mean PFRs were very large. The results were elegantly presented in terms of histopathology and technique and spurred many urologists to assess the TUMT in their own departments.

At this stage in the development of the technique the concept was specifically that heat treatment even with lower energy caused necrosis of prostatic tissue. The other ideas about sympathetic nerve damage and apoptosis were introduced later.

Open Studies

In an attempt to find medium- to long-term efficacy results, only studies with a follow-up of 1 year or greater are reviewed. A study performed with the Prostatron 2.0 software (Blute et al, 1993) evaluated 150 patients; 44% of these required oral or intravenous sedation. There were 150 patients, and results were presented from 118 who had Madsen symptom scores before treatment and at 12 months and from 104 who had PFRs. **The American Urological Association (AUA) Symptom Index** (AUA-7 or AUASI, equivalent to the IPSS) **score improved from a mean of 13.7 to 5.4 and the PFR improved from 8.5 to 11.3 mL/sec. A total of 43 patients (36%) required catheterization for urinary retention; 63% required catheterization for 1 week or less, but it was necessary for more than 30 days in 4 patients.** In another study with the same device, 30 patients were treated and 20 of these were evaluable at 1 year. The mean symptom score improvement was from 16.5 to 6.9, and the PFR improved from 7.2 to 10.7 mL/sec (Homma and Aso, 1993). The study reported in 1996 by Baba and coworkers entered 135 patients into treatment with the same device, and although they refer to "durability of response," it can be seen that less than 20% of the total are followed to 2 years and less than 50% for 12 months. They noted that by 2 years 61 patients had been lost to follow-up. The same 3 mL/sec improvement as just mentioned was noted in those evaluable at 1 year.

A 4-year open study observed 187 patients treated with the Prostatron software 2.0 (Hallin and Berlin, 1998). At the end of the 4-year period, 56 were evaluable, although only 9 were truly lost to follow-up because the fate of all the rest was known. A total of 97 patients had needed further treatment for their LUTS. The satisfaction rate was 62% at 1 year, 34% at 2 years, and 23% at 4 years, with 66% having required further treatment and 11% being dissatisfied at the same time point. The authors believed that the patients who would respond best to this treatment were those with a PFR of 10 mL/sec or more or those with an initial irritative score in the lower range. The fact that many patients do not respond to TUMT treatment but that some do for long periods of time was commented on. The patterns of treatment after the introduction of TUMT in Sweden were reported on by Blomqvist and coworkers (1997), who found that the number of TUMT procedures performed in Sweden increased rapidly after the technique was introduced but then decreased equally rapidly. Three years after the introduction of drugs for BPH, the number of men receiving drug treatment was greater than the number of men having both TURP and TUMT annually.

Pressure-flow analysis has also been performed on patients being treated by the lower-energy TUMT (De la Rosette et al, 1995; Tubaro et al, 1995). These authors found that **there was no noticeable change in the Pdet at PFR at 6 months but that there was a marginally greater improvement (although not statistically better) in those with constrictive obstruction as opposed to those with compressive obstruction.** Finally, a series of patients being treated with the Prostatron 2.0 were observed to 5 years (Keijzers et al, 1998). Of the 231 patients treated, only 89 patients reached 5 years without requiring further treatment for BPH. The total number of patients treated in six European centers was 1092. Overall, the improvement in PFR was between 2 and 3 mL/sec and the re-treatment rate relatively high (Francisca et al, 1999).

It was thought that by increasing the energy the results achieved with TUMT could be improved. Of 85 patients treated with the Prostasoft 2.5 protocol, 74 were evaluable at 1 year (De Wildt et al,

1996a). **The mean Madsen symptom score improved from 13.9 to 5.8, and the mean PFR increased from 9.4 to 14.9 mL/sec. The Pdet at PFR improved from a mean of 63.6 to a mean of 38.9 cm H_2O** at 26 weeks. A further study of 116 patients using the same protocol was reported by a European group (De la Rosette et al, 1996), with 67 patients having reached 52 weeks of observation. The Madsen score improved from 13.6 to 4.9 and the PFR from 9.6 to 14.5 mL/sec. More recently, the Prostasoft 3.5 protocol has been introduced and has been found to be well tolerated (Francisca et al, 2000b). Early results of its use in a small number of patients in urinary retention have indicated some value (Floratos et al, 2000).

A large open study was performed into the use of the 30-minute algorithm for high-energy TUMT with the Prostasoft 3.5 protocol (De La Rosette et al, 2000). Of 108 men treated, 86 were evaluable at 6 months (with only 41 at 1 year). At 6 months, the IPSS had improved from 20.0 to 9.3 and the PFR improved from 9.5 to 14.6 mL/sec. The Pdet at PFR decreased from 58.7 cm H_2O at baseline to 46.9 cm H_2O at 6 months. As reflected on the Abrams-Griffiths nomogram, this represented a shift from the obstructed to the equivocal zone for most patients. The mean duration of catheterization after treatment was 17.9 days, with a range of 6 to 62 days. The authors commented that at 3 months all treatment-related complications had disappeared. It was noted that the faster treatment was an improvement on previous methods from the viewpoint of tolerability to patients but had the same subjective and objective improvement as the Prostasoft 2.5 protocol.

In a study using the high-energy T3 Urologix device it was found that at 1 year there was a 63% improvement in symptom score and a 64% improvement in PFR. Urodynamic analysis showed that there was a better improvement in patients with marginal obstruction rather than unequivocal obstruction (Javlé et al, 1996).

A full urodynamic evaluation of the Prostalund Compact Device was carried out by Alivizatos and coworkers (2005). **In this study 38 patients were evaluated, 19 of whom had an indwelling catheter. The treatment lasted a mean of 43.1 minutes, and the maximum intraprostatic temperature achieved was 58.7° C; a mean of 18.4 ± 14.3 g of prostatic tissue was destroyed. All of the urodynamic parameters improved in the patients without a pretreatment catheter. The mean changes were IPSS from 21.5 to 6.5, PFR from 7.2 to 18.1 mL/sec, and Pdet at PFR from 87.5 to 48.4 cm H_2O. In those who had a pretreatment catheter, the PFR at 3 months was 13.2 mL/sec. This is a small series, but the results are encouraging.**

To complete the equipment types the Core Therm–monitored feedback TUMT was used in 102 patients, but only early results were presented, and, of note, the median catheter time was 8.5 days (David et al, 2004). The results of the Cooled Thermo Cath (Urologix) have been published in abstract form (Roehrborn et al, 2005), and again in a small relatively short-term study it is hard to draw too many conclusions, although at 6 months the symptom score improved from a mean of 21.0 to 8.3, with a less encouraging improvement in PFR, from 7.8 to 12.5 mL/sec.

In a prospective cohort study, 31 patients with acute urinary retention were treated with the Targis machine (Djavan et al, 1999a). **By 4 weeks, 29 of the 31 were able to void, with a median time to spontaneous voiding being 3.0 weeks. The flow rate gradually improved to a maximum at 12 weeks.** The authors suggested that this type of treatment is helpful in patients who present with acute urinary retention but are unsuitable for surgical treatment.

A further study attempted to determine the efficacy of high-energy TUMT in treating patients with medically refractory urinary retention secondary to BPH (Kellner et al, 2004). This was a relatively small series of 39 patients, all of whom received treatment. The mean prostate volume was quite large (75.2 mL), but the standard deviation was 57.6. The treatment was unsuccessful in 18%. **Of the 32 patients (82%) in whom success was achieved there was a mean of 1.6 voiding trials, and these patients required a catheter for a mean period of 4.1 weeks after treatment. Only 6 patients (15%) were able to stop their medication for BPH. The follow-up for this study was relatively short, 18 ± 10.2 months.**

Berger and colleagues (2003) evaluated the use of TUMT in a similar but larger group of patients. A total of 78 patients in poor general health presented with acute urinary retention secondary to BPH with a mean prostatic volume of 53.9 mL. The mean follow-up was 34 months (range 6 to 42 months), with 38.5% lost to follow-up (30 patients), but early results in these were evaluable. Three months after the procedure, 68 (87.1%) were able to urinate spontaneously. Of the 68, 5 (7.3%) developed a further episode of retention within 2 years. The catheter was in place for a mean of 21 days, with 6 patients requiring prolonged catheterization. **It can be seen therefore that treating patients in acute urinary retention with TUMT is a possibility, but the requirement for maintaining medical therapy is a cost burden that may limit its acceptability.**

Long-term results are becoming available. Trock and colleagues (2004) reported the long-term pooled analysis of results using the Targis cooled thermotherapy system. Although the article is entitled results of 3 months to 4 years, only 171 of 540 patients had symptoms evaluable at 4 years and only 67 of 524 had a PFR result. In fact, there is no parallel between the number of patients who had a symptom score result or a PFR result at any given time point with a significant dropoff in the number of flow rate results occurring at 2 years. The 4-year results must be viewed with some caution; the mean symptom score fell from 20.91 to 11.54, and the mean PFR rose from 7.91 to 10.94 mL/sec. It was not possible to conclude how many patients dropped out of the study because of lack of efficacy or how many required alternative treatment. In another study using the same technology Miller and colleagues (2003) reported on 5-year data. Of note was that they previously reported on their 1-year and 3-year results in separate publications, but even in this report only 132 of 150 were evaluable at 1 year, 90 of 150 at 3 years, and 59 of 150 at 5 years. The results are similar to those of the multicenter trial mentioned earlier. Other long-term results have been published by Ohigashi and colleagues (2002), showing that in their experience using the Prostatron the durability of successful results was limited.

In another 2-year study (Thalmann et al, 2002), 200 patients with urodynamically proven outflow obstruction were found to have derived benefit from TUMT. However, as observed clearly by the authors, 13 (6.5%) were lost to follow-up, 15 (7.5%) had died, and 43 (21.5%) required a second or third treatment (TUMT or TURP). Of the 10 patients who required a repeated TUMT, only 4 voided successfully without obstruction and without requiring another intervention.

TUMT versus Sham Procedure

A short-term, 3-month study compared TUMT (21 patients) with the Prostasoft 2.0 to a sham procedure (19 patients) (Ogden et al, 1993). The mean Madsen score changed from 14.2 to 12.8 in the sham group and 14.5 to 4.3 in the TUMT group. The PFR changed

from 8.6 to 9.2 mL/sec in the sham group and from 8.5 to 13.0 mL/sec in the TUMT group. A further study was performed in which 50 patients were randomly assigned to TUMT or sham treatment (De la Rosette et al, 1994). Twenty-four of the 25 patients in each group were evaluable at 12 weeks. In the sham group, the mean Madsen score had changed from 12.1 to 8.2 and in the TUMT group it changed from 13.2 to 5.9. The PFR had changed from 9.7 to 9.5 mL/sec in the sham group and from 9.6 to 13.0 mL/sec in the TUMT group. **In a U.S. study, 110 patients were randomly assigned to sham treatment (35 patients) or TUMT (75 patients)** (Blute et al, 1996). At 3 months the sham-treated patients had changed their symptom score from 14.9 to 10.8 and the TUMT patients' scores had changed from 13.9 to 6.3. The PFR had changed in the sham group from 7.4 to 9.4 mL/sec and in the TUMT group from 7.2 to 11.5 mL/sec.

A randomized controlled trial compared TUMT with the Prostatron 2.0 to a sham procedure (Nawrocki et al, 1997). There were three groups: group 1 received standard TUMT; group 2, a sham treatment; and group 3, no treatment. Patients were observed for 6 months after treatment. In group 1, the AUASI score improved from 19 to 9.5, in group 2 from 17.5 to 9.5, and in group 3 from 18 to 17. The PFR changed from 8.83 to 9.94 mL/sec in group 1, from 9.44 to 9.49 in group 2, and from 8.79 to 8.47 mL/sec in group 3. That is, there was no difference in the degree of improvement in PFR whether the patient had the machine switched on or off or had no treatment. However, the symptomatic improvement was greater than with no treatment, but once again it did not matter whether the machine was on or off.

In a further study, using the Dornier microwave, 147 patients received TUMT and 73 received a sham procedure (Roehrborn et al, 1998). The AUASI score changed from 23.9 to 18.0 in the sham group and from 23.6 to 12.7 in the TUMT group. PFR changed from 8.1 to 9.8 mL/sec in the sham group and from 7.7 to 10.7 mL/sec in the TUMT group, all observations being made at 6 months. Using the T3 Targis, 125 were treated with TUMT and 44 with a sham procedure and results reviewed at 6 months (Larson et al, 1998b). **The sham group showed a symptom score improvement from 21.3 to 14.3 and the TUMT group improved from 20.8 to 10.5. The PFR increased from 7.8 to 9.8 mL/sec in the sham group and to 11.8 mL/sec in the TUMT group.**

A further sham-controlled study was performed using the ECP system (Brehmer et al, 1999). In this study, patients' results were reviewed at 1 year, and a PFR improvement of 3.6 mL/sec was noted in the TUMT group, with a change of 0.4 mL/sec in the sham group. The changes in symptom score were similar in that there was a relatively smaller improvement in the sham group.

Finally, it is appropriate to include the results of a study in which α-adrenergic blockers were given either adjuvantly or neoadjuvantly in addition to TUMT with the Targis machine. It was found that the use of this treatment improved the early results achieved in the treatment of LUTS (Djavan et al, 1999b).

Sham-controlled studies are helpful in assessing whether the improvement noted after a specific treatment is merely a placebo effect. They are sometimes difficult to justify in that they involve a nontreatment arm, but several have been performed in the treatment of LUTS. In one, results were reviewed at 3 months; and those patients who had had a sham treatment and were not improved were given definitive TUMT (De Wildt et al, 1996b). Virtually all of the sham-controlled studies showed a greater improvement in the TUMT group except one (Nawrocki et al, 1997), in which the results suggested a placebo improvement only. In a further study, in which TUMT was compared with urethral catheterization the changes in symptom score and PFR were no different at 3 months (Mulvin et al, 1994).

TUMT versus TURP

Comparative studies between TUMT and TURP can help to define the exact place TUMT occupies in the management of BPH. For example, the weight of evidence was that it had a therapeutic benefit when compared with sham treatment or when viewed singly. However, it was unlikely that it would compete realistically with TURP in terms of symptomatic or flow rate improvement, and a more valuable approach might have been to concede the battle in terms of efficacy and concentrate almost entirely on post-treatment morbidity.

The earliest comparative trial against TURP randomly assigned 39 patients to TUMT and 40 patients to TURP (Dahlstrand et al, 1993). **One-year follow-up was possible in 25 and 22 patients, respectively. The mean Madsen symptom score improved from 11.2 to 2.7 in the TUMT group and from 13.3 to 0.9 in the TURP group. The PFR improved from 8.0 to 12.3 mL/sec in the TUMT group and from 7.9 to 17.7 mL/sec in the TURP group.** Both of these differences are statistically significant in favor of TURP-treated patients. Retrograde ejaculation occurred in 25% of the sexually active patients treated by TURP and in none of those treated by TUMT. In addition, the urethral stricture rate was 7.5% in the TURP group but zero in the TUMT group. The authors concluded that the improvements were not as great as with TURP but that the complication rate was much lower, although a detailed evaluation of all the complications would have been interesting.

In a follow-up study the results achieved by these treatments in 69 patients were evaluated at 2 years (Dahlstrand et al, 1997). There were 31 patients treated by TUMT and 30 treated by TURP who had reached 2 years of follow-up. In the TUMT group the Madsen-Iversen score had improved from 12.1 to 2.3 and in the TURP group from 13.6 to 1.2. The PFR increased from 8.6 to 12.3 mL/sec in the TUMT group and from 8.6 to 17.6 mL/sec in the TURP group. The authors carried out pressure-flow studies 6 months after treatment and found that the decrease in infravesical outflow resistance was greater after TURP than after TUMT. However, they also found that when the obstruction was calculated in terms of urethral resistance there was a statistically significant decrease in both groups. This is in keeping with other observations on pressure-flow and urethral resistance changes after TUMT, when previous studies had suggested that TUMT induced a change from constrictive to compressive obstruction, with an increased elasticity in the prostatic urethra (Höfner et al, 1993). The long-term complications were not discussed.

The higher-energy Prostatron 2.5 was also evaluated against TURP in a 6-month study (Ahmed et al, 1997). After TUMT the AUASI score changed from 18.5 to 5.3, and, after TURP, it changed from 18.4 to 5.2. The PFR actually worsened slightly from 10.1 to 9.1 mL/sec after TUMT and improved from 9.5 to 14.6 mL/sec after TURP. Pressure-flow studies showed a change from 98.5 to 105.6 cm H_2O in the TUMT group and from 96.7 to 48.8 mL/sec in the TURP group. Obviously, in this study not only did TUMT not relieve obstruction but it also was associated with a marginal worsening of flow rate. However, in spite of this, the improvement in symptom score was exactly comparable to the symptom score of TURP at 6 months. **Complications were higher in the TURP group, but prolonged catheter time (either clean intermittent or indwelling) was more marked in the TUMT group.**

A further comparative study was performed using the Prostatron 2.5 device and comparing results with those of TURP in a prospective randomized trial (D'Ancona et al, 1997). A total of 31 patients underwent TUMT and 21 underwent TURP, of whom 26 and 18, respectively, were evaluable at 12 months. **The Madsen symptom score improved from 13.3 to 4.2 in the TUMT group and from 13.8 to 2.8 in the TURP group. The PFR improved from 10.0 to 16.9 mL/sec in the TUMT group and from 9.3 to 18.6 mL/sec in the TURP group. Pressure-flow studies showed that whereas 62% of the TUMT group and 76% of the TURP group were obstructed before their respective treatments, at 6 months 40% and 15%, respectively, were still considered to be obstructed.** All of the TUMT procedures were done as day cases, and the average number of days in hospital for patients having TURP was 4.1. The length of catheterization was 4.1 days for TURP with a range of 4 to 5 days and was 12.7 days for TUMT with a range of 6 to 35 days. The incidence of urinary tract infections was 4% and 16%, respectively. Irritative voiding symptoms were present in 19% of those who underwent TURP and 29% of those who were treated by TUMT.

Later evaluation of these results took place at a mean of 2.4 years, although 17 of 31 patients who had TUMT and 12 of 21 who had TURP were all who remained in the study. Eight of the original 31 TUMT patients and 1 of the 21 who had TURP required alternative treatment. The Madsen score improved from 13.3 to 5.8 in the TUMT group and from 13.8 to 3.6 in the TURP group. The PFR increased from 9.3 to 15.1 mL/sec in the TUMT group and from 9.3 to 19.1 mL/sec in the TURP group (D'Ancona et al, 1998).

A full quality of life study was performed on 147 patients randomly assigned to either TUMT with the Prostasoft 2.5 protocol or TURP. It was found that both treatments had a positive effect on various aspects of quality of life. The areas of perception of urinary difficulties and daily activities particularly were improved. However, TURP caused a greater improvement in both quality of life and clinical outcome, with neither treatment influencing sexual function (Francisca et al, 2000a).

Overall, the main complication, particularly with the higher energy TUMT, was prolonged catheterization and, with it, urinary infection. It would seem that sexual side effects such as erectile dysfunction and retrograde ejaculation were significantly less common than after TURP.

There have been two systematic reviews of the literature, which give level I evidence concerning the value of this technique. It must be remembered that these reviews are only as good as they are allowed to be by the data put into them. One of the issues characterizing the entire technology in BPH literature is the large number of poorly constructed trials that have been performed.

The first of these systematic reviews came from an Australian group attached to the Royal Australian College of Surgeons (Wheelahan et al, 2000) and covers trials performed up to 1999. **It found that TUMT offered less morbidity than TURP but was not as effective as TURP in improving symptoms or reducing BOO. TUMT was associated with a lengthy period of catheterization after treatment, thus causing the higher rates of urinary tract infection and urinary retention. The durability of TUMT, which showed that 23% of patients remained satisfied with a single such treatment after 4 years, was not particularly convincing. The authors concluded that it was not possible to determine the safety and efficacy of TUMT because of the poor-quality evidence base.**

The second systematic review came from the United States and included all the trials from the previous review up to 1999 but added four other papers up to 2002 (Hoffman et al, 2004). The authors were specific in including only randomized trials of TUMT and TURP and found that this meant only 6 of 26 possible trials could be reviewed, with 540 participants (322 TUMT, 218 TURP). Without being directly critical of the standard of these trials, the authors outlined clearly the shortcomings of each of them, showing a lack of uniformity that makes it difficult to draw definite conclusions. **The pooled mean PFR increased from 7.9 to 13.5 mL/sec after TUMT and from 8.6 to 18.7 mL/sec after TURP. Only two studies reported a mean PFR after TUMT that had reached 15 mL/sec or greater.** The authors were unable to find statistically significant differences between low-energy and high-energy systems. Only four studies provided a follow-up of 12 months or greater with 85% to 93% of patients available for follow-up. There was an absence of comprehensive reporting of adverse perioperative events in most of the trials, but the findings of previous systematic reviews in this regard appeared to remain the same. **The very definite conclusion once again was that TURP produced greater improvement in symptom scores and PFR and that fewer men required re-treatment for BPH than with TUMT. The recommendation was that further research was required to evaluate the long-term efficacy and safety of TUMT.**

Summary

TUMT is not as effective as TURP in improving the objective signs of outflow obstruction, in terms of either PFR or Pdet at PFR. However, it does seem to have a measurable effect on the prostate because the elasticity of the urethra is increased after treatment.

The symptomatic improvement that occurs after TUMT seems to be energy related. However, the surprising finding is that even when no objective signs of improvement are seen in comparative trials, the improvement in symptom score caused by TUMT can be considerable. Whether this is a placebo effect or not is unclear because in the two trials in which it occurred the results are given only from the 6-month time point, at which the placebo effect would be at its maximum. Long-term results from these two trials are needed.

Complications are less than with TURP, with prolonged catheterization and infection being the most common. However, the fact that the procedure can be performed as a day case with the patient under mild sedation is an important positive side of the procedure. **The success associated with this treatment cannot be guaranteed in every patient, as can be seen from the relatively high number of nonresponders in many series.** Why this should be is unclear, but several possible explanations have been given and were outlined earlier.

It would seem that the higher-energy devices will be used preferentially to those producing lower energy, but long-term studies, particularly multicenter studies, would be particularly helpful in being able to assess them fully. Because it is clear that TUMT does not outperform TURP, it is to be hoped that trials will be aimed specifically at assessing the exact place of TUMT in the treatment of symptomatic BPH and that the standard of trials will improve.

LASERS

The introduction of the laser as a treatment option for BPH was greeted by urologists and patients with a high degree of expectancy. However, as with other types of minimally invasive therapy, an initial excess of optimism gave way to realism, with the development of a clearer view of the indications for this type of treatment and, indeed, of its limitations. Newer modifications have taken place, allowing even an endoscopic "enucleation" to be performed. When the original laser techniques were introduced, it was hard to predict this being possible, and so it is reasonable to suggest that with technologic advances happening at an increasingly fast rate the laser may well play a greater role in the management of BPH in the future. However, although TURP is now recognized as the gold standard, it was not always the case; in fact, it took TURP several decades to achieve this exalted status. It may be that the absence of randomized clinical trials delayed the ultimate recognition of TURP as the treatment against which all others must be compared. For this reason, large multicenter randomized clinical trials comparing the laser with other modalities are needed for this technology to achieve widespread acceptance; these must be adequately statistically powered and have a sufficiently long follow-up time. In addition, it would probably be a more satisfactory approach if the authors of these trials tried to find the exact role of the laser in the treatment of BPH rather than suggesting that it is a method that will supplant TURP. It is likely that both methods of treatment will have a role to play, but that of the laser still needs to be accurately defined (Fitzpatrick, 1998, 2000).

The volume of papers in the literature on lasers has increased beyond all expectations in the past decade. This reflects a continuing interest in the technology and a belief on the part of urologists that the laser will be the way that symptomatic BPH should be treated. Many of the older technologies are now of no interest to urologists, but it is to be hoped that the somewhat uncritical approach that was taken toward the earlier lasers will not be taken toward the new favorites, the holmium laser and the photoselective KTP laser.

Types of Laser

As is well known, "laser" stands for light amplification by the stimulated emission of radiation. The mechanism of the operating principle of lasers is a process known as stimulated emission of radiation (Nau et al, 2000). In the laser, a flashlamp gives out high-intensity light, which then bombards a resonator cavity with photons. These excite electrons in the resonator cavity to higher energy status. Most of the photons that come from the flashlamp to the resonator cavity are wasted in the form of heat, with less than 5% being absorbed. For this reason, lasers used in the treatment of BPH require rather elaborate cooling devices.

The electrons in the resonator cavity, which are excited by the bombardment of photons, are caused to jump to higher or "excited state" orbitals. Because of the instability of these excited state orbitals there is a very rapid decay of the electrons, which emit a photon. This process is known as spontaneous emission of radiation. However, the emitted photon has the energy required to interact with other excited state atoms. If this interaction happens, further electron orbital decay and photon emission are induced. This photon has the same characteristics and travels in the same direction as the incident photon. This is known as stimulated emission of radiation and, as stated earlier, is the operating principle of lasers. These photons leave the resonator cavity as a coherent laser beam.

There are four types of laser that can be used to treat the prostate.

Neodymium:Yttrium-Aluminum-Garnet Laser

The neodymium:yttrium-aluminum-garnet (Nd:YAG) laser emits light at a wavelength of 1064 nm, and its active medium consists of neodymium atoms in an yttrium-aluminum-garnet rod. Because this light is poorly absorbed by water and body pigments it can penetrate tissues relatively deeply. This poor absorption in a fluid medium causes thermal coagulation of the surface tissue and of areas just under the surface. The tissue that has been coagulated becomes white, and hemostasis is total. Subsequently, the coagulated tissue sloughs, and this may occur over a period of some weeks. It may take up to 3 months to achieve complete healing.

One of the more recent modifications of laser application is the process of tissue vaporization and desiccation, and this can be achieved with the Nd:YAG laser. This technique requires a higher energy density for a longer period of time, and surface carbonization occurs, leading to increased laser light absorption superficially and a limitation of the depth of penetration, further increasing the energy density.

Potassium-Titanyl-Phosphate Laser

The potassium-titanyl-phosphate (KTP) laser uses a KTP crystal to double the frequency of an Nd:YAG laser and produces a 532-nm wavelength. This provides an intermediate level of coagulation and vaporization. Only half the depth of tissue penetration is reached compared with that of the Nd:YAG laser. However, the consequent higher energy per unit tissue volume produced may increase tissue vaporization and desiccation. This may be used as an advantage in that the prostate and bladder neck may be incised with the KTP laser.

Holmium:Yttrium-Aluminum-Garnet Laser

The holmium:yttrium-aluminum-garnet (Ho:YAG) laser emits light at a frequency of 2100 nm. The energy is emitted in a series of rapid pulses over a few milliseconds, the Q-switched laser. This is unlike the continuous wave of the Nd:YAG or KTP lasers. Whereas the same type of standard optical fiber can be used for the Nd:YAG or the KTP laser, a different flexible optical fiber is required for the Ho:YAG laser. Because it produces a cutting effect by vaporization of the tissue water, its hemostatic properties are less than those of the continuous wave lasers.

Diode Laser

With conventional lasers, less than 5% of the electrical input is converted into laser light, and this inefficiency means that conventional lasers require high-energy cooling devices and radiators, thus increasing the size of the machine. The high gain of the diode laser allows the more efficient use of the photons that are generated. Thus the available diode lasers used for medical purposes are small and portable, and special connections are not required.

Methods of Delivery

The energy from lasers can be delivered as follows:

End firing
- Bare tip
- Sculptured tip
- Sapphire tip

Side firing
- Metal or glass reflector
- Prismatic internal reflector

Interstitial
- Bare tip
- Diffuser tip
- Diffuser tip with temperature transducer

Energy levels can be varied, depending on the type of laser, to allow coagulation or evaporation to occur, as alluded to earlier. As with any form of heat treatment, an increase in the temperature of the tissue being treated has different effects, and it is important to be able to control and localize this temperature rise. When the temperature is between 45° C and 50° C, desiccation of tissue occurs, and then, as the temperature increases from 50° C to 100° C, coagulation begins and becomes irreversible. When the temperature exceeds 100° C, the tissue boils and there is resultant carbonization and vaporization.

Coagulation alone may make the procedure imprecise, with danger to neighboring tissue such as the distal sphincter mechanism. During the process of vaporization, tissue water is converted to steam and miniexplosions occur within tissues, increasing the mechanical rupture. The vaporization is determined by the intensity of laser application to tissue rather than its duration. Once the cells become coagulated, laser energy penetrates through them less well, halting the forward process of ablation and increasing backscatter and surrounding coagulation (Stein and Narayan, 2000).

Delivery Systems and Laser Techniques

The laser experience has shown that it is possible to adapt a technique and then evolve it almost completely into something new while still using the same basic form of energy. For example, the evolution from the transurethral ultrasound–guided laser-induced prostatectomy (TULIP) device (Intrasonic, Burlington, MA) to the currently used interstitial and contact devices has been relatively quick but demonstrates clearly the wish on the part of investigators to remove imperfections and to improve results. The aim to find a truly minimally invasive technique is encapsulated in this evolution.

There are two ways in which lasers can have an effect on the prostate, either by coagulation or by vaporization. In the first of these coagulation is achieved at temperatures of 70° C to 90° C. The Nd:YAG laser supplies a wide scatter of power over a relatively large surface area with deep penetration. The second way is by vaporization, which raises the temperature to several hundred degrees Celsius. The power density is high, delivered by a narrow beam. Vaporization can be achieved by using a laser tip that increases the absorption of power by the prostate. **Therefore the factors determining whether coagulation or vaporization occurs are essentially the power density of the laser beam itself, the total energy delivered, and the time for which it is applied.**

The TULIP device was one of the earliest laser systems and consisted of a characteristic balloon, which maintained the distance between the laser beam and the prostate. Also contained in the tip was a 7.5-MHz ultrasonic transducer and an Nd:YAG laser. The probe was moved from the bladder neck to the verumontanum and was then moved to another position, so that, in this longitudinal manner, the entire circumference of the prostate could be treated. The TULIP device has not withstood the test of time in spite of many improvements made to the original model. It is likely that the reason is that urologists prefer being able to visualize a technique directly rather than indirectly by ultrasonography.

Side-Firing Laser

Probably the first study of the side-firing laser was performed by Costello and colleagues (1992) using a canine model. **The energy used was 60 W for a duration of 60 seconds in four quadrants of the prostate, which caused coagulative necrosis.** The canine prostate is different from the human prostate, but it served as an indicator to how the procedure could be performed in humans. Considerable improvements have been made since that time in terms of the laser fibers, the formula for dosimetry, and the technique used.

A large volume of work has been performed on the side-firing laser systems, and this has up to now dominated the literature. **The fiber bends the laser beam at various angles, and this is accomplished by reflection or refraction, depending on the fiber used.**

Reflective systems use a gold-plated mirror or solid gold tip to deflect the beam. The angle of reflection varies from 45 to 105 degrees, with 90 degrees being the most common. There is a further divergence depending on the design of the reflector mechanism that also is variable. This is important because it determines the power density by establishing the size of the laser spot on the prostate. Reflective systems tend to absorb more energy than refractive systems. At present, this type of system is more suited to tissue coagulation. Refractive systems either are glass capped or use a quartz tip to deflect the beam. The angle of divergence is narrow, allowing either coagulation or vaporization.

The most popular method using the side-firing laser is that of coagulation. Some surface vaporization occurs, but most of the tissue is coagulated, followed later by sloughing, which lasts for some weeks. The power settings have been recommended as 40 to 60 W for 60 seconds or even 90 W for 60 seconds. This latter higher power may cause mainly vaporization. In this situation the lack of coagulative necrosis means an absence of tissue sloughing. A hybrid procedure has also been described that combines coagulation of the prostate with contact incision through the prostate.

The technique has also varied in description. One method is the use of a quadrant spot application, or even a sextant approach for larger glands, extending every 1 to 2 cm along the prostate from bladder neck to verumontanum (Kabalin, 1993; Norris et al, 1993; Kabalin et al, 1995). The beam is applied until the treated area becomes white. It is then moved onto a normally colored area, which is then treated until the entire surface of the prostate gland has been rendered white. After an initial increase in prostate size from edema, sloughing of the tissue takes place, with the tissue being passed urethrally.

Another technique has been described (Nau et al, 2000). The treatment begins proximal or distal to the bladder neck, dependent on whether retrograde ejaculation is a factor of importance. If the procedure is begun 1 cm distal to the bladder neck, it can reduce the incidence of this complication from up to 15% to zero, according to these authors. They scan the laser beam either longitudinally or radially. That is, from the beginning of their treatment in the region of the bladder neck, the fiber is scanned distally at a rate of 1 mm/sec to the level of the verumontanum; it is then returned to the starting point and rotated slightly so that the next line of tissue that is coagulated is immediately beside the previously treated line. This is continued until the entire prostate appears white.

Alternatively, a radial scanning technique can be used. With this method, the probe is rotated through 360 degrees at a speed of 1 mm/sec, starting in the region of the bladder neck. The fiber

is then withdrawn 5 mm distally and the circumferential treatment continued. This is repeated at 5-mm distances until the level of the verumontanum is reached.

Contact Laser

Although the technique of the side-firing laser is well described and the results are well known, a number of possible criticisms have led to further evolution of the laser technique. For example, there is difficulty in controlling the distribution of energy and predicting the eventual result; the side effects of post-treatment retention and urethral discomfort with irritable bladder symptoms have also deterred many urologists from using it. These criticisms have led to the evolution of other methods, one of which is the use of the contact laser, which removes some tissue immediately, thereby decreasing post-treatment voiding difficulties (McNicholas and Singh, 2000).

Contact laser tips are made of synthetic sapphire and can be made in different shapes, either conventionally round or in the shape of a wedge. Initially, the size of the tips was 1.5 mm (Watson et al, 1994). The success of these led to the introduction of tips of 5 mm (Bartsch et al, 1994) and most recently to tips of 10 mm (McNicholas and Hines, 2000). A removable side-firing contact probe has been introduced. This allows the surgeon to remove the contact tip and replace it with a side-firing free-beam device.

Because the size of the contact tip exceeds the size of the instrument channel of the cystoscope, it is usual to advance the fiber until it protrudes through the end of the instrument and then to attach the contact tip. It is then advanced along the length of the urethra. Special instruments to facilitate the passage of this type of laser have been designed (Press and Smith, 1995).

Once in position, the contact tip should be placed just above the verumontanum and 20 W power applied at this level. After allowing this power to raise the temperature at the treatment position and visually obvious tissue contraction to occur, the tip is advanced proximally in the curve of the prostate to the bladder neck, taking care not to undermine it. This procedure is then repeated, from verumontanum to bladder neck, by rotating the instrument so that a further channel can be cut adjacent to the previous one. At the end of the procedure, a bladder neck incision can be performed if required (McNicholas and Hines, 2000).

Interstitial Laser

The purpose of this method of applying laser energy is to reduce post-treatment voiding difficulty and urethral obstruction because the integrity of the prostatic urethra can be preserved. A small fiber is introduced into the prostate, usually transurethrally, and energy from either the Nd:YAG or the diode laser at low power heats the prostate and induces coagulative necrosis. **The necrotic tissue is removed by the process of tissue repair and is not sloughed off and passed urethrally as with other methods.**

The laser energy is applied to the prostate by one of three possible fibers: (1) a bare fiber, (2) a bare fiber within a cannula with saline solution irrigation, and (3) a fiber with a distal diffusor tip.

In a study by McNicholas and colleagues (1993) **it was shown that the size of the intraprostatic lesion is dependent on the power applied, the duration of treatment, and the vascularity of the tissue.** In addition, the ratio of fibrovascular to epithelial tissue is important. The aim of interstitial treatment is to create spherical lesions of 1 to 2 cm diameter within the prostate. The prostate should be heated slowly to avoid carbonization, which limits the effect of the treatment and prevents further coagulative necrosis.

Two types of laser generators are used for interstitial laser therapy. The Dornier ITT system (Dornier, Germering, Germany, and Kennesaw, GA) uses the Nd:YAG laser to generate 1064-nm energy with a power range of 2 to 100 W. The other generator is the Indigo LASEROPTIC system (Indigo Medical, Johnson & Johnson, Cincinnati, OH). This generator is portable, weighing about one eighth as much as the Dornier system. It is a diode laser generator, which uses a diode pump source and gallium-aluminum-arsenide to generate a 830-nm wavelength with a power range of 2 to 20 W.

The laser fiber is inserted through a standard cystoscope and is passed transurethrally into the prostatic adenoma. With the use of the Nd:YAG interstitial laser, it is left in each position for 10 minutes at 5 to 7 W. The diode laser requires a 3-minute treatment session at each location. The length of the procedure depends on the size of the gland and the type of laser system being used.

The position of the laser tip within the prostate can be visualized by the use of TRUS. It is possible that conventionally positioning the fiber under vision will place it too close to the prostatic urethra, risking urethral damage and edema with resultant post-treatment voiding problems. Issa and colleagues (1998) have modified this using the Indigo laser so that the fiber can enter the prostate at a greater angle, thus keeping it away from the prostatic urethra.

There is no definite agreement about how much tissue should be ablated, with some investigators using a lower number of treatment sites, paying particular attention to the position of the tip of the fiber. Others suggest a more aggressive approach, such as one lesion per 5 to 7 mm^3 (Arai et al, 1996).

Prostatectomy with Holmium Laser

The vaporization techniques described earlier using the Nd:YAG laser with high-energy-density beams at high power (60 to 100 W) at a wavelength of 1064 nm have been effective in removing small amounts of tissue immediately during the procedure. However, it is a relatively inefficient way to do this because of the high power required. The Ho:YAG laser beam is absorbed by water (unlike the Nd:YAG beam) at a wavelength of 2140 nm and causes considerable tissue vaporization.

This technique was first evaluated in canine experiments in 1992 (Johnson et al, 1992) and subsequently with improved technology in 1996 by Kabalin. In the latter study the mean transverse diameter of the defect was almost 2 cm. A surrounding rim of 2 mm of tissue coagulation was also produced.

The methods of using the Ho:YAG laser have evolved because of several modifications in both technology and methodology (Webb et al, 1993; Dennstedt et al, 1995; Gilling et al, 1995, 1996, 1999). The technique has passed through simple vaporization to combined endoscopic laser ablation of the prostate (CELAP) and is now used to resect large pieces of prostatic tissue.

The dual-wavelength Versa Pulse Select laser (Coherent, Inc., Santa Clara, CA) was used, and a maximal power of 60 W in a pulsed mode was used to resect tissue. A 26-Fr continuous-flow resectoscope was modified, and an end-firing bare fiber was passed through it; its position was stabilized by passing it through a 6-Fr ureteral catheter. **The median lobe was first resected by initial bilateral bladder neck incisions and then with a transverse incision just proximal to the verumontanum. The median lobe was then undermined to the bladder neck and detached back into the bladder. The lateral lobes were removed by making incisions at 1 and 5 o'clock and then at 7 and 11 o'clock and then beginning distally and undermining proximally by detaching them**

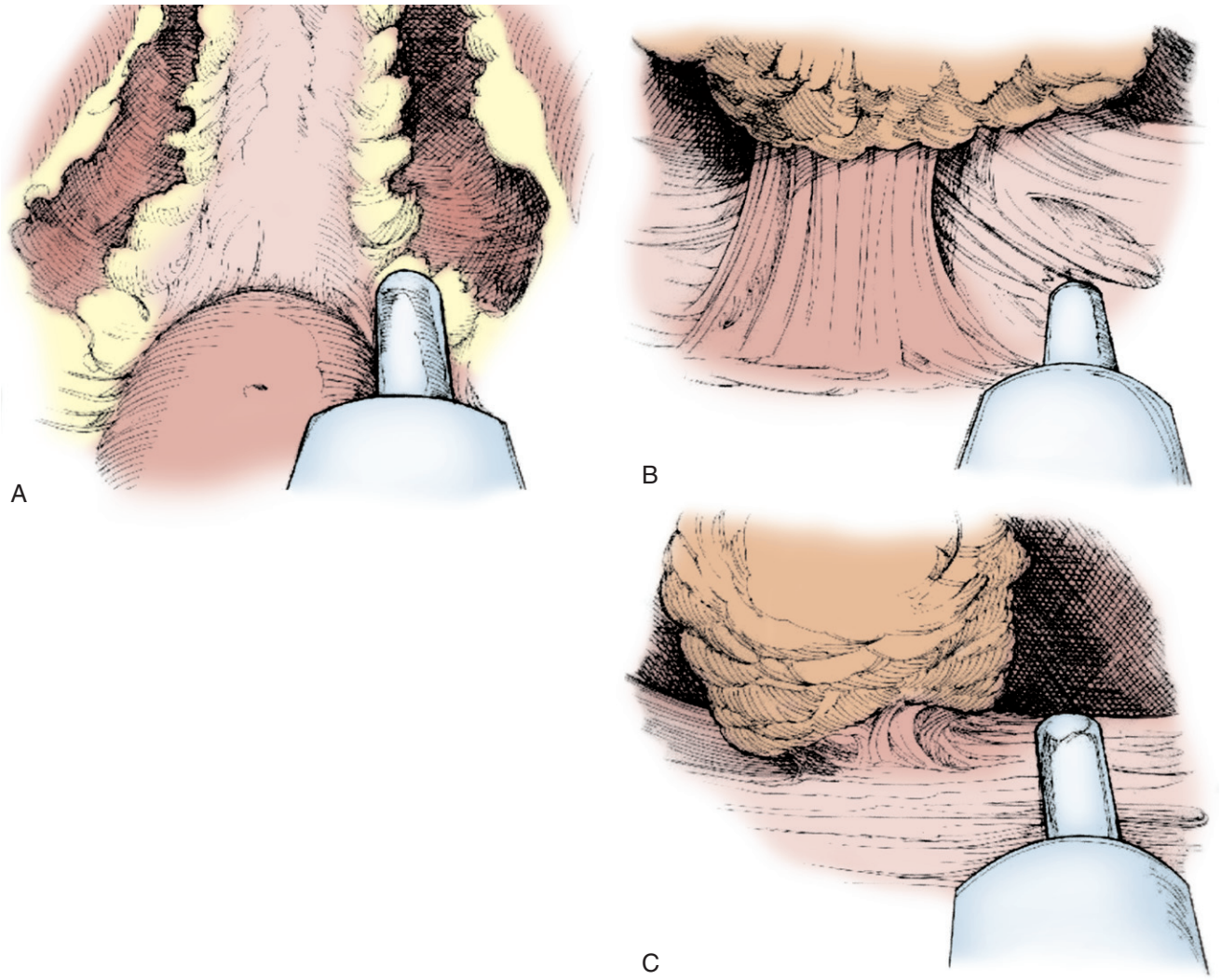


Figure 93–5. Holmium laser resection. **A,** Bilateral bladder neck incisions. **B,** Undermining the median lobe. **C,** Releasing the median lobe. (Courtesy of Peter Gilling, Tauranga, New Zealand.)

backward into the bladder. If the lobes were large, they could be cut into smaller pieces. They were retrieved from the bladder with a modified grasping forceps, or more recently using a morcellator, and by irrigation (Fig. 93–5).

Clinical Results

Part of the difficulty with trials using surgical instruments such as the laser is that a placebo-based randomized controlled trial cannot be performed. This effectively means that to test efficacy the laser must be compared against what is accepted as the best method to treat LUTS endoscopically, which is recognized as TURP. Unfortunately, and particularly with the laser (whose name implies modernity and success in the public's mind), this does not exclude a pre-existing bias that might be present toward the laser. In addition, and this is similar to the other technologies for treating BPH, none of the comparative trials is as carefully statistically powered as those testing medical management of BPH. It might be said that a large number of the open studies are too large and that a comparative study should have been introduced at an earlier stage. However, there have been many trials, both open and comparative, and a large amount of relevant information is available.

Transurethral Ultrasound-Guided Laser-Induced Prostatectomy

TULIP has ceased to be used by urologists, but because it was the first to be introduced and is currently out of favor because it has been surpassed by instruments that are easier to use rather than because of its lack of efficacy, it is worth looking briefly at the results achieved with its use.

The initial results came from the TULIP National Human Cooperative Study Group (McCullough et al, 1993; McCullough, 1994). These showed that in a small subset observed for 6 months only (68 of 242 patients) there was a 78% improvement in PFR (6.7 to 11.8 mL/sec), although, as can be seen, the final mean PFR is still rather low, in spite of treatment. There was also a 68% improvement in symptom score. However, 4% of the patients underwent TURP, and irritative symptoms and urgency lasted for 2 to 3 months in a high percentage of patients. When patients were observed up to 1 year, it could be seen that the incidence of post-treatment retention was 22%, with a stricture rate of 5% and bladder neck contractures in 1%.

Schulze and coworkers (1995) carried out the procedure in 89 patients who were observed for a maximum of 1 year. **The mean PFR increased from 7 to 15 mL/sec but was reported as**

exceeding 20 mL/sec in about half. The modified Boyarsky symptom score decreased from 17 to 5 at 1 year. Although it was efficacious in this group, the patients were chosen only as candidates for TURP rather than having strict inclusion and exclusion criteria.

Chatzopoulos and colleagues (1996) evaluated 38 patients with a maximal follow-up of 30 months after the TULIP procedure. **The authors pointed out that the mean symptom score decreased by 54% and PFR increased by 112%. However, an improvement in symptom score was seen in 43.6% and in the PFR in 41%, but in only 28.2% was there an improvement in both.** In addition, reoperation was required in 16% and the incidence of complications was considered high.

In a further study (Horninger et al, 1997) it was found that the efficacy of TULIP, contact laser, and interstitial laser was similar. However, because simpler machines were becoming available, interest waned in the TULIP and techniques with an improved side effect profile were sought.

Side-Firing Laser

The side-firing laser has several advantages over the TULIP technique, related to the ease with which it can be used. The fact that it can be passed through an endoscope and the effect that the procedure is having can be visualized (at least on the urethral surface) make it especially attractive to the urologist. When viewing the results achieved with this technology, the reader must remember that ultimately it should be compared with TURP in terms of efficacy and side effects, to say nothing of cost-effectiveness.

The initial study (Costello et al, 1992), looking at 6-week results in 17 patients, found an increase in the PFR from 5 to 9 mL/sec and an improvement in the Madsen-Iversen symptom score from 15 to 4. Costello and coworkers (1994) reported on 33 patients observed for 3 months. They showed that the PFR increased from 8.5 to 15.2 mL/sec and that the AUASI score improved from 21.5 to 9.5. That the short-term results were encouraging was also supported by a further study (Norris et al, 1993). One hundred eight patients were observed for a maximum of 6 months; the PFR increased from 7.6 to 12 mL/sec, and the AUASI score improved from 22.3 to 9.2. These studies were noncomparative and were performed essentially to find out whether the technique might be submitted to trials against TURP. It can be seen that there is a variation to the PFR improvement in the important series just cited.

However, the longer-term study of Kabalin (1996) suggested that the results could be maintained. **In 227 patients the PFR was 7.3 mL/sec before treatment and the improvement to 15.2 mL/sec at 3 months was still attained through 1 year (17 mL/sec), 2 years (18.3 mL/sec), and 3 years (18.5 mL/sec). The AUASI score decreased from 20.3 to 10 at 3 months and to 5.7 in those who had been observed to 3 years.** Therefore, although a symptom score of 10 after treatment might have appeared disappointing because it is still in the moderately symptomatic range, the fact that it had further decreased to 8 at 1 year and 8.6 at 2 years, with a further drop to 5.7 at 3 years, showed the benefit of long-term follow-up.

The efficacy of visual laser ablation of the prostate (VLAP) has been subjected to urodynamic analysis. James and colleagues (1995) reported on 79 patients waiting for TURP who were treated by VLAP as an alternative treatment. They had preoperative symptom scores and urodynamic evaluation, and these were repeated 3 months after treatment. The AUASI score decreased from 21.4 to 9.4, and the PFR increased from 6.5 to 10.6 mL/sec. **The Pdet at PFR decreased from 74 to 54.2 cm H_2O.** In another carefully performed urodynamic study (Te Slaa et al, 1995), results were assessed preoperatively and at 6 months after the procedure. The IPSS decreased from 21.3 to 5.3, and the PFR increased from 7.9 to 17.8 mL/sec. The percentage of patients demonstrating urodynamically proven obstruction decreased from 80% before treatment to 5% at 6 months after treatment.

All of these were, of course, open studies, but they did lead to a number of comparative studies, in each case against TURP. In 60 patients observed for 6 months it was found that VLAP gave a significantly better result in terms of symptom score than TURP but that TURP gave a significantly greater improvement in PFR (Sengor et al, 1996). However, in a multicenter trial in the United States at six investigational sites, a longer follow-up took place (Cowles et al, 1995). In this study, 115 men who did not have urinary retention were randomly assigned to TURP (59 patients) or VLAP (56 patients); initially, all of these men were observed for 1 year after treatment. The authors showed that VLAP required less operating time (23.4 against 45.2 minutes) and a shorter hospitalization (1.8 against 3.1 days). The AUASI score improved by 13.3 in the TURP group and by 9.0 in the VLAP group, and the PFR improved by 7.0 mL/sec in the TURP group and by 5.3 mL/sec in the VLAP group. The IPSS improvement was statistically significantly better in the patients who had TURP. The authors noted a quality of life improvement in 93.0% of the patients who had TURP and in 78.2% of those who had VLAP.

A further comparative study showed 1-year results in 151 patients (Anson et al, 1995). In this trial, **75 patients were randomly assigned to TURP and 76 to VLAP. In 1 year, the AUASI score had improved from 18.2 to 5.1 in the TURP group and from 18.1 to 7.7 in the VLAP group; the PFR increased from 10.0 to 21.8 mL/sec (improvement of 11.8) in the TURP group and from 9.5 to 15.4 mL/sec (improvement of 5.9) in the VLAP group.** These authors and those of the previously mentioned trials concluded on the evidence described that VLAP was a safe and viable or useful alternative therapy to TURP.

However, the last-mentioned study has been re-evaluated at 5 years (McAllister et al, 2000). **Of the original 151 patients, 109 could be traced; of these, 69 patients had not required further treatment.** In those in whom further treatment was not required and who had not been lost to follow-up, VLAP had produced results comparable with those of TURP. Unfortunately, because this was less than 50% of the original sample, it is difficult to be absolutely certain which patients respond better than others to VLAP. Of the original group treated, 26 patients had required further surgical treatment: 8 of 51 (16%) TURP patients and 18 of 47 (38%) VLAP patients. These authors then admitted that the figures did not support their original conclusion that VLAP could be offered to every patient with BPH.

A urodynamic study was performed on 90 patients having VLAP and 43 having TURP (Jung et al, 1996). This suggested that TURP eliminated obstruction in all patients but that the grade of obstruction was lowered to normal in those treated by VLAP having prostate sizes of 50 mL or less.

The complication rates vary from center to center. The figures related to blood loss and blood transfusion are absolutely clear. Neither the U.K. study (Anson et al, 1995) nor the U.S. study (Cowles et al, 1995) had any patient treated with VLAP requiring a blood transfusion. In fact, two studies have shown that **VLAP can be performed on patients either on full anticoagulation therapy or having abnormal coagulation indices because of hematologic disorders** (Costello and Crowe, 1994;

Kingston et al, 1995). It is also certain that VLAP causes neither "TURP syndrome" nor any particular effect on serum sodium levels (Cummings et al, 1995).

The retrograde ejaculation rate varies from 27% to 33%, urethral stricture rate varies from 0% to 1.8%, and bladder neck contracture occurs in 4.4% (Anson et al, 1995; Cowles et al, 1995). The U.K. study showed a higher incidence of post-treatment dysuria (15% at 3 months) and bacteriuria (28 of 76 patients). The development of post-treatment urinary retention was 30.4% in the patients treated by VLAP by Cowles and colleagues (1995). This has led them and other authors to recommend catheterization after VLAP for 4 to 7 days.

The incidence of post-treatment retention has led some urologists to advocate a "hybrid" technique, in which a side-firing laser is first used to coagulate the adenoma and then a contact laser is introduced to perform bladder neck incisions, usually with a KTP:YAG laser for the latter procedure. Carter and coworkers (1999) found that this technique gave statistically similar improvements in both symptom score and PFRs at 1 year to TURP in a randomized study involving 204 patients. These results were still maintained when viewed at 18 months (Pearcy et al, 1999). In a further but smaller study of 45 patients, TURP was found to be more effective than the hybrid treatment in prostates larger than 40 mL; 38% of patients who had received the hybrid treatment were discharged with a suprapubic catheter, whereas all TURP patients were able to void at the time of discharge from hospital (Tuhkanen et al, 1999).

Contact Laser

In a study performed in the United States (Narayan et al, 1995), **100 patients were treated by transurethral evaporation of the prostate (TUEP) using the Nd:YAG laser and were stratified according to gland size: in 41 it was less than 40 mL, in 39 it was 41 to 80 mL, and in 20 it was greater than 80 mL. The mean improvement of PFR at 6 months was 9.9 mL/sec in the first group and 9.2 mL/sec in the third group;** the mean improvement in AUASI score was 14.6 in the first group and 16.2 in the third group at the same time. The authors believe that the efficacy of the treatment was independent of the size of the prostate gland and also showed that it was effective in patients who presented in acute urinary retention. In this and in another study (Fournier et al, 1996), the length of time that patients required indwelling catheters after treatment was 2.9 to 4.7 days.

In a urodynamic study comparing contact laser vaporization of the prostate with TURP, patients with prostate glands smaller than 40 mL were evaluated before treatment and at 6 months. There was a similar statistical improvement in both symptom scores and PFRs in both groups. The authors also found that both treatments were equally effective in relieving obstruction; the mean Pdet at PFR was 38.3 cm H_2O in the contact laser vaporization group and 31.3 cm H_2O in the TURP group (Tuhkanen et al, 1999).

The Oxford Laser Prostate Trial was first reported on by Keoghane and colleagues in 1996. A total of 148 patients were randomly assigned to contact laser (72 patients) or to TURP (76 patients). **At 3 months the AUASI score had improved by 7.3 in the laser arm and by 11.9 in the TURP arm, a statistically significant difference in favor of TURP.** However, the authors also found that at 3 months there was an equal distribution in bothersome score in both groups. They also found an equal effect on loss of sexual function in both groups (Keoghane et al, 1996). At 3 years the improvement in the mean symptom score was 11.0 for the laser patients and 12.0 for the TURP patients. These improvements were virtually the same as had been noticed at 1 year, indicating that patients had a symptom improvement roughly equal to that of TURP and equally maintained for 3 years. The improvement in mean PFR in the two groups showed a different trend: at 1 year it was 9.4 for TURP and 6.2 for laser, at 2 years it was 4.9 for TURP and 5.2 for laser, and at 3 years it was 2.1 for TURP and 1.8 for laser. That is, the pre-laser PFR was 11.8 mL/sec and at 3 years this was 13.4, having been 17.1 at 1 year. The same downward trend was noticed in PFRs after TURP, which also reached a maximum at 1 year. In spite of a gradual but obvious decrease in PFR after both types of treatment there was no such decrease in symptom scores. At 3 years, 18% of the laser patients and 9% of the TURP patients required reoperation (Keoghane et al, 2000).

Interstitial Laser

McNicholas and colleagues introduced the topic of interstitial lasers with a description of their use in an experimental study (1993). Further experimental results were described by Muschter and coworkers, and, in addition, the first large clinical experience was described (1994). **They had 221 patients with LUTS treated with interstitial laser and observed for 12 months. The results were encouraging, with a mean AUASI score improvement from 25.4 before treatment to 6.1 at 12 months. In addition, the PFR increased from 7.7 to 17.8 mL/sec.** The authors found that the prostate volume (measured by TRUS) decreased by 40%. A further large open study confirmed these results; sexual side effects were few, but irritative symptoms occurred in 12.6% and urethral strictures in 4% (Muschter and Hofstetter, 1995). A further but much smaller study reported 3-month results in 16 patients; the AUASI score decreased from 16.5 to 5.8 and the PFR increased from 8.8 to 11.9 mL/sec (Orovan and Whelan, 1994). A short-term open study on 61 patients revealed a similarly low improvement in the PFR at 3 months, from 6.7 to 10.0 mL/sec, whereas the AUASI score improved from 18.9 to 7.7 (Arai et al, 1996).

All of these open studies show that, at 3 months, the improvements in PFR are less than might have been expected, demonstrating the importance of longer-term studies and the relative lack of value of short-term studies; they also show that large numbers of patients can be treated safely with this technique with a good side effect record, considerably improving on previous laser techniques. However, the results of a comparative trial, against TURP or TUNA, would make interesting reading and would also give valuable clinical information.

In an excellent summary of the procedure, Muschter (1999) reviewed the reported literature, indicating that the interstitial laser technique had been performed on a total of 785 patients. **The length of follow-up was very variable, but improvement in symptom score for 70% was noted overall (range, 32% to 92%). The average improvement in PFR was 98% (range, 35.2% to 203%). The decrease in prostate volume ranged from 8.3% to 41.6%, and the re-treatment rate at 12 months ranged from 0% to 15.4%.**

All of these results are with the interstitial Nd:YAG laser, and results with the more recently introduced diode interstitial laser have not been reported as frequently. Although comparative trials with the diode laser are ongoing, short-term results of small open studies indicate a safe and reliable technology. At 3 months, 25 patients thus treated had an improvement in symptom score from 20.6 to 6.9; the PFR increased from 9.1 to 20.3 mL/sec (De la Rosette et al, 1997). A further open study reported on results in 104 patients reviewed at 1 year (Conn et al, 1999). The AUASI

score showed a mean improvement from 22.4 to 8.3 and the PFR from 8.6 to 14.2 mL/sec. The mean catheterization time after treatment was 4.8 days.

Transurethral interstitial laser coagulation (TUILC) was compared in a small randomized trial with TUMT and TURP (Norby et al, 2002) and was found to be effective but associated with a relatively high morbidity (64%), principally urinary tract infection. In another small noncomparative trial, TUILC combined with minimal TURP was assessed in 41 patients with BOO caused by BPH (Corvin et al, 2002). The authors believed that this combination could reduce the morbidity associated with TURP, which was irrigation fluid absorption and blood loss. The case was not made particularly strongly, because of the absence of a comparator group, that there was an unacceptably high morbidity associated with TURP.

Kursh and coworkers (2003) **described a randomized multicenter trial comparing TUILC and TURP with a 2-year follow-up. They found that TUILC performed well, and although the authors concluded that TUILC was an acceptable alternative to TURP it was noted that 16% of the TUILC group required TURP within the first year. In another small randomized trial, Liedberg and colleagues** (2003) **randomly assigned 20 to a TUILC group and 11 to a TURP group. These authors found a significantly greater improvement in symptom score and PFR in the TURP group and a greater morbidity rate in the TUILC group. Urinary infections occurred in 13 TUILC patients (65%) as against 1 TURP patient. Post-treatment catheterization was required for 24 days after TUILC and 2 days after TURP. In a small study of 28 patients in acute urinary retention, TUILC was performed with urinary infection in 2 and a mean catheterization time after TUILC of 6.3 days** (Nishizawa et al, 2003). **The mean prostatic volume decreased by 19.4% at 6 months, and the IPSS and PFR were 8.0 and 11.2 mL/sec, respectively, at 3 months. In a study of 82 patients observed for a mean of 48.4 months, 29 (35%) were re-treated, 18 (22%) had TURP, and 11 (13%) had additional pharmacotherapy** (Terada et al, 2004).

Holmium:Yttrium-Aluminum-Garnet Laser

The Ho:YAG laser was introduced for use in a number of urologic conditions (Webb et al, 1993) and was then used in combination with the Nd:YAG laser in the treatment of BPH (Gilling et al, 1995).

Prostate resection with the Ho:YAG laser was first reported on 84 patients with a mean follow-up of 4.3 months (range, 1.5 to 9); the mean prostate volume was 50 mL, and the mean resection time was 35.1 minutes (Gilling et al, 1996). Recatheterization was required in 2 patients before they left the hospital and in a further 2 within the first week but was in every case short term. The side effects were minimal, with irritative symptoms and dysuria being negligible. The mean AUASI score improved from 21.3 to 4.1 at 3 months, and the PFR increased from 7.5 to 19.3 mL/sec at 3 months.

A combined review of data in a single center in New Zealand and a single center in the United Kingdom showed that the procedure had been safely performed in 967 patients (Mackey et al, 1998). Of these, 503 had been observed to 3 months, and the mean AUASI score had improved from 20.6 to 7.0 and the PFR increased from 8.8 to 21.1 mL/sec. Because only 33% of the total number had been observed to 6 months, it is difficult to draw conclusions from the results, but the improvements were being maintained (AUASI score, 4.8; PFR, 22.3 mL/sec).

These encouraging results from large open studies led to a comparative trial between two centers in New Zealand and the United States. Patients were randomly assigned to TURP (59 patients) or Ho:YAG prostatic resection (61 patients). In a well-described study, 102 patients were observed to 1 year. The AUASI score improved from 21.9 to 4.2 in the Ho:YAG group and from 23.0 to 4.3 in the TURP group at 1 year. At the time point, the PFR had increased from 8.9 to 25.2 mL/sec in the holmium group and from 9.1 to 20.4 mL/sec in the TURP group. All cases were urodynamically studied; the mean Pdet at PFR decreased from 75.9 to 35.2 cm H_2O at 6 months in the holmium group and from 83.4 to 39.2 cm H_2O in the TURP group. Complications were low and were equal in both groups. Prolonged catheterization was not required in either group (Gilling et al, 1999).

This type of treatment can also be applied to large prostates. A total of 43 patients with prostates larger than 100 g were treated by Ho:YAG prostate resection. The mean catheter time was 19.7 hours, and the mean hospitalization time was 28.4 hours. At 6 months follow-up the AUASI score had improved from 23.5 to 2.8 and the PFR increased from 9.0 to 24.8 mL/sec.

The Ho:YAG laser has been used in both smaller and larger prostates. These are several descriptions of holmium laser enucleation of the prostate (HoLEP) in this context. Thirty-eight men with a mean prostatic volume of less than 60 mL were treated as day cases (Larner et al, 2003). This treatment was found to be safe and effective with outcomes equivalent to those expected from TURP, but it must be remembered that this was not a comparative trial. In another study, Ho:YAG laser bladder neck incision was compared with HoLEP as an outpatient procedure (Aho et al, 2005). HoLEP was superior in producing relief of obstruction, and fewer patients required recatheterization or reoperation. Catheter time, hospital stay, and postoperative morbidity were found to be similar. Both techniques were believed to be effective, but the bladder neck incision was quicker to perform. Using the slightly older holmium technology, holmium laser ablation of the prostate (HoLAP), there was a 7-year follow-up from a study of 79 patients (Tan et al, 2003a). Only 43% of the sample were available for follow-up, the mean AUA score of the remainder was 10.0, and the mean PFR was 16.8 mL/sec. The reoperation rate was 15%.

There have been a number of studies of the use of HoLEP in large prostates. The definition of a large prostate varies, as does the type of trial. Two studies from the same unit in the United States evaluated HoLEP in patients with prostates weighing more than 75 g and more than 125 g, respectively (Kuo et al, 2003; Matlaga et al, 2006). **Of note was the tissue retrieval rate of 1.09 g/min for this technique, with an operative time of 94.7 minutes, a range of 27 to 263 minutes for enucleation, and a further mean of 33.4 minutes for morcellation. If the long operating time was a negative, the fact that the mean postoperative catheterization was 15.1 hours and the mean length of hospitalization was 26.0 hours was a strong positive.**

A number of randomized trials comparing HoLEP with TURP have been performed. The statistical powering of these studies was not commented on in many cases, leading the reader to question the outcomes of the studies. However, the comments of the authors were all clearly in favor of the value of HoLEP to patients with LUTS. Tan and colleagues (2003b) found that HoLEP was superior to TURP in terms of time of catheterization, hospital stay, and amount of tissue removed, but it took almost twice as long

as TURP to perform. It was also superior to TURP in relieving urodynamically proven obstruction at 6 months, but there was no significant difference in the improvement in AUASI score and PFR. Exactly the same findings were produced in other randomized trials (Kuntz et al, 2004a, 2004b; Montorsi et al, 2004). The most recent holmium laser technology, holmium laser resection of the prostate (HoLRP), was subjected to a randomized trial against TURP (Westenberg et al, 2004). There were 120 patients, of whom 73 completed a 48-month assessment. The authors found no difference between the two techniques in terms of urodynamic indices, potency, continence, and symptom scores. As in the other studies, HoLRP took much longer to perform than TURP but was associated with less perioperative morbidity, catheter time, and hospital stay.

There have been three systematic literature reviews, one specifically of holmium laser prostatectomy (Tooher et al, 2004) **and two of laser prostatectomy in general** (Wheelahan et al, 2000; Hoffman et al, 2004). **These reviews showed that there were three randomized controlled trials comparing HoLRP and TURP and two comparing HoLEP and TURP. As with the other minimally invasive procedures, the majority of the studies were nonrandomized comparative studies or case series. The quality of the available evidence was found to be poor in most cases; most studies were lacking information on statistical powering, methods of randomization, allocation concealment, and blinding; had short follow-up periods; and had significant losses to follow-up. All three studies suggested that it was impossible to draw any long-term conclusions but that the laser techniques offered an option other than TURP for treating symptomatic BPH. However, the report of Wheelahan and colleagues** (2000), **which did not look at holmium laser therapy, photoselective vaporization of the prostate, or interstitial laser therapy, stated that safety or efficacy could not be determined owing to an incomplete and poor evidence base.**

Photoselective KTP Laser

Photoselective vaporization of the prostate (PVP) using a high-power 80-W KTP laser (Greenlight PV Laser System, Laserscope, San Jose, CA) has produced an alternative laser technology seen by many as an exciting new advance. KTP/532 laser energy is delivered by a side-firing glass fiber through a 27-Fr continuous-flow resectoscope. Sterile water irrigation is used, and the procedure is performed with the use of spinal anesthesia. The end point of the procedure is the production of a TURP-like cavity that has resulted from complete vaporization of the prostatic adenoma.

The only comparative trial thus far reported is an experimental one using a porcine kidney model, where ex-vivo blood-perfused kidneys were used to verify the hemostatic effect of KTP laser vaporization against TURP-like tissue resection. The laser technique was associated with highly significantly decreased bleeding with larger coagulation zones (Reich et al, 2004).

The remainder of the reported literature indicates a low level of evidence on which to base clinical decision-making. Kumar (2005) treated 18 patients and found a mean 51% reduction in prostate volume, but the follow-up was only 2.8 months. Sulser and coworkers (2004) described their early experience with PVP in 65 patients. The mean operating time was 57 minutes and the mean prostatic volume before treatment was 49 mL. All patients were catheter free by 1 month, but this was only a short-term 3-month observational study. PFR increased from a mean of 7.7 to 18.2 mL/sec, and IPSS decreased from 18.5 to 7.2. There were no major complications. Hai and Malek (2003) reported on only 10 patients who had a mean prostate volume decrease of 27%. There was a significant improvement in PFR and AUASI.

There has been a prospective clinical trial from six American medical centers on 139 men with symptomatic BOO related to BPH, and the 1-year efficacy and safety data have been reported (Te et al, 2004). The mean symptom score had decreased at 1 year from 23.9 to 4.3 and the mean PFR increased from 7.8 to 22.6 mL/sec. No significant complications were noted. The authors conceded that although the results were encouraging, long-term follow-up data were required.

PVP has been performed in 64 men with symptomatic BPH who had large-volume prostates (>60 mL). The mean operative time was over 2 hours (123 minutes), and 62 of the 64 patients were discharged within 23 hours. At 12 months the mean IPSS had decreased from 18.4 to 6.7 and the mean PFR had improved from 7.9 to 18.9 mL/sec (Sandhu et al, 2004). There has also been a report of PVP being performed in 66 high-risk patients, who had an American Society of Anesthesiologists score of 3 or greater; 29 patients were treated with ongoing oral anticoagulants or had severe bleeding disorders (Reich et al, 2005). No major complications occurred, nor was blood transfusion required. The average catheterization time was 1.8 days. The mean IPSS improved from 20.2 to 6.5 at 1 year, and the mean PFR improved from 6.7 to 21.6 mL/sec at 1 year.

Summary

The use of the laser to treat symptomatic BPH has evolved from the relatively cumbersome TULIP technique to other methods that require smaller pieces of equipment or that can treat a wider range of prostates. The difficulties in treating large prostates have been overcome using the newer technology. The minimal invasiveness of the laser has been improved, and the complications, particularly prolonged catheterization, bacteriuria, and urethral strictures, have been lowered very considerably. Cost-effectiveness still remains a question in urologists' minds, but it would appear that quality of life improvement is as good as that achieved with TURP (Arai et al, 2000). Further long-term results from comparative studies are required from multicenter groups, which it is hoped would also answer the question of a higher reoperation rate seen in some long-term laser studies.

Recently, a systematic literature review assessed the evidence presented between 2006 and 2008 for the 532-nm photoselective laser vaporization and holmium laser enucleation of the prostate (Naspro et al, 2009). Although the authors suggested that both of these techniques are promising alternatives to both TURP and open prostatectomy, the quality of the trials was not universally high and the follow-up relatively short in many of them, particularly in the case of the KTP laser. More high-quality randomized controlled trials with adequate follow-up are required.

TRANSURETHRAL RESECTION OF THE PROSTATE

History

TURP, as we know it today, was developed in the United States in the 1920s and 1930s. Nesbit (1975) pointed out that there were several significant factors important in its development: (1) the invention of the incandescent lamp by Edison in 1879; (2) the

cystoscope, developed independently by Nitze and Lieter in 1887; and (3) the development of the fenestrated tube by Hugh Hampton-Young, which allowed the obstructing tissue to be sheared off blindly. Other important factors were the invention of the vacuum tube in 1908 by De Forest, which allowed the constant production of high-frequency electrical current that could be used in resecting tissue. In 1926, Bumpus combined the cystoscope and the tubular punch. Also, at that time, Stearns developed the tungsten loop that could be used for the resection. This was put together by McCarthy in 1932, using a foroblique lens so that he could resect the tissue under direct vision using a wire loop.

In the 1970s the development of the fiberoptic lighting system, together with the Hopkins (1976) rod lens wide-angle system, significantly improved visualization for endoscopic surgery. Previously, the optical system was a series of small lenses placed in a rigid tube. In the Hopkins rod lens wide-angle system the air spaces were replaced by solid glass rods. The spacer tubes were shorter, resulting in minimal obstruction and increased admission of light.

Over the years, TURP, as a treatment modality for obstructing BPH, gained popularity throughout the world. It is now considered the gold standard for the surgical management of BPH. In the 1986 National Health Survey, 96% of patients had TURP when they had surgery done for BPH. It was estimated that 350,000 Medicare patients had TURP that year. However, today there are many medical and surgical alternatives to transurethral prostatectomy, and the number of TURPs has fallen to less than 200,000 per year in the Medicare age group.

Another factor that may have influenced the incidence of transurethral prostatectomy was the formal development of care guidelines for patients with BPH (McConnell et al, 1994). In 1989, the Omnibus Budget Reconciliation Act created the Federal Agency for Health Care Policy and Research (AHCPR). Patient care guidelines were demanded by Congress, and two of the first selected were the diagnosis and management of BPH. **It was the BPH Guideline Panel's recommendation that patients with minimal symptoms should undergo watchful waiting and that if intervention was to be considered in patients who were more symptomatic the patient should be informed of the harms and benefits of each therapeutic modality and participate actively in making the decision, not only whether to intervene but which treatment modality would be his choice.** Many patients opted for a less invasive procedure, although less effective than TURP.

Indications

In 1968, Lytton and coworkers (1968) estimated that the chance of a 40-year-old man having a prostatectomy in his lifetime was approximately 10%. However, Glynn and colleagues in 1985 raised the estimate to 29%. Arrighi and associates (1991), in reviewing the Baltimore Longitudinal Study on Aging (BLSA), believed that men older than 60 years had a 39% risk of requiring surgery in the next 20 years; men 50 to 59 years of age, a 24% chance; and men 40 to 49 years of age, a 13% chance.

There are very few studies of the natural history of patients who are seen initially because of modest symptoms of prostatism without an absolute indication for intervention (i.e., acute refractory urinary retention, recurrent infections). Ball and coworkers (1981) observed 97 patients for 5 years and found that the patients' symptoms were essentially the same in 52% and worse in only 16.5%. The urodynamic studies revealed little change in that group, and only 1.6% of the patients developed retention. Conversely, Birkhoff and associates (1976) observed 26 patients for 3 years and found a 50% to 70% worsening of the patients' subjective symptoms and 71% deterioration in objective criteria. Furthermore, acute retention was unpredictable.

The most common reasons for recommending intervention in a patient with symptoms of BOO and irritability are that the symptoms are moderate to severe, bothersome, and interfere with the patient's quality of life. Mebust and colleagues (1989) noted that 90% of patients undergoing TURP had symptoms of prostatism but 70% had another indication as well (e.g., acute urinary retention, occurring in 27%).

In 1989, the AUA initiated the Guideline Panel for Diagnosis and Management of Benign Prostatic Hyperplasia. Recognizing the significance of assessing the patients' symptoms, a system score was developed by the AUA's Measurement Committee, Winston Mebust, Chairman. Barry (1992) was the senior author of this questionnaire, which came to be known as the AUA-7 Symptom Index (shortened to AUASI and now also known as the IPSS) (Table 93–3). Other scoring systems have been developed, such as those by Madsen and Iversen (1983), Boyarsky and associates (1977), and the International Continence Society Study on BPH. However, the AUASI was validated as to its clarity, test-retest reliability, internal consistency, and criteria validity. The AHCPR took over the AUA BPH Guideline Panel in 1990. The Guideline Panel subsequently recommended a formal assessment of the patients' symptoms, using any scoring system but preferring the AUASI. Patients with mild symptoms (with a score of 0 to 7) were assigned to watchful waiting; those with moderate (8 to 19) or severe (20 to 35) symptoms would undergo further testing or treatment, or both. **The AUASI is not disease specific.** The questionnaire has been given to older women, who obviously do not have a prostate but may have bladder dysfunction, resulting in a significant score. The AUASI was considered to be part of the patient's initial evaluation but did not make the diagnosis of BPH.

The AUASI was adopted at the World Health Organization Consultation on BPH in Paris in 1991 (Mebust et al, 1991). In addition to the AUASI, one global quality of life question was added—"If you were to spend the rest of your life with your urinary condition, just the way it is now, how would you feel about it?" Responses ranged from "delighted" to "terrible." Therefore, not only should the patient's severity of symptoms be considered in deciding whether intervention is warranted, but also how much the patient is being bothered by his symptoms and how they affect his overall quality of life. It should be pointed out that patients having symptoms secondary to an obstructing prostate may have a variation in their symptoms over time. Ball and Smith (1982) noted that 31% of the patients they were observing had improvements in their symptoms. More recently there have been efforts to develop a concise questionnaire to evaluate further the degree to which the condition is bothersome or the impact on quality of life of patients with symptoms from BPH. Such an example is the BPH Impact Index (Barry et al, 1995) (Table 93–4).

Although symptoms constitute the primary reason for recommending intervention, in patients with an obstructing prostate there are some absolute indications. These are acute urinary retention, recurrent infection, recurrent hematuria, and azotemia. A postvoid residual urine has been used by some urologists as an indication, but, as pointed out by Bruskewitz and coworkers (1982), there can be extreme variability within a given patient as to the amount of postvoid residual when this factor is assessed repetitively over

Table 93–3.

American Urological Association (AUA) Symptom Index for Benign Prostatic Hyperplasia

	NOT AT ALL	LESS THAN 1 TIME IN 5	LESS THAN HALF THE TIME	ABOUT HALF THE TIME	MORE THAN HALF THE TIME	ALMOST ALWAYS
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	4	5
3. Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	None	1 time	2 times	3 times	4 times	5 or more times

AUA Symptom Score = sum of questions A1 to A7 = _____

Modified from McConnell, JD, Barry MJ, et al. Benign prostatic hyperplasia: diagnosis and treatment. Clinical practice guideline no. 8. Rockville (MD): U.S. Department of Health and Human Services, Agency for Health Care Policy and Research, Public Health Service; 1994. p. 1–17.

Table 93–4.

Benign Prostatic Hyperplasia (BPH) Impact Index

1. Over the past month, now much physical discomfort did any urinary problems cause you?	None	Only a little	Some	A lot
2. Over the past month, how much did you worry about your health because of urinary problems?	None	Only a little	Some	A lot
3. Overall, how bothersome has any trouble with urination been during the past month?	Not at all bothersome	Bothers me a little	Bothers me some	Bothers me a lot
4. Over the past month, how much of the time has any urinary problem kept you from doing the kinds of things you would usually do?	None of the time	A little of the time	Most of the time	All of the time

BPH Impact Index = sum of questions B1 to B4 = _____

From Barry MJ, Fowler FJ Jr, O'Leary MP, et al. Measuring disease-specific health status in men with benign prostatic hyperplasia. Med Care 1995;33(Suppl.):AS145–55.

a period of time. Furthermore, there is no information on the amount of postvoid residual urine that represents the point "that if nothing is done, irreparable damage to the bladder will occur." It was believed by the AHCPR BPH Panel (McConnell et al, 1994) that it might be of some use in following patients who are assigned to watchful waiting. In the AHCPR BPH Guideline, the patient's history is taken with focus on the urinary tract. Many of these patients have other comorbidity problems, and Mebust and colleagues (1989) noted that only 23% did not have a significant medical problem before surgery. The most common were pulmonary disorders (14.5%), gastrointestinal disorders (13.2%), myocardial infarction (12.5%), arrhythmia (12.4%), and renal insufficiency (4.5%). Therefore, a general medical evaluation is warranted.

A urinalysis is also recommended to be sure that the patient's symptoms are not related to infection. A digital rectal examination should be done, taking into consideration the consistency of the prostate, to help the urologist in determining whether the patient has cancer, and also for an estimate of size. The size of the prostate might be important in selecting what type of surgical therapy would be warranted (e.g., transurethral incision of the prostate or, in the very large prostate, an open prostatectomy). A serum creatinine value is also to be obtained. It was noted by Mebust and colleagues (1989) that patients with a serum creatinine level greater than 1.5% had a 25% incidence of postoperative complications versus 17% in those who had a normal creatinine level.

A number of tests are considered to be optional for the urologist in evaluating the patient with moderate to severe symptoms from BPH. Many consider uroflowmetry to be the single best noninvasive urodynamic test to detect lower tract obstruction. However, it should be pointed out that the patient's obstructive symptoms, when evaluated with a formal questionnaire, correlate poorly with uroflowmetry measurements. Furthermore, there is no specific cutoff point at which one can state that the patient is definitely obstructed. **A PFR less than 15 mL/sec does not differentiate between outflow obstruction and detrusor impairment.** Pressure-flow studies are recommended as an optional test.

This is one of the best ways to evaluate a patient's degree of obstruction and detrusor function, particularly when the diagnosis is unclear. However, it is invasive, is uncomfortable for the patient, requires expensive equipment, and requires considerable experience in performing so that the results are reproducible.

A number of tests are not recommended, such as a filling cystometrogram. Although this test can demonstrate uninhibited bladder contractions, it is invasive and does not give much more information than can be obtained from the patient's history of bladder irritability symptoms. **Cystoscopy, done routinely in the physician's office as a diagnostic procedure, is not recommended.** The only reason for performing cystoscopy in the urologist's office is if the urologist needs to know the size of the prostate and its configuration in making a recommendation about the type of therapy that would be useful for the patient (e.g., transurethral incision if a small prostate or an open prostatectomy if a very large prostate). If it is critical for the urologist to know the exact size when deciding whether the patient should have an open prostatectomy, TRUS is more precise than cystoscopy. Upper tract imaging is also not recommended to be performed routinely. Rather, it should be reserved for patients with hematuria or renal insufficiency or for those with a history of urinary infection, urinary tract surgery, or stones.

Anesthesia

Transurethral surgery of the prostate is usually performed with the use of a general or spinal anesthetic. However, Sinha and associates (1986) have reported doing TURP with the patient under local anesthesia. Birch and colleagues (1991) have recommended performing TURP using sedation and local anesthesia. However, they pointed out that the gland size should be less than 40 g. Nielsen and associates (1981) noted no difference in blood loss when the surgery was done with either an epidural or a general anesthetic. McGowan and Smith (1980) evaluated spinal anesthesia versus general anesthesia and found no difference in blood loss, postoperative morbidity, or mortality.

Use of an anesthetic should be individualized. During the procedure, the anesthetist should monitor the patient's tissue oxygen saturation, electrocardiogram, and, if warranted, a serum sodium level, in addition to the usual parameters.

Perioperative Antibiotics

Urinary tract infections can be found in 8% to 24% of BPH patients preoperatively. The infection should be treated before surgery. Prophylactic use of antibiotics, usually a single dose just before the start of surgery, has become the norm; and postoperative sepsis has been kept to a minimum in this way. In patients who have preoperative bacteriuria or a catheter in situ before surgery, the antibiotics should be continued until the catheter at time of surgery is removed. **It is recommended that patients should be given a first-generation cephalosporin in combination with gentamicin before the initiation of surgery.**

Monopolar versus Bipolar Techniques

Traditionally, TURP has been performed using monopolar technology with 1.5% glycine or mannitol as nonhemolytic fluids for irrigation. This technique has been used for a very long time with considerable success, but concerns about TUR syndrome have led to the introduction of bipolar TURP.

The standard monopolar TURP is now being challenged by the use of bipolar resection (Gyrus PlasmaKinetic System, Gyrus Medical, Maple Grove, MD). The rationale for the introduction of this system is that the complications of standard monopolar TURP need to be reduced to improve acceptability by patients. There has been a series of studies with the Gyrus system (Botto et al, 2001; Dunsmuir et al, 2003) and with the Vista CTR system (ACMI Corp.) (Singh et al, 2005). In a small retrospective study, 18 patients had conventional monopolar TURP, and 26 had bipolar TURP. The point was made by the authors that there have been few innovations in TURP technique in recent years and that this latest change has allowed earlier removal of the catheter and earlier discharge from hospital. The fact that all of these studies are short term, nonrandomized, and in some cases retrospective means that the observations on relative complication rates must be taken with some caution. However, this new technology may have something to offer. The Gyrus bipolar system consists of a generator with 200-W capability, an RF range of 320 to 450 kHz, and a voltage range of 254 to 350 V. There is a plasmakinetic resectoscope with a TUR loop of 80/20 platinum/iridium alloy electrode with the active and return electrode on the same axis (axipolar) separated by a ceramic insulator (Botto et al, 2001; Patel and Adshead, 2004).

In a systematic review of the literature and meta-analysis of randomized controlled trials, Mamoulakis and colleagues (2009) compared the two techniques. They found 16 randomized controlled trials with 1406 patients involved. Unfortunately, the overall trial quality was poor. A lack of information about allocation concealment and blinding outcome assessors was very frequently observed and the absence of prevention of statistical errors of bias because of underpowered studies was also commonly noted. Long-term efficacy evaluation of bipolar TURP was not possible and although the numbers of TUR syndrome and postoperative clot retention were significantly less than in monopolar TURP, owing to the relatively small patient volume in each treatment arm, in absolute numbers there was not a great deal of difference between the two techniques. Bipolar TURP may well turn out to be the technology of the future, but it is hoped there will be a number of well-designed multicenter randomized controlled trials with a longer follow-up and a cost analysis to prove this.

Surgical Technique

The surgical technique employed has been described in detail in previous editions of this textbook (Fitzpatrick and Mebust, 2002). It is not necessary to describe the technique in detail, but it is appropriate to show the diagrams of the technique described (Figs. 93-6 to 93-12).

Various surgical techniques have been developed by urologists for removing the adenoma. Every surgical technique employs the principle that the resection should be performed in a routine step-by-step manner. Another technique is demonstrated in Figures 93-13 to 93-15.

Management of Intraoperative Problems

Hemostasis

The amount of intraoperative bleeding depends on the size of the prostate, the length of time required to resect the adenoma, and, to a degree, the surgeon's skill. Arterial bleeding is controlled by electrocoagulation. This should be done as one completes each

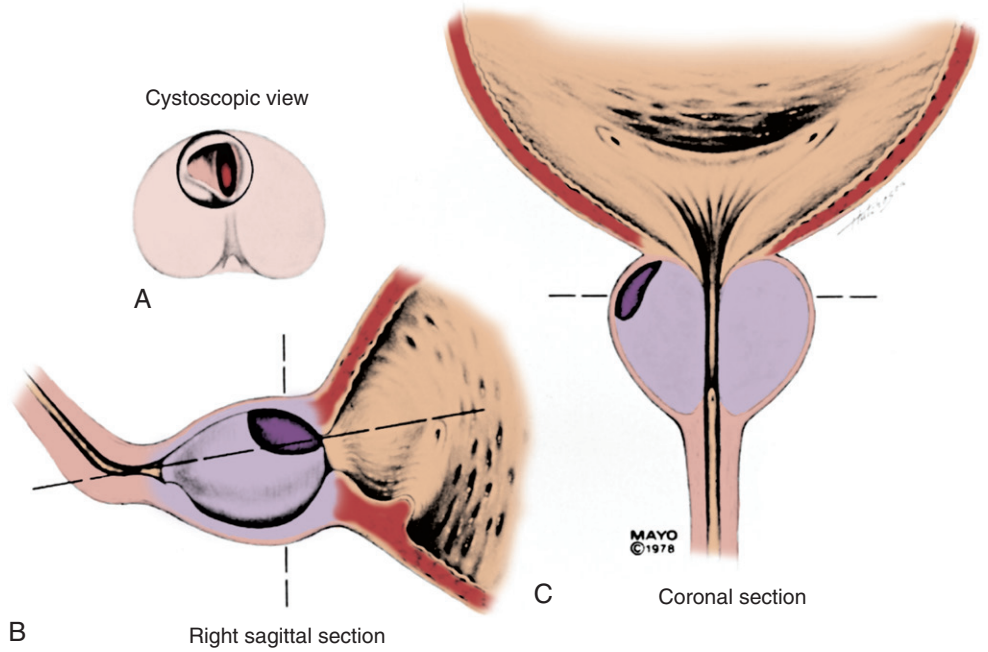


Figure 93–6. **A** to **C,** First stage of resection of the prostate. The resection is begun at the 12-o'clock position, and the tissue at the bladder neck and the adjacent adenoma are resected in quadrants. (©1978, the Mayo Foundation.)

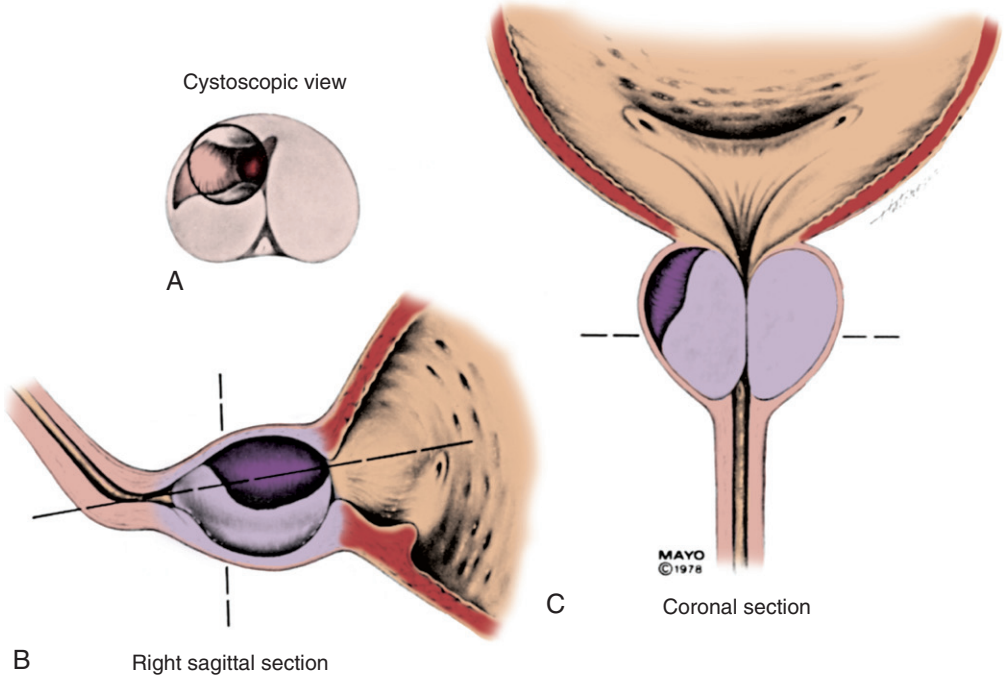


Figure 93–7. **A,** The midportion of the gland is resected starting at the 12-o'clock position and carrying it down to the 9-o'clock position. **B** and **C,** The sagittal and coronal section views are shown. (©1978, the Mayo Foundation.)

stage of the resection, before moving on to the next stage. **After the catheter is inserted, at the end of the surgical procedure, the irrigation fluid should be light pink.** If the irrigation fluid has a continued red color, one should suspect arterial bleeding. The surgeon should reinsert the resectoscope and coagulate the arterial bleeding. Venous bleeding is apparent at the end of the procedure, when on irrigating the catheter the return is initially clear but then dark blood later oozes from the catheter. Venous bleeding can be controlled by filling the bladder with 100 mL of irrigating fluid and placing the catheter on traction for 7 minutes at the operating table. The balloon of the catheter is overinflated to 50 mL of fluid.

Extravasation, or perforation of the prostatic capsule, occurs in about 2% of patients. The symptoms of extravasation are restlessness, nausea, vomiting, and abdominal pain, despite spinal anesthesia. Pain is usually localized to the lower abdomen and back.

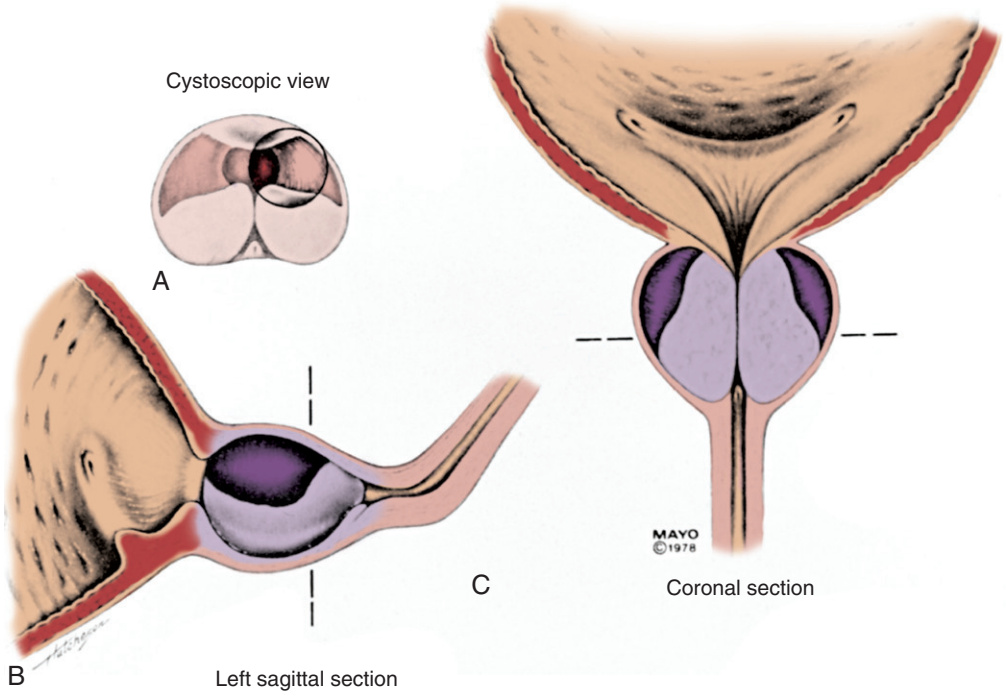


Figure 93–8. **A,** The resection is now begun at the 12-o'clock position, and the left side of the patient's gland in the midfossa is resected down to the 3-o'clock position. **B** and **C,** Sagittal and coronal sections are shown. (©1978, the Mayo Foundation.)

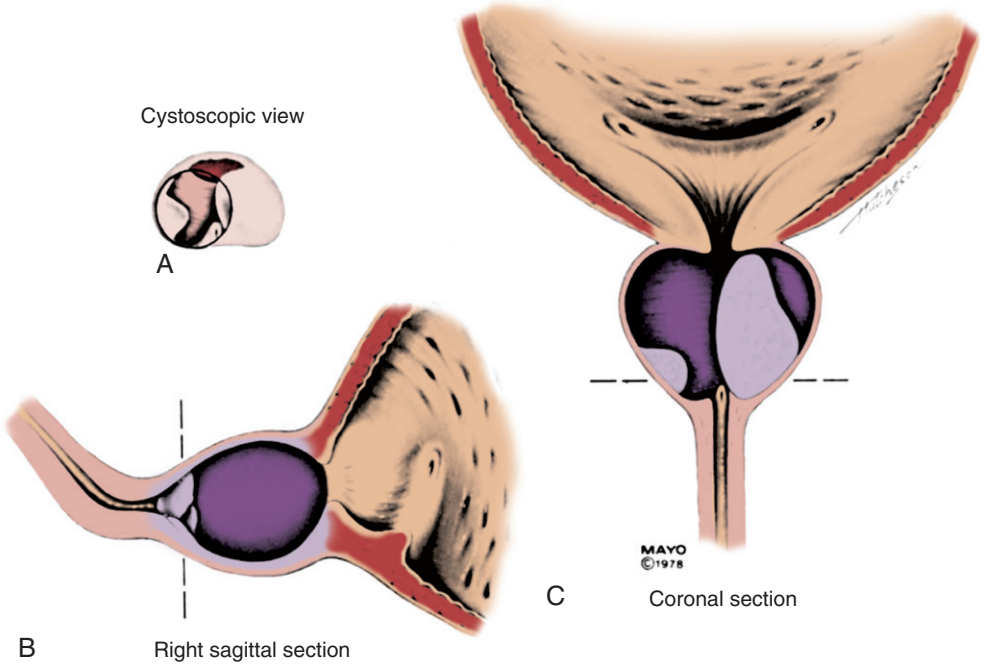


Figure 93–9. **A,** The midportion of the gland is resected farther down from the 9-o'clock position to the 6-o'clock position. **B** and **C,** Sagittal views. (©1978, the Mayo Foundation.)

If extravasation is suspected, the operation should be terminated as rapidly as possible but hemostasis must be secured. Bleeding must be controlled, even as the extravasation is increased, because simultaneous postoperative management of extravasation and hemorrhage is difficult. Cystography may provide information about the diagnosis and, to some degree, the extent of the extravasation. Over 90% of these patients can be managed simply by urethral catheter drainage and cessation of the operative procedure. If there is extensive extravasation and concern about infecting the perivesical tissue, suprapubic drainage should be instituted.

Transurethral Resection Syndrome

In the AUA cooperative study (Mebust et al, 1989), TUR syndrome occurred in 2% of the patients. The syndrome was characterized by mental confusion, nausea, vomiting, hypertension,

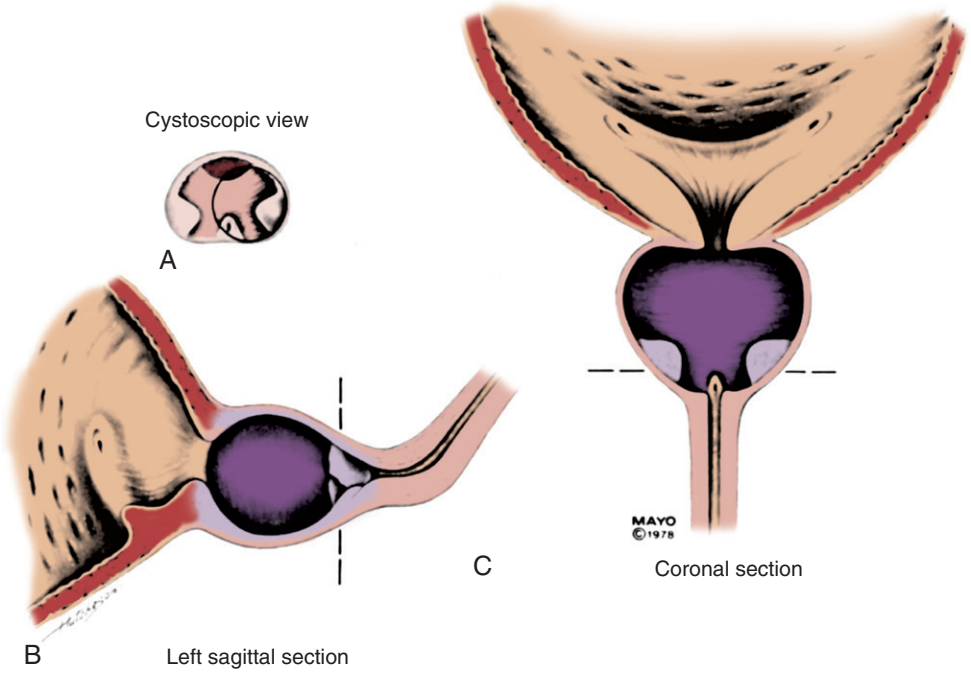


Figure 93–10. **A** to **C,** The tissue remaining at the apex is now resected. It is begun by initiating the resection next to the verumontanum and carrying it toward the 12-o'clock position. (©1978, the Mayo Foundation.)

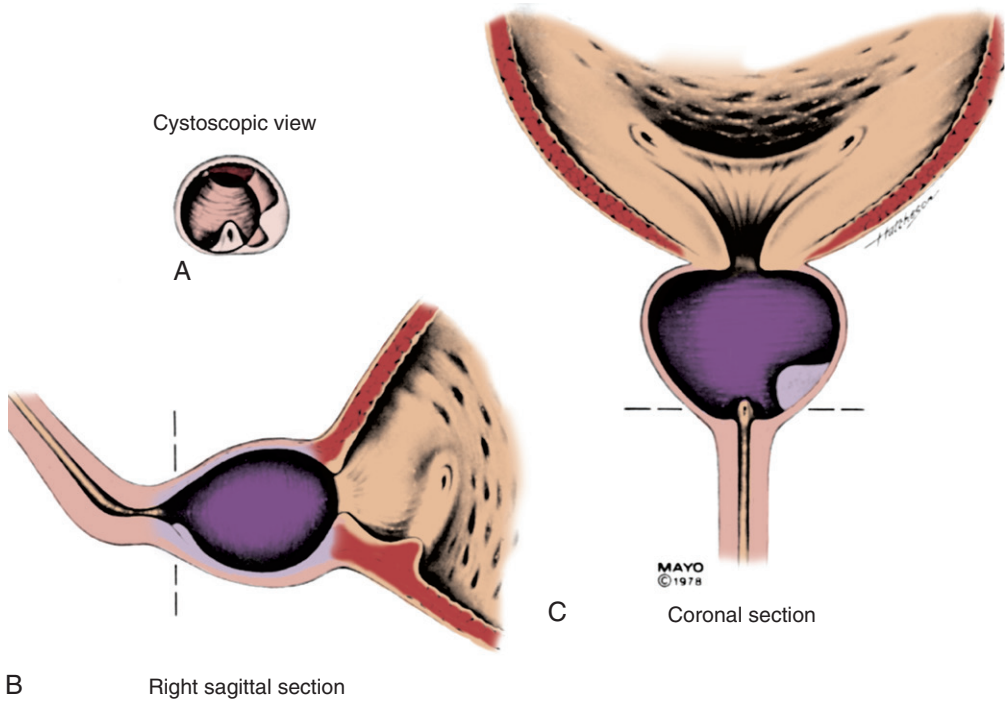


Figure 93–11. **A** to **C,** Residual tissue is carefully cleared on the patient's right side. (©1978, the Mayo Foundation.)

bradycardia, and visual disturbance. Usually, the patients do not become symptomatic until the serum sodium concentration reaches 125 mEq/dL. The risk is increased if the gland is larger than 45 g and the resection time is longer than 90 minutes.

In 1950, several studies were undertaken to determine the amount of fluid absorbed during TURP. Hagstrom (1955) weighed patients preoperatively and postoperatively and calculated that approximately 20 mL/min of fluid was absorbed by the patient. However, there was significant variation in patients. Oester and Madsen (1969), using a double-isotope technique, demonstrated that the average amount of fluid absorbed by the patient was 1000 mL and that one third of this fluid was absorbed intravenously. Madsen and Naber (1973) demonstrated that pressure in the prostatic fossa and the amount of fluid absorbed were dependent on the height of the fluid by the patient. They noted that when the height of the fluid was changed from 60 to 70 cm, fluid absorption was greater than twofold. They also reported that approximately 300 mL/min of fluid was needed for a good vision

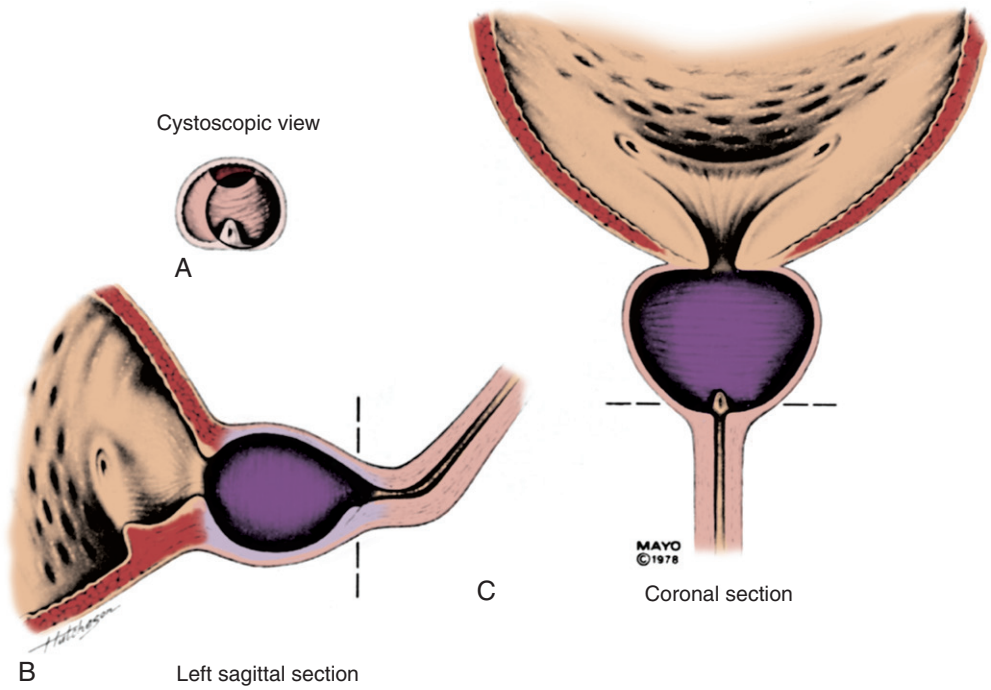


Figure 93–12. **A** to **C,** The remaining residual tissue is cleared from the patient's left side, leaving an unobstructed view from the verumontanum through the bladder neck into the bladder. (©1978, the Mayo Foundation.)

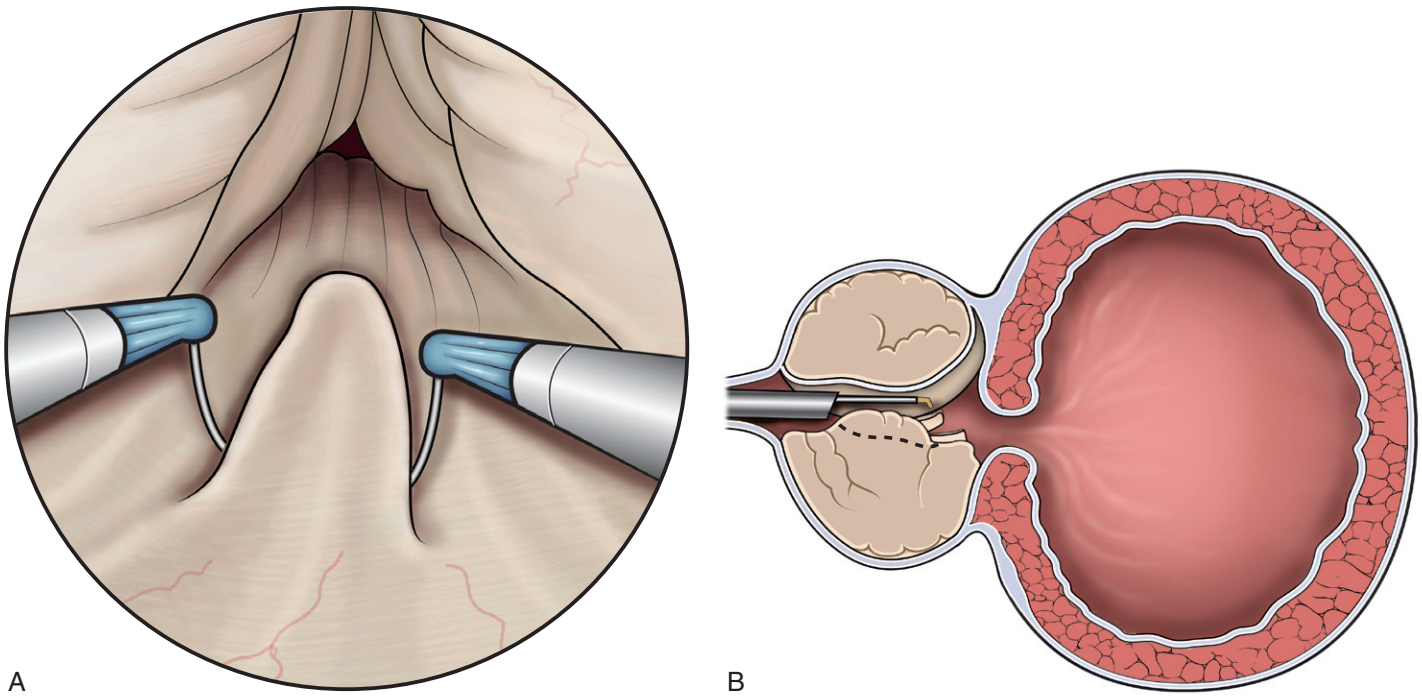


Figure 93-13. **A** and **B,** Resection usually begins at the proximal portion of the middle lobe at the 6-o'clock position. The resectoscope is placed just proximal to the verumontanum and the resection performed always controlling the end point of each cut. It is necessary to be aware of the position of the verumontanum to see that the lower part of the cut is not extending below this level or otherwise damage to the sphincter mechanism may occur. (Modified from May F, Hartung R. Surgical atlas: transurethral resection of the prostate. BJU Int 2006;98:921–34.)

field. This could not be achieved when the fluid level was below 60 cm H_2O. Harrison and colleagues (1956) believed that the TUR syndrome was related to dilutional hyponatremia. Certainly, the syndrome can be reduced by the administration of 3% saline solution. However, other factors have been suggested as a possible cause. Glycine is metabolized to glycolic acid and ammonium. Ammonium intoxication has been suggested as a possible cause of the TUR syndrome or direct toxic effect of the glycine. **Nevertheless, it is our belief that the TUR syndrome is secondary to dilutional hyponatremia.** This can be corrected by

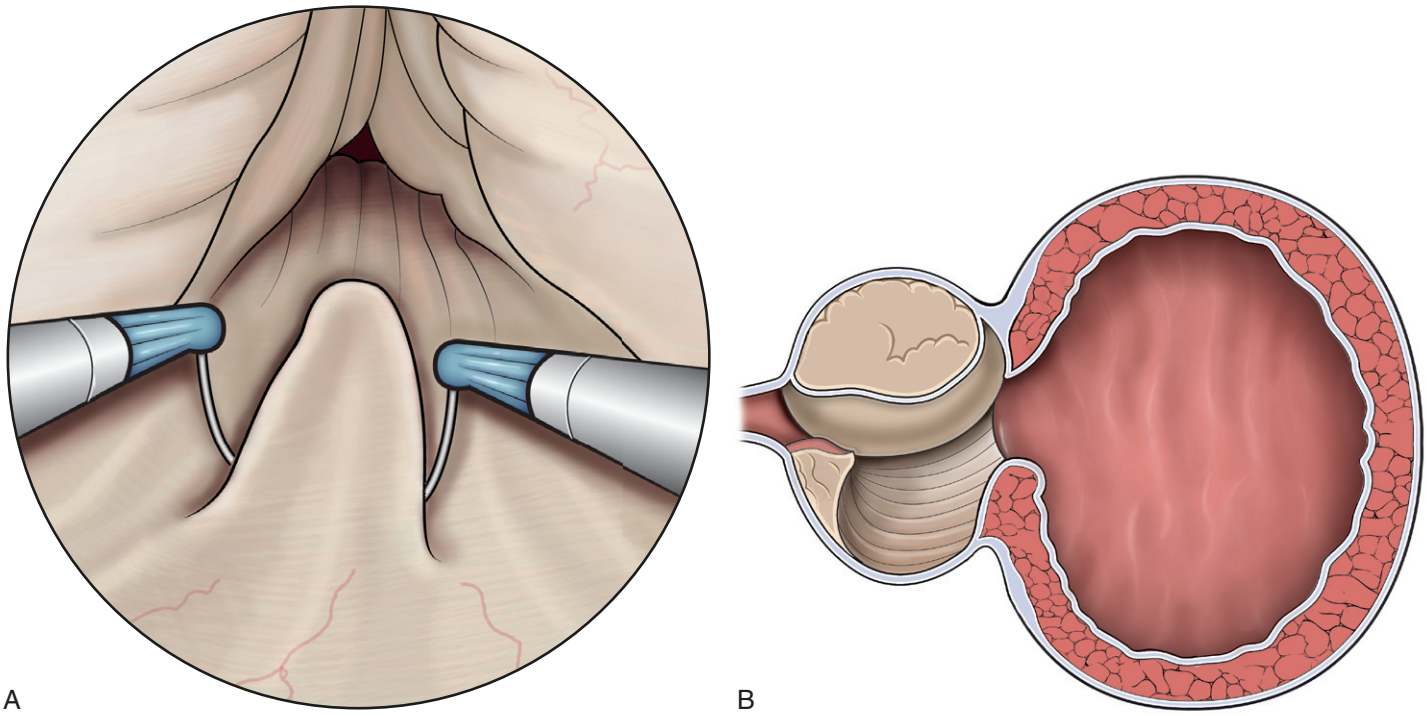


Figure 93-14. **A** and **B,** Resection should be performed with long cuts toward the verumontanum. A large overhanging middle lobe should be resected with special care. It is important to make short cuts in the region of the bladder neck, because the surgeon might not be aware that he or she is cutting down the trigone toward the ureteral orifices. Subsequent cuts are made down to the peripheral tissue, which is recognized as a rather fibrous structure compared with the granular appearance of the prostatic adenoma. (Modified from May F, Hartung R. Surgical atlas: transurethral resection of the prostate. BJU Int 2006;98:921–34).

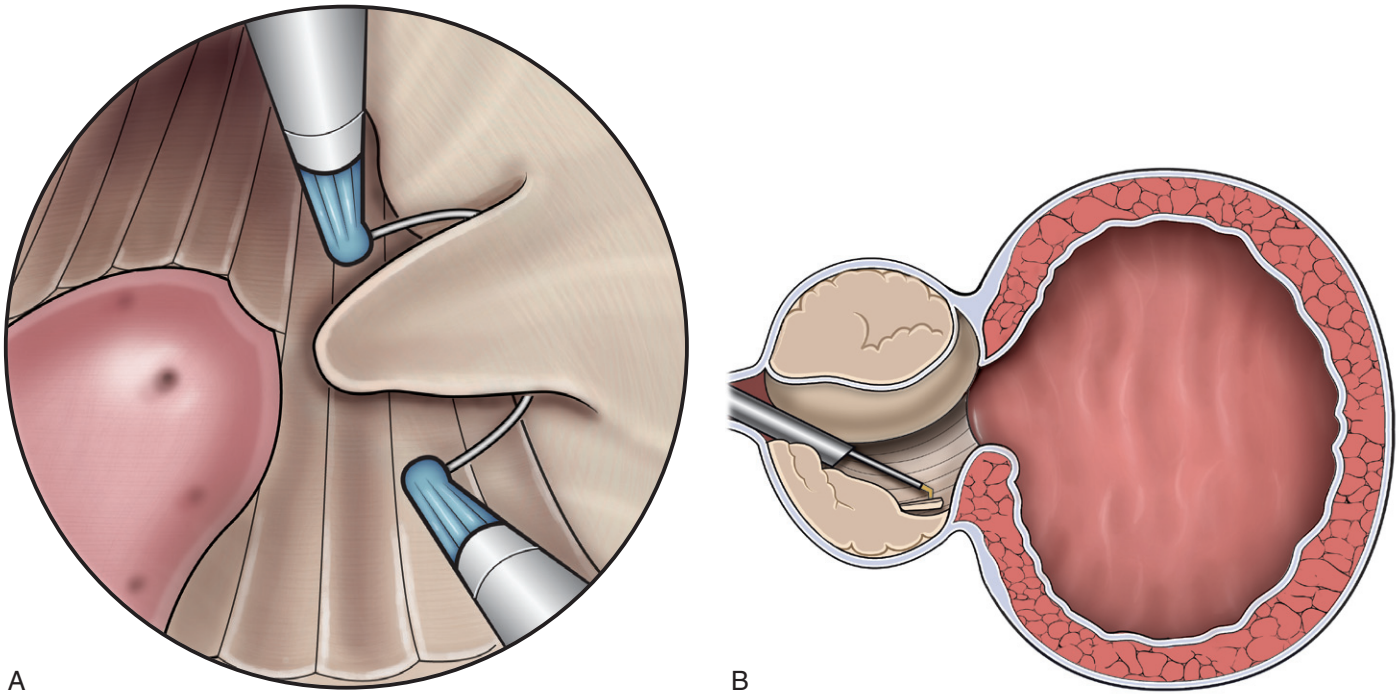


Figure 93-15. **A** and **B,** Resection in smaller adenomas is now carried directly to the side lobe. It depends on the preference of the surgeon whether to begin on the left and then to resect the other side or vice versa. (Modified from May F, Hartung R. Surgical atlas: transurethral resection of the prostate. BJU Int 2006;98:921–34).

giving the patient 200 mL of 3% saline solution very slowly over a period of time.

Conversely, one can attempt to calculate the amount of water overload by determining the serum sodium preoperatively and postoperatively, knowing the patient's weight, and determining the amount of extracellular fluid. Stalberg and coworkers (1992), in patients undergoing TURP with general anesthesia, tagged the irrigating fluid with 1% ethanol and measured the amount of ethanol excreted in the breath. This is believed to be a very effective and quick way of determining which patients are becoming

overloaded with fluid. In patients who have a large gland or when the operating time is being prolonged, a serum sodium value is routinely obtained, although the patient is still undergoing surgery. When patients demonstrate a drop in serum sodium level, diuretics (e.g., furosemide [Lasix]) are administered. The serum sodium concentration is measured in the postoperative recovery area, and, if need be, a further dose of diuretic is administered.

Intraoperative Priapism

During the surgical procedure a penile erection may occur, which may obviate the surgery unless a penile urethrostomy is performed. This has usually been managed by injecting an α-adrenergic agent directly into the corpora cavernosa. The solution of ephedrine or phenylephrine is usually diluted (e.g., 0.3 mL 1% phenylephrine diluted to 3 mL with normal saline solution for 100 μg/1 mL) (Lee et al, 1995).

Outcomes

Patients' Symptoms

In developing the guideline for the diagnosis and management of BPH, the AHCPR Guideline Panel (McConnell et al, 1994) asked patients what was the most significant factor they considered in deciding what type of therapy should be used in treating their BOO secondary to BPH. The foremost factor was relief of symptoms.

In reviewing the literature, the AHCPR Guideline Panel used meta-analysis to combine the various clinical studies. They noted that the chance of improvement of patients' symptoms after TURP was 70% to 96% confidence interval (CI), with a mean of 88%. The magnitude of reduction in symptom score was 85%. **This was significantly better than with less invasive procedures.**

Mortality

Over the past 50 to 60 years there has been a gradual reduction in the immediate postoperative mortality rate associated with TURP. Perrin and colleagues (1976) found a mortality rate of 5%, reported in the 1930s. Holtgrewe and Valk (1962) reported 2.5%; Melchior and associates (1974), 1.3%; and Mebust and coworkers (1989), 0.2%. This was the mortality rate noted at 30 days. The number of patients noted in each of these three studies was well over 2000.

Roos and colleagues (1989), using insurance claim data from England, Denmark, and Manitoba, Canada, noted that the death rate at 90 days was significantly higher compared with an open prostatectomy. They noted an early postoperative death rate of 2.9% in a study involving almost 40,000 patients. A meta-analysis of other series showed a mortality rate of 1.18%. However, including the study by Roos and colleagues with other reports, the mean estimate was 1.5% (90% CI, 0.5% to 0.3%).

In more recent studies, Ala-Opas and colleagues (1993) found no immediate mortality in a series of over 400 patients undergoing TURP. Chute and associates (1991), in an epidemiologic study, compared patients who had TURP with those who did not have TURP and found that the mortality rate over time was identical. Montorsi and coworkers (1993) compared a group of patients who underwent either TURP or open prostatectomy and found the mortality rate in each group was identical. Concato and colleagues (1992) compared a group of patients retrospectively, undergoing TURP or prostatectomy; and, when corrected for comorbidity, the mortality rate was the same for both groups. However, a chart review had been conducted by Malenka and associates (1990) looking at comorbidity factors in the Canadian population. They could not identify comorbidity factors to account for the apparent difference in mortality rate between TURP and open prostatectomy.

Fuglsig and coworkers (1994) age matched a group of patients who had undergone TURP with those who had not, and the mortality rate for the two groups was identical. The mortality rate could not be influenced by many factors, such as the type of hospital where the surgery was performed, the skill of the surgeon, the size of the gland, the operating time, or, again, comorbidity factors.

In reviewing the cause of death in the Canadian series it was found to be secondary to cardiac disease. In the patients who were studied in Denmark, death resulted from pulmonary complications. **This suggests that the observation by Roos and associates** (1989) **was truly related to comorbidity being significant in those undergoing TURP as opposed to those who underwent an open prostatectomy.**

The immediate morbidity rate after TURP was reported by Mebust and coworkers (1989) as 18%. This was similar to the rates reported by Holtgrewe and Valk (1962) and Melchior and associates (1974). Although the incidence was unchanged, in the Mebust report the incidence of significant complications (e.g., acute pyelonephritis) was not as high as that noted in the previous studies. The most common complications in the immediate postoperative period were failing to void (6.5%), bleeding requiring transfusion (3.9%), and clot retention (3.3%). The AHCPR BPH Guideline Panel (McConnell et al, 1994) found a mean immediate postoperative complication rate of 14.95% with a 90% CI of 5.2% to 30.7%. In more recent studies, the immediate postoperative complication rate has been noted by Plentka and associates (1991) (3.1%), Estey and colleagues (1993) (7.8%), and Chute and coworkers (1991) (4.2%). However, these are all retrospective studies.

Wasson and associates (1995) reported on a prospective randomized study in which patients were assigned to either watchful waiting or TURP. **Ninety-one percent of the men had no complication during the first 30 days after surgery. Specifically, there was no difference between either group in the incidence of urinary incontinence or impotence.** The most frequent complications noted were a need for replacement of urinary catheter (4%), perforation of the prostatic capsule (2%), and hemorrhage requiring transfusion (1%). At the end of 3 years of follow-up, the mortality rate was the same for each group. Twenty-three patients in the treatment group were considered treatment failures, and 47 patients were in the watchful waiting group. The failure rate in the watchful waiting group was 6.1 per 100 man-years of follow-up compared with 3 per 100 man-years of follow-up in the surgery group ($P = .002$). The higher rate in the watchful waiting group was largely attributed to a higher incidence of three outcomes: (1) intractable urinary retention (2.9% vs. 0.9%), (2) a high volume of residual urine (5% vs. 1.1%), and (3) a high urinary symptom score (4.3% vs. 0.4%). In those undergoing surgery there was improvement in PFR, reduction in the severity of symptoms, and reduction in the degree to which the symptoms bothered the patient. The authors noted that the outcomes of surgery were best for the men who were most bothered by urinary symptoms at baseline. This study refutes the uncontrolled observations in prior retrospective series that TUR frequently leads to incontinence and impotence, and it confirms that the incidence of short-term complications and re-treatment after surgery is low.

There are few data on the long-term outcomes of patients undergoing TURP. In the study conducted by Wasson and colleagues of 280 men undergoing surgery, at 3-year follow-up, 9 men had vesical neck contracture requiring endoscopic surgery, 9 had a urethral stricture that required dilatation, and 8 underwent a second TUR, 4 because of adenocarcinoma. Bruskewitz and coworkers (1986), in observing a series of patients over 3 years, noted that at 1 year most patients' symptoms improved (84%) and 10% remained approximately the same. At 3 years, 75% had improved and 13% remained the same. The change in symptomatology was the development of urge incontinence occurring in those patients several years after surgery. Only 1 of the 84 patients required a repeated resection, resulting in an incidence of 2%. However, 10% of the patients developed a vesical neck contracture.

Meyhoff and Nordling (1986) noted that 90% of their patients were considered to have satisfactory results at 5 years after TURP. Flow rates were improved from preoperative values, although there had been a slight decline in flow rates over the 5-year period. They did note an 8% re-resection rate, but all patients were noted to have especially small glands, suggesting that these might have been postoperative vesical neck contractures, as had been noted in the prior studies.

Ala-Opas and associates (1993) found that 92% of the patients were satisfied with the results of their surgery 6.5 years after the procedure had been done. Montorsi and associates (1993), in a group of patients observed for 5 years, found that 95% of the patients were unobstructed and subjectively satisfied about their urinary status.

In a large U.K. study, entitled The National Prostatectomy Audit (Emberton et al, 1995, 1996; Neal, 1997), 5361 patients who had undergone prostatectomy were reviewed by questionnaire. The findings were significant because of the large number of patients who responded, representing 89% of all those who had undergone the operation in four health regions of the United Kingdom. It was found that patients who were most bothered by their symptoms had the best response to surgery. The degree of preoperative evaluation varied greatly from urologist to urologist. Men who waited longer for surgery had worse symptoms by the time of their operation. Older men and those of a higher social class were more likely to undergo prostatectomy with fewer symptoms. Twelve percent of men throughout the study were undergoing surgery for the second time, and the clinical course of men having a second operation differed considerably from that of men having a first procedure.

A large study from Australia assessed the mortality and prostate cancer risk in 19,598 men after surgery for BPH. This was a population-based cohort of men in Western Australia operated on over a 17-year period (Holman et al, 1999). It was found that at 10 years the relative survival was 116.5% in patients who had TURP and 123.5% in patients after open prostatectomy. However, the relative risk of 1.20 fell to 1.10 (0.99 to 1.23) after adjustment for comorbidity. It was concluded that any excess mortality risk from TURP was small and clinically unimportant.

Another study found that just looking at mortality after TURP without attention to other issues could be misleading (Hargreave et al, 1996). A total of 81,997 men underwent prostatectomy in Scotland between 1968 and 1989. Although the study confirmed the increased risk of late mortality after TURP compared with open prostatectomy, it was found that limitations in the coding of the comorbidities and the absence of coding of more subtle aspects of the condition of the patient that may influence the choice between different types of prostatectomy mean that the differential mortality after the two procedures could reflect preoperative selection rather than the effects of the procedure itself.

Finally, in a review of 166 patients older than 80 years who had undergone TURP, with a mean follow-up of 60 months, it was found that 88.5% had an American Society of Anesthesiologists operative risk classification of III or IV, indicating a poor risk. All patients had at least one serious associated medical disease. Early complications occurred in 25.9%, late complications in 13.2%, and reoperation in 4.2%. The mortality rate within 30 days of operation was 1.2%, and 43 patients died during the follow-up period. The authors compared the Kaplan-Meier survival curves of the group under review with the expected survival rate of the age-matched population and found no statistical difference (Matani et al, 1996).

Summary

TURP was introduced as a method of treatment that was less invasive than open prostatectomy. Although evidence-based medicine now considers it imperative that a new treatment should be compared in a randomized fashion against a known standard, this did not happen with TURP. Thus it took at least 50 years for it to be accepted as the established treatment and it took even longer for its exact role in the therapeutic armamentarium to be found. Although comparative trials evaluating minimally invasive treatments against TURP in terms of efficacy have lost that particular battle in the majority of cases, the complication rate after TURP has not been thus compared. When looked at without the benefit of comparison in a randomized trial, TURP is still an incomparable treatment for BPH, particularly if the patient has a high "bother" score, has recurrent urinary tract infections caused by incomplete bladder emptying, or has outflow obstruction when measured by pressure-flow urodynamic studies.

TRANSURETHRAL VAPORIZATION OF THE PROSTATE

Whereas TURP removes tissue by resection of prostatic tissue and causes hemostasis by fulguration, transurethral vaporization of the prostate (TUVP) is brought about by combining the concepts of vaporization and desiccation. Desiccation is the drawing out of water from tissue, by drying out, rather than vaporizing the cells. This concept was introduced by Mebust and coworkers (1972, 1977) using a transurethral probe with direct-vision capabilities to heat and desiccate the prostate. TUVP was first described by Kaplan and Te (1995a, 1995b).

Mechanism of Action

With TUVP, two electrosurgical effects are combined: vaporization and desiccation. Vaporization steams tissue away using high heat, and coagulation uses lower heat to dry out tissue. Other factors are also involved that modify the delivery of electrical energy. These include the voltage production by the generator, the current density of the surface area of contact of the electrode, and the electrical resistance of the tissue being treated (Kaplan et al, 1998).

In the case of TUVP the electrode's leading edge is the point at which maximal efficiency for vaporization occurs, as well as that of current density delivery. At the point of the trailing edge of the electrode there is a decrease in the delivery of current, lowering the power and permitting tissue desiccation to occur.

Therefore vaporization occurs at the leading edge and desiccation occurs at the trailing edge (Kaplan et al, 1998).

The power of the generator determines whether vaporization occurs at the leading edge of the electrode. The electricity that is transmitted to the cell is converted to heat, resulting in the cell exploding or drying out. This is dependent on the conduction of electricity by the cell or the tissue resistance encountered by the current. In simple terms, the well-hydrated cell conducts electricity well, whereas the drier the tissue, the greater the electrical resistance. Clearly, a higher power is required to overcome this resistance, which may lead to poor vaporization if the power cannot be varied.

The type of generator used is also important in deciding the effectiveness of the vaporization. Older machines do not have a method of modulating delivery of power to the tissues depending on the degree of resistance encountered. Usually, therefore, the power is switched high to overcome this problem. The balance then is in some cases controlled by the limitation of the amount of current required to maintain a constant power. This safety feature prevents the delivery of an ever-increasing voltage that would compensate for the increase in resistance associated with the drying out of tissue that would occur with vaporization. This could potentially lead to unwanted damage both to the local tissues and to other areas such as the urethra. For this reason, modern generators specifically designed for TUVP can vary the delivery of power by reading tissue resistance. In addition, the safety feature described earlier whereby power can be limited is set at a higher level, thus making TUVP more efficient.

For TUVP, the cutting current power should be set to a maximum of 75% higher power than for a standard TURP, but the power used need not always be as high as this. In fact, it has been estimated that a minimal power delivery of 150 W is required for TUVP (van Swol et al, 1999).

Electrode Design

The *rollerball,* which is traditionally used for fulgurating the base of superficial bladder tumors, can be used for TUVP. However, it should not be used for prostates that are particularly large. In the study by Juma (1996), it was most effective in patients with glands whose mean volume as estimated by TRUS was 31.9 mL. The effectiveness in larger glands is probably limited by the shape of the rollerball, where the most satisfactory vaporization takes place at the middle part of the leading edge, assuming an equal distribution of contact pressure.

A *grooved rollerbar* has been widely used and consists of a bar that is 3 mm wide and 3 mm in diameter, which is composed of nickel-silver and insulated with Teflon (Vapor Trode, Circon-ACMI, Stamford, CT). The design is superior to the standard rollerball because the grooved design increases the number of leading edges at which electrovaporization takes place, and this allows increased efficiency of vaporization to a wide contact area and thus to a larger volume of tissue (Narayan et al, 1996; Reis et al, 1999). A similar grooved electrode has also been produced (Richard Wolf, Germany), known as the EVAP.

New second-generation vaporizing electrodes have been manufactured and evaluated. They have the aim of both vaporizing and resecting prostatic tissue simultaneously and have been termed *vaporizing loops* by some. The technique has been given several possible names in the literature, all amounting to the same thing: transurethral vaporization-resection of the prostate (TUVRP), thick-loop TURP, vapor-cut electrovaporization-resection (Cabelin et al, 2000).

Some examples of these are testament to the inventiveness of many of the instrument companies in relation to design. The Vapor Tome (Circon-ACMI, Stamford, CT) is a thick loop with grooves, giving a thin leading edge for vaporization and a thick trailing edge for desiccation. The Wedge (Microvasive, Natick, MA) is a smooth loop with the same edge configuration, made of stainless steel, tungsten, and chromium. The Wing EVAP (Richard Wolf, Germany) is a semicircular gold-plated wide loop that is wider and thicker than the standard TURP loop (Cabelin et al, 2000). Other modifications are under investigation, in which not only new electrodes but also specific electrosurgical generators are being developed, the aim of which is to reduce side effects while maintaining efficacy and also decreasing the potential risks of high-voltage power to the tissues surrounding the prostate.

Clinical Experience with Electrovaporization

The first report of TUVP was from Kaplan and Te (1995a), using the Vapor Trode. They reported on 25 men with moderate LUTS with a mean prostatic size of 57.6 mL. **There was an improvement in AUASI from 17.8 to 4.2 at 3 months and in PFR from 7.4 to 17.3 mL/sec at the same time.** The most encouraging findings were that all of the patients had their catheters removed within 24 hours (mean, 14.6), but by 3 months 1 patient had developed a distal urethral stricture. In the study by Juma (1996) using the standard rollerball in a study of 20 patients for 3 months, the results were similar, although 1 patient developed a bladder neck stenosis and 1 required repeated TURP.

Other pilot studies also suggested that a comparative trial would be appropriate because of the efficacy and safety that had been demonstrated. Galluci and his colleagues (1996) treated 35 patients with the Vapor Trode and found that improvements at 28 days were as encouraging as those at 3 months in other studies (PFR, 9.8 to 20.74 mL/sec; AUASI score, 18.2 to 10.4), but of note was that the standard deviation of the mean in both cases was very wide. Stewart and colleagues (1995) with the same electrode treated 34 patients, 20 of whom were in urinary retention; 33 of 34 were voiding satisfactorily. In a study of 22 patients subjected to pressure-flow analysis at 6 months, the mean Pdet at PFR decreased from 108 to 39 cm H_2O (Okada et al, 1998). Similar results related to relief of obstruction in 91 patients were reported by Matos Ferreira and Varregoso (1997).

Comparative Studies

All of the pilot studies were short term, none longer than 6 months, but comparative studies were indicated, and several of these compare TUVP with TURP. Patel and colleagues (2000) have carefully reviewed five of these in which different types of electrode were used (Galluci et al, 1996; Patel et al, 1997; Shokeir et al, 1997; Hammadeh et al, 1998; McAllister et al, 1998). **A total of 270 patients had TURP, whereas 262 patients had TUVP. A comparison of complications shows that postoperative irritative symptoms, urinary infection, 1-year reoperation rate, and urethral stricture were the same in both groups. However, catheter duration postoperatively, hematuria, transfusion rate, and retrograde ejaculation were lower in the TUVP group, as was hospital stay.** Operating time, postoperative urinary retention, impotence, and urinary incontinence were higher in the TUVP group. Again, these

were all short-term studies, with follow-up to a maximum of 1 year. In some cases, the numbers of patients who had actually reached 1-year follow-up were not stated. In addition, the range on either side of the mean was quite wide. All of the studies showed significant improvements in symptom score and PFR, which were maintained to the time of maximal follow-up in the study reported.

In most studies the size of the prostate gland operated on was 60 mL or less as measured by TRUS. The follow-up period for these studies needs to be much longer than 1 year so that the comment "TUVP is an acceptable alternative to TURP" can be sustained. In addition, the complication rates in some studies are rather high; for example, the study by De Sautel and colleagues (1998) shows that in a relatively small number of cases TUVP is as effective as TURP in relieving urodynamically proven outflow obstruction, but the overall complication rate for TUVP was 17.5%.

There has been a somewhat longer randomized trial comparing TUVP with TURP (McAllister et al, 2003). In this study, 235 patients with symptomatic BPH were randomly assigned to the two treatment options and it was a multicenter trial from four study centers in the United Kingdom. Forty-five of the 235 presented with acute urinary retention, and for the remainder a reduction in IPSS of 5 or more points was defined as success; statistically, and using this definition of success, 220 patients were required in the study to be able to detect a 15% difference in treatment outcome with 80% power at the 5% level. The mean reduction in prostate volume was the same in both groups, as were the operating time, hospital stay, and the improvement in symptom score, PFR, and postvoid residual volume. The transfusion rate was higher in the TURP group. At 6 months, 9% of the TURP group had become impotent, compared with 17% in the TUVP group, but this difference was not statistically significant.

A meta-analysis was performed comparing the efficacy and safety of TUVP and TURP for symptomatic BOO secondary to BPH. From a total of 25 randomized controlled trials, 20 met the predefined inclusion criteria and were subjected to a formal analysis. A total of 1489 patients were randomly assigned to TUVP (708) or TURP (781). There was a considerable variation in the follow-up, but the median was 12 months. The meta-analysis found a considerable limitation to most of the studies, particularly pertaining to the justification of sample size, randomization, the procedure for concealing treatment allocation, and the appropriate handling of study withdrawals to maintain the principle of intention-to-treat analysis. None of the studies estimated the sample size before starting the study as part of their calculation of statistical power, and only two described how the random allocation sequence was generated. There was also a considerable variation in the method of reporting the outcomes of the individual studies. Once again, this meta-analysis, as others related to other minimally invasive treatments have shown, demonstrates a poor database for drawing meaningful conclusions. However, it did suggest that TURP and TUVP provide comparable improvements in AUASI score and PFR for up to 1 year of follow-up (Poulakis et al, 2004).

Vaporization-Resection

A number of relatively short-term pilot studies using the Wing, Wedge, and Vapor Cut electrodes have been published and have been summarized by Cabelin and colleagues (2000). They have shown that the efficacy and complication rates are the same as with the standard Vapor Trode. The number of patients treated varied from 31 to 91, and the size of the gland ranged from 39 to 59.6 mL. The operating time was long (49.3 to 56.7 minutes), but the AUASI score decreased from 24.3 to 4.1 with the Wing and from 19.0 to 7.2 with the Vapor Cut. The PFR improved from 5.2 and 8.9 to 16.0 and 18.4 mL/sec, respectively (Perlmutter and Schulsinger, 1998; Küpeli et al, 1999; Perlmutter and Vallencien, 1999; Talic, 1999).

A comparative study between TUVRP and TURP has been reported by Talic and coworkers (2000). The Wing resection electrode was used in the TUVRP group. All patients were observed for about 9 months, with a range of 6 to 15 months. At 6 months the TUVRP group had improvements in AUASI score (24.9 to 4 ± 3.4) and PFR (7.5 to 19 ± 6.5 mL/sec); the TURP group had comparable improvements in symptom score (20.1 to 5.6 ± 3.1) and PFR (9.1 to 15.2 ± 10 mL/sec). Of particular note is the very wide range on either side of the mean values.

Summary

TUVP and TUVRP are technologic innovations based on an idea that has been present for some years. Modifications are being made in the equipment that will make this even safer and that will prevent some of the potential problems associated with the delivery of high power to tissues. **Efficacy appears similar to that of TURP, but the studies are short-term evaluations and the glands operated on are relatively small. The short-term complication profile appears to be better than with TURP, but further studies are required to prove this because there is a certain variability in the rate of occurrence of some of them.** In general, although the catheterization time is shorter than with TURP, the operating time is longer. Before this can be accepted as a technique that will replace TURP, long-term multicenter randomized trials are required. However, the technologic improvements and the consistently similar short-term improvements in AUASI score and PFR are encouraging.

TRANSURETHRAL INCISION OF THE PROSTATE

If a poll were to be taken among urologists as to how many would favor a transurethral incision of the prostate (TUIP) as treatment for symptomatic BPH, it is likely that the number would be very small. However, TUIP has been available since the 19th century. Edwards and colleagues (1985) credit Bottini with describing the technique in 1887, but Hedlund and Ek (1985) credit Guthrie in 1834. Guthrie's technique was to disrupt the bladder neck, whereas Bottini used diathermy to divide it. However, in 1973, Orandi published the first significant series on TUIP. The procedure seemed to be most useful in those who had a small prostate and who had obstructive bladder outflow symptoms. Classically, the patient was a younger man when compared with those having TURP (Orandi, 1973).

Technique

The surgical technique is relatively simple. With a Collings knife, an incision is made at the 5- and 7-o'clock positions or on one side of the midline only. It starts just distal to the ureteral orifice and ends just proximal to the verumontanum (Fig. 93–16). The incision depth should be

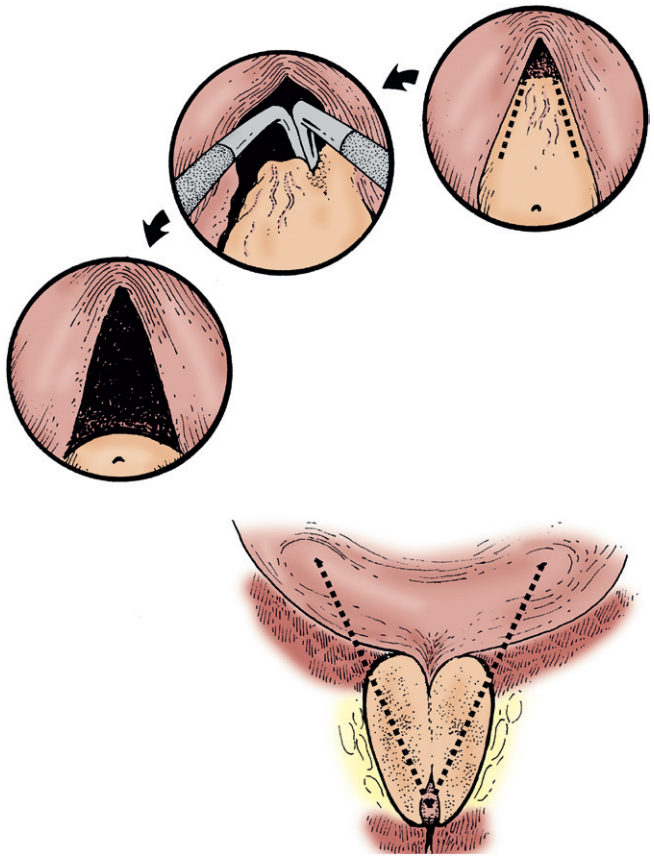


Figure 93–16. Transurethral incision of the prostate. The incision is started at the ureteral orifice and carried through the bladder neck up to the verumontanum. This procedure is done bilaterally. (From Mebust WK. A review of TURP complications and the National Cooperative Study, lesson 24, volume VIII. 1989. p. 189–90.)

to the point at which fine filaments of the external capsule are seen. Care must be taken not to incise too deeply because extravasation of irrigation fluid or rectal injury may occur. With completion of the incisions and with the scope in the more distal urethra there should be no visible obstruction to the bladder outflow.

Complications

The advantage of TUIP is that it is quick, technically easier, and associated with less morbidity and a decrease in retrograde ejaculation compared with TURP. The incidence of retrograde ejaculation after TURP ranges from 50% to 95%; but after TUIP it has been reported as occurring in 0% to 37% of cases. Turner-Warwick (1979) noted that with one incision the incidence of retrograde ejaculation was less than 5% but with two incisions it was 15%. Hedlund and Ek (1985) reported no difference between this incidence with one and with two incisions.

Clinical Efficacy

The procedure has been assessed by some open studies using strict urodynamic criteria for evaluation. Edwards and Powell (1982) found a significant reduction in voiding pressure after TUIP. Kelly and colleagues (1989) used pressure-flow curves and showed a significant fall in voiding pressure, with shift of the Pdet at PFR from the obstructive to the equivocal range on the Abrams-Griffiths nomogram. They found it to be less effective than TURP in relieving obstruction. Katz and colleagues (1990) noted a satisfaction rating of up to 94% with a significant improvement in symptoms and PFR after TUIP.

Sirls and colleagues (1993) reviewed 41 men (mean age, 63.4 years) for a mean follow-up of 53 months. **The Boyarsky symptom score decreased from 12.5 to 6.9, and the PFR improved from 10.3 to 15.3 mL/sec. The postvoid residual urine volume decreased from 179.8 to 99.4.** The Pdet at PFR decreased from 84.5 to 44.5 cm H_2O, all of which indicated an excellent response to TUIP, particularly if the prostate gland weighed 30 g or less.

In the largest series, Orandi (1985) reported on 646 patients whom he had observed from 3 months to 15 years, finding a reoperation rate of 9.6%.

Comparative Studies

Orandi (1973), in a prospective study over a 2-year period of 132 patients managed with TURP or TUIP, found that the results and complications did favor TUIP but there was no statistically significant difference between the two treatments. The only apparent difference was the higher incidence of bladder neck contraction after TURP.

Miller and associates (1992) reported on 108 patients who underwent a bladder neck incision and compared them with a similar group undergoing TURP. They believed that bladder neck incision was better than TURP in terms of a shorter operative time and shorter duration of catheterization. No other perioperative differences were found. For the 10-year follow-up there was no difference in reoperation rates between the two groups, with an equally high approval by patients after both procedures. In another comparative study, Soonawalla and Pardanini (1992) found that the PFR increased from 8 to 19 mL/sec after TUIP and from 8 to 21 mL/sec after TURP.

Dorflinger and coworkers (1992) randomly assigned 60 patients to either TURP or TUIP. They found that both operations significantly improved AUASI score and PFR, but the improvement in PFR was better for the TURP group. Neither operation caused any significant change in sexual activity or erectile function postoperatively. Retrograde ejaculation was a more common occurrence in patients treated by TURP. Riehmann and colleagues (1995) randomly assigned 56 patients to TURP and 61 to TUIP, and there was a mean follow-up of 34 months. Differences in PFR improvement were significant statistically at 3 months and 24 months only and not at any other time. Retrograde ejaculation was twice as common in the TURP group. Reoperation was required in slightly more patients in the TUIP group, but the difference was not statistically significant. The AHCPR BPH Guideline Panel (McConnell et al, 1994) performed a meta-analysis of the various studies, and the results are noted in Table 93–5. There is a slightly better chance of improvement of symptoms of patients treated by TURP, as there is in the degree of that improvement.

Summary

TUIP is effective in treating patients with LUTS caused by BOO. It has been shown to have an important role in the management of younger patients, especially if the prostate is smaller than 30 g. The efficacy is comparable in such patients with TURP, and the results are maintained in the long term. The technique is simple, and the morbidity is low.

Table 93–5.

Treatment Outcomes Balance Sheet

OUTCOME	TUIP	TURP
Chance of symptom improvement	78%-83% (80)	75%-96% (88)
Degree of symptom improvement	73%	85%
Morbidity (20% significant)	2.2%-33% (14)	5.2%-30.7% (16)
Mortality (30-90 days)	0.2%-1.5%	0.53%-3.31%
Incontinence (total)	0.061%-1.1%	0.68%-1.4%
Operative treatment for surgical complications	1.34%-2.65%	0.68%-10%
Impotence	3.9%-24.5%	3.3%-34.8%
Retrograde ejaculation	6%-55%	25%-99%

TUIP, transurethral incision of the prostate; TURP, transurethral resection of the prostate.

From Barry MJ, Fowler FJ Jr, O'Leary MP, et al. The American Urological Association's symptom index for benign prostatic hyperplasia. J Urol 1992; 148:1549–57. ©1992, Lea & Febiger.

OTHER TECHNOLOGIES

There are some other approaches that have not been previously mentioned in this chapter but they are included only to complete the picture. There is no significant evidence available to support any of these as having a future in the treatment of symptomatic BPH. The literature mainly consists of open studies, which in many cases would correspond to phase 1 trials or very small phase 2 trials.

Water-Induced Thermotherapy

Water-induced thermotherapy is another treatment introduced to treat LUTS and to reduce BOO secondary to BPH. An early article (Corica et al, 2000) assessed its effect on prostatic tissue, using it in both benign and malignant prostates, in 27 patients. The patients were awake, with local anesthetic gel inserted urethrally. The discomfort experienced by patients was recorded as mild. Pathologic examination of the removed prostate consistently showed periurethral hemorrhagic necrosis extending up to 11 mm from the urethra, focal or extensive urothelial denudation, and mild inflammation.

The same group of authors subsequently developed a novel rapid high-temperature, liquid-filled, flexible balloon thermotherapy system (Corica et al, 2003). The same anesthesia as previously was used in 17 patients, and a full histologic study was performed. Again, consistent findings were recorded, including periurethral hemorrhagic necrosis, extensive denudation, and varying degrees of inflammation. The mean depth of necrosis was 0.9 cm, involving a mean of 16% of the prostatic adenoma. In the prostates examined later, the necrotic tissue had been replaced by scar tissue (fibrosis and hyalinization) with a mean depth of 0.13 cm.

In a small open study, two slightly different temperatures were used in two groups of patients (Breda and Isgro, 2002). Because of the small numbers the results are somewhat difficult in that the temperature did not matter and that previously catheter-dependent patients were able to void with a PFR of 10.7 to 11.5 mL/sec in 73% to 88% of patients.

There has been a prospective multicenter trial performed involving 125 patients (Muschter et al, 2000). **Improvement was noted at 3 months, extending to 12 months. The IPSS at 12 months had improved by a median of 12.5 symptom units and the PFR improved by 6.4 mL/sec over baseline. This was not a comparative study. Side effects were minimal. The authors concluded that the treatment held promise as a useful and cost-effective option for management of BPH. In a later review of the topic, the failure rate and rate of subsequent TURP were reported as 5.6% after 12 months, 9.6% after 24 months, and 11.2% after 36 months** (Muschter, 2003).

Transurethral Ethanol Ablation of the Prostate

This technique has not been subjected to a great deal of in-depth study. It was initially introduced as a transperineal injection, with phenol being the agent injected (Talwar and Pande, 1966; Angell, 1969). There was clear evidence from several early studies that the agent injected leaked extraprostatically, with consequently a relatively high incidence of significant adverse events. The development of a transurethral method of injecting ethanol has been seen as a safer approach (Goya et al, 1999; Ditrolio et al, 2002). A detailed description of the injection technique is to be found in these articles and in the study presented by Plante and colleagues (2003), who also describe the histologic findings observed in the canine prostate. They found a considerable lobular volume of necrosis (mean of 42.6%); and although the findings were not absolutely consistent, they found that the prostate capsule always acted as a relative barrier to ethanol diffusion after transurethral injection.

A European multicenter study has been performed in 115 symptomatic BPH patients using transurethral ethanol ablation of the prostate (Grise et al, 2004), **and 94 of these patients were observed for 12 months. An average reduction in prostate volume of 16% was found, with a small adverse event rate and a requirement for TURP in 7% of patients in that time period. Relatively modest improvements in IPSS and PFR were reported, with 98% of patients voiding spontaneously 4 days after treatment.**

Rotoresection of the Prostate

This technique has not been widely reported, but early studies, both experimental and clinical, have been published. It has been designed for conventional transurethral application, with an axially adjustable actively rotating crank with a milling-head spiked electrode fitting into a specifically designed working element instead of a loop electrode. It is driven by a micromotor, which transmits rotation to the electrode by an angled drill handle. The first use of this system was reported by Michel and coworkers in 1996. In an experimental porcine model these researchers found a rate of time ablation comparable to that of a standard resection loop (5.5 to 6.0 g/min) and more than twice that of electrovaporization (1.7 to 2.0 g/min). The rate of bleeding was significantly better than for either, and the depth of tissue coagulation was 1.5 mm, compared with 0.4 mm with TURP.

There have been three clinical studies. Michel and coworkers (2003) used the rotoresect system in 84 patients and evaluated them for up to 4 years. They found no change in hemoglobin or serum sodium values. The mean duration of catheterization was 1.4 days. There was an early significant improvement in IPSS and PFR, which lasted to the 4-year evaluation.

A prospective study was carried out, and results at 12 months (Wadie et al, 2003) **and 24 months** (Wadie et al, 2005) **have been published. In the latter report the results of 23 of the original 24 patients have been evaluable. The AUASI score decreased from 20.5 ± 3.8 to 1.12 ± 1.56, and the PFR rose from 8.7 ± 2.1 to 21.8 ± 8.5 mL/sec, results comparable to those reported earlier. Again, the complication rate was found to be low.**

SUMMARY

Since the previous edition of this book there is very little new apart from the explosion of interest in the newer types of laser therapy. Many of the recent papers on thermotherapy describe newer techniques but once again fail to get to the "meat" of the subject, which is to answer the question as to the exact position of thermotherapy in the management of BPH. Even in the case of the laser therapies, the authors do not tell the reader if they consider that they will actually overtake TURP and supplant it in the future. In addition, the standard of trials has not improved greatly, with many still being open label studies with no comparator group; some of the comparative studies have group sizes that do not give the impression of having been powered statistically to show either equivalence or a specifically stated difference. There have been several new meta-analyses or systematic literature reviews, which may help the reader to make a more balanced, evidence-based decision.

There has been much discussion as to which of these therapies is better than TURP. At present, it would seem that TURP is either equivalent to the best of the minimally invasive therapies or better than most in terms of improvement of subjective and objective indices. As was stated in the introduction, however, it is not only the efficacy of the treatment that must be compared with TURP. The adverse event profile, the requirement for intravenous sedation, length of hospitalization, and cost also are all very important.

The vast majority of trials that have been reported compare a treatment with TURP only against efficacy, whereas it would be of benefit to the urologist if trials could view the comparison of the other factors in a prospective way, perhaps even excluding efficacy. This has been done by some authors, but a major multicenter approach would give the best information. In this way, it would be clear which is the best way to treat BPH.

However, the view could be taken that it is not necessary to find a minimally invasive treatment that is better than TURP. For example, none of the drug treatments has even come close to the efficacy of TURP, but they have been demonstrated to be of lasting value in management and have found a very specific place in the treatment armamentarium of BPH. In that case, the questions just posed would need to be answered very carefully.

It might be considered controversial to state that perhaps patients should be allowed to have sequential treatments. It is known that some patients do not respond well to specific minimally invasive treatments, so perhaps they might have a second treatment with the same modality, even a relatively short time after the first. There may be cost implications that would have the hospital managers shaking their heads, but it would certainly lower hospital bed requirements if it proved successful. In the same way, if a treatment proved efficacious for a 3-year period and then the symptoms returned, it is conceivable that a further treatment might return the patient to symptomatic well-being, even if a further full evaluation was required.

What is definitely necessary is that the exact place for each treatment modality should be found. Some may well have a small but well-defined role in the management of BPH, and, in the case of others, this role may be larger. One of the problems with extracorporeal shockwave lithotripsy was that it took a long time to find exactly how it should be used to treat, for example, staghorn renal calculi; no comparative trial was performed. In the same way, TURP was introduced without a comparative trial; and although it is recognized now as the gold standard, it took several decades before this happened. Minimally invasive treatments are in most cases pitted against TURP, but with many of them this has been a wasted exercise because in the preliminary open studies they could have clearly been seen not to be as efficacious. Commercial necessity requires comparison against a recognized treatment, but often this is not in the patients' best interests. It may be that the treatment has a lesser, but equally important, role to play.

At the International Consultation on BPH, held in July 2000, the committee that discussed "International Therapy for Benign Prostatic Hyperplasia" prepared a report (Debruyne et al, 2001). In it was outlined final recommendations on the use of such treatments, which were defined as acceptable, acceptable with restriction, investigational, or unacceptable. This decision was based on several meetings between the members of the panel and is rather a suggestion than an instruction to urologists.

The panel found that a number of treatments for BPH were unacceptable: balloon dilatation, hyperthermia, and high-intensity focused ultrasonography. It is widely accepted that this is so, and these treatments have not been dealt with in this discussion because it is unlikely that they will have a role in the future in their present form. Prostatic stents are deemed acceptable with restriction, which once again is not controversial because that restriction has been clearly described in the large number of original and review articles related to them.

Key Points

- Intraprostatic stents are confined to alternative therapy for BPH for patients unfit for TURP.
- Transurethral needle ablation has been modified several times and has a significant beneficial effect on PFR and IPSS. Not enough long-term studies are available.
- The literature base for TUMT is inconsistent, and it is not possible to draw conclusions on long-term efficacy. It also improves PFR and IPSS.
- The holmium laser and the high-power PVP laser are the most popular instruments in this technology section and are efficacious in improving PFR and IPSS, probably in a way that is comparable to TURP. Long-term studies are required.
- TUVP and TUIP are also effective, particularly for small prostates, but have not overtaken TURP as the chosen method to treat obstructive BPH.
- In well-trained hands, TURP is a safe and effective way of treating BPH, with an acceptable side effect profile.
- Other means of prostatic resection, such as rotoresection of the prostate, are under evaluation, without long-term multicenter trials as yet. The efficacy of water-induced thermotherapy and ethanol injection of the prostate remains unproved.

Rather more interesting is the list of treatments described as being acceptable, presumably without restriction in the minds of the panel: TUMT, transurethral needle ablation, interstitial laser coagulation, laser-vaporization, and transurethral electrovaporization (naturally, TURP and open prostatectomy are also included). It may be that these newer treatments are acceptable, but it is absolutely necessary to define in what way and to remember that, in most of these treatments, the results are short term. In some cases, they may be considered as possible replacements for TURP, but, in that case, a large amount of further information is required related to the points previously discussed and to long-term efficacy. In the case of those being considered as alternative treatments for BPH not necessarily as good as TURP, their exact role needs to be defined.

It is very likely that some day TURP will be replaced as the ideal interventional treatment for BPH. It took a considerable amount of time for TURP to achieve its exalted position, but it could happen soon that some other treatment will occupy that position.

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chapter 94

Retropubic and Suprapubic Open Prostatectomy

Misop Han, MD, MS • Alan W. Partin, MD, PhD

Indications for Open Prostatectomy
Preoperative Evaluation
Operating Day Preparation
Surgical Technique
Postoperative Management
Complications
Summary

The treatment options for bladder outlet obstruction due to benign prostatic hyperplasia have been expanded dramatically over the past 2 decades with the development of medical and minimally invasive therapies. The current medical therapies for lower urinary tract symptoms (LUTS) include selective long-acting α_1-adrenergic antagonists, such as terazosin (Hytrin [Lepor et al, 1992; Roehrborn et al, 1996]), doxazosin (Cardura [Gillenwater et al, 1995]), and tamsulosin (Flomax [Abrams et al, 1995]), and the 5α-reductase blockers, such as finasteride (Proscar [Gormley et al, 1992; Andersen et al, 1995; Lepor et al, 1996]) and dutasteride (Avodart [Roehrborn et al, 2002, 2004]). Minimally invasive procedures include visual laser ablation of the prostate (VLAP [Cowles et al, 1995]), transurethral electrovaporization of the prostate (TVP [Kaplan et al, 1996]), transurethral needle ablation (TUNA [Schulman et al, 1993; Campo et al, 1997]), transurethral microwave thermotherapy (TUMT [Ogden et al, 1993; Javle et al, 1996]), interstitial laser coagulation (ILC [Muschter and Hofstetter, 1995]) and transurethral incision of the prostate (TUIP [Cornford et al, 1997]). However, these approaches are usually reserved for men with moderate symptoms and a small to medium-sized prostate gland (Reich et al, 2006). For larger prostate glands, open prostatectomy has been frequently performed. Lately, holmium laser enucleation of the prostate (HoLEP) with the holmium:yttrium-aluminum-garnet (Ho:YAG) laser has been performed as a minimally invasive alternative to open surgery (Gilling et al, 1998). Most recently, as urologists gain experience in minimally invasive therapy, a simple prostatectomy has been performed using a laparoscopic or robotic approach (Sotelo et al, 2005, 2008; Mariano et al, 2006).

For patients with acute urinary retention, persistent or recurrent urinary tract infections, severe hemorrhage from the prostate, bladder calculi, severe symptoms unresponsive to medical therapy, and/or renal insufficiency as a result of chronic bladder outlet obstruction, transurethral resection of the prostate (TURP) or open prostatectomy is indicated. **When compared with TURP, open prostatectomy offers the advantages of lower re-treatment rate and more complete removal of the prostatic adenoma under direct vision and avoids the risk of dilutional hyponatremia (the TUR syndrome) that occurs in approximately 2% of patients undergoing TURP** (Mebust et al, 1989; Roos et al, 1989). Several contemporary series have demonstrated objective improvement in urinary symptoms after open prostatectomy (Tubaro et al, 2001; Gacci et al, 2003; Varkarakis et al, 2004). **The disadvantages of open prostatectomy, as compared with TURP, include the need for a lower midline incision and a resultant longer hospitalization and convalescence period. There also may be an increased potential for perioperative hemorrhage** (Serretta et al, 2002).

Open prostatectomy can be performed by either the retropubic or the suprapubic approach. **In retropubic prostatectomy the enucleation of the hyperplastic prostatic adenoma is achieved through a direct incision of the anterior prostatic capsule.** This approach to open prostatectomy was popularized by Terrence Millin, who reported the results of the procedure on 20 patients in *Lancet* in 1945 (Millin, 1945). **The advantages of this procedure over the suprapubic approach are (1) excellent anatomic exposure of the prostate, (2) direct visualization of the prostatic adenoma during enucleation to ensure complete removal, (3) precise transection of the urethra distally to preserve urinary continence, (4) clear and immediate visualization of the prostatic fossa after enucleation to control bleeding, and (5) minimal to no surgical trauma to the urinary bladder. The disadvantage of the retropubic approach, as compared with the suprapubic prostatectomy, is that direct access to the bladder is not achieved.** This may be important when one considers excising a concomitant bladder diverticulum or removing bladder calculi. The suprapubic approach also may be the preferred method when the obstructive prostatic enlargement includes a large intravesical median lobe.

Suprapubic prostatectomy, or transvesical prostatectomy, consists of the enucleation of the hyperplastic prostatic adenoma through an extraperitoneal incision of the lower anterior bladder wall. This approach to open prostatectomy was first performed by Eugene Fuller in New York in 1894; it was later popularized by Peter Freyer in London, England, who described the procedure in 1900 and later reported the results of his first 1000 patients in 1912 (Freyer, 1912). The major advantage of this suprapubic procedure over the retropubic

approach is that it allows direct visualization of the bladder neck and bladder mucosa. As a result, **this operation is ideally suited for patients with (1) a large median lobe protruding into the bladder, (2) a clinically significant bladder diverticulum, or (3) large bladder calculi. It also may be preferable for obese men, in whom it is difficult to gain direct access to the prostatic capsule and dorsal vein complex** (Culp, 1975). **The disadvantage, as compared with the retropubic approach, is that direct visualization of the apical prostatic adenoma is reduced. As a result, the apical enucleation is less precise and this factor may affect postoperative urinary continence. Furthermore, hemostasis may be more difficult because of inadequate visualization of the entire prostatic fossa after enucleation.**

INDICATIONS FOR OPEN PROSTATECTOMY

The indications for prostatectomy, by either open approach or transurethral resection, include (1) acute urinary retention; (2) recurrent or persistent urinary tract infections; (3) significant symptoms from bladder outlet obstruction not responsive to medical therapy; (4) recurrent gross hematuria of prostatic origin; (5) pathophysiologic changes of the kidneys, ureters, or bladder secondary to prostatic obstruction; and (6) bladder calculi secondary to obstruction.

Open prostatectomy should be considered when the obstructive tissue is estimated to weigh more than 75 g. If sizable bladder diverticula justify removal, suprapubic prostatectomy and diverticulectomy should be performed concurrently. If the prostatectomy is performed without the diverticulectomy, incomplete emptying of the bladder diverticulum and subsequent, persistent infection may occur. Large bladder calculi that are not amenable to easy transurethral fragmentation may also be removed during the open procedure. Open prostatectomy should also be considered when a patient presents with ankylosis of the hip or other orthopedic conditions that prevent proper positioning for TURP. Also, it may be wise to perform an open prostatectomy in men with recurrent or complex urethral conditions, such as urethral stricture or previous hypospadias repair, to avoid the urethral trauma associated with TURP. Finally, the association of an inguinal hernia with an enlarged prostate suggests an open procedure, because the hernia may be repaired via the same lower abdominal incision (Schlegel and Walsh, 1987; Brunocilla et al, 2005).

Contraindications to open prostatectomy include a small fibrous gland, the presence of prostate cancer, and previous prostatectomy or pelvic surgery that may obliterate access to the prostate gland.

PREOPERATIVE EVALUATION

In deciding whether to perform an open prostatectomy for symptomatic obstruction due to benign prostatic hyperplasia, it may be necessary to consider the upper and lower urinary tracts. Usually the patient will have already completed the International Prostate Symptom Score (IPSS) questionnaire and had a peak urinary flow rate determination. The postvoid residual urine volume also may have been verified with abdominal ultrasonography. **A cystoscopic examination is not indicated in the routine evaluation of a patient with obstructive voiding symptoms** (McConnell et al, 1994). **However, cystoscopy should be performed in men with hematuria, suspected urethral stricture, and bladder calculus or diverticulum.** It also can be helpful in confirming the presence of a large median lobe or in assessing the length of the prostatic urethra. For this indication it is most ideal to perform the cystoscopic examination with the patient under anesthesia just before surgery, when the pelvic floor musculature is relaxed.

Before performing an open prostatectomy the presence of prostate cancer should be excluded. All men should undergo a digital rectal examination and have a serum prostate-specific antigen determination. If the digital rectal examination detects induration or nodularity, or the serum prostate-specific antigen level is elevated, a transrectal ultrasound-guided biopsy of the prostate gland should be performed. Transrectal ultrasonography, by itself, is not indicated as a first-line diagnostic test for evaluating the prostate gland to detect early, curable prostate cancer. However, it can be useful in determining prostate size.

The upper urinary tracts should be evaluated preoperatively in men with known renal disease, abnormal renal function, recurrent urinary tract infection, or hematuria. This can be accomplished by an intravenous pyelogram with a postvoid drainage film, by computed tomography in patients with normal renal function, or by renal ultrasonography in men with compromised renal function. Magnetic resonance imaging is not commonly indicated.

Before surgery the patient should undergo a complete medical evaluation consisting of a detailed history, thorough physical examination, and appropriate laboratory assessment. Most patients will be of an age with an increased risk for cardiovascular and pulmonary disease, hypertension, diabetes mellitus and other medical conditions. All abnormalities uncovered in this evaluation should be addressed. The patient's medications should be reviewed and attention should be given to the agents such as aspirin and nonsteroidal anti-inflammatory agents that can contribute to perioperative bleeding. **These medications should be discontinued and therapeutic anticoagulation reversed before surgery.** In addition, a chest radiograph, electrocardiogram, routine electrolyte studies, coagulation studies, and a complete blood cell count are usually required for these patients before surgery.

Men in urinary retention should have an evaluation of renal function. If the serum creatinine value is elevated, surgery should be delayed until this parameter stabilizes. Urinalysis is performed to rule out a urinary tract infection; and, if an infection is suspected, a urine specimen should be sent for culture and sensitivity. If an infection is present, appropriate antimicrobial therapy must be instituted before surgery to prevent urinary sepsis (Serretta et al, 2002).

Historically, 3% to 10% of men undergoing an open prostatectomy will require one or more units of blood in the perioperative period (Serretta et al, 2002; Varkarakis et al, 2004; Zargooshi, 2007). Thus **it may be prudent to have one or two units of blood available intraoperatively.** Patients who are concerned about infectious processes associated with blood transfusion can donate one to two units of autologous blood before surgery so that it is available at the time of the procedure. The preferred autologous donation schedule is one unit per week, with the last donation 2 weeks before surgery. During this process, the patient

should receive oral iron supplementation (ferrous sulfate or ferrous gluconate).

Lastly, the patient must be informed of the benefits and risks associated with open prostatectomy and written informed consent should be obtained. The benefit to be achieved is improved urination. **Potential risks include urinary incontinence, erectile dysfunction, retrograde ejaculation, urinary tract infection, bladder neck contracture, urethral stricture, and the need for a blood transfusion. Other potential untoward effects include deep vein thrombosis and pulmonary embolus.**

OPERATING DAY PREPARATION

The patient is kept without oral intake after midnight and self-administers a Fleet enema the morning of surgery. The type of the anesthesia to be used and the risks associated with it are discussed and finalized with the patient and his family in conjunction with the anesthesiologist. One dose of a second-generation cephalosporin is administered before making the incision.

SURGICAL TECHNIQUE

Anesthesia

The preferred anesthesia is spinal or epidural. Regional anesthesia may reduce intraoperative blood loss and the frequency of postoperative deep vein thrombosis and pulmonary embolus (Peters and Walsh, 1985). **General anesthesia is utilized when there is a medical or anatomic contraindication to regional anesthesia or when the patient simply prefers general anesthesia.**

Retropubic Prostatectomy

Proper Positioning of the Patient

Once anesthesia has been induced the patient is positioned on the operating table in a supine position. If a cystoscopic examination is to be performed, the patient is prepped and draped in the usual manner for a transurethral diagnostic procedure. Flexible cystoscopy, in this situation, will obviate major repositioning of the patient. After the cystoscopy the table is placed in a mild Trendelenburg position without extension.

Incision and Exposure of the Prostate

The suprapubic area is shaved, prepped, and draped in the usual sterile manner. A 22-Fr urethral catheter with a 30-mL balloon is passed into the bladder and connected to a sterile closed drainage system, and the balloon is inflated with 30 mL of saline. A lower midline incision from the umbilicus to the pubic symphysis is made. It is deepened through the subcutaneous tissue. **The linea alba is incised, allowing the rectus abdominis muscles to be separated in the midline. The transversalis fascia is incised sharply to expose the space of Retzius.** At the superior aspect of the wound the posterior rectus abdominis fascia is incised above the semicircular line to the level of the umbilicus and the peritoneum is mobilized cephalad starting at the pubic symphysis and swept anterolaterally. The pelvis is inspected for any abnormalities, and the inguinal area is examined for hernias. If a hernia is identified, it can be repaired using the preperitoneal approach described by Schlegel and Walsh (1987). A self-retaining Balfour retractor is placed in the incision and widened. A well-padded, malleable blade is connected to the retractor and used to displace the bladder posteriorly and superiorly. Unlike an anatomic radical retropubic prostatectomy, the balloon of the catheter is not positioned beneath the malleable blade. Instead it is allowed to rest at the level of the bladder neck and aids in identifying the prostatovesical junction later in the operation. The anterior surface of the bladder and prostate are exposed. With the use of DeBakey forceps and Metzenbaum scissors, the preprostatic adipose tissue is gently removed to expose the superficial branch of the dorsal vein complex and the puboprostatic ligaments (Fig. 94–1).

Hemostatic Maneuvers

Before proceeding with enucleation of the prostatic adenoma it is important to achieve complete control of the dorsal vein complex as well as the lateral pedicles at the bladder neck (the main arterial blood supply to the prostate gland) (Walsh and Oesterling, 1990). To accomplish this task the endopelvic fascia is incised laterally and the puboprostatic ligaments are partially transected, similar to the maneuver in an anatomic radical retropubic prostatectomy (Reiner and Walsh, 1979). In patients with marked prostatic enlargement this maneuver can be easier because the enlarged prostate gland protrudes out from beneath the pubic symphysis. A 3-0 Monocryl suture on a ⅝-inch circle-tapered needle is passed in the avascular plane between the urethra and the dorsal vein complex at the apex of the prostate and tied (Fig. 94–2A). The superficial branch of the dorsal vein at the bladder should be coagulated or ligated.

At this point attention is focused on securing the lateral pedicles at the prostatovesical junction. The 30-mL balloon of the catheter is used to identify the junction between the bladder and the prostate. The balloon is then deflated and 2-0 chromic suture material on a large CTX needle is used to place a figure-of-eight suture deep into the prostatovesical junction at the level where the seminal vesicles approach the prostate gland bilaterally (see Fig. 94–2B). With this maneuver, the main arterial blood supply to the prostate

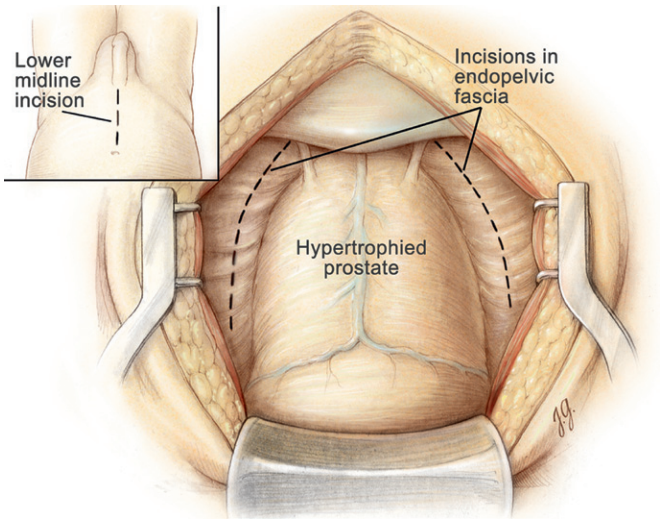


Figure 94–1. Retropubic prostatectomy. The space of Retzius has been opened and the periprostatic adipose tissue has been dissected free from the superficial branch of the dorsal vein complex. The endopelvic fascia is incised bilaterally *(dotted lines)*, and the puboprostatic ligaments are transected bilaterally. (© Brady Urological Institute.)

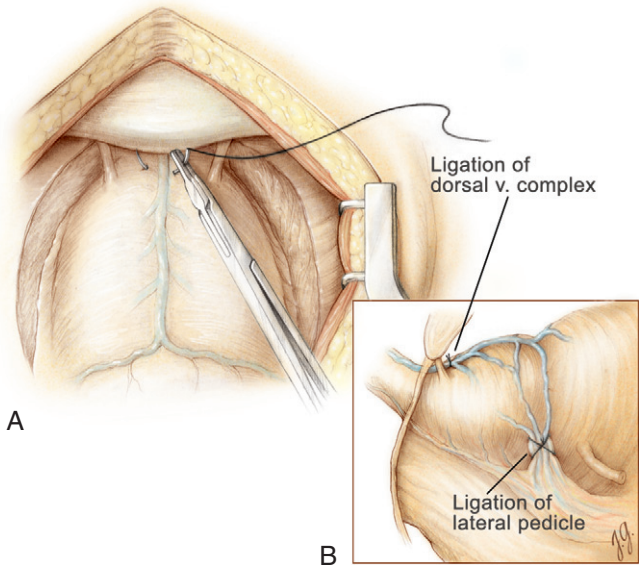


Figure 94–2. Retropubic prostatectomy. **A,** A 2-0 chromic suture on a ⅜-inch circle-tapered needle is passed in the avascular plane between the urethra and the dorsal vein complex at the apex of the prostate. A tie is grasped and tied around the dorsal vein complex. **B,** With 2-0 chromic suture material on a CTX needle, a figure-of-eight suture is placed through the prostatovesicular junction just above the level of the seminal vesicles to control the main arterial blood supply to the prostate gland. When placing this suture, care must be taken to avoid entrapment of the neurovascular bundles located posteriorly and slightly laterally. (© Brady Urological Institute.)

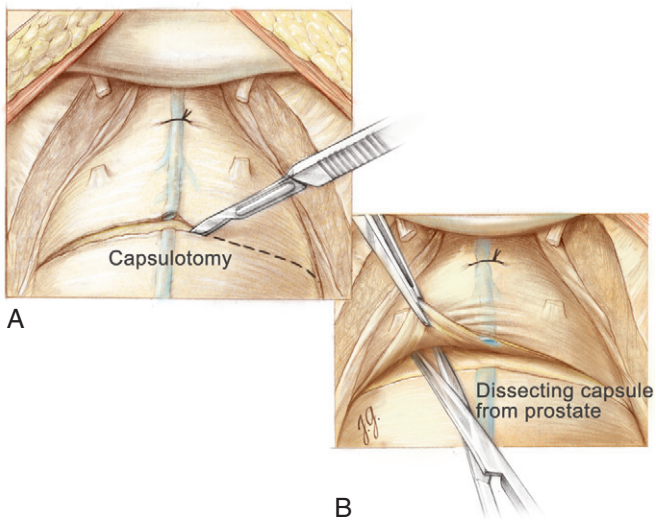


Figure 94–3. Retropubic prostatectomy. **A,** With the superficial branch of the dorsal vein complex secured proximally and distally, a No. 15 blade on a long handle is used to make the transverse capsulotomy. **B,** Metzenbaum scissors are used to develop the plane anteriorly between the prostatic adenoma and the prostatic capsule. (© Brady Urological Institute.)

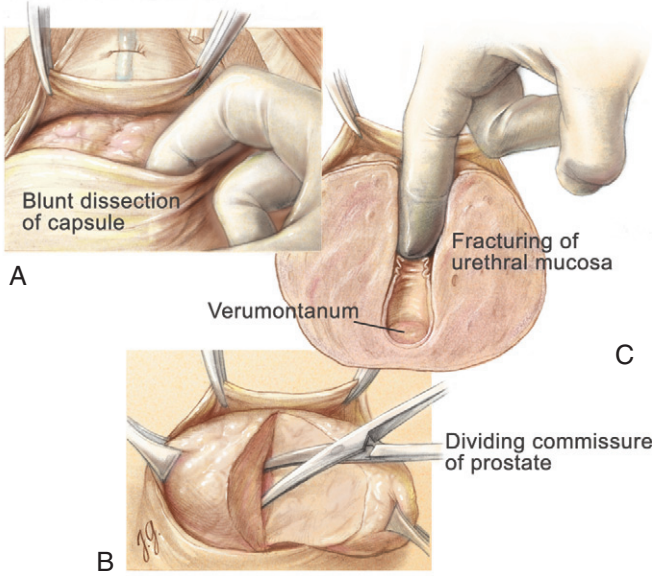


Figure 94–4. Retropubic prostatectomy. **A,** With blunt dissection with the index finger, the prostatic adenoma is dissected free laterally and posteriorly. **B,** Metzenbaum scissors are used to divide the anterior commissure to visualize the posterior urethra and verumontanum. **C,** The index finger is then used to fracture the urethral mucosa at the level of the verumontanum. With this last maneuver, extreme care is taken not to injure the external sphincteric mechanism. (© Brady Urological Institute.)

adenoma is controlled. Having secured the dorsal vein complex earlier, the major sources of hemorrhage for this operation have been eliminated.

Enucleation of the Adenoma

With a sponge stick on the bladder neck to depress the bladder posteriorly, a No. 15 blade on a long handle is used to make a transverse capsulotomy in the prostate 1.5 to 2.0 cm distal to the bladder neck (Fig. 94–3). The superficial branch of the dorsal vein complex is transected as the transverse capsulotomy is made. It does not bleed because hemostasis of the dorsal vein complex has previously been controlled both proximally and distally. The incision is deepened to the level of the adenoma and extended sufficiently lateral in each direction to permit complete enucleation. A pair of Metzenbaum scissors is used to dissect the overlying prostatic capsule from the underlying prostatic adenoma. Once a well-defined plane is sufficiently developed, the index finger can be inserted between the prostatic adenoma and the capsule to further develop the plane laterally and posteriorly (Fig. 94–4). A pair of Metzenbaum scissors is then used to incise the anterior commissure from the bladder neck to the apex separating the lateral lobes of the prostate anteriorly. The posterior prostatic urethra is exposed, and the index finger is inserted down to the verumontanum. The mucosa of the urethra overlying the left lateral lobe is divided sharply at the level of the apex under direct vision without injury to the external urinary sphincter. With the aid of a Babcock clamp, the left lateral lobe is removed safely. This maneuver is then repeated for the right lateral lobe. If a median lobe is present, the overlying mucosa is incised at the level of the bladder neck and this lobe is removed (Fig. 94–5). In this manner the entire prostatic adenoma is removed with preservation of a strip of posterior prostatic urethra. Because the capsulotomy was a transverse rather than longitudinal incision there is little risk that the incision will

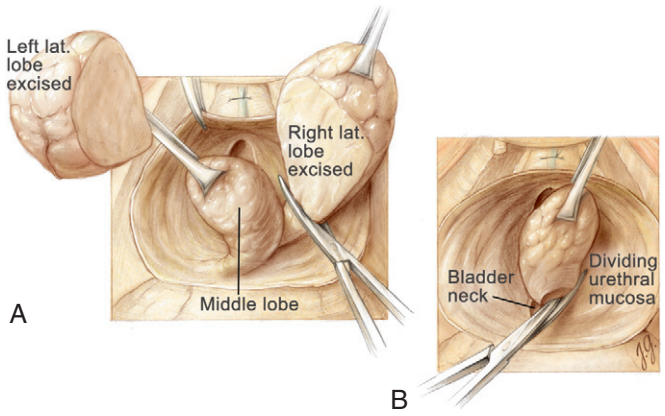


Figure 94–5. Retropubic prostatectomy. **A,** After removal of the left lateral lobe of the prostate, the right lateral lobe is excised with the aid of a tenaculum and Metzenbaum scissors. **B,** Lastly, the median lobe is removed under direct vision. (© Brady Urological Institute.)

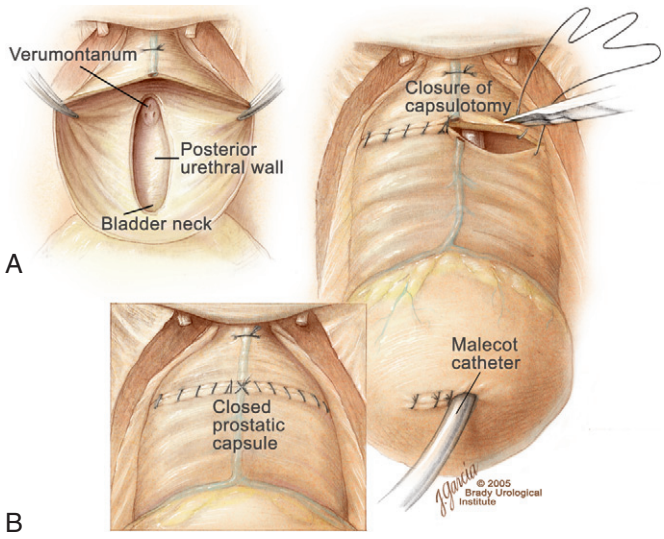


Figure 94–6. Retropubic prostatectomy. **A,** View of the prostatic fossa and posterior urethra after enucleation of all the prostatic adenoma. Note that the verumontanum and a strip of posterior urethra remain intact. **B,** After placement of a urethral catheter and, if needed, a Malecot suprapubic tube, the transverse capsulotomy is closed with two running 2-0 chromic sutures. The two sutures are tied first to themselves and then to each other across the midline to create a watertight closure of the prostatic capsule. (© Brady Urological Institute.)

be inadvertently extended into the sphincteric mechanism during the enucleation process, which would compromise subsequent urinary continence.

The prostatic fossa is now carefully inspected to ensure that all of the adenoma has been removed and that hemostasis is complete. **If hemorrhage is persistent, 4-0 chromic suture material can be used to place a figure-of-eight suture in the bladder neck at the 5- and 7-o'clock positions as in suprapubic prostatectomy** (see Fig. 94–11). **When placing these sutures it is necessary to visualize the ureteral orifices so that they are not incorporated.** Indigo carmine dye may be given intravenously to aid in the visualization of the ureteral orifices if necessary. If the bladder neck appears obstructive at the completion of the operation, it may be appropriate to perform a wedge resection at the 6-o'clock position and advance the bladder mucosa into the prostatic fossa. The maneuver helps prevent the development of a bladder neck contracture.

Closure

After inspecting the bladder for complete adenoma removal and hemostasis, a 22-Fr, three-way Foley catheter with a 30-mL balloon is inserted through the anterior urethra and prostatic fossa into the bladder. With the urethral catheter in place, the prostatic capsule is closed (Fig. 94–6). Then 2-0 chromic suture material on a ⅝-inch circle-tapered needle is used to create two running sutures. These sutures begin laterally and meet in the midline; they are first tied separately and then together to create a watertight closure. Fifty milliliters of water is then placed in the balloon to ensure that the catheter balloon remains in the bladder and does not retract into the prostatic fossa. The bladder is then irrigated with saline to ensure continued hemostasis and to test the capsular closure for leakage. A small, closed-suction drain is placed via a separate stab incision lateral to the prostate and bladder on one side to prevent hematoma and urinoma formation. The pelvis is irrigated with copious amounts of normal saline solution, and the rectus fascia is reapproximated with a size 1 PDS suture on a TPI needle in a running fashion. The skin is closed with skin staples. The drain is secured to the abdominal wall, and the urethral catheter is secured to the lower extremity.

Suprapubic Prostatectomy

Proper Positioning of the Patient

After anesthesia has been induced, the patient is positioned on the operating table in a supine position. Cystoscopy, if clinically indicated, is performed as previously described. **The table is placed in a mild Trendelenburg position without extension.** The patient's suprapubic area is shaved. **After the lower abdomen and external genital area are prepped and draped in the usual sterile manner, a 22-Fr catheter is inserted into the bladder. After residual urine is drained, 250 mL of saline is instilled into the bladder and the catheter is clamped.**

Incision and Exposure of the Prostate

A lower midline incision is made from the umbilicus to the pubic symphysis (Fig. 94–7). It is deepened through the subcutaneous tissue. The linea alba is incised, allowing the rectus abdominis muscles to be separated in the midline. The transversalis fascia is incised sharply to expose the space of Retzius. At the superior aspect of the wound the posterior rectus abdominis fascia is incised above the semicircular line to the level of the umbilicus and the peritoneum is then swept cephalad to develop the prevesical space. A self-retaining Balfour retractor is placed in the incision to retract the rectus muscles laterally. The anterior bladder wall is identified, and two 3-0 Vicryl stitches are placed on each side of the midline below the peritoneal reflection. **A vertical cystotomy is made with an electrocautery. With the use of a pair of Metzenbaum scissors, a cystotomy is then extended cephalad and caudally to within 1 cm of the bladder neck** (Fig. 94–8). **Several pairs of stay sutures are placed using 3-0 Vicryl on each side of the midline to facilitate exposure. A figure-of-eight suture using 3-0 Vicryl is placed and tied at the most caudal position of**

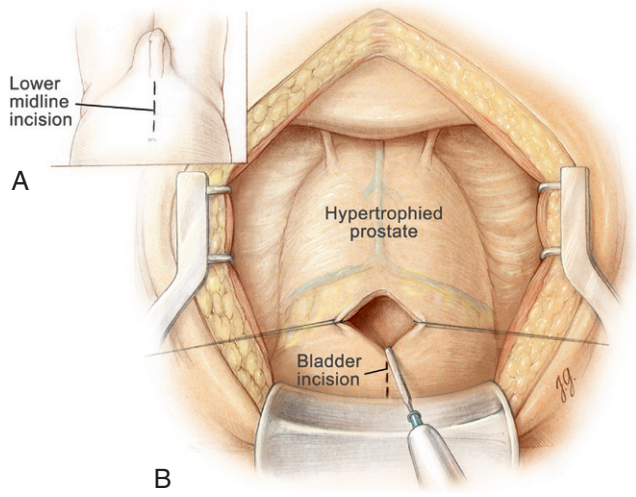


Figure 94–7. Suprapubic prostatectomy. **A,** A lower midline incision is made from the umbilicus to the pubic symphysis. **B,** After developing the prevesical space, a small, longitudinal cystotomy is made with an electrocautery. (© Brady Urological Institute.)

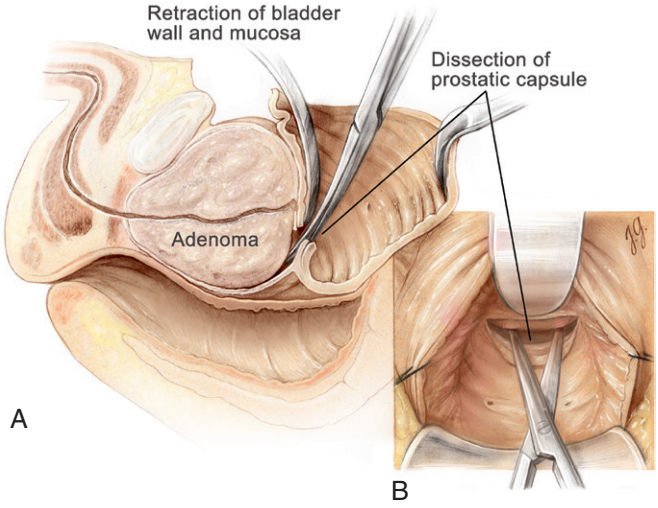


Figure 94–9. Suprapubic prostatectomy. **A,** Starting at the bladder neck posteriorly, Metzenbaum scissors are used to develop the plane between the prostatic adenoma and the prostatic capsule (lateral view). **B,** Anterior view of the same maneuver. (© Brady Urological Institute.)

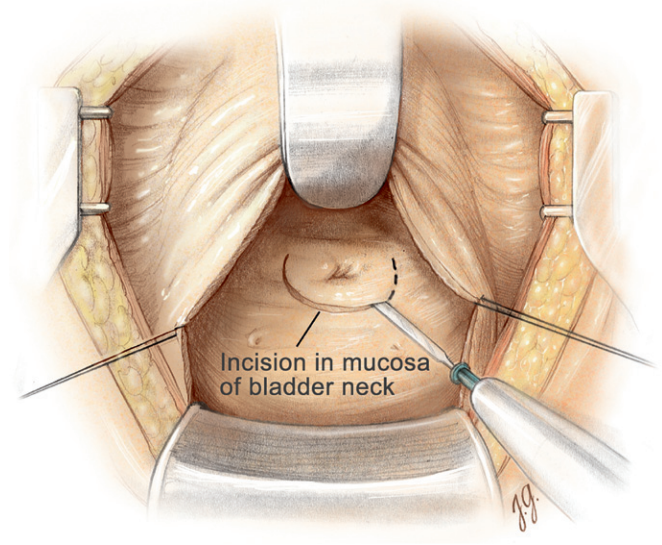


Figure 94–8. Suprapubic prostatectomy. With adequate exposure of the bladder neck, a circular incision in the bladder mucosa is made distal to the trigone, using an electrocautery. (© Brady Urological Institute.)

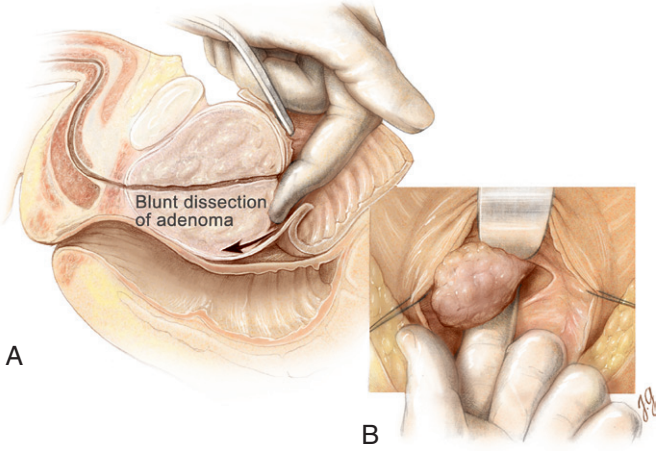


Figure 94–10. Suprapubic prostatectomy. **A,** Using the index finger, the prostatic adenoma is enucleated from the prostatic fossa (lateral view). **B,** Anterior view of the same maneuver. With extreme large prostate glands, the left, right, and median lobes should be removed separately. (© Brady Urological Institute.)

the cystotomy to prevent further extension of the cystotomy incision during blunt finger dissection of the adenoma. Alternatively, a transverse bladder incision can be utilized. After inspecting the bladder, a well-padded, malleable blade is placed in the bladder, connected to the Balfour retractor, and used to retract the bladder cephalad. The bladder neck and prostate gland now can be visualized. A narrow Deaver retractor can be placed over the bladder neck and used to further expose the trigone. **Indigo carmine dye may be given intravenously to aid in the visualization of the ureteral orifices if necessary.**

Enucleation of the Adenoma

An electrocautery is used to create a circular incision in the bladder mucosa distal to the trigone (see Fig. 94–8). Care is taken not to injure the ureteral orifices. With the use of a pair of Metzenbaum scissors, the plane between the prostatic adenoma and prostatic capsule is developed at the 6-o'clock position (Fig. 94–9). Once a well-established plane is created posteriorly, the prostatic adenoma is dissected circumferentially and inferiorly toward the apex, using blunt dissection (Fig. 94–10). At the apex the prostatic urethra is transected using a pinch action of the two fingertips and avoiding excessive traction so as not to avulse the urethra and injure the sphincteric mechanism. At this point the prostatic adenoma, either as one unit or separate lobes, can be removed from the prostatic fossa.

Hemostatic Maneuvers

After enucleation of the adenoma the prostatic fossa is inspected for residual tissue. If found, these nodules are removed by sharp

or blunt dissection. **The prostatic fossa also must be examined for discrete bleeding sites that frequently can be controlled with an electrocautery or 4-0 chromic suture ligatures. In addition, a 0-chromic suture is used to place two figure-of-eight sutures to advance the bladder mucosa into the prostatic fossa at the 5-o'clock and 7-o'clock positions at the prostatovesical junction to ensure control of the main arterial blood supply to the prostate** (Fig. 94–11). With this maneuver, hemostasis is usually complete.

If hemorrhage remains pronounced despite the hemostatic sutures, a size 2 nylon purse-string suture can be placed around the vesical neck, brought out through the skin, and tied firmly, as described by Malament (1965). This maneuver closes the bladder neck and tamponades the prostatic fossa. The nylon suture is removed by cutting it at the skin and applying gentle traction on postoperative day 2 or 3. Plicating sutures can be placed transversely in the posterior prostatic capsule to prevent further bleeding, as described by O'Conor (1982).

Closure

A 22-Fr urethral catheter with a 30-mL balloon is passed through the urethra into the bladder. In addition, a 20- to 24-Fr Malecot suprapubic tube is placed into the dome of the bladder and secured with a 4-0 chromic purse-string suture. The suprapubic tube exits the bladder via a separate stab incision at the lateral aspect of the dome, avoiding the peritoneal cavity (Fig. 94–12). Next, **the cystotomy incision is closed in two layers.** The first layer of closure is performed using a 2-0 Vicryl to create two running sutures. Care is taken to get a small amount of bladder mucosa in the suture. The two sutures begin cephalad and caudally and meet in the midbladder where they are first tied separately and then together. Previously placed 3-0 Vicryl stay-sutures are tied over the first layer of closure to complete the two-layer closure. With this approach the bladder closure is watertight and completed in a timely manner. Fifty milliliters of saline is placed in the balloon to ensure that the catheter balloon remains in the bladder and does not retract into the prostatic fossa. The urethral catheter and suprapubic tube are irrigated to confirm a watertight closure and to verify that hemorrhage is minimal. A small, closed-suction drain is placed via a separate stab incision lateral to the bladder. The drain exits the skin on the opposite side of the suprapubic tube. The pelvis is irrigated with copious amounts of normal saline solution, and the rectus fascia is closed with a size 1 PDS suture on a TPI needle in a running fashion. The skin is closed with skin staples. Next, the suprapubic tube and drain are secured to the abdominal wall, and the urethral catheter is anchored to the lower extremity.

POSTOPERATIVE MANAGEMENT

In the recovery area the outputs from the pelvic drain, suprapubic tube, and urethral catheter are monitored. In addition, it is routine to verify the hematocrit. **If significant hemorrhage is noted, the urethral catheter may be placed on traction so that the balloon containing 50 mL of saline can compress the bladder neck and prostatic fossa. Constant and reliable traction can be maintained by securing the catheter to the abdomen. In addition, continuous bladder irrigation should be initiated to prevent clot formation. For maximal effect the inflow should be through the urethral catheter and the outflow through the suprapubic tube.** For most patients these measures are adequate and effective. **However, if excessive bleeding persists after these measures, the urethral catheter can be removed in the operating suite and a cystoscopic inspection of the prostatic fossa and bladder neck can be performed to identify and fulgurate discrete bleeding sites. If marked hemorrhage should continue to persist, open re-exploration should be strongly considered.**

On the evening of the day of surgery the patient is asked to perform the dorsiflexion and plantarflexion exercises 100 times per hour while awake and to perform pulmonary exercises.

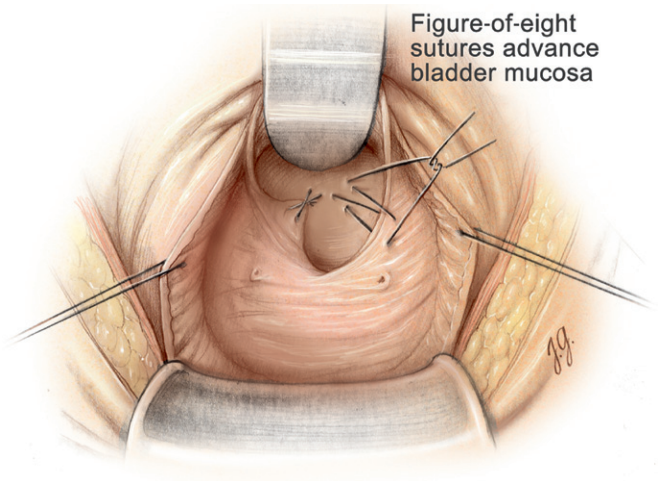


Figure 94–11. Suprapubic prostatectomy. After enucleation of the entire prostatic adenoma, a 0-chromic suture is used to place two figure-of-eight sutures to advance bladder mucosa into the prostatic fossa at the 5- and 7-o'clock positions at the prostatovesicular junction to ensure control of the main arterial blood supply to the prostate. (© Brady Urological Institute.)

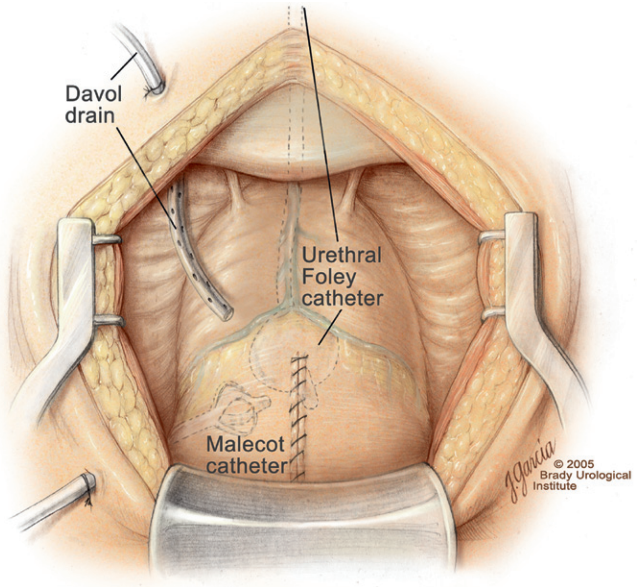


Figure 94–12. Suprapubic prostatectomy. After placement of a urethral catheter and a Malecot suprapubic tube, the cystotomy is closed in two layers using a running 2-0 Vicryl suture, enforced by tying of multiple interrupted 3-0 Vicryl stay sutures. A closed Davol suction drain is placed on one side of the bladder and exits via a separate stab incision. (© Brady Urological Institute.)

Effective pain management consists of intravenous morphine sulfate on an as-needed basis via a patient-controlled analgesic pump.

On the first postoperative day the patient is started on a clear liquid diet and asked to ambulate four times per day. Pulmonary exercises are continued. **If the hematuria is resolved, continuous bladder irrigation can be discontinued with both urethral catheter and suprapubic tube placed to gravity drainage. Also, the balloon in the urethral catheter is partially deflated to 30 mL of saline and residual clots are removed by irrigation.**

On the second postoperative day, if urine is clear, the urethral catheter may be removed and the suprapubic tube is clamped to allow a voiding trial. The patient is encouraged to ambulate and continue pulmonary exercises. **When the patient tolerates a regular diet, oral analgesics can be given and parenteral narcotics discontinued.** Appropriate discharge instructions are reviewed with the patient at this time in preparation for discharge on the third day after surgery. **On the third postoperative day the pelvic drain is removed if the drainage is less than 75 mL/24 hr.** The skin staples are removed and replaced with Steri-strips in nonobese men. The pathologic examination of the enucleated prostatic adenoma should be performed to confirm the absence of adenocarcinoma of the prostate.

On discharge from the hospital the patient is encouraged to gradually increase his activity. If the patient voids well with a minimal postvoid residual urine volume, the suprapubic tube is then removed in the clinic on the fifth day after surgery. The patient should be able to resume full activity 4 to 6 weeks postoperatively with outpatient visits at 6 weeks and 3 months.

COMPLICATIONS

The overall rate of morbidity and mortality associated with open prostatectomy is extremely low. Historically, excessive hemorrhage had been a major concern. But with modern surgical techniques, blood loss is now minimal and the need for a blood transfusion is uncommon (Zargooshi, 2007). In retropubic open prostatectomy, controlling the dorsal vein complex distal to the apex of the prostate and ligating the lateral pedicles to the prostate at the prostatovesical junction markedly reduces venous and arterial bleeding, respectively. Nevertheless, it may still be prudent to have one to two units of autologous blood available at the time of open prostatectomy.

Urinary extravasation can also be of concern in the immediate postoperative period; this most likely results from an incomplete closure of the prostatic capsulotomy in retropubic prostatectomy or the cystotomy in suprapubic prostatectomy. This will usually resolve spontaneously with continued catheter drainage. The drain should be left in place until urinary extravasation ceases.

After an open prostatectomy, urgency and urgency incontinence may be present for several weeks to several months, depending on the preoperative bladder status. If the condition is severe, the patient may be given an anticholinergic agent such as oxybutynin (Ditropan). Stress incontinence and total incontinence are rare. With a precise enucleation of the prostatic adenoma, risk of injury to the external sphincter mechanism is minimal. If stress incontinence does result after the procedure, the patient may benefit from transurethral collagen injections for a mild condition or an artificial urinary external sphincter when the situation is more severe.

Late urologic complications are not common. Acute cystitis rarely occurs as long as the patient voids to completion. Acute epididymitis can occur occasionally if infected urine refluxes into the ejaculatory ducts.

Erectile dysfunction occurs in 3% to 5% of patients undergoing an open prostatectomy; it is more common in older men than in younger men. Retrograde ejaculation occurs in 80% to 90% of patients after surgery. The risk of this adverse effect is reduced if the bladder neck is preserved at the time of surgery. Also, 2% to 5% of patients will develop a bladder neck contracture 6 to 12 weeks after an open prostatectomy (Tubaro et al, 2001; Varkarakis et al, 2004). This commonly occurs in men who have a relatively small opening at the bladder neck at the end of the operation. As stated earlier, for these men it may be appropriate to perform a wedge resection at the 6 o'clock position and advance the bladder mucosa into the prostatic fossa in the retropubic prostatectomy. However, if a bladder neck contracture does develop, the initial management should be dilatation with urethral sounds or a direct vision incision of the bladder neck using a Collings knife to create a 22-Fr opening.

The most common nonurologic adverse effects include deep vein thrombosis, pulmonary embolus, myocardial infarction, and a cerebrovascular event. The incidence of any one of these complications is less than 1% and the overall mortality rate resulting from this operation should approach zero (Varkarakis et al, 2004).

SUMMARY

Open prostatectomy, whether performed via a retropubic approach or a suprapubic approach, is an excellent treatment option for (1) men with symptomatic bladder outlet obstruction due to benign prostatic hyperplasia causing a markedly enlarged prostate gland, (2) individuals with a concomitant bladder condition, such as a bladder diverticulum or large bladder calculi,

Key Points

- Open prostatectomy should be considered when the obstructive tissue is estimated to weigh more than 75 g or sizable bladder diverticular or calculi exist.
- Before performing an open prostatectomy, the presence of prostate cancer should be excluded.
- Potential risks of open prostatectomy include urinary incontinence, erectile dysfunction, retrograde ejaculation, urinary tract infection, bladder neck contracture, urethral stricture, deep vein thrombosis, pulmonary embolus, and the need for blood transfusion.
- Advantages of open prostatectomy over TURP are a lower re-treatment rate, more complete removal of the prostatic adenoma under direct vision, and no risk of TUR syndrome.
- Disadvantages of open prostatectomy over TURP are a lower midline incision, longer hospitalization, and increased potential for perioperative hemorrhage.
- Two approaches to open prostatectomy are retropubic and suprapubic.
- Suprapubic prostatectomy is ideal for men with a large median lobe, clinically significant bladder diverticulum, or large bladder calculi.

and (3) patients who cannot be placed in the dorsal lithotomy position for TURP. With improved surgical technique these procedures can be routinely performed in a precise manner with minimal hemorrhage. Efficacy, in terms of durable improvement in symptom score and peak urinary flow rate, is superior than other treatment options available for the obstructing prostate gland, including TURP. Meanwhile, complications are minimal and the length of hospitalization has been markedly reduced. For most patients, the length of hospital stay is 3 days or less. Thus, for the properly selected individual, an open prostatectomy is a highly effective and well-tolerated operation.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

SUGGESTED READINGS

Roos NP, Wennberg JE, et al. Mortality and reoperation after open and transurethral resection of the prostate for benign prostatic hyperplasia. N Engl J Med 1989;320(17):1120–4.

Walsh PC, Oesterling JE. Improved hemostasis during simple retropubic prostatectomy. J Urol 1990;143(6):1203–4.

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chapter
95

Epidemiology, Etiology, and Prevention of Prostate Cancer

Robert Abouassaly, MD, MSc ● Ian M. Thompson, Jr., MD ● Elizabeth A. Platz, ScD, MPH ● Eric A. Klein, MD

Epidemiology
Risk Factors
Etiology and Molecular Genetics
Chemoprevention
Conclusion

EPIDEMIOLOGY

Incidence and Mortality Trends

Incidence

Prostate cancer has been the most common noncutaneous malignancy in U.S. men since 1984, now accounting for one quarter of all such cancers (American Cancer Society, 2008)**. The estimated lifetime risk of disease is 16.72%, with a lifetime risk of death at 2.57%.** Prostate cancer incidence varies by race/ethnicity, with African-Americans at highest risk (Table 95–1). The incidence of prostate cancer peaked in 1992 (approximately 5 years after introduction of the prostate-specific antigen [PSA] screening test), fell precipitously until 1995, increased slowly until 1995 at a slope similar to that observed prior to the PSA era, and has decreased again in recent years (Fig. 95–1). The years in which peak rates were observed can be differentiated by race: 1992 for whites (237.8 per 100,000 men) and 1993 for African-Americans in (343.1 per 100,000). **The decrease in incidence between 1992 and 1995 has been attributed to the "cull effect" of identifying previously unknown cancers in the population by the use of the PSA test, followed by a return to baseline where fewer cases were detected in previously screened individuals** (Stephenson et al, 1996). For 2008, the American Cancer Society estimated 186,320 new cases of prostate cancer in the United States (American Cancer Society, 2008).

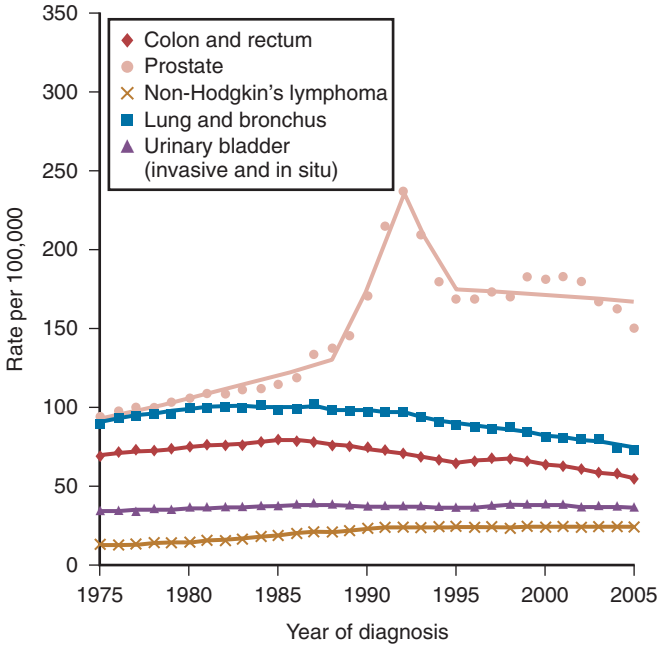
Mortality

Prostate cancer mortality rates in the United States rose slowly between 1973 and 1990 (Fig. 95–2). This may have resulted from a gradual increase in the number of biologically lethal cancers or a decreasing use or effectiveness of therapy during this interval. In the early 1990s, an abrupt rise in mortality was observed. This increase may have been caused by an increase in attribution bias occurring when the National Center for Health Statistics made a change from manual to automated methods for assignment of cause of death (Feuer et al, 1999). **Subsequent to 1991, the peak mortality year, steady declines in prostate cancer mortality were reported. The magnitude of this decline is nearly 2.5 times larger than the increase in mortality seen as a result of attribution bias; thus it seems likely that the declines in prostate cancer mortality in the United States since 1991 are real and clinically significant** (Stephenson, 2005). In 2008, the American Cancer Society estimated 28,660 prostate cancer–related deaths in the United States, for an approximate annual rate of 23.3 per 100,000 population, representing a 41% decrease from the peak in 1991 (American Cancer Society, 2008). **Furthermore, the mortality rate for prostate cancer in white men in the United States has declined to a level lower than that observed prior to the introduction of PSA-based screening in 1987** (Tarone et al, 2000).

The observed decline in mortality since 1991 is unlikely to be explained by PSA screening alone. Based on our current beliefs concerning lead time, the decline would have occurred too soon after the initiation of screening (Etzioni et al, 1999). **One hypothesis is that it is the result of the more aggressive treatment of prostate cancer that began in the 1980s** (Walsh, 2000)**.** Rates of both radical prostatectomy (RP) and radiation therapy rose steadily through the 1980s (pre-PSA era), whereas hormone therapy and no-treatment rates remained stable (Stephenson, 2005). Outcomes for patients treated in the 1980s should be reflected in the mortality data of the 1990s, while outcomes for patients treated in the PSA era (the 1990s) have had less time to affect recent mortality data. **Given the long natural history of low-stage cancers detected in the PSA era, their treatment would not be expected to have a substantial effect on mortality statistics for another 5 to 10 years. Additional observation time is necessary to determine if screening, PSA-induced stage migration, and more aggressive use of therapy have contributed to declining mortality.**

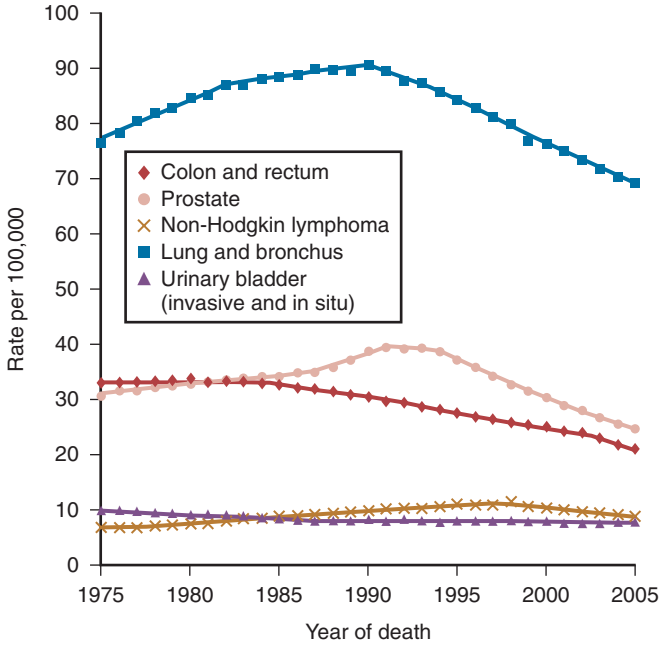
Racial Differences

Although anthropologists accept that there are subtle biologic differences among populations, commonly used categories, such as African-American, white, and Hispanic, are social and cultural descriptors that have no defined biologic basis. **Observed disease-related differences between groups defined in this fashion may therefore be more reflective of common environmental exposure, diet, lifestyle, and attitudes**



Cancer sites include invasive cases only unless otherwise noted.
Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.3, April 2008, National Cancer Institute.

Figure 95–1. Age-adjusted cancer incidence rates for men, United States, 1975-2005. (From Surveillance, Epidemiology, and End Results Program, 1975-2005, Division of Cancer Control and Population Sciences, National Cancer Institute, 2008.)



Cancer sites include invasive cases only unless otherwise noted.
Mortality source: US Mortality Files, National Center for Health Statistics, CDC.
Rates are per 100,000 and are age-adjusted to the 2000 U.S. Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.3, April 2008, National Cancer Institute.

Figure 95–2. Age-adjusted cancer death rates for men, United States, 1975-2005. (From Surveillance, Epidemiology, and End Results Program, 1975-2001, Division of Cancer Control and Population Sciences, National Cancer Institute, 2008.)

Table 95–1.

Prostate Cancer Incidence and Mortality by Race/Ethnicity, United States, 2000–2004

	INCIDENCE*	MORTALITY*
White	161.4	25.6
African-American	255.5	62.3
Hispanic/Latino	140.8	21.2
Asian-American and Pacific Islander	96.5	11.3
American Indian and Alaska Native	68.2	21.5

*Per 100,000, age adjusted to the 2000 U.S. standard population.
Data from American Cancer Society. Cancer facts and figures 2008. <http://www.cancer.org/acs/groups/content/@nho/documents/document/2008cafffinalsecuredpdf.pdf>; 2008 [accessed 06.04.11].

toward health care than of differences in genetic structure or function. Recognizing these caveats, it is noteworthy that African-American men have the highest reported incidence of prostate cancer in the world, with a relative incidence of 1.6 compared with white men in the United States (American Cancer Society, 2008). **Although African-Americans have experienced a greater decline in mortality than white men since the early 1990s, their death rates remain more than 2.4 times higher than whites.** A recent meta-analysis quantifies this difference, demonstrating a higher risk of biochemical recurrence (risk ratio = 1.34, 95% confidence interval [CI] = 1.23 to 1.46), prostate cancer–specific death (risk ratio = 1.29, 95% CI = 1.13 to 1.47), and all-cause mortality (risk ratio = 1.35, 95% CI = 1.23 to 1.48) (Evans et al, 2008). These differences were not fully explained by differences in comorbidity, PSA screening, or access to health care. One study that analyzed Medicare data found shorter survival intervals for African-Americans: 1.8 years shorter with localized disease treated by RP, 0.7 years shorter after radiation, and 1 year shorter in those choosing watchful waiting, findings that persist after adjusting for other covariates, including education and income levels (Godley et al, 2003).

Many biologic, environmental, and social hypotheses have been advanced to explain these differences, ranging from postulated differences in genetic predisposition; differences in mechanisms of tumor initiation, promotion, and/or progression; higher fat diets, higher serum testosterone levels, or higher body mass index; structural, financial, and cultural barriers to screening, early detection, and aggressive therapy; and physician bias. Differences in screening rates between whites and African-Americans may play a role in explaining the differences in mortality, although the 2005 National Health Interview Survey demonstrated that among men ages 40 to 49 years, African-American men were more likely to have had a PSA test than white men, and there were no significant differences in PSA screening rates by race/ethnicity in men ages 50 to 79 years (Ross et al, 2008). Studies have consistently shown that African-American men are more likely to receive androgen-deprivation therapy, expectant management or external beam radiation therapy, and are less likely to undergo radical

prostatectomy compared with white men (Underwood et al, 2005). Even among those treated with "watchful waiting," African-American men may receive less intensive follow-up (Shavers et al, 2004). **There are currently no data that clearly indicate any of these hypotheses are the determinants of the observed differences in incidence or mortality, and it seems likely that the source of the disparity is multifactorial.** Recent observations suggest that the incidence of organ-confined disease at diagnosis among African-Americans is increasing, that the disparity in mortality is lessening in the PSA era, and that those with organ-confined disease can be cured at a high rate regardless of race (Powell et al, 2004; American Cancer Society, 2008).

The incidence of prostate cancer in other ethnic groups is lower than that of whites and African-Americans. Comparative data for prostate cancer–related incidence and mortality are now available for these groups (see Table 95–1).

Worldwide Incidence and Mortality

Incidence rates show that prostate cancer is the fifth most common malignancy worldwide and the second most common in men (Parkin et al, 2005). **Prostate cancer makes up 11.7% of new cancer cases overall, 19% in developed countries, and 5.3% in developing countries. Its incidence varies widely between countries and ethnic populations, with disease rates differing by more than 100-fold. The lowest yearly incidence rates occur in Asia (1.9 cases per 100,000 in China) and the highest in North America and Scandinavia, especially in African-Americans (249 cases per 100,000)** (Parkin et al, 2005; American Cancer Society, 2008). As in the United States, prostate cancer incidence has increased in many countries since the early 1990s, with the largest increases in high-risk countries (Hsing et al, 2000). Although much of the increase can be correlated with the introduction of PSA, some of the increase predates screening and is perhaps partly due to the increasing diagnosis of latent cancers following transurethral resection of the prostate (Potosky et al, 1990; Oliver et al, 2001). Large increases have also been noted in low-risk countries between 1973 and 1992 (e.g., 104% among Chinese in Singapore and 84% in Miyagi, Japan) (Hsing et al, 2000). **Mortality also varies widely among countries, being highest in the Caribbean (28 per 100,000 per year) and lowest in Southeast Asia, China, and North Africa (<5 per 100,000 per year)** (Parkin et al, 2005). Mortality rates increased slowly for most countries between 1985 and 1995 (Quinn and Babb, 2002). The CONCORD study, a worldwide population-based analysis of cancer survival in five continents, recently analyzed international differences in survival for breast, colorectal, and prostate cancer (Coleman et al, 2008). **Using data from cancer registries, age-standardized 5-year survival rates were found to vary greatly, ranging from 80% or higher in the United States (92%), Australia, and Canada, to less than 40% in Denmark, Poland, and Algeria.**

There are multiple potential explanations for the worldwide and ethnic variations in prostate cancer incidence and mortality. Access to and quality of health care, the accuracy of cancer registries, and the penetrance of PSA screening all affect how rates of disease are reported. Before reliable data were available from African countries, rates of prostate cancer in Africa were thought to be much the same as those in Asia. However, in Uganda and Nigeria, prostate cancer is very common, and in Nigeria it is the most common cancer in men (Gronberg, 2003). Interestingly, there has been a more marked decline in prostate cancer mortality in countries with a higher uptake of PSA screening when compared with countries where routine screening is not widely performed (Collin et al, 2008). Possible explanations for the observed mortality differences include international variability in treatment approaches and bias related to the misattribution of cause of death.

Environment also plays an important role in modulating prostate cancer risk around the world. Japanese and Chinese men in the United States have a higher risk of developing and dying from prostate cancer than do their relatives in Japan and China (Muir et al, 1991; Shimizu et al, 1991). Likewise, prostate cancer incidence and mortality have increased in Japan as the country has become more Westernized (Hsing et al, 2000). It is important to note, however, that Asian-Americans have a lower prostate cancer incidence than white or African-American men, indicating that genetics still plays a role in determining prostate cancer predisposition.

Age at Diagnosis

Prostate cancer is rarely diagnosed in men younger than 50 years old, accounting for only 2% of all cases (Jani et al, 2008). **The median age at diagnosis is 68 years, with 63% diagnosed after age 65** (Ries et al, 2011). At 85 years of age, the cumulative risk of clinically diagnosed prostate cancer ranges from 0.5% to 20% worldwide, despite autopsy evidence of microscopic lesions in approximately 30% of men in the fourth decade, 50% of men in the sixth decade, and more than 75% of men older than 85 years (Sakr et al, 1993; Gronberg, 2003). PSA-based screening has induced an important age migration effect; the incidence of prostate cancer in men 50 to 59 years of age has increased by 50% between 1989 and 1992 (Hankey et al, 1999), with important implications for deciding on the need for, type of, and complications after therapy.

Stage at Diagnosis

In addition to changes in prostate cancer incidence and mortality over the last several decades, there has been a substantial shift to more favorable stage at presentation in men with newly diagnosed disease. **This clinical stage migration is largely if not exclusively accounted for by PSA screening** (Catalona et al, 1993; Mettlin et al, 1993). **Since the introduction of PSA testing, the incidence of local-regional disease has increased, whereas the incidence of metastatic disease has decreased** (Newcomer et al, 1997). Nonpalpable cancers (American Joint Committee on Cancer [AJCC] clinical stage T1c) now account for 60% to 75% of newly diagnosed disease (Derweesh et al, 2004; Gallina et al, 2008). Clinical stage migration has also been associated with improvements in 5- and 10-year disease-specific survival, which for all stages combined now are 99% and 91%, respectively (American Cancer Society, 2008).

The use of PSA has also resulted in a substantial downward pathologic stage migration as evidenced by an increase in the proportion of patients with organ-confined disease (Catalona et al, 1993; Jhaveri et al, 1999; Derweesh et al, 2004;) **and a decrease in the proportion with seminal vesicle involvement** (Gallina et al, 2008). These observations have been consistent across the United States and Europe (Noldus et al, 2000; Gallina et al, 2008). Since 1995, however, a slowing in this trend has been observed, suggesting a diminishing effect of PSA screening on pathologic stage migration (Fig. 95–3) (Dong et al, 2007b). The improvement in pathologic stage has been seen for clinical stages T1-T3 tumors and all tumor grades (Fig. 95–4) and has resulted in improved cancer-specific

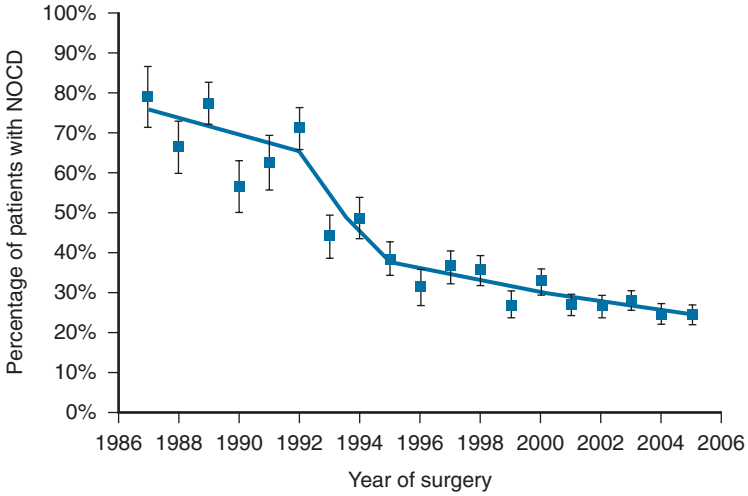


Figure 95–3. Declining rate of extracapsular extension (resulting in increased rate of organ-confined disease) on radical prostatectomy specimens at the Cleveland Clinic, 1987-2005. Trends in pathologic stage migration with joinpoint regression analysis. Annual change: 1987 to 1992: –2.9%; 1992 to 1995: –16.9%; 1995 to 2005: –4.2%. NOCD, non–organ-confined disease.

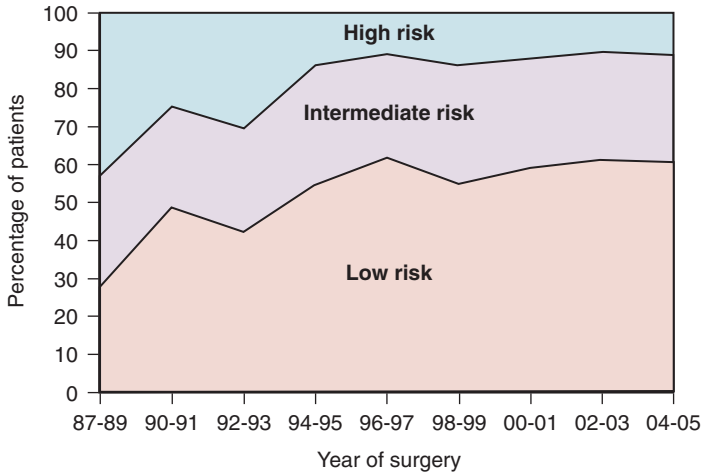


Figure 95–4. Risk stratification of surgical population over time. Low risk: prostate-specific antigen (PSA) less than 10, and stage T1 or T2a, and biopsy Gleason score = 6 or lower. Intermediate risk: PSA 10 to 20, or stage T2b or T2c, or biopsy Gleason score = 7. High risk: PSA more than 20, or stage T3, or biopsy Gleason score = 8 or higher, or any two or more intermediate risk factors.

survival after external radiation or surgery for patients treated late in the PSA era (Jhaveri et al, 1999; Derweesh et al, 2004; Kupelian et al; 2005).

Effect of Screening on Mortality

Recently, the results of two large randomized trials assessing the effect of PSA screening on prostate cancer mortality were published. **The first examined results from the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial and reported on 76,693 men aged 55 to 74 years at 10 U.S. centers receiving either annual screening or usual care** (Andriole et al, 2009). **After 7 years of follow-up, no difference in prostate cancer mortality was detected between the groups, with an incidence of 2.0 deaths per 10,000 person-years (50 deaths) in the screening group and 1.7 deaths per 10,000 person-years (44 deaths) in the control group (rate ratio = 1.13, 95% CI = 1.16 to 1.29). However, the trial has been criticized for its relatively short follow-up, given the long natural history for prostate cancer and because more than half the men in the control arm actually had a PSA test done outside of the trial. The second trial, the European Randomized Study of Screening for Prostate Cancer (ERSPC), included 162,243 men between the ages of 55 and 69 years randomized to either PSA screening every 4 years or no screening** (Schroder et al, 2009). **After a median follow-up of 9 years, screening reduced the rate of death from prostate cancer by 20% (rate ratio = 0.80, 95% CI = 0.65 to 0.98). However, they estimated that to prevent one prostate cancer death, one would need to screen 1410 men (95% CI = 1142 to 1721), and treat 48 additional cases of prostate cancer.**

The results of these trials highlight two important points. First, overall, prostate cancer is an indolent disease with a very low cause-specific death rate and will only impact life expectancy in a minority of men. Second, the morbidity of treatment needs to be strongly considered when evaluating population screening. Prior to the release of the above-mentioned studies, an evidence update for the U.S. Preventative Task Force on the benefits and harms of PSA screening concluded that false-positive PSA test results cause psychologic adverse effects for up to 1 year and that the benefits of screening remain uncertain (Lin et al, 2008). On the other hand,

Key Points: Epidemiology

- In the United States, prostate cancer:
  - Is the most common visceral malignancy in men.
  - Is the second leading cause of cancer-related deaths.
  - Incidence peaked in 1992 approximately 5 years after the introduction of PSA as a screening test, declined until 1995, subsequently increased at a rate similar to that observed in the pre-PSA era, and is declining again in recent years.
  - Mortality has declined since 1991 and for whites is now lower than before PSA was introduced.
- Worldwide, prostate cancer incidence and mortality rates:
  - Vary significantly between countries and regions.
  - Are highest in African-American men.
- PSA has induced a significant downward migration in age and stage (both clinical and pathologic) at diagnosis.
- PSA screening may have a beneficial effect on prostate cancer mortality; however, the absolute effect is small relative to the number needed to screen and treat to cure a single individual.

in 2009 the American Urological Association (AUA) released a Best Practice Statement suggesting that early detection of and risk assessment for prostate cancer should continue to be offered to asymptomatic men 40 years of age or older who have a life expectancy of at least 10 years (American Urological Association, 2009).

RISK FACTORS

Although the specific causes of prostate cancer initiation and progression are not yet known, considerable evidence suggests that **both genetics and environment play a role in the origin and evolution of this disease.** Traditional and molecular epidemiology have identified a number of potential risk factors associated with the development of prostate cancer.

Familial and Genetic Influences

Ample epidemiologic evidence suggests that prostate cancer has both a familial and genetic component. The first reports of a familial clustering were published in the mid-20th century and suggested that the risk of developing prostate cancer was higher in those with an affected first-degree relative (Woolf, 1960). Subsequent case control and cohort studies have confirmed this observation (Eeles et al, 1997). Twin studies have also suggested a genetic component, with higher rates of concordance for monozygotic than dizygotic brothers (Gronberg et al, 1994; Ahlbom et al, 1997; Page et al, 1997). **Results of a meta-analysis demonstrate that relative risk increases according to the number of affected family members, their degree of relatedness, and the age at which they were affected** (Table 95–2) (Zeegers et al, 2003). A consistent finding is the increased risk when a brother is affected compared with when a father is affected. This is consistent with either X-linked or recessive genetic components (Monroe et al, 1995). However, the bias associated with the fact that brothers of affected men are more likely to seek prostate cancer screening may also explain the differential association.

For investigative purposes, prostate cancer may be conveniently divided into three phenotypes: sporadic, familial, and hereditary. Sporadic cancers occur in individuals with a negative family history. Familial prostate cancer is defined as cancer in a man with more than one affected relative. Hereditary prostate cancer is a subset of the familial form and has been operationally defined as nuclear families with more than three affected members, prostate cancer in three successive generations, or two affected individuals diagnosed with cancer before age 55 (Carter et al, 1993). **Although most prostate cancer is likely to be polygenic in origin, the existence of true hereditary prostate cancer is suggested by three epidemiologic observations: (1) relatives of patients < 55 years old are at higher risk of getting prostate cancer than those with older affected relatives; (2) there is stronger familial clustering in families with early onset prostate cancer; and (3) the number of affected family members and their age at onset are the most important determinants of risk among relatives.** Sporadic cancers account for about 85% of all prostate cancers and about 15% are familial and/or hereditary. Hereditary prostate cancer accounts for 43% of early onset disease (55 years of age or younger) but only 9% of all cancers that occur by 85 years of age (Carter et al, 1992).

Table 95–2.

Family History and Risk of Prostate Cancer

FAMILY HISTORY	RELATIVE RISK	95% CONFIDENCE INTERVAL
None	1	
Father affected	2.17	1.90-2.49
Brother affected	3.37	2.97-3.83
First-degree family member affected, age less than 65 years at diagnosis	3.34	2.64-4.23
Greater than two first-degree relatives affected	5.08	3.31-7.79
Second-degree relative affected	1.68	1.07-2.64

Data derived from meta-analysis assessing risk of prostate cancer for relatives of patients with prostate carcinoma (Zeegers, Jellema A, Ostrer H. Empiric risk of prostate carcinoma for relatives of patients with prostate carcinoma: a meta-analysis. Cancer 2003;97:1894–03).

A number of studies have suggested a familial coaggregation of prostate cancer with breast cancer (Thiessen, 1974; Tulinius et al, 1992; Goldgar et al, 1994). The two major susceptibility genes in breast cancer, *BRCA1* (17q21) and *BRCA2* (13q12), have also been studied in prostate cancer. Two large epidemiologic studies have estimated the risk of prostate cancer in men who are carriers of specific *BRCA1* founder mutations to be double that of noncarriers, with a cumulative risk of 30% by 80 years of age (Struewing et al, 1997; Warner et al, 1999). Moreover, the *BRCA2* gene has provided consistent association with an increased risk of prostate cancer, estimated at 5- to 7-fold, and may play a more important role in early onset disease (Breast Cancer Linkage Consortium, 1999; Edwards et al, 2003). However, due to their rarity, these mutations only contribute to a small fraction of hereditary prostate cancer cases.

Linkage studies have identified a number of **candidate prostate cancer susceptibility genes, including *RNaseL* (hereditary prostate cancer-1 [*HPC1*] region, 1q23-25)** (Carpten et al, 2002)**, *ELAC2* (*HPC2* region, 17p)** (Tavtigian et al, 2001), **and *MSR1* (8p22-23)** (Xu et al, 2002). Segregation studies have also suggested the existence of prostate cancer susceptibility loci on chromosomes 1q42.2-43 (*PCAP*) (Berthon et al, 1998), 1p36 (*CAPB*, also linked to brain tumors) (Gibbs et al, 1999), and Xq27-28 (Xu et al, 1998), but the gene or genes linked to these regions have not been identified. Many other genetic loci and prostate cancer susceptibility genes have been more recently identified, and the list is continually growing (Online Mendelian Inheritance in Man, 2009).

More recently, genome-wide association studies (GWAS) have emerged as a new approach to indentify alleles associated with prostate cancer without prior knowledge of position or function (Wellcome Trust Case Control Consortium, 2007). Genotype frequencies are compared among cases and controls at DNA sequence variations called single nucleotide polymorphisms (SNPs). Using this technique, studies have demonstrated SNPs on 8q24 and 17q, as well as on chromosomes 3, 6, 7, 10, 11, 19, and X, to be associated with prostate cancer risk (Amundadottir et al, 2006; Gudmundsson et al, 2007; Eeles et al, 2008). A worldwide consortium of 13 groups was recently formed to compile the large series necessary to provide accurate estimates of the risks associated with genetic variants and to evaluate the combined association of these variants (Kote-Jarai et al, 2008). The combined risks associated with each pair of SNPs were found to be consistent with a multiplicative risk model. In total, they determined that the 15 susceptibility variants studied only explained 16% of the familial risk of prostate cancer. **This indicates that, to date, only a small piece of the prostate cancer genetic puzzle has been**

discovered, and with the continued improvement in genetic technology, it is likely that the number of known susceptibility genes will increase. A commercially available genetic test, which assesses nine genetic variants associated with prostate cancer risk, is currently offered to the general public (deCODE Genetics, Reykjavík, Iceland). Although the test is being marketed as a preventative tool, its clinical utility in the general population requires further study.

Of the known susceptibility genes, *HPC1* is the best characterized. The existence of *HPC1* was suggested by a genome-wide scan of families with hereditary prostate cancer (Smith et al, 1996) and later confirmed by linkage studies (Cooney et al, 1997; Eeles et al, 1998). A recent genome-wide association screen also identified an association between this locus and sporadic prostate cancer (Nam et al, 2008). ***HPC1* was mapped to the human gene that encodes for the antiviral and pro-apoptotic enzyme RNaseL** (Carpten et al, 2002). RNaseL is part of the innate immune system that responds to a pathogen-associated molecular pattern (PAMP) to induce degradation of viral and cellular RNAs, thereby blocking viral infections (Klein and Silverman, 2008). It is the terminal enzyme of the 2-5A synthetase family, an RNA degradation pathway that plays an important role in mediating the biologic effects of interferons, especially in response to viral infection. **2-5A binds with high affinity to RNaseL, converting it from its inactive form as a monomer to a potent dimer that degrades single-stranded RNA, thus preventing viral replication, interfering with protein synthesis, and causing caspase-mediated apoptosis** (Fig. 95–5) (Silverman, 2003). *RNaseL* knockout mice are more prone to viral infections (Silverman, 2003).

A variety of inactivating and missense mutations of *RNaseL* have been identified in families with hereditary prostate cancer (Xiang et al, 2003). **Of these, SNP R462Q, resulting from an arginine to glutamine substitution, has been shown to be associated with an increased risk of prostate cancer** (Casey et al, 2002); **men and cell lines with this allelic variant have been shown to have reduced RNaseL activity leading to deficient apoptosis** (Carpten et al, 2002; Xiang et al, 2003; Malathi et al, 2004), **presumed to lead to an accumulation of genetic defects ultimately resulting in cancer formation.**

The epidemiologic data suggest that *HPC1* is a rare autosomal dominant gene that has high penetrance, meaning that while it does not account for many prostate cancers, an individual carrier is highly likely to be affected by prostate cancer. Although cancers with specific mutations of the *HPC1/RNaseL* gene have been reported to present with higher-grade and more advanced stages (Gronberg et al, 1997; Goode et al, 2001; Rennert et al, 2005), other mutations have not shown such an association (Larson et al, 2008).

The biologic functions of the other known susceptibility genes fall into several classes. As with other malignancies, these genes include mediators of inflammation (e.g., *MIC1, MSR1*), antioxidant enzymes (e.g., *MSR1, PON1*), DNA repair (e.g., *OGG, CHEK2,* and *BRCA2*), susceptibility to infection (e.g., *MSR1, RNaseL,* and *TLR4*), and apoptosis (e.g., *RNaseL*).

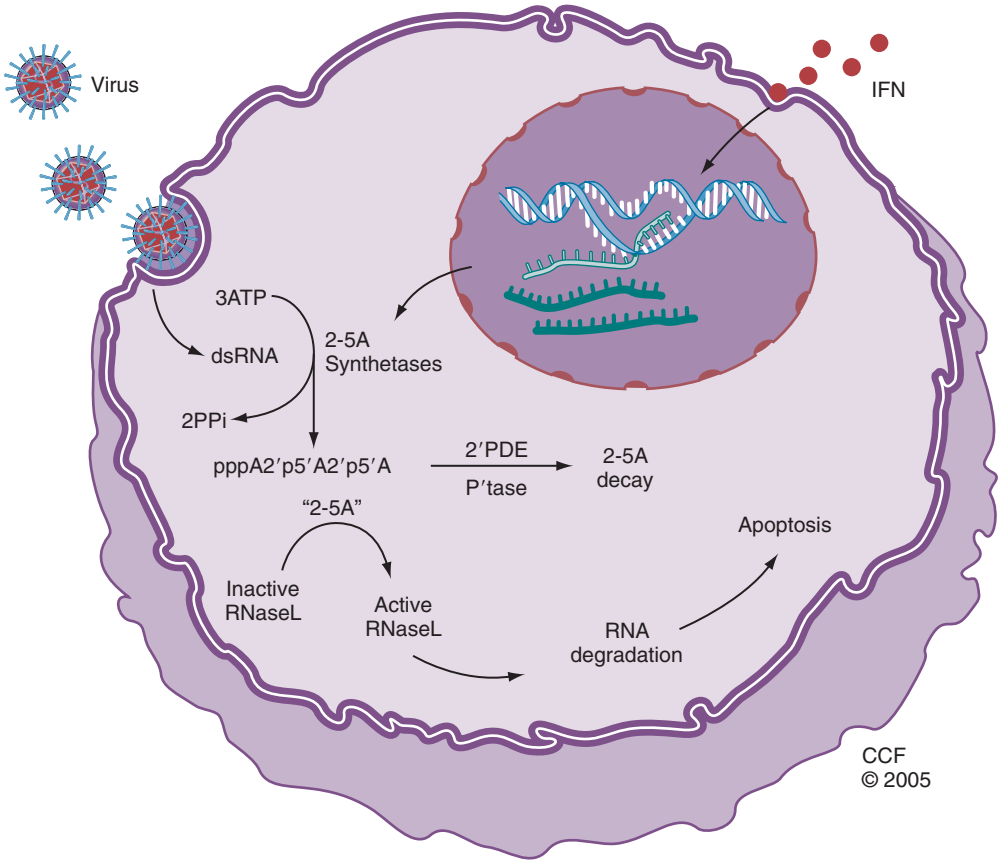


Figure 95–5. Cellular effects of RNaseL. In response to interferon (IFN) and viral infection, a family of oligoadenylate synthetases are activated, resulting in the conversion of ATP to a series of short 2′- to 5′- linked oligoadenylates (2-5A). 2-5A binds with high affinity to RNaseL, converting it from its inactive form as a monomer to a potent dimer that degrades ssRNA and causes caspase-mediated apoptosis of the host cell. Prostate cancer cells deficient in RNaseL are resistant to apoptosis. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2005-2011. All Rights Reserved.)

Key Points: Risk Factors

- Both genetics and environment are important in the origin and evolution of prostate cancer.
- Most prostate cancer is polygenic, but some hereditary forms may be determined by variants in a single or relatively few genes.
- *HPC1* is an autosomal-dominant gene with high penetrance and encodes for the enzyme RNaseL, which has both antiviral and pro-apoptotic activity.
- Commonly observed variants in *RNaseL* result in reduced enzymatic activity and have been associated with an increased risk of prostate cancer.
- Infectious agents, both viruses and bacteria, may be important in the genesis of prostate cancer.
- Other prostate cancer susceptibility genes are mediators of inflammation, DNA repair, and defenses against oxidative stress.

Inflammation, Infection, and Genetic Susceptibility

It is estimated that infections cause almost 20% of all cancers worldwide (American Cancer Society, 2008). **Chronic inflammation leading to cellular hyperproliferation to replace damaged tissue contributes to the development of infection-associated cancers of the colon, esophagus, stomach, bladder, and liver** (Coussens and Werb, 2002; De Marzo et al, 2007). **Accumulating epidemiologic, histologic, and genetic evidence suggests that a similar process may underlie the development of prostate cancer.**

Some evidence suggests that prostate cancer may have an infectious etiology. Two meta-analyses examining 34 case-control studies reported statistically significant associations of prostate cancer with a history of sexually transmitted infection (RR = 1.4) or prostatitis (OR = 1.57) (Dennis et al, 2002b; Dennis and Dawson, 2002). Supportive evidence is provided by studies demonstrating positive associations of antibodies against syphilis, human papillomavirus (HPV), and human herpesvirus-8 (HHV-8) with prostate cancer (De Marzo et al, 2007). Case-only or case-control studies have also reported higher plasma concentrations of acute-phase reactants and proinflammatory cytokines in men with prostate cancer (De Marzo et al, 2007). Two studies have demonstrated evidence of viral pathogens in human prostate tissue, including HPV, human herpes simplex virus type 2 (HSV2), cytomegalovirus (CMV), and HHV-8 (Strickler and Goedert, 2001; Zambrano et al, 2002; Samanta et al, 2003).

However, recent studies assessing the association between infection and prostate cancer have shown mixed results. In the Health Professionals Follow-up Study (Sutcliffe et al, 2006), a prospective study of 51,529 American male health professionals aged 40 to 75 years, no association was found between a self-reported history of gonorrhea or syphilis and prostate cancer, although the incidence of sexually transmitted infections was very low in this population. In addition, no overall correlation between prostate cancer and clinical prostatitis was found. Similarly in this cohort, no associations were observed between *Chlamydia trachomatis*, HPV-16, HPV-18, and HPV-33 antibody seropositivity and prostate cancer (Sutcliffe et al, 2007a). Conversely, in a small case-control study in African-American men (Sarma et al, 2006), a history of gonorrhea or prostatitis increased the odds of prostate cancer by 1.78-fold (95% CI = 1.13 to 2.79) and 4.93-fold (95% CI = 2.79 to 8.74), respectively, even after adjusting for potential confounders. Furthermore, men reporting 25 or more sexual partners had 2.80 times the odds of being diagnosed with cancer (95% CI = 1.29 to 6.09) compared with men with five or fewer partners.

Inflammatory infiltrates and the histologic lesion called proliferative inflammatory atrophy (PIA) are frequent in clinical prostate specimens (De Marzo et al, 1999). **PIA is a spectrum of lesions characterized by epithelial atrophy, low apoptotic index, and an increased proliferative index usually associated with inflammatory infiltrates** (Putzi and De Marzo, 2000). Inflammation in PIA may include mononuclear infiltrates in the stroma and macrophages and/or neutrophils in the glandular lumen or epithelium. Macrophages activated by interferon-γ secrete proinflammatory cytokines and reactive nitrogen species (e.g., nitric oxide). Inducible nitric oxide synthase, which catalyzes the generation of nitric oxide, is overexpressed in macrophages in PIA but not in normal epithelium (Nelson et al, 2003). **PIA appears to be a regenerative lesion appearing as a consequence of infection or cell trauma resulting from oxidant damage, hypoxia, infection, or autoimmunity, and its hyperproliferative state may lead to cancer.** PIA is often found adjacent to high-grade prostatic intraepithelial neoplasia (HGPIN) or early cancer (Putzi and De Marzo, 2000), and there is an identifiable genetic pathway between PIA, HGPIN, and cancer (Shah et al, 2001; Nakayama et al, 2003; Nelson et al, 2003).

The previously described genetic and histologic observations in prostate cancer strongly suggest that compromised cellular defenses against inflammatory oxidants may initiate and/or perpetuate prostatic carcinogenesis. Oxidative stress is mediated by reactive oxygen and nitrogen species that bind DNA and cause mutations, and oxidant stresses from exogenous and endogenous sources are implicated in the accumulation of DNA damage that occurs with aging and subsequently leads to malignant change (Coussens and Werb, 2002). Cellular defense mechanisms against this process include frontline antioxidant enzymes, which scavenge reactive oxygen and nitrogen species and prevent mutations; DNA repair enzymes; and the ability to undergo apoptosis if the DNA damage is too severe to repair. **A recent model proposes that inherited and acquired defects in cellular defense mechanisms against infection and oxidative stress allow prostate cancer to develop.** This model suggests that, as in other inflammatory-mediated cancers, persistent infection leads to chronic inflammation, and that defects in antioxidant enzymes, DNA repair mechanisms, and apoptosis lead to cancer. Subsequent expression by tumor cells of α-methylacyl-CoA racemase (Kumar-Sinha et al, 2004), an enzyme that oxidizes branched-chain fatty acids from dietary sources, results in generation of hydrogen peroxide, which may contribute to continued oxidative stress, and tumor growth. This model is illustrated in Figure 95–6. **In addition to providing a framework for further experimental study, this model gives a theoretical rationale for the use of antioxidants as chemopreventative agents (see later).**

Like cervical cancer, which is characterized by viral infection coincident with the onset of sexual activity, histologic evidence of preinvasive lesions, and a latency period of 15 to 20 years before the development of invasive cancer, **the accumulating**

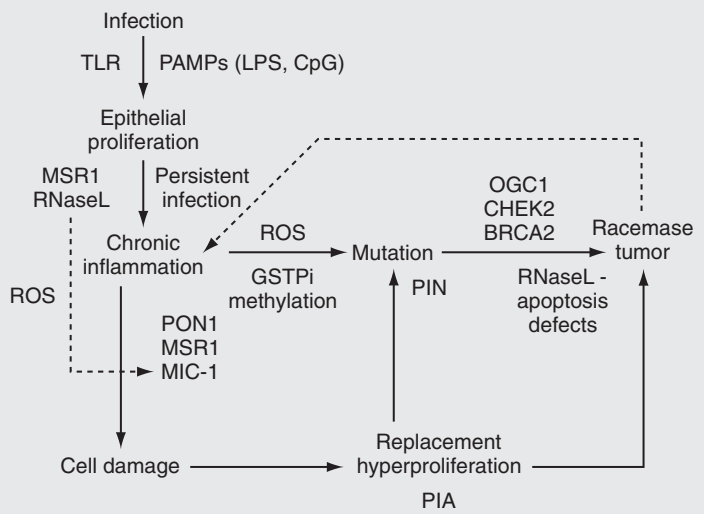


Figure 95–6. Model of prostate cancer pathogenesis related to infection, chronic inflammation, and defects in cellular defense against oxidative stress. Defects in Toll-like receptor (TLR) genes lead to immortalization of benign prostatic epithelium, and allelic variants of *RNaseL* and *MSR1* allow persistent infection, leading to a proinflammatory cellular microenvironment. Defects in genes that control the intensity of the inflammatory response (*MSR1* and *MIC1,* the latter of which is regulated by *RNaseL*) permit a robust inflammatory response. Defects in cellular defenses against the resultant oxidative stress, including deficiencies in antioxidant enzymes (allelic variants in *PON1,* methylation of *GSTP1*), DNA repair (*OGG1, CHEK2, BRCA2*), and apoptotic defects (*RNaseL*), lead to cancer through the histologic intermediates proliferative inflammatory atrophy (PIA) and prostatic intraepithelial neoplasia (PIN). Established tumors make racemase, an enzyme that converts fatty acids to free radicals, creating an autocrine growth loop based on perpetuation of oxidative stress. CpG, DNA CpG island repeats (representing viral genomes in this context); LPS, bacterial lipopolysaccarhide; PAMP, pathogen-associated molecular profile; ROS, reactive oxygen species.

histologic, epidemiologic, and genetic evidence suggests the possibility that at least some prostate cancer cases have a viral pathogenesis. The epidemiologic data linking prostate cancer risk to prior infections and the association of a functionally important mutation in the antiviral *HPC1/RNaseL* gene support this hypothesis. Recently reported studies have identified a previously undescribed γ-retrovirus, xenotropic murine leukemia–related virus (XMRV), from prostate cancer tissue in men with the R462Q allelic variant of *HPC1/RNaseL*. The initial experiment demonstrated the presence of viral genomes for XMRV in prostate tumors in 8 of 20 patients with the R462Q SNP in *RNaseL*, but in only 1 of 62 wild-type or heterozygous patients (Urisman et al, 2006). XMRV infections were visualized by immunohistochemistry and fluorescence in-situ hybridizations in prostatic stromal cells adjacent to the tumor. A full-length, replication-competent, and infectious viral molecular clone of XMRV was subsequently cloned from prostate tissue cDNA and has been used for in-vitro studies (Dong et al, 2007a). In addition, XMRV integration sites have been mapped in host chromosomal DNA (Kim et al, 2008), suggesting that modulation of cancer-related gene function by XMRV could be important. The presence of XMRV in prostate tissue has been recently confirmed by two other groups, including evidence of expression of XMRV proteins in malignant prostatic epithelium using a rabbit polyclonal antibody (Fischer et al, 2008; Singh Laboratory, 2010). **Together these observations suggest that XMRV infects and persists in the prostate when there is a deficiency in RNaseL activity, providing a proposed mechanism by which XMRV could be oncogenic in genetically susceptible individuals.**

Other infectious agents have also been implicated in prostate cancer. BK virus (BKV), a member of the polyomavirus family, infects almost 90% of the human population by early childhood and resides in a subclinical persistent state in the urinary tracts of healthy individuals. BKV transforms rodent cells in culture, causes kidney tumors in transgenic mice, and immortalizes primary human cells alone or in the presence of other oncogenes such as c-*RAS* and adenovirus *E1A* (Das et al, 2008). The occurrence of mutations in *TP53* and *RB1* in the early stages of prostate cancer is relatively low, suggesting the possibility that a virus, such as BKV (encoding tumor antigens that inactivate these tumor suppressors), may play a role in the etiology of prostate cancer. BKV DNA has been demonstrated in epithelial cells of benign and PIA ducts of cancerous prostate specimens, and BKV large tumor antigen (Tag) expression has been observed specifically in atrophic epithelial cells, PIA, and prostatic intraepithelial neoplasia (PIN) but not in cancer nor in the epithelium of normal prostates (Das et al, 2004, 2008). These observations suggest a role for BKV in PIA and the early development of prostate cancer. Furthermore, in a study examining the bacterial flora of prostate cancer, Sfanos and Isaacs (2008) demonstrated the presence of 83 distinct microorganisms by sequencing bacterial 16S rDNA in core samples of 30 prostate cancers, most of which were not found by routine culture methods. If XMRV, BKV, or specific bacteria are proven to be oncogenic, their effects may be preventable by development of a protective vaccine.

Key Points: Inflammation, Infection, and Genetic Susceptibility

- Chronic inflammation leading to cellular hyperproliferation to replace damaged tissue contributes to the development of infection-associated cancers, possibly including prostate cancer.
- Some epidemiologic data suggests that a history of sexually transmitted infection or prostatitis is associated with a higher risk of prostate cancer.
- Histologic evidence of inflammation, as manifested by proliferative inflammatory atrophy, is common in prostate cancer and may represent a key pathobiologic process in its development.
- Both genetic and histologic observations suggest that compromised cellular defenses against inflammatory oxidants are important in prostate cancer initiation and promotion.

Molecular Epidemiology

Molecular epidemiologic approaches have identified many biomarkers of exposure measured in blood or other tissues and evaluated them in relation to incidence or mortality. These biomarkers capture aspects of diet, environmental contaminants, and factors for which concentrations are partly genetically determined. A brief

survey of major molecular epidemiologic studies relating to prostate cancer is presented.

Gene Fusions

Gene fusions resulting from chromosomal translocations are the most common genetic alteration in human cancers (Futreal et al, 2004). These were previously thought to be the oncogenic mechanism exclusively limited to hematologic malignancies and sarcomas, as exemplified by the BCR-ABL1 fusion protein in chronic myeloid leukemia. **In 2005, recurrent genomic rearrangements in prostate cancer were identified, resulting in the fusion of the 5′ untranslated end of *TMPRSS2* (21q22.2, an androgen-responsive, prostate-specific, transmembrane serine protease gene) to members of the *ETS* family of oncogenic transcription factors** (Tomlins et al, 2005). **In over two dozen published reports using PSA-screened patient cohorts, the most common fusion identified in localized prostate cancer involves *TMPRSS2* fused to *ERG* (*ETS*-related gene, 21q22.3) in approximately 50% of patients** (Kumar-Sinha et al, 2008). However, this gene fusion may be less common (15%) in population-based cohorts (Demichelis et al, 2007). Gene fusions involving other members of the *ETS* family, most commonly *ETV1* (*ETS* variant gene 1, 7q21.2), but also *ETV4* and *ETV5,* are likely present in less than 10% of prostate cancer samples collectively (Kumar-Sinha et al, 2008).

The *TMPRSS2* gene is prostate specific, and is expressed in both benign and malignant prostatic epithelium. *TMPRSS2* expression has been shown to be induced by androgens in hormone-responsive prostate cancer cell lines (Lin et al, 1999). Therefore it is hypothesized that *TMPRSS2* drives *ETS* gene overexpression in prostate cancers positive for *TMPRSS2-ETS* gene fusions (Fig. 95–7) (Kumar-Sinha et al, 2008). Although some studies have demonstrated an association between *TMPRSS2-ERG* with high pathologic stage (Mehra et al, 2007), higher recurrence rates (Nam et al, 2007), and prostate cancer–specific death (Demichelis et al, 2007), others have failed to report such clinical correlations. It is notable, however, that the presence of *TRMPSS-ETS* gene fusion was associated with a markedly higher risk of death in men managed by watchful waiting in one Swedish cohort (Demichelis et al, 2007).

Currently, the clinical application of this discovery is uncertain. Given that *ETS*-positive and *ETS*-negative tumors have distinct morphologic features, expression signatures, and potentially different clinical outcomes, some have proposed classifying prostate cancer as two categories: *ETS* gene fusion–positive and *ETS* gene fusion–negative disease (Kumar-Sinha et al, 2008). Because these gene fusions do not occur in benign prostate tissue, a sensitive and specific screening test based on their presence could be developed for the detection of prostate cancer. Eventually, gene fusion status may be used to decide the need for initial or repeat biopsy, for enrollment in therapeutic trials, or for surveillance after therapy. It also follows that targeting ERG activity in fusion-positive prostate cancers may provide an effective therapeutic approach for this subset of patients. Presently, attempts at identifying small molecular inhibitors of the ERG pathway that could serve as therapeutic agents are underway. **At this time, the emerging consensus suggests that *TRMPSS*-related gene fusions are highly specific for the presence of prostate cancer, but their utility as prognostic markers requires further study.**

Androgens

Androgens influence the development, maturation, and maintenance of the prostate, affecting both proliferation and differentiation of the luminal epithelium. There is little doubt that exposure of the prostate at key developmental times to androgens plays an important role in prostate carcinogenesis. Androgens are also important in the maintenance of established cancers, as supported by the historical observation that the majority of prostate cancers initially respond to androgen-deprivation therapy, and more recently by results of the Prostate Cancer Prevention Trial, which indicated that inhibition of the conversion of testosterone to the more potent dihydrotestosterone by finasteride reduces the incidence of prostate cancer by approximately 25% (Thompson et al, 2003). In addition, genetic polymorphisms of the androgen receptor (AR) (Balic et al, 2002; Taplin et al, 2003), the 5α-reductase type 2 isoenzyme (Makridakis and Reichardt, 2004), and the genes involved in biosynthesis of testosterone have also been implicated in prostate carcinogenesis (Chang et al, 2002).

High serum androgen levels have long been hypothesized to be a risk factor for prostate cancer. However, studies examining this association have been inconsistent, with some studies finding an association between specific hormones and prostate cancer risk. Recently, a collaborative group performed a pooled analysis of 18 prospective studies assessing this association using data from 3886 men with prostate cancer and 6438 control subjects (Endogenous Hormones, Prostate Cancer Collaborative Group, 2008). **The collaborative analysis failed to detect an association between the risk of prostate cancer and serum concentrations of testosterone, calculated free testosterone, dihydrotestosterone, dehydroepiandrostenedione sulfate, androstenedione, androstanediol glucuronide, estradiol, or calculated free estradiol.** The only positive finding in this study was a modest inverse association between prostate cancer risk and serum concentration of sex-hormone binding globulin. **This study suggests that one-time**

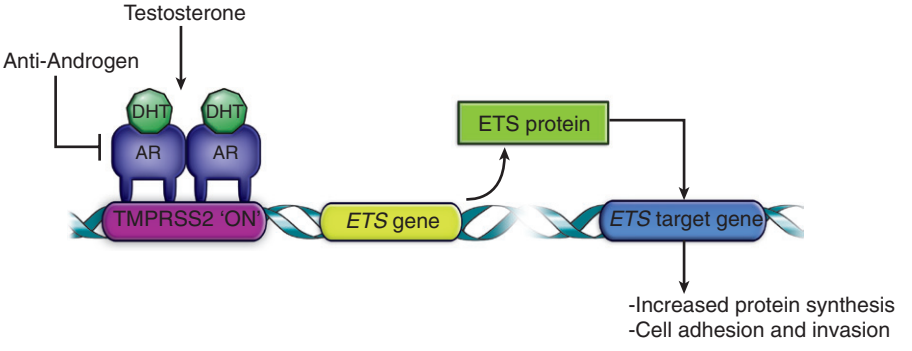


Figure 95–7. Role of gene fusion in prostate cancer. Androgen-mediated upregulation of *ETS* genes (for example, ERG or *ETV1*) leads to the activation of *ETS* target genes involved in increased protein synthesis, and cell adhesion and invasion. DHT, dihydrotestosterone.

measurements of serum sex hormones in adulthood are not a good measure of prostate cancer risk.

Estrogens

Estrogens have both direct and indirect effects on prostatic growth and development and have been postulated to play a role in prostate cancer initiation and progression. **Traditionally, estrogens have been considered protective against prostate cancer and have been used as a treatment for advanced disease.** This treatment effect is primarily through a negative feedback on the hypothalamo-pituitary-gonadal axis, and also through a direct inhibitory effect of estrogens on prostate epithelial cell growth. **However, there is increasing evidence from animal studies that estrogens may act as procarcinogens in the prostate** (Leav et al, 1988). Aromatase-knockout mice cannot produce 17β-estradiol locally in the prostate, and despite elevated testosterone and dihydrotestosterone, they do not develop prostate cancer (McPherson et al, 2001). There is evidence across multiple species that estrogens acting through stromal estrogen receptor (ER) α may contribute to prostate carcinogenesis and cancer progression (Prins and Korach, 2008). ERα expression is silenced in early prostate cancers, and re-emerges with disease progression. Prostate epithelial ERβ may play an important role in initiation of prostate cancer, with loss of ERβ potentially contributing to disease progression in organ-confined disease (Prins and Korach, 2008). In addition, the re-emergence of ERβ expression in metastatic prostate cancer also suggests a potential role in progression to castrate-resistant disease. Age-related prostatic disease parallels increases in serum estrogen levels, and there is a low incidence of prostate cancer in cultures with diets rich in phytoestrogens (Denis et al, 1999). However, the data on serum estrogen levels and prostate cancer risk are mixed (Barrett-Connor et al, 1990; Gann et al, 1996; Chen et al, 2003). Complicating interpretation of serum measurements is the fact that estradiol can be produced from testosterone by intraprostatic aromatase (Risbridger et al, 2003).

Insulin-Like Growth Factor Axis

Insulin-like growth factor (IGF)-1 is a peptide hormone that promotes growth in adolescence and childhood and is correlated with adult lean body mass (Severson et al, 1988). **IGF-1 promotes proliferation and inhibits apoptosis in normal prostate and tumor cells in vitro** (Cohen et al, 1991; Cohen et al, 1994). IGF-1 circulates bound to binding proteins, the most prevalent of which is insulin-like growth factor binding protein (IGFBP)-3. In the prostate IGFBP-3 promotes apoptosis and may mediate growth inhibition by 1,25-dihydroxyvitamin D (Boyle et al, 2001). IGFBP-3 can be cleaved by PSA, reducing its pro-apoptotic activity (Koistinen et al, 2002).

Results of epidemiologic studies suggest an association between IGFs and their associated binding proteins (IGFBPs) with prostate cancer risk. A recent combined analysis of individual patient data from 12 studies attempted to quantify the magnitude of the association (Roddam et al, 2008). The study included data on 3700 men with prostate cancer and 5200 control subjects. They found a **positive correlation between serum concentration of IGF-1 and subsequent prostate cancer risk.** The OR in the highest versus lowest quintile was 1.38 (95% CI = 1.19 to 1.60). Serum IGFBP-3 concentration was not found to be independently associated with prostate cancer risk; the observed association was secondary to its association with IGF-1 levels. Neither IGF-2 nor IGFBP-2 concentrations were associated with prostate cancer risk.

Leptin

Leptin, a peptide hormone produced by adipocytes, contributes to the control of body weight by appetite suppression and modulating energy use (Friedman, 2002). Obese men become leptin resistant and exhibit elevated plasma leptin (Chu et al, 2001). **Epidemiologic studies assessing the association between circulating leptin concentrations with prostate cancer have yielded mixed results** (Chung and Leibel, 2006). A genetic study found that prostate cancer patients were almost 5 times more likely to carry a polymorphism that results in increased leptin expression compared with controls (Ribeiro et al, 2004). **There is significant evidence, however, suggesting that leptin plays a role in the development of advanced prostate cancer** (Ribeiro et al, 2006). Leptin has been shown to stimulate proliferation of the androgen-independent prostate cancer cell lines DU145 and PC-3 (Somasundar et al, 2004; Deo et al, 2008). In addition, leptin appears to induce expression of vascular endothelial growth factor (VEGF) and basal fibroblast growth factor (BFGF), and stimulate cell migration (Frankenberry et al, 2004). Energy imbalance, perhaps mediated by leptin, is emerging as a possible contributor to the progression of prostate cancer to metastasis and death (Calle et al, 2003; Platz et al, 2003).

Vitamin D, Vitamin D Receptor, and Calcium

Vitamin D (1,25 dihydroxyvitamin D_3) is an essential vitamin that is a part of the steroid hormone superfamily. Human sources include both dietary intake and conversion from an inactive to active vitamin D in the skin through sunlight exposure. Interest in vitamin D as a determinant of prostate cancer risk comes from several epidemiologic observations (Peehl et al, 2003):

1. Men living in northern latitudes with less exposure to sunlight-derived ultraviolet exposure have a higher mortality rate from prostate cancer.
2. Prostate cancer occurs more frequently in older men, in whom vitamin D deficiency is more common both because of less ultraviolet exposure and age-related declines in the hydroxylases responsible for synthesis of active vitamin D.
3. African-Americans, whose skin melanin blocks ultraviolet radiation and inhibits activation of vitamin D, have the highest worldwide incidence and mortality rates for prostate cancer.
4. Dietary intake of dairy products rich in calcium, which depresses serum levels of vitamin D, is associated with a higher risk of prostate cancer.
5. Native Japanese, whose diet is rich in vitamin D derived from fish, have a low incidence of prostate cancer.

In addition, prostate cancer cells express the vitamin D receptor, and several studies have demonstrated an antiproliferative effect of vitamin D on prostate cancer cell lines by inducing cell cycle arrest (Krishnan et al, 2003).

Many studies show no or a weak association between vitamin D levels and prostate cancer risk (Chan and Giovannucci, 2001; Freedman et al, 2002; Jacobs et al, 2004; Ahn J et al, 2008). The Cancer Prevention Study II Nutrition Cohort, a prospective cohort of 65,321 men demonstrated a modestly increased relative risk of 1.2 for total calcium intake (dietary and with supplements) and 1.6 for high dietary calcium intake alone (≥2000 vs. <700 mg/day), but not for dairy intake (Rodriguez et al, 2003). The results suggest that very high calcium intake, above daily recommendation, may modestly increase risk. **These conflicting results regarding vitamin D, calcium, and prostate cancer risk may be explained by variants in the**

vitamin D receptor (VDR). Polymorphisms resulting in a VDR with lower activity have been associated with increased risk for prostate cancer, as well as with increased risk of biochemical recurrence following radical prostatectomy (Oakley-Girvan et al, 2004; Williams et al, 2004; John et al, 2005).

Other Influences

Sexual Activity/Sexually Transmitted Diseases

Sexual activity has been hypothesized to expose the prostate to infectious agents, which may increase the risk of prostate cancer, akin to the causal relationship between HPV and cervical cancer in women. **Some studies have found a link between sexually transmissible infections (STIs) and prostate cancer risk** (Fernandez et al, 2005; Sarma et al, 2006), **although not consistently** (Patel et al, 2005; Huang et al, 2008). A meta-analysis of 6022 cases of prostate cancer and 7,320 controls found significant associations between prostate cancer and any STI (odds ratio [OR] = 1.48, 95% CI = 1.26 to 1.73), gonorrhea (OR = 1.35, 95% CI = 1.05 to 1.83), and human papillomavirus (OR = 1.39, 95% CI = 1.12 to 2.06) but not for syphilis (Taylor et al, 2005). Studies have also suggested a protective association between prostate cancer and frequency of ejaculation, with RR ranging from 0.66 to 0.89 (Giles et al, 2003; Leitzmann et al, 2004). In the Giles study, the protective effect was seen in men in their 20s, who reported greater than 5 ejaculations per week; the large prospective cohort study by Leitzmann demonstrated a protective effect for men in their 20s and 40s, reporting greater than or equal to 21 ejaculations per month in the previous year and as a lifetime average. The biologic basis for this effect is not known.

Vasectomy

A relationship between vasectomy and prostate cancer risk was initially suggested in 1993 with a relative risk of 1.6 based on two large cohort studies (Giovannucci et al, 1993a, 1993b). Risk increased with time so that men who underwent vasectomy at an early age had a higher risk. A recent meta-analysis reported a pooled relative risk of 1.37, with a linear trend suggesting a 10% increase for each additional 10 years since vasectomy (Dennis et al, 2002a). On the other hand a large, population-based, case-control study found no association between prostate cancer and vasectomy, nor with time since vasectomy (Cox et al, 2002). The biologic mechanism by which vasectomy might predispose to cancer is unknown, although presence of antisperm antibodies, and decreased seminal androgen concentrations or secretory activity have been proposed. The magnitude of the relative risk is small enough to potentially be explained by inadequate selection of controls and/or selection bias, because men who have undergone vasectomy may be more likely to seek follow-up with a urologist. After excluding studies that were likely biased, one analysis found that the association became nonsignificant (Millard, 1999).

Smoking

Cigarette smoke may be a risk factor for prostate cancer, because it is a source of cadmium exposure, increases circulating androgen levels, and causes significant cellular oxidative stress. Both case-control and cohort studies have produced conflicting results and none have demonstrated a clear dose-response relationship, although some recent studies have suggested an association with more advanced stage at diagnosis and increased prostate cancer–related mortality (Bostwick et al, 2004).

Diet

Descriptive epidemiologic studies of migrants, geographic variations, and temporal studies suggest that dietary factors may contribute to prostate cancer development (Bostwick et al, 2004). The incidence of latent prostate cancers is similar around the world, but the incidence of clinically manifest cancers differs, with Asians having the lowest rates of clinical prostate cancer. Thus the most convincing evidence for the role of the diet and other environmental factors in modulating prostate cancer risk comes from migration studies showing an increased incidence of prostate cancer in first-generation immigrants to the United States from Japan and China (Muir et al, 1991; Shimizu et al, 1991). These observations suggest that diet may play a role in converting latent tumors into clinically manifest ones. A strong positive correlation exists between prostate cancer incidence and the corresponding rates of several other diet-related cancers, including breast and colon cancers (Bostwick et al, 2004).

Dietary Fat

Prostate cancer incidence and mortality rates around the world correlate highly with the average level of fat consumption, especially for polyunsaturated fats (Bostwick et al, 2004). Potential mechanisms of action include fat-induced changes in the hormonal milieu, induction of oxidative stress, and/or insulin-like growth factor-1 (IGF-1). High levels of dietary fat stimulate proliferation of prostate cancer cells both in vitro and in vivo, and animal models have shown that a fat-free diet can reduce the growth of androgen-dependent tumors in the Dunning model (Clinton et al, 1988; Wang et al, 1995; Aronson et al, 1999).

Epidemiologic studies have suggested a moderate to strong association between total and specific fats and the risk of developing prostate cancer (Chan et al, 2005). However, results from large prospective studies showed no association between dietary fat intake and prostate cancer risk (Park et al, 2007; Wallstrom et al, 2007; Crowe et al, 2008). **A meta-analysis of observational studies demonstrated only a weak association between higher intake of total fat and risk of prostate cancer (RR = 1.2, 95% CI = 1.1 to 1.3), and noted a large degree of heterogeneity between studies** (Dennis et al, 2004). Observations on the association of dietary fat and risk may have alternative explanations. Diets high in meats, which are sources of fat, are also usually low in vegetables containing nutrients that may protect against prostate cancer. Furthermore, meats and dairy products contain other constituents, such as zinc (Zn) and calcium (Ca), that may affect prostate cancer risk.

Obesity

Obesity as measured by body mass index (BMI) has been suggested as a risk factor for prostate cancer, because of their common occurrence in middle-aged men and clear links to colon and breast cancer risk (Giovannucci, 1995; Madigan et al, 1998). White fat in mammals serves not only as an important energy reservoir but also as an endocrine organ, with secretion of cytokines and agents with cytokine-like activity (tumor necrosis factor [TNF]-α, interleukin [IL]-1β, IL-6, IL-8, IL-10, transforming growth factor [TGF]-β), as well as their soluble receptors (Trayhurn and Wood, 2004). Several studies have shown that BMI and waist circumference show significant positive correlation with markers of oxidative stress (Keaney et al, 2003; Furukawa et al, 2004). Treatment of obesity through reduction in fat intake and increased exercise has been shown to reduce oxidative stress, suggesting that lifestyle

modification could be important in reducing the risk of prostate cancer (Roberts et al, 2002).

Studies examining the association between adult body mass index and the risk of prostate cancer have yielded conflicting results. **Two recent meta-analyses of observational studies have estimated the RR of prostate cancer to be 1.05 (95% CI = 1.01 to 1.08) and 1.03 (95% CI = 1.00 to 1.07) per 5 kg/m² increment in BMI** (MacInnis and English, 2006; Renehan et al, 2008). **Recently, three large prospective studies, examining the association between obesity and prostate cancer risk by stage and/or grade at diagnosis, suggested that obesity was associated with a lower risk of low-grade disease but a greater risk of high-grade disease** (Gong et al, 2006; Rodriguez et al, 2007; Wright et al, 2007). Potential explanations for the latter observation include the association of obesity with higher serum estradiol, insulin, free IGF-1, and leptin levels, and lower free testosterone and adiponectin levels, which have also been associated with more aggressive prostate cancer (Buschemeyer and Freedland, 2007). Another possible explanation is detection bias. Higher BMI has been shown to be associated with lower serum PSA (Baillargeon et al, 2005), which in obese men could lead to fewer prostate biopsies. However, given that the association between obesity and high-grade disease was also observed in the Prostate Cancer Prevention Trial, a study in which all men underwent biopsy, it is unlikely that detection bias is solely responsible for this finding (Gong et al, 2006).

Alcohol Consumption

Alcohol consumption and risk of prostate cancer is of interest because of its association with other cancers, its effect on estrogen and testosterone, and the high content of polyphenolic compounds with antioxidant activity in red wine. Although initial studies suggested an association between alcohol intake and prostate cancer risk (Sesso et al, 2001; Velicer et al, 2006), and a possible protective effect of red wine (Schoonen et al, 2005), recent large studies have failed to detect an association between total alcohol intake and the incidence of prostate cancer (Schoonen et al, 2005; Baglietto et al, 2006; Sutcliffe et al, 2007b; Rohrmann et al, 2008), suggesting that alcohol does not contribute appreciably to the etiology of this disease.

Key Points: Molecular Epidemiology

- Androgen exposure of the prostate plays an important but incompletely defined role in prostate carcinogenesis.
- Long-term absence of androgen exposure to the prostate appears to protect against the development of cancer, but a dose-response relationship between androgen levels and cancer risk has not been established.
- Polymorphisms in genes encoding for the androgen receptor and various enzymes related to androgen metabolism may be important determinants of prostate cancer risk.
- Estrogen is also important in prostate cancer development and may have varying effects depending upon local tissue activity of ERα and ERβ.
- Elevated serum levels of IGF-1 have been associated with prostate cancer risk.
- Dietary factors, including saturated fat consumption, may also be important in prostate cancer risk.

ETIOLOGY AND MOLECULAR GENETICS

Prostate cancer is unique among solid tumors in that it exists in two forms: a histologic or clinically occult form, which can be identified in approximately 30% of men greater than 50 years old and 60% to 70% of men greater than 80 years old, and a clinically evident form, which affects approximately one of six U.S. men. Latent prostate cancer is believed to have a similar prevalence worldwide and among all ethnicities, whereas the incidence of clinical prostate cancer varies dramatically between and within different countries. For this reason, an understanding of prostate cancer etiology must encompass the steps leading to both the ***initiation*** of histologic cancer and ***progression*** to clinically evident disease. **The exact molecular relationship between latent and clinical cancers is not known, and it is likely that the progression from latent to clinically evident cancer is a biologic continuum with overlap in the associated molecular events.** Mutations, downregulation by promoter methylation and other mechanisms, and protein modification have all been implicated in progression of prostate cancer (Fig. 95–8).

The Influence of Androgens

As previously discussed, androgens play an important role in prostate carcinogenesis. **The primary androgen of the prostate is dihydrotestosterone (DHT), irreversibly catalyzed from testosterone by 5α-reductase. DHT binds to intracytoplasmic AR with much greater affinity than testosterone, and binding of DHT to the AR enhances translocation of the steroid-receptor complex into the nucleus and activation of androgen response elements** (Steers, 2001). There are two isoenzymes of 5α-reductase, the products of two separate genes. **Type 1 5α-reductase is expressed primarily in the skin and liver and, to a lesser extent, in the prostate, while the type 2 enzyme is expressed predominantly in prostate epithelium and other genital tissues** (Andriole et al, 2004b).

Functional type 2 5α-reductase is a prerequisite for normal development of the prostate and external genitalia in males, and insufficient exposure of the prostate to DHT appears to protect against the development of prostate cancer. Transrectal ultrasonography (TRUS) in males with inherited 5α-reductase deficiency demonstrates miniscule prostatic tissue, and biopsies demonstrate stroma but no epithelium (Imperato-McGinley and Zhu, 2002). **In addition to the lack of enzyme activity, a lack of testosterone may also protect against the development of prostate cancer, as evidenced by the atrophic prostates seen in men after surgical castration** (Wilson and Roehrborn, 1999).

Although exposure of the prostate to androgens seems to be prerequisite for later development of prostate cancer, the duration and magnitude of androgen exposure needed to set the stage for carcinogenesis is unknown. As mentioned above, studies assessing the association between serum testosterone or sex hormone–binding globulin (SHBG) and prostate cancer have been inconsistent. Single measures of serum testosterone levels may not accurately reflect the amount of bioavailable testosterone; furthermore, they do not accurately quantify the testosterone exposure in the individual over the years it takes to develop prostate cancer. Future research

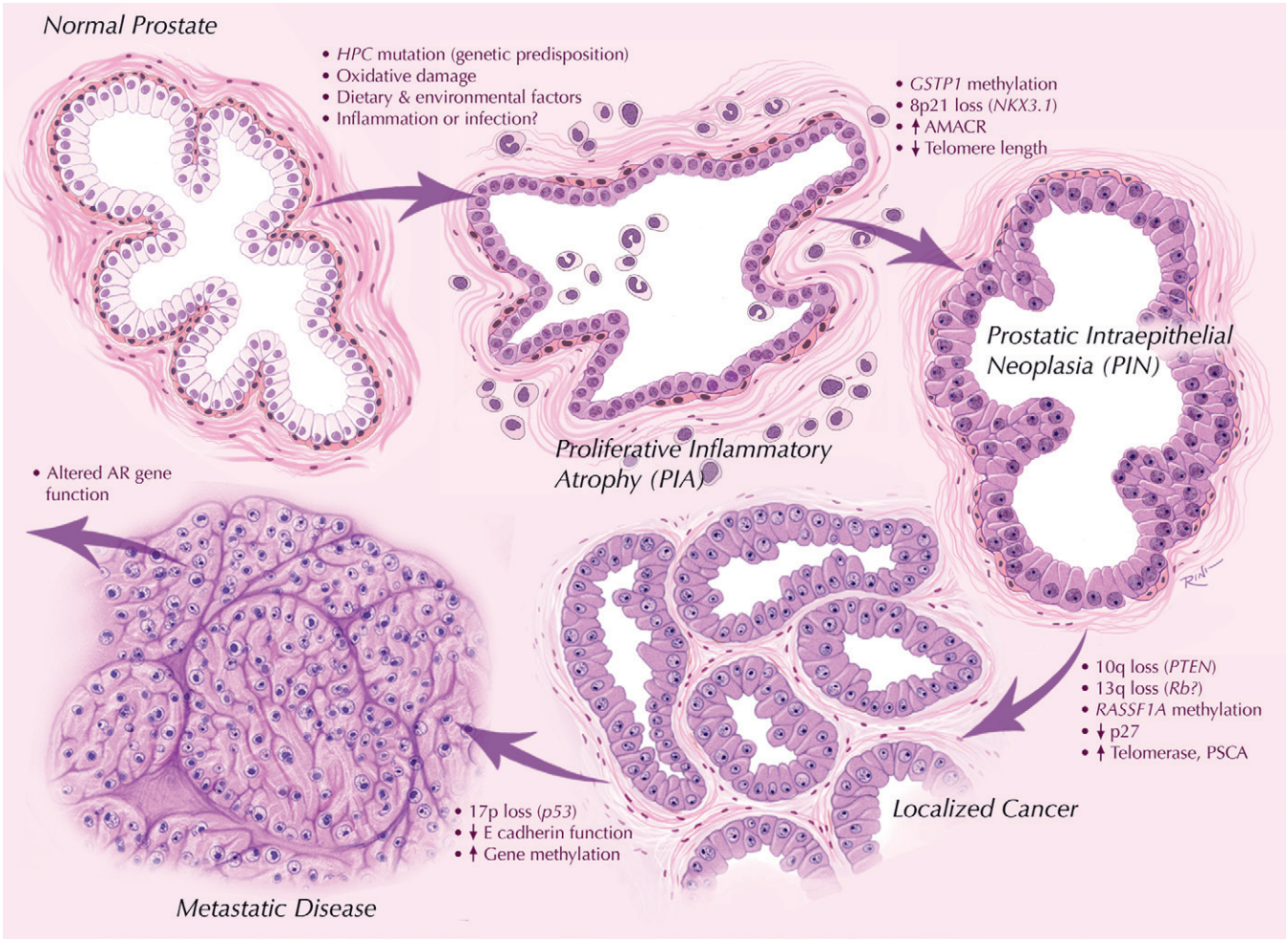


Figure 95–8. Contemporary model of prostate cancer progression. Genetic predisposition, oxidative damage, and inflammatory changes are associated with earliest steps of prostate cancer development. Downregulation of caretaker genes, such as *GSTP1,* by aberrant promoter methylation may increase potential for neoplastic transformation. Chromosomal loss and telomere shortening may also contribute to genetic instability and progression to invasive disease. Further methylation changes, loss of tumor suppressor gene function and additional mutational events are associated with metastases and androgen independence. (From Gonzalgo ML, Isaacs WB. Molecular pathways to prostate cancer. J Urol 2003;170:2444–52.)

will likely improve our understanding of the factors that may affect tissue concentrations of androgen at the biochemical and molecular level.

Stem Cells

Stem cells are required for the maintenance of high-cell turnover–tissues where cells continually need to be replaced, and like most epithelial organs, the prostate is believed to contain stem cells capable of multilineage differentiation. The existence of prostatic stem cells is suggested by studies demonstrating the ability of prostate epithelium to regenerate when androgen is administered to castrated rodents (Isaacs and Coffey, 1989; Bui and Reiter, 1998; Tsujimura et al, 2002). Supportive evidence includes observations that (1) basal and luminal cells of prostate glands have distinct phenotypes as measured by immunohistochemical marker expression, especially for various forms of keratin; (2) cell culture experiments demonstrate that some prostate cancer cells are self-replicating while others are not; and (3) stem cell–enriched populations of cells can produce three-dimensional structures with basal cells and fully differentiated luminal cells in nude mice (Taylor and Risbridger, 2008). These observations led to the development of a stem cell theory for prostate cancer that postulated that an androgen-independent stem cell produces androgen-independent transit-amplifying (TA) cells that, in turn, give rise to androgen-dependent, fully differentiated luminal secretory cells (Isaacs and Coffey, 1989). Although it was originally believed that prostatic stem cells reside within the basal epithelium, recent models have challenged this notion (Tsujimura et al, 2002). A recent study has suggested that *TROP2* may be a marker for a subpopulation of basal cells with stem cell characteristics (Goldstein et al, 2008). **Once their biology is fully understood, stem cells are likely to be an attractive target for both prevention and therapy.**

Epigenetic Changes

Epigenetic events affect gene expression without altering the actual sequence of DNA. Known mechanisms include DNA hyper- and hypomethylation, chromatin remodeling, histone modification, and RNA interference (Dobosy et al, 2007). **A variety of genes implicated in prostate cancer initiation and progression are affected by these processes,** including hypermethylation of hormonal response genes (*ERαA, ERβ,* and *RARβ*), genes controlling the cell cycle (*CYCLIND2, 14-3-3σ*), tumor cell invasion/tumor architecture genes (*CD44*), DNA repair genes

(*GSTpi, GPX3,* and *GSTM1*), tumor suppressor genes (*APC, RASSF1α, DKK3, TP16^{INK4α}, E-cadherin,* and *TP57^{WAF1}*), signal transduction genes (*EDNRB* and *SFRP1*), and inflammatory response genes (*PTGS/COX2*); hypomethylation of *CAGE, HPSE,* and *PLAU;* histone hypoacetylation of *CAR, CPA3, RARB,* and *VDR;* and histone methylation of *GSTP1* and *PSA* (Li et al, 2005). **Clinical studies have shown that quantitative methylation analysis of the *GSTpi, APC, PTGS2, RASSF1α, MDR1, TP16,* and *MGMT* genes can improve sensitivity and specificity for the diagnosis of cancer, and efforts to develop global gene methylation profiles in serum, urine, and tissue as an adjunct to predicting risk of cancer, determining the need for rebiopsy, and tumor aggressiveness are underway** (Dobosy et al, 2007). Furthermore, agents that can inhibit or reverse the effects of DNA methyl transferases (DNMTs) and histone deacetylases (HDACs) and restore normal gene expression are under study for both prevention and therapy.

Cyclooxygenase

Inflammatory cells in the prostate produce a variety of compounds designed to eradicate infectious microorganisms, many of which have potential to cause oxidative DNA damage. These compounds include superoxide, hydrogen peroxide, oxygen free radicals, and peroxynitrite (Potts and Pasqualotto, 2003). The inflammatory response stimulates the production of prostaglandins that are part of the eicosanoid family, which includes long-chain polyunsaturated fatty acids. Cyclooxygenase (COX) enzymes catalyze the rate-limiting step of prostaglandin synthesis, converting arachidonic acid to the intermediate prostaglandin G2 (Zha et al, 2004). Two isoforms of COX (COX-1 and COX-2) have been identified (DeWitt and Smith; 1988, Hla and Neilson, 1992). COX-1 is constitutively expressed in many tissues and cell types and helps mediate normal cellular physiologic functions. **COX-2 is an inducible enzyme that mediates acute and chronic inflammation, pain, and cellular repair mechanisms.** COX-2 expression is rapidly induced in response to inflammatory or mitogenic stimuli, cytokines, tumor promoters, and growth factors (Zha et al, 2004; Patel et al, 2008). Prostaglandins resulting from COX-2 expression mediate a variety of responses to tissue injury and hypoxia that promote tumor formation, including inhibition of apoptosis, promotion of cellular proliferation, and angiogenesis (Patel et al, 2008). **Most studies suggest increased COX-2 expression in prostate cancer and HGPIN compared with benign prostatic epithelium** (Patel et al, 2008). **Epidemiologic studies and clinical observations suggest that nonsteroidal anti-inflammatory drugs (NSAIDs) and certain selective COX-2 inhibitors may reduce the risk of prostate cancer** (Aparicio Gallego et al, 2007). However, the recent observation of increased cardiovascular morbidity associated with long-term COX-2 inhibitor use led to the early closure of a drug sponsored prostate cancer prevention trial in 2004. **Further clinical trials of COX-2 inhibitors may be difficult to complete, and the expected benefit must be weighed against the potential risks of the drug in the target population.**

Somatic Mutations Associated with Tumor Initiation and Progression

A number of somatic mutations in tumor DNA are acquired during clonal expansion of nascent tumors as a result of mitotic errors, defects in DNA repair mechanisms, loss of apoptotic ability, and other mechanisms. A variety of genes are so affected in prostate cancer.

Androgen Receptor

As discussed earlier, polymorphisms of the AR are linked epidemiologically to prostate cancer risk. There is also growing evidence that the AR itself may in fact be oncogenic under certain circumstances (Scher and Sawyers, 2005). **Alterations in AR signaling can occur at various levels, all of which could potentially contribute to the development and/or progression of prostate cancer. These include (1) changes in ligand concentration in tumor cells (e.g., intracrine mechanism)** (Labrie et al, 1993), **(2) increased AR protein expression (e.g., this has been detected in castrate-resistant disease, leading to increased sensitivity to low ligand levels)** (Bubendorf et al, 1999), **(3) mutations leading to altered structure and function (shown to be present in 50% of prostate cancers)** (Bostwick et al, 2004)**, (4) changes in coregulatory molecules (e.g., coactivator proteins such as ARA54 and ARA70 can selectively enhance the activity of AR to alternative or low concentrations of ligand, or lead to independent activation)** (Scher and Sawyers, 2005), **and (5) factors leading to activation of the receptor independent of the ligand (e.g., many of the growth factors and tyrosine kinases implicated in prostate cancer initiation and progression may exert their effects by cross talk with the AR**) (Culig et al, 1994; Craft et al, 1999). A recent study shows that knockout of AR causes regression of even castrate-resistant prostate cancer, suggesting that AR is biologically and clinically important even after androgen deprivation (Snoek et al, 2009).

NKX3-1

***NKX3-1* is an androgen-regulated and prostate-specific gene located on chromosome 8p21** and belongs to the homeobox gene family (He et al, 1997; Prescott et al, 1998). Mice deficient in *NKX3.1* show defects in prostate ductal morphogenesis and secretory protein production and with age develop dysplasia, PIN, and cancer (Bhatia-Gaur et al, 1999; Tanaka et al, 2000; Abdulkadir et al, 2002). Loss of either one or both *NKX3-1* alleles becomes increasingly common in prostate lesions as they progress from PIN to local, metastatic, and androgen-independent tumors (Bowen et al, 2000).

PTEN

PTEN on chromosome 10q23 is among the best studied tumor suppressor genes in prostate cancer. Genetic, functional, and molecular studies suggest a role of *PTEN* in both initiation and progression of prostate cancer (Dong, 2006). *PTEN* deletion has been shown to induce prostate cancer in mice (Wang et al, 2003). Loss of *PTEN* function is seen in PIN and is associated with a high Gleason score and advanced stage (Rubin et al, 2000).

Classical Oncogenes

Genetic alterations in the tumor suppressor genes *RB1* and *TP53* are commonly present in metastatic or hormone-refractory disease, suggesting a role in tumor progression. Alterations in c-*MYC,* c-*ERBB2,* and *BCL-2* have also been observed in advanced and hormone-refractory prostate cancer but not commonly in lower-stage and -grade cancers, suggesting that mutations of proto-oncogenes usually occur as secondary events associated with tumor progression (Gurumurthy et al, 2001; Fossa et al, 2002; Qian et al, 2002).

Telomerase

Eukaryotic chromosomes have telomeres on their ends that consist of repeating units of 6 base pairs (TTAGGG) that protect the chromosomal ends from inappropriate recombination. **Normal cellular aging is characterized by the progressive loss of these repeated elements, and consequently telomere length decreases successively with every cell replication.** Critical telomere shortening leads to chromosomal instability, further leading to an increased incidence of cancers due to chromosomal fusions, breakage, and rearrangements (Blasco et al, 1997). There is increasing evidence that telomere shortening during cell division and oxidative cell damage, possibly as a result of chronic inflammation, may play a role in prostate carcinogenesis (Meeker, 2006). Prostate cancer and high-grade PIN appear to result in an activation of the telomerase enzyme, a reverse transcriptase that maintains or increases telomere length (Meeker et al, 2002; Meeker, 2006). In addition to prostate cancer causation, telomeres may also play a role in disease progression, and studies suggest that telomerase suppression may contribute to the emergence of androgen-independent disease (Meeker, 2006).

Glutathione-*S*-Transferase

Reactive oxygen species are inactivated by a host of protective enzymes, including glutathione-*S*-transferase (GST), glutathione peroxidase, and superoxide dismutase. **The expression of one of these enzymes, GSTP1, is absent in approximately 70% of PIN and virtually all cases of prostate cancer, making it the most common genetic alteration in this malignancy** (Nelson et al, 2003). This loss of expression results from hypermethylation of CpG islands in the *GSTP1* promoter and causes a defect in cellular defense against oxidant stress, leading to a higher mutation rate. Additionally, *GSTP1* hypermethylation has been identified in prostate biopsies with histologic findings of PIN (Nakayama et al, 2004). DNA methylation assays that may soon be used in diagnostic testing of serum and tissue for prostate cancer are under development.

TP27

TP27 belongs to the CIP/KIP family of cyclin-dependent kinase (CDK) inhibitors and regulates progression of the cell cycle from G1 to S phase. Loss of TP27 may accelerate tumorigenesis by enabling cells to progress unregulated through the cell cycle. Mice deficient in TP27 develop prostate hyperplasia, and mice deficient in both TP27 and PTEN have a high incidence of prostate cancer (Cordon-Cardo et al, 1998; Di Cristofano et al, 2001). Studies in humans have found loss of heterozygosity for TP27 in 50% of patients with metastatic prostate cancer (Kibel et al, 2000). Studies of patients undergoing RP have found an association between loss of TP27 expression and increased risk of biochemical recurrence (Guo et al, 1997; Cordon-Cardo et al, 1998).

Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF), which is an important mediator of tumor angiogenesis, is expressed in a majority of prostate cancers, and increased expression has been associated with disease progression and survival (Green et al, 2007; Peyromaure et al, 2007). VEGF is regulated by androgen, suggesting a potential pathway by which androgen regulates prostate cancer growth (Joseph and Isaacs, 1997). Several SNPs in the *VEGF* gene have been associated with protein expression; however to date, studies examining the influence of these polymorphisms on prostate cancer risk have been inconsistent (Langsenlehner et al, 2008). Therapeutic inhibition of the VEGF receptor signaling pathway is currently being investigated in the treatment of prostate cancer.

E-Cadherin

The *E-cadherin* gene, which is located on chromosome 16q22.1, encodes a transmembrane glycoprotein that mediates intercellular adhesion as well as cell signaling (Takeichi, 1991). **E-cadherin expression is reduced in a significant percentage of prostate cancers, particularly in poorly differentiated tumors, and E-cadherin expression in prostate cancer correlates inversely with grade, stage, metastasis, recurrence, and survival** (Umbas et al, 1992; Bostwick et al, 2004). However, studies of the association between SNPs of E-cadherin and prostate cancer risk have yielded conflicting results.

α-Methylacyl-CoA Racemase (AMACR)

AMACR (racemase) is an enzyme that plays a critical role in the metabolism of branched-chain fatty acids. AMACR expression has been shown to decrease in metastatic prostate cancer compared with localized disease, and is associated with cancer-specific survival (Rubin et al, 2005). In addition, studies suggest that polymorphisms within the *AMACR* gene may be associated with prostate cancer risk (Levin et al, 2007), although further experimental studies are needed to better characterize this association.

Prostate-Specific Membrane Antigen

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein that is expressed by prostate cancer epithelium and on the neovasculature of other solid tumors (Ghosh et al, 2005). **Overexpression of PSMA is observed after androgen withdrawal and in hormone-refractory disease, and is the basis of clinical imaging studies using anti-PSMA monoclonal antibodies.** Because of its restricted tissue expression, PSMA is being actively investigated as an immunotherapeutic target (Schulke et al, 2003).

Epidermal Growth Factor and Epidermal Growth Factor Receptor

There is substantial evidence that epidermal growth factor (EGF) signaling through the epidermal growth factor receptor (EGFR) is important in prostate cancer. EGF levels are frequently elevated, and EGFR is commonly

Key Points: Etiology and Molecular Genetics

- The primary androgen of the prostate is dihydrotestosterone (DHT), formed by the action of 5α-reductase on testosterone.
- Epigenetic regulation of gene expression by promoter methylation and histone acetylation has been implicated in the progression of prostate cancer.
- *TMPRSS2-ETS* gene fusions have been identified in most prostate cancers, and their role in disease detection and prognosis is currently being investigated.
- Somatic mutations in a variety of genes with diverse biological functions have been implicated in prostate cancer development and progression.
- Mutations, amplification, and ligand promiscuity of the AR are important determinants of progressive castrate-resistant prostate cancer.

overexpressed in prostate cancer cells (Vicentini et al, 2003). In addition, EGFR expression increases as the disease progresses to hormone resistance (Di Lorenzo et al, 2002). A genetic polymorphism in the *EGF* gene has been shown to be associated with progression-free survival in patients on androgen-deprivation therapy, identifying a potential therapeutic target in these patients (Teixeira et al, 2008).

EZH2

EZH2 is a histone-lysine methyltransferase with activity dependent on its association with other components of the polycomb repressive complexes 2 (PRC2). EZH2 levels are increasingly elevated during prostate cancer progression (LaTulippe et al, 2002). EZH2 expression in localized prostate cancer has also been shown to be associated with poor prognosis and disease recurrence (Varambally et al, 2002; van Leenders et al, 2007).

CHEMOPREVENTION

Rationale

Prevention is so much better than cure, because it saves the labor of being sick.

—Thomas Adams, 1618

As previously discussed, prostate carcinogenesis is a multistep molecular process induced by genetic and epigenetic changes that disrupt pathways controlling the balance between cell proliferation, apoptosis, differentiation, and senescence. **The presence of precursor lesions that represent intermediate stages between normal and malignant cells—as long as 20 years before the appearance of cancer, coupled with the age-dependent incidence of most cancers—suggests that carcinogenesis occurs slowly during a protracted interval. In theory, this provides the opportunity to intervene before a malignancy is established, using lifestyle changes (dietary alterations, smoking cessation, exercise) or by chemoprevention, defined as the use of natural or synthetic agents that reverse, inhibit, or prevent the development of cancer. The goal of primary chemoprevention is to decrease the incidence of a given cancer, simultaneously reducing both treatment-related side effects and mortality. Effective chemoprevention requires the use of nontoxic agents that inhibit specific molecular steps in the carcinogenic pathway.**

Prostate cancer is an attractive and appropriate target for primary prevention because of its incidence, prevalence, and disease-related mortality (see Table 95–1). The burden of prostate cancer can also be measured in other terms. A recent study of complications after surgical therapy for localized disease in an unselected population-based cohort reported that, at greater than 18 months following RP, 8.4% of men were incontinent, and 41.9% reported that their sexual performance was a moderate-to-large problem (Stanford et al, 2000). In a prospective cohort study comparing outcomes 5 years after radiation or surgery to age-matched controls, the authors concluded that "…declines in urinary and sexual function domains after diagnosis and treatment of localized cancer far exceeded any effects from aging…" (Hoffman et al, 2004). A large study assessing health-related quality of life after primary treatment for prostate cancer found that although each treatment modality was associated with a distinct pattern of change in quality-of-life domains, they all had a significant effect on urinary, sexual, bowel, and/or hormonal function (Sanda et al, 2008). Although many single-institution studies have reported better results in highly selected cohorts of treated patients, it is clear that the majority of men treated for localized disease in the community pay a substantial price to be cured, and fear of cancer recurrence remains substantial for as long as 2 years after treatment (Mehta et al, 2003). It seems self-evident that an effective prevention strategy would spare many men this burden of diagnosis and cure.

The molecular pathogenesis of prostate cancer also lends itself to a primary prevention strategy. Histologic lesions, including atypical small acinar proliferation (ASAP), PIA, and PIN contain both genetic and epigenetic changes intermediate between normal prostatic epithelium and prostate cancer. Clinically evident prostate cancer is rare in men younger than 50 years, whereas prostatic intraepithelial neoplasia is apparent at autopsy in men younger than 30 years. Furthermore, the prevalence of PIN is similar in populations at much different risks of developing clinically evident cancer, suggesting that external environmental influences are important and potentially modifiable.

Clinical Trial Design

Target populations appropriate for primary prevention studies can be subdivided into those with low, intermediate, and high risk of developing prostate cancer based on current epidemiologic evidence (Klein and Meyskens, 2001). Each group has its own clinical characteristics that lend advantages and disadvantages for trial design, end points, and statistical analysis (Table 95–3). Based on the hypothesis that the specific molecular mechanisms underlying the development and/or progression of disease in each risk group and model may be unique and that different agents may be useful for each situation, it seems apparent that multiple potential chemopreventative agents should be tried in all risk groups and clinical models to best define which agents appear promising for large-scale studies. Testing of potentially active agents for secondary prevention in clinical models of patients with active disease is also appropriate (Table 95–4). **The presurgical model allows for pre- and post-treatment tissue biopsies and is thus useful for proof-of-principle demonstrations that a given agent is affecting its intended molecular target.** The other models may yield useful strategies for the management of patients in specific clinical situations. **The molecular mechanisms that underlie disease progression is likely different for each primary and secondary target population, and it may not be possible to generalize the results from a particular trial to other clinical scenarios.**

Numerous observations in the epidemiologic literature suggest associations between various dietary, lifestyle, genetic, and nontraditional factors and the risk for developing prostate cancer. It is generally not practical to quantitate all of these factors in the course of a prevention trial, but if the trial is large enough, the effects of these factors are likely to be equally and randomly distributed across all study arms. Most trials are designed to collect data relevant to these factors for secondary analysis and analysis of potential confounds for unexpected results.

Prostate Cancer Prevention Trial

The most significant event in chemoprevention of prostate cancer occurred with the publication of the results

Table 95–3.

Target Populations for Primary Prevention

RISK GROUP	SPECIFIC POPULATION	ADVANTAGES	DISADVANTAGES
Low	General population	Easily definable	Rate of progression slow
		Readily available	Requires large study population and long follow-up interval
		Results widely applicable	Studies costly
Intermediate	African-Americans	Higher risk than general population	Difficult to define
			Difficult to recruit because of perceived bias
	Genetic:	Double or greater the risk of prostate cancer	Ascertainment bias
	Family history		Risk varies with number of affected family members, age of onset, and degree of relatedness
	HPC-1 linked	Genetically homogeneous	Likely to be genetically heterogeneous
			Identification invasive and costly
			Affected subjects rare
	Other genes	Genetically homogeneous	Identification invasive and costly
			Affected subjects rare
			Risk of progression undefined
High	High-grade PIN	Highest known risk	Sampling error
			Diagnosis subjective
			Uncommon

HPC, hereditary prostate cancer; PIN, prostatic intraepithelial neoplasia.
From Klein EA, Meyskins FL. Potential target populations for testing chemopreventive agents. Urology 2001;57(Suppl. 4A):171–3.

Table 95–4.

Models of Secondary Prevention

MODEL	ADVANTAGES	DISADVANTAGES
Presurgical	Early-stage disease	Treatment period short
	Readily available study population	
	Pre- and post-treatment tissue available for biologic study	
Elevated PSA/ negative biopsy	Well-defined histologic end point	Risk of progression undefined
		Sampling error
Adverse pathology after RP	High risk of progression	More advanced disease
		Clinical end point
Rising PSA after RP or RT	High risk of progression	Most advanced disease
		Clinical end point

PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy.
From Klein EA, Meyskins FL: Potential target populations for testing chemopreventive agents. Urology 2001;57(Suppl. 4A):171–3.

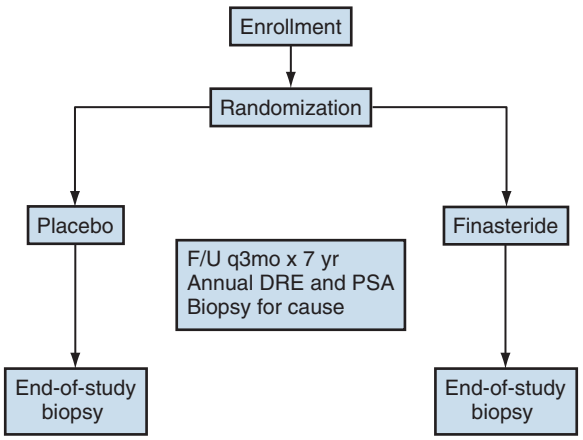


Figure 95–9. Design of the Prostate Cancer Prevention Trial. DRE, digital rectal examination; PSA, prostate-specific antigen.

of the Prostate Cancer Prevention Trial (PCPT) (Thompson et al, 2003). This landmark study, opened in 1993, was the first large-scale population-based trial to test a chemopreventative strategy in men at risk for prostate cancer. The PCPT was based on two observations: (1) Androgens are required for the development of prostate cancer and (2) men with congenital deficiency of type 2 5α-reductase are unaffected by benign prostatic hyperplasia (BPH) and prostate cancer. **The PCPT tested the hypothesis that treatment with finasteride, which induces an acquired deficiency of type 2 5α-reductase, would lower intraprostatic DHT levels and thereby prevent prostate cancer.** In the PCPT, 18,882 men greater than or equal to 55 years of age with a normal digital rectal examination (DRE) and a prostate-specific antigen (PSA) level of less than or equal to 3.0 ng/mL were randomly assigned to treatment with finasteride (5 mg/day) or a placebo for 7 years (Fig. 95–9). Prostate biopsy was recommended if the annual PSA level, adjusted for the effect of finasteride, exceeded 4.0 ng/mL or if the DRE was abnormal. The primary end point was the prevalence of prostate cancer during the 7 years of the study, as diagnosed by either for-cause biopsies (abnormal DRE or PSA) or by end-of-study biopsy. **The trial was stopped approximately 15 months early by an independent data safety and monitoring committee, because the primary end point of a 25% risk reduction on the finasteride arm was reached, and sensitivity analyses suggested that additional follow-up would not change that outcome.**

The main findings of the PCPT are as follows:

1. The prevalence of prostate cancer was reduced by 24.8% (hazard ratio [HR] = 0.75, 95% CI = 18.6 to 30.6) from 24.4% to 18.4% in those participants randomized to finasteride compared with placebo.
2. The prevalence of Gleason grade 7 to 10 tumors was higher in the finasteride group than the placebo group (6.4% versus 5.1%, HR = 1.27, 95% CI = 1.07 to 1.50).
3. The risk reduction associated with finasteride among risk groups defined by age, family history, race, and PSA were of the same general magnitude.

4. Sexual side effects were more common with finasteride, whereas urinary symptoms were more common with the placebo.

Additional important observations were as follows: (1) the risk reduction in the finasteride arm was seen in both clinically apparent tumors (those diagnosed "for cause" because of an elevated PSA or abnormal DRE) and end-of-study biopsies; (2) there were an equal number of deaths due to prostate cancer (five) in each study arm; (3) 98% of the tumors were clinically localized; and (4) finasteride-treated glands were 25% smaller than those in the placebo arm.

A number of relevant observations can be made about the results of the trial. Most surprising was the 24.4% prevalence of prostate cancer in the placebo arm, 4 times higher than the 6% assumed for the trial design. This discrepancy can be explained by the fact that the 6% assumption was based on Surveillance, Epidemiology, and End Results (SEER) incidence estimates, which are derived from clinically evident cases and not on the prevalence in men undergoing biopsy for no reason other than being on the trial. The incidence of clinically evident cancers detected "for cause" by elevations in PSA or abnormal PSA was 7.2% at 7 years, roughly what was estimated by use of the SEER data. Another observation was a marked effect of finasteride on the prevalence of Gleason sum 6 tumors, no effect on the prevalence of Gleason sum 7 tumors, and a slight increase in the prevalence of Gleason sum 8 to 10 tumors. The higher incidence of high-grade tumors was restricted to those men undergoing "for-cause" biopsy. Finally, **secondary analyses of the PCPT trial have demonstrated an overall improved sensitivity of DRE** (Thompson et al, 2007b), **as well as a higher sensitivity and area under the curve for PSA for the diagnosis of prostate cancer in the finasteride arm** (Thompson et al, 2006). However, given that the latter finding was demonstrated for all grades, the bias would lead to a greater detection of all grades of prostate cancer with finasteride.

There are two areas of continued debate over the results of the PCPT. The first is whether Gleason sum 6 cancers that were "prevented" are biologically significant, which can be defined as destined to metastasize or kill the host. A review of the pathologic characteristics of prostate biopsies from men in the placebo and finasteride groups of the PCPT found that 75% of all cancers and 62% of cancers with a Gleason score less than or equal to 6 met the accepted biopsy criteria for clinically significant tumors (Epstein et al, 1994; Lucia et al, 2008). Although the proportion of insignificant cancers was directly correlated with serum PSA, even at the lowest PSA values (0 to 1.0 ng/mL) almost half of the tumors met the definition of clinical significance. Moreover, an analysis of the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) found that of men with prostate cancer who met this definition, 91% choose some form of definitive therapy instead of watchful waiting (Barocas et al, 2008). **Viewed in the context of "clinical relevance" as defined by current urologic practice, preventing grade 6 tumors by finasteride also prevents the anxiety, cost, and morbidity associated with their treatment. From a public health perspective, preventing the "burden of cure" in newly diagnosed patients should be added as a positive to the 25% reduction in risk of diagnosis and significant reduction in urinary symptoms associated with finasteride use.**

The second question still under debate is whether the increased prevalence of higher-grade tumors is real or artifactual. Finasteride is known to change the appearance of prostatic epithelium in a way that could bias interpretation, and the Gleason grading system has never been validated on glands treated with antiandrogenic agents (Civantos et al, 1996). However, when this was examined in the PCPT, degenerative hormonal changes in high-grade biopsies were equivalent between the finasteride and placebo groups (Lucia et al, 2007). Another potential explanation for the observed increase in high-grade tumors in the finasteride group is ascertainment bias. As stated above, finasteride has been shown to increase the sensitivity of PSA and DRE, as well as decrease prostate volume by approximately 25%. Data suggest that having a smaller prostate results in more high-grade cancers diagnosed at biopsy (Kulkarni et al, 2006). This was demonstrated in the PCPT, where biopsy identified a greater proportion of patients with high-grade disease present at prostatectomy in the finasteride group than in the placebo group (Lucia et al, 2007). Therefore **when accounting for all biases, the adjusted prostate cancer rates were estimated to be 21.1% for the placebo group and 14.7% in the finasteride group, a 30% risk reduction for all cancers (relative risk [RR] = 0.70, 95% CI = 0.64 to 0.76), and a nonstatistically significant 14% increase in high-grade cancer** (Redman et al, 2008). **Using known predictive factors to estimate true tumor grade in those men who did not undergo end-of-study biopsy, and incorporating grading information from those who had radical prostatectomies, the rate of high-grade cancer was estimated to be 8.2% and 6.0% in the placebo and finasteride groups, respectively, suggesting that finasteride may in fact reduce the risk of high-grade disease (27% risk reduction [RR = 0.73, 95% CI = 0.56 to 0.96])** (Fig. 95–10). Using a different analysis methodology in an independent analysis, another study concurred that the rate of true high-grade disease may have been lower in the finasteride group compared with the placebo group (Pinsky et al, 2008). In March 2009, the American Urological Society and the American Society for Clinical Oncology jointly published guidelines based on expert review of the available evidence, stating that use of finasteride for the prevention of cancer should be discussed with at-risk men (Kramer et al, 2009).

Deciding whether or not the advantages of taking finasteride (Table 95–5) **outweigh the potential disadvantages is not a simple task.** An initial mathematical model suggested a baseline 5:1 benefit to risk ratio, as defined by the number of cancers prevented for each excess high-grade cancer in

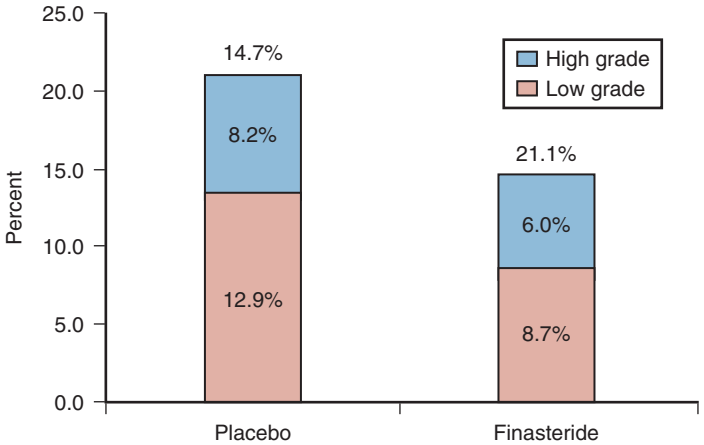


Figure 95–10. Estimated bias-adjusted fractions of total subjects with low-grade and high-grade prostate cancers in the finasteride and placebo arms of the Prostate Cancer Prevention Trial.

Table 95–5.

Benefits and Costs of Finasteride When Used to Prevent Prostate Cancer

Benefits
6.4% reduction in cancer prevalence
Fewer urinary symptoms and lower risk of acute urinary retention and need for surgical intervention for obstructive urinary symptoms
Avoids "burden of cure"
Costs
1.3% increase in high-grade tumors
Potential for more aggressive therapy
Potential excess mortality
Sexual side effects and cost of treatment
Cost of finasteride

those taking finasteride (Klein et al, 2005). Another study using a person-years–saved model estimated that the use of finasteride as a preventative could reduce the lifetime risk of prostate cancer for a U.S. man from 17% to 13%, while saving more than 250,000 lives every 10 years (Unger et al, 2004). However, more recently published decision-analytic models examining finasteride chemoprevention found that its widespread use is unlikely to be cost effective when considering the usually indolent natural history of treated prostate cancer (Zeliadt et al, 2005; Svatek et al, 2006, 2008). Nonetheless, they suggested that chemoprevention may be cost effective in high-risk populations.

In addition to the prevention of prostate cancer, 5α-reductase inhibitors (5ARIs) have other benefits that need to be considered. As mentioned earlier, finasteride improves the sensitivity of PSA (Thompson et al, 2006) and DRE (Thompson et al, 2007b) in prostate cancer screening, decreases the risk of high-grade prostatic intraepithelial neoplasia (HR = 0.79, 95% CI = 0.70 to 0.89) (Thompson et al, 2007a), and may be effective in the treatment and possibly prevention of chronic nonbacterial prostatitis (Nickel et al, 2004). Furthermore, benign prostatic hyperplasia (BPH) treatment trials in patients with moderate to severe lower urinary tract symptoms demonstrated: (1) a reduction in AUA symptom sores by 20% to 39% compared with 13% to 29% for the placebo, (2) a reduction in the risk of acute urinary retention by one half in long-term trials (RR = 0.51, 95% CI = 0.38 to 0.69; absolute risk reduction [ARR] = 2.2%), and (3) a reduction in the risk of surgical intervention due to BPH progression by one half (RR = 0.50, 95% CI = 0.43 to 0.58, ARR = 1.7%) (Wilt et al, 2008).

On the other hand, adverse effects that are more common with finasteride than with the placebo include impaired sexual or erectile function and endocrine effects. Pooled data from randomized trials indicate absolute differences of 2% (95% CI = 1 to 2) for gynecomastia, 3% (95% CI = 1 to 6) for decreased libido, 4% (95% CI = 1 to 8) for erectile dysfunction, and 4% (95% CI = 8 to 17) for reduced volume of ejaculate (Wilt et al, 2008). **Sexual dysfunction was also assessed in the PCPT participants during the 7-year trial period. As measured by the Sexual Activity Scale in a companion quality-of-life (QOL) study to the PCPT, comparing baseline scores over the course of 7 years, finasteride increased sexual dysfunction relative to the placebo by a mere 3.21 points (95% CI = 2.83 to 3.59 on a scale of 0 to 100), a clinically meaningless effect.**

Other 5α-Reductase Inhibitors

A second large-scale trial of another 5ARI, dutasteride, completed accrual in the spring of 2005. This agent inhibits both type 1 and type 2 forms of 5α-reductase, is antiandrogenic, and promotes death of prostate cancer cell lines (Lazier et al, 2004), **and has been shown to reduce the risk of prostate cancer in men treated for lower urinary tract symptoms related to benign prostatic enlargement when compared with the placebo** (Andriole et al, 2004c). The Eligibility for the Reduction by Dutasteride of Prostate Events (REDUCE) trial included men aged greater than or equal to 50 and less than or equal to 75 years who had PSA scores from 2.5 to 10 ng/mL, prostate volumes less than or equal to 80 cc, and one prior negative prostate biopsy within 6 months of enrollment, thus representing a group at high risk for cancer on subsequent biopsy (Andriole et al, 2004a). The primary end point of REDUCE is the prevalence of cancer on study-mandated prostate biopsies performed at 2 and 4 years after entry. The trial accrued 8231 men, of whom 6726 (82.6%) underwent at least one biopsy and 1516 (22.5%) were diagnosed with prostate cancer. Dutasteride reduced the risk of prostate cancer over 4 years by 23% (857 in the placebo arm vs. 659 in the dutasteride arm, $P < .0001$). Interestingly, no significant increase in Gleason sum 8 to 10 tumors was observed in the study (19 in the placebo arm vs. 29 in dutasteride arm, $P = .15$). Preliminary analyses also suggest that dutasteride enhanced the utility of PSA as a diagnostic test for prostate cancer, demonstrated beneficial effects on BPH outcomes (relative risk reductions of 77% for acute urinary retention and 73% for BPH-related surgery), and was generally well tolerated (15% drug-related adverse events in the placebo arm vs. 22% in dutasteride arm). The fact that the results of REDUCE were congruent with those of the PCPT with respect to the magnitude of risk reduction, benefits for BPH end points, minimal toxicity, and no issues related to tumor grade suggests a class effect for 5ARIs and that these agents should be used more liberally for prevention of prostate cancer.

Antioxidants and the Selenium and Vitamin E Cancer Prevention Trial (SELECT)

Selenium

Selenium (Se) is an essential trace element occurring in both organic and inorganic forms. The organic form is found predominantly in grains, fish, meat, poultry, eggs, and dairy products and enters the food chain through plant consumption. There is marked geographic variability of Se in food related to local soil content. **The strongest evidence for a protective effect of Se came from the Nutritional Prevention of Cancer Trial, a randomized study of oral selenized yeast in patients with nonmelanoma skin cancer, which showed a 65% reduction in the prostate cancer incidence when compared with the placebo** (Clark et al, 1996). In that trial, 1312 participants took the equivalent of 200 μg yeast per day versus the placebo, and with a mean follow-up of 4.5 years, the incidence of prostate cancer was reduced in the Se arm by 65% compared with the placebo. Of note, the effect was strongest for those with a PSA value less than 4 ng/mL and those with the lowest serum Se levels at study entry (Duffield-Lillico et al, 2003).

Vitamin E

Vitamin E is a family of naturally occurring, essential, fat-soluble vitamin compounds that functions as the major lipid-soluble antioxidant in cell membranes. The most active form of vitamin E is α-tocopherol; it is also among the most abundant, is widely distributed in nature, and is the predominant form in human tissues. Alpha-tocopherol may influence the development of cancer through several mechanisms, including induction of cell cycle arrest and through direct antiandrogen activity (Ni et al, 2003; Thompson and Wilding, 2003). **The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial (ATBC),** a randomized, placebo-controlled trial of α-tocopherol (50 mg/day) and beta-carotene (20 mg/day) alone or in combination in male smokers, with a primary end point of lung cancer incidence and mortality (Albanes et al, 1996), **on secondary analysis found a statistically significant 32% reduction in prostate cancer incidence and a 41% lower mortality in those receiving α-tocopherol** (Albanes et al, 1995).

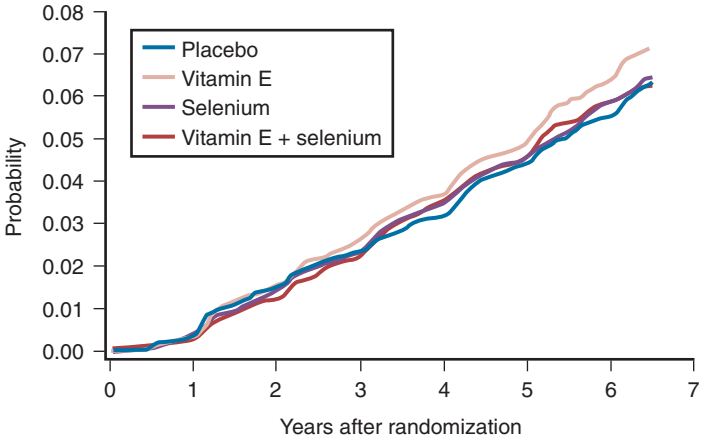


Figure 95–11. Cumulative incidence of prostate cancer detection over time by intervention group: results from the Selection and Vitamin E Cancer Prevention Trial. (From Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial [SELECT]. JAMA 2009;301:39–51.)

Selenium and Vitamin E Cancer Prevention Trial (SELECT)

The accumulated epidemiologic and biologic evidence that Se and vitamin E may prevent prostate cancer led to the design and launch of SELECT, the Selenium and Vitamin E Cancer Prevention Trial (Klein et al, 2001; Lippman et al, 2005). **SELECT was a phase III, randomized, double-blind, placebo-controlled, population-based trial designed to test the efficacy of selenium and vitamin E alone and in combination in the prevention of prostate cancer.** It was the largest cancer prevention trial ever performed. Eligibility criteria include age greater than or equal to 50 years for African-Americans, greater than or equal to 55 years for whites, a DRE not suspicious for cancer, serum PSA less than or equal to 4 ng/mL, and normal blood pressure. Randomization was equally distributed among four study arms (selenium + placebo, vitamin E + placebo, selenium + vitamin E, and placebo + placebo). **Although the study duration was planned for 12 years, as a result of a planned interim analysis in August 2008, an independent data and safety monitoring committee recommended discontinuation of the study because the data convincingly demonstrated no effect on the risk of prostate cancer by either agent alone or in combination, and no chance of a beneficial effect of the hypothesized magnitude with continued supplementation** (Fig. 95–11) (Lippman et al, 2009). There were statistically nonsignificant increased risks of prostate cancer in the vitamin E group (HR = 1.13, 99% CI = 0.95 to 1.35, P = .06) and type 2 diabetes mellitus in the selenium group (RR = 1.07, 95% CI 0.94 to 1.22, P = .16). However, neither of these findings was observed in the combination group. Secondary analyses also showed no effect on the risks of lung, colorectal, or overall cancer incidence, no effect on cardiovascular events, and no effect on overall survival. **Null results for the effect of vitamin E on prostate cancer risk were also reported in the Physicians' Health Study II (PHS), a randomized trial of vitamins E (400 IU every other day) and C (500 mg daily) versus placebo in the prevention of prostate and other cancers** (Gaziano et al, 2009). **Together, these results suggest that neither selenium nor vitamin E should be used in the hope of preventing prostate or other cancers.**

Other Agents

Selective Estrogen Receptor Modulators (SERMs)

SERMs possess both agonistic and antagonistic estrogen-like activity and have been shown to repress prostate cancer growth in several transgenic mouse models. In the transgenic mouse model of prostate cancer (TRAMP), toremifene reduces the incidence of high-grade PIN and cancer in an estrogen-dependent, androgen-independent mechanism (Raghow et al, 2002). A randomized, double-blind, placebo-controlled trial is currently open to assess the activity of toremifene against high-grade PIN and prostate cancer incidence.

Soy

Legumes play an important role in the traditional diets of Asian countries, where prostate cancer incidence is low, but only a minor role in the West, where the incidence is the highest worldwide. Soybeans are unique among legumes because they are a concentrated source of isoflavones, which have weak estrogenic activity. **The major isoflavone components of soy, including genistein, daidzein, and their metabolites, inhibit benign and malignant prostatic epithelial cell growth, downregulate androgen-regulated genes, and reduce tumor growth in animal models** (Cohen et al, 2003; Hedlund et al, 2003; Yu et al, 2003). Migration studies and lower prostate cancer rates in Asian men with higher soy intake also support the role of soy as an anticancer agent (Severson et al, 1989). However, results from small clinical trials have not shown promise thus far. Dietary trials conducted in men prior to prostatectomy (Dalais et al, 2004), as well as in men on active surveillance (Kumar et al, 2004; Ornish et al, 2005), showed modest or no decrease in PSA values (the primary end point of these studies) with soy intake.

Lycopene

Lycopene is a red-orange carotenoid found primarily in tomatoes, tomato-derived products, and other red fruits and vegetables. Lycopene is a highly unsaturated acyclic isomer of β-carotene, is the predominant carotenoid in human plasma, and possesses

potent antioxidant activity. Lycopene has been shown to inhibit the growth of benign and malignant prostatic epithelial cells in vitro (Obermuller-Jevic et al, 2003). **There is mixed epidemiologic evidence that lycopene consumption is associated with a lower risk of prostate cancer** (Giovannucci and Clinton, 1999). A meta-analysis of observational studies reported a 23% reduction in prostate cancer risk with high tomato and lycopene intake (Etminan et al, 2004). However, a nested case-control study in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial prospectively examined the intake of more than 25 tomato-containing foods in 29,361 men and found no correlation with the incidence of prostate cancer (Peters et al, 2007). To date, results of initial clinical trials have demonstrated potential beneficial activity of lycopene in prostate cancer; however, treatment length has been relatively short, participants have included men at various stages of disease, and surrogate markers have been used rather than clinical meaningful end points (Bunker et al, 2007; Dahan et al, 2008). Currently, no phase III trials examining the role of lycopene in prostate cancer prevention are being conducted.

Green Tea (*Camellia sinensis*)

Green tea has been suggested as a prostate cancer preventative based on epidemiologic observations of a low incidence of prostate cancer among Asians with a high dietary intake. Previous work has focused on the effects of polyphenols (i.e., flavanols; also know as catechins), which accounts for 30% to 40% of extractable solids from dried green tea leaves. Prostate cancer cell culture experiments have demonstrated that the major polyphenolic constituent of green tea, (–)-epigallocatechin-3-gallate (EGCG), induces apoptosis, cell-growth inhibition, and cell-cycle dysregulation (Adhami et al, 2003). In the TRAMP model, oral infusion of a polyphenolic fraction isolated from green tea significantly inhibited tumor development and metastasis (Brusselmans et al, 2003; Hastak et al, 2003). A small randomized, double-blind, placebo controlled trial of green tea catechin tablets in 60 men with HGPIN demonstrated cancer at 1-year biopsy in 9 patients in the placebo group, compared with only 1 patient in the treatment group (Bettuzzi et al, 2006). Another small trial in men with hormone-refractory prostate cancer found only minimal clinical activity (Choan et al, 2005). Confirmatory trials are needed to better assess the role of green tea consumption in prostate cancer prevention.

Statins

Statins are widely used cholesterol-lowering drugs given for the treatment and prevention of atherosclerotic cardiovascular disease. They inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), the rate-limiting enzyme in cholesterol biosynthesis. Statins are hypothesized to play a role in the prevention of cancer by inhibiting inflammation, angiogenesis, cell proliferation, migration/adhesion, invasion, and/or by preferentially promoting apoptosis in tumor cells (Hamilton and Freedland, 2008). Observational studies of statin use demonstrate high heterogeneity with mixed results for prostate cancer risk. **Statin users have been shown to have lower serum PSA levels than nonusers** (Cyrus-David et al, 2005; Hamilton et al, 2008), **suggesting an anticancer effect, but potentially leading to fewer prostate biopsies, and thus biasing results of epidemiologic and clinical studies. A meta-analysis of six randomized clinical trials, six cohort, and seven case-control studies found no association between statin use and overall prostate cancer incidence but did find a protective association with advanced prostate cancer (RR = 0.77, 95% CI = 0.64 to 0.93)** (Bonovas et al, 2008). Statin users tend to be healthier and more medically compliant than nonusers, making them more likely to undergo PSA screening and possibly resulting in earlier cancer detection. Further research is needed to help determine the role, if any, of statins in the prevention of prostate cancer.

Key Points: Chemoprevention

- The goal of primary chemoprevention is to decrease the incidence of a given cancer, simultaneously reducing both treatment-related side effects and mortality.
- Effective chemoprevention requires the use of nontoxic agents that inhibit specific molecular steps in the carcinogenic pathway.
- Prostate cancer is an attractive and appropriate target for primary prevention, because of its incidence, prevalence, and disease-related mortality.
- Target populations appropriate for primary prevention studies can be subdivided into those with low, intermediate, and high risk of developing prostate cancer. The molecular mechanisms that underlie disease progression are likely to be different for each target population, and it may not be possible to generalize the results from a particular trial to other clinical scenarios.
- The Prostate Cancer Prevention Trial demonstrated that finasteride reduces the period prevalence of prostate cancer by 25%. The apparent increase in high-grade disease in men on finasteride may be due to ascertainment bias induced by the effects of finasteride on PSA, DRE, and prostate volume.
- SELECT demonstrated that neither vitamin E nor selenium prevent prostate cancer. The lack of efficacy of vitamin E was confirmed by the SELECT Trial.
- 5α-Reductase inhibitors and other hormonal agents, antioxidants, and statins are among the many agents currently being investigated in prostate cancer chemoprevention.

CONCLUSION

It is clear that the process of prostate carcinogenesis is complex. The interplay of constitutional, behavioral, molecular, and environmental factors—against the backdrop of various processes occurring during aging—interact to set in motion a series of events that ultimately are manifest through the diagnosis of prostate cancer. The understanding of this process is complicated by the various confounds associated with the diagnosis of the disease in clinical trials, general populations, and epidemiologic studies. Additionally, the current inability to distinguish biologically significant from biologically insignificant disease complicates full understanding of the interaction of these factors.

Prostate cancer is an attractive target for chemoprevention, because of its ubiquity, treatment-related morbidity, long latency between premalignant lesions and clinically evident cancer, and defined molecular pathogenesis. The PCPT provides the first firm evidence that this cancer can be prevented by a relatively nontoxic oral agent. The current body of evidence argues against a routine recommendation of any dietary or nutritional supplement for the prevention of prostate cancer.

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The complete reference list is available online at www.expertconsult.com.

chapter
96

Pathology of Prostatic Neoplasia

Jonathan I. Epstein, MD

Prostatic Intraepithelial Neoplasia

Adenocarcinoma

Subtypes of Prostate Adenocarcinoma

This chapter covers the pathology of adenocarcinoma of the prostate from its precursor lesions to invasive carcinomas, from needle biopsies to radical prostatectomies. Other tumors involving the prostate are also discussed. In particular, practical points of pathology that are critical for urologists to know for the management of their patients are emphasized.

PROSTATIC INTRAEPITHELIAL NEOPLASIA

Prostatic intraepithelial neoplasia (PIN) consists of architecturally benign prostatic acini or ducts lined by cytologically atypical cells and is classified as low-grade and high-grade neoplasias (McNeal and Bostwick, 1986) (Fig. 96–1). **Diagnostic reports should not comment on low-grade PIN.** First, pathologists cannot reproducibly distinguish between low-grade PIN and benign prostate tissue (Epstein et al, 1995). Second, when low-grade PIN is diagnosed on needle biopsy, these patients are at no greater risk of having carcinoma on repeated biopsy than are men with a benign biopsy finding (Epstein and Herawi, 2006). Evidence that high-grade PIN (HGPIN) is a precursor to some prostate carcinomas includes the following: There is an increase in the size and number of high-grade PIN foci in prostates with cancer compared with prostates without carcinoma; with increasing amounts of high-grade PIN, there are a greater number of multifocal carcinomas; both high-grade PIN and carcinoma preferentially involve the peripheral zone; and biomarkers and molecular changes show similarity between high-grade PIN and carcinoma (Bostwick et al, 1996; Haggman et al, 1997). About 20% of high-grade PIN lesions harbor a *TMPRSS2-ERG* fusion gene, which is a common molecular abnormality detectable in about 50% of prostate cancers (Cerveira et al, 2006; Perner et al, 2007).

The incidence of high-grade PIN on biopsy averages 7.6% among 38 studies, with a median of 5.2%. There is a tremendous variation in the percentages reported, ranging from 0% to 25%, with no apparent correlation to number of cores sampled or whether the study was from an academic or community hospital setting (Epstein and Herawi, 2006). The most likely explanation accounting for this variation is interobserver threshold. The distinction between low-grade and high-grade PIN is based on the prominence of the nucleoli. This is a subjective exercise, and those pathologists with a lower threshold as to what defines prominent nucleoli will have a higher incidence of high-grade PIN. **The largest studies reported a 16% to 44.6% risk of cancer on subsequent biopsy. Of the 11 studies with at least 50 cases of high-grade PIN on needle biopsy with follow-up, the mean risk of cancer is 26.4%** (Epstein and Herawi, 2006). **In the majority of studies, serum prostate-specific antigen (PSA) levels, results of digital rectal examination, and transrectal ultrasonography findings do not enhance the prediction of who is more likely to have carcinoma on repeat biopsy.** PIN by itself does not give rise to elevated serum PSA values (Ronnett, et al, 1993). Of 8 studies in which the risk of cancer after a needle biopsy diagnosis of high-grade PIN was compared with the risk of cancer after a benign biopsy finding, 6 showed no difference between the groups (Epstein and Herawi, 2006). **For patients diagnosed with unifocal high-grade PIN on extended initial core sampling, a repeat biopsy within the first year is unnecessary in the absence of other clinical indicators of cancer and in the absence of extensive high-grade PIN.** High-grade PIN on greater than or equal to two cores is associated with a sufficiently high risk of subsequent cancer that rebiopsy within a year of the initial PIN diagnosis is warranted (Abdel-Khalek et al, 2004; Netto and Epstein, 2006; Merrimen et al, 2009). Lefkowitz and colleagues (2002) described 31 men who had an initial diagnosis of high-grade PIN on 12-core biopsy with an interval to follow-up prostate biopsy of 3 years. The rate of cancer on repeat 12-core biopsy was 25.8% compared with their earlier study in which rebiopsy within 1 year of a diagnosis of high-grade PIN yielded cancer in only 2.3%. They hypothesized that the 3-year interval allowed unsampled small cancers that were associated with the high-grade PIN at the time of initial biopsy to grow to a size that was detectable on repeat biopsy, or alternatively, some of the high-grade PIN lesions progressed to cancer during the 3-year interval. **If a repeat prostate needle biopsy is performed, it should sample the entire prostate and not just the initial sextant site where the high-grade PIN was found** (Epstein and Herawi, 2006).

The significance of HGPIN on transurethral resection (TUR) is not clear, with conflicting data as to the risk for subsequent discovery of cancer (Gaudin et al, 1997; Pacelli and Bostwick, 1997). In an elderly patient with HGPIN on TUR, often no further workup is instituted. In a younger man, a more aggressive workup to rule out a clinically significant tumor is warranted. The one piece of evidence we have for premalignant lesions in other organs that is lacking in the prostate is the natural history of high-grade PIN. With the prostate, there is no capability to monitor a PIN focus to determine whether there is already infiltrating carcinoma at that site or whether infiltrating carcinoma has evolved in the immediate vicinity of the PIN focus. Because we do not know what

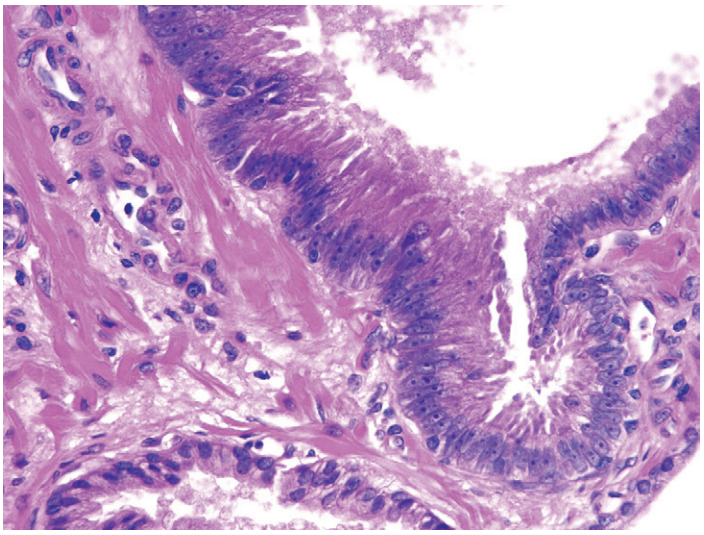


Figure 96–1. High-grade prostatic intraepithelial neoplasia. Note cytologically atypical cells with prominent nucleoli in an architecturally benign gland *(top)*, contrasted to a benign gland *(bottom)*.

percentage of patients develop infiltrating carcinoma during a given follow-up interval, when high-grade PIN is found on biopsy material, most authorities do not use the term *carcinoma in situ of the prostate*. **It appears that high-grade PIN is a precursor lesion to many peripheral intermediate- to high-grade adenocarcinomas of the prostate.** However, PIN need not be present for carcinoma to arise. Low-grade carcinomas, especially those present within the transition zone, are not closely related to high-grade PIN.

Intraductal carcinoma of the prostate (IDC-P) has, in several studies, been described in radical prostatectomy specimens (McNeal et al, 1986; McNeal and Yemoto, 1996; Rubin et al, 1998; Wilcox et al, 1998; Cohen et al, 2007; Robinson and Epstein, 2010). Rarely, IDC-P may be identified on biopsy material in the absence of infiltrating carcinoma (Guo and Epstein, 2006). IDC-P on prostate biopsies is frequently associated with high-grade cancer and poor prognostic parameters at radical prostatectomy, as well as potentially advanced disease following other therapies (Guo and Epstein, 2006). These findings support the idea that in most cases IDC-P represents intraductal spread of carcinoma within pre-existing ducts and acini and that IDC-P in the vast majority of cases should not be categorized as a preinvasive neoplastic condition. Consideration should be given to aggressively treating patients with IDC-P on biopsy, even in the absence of documented infiltrating cancer.

ADENOCARCINOMA

Location

In clinical stage T2 carcinomas and in 85% of nonpalpable tumors diagnosed on needle biopsy (stage T1c), the major tumor mass is peripheral in location (McNeal, 1969; Byar and Mostofi, 1972; Epstein et al, 1994b). In the remaining cases, tumors are predominantly located in the transition zone (i.e., periurethrally or anteriorly). Tumors that appear to be unilateral on rectal examination are bilateral in approximately 70% of cases when they are examined for pathology. Adenocarcinoma of the prostate is multifocal in more than 85% of cases (Byar and Mostofi, 1972). In many of these cases of bilateral or multifocal tumor, the other tumors are small, low grade, and clinically insignificant. Consequently, the distinction between pathologic stages T2a and T2b is meaningless (Freedland et al, 2004). In a highly selected population with limited unilateral biopsy cancer, the mean number of separate tumor nodules per radical prostatectomy is 2.9. A contralateral tumor to the positive biopsy side at radical prostatectomy is typically small. However, 20% have some contralateral adverse pathology in terms of size, extraprostatic extension, grade, or margins (Yoon et al, 2008).

Spread of Tumor

Because the prostate lacks a discrete histologic capsule, *extraprostatic extension* is preferable to "capsular penetration" as the term to describe a tumor that has extended out of the prostate into periprostatic soft tissue (Ayala et al, 1989). Some authors use the term *capsular invasion* when they believe that the "capsule" is infiltrated by a tumor but the tumor does not extend out of the prostate. Because there is no such entity as the prostatic capsule, "capsular invasion" makes no sense. Peripherally located adenocarcinomas of the prostate tend to extend out of the prostate through perineural space invasion (Villers et al, 1989). Perineural invasion by itself in radical prostatectomy specimens does not worsen prognosis, because perineural invasion merely represents extension of a tumor along a plane of decreased resistance and not invasion into lymphatics (Hassan and Maksem, 1980). In contrast, vascular invasion increases the risk of recurrence after radical prostatectomy (Baydar et al, 2008). Extraprostatic extension preferentially occurs posteriorly and posterolaterally, paralleling the location of most adenocarcinomas.

Further local spread of tumor may lead to seminal vesicle invasion, which is diagnosed when a tumor extends into the muscle wall of the seminal vesicle. The most common route of seminal vesicle invasion is by tumor penetration out of the prostate at the base of the gland, with growth and extension into the periseminal vesicle soft tissue and eventually into the seminal vesicles. Less commonly, there may be direct extension through the ejaculatory ducts into the seminal vesicles or direct extension from the base of the prostate into the wall of the seminal vesicles. Least commonly, there may be discrete metastases to the seminal vesicle (Fry et al, 1979; Ohori et al, 1993). Local spread of prostate cancer may also rarely involve the rectum, where it may be difficult to distinguish from a rectal primary tumor (Fry et al, 1979; Lane et al, 2008).

The most frequent sites of metastatic prostate carcinoma are lymph nodes and bone. Prostate cancer may present with metastases to the left supradiaphragmatic, typically the supraclavicular, lymph nodes (Cho and Epstein, 1987). Lung metastases from prostate carcinoma are extremely common at autopsy, and almost all cases have bone involvement as well (Varkarakis et al, 1974). Metastatic lesions usually take the form of multiple small nodules or diffuse lymphatic spread rather than large metastatic deposits. Clinically, prostate carcinoma metastatic to the lung is usually asymptomatic. In addition to lymph nodes, bones, and lung, the next most common regions of spread of prostate cancer at autopsy are bladder, liver, and adrenal gland (Hess et al, 2006).

Tumor Volume

In general, the size of a prostate cancer correlates with its stage. Extraprostatic extension is uncommon in tumors of less than 0.5 cm^3, and tumors that are less than 4 cm^3 uncommonly reveal lymph node metastases or seminal vesicle invasion (McNeal et al, 1990). Tumor volume is also proportional to grade (see following

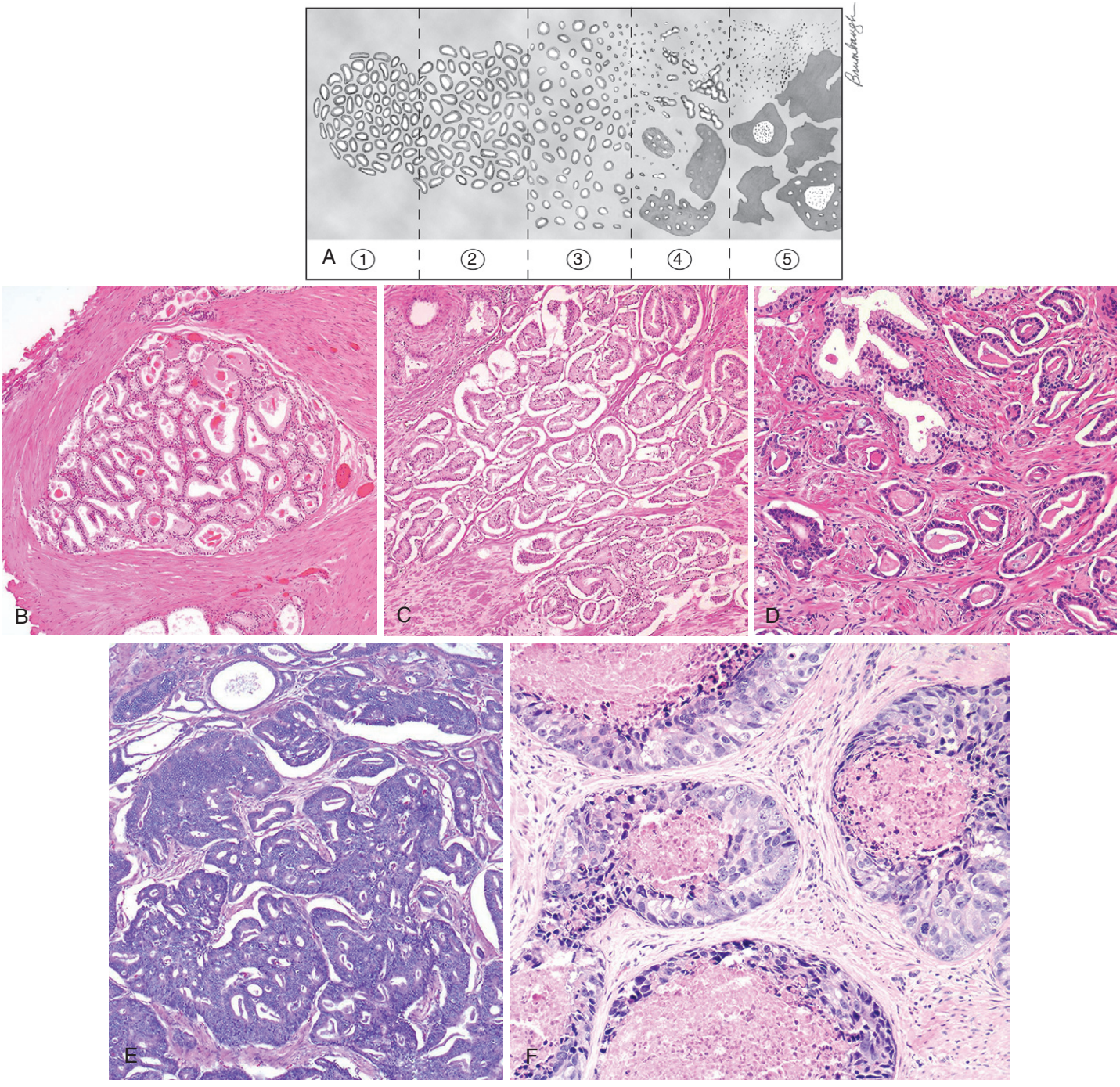


Figure 96–2. The Gleason grading system. **A,** Schematic diagram of the Gleason grading system. **B,** Gleason pattern 1: Well-circumscribed nodule of closely packed glands. **C,** Gleason pattern 2: nodule with more loosely arranged glands. **D,** Gleason pattern 3: small glands with an infiltrative pattern between benign glands. **E,** Gleason pattern 4: large irregular cribriform glands. **F,** Gleason pattern 5: solid nests of tumor with central comedonecrosis.

discussion). The location and grade of the tumor also modulate the effect of tumor volume (Christensen et al, 1990; McNeal et al, 1990; Greene et al, 1991). For example, **transition zone tumors extend out of the prostate at larger volumes than do peripheral zone tumors, because of their lower grade and greater distance from the edge of the gland.**

Grade

Although numerous grading systems exist for the evaluation of prostatic adenocarcinoma, the Gleason grading system is the most widely accepted (Gleason and Mellinger, 1974). The Gleason system is based on the glandular pattern of the tumor as identified at relatively low magnification (Fig. 96–2). Cytologic features play no role in the grade of the tumor. **Both the primary (predominant) and the secondary (second most prevalent) architectural patterns are identified and assigned a grade from 1 to 5, with 1 being the most differentiated and 5 being the least differentiated** (Table 96–1). **Because both the primary and the secondary patterns are influential in predicting prognosis, there is a Gleason sum or score obtained by the addition of the primary**

Table 96–1.

2005 International Society of Urological Pathology Modified Gleason System

Pattern 1

Circumscribed nodule of closely packed but separate, uniform, rounded to oval, medium-sized acini (larger glands than pattern 3)

Pattern 2

Like pattern 1, fairly circumscribed, yet at the edge of the tumor nodule there may be minimal infiltration

Glands are more loosely arranged and not quite as uniform as Gleason pattern 1

Pattern 3

Discrete glandular units

Typically smaller glands than seen in Gleason pattern 1 or 2

Infiltrates in and amongst non-neoplastic prostate acini

Marked variation in size and shape

Pattern 4

Fused microacinar glands

Ill-defined glands with poorly formed glandular lumina

Large cribriform glands

Cribriform glands

Hypernephromatoid

Pattern 5

Essentially no glandular differentiation, composed of solid sheets, cords, or single cells

Comedocarcinoma with central necrosis surrounded by papillary, cribriform, or solid masses

and secondary grades. If a tumor has only one histologic pattern, then for uniformity, the primary and secondary patterns are given the same grade. Gleason scores range from 2 (1 + 1 = 2), which represents tumors uniformly composed of Gleason pattern 1 tumor, to 10 (5 + 5 = 10), which represents totally undifferentiated tumors. This author prefers to assign both a primary and a secondary pattern even when presented with limited cancer so as to not to create any confusion. For example, cases that the pathologist signs out as only "Gleason grade 4" could be interpreted to mean Gleason pattern 4 (high-grade cancer) or Gleason score 4 (low-grade cancer). In radical prostatectomy specimens, it has been demonstrated that tertiary (third most common pattern) high-grade components adversely affect biologic behavior, yet are not always equivalent to the sum of the primary pattern and highest-grade pattern. It is recommended that in radical prostatectomy specimens, the routine Gleason score, consisting of the most prevalent and the second most prevalent architectural patterns, be recorded along with a note stating that there is a tertiary high-grade pattern (Pan et al, 2000; Trock et al, 2009). **There are a few exceptions to the Gleason system, as described above. For needle biopsy specimens in which the typical scenario includes tumors with patterns 3, 4, and 5 in various proportions, both the primary pattern and the highest grade should be added to derive the Gleason score. Any amount of high-grade tumor sampled on needle biopsy most likely indicates a more significant amount of high-grade tumor within the prostate because of the correlation of grade and volume and the problems inherent with needle biopsy sampling. In the setting of high-grade cancer, one should ignore lower-grade patterns if they occupy less than 5% of the area of the tumor. For example, a tumor composed of 98% Gleason pattern 4 and 2% Gleason pattern 3 should be diagnosed as Gleason score 4 + 4 = 8** (Epstein et al, 2005).

It is important to recognize Gleason pattern 4 tumors because tumors with this pattern have a significantly worse prognosis than those with pure Gleason pattern 3 (McNeal et al, 1990; Epstein et al, 1993b). It has also been demonstrated in radical prostatectomy specimens that tumors with Gleason score 4 + 3 = 7 have a worse prognosis than those with Gleason score 3 + 4 = 7 (Chan et al, 2000). **There is fairly good interobserver reproducibility of the Gleason system among uropathology experts and poorer reproducibility among practicing pathologists** (Allsbrook et al, 2001a, 2001b). It has been demonstrated that although current use of the Gleason grading system is not optimal, significant improvements can be made after participation in relatively brief educational programs, such as those available on websites (e.g., www.isuporg.org [International Society of Urological Pathology]).

The Gleason grade on biopsy material has also been shown to correlate fairly well with that of the subsequent prostatectomy specimen (Fine and Epstein, 2008). Several studies have demonstrated that there is better correlation between the biopsy and prostatectomy grade with extended as opposed to sextant needle biopsy sampling. In general, a Gleason score less than or equal to 6 or greater than or equal to 7 on biopsy corresponds to a Gleason score less than or equal to 6 or greater than or equal to 7 in the radical prostatectomy, respectively, in 80% of cases. An unavoidable cause of discordant grading between the biopsy and subsequent prostatectomy specimen(s) concerns sampling errors with the needle biopsy. One of the most frequent causes of discordant grading is grading of tumors that straddle two grades. One way the practice of Gleason scoring can be improved is by virtually never assigning Gleason score 2 to 4 for adenocarcinoma of the prostate on needle biopsy. The reasons for this approach are as follows: (1) most tumors graded as Gleason score 2 to 4 on needle biopsy are graded as Gleason score 5 to 6 or higher when reviewed by uropathology experts (Steinberg et al, 2005); (2) there is poor reproducibility in the diagnosis of Gleason score 2 to 4 on needle biopsy even among uropathology experts (Allsbrook et al, 2001b); and (3) most important, assigning Gleason score 2 to 4 to an adenocarcinoma on needle biopsy can adversely affect the patient's care, because clinicians may incorrectly assume that all low-grade cancers on needle biopsy do not need definitive therapy. Although low volume, Gleason score 2 to 4 adenocarcinoma of the prostate, on transurethral resection of the prostate, has a relatively indolent course; low-grade cancer on needle biopsy does not. Pathologists, in general, are less frequently overdiagnosing Gleason scores 2 to 4 on biopsy in recent years. In one study, 24% of pathologists rendered a diagnosis of Gleason score 2 to 4 on biopsy in 1991, which decreased to 2.4% in 2001 (Ghani et al, 2005).

The ultimate value of any grading system is its prognostic ability. Both Gleason's data with 2911 patients and subsequent studies with long-term follow-up have demonstrated a good correlation between the Gleason sum and prognosis (Mellinger, 1977; Sogani et al, 1985). When stage of disease is factored in with grade, prognostication is enhanced. Some men with low-grade cancers develop high-grade tumors after several years (Brawn, 1983). It is not clear whether the residual low-grade cancer progressed or whether there was a subsequent development of a multifocal, more aggressive tumor. Although, in general, larger tumors are high grade and small tumors are low grade, exceptions occur (Epstein et al, 1994a). There is a tendency to hypothesize that

Table 96–2.

Reasons to Submit Needle Cores in Separate Jars for Each Sextant Site

- In "atypical" cases, the atypical site can be preferentially targeted on repeated biopsy, in addition to other sites.
- More specific location of cancer helps pathologists target additional tissue or block sampling in cases with no cancer on initial sampling of radical prostatectomy.
- Knowledge of sextant site helps pathologists recognize certain diagnostic pitfalls (i.e., seminal vesicle tissue or central zone mimicking high-grade prostatic intraepithelial neoplasia at the base and Cowper's gland mimicking cancer at the apex).
- With brachytherapy, this helps target areas where extra seeds can be distributed.
- Having a maximum of two cores per block or slide preparation with complete visualization of cores helps prevent missing small foci of cancer that could be "buried" in the paraffin block.
- Maximum of two cores per block or slide helps prevent core fragmentation where one cannot determine the number of involved cores, their percentage involvement, and the highest grade of cancer in the case.

tumors begin as low-grade tumors and, on reaching a certain size, dedifferentiate into higher-grade lesions, accounting for the relationship between size and grade. Alternatively, high-grade tumors may be high grade at their inception but are detected at an advanced size because of their rapid growth. Similarly, low-grade tumors may evolve so slowly that they tend to be detected at lower volumes. During a 2- to 3-year period after biopsy, there is no evidence that prostate cancer grades worsen significantly (Sheridan et al, 2008).

Assessment of Needle Biopsy Specimens

Processing. **When biopsy specimens are taken from different areas of the prostate, they should be submitted to pathology in separate containers** (Table 96–2). As long as cores are submitted in separate containers or the cores are in the same container yet specified by the urologist as to their location (i.e., by different color inks), pathologists should assign individual Gleason scores to separate cores (Epstein et al, 2005). If cores are combined in a container, one can try to give separate scores for each core or can give an overall Gleason score. For example, in a case with Gleason score 4 + 4 = 8 on one core and with pattern 3 (3 + 3 = 6, 3 + 4 = 7, 4 + 3 = 7) on other cores in the same container, the overall score for that container, averaging all involved needle biopsy specimens together as if they were one long positive core, would be Gleason score 4 + 3 = 7 or 3 + 4 = 7, depending on whether pattern 4 or 3 predominated.

Differential Diagnosis. The underdiagnosis of limited adenocarcinoma of the prostate on needle biopsy is one of the most frequent problems in prostate pathology (Epstein, 2004). There are also numerous benign mimickers of adenocarcinoma of the prostate (Srigley, 2004). In some of these cases, the use of antibodies to high-molecular-weight cytokeratin and p63 may resolve the diagnosis (Wojno and Epstein, 1995). Benign glands contain basal cells and are labeled with these antibodies, whereas prostate cancer shows no staining. Immunohistochemistry with antibodies to α-methylacyl-CoA racemase, which preferentially labels prostatic carcinoma and high-grade PIN, can also be used as an adjunct in the diagnosis of limited cancer, yet pathologists must be careful because false-positive and false-negative staining with α-methylacyl-CoA racemase has been reported (Jiang et al, 2004).

In certain cases, there are findings suggestive of but not diagnostic of carcinoma. **The incidence of atypical needle biopsy specimens reported from the 39 studies in the literature averages 7.6% with a median of 5.2%** (Epstein and Herawi, 2006). **Pathologists should sign out atypical cases descriptively as "a focus of atypical glands" rather than use ambiguous terminology such as "atypical hyperplasia" or "atypical small acinar proliferation."** A comment should be added in the report describing why the focus is suggestive of cancer yet not diagnostic, with a recommendation for repeat biopsy. In this way, there is no confusion in the urologist's mind that he or she is dealing with a lesion likely to be infiltrating cancer but for which the pathologist is not comfortable establishing the diagnosis. **The likelihood of cancer after an atypical diagnosis is 42% or 49%, according to the two largest studies from the Mayo Clinic and Johns Hopkins Hospital, respectively** (Iczkowski et al, 1997; Chan and Epstein, 1999). **Surprisingly, in men with a prior atypical biopsy result, the level of serum PSA elevation or the results of digital rectal examination do not correlate with the risk of a subsequent biopsy specimen showing carcinoma. Regardless of the serum PSA level, all patients with an initial atypical diagnosis on needle biopsy should undergo a repeat biopsy.** In a series of second-opinion prostate needle biopsy cases that were patient- and urologist-driven, on expert review, only 36.8% of outside atypical diagnoses were confirmed; on review, 92 of the 204 (45.1%) outside atypical cases in one study were diagnosed as cancer and 33 (16.2%) as benign (Chan and Epstein, 2005). **Cases diagnosed as atypical have the highest likelihood of being changed on expert review, and urologists should consider sending such cases for consultation to attempt to resolve the diagnosis as either definitively benign or malignant before subjecting the patient to repeat biopsy.**

Prognosis. Adverse findings on needle biopsy, in terms of Gleason grade and tumor extent, in general accurately predict adverse findings in the radical prostatectomy specimen. However, favorable findings on needle biopsy do not necessarily predict favorable findings in the radical prostatectomy specimen, as a result of sampling error. The ways in which cancer may be measured on needle biopsy include number of positive cores, total millimeters of cancer among all cores, percentage of cancer per core, and total percentage of cancer in the entire specimen. An equal number of studies claim superiority of one technique over the other, with no one technique adopted uniformly (Epstein, 2004). It is proposed that pathologists report the number of positive cores along with one other measurement of tumor extent. At the Johns Hopkins Hospital, the percentages of each involved core are reported, for example, as "adenocarcinoma of the prostate, Gleason grade 3 + 3 = 6, involving two cores (70%, 30%)." By combining needle biopsy grade with clinical stage and serum PSA values, the extent of cancer within the prostate can be more accurately predicted (Makarov et al, 2007).

Whether perineural invasion that is extensive enough to be sampled on needle biopsy signals an increased risk of extraprostatic extension of cancer is controversial. Harnden (2007), in a systematic review of the importance of perineural invasion on needle biopsy to predict recurrence following radiotherapy or surgery, concluded that the weight of the evidence in 21 studies showed it was a significant prognostic indicator, particularly in specific patient subgroups defined by serum PSA and Gleason

scores. Over two thirds of the studies using external beam radiotherapy but none using brachytherapy showed prognostic significance for perineural invasion. Given that perineural invasion is readily identifiable in most cases, that it is prognostic in some studies, although the data is conflicting, and that it is uncertain what factors an individual clinician may consider in treatment decisions, it is the opinion of these authors that perineural invasion should be noted on the biopsy pathology report.

One can also use information from needle biopsy pathology reports to help determine whether to sacrifice the neurovascular bundle on a given side in cases with a higher likelihood of extraprostatic extension (Shah et al, 2003; Ohori et al, 2004; Tsuzuki et al, 2005).

There is emerging data that atrophy and associated inflammation are linked with prostate carcinogenesis (DeMarzo et al, 2003). However, the hypothesis is that these factors are involved in the initiation of prostate cancer and are not proximately related to cancer by the time atrophy is identified on needle biopsy. Atrophy of all morphologic types are very common on needle biopsy and are not associated with an increased risk of cancer or PIN on subsequent biopsy (Postma et al, 2005).

Assessment of Transurethral Resection Specimens

Processing. The recommended system is based on the percentage of the specimen involved by tumor, with 5% being the cutoff between stage T1a and T1b (Cantrell et al, 1981). All stage T1b tumors are detected by processing of between 6 and 8 cassettes of a transurethral resection (TUR) specimen. By processing 8 to 10 cassettes, more than 90% of stage T1a lesions are identified (Newman et al, 1982; Murphy et al, 1986; Vollmer, 1986; Rohr, 1987). Depending on the institution, all TUR tissues may be examined in men younger than 65 years in whom aggressive therapy for stage T1a disease might be pursued. There are conflicting opinions as to whether the grade of the cancer should be factored into the staging system for limited cancer detected on transurethral prostatectomy. On the basis of data from the author's institution, cases with less than 5% of tumor detected on TUR and with Gleason scores below 7 are staged T1a; if the Gleason scores are above 7, they should be staged T1b (Larsen et al, 1991).

Differential Diagnosis. One of the most common lesions to be confused with low-grade adenocarcinoma is adenosis (atypical adenomatous hyperplasia) (Gaudin and Epstein, 1994). In the author's institution, 1.6% of benign TUR specimens and 0.8% of all needle biopsy specimens contain adenosis. It is characteristically found in the transition zone of the prostate, is frequently multifocal, and most often is an incidental finding in TURs performed for urinary obstruction. **Although adenosis mimics carcinoma, there is no conclusive evidence suggesting that patients with adenosis have an increased risk of harboring or developing adenocarcinoma of the prostate.**

Assessment of Radical Prostatectomy Specimens

Assessment. Within institutions that do not totally embed radical prostatectomy specimens, there are sampling techniques that provide accurate pathologic staging (Hall et al, 1992; Sehdev et al, 2001). **Whole-mount sectioning of the prostate provides more aesthetically pleasing sections for teaching and publication, yet the information obtained by routine sections is identical.** In a minority of cases, routinely processed thinly sliced sections allow identification of positive margins not identified with use of thicker slices of tissue, which are necessary for whole-mount processing.

It is recommended that pathologists assign a separate grade to each dominant tumor nodule. Most often, the dominant nodule is the largest tumor, which is also the tumor associated with the highest stage and highest grade. In the unusual occurrence of a nondominant nodule (i.e., smaller nodule) that is of higher stage, one should also assign a grade to that nodule. If one of the smaller nodules is the highest-grade focus within the prostate, the grade of this smaller nodule should also be recorded. In general, this will be the exception; in most cases, separate grades will be assigned to only one or at most two dominant nodules.

If the urologist plans on aborting radical prostatectomy when lymph nodes are positive, the pathologist should freeze representative nodes, because approximately two thirds of microscopic metastases can be identified with random frozen sections. For urologists who perform radical prostatectomy in the face of microscopic metastases for local control, it has been demonstrated that men with a Gleason score below 8 on needle biopsy have a relatively prolonged interval before distant metastases appear; the pathologist need not examine the nodes at frozen section in these cases, because the urologist will proceed with surgery even if nodal metastases are found (Sgrignoli et al, 1994). Preoperatively, the physician and patient should decide and agree on what to do if there is a positive lymph node when the biopsy grade is Gleason score 8 to 10. In patients with Gleason scores of 8 to 10 on needle biopsy, it has been shown that if the lymph nodes are involved, these men will not benefit from radical surgery, whereas if the nodes are free of tumor, cure after radical prostatectomy is possible (Sgrignoli et al, 1994). Current data support that in men with Gleason scores of 8 to 10 on biopsy, all the nodes should be examined at the time of surgery, and the urologist should abort the prostatectomy if the nodes are positive. Other features that have correlated with prognosis are extent, grade, and ploidy of nodal metastases (Boorjian et al, 2007).

Prognosis. Only 25% of men with seminal vesicle invasion and none with lymph node metastases are biochemically progression-free at 10 years after radical prostatectomy, with grade and, in some studies, margins of resection influencing prognosis (Epstein et al, 1993b; Salomon et al, 2003; Bloom et al, 2004; Johnson et al, 2004). There is some controversy as to the definition of seminal vesicle invasion. Some investigators recognize both an intraprostatic and an extraprostatic portion of the seminal vesicle, whereby one can have organ-confined disease and seminal vesicle invasion (Ohori et al, 1993; Wheeler et al, 1998). However, these studies have demonstrated that the finding of intraprostatic seminal vesicle invasion does not adversely affect prognosis beyond that of finding extraprostatic extension without seminal vesicle invasion. Consequently, the author diagnoses seminal vesicle invasion only when the tumor extends out of the prostate into the muscle coat of the seminal vesicle; with use of this definition, seminal vesicle invasion is associated with a markedly adverse prognosis (Epstein et al, 1993b). The presence of extraprostatic extension and its extent also influence progression. Pathologists frequently underdiagnose extraprostatic extension. When tumor extends out of the prostatic gland, it induces a dense desmoplastic response in the periprostatic adipose tissue, where it can be difficult to judge whether the tumor has extended out of the gland

or is within the fibrous tissue of the prostate. Posterior, posterolateral, and lateral regions account for 18%, 17%, and 4% of positive margins, respectively, in the author's material. These sites parallel the location of most stage T2 carcinomas. In particular, these sites are disproportionately involved toward the apex (Stamey et al, 1990; Epstein et al, 1993b). **Only approximately 50% of men with positive margins progress after radical prostatectomy** (Epstein et al, 1993b). A major source of this discrepancy is that even in cases in which margins histologically appear to be positive, additional tissue removed from the site does not always show tumor (Epstein, 1990). It has also been demonstrated that tumor close to the margins does not result in a higher risk of recurrence (Epstein, 1990; Epstein and Sauvageot, 1997). Artifactually positive margins relate to the scant tissue surrounding the prostate, which may easily be disrupted during surgery or pathologic evaluation of the gland. Positive margins also may arise as a result of the surgical transection of intraprostatic tumor (intraprostatic incision). The reported incidence of intraprostatic incision ranges from 1.3% to as high as 71%. In the author's opinion, much of this variation relates to the difficulties described in recognizing extraprostatic extension. If an extraprostatic tumor associated with a desmoplastic stromal response at a margin is misdiagnosed as organ-confined, it will be misclassified as a positive margin due to intraprostatic incision. At the apex of the prostate, the boundaries of the prostate are especially vague such that it can be difficult to determine whether a cancer with a positive margin is intraprostatic. The other relatively frequent site of intraprostatic incision is in the region of the neurovascular bundles, where the urologist tries to preserve the bundle(s) for potency, yet cuts into the prostate. This author diagnoses a positive margin as a result of intraprostatic incision only if both tumor and benign glands are transected in the same area and are present at the inked margin. **Intraprostatic incision is associated with an increased risk of postoperative progression equivalent to that associated with focal extraprostatic extension and a positive margin** (Chuang et al, 2007). Preliminary studies have not shown a difference in sites of positive margins between open surgery and robotic radical prostatectomy, with the apex being the most commonly affected region (Smith et al, 2007). **In a multivariate analysis, Gleason grade, extraprostatic extension, and margins of resection are strong independent predictors of progression (i.e., elevated postoperative serum PSA level).** A more refined prognostication is not needed for men with Gleason scores of 2 to 4, because these men are almost all invariably cured by surgery. Men with Gleason scores of 8 to 10 have a poor prognosis after prostatectomy, with nodal metastases as the major prognostic determinant. Of cases with negative seminal vesicles and lymph nodes, Gleason scores of 5 to 7 account for 88% of tumors removed by radical prostatectomy and have a prognosis that can be stratified by various clinical and pathologic parameters (Epstein, in press; Epstein et al, 1993b; Diblasio and Kattan, 2003; Stephenson et al, 2005).

Tumor volume correlates well with pathologic stage and Gleason grade in clinical stage T2 cancers (McNeal et al, 1990). **However, most studies have found that tumor volume does not independently predict postradical prostatectomy progression once grade, pathologic stage, and margins are taken into account** (Epstein et al, 1993a; Kikuchi et al, 2004). Consequently, it is not currently recommended that tumor volume be calculated for clinical purposes in radical prostatectomy specimens. Rather, there should be some overall subjective indication of tumor volume to identify those cases with a minute amount of tumor and an excellent prognosis versus those cases with extensive tumor and a worse prognosis.

The evaluation of ploidy on radical prostatectomy specimens is controversial (Shankey et al, 1993; Adolfsson, 1994). The strongest data to support the prognostic importance of ploidy are in patients undergoing radical prostatectomy with pelvic node metastases (Boorjian et al, 2007). This author does not recommend that ploidy be routinely evaluated on radical prostatectomy specimens.

Adenocarcinoma with Treatment Effect

The major effect of combination endocrine therapy on benign prostate tissue is the presence of atrophic changes with immature squamous metaplasia (Vailancourt et al, 1996). This therapy may result in three different histologic patterns in prostate cancer: (1) atrophic prostate cancer, (2) cells with pyknotic nuclei with abundant xanthomatous cytoplasm resembling histiocytes, and (3) individual tumor cells resembling lymphocytes (Vailancourt et al, 1996). One of the problems with evaluating carcinomas that have been treated with hormone therapy is that the grade often appears artifactually higher (Smith and Murphy, 1994). **Pathologists should not assign a Gleason score to carcinomas with treatment effect.** However, if other areas of the tumor do not show a pronounced hormone effect, these areas can be Gleason graded. It has been demonstrated that finasteride does not alter the histology of either benign or malignant tissue (Yang et al, 1999; Rubin et al, 2005).

Radiation-related changes in the prostate are usually seen in patients who have been irradiated for adenocarcinoma of the prostate. When carcinoma is present in a biopsy specimen obtained 12 to 18 months after radiotherapy, it is a powerful predictor of either local or distant postirradiation failure (Scardino et al, 1986). Some studies have demonstrated that the morphologic appearance of the cancer (whether or not the cancer appears altered by the radiation) correlates with prognosis (Crook et al, 1997). Radiation alters the histologic features of benign prostate tissue so that it may mimic prostate cancer (Bostwick et al, 1982). Radiation atypia in benign prostate glands may persist for a long time (up to 72 months) after the initial treatment, resulting in a significant pitfall in evaluating prostate biopsy specimens (Magi-Galluzzi et al, 2003). If clinicians are aware of such treatment, this information should be provided to the pathologist.

SUBTYPES OF PROSTATE ADENOCARCINOMA

Mucinous adenocarcinoma of the prostate gland is one of the least common morphologic variants of prostatic carcinoma (Epstein and Lieberman, 1985; Ro et al, 1990). They behave like nonmucinous prostate carcinomas, having a propensity to develop bone metastases with advanced disease. **Mucinous adenocarcinoma of the prostate treated by radical prostatectomy is not more aggressive than nonmucinous prostate cancer** (Osunkoya et al, 2008). Even in ordinary adenocarcinomas of the prostate without light microscopic evidence of neuroendocrine differentiation, almost half show neuroendocrine differentiation on evaluation with immunohistochemistry for multiple neuroendocrine markers (di Sant'Agnese, 1992). Most studies do not demonstrate a convincing relation between the extent of neuroendocrine differentiation in ordinary prostate cancer and prognosis. Small cell carcinomas of the prostate are identical to small cell

carcinomas of the lung (Tetu et al, 1987, 1989). In approximately 50% of the cases, the tumors are mixed small cell carcinoma and adenocarcinoma of the prostate. Although most small cell tumors of the prostate lack clinically evident hormone production, they account for the majority of prostatic tumors with clinically evident adrenocorticotropic hormone or antidiuretic hormone production. **The average survival of patients with small cell carcinoma of the prostate is less than a year.** There is no difference in prognosis between patients with pure small cell carcinoma and those with mixed glandular and small cell carcinomas. Small cell carcinomas are not assigned a Gleason grade.

Between 0.4% and 0.8% of prostatic adenocarcinomas arise from prostatic ducts (Epstein and Woodruff, 1986; Christensen et al, 1991). When prostatic duct adenocarcinomas arise in the large primary periurethral prostatic ducts, they may grow as an exophytic lesion into the urethra, most commonly in and around the verumontanum, and give rise to either obstructive symptoms or hematuria. Tumors arising in the more peripheral prostatic ducts may present like ordinary (acinar) adenocarcinoma of the prostate and may be diagnosed on needle biopsy (Brinker et al, 1999). Tumors are often underestimated clinically because rectal examination findings and serum PSA levels may be normal. **Most prostatic duct adenocarcinomas are advanced stage at presentation and have an aggressive course; they should be regarded as Gleason score 4 + 4 = 8, because of their shared cribriform morphologic features with acinar adenocarcinoma Gleason score 8 and similar prognosis** (Brinker et al, 1999). **Pure primary squamous carcinoma of the prostate is rare and is associated with poor survival** (Parwani et al, 2004). These tumors develop osteolytic metastases, do not respond to estrogen therapy, and do not develop elevated serum acid phosphatase levels with metastatic disease. More commonly, squamous differentiation occurs in the primary and metastatic deposits of adenocarcinomas that have been treated with estrogen therapy. Sarcomatoid carcinomas (carcinosarcomas) have also been reported within the prostate and have a dismal prognosis (Lauwers et al, 1993).

Mesenchymal Tumors

Sarcomas of the prostate account for 0.1% to 0.2% of all malignant prostatic tumors (Sexton et al, 2001). Rhabdomyosarcomas are the most frequent mesenchymal tumor within the prostate and are seen almost exclusively in childhood. Leiomyosarcomas are the most common sarcomas involving the prostate in adults (Cheville et al, 1995). A spindle cell lesion that can occur at any age can closely simulate a leiomyosarcoma. Inflammatory myofibroblastic tumors may occur soon after TUR or without a history of TUR (Montgomery et al, 2006). There are also mesenchymal tumors of the prostate arising from the unique prostatic specialized stroma. These lesions range from prostatic stromal tumors of uncertain malignant potential to prostatic sarcomas. On histologic examination, these lesions are variable; one subtype resembles a tumor seen in the breast and is termed *phyllodes tumor of the prostate* (Herawi and Epstein, 2006).

Urothelial Carcinoma

Primary urothelial carcinoma of the prostate without bladder involvement accounts for 1% to 4% of all prostate carcinomas (Sawczuk et al, 1985). Primary urothelial carcinomas of the prostate show a propensity to infiltrate the bladder neck and the surrounding soft tissue such that more than 50% of the patients present with stage T3 or T4 tumors (Greene et al, 1976). Twenty percent of the patients present with distant metastases, with bone (predominantly osteolytic), lung, and liver being the most common sites. Treatment of stage T3 disease with radiation results in a 5-year survival of approximately 34%. In the minority of cases with tumor localized to the prostate (T2), radical surgery has resulted in long-term disease-free survival in several patients.

More commonly, urothelial carcinoma involves prostatic ducts and acini in patients with a history of carcinoma in situ (CIS) of the bladder who have been treated for a period of months to years with intravesical topical chemotherapy (Schellhammer et al, 1977; Mahadevia et al, 1986; Wood et al, 1989; Njinou Ngninkeu et al, 2003). Between 35% and 45% of cystoprostatectomies performed for urothelial carcinoma contain prostatic involvement. However, this number is dependent on the amount of histologic sampling of the prostate tissue and may be much higher in completely mapped specimens. If cystoprostatectomy is performed and only intraductal urothelial carcinoma is present, the prostatic involvement does not worsen the prognosis, which is determined by the stage of the bladder tumor (Esrig et al, 1996). Intraductal urothelial carcinoma of the prostate appears to involve the prostate by direct extension from the overlying urethra, which is usually involved by CIS. Intraductal and infiltrating urothelial carcinoma involving the prostate tends to be seen in higher-stage bladder tumors, in which the patients have a poor prognosis attributable to either advanced bladder or prostatic disease. A minority of these cases will have low-stage bladder tumor and a poorer prognosis,

Key Points

- Low-grade PIN should not be commented on in diagnostic reports, because the diagnosis is not reproducible among pathologists and lacks clinical significance.
- For patients diagnosed with isolated high-grade PIN on extended initial core sampling, repeat biopsy within the first year is unnecessary in the absence of other clinical indicators of cancer, because the risk of cancer on rebiopsy is similar to the risk associated with repeat biopsy after a benign diagnosis. Further studies are needed to determine whether biopsy should be routinely repeated several years after a high-grade PIN diagnosis, and, if so, how often and when.
- Regardless of the serum PSA level, all patients with an initial atypical diagnosis on needle biopsy should undergo repeat biopsy; the risk of cancer is approximately 40%, and clinical findings are not helpful in predicting who is more likely to have cancer.
- Cases diagnosed as atypical have the highest likelihood of being changed on expert review. Urologists should consider sending such cases for consultation to attempt to resolve the diagnosis as either definitively benign or malignant before subjecting the patient to repeat biopsy.
- Tumor volume measured in the radical prostatectomy specimen does not independently predict postsurgical progression once grade, pathologic stage, and margins are taken into account and should not be required for routine pathologic analysis.
- Gleason grade, whether it is assessed on needle biopsy, transurethral resection, or radical prostatectomy specimens, remains one of the most influential prognostic factors.

demonstrating the adverse effect of prostatic stromal infiltration (Esrig et al, 1996). **Extensive sampling of the periurethral area in cystoprostatectomy specimens performed for urothelial carcinoma is necessary to identify and to evaluate the prostate for urothelial carcinoma.**

Finally, one may find direct invasion from bladder urothelial carcinoma into the stroma of the prostate. The distinction between poorly differentiated urothelial carcinoma and poorly differentiated adenocarcinoma of the prostate can be difficult. Approximately 95% of poorly differentiated prostatic adenocarcinomas show PSA staining, although it may be focal (Chuang et al, 2007). In some cases of poorly differentiated prostatic adenocarcinomas, there may be weak or negative PSA staining where the tumor reacts to a greater degree with newer prostate specific markers, including prostate specific membrane antigen (PSMA), p501S (Prostein), and NKX 3.1 (Chuang et al, 2007). However, the lack of immunoreactivity to prostate specific markers in a poorly differentiated tumor within the prostate, especially if present in limited amount, does not exclude the diagnosis of a poorly differentiated prostatic adenocarcinoma. Although CK7 and CK20 are more frequently seen in urothelial carcinoma as compared to adenocarcinoma of the prostate, they may also be positive in adenocarcinoma of the prostate. Markers that label urothelial carcinoma and not prostate carcinoma include uroplakin and thrombomodulin (49% to 69% sensitivity) and TP63 and high molecular weight cytokeratin (83% to 90% sensitivity) (Chuang et al, 2007).

Miscellaneous Malignant Tumors

Primary prostatic lymphoma without lymph node involvement appears to be much less common than secondary infiltration of the prostate (Bostwick and Mann, 1985). The most common form of leukemic involvement of the prostate is that of chronic lymphocytic leukemia, although monocytic, granulocytic, and lymphoblastic leukemias have also been found in the prostate (Dajani and Burke, 1976).

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chapter 97

Ultrasonography and Biopsy of the Prostate

Edouard J. Trabulsi, MD, FACS ● Ethan J. Halpern, MD, MSCE ● Leonard G. Gomella, MD, FACS

Ultrasonographic Anatomy of the Prostate
Gray-Scale Transrectal Ultrasonography (TRUS)
Prostate Biopsy Techniques and Outcomes
Advanced Ultrasonographic Techniques for Prostate Imaging

Deaths due to prostate cancer in the United States were estimated to be almost 29,000 in 2008, representing a 25% decrease in the mortality rate compared with a decade ago (Jemal et al, 2008). Although the reasons for this improvement are often debated, early prostate cancer detection programs have likely played a role. Early detection has benefited greatly from prostate-specific antigen (PSA) screening efforts, the introduction and refinement of systematic transrectal ultrasonography (TRUS)–guided prostate biopsy techniques, and increased public awareness about prostate cancer.

TRUS of the prostate, first described by Watanabe and colleagues (1968), **expanded to routine clinical use with improvements in ultrasound technology and the introduction of the TRUS-guided systematic sextant biopsy protocol by Hodge and associates** (Hodge et al, 1989a, 1989b). Concurrent with improved biopsy techniques, the use of PSA screening increased the number of men undergoing early prostate cancer screening and prostate biopsy, with estimates as high as 800,000 biopsies annually in the United States alone (Halpern and Strup, 2000). Given the prevalence of prostate cancer and the frequency with which TRUS-guided prostate biopsies are performed, significant efforts have been focused on determining the appropriate indications for biopsy and the ideal technique by which to image and biopsy the prostate.

TRUS technology has become a mainstay of many image-guided prostate interventions, including prostate biopsy, brachytherapy, cryotherapy, and high-intensity focused ultrasonography (HIFU), as well as being used in the evaluation of appropriate patients for treatment of benign prostatic hyperplasia (BPH) (Beerlage, 2003). Fiducial gold seeds are being placed under ultrasound guidance to verify and correct the position of the prostate during megavoltage irradiation (Linden et al, 2009). In this chapter our focus is primarily on the use of TRUS and biopsy techniques for the diagnosis of prostate cancer.

ULTRASONOGRAPHIC ANATOMY OF THE PROSTATE

The prostate lies between the bladder neck and the urogenital diaphragm, just anterior to the rectum, an ideal position to be imaged by TRUS. The prostate gland is traditionally described based on a pathologic zonal architecture. These divisions consist of the anterior fibromuscular stroma (AFS) that is devoid of glandular tissue, transition zone (TZ), central zone (CZ), periurethral zone, and peripheral zone (PZ). Unfortunately, these regions are not visible sonographically as distinct entities (Fig. 97–1).

However, the TZ may often be discernible from the PZ and CZ, particularly in glands with significant BPH. Located posteriorly, the normal CZ and PZ, from which a majority of adenocarcinomas arise, have a homogeneous echogenic appearance, whereas the anteriorly situated TZ is more heterogeneous. **Frequently, calcifications along the surgical capsule known as "corpora amylacea" highlight the plane between the PZ and TZ** (Halpern, 2002). **Small, multiple diffuse calcifications are a normal, often incidental ultrasonographic finding in the prostate and represent a result of age rather than a pathologic entity.** Larger prostatic calculi associated with symptoms may be related to underlying inflammation and require further evaluation and, possibly, treatment (Geramoutsos et al, 2004).

The prostatic urethra traverses the length of the gland in the midline and thus must be imaged in the sagittal plane to be simultaneously viewed along its entire course (Fig. 97–2A and B). The distended urethral lumen has a hypoechoic appearance, whereas periurethral calcifications may produce a thin echogenic outline. The smooth muscle of the internal sphincter extends from the bladder neck, encircling the urethra to the level of the verumontanum. These muscle fibers may be visualized sonographically as a hypoechoic ring around the upper prostatic urethra, giving it a funneled appearance proximally as it arises from the bladder neck. On reaching the verumontanum the urethra angles anteriorly and runs through the remainder of the gland to exit at the apex of the prostate. This angle gives the prostatic urethra an anteriorly concave appearance when viewed along its entire course in the sagittal plane.

The paired seminal vesicles (SVs) are positioned posteriorly at the base of the prostate (Fig. 97–2C). **They have a smooth, saccular appearance and should be symmetrical. The normal SV measures 4.5 to 5.5 cm in length and 2 cm in width.** A cystic SV mass is presumptively benign, whereas a solid lesion has a small probability of being malignant, especially if the patient

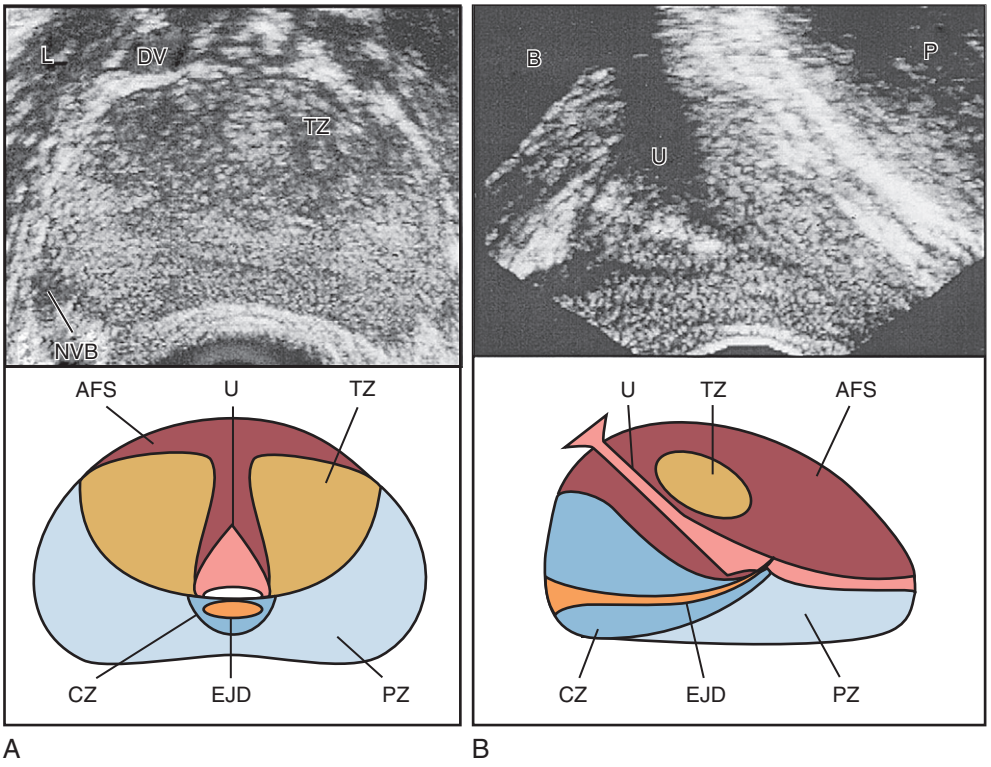


Figure 97–1. Normal prostate ultrasound images *(top)* with diagrams *(bottom)* at approximately the level of the verumontanum demonstrating zonal anatomy. **A,** Transverse view. **B,** Sagittal view. AFS, anterior fibromuscular stroma; CZ, central zone; DV, dorsal vein complex; EJD, ejaculatory ducts; NVB, neurovascular bundle; L, levator muscles; PZ, peripheral zone; TZ, transition zone; U, urethra.

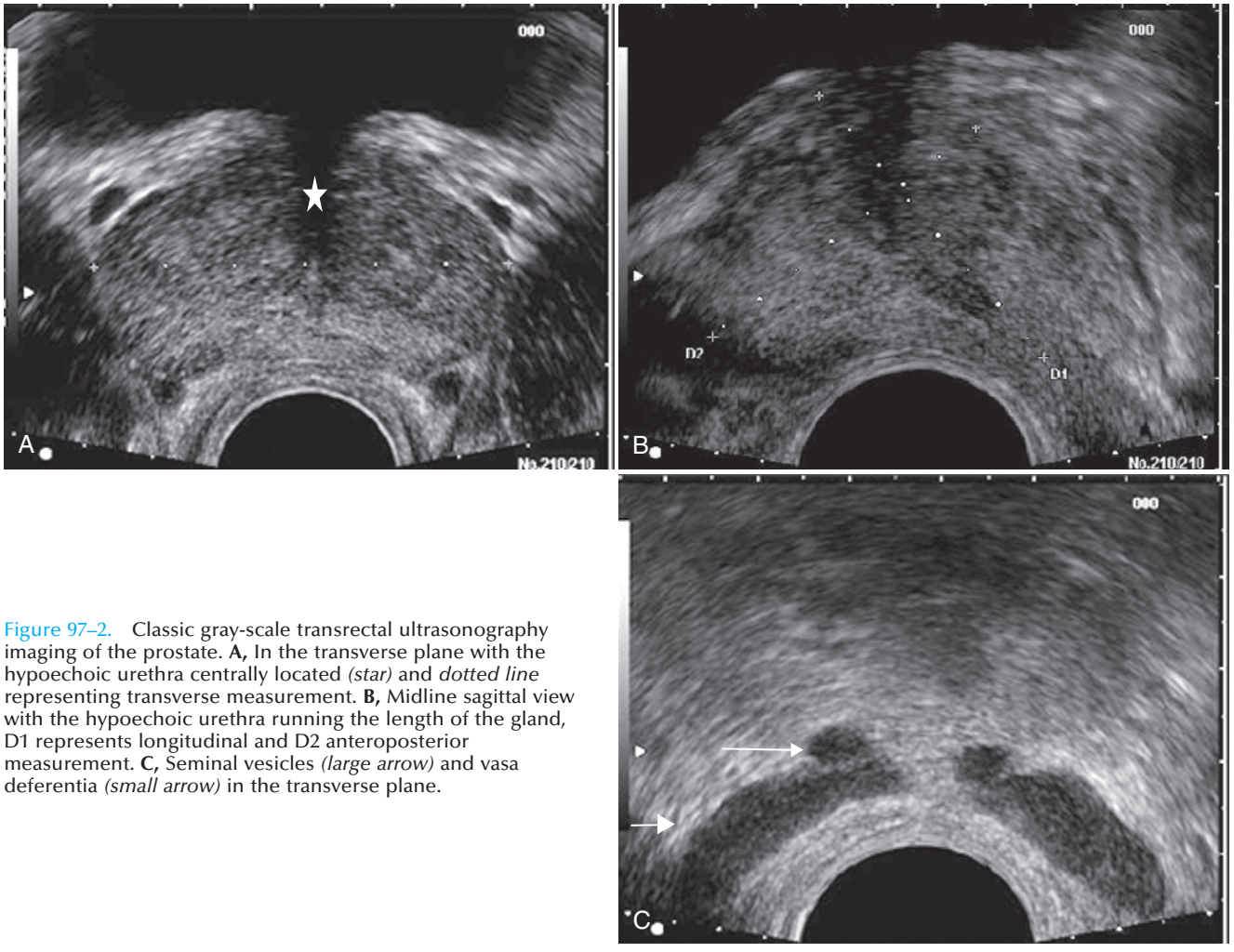


Figure 97–2. Classic gray-scale transrectal ultrasonography imaging of the prostate. **A,** In the transverse plane with the hypoechoic urethra centrally located *(star)* and *dotted line* representing transverse measurement. **B,** Midline sagittal view with the hypoechoic urethra running the length of the gland, D1 represents longitudinal and D2 anteroposterior measurement. **C,** Seminal vesicles *(large arrow)* and vasa deferentia *(small arrow)* in the transverse plane.

has a primary neoplasm elsewhere. Schistosomiasis should be considered when making a differential diagnosis in patients who live in areas where infestation is endemic with a solid SV mass (Al-Saeed et al, 2003). In the transverse plane, the vasa deferentia course just above their ipsilateral SV before diving caudally toward the prostate near the midline. Here they lie just medial to the tapering ipsilateral SV before the two structures fuse to form an ejaculatory duct. The ejaculatory ducts (occasionally seen as a hypoechoic structure) enter the gland posteriorly and empty into the urethra at the verumontanum (see Fig. 97–2C). Their course parallels that of the prostatic urethra distal to the verumontanum.

GRAY-SCALE TRANSRECTAL ULTRASONOGRAPHY (TRUS)

Gray-scale TRUS has become the most common imaging modality for the prostate. Most commonly used for prostate cancer detection, TRUS may also be used in the evaluation of other conditions such as infertility (see Chapter 21). Although the role of TRUS is expanding in directing the biopsy of prostate cancer, the role of staging localized prostate cancer using TRUS is very limited (Onur et al, 2004).

Commercially available endorectal probes are available in both side- and end-fire models and transmit frequencies of 6 to 10 MHz. Most modern ultrasound machines have optimized self-programming for TRUS and biopsy. Some newer biplane probes provide simultaneous sagittal and transverse imaging modes. Probes provide a scanning angle approaching 180 degrees to allow simultaneous visualization of the entire gland in both the transverse and sagittal planes. Increasing frequency yields increased resolution. As the frequency of the probe is increased, the portion of the image that is in focus (*focal range*) is closer to the transducer (Kossoff, 2000). The commonly used 7-MHz transducer produces a high-resolution image with a focal range from 1 to 4 cm from the transducer (best for PZ where most cancers arise). Lower-frequency transducers (e.g., older 4-MHz transducers) have a focal range from 2 to 8 cm but at lower resolution. Lower-frequency transducers improve anterior delineation of large glands, increasing the accuracy of volume measurements, but provide poor internal architecture visualization. **Acoustic properties of soft tissue are similar to those of water, but clinically useful ultrasound energy does not propagate through air. For this reason, a water-density substance, termed a *coupling medium*, is used.** The coupling medium, usually sonographic jelly or lubricant, is placed between the probe and the rectal surface. If the probe is covered with a protective condom, the coupling medium is placed between the probe and the condom, as well as between the condom and the rectal surface.

Techniques

The complete TRUS evaluation of the prostate includes scanning in both the sagittal and transverse planes to obtain a volume calculation. The CZ and PZ are inspected for hypoechoic lesions and contour abnormalities, and the SVs and vasa deferentia are fully visualized.

Machine Settings

The image magnification is adjusted so that most of the prostate is visible without the image being too small to allow detection of abnormalities. In general, the magnification is low during prostate measurements so that the entire gland is seen. During biopsies, magnification is maximal for visualization of needle passage. The ultrasonographer can manually alter the brightness (or gain) slightly with each new patient, and occasionally during imaging of different areas within the same prostate. **The optimal brightness setting results in a medium-gray image of the normal PZ. This gray tone serves as the reference point for judging lesions as hypoechoic (darker than the normal PZ), isoechoic (similar to the normal PZ), hyperechoic (lighter than the normal PZ), or anechoic (completely black).**

Probe Manipulation

Patients are typically scanned in the left lateral decubitus position (see Patient Positioning later). **TRUS should be performed in both the transverse and the sagittal planes.** There are two approaches to probe manipulation for transverse imaging (see Fig. 97–2A). With radial and some biplane probes, advancing the probe cephalad into the rectum images the prostate base, the SVs, and the bladder neck. Pulling the probe caudally toward the anal sphincter images the prostatic apex and proximal urethra. Transverse imaging with end-fire, side-fire, and some biplane probes is accomplished by angling the handle of the probe right or left using the anal sphincter as a fulcrum (see Fig. 97–2B). Angling the probe toward the scrotum produces more cephalad images, and angling the probe toward the sacrum produces more caudal images. There are also two approaches to probe manipulation for sagittal imaging. One method is rotation of the probe. Clockwise rotation yields images of the left side of the prostate, and counterclockwise rotation yields images of the right side. Alternatively, sagittal imaging can be accomplished by angling the probe up or down using the anal sphincter as a fulcrum. In the left lateral decubitus position, angling the handle of the probe down (toward the floor) images the right side of the prostate, and angling the handle of the probe up (toward the ceiling) images the left side. Urologists often prefer angling the probe because this method is similar to manipulation of a cystoscope and is less uncomfortable for the patient.

Volume Calculations

Prostate volume can be calculated through a variety of formulas. Volume calculation requires measurement of up to three prostate dimensions. In the axial plane, the transverse and anteroposterior (AP) dimensions are measured at the point of widest transverse diameter (see Fig. 97–2A and B). The longitudinal dimension is measured in the sagittal plane just off the midline, because the bladder neck may obscure the cephalad extent of the gland (see Fig. 97–2B). Most formulas assume that the gland conforms to an ideal geometric shape: either an ellipse ($\pi/6 \times$ transverse diameter $\times$ AP diameter $\times$ longitudinal diameter), sphere ($\pi/6 \times$ transverse diameter^3), or a prolate (egg-shaped) spheroid ($\pi/6 \times$ transverse diameter$^2 \times$ AP diameter). Despite the inherent inaccuracies that arise from these geometric assumptions, all formulas reliably estimate gland volume and weight, with correlation coefficients greater than 0.90 with radical prostatectomy specimen weights, because 1 cm^3 equals approximately 1 g of prostate tissue (Terris and Stamey, 1991). **The mature average prostate is between 20 and 25 g and remains relatively constant until about age 50, when the gland enlarges in many men** (Griffiths, 1996).

When a more accurate determination of gland volume is required, such as during brachytherapy, planimetry may be employed. With the patient in the lithotomy position, the probe is mounted to a stepping device, and serial transverse images are obtained at set intervals (e.g., 3 to 5 mm) through the entire length of the gland. The surface area of each serial image is determined, and the sum of these measurements is then multiplied by total gland length to yield the prostate volume.

Once gland volume has been obtained, one can calculate derivatives such as the PSA density (PSAD = serum PSA/gland volume). An elevated PSAD of the entire gland has been shown to have a sensitivity and specificity of 75% and 44%, respectively, for predicting a positive cancer diagnosis on repeat biopsy (Djavan et al, 2000). Unfortunately, there is high interoperator and intraoperator variability in PSAD determinations, and similar predictive information can now be obtained using serum free:total PSA (Djavan et al, 2003).

Cystic Lesions of the Prostate

Cystic prostatic structures are common on TRUS. Simple cysts have the same sonographic appearance as in any other part of the body: They are thin walled, anechoic, and show acoustic enhancement posterior to the cyst. Prostatic cysts may be congenital or acquired but are rarely clinically significant regardless of etiology.

Congenital prostatic cystic lesions may arise from either müllerian (müllerian duct cysts and prostatic utricles) or wolffian (ejaculatory duct and seminal vesicle cysts) structures. An enlarged prostatic utricle represents a diverticular projection from the posterior urethra at the level of the verumontanum (Cochlin, 2002) and appears as a midline anechoic structure. These are associated with genital anomalies, including hypospadias (most common), ambiguous genitalia, undescended testes, and congenital urethral polyps (Gregg and Sty, 1989). Müllerian duct cysts also appear as midline anechoic lesions that result from failure of the müllerian ducts to fuse with the urethra. They are generally ovoid to pear shaped with the cyst neck oriented toward the verumontanum. When müllerian duct cysts are present, men should be evaluated for unilateral renal agenesis (McDermott et al, 1993).

Lateral paraprostatic cystic structures include seminal vesicle and vas deferens cysts (wolffian in origin). Ejaculatory duct cysts are typically small, lie off of the midline, and may accompany ejaculatory duct obstruction/obliteration with azoospermia (Fig. 97–3A and B). Seminal vesicle cysts can be caused by congenital or acquired obstruction of the ejaculatory duct and are associated with cystic renal disease; up to two thirds of men with seminal vesicle cysts may also have renal agenesis (King et al, 1991). Acquired cysts of the TZ result from hemorrhagic degeneration of BPH nodules (Hamper et al, 1990), whereas those of the outer gland have no proven etiology.

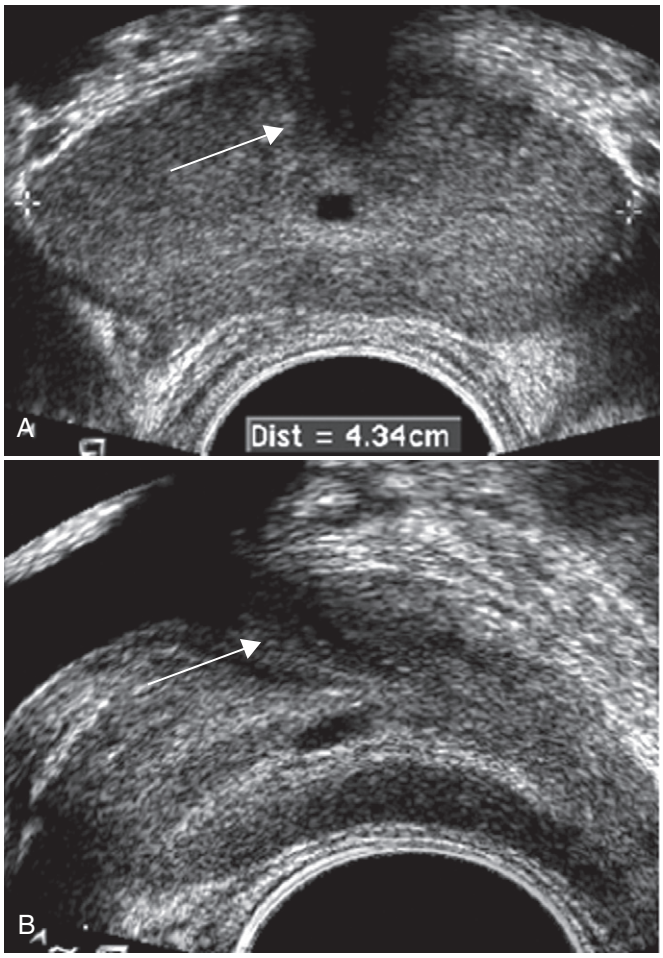


Figure 97–3. A hypoechoic midline cystic structure *(arrow)* arising from the ejaculatory duct is shown in the transverse **(A)** and sagittal **(B)** planes and demonstrates through-transmission classic for simple cysts.

Prostate Cancer Imaging on TRUS

All hypoechoic lesions within the PZ should be noted and included in the biopsy material (Fig. 97–4). The lack of a distinct hypoechoic focus does not preclude proceeding with biopsy, because 39% of all cancers are isoechoic and up to 1% of tumors may be hyperechoic on conventional gray-scale TRUS (Shinohara et al, 1989). Despite the higher prevalence of cancers discovered in prostates with hypoechoic areas, the hypoechoic lesion itself was not associated with increased cancer prevalence compared with biopsy cores

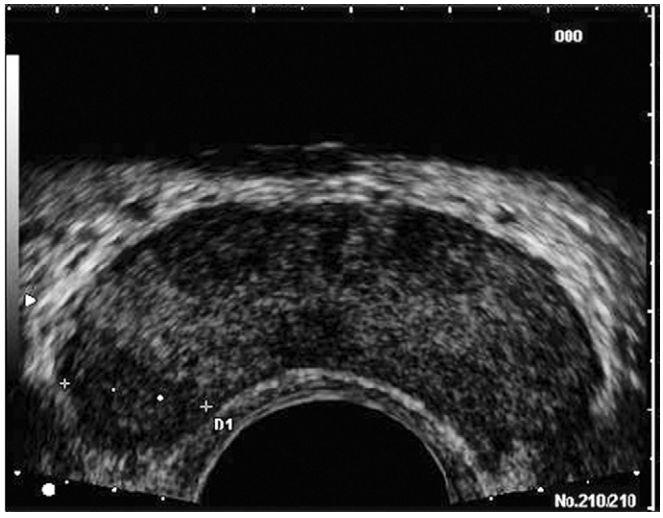


Figure 97–4. Classic hypoechoic peripheral zone (PZ) lesion *(dotted line)* in the right midgland that transrectal ultrasonography–guided biopsy proved to be a Gleason 3 + 3 = 6 adenocarcinoma.

from isoechoic areas in a contemporary series of almost 4000 patients (Onur et al, 2004). Furthermore, other disease processes, such as granulomatous prostatitis (Terris et al, 1997a), prostatic infarct (Purohit et al, 2003), and lymphoma (Varghese and Grossfeld, 2000), may all produce hypoechoic lesions. TZ BPH nodules are typically hypoechoic but may contain isoechoic or even hyperechoic foci. A hypoechoic lesion is malignant in 17% to 57% of cases (Frauscher et al, 2002), highlighting the need to biopsy these lesions but recognizing they are not pathognomonic for cancer as once thought.

Any focal contour abnormalities along the outer edge of the gland and any asymmetries in echotexture from the PZ of one lobe to that of the other are noted. **Extracapsular extension of prostate cancer, although not well visualized if present as a microfocus, is suggested by a focal loss of the typically bright white periprostatic fat.**

TRUS Appearance after Treatment

External-beam radiation therapy typically decreases volume by 6 months after treatment. Irradiated prostates are diffusely hypoechoic, with poorly defined anatomy. Large hypoechoic tumors, particularly those not responding to therapy, show little change in echogenicity once irradiated, but smaller foci responding well to therapy tend to become isoechoic (Egawa et al, 1991). In general, TRUS findings correlate poorly with pathologic findings and outcomes in irradiated prostates.

With interstitial brachytherapy, there is initial postimplantation edema followed by long-term changes as with external-beam radiation therapy (Whittington et al, 1999). With an ideal permanent implant, seeds should be distributed evenly throughout the gland. These seeds are hyperechoic and demonstrate posterior shadowing. The prostate volume declines significantly after treatment, with a 37% size reduction at 1 year after treatment and over 50% reduction 8 years after implantation (Stone and Stock, 2007). This decline is unaffected by neoadjuvant hormonal therapy.

Androgen ablation with luteinizing hormone–releasing hormone (LHRH) analogs will cause an average 30% volume decrease with androgen deprivation in prostates with and without cancer (Whittington et al, 1999). The decrease ranges up to 60% in large glands and as little as 10% in small glands. Volume decreases by approximately 21% at 6 months using agents such as finasteride (Marks et al, 1997).

Postradical prostatectomy TRUS is considered normal if there is smooth tapering of the bladder neck to the urethra (Kapoor et al, 1993). Many patients demonstrate a nodule of tissue anterior to the anastomosis, representing the ligated dorsal vein complex (Goldenberg et al, 1992). Any other hyperechoic or hypoechoic lesions or interruptions of the retroanastomotic fat plane are considered suspicious (Kapoor et al, 1993). Hypoechoic lesions have been reported in 75% to 95% of patients with locally recurrent cancer, and color Doppler has been used to improve cancer detection in the prostatic fossa (Sudakoff et al, 1996; Tamsel et al, 2006). Patients with detectable PSA who are candidates for salvage radiation therapy were once considered for routine biopsy of the anastomotic area. **Biopsy of the anastomotic region with PSA recurrence in the absence of a palpable nodule is not usually informative** (Scattoni et al, 2004). However, biopsy of an abnormality seen on TRUS, even with a normal digital rectal exam (DRE), can be diagnostic of locally recurrent disease (Naya et al, 2005).

TRUS and Other Malignancies

Prostatic involvement with transitional cell carcinoma (TCC) from the bladder is generally not detectable by TRUS, but 71% of prostatic stromal TCC lesions are hypoechoic. Prostatic TCC detected by TRUS must be confirmed by biopsy, because granulomas resulting from instillation of bacille Calmette-Guérin are common in TCC patients and are also hypoechoic (Terris et al, 1997a).

Extension to the prostate from the bladder, or urethral squamous cell carcinoma (SCC), is much more common than is primary prostatic SCC. Prostatic SCC appears as an irregular, anterior mass demonstrating relative hyperechogenicity (Terris, 1999).

Adenoid cystic/basal cell carcinoma of the prostate is rare but potentially fatal. Histologically, cribriform or adenoid cystic patterns predominate. Numerous cystic glands give this tumor an unusual appearance on TRUS, characterized by multiple, evenly distributed, small, anechoic cysts (Iczkowski et al, 2003).

Prostatic sarcoma is a rare complication of prostatic irradiation, and the TRUS appearance is typified by an irregular, hypoechoic mass with an anechoic area consistent with necrosis (Terris, 1998). Unlike radiation-induced sarcoma, the echogenicity of rhabdomyosarcoma is similar to that of normal prostate tissue.

Hematologic and lymphoid malignancies involving the prostate are generally not visualized with TRUS (Terris and Freiha, 1998). Biopsies may demonstrate a lymphocytic infiltrate, but this is often attributed to chronic inflammation if no suspicion of nonprostate malignancy exists.

PROSTATE BIOPSY TECHNIQUES AND OUTCOMES

Indications for Prostate Biopsy

Before TRUS improvements and serum PSA testing became widespread, clinicians relied mainly on digital rectal examination to establish a suspicion of prostate cancer and performed digitally

Key Points: Gray-Scale Transrectal Ultrasonography (TRUS)

- TRUS technology has become a mainstay of many image-guided prostate interventions, including prostate biopsy, brachytherapy, cryotherapy, and high-intensity focused ultrasonography (HIFU).
- The classic zonal anatomy of the prostate is not evident on TRUS, but the peripheral zone (PZ) may typically be distinguished from the transition zone (TZ), allowing biopsies to be reliably aimed toward the more commonly cancer-bearing PZ.
- Typically, benign cystic lesions of the prostate demonstrate thin-walled architecture with sonographic through-transmission and may become symptomatic if infected.
- Several formulas exist for determining prostate volume on TRUS. For highly accurate volume determinations, such as for brachytherapy, planimetry is required.
- Hypoechoic foci seen on gray-scale TRUS should be considered suggestive of adenocarcinoma of the prostate and included in the biopsy specimen. However, up to 39% of cancers are not visible on routine gray-scale ultrasound imaging.

directed lesional biopsies. **Today, PSA-based screening of asymptomatic men has resulted in the adaptation of TRUS biopsy as the standard of care for routine prostate biopsy.** The presence of focal nodules on digital rectal examination still will prompt a biopsy using the TRUS technique regardless of PSA levels. **TRUS-directed prostate needle biopsy remains the gold standard for diagnosis of prostate cancer.**

Early prostate cancer detection has been markedly improved by PSA-based screening programs. These initiatives have been shown to significantly increase the rate of organ-confined and potentially curable disease (Catalona et al, 1993). **Currently, most clinicians recommend biopsy once a patient's serum PSA rises above 4.0 ng/mL, although significant research efforts are ongoing to identify the optimal PSA threshold to recommend prostate biopsy in the asymptomatic patient.** Evidence for lowering the PSA threshold from work by Catalona's group showed higher rates of organ-confined disease at the time of radical retropubic prostatectomy in samples from PSAs in the 2.6- to 4.0-ng/mL range (Krumholtz et al, 2002). **These findings have led many urologists to now recommend prostate biopsy to men younger than 60 years of age once their PSA level rises above 2.5 ng/mL.** Despite this downward shift in the PSA cutoff for younger men, there remains a general trend toward allowing older men (70 years or older) to have slightly higher "normal" PSAs, in the range of 5.5 to 6.5 ng/mL, although this is not universally accepted (American Urological Association, 2000; Scardino, 2005). **Subsequent data from the Prostate Cancer Prevention Trial have shown that there is no safe PSA threshold that can rule out prostate cancer in any age range** (Thompson et al, 2005). When examining men whose serum PSA was less than or equal to 4.0, significant numbers of men were diagnosed with prostate cancer at all PSA levels, with an overall prostate cancer detection rate of 15% for all men with a value less than 4.0, and nearly 15% having a Gleason score of 7 or greater (Thompson et al, 2004).

Adjuncts to serum PSA testing have been advocated to improve the performance characteristics of PSA for prostate cancer detection, including measuring the free:total PSA, PSA velocity, PSA density (PSAD), and PSAD of the transition zone (PSAD-TZ) (Djavan et al, 2002). For patients with a serum PSA value between 4.0 and 10.0 ng/mL, using a percentage of free PSA threshold of less than 25% allowed detection of 95% of cancers while eliminating 20% unnecessary biopsies, and within this group the risk of prostate cancer increased dramatically as the percentage of free PSA level declined (Catalona et al, 1998).

Regardless of initial PSA value, a PSA velocity greater than 0.75 ng/mL/year is frequently associated with prostate cancer and warrants biopsy (Carter et al, 1992). Lower PSA velocity ranges, as low as 0.35 ng/mL/year, may be indicative of occult prostate cancer (Carter et al, 2006). The clinical utility of PSA velocity to detect clinically significant prostate cancer remains controversial, however, with a recent European Organization for Research and Treatment of Cancer (EORTC) study indicating the PSA velocity, on multivariable analysis, was not an independent predictor of detecting prostate cancer or clinically significant prostate cancer on transrectal biopsy (Wolters et al, 2009). An elevated PSAD and PSAD-TZ have both been shown to increase the likelihood of diagnosing prostate cancer on repeat biopsy (Djavan et al, 2000). The indications for TRUS and prostate biopsy are rapidly evolving and being continually refined (Table 97–1). Details concerning screening for prostate cancer and the role of prostate biopsy are discussed in Chapter 99.

Table 97–1.

Commonly Cited Recommendations for Transrectal Ultrasonography (TRUS) and/or Biopsy

TRUS without Biopsy

- Treatment planning volume measurements: brachytherapy, cryotherapy, benign prostatic hyperplasia therapy (e.g., transurethral microwave thermotherapy, radiofrequency ablation)
- Volume measurement during hormonal downsizing for external-beam radiation therapy or brachytherapy
- Placement of fiducial markers for external-beam radiation therapy
- Evaluation of azoospermia: ejaculatory duct cysts, seminal vesicle cysts, etc.
- Therapeutic aspiration or unroofing of prostatic cysts; drainage of prostatic abscess

TRUS-Directed Biopsy

- Diagnosis of suspected symptomatic prostate cancer (i.e., bone metastasis, cord compression)
- Screening for prostate cancer in asymptomatic patient > age 50 with > a 10-year life expectancy (if strong family history or if African-American, consider screening at age 45)
  Prostate nodule or significant prostate asymmetry regardless of PSA level
  PSA > 4.0 ng/dL regardless of age
  In men < age 60 to 65 years, consider biopsy if PSA > 2.5 ng/dL
  If PSA > 0.6 ng/dL at age 40
  Increased PSA velocity (>0.75 ng/dL/year)
  Free PSA in considering initial biopsy with PSA < 10 ng/mL: >25% no biopsy; >10% and <15%, consider biopsy; <10%, biopsy
- Prior to intervention in symptomatic benign prostatic hyperplasia (e.g., surgical therapy or initiation of 5α-reductase inhibitors)
- Prior to cystoprostatectomy or orthotopic urinary diversion
- To diagnose failed radiation therapy before use of second-line therapy
- Follow-up biopsy (3-6 months) after diagnosis of high-grade PIN or ASAP

ASAP, atypical small acinar proliferation; PIN, prostatic intraepithelial neoplasia; PSA, prostate-specific antigen.

Data from American Urological Association (AUA, 2000) and National Comprehensive Cancer Network (Scardino, 2005).

Prostate biopsy may also be indicated on the basis of the pathologic analysis of previous biopsy specimens. In men who have undergone prostate biopsy and are found to have only high-grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP), a follow-up biopsy should be performed. HGPIN represents a premalignant lesion and carries a 23% to 35% risk of diagnosing prostate cancer on subsequent biopsy (Davidson et al, 1995; Kronz et al, 2001). The natural history of ASAP is less well defined than that of HGPIN, but, if ASAP is present in the initial biopsy specimen, the risk of diagnosing prostate cancer on subsequent biopsy is significantly increased (Iczkowski et al, 1998; Ouyang et al, 2001). **Thus irrespective of follow-up PSA values, current recommendations are to rebiopsy all patients with either HGPIN or ASAP in their initial biopsy specimen within 3 to 6 months.**

Contraindications to Prostate Biopsy

Significant coagulopathy, painful anorectal conditions, severe immunosuppression, and acute prostatitis are all contraindications to prostate biopsy.

Preparing Patients for Biopsy

Patients should be informed of the risks and benefits of the procedure and provide informed consent. All anticoagulant therapy (warfarin, clopidogrel, aspirin/nonsteroidal anti-inflammatory drugs [NSAIDs], herbal supplements) should be stopped 7 to 10 days before prostate biopsy. For those patients with underlying coagulopathy or who are on warfarin, prostatic biopsy should not be performed until the international normalized ratio has been corrected below 1.5. A small amount of urine in the bladder can facilitate the examination.

Antibiotic Prophylaxis

A wide variety of prophylactic regimens have been studied using both oral and intravenous antibiotics, with widely varying opinions of the use of antibiotics and the choice of agents. **The American Urological Association Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis advocates antibiotic prophylaxis prior to transrectal prostate biopsy** (Wolf et al, 2008). Our current practice is to give patients a dose of an oral fluoroquinolone 30 to 60 minutes before biopsy and continue therapy for 2 to 3 days. By using similar protocols, recent large studies have reported minimal infectious complications, although bacteremia/sepsis still occurs in 0.1% to 0.5% of patients (Djavan et al, 2001b; Raaijmakers et al, 2002). The postbiopsy duration of antibiotics also remains controversial even in those who agree the antibiotics are indicated; single-dose oral fluoroquinolone prophylactic regimens demonstrated equivalent efficacy to 3-day regimens in preventing infections (Kapoor et al, 1998; Sabbagh et al, 2004; Wolf et al, 2008). For those patients at risk of developing endocarditis or infection of prosthetic joints, pacemakers, and automated implanted cardiac defibrillators, prophylaxis should consist of intravenous ampicillin (vancomycin, if penicillin allergic) and gentamicin preoperatively, followed by 2 to 3 days of an oral fluoroquinolone.

Cleansing Enema

We routinely have patients self-administer a cleansing enema at home before biopsy. **This practice decreases the amount of feces in the rectum, thereby producing a superior acoustic window for prostate imaging.** However, many clinicians may elect not to use an enema because this option may allow more spontaneous performance of a prostate biopsy. The enema's effect on reducing infections is debatable, but it seems logical that a cleansing enema and empty rectal vault may reduce bacterial seeding of the prostate.

Analgesia

Comments on periprocedural pain control using topical lidocaine jelly have been published (Issa et al, 2000; Obek et al, 2004); in our experience and in the literature, this provides only suboptimal analgesia. **Data now suggest that infiltration anesthesia around the nerve bundles with local anesthetic may provide excellent pain control, which is increasingly important when using extended biopsy techniques** (Berger et al, 2003; Trucchi et al, 2005). A local prostatic block is achieved using 2% lidocaine, a long spinal needle (7-inch, 22-gauge), and TRUS guidance along the biopsy channel of the transducer. Multiple variations exist for the infiltration of local anesthetic for transrectal biopsy (Nash et al, 1996; Soloway and Obek, 2000). We have found that injecting 5 mL of lidocaine at the level of the seminal vesicles near the bladder base, at the hyperechoic fat pad that demarcates the junction of the seminal vesicles and the prostate bilaterally, produces an excellent block. Other approaches include infiltration of 10 mL starting at the junction of the seminal vesicles and infiltration along the lateral aspect of the prostate from base to apex. **Direct infiltration into the prostate (intraprostatic injection) can augment the anesthetic benefit seen with periprostatic injection** (Lee et al, 2007; Cam et al, 2008). One must be cautious, however, to avoid direct intravascular injection, because of the risk of systemic lidocaine absorption. Local anesthesia for transperineal biopsies should include infiltration of the skin and subcutaneous tissues of the perineum initially. Ultrasound guidance may then be employed to aid infiltration of deeper tissues along the anticipated tracts of the biopsy needle. Postbiopsy analgesic regimens, if used, should avoid aspirin and NSAIDs because of increased risk of bleeding.

Patient Positioning

Patients are usually placed in the left lateral decubitus position with knees and hips flexed 90 degrees. An armboard attached parallel to the table and a pillow between the knees helps maintain this position. The buttocks should be flush with the end of the table to allow manipulation of the probe and biopsy gun without obstruction. If necessary, the right lateral decubitus or lithotomy position can be used. **The lithotomy position is used by some clinicians and is preferred for transperineal biopsies, brachytherapy treatment planning, or placement of fiducial gold markers for external-beam therapy** (Dehnad et al, 2003). Because the distribution of color Doppler flow within the prostate is dependent on patient position, the lithotomy position is preferred when color Doppler imaging is used to identify areas of hyperemia for targeted biopsy of the prostate (Halpern et al, 2002b).

Transrectal Prostate Biopsy Techniques

The prostate volume is assessed, and imaging of the prostate in both the transverse and sagittal planes is begun. The examination usually starts at the base of the gland and extends to the apex. Most modern ultrasound units are automatically set for optimal prostate visualization, and the TRUS gray-scale exam of the prostate is conducted as previously described, noting the location and characteristics of any lesions (i.e., hypoechoic, hyperechoic, calcifications, contour abnormalities, cystic structures).

A spring-driven, 18-gauge, needle core biopsy device or biopsy gun, which can be passed through the needle guide attached to the ultrasound probe, is most often used. Most ultrasound units provide best visualization of the biopsy needle path in the sagittal plane. Images are typically superimposed with a ruled puncture path that corresponds to the needle guide of the TRUS unit. The biopsy gun advances the needle 0.5 cm and samples the subsequent 1.5 cm of tissue with the tip extending 0.5 cm beyond the area sampled (Kaye, 1989). Therefore when sampling the PZ, the needle tip may be placed 0.5 cm posterior to the prostate capsule before firing; advancing the needle to or through the capsule can result in sampling of more anterior tissue, missing the most common location of cancers. Avoiding adjustment of the probe position while the biopsy needle is in contact with the rectal surface and applying pressure with the probe to compress the rectal mucosa before biopsy can help avoid rectal bleeding. Pressing the probe against the rectum also minimizes the discomfort of the biopsy needle traversing the rectal mucosa, similar to pulling the skin tight to minimize the discomfort of phlebotomy.

The biopsy sample is typically placed in 10% formalin or per local protocol. There is currently no uniformly accepted method for submission of the biopsy samples (e.g., all samples submitted individually or multiple samples placed in one container). Some pathologists believe strongly that each site should be specifically identified, because certain locations may be predisposed to cancer "look-alikes" (e.g., Cowper gland at the apex, seminal vesicles at the base) (Levin, 2004). At the very least, samples should be segregated into left- and right-sided containers or processed by local guidelines.

Sextant Biopsy

The original sextant biopsy scheme (one core, bilaterally, from the base, mid, and apex) significantly improved cancer detection for digital-directed biopsy of palpable nodules and ultrasound-guided biopsy of specific hypoechoic lesions (Hodge et al, 1989a, 1989b). Taken in the parasagittal plane, these cores sampled a portion of the PZ but also included a significant amount of tissue from the TZ, with subsequent studies of radical prostatectomy specimens demonstrating that the vast majority of adenocarcinomas arise in the posterolateral PZ (McNeal et al, 1988), thus explaining some of the false-negative results of standard sextant biopsy (Eskew et al, 1997).

Extended Core Biopsy Techniques

Modifications to the standard sextant biopsy scheme have focused on the importance of laterally directed cores (Terris et al, 1992). Numerous studies have shown improved cancer detection rates by incorporating additional laterally directed cores into the standard systematic sextant technique, ultimately taking anywhere from 8 to 13 cores (Eskew et al, 1997; Chang et al, 1998a; Levine et al, 1998; Babaian et al, 2000; Brossner et al, 2000; Presti et al, 2000; Durkan et al, 2002; Fink et al, 2003). Selected extended biopsy series are compared in Table 97–2. In a prospective study of 483 patients, Presti and colleagues (2000) found that adding laterally directed cores from the base and midgland bilaterally improved cancer detection from 80% with standard sextant to 96% with this 10-core scheme (only 4% of cancers were detected on the lesionally directed or TZ biopsy). **At present, 6 cores are considered inadequate for routine prostate biopsy for cancer detection.** Figure 97–5 depicts the originally proposed sextant technique and several common extended core biopsy strategies. TZ and SVs are not routinely sampled, because these regions have been shown to have consistently low yields for cancer detection at initial biopsy (Epstein et al, 1997; Terris et al, 1997b), but TZ and anteriorly directed biopsies may occasionally prove necessary to diagnose prostate cancer in those patients with persistently elevated PSA levels and prior negative biopsies (Mazal et al, 2001). **However, there may be a role for TZ biopsies in men with gland size of more than 50 mL, with an additional yield of 15% cancer detection in these larger prostates** (Chang et al, 1998b). Seminal vesicle biopsy is not routinely performed unless there is a palpable abnormality, with some authors recommending SV biopsy when the PSA value is greater than 30 or if brachytherapy is being considered (Gohji et al, 1995).

Table 97–2.

Increasing Prostate Cancer Detection Rates with Extended Core Biopsy Protocols

STUDY	NO. OF CORES	CANCER DETECTION RATE
Eskew et al, 1997	6	26.1%
	13	40.3%
Naughton et al, 2000	6	26%
	12	27%
Presti et al, 2000	6	33.5%
	8	39.7%
	10	40.2%
Babaian et al, 2000	6	20%
	11	30%

Repeat and Saturation Prostate Biopsy

Physicians are frequently presented with the dilemma of a patient who has had one or more negative prostate biopsies yet continues to have an elevated PSA value or abnormal digital rectal examination of concern for prostate cancer. Often these patients have undergone multiple biopsies despite the well-documented decline in cancer detection with each successive biopsy (Djavan et al, 2003). Keetch and coworkers (1994) reported an initial positive biopsy rate of 34% in 1136 men from their PSA-based prostate cancer screening program. Cancer detection rates then fell to 19%, 8%, and 7% on biopsy 2, 3, and 4, respectively. These findings were confirmed by results from the European Prostate Cancer Detection Study. **In this cohort of 1051 men with PSA values between 4.0 and 10.0 ng/mL, the initial cancer detection rate with sextant biopsy was 22%. Positive cores were then found in only 10%, 5%, and 4% of patients on subsequent biopsies 2, 3, and 4, respectively** (Djavan et al, 2001a).

These diminishing returns coupled with improved cancer detection rates on initial biopsy with extended core protocols have led some researchers to examine "saturation biopsy" techniques in this difficult subset of patients. In a study of 57 men with an average of two prior negative sextant biopsies, a cancer detection rate of 30% was obtained with an average of 22.5 cores per patient (Borboroglu et al, 2000). Similar protocols from the Mayo Clinic (Stewart et al, 2001) and Toronto (Fleshner and Klotz, 2002) demonstrated improved cancer detection rates. **A drawback to these techniques is that additional anesthetic requirements often require these "saturation"**

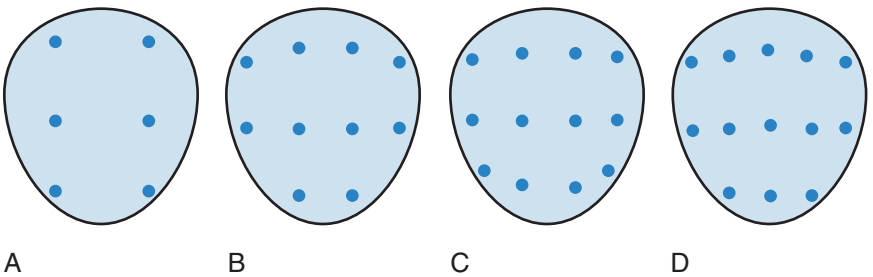


Figure 97–5. Various reported systematic biopsy schemes. **A,** Sextant biopsy scheme originally proposed by Hodge and associates (Hodge et al, 1989b). **B,** The 10-core biopsy of Presti and coworkers (2000). **C,** The 12-core, or double sextant, biopsy. **D,** The 13-core "5-region biopsy" of Eskew and colleagues (1997). Base is at the top of figure, apex is at bottom.

biopsies to be performed in a hospital setting. More recent reports question the benefit of a saturation biopsy scheme, considering the attendant increased cost and potential morbidity. In a reassessment of their previous work on saturation biopsy, investigators at the Mayo Clinic performed a large prospective study of standard systematic and saturation biopsy techniques and did not find a significant increase in prostate cancer detection (Ashley et al, 2008).

Our study suggests that equally improved cancer detection rates can be achieved in this setting using contrast medium–enhanced TRUS (CE-TRUS) and a targeted biopsy protocol of only 10 cores in an outpatient setting (Halpern et al, 2005), thereby minimizing the morbidity and costs associated with saturation biopsies. The use of the free and total PSA may also allow patient classifications of low probability or high probability of having prostate cancer with a PSA level less than 10 ng/mL and determine the need for additional prostate biopsy after an initial negative result (Catalona et al, 1998).

When should we stop ordering biopsies for the patient who has a high degree of suspicion for undiagnosed prostate cancer? Unfortunately there is no clear answer. By using available data from large series such as the European Prostate Cancer Detection Study, we can consider some reasonable recommendations to our patients. In this series of over 1000 men, despite differences in location and multifocality, pathologic and biochemical features of cancers detected on first and second biopsy were similar, suggesting similar biologic behavior. Cancers found on third and fourth biopsies had a lower grade, stage, and cancer volume compared with cancers on first and repeat biopsies. Morbidity of first and repeat biopsies was similar, whereas third and fourth biopsies had a slightly higher complication rate. **The use of a second prostate biopsy in all cases of a negative finding on initial biopsy appears justified. Third and fourth repeat biopsies, however, should only be obtained in selected patients with high suspicion of cancer and/or poor prognostic factors on the first or second biopsy** (Djavan et al, 2005).

Fine-Needle Aspiration Biopsy

The use of transrectal fine-needle aspiration (FNA) of palpable abnormalities of the prostate still is advocated in many countries outside the United States, because it is less expensive, faster, and easier to perform and results in lower morbidity than any other technique. High sensitivity, specificity, and efficacy depend on appropriate training in performing transrectal FNA of the prostate and in interpreting the smears (Perez-Guillermo et al, 2005). **Controversy exists as to whether FNA is as reliable as core biopsy for grading purposes** (Algaba et al, 1996).

Transperineal Prostate Biopsy

Transperineal biopsy offers an approach to the prostate in those patients lacking a rectum (e.g., surgical extirpation, congenital anomaly). The patient is positioned in dorsal lithotomy with the perineum shaved and prepared as for a sterile surgical procedure. An end-fire ultrasound transducer is used. Despite significant limitations in visualization using this technique compared with TRUS, the prostate can and should be imaged in both the coronal and sagittal planes with calculation of the gland volume. Focal PZ hypoechoic lesions are difficult to visualize through the transperineal window, as are the SVs. The urethra will appear as a hypoechoic midline structure and may be readily identified by following the corpus spongiosum proximally from the base of the penis. Once the boundaries of the gland have been clearly delineated in the coronal plane, six cores should be taken, three from either side of midline.

The diagnostic yield of transperineal ultrasound–guided prostate biopsy was compared with that of TRUS-guided biopsies in a routine biopsy setting (Vis et al, 2000). By using radical prostatectomy specimens with TRUS biopsy–detected prostate cancer, simulated transperineal biopsies were performed and transrectal biopsies were repeated. Significantly, 82.5% of the known tumors were detected with the longitudinal transperineal approach versus 72.5% of cancer detection with repeat transrectal biopsy. The authors postulate that the longitudinal orientation of their cores allows more efficient sampling of the PZ, thereby improving cancer detection. By using this approach in the repeat biopsy setting, researchers at Mayo Clinic in Jacksonville, Florida, obtained a mean of 21.2 cores (range, 12 to 41) in 210 men using a template perineal biopsy (Pinkstaff et al, 2005). The transperineal approach enhanced identification of transition zone cancers not detected by previous transrectal prostate biopsy in high-risk patients. **Conversely, in a recent Japanese randomized trial comparing transrectal and transperineal techniques for initial prostate biopsy, the cancer detection rate was similar for both, with higher complications noted in the transperineal approach** (Hara et al, 2008). Therefore the authors concluded that transrectal prostate biopsy should be the preferred technique for initial prostate biopsy.

Transurethral Prostate Biopsy

Transuretheral resection biopsy was once advocated for the diagnosis of TZ cancers or after negative TRUS sampling. In contemporary series, solitary TZ cancers, without concomitant peripheral zone tumors, are estimated to occur in less than 5% of prostate cancer patients (Pelzer et al, 2005). **With improved TRUS techniques including local anesthesia, the TZ can be adequately sampled, and the value of transurethral biopsy has been questioned for the vast majority of patients** (Bratt, 2006).

Risks and Complications of Prostate Biopsy

Postbiopsy Infections

Most infectious complications after TRUS biopsy are limited to symptomatic urinary tract infection and low-grade febrile illness, which can be readily treated with oral or intravenous antibiotics; however, rare case reports of fatal septicemia after prostate biopsy have been published (Breslin et al, 1978; Brewster et al, 1993; Bates et al, 1998; da Silva et al, 1999). Historical series prior to the routine use of antibiotic prophylaxis found bacteriuria in 32% to 36% of patients and bacteremia/febrile illness in 48% to 69% of patients undergoing TRUS biopsy (Brown et al, 1981; Crawford et al, 1982). **Recent studies show that 2% of patients will go on to develop a febrile urinary tract infection, bacteremia, or acute prostatitis and require hospitalization for intravenous antibiotics** (Kapoor et al, 1998; Lindert et al, 2000). Additional infections such as epididymitis have been reported infrequently (Donzella et al, 2004). **There is considerable concern, however, regarding the rising incidence of community-acquired antibiotic-resistant organisms resistant to standard fluoroquinolone prophylaxis** (Patel and Kirby, 2008).

Bleeding

Even with normal coagulation parameters, bleeding is the most common complication seen after prostate biopsy. As noted, any potential medications that can alter coagulation parameters, including herbal remedies, should be held for 5 to 7 days before biopsy and those on warfarin managed as noted. Two large European screening programs noted hematuria in 23% to 63% of men after sextant biopsy, with clot retention developing in 0.7% (Djavan et al, 2001b; Raaijmakers et al, 2002). Rectal bleeding is common and seen in 2.1% to 21.7% of patients (Enlund and Varenhorst, 1997; Djavan et al, 2001b). **Rectal bleeding is typically minor and readily controlled with direct pressure by the ultrasound probe or digitally; persistent brisk hematochezia may require anoscopic intervention for control.** Hematospermia, commonly seen postbiopsy, is of minimal clinical importance but can be cause for significant concern on the part of the patient if not discussed at the time of biopsy; 9.8% to 50.4% of men experience some blood in their ejaculate (Djavan et al, 2001b; Raaijmakers et al, 2002), which may persist for 4 to 6 weeks after prostate biopsy.

Other Complications

Excessive anxiety and discomfort from the endorectal probe may produce a moderate or severe vasovagal response in 1.4% to 5.3% of patients (Rodriguez and Terris, 1998; Djavan et al, 2001b) and may require termination of the procedure. Placing the patient in the Trendelenburg position and use of intravenous hydration usually resolve these symptoms, with further intervention as clinically indicated.

Acute urinary retention requiring temporary catheterization develops in 0.2% to 0.4% of patients after TRUS biopsy (Enlund and Varenhorst, 1997; Raaijmakers et al, 2002). Men with significantly enlarged glands and those with significant lower urinary tract symptoms (e.g., high International Prostate Symptoms Score), are more prone to develop retention (Rodriguez and Terris, 1998; Raaijmakers et al, 2002).

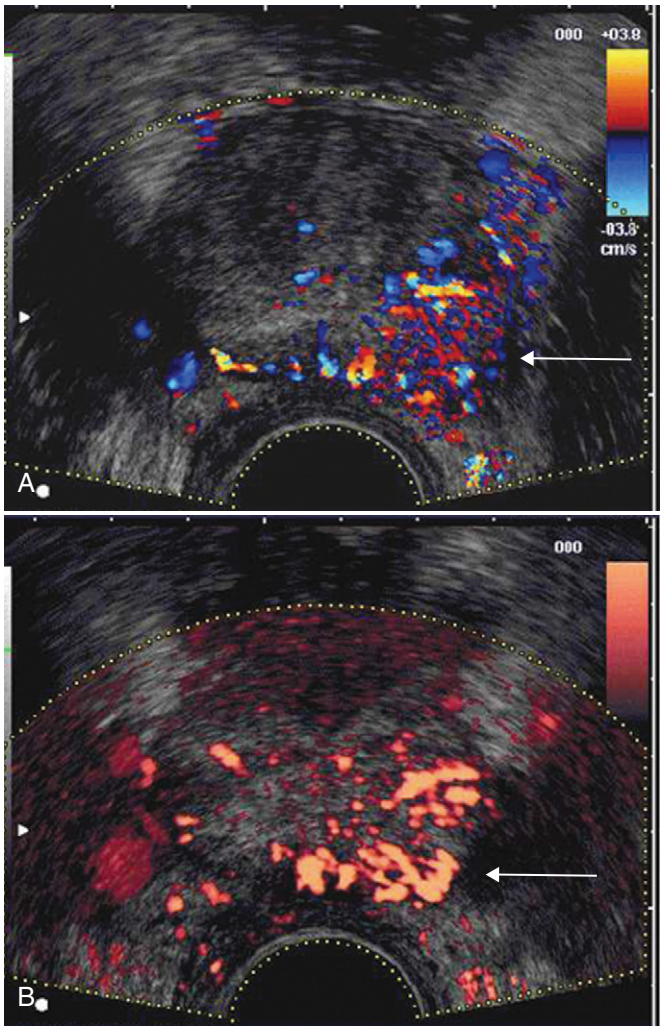


Figure 97–6. Color Doppler **(A)** transrectal ultrasonography (TRUS) and power Doppler **(B)** TRUS identify a Gleason 4 + 4 = 8 adenocarcinoma in the left midgland.

ADVANCED ULTRASONOGRAPHIC TECHNIQUES FOR PROSTATE IMAGING

Color and Power Doppler TRUS

Color Doppler imaging is based on the frequency shift in the reflected sound waves from the frequency of insonation and thus depicts the velocity of blood flow in a directionally dependent manner (Fig. 97–6A). **Color assignment is based on the direction of blood flow related to the orientation of the transducer receiving the signal; flow toward the transducer is depicted in shades of red and flow away in shades of blue; the color is not specific for arterial or venous flow.** Power Doppler imaging (also known as enhanced color Doppler, color amplitude imaging [CAI], or color angiography) uses amplitude shift to detect flow in a velocity and directionally independent manner (Bude and Rubin, 1996) (see Fig. 97–6B). The advantages of power Doppler imaging are its ability to detect slower flow and to have less reliance on the Doppler angle, making it more suitable for detection of prostate cancer neovascularity. Although power Doppler imaging offers improved sensitivity to small amounts of flow, neither modality has yet proved itself superior to the other for cancer detection. In 251 patients, Halpern and Strup (2000) found color Doppler sensitivity and specificity of 14.6% and 93.9%, respectively, to identify cancer. Whereas Doppler modes showed an improved diagnosis versus gray-scale TRUS, 45% of cancers still went unidentified by any sonographic modality. Others have shown increased cancer detection rates using Doppler-targeted biopsy strategies (Kelly et al, 1993; Rifkin et al, 1993; Newman et al, 1995; Sakarya et al, 1998; Cornud et al, 2000; Okihara et al, 2000; Shigeno et al, 2000), but none is sufficiently accurate to replace systematic biopsy (Halpern et al, 2002a). Enhancements in the technical aspects of color Doppler TRUS, including the use of contrast agents (see later), may provide the necessary improvements to specifically identify cancer sites in the future.

Multiple studies have shown that angioneogenesis and the resultant increase in microvessel density that occurs within foci of prostatic adenocarcinoma correlates with the presence of metastasis (Weidner et al, 1993), stage of disease (Fregene et al, 1993; Brawer et al, 1994; Bostwick et al, 1996), and disease-specific survival (Lissbrant et al, 1997; Borre et al, 1998). Interest in using color and power Doppler TRUS to aid in prostate cancer detection stems from studies of radical prostatectomy specimens demonstrating that foci of adenocarcinoma possess an increased density of microvessels compared with surrounding normal parenchyma (Bigler et al, 1993).

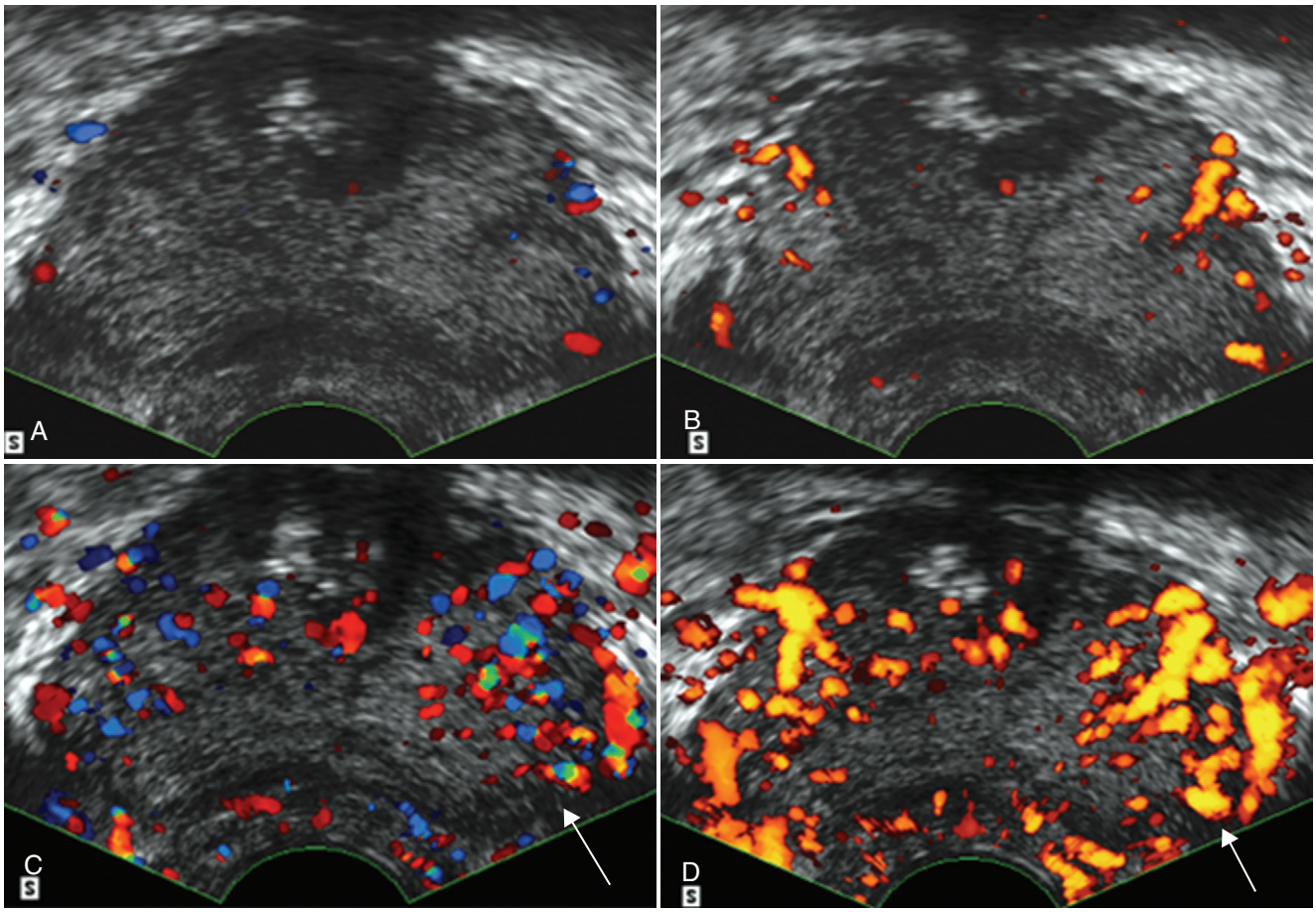


Figure 97–7. Unenhanced color **(A)** transrectal ultrasonography (TRUS) and power Doppler **(B)** TRUS fail to detect evidence of an underlying malignancy. After infusion of a microbubble contrast agent, color **(C)** TRUS and power Doppler **(D)** TRUS demonstrate an area of increased flow in the left midgland that proved to be a Gleason 3 + 4 = 7 adenocarcinoma on targeted biopsy *(arrows)*.

Patients with detectable color Doppler flow within their dominant tumor at the time of TRUS-guided biopsy are at a 10-fold increased risk for PSA recurrence after radical retropubic prostatectomy (Ismail et al, 1997). The presence of increased flow was also associated with a higher Gleason grade, increased incidence of SV invasion, and a lower biochemical disease-free (bNED) survival rate versus subjects without increased flow on preoperative TRUS (50% vs. 96% bNED at 31 months) (Ismail et al, 1997). Other investigators have also shown the association of power Doppler flow signals as an indicator of microvessel density with a higher Gleason score and have suggested a correlation with outcome (Wilson et al, 2004).

Current unenhanced Doppler modalities are not able to identify the microvessels of prostate cancer, which are typically 10 to 15 μm in diameter. The flow signals associated with malignant foci detected by unenhanced color and power Doppler imaging are due to detection of larger feeding vessels (Ismail and Gomella, 2001). Intravenous microbubble ultrasound contrast agents, similar to those currently approved and used in echocardiography, have been infused systemically during gray-scale and TRUS Doppler imaging to amplify flow signals within the microvasculature of prostate tumors, allowing selective visualization of malignant foci in clinical trials (Halpern et al, 2000; Ismail and Gomella, 2001). **These intravenous "bubble" contrast agents are constructed with air or higher-molecular-weight gas agents encapsulated (albumin or polymer hard shell, lipid- or surfactant-coated) for longevity and are generally 1 to 10 μm.**

Using contrast-enhanced TRUS (CE-TRUS) for prospective prostate cancer detection, Halpern and associates (Halpern et al, 2001) demonstrated an increase in sensitivity from 38% to 65% versus baseline unenhanced imaging, without significantly altering specificity. Subsequent studies by our group and others have improved sonographic detection of malignant foci using CE-TRUS and targeted biopsy of enhancing lesions (Frauscher et al, 2001; Halpern et al, 2002a; Roy et al, 2003; Halpern et al, 2005; Heijmink and Barentsz, 2007). In a multi-institutional trial involving several European centers, CE-TRUS has been recommended for routine care in prostate biopsy (Wink et al, 2008). Imaging using microbubble contrast agents combined with three-dimensional image reconstruction of enhanced power Doppler images also demonstrated increased diagnostic accuracy (Unal et al, 2000) (Fig. 97–7). Gray-scale harmonic imaging is a relatively newer method for imaging ultrasound contrast agents that provides better spatial and temporal resolution compared with color Doppler imaging. A variation on gray-scale harmonic imaging, flash-replenishment imaging, provides improved visualization of neovessels that are below the standard resolution of even gray-scale ultrasonography. Flash-replenishment imaging uses a combination of high-power flash pulses to destroy contrast microbubbles, followed by low-power pulses to demonstrate contrast replenishment. A composite image is constructed depicting the vascular architecture through maximum intensity capture of temporal data in consecutive

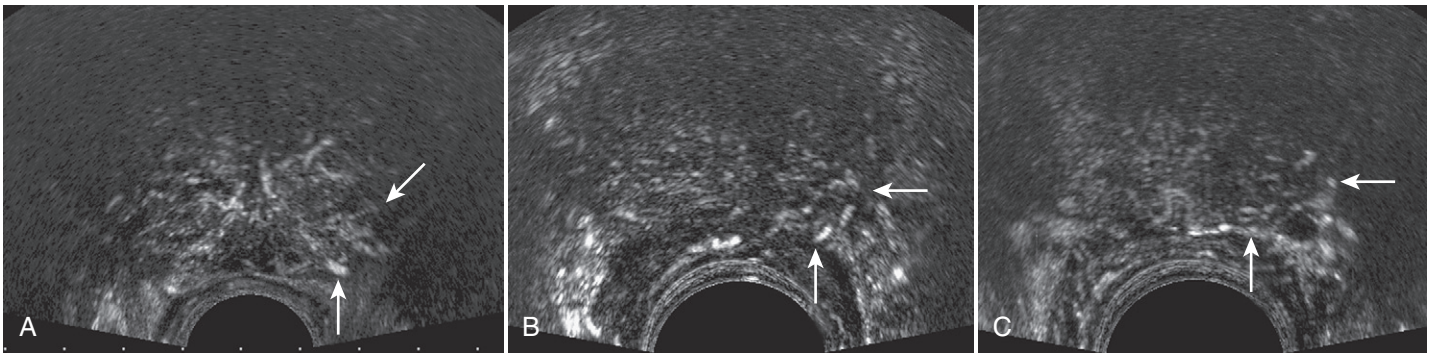


Figure 97–8. Flash-replenishment imaging demonstrating areas of increased and/or abnormal vascularity (*arrows*) to target for biopsy. **A,** Gleason 4 + 4 = 8 adenocarcinoma in the left base. **B,** Gleason 3 + 3 = 6 adenocarcinoma in left base and **(C)** left midgland.

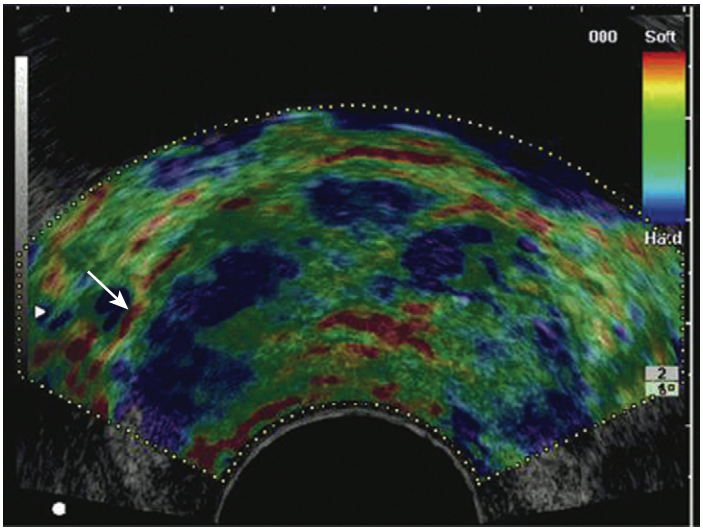


Figure 97–9. Elastography demonstrates an area of decreased compliance in the right base consistent with an underlying malignancy *(blue near arrow)*. Note color scale in upper right corner indicating relative tissue "firmness." Targeted biopsy of this region revealed a Gleason 4 + 4 = 8 adenocarcinoma.

low-power images, and it can be used for real-time targeted transrectal biopsy of areas of increased or abnormal vascularity. Using this technique, we have demonstrated much finer vascular detail for targeting biopsy, and targeted biopsy cores were significantly more likely to be cancerous than random systematic biopsy cores (Linden et al, 2007) (Fig. 97–8). Future developments in these and other imaging modalities that can selectively visualize prostate cancers based on the presence of angioneogenesis may ultimately allow more accurate localization of the sites of cancer.

Other Investigational Techniques

Artificial neural networks are another potential way to enhance TRUS images and identify malignant foci. Investigational automated image analysis, including pattern recognition and artificial neural networks applied to TRUS images, may successfully identify lesions that cannot be seen by the human eye (Loch et al, 1999).

A new sonographic technique known as elastography may prove to be superior to color Doppler imaging in the identification of malignant areas in the prostate (Nelson et al, 2007; Sumura et al, 2007). This technique employs real-time sonographic imaging of the prostate at baseline and under varying degrees of compression (Fig. 97–9). Through computerized calculations, differences in displacement between ultrasonic images from baseline and during compression may be visualized, and regions with decreased tissue elasticity may be tagged as suggestive of malignancy. In a preliminary study of 404 cases, with 151 cases positive for prostate cancer, the malignancy was found in 127 patients (84.1%) with real-time elastography directing the biopsy (Konig et al, 2005).

Endorectal magnetic resonance imaging (MRI) and MR spectroscopy as combined modalities might be able to guide and therefore limit the number of iterative biopsies and cores for patients (Amsellem-Ouazana et al, 2005). Use of MRI will require modifications in instrumentation and the technique of biopsy (Beyersdorff and Hamm, 2005). These MRI-directed biopsy techniques require expensive equipment that is not widely available for biopsy procedures.

New Doppler, contrast medium–enhanced, and other developing techniques have the potential to allow accurate localization and diagnosis of prostate cancer and minimize or eliminate the need for multiple biopsy sites to diagnose prostate cancer in the future. However, until these techniques are proved superior in

Key Points: Advanced Ultrasonographic Techniques for Prostate Imaging

- TRUS alone cannot diagnose prostate cancer without a tissue biopsy.
- Local prostate anesthesia is becoming commonplace and most useful when using extended core biopsy schemes.
- Patients undergoing TRUS-guided prostate biopsy require oral antibiotic prophylaxis for at least 24 hours perioperatively.
- Sextant biopsy of the prostate for prostate cancer detection is inadequate, and systematic biopsy procedures should include a minimum of 10 to 14 cores.
- In the future, investigational imaging modalities, such as contrast medium–enhanced TRUS and elastography, may allow more precise targeted biopsy protocols to replace extended core schemes by improved localization of malignant foci within the prostate.
- Color and power Doppler imaging modes improve cancer detection but do not reliably identify all malignant foci and thus cannot obviate the need for systematic biopsy at the present time.

the localization of prostate cancer, systemic TRUS gray-scale core needle biopsy will continue to be regarded as the gold standard for the diagnosis of prostate cancer.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter

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Prostate Cancer Tumor Markers

Robert H. Getzenberg, PhD ● Alan W. Partin, MD, PhD

Tissue Biomarkers

Blood and Urine Biomarkers

Cellular Biomarkers

Molecular Biology

Summary

The discovery and use of tumor markers have positively affected early detection, diagnosis, and staging for many malignancies. By improving early detection, tumor markers contribute to improved curative success rates. Optimal treatment and cure depend not only on accurate and early diagnosis but also on reliable follow-up for efficient detection of clinical recurrence. The identification of new markers and the development of sensitive tools to measure them will contribute to improved cure rates.

Among urologic malignancies, prostate cancer has greatly benefited from the discovery and application of tumor markers. **Since its discovery in 1979 until clinical application in the late 1980s through 1990s, the prostate-specific antigen (PSA) has evolved into an invaluable tool for detecting, staging, and monitoring prostate cancer in men** (Sensabaugh, 1978; Wang et al, 1979, 1981; Papsidero et al, 1980; Kuriyama et al, 1981). The widespread use of PSA screening has generated greater awareness about prostate cancer. During the PSA era, cancers identified when confined to the prostate have improved cure rates using either radical prostatectomy or radiation therapy. **Whereas the majority of prostate cancers in the 1980s and early 1990s commonly arose through finding an abnormal digital rectal examination (DRE) or elevated PSA, or both, today most prostate cancer arises as clinically nonpalpable (stage T1c) disease with PSA levels between 2.5 and 10 ng/mL. The evolving demographics and natural history of prostate cancer have resulted in a stage migration to nonpalpable, clinically localized (stage T1c) disease and a parallel reduction in mortality** (Pound et al, 1997, 1999; Stephenson et al, 1997; Polascik et al, 1999). However, these PSA-detected T1c cancers are not homogeneous. Although PSA screening has improved survival, outcomes are not the same for all T1c-detected disease because some of these cancers may not pose a threat to survival (Gretzer et al, 2002). Methods for improved detection of clinically significant prostate cancer are needed.

Despite routine application of PSA assays, limitations of specificity for this marker remain. Although PSA is widely accepted as a prostate cancer tumor marker, it is organ specific and not disease specific. **Unfortunately, there is an overlap in the serum PSA levels among men with cancer and those with benign disease. Thus elevated serum PSA levels may reflect alterations within the prostate secondary to tissue architectural changes such as cancer, inflammation, or benign prostatic hyperplasia (BPH).** Currently, serum PSA levels as low as 2.6 ng/mL are used as a threshold to perform transrectal ultrasound-guided biopsy. **Although up to 30% of men presenting with an elevated PSA may be diagnosed following this invasive procedure, as many as 75% to 80% are not found to have cancer.** In some instances the biopsy needle may fail to sample representative areas, thus failing to detect present cancer. To this end, application of PSA derivatives such as PSA density, PSA velocity, age-adjusted values, and, more recently, molecular derivatives have attempted to improve the performance of PSA (Christensson et al, 1990; Benson et al, 1992a, 1992b; Carter et al, 1992a, 1992b; Oesterling et al, 1993a, 1993b, 1993c; Riehmann et al, 1993; Seaman et al, 1993; Bazinet et al, 1994; Rommel et al, 1994; McCormack et al, 1995; Morgan et al, 1996; Lilja, 1997).

We are in a midst of a PSA biomarker crisis because the specificities of PSA and its derivatives require supplementation to improve specificity and to differentiate cancer from benign diseases of the prostate. Research into the biochemistry of PSA is yielding advances that have the potential to contribute to the detection and management of prostate cancer. New understanding of the molecular biology of carcinogenesis and prostate cancer is beginning to yield a new era in prostate cancer tumor research. Exploiting the knowledge of molecular oncology and application of novel techniques has provided innovative tools for the discovery of new biomarkers. Application of these promising diagnostic tests may be instrumental not only for detection but also to aid in discrimination between aggressive and indolent cancers. This chapter reviews our currently used markers in tissue, blood and urine, as well as the cellular-based components, and describes some promising markers that may evolve from the improved knowledge and methods used to evaluate genomic alterations, epigenetic modifications, and protein expression.

TISSUE BIOMARKERS

Glutathione-*S*-Transferase Pi (GSTP1)

Changes in gene expression may occur as a result of alterations in DNA. Alterations known as epigenetic modifications include changes in DNA methylation and histone acetylation status. **Segments within the gene promoter that are composed of GC-rich regions are termed CpG islands. Alterations in the methylation status of these regions may affect gene expression and have been shown to play a role in**

carcinogenesis (Jones and Baylin, 2002). **Furthermore, cumulative effects of environmental exposures, such as diet and stress throughout life, may affect DNA methylation status and thus contribute to the risk of cancer development** (Li et al, 2004). Assays for detection of CpG island hypermethylation include Southern blotting, restriction endonuclease PCR (RE-PCR), bisulfite genomic sequencing (BCR), and methylation-specific (MSP) PCR. Although each assay is sensitive, technical limitations exist. Currently, MSP PCR is most commonly employed for the detection of methylated CpG islands (Jones, 2002). **The products of two hypermethylated genes that have been evaluated in prostate cancer development are glutathione-*S*-transferase P1 (GSTP1) and RAS association domain family protein isoform A (RASSF1A).**

GSTP1 belongs to a family of detoxifying enzymes that are involved in metabolic reduction of electrophilic carcinogens. These enzymes are thought to be involved in the development of prostate cancer. Elevated levels of *GSTP1* CpG hypermethylation have been detected in tissues from precancerous lesions (atypia and prostatic intraepithelial neoplasia [PIN]) and within ejaculates, urine, and plasma from men with prostate cancer (Nakayama et al, 2003). To date, many studies have evaluated these hypermethylated CpG islands as a prostate cancer tumor marker (Cairns et al, 2001; Goessl et al, 2001a, 2001b; Gonzalgo et al, 2003; Bastian et al, 2004). Cairns and coworkers (2001) have demonstrated the presence of elevated *GSTP1* hypermethylation in up to 79% of prostate cancer specimens. Using urine specimens obtained after prostate massage, Goessl and colleagues (2001a, 2001b) found elevated levels of this marker in 68% of men with organ-confined disease, 78% of men with locally advanced or metastatic disease, 29% of men with PIN, and 2% of men with BPH.

Gonzalgo and coworkers (2003) demonstrated elevated *GSTP1* hypermethylation in up to 50% of urine sediments taken from men immediately after transrectal prostate biopsy. Hypermethylation was also detected in 33% of men with negative biopsies and in up to 67% of men found to have PIN or atypia, suggesting that these patients may harbor occult prostate cancer and require more rigid follow-up with a low threshold for repeat biopsy. The use of MSP to measure *GSTP1* hypermethylation in body fluids represents an emerging tool that is feasible and has demonstrated reproducible results, and it is likely to become a valued screening modality for prostate cancer detection.

In addition to *GSTP1,* hypermethylation of *RASSF1A* has been noted to occur in up to 70% of prostate cancers (Kuzmin et al, 2002; Liu et al, 2002). Early findings have noted an association of this marker with more aggressive tumors, and it may aid in distinguishing between these cancers and more indolent cancers. Although early, this work is promising, and the subject remains under investigation.

Many men continue to undergo biopsy procedures even though only 10% to 36% of men having an initial negative biopsy are found to have cancer on second biopsy (Djavan et al, 2000; O'Dowd et al, 2000; Lopez-Corona et al, 2003; Singh et al, 2004; Eggener et al, 2005), and cancer detection decreases with each subsequent negative biopsy (Keetch et al, 1994). Improved methods are needed to identify men who can forgo a repeat biopsy, particularly if the trigger for initial biopsy or the initial biopsy histology indicates high-risk features. Therefore emphasis on achieving a high negative predictive value (NPV) and low false-negative rate has been championed following many biomarker evaluations. In initial studies of prostate cancer, DNA methylation markers have exhibited high sensitivity and specificity (Maruyama et al, 2002; Yegnasubramanian et al, 2004), and improved upon the sensitivity of histology alone by 15% (Harden et al, 2003a). We therefore conducted this study to evaluate whether DNA methylation markers could improve upon the NPV of histology alone in men without cancer on initial biopsy but with a high index of suspicion for a missed cancer.

The first tissue methylation-biomarker to be discovered was glutathione-*S*-transferase π (GSTP1). Glutathione *S*-transferases (GSTs) are a family of detoxification enzymes that conjugate reactive substrates with reduced glutathione. The enzymes are dimers classified into four groups: α, μ, π, and θ (Hayes et al, 1995). Li and coworkers (2004) noted that the glutathione-*S*-transferase π *(GSTP1)* gene was unmethylated in all normal human tissues and BPH but was hypermethylated in all 20 prostate cancer (CaP) specimens analyzed. Eighty-eight of 91 CaP specimens did not stain for GSTP1 protein. Harden and coworkers (2003a, 2003b) used PCR to detect hypermethylated *GSTP1* in prostate biopsy specimens. Twenty-nine (of 45 patients) were able to be evaluated using this method. *GSTP1* methylation was detected in 11 of 15 (73% sensitivity) CaP cases and in none of 14 (100% specificity) benign controls. Quantitation of *GSTP1* hypermethylation accurately detected CaP even in small, limited tissue samples. This would indicate that methylated *GSTP1* represents a marker useful for CaP screening.

Bastian and coworkers (2005) used a restriction endonuclease, QMSP (RE-MSP), to detect abnormalities in the CpG islands found in serum *GSTP1* DNA. No men with a negative biopsy had *GSTP1* DNA detected in their sera, compared with 12% of men with clinically localized CaP and 28% with metastatic disease.

Gene Fusions

With the landmark discovery of the presence of gene fusions in prostate cancer by Chinnaiyan and colleagues (Tomlins et al, 2005), considerable work has been performed to determine if assays can be developed that can accurately detect prostate cancer or provide prognostic information. The *TMPRSS2* and *ETS* transcription factor fusions have revealed novel biology about solid tumors with great potential implication (Tomlins et al, 2005). Because this discovery has such great potential, the concept has been to determine if we can detect these fusions in the urine of men with prostate cancer (Barry et al, 2007). A feasibility study that examined urine samples post-DRE, revealed that indeed the *TMPRSS2-ERG* fusion can indeed be found within the urine and has the potential to be an interesting marker (Laxman et al, 2008) with potential to aid in the detection of prostate cancer in men about to undergo a biopsy for the disease. In a larger follow-up study, investigators were able to determine that gene fusions are detectable in approximately 37% of the urine samples obtained from men with prostate cancer (Hessels et al, 2007). Using tissue samples, the presence of these gene fusions was observed in about half of the prostate cancer cases and was, in fact, observed in an even lower percentage of the more aggressive tumors (Perner et al, 2007; Mosquera et al, 2008). Several assays are being developed to detect these fusions in tissue and urine samples (Lu et al, 2008). Further delineation of the various splice variants that have been produced has the potential to add to the diagnostic utility of these fusions, indicating that the detection of a single fusion may not be sufficient (Hu et al, 2008). The clinical utility of the detection of a single gene fusion alone has been questioned recently with findings that the *TMPRSS2-ERG* fusion does not correlate with outcome in men undergoing prostatectomies (Gopalan et al, 2009). Moving toward the concept that single biomarkers will probably not answer the important clinical questions in prostate

cancer alone, many investigators have begun to multiplex markers, resulting in additive value. Combining both the prostate cancer–3 (PCA-3) test, that will be described later in the chapter, together with the detection of these gene fusions in urine resulted in increasing sensitivity to 73%, although it was not possible to determine the specificity of the combined tests in these clinical populations. Overall, the current data related to the use of urine-based gene fusions seems to indicate that, at best, they may add slightly to PSA or even PCA-3 detection of prostate cancer and does not appear to have the ability to distinguish aggressive from nonaggressive disease.

Gene and Androgen Receptor Polymorphisms

As the genetic alterations associated with disease states are mapped, novel information is being revealed related to the potential of these differences to serve as biomarkers for prostate cancer. These findings have been specifically associated with more advanced prostate cancer. Using arrays that can specifically analyze single nucleotide polymorphisms (SNPs), investigators have begun to perform large-scale genomic comparisons of genetic alterations associated with prostate cancer. Much of the initial work has been done on individuals who have family histories of prostate cancer. In work performed through a collaborative effort that examined large numbers of individuals who are part of these hereditary study cohorts, investigators have revealed SNP patterns that impart a higher risk for developing prostate cancer. Because these are genomic differences, a simple blood draw or cheek swab can be used to make such a determination (Sun et al, 2008). Although the data are quite dramatic, the question has been raised about how these data should be handled clinically. For example, if an individual is found to have a fivefold increase in their risk for prostate cancer, what should be done? Should they be screened more carefully or more frequently? Should they simply undergo a prostate biopsy or treatment? Certainly this seems like an application where some type of preventive strategy might work. Unfortunately, we have little, if anything available that has been used to effectively prevent the disease.

In an attempt to discern genomic polymorphisms that may be predictive of castrate-resistant prostate cancer, Luo and colleagues (Hu et al, 2009) have examined the androgen receptor to determine if there may be gene variants that are predictive of the ability of the tumor to continue to grow in the absence of androgens. The hypothesis is that there are distinct forms of the androgen receptor that may be active in the absence of ligands. This may permit the cancer cells to continue to grow even in a castrate environment. They have recently revealed the presence of several unique forms of the androgen receptor. One form, variant 7, is shown to be increased in men with advanced prostate cancers (Hu et al, 2009). Using an antibody being constructed, the researchers are proposing to develop a blood test that can be used to identify individuals with castrate- resistant prostate cancer.

BLOOD AND URINE BIOMARKERS

Prostate-Specific Membrane Antigen

The glycoprotein prostate-specific membrane antigen (PSMA) is a folate hydrolase and is found embedded within the cell membrane of all prostatic epithelial cells. The hydrophobic amino acids found on amino acid residues 20 to 43 suggest that this protein is a type II integral membrane protein with a small intracellular domain and a large extracellular domain (Israeli et al, 1997; Fair et al, 1997). The gene for PSMA has been cloned, fully sequenced, and localized to the short arm of chromosome 11 (11p11-p12). PSMA has been identified in the central nervous system, intestine, and prostate. In the brain, PSMA functions to metabolize the neurotransmitter *N*-acetyl-aspartyl-glutamate. In the intestine, PSMA has been localized to the proximal small bowel, where it works as a carboxypeptidase. Although isolated in these other tissues, PSMA is predominantly expressed in the prostate gland.

Of interest for diagnosis (Douglas et al, 1997), prognosis (Perner et al, 2007), and imaging (Wynant et al, 1991; reviewed by Abdel-Aziz et al, 2000) is the discovery of elevated expression of this protein in tissue from prostate cancer compared with normal prostate tissue (Silver et al, 1997; Chang et al, 1999a; Elgamal et al, 2000). More work has focused on use of PSMA in treatment strategies than for diagnostic tests (Elsässer-Beile et al, 2009). Multiple monoclonal antibodies have been designed to identify both the intracellular and extracellular domains of the PSMA protein; however, few have shown "diagnostic promise" immunohistochemically or as serum/urine assays (Horoszewicz et al, 1987; Douglas et al, 1997). However, PSMA mRNA expression among prostate cancers is highest in the hormone-deprived state (Henttu et al, 1992; Israeli et al, 1994). **During cancer progression, differentially expressed variants of PSMA have been identified. Of three alternatively spliced variants of PSMA, one, known as PSM′, is differentially expressed in normal tissue, BPH, and prostate cancer.** Su and colleagues (1995) demonstrated that the PSMA/PSM′ ratio is upregulated three- to sixfold in prostate cancer compared with BPH (0.76 to 1.6) and normal (0.075 to 0.45) tissue. Further reports to date have demonstrated the production of antibodies to PSMA. Horoszewicz and coworkers (1987) have found increased PSMA levels in 47% of prostate cancer patients (20 of 43) versus only 5% of noncancer patients (3 of 66) and negative results in 30 normal blood donors. Using the antibody produced by Horoszewicz and coworkers, Xiao and colleagues (2001) reported use of an immuno-SELDI (surface-enhanced laser desorption ionization) assay for PSMA. Applying the antibody to PSMA on a ProteinChip array, these authors were able to differentiate cases of prostate cancer from BPH. Perner and colleagues (2007) demonstrated marked differences, immunohistochemically, in the levels of PSMA in tissues from various prostate tumors that progressed after surgery (HR = 1.5, 95% CI = 1.1 to 2.8, P = .17) and suggested that PSMA might act independently as a prognostic biomarker of disease progression. The development of an accurate enzyme-linked immunosorbent assay (ELISA) for PSMA in serum/urine has potential significance for diagnostic and prognostic evaluation for prostate cancer. The clinical usefulness of PSMA for diagnosis, monitoring, and imaging continues to be promising and remains under investigation in many laboratories.

Human Kallikrein Gene Family

Another source of blood-based prostate cancer biomarkers has been identified among the protein products of the human kallikrein gene family (Fig. 98–1). Originally, only three genes of this family of genes were identified: the pancreatic/renal kallikrein *(hKLK1),* human kallikrein 2 *(hKLK2),* and PSA *(hKLK3)* genes (McCormack et al, 1995; Rittenhouse et al, 1998; Diamandis et al, 2000; Lilja, 1997). Since the identification of 12 other kallikrein genes, this family of proteases now consists of 15 members and is described with a distinct nomenclature (Diamandis et al, 2000; Yousef and Diamandis, 2001). Located on the long arm of

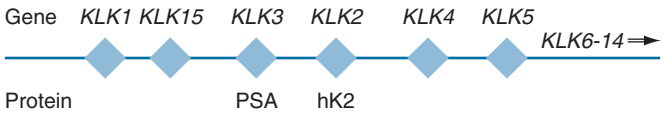


Figure 98–1. Human kallikrein gene map. Map of the human kallikrein locus and corresponding proteins as described by Yousef and Diamandis (2001).

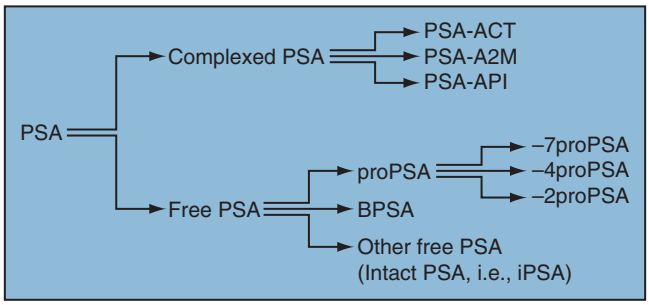


Figure 98–2. Molecular forms of prostate-specific antigen (PSA). Molecular derivatives of PSA include free PSA, such as proPSA (and the various clipped forms), BPSA (benign PSA), and other free PSA forms such as intact, inactivated PSA. Complexed PSA includes free PSA that is bound to proteases such as ACT (α_1-antichymotrypsin), API (α_1-protease inhibitor), and A2M (α_2-macroglobulin).

chromosome 19 within the region spanning q13.2-q13.4, these genes share similar structural similarities. The serine proteases encoded by the three originally described genes have been identified as hK1 or hPRK (*KLK1* gene), hK2 or hGK-1 (*KLK2* gene), and hK3 or PSA (*KLK3* gene). These serine proteases have similar amino acid sequences, with hK1 expressing 60% and hK2 expressing 78% homology with PSA (Schedlich et al, 1987; Clements, 1989). Both hK2 and hK3 are released in zymogen form from the prostatic epithelium and are found in seminal fluid as well as serum. Because they share structural homology, they can both form complexes with endogenous protease inhibitors such as α_2-macroglobulin and α_1-antichymotrypsin (ACT) (Young et al, 1995; Lilja, 1997; Rittenhouse et al, 1998). **hK2 has been shown to regulate PSA activity by cleaving a leader amino acid sequence from PSA (proPSA), thus activating PSA** (Kumar et al, 1997; Lovgren et al, 1997; Takayama et al, 1997). **Although PSA is less expressed in prostate cancer tissue, hK2 levels have been shown to be elevated in poorly differentiated prostate cancer** (Darson et al, 1997; Tremblay et al, 1997). Similar to PSA, hK2 has been shown to aid in the detection of prostate cancer (Kwiatkowski et al, 1998; Partin et al, 1999; Nam et al, 2000). It is likely that several other members of the kallikrein family of serine proteases will become useful tumor markers. Both hK6 and hK10 have been described as potential serum biomarkers for nonprostatic diseases, especially ovarian cancer (Luo et al, 2001; Yousef and Diamandis, 2001).

Prostate-Specific Antigen (PSA or hK3)

The most notable marker in the kallikrein family is hK3, also known as PSA. It was first identified and purified in the late 1970s, but widespread use in clinical urology did not occur for another decade (Ablin et al, 1970; Sensabaugh, 1978; Wang, 1979; Papsidero, 1980; Kuriyama, 1980, 1981; Wang, 1981; Seamonds, 1986; Chan et al, 1987; Stamey et al, 1987; Oesterling et al, 1988). PSA is a 33-kD glycoprotein that acts as a serine protease. The ectopic expression of PSA has been reported in smaller concentrations in the tissue of malignant breast tumors (Yu et al, 1994a, 1994b, 1994c), normal breast tissue (Monne et al, 1994; Yu et al, 1995), breast milk (Yu and Diamandis, 1995), female serum (Yu et al, 1995), and adrenal and renal carcinomas (Levesque et al, 1995a); however, for practical and clinical purposes, PSA is organ specific, primarily produced by the prostatic luminal epithelial cells (Yu et al, 1995; Levesque et al, 1995b; Diamandis et al, 2000). Although it is organ specific, PSA is not cancer specific, as demonstrated by the substantial overlap in values between men with benign versus malignant prostate disease (Oesterling et al, 1988; Partin et al, 1990).

The function of this androgen-regulated protease is to liquefy semen through its action on the gel-forming proteins semenogelin and fibronectin within the semen following ejaculation (Lilja and Laurell, 1984; Lilja, 1985; Lilja et al, 1987; McGee and Herr, 1988; Christensson et al, 1990). **PSA is normally found in low concentration in sera (ng/mL). Within sera, PSA circulates in both bound and unbound forms** (Fig. 98–2). **Most PSA in sera is bound or complexed to the antiproteases ACT and macroglobulin (MG)** (Christensson et al, 1990; Lilja et al, 1991; Stenman et al, 1991). Binding of free PSA to ACT inactivates the protease, but the complex PSA-ACT remains immunodetectable by current assays (Partin et al, 2003). Binding of PSA to MG still allows some proteolytic activity but renders the PSA-MG complex undetectable by most current assays (Christensson et al, 1990). **Free PSA without proteolytic activity is probably rendered inactive within the prostatic epithelial cell before release into the sera. This free inactive PSA does not form complexes with antiproteases, circulates unbound in sera, and is immunodetectable by current assays** (Lilja et al, 1991). The primary release of PSA into the seminal fluid results in 10^6-fold higher seminal concentrations than levels measured within serum (Sensabaugh, 1978; Wang et al, 1981; Lilja and Abrahamsson, 1988; McCormack et al, 1995). The concentrations found in seminal plasma range from 0.5 to 5.0 mg/mL, whereas the normal serum concentration in men aged 50 to 80 years without prostate disease ranges between 1.0 and 4.0 ng/mL (Catalona et al, 1991).

Prostate cancer cells do not necessarily make more PSA than do normal prostate cells, and elevated serum levels are probably a result of cancer progression and destabilization of the prostate histologic architecture (Stamey et al, 1987). Studies have demonstrated that **prostate cancer cells do not make more PSA but rather make less PSA than normal prostatic tissue** (Meng et al, 2002). **Evaluation of tissue from prostate cancer specimens has demonstrated up to 1.5-fold lower messenger RNA (mRNA) expression levels compared with normal prostate tissue** (Meng et al, 2002).

PSA expression is strongly influenced by androgens (Young et al, 1991; Henttu et al, 1992). Immunohistochemical detection of PSA within the prostate is characterized by bimodal peaks between 0 and 6 months and after 10 years, correlating directly with testosterone levels (Goldfarb, 1986). Serum PSA becomes detectable at puberty with increases in luteinizing hormone and testosterone (Vieira et al, 1994). **In the absence of prostate cancer, serum PSA levels vary with age, race, and prostate volume.**

In men without BPH, the rate of change in PSA is 0.04 ng/mL per year (Carter et al, 1992b; Oesterling, 1993), compared with

0.07 to 0.27 ng/mL per year in men with BPH who are between the ages of 60 and 85 years (Carter et al, 1992b). Cross-sectional data suggest that PSA increases 4% per milliliter of prostate volume and that 30% and 5% of the variance in PSA can be accounted for by prostate volume and age, respectively (Oesterling et al, 1993a). Blacks without prostate cancer have higher PSA values than whites (Morgan et al, 1996; Fowler et al, 1999). Fowler and colleagues (1999) have demonstrated that, on a volume/volume basis, the benign prostatic tissue of black men contributes more PSA to sera than does the benign prostatic tissue of white men, a difference that increases with age.

Elevated serum PSA levels are probably a product of disruption of cellular architecture within the prostate gland (Stamey et al, 1987). **The loss of the barrier afforded by the basal layer and basement membranes within the normal gland is a likely site for the egress of PSA into the circulation. This can occur in the setting of prostate disease (BPH, prostatitis, prostate cancer) and with prostate manipulation (prostate massage, prostate biopsy)** (Stamey et al, 1987). Prostatic inflammation (acute and chronic) and urinary retention can cause PSA elevations to variable degrees (Armitage et al, 1988; Dalton, 1989; Nadler et al, 1995). PSA elevations may not be related to the histologic finding of inflammation in men without clinical prostatitis (Morote et al, 2000). **Prostatic trauma, such as occurs after prostatic biopsy, can result in a leak of PSA into the circulation that may require more than 4 weeks for return to baseline values** (Yuan et al, 1992). **DRE as performed in an outpatient setting can lead to increases in serum PSA** (Thompson and Zeidman, 1992). **However, the change in PSA after DRE does not appear to be clinically significant, because the change is within the error of the assay and rarely causes false-positive tests** (Chybowski et al, 1992; Crawford et al, 1992; Thompson and Zeidman, 1992).

Studies of the effect of ejaculation on serum PSA have shown both no significant change in PSA (Kirkali et al, 1995) and a significant decrease in serum PSA (Simak et al, 1993; Heidenreich et al, 1997) in men 30 to 40 years old or younger. However, in the age group in which PSA testing is primarily used for early detection of prostate cancer (50 years and older), ejaculation can lead to an increase in PSA that can result in a false-positive elevation (Tchetgen et al, 1996; Herschman et al, 1997). After 48 hours, this fractional increase in PSA would be expected to return to baseline levels in most men (Tchetgen et al, 1996). A history of sexual activity and a repeated PSA test after 48 hours of sexual abstinence may be helpful in the interpretation of serum PSA levels that are minimally elevated.

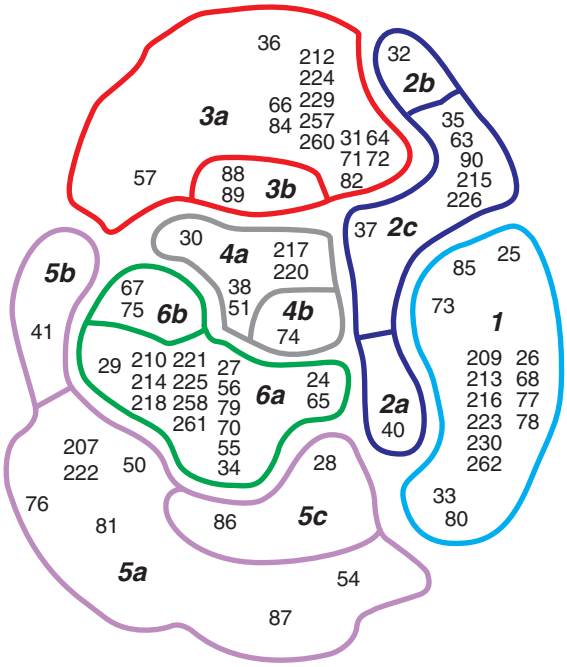
The presence of prostate disease (prostate cancer, BPH, and prostatitis) is the most important factor affecting serum levels of PSA (Wang et al, 1981; Ercole et al, 1987; Robles et al, 1988). **PSA elevations may indicate the presence of prostate disease, but not all men with prostate disease have elevated PSA levels. Furthermore, PSA elevations are not always specific for prostate cancer.**

Prostate-directed treatment (for both BPH and cancer) can lower serum PSA by decreasing the volume of prostatic epithelium available for PSA production and by decreasing the amount of PSA produced per cell. Manipulation of the hormonal environment for treatment of cancer and BPH with orchiectomy, luteinizing hormone–releasing hormone analogs, and 5α-reductase inhibition; radiotherapy; and surgery for BPH or cancer can all lead to reductions in serum PSA (Henttu and Vihko, 1992). **Finasteride (5 mg) and other 5α-reductase inhibitors (dutasteride) for treatment of BPH have been shown to lower PSA levels by an average of 50% after 6 months of treatment** (Guess, 1993). **Thus one can multiply the PSA level by two to obtain the "expected" PSA level of a patient who has been taking a 5α-reductase inhibitor—for 6 months or more. Men who are to be treated with a 5α-reductase inhibitor should have a baseline PSA measurement before initiation of treatment and should be observed with serial PSA measurements, because this drug may decrease PSA serum levels by up to 50%. If PSA does not decrease by 50% or if there is a rise in PSA when the patient is taking a 5α-reductase inhibitor, the patient should be suspected of having occult prostate cancer and undergo further testing.** Finasteride (1 mg), also marketed for the treatment of male baldness, may also lower PSA levels to a lesser extent than the 5-mg dosage. Other over-the-counter medications and neutraceutical use should always be documented. **Although saw palmetto has not been shown to affect PSA levels, these unregulated supplements may contain compounds that can alter PSA levels (e.g., PC-SPES, now off the market). Interpretation of PSA values should always take into account the presence of prostate disease, previous diagnostic procedures, and prostate-directed treatments.**

Molecular Derivatives of Prostate-Specific Antigen

One of the most exciting and clinically useful discoveries since the introduction of PSA testing has been the demonstration of different molecular forms of PSA in serum (Christensson and Lilja, 1994; Christensson et al, 1990, 1993; Lilja et al, 1991; Stenman et al, 1991; McCormack et al, 1995; Lilja et al, 1997; Polascik et al, 1999). Measurable PSA found circulating in the blood exists either complexed (bound, cPSA) to proteins or as a free (unbound) form (fPSA) (see Fig. 98–2). **Three proteins that are known to bind to PSA in the blood are ACT, α_2-macroglobulin (A2M), and α_1-protease inhibitor (API)** (Christensson et al, 1990, 1993, 1994; Lilja et al, 1991; McCormack et al, 1995; Tewari et al, 1996; Lilja, 1997). Figure 98–3 illustrates the molecular model of PSA and its epitope sites. **The majority of PSA that enters the serum is bound (70%) to these proteins.** When bound to A2M, all PSA epitope sites become masked, making this complex difficult to measure (Fig. 98–4). **Of the complexed PSA derivatives found in serum, PSA bound to ACT (PSA-ACT) is immunoreactive and found in the greatest concentration.** Although representing a lower proportion of total PSA in the blood, fPSA is also immunoreactive and therefore measurable. Development of new monoclonal antibodies specific for fPSA and cPSA has allowed more accurate measurement of the different molecular forms of PSA and their ratios in serum (Table 98–1) (Lilja et al, 1991; Stenman et al, 1991).

Free PSA and the Percent Free PSA. Although the majority of serum PSA is found complexed to the proteases (most to ACT), 5% to 35% of PSA exists as fPSA (McCormack et al, 1995; Tewari et al, 1996; Woodrum et al, 1998). **Although prostate cancer cells do not produce more PSA than benign prostate epithelium, the PSA produced from malignant cells appears to escape proteolytic processing. Thus men with prostate cancer have a greater fraction of serum PSA complexed to ACT and a lower percentage of total PSA that is free compared with men without prostate cancer** (Christensson et al, 1993; Leinonen et al, 1993; Lilja, 1993; Stenman et al, 1994; Catalona et al, 1997). Using this



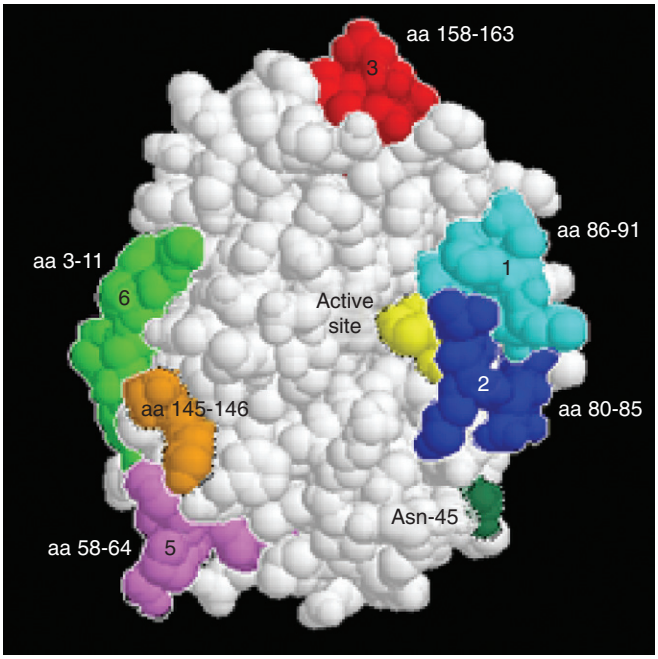


Figure 98–3. Molecular model of prostate-specific antigen demonstrating the available epitopes.

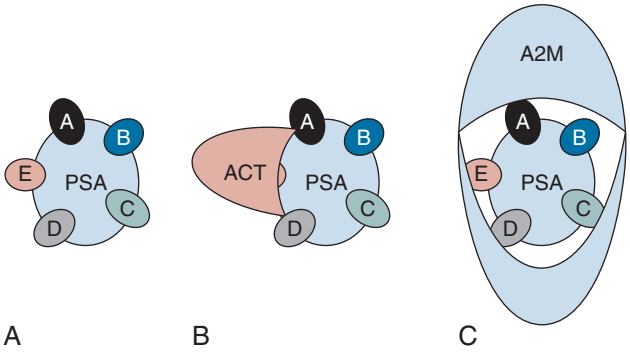


Figure 98–4. Prostate-specific antigen (PSA)–binding proteases. **A,** Free PSA with *A* to *E* representing immunoreactive epitopes of free PSA. **B,** α_1-Antichymotrypsin (ACT) blocks the E epitope during binding. **C,** α_2-Macroglobulin (A2M) blocks all immunoreactive sites on PSA, making this derivative difficult to measure in serum.

Table 98–1.

Molecular Derivatives of Prostate-Specific Antigen

PSA TYPE	% IN SERUM
Complexed PSA	60-95
PSA-ACT	60-90
PSA-API	1-5
PSA-A2M	10-20
Free PSA	5-40

ACT, α_1-antichymotrypsin; API, α_1-protease inhibitor; A2M, α_2-macroglobulin; PSA, prostate-specific antigen.

important observation led to the measurement of the percentage of the ratio of free to total PSA (%fPSA) and has since provided an additional degree of specificity for prostate cancer detection (Catalona et al, 1998; Partin et al, 1998). The difference in the ratio of free to total PSA (percentage of free PSA or %fPSA) is greatest when comparing men without prostate cancer who have prostate enlargement (BPH) with those with prostate cancer and no prostate enlargement. This difference may be due to differential expression of PSA isoforms by transition zone (zone of origin of BPH) tissue compared with peripheral zone (zone of most prostate cancer) tissue (Chen et al, 1997; Mikolajczyk et al, 2000). **The role for %fPSA is more applicable to PSA levels less than 10 ng/mL, because the positive predictive rate of total PSA above 10 to 20 ng/mL has been demonstrated to be as high as 80%. Currently, %fPSA is approved by the Food and Drug Administration (FDA) for use to aid PSA testing in men with benign DRE and minimal PSA elevations, within the diagnostic gray zone of 4 to 10 ng/mL.** If PSA levels are less than 4.0 ng/mL, more recent data have demonstrated the utility of %fPSA when deciding whether a patient requires an initial or repeat biopsy.

Christensson and coworkers (1993) measured free and total PSA fractions in men with and without prostate cancer and found that a free/total PSA cutoff of 0.18 (18% free/total PSA) significantly improved the ability to distinguish between subjects with and without cancer compared with use of total PSA alone. Other %fPSA cutoff values have also been identified to improve risk stratification. Catalona and colleagues (1995) have found that %fPSA provided independent predictive information regarding the presence or absence of cancer above that provided by other clinical indices, including age, total PSA, DRE results, and prostate size. As many as 20% to 65% of unnecessary biopsies may be avoided when using %fPSA cutoff values ranging between 14% and 28%, while maintaining sensitivity rates from 70% to 95% within the tPSA range of 4 to 10 ng/mL (Catalona et al, 1998; Partin et al, 1998; Veltri and Miller, 1999; Vessella et al, 2000;

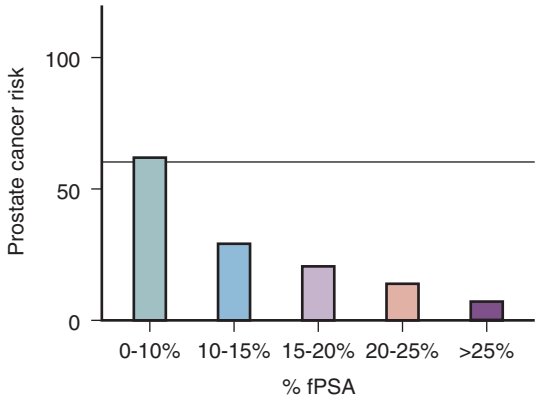


Figure 98–5. Prostate cancer risk stratification for men with prostate-specific antigen (PSA) values between 4 and 10 ng/mL (the diagnostic gray zone) based on percent free PSA (%fPSA). (From Catalona WJ, Partin AW, Slawin KM. Percentage of free PSA in black versus white men for detection and staging of prostate cancer: a prospective multicenter clinical trial. Urology 2000;55:372–6.)

Stephan et al, 2002). In a prospective, multi-institutional study of men 50 to 75 years old with PSA levels between 4 and 10 ng/mL and palpably benign prostate glands, a %fPSA cutoff of 25% (biopsy less than 25%) detected 95% of cancers while avoiding 20% of unnecessary biopsies (Catalona et al, 1998). **These data confirm that the application of %fPSA can help counsel men with PSA elevation between 4 and 10 ng/mL regarding their risk of cancer and the need for further evaluation to rule out the disease** (Fig. 98–5).

A number of other studies have demonstrated the usefulness of %fPSA in prostate cancer detection (for reviews see Polascik et al, 1999; Karazanashvili et al, 2003). Increased use of PSA as a screening tool has led to increased interest in the evaluation of PSA levels below 4.0 ng/mL. Examination of cancers detected within the PSA range 2.5 to 4.0 ng/mL has shown numbers of cancers similar to those detected in the 4 to 10 ng/mL range and also that these cancers are clinically significant and may exhibit aggressive pathologic potential (Colberg et al, 1993; Smith et al, 1998; Schroder et al, 2000; Recker et al, 2001). Djavan and colleagues (1999) demonstrated that for men with PSA levels less than 4 ng/mL, a %fPSA cutoff value of 27% could detect up to 90% of cancers while preventing 18% of unnecessary biopsies. Furthermore, comparison against PSA derivatives, such as prostate-specific antigen density (PSAD), PSA velocity, and transition zone density favored %fPSA. Haese and coworkers (1997) demonstrated that %fPSA in the total PSA (tPSA) range of 2 to 4.0 ng/mL does not substantially increase the number of biopsies needed to detect clinically significant prostate cancer compared with that in the 4 to 10 ng/mL range. In this study, a %fPSA cutoff value of 18% to 20% detected almost half of cancers while sparing 73% of men from undergoing biopsy, with a biopsy-to-cancer ratio of 3:1 to 4:1.

One study has demonstrated that a %fPSA cutoff of 25% would lead to detection of 95% of prostate cancers in both white and black men (Catalona et al, 2000), suggesting that race may not be important when using %fPSA in cancer detection. **Free PSA and total PSA both decrease in men receiving finasteride. As both decline, the percentage of fPSA is not altered significantly by this medication** (Keetch et al, 1997; Pannek et al, 1998).

In addition to contributing to detection, %fPSA has been shown to provide prognostic information. Serial measurement of %fPSA within archival serum demonstrated early marked and sustained differences in aggressive and nonaggressive prostate cancers (Carter et al, 1997). This group identified a statistically significant difference in %fPSA in men with and without metastatic disease up to 10 years prior to the development of prostate cancer. For the same cohort of men, total PSA levels failed to differentiate aggressive from nonaggressive prostate cancer 10 years prior to diagnosis. This study suggests that the longitudinal measurement of %fPSA changes may aid in detection and contribute information regarding disease behavior, thus providing useful information for therapeutic decision making.

Despite these encouraging results, several important factors should be kept in mind with regard to interpretation of %fPSA in clinical practice for cancer detection (Meyer et al, 1997). Such factors include prostatic manipulation, specimen handling, and assay variation (Partin et al, 1996a, 1996b; Stephan et al, 1997; Roth et al, 1998; Woodrum et al, 1998). Prostatic manipulation and urethral instrumentation have been shown to affect the interpretation of the ratio of fPSA to total PSA. Although there may be marginal changes in total PSA, fPSA levels may fluctuate, affecting the %fPSA calculation. Furthermore, because fPSA is cleared more rapidly from serum than complexed PSA forms (i.e., total PSA), the resulting calculated %fPSA is directly affected. Thus it is recommended that PSA determinations be avoided for several weeks following prostatic manipulation (surgery, biopsy, cystoscopy) (Partin et al, 1996b; Lein et al, 1997; Bjork et al, 1998).

Prostate volume has also been shown to influence the serum ratio of free to total PSA (Catalona et al, 1995; Partin et al, 1996; Haese et al, 1997; Stephan et al, 1997; Woodrum et al, 1998). The cutoff for %fPSA that optimizes sensitivity and specificity for cancer detection depends on prostate size because overlap in %fPSA is greatest among men without cancer who have enlarged prostates and men with cancer in the setting of prostate enlargement (Catalona et al, 1995). This group demonstrated that using a %fPSA cut point of 23% in men with PSA levels between 4 and 10 ng/mL and a prostate volume of less than 40 cm^3 could yield 90% sensitivity. However, for men with larger prostates, the %fPSA cut point dropped to 14% in order to maintain this degree of sensitivity.

The recommended and FDA-approved use for %fPSA remains for men with PSA levels within the diagnostic gray zone of 4 to 10 ng/mL. However, many clinicians use this ratio to aid in the decision making process regarding repeat biopsy (Stephan et al, 1997; Hayek et al, 1999; Djavan et al, 2000). For an initial biopsy, %fPSA ranges of 18% to 25% are commonly suggested; however, a widely accepted cutoff value has yet to be determined. For a repeat biopsy, Stephan and colleagues (1997) reported a 5% cancer miss rate when using a %fPSA value of 21% to trigger rebiopsy. A study by Hayek and coworkers (1999) illustrated a 16% positive rebiopsy rate regardless of %fPSA and concluded that this derivative was unable to provide further risk stratification for men in their population. Djavan and colleagues concluded that %fPSA is an accurate predictor of prostate cancer at rebiopsy. This group identified a %fPSA of 30% as the most accurate predictor of cancer in repeat biopsy specimens. However, until more series mature, the aggressiveness of this application in screening and follow-up biopsies should be tailored on a case-by-case basis (Luderer et al, 1995; Catalona, 1996; Partin et al, 1996b; Stephan et al, 1997; Catalona et al, 1998; Hayek et al, 1999; Djavan et al, 2000).

Classification of free PSA isoforms can be done by assessing the presence or absence of internal cleavages, in which case the respective "forms" are termed "nicked" or "intact." **PSA originates with a 17–amino acid chain that is cleaved to yield**

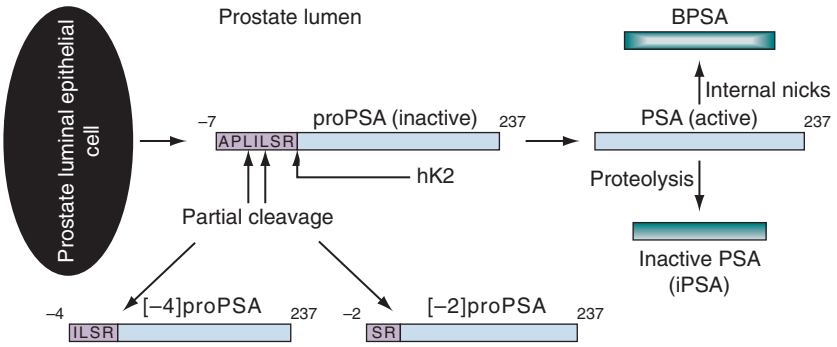


Figure 98–6. Differential cleavage and activation of pro–prostate-specific antigen (PSA). ProPSA is released from the prostate epithelial cell with a 7–amino acid leader sequence. hK2 cleaves the amino acid leader to activate PSA. Active PSA undergoes proteolysis to yield inactive PSA (iPSA) and may also undergo internal degradation to form benign PSA (BPSA). Partial cleavage of the 7–amino acid leader sequence yields inactive forms of proPSA (i.e., [–2]pPSA or [–4]pPSA).

a precursor inactive form of PSA termed proPSA (pPSA) (Zhang et al, 1995; Kumar et al, 1997, 2000; Mikolajczyk et al, 1997, 2001, 2002; Peter et al, 2001). As depicted in Figure 98–6, **the precursor form of PSA contains a 7–amino acid pro-leader peptide, in addition to the 237 constituent amino acids of mature PSA, and is termed [–7]pPSA.** Once released, the proleader amino acid chain is cleaved at the amino terminus by hK2, converting pPSA to its active 33-kD PSA form. In addition to hK2, pPSA may be activated to PSA by other prostate kallikreins, including hK4 (Takayama et al, 1997). Incomplete removal of the 7–amino acid leader chain has led to the identification of various other truncated or clipped forms of pPSA. These include pPSAs with 2, 4, and 5 leader amino acids ([–2]pPSA, [–4]pPSA, and [–5] pPSA) (Zhang et al, 1995; Kumar et al, 1997, 2000; Mikolajczyk et al, 1997, 2001, 2002; Peter et al, 2001). **With cellular disruption, these inactive forms circulate as free PSA and may constitute the majority of the circulating free PSA in patients with prostate cancer** (Mikolajczyk et al, 1997) (Fig. 98–7).

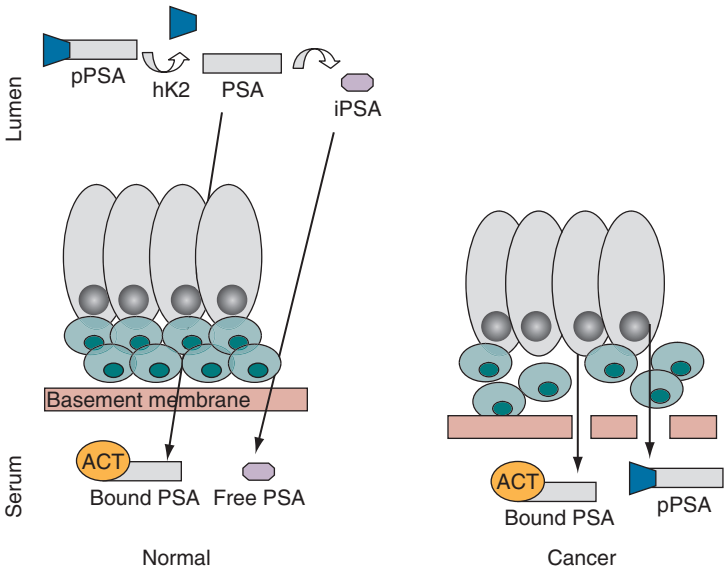


Figure 98–7. Prostate-specific antigen (PSA) synthesis in normal versus cancer tissue. ProPSA is secreted into the lumen, where the 7–amino acid leader sequence is cleaved by hK2 to yield active PSA. Some of the active PSA diffuses into the serum, where it is bound to proteases such as α_1-antichymotrypsin (ACT). The luminal active PSA undergoes proteolysis, and the resulting inactive PSA (iPSA) may also enter the circulation to circulate in the unbound or free state. In prostate cancer, loss of the tissue architecture may permit a relative increase in bound PSA and proPSA in serum.

Reports by Mikolajczyk and colleagues (2000, 2001) have revealed significantly elevated levels of these truncated forms of pPSA in prostate cancer tissue. Incomplete cleavage and processing of pPSA may contribute to the relative increase of these PSA isoforms identified in prostate cancer tissue. One of these clipped forms that is cleaved between leucine 5 and serine 6 of the propeptide has been termed [–2]pPSA. The decreased PSA processing in prostate cancer may result in a relative increase in pPSA and its cleaved forms, in particular [–2]pPSA. Immunohistochemical studies by Mikolajczyk and colleagues (2001) have demonstrated increased binding of monoclonal antibodies recognizing [–2]pPSA in prostate cancer tissue. Measuring the ratio of this clipped form of PSA to total PSA may serve as a strong discriminator between men with and without prostate cancer. These truncated forms in serum are being studied as potential prostate cancer markers.

From a clinical point of view, the present literature associates some isoforms with malignant prosate cells ([–2]proPSA) and others with BPH (BPSA) (Canto et al, 2004; Slawin et al, 2005). Two studies (Khan et al, 2003; Sokoll et al, 2003) support these findings regarding cancer detection and cancer "aggressiveness," demonstrating a positive diagnostic impact of pPSA in the early detection of prostate cancer in men with total PSA levels between 2.5 and 4 ng/mL and between 4 and 10 ng/mL. In the study by Sokoll and colleagues (2003), %pPSA detected up to 75% of cancers and avoided 59% of unnecessary biopsies (compared with 33% when %fPSA was applied) in men presenting with PSA levels between 2.5 and 4 ng/mL. In addition, studies by Catalona and colleagues (2003, 2004) showed an improved prostate cancer detection rate among men with total PSA between 2 and 4 ng/mL, where the ratio of proPSA ([–2]proPSA) to fPSA (%proPSA) spared nearly 20% of unnecessary biopsies while %fPSA only spared 10%. They also demonstrated—for PSA between 4 and 10 ng/mL—a 90% sensitivity and 31% specificity with %proPSA compared to only 20% (specificity) with %fPSA. Recently, in a multicenter validation effort sponsored by the National Cancer Institute (NCI) Early Detection Research Network (EDRN), Sokoll and colleagues (2008b) demonstrated excellent receiver operator characteristic (ROC) curves for the %[–2]proPSA assay for the diagnosis of prostate cancer. Likewise, a single institution study (Bangma et al, 2004) and a large multicenter study (Lein et al, 2005) showed no improvement in diagnostic accuracy when comparing [–5, –7] proPSA and the corresponding ratios with tPSA or f/tPSA. Further studies using other proPSA forms or tumor-associated proteins should be done.

Another isoform of fPSA, referred to as benign PSA or BPSA, represents a cleaved form of PSA that has been identified in tissue

from the nodular BPH transition zone tissue (Chen et al, 1997; Mikolajczyk et al, 2000; Wang et al, 2000; Canto et al, 2004; Slawin et al, 2005). In a study by Marks and colleagues (2001), BPSA discriminated men with symptomatic BPH from men without BPH. Although serum BPSA alone is unlikely to differentiate between hyperplasia and cancer, in combination with assays for pPSA, it may allow additional discrimination.

In addition to BPSA and pPSA, other isoforms of PSA have been identified in serum and have demonstrated promise as additional tools to aid in clinical detection of prostate cancer (Mikolajczyk et al, 2001, 2002; Peter et al, 2001). An additional form of pPSA that is found intact and inactive and that does not form a complex with ACT has been identified. This form of pPSA has been termed intact PSA and has been identified in human prostate cancer cells (Nurmikko et al, 2000, 2001; Steuber et al, 2002). It is likely that pPSA exists in various forms in tissue and serum from men with and without prostate cancer. Preliminary studies have demonstrated that the ratio of intact to free PSA may improve the accuracy of prostate cancer detection (Nurmikko et al, 2000, 2001; Steuber et al, 2002). Although encouraging, these studies using subfractions of fPSA await further scrutiny.

Human Kallikrein 2 (hK2)

The human kallikrein hK2 has been found to share many important properties with PSA and has demonstrated potential as another prostate cancer tumor marker (Young et al, 1992; Darson et al, 1997; Kumar et al, 1997; Rittenhouse et al, 1998; Lovgren et al, 1999; Becker et al, 2000; Yousef et al, 2001a). **Among many similarities, hK2 and PSA share 80% amino acid homology** (see Fig. 98–1), **exhibit similar specificity for prostate tissue, and are both hormonally regulated by androgens.** The exact function of hK2 remains under further study, but this protease has been shown to perform enzymatic activities, one of which is to activate the zymogen (pPSA) to the active PSA through cleavage of the amino acid presequence (see Fig. 98–7) (Young et al, 1992; Kumar et al, 1997; Yousef et al, 2001a).

The concentration of hK2 in samples of prostatic tissue, seminal fluid, and serum is many times lower than that of PSA (Young et al, 1992; Darson et al, 1997; Lovgren et al, 1999). In prostatic tissue, the hK2 mRNA concentration represents only 10% to 50% of PSA mRNA concentrations, and in semen and serum samples, the concentration of hK2 is 1% to 3% that of PSA (Young et al, 1992; Darson et al, 1997; Lovgren et al, 1999). Together with specificity issues, cross-reactivity with PSA and the detection limits of the available assays for these low hK2 concentrations challenged earlier analytic experiments. However, the development of hK2 purification techniques and more specific monoclonal antibodies has resulted in more reliable assays and thus increased study in the clinical setting (Piironen et al, 1996; Finlay et al, 1998; Klee et al, 1999; Becker et al, 2000).

Immunohistochemical studies revealed different tissue expression patterns for hK2 and PSA. In benign epithelium, PSA is intensely expressed compared with the minimal immunoreactivity of hK2 (Tremblay et al, 1997; Darson et al, 1999). **In contrast, in cancerous tissue hK2 is expressed more intensely.** Furthermore, hK2 immunohistochemically stains the different Gleason grades of prostate cancer differently than does PSA. This inverse staining relationship of hK2 is seen as intense staining in high-grade (Gleason primary grade 4 or 5) cancers and lymph node metastasis compared with minimal staining in low-grade (Gleason primary grade 1 to 3) cancers and even weaker association in benign tissue, in which PSA exhibits intense staining (Darson et al, 1997, 1999; Tremblay et al, 1997; Kwiatkowski et al, 1998).

The development of improved monoclonal antibodies for hK2 has minimized the previous cross-reactivity with PSA and permitted more accurate measurement of hK2 in serum samples (Finlay et al, 1998; Klee et al, 1999; Becker et al, 2000). Since the introduction of these assays, many researchers have demonstrated elevated levels of hK2 in men with prostate cancer compared with men without cancer (Becker, 2000). Furthermore, men with low-grade disease have lower concentrations of serum hK2 than men with more aggressive cancer (Darson et al, 1999; Becker et al, 2000). Application of the ratio of hK2 to free PSA (hK2/fPSA) allows discrimination between benign tissue and cancer (Kwiatkowski et al, 1998). For men with tPSA in the 4 to 10 ng/mL range, hK2/fPSA significantly differentiated prostate cancer from BPH, whereas hK2/tPSA did not (Becker et al, 2000). Data from a multicenter study demonstrated a statistically significant difference between men with biopsies positive for cancer, looking at hK2 alone and in combination with fPSA/tPSA (Kwiatkowski et al, 1998). Combining %fPSA and hK2/fPSA, Partin and associates (1999) demonstrated an increased cancer detection rate within the tPSA range of 2 to 10 ng/mL. Furthermore, this group was able to identify up to 40% of men with cancer in the 2 to 4 ng/mL range measuring hK2/fPSA.

Additional reports have demonstrated the ability of hK2 levels to predict pathologic outcome and to aid in repeat prostate biopsy decision making (Haese et al, 2000, 2003; Nam et al, 2001). Haese and colleagues (2000, 2003) evaluated the ability of hK2 levels to distinguish between pathologic organ-confined and non–organ-confined prostate cancer. In univariate ROC and multivariate logistic regression analyses, hK2 optimally predicted organ-confined disease. Nam and coworkers (2001) showed that men found to have cancer upon repeat biopsy had higher hK2 and hK2/fPSA levels than men with a negative biopsy, suggesting that hK2 may be helpful in improving the selection criteria for repeat biopsy. Recently, Vickers and coworkers (2008) used a large cohort of men to combine, within a multivariable model, hK2 with PSA and its isoforms to better predict prostate cancer detection. Although these results are encouraging, further evaluation is under way before recommending widespread application of hK2 to the clinical armamentarium of prostate cancer tumor markers.

Additional Kallikrein Tumor Markers

In addition to PSA (hK3) and hK2, 15 other kallikrein genes have been identified (reviewed in Paliouras et al, 2007). The expression products of these genes have demonstrated diagnostic potential as prostate cancer tumor markers. Many of these proteases have a highly conserved structural organization and have been shown to contribute to biologic events such as angiogenesis and growth factor release (Diamandis and Yousef, 2001). Study of these proteins suggests interaction among the kallikreins in pathways that affect normal physiologic and pathologic processes (Yousef and Diamandis, 2002). Among these genes, the studies have evaluated some of the potential of the expression products of *KLK4*, *KLK11*, *KLK14*, and *KLK15* as biomarkers for prostate cancer.

KLK4

The gene *KLK4* encodes hK4 and is predominantly expressed in basal cells of the normal prostate (Xi, 2004). Although its function and structure continue to be evaluated, current studies suggest that this peptide is not targeted for secretion and is predominantly localized to the nucleus (Xi et al, 2004). It was originally

demonstrated to be unique to prostatic expression, but improved reverse transcription polymerase chain reaction (PCR) techniques have identified *KLK4* mRNA expression in the testis, adrenal, uterus, and thyroid (Nelson et al, 1999). Although hK4 expression has been shown to occur in both normal and cancerous prostate tissue, *KLK4* mRNA was found to be expressed at higher levels in the majority of prostate cancer tissues compared with matched normal prostate tissues (Obiezu et al, 2002; Xi et al, 2004) and may represent a proliferative factor (Klokk et al, 2007). In ovarian cancer, hK4 is associated with advanced disease. Further evaluation is under way to explore the value of this kallikrein as a biomarker for prostate cancer.

KLK11

The gene *KLK11* encodes hK11, formally referred to as hippostasin or PRSS20 (Diamandis et al, 2002). It was initially found in the serum of cancer patients, but further studies have demonstrated that this protease may aid in differentiating prostate cancer patients from those with BPH, because immunofluorometric assays have displayed lower hK11 values in prostate cancer patients compared with men with BPH (Nakamura et al, 2003a, 2003b). Applying the ratio of hK11 to total PSA resulted in a further reduction in unnecessary biopsies. Nakamura and colleagues (2003a, 2003b) have demonstrated that at 90% sensitivity, the ratio of hK11 to total PSA has a specificity of 51.5%. Confirmatory studies are under way for this promising biomarker.

KLK14

Yousef and coworkers (2001b) have identified *KLK14* of the kallikrein gene family. Expression of this gene has been demonstrated in brain, spinal cord, prostate, thyroid, and testis. The expression of hK14 is similar to that of hK2 and PSA and has been noted in the secretory epithelial cells of the prostate (Hooper et al, 2001). Rabien and colleagues (2008) demonstrated the association of *KLK14* levels with biochemical progression after radical prostatectomy among men with prostate cancer. Elevated levels of this protein have been demonstrated in prostate cancer tissues compared with normal prostate tissues. Although it is still early in development, this marker may aid in prognosis because this protease appears to correlate with aggressiveness of disease (Yousef et al, 2003; Rabien et al, 2008).

KLK15

The gene *KLK15* encodes hK15. Although it is most notably expressed in the thyroid, lower levels of hK15 expression have also been measured from the prostate, salivary gland, adrenal, colon, testis, and kidney (Yousef et al, 2001). Using a human prostate cancer cell line, *KLK15* expression was found to be upregulated compared with normal prostate tissues (Yousef et al, 2001c). As with hK14, hK15 has shown an association with tumor aggressiveness and has potential as a diagnostic and prognostic prostate cancer biomarker (Stephan et al, 2003).

Proteomic Patterns

A number of years ago, the "holy grail" of cancer biomarkers was to develop protein signatures of the disease. The goal was to discern proteomic patterns that could serve as fingerprints that would not only identify the presence of cancers but also subclassify patients into groups that may have different prognoses or potential responses to therapy. Application of sensitive tools in the study of molecular biology is becoming essential for the discovery of novel tumor markers. Identifying unique genetic expression in cancer states compared with normal tissues will provide not only insight into the molecular etiology of disease but also novel methods for detection. In addition to identifying genes that are either on or off, identification of post-translational events that are unique to disease states will undoubtedly become invaluable in the discovery of cancer biomarkers. The identification of biomarkers from human serum and body fluids has been assessed by a variety of proteomic technologies. Much of the approach to develop such fingerprints came from the use of mass spectrometric (MS) analysis of blood and/or urine samples. The early MS studies used large machines with relatively low throughput. To increase the ability of this approach to analyze larger numbers of samples more rapidly, an approach known as surface-enhanced laser desorption ionization (SELDI) was developed. A large number of these instruments were placed in centers around the world. SELDI separates relatively small fragments of proteins (peptides) and uses these patterns to distinguish patients with cancer from those with benign diseases (Malik et al, 2007). Although in principle this approach is sound, it suffers from several significant drawbacks. These include the lack of ability to define the individual protein components and therefore the inability to produce more typical antibody-based tests. Also, while operating at single institutions, the instruments performed in a reasonably reproducible fashion, but the design of the instruments was such that no two instruments performed with sufficiently high levels of concordance. After extensive investigation, it was concluded that SELDI-based approaches to analyzing serum samples are not a reliable tool with which to diagnose prostate cancer, at least at this time (McLerran et al, 2008).

In order to address these limitations, MS approaches have been developed that reveal the identities of the components. Prior to applying these approaches, a significant amount of attention has been spent on standardizing protocols by which tissue, blood, and urine samples have been collected. The apparently subtle differences in collection techniques have been shown to result in somewhat major and therefore confounding differences in proteomic patterns (Diaz et al, 2008). Much progress has been made toward this end, and the more recent findings have demonstrated the ability of MS approaches to distinguish diseased and normal populations. These include the use of two-dimensional difference gel electrophoresis (2D-DIGE) as a means to identify serum markers for the differentiation of more aggressive prostate cancer (Byrne et al, 2009). Similar studies have been performed with urine samples to develop a "urine proteome" for the identification of prostate cancer (M'Koma et al, 2007). The idea of a fingerprint for the detection and classification of prostate cancer is still one that holds much promise but still needs further investigation and validation.

Endoglin

Endoglin is a transmembrane glycoprotein that is otherwise known as CD105. Although the expression of this protein is not prostate restrictive or even prostate cancer selective, it has been shown by a number of groups to be expressed in vascular endothelial cells and therefore found to be elevated in cancerous states. Investigators have examined the possibilities for detecting endoglin in the plasma as well as in the urine of men with prostate cancer. When examining the plasma levels of the protein, the investigators demonstrated that with approximately 3 years of follow-up, preoperative endoglin levels correlate with an increased risk for biochemical progression of

prostate cancer (Svatek et al, 2008). Similarly, when endoglin is used in combination with several other blood-based biomarkers, further discrimination regarding the risk for biochemical recurrence is provided (Svatek et al, 2009). Endoglin is also expressed in the urine of men with prostate cancer compared with those who are biopsy negative after each group received a DRE. These urinary levels correlate with tumor volume and appear to be more accurate than PSA in the discrimination of biopsy outcome (Fujita et al, 2009). These same investigators also examined the serum levels of endoglin and demonstrated that although the serum levels were not predictive of a diagnosis of prostate cancer, it was possible to distinguish between organ-confined and non–organ-confined disease. These initial studies have been intriguing and certainly will need validation in multi-institutional trials.

PCA-3

Using differential display and Northern blot analysis to compare normal and prostate cancer tissue, Bussemakers and colleagues (1999) identified the *DD3* prostate-specific gene on chromosome 9q21-22. Study of this gene has determined that it may function as noncoding RNA because it has been found to be alternatively spliced, contains a high density of stop codons, and lacks an open reading frame. **Expression of the DD3^{PCA-3} protein has been localized to prostatic tissue and has been found in 95% of prostate cancer and prostate metastasis specimens.** de Kok and colleagues (2002) developed a real-time quantitative reverse transcriptase PCR (QRT-PCR) assay for DD3 and showed **66-fold upregulation of this protein in cancerous tissues compared with normal control tissues. Furthermore, DD3 was detected from specimens containing as little as 10% cancer, indicating that this test was capable of finding cancer within a large background of normal cells.** Using this discovery, Hessels and coworkers (2003) developed a test to detect DD3 in urine specimens from men, following prostate massage and biopsy. Using QRT-PCR to analyze the urine from these men undergoing biopsy for serum PSA greater than 3 ng/mL, the test demonstrated 67% sensitivity and 83% specificity for men diagnosed with cancer after confirmatory biopsy. As also reported, a negative predictive value of 90% supports the potential of the test as a modality to reduce the number of invasive diagnostic procedures, such as transrectal ultrasonography (TRUS) biopsy. Several clinical studies and further assay development are currently under way for evaluation of DD3/PCA-3.

This urine-based biomarker has been investigated most extensively and will soon be evaluated by the FDA. After its identification in the prostate cancer tissue, investigators have been able to demonstrate its detection using RT-PCR within the urine of men with prostate cancer. To enhance the sensitivity of such assays, urine samples have been collected after an "attentive" digital rectal examination, which conceptually will loosen and shed the cells within the prostate and therefore enhance the chance of detection (Fig. 98–8). Using this approach, urine-based assays have been developed that can detect prostate cancer (Tinzl et al, 2004). Several clinical studies have been performed that evaluate the utility of PCA-3 to serve as a prostate cancer biomarker. Some studies have focused on the utility of this biomarker in the setting of individuals who have undergone at least one biopsy of their prostate for the determination of prostate cancer (Hessels et al, 2003; van Gils et al, 2008). Assaying PCA-3 has been shown to have some utility to discriminate among those who would benefit from a second biopsy in that these individuals end up with prostate cancer (Deras et al, 2008). PCA-3 has also been reported to be associated with Gleason score of men with the disease in that higher levels of the message appear to correlate with Gleason score. PCA-3 levels are reported as a ratio of PCA-3 message over PSA message within the urine. The levels of PSA message are therefore used as a means to normalize these levels. Interestingly, in a recent report, it was noted that urinary levels of PCA-3 do not appear to be elevated with increasing prostate size but do correlate with tumor volume (Whitman et al, 2008). Although this supports the concept that enlarged prostates would not by themselves result in higher PCA-3 levels, it is somewhat surprising because the PSA message is used as a normalization factor to evaluate PCA-3 levels. In men with enlarged prostates, one would expect to have an elevated level of PSA message in urine as a result of the increase in cells in the prostate. Also, a breakdown of architecture would result in more PSA message being released into the urine and therefore an actual decline in urine-based PCA-3 message. The investigators actually did not note any change in PCA-3 levels and do not provide an explanation for this result (Whitman et al, 2008).

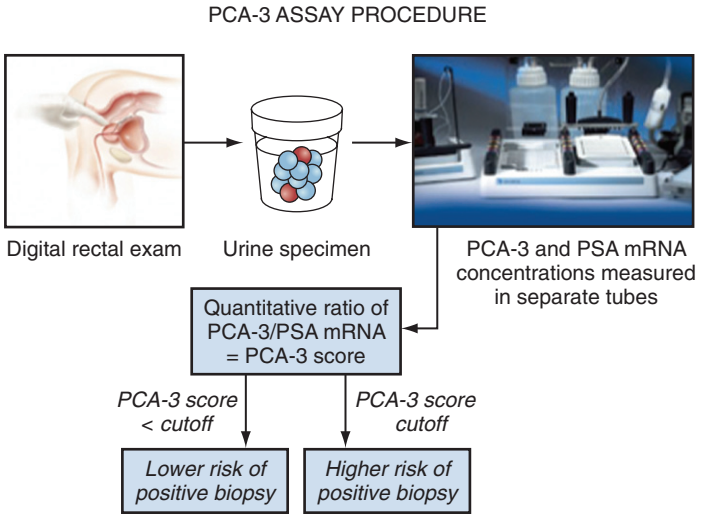


Figure 98–8. PCA-3 assay protocol. Following "attentive" digital rectal exam, urine is collected. RT-PCR determines the mRNA levels for PCA-3 and PSA. The ratio between PCA-3/PSA determines the PCA-3 score. Prostate cancer risk level suggests need for biopsy. (From Groskopf J, Aubin SM, Deras IL, et al. APTIMA PCA3 molecular urine test: development of a method to aid in the diagnosis of prostate cancer. Clin Chem 2006;52:1089–95.)

Recently, the PCA-3 diagnostic test has been standardized for whole urine, in an easy-to-use platform retaining the 69% sensitivity and 79% specificity (area under curve [AUC]-ROC = 0.746) in men undergoing prostate biopsy (Groskopf et al, 2006). However, the AUC-ROC was only 0.69 in a larger cohort of men (Deras et al, 2008). The molecular assay has been further evaluated in a multicenter trial in Holland (van Gils et al, 2007) and in the United States (Sokoll et al, 2008a), where the test has also been performed similarly. Although these results are promising, further validation is necessary to understand fully the potential clinical utility of this test. The U.S. FDA has not yet approved the PCA-3 diagnostic test, but several reference laboratories that run the test are available in the United States.

CELLULAR BIOMARKERS

Circulating Tumor Cells

There has been significant interest over the last several years in the development and evaluation of tests that can detect circulating tumor cells. The excitement in this area of research goes back fifteen years when investigators using polymerase chain reaction (PCR)–based approaches demonstrated PCR positivity for PSA among men with advanced prostate cancer (Katz et al, 1994). The problem with this approach was that PCR positivity was also found among men with localized prostate cancer, and even in men without prostate cancer (Sokoloff et al, 1996; Thiounn et al, 1997).

As described earlier in this chapter, one of the unmet needs in prostate cancer is the ability to use a marker that can predict the presence of disease that either has the ability to spread outside of the prostate or has already spread outside of the prostate. The concept behind using detection of epithelial cells in blood is that, if present, they might indicate the presence of tumor cells that have left the prostate and therefore perhaps metastatic disease.

Using a combination of antibodies that are designed to detect epithelial cells in blood, a system has now been developed that can be used with clinical samples. The CellSearch Circulating Tumor Cell Kit is now approved by the FDA for use in disease monitoring. This system is produced by Veridex (Raritan, NJ). The CellSearch system uses antibodies against CD45, EpCAM, and cytokeratins 8, 18, and/or 19. Positive cells are indicated by negative staining for CD45 and positive staining for EpCAM and the various cytokeratins. Using a magnetic core separation system, blood samples are analyzed using the disposable cartridges provided by the system. Men with prostate cancer can have samples taken before and after a therapeutic regimen. Response to therapy is then measured by alterations in the numbers of positive cells that are observed in the system. Based upon the studies performed using this system, a circulating tumor cell (CTC) count of 5 or more cells per 7.5 mL of blood at any time during the course of the disease has been associated with a poor prognosis (Shaffer et al, 2007). A principal limitation to this approach is that only cells that stain positively for EpCAM and the cytokeratins will be detected. Any degradation of cell surface molecules, or the cells themselves, will result in a failure to detect cells that may indeed to be present in blood. In a study of 422 patients with metastatic prostate cancer, using the Veridex platform, the investigators demonstrated that there was a difference between baseline numbers of cells and those present 2 to 5 weeks post-treatment (Fig. 98–9). For example, 57% of the patients had greater than 5 cells per 7.5 mL of blood before treatment, and 39% had greater than 5 cells per 7.5 mL after treatment (Shaffer et al, 2007).

Using a similar type of approach, investigators at the Harvard Medical School developed their own system to detect circulating tumor cells in blood. This microfluidic system has a number of advantages over the FDA-approved system. This "CTC-Chip" uses microposts that are embedded with anti-EpCAM antibody. The investigators have reported that they can detect 1 EpCAM-positive cell among one billion blood cells. This system provides the opportunity to subsequently isolate and therefore further study the circulating tumor cells (Nagrath et al, 2007).

In a more recent study, using the cutoff of greater than or equal to 5 CTCs per 7.5 mL of blood, patients were classified into populations that were considered to have either favorable or unfavorable responses. Among 276 men, they demonstrated that the group with the higher numbers of CTCs had a shorter overall survival and that this prediction was more accurate than the use of PSA (de Bono et al, 2008).

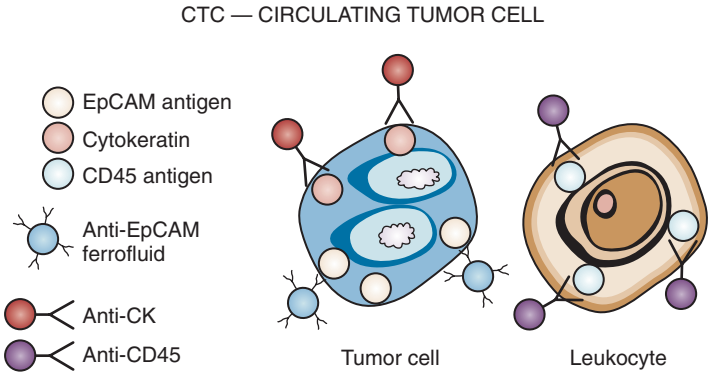


Figure 98–9. CellSearch CTC: Circulating Tumor Cell (Veridex) cell enumeration system. EpCAM, epithelial cell adhesion molecule; CK, cytokeratin; CD45, CD stands for "*cluster of differentiation,*" which was originally called *leukocyte common antigen*. The anti-EpCAM ferrofluid captures the cells, and they are then validated with cytokeratin-positive and CD45-negative staining.

In general, the potential use of CTCs as a measurement of prostate cancer cells appears to be promising. At the same time, we must realize that the markers being used to select cells from the blood can detect epithelial cells but are not tumor cell–associated. This may lead to the detection of cells that are not cancerous but actually represent normal epithelial cells in blood. On the other hand, the sensitivity of the currently used CTC assays may be somewhat limited in that tumor cells may exist at metastatic sites, such as in bones, without being easily detectable in blood. It is clear that the integration of more specific antibodies, as well as other approaches that can more accurately and sensitively detect tumor cells, may further enhance the utility of these types of assays.

Autoimmune Reponses

Although we classically think of biomarkers as substances that are abnormally expressed by the tumors and which are then detectable in a body fluid such as urine, blood, or prostatic fluids, this is not the only type of biomarkers that may be predictive. The response of the body to the presence of the cancer cell can itself be used as biomarkers. The immune response to the presence of a tumor can be predictive. Using a high-throughput approach, investigators at the University of Michigan were able to develop autoimmune profiles that could distinguish individuals with prostate cancer from those without the disease (Wang et al, 2005). Although the results appeared to be promising, further studies have not validated these findings. It is still likely that the immune response to tumors can indeed be used to detect tumors, or even the presence of metastases.

MOLECULAR BIOLOGY

New understanding of the molecular biology of carcinogenesis and prostate cancer is beginning to yield a new era in prostate cancer tumor research. Applications of sensitive tools are providing clinicians with improved methods for diagnosis and management of disease. These advances in molecular oncology have vastly improved our current understanding of prostate cancer etiology and molecular pathogenesis and have identified the

importance of genomic alterations, epigenetic modifications, and gene-protein expression that contribute to the development and progression of prostate cancer.

Future Directions in Prostate Cancer Biomarker Research

Gene Susceptibility Loci

The presence of a positive family history has been known to be a risk factor for the development of prostate cancer. A number of susceptibility loci probably involved in the risk of development of cancer have been identified (Lichtenstein et al, 2000) through studies of affected families with prostate cancer. Prostate cancer susceptibility genes have been located on chromosome 1q24-25 (*HPC1*), 1q42-2-q43 (*PCaP*), 1p36 (*CAPB*), 16q23.2, 17p11 (*ELAC2* or *HPC2*), 20q13 (*HPC20*), and Xq27-28 (*HPCX*) (Monroe et al, 1995; Lichtenstein et al, 2000; Nam et al, 2003; Simard et al, 2003). Key susceptibility genes that have been proposed to be involved in the inflammatory response are *MSR1* and *RNAEL* (DeMarzo et al, 2003).

Within these families, genetic polymorphisms are likely to occur at higher frequency and contribute to the increased risk of prostate cancer. **Polymorphic variants in genes encoding the androgen receptor (AR), CYP17, and 5α-reductase type 2 (SRD5A2) have been evaluated and suggest a role for infection and inflammation in the development of prostate cancer** (DeMarzo et al, 2003). Other polymorphic variants in genes encoding CYP3A, vitamin D receptor, PSA, GSTT1, GSTM1, GSTP1, IGF-1, and IGF-binding protein 3 have also been studied. Among these, GSTP1 and IGF have shown a correlation with the presence of cancer on biopsy of men with elevated PSA levels (Nam et al, 2003).

Although this information has aided and continues to contribute to the study of prostate cancer, familial susceptibility genes and polymorphisms are unlikely to account completely for the development of prostate cancer. Development of a large-scale test for these genes as a screening modality in the male population would probably not be very effective. Other factors such as diet, lifestyle, and chronic inflammation have also been implicated in the cause and progression of prostate cancer (Nelson et al, 2002; Foley et al, 2004; Montironi et al, 2004).

microRNAs

Based upon the realization that a majority of the DNA in the genome does not encode protein sequences, the utility of these sequences in the regulation of gene expression has been under intense investigation. Among the most important components of this regulation are microRNAs (miRNAs). These are small (usually less than 22-nucleotide (nt) sequences that are involved in the regulation of mRNA. With the association of a number of these miRNAs with cancer, the idea of using these nucleotides as markers of the disease has been attractive. A test has been developed to detect miRNAs in the plasma of men with prostate cancer. Although the study populations were small, the investigators demonstrated that detection of miR-141 has excellent potential for distinguishing men with prostate cancer from those without the disease (Mitchell et al, 2008). Additionally, microRNAs assays have been developed that can robustly detect even small amounts of these small RNAs in human tissues (Siva et al, 2009). Although these findings need to be expanded to larger populations of individuals, there is interesting data to demonstrate that this is an interesting family of potential markers.

α-Methylacyl Coenzyme A Racemase

The α-methylacyl coenzyme A racemase *(AMACR)* gene, located on chromosome 5, is upregulated in prostate cancer tissues (Luo et al, 2001; Rubin et al, 2002). AMACR functions as an enzyme responsible for the beta-oxidation of branched-chain fatty acids obtained in diets consisting of beef and dairy products. Upregulated AMACR mRNA levels have been identified using immunohistochemical analysis and Western blot assays in clinical prostate cancer tissue. Luo and colleagues (2002) demonstrated that 88% of prostate cancer cases and both untreated metastasis and hormone-refractory prostate cancers were strongly positive for AMACR. Rogers and colleagues (2004) measured AMACR levels in the voided urine from 26 men following transrectal prostate biopsy. Elevated AMACR levels were detected in 18 of 26 (69%) of the men and provided 100% sensitivity (12 of 12 positive biopsies) and 58% specificity. Immunohistochemical studies by Rubin and coworkers (2002) have shown that *AMACR* expression in biopsy tissue may provide 97% sensitivity and 100% specificity for prostate cancer detection. Furthermore, in combination with other markers, such as TP63, that aid in identifying basal cells absent in prostate cancer, measurement of AMACR has potential for the development of molecular probes to aid in the detection of prostate cancer.

However, there is new literature examining an expanded role for AMACR in noninvasive CaP screening. For example, Rogers and coworkers (2004) assessed the feasibility of a urine test for CaP based on measuring AMACR levels. They performed immunoblot analysis on voided urine from 26 men with suspected CaP following transrectal prostate biopsy. Elevated AMACR levels were detected in 18 of 26 (69%) of these patients. All 12 men with CaP demonstrated AMACR-positive urine (100% sensitivity), while 5 of 12 men without cancer had false-positive urine tests (58% specificity). Fifty percent of men with atypical biopsies were positive for AMACR as well. Zielie and coworkers (2004) developed an assay to detect CaP based on urine samples collected after prostatic massage. The researchers used polymerase chain reaction (PCR) to detect AMACR levels from total cellular RNA collected from the spun urine. When AMACR levels were normalized to cellular PSA mRNA levels, a diagnostic cutoff value of 2 SDs above the mean correctly identified all 9 cancer-free controls (100% specificity) and 7 of 10 (70% sensitivity) patients with CaP. Such assays for the detection of CaP from urine specimens show early promise but still require additional investigation.

Prostate Breast Overexpressed Gene1 *(PBOV1)* or *UROC28*

An and colleagues (2000) have cloned and characterized a novel gene, *UROC28,* found to be overexpressed in prostate, breast, and bladder carcinomas. This gene is on chromosome 6q23-24, and the expression protein product is measurable in serum. Early immunohistochemical studies have demonstrated differential expression and characterization between normal and cancerous tissues. This group has also identified and measured the protein UC28 in serum. Application of the antibody to a ProteinChip and SELDI analysis has provided encouraging results that correctly distinguish cancer specimens from normal and BPH specimens. This preliminary work remains under investigation.

Annexin A3

Among the potential urine-based proteins that can be used as biomarkers for prostate cancer is annexin A3. This protein is part

of a family of calcium and phospholipid binding proteins that have been shown to be altered in cancer (Wozny et al, 2007; Köllermann et al, 2008). Recently, using an immunoblot in which urine samples were blotted onto a membrane and probed for annexin A3 using an antibody, investigators were able to determine the potential clinical utility of urine-based annexin A3, either as a stand-alone biomarker or together with PSA. In a blinded study that consisted of training and evaluation sets of 243 and 264 men, respectively, the investigators were able to show that the addition of annexin A3 added to the ability of PSA to discriminate between these groups. Annexin A3 levels are inversely related to the presence of prostate cancer. Although this marker appears to have potential utility, further studies are certainly warranted to validate this work.

Hepsin

Complementary DNA (cDNA) microarray analysis has demonstrated overexpression of hepsin in prostate cancer compared with normal prostate and BPH tissues (Luo et al, 2001; Magee et al, 2001; Stamey et al, 2001). Hepsin is a type II transmembrane serine protease and was originally found as a cDNA clone in a human liver cDNA library (Leytus et al, 1988). Immunohistochemical studies have shown abundant staining of hepsin in tumor cell membranes. Stephan and coworkers (2004) have shown hepsin staining in 90% of all cases of prostate cancer. Furthermore, these authors demonstrated that in 53% of cases hepsin overexpression was more than 10-fold in cancerous tissue. In addition to providing a method for cancer detection, hepsin expression may provide prognostic information that may be used to assess prostate cancer aggressiveness.

NMP 48 (50.8 kD)

Using proteomic patterns based on surface-enhanced laser desorption ionization–time-of-flight (SELDI-TOF) mass spectroscopy, Hlavaty and colleagues (2003) discovered a unique 50.8-kD protein. This protein was subsequently characterized as a vitamin

Key Points

- Today, most prostate cancer arises as clinically nonpalpable (stage T1c) disease with PSA between 2.5 and 10 ng/mL. The evolving demographics and natural history of prostate cancer have resulted in stage migration to nonpalpable, clinically localized (stage T1c) disease and a parallel reduction in mortality.
- Although PSA is widely accepted as a prostate cancer tumor marker, it is organ specific and not disease specific.
- PSA is normally found in low concentration in serum (ng/mL). In serum, PSA circulates in both bound and unbound forms. Three proteins that are known to bind to PSA in blood are α_1-antichymotrypsin (ACT), α_2-macroglobulin (A2M), and α_1-protease inhibitor (API).
- Although prostate cancer cells do not produce more PSA than benign prostate epithelium, the PSA produced from malignant cells appears to escape proteolytic processing. Thus men with prostate cancer have a greater fraction of serum PSA complexed to ACT and a lower percentage of total PSA that is free compared with men without prostate cancer.
- The serum half-life of PSA, calculated after removal of all prostate tissue, is 2 to 3 days.
- Uncomplexed PSA is cleared from the serum within 2 to 3 hours.
- Finasteride (5 mg) and other 5α-reductase inhibitors used for treatment of BPH have been shown to lower PSA levels by an average of 50%.
- Although saw palmetto has not been shown to affect PSA levels, possible contaminants of these unregulated supplements may include compounds that can alter PSA levels (i.e., PC-SPES, now off the market). Interpretation of PSA values should always take into account the presence of prostate disease, previous diagnostic procedures, and prostate-directed treatments.
- The role for %fPSA is more applicable to PSA levels less than 10 ng/mL because the positive predictive rate of total PSA greater than 10 to 20 ng/mL has been demonstrated to be as high as 80%.
- PSA originates as a 17–amino acid chain that is cleaved to yield an inactive precursor form of termed proPSA (pPSA).
- The current clinically relevant immunodetectable complexed forms of PSA are bound to ACT and, to a lesser extent, to API. The sum of these and other presently unknown PSA complexes is represented by the term complexed PSA (cPSA).
- Immunohistochemical studies reveal different tissue expression patterns for hK2 and PSA. In benign epithelium, PSA is intensely expressed compared with the minimal immunoreactivity of hK2. In contrast, in cancerous tissue hK2 is expressed more intensely.
- Polymorphic variants in genes encoding the androgen receptor (AR), CYP17, and 5α-reductase type 2 (SRD5A2) have been evaluated and suggest a role for infection and inflammation in the development of prostate cancer. Notable among these are the AR variant 7, which has been shown to be associated with more aggressive disease.
- Segments within the gene promoter that are composed of GC-rich regions are termed CpG islands. Alterations in the methylation status of these regions may affect gene expression and have been shown to play a role in carcinogenesis.
- The products of two hypermethylated genes that have been evaluated in prostate cancer development are glutathione-*S*-transferase P1 (GSTP1) and RAS association domain family protein isoform A (RASSF1A).
- The *AMACR* gene, located on chromosome 5, has been found to be upregulated in prostate cancer tissues.
- Expression of the $DD3^{PCA-3}$ protein has been localized to prostate tissue and has been found in 95% of prostate cancer and prostate metastasis specimens. This message has been used to develop a urine-based test for the disease.
- Circulating tumor cells are being used as novel tools to correlate with response to therapy, as well as provide valuable resources with which to study metastatic disease.
- The discovery of the gene fusions associated with prostate cancer has revealed the potential to develop new tools with which to characterize the disease, although the clinical utility of these fusions must still be evaluated.
- Given the novel biomarkers that have been developed, multiparametric testing would seem to be a logical application with the currently existing PSA tests.

D binding protein using peptide mass fingerprinting. Using preprocessed serum samples from men with prostate cancer, BPH, and no cancer, this group was able to identify correctly vitamin D binding protein in the samples from men with cancer. SELDI-TOF identified the protein in 50 of 52 (96%) cancer cases, 5 of 20 (25%) biopsy-confirmed benign cases, 3 of 10 (30%) BPH cases, and 2 of 50 (4%) normal controls. Validation studies are under way for this potential prostate cancer tumor marker.

Metabolites

One of the characteristics of cancer cells are modifications in their metabolism. The cancer cell, in general, uses a less efficient source of generating energy and therefore surviving. Even with the explosion of molecular biology and the large amount of information that has been learned about cell cycle regulation, little attention has been given to the differences that exist between the metabolic processes of the cancer cell versus normal cells. Using a high-throughput approach that combines chromatography with mass spectroscopy, a number of potentially important differences in metabolomic profiles have been observed when comparing prostate cancer tissue with normal tissue. Among the molecules profiled, one of the differences appearing is with sarcosine, which has been demonstrated in the urine of men with prostate cancer (Sreekumar et al, 2009). Although the average levels of urine-based sarcosine are indeed different between men with prostate cancer and those without the disease, from the data provided, it seems that a cutoff able to separate these populations in a clinically robust fashion is unlikely. Despite this, there certainly is potential for the use of cancer metabolites to serve as markers of the disease, and this is an area of active investigation.

SUMMARY

Early detection when cancer remains confined to the prostate will not only improve cure rates but also decrease mortality from this disease. Although the discovery and application of PSA have revolutionized current prostate cancer detection and management, stage migration and changes in the natural history of this cancer have outrun the currently maximized application of this tumor marker. Application of various PSA derivatives, although improving sensitivity, risks impairing specificity. Discovery of molecular derivatives of PSA and new kallikrein markers has also improved prostate cancer detection.

Innovations and new understanding in the field of molecular oncology have provided a host of potential prostate cancer tumor markers. Because prostate cancer has been shown to be a heterogeneous disease, application of a panel of markers will probably ultimately provide added sensitivity and specificity for detection of the disease. Identification of hypermethylated regions, such as for *GSTP1*, and over- and underexpressed proteins and genes, such as PCA-3, provides greater diagnostic and prognostic potential to improve detection of prostate cancer. As these discoveries mature, development of these markers from research into clinically applicable tools will improve detection and management of prostate cancer.

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chapter 99

Early Detection, Diagnosis, and Staging of Prostate Cancer

Stacy Loeb, MD ● Herbert Ballentine Carter, MD

Early Detection

Staging

Prostate cancer rarely causes symptoms at an early stage. The presence of symptoms suggests locally advanced or metastatic disease. Manifestations of locally advanced prostate cancer include urinary symptoms, ureteral obstruction causing renal failure, hematospermia or decreased ejaculate volume, and, rarely, impotence. Manifestations of metastatic disease include bone pain, pathologic fractures, anemia, and lower extremity edema, and, less commonly, malignant retroperitoneal fibrosis, paraneoplastic syndromes, and disseminated intravascular coagulation (DIC). Locally advanced and metastatic disease are uncommon presentations due to widespread screening with prostate-specific antigen (PSA) and digital rectal examination (DRE). A histologic diagnosis of prostate cancer is typically made by prostate needle biopsy using transrectal ultrasound guidance.

Following a diagnosis of prostate cancer, the goal of staging is the accurate determination of disease extent for management decisions and prognostication. In addition to PSA and DRE, the pathologic features of a prostate biopsy (grade and extent) help inform management decisions. Imaging studies are useful in specific situations.

This chapter will review diagnostic and staging modalities for prostate cancer.

EARLY DETECTION

Screening

General Concepts of Screening

Screening refers to testing for disease in healthy, asymptomatic populations, whereas diagnosis is the identification of disease among individuals with signs or symptoms. The principal goal of screening is to improve overall health outcomes by identifying and treating disease at an earlier stage. Despite the common misperception that early diagnosis through screening is invariably beneficial, it also has the potential for harm (Welch, 2004). There is strong evidence that prostate cancer screening reduces the rates of advanced disease (van der Cruijsen-Koeter et al, 2006; Aus et al, 2007), but controversy exists regarding the balance of benefit and harm (Barry, 2009).

From 1993 to 2003 after the onset of widespread PSA testing, the mortality rate from prostate cancer declined by 32.5% (Surveillance, Epidemiology, and End Results [SEER] Program), along with a 75% reduction in the proportion of advanced-stage disease at diagnosis. It was estimated that PSA screening could have accounted for 45% to 70% of this reduction in prostate cancer mortality in the United States (Etzioni et al, 2008). However, randomized trials comparing the disease-specific outcomes of men who are screened and those who are not represent the highest level of evidence for screening.

Randomized Trials

The Prostate, Lung, Colon, and Ovary (PLCO) trial of the National Cancer Institute (NCI) and the European Randomized Trial of Prostate Cancer Screening (ERSPC) were initiated in 1993 to compare prostate cancer–specific mortality (primary end point) between screened and unscreened arms (Auvinen et al, 1996; de Koning et al, 2002; Schroder, 2003; Andriole et al, 2004). Reductions in high-grade cancer and locally advanced/metastatic disease with serial screening were reported in the ERSPC (van der Cruijsen-Koeter et al, 2006; Aus et al, 2007), as well as a 20% reduction in prostate cancer–specific mortality among those screened compared with controls at a median follow-up of 9 years (Schroder et al, 2009). However, in the ERSPC, it was estimated that to prevent one prostate cancer death would require screening 1410 men and treating an additional 48 men. With longer follow-up, the Goteborg randomized population-based screening trial reported a greater mortality benefit with screening. By comparison, there was no difference in prostate cancer mortality between the screened and control arms of the PLCO at a median follow-up of 11 years (Andriole et al, 2009). Both trials reported results early when considering the long natural history of prostate cancer; and, with further follow-up, the findings could change. Further, the disparate findings between the studies may result from high rates of screening in the control arm of the PLCO (contamination) and lesser ability to detect a mortality difference given that the PLCO had approximately threefold fewer events than the ERSPC (Barry, 2009).

These randomized trials emphasize the potential for overdiagnosis (detection of cancers that would have otherwise remained undetected) and overtreatment of prostate cancer with screening. Overtreatment is especially concerning among older men (age greater than 65 years), for whom treatment was associated with minimal benefit in a randomized trial of surgery versus watchful waiting (Bill-Axelson et al, 2008). Given that the average age at diagnosis today is approximately 67 years, the risk of overtreatment is high.

Specialty Group Recommendations

Professional groups have published statements and guidelines on prostate cancer screening (National Comprehensive Cancer

Network, 2007; Lim and Sherin, 2008; Lin et al, 2008; U.S. Preventive Services Task Force, 2008). The U.S. Preventive Services Task Force (2008) concluded that the evidence is insufficient to assess the balance of benefit and harm of screening among men age 75 years or less, whereas screening is not recommended for men age 75 years or older. The American College of Preventive Medicine recommends against routine population screening with PSA and DRE (Lim and Sherin, 2008) and suggests shared decision making for men age 50 years or older with a life expectancy greater than 10 years. The American Cancer Society and the American Urological Association recommend annual prostate cancer screening beginning at age 50 years for average-risk men and earlier for higher-risk men (positive family history or black race). The National Comprehensive Cancer Network (2007) recommends offering baseline PSA screening at age 40 years with the frequency of follow-up testing based on PSA test results. The appropriate age to start and discontinue screening (Ross et al, 2005; Catalona et al, 2006; Schaeffer, 2009) and the appropriate interval between screens will continue to be a matter of debate (Carter et al, 1997; Ross et al, 2000; Hugosson et al, 2003b).

Despite the controversy associated with prostate cancer screening and disparate recommendations from professional organizations, opportunistic prostate cancer screening is highly prevalent in the United States (Lu-Yao et al, 2003; Sirovich et al, 2003; Ross et al, 2004; Schwartz et al, 2004; Chan et al, 2006; Walter et al, 2006). **Although prostate cancer screening remains controversial, men who present for periodic health examinations should be made aware of the availability of the PSA test so that they can make an informed decision whether or not to be screened.**

Diagnostic Modalities

Digital Rectal Examination

Before the availability of PSA, physicians relied solely on DRE for early detection of prostate cancer (Cooner et al, 1990; Catalona et al, 1994; Ellis et al, 1994; Schroder et al, 1998; Vis et al, 2001; Okotie et al, 2007). DRE has only fair reproducibility in the hands of experienced examiners (Smith and Catalona, 1995) and misses a substantial proportion of early cancers (Cooner et al, 1990; Catalona et al, 1994; Ellis et al, 1994). It has been suggested that the value of DRE for screening at PSA levels less than 3.0 ng/mL is limited (Schroder et al, 1998; Vis et al, 2001). **Due to the risk of prostate cancer among men with abnormalities on DRE and the simplicity of the examination, most urologists use PSA and DRE together for prostate cancer detection.**

Further, **PSA improves the positive predictive value of DRE for cancer** (Schroder et al, 1998). The positive predictive value of DRE ranged from 4% to 11% in men with PSA levels of 0 to 2.9 ng/mL, and from 33% to 83% in men with PSA levels of 3 to 9.9 ng/mL or more (Schroder et al, 1998).

Overall, when DRE and PSA are used in prostate cancer screening, detection rates are higher with PSA than with DRE and highest with both tests together (Catalona et al, 1991). **Because DRE and PSA do not always detect the same cancers** (Okotie et al, 2007), **the tests are complementary and are recommended in combination as methods of assessing prostate cancer risk.**

Prostate-Specific Antigen (PSA)

PSA is a member of the human kallikrein gene family, is secreted in high concentrations (mg/mL) into seminal fluid, and circulates in bound (complexed) and unbound (free) forms that can be measured using assays approved by the U.S. Food and Drug Administration (FDA).

Factors Influencing PSA. Serum PSA levels vary with age, race, and prostate volume. Blacks without prostate cancer have higher PSA values than whites (Morgan et al, 1996; Fowler et al, 1999). PSA increases 4% per milliliter of prostate volume; and 30% and 5% of the variance in PSA can be accounted for by prostate volume and age, respectively (Oesterling et al, 1993).

PSA expression is strongly influenced by androgens (Young et al, 1991; Henttu et al, 1992). Serum PSA becomes detectable at puberty with increases in luteinizing hormone and testosterone (Vieira et al, 1994). In hypogonadal men with low testosterone levels, serum PSA may be low because of decreased expression and may not reflect the presence of prostate disease such as cancer (Morgentaler et al, 1996).

Metabolic factors can influence the serum PSA concentration. Obese men have slightly lower PSA levels than nonobese men (Baillargeon et al, 2005), possibly due to hemodilution (Banez et al, 2007). Statin use may reduce PSA levels by lowering lipids (Hamilton et al, 2008).

Overall, the presence of prostate disease (prostate cancer, benign prostatic hyperplasia [BPH], and prostatitis) is the most important factor affecting serum PSA levels (Wang et al, 1981; Ercole et al, 1987; Dalton, 1989; Nadler et al, 1995). **Although PSA elevations may indicate the presence of prostate disease, not all men with prostate disease have elevated PSA levels, and PSA elevations are not specific for cancer.**

It is postulated that serum PSA elevations occur from disruption of the normal prostatic architecture, allowing PSA to gain access to the circulation. This can occur in the setting of prostate disease (BPH, prostatitis, prostate cancer) and with prostate manipulation (e.g., prostate massage, prostate biopsy, transurethral resection) (Klein and Lowe, 1997). Although DRE can lead to slight increases in serum PSA, the resultant change in PSA falls within the error of the assay and rarely causes false-positive tests (Crawford et al, 1992).

Studies examining the effect of ejaculation on serum PSA have reported conflicting results (Simak et al, 1993; Kirkali et al, 1995; Tchetgen et al, 1996; Heidenreich et al, 1997; Herschman et al, 1997; Stenner et al, 1998; Yavascaoglu et al, 1998). A repeat PSA after 48 hours of sexual abstinence may be helpful for interpreting serum PSA levels that are minimally elevated.

Prostate-directed treatments (for BPH or prostate cancer) can lower serum PSA by decreasing the volume of prostatic epithelium available for PSA production and by decreasing the amount of PSA produced per cell (Shingleton et al, 2000).

5α-Reductase inhibitors that are used for BPH treatment have been shown to lower PSA levels, including both type 2 isoenzyme inhibitors (finasteride) and dual type 1 and 2 isoenzyme inhibitors (dutasteride) (Guess et al, 1993; Roehrborn et al, 2002). Finasteride 1 mg (trade name Propecia) used for male pattern hair loss (androgenic alopecia) results in the same decline in serum PSA levels as the 5-mg dosage (D'Amico and Roehrborn, 2007).

Men initiating treatment with 5α-reductase inhibitors should first have a baseline PSA measurement and should be followed with serial measurements. Although the PSA level is often multiplied by two to estimate the "true" PSA level of a patient who has been taking a 5α-reductase inhibitor for 12 months or more (Andriole et al, 1998), the PSA response to finasteride treatment can be highly variable (Marks et al, 2006). It has been suggested

that the PSA should instead be multiplied by a factor of 2.3 after 2 years and 2.5 after 7 years of treatment (Etzioni et al, 2005; Thompson et al, 2007; Walsh, 2008). Because this "moving target" can complicate the use of PSA in daily clinical practice, some have recommended using the PSA nadir on finasteride as the new baseline and performing a biopsy for subsequent PSA increases (Morgentaler, 2007).

Surgical therapy for BPH can lead to reductions in the serum PSA level (Shingleton et al, 2000) and "reset" the PSA baseline to a variable extent by removing the main contributor to PSA (transition zone).

Finally, prostate cancer treatments (medical or surgical), such as manipulation of the hormonal axis (e.g., luteinizing hormone–releasing hormone (LHRH) agonists, orchiectomy), radiation therapy, and radical prostatectomy lead to reductions in PSA.

The interpretation of PSA values should always take into account age, the presence of urinary tract infection or prostate disease, recent diagnostic procedures, and prostate-directed treatments.

Clinical Use for Diagnosis. The initial assays for PSA that were approved by the FDA in 1994 for early detection of prostate cancer detected both free PSA and PSA complexed to alpha 1 antichymotrypsin (ACT). Thus measurement of free and complexed PSA by these assays is generally referred to as the serum PSA level (Smith et al, 1996). Specific assays that detect free PSA alone and PSA complexed to ACT alone have been evaluated and approved for prostate cancer detection (see later).

It is now well-established that the use of PSA increases the detection of prostate cancers that are more likely to be organ-confined when compared with detection without PSA (Thompson et al, 1987; Mueller et al, 1988; Chodak et al, 1989; Rietbergen et al, 1999; Hoedemaeker et al, 2000). **Observational studies and randomized trials have shown that both the future risk of prostate cancer and the chance of finding cancer on a prostate biopsy increase incrementally with the serum PSA level** (Catalona et al, 1991, 1994; Brawer et al, 1992; Labrie et al, 1992; Gann et al, 1995; Fang et al, 2001; Thompson et al, 2004; Andriole et al, 2005; Whittemore et al, 2005; Loeb et al, 2006; Lilja et al, 2007).

Gann and associates (1995) were the first to demonstrate the association between the baseline PSA level and subsequent prostate cancer detection, which has been verified by others (Fang et al, 2001; Antenor et al, 2004; Whittemore et al, 2005; Loeb et al, 2006).

In addition to predicting future risk, PSA is directly associated with the present risk of prostate cancer. The probability of detecting prostate cancer on biopsy increases directly with PSA across the full spectrum of PSA levels (Table 99–1) (Thompson et al, 2004).

In summary, **both PSA and DRE are used to assess prostate cancer risk. The addition of PSA to DRE increases both the detection rate of prostate cancer and detection of cancers with a more favorable prognosis.**

Triggers for Biopsy. The choice of a PSA threshold for recommending a prostate biopsy is controversial (Catalona et al, 1994; Gann et al, 1995; Carter, 2004; Nadler et al, 2005; Thompson et al, 2005) and has recently been reviewed (Schroder et al, 2008). Gann (1995) pointed out that "dichotomization of PSA results into normal and abnormal obscures important information contained in levels below the usual cutoff." Data from the Prostate Cancer Prevention Trial clearly show that the risk of prostate cancer is continuous as PSA increases (Thompson et al, 2005). Some investigators have recommended against referring to PSA as "elevated" or "abnormal," and instead they advise using PSA together with other methods of risk assessment, such as family history, race, and DRE findings (Thompson et al, 2006). Nevertheless, most urologists continue to use total PSA thresholds for prostate biopsy decisions.

Table 99–1.

Prostate Cancer Detection as a Function of Serum Prostate-Specific Antigen (PSA) Level and Digital Rectal Examination (DRE) Findings in Contemporary Series

PSA LEVEL (ng/mL)	DRE FINDINGS*	CANCER DETECTION RATE (%)†	CANCER YIELD ON BIOPSY (%)‡	RATE OF HIGH-GRADE CANCER ON BIOPSY (%)§
0-1	–		8.8	0.9
1-2	–		17.0	2.0
0-2	–		12	1.4
		0.7	8	
2-4	–		15-25	5.2
		2	21	
4-10	+	11	17-32	4.1
		11-27	45-51	11.7
>10	–	41	43-65	19.4
	+	31-76	70-90	50.5
<4	–		15	2.3
	+	1-3	13-17	
>4	–	14	23-38	5.8
	+	14-38	55-63	20.6

Data in table extracted from the results of contemporary series: Crawford et al, 1996; Catalona et al, 1998; Schroder et al, 1998; Thompson et al, 2004; Andriole et al, 2005.

*DRE nonsuspicious for cancer (–); DRE suspicious for cancer (+).

†Cancer detection rate is the number of cancers found in those screened (total number of detected cancers divided by the total number of men screened).

‡Cancer yield is the total number of cancers detected divided by the total number of men undergoing a biopsy. For DRE (–) this indicates the positive predictive value of PSA at a specified level when the DRE is not suspicious for cancer; for DRE (+) it is the positive predictive value of a suspicious DRE when the PSA is at a specified level.

§Gleason score of 7 or more.

The use of higher PSA thresholds risks missing important cancers during the window for cure, whereas the use of lower thresholds increases the proportion of unnecessary biopsies and overdiagnosis. Although PSA was initially approved using 4 ng/mL as the upper limit of normal, many clinicians now use lower thresholds (2.5 to 3 ng/mL) to trigger a biopsy.

A PSA level that is considered suspicious for prostate cancer should be remeasured before performing a prostate biopsy, because of fluctuations in PSA that could create false-positive elevations (Eastham et al, 2003).

PSA Derivatives and Molecular Forms

Numerous variations on PSA-based screening have been proposed to improve test performance, including the adjustment of the PSA level for total prostate volume (PSA density) (Babaian et al, 1990; Veneziano et al, 1990; Littrup et al, 1991; Benson et al, 1992a, 1992b; Bazinet et al, 1994; Rommel et al, 1994; Catalona et al, 2000; Djavan et al, 2002; Egawa et al, 2002; Naya et al, 2002; Gjengsto et al, 2005) or transition zone volume (Djavan et al, 1999a, 1999b; Taneja et al, 2001; Singh et al, 2004; Gjengsto et al, 2005), and the evaluation of rate of change in PSA (PSA velocity) (Carter et al, 1992; Smith and Catalona, 1994; Fowler et al, 2000; Fang et al, 2002; D'Amico et al, 2004; Roobol et al, 2004; Berger

et al, 2005; D'Amico et al, 2005; Schroder et al, 2006; Berger et al, 2007; Loeb et al, 2007a, 2007b, 2008c; Eggener et al, 2008; Vickers et al, 2009). The discovery that PSA circulates in both bound (complexed) and unbound (free) forms and development of assays to measure these forms separately, have resulted in the investigation of their use for prostate cancer detection (McCormack et al, 1995; Lilja, 1997, 2003; Polascik et al, 1999; Gretzer and Partin, 2003) and this topic has recently been reviewed (Jansen et al, 2009).

Volume-Based PSA Parameters. Distinguishing between men with PSA elevations driven by BPH or cancer is difficult, because PSA is not specific for cancer and the prevalence of BPH is high. Volume-based PSA parameters (with prostate volume typically determined by ultrasonography) have been evaluated to reduce confounding from BPH. These include PSA density (PSAD, PSA divided by prostate volume), complexed PSA density (complexed PSA divided by prostate volume), and PSA transition zone density (PSA divided by transition zone volume) (Babaian et al, 1990; Veneziano et al, 1990; Littrup et al, 1991; Benson et al, 1992a, 1992b; Bazinet et al, 1994; Rommel et al, 1994; Djavan et al, 1999a, 1999b, 2002; Catalona et al, 2000; Naya et al, 2002; Gjengsto et al, 2005).

Benson and colleagues (1992a, 1992b) suggested that adjusting PSA for prostate size by dividing PSA by prostate volume (PSAD) could help distinguish between PSA elevations caused by BPH and those caused by prostate cancer. A direct relationship between PSAD and the chance of cancer has been documented (Seaman et al, 1993; Bazinet et al, 1994; Rommel et al, 1994), and a PSAD of 0.15 or greater was proposed for recommending prostate biopsy in men with PSA levels between 4 and 10 ng/mL and a normal DRE (Seaman et al, 1993; Bazinet et al, 1994). The usefulness of PSAD in prostate cancer detection has not been confirmed in all studies (Cooner, 1994; Taneja et al, 2001). An advantage of PSAD is that it has been directly associated with prostate cancer aggressiveness (Carter et al, 2002, 2007; Kundu et al, 2007).

PSA has been adjusted for the transition zone volume (Kalish et al, 1994), the prostatic region that is the major determinant of serum PSA in men without prostate cancer (Lepor et al, 1994). Djavan and associates (1999b) found that PSA transition zone volume was the parameter with the highest overall sensitivity and specificity for prostate cancer detection when PSA was between 4 to 10 ng/mL.

In general, although PSAD and its associated measures are imperfect predictors of cancer, they represent an additional method of risk assessment with potential utility for counseling men with intermediate PSA levels (4 to 10 ng/mL) regarding the need for prostate biopsy (Benson and Olsson, 1994) or repeat biopsy if PSA is persistently elevated (Keetch et al, 1996).

Prostate-Specific Antigen Velocity. Short-term fluctuations in PSA can occur between measurements in the presence or absence of prostate cancer, primarily due to physiologic variation (Carter et al, 1992, 1995; Riehmann et al, 1993; Prestigiacomo and Stamey, 1996; Eastham et al, 2003). However, the rate of change in PSA (PSA velocity, or PSAV)—PSA corrected for the elapsed time between measurements (Carter et al, 1992)—is associated with the risk of prostate cancer (Carter et al, 1992; Smith and Catalona, 1994; D'Amico et al, 2004, 2005; Roobol et al, 2004; Berger et al, 2005, 2007; Sengupta et al, 2005; Schroder et al, 2006; Loeb et al, 2007a, 2007b, 2008a; Eggener et al, 2008; Vickers et al, 2009). Using frozen sera to measure PSA years before diagnosis, Carter and colleagues (1992) showed that a PSAV more than 0.75 ng/mL per year was a specific marker for the presence of prostate cancer in men with PSA levels between 4 and 10 ng/mL. Other studies have demonstrated that men with prostate cancer have more rapid rises in PSA than men without prostate cancer (Smith and Catalona, 1994; Carter et al, 1995; Raaijmakers et al, 2004; Thompson et al, 2004; Loeb et al, 2008a). More recently, it has been shown that PSAV might be useful for prostate cancer detection among men with PSA levels less than 4.0 ng/mL (Carter et al, 2006; Loeb et al, 2007b). Some investigators have suggested the use of lower PSAV thresholds for men with lower total PSA levels (Loeb et al, 2007b; Moul et al, 2007).

Some studies have failed to demonstrate the value of PSAV for prostate cancer prediction beyond that of a single PSA measurement (Roobol et al, 2004; Vickers et al, 2009). Differences between studies could be due to the method of calculating PSAV (Yu et al, 2006; Connolly et al, 2007) and the point in the PSA history at which PSAV is calculated (Carter et al, 1992; D'Amico et al, 2004).

PSAV may play a role in the prediction of life-threatening prostate cancer (D'Amico et al, 2004, 2005; Carter et al, 2006; Loeb et al, 2008a, 2008b). A PSAV greater than 0.35 ng/mL/year 10 to 15 years prior to diagnosis was associated with a fivefold increased risk of life-threatening prostate cancer more than a decade later (Carter et al, 2006), while a PSAV greater than 2 ng/mL/year during the year prior to a prostate cancer diagnosis was associated with prostate cancer–specific mortality following radical prostatectomy or radiation therapy (D'Amico et al, 2004, 2005; Sengupta et al, 2005). However, a recent meta-analysis suggested that PSAV prior to treatment provides no additional information regarding prostate cancer outcome when compared with PSA alone (Vickers et al, 2009).

Free Prostate-Specific Antigen. Men with prostate cancer generally have a greater fraction of serum PSA that is complexed—and therefore a lower percentage of total PSA circulating in the free (unbound) form—than men without prostate cancer (Christensson et al, 1993; Leinonen et al, 1993; Lilja, 1993; Stenman et al, 1994; Catalona et al, 1995, 1998, 2000; Keetch et al, 1997; Pannek et al, 1998; Woodrum et al, 1998; Gann et al, 2002; Roehl et al, 2002; Hugosson et al, 2003a; Raaijmakers et al, 2004). This difference is thought to be due to differential expression of PSA isoforms by transition zone (zone of origin of BPH) tissue compared with peripheral zone tissue (where most prostate cancers arise) (Chen et al, 1997; Mikolajczyk et al, 1997, 2000a, 2000b).

Free PSA levels vary directly by age and prostate volume, and vary indirectly with the total PSA level (Woodrum et al, 1998). In addition, because assays differ in their ability to determine both free and total PSA, results may differ depending on the assay or combination of assays used (Woodrum et al, 1998). The percentage of free PSA (%fPSA) does not appear to be significantly altered by race (Catalona et al, 2000) or 5α-reductase inhibitors (Keetch et al, 1997; Pannek et al, 1998).

%fPSA has been shown to significantly improve the ability to distinguish between individuals with and without prostate cancer, compared with total PSA alone (Christensson et al, 1993). The %fPSA cutoff that optimizes sensitivity and specificity for cancer detection depends on prostate size, because overlap is greatest among men with enlarged prostates, with or without concomitant prostate cancer (Catalona et al, 1995).

%fPSA appears to be most useful in distinguishing between those with and without prostate cancer at intermediate total PSA levels. In men with PSA levels of 4 to 10 ng/mL and palpably benign prostate glands, a %fPSA cutoff of 25% detected 95% of cancers while avoiding 20% of unnecessary biopsies (Catalona et al, 1998). The value of %fPSA to predict prostate cancer at levels less than 4.0 ng/mL is unclear (Gann et al, 2002; Roehl et al, 2002; Hugosson et al, 2003a; Raaijmakers et al, 2004).

%fPSA (at a cutoff of 25%) and PSAD (using a threshold of 0.078) have been shown to have comparable specificity (at a sensitivity of 95%) although %fPSA does not require transrectal ultrasonography (TRUS) (Catalona et al, 2000). Thus %fPSA can be used to counsel men with PSA elevations in the range 4 to 10 ng/mL regarding their risk of cancer.

Complexed Prostate-Specific Antigen. Because men with prostate cancer have a greater fraction of total PSA that is complexed to protease inhibitors than men without prostate cancer, measurement of complexed PSA (cPSA) has been studied as a marker for detection (Brawer et al, 2000, 2002; Okegawa et al, 2000; Parsons et al, 2004). When total PSA levels were between 4 and 10 ng/mL, cPSA provided improved specificity compared with total PSA, and similar specificity compared with the percentage of free PSA at a sensitivity of 95% (Brawer et al, 2000), findings that were subsequently confirmed (Okegawa et al, 2000). Similar results were reported in the 2.6 to 4.0 ng/mL PSA range (Parsons et al, 2004). **Overall, at a high sensitivity, cPSA provides higher specificity compared with total PSA and comparable specificity to %fPSA in prostate cancer detection.** A potential advantage of cPSA is the requirement for one assay.

PSA Isoforms. PSA is secreted from the prostatic luminal epithelium in a precursor form (pPSA or proPSA) (see Chapter 98) (Mikolajczyk et al, 2001, 2004; Peter et al, 2001; Catalona et al, 2003, 2004; Gretzer and Partin, 2003; Khan et al, 2003; Lilja, 2003; Canto et al, 2004; Lein et al, 2005; Makarov et al, 2009). Active free PSA can be further cleaved to BPSA or intact PSA (iPSA) that is inactive and not complexed. Research assays have been developed for measuring BPSA and pPSA (both native and truncated forms).

The relative concentration of these isoforms differs in the presence of prostatic disease. BPSA is found preferentially in nodular BPH tissue from the transition zone and can be considered a marker for BPH (Mikolajczyk et al, 2000b; Canto et al, 2004), whereas a larger relative proportion of proPSA has been associated with prostate cancer (Mikolajczyk et al, 1997, 2000a, 2001; Peter et al, 2001). Some studies have suggested that proPSA may improve the identification of prostate cancer among men with PSA levels of 2 to 4 ng/mL (Catalona et al, 2003, 2004), 4 to 10 ng/mL (Khan et al, 2003; Mikolajczyk et al, 2004), and 2 to 10 ng/mL (Catalona et al, 2003), while other studies have not shown incremental predictive value of specific subtypes beyond %fPSA (Lein et al, 2005).

hK2. hK2 is a closely related serine protease in the PSA/kallikrein gene family that has also been evaluated for prostate cancer detection (Kwiatkowski et al, 1998; Partin et al, 1999; Becker et al, 2000, 2003; Haese et al, 2003; Bangma et al, 2004; Steuber et al, 2005; Vickers et al, 2008). Expression of hK2 is higher in more poorly differentiated cancer tissues than in normal and benign tissues (Tremblay et al, 1997). Although some studies have suggested that the ratio of hK2 and free PSA might improve the ability of PSA to identify men with prostate cancer (Kwiatkowski et al, 1998; Partin et al, 1999; Becker et al, 2000; Vickers et al, 2008), other analyses have not (Becker et al, 2003; Bangma et al, 2004). hK2 does appear to correlate directly with grade and cancer volume and could be useful in patient assessment after diagnosis (Haese et al, 2003; Steuber et al, 2005).

Other Markers (see Chapter 98)

Prostate cancer gene 3 (*PCA-3*) is a noncoding prostate-specific mRNA overexpressed in prostate cancer tissue compared with benign tissue (Bussemakers et al, 1999; Marks et al, 2007; Deras et al, 2008; Haese et al, 2008; Nakanishi et al, 2008; Sokoll et al, 2008; van Gils et al, 2008; Whitman et al, 2008). Urine assays have been developed to measure PCA-3 mRNA (Sokoll et al, 2008), which is associated with the likelihood of a positive initial or repeat prostate biopsy (Marks et al, 2007; Deras et al, 2008; Haese et al, 2008). There are conflicting results on the association between *PCA-3* with prostate cancer aggressiveness (Nakanishi et al, 2008; van Gils et al, 2008; Whitman et al, 2008). In the future, it is likely that panels of biomarkers will be used in combination with standard measures of risk (age, family history, race) to selectively identify men who should undergo further evaluation for the presence of prostate cancer (Etzioni et al, 2003).

STAGING

General Concepts of Staging

The clinical staging of prostate cancer uses pretreatment parameters to predict the extent of disease, both for assessment of prognosis and to inform decisions regarding appropriate treatment. Available pretreatment modalities used to predict disease extent in men with prostate cancer include DRE (T stage), PSA and its derivatives, prostate cancer features on needle biopsy, and radiologic imaging. Because imaging modalities cannot reliably visualize microscopic disease, they are not helpful in most newly diagnosed cases. Pelvic lymph node biopsy is rarely performed prior to definitive therapy.

Clinical versus Pathologic Staging

Clinical staging is the assessment of disease extent using pretreatment parameters (DRE, PSA, needle biopsy findings, and radiologic imaging); whereas pathologic stage is determined after prostate removal and involves histologic analysis of the prostate, seminal vesicles, and pelvic lymph nodes if lymphadenectomy is performed. Pathologic staging more accurately estimates disease burden and is more useful than clinical staging for outcome prediction (Pound et al, 1997). Biochemical recurrence-free survival and cancer-specific survival are both inversely related to the pathologic stage of disease (Roehl et al, 2004). The most important pathologic criteria that predict prognosis after radical prostatectomy are tumor grade, surgical margin status, extracapsular disease, seminal vesicle invasion, and pelvic lymph node involvement (Jewett, 1975; Walsh and Jewett, 1980; Epstein et al, 1990, 1993a, 1993b; Partin et al, 1993; Pound et al, 1997).

Classifications

The Whitmore and Jewett staging system is now of historical interest (Jewett 1956; Whitmore 1956). Today, clinical staging is based upon the tumor-node-metastases (TNM) classification system (Table 99–2). This system was first adopted in 1975 by the American Joint Committee on Cancer (AJCC) and has since undergone numerous modifications (Schroder et al, 1992). The most recent 1997 modification reduced the subdivision of T2 disease from three categories (T2a, T2b, and T2c) to two categories by combining single-lobe disease (T2a and T2b) into a single stage (Schroder et al, 1992). However, some believe that a distinction between stages T2a and T2b is clinically important (Iyer et al, 1999; Han et al, 2000). Also, a nonpalpable lesion identified by TRUS is considered T2 by the current TNM clinical staging system. However, TRUS findings do not predict tumor extent in PSA-detected nonpalpable lesions (Epstein et al, 1994; Ferguson et al, 1995) so that many urologists classify men with nonpalpable disease as T1c regardless of TRUS findings.

Table 99–2.

1997 and 1992 TNM Clinical Staging Systems for Prostate Cancer

1997	1992	DESCRIPTION
TX	TX	Primary tumor cannot be assessed
T0	T0	No evidence of primary tumor
T1	T1	Nonpalpable tumor—not evident by imaging
T1a	T1a	Tumor found in tissue removed at TUR; 5% or less is cancerous and histologic grade <7
T1b	T1b	Tumor found in tissue removed at TUR; >5% is cancerous or histologic grade >7
T1c	T1c	Tumor identified by prostate needle biopsy due to elevation in PSA
T2	T2	Palpable tumor confined to the prostate
T2a		Tumor involves one lobe or less
	T2a	Tumor involves less than half of one lobe by normal tissue on all sides
T2b		Tumor involves more than one lobe
	T2b	Tumor involves more than half of a lobe but not both lobes
None	T2c	Tumor involves more than one lobe
T3	T3	Palpable tumor beyond prostate
T3a	T3a	Unilateral extracapsular extension
T3b	T3b	Bilateral extracapsular extension
T3c	T3c	Tumor invades seminal vesicle(s)
T4	T4	Tumor is fixed or invades adjacent structures (not seminal vesicles)
T4a	T4a	Tumor invades bladder neck, external sphincter, and/or rectum
T4b	T4b	Tumor invades levator muscle and/or fixed to pelvic wall
N(+)	N(+)	Involvement of regional lymph nodes
NX	NX	Regional lymph nodes cannot be assessed
N0	N0	No lymph node metastases
N1	N1	Metastases in single regional lymph node, ≤2 cm in dimension
N2	N2	Metastases in single (>2 but ≤5 cm) or multiple with none >5 cm
N3	N3	Metastases in regional lymph node >5 cm in dimension
M(+)	M(+)	Distant metastatic spread
MX	MX	Distant metastases cannot be assessed
M0	M0	No evidence of distant metastases
M1	M1	Distant metastases
M1a	M1a	Involvement of nonregional lymph nodes
M1b	M1b	Involvement of bones
M1c	M1c	Involvement of other distant sites

TNM, tumor-node-metastasis; TUR, transurethral resection.

Prediction of Tumor Extent

Prostate-Specific Antigen

Despite controversy over its correlation with prostate cancer volume (Stamey et al, 2004), PSA is associated directly with pathologic stage and tumor extent (Stamey et al, 1987, 1989). PSA cannot be used alone to accurately predict disease extent for an individual patient due to significant overlap in PSA levels between stages, the variable contribution from BPH to PSA, and the fact that, on average, poorly differentiated tumors produce less PSA per gram of tumor (Partin et al, 1990). Despite these confounding factors, pathologic organ-confined disease is found in 80% of men with a PSA less than 4.0 ng/mL, 66% of those with PSA levels between 4.0 and 10.0 ng/mL, and fewer than 50% of men with PSA greater than 10.0 ng/mL (Catalona et al, 1997; Rietbergen et al, 1999). Also, 20% of men with PSA greater than 20 ng/mL and 75% of those with PSA greater than 50 ng/mL are found to have pelvic lymph node involvement.

In addition to the total PSA level, free PSA, hK2, proPSA, PSAD, and PSAV (see above) have been evaluated as predictors of prostate cancer grade and extent (Carter et al, 1997, 2006, 2007; Southwick et al, 1999; D'Amico et al, 2004, 2005; Kundu et al, 2007; Loeb et al, 2008b). Although prostatic acid phosphatase (PAP) has been associated with pathologic stage and progression following radical prostatectomy, (Moul et al, 1998; Han et al, 2001) the closer relationship between PSA and disease extent has virtually eliminated the clinical use of this parameter (Heller, 1987).

Digital Rectal Examination

DRE is used to determine whether a lesion is palpable and is associated with local disease extent (clinical T stage). Also, an abnormal DRE was associated with an increased risk of detecting high-grade (Gleason 8 to 10) prostate cancer in a screened population (Gosselaar et al, 2008).

However, because of its poor sensitivity and lack of reproducibility, DRE can both overestimate and underestimate the extent of disease (Turner and Belt, 1957; Byar and Mostofi, 1972; Walsh and Jewett, 1980). In one series of 565 men with presumed organ-confined disease based upon DRE, the sensitivity and specificity were 52% and 81%, respectively, for prediction of organ-confined disease (Partin et al, 1993). Nevertheless, DRE can be used in combination with other parameters to help predict tumor extent.

Prostate Needle Biopsy

Histologic grade is the most important information obtained from prostate needle biopsy and the Gleason grading system is the most commonly used (Gleason, 1966). At low-power magnification, the sum of a grade (1 to 5) assigned to the predominant pattern (occupying the largest area of the specimen) and the second most common pattern yields a score ranging from 2 to 10.

Recent studies have shown that tertiary Gleason patterns may affect prognosis (Patel et al, 2007), leading a 2005 consensus conference to recommend modification of the Gleason grading system (see Chapter 96). Accordingly, a biopsy Gleason score of 3 + 4 or 4 + 3 with a tertiary pattern 5 would be considered Gleason 3 + 5 and 4 + 5, respectively (Epstein et al, 2005).

Although a higher Gleason grade is associated with worse prognosis, it is not used alone for risk prediction (Stein et al, 1991; Epstein et al, 1993a, 1993b; Partin et al, 1993; Zincke et al, 1994). Other biopsy findings provide information regarding the extent of disease, including the number of positive cores, percentage of positive cores, and presence of perineural invasion (PNI). These features are associated with radical prostatectomy findings, and have been used to guide the selection of candidates for active surveillance programs (Egan and Bostwick, 1997; de la Taille et al, 1999a; Carter et al, 2002; O'Malley et al, 2002; Bismar et al, 2003).

Findings of seminal vesicle invasion or involvement of the periprostatic fat on prostate needle biopsy are associated with worse prognosis (Stone et al, 1998). Although some authors have recommended biopsy of the seminal vesicles and/or prostatic capsule to improve staging (Terris et al, 1993; Ravery et al, 1994; Vallancien et al, 1994; Stone et al, 1995, 1998), others suggest biopsy of these structures only when there is a large palpable tumor located at the base of the prostate (Guillonneau et al, 1997; Terris et al, 1997).

Combined Use of Pretreatment Parameters

Nomograms and algorithms have been developed to integrate multiple clinical parameters for improved staging. Considering the primary T stage based on DRE findings, serum PSA level, and Gleason grade, these algorithms/nomograms have been shown to more accurately predict both cancer extent and long-term outcomes after treatment compared with use of a single parameter (Humphrey et al, 1991; Kleer et al, 1993; Kleer and Oesterling, 1993; Partin et al, 1993, 1997, 2001; Bluestein et al, 1994; Kattan et al, 1998; Han et al, 2003; Stephenson et al, 2006; Makarov et al, 2007).

Several classification schemes have also been proposed that correlate with clinical outcomes. D'Amico demonstrated that stratification into low-risk (clinical stage T1 to 2a, PSA 10 ng/mL or less and Gleason score 6 or less), intermediate-risk (stage T2b, PSA greater than 10 but less than 20 ng/mL or Gleason score 7), and high-risk disease (stage T2c, PSA greater than 20 ng/mL or Gleason score 8 to 10) (D'Amico et al, 1998) was significantly associated with freedom from disease at 10 years after radical prostatectomy; 83% for low-risk, 46% for intermediate-risk, and 29% for high-risk disease (D'Amico et al, 2001). Other validated classification schemes have since been developed, including the Cancer of the Prostate Risk Assessment (CAPRA) score (Cooperberg et al, 2005, 2006; May et al, 2007). Pretreatment risk stratification using multiple parameters is useful for patient counseling.

Imaging

Numerous imaging modalities have been evaluated for staging prostate cancer. No technique is reliably sensitive to detect extraprostatic disease. The inability to image microscopic disease limits the accuracy of current modalities.

Radionuclide bone scan (bone scintigraphy) is the most sensitive modality for the detection of skeletal metastases (Terris et al, 1991). Bone survey films (skeletal radiography) have lower sensitivity for the identification of distant spread and are typically used only to confirm a positive bone scan in men at low risk for bone metastases. Because bone metastases at diagnosis are rare in asymptomatic men in the PSA era, the routine use of bone scans in this population may lead to false-positive results, unnecessary anxiety, and cost (Chybowski et al, 1991). Accordingly, recent guidelines recommend the use of bone scans for patients with a PSA greater than 20 ng/mL, a Gleason score of 8 to 10, clinical stage T3 or T4, or clinical symptoms (National Comprehensive Cancer Network, 2009).

The use of computed tomography (CT) and magnetic resonance imaging (MRI) to evaluate the local extent of disease and the possibility of nodal involvement is not routinely recommended due to low sensitivity (Rifkin, 1990; Tempany et al, 1994; Wolf et al, 1995). Cross-sectional imaging may be reserved for high-risk patients, such as those with clinical stage greater than or equal to T3 disease or greater than 20% nomogram probability of lymph node metastases. Given the rarity of lymph node involvement in contemporary screened populations, it appears that imaging is being overused (Kindrick et al, 1998; Cooperberg et al, 2002; Abraham et al, 2007).

Combined MRI and MRI spectroscopy have been evaluated for staging prostate cancer, but there is no evidence that these methods will overcome the current limitations of imaging microscopic disease (Yu et al, 1999; Kurhanewicz et al, 2000). Specialized techniques such as high-resolution MRI used in tandem with the intravenous administration of lymphotropic superparamagnetic nanoparticles may allow the detection of small and otherwise undetectable lymph node metastases in patients with prostate cancer (Harisinghani et al, 2003). These techniques, however, require further clinical evaluation before widespread use.

Advances in ultrasound imaging are also being studied for improving prostate cancer detection (Purohit et al, 2003). Color ultrasonography with power Doppler to evaluate the blood flow within prostate vessels and three-dimensional Doppler using contrast agents could improve the visualization of more subtle tissue alterations caused by cancer.

Finally, monoclonal antibody radioimmunoscintigraphy (radiolabeled monoclonal antibody scan) have been used for identification of microscopic cancer deposits in regional and distant sites. The ProstaScint scan (Cytogen, Princeton, NJ) uses this technology but has had limited accuracy in the detection of lymph node metastases because the antibody targets an intracellular epitope that is only exposed in dying or dead cells (Troyer et al, 1997; Chang et al, 1999). Future generations of this technology circumventing this limitation are under development.

Molecular Staging

Molecular staging has focused on the detection of circulating prostate cancer cells either directly through centrifugation/immunostaining methods or indirectly by identifying the genetic message (messenger RNA [mRNA]) for prostate-specific biomarkers (e.g., PSA) from circulating prostate cells (Moreno et al, 1992; Ts'o et al, 1997). Although these polymerase chain reaction (PCR)–based assays have been associated with pathologic stage, sensitivity for detecting circulating cancer cells is variable between studies (Cama et al, 1995; Israeli et al, 1995; de la Taille et al, 1999b). With the recent FDA approval of the semiautomated CellSearch system (Veridex, Raritan, NJ) for monitoring metastatic breast and prostate cancer, considerable investigation is underway to determine whether circulating tumor cells have a role in the staging of early disease (Davis et al, 2008; Helo et al, 2009).

Pelvic Lymphadenectomy

The presence of lymph node metastasis in men diagnosed with clinically localized prostate cancer portends a poor prognosis. Identification of patients harboring nodal metastases could have important implications for the initiation of adjuvant therapy. Although the prevalence of pelvic lymph node metastases correlates directly with T stage, serum PSA level, and biopsy grade, pelvic lymphadenectomy (PLND) remains the most accurate way to detect occult nodal involvement (Parker et al, 1999).

PSA screening has resulted in a steady decline in the rates of lymph node metastases from 20% to 40% in the 1970s and 1980s to less than 4% today (Partin et al, 1997; Parker et al, 1999). Currently, lymphadenectomy is often omitted before curative treatment (e.g., radical prostatectomy, radiation therapy) (Bishoff et al, 1995; Kawakami et al, 2006). Laparoscopic pelvic lymphadenectomy prior to treatment is typically reserved for patients with a Gleason score greater than 8, extraprostatic extension on DRE, PSA greater than 20 ng/mL, or suspicion of enlarged lymph nodes on radiologic evaluation.

Given the individual variation in prostatic lymphatic drainage patterns (Mattei et al, 2008), some investigators favor an extended pelvic lymphadenectomy in lieu of a limited dissection (Bader et al, 2002; Burkhard et al, 2006). Given the greater complication rates with a more extended PLND, risks may outweigh benefits for most men diagnosed with low-risk cancer today (Klein et al, 2008). Information regarding the therapeutic value of these strategies is confounded by stage migration and is difficult to evaluate without prospective trials.

Key Points

- Although the value of PSA screening remains controversial, men who present for periodic health examinations should be made aware of the availability of the PSA test so that they can make an informed decision about the need for routine screening.
- The combination of DRE and serum PSA is the most useful first-line test for assessing the risk that prostate cancer is present. The presence of prostate disease (prostate cancer, BPH, and prostatitis) is the most important factor affecting serum levels of PSA.
- PSA increases detection rates of prostate cancer and leads to the detection of prostate cancers that are more likely to be confined when compared with detection without the use of PSA.
- The future risk of prostate cancer detection and the chance of finding cancer on a prostate biopsy increase incrementally with the serum PSA level.
- Biochemical recurrence-free survival and cancer-specific survival are both inversely related to the pathologic stage of disease.
- The most important pathologic criteria that predict prognosis after radical prostatectomy are tumor grade, surgical margin status, presence of extracapsular disease, seminal vesicle invasion, and pelvic lymph node involvement.
- The Gleason grading system is the most commonly used classification scheme for the histologic grading of prostate cancer.

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Definitive Therapy for Localized Prostate Cancer: An Overview

William J. Catalona, MD ● Misop Han, MD, MS

Background
Conservative Management
Radical Prostatectomy
Radiation Therapy
Other Treatments
Recommendations for Treatment by Patient Risk Groups

The purpose of this chapter is to provide an overview of the definitive treatment of clinically localized prostate cancer. **In reporting differences in treatments, we have attempted to be objective but have included our editorial perspective. For balance, we have included in our suggested reading list several recent articles focusing on the relative advantages and disadvantages of the different management strategies, some expressing opinions contrary to ours.** We have grouped treatments into *established treatments,* such as radical prostatectomy and radiotherapy, for which abundant published information is available, and *other treatments,* including active surveillance, primary hormone therapy, cryoablation, radiofrequency ablation, and high-intensity focused ultrasound (HIFU), for which data are more limited for localized disease.

BACKGROUND

Prostate cancer is the most common nonskin cancer and the second-leading cause of death from cancer in men in the United States (Jemal et al, 2009). In 2009, it was estimated that more than 192,280 new cases would occur; for more than 27,000, it was predicted to be the cause of death (Jemal et al, 2009). Because prostate cancer is prevalent in many countries and exhibits a wide spectrum of aggressiveness, different methods of treatment have been developed, and the preferred methods for detection and treatment are controversial. The prevalence of prostate cancer increases strikingly with age. Autopsy studies have documented microscopic foci of prostate cancer in about one fourth to one third of men in the fourth and fifth decades of life and in more than three fourths in the ninth decade (Sakr et al, 1993; Yin et al, 2008). Yet, a disproportionately lower but still substantial number of men (about one in six) are diagnosed with prostate cancer during their lifetime (Jemal et al, 2009). **Because of effective treatment of some prostate cancers and the biologic indolence relative to life expectancy of others, only about 16% of men diagnosed with prostate cancer ultimately die of it. Prostate cancer is the cause of death in about 3% of the U.S. male population** (Jemal et al, 2009). An additional (unquantified) proportion suffers from prostate cancer but dies of other causes.

The marked disparity between prevalence and incidence rates of prostate cancer, on the one hand, and morbidity and mortality rates, on the other, has led some to conclude that many prostate cancers are harmless and perhaps would better be left undetected. Nevertheless, if the present trends of increasing life expectancy continue, given the current age-specific incidence, morbidity, and mortality rates of prostate cancer, this disease will become a far greater public health problem in the future.

Since the 1980s, the methods of diagnosis of clinically localized prostate cancer have changed. Widespread screening with serum prostate-specific antigen (PSA) and digital rectal examination (DRE) has allowed earlier detection (Catalona et al, 1991, 1993). Furthermore, with a remarkable stage migration, approximately 90% of cases are being detected in a clinically localized stage, whereas metastases at the time of diagnosis are now rare in the United States (Han et al, 2001a). The natural history of prostate cancer varies from indolent disease that might not cause symptoms during a patient's lifetime to highly aggressive cancer that metastasizes quickly and causes terrible suffering and untimely death. The challenge for the physician who treats patients with prostate cancer is to advise effective treatment in those for whom treatment is necessary. Selection of the appropriate treatment requires assessment of the tumor's potential aggressiveness and the general health, life expectancy, and quality of life preferences of the patient.

Patients whose tumor has a low malignant potential are predetermined to fare better with most treatments. Therefore the treatment outcomes in any patient series may be influenced by the malignant potential of the tumors as well as by the treatment used. Accordingly, it is difficult to compare the results of different reports because the populations of patients are usually heterogeneous and not strictly comparable. Furthermore, outcome measurements are not necessarily comparable between different forms of therapy (e.g., different definitions of biochemical progression for surgery and radiotherapy), confounding comparisons between them.

Characterization of the Primary Tumor

DRE and prostate ultrasound findings usually provide useful information about the extent of the primary tumor. The serum PSA data, including the total PSA level, the rate of change of PSA (PSA velocity and doubling time), the PSA density (serum PSA divided by prostate volume), and the percentage of PSA in the free or complexed isoforms, are significantly associated with prostate cancer aggressiveness (Benson et al, 1992; Carter et al, 1997; Catalona et al, 1998; D'Amico et al, 2004; Thompson et al, 2004; Kundu et al, 2007). The biopsy findings—Gleason score; the number of cores containing cancer; the distribution and volume of cancer in the biopsy cores; the presence of perineural space invasion, lymphovascular invasion, or ductal or neuroendocrine differentiation—also correlate with cancer aggressiveness and the likelihood of the cancer being organ confined. Prediction tables and algorithms have been developed to assist in this assessment (Partin et al, 1997, 2001). However, such statistical aids are more useful in *groups* of patients than in individual patients, and wide confidence intervals surrounding estimates of outcomes sometimes limit the usefulness of risk assessment for an individual patient. In this regard, it has been claimed that the simultaneous assessment of multiple variables in nomograms provides more accurate predictions than tables do for individual patients (Kattan, 2003).

Evaluation of the Patient

There is no general agreement about how extensive the initial staging workup should be. Some physicians believe that a radionuclide bone scan, abdominal-pelvic computed tomography (CT) scan, and magnetic resonance imaging (MRI) scan are not indicated if the tumor has a Gleason sum of less than 7, the serum PSA level is less than 10 ng/mL, and the biopsy findings do not reveal an extensive or highly aggressive cancer because the likelihood of finding metastases is quite low.

In patients contemplating surgical treatment, a more complete workup should be considered, including coagulation studies, baseline bone scan for future reference with confirmatory imaging studies, if necessary, and a CT or MRI scan of the abdomen and pelvis to evaluate the primary tumor and regional lymph nodes and to rule out other possibly important conditions that might need to be addressed at the time of surgery. However, tumor-selective imaging tests, such as monoclonal antibody scans, positron emission tomographic scans, magnetic resonance spectroscopy, and lymphotrophic MRI are not widely used, although they might prove more useful in the future. In this regard, with increasing availability of endorectal MRI technology, there is increasing use of endorectal MRI to evaluate the local extent of the tumor.

CONSERVATIVE MANAGEMENT

Active Surveillance or Watchful Waiting

Active surveillance and *watchful waiting* are almost unique to prostate cancer. There are different concepts of deferred treatment of prostate cancer. Watchful waiting refers to monitoring the patient until he develops metastases that require palliative treatment. Active surveillance or expectant management allows delayed primary treatment if there is biochemical or histologic evidence of cancer progression (Dall'Era et al, 2008). Active surveillance is a less established strategy in patients with a long life expectancy, because criteria for selecting candidates and trigger points for instituting treatment have yet to be defined and validated. Currently, treatment is frequently initiated because of the patient's anxiety from living with untreated cancer combined with a rising PSA level or biopsy findings that suggest an increase in the volume or Gleason grade of the cancer. Findings on DRE or transrectal ultrasonography are seldom the sole indications for intervention.

Traditionally, deferred treatment has been reserved for men with a life expectancy of less than 10 years and a low-grade (Gleason score 2 to 5) prostate cancer. However, active surveillance is now being evaluated as a management strategy in younger patients with low-volume, low- or intermediate-grade (up to Gleason score 3 + 4 = 7) tumors to avoid or to delay treatment that might not be immediately necessary. In one study, approximately 16% of patients with newly diagnosed prostate cancer would fulfill the criteria for active surveillance, about 10% chose surveillance, and an additional 4%, who did not meet all criteria, chose active surveillance (Barocas et al, 2008).

Statistical models have been generated in an attempt to predict which tumors can be observed without aggressive treatment. For example, Epstein and associates (1994, 1998) proposed a model involving preoperative clinical and pathologic features that would predict "insignificant tumors" (tumor volume less than 0.2 cc, Gleason score below 7, and organ-confined cancer). The preoperative features used in the model include no Gleason pattern 4 or 5 in the biopsy specimen, PSA density of 0.1 ng/mL/g or less, fewer than three biopsy cores involved (with a minimum of six total cores being obtained), and no core with more than 50% involvement or PSA density of 0.1 to 0.15 ng/mL/g and cancer smaller than 3 mm on only one prostate biopsy sample. Characteristically for statistical models, **this model was reported to have a predictive value of 95% for identifying a "significant" cancer but a predictive value of only 66% for identifying an "insignificant" cancer** (Epstein et al, 1994). Approximately 16% of the men in this series met criteria for an insignificant cancer (Epstein et al, 1994). Subsequently, Epstein and colleagues (1998) updated the model to include a free/total PSA ratio (≥0.15) and favorable needle biopsy findings (fewer than three cores involved, no core with more than 50% tumor, and Gleason score of 6 or lower).

Kattan and associates (2003) proposed another statistical model to predict small, moderately differentiated, organ-confined cancer on the basis of PSA, clinical stage, biopsy Gleason score, ultrasound-determined prostate volume, and variables derived from systematic biopsies. **They defined indolent cancer as being organ confined, having less than 0.5 cc tumor volume, and without poorly differentiated elements.** Approximately 20% of their patients treated with radical prostatectomy met the criteria for indolent tumors according to their prediction model.

Some authors have claimed that even patients who do not fulfill such criteria may be legitimate candidates for active surveillance (Eastham et al, 2003). **A potential untoward consequence of recommending active surveillance for all men without obviously aggressive, clinically localized disease is that only men with clearly aggressive and often incurable disease would be treated immediately, whereas a substantial proportion of those with curable disease destined to progress would be monitored, often with multiple extended biopsy procedures that could**

complicate subsequent attempts at nerve-sparing surgery or delay treatment until the window of opportunity for cure has closed.

All prostate cancer patients are at risk for progression. **In reports of deferred therapy for prostate cancer, patients are usually observed with semiannual PSA determinations, DRE, and annual biopsies** (Zietman et al, 2001; Choo et al, 2002; el-Geneidy et al, 2004; Klotz, 2004; Patel et al, 2004; Carter et al, 2007; Dall'Era et al, 2008). **Intervention is recommended if Gleason pattern 4 or 5 is present, more than two biopsy cores are involved, or more than 50% of a biopsy core is involved. Progression is more likely in patients who have cancer present on every biopsy procedure. The absence of cancer on repeated biopsy significantly decreases the likelihood of progression** (Carter et al, 2007). In this regard, biopsy criteria have been reported to be more accurate than PSA criteria in predicting progression. No study has found DRE or imaging studies to independently predict progression.

The percentage of patients with curable cancer at the time of progression has been reported to vary from 33% to 92%. **In most studies of active surveillance, approximately 25% to 50% of patients, depending on their individual risk factors, develop objective evidence of tumor progression within 5 years** (Neulander et al, 2000; Patel et al, 2004; Warlick et al, 2006). Carter and colleagues (2007) reported that 59% remained on surveillance, 25% underwent curative treatment, and 16% either withdrew, were lost to follow-up, or died of other causes. Although some studies suggest that patients with Gleason score 2 to 4 tumors do not suffer or die of prostate cancer with conservative management, those with higher Gleason score tumors have a substantial risk for morbidity and mortality (Albertsen et al, 1995, 2005; Johansson et al, 2004). Klotz and colleagues (2006) reported that of patients who underwent radical prostatectomy for evidence of cancer progression during active surveillance, 58% had tumor extension beyond the prostate and 8% had lymph node metastases.

A prospective, randomized clinical trial from Scandinavia reported that patients with clinically localized prostate cancer managed with watchful waiting have significantly higher rates of local cancer progression, metastases, and death from prostate cancer and a shorter cancer-specific (lower death rate from prostate cancer) and overall survival than those treated initially with radical prostatectomy (Bill-Axelson et al, 2008). Similarly, an observational study of Medicare patients treated with observation, radiation, or surgery showed a survival advantage for active treatment of men aged 65 to 80 years; however, the absolute difference in cancer-specific death at 12 years was small (Wong et al, 2006).

One rationale for active surveillance is the belief that there is substantial overdiagnosis of prostate cancer as a result of widespread PSA screening coupled with aggressive biopsy regimens. ***Overdiagnosis*** **often refers to a cancer detected by screening that would not be detected during the patient's lifetime without screening or would never cause disability or death. It is axiomatic that any effort to detect cancer early will involve detection of some cancers that would not have been otherwise detected. Therefore some overdiagnosis is necessary to reduce suffering and death from prostate cancer.**

There are two methods of estimating the extent of overdiagnosis. The epidemiologic method applies only to populations, not to individuals. With this method, statisticians look at population trends in prostate cancer cases and use statistical models to estimate whether more cases are being diagnosed than should be, considering past incidence rates of prostate cancer and prostate cancer deaths. Statisticians estimate lead time in prostate cancer diagnosis with PSA screening (3 to 12 years) and use the lead time to estimate overdiagnosis; however, statistical models have not accurately predicted the observed incidence of prostate cancer nor fully explained the observed decrease in advanced disease.

The second method of estimating overdiagnosis is for a pathologist to examine a surgically removed cancerous prostate gland and determine whether it contained only a tiny amount of cancer with no high Gleason pattern glands and that was completely encapsulated within the prostate gland. If so, they call it an overdiagnosed cancer.

Some reports have estimated that 50% or more of prostate cancer cases are overdiagnosed (Etzioni et al, 2002; Draisma et al, 2003). **However, recent studies suggest that epidemiologic estimates of overdiagnosis are exaggerated. Epidemiologic estimates based upon both statistical models and data from the United States yield a 23% to 28% incidence of possible overdiagnosis** (Draisma et al, 2009). **Estimates based upon clinicopathologic data range from 6% to 20%** (Graif et al, 2007; Pelzer et al, 2007).

Estimates of overdiagnosis derived from older men should not be generalized to younger men. Prostate cancers diagnosed in younger men are less likely to be harmless in the long term, and it is uncertain whether all cases labeled as overdiagnosed are clinically insignificant. Contrary evidence suggests that screening with low PSA thresholds for biopsy in young patients detects tumors that fulfill the criteria for insignificant cancer in only 12% of patients (Krumholtz et al, 2002). Even among those that do, some tumors are multifocal or do not have a diploid complement of chromosomes**. Presently, no tumor marker can identify indolent tumors with certainty.**

An accumulating body of increasingly compelling evidence shows that PSA screening can reduce prostate cancer deaths. First, there would be no point in trying to detect prostate cancer early if there were no effective treatment for early stage disease. The study on the long-term results of a Swedish randomized trial of radical prostatectomy versus watchful waiting for early prostate cancer showed that surgery can reduce the rates of metastases and prostate cancer deaths, and even increase overall survival (Bill-Axelson et al, 2011).

The "holy grail" of screening is the randomized trial. In the initial report from the European Randomized Study of Screening for Prostate Cancer (ERSPC), men randomized to screening had a 20% lower prostate cancer death rate. Not surprisingly, this mortality benefit was observed largely in men under age 70 (Schroder et al, 2009).

The initial report of the ERSPC contained the sobering estimate that 48 men had to be treated to prevent one prostate cancer death. This high number-needed-to-treat (NNT) raised many eyebrows, because it is shocking to think that 48 men would have to undergo surgery or radiation to prevent one man from dying of prostate cancer. However, because the risk of dying from prostate cancer is influenced by a patient's life expectancy, the NNT to save one life is also strongly influenced by a patient's age and health, and the length of follow-up of the trial. The NNT is lower in younger, healthier men and in trials that have longer follow-up. Subsequent studies have reported a far lower NNT to save one life.

The mortality curves of the screened and control groups from the ERSPC began to separate at 9 years of follow-up when the trial

was first reported. By 12 years follow-up, the NNT had decreased to 12 (Schröder FH, presented at the 2011 American Urological Association Meeting in Washington, DC).

In the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) (Andriole et al, 2009), the results were initially reported on the entire study group—young and old, healthy, and not so healthy. They concluded, "…we now know that prostate cancer screening provided **no** reduction in death rates at 7 years… ." Many authors summarized these two large screening trials as yielding conflicting results; however, this conclusion is not correct. From a subsequent data analysis of the healthier participants, a far different picture emerged. A follow-up analysis of PLCO data showed a striking mortality benefit in the roughly one third of PLCO participants with minimal or no co-morbidities (Crawford et al, 2010). This analysis showed the prostate cancer death rates of relatively healthy PLCO participants randomized to screening were 44% lower than in the control arm, and the NNT to save one life in these healthier men was reported to be only 5.

The Norrkoping Trial from Sweden (Sandblom et al, 2011) also was widely publicized as a negative screening trial. This trial has many limitations. First, it is a small study with only 85 screen-detected prostate cancer cases. Men were screened every 3 years, but the first two screens involved only digital rectal examination. There was no PSA screening until 6 and 9 years into the trial. Fine-needle aspiration cytology (rather than core needle biopsy) was used for diagnosing prostate cancer. The median age of the patients at diagnosis was nearly 70 years old, and the median follow-up of prostate cancer patients was only 6 years. Moreover, nearly half of the screen-detected patients were managed with watchful waiting, and only one third were treated with radical prostatectomy. Despite these limitations, the data actually provides considerable support for PSA screening. The screened patients had far fewer advanced tumors at diagnosis. There was a **strong** trend for better prostate cancer–specific survival in the screening arm that approached statistical significance, and there **was** a significantly lower risk ratio for prostate cancer death in the screening arm.

The Goteborg Screening Trial used perhaps the **best** methodology (Hugosson et al, 2010). It is a **population-based study of younger patients**—20,000 men aged 50 to 64. The contamination rate (i.e., opportunistic PSA screening of controls) was only 3% when the trial started versus an estimated 15% contamination rate in ERSPC and 40% to 50% in PLCO. Trial participants were screened every 2 years with **progressively lower** PSA cutoffs over time, beginning with a 3.4 ng/mL cutoff and ending with a cutoff of 2.5 ng/mL. Ninety-three percent of the men complied with the biopsy recommendation when they had an abnormal screening test, in contrast to PLCO, in which only 40% underwent prompt biopsies. Seventy-seven percent had 14 years of follow-up. The results showed that 41% fewer screened patients presented with advanced disease, and the screening arm had a 44% lower prostate cancer death rate. Moreover, the NNT was 12, which compares favorably with the NNT for breast cancer (NNT = 10 at 10 years of follow-up). The Gotebörg trial has not yet demonstrated a significant improvement in overall survival; however, overall survival benefit takes the longest time to demonstrate of any survival parameter.

Pound and colleagues (1999) reported that **the median time from PSA failure to the development of metastases after radical prostatectomy is 8 years, and the median time from metastases to death is 5 years** (Pound et al, 1999). **Thus the median time from diagnosis to death is more than 13 years.** The median follow-up time for patients in U.S. screening trial was only 5.2 years for controls and 6.3 years for cases—2 years before the expected metastases and 6 years before prostate cancer death. In the European trial, there also was no improvement in survival until after 7 years.

The United States trial has been portrayed as the underpinning for a proposed shift in the mind-set of physicians and patients that screening and treatment of prostate cancer do more harm than good. However, this trial was flawed at the beginning, is a mere snapshot taken halfway through the relevant follow-up period, and will never be informative of the true impact of screening on prostate cancer death of healthy men managed with intelligent screening, prompt biopsy, and effective treatment.

There is other compelling evidence to suggest that early diagnosis through PSA testing and prompt, effective, and high-quality treatment saves lives. This evidence comes largely from the cancer registries of the United States and World Health Organization databases. The percentage of men who have advanced prostate cancer at the time of diagnosis has decreased by 75% in the United States during the PSA era, and there has been a 40% decrease in the prostate cancer death rate during the PSA screening era (National Cancer Institute, 2010). **Statistical studies suggest that 45% to 70% of this decrease is due to PSA screening** (Etzioni et al, 2008).

Other studies have shown that in regions of the United States where more PSA testing is performed, there is a lower rate of advanced prostate cancer and prostate cancer death rates (Colli and Amling, 2008). In a population-based study, PSA screening reduced the prostate cancer-specific mortality rate by 62% (Agalliu et al, 2007; Kvale et al, 2007). **Globally, the death rate also has fallen in countries where PSA testing is practiced, while it continues to rise in countries where it is not** (Bouchardy et al, 2008).

The frequently cited decrease in prostate cancer mortality reported in the United Kingdom from 1992 to 2004 in the absence of widespread PSA screening is due largely to the method of attributing the cause of death in the United Kingdom databases during that time. Before the PSA era, if a man with metastatic prostate cancer died of pneumonia, the cause of death was attributed to prostate cancer, but during the early years of the PSA era, the cause of death was attributed to pneumonia. Thus there was a spurious decrease in the prostate cancer mortality rate in the PSA era in the absence of widespread PSA screening (Hussain et al, 2008).

The physician confronting the patient with newly diagnosed prostate cancer must decide on management based on the PSA level, the estimated tumor volume, and the Gleason score (up to one third of patients are upgraded on the basis of the radical prostatectomy specimen (Pinthus et al, 2006) to select patients for immediate treatment or active surveillance. Repeated biopsies are always subject to sampling errors (Harnden et al, 2008) and may induce fibrosis in and around the prostate gland that could compromise subsequent nerve-sparing surgery, rendering it impossible to perform in more than half of patients (Barzell and Melamed, 2007), as well as trigger inflammation leading to PSA fluctuations that are difficult to interpret.

Treatment is more likely to be successful if given earlier while the tumor is smaller and the prospects for potency-sparing surgery are greater. Deferred treatment is more appropriate for older patients with a limited life expectancy or comorbidities. Additional clinical and

laboratory research are needed to define the parameters for safe use of active surveillance in younger men, including the appropriate selection criteria, follow-up procedures, and trigger points for intervention (Carter et al, 2003; Allaf and Carter, 2004; Wilt, 2008). It will also be necessary to determine the proportion of patients that would still have curable disease when they are treated at the time of objective disease progression. In many instances, active surveillance delays the treatment by only a few years; however, Freedland and colleagues (2006) reported that delays of more than 6 months conferred a 2.73-fold increased risk of progression in patients with low-risk prostate cancer. Active surveillance frequently amounts to *delayed* treatment, and patients selected for active surveillance have cancers that are most curable with the fewest side effects. Some with curable disease would have surveillance until the window of opportunity for cure is closed, and it would be a mistake to treat only patients with incurable disease. **For the present, patients who opt for active surveillance should be evaluated with DRE and PSA testing quarterly or semiannually, and they should consider having repeated prostate biopsy procedures yearly or biennially.** In patients with a consistent PSA velocity of greater than 0.35 ng/mL/year, there is a fivefold increased risk of prostate cancer death in the next two to three decades (Carter et al, 2006). **Although it is assumed that quality of life should be largely preserved with active surveillance, studies have demonstrated significant decrements in quality of life with time, including waning erectile function, diminished urinary continence, and adverse psychologic effects from living with untreated cancer** (Penson et al, 2005). For example, in the Scandinavian study, men randomized to watchful waiting had a significantly worse quality of life than men randomized to radical prostatectomy (Johansson et al, 2008). This was especially true in men who received androgen deprivation (Johansson et al, 2008). **If the PSA level is rising, the DRE suggests tumor growth, or surveillance biopsy specimens show evidence of increased involvement by cancer, treatment should be instituted. Patients may change their minds about remaining on an active surveillance protocol; therefore the physician should review management options on follow-up visits.**

In patients with a long life expectancy, there is a certain risk associated with active surveillance. Clearly, it can avoid or delay treatment for some patients, but there will inevitably be those who will miss their opportunity for cure and, tragically, ultimately progress to metastases and death from prostate cancer. Favorable outcomes have been reported in potential candidates for active surveillance treated with prompt nerve-sparing radical prostatectomy (Loeb et al, 2008).

The ERSPC trial has provided an unequivocally affirmative answer to half of the often quoted aphorism of Willett Whitmore Jr. concerning prostate cancer—"Is cure possible when it is necessary?" To answer the second part, "Is cure necessary when it is possible?," will require more clinical research evaluating the trade-offs.

RADICAL PROSTATECTOMY

Radical prostatectomy was the first treatment used for prostate cancer and has been performed for more than 100 years (Kuchler, 1866; Young, 1905). It is a technically formidable operation, and as a result, simpler treatments have been sought for the treatment of early-stage disease. However, **no treatment has supplanted radical prostatectomy, and it still remains the gold standard because of the realization that hormone therapy and chemotherapy are never curative, and not all cancer cells can be eradicated consistently by radiation or other physical forms of energy, even if the tumor is contained within the prostate gland.**

Key Points: Conservative Management

- Prostate cancer treatment outcomes may be influenced by the malignant potential of the tumors as well as by the treatment used. Furthermore, outcome measurements are not necessarily comparable between different forms of therapy, confounding comparisons between them.
- Traditionally, deferred treatment has been reserved for men with a life expectancy of less than 10 years and a low-grade prostate cancer. Additional research is needed to define the parameters for safe use of active surveillance in younger men, including the appropriate selection criteria, follow-up procedures, and trigger points for intervention.
- A prospective, randomized clinical trial reported that patients with clinically localized prostate cancer managed with watchful waiting have significantly higher rates of local cancer progression, metastases, and death from prostate cancer than do those treated initially with radical prostatectomy and, as discussed above, a prospective, randomized screening trial reported that prostate cancer screening with PSA and DRE reduces prostate cancer-specific mortality by 20% to 27% with early follow-up. Because many of these patients were treated with radical prostatectomy, it may also be inferred to be evidence of the efficacy of radical prostatectomy for localized prostate cancer.

Innovations have led to the wider use of radical prostatectomy:

1. the development of the anatomic radical retropubic prostatectomy that allows the dissection to be performed with good visualization and preservation of the cavernous nerves responsible for erectile function and preservation of the external sphincter muscle that yields urinary continence rates in excess of 90% (Walsh and Donker, 1982);
2. the development of extended ultrasound-guided biopsy regimens, performed under local anesthesia as an office procedure (Arnold et al, 2001); and
3. the widespread use of PSA testing that has led to the majority of patients being diagnosed with clinically localized disease.

In recent years, the laparoscopic approach has been developed for performing the operation.

The main advantage of radical prostatectomy is that when skillfully performed, it offers the possibility of cure with minimal collateral damage to surrounding tissues (Han et al, 2001b; Hull et al, 2002). **Further, it provides more accurate tumor staging by pathologic examination of the surgical specimen. Also, treatment failure is more readily identified, and the postoperative course is much smoother than in the past.** Few patients require nonautologous blood transfusions. The hospital stay is usually 1 to 3 days, and operative mortality is rare in the modern era. Moreover, radical prostatectomy significantly reduces local progression and distant metastases and improves cancer-specific and overall survival rates compared with watchful waiting (Bill-Axelson et al,

2008). **Some patients with tumor recurrence after radical prostatectomy can be salvaged with potentially curative postoperative radiotherapy** (Stephenson et al, 2004b; Trock et al, 2008).

The potential disadvantages of radical prostatectomy are the necessary hospitalization and recovery period; a possibility of incomplete tumor resection, if the operation is not performed properly or if the tumor is not contained within the prostate gland; and a risk for erectile dysfunction and urinary incontinence. However, erectile dysfunction and rectal complications are less likely with nerve-sparing surgery than with radiotherapy, and good treatment options are available for both urinary incontinence and erectile dysfunction. Results reported from high-volume centers are more favorable than those from national surveys (Rabbani et al, 2000; Stanford et al, 2000, Kundu et al, 2004; Sanda et al, 2008).

Surgical Approaches to Radical Prostatectomy

Perineal. Total perineal prostateactomy is an acceptable surgical treatment when performed by a surgeon familiar with this approach (Scolieri and Resnick, 2001). It is usually associated with **less blood loss and a shorter operative time than the retropubic approach. The disadvantages are that it does not provide access for a pelvic lymph node dissection, there is a higher rate of rectal injury, and there is occasional postoperative fecal incontinence that does not occur commonly with other approaches** (Bishoff et al, 1998). It is more difficult to spare the cavernous nerves through the perineal approach.

Retropubic. The open retropubic approach is **preferred by many urologists because of their familiarity with the surgical anatomy, the lower risk for rectal injury and postoperative fecal incontinence, the wide exposure and ready access provided for pelvic lymphadenectomy and prostate excision with preservation of the neurovascular bundles, and the lower risk for positive surgical margins.**

Laparoscopic. The laparoscopic approach is the most daunting method of performing radical prostatectomy. It has been suggested that laparoscopic prostatectomy **may be associated with less bleeding, better visualization, less postoperative pain, and shorter convalescence than the standard open approach. However, the claimed advantages are not always realized with many surgeons and are usually less important to the patient than the cure of his cancer, the preservation of his potency, and the avoidance of other more serious complications. Laparoscopic prostatectomy can be performed through a transperitoneal or extraperitoneal approach, but the extraperitoneal approach poses logistical limitations, especially with the use of robotic assistance. The transperitoneal approach facilitates the lymphadenectomy but carries a higher risk of intestinal and vascular injury, urinary ascites, and postoperative intestinal obstruction.**

Furthermore, laparoscopic prostatectomy is associated with a higher risk for severe complications. Hemostasis in the neurovascular bundles is difficult to achieve without thermal injury to the neurovascular bundles because of the relative difficulty in rapidly placing hemostatic sutures or applying hemostatic clips laparoscopically. Heat from a harmonic scalpel or electrocautery can irreversibly damage the cavernous nerves. Although intraoperative blood loss is less with laparoscopic surgery, postoperative bleeding may occur after the release of positive pressure in the operative field. Rectal, ureteral, and vascular injuries and anastomotic leaks have also been more common with laparoscopic prostatectomy (Rassweiler et al, 2003).

When laparoscopic prostatectomy is performed by a skilled laparoscopic surgeon, reported incontinence and anastomotic stricture rates are comparable to those achieved with open surgery. It has been claimed that nerve sparing is equivalent or even better with laparoscopic surgery, but direct comparisons and validated results are lacking (Menon et al, 2007). **The early reported rates of positive surgical margins have been higher with laparoscopic prostatectomy, and the adequacy of cancer control is as yet uncertain because of lack of long-term results.**

Robotic. Remotely controlled laparoscopic surgery has recently been popularized because of its **greater technical ease for the surgeon, especially for tying sutures and performing the vesicourethral anastomosis.** It has been aggressively marketed as a less invasive, technologically more advanced method of performing the operation with less pain and a quicker recovery. **The availability of three-dimensional visualization is an advantage over standard laparoscopic techniques.** Early reported results are favorable but have not been validated (Menon et al, 2002, 2007). It is uncertain whether the results of laparoscopic prostatectomy are as good as those achieved with open prostatectomy (Smith, 2004; Webster et al, 2005; Hu et al, 2006; Rogers et al, 2006; Touijer and Guillonneau, 2006).

There has been a dramatic shift from open to robotic prostatectomy in the United States that has been driven largely by marketing. However, until recently, there has been little objective data to substantiate these claims (Smith et al, 2007; Weizer et al, 2007; Wood et al, 2007). **Recent reports based on comparative data have shown disadvantages in laparoscopic and robotic prostatectomy in tumor recurrence, urinary incontinence, and patient satisfaction.**

In performing a radical prostatectomy, the surgeon must dissect in the proper tissue plane to remove the prostate from between the neurovascular bundles without permanently damaging the nerves or cutting into the prostate, or worse, leaving part of the prostate behind.

Most prostate cancer patients have similar priorities. First, they want to survive; second, they want to remain continent; and third, they want to preserve their potency. These are their main priorities, but they want all three. This constellation of favorable outcomes is known as the "trifecta" (Eastham et al, 2008), and, understandably, patients want to achieve it as quickly and painlessly as possible. Often, patients with newly diagnosed prostate cancer would like to avoid any treatment, if possible, or, after realizing that treatment is necessary, seek the easiest way out. This frequently leads to consideration of options such as active surveillance, cryoablation, high-frequency ultrasound, or minimally invasive prostatectomy.

It is important to examine the claims concerning laparoscopic and robotic prostatectomy. Usually six incisions are made in laparoscopic surgery, and, in most cases, the procedure is performed within the peritoneal cavity, while for open surgery, one incision is made—4 to 5 inches in length and that does not enter the peritoneal cavity. **Comparative studies have shown that open prostatectomy has a similar recovery time and return to normal activity** (Weizer et al, 2007; Wood et al, 2007).

It is also more difficult to perform a lymph node dissection with laparoscopic approaches. Other factors come into play as well, such as lack of a sense of touch or tactile feedback. Furthermore, some surgeries that start out as laparoscopic must be converted to open, because of failure to progress or complications that cannot be handled laparoscopically. **Perhaps the most important consideration is that the laparoscopic approaches have no long-term track record of cancer control.** If small amounts of cancer are left behind, it may not become apparent for years.

A comparison of a sample of patients from the Medicare database who underwent minimally invasive or open prostatectomy between 2003 and 2005 revealed a lower rate of medical complications with the laparoscopic approaches; however, the men undergoing minimally invasive prostatectomy had more than a threefold higher rate of requiring salvage therapy for tumor recurrence within 6 months of surgery (Hu et al, 2008). In this study, the more experienced surgeons in minimally invasive radical prostatectomy had better results than less experienced surgeons; however, even the highest-volume laparoscopic surgeons had twice the rate of patients requiring salvage treatment for cancer recurrence when compared with all surgeons performing open radical prostatectomy. **Patients undergoing minimally invasive surgery also were 40% more likely to develop anastomotic strictures.**

Another study comparing the results of laparoscopic and open radical prostatectomy revealed that **the laparoscopic approach was associated with less blood loss, but, of more concern, had a higher rate of postoperative emergency room visits, readmissions to the hospital, and further surgery for complications** (Touijer et al, 2008). **Also, patients who underwent a laparoscopic radical prostatectomy were less likely to become continent than those treated with open prostatectomy.**

In a few studies including a small number of patients, potency rates have been reported to be similar with both techniques when experienced surgeons performed the operations (Menon et al, 2007). **However, in general, potency rates have not matched the best rates achieved by the most experienced surgeons performing open surgery.**

Schroeck and colleagues (2008) compared patient satisfaction and regret following radical prostatectomy**. Patients who underwent a robotic prostatectomy were more than four times more likely to regret their decision**. The authors suggested that these patients were more likely to be regretful and dissatisfied because of the higher expectations from an "innovative" procedure. These results raise concerns that patients are being misled about the true risks and benefits of minimally invasive procedures to treat prostate cancer.

Thus the outcomes of cancer control, potency, and continence are well documented for open prostatectomy, but the jury is still out with laparoscopic approaches.

Salvage Radical Prostatectomy

Radical prostatectomy can be performed in patients for whom other local treatments have failed (Pontes, 1994; Chen and Wood, 2003). **However, the rate of complications is far higher, and the complications are more serious and much more difficult to manage** (Stephenson et al, 2004a; Sanderson et al, 2006). **Moreover, the prospects for long-term disease-free survival are more limited for salvage prostatectomy than for primary radical prostatectomy.**

Most of the reported experience with salvage radical prostatectomy is from the pre-PSA era. Contemporary series of patients selected because of biochemical recurrence have lower morbidity and better cancer control rates (Stephenson et al, 2004a; Ward et al, 2005). **Nevertheless, postoperative incontinence rates are as high as 44% and bladder neck contracture rates as high as 22%** (Ward et al, 2005). The incontinence rate is even higher after brachytherapy, presumably because of the higher dose of radiation administered. **Long-term progression-free survival rates after salvage prostatectomy in the absence of hormone therapy have not been well documented.**

Selection of Patients for Radical Prostatectomy

An ideal candidate for radical prostatectomy is healthy and free of comorbidities that might make the operation unacceptably risky. He should have a life expectancy of at least 10 years, and his tumor should be deemed to be biologically significant and completely resectable. The generally accepted upper age limit for radical prostatectomy is about 75 years.

Because imaging studies are not accurate for staging prostate cancer, **preoperative clinical and pathologic parameters are often used to predict the pathologic stage and thus identify patients most likely to benefit from the operation** (Partin et al, 1997, 2001). These parameters are frequently used in tables and nomograms designed to predict pathologic tumor stage or post-treatment recurrence-free survival probabilities (Han et al, 2003; Kattan et al, 1998, 2000; Ross et al, 2001). New methods of predicting the outcome after radical prostatectomy that incorporate cellular and biologic features to improve accuracy have been reported (Donovan et al, 2009).

Patients with a low probability of resectable disease or a short life expectancy should not be advised to have surgery. Neoadjuvant hormone therapy does not enhance the resectability of prostate cancer and often increases the difficulty of performing nerve-sparing surgery (Soloway et al, 2002). **Similarly, neoadjuvant chemotherapy rarely produces pathologically complete responses** (Chi et al, 2008).

The surgeon should realistically counsel the patient on the nerve-sparing aspects of the operation. Nerve-sparing prostatectomy does not materially compromise cancer control in appropriately selected patients; however, it is inappropriate in men with advanced disease. **The feasibility of performing nerve-sparing surgery is questionable when there is extensive cancer in the biopsy specimens, palpable extraprostatic tumor extension, serum PSA level above 10 ng/mL, biopsy Gleason score higher than 7, poor-quality erections preoperatively, current and future lack of a sexual relationship, or other medical conditions that may adversely affect erections (e.g., diabetes mellitus, hypertension, psychiatric diseases, neurologic diseases, or medications that produce erectile dysfunction).**

Postoperative treatment of erectile dysfunction also should be discussed, including information on phosphodiesterase type 5 (PDE-5) inhibitors, intraurethral and intracorporeal administration of vasodilators, vacuum

erection devices, venous flow constrictors, and implantable penile prostheses. The discussion also should include the timing of the return of erections. The patient should be warned about the risk for development of Peyronie disease from injury to the penis during sexual activity without a rigid erection (Ciancio and Kim, 2000). He should also be informed that early postoperative use of intracavernosal injection therapy with vasodilating drugs allows most patients to have normal erections (with arterial blood) shortly after the catheter is removed. This protects against the occurrence of atrophic changes in the penis and allows the resumption of sexual activity early in the postoperative period. If erectile function is a high priority for the patient, he should be reassured that erections almost always can be restored, regardless of whether nerve-sparing surgery could be performed.

The preoperative evaluation should consider the likelihood of success in achieving all goals of surgery and in determining whether nerves can safely be spared. The surgeon should also discuss **the possibility of performing cutaneous nerve graft interposition if one or both cavernous nerves must be resected** (Kim et al, 1999; 2001; Quinlan et al, 1991; Secin et al, 2007). **There are limited data concerning the effectiveness of such grafts. In most patients with a tumor so advanced that one or both nerves must be resected, postoperative radiotherapy or hormone therapy is likely to be required, which could nullify the potential benefits of nerve grafting. Some studies question whether nerve grafting is effective** (Davis et al, 2008). The surgeon should also discuss the possible need for and potential side effects of adjuvant postoperative radiotherapy and/or hormone therapy, if the final pathology specimen reveals adverse prognostic features.

Surgical Technique

Radical prostatectomy involves complete removal of the prostate gland and seminal vesicles and usually includes a modified pelvic lymph node dissection as well. The key steps in performing anatomic nerve-sparing radical retropubic prostatectomy are as follows:

1. pelvic lymphadenectomy;
2. opening of the endopelvic fascia and limited incision of the puboprostatic ligaments;
3. suture ligation and transection of the Santorini dorsal venous complex;
4. dissection of the urethra at the apex of the prostate and transection of the urethra (sometimes the anastomotic sutures are placed at this point in the operation);
5. dissection of the prostate from the neurovascular bundles;
6. securing and transection of the prostatic pedicles;
7. transection and reconstruction of the bladder neck;
8. dissection of the seminal vesicles and ampullary portions of the vasa deferentia; and
9. performance of the vesicourethral anastomosis.

The surgeon should strive for complete apposition of the bladder neck and the urethra, with a watertight, tension-free closure.

Pelvic lymphadenectomy is optional in patients at low risk for lymph node metastases. Patients who elect to undergo lymphadenectomy should decide in advance whether they wish to proceed with the prostatectomy if there are nodal metastases. If they do not wish to proceed, the excised lymph nodes are sent for frozen-section examination during the operation. Otherwise, intraoperative frozen-section analysis of pelvic lymph nodes is unnecessary. Some have argued that a more extensive pelvic lymphadenectomy yields better outcomes, but compelling evidence for this is lacking (Weight et al, 2008), and more extensive lymphadenectomy carries a greater risk for postoperative genital and lower extremity lymphedema and lymphocele (Bader et al, 2002; Allaf et al, 2004; Musch et al, 2008). Thromboembolic events and reinterventions are more common in patients with symptomatic lymphocele (Musch et al, 2008).

The key to preserving urinary continence is to perform a meticulous dissection, avoiding injury to the external urinary sphincter. Preservation of the bladder neck is unnecessary to achieve good urinary continence. In patients with high-volume or high-grade tumors involving the base of the prostate, preservation of the bladder neck may risk positive surgical margins.

Meticulous dissection is required to preserve the neurovascular bundles. In performing nerve-sparing surgery, the neurovascular bundles are identified at the apex of the prostate (the dissection can also be performed in an antegrade fashion beginning at the base), and the bundles are dissected free of the posterolateral surface of the prostate gland. Hemostatic sutures or clips may be used to control bleeding from the neurovascular bundles. Use of electrocautery or a harmonic scalpel risks irreversible thermal injury to the neurovascular bundles.

The prostatic pedicles are suture ligated or hemoclipped and divided close to the gland, avoiding incision into the prostatic capsule. In performing the seminal vesicle dissection, care must be taken to avoid injury to the neurovascular bundles situated immediately lateral and posterior to them.

Postoperative Care

Patients should ambulate with assistance beginning on the afternoon or evening of surgery. **The catheter may be removed 3 to 21 days after surgery, depending on the integrity and the amount of tension on the vesicourethral anastomosis. Removal of the catheter before 7 days is associated with a 15% to 20% risk of urinary retention.**

After the catheter has been removed, Kegel exercises should be initiated. A protective pad is used until complete urinary control is achieved. The postoperative serum PSA level should be undetectable by 1 month after the operation. Ultrasensitive PSA measurements frequently falsely classify patients has having tumor recurrence (Taylor et al, 2006).

Cancer Control

The principal objective of radical prostatectomy is to completely excise the cancer. Important cancer control end points are pathologically organ-confined disease with clear surgical margins, biochemical recurrence (detectable serum PSA), local progression, metastases, cancer-specific survival, and overall survival. **As discussed above, depending on the Gleason score and the PSA doubling time, biochemical (PSA) evidence of recurrence usually precedes clinical metastases by a mean of about 8 years and cancer-specific mortality by about 13 years** (Pound et al, 1999).

Nonprogression rates vary with clinical and pathologic risk factors. Independent clinical prognostic factors are tumor stage, Gleason score, preoperative PSA level,

and calendar year of diagnosis and treatment. Adverse prognostic features include non–organ-confined disease, perineural or lymphovascular space invasion, extracapsular tumor extension, positive surgical margins, seminal vesicle invasion, and lymph node metastases (Grossfeld et al, 2000; Shariat et al, 2004). **In the PSA era, there has been a dramatic stage migration and improvement in prognostic features and treatment outcomes** (Han et al, 2001a; Moul et al, 2002).

A rising serum PSA level is usually the earliest evidence of tumor recurrence after radical prostatectomy (Pound et al, 1999). **Biochemical recurrence is frequently used as an intermediate end point for treatment outcomes; however, not all patients with biochemical recurrence ultimately develop metastases or die of prostate cancer. In rare instances with high-grade or neuroendocrine tumors that do not produce much PSA, there can be palpable evidence of recurrence despite an undetectable PSA level, indicating a role for DRE in monitoring of patients.**

In the first author's personal series, including more than 5000 open anatomic radical retropubic prostatectomies dating to 1983, the actuarial 10-year cancer progression-free survival probability was approximately 85% for patients with organ-confined disease, 65% for men with extracapsular tumor extension without cancerous surgical margins, 55% for men with extracapsular tumor extension and cancerous surgical margins, 25% for patients with seminal vesicle invasion, and 10% for patients with lymph node metastases. Patients treated in the PSA era have approximately five percentage points more favorable results within each pathologic category. Within these pathologic tumor stages, cancer progression rates also were strongly associated with other parameters. Case selection and the duration and frequency of follow-up monitoring are also important determinants of postoperative outcomes.

Radical prostatectomy also provides long-term cancer control in about half of highly selected men with clinical stage T3 disease (Freedland et al, 2007; Loeb et al, 2007).

Urinary Continence

Urinary continence after radical retropubic prostatectomy is generally good and varies according to the experience and skill of the surgeon. For high-volume radical prostatectomy surgeons, more than 90% of men recover complete urinary continence. **The return of urinary continence is associated with the patient's age:** approximately 95% of men younger than 60 years can attain pad-free urinary continence after surgery; 85% of men older than 70 years regain continence. **Few require implantation of an artificial urinary sphincter or a sling procedure for stress urinary incontinence.**

Erectile Function

Potency after radical prostatectomy is usually defined as the ability to maintain erections sufficiently rigid for penetration and sexual intercourse with or without the help of a PDE-5 inhibitor. Most patients with intact libido and erections wish to maintain these functions. Others with poor-quality erections usually wish to have erections that at least offer some rigidity to provide sensory satisfaction for both sexual partners. **The return of erectile function after radical retropubic prostatectomy correlates with the age of the patient, preoperative potency status, extent of nerve-sparing surgery, and era of surgery.** In the most favorable candidates in whom preoperative potency is normal and bilateral nerve-sparing surgery can be performed, up to 95% in their 40s, 85% in their 50s, 75% in their 60s, and 50% in their 70s can attain recovery of erections sufficient for penetration and intercourse. However, in most instances, erections are not as good as they were preoperatively.

In most patients, erections usually begin to return as partial erections 3 to 6 months after surgery and may continue to improve for up to 3 years or more (Burnett, 2005; Glickman et al, 2009). **Patients should be encouraged to use erectile aids postoperatively, including PDE-5 inhibitors, intraurethral suppositories, intracavernosal injections, or vacuum erection devices.** Erection rehabilitation programs using intracavernosal injection therapy or PDE-5 inhibitors might hasten the return of erections and increase the proportion of men who recover erections (Montorsi et al, 1997). However, it has been reported that on-demand, rather than nightly, dosing of PDE-5 inhibitors was efficacious in men with erectile dysfunction following bilateral nerve-sparing radical prostatectomy (Montorsi et al, 2008).

Complications

Anatomic nerve-sparing radical prostatectomy provides excellent cancer control with an acceptable complication rate in appropriately selected patients. The overall early complication rate after radical prostatectomy is less than 10% in experienced hands (Kundu et al, 2004). **With a careful selection of patients and performance of necessary preoperative cardiovascular evaluation, perioperative mortality has been largely avoided** (Mettlin et al, 1997; Kundu et al, 2004).

Early Complications

Early complications include hemorrhage; rectal, vascular, ureteral, or nerve injury; urinary leak or fistula; thromboembolic and cardiovascular events; urinary tract infection; lymphocele; and wound problems. It is advisable routinely to use support stockings and to ensure early ambulation. Prophylactic anticoagulation and sequential compression devices are advisable in patients at high risk for thromboembolic complications.

Inadvertent injury to the obturator nerve can occur during the pelvic lymphadenectomy. When a tension-free primary nerve repair is not feasible, nerve grafting can be performed by a cutaneous or genitofemoral nerve graft. However, even without a nerve repair, conservative management with physical therapy can compensate for the deficit, and therefore many patients do not have a significant thigh adductor deficit after the injury (Kirdi et al, 2000).

Ureteral injury is a rare complication. A minor injury or ligation can be managed with removal of the ligature and ureteral stenting. Mobilization of the distal ureter and reimplantation should be performed for more severe injuries.

Although uncommon, a rectal injury can occur and be repaired primarily by a multiple-layer closure (Lepor et al, 2001). However, a diverting colostomy should be considered in

men with a large rectal defect, a history of pelvic radiotherapy, or long-term preoperative glucocorticoid therapy.

Late Complications

The most common late complications of radical prostatectomy are erectile dysfunction, urinary incontinence, inguinal hernia, and urethral stricture. Early rehabilitation measures, including Kegel exercises to increase the strength and the bulk of the external sphincter muscle and the use of a PDE-5 inhibitor, vacuum erection device, and intraurethral or intracavernosal vasodilator appear to be helpful. Anastomotic or other urethral strictures should be managed initially with dilation, but internal incision and endoscopic injection of glucocorticoids may be required. For a long or persistent anastomotic stricture, a transurethral resection of the scar tissue cephalad to the external sphincter may be necessary. After the resection, an interval of catheter self-dilation of the anastomosis is usually required. Continued self-dilation or intermittent dilation by the urologist is required in difficult, persistent cases. Urethroplasty is rarely needed.

Key Points: Radical Prostatectomy

- Radical prostatectomy was the first treatment used for prostate cancer, and it still remains the gold standard. An ideal candidate for radical prostatectomy is a healthy man with a life expectancy of at least 10 years. Preoperative clinical and pathologic parameters are often used to predict the pathologic stage and thus to identify patients most likely to benefit from the operation.
- A rising serum PSA level is usually the earliest evidence of tumor recurrence after radical prostatectomy and is frequently an intermediate end point for treatment outcomes. However, not all patients with biochemical recurrence ultimately develop metastases or die of prostate cancer.
- The most common late complications of radical prostatectomy are erectile dysfunction, urinary incontinence, inguinal hernia, and urethral stricture. The return of erectile function after surgery correlates with age of the patient, preoperative potency status, extent of nerve-sparing surgery, and era of surgery; the return of urinary continence is associated with the patient's age.
- The relative safety and efficacy of laparoscopic radical prostatectomy in achieving the "trifecta" of cancer control, preservation of potency, and return of urinary continence is uncertain at this time.

RADIATION THERAPY

External Beam Radiotherapy (Three-Dimensional Conformal Radiotherapy)

External beam radiotherapy involves the use of beams of gamma radiation, usually photons, directed at the prostate and surrounding tissues through multiple fields. To minimize radiation injury to the bladder and rectum, three-dimensional conformal radiotherapy (3D-CRT), in which a computer alters the radiation beams to focus the radiation dose to the region of the prostate gland, was developed (Fraass, 1995). **The most sophisticated form of 3D-CRT, called intensity-modulated radiation therapy (IMRT), can provide localization of the radiation dose to geometrically complex fields** (Burren et al, 1999; Zelefsky et al, 2006). **Heavy-particle therapy that uses beams of high-energy protons** (Shipley et al, 1995; Rossi, 1999) **or neutrons** (Lawton et al, 1991; Russell et al, 1994) **has also been used to treat patients with prostate cancer. Heavy-particle therapy is another form of 3D-CRT in which the radiation beam can be virtually "stopped" within the tissue, allowing high doses of radiation to be delivered to a localized region. However, proton beam therapy is extremely expensive, and limited long-term results have been reported** (Brada et al, 2007).

A possible disadvantage of extreme conformal therapy with IMRT and heavy particles is that they can be too narrowly targeted so that movement of the prostate caused by differences in rectal or bladder filling could result in geographic miss of the tumor, especially in the important posterior peripheral region of the prostate.

Radiation therapy has been extensively studied for localized prostate cancer. **The outcomes of radiation therapy corrected for anatomic disease extent and other prognostic factors have been reported to be comparable to those of radical prostatectomy; however, this is misleading because the end points for determining treatment success or failure are different for radiotherapy and surgery** (Gretzer et al, 2002).

Radiation Dose and Field of Treatment

There is evidence from prospective, randomized trials that **dose escalation and three-dimensional definition improve results considerably** (Pollack et al, 2002). **Currently, doses of 76 to 80 Gy or more have been shown to improve cancer control** (Pollack et al, 2000; Dearnaley et al, 2007). **Low-risk patients are now frequently treated with 70 to 72 Gy, intermediate-risk patients with 75 to 76 Gy, and high-risk patients with 80 Gy or more. Doses above 75 Gy are now considered to be indicated; however, doses above 80 Gy have not been demonstrated to be beneficial.**

Image guidance for better target definition is crucial for dose escalation, and high radiation doses require protection of normal tissues. IMRT produces steep dose gradients where the gradient between 100% and 50% of dose can be as little as 1 to 1.5 cm. Radiation dose escalation requires precision in target definition and a high degree of accuracy in the daily placement of the radiation dose.

CT imaging is considered the standard imaging modality for 3D-CRT and 3D-IMRT, but CT is less precise than MRI. Therefore larger margins are required to accurately ensure that the entire prostate gland received the daily radiation dose. When CT imaging uses only the bone landmarks to localize the prostate gland, the daily radiation treatments might be directed inconsistently, and the rectum might receive increased doses of radiation. New technologies are being developed to accurately place the radiation beam before every treatment (Litzenberg et al, 2002, 2005, 2007; Cheng et al, 2003).

Radiation Side Effects

The main adverse side effects of radiation therapy are related to injury to the microvasculature of the bladder, rectum, striated sphincter muscle, and urethra. However,

urinary incontinence or radiation-induced complications requiring surgical correction are uncommon. **Approximately one third of patients experience acute symptoms of proctitis or cystitis during the course of radiotherapy, usually after the dose exceeds 50 Gy. In the great majority, symptoms subside after the completion of therapy. About 5% to 10% have permanent symptoms, such as irritable bowel syndrome and intermittent rectal bleeding or bladder irritability and intermittent gross hematuria.** In some cases, chronic symptoms develop years after treatment. Some patients require laser cauterization of radiation-induced telangiectasia for bleeding from the bladder or the rectum. External beam radiotherapy causes more rectal toxicity and less urinary toxicity than brachytherapy does.

A prior transurethral resection of the prostate is a relative contraindication to brachytherapy and external beam radiation therapy because the prostate does not hold the seeds well, and radiation after transurethral resection of the prostate is associated with an increased risk for urethral stricture. The presence of severe obstructive urinary symptoms is also a relative contraindication because of the risk for acute urinary retention, which is an even greater risk in patients treated with brachytherapy. Another relative contraindication is inflammatory bowel disease.

Approximately half of patients develop erectile dysfunction after radiotherapy for prostate cancer. This is caused by injury to the vasculature of the cavernous nerves and to the corpora cavernosa of the penis, usually beginning about 1 year after the completion of treatment. Younger patients with good baseline erectile function are more likely to retain adequate erections. PDE-5 inhibitors are useful in ameliorating the erectile dysfunction associated with radiotherapy (Merrick et al, 1999; Valicenti et al, 2001). Lower doses of radiation to the penile bulb have been investigated as a means of minimizing radiation-induced erectile dysfunction (Roach et al, 2004). The use of adjuvant hormone therapy also adversely affects erectile function.

Combined External Beam Radiation Therapy and Hormone Therapy for Locally Advanced Prostate Cancer

Randomized clinical trials have demonstrated that **patients with a high PSA, high Gleason score, or large-volume tumor benefit from androgen-deprivation therapy in conjunction with radiotherapy, whereas those with lower risk tumors do not.** For example, Bolla and colleagues (1997, 2002) reported that a 3-year adjuvant hormone therapy started concurrently with external beam radiation improved local tumor control and survival in patients with locally advanced prostate cancer. Hanks and associates (2003) explored the optimal duration of hormone therapy after radiation therapy. They showed that 28 months of hormone therapy before, during, and after radiation therapy, compared with 4 months of hormone therapy before and during the radiation therapy, provides significant improvement in all clinical end points, except for overall survival (Hanks et al, 2003). However, **the overall survival benefit of a longer course of hormone therapy was observed in patients with Gleason grade 8 to 10 disease.**

A Scandinavian trial comparing hormone therapy alone to hormones plus radiation in patients with locally advanced prostate cancer revealed clear and significant survival gains and no quality-of-life disadvantage for the radiation arm, indicating that **both the hormone and the radiation components contribute significantly to the therapeutic effect** (Widmark et al, 2009).

Concern has been expressed about the possible cardiovascular risks of hormone therapy, particularly the risk of fatal myocardial infarction. Although some studies have reported an increased rate of cardiovascular deaths (Tsai et al, 2007), two prospective trials revealed that although hormone therapy increases the risk of diabetes mellitus, heart disease, and myocardial infarction, there is no detectable increase in the risk of cardiovascular mortality (Van der Kwast et al, 2007; Efstathiou et al, 2008, 2009).

Radiation Therapy for Localized Prostate Cancer

High-Risk Localized Prostate Cancer (PSA greater than 20 ng/mL or Gleason score 8 to 10). No randomized trial has exclusively studied the additional benefit of hormone therapy in the high-risk patients receiving radiotherapy for localized prostate cancer. However, on the basis of the randomized trials involving locally advanced disease, long-term concurrent hormone therapy is advocated for the high-risk patients treated with radiotherapy for localized prostate cancer.

Intermediate-Risk Localized Prostate Cancer (PSA between 10 and 20 ng/mL, Gleason score 7, or clinical stage T2b). In a retrospective cohort study, D'Amico and coworkers (2000) demonstrated that 6 months of androgen-deprivation therapy (beginning 2 months before and continuing during and after radiation therapy) improved the PSA outcomes in intermediate- and high-risk patients but not in low-risk patients. In a subsequent randomized trial, D'Amico and colleagues (2008) confirmed that **6 months of hormone therapy improves outcomes, mostly in intermediate-risk patients**; hormone therapy was associated with an *earlier onset* of fatal myocardial infarcts in this study (D'Amico et al, 2007).

On the basis of these studies**, long-term hormone therapy is usually recommended along with external beam radiotherapy in patients with locally advanced disease or localized, high-risk disease. In patients with intermediate-risk, localized disease, short-term (6-month) hormone therapy is usually recommended.**

End Points for Treatment Success or Failure

Evaluation of the outcomes of radiotherapy is complicated because cancer cells are not killed immediately after exposure to ionizing radiation. Rather, they sustain lethal DNA damage but do not die until their next attempt to enter into cell division. Thus **the PSA level gradually decreases for up to 2 to 3 years after the completion of radiotherapy.** Accordingly, the PSA level is usually monitored at 6-month intervals until it reaches a nadir. In patients treated with external beam radiotherapy, the prostate gland is not completely ablated, and the remaining prostate epithelium continues to produce PSA. Also**, inflammation in the prostate gland can produce transient PSA elevations, called a PSA "bounce"** (Critz et al, 2000). **PSA bounce occurs in about 20% of patients, usually during the first 2 years after treatment and is less common with external beam therapy than with brachytherapy. Patients having PSA bounce are more likely to have biochemical failure, and a PSA bounce of greater that 1.4 ng/mL has been associated with biochemical failure, metastases, and prostate cancer death** (Feigenberg et al, 2006).

The biochemical end point used to determine treatment success after external beam radiation therapy is controversial. Until recently, the most frequently used

definition was the American Society of Therapeutic Radiology and Oncology (ASTRO) definition (Cox, 1997). **It requires three consecutive PSA increases measured 6 months apart and back-dates the time of cancer progression to halfway between the PSA nadir and the first rising PSA level. Thus it usually takes years to determine whether progression has occurred after radiotherapy.** Without long-term follow-up, the ASTRO definition yields progression-free survival estimates that appear 10% to 20% better than they actually are because it takes time for the PSA level to reach a nadir and even more time for three consecutive PSA increases to occur. Moreover, in clinical series, there are always more patients with shorter follow-up than with longer follow-up. Thus back-dating of the time of the recurrence moves the time of the recurrence event to a point in the series where the denominator is larger, and therefore the impact of the recurrence on the survival curve is diminished.

In recent years, the Phoenix definition was proposed to replace the ASTRO definition (Roach et al, 2006b). It eliminates back-dating but requires the PSA level to rise by 2 ng/mL before treatment failure is declared. Thus the time to recurrence is further prolonged after the PSA level begins to rise, and often it takes a considerably longer time for the PSA level to increase by 2 ng/mL. In some instances, adjuvant hormone therapy may be initiated before the PSA rises to 2 ng/mL. In practice, the Phoenix definition can yield results that are even more favorable than those obtained with the ASTRO definition. **Accordingly, it is not possible to make fair comparisons between radical prostatectomy and radiotherapy by use of these outcome measurements.**

Treatment Results of External Beam Radiotherapy

With conventional external beam radiotherapy, the 10-year cancer cure rates for patients with clinically localized prostate cancer were approximately 50% (Zietman et al, 2004). **Better results have been achieved with 3D-CRT and dose escalation. However, with dose escalation, there is not only a higher chance for cure, but also a higher risk of rectal morbidity** (Kuban et al, 2008). **High-risk patients are frequently treated with 2 to 3 years of androgen deprivation after radiotherapy** (Bolla et al, 1997; Pilepich et al, 1997). With this regimen, the 5-year progression-free probabilities have been reported to be 70% to 85% (Bolla et al, 1997; Kuban et al, 2008). There are limited data concerning the durable and favorable responses to radiation therapy, especially in young patients. A substantial proportion of patients who are unsuccessfully treated with radiotherapy have tumor recurrence within the radiation field, usually in the central part of the tumor.

High-dose proton or neutron beam therapy has been advocated as a more effective method of conformal radiotherapy, but there is no convincing evidence that treatment results are superior to those achieved with photons (Zietman et al, 2005).

In high-risk patients, external beam radiotherapy has also been combined with brachytherapy. The brachytherapy is usually given first, so that the external beam therapy can be discontinued if the patient begins to experience toxicity (Ragde et al, 1997, 1998; Critz et al, 1998).

Current research involves the use of magnetic resonance spectroscopy to guide radiation administration by directing higher doses to the metabolically active areas of the tumor. Similarly, imaging of hypoxic areas of the tumor with positron emission tomography is being evaluated to direct higher doses of radiation to hypoxic regions of the tumor.

Brachytherapy

With brachytherapy, radioactive sources (seeds or needles) are implanted directly into the prostate gland, and sometimes into the surrounding tissues, to deliver a high dose of radiation to the tumor while sparing, to the extent possible, the bladder and the rectum. Modern brachytherapy for prostate cancer was originally unsuccessful because freehand implantation of the seeds provided a poor radiation dose distribution; however, newer external template-based techniques provide more uniform implantation patterns.

Brachytherapy is relatively easy to perform and therefore has become popular for treatment of patients with clinically localized prostate cancer. It can be performed under general or regional anesthesia. The most commonly used permanent implants are iodine-125 or palladium-103 seeds. Theoretically, palladium offers a higher radiation dose rate that would be expected to be advantageous for treatment of poorly differentiated tumors that have a shorter cell cycle. However, in practice, **no significant advantage has been demonstrated for the use of palladium.** Although high-dose rate temporary implantation with iridium-192 wires has been used for more aggressive tumors, logistical considerations make it time-consuming, inconvenient, and impractical in many clinical settings.

Radiation Dose and Fields

After the implant has been completed, a post-treatment CT scan is routinely obtained to check the postimplant dosimetry. Dosimetry can be adversely affected by poor implantation or migration of the seeds after implantation. The radiation doses delivered to the prostate are approximately 145 Gy for iodine and 125 Gy for palladium, which are substantially higher than those with external beam radiotherapy. As with external beam radiotherapy, radiation dose is important with brachytherapy (Stone et al, 2007a; Kao et al, 2008). Biochemical recurrence is associated with dosimetry; however, it is unclear if dose-escalated brachytherapy produces better overall results. Randomized clinical trials are planned.

Direct comparisons of radiation doses between external beam radiotherapy and brachytherapy are not valid. **Although the prostate itself can tolerate high doses of radiation, the rectal toxicity limits the dose that can be given in brachytherapy.** Because of the much higher doses of radiation delivered, brachytherapy causes more ablation of the prostate gland than external beam radiotherapy does. In many patients treated with brachytherapy, post-treatment PSA levels decrease into the undetectable range. Despite this, **brachytherapy is seldom used for the treatment of high-volume, high-risk prostate cancers, because 3D-CRT is the preferred method for treatment of aggressive tumors.**

In patients who have an enlarged prostate gland, it can be technically challenging to implant the entire prostate volume, especially anteriorly. Accordingly, patients are often treated with androgen-deprivation therapy to shrink the prostate before brachytherapy is performed. Long-term androgen-deprivation therapy confounds assessment of the response to brachytherapy

because it delays PSA rises signaling tumor persistence or recurrence.

At present, transrectal ultrasound-guided brachytherapy is the standard approach. MRI is currently being investigated for use in preplanning and postplanning dosimetry with urethral sparing. MR-CT fusion scans have also been used for this purpose. Magnetic resonance spectroscopy–optimized implants are also under study to give higher doses to metabolically active regions of the tumor.

Results of Brachytherapy

Excellent short-term cancer control rates have been reported with brachytherapy. With the ASTRO failure criteria, 5- and 7-year progression-free survival estimates of 85% and 80%, respectively, have been reported for groups of largely low-risk patients (Ragde et al, 2001). Permanent brachytherapy alone also has been reported to be effective for intermediate-risk patients (Zelefsky et al, 2007). Obesity was reported to be associated with a higher prostate cancer–specific mortality rate (Efstathiou et al, 2007).

External beam radiotherapy combined with permanent-source brachytherapy has been reported to have an efficacy similar to high-dose external beam radiotherapy alone with possibly increased urinary toxicity (Lee et al, 2007).

Side Effects of Brachytherapy

Urinary symptoms are more common after brachytherapy than after external beam radiotherapy, especially in patients with prostatic hyperplasia. To avoid these problems, α-adrenergic blockers and hormone therapy are usually administered before treatment. Urinary retention occurs in up to 22% of patients. Approximately 10% of patients require transurethral resection of the prostate after brachytherapy. If an aggressive transurethral resection of the prostate is performed, there is a high rate of incontinence, occurring in 20% to 40% of patients. However, a more conservative, "channel" transurethral resection or laser prostatectomy can usually restore voiding function while preserving continence. Preservation of erectile function has been reported in 62% to 86% of patients treated with brachytherapy alone. **Impotence rates are higher when brachytherapy is combined with external beam radiotherapy. Furthermore, neoadjuvant hormone therapy frequently used before brachytherapy adversely affects postoperative erectile function. PDE-5 inhibitors may be helpful in restoring erections.**

Proctitis and rectal injury are less common with brachytherapy than with external beam therapy, whereas erectile dysfunction occurs more commonly with brachytherapy than with external beam radiation. Other complications associated with brachytherapy include seed migration and rectourethral fistula (Theodorescu et al, 2000; Di Muzio et al, 2003).

Stereotactic Radiotherapy ("Cyberknife")

"Cyberknife" radiotherapy involves a linear accelerator mounted on a robotic arm that gives large doses of radiation in a small number of fractions (hypofractionation). Limited results have been published in a small number of patients with low-risk disease. These results provide some evidence of short-term safety and evidence of PSA decline, but evidence of long-term safety and efficacy is lacking (King et al, 2009). More research is needed to put hypofractionated radiotherapy on a sound scientific basis (Kupelian et al, 2007; King et al, 2009).

Adjuvant Radiotherapy after Radical Prostatectomy

Patients with adverse findings in the radical prostatectomy specimen may benefit from adjuvant radiotherapy. Adjuvant radiotherapy is usually administered to the bed of the prostate gland, usually in doses in the range of 64 to 68 Gy. It is advisable to wait at least 3 to 4 months after surgery to allow complete wound healing and return of urinary continence. Radiation to the whole pelvis is usually discouraged, because of the higher risk for bowel complications. A long-term randomized trial reported that whole-pelvis radiation improves progression-free survival in men with greater than a 15% risk of pelvic node involvement (Roach et al, 2006a; Lawton et al, 2007). However, the preponderance of evidence suggests that pelvic radiation increases toxicity but has no proven effect on survival (Lawton et al, 2007; Pommier et al, 2007). Depending on the risk for recurrence, some patients do not opt for adjuvant radiotherapy but rather choose to monitor their PSA levels and avoid further treatment unless there is convincing biochemical (PSA) evidence of tumor progression.

Retrospective cohort studies have shown that postoperative radiotherapy reduces recurrence rates in patients with pathologic stage T3 disease and positive margins (Leibovich et al, 2000). Trock and colleagues (2008) reported on a retrospective study of men with PSA failure after radical prostatectomy that is unique because patients received either no treatment, salvage radiation therapy, or salvage radiation therapy with androgen-deprivation therapy. They **reported that salvage radiation was associated with a threefold reduction in prostate cancer mortality, and although the addition of hormone therapy provided no additional decrease in the risk for mortality, the patients who received hormone therapy had higher-risk disease. Therefore hormone therapy probably provided additional benefit for these high-risk patients. The benefit was strongest in those with the shortest PSA doubling times, but it is possible that with longer follow-up, a significant benefit also might become apparent in patients with less aggressive tumors. This study has changed the previous dogma that patients with the most aggressive tumors (i.e., rapid PSA recurrence, seminal vesicle invasion, rapid PSA doubling time) do not benefit from postoperative radiation.**

Randomized prospective trials have demonstrated the benefit of postoperative radiotherapy compared with observation in preventing tumor recurrence and increasing survival (Bolla et al, 2005; Swanson et al, 2007, 2008; Thompson et al, 2009). **However, there has not been a randomized trial that compared adjuvant postoperative radiotherapy with early salvage radiotherapy.** A European Organization for Research and Treatment of Cancer trial showed benefit not only in patients with positive surgical margins but also in those with extracapsular tumor extension and seminal vesicle invasion (Bolla et al, 2005). A Southwest Oncology Group trial

revealed benefits in reducing recurrence and PSA progression at 10 years with an overall significant survival advantage (Swanson et al, 2007). There was a lesser improvement but still a significant benefit for the subset with seminal vesicle involvement (Swanson et al, 2008).

A trial of adjuvant radiation after radical prostatectomy of men with stage pT3 prostate cancer or positive margins revealed that adjuvant radiation reduced the recurrence rate and that positive margins were the strongest predictor of benefit (Van der Kwast et al, 2007).

Adjuvant radiotherapy is most likely to benefit patients with positive surgical margins or extracapsular tumor extension without seminal vesicle invasion or lymph node involvement. However, not all patients with extracapsular tumor extension or positive margins have tumor recurrence without radiotherapy, and many patients with highly adverse findings have treatment failure with distant metastases despite adjuvant radiotherapy. Nevertheless, it is possible that some patients with seminal vesicle invasion or lymph node metastases might benefit from adjuvant radiotherapy (Cozzarini et al, 2004).

Side Effects of Adjuvant Radiotherapy

Side effects of adjuvant radiotherapy also include a 5% to 10% risk of radiation proctitis and a 50% probability that return of erectile function will be materially compromised. Radiotherapy also can compromise borderline postoperative urinary continence, but radiation-induced incontinence is relatively uncommon. Patients with highly unfavorable prognostic parameters who are more likely to fail with distant metastases probably derive benefit from postoperative androgen-deprivation therapy.

Adjuvant Hormone Therapy

In high-risk patients who opt for postoperative radiotherapy, it is uncertain whether they also should receive adjuvant hormone therapy. Clinical trials are under way to answer this question. The only disadvantages of adding hormone therapy in this setting are the expense and associated side effects of the hormone therapy. In patients with lymph node metastases, a prospective, randomized trial has demonstrated significantly improved survival in those treated with early androgen-deprivation therapy (Messing et al, 1999).

D'Amico and colleagues (2008) reported on a randomized trial of androgen suppression and radiation versus radiation alone for prostate cancer. There was a survival advantage of 6 months for patients receiving hormone therapy. However, all the benefit was observed in patients with no or minimal morbidity. Men with comorbidity fared worse with hormone therapy. Tsai and colleagues (2007) also reported an increased risk of cardiovascular death associated with hormone therapy. In contrast, Roach and colleagues (2008) found no difference in fatal cardiac events with 4 months of androgen-deprivation therapy. Despite the conflicting results, patients should have cardiac risk evaluation before beginning hormone therapy, particularly in patients with high-risk disease for whom 2 to 3 years of hormone therapy is considered standard.

Future Research

Future research will address issues about whether adjuvant radiotherapy offers an advantage over early salvage radiotherapy. Another issue being addressed in research is the definition of optimal target volume and mapping of postoperative recurrence patterns to ensure that the radiation addresses the right areas.

Comparison of Radiotherapy with Radical Prostatectomy

An important limitation of radiotherapy as a curative modality is tumor heterogeneity with respect to radiation sensitivity. Tumor persistence within the fields of radiation occurs in up to 40% of patients with clinically localized prostate cancer treated with radiation therapy (Stone et al, 2007b; Zelefsky et al, 2008; Crook et al, 2009). Thus in many patients, there are some tumor cells that are not eradicated by therapeutic doses of radiation (Kaplan et al, 2008). Accordingly, even if the tumor is confined to the prostate, radiotherapy might not cure it. Despite high-dose (>75 Gy) 3D-CRT, nearly half of patients had cancerous biopsy findings more than 2.5 years after treatment (Zelefsky et al, 1998). In addition, cancerous biopsy findings after treatment are usually associated with a poor prognosis (Scardino and Wheeler, 1985; Stone et al, 2007b; Zelefsky et al, 2008). The patterns of failure after surgery are different from those after radiotherapy. No modality affords 100% local control. Surgery is more likely to fail at the margins, and radiation therapy is more likely to fail in the center of the tumor. The strategies of dose escalation and better dose placement are designed to improve the central local control.

A study with a minimum follow-up of 23 years of men treated with radiotherapy for stage T1 to T3 prostate cancer revealed that more than two thirds developed recurrence, and more than half died of prostate cancer. Half of the recurrences occurred after 10 years, and some recurrences developed after 20 years; however, late recurrences might represent a new primary tumor (Swanson et al, 2004).

A systematic overview of radiotherapy for prostate cancer, involving more than 150,000 patients, reported that there are no randomized studies to compare the outcomes of radiotherapy with radical prostatectomy for patients with low-risk disease. Risk group comparisons of T stage, Gleason score, and PSA value have reported similar results between radiotherapy and surgery; however, different end points were used for treatment failure (Nilsson et al, 2004).

It is impossible to compare the results of surgery with those of radiotherapy because of the difference in the end points used for treatment failure, that is, undetectable PSA for surgery versus the ASTRO or Phoenix criteria for radiotherapy. For instance, applying the ASTRO criteria to patients treated with radical prostatectomy, the respective 5-, 10-, and 15-year progression-free rates improved from 85%, 77%, and 68% to 90%, 90%, and 90%, respectively (Gretzer et al, 2002).

In a study of conventional external beam radiotherapy in men with clinical stage T1-2 disease treated from 1991 to 1993, freedom from progression by use of the ASTRO criteria was 49% with back-dating the time of recurrence and 42% without back-dating (Zietman et al, 2004).

The use of PSA nadir of 0.2 ng/mL for patients treated with combined external beam therapy and brachytherapy has been recommended. Failure to achieve this nadir by 60 months almost always is associated with persistent disease (Critz, 2002). However, because external beam radiotherapy is more organ sparing than brachytherapy is, post-treatment PSA levels usually are higher in patients treated with external beam radiotherapy only and thus might not easily achieve a nadir of 0.2 ng/mL.

Valid comparisons of radiotherapy with current treatment methods are lacking. However, the available evidence suggests that radical prostatectomy is more effective in achieving long-term progression-free survival in patients with clinically localized prostate cancer. In a population-based study of long-term survival in nearly 60,000 patients with clinically localized prostate cancer from the U.S. Surveillance, Epidemiology, and End Results (SEER) cancer registry, radical prostatectomy yielded better results than radiotherapy (Lu-Yao and Yao, 1997). However, better results from both treatments would be expected in the PSA era and with recent technical advances.

A comparison of health-related quality of life after primary treatment of localized prostate cancer in patients and spouses from multiple centers from 0 to 2 years after radical prostatectomy, brachytherapy, or external beam radiation therapy revealed that **adjuvant hormone therapy with radiation was associated with worse quality of life outcomes. Patients receiving brachytherapy reported having more long-lasting urinary irritation, bowel, and sexual symptoms and transient problems with vitality or hormonal function. The adverse effects of prostatectomy on sexual function were mitigated by nerve-sparing procedures. After prostatectomy, urinary incontinence was observed, but urinary irritation and obstruction improved, particularly in patients with a large prostate gland. External beam radiation was associated with less urinary irritation and more rectal side effects. Each treatment is associated with a distinct pattern of change in quality of life domains related to urinary, sexual, bowel, and hormonal function. These changes influenced satisfaction with treatment outcomes among patients and their spouses or partners** (Sanda et al, 2008).

Concerns have been raised about highly aggressive second malignancies occurring after radiation therapy, that is, in 1 of 70 patients living more than 10 years after radiation therapy for prostate cancer, especially cancers of the bladder and rectum (Herr and Carver, 2008; Oh and Sandler, 2008).

Management of Postoperative Biochemical Recurrence

Patients with detectable PSA (>0.1 ng/mL) after radical prostatectomy usually have persistent cancer, although some have only retained benign prostate tissue causing the PSA elevation. In the latter case, the serum PSA level increases slowly. Of patients destined to have biochemical recurrence after radical prostatectomy, approximately 50% appear within 3 years, 80% within 5 years, and 99% within 10 years. Rarely, recurrences appear more than 15 years after radical prostatectomy.

The PSA velocity or doubling time, the interval from surgery to biochemical recurrence, and the Gleason score usually reflect how rapidly the tumor is likely to progress (Freedland et al, 2005). In many patients, progression occurs relatively slowly, and only about one third actually develop metastases (Pound et al, 1999; Ward et al, 2004). Numerous studies have demonstrated that patients with a rapidly rising PSA level after biochemical recurrence have a high risk of progression to metastases and prostate cancer-specific mortality (Albertsen et al, 2004; D'Amico et al, 2004). **In a study of men with a rising PSA level after radical prostatectomy who did not receive immediate radiation therapy, the median time to metastases was 8 years after PSA elevation, and only 34% of men developed clinically apparent metastases** (Pound et al, 1999).

If salvage radiotherapy is planned, it should be initiated before the PSA level rises much above 0.5 ng/mL (Cox et al, 1999). **Patients most likely to have favorable responses to salvage radiotherapy are those with PSA recurrence long after surgery, slowly rising PSA level, low-grade tumor, and no seminal vesicle invasion or lymph node metastases.** There is conflicting evidence concerning whether cancer at the surgical margins is a favorable or unfavorable parameter for predicting response to postoperative radiation therapy, although reports suggest that patients with positive margins have a more favorable response rate. In one study, a multivariate analysis revealed that PSA doubling time, pathologic grade, and PSA level at the time of salvage radiotherapy were independent predictors of clinical recurrence, whereas the interval from prostatectomy did not add independent predictive information (Ward et al, 2004).

A multi-institutional retrospective analysis reported that 50% of patients had disease progression at a median follow-up of 45 months after radiation therapy, 10% developed metastases, and 4% died of prostate cancer (Stephenson et al, 2004b). **The actuarial 4-year progression-free probability was about 45%. In this series, predictors of progression were Gleason grade of 8 or higher, preradiation PSA level above 2 ng/mL, negative surgical margins, and PSA doubling time of 10 months or less.**

As with adjuvant radiotherapy, the beneficial effects of salvage radiotherapy are controversial. Some patients fare well without it, whereas others will fail with distant metastases despite receiving it. Some patients with PSA recurrence are better managed with hormone therapy than with salvage radiotherapy. Although many men with biochemical failure are treated with hormone therapy, there are no data from prospective trials to address a possible progression-free or overall survival benefit. **The most appropriate PSA level at which to institute hormone therapy is unknown. Because of the substantial side effects associated with long-term, continuous hormone therapy (decreased libido, impotence, hot flashes, osteopenia with increased fracture risk, metabolic alterations, and changes in cognition and mood), delayed or intermittent hormone therapy is frequently used in patients who have biochemical recurrence, especially those with a slowly rising PSA level** (Sharifi et al, 2005).

The Veterans Administration Cooperative Urological Research Group trials conducted in the 1960s did not show a survival benefit in patients with metastases treated with early hormone therapy (Walsh et al, 2001). However, since then, other prospective, randomized clinical trials have suggested that early hormone therapy is more effective than delayed hormone therapy in patients with pelvic lymph node metastases (Messing et al, 1999) or those with locally advanced or asymptomatic metastatic disease (Immediate versus deferred treatment, 1997). Nevertheless, it is uncertain whether these studies can be extrapolated to patients who have biochemical recurrence after primary treatment. A retrospective study reported no difference in early clinical outcome between early and delayed hormone therapy in men with biochemical recurrence after radical prostatectomy (Moul et al, 2004). However, in high-risk patients, early hormone therapy delayed the time to bone metastases.

High-dose bicalutamide administration has been reported to delay disease progression and yield overall survival results equivalent to those of treatment with orchiectomy among patients with PSA recurrence (Wirth et al, 2004). A possible advantage of this form of early hormone therapy is that it is associated with less risk for sexual dysfunction and osteoporosis than other forms of androgen-deprivation therapy are. A disadvantage is a possible increased risk for cardiovascular complications and death associated with high-dose bicalutamide therapy.

Intermittent hormone therapy is a reasonable alternative to providing early androgen-deprivation therapy while limiting the adverse side effects and expense of continuous hormone therapy. There is accumulating evidence from prospective randomized trials that intermittent androgen deprivation is safe and has survival outcomes comparable to those of continuous hormone therapy (Lane et al, 2004; Da Silva et al, 2005a, 2005b).

OTHER TREATMENTS

Primary Hormone Therapy

Primary androgen-deprivation therapy may be appropriate for older men, those with significant medical comorbidities precluding the use of curative therapy, or those who do not wish to undergo curative therapy. There are limited published contemporary data of men treated with primary hormone therapy for clinically localized prostate cancer. Nevertheless, increasing numbers of patients are receiving primary androgen-deprivation therapy for the treatment of localized prostate cancer. In a large population-based Medicare cohort study, **primary hormone therapy did not improve survival among the majority of elderly with localized prostate cancer compared to conservative management** (Lu-Yao et al, 2008). **However, it could not be ruled out that in this study, men with higher-risk disease were more likely to have been treated with primary hormone therapy, so it is not possible to exclude a benefit.**

The American Society of Clinical Oncology practice guidelines did not make a strong recommendation for early hormone therapy, even in patients with positive lymph nodes, because the concern that any decrease in prostate cancer-specific mortality may be offset by an increased risk of nonprostate cancer mortality, with no overall survival benefit (Loblaw et al, 2007; Saigal et al, 2007).

Cryoablation

Cryoablation destroys prostate tissue through freezing. **Current technology uses argon gas circulating through hollow needles to freeze the prostate and helium gas to warm the urethra. Cryoablation has been used as primary treatment for salvage after radical prostatectomy or radiotherapy** (Babaian et al, 2008). A prior transurethral resection of the prostate is considered a relative contraindication to cryoablation. The initial results of cryoablation were poor with incomplete eradication of the tumor and high complication rates, including urinary retention, incontinence, urinary-intestinal fistula, stricture, chronic rectal or perineal pain, and nearly uniform loss of erections (Porter et al, 1997; Perrotte et al, 1999; Long et al, 2001). **With technical modifications, the complication rates have decreased, cancer control has improved somewhat, and the procedure is better tolerated** (Chang et al, 1994; Long et al, 2001; Onik, 2001, Cytron et al, 2003; Aus, 2006; Babaian et al, 2008).

Although a multicenter cryotherapy study has been published, **recurrence-free outcomes are difficult to interpret,**

Key Points: Radiation Therapy

- External beam radiotherapy uses gamma radiation beams directed at the prostate and surrounding tissues through multiple fields. To minimize radiation injury to the bladder and the rectum, three-dimensional conformal radiotherapy and intensity-modulated radiation therapy have been developed. Patients with a high PSA level, high Gleason score, or large-volume tumor benefit from androgen-deprivation therapy in conjunction with radiotherapy.
- Currently, the most frequently used definition to determine treatment success after radiation therapy is the Phoenix definition, which requires PSA increases of 2 ng/mL above the nadir PSA level.
- With brachytherapy, radioactive seeds or needles are implanted directly into the prostate gland to deliver a high dose of radiation to the tumor while possibly sparing the bladder and the rectum. Brachytherapy is relatively easy to perform and therefore has become popular for treatment of patients with clinically localized prostate cancer, but it is seldom used for the treatment of high-volume, high-risk prostate cancers. Urinary symptoms are more common after brachytherapy than after external beam radiotherapy, especially in patients with prostatic hyperplasia.
- Adjuvant radiotherapy shortly after surgery is most likely to benefit patients with positive surgical margins or extracapsular tumor extension without seminal vesicle invasion or lymph node involvement. Patients most likely to have favorable responses to salvage radiotherapy are those with PSA recurrence long after surgery, slowly rising PSA level, low-grade tumor, and no seminal vesicle invasion or lymph node metastases. However, mortality benefits have been demonstrated in patients with rapid PSA doubling times and high-risk tumors.
- It is unknown whether early adjuvant radiation is better than delayed salvage therapy in patients with adverse pathology findings after radical prostatectomy.

Key Points: Primary Hormone Therapy

- Primary androgen-deprivation therapy may be appropriate for older men, those with significant medical comorbidities precluding the use of curative therapy, and those who do not wish to undergo curative therapy; however, cardiovascular evaluation is prudent prior to treatment of men at risk for cardiovascular complications.
- Hormone therapy is never curative; nevertheless, many patients experience long-term remissions. Bilateral orchiectomy and estrogen administration have largely been replaced by luteinizing hormone–releasing hormone analogs. Antiandrogens produce less sexual dysfunction and osteoporosis but have a greater risk for adverse cardiovascular complications.

because no clear definition of recurrence after cryotherapy has been established (Long et al, 2001). In addition, many patients in the study received neoadjuvant hormone ablation. **An undetectable PSA level is seldom attainable after cryoablation. The ASTRO definition has been used for recurrence where biochemical progression rates have ranged from 91% for low-risk disease to 62% for high-risk disease. However, definitions of biochemical recurrence used for radiotherapy are not appropriate for ablative treatments such as cryoablation.**

Cryoablation has also been evaluated as a possible salvage therapy for men who have failed radiotherapy, but limited long-term data are available. One study reported undetectable PSA in 74% with 2 years of follow-up (Pisters et al, 1999). Reports from an Internet-based registry claim 5-year progression-free survival of 59% using ASTRO criteria and 55% using Phoenix criteria following salvage cryoablation (Pisters et al, 2008). However, 83% had PSA greater than 2 ng/mL after 5 years of follow-up, and 33% had positive biopsies. **Complications associated with salvage cryoablation were much more frequent than for primary treatment (**Bales et al, 1995; Perrotte et al, 1999; Pisters et al, 1999). Complications of salvage cryotherapy included 4.4% incontinence, 1.2% rectal fistula, and 3.2% requiring a transurethral resection of the prostate for obstruction (Pisters et al, 2008). The morbidity profile is improved with current argon-based technology, which dates to 2000. Rectal pain is reported in 17% to 37%, urethral sloughing and obstruction in 5% to 10%, and erectile dysfunction in more than 80%. A PSA nadir greater than 0.1 ng/mL is associated with tumor recurrence and short-term "cure" rates ranging from 34% to 74% have been reported (Babaian et al, 2008).

Potential advantages of cryoablation are that it is minimally invasive, it does not involve radiation exposure or surgical risk, repeated treatments are possible, and preservation of potency is possible but infrequent, even with cavernous nerve warming (Asterling and Greene, 2009). For salvage therapy, the main potential advantage of cryoablation may be that it could delay the need for hormone therapy (Ng et al, 2007). However, these advantages have yet to be documented or validated. In addition, **long-term unequivocal biochemical control and quality of life outcomes data for cryoablation are not yet available.**

Focal Cryoablation

Focal targeted therapy has been proposed as a potential treatment for localized prostate cancer in an attempt to reduce morbidity. **Subtotal cryoablation has also been proposed as a management strategy for patients managed with active surveillance, but there are no long-term results available. However, these modalities rely heavily on accurate tumor localization to achieve total tumor ablation. Extended pattern prostate biopsy fails to provide reliable localization of tumors to specific regions of the prostate** (Schulte et al, 2008).

In summary, there is no substantial evidence to support cryoablation over the other therapeutic treatment options, and there are insufficient data on subtotal cryoablation. Current cryoablation methods have a lower complication rate, but their effectiveness at achieving cancer control is not established. The reported results are inferior to those reported for salvage radical prostatectomy. In many studies, the PSA results are confounded by concomitant hormone therapy, and there remains concern about viable cancer cells near the warmed urethra.

Radiofrequency Interstitial Tumor Ablation

Heating prostate tissue to temperatures substantially above 38° C destroys it nonselectively, whereas it is claimed that *hyperthermia* at less elevated temperatures kills cancer cells selectively. **Radiofrequency interstitial tumor ablation-induced hyperthermia has been investigated as a treatment of the primary tumor, in combination with radiotherapy, and for salvage after radiotherapy failure** (Prionas et al, 1994; Zlotta et al, 1998; Shariat et al, 2005).

Like cryoablation, this office-based treatment can be repeated. Careful and constant monitoring is critical to limit the risk of damage to normal tissue (Shariat et al, 2005). Advantages claimed for hyperthermia are that it can be repeated and does not preclude the use of other therapies. However, **long-term data on complications and cancer control are not available** (Beerlage et al, 2000).

High-Intensity Focused Ultrasound (HIFU)

Acoustic energy can be used with ultrasound focusing to generate heat within the prostate gland, thus ablating focal lesions or the entire gland. Transrectally applied high-intensity focused ultrasound (HIFU) can elevate the tissue temperature of the prostate up to 100° C (Madersbacher et al, 1995). Within several seconds, a lesion develops with a sharp and predictable volume, leaving the surrounding tissue intact. Mechanisms of action of HIFU involve mechanical interaction of ultrasound waves with tissue, producing coagulating heat, high pressure, cavitation bubbles, and chemically active free radicals that ultimately induce tissue destruction by coagulation necrosis (Chapelon et al, 1999). **Days to months are required for necrosis and cavitation to occur.** Because HIFU energy is nonionizing, treatment can be repeated.

Treatment is performed under general or spinal anesthesia and takes 1 to 4 hours, depending on the prostate volume, which should not exceed 40 cc. The rectal mucosa is cooled (Blana et al, 2004), and a limited transurethral resection of the prostate or a bladder neck incision is often performed at the beginning of the procedure to reduce the risk of postoperative urinary retention (Chaussy and Thuroff, 2003). **Most patients require a urethral or suprapubic catheter for several days**.

One commercially available apparatus for HIFU has been tested in a multicenter trial and is available in Europe (Thuroff et al, 2003). Another is investigational with multicenter phase III trials under way (Uchida, 2005). Both devices are undergoing United States Food and Drug Administration phase II/III studies for efficacy.

The procedure is usually well tolerated; the most common side effect is acute urinary retention, occurring in about 20% of patients. **Other potential complications are urinary fistula, incontinence, urethral stricture, and perineal pain** (Blana et al, 2004). **Erectile dysfunction** has been reported in 27% to 61% (Blana et al, 2004; Pickles et al, 2005).

The initial results report a 70% progression-free survival rate with a mean follow-up of 23 months, which is insufficient to be clinically meaningful. The progression criteria used were any

Table 100–1.

The Definition of Risk Group

RISK GROUP	CLINICAL STAGE	PSA (ng/mL)	GLEASON SCORE	BIOPSY CRITERIA
Low	T1a or T1c	<10	2-5	Unilateral or <50% of core involved
Intermediate	T1b or T2a	<10	6 or 3 + 4 = 7	Bilateral
High	T2b or T3	10-20	4 + 3 = 7	>50% of core involved or perineural invasion or ductal differentiation
Very high	T4	>20	8-10	Lymphovascular invasion or neuroendocrine differentiation

Table 100–2.

Recommended Treatment

RISK GROUP	LIFE EXPECTANCY (YEARS)	RECOMMENDED TREATMENT
Low	0-5	AS, HT
	5-10	AS, RT, HT, O
	>10	RP, RT, AS, O
Intermediate*	0-5	AS, HT, RT, O
	5-10	RT, HT, RP, O
	>10	RP, RT, O, HT
High*	0-5	AS, RT + HT, O
	5-10	RT + HT, HT, RP, O
	>10	RT + HT, RP + RT + HT, HT
Very high*	0-5	AS, RT + HT, O
	5-10	H, RT + HT, ST
	>10	RT + HT, RP + RT + HT, HT, ST, IT

AS, active surveillance; HT, hormone therapy; IT, investigational multimodal therapy; RT, radiation therapy; O, others; RP, radical prostatectomy; ST, systemic therapy.

*If there is more than a 20% probability of positive lymph nodes, AS, HT, ST + HT.

cancerous biopsy finding or a PSA rise of more than 0.4 ng/mL, but the durability of responses has not been documented (Blana et al, 2004). HIFU has also been used to treat radiation failures, but limited results have been reported (Gelet et al, 2004). Early outcomes reflect the risk characteristics of the tumors before radiation therapy. Adverse effects associated with salvage HIFU include rectourethral fistula in 6%, severe incontinence in 7%, and bladder neck contracture in 17% (Gelet et al, 2004).

Rebillard and colleagues (2008) reported negative biopsy rates in 64% to 93%, PSA less than 0.5 ng/mL in 55% to 84%, and 5-year progression-free survival of 60% to 70%. The most common complications are stress incontinence, infection, stricture, and erectile dysfunction. **Complication rates are lower than previously reported because of technical improvements and the frequent performance of transurethral resection of the prostate prior to HIFU** (Rebillard et al, 2008).

Overall, **there is insufficient information to recommend HIFU as a standard therapy. The preponderance of current evidence suggests that HIFU is not equivalent to cancer control obtained with surgery or radiation.** For instance, Koch and colleagues (2007) reported on a small series of patients treated in the United States with one commercially available device and no adjuvant hormone therapy. Ten percent of patients developed urinary retention following treatment, 20% were incontinent, and 5% had a rectal injury. Only 42% of patients achieved PSA less than 0.5 ng/mL and a negative biopsy. On the other hand, HIFU has been extensively studied in Europe where it is no longer considered experimental. The results with different machines may not be equivalent. The published reports from Europe are confounded by deficiencies in study design, inhomogeneous patient populations, undersampling of the prostate on biopsies, frequent use of transurethral resection of the prostate, and androgen ablation therapy. These limitations make it impossible to know the true safety or efficacy of HIFU (Koch et al, 2007).

RECOMMENDATIONS FOR TREATMENT BY PATIENT RISK GROUPS

The tumor is staged at the time of diagnosis and the patient evaluated for comorbidities. The legitimate treatment options and their associated risks and potential benefits are discussed in Tables 100–1 and 100–2. Choice of therapy for an individual patient depends on the availability of high-quality delivery.

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chapter 101

Expectant Management of Prostate Cancer

James A. Eastham, MD ● Peter T. Scardino, MD, FACS

Watchful Waiting versus Active Surveillance with Selective Delayed Definitive Therapy
Watchful Waiting
Watchful Waiting versus Treatment
Active Surveillance
Identifying Men with "Low-Risk" Prostate Cancer
Current Results of Active Surveillance with Selective Delayed Definitive Therapy
Summary

The natural history of newly diagnosed prostate cancer is difficult to predict. Men with similar findings on digital rectal examination (DRE) and serum prostate-specific antigen (PSA) level (clinical stage), as well as histologic features on prostate biopsy (pathologic stage), can have markedly different outcomes. Whereas prostate cancer proves lethal in some patients, most men do die with, rather than of, their cancer. The ratio of approximately six newly diagnosed cases for every one death from prostate cancer each year—relatively constant during the past 30 years—is a result of the protracted natural history of the disease in most patients. Further highlighting the remarkable variation in behavior of this disease, autopsy studies have demonstrated that, on histologic examination, **cancer can be found at autopsy in the prostate of approximately 42% of American men 50 years or older who die of causes other than prostate cancer; yet the lifetime risk that an American man will be diagnosed with prostate cancer is estimated to be about 17% and the risk of dying of the disease only 3.6%** (Scardino et al, 1992; Sakr et al, 1993; Landis et al, 1999; Stanford et al, 1999) (Table 101–1). The challenge for physicians today is to identify the minority of men with aggressive localized prostate cancer that can be altered by definitive local therapy, while sparing the remainder of patients the morbidity of unnecessary treatment.

Epidemiologic data demonstrate a high incidence of prostate cancer relative to historical norms and a profound migration toward earlier-stage disease at the time of diagnosis. Implementation of large-scale screening programs and more extensive biopsy strategies are largely responsible for this increase. A retrospective analysis of the control group in the Prostate Cancer Prevention Trial (a phase 3, randomized, double-blind, placebo-controlled study sponsored by the National Cancer Institute) illustrates the potential for indiscriminant biopsy strategies to result in overdiagnosis of prostate cancer (Thompson et al, 2004). Among 2950 men with normal findings on DRE and PSA levels less than 4 ng/mL, 15.2% were found by biopsy to have prostate cancer, including 6.2% of men with PSA levels of 0.5 ng/mL or less (Table 101–2). As the serum PSA thresholds for recommending prostate biopsy decrease and more extensive biopsy strategies result in stage migration toward earlier disease, appropriate management of the disease requires careful assessment of risk: How likely is a given man's cancer to progress or metastasize during his remaining lifetime? What is the probability of success with treatment? What are the risks of side effects and complications with each treatment?

Although the clinical course of newly diagnosed prostate cancer cannot be predicted with certainty, most will turn out to be relatively slow growing, with doubling times for local tumors estimated at 2 to 4 years. **The majority of these cancers prove to be so small, low grade, and noninvasive that they appear to pose little risk to the life or health of the host.** Recent patient series suggest that 20% to 30% of men undergoing radical prostatectomy have pathologic features in the radical prostatectomy specimen consistent with an insignificant or indolent cancer that poses little immediate threat to life or health (e.g., organ-confined cancer < 0.5 mL, no Gleason grade 4 or 5 component). However, **the biologic potential of microscopically detectable cancer is difficult to characterize with certainty** and biopsy may underestimate the extent of cancer in the prostate. Consequently, most physicians recommend aggressive treatment even for small cancers detected by biopsy. Nevertheless, **conservative management (i.e., deferring definitive therapy until evidence that the cancer is sufficiently aggressive to warrant therapy) may be appropriate for many patients with a favorable (low-risk) cancer, and identification of such cancers before treatment would be a significant benefit to these patients.**

WATCHFUL WAITING VERSUS ACTIVE SURVEILLANCE WITH SELECTIVE DELAYED DEFINITIVE THERAPY

Traditionally, watchful waiting has meant that no active treatment is begun until a patient develops evidence of symptomatic disease progression, at which time

Table 101–1.

Lifetime Risk for Development of or Dying of Prostate Cancer for a 50-Year-Old Man in the United States

LIFETIME RISK FOR	RISK (%)	RISK RATIO	PROPORTIONAL RISK
Development of incidental cancer	42	11.7	100
Development of clinical cancer	16.7	4.4	38
Dying of prostate cancer	3.6	1	8.6

Modified from Scardino, 1989; Scardino et al, 1992; Greenlee et al, 2000.

Table 101–2.

Prevalence of Prostate Cancer Found by Biopsy in the Placebo Arm of the Prostate Cancer Prevention Trial

PSA LEVEL	NO. OF MEN (N = 2950)	MEN WITH PROSTATE CANCER (N = 449) NO. OF MEN (%)
≤0.5 ng/mL	486	32 (6.6)
0.6-1.0 ng/mL	791	80 (10.1)
1.1-2.0 ng/mL	998	170 (17.0)
2.1-3.0 ng/mL	482	115 (23.9)
3.1-4.0 ng/mL	193	52 (26.9)

PSA, prostate-specific antigen.
From Klotz L. Active surveillance with selective delayed intervention: using natural history to guide treatment in good risk prostate cancer. J Urol 2004;172:S48–50.

Table 101–3.

Contrasts between Active Surveillance and Watchful Waiting

	ACTIVE SURVEILLANCE	WATCHFUL WAITING
Aim	To individualize treatment	To avoid treatment
Patient characteristics	Fit for radical treatment; Age 50-80 yr	Age >70 yr or life expectancy <15 yr
Tumor characteristics	T1-T2, GS ≤7, initial PSA <15 ng/mL	Any T stage, GS ≤7, any PSA
Monitoring	Frequent PSA testing	PSA testing unimportant
	Repeated biopsies	No repeated biopsies
Indications for treatment	Short PSADT	
	Higher grade/more extensive cancer on repeat biopsy	Symptomatic progression
Treatment timing	Early	Delayed
Treatment intent	Radical	Palliative

GS, Gleason sum; PSA, prostate-specific antigen; PSADT, PSA doubling time.
From Parker C. Active surveillance: towards a new paradigm in the management of early prostate cancer. Lancet Oncol 2004;5:101–6.

Table 101–4.

Life Expectancy of Men (All Races) in the United States by Age in 5-Year Increments

AGE	LIFE EXPECTANCY (YR), 1999-2001
50	27.8
55	23.6
60	19.7
65	16.1
70	12.8
75	9.9
80	7.4
85	5.5

Modified from Arias E, Curtin LR, Wei R, Anderson RN. United States decennial life tables for 1999-2001, United States life tables. National vital statistics reports; vol 57 no 1. Hyattsville (MD): National Center for Health Statistics; 2008.

androgen deprivation therapy is initiated. The goal of this approach is to limit morbidity from either the disease or the therapy, not to administer potentially curative treatment (Table 101–3). The assumption is that definitive local therapy provides little or no benefit to the majority of men diagnosed with prostate cancer.

An alternative and more widely practiced strategy is to delay curative local therapy until the natural history and threat posed by the cancer can be more accurately characterized. **Active surveillance (AS) with selective delayed definitive therapy attempts to distinguish clinically insignificant cancers from life-threatening cancers while they are still localized and potentially curable.** This approach weighs the threat posed by the cancer within the patient's remaining lifespan and the risks of definitive, local therapy, continually reassessing the risk-benefit ratio at each evaluation. The assumption is that the risk posed by a given cancer can be assessed with some degree of certainty. **The goal is to avoid overtreating the majority of patients while administering curative therapy when needed in selected cases** (Table 101–3). The risks are the delayed therapy may be less effective or would need to be more intensive, with greater morbidity, to be as effective as immediate treatment.

WATCHFUL WAITING

Many clinicians recommend watchful waiting for the treatment of prostate cancer in elderly men with competing comorbidities. Several investigators have attempted to document the long-term risk of metastatic disease and death for men whose clinically localized prostate cancer was treated conservatively (Adolfsson et al, 1994; Chodak et al, 1994; Albertsen et al, 1995, 1998, 2005; Johansson et al, 1997, 2004; Cuzick et al, 2006). The impact of this slow-growing cancer depends on the life expectancy (age and comorbidities) of the patient and the clinical features (Gleason score, PSA) of the cancer (Table 101–4). **Those patients expected to live less than 5 years may develop local symptoms, but few patients will develop metastases or die of the disease.**

The risk of metastases or death from clinical stage T1 to T2 cancer managed conservatively was estimated in a meta-analysis of six watchful waiting series (Chodak et al, 1994). **The risk of metastasis at 10 years was 19% for well-differentiated cancers, 42% for moderately differentiated cancers, and 74% for poorly differentiated cancers.** Furthermore, if the primary tumor was not controlled, the risk for development of metastases persisted, even accelerated, after 10 years. These findings were confirmed by Johansson and colleagues (2004), who reported their long-term results among men with early-stage prostate cancer (T1-T2, NX, M0) or watchful waiting. They observed a consecutive sample of 223 men for a mean period of 21 years.

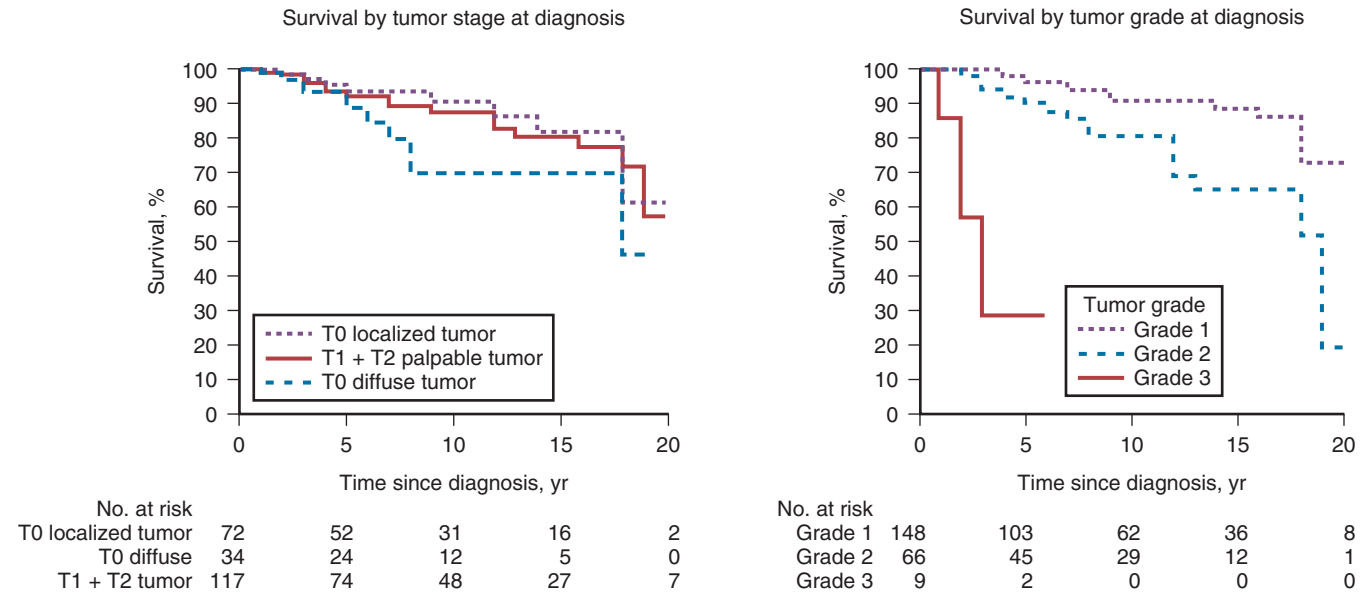


Figure 101–1. Cause-specific survival of men with prostate cancer managed conservatively, by stage of disease and tumor grade at diagnosis. Disease stages were T0 localized, T0 diffuse, and T1-T2. Grades were as follows: grade 1, highly differentiated; grade 2, moderately differentiated; and grade 3, poorly differentiated. (From Johansson JE, Andren O, Andersson SO, et al. Natural history of early, localized prostate cancer. JAMA 2004;291:2713–9.)

Most cancers had an indolent course during the first 10 to 15 years. However, further follow-up from 15 to 20 years revealed a substantial decrease in cumulative progression-free survival (from 45% at 15 years to 36% at 20 years), survival without metastases (from 77% to 51%), and prostate cancer-specific survival (from 79% to 54%) (Fig. 101–1). The authors concluded that **although most prostate cancers diagnosed at an early clinical stage have an indolent course, local tumor progression and aggressive metastatic disease may develop in the long term and early local treatment should be considered for men with a life expectancy exceeding 15 years.**

The impact on mortality was further documented in a large, population-based study (Albertsen et al, 1998, 2005). The probability of death from prostate cancer within 20 years of diagnosis depended on the Gleason sum of the cancer and the age of the patient at diagnosis. **Patients with a well-differentiated cancer (Gleason sum 2 to 4) had a low probability of death from cancer within 20 years (6 deaths per 1000 person-years; 95% confidence interval [CI], 2-11); higher-grade cancers took a substantial toll even among older men (Gleason score of 8 to 10, 121 deaths per 1000 person years; 95% CI, 90-156). In contrast to Johannsen, the Albertson cohort did not experience acceleration in the rate of metastases or death from cancer between 15 and 20 years.**

Kattan and colleagues (2008) reviewed United Kingdom cancer registry data to determine predictors of long-term outcomes for men with clinically localized prostate cancer managed without curative intent in the PSA era. The study included men who at the time of diagnosis were aged 30 to 75 years (inclusive), had a baseline serum PSA level of less than 100 ng/mL, had no evidence of metastatic disease, were not treated with curative intent, and were alive for at least 6 months after diagnosis of their disease. Diagnosis was by transurethral resection of the prostate in 1358 (56%) and needle biopsy in 1088 (44%). Most men were managed without initial treatment, while 30% were treated with hormone therapy within 6 months of diagnosis. In a competing risk analysis, 30% of the patients died of prostate cancer and 30% of other causes within 12 years. This was the first long-term watchful waiting study to include PSA at diagnosis and Gleason grade (reviewed centrally). Figure 101–2 shows the 10-year probability of death from prostate cancer and death from any cause by PSA and Gleason score at diagnosis (Cuzick et al, 2006). However, among men who did not die of another cause in this cohort, the probability of metastases, death from prostate cancer, or additional therapy within 12 years was 90%. These results suggest that localized prostate cancer detected clinically, in an unscreened population, results in a high rate of progression or secondary treatment within 12 years when managed with watchful waiting. **In these watchful waiting cohorts, age, Gleason grade, and PSA were able to identify men at increased risk for the development of metastatic disease and death from prostate cancer. Nevertheless, not all men with "adverse" features do poorly, nor do all men with favorable features do well.** Additional clinical and pathologic parameters are necessary to predict outcomes more accurately and to place expectant management of some patients on a sound basis.

WATCHFUL WAITING VERSUS TREATMENT

Perhaps the most compelling evidence that selected patients with prostate cancer benefit from active treatment compared with watchful waiting comes from the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4), which randomized 695 men with clinically localized prostate cancer to either radical prostatectomy or watchful waiting, with systemic treatment deferred until the development of symptomatic progression (Bill-Axelson et al, 2005, 2008). During a median of 10.8 years of follow-up, 47 of the 347 men (13.5%) who were randomly assigned to surgery died of prostate cancer, as did 68 of the 348 men (19.5%) assigned to watchful waiting (Fig. 101–3). **At 12 years, 12.5% of the surgery group and 17.9% of the watchful waiting group**

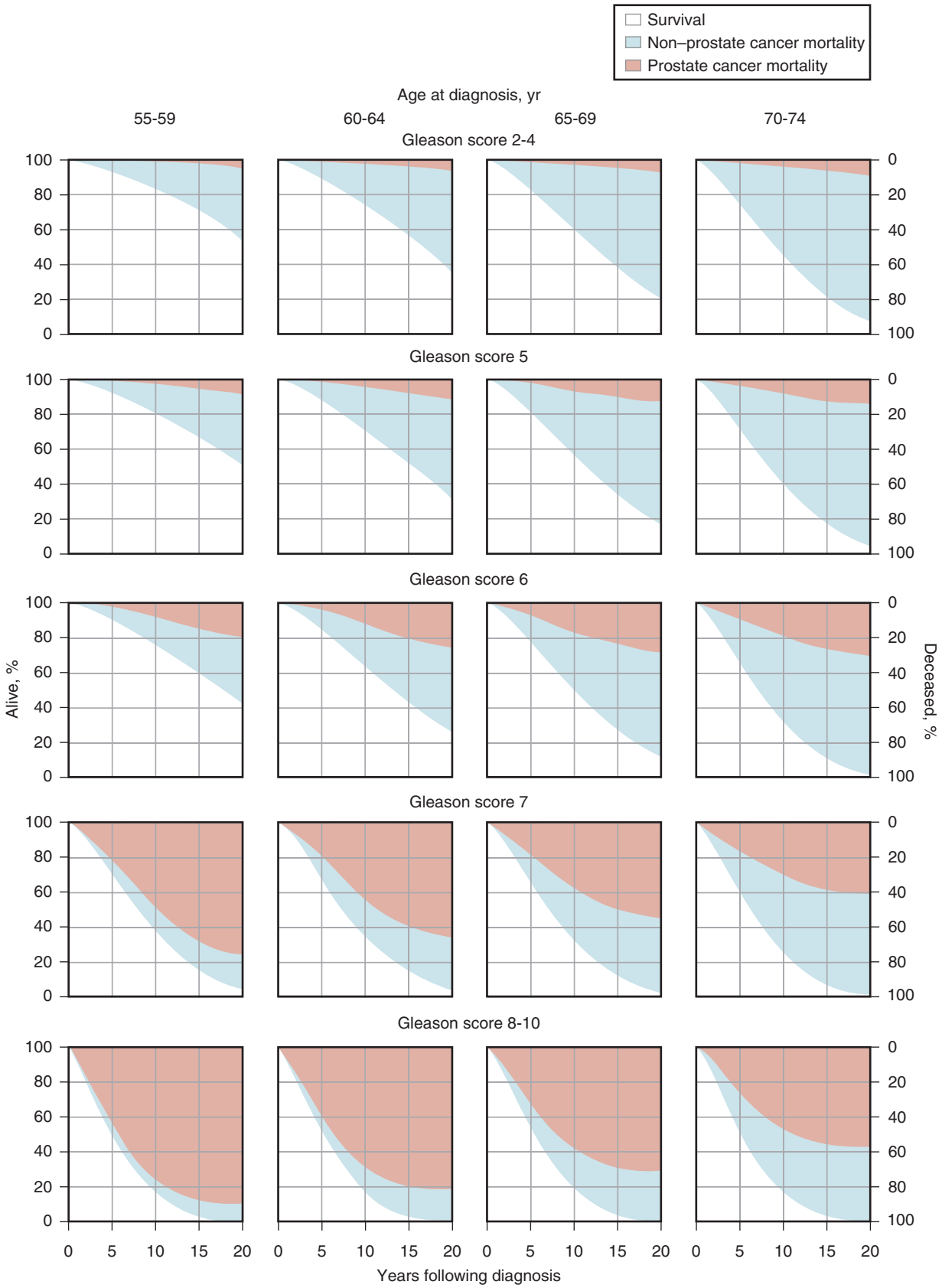


Figure 101–2. Proportion of patients dead from prostate cancer *(orange)*, dead from other causes *(blue)*, at different follow-up times up to 10 years, according to baseline PSA and Gleason score, separately for patients aged 70 years or younger at diagnosis and patients aged older than 70 years at diagnosis. (From Cuzick J, Fisher G, Kattan MW, et al. Long-term outcome among men with conservatively treated localized prostate cancer. Br J Cancer 2006;95(9):1186–94.)

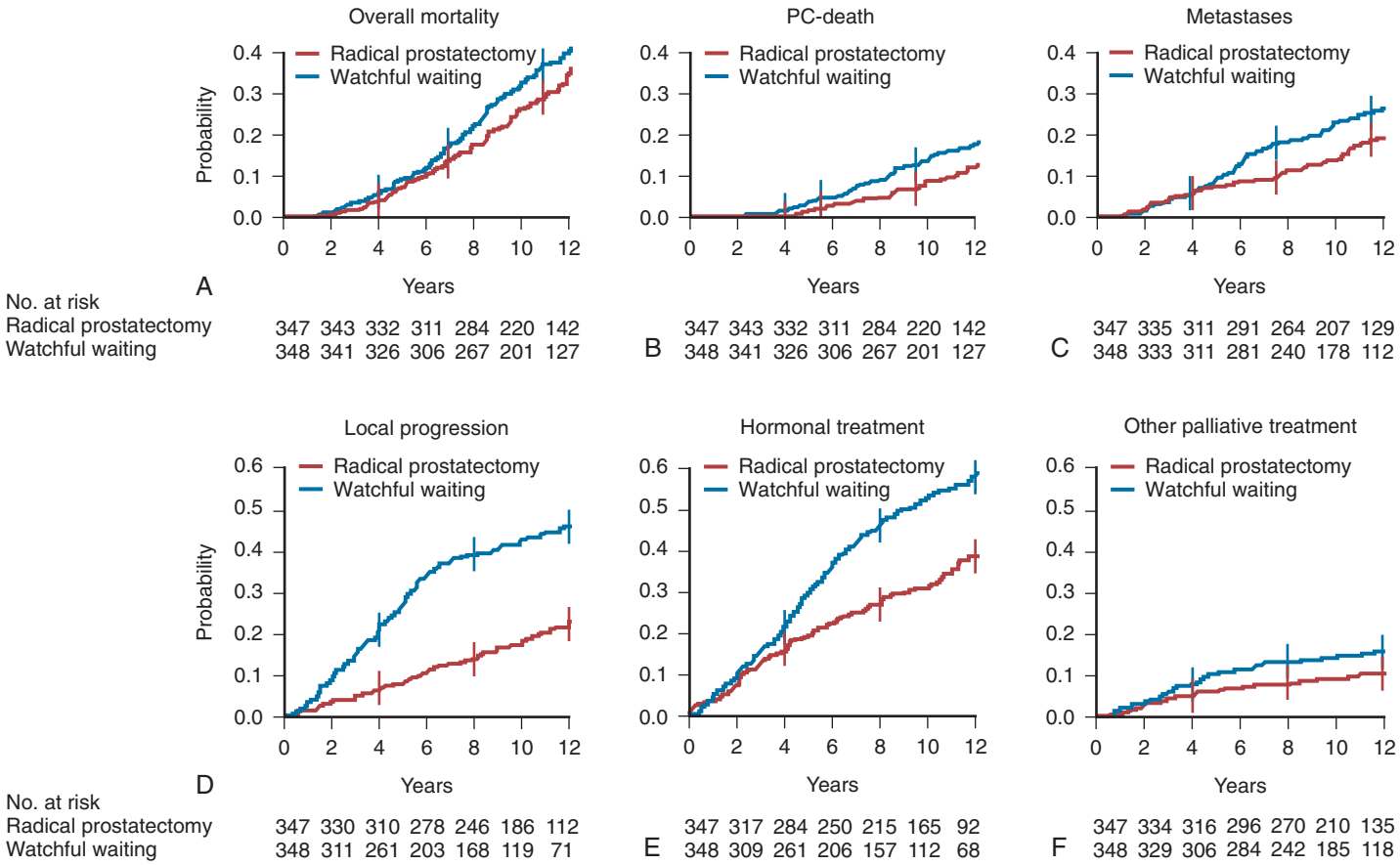


Figure 101–3. Scandinavian randomized trial comparing radical prostatectomy and watchful waiting for localized prostate cancer (PC) detected clinically in the absence of prostate-specific antigen screening. Surgical excision altered the natural history of prostate cancer, reducing cumulative incidence of **A,** overall mortality, **B,** prostate cancer death, **C,** metastases, **D,** local progression, **E,** hormonal treatment, and **F,** other palliative treatment. (From Bill-Axelson A, Holmberg L, Filen F, et al. Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial. J Natl Cancer Inst 2008;100(16):1144–54.)

had died of prostate cancer (difference = 5.4%, 95% CI, 0.2 to 11.1), for a relative risk of 0.65 (95% CI = 0.45 to 0.94; *P* = .03), and 19.3% in the surgery group and 26% in the watchful waiting group had distant metastases (difference = 6.7%, 95% CI = 0.2 to 13.2), for a relative risk of 0.65 (95% CI = 0.47 to 0.88; *P* = .006). This elegant study, which was carried out in a population not screened for prostate cancer with PSA, documents the overall benefit of radical prostatectomy for patients whose cancer is detected clinically. Because the estimated lead time for PSA screen–detected cancers is 6 to 8 years compared with clinically detected prostate cancers, the relevance of the Scandinavian study to the cancers detected by screening is uncertain.

Although the development of metastatic disease and death from prostate cancer are important adverse outcomes, local cancer progression and the need for treatment also have significant impact on quality of life (Fig. 101–3). For example, **the Scandinavian Prostate Cancer Group reported that fewer men in the radical prostatectomy group than in the watchful waiting group developed local recurrence or disease progression** (Steineck et al, 2002; Bill-Axelson et al, 2008). At 12 years, the cumulative incidence of local recurrence and/or progression was 21.7% in the surgery group and 45.6% in the watchful waiting group (difference = 23.9, 95% CI = 16.8 to 30.9). A total of 132 men in the radical prostatectomy group versus 205 in the watchful waiting group started hormonal therapy. The difference in cumulative incidence of hormonal therapy at 12 years was 19.3% (95% CI = 11.7 to 26.9), with **a lower probability of starting hormonal therapy in the radical prostatectomy group. All other palliative treatments (including radiation, treatment with cytotoxic drugs, and laminectomy) were also less common in the radical prostatectomy group.** The difference in the cumulative incidence of palliative treatment at 12 years was 5.2% (95% CI = 0.1 to 10.3). **Erectile dysfunction and incontinence were higher in men treated with radical prostatectomy, whereas men on watchful waiting experienced significantly more obstructive voiding complaints and bowel problems, resulting in similar levels of treatment-related distress** (Table 101–5).

ACTIVE SURVEILLANCE

Widespread use of PSA screening, combined with low thresholds for recommending prostate biopsy and more aggressive biopsy techniques (12 core, saturation), have resulted in a profound shift toward detection of prostate cancer earlier (Draisma et al, 2009). Furthermore, large randomized trials of PSA screening have shown a limited impact on cancer specific mortality (Andriole et al, 2009; Schroder et al, 2009). These studies suggest that a proportion, estimated in one study as 23% to 42% (Draisma et al, 2009), of prostate cancers are being detected by PSA screening that would

Table 101–5.

Comparison of Urinary Quality of Life (Function) between Radical Prostatectomy and Watchful Waiting in Patients from the Scandinavian Prostate Cancer Group

FUNCTION	RP	WW	RELATIVE RISK (95% CI)
Leak once per week or more often	49%	21%	2.3 (1.6-3.2)
Distress from leakage	29%	9%	3.0 (1.8-5.2)
Urinary obstruction	28%	44%	0.6 (0.5-0.9)
Low/moderate urinary quality of life	40%	45%	0.9 (0.7-1.2)

RP, radical prostatectomy; WW, watchful waiting.
From Steineck G, Helgesen F, Adolfsson J, et al. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med 2002;347:790–6.

never have been detected in the subjects' lifetime. These cancers are considered by some to be "overdetected," and this concept has led to wider acceptance of AS for low-risk prostate cancers.

AS refers to a systematic program of periodic monitoring of men diagnosed with a prostate cancer judged to pose little immediate threat to life or health. Such patients are offered AS as an alternative to immediate radical therapy. They return frequently for examination and PSA testing and periodically for prostate biopsy. Active intervention is delayed until there is clear evidence of progression of the cancer, although some patients become anxious and choose definitive therapy in the absence of progression. Although AS is now more widely accepted for very early, low-risk prostate cancer, the appropriate criteria for inclusion in an AS program and the definition of progression of the cancer are controversial, and the results of interim intervention and the long-term outcomes remain uncertain.

IDENTIFYING MEN WITH "LOW-RISK" PROSTATE CANCER

Many physicians and patients consider AS for selected low-risk prostate cancers. The difficulty is in defining "low risk." Initial clinical staging, when limited to digital rectal examination, PSA, and diagnostic biopsy results, has limited potential for accurately characterizing localized prostate cancers, although systematic needle biopsies, serial PSA determinations, and modern imaging are promising tools for more accurately assessing the size, grade, and extent of the cancer.

Systematic Biopsy Results

In an attempt to identify patients who have low-risk cancer, Epstein and colleagues (1994) examined preoperative clinical and pathologic features in 157 men with clinical stage T1c prostate cancer (who later underwent radical prostatectomy) to find features that could predict "insignificant" cancer (pathologically organ-confined, < 0.2 mL, Gleason sum ≤ 6). Their **model for predicting an insignificant cancer included no Gleason grade 4 or 5 in the biopsy specimen and either:**

- PSA density of 0.1 ng/mL per gram or less, fewer than three biopsy cores involved with cancer (minimum of six cores obtained), and no core with more than 50% involvement; or
- PSA density of 0.15 ng/mL per gram or less and on only one (of six or more) biopsy cores with cancer smaller than 3 mm.

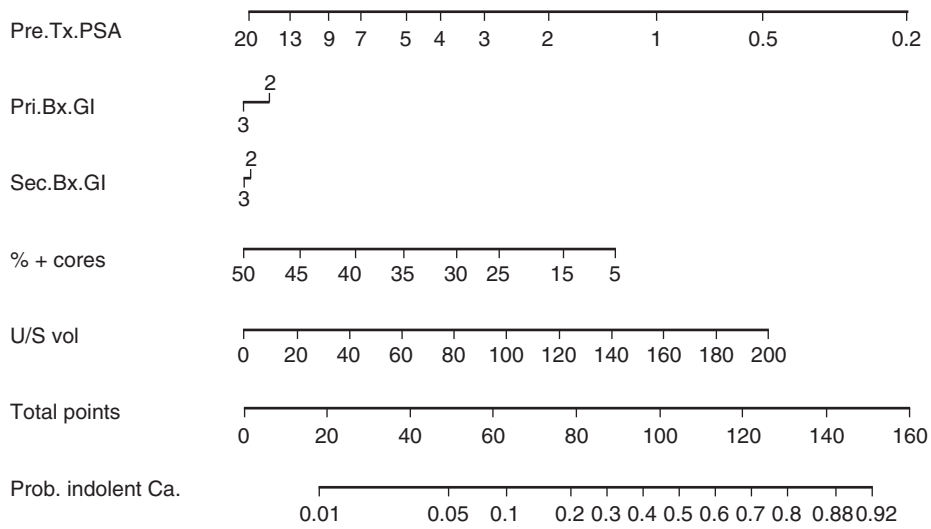
As a test for insignificant disease, this model had a negative predictive value of 95% and a positive predictive value of 66% in their own dataset.

Similarly, Goto and colleagues (1996) evaluated 170 patients who had six or more systematic needle biopsies and determined that a PSA density of less than 0.1 ng/mL, no Gleason grade 4 or 5 in the prostate biopsy specimen, and cancer smaller than 2 mm in a single biopsy core predicted a 75% probability of an unimportant or indolent cancer (<0.5 mL, organ confined, no Gleason grade 4 or 5) at radical prostatectomy. Epstein and colleagues (1998) evaluated 163 radical prostatectomy specimens of clinical stage T1c prostate cancer to determine whether free/total serum PSA ratios, which reflect prostate volume indirectly, combined with needle biopsy results would be more accurate. Using the same definition of indolent cancer that Goto and colleagues used, they determined that the best model to predict indolent tumor is a free/total serum PSA ratio of 0.15 or greater and favorable needle biopsy findings (defined as fewer than three cores involved, none of the cores with more than 50% tumor involvement, and Gleason sum < 6). This model had a 94% positive predictive value for significant cancer. None of these models, however, have been validated prospectively or on a separate cohort.

Because patient selection for deferred therapy is critically dependent on the results of the prostate biopsy (Gleason grade and amount of cancer), some investigators have suggested more extensive biopsy strategies to better assess the true extent of cancer within the prostate. Transrectal ultrasound-guided (TRUS) prostate biopsy has been shown to poorly reflect the grade and extent of a patient's cancer when compared with the radical prostatectomy specimens (Sved et al, 2004). Crawford and colleagues (2005), using computer simulations on 106 autopsy and radical prostatectomy specimens, suggested that transperineal prostate biopsies using a brachytherapy template, spaced at 5-mm intervals throughout the volume of the prostate, could determine grade and detect significant cancers with greater sensitivity. Onik and Barzell (2008) used a transperineal three-dimensional mapping method to restage 110 patients, all of whom had had unilateral prostate cancer diagnosed by TRUS biopsies. The median number of cores taken was 46 (SD ± 19). Bilateral cancer was found in 60 patients (55%), and the Gleason score was increased in 25 (23%). Complications were self-limited and included nine patients (8%) who required short-term catheterization and two (2%) with hematuria. Although this study was primarily designed to assess the role of transperineal biopsy in selecting men for focal therapy, the investigators hypothesized that 75% of patients thought to have low-risk cancers eligible for AS were found to have larger, higher-grade tumors better treated with definitive therapy. Although extensive biopsy strategies provide more information than a standard TRUS-guided biopsy does, their role in routinely evaluating a patient for AS is unclear. None of the commonly used guidelines for identifying candidates for AS have relied on extended prostate biopsy. Further information is necessary before a routine recommendation for this procedure is embraced.

Indolent Cancer Nomogram

To better counsel men diagnosed with prostate cancer, a statistical model to predict the presence of an indolent cancer was developed and validated from standard clinical variables (serum PSA level, prostate volume determined by TRUS examination, clinical stage, prostate biopsy Gleason grade, and systematic biopsy findings) (Kattan et al, 2003; Steyerberg et al, 2007). The biopsy features included number and percentage of biopsy cores involved with



Instructions for Physician: Locate the patient's PSA on the PreTx PSA axis. Draw a line straight upward to the Points axis to determine how many points toward having an indolent cancer the patient receives for his PSA. Repeat this process for the remaining axes, each time drawing straight upward to the Points axis. Sum the points achieved for each predictor and locate this sum on the Total Points axis. Draw a line straight down to find the patient's probability of having indolent cancer.

Instruction to Patient: "Mr. X, if we had 100 men exactly like you, we would expect <predicted probability from nomogram * 100> to have indolent cancer."

Figure 101–4. Nomogram for predicting an indolent prostate cancer from clinical data and systematic biopsy results (full model). Ca, cancer; Clin., clinical; Pre.Tx., pretreatment; Pri.Bx.Gl, primary biopsy Gleason grade; Prob., probability; Sec.Bx.Gl, secondary biopsy Gleason grade; U/S, ultrasound. (From Kattan MW, Eastham JA, Wheeler TM, et al. Counseling men with prostate cancer: a nomogram for predicting the presence of small, moderately differentiated, confined tumors. J Urol 2003;170:1792–7.)

cancer, total length of cancer in all cores, and total length of noncancerous tissue.

The analysis included men whose cancer was diagnosed after systematic needle biopsy that had features of a low-risk cancer (clinical stage T1c or T2a, biopsy Gleason patterns 2 or 3, PSA < 20 ng/mL). Analysis of the radical prostatectomy specimens found that 80 patients (20%) had an indolent cancer (as defined earlier). Logistic regression was used to construct prediction models of increasing complexity, from a base model that included only stage, grade, and PSA to a full model that added prostate volume, length of cancer, and length of noncancerous tissue in the cores. The nomograms predicted the presence of an indolent cancer with discrimination (area under the receiver operating characteristic curve) that increased from 0.64 for the base model to 0.79 for the full model (Fig. 101–4). Using such prognostic information, physicians can identify, with reasonable accuracy, patients with low tumor burden for whom initial aggressive management may not be indicated, especially in men who are older or with significant comorbidities.

Role of Imaging in Selecting Men for Active Surveillance

To improve the accuracy of gray-scale TRUS technology, a number of alternatives including color Doppler TRUS (CDUS), power Doppler imaging (PDI) with or without intravenous contrast administration, and elastography have been developed (Remzi et al, 2004; Halpern et al, 2005; Pelzer et al, 2005; Amiel and Slawin, 2006; Salomon et al, 2008). CDUS is based on the premise that increased microvascularity and abnormal blood flow patterns accompany cancer growth, whereas PDI is considered an improvement in CDUS because it has the advantage of increased sensitivity for detecting small, low-flow blood vessels. Ultrasound-based real-time elastography imaging visualizes differences in tissue strain produced by freehand compression, permitting the investigator to discriminate hard from soft tissue regions within the prostate. Studies examining CDUS and PDI have demonstrated varying degrees of benefit. Overall, the sensitivity of CDUS for the diagnosis of prostate cancer ranged between 49% and 87%, and specificity ranged between 38% and 93% (Amiel and Slawin, 2006). Some investigators have concluded that PDI offers no advantage over CDUS, whereas others have reported that PDI has a high negative predictive value and may help to reduce the number of unnecessary biopsies (Remzi et al, 2004; Halpern et al, 2005). Elastography has been reported to have a sensitivity and specificity of 75% and 77%, respectively, for detecting prostate cancer, with a positive predictive value, negative predictive value, and accuracy of 87.8%, 59%, and 76%, respectively (Salomon et al, 2008). However, this study was limited to selected patients with a diagnosis of prostate cancer who were scheduled for surgery.

Shukla-Dave and colleagues (2007) evaluated the utility of combining clinical data, biopsy data, and magnetic resonance imaging (MRI) with magnetic resonance spectroscopic imaging (MRSI) to predict the probability of insignificant prostate cancer in 220 patients with low-risk prostate cancer (defined as clinical stage T1c or T2a, PSA level < 20 ng/mL, biopsy Gleason score 6) undergoing radical prostatectomy. The probability of insignificant cancer was recorded retrospectively and separately for MRI and combined MRI/MRSI on a scale of 0 to 3 (0, definitely insignificant prostate cancer: no regions with abnormal T2-weighted signal; 1, probably insignificant: non-nodular decreased T2-weighted signal, smaller

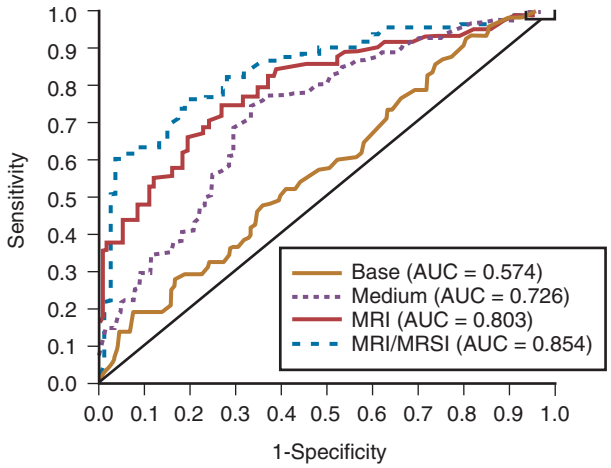


Figure 101–5. A comparison of receiver operating characteristic curves of models to predict the presence of an indolent cancer before radical prostatectomy. The base and medium models include clinical variables only, and the magnetic resonance imaging (MRI) and MRI/magnetic resonance spectroscopic imaging (MRSI) models add information from MRI and spectroscopy, respectively. The base model includes the serum PSA, primary and secondary biopsy Gleason grades, and clinical stage; the medium model adds percent biopsy cores positive and prostate volume on MRI. The MRI model adds the MRI score to the medium clinical model. MRI/MRSI adds the MRI/MRSI score to the MRI model. The P values for the differences between the models were base versus medium model, less than 0.001; base versus MRI model, less than 0.001; base versus MRI/MRSI model, less than 0.001; medium versus MRI model, less than 0.018; medium versus MRI/MRSI model, less than 0.001. (From Shukla-Dave A, Hricak H, Kattan MW, et al. The utility of magnetic resonance imaging and spectroscopy for predicting insignificant prostate cancer: an initial analysis. BJU Int 2007;99:786–93.)

than 0.5 cm^3; 2, indeterminate: non-nodular reduced T2-weighted signal, larger than 0.5 cm^3 or nodular but smaller than 0.5 cm^3; 3, definitely significant: nodular reduced T2-weighted signal, larger than 0.5 cm^3). At pathology, 41% of patients had insignificant cancer (organ-confined, ≤0.5 mL, no poorly differentiated elements in the prostatectomy specimen). Both MRI (AUC 0.803) and MRI/MRSI (AUC 0.854) models incorporating clinical, biopsy, and magnetic resonance data performed significantly better than models based on clinical data alone (Fig. 101–5). The addition of MRI and/or MRI/MRSI information to routinely collect clinical data may help in counseling patients who are considering deferred therapy.

CURRENT RESULTS OF ACTIVE SURVEILLANCE WITH SELECTIVE DELAYED DEFINITIVE THERAPY

AS with selective delayed definitive therapy, like watchful waiting, has the goal of avoiding unnecessary treatment of men with low-risk cancers, those that would seem to pose little risk to life or health during the next 5 to 10 years (Choo et al, 2001, 2002; Patel et al, 2004; Klotz, 2005; Carter et al, 2007; Soloway et al, 2008). The initial evaluation of a candidate for AS aims to reduce the chance that a large, aggressive cancer has been missed; subsequent evaluations aim to detect progression before the cancer metastasizes. Studies of watchful waiting (Adolfsson et al, 1994; Chodak et al, 1994; Albertsen et al, 1995, 1998, 2005; Johansson et al, 1997, 2004) suggest that the risk of progression *accelerates* over time, a pattern different from the risk of progression or recurrence after definitive therapy, which diminishes over time. Hence AS patients must accept frequent, regular, detailed evaluations of the status of their cancer for as long as they are healthy and young enough to be candidates for definitive therapy.

Outcomes of Active Surveillance

There are, as yet, few reports of outcomes of deferred definitive therapy for localized prostate cancer (Choo et al, 2001, 2002; Zietman et al, 2001; Carter et al, 2002, 2007; el-Geneidy et al, 2004; Klotz, 2004, 2007; Patel et al, 2004; Soloway et al, 2008). The University of Toronto conducted a prospective phase II study of AS, incorporating selective delayed intervention for the subset of patients with short PSA doubling time or grade progression on repeat biopsy (Choo et al, 2001, 2002; Klotz, 2004, 2007). The eligibility criteria for this study included patients with clinical stage T1c or T2a cancer, biopsy Gleason score of 6 or lower, and a serum PSA of 10 ng/mL or less. For patients older than the age of 70 years, these eligibility criteria were relaxed to include biopsy Gleason score 7 (3 + 4) or lower and/or PSA of 15 ng/mL or less. The core prospective cohort of 331 patients had a median follow-up of 8 years (range, 2 to 11). Patients were observed until they met one of three specific criteria defining rapid or clinically significant progression:

1. PSA progression, defined as a PSA doubling time (PSADT) of 3 years or less, based on multiple serum PSA determinations at 3-month intervals, calculated using a General Linear Mixed Model, which corrects for baseline PSA, grade, and age. This model is freely available at http://psakinetics.sunnybrook.ca.
2. Clinical progression, defined by meeting any of four conditions: more than a doubling of the product of the maximum perpendicular diameters of the primary lesion as measured by DRE, local progression of prostate cancer requiring transurethral resection of the prostate, development of ureteral obstruction, or radiologic or clinical evidence of distant metastasis.
3. Histologic progression (i.e., Gleason sum 4 + 3 or higher on repeat biopsy of the prostate).

Patients who had progression were offered radical intervention; those without progression were closely monitored. Biopsies were performed for cause at 1 year, then every 4 to 5 years. The median PSADT was 7 years; 42% had a PSADT longer than 10 years, suggesting an indolent course of disease in these patients. Twenty-two percent of patients had a PSADT of less than 3 years. With a median follow-up of 72 months, 34% of the patients had received radical treatment. Fifteen percent were treated because of a PSADT of less than 3 years; 7% because of histologic or clinical progression; and 12% because of patient preference. Ten percent have been treated with radical prostatectomy, and 36% of these had cancer outside of the prostate. The remainder has not required local or systemic therapy. Overall survival is 85% and disease-specific and metastasis-free survival is 99% at 8 years.

In a prospective, longitudinal surveillance program, Carter and colleagues (2007) observed a cohort of men (with clinical stage T1c prostate cancer suspected of harboring small-volume cancer based on needle biopsy findings and PSA density (Epstein et al, 1994). Median age was 65.7 years (range, 45.8 to 81.5), and median follow-up was 2.8 years (range, 0.4 to 12.5). Semiannual measurements of total and free PSA, a semiannual DRE, and an annual surveillance prostate biopsy examination were performed.

Treatment was recommended if there were findings of adverse pathologic features on an annual surveillance biopsy examination (any Gleason pattern 4 or 5, more than two cores that were positive for cancer, or more than 50% of any one core that was involved with cancer) or if a patient requested a change in management. Of 407 men, 239 (59%) remained on AS; 103 (25%) were treated definitively at a median of 2.2 years after diagnosis (range, 0.96 to 7.39); and 65 (16%) were lost to follow-up (12), withdrew from the program (45), or died of causes other than prostate cancer (8). Of the 103 men, 53 (51%) were treated with radical prostatectomy. Twenty percent of these men were considered to have noncurable disease, defined as pathologic stage T2 if Gleason score was 4 + 3 or greater, positive surgical margins of any grade, stage pT3aN0 (extraprostatic extension) if Gleason sum was 7 or greater and/or surgical margins were positive, any stage higher than pT3a regardless of grade or margin status, or any N+ stage. The investigators concluded that a program of careful selection and monitoring of older men who are likely to harbor small-volume, low-grade disease may be a rational alternative to immediate radical therapy for all.

Two hundred and seventy patients diagnosed in the Swedish arm of the European Randomized Study of Screening for Prostate Cancer have been managed with AS (Khatami et al, 2006). During a mean follow-up of 63 months, 104 (39%) received active treatment: 70 with radical prostatectomy, 24 with radiation, and 10 with endocrine treatment. There were no prostate cancer–related deaths. Those who received active treatment were significantly younger (62.6 vs. 65.5 years, $P < .0001$) and had a shorter PSADT (3.7 vs. 12 years, $P < .0001$). PSA relapse was observed in 9 (12%) of 70 of the radical prostatectomy patients during a mean follow-up of 37 months. Seven of these nine PSA relapses were in the patients with preoperative PSADT of less than 2 years. None of the 37 radical prostatectomy patients with a PSADT longer than 4 years had a PSA relapse. The investigators concluded that the optimal candidate for surveillance is a man with early, low-grade, low-stage cancer and a PSADT of longer than 4 years. In those with a PSADT less than 4 years, AS should be recommended with caution.

Patel and colleagues (2004) studied outcomes for patients with low-risk cancer who were eligible for definitive therapy but chose AS. This prospective study enrolled 88 patients with clinical stages T1-T2, N0 or NX, M0 prostate cancer, mean age of 65.3 years, and mean initial PSA value of 5.9 ng/mL. They were observed for a median of 44 months (range, 7 to 172). Follow-up involved DRE and serum PSA levels every 3 months for year 1 and every 6 months thereafter. Repeated TRUS-guided needle biopsy was recommended at baseline, 1 year later, and then every 2 to 3 years or sooner if DRE, TRUS (endorectal MRI was not available during this study), or PSA level indicated progression. Retrospectively reviewed data were used to develop criteria for "objective progression." Points were assigned for changes in Gleason score, PSA level, DRE/TRUS, and biopsy results (Table 101–6); patients with three or more points were classified as having objective progression. Progression criteria were met by 22 patients. The actuarial probability of progression was 36% at 5 years and 45% at 10 years (Fig. 101–6A). Of the 88 patients, 70 had a repeat biopsy within 6 months of diagnosis and 47 (47/70%) of these showed no cancer. In multivariable analysis, the result of the repeat biopsy was the most important predictor of progression (Fig. 101–6B). Only 36%

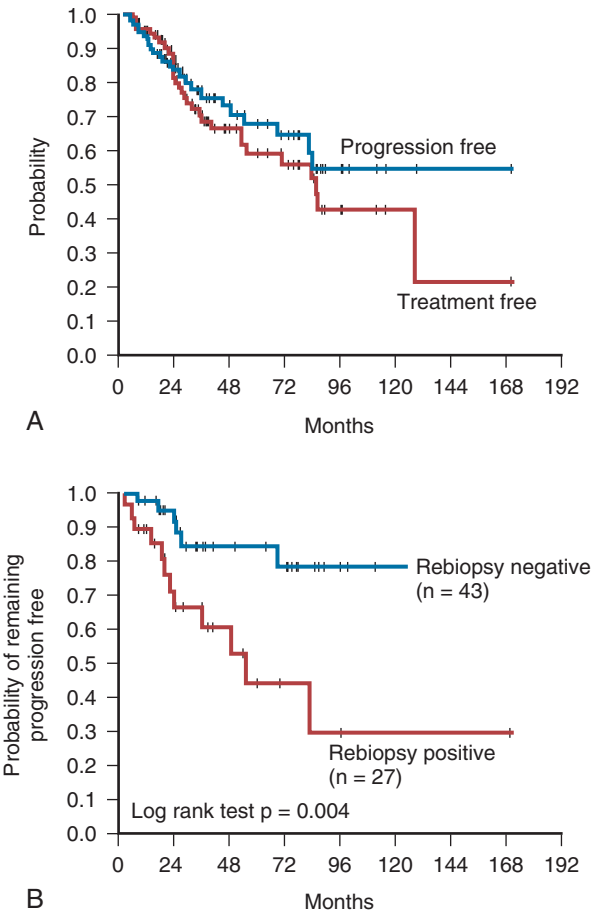


Figure 101–6. **A,** Probability of remaining progression free and treatment free for patients on active surveillance. **B,** Probability of remaining progression free, stratified by first repeat biopsy result. (From Patel MI, DeConcini DT, Lopez-Corona E, et al. An analysis of men with clinically localized prostate cancer who deferred definitive therapy. J Urol 2004;171:1520–4.)

Table 101–6.

Point System for Evaluating Progression in Patients Treated with Deferred Therapy

	1 POINT	2 POINTS	3 POINTS
Gleason score increase	1	>1	Any new Gleason pattern 4 or 5
PSA velocity (ng/mL/yr)		>0.75 during 12 mo	>0.75/yr during 24 mo
DRE/transrectal ultrasonography	Increasing old lesion*	New lesion not biopsy proven†	New biopsy-proven lesion†
Biopsy specimens		Bilateral or multifocal cancer	>4 cores with cancer

*More than 25% increase in cross-sectional area ($\pi/4 \times$ length $\times$ perpendicular width).
†New nodule on DRE or hypoechoic lesion on transrectal ultrasonography separate from any previously recorded lesion.
DRE, digital rectal examination; PSA, prostate-specific antigen.
From Patel MI, DeConcini DT, Lopez-Corona E, et al. An analysis of men with clinically localized prostate cancer who deferred definitive therapy. J Urol 2004;171:1520–4.

Table 101–7.
Likelihood of Prostate Cancer Remaining Untreated after Active Surveillance (AS)

SERIES	NO. OF PATIENTS	MEDIAN FOLLOW-UP, YR (RANGE)	REMAIN ON AS (%)
Klotz, 2008	331	8 (2-11)	65
Carter et al, 2007	407	2.8 (0.4-12.5)	59
Khatami et al, 2006	270	5.3 (0.9-10)	61
Patel et al, 2004	88	3.7 (0.6-14.3)	65
Soloway et al, 2008	99	3.8 (1-14.8)	92

of the patients showed objective progression within 5 years, whereas 44% were treated; patient preference accounted for the higher percentage of patients treated. Of the 31 patients with progression, 17 were treated with radical prostatectomy, 13 with radiation therapy, and 1 with androgen ablation. Seven men without objective progression were treated. Only one patient, who was treated with radiation therapy, had biochemical recurrence. The investigators concluded that AS is a feasible alternative to initial curative treatment in select patients with favorable, low-risk prostate cancer. About half of these patients remained free of progression at 10 years, and definitive treatment appeared effective in those with progression. Consistent with the study by Carter and colleagues (2002), the absence of cancer on repeated needle biopsy early after initial diagnosis identified cases unlikely to progress during 10 years.

These series confirm that in appropriately selected men, AS is associated with an extremely low rate of progression to metastatic disease and/or death and the majority of patients do not require intervention (Table 101–7). Further follow-up is necessary to determine the long-term risk of progression.

What Factors Predict Progression for Men on Active Surveillance?

One assumption about AS is that signs of progression can be identified while the cancer is still curable. Various clinical criteria have been investigated in an attempt to define those patients requiring definitive treatment and those still suitable for AS. Serial serum PSA testing including free and total levels has been examined by a number of investigators (Gerber et al, 1998; Choo et al, 2001, 2002; Do et al, 2002; Stephenson et al, 2002; de Vries et al, 2004; Klotz, 2004, 2008; Panagiotou et al, 2004). Gerber and colleagues (1998) examined changes in serum PSA levels in 49 men (mean age, 72 years) with untreated clinically localized prostate cancer. All patients had at least three PSA levels, which were measured at intervals of at least 6 months. **The investigators found significant variability in the rate of change of PSA with time.** They concluded that changes in PSA level may not be helpful in determining the need for therapy in men on AS. In men with small-volume cancers, the benign rather than malignant portion of the prostate drives the serum PSA level. Because PSA levels are highly variable in men with an untreated prostate gland (Eastham et al, 2003), reliance on PSA dynamics as inclusion or intervention criteria for the management of prostate cancer is problematic.

Numerous studies have examined the role of PSADT as a prognostic factor in men on AS, and the majority conclude that PSADT can be used a predictor of progression. Choo and colleagues (2002) observed 206 men with clinically localized prostate cancer who were managed with AS for a median of 29 months. PSADT was estimated from a linear regression of ln(PSA) on time, assuming a single exponential growth model. The median PSADT was 6.68 years, with 42% of patients having a PSADT of 10 years or longer. These investigators suggest that the definition of progression for men on AS should include a PSADT of less than 2 years on the basis of at least three separate measurements during a minimum of 6 months. This PSADT may, however, be too short, because six of nine men who underwent radical prostatectomy had extraprostatic disease. These results led the investigators at the University of Toronto to change their definition of progression to a PSADT of 3 years or less (Klotz, 2008). Further concern about PSADT as a predictor of progression for men on AS comes from studies examining PSADT before radical prostatectomy. Egawa and colleagues (2000) examined changes in PSA levels before radical prostatectomy and concluded that men with a PSADT of 3 years or less were more likely to have stage pT3 cancer at surgery, and 3 of 19 men with a PSADT longer than 6 years had pT3 cancer, 2 of them with positive nodes. D'Amico and colleagues (2004) studied 1095 men with localized prostate cancer to assess whether the rate of rise in PSA level—the PSA velocity—during the year before diagnosis, the PSA level at diagnosis, the Gleason score, and the clinical tumor stage could predict the time to death from prostate cancer and death from any cause after radical prostatectomy. An annual PSA velocity of more than 2.0 ng/mL was associated with a significantly shorter time to death from prostate cancer ($P < .001$) and death from any cause ($P = .01$). An increasing PSA level at diagnosis ($P = .01$), a Gleason score of 8, 9, or 10 ($P = .02$), and a clinical tumor stage of T2 ($P < .001$) also predicted the time to death from prostate cancer. The investigators concluded that men whose PSA level increases by more than 2 ng/mL during the year before the diagnosis of prostate cancer may have a relatively high risk of death from prostate cancer despite undergoing radical prostatectomy. Although these studies suggest that **PSA kinetics may be a useful predictor of cancer progression, the exact trigger point at which to recommend treatment requires further investigation. By the time the PSADT or PSAV is rapid, it is too late to successfully intervene with high probability of cure. More information is necessary to determine the performance characteristics of PSADT in identifying progression of localized prostate cancer up to but before the development of metastatic cancer.**

A number of other promising biomarkers identify patients at risk for cancer progression including PSA density, free versus total PSA ratio, and PCA3 (Do et al, 2002; Khan et al, 2003; Nakanishi et al, 2008). Genetic biomarkers may also allow better prediction of patient risk within the next decade. Although none of these has yet demonstrated benefit in routine practice, this remains an active area of research.

Although all AS studies have included periodic DRE as part of routine follow-up, none has found this to be an independent predictor of cancer progression. DRE is therefore unlikely to provide prognostic benefit if serial PSA measurements and prostate biopsy specimens are taken. In addition, DRE is subjective and there is significant interexaminer variation. **DRE remains important, however, not only as an indicator that a repeated prostate biopsy is warranted** but also in clinical staging and in the prediction of outcome if active treatment is recommended.

Serial imaging studies have also proven to be of limited value to patients on AS. In a prospective study of AS (Hruby

et al, 2001), the value of performing TRUS every 6 months was examined in 174 men. Findings on TRUS were scored as consistent with clinical progression if they demonstrated a new or enlarging hypoechoic peripheral zone lesion or a 30% or greater increase in overall prostate volume at the time of progression. The group of 28 men who progressed to require radical intervention underwent 83 TRUS examinations (median, 3 per patient). Of the 28, only 7 had changes on TRUS that were regarded as consistent with progression; in all 7, the change consisted of the growth of an existing nodule or the appearance of a new nodule. In only one case was this accompanied by an increase in gland volume of 30% or more. In the 136 men who underwent two or more serial TRUS examinations, there was no correlation between changes in either gland volume or the number of peripheral zone hypoechoic lesions and the rate of change of PSA. The investigators concluded that serial TRUS is of limited value as a determinant of disease progression in men with known but untreated prostate cancer.

The role of serial pelvic imaging with either computed tomography or endorectal MRI has not been investigated but is likely to be limited. These men are at low risk for macroscopic extraprostatic disease, so interval changes in any of these examinations are unlikely. Improvement in imaging tools to better characterize intraprostatic disease is necessary before serial imaging can be routinely recommended for men on AS.

Yap and colleagues (2003) assessed the role of serial bone scans in men being treated with AS at the University of Toronto. This aspect of their study included 244 eligible patients. Bone scintigraphy was repeated annually for the first 2 years, then every 2 years thereafter if the patient remained on AS. If the follow-up PSA level was above 15 ng/mL, the patient underwent annual bone scintigraphy. During follow-up (median, 30 months), 299 bone scans were taken. All 299 were negative for bone metastasis. The probability of a normal bone scan was estimated to be 88% to 100% (95% CI) when PSA level was below 15 ng/mL. The investigators concluded that bone scans are unnecessary for men on AS. The role of serial bone scintigraphy remains undefined even for men with a PSA level above 15 ng/mL.

Repeated prostate biopsies are considered an important aspect of continued evaluation of men managed with AS, not only to identify men with cancer progression but also to identify men whose disease is unlikely to progress. Virtually all AS studies have incorporated serial prostate biopsy in their follow-up regimen. The University of Toronto group advises performing a confirmatory biopsy at 1 year to identify high-risk features that might have been missed on the original biopsy (Klotz, 2008) and thereafter performing a prostate biopsy every 4 to 5 years or earlier if clinically indicated. Carter and colleagues (2007) recommend a first repeat biopsy at 1 year and then an annual prostate biopsy. Patel and colleagues (2004) performed a confirmatory biopsy in men with low-risk prostate cancer within 6 months of the diagnosing biopsy. This second biopsy showed no cancer in 61% of cases. Cancer in the second biopsy was the most significant prognostic factor for progression in their cohort of men on AS (Patel et al, 2004) (see Fig. 101–6B). Progression occurred in 5 of the 43 men (11%) who had a first repeat biopsy that was negative for cancer, compared with 12 of 27 (40%) who had an abnormal finding on first repeat biopsy. Actuarial progression-free probability at 5 years was 83% for patients with normal findings on repeat biopsy, compared with 43% for those with abnormal findings. An increase in Gleason sum was noted in 59% of patients with any prostate cancer on repeat biopsy. Patel and colleagues recommend performing an early (within 6 months) repeat prostate biopsy on men considering AS.

The National Cancer Institute of Canada together with four U.S.-based cooperative oncology trials groups (SWOG, CALGB, ECOG, and RTOG) and the United Kingdom Coordinating Committee on Cancer Research initiated a clinical trial entitled Surveillance Therapy Against Radical Treatment (START). This trial, which opened to 2007, will randomize 2100 patients between AS and the patient's choice of radical treatment (surgery or radiation). Eligible patients have histologically confirmed adenocarcinoma of the prostate diagnosed within 6 months before study randomization and must be suitable candidates for either surgery or radiotherapy (life expectancy of > 10 years and ECOG performance status 0, 1, or 2).

Patients are considered to have low-risk cancer defined as follows:

- Clinical stage T1b, T1c, T2a, or T2b at the time of diagnosis
- Clinical (diagnostic biopsy) Gleason score of 6 or lower
- PSA less than or equal to 10 ng/mL

To primary end point is to compare prostate cancer–specific survival of patients with favorable risk prostate cancer treated with radical prostatectomy or radical radiotherapy at the time of initial diagnosis versus AS and selective intervention based on prespecified biochemical, histologic, or clinical criteria.

Key Points

- Many prostate cancers pose little risk to life or health.
- Low-risk prostate cancer can be identified, with high probability, by any of several models on the basis of various combinations of biopsy Gleason grade, clinical stage, amount of cancer in biopsy cores, PSA level, prostate size, or ratio of free to total PSA.
- The goal of watchful waiting is to allow men with low-risk cancer to avoid treatment and the associated morbidity. Palliative treatment is offered only if symptoms develop.
- For patients with early-stage prostate cancer managed by watchful waiting, the probability of death from cancer is low for the first 10 years after diagnosis but may rise rapidly during the next 10 years if the cancer is not treated before it progresses to metastases.
- Watchful waiting is a reasonable option for patients with a life expectancy of less than 10 years and clinically localized, well-differentiated, or moderately differentiated prostate cancer.
- AS with selective delayed definitive therapy involves careful monitoring of men with prostate cancer. Definitive therapy is recommended for men who show clear signs of cancer progression.
- Men on AS should be monitored by periodic PSA measurements, DRE, and prostate biopsy.
- Increased Gleason sum or amount of cancer on repeated biopsy and decreased PSA doubling time indicate that definitive therapy may be warranted. Absence of cancer on repeated biopsy is a strong indicator that the cancer is unlikely to progress.
- Long-term outcomes for patients on AS are not yet available, but the majority of patients remain on AS and free of progression at 4 years after diagnosis. Definitive therapy appears to be effective in the majority of patients with signs of disease progression.

SUMMARY

Patients with a life expectancy (based on age and comorbidities) of less than 10 years and cancer with Gleason score of 6 or lower may be suitable for watchful waiting, especially if clinical stage and PSA values are favorable. Cancer progression and prostate cancer death are unlikely in this group of patients (see Fig. 101–2). Routine PSA testing is less important in the management of these patients, and follow-up radiographic studies or biopsies are not performed according to any predetermined schedule. Intervention is palliative and delayed until symptoms develop.

AS may be a safe alternative to immediate treatment in compliant men with a low risk of cancer progression, and it appears to be feasible in many men diagnosed with prostate cancer. Studies suggest that less than half of such patients have progression on long-term follow-up (see Table 101–7), and treatment appears to be effective in those whose cancer does progress. More detailed recommendations cannot be given at this point because of our current inability to predict the course of the disease with certainty. Major areas of future study include identifying appropriate baseline clinical parameters in selecting men for AS, defining the role of imaging in diagnosing low-risk prostate cancer, identifying additional circulating and tissue markers defining risk, and developing appropriate follow-up regimens and definitions of progression. Repeat prostate biopsy appears to be critical to defining progression, and PSADT has been widely employed, although its accuracy requires confirmation. With appropriate selection of patients, close follow-up, and selective use of local therapies in those with local cancer progression, AS is an acceptable choice for the management of selected patients with low-risk, early-stage prostate cancer.

SUGGESTED READINGS

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The complete reference list is available online at www.expertconsult.com.

chapter 102

Radical Retropubic and Perineal Prostatectomy

Edward M. Schaeffer, MD, PhD ● Alan W. Partin, MD, PhD ● Herbert Lepor, MD ● Patrick C. Walsh, MD

Radical Retropubic Prostatectomy: Surgical Anatomy
Surgical Technique
Postoperative Management
Complications
Surgical Modifications to Classic Anatomic Radical Prostatectomy
Salvage Radical Prostatectomy
Summary of Radical Retropubic Prostatectomy
Radical Perineal Prostatectomy: Selection of Patients
Preoperative Care/Position
Exposure of the Prostate
Nerve-Sparing Dissection
Vesicourethral Anastomosis
Pathologic Outcomes
Summary of Radical Perineal Prostatectomy

There is no better way to cure cancer that is confined to the prostate than total surgical removal. Radical prostatectomy is the only form of treatment for localized prostate cancer that has been shown in a randomized controlled trial to reduce progression to metastases and death from the disease (Holmberg et al, 2002; Bill-Axelson et al, 2008). Furthermore, on the basis of improved understanding of the periprostatic anatomy, today there is less bleeding and improved rates of postoperative continence and potency (Walsh, 1998, 2000; Nielsen et al, 2008).

The open surgical approach to radical prostatectomy has been challenged by advocates of laparoscopic and robotic techniques. It is the authors' opinion that the open procedure is still the "gold standard" providing the best outcomes in terms of cancer control and quality of life.

Technically, radical retropubic prostatectomy is one of the most difficult operations in the field of urology. **The three goals of surgery, in order of importance, are cancer control, preservation of urinary control, and preservation of sexual function.** Great skill and experience in the selection of surgical candidates and operative technique are necessary to achieve all three. This chapter summarizes the authors' experience with the hope that it will shorten the reader's learning curve. A video demonstrating a detailed description of the surgical technique is also available (Walsh and Garcia, 2004).

RADICAL RETROPUBIC PROSTATECTOMY: SURGICAL ANATOMY

Venous and Arterial Anatomy

The veins of the prostate drain into the Santorini plexus. It is necessary to have a complete understanding of these veins to avoid excessive bleeding and to ensure a bloodless field in exposing the membranous urethra and the apex of the prostate. **The deep dorsal vein leaves the penis under the Buck fascia between the corpora cavernosa and penetrates the urogenital diaphragm, dividing into three major branches: the superficial branch and the right and left lateral venous plexuses** (Reiner and Walsh, 1979) (Fig. 102–1). The superficial branch, which travels between the puboprostatic ligaments, is the centrally located vein overlying the bladder neck and prostate. This vein is easily visualized early in retropubic operations and has communicating branches over the bladder itself and into the endopelvic fascia. The superficial branch lies outside the anterior prostatic fascia.

The common trunk and lateral venous plexuses are covered and concealed by the prostatic and endopelvic fascia. The lateral

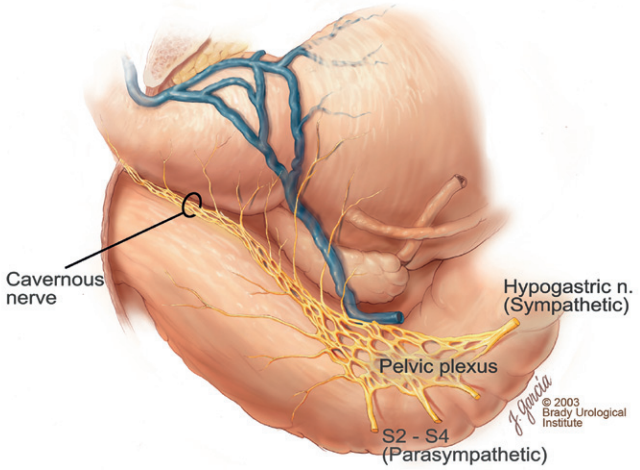


Figure 102–1. Location of the superficial and deep branches of the dorsal vein as they travel over the anterior and anterolateral surfaces of the prostate. Note the common trunk located immediately over the urethra. This is the site where the dorsal vein is transected. The pelvic plexus: The autonomic innervation of the pelvic organs arises from the pelvic plexus, which is formed by parasympathetic fibers that arise from the sacral center (S2 to S4) and sympathetic fibers via the hypogastric nerve from the thoracolumbar center. The pelvic plexus provides visceral branches that innervate the bladder, ureter, seminal vesicles, prostate, rectum, membranous urethra, and corpora cavernosa. The branches that innervate the corpora cavernosa enter in a spraylike distribution 20 to 30 mm distal to the junction of the prostate and bladder, where they continue distally posterolateral to the prostate. (© Brady Urological Institute.)

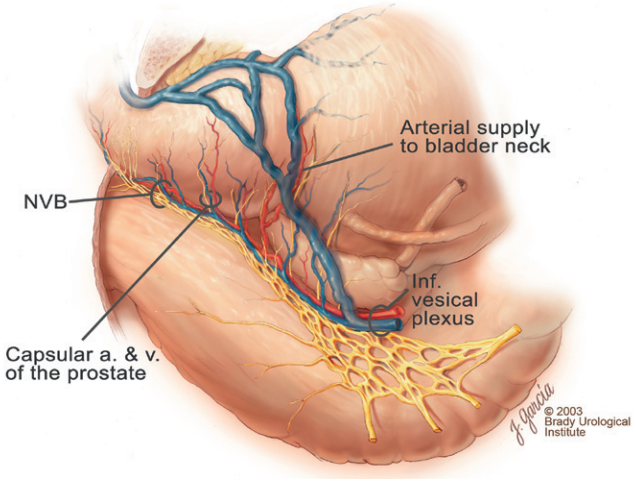


Figure 102–2. Arterial supply to the prostate. The inferior vesical artery terminates in two large groups of vessels. One group, called the urethral vessels, enters the prostate at the posterolateral vesicoprostatic junction to supply the bladder neck and periurethral portions of the gland. The second group, the capsular branches, runs along the pelvic sidewall in the lateral pelvic fascia posterolateral to the prostate, providing branches that course ventrally and dorsally to supply the outer portion of the prostate. These capsular arteries and veins are intimately associated with the branches of the pelvic plexus forming the neurovascular bundle (NVB) that is used as the macroscopic landmark to aid in the identification of the microscopic branches of these nerves. Note at the apex that small branches of the nerves travel anteriorly away from the vessels. (© Brady Urological Institute.)

venous plexuses traverse posterolaterally and communicate freely with the pudendal, obturator, and vesical plexuses. Near the puboprostatic ligaments, small branches from the lateral plexus often penetrate the pelvic sidewall musculature and communicate with the internal pudendal vein. The lateral plexus interconnects with other venous systems to form the inferior vesical vein, which empties into the internal iliac vein. With the complex of veins and plexuses anastomosing freely, any laceration of these friable structures can lead to considerable blood loss.

The prostate receives arterial blood supply from the inferior vesical artery. According to Flocks (1937), **after the inferior vesical artery provides small branches to the seminal vesicle and the base of the bladder and prostate, the artery terminates in two large groups of prostatic vessels: the urethral and capsular groups** (Fig. 102–2). The urethral vessels enter the prostate at the posterolateral vesicoprostatic junction and supply the vesical neck and periurethral portion of the gland. The capsular branches run along the pelvic sidewall in the lateral pelvic fascia posterolateral to the prostate, providing branches that course ventrally and dorsally to supply the outer portion of the prostate. The capsular vessels terminate as a small cluster of vessels that supply the pelvic floor. On histologic examination, the capsular arteries and veins are surrounded by an extensive network of nerves (Walsh and Donker, 1982; Walsh et al, 1983; Lue et al, 1984; Lepor et al, 1985). These capsular vessels provide the macroscopic landmark to aid in the identification of the microscopic branches of the pelvic plexus that innervate the corpora cavernosa.

The major arterial supply to the corpora cavernosa is derived from the internal pudendal artery. However, **pudendal arteries can arise from the obturator, inferior vesical, and superior vesical arteries. Because these aberrant branches travel along the lower part of the bladder and anterolateral surface of the prostate, they are divided during radical prostatectomy.** This may compromise arterial supply to the penis, especially in older patients with borderline penile blood flow (Breza et al, 1989; Polascik and Walsh, 1995; Rogers et al, 2004).

Pelvic Plexus

The autonomic innervation of the pelvic organs and external genitalia arises from the pelvic plexus, which is formed by parasympathetic, visceral, efferent, preganglionic fibers that arise from the sacral center (S2 to S4) and sympathetic fibers via the hypogastric nerve from the thoracolumbar center (Walsh and Donker, 1982; Lue et al, 1984; Lepor et al, 1985; Schlegel and Walsh, 1987; Walsh, 2007) (see Fig. 102–1). The pelvic plexus in men is located retroperitoneally beside the rectum 5 to 11 cm from the anal verge and forms a fenestrated rectangular plate that is in the sagittal plane with its midpoint at the level of the tip of the seminal vesicle.

The branches of the inferior vesical artery and vein that supply the bladder and prostate perforate the pelvic plexus. For this reason, ligation of the so-called *lateral pedicle* in its midportion not only interrupts the vessels but also transects the nerve supply to the prostate, urethra, and corpora cavernosa. The pelvic plexus provides visceral branches that innervate the bladder, ureter, seminal vesicles, prostate, rectum, membranous urethra, and corpora cavernosa. In addition, branches that contain somatic motor axons travel through the pelvic plexus to supply the levator ani, coccygeus, and striated urethral musculature. **The nerves**

innervating the prostate travel outside the capsule of the prostate and Denonvilliers fascia until they perforate the capsule where they enter the prostate.

The branches to the membranous urethra and corpora cavernosa also travel outside the prostatic capsule in the lateral pelvic fascia dorsolaterally between the prostate and rectum (see Fig. 102–1). Although these nerves are microscopic, their anatomic location can be estimated intraoperatively by use of the capsular vessels as a landmark. This structure, which is referred to here as the neurovascular bundle, has been termed the *neurovascular bundle of Walsh* (Stedman's Medical Dictionary, 2000) (see Fig. 102–2). As emphasized by Takenaka and colleagues (2004) and Costello and colleagues (2004), the cavernous branches join the capsular arteries and veins in a spraylike distribution to form the neurovascular bundle 20 to 30 mm distal to the junction of the bladder and prostate (see Fig. 102–2). The neurovascular bundles are located in the lateral pelvic fascia *between* the prostatic fascia and the levator fascia. At the apex of the prostate, the branches of the nerves to the cavernous bodies and striated sphincter also have a spraylike distribution both anteriorly and posteriorly with wide variation (Costello et al, 2004; Takenaka et al, 2005a). After piercing the urogenital diaphragm, the nerve branches pass behind the dorsal penile artery and dorsal penile nerve before entering the corpora cavernosa (Walsh and Donker, 1982).

Striated Urethral Sphincter

The external sphincter, at the level of the membranous urethra, is often depicted as a "sandwich" of muscles in the horizontal plane. However, Oelrich (1980) demonstrated clearly that the striated urethral sphincter with its surrounding fascia is a vertically oriented tubular sheath that surrounds the membranous urethra. In utero, this sphincter extends without interruption from the bladder to the perineal membrane. As the prostate develops from the urethra, it invades and thins the sphincter muscle, causing a reduction or atrophy of some of the muscle (Fig. 102–3).

In the adult the fibers at the apex of the prostate are horseshoe shaped and form a tubular, striated sphincter surrounding the membranous urethra. Near the apex of the prostate, the edges fuse in the midline posteriorly (Fig. 102–4A). Thus as Myers (1987) has shown, the prostate does not rest on a flat, transverse urogenital diaphragm like an apple on a shelf, with no striated muscle proximal to the apex. Rather, the external striated sphincter is more tubular and has broad attachments over the fascia of the prostate near the apex. This has important implications in the apical dissection and reconstruction of the urethra for preservation of urinary control postoperatively (Walsh et al, 1990).

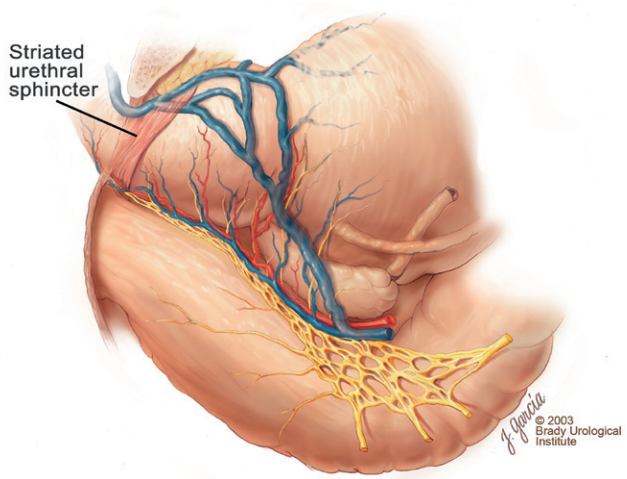


Figure 102–3. The striated urethral sphincter with its surrounding fascia is a vertically oriented tubular sheath that surrounds the membranous urethra. The dorsal vein complex travels through the sphincteric complex. (© Brady Urological Institute.)

The striated sphincter contains fatigue-resistant, slow-twitch fibers that are responsible for passive urinary control. Active continence is achieved by voluntary contraction of the levator ani musculature, which surrounds the apex of the prostate and membranous urethra. Some fibers of the levator ani (levator urethrae, pubourethralis) surround the proximal urethra and the apex of the prostate and insert into the perineal body in the midline posteriorly (Myers, 1991, 1994). **The pudendal nerve provides the major nerve supply to the striated sphincter and levator ani.** When patients are instructed to perform sphincter exercises postoperatively, they are actually contracting the levator ani musculature. However, because the striated urethral sphincter has similar innervation, patients are exercising this important muscle as well. Somatic motor nerves traveling through the pelvic plexus provide additional innervation to the pelvic floor musculature (Zvara et al, 1994; Costello et al, 2004, Takenaka et al, 2005a).

Pelvic Fascia

The prostate is covered with three distinct and separate fascial layers: Denonvilliers fascia, the prostatic fascia (also called the *capsule of the prostate*), and the levator fascia. Denonvilliers fascia is a filmy, delicate layer of connective tissue located between the anterior walls of the rectum and prostate (Fig. 102–4B). This fascial layer extends cranially to cover the posterior surface of the seminal vesicles and lies snugly against the posterior prostatic capsule. This fascia is most prominent and dense near the base of the prostate and the seminal vesicles and thins dramatically as it extends caudally to its termination at the striated urethral sphincter. On microscopic examination, it is impossible to discern "posterior" and "anterior" layers of this fascia (Jewett et al, 1972). For this reason, one must excise this fascia completely to obtain an adequate surgical margin.

In addition to Denonvilliers fascia, the prostate is also invested with the prostatic fascia and levator fascia. Anteriorly and anterolaterally, the prostatic fascia is in direct continuity with the parenchyma of the prostate. The major tributaries of the dorsal vein of the penis and Santorini plexus travel within the anterior prostatic fascia. Laterally, the prostatic fascia fuses with the levator fascia, which covers the pelvic musculature, to form the lateral pelvic fascia (Fig. 102–5) (Myers, 1991, 1994). Posterolaterally, the levator fascia separates from the prostate to travel immediately adjacent to the pelvic musculature surrounding the rectum. **The prostate receives its blood supply and autonomic innervation between the layers of the levator fascia and prostatic fascia** (see Figs. 102–4B and 102–5).

In an effort to avoid injury to the dorsal vein of the penis and Santorini plexus during radical perineal prostatectomy, the lateral and anterior pelvic fasciae are reflected off the prostate. This accounts for the reduced blood loss associated with radical

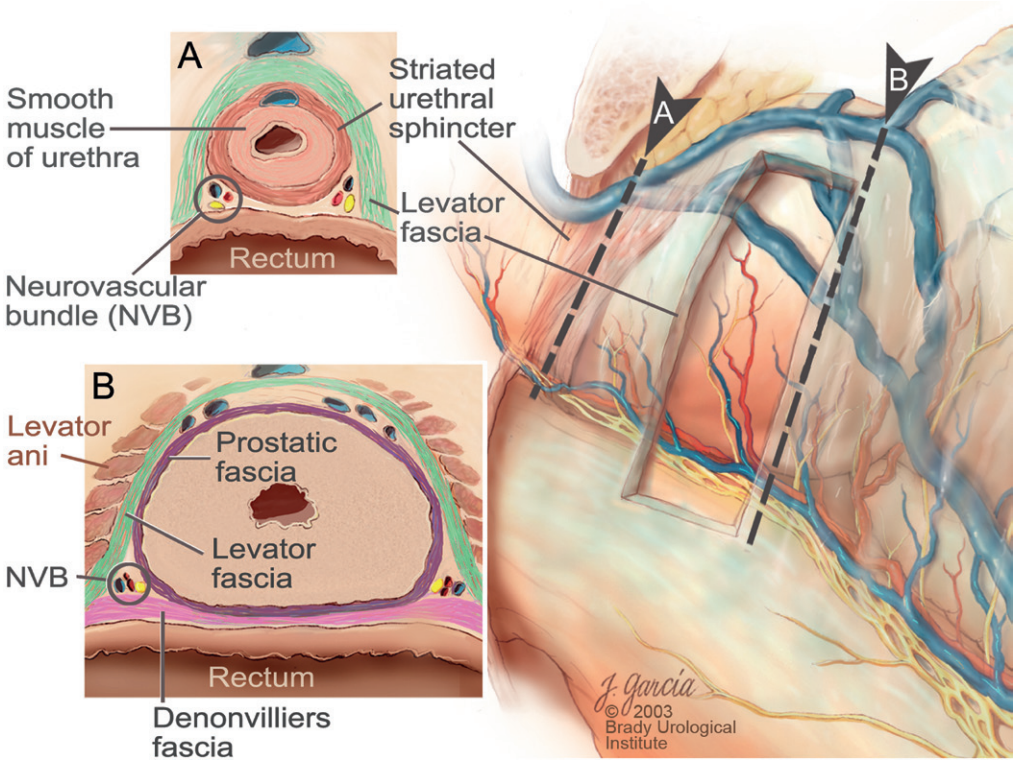


Figure 102–4. **A,** A cross section through the apex of the prostate demonstrating the relationship among the fascia surrounding the striated sphincter, striated sphincter, and smooth muscle of the urethra. Note that at this level, the striated sphincter circumferentially surrounds the urethra. Note that the neurovascular bundles are posterolateral to the circumferential striated sphincter. **B,** A cross section through the midportion of the prostate demonstrating the relationship between the levator fascia, Denonvilliers fascia, and prostatic fascia. Note that the neurovascular bundles are located between the layers of the levator fascia and prostatic fascia. In performing a proper nerve-sparing operation, the prostatic fascia must remain on the prostate. (© Brady Urological Institute.)

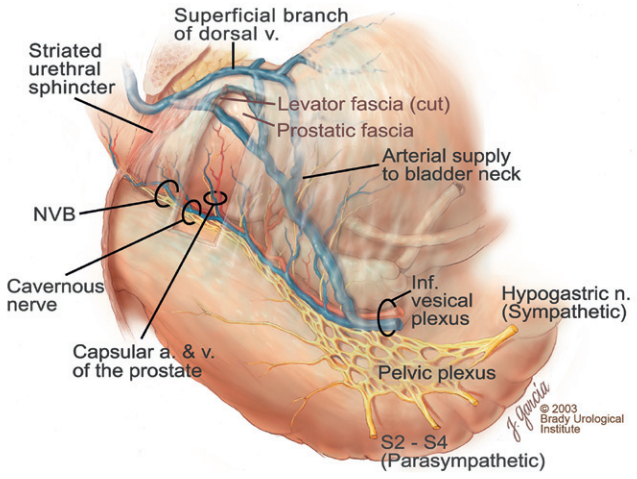


Figure 102–5. A lateral view illustrating that the prostate receives its blood supply and autonomic innervation between the layers of the levator fascia and prostatic fascia. NVB, neurovascular bundle. (© Brady Urological Institute.)

perineal prostatectomy. In performing radical retropubic prostatectomy, the prostate is approached from outside these fascial investments. For this reason, the dorsal vein complex must be ligated and the lateral pelvic fascia must be divided (Walsh et al, 1983).

SURGICAL TECHNIQUE

Preoperative Preparation

The preoperative assessment must include a focused review of systems; a complete medical, surgical, and anesthesia history; an inquiry of all prescription and nonprescription medications; a physical examination; and routine preoperative laboratory testing. Life-threatening complications associated with radical retropubic prostatectomy are rare and include myocardial infarction, cerebrovascular accident (stroke), cardiac arrhythmias, pulmonary embolus, hemorrhage, and anesthesia reactions. The preoperative assessment must identify those candidates who are at increased risk for these mortality events in order to intervene to attenuate these risks.

The preoperative assessment should identify factors that may add to the technical challenge of the surgical procedure including prior abdominal or pelvic surgery and irradiation, prior transurethral surgery, extensive prostate biopsies, history of significant inflammatory bowel disease, the prior use of mesh during inguinal or incisional hernia repairs, and the size of the prostate. Although none of these factors are contraindications for radical retropubic prostatectomy, a greater level of skill and experience may be required to minimize complications.

The observation that up to 15% to 20% of men develop an inguinal hernia following radical retropubic prostatectomy implied that this surgical procedure directly predisposes to the development of hernias (Regan, 1996; Lodding, 2001; Nielsen and Walsh,

2005). Approximately 15% of men undergoing radical prostatectomy will have a coexisting inguinal hernia detected if an appropriate inguinal examination is performed (Lepor and Robbins, 2007). In most of these cases, the inguinal hernias are asymptomatic. These observations suggest that a radical retropubic prostatectomy may transform an asymptomatic inguinal hernia into a symptomatic hernia. Therefore examination of the inguinal canal with Valsalva should be performed, enabling properitoneal hernia repairs at the time of the radical prostatectomy.

Surgery is deferred for 6 to 8 weeks after needle biopsy of the prostate and 12 weeks after transurethral resection of the prostate. This delay enables inflammatory adhesions or hematomas to resolve so that the anatomic relationships between the prostate and the surrounding structures return to a nearly normal state before surgery. This is especially important if one hopes to preserve the neurovascular bundles intraoperatively and avoid rectal injury.

During this delay, patients may be offered the opportunity to donate autologous blood, although the utilization of autologous transfusions at our institutions has declined as continuous modifications to our technique have reduced blood loss. One of the limitations of autologous blood donation is that many donated units are not transfused if the hematocrit is higher than 30% (Goad et al, 1995). Therefore hemodilution and erythrocyte stimulating proteins have been recommended as alternative blood management strategies (Gilbert and Smith, 2000). Erythrocyte-stimulating proteins, which are not approved by the U.S. Food and Drug Administration, have been shown to raise the hematocrit on average percentage points, diminishing postprostatectomy anemia (Rosenblum et al, 2000). The relatively higher discharge hematocrit attributable to the use of erythrocyte stimulating proteins affects the pace of recovery because postoperative hematocrit has been shown to influence both time to work and return to activities (Sultan et al, 2006).

The American Urological Association recently published best practice guidelines for the use of prophylactic antibiotics for urologic surgical procedures (Wolf et al, 2008). The recommended prophylactic regimens for open or laparoscopic surgery involving entry into the urinary tract are a first- or second-generation cephalosporin or an aminoglycoside in combination with metronidazole or clindamycin. The duration of therapy should be no longer than 24 hours. The authors routinely use a first-generation cephalosporin alone and have an infection rate much less than 1%.

While donating blood and immediately before surgery, patients should avoid taking high doses of vitamin E, aspirin, nonsteroidal anti-inflammatory agents, omega-3 fish oils, and thienopyridines (Plavix and Ticlid), which interfere with platelet function. Products that are not medically indicated should be discontinued at least 1 week before surgery. **The preoperative management of anticoagulants and antiplatelet agents that are used for the treatment of specific medical conditions such as prosthetic valves, atrial fibrillation, and coronary artery stent implants should be performed in conjunction with the internist or cardiologist.** With nearly 1 million coronary interventions occurring every year and the majority including an implant of a drug-eluting stent, managing prescribed antiplatelet therapy can create a dilemma balancing the risk of stent stenosis and perioperative bleeding. In the majority of cases, stent thrombosis is a catastrophic event resulting in life-threatening complications (Cutlip et al, 2001). A reasonable compromise for men with drug-eluting stents undergoing a radical retropubic prostatectomy is to preoperatively discontinue the thienopyridine while continuing aspirin therapy and restarting the thienopyridine as soon as clinically indicated (Grines et al, 2007).

Patients are prescribed a clear liquid diet on the day before surgery, are requested to drink half a bottle of magnesium citrate in the evening, and have an enema on the morning of surgery. They are admitted to the hospital on that day.

Special Instruments

Unlike radical perineal or robot-assisted laparoscopic prostatectomy, radical retropubic prostatectomy requires few special instruments. A fiberoptic headlight is essential because much of the procedure is performed beneath the pubis in an area where visualization can be difficult. A standard Balfour retractor with both narrow and wide malleable blades is useful during lymph node dissection and is necessary during radical prostatectomy to provide cranial and posterior retraction on the peritoneum and bladder. Coagulating forceps; small, fine, and regular right-angled clamps; Metzenbaum and Jamison scissors; and 2.5- to 4.5-power loupes are the only other specialized instruments that should be available.

Anesthesia, Incision, and Lymphadenectomy

A spinal or epidural anesthetic is preferable for this procedure. **Regional anesthesia is associated with less blood loss and a lower frequency of pulmonary emboli** (Peters and Walsh, 1985; Shir et al, 1995). The anesthesiologist is encouraged to maintain relative hypotension with systolic blood pressure of no more than 100 mm Hg and to limit the replacement of crystalloid to 1500 mL until the prostate is removed (Davies et al, 2004). The patient is placed in the supine position with the table flexed to increase the distance between the umbilicus and pubis.

The skin is prepared and draped in the usual way. A No. 16 Silastic Foley catheter is passed into the bladder, inflated with 20 mL of saline, and connected to sterile, closed, continuous drainage. The use of a 16-Fr catheter facilitates placement of sutures in the mucosa of the urethra. A right-handed surgeon always stands on the left side of the patient.

An 8-cm midline, extraperitoneal, lower abdominal incision is made extending from the pubis toward the umbilicus. Alternately, in thin patients, a transverse skin incision just above the pubis can be used. This short incision provides excellent exposure of the prostate because the rectus muscles are separated maximally by the retractor at the pubis. It also limits traction on the prostate and neurovascular bundles when using the sponge stick and malleable blade. For reasons that are not entirely clear, the authors have also noted a marked reduction in thromboembolic events since they began using this incision; none in 700 consecutive patients compared with 10 in the prior 700 ($P = .002$). The anterior fascia is incised down to the pubis, the rectus muscles are separated in the midline, and the transversalis fascia is opened sharply to expose Retzius space. Laterally, the peritoneum is mobilized off the external iliac vessels to the bifurcation of the common iliac artery. **Care is taken to preserve the soft tissue covering the external iliac artery that contains the lymphatics draining the lower extremity. Interruption of these lymphatics may lead to lower extremity edema and lymphocele formation.** This maneuver is accomplished without dividing the vas deferens. Next, a self-retaining Balfour retractor is placed. Exposure for the lymph node dissection is facilitated by placement

of a narrow, malleable blade attached to the Balfour retractor beneath the mobilized vas deferens to displace the peritoneum superiorly and a deep Deaver retractor to retract the bladder medially. Previously, when the vas deferens was routinely divided, some patients complained of persistent testicular pain that the authors attributed to excessive traction on the spermatic cord during this maneuver. However, if the vas deferens is not divided, the traction on the spermatic cord is absorbed by the vas deferens and persistent testalgia is rare.

The pelvic lymph node dissection is performed before the radical prostatectomy. The dissection is initiated on the ipsilateral side of the major tumor in the prostate by dividing the adventitia over the external iliac vein (Fig. 102–6). The lymphatics overlying the external iliac artery are preserved. The dissection proceeds beneath the external iliac vein out to the pelvic sidewall and then inferiorly to the femoral canal, where the lymphatic channels are ligated at a convenient point. There is no need to remove the Cloquet node. The dissection then proceeds superiorly along the pelvic sidewall to the bifurcation of the common iliac artery, where the lymph nodes in the angle between the external iliac and hypogastric arteries are removed. Next, the obturator lymph nodes are removed with care to avoid injury to the obturator nerve. The obturator artery and vein are skeletonized but are usually left undisturbed and are not ligated unless excessive bleeding occurs. The dissection then continues down to the pelvic floor, exposing the hypogastric veins. This extended dissection removes more lymph nodes than in a more limited dissection, improving staging and providing potential therapeutic benefit in some patients (Allaf et al, 2004; Palapattu et al, 2004). A similar procedure is performed on the opposite side. **If the patient has a well-differentiated to moderately well-differentiated tumor (Gleason grade < 8) and the lymph nodes are normal to palpation, frozen-section analysis is not performed** (Sgrignoli et al, 1994; Cadeddu et al, 1997).

Exposure

To expose the anterior surface of the prostate, it is necessary to displace the peritoneum superiorly. **The authors no longer place the balloon on the Foley catheter in the dome of the bladder beneath the malleable blade because they believe that excessive traction on the bladder can damage the detrusor musculature, thereby delaying recovery of urinary continence, and produce traction injury to the neurovascular bundle.** Also, the short incision limits the amount of traction. A malleable blade is used to retract the peritoneum superiorly and to gently displace the bladder posteriorly.

Incision in Endopelvic Fascia

The fibroadipose tissue covering the prostate is carefully dissected away to expose the pelvic fascia, puboprostatic ligaments, and superficial branch of the dorsal vein.

The endopelvic fascia is entered where it reflects over the pelvic sidewall, well away from its attachments to the bladder and prostate (Fig. 102–7). The point of incision is where the fascia is transparent, revealing the underlying levator ani musculature. After the fascia has been opened, one can usually visualize the bulging lateral venous plexus of Santorini, which is located medially. Therefore **an incision in the endopelvic fascia too close to the bladder or the prostate risks laceration of these veins, with potential severe blood loss.** Beneath this venous complex lie the prostatic arteries and the branches of the pelvic plexus that course toward the prostate, urethra, and corpora cavernosa.

The incision in the endopelvic fascia is then carefully extended in an anteromedial direction toward the puboprostatic ligaments. This allows the surgeon to palpate the lateral surface of the prostate. **At this point, one often encounters small arterial**

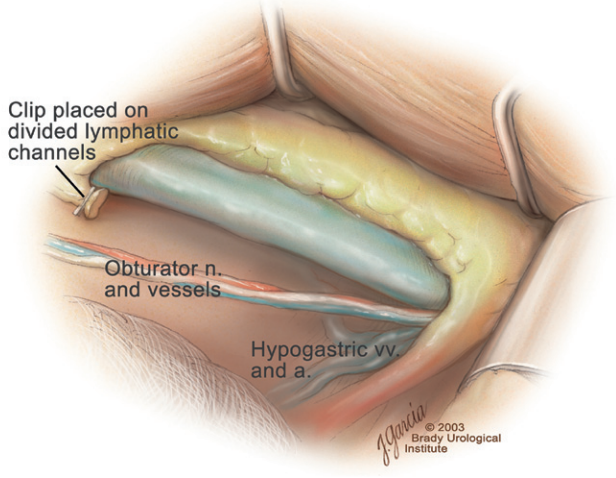


Figure 102–6. View of the right pelvis after completion of the staging pelvic lymph node dissection. Note that the fibroadipose tissue overlying the external iliac artery has not been disturbed and that the obturator nerve, obturator vessels, and hypogastric veins over the pelvic floor have been skeletonized. (© Brady Urological Institute.)

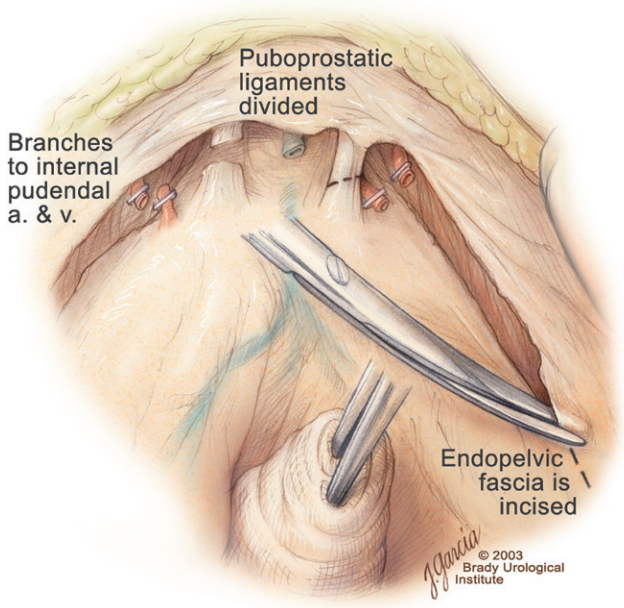


Figure 102–7. Incision in the endopelvic fascia and division of the puboprostatic ligaments. The incision in the endopelvic fascia is made at the juncture with the pelvic sidewall well away from the prostate and bladder. Anteriorly, near the puboprostatic ligaments, small arterial and venous branches from the internal pudendal vessels have been clipped and divided. The puboprostatic ligaments are divided superficially far enough down to expose the juncture between the apex of the prostate and the anterior surface of the dorsal vein complex. However, the pubourethral component of the complex is intact to preserve anterior fixation of the striated sphincter to the pubis. (© Brady Urological Institute.)

and venous branches from the pudendal vessels that perforate the pelvic musculature to supply the prostate. These vessels should be ligated with clips to avoid coagulation injury to the pudendal artery and nerve, which are located just deep to this muscle as they travel along the pubic ramus.

Division of the Puboprostatic Ligaments

The fibrofatty tissue covering the superficial branch of the dorsal vein and puboprostatic ligaments is gently teased away to prepare for division of the ligaments without injury to the superficial branch of the dorsal vein. After the superficial branch has been dissected away from the medial edge of the ligaments, it is coagulated and divided. After all fibrofatty tissue has been removed, a sponge stick is used to displace the prostate posteriorly, and scissors are used to divide each ligament (see Fig. 102–7).

The dissection should continue down far enough to expose the juncture between the apex of the prostate and the anterior surface of the dorsal vein complex at the point where it will be divided. The pubourethral component of the complex must remain intact to preserve the anterior fixation of the striated urethral sphincter to the pubis (Burnett and Mostwin, 1998).

Preservation of Accessory Pudendal Arteries

Arterial insufficiency is a factor contributing to erectile dysfunction in patients after nerve-sparing radical retropubic prostatectomy. One source for this insufficiency may arise from accessory pudendal arteries that travel over the anterolateral surface of the prostate. These arteries have been found in 70% of cadaveric dissections and in 7% of patients by selective internal pudendal angiography. In the authors' experience, large visible accessory pudendal arteries are present in 4% of men (Rogers et al, 2004).

Because release of accessory arteries may be associated with significant blood loss necessitating prompt ligation and division of the dorsal vein complex, it is useful to have the contralateral dissection completed before accessory vessels are released. For this reason, when these vessels appear to be prominent and are present unilaterally, the endopelvic fascia and puboprostatic ligament on the contralateral side should be divided first. The surgical technique for preservation of the arteries begins with division of the endopelvic fascia lateral to the vessels and division of the puboprostatic ligament (the vessels are beneath the puboprostatic ligament) (Rogers et al, 2004). Next, a vessel loop is used to elevate the artery and then with sharp dissection and a right-angled clamp, the accessory artery is released from its investing fascia (Fig. 102–8). As the dissection proceeds, venous tributaries are divided. At times, there may be substantial blood loss from the venous complex over the prostate; hemostasis, however, is usually easily obtained with a 2-0 running absorbable suture. The dissection must extend caudally beyond the site at which the dorsal vein complex will be divided.

Ligation of the Dorsal Vein Complex

The goal is to divide the complex with minimal blood loss while avoiding damage to the striated sphincter and inadvertent entry into the anterior apex of the prostate. With use of the sponge stick to push the prostate posteriorly, a 3-0 Monocryl suture is passed superficially through the dorsal vein complex just distal to the apex of the prostate (Fig. 102–9). In placing this stitch, the surgeon should face the head of the table, holding the needle driver against the pubis perpendicular to the patient. Next, the needle is reversed in the needle holder and the same suture is placed through the perichondrium of the pubic symphysis (Fig. 102–10). Once this horizontal mattress suture is tied, three important goals are accomplished: (1) control of much of the venous bleeding without a "bunching" effect—this flat surface is much easier to divide; (2) recapitulation of the puboprostatic ligaments to provide additional anterior support of the striated sphincter; and (3) fixation of the dorsal vein complex anteriorly. This enables the surgeon to visualize the plane on the anterior apex of the prostate during division of the dorsal vein complex. The suture is not cut; it will be used once the dorsal vein is divided to oversew bleeders. A figure-of-eight 2-0 chromic suture is next placed on the anterior surface of the prostate near the bladder neck to reduce bleeding from the proximal dorsal veins, which can be excessive in some patients who have incompetent venous valves (Fig. 102–11).

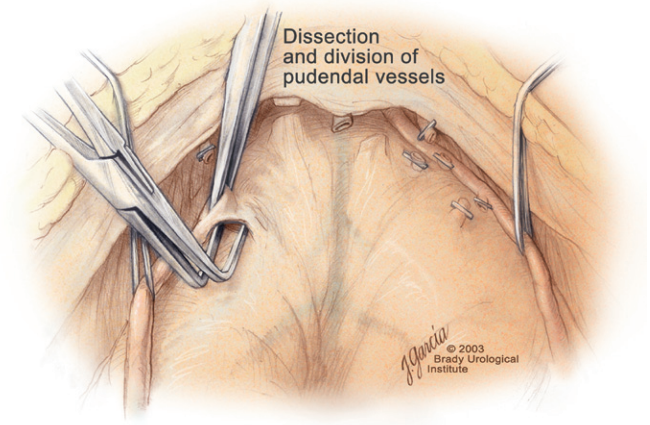


Figure 102–8. Preservation of bilateral large accessory pudendal arteries. The anterior prostatic fascia is elevated with a right-angled clamp to facilitate release of the accessory pudendal vessels. (© Brady Urological Institute.)

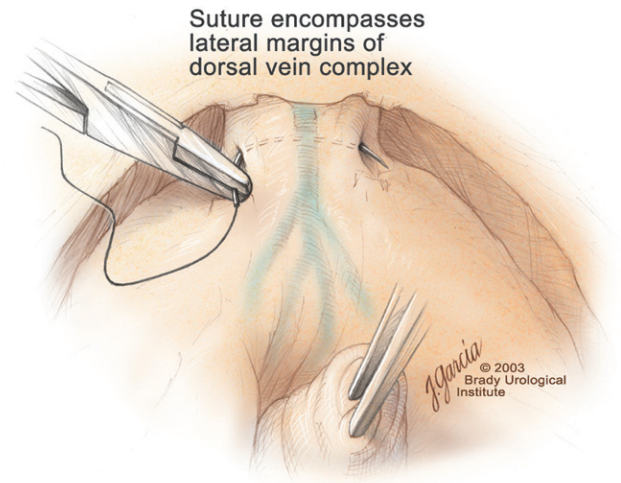


Figure 102–9. Steps in ligation and division of the dorsal vein complex. A 3-0 Monocryl suture is passed superficially through the dorsal vein complex just distal to the apex of the prostate. (© Brady Urological Institute.)

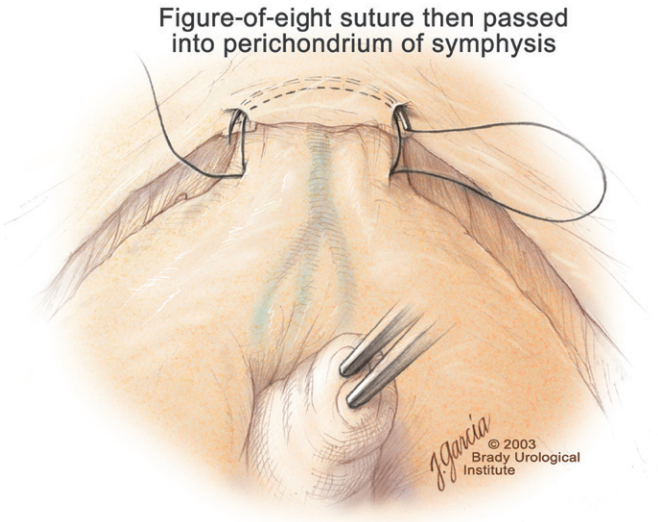


Figure 102–10. Next, the needle is reversed in the needle holder, and the same suture is passed through the perichondrium of the pubic symphysis. This maneuver is repeated to form a figure-of-eight horizontal mattress suture, which is then tied. (© Brady Urological Institute.)

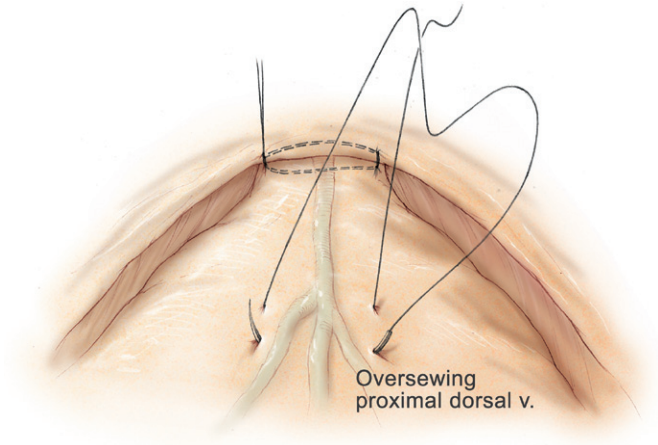


Figure 102–11. A figure-of-eight 2-0 absorbable suture is placed on the anterior surface of the prostate to reduce bleeding from the proximal dorsal venous complex. (© Brady Urological Institute.)

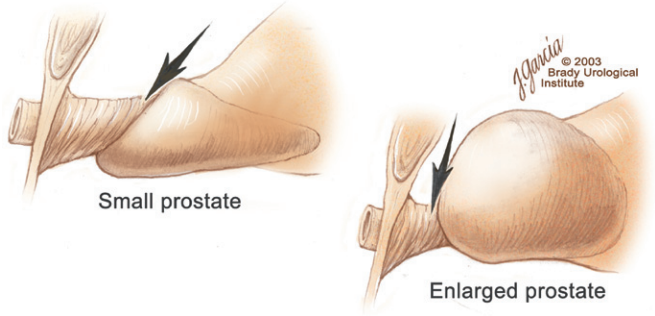


Figure 102–12. As Myers (1991) has pointed out, there is marked variability in the shape of the apex of the prostate. In patients with a small prostate it can have a gentle slope, whereas in patients with an enlarged prostate, there can be an abrupt 90-degree angle. Knowledge of this variability is important to avoid excising excessive amounts of the striated sphincter. (© Brady Urological Institute.)

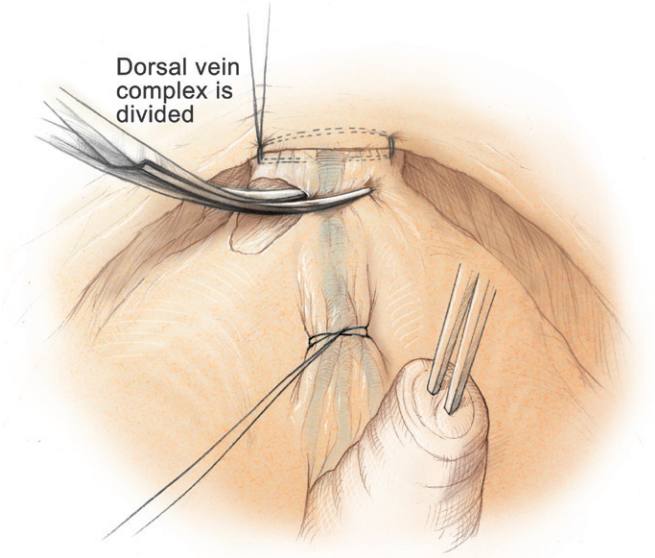


Figure 102–13. With a sponge stick depressing the prostate posteriorly, the dorsal vein complex is divided beginning at the left edge. (© Brady Urological Institute.)

Apical Dissection

The apical dissection is the most complex and important step in the operation. The striated sphincter and the surrounding dorsal vein must be divided with care to avoid inadvertent incision into the apex of the prostate, the most common site for positive margins. Bleeding from the dorsal vein complex must be controlled without injury to the surrounding striated sphincter, the continence mechanism responsible for passive urinary control. During these maneuvers, the apical neurovascular bundles must not be injured by excessive traction, cautery, or inadvertent transection.

The standard approach to division of the dorsal vein complex is presented first. This is a validated technique that maximizes the amount of soft tissue covering the apex of the prostate. As a consequence, in Walsh's hands, the probability of a positive surgical margin in a patient with organ-confined disease is only 1.3%.

With recognition that high release of the levator fascia at the apex can result in earlier recovery of potency in selected patients (Nielsen et al, 2008), **an alternative technique using high anterior release of the neurovascular bundle, before division of the dorsal vein, is also described.**

Standard Division of the Dorsal Vein Complex. As Myers (1991) has pointed out, there is marked variability in the shape of the apex of the prostate (Fig. 102–12). For this reason, it is not wise to pass an instrument bluntly through the complex blindly. Rather, the dissection should be approached by direct division and visual assessment of the landmarks. With the application of downward pressure on the anterior surface of the prostate with a sponge stick, Metzenbaum scissors are used to divide the complex. This is usually started on the left edge of the complex where the junction with the apex of the prostate can usually be seen well (Fig. 102–13). Because the distal complex is fixed anteriorly, with downward pressure on the sponge stick, the exact plane between the juncture of the anterior surface of the prostate and the striated musculature can be visualized. Here the 4.5-power loupes enable the surgeon to distinguish tissue textures and avoid positive margins. This is

the most common site for positive surgical margins because it can be difficult to identify the anterior apical surface of the prostate. It also helps to rest the scissors on the anterior apex to find the correct plane.

There is one important caveat in performing this maneuver. As the dissection proceeds posteriorly, **if the striated sphincter is divided too close to the apex of the prostate, there is risk that the neurovascular bundle may be damaged. As the neurovascular bundle approaches the apex of the prostate, it is often fixed medially beneath the striated sphincter by an apical vessel** (Walsh et al, 2000b). For this reason, the lateral edges of the sphincter along the urethra should be divided obliquely midway between the apex of the prostate and the pelvic floor. Absolute control of venous bleeding from the dorsal vein complex is mandatory so that the remainder of the procedure can be performed in a bloodless field. To achieve hemostasis, the 3-0 Monocryl suture on a ⅝-circle needle that was placed previously is used to oversew the superficial edges of the striated urethral sphincter–dorsal vein complex (Fig. 102–14). **In placing this running suture, the surgeon should face the head of the table, holding the needle driver against the pubis perpendicular to the patient.** If the needle driver is held loosely, the superficial edges of the complex can be easily approximated, forming a hood over the anterior urethra. Circumflex veins are often present at the posterior edge of the complex at the 5- and 7-o'clock positions; hemoclips are often used to control these bleeders. At the completion of this maneuver, hemostasis should be excellent.

Finally, to control back-bleeding from the anterior surface of the prostate, **the edges of the proximal dorsal vein complex on the anterior surface of the prostate are sewn in the shape of a V with a running 2-0 absorbable suture** (Fig. 102–15). **If one tries to pull these edges together in the midline, the neurovascular bundles can be advanced too far anteriorly on the prostate** (Walsh et al, 2000b). If one begins by placing a figure-of-eight suture at the bladder neck before dividing the dorsal vein complex and then uses the same suture to oversew the proximal dorsal vein, there is less back-bleeding.

Division of the Urethra and Placement of the Urethral Sutures. By gently displacing the prostate posteriorly with a sponge stick, the prostatourethral junction should be well visualized. The lateral bands of the striated musculature should be released as described earlier at their midpoint to free up as much of the urethra as possible. A right-angled clamp is then passed around the smooth musculature of the urethra near the apex of the prostate to ensure that the urethra is transected as close to the apex as possible (Fig. 102–16). With scissors, the anterior two thirds of the urethra is divided with care to avoid damage to the Foley catheter. This provides excellent exposure for placement of five sutures in the distal urethral segment at the 12-, 2-, 5-, 7-, and 10-o'clock positions. With 3-0 Monocryl on a ⅝-circle tapered needle, **the**

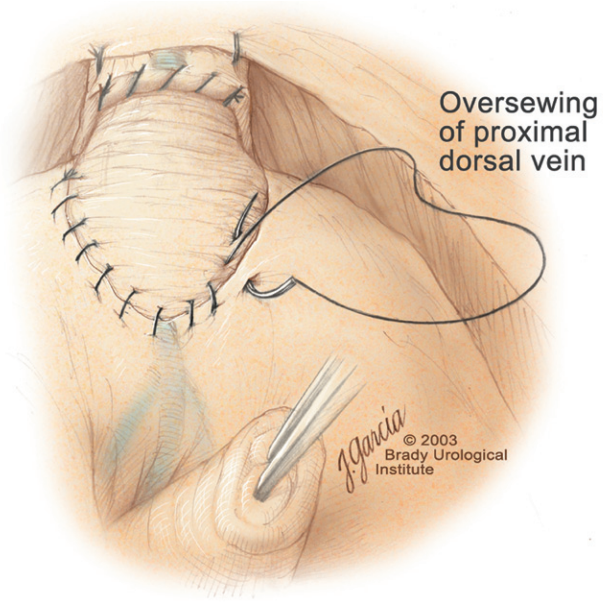


Figure 102–15. The dorsal vein complex over the anterior surface of the prostate is oversewn in the shape of a V with a running 2-0 absorbable suture. (© Brady Urological Institute.)

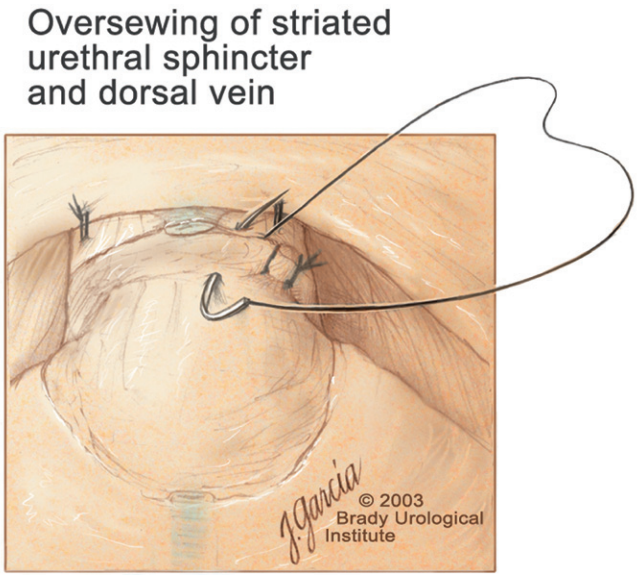


Figure 102–14. With the same 3-0 Monocryl suture that was used earlier to ligate the dorsal vein complex, the superficial edge of the distal striated urethral sphincter–dorsal vein complex is gently oversewn to perfect hemostasis. (© Brady Urological Institute.)

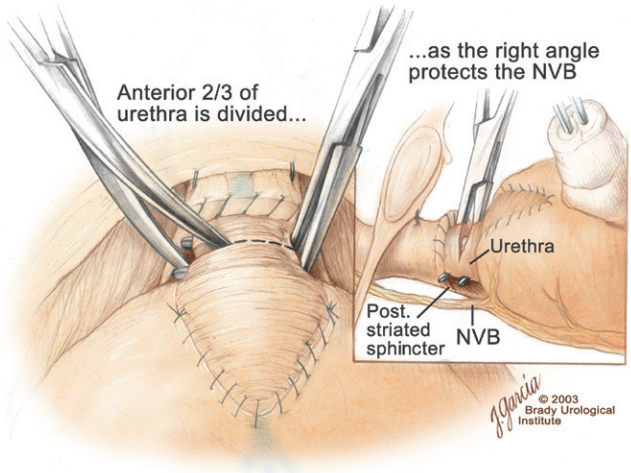


Figure 102–16. A right-angled clamp is placed around the smooth muscle of the urethra close to the apex of the prostate. Note in the inset that the neurovascular bundles (NVBs) are protected from injury by the posterior component of the striated sphincter, which is still intact. Also see Figure 102–5. (© Brady Urological Institute.)

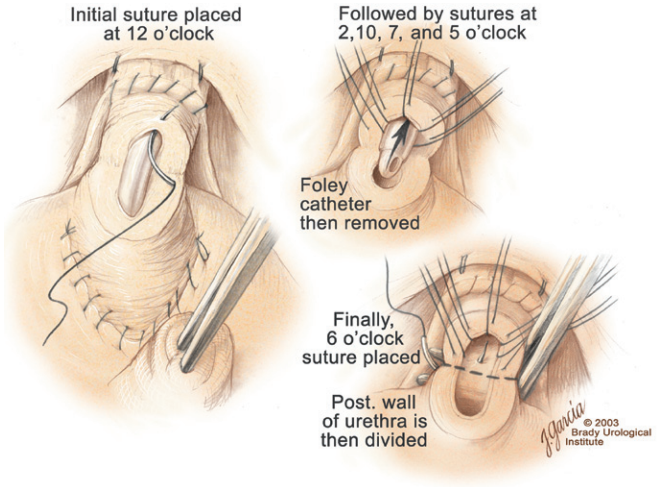


Figure 102–17. The 3-0 Monocryl sutures are placed in the distal urethral mucosa and submucosa at the 12-, 2-, 10-, 7-, and 5-o'clock positions. The Foley catheter is then removed, the 6-o'clock suture is placed, and the posterior wall of the urethra is divided. (© Brady Urological Institute.)

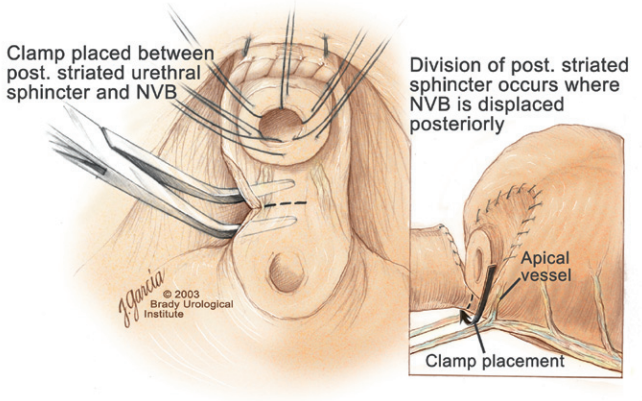


Figure 102–18. Division of the posterior component of the striated sphincter. A right-angled clamp is passed beneath the left edge of the striated sphincter midway between the apex of the prostate and urethra, at a site where the neurovascular bundles (NVBs) have fallen posteriorly. After the left edge of the complex is divided, a right-angled clamp is then passed along the right edge and the maneuver is repeated. (© Brady Urological Institute.)

needle should incorporate just the urethral mucosa and submucosa but not the smooth muscle (Fig. 102–17). As stated previously, the surgeon should face the head of the table to place these sutures and should hold the needle driver against the pubis perpendicular to the patient. The first suture is placed in the mucosa and submucosa of the urethra at the 12-o'clock position. By use of a 16-Fr catheter, the mucosa is easily identified. The smooth muscle should not be incorporated in this stitch because stitches in the smooth muscle delay the recovery of urinary control. If the urethral tissue appears flimsy, this suture should then be placed through the dorsal vein complex to improve tensile strength. Once the mucosa and submucosa have been elevated by the 12-o'clock stitch, the remaining sutures are more easily placed. For a right-handed surgeon, it is easiest to place the 7- and 10-o'clock sutures from the outside of the lumen to the inside. The other three sutures are more easily placed beginning on the luminal surface and then proceeding outside. In performing the final anastomosis, a French eye needle can be used to place these three sutures through the lumen of the bladder. The sutures are covered with towels to avoid inadvertent traction or displacement.

After the sutures are placed, the catheter is removed. The 6-o'clock suture is placed through the mucosa of the urethra, from the outside to the inside. The posterior band of urethra is now divided to expose the posterior portion of the striated urethral sphincter complex (see Fig. 102–17). The posterior wall of the striated sphincter complex is composed of skeletal muscle and fibrous tissue. **Identification and precise division of this complex are important in (1) obtaining adequate margins of resection for apical lesions, (2) identifying the correct plane on the anterior wall of the rectum to ensure that all layers of Denonvilliers fascia are excised, (3) avoiding blunt trauma to the neurovascular bundles that are located immediately posteriorly, and (4) preserving urinary continence.**

To divide the posterior portion of the sphincter safely, a right-angled clamp is passed immediately beneath the left edge of this complex (Fig. 102–18). The clamp should pass midway between the apex of the prostate and the urethra. If it is passed too close to the apex of the prostate, it may damage the neurovascular bundle. However, midway, the neurovascular bundle is located more posteriorly and is beneath the right-angled clamp (Walsh et al, 2000b) (see Fig. 102–5).

The left border of the complex is then divided with scissors. Next, the right-angled clamp is placed beneath the right edge of the complex and the complex is divided. It is necessary to divide the complex from each side because if one tries to divide the entire complex from one side, the contralateral neurovascular bundle may be damaged. Finally, the central component of the complex is divided.

High Anterior Release of the Neurovascular Bundles at the Apex before Division of the Dorsal Vein Complex. **The purpose of this approach is to speed up the recovery of sexual function and continence by reducing traction on the branches of the nerves to the cavernous bodies and striated sphincter or to avoid inadvertent transection of the small branches that travel anteriorly** (Costello et al, 2004; Takenaka et al, 2004, 2005a; Horninger et al, 2005; Menon et al, 2005; Montorsi et al, 2005). **However, because there is less soft tissue at the apex, the risk of positive surgical margins could be increased by this approach. The authors select candidates for this approach using** parameters that identify patients with a low risk of extraprostatic extension in the region of the neurovascular bundle (Tsuzuki et al, 2005), **and in the authors' hands, they have not noted an increased rate of positive surgical margins** (for a detailed discussion of Tsuzuki parameters, see later).

The procedure begins after the endopelvic fascia has been opened as previously described. The levator fascia over the anterior apex of the prostate is incised as suggested by Takenaka (2005b), and the incision is extended distally along the lateral edge of the dorsal vein complex on the anterolateral surface of the prostate, preserving the underlying prostatic fascia (Fig. 102–19A). The prostatic fascia is the glistening white fascia immediately below the veins that travel along the lateral surface of the prostate. **To identify the correct plane and to avoid inadvertent incision into the prostate, it is essential to have excellent visualization and magnification (4.5-power loupes).** In many patients, these venous tributaries must be

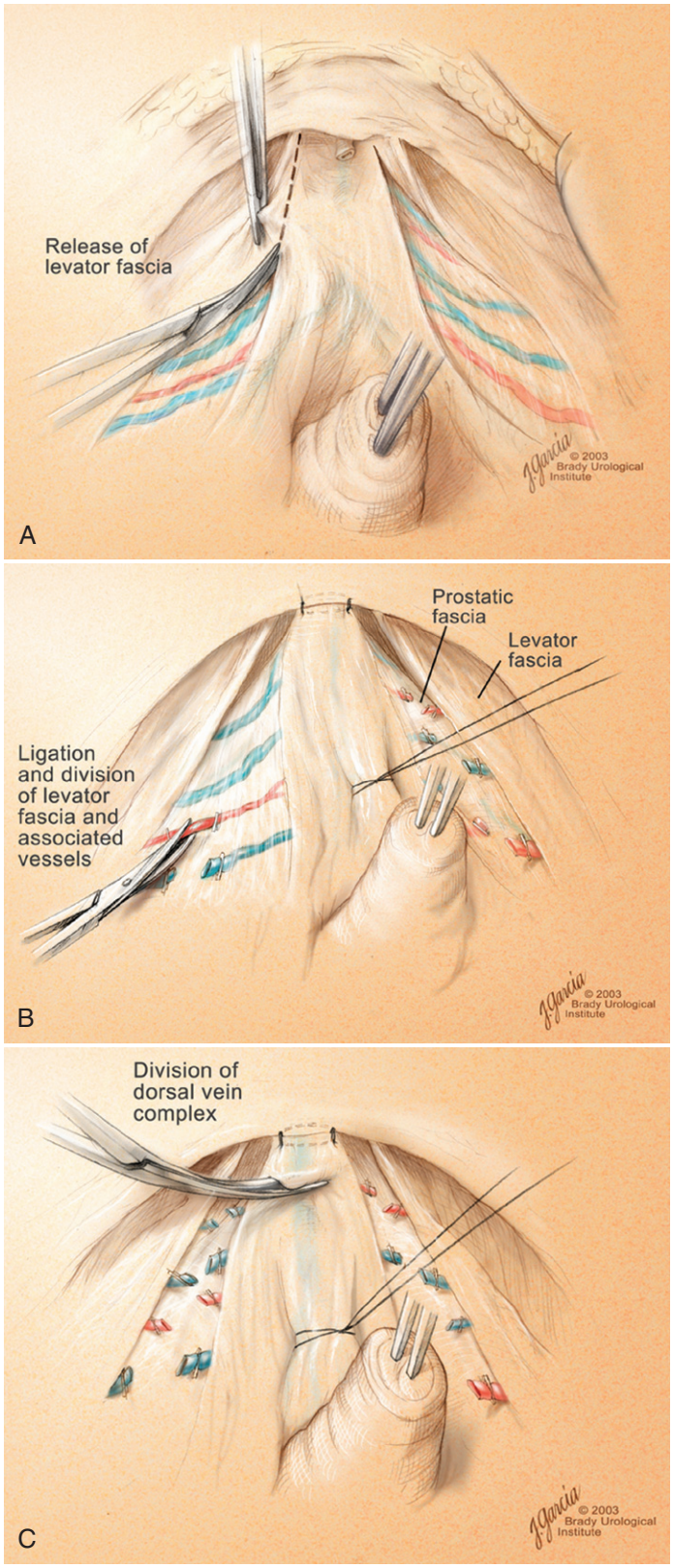


Figure 102–19. High anterior release of the levator fascia. **A,** The levator fascia over the anterior apex of the prostate is incised along the lateral edge of the dorsal vein complex, preserving the underlying prostatic fascia. **B,** The dissection extends distally beyond where the dorsal vein was ligated. Venous tributaries are controlled with clips. **C,** The dorsal vein complex is divided to the urethral between the two preplaced dorsal vein sutures. (© Brady Urological Institute.)

divided and controlled. Cautery should not be used. Instead, hemostasis should be achieved by use of small hemoclips. As the dissection proceeds distally, the levator fascia should be released from the lateral shoulders of the prostate, with care taken not to enter the underlying prostatic fascia. **Because the recovery of sexual function at 12 months following unilateral high release was the same as with bilateral high release, the authors now routinely perform it on only one side, the side with the most favorable pathology.** Once the dissection has extended distally beyond the apex of the prostate, the dorsal vein is ligated distally and proximally as described previously (Fig. 102–19B). Next, while the prostate is immobilized by the dorsal vein complex, the prostate is turned on the side using a sponge stick and the levator fascia and associated veins are released further from the prostatic fascia posterolaterally, exposing and releasing the neurovascular bundle. Next the dorsal vein complex, which has been skeletonized by these maneuvers, is ligated further with the Monocryl suture to reduce blood loss when it is divided. The prostate is then displaced posteriorly by the sponge stick, and the dorsal vein complex is divided between the two ties down to the urethra (Fig. 102–19C). Because the levator fascia has previously been released, prominent neurovascular bundles can usually be visualized lateral to the urethra. Bleeding from the distal dorsal vein complex is controlled with the 3-0 Monocryl suture. Residual back-bleeding from the proximal dorsal vein on the anterior surface of the prostate is controlled with the 2-0 chromic suture. Because less of the striated sphincter is excised by this technique, the bleeding edges can usually be brought together in the midline.

Next, the urethra is transected and the urethral sutures placed. The posterior component of the striated sphincter is transected. If high release of the levator fascia was only performed unilaterally, insert a right-angled clamp under the levator fascia at the apex on the side contralateral to the high release. This facilitates identification of the same dissection plane beneath the levator fascia as the contralateral side without the need for approaching the plane by first dividing the levator fascia from the outside (Fig. 102–20). At this point, as described by Masterson and colleagues (2008), the neurovascular bundle is released from the lateral surface of the prostate to just above the seminal vesicles. This approach avoids traction on the neurovascular bundles and makes the subsequent steps in preservation of the neurovascular bundles much easier (Fig. 102–21).

Identification and Preservation or Wide Excision of the Neurovascular Bundles

Today, in most men who are candidates for surgery, it is safe to preserve both neurovascular bundles and rarely necessary to excise both of them (Walsh, 2001). With improved surgical techniques and the availability of phosphodiesterase type 5 inhibitors, most healthy potent men younger than 65 years should be potent after surgery. As discussed earlier, **the neurovascular bundle is outside the prostate between layers of lateral pelvic fascia (the levator fascia and prostatic fascia). If nerve sparing is performed correctly, the prostatic fascia must remain on the prostate. This is called an *interfascial* dissection. Furthermore, when cancer extends through the capsule, it rarely penetrates more than 1 to 2 mm, and this much tissue is often present even when the neurovascular bundle is preserved** (Hernandez et al, 2005). As Costello and colleagues (2004) have shown, the cavernous branches are positioned posterior to the capsular vessels and the nerves immediately adjacent to the

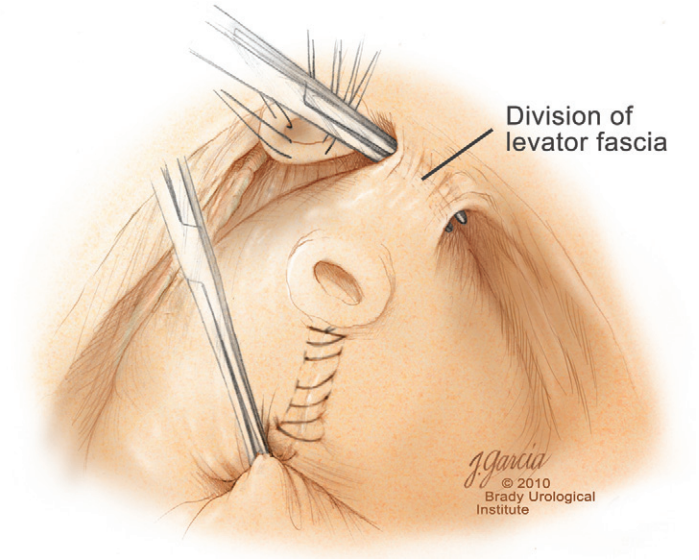


Figure 102–20. If high release of the levator fascia was only performed unilaterally, after the posterior component of the striated sphincter has been divided, insert a right-angled clamp under the levator fascia on the side contralateral to the high release at the apex. This facilitates identification of the same dissection plane beneath the levator fascia as the contralateral side without the need for approaching the plane by first dividing the levator fascia from the outside. (© Brady Urological Institute.)

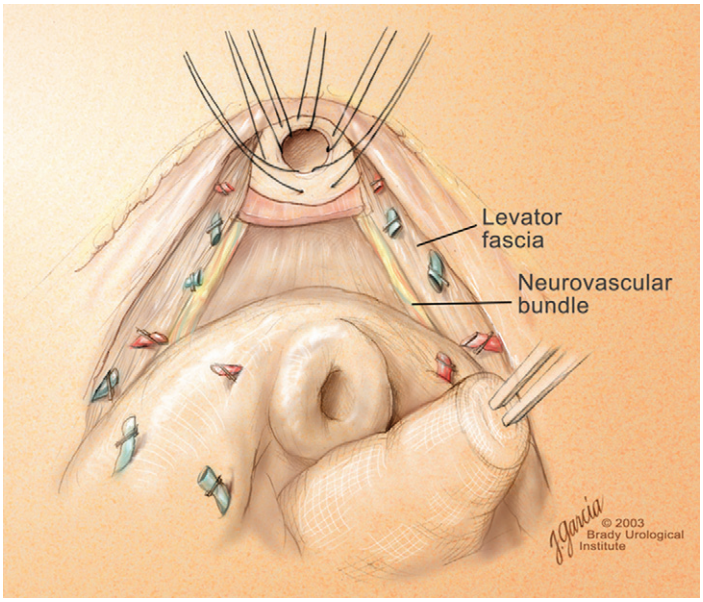


Figure 102–21. A view of the completed dissection. (© Brady Urological Institute.)

prostatic capsule are nerves going into the prostate, not the cavernous nerves.

To avoid bleeding from the capsular arteries and veins, some surgeons dissect beneath the prostatic fascia. This is called an *intrafascial* dissection. Because this plane is directly on the prostatic parenchyma, the risk of positive surgical margins is high. For this reason, this approach should never be used. Many well-meaning surgeons believe that if they excise the neurovascular bundle, they can avoid a positive surgical margin. Unfortunately, this is not the case because the neurovascular bundle is not the most common site for positive margins. Rather, the most common site is the apex, followed by posterior and then posterolateral. In 22% the positive margins are multiple. In multiple studies, it has been demonstrated that the rate of positive margins in nerve-sparing and non–nerve-sparing procedures is the same (Ward et al, 2004). In Walsh's hands, the neurovascular bundles are preserved bilaterally in 87% of patients; one neurovascular bundle is excised in 13%. This has resulted in an overall rate of positive surgical margins of approximately 5% (Epstein, 2001). The neurovascular bundles are rarely if ever excised bilaterally. The authors have always believed that if there is capsular penetration bilaterally to the point where it is necessary to excise both neurovascular bundles, the patient most likely has distant dissemination and is not curable. Between 1986 and 1999, only seven potent men had both neurovascular bundles excised. Four were not cured because they had positive lymph nodes, positive seminal vesicles, or positive surgical margins elsewhere. In the three other patients, it was not necessary to excise both neurovascular bundles because there was no capsular penetration on one side.

How does one decide when and where to excise the neurovascular bundle? Preoperatively, no definite decision is made. Consideration is given to the status of sexual function, but in impotent patients, the authors do not always excise the neurovascular bundles because there is evidence that the bundles provide both somatic and autonomic innervation to the continence mechanism and that patients who undergo excision of both neurovascular bundles have more incontinence than do patients in whom the neurovascular bundles are preserved (Nelson et al, 2003). Consideration is also given to other important factors such as the presence of a *palpable apical lesion* and a high probability of capsular penetration based on the Partin tables (Partin et al, 1997, 2001). **However, no final decision is made until the time of surgery. When the endopelvic fascia is opened, if induration is palpable in the lateral pelvic fascia, the neurovascular bundle on that side is widely excised. If there is no induration but the neurovascular bundle appears to be fixed to the prostate at the time it is being released, it is also excised. However, the final decision about preservation or wide excision of the neurovascular bundle does not need to be made until the prostate is removed. If there appears to be inadequate tissue over the posterolateral surface after the prostate has been removed, the neurovascular bundle can then be widely excised.** For surgeons who are not comfortable or experienced in using intraoperative findings, Tsuzuki and colleagues (2005) have defined preoperative parameters to identify patients with a higher likelihood of extraprostatic extension in the region of the neurovascular bundle. If patients have two or more of the following criteria, the risk of extraprostatic extension in the region of the neurovascular bundle on that side is greater than 10%: prostate-specific antigen (PSA) level above 10 ng/mL, Gleason score higher than 6, average percentage of biopsy core on the side involved greater than 20%, percentage of cores with tumor on that side greater than 33%, or an abnormal finding on digital rectal examination. **The authors use these parameters when selecting candidates for high anterior release of the neurovascular bundles.**

Identification and Preservation of the Neurovascular Bundle. This is where the tactile sensation provided by open surgery is so important. If induration is palpable in the lateral pelvic fascia, the bundle should be excised. Also, in gently releasing the bundle with a right-angled clamp, if the bundle is fixed to the prostate, it should not be

preserved. Tactile sensation is muted with the laparoscopic technique, and with the robot, it is absent. When the neurovascular bundle is released, there should be no upward traction on the prostate. Rather, the prostate should be rolled from side to side. Also with the catheter out, the prostate is softer and it appears easier to identify the correct plane for release of the neurovascular bundle.

Recall that the lateral pelvic fascia is composed of two layers, the levator fascia and the prostatic fascia. The neurovascular bundle travels between these two layers (see Figs. 102–4B and 102–5). With a right-angled clamp, the superficial layers of levator pelvic fascia are released. The use of 4.5-power loupes is helpful during this maneuver to assure the surgeon that the prostatic fascia has not been violated. The magnification also facilitates a more gentle dissection with less traction on the neurovascular bundle. **A Babcock clamp, rather than a sponge stick, is used during release of the neurovascular bundle to manipulate the prostate. This clamp facilitates gentle elevation of the prostate during the release and results in less traction on neurovascular bundle because the prostate is released from the bundle rather than the bundle being released from the prostate.** This dissection should begin at the bladder neck, where this fascia forms a thick band (Fig. 102–22). When this band is divided, the prostate immediately becomes more mobile. The superficial fascia should be released from the bladder neck to the apex. This maneuver releases the bundle laterally, thus making it easier to perform the next step, in which the bundle is released posteriorly at the apex.

Once the superficial fascia has been released, the location of the neurovascular bundle can be identified by the presence of a subtle "groove" on the posterolateral edge of the prostate (Fig. 102–23). **By tracing this groove to the apex of the prostate, one can determine where the neurovascular bundle begins to travel caudally and laterally away from the prostatic apex toward the urethra. Once the medial border of the neurovascular bundle has been identified at the apex, the dissection in the midline can be safely carried posteriorly toward the rectum.**

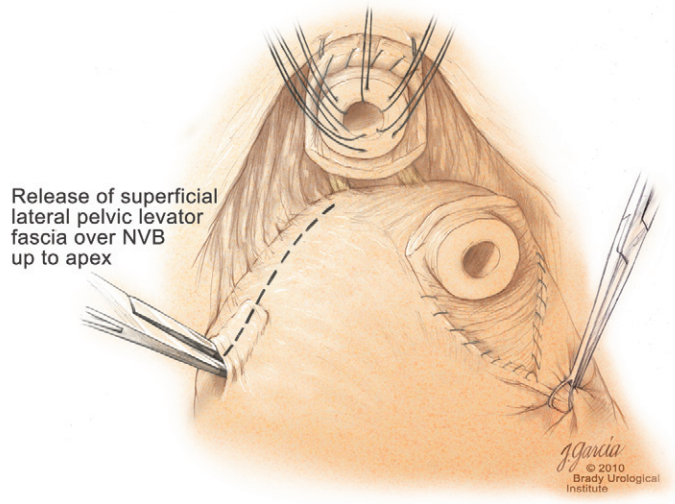


Figure 102–22. The lateral surface of the prostate is exposed by displacing the prostate on its side with use of a Babcock clamp. A right-angled clamp is then inserted under the superficial layer of the levator fascia, beginning at the bladder neck and continuing all the way out to the apex. NVB, neurovascular bundle. (© Brady Urological Institute.)

The plane between the rectum and prostate having been developed in the midline, it is now possible to release the neurovascular bundle from the prostate, beginning at the apex and moving toward the base, using the Babcock clamp to elevate and displace the prostate over on its side. **Beginning on the rectal surface, the bundle is released from the prostate by spreading a right-angled clamp gently.** At the apex, there are often prominent apical vessels. Because the prostate has been elevated on its side across the midline, this distorts the direction of the neurovascular bundle by kinking it (Fig. 102–24). If this artifact is not

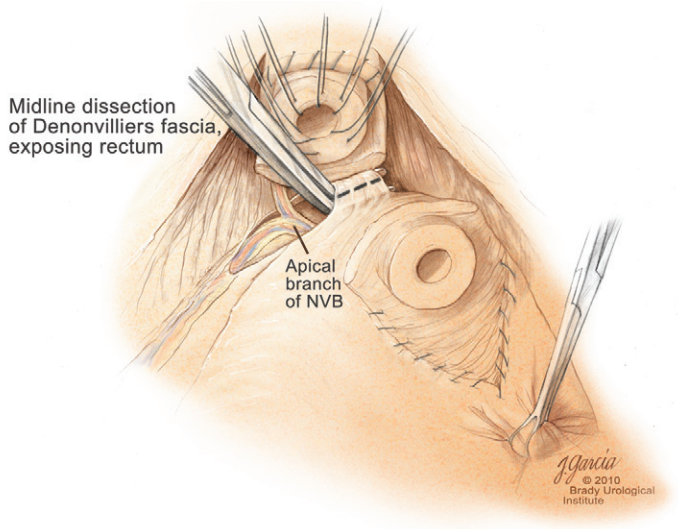


Figure 102–23. Once the levator fascia has been released, the neurovascular bundle (NVB) can be located by the presence of a subtle "groove" on the posterolateral edge of the prostate. This groove should be traced out to the apex of the prostate, and once the medial border has been identified, the dissection in the midline can be pursued, dividing residual layers of Denonvilliers fascia down to the rectum. (© Brady Urological Institute.)

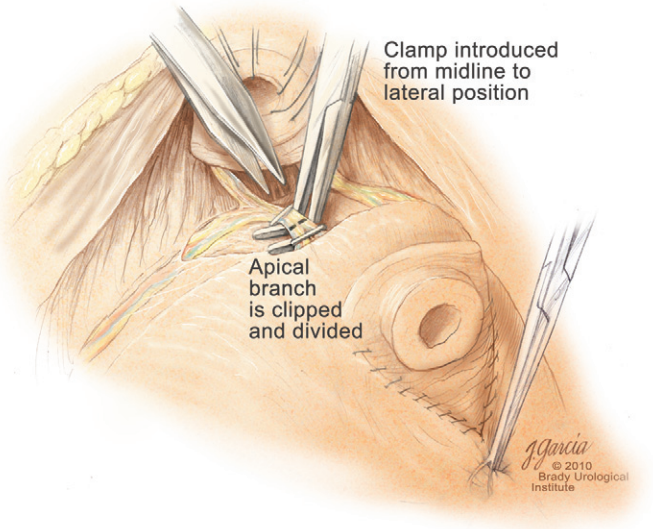


Figure 102–24. At the apex, there are often prominent apical vessels. Because the prostate has been elevated on its side across the midline, note that the neurovascular bundle appears to be kinked. If this artifact is not recognized, the neurovascular bundle can be inadvertently transected. Once these vessels are clipped and divided, the neurovascular bundle returns to its natural straight course. (© Brady Urological Institute.)

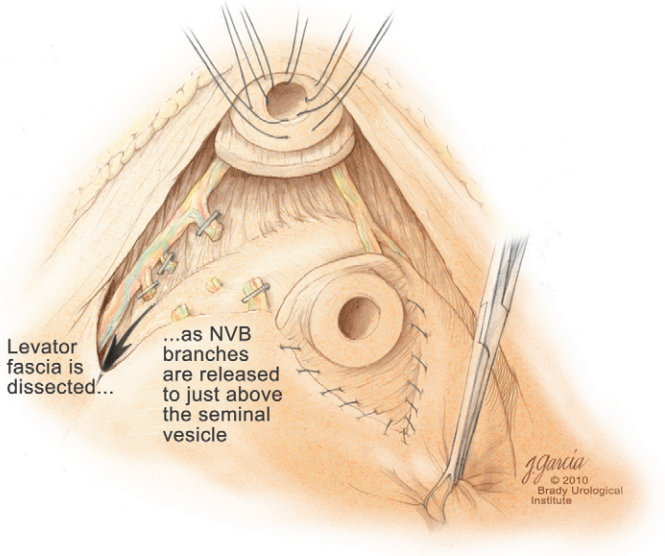


Figure 102–25. The neurovascular bundle (NVB) has been released to just above the seminal vesicle. (© Brady Urological Institute.)

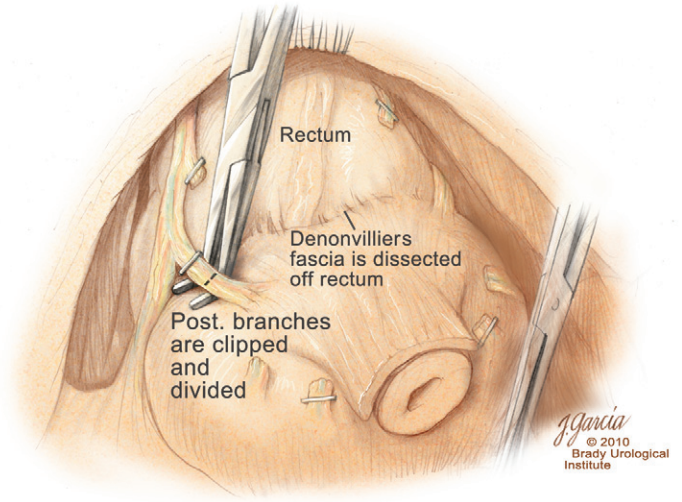


Figure 102–26. Posterior dissection. The attachment of Denonvilliers fascia to the rectum is released, maintaining all layers of Denonvilliers fascia over the posterior surface of the prostate and seminal vesicles. Prominent branches from the neurovascular bundle to the posterior surface of the prostate are identified at the posterolateral angle of the rectum. By dividing these posterior branches, the neurovascular bundle is free to fall away from the prostate posteriorly. (© Brady Urological Institute.)

recognized, the neurovascular bundle can be inadvertently transected. These vessels should be clipped and divided. Once the dissection has been initiated at the apex, it should proceed to the midpoint of the prostate. Because the superficial layers of the levator fascia have already been released, this dissection often proceeds easily. Furthermore, in using this plane, Denonvilliers fascia and the prostatic fascia remain on the prostate; only the residual fragments of the levator fascia are released from the prostate laterally. At this point in the procedure, the bundle should be released to the seminal vesicle (Fig. 102–25).

The vascular branches to the neurovascular bundles are best controlled by small hemoclips placed parallel to the bundle (see Fig. 102–24). **Thermal energy of any form (unipolar, bipolar, or harmonic scissors) should never be used on the neurovascular bundle or its branches** (Ong et al, 2004). There is usually no need to clip the prostatic side of these tiny vessels; fine scissors should be used to divide them. The number of arterial and venous branches is extremely variable. By starting at the apex, however, one can easily identify them prospectively. If the fixation of the bundle to the prostate cannot be explained by vascular branches, the neurovascular bundle should be excised. The surgeon should be aware that the bundle may travel more anteriorly in some patients. In these patients, one can confuse the groove with the potential space between the prostate and rectum. This is another good reason to release the bundle at the apex first. In addition, some patients have many veins on the lateral surface of the prostate that anastomose between Santorini's plexus anteriorly and the neurovascular bundle posteriorly. The apical approach to the bundle facilitates management of this condition as well.

Furthermore, to make certain that Denonvilliers fascia is maintained on the prostate, the neurovascular bundles should be released by dissecting from the rectal surface anteriorly. Using the principles described previously, positive surgical margins in patients with organ-confined disease that are caused by inadvertently cutting into the prostate are rare. Also, because the neurovascular bundle is more mobile, it is easier to interrogate the surgical field with tactile sensation and magnification to find the correct plane. For this reason, even in patients with extraprostatic extension in the region of the neurovascular bundle, it is possible to partially excise the bundle, preserve potency, and obtain negative margins of excision (Hernandez et al, 2005).

To avoid traction on the neurovascular bundle, this dissection should continue cephalad to the level of the seminal vesicles (Masterson et al, 2008). At this point, the surgeon should look for a prominent arterial branch traveling from the neurovascular bundle over the seminal vesicles to supply the base of the prostate (Fig. 102–26). This posterior vessel should be ligated on each side and divided. In doing so, the neurovascular bundles are no longer tethered to the prostate and fall posteriorly.

Wide Excision of the Neurovascular Bundle. **Before excision of the neurovascular bundle unilaterally, the contralateral neurovascular bundle should be freed from the prostate, starting at the apex.** This avoids traction injury, which can occur during wide excision of the contralateral bundle. The neurovascular bundle to be excised is identified at the apex, and a right-angled clamp is passed from medial to lateral, immediately on the anterior surface of the rectum (Fig. 102–27). The bundle is divided without ligation in an effort to excise as much soft tissue as possible. Later, if bleeding is troublesome, the distal end can be clipped. The dissection is continued by dividing the fascia on the lateral surface of the rectum from the apex to the base so that the neurovascular bundle and abundant fascial tissue are included in the specimen. This procedure is performed under direct vision, with the dissection terminating at the tip of the seminal vesicle, where the neurovascular bundle is ligated and divided. In this way, the neurovascular bundle and the lateral pelvic fascia are excised under direct vision in a more complete way than was previously possible (Fig. 102–28).

Posterior Dissection and Division of the Lateral Pedicles

Once the neurovascular bundles have been either preserved at the apex or widely excised and the prostate has been mobilized to the level of the seminal vesicles, the catheter is replaced, and with

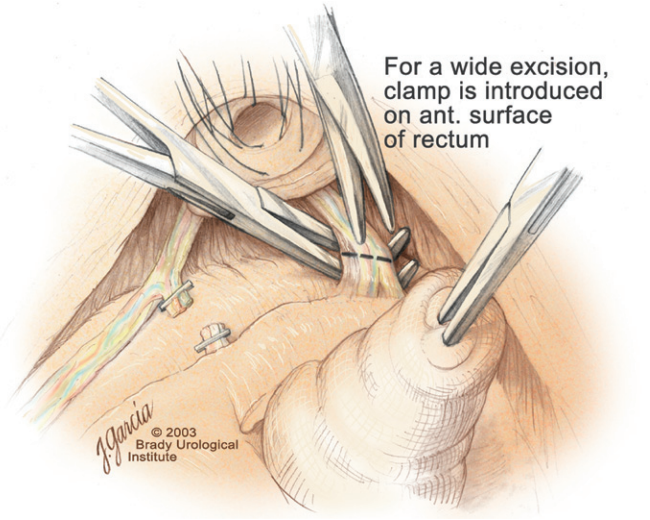


Figure 102–27. Wide excision of the neurovascular bundle. Once the contralateral neurovascular bundle has been released and residual attachments of the rectum to the prostate at the apex are freed up, a right-angled clamp is then passed directly on the anterior surface of the rectum from the midline laterally. If the right-angled clamp is passed lateral to medial, a rectal injury is more likely to occur. (© Brady Urological Institute.)

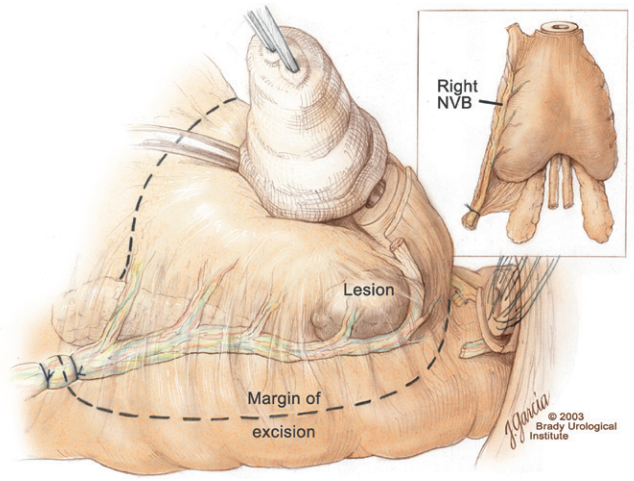


Figure 102–28. Extent of the division of the neurovascular bundle (NVB) from the apex laterally to the tip of the seminal vesicle, where the neurovascular bundle is ligated. This provides excellent soft tissue covering the primary lesion. (© Brady Urological Institute.)

light upward traction on the catheter, the attachment between the rectum and Denonvilliers fascia is divided in the midline posteriorly (Fig. 102–29). Because the neurovascular bundles have been freed up, one may now apply traction to the catheter to gain exposure to the base of the prostate and seminal vesicles. However, to improve exposure, the sponge stick should never be placed on the prostate itself because it may displace tissue, producing a false-positive margin. Instead, the sponge stick should be placed on the catheter. In developing this plane, all layers of Denonvilliers fascia should be left covering the seminal vesicles.

At this point the lateral pedicle can be divided safely on the lateral surface of the seminal vesicles without injury to the neurovascular bundle (see Fig. 102–29). **The lateral pedicles are thick, and therefore they need to be divided in a sequential way: superficial, middle, deep (next to the seminal vesicles). If one tries to divide them all at once, one risks cutting into the overlying prostate.**

Obvious arterial bleeders are simply controlled with hemoclips. With this approach, one can leave more soft tissue on the prostate and protect the neurovascular bundles from injury. The dissection proceeds superiorly onto the anterolateral surface of the junction between the bladder and the prostate. Finally, Denonvilliers fascia is divided over the tips of seminal vesicles to facilitate removal. At this point, many surgeons elect to divide the vasa deferentia and free up the seminal vesicles.

Division of the Bladder Neck and Excision of the Seminal Vesicles

The prostate has now been mobilized almost completely. The bladder neck is incised anteriorly at the prostatovesicular junction (Fig. 102–30). The incision is carried down to the mucosa, the mucosa is incised, the Foley balloon is deflated, and the two ends of the catheter are clamped together to provide traction. As the incision in the bladder neck is widened, branches running from the inferior vesical pedicle to the prostate are noted at 5- and 7-o'clock positions (Fig. 102–31). **After these pedicles are divided, it should be possible to visualize the plane between the anterior surface of the seminal vesicles and the posterior wall of the bladder. By scissor dissection hugging the anterior surface of the seminal vesicles, the posterior bladder neck can be divided safely while observing the location of the ureteral orifices** (Fig. 102–32).

After the posterior bladder wall is divided, the bladder neck is retracted with an Allis clamp, and the vasa deferentia are ligated with hemoclips and divided. The seminal vesicles are dissected free from surrounding structures (Fig. 102–33). Recall that the pelvic plexus is located on the lateral surface of the seminal vesicles. **To avoid injury to the pelvic plexus, the surgeon should perform this dissection with great care, especially laterally, and under direct vision should identify the small arterial branches that travel to the seminal vesicles and stay close to the seminal vesicles when these small vessels are ligated with small clips.** As the tips of the seminal vesicles are freed, small arterial branches at the tip of each seminal vesicle should be identified, ligated, and divided. Any residual attachments of Denonvilliers fascia are then divided, and the specimen is removed. The specimen is inspected carefully to identify any areas where the margin of resection is uncertain. If there is any concern about the margin on the posterolateral surface of the prostate, the neurovascular bundle on that side should be excised.

The operative site is inspected carefully for bleeding. **Small bleeding vessels near the neurovascular bundle should not be cauterized to avoid injury to the fine nerve fibers.** Bleeding from these small vessels should be controlled with small hemoclips. If not, the patient may develop a hematoma between the rectum and bladder. Inflammation surrounding the neurovascular bundles secondary to this hematoma may delay the return of sexual function (Walsh et al, 2000b). To avoid this adverse event, one can make a small opening in the peritoneum in the rectovesical cul-de-sac to facilitate decompression of a hematoma if it develops.

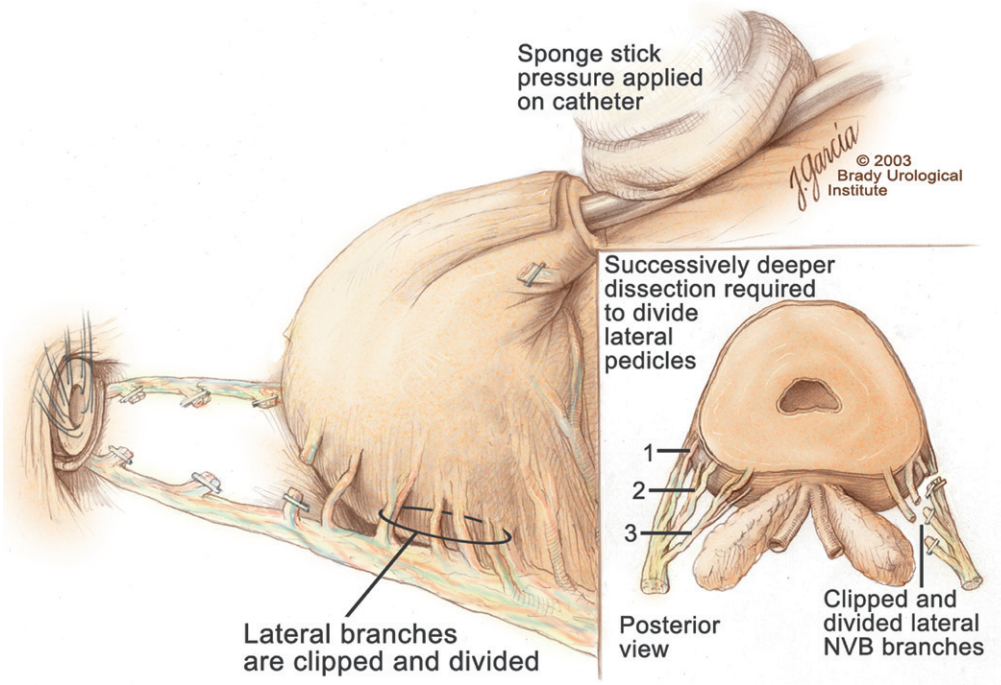


Figure 102–29. Lateral view demonstrating the location of the neurovascular bundle (NVB) after ligation of the posterior branch to the prostate. The site for division of the lateral pedicle is indicated. The lateral pedicle is thick and should be divided in layers: 1, superficially; 2, in the middle; and then 3, deep next to the seminal vesicle. If one tries to divide this thick pedicle all at once, one risks cutting into the overlying prostate. (© Brady Urological Institute.)

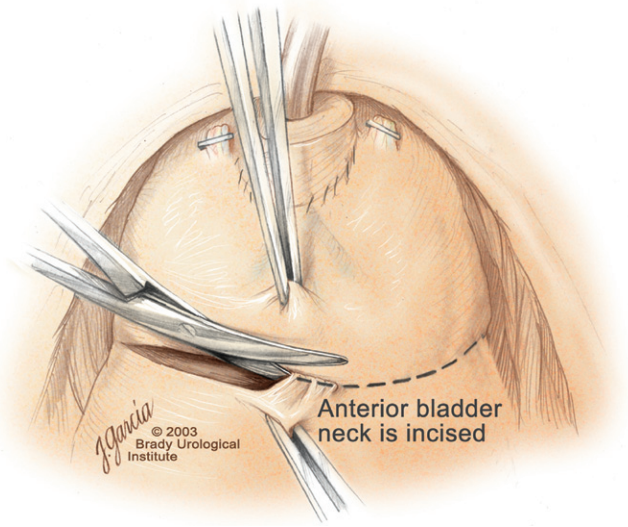


Figure 102–30. Division of the anterior bladder neck. (© Brady Urological Institute.)

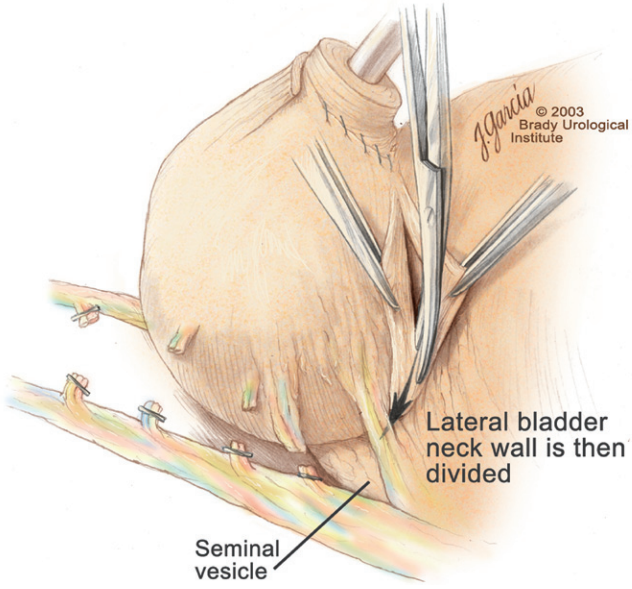


Figure 102–31. Ligation of the branches from the inferior vesical pedicle at 5- and 7-o'clock. This exposes the angle between the bladder and seminal vesicles. (© Brady Urological Institute.)

Bladder Neck Reconstruction and Anastomosis

The bladder neck is reconstructed with a running suture or interrupted 2-0 absorbable sutures to approximate full-thickness muscularis and mucosa, forming a tennis racquet closure (Fig. 102–34). At this point, it is useful to have previously injected indigo carmine to facilitate visualization of the ureteral orifices; ureteral catheters are not usually necessary. **By incorporating the mucosa in the closure, troublesome hematuria can be avoided.** The closure is initiated in the midline posteriorly and proceeds anteriorly until the bladder neck is narrowed to approximate the diameter of the urethra. Interrupted or running 4-0 absorbable sutures are used to advance the mucosa over the raw musculature of the bladder neck. In this way, a rosette of mucosa covers the bladder neck, facilitating a mucosa-to-mucosa urethrovesical anastomosis. The suture at the 6-o'clock position is left long to facilitate placement of the urethral sutures for the final anastomosis (see later).

At this point, the bladder neck can be anastomosed to the urethra, or buttressing sutures can be used to intussuscept the bladder neck (Walsh and Marschke, 2002). **These**

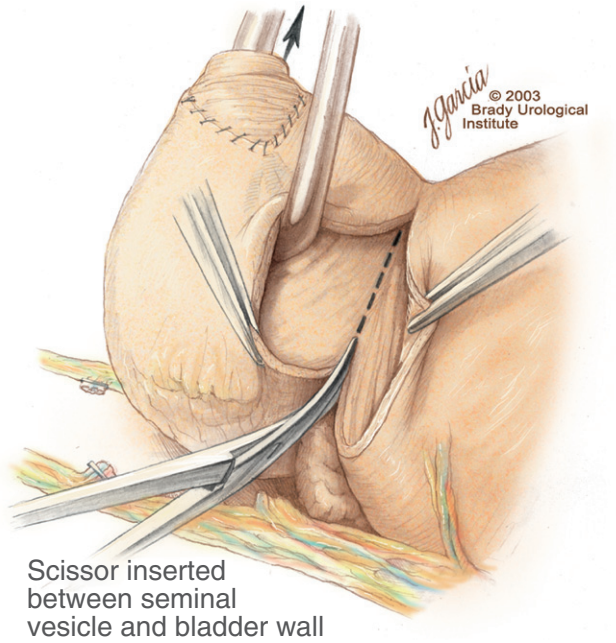


Figure 102–32. The plane between the anterior wall of the seminal vesicles and the posterior wall of the bladder neck for division of the posterior bladder wall. (© Brady Urological Institute.)

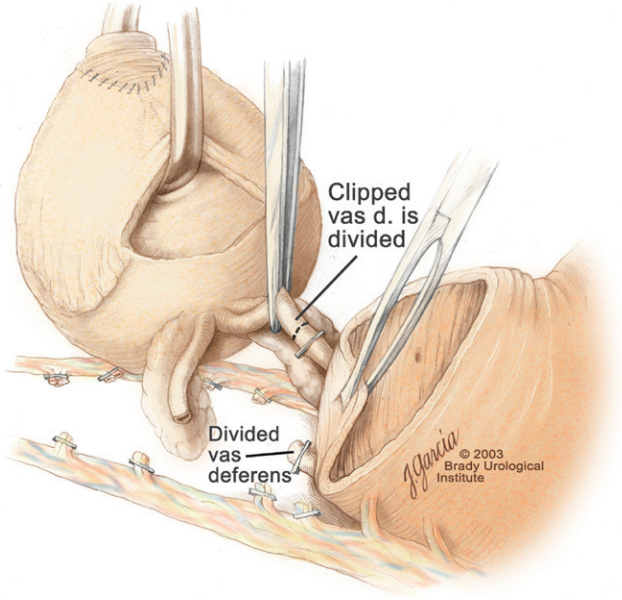


Figure 102–33. Dissection of the vas deferens and seminal vesicles. The left vas deferens has been divided and ligated. The seminal vesicles are carefully dissected free from the pelvic plexus with direct visualization and ligation of small arterial branches. (© Brady Urological Institute.)

sutures prevent the bladder neck from pulling open as the bladder fills. The standard surgical technique described in this chapter emphasizes ample margins to ensure excellent cancer control, especially at the apex. Some surgeons preserve the puboprostatic ligaments and dissect beneath them closer to the apical prostate. Although this may preserve more of the striated sphincter, there is concern that it may lead to inadequate apical margins. The technique described herein may excise more striated musculature, and consequently it takes longer for some men to be pad free. Walsh has found that with intussusception of the bladder

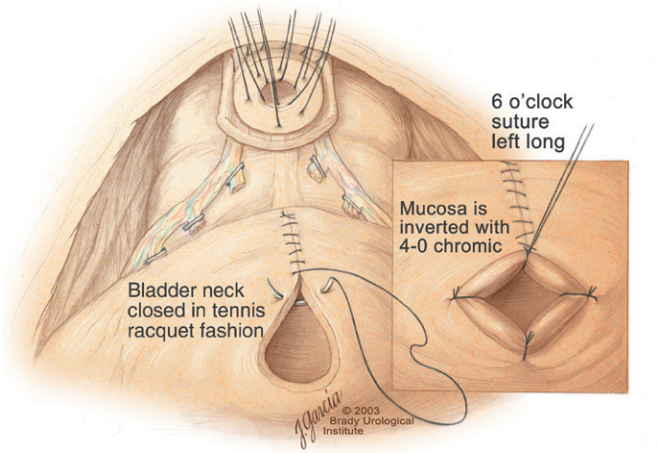


Figure 102–34. Tennis racquet closure of the bladder neck with a running 2-0 absorbable suture incorporating all layers of the bladder wall. The bladder mucosa is then advanced over the raw bladder edges with interrupted 4-0 absorbable suture material to ensure a mucosa-to-mucosa anastomosis. The posterior midline suture (at the 6-o'clock position) is left long. (© Brady Urological Institute.)

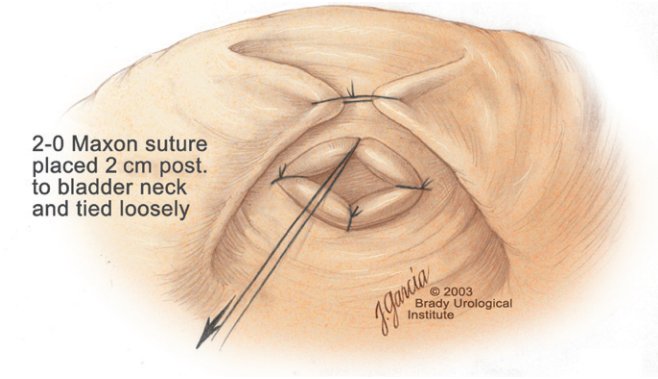


Figure 102–35. Intussusception of the bladder neck. A 2-0 Maxon suture is placed in the edges of the posterior bladder wall, where the bladder was previously attached to the prostate, about 2 cm from the reconstructed bladder neck and tied in the midline. (© Brady Urological Institute.)

neck, 80% of men are pad free at 3 months and 98% at 1 year (Parsons et al, 2004). A 2-0 Maxon suture is placed into the edges of the posterior bladder wall, where the bladder was previously attached to the prostate, about 2 cm from the reconstructed bladder neck (Fig. 102–35). If there are any hemoclips in this area, they should be removed because they may be folded into the bladder neck, causing a bladder neck contracture. The suture is tied in the midline. The next suture is placed more anteriorly. Before this suture is placed, it is wise to release tension on the anterior bladder wall by loosening the malleable blade. This will aid in identifying the loose perivesical tissue that should be incorporated into this stitch. A second figure-of-eight 2-0 Maxon suture is placed about 2 cm lateral to the bladder neck on each side (Fig. 102–36). At this point, the bladder neck should protrude beneath the anterior hood of tissue that was created by the anterior stitch, like a turtle that is poking its head outside its shell. When the bladder neck is filled with saline, it should be competent with little leakage. After this test is completed, the bladder should be emptied completely by placing a forceps through the bladder neck. The 6-o'clock suture should again be placed on traction to facilitate placement of the urethral sutures.

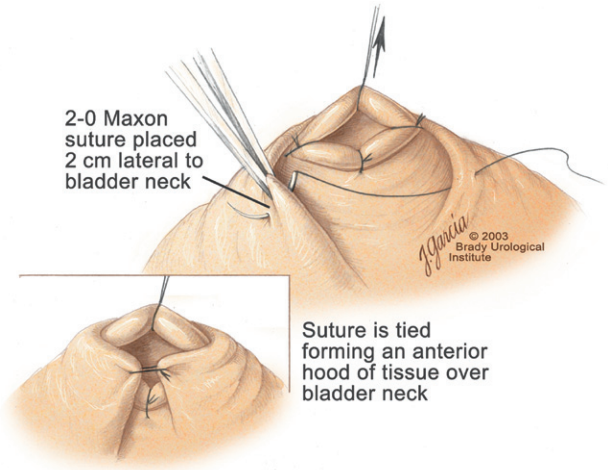


Figure 102–36. Intussusception of the bladder neck. A second figure-of-eight 2-0 Maxon suture is placed anteriorly about 2 cm lateral to the bladder neck on either side and tied. (© Brady Urological Institute.)

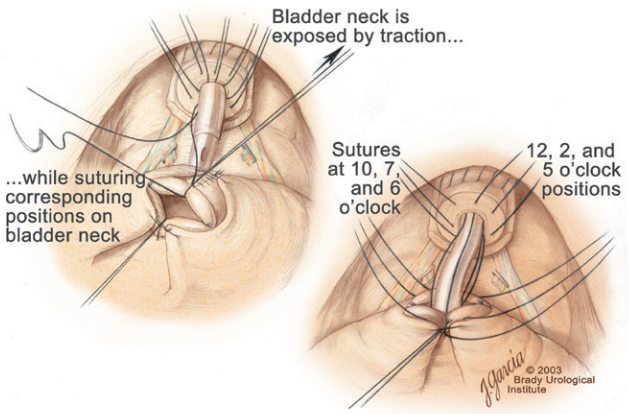


Figure 102–37. The bladder neck is exposed by placing traction on the 4-0 absorbable suture at the 6-o'clock position. The final anastomosis is performed by placing 3-0 Monocryl sutures at the 12-, 2-, 5-, 7-, and 10-o'clock positions. (© Brady Urological Institute.)

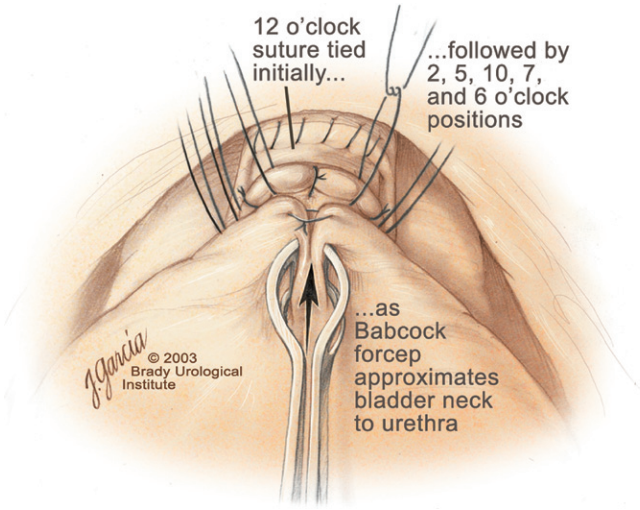


Figure 102–38. A Babcock clamp is used to displace the reconstructed bladder neck into the pelvis and is held in place until all sutures are tied. With this maneuver, one can be certain that there is excellent coaptation of the reconstructed bladder neck to the urethra while the sutures are being tied. (© Brady Urological Institute.)

The operative site is inspected carefully for bleeding. A new silicone Foley catheter (16-Fr, 5-mL balloon) is placed through the urethra into the pelvis. The six 3-0 Monocryl sutures that were previously placed in the distal urethra are now placed through the bladder neck in their corresponding positions from inside to outside (Fig. 102–37). Use of traction on the 4-0 suture that was placed at the 6-o'clock position to exteriorize the mucosa facilitates placement of the sutures. As mentioned previously, a French eye needle is used for placement of the 12-, 2-, and 5-o'clock sutures. The catheter is irrigated free of clots, the balloon is tested, and the catheter is placed through the bladder neck and inflated with 15 mL of saline. The catheter is no longer placed on traction while the sutures are tied. Instead, a Babcock clamp, which is placed on the anterior bladder wall close to the reconstructed bladder neck, is used to hold the bladder in place while the sutures are tied (Fig. 102–38). This ensures excellent coaptation of the mucosa to mucosa and has markedly reduced the probability of bladder neck contractures.

The anterior suture is tied initially. There should be no tension. If there is, the bladder should be released from the peritoneum. The 2-, 5-, 10-, 7-, and 6-o'clock sutures are tied sequentially. After all sutures are tied, the catheter is manipulated to make certain it is not caught in one of the sutures. The catheter is irrigated with saline to eliminate clots. After the operative site is irrigated vigorously with saline, a small suction drain is placed through the fascia (away from the midline) and directed into the operative site in the midline, between (not through) the rectus muscles. The incision is closed with a running No. 2 nylon suture and skin clips. The catheter is carefully taped to the thigh.

POSTOPERATIVE MANAGEMENT

The postoperative recovery of men who undergo radical retropubic prostatectomy is usually uneventful. Patients ambulate the morning after the procedure. Pain control is achieved by intravenous patient-controlled analgesia with morphine on the night of surgery; the next morning, intravenous ketorolac tromethamine is instituted. **This combination of analgesic agents reduces postoperative ileus.** Patients are fed a clear liquid diet on the night of surgery and a regular diet the next day. Closed-suction drains are left in place until they cease to function. Patients are discharged from the hospital on day 1 or 2 with a Foley catheter in place. The urinary catheter represents the source of significant bother (Lepor et al, 2001) and limits the return to activities and work (Sultan et al, 2006). Therefore the urinary catheter should be removed as soon as possible without compromising outcomes. Most would agree that removing the urinary catheter in the presence of significant extravasation would be unwise. Eighty percent of vesicourethral anastomosis exhibits no evidence of cystographic extravasation by the fourth postoperative day. Removal of the urinary catheter at this time is not recommended because of the high rate of acute urinary retention (Patel and Lepor, 2003). Approximately 10% of men will exhibit moderate extravasation on postoperative cystograms performed 1 week after surgery. Routinely performing cystography at 1 week allows "early" removal of the urinary catheter while also identifying the small subset of men who might benefit from longer bladder drainage. Alternatively, the urinary catheter may be removed between days 9 and 14 without a cystogram.

Bladder spasms arising from the indwelling urinary catheter can be a greater problem than incisional pain during hospitalization. Bladder spasms will generally spontaneously subside, and reassurance is often sufficient. In cases of severe bladder spasms, an oral anticholinergic agent or diazepam may be administered.

COMPLICATIONS

Radical retropubic prostatectomy is well tolerated, with minimal morbidity and low mortality (0.2%). Complications can be divided into those occurring intraoperatively and those occurring postoperatively.

Intraoperative Complications

The most common intraoperative problem is hemorrhage, usually arising from venous structures. Hemorrhage may occur during pelvic lymphadenectomy if one of the branches of the hypogastric vein is torn inadvertently. Venous injury like this can often be controlled by temporary packing. If this is not successful, it can be repaired with fine cardiovascular sutures. Hemorrhage can also occur during incision in the endopelvic fascia if the incision is made too close to the prostate, during division of the puboprostatic ligaments if the ligaments are not dissected free from the superficial branch of the dorsal vein or anterior prostatic fascia, and during exposure of the apex of the prostate with transection of the dorsal vein complex. If one understands fully the anatomy of the dorsal vein complex, this bleeding is usually satisfactorily controlled once the dorsal vein has been divided and ligated. **Consequently, if there is troublesome bleeding from the dorsal vein complex at any point, the surgeon should completely divide the dorsal vein complex over the urethra and oversew the end. This is the single best means to control bleeding from the dorsal vein complex. Any maneuver short of this only worsens the bleeding.** To gain exposure for the prostatectomy, one must put traction on the prostate. If the dorsal vein is not completely divided, traction opens the partially transected veins and usually worsens the bleeding. It is imperative to obtain excellent hemostasis before the apex of the prostate is approached so that the anatomy can be viewed in a bloodless field. With careful technique and a thorough knowledge of anatomy, the average blood loss during radical prostatectomy is 500 to 1000 mL. However, because substantial bleeding may occur unexpectedly, the surgeon should always be prepared by having adequate blood available from the blood bank.

Less common complications include obturator nerve injury during pelvic lymph node dissection, rectal injury, and ureteral injury. If the obturator nerve is inadvertently severed, an attempt should be made at reanastomosis with fine nonabsorbable sutures. Rectal injury is an infrequent but serious complication. In 3500 consecutive cases, 11 injuries to the rectum were experienced. They occur during apical dissection in attempting to develop the plane between the rectum and Denonvilliers fascia. If a rectal injury occurs, the prostatectomy should be completed, the bladder neck should be reconstructed, and hemostasis should be excellent. It is wise to interpose omentum between the rectal closure and the vesicourethral anastomosis to reduce the possibility of a rectourethral fistula. This maneuver can be accomplished simply by making a small opening in the peritoneum; finding the omentum and fashioning a slender, well-vascularized pedicle that will be long enough to reach the pelvic floor; dividing the peritoneum in the rectovesical cul-de-sac; and feeding the end of an omental pedicle through this opening. The anal sphincter is dilated widely by an assistant, and the rectal injury is clearly delineated. While there is excellent visualization, the edges of the wound are freshened and closed in two layers. The omental pedicle is immobilized over the repair, with absorbable sutures, and the vesicourethral anastomosis is performed. The wound should be copiously irrigated with antibiotic solution, and the patient should be maintained on broad-spectrum antibiotics for both aerobic and anaerobic bacteria. When this technique was used without a colostomy, all patients recovered without development of a wound infection, pelvic abscess, or rectourethral fistula (Borland and Walsh, 1992). However, if the patient has received prior radiotherapy, it is prudent to perform a diverting colostomy. Ureteral injury occurs secondary to inadvertent dissection within the layers of the trigone while attempting to identify the proper cleavage plane between the bladder and seminal vesicles. If this injury occurs, ureteral reimplantation should be undertaken.

Postoperative Complications

Delayed Bleeding

Life-threatening hemorrhage is a rare complication of radical retropubic prostatectomy with nonautologous transfusion rates of 1% at our institutions. Significant bleeding after radical prostatectomy is defined as postoperative hemorrhage requiring the acute transfusion of blood to support blood pressure. In 1350 consecutive radical prostatectomies, 7 cases (0.5%) met this criterion (Hedican and Walsh, 1994). Of these, four patients were explored for bleeding and three were managed expectantly. The mean blood product requirements for explored patients were comparable with those for patients managed conservatively, although total hospitalization was shorter in patients who underwent a secondary operation. In the three patients managed nonoperatively, the pelvic hematoma drained through the urethrovesical anastomosis, resulting in symptomatic bladder neck contractures in all three and long-term problems with urinary control in two. Only one of four patients explored (25%) experienced prolonged mild incontinence. **These results suggest that patients requiring acute transfusions for hypotension after radical prostatectomy should be explored to evacuate the pelvic hematoma in an effort to decrease the likelihood of bladder neck contracture and incontinence.**

Thromboembolism

Thrombophlebitis with pulmonary embolism is the major cause of mortality after radical prostatectomy. Measures to prevent this complication include careful positioning on the operating room table to avoid compression of the veins in the lower extremity, use of intermittent compression devices, early ambulation, and a shorter incision. With an 8-cm incision, Walsh has not had a thromboembolic event in his most recent 700 cases, in contrast to a rate of 1.4% in the prior 700 cases. Although the precise mechanism behind this reduction is unknown, the authors believe that the lower and shorter incision reduces exposure, dehydration, and traction on the external iliac veins during the procedure. Minidose heparin or low-dose, low-molecular-weight heparin is used at some centers (but not the authors' centers).

Most important, patients should be informed of the signs and symptoms of this complication before they go home and should be instructed to call the physician immediately if they have any of the following symptoms: swelling or pain in the leg, especially in the calf; sudden chest pain that is worse on taking a deep breath; hemoptysis; shortness of breath; or the sudden onset of

weakness or fainting. The authors have found that the informed patient is the best way to reduce the morbidity and mortality from this complication. When patients develop thromboembolic events, twice-daily subcutaneous administration of low-molecular-weight heparin without monitoring of clotting factors appears to be at least as effective and safe as an adjusted-dose, intravenous administration of unfractionated heparin (Buller et al, 2003).

Bladder Neck Contracture

Bladder neck contractures occur in 0.5% to 10% of patients after radical prostatectomy. They arise from inadequate coaptation of the mucosal surfaces. This may be due to inadequate approximation at the time of surgery, urinary extravasation, or distraction of the bladder neck from a hematoma. The use of a Babcock clamp to approximate the bladder neck and urethra while the anastomotic sutures are tied has virtually eliminated bladder neck contractures in our practice. The diagnosis should be considered in any patient who complains of a poor urinary stream or in patients who have prolonged unexplained incontinence. If treatment with simple dilation fails, direct cold-knife incision of the bladder neck at 3-, 6-, and 9-o'clock followed by intermittent self-catheterization for a limited time usually corrects the problem. In patients with recalcitrant bladder neck contractures, the injection of triamcinolone acetonide (200 mg in 5 mL) after cold-knife incision may be useful.

Urinary Incontinence

After radical prostatectomy, incontinence is usually secondary to intrinsic sphincter deficiency. In some men, the striated sphincter may be poorly developed; in older men, it is thinner and contains more collagen (Burnett and Mostwin, 1998; Strasser et al, 1999). However, the predominant cause of this deficiency is injury during ligation and division of the dorsal vein complex. The smooth musculature of the urethra, which also contributes to continence, can be damaged by placement of large, deep sutures for the anastomosis or denervated by injury to the neurovascular bundles. Furthermore, the bladder neck must be supple, with a diameter that is not excessively large, because urinary continence can be hampered by the development of a bladder neck contracture or by a wide bladder neck (Horie et al, 1999; Groutz et al, 2000). To avoid these complications, as outlined previously, it is important to preserve the striated sphincter during the apical dissection, to avoid tension on the final anastomosis by releasing the bladder from the peritoneum if necessary, to reconstruct the bladder neck so that the opening is small and supple, and to accomplish a precise mucosa-to-mucosa anastomosis facilitated by use of a Babcock clamp. Buttressing sutures to intussuscept the bladder neck to prevent it from pulling open as the bladder fills have also proved useful (Walsh and Marschke, 2002). Finally, many men have detrusor hypertrophy and decreased bladder compliance from pre-existing bladder outlet obstruction. It takes these patients longer to achieve full urinary control. For this reason, it is important to avoid excessive traction on the bladder intraoperatively, which may aggravate this condition.

It is beyond the scope of this chapter to review all of the literature on urinary incontinence. In a population-based longitudinal cohort follow-up study up to 24 months, Stanford and colleagues (2000) reported that after radical prostatectomy, 8.4% of men had either frequent urinary leakage or no control. In contrast, in Walsh's patient-reported outcome study in which patients returned a validated questionnaire to an independent third party, 93% of the patients were wearing no pads at 1 year and 98% stated that they had no significant urinary problem (Walsh et al, 2000a). In a more recent study performed after introduction of the bladder neck intussusception, 98% of the patients were pad free at 1 year and no patient reported having a significant problem with urinary control (Parsons et al, 2004).

During their recovery, patients need constant encouragement and advice at regular intervals. The details of this program are reported elsewhere (Walsh and Worthington, 1995, 2001). Until urinary control has returned completely, patients are advised to reduce their fluid intake, avoid caffeinated beverages and alcohol, and stop α-adrenergic antagonists if they take them for the treatment of hypertension. Treatment with imipramine or α agonists in men who are not hypertensive can be helpful. In patients who have not developed a bladder neck contracture and who have not been treated with external beam radiotherapy, the postoperative injection of collagen into the submucosa adjacent to the bladder neck is helpful for many.

Erectile Dysfunction

Three factors are important in the recovery of erectile function after radical prostatectomy: age of the patient (younger than 65 years), status of potency preoperatively, and ability to preserve both neurovascular bundles. With use of the surgical technique described herein, recovery of sexual function was evaluated by a validated questionnaire that was sent to an independent third party (Walsh et al, 2000a). At 18 months, 86% of the patients were able to have unassisted intercourse with or without sildenafil citrate. Although a third of patients were taking sildenafil citrate, only 4% of men reported that they could not have intercourse without it. The recovery of sexual function occurred gradually: 38% were potent at 3 months, 54% at 6 months, 73% at 12 months, and 86% at 18 months. Recovery of sexual function also correlated with the age of the patient at the time of surgery: 100% in men 30 to 39 years, 88% in men 40 to 49 years, 90% of men 50 to 59 years, and 75% in men 60 to 67 years. These data were recently updated with a similar questionnaire (Parsons et al, 2004). At 3 months, 42% of the patients were potent; at 6 months, 49%; and at 1 year, 73%. In both series, most patients had both neurovascular bundles preserved. In patients in whom only one neurovascular bundle is preserved, 65% of patients are potent. In patients with an accessory pudendal artery, preservation was associated with a twofold increase in the likelihood of recovery of erections (Rogers et al, 2004).

High anterior release of the neurovascular bundle is associated with significantly earlier recovery and return to baseline sexual function. In potent men undergoing high anterior release, 93% were potent 12 months after surgery and 70% reported a return to their baseline erectile function. In men who preoperatively reported a frequency of intercourse more than once per week, 78% reported a return to their baseline sexual function at 12 months. Interestingly, this recovery and return to baseline function was noted in men who underwent either a unilateral or bilateral high release. This suggests that the improved sexual recovery associated with this technique is not likely due to preservation of anterior branches of the cavernous nerves but rather due to improved accuracy in the preservation of the nerves with less traction. **Other experienced surgeons have also noted improved recovery of sexual function using similar early nerve release techniques providing further merit to this technical modification** (Masterson et al, 2008).

In patients who are medically cleared, phosphodiesterase type 5 (PDE5) inhibitors augment sexual recovery after radical prostatectomy. Until recently, however, the best dosing schedule (nightly or on demand) for these medications was unclear. In a small study, Padma-Nathan reported improved recovery of sexual function in patients given nightly sildenafil versus patients given placebo (Padma-Nathan et al, 2008). However, men in the placebo arm never received any therapy. In 2008 Montorsi and colleagues reported on a multi-institution randomized, double-blinded study examining recovery of erectile function using either vardenafil "on demand," nightly, or placebo for 9 months. At the end of the blinded treatment period, vardenafil "on demand" was of greater benefit than nightly treatment. In a similarly devised trial, Pavlovich noted no difference in recovery of sexual function in patients using either "on-demand" or nightly sildenafil, with a trend toward improved recovery in the "on-demand" arm (Pavlovich et al, 2009). **Thus on-demand dosing of PDE5 inhibitors appears to be the most effective method to aid in recovery of sexual function.**

SURGICAL MODIFICATIONS TO CLASSIC ANATOMIC RADICAL PROSTATECTOMY

Since the initial report of the anatomic radical prostatectomy, refinements in the surgical technique have been made. Some modifications have minimized the short-term and long-term morbidity of the procedure or the oncologic outcome and have been incorporated into the classic operation (Walsh et al, 2000b; Walsh and Marschke, 2002; Rogers et al, 2004); others have demonstrated no or minimal measurable benefit or negative benefit and have been abandoned (Steiner et al, 1993; Parsons et al, 2004). Several modifications to the classic anatomic radical prostatectomy have been suggested to improve early return of urinary continence, erectile function, or both. These surgical modifications have focused on the function of the bladder neck in urinary control, dissection around the seminal vesicles, and placement of interposition nerve grafts when resection of the neurovascular bundles is required.

Bladder Neck (Sparing) Preservation

Investigators have proposed that preservation of as much of the bladder neck as possible at the time of removal of the prostate can hasten return of urinary control after radical retropubic prostatectomy (Klein, 1992; Licht et al, 1994; Braslis et al, 1995; Lowe, 1996; Shelfo et al, 1998; Poon et al, 2000; Soloway and Neulander, 2000; Srougi et al, 2001; Deliveliotis et al, 2002). Klein (1992) was the first to suggest that modification of the bladder neck resection and reconstruction at the time of radical retropubic prostatectomy might influence urinary control. The group at the University of Miami has reported on a large nonrandomized series of men who underwent radical retropubic prostatectomy with bladder neck preservation (Braslis et al, 1995; Soloway and Neulander, 2000). In 2000 they reported only a 1% bladder neck contracture rate and 1% positive margins at the bladder neck site only and suggested that "extensive" resection at the bladder neck did not add to the curative nature of the procedure yet did not elaborate in detail on the return of urinary control.

In 1996 Lowe compared bladder neck preservation with bladder neck resection (classic method) in a nonrandomized group of nearly 200 men divided between bladder neck preservation and excision. No difference was seen in positive margins, and bladder neck preservation hastened the return of urinary control but did not improve overall continence in the long term. Poon and colleagues (2000) and the group from Loma Linda also reported on a comparative study of 220 men divided into three groups: bladder neck preservation, classic tennis racquet closure, and anterior bladder tube reconstruction. Bladder neck contracture occurred in 10% overall and in 5%, 11%, and 18% by group, respectively. Urinary continence, ascertained by third-party telephone interview, demonstrated 12-month rates of 93%, 96%, and 97% by group, respectively (no difference). These authors concluded that there was no major difference between groups with respect to return of urinary control. Similarly, Deliveliotis and colleagues (2002) showed no difference in continence rates in the long term (1 year) but significant difference ($P < .05$) in the short term (3 to 6 months) when preservation of the bladder neck was exercised.

In several series, higher margins were seen with bladder neck preservation. Srougi and colleagues (2001) from São Paulo, Brazil, reported on a planned enrollment of 120 men in a truly randomized trial between bladder neck preservation and classic reconstruction. Enrollment was stopped because the rate of positive surgical margins in the preservation arm was 10-fold higher (10% vs. 0%) compared with the classic reconstruction arm. Within the group of 70 who finished the trial, the authors measured continence rates and found no difference concluding that the external sphincter appears to play a more important role than the bladder neck in continence after radical prostatectomy. Marcovich and colleagues (2000) also demonstrated that bladder neck–sparing surgery resulted in significantly higher rates of positive surgical margins at the bladder neck compared with standard radical retropubic prostatectomy (47% vs. 20%).

All would agree with the number one goal of anatomic radical prostatectomy, namely, cancer control. These studies seem to agree that there is little difference in the positive margin rates (bladder neck only) with this modification. **The randomized controlled trials suggest that there may be a small (question clinical significance) difference in the early (short-term, 3 to 6 months) return of urinary control with little or no difference in long-term (1-year) urinary control. Finally, the high rate of bladder neck contracture and positive margins in some studies makes this modification less than desirable. The risks need to be weighed against the benefits.**

The authors of this chapter do not perform bladder neck–sparing surgery.

Seminal Vesicle Sparing

The dramatic stage shift witnessed during the past 2 decades (Han et al, 2004), primarily brought about through early detection with PSA, has dramatically decreased the numbers of men presenting with regionally advanced disease (T3b) within the seminal vesicles (Han et al, 2001). Seminal vesicle involvement has been widely accepted as a poor prognostic feature; however, contemporary studies have demonstrated that few men (<8%) presenting with "localized" prostate cancer (near 0% in cT1c) have disease that has already spread to the seminal vesicle. Are we removing this tissue unnecessarily? Some investigators suggested that the close approximation of the seminal vesicles to the neurovascular bundle, pelvic plexus, and bladder base and neck blood supply may allow the dissection in this area to play a major role in postoperative urinary and erectile function and have developed algorithms to predict

seminal vesicle involvement before surgery (reviewed by Zlotta et al, 2004).

A modification to the classic anatomic radical prostatectomy has been proposed—seminal vesicle sparing. Korman and colleagues (1996) were the first to investigate the importance of complete resection of the seminal vesicle during radical retropubic prostatectomy. They investigated the incidence of histologic evidence of cancer within the distal 1 cm of seminal vesicle tissue in 71 consecutive radical retropubic prostatectomy specimens. Of 71 specimens, 12 had seminal vesicle invasion whereas 0 (0%) had disease in the distal 1 cm of the seminal vesicles bilaterally, which led the investigators (who advocated complete resection of the seminal vesicles at that time) to suggest that it is not necessary to remove the seminal vesicle in its entirety when the dissection is difficult. This might eliminate the potentially damaging dissection near other important anatomic structures.

In a follow-up study, Theodorescu and colleagues (1998) looked at the importance of complete seminal vesicle excision by comparing radical retropubic prostatectomy with radical perineal prostatectomy. In two similar groups (stage, race, age, PSA level, and grade), 64% underwent radical retropubic prostatectomy and 36% underwent radical perineal prostatectomy (seminal vesicles are not routinely removed). In the follow-up period, 45% of the men in the perineal prostatectomy group demonstrated biochemical (PSA) elevation (>0.2 ng/mL) compared with only 18% in the retropubic prostatectomy group. When they broke down the perineal prostatectomy group on the basis of no seminal vesicle excision or seminal vesicle excision, the PSA recurrence rate was 69% versus 20%, respectively. The authors concluded that complete excision of the seminal vesicle during radical prostatectomy is essential for cancer control.

John and Hauri (2000) investigated the influence of seminal vesicle preservation during radical retropubic prostatectomy on urinary continence. They observed 54 men, of whom 34 underwent radical retropubic prostatectomy with seminal vesicle removal and 20 with seminal vesicle preservation. A modified pad test at 6 weeks and 6 months postoperatively demonstrated continence rates of 60% at 6 weeks and 95% at 6 months for the seminal vesicle preservation group compared with 18% at 6 weeks and 82% at 6 months for the seminal vesicle resected group. They concluded that seminal vesicle preservation may preclude damage to the pelvic nerves and maintain urinary continence during radical retropubic prostatectomy. Clearly, a double-blinded (patient and third-party reviewer) randomized trial of this method must be performed to fully understand these results.

The authors of this chapter do not perform seminal vesicle–sparing surgery.

Interposition Nerve Grafting

Although wide resection of both neurovascular bundles is rarely indicated when curative intent is the desired effect for anatomic radical prostatectomy (Walsh and Worthington, 2001), investigators have suggested interposition sural nerve grafts after unilateral and bilateral neurovascular bundle resection during radical retropubic prostatectomy (Kim et al, 1999, 2001a, 2001b, 2001c; Scardino and Kim, 2001; Walsh, 2001; Singh et al, 2004). Early studies in the rat (Burgers et al, 1991; Quinlan et al, 1991b; Ball et al, 1992a, 1992b) provided experimental evidence documenting the beneficial effect of interposition nerve grafting after unilateral or bilateral cavernous nerve damage or resection. However, in man, as opposed to the rat, the cavernous nerves are composed of many fibers that are separated by as much as 3 cm (Costello et al, 2004; Takenaka et al, 2004). This raises the legitimate question of whether it is possible to perform a classic end-to-end nerve graft. The precise pathophysiologic mechanism of cavernous nerve regeneration has yet to be fully understood; however, basic science studies and human clinical testing have suggested that return of parasympathetic function can be demonstrated after interposition grafting of the brachial plexus, facial nerves, and peripheral nerves.

It is universally accepted that preservation of erectile function after radical prostatectomy is quantitatively related to preservation of the autonomic innervation and that, with resection of both neurovascular bundles, recovery of erectile function satisfactory for spontaneous erection and intercourse is limited (Quinlan et al, 1991a). Kim and colleagues (1999) first suggested interposition sural nerve grafting at the time of anatomic radical prostatectomy to replace resected cavernous nerves. This group later reported on 28 men with bilateral non–nerve-sparing radical prostatectomy who underwent bilateral sural nerve grafts with 12-month follow-up that 26% had unassisted erections sufficient for intercourse, 26% had partial erections, and 43% had erections sufficient for intercourse with the aid of sildenafil citrate (Kim et al, 2001a). Sexual function returned 5 months after grafting at the earliest time. Another group (Singh et al, 2004) investigated the return of urinary control with respect to sural nerve grafting. They reported a series of 111 men with purposeful unilateral nerve excision, 53 of whom underwent unilateral sural nerve graft after the prostatectomy. At 12 months, 95% of the grafted group reported "complete" urinary control (leakage of only a few drops) compared with only 53% of the nongrafted group ($P < .012$). The authors suggested that the cavernous nerves may play a role in return of continence. These findings have yet to be validated and should be viewed cautiously until a randomized study can be conducted.

Most urologists performing radical retropubic prostatectomy and neurovascular bundle excision require the participation of a plastic surgeon to perform the harvest and implantation of the nerve graft material. Kim and Seo (2001) suggest that with experience, the urologic oncologist performing the radical retropubic prostatectomy should feel comfortable with harvest of the nerve and placement of the graft with limited impact on surgical time and blood loss. Technically, the sural nerve (width of 1.5 to 3 mm, ovoid) graft is harvested with iris scissors through a 3-cm incision that is placed 1 cm inferior to the lateral malleolus. The saphenous vein will be encountered. Dissection should be carried out with loupe magnification. The nerve is divided at the distal end and the foot-side end fulgurated. A tendon stripper (6 mm in diameter) is used to strip the nerve proximally for about 20 cm toward the back of the calf, and a 1-cm incision is used to retrieve the proximal end. Fulguration of the proximal (leg) side of the nerve is also required. The graft is placed in cooled saline. The skin is closed, and compression stockings ensure decreased hematoma formation (Kim and Seo, 2001). The average length of nerve needed per side is 5 to 6.5 cm; however, 40-cm segments can be isolated for bilateral procedures with minimal sensory deficit (Kim and Seo, 2001). The nerve graft is reversed, and the distal nerve is attached to the proximal cavernous nerve endings under magnification; similarly, the proximal nerve end is attached to the distal cavernous nerve endings. The nerve endings can be identified at the time of resection and marked with a stitch through the use of the CaverMap nerve stimulator (Canto et al, 2001). The nerves are attached to the nerve endings with 7-0 polypropylene sutures secured with

microclips. After the procedure, suction drains are placed and directed away from the graft site.

Many questions remain with respect to the need for nerve grafting following wide excision of the neurovascular bundle after radical retropubic prostatectomy (Walsh, 2001). **Davis and colleagues** (2009) **reported a large series of patients undergoing unilateral nerve-sparing procedures with randomization to sural nerve grafting or standard erectile dysfunction therapy. At 2 years, no difference in potency was noted in the two groups (71% in nerve graft group and 67% in the standard group). Bilateral nerve grafting has resulted in a 5-year cumulative recovery of erectile function permitting penetration of 34% and the rate of consistent penetration of 11%** (Secin et al, 2007). **Thus although the techniques of nerve grafting are safe and feasible, the overall benefits appear limited.**

The authors of this chapter do not perform nerve-grafting surgery.

SALVAGE RADICAL PROSTATECTOMY

The goal of primary external beam radiation therapy (intensity-modified or three-dimensional conformal) or primary brachytherapy in the treatment of clinically localized prostate cancer is to eradicate all tumor. Failure to achieve this goal leads to local progression, distant metastasis, and potentially death. The recognition of local recurrence after definitive radiation therapy is complex (American Society of Therapeutic Radiology and Oncology criteria, PSA nadir, PSA bump), yet all would agree that it portends a poor outcome with few options for salvage. This poor prognosis has led to development of several options to salvage cure: cryosurgery (Chapter 105), watchful waiting (Chapter 108), androgen deprivation (Chapter 109), and salvage prostatectomy. **Salvage radical prostatectomy has been used successfully to eradicate locally recurrent cancer after definitive radiotherapy, but complications are common and the effects on overall survival uncertain** (Rogers et al, 1995; Cheng et al, 1998; Garzotto and Wajsman, 1998; Gheiler et al, 1998; Tefilli et al, 1998a, 1998b; reviewed by Chen and Wood, 2003; Stephenson et al, 2004; Ward et al, 2005; Paparel et al, 2009). From the literature, several generalizations can be made:

- The procedure (salvage prostatectomy) is reserved for patients with excellent health and with a life expectancy of more than 15 years.
- Patients must have no evidence of metastatic disease.
- Salvage surgery should be offered only to men who at initial presentation had unequivocally clinically localized prostate cancer.
- Prostate biopsy, histologic grade, clinical examination findings, and serum PSA levels must continue to suggest localized disease.

In summary, candidates for salvage surgery should be unrecognizable from the candidates we would choose for initial therapy with radical retropubic prostatectomy and be highly motivated individuals who understand and accept the potentially higher morbidity associated with salvage surgery.

Scardino and colleagues (Rogers et al, 1995) have reported a large series (N = 80) with long-term outcome data for salvage radical prostatectomy. Early in their series, the estimated blood loss, transfusion requirements, and average length of stay in the hospital were greater than with standard classic radical prostatectomy. Since the mid-1990s, they have reported major improvements in the morbidity associated with this operation. **Whereas rectal injuries occurred in 15% of the first 39 cases, this morbidity is now rare** (Chen and Wood, 2003). **With complete bowel preparation (mechanical and intraluminal antimicrobial) before the operation, rectal injuries, if encountered, can be primarily repaired without altering postoperative recovery. Urinary incontinence rates remain high. Scardino and colleagues reported an estimated 58% with persistent leakage requiring two or more pads per day, and 20% required placement of an artificial urinary sphincter; 27% developed an anastomotic stricture** (Rogers et al, 1995). A summary of the published literature (1985-2000) regarding salvage prostatectomy (Chen and Wood, 2003) demonstrates that the length of hospital stay has dropped from 13 days to 3.2 days, mean estimated blood loss has remained stable around 1000 mL, overall incontinence (stress, total) rates have remained stable at nearly 50% and total incontinence rates have remained stable at 20% to 30%, rectal injury has decreased from 30% to nearly 6%, and bladder neck contracture has remained constant at 20% to 30%. Erectile dysfunction is nearly universal; however, sural nerve grafting (Kim and Seo, 2001; Kim et al, 2001a, 2001b) has been suggested to improve potency after salvage surgery.

Another review of a salvage prostatectomy experience by Stephenson and colleagues (2004) recounted a series of nearly 100 men treated between 1984 and 2003 with either external beam (N = 58) or interstitial (N = 42) radiotherapy. The authors saw a decrease in complication rates (overall from 33% to 13%, rectal injuries from 15% to 2%). They also reported urinary continence rates of 39% totally dry and 86% with one or fewer pad per day. Nearly 20% required an artificial sphincter. The 5-year actuarial recovery of potency rate for this group was 16% (Masterson et al, 2005). Another recent report (Ward et al, 2005) recounted a 30-year experience with salvage retropubic prostatectomy and cystoprostatectomy for radioresistant adenocarcinoma of the prostate. From 1967 to 2003, they found sufficient data to comment on 199 men; 138 were treated with retropubic prostatectomy and 61 with cystoprostatectomy. Average follow-up was 7 years. Rectal injury occurred in 5% of radical retropubic prostatectomies and 10% of cystoprostatectomies. Incontinence was "zero pads" in 43% of the more contemporary cohort. Cancer-specific survival was 65% at 10 years.

Data on oncologic outcomes after salvage radical prostatectomy are limited. Eastham and colleagues report excellent local control and a 45% 5-year recurrence in patients with presurgical biopsies demonstrating a Gleason score of less than 8 (Paparel et al, 2009). However, the overall effect of salvage prostatectomy on prostate cancer–specific mortality remains unclear (Paparel et al, 2009).

The surgical technique for salvage prostatectomy does not differ from that of classic radical prostatectomy. Radiation effects (vasculitis, ischemia, and fibrosis) can make the surgical dissection technically challenging (Chen and Wood, 2003). Special care should be taken in separating the apical region of the prostate, wide dissection of the neurovascular bundles, and dissection of Denonvilliers fascia near the base of the prostate because these regions represent the most common sites for rectal injury.

SUMMARY OF RADICAL RETROPUBIC PROSTATECTOMY

A number of advances have been made in the diagnosis and treatment of localized prostate cancer. Today, more men are diagnosed with curable disease at a younger age. Men are also living longer;

a man 65 to 70 years old has a 50% chance of living for another 15 years. Open radical prostatectomy is an ideal form of treatment for patients who can be cured and who will live long enough to benefit from it. These are also the patients who will have the best quality of life postoperatively (Walsh, 2000).

Radical Perineal Prostatectomy

This section is included in honor and the memory of Marty Resnick, MD. This slightly modified version of his chapter in *Campbell-Walsh Urology, 9th Edition* reflects his career efforts in the field of urology and his expertise in performance of the radical perineal prostatectomy (RPP).

Hugh Hampton Young described the first RPP for treatment of cancer in 1905. In 1939 Belt and colleagues modified the procedure, and until the description of the radical retropubic approach by Walsh, this approach represented the principal method for treatment of patients with localized prostate malignant disease. Furthermore, Walsh improved on the retropubic technique, demonstrating functional anatomic relationships that reduced intraoperative blood loss and improved outcomes of impotence and urinary continence (Reiner and Walsh, 1979; Walsh and Donker, 1982; Walsh et al, 1983).

Surgical and anatomic techniques of the retropubic prostatectomy were applied to the perineal approach, resulting in potency comparable with that of the early radical retropubic prostatectomy (RRP) results (Weiss et al, 1985; Weldon, 1988; Weldon and Tavel, 1988). **In addition, the perineal approach offers visualization of the urethral dissection and anastomosis, resulting in excellent urinary continence similar to the results achieved through the laparoscopic approach. Finally, RPP demonstrates the proven long-term cancer control of RRP with low morbidity and rapid convalescence** (Sullivan et al, 2000; Guillonneau et al, 2002; Harris, 2003; Lotan et al, 2004; Silverstein et al, 2004).

RADICAL PERINEAL PROSTATECTOMY: SELECTION OF PATIENTS

Like the RRP, RPP is offered to those patients with a life expectancy of more than 10 years who demonstrate a high likelihood of organ-confined disease. A nerve-sparing approach is accomplished for most of these patients, and the decision to excise a neurovascular bundle is usually made intraoperatively on the basis of the adherence of the neurovascular bundle to the prostate or preoperatively on the basis of the biopsy report or results of the DRE. A pre-RPP laparoscopic pelvic lymphadenectomy is deemed unnecessary if the biopsy Gleason score is below 7 and the serum PSA level is less than 10 ng/mL (low- to moderate-risk disease).

In patients with localized cancer, **there are few contraindications to this procedure.** Patients with severe ankylosis of the hips or spine and those with unstable artificial hip replacements may not tolerate the exaggerated lithotomy position. However, **common degenerative disk disease is not a contraindication to positioning.** Some patients, such as those having renal transplantation or those with severe inflammation secondary to placement of synthetic mesh for repair of a hernia or the morbidly obese, who may not be amenable to RRP, typically may undergo

Key Points: Anatomic Radical Retropubic Prostatectomy

- There is no better way to cure cancer that is confined to the prostate than total surgical removal.
- The three goals of the surgeon, in order of importance, are cancer control, preservation of urinary control, and preservation of sexual function.
- Surgery is deferred for 6 to 8 weeks after needle biopsy of the prostate and 12 weeks after transurethral resection of the prostate.
- A fiberoptic headlight and 2.5- to 4.5-power loupes are most useful because much of the procedure is performed beneath the pubis in an area where visualization can be difficult. Magnification can enable the surgeon to exert less traction on the neurovascular bundles and more easily identify the correct plane of dissection.
- Regional anesthesia is associated with less blood loss and a lower frequency of pulmonary emboli.
- If the patient has a well-differentiated to moderately well-differentiated tumor (Gleason grade < 8) and the lymph nodes are normal to palpation, frozen-section analysis is not performed.
- With the recent recognition that branches of the nerves innervating the striated sphincter and cavernous bodies may travel more anteriorly at the apex, an alternative technique involving high anterior release of the neurovascular bundles at the apex before division of the dorsal vein is described. This technique is associated with earlier recovery of sexual function.
- Today, in most men who are candidates for surgery, it is safe to preserve both neurovascular bundles and rarely necessary to excise both of them, thus making cavernous nerve replacement or transplantation unnecessary in most cases.
- The tactile sensation provided by open surgery is so important. If induration is palpable in the lateral pelvic fascia, the bundle should be excised. In gently releasing the bundle with a right-angled clamp, if the bundle is fixed to the prostate, it should not be preserved. With the laparoscopic technique, tactile sensation is muted; with the robot, it is absent.
- Patients requiring acute transfusions for hypotension after radical prostatectomy should be explored to evacuate the pelvic hematoma in an effort to decrease the likelihood of bladder neck contracture and incontinence.
- Thrombophlebitis with pulmonary embolism is the major cause of mortality after radical prostatectomy. Measures to prevent this complication include careful positioning on the operating room table to avoid compression of the veins in the lower extremity, the use of intermittent compression devices, and early ambulation.
- The authors concluded that complete excision of the seminal vesicle during radical prostatectomy is essential for cancer control.
- Open radical prostatectomy is an ideal form of treatment for patients who can be cured and who will live long enough to benefit from it.

prostatectomy by the perineal approach (Yiou et al, 1999; Boczko and Melman, 2003). Additionally, a large (>100 g) prostate and a narrow pelvis can cause difficulties with this surgical approach.

PREOPERATIVE CARE/POSITION

A full bowel preparation is administered on the day before surgery on the basis of the surgeon's preference; the patient is instructed to consume polyethylene glycol or administer a Fleet Phospho-Soda enema in the afternoon before surgery. Also, 1 g of neomycin is administered orally at 12:00, 2:00, 4:00, 6:00, 8:00, and 10:00 PM. This bowel preparation allows primary closure of any inadvertent rectal injury at the time of surgery without problem. A sample for blood type and antibody screen is obtained from all patients in the days or hours before surgery, but because blood loss is minimal and transfusion rarely required, a cross-match is unnecessary; preoperative donation and storage of blood by the patient is not required, either.

In the preoperative holding area, antithromboembolic surgical stockings are positioned and the patient is administered a second-generation cephalosporin intravenously. Although perineal prostatectomy lends itself to regional anesthetics such as spinal or epidural anesthesia, most patients receive a general anesthetic. The only specialized instruments needed are curved and straight Lowsley tractors, a self-retaining retractor such as the mini-crescent or Thompson, and a headlight.

After the induction of anesthesia, the patient is positioned supine so that when the leg portion of the operating table is lowered, the buttocks are extended beyond the table edge. Allen stirrups are stationed 2 inches cranially on the rail so that there is ample room for the attachment of the self-retaining retractor. The patient is then placed in an exaggerated lithotomy position with the perineum almost parallel to the floor or in a modified exaggerated lithotomy position with the perineum only slightly elevated (Fig. 102–39). The perineum, anus, and scrotum are shaved, and the abdomen inferior to the umbilicus, penis, scrotum, perineum, anus, and both thighs are painted with povidone-iodine in the standard sterile fashion. After gowning, a sterile towel is sewn from the 9-o'clock to the 3-o'clock position around the anus at the mucocutaneous pigmentation line with silk suture, maintaining a sterile environment. Leg and perineal drapes are placed. The upright of the self-retaining retractor is secured to the table rail on the patient's left while the sterility of the upright is maintained.

EXPOSURE OF THE PROSTATE

A curved Lowsley tractor is placed transurethrally into the bladder and its wings opened. A curvilinear incision is made from a position just medial to the right ischial tuberosity to a position just medial to the left ischial tuberosity. The incision should not extend posteriorly beyond the 3- and 9-o'clock positions relative to the anus. Blunt dissection is employed to open and develop each ischiorectal fossa lateral to the central tendon, and the central tendon is then divided by electrocautery (Fig. 102–40). In the original description by Young, the dissection is carried anteriorly along the external anal sphincter until arriving at the rectourethralis muscle (1905). However, with the Belt approach preferred by the authors, the fibers of the external anal sphincter are dissected and retracted anteriorly with an appendiceal retractor; these fibers are not incised (1939). The longitudinal muscle fibers of the rectum are identified, and gentle traction is placed dorsally on the rectum by a dampened sponge. The plane is developed leading to the rectourethralis muscle, which is formed by fascicles of the rectal muscle, connecting the rectum to the perineal body. It appears as a strap of muscle tenting the rectum ventrally. **Without any traction on the Lowsley tractor, the rectourethralis muscle is divided close to the apex of the prostate with vertically oriented scissors, allowing the rectum to fall dorsally; caution must be exercised to prevent rectal injury at this point of the procedure.** Gentle pressure is then applied on the Lowsley tractor toward the anterior abdominal wall. This maneuver delivers the prostate well into the field of view and allows the blunt, digital dissection of the prostate from the rectum in a cephalad direction until the base of the prostate is identified at the vesicoprostatic junction (Fig. 102–41). Classically, the proper plane is between the anterior and posterior leaves of Denonvilliers fascia.

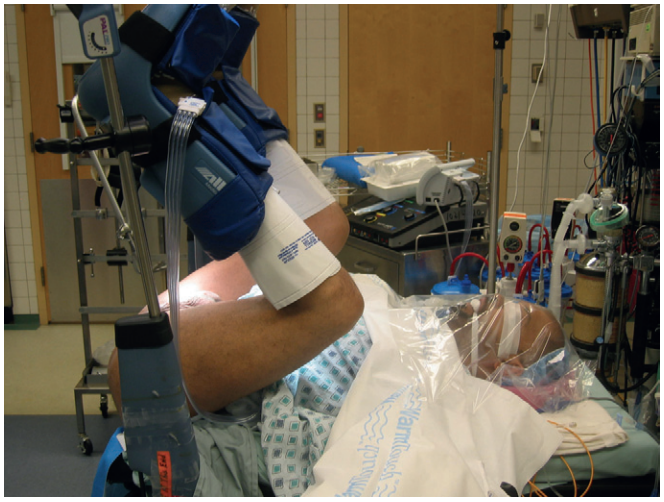


Figure 102–39. The modified exaggerated lithotomy position. The perineum is only slightly elevated and almost at a 90-degree angle with the floor. The legs are positioned at nearly a 75-degree angle with the floor.

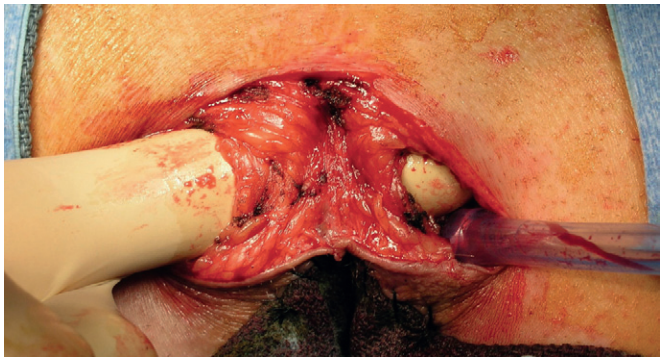


Figure 102–40. Each ischiorectal fossa is dissected bilaterally, and the finger is bluntly brought beneath the central tendon. The central tendon will be divided with electrocautery as traction is maintained with the finger.

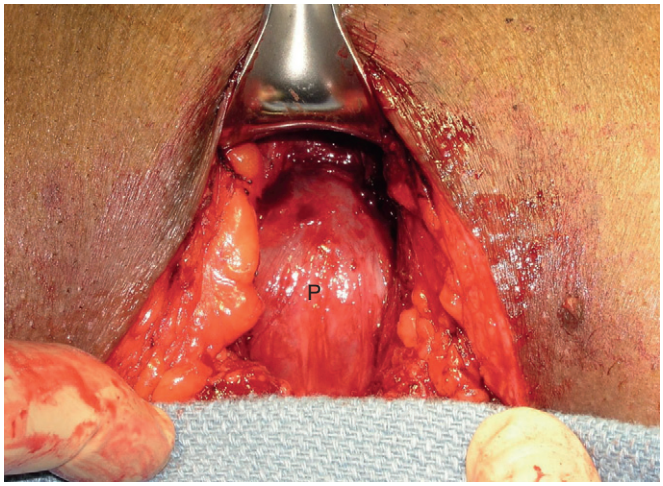


Figure 102–41. The external anal sphincter is retracted anteriorly, and the rectourethralis muscle is divided. The prostate (P) is delivered into the field of view.

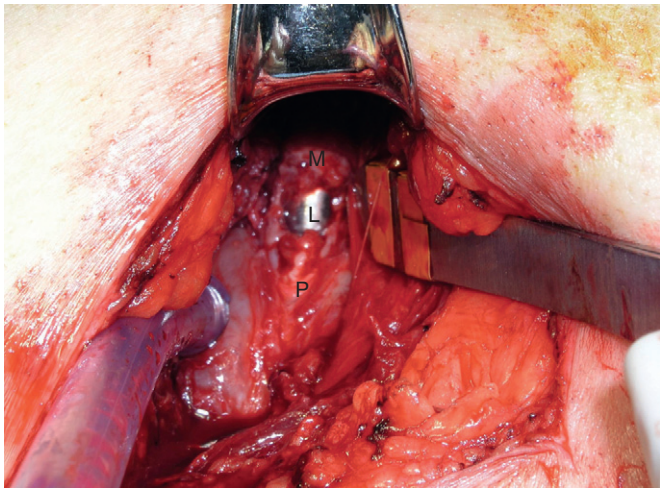


Figure 102–42. The anterior urethra is incised over the curved Lowsley tractor (L) between the membranous urethra (M) and prostate (P).

NERVE-SPARING DISSECTION

Resumed traction on the Lowsley tractor toward the anterior abdominal wall again brings the prostate into the incision. If preservation of the neurovascular bundles is intended, the exposed anterior layer of Denonvilliers fascia is incised vertically in the midline from the vesicoprostatic junction to the apex of the prostate with a No. 15 blade scalpel. **Avoiding use of electrocautery, careful lateral dissection with gentle lateral traction preserves the neurovascular bundles as they course between the layers of Denonvilliers fascia at the posterolateral edge of the prostate. The fascia and enclosed nerves must be sufficiently mobilized to allow eventual extraction of the prostate without stretching or damage of the bundles.**

Attention is then directed toward the prostatic apex and urethra. The Lowsley tractor can be palpated within the urethra, and a right-angled clamp is placed with the open points facing cephalad on either side of the urethra to dissect the neurovascular bundles away from the urethra as they course distally. The No. 15 blade scalpel is again used to incise the posterior aspect of the urethra over the Lowsley tractor (Fig. 102–42). The curved Lowsley tractor is then replaced by a straight Lowsley, and the wings are opened in a vertical fashion. With moderate traction on the Lowsley tractor, the remaining intact anterior aspect of the membranous urethra is sharply transected from the prostatic apex and the anterior prostate is freed to the bladder neck by sharp and blunt dissection.

The self-retaining retractor is attached to the previously placed upright, and blades are placed in the 3-, 9-, and 12-o'clock positions. Dissection is then directed over the anterior prostate from the apex toward the bladder neck. Traction on the Lowsley tractor aids in this portion by bringing the prostate into the incision. **The surgeon must be mindful not to dissect too far ventrally and to touch on the dorsal venous complex.** To sufficiently expose the anterior prostate, the puboprostatic ligaments are encountered and divided with scissors (Fig. 102–43).

The junction of the bladder neck and prostate base is then identified by palpating the wings of the Lowsley tractor. This junction is then further developed with blunt and sharp dissections, preserving the bladder neck. The bladder is entered anteriorly with a scalpel, the Lowsley tractor is removed from the urethra, and a

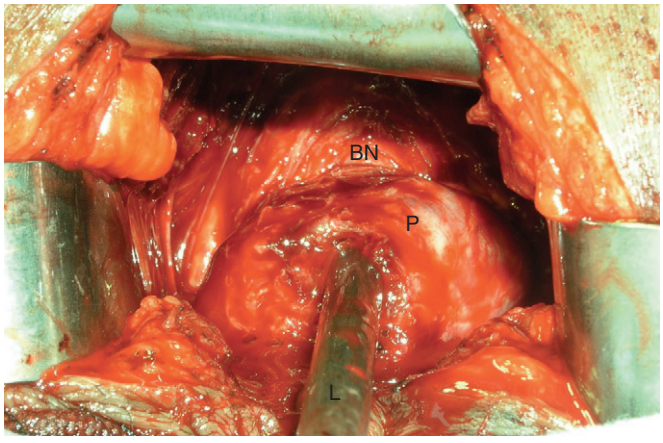


Figure 102–43. The urethra is divided, and the curved Lowsley has been replaced with a straight Lowsley tractor (L). The anterior prostate (P) has been dissected, and the puboprostatic ligaments are divided, exposing the bladder neck (BN).

long right-angled clamp is passed retrograde through the prostatic urethra and bladder neck. A 14-Fr red rubber catheter is then fed into the open right-angled clamp and pulled through the prostatic urethra; the ends are clamped together with a Kelly clamp, making a loop that may be used for manipulation of the specimen (Fig. 102–44). Traction on the catheter further delivers the prostate into the incision, and dissection of the anterior bladder neck is continued circumferentially around the prostate base. Identification of the ureteral orifices is generally unnecessary unless the dissection inadvertently involves the trigone. The lateral attachments and vascular pedicles are found coursing toward the base of the prostate and are dissected, sharply divided between right-angled clamps, and secured with 3-0 absorbable ties. **To preserve the neurovascular bundles, the lateral pedicles should be divided close to the prostate, taking care not to compromise the surgical margin. Electrocautery is avoided during this phase.**

The dissection is continued posteriorly at the bladder neck to separate it completely from the prostate. The red rubber catheter is then removed, and a right-angled clamp is passed along the midline posterior surface of the prostate with tips directed toward

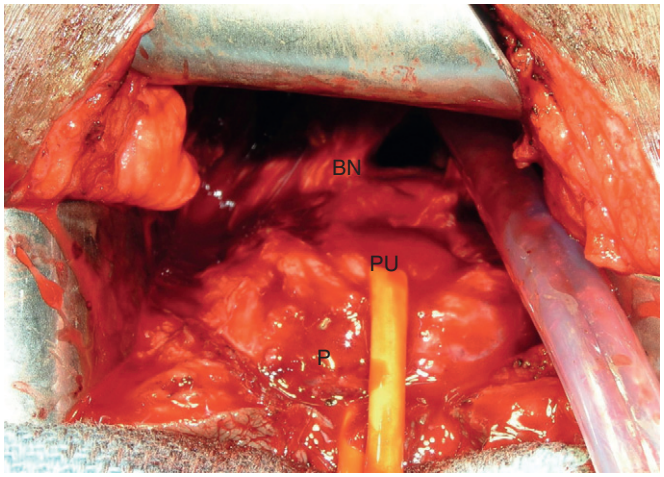


Figure 102–44. The bladder neck (BN) is incised, and a red rubber catheter is placed through the prostatic urethra (PU) and used to hold traction on the prostate (P).

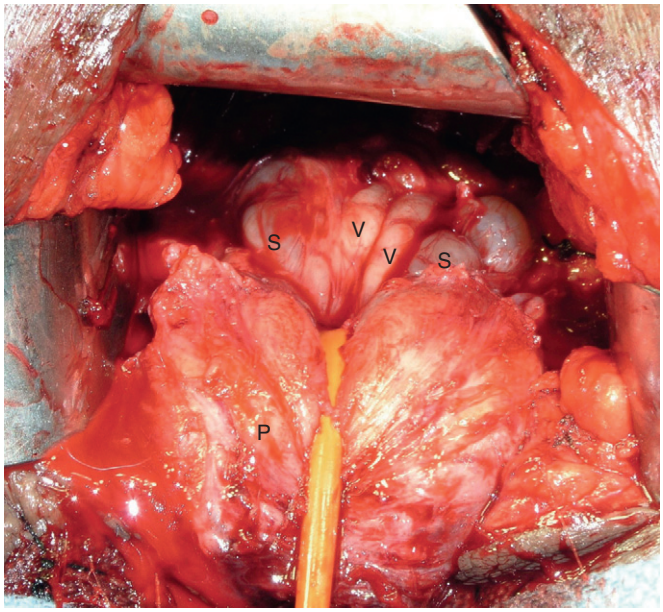


Figure 102–45. The bladder neck is freed from the prostate, and a red rubber catheter is clamped around the entirety of the prostate (P). Further dissection at the prostate base exposes the right and left vas deferens (V) and bilateral seminal vesicles (S).

the base. The 14-Fr red rubber catheter is passed through the open tips of the right-angled clamp and pulled through, and the ends are secured together with a Kelly clamp, making a loop around the whole prostate. Traction can then be applied around the entirety of the prostate toward the incision, and an appendiceal retractor may be placed under the trigone, exposing the vasa deferentia and seminal vesicles (Fig. 102–45). Each vas deferens is grasped with a right-angled clamp, bluntly dissected, and divided with electrocautery. Each seminal vesicle is similarly grasped with a right-angled clamp, bluntly dissected, and divided, ligating the seminal vesicle artery with 3-0 absorbable ties. The complete surgical specimen is thus removed and passed off for pathologic examination.

VESICOURETHRAL ANASTOMOSIS

On occasion, it may be necessary to reconstruct the posterior bladder neck with simple interrupted absorbable suture placed in a tennis racquet fashion. **The ureteral orifices should be identified, and care should be taken to prevent damage to them.**

The retractor placed at the 12-o'clock position is removed, and the red rubber catheter is placed retrograde through the penile urethra and clamped at the level of the glans so that traction can be applied to it while retaining it in the urethra. This catheter is used to identify and provide traction on the membranous urethra, enabling accurate anastomotic suture placement (Fig. 102–46). A 3-0 polyglycolic acid suture is placed from outside the anterior bladder neck at the 12-o'clock position and from inside to outside the membranous urethra at the same position and tied. While the assistant places traction on the red rubber catheter toward the contralateral side, the surgeon places sutures at the 2- and 10-o'clock positions. The red rubber catheter is removed, and a 22-Fr Silastic Foley catheter is carefully passed retrograde from the penile urethra and into the bladder. The 5-mL balloon is inflated with 15 mL of sterile water. Sutures are then placed at the 4-, 6-, and 8-o'clock positions and tied, completing the anastomosis.

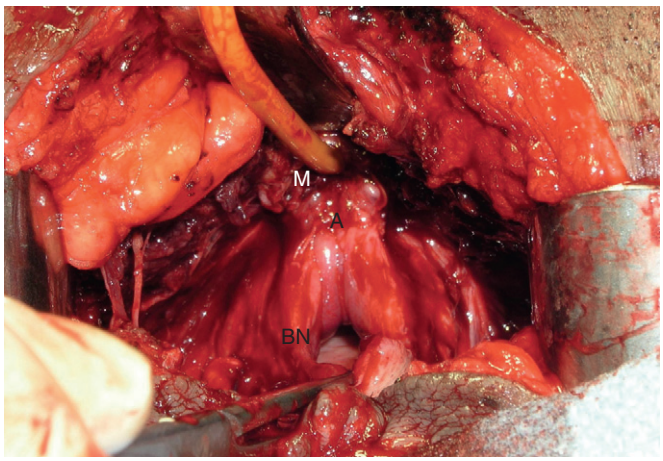


Figure 102–46. The specimen is removed from the field. A red rubber catheter emanates from the membranous urethra (M), and the bladder neck (BN) is open. The anterior aspect of the vesicourethral anastomosis (A) is complete. This exposure is unmatched with any other approach to radical prostatectomy.

Closure

The field is inspected for hemostasis and again for rectal injury. A Penrose drain is positioned near the vesicourethral anastomosis and brought through the incision. The levator ani are reapproximated with 2-0 absorbable sutures, avoiding damage to the neurovascular bundles and Penrose drain. **The central tendon and Colles fascia are reapproximated, respectively, with 2-0 absorbable sutures; care must be exercised to use superficial "bites" posteriorly during this portion of the procedure because the anterior rectal wall is only a short distance away.** The skin is closed with 4-0 absorbable suture interrupted in a vertical mattress fashion. The wound is dressed with a fluffed gauze dressing.

Postoperative Care

Patients are started on a clear liquid diet on the day of surgery and advanced to a regular diet as tolerated. Patients are encouraged to

ambulate routinely beginning the evening of surgery. Lower-extremity sequential compression devices are used while the patient is in bed. **Rectal stimulation, instrumentation, and medication insertion are prohibited.** Furthermore, gentle irrigation of the catheter is performed only when absolutely necessary. The patient is provided oral analgesia and stool softeners. All patients are maintained on a prophylactic oral antibiotic until the catheter is removed. The Penrose drain is typically removed on postoperative day 1, and the urethral catheter is removed in the office 2 to 3 weeks after surgery, although it is recognized that earlier removal is feasible. **Patients are discharged on postoperative day 1 or 2** (Ruiz-Deya et al, 2001; Harris, 2003).

PATHOLOGIC OUTCOMES

RPP demonstrates excellent pathologic outcomes consistent with those of RRP. In a retrospective review, Korman and colleagues (2002) failed to demonstrate a significant difference in the incidence of positive margins between RPP specimens and those of RRP, 22% and 16%, respectively, and each had a 4% incidence of capsular incision. Furthermore, it has been shown that there is no significant difference in the time to PSA failure between patients who underwent RPP with complete excision of the seminal vesicles and those undergoing RRP (Theodorescu et al, 1998). A review of the literature demonstrates an incidence of positive margins of 15% to 44% of radical perineal specimens, with the prostate base being the most likely positive margin (Weldon et al, 1995; Iselin et al, 1999; Lance et al, 2001; Harris, 2003; Gillitzer et al, 2004). In the 20-year experience of Paulson, consisting of 1242 consecutive radical perineal prostatectomies for clinically organ-confined prostate cancer, 18% of patients with organ- or specimen-confined disease died either with or of prostate cancer. After 5 years, PSA failure (defined by PSA level > 0.5 ng/mL) occurred in 8%, 35%, and 65% of men with organ-confined, specimen-confined, and margin-positive disease, respectively. In patients with positive margins, the median time to PSA failure was 2.4 years; however, approximately 20% of patients with positive margins did not demonstrate biochemical failure. Cancer-associated death occurred approximately 10 years after the time of PSA failure (Iselin et al, 1999).

Morbidity

As a result of short operative times and relatively low blood loss, perioperative morbidity is low. Weldon and colleagues (1997) reported that 18% of their perineal prostatectomies experienced adverse events; however, most events were not serious, and no deaths were reported. Anastomotic strictures occur in 1% to 8% and usually within the first 4 months of surgery (Frazier et al, 1992; Levy and Resnick, 1994; Weldon et al, 1997; Gillitzer et al, 2004). Lower-extremity neurapraxia, unique to the perineal approach, is often sensory and reported by Weizer and colleagues (2003) to occur in 25.5% of patients. **However, most series report an incidence of neurapraxia less than 2% and it is transient** (Weldon et al, 1997; Gillitzer et al, 2004). Keller (1999) reported a 0% incidence of neurapraxia in 284 prostatectomies and concluded that an operative time of less than 180 minutes is preventive. In experienced hands, **blood loss typically ranges from 200 to 800 mL and transfusions are necessary in approximately 5% of patients** (Weldon et al, 1997; Lance et al, 2001; Gillitzer et al, 2004). These rates of transfusion are comparable with those of laparoscopic radical prostatectomy (Guillonneau et al, 2002; Rassweiler et al, 2003). Rectal injuries have been reported to occur during 1% to 11% of radical perineal prostatectomies (Parra et al, 1994, 1996; Levy and Resnick, 1994; Lassen and Kearse, 1995; Weldon et al, 1997; Gillitzer et al, 2004). **When rectal injury is recognized at the time of surgery and repaired primarily with a two-layer closure, clinical sequelae are typically avoided.** If it is unrecognized or when it occurs in concert with postoperative urinary extravasation, a rectocutaneous or rectourethral fistula may develop. Like rectal injury, fecal incontinence occurs at a higher rate after RPP than after RRP. Bishoff and colleagues (1998) surveyed 227 patients 12 months after radical prostatectomy and reported that 18% of perineal patients had new onset of fecal incontinence compared with only 5% in the retropubic group. In a prospective longitudinal assessment by Dahm and colleagues (2003), rectal urgency was the most common complaint and symptoms resolved over time; only 2.9% of patients reported involuntary stool leakage by 12 months after RPP. The exposure of the vesicourethral anastomosis generated with the perineal approach results in excellent continence outcomes. In a series of 220 cases, with incontinence defined as daily use of pads, Weldon and colleagues (1997) reported a 95% continence rate within 1 year, with younger age being a significant predictor of improved urinary continence. Yang and colleagues (2004) confirmed these results in a prospective study. **In studies comparing the outcomes of perineal prostatectomy and RRP, urinary continence was either improved by the perineal approach or not significantly different** (Parra et al, 1994; Bishoff et al, 1998; Gray et al, 1999; Sullivan et al, 2000; Lance et al, 2001). To date, studies comparing laparoscopic radical prostatectomy and perineal prostatectomy are not available. **A review of the literature demonstrates potency in 35% to 70% of patients after nerve-sparing RPP** (Lerner et al, 1994; Harris and Thompson, 1996; Weldon et al, 1997; Ruiz-Deya et al, 2001; Harris, 2003; Rabbani, 2000). At 24 months of follow-up, Weldon and colleagues (1997) reported 73% potency in 22 patients who had a bilateral nerve-sparing procedure and 63% potency in 28 patients who had a unilateral bundle preserved, although these results were not statistically different. Lerner and colleagues (1994) demonstrated unassisted potency in 22% of nerve-spared patients and an additional 30% who achieved vaginal penetration with pharmacotherapy.

SUMMARY OF RADICAL PERINEAL PROSTATECTOMY

The use of RPP for the treatment of localized prostate cancer has been facilitated by the emphasis on the identification of prostate cancer at earlier stages. This technique provides cancer control for localized prostate cancer similar to RRP.

Key Points: Radical Perineal Prostatectomy

- There are few contraindications to RPP.
- RPP demonstrates proven long-term cancer control.
- A nerve-sparing approach may be applied to RPP with excellent potency outcomes.
- RPP is renowned for rapid convalescence and overall low morbidity.



Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter
103

Laparoscopic and Robotic-Assisted Laparoscopic Radical Prostatectomy and Pelvic Lymphadenectomy

Li-Ming Su, MD ● Joseph A. Smith, Jr., MD

Evolution of Minimally Invasive Laparoscopic Prostatectomy
Patient Selection
Instrumentation
Preoperative Preparation
Surgical Technique
Postoperative Management
Results
Complications
Laparoscopic Pelvic Lymph Node Dissection
Summary

EVOLUTION OF MINIMALLY INVASIVE LAPAROSCOPIC PROSTATECTOMY

Over a century has passed since Hugh Hampton Young (1905) performed the first open prostatectomy for carcinoma through a perineal approach. In 1947, Millin was the first to describe the retropubic approach to radical prostatectomy. In the late 1970s and early 1980s several detailed anatomic studies performed in fetal and adult cadavers provided important insights into the periprostatic anatomy, especially that of the dorsal vein complex (DVC; Reiner and Walsh, 1979), the neurovascular bundle (NVB; Walsh and Donker, 1982), and the striated urethral sphincter (Oelrich, 1980). These observations provided a more anatomic approach to radical prostatectomy with a consequent reduction in operative morbidity. Subsequently, anatomic, nerve-sparing radical prostatectomy has maintained a cardinal role in the management of localized prostate cancer for more than 2 decades.

Schuessler and colleagues (1997) performed the first successful laparoscopic radical prostatectomy (LRP) in 1997. In their series of nine patients, operative duration was lengthy (8 to 11 hours) and the length of stay was 7.3 days on average. Although the authors concluded that cure rates with LRP may be comparable with open surgery, they could not define any significant advantages. As a result, LRP was not immediately widely adopted in the field of urology.

Advances in task-specific surgical instrumentation, optics, digital video equipment, and computer and robotic technology opened a new frontier for minimally invasive laparoscopic prostatectomy. These advances led urologists to revisit LRP, spearheaded by two centers in France that reported on their techniques and early results (Abbou et al, 2000; Guillonneau and Vallancien, 2000). Their stepwise approach to LRP proved to be both reproducible and teachable, although the learning curve remained challenging. Operative times were in a more acceptable 4- to 5-hour range with reported overall positive margin rates of 15% to 28%. Both groups had good continence and potency rates. This work rekindled worldwide interest in LRP, and in the ensuing years surgeons at a number of centers throughout the world acquired the skills and experience to perform LRP. However, advanced laparoscopic skills are necessary to perform a proficient LRP, especially for suturing of the vesicourethral anastomosis.

Computer-assisted surgical devices using mechanical robotic arms were adopted for use with radical prostatectomy in part due to their ability to aid the surgeon in performing the challenging task of laparoscopic suturing. One such device, the da Vinci Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA) has become the dominant robotic surgical device in the field of urology. By incorporating sophisticated wristed technology at the terminal ends of the robotic instruments, a surgeon can operate, dissect, and suture with the facility of a human wrist. In addition, a 10× magnified, three-dimensional image is displayed as a result of a specialized stereo endoscope lens and camera, providing the surgeon with an unprecedented view of the operative field and periprostatic anatomy. The first-generation robotic platform, originally launched in the United States in 2000, allows for the surgeon to control three robotic arms simultaneously, two arms for robotic instrumentation and a third arm that controls the stereo endoscope and camera. The newer da Vinci S system, made available in 2006, incorporates high-definition image capability with an additional fourth robotic arm for grasping and retraction. Finally the latest-generation robot, the da Vinci Si HD, which was

launched in 2009, offers two separate surgeon consoles allowing two surgeons to operate simultaneously, providing an opportunity for improved operative efficiency and teaching.

There has been an almost revolutionary introduction of robotic surgery into the surgical management of carcinoma of the prostate. Since its introduction into the United States in 2000, robotic-assisted laparoscopic prostatectomy (RALP) has rapidly grown in popularity with surgeons and patients alike. With rapid dissemination of this robotic platform into large tertiary referral centers and community hospitals throughout the country, it is now estimated that RALP is the dominant surgical approach for radical prostatectomy in the United States. In addition, robotic technology is rapidly expanding throughout centers worldwide.

There have been considerable and ongoing debates about the merits of RALP versus an open surgical approach by either the retropubic or perineal route. Issues with equipment expense, the learning curve for the surgeon and surgical team, and patient-related outcomes remain. **Nonetheless, RALP has virtually replaced LRP in the United States, and the overwhelming majority of new surgeons have adopted RALP as their preferred surgical approach for prostate cancer.** Thus it seems virtually certain that the use of RALP will continue to proliferate.

This chapter highlights some of the surgical advances for both LRP and RALP. Further, technical details for the surgical dissection and currently available data on oncologic, as well as functional outcomes, are presented. Finally, the authors review the role of pelvic lymph node dissection (PLND) in conjunction with minimally invasive approaches to prostatectomy along with technical considerations and potential complications.

PATIENT SELECTION

Indications and Contraindications

The indications for LRP and RALP are identical to that for open surgery (i.e., patients with ≤ clinical stage T2 with no evidence of metastasis either clinically or radiographically [computed tomography (CT) and bone scan]). Absolute contraindications to minimally invasive laparoscopic prostatectomy include uncorrectable bleeding diatheses and the inability to undergo general anesthesia because of severe cardiopulmonary compromise. Patients who have received neoadjuvant hormonal therapy or who have a history of prior complex lower abdominal and pelvic surgery such as partial colectomy, inguinal mesh herniorrhaphy, or prior transurethral resection of the prostate (TURP) pose a greater technical challenge due to distortion of normal anatomy and adhesions but are not an absolute contraindication to LRP and RALP. In those patients with a history of prior laparoscopic extraperitoneal mesh herniorrhaphy, a transperitoneal approach may be preferred over the extraperitoneal approach because dense adhesions in the retropubic space often make attempts at initial access to the space of Retzius challenging.

Morbidly obese patients pose additional challenges due to the potential respiratory compromise encountered when placing these patients in a steep Trendelenburg position, as well as the relatively limited working space and limitations of trocar size and instrumentation length, especially with LRP. Patients with large prostate volumes (e.g., >70 g) are often met with longer operative times, blood loss, and hospital stay than those with smaller glands; however, long-term urinary outcomes appear comparable (Levinson et al, 2008, 2009; Link et al, 2008). Salvage surgery after failure of primary treatment (e.g., radiation, brachytherapy, cryotherapy, high-intensity focused ultrasound) has been successfully reported in properly selected patients but should be approached with caution due to the attendant risks and complications (Kaouk, 2008; Boris et al, 2009). Due to the effects of prior local radiotherapy or ablation, the tissue planes surrounding the prostate and especially between the posterior prostate and anterior rectum are often fibrotic and obliterated, increasing the risk of inadvertent entry into the rectum during salvage surgery. As a result, patients undergoing salvage prostatectomy need to be counseled on the potential risk of rectal injury in addition to the higher incidence of impotence and incontinence as compared with primary surgery. **It is strongly advised that these more complex patient scenarios be avoided in a surgeon's early experience with LRP and RALP; however, these patient features are not by themselves absolute contraindications for a minimally invasive approach to prostatectomy** (Brown et al, 2005a; Erdogru et al, 2005; Singh et al, 2005; Stolzenburg et al, 2005).

INSTRUMENTATION

Instrumentation required for LRP and RALP is dependent on the chosen approach and model of da Vinci system being used (i.e., three- vs. four-arm robot) in the case of RALP. A list of suggested instrumentation for LRP and RALP are listed in Table 103–1. For LRP, the AESOP 3000 robotic arm (Intuitive Surgical, Inc., Sunnyvale, CA) may be used to stabilize and control the laparoscopic lens and camera by hand-held remote control, voice activation, or foot pedal control. Alternatively, a surgical assistant can be used for this purpose. During RALP, the use of the da Vinci S or Si HD system allows the surgeon to control a total of four robotic arms with one being the endoscope as compared with only three robotic arms with the first-generation standard robotic platform. The surgeon generally begins the operation by using a 0-degree stereo endoscope and controlling a grasping forceps in the left robotic arm (such as the Maryland curved bipolar forceps or plasma kinetic dissector) and the curved monopolar scissors in the right robotic arm. The fourth robotic arm controls the ProGrasp forceps (Intuitive Surgical, Inc., Sunnyvale, CA), a large atraumatic blunt grasper for retraction and exposure of tissues. The surgeons then toggle between control of any two of the three working robotic arms at any given time to allow for greater autonomy and to achieve optimal exposure and dissection.

PREOPERATIVE PREPARATION

Bowel Preparation

As with open surgery, a preoperative mechanical bowel preparation may be used. Most commonly, one bottle of citrate of magnesium is taken the day before surgery and the patient's diet is limited to clear liquids. An enema administered the morning of surgery is recommended by some surgeons. A broad-spectrum antibiotic such as cefazolin is administered intravenously 30 minutes before surgery.

Informed Consent

In addition to bleeding, transfusion, and infection, patients undergoing LRP and RALP must be aware of the potential for conversion to open surgery. As with open surgery, patients must be counseled on the risk of impotence, incontinence, incisional hernia, and adjacent organ injury (e.g., ureter, rectum, bladder, small bowel).

Table 103–1.

Suggested Instrumentation for LRP and RALP

Laparoscopic Radical Prostatectomy
AESOP 3000 Robotic arm, if available (Intuitive Surgical, Sunnyvale, CA)
Monopolar electrocautery scissors
Monopolar electrocautery hook device
Bipolar forceps
Ultrasonic shears
Maryland dissector
60-degree and 90-degree fine-tipped (0.8-mm) dissectors for neurovascular bundle preservation
Laparoscopic needle drivers (2)
Suction-irrigation device
10-mm, 0-degree and 30-degree laparoscope lens
Veress needle
5-mm trocars (3)
12-mm trocars (2)
20-Fr van Buren urethral sound
18-Fr urethral catheter
Small and medium-large Hem-o-Lok clips (Teleflex Medical, Research Triangle Park, NC)
0 polyglactin suture (GS21) for dorsal venous complex
2-0 polydioxanone suture for posterior reconstruction
3-0 poliglecaprone (Monocryl) double-armed suture for anastomosis
Robotic-Assisted Laparoscopic Prostatectomy
da Vinci S or Si Surgical System (Intuitive Surgical, Sunnyvale, CA)
Endowrist Maryland bipolar forceps or PK dissector (Intuitive Surgical, Sunnyvale, CA)
Endowrist curved monopolar scissors (Intuitive Surgical, Sunnyvale, CA)
Endowrist ProGrasp forceps (Intuitive Surgical, Sunnyvale, CA)
Endowrist needle drivers (2) (Intuitive Surgical, Sunnyvale, CA)
InSite Vision System with 0-degree and 30-degree lens (Intuitive Surgical, Sunnyvale, CA)
12-mm trocars (2)
8-mm metal robotic trocars (3 if using a fourth robotic arm)
18-Fr urethral catheter
Small and medium-large Hem-o-Lok clips (Teleflex Medical, Research Triangle Park, NC)
0 polydioxanone suture for dorsal venous complex
2-0 polydioxanone suture for posterior reconstruction
3-0 Monocryl double-armed suture for anastomosis

LRP, laparoscopic radical prostatectomy; RALP, robotic-assisted laparoscopic prostatectomy.

The risks of general anesthesia must also be presented to the patient because LRP and RALP cannot be performed under regional anesthesia. In addition, it may be appropriate for the surgeon to discuss his or her overall operative experience with radical prostatectomy and provide a realistic forecast of cancer control, as well as return to normal urinary and sexual function on the basis of each patient's unique characteristics.

Operating Room Personnel

LRP and RALP require that the surgical team including the scrub technician, circulating nurse, and surgical assistant(s) be fully trained and skilled in the instrumentation, operative setup, and technical steps of these minimally invasive techniques. Only one skilled assistant is generally required for these procedures, but a second assistant may be used if available to provide retraction of tissues. The scrub technician is an integral part of the operative team and must be versed in the wide array of laparoscopic and robotic instruments that may be used to accomplish this procedure. **For RALP, it is important for the tableside assistant to have adequate training in basic laparoscopy and the mechanics, setup, and troubleshooting of the robotic system.** Typical operating room equipment and setup for RALP and LRP are shown in Figure 103–1.

Patient Positioning

After induction of general endotracheal anesthesia, the patient is placed in a supine position in steep Trendelenburg with arms tucked and padded at the sides. Sequential compression stocking devices are placed on both legs and activated. The patient's legs are spread apart and supported by spreader bars to allow for access to the rectum and perineum. Alternatively, the patient's legs may be placed in stirrups in the low lithotomy position. The patient is then secured to the table using tape and egg-crate padding. An orogastric tube and urethral catheter are placed to decompress the stomach and bladder, respectively.

Anesthesia Considerations

Both LRP and RALP require general anesthesia. Because the patient's arms are tucked at the side and difficult to access, establishing accurate pulse oximetry, blood pressure cuff placement, and intravenous access is critical before patient positioning. The anesthesiologist must be aware of the potential consequences of CO_2 insufflation and pneumoperitoneum including oliguria and hypercarbia. Prompt adjustments in minute and tidal volumes may be required by the anesthesiologist in the event of rising end-tidal CO_2 levels and hypercarbia (Meininger et al, 2004). Adjustments in CO_2 insufflation pressures may also be required by the surgeon to reduce the risk of continued hypercarbia. Taken together, maintaining good communication between the surgeon and the anesthesia team is important during these procedures.

SURGICAL TECHNIQUE

Robotic-Assisted versus Pure Laparoscopic Approach

Most of the principles and considerations for the surgical dissection are similar regardless of whether a pure laparoscopic or robotic-assisted approach is used. For RALP, the da Vinci Surgical System is a master/slave system with three components: surgical robot (also called the patient side cart), surgeon console, and video cart (Fig. 103–2). For the purpose of this chapter and for simplicity, the technique using the four-arm da Vinci S system is described. The robot is docked at the foot of the operating table between the patient's legs. The tableside assistant is responsible for docking/undocking the robot, suction-irrigation, retraction of tissues, passing sutures into the operative field, and robotic instrument changes. The surgeon is seated at the surgeon console, which provides a superb three-dimensional, 10× magnified, high-definition operative view and allows for the surgeon to have complete control of all camera movements and three additional robotic arms. The surgeon's thumb and index fingers are inserted into master controls that allow natural hand

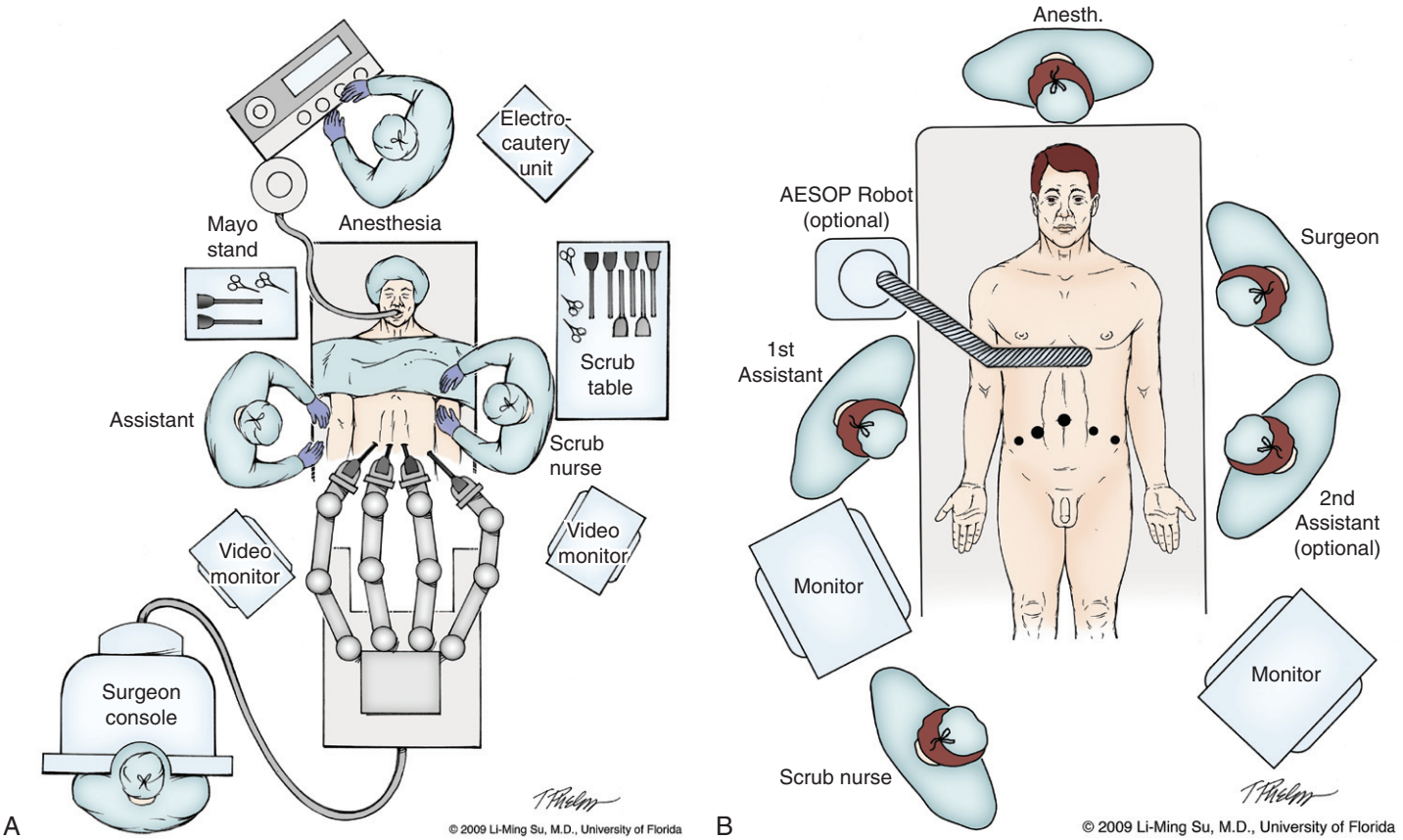


Figure 103–1. Operating room equipment and setup for robotic-assisted **(A)** and pure laparoscopic radical prostatectomy **(B)**. (Copyright Li-Ming Su, MD, University of Florida, 2009.)



Figure 103–2. Three components of the da Vinci S Surgical System (Copyright 2009, Intuitive Surgical, Inc.)—the surgeon console, patient side cart, and video cart.

and wrist movements to be precisely replicated by wristed instruments at the terminal ends of the robotic arms in real time.

Highly skilled laparoscopic surgeons may find the robotic technology unnecessary and discover that they are equally as facile with pure laparoscopic suturing and dissection as with the robot (Guillonneau, 2005). **Most surgeons, however, feel that the robotic technology significantly facilitates suturing of the vesicourethral anastomosis and aids in other aspects of the surgical dissection such as achieving the critical angles of dissection required to optimize cavernous nerve preservation.**

Other than setup of the operating room and surgical fields, there is little difference in the surgical technique between LRP and RALP. In general, the following discussion of technique and the pros and cons of various maneuvers and approaches apply to either surgical approach.

Transperitoneal Approach

The most common approach to LRP and RALP is the transperitoneal anterior approach in which following transperitoneal access and insufflation, the space of Retzius is immediately entered and the prostate gland, seminal vesicle, and vasa are approached and dissected from an anterior approach. This is in contrast to the transperitoneal retrovesical approach in which the seminal vesicles and vasa are initially approached and completely dissected behind the bladder near the cul-de-sac. The transperitoneal access and approaches are favored by most surgeons over the extraperitoneal approach due to the greater working space and familiar landmarks of the pelvis and its contents. For the purposes of this chapter, the transperitoneal anterior approach will be primarily described with brief mention about the extraperitoneal approach.

Abdominal Access, Insufflation, and Trocar Placement. For a transperitoneal approach, pneumoperitoneum is established using either a Veress needle inserted at the base of the umbilicus or an open Hasson technique. Following initial trocar placement, CO_2 insufflation pressure in general is maintained between 12 and 15 mm Hg. Secondary trocars are then placed under laparoscopic view. For RALP, an example of a trocar configuration is shown in Figure 103–3A. A 12-mm trocar is initially placed at or slightly above the umbilicus for insertion of the stereo endoscope. In a morbidly obese or very tall patient, infraumbilical camera placement may be preferable. Three 8-mm metal robotic trocars are used by the working robotic arms of the surgeon while the assistant provides retraction, suction, and irrigation and passes clips and sutures via the 12-mm and 5-mm trocars placed along the patient's right side. The surgeon controls camera movement by depressing a foot pedal and using brief, simultaneous arm movements to affect camera positioning and rotation. Endoscopes with either angled (30-degree) or straight-ahead (0-degree) viewing are available and interchangeable at various portions of the procedure. In general, most surgeons use the 0-degree endoscope lens throughout the operation; however, some surgeons prefer to switch to the 30-degree down lens when approaching the bladder neck, NVBs, and apical dissection. Figure 103–3B depicts the trocar configuration for LRP. The surgeon stands at the patient's left side and operates through the two pararectus trocars while one or two assistants use the lateralmost trocars. The endoscope is held and controlled by an AESOP robotic arm or surgical assistant through the umbilical trocar.

Extraperitoneal Approach. For an extraperitoneal approach, a 1.5-cm incision is made at the level of the umbilicus and dissection is carried out down through the anterior rectus sheath. Using blunt finger dissection, a space is created immediately anterior to the posterior rectus sheath and underlying peritoneum. A trocar-mounted balloon dilator device (PDB Balloon, Covidien Autosuture, Mansfield, MA) is inserted into the preperitoneal space anterior to the posterior rectus sheath and advanced down to the pubis along the midline. Using a 0-degree, 10-mm endoscope inserted through the balloon trocar, approximately 500 mL of air is inflated to develop the space of Retzius under laparoscopic view (Fig. 103–4). Secondary trocars are then inserted as described previously under laparoscopic view. The operation then proceeds in the exact manner to that of the transperitoneal anterior approach.

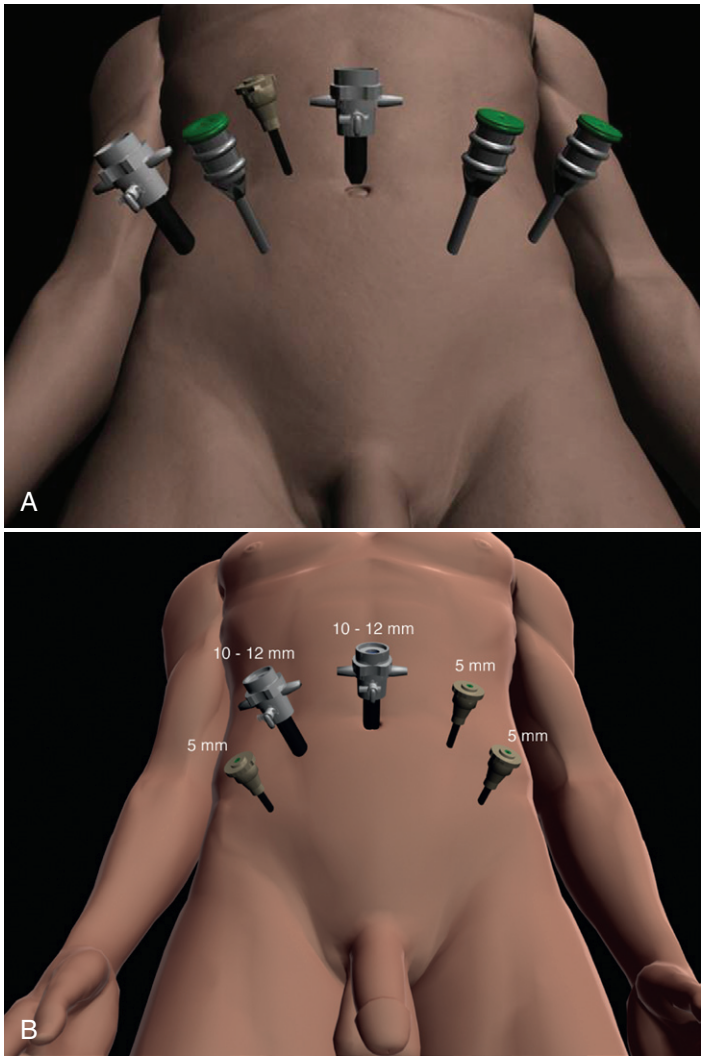


Figure 103–3. Trocar configuration for robotic-assisted laparoscopic prostatectomy **(A)** and laparoscopic radical prostatectomy **(B)**.

Pros and Cons of Extraperitoneal versus Transperitoneal Approach. In a retrospective comparison between extraperitoneal versus transperitoneal LRP, Hoznek and colleagues (2003) found that the mean operative time was shorter with the extraperitoneal approach (169.6 vs. 224.2 minutes, $P < .001$) with the greatest time saved during access to the space of Retzius. They suggested that time to full diet was less with the extraperitoneal versus the transperitoneal LRP approach (1.6 vs. 2.6 days, $P = .002$) because the peritoneum had not been violated and postoperative ileus was minimized. Eden and colleagues (2004) found a statistical significant advantage in operative time, hospital stay, and return of early

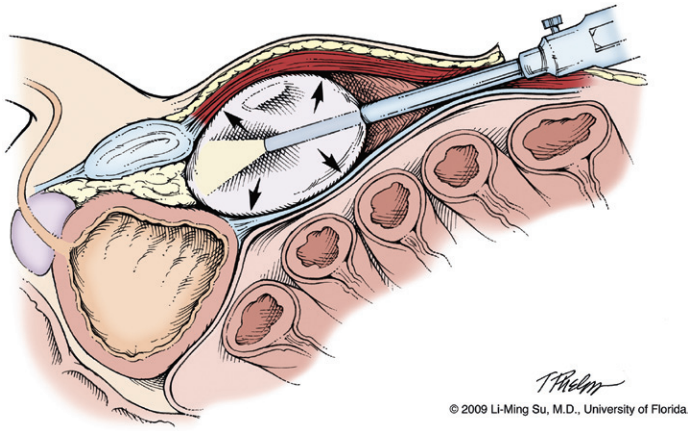


Figure 103–4. Creation of working space for extraperitoneal pure laparoscopic or robotic-assisted radical prostatectomy using a trocar-mounted balloon dilator device. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

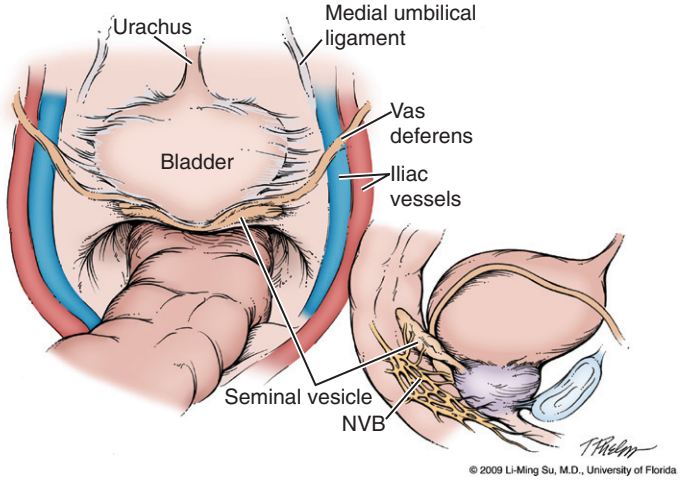


Figure 103–5. Initial transperitoneal view detailing the relevant landmarks within the male pelvis. NVB, neurovascular bundle. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

continence favoring patients undergoing extraperitoneal versus transperitoneal LRP, postulating that earlier return to urinary control may be secondary to less bladder dissection and, perhaps, less bladder dysfunction as compared with transperitoneal LRP. **Most studies, however, have found little or no difference in operative time and perioperative outcomes between transperitoneal and extraperitoneal approaches** (Cathelineau et al, 2004a; Erdogru et al, 2004; Brown et al, 2005b; Atug et al, 2006).

With an extraperitoneal approach, the simultaneous laparoscopic management of concurrent inguinal hernias using prosthetic mesh is feasible (Stolzenburg et al, 2003). Simultaneous inguinal herniorrhaphy has also been reported during transperitoneal LRP (Allaf et al, 2003); however, proper coverage of the mesh prosthesis is necessary using peritoneal flaps, omentum, or a second absorbable mesh to reduce the risk of direct contact between the mesh and bowel with subsequent fistula. The extraperitoneal technique may be preferable in patients with previous extensive abdominal surgery or morbid obesity. **With the extraperitoneal approach, the peritoneum acts as a natural barrier, minimizing the potential for bowel injury and preventing the bowels from falling into the operative field and obscuring the surgeon's view. Furthermore, this approach helps to confine any urine leak that may occur from the vesicourethral anastomosis within the extraperitoneal space. One limitation with the extraperitoneal approach is the reduced working space as compared with the relatively larger working space of the peritoneal cavity gained with transperitoneal access.** This is especially relevant when a well-meaning assistant attempts to clear the operative field of blood or smoke. Suctioning can evacuate CO_2 gas and rapidly collapse the already limited extraperitoneal working space, thus significantly compromising visualization. A second limitation to the extraperitoneal approach is in patients with a prior history of laparoscopic extraperitoneal mesh herniorrhaphy because the retropubic space is often obliterated, making attempts at extraperitoneal access challenging. Lastly, higher CO_2 absorption has been reported with extraperitoneal versus transperitoneal insufflation, requiring a higher minute volume to compensate for hypercarbia and associated acidosis (Meininger et al, 2004). **Overall, whether to use an extraperitoneal or transperitoneal approach for LRP or RALP is largely a matter of surgeon preference and experience and there is no consistently demonstrated advantage for either approach.**

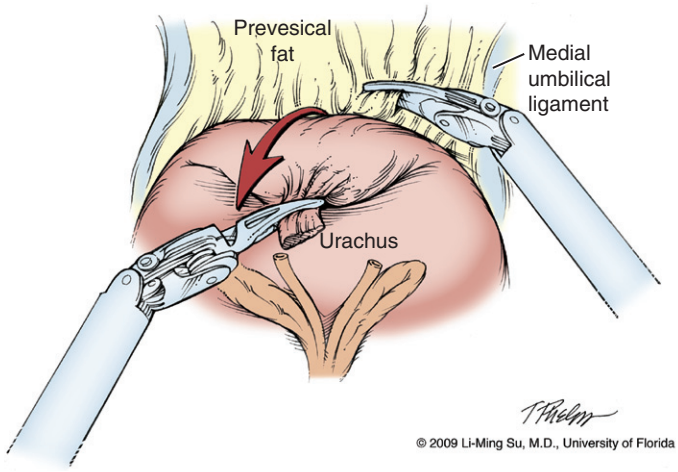


Figure 103–6. Division of urachus and entry into the space of Retzius. Cephalad traction on the urachus with the left hand helps to identify the fatty alveolar tissue immediately anterior to the bladder, which marks the proper plane of dissection. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

Developing the Space of Retzius. Following abdominal access and trocar placement for the transperitoneal anterior approach, the pelvic contents are inspected (Fig. 103–5) and adhesions are lysed if present. The initial step is entry and development of the space of Retzius. The bladder is dissected from the anterior abdominal wall by dividing the urachus high above the bladder and incising the peritoneum bilaterally immediately lateral to the medial umbilical ligaments using monopolar electrocautery. The presence of prevesical fatty alveolar tissue confirms the proper plane of dissection. Applying posterior and cephalad traction on the urachus, the retropubic space is rapidly developed with a combination of blunt and sharp dissection along the relatively avascular plane within the space of Retzius (Fig. 103–6). **Lateral dissection of the bladder is carried out down toward the crossing of the median umbilical ligament and vas deferens in order to ensure optimal mobility of the bladder**

and to minimize future tension at the vesicourethral anastomosis. The fat overlying the prostate is removed using sharp dissection and electrocautery as needed, and the superficial branches of the DVC coagulated using bipolar electrocautery.

At this point, visible landmarks include the anterior aspect of the bladder and prostate, puboprostatic ligaments, endopelvic fascia, and pubis (Fig. 103–7). The endopelvic fascia and puboprostatic ligaments are sharply divided, exposing levator muscle fibers attached to the lateral and apical portions of the prostate. These fibers are meticulously and bluntly dissected from the surface of the prostate exposing the deep DVC and urethra at their confluence with the apex of the prostate. Electrocautery is avoided if possible to minimize thermal damage to the external sphincter and nearby NVBs.

Accessory pudendal arteries traveling longitudinally along the anteromedial aspect of the prostate are easily recognized during LRP and RALP. Attempt at preservation of these arteries is important for erectile function because in some men these arteries may be the dominant source of arterial blood supply to the corpora cavernosa (Nehra et al, 2008). These accessory arteries can usually be preserved, although separation of the artery from the prostatic apex can be somewhat challenging. Most commonly, though, careful and meticulous dissection allows enough mobilization of the artery away from the deep DVC and prostatic apex that both good anatomic dissection of the prostatic apex and preservation of the accessory vessel are feasible.

Ligation of the Deep Dorsal Venous Complex. As with open surgery, different methods have been described for control of the DVC. **A common observation, though, is that the profuse bleeding, which is sometimes encountered during open surgery, is not usually problematic because of the tamponade effect on venous bleeding offered by the pneumoperitoneum.** In fact, some techniques involve simple cutting of the DVC with or without the use of electrocautery and placement of a suture only if necessary. Typically, there are one or two small arteries in the DVC. Most described techniques use placement of an absorbable suture for hemostasis before initiation of the surgical dissection of the prostate. During RALP, the Pro-Grasp forceps can be used for fixed cephalad retraction of the prostate and bladder to achieve optimal exposure of the DVC and prostatic apex before DVC ligation. Similar retraction can be applied by the surgical assistant during LRP. The deep DVC is suture ligated using a 0-polydioxanone suture or polyglactin suture as close to the pubis and as far from the prostatic apex as possible (Fig. 103–8). **Securing the DVC as far away from the prostatic apex as possible can help minimize iatrogenic entry into the prostatic apex during later division of the DVC.** The needle is passed beneath the DVC and anterior to the urethra. An alternative method to DVC ligation is the use a laparoscopic linear stapling device, which ligates and divides the DVC all in one step (Ahlering et al, 2004b; Nguyen et al, 2008). Regardless of the method used, it is important to avoid damage to the anterior urethral sphincter muscle from placing the sutures or staples too deep. With most techniques, the DVC is not divided until later in the operation and immediately before prostatic apical dissection and division of the urethra. A back-bleeding suture may be placed along the anterior base of the prostate to help identify the contour of the prostate and to aid in subsequent bladder neck identification and transection.

Bladder Neck Identification and Transection. Proper identification of the bladder neck during RALP and LRP can be initially challenging due to the lack of tactile feedback in delineating the precise margin between the prostate and bladder. **Several maneuvers are helpful in identifying the proper plane of dissection and in minimizing inadvertent entry into the prostate. First, visual identification of the point of transition of the prevesical fat to the anterior prostate can serve as a guide. Second, intermittent and repetitive**

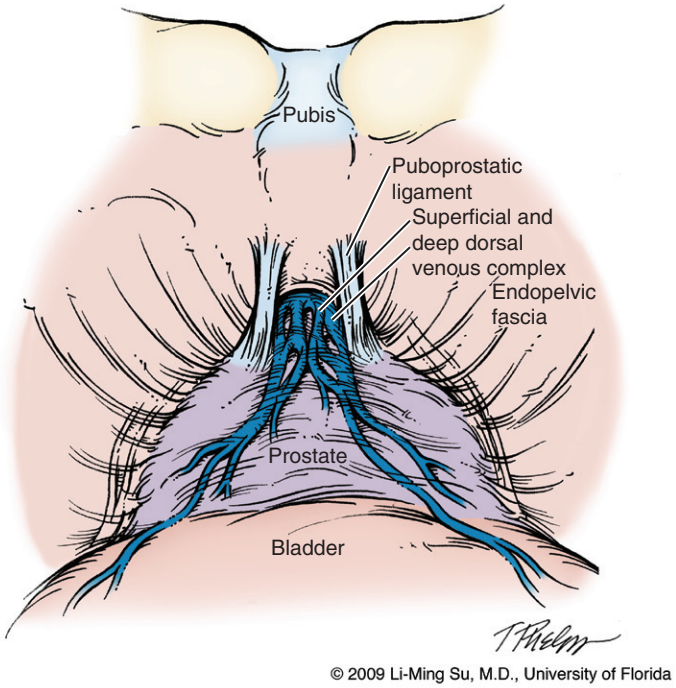


Figure 103–7. Retropubic view of the bladder and prostate following entry into the space of Retzius. The fatty tissue overlying the anterior aspect of the prostate has been removed, exposing the puboprostatic ligaments, superficial and deep dorsal venous complex, and endopelvic fascia. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

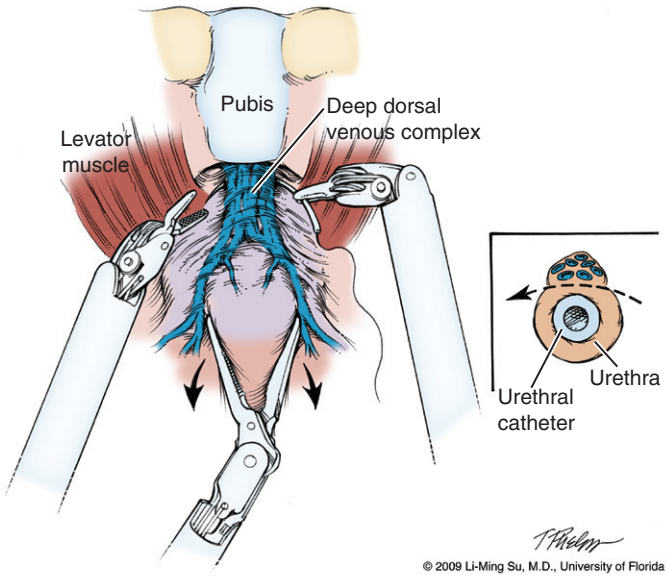


Figure 103–8. Ligation of the deep dorsal venous complex. A suture is passed from right to left, ligating the dorsal vein as distal as possible from the apex. Inset demonstrates the proper passage of the needle immediately anterior to the urethra. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

caudal retraction of the urethral catheter balloon can help identify and confirm the transition between bladder neck and prostate. Third, using a forceps to grasp and retract the dome of the bladder in a cephalad direction results in "tenting" of the bladder neck at its attachment to the prostate. Lastly, further confirmation of this margin between the bladder and prostate is made by a bimanual "palpation" or "pinch" of the bladder neck using the tips of two robotic or laparoscopic instruments.

The anterior bladder is divided horizontally using monopolar electrocautery along the midline until the urethral catheter is identified. **The anterior bladder neck incision should not be carried too laterally because branches of the bladder pedicle are often encountered, resulting in unwanted bleeding.** The balloon is decompressed, and the tip of the urethral catheter is brought through the anterior bladder neck opening and lifted anteriorly with the assistant applying counter traction externally at the penile meatus to suspend the prostate.

The posterior bladder neck is inspected for the presence of a median lobe and to locate the ureteral orifices. If a vertical drop-off of the posterior bladder neck mucosa is noted, this would suggest the absence of a median lobe. Alternatively, if a mass effect from a large median lobe is identified, further exposure may be required to visualize beneath the protruding median lobe and identify the posterior bladder neck. The median lobe is lifted anteriorly using either the ProGrasp forceps or the surgical assistant. **The posterior bladder neck is horizontally divided with monopolar electrocautery, staying along the midline to avoid bleeding from the lateral pedicles** (Fig. 103–9). **Dissection is carried out in a 45-degree downward angle to avoid entry into the base of the prostate, as well as creating a buttonhole in the posterior wall of the bladder.** In case of a prior TURP, the bladder neck margin is less evident and often distorted as a result of prior resection and scarring. Careful inspection is made of the posterior bladder neck paying specific attention to the location of the ureteral orifices because they are often found close to the posterior bladder neck margin. Attempt at bladder neck sparing should be avoided in post-TURP and median lobe cases. When in doubt, the posterior bladder neck should be divided slightly more proximally in these particular cases so as to avoid inadvertent entry into the prostate gland.

Dissection of the Seminal Vesicles and Vasa Deferentia. Following bladder neck transection, the seminal vesicles and vasa deferentia are individually identified, dissected, and divided, avoiding electrocautery if possible to prevent damage to the nearby NVB (Fig. 103–10). One unique distinction between the transperitoneal anterior and retrovesical approach is in dissection of the seminal vesicles and vasa deferentia. During a transperitoneal retrovesical approach, the initial step of the operation is complete dissection of the vasa deferentia and seminal vesicles deep within the cul-de-sac. Following abdominal access, the vasa are dissected from lateral to medial toward their confluence at the ejaculatory ducts. The seminal vesicles are found immediately lateral to the vasa and are dissected free from the nearby NVB using hemoclips while avoiding the use of thermal energy (Fig. 103–11). With the dissection of the seminal vesicles and vasa now completed, once the bladder neck is divided from the prostate, these structures are simply grasped and brought through the opening. **This retrovesical approach to the seminal vesicles and vasa deferentia is particularly useful in cases of a median lobe where identification and dissection of these structures by the anterior approach may be more challenging due to the protruding median lobe.**

Development of the Plane between the Prostate and Rectum. Separation of the posterior prostate from the anterior rectal wall is a key surgical maneuver to avoid rectal injury but also to permit adequate identification of the prostatic pedicles and establish the medial border of the NVB. Development of this plane in an antegrade fashion is a

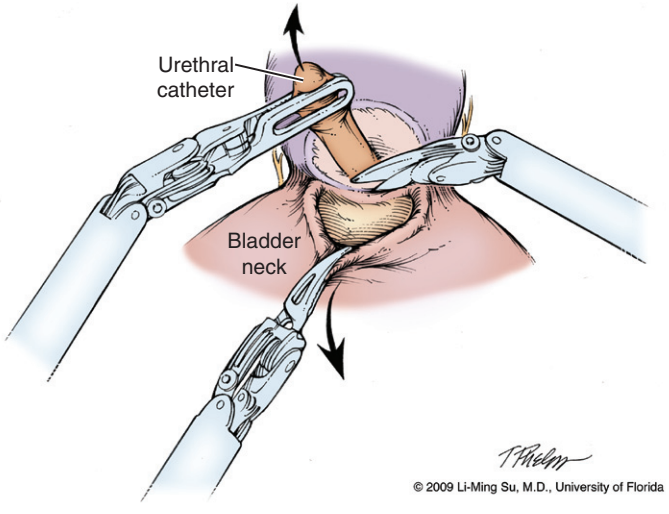


Figure 103–9. Division of the posterior bladder neck. An assistant or ProGrasp forceps is used to grasp and elevate the urethral catheter anteriorly, providing exposure to the posterior bladder neck. Dissection is carried out along the midline, avoiding bleeding from the lateral pedicles. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

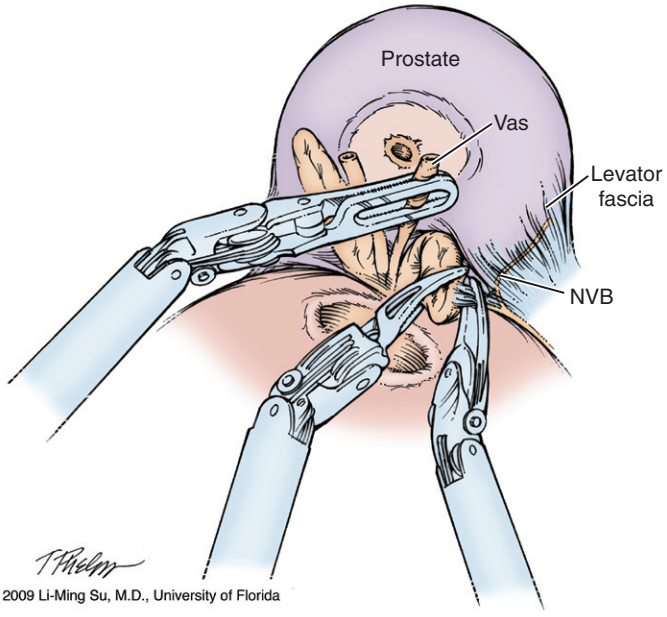


Figure 103–10. Dissection of seminal vesicles and vasa deferentia via the transperitoneal anterior approach. The seminal vesicles and vasa are identified and dissected within the opening created between the posterior bladder neck and prostate following division of the bladder neck. Hemoclips are used in lieu of electrocautery to avoid thermal injury to the nearby neurovascular bundles (NVB). (Copyright Li-Ming Su, MD, University of Florida, 2009.)

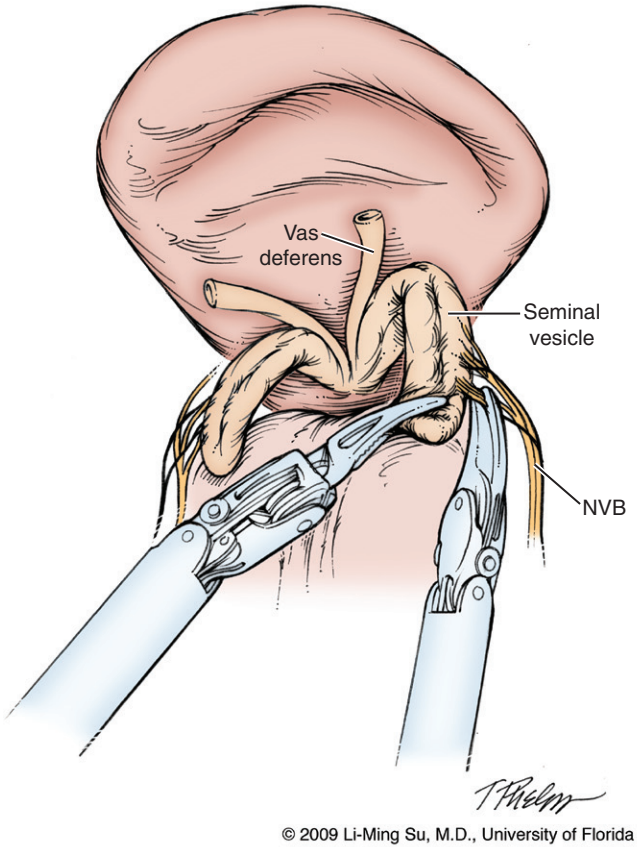


Figure 103–11. Dissection of the seminal vesicles and vasa deferentia via the transperitoneal retrovesical approach. The vasa and seminal vesicles are identified as the initial step in this approach deep within the retrovesical space. The neurovascular bundles (NVB) are dissected off of the seminal vesicles in an antegrade direction from the tip toward the base using hemoclips. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

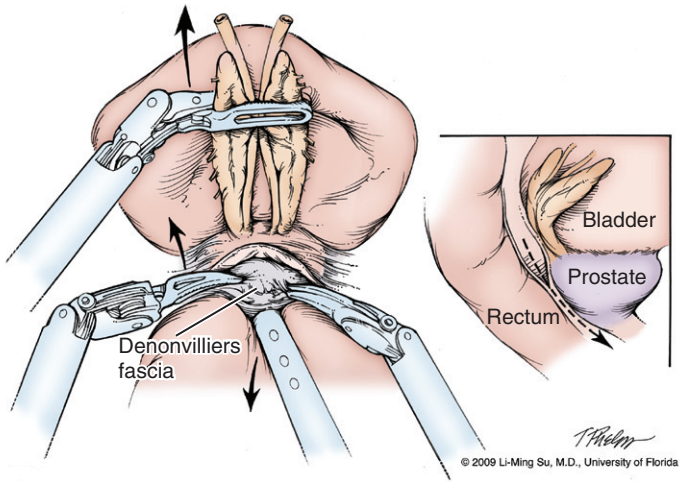


Figure 103–12. Development of the plane between the prostate and rectum. As the assistant or ProGrasp forceps is used to apply anterior traction on the seminal vesicles and vasa deferentia and downward traction on the rectum, a transverse incision is made in Denonvilliers fascia below the seminal vesicles, and blunt dissection is used to develop a plane between the posterior prostate and the rectum. Inset demonstrates the direction of dissection toward the prostatic apex. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

maneuver often unfamiliar to surgeons experienced with open surgery but one that is rapidly adaptable to laparoscopic and robotic approaches. Anterior retraction of the vasa deferentia and seminal vesicles by either a surgical assistant or the robotic ProGrasp forceps helps with identification of the proper plane for the initial dissection (Fig. 103–12).

Denonvilliers fascia is an inferior extension of the peritoneal cul-de-sac that lies between the prostate and rectum. With an intrafascial or interfascial dissection, Denonvilliers fascia can be separated from the posterior prostate by careful blunt and sharp dissection. The separation can be carried all the way to the prostatic apex and laterally to the prostatic pedicle. The proper surgical plane is relatively avascular. **When a wider margin of tissue is desired on the posterior prostate such as in cases of palpable disease, Denonvilliers fascia should be sharply incised just posterior to the junction of the seminal vesicle and the prostate. This allows immediate entry into the anterior perirectal fat plane of dissection. Good visualization can be achieved as the dissection proceeds distally toward the apex staying between Denonvilliers fascia anteriorly and the anterior propria fascia of the rectum posteriorly.**

Substantial bleeding typically suggests that the dissection may be too close to the prostate. If difficulty is encountered in establishing the proper plane of dissection, a new attempt can be directed to one side or the other of the initial entry point. Once the proper plane is entered, the dissection characteristically progresses rather smoothly. The rectal wall should be mobilized far enough laterally that there is sufficient separation for dissection of the NVB and prostatic apex.

Prostatic Pedicle Control. Various methods have been described for control of the prostatic pedicle. Some techniques use pure electrocautery, either monopolar or bipolar. **Because of the propagation of thermal energy through tissue, which may result in damage to the nearby NVB, limitation of the use of electrocautery is advised even in the prostatic pedicle.** Locking polymer Hem-o-Lok clips (Teleflex Medical, Research Triangle Park, NC) are commonly employed, but engagement of the clipping mechanism does require good delineation and thinning of the pedicle tissue so that the clipping mechanism will engage. This is best facilitated by adequate mobilization of the rectum and lateral prostate for identification of the prostatic pedicle. Application of a bulldog clamp to the pedicle with subsequent suturing after the specimen has been removed has also been described (Ahlering et al, 2005; Gill et al, 2005). Regardless of the method used, though, successful division of the prostatic pedicle in the correct anatomic location is an important step in avoiding positive margins and damage to the nearby NVB.

Preservation of the Neurovascular Bundle. Preservation of the periprostatic parasympathetic nerve fibers important for erectile function is one of the key and most difficult maneuvers during radical prostatectomy, regardless of surgical approach. **Increasingly, it is recognized that the periprostatic nerves of significance have a more diffuse and highly variable course than previously believed** (Costello et al, 2004; Takenaka et al, 2004; Lunacek et al, 2005), **but there is a confluence of nerves along the posterolateral prostate commonly termed the NVB.** Nerve tissue extends posteriorly around the prostate, forming a virtual hammock of nerves. In addition, nerve fibers can be identified in the periprostatic tissue along the more anterior portion of the prostate gland, although there is still debate about their relative contribution to erectile function. A well-performed, nerve-sparing radical prostatectomy

takes all of these considerations into account and preserves as much periprostatic nerve tissue as possible.

The superb visualization of the periprostatic tissues with laparoscopic surgery has led to a greater appreciation of the periprostatic fascial layers. Although there is some confusion in the literature regarding the terminology used for the various fascial layers, an extra fascial dissection typically implies dissection laterally between the lateral prostatic fascia and the levator fascia and posteriorly between Denonvilliers fascia and the anterior propria rectal fascia. **An interfascial dissection is carried out laterally between the prostatic fascia and the levator fascia and posteriorly between Denonvilliers fascia and the posterior prostate** (Fig. 103–13). **This is the preferred approach in patients with presumed organ-confined disease because it permits safe preservation of the cavernous nerves without violating the anatomic limits of the prostate gland and capsule.** An intrafascial dissection is between the prostatic capsule and the prostatic fascia and leaves virtually no periprostatic tissue overlying the prostate. Although technically feasible, this approach may lead to a higher incidence of positive margins due to the relatively closer dissection to the prostate gland. Even though these fascial layers as described do have some true integrity for intraoperative identification, it is also well recognized that they can be multilayered.

Damage to the NVB can occur because of direct incision, entrapment in a suture or clip, thermal injury, or traction. Some surgeons advocate release of the NVB from the prostate before mobilization of the specimen to help avoid traction injury. **With the antegrade approach typically used for LRP and RALP, identification and at least partial release of the NVB along the lateral aspect of the prostate before controlling the prostatic pedicle can help drop the nerve tissue away from the gland and permit a more precise placement of sutures, hemoclips, or clamps on the pedicle while preventing inadvertent entrapment of the nerve bundles.** To accomplish this, the levator fascia is first incised sharply along the anteromedial aspect of the midprostate entering into the interfascial plane of dissection (Fig. 103–14). Blunt dissection is carried out along the prostatic fascia in a posterolateral direction, thus partially releasing the lateral NVB and developing a visible NVB groove, which aids in precise hemoclip placement and division of the prostatic pedicle (Fig. 103–15). The ergonomics and scaled motion of the wristed robotic instruments are helpful in achieving this delicate dissection. During LRP, specially designed fine-tipped (0.8-mm) dissectors have been described to aid in NVB dissection and preservation (Su et al, 2004). Some discussion and debate has centered around how far anteriorly on the prostate the interfascial dissection of the nerve bundles should be performed. Whether high release (vs. standard

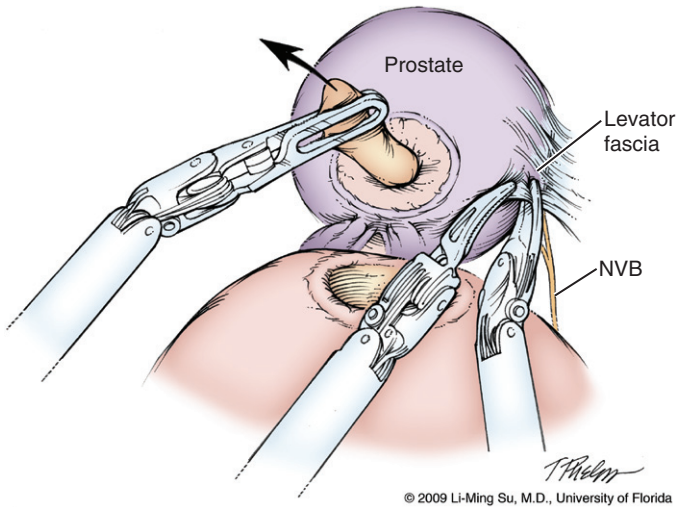


Figure 103–14. Entering into the interfascial plane of dissection for neurovascular bundle (NVB) preservation. The levator fascia is first incised along the anteromedial aspect of the midprostate, allowing entry into the interfascial plane of dissection. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

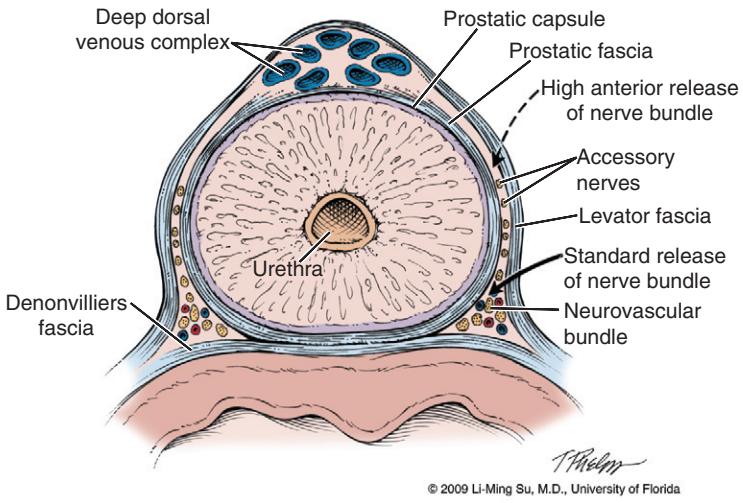


Figure 103–13. Cross section of the prostate demonstrating the periprostatic fascial planes with respect to the location of the neurovascular bundles. The *dashed line* indicates the direction of interfascial dissection (i.e., between the levator and prostatic fascia) to accomplish a high anterior release of the neurovascular bundle from the prostate and establish the lateral neurovascular bundle groove. The *solid line* indicates the incision made for a standard release of the neurovascular bundle. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

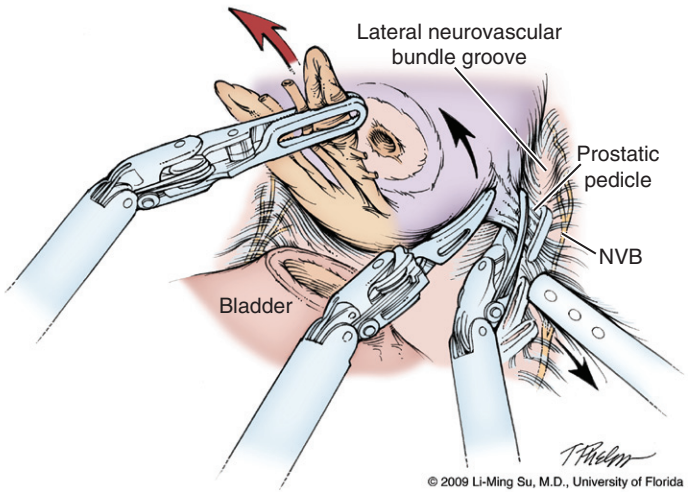


Figure 103–15. Developing the interfascial plane of dissection. Using blunt dissection, the nerve bundle is partially released from the prostate in a posterolateral direction, forming a visible lateral neurovascular bundle groove. This step serves to delineate the prostatic pedicle and course of the nerve bundle and allow for precise placement of hemoclips, while avoiding nerve entrapment. NVB, neurovascular bundle. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

release) preserves important nerves or simply allows for a physical handle to permit more precise, meticulous dissection and preservation of the true cavernous nerves located at the 5- and 7-o'clock positions without direct manipulation of these main nerve fibers is uncertain (see Fig. 103–13). **However, there is a general consensus that thermal energy should be minimized and, ideally, completely avoided during dissection of the NVB. These microscopic postganglionic parasympathetic nerve fibers are highly susceptible to thermal injury as shown in both animal and human studies** (Ong et al, 2004; Ahlering et al, 2005). Bleeding along the NVB is usually relatively minimal and may require no specific hemostatic measures. There may be small arteries or larger veins that require suturing with small tissue bites to avoid entrapment of adjacent nerves. Overdissection of the NVB at the prostatic apex should be avoided.

Patients with extremely large prostate glands (especially those > 100 g) offer a unique challenge during preservation of the NVB. Maneuvering a large prostate gland in the tight confines of the bony pelvis can be challenging, especially during exposure of the prostatic pedicles and NVB. Effective exposure of tissues by the surgical assistant, as well as the fourth robotic arm, is critical and can optimize visualization during prostatic pedicle ligation and NVB preservation.

Apical Dissection. **The prostatic apex is a common location for tumor involvement and the most common site of positive margins with radical prostatectomy.** Further, the steps required for apical dissection are crucial to preservation of erectile function and avoidance of urinary incontinence. The visualization of the operative field and the ability to limit bleeding from the DVC facilitate apical prostatic dissection during LRP and RALP.

Up to this point in the operation, antegrade dissection has permitted complete mobilization of the lateral, base, and posterior prostate, leaving division of the DVC and urethra from the prostatic apex for last. **It is critical to avoid entry into the anterior prostate during division of the DVC because this may result in an iatrogenic positive margin.** Although the previously placed DVC stitch may become dislodged or divided during this step, further sutures to secure the DVC can be easily placed. Also, bleeding from the DVC during attempts at resuturing can be kept to a minimum by transiently increasing the CO_2 insufflation pressure to 20 mm Hg to improve the tamponade effect on venous bleeding. Once the DVC is divided, there should be good visualization of the prostatic apex and its junction with the urethra (Fig. 103–16). **The anatomy of the prostatic apex is variable and should be carefully inspected before division of the urethra. As much urethral length as possible should be maintained, but an overlying anterior lip of prostate must be recognized, as well as posterior extension of prostatic tissue beneath the urethra.** Nevertheless, leaving a small rim of urethra along the prostatic apex may be advisable to reduce the incidence of apical positive margins because this does not appear to have an adverse effect on the return of urinary continence (Borin et al, 2007). Sharp dissection with limited use of electrocautery is preferred during the prostatic apical dissection and division of the urethra so as to prevent thermal injury to the external striated sphincter and nearby NVBs.

Intraoperative Inspection of Prostate. **Upon completely freeing the prostate gland and before entrapment of the specimen, the entire surface of the gland can be inspected laparoscopically to assess the adequacy of resection and integrity of the tissues covering the prostate specimen.** If concern exists regarding a close surgical margin, additional tissue may be excised specific to the location of concern; however, with experience this should rarely be necessary.

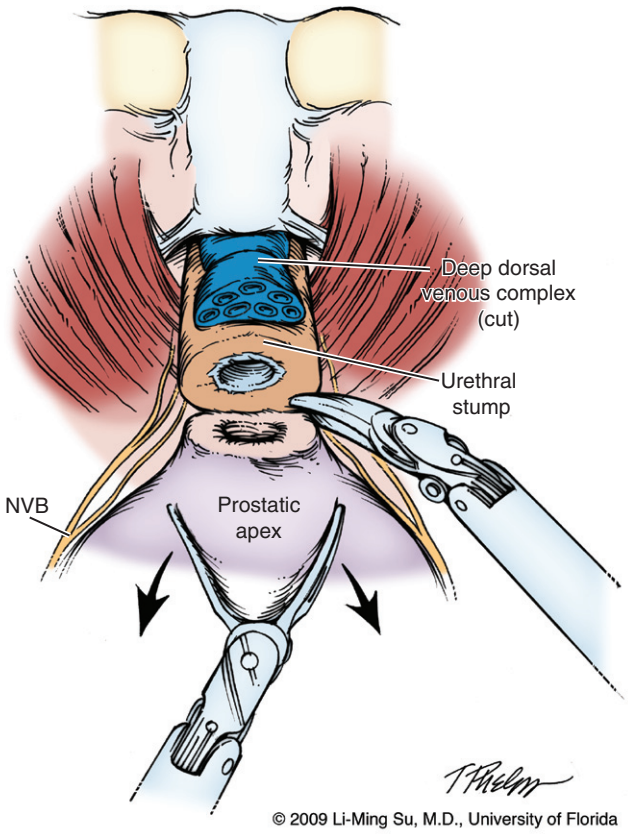


Figure 103–16. Division of urethra. Following division of the deep dorsal venous complex, the anterior and posterior urethra is divided sharply without electrocautery. A small rim of urethra may be safely left on the prostate apex to avoid an iatrogenic positive apical margin. Great care must be taken to avoid damage to the nearby nerve bundles. NVB, neurovascular bundle. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

Pelvic Lymphadenectomy. It is generally at this time that pelvic lymphadenectomy takes place because prior mobilization of the bladder allows for excellent exposure of the obturator lymph node region. The extent of pelvic lymphadenectomy remains controversial but can be tailored on the basis of patient-specific risk factors including prostate-specific antigen (PSA), clinical stage, and Gleason score. Technical description of laparoscopic pelvic lymphadenectomy follows later in this chapter.

Entrapment of Specimens. The prostate and pelvic lymph nodes are entrapped within a laparoscopic entrapment sack introduced into the abdomen by the surgical assistant through the 12-mm assistant trocar and stored in the abdomen until completion of the vesicourethral anastomosis.

Bladder Neck Reconstruction. The bladder opening is often slightly larger than the urethral lumen, but a parachuting effect can be achieved during the vesicourethral anastomosis that allows direct approximation of the bladder neck to the urethra. If the bladder neck opening is considerably larger than the urethra, a tennis racquet handle closure can be performed using absorbable suture either posteriorly or anteriorly to allow a better size match with the urethra. **In the event of a large prostate gland, median lobe, or prior TURP, the bladder neck may often be disproportionately larger than the urethra and thus may require extensive reconstruction before performing**

the vesicourethral anastomosis. Often, in these circumstances, the ureteral orifices are located at or near the posterior margin of the bladder neck where they are at risk of injury or obstruction during suturing of the anastomosis. In such cases the ureteral orifices can be imbricated by placing a few interrupted sutures at the 5- and 7-o'clock position along the posterior bladder neck using 3-0 polyglactin or polydioxanone suture. This maneuver can help avoid inadvertent sutures passing through or near the ureteral orifices during the anastomosis while at the same time reduce the size of the bladder neck opening.

Posterior Support of the Vesicourethral Anastomosis. As a result of prostatectomy the posterior supportive layers of the bladder and prostate are divided, including the Denonvilliers fascia and its confluence with the posterior rhabdosphincter. Recent reports of attempts at reconstruction of these posterior supportive structures have suggested improvement in earlier postoperative return of urinary control (Rocco et al, 2007), whereas others have found no significant benefit (Menon et al, 2008). Reconstituting the posterior support to the anastomosis is accomplished by reapproximating the remnant Denonvilliers fascia and posterior bladder neck to the posterior rhabdosphincter beneath the urethra using a running continuous 2-0 poliglecaprone (Monocryl) suture before completion of the vesicourethral anastomosis (Fig. 103–17). Although the exact mechanism remains unclear, suggested mechanisms include re-establishment of the posterior anatomic support to the bladder and urethra improving urethral coaptation during voiding, reduced tension at the vesicourethral anastomosis, and increase in the functional length of the striated urethral sphincteric complex. **Despite the ongoing debate on its effectiveness, many believe that this step at the very least reduces the distance between the bladder neck and urethra, thus facilitating completion of a tension-free vesicourethral anastomosis.** Resuspension of the anastomosis and distal bladder neck to the arcus tendineus is used by some to restore anterior urethral support and preserve the vesicourethral angle (Tewari et al, 2007).

Vesicourethral Anastomosis. With LRP, the vesicourethral anastomosis is one of the most difficult aspects of the procedure due to the challenges of performing laparoscopic suturing. The da Vinci surgical robot greatly facilitates suturing of the anastomosis due to the ergonomics of the wristed robotic instrumentation. Although interrupted sutures may be used for the anastomosis, van Velthoven and colleagues (2003) described a running suture technique, which distributes tension broadly across multiple points along the bladder and urethra. Typically, two separate sutures are tied together at their ends, each 6 to 8 inches in length. The anastomosis between the bladder and urethra begins posteriorly, leaving two needles to run progressively in an anterior direction on either side, finally ending at a single anterior tie. **Dedicated mucosal eversion sutures at the bladder neck, commonly used during radical retropubic prostatectomy (RRP), are seemingly unnecessary with the excellent running mucosa-to-mucosa anastomosis achieved with LRP and RALP.** Multiple sutures are first placed through the urethra and bladder before progressive cinching of the anastomosis by lifting each arm of the suture in an anterior direction (Fig. 103–18). Either an assistant or the robotic ProGrasp forceps can be used to grasp one arm of the suture to maintain tension and approximation of the posterior anastomosis while the surgeon reapproximates the contralateral side of the anastomosis using the second suture. The final urethral catheter is passed under direct vision immediately before completion of the anastomosis and the bladder is irrigated to make certain that there are no anastomotic leaks. Further sutures may be required if a leak is identified.

Delivery of the Specimens and Exiting the Abdomen. Prior to undocking the robot and removal of the specimens, the pelvis and operative field should be carefully reinspected for bleeding under low insufflation pressure (<10 mm Hg). The bowel should be examined closely to make certain that there is no injury resulting from instrument exchanges. The string for the laparoscopic entrapment sack is

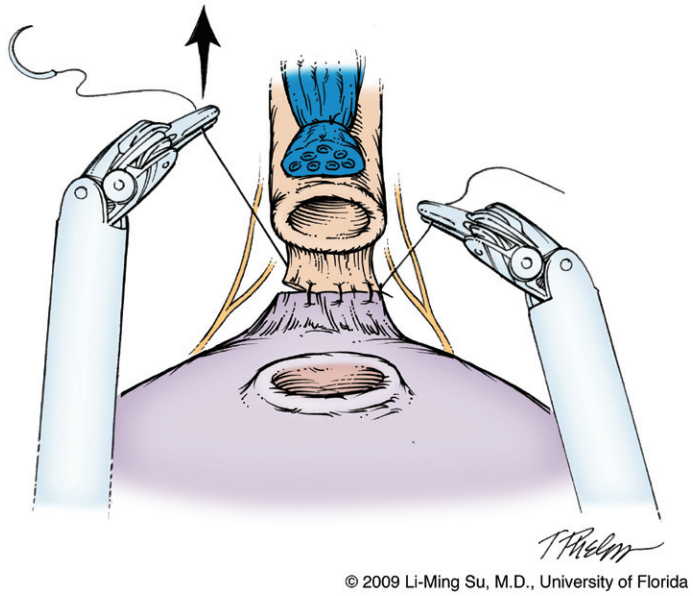


Figure 103–17. Modified Rocco stitch. Posterior support is provided to the vesicourethral anastomosis by reapproximating the remnant Denonvilliers fascia and posterior detrusor along the posterior bladder neck to the posterior rhabdosphincter using a running continuous 2-0 Monocryl suture. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

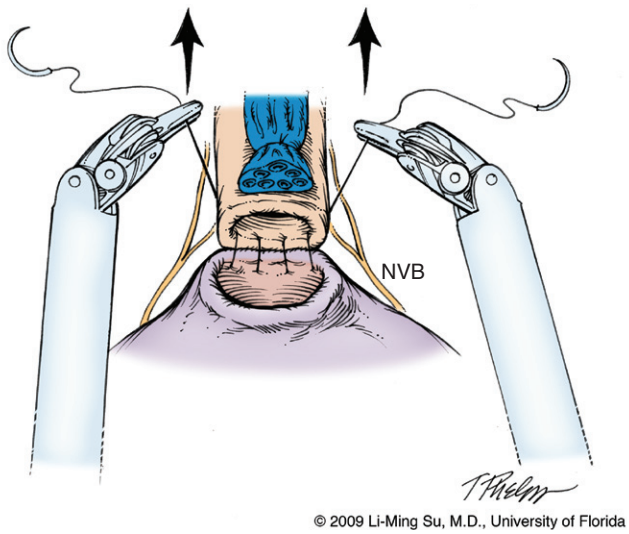


Figure 103–18. Running vesicourethral anastomosis. The posterior anastomosis is reapproximated after preplacing two to three sutures on either side and cinching the sutures by lifting anteriorly. Great care must be taken to avoid incorporating the neurovascular bundles (NVB) when placing sutures within the urethra. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

transferred to the camera port site at the umbilicus and the abdomen is completely desufflated. The specimens within the laparoscopic entrapment sack are extracted intact through extension of the periumbilical trocar site. The fascial defect is then closed by open suture placement, and the skin defects are closed with a subcuticular absorbable suture or a skin adhesive. Closure of the fascial defect for the 5-mm trocar sites is generally not necessary. Due to the potential risk of a trocar site hernia, it is advisable to close the 12-mm trocar sites with a Carter Thomason fascial closure device, especially if a bladed (vs. dilating) trocar is used.

POSTOPERATIVE MANAGEMENT

With the secure and watertight running anastomosis typically achieved, a pelvic drain may not always be necessary. However, a drain may be placed through one of the 8-mm robotic trocar sites and does not require a separate stab wound. The drain may evacuate an unanticipated urine leak or lymphatic fluid collection. Often, though, drainage is minimal and the drain typically can be removed on the first postoperative day. Parenteral narcotic medications may be required for the first 24 hours following surgery but should be used sparingly. Instead, ketorolac may be used in select patients for postoperative pain control.

The duration of time required for the urethral catheter depends to a great extent on the preferred approach of the surgeon, as well as the extent of bladder neck reconstruction. The 2-week period commonly used with open surgery is in general unnecessary if a good running anastomosis is achieved. With 1 week or more of an indwelling urethral catheter, the vast majority of patients are able to void adequately with minimal risk of urinary retention and need for catheter replacement. Performing a cystogram before removal of the catheter is based on surgeon preference. If catheter removal before a week is planned, it may be advisable to obtain a cystogram to ensure that there is no extravasation from the anastomotic site. In cases of a leak, longer duration of the urethral catheter is required to allow for spontaneous healing. Although this may prolong the time to achieve urinary continence, long-term urinary outcomes do not appear to be affected (Patil et al, 2009). Some surgeons are exploring an approach that uses suprapubic catheter drainage of the bladder with a specially designed anastomotic splint rather than a urethral catheter with good initial results (Tewari et al, 2008a).

Even with LRP and RALP, some degree of postoperative ileus occurs. Most patients can tolerate a regular diet within 24 hours of surgery, and hospitalization beyond the first postoperative day is not typically necessary. Patients can characteristically return to their preoperative activities shortly after catheter removal but must avoid strenuous activity.

Key Points: Technique of Laparoscopic and Robotic-Assisted Laparoscopic Radical Prostatectomy

- Use of a transperitoneal or extraperitoneal approach is based primarily on surgeon preference because there is no demonstrable advantage to either approach.
- The robotic technology facilitates suturing and dissection for surgeons who do not have advanced laparoscopic skills.
- Identification of the precise margin between the bladder neck and prostate can be accomplished by using a set of physical and visual cues.
- Following division of the anterior bladder neck, the presence or absence of a median lobe should be defined before division of the posterior bladder neck.
- Complete mobilization of the plane between the posterior prostate and rectum is an important step in avoiding rectal injury and defining the medial aspect of the neurovascular bundle.
- Use of thermal energy should be minimized during control of the prostatic pedicles and dissection near the neurovascular bundles because thermal energy has been shown to be deleterious to cavernous nerve function in both animal and human studies.
- An interfascial dissection of the neurovascular bundle is preferred in patients with presumed organ-confined cancer.
- An anterior or posterior protruding lip of prostate should be anticipated when dividing the prostatic apex from the urethra so as to avoid an iatrogenic apical positive margin.
- Bladder neck reconstruction may be required if there is a size discrepancy between the bladder neck and urethra, especially in patients with prior TURP, median lobe, or large prostate gland.
- The vesicourethral anastomosis is best accomplished with a running continuous suture.

RESULTS

Published results continue to emerge with regards to midterm outcomes of LRP and RALP both in the United States and abroad, suggesting comparable outcomes with RRP. Most of these reports, however, are case series. No randomized trials have been conducted evaluating laparoscopic and robotic versus open techniques, and retrospective comparisons are limited by disparities in surgeon experience, the influence of patient selection, and nonstandardized methods of outcome assessment.

Perioperative Outcomes

Operative Time. The duration of surgery is typically longer with LRP or RALP compared with open surgery, especially early in the surgeon's experience. In fact, operating times are often used as a surrogate for assessing the "learning curve" with laparoscopic prostatectomy (Herrell and Smith, 2005). As both surgeon and operating team experience is gained, virtually all reported series have documented a substantial decrease in operative times that approach and in some series surpass those for open surgical techniques. At experienced centers of excellence with LRP, operative times less than 3 to 4 hours are common (Turk et al, 2001; Salomon et al, 2004; Stolzenburg, 2008). Similar findings have been observed with RALP. Inexperience of both the console surgeon and the tableside operating team can lead to lengthy procedures initially. Once experience is gained, operative times of less than 3 hours have been reported for the total procedure (Smith, 2004; Badani et al, 2007; Patel et al, 2008).

Postoperative Pain. One of the distinct advantages of laparoscopy for many surgical procedures (e.g., laparoscopic nephrectomy) is its minimally invasive nature resulting in less postoperative pain than comparative open approaches. For radical prostatectomy, however, this advantage seems to be less dramatic because RRP is performed through an infraumbilical muscle-splitting incision. In addition, relatively little pain occurs after radical perineal prostatectomy. Some series have shown decreased pain in patients undergoing either LRP or RALP compared with RRP (Menon et al, 2002; Bhayani et al, 2003). Other reports have

shown no substantial difference in postoperative narcotic use or in patient-reported pain (Webster et al, 2005). **The lack of a significant advantage for laparoscopic prostatectomy is attributable primarily to low pain scores even in the open surgical group.**

Intraoperative Blood Loss. Because most of the blood loss that occurs during radical prostatectomy is from venous sinuses, the tamponade effect from the pneumoperitoneum helps diminish ongoing blood loss during LRP and RALP. **Further, the antegrade approach used during LRP and RALP entails earlier control of the prostatic pedicles and late division of the DVC as compared with RRP, in which the DVC is divided early and the arterial supply to the prostate managed late in the operation.** Thus the potential for ongoing bleeding is reduced during LRP and RALP as compared with open surgery. Both of these factors, as well as the excellent visualization with laparoscopy, account for the minimal blood loss reported in most series. Blood loss of less than a few hundred milliliters is routinely reported (Ficarra et al, 2009).

Perhaps the most meaningful parameter clinically is the proportion of patients requiring transfusion of homologous blood products. Most studies have shown a significant decrease in transfusion requirement for patients undergoing LRP or RALP compared with RRP (Tewari et al, 2003; Ahlering et al, 2004a). Others have shown no statistically significant difference if the transfusion requirement with RRP can be limited to only a few percent of patients (Farnham et al, 2006).

Hospital Stay. Over the past decade, hospital stay after radical prostatectomy has diminished remarkably regardless of the surgical approach. Some centers have reported a length of stay as short as 1 or 2 days after RRP (Holzbeierlein and Smith, 2000). With LRP and RALP, a hospital stay of only 1 day has become routine in many centers. Ileus and inability to tolerate a regular diet are the most common factors limiting early discharge. Pain control does not typically contribute to prolonged length of stay because parenteral narcotics are rarely required. **With early discharge programs for radical perineal and RRP being commonly used at many centers within the United States, no distinct advantage exists for LRP or RALP, although discharge on the first postoperative day may be more easily accomplished routinely with the minimally invasive approaches.**

Functional Outcomes

The complications of radical prostatectomy with the greatest potential for an adverse effect on quality of life are urinary incontinence and erectile dysfunction. Greater surgical experience with radical prostatectomy and refinements in surgical technique have reduced the frequency with which these problems are observed in most radical prostatectomy series from centers of excellence. However, most large population-based studies show substantial rates of erectile dysfunction and incontinence after both RRP and radical perineal prostatectomy (Fowler et al, 1993). Whether laparoscopic or robotic approaches offer improved functional outcomes is still a matter of debate, and comparison of published series is difficult because of differences in patient populations and methods of outcome assessment.

Urinary Incontinence. Urinary incontinence after radical prostatectomy is usually manifested as stress incontinence secondary to intrinsic sphincter deficiency. Although more than 90% of patients ultimately regain good urinary control and do not require pads for incontinence in reports from high-volume centers (Walsh, 1998; Catalona et al, 1999), other studies have shown that a substantial proportion of patients may be bothered by some degree of stress incontinence (Fowler et al, 1993). The exact physiologic mechanisms that contribute to urinary control after radical prostatectomy are not entirely understood and are likely multifactorial. However, surgical technique is undoubtedly a contributing factor (Smith, 2002).

With LRP and RALP, visualization of the prostatic apex is typically superb. The minimal bleeding and magnification of the operative field allow precise dissection of the prostatic apex with limited trauma to the periurethral striated sphincter and genitourinary diaphragm. As mentioned previously, the ability to more reliably accomplish a tension-free, watertight anastomosis under the superior and direct visualization offered by laparoscopic approaches in theory favors LRP and RALP over open surgery. A common observation after radical prostatectomy, regardless of surgical approach, is that urinary incontinence improves substantially within the first 3 to 6 months after surgery and to some extent for another year or more. Therefore the time points at which data on incontinence are collected are highly influential. Differences exist whether the information is gathered by questionnaire, the physician, or an independent third party. Further, even though validated instruments for assessment of incontinence exist, the manner and location in which the data are collected can affect results. Although the method used to evaluate continence in reported series varies, the recovery of urinary continence is excellent at 1 year following LRP and RALP (Table 103–2). More recent reports of techniques that provide both posterior and anterior support to the vesicourethral anastomosis report even further improvements in urinary continence, especially at earlier time points (Tewari et al, 2007).

Erectile Dysfunction. Preservation of erectile function after radical prostatectomy depends on precise and meticulous separation of the cavernous nerves within the NVB from the prostate gland (Walsh and Donker, 1982). The anatomic course of these nerves has been described but can be variable (Costello et al, 2004; Takenaka et al, 2004; Lunacek et al, 2005). Intraoperative localization using nerve stimulation has not been sufficiently accurate for clinical utility (Holzbeierlein et al, 2001). The principles and anatomic dissection for nerve preservation are the same regardless of surgical approach. It is still uncertain whether the magnified image of the operative field afforded by laparoscopy and the precision of the surgical instruments allows more anatomically accurate and less traumatic dissection of the NVBs, resulting in improved postoperative erectile function. As with incontinence, comparison of the published literature is difficult (Salomon et al, 2004). Differences in the method of assessment, definition of potency (e.g., spontaneous erections vs. intercourse), and patient selection complicate comparisons. In addition, the use of adjunctive therapies such as phospho-diesterase-5 inhibitors or vasoactive injections can substantially influence results. Also, in concordance with other nerve injuries, improvement in erectile function is a prolonged process that is ongoing for years after radical prostatectomy. Good results with erectile function after both LRP and RALP have been reported (Table 103–3). **However, there are no published data that allow definitive conclusions about the relative merits of either LRP or RALP in avoiding erectile dysfunction compared with open surgical approaches.** Nevertheless, the avoidance of hemostatic energy sources during NVB preservation and the performance of meticulous interfascial dissection and preservation of the cavernous nerves appear to be critical to optimizing postoperative recovery of potency.

Anatomic studies indicate that the cavernous nerves in the NVB course posterolateral to the prostate and urethra. A technique

Table 103–2.

Reported Urinary Continence Outcomes following LRP and RALP

REFERENCE	EVALUATED PATIENTS	MEAN AGE, YR	METHOD OF ASSESSMENT	DEFINITION USED	TIME OF ASSESSMENT	CONTINENCE RATE
Laparoscopic Radical Prostatectomy						
Hoznek et al, 2001	200	64.8	Questionnaire	No pad	12 mo	86%
Olsson et al, 2001	228	65.2	Questionnaire	No pad	12 mo	78.4%
Salomon et al, 2002	235	63.8	Questionnaire	No pad	12 mo	90%
Eden et al, 2002	100	62.2	Physician	No pad	12 mo	90%
Guillonneau et al, 2002	550	NA	Physician	No pad	12 mo	82.3%
Anastasiadis et al, 2003	230	64.1	Questionnaire	No pad	12 mo	71.6%
Rassweiler et al, 2004	500	64	Questionnaire	No pad	12 mo	83.6%
Link et al, 2005	122	58.3	Questionnaire	0-1 pad	12 mo	93%
Rozet et al, 2005	498	62	Questionnaire	No pad	12 mo	98%
Stolzenburg et al, 2008	1407	63.2	Questionnaire	No pad	12 mo	92%
Robotic-Assisted Laparoscopic Prostatectomy						
Menon et al, 2003b	100	60	Physician	0-1 pad	6 mo	92%
Ahlering et al, 2004a	60	62.9	Questionnaire	No pad	3 mo	76%
Costello et al, 2005	89	NA	Questionnaire	0-1 pad	6 mo	82%
Patel et al, 2005	200	59.5	Questionnaire	No pad	12 mo	97%
Zorn et al, 2007b	300	59.4	Questionnaire	0-1 pad	12 mo	90.2%
Menon et al, 2007	1142	60.2	Questionnaire	0-1 pad	12 mo	95%
Tewari et al, 2008b	182	62.1	Questionnaire	0-1 pad	6 mo	97%
Krambeck et al, 2009	294	61	Questionnaire	0-1 pad	12 mo	91%

LRP, laparoscopic radical prostatectomy; RALP, robotic-assisted laparoscopic prostatectomy.

Table 103–3.

Reported Potency Outcomes following Bilateral Nerve-Sparing LRP and RALP

REFERENCE	TOTAL PATIENTS	EVALUABLE PATIENTS	MEAN AGE, YR	PERCENT OF PATIENTS RECEIVING BNS*	METHOD OF ASSESSMENT	DEFINITION USED	TIME OF ASSESSMENT	POTENCY RATE
Laparoscopic Radical Prostatectomy								
Salomon et al, 2002	235	43	63.8	39.5	Questionnaire	Intercourse	12 mo	58.8%
Eden et al, 2002	100	100	62.2	58	Physician	Erections	12 mo	62%
Katz et al, 2002	232	143	63	44	Questionnaire	Erections	12 mo	87.5%
Anastasiadis et al, 2003	230	230	64.1	33.5	Questionnaire	Intercourse	12 mo	53%
Roumeguere et al, 2003	85	85	62.5	30.9	Questionnaire	Intercourse	12 mo	65.3%
Su et al, 2004	177	177	57.8	51.4	Questionnaire	Intercourse	12 mo	76%
Rassweiler et al, 2004	500	109	67	37.6	Questionnaire	Intercourse	12 mo	67%
Wagner et al, 2006	220	60	NA	66	Questionnaire	Intercourse	12 mo	72%
Gill et al, 2007	200	76	NA	38	Questionnaire	Intercourse	12 mo	88%
Stolzenburg et al, 2008	2000	730	63.2	65.3	Questionnaire	Intercourse	12 mo	67.7%
Robotic-Assisted Laparoscopic Prostatectomy								
Menon et al, 2003a	250	200	59.9	NA	Questionnaire	Intercourse	6 mo	64%
Zorn et al, 2007b	300	258	59.4	59.7	Questionnaire	Intercourse	12 mo	80%
Patel et al, 2007	500	200	NA	NA	Questionnaire	Intercourse	12 mo	78%
Tewari et al, 2008b	215	215	60	85	Questionnaire	Intercourse	12 mo	87%

LRP, laparoscopic radical prostatectomy; RALP, robotic-assisted laparoscopic prostatectomy.
*Bilateral nerve-sparing surgery.

during RALP for preservation of more anteromedial periprostatic fascia in addition to the conventional NVB regions has been reported to significantly improve potency outcomes (Menon et al, 2005; Savera et al, 2006). Although some neural tissue can be shown histologically to travel within the anterior and medial periprostatic fascia, the purpose and significance of these nerves and their relative contribution to erectile function remains uncertain. Nevertheless, the concept of optimizing both qualitative and quantitative preservation of nerve fibers traveling within the periprostatic fascial planes irrespective of whether they affect penile erections or urinary continence seems reasonable. In cases where wide excision of the nerve bundles is required, cavernous nerve grafting and nerve advancement have been described; however, the true merits of these techniques remain unclear (Martinez-Salamanca et al, 2007; Zorn et al, 2008).

Oncologic Outcomes

Surgical margin status and biochemical recurrence have generally been used as surrogates for oncologic efficacy following radical prostatectomy.

Surgical Margins. The goal of radical prostatectomy is complete surgical removal of the entire prostate and its investing fascia, as well as the seminal vesicles. Because most adenocarcinomas of the prostate occur in the peripheral zone and approach the capsular margin, surgical technique can influence oncologic outcomes. Proper surgical dissection should allow negative margins with pathologic stage T2 tumors while also permitting complete excision and negative margins for some extracapsular lesions. Efforts to avoid urinary incontinence or erectile dysfunction by dissecting too closely to the prostatic apex or the posterolateral aspect of the prostate can compromise margins, regardless of the surgical approach. Once again, comparison of positive margin rates in reported series is difficult because of patient selection. **Importantly, the method and detail of pathologic analysis of the surgical specimen can be highly influential in assessing surgical margin status.** Some reports have used only biopsies of remaining tissue after removal of the surgical specimen to assess margin status, whereas others rely on step-sectioned routine or whole mount histology. **According to the World Health Organization International Consultation Consensus Committee guidelines established for the pathologic analysis of prostatectomy specimens, whole mount histologic sectioning may miss areas of extraprostatic extension in 7% to 15% of cases and positive margins in up to 12% as compared with specimens analyzed by routine sectioning** (WHO International Consultation on Prediction of Patient Outcome in Prostate Cancer, 2004). This finding is thought to be due to the relatively thicker slices required during sectioning of the prostate for whole mount technique as compared with the serial 3- to 5-mm slices used during routine sectioning.

In most series of LRP and RALP, positive margin percentages decrease with experience (Ahlering et al, 2004b; Salomon et al, 2004; Rassweiler et al, 2005). This implies that inexperience with the surgery accounts for positive margins in some cases. Sometimes, this may be from difficulty in identifying the proper anatomic plane of dissection between the bladder neck and the base of the prostate. The most common site of a positive margin, whether the operation is performed via open or laparoscopic approaches, is the prostatic apex (Touijer et al, 2005). Insufficient removal of prostatic tissue at the apex in an effort to optimize urethral length and avoid incontinence can result in positive margins even with tumors that do not pathologically violate the capsule (i.e., stage pT2). **As mentioned previously in the surgical techniques section of this chapter, adhering to specific surgical principles can help reduce site-specific positive margins at the apex, bladder neck, and posterolateral regions of the prostate.** Published rates of pathologic stage-specific positive margins for LRP or RALP are shown in Table 103–4.

The primary factor that determines the positive margin rate in a given series is patient selection. As discussed earlier, the method and detail of pathologic analysis is also influential. Evaluating positive margin rates from one series to another, then, is not necessarily a comparison of surgical technique. A more accurate technical comparison is analysis of the pathologic results in stage T2 tumors wherein a positive margin implies surgical violation of the prostatic capsule. Even in this circumstance, though, the methodology for pathologic sampling is important. Intrainstitutional comparisons from some studies have shown a reduced rate of positive margins with laparoscopic approaches compared with RRP. **However, comparison of margin status between high-volume centers with operations performed by experienced surgeons has shown no definitive advantage for one surgical approach over the other in achieving negative surgical margins** (Brown et al, 2003; Khan et al, 2005).

Table 103–4.

Reported Pathologic Stage-Specific Positive Margin Rates with LRP and RALP

REFERENCE	NO. OF PATIENTS	POSITIVE MARGINS (%) pT2	pT3
Laparoscopic Radical Prostatectomy			
Hoznek et al, 2002	250	16.4	39.3
Guillonneau et al, 2003b	1000	15.5	31.1
Roumeguere et al, 2003	85	18.4	45.7
Su et al, 2004	177	4.7	44.8
Rozet et al, 2005	599	14.6	25.6
Rassweiler et al, 2005	500	7.4	31.8
Lein et al, 2006	1000	14.8	21.1
Stolzenburg et al, 2008	2000	9.7	33.9
Robotic-Assisted Laparoscopic Prostatectomy			
Wolfram et al, 2003	81	12.7	42
Ahlering et al, 2004b	140	12.3	48.8
Cathelineau et al, 2004b	105	11.7	43
Atug et al, 2006	140	18.1	53.8
Joseph et al, 2006	325	9.9	32.7
Zorn et al, 2007b	300	15.1	52.1
Smith et al, 2007	200	9.4	50
Badani et al, 2007	2766	13	35
Patel et al, 2008	1500	4	34

LRP, laparoscopic radical prostatectomy; RALP, robotic-assisted laparoscopic prostatectomy.

Biochemical Recurrence. Biochemical recurrence following prostatectomy may perhaps provide a more accurate assessment of oncologic control than margin status. Guillonneau and colleagues reported on their oncologic outcomes with 1000 consecutive LRPs performed over a 4-year period with a median follow-up period of 12 months (Guillonneau et al, 2003b). Their overall actuarial biochemical progression-free survival rate was 90.5% at 3 years. By pathologic stage, the rates were 92% for pT2a, 88% for pT2b, 77% for pT3a, and 44% for pT3b. Pavlovich and colleagues (2008) reported on 528 consecutive LRP patients with a mean follow-up of 13 months. The 3-year, actuarial, biochemical-free survival was 94.5% overall, 98.2% for pT2, and 78.7% for pT3 disease.

With regard to RALP, Badani and colleagues in 2007 reported on their large series of 2766 consecutive RALP patients with a mean follow-up period of 22 months. Their overall 5-year, actuarial, biochemical-free survival was 84% overall, 84% for pT2, and 66% for pT3 patients. It should be noted that their patient population included higher-risk patients than most reported series with a Gleason score of 7 or higher in 64% and a pathologic stage of pT3 or higher in 22% of their patients. In a retrospective comparison of biochemical recurrence between RALP and a contemporary series of RRP performed at a single center, no difference was found between the two groups after controlling for clinical and pathologic features (Schroeck et al, 2008). In the end, longer-term follow-up is required to compare the results of LRP and RALP with results of RRP from established and experienced centers of excellence.

Economic Considerations

Both the duration of surgery and equipment expenses contribute to operating room costs for LRP and RALP, which typically are

higher than those for open approaches (Link et al, 2004; Lotan et al, 2004; Scales et al, 2005). This is particularly true with robotic-assisted surgery. Current purchase cost of a da Vinci S system is approximately $1.65 million with an average cost of $2400 for each multiple-use (10 lives) robotic instrument. For robotic instrumentation, this would translate to approximately $1200 per case for the use of five separate robotic instruments with an additional $325 per case for disposables (sterile robotic drapes and trocar seals).

In the study by Link and colleagues (2004), **the factors that most influenced overall LRP cost in order of importance included operative time, length of hospital stay, and consumable items (e.g., disposable laparoscopic equipment and trocars).** They found that the calculated cost equivalence between RRP and LRP could be met if disposable equipment was eliminated by using reusable items and operative times for LRP were reduced to 3.4 hours. Lotan and colleagues (2004) found that RALP costs were approximately $1155 per case more than RRP if the initial purchase cost of the robot were excluded. In a local cost analysis performed by Scales and colleagues (2005), they found that RALP would be less expensive than RRP in some practice settings in which RALP hospital stay was less than 1.5 days if case volumes increased to 14 cases per week. This study suggested that RALP may be more economically viable in high-volume centers with multispecialty robotic use.

These increased costs may be partially mitigated by shorter hospital stays compared with open surgery. The decrease in expense for hospital stay depends partly on the discharge day for the laparoscopic procedure but also the customary length of stay at a given hospital for open radical prostatectomy. Published reports detailing a length of stay of a week or more for RRP are not in concordance with other contemporary reports wherein patients are discharged on the second or even first postoperative day after radical perineal or RRP (Holzbeierlein and Smith, 2000).

COMPLICATIONS

Complications Related to Patient Positioning

LRP and RALP are typically performed with the patient in a steep exaggerated Trendelenburg position and with the legs in lithotomy position. Careful padding of vulnerable body parts such as the hips, shoulders, knees, and calves is important to prevent pressure injury and neuromuscular complications. Increased intraocular pressure can occur in patients in an exaggerated Trendelenburg position, but in patients undergoing RALP this does not appear to have any apparent clinical long-term consequence. However, there may be an increased risk of corneal abrasion, making it even more important for the anesthesiologist to maintain good eye lubrication and protection.

Vascular and Bowel Injury

Vascular or bowel perforations are rare but can occur during placement of abdominal trocars. In addition, once safe trocar placement is established and the robot is docked, care must be taken to avoid injury along the path of the multiple instruments, which must be interchanged and directed toward the pelvis. The key to avoiding major postoperative complications is prompt recognition and immediate management of injury to bowel or blood vessels. Often, relatively minor injuries can be repaired laparoscopically, although there should be no hesitation to convert to an open approach in the face of a difficult problem.

Open Conversion

Open conversion is rare (<2%) and has been cited in the literature, usually during a surgeon's early experience with LRP or RALP, mainly as a result of failure to progress or uncertainty of dissection planes (Bhayani et al, 2004). With experience, the need for open conversion is rare; however, patients must be properly counseled on this possibility.

Rectal Injury

Rectal injuries, although uncommon during LRP and RALP (0.7% to 2.4%), have been reported and repaired successfully by laparoscopic means (Guillonneau et al, 2003a; Katz et al, 2003; Gonzalgo et al, 2005). Intraoperative recognition and repair of the injury is crucial. Multilayered primary closure and interposition of omentum between the rectum and anastomosis can usually avoid long-term problems, as well as the need for open conversion and intestinal diversion. Inadequate closure or lack of recognition can result in a fistula between the vesicourethral anastomosis and the rectum. If a small rectal injury is suspected but not readily identified, insufflation of air into the rectum using a catheter inserted into the rectum with fluid within the pelvis can often demonstrate small bubbles at the site of the injury.

Thromboembolic Complications

The incidence of thromboembolic complications is low after LRP and RALP (0.5%) likely, in part, due to faster postoperative patient mobilization and Trendelenburg positioning, used for decreasing the venous stasis in the lower extremities as compared with open surgery (Secin et al, 2008). The American Urological Association guidelines do not recommend routine use of prophylactic anticoagulants for laparoscopic procedures unless a patient has known risk factors such as obesity or a prior history of deep venous thrombosis. Nonetheless, because of the known venous stasis and hypercoagulable state that can occur during pelvic surgery in patients with known malignancy, these patients are still at risk for thromboembolic problems. Secin and colleagues (2008) propose the use of heparin only in patients at high risk for venous thromboembolism. Sequential compression stockings are advised during the operative and perioperative period. The presentation of deep venous thrombosis in the lower extremities should prompt a pelvic CT scan or ultrasound to exclude a lymphocele, hematoma, or urinoma that could be compressing the external iliac vein.

Anastomotic Complications

Failure to achieve a watertight closure of the anastomosis can result in urinary extravasation and accumulation of urine even if a pelvic drain is placed. This is even more problematic with a transperitoneal approach because the entire abdominal cavity becomes accessible for urine egress. In such cases a cystogram should be performed to make certain that there is some degree of integrity of the anastomosis. Fluid accumulations may require percutaneous drainage. If complete disruption of the anastomosis has occurred, surgical revision, either laparoscopic or open, is indicated if the problem is recognized in the first few days after surgery. Anastomotic stricture resulting in bladder neck contracture seemingly occurs at a lower rate after LRP and RALP compared

with open surgical approaches, especially in the hands of experienced surgeons. Rates of less than 2% have been reported (Msezane et al, 2008; Webb et al, 2009). This implies that achievement of a watertight anastomosis with good mucosal approximation is the key measure in preventing postoperative bladder neck contracture.

Bleeding and Transfusion

Virtually all published reports have documented a distinct advantage for laparoscopic surgery in diminishing the amount of bleeding that occurs with radical prostatectomy. Transfusion requirements of 2% or less are commonly reported (Ficarra et al, 2009). The tamponade effect of the pneumoperitoneum compresses venous bleeding, and the superb visualization allows prospective identification of bleeding vessels that require hemostasis. However, in addition to the risk of major vascular injury from the surgical dissection or trocar placement, there is the possibility of postoperative bleeding once the pneumoperitoneum is relieved. As mentioned previously, the pelvis and surgical field should be carefully inspected for the presence of bleeding at the end of the operation under low insufflation pressure. Because of the low incidence of postoperative bleeding, though, routine use of topical hemostatic agents along the prostate bed is not generally required.

Equipment Malfunction

The surgeon is highly dependent on sophisticated technology and equipment for performance of LRP and, in particular, RALP. Equipment malfunction, especially with RALP, can create problems that make it difficult to progress with surgery and may result in case cancellation or conversion to pure laparoscopic or even open surgery. Zorn and colleagues (2007a) identified recoverable errors in 0.4% of RALP cases performed at their institution. Lavery and colleagues (2008) found a 0.4% nonrecoverable malfunction rate in their multi-institutional study of high-volume RALP centers. Although extremely rare, patients need to be properly counseled about the possibility of conversion to a pure laparoscopic or open surgical approach in the event of an unrecoverable equipment malfunction.

Key Points: Results and Complications of Laparoscopic and Robotic-Assisted Laparoscopic Radical Prostatectomy

- Blood loss is minimal in part due to the tamponade effect of the pneumoperitoneum.
- Hospital length of stay is often only 1 day.
- Whether postoperative continence and/or potency are better with laparoscopic and robotic-assisted approaches compared with open surgery in expert hands remains uncertain.
- Surgical margins are comparable with those with open approaches and are partly influenced by patient selection, surgical technique, and experience.
- Higher costs are still a concern, especially with the robotic-assisted approach.
- Thromboembolic events, rectal injury, transfusion, and equipment malfunction are rare events.

LAPAROSCOPIC PELVIC LYMPH NODE DISSECTION

Indications

Currently, PLND is rarely indicated as an independent staging procedure. In some patients with a significant risk for nodal metastasis, such as those with a high Gleason grade tumor, a large tumor volume, or a markedly elevated PSA level, PLND may be useful for staging and selection of therapy before external beam irradiation. Also, staging PLND may have a role in some patients in whom radical perineal prostatectomy is planned. With RRP, LRP, or RALP, it is the usual practice that PLND be performed simultaneously with the radical prostatectomy.

Expert opinion about the role of PLND in patients undergoing surgery for carcinoma of the prostate is evolving. **Current debate centers around the anatomic boundaries for the procedure, the merits of an extended lymph node dissection, and whether there is any meaningful clinical (i.e., therapeutic) benefit to surgical removal of involved nodes.** Most studies show histologic evidence of nodal metastasis in less than 5% of patients with low-risk features in the primary tumor. Consequently, PLND may not be required in these patients.

PLND is generally recommended in patients with intermediate or high-risk parameters of the primary tumor, generally implying a PSA of greater than 10, a large palpable nodule, or a Gleason sum of 7 or greater.

Surgical Technique

In laparoscopic staging PLND, trocar configuration is similar to that of LRP and RALP but only one assistant trocar is generally necessary, if at all. Abdominal access is established, and an incision is made just lateral to the medial umbilical ligament back toward its confluence with the hypogastric artery and down to the pubis (Fig. 103–19). Great care must be taken so as to avoid injury to the nearby ureter. If PLND is performed during LRP or RALP, the dissection is simplified because previous mobilization of the bladder provides excellent exposure of the obturator space. As with an open approach, a key initial step to standard laparoscopic PLND is separation of the nodal packet from the external iliac vein. The lymph node packet is grasped and retracted medially. A relatively avascular plane between the lymph node packet and lateral pelvic sidewall is identified and dissected bluntly using a suction-irrigation device. Dissection is carried out proximally to the iliac bifurcation and distally to the pubis, thus defining the lateral extent of the lymph node packet. By retracting the lymph node packet medially, the precise course of the obturator nerve and vessels can be identified and protected (Fig. 103–20). After securing the distal extent of the lymph node packet, the packet is divided, retracted cranially, and bluntly separated from the obturator vessels and nerve. Hemoclips are used to control lymphatic vessels at the most proximal and distal extent of the dissection (Fig. 103–21). The lymph nodes can usually be removed as a single packet and extracted either through the 12-mm trocar or by placing them in the entrapment sack along with the prostate specimen.

An extended lymph node dissection typically includes nodes categorized as external iliac, obturator, and hypogastric and has a boundary of the genitofemoral nerve laterally, the bladder wall medially, the node of Cloquet distally, and a point 2 cm above the bifurcation of the common iliac artery proximally. Importantly,

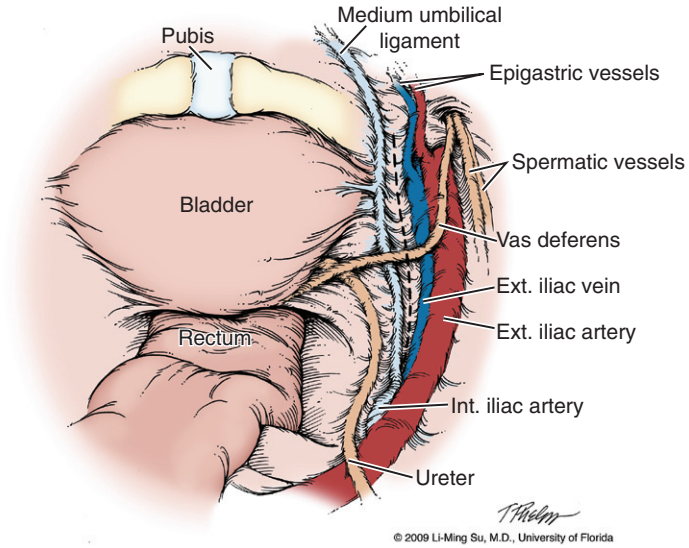


Figure 103–19. Laparoscopic pelvic lymph node dissection. Initial transperitoneal view of the obturator fossa and relevant anatomy. The *dashed line* indicates the longitudinal incision that is made in the peritoneum lateral and parallel to the median umbilical ligament back toward the bifurcation of the iliac vessels in efforts to provide exposure to the obturator fossa and lymph nodes. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

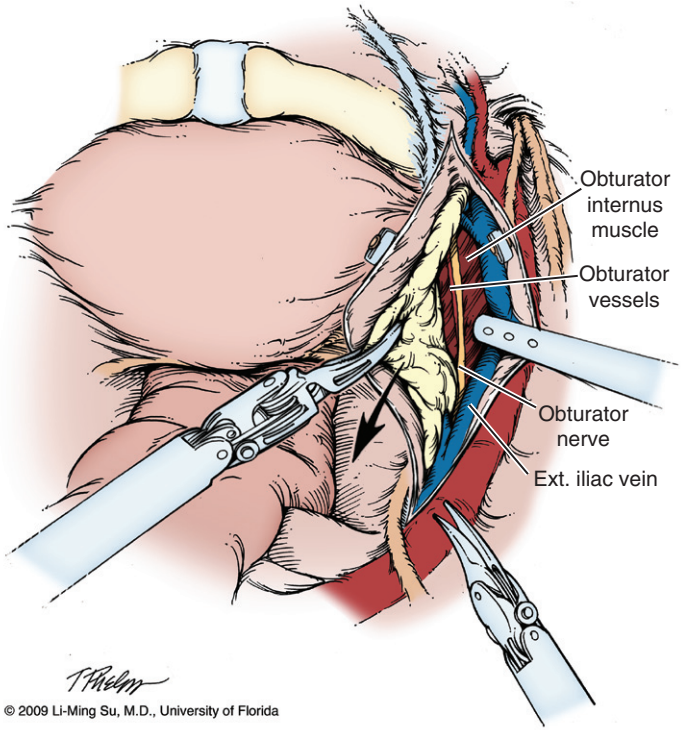


Figure 103–20. Initial dissection of a standard pelvic lymph node template. The vas deferens has been clipped and divided. With medial traction on the lymph node packet, the lateral extent of the dissection is defined using mainly blunt dissection. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

the posterior dissection involves complete skeletonization of the hypogastric artery and its medial branches, as well as the area posterior to the obturator. **Studies show that an extended dissection has a higher diagnostic yield than standard or limited PLND because it recognizes and removes positive lymph nodes more commonly.**

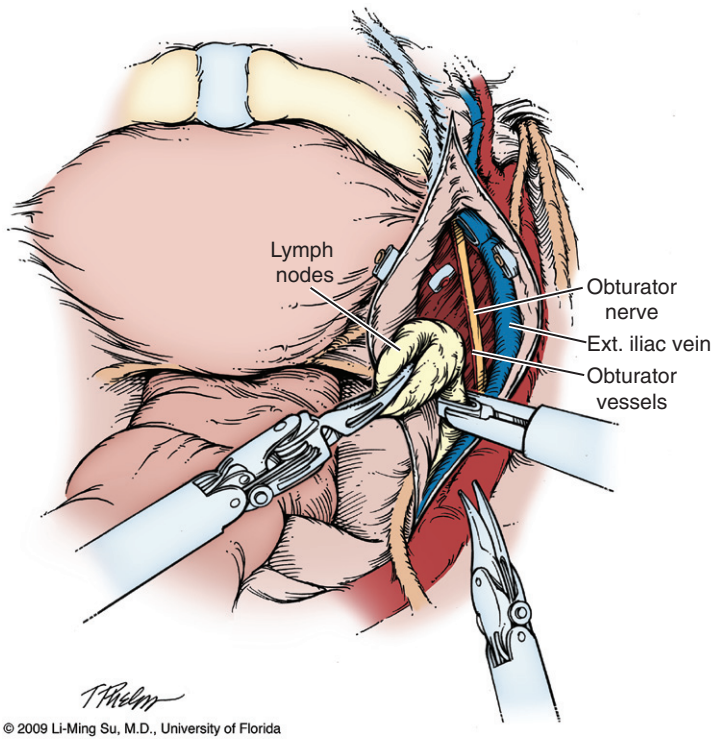


Figure 103–21. Final dissection of a standard pelvic lymph node template. The proximal and distal extent of the lymph node packet are clipped and divided, taking great care to avoid injury to the obturator nerve and vessels, as well as the accessory obturator vein. (Copyright Li-Ming Su, MD, University of Florida, 2009.)

Extended lymph node dissection can be performed laparoscopically and robotically. The da Vinci S system allows more proximal angulation of the instruments, and this can significantly facilitate dissection around the bifurcation of the common iliac artery. A thorough dissection adds time to the surgical procedure, but this is true regardless of whether laparoscopic or open surgery is performed. No valid comparative studies exist to support the superiority of open versus laparoscopic PLND. Using lymph node count as a surrogate for adequacy of the dissection is problematic because the method and thoroughness of pathologic evaluation is, perhaps, even more influential than the anatomic extent of the surgical dissection. With careful attention to meticulous dissection, though, all of the fibrous, fatty, and lymphatic tissue within the commonly accepted anatomic boundaries for an extended lymph node dissection can be removed laparoscopically or robotically. Use of clips on identifiable lymphatic channels can minimize the occurrence of a postoperative lymphocele.

Complications of Pelvic Lymph Node Dissection

Because, by definition, PLND requires skeletonization of portions of the common iliac, external iliac, and hypogastric arteries and veins, the possibility of major vascular injury exists. A small venotomy or arteriotomy can be closed laparoscopically with a fine polypropylene (Prolene) suture. A major injury may require rapid conversion to an open approach. However, the incidence of major vascular injury resulting in enough bleeding to require transfusion is well under 1% with PLND.

Transection of the obturator nerve may occur. Direct repair with suturing of the ends of the obturator nerve can restore partial function. Ureteral injury is uncommon, but caution must be observed during the proximal portion of the dissection as the ureter crosses the anterior portion of the common iliac artery.

A transperitoneal approach is not protective against the formation of a lymphocele. Theoretically, the communication with the entire peritoneum would allow distribution and absorption of any lymphatic fluid throughout the peritoneal lining of the abdomen and decrease the risk of lymphocele. Despite this, however, a loculation of lymphatic fluid can occur. Asymptomatic lymphoceles do not necessarily require drainage or treatment. A larger collection can compress the bladder and cause voiding symptoms. Compression of the external iliac vein can predispose the patient to deep vein thrombosis in the lower extremity. Secondary infection of lymphoceles may also occur. In the presence of symptoms or complications from a lymphocele, percutaneous drainage is typically successful. However, lymphatic fluid can reaccumulate, requiring repeat drainage with injection of a sclerosing agent or surgical opening of a window with marsupialization of the lymphocele wall by laparoscopic means.

Key Points: Laparoscopic Pelvic Lymph Node Dissection

- PLND is generally recommended in patients with intermediate or high-risk parameters of the primary tumor, generally implying a PSA of greater than 10, a large palpable nodule, or a Gleason sum of 7 or higher.
- Although an extended PLND may yield a higher lymph node count, debate continues as to the extent of PLND and the clinical benefit of removing cancerous nodes.
- Use of clips on identifiable lymphatic channels can minimize the occurrence of postoperative lymphoceles.
- A transperitoneal approach is not protective against the formation of a lymphocele because loculation of lymphatic fluid can still occur within the peritoneal cavity.
- Symptomatic lymphoceles may require percutaneous or laparoscopic drainage.

SUMMARY

In the past decade, LRP and RALP have become accepted surgical approaches for the management of patients with localized carcinoma of the prostate both in the United States and abroad. As expertise with these procedures is achieved, operative times have diminished. In experienced centers operative times are similar to that of RRP. The robotic-assisted technique provides ergonomic advantages for the surgeon and facilitates suturing and other technical aspects of the operation for surgeons who do not have highly advanced laparoscopic skills.

Comparison of outcomes between reported series is imprecise because of differences in patient selection, methods of collecting and reporting data, and the technique of pathologic sectioning and analysis. However, intraoperative blood loss with LRP and RALP has consistently been reported as minimal and transfusion is required in only a small percentage of patients. Postoperative morbidity and return to activity are both improved compared with open surgery in most reports. Good results with postoperative urinary continence and erectile function are reported with mature LRP and RALP series, although there is still debate about whether these outcomes are superior to open RRP performed by experienced surgeons. Pathologic tumor margins status seems to be comparable between laparoscopic, robotic, and open series overall (Parsons and Bennett, 2008; Ficarra et al, 2009).

Improvements in the available instruments are highly likely to advance even further the technologic capabilities of surgeons performing LRP and RALP. Equipment expense remains a significant issue for some hospitals, and not all may be able to offer this state-of-the-art technology. Nonetheless, there seems to be little doubt that minimally invasive approaches for radical prostatectomy, especially RALP, have become the dominant surgical treatment for localized prostate cancer in the United States and are having continued growth and acceptance worldwide.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter
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Radiation Therapy for Prostate Cancer

Anthony V. D'Amico, MD, PhD ● Juanita M. Crook, MD, FRCPC ● Clair J. Beard, MD ● Theodore L. DeWeese, MD ● Mark Hurwitz, MD ● Irving D. Kaplan, MD

Historical Perspective
Localized Disease
Treatment: Cancer Control and Quality of Life

HISTORICAL PERSPECTIVE

Two major advances in the radiotherapeutic management of adenocarcinoma of the prostate have occurred since the early 1980s. The first advance was the generation of linear accelerators and conformal techniques capable of delivering high doses of radiation deep within the pelvis while simultaneously respecting the normal tissue tolerance of the anterior rectal wall, prostatic urethra, femoral heads, and bladder neck. The second advance occurred when image-guided techniques were introduced for use during the insertion of radioactive sources directly into the prostate gland. Eliminating the former freehand technique has vastly improved the physician's ability to deliver high doses of radiation to the prostate gland while sparing interposed and juxtaposed normal structures. These two advances have increased the therapeutic ratio of radiation therapy (RT) in the management of prostate cancer. Specifically, decreased gastrointestinal toxicity has been documented (Dearnaley et al, 1999), and improved cancer control has been suggested (Pollack et al, 1999).

The physical property that permits the photon radiation generated from a linear accelerator to penetrate deeply and spare normal tissue is the high energy of the beam. As the energy of the beam increases, the beam penetrates deeper before exerting its cytocidal effect. Whereas orthovoltage and ^{60}Co units deposited their maximum dose within 1.25 cm below the skin surface, high-energy linear accelerators deliver the maximum dose of radiation at more than 15 cm below the skin surface. In addition, the use of multiple and conformal fields, as well as intensity-modulated and image-guided radiation therapy (Jani et al, 2003), has minimized the amount of rectum receiving the high-dose radiation volume, leading to lower rates of radiation-induced proctitis (Pollack et al, 1999).

With respect to image guidance and brachytherapy, transrectal ultrasonography (TRUS) has provided an improved monitoring system compared with freehand or fluoroscopically guided radioactive source deposition. Using this image guidance system, geometric feedback on source location within the prostate gland intraoperatively has provided the potential for delivering high doses of radiation within the prostate gland while limiting dose to the prostatic urethra and the anterior rectal wall. The theoretical advantage of brachytherapy is the physical property of rapid dose falloff (a few millimeters) because of the low energy of the radioactive sources used—only 21 and 28 keV for palladium 103 and iodine 125, respectively. This rapid falloff, however, also mandates millimeter precision in the placement of these sources to ensure that the tumor-bearing regions within the prostate gland are not underdosed. These issues are discussed in more detail in the brachytherapy sections.

In brief, the close of the 20th century saw the introduction of three-dimensional, conformal-based, image-guided RT using high-energy radiation beams and image guidance for the placement of permanent radioactive sources into the prostate gland. As discussed in this chapter, these advances in the radiotherapeutic management of adenocarcinoma of the prostate provided the basis for improvement in both quality of life and cancer control.

LOCALIZED DISEASE

Pretreatment Prognostic Factors

Recommendations for the treatment of clinically localized adenocarcinoma of the prostate should be made using the results of evidence-based medicine. The ideal end point on which to make therapeutic decisions is cause-specific survival. At present, follow-up is too short to make statistically meaningful statements regarding cause-specific survival for men diagnosed and treated for clinically localized disease in the prostate-specific antigen (PSA) era as a function of pretreatment prognostic factors and treatment modality. However, pretreatment prognostic factors have established roles in predicting recurrence (PSA, clinical) after external-beam RT (Pisansky et al, 1993; Zietman et al, 1994; Hanks et al, 1995; Lee et al, 1995; Zagars et al, 1995; Pisansky et al, 1997). These pretreatment factors include PSA level, biopsy Gleason grade, and 1992 American Joint Commission on Cancer Staging (AJCC) clinical stage. Combining these three factors has led to a definition of the three risk groups for patients managed with RT who have clinically localized disease. These three risk groups are as follows:

- Low risk: more than 85% 5-year PSA failure-free survival, 1992 AJCC clinical stage T1c-T2a and PSA level of 10 ng/mL or lower, and biopsy Gleason grade of 6 or lower

- Intermediate risk: approximately 50% 5-year PSA failure-free survival, 1992 AJCC clinical stage T2b or PSA higher than 10 but no higher than 20 ng/mL, or biopsy Gleason grade of 7
- High risk: approximately 33% 5-year PSA failure-free survival, 1992 AJCC clinical stage T2c or PSA higher than 20 ng/mL, or biopsy Gleason grade of 8 or more; patients having at least clinical stage T3a disease are grouped with high-risk patients with localized disease

Figure 104–1 shows 5-year actuarial data for 473 patients stratified using the clinical risk groups based on pretreatment PSA, biopsy Gleason grade, and 1992 AJCC clinical stage.

Pretreatment Risk Groups and Prostate Cancer–Specific Mortality

Data (D'Amico et al, 2003) now exist to support the significant association of the pretreatment risk groups and prostate cancer–specific mortality (PCSM) following external-beam radiation as shown in Figure 104–2. Specifically, in a multi-institutional study of 2370 radiation-managed patients, the relative risk of PCSM for patients with high- or intermediate-risk disease compared with low-risk disease was 14.3 (95% confidence interval [CI]: 5.2 to 24.0; $p_{Cox} < .0001$) and 5.6 (95% CI: 2.0 to 9.3; $p_{Cox} = .0012$), respectively. For illustration, Figure 104–3 contains the relative contribution of PCSM and non-PCSM following treatment to all-cause mortality stratified by the patients' age at the time of RT and the pretreatment risk group. These findings have been validated by others at Johns Hopkins (Hernandez et al, 2007) and the Mayo Clinic (Boorjian et al, 2008).

Percentage of Positive Prostate Biopsies and Intermediate-Risk Patients

The fraction of prostate biopsies found to contain prostate cancer is readily available information for all patients with PSA-detected or clinically palpable prostate cancer. The fraction of positive biopsies is obtained by dividing the number of positive cores by the number of cores sampled. Studies investigating the ability of the fraction of positive prostate biopsies × 100 (percentage of positive biopsies) to predict pathologic end points after RT suggest a role for this clinical factor in predicting tumor volume (Terris et al, 1995), extracapsular extension (Badalment et al, 1996; Borirakchanyavat et al, 1997), seminal vesicle invasion (D'Amico et al, 1996), lymph node involvement (Conrad et al, 1998), and percentage of Gleason grade 4 and 5 disease in the radical prostatectomy specimen (Epstein et al, 1994).

The percentage of positive prostate biopsies has been shown to be an independent predictor of time to postoperative PSA failure after controlling for the established prognostic factors (D'Amico et al, 2000b). The percentage of positive prostate biopsies has also been shown to provide information in addition to the known prognostic factors for predicting PSA control after external-beam RT. Specifically, 473 men treated using three-dimensional conformal external-beam RT at the Joint Center for Radiation Therapy between 1989 and 1998 had detected PSA or clinically palpable prostate cancer. Figure 104–1 illustrates the ability of the previously described risk group system (D'Amico et al, 1998b) that was based on pretreatment PSA level, biopsy Gleason grade, and 1992 AJCC clinical stage to stratify patients according to PSA outcome. Specifically, 5 years after RT, 91%, 62%, and 43% of low-, intermediate-, and high-risk patients, respectively, had not experienced PSA failure as defined by the American Society for Therapeutic Radiology and Oncology (ASTRO) consensus panel (Consensus statement, 1997).

Figure 104–4 illustrates the clinically relevant stratification provided by the percentage of positive biopsies in the previously defined intermediate-risk group on the basis of pretreatment PSA level, biopsy Gleason grade, and the 1992 AJCC clinical stage. Specifically, patients in the intermediate-risk subgroups who also had less than 34% of the positive biopsies improved their risk stratification for PSA outcome by one category to low risk. Conversely, patients with more than 50% of the positive biopsies

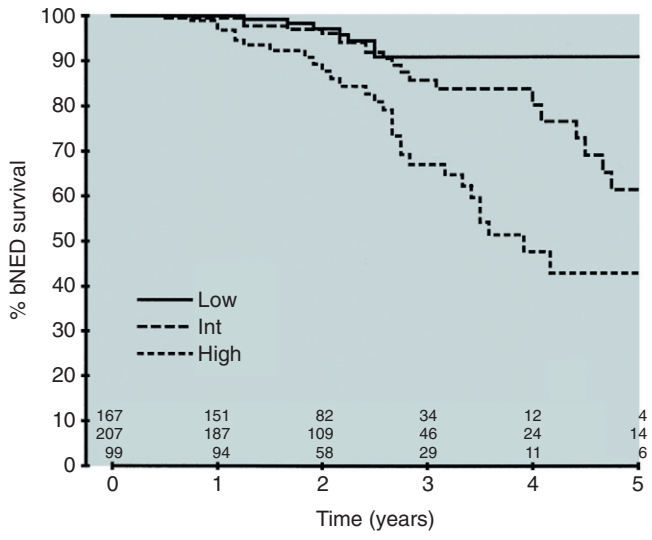


Figure 104–1. Prostate-specific antigen (PSA) failure-free survival stratified by risk group, defined using PSA value, biopsy Gleason grade, and 1992 American Joint Commission on Cancer Staging clinical T stage for 473 patients managed using external-beam radiation therapy. Pairwise, *P* values are as follows: low versus intermediate, *P* = .02; intermediate versus high, *P* = .0004; low versus high, *P* = .0001.

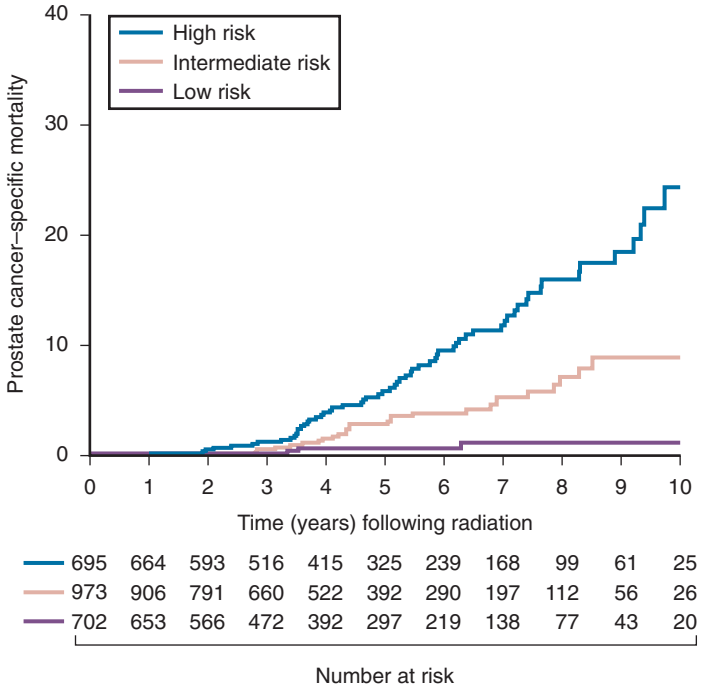


Figure 104–2. Pretreatment risk groups and prostate cancer–specific mortality following external-beam radiation.

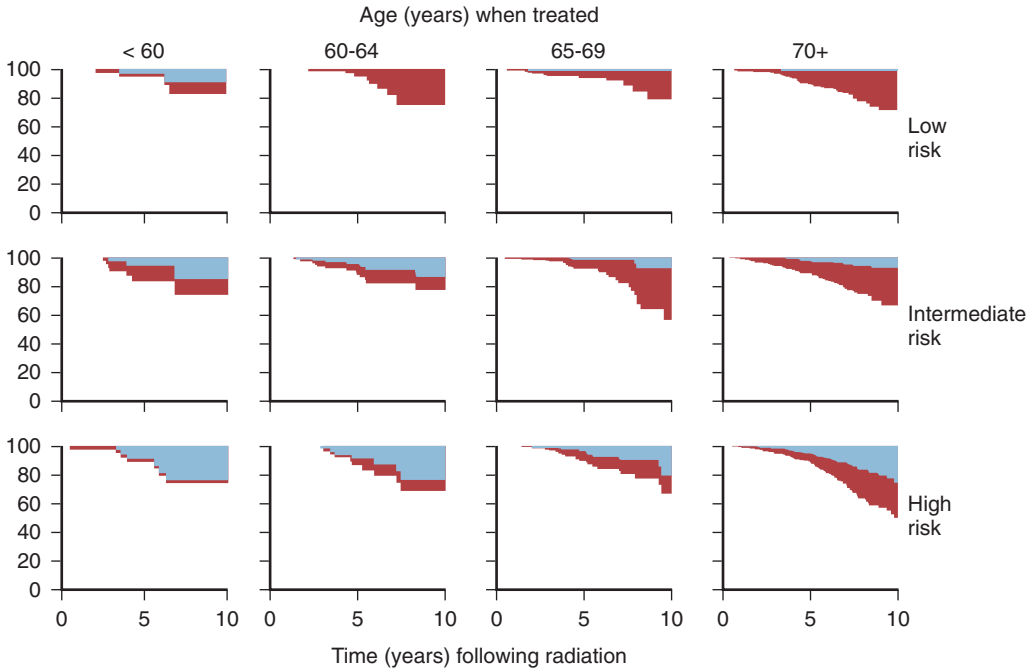


Figure 104–3. Relative contribution of prostate cancer–specific mortality (PCSM) and non-PCSM following treatment to all-cause mortality stratified by the patients' age at the time of radiation therapy and the pretreatment risk group.

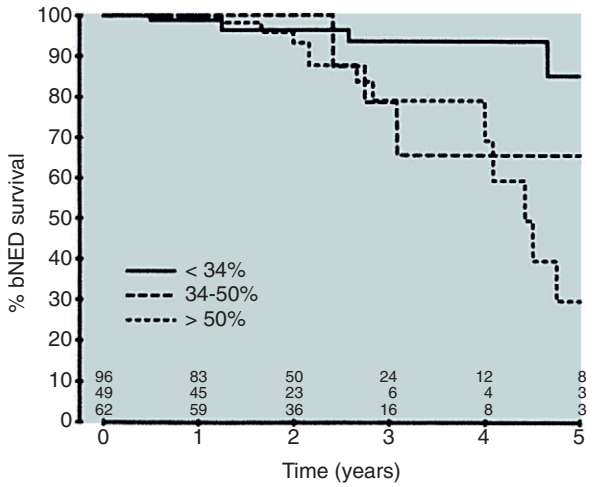


Figure 104–4. Prostate-specific antigen failure-free survival stratified by percentage of positive biopsies for 207 intermediate-risk patients managed using external-beam radiation therapy. Pairwise, *P* values are as follows: 34% versus greater than 34% to 50%, *P* = .02; greater than 34% to 50% versus greater than 50%, *P* = .06; 34% versus greater than 50%, *P* = .002.

performed less well than expected and were comparable with the high-risk patients.

Of particular importance, however, is that the majority of patients (158 of 207 [76%]) in the intermediate-risk group could be classified into either a 30% or an 85% 5-year PSA control high- or low-risk cohort, respectively, using the preoperative prostate biopsy data. Therefore of the 473 study patients, all but 49 (10%) were classified into high- or low-risk groups regarding PSA outcome after RT, using the percentage of positive prostate biopsies, the PSA level, the biopsy Gleason grade, and the 1992 AJCC clinical stage.

Percentage of Positive Prostate Biopsies and Prostate Cancer–Specific Mortality in Low-Risk and Favorable Intermediate-Risk Patients

With longer follow-up, the impact of the percentage of prostate positive biopsies (PPBs) on prostate cancer–specific mortality in low-risk and favorable intermediate-risk patients has become available (D'Amico et al, 2004). Specifically, from a series of 421 patients with low-risk (PSA ≤ 10 ng/mL and biopsy Gleason score ≤ 6) or favorable intermediate-risk (PSA > 10 to 15 ng/mL or biopsy Gleason score 7 but not both factors) disease who underwent three-dimensional conformal radiation therapy (3DCRT) to a median dose of 70.4 Gy, a significant association between PCSM and the percentage of positive prostate biopsies at diagnosis was documented. In particular, the relative risk of PCSM following 3DCRT for patients with 50% or more as compared with less than 50% PPB was 10.4 (95% CI: 1.2 to 87; p_{Cox} = .03), 6.1 (95% CI: 1.3 to 28.6; p_{Cox} = .02), and 12.5 (95% CI: 1.5 to 107; p_{Cox} = .02) in men with a PSA of 10 or less and Gleason score 6 or less, PSA 10 or less and Gleason score 7 or less, and PSA 15 or less and Gleason score 6 or less, respectively. By 5 years after 3DCRT, up to 10% as compared with 2% or less ($p_{log\ rank}$ ≤ .01) of these patients experienced PCSM if they had 50% or more as compared with less than 50% PPB as shown in Figures 104–5, 104–6, and 104–7. For the purpose of illustration, Figure 104–8 contains the relative contributions of PCSM and non-PCSM following treatment to all-cause mortality stratified by the % PPB (<50% vs. 50% or more) and the PSA level and biopsy Gleason score at diagnosis.

Therefore the percentage of positive prostate biopsies should be considered in conjunction with the PSA level, the biopsy Gleason grade, and 1992 AJCC clinical stage at diagnosis when counseling patients with newly diagnosed and clinically localized prostate cancer about both PSA outcome and, more important, the chance of avoiding PCSM after RT.

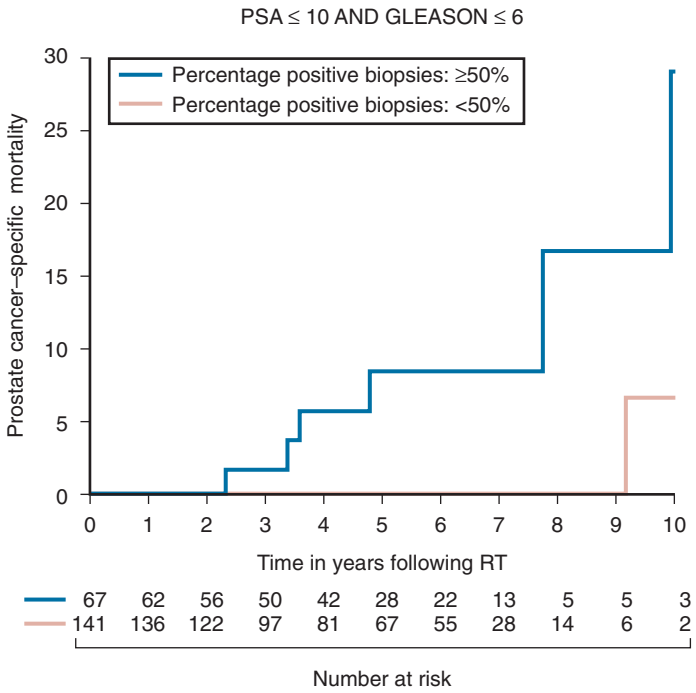


Figure 104–5. Prostate cancer–specific mortality following three-dimensional conformal radiation therapy for patients with 50% or more as compared with less than 50% prostate positive biopsy in men with a prostate-specific antigen (PSA) of 10 or less and Gleason score of 6 or less. RT, radiation therapy.

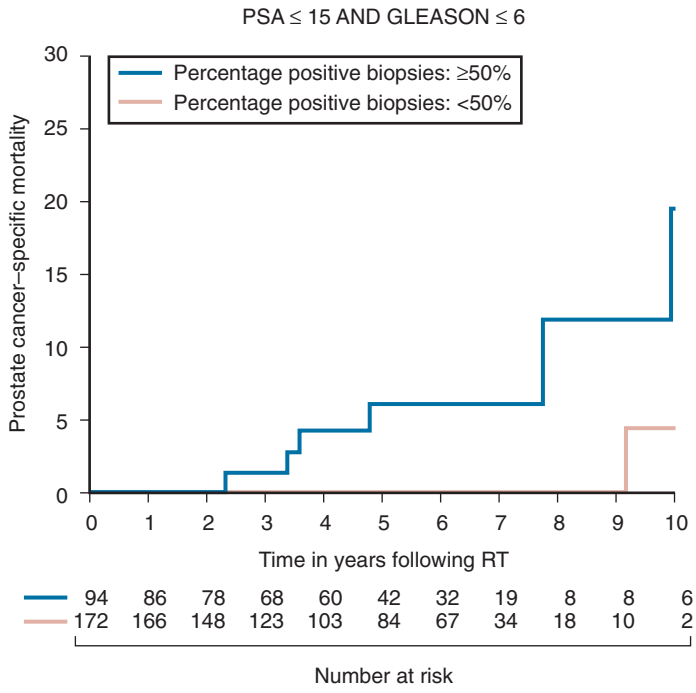


Figure 104–6. Prostate cancer–specific mortality following three-dimensional conformal radiation therapy for patients with 50% or more as compared with less than 50% prostate positive biopsy and a prostate-specific antigen (PSA) of 15 or less and Gleason score of 6 or less, respectively. RT, radiation therapy.

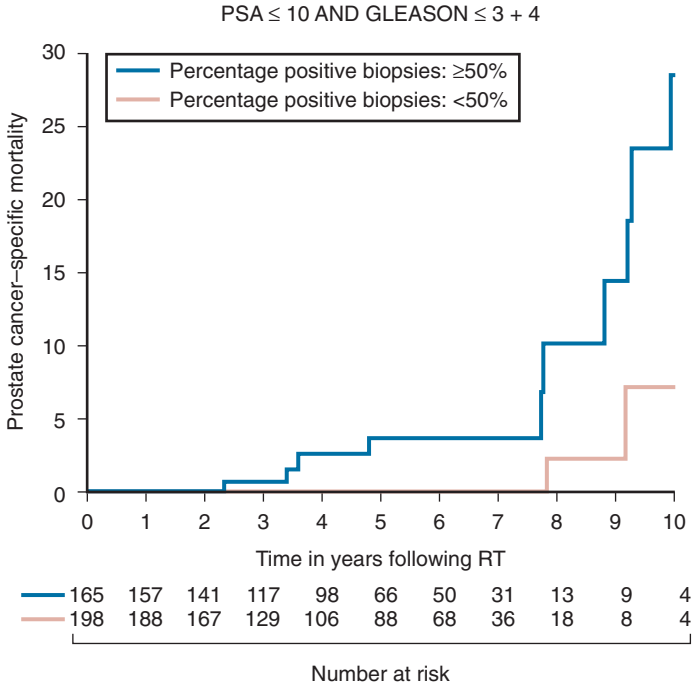


Figure 104–7. Prostate cancer–specific mortality following three-dimensional conformal radiation therapy for patients with 50% or more as compared with less than 50% prostate positive biopsy in men with a prostate-specific antigen (PSA) of 10 or less and Gleason score of 7 or less. RT, radiation therapy.

Pretreatment PSA Velocity and the Risk of Prostate Cancer–Specific Mortality

Studies (D'Amico et al, 2005; Palma et al, 2008) have documented that a pretreatment PSA velocity greater than 2 ng/mL/year is associated with an increased risk of biochemical recurrence, metastasis, and cancer-specific death following treatment with RT or RT and hormonal therapy. In particular, in men with otherwise low-risk disease undergoing external beam RT, a pretreatment PSA velocity greater than 2 ng/mL/year increased the risk of death from prostate cancer x-fold, which translated into 19% [95% CI: 2 to 39%] as compared with 0% of men dying of prostate cancer within 7 years following treatment with RT if the PSA velocity was more than as compared with 2 ng/mL/year or less, respectively. As a result such men planning to undergo RT should be considered for RT and hormonal therapy because of the known survival benefit when adding hormonal therapy to RT in men with locally advanced (Pilepich et al, 1995, 1998, 2001; Bolla et al, 2002) or localized high-risk disease (D'Amico et al, 2008).

Key Points: Pretreatment Prognostic Factors

- Prostate cancer–specific mortality can be estimated on the basis of the pretreatment PSA level, biopsy Gleason score, and clinical T category.
- The percentage of positive prostate biopsies and the pretreatment PSA velocity, particularly when greater than 2 ng/mL/year provides additional information regarding prostate cancer–specific mortality in men with low-risk or favorable intermediate-risk disease.

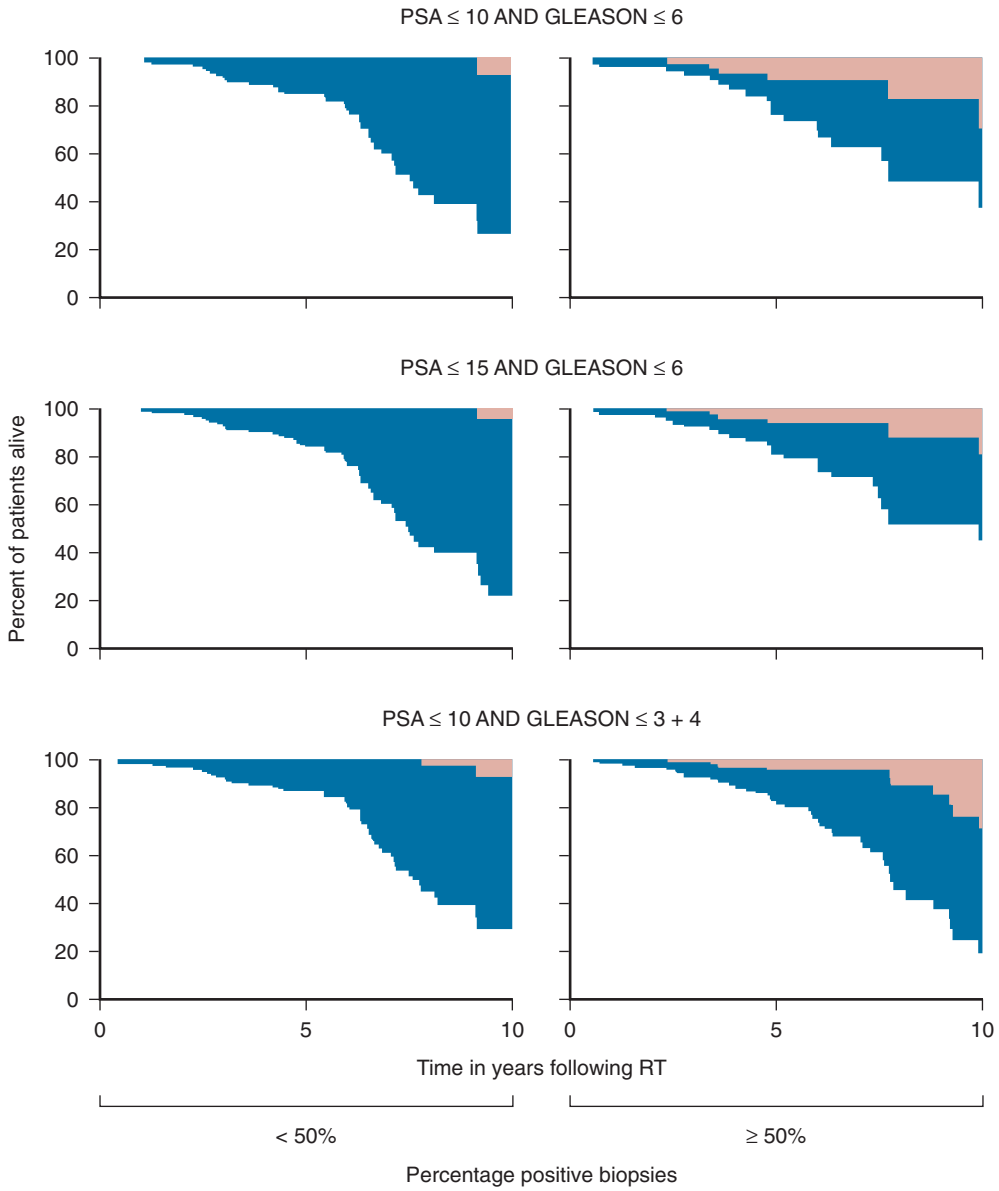


Figure 104–8. Relative contributions of prostate cancer–specific mortality (PCSM) and non-PCSM following treatment to all-cause mortality stratified by the percentage of prostate-positive biopsy (<50% vs. ≥ 50%) and the prostate-specific antigen (PSA) level and biopsy Gleason score at diagnosis. RT, radiation therapy.

Post-Treatment Prognostic Factors

Localized Disease—Evaluating the Response to Radiation

PSA Follow-up—Definition of Failure. Serum PSA has become widely accepted as a surrogate end point for monitoring the success of definitive treatment for localized prostate cancer. However, the definition of biochemical failure after RT remains controversial. Unlike the situation after radical prostatectomy, the patient successfully treated with radiotherapy still has a prostate gland and therefore is not expected to achieve an undetectable PSA reading. However, an "acceptable" PSA level after successful radiotherapy is markedly lower than the range of normal for an age-matched unirradiated population because of marked atrophy and a reduction in the size and number of nonmalignant acini (Grignon and Sakr, 1995).

Ablation of normal prostatic epithelium appears to be dose dependent. In a randomized trial comparing 70 and 78 Gy, Pollack and colleagues (2002b) found that with 78 Gy, 80% of patients achieved a nadir of less than 0.5 ng/mL, compared with 67% who received 70 Gy (P = .02). Although higher nadirs are associated with decreased disease-free survival, it is probably not necessary to ablate all the normal epithelium in order to achieve cure. Five-year freedom from biochemical failure is in the range of 80% to 90% for nadirs less than 0.5 ng/mL (Zincke et al, 1994; Lee et al, 1996; Crook et al, 1998; Critz et al, 1999; Kestin et al, 1999; DeWitt et al, 2003) but drops to 29% to 60% for nadirs of 0.6 to 1.0. However, even for PSA nadirs above 1.0 ng/mL, up to one third of patients remain free of recurrence at 5 years (DeWitt et al, 2003). Nadir PSA is a significant predictor of outcome, but no absolute nadir threshold can or should be used to define cure (DeWitt et al, 2003; Ray et al, 2004).

The 1996 ASTRO Consensus Conference (Consensus statement, 1997) proposed a standardized definition of biochemical failure after radiotherapy. Although there is no distinct PSA threshold that defines successful treatment, PSA stability following the nadir is important. The panel concluded that three consecutive increases in PSA is a reasonable definition of biochemical failure, recommending that the PSA determinations be 3 to 4 months apart in the first 2 years after radiotherapy and every 6 months thereafter. The requirement for three readings and the temporal spacing between the readings are necessary to avoid overcalling failure on the basis of temporary instability related to biologic noise or fluctuations in PSA of benign etiology (Crook et al, 1997a). It must be emphasized that establishing that a patient meets the criteria for biochemical failure is not justification for intervention. However, for the purposes of clinical trials and the reporting of data, a standard definition of failure is required. For these purposes, the date of failure should be backdated to midway between the PSA nadir and the date of the first increase.

Although the ASTRO definition provided uniformity in reporting of results, it is not a perfect solution to the problem of defining biochemical failure after radiotherapy. Waiting for three rises delays the establishment of failure by 18 months or more (Cherullo et al, 2002). This has no consequences for the individual patient because no individual requires intervention before the third rise, which defines the change in status. Furthermore, biochemical failure is not equivalent to clinical failure and is not of itself an indication for additional treatment. However, when reporting results, waiting for three rises and then backdating failure to midway between the nadir and the first rise tends to flatten the tail of the survival curve, underestimating late failures (Coen et al, 2003). Long follow-up minimizes this effect and short follow-up overestimates treatment success (Horwitz et al, 2003) because outcome cannot be predicted when the median follow-up is shorter than the median time to failure. One means of overcoming this shortcoming in the ASTRO definition is to backdate the follow-up time for all patients with one or two PSA rises (Coen et al, 2003; Thames et al, 2003). These patients can be censored (as disease free) midway between their nadir and first rise at the same time as they would be censored as a failure should they go on to have a third rise. In this way, the actuarial calculation does not benefit from extended follow-up for these patients whose status is uncertain. An alternative definition of biochemical failure that is particularly useful when few PSA values are available, as occurs when a patient has been lost to follow-up for a period of time or when PSAs are checked only annually, is any PSA value that is more than 2 ng/mL above the nadir (Coen et al, 2003).

Time to Nadir. Serum PSA declines slowly after completion of radiotherapy. The time to nadir has been shown to be inversely proportional to disease-free survival (Ray et al, 2004). The median time to nadir in patients who remain with no evidence of disease (NED) is 22 to 34 months (Hanlon et al, 2002; Pollack et al, 2002a). In a series of 615 men with a median follow-up of 64 months, Hanlon and colleagues (2002) reported that a lower nadir ($P < .0001$) and longer time to nadir are independent predictors of freedom from distant metastases ($P = .0002$). Lee and colleagues (1996) reported that 75% of men whose PSA reached a nadir in less than 12 months had distant metastases by 5 years as compared with 25% of those whose PSA took more than 12 months to reach a nadir ($P < .001$). Kestin and colleagues (1999) found that 92% of men whose PSA reached a nadir at 36 months or longer remained disease free as compared with 30% of those who reached a nadir in less than 12 months. The slow decline in PSA and the long time to PSA nadir are explained by the fact that, unlike other ablative treatment modalities such as surgery and cryotherapy, radiotherapy does not cause immediate cell death. The double-stranded DNA chromosomal breaks caused by radiotherapy are not immediately fatal but do not permit successful cell reproduction. Postmitotic cell death is not expressed until a cell tries to reproduce. Given the long doubling time of most prostate cancers, a fatally damaged cell may survive 18 to 24 months before unsuccessfully attempting cell division and dying.

Table 104–1.

Failure Pattern According to Level of PSA Nadir, Time to Nadir, and PSA Doubling Time

	PSA NADIR (ng/mL)	TIME TO NADIR (mo)	PSA DOUBLING TIME
NED	0.4-0.5	22-33	NA
Local failure	1.0-2.0	12-18	11-13 mo
Distant failure	>2.0	<12	3-6 mo

NA, not applicable; NED, no evidence of disease; PSA, prostate-specific antigen.

Significance of Nadir Value and Doubling Time. The level of PSA nadir achieved to some extent reflects the type of failure (Table 104–1). The median PSA nadir for NED patients in most series treated with external-beam radiotherapy is 0.4 to 0.5 ng/mL (Zietman et al, 1996; Critz et al, 1999; Crook et al, 2000), whereas for those exhibiting local failure it is often greater than 1.0 ng/mL and for distant failure greater than 2 ng/mL. A study by Hanlon and colleagues (2004) ($n = 615$, follow-up median 64 months) reported that freedom from distant metastases was 96% for a nadir less than 1 ng/mL, 89% for nadirs 1.1 to 2 ng/mL, and 61% for nadirs greater than 2 ng/mL. The postnadir doubling time of the PSA also correlates with the type of failure, with distant failures having shorter PSA doubling times of 3 to 6 months (Zagars et al, 1993; Hancock et al, 1995; Lee et al, 1997) and local failures having longer PSA doubling times of 11 to 13 months (Zagars et al, 1993; Hancock et al, 1995). D'Amico and coauthors (2003) reported that a PSA doubling time of less than 3 months is associated with prostate cancer mortality. Kuban and colleagues (2004) ($n = 4839$) found that PSA doubling time (<10 months vs. >10 months) and time to PSA failure (<2 years vs. >2 years) were the most significant factors in predicting distant metastasis-free survival after PSA failure.

The manner in which PSA nadir and time to nadir reflect the type of failure requires explanation. Three sources of PSA potentially contribute to the nadir: residual benign prostatic epithelium, residual local prostate cancer cells, and subclinical disseminated micrometastases. The longer the time to nadir and the lower the absolute nadir, the more likely it is that only benign prostatic epithelium remains, hence the NED status. A higher radiation dose achieves a more complete ablation of normal epithelium and thus a lower nadir. For patients in whom radiotherapy fails to eradicate all the local tumor, the PSA declines progressively until the rate of growth of the surviving prostate cancer cells is greater than the death rate of those fatally damaged by the radiation, at which point the PSA begins to rise. In the third scenario, subclinical micrometastases continue to grow unchecked despite successful treatment of the primary tumor. This growth rate outstrips the rate of decline in the local tumor population relatively early after treatment, leading to a higher and earlier nadir.

In any multivariate analysis of prognostic factors, if PSA nadir is included in the model with pretreatment PSA, Gleason score, and T stage, it becomes the strongest independent predictor of outcome (Ben-Josef et al, 1998; Crook et al, 1998; Preston et al,

1999). This is not surprising considering the close temporal relationship between the PSA nadir and the definition of biochemical recurrence. Although it is common practice to mix pretreatment prognostic factors in the same multivariate model with postradiotherapy PSA nadir, the latter should more correctly be considered a means of evaluating the response to radiotherapy.

Neoadjuvant Hormones and the Definition of Biochemical Failure. When neoadjuvant androgen deprivation is used before radiotherapy, patients often start radiotherapy with an already undetectable PSA. If the PSA remains undetectable, it is impossible to determine a true nadir or time to nadir. If hormonal therapy is only neoadjuvant or concurrent, or both, rapid recovery of the serum testosterone may cause a temporary increase in PSA shortly after completion of radiotherapy and cessation of hormonal therapy. Subsequently, as the effect of the radiotherapy is expressed, the PSA declines once again. Although complete data from randomized trials are still pending on this point, this secondary nadir probably has the same prognostic significance as PSA nadir in the absence of neoadjuvant hormonal therapy. Adherence to the ASTRO definition of biochemical failure, requiring three successive PSA increases 3 to 4 months apart, usually allows sufficient time for this phenomenon to pass and to avoid incorrectly labeling the patient as a radiotherapy failure.

Benign Bounce Phenomenon. In the presence of residual benign epithelium or before the full effect of radiotherapy has been expressed, PSA may fluctuate or show several consecutive increases. A spike or bounce can be defined as a rise greater than 0.2 ng/mL followed by a durable decline (Merrick et al, 2003b). This phenomenon is especially common after brachytherapy, where it is reported to occur in 24% to 35% of men (Critz et al, 2000; Smathers et al, 2001; Merrick et al, 2002a, 2003b; Reed et al, 2003). Spikes have been reported to be more common in younger men and after implantation with ^{125}I rather than ^{103}Pd (33% vs. 17%) (Merrick et al, 2003a). Spikes can start any time from 9 to 30 months after brachytherapy (Reed et al, 2003) and may reach a maximum PSA value up to 10 ng/mL, although the majority shows a cumulative rise of not more than 2 to 3 ng/mL. Spikes may last as long as 12 to 18 months, and double peaks can be seen. Biopsies performed to investigate the rising PSA may show residual cancer with treatment effect (indeterminate) (Reed et al, 2003). Currently, there is no reliable way to discern whether a rising PSA in the first 3 years after brachytherapy represents treatment failure. Many meet the ASTRO definition of biochemical failure. Only patience and careful follow-up demonstrate the subsequent spontaneous PSA decline to low levels.

Postradiation Therapy Biopsy

Although serum PSA nadir has been widely adopted as a surrogate end point to determine treatment efficacy, it cannot distinguish between local and systemic failure. Postradiotherapy prostate biopsies would seem to be the logical means of evaluating the local effect of radiotherapy. The major issues involve the following:

- Timing of the biopsies with respect to completion of radiotherapy
- Interpretation of indeterminate biopsies that show residual tumor with marked radiation effect and uncertain viability
- The usefulness of markers of cellular proliferation
- The uncertainty imposed by sampling error

Timing. In early reports, little was known about the rate of histologic clearance of irradiated tumor and failures were declared as early as 6 months after completion of radiotherapy (Scardino and Wheeler, 1985). It is now recognized that the time for histologic resolution of tumor parallels the time to serum PSA nadir and for the same reasons. Radiation causes postmitotic cell death, and fatally damaged cells may survive a limited number of cell divisions (Mostofi et al, 1992, 1993). Biopsies taken before histologic resolution is complete show a moderate to marked radiation effect (Crook et al, 1997b). Ultimate viability of these cells cannot be predicted. Crook and colleagues (1995) have determined that the optimal time to biopsy is 30 to 36 months after radiotherapy.

Interpretation. Gleason scoring of irradiated prostate cancer should be performed only if the histologic evidence of radiation effect is absent or minimal. Gleason's original work was based on surgically obtained material that had not been exposed to prior radiotherapy or hormonal therapy. It is based on gland architecture, which is known to be markedly altered by radiotherapy. Inappropriate application of the Gleason scoring system to disintegrating malignant glands showing a marked RT effect (Siders and Lee, 1992; Grignon and Sakr, 1995) results in a false-positive biopsy and perhaps unnecessary "salvage" therapy.

Radiation atypia in benign glands can be severe enough to mimic malignancy (Bostwick et al, 1982; Grignon and Sakr, 1995; Cheng et al, 1999). Anticytokeratin monoclonal antibody for high-molecular-weight keratin labels the basal cell layer of benign glands and therefore helps to distinguish radiation atypia in benign glands from residual tumor where the basal cell layer would be absent (Brawer et al, 1989).

Scoring systems for the degree of radiation effect have been proposed (Dhom and Degro, 1982; Bocking and Auffermann, 1987) on the basis of cytoplasmic and nuclear changes (Table 104–2) and can be helpful in interpreting the significance of residual tumor in the biopsy (Crook et al, 1997a). Their importance is to emphasize the need to differentiate between biopsies showing no or minimal radiation effect and those showing marked treatment effect (Zelefsky et al, 2004). Failure to do so dilutes the prognostic significance of biopsy status and may lead to inappropriate salvage therapy.

Markers of Cellular Proliferation. Immunohistochemical stains for markers of cellular proliferation can also be useful in interpretation of the significance of residual tumor. The two nuclear proteins expressed in proliferating cells for which there is the most clinical experience are proliferative cell nuclear antigen or PCNA (Crook et al, 1994) and Ki-67 (Ljung et al, 1996). PCNA is expressed both at DNA replication for cell division and during cellular repair.

Table 104–2.

Grading Scheme for Cytoplasmic and Nuclear Radiation Effect

(The scores for cytoplasmic and nuclear changes are added together. A score of 5-6 represents marked treatment effect, 3-4 is moderate, and 0-2 minimal.)
Cytoplasmic changes 0 No identifiable RT effect
1 Swelling and microvesicular change
2 Extensive vacuolation, macrovesicular change, and voluminous cytoplasm
3 Indistinct or ruptured cytoplasm
Lipofuscin pigment accumulation
Glands dilated or just single cells with no glandular formation
Nuclear changes 0 No identifiable RT effect
Some swelling or smudging of nuclei but nucleoli still visible
Smudged and distorted chromatin
Nucleoli rare or absent
Large bizarre nuclei
Pyknotic small condensed nuclei

RT, radiation therapy.

It is not formalin stable and is unreliable if the duration of formalin fixation is not closely monitored (Wiatrowska et al, 1997). On the other hand, Ki-67 is expressed exclusively in proliferating cells, reaches a maximum in the mitotic phase, and is formalin stable. Positive immunohistochemical staining for either of these markers in residual tumor is strongly associated with subsequent failure (Crook et al, 2000).

Sampling Error. Although TRUS guidance is recommended for postradiotherapy prostate biopsies to ensure adequate and systematic sampling, TRUS alone is of limited diagnostic use because the increase in fibrosis alters the echogenic characteristics of the irradiated prostate (Crook et al, 1993; Svetec et al, 1998). Surviving malignant cells may be in the form of minimal scattered microscopic foci. False-negative rates approaching 20% have been reported (Crook et al, 2000).

Biochemical freedom from disease, as determined by a nonrising serum PSA, is the accepted surrogate end point in determining treatment outcome and tumor eradication. It does not, however, distinguish between local and systemic failure. Local therapy should be evaluated in terms of local tumor eradication. Local failures can be reduced by treatment refinements such as dose escalation and improvements in treatment planning and delivery. Systemic failures are a problem of selection of patients and a failure to recognize high-risk features that require a combined modality approach to address a potential systemic component. Although postradiotherapy prostate biopsies are fraught with problems of timing, interpretation, and sampling error, they do help to distinguish between local and systemic failures and are a valuable research tool. Clearly viable residual tumor should be in evidence before considering radical local salvage for radiation failure.

Key Points: Post-Treatment Prognostic Factors

- The level of PSA nadir achieved following radiation therapy reflects the pattern of failure. Specifically, a nadir greater than 2 ng/mL is associated with distant failure.
- The PSA doubling time following radiation therapy also predicts the pattern of failure. Specifically, a PSA doubling time of less than 3 months is almost always associated with distant failure.

TREATMENT: CANCER CONTROL AND QUALITY OF LIFE

The question of whether the absence or presence of local control of a treated tumor is related to the subsequent development of metastatic disease was explored experimentally as far back as 1970. Mice with sarcomas of the extremity developed fewer pulmonary metastases if their affected limbs were amputated early in the course of disease (Suit et al, 1970). Given that RT is a local treatment modality, one of the goals of treatment became local control, with the expectation that only patients who achieved such control could be expected to be cured of their cancer. This principle was first examined in prostate cancer in the 1980s, when a relationship between treatment planning technique and cancer control was demonstrated in the Patterns of Care Studies (Leibel et al, 1984; Hanks et al, 1988). Patients' treatment records were reviewed from 163 randomly selected radiation oncology departments located across the United States.

Tumor control was better in patients who received higher doses of radiation to larger fields, at the expense of increased complications. Fully 40% of patients' records indicated departure from current cancer guidelines for diagnostic evaluation and treatment. These studies sparked an intense interest in and ongoing effort to improve outcomes in men with prostate cancer by providing the best treatment planning and delivery systems possible (Leibel et al, 1994).

Although external-beam RT has been used for decades to treat prostate cancer, it is still an evolving specialty. Until the 1970s, radiation oncologists had to treat cancers without precise knowledge of their location within the body. Knowledge of normal anatomy, routes of spread of a particular cancer, and limited information from diagnostic radiology were used for treatment planning (Asbell et al, 1980). Radiation oncologists became adept at designing their portals on the basis of skeletal anatomy. For the treatment of prostate cancer, the radiation portals were centered on the pubic symphysis and femoral heads. One group designed a rotating platform treatment; men with prostate cancer stood on a small mechanical platform that rotated 360 degrees while the radiation beam was aimed at the level of their pants pockets. This was considered advanced for its time.

Later, oncologists learned to use additional tools for treatment planning. The location of the prostate was inferred indirectly by introducing a contrast-filled Foley catheter and rectal tube into the patient. The prostate was assumed to be located in the space between these two organs, as shown in Figure 104–9. As recently as the mid-1980s, this technique was considered state of the art.

With the advent of computed tomography (CT) scanners, a direct method to localize the prostate within the bony pelvis became available, and optimization of radiation with both physical and biologic end points was finally possible (Mohan et al, 1992; Niemierko et al, 1992). Clinicians knew as early as 1980 that they were making significant errors in field placement without CT data, but limitations in computer hardware and software allowed no solution to the problem (Rosenman et al, 1991; Fraass, 1993). Fortunately, the dramatic and rapid improvement in computer availability, lowered costs, improved graphics, and rapid computational power has changed forever the field of radiation oncology. Men with prostate cancer are the direct beneficiaries of the new technologies, and prostate cancer is one disease for which the treatment of today bears little resemblance to that used as recently as the late 1980s (Fraass, 1995).

The 1990s began the era of three-dimensional tumor visualization and treatment planning. For the first time, the internal organs—the prostate and surrounding structures—could be identified with increased precision, and the beam's eye view, a technique allowing visualization of the regional anatomy from the perspective of the beam apertures, enabled the design of plans that could more accurately treat the prostate target while minimizing dose to the surrounding normal tissues. The result is loosely described as conformal radiation therapy (CRT) because the radiation beams conform to the shape of the treatment target (Fraass, 1995). The ability to deliver CRT requires special hardware, software, and training. In the United States, there are approximately 1500 radiation facilities, only 20% of which are associated with a university or residency training program (D'Amico and Hanks, 1999). Today's residency programs all educate their radiation oncology residents in the art of CRT, and each year more practices offer this treatment as a standard therapy.

One of the goals of conformal prostate radiation is to lower the dose to the surrounding normal tissues, such as the rectum and bladder, while simultaneously increasing the dose delivered to the

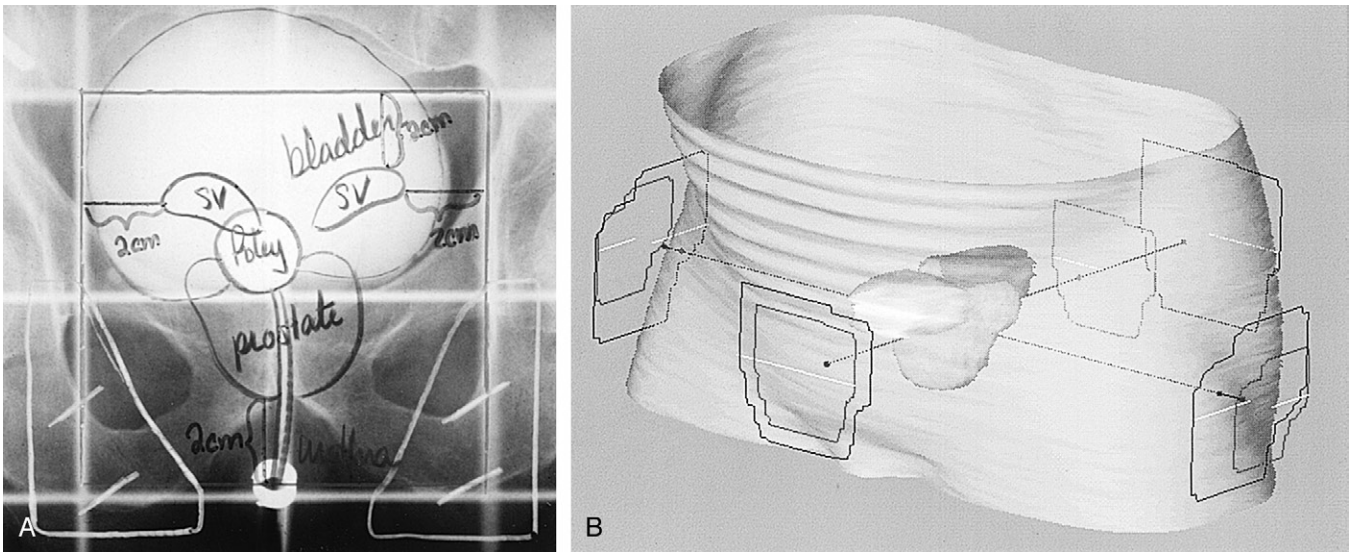


Figure 104–9. **A,** Conventional radiation therapy treatment portal, anterior view. The location of the prostate is inferred from the location of the Foley balloon and from contrast in the bladder, as well as from the location of the wire anal marker. **B,** Conformal radiation therapy portal, anterior view. The fully three-dimensional prostate volume is reconstructed from the planning computed tomography scan.

Table 104–3.

Side Effects in Patients Receiving Radiation Therapy

INSTITUTION AND REFERENCE	NO. OF PATIENTS STUDIED AND RADIATION THERAPY TECHNIQUE	PERCENTAGE WITH MODERATE TO SEVERE INTESTINAL COMPLICATIONS	PERCENTAGE WITH MODERATE TO SEVERE GENITOURINARY COMPLICATIONS
Medical College of Wisconsin (Lawton et al, 1991)	1020 Nonconformal	3.3	7.7
Memorial Sloan-Kettering (Zelefsky et al, 1999a)	743 Conformal 64.8-81 Gy	11.8	13
Fox Chase Cancer Center (Schultheiss et al, 1995)	616 Conformal 68-75 Gy	2.7	3.2
Joint Center for Radiation Therapy (Beard et al, 1998)	354 Nonconformal 66 Gy	2.6	4
University of Michigan Medical Center (Sandler et al, 1995)	721 Conformal 59.4-80.4 Gy	3	N/S
University Hospital Rotterdam (Koper et al, 1999)	266 66 Gy conformal vs. 66 Gy conventional	 19 32	
Royal Marsden Hospital (Dearnaley et al, 1999)	225 64 Gy conformal vs. 64 Gy conventional	 5 15	 20 23

prostate itself (Burman et al, 1991; Niemierko et al, 1992). All radiation oncologists agree that CT data allow more accurate placement of the radiation fields. This was first demonstrated by Pilepich and colleagues (1982), who found a 53% error rate in field placement and portal size in patients simulated without CT data. In theory, better pretreatment visualization and localization of the prostate eliminate the need to enlarge the radiation portal to account for anatomic and geometric uncertainties. It follows that smaller radiation portals allow less irradiation of nontarget structures such as the bladder or rectum. However, some data suggest that the geometric relationships between the prostate and the contiguous normal tissues vary within the same patient owing to physiologic motion of the pelvis in a random fashion that can be difficult to categorize (Ten Haken et al, 1991; Beard et al, 1996; Zelefsky et al, 1999b). The proximity of the prostate to the radiation-sensitive bladder, rectum, neurovascular bundles, and erectile tissue of the penis has always been a concern; patients who undergo external-beam radiation are at risk for gastrointestinal, genitourinary, and sexual side effects. The percentage of patients who experience side effects and the severity of the side effects differ somewhat from series to series, depending on the morbidity scale used and also on whether the assessment is physician based or patient based (Table 104–3) (Pilepich et al, 1987; Lawton et al, 1991; Austin-Seymour et al, 1994; Beard et al, 1997, 1998). In general, prospective patient-based assessments yield higher percentages of patients experiencing side effects, irrespective of the type of treatment studied (Beard et al, 1997; Talcott et al, 1998). If there is still some debate about whether complication rates have decreased as a result of conformal treatment, it is probably because clinicians increased their doses as treatment portals became smaller. Also, although normal tissue complication rates have been established to be related to radiation dose and volume, they

are also influenced by other dosimetric and clinical factors such as coexisting disease in individual patients that cannot be fully controlled or described in clinical studies (Pollack et al, 2003).

Several authors (Sandler et al, 1992, 1995; Leibel et al, 1994; Schultheiss et al, 1995, 1997) have compared the complication rates in their own prostate cancer patients receiving conventional versus conformal radiation. Most authors use the Radiation Therapy Oncology Group (RTOG) late-radiation morbidity scales, as shown in Table 104–4.

A prospective randomized trial was performed in the University Hospital of Rotterdam and the Daniel den Hoed Cancer Center of the Netherlands comparing the effect of 66 Gy delivered by either conventional therapy or CRT in a group of 266 patients (Koper et al, 1999). All patients were evaluated for gastrointestinal and genitourinary outcomes. A statistically significant reduction was seen in the proportion of patients experiencing grade 2 rectal toxicity in the conformal arm of the study (19% vs. 32%) ($P = .02$). Most of the benefit with conformal RT was due to a low incidence of anal side effects (8% compared with 16% experienced by the control group). Interestingly, no difference was seen in the percentages of patients who experienced bladder symptoms, which were minimal in both arms of the trial. A second prospective randomized trial comparing conformal and conventional radiation was performed at the Royal Marsden Hospital (Dearnaley et al, 1999). In that trial, 225 men were randomly assigned to receive 64 Gy of one or the other form of radiation. Only 5% of the conformal group developed grade 2 proctitis and bleeding, compared with 15% of the conventional group ($P = .01$). As in the Dutch study, no difference was seen between the groups in the development of grade 1 or 2 bladder symptoms.

Sexual function after conformal RT has been evaluated by several groups. At the Joint Center for Radiation Therapy and the Dana-Farber Cancer Institute (DFCI), patients participating in a prospective multi-institutional outcomes trial were divided into three groups on the basis of their RT treatment technique (Beard et al, 1997). As shown in Table 104–5, fewer patients reported sexual side effects after treatment with conformal radiation than with small-field or whole-pelvis treatment. None of the values were statistically significant, but this may have been due in part to the small sample size studied.

New data exist on the relationship between dose and morbidity. For prostate cancer, most of the progress has been made in the area of rectal complications. Predictors of bladder complications have yet to be identified, perhaps because they manifest many years after treatment (Gardner et al, 2002). Most "late" rectal complications, however, are seen within 2 years and almost always within 4 years of treatment (Pollack et al, 2002b) and are more easily evaluated. In the M.D. Anderson Cancer Center trial, the

Table 104–4.

RTOG Late Gastrointestinal and Genitourinary Morbidity Scales

GRADE	GENITOURINARY	GASTROINTESTINAL
2	Moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria	More than two antidiarrheals per week; regular non-narcotic for pain; occasional blood transfusion; occasional steroids; occasional dilation; intermittent use of pads
3	Severe frequency and dysuria; severe generalized telangiectasia; frequent hematuria; reduction in bladder capacity (<150 mL)	More than two antidiarrheals per day; regular narcotic for pain; frequent blood transfusions; steroid enemas; hyperbaric oxygen for ulceration; regular dilation; daily use of pads
4	Necrosis; contracted bladder (<100 mL); severe hemorrhagic cystitis	Perforation; life-threatening bleeding; surgical repair
5	Fatal toxicity	Fatal toxicity

RTOG, Radiation Therapy Oncology Group.

Table 104–5.

Prospective Multi-Institutional Outcomes Data on Sexual Symptoms over Time in Patients Treated with Conventional Whole-Pelvis Irradiation, Conventional Small-Field Irradiation, and Conformal Irradiation without Dose Escalation

VARIABLE	TREATMENT GROUP	NO. OF PATIENTS	PRE-XRT	3 MO (%)	12 MO (%)	P VALUE
No erections at all	WP	16	6	25	44	.31
	SF	34	18	24	32	
	C	20	15	5	20	
Erections present but inadequate for intercourse	WP	15	33	60	73	.69
	SF	32	38	56	63	
	C	20	60	55	60	
Difficulty achieving erections	WP	18	56	78	50	.25
	SF	45	56	64	38	
	C	24	50	50	25	
No or infrequent sexual desire	WP	21	19	43	43	.22
	SF	41	49	46	37	
	C	25	40	28	20	
No sexual satisfaction	WP	18	33	50	56	.13
	SF	39	38	49	38	
	C	21	38	33	24	

C, conformal; SF, small field; WP, whole pelvis; XRT, external-beam radiation therapy.

From Beard C, Propert K, Rieker P, et al. Complications after treatment with external-beam irradiation in early-stage prostate cancer patients: a prospective multiinstitutional outcomes study. J Clin Oncol 1997;15:223–9.

5-year freedom from a complication above grade 2 was 26% in the 78-Gy arm and 12% for those in the 70-Gy arm, nicely demonstrating the relationship that can exist between dose and complications. When further analysis was performed to identify factors other than total dose that might be used to predict for rectal toxicity, it was shown that the risk of complications increased from 25% to 46% when the rectal volume exposed to 70 Gy increased from less than 25% to greater than 25% (Pollack et al, 2002a). A more detailed analysis followed and showed that it was the proportion of the rectum receiving greater than 70 Gy that was more significant than the absolute rectal volume (Huang et al, 2002b), but the basic premise remained the same.

Unlike that after radical prostatectomy, sexual dysfunction after RT increases slowly with time (Talcott et al, 1998). Zelefsky and colleagues (1999a) from Memorial Sloan-Kettering Cancer Center reported that 39% of 542 previously potent patients given 64.8 to 81 Gy of conformal radiation became impotent within 5 years of treatment. A retrospective evaluation of 287 men from the University of Chicago yielded similar results, with 53% of previously potent men reporting impotence by 60 months after conformal therapy (Mantz et al, 1999). As with other studies of sexual function after radiation, the men most likely to remain potent after treatment were those with good pretreatment sexual function and little or no comorbid illness and those who did not receive androgen therapy.

Key Point: Treatment—Cancer Control and Quality of Life

- Randomized control trials show a benefit in PSA control for doses of radiation therapy of 78 to 79 Gy as compared with 70 Gy primarily in men with low- or intermediate-risk prostate cancer.

Tumor Control after Conformal Radiation Therapy

Long-term (more than 10 years of follow-up) data after conformal RT are not yet available, but early data have been reported by several centers. Most of these data are measured by freedom from PSA failure.

Zelefsky and colleagues (1998) reported their results for the first 743 men with prostate cancer treated with prospective dose-escalation conformal radiation. Patients were divided into favorable (stage T1 or T2, PSA < 10 ng/mL, Gleason grade < 6), intermediate (having one unfavorable feature), and unfavorable (having two unfavorable features) groups. For these three groups, the 5-year PSA freedom-from-relapse rates were 85%, 65%, and 35%, respectively. Almost identical data were obtained by Fukunaga-Johnson and colleagues (1997) at the University of Michigan. In that series, 707 patients received conformal radiation at doses of up to 80 Gy, with most patients receiving more than 69 Gy. Patients with favorable features (defined as stage T1 or T2, Gleason grade 7, and PSA < 10 ng/mL) enjoyed a 75% 5-year freedom from PSA relapse, compared with a 37% rate in those with unfavorable features (T3 or T4, Gleason grade > 7, or PSA > 10 ng/mL). Researchers at the Fox Chase Cancer Center in Philadelphia modeled the effect of dose levels less than 74 Gy against those greater than 74 Gy using pairs of patients matched by stage, pretreatment PSA level, and Gleason grade (Hanks et al, 1999). When PSA was discounted, delivered dose greater than 74 Gy correlated significantly with freedom from local disease progression and freedom from distant metastases and increased cause-specific and overall survival. The results were still significant for freedom from disease progression and freedom from distant metastases when PSA was included as an independent variable.

Six hundred eighteen patients who received conformal radiation were divided into groups on the basis of their pretreatment tumor characteristics (Gleason grade, clinical stage, and PSA level) and their total radiation dose (76 Gy vs. more than 76 Gy). Six subgroups were created. Patients with favorable tumors (Gleason grade 6, stage T1 or T2a) who also had a PSA less than 10 ng/mL derived no benefit from dose escalation because all patients in this group did well. Patients with unfavorable tumors (Gleason grade 7 to 10, stage T2b or T3) who had a PSA greater than 20 ng/mL also derived no benefit from dose escalation. In this cohort, both arms fared poorly, with freedom-from-relapse rates that were less than 30%. All other patients demonstrated statistically significant improved freedom-from-relapse rates with high-dose conformal treatment, as shown in Figure 104–10.

It has long been understood that increased doses of external RT are associated with better cancer control rates for patients with prostate cancer. For many years, an isocenter dose of 70 Gy was considered the maximum dose that could be safely delivered. With the advent of CRT, several groups looked at higher doses in the setting of a randomized trial. At Massachusetts General Hospital, a trial randomizing between 67.2 Gy (conventional arm) and 75.6 Gy (proton boost arm) was undertaken in patients with locally advanced disease. The study showed a significant increase in local control with the higher dose, with 8-year rates of 19% and 84% (P = .0014) for patients in the high- and low-dose arms, respectively (Shipley et al, 1995). Disease-free survival was also better for a subset of patients with Gleason grade 8 to 10 cancer, but no differences in overall or cancer-specific survival were noted.

A number of CRT and intensity-modulated radiotherapy (IMRT) dose escalation trials are under way or have completed accrual

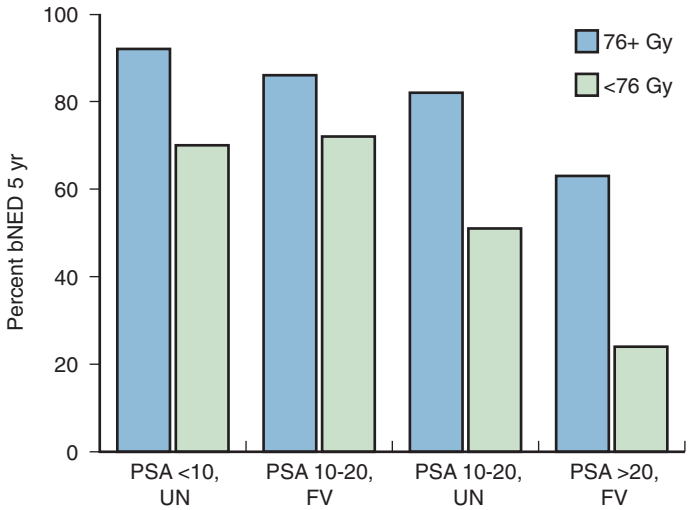


Figure 104–10. The advantage of dose escalation is shown in these dose-response graphs. Patients are divided into groups on the basis of their pretreatment clinical characteristics and the dose of radiation they received. FV, favorable characteristics (Gleason grade 6, stage T1c-T2a); UN, unfavorable characteristics (Gleason grade 7-10, stage T2b-T3). (Modified from Hanks G, Hanlon A, Pinover W, et al. Survival advantage for prostate cancer patients treated with high-dose three-dimensional conformal radiotherapy. Cancer J Sci Am 1999;5:152–8.)

(Pollack), but only the M.D. Anderson Cancer Center trial has reached maturity and been published. In this trial, 301 patients were randomized; 150 received the standard CRT dose of 70 Gy at isocenter, and the other 150 received the higher dose of 78 Gy at isocenter (Pollack et al, 2002b). The 6-year rates of freedom from failure were significantly higher for those randomly assigned to the 78-Gy arm (70% vs. 64%, $P = .03$). The greatest benefit was observed for patients with a pretreatment PSA greater than 10 ng/mL. These intermediate- to high-risk patients had 6-year freedom-from-failure rates of 62% and 43% when treated with 78 and 70 Gy, respectively ($P = .12$). There was also a borderline reduction in distant metastases for patients in this group who received the higher dose (2% vs. 12%, $P = .056$).

Patients who receive conformal radiation, as opposed to conventional radiation, may be treated with higher doses safely. They appear to develop fewer complications and enjoy a decreased risk of tumor recurrence during the first 5 years after treatment. Given the benefit demonstrated by both single-institutional retrospective reviews and prospective randomized trials, conformal radiation has become the standard against which other therapies must be measured. Dose escalation therapy to doses greater than 75 Gy is still experimental, but the early data appear to be highly favorable.

Intensity Modulation

Although CRT was a major technological advance, it represented advancement of treatment planning processes that had been in place since the 1980s. Real progress in the delivery of radiation came with the advent of IMRT. IMRT is an exciting form of conformal RT that uses extremely advanced software, specialized personnel, and hardware adaptations to linear accelerators (Burman et al, 1997). At present, its availability is limited to a small number of radiation centers because of its complexity, but in time it may replace CRT in popularity and availability. The goal of IMRT treatment planning and delivery is to maximize treatment to the target (e.g., the prostate) while minimizing treatment to the surrounding tissues to a degree that is not possible with conformal therapy (Oh et al, 1999).

The term *IMRT* is now applied to a family of methodologies that use different methods of treatment planning and delivery in order to achieve a precise, nonuniform beam fluence (Jani et al, 2003). IMRT uses a new planning approach referred to as inverse treatment planning. This approach gives equal attention to the areas where radiation dose is to be minimized and the areas that are to receive high-dose treatment. Inverse planning uses a mathematic approach to convert a desired dose distribution to the target volume and normal organs into a clinically applicable treatment plan. The planning computer, using a mathematic optimization technique known as simulated annealing, determines the optimized beam arrangement. The second component of IMRT is computer-controlled modulation of the intensity of the radiation beam during treatment. The outcome is a set of radiation beams with changing intensities across the field, as shown in Figure 104–11. With this technology, the prostate can receive a daily dose of 180 cGy, whereas the majority of the adjacent bladder receives less than half of this dose.

An example of an intensity-modulated beam is shown in Figure 104–12. The tight distribution of radiation around the prostate with avoidance of most of the rectum and bladder is seen on inspection of the figure. IMRT for prostate cancer generally uses five or seven radiation ports or fields per day, as shown in Figure 104–13. Prostate cancer is currently the single most common tumor site treated with IMRT worldwide (Guerrero Urbano et al, 2004). When IMRT is compared with CRT in the same patient, using the same prescribed dose, statistically significantly lower doses are delivered to the critical normal tissues: rectum, bladder, and small bowel (Luxton et al, 2004).

Because the risk of rectal and bladder complications is believed to be a continuous function of dose, the lower the proportion of

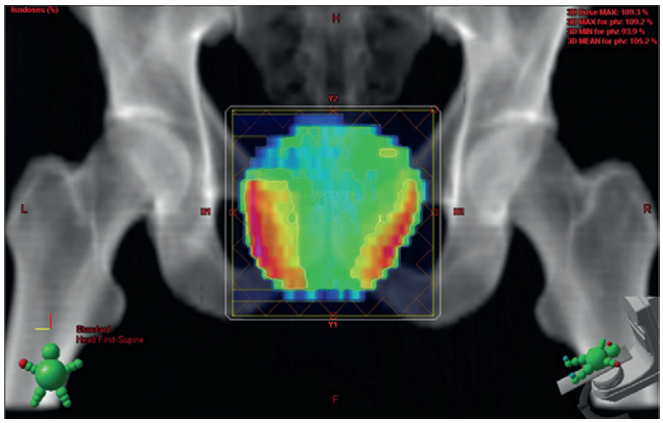


Figure 104–11. Intensity-modulated radiotherapy fluence.

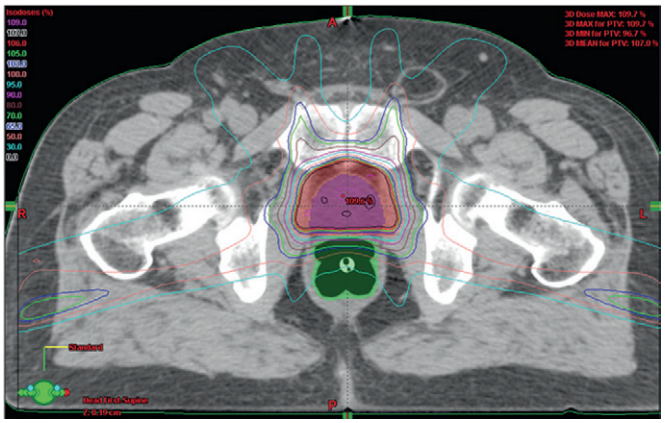


Figure 104–12. New intensity-modulated radiotherapy.

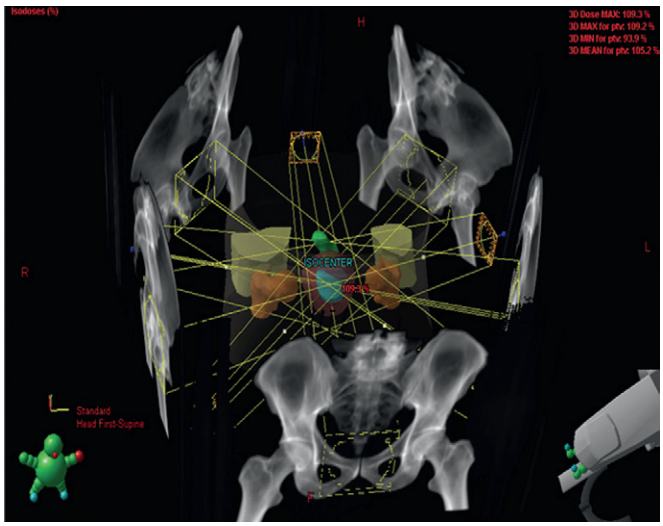


Figure 104–13. Intensity-modulated radiotherapy setup.

these organs that receive high dose, the lower the complication probability, all else being equal. For this reason, radiation oncologists who deliver IMRT choose dose constraints before initiating treatment planning. At the Brigham and Women's Hospital, we limit the volume of rectum that receives more than 65 Gy to 25%. The volume of rectum that receives more than 47 Gy is limited to less than 43%. Although the exact relationship between bladder dose and complication rates has not been established, it is common practice to define constraints for the bladder as well. In general, the goal is to limit less than 25% of the bladder volume to more than 65 Gy and less than 50% of the bladder volume to more than 40 Gy. Each practitioner may have his or her own set of constraints. There is no universally accepted standard.

One of the important considerations for radiation oncologists who treat prostate cancer is the issue of prostate motion. That prostate motion occurs is well documented, both on a day-to-day basis (Ten Haken et al, 1991; Beard et al, 1996) and, to a lesser extent, during the time it takes to deliver a daily radiation treatment (Huang et al, 2002a). Radiation oncologists can either expand the size of the radiation beam to accommodate prostate motion and accept the risk of increased morbidity or, if small fields are to be used, check the location of the prostate each day before delivering radiation. This can be done with a daily ultrasound determination of the prostate location immediately before treatment while the patient is on the treatment table, but this approach is highly operator independent and susceptible to error (Lee et al, 2002). Another option is to introduce radiopaque markers into the prostate under ultrasound guidance and to use a commercially available software program to localize the prostate each day before treatment while the patient is on the treatment table. Neither approach, however, addresses the issue of intrafraction motion. The solution to this problem may be prostate immobilization. At Brigham and Women's Hospital, a balloon immobilization device is introduced through the rectum before treatment planning and each of the first 15 treatments. The balloon is inflated with 60 to 100 cm^3 of air. Inflation of the balloon pins the prostate against the pubic bone. Each day with the patient on the treatment table, positioning films are taken and the fields are set up to the balloon immobilizer. Because the immobilized prostate does not move during treatment, small posterior margins can be used (Fig. 104–14), thus minimizing dose to the rectum. In the first 28 patients studied with this approach at Brigham and Women's Hospital, the use of the balloon immobilizer decreased the percentage of rectum receiving more than 70 Gy from 36% if no balloon was used to 3.5% with 15 immobilized treatments (Sanghani et al, 2004).

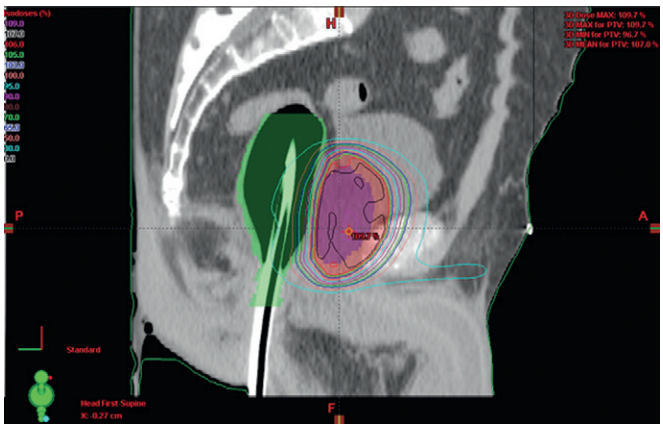


Figure 104–14. Balloon intensity-modulated radiotherapy. (Courtesy of Fred Hacker, PhD, Department of Radiation Oncology, Brigham and Women's Hospital.)

In a retrospective analysis of patients treated in a phase I/II trial, investigators from Memorial Sloan-Kettering Cancer Center reported a reduction in morbidity from 14% at 3 years to 2% after moving from CRT (81 Gy, $n = 189$) to IMRT (81 Gy, $n = 61$) (Zelefsky et al, 2002). Ninety percent of the patients in this study were treated to 81 Gy and 10% to 86.4 Gy, doses never attempted before in prostate cancer patients. After 2 years, only 4.5% of patients had acute grade 2 rectal toxicity and none experienced grade 3 or 4. Late grade 2, 3, and 4 toxicity occurred in 1.5%, 0.1%, and 0% of patients, respectively. One caveat in the interpretation of these data is as follows. Rectal blocks were used and the entire prostate gland with a margin did not receive the prescribed dose. Specifically, prostate tissue in the region of the anterior rectal wall received much lower doses, on the order of 74 to 76 Gy. However, much of the gland was treated to the prescribed dose and the complication rates were low. In a retrospective analysis of 77 patients treated at Baylor College of Medicine, investigators demonstrated a statistically significant difference for both rectal and bladder toxicity ($P < .001$) between the IMRT and CRT groups. These publications created immediate interest in dose escalation and IMRT for prostate cancer.

Published reports suggest that erectile dysfunction after radiation is caused predominantly by vascular damage. More recent data suggest that it is dose to the penile bulb that correlates best with erectile dysfunction after CRT (Roach et al, 2000; Fisch et al, 2001; Merrick et al, 2001). With the interest in dose escalation, there is some concern that post-therapy potency rates will decline (Kao et al, 2004), and preliminary data from Memorial Sloan-Kettering suggest that this may be true (Zelefsky et al, 1999a). In order to maintain or lower the risk of erectile dysfunction after dose escalation, it is necessary to modify existing techniques with this goal in mind. Researchers at the University of Chicago Medical Center undertook a planning exercise in 10 consecutive patients with prostate cancer. They planned each patient with an optimized CRT technique and then replanned each for IMRT, without adding dose constraints for the erectile tissue. IMRT significantly decreased the percentage of the penile bulb receiving 40 Gy ($P < .001$), and the percentage of volume receiving more than 70 Gy was nearly identical for both CRT and IMRT.

A similar modeling study was undertaken by investigators at Fox Chase Cancer Center (Buyyounouski et al, 2004). In this study, the object was to limit the radiation dose to the penile bulb and corpora without increasing radiation dose to the rectum and bladder. Twenty-three patients were studied. The dose to the erectile tissue was easily decreased by 60% (compared with standard CRT) in all patients. Limiting the dose received by erectile tissue to 15 Gy was easily accomplished in 80% of patients but required significant alteration of field arrangement in the other 20%. These investigations provided interesting dosimetric evidence that IMRT allows an increased therapeutic ratio in prostate cancer. However, long-term clinical data to prove this hypothesis are not yet available.

Only a few groups have used IMRT for enough time to report any efficacy data. The group at Memorial Sloan-Kettering has the most experience in the United States with IMRT. As shown in their outcome data, the PSA-relapse-free survival rates were highest after treatment with IMRT when the dose of radiation delivered was greater than 81 Gy (Leibel et al, 2003). The median time to follow-up for these patients was 50 months, but the range was broad (6 to 150 months) and presumably the patients who received the highest doses were also those treated most recently.

Key Point: Intensity Modulation

- IMRT provides the ability to deliver higher doses of radiation with lower rates of rectal bleeding.

Heavy Particle Beams

Since the 1950s, radiation oncologists have used particle beam therapy for their patients with cancer. The common application of particle therapy is with the electron beam, which is created by all modern linear accelerators. Other particles such as protons, neutrons, helium ions, heavy ions (neon, argon, carbon), and negative ions are available as well. These heavy particle beams are difficult to produce and to control but have certain theoretic advantages over conventional x-ray and electron beams. They are more densely destructive in tissue, and the damage they create is less easily repaired by tumor cells. In addition, they travel differently in tissue and exhibit a Bragg peak, which refers to a sharp cutoff in dose at the end of the particle's range in tissue; see Figure 104–15. Beyond this depth, the tissue receives little or no radiation. Thus with appropriate focus and application, it can be easier to spare the normal tissues surrounding the cancerous target.

The most commonly used particles are neutrons and protons. The RTOG sponsored a phase III trial in 1977 (Lawton et al, 1991) in which 91 patients with prostate cancer were randomly assigned to receive treatment with neutrons or conventional radiographs. At 10 years, survival was better in the neutron arm (46%) than in the photon arm (26%). However, the patients were not equally divided between the two arms. Poor prognosticators such as stage D1 disease were more common in the photon arm. A survival difference between the two groups may have been due to this aspect more than to any therapeutic benefit of neutrons per se.

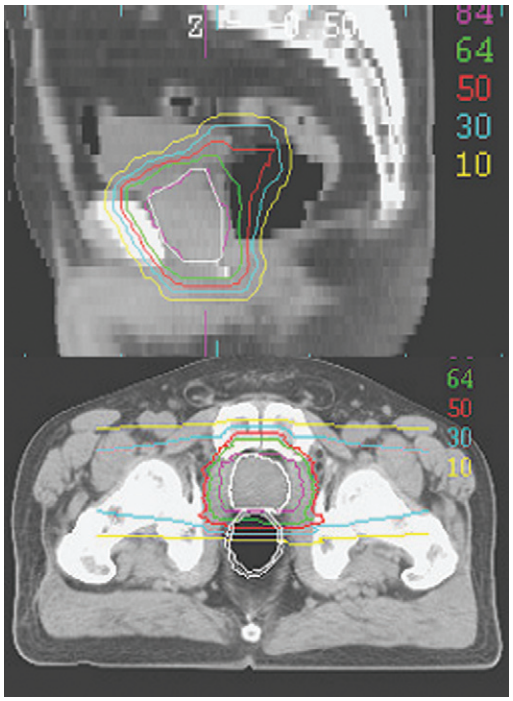


Figure 104–15. Proton beam therapy. (Courtesy of Anthony Zietman, Massachusetts Hospital.)

However, the data were compelling enough to lead the National Cancer Institute to fund the construction of several state-of-the-art neutron beam facilities. Again, trials were undertaken to study the efficacy and morbidity of neutron treatment. Because today's cyclotrons are large and extremely expensive, there are few national facilities using neutron beam treatment for cancer patients. In the mid-1980s, a second prospective randomized trial was undertaken by the RTOG (Russell et al, 1994). One hundred seventy-eight prostate cancer patients were randomly assigned to receive either neutron beam or conventional x-ray treatment (nonconformal). The local control rate was higher for the patients who received neutron therapy than for those who received photons (89% vs. 68%), as was the 5-year rate of freedom from PSA failure (83% vs. 55%). However, survival rates were the same for both arms. Morbidity was higher in patients who received neutron beam treatment and was described as severe in 11% compared with 3% for those who underwent photon irradiation.

In general, acceptance of neutron beam therapy by radiation oncologists has been limited because of the perception that complication rates are high without much gain in tumor control, as well as because of the limited availability and expense associated with neutron production. Nonetheless, efforts are ongoing in neutron beam facilities to improve outcomes using the same computer-driven technologies used in x-ray treatment. A form of conformal neutron beam therapy is now possible in several centers (Forman et al, 1995). At Wayne State University, 300 patients were entered into a phase III trial and randomly assigned to conformal neutron therapy followed by standard CRT or CRT followed by a neutron therapy boost. A statistically significant difference in 5-year disease-free survival was seen for patients treated with neutrons first (93% compared with 73%, $P = .008$) (Forman et al, 2002). Treatment-related morbidity was the same for both groups in this study. A larger retrospective review from the same group of neutron therapy and standard x-ray CRT revealed a statistically significant improvement in 5-year relapse-free survival for the group that received neutrons as any component of their therapy. The effect was most pronounced for high-risk patients who had a 35% 5-year relapse-free survival rate versus 7% in the photon-only group ($P = .0004$). Although these data are provocative, one criticism is that the relapse-free survival in the photon-only group from Wayne State is much lower than that of other series reporting on the same population of patients.

Despite the data from Wayne State, most radiation oncologists believe that neutron beam therapy causes greater normal tissue damage than x-ray photon beam therapy. Investigators from the Catholic University of Louvain, Belgium, used a mailed questionnaire to assess quality-of-life changes in 262 patients who received mixed neutron-photon irradiation. Twenty-two percent of the 230 patients who replied had four or more bowel movements per day. Retaining stool was a problem in 26% of the patients, and only 38% reported full bowel continence. The patients in this trial received neutron beam therapy using equipment that was not conformal. These data were sufficiently concerning to close their program and demonstrate the importance of up-to-date equipment and technology for the delivery of neutron beam therapy.

Proton beams are also used to treat cancer. These charged particles are generated by a linear accelerator, cyclotron, or synchrotron. Each method of manufacturing has strengths and weaknesses, and, to date, it has been difficult to create a simple, cost-effective, and robust system that can be used for cancer treatment. Most proton facilities are located near nuclear physics laboratories, but a free-standing unit does exist at Loma Linda Medical Center in California.

Protons have the same theoretic advantage over conventional x-rays as neutrons (i.e., they are more densely ionizing in tissue and have a sharp dose falloff in tissue; see Fig. 104–14). At Massachusetts General Hospital, clinicians have used a cyclotron housed at Harvard University for the treatment of patients for many years. In the 1980s, a prospective randomized trial was undertaken in men with locally advanced prostate cancer (Shipley et al, 1995). Patients treated with proton beams had a 95% incidence of clinical local control at 5 years, compared with a 64% incidence for those treated with photons. Although no grade 3 to 5 toxicities were reported in either arm of this trial, grade 1 and 2 rectal bleeding rates were higher in the proton group (32% vs. 12%, $P = .002$), as were urethral strictures (19% vs. 8%, $P = .07$). When the group with rectal bleeding was carefully analyzed, a relationship between the volume of rectum treated and the dose of protons given was established and guidelines were developed for future trials (Hartford et al, 1999).

At Loma Linda University Medical Center, 643 patients have received treatment with protons alone or in combination with photons (Rossi, 1999). Eighty-nine percent of early-stage patients (stage T1b or T2b, PSA < 15 ng/mL) achieved 5-year biochemical disease-free survival, as opposed to 68% of those with more advanced tumors. In this series 21% of patients developed minimal radiation proctitis, and severe side effects were seen in less than 1%. Similar results were published in 16 patients from Kobe University of Japan, emphasizing how few new data are available on this form of therapy. In this study, none of the patients evidenced PSA failure within the first 12 months.

The same technical advances that allow delivery of improved photon therapy (conformal radiation) must be used by particle beam specialists. In time, it may be possible to deliver particle beams safely and inexpensively. At present, conformal particle beam treatment units are extremely expensive to construct and operate, and this poses a problem for those interested in particle beam therapy, particularly because, to date, the single-institution results in prostate cancer demonstrate disease control rates that are similar to those seen with conformal radiation.

Key Point: Heavy Particle Beams

- Proton radiation therapy also provides the ability to deliver higher doses of radiation therapy while minimizing rectal bleeding.

Brachytherapy

Brachytherapy ("close" therapy) is the placement of radioactive sources into or near tumors for therapeutic purposes. The discovery of x-rays and the purification of radium in the early 20th century paved the way for the development of this form of therapy. Subsequent technical advances and refinements led to the increasingly accurate techniques currently in use, which are associated with lower cost and morbidity rates. Today, the number of patients undergoing brachytherapy for early-stage prostate cancer has increased dramatically. The CaPSURE database reported an increase in the use of brachytherapy from 3.1% to 12.0% in the past decade (Cooperberg et al, 2004).

Pasteau and Degrais described the temporary placement of radium-containing needles into the prostate through the urethra (Pasteau et al, 1913). During the 1920s, Young (1922) at Johns Hopkins performed prostate brachytherapy using intracavitary radium sources in the bladder, rectum, and urethra "cross-firing" into the prostate (Young, 1922). This technique was refined at Memorial Hospital in New York by Benjamin Stockwell Barrington, who pioneered implanting needles containing radioactive radon gas into the prostate by a transperineal approach. During the 1970s, Whitmore and colleagues (1972) at Memorial Sloan-Kettering in New York performed ^{125}I implantation in patients after they underwent lymph node dissection. The prostate was exposed by the retropubic approach for implantation. However, this "free-hand" technique resulted in suboptimal distribution of seeds and poor dosimetry (Zelefsky et al, 1977).

Holm and colleagues (1983) described closed transperineal implantation with the aid of TRUS. With this approach, the needles used to insert the radioactive seeds could be visualized, with an improvement in the accuracy of seed placement compared with the retropubic approach. Surgical morbidity and cost were reduced. For this procedure, the patient is placed in the high lithotomy position to maximize the transperineal exposure of the prostate. A transrectal ultrasound probe is then inserted and affixed to a mount or stabilizer through a stepping device. A template with a predrilled pattern of parallel holes is attached to the stepper. This permits accurate and reproducible imaging of the prostate throughout the procedure. The template pattern can also be superimposed over the ultrasound image by computer software in the ultrasound device. Seventeen- or 18-gauge needles are inserted through the template into the prostate. The position of the needle can be confirmed on either transverse or parasagittal imaging. The sealed metallic seeds containing the radioactive isotope are deployed as the needle is withdrawn (Figs. 104–16 through 104–19).

Several methods are currently in use for permanent radioactive seed implantation. The method popularized by Blasko and colleagues (1993) in Seattle uses preimplant transrectal ultrasound images to calculate a dosimetric plan. These images are then used in the operating room to determine locations for planned seed placement. Kaplan and colleagues (2000) have described a method in which the dosimetric plan is calculated intraoperatively. Computer programs using sophisticated algorithms to optimize dosimetry have been developed. Stone and Stock (1999) determined the number of seeds to be implanted on the basis of the size of the gland and the nomogram reported by Anderson (1976). The



Figure 104–16. Patient in the high lithotomy position with the transrectal ultrasound probe fixed to the stepper device. Needle containing radioactive seeds is implanted through the perineum using a grid system.

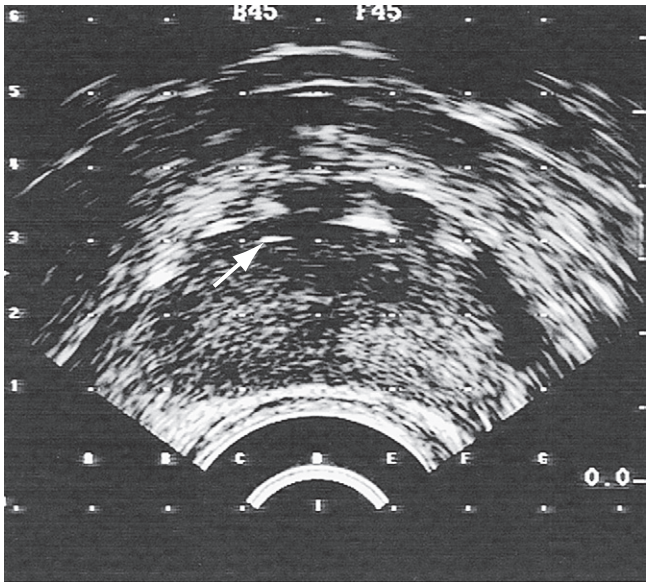


Figure 104–17. Transverse ultrasound image of the prostate. Several seeds are visible in the anterior gland. The arrow delineates the target location for the insertion of a needle.

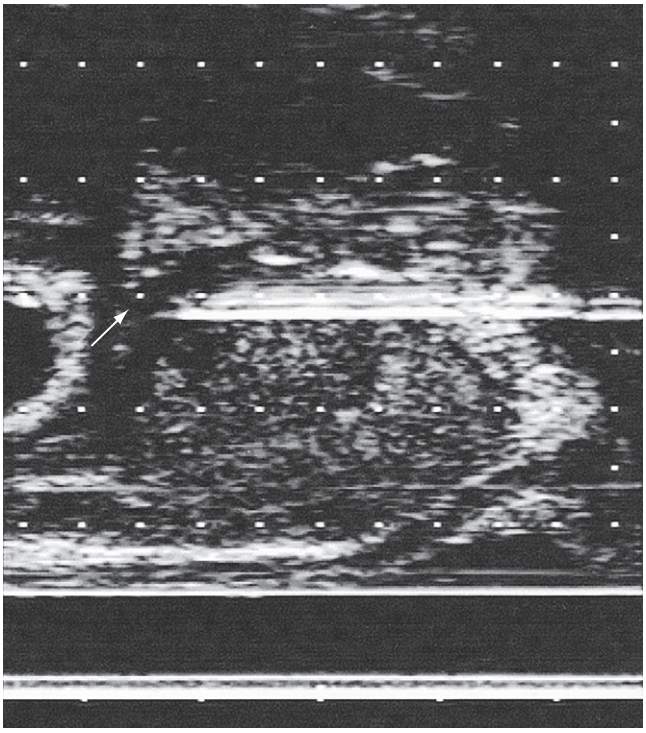


Figure 104–18. Parasagittal ultrasound image of the prostate. The arrow demonstrates that the needle depth goes to the prostatic capsule before deployment of the radioactive seeds.

needles are implanted using the empirical rules defined by Patterson and Parker in the 1930s (Fletcher, 1980). Other methods for seed implantation using CT (Koutrouvelis, 1998) and an intraoperative magnetic resonance imaging (MRI) device (D'Amico et al, 1998a; Saul et al, 2004) have also been described.

High-dose-rate (HDR) brachytherapy techniques for treatment of prostate cancer have been developed. In this procedure, needles are placed through the perineum into the prostate. For treatment planning the prostate is imaged postoperatively, with needles in

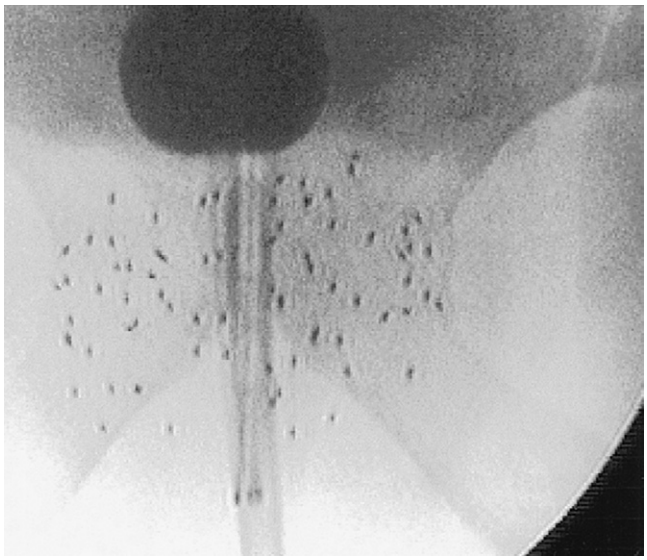


Figure 104–19. Intraoperative fluoroscopic image of the prostate demonstrating the placement of palladium 103 seeds.

place. One- to 10-curie iridium 192 sources in a flexible catheter are inserted remotely into the needles at various positions for variable lengths of time, in the order of seconds to minutes. The radiation dose is delivered in this way over several applications.

Postimplantation CT is performed to determine seed localization and reference the dose to the prostate and other structures of importance (Willins and Wallner, 1997). However, defining prostate volume on CT images is not unambiguous (Lee et al, 2002). Some groups fuse postimplantation MRI images to the CT to better define pelvic anatomy, to improve the accuracy of post-treatment dosimetry (Mizowaki et al, 2002).

Isotopes

There are several choices for isotopes for permanent seed implantation. ^{125}I is the most commonly used isotope. ^{125}I emits low-energy x-rays at 27 keV with a half-life of 59.6 days. The use of ^{103}Pd was introduced in 1986. The radiation from palladium has an energy spectrum similar to that of ^{125}I, with 21 keV x-rays, but with a significantly shorter half-life of 17 days. Therefore higher activity seeds are required for ^{103}Pd versus ^{125}I to deliver a similar tumoricidal dose (i.e., 1.3 to 1.5 mCi per palladium seed vs. 0.4 to 0.5 mCi per iodine seed).

Increasingly, palladium implants are being performed for patients with higher Gleason scores (specifically, Gleason score above 8) or patients receiving an implant boost after external-beam irradiation. This has made retrospective analysis of outcome for different isotopes difficult (Stone and Stock, 1999). However, in single-institution retrospective series that control for presenting prognostic variables, no difference in outcome was observed. Similarly, no difference in cancer control has been reported to date in a prospective trial evaluating isotope selection.

Outcome of Implants

Prostate cancer has a long natural history and generally occurs in a population in which competing mortalities and morbidities are important factors in analyzing outcomes. Because image-guided implantation of the prostate is a relatively new procedure, there are few long-term survival data. Surrogate end points can be used to evaluate its efficacy. However, with the advent of serum PSA determination there has been an improvement in outcome-based

staging, making comparison with results of therapy reported before the PSA era difficult. With the widespread use of PSA and the Gleason system for grading pathology since the late 1980s, there is now 15 years' follow-up after therapy (Sylvester et al, 2004).

Postimplantation Biopsies

Post-treatment biopsies can be used to assess the efficacy of local therapies to control cancer. However, there are several limitations to using this technique in prostate cancer. The typical rate of PSA decline after local prostate irradiation suggests that the complete effect is not observed until 18 months or longer after completion of radiotherapy (Ragde et al, 1998). In addition, there are potential sampling errors and difficulties in interpretation of postirradiation biopsy pathology. Early studies that included in their analyses a significant proportion of higher-stage patients or suboptimal dosimetry show a high proportion of positive post-treatment biopsies (Kuban et al, 1992; Vijverberg et al, 1993). More recent studies with biopsies after treatment for early-stage disease with improved implant quality report a post-treatment positive biopsy rate of 3% to 20%. Table 104–6 summarizes the results of several studies. The clinical significance of a positive post-treatment biopsy, especially when obtained within the first 2 years after RT, is unclear and is not an indicator.

Post-Treatment Prostate-Specific Antigen

Serum PSA is the most useful marker to assess relapse. Experts generally agree that a rising PSA after treatment is a harbinger for eventual clinical recurrence. A rising PSA level after irradiation predicts local or distant relapse, or both, often many years before clinical evidence of recurrence (Kaplan et al, 1993). However, the variability of PSA, especially at low levels, often makes interpretation problematic. In addition, the suppression of PSA with even short courses of antiandrogen therapy can complicate interpretation of results. The definition of treatment failure itself remains controversial. Absolute threshold levels of 0.5 or 1.0 ng/mL after treatment have been suggested as alternative end points (Critz et al, 1996; Borghede et al, 1997). ASTRO proposed that biochemical failure after RT be defined as three consecutive increases in PSA, with the date of failure being the midpoint between PSA nadir and the first of the consecutive rises.

A PSA bounce has been reported in approximately 25% of patients after brachytherapy. This is a temporary rise in PSA followed by a decline in PSA levels at subsequent follow-up (Critz et al, 2000; Stock et al, 2003). This rise in the PSA can be confused with a PSA failure. Patel and colleagues (2004) reported that 11% of patients who experienced a PSA bounce would have met the ASTRO criterion for PSA failure. In addition, Reed and colleagues (2003) reported eight patients who had a positive post-treatment prostate biopsy during a PSA bounce and subsequently remained free from recurrence. Some investigators have reported improved rates of cancer control in patients who experience a PSA bounce (Das et al, 2002; Patel et al, 2004).

Pretreatment prognostic factors such as pretreatment PSA, clinical examination, Gleason score, and percentage of biopsy cores positive have been used to define risk groups in relation to pathologic findings at surgery and freedom from PSA relapse after RT or radical surgery (D'Amico et al, 1998b, 2002; Partin et al, 2001; Kuban et al, 2003). There is no consensus in the definition of these prognostic groupings. However, there is general agreement that "low risk" (defined as a low risk for extracapsular disease at prostatectomy and a high probability of disease-free survival after treatment) includes patients with clinical T1-T2 disease, a Gleason score less than 6, and a pretreatment PSA less than 10 ng/mL (D'Amico et al, 1998b, 2002; Partin et al, 2001; Kuban et al, 2003). Some investigators exclude T2b from the low-risk group (D'Amico et al, 1998b). There is no consensus in the definition of risk groups with an intermediate risk or high risk of failure after local treatment (D'Amico et al, 1998b; Blasko et al, 2002; Kollmeier et al, 2003). The high-risk grouping typically includes patients with multiple high-risk features such as Gleason score greater than 7, PSA above 10 ng/mL, or large palpable tumors. The intermediate group is heterogeneous and includes patients who have features in between low and high risk.

Table 104–7 summarizes the clinical outcomes of permanent implant monotherapy without hormone ablation in several large series using the ASTRO definition for biochemical failure. These studies report on more than 1000 patients treated with permanent implant monotherapy. Although these are retrospective single-institution studies (with the exception of RTOG 98-05), they represent results from a uniform population of patients. These results compare favorably with those of similarly selected patients treated with external-beam irradiation or radical prostatectomy (D'Amico et al, 1998b; Quaranta et al, 2004).

Seed Brachytherapy with External Irradiation

Seed brachytherapy can be used as a boost either before or after external-beam irradiation for prostate cancer. Generally, brachytherapy combined with external-beam irradiation, rather than brachytherapy alone, is used for patients with higher-stage disease. External-beam irradiation is employed in these higher-stage patients to treat the prostate and periprostatic tissues. Typically, a dose of 4500 cGy of external-beam RT is delivered (compared with 7560 to 7920 cGy when external-beam irradiation is used alone). The dose of the implant boost in such combination therapy is generally 60% to 70% of the dose prescribed for patients treated with implant alone. Table 104–8 summarizes the results of several

Table 104–6.

Postimplantation Biopsy Results

AUTHOR	ISOTOPE	RESULTS
Prestidge et al, 1997	^{125}I and ^{103}Pd	201 Postimplantation biopsies—80% negative, 17% indeterminate, 3% positive
Ragde et al, 1997	^{125}I	82% Negative 13% Indeterminate 5% Positive
Stock et al, 1996a	^{125}I and ^{103}Pd	Post-treatment biopsies on patients (T1b-T2c)—26% positive
Stock et al, 2004	9 mo hormonal therapy, external beam with ^{103}Pd boost	4% Post-treatment biopsies at 2 yr in a "high-risk" group
Sharkey et al, 1998	^{103}Pd	11% Positive at 2 yr after implant
Kuban et al, 1992	^{125}I	Biopsy at least 18 mo after implant, negative DRE, 18% positive biopsy
Stone et al, 2004	^{125}I, ^{103}Pd monotherapy or as boost ± hormones	"Low-risk" group, 4.1% positive

DRE, digital rectal examination.

Table 104–7.

Actuarial Freedom from Biochemical Relapse: Implant Monotherapy and Combined Implant and External Beam

IMPLANT MONOTHERAPY	AUTHOR	NO. OF PATIENTS	ISOTOPE	FREEDOM FROM RELAPSE (%)	TIME (yr)
	Zelefsky et al, 2000	146	^{125}I	88	5
	Potters et al, 1999	112	^{125}I	92	5
	Kollmeier et al, 2003	73	^{125}I, ^{103}Pd	88	8
	Brachman et al, 2000	392	^{125}I, ^{103}Pd	82	5
	Grado et al, 1998	62	^{125}I, ^{103}Pd	95	5
	Kwok et al, 2002	41	^{125}I	85	5
	Ellis et al, 2003	67	^{125}I, ^{103}Pd	97	4
	D'Amico et al, 1998b*	32	^{103}Pd	85	5
	Lawton et al, 2004 (RTOG)	97	^{125}I	96.8	3
	Blasko et al, 2000†	103	^{103}Pd	94	5
	Grimm et al, 2000†	97	^{125}I	87	10
External beam with implant boost	Brachman et al, 2000	465	^{125}I, ^{103}Pd	85	5
	Sylvester et al, 2003†	232	^{125}I, ^{103}Pd	85	10
		212		86*	

*Excludes patients with T2b disease.
†Prostate-specific antigen (PSA) failure—two consecutive rises in serum PSA.

Table 104–8.

High Dose Rate Boost with External-Beam Irradiation

Martinez phase I prospective trial (Martinez et al, 2002)	58 pts	46 Gy external beam + "Low-dose"	52%	5 yr	Fewer patients with Gleason ≥ 8 and PSA
	149 pts	HDR (≤6.5 Gy × 3 applications) "High-dose" HDR (≤11.5 × 2 applications)	87%	5 yr	>20 ng/mL in "high-risk" group
Galalae prospective phase II trial (Galalae et al, 2002)	46 pts	50 Gy pelvis, 40 Gy prostate	94.7%	5 yr	WHO grading used
	22 pts	2 HDR applications of 15 Gy	93%	8 yr	
	25 pts	PSA < 10 and grade 1-2	67.7	5 yr	
		PSA > 20 and grade 1-2	63.9	8 yr	
		PSA > 20 and grade 3	38%	5 yr	
			32%	8 yr	
Mate et al, 1998		50.4 Gy external beam			Mean follow-up 46 mo
	54 pts	4 HDR applications of 3-4 Gy	93%		
	29 pts	PSA < 10 ng/mL	90%		
	20 pts	PSA 10-20 ng/mL	60%		
		PSA ≥ 20			
Deger et al, 2002		45 Gy external beam	100%	5 yr	
		Two applications of 9-10 Gy	75%	5 yr	
		T1	60%	5 yr	
		T2			
		T3			

HDR, high dose rate; PSA, prostate-specific antigen; pts, patients; WHO, World Health Organization.

studies employing combined external-beam radiation and implant boost for low-risk-group patients. Potters (1999) and Grado (1998) and their colleagues did not find the addition of external beam to implantation to be statistically significant in a multivariate analysis. The role of external beam with permanent seed brachytherapy versus brachytherapy alone is being investigated in a randomized clinical trial by the RTOG (RTOG trial 02-32).

Assessment of Implant Quality

The goal of prostate brachytherapy is to deliver a homogeneous dose to the prostate while minimizing dose to nearby sensitive normal structures such as the rectum and urethra. Postimplant dosimetry in these dose-limiting regions is important for an assessment of implant quality. The matched peripheral dose is defined as the dose to a volume of an ellipsoid having the calculated volume of the prostate ([height] × [length] × [width] × [pi/6]). However, this dosimetric calculation does not take into account geographic misses and cannot directly calculate point doses to structures such as the urethra, rectum, or prostatic apex. To determine the minimum dose within the prostate and to assess the distribution of volume and dose, three-dimensional reconstruction of the prostate and unambiguous determination of seed location within the prostate are necessary. These factors can be calculated with postimplantation imaging using either CT or MRI (Moreland et al, 1997; Willins and Wallner, 1997; Amdur et al, 1999). The American Brachytherapy Society (ABS) has proposed the D_{90} (the minimal dose covering 90% of the prostate volume) and the V_{100} and V_{150} (the percent volume of the prostate receiving 100% and 150% of the prescribed dose, respectively) as parameters

to assess implant quality (Nag et al, 1999). However, these descriptive parameters may not adequately predict for tumor control, and more sophisticated measures have been proposed.

A significant source of error in these calculations is prostatic edema, which is invariably observed after implantation (Prestidge, 1998; Waterman et al, 1998). Accordingly, Yue and colleagues (1999) suggested that postimplantation scans should be performed 2 weeks after ^{103}Pd and 6 weeks after ^{125}I. However, Taussky and colleagues (2004) analyzed serial postimplantation MRI images and reported that edema effects are minimal and the time to postimplantation scan is not important.

Toxicity

Implant techniques and procedures vary from institution to institution. Variations in these factors are important when assessing rates of treatment toxicity. Implants are currently performed using peripheral loading techniques. With this scheme, there is a greater density of seeds placed in the periphery of the gland than in the center. This ensures a more uniform distribution of dose throughout the gland and minimizes "hot spots" around the urethra. Some investigators completely exclude the transitional zone of the prostate from the treatment volume, significantly reducing the urethral dose (D'Amico et al, 2000a). Other groups intentionally place seeds outside the gland to improve peripheral dose coverage. This increases the dose received by the rectum and the neurovascular bundles. Age, existing comorbid diseases such as peripheral vascular disease or diabetes mellitus, and tobacco use may also predispose to increased toxicity from treatment.

Determining incidence rates and severity of treatment-related morbidity is also dependent on the instrument used and how the information is gathered. The ABS proposed as a minimal set of assessment criteria the International Prostate Symptom Score (IPSS) for assessing urinary function, the International Index of Erectile Function for erectile function, and RTOG toxicity grading criteria for rectal toxicity.

Urinary Toxicity

Brachytherapy after TURP was initially reported to be associated with a significant rate of serious urethral toxicity. Blasko and colleagues (1993) reported that 24% of patients who underwent implantation after TURP developed urinary morbidity, compared with 3% of patients who did not undergo this procedure. However, several more recent reports have demonstrated that men who have undergone prior TURP can be implanted as long as there is adequate tissue remaining to accommodate the seed sources. Most patients who have had a TURP can be safely implanted without an increased risk of urinary retention (Stone et al, 2000).

The IPSS tends to increase significantly immediately after implantation. Subsequently, the score decreases, but it is still significantly elevated at 3 months after treatment (Lee et al, 1999). Gelblum and colleagues (1999) observed that 37% of patients report grade 1 urinary toxicity (defined as symptoms not requiring medical intervention) within the first 60 days after implantation. Zelefsky and colleagues (1999a) reported grade II urinary toxicity (symptoms requiring medical intervention) occurring at a mean duration of 19 months after implantation, with a likelihood of resolution of 68% at 36 months. Continued significant urinary obstruction requiring self-catheterization occurs in 1% to 5% of patients (Grado et al, 1998; Gelblum et al, 1999; Peschel et al, 1999). The use of α blockers before implantation may decrease the severity and duration of urinary symptoms (Merrick et al, 2002b).

Longitudinal studies are being conducted to assess late urinary morbidity. Merrick and colleagues (2003a) reported the results of a survey of 225 patients who reached an average of 5.5 years after brachytherapy and compared their urinary symptoms with those in a cohort of more recently diagnosed patients. No significant difference was seen between the two groups (Merrick et al, 2003a). Stone and Stock (2003) reported a small but significant long-term increase in urinary frequency and weak stream in their series.

Wallner and colleagues (1995) reported the risk of urinary toxicity to be a function of the length of the urethra receiving a high dose. Grade 2 to 3 morbidity was observed when 20 mm + 11 mm of the urethra received more than 400 Gy with ^{125}I implants. Larger prostatic volumes—specifically, glands greater than 60.0 cm^3—were also associated with higher rates of urinary toxicity (Wallner et al, 1995). Terk and colleagues (1998) reported on 251 patients using the IPSS to assess urinary function before and after ^{125}I or ^{103}Pd implantation. Patients with a pretreatment IPSS above 20 demonstrated a 29% risk of developing urinary retention, and a pretreatment score less than 10 was associated with only a 2% risk. Overall, significant postbrachytherapy obstructive symptoms refractory to medical management occur in approximately 2% to 3% of patients. Postbrachytherapy TURP can be performed with a low rate of post-TURP incontinence if care is taken to preserve the urethral blood supply (Flam et al, 2004).

Rectal Toxicity

Minor rectal symptoms secondary to brachytherapy are usually self-limiting. The usual scale to assess rectal toxicity, the RTOG acute and late toxicity scale, is not a sensitive enough measure to report minor changes in rectal function after treatment. Rectal toxicity—specifically, rectal bleeding secondary to radiation proctitis—can be a minor, self-limiting side effect of radiation or a major toxicity requiring surgical intervention such as argon plasma coagulation (Smith et al, 2001) or, in the worst cases, diverting colostomy. The rate of minor rectal bleeding after implant therapy has been reported to be approximately 1% to 4% (Zelefsky et al, 1999a). The incidence of significant rectal complications has been reported to be 0% to 1% (Grado et al, 1998; Zelefsky et al, 1999a). A postimplantation colostomy rate of 0.3% was observed in a study of Medicare claims (Benoit et al, 2000a, 2000b). The rate of rectal complications is correlated with the dose and the length of rectum receiving a high dose. For example, rectal complications have been observed when 17 mm^2 (±5 mm) of the rectal wall received more than 100 Gy (Wallner et al, 1995). Wallner and colleagues (1995) accordingly recommended minimizing the amount of rectum receiving 100 Gy in ^{125}I implants. Merrick and colleagues (2003a) reported that rectal complications were rarely observed when the rectal wall received 85% of the prescribed dose.

Potency

Impotence is defined by the National Institutes of Health (NIH) consensus on erectile dysfunction (ED) as the "inability to attain and maintain a penile erection sufficient to permit satisfactory sexual intercourse" (NIH Consensus Conference, 1993). The cause of implant-related ED is multifactorial. Factors such as underlying small vessel disease, nerve damage, and dose to specific tissues have been implicated in postimplantation ED.

DiBiase and colleagues (2000) reported that dose to the neurovascular bundle was related to development of postbrachytherapy ED. Merrick and colleagues (2001) reported that dose to the penile bulb correlates with rates of ED, although the penile bulb is composed of corpus spongiosum, not corpus cavernosum (Muhall and Yanover, 2001). In any case, potency preservation rates for patients undergoing implantation are superior to those reported for

patients receiving external-beam irradiation or neoadjuvant hormonal therapy, external beam, and brachytherapy boost. Zelefsky (1999c) and Stock (1996b) and their colleagues reported that potency was maintained in 79% of patients undergoing brachytherapy compared with 68% receiving external-beam irradiation. There is continued drop-off in potency with continued follow-up in the past 3 years (Zeitlin et al, 1998). Merrick and colleagues (2002a) reported that 50% of men who were fully potent before brachytherapy maintained potency at 6 years after treatment.

The potency rate has been reported to be 62% in patients receiving combined external beam with an implant boost (Zeitlin et al, 1998). Potters and colleagues (2001) reported a 5-year potency maintenance rate of 76% with brachytherapy monotherapy and 56% with combined external beam and brachytherapy boost. The addition of hormones to external beam and brachytherapy boosted lower potency rates to 52%. Similarly, Stock and Stone (2002) reported that potency was maintained in 43% at 3 years after combined neoadjuvant hormonal therapy with external beam and brachytherapy boost. Age was a significant prognostic factor in a univariate analysis (Merrick et al, 2002a), and the addition of external beam and a history of diabetes mellitus were significant factors in a multivariate analysis (Robinson et al, 2002). In a meta-analysis, the probability of maintaining potency at 1 year after treatment was 76% (69% to 82%) with brachytherapy monotherapy and 60% (48% to 73%) with external beam with brachytherapy boost (Robinson et al, 2002). When the probability of ED was adjusted for age, the difference between prostate brachytherapy and prostatectomy increased (Robinson et al, 2002). Sildenafil citrate and other phosphodiesterase-5 inhibitors have been reported effective in 74% to 81% of patients who avail themselves of oral therapy for ED (Albert et al, 2003; Merrick et al, 2003a; Raina et al, 2003).

High-Dose-Rate Brachytherapy

HDR brachytherapy afterloading techniques have been developed to treat prostate cancer. This procedure uses high-activity ^{192}Ir sources in cables stored in a mobile computer-controlled lead safe. ^{192}Ir emits gamma radiation at 400 keV, which is significantly more penetrating than either ^{125}I or ^{103}Pd. Needles are first implanted transperineally into the prostate under ultrasound guidance. The precise positions of the needles are then determined by CT, and a dosimetric plan is calculated before the radiation is administered. Under computer guidance, the ^{192}Ir sources are transferred to the needles for a predetermined time. A precise dose is administered by varying the dwell times of the source in each needle. Kini and colleagues (1999) reported on 20 HDR treatments delivered in 11 patients. An average of 16 needles was used. Ninety-two percent of the prostatic volume received 100% of the prescribed dose; this is slightly superior to the dosimetry generally achieved during permanent seed implantation (Merrick et al, 1999).

HDR has been used primarily in combination with external-beam irradiation for patients with intermediate- or high-risk features. It is delivered as a boost in two to four applications, either before or after external-beam irradiation. HDR is a new technology, and there is heterogeneity in dose per fraction delivered and techniques employed. Consequently, the reports with the longest follow-up are from phase I dose escalation studies. Dinges and colleagues (1998) reported on 82 patients with a mean pretreatment PSA of 14.0 ng/mL. All patients had pathologic node-negative disease as determined by laparoscopic staging. Two HDR treatments calculated to deliver 9 to 10 Gy were followed by 40 to 45 Gy of external-beam irradiation. Seventy-three percent of patients had negative biopsies at 2 years. Local failure (defined as a positive post-treatment biopsy and a PSA > 1.0 ng/mL) was observed in 21.5% of patients. In a multi-institution report in which different dose fractionation schemes and doses of external beam were used, a 5-year biochemical disease-free survival (ASTRO definition) of 96% was observed in patients with low-risk disease, with 87% and 69% for an intermediate- and high-risk group of 137 and 240 hormonally naïve patients, respectively (Galalae et al, 2004). Table 104–8 summarizes results of trials of HDR delivered as a boost with external-beam irradiation, using the ASTRO definition for biochemical failure.

Early results with HDR used as monotherapy for patients with low-risk prostate cancer have demonstrated acceptable toxicity and early biochemical freedom-from-relapse rates similar to those for permanent seed implants (Grills et al, 2004). Further experience with more patients and longer follow-up is required to assess the efficacy of this approach.

Key Point: Brachytherapy

- Prostate brachytherapy is best performed using intraoperative real-time dosimetry in order to minimize normal tissue complications and maximize tumor control.

Radiation Therapy and Androgen Suppression Therapy

Locally Advanced Prostate Cancer

Among strategies to improve outcome for patients with locally advanced prostate cancer, hormonal manipulation in combination with RT has consistently demonstrated improvement in treatment outcome as compared with standard-dose radiation alone (Pilepich et al, 1995, 1997; Bolla et al, 1997; Vicini et al, 1999). A meta-analysis of both retrospective and prospective trials of androgen deprivation in combination with RT demonstrated near-universal benefit in regard to local/regional control, disease-free survival, and freedom-from-failure survival. However, the ultimate impact on overall and cause-specific survival remains to be fully defined (Vicini et al, 1999). There are now three published cooperative group phase III trials and a single-institution phase III trial reporting advantage in various outcome parameters with the use of androgen deprivation compared with use of radiation alone.

In RTOG 86-10, 456 patients with large (25 cm^3), stage T2B to T4, Nx tumors randomly assigned to 4 months of total androgen suppression with RT given after the first 2 months had improved local control, disease-free survival, and freedom from metastases compared with patients receiving RT alone. At 8 years significant improvements in rates of local control of 42% versus 30%, distant metastases of 34% versus 45%, disease-free survival of 33% versus 21%, biochemical disease-free survival (PSA < 1.5 ng/mL) of 24% versus 10%, and cause-specific mortality of 23% versus 31% were noted with versus without addition of this short course of neoadjuvant androgen suppression. A hypothesis-generating subset analysis indicates that the beneficial effect of short-term androgen ablation appears preferentially in patients with Gleason score 2 to 6. In that population, there is a highly significant improvement in all end points including survival (70% vs. 52%, P = .015) (Pilepich et al, 1995, 1998, 2001).

In European Organization for Research in the Treatment of Cancer (EORTC) 22863, a phase III trial of androgen suppression,

Bolla and colleagues (1997, 1999) reported an overall survival advantage for patients receiving 3 years of goserelin starting at the initiation of RT. Most of the patients in this study had stage T3 disease, and the remainder were eligible owing to high-grade tumors. With median follow-up of 66 months, 5-year clinical disease-free survival was 40% (95% CI 32 to 48) in the radiotherapy-alone group and 74% (67 to 81) in the combined-treatment group ($P = .0001$). Five-year overall survival was 62% (95% CI 52 to 72) and 78% (95% CI 72 to 84), respectively ($P = .0002$), and 5-year specific survival 79% (95% CI 72 to 86) and 94% (95% CI 90 to 98), supporting the use of androgen suppression (Bolla et al, 2002).

The optimal type, timing, and duration of androgen suppression in combination with RT remain to be defined. In RTOG 92-02, patients with stage T2c-T4, N0-1, M0 disease were randomly assigned to 4 months of total androgen suppression with radiation administered after 2 months or the same regimen followed by an additional 2 years of goserelin. A hypothesis-generating subgroup analysis revealed significant improvement in overall survival, 80% versus 69%, and disease-specific survival, 90% versus 78%, in patients with Gleason grade 8 to 10 tumors.

Should Pelvic Lymph Nodes Be Treated?

The question of timing of hormonal therapy and impact of radiation field size was addressed by RTOG 94-13, a four-arm study comparing whole-pelvis versus small-field radiation with 4 months of either neoadjuvant or adjuvant total androgen suppression. Eligible patients had adverse risk factors, with estimated risk of positive-node disease of more than 15%. A difference was initially seen in progression-free survival at 4 years, 54% versus 47% for the whole-pelvis versus prostate-only radiation, respectively ($P = .022$), but no difference was seen in overall survival. However, an update of this study (Lawton, 2007) shows loss of this benefit, so pelvic lymph node treatment can no longer be recommended for all men with high-risk or locally advanced prostate cancer.

Localized Prostate Cancer

Two studies (Denham et al, 2005, D'Amico et al, 2008) have investigated the use of 6 months of combined hormonal blockade and RT versus RT alone. Both show benefits in cancer-specific survival, and one shows an overall survival benefit for men who were randomized to receive RT and 6 months of combined hormonal blockade as compared with RT alone. Specifically, in the study by Denham and colleagues, 802 men with a median PSA of 15 ng/mL and in whom 55% had Gleason score 7 or higher disease and 40% had clinical T3/4 disease, a prolongation in time to prostate cancer death was noted. D'Amico and colleagues (2008) studied 206 men, all with clinical T1/2 disease and followed for a median of 7.6 years. Their median PSA was 11 ng/mL, and 73% had Gleason score 7 or higher disease. Benefits in both overall and cancer-specific survival were noted. Of note, it appeared that the survival benefit may have been limited to only those men with no or minimal comorbid illness.

Key Points: Radiation Therapy and Androgen Suppression Therapy

- Randomized controlled trials have shown a survival benefit for the addition of androgen suppression therapy to external-beam radiation therapy.
- Six months of hormonal therapy compared with 3 years of hormonal therapy provides a survival benefit for men with localized high-risk versus locally advanced prostate cancer, respectively. However, this benefit may only apply to men with no or minimal comorbid disease.

Radiation Therapy for Palliation

Bone Metastases

In genitourinary cancers, bone metastases are a common problem (Abrams et al, 1950; Gilbert and Dagan, 1976). Many therapies are available for bone metastases including surgery, medical management, and radiation. RT can treat most patients with highly effective symptom relief.

The hallmark of osseous metastases is localized pain, which is frequently continuous and unrelenting regardless of the site. The pain caused by bone metastases is not well understood. Some investigators have hypothesized that irritation of the periosteal membrane or release of biologic mediators is responsible for bone pain. The most serious complication of osseous metastases is spinal cord compression, which is discussed later.

Most bone metastases can be diagnosed by physical examination, plain radiographs, and bone scan. CT and MRI are sometimes required if there is suspicion of bone involvement, but x-ray and bone scans are negative if there is soft tissue involvement.

With respect to treatment, reviewing the currently available data from prospective studies has shown overall response rates ranging from 85% to 100% using various treatment schedules (Madsen, 1983; Price et al, 1988; Cole, 1989). A single-fraction regimen (800 cGy × 1) appears to be as effective as other, more protracted regimens but is also associated with increased acute morbidity, particularly to the abdominal organs. A frequently used regimen in the United States is 3000 cGy in 10 divided fractions. This dosage is adequate for most osseous metastases.

Metastasis to a weight-bearing region raises many concerns. A pathologic fracture can be painful and disabling, both functionally and psychologically. Radiographic and clinical factors that warrant consideration of prophylactic surgical fixation include the following:

- An intramedullary lytic lesion equal to or greater than 50% of the cross-sectional diameter of the bone
- A lytic lesion involving a length of cortex equal to or greater than the cross-sectional diameter of the bone or greater than 2.5 cm in axial length (Lane et al, 1980)

These patients should be evaluated by an orthopedic surgeon. If a pathologic fracture has occurred in a weight-bearing region, surgical fixation is required for pain control and to promote adequate healing. In all situations, postoperative radiation is required. Because prostate cancer produces primarily blastic metastases, pathologic fracture is correspondingly infrequent.

Spinal Cord Compression

Spinal cord compression is a medical emergency. Failure to diagnose and treat promptly can lead to significant morbidity including paraplegia and autonomic dysfunction. The predominant symptom of cord compression is pain, which occurs in about 95% of patients (Gilbert et al, 1978). Pain usually precedes a diagnosis of spinal cord compression by about 4 months. Symptoms, however, can progress rapidly to neurologic dysfunction in a matter of hours to days. When a patient has progressed to paraplegia, return of function is infrequent. Therefore early diagnosis and therapy are critical. The diagnostic tool of choice to evaluate spinal cord compression is MRI.

Table 104–9.

Physical Characteristics of Radionuclides Reviewed

RADIONUCLIDE	PHYSICAL HALF-LIFE	BETA ENERGY (MeV)	GAMMA ENERGY (keV)	CHELATE
^{32}P	14.3 days	1.71	0	Orthophosphate
^{89}Sr	50.6 days	1.46	0	Chloride
^{186}Re	90.6 hr	1.07	137	HEDP
^{153}Sm	46.3 hr	0.84	103	EDTMP

EDTMP, ethylenediamine tetramethylene phosphonate; HEDP, hydroxyethylidene diphosphonate.

Table 104–10.

Clinical Efficacy and Toxicity of Radionuclides Reviewed

RADIONUCLIDE	RESPONSE RATE (%)	RESPONSE DURATION (MO)	TOXICITY
^{32}P	60-80	≈5	++
^{89}Sr	60-90	≈6	+
^{186}Re	75-80	1-2	+
^{153}Sm	75-90	2-3	+

Once the diagnosis of spinal cord compression is made, the physician is left with the dilemma of how to treat. There are a few instances in which surgery should be considered as an option before radiation including pathologic fracture with spinal instability or compression of the spinal cord by bone, unknown tissue diagnosis, or history of previous radiation to the same area.

When the diagnosis of cord compression is made or even suspected, all patients should receive steroid therapy. Steroids can decrease vasogenic edema and provide striking analgesic benefit. The loading dose of dexamethasone (Decadron) is 4 to 10 mg, followed by a maintenance dosage of 4 to 24 mg every 6 hours.

Systemic Radionuclide Therapy

The first report on the use of systemic radionuclides for the treatment of bone metastases was published by Pecher in 1942. Tables 104–9 and 104–10 provide a summary of the physical characteristics and the clinical usefulness of the radionuclides discussed.

Clinical Experience with Strontium 89

The efficacy of strontium 89 has been demonstrated in multiple studies (Firusian et al, 1976; Correns et al, 1979; Silberstein and Williams, 1985; Robinson et al, 1987; Tennvall et al, 1988; Montebello and Hartson-Eaton, 1989; Williams and Dillehay, 1989; Laing et al, 1991). Most of these studies involved patients with hormone-refractory prostate cancer. The limited experience in patients with metastatic breast cancer, however, suggests similar efficacy. In one retrospective review, 89% of 28 patients reported moderate or good relief of pain (Robinson et al, 1992).

Toxicity of strontium 89 is mainly hematologic. Platelet depression is dose dependent. Most patients have a 20% to 50% drop in their counts after doses of 3 to 4 mCi (1.5 to 2 MBq/kg).

Key Point: Radiation Therapy for Palliation

- Spinal cord compression, bone metastasis, and pathologic fractures are conditions that require external-beam radiation therapy for palliation.

Gene Therapy for Prostate Cancer

Advances in RT technique have clearly resulted in improved biochemical control of clinically localized prostate cancer (Shipley et al, 1999). Although continued refinement of these techniques will result in further gains, other innovative approaches such as gene therapy may enhance or complement radiation-induced cell killing. In addition, gene therapy may have a role in the management of patients with prostate cancer that is locally recurrent after RT.

A rapid escalation in knowledge of molecular and biologic mechanisms that characterize the cellular response to radiation-induced damage, combined with new molecular biologic techniques, has allowed the possibility of novel genetic therapies. In general, these genetic therapies as applied to prostate cancer can be divided into three major categories: corrective therapy, immunotherapy, and cytolytic/proapoptotic therapy. A brief synopsis of gene therapy as it relates to RT for the treatment of prostate cancer follows.

Corrective Gene Therapy

Corrective gene therapy can generally be thought of as the functional complementation of abnormal or absent genes in a cell. However, the application of p53-corrective gene therapy strategies in combination with RT for the treatment of clinically localized disease remains controversial (Waldman et al, 1997; DeWeese et al, 1998).

Immunotherapy

Defects in major histocompatibility complex class I expression have been noted in 85% of primary prostate cancers and essentially all metastatic tumors (Blades et al, 1995). As with other tumors, these data suggest that evasion of host immunity may be a critical factor in prostate cancer development. Strategies designed to improve tumor antigen presentation to the host immune system are termed *cancer vaccines* and frequently employ targeted expression of cytokines in tumor cells. This approach results in improved cancer cell vaccine antigen presentation and activation of antigen-presenting cells, both of which are necessary to effect a cellular immune response. A number of cytokines have been tested for their efficacy in inducing an antitumor immune response (Dranoff et al, 1993). Granulocyte-macrophage colony-stimulating factor has emerged as the most potent cytokine for activation of antigen processing and presentation by dendritic cells (Cella et al, 1997). When tumor antigens are presented in the context of high-level cytokine expression, cytotoxic T lymphocyte–based antitumor immune responses can be enhanced.

It has been suggested that therapies like radiation can result in the presentation of tumor-associated antigens, which subsequently enhance vaccine-based immunotherapies. One such study using an autochthonous murine model of prostate cancer tested whether

radiation in combination with a granulocyte/macrophage colony-stimulating factor (GM-CSF)-based vaccine could augment the CD4 T cell response (Harris et al, 2008). Although vaccine alone or radiation alone was not capable of priming an antitumor T-cell activation, the combination of radiation with vaccine substantively enhanced antitumor T-cell activation. This effect was dependent on the relative timing of radiation and vaccination. An interesting clinical trial that tested this general concept has also been completed (Gulley et al, 2005). In this phase I study, a PSA-targeted vaccine and radiation were used to treat men with localized prostate cancer. The combination resulted in significant T-cell responses in the majority of treated patients. These studies and others offer the promise of combination therapies that have both local and systemic anticancer potential.

Cytolytic/Proapoptotic Gene Therapy

Cytoreductive approaches to gene therapy that result in cytolytic or apoptotic cell death are generally grouped into three categories: (1) enzyme/prodrugs ("suicide gene" therapy), (2) oncolytics, and (3) cytotoxins. A rational combination of these approaches with a more standard cytotoxic therapy such as RT may provide superior cell killing as a result of nonoverlapping modes of cell death.

Enzyme/Prodrug Gene Therapy

This method of gene therapy relies on the conversion of an inactive prodrug into a toxic drug using an enzyme vectored only to target tumor cells. In this way, active drug is limited to the transduced cells and adjacent surrounding cells. In this therapy, it is critical that the vector have high tumor cell specificity to minimize normal tissue toxicity. Prodrug-activating enzymes employed include those not normally found in humans such as cytosine deaminase, which catalyzes the conversion of nontoxic 5-fluorocytosine to cytotoxic 5-fluorouracil, and herpes simplex virus (HSV)-thymidine kinase, which assists in the conversion of ganciclovir to toxic ganciclovir triphosphate. Even when only a small percentage of cells contain the enzyme, substantial tumor reductions have been noted, given the significant cell death attributed to the bystander effect (Kim et al, 1998). A recently reported study of HSV-thymidine kinase and ganciclovir suicide gene therapy in combination with replication-competent adenovirus and radiation revealed this approach to be safe and associated with frequent negative post-treatment biopsies of the prostate (Freytag et al, 2007).

Oncolytics

Viruses alone can infect and kill tumor cells without insertion of a transgene. Certain viruses have, as part of their normal life cycle, a lytic phase that is lethal to the host cell. In the 1950s, the potential therapeutic activity of this lytic life cycle was documented when cervical cancer was treated with intratumoral injections of wild-type adenovirus with subsequent tumor responses (Smith et al, 1956). Examples of oncolytic viruses that could be used for therapy include adenovirus, vaccinia, Newcastle disease virus, HSV, influenza virus, and mumps virus. Adenoviruses are attractive vectors for gene transfer and therapy for several reasons. They have low pathogenicity for normal tissue, are not tumorigenic, and, when present, result in only mild to moderate clinical symptoms (Anderson, 1998). They can also effect relatively high gene transfer.

The adenovirus exerts its control over host cell growth regulation by a complex set of proteins that facilitate viral replication. A prostate-specific construct has been developed and tested in vitro, in vivo, and in humans. This vector, CN-706, has a minimal promoter enhancer construct of the human PSA gene inserted 5′ of E1A and shows potent PSA selective cytotoxic activity in preclinical testing (Rodriguez et al, 1997). Phase I testing of this virus has been completed in patients with prostate cancer that is locally recurrent after radiation (DeWeese et al, 2000). In this study, the prostate received the oncolytic vector by multiple injections delivered by TRUS-guided transperineal needles. No serious adverse events were noted, and no irreversible grade 3 or any grade 4 toxicities were documented. Preliminary analysis of PSA response found that 4 of 19 patients exhibited more than 50% reduction in PSA from pretreatment values. Viral replication was also documented by electron microscopy of post-treatment biopsy specimens. Strong evidence indicates that radiation can modify adenoviral infectability or gene transfer, or both.

Numerous challenges lie ahead in the development of effective gene therapeutic approaches for prostate cancer. Vector development will continue to be critical in establishing less immunogenic viruses with the capacity to carry large transgenes and with high transduction efficiency. Newer molecular biologic techniques combined with the explosion in genomic information will facilitate development of the next generation of prostate-specific promoters and regulators that will enhance targeted therapy. This new genetic information may also allow individualized gene therapy based on bioassays of newly discovered pretreatment molecular characteristics. Finally, the concept of combined-modality therapy, which has shown success in other tumor sites, will become more standard in prostate cancer management. The combination of gene therapy with conventional therapies such as RT and surgery provides new hope for uniform cure of patients with prostate cancer.

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chapter 105

Cryotherapy for Prostate Cancer

David C. Miller, MD, MPH ● Louis Leon Pisters, MD ● Arie S. Belldegrun, MD

History of Cryotherapy
Cryobiology
Technical Improvements in Cryotherapy Equipment
Patient Selection
Surgical Technique
Patient Follow-up
Outcomes after Primary Cryotherapy
Outcomes after Salvage Cryotherapy
Management of Local Recurrence after Cryotherapy
Adjunctive Therapy
Complications
Health-Related Quality of Life
Costs of Cryotherapy
Future Directions

Historically, the principal treatment options for patients with clinically localized prostate cancer have included radical prostatectomy, radiation therapy, and active surveillance or watchful waiting (Middleton et al, 1995). With the exception of radical prostatectomy and watchful waiting (Bill-Axelson et al, 2005), however, randomized, prospective clinical trials comparing the efficacy of primary prostate cancer therapies are lacking. Radical prostatectomy has been perceived as morbid by some, whereas radiation therapy has been criticized for its uncertain efficacy (Scardino and Wheeler, 1988; Kabalin et al, 1989; Fowler et al, 1993; Crook et al, 2000; Potosky et al, 2000, 2004; Zelefsky et al, 2001; Pollack et al, 2002; Penson et al, 2005). Active surveillance is an early option for some patients; however, these patients often proceed with definitive local therapy during longer-term follow-up (Koppie et al, 2000). These and other concerns regarding conventional treatment have fueled an interest, among both patients and physicians, in alternative treatments that are both efficacious and associated with limited treatment-related morbidity.

In fact, cryotherapy—the ablation of tissue by local induction of extremely cold temperatures—has re-emerged as a therapeutic modality that meets these criteria. In 1996 the American Urological Association (AUA) recognized cryotherapy as a therapeutic option for prostate cancer and removed the "investigational" label from this procedure. In late 2008 the AUA released a consensus "Best Practice Statement" on cryosurgical ablation as a treatment option for patients with clinically localized prostate cancer (Babaian et al, 2008). The consensus panel concluded that cryosurgery is an established treatment option for men with newly diagnosed, or radio-recurrent, organ-confined prostate cancer. Moreover, the consensus panel concluded that advances in cryotherapy technology including ultrasonographic ice ball monitoring and use of multipoint thermal sensors have allowed more efficient freezing of the prostate gland while reducing collateral damage to surrounding tissues, notably, the rectum, urethra, and external urinary sphincter (Babaian et al, 2008). **Accordingly, contemporary cryotherapy offers patients a minimally invasive treatment option with low morbidity, minimal blood loss, short hospital stay, good recurrence-free survival, and high rates of negative post-treatment biopsies** (Shinohara et al, 1996; Koppie et al, 1999; Long et al, 2001; Bahn et al, 2002; Donnelly et al, 2002; Han et al, 2003; Prepelica et al, 2005; Cohen et al, 2008; Jones et al, 2008; Pisters et al, 2008).

HISTORY OF CRYOTHERAPY

Human cancers were first managed with cryotherapy in the 19th century when cervical and breast cancers were treated with a salt and ice mixture (Gage, 1998). Although the method was crude, tumor size could be reduced and local tumor control was an attainable goal. In 1961 Cooper and Lee built the first closed cryoprobe system, which circulated liquid nitrogen through a closed metal tube that was placed in contact with the tissue to be treated. This system was used for treating patients with Parkinson disease and other neuromuscular disorders. The first urologic application of prostate cryotherapy was by Gonder and colleagues (1964), who developed probes suitable for transurethral freezing of prostate tissue for benign prostatic hyperplasia and prostate cancer.

As of 2008, four distinct generations of cryotherapy for prostate cancer have been described, highlighting both the progressive evolution of relevant technology and improved patient selection (Table 105–1). During the 1960s and 1970s, early cryosurgeons applied both transurethral and open transperineal approaches in their attempts to eradicate prostate cancer (Gonder et al, 1964). In 1972 Flocks and colleagues described a refined transperineal approach. An incision was made anterior to the rectum, allowing separation of the rectum and prostate and exposure to the most posterolateral aspects of the prostate gland. Freezing was then performed on the surface of the gland and monitored by direct vision. Although the technique compared favorably with treatment modalities such as radical prostatectomy and external-beam radiation therapy (EBRT) with respect to survival, morbidity was significant and included urethral sloughing, rectourethral or urethrocutaneous fistulae, bladder neck obstruction, and urinary

Table 105–1.
Evolution of Prostate Cryotherapy

GENERATION	TRUS	URETHRAL WARMER	PSA	PINPOINT THERMOCOUPLES	CRYOGEN	SMALL-DIAMETER PROBES
First (1960s)	No	No	No	No	Liquid nitrogen	No
Second (1990s)	Yes	After 1995	Yes	No	Liquid nitrogen	No
Third (2000s)	Yes	Yes	Yes	Yes	Argon*	Yes
Fourth (2000s)	Yes	Yes	Yes	Yes†	Argon	Yes (1.47 mm)

PSA, prostate-specific antigen; TRUS, transrectal ultrasound.
*Joule-Thompson principle.
†Multipoint (rather than single-point) thermocouples.

incontinence (Bonney et al, 1982). In 1974 Megalli and colleagues were the first to report a transperineal percutaneous approach using a single 6.3-mm (18-Fr), sharp-tipped liquid nitrogen cryoprobe (Megalli et al, 1974). This cryoprobe was introduced through perineal skin incisions performed on either side of the midline, and its placement was guided by digital palpation. The digitally monitored freezing process was often augmented by a single thermostat placed in the perirectal region. The cryoprobe was typically repositioned to achieve adequate coverage of the prostate, seminal vesicles, and any identifiable extraglandular extension. In an attempt to improve monitoring, Reuter (1972) described the use of a rigid cystoscope, as an adjunct to the rectal index finger, to directly monitor the bladder and ureteral orifices. Unfortunately, the inability, with first-generation cryotherapy, to precisely place cryoprobes and monitor the extent of freezing in real time resulted in the abandonment of the technology until the late 1980s (Gonder et al, 1964; Flocks et al, 1972).

The development and implementation of transrectal ultrasound (TRUS) guidance and urethral warming heralded the second generation of prostate cryotherapy and significantly reduced the number of treatment-related complications. Onik and colleagues (1984) first demonstrated that the frozen area could be visualized ultrasonographically as a well-marginated, hyperechoic rim with acoustic shadowing, and that the leading edge of the growing iceball could be monitored in real time with TRUS imaging (Onik et al, 1988). In the 1990s TRUS technology achieved widespread adoption for the early detection of prostate cancer, and this trend fueled the development of a transperineal, percutaneously introduced, multiple cryoprobe system (Chang et al, 1994). TRUS guidance allowed accurate placement of cryoprobes, real-time monitoring, control of freezing, and visualization of the rectum to protect it from injury. At the same time, the use of urethral warmers with a continuous irrigation system maintains the urethral mucosa above freezing and preserves a thin layer of the mucosa. Urethral warming has been credited with significantly reducing urethral sloughing, stricture formation, and urinary incontinence (Cohen and Miller, 1994; Cohen et al, 1995; Wong et al, 1997; Lee et al, 1999). **Another significant advance for modern prostate cryotherapy was the development of cryogenic systems with multiple cryoprobes.** Multiple, simultaneously controlled cryoprobes achieve a uniform and effective distribution of lethal temperature throughout the iceball, thereby increasing clinical efficacy and reducing the risk of collateral injury. In addition, the availability of multiple cryoprobes provides surgeons with greater flexibility to conform ice formation to each patient's unique anatomy. During this same time period, the **emergence and widespread adoption of the prostate-specific antigen (PSA) assay allowed for better selection of patients and more precise assessment of postcryotherapy cancer control outcomes** (Stamey et al, 1987).

The first modern cryoprobe system was a liquid nitrogen system that supported independent throttle control of five cryoprobes (Accuprobe System, Cryomedical Sciences, Inc., Rockville, MD) that delivered high-efficacy freezing. An advancement of the system over earlier liquid nitrogen systems was refrigeration ("supercooling") of the liquid nitrogen from its usual boiling point at below –195.8° C down to –209° C. This improved efficiency by overcoming problems with nitrogen bubbles forming in the cryoprobe transport tubes or in the cryoprobes, which could unpredictably impede liquid nitrogen cryogen circulation. The first clinical application of such a system in humans was in 63 patients with localized prostate cancer (Onik et al, 1993). Although essential to the successful reintroduction of cryotherapy, liquid systems have intrinsic difficulties in containing, controlling, and circulating liquid nitrogen. **Therefore the hallmark of third-generation cryotherapy was the transition from liquid to gas systems. With this technologic advance, surgeons could now use pressurized gas to both freeze (argon gas) and actively warm (helium gas) tissue via the Joule-Thompson effect. According to the Joule-Thompson effect, different gases undergo unique temperature changes when depressurized according to unique gas coefficients** (Fig. 105–1). In the case of argon gas, this is a constant enthalpy expansion that results in rapid cooling to its boiling point of argon gas (–185.7° C). To accomplish this, high-pressure (3000 psi) ambient temperature argon gas is circulated to the cryoprobe tip, where it expands rapidly as it decreases to room pressure (15 psi). The expanded gases are circulated back to the cryogenic unit through the larger outer lumen of the cryoprobe and the supply hose. The venting of used gas, usually into the room, occurs at the cryogenic machine. The use of helium gas (67° C), which warms up rather than cools when expanded, provided an active defrosting capability that was not available in the second-generation systems, improving the control of iceball formation. It is noteworthy that both argon and helium are inert gases and therefore safe. However, both will displace oxygen from a room and thus adequate air circulation should be maintained within the cryogenic suite.

Importantly, the transition from liquid to gas allowed for the development of ultra-thin, 17-gauge (1.47-mm) cryoprobes, which permitted direct transperineal needle placement through a template without making incisions or using tract dilatation and insertion kits (Fig. 105–2). Another advantage is that gas systems are more compact and easier to use and maneuver within the operating room environment. The introduction of pinpoint thermocouples for systematic temperature monitoring has also substantially contributed to a

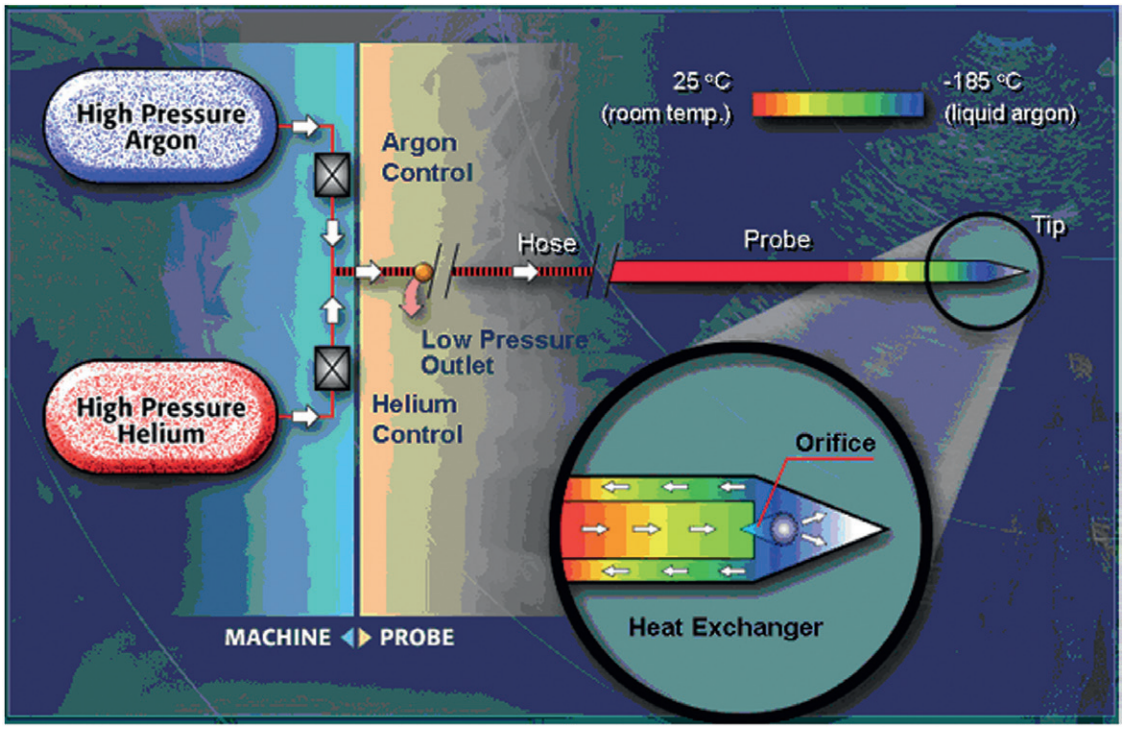


Figure 105–1. Joule-Thompson principle. High-pressure gases enter through the spiraled central port and expand at a narrow terminal port to effect cooling. In accordance with the gas coefficient and the dimension of the nozzle, different gaseous elements generate different thermal exchange events at the area close to the nozzle. Expanded gases return back through the larger, outer lumen and are vented outside the patient into the room. Argon gas is used for cooling (–185.7° C), and helium is used for heating (67° C).

reduction in cryotherapy-associated morbidity. They are used to ensure both that adequately cold temperatures are reached within the prostate and that sensitive adjacent structures, namely, the rectum and external sphincter, are maintained at temperatures warm enough to ensure maintenance of their structural and functional integrity. In addition, the risk of rectal freezing can be lessened by injection of saline solution into Denonvilliers fascia, increasing the space between the prostate and the rectum.

The development of multipoint thermal sensors marked the emergence of fourth-generation prostate cryosurgical technology. With multipoint sensors, surgeons are now able to monitor temperatures along an entire plane (e.g., between the prostate and rectum), rather than at isolated anatomic sites. Although empiric data are not yet available, it is anticipated that the routine utilization of multipoint thermal sensors will further reduce the incidence of postcryotherapy morbidity including both fistulae and urinary incontinence. Fourth-generation technology also involves the use of newly introduced, variable-length cryosurgery probes. The principal advantage of variable-length probes is that they allow surgeons to conform the iceball to the length of the prostate under treatment, thereby obviating the need for a pullback procedure in a majority of cases. Finally, the newest generation of cryosurgical technology also includes computer software that allows surgeons to construct preoperative temperature maps on the basis of theoretic cryoprobe placement (Babaian et al, 2008). With these computer models, surgeons are able to prospectively plan cryoprobe configuration in an attempt to further optimize targeting of diseased tissue, while minimizing damage to adjacent important structures including the rectum, urethra, and external urinary sphincter (Babaian et al, 2008).

CRYOBIOLOGY

Mechanisms of Cell Injury and Death by Cryotherapy

The principles of cryotherapy including the mechanisms of cell injury and cell death have been well studied (Gonder et al, 1964; Gage and Baust, 1998, 2007; Hoffman and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007) (Table 105–2). Unlike radiation (mitotic arrest) or androgen deprivation (apoptosis), the main mechanism of cryotherapy-produced cytotoxicity is the induction of targeted areas of coagulative necrosis in the prostate gland. **The key factors involved in freezing injury include direct mechanical shock, osmotic shock, and cellular hypoxia.** Mechanisms of action include protein denaturation via dehydration, transfer of water from the intracellular space to the extracellular space, rupture of cell membranes from ice crystal expansion, toxic concentration of cellular constituents, thermal shock from rapid supercooling, slow thawing, vascular stasis, and increased apoptosis (Cooper and Hirose, 1966; Hoffman and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007).

The extracellular fluid begins to crystallize after reaching a tissue temperature below 0° C. The osmotic pressure of the unfrozen portion of the extracellular fluid compartment increases, causing dehydration of cells to occur due to the shift of water from the intracellular to the extracellular space, which also results in an accumulation of toxins within the cell (Hoffman and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007). Changes in cellular pH lead to the denaturing of cellular

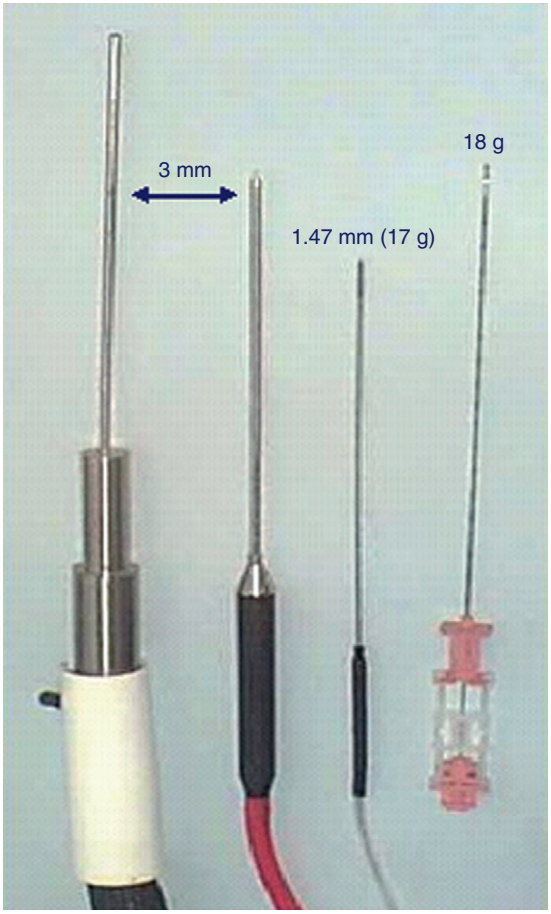


Figure 105–2. Evolution of cryoprobes. Development of third-generation cryotherapy included the transition from liquid nitrogen to gas-driven cryoprobes, which permitted the use of smaller-diameter cryoprobes that allow for direct transperineal probe placement through a brachytherapy-like template, without using tract dilatation and insertion kits.

Table 105–2.

Cytotoxic and Antineoplastic Effects of Cryotherapy

Mechanical
Rapid formation of intracellular and extracellular ice crystals exerting mechanical shear forces on cell membranes and organelles
Biochemical
pH change
Osmolarity
Electrolyte concentration
Lipoprotein damage (thermal shock from rapid supercooling)
Ischemic
Microvascular damage: stasis of blood leading to thrombosis
Freeze major blood supply (neurovascular bundle)
Apoptotic
Activation of programmed cell death pathways (only in injury zone)
Immunologic
Freezing may release antigens that stimulate an antitumor immune response

proteins. At a temperature of –15° C, most of the extracellular environment is frozen, which causes trapping of tissue and shearing forces to disrupt cellular structure (i.e., mechanical shock) (Hoffman and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007). Further decreases in temperature lead to crystallization of water in the intracellular space that mechanically breaks the cellular membrane (Hoffman and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007).

The delayed or indirect destructive effects of cryotherapy continue primarily because of injury to the vasculature, resulting in tissue hypoxia and vascular thrombosis (Hoffman and Bischof, 2002; Chao et al, 2004; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007). Zacarian and colleagues (1970) reported that at temperatures below –20° C, venules were more susceptible to injury than arterioles. Freezing promotes stasis of blood, leading to thrombosis and subsequent coagulative necrosis of tissue. This process includes local edema with activation of the inflammatory cascade. On thawing, extracellular fluid shifts back into the intracellular space, leading to lysis of both the intracellular organelles and the cell membrane itself. The blood vessels around the targeted tissue initially dilate after thawing, and hyperpermeability of the vessel wall occurs. After a few hours of this hyperemic state, microthrombi form on the damaged vessel wall, leading to regional tissue ischemia (Hoffman and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007).

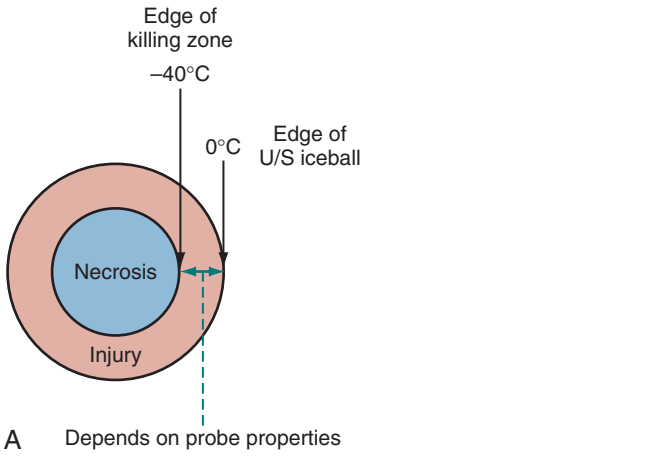
Apoptosis is recognized as a mechanism of cell death that occurs in both normal tissues and various pathologic conditions. Apoptotic cells are characterized by nonrandom DNA cleavage, blebbing of membranes, phospholipid inversion in the membranes, and caspase activation (Kerr et al, 1994). **Following cryosurgical ablation, apoptotic cells are found primarily in the peripheral zone of the cryogenic lesion outside the killing zone, where the temperature was not sufficiently cold to kill all the cells** (Hollister et al, 1998; Hoffman and Bischof, 2002). In addition, kinetic studies have shown that cells are susceptible to entering the apoptotic state up to 8 hours after rewarming (Yang et al, 2003). The recent finding of apoptosis in cells in the peripheral zone of the cryogenic injury may one day be exploited therapeutically using other proapoptotic stimuli to extend the zone of cell death (Yang et al, 2003; Clarke et al, 2007). Currently, however, the precise role of apoptosis in cryosurgery-induced tissue injury remains incompletely understood (Hoffman and Bischof, 2002; Baust et al, 2004).

In-vivo experiments have suggested that cryodestruction of living tissues can elicit an immunologic response by the host that may itself eradicate cancer cells (Ablin, 1972). Experiments with MRMT-1 mammary adenocarcinoma cells and R3327 prostate adenocarcinoma cells in rats have demonstrated the appearance of tumor immunity by 7 to 10 weeks after cryotherapy that was associated with a decrease in growth of metastatic lesions. However, cryotherapy of the Dunning AT-1 cell line, an androgen-insensitive cell line, in Copenhagen rats was associated with a minimal increase in T-cell counts without an effect on the local tumor growth rate (Hoffmann et al, 2001). **Although the potential for a cryoimmunologic effect against residual prostate cancer cells is intriguing, cryotherapy must still be considered as a local therapy.**

Tissue Response to Freezing

The response of human tissue to freezing injury varies from inflammatory to destructive, depending on the

severity of freezing (Hoffman and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007). Minor freezing injury features only inflammatory responses, whereas severe freezing injury destroys cells and tissues, which is the prime requirement for treating tumors. The cryogenic lesion is characterized by a central region of uniform coagulation necrosis. Surrounding the central lesion is a peripheral zone that develops several days after freezing (Fig. 105–3). In this region, tissue temperatures ranged 0° C to –0° C, and only partial cell death has occurred (Hoffman and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007). The process of wound repair begins in the peripheral zone in the areas in contact with viable tissue; inflammatory cells infiltrate and new blood vessels may grow into the injured tissue. Over the following weeks or months, the dead tissue is slowly replaced by fibroblasts and new collagen formation, yielding a contracted healed area in lieu of the previously ablated tissue.



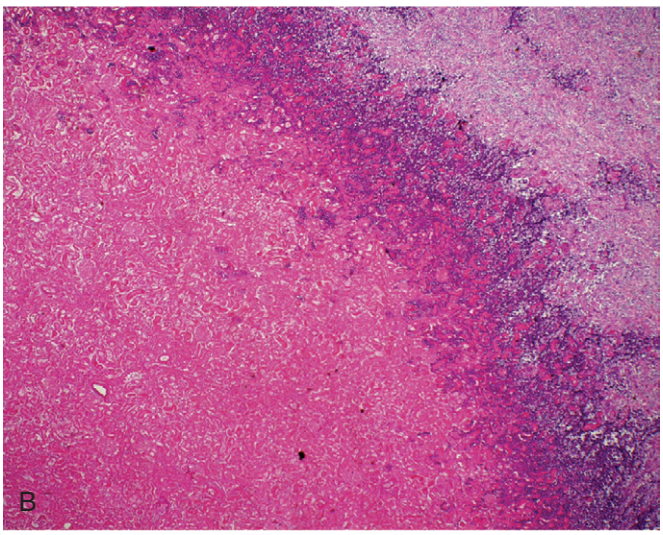


Figure 105–3. **A,** The cryogenic lesion is characterized by a central uniform coagulation necrosis surrounded by a peripheral zone. Tissue temperatures range from 0° C to –40° C in the peripheral zone leading to partial cell death and apoptosis. **B,** Complete necrosis within central portion of scar with rim of sublethal injury was seen after cryotherapy. (Hematoxylin and eosin, reduced from ×80.)

Factors Affecting Tissue Destruction during Cryotherapy

Optimal technical application of cryotherapy requires a thorough understanding of the freeze-thaw cycle and its components (Table 105–3). **The variables that correlate with the likelihood of cell destruction include the cooling rate during freezing, the warming rate during thawing, and the lowest temperature achieved in the tissue** (Hoffman and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007; Babaian et al, 2008). Tatsutani and colleagues (1996) described these effects in an in-vivo prostate cancer cell experiment. In this study, complete cell death was unlikely to occur at temperatures higher than –20° C and temperatures lower than –40°C were required to completely destroy cells (Tatsutani et al, 1996). Moreover, the investigators noted that a faster freezing rate and a slower thawing rate resulted in optimal cellular destruction.

For optimal results, a tissue temperature of –40° C to –50° C, which is lethal for cells, should be produced within the tumor including a safe distance around the tumor (Bischof et al, 1997; Gage and Baust, 1998; Hoffmann and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007). In addition to the nadir temperature, the duration of freezing appears to be an important determinant of tissue destruction (Hoffman and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007). Once the tissue temperature reaches a certain nadir level, more cellular destruction can be achieved by prolonged freezing at this temperature. The target tissue should therefore be held in the frozen state for several minutes to allow time for solute effects, ice crystal formation, and recrystallization effects. When the tissue is held at –15° C to –40° C, biochemical changes and growth of ice crystals are enhanced, increasing the rate of cell death (Hoffman and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007). Nonetheless, the optimum duration of freezing is not well defined and may prove to be cell/tissue-type specific (Hoffman and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007).

Slow thawing of the frozen tissue is also a crucial determinant of tissue destruction (Hoffman and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007). In fact, the rate of thawing should be as slow as clinically practical. A longer thaw will yield greater cellular damage due to solute effects, ice crystal restructuring (recrystallization), prolonged oxidative stress, and growth of ice crystals (Hoffman and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007). The large ice crystals that form during "warming" recrystallization create shearing forces, thereby disrupting the target tissues and

Table 105–3.

Factors Affecting Tissue Destruction during Cryotherapy

Rate of tissue freezing
Rate of tissue thawing
Nadir tissue temperature
Duration of freezing
Number of freeze-thaw cycles
Existence of heat sinks

promoting cellular death. Repetition of the freeze-thaw cycle is also important (Hoffman and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007; Babaian et al, 2008). The first freeze-thaw cycle increases the thermal conductivity of the tissue caused by cellular breakdown; the second freeze-thaw subjects the tissue to extended physiochemical changes, while passing through damaging thermal conditions for the second time (Hoffman and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007). With repetition, the second cycle increases the extent of necrosis up to 80% of the previously frozen volume (Hoffman and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007). The second cycle also moves the lethal isotherm close to –20° C, permitting a closer approach to the margins of the prostate without endangering the rectum. The interval between freeze-thaw cycles is also an important factor in tissue injury. A longer thaw time supports complete vasoconstriction of larger blood vessels, continued ice crystal growth, and more extensive osmotic damage. A further delay after thawing, but before the second freeze cycle, leaves the tissue in a hypothermic state and allows time for the microcirculation to fail. In combination, these events provide the targeted tissue with conditions consistent with severe oxidative stress that may ultimately give rise to additive post-thaw cell death (Hoffman and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007).

In a clinical setting therefore the number of freezing cycles, the lowest temperature achieved, and the existence of any regional "heat sinks" may be important factors relating to cancer destruction. **Double freeze-thaw cycles during cryotherapy for prostate cancer in humans have been associated with lower positive biopsy rates, as well as improved PSA results, when compared with a single freeze-thaw cycle, without an increase in the development of cryotherapy-related morbidities** (Shinohara et al, 1996; Pisters et al, 1997; Wong et al, 1997; Mouraviev and Polascik, 2006; Babaian et al, 2008). Temperature mapping studies performed in patients with localized prostate cancer, who agreed to undergo focal cryotherapy of the prostate before undergoing radical prostatectomy, demonstrated that cryotherapy resulted in a central zone of complete cellular necrosis surrounded by a more peripheral zone of cell damage, and that **two consecutive 10-minute freeze cycles produced a larger area of coagulative necrosis than a single 20-minute freeze** (Larson et al, 2000). Furthermore, a **double freeze at temperatures below –40° C appears to yield more complete tissue necrosis** (Larson et al, 2000). This fact has important clinical implications because the hyperechoic edge of the iceball visualized is 0° C to –2° C, and temperatures as low as –20° C to –40° C are inside this edge (see Fig. 105–3). Therefore the iceball should be extended beyond the edge of the prostate to ensure adequate tissue ablation. Although the available literature supports the use of a minimum of two freeze-thaw cycles (Shinohara et al, 1996; Pisters et al, 1997; Wong et al, 1997; Mouraviev and Polascik, 2006; Babaian et al, 2008), it remains unknown whether additional therapeutic efficacy may be derived from more than two treatment cycles. Finally, cryosurgeons should be aware that large blood vessels may act as heat sinks and highly vascular areas may not achieve target temperatures even though they are completely enclosed in the treatment area.

Recognizing the critical importance of these technical concerns and determinants of tissue destruction, authors of the AUA's Best Practice Statement for prostate cryosurgery recommended that the following procedural requisites be considered in every case (Babaian et al, 2008):

1. Tissue freeze rate: The authors concluded that rapid freezing is more efficacious than slow freezing with respect to cell death (Babaian et al, 2008).
2. Temperature monitoring: The consensus panel strongly recommended the use of thermal couples during cryosurgical ablation, despite the absence of clear scientific evidence to support their use. It is believed that real-time temperature monitoring allows the cryosurgeon to better control the freezing process while at the same time protecting key vital structures (e.g., rectum, urethra) from unintended injury (Babaian et al, 2008).
3. Nadir temperature: On the basis of in-vitro and in-vivo data, the panel recommended attaining intraprostatic temperatures of –40° C or lower whenever possible during cryosurgical ablation. They recognized, however, that prostate cancer may be relatively temperature labile and that lethal temperatures may occur closer to –20° C.
4. Thaw rate: The authors concluded that prostate cancer ablation is more effective with slow (passive) versus rapid (active) tissue thawing. They note, however, that active thawing may not affect thaw rates at the distal edges of the gland (Babaian et al, 2008).
5. Freeze cycles: Members of the panel endorsed the use of a double freeze-thaw cycle during cryosurgical ablation of the prostate. They based this recommendation on experimental and clinical evidence that cancer cells not killed by the first freeze cycle may be stressed to such an extent that a second cycle achieves complete cellular death (Babaian et al, 2008).

TECHNICAL IMPROVEMENTS IN CRYOTHERAPY EQUIPMENT

Transrectal Ultrasound Systems

One of the most significant advances in the application of prostate cryosurgery has been the implementation of real-time, ultrasound-guided placement of the cryoprobes and continuous sonographic monitoring of the freezing process. **Biplanar transrectal ultrasound systems (TRUSs) allow for transverse and longitudinal views of the prostate, and the views are easily interchangeable during the procedure.** Frozen tissue is significantly different from unfrozen tissue in sound impedance, resulting in strong echo reflection at the interface of frozen and normal tissue. Accordingly, **the leading edge of frozen tissue is easily visualized as a bright line** (Fig. 105–4). The tissue inside this leading edge is concealed within the acoustic shadow created by this boundary so that the anterior boundary of the freezing area cannot be monitored (Mouraviev and Polascik, 2006). The refraction and reflection of the sound wave can also overestimate the lateral boundary of the iceball. The use of color Doppler imaging may be helpful for monitoring tissue viability (vascularity) as freezing approaches the rectum. Although not an objective parameter, color Doppler imaging provides some indication about the vascular state between the ice and the rectal mucosa and may therefore potentially provide some information about the likely speed of freezing in this area. Sonography provides no information about the temperature distribution within the ice, nor does it show the extent of freezing at the lateral or anterior aspects of the prostate. Reports of three-dimensional ultrasound during cryosurgery show potential, especially for preoperative planning of a procedure and cryoprobe placement (Chin et al, 1998). In practice, however, these have been relatively slow and

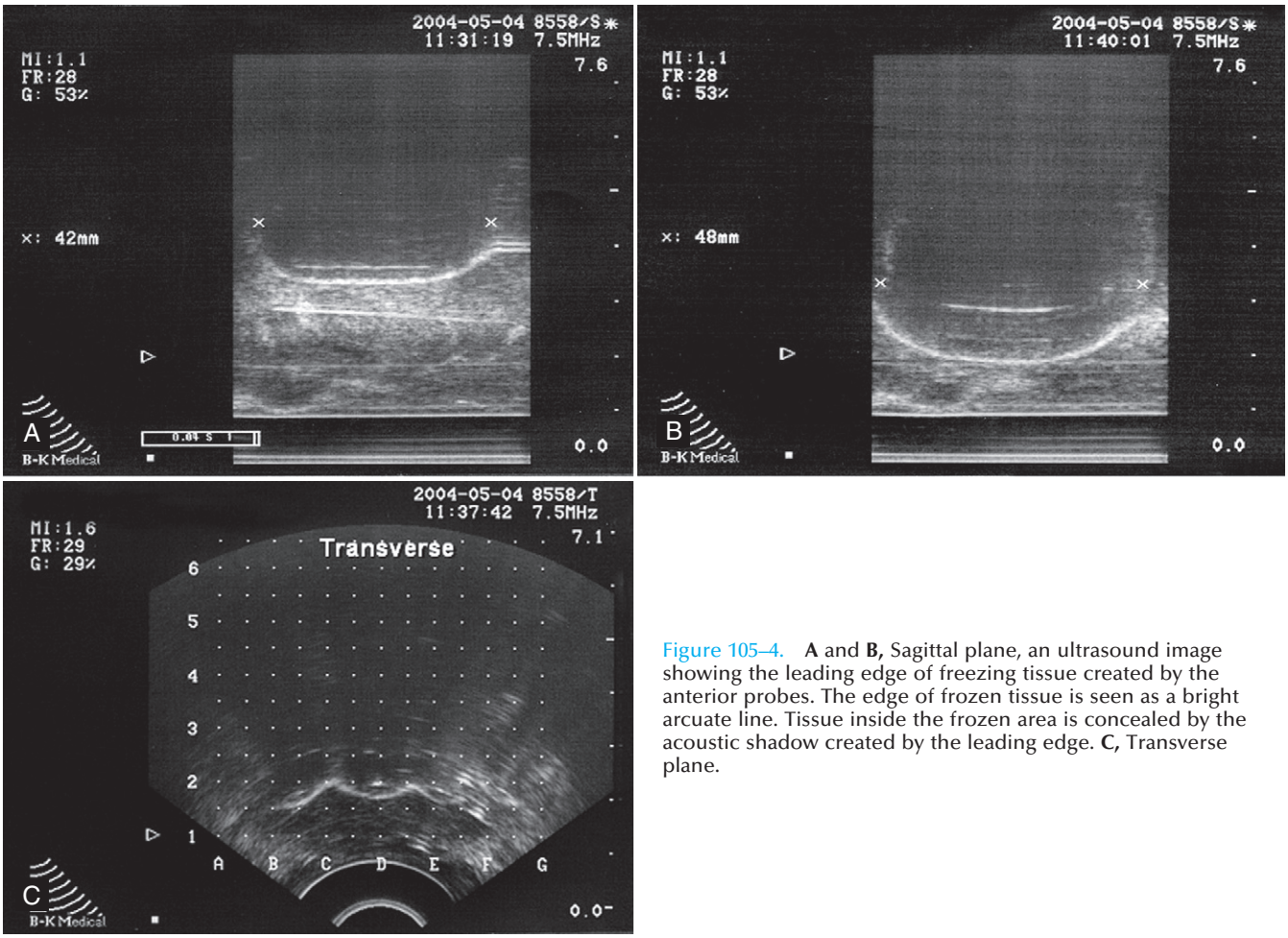


Figure 105–4. **A** and **B,** Sagittal plane, an ultrasound image showing the leading edge of freezing tissue created by the anterior probes. The edge of frozen tissue is seen as a bright arcuate line. Tissue inside the frozen area is concealed by the acoustic shadow created by the leading edge. **C,** Transverse plane.

cumbersome to apply, making their clinical implementation difficult.

Template and Stands

A brachytherapy-like stepper includes a cradle to which the multifrequency biplanar TRUS probe is attached. A brachytherapy-like template drilled with a matrix of holes that will accommodate the cryoprobes is then attached to the holding device (Fig. 105–5). Systems are available with a floor stand or table-mounted device. The brachytherapy-like grid can be adjusted to ensure accuracy with any ultrasound system.



Figure 105–5. Brachytherapy-like template drilled with a matrix of holes to accommodate cryoprobes.

Cryogenic Systems

Liquid nitrogen (–195.8° C) is the coldest practical cryogenic agent and has the greatest freezing capacity, but it cannot be used in probes of less than 3 mm in diameter. The transition from systems circulating liquid nitrogen to gas-driven probes now permits the use of ultra-thin cryoprobes. In accordance with gas coefficient and nozzle dimensions, different gaseous elements generate different thermal exchange events (Joule-Thompson principle). **In clinical practice, argon gas is used for cooling and helium gas is used for heating (thawing).** Third-generation cryotherapy using gas-driven delivery systems and 17-gauge cryoprobes inserted via a direct transperineal route into the prostate without using an insertion kit were first reported in 2000 (Zisman et al, 2000). At present in the United States, there are two available systems for cryosurgical ablation of the prostate. The Precise system (Galil Medical, Plymouth Meeting, PA) uses pressurized argon gas as the source of freezing, and up to twenty-five 17-gauge (1.47-mm) cryoprobes (IceSeeds) can be used to create a conformal

freezing pattern. The iceball created with the IceSeeds is approximately 18 mm in diameter and 27 mm in length. The Precise system also has available the IceRod needles in which a bigger iceball is created (32 mm × 56 mm), thereby facilitating treatment of men with larger prostate glands. The CRYOcare system (Endocare, Inc., Irvine, CA) also uses pressurized argon gas as a cryogen and can freeze up to eight 2.4-mm, vacuum-insulated cryoprobes simultaneously; the iceball created is approximately 33 mm in diameter and 54 mm in length. An important recent advance is the introduction of variable-length cryotherapy probes that tailor the length of the iceball to the length of the prostate. The authors anticipate that, in the future, cryotherapy probes may be further modified to also allow intraoperative tailoring of the iceball width.

Warming Probes

Warming probes can be used to protect tissues and organs from being inadvertently damaged during cryotherapy. Warming probes actively warm by using helium gas, which warms when it expands through the Joule-Thompson principle. In selected cases, warming probes may be used to protect the neurovascular bundles (NVBs) in an attempt to preserve sexual function.

Thermocouples

Because fairly reliable coagulative necrosis can be achieved when temperatures below –40° C are reached in the target tissues (Gage and Baust, 1998; Hoffman and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007), many surgeons now place thermocouples at the margins of the targeted treatment zones to ensure that cytotoxic temperatures are achieved during freezing. Several studies reported improved PSA recurrence-free rates and postcryotherapy biopsy results with thermocouple monitoring when compared with patients in whom this had not been used (Lee et al, 1997; Wong et al, 1997). In most cases, thermocouples are also used to ensure maintenance of nonablative temperatures within Denonvilliers fascia, the anterior rectal wall, the external sphincter, and/or the neurovascular bundle(s).

Urethral Warming Device

The primary role for the urethral warming device during prostate cryotherapy is to protect the urethra and the external urinary sphincter to minimize urethral sloughing and prevent urinary incontinence. The urethral warmer is a closed double-lumen catheter made of a polyethylene membrane through which saline heated to 43° C is continuously circulated by a water pump at a rate of 350 to 500 mL/min. The first urethral warming system was marketed as a nonsignificant risk device until approximately July 1994. Initial experiences with this system were notable for fairly low rates of urethral sloughing, ranging from 4% to 10% (Onik et al, 1993; Coogan and McKiel, 1995; Wieder et al, 1995). Because of concerns submitted to the U.S. Food and Drug Administration (FDA) surrounding the safety of this particular device, it was taken off the market in mid-1994 for approximately 18 months while it underwent regulatory review. During this time period, numerous investigators reported a sharp increase in postcryotherapy transurethral resection of the prostate (TURP) and overall urethral sloughing rates due to the use of alternative urethral warmers or warming systems that did not have many of the features of the original one (Cohen et al, 1996a, 1996b; Lee et al, 1997). As expected, the safety of the original warmers was confirmed and, since 1996, FDA-approved urethral warming devices have been widely available. Studies directed toward improving catheter design and urethral warming efficacy are ongoing, with the hope that slough rates will decline even further as new devices are marketed. Moreover, because urethral warming catheters necessarily preserve a ring of viable tissue around the urethra, further improvements in the efficiency of these devices may allow surgeons to achieve a tighter treatment margin by reducing the diameter of viable periurethral tissue. This may, in turn, yield improved cancer control following cryosurgical ablation as preserved prostate tissue around the urethra represents a sanctuary site for residual and/or recurrent cancer.

Computerized Planning

Computer-guided systems now provide improved intraoperative treatment planning with a potential for more precise and complete tissue destruction. The thermal distribution is predictable around a cryoprobe and can be modeled using computer simulation (Rewcastle et al, 1998, 2001; Babaian et al, 2008). Similar to the treatment planning strategies used for radiation therapy, it is possible to determine optimal placement of cryoprobes in the prostate to maximize ablation of the prostate while minimizing collateral damage (Sandison, 2002; Babaian et al, 2008). Research and development are focusing on the incorporation of functional and multimodality imaging data, as well as on the development of accurate mathematic models for in-vivo tissue injury response to thermal history (including cryotherapy-induced ischemia) to optimize treatment planning.

PATIENT SELECTION

Primary Cryotherapy

As with other forms of local therapy for prostate cancer, outcomes after cryotherapy correlate with cancer severity including the stage and grade of the primary tumor. In general, **primary cryotherapy is suitable for patients with clinical stage T1c-T3 disease of any tumor grade who are not potent or not interested in maintaining their potency;** in this setting, primary cryosurgical ablation is regarded mainly as an alternative treatment to radiation therapy. The authors believe that radical prostatectomy remains the gold-standard therapy for localized prostate cancer and the preferred treatment in younger patients. For patients with clinical stage T3 disease, primary cryotherapy is more appropriate for smaller-volume disease in which the tumor is likely to be encompassed in the freezing process. Moreover, extensive disease in a periurethral location is a contraindication to primary cryotherapy because use of the urethral warming catheter will preclude complete eradication of disease in this group of patients.

Because of the minimally invasive nature of cryotherapy, it may have specific advantages in select patients with certain comorbidities including those who are poor candidates for radical prostatectomy or radiation therapy (e.g., men with Crohn disease, ulcerative colitis, prior pelvic irradiation or pelvic surgery, cardiac disease, morbid obesity, and/or body habitus unfavorable for radical prostatectomy or radiation therapy). Primary cryotherapy can also be offered to patients who have no evidence of metastatic disease with more than a 10-year life expectancy who, after reviewing available information on prevailing therapeutic options for new diagnoses of prostate cancer, are either unsatisfied with or refuse to undergo radical prostatectomy or radiation therapy. In particular, many patients who are candidates for EBRT may wish to

consider primary cryotherapy because treatment can be administered as a 1-day ambulatory procedure as opposed to 7 to 9 weeks of treatment.

Before proceeding with cryosurgery, patients with a high risk of metastatic disease should undergo imaging, radionuclide bone scan, or cross-sectional imaging of the abdomen and pelvis on the basis of the stage and grade, as well as serum PSA concentrations. Patients at high risk for lymph node metastases may undergo regional lymph node dissection if identification of disease would alter treatment choice. Patients with gross extracapsular extension or seminal vesicle invasion are treated with neoadjuvant hormone therapy to reduce the tumor volume and allow for easier inclusion within the iceball. **If the prostate size exceeds 50 cm^3, complete freezing of the prostate may be difficult and neoadjuvant hormone therapy is indicated to reduce the target volume and allow** uniformly cold temperatures throughout the gland (Bales et al, 1995; Miller et al, 1996; Shinohara et al, 1996; Baust et al, 1997; Cespedes et al, 1997; Pisters et al, 1997; Babaian et al, 2008). There are no data, however, that neoadjuvant or concurrent androgen deprivation therapy influences postcryosurgery cancer control outcomes (Babaian et al, 2008).

Salvage Cryotherapy

Nearly one third of men with newly diagnosed prostate cancer are treated with EBRT and/or brachytherapy as primary therapy each year (Mettlin et al, 1998, 1999). Despite advances in radiation therapy techniques including image-guided and intensity-modulated radiation therapy (IMRT), three-dimensional conformal radiation therapy (3DCRT), and image-guided implantation of electromagnetic sensors to improve treatment planning (Pisansky, 2006), urologists will continue to see men with recurrent prostate cancer following primary radiation therapy (Allen et al, 2007; Nguyen et al, 2007). In fact, depending on failure definitions and initial cancer severity, it estimated that between 20% and 60% of men who undergo initial definitive radiation therapy for prostate cancer may develop a postradiotherapy PSA recurrence (Allen et al, 2007; Nguyen et al, 2007); among this group, local-only failure rates range from 25% to 32% (Touma et al, 2005). Radioresistant or radio-recurrent prostate cancer is typically an aggressive form of localized prostate cancer that represents a serious health risk for patients treated with primary radiation therapy for clinically localized prostate cancer. Many patients with radio-recurrent disease harbor large-volume and/or poorly differentiated tumors at the time of diagnosis (Allen et al, 2007; Nguyen et al, 2007), making it a challenge for salvage therapies to fully eradicate the cancer. Early detection with serum PSA monitoring and prostate needle biopsy after primary radiation therapy may identify residual adenocarcinoma at an earlier stage and increase the likelihood of successful salvage therapy (Allen et al, 2007; Nguyen et al, 2007). The goal of salvage therapy is to provide a treatment option with curative intent that improves local control and possibly affect long-term survival (Babaian et al, 2008).

Radical prostatectomy, cryotherapy, brachytherapy, and radiation therapy are the options available for salvage treatment of radiorecurrent prostate cancer (Touma et al, 2005; Allen et al, 2007; Nguyen et al, 2007). Salvage prostatectomy is associated with significant morbidity and therefore used relatively infrequently, particularly among older men with radio-recurrent prostate cancer (Krupski et al, 2006). Salvage brachytherapy and/or radiation therapy confer the potential for increased rectal and urinary toxicity in a patient who has previously received prostate irradiation (Allen et al, 2007; Nguyen et al, 2007). As a result, patients are often left with the option of either watchful waiting or temporary palliation with hormone deprivation therapy and its attendant toxicity. Notably, recent modifications in the technique of salvage cryotherapy have led to the ability to eradicate radiorecurrent prostate cancer safely and with decreased morbidity (Spiess et al, 2006; Ismail et al, 2007; Ng et al, 2007). However, complications associated with salvage cryotherapy are higher than those associated with primary treatment (Bales et al, 1995; Pisters et al, 1997; Long et al, 1998; Perrotte et al, 1999; Han et al, 2003; Spiess et al 2006; Ismail et al, 2007; Ng et al, 2007).

Only patients with a rising PSA value after radiation, a positive postradiation biopsy, and a negative metastatic survey are candidates for salvage cryotherapy (Mouraviev et al, 2006; Babaian et al, 2008). The authors' practice has been to wait at least 18 to 24 months after radiation therapy and to perform a biopsy of the prostate if the PSA value rises above the nadir level and there are three consecutive rises. Patients with a postradiation PSA greater than 10 ng/mL and/or a PSA doubling time of 16 months or less have been shown to be more likely to have unsuccessful salvage cryotherapy (Spiess et al, 2006; Ng et al, 2007; Babaian et al, 2008). **If a biopsy is undertaken, multiple cores should be obtained and the pathologist needs to be informed that the patient has had previous radiation.** Severe radiation effects with both nuclear and cytoplasmic alterations are seen in many prostatic biopsies and may confound the diagnosis of residual cancer (Cheng et al, 1999). **Given the high prevalence of seminal vesicle involvement in series of patients undergoing salvage radical prostatectomy, consideration should also be given to performing concurrent seminal vesicle biopsies** (Babaian et al, 2008). The incidences of positive biopsy results after primary radiation therapy vary widely in the literature but seem to be higher after EBRT than after brachytherapy (Stone et al, 2000).

Once it has been determined that primary therapy has failed, local recurrences must be distinguished from systemic recurrences. Local failure has been defined as histologically proven active adenocarcinoma on repeat prostate biopsy in the absence of radiographic evidence of metastatic disease. Unfortunately, multiple studies have demonstrated the relative lack of sensitivity and specificity of most radiographic tests including computed tomography (CT), magnetic resonance imaging (MRI), bone scan, and, more recently, monoclonal antibody-labeled nuclear scans for the diagnosis of systemic disease in biochemically recurrent prostate cancer (Albertsen et al, 2000; Sodee et al, 2000). High-resolution MRI with a lymphotropic superparamagnetic nanoparticle imaging agent may offer greater sensitivity for the detection of lymph node metastases; however, this technology is not yet available in clinical practice (Harisinghani et al, 2003; Nguyen et al, 2007). Despite the shortcomings of currently available imaging techniques, these modalities should be applied if recurrence is suspected because the presence of overt metastatic disease may obviate the patient being exposed to unnecessary local therapies. In this setting, pathologic confirmation via prostate biopsy of locally recurrent disease is warranted before consideration of invasive salvage therapies. In rare cases, **there may be a role in performing an open or laparoscopic biopsy of the pelvic lymph nodes because between 20% and 40% of patients will have lymph node metastases** (Rogers et al, 1995; Babaian et al, 2008). Caution is advised for novice laparoscopic surgeons because the dissection of these nodes can be technically challenging owing to potential adherence to the pelvic side wall and external iliac vessels.

Contraindications

Relative contraindications to cryotherapy are similar to those for brachytherapy and include prior TURP with a large tissue defect, significant symptoms of urinary obstruction before treatment, large prostate size, and a history of abdominoperineal resection for rectal cancer, rectal stenosis, or other major rectal pathology (Babaian et al, 2008). Prior TURP is associated with an increased risk for sloughing and urinary retention (Babaian et al, 2008). **Absolute contraindications include fistulae for any reason (including but not limited to inflammatory bowel disease) and previous surgery or trauma to the pelvis (e.g., urethroplasty, open book fracture) that may distort the anatomy of the prostate.** Significant preoperative obstructive symptoms increase the likelihood of postoperative urinary retention. Cryotherapy is not as sensitive to pubic arch interference as brachytherapy because the iceball migrates away from the cryoprobe. In rare cases, pubic arch interference may preclude adequate placement of cryoneedles. In these cases the prostate may be cytoreduced with neoadjuvant hormonal ablation (Babaian et al, 2008).

Combination Treatment

Patients with locally progressive disease despite hormonal ablation may be treated with cryotherapy to prevent urinary obstruction or bleeding (Cohen et al, 1996; Shinohara et al, 1996). Cryotherapy could also be used in combination with radiation therapy to more effectively manage the primary or dominant cancer lesion. Whether such combination therapy will improve cancer-specific outcomes compared with radiation alone or neoadjuvant androgen deprivation in combination with radiation is unknown at this time but merits further evaluation. A study evaluating the feasibility and complications of cryotherapy followed by radical prostatectomy in patients with clinical stage T3 disease demonstrated complete tumor destruction in four of seven patients (Fig. 105–6) (Pisters et al, 1999a). However, all seven patients who underwent radical prostatectomy had significant urinary incontinence requiring the use of pads. Cryotherapy has also been used to treat select patients with ultrasonically visible bulky local recurrences after radical prostatectomy (Siddiqui et al, 2007).

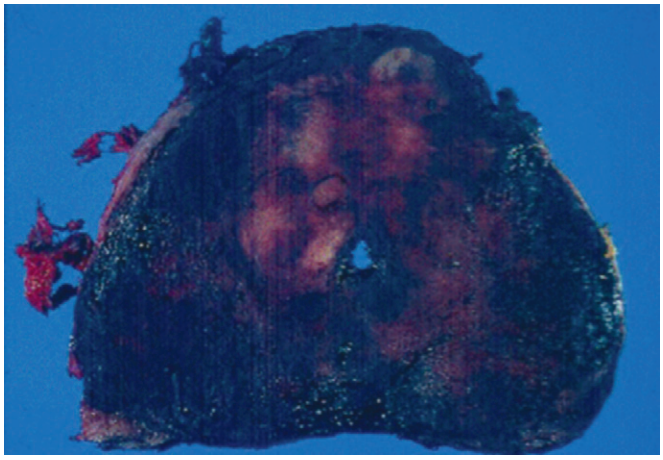


Figure 105–6. Cross section of prostatectomy specimen after two freeze-thaw cycles during cryotherapy of the prostate without the use of a urethral warming catheter. There was no histologic evidence of residual viable prostate cancer (pT0).

SURGICAL TECHNIQUE

Patient Preparation

Patients undergo a light bowel preparation consisting of oral magnesium citrate the day before and a phospho-soda enema the morning of the procedure. After induction of regional or general anesthesia (in the authors' experience, the latter is preferable), the patient is placed in an exaggerated dorsal lithotomy position, which provides excellent transperineal access to the prostate. Sequential compression devices are used preoperatively and during the procedure. A Foley catheter is inserted and clamped to allow the bladder to distend, thereby displacing the intraperitoneal contents.

Transrectal Ultrasound Evaluation

A multifrequency biplanar TRUS probe is inserted in the rectum and secured within the adapting cradle of a brachytherapy-like stepper. The prostate is imaged and its dimensions measured. The aiming grid software is activated and projected on the corresponding TRUS image. The attached probe is lowered posteriorly until either slight resistance is encountered from the posterior rectal wall or the sonographic image of the shiny anterior fibromuscular stroma is lost at 5 MHz. This maneuver opens up the distance between the prostate gland and the rectum, thereby increasing the safety of the procedure by reducing the risk of freezing injury to the anterior rectal wall. Once the necessary adjustments of the TRUS probe are complete, the holding device is fixed in place for the remainder of the case. A brachytherapy-like template, drilled with a matrix of holes to accommodate the cryoprobes, is attached to the holding device (see Fig. 105–5), gently fixed against the perineum, and stabilized with the stepper. The holes in the template are 5 mm apart and correspond to the aiming grid projected on the ultrasound image.

Cryoneedle Placement

At present, techniques for cryoneedle placement vary on the basis of the cryotherapy system employed for a particular case. Irrespective of the system employed, however, knowledge of the isotherm profile (i.e., the temperature range within the iceball) and iceball geometry for a particular cryoneedle is essential to achieving adequate overlap and confluence between adjacent iceballs (Fig. 105–7). Both cryotherapy systems currently on the market allow for direct transperineal placement of cryoprobes using a brachytherapy-like template without the use of insertion or dilation kits (Fig. 105–8). Cryoneedles are inserted under TRUS guidance and positioned in layers so that prostate is adequately covered (Fig. 105–9). Because the iceball progresses longitudinally past the needle tip, the cryoneedles are advanced into the base of the prostate and positioned just caudal to the bladder neck, depending on the cryoprobe-specific iceball geometry. The distance between the most posterior layer of cryoneedles and the prostate capsule also depends on the probe-specific iceball geometry. Given the propensity of prostate cancer to expand through the capsule in locations pierced by the branches of the NVB, lateral needles are placed as indicated to permit extraprostatic freezing and facilitate killing by early shutdown of the arterial supply to the gland. The prostatic urethra is identified by TRUS in both the longitudinal and the transverse views, and each cryoneedle is placed a safe distance away from the urethra. A complete description of specific

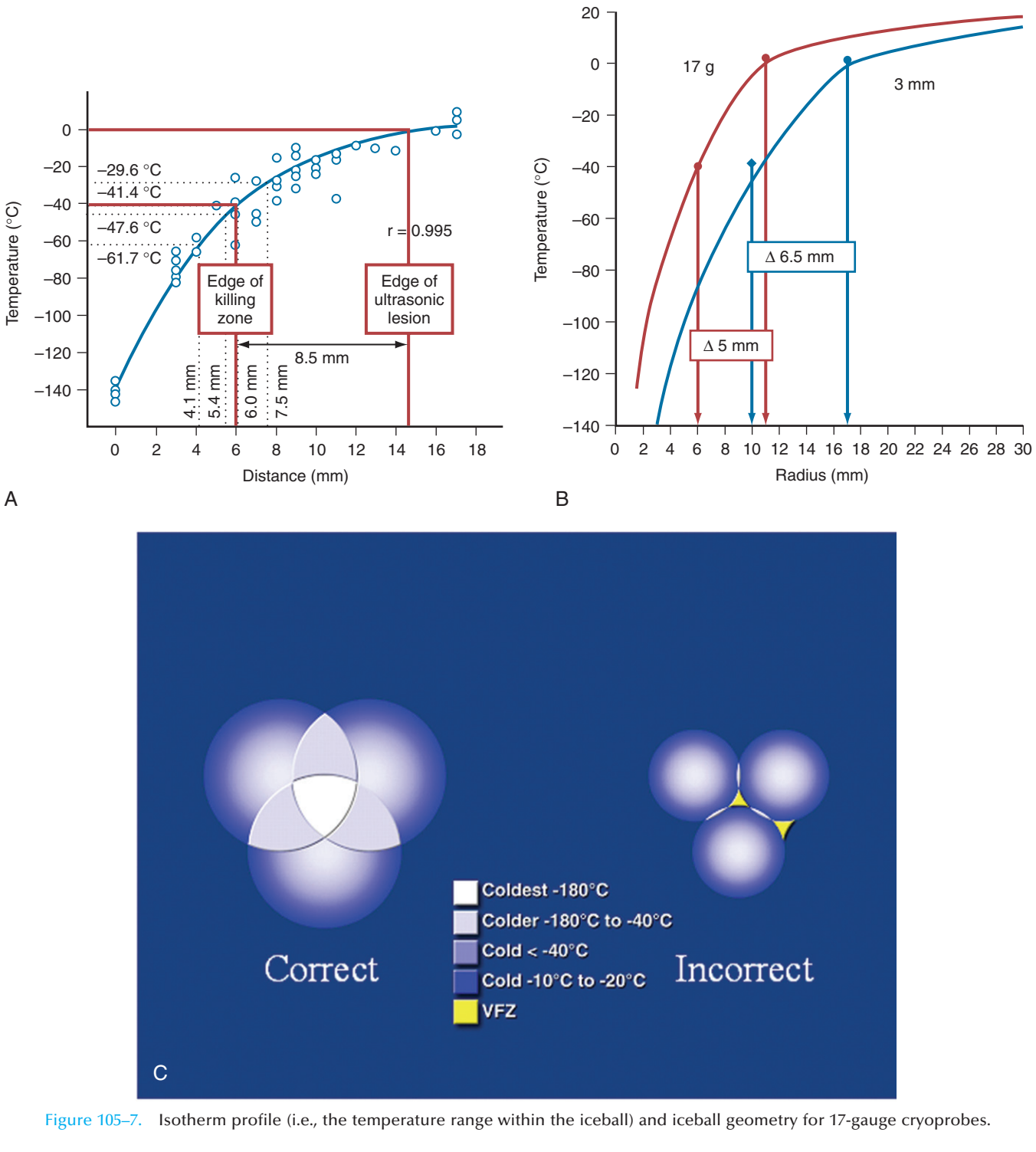


Figure 105–7. Isotherm profile (i.e., the temperature range within the iceball) and iceball geometry for 17-gauge cryoprobes.

techniques using the different cryogenic systems has been reported previously (Zisman et al, 2001; Ellis, 2002).

As described earlier, computerized treatment planning systems are now available. They incorporate serial transverse TRUS images of the prostate to render an individualized plan for optimal cryoprobe positioning (Babaian et al, 2008). However, there are currently no empiric data demonstrating that utilization of computerized treatment planning influences the safety and/or efficacy of cryosurgical ablation.

Thermocouple and Urethral Warmer Placement

Depending on the preference and experience of the surgeon, thermocouples may be placed in the mid gland, at the level of the external sphincter, at each NVB, and in Denonvilliers fascia. Thermocouples placed at the level of the external sphincter and in Denonvilliers fascia are used to minimize the risk of incontinence

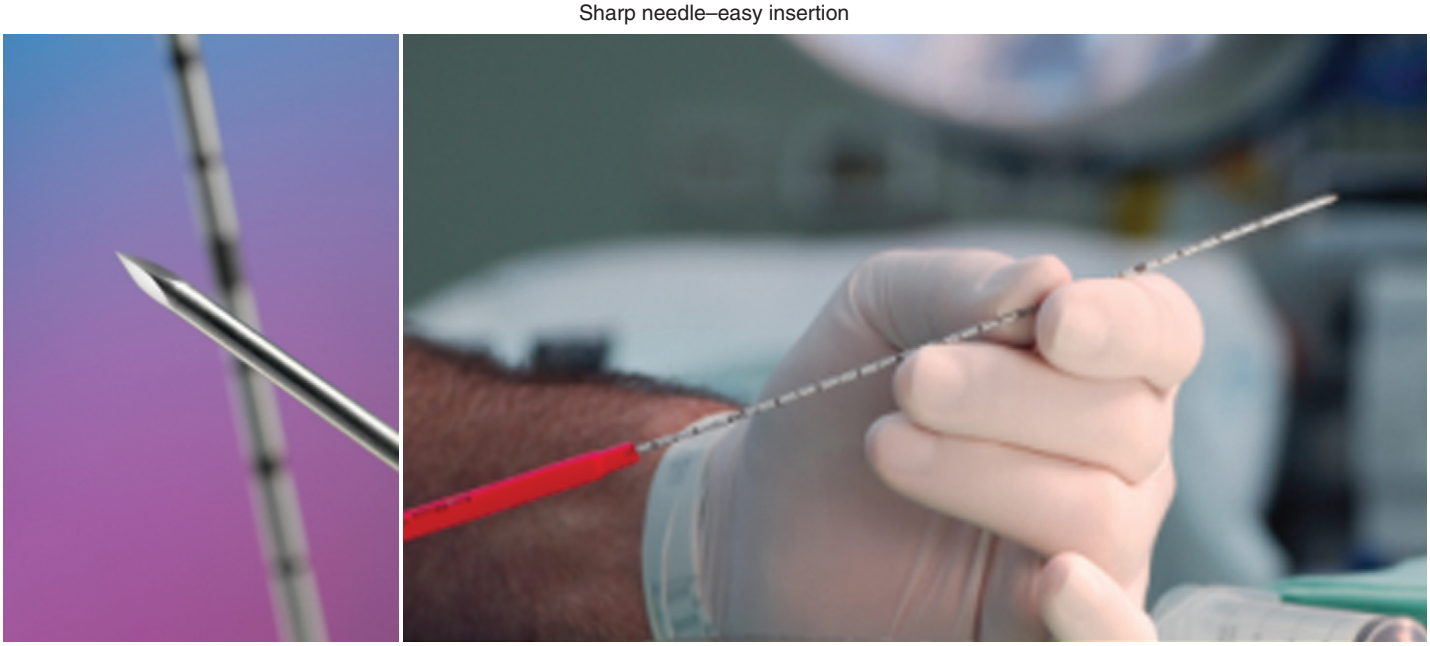


Figure 105–8. Currently available cryotherapy systems include sharp, small-diameter cryoneedles that allow direct transperineal placement using a brachytherapy-like template without the use of insertion or dilation kits.

and rectourethral fistula, respectively, whereas those in the mid gland and NVB ensure that the required temperature of –40° C is reached (Fig. 105–10). When possible, it is recommended that the temperature in the sphincter be maintained above 15° C. Some operators place a thermocouple in the distal apex to ensure adequate freezing at the apex and adequate coverage of the prostate. The use of newly introduced MultiThermal Sensor (MTS) needles, which enable four separate temperature readings from each sensor, has improved significantly the safety of cryosurgical ablation and decreased dramatically the risk of postablation fistulae (Fig. 105–11).

After all the needles have been positioned, the Foley catheter is gently removed. Any difficulty may indicate that a probe is wrongly positioned and potentially piercing the urethra. A meticulous 360-degree examination of the urethra is performed using a flexible cystoscope. If a misplaced probe is visualized in the urethra or a wall hematoma is detected, probe repositioning is indicated to avoid the detrimental outcome of direct urethral freezing or freezing the circulating urethral warmer fluid into a standstill position. The bladder is also inspected to ensure that no misplaced probes have pierced the bladder neck. Once the urethra and the bladder are found to be normal, some cryosurgeons proceed to place a soft 10- to 12-Fr suprapubic catheter under direct vision. On the other hand, some surgeons prefer to conclude the procedure with a 16-Fr Foley catheter left indwelling for a duration of 1 to 10 days. A 0.038-inch super-stiff guidewire is inserted through the working channel of the cystoscope, which is then withdrawn, and a heavily lubricated urethral warming catheter is introduced into the bladder over the guidewire and under sonographic guidance. During the procedure, the bladder is kept nearly full to prevent injury from the rigid tip of the warmer device.

Monitoring of Freezing Process

To maintain TRUS visibility, the freezing is started at the anterior probe layer and continued posteriorly. Using this technique, untreated areas may be visualized and a correcting maneuver may be used. Two freezing cycles are performed. Between the cycles, the prostate may be allowed to thaw passively (≈15 to 20 minutes) or actively (≈7 to 8 minutes) using helium. If the apex-to-base measurement of the prostate is greater than the length of the iceball that the cryoprobe produces, pull-back of the cryoprobes is performed to cover the inadequately treated portion of the gland and two additional freeze-thaw cycles are performed. To ensure adequate cancer treatment, the iceball is often allowed to extend 2 to 4 mm laterally into the periprostatic tissues, beyond the apex, and into the muscularis propria of the rectum posteriorly. In areas of extracapsular cancer extension, greater propagation of the iceball is permitted laterally and, if necessary, an additional cryoprobe may be placed in such areas. When seminal vesicle invasion is present, a cryoprobe may be placed deep into the invaded seminal vesicle. After completion of the last freeze cycle, the urethral warmer is left in place for up to 20 minutes to minimize the risk of urethral sloughing and subsequent urinary retention and irritative voiding symptoms. At this point, a full TRUS image of the prostate is regained and no iceball is seen. Cryoprobes are removed and pressure is applied to the perineum for 2 to 5 minutes. The urethral warmer is gently removed, and a Foley catheter is inserted afterward or, alternatively, the suprapubic catheter is opened if one was inserted before the procedure.

In patients undergoing salvage cryotherapy, previously placed radioactive seeds may cause some confusion because their sonographic appearance is similar to that of the tip of the cryoprobes. This can be overcome by using the sagittal view to assist in placing the cryoprobes. In this view, the length of the cryoprobes can be easily followed. Some degree of fibrosis may be encountered during placement in patients undergoing salvage cryotherapy. The gland may be adherent to the anterior rectal wall due to the previous radiation, diminishing the thickness of the Denonvilliers fascia. If the space between the anterior rectal wall and posterior prostatic capsule is less than 5 mm, it may not be possible to drive the temperature down to

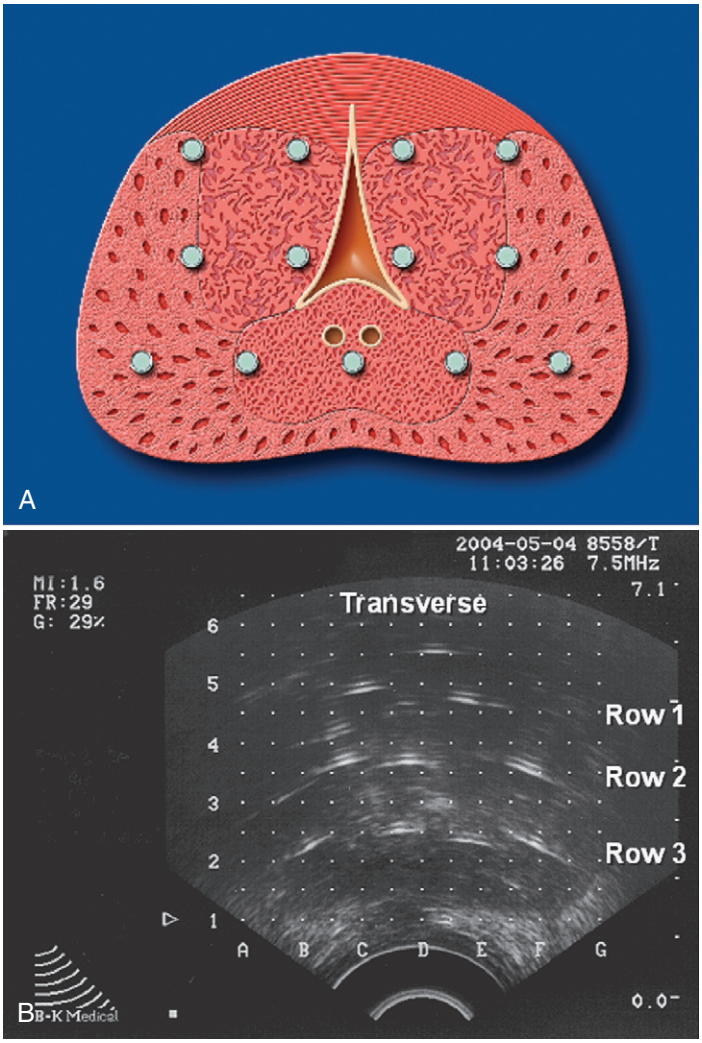


Figure 105–9. **A,** Tranverse template for placement of 17-gauge cryoprobes. **B,** Transverse ultrasound image showing placed cryoprobes in prostate.

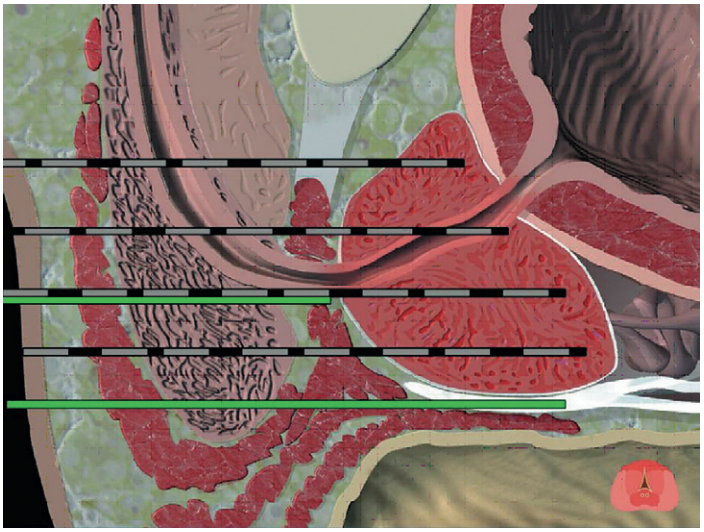


Figure 105–10. Sagittal view of placed cryoprobes *(gray)* and thermocouples *(green)* in prostate. Cryoprobes are placed in layers with the tip at the base of the prostate. Thermocouples are placed at the level of the external sphincter and in Denonvilliers fascia.

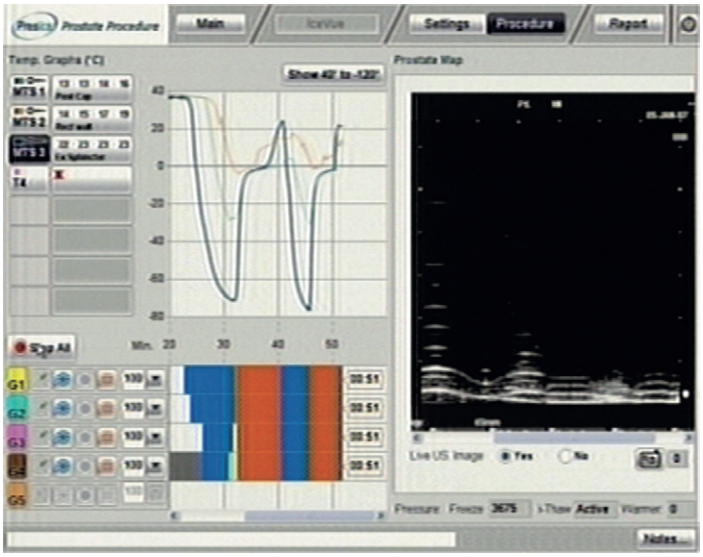


Figure 105–11. Newly introduced multipoint thermal sensors allow simultaneous intraoperative assessment of temperatures in multiple tissue planes (four separate temperature readings are provided from each needle). The availability of MTS needles has improved significantly the safety of cryosurgical ablation and decreased dramatically the risk of postablation rectal fistulae.

–40° C safely, and freezing should be terminated when the leading edge of the iceball has extended just beyond the capsule, even if the target temperature of –40° C is not reached. Injection of saline into the area of Denonvilliers fascia may help increase the distance between the prostate and anterior rectal wall provided the tissue is not too fibrotic to separate. Urologists learning to perform cryotherapy should be aware of these considerations and should maintain a heightened awareness of the potential increased risk of incontinence in previously irradiated patients.

Postoperative Care

Patients are discharged on the same day or on postoperative day 1 with antibiotics (usually a fluoroquinolone), oral analgesics, an α-adrenergic blocker (maintained for at least a month), and a Foley catheter to be removed in 2 to 10 days. If a suprapubic catheter was placed, it is kept open for 72 hours and then closed. The patient documents voiding frequency and volumes, and once normal voiding is regained the suprapubic catheter is removed.

PATIENT FOLLOW-UP

Patients are followed with clinical examinations and serial PSA measurements at 3-month intervals. After the first year, follow-up intervals can be increased to 6 months. Serum PSA levels after cryotherapy may not decrease to undetectable levels owing to the necessary preservation of a thin rim of periurethral prostatic tissue (Babaian et al, 2008). Immediately after the procedure, serum PSA levels rise to a high value due to release of intracellular PSA from cellular necrosis (Leibovici et al, 2005). The PSA nadir is usually achieved in 3 months (Wieder et al, 1995). In truth, however, the PSA nadir level that should be achieved after cryotherapy is not known with certainty, and nadir values have been achieved more than 3 months after cryotherapy. **There is no established definition of biochemical failure after cryotherapy. Investigators have often employed various static PSA cutoffs including 0.3, 0.4, 0.5, and 1 ng/mL** (Greene et al, 1998;

Koppie et al, 1999; Ghafar et al, 2001; Long et al, 2001; Bahn et al, 2002; Han et al, 2003; Chinn et al, 2004; Donnelly et al, 2005; Polascik et al, 2007). More recently, **American Society for Therapeutic Radiology and Oncology (ASTRO) definitions for biochemical failure have been leveraged by cryotherapy investigators including both the traditional ASTRO failure definition of three consecutive PSA rises after the post-treatment nadir and the more recent Phoenix (i.e., PSA nadir plus 2) definition for biochemical recurrence** (Long et al, 2001; Prepelica et al, 2005; Cohen et al, 2008). Given the uncertainty surrounding optimal definitions of biochemical failure following cryosurgical ablation, it is not surprising that establishment of a scientifically based definition for postcryotherapy PSA failure is a priority for clinical investigators working in this area (Jones et al, 2008). Finally, some surgeons perform a prostate biopsy after cryotherapy to assess local control. If biopsies are considered, however, they should not be performed until 6 months or longer after cryotherapy to allow for resolution of most of the acute inflammation.

OUTCOMES AFTER PRIMARY CRYOTHERAPY

Local Control

Prostate biopsy has been performed in patients 6 to 12 months after cryotherapy in several series. **The positive biopsy rate after cryotherapy ranges from 7.7% to 25%** (Shinohara et al, 1996; Connolly et al, 1997; Pisters et al, 1997; Wong et al, 1997). Ellis and colleagues (2007) reported that 17 of 168 (10.1%) men treated with third-generation cryosurgical technology had a positive biopsy at an average of 10 months postablation. In a series with longer-term follow-up, Cohen and colleagues (2008) reported a 10-year negative biopsy rate of 77%. The authors also observed that higher pretreatment PSA levels and clinical T stage were independently associated with an increased risk of positive postcryosurgical biopsy (Cohen et al, 2008). Among nearly 1200 cases included in the Cryo On-Line Data (COLD) Registry, 336 patients underwent post-treatment biopsy. For this group, the positive biopsy rate was 38% (49 of 129) for patients with a documented biochemical recurrence versus only 14.5% (30 of 207) with no clinical evidence for biochemical recurrence (Jones et al, 2008). In fact, data from the COLD Registry highlight the important caveat that rates of local control may vary substantially depending on whether biopsies are performed as part of standard follow-up (i.e., regardless of postcryotherapy PSA levels) or performed only "for cause" in those patients with a rising PSA following cryosurgical ablation. In most series in which surgeons routinely perform postcryotherapy biopsies, positive biopsies are generally reported in less than 10% of patients treated with a double-freeze thaw cycle procedure. As illustrated in the COLD Registry data, however, rates of positive biopsies tend to be higher in series where post-treatment biopsies are performed only "for cause" (Jones et al, 2008). Moreover, the likelihood of a positive biopsy is related to the post-treatment PSA kinetics, with residual cancer noted rarely among patients with a PSA nadir less than 0.5 ng/mL (Greene et al, 1998).

Finally, certain areas of the prostate and/or seminal vesicles have been reported to be more likely sites of treatment failure (Bahn et al, 1995; Shinohara et al, 1997). For instance, Shinohara and colleagues (1997) reported that recurrence was more common in cancers located at the apex (9.5%) and the seminal vesicles (43.8%), in contrast to those located in the mid gland (4.1%) and base (0%).

Biochemical Failure

Biochemical failure rates after primary cryosurgical ablation from several contemporary series are summarized in Table 105–4. Recently, investigators from the multicenter COLD Registry reported pooled biochemical control outcomes for 1198 patients treated with primary cryosurgical ablation at an international collection of academic and community medical centers (Jones et al, 2008). For this cohort, the 5-year actuarial biochemical (i.e., PSA recurrence) disease-free survival was 77.1% on the basis of the traditional ASTRO definition and 72.9% on the basis of the newer Phoenix definition. In risk-stratified analyses (using the D'Amico risk categories), 5-year biochemical disease-free survival rates based on the ASTRO criteria were 84.7% for patients in the low-risk group, 73.4% for moderate-risk patients, and 75.3% for patients in the high-risk group. Using the Phoenix (nadir plus 2) definition, corresponding 5-year biochemical disease-free survival rates were 91.1%, 78.5%, and 62.2% for low-, intermediate-, and high-risk groups, respectively (Jones et al, 2008).

Cohen and colleagues (2008) also recently reported long-term biochemical control outcomes among more than 200 patients treated with cryosurgical ablation of the prostate from 1991 through 1996. On the basis of the Phoenix definition, the authors reported 10-year PSA-recurrence-free survival rates of 80.6%, 74.2%, and 45.5% for low-, intermediate-, and high-risk groups, respectively. In multivariable analyses, the authors noted several variables significantly associated with postcryosurgery biochemical recurrence including patient age, pretreatment PSA, and the postcryosurgery PSA nadir (Cohen et al, 2008). Likewise, Shinohara and colleagues (1997) correlated the rate of biochemical and biopsy failure with the PSA nadir after cryotherapy in 132 patients. Biochemical failure was lowest in patients who achieved PSA nadirs less than 0.1 ng/mL (21%) but was common in those with higher nadir values. Biopsy failure was lowest in those with a PSA nadir less than 0.1 ng/mL (1.5%) and those with a nadir less than 0.4 ng/mL (10%). In contrast, 55% of patients with a PSA nadir greater than 0.5 ng/mL had a positive result at follow-up prostate biopsy. Biochemical and biopsy failure tended to occur within the first 12 months after treatment (96% and 88% of biochemical and biopsy failures, respectively).

In a separate multi-institutional collaborative based on 175 patients treated with third-generation technology at several institutions in the United States, Han and colleagues (2003) reported that 80 (73%) of 110 patients remained with a PSA of less than or equal to 0.4 ng/mL, whereas 42 (76%) of 65 low-risk patients (Gleason ≥ 6, PSA ≤ 10 ng/mL, ≤cT2) remained free from biochemical progression at 1 year (Han et al, 2003). For men with high-risk features (defined as a pretreatment PSA ≥ 10 ng/mL and/or a Gleason score ≥8), Prepelica and colleagues (2005) demonstrated 6-year biochemical disease-free rates of 81.7%, 50%, and 35% according to the ASTRO criteria, PSA less than 4 ng/mL, and PSA less than 1 ng/mL, respectively. **Taken together, results of recent series suggest that, depending on the definition of PSA failure, 5-year biochemical disease-free survival rates following primary cryosurgical ablation range from 60% to 90%, with more favorable cancer control outcomes reported for patients with low- and intermediate-risk cancers** (Koppie et al, 1999; De La Taille et al, 2000; Long et al, 2001; Bahn et al, 2002; Donnelly et al, 2002; Chinn et al, 2004; Prepelica et al, 2005; Ellis et al, 2007;

Table 105–4.

Recent Primary Prostate Cryotherapy Series: Biochemical Disease-Free Survival

SERIES, YEAR	NO. PATIENTS	CRYOGEN	PSA FOLLOW-UP	PSA CUTOFF (ng/mL)	RECURRENCE-FREE RATE (%)
Jones et al, 2008	1198	Nitrogen/argon	5 yr	ASTRO	85 (L)
					73 (I)
					75 (H)
				Phoenix	91 (L)
					79 (I)
					62 (H)
Cohen et al, 2008	204	Nitrogen/argon	10 yr	Phoenix	81 (L)
					74 (I)
					46 (H)
Ellis et al, 2007	416	Argon	4 yr	<0.4	84 (L)
					82 (I)
					69 (H)
Prepelica et al, 2005	65	Argon	6 yr	ASTRO	82 (H)
				<4.0	50 (H)
				<1.0	35 (H)
Chinn et al, 2004	48	Nitrogen	8 yr	≤0.5	82 (L)
					72 (I)
					50 (H)
Han et al, 2003	122*	Argon	12 mo	≤0.4	76 (L)
					73 (A)
Donnelly et al, 2002	76	Nitrogen	5 yr	<1.0	75 (L)
				<0.3	89 (I)
					76 (H)
					60 (L)
					77 (I)
					48 (H)
Bahn et al, 2002	590	Nitrogen/argon	7 yr	ASTRO	92 (L)
				<1.0	89 (I)
				<0.3	89 (H)
					87 (L)
					79 (I)
					71 (H)
					61 (L)
					68 (I)
					61 (H)
Long et al, 2001†	975	Nitrogen/argon	5 yr	<1.0	76 (L)
				<0.5	71 (I)
					61 (H)
					60 (L)
					61 (I)
					36 (H)
De La Taille et al, 2000	35	Argon	9 mo	<0.1	86 (L)
					70 (A)
Koppie et al, 1999	176	Nitrogen	12 mo	<0.5	82 (L)
			3 yr	<0.5	58 (H)
					69 (L)
					45 (H)

*Recently updated to 175 patients.
†Review of five cryotherapy series: L, low-risk patients (Gleason ≤ 6, PSA ≤ 10, ≤cT2); I, intermediate-risk patients; H, high-risk patients; A, all patients.
ASTRO, American Society for Therapeutic Radiology and Oncology.

Polascik et al, 2007; Cohen et al, 2008; Jones et al, 2008). To date, there are no long-term data available regarding metastasis-free or overall survival following cryosurgical ablation of the prostate (Babaian et al, 2008).

Comparison with Other Minimally Invasive Options

Primary cryotherapy has several potential advantages over other local therapies. **Cryotherapy can destroy a biologically heterogeneous population of cancer cells including cell populations that are resistant to radiation therapy and hormonal therapy.** Prostate cryotherapy can also be used to treat more extensive and aggressive tumors than brachytherapy. In particular, the **freezing process can extend beyond the capsule of the prostate, potentially eradicating extracapsular disease in patients with low-volume T3 cancers. Another advantage is that cryotherapy can be repeated with minimal morbidity. To date, however, there are actually little data that directly compare cancer control**

outcomes following cryosurgery versus other therapies for localized prostate cancer.

In 2001 Long and colleagues reported on a 5-year retrospective, multi-institutional pooled analysis of 975 patients who had cryotherapy and compared the results with those in recently published series of brachytherapy and EBRT. The 75 patients who had mainly second-generation cryotherapy had a 5-year biochemical freedom from recurrence of 76% when the PSA threshold was 1 ng/mL; these results were similar to those reported by the combined eight series that used EBRT or brachytherapy. The review also concluded that the 93% rate of impotence for cryotherapy was higher than the 37% to 70% (EBRT) and 10% to 40% (brachytherapy) rates reported by other investigators. Fistula rates were reported as 1% to 9%, 0% to 7%, and 0.5%, respectively, with incontinence rates of 0% to 13%, 0% to 5%, and 7.5%, respectively (Long et al, 2001).

Katz and Rewcastle (2003) also performed a retrospective comparative analysis on the basis of all studies of primary prostate cancer therapies (radical prostatectomy, cryotherapy, brachytherapy, 3DCRT, and EBRT) from 1992 to 2002. They reported rates of 5-year biochemical disease-free survival stratified by risk group. Although biochemical disease-free survival definitions varied across the studies, this analysis was intended only to evaluate trends for the different therapies. For low-risk disease, the 5-year biochemical disease-free survival rates for patients treated with radical prostatectomy, cryotherapy, brachytherapy, 3DCRT, and EBRT were 78% to 98%, 60% to 92%, 78% to 89%, 76% to 87%, and 81% to 86%, respectively (Katz and Rewcastle, 2003). Notably, the durable long-term results (>15-year follow-up) for radical prostatectomy reinforce its role as the gold-standard therapy for localized prostate cancer.

More uncertainty arises, however, in determining the optimal approach for patients with intermediate- and high-risk disease. In the retrospective observational comparison performed by Katz and Rewcastle, the 5-year biochemical disease-free survival rates for patients treated with radical prostatectomy, cryotherapy, brachytherapy, 3DCRT, and EBRT were 60% to 76%, 61% to 89%, 66% to 82%, 51% to 85%, and 26% to 60% for those with intermediate-risk disease and 30% to 61%, 36% to 89%, 0% to 65%, 21% to 43%, and 19% to 25% for those with high-risk disease, respectively (Katz and Rewcastle, 2003). Moreover, the positive biopsy rate after cryotherapy appears to be similar to, if not less than, those observed in series of patients with brachytherapy or EBRT (Babaian et al, 1995; Ljung et al, 1995; Stock et al, 1996; Laverdiere et al, 1997; Ragde et al, 1997, 1998; Crook and Bunting, 1998; Dinges et al, 1998). Taken together, these observational data suggest that cryotherapy may be equivalent to radiotherapy and surgery in terms of efficacy among patients with intermediate- and high-risk prostate cancer.

In contrast to these observational data, however, Chin and colleagues (2008) recently reported results from a small, randomized, controlled trial comparing cancer control outcomes following cryosurgical ablation versus external beam radiotherapy for patients with locally advanced, nonmetastatic prostate cancer. Specifically, patients with clinical stage T2c, T3a, or T3b tumors were randomized to receive 6 months of hormonal therapy along with either cryosurgical ablation or external beam radiotherapy. In terms of cancer control, 64% of patients in the cryosurgery group developed a biochemical recurrence (ASTRO definition) versus only 45% of patients in the external beam radiotherapy arm. Four-year actuarial biochemical disease-free survival also favored EBRT (47%) over cryosurgery (13%) in this group of patients. The investigators concluded that, despite flaws in the trial design and failure to accrue targeted numbers of patients, external beam radiotherapy provides better biochemical control than cryosurgical ablation for patients with locally advanced prostate cancer (Chin et al, 2008).

OUTCOMES AFTER SALVAGE CRYOTHERAPY

Prognostic Factors

Several clinical variables appear to influence the efficacy of salvage cryosurgical ablation. Pisters and colleagues (1999b) were among the first to identify clinical pretreatment factors associated with early treatment failure after salvage cryotherapy. From an analysis of 145 men who underwent salvage cryotherapy, those for whom initial radiation therapy was unsuccessful with a **PSA greater than 10 ng/mL and Gleason score of the recurrent cancer greater than or equal to 9 were unlikely to be successfully salvaged.** Izawa and colleagues (2002) analyzed 131 patients who had received definitive EBRT and subsequent salvage cryotherapy for locally recurrent prostate cancer. This group reported that androgen-independent local recurrences, Gleason score, and preradiation clinical stage were important determinants of disease-specific survival and disease-free survival. **In more contemporary studies, patients with a postradiation PSA greater than 10 ng/mL and/or a PSA doubling time of 16 months or less have been shown to be more likely to develop recurrent cancer following salvage cryosurgical ablation** (Spiess et al, 2006; Ng et al, 2007; Babaian et al, 2008).

Local Control

Estimates of the proportion of men with positive biopsies after salvage cryosurgical ablation are variable but generally range from 15% to 35% in contemporary series of patients treated for radiorecurrent disease (Ng et al, 2007; Pisters et al, 2008). For instance, among 279 salvage cases included in the COLD Registry, 15 of 46 (32.2%) patients who underwent postcryotherapy prostate biopsy were found to have residual cancer. Among those with documented biochemical recurrence, 8 of 15 (53.3%) had a positive biopsy. Ng and colleagues reported a lower positive biopsy rate (16.6%) among their series of 187 patients, most of whom were treated with third-generation cryosurgical technology. In terms of determinants of a positive biopsy after salvage cryosurgery, Izawa and colleagues (2001) reported that patients with initial clinical stage T1-2N0M0 disease and PSA less than 10 ng/mL have a higher rate of negative biopsies after salvage cryotherapy.

Biochemical Failure

The results from several recent salvage cryotherapy series, based on third-generation argon technology, are summarized in Table 105–5 (Han and Belldegrun, 2004; Donnelly et al, 2005; Ismail et al, 2007; Ng et al, 2007; Pisters et al, 2008). In the multicenter study using third-generation 17-gauge cryoprobes, 13 of 18 (72%) patients who had undergone salvage cryotherapy and were followed for at least 12 months remained with a PSA less than or equal to 0.4 ng/mL. Similarly, Katz (2004) reported on a 6-year experience with 67 men who underwent salvage cryotherapy. Multiple thermocouples were used, and all patients received 3 months of hormone deprivation before salvage cryotherapy. On the basis of a PSA cutoff value of more than 1 ng/mL, 72% of patients remained free of biochemical recurrence at 12 months.

Table 105–5.

Recent Salvage Cryotherapy Series: Biochemical Disease-Free Survival and Complications

Series, Year	Donnelly et al, 2005	Han et al, 2003	Ng et al, 2007	Ismail et al, 2007	Pisters et al, 2008
No. Patients	46	29	187	100	279
Technique	Argon	Argon	Argon	Argon	Argon/Nitrogen
PSA Cutoff (ng/mL)	0.3	0.4	Phoenix	ASTRO	ASTRO
Recurrence-Free Rate (%)	51	72	56	59	59
Mean Follow-up (mo)	*20 (2-50)	12	39	34	22
Complications (%)					
Fistula	2.2	0	2	1	1
Incontinence	6.5	9	40†	13	5
Sloughing		0			
Retention/LUTS	4.3	3	21/10	18	
Impotence	46			86	69

*Median follow-up (range).
†37% with mild to moderate incontinence, 3% with severe incontinence.
LUTS, lower urinary tract symptoms.

More recently, Ismail and colleagues (2007) reported cancer control data for a cohort 100 patients treated with salvage cryosurgical ablation of the prostate between May 2000 and November 2005. With a median follow-up of 33.5 months, the authors observed biochemical recurrence-free survival (defined as PSA < 0.5 ng/mL) for 73%, 45%, and 11% of men with low-, intermediate- and high-risk cancers, respectively. The authors further noted significantly more favorable biochemical recurrence-free survival among those patients with a postablation PSA nadir less than or equal to 0.1 ng/mL (Ismail et al, 2007). Ng and colleagues reported intermediate biochemical failure outcomes among 187 treated with salvage cryosurgical ablation between March 1995 and September 2004. For this cohort, the authors noted that the preablation PSA level was a significant predictor of postsalvage treatment failure. Specifically, for patients with a presalvage PSA level less than or equal to 4 ng/ml, 5-year biochemical recurrence-free survival was 56% and 8-year biochemical recurrence-free survival was 37%. Conversely, for patients with a presalvage PSA greater than or equal to 10 ng/mL, biochemical recurrence-free survival rates were only 14% and 7% at 5 and 8 years, respectively (Ng et al, 2007). Finally, the COLD Registry collaborators reported biochemical cancer control outcomes among 279 patients treated with salvage cryosurgical ablation. The authors specifically observed 5-year biochemical recurrence-free survival rates of 59% and 55%, on the basis of ASTRO and Phoenix criteria, respectively (Pisters et al, 2008). Taken together, these data suggest that salvage cryosurgical ablation of the prostate is associated with biochemical control rates of 50% to 60% at 4 or more years after salvage therapy, with more favorable outcomes observed among patients with lower presalvage PSA levels and postsalvage PSA nadirs (Ismail et al, 2007; Ng et al, 2007; Pisters et al, 2008).

Comparison with Other Salvage Treatments

In addition to cryosurgical ablation, patients with documented local recurrences following initial radiation therapy may also be treated with salvage radical prostatectomy or salvage brachytherapy. Salvage radical prostatectomy has been the most commonly performed curative treatment for clinically localized prostate cancer after radiation therapy, although its use is distinctly uncommon among older men with radio-recurrent prostate cancer (Krupski et al, 2006). This procedure is capable of eradicating the local lesion and providing long-term disease-specific survival (Ward et al, 2005; Allen et al, 2007; Nguyen et al, 2007). Despite the potential for successful extirpation of the cancer, the surgical procedure is complicated by the tissue effects of radiation and is associated with significant side effects (Bianco et al, 2005; Ward et al, 2005; Allen et al, 2007; Nguyen et al, 2007). Radiation results in vascular occlusion with resulting tissue hypoxia, whereas alterations in basement membrane proteins lead to increased fibrosis. Anatomic planes between pelvic organs are often obliterated, with a poorly vascularized bladder and urethra available for surgical reconstruction. As such, there is an increased likelihood of postprostatectomy incontinence and impotence, as well as the possibility of rectal injury, which may necessitate fecal diversion (colostomy) (Bianco et al, 2005; Ward et al, 2005; Allen et al, 2007; Nguyen et al, 2007). Salvage brachytherapy has emerged more recently as a treatment option for men with local-only recurrence following primary external beam radiotherapy, although the total number of cases reported in the literature remains quite small (Allen et al, 2007; Nguyen et al, 2007).

In terms of comparative efficacy, cancer control and morbidity outcomes following salvage cryosurgery, salvage prostatectomy, and salvage brachytherapy have recently been meticulously reviewed by both Nguyen and colleagues (2007) and Allen and colleagues (2007). The authors concluded that because no prospective comparative trials are available, it is currently not possible to determine whether one treatment is superior with respect to biochemical recurrence-free survival or other cancer control outcomes. Generally speaking, 5-year biochemical recurrence-free survival rates following salvage radical prostatectomy (RP) range from 50% to 60% across the various case series reported in the literature (Allen et al, 2007; Nguyen et al, 2007), with perhaps slightly less favorable PSA control rates following salvage cryotherapy and brachytherapy. In a recent study that supports this conclusion, Pisters and colleagues (2009) reported their findings from a retrospective comparison of cancer control outcomes following salvage cryotherapy versus salvage RP among a cohort of patients with presalvage PSA less than 10 ng/mL, postradiation therapy biopsy Gleason score less than 8, and no prior exposure to hormonal therapy. Compared with salvage cryosurgery, salvage RP yielded superior outcomes on the basis of two separate definitions of biochemical failure (PSA > 0.4 ng/mL: salvage cryo 21% vs. salvage RP 61% at 5 years; 2 rises above PSA nadir: salvage cryo 42% vs. salvage RP 66%), as well as superior overall survival at 5 years (salvage cryo 85% vs. salvage RP 95%). Disease-specific

survival at 5 years did not differ by treatment group (salvage cryo 96% vs. salvage RP 98%). Even after adjustment for postradiation therapy biopsy Gleason score and presalvage treatment serum PSA level, salvage RP remained superior to salvage cryosurgery for the biochemical recurrence and overall survival end points. On the basis of these data, the authors concluded that young, healthy patients with recurrent prostate cancer after radiation therapy should consider salvage RP because it may offer superior progression-free survival (Pisters et al, 2009).

Irrespective of the salvage therapy, Nguyen and colleagues reported that the following clinical variables predict a greater likelihood of PSA recurrence-free survival: (1) low-risk tumor (i.e., clinical stage T1c or T2a, PSA < 10 ng/mL, and GS ≤ 6) at the time of original diagnosis; (2) PSA velocity before initial radiation therapy <2 ng/mL per year; (3) time to postradiation PSA failure >3 years; (4) postradiation PSA doubling time >12 months; and (5) negative bone scan and pelvic imaging (Nguyen et al, 2007).

In terms of morbidity, complications appear to be more common following salvage versus primary therapy for all three treatment modalities, with urinary incontinence, erectile dysfunction (ED), urethral/bladder neck stricture, and rectal injury/fistulae representing increasingly infrequent, but still significant, adverse outcomes (Allen et al, 2007; Nguyen et al, 2007; Babaian et al, 2008).

MANAGEMENT OF LOCAL RECURRENCE AFTER CRYOTHERAPY

Repeat Cryotherapy

Treatment options for patients in whom primary cryotherapy has failed are not well documented in the literature but commonly practiced by all users. Repeat cryoablation of the prostate is safe and can be effective for the properly selected candidates with truly localized disease. Bahn and colleagues (2002) reported repeat cryotherapy on 32 patients who had a positive biopsy result after primary cryotherapy. For these patients, biochemical recurrence-free survivals at 63 months after repeat freezing were 68%, 72%, and 91% using a definition of failure of 0.5 ng/mL, 1 ng/mL, and the ASTRO criteria, respectively. A more precise understanding of the efficacy of repeat cryotherapy will require further study in a larger number of patients.

Salvage Radiation Therapy

Although limited data exist, salvage radiation appears to be safe and potentially effective for patients with local recurrence after primary cryotherapy. McDonough and colleagues (2001) treated six patients with biopsy-proven local recurrence after primary cryotherapy with 66 Gy of EBRT. Sixty-six percent of patients were rendered disease free, and two patients developed biochemical failure as defined by ASTRO criteria. No patient developed distant metastasis at a median follow-up of 34 months. Complications included proctitis in two patients. Burton and colleagues (2000) reported outcomes of 49 patients treated with salvage 3DCRT for prostate cancer recurrence after primary cryotherapy. The initial three patients were treated to 50 Gy without severe toxicity. Six patients treated with dose escalation to 55 to 60 Gy did not encounter grade 3 or greater toxicity. Twenty patients were then initially treated to a dose range between 60 and 65 Gy, and another 20 patients then received a dose between 65 and 68.4 Gy. The investigators have since increased their typical total dose, with three patients receiving a dose of 70.2 Gy who were not included in this study because of limited follow-up, but none has experienced a significant increase in acute toxicity. As the total dose was increased, special effort was made to limit the dose to the rectum (as outlined earlier) to decrease the potential morbidity. The PSA nadir was less than 1 ng/mL in 42 patients, greater than 1 ng/mL in 5 patients, and stable in 2 patients. With a median follow-up time of 32 months (range: 12 to 85 months), the overall biochemical control rate was 61%. Only two patients developed subacute morbidity (proctitis and a urethral stricture), and all complications resolved with conservative measures. Additional prospective randomized studies are necessary to better assess the role of salvage radiation therapy in the treatment of these patients.

Salvage Prostatectomy

Grampsas and colleagues (1995) performed a salvage radical prostatectomy in six patients 3 to 10 months after unsuccessful prostate cryotherapy. They reported the presence of marked scarring and adhesions after cryotherapy but were able to avoid injury to the rectum, ureters, or other surrounding structures. The most significant postoperative complications were temporary incontinence and impotence. Future studies are necessary to define cancer control and complications of these various treatment modalities for PSA failure after cryotherapy.

ADJUNCTIVE THERAPY

One potential strategy for improving the efficacy of cryosurgical ablation is to identify adjuvant therapies that can optimize the freezing process in the border zone of the cryogenic region where tissue temperatures often exceed –20° C and therefore may not reach lethal values less than –40° C (Baust et al, 2007). Potential adjunctive therapies described in the literature include irradiation, cytotoxic chemotherapy, and even apoptotic and immunologic promoters (Baust et al, 2007). Each of these has been shown in various preclinical settings to potentially increase the efficacy of cryosurgical ablation (Baust et al, 2007).

For instance, in-vitro experiments have shown that cooled cells have a greater sensitivity to irradiation (Znati et al, 1998). Nevertheless, this has not yet been investigated in a clinical setting and it is unclear what the optimal timing would be for delivering radiation therapy in an adjuvant setting. Many cryotherapy treatments for various cancers already use adjuvant chemotherapy; however, the optimum time and dose for delivery of chemotherapeutic drugs remain uncertain. Drugs that are given during the period of tissue thawing remain concentrated in the frozen tissue for a longer time. Therefore the appropriate cytotoxic drug should probably be delivered systemically during the period of thawing and before the microcirculation fails, generally within approximately 1 hour of the last freeze cycle (Gonder et al, 1964; Gage and Baust, 1998; Hoffman and Bischof, 2002; Baust and Gage, 2005; Baust et al, 2007; Gage and Baust, 2007). An alternative technique may be instillation of the drug locally into the previously frozen tissue, possibly attached to an agent for slow release (Baust et al, 2004; Le Pivert et al, 2004). As adjunctive therapeutic agents, the role of immunologic enhancers should also be considered in future investigations (Baust et al, 2007). Many investigations have been directed at the nature of the immunologic response (Chao et al, 2004). **Despite their promise, however, no therapy has proven beneficial in an adjuvant setting with cryotherapy and none of these strategies is currently ready for clinical application.**

Table 105–6.
Complication Rates of Cryosurgical Ablation (Selected Series)

SERIES, YEAR	NO. PATIENTS	ED (%)	COMPLICATION RATES (%)		
			Fistula	Incontinence	Sloughing/TURP
Han et al, 2003	122	87	0	4.3	5.8
Ellis, 2007	416	49	0	4.0	
Polascik et al, 2007	50	50*	0	3.7	0
Jones et al, 2008	1198	92	0.4	4.8	2.1

*Among men potent preoperatively.
ED, erectile dysfunction; TURP, transurethral resection of the prostate.

COMPLICATIONS

Erectile Dysfunction

ED after cryotherapy of the prostate is common (Table 105–6). Although some series have reported rates ranging from 40% to 47% (Bahn et al, 1995), **more contemporary series report rates between 50% and 90%** (Long et al, 2001; Bahn et al, 2002; Han et al, 2003; Ellis et al, 2007; Polascik et al, 2007; Jones et al, 2008). The high incidence of ED following cryosurgery is likely due to the use of multiple freeze-thaw cycles and extension of the iceball beyond the prostate, into the areas adjacent to the neurovascular bundles. Although some authors have reported that up to 50% of patients regain erectile function 3 to 5 years after cryosurgical ablation (Donnelly et al, 2002; Ellis et al, 2007), the authors of this chapter do not routinely perform cryotherapy in patients interested in maintaining their potency. They currently believe that complete ablation of the NVB is necessary to ensure complete eradication of tissue at the periphery of the prostate gland. Early studies of subtotal and focal cryotherapy report potency rates in the range of 71% to 85%, although subtotal or focal cryoablation should be regarding as investigational until optimal patient selection is determined and long-term oncologic outcomes are available (Lambert et al, 2007; Onik et al, 2007).

Urinary Incontinence

The incidence of incontinence varies among series, probably owing to different definitions of incontinence, and variable use of an effective urethral warming catheter. Generally speaking, long-term urinary incontinence develops in approximately 1% to 10% of patients undergoing contemporary (i.e., third or fourth generation) cryosurgical ablation, with the higher end of this range seen mainly in series of patients undergoing salvage cryosurgery (Mouraviev and Polascik, 2006; Ellis et al, 2007; Ismail et al, 2007; Nguyen et al, 2007; Babaian et al, 2008; Jones et al, 2008; Pisters et al, 2008). The potential causes of postcryotherapy urinary incontinence include sphincter muscle destruction/scarring leading to intrinsic sphincter deficiency, disruption of the pudendal nerve, urethral sloughing, and possibly even detrusor factors such as detrusor instability or overflow incontinence. Prior TURP is an important risk factor for development of de-novo urinary incontinence among patients undergoing cryotherapy (Shinohara et al, 1996). As described previously, the major risk of salvage cryotherapy remains incontinence, although this risk is lower than with salvage radical prostatectomy (Nguyen et al, 2007). Historically, postsalvage cryotherapy urinary incontinence rates ranged from 0% to 83% (Miller et al, 1996; Cespedes et al, 1997; Pisters et al, 1997; Long et al, 2001; Han et al, 2003). More recently, however, the use of urethral warming catheters and an external sphincter thermocouple has decreased urinary incontinence rates to less than 10% to 15% in contemporary salvage cryosurgery series (Ghafar et al, 2001; Han and Belldegrun, 2004; Ismail et al, 2007; Ng et al, 2007; Pisters et al, 2008).

Complications Specific to Cryotherapy

Urethral Sloughing and/or Urethral Stricture

In earlier cryosurgery series, urethral tissue **sloughing occurred in 3.8% to 23% of cases** (Coogan and McKiel, 1995; Wieder et al, 1995; Cohen et al, 1996; Shinohara et al, 1996; Long et al, 1998; Han et al, 2003). With the current refinement of the freezing technique, however, symptomatic sloughing is a minor and infrequent event occurring in less than 5% to 15% of patients (Babaian et al, 2008; Jones et al, 2008). When present, treatment of urethral sloughing consists of antibiotics and adequate urinary drainage. Clean intermittent catheterization may lead to spontaneous tissue dislodgment and should be encouraged as an initial therapeutic maneuver. However, transurethral resection or removal of the necrotic tissue may be required if the condition persists. Urethral stricture is rare following cryotherapy if an effective urethral warming device is used. If extensive tissue sloughing occurs, however, strictures at the bladder neck or the middle of the prostatic urethra may develop and are best treated with either balloon dilation or transurethral incision. In rare cases, calcification of the stricture may also occur, necessitating transurethral resection. The authors cannot overemphasize that the use of an effective urethral warming catheter is essential to minimize the risk of tissue sloughing.

Pelvic and/or Rectal Pain

Pelvic, rectal, and/or perineal pain after the procedure is an event that occurs in anywhere from 0% to 50% of cases (Coogan and McKiel, 1995; Cohen et al, 1996; Shinohara et al, 1996; Long et al, 1998; Han et al, 2003; Ismail et al, 2007; Babaian et al, 2008; Pisters et al, 2008). This complaint has been reported to be more common in older series and especially in previously irradiated patients (Pisters et al, 1997; De La Taille et al, 2000). One explanatory factor for this symptom complex is that periosteum and bone may be frozen by anterior probes placed close to the symphysis pubis, which may lead to osteitis pubis. Seigne and colleagues (1996) reported that 4 (2.7%) of 147 patients undergoing postradiation salvage cryotherapy developed symptomatic osteitis pubis. Generally, such patients are best managed with anti-inflammatory agents, once a urinoma or abscess has been excluded by imaging. Han and colleagues (2003) reported that 3% of patients treated with cryotherapy developed transient

penile numbness, most likely **caused by damage to the dorsal nerve of the penis due to close proximity of the cryoprobe.** This complication generally resolves spontaneously.

Rectourethral Fistula

Rectourethral fistula formation has been reported to occur in 0% to 3% of patients treated with contemporary cryosurgical ablation of the prostate (Cox and Crawford, 1995; Izawa et al, 2000; Ghafar et al, 2001; Long et al, 2001; Han et al, 2003; Babaian et al, 2008; Jones et al, 2008; Pisters et al, 2008). This complication is distinctly more common among patients treated with salvage versus primary cryosurgical ablation (Mouriavev and Polascik, 2006; Babaian et al, 2008; Jones et al, 2008; Pisters et al, 2008). Importantly, however, given the high accuracy of modern-day TRUS combined with temperature monitoring at the anterior rectal wall, the incidence of this dreaded complication is near 0% in contemporary series (Mouriavev and Polascik, 2006; Babaian et al, 2008; Jones et al, 2008; Pisters et al, 2008). **Fistulae may present either early after the procedure or up to several months postoperatively. Watery diarrhea, pneumaturia, or fecaluria should alert the clinician to the possibility of fistula formation.** A voiding urethrogram or CT scan will confirm the diagnosis and location of the fistula. Conservative treatment with Foley catheter drainage is sometimes successful and should be tried initially in patients who underwent primary cryotherapy. Conservative measures are unlikely to be successful in patients treated with postradiation salvage cryotherapy. Early fecal and urinary diversion is an important component of fistula management in these patients. If the fistula tract matures and epithelializes, fulguration may facilitate spontaneous closure. Formal fistula repair should be delayed until the inflammatory process has resolved completely, usually in 4 to 6 months. **A transperineal, posterior, or anterior approach for closure is recommended** (Nyam and Pemberton, 1999; Izawa et al, 2000).

Other Complications

Penile and scrotal swelling, generally self-limited, may occur in the first several weeks after cryosurgical ablation (Babaian et al, 2008). In experienced hands, where the needles are accurately placed with minimal tissue damage, this complication is less common and occurs in less than 5% of patients. Hydronephrosis is a relatively uncommon complication that may manifest from extensive freezing of the bladder neck area or placement of a cryoprobe probe deep into the seminal vesicle leading to freezing of the ureteral orifices or distal ureters (Bales et al, 1995). Small bowel obstruction may occur if the iceball is allowed to extend into the cul-de-sac of the peritoneal cavity (Koppie et al, 1999). Distention of the bladder with normal saline during the procedure and placing patients in a Trendelenburg position if the cul-de-sac is anatomically low generally prevents this complication by moving the peritoneal contents away from the freezing process.

HEALTH-RELATED QUALITY OF LIFE

The importance of assessing health-related quality of life (HRQOL) in evaluating treatment outcomes for patients with prostate cancer is now well established. Moreover, such data are increasingly used by both patients and physicians during the treatment decision-making process. To date, there is a limited but growing literature describing generic and disease-specific HRQOL outcomes after primary or salvage cryosurgical ablation. In one of the first studies, Robinson and colleagues (1999) assessed 69 patients undergoing cryotherapy for localized prostate cancer. Patients were asked to complete the Functional Assessment of Cancer Treatment-Prostate (FACT-P) and the Sexuality Follow-up Questionnaire (SFQ) before treatment and again at 6 weeks and 3, 6, and 12 months afterward. For this cohort, FACT-P scores demonstrated a significant decrease from baseline at 6 weeks postoperatively. Subsequently, FACT-P scores demonstrated a progressive increase during the first postoperative year such that the 12-month FACT-P scores did not differ significantly from those reported at baseline. Conversely, the 12-month SFQ scores remained significantly below baseline, suggesting persistent decrement in sexual HRQOL. Emblematic of this concern is that only 1 of the 46 sexually active participants who were potent before treatment had recovered the ability to have erections sufficient for intercourse at 12 months (Robinson et al, 1999). In a follow-up publication, the authors reported 3-year HRQOL outcomes for the same patient cohort. In general, disease-specific HRQOL remained stable over the subsequent 2 years. Notably, at 3 years post-treatment, 13% of patients had regained erectile function, and an additional 34% of patients were sexually active with the help of aids. All other areas of functioning remained high, and no delayed-onset morbidity was associated with cryotherapy (Robinson et al, 2002).

Perrotte and colleagues (1999) evaluated HRQOL after salvage cryotherapy using a modification of the validated UCLA Prostate Cancer Index (PCI). In this study, treatment without an effective urethral warming catheter was highly associated with urinary incontinence, perineal pain, tissue sloughing, and AUA symptom score greater than 20. ED was higher in the double freeze-thaw cycle group (Perrotte et al, 1999). Importantly, however, this study was performed on patients who had undergone cryotherapy with older-generation technology. Anastasiadis and colleagues (2003) compared HRQOL among 81 patients who underwent primary or salvage cryotherapy. Primary cryotherapy patients fared significantly better regarding physical and social functioning. **The most prominent disease-specific HRQOL concern for both patient groups was sexual dysfunction, followed by urinary symptoms. The latter were significantly more severe in the salvage group.** Incontinence rates were 5.9% and 10% in the primary and salvage groups, respectively. Severe ED was reported in 86% and 90% of the primary and salvage groups, respectively.

Finally, Hubosky and colleagues (2007) recently provided one of the first reports of comprehensive disease-specific HRQOL outcomes for patients treated with third-generation cryosurgical ablation. The median follow-up for this 89-patient cohort was 11 months (range 1 to 32). The authors specifically used the UCLA PCI and American Urologic Association Symptom Index Score to prospectively measure HRQOL evolution following cryosurgical ablation and to compare postcryosurgical HRQOL to that observed for a contemporaneous series of patients treated with permanent interstitial brachytherapy. At 12 months post-therapy, the authors noted that patients treated with cryosurgery had largely returned to their baseline urinary and bowel function; however, both sexual function and bother remained significantly below reported levels of baseline function (Hubosky et al, 2007). Relative to patients treated with brachytherapy (who had better baseline sexual and urinary function), patients who underwent cryosurgical ablation reported less favorable sexual HRQOL during the first postoperative year. In contrast, urinary function was similar between the two groups until 18 months postoperatively, at which time urinary HRQOL became more favorable among cryosurgery patients. The more favorable urinary HRQOL among cryosurgery patients persisted until at least 24 months. On the basis of these data, the

authors concluded that, relative to patients treated with brachytherapy, patients undergoing primary cryosurgical ablation experience fewer irritative and obstructive voiding complaints with their consequent detrimental effects on urinary HRQOL. Moreover, urinary function among patients treated with cryosurgery may improve up to 24 months after treatment (Hubosky et al, 2007).

Taken together, existing studies have started to define the evolution of HRQOL following primary or salvage cryosurgical ablation. Nonetheless, there is much work to be done in this area before the postcryotherapy HRQOL roadmap is defined as precisely for cryotherapy as it is for radical prostatectomy, external beam radiation therapy, and permanent interstitial brachytherapy (Sanda et al, 2008).

COSTS OF CRYOTHERAPY

The cost of care is an increasingly important consideration in the delivery of health care services. Several studies have evaluated the cost of cryotherapy for prostate cancer (Miller et al, 1996; Benoit et al, 1998; Schmidt et al, 1998). Schmidt and colleagues (1998) estimated that the typical cryotherapy-related charges approximate $13,000 including all professional fees and hospital and technical components. This represented roughly half of the typical cost for radical prostatectomy or radiation therapy at their institution during the same time period (Schmidt et al, 1998). Benoit and colleagues (1998) reviewed the costs of 114 cryotherapy cases performed in the same period time as 67 radical prostatectomies. Average hospital costs, excluding physician fees, were significantly lower for cryotherapy ($4150) than for radical prostatectomy ($5660). Much of this difference was explained by the shorter hospital stay for patients undergoing cryoablation (1.1 days vs. 3.4 days for radical prostatectomy). Given the progressively shorter length of stay for patients undergoing RP, it is unknown whether these significant cost differences persist in 2011.

FUTURE DIRECTIONS

Nerve-Sparing Cryoablation

Nerve-sparing cryotherapy represents an attempt to protect a neurovascular bundle (NVB) during cryosurgical ablation by active warming or injection of antifreeze proteins. The feasibility of nerve-sparing cryotherapy by active warming of the NVB has been evaluated in a canine model (Janzen et al, 2005). Cryotherapy was performed using 17-gauge, gas-driven cryoprobes on nine prostate lobes from five dogs. Seven lobes were treated with active warming of the NVB, and two lobes were treated without active warming. All seven prostate lobes treated with active warming demonstrated complete or partial NVB preservation, but four prostate lobes demonstrated adjacent gland preservation (Fig. 105–12). All prostate lobes treated with a double freeze-thaw cycle demonstrated complete and uniform ablation of prostate tissue, whereas one of three prostate lobes treated with a single freeze-thaw cycle demonstrated incomplete ablation of the prostate tissue. Future studies include the feasibility of injecting antifreeze proteins (Jia and Davies, 2002) or saline to protect or separate the NVB. Although promising, the optimal clinical application of nerve-sparing cryosurgical ablation (in the absence of a planned subtotal or focal ablation) remains undetermined. Whereas these results are provocative and intriguing, the authors currently do not recommend nerve-sparing cryotherapy as a mainstream therapy given the current inability to determine accurately the aggressiveness, extent, and spatial distribution of cancer within the prostate.

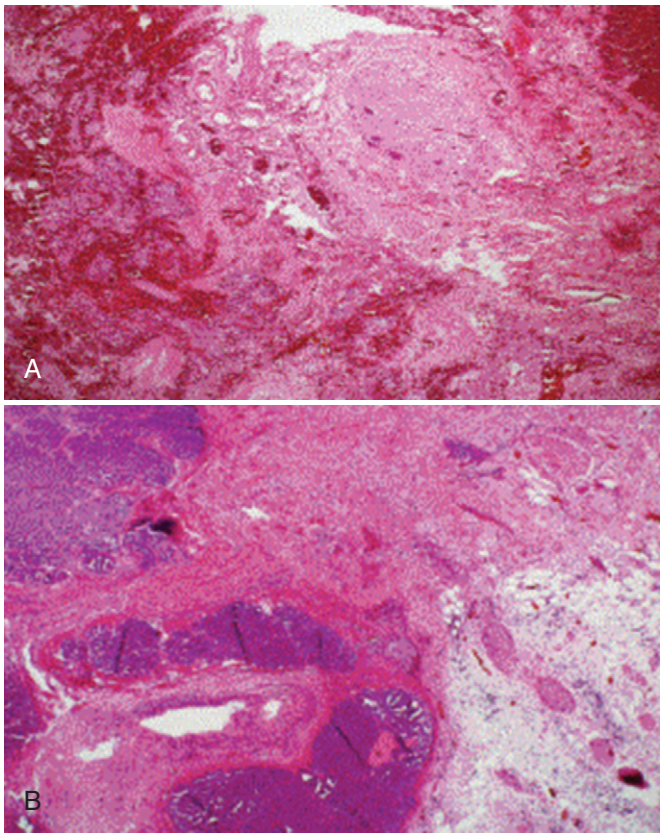


Figure 105–12. Preservation of the neurovascular bundle by active warming. **A,** Preserved nerve adjacent to hemorrhagic necrosis of the prostate. **B,** Presence of viable prostate glands immediately adjacent to a preserved neurovascular bundle.

Subtotal Cryoablation

There is general consensus that widespread early detection efforts have led to potential overdetection and overtreatment of early-stage prostate cancer (Cooperberg et al, 2004; Miller et al, 2006; Eggener et al, 2007). Because radical whole-gland therapy (and its consequent implications for urinary and sexual function) may be more than what is necessary for patients with lower-risk cancers, there is growing interest in the potential development and refinement of subtotal and focal therapies for men with prostate cancer (Eggener et al, 2007). **Subtotal cryotherapy is generally defined as an ablation of less than the entire prostate gland in an attempt to reduce cryotherapy morbidity by sparing one of the neurovascular bundles** (Ward et al, 2009). **Accordingly, the concept of subtotal cryotherapy encompasses both focal cryotherapy (in which just the region of the prostate harboring the index cancer is targeted) and more extensive ablations intended to treat half or even a majority of the prostate gland (i.e., 70% to 80%) while still preserving one NVB** (Fig. 105–13). An example of the latter treatment paradigm is the "hockey-stick" pattern of freezing described by Ward and colleagues (2009). **In general, it is important to recognize that there is as yet no standard treatment volume for patients undergoing subtotal cryosurgery and this critical issue will need to be addressed in future studies.**

Despite the interest in and rationale for subtotal and focal therapy(ies), prostate cancer poses a particular challenge for these techniques because it remains difficult to reliably define the

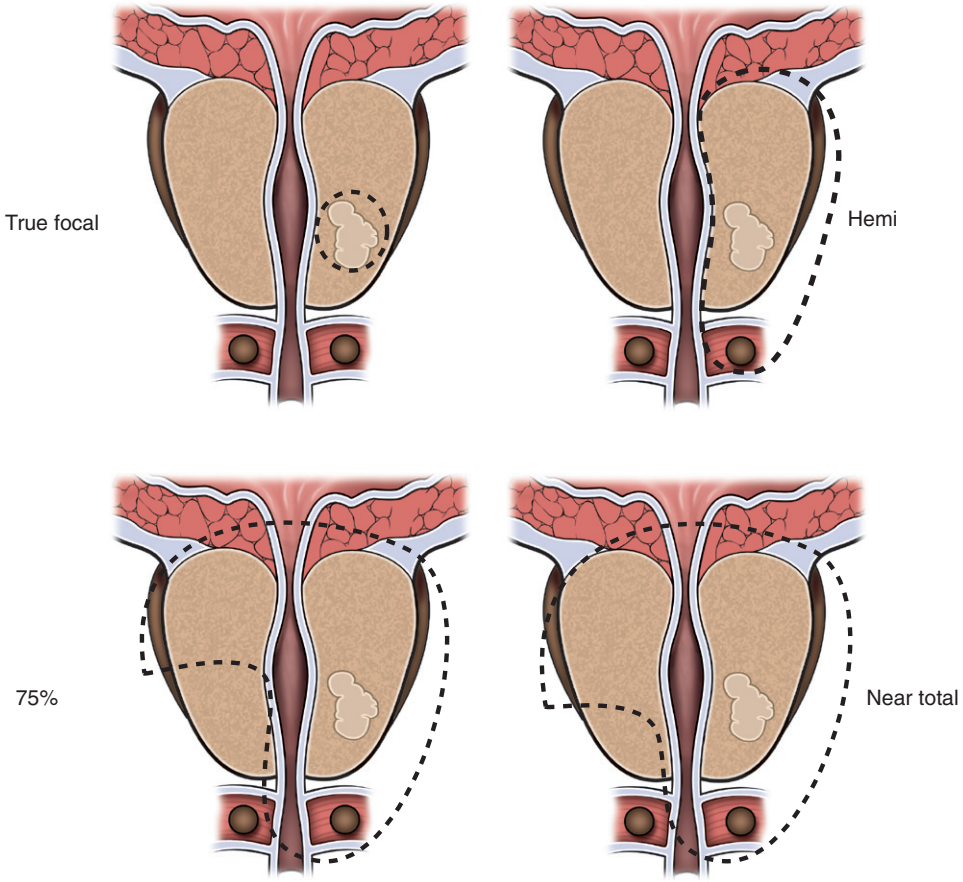


Figure 105–13. Patterns of ablation currently employed for subtotal and focal cryosurgical ablation of the prostate.

location or extent of the local tumor burden (Eggener et al, 2007). It has been shown that prostate cancers are usually multifocal and often include two to five tumor foci per gland (Miller and Cygan, 1994). However, stage migration resulting from widespread PSA screening has led some investigators to question the clinical significance of ancillary multifocal tumors and to ask whether it is possible to predict unifocal cancer, unilateral cancer, or clinically insignificant multifocal prostate cancer preoperatively (Eggener et al, 2007). Emblematic of the growing interest in potential focal therapies is the recent publication from the International Task Force on Prostate Cancer and the Focal Lesion Paradigm, which comprehensively explained the rationale for focal therapy for men with low-risk prostate cancer, potential concerns related to this approach, and recommendations for the further study of this treatment paradigm (Eggener et al, 2007).

An important rationale for focal prostate cancer therapy is that this approach may allow eradication of clinically important tumors while at the same time minimizing injury to adjacent vital structures including the urethra, external urinary sphincter, and neurovascular bundles. In theory, focal prostate cancer therapy could potentially provide excellent cancer treatment while minimizing downstream treatment-related consequences including, most importantly, ED and urinary incontinence. Subtotal or focal cryotherapy involves no manipulation and minimal vascular disruption of the spared NVBs and therefore a reasonable likelihood of preserving sexual function in patients who are potent at the time of ablation. In 2002 Onik and colleagues reported an initial pilot study of nine patients treated with focal, unilateral nerve-sparing cryotherapy. With this technique, they attempted to exploit the advantages of cryotherapy, particularly with respect to excellent treatment of potential extracapsular extension while minimizing the sexual function morbidity associated with whole-gland ablation. At a mean follow-up of 36 months, all nine men had stable PSA levels and the six patients who had post-treatment biopsies had no evidence for residual cancer in the ablation field (Onik et al, 2002). More recently, the authors reported longer-term follow-up on a larger cohort of patients treated with focal cryosurgical ablation between June 1995 and December 2005 (Onik et al, 2007; Onik et al, 2008). In this study the eligibility criteria for focal ablation included cancer confined to one lobe of the prostate and a desire to preserve both continence and potency. Among the 55 patients undergoing focal ablation, 52 (95%) had a stable PSA level at the time of most recent follow-up. The authors reported that the postcryosurgery PSA stabilization was at some fraction of the preoperative PSA level, depending on the extent of the gland ablation. The mean preoperative PSA level for this cohort was 8.3 ng/mL, whereas the mean postoperative PSA was 2.4 ng/mL. Among the four patients noted to have an "unstable" PSA level in the first year post treatment, prostate biopsy revealed that each patient harbored persistent cancer in an untreated portion of the gland. Among 51 patients with normal preoperative erections, 44 (85%) reported maintenance of erections following the focal ablative procedure (Onik et al, 2007). No patients developed de-novo urinary incontinence (Onik et al, 2007).

Lambert and colleagues (2007) reported their experience with subtotal cryosurgical ablation of the prostate among 25 patients with primary unilateral prostate cancer treated from June 2000 to December 2005. The median follow-up for this cohort of patients

was 28 months with a range of 9 to 72 months. In this study, each patient had unilateral, histologically proven prostate cancer meeting the following criteria: (1) Gleason score 6 or Gleason score 7 (3 + 4) prostate cancer that involved only a single lobe of the gland; (2) involvement of only 1 or 2 contiguous biopsy cores; and (3) tumor volume of less than 10% in a 12-core biopsy. The specific procedure involved hemigland ablation of the lobe harboring cancer. The NVB on the treated side was destroyed, while the contralateral NVB was spared. Depending on the definition employed, the authors reported a range of biochemical disease-free survival rates. For instance, using a PSA nadir of less than 1 ng/mL as the definition of biochemical failure, the authors reported 36% biochemical disease-free survival (median follow-up 28 months). Using PSA less than 2 ng/mL or less than 3 ng/mL as the definitions for biochemical control, the PSA recurrence-free survival rates were higher at 48% and 72%, respectively. When the authors applied more liberal definitions (e.g., PSA nadir > 50% lower than the pretreatment PSA level, Phoenix [nadir + 2]), they observed even more favorable biochemical recurrence-free survival outcomes (Lambert et al, 2007). Among seven patients who underwent post-treatment biopsy, three had recurrent cancer including one patient with tumor in the previously ablated lobe. In terms of morbidity, 71% of patients maintained potency and no patients developed postoperative urinary incontinence.

Finally, in a recent study, Eisenberg and Shinahara (2008) reported preliminary results with partial salvage cryoablation of the prostate among men with radio-recurrent prostate cancer. In this series, 19 patients with a unilateral focus of radio-recurrent prostate cancer were treated with hemigland ablation in the salvage setting. The authors reported biochemical recurrence-free survival rates (ASTRO definition) of 89%, 67%, and 50% at 1, 2, and 3 years, respectively. Using the Phoenix criteria, biochemical control rates were 89%, 79%, and 79% at 1, 2, and 3 years, respectively. At 1 year, 1 of 10 (10%) patients undergoing post-treatment biopsy harbored residual cancer. Reported complications in this series were rare and included one case of incontinence, one case of urethral stricture, and one case of urethral ulcer. The authors concluded that, in selected patients with a unilateral focus of radio-recurrent prostate cancer, acceptable oncologic results may be achieved with partial cryoablation of the prostate, while at the same time minimizing postcryotherapy morbidity.

Despite the promising and provocative data that continue to emerge for subtotal (including focal) cryoablation, overall clinical experience is limited and long-term results are largely unavailable (Babaian et al, 2008). Moreover, there is still no precise means to definitively identify histologically and/or biologically unifocal tumors (Eggener et al, 2007). At present therefore the authors believe that subtotal and focal cryotherapy should be considered only in the context of a clinical research protocol. Furthermore, **the authors agree strongly with recommendations from the AUA Best Practices Consensus Panel and the International Task Force on Prostate Cancer and the Focal Lesion Paradigm that the potential application of subtotal or focal cryotherapy be carefully investigated in prospective clinical trials** (Eggener et al, 2007; Babaian et al, 2008).

Technologic Advances for Cryosurgical Ablation

As with all treatments for clinically localized prostate cancer, cryotherapy is being refined. Clinical experience continues to grow, as does an understanding of cryobiology. Patient selection has been better defined, and complication rates have declined. The development of new imaging systems such as interventional MRI (Gilbert et al, 1997) and three-dimensional ultrasound units (Chin et al, 1998) may allow more effective freezing. The use of biologic modifiers such as antifreeze proteins at the time of the procedure is also being investigated and may improve the efficiency of the freezing process (Pham et al, 1999).

A modified technique of active rectal wall protection has been reported to permit deeper freezing of the peripheral zone of the prostate and for longer duration, rendering the procedure safer and more effective (Cytron et al, 2003). Two warming probes are placed in between the prostate and rectal wall to serve as active warming using the thawing mode when temperatures drop to approximately 0° C and as rectal lumen washing with warm water (40° C) when the temperature drops to –8° C to –10° C. This technique enabled a safe generation of an iceball at the peripheral zone of the prostate, which resulted in no rectal injuries and was effective in ablating the prostate gland.

Imaging techniques used in the definition of the extent of disease and in monitoring the process of tissue freezing have improved substantially over the years, and further advances are expected from CT and MRI in the next decade. Both CT and MRI are able to visualize the complete circumference of frozen tissue, as well as demonstrate its internal structure, potentially permitting continuous real-time monitoring of the complete three-dimensional progression of prostate freezing (Rubinsky et al, 1993). CT application is hindered by imaging artifacts created by metal cryoprobes, the physical restriction of the gantry, and the need for continuous radiation for real-time monitoring. CT also cannot directly determine the temperature of completely frozen tissue by objective assessment of tissue density or other parameters (Sandison et al, 1998). In addition to visualizing the entire frozen surface of tissue, magnetic resonance (MR) thermometry can potentially correlate measurable MR signal with the actual temperature of frozen tissue down to the critical level of about –40° C and could assist in objectively monitoring target tissue temperature within the iceball (Daniel et al, 1999; Wansapura et al, 2001). MRI is not ionizing and readily generates three-dimensional imaging. There are also evolving scanner designs that

Key Points: Cryotherapy for Prostate Cancer

- Fourth-generation cryotherapy includes TRUS guidance, pinpoint thermocouples, and the use of a brachytherapy-like template, with argon gas (freeze) and helium gas (thaw). The development of multipoint thermal sensors (MTS), which allow temperature monitoring along an entire tissue plane, marked the emergence of fourth-generation prostate cryosurgical technology.
- Two main mechanisms of cryotherapy-induced cytotoxicity exist: direct cellular toxicity (e.g., ice crystals disrupting cellular membrane) and vascular complications (thrombosis and ischemia).
- A minimum temperature of –40° C must be reached.
- At least two freeze-thaw cycles must be used.
- Long-term PSA follow-up is necessary before cryotherapy can be considered a minimally invasive first-line option, especially in younger men.
- Morbidity is minimal and decreasing with newer-generation technology and increasing cryosurgical experience.
- Subtotal and focal cryotherapy is under investigation.
- Salvage cryotherapy is associated with minimal morbidity and is an alternative to salvage radical prostatectomy.
- Cryotherapy may be repeated.

use a relatively "open" magnet that is easily applicable to intraoperative application. Even without thermometry, both MRI and CT lend themselves to computer integration with mathematic models that can generate real-time three-dimensional thermal maps of tissue freezing (Gilbert et al, 1997; Rewcastle et al, 1998; Jankun et al, 1999). These models can potentially integrate the visualized margin of freezing and a finite number of measurable temperature readings into a volumetric thermal model of frozen tissue. These interpolations could then be overlaid as graphical models on real-time images to create a virtual thermal map of the inside of a frozen prostate. Finally, electrical impedance tomography has also been proposed as a novel method for monitoring the iceball form during cryosurgical ablation (Baust et al, 2007). Although not yet ready for clinical application, this technology introduces low-amplitude AC currents into the body, allowing measurement of electrical potentials on the body surface. These potentials can then be recorded and analyzed to create tomographic images that monitor progression of the iceball (Baust et al, 2007).

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chapter 106

High-Intensity Focused Ultrasound for the Treatment of Prostate Cancer

Michael O. Koch, MD

High-Intensity Focused Ultrasound Technology
General Clinical Use of High-Intensity Focused Ultrasound
High-Intensity Focused Ultrasound in Localized Prostate Cancer
Summary

Conventional treatments for localized prostate cancer have been consistently associated with untoward effects on patients' quality of life, primarily urinary incontinence and sexual dysfunction. Although quality of life outcomes have been shown to be minimized when treatment is performed by high-volume surgeons, even the most capable surgeons have significant rates of impotence and urinary incontinence (Begg et al, 2002). The significance of these side effects of therapy is further amplified by the frequently indolent nature of this disease, which may take more than a decade to progress. Thus while the severity of these side effects of therapy may pale in comparison with other cancer surgeries, their overall impact after adjusting for the remaining years of life affected is quite large. Thus there remains a need for therapies that reduce the side effects of prostate cancer therapy while maintaining efficacy.

The application of thermal-based therapies in the treatment of localized prostate cancer has the potential to eliminate many of the treatment-related side effects while maintaining efficacy. Two basic forms of thermal therapy have been developed: cryotherapy, which freezes tissue to destroy it, and HIFU (*H*igh-*I*ntensity *F*ocused *U*ltrasound), which uses focused sound energy to heat tissue to destroy it. HIFU is different from cryotherapy in that the focal zone is extremely discrete with little or no tissue effects in areas immediately adjacent to the treatment zone. In this chapter the author reviews the development of HIFU, the scientific basis for its use in prostate cancer, and the published trials in localized prostate cancer.

HIGH-INTENSITY FOCUSED ULTRASOUND TECHNOLOGY

HIFU uses high-energy ultrasound waves to destroy the tissue at the focal point of a transducer without injuring the intervening tissue. **Strong ultrasound waves in the inaudible sound range and approximately 10,000 times stronger than diagnostic ultrasound are generated by a transducer with a parabolic configuration** (Fig. 106–1). **This parabolic configuration focuses these sound waves into a discrete focal point measuring approximately 3 mm × 3 mm × 11 mm. This focal point is located 3 to 4 cm distant from the transducer, and its size and shape is dependent on the energy emitted by the transducer, the geometric configuration of the transducer, and the characteristics of the tissue. At the focal point of the transducer, ultrasound energy is concentrated, is absorbed by the tissue, and generates temperatures that can exceed 80° C, resulting in coagulative necrosis and the destruction of tissue.**

The procedure is performed by imaging the prostate in the coronal and sagittal planes with a transrectally placed stationary probe. This probe allows both imaging and treatment of the prostate. The treating physician outlines the areas to be treated in both planes (Fig. 106–2). This focal point is then sequentially moved through the tissue to be destroyed by a computer-driven system that moves the parabolic transducer sagittally and coronally until the entire selected area has been coagulated. Treatment of contiguous areas of the prostate consecutively would result in heat build-up within that area of the prostate and the conductive spread of heat and thermal injury of the tissue. Conductive spread of the heat energy would negate the anatomic precision of the treatment, and the primary advantage of HIFU technology is the precise nature of the coagulated treated foci. In order to prevent the conductive spread of thermal energy through the prostate, the computer-controlled transducer is moved throughout the treatment to noncontiguous areas to allow treated areas to cool down. Eventually, all areas are treated as the transducer moves back and forth. **Because of the lack of adjacent tissue damage, HIFU is a repeatable precise technology.**

HIFU results in coagulative necrosis of the treated tissue. In the case of complete prostate ablation with HIFU, the prostate gland retains its general anatomic configuration but shrinks to a small size (≈15 mL) over 3 to 6 months post therapy. Post-HIFU biopsies show fibrosis only.

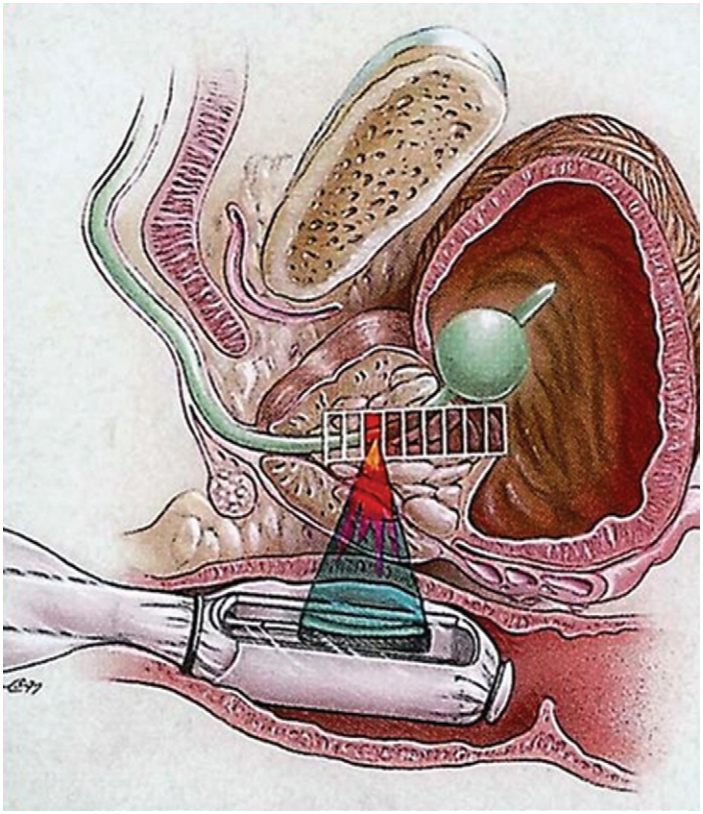


Figure 106–1. High-intensity focused ultrasound schematic shows parabolic dish concentrating sound waves remote from the transducer in a small focal point.

GENERAL CLINICAL USE OF HIGH-INTENSITY FOCUSED ULTRASOUND

This technique was initially investigated in both animals and humans in the 1940s and 1950s to destroy selective regions in the central nervous system (Fry et al, 1954; Fry and Johnson, 1978). It is now recognized that HIFU has the capability of transdermally or transmucosally coagulating and destroying tissue in a variety of conditions that have medical applications including spleen, liver, kidney, breast, uterus, and bone (Vaezy et al, 1997, 1999; Wu et al, 2001).

HIFU has been most well studied in the treatment of prostatic conditions. HIFU was initially tested in experiments in the canine prostate by Gelet and colleagues (1993), Bihrle and colleagues (1994a), and Kincaide and colleagues (1996). The use of the transrectal probe for the treatment of benign prostatic hypertrophy (BPH) in humans was first reported in the mid-1980s at Indiana University and by Madersbacher and colleagues in Vienna (Bihrle et al, 1994a; Madersbacher et al, 1994). HIFU was used to coagulate the periurethral area of the prostate in these series. The most common complication from the HIFU treatment was transient urinary retention, which occurred in 73% of patients. Two subsequent and larger studies have examined the efficacy and safety of the use of HIFU for the treatment of symptomatic BPH (Nakamura et al, 1997; Madersbacher et al, 2000). HIFU has not been widely used for the treatment of symptomatic BPH because of its relatively invasive nature in comparison to other thermal-based modalities such as microwave and radiofrequency ablation. Currently, HIFU does not have U.S. Food and Drug Administration (FDA) approval for the treatment of BPH in the United States. HIFU currently has FDA approval for the treatment of uterine fibroids in the United States.

Two companies are currently producing HIFU devices for the treatment of the prostate. The Ablatherm is produced by EDAP TMS (Lyons, France), and the Sonoblate-500 is produced by Focus Surgery (Indianapolis, IN).

HIGH-INTENSITY FOCUSED ULTRASOUND IN LOCALIZED PROSTATE CANCER

Madersbacher and colleagues (1995) were the first to examine the feasibility of HIFU for the treatment of localized prostate cancer. These investigators treated 29 patients with HIFU therapy immediately before radical prostatectomy using a predecessor of the currently used Sonoblate-500 device. They demonstrated that HIFU resulted in a sharply demarcated lesion with no treatment effects in areas immediately adjacent to the treatment zone. Two of these patients had sharply demarcated cancerous lesions on ultrasound and had this area targeted with HIFU (i.e., partial prostatic treatment). In these patients, no heat damage was noted to the rectum or neurovascular bundle even though HIFU was extended to the prostatic capsule (Fig. 106–3). Beerlage and colleagues (1999) subsequently confirmed these findings using the EDAP device.

HIFU is generally performed under general or regional anesthesia. A high-frequency transducer probe placed in a balloon filled with liquid, either cooled or room temperature, is inserted into the rectum to both serve as an acoustical interface and to cool the rectal wall. There are two transducers on these devices, low-energy transducers (3 to 4 MHz) for imaging and high-energy transducers for treatment. The prostate is imaged in both the sagittal and coronal planes, and the target treatment zone is outlined. With both systems, there is a treatment cycle in which the treatment zone is heated and then a cooling period during which the computer-controlled device moves to the next treatment zone distant from the first. Significant differences in these two devices do exist in terms of prostate imaging, geometric configuration of the treatment zone, tissue penetration, and safeguards. These devices are continually being modified to improve treatment ease, efficacy, and safety.

Gelet and colleagues (1996, 2000) reported on the use of the Ablatherm device in 82 patients with stage T1-2 prostate cancer and subsequently presented comprehensive outcome data in 2000 (Table 106–1). In the latter report, patients with stage T1-2 disease with prostate-specific antigen (PSA) less than 20 ng/mL were considered appropriate candidates for treatment with total prostatic ablation. Forty-six percent were stage T1, 49% were stage T2, and 5% were local failures after definitive external radiotherapy. Neoadjuvant hormonal therapy was administered in 9% of patients. Forty-one percent, 39%, 11%, 7%, and 1% of patients were treated with 1, 2, 3, 4, and 5 HIFU sessions, respectively.

Seventy-eight percent had negative sextant biopsies at 3 and 12 months. Fifty-six percent of patients had a PSA nadir of less than 1 ng/mL. Forty-two patients (51%) had both negative biopsies and a PSA nadir less than 1 ng/mL. Actuarial analysis was also performed on low-risk (PSA < 10 and Gleason < 7) and moderate-risk patients (PSA < 15 and Gleason < 8), and disease-free survival as defined by a PSA less than 1 ng/mL and negative sextant biopsies were 83% and 68% at 5 years, respectively. Mean follow-up for the overall series of patients was 17.6 months (range 3 to 68.5 months).

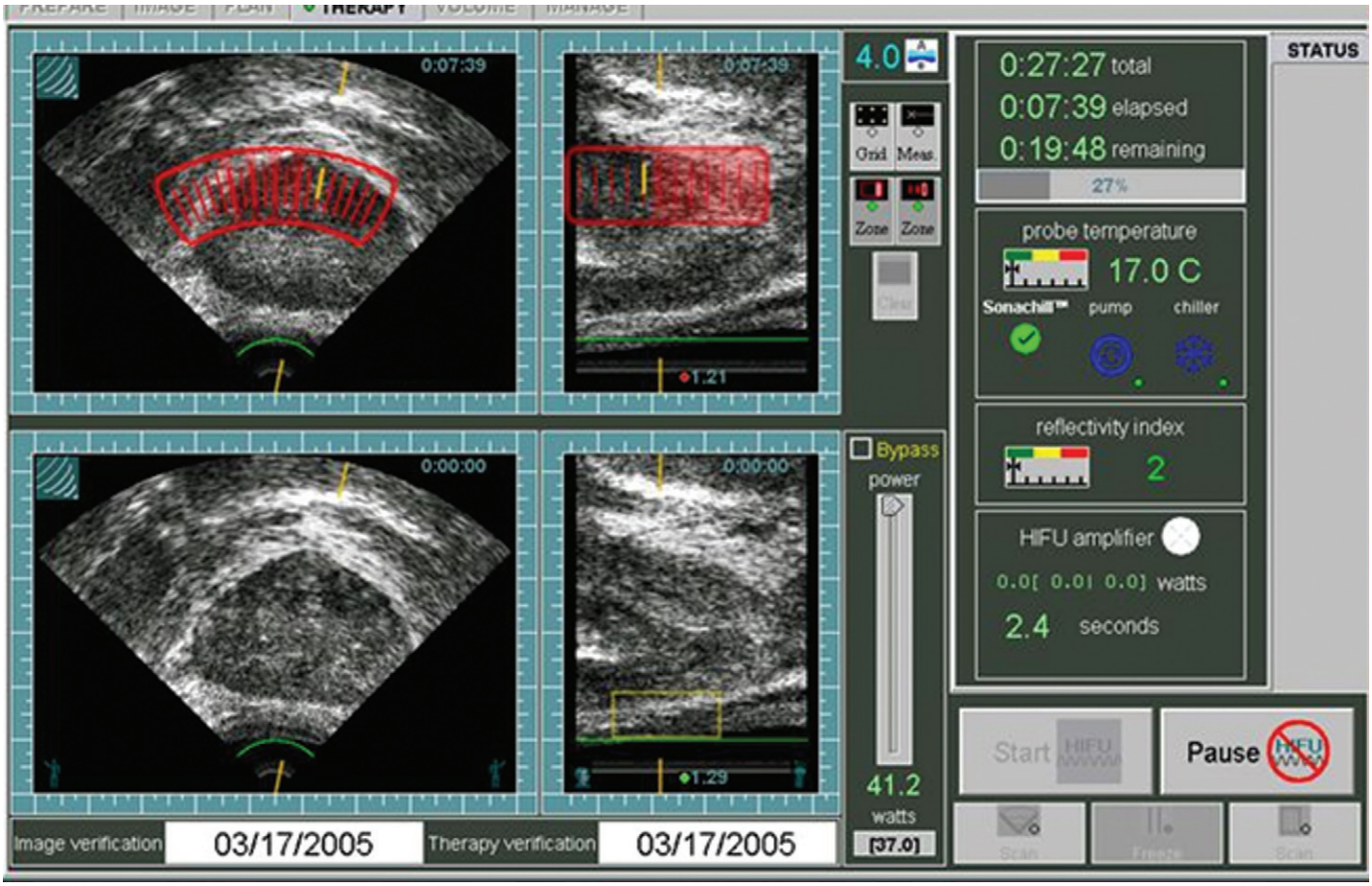


Figure 106–2. Treatment console of the Sonoblate-500 device. The two ultrasound images to the left are the coronal images, and the two images to the right are the sagittal images. The images on the upper part of the screen are the planned treatment area before high-intensity focused ultrasound treatment, and the two images at the bottom are live images during therapy. The right side of the screen reflects the treatment settings and ongoing measurements of rectal wall changes and machine settings.

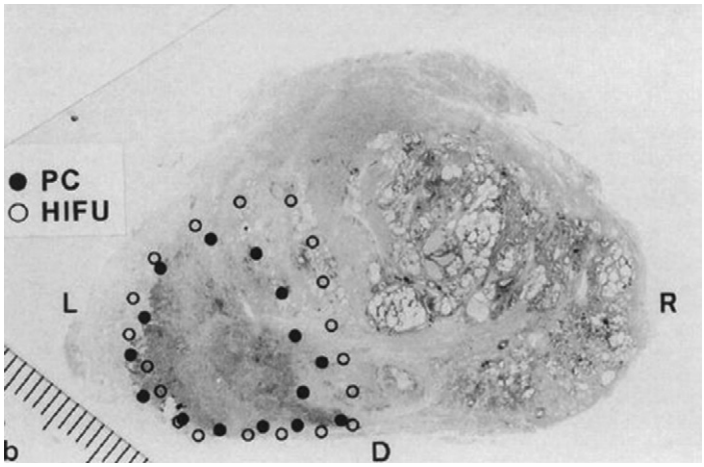


Figure 106–3. This whole mount section of the prostate was from a patient who underwent radical prostatectomy immediately after high-intensity focused ultrasound treatment of the left side of the prostate. Complete coagulative necrosis is noted in the treatment zone with no histologic evidence of tissue injury in areas immediately adjacent to the treatment zone. (From Madersbacher S, Pedevilla M, Vingers L, et al. Effect of high-intensity focused ultrasound on human prostate cancer in vivo. Cancer Res 1995;55:3346–51.)

Mean postoperative catheterization time was 8.5 days. Mean time to PSA nadir was 5 months.

A multi-institutional report on the results of the Ablatherm device was reported in 2003 (Thüroff et al, 2003). This report describes the results of HIFU treatment in 402 patients treated across six sites in Europe. This was a noncontrolled clinical trial in patients considered unsuitable candidates for radical prostatectomy. Thirty-five patients (9%) had undergone previous radiation therapy, and 104 patients (26%) were being treated with some form of hormonal therapy. Patients were stratified into low-, intermediate-, and high-risk groups for efficacy analysis. Efficacy was assessed by sextant biopsy of the prostate and serum PSA.

There were an average number of treatments of 1.47 treatments per patient with 28% of patients requiring two treatment sessions. Post HIFU, 288 patients underwent sextant biopsy and 87% had a negative biopsy; 92%, 86%, and 82% in the low-, intermediate-, and high-risk groups, respectively. Mean nadir PSA in the low-, intermediate-, and high-risk groups was 1.3 ng/mL, 1.4 ng/mL, and 3.1 ng/mL, respectively. Larger prostate volumes were predictive of failure by both biopsy and PSA. Transient urinary retention was the most common complication occurring in all patients and lasting for a median of 5 days (Table 106–2). Prolonged retention was reported in 9% of patients. Although one might predict a high degree of urethral strictures and bladder neck contractures with complete urethral treatment, these were seen in only 3.6% of patients. The most serious complication of this technology was

Table 106–1.

Disease Outcome in Early High-Intensity Focused Ultrasound Trials*

SERIES	NO. PATIENTS	DEVICE	PERCENT STAGE T1	MEAN FOLLOW-UP (MO)	MEAN PREOP PSA	NADIR PSA ≤ 0.5/1 ng/mL	NEGATIVE BIOPSY	NEGATIVE BIOPSY AND PSA ≤ 0.5/1 ng/mL	5-YR PROGRESSION-FREE SURVIVAL
Gelet et al, 2000	82	Ablatherm	48%	17.6	8.11 ± 4.64	?/56%	78%		68%-83%
Kiel et al, 2000		Ablatherm		15					Not reported
Low risk	28		T1 and T2		7.64 ± 5.26	Not reported	88%	46%/71%	
Moderate risk	11		T1-T3		6.06 ± 4.54	Not reported	55%	18%/36%	
Uchida et al, 2002	20	Sonoblate	35%	13.5	9.65 ± 4.43	65%/90%	100%	65%/90%	Not reported
Chaussy and Thüroff, 2000	184	Ablatherm	Not reported	6.3	12.0	Not reported	80%	61%/?	Not reported
European Multicentre Study (Thüroff et al, 2003)	402	Ablatherm	Not reported	13.3	10.9 ± 8.7	Average nadir PSA was 0.6	87%	?	Not reported

*Results are generally reported as mean ± one standard deviation.

Table 106–2.

High-Intensity Focused Ultrasound Complications

COMPLICATION	GELET ET AL, 2000	KIEL ET AL, 2000	THÜROFF ET AL, 2003	EUROPEAN MULTICENTRE STUDY (THÜROFF ET AL, 2003)	UCHIDA ET AL, 2002
Mild-moderate incontinence	13%	6%	11.4%	14%	0%
Severe incontinence	4%	5%	1%	1.5%	0%
Impotence*	77%	44%	24%	35%	30%
Prolonged retention	6%	32%	30%	9%	0%
Rectourethral fistula	1%	3%	0.5%-3%	1.2%	5%
Urethral stenosis	17%	2%	6%	3.6%	10%

*Of patients potent preoperatively.

the development of urethrorectal fistulas, which occurred in five patients (1.2%) before the use of the rectal cooling device. Mild to moderate stress incontinence developed in 11% and 3% of patients, respectively, whereas severe incontinence requiring intervention developed in 1.5% of patients. Finally, impotence was reported in only 35 patients (9%).

The Sonoblate devices have been most extensively studied in Japan. Uchida and colleagues (2002) are the only investigators to report an experience with the Sonoblate-200 device for the treatment of localized prostate cancer. The Sonoblate-200 device uses a 4-MHz power generator, which has different tissue characteristics than the Ablatherm and employs a rectal cooling device. In the initial report, 20 patients were treated with 28 treatments (1.4 treatments per patient). Patients all had localized disease, the average PSA was 9.65 ng/mL, and all had Gleason score 7 or less disease. Four patients (20%) received pretreatment hormonal therapy, and none received post-treatment hormonal therapy. A PSA nadir of less than 0.5 ng/mL, 0.5 to 1 ng/mL, and 1.01 to 2 ng/mL was achieved in 65%, 25%, and 10% of patients, respectively. This same center subsequently published overall 5-year biochemical disease-free rates of 67% (Uchida, 2005). Patients with preoperative PSA less than 10 ng/mL demonstrated 5-year disease-free survivals of 88%.

Contemporary Series

The Sonoblate-500 device has just recently completed the first successful U.S.-based trial on the use of HIFU for the treatment of localized prostate cancer at Indiana University. This trial was structured as a feasibility trial to demonstrate the safety and, to a lesser degree, the efficacy of this technology before petitioning the FDA to allow Focus Surgery to conduct a multi-institutional pivotal trial to examine the true efficacy of this technology. Twenty patients with early-stage prostate cancer (T1-2, ≤Gleason score of 7, and PSA ≤ 10 ng/mL) were treated with this device. Follow-up included a mandatory extended field biopsy (minimum 10 cores) at 6 months post treatment. Success defined as a negative extended field biopsy at 12 months and a PSA nadir less than 1 ng/mL were achieved in 58% of patients overall and in 65% of patients that underwent retreatment when indicated. Transient urinary retention occurred in all patients, and a single patient developed a rectourethral fistula that healed with temporary fecal diversion. One patient developed mild stress incontinence, and potency was not well evaluated. Follow-up beyond 6 months was not reported.

Two series report moderately long-term results with HIFU for localized prostate cancer. Blana and colleagues (2007) reported on a multi-institutional group of patients treated from 1997 through

2001 with early prototypes of the Ablatherm device. This series included 140 patients with moderate- to low-risk prostate cancer; cT1-cT2, PSA less than 15 ng/mL, and Gleason score of 7 or less. Efficacy was based on a prostate biopsy, and the researchers used the ASTRO Phoenix criteria (PSA nadir + rise of 2 ng/mL). Twenty-three patients (16%) received some period of androgen blockade around the time of therapy. In this population of patients, a PSA nadir of less than or equal to 0.5 ng/mL was achieved in 68% of patients and actuarial biochemical-free survival was reported as 77% and 69% at 5 and 7 years, respectively. Biopsies (minimum of six cores) were done on patients between 3 and 6 months post treatment and were negative in 86% of patients. The average follow-up in this series was 6.4 years. Uchida and colleagues (2006a) reported on a 5-year experience with 181 consecutive patients treated with the Sonoblate-500 device. The median follow-up in this series of patients was only 18 months, and in this series 52% of patients were treated with neoadjuvant androgen ablation. Biochemical disease-free survivals using the ASTRO consensus panel criteria were 84%, 80%, and 78% at 1, 3, and 5 years, respectively.

High-Intensity Ultrasound after Radiation Failure

Both HIFU devices have also been tested for use as salvage therapy after radiation failure. Murat and colleagues (2009) reported on the use of HIFU for the treatment of 167 patients after failure of external beam radiotherapy. Ninety-five patients were on androgen ablation therapy before HIFU, but none were continued on it after treatment. Sextant biopsies at 3 months were negative in 73% of patients, and the median PSA nadir was 0.21 ng/mL. Although this follow-up is quite short, 63% of these patients did have Gleason score 7 or higher disease and a median of three positive biopsies cores preoperatively. Although technical modifications over time did reduce treatment-related side effects, 31.5% experienced grade 2 to 3 incontinence, bladder neck stenosis occurred in 15% to 30%, and five patients (3%) developed urethrorectal fistulae.

Zacharakis and colleagues (2008) examined the use of the Sonoblate-500 device in 31 men with recurrent prostate cancer after external beam radiation therapy. Mean follow-up was only 7.4 months. Half of these men achieved a PSA nadir of less than 0.2 ng/mL. Unfortunately again, side effects were common with 36% developing obstruction from urethral sloughing or stricture, 7% developing urinary incontinence, and 6% developing urethrorectal fistulas.

High-Intensity Focused Ultrasound End Points

The accurate assessment and understanding of the efficacy of any technology is highly dependent on the selection of appropriate end points, particularly in the case of prostate cancer where mortality of the disease in the short term is low and alternate end points such as PSA criteria are used. Ganzer and colleagues (2008) examined the use of PSA nadir in predicting ultimate treatment efficacy after HIFU in 103 patients who underwent HIFU at two different centers for the treatment for localized prostate cancer (Ganzer et al, 2008). Treatment failure was defined as PSA nadir + 2 ng/dL, a positive biopsy, or the use of salvage therapy. A PSA nadir of less than or equal 0.2 ng/mL, 0.21 to 1 ng/mL, and greater than 1 ng/mL occurred in 64%, 22%, and 14% of patients, respectively. Failures occurred in 4.5%, 30%, and 100% of these three groups, respectively. Because the median follow-up in this series was only 4.9 years, these failure rates are best-case scenarios with HIFU treatment. Uchida and coworkers reported similar findings with the Sonoblate-500 device (Uchida et al, 2006b). In this series, patients with a PSA nadir of 0.0 to 0.2 ng/mL had an 11% chance of having a positive post-treatment biopsy at 6 months, whereas patients with PSA nadirs of 0.21 to 1 ng/mL and greater than 1 ng/mL had positive biopsy rates of 46% and 48%, respectively. Again, because of the false-positive rates of prostate biopsies and the lack of biopsies at longer follow-up, these figures paint the most optimistic picture of HIFU therapy.

Most series of HIFU therapy for prostate cancer have included some form of prostate biopsy ranging from 4 to 10 cores. Prostate glands do shrink considerably after HIFU therapy, lessening the likelihood of a false-negative biopsy. Nevertheless, that problem still exists and as in the Uchida publication mentioned earlier, most series have not included biopsies after 6 to 12 months.

The most current studies on the use of HIFU are highly flawed by the use of inappropriate PSA end points to assess efficacy. The original ASTRO consensus panel recommendations were that treatment failure *after external beam radiotherapy* should be defined as two consecutive rises in the PSA after the occurrence of the PSA nadir. It specifically stated that this criterion for failure was not appropriate for other forms of radiation, for radiation combined with hormonal therapy, or for cryotherapy (and therefore other thermal-based approaches). In order to improve on this definition and enable radiation oncologists to compare one form of radiation therapy to another and account for the common use of hormonal therapy in these patients, a second consensus panel was formed and reported a new recommendation in 2006. Their consensus was that biochemical failure after radiation be defined as a rise of 2 ng/mL after nadir occurred, the so-called Phoenix criteria (Roach et al, 2006). They specifically addressed the issue of whether the Phoenix criteria were to be interpreted as indicative of cure and chose instead a criteria that predicted likely morbidity from prostate cancer rather eradication of all disease (i.e., treatment success by the Phoenix criteria are not to be considered synonymous with cure). **Moreover, they expressly state that because of the prolonged period of time necessary to demonstrate failure by these criteria, the results of prostate cancer treatment by Phoenix criteria should never be reported more than 2 years less than the median follow-up and that the Phoenix criteria were again inappropriate for thermal-based therapies for prostate cancer.** Unfortunately, these specifics have been overlooked by proponents of HIFU for prostate cancer who report efficacy results that are inappropriately long and scientifically invalid.

Treatment of High-Intensity Focused Ultrasound Failures

Despite the failings of the HIFU trials published thus far, HIFU remains unique compared with other modalities for localized prostate cancer in that it results in much less adjacent tissue damage. This makes it a repeatable technology and thus potentially more salvageable by other techniques when it fails. Stolzenburg and coworkers (2007) reported a series of nine patients who successfully underwent laparoscopic salvage prostatectomy, three of whom were after HIFU failure and the other six of whom were after external beam radiotherapy. Results were generally favorable

and felt to be comparable in the two groups. Pasticier and colleagues (2008) reported a larger group of 45 patients who had local failure after HIFU and were treated either with external beam monotherapy (32 patients) or external beam radiotherapy in combination with androgen ablation (Pasticier et al, 2008). The median total prescribed radiation dose to the prostate in this series was 71 Gy. These investigators noted no additional toxicity compared with patients undergoing primary external beam radiotherapy for prostate cancer. No rectal fistulae occurred, and only 15% of patients experienced new grade 2 urinary incontinence. Oncologic efficacy was not well evaluated in this study.

SUMMARY

It seems clear at this point that HIFU treatment of prostate cancer has the potential to completely eradicate the prostate gland and therefore prostate cancer in some patients. Technical modifications continue to improve the ability to use these modalities effectively and with ever-decreasing morbidity from damage to adjacent structures. These treatments offer potential major advantages over surgical and radiation-based treatment modalities in terms of its lack of invasiveness and its repeatability. However, the available published trials have been severely limited by the concomitant use of hormonal therapy and transurethral prostatectomy, inadequate sampling of the prostate, the lack of long-term follow-up, and most importantly, inappropriate end points. As results are published, the technology continues to evolve. This will make the technology even more difficult to evaluate. At present, this technology is not approved for the treatment of prostate cancer in the United States. Two phase III trials were initiated in 2006-2007 to compare HIFU to cryotherapy for the treatment of prostate cancer. If these trials are successfully completed and results are favorable, this technology may become an important form of treatment for prostate cancer.

SUGGESTED READING

Tsakiris P, Thüroff S, De La Rosette J, Chaussy C. Transrectal high-intensity focused ultrasound devices: a critical appraisal of the available literature. J Endourol 2008;22(2):221–9.

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The complete reference list is available online at www.expertconsult.com.

chapter 107

Treatment of Locally Advanced Prostate Cancer

Maxwell V. Meng, MD ● Peter R. Carroll, MD, MPH

Definition
Trends in Incidence and Treatment
Natural History
Radical Prostatectomy
Radiation Therapy
Focal Ablative Therapy
Androgen Deprivation and Its Timing
Management of Delayed Sequelae
Clinical Trials

The widespread application of prostate cancer early-detection efforts in the United States has resulted in both an increased number of prostate cancers diagnosed and the earlier identification of these tumors. Despite the stage migration associated with prostate-specific antigen (PSA) testing and the growing number of low-stage and organ-confined tumors, at least 10% of men with newly diagnosed prostate cancer have locally advanced disease (T3NX/+M0). Although this proportion has declined somewhat, it remains significant and has been relatively constant during the past decade. Those men with locally advanced or metastatic prostate cancer at the time of presentation contribute disproportionately to prostate cancer mortality, and improved treatments for such men could have a significant positive impact on overall morbidity and mortality due to this disease.

Currently, no consensus exists regarding the optimal management of locally advanced prostate cancer. Unlike with clinically localized and low-grade prostate cancer, for which comparable and excellent outcomes may be achieved with a variety of interventions, treatment of disease with local or regional spread by any single modality is associated with significant risk of recurrent disease. Ongoing interest in and the development and evaluation of combination therapy, as well as improvements in risk assessment, should improve cancer outcomes while minimizing treatment-related morbidity and adverse impact on quality of life in these patients.

DEFINITION

Traditionally, the identification of patients with locally advanced disease was based on clinical examination (e.g., digital rectal examination) and clear evidence of spread outside of the prostate capsule (clinical stage T3a), involvement of the seminal vesicles (cT3b), or involvement of adjacent organs (cT4) (Greene et al, 2002). However, the contemporary use of PSA has led to the majority of men diagnosed with prostate cancer initially having nonpalpable cancers (cT1c). **Features other than clinical T stage most often contribute to the identification of men with advanced disease and a concomitant increased risk of failure after primary therapy.** Thus improved methods of risk assessment have facilitated categorization of men as "high risk" and involve consideration of variables such as serum PSA level and Gleason score in addition to clinical stage. The subsequent discussion focuses on this broader definition of locally advanced disease, with inclusion of those with regional or lymph node involvement without distant metastasis (T3-4N ±M0).

Contemporary Risk Assessment

Multiple methods are currently available to accurately risk stratify men with prostate cancer (Partin et al, 1997; D'Amico et al, 1999; Tewari et al, 2001; Shariat et al, 2008). The Partin tables were initially constructed in the 1990s and updated in 2001, assisting in the preoperative prediction of final pathologic stage in men with clinically localized prostate cancer undergoing radical prostatectomy (Partin et al, 2001). Although clinical stage, serum PSA level, and Gleason score individually predict pathologic stage and prognosis, the combination of these three variables increases the accuracy of this assessment. These data continue to illustrate that a significant number of men thought to harbor organ-confined tumors have more advanced disease. The ability to assess pathologic stage permits better pretreatment counseling of patients and more appropriate selection of therapy and consideration of those with more advanced disease for novel clinical trials. **The most important pathologic criteria predicting prognosis after radical prostatectomy are Gleason score, surgical margin status, and presence of non-organ-confined disease (e.g., extracapsular extension, seminal vesicle invasion, lymph node involvement).**

In addition, to help predict pathologic stage, biopsy information has been incorporated into models estimating cancer outcomes, primarily PSA- or biochemical-free survival, after treatment. Whereas biochemical-free survival is a frequent end point of current prostate cancer studies, it merely represents an intermediate surrogate outcome variable; further trials and studies are necessary to confirm the utility of biochemical recurrence as a marker for reduced prostate cancer-specific survival after treatment. The

most widely used tools to predict disease recurrence after local therapy are the nomograms developed by Kattan and colleagues (1998, 2000). In all pretreatment nomograms, clinical stage, biopsy Gleason grade, and pretreatment serum PSA level are incorporated to predict the continuous risk of disease progression after definitive local therapy; models for radiation therapy (RT) also include data on use of androgen deprivation (AD), total radiation dose, and combination treatment (i.e., external beam and permanent brachytherapy). The radical prostatectomy nomogram was based on nearly 1000 patients with clinically localized disease (T1c-T3aNXM0); thus this model is not applicable for those men with evidence of seminal vesicle involvement or regional spread.

Key Points: Risk Assessment

- Risk assessment is best performed by a combination of serum PSA level, T stage, cancer grade, and extent of cancer on biopsy.
- Imaging plays a limited role in identifying most patients with high-risk features for whom local therapy may fail.

To simplify risk stratification, men with prostate cancer can be grouped into fewer categories but with maintenance of ability to predict disease behavior and response to intervention. D'Amico and colleagues (1998) defined patients at low, intermediate, and high risk for biochemical failure, still based on pretreatment disease characteristics (clinical stage, PSA value, Gleason score). Recurrence after treatment may be due to unrecognized micrometastatic disease or persistence of locoregional disease. Other variations of simplified risk stratification have been developed and validated, with inclusion of features such as ethnicity and pathologic findings (Moul et al, 2001; Cooperberg et al, 2005). The Cancer of the Prostate Risk Assessment score, ranging from 0 to 10, provides another method to assess risk with each 2-point increase in score doubling the risk of recurrence after prostatectomy. **Although men with "low-risk" disease generally do well and are unlikely to have biochemical recurrence, men in the intermediate- and high-risk groups may have widely discrepant outcomes. Therefore men in these groups benefit from more modern and accurate risk prediction models and nomograms** (Mitchell et al, 2005).

Imaging Modalities

Although observations on traditional gray-scale ultrasonography can identify extraprostatic disease, the general ability to improve cancer staging is limited (Figs. 107–1 and 107–2). Directed biopsy of the seminal vesicles or prostate capsule can be obtained to confirm cT3 disease. Smith and colleagues (1997) found that transrectal ultrasonography did not improve the ability to stage prostate cancer; the area under the curve was .69 and .74 for transrectal ultrasonography in predicting extracapsular extension and seminal vesicle invasion, respectively, compared with .72 and .69 for digital rectal examination, respectively. Salo and colleagues (1987) reported high sensitivity (86%), specificity (94%), positive predictive value (92%), and negative predictive value (89%) of ultrasonography in predicting extracapsular extension in patients undergoing radical prostatectomy. However, more contemporary studies suggest otherwise, with lower sensitivities (23% to 66%), specificities (46% to 86%), positive predictive values (50% to 62%), and negative predictive values (49% to 69%). The inaccuracy of ultrasound staging for prostate cancer is likely to be the result of significant interobserver variability, often subtle signs of extraprostatic spread, and lower-volume tumors currently diagnosed. In general, transrectal ultrasonography understages rather than overstages prostate cancer. Newer ultrasound techniques such as color and power Doppler studies are under investigation to

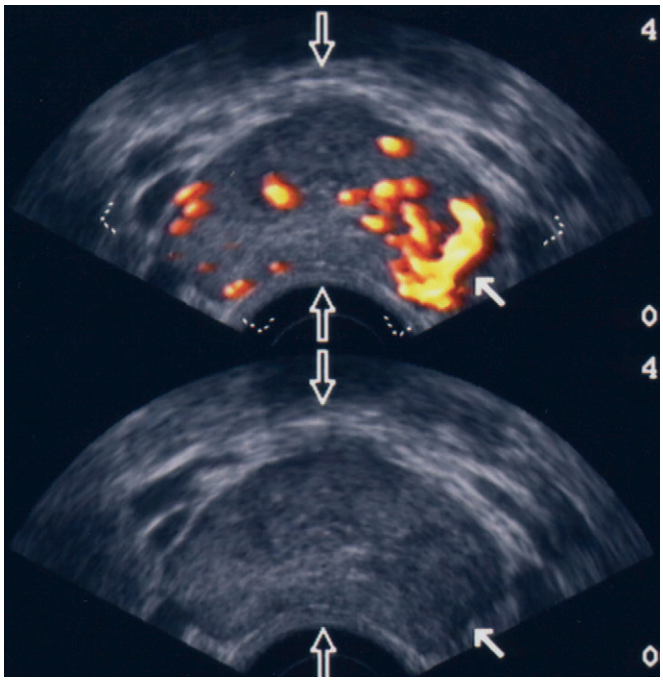


Figure 107–1. Transrectal ultrasound examination demonstrates increased flow on color Doppler study at the left posterior *(upper panel, arrow)* with corresponding hypoechoic area on gray-scale images *(lower panel, arrow)*. Note the left lateral distortion and squaring of the capsule, suggesting extracapsular extension. (Courtesy of Dr. Katsuto Shinohara.)

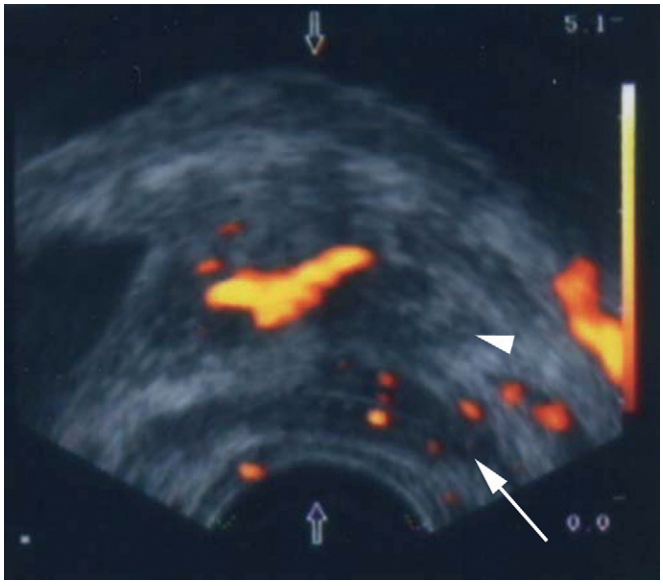


Figure 107–2. Transrectal ultrasound examination demonstrates hypoechoic tumor in the left base *(arrowhead)* with likely extension into the ipsilateral seminal vesicle *(arrow)*. (Courtesy of Dr. Katsuto Shinohara.)

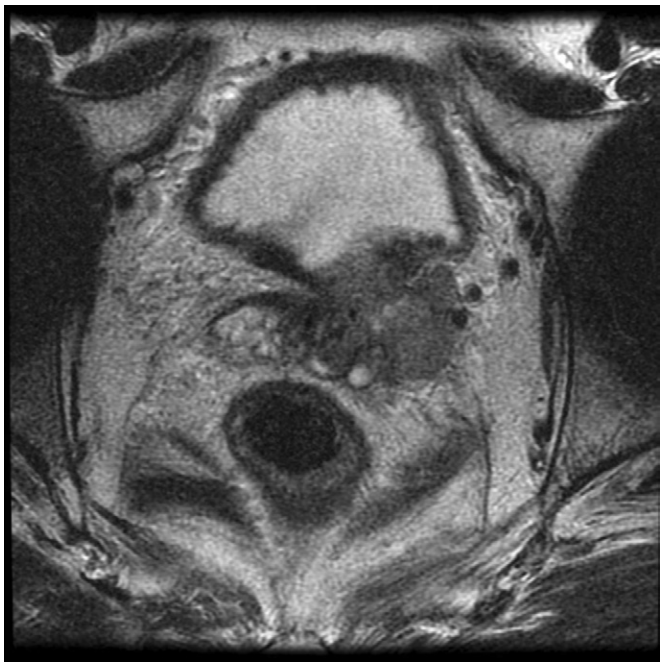


Figure 107–3. Axial T2-weighted MRI shows tumor involving the seminal vesicle and bladder base and extending into the adjacent fat.

Table 107–1.

Chromosome Abnormalities Associated with Pathologic Stage

CHROMOSOME ABERRATION (INDEPENDENT OR IN COMBINATION)	*P* VALUE
–8p	.001
–8p/–10q23 → qter	.002
–10q25 → qter	.029
–6p21	.031
–6q24 → qter	.031
–18cen-q12	.035
–5q31/–10q24 → qter	.04
–5q31 → qter/–8p	.04
–6p21/–10q24 → qter	.04
–6p12 → pter/–6q24 → qter	.04
–6q25 → qter/–11q23 → qter	.04
+7p11/–10q24 → qter	.04
–8p/–15q22	.04
–8p/–11q24 → qter	.42

determine if observations of abnormal blood flow can increase the ability to detect and stage prostate tumors.

Endorectal magnetic resonance imaging (MRI) uses a magnetic coil placed in the rectum to achieve better visualization of the zonal anatomy of the prostate and may delineate subtle distinctions between T2a/b disease and T3 disease (Fig. 107–3). However, use of MRI, alone or in combination with magnetic resonance spectroscopy (MRS), for tumor staging remains controversial. Variable sensitivities (13% to 91%) and specificities (49% to 97%) have been reported for predicting extracapsular extension, in part attributed to variability in interpreting MRI and lack of uniform diagnostic criteria. In a cohort of 336 men with more than three cores involved with cancer, abnormal findings on digital rectal examination, and PSA level higher than 10 ng/mL undergoing radical prostatectomy, the specificity of MRI in predicting pT3 disease was 95% (Cornud et al, 2002). Thus the use of MRI may be best limited to those patients with higher-risk features.

Novel Markers

It is clear that traditional clinical and pathologic parameters are limited in their ability to accurately predict local extent of tumor before treatment. Given the importance of assessing true pathologic stage, novel markers of advanced disease are necessary. Chu and colleagues (2003) used comparative genomic hybridization in primary prostate specimens and identified chromosomal regions potentially useful in discriminating between organ-confined and locally advanced tumors (Table 107–1). Prediction of stage by a model incorporating six aberrations in a stepwise fashion was accurate in 91.1% of cases. Further metabolic, genetic, and proteomic signatures will likely better define and discriminate between organ-confined and non–organ-confined prostate cancer (Ashida et al, 2004; Paris et al, 2004; Mehra et al, 2007; Sreekumar et al, 2009). Chromosomal rearrangements involving the androgen-regulated gene *TMPRSS2* and the *ETS* family genes are associated with higher pathologic stage, whereas the glycine-metabolite sarcosine was more often elevated in metabolomic profiles of men with metastatic prostate cancer.

TRENDS IN INCIDENCE AND TREATMENT

Within the Cancer of the Prostate Strategic Urological Research Endeavor (CaPSURE), **Cooperberg and colleagues (2003) observed a significant decrease in the fraction of men presenting with high-risk disease characteristics, as defined by D'Amico criteria, from 40.9% in 1989-1990 to 14.8% in 2001-2002.** However, alterations in cancer screening and use of PSA are likely to account for this reduction, with significantly fewer men presenting with elevations in PSA level higher than 20 ng/mL (32.8% to 7.2%); indeed, currently, higher Gleason grade defines a larger number of high-risk patients (61.5%). Overall, **the presence of clinically advanced disease (i.e., T3-4) decreased from 11.8% to 3.5%, with a decline from 32.3% to 21.9% in the high-risk group during the observation period.**

In men undergoing radical prostatectomy, the number of men with clinical evidence of locally advanced disease, as defined by clinical stage (T3), has declined from 25.3% in 1987 to 2.8% in 2001 (Ward and Zincke, 2003). Although the use of PSA screening can account for part of this change, the more selective application of surgery and improved techniques of RT may also explain the decline in patients with cT3 disease undergoing prostatectomy. Within reports of men undergoing radical prostatectomy, the fraction of men with pT3 disease has decreased; these are highly selected patients with largely clinically localized disease at the time of treatment (Table 107–2). Roehl and colleagues (2004) reported that pathologically advanced disease decreased from 39% (1983-1991) to 31% (1992-2003). In men undergoing radical prostatectomy alone at the Cleveland Clinic, the overall rate of extracapsular extension declined from 65.8% (1987-1989) to 25.2% (2000-2001), and this trend was true for all clinical stages of tumor (T1c-T2b/c), as well as for pretreatment variables (PSA value, Gleason score).

Table 107–2.

Pathologic Findings in Men Undergoing Radical Prostatectomy

AUTHOR (YR)	NO. PATIENTS	ERA	ECE	SEMINAL VESICLE/LYMPH NODE
Stamey et al (1998)	896	1988	60%	18%/NR
		1996	25%	5%/NR
Quinn et al (2001)	732	1986-1999	42.8%	13.1%/2.3%
Hull et al (2002)	1000	1993-1998	25%	8.1%/6.9%
Han et al (2003)	2091	1982-1999	41%	4%/5%
Derweesh et al (2004)	1505	1987-1998	66%	NR
		2000-2001	25%	NR
Roehl et al (2004)	3478	1983-1991	25%	14% (combined)
		1992-2003	27%	4% (combined)
Bott et al (2005)	1001	1988-2001	47%	10%/2%
Badani et al (2007)	2766	2000-2006	16.9%	5.1%/9%
Patel et al (2008)	1500	NR	13.8%	5.7%/NR
UCSF	2349	1986-2009	16%	11%/3%

ECE, extracapsular extension; NR, not reported.

Key Points: Trends in Incidence and Treatment

- Fewer men are presenting with locally advanced prostate cancer.
- There has been an increase in organ-confined cancers identified after radical prostatectomy.
- There is an increasing use of treatment modalities other than surgery for high-risk prostate cancers.

The National Comprehensive Cancer Network (2004, 2009) provided updated decision trees for men with prostate cancer to aid in treatment selection. High risk of recurrence includes men with clinically advanced disease, both cT3a and cT3b-T4. Bone scans are indicated in these men, as well as in those with PSA greater than 20 ng/mL or Gleason score greater than or equal to 8; pelvic computed tomography (CT) or MRI is also indicated for cT3-T4 or if the calculated probability of lymph node involvement is greater than 20%. In general, radical prostatectomy with pelvic lymphadenectomy is reserved for those high-risk men with low-volume tumors that can be completely excised. The alternative treatment strategy for these men with locally advanced disease and higher risk of biochemical failure is AD therapy combined with RT. The shift in treatment is also reflected within the CaPSURE database (Meng et al, 2005). A total of 6074 men with prostate cancer (clinical stage lower than T3a,N0,M0) was stratified according to risk group, of whom 26% were high risk. Fewer men in this group underwent radical prostatectomy compared with the low-risk cohort, with older age, advanced disease, and increased number of comorbidities significant predictors of treatment (external beam radiation or AD therapy) in multivariate modeling. In addition, more than half of high-risk men receiving radiation therapy also received AD, significantly more than in the low- and intermediate-risk groups ($P < .0001$).

NATURAL HISTORY

Active surveillance, with deferred treatment when necessary, is becoming a viable treatment alternative in men with prostate cancer. Multiple studies have suggested that cancer-specific mortality is low and primarily associated with higher-grade and higher-stage disease. Even in those low-risk cancers, however, an increased and unexpected progression of disease and associated prostate cancer mortality may be seen during an extended period (Johansson et al, 2004). In men with higher-risk disease characteristics, it has been recognized that disease progression occurs more rapidly and that some form of intervention is typically warranted in healthy patients.

Few reports address the specific question of outcome in men with locally advanced cancers merely observed for a prolonged period. Older studies such as that from Nesbit and Plumb (1946) have little relevance to current disease management. Other studies have included only a small number of patients with higher clinical stage. A range of clinical progression (22% to 75%), local progression (22% to 84%), and development of distant metastases (27% to 56%) has been reported during 5 and 10 years of follow-up. **Overall survival is reported from 10% to 92% at 5 years and 14% to 78% at 10 years for patients who harbor cancers of high grade or stage.** The Veterans Administration Cooperative Urological Research Group (VACURG) study reported a 58% overall 5-year survival in 248 men with clinical stage III disease treated with placebo. Comparable survival outcomes were reported within the Medical Research Council study (Adib et al, 1997) randomizing previously untreated patients with locally advanced, nonmetastatic disease ($n = 501$) to early or delayed AD therapy (castration or luteinizing hormone-releasing hormone [LHRH] agonist). The median time to clinical progression and death from prostate cancer in the 244 patients receiving delayed treatment was 10 months and 48 months, respectively.

In the analysis from Chodak and colleagues (1994), grade 3 tumors were significantly associated with disease-specific mortality (risk ratio, 10.04) in men treated conservatively, compared with low-grade (grade 1) cancers. The 10-year disease-specific survival was 87% in men with grade 1 or grade 2 tumor and 34% with grade 3 tumor, with metastasis-free survival of 81% for grade 1, 58% for grade 2, and 25% for grade 3 diseases. Johansson and colleagues (1997) prospectively observed 642 men with prostate cancer diagnosed between 1977 and 1984, with any stage of disease. Of those with clinically localized disease, 11% of men died of prostate cancer with corrected 15-year survival comparable for those who received initial and deferred treatment. Conversely, the corrected 15-year survival was 57% in patients with locally advanced cancer. Approximately half of men had well-differentiated tumors, and only 6% of these men died of prostate cancer. Death from prostate cancer increased with moderately differentiated (17%) and poorly differentiated (56%) disease. These data are summarized in Table 107–3. Albertsen and colleagues (1998) reported the long-term outcomes of watchful waiting in 767 men identified from the Connecticut Tumor Registry with clinically localized prostate cancer (1971-1984). The 15-year cancer-specific mortality in men with Gleason sum 6 was 18% to 30%, compared with the 25% to 59% risk of death from other causes. The chances of death from prostate cancer increased with Gleason score 7 (42% to 70%) and 8 to 10 (60% to 87%). It is likely that a significant proportion

of this cohort had non–organ-confined disease because none of the men underwent PSA testing and therefore probably had more advanced stages of disease compared with contemporary cohorts. In contrast to the report from Johansson and colleagues (2004), the annual mortality rate from low-grade prostate cancer appears to remain stable beyond 15 years after diagnosis (Albertsen et al, 2005) (Fig. 107–4). **Men with high-risk prostate cancer including those with locally advanced disease are at significant risk of disease progression and cancer-specific death if left untreated.**

RADICAL PROSTATECTOMY

The use of radical prostatectomy for management of locally advanced prostate cancer has decreased. In part, the shift in paradigm is due to the recognition that prostatectomy alone is often insufficient. In addition, improved risk assessment has permitted better identification of these patients before treatment. Advances in delivery of RT and recognition that combined modality treatment (e.g., RT and AD) improved outcomes compared with monotherapy have further contributed to the migration away from surgery for high-risk and locally advanced tumors. Nevertheless, radical prostatectomy can cure some men with high-risk disease features, and the addition of adjuvant and combined therapy may further improve outcomes of surgery alone.

Table 107–3.

Conservative Management of Patients with Prostate Cancer

CLINICAL STAGE	NO. PATIENTS	Progression-Free Survival		Disease-Specific Survival	
		%	95% CI (%)	%	95% CI (%)
T1-T2	300	48	37-59	81	74-88
T3-T4	183	47	33-61	57	45-68
M+	159	6	0.8-11	6	–0.1-12

From Johansson JE, Holmberg L, Johansson S, et al. Fifteen-year survival in prostate cancer. A prospective, population-based study in Sweden. JAMA 1997;277:467–71.

Surgery for Clinical Stage T3 Prostate Cancer

Several series report outcomes of radical prostatectomy for clinical stage T3 tumors (Table 107–4). In examining all reports, **overall survival ranges from 64% to 96% at 5 years, 12.5% to 72% at 10 years, and 20% to 51% at 15 years after treatment.** Earlier data reflected less accurate risk assessment and a potentially greater number of patients with unsuspected lymph node metastases and associated earlier progression and death. Less variability exists in more contemporary cohorts, in which the **cancer-specific survival rates are 85% to 92% and 79% to 82% at 5 and 10 years, respectively, regardless of adjuvant therapy.**

Pound and colleagues (1999) found that a reasonable outcome was possible after prostatectomy for clinical stage T3a disease, with a 52% 8-year, recurrence-free survival. Similarly, Ward and Zincke (2003) reported 5- and 10-year cancer-free survival of 60% and 44%, respectively, without application of adjuvant AD. Freedom from local or systemic disease at 5 and 15 years after surgery was 73% and 67%, respectively (Ward et al, 2005). In the 812 patients from the series of Lerner and colleagues (1995), 10-year cancer-specific survival was 80%, with only 31% of men with clinical stage T3 disease dying of prostate cancer 15 years after radical prostatectomy. It is unclear, however, whether surgical intervention improves survival compared with alternative treatment strategies. Another interesting observation from the Mayo Clinic was

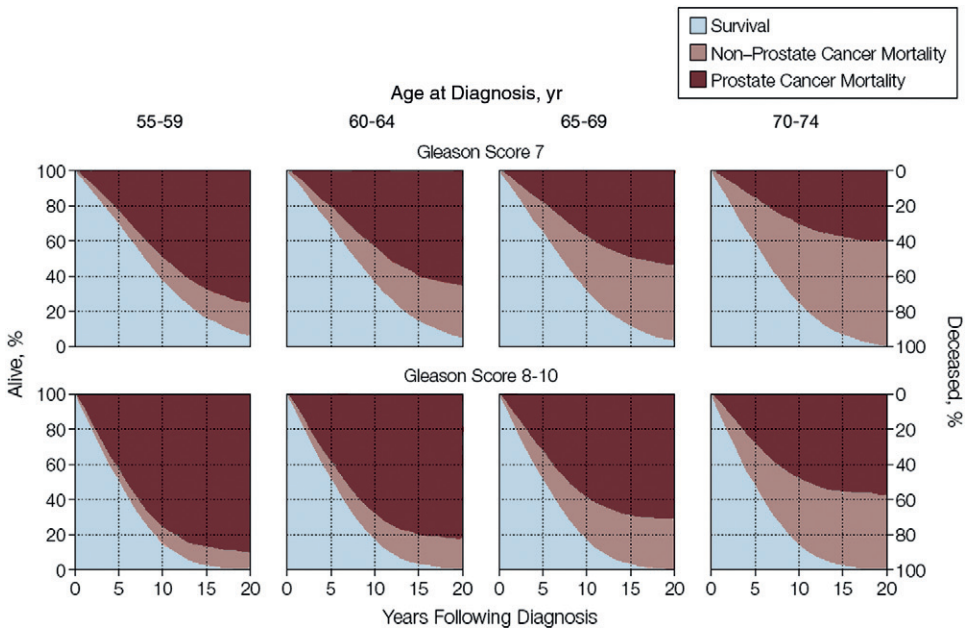


Figure 107–4. Prostate cancer mortality as a factor of Gleason grade and age at diagnosis in men managed conservatively. *Brown-shaded areas* represent proportion of patients dying of prostate cancer. *Light brown-shaded areas* represent death from competing causes. *Light-blue areas* represent proportion of patients alive. (Modified from Albertsen PC, Hanley JA, Fine J: 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA 2005;293:2095–101.)

Table 107–4.

Radical Prostatectomy for Higher Clinical Stage in Contemporary Series

AUTHOR (YR)	NO. PATIENTS	ADJUVANT TREATMENT	Overall Survival		Cancer-Specific Survival	
			5 Yr	10 Yr (15 Yr)	5 Yr	10 Yr (15 Yr)
Morgan et al (1991)	232	54%	85%	72%	89%	82%
van den Ouden et al (1994)	59	—	83%	—	90%	—
Lerner et al (1995)	812	60%	86%	70%	90%	80%
Gerber et al (1997)	242	NR	—	—	88%	70%
van den Ouden et al (1998)	83	0%	75%	60%	85%	72%
Pound et al (1999)*	55	0%	—	—	60%†	49%†
Ward et al (2005)	842	62%	90%	76% (53%)	95%	90% (79%)
Carver et al (2006)	176	36%‡	88%	75% (69%)	94%	85% (76%)
Loeb et al (2007)	288	15%	91%°	74%	92%§	88%
Freedland et al (2007)	56	0%	—	—	98%	91% (84%)
Xylinas et al (2009)	100	25%	85%	—	90%	—

*Updated data from Han M, Partin AW, Pound CR, et al. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. Urol Clin North Am 2001;28:555–565.
†Biochemical-free survival (PSA < 0.2 ng/mL); 15-year actuarial metastasis-free survival of 82% in *entire* cohort.
‡Neoadjuvant therapy.
§7-year figures.

that clinical *overstaging* was identified in 27% of patients, consistent with other reported rates of 7% to 26%, suggesting that uniformly excluding patients from prostatectomy on the basis of clinical staging may not be appropriate (Ward et al, 2005). Gerber and colleagues (1997) reviewed results in 298 men with clinical stage T3 disease undergoing radical prostatectomy and pelvic lymphadenectomy. Although the overall 10-year cancer-specific survival was 57%, an apparent benefit of radical prostatectomy in some men with locally advanced disease was suggested by the increased survival (70%) in those who actually underwent prostatectomy and lymph node dissection. **Many men with clinical stage T3 disease have regional spread and may not benefit from prostatectomy; however, select patients (e.g., lower-volume disease) may benefit because local control may be achieved in most, and complete cancer excision is possible in some men.**

Biochemical progression after radical prostatectomy is difficult to assess, given the frequent use of adjuvant therapy (e.g., RT or AD). Without the use of secondary treatment, 5-year biochemical relapse is higher than 60% (van den Ouden et al, 1998). In other series with variable use of adjuvant therapy, 5- and 10-year biochemical progression was observed in 42% to 49% and 59% to 62%, respectively. The impact of adjuvant therapy may be minimal with respect to clinical progression (i.e., biopsy-proven local recurrence or objective distant metastasis) after radical prostatectomy. Rates of clinical progression at 5, 10, and 15 years are 12% to 45%, 39% to 49%, and 50% to 71%, respectively.

Outcomes of Prostatectomy for Pathologically Advanced Disease

A significant minority of patients undergoing radical prostatectomy for clinically organ-confined disease will ultimately be found to have *pathologic* evidence of spread outside the prostate. Although these patients may be expected to have progression and survival rates comparable with those of patients with clinically advanced disease, as defined by grade and serum PSA level, those men who present with clinical stage T3 disease are likely to have greater tumor volume, higher grade, and increased likelihood of regional spread. Currently, the majority of men undergoing prostatectomy for pathologically advanced disease are categorized as high risk on the basis of serum PSA value or biopsy Gleason score. Nevertheless, there is overlap in the groups of men undergoing radical prostatectomy for *clinical* stage T3 and *pathologic* stage T3.

As discussed, pathologic stage after radical prostatectomy provides important prognostic information and is a powerful predictor of outcome, considering all clinical and pathologic factors (Fig. 107–5). **The presence of focal and established extracapsular extension increases the rate of clinical progression from 7% for organ-confined disease to 18% and 35%, respectively, at 5 years.** Patients with evidence of seminal vesicle invasion or lymph node metastasis are highly likely to develop clinical progression (86% and 95%, respectively) after radical prostatectomy. In men undergoing radical prostatectomy for clinically organ-confined disease, Hull and colleagues (2002) reported 5-year PSA-free survival of 95%, 76%, 37%, and 18% for men with pathologic organ-confined disease, extracapsular extension, seminal vesicle invasion, and positive lymph nodes, respectively. In multivariate analysis, pathologic parameters increasing the relative risk (RR) for progression included extracapsular extension (RR, 2.17 to 2.72), seminal vesicle involvement (RR, 2.61), and lymph node involvement (RR, 3.31). The presence of a positive surgical margin was associated with the greatest relative risk (4.37; range, 2.90 to 6.58). This reinforces the concept that complete surgical removal of all prostatic tissue, regardless of clinical or pathologic stage, should be accomplished when prostatectomy is undertaken. Even with seminal vesicle invasion, however, men without concomitant lymph node involvement can achieve 15-year cancer-specific survival and biochemical relapse-free rates of 81% and 32%, respectively (Secin et al, 2006).

Biochemical progression after prostatectomy for pathologically advanced tumors depends on the definition applied. Five-year rates of biochemical recurrence have been as high as 65% to 72% when a PSA threshold of 0.2 ng/mL is used; less stringent thresholds such as 0.4 ng/mL may yield recurrence rates of 26% at 5 years and at least 50% at 10 years. Seminal vesicle involvement not only increases the risk of biochemical recurrence but also

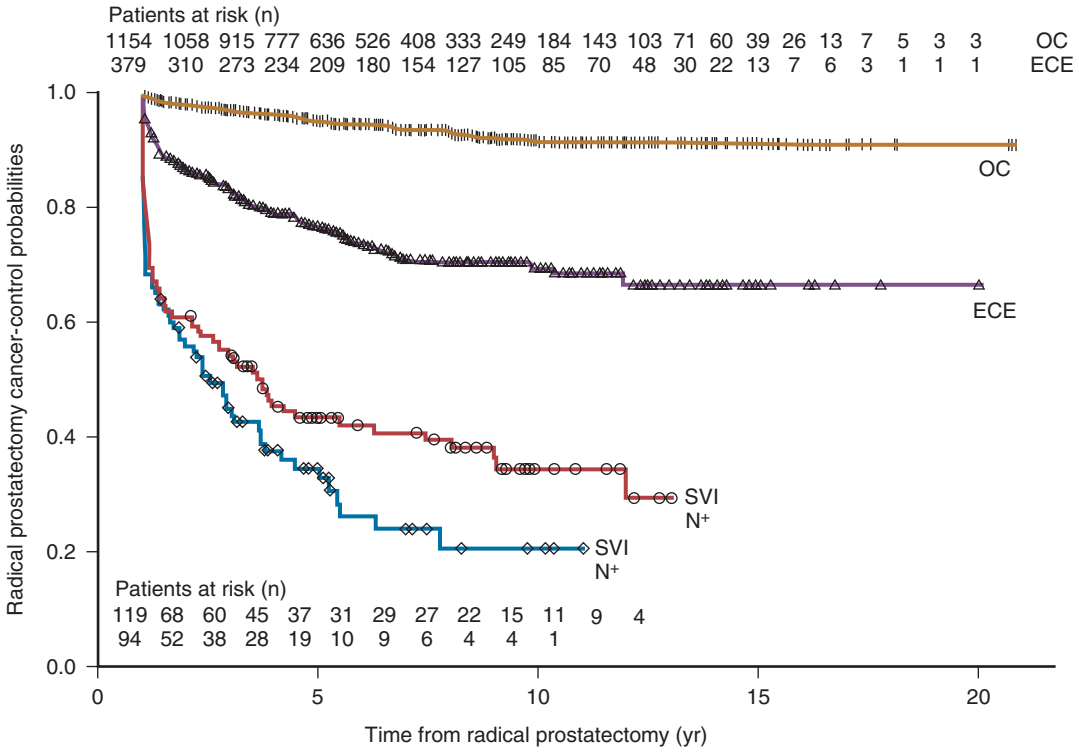


Figure 107–5. Probabilities of cancer control after radical prostatectomy based on pathologic stage. ECE, extracapsular extension; OC, organ confined; SVI, seminal vesicle invasion. (Modified from Bianco FJ Jr, Scardino PT, Eastham JA. Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ("trifecta"). Urology 2005;66:83–94.)

significantly increases the risk of local recurrence after radical prostatectomy. With prolonged follow-up, Hawkins and colleagues (1995) reported local recurrence in nearly half of patients. This risk appears to be lower in contemporary series of patients because of improved selection of patients for surgery, improved surgical technique, and earlier use of secondary treatment either as adjuvant therapy or at the time of biochemical relapse.

Predictive models have permitted preoperative estimation of PSA-free survival after prostatectomy. Patients with higher biopsy Gleason score and more elevated serum PSA level are at increased risk of failure after surgery. **Overall, the actuarial PSA-free survival after surgery in high-risk men is approximately 50% at 5 to 7 years.** The validity of the Kattan preoperative nomogram was examined in a community-based cohort of patients undergoing radical prostatectomy (Greene et al, 2004). Interestingly, although the overall concordance index (.68) supported the applicability of the tool to a broad spectrum of patients, the nomogram underestimated recurrence in lower-risk men and overestimated recurrence in men at higher calculated risk. Indeed, up to half of men with Gleason sum 8 to 10 or higher PSA level (>20 ng/mL) may achieve prolonged disease-free survival with prostatectomy alone. Further refinements of risk assessment and novel markers will help determine which high-risk men and locally advanced tumors truly benefit from aggressive surgical intervention, either alone or in combination with other therapy.

Table 107–5.

Prospective Randomized Trials of Neoadjuvant Androgen Deprivation in Patients with Prostate Cancer (Stage cT1-T3) before Radical Prostatectomy

REFERENCE (yr)	LHRH AGONIST	ANTIANDROGEN	DURATION (mo)
Labrie et al (1997)	Leuprolide	Flutamide	3
Witjes et al (1997)*	Goserelin	Flutamide	3
Soloway et al (1995)†	Leuprolide	Flutamide	3
Hugosson et al (1996)‡	Triptorelin	Cyproterone	3
Dalkin et al (1996)	Goserelin		3
Goldenberg et al (1996)§		Cyproterone	3
Van Poppel et al (1995)		Estramustine	1.5

Follow-up reports:
*Schulman et al (2000).
†Soloway et al (2002).
‡Aus et al (1998).
§Klotz et al (1999).
LHRH, luteinizing hormone-releasing hormone.

Neoadjuvant Androgen Deprivation

To improve outcomes of radical prostatectomy in men with locally advanced or high-risk tumors, several investigators have assessed the use of neoadjuvant AD (NAD) before radical prostatectomy. In 1944 Vallet reported performing radical perineal prostatectomy after orchiectomy in a 59-year-old man with prostate cancer. Others reported the use and efficacy of diethylstilbestrol (DES) before surgery. In 1964 Scott evaluated the results of NAD in 31 men who were observed for 10 years. The majority of patients (52%) were alive and free of clinical recurrence. The prospective randomized trials of NAD in patients with stage cT1-T3 prostate cancer before radical prostatectomy are summarized in Table 107–5.

Key Points: Radical Prostatectomy

- Radical prostatectomy alone can result in cancer-free survival in at least half of men at 8 to 10 years despite clinically advanced disease.
- The risk of cancer recurrence after surgery can be quantitated on the basis of pathologic stage, cancer grade, and surgical margin status.
- Neoadjuvant androgen deprivation therapy before radical prostatectomy does not appear to improve cancer-specific or overall survival.

Various measures of outcome have been evaluated in these studies including changes in digital rectal examination (clinical stage), appearance of tumor on imaging, detection of micrometastatic or circulating cancer cells, and pathologic features such as T stage, surgical margin and lymph node status, and histopathologic changes. Ultimately, the utility of AD must be assessed by its impact on disease-specific survival or its current surrogate, biochemical-free survival. It is clear that NAD affects tumor behavior and biology, evaluable by changes in metabolic patterns of atrophy on MRS, lowering of serum PSA level, and histologic atrophy (fibrosis, vacuolization, glandular collapse). Studies have demonstrated that significant reductions in prostate volume (30% to 50%), tumor volume, and PSA level (90%) are consistently noted, with maximal effects occurring during the first 2 months of treatment. However, conflicting results have been reported with respect to pathologic downstaging after NAD in patients with clinical stage T3 cancer. **Overall, only 20% of such patients have organ-confined disease at the time of radical prostatectomy despite clinical downstaging in 32% to 90%.** Schulman and colleagues (2000) described 402 patients with cT2-T3N0M0 tumors randomized to either radical prostatectomy alone or 3 months of total androgen blockade followed by surgery. Pathologic downstaging was seen more frequently in the neoadjuvant group (15%) than in the prostatectomy-alone group (7%; $P < .01$); however, in men with cT3 disease, there was no difference in pathologic downstaging ($P = .18$) and the incidence of lymph node metastases ($P = .36$) in the neoadjuvant and surgery-alone cohorts. Thus whereas clinical downstaging may occur frequently, **pathologic downstaging is significantly less common after NAD, ranging between 8% and 31%.** Most studies do not show decreased seminal vesicle invasion (Table 107–6). Similarly, rates of lymph node metastases are not altered, with the incidence varying between 3.3% and 16% in both the prostatectomy-alone and NAD groups.

Klotz and colleagues (2003) provided long-term follow-up (median, 6 years) of a prospective randomized trial comparing 3 months of NAD before prostatectomy and surgery alone. There was no overall benefit of NAD as measured by biochemical recurrence (34% to 38%), although in the subgroup of men with PSA level above 20 ng/mL, those receiving NAD had greater PSA-free survival (53%) compared with those undergoing prostatectomy alone (35%; $P = .015$). The Southwest Oncology Group (SWOG) Study 9109 was a phase II feasibility study of 16 weeks of goserelin and flutamide before radical prostatectomy in men with T3-T4N0M0 prostate cancer (Powell et al, 2002). Of the 55 patients who underwent prostatectomy, 31% had seminal vesicle invasion and 19% had lymph node metastasis. Organ-confined disease was identified in 67% of cases. At median follow-up of 6.1 years, 5-year progression-free and overall survival estimates were 70% and 90%, respectively. The study demonstrated the feasibility of 4 months of AD before surgery, with acceptable morbidity, and outcomes comparable with RT for this population of patients.

Table 107–6.

Pathologic Findings from Studies of Neoadjuvant Androgen Deprivation (NAD) in Patients with cT1-T3 Prostate Cancer before Radical Prostatectomy

AUTHOR (yr)	NO. PATIENTS	Seminal Vesicle		Lymph Node	
		CONTROL	NAD	CONTROL	NAD
Vailancourt et al (1996)	96	6%	0%		NR
Soloway et al (1995)	282	22%	15%	5.8%	6.3%
Dalkin et al (1996)	56	14%	18%		NR
Aus et al (1998)	122	14.5%	21.8%	16%	5.5%
Meyer et al (1999)	680	16%	17%	16%	14%
Klotz et al (1999)	213	14%	28%*	6.9%	3.3%
Schulman et al (2000)	402	23%	20%	23%	15.%

*$P = .035$.
NR, not reported.

Studies have also examined the incidence of positive surgical margins in those with cT3 disease. Witjes and colleagues (1997) reported similar rates of positive margins in men receiving NAD and those undergoing radical prostatectomy alone (43% and 59%, respectively; $P = .14$). Van Poppel and colleagues (1995) did not find a statistically significant difference between these groups with respect to positive margins—41.3% in the neoadjuvant cohort and 44% in the surgery-alone group. SWOG 9109 reported positive surgical margins in 30% of patients. In contrast, the randomized and nonrandomized studies of NAD in men with lower clinical stage (cT1-T2) clearly demonstrate a reduction in the rate of positive surgical margins. This advantage has not translated into improved long-term PSA-free survival. **For locally advanced tumors (specifically cT3), current data, both retrospective and prospective, do not support a significant benefit of neoadjuvant androgen deprivation before surgery** (Table 107–7).

The apparent lack of benefit of NAD before radical prostatectomy, in men with both lower-stage and locally advanced prostate cancer, may be due to a number of factors. It has been suggested that 3 months of AD may be insufficient to cause an improvement in disease-free survival compared with prostatectomy alone. Meyer and colleagues (1999) followed 680 men treated with radical prostatectomy, of whom 292 received NAD. Although there was no difference in risk of biochemical recurrence between the two groups, patients receiving both LHRH agonist and antiandrogen for more than 3 months had a significantly lower risk of PSA failure than did those treated with surgery alone (hazard rate [HR], 0.52; 95% confidence interval [CI], 0.29 to 0.93). Subsequently, the Canadian Urologic Oncology Group (Gleave et al, 2001) randomized patients with clinically localized disease to either 3 or 8

months of NAD before radical prostatectomy. In the 500 patients with pathologic staging, positive surgical margins were identified in 23% of the 3-month group and 12% of the 8-month group (P = .011); organ-confined disease was found in 68% and 80% of the 3- and 8-month groups, respectively (P = .0019). In addition, the rate of non–specimen-confined or lymph node extension was greater in the 3-month group (25.6%) compared with the 8-month group (12.6%). However, despite evidence of continued biochemical and pathologic regression of the tumor between 3 and 8 months, no significant difference in PSA recurrence rates was observed at 4 years.

Neoadjuvant Chemotherapy and Chemotherapy-Hormone Therapy

The role of chemotherapy in the treatment of prostate cancer has primarily been limited to men with the most advanced disease. Taxanes, alone or in combination with other agents, have proved effective in those with hormone-refractory prostate cancer, with significant PSA declines (>50%) in more than half of patients and measurable disease response in 28% to 75% (Oh, 2004). Mitoxantrone plus low-dose steroids has shown benefit in pain relief compared with steroids alone and is approved for use in hormone-refractory disease (Tannock et al, 1996; Kantoff et al, 1999). On the basis of these observations, interest has increased in earlier use of chemotherapy in high-risk patients or those with locally advanced disease. These studies are summarized in Table 107–8.

Pettaway and colleagues (2000) treated 33 higher-risk patients with a 3-month combination regimen consisting of two 6-week cycles of ketoconazole and doxorubicin alternating with vinblastine and estramustine. In addition, concurrent AD was accomplished with an LHRH agonist and antiandrogen. Lower pathologic stage was found in 18% of patients with cT3 disease, and the overall positive surgical margin rate of only 17% suggests that the regimen may have improved the ability to resect the cancer above that achieved with NAD alone. A second report of chemotherapy and hormone therapy before surgery combined 4 to 6 months of NAD with paclitaxel, estramustine, and carboplatin in patients with androgen-dependent, high-risk prostate cancer (Konety et al, 2004). No patients were downstaged to pT0 after neoadjuvant therapy, and organ-confined disease was reported in 36%, with a 22% positive surgical margin rate. Overall, 45% remain without biochemical relapse, defined as PSA level above 0.05 ng/mL on three occasions, at median follow-up of 29 months, and no patient has had documented local recurrence. At 43 months follow-up, Chi and colleagues (2008) reported a 3% complete pathologic response rate and distant relapse rate of 30% in patients treated with NAD and docetaxel.

Other centers have used chemotherapy without concurrent NAD. At the Cleveland Clinic, 16 patients with locally advanced disease (clinical M0) underwent three cycles of oral estramustine and etoposide and subsequent surgery (Clark et al, 2001). Although grade 3 or grade 4 toxicity was seen in 34% of patients, surgery was not delayed in any individual and surgical outcomes were comparable with those in series of prostatectomy without

Table 107–7.

Neoadjuvant Androgen Deprivation (NAD) Therapy for 3 Months before Radical Prostatectomy in Patients with Localized Prostate Cancer: Impact on PSA Recurrence after Surgery

AUTHOR (yr)	NO. OF PATIENTS	CONTROL	NAD	FOLLOW-UP (mo)
Fair et al (1997)	194	16%	11%	29
Aus et al (1998)	122	41%	35%	38
Meyer et al (1999)	680	30%	35%	38
Klotz et al (1999)	213	30%	40%	36
Schulman et al (2000)	398	32.5%	26.4%	48
Soloway et al (2002)	255	32%	35%	60

PSA, prostate-specific antigen.

Table 107–8.

Trials of Chemotherapy, Hormonal Therapy, and Combined Chemo-Hormonal Therapy before Radical Prostatectomy

	PETTAWAY ET AL (2000)	CLARK ET AL (2001)	KONETY ET AL (2004)	MAGI-GALLUZZI ET AL (2007)	CHI ET AL (2008)	NAD*
Number of patients	33	16	36	28	64	—
Clinical stage T3	55%	13%	75%	18%	39%	100%
Regimen	KAVE	E/VP-16	TEC	D	D	—
Androgen deprivation	3 mo	—	4-6 mo	—	6 mo	—
Organ confined	33%	31%	36%	18%	53%	21%
Positive margins	17%	44%	22%	25%	27%	37%
Positive lymph nodes	37%	13%	5.50%	14%	6%	21%
Seminal vesicle invasion	85%	—†	56%	39%	22%	39%
Undetectable preoperative PSA	50%	50%	45%	—	—‡	—
pT0	0%	0%	0%	0%	3%	0-4%

*Combined results of 23 trials of neoadjuvant hormonal therapy in cT3 disease.
†Grouped together with positive lymph nodes.
‡Median PSA 0.15 ng/mL (range 0.02-3.8).
D, docetaxel; E/VP-16, estramustime + etoposide; KAVE, ketoconazole + doxorubicin/vinblastine + estramustine; NAD, neoadjuvant androgen deprivation; TEC, paclitaxel + estramustine + carboplatin.

Table 107–9.

Early Adjuvant Radiation Therapy for Locally Advanced Prostate Cancer (pT3 N0 M0)

AUTHOR (yr)	NO. OF PATIENTS	RADIATION DOSE (GY)	PROGRESSION-FREE SURVIVAL	*P* VALUE	FOLLOW-UP (mo)
Morgan et al (1991)	33	—	64%	.02	11
	17	60-66	94%		
Stein et al (1992)	91	—	43%	.04	48
	24	55-60	75%		
Anscher et al (1995)	113	—	37%	.16	120
	46	55-65	55%		
Schild (1998)	228	—	40%	.0003	32
	60	57-68	90%		
Valicenti et al (1998a)	20	—	48%	.01	36
	15	64.8	85%		
Valicenti et al (1999)	36	—	55%	—	41
	36	59-70	88%		
Petrovich et al (1999)	40	—	69%	NS	60
	201	48	68%		
Eggener et al (2005)	144	—	53%/37%*	.4/.9*	48
	58	NR	62%/38%*		
Thompson et al (2009)	211	—	61%†	.016	151
	214	60-64	71%†		

*Negative surgical margin/positive surgical margin.
†Metastasis-free survival at 10 years.

neoadjuvant therapy. With a median follow-up of 14 months, 88% were free of disease and the early PSA failures occurred in the two patients with lymph node metastases.

Single-agent docetaxel is well tolerated before radical prostatectomy, with minimal toxicity (Oh et al, 2001; Dreicer et al, 2004). No cases of complete pathologic response were observed, but no lymph node metastases were identified in one series, whereas the other reported 11% with organ-confined disease. Two thirds and 24% of patients, respectively, experienced a more than 50% reduction in PSA level in response to docetaxel alone. Similar observations have been made using a novel nanoparticle-based formulation of paclitaxel, with no complete pathologic responses (Shepard et al, 2009). Combination therapy with mitoxantrone or estramustine has been reported in small numbers, and the use of chemotherapy or novel therapy with surgery requires additional study. Agents described in recent reports include granulocyte macrophage colony-stimulating factor and thalidomide (Garcia et al, 2008), as well as the epidermal growth factor receptor inhibitor gefitinib (Vuky et al, 2009).

Adjuvant Radiation Therapy

Withholding regional or systemic therapy until after the prostate has been removed may (1) prevent delay in time to surgery, (2) reduce operative morbidity, and most importantly (3) identify those men with adverse pathologic features or evidence of residual disease who truly need additional therapy, thereby avoiding overtreatment in those found to have more favorable disease. The selection of appropriate adjuvant therapy remains difficult because knowledge of the ultimate site of failure (discriminating local-regional from distant recurrence) determines the actual type, timing, and efficacy of such intervention.

Until recently, adjuvant RT was not clearly demonstrated to be beneficial after radical prostatectomy; older studies demonstrated no impact on development of distant metastasis or cancer-specific survival, and more recent data show improved biochemical control. Table 107–9 summarizes selected comparative series of adjuvant RT for pathologically advanced disease. In the matched pair analysis of Valicenti and colleagues (1999), early adjuvant RT was administered within 3 to 6 months of surgery with undetectable PSA; control subjects were observed until PSA recurrence. The reduction in risk of PSA relapse was 88% after adjuvant RT with 5-year PSA-free survival of 89%. Anscher and colleagues (1995) provided long-term follow-up (median, 10 years) in 46 patients receiving adjuvant RT after radical prostatectomy for pT3-T4. At 10 and 15 years, overall survival and disease-free survival in the RT groups were 62% and 62% and 55% and 48%, respectively; these were not statistically different from the rates in the group not receiving adjuvant RT. In addition, development of distant metastases was comparable in the two cohorts. Nevertheless, local control was better after adjuvant RT (82% at 15 years) compared with surgery alone (53%).

The use of adjuvant RT is associated with a range of biochemical-free survival, from 50% to 88% at 5 years. This appears to be an improvement (30% to 50%) compared with the results of surgery alone in high-risk patients. Nevertheless, the benefit of adjuvant RT needed to be proven in appropriately designed clinical trials, of which the European Organization for Research in the Treatment of Cancer (EORTC) 22911 (Bolla et al, 2005) and SWOG 8794 (Thompson et al, 2006) have recently been reported. Both studies randomized patients with pathologically advanced disease, defined as extraprostatic extension (pT3) and/or positive surgical margins without lymph node metastasis, to either immediate RT or observation after surgery. In EORTC 22911, immediate RT was associated with improved biochemical relapse-free survival (74% vs. 53% without RT, $P < .001$) at 5 years. Similarly, SWOG 8794, with 10.6 years median follow-up, supported immediate RT with a nearly 50% reduction in biochemical recurrence (35% vs. 64% without RT, $P < .001$) in those with PSA less than 0.4 ng/mL after prostatectomy In addition, adjuvant RT significantly reduced the risk of clinical local recurrence in both trials. SWOG 8794 demonstrated a surprisingly low risk of metastatic disease (16%) in patients with adverse pathologic features that was further reduced with adjuvant RT (7%) (Swanson et al,

2007), as well as improved freedom from subsequent AD. Moreover, both metastasis-free and overall survival were improved with adjuvant RT (HR, 0.71 and 0.72, respectively) (Thompson et al, 2009).

The decision to administer adjuvant RT is often based on various adverse pathologic features, not all of which carry the same prognosis; indeed, SWOG 8794 combined extracapsular extension, seminal vesicle invasion, and positive surgical margin within a single classification. Thus it is difficult to assess the outcomes of adjuvant RT when the populations are composed, variably, of those with positive surgical margins, extracapsular extension, seminal vesicle invasion, or a combination of these features. Those men with positive surgical margins are at an increased risk of biochemical recurrence. A decision analytic model examining this question demonstrated that the benefit may be limited to those with high likelihood of recurrent local, rather than distant, disease; thus initial RT was recommended for patients with low- to intermediate-grade disease without evidence of seminal vesicle invasion (Grossfeld et al, 2000). This report suggested that adjuvant RT should be considered in those with extensive or multiple positive surgical margins. Secondary analyses of EORTC 22911 also support the role of immediate RT in the specific subset with positive surgical margin (Van der Kwast et al, 2007). The treatment benefit of adjuvant RT was primarily seen in patients with positive surgical margins (HR, 0.38, $P < .0001$), whereas no benefit was observed in those with negative margins independent of other risk factors. However, the report from Stephenson and colleagues (2004) suggests that the application of adjuvant RT in a broader group of men may be beneficial; 501 men received salvage RT for biochemical recurrence after radical prostatectomy, and 50% experienced disease progression after treatment at a median follow-up of 45 months. Although higher Gleason score and seminal vesicle invasion were poor prognostic variables in predicting response to salvage RT, selected patients with high-grade disease or other adverse features (e.g., rapid PSA doubling time) could still achieve a durable response. Indeed, more than half of patients with Gleason sum 8 to 10 and positive surgical margins had a PSA nadir of 0.1 ng/mL or less without subsequent rise above this level. **Thus early use of secondary therapy, be it RT or AD, may be beneficial in locally advanced tumors, as well as at the time of biochemical recurrence in select patients.** However, the optimal timing and how these interventions may differentially affect local control, development of distant disease, and survival remains to be determined. Trock and colleagues (2008) reported an improvement in overall survival in patients with pT3 receiving salvage RT, with 5-year overall survival of 98%.

In general, men with seminal vesicle invasion are at significant risk for distant metastasis and may not benefit from local or regional RT; nevertheless, some men with pT3b may have local recurrence alone. Valicenti and colleagues (1998a) identified a group of 53 men undergoing radical prostatectomy with pT3b N0 disease, with 35 achieving undetectable PSA after surgery. The biochemical-free survival (3 years) in the 15 patients receiving adjuvant RT was 86% compared with 48% in the 20 men who were observed ($P = .01$). In EORTC 22911, there was no statistically significant predictive impact of seminal vesicle invasion on the benefit from RT as measured by biochemical progression-free survival, regardless of whether PSA was less than or greater than 0.2 ng/mL after surgery (Van der Kwast et al, 2007). However, even with pT3b disease, there was a benefit of adjuvant RT in patients with positive surgical margins. Men in SWOG 8794 with seminal vesicle invasion receiving RT had improved 10-year biochemical failure-free survival (36% vs. 12% for observation) but no significant improvement in metastasis-free and overall survival. **On the basis of limited data, it appears that men with seminal vesicle invasion who achieve a low PSA level (<0.3 ng/mL) after prostatectomy or have positive surgical margins may be a more favorable group in whom adjuvant RT may be considered. Conversely, those men with more advanced disease never reaching an undetectable PSA level generally constitute a poor prognostic group likely harboring unrecognized lymph node or distant disease.**

Traditionally, adjuvant RT has been delivered in lower doses compared with the dose for salvage therapy, with the range from 45 Gy to more than 60 Gy. Most contemporary series of adjuvant RT report doses greater than 60 Gy. Valicenti and colleagues (1998b) evaluated the dose response in a small number of patients ($n = 52$) receiving adjuvant RT for pT3 N0 disease. The difference in 3-year biochemical-free survival between those treated with less than 61.2 Gy (64%) and more than 61.2 Gy (90%) was statistically significant ($P = .015$), suggesting that higher doses may be necessary. In 27 men with detectable PSA 6 months after prostatectomy, Schild and colleagues (1994) noted that RT doses of 64 Gy or more had improved 30-month freedom from failure (62%) compared with lower RT doses (17%; $P = .03$), supporting the hypothesis of a postoperative RT dose response similar to what has been observed for primary RT in prostate cancer.

Key Points: Adjuvant Radiation Therapy

- Adjuvant radiation therapy improves local control and reduces biochemical relapse in selected patients after radical prostatectomy and likely improves metastasis-free and overall survival.
- The benefit of adjuvant radiation therapy may be greatest in cases of positive surgical margins.
- Improved outcomes of adjuvant radiation therapy are associated with dose escalation.

Adjuvant Androgen Deprivation

Indirect evidence from the Medical Research Council and VACURG trials suggesting a benefit of early AD compared with delayed AD, in men with various stages of prostate cancer, served as the impetus for studying adjuvant AD after radical prostatectomy. In addition, evidence of a benefit of continued AD after therapeutic RT supports a potential role for combined systemic treatment after local therapy in the form of prostatectomy. However, limited clinical data are currently published on this issue in men with locally advanced tumors.

Beyer and colleagues (1993) retrospectively reviewed the outcomes of 86 patients undergoing radical prostatectomy and any form of adjuvant therapy (89% endocrine treatment). In the subset of patients with stage pT3N0 tumors, adjuvant treatment did not demonstrate an advantage with respect to time to progression or survival. Cheng and colleagues (1993) reviewed the Mayo Clinic experience with 1035 patients undergoing radical prostatectomy for pathologic stage C prostate cancer; a significant number ($n = 103$) received adjuvant AD with orchiectomy. Adjuvant therapy of any type (AD or RT) decreased the rate of progression but did not improve cancer-specific or overall survival, with no difference between the two modalities. Prayer-Galetti and

Table 107–10.

Trials of Androgen Deprivation with External Beam Radiation Therapy

STUDY (AUTHOR, YEAR)	NO. PATIENTS	ELIGIBILITY	RT DOSE (Gy)	STUDY ARM	DISEASE-FREE SURVIVAL	OVERALL SURVIVAL	MEDIAN FOLLOW-UP
Neoadjuvant							
RTOG 86-10 (Pilepich et al, 2001)*	471	cT2-4, ≥25 cm^2	44-46 WP 65-70 p	RT RT + nAD + cAD	3%† 11%†	34%‡ 43%‡	12.5 yr
Canadian trial (Laverdiere et al, 1997)	120	cT2b-4	64 p	RT RT + nAD RT + n/c/aAD (6 mo)	22% 72% 90%	NR NR NR	24 mo
Canadian trial (Crook et al, 2009)	378		66-67 p	RT + nAD (3 mo) RT + nAD (8 mo)	58% 65%	81% 79%	6.6 yr
Adjuvant							
RTOG 85-31 (Pilepich et al, 2003)	977	cT3, pT3 or N1	44-46 WP 65-70 p	RT RT + aAD (∞)	8% 32%	38% 53%	7.3 yr
EORTC 22863 (Bolla et al, 2002)	412	T1-2 + grade 3, T3-4	50 WP 70 p	RT RT + aAD (3 yr)	40% 74%	62%§ 78%§	66 mo
Swedish trial (Granfors et al, 1998)	91	T1-4, pN0-3, M0	50 WP 65 p	RT RT + orchiectomy	39% 69%	38%† 61%†	9.3 yr
RTOG 92-02 (Hanks et al, 2003)	1514	T2c-4 + PSA <150	44-50 WP 65-70 p	RT + n/cAD RT + n/c/aAD (2 yr)	28% 46%	79% 80%	5.8 yr
RTOG 94-13 (Roach et al, 2003)‖	1292	PSA <100 + >15% risk of nodes	50.4 WP 70.2 p	n/cAD + WP n/cAD + pRT WP + aAD (4 mo) pRT + aAD (4 mo)	38% 34% 31% 38%	67% 69% 59%‖ 68%	84 mo

*Updated data from Roach et al (2008).
†P = .02.
‡P = .12, different only for Gleason 2-6.
§P = .0002.
‖Updated data from Lawton et al (2007); lower survival with WP + aAD (P = .027).
aAD, adjuvant androgen deprivation; cAD, concurrent androgen deprivation; nAD, neoadjuvant androgen deprivation; p, prostate; RT, radiation therapy; WP, whole pelvis.

colleagues (2000) presented data of 201 men with pT3 disease receiving adjuvant goserelin, demonstrating a 25.4% improvement in disease-free survival at median follow-up of 5 years (P < .05).

Recent publications provide some evidence supporting a benefit of early AD after radical prostatectomy in high-risk men with locoregional disease spread. Zincke and colleagues (2001) retrospectively reviewed data of men with stage pT3b cancer and found that early, adjuvant AD positively affected time to progression and cancer-specific survival. These findings were true not only with seminal vesicle invasion but also with limited lymph node disease, with a 10-year cause-specific survival of 94% after prostatectomy and adjuvant AD with a single positive lymph node. Similar findings arose from the Eastern Cooperative Oncology Group (ECOG 7887) study randomizing men with nodal metastases after radical prostatectomy (cT1-T2) to immediate (adjuvant) or delayed AD (Messing et al, 1999). At a median follow-up of 11.9 years, men receiving adjuvant AD had improved overall (HR, 1.84), cancer-specific (HR, 4.09), and progression-free survival (HR, 3.42).

RADIATION THERAPY

The contemporary trend is to treat high-risk or locally advanced prostate tumors with methods other than surgery. Although a plethora of studies describe the results of RT for clinical stage C and T3 disease, many were performed before the widespread use of serum PSA determinations for early detection and modern radiation techniques for treatment such as three-dimensional conformal RT, intensity-modulated RT, and irradiation of the whole pelvis in addition to the prostate (Kupelian et al, 2003). In addition, contemporary data suggest that the optimal radiation dose is higher than that used in previous reports. In the treatment of men with locally advanced or high-risk prostate tumors, monotherapy with RT or permanent interstitial brachytherapy is likely to be inadequate. Yet it must be emphasized that the outcome measures with demonstrated benefit of AD and RT compared with RT alone often do not include overall survival. The focus has shifted to improving outcomes by combining RT with AD, often in conjunction with whole-pelvis irradiation (Table 107–10).

Overall survival after RT alone for stage C cancer is approximately 60% to 70% at 5 years and below 50% at 10 years. In high-risk patients, defined by individual parameters alone or in combination, the 5-year progression-free survival rates after RT are typically less than 50%.

Neoadjuvant Androgen Deprivation and Radiation Therapy

The theoretic benefits of AD before RT in men with locally advanced cancers are the ability to reduce target volume and the potential cytotoxic synergy of radiation and hormone manipulation. Several Radiation Therapy Oncology Group (RTOG) trials (75-06, 83-07, 85-19) examined the combination of AD and RT in locally advanced disease, suggesting that the regimen was tolerable and improved local tumor control. On the basis of this

information, RTOG 86-10 was designed to compare short-term AD combined with RT with RT alone (Pilepich et al, 2001; Roach et al, 2008). The phase III trial randomized 471 men with cT2-T4 tumors (surface area > 25 cm^2 on rectal examination) to either goserelin plus flutamide for 2 months before and during external beam RT or RT alone. The 4 months of AD was associated with reduction in distant metastases and improvements in local control, disease-free survival, and cancer-specific mortality. At 10 years, the disease-free survival in the AD plus RT and RT-alone groups was 11% and 3%, respectively ($P < .0001$), whereas cancer-specific mortality was 23% and 36%, respectively ($P = .01$). No difference in overall survival between the two groups (43% AD plus RT vs. 34% RT) was found, although men with lower Gleason sum (2 to 6) appeared to have a survival benefit from combined AD and RT. In men with Gleason sum 7 to 10, no significant improvement was observed from AD with respect to locoregional control or survival. Subsequent analysis of RTOG 86-10 (Chakravarti et al, 2003) revealed that loss of p16 expression on immunohistochemistry was associated with reduced overall survival ($P = .039$), disease-specific survival ($P = .006$), and higher risk of local progression ($P = .0007$) and distant metastasis ($P = .026$); overall survival was not significantly associated ($P = .07$) in multivariate analysis. Other correlative studies of tissue from RTOG 86-10 found that the proliferative marker Ki-67 was significantly associated with distant metastasis and cancer-specific survival but not with overall survival (Li et al, 2004).

Similar observations were made by Laverdiere and colleagues (1997) in a prospective randomized study of 120 men with cT2b-T4 disease. Treatments included (1) external beam RT alone, (2) 3 months of NAD before RT, and (3) 3 months of NAD before RT and 6 months of adjuvant AD. Evidence of residual cancer on prostate biopsy was present in 62%, 30%, and 4% of the treatment arms, respectively, at 12 months and 65%, 28%, and 5% at 24 months. Biochemical-free survival at 12 and 24 months paralleled the biopsy data, with the difference between the neoadjuvant and adjuvant AD groups disappearing at 24 months. These observations not only supported neoadjuvant and concurrent AD with RT but also suggest a benefit of prolonged AD. In a group of men randomized to either 3 or 8 months of NAD before RT, of whom 31% were categorized as high risk, longer NAD did not improve freedom from or pattern of failure; the only benefit of 8 months was improved 5-year disease-free survival (71% vs. 42%) (Crook et al, 2009).

Key Points: Neoadjuvant Androgen Deprivation and Radiation Therapy

- Neoadjuvant and concurrent androgen deprivation appears to be appropriate in high-risk patients undergoing radiation therapy.
- Adjuvant androgen deprivation after radiation therapy may benefit those with very high-risk disease.

Adjuvant Androgen Deprivation and Radiation Therapy

Several prospective studies have assessed the role of adjuvant AD after RT, as well as the appropriate duration of such therapy. RTOG 85-31 (Pilepich et al, 1997; Lawton et al, 2001) randomized 977 patients with T3NXM0 or T1-T2N+M0 prostate cancer to RT and either goserelin, started during the last week of RT, continued indefinitely, or goserelin at the time of relapse (i.e., early or late AD). The groups were matched with respect to disease risk characteristics, and less than 30% had lymph node involvement. Improved local control and biochemical disease-free and metastases-free survival were noted in the adjuvant AD group at 8 years of follow-up, and this advantage was most prominent with Gleason sum 8 to 10. Overall survival was not statistically different at 5 years (75% vs. 72%) and 8 years (49% vs. 42%). In those with high-grade tumors, adjuvant AD improved cancer-specific (90% vs. 78%) and overall (80% vs. 69%) survival at 5 years.

In the EORTC 22863 study (Bolla et al, 1997), men undergoing external beam RT for clinically localized disease (cT1-T2 and grade 3, cT3-T4 any grade) were randomized to RT alone or the addition of goserelin starting at the beginning of treatment and continuing for 3 years. This is the only study to demonstrate an overall survival benefit, with 5-year survival of 79% in the adjuvant AD group and 62% in the RT-alone group ($P = .001$). Disease-free survival was 85% and 48%, respectively, and local control was also improved with AD (97% vs. 79%). Of note, the cohort presented with very high-risk disease, with a median PSA level of 30 ng/mL, and this may account for the relatively low overall survival in the RT-alone cohort.

It does not appear that the method of AD affects the outcome of combined treatment with RT. Granfors and colleagues (1998) randomized men with cT1-T4pN0-3M0 cancer to either external beam RT alone or combined orchiectomy and RT; men treated with RT alone received AD at clinical disease progression. At median follow-up of 9.3 years, clinical progression in the RT-alone and RT-plus-AD patients was 61% and 31%, respectively ($P = .005$). Cancer-specific mortality was not different; overall mortality was 61% and 38%, respectively ($P = .02$). However, in men with negative lymph nodes, there was no significant difference in survival rates, and the poor survival was primarily due to metastatic disease at the time of initial treatment.

A meta-analysis of 2742 men treated for clinically localized prostate cancer within RTOG trials from 1975 to 1992 supports use of adjuvant AD in subsets of patients (Roach et al, 2000). Patients were stratified into four prognostic risk groups, and those in risk group 2 (cT3NX, Gleason 2 to 6; cT1-T2NX, Gleason 7; N+, Gleason 2 to 6) appeared to have improved disease-specific survival with addition of short-term (4 months) AD. In further refining the population of patients, limiting the analysis to men with bulky or cT3 disease alone demonstrated a significant survival advantage.

If adjuvant AD is of benefit, the duration of such therapy remains uncertain. RTOG 92-02 supports the use of long-term AD after initial AD with external beam RT (Hanks et al, 2003). Men with locally advanced tumors (cT2c-T4N0-1M0) received either 4 months of AD (2 months neoadjuvant and 2 months concurrent) with RT or that and 24 additional months of AD. Long-term AD was beneficial in all end points evaluated *except* overall survival, with 5-year rates of both approximately 80%. Subset analysis of men with Gleason sum 8 to 10 noted improved overall survival with 24 months of AD (81%) compared with short-term AD (71%; $P = .044$), as well as improved disease-specific survival; these findings were confirmed during 10-year follow-up (Horwitz et al, 2008). D'Amico and colleagues (2004) described 206 men with clinically localized but higher-risk (PSA ≥ 10 ng/mL, Gleason sum ≥ 7, cT3) prostate cancer randomized to RT alone (70 Gy) or RT with 6 months of AD. Overall and cancer-specific survival rates were improved with AD compared with RT alone. Actuarial 5-year

survival and freedom from salvage AD was 88% and 82%, respectively, after early AD and 78% and 57% with RT alone. **Thus a limited period of AD (2 to 4 months) appears to be appropriate for those men with intermediate-risk cancers; more prolonged AD may be beneficial for those with high-risk disease characteristics including high-stage cancers or men with high pretreatment serum PSA values.**

Other aspects of RT for men with more advanced tumors require clarification including the dose and extent (i.e., prostate only vs. prostate and pelvis) applied. RTOG 94-13 randomized men with an estimated risk of lymph node metastasis of 15% into one of four arms: (1) whole-pelvis RT plus neoadjuvant and concurrent AD, (2) prostate-only RT plus neoadjuvant and concurrent AD, (3) whole-pelvis RT plus adjuvant AD, and (4) prostate-only RT plus adjuvant AD (Roach et al, 2003; Lawton et al, 2007). Initial analysis suggested improved progression-free survival for whole-pelvis compared with prostate-only RT and no difference for the two types of AD. In comparing the four groups after longer follow-up, however, progression-free survival rates were similar, with significant difference only in overall survival among the groups (P = .027). Surprisingly, overall survival was worse in patients receiving whole-pelvis RT plus adjuvant AD compared with all other cohorts.

The differences in RT dose among the various prior and contemporary studies make comparisons of efficacy difficult because emerging data support doses greater than 72 Gy as being more effective (Cheung et al, 2005; Jacob et al, 2005). In addition, the role of combined external beam RT and brachytherapy (both permanent and high-dose rate) needs to be better elucidated. Brachytherapy has generally been used to treat patients with lower-risk features. Its use in those with high-risk disease characteristics, often in combination with AD and external beam RT, has been less well studied. Potters and colleagues (2005) noted a 63% biochemical-free survival in those treated with permanent prostate brachytherapy. A similar outcome has been noted with the use of high-dose-rate intensity-modulated brachytherapy with external beam RT (Demanes et al, 2005). Sylvester and colleagues (2003) treated men with interstitial permanent brachytherapy combined with moderate-dose (45 Gy) neoadjuvant external beam RT. In those with high-risk disease (D'Amico criteria), the 10-year biochemical relapse-free survival was 48%; of note, AD was not used. Stock and colleagues (2004) evaluated a multimodal protocol using neoadjuvant and concomitant AD (9 months total), brachytherapy, and three-dimensional conformal RT in a high-risk cohort. The 5-year biochemical-free survival was 86%, with Gleason sum the only variable associated with PSA failure. Excellent local control was also demonstrated, with no patient harboring cancer on the last post-treatment biopsy.

Radiation Therapy and Chemotherapy

The role of chemotherapy in conjunction with RT is less well studied than that for surgery and chemotherapy. Khil and colleagues (1997) administered estramustine and vinblastine concurrently with RT (total, 65 to 70 Gy) in men with locally advanced disease. Although clinical control was reasonable at 5 years at 81%, only 48% of patients had a PSA level below 4 ng/mL at this time. Zelefsky and colleagues (2000) enrolled 27 patients with high-risk disease (Gleason sum ≥ 8 and PSA > 10 ng/mL; Gleason sum 7 and PSA > 20 ng/mL; cT3N0M0 and PSA > 20 ng/mL; cT4N0M0; cTXN1M0) in a phase II clinical trial of the same agents, with RT at 75.6 Gy. Only modest increase in grade 2 toxicity was noted, and no late grade 3 or grade 4 toxicities were observed. The 2-year biochemical-free survival was 60%. An update reported median time to PSA relapse of 12 months, with 48% of patients receiving no additional therapy, and median time to metastasis had not been reached (Ryan et al, 2004).

An estramustine-based regimen has also been examined with etoposide before and during definitive RT (Ben-Josef et al, 2001). Actuarial disease-free and overall survival was 73% and 88%, respectively, at 3 years. Local control as determined by biopsy was 71% at 18 months. A phase I study examined concurrent docetaxel and RT (70.2 Gy) in 22 men (Kumar et al, 2004). The maximal tolerated dose was determined to be 20 mg/m^2, with diarrhea and dysuria the primary toxic effects. All patients were alive at last follow-up, and 77% had continued biochemical response. These promising results support further study of the combined use of RT and chemotherapeutic agents.

FOCAL ABLATIVE THERAPY

Advances in technology have provided methods to ablate prostate tissue while being minimally invasive. There is renewed interest in primary cryoablation, particularly as focal treatment for localized disease, as well as salvage therapy, while high-intensity focused ultrasound (HIFU) appears promising. The ability to treat local disease within the prostate by these modalities may play a role even in men with locally advanced disease, most likely in combination with AD or other systemic therapy.

Cryoablation

Several series have been reported regarding primary cryoablation of the prostate and include many men with high-risk disease (Ahmed et al, 2009). Among 975 men undergoing cryoablation, 41% were high risk and 24% were cT3 in the report from Long and colleagues (2001). At median follow-up of 24 months, the 5-year actuarial biochemical-free survival, defined as PSA less than 1 ng/mL, was 41%. A similar PSA outcome (35%) using the same definition was observed in another group of men with PSA greater than or equal to 10 ng/mL and/or Gleason sum greater than or equal to 8 undergoing primary cryoablation (Prepelica et al, 2005). However, use of more stringent PSA cutoff values may result in significantly worse outcomes, with 2-year rates of biochemical failure higher than 80% if thresholds of 0.5 or 0.2 ng/mL are applied (El Hayek et al, 2008). Chin and colleagues (2008) randomized men with clinical stage T2c-T3 to 6 months of AD and either cryoablation or RT at 66 Gy. At mean follow-up of 37 months, there were no differences in disease-specific (95% to 97%) and overall survival (87%), but cryoablation was associated with shorter PSA-free survival (28 months vs. 41 months) and higher biochemical failure (87% vs. 53%).

High-Intensity Focused Ultrasound

The role of HIFU continues to be elucidated, particularly in men with locally advanced prostate cancer. The limited existing data are confounded by frequent omission of risk stratification and common use of AD to reduce prostate size. At 1-year follow-up, 30 men with locally advanced or high-risk disease receiving AD plus HIFU had reasonable local control, with PSA less than 0.3 ng/mL and negative sextant biopsies in 90%; no patient had clinical disease progression (Ficarra et al, 2006). A larger series from Sumitomo and colleagues (2008) compared men receiving HIFU with and without NAD and without subsequent adjuvant

therapy. In the 29% with D'Amico high-risk cancers, NAD reduced both positive biopsy rate and biochemical failure. Three-year disease-free survival was independently affected by stage cT2c or higher (HR, 2.34) and lack of NAD (HR, 2.19) in multivariable analysis. Parallel to studies of RT, outcomes of local treatment using HIFU may be improved when combined with NAD, primarily in men with intermediate- and high-risk disease characteristics.

ANDROGEN DEPRIVATION AND ITS TIMING

The VACURG and Medical Research Council trials suggest a benefit to early application of AD in men with locally advanced prostate cancer. The first VACURG study randomized 1050 patients with stage III disease and 853 patients with stage IV disease to placebo, 5 mg of DES, orchiectomy plus placebo, or orchiectomy plus 5 mg of DES. All three AD arms had significantly less progression than the placebo group had, but this did not translate into an overall survival benefit. The inability to demonstrate a survival benefit cannot be completely attributed to the increased cardiovascular deaths within the DES groups because survival in the orchiectomy plus placebo group was not significantly different from that in the placebo-alone group. The second VACURG study randomized 1506 men with stage III and stage IV disease to placebo or one of three doses of DES (0.2 mg, 1 mg, 5 mg). DES at 1 mg and 5 mg delayed progression of stage III disease, and patients receiving 1 mg had improved overall survival. However, the 5-mg dose of DES again resulted in increased cardiovascular death. Subsequent analysis suggested that immediate estrogen therapy was most beneficial in patients younger than 75 years with high-grade tumors (Gleason sum 7 to 10). The third VACURG study supported that only a subset of men with prostate cancer benefit from early AD. In men with stage II disease, 5-year survival with placebo and 1 mg of DES was 48% and 75%, respectively. **Taken together, the VACURG data provide evidence of benefit for early AD with respect to disease progression and potential survival only in subsets of men with more aggressive disease** (Byar, 1973; Byar and Corle, 1988). **The studies also clearly show that alternatives to estrogen should be used, given the cardiovascular toxicity associated with higher doses of DES.** The current ability to better monitor disease progression, with use of PSA kinetics and imaging modalities, may improve the outcomes of delayed AD by better determining when institution of AD is necessary.

The Medical Research Council also evaluated the issue of early versus delayed AD (orchiectomy or LHRH agonist) in 938 patients with prostate cancer, of whom 501 had locally advanced disease. The majority of deaths (67%) were attributed to prostate cancer. Cancer-specific mortality was 55% in the early AD group and 43% in the deferred group ($P = .001$). Overall survival was also improved in the immediate AD arm ($P = .02$). The reduction in prostate cancer death was primarily due to patients with M0 disease. This study also provides important data for comparison to other forms of treatment. Median time to death due to prostate cancer (cT3 M0) was 90 months, comparing favorably to EORTC 22863, in which median time was not reached after 65.7 months. Similarly, median overall survival in the Medical Research Council study was 64 months but not reached in EORTC 22864 (56.7 months of follow-up). Thus the apparent beneficial effects of combined AD and RT may be due in part to AD alone with uncertain incremental advantage of RT. The recent results from SPCG-7/SFUO-3 suggest an important role of RT, in addition to AD, in men with locally advanced disease (78% cT3) (Widmark et al, 2009). Men were randomized to either total AD followed by continuous flutamide or endocrine therapy combined with RT. At median follow-up of 7.6 years, both prostate cancer-specific and overall mortality were decreased in the group receiving AD plus RT (RR, 0.44 and 0.68, respectively), and PSA recurrence was higher in men receiving AD alone (75%) compared with the RT group (26%). Despite limitations including the unconventional endocrine regimen and open study design, use of RT and potentially other local treatment modalities appears warranted in men with locally advanced prostate cancer.

Studer and colleagues (2004) evaluated the timing of AD in a study randomizing 197 asymptomatic men with prostate cancer to either immediate or deferred subcapsular orchiectomy; of note, patients were either unsuitable for or unwilling to undergo surgery or RT. A significant fraction of the cohort had higher-risk features, with clinical stage T3 or higher in 67% and median serum PSA level above 46 ng/mL. Of the 92 men in the deferred treatment arm, 42% never required AD; the majority died of causes unrelated to prostate cancer. The median time to deferred AD was 3.2 years, the most common indication being skeletal metastases (45%) and ureteral obstruction (25%). Although overall survival was not different between the immediate and deferred groups ($P = .96$), a trend toward improved cancer-specific survival was noted in those men receiving immediate AD, with a hazard rate for death from prostate cancer of 0.63 ($P = .09$).

To minimize adverse impact on quality of life, antiandrogen therapy alone has been proposed as an alternative to orchiectomy or LHRH agonists. Iversen and colleagues (2004) reported on the effects of 150 mg of bicalutamide in men with localized or locally advanced prostate cancer, the majority of whom were untreated initially (81%). At median 5.3 years of follow-up, survival in those with locally advanced disease was improved with bicalutamide compared with placebo (HR, 0.68). Overall, risk of disease progression was reduced by 43%, with the greatest benefit in locally advanced tumors (HR, 0.4). The combined analysis of the three Early Prostate Cancer bicalutamide trials ($n = 8113$) confirmed improved progression-free survival in the bicalutamide group (Wirth et al, 2004a). Overall survival was not different between the treatment and placebo arms in each trial, but men with locally advanced disease receiving bicalutamide alone (i.e., no surgery or RT) appeared to have improved survival. Although apparently promising in men with high-risk tumors, bicalutamide at 150 mg must be approached cautiously, both in men deferring local therapy and after definitive treatment. In analysis of the Early Prostate Cancer data (median follow-up of 5.4 years), men with localized prostate cancer receiving bicalutamide as primary therapy had an increased risk of death (HR, 1.23; 95% CI, 1.00 to 1.50) compared with surveillance alone. Immediate high-dose bicalutamide is not currently appropriate in men with low risk of disease progression, and potentially adverse effects should be sought in higher-risk patients with extended follow-up.

Wirth and colleagues (2004b) tested adjuvant flutamide (750 mg) after radical prostatectomy in men with pT3-T4N0 disease. Recurrence-free survival, defined as a single PSA value above 5 ng/mL or two PSA values above 2 ng/mL, was improved with flutamide (HR, 0.51) at median follow-up of 6.1 years; however, overall survival was comparable (HR, 1.04). Significant toxicity was associated with flutamide and accounted for nearly half of withdrawals from the treatment arm.

Key Points: Androgen Deprivation

- Early androgen deprivation may improve survival.
- Alternative methods of androgen manipulation (antiandrogen, intermittent) remain investigational.

Intermittent Androgen Deprivation

Another approach to minimizing AD-related morbidity is the intermittent application of androgen suppression. Forty-nine patients (28 with cT3-T4N0M0) were treated with total AD until the PSA level was less than 4.0 ng/mL between 24 and 32 weeks, after which treatment was withheld after 36 weeks (Sato et al, 2004). PSA level was monitored and treatment was recommended when the PSA level reached either pretreatment level (when it was <15 ng/mL) or 15 ng/mL (when the initial PSA level was higher than that). During median follow-up of 126.1 weeks, mean time off treatment during cycles 1, 2, and 3 was 46.1, 36.9, and 23.3 weeks, respectively. No symptomatic or clinical disease was reported in the nonmetastatic subgroup, and PSA failure was observed in 3 (11%) of these patients, with all patients alive at last evaluation. The optimal timing of intermittent AD for reduction of patient morbidity and disease-specific end points remains to be determined.

Quality of Life

The early institution of AD in men with prostate cancer, whether it is localized or locally advanced, must be balanced against the known side effects and long-term morbidity. Only recently has the impact of AD been appreciated and reported on bone events, cognitive function, and quality of life. In comparing bicalutamide (150 mg) and castration with locally advanced but nonmetastatic disease, both sexual interest and physical capacity were better with bicalutamide monotherapy (Iversen et al, 2000). Although hot flashes were more common with castration, a trend toward reduced quality of life was associated with bicalutamide including higher incidence of gynecomastia, breast pain, and asthenia. In the study of intermittent AD from Sato and colleagues (2004), many quality of life domains were improved during off-treatment cycles including potency and social and family well-being.

The multimodal approach with AD and RT may increase the relative toxicity compared with each intervention alone. Schultheiss and colleagues (1997) reported that NAD was correlated with later gastrointestinal and genitourinary (grade 2 or higher) morbidity. Another study found that adjuvant AD after RT predicted for late grade 2 to grade 4 rectal toxicity (Sanguineti et al, 2002). Within RTOG 86-10, potency after RT with or without AD was similar at 81% and 74%, respectively. Chen and colleagues (2001) also found that the addition of AD did not further contribute to decline in sexual function after RT. Zelefsky and colleagues (1999) evaluated predictors of late toxicity in men treated with three-dimensional conformal radiotherapy. Although the 5-year actuarial likelihood of gastrointestinal and urinary toxicities was low (<10% overall), use of NAD was an independent predictor ($P = .01$) of post-treatment erectile dysfunction. The incidence of rectal morbidity and sexual dysfunction may be related to duration of AD longer than 6 or 9 months.

The benefits of adjuvant AD plus RT for locally advanced prostate cancer, both short and long term, appeared to outweigh the associated side effects in a number-needed-to-treat analysis (Jani et al, 2003). A model that compared treatment options while incorporating benefit and complications was constructed, and data from randomized trials of RT with or without AD for cT2c-T4 N0-1 were input into the calculation. Even considering the increased incidence of side effects of long-term AD, this approach appeared to be better than short-term AD for virtually all end points evaluated.

Given concerns regarding AD and impact on body mass index, lipid profile, diabetes, and cardiovascular disease, Efstathiou and colleagues (2009) assessed the relationship between AD and cardiovascular events within RTOG 85-31. Adjuvant AD (median duration 4.2 years) was not associated with increased cardiovascular mortality. Additional evidence from RTOG 86-10 suggests that short-term NAD also does not increase the risk of fatal cardiac events.

MANAGEMENT OF DELAYED SEQUELAE

The direct comparison of prostatectomy and RT in the treatment of locally advanced prostate cancer is challenging and primarily based on historical studies. Even with the addition of neoadjuvant and adjuvant systemic therapy, leaving the prostate gland in situ poses potential problems. First, effective local control of some high-risk cancers may influence survival. Second, local recurrence may lead to the need for additional treatment of the prostate. At 10 years, local recurrence rates after RT for cT3 or stage C range from 24% to 74%. Holzman and colleagues (1991) reported that 36% of patients required transurethral resection of the prostate because of urinary obstruction after RT alone, without AD. Other morbidity included hydronephrosis (20%) and incontinence (13%). An older report (Tomlinson et al, 1977) also demonstrated significant local complications of stage C prostate cancer with nonextirpative interventions—infection (80%), bladder outlet obstruction (75%), gross hematuria (45%), and ureteral obstruction (40%). Systemic therapy in the form of AD may not prevent local progression or reduce need for palliative intervention. Despite orchiectomy for bladder outlet obstruction, 31% of men with locally advanced disease required transurethral prostate resection because of persistent voiding dysfunction after 60 days. Similarly, in 277 patients with cT2-T4 randomized to orchiectomy, RT, or both, rates of local disease control were comparable (Fellows et al, 1992). Studer and colleagues (2004) demonstrated that AD alone, whether it is instituted early or late, does not prevent local morbidity. More than half of the men in their study required transurethral resection of the prostate. In addition, delayed institution of AD was necessary because of ureteral obstruction (25%), anticipation of local complications (10%), and rectal infiltration (4%).

Quality of life is an increasingly important end point for prostate cancer. However, the impact of untreated local tumor progression or the various treatment modalities for locally advanced disease on quality of life outcomes is poorly characterized. Rosenfeld and colleagues (2004) examined the relationship between cancer stage and quality of life in 341 ambulatory men with prostate cancer. Instruments used included the Functional Assessment of Cancer Therapy (FACT), urinary function subscale of the UCLA Prostate Cancer Index, and Hospital Anxiety and Depression Scale (HADS). The stage of prostate cancer was significantly associated with most FACT scales—increasing stage was negatively correlated with nearly every FACT subscale score; the observation persisted in multivariate models, accounting for covariates such as comorbidity and time since diagnosis. Interestingly, stage was more strongly associated with physical domains of health-related quality

Table 107–11.

Current Phase III Clinical Trials in Locally Advanced/High-Risk Prostate Cancer

STUDY	ELIGIBILITY CRITERIA	TREATMENTS
Radical Prostatectomy		
NEOADJUVANT		
CALGB 90203	Clinically localized, ≤60% 5-yr disease free, Gleason 8-10	Surgery alone vs. estramustine/docetaxel
ADJUVANT		
SWOG 9921	Gleason 8-10, pT3b-4, PSA > 20 ng/mL, N1, Gleason 7 and + margin	AD (2 yr) vs. AD + mitoxantrone/prednisone
VA Study 553	pT3b-4, pT3a and Gleason ≥7, pT2 and Gleason 8-10 and + margin, PSA > 20 ng/mL	Surveillance vs. docetaxel/prednisone
SPCG 12	pT3a and Gleason ≥4+3, pT2 and + margin and Gleason ≥4+3, pT3b and Gleason ≥7	Surveillance vs. docetaxel
NCT 00667069	>pT2 or R1 N0/x and PSA ≤0.1 ng/mL	Immediate vs. delayed RT + triptorelin
MRC PR 10	After radical prostatectomy with PSA ≤0.2 ng/mL: pT3-4, Gleason 7-10, preoperative PSA ≥10 ng/mL, + margin	Immediate vs. delayed RT RT vs. RT + 6 mo AD vs. RT + 24 mo AD
External Beam Radiation Therapy		
NEOADJUVANT		
RTOG 9910	Gleason 2-6 and PSA 10-100 ng/mL, Gleason 7 and PSA < 20 ng/mL, cT1 and Gleason 8-10 and PSA < 20 ng/mL	8 wk NAD vs. 28 wk NAD
CAN-NCIC-PR12	≥T3a, Gleason ≥ 8, PSA > 20 ng/mL	NAD + docetaxel vs. NAD
ADJUVANT		
RTOG 9902	Gleason ≥ 7 and PSA 20-100 ng/mL, ≥cT2 and Gleason ≥ 8 and PSA < 100 ng/mL	AD vs. AD + estramustine/etoposide/paclitaxel
NCT 116142	cT1-T2a and PSA < 10 ng/mL or Gleason ≥4+3 or PSA velocity >2 ng/mL/yr, cT2c-4 and tertiary Gleason 5 or T3b or Gleason ≥3+4 with ≥50% cores positive	AD vs. AD + docetaxel
RTOG 0521	Gleason ≥ 9 and PSA ≤ 150 ng/mL, Gleason 8 and PSA < 20 ng/mL and ≥cT2, Gleason 7 or 8 and PSA 20-150 ng/mL	AD vs. AD + docetaxel/prednisone
SPCG 13	cT2 and Gleason 4+3 and PSA 10-70 ng/mL, cT2 and Gleason 8-10 and PSA < 70 ng/mL, cT3	AD vs. AD + docetaxel
Androgen Deprivation		
CAN-NCIC-PR3	cT3-4N0/M0, cT2 and PSA > 40 ng/mL, cT2 and PSA > 20 ng/mL and Gleason ≥ 8	AD alone vs. additional pelvic RT
NCT 00055731	Gleason > 7, cT3-4, N1, PSA > 20 ng/mL	AD vs. AD + docetaxel/estramustine

of life and there was no association with psychologic symptoms as measured by HADS.

Berg and colleagues (2007) treated high-risk patients with RT monotherapy and characterized quality of life using validated instruments. Although mean scores for bowel function were similar to those for a normative control population, bowel bother and diarrhea were greater after RT. Patients who had clinical progression or required AD reported worse sexual, urinary, and social function, and more sleeping problems and exhibited great declines in all domains over time. Data from CaPSURE (Wu et al, 2008) also suggest that men with high-risk cancer are likely to suffer negative effects beyond cancer outcomes. Use of AD with both surgery and RT was associated with a loss of sexual function that improved within 9 months, whereas the combination of external beam RT and brachytherapy resulted in continuous worsening of urinary function and bother.

Additional evidence from SWOG 8794 supports an adverse impact of multimodal therapy on quality of life (Moinpour et al, 2008). Men receiving adjuvant RT reported worse bowel and urinary function, but not erectile function, compared with surgery alone. Although symptom distress was significantly worse for the adjuvant RT group, likely correlating with bowel and urinary problems, there were no differences in other general measures of health-related quality of life, whereas global health-related quality of life was initially worse but continuously improved over time after adjuvant RT.

CLINICAL TRIALS

Given that outcomes of therapy are not optimal for those men with high-risk disease features, patients who present with such cancers should be considered for enrollment in novel clinical trials (http://clinicaltrials.gov/). Table 107–11 summarizes phase III clinical trials for high-risk or locally advanced prostate cancer, some of which have completed accrual; others are ongoing. The resulting data should answer some of the current questions regarding the optimal type and timing of traditional combination treatment, as well as the role of chemotherapy in men with locally advanced and high-risk prostate cancer.

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chapter
108

Clinical State of the Rising PSA Value after Definitive Local Therapy: A Practical Approach

Michael J. Morris, MD ● Howard I. Scher, MD

When Does a Patient Occupy the Clinical State of a Rising PSA Value?

Radiographic and Other Tests to Determine Whether the Rising PSA Value Signifies Localized Disease, Metastatic Disease, or Both

Models to Predict Local versus Systemic Recurrence and to Predict Survival

Treatment Strategies for the Patient with a Rising PSA Value

Clinical Considerations Regarding Local Treatments

Clinical Trial Considerations

Summary

No tumor marker has had as great an impact on the diagnosis, management, and treatment of a disease as prostate-specific antigen (PSA) has had on prostate cancer. PSA assessments are used during every phase of the disease—screening and early detection, determining extent of local disease, defining the probability of disease control after surgery or radiation therapy, and indicating whether a patient is responding to treatment, be it local or systemic.

Perhaps the most controversial and problematic aspect of PSA monitoring is that it has created a new "clinical state" to characterize patients whose sole manifestation of disease recurrence after definitive local therapy is a detectable and increasing PSA value, in the absence of detectable disease according to the currently available imaging modalities. Based on the estimated probability of relapse after surgery or radiation therapy, upward of 50,000 American men fall into this category (Moul, 2000). Unfortunately, the management of these patients remains controversial because the course of the disease is highly variable and there are no completed prospective randomized studies that directly address the questions of when therapy should be initiated, should treatment should be systemic or local, and whether an intervention prolongs life.

Within the clinical spectrum of men with a rising PSA value are (1) those in whom the rising PSA value reflects persistent or recurrent disease in the prostate or prostate bed, (2) those in whom the rising PSA value is a harbinger of detectable metastases, and (3) those with both local and systemic disease. Within the category of those with systemic disease are men who are at high risk of developing symptoms of or dying of their cancer. Such patients may well benefit from the early administration of systemic treatments to prevent metastases, to preserve quality of life, to delay the complications of osseous lesions, and to prolong survival. In other patients with systemic involvement the disease will follow a more indolent clinical course for which observation may be appropriate because the risk of developing metastases or symptoms, or of dying of the disease, may be very low during their life expectancy (Pound et al, 1999; Antonarakis et al, 2009). For these individuals, side effects from treatment may be worse than the anticipated morbidity of the cancer itself, exposing men to unnecessary toxicities. Some patients fall within these two extremes and warrant neither observation nor systemic treatments but rather additional therapy directed at the prostate or prostate bed.

Given this spectrum of disease, accurate methods of determining the clinical risk represented by a rising PSA value are critical to developing rational treatment strategies. Such clinical risks include the development of systemic rather than local disease, developing metastases, or dying of a prostate cancer–related cause. **In turn, evaluation of these risks will determine whether the cancer can potentially be eliminated by additional local therapy, and whether systemic therapy is likely to prevent a clinically significant event such as detectable metastases on imaging or death from disease. In both scenarios the therapeutic question is how to balance the need for therapy with the anticipated decrease in quality of life associated with treatment.**

A critical issue for patients is the anxiety associated with knowing that the cancer is "progressing." Men are diagnosed with and treated for prostate cancer earlier than ever, yet the symptoms most experience are related more to therapy than cancer. The clinical dilemma facing both the patient and the physician is how to balance the anxiety provoked by the rising PSA against the

paucity of objective data regarding who would benefit from treatment and what the tangible benefits might be from such interventions. In this discussion a framework is provided to assess the prognosis of patients in the state of a rising PSA (Scher and Heller, 2000) so that a rational risk-adapted approach can be implemented. This is done with the recognition that the tools for both prognostication and treatment continue to evolve and at present must be considered works in progress.

WHEN DOES A PATIENT OCCUPY THE CLINICAL STATE OF A RISING PSA VALUE?

Prostate Cancer: A States-Based Model

Prostate cancer presents a wide clinical spectrum from localized to metastatic and asymptomatic to symptomatic and is driven by a range of biologic factors that often change as the disease evolves. These variable disease manifestations can be segregated into patient groups, represented as easily recognizable clinical states that have shared clinical needs and treatment goals (Fig. 108–1) (Scher and Heller, 2000). Common treatment aims for patients with localized disease are eradication of the disease along with preservation of potency, continence, bladder and rectal integrity, and other quality-of-life measures. Patients with newly diagnosed metastatic disease have the treatment goal of maintaining disease control and prolonging hormonal sensitivity while minimizing the impact of hormones and other treatment strategies on quality of life and bone integrity. For patients with disease that is progressing despite androgen deprivation, the most acute issues are prolonging life and finding treatment strategies to mitigate the effects of an increasing burden of disease, such as pain, neurologic compromise, fatigue, hematologic disorders, and bone fracture.

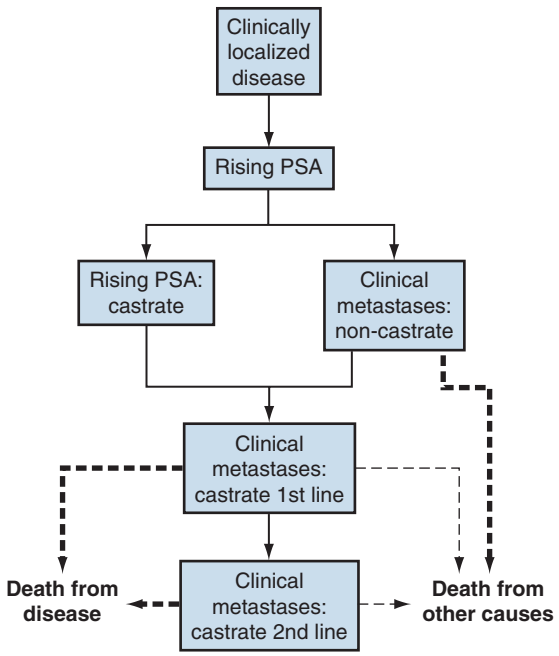


Figure 108–1. Prostate cancer can be considered as a series of clinical states. Each state defines a discrete set of patient characteristics, clinical needs, and treatment aims and therefore is a practical means of distinguishing patient populations and developing clinical trials. Prognostic models are developed on a state-by-state basis to risk-stratify patients in each state. PSA, prostate-specific antigen. (Modified from Scher HI, Heller G. Clinical states in prostate cancer: towards a dynamic model of disease progression. Urology 2000;55:323–7.)

Defining the Clinical State of a Rising PSA Value

Determining when a patient has entered the clinical state known as a "rising PSA" depends on the primary therapy the patient has received and the sensitivity of the assay used to measure his PSA level. By consensus, this clinical state does not include patients with localized disease who are being observed expectantly with "watchful waiting" or "deferred therapy." It also does not include patients who are receiving androgen deprivation in lieu of definitive treatment. As with many issues relating to prostate cancer there is no single uniform definition for "biochemical relapse." **A patient who has undergone a prostatectomy should have no (or minimal) remaining normal, viable, PSA-producing nonmalignant prostate tissue. In contrast, patients who have received external-beam radiation therapy or brachytherapy, whether alone or in combination, have an intact, although irradiated, gland with nonmalignant prostate epithelial cells that will produce low levels of PSA that are not indicative of treatment failure.** In addition, not all PSA assays have the same degree of sensitivity, so a patient's PSA level may be reported as undetectable in one laboratory but detectable at another. A further confounder is that PSA production can vary with testosterone levels. Patients who have undergone neoadjuvant or adjuvant hormonal strategies in conjunction with their local therapy may have variable rates of treatment failure on the basis of testosterone recovery rates. In general, testosterone levels return to baseline within 3 to 6 months after cessation of short-term gonadotropin-releasing hormone analogue treatment, but the recovery can be quite prolonged in individual patients (Padula et al, 2002; Gulley et al, 2005). Age, length of androgen deprivation, and even the type of gonadotropin-releasing hormone analogue therapy used will all impact the rate of biochemical failure (Lukka et al, 2001).

Radical Prostatectomy

As noted, post-prostatectomy patients may have very low levels of PSA that can represent benign prostate tissue at the surgical margin, and as a result there is debate as to what precise level of PSA definitively represents postsurgical treatment failure. The American Urological Association (AUA) Guideline Update Panel examined 319 publications reporting on patients with biochemical relapse, revealing that 166 different definitions were applied to these various studies. The most commonly used cut point was greater than 0.2 ng/mL. The panel recommended using a cut point of greater than or equal to 0.2 ng/mL, with a second confirmatory level of greater than 0.2 ng/mL, to define surgical failure (Cookson et al, 2007), although some authors have recognized that low levels such as 0.01 to 0.07 ng/mL can also represent failure (Amling et al, 2001; Gretzer et al, 2002; Han et al, 2003). It is important to be mindful that the detection of a single abnormal PSA level does not, in and of itself, necessarily indicate that a clinically significant event has occurred, and the presence of a rising PSA level alone does not necessarily imply that a patient will develop symptoms or die of his disease. A recent analysis of 3125 patients treated at Memorial Sloan-Kettering Cancer Center (MSKCC) demonstrated that the best cut point to predict the probability of metastatic

progression was greater than 0.4 ng/mL, followed by another rise (Stephenson et al, 2006). For clinical trial purposes, current consensus guidelines from the Prostate-Specific Antigen Working Group (Scher et al, 2004) recommend that a patient's disease is considered to have progressed after a radical prostatectomy if the PSA value is greater than or equal to 0.4 ng/mL 8 weeks or more after the procedure and rises on a subsequent measurement. Eight weeks is ample time to allow PSA levels to clear, given a half-life of 2 to 3 days (Oesterling, 1991). The "date of failure" is the date that the PSA level is first detectable.

Radiation Therapy

Biochemical failure after radiation therapy was traditionally defined by the American Society for Therapeutic Radiation Oncology (ASTRO) as three consecutive PSA rises, optimally separated by 3 months between measurements, beginning at least 2 years after the start of radiation therapy, with the time of failure as the midpoint between the nadir and the first confirmed rise, or any rise significant enough to trigger therapy (Consensus statement, 1997). Such a definition, however, has not been wholly satisfactory even to its authors. The guidelines did not adequately account for recovering testosterone levels in patients who had received neoadjuvant or adjuvant hormones, for transient post-treatment elevations in PSA (so-called "bounces") that do not represent disease relapse, for small serial rises in PSA that do not represent treatment failure, or for circumstances in which recurrent disease is not manifest in the form of strictly consecutive rises. In addition, bias was introduced by backdating the time of progression, given its sensitivity to the length and rigor of follow-up. To address these issues, new guidelines, termed the ASTRO Phoenix Criteria, were issued. These criteria recommend that biochemical failure be defined as a PSA rise of 2 ng/mL above the post-treatment nadir, whether or not the patient received hormonal therapy in conjunction with radiation therapy. The date at which that level was reached would be the date of relapse, and the practice of backdating would be abandoned. For patients who undergo salvage therapies such as with hormones, prostatectomy, or cryotherapy, failure would be declared not at the time of biochemical relapse but instead at the time of a positive biopsy or when salvage therapy was initiated. The consensus guidelines allowed, however, that the traditional ASTRO definitions were permissible if a patient underwent only external-beam radiation therapy or brachytherapy, provided that adequate follow-up was given and reported (Roach et al, 2006).

RADIOGRAPHIC AND OTHER TESTS TO DETERMINE WHETHER THE RISING PSA VALUE SIGNIFIES LOCALIZED DISEASE, METASTATIC DISEASE, OR BOTH

One of the most difficult aspects of formulating a treatment plan for the patient with a rising PSA level is determining whether it represents locally persistent disease or nonlocalized systemic disease or both. The stakes of such a decision are high. Treating every patient who has undergone a prostatectomy with salvage radiation therapy exposes patients with systemic disease to unnecessary radiation therapy and the risk, albeit low, of proctitis, cystitis, and a reduced likelihood of maintaining or preserving erectile function. On the other hand, with careful patient selection, salvage radiation therapy has the potential to eliminate the disease completely. **Current methods of detecting disease, whether in the prostatectomy bed, an irradiated gland, or metastatic sites such as bone or lymph nodes, are usually of very limited value.** Moreover, the finding of local disease on an imaging study does not exclude a systemic component, which explains in part why radiation therapy to the prostate bed, or salvage surgery after radiation therapy, is not curative for many patients (Laufer et al, 2000; Leventis et al, 2001).

Bone Scintigraphy and Computed Tomography

By definition, the finding of overt radiographic metastases on an imaging study signifies that a patient is no longer in the clinical state of rising PSA but rather has metastatic disease (see Fig. 108–1). Nevertheless, to ensure that patients do indeed have a rising PSA level in the absence of radiographically evident metastases, a staging evaluation should be undertaken. However, bone scintigraphy and computed tomography (CT) of the abdomen and pelvis, the traditional modalities utilized, are of limited value because they are insensitive at detecting early metastatic disease.

Bone scintigraphy will only detect metastatic disease that interferes with normal osteoblast/osteoclast interactions to produce abnormal bone deposition. Areas of marrow involvement that do not impact bone metabolism will remain undetected. Frequently, patients present to their clinician years before bone scintigraphy is likely to be positive. There is no single PSA value that predicts for scan positivity, although in most series PSAs will be well above 20 to 30 ng/mL before bone scintigraphy reflects metastatic disease (Cher et al, 1998). Even when bone scintigraphy is positive, tracer uptake in areas of trauma, infection, or inflammation can easily be mistaken for metastatic disease. More recently, a nomogram was developed to predict the likelihood of a positive scan. The nomogram included parameters that describe PSA kinetics—the PSA slope (odds ratio [OR], 2.71; $P = .03$) and PSA velocity (OR, 0.93; $P = .003$)—as well as the trigger PSA or current PSA value (OR, 1.022; $P < .001$). The concordance index for predicting the bone scan result was 0.93 (Dotan et al, 2005).

Another model has been generated from the CaPSURE database, a national registry of over 13,000 patients treated in more than 40 urology practices in the United States. Of 7311 patients treated with definitive local therapy from 1990 to 2004, 1551 experienced biochemical recurrence (using the traditional ASTRO definition for postirradiation patients and a cutoff of 0.2 ng/mL for postprostatectomy patients). Of the 292 patients who had imaging studies and adequate PSA data, trigger PSA (≥5 ng/mL) and PSA doubling time (PSADT) (<10 months) predicted positive imaging results (which included both bone scintigraphy and CT) with a high concordance index (c-adj 0.84) in a multivariate model (Choueiri et al, 2008).

CT is also suboptimal for the detection of metastasis not only because it has a lower limit of detection of 0.5 cm but also because the scans are nonspecific, making it difficult to distinguish scar tissue or fibrosis from tumor (Moul et al, 2001b).

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) using an endorectal coil and a pelvic-specific acquisition methodology can reveal sites of recurrent disease in and around the prostate bed and bladder. In a preliminary study of endorectal MRI this modality correctly identified 39 of 41 patients (95%) thought to have locally recurrent

disease on the basis of a positive biopsy, reduction in PSA level after radiation therapy, or serial MR images that demonstrated an increase in local disease in the fossa. **Endorectal MRI may be able to identify sites of disease that would otherwise not be sampled by routine blind biopsies of the prostate bed and therefore may be useful for identifying areas suggestive of locally recurrent disease or for guiding biopsies** (Sella et al, 2004). In a prospective study of men who had undergone a prostatectomy, endorectal MRI detected locally recurrent disease in all 31 men with clinical evidence of locally recurrent disease, as confirmed by biopsy. Taking together these true positives with nine true negatives found in the study, the investigators considered the sensitivity and specificity of the modality to be 100% (Tatli et al, 2006). This modality, however, may well be more appropriate for the patient who has undergone a prostatectomy rather than radiation therapy, because of treatment-related changes in the latter group.

Positron Emission Therapy

Positron emission tomography (PET) is another area actively under investigation for identifying occult metastatic or locally recurrent disease. Because fluorodeoxyglucose (FDG) is excreted through the kidneys, detection of nodal and locally recurrent disease, even in highly controlled patient populations with known progressive metastatic disease, can be challenging. In one study of 43 patients with definitively established progressive metastatic disease, patients were scanned both with FDG PET imaging as well as standard bone scintigraphy. Of the 1720 bones examined, the PET and bone scans were concordant in 1600 bones (93%) in terms of reflecting the presence or absence of metastatic disease. Of the 121 bones in which there was metastatic disease on the PET but not the bone scan, 84 (80%) ultimately became positive on the bone scan, suggesting that PET can detect disease earlier than bone scintigraphy in many patients (Meirelles et al, 2010).

Schoder and colleagues (2005) used FDG-PET to examine patients with prostate cancer with a rising PSA level. Images were interpreted using a composite, though unvalidated, reference: a positive biopsy, decrease in PSA value after irradiation to the primary site, development of a detectable lesion in the primary site on follow-up conventional imaging studies, and increase in lesion size on follow-up imaging or concurrent other imaging studies within 90 days of PET. A positive FDG-PET was found to correlate with these standards in 31% of cases. Positive cases were more likely to be found in patients with higher PSA values (>9.5 ng/mL), and the probability of a positive scan correlated with PSADT (Schoder et al, 2005). In a retrospective study Chang and colleagues (2003) examined 24 patients with a rising PSA level; PET findings were correlated with pathologic evaluation from a lymph node dissection, the gold standard for disease confirmation. At the sites of pathologically proven metastases, increased FDG uptake suggestive of metastatic disease was found in 12 of 16 patients (75%) (Chang et al, 2003).

Although there have been few well-controlled prospective studies of FDG-PET there are concerns about the ability of FDG to detect local and early metastatic disease, prompting investigations of newer PET modalities. Prostate cancer is associated with upregulated choline kinase activity and increased choline uptake. Choline is a component of phosphatidylcholine, which is a class of phospholipids and a major component of biologic membranes. Choline can be labeled with either carbon-11 ([^{11}C]choline) or fluorine-18 ([^{18}F]fluorocholine). In a prospective study, Scattoni and colleagues (2007) assessed 25 patients with PSA relapse and no evidence of local disease or bone metastases on conventional imaging who were imaged with [^{11}C]choline-PET/CT and then underwent pelvic lymph node dissection. [^{11}C]choline-PET/CT showed abnormal uptake in lymph nodes in 21 patients, 19 of whom had nodal metastases confirmed by histopathology. By comparison, CT or MRI revealed abnormal lymph nodes in 12 patients (Scattoni et al, 2007). Rinnab and colleagues (2007) retrospectively evaluated [^{11}C]choline-PET/CT detection of nodal recurrence in 50 patients in the presence of a rising PSA value. The overall sensitivity of PET/CT was 95% and specificity was 40%. Fluorinated choline (FCH) is also being studied because it has the advantage of a half-life of 110 minutes versus a half-life of only 20 minutes with [^{11}C] choline (DeGrado et al, 2001a, 2001b, 2002; Hara et al, 2002; Cimitan et al, 2006).

Another PET tracer under investigation is [^{11}C]acetate, because a high concentration of [^{11}C]acetate in primary and metastatic lesions has been seen in prostate cancer (Oyama et al, 2002). An advantage of [^{11}C]acetate is that it is not excreted by the kidneys, making it easier to visualize pelvic disease. In a preliminary study, uptake of [^{11}C]acetate and [^{11}C]choline radiotracers appeared similar (Kotzerke et al, 2003). Other preliminary studies suggest that radiolabeled acetate may detect locally recurrent disease, although all of these studies have been small and have had heterogeneous end points and populations (Sandblom et al, 2006). **At this time, PET should be considered investigational, and a positive PET should not be considered definitive proof that a patient has either metastatic or locally persistent disease.**

Antibody-Based Imaging

ProstaScint is the only imaging agent approved by the U.S. Food and Drug Administration (FDA) to detect occult metastatic disease in patients with early prostate cancer. It also is indicated for patients with a rising PSA and a negative or equivocal standard metastatic evaluation when there is a high clinical suspicion of metastatic disease. The basis of this scan is a murine antibody, 7E11, that is combined with indium-111 to target the internal domain of prostate-specific membrane antigen (PSMA), a transmembrane type II glycoprotein found on normal prostate tissue and prostate cancers (Israeli et al, 1993, 1994). However, anti-PSMA antibodies also are taken up in the gut, liver, kidney, and other normal tissues. ProstaScint scanning is associated with a significant number of false-positive and false-negative results, in part related to these areas of uptake (Sartor and McLeod, 2001) in part owing to inflammation and even in part owing to vascular sludge (Hinkle et al, 1998). The specificity of the test may be increased if the images obtained are fused with MRI (Schettino et al, 2004).

Biopsies and Clinical Decision Making

Many clinicians opt to sample palpable abnormalities in the prostate bed in a postprostatectomy patient. Indeed, even radiographic findings that are suggestive of locally recurrent or locally persistent disease may warrant pathologic confirmation. **Biopsy specimens that reveal locally persistent disease may prompt a decision to choose salvage radiation therapy or systemic therapy for at least local control of palpable tumor masses. However, most patients will not have palpable lesions, and most patients will not have evidence of locally recurrent disease. The yield of blind biopsies in the prostate bed is usually low, tends not to affect**

clinical decision making, poorly predicts for the efficacy of salvage radiation therapy, and should not be considered a standard of care (Leventis et al, 2001; Scher et al, 2004).

By contrast, performing a biopsy to prove locally persistent disease in the prostate after external-beam radiation therapy is essential before recommending that a patient receive a salvage radical prostatectomy, cryosurgery (Izawa et al, 2002), brachytherapy (Beyer 1999), or intraprostatic biologic or cytotoxic treatment. Because the risk of false-positive biopsy findings declines 2 years after the completion of radiation therapy, clinicians should wait at least that long before opting for biopsy.

MODELS TO PREDICT LOCAL VERSUS SYSTEMIC RECURRENCE AND TO PREDICT SURVIVAL

For the overwhelming majority of patients, biochemical relapse occurs far earlier than the development of radiographically evident findings or findings on physical examination or by biopsy. Given the limitations of these diagnostic studies, the focus of the clinician should be on using the PSA as a predictor of whether the patient will develop overt metastases, symptoms, or a high risk of death from disease. With such prognostic tools of clinical events the need for treatment can be determined and consideration can be given to what options are available and their likelihood of success in controlling the disease or, preferentially, eliminating it completely (Beekman et al, 2005).

Many prognostic and predictive models have been reported. Some use determinants that reflect the disease at the time of initial diagnosis and treatment, others at the time of relapse, whereas others center on PSA kinetics after the disease has definitively relapsed biochemically. All of the models "work" in defining what they are designed to predict. Indeed, clinicians are often at a loss to decide which of several models to use in predicting a key clinical event. Multiple models now exist to predict the likelihood of a patient transitioning to the clinical state of a rising PSA value (D'Amico et al, 1998; Zelefsky et al, 1998; Moul et al, 2001a), the likelihood that a surgically removed tumor would have a specific pathologic stage according to pretreatment clinical features such as PSA or Gleason score (Partin et al, 1993, 2001; Roach, 1993, 1996), and the likelihood a patient with localized disease would achieve a given median survival (Roach et al, 2000; Vollmer and Humphrey, 2001; D'Amico et al, 2002; Sandler et al, 2000). Nomograms also have been developed that combine many of these prognostic determinants, treat them as continuous variables in multivariate models, and allow specific predictions of an outcome for a patient with given clinical features (Kattan et al, 2000).

The models that have specific relevance to patients in the clinical state of a rising PSA value fall into several categories and are summarized in Table 108–1.

Predicting Local versus Systemic Relapse

The first question the clinician evaluating a patient with a rising PSA value must address is where is the disease? In general, low pretreatment PSA levels, lower-grade tumors, low clinical or pathologic staging, late time from definitive local therapy to PSA relapse, and long PSADTs generally indicate a low likelihood of developing distant radiographically apparent metastases (Pound et al, 1999). Such patients can have durable remissions after salvage radiation therapy to the prostate bed (Moul, 2000; Leventis et al, 2001). Another modeling strategy is to examine patients who have successfully been "cured" using salvage radiation therapy and extrapolate from those data which features predict for exclusively locally recurrent disease. Features such as negative/close margins ($P = .03$), absence of extracapsular extension ($P < .01$), and presence of seminal vesicle invasion ($P < .01$) have been shown to predict for successful salvage radiation therapy (Katz et al, 2003). One multivariate model, derived from a retrospective examination of a multi-institutional database of patients who underwent salvage radiation therapy, showed that predictors of progression following salvage radiation therapy were Gleason score of 8 to 10 (hazard ratio [HR], 2.6; 95% CI, 1.7 to 4.1; $P < .001$), pre-radiotherapy PSA level greater than 2.0 ng/mL (HR, 2.3; 95% CI, 1.7 to 3.2; $P < .001$), negative surgical margins (HR, 1.9; 95% CI, 1.4 to 2.5; $P < .001$), PSADT of 10 months or less (HR, 1.7; 95% CI, 1.2 to 2.2; $P = .001$), and seminal vesicle invasion (HR, 1.4; 95% CI, 1.1 to 1.9; $P = .02$) (Stephenson et al, 2004).

A subsequent report by Stephenson and colleagues (2007), which included a larger group of patients (1540) from 17 tertiary care centers who were observed over a median of 53 months, validated the accuracy of the previous model. In the updated model the same cut points yielded a clinical outcome within 10% of the original model. Based on these data a nomogram predicting the 6-year progression-free probability was constructed. The trigger PSA for radiation therapy was found to be highly predictive of progression-free probability because patients with a trigger PSA of 0.5 ng/mL or lower had nearly double the likelihood of remaining disease free than those treated at higher PSA levels (26% vs. 48%). Other predictive factors were Gleason grade, doubling time, margin status, neoadjuvant hormonal treatment, and nodal status (Stephenson et al, 2007).

A second model examined 368 patients treated at multiple Mayo Clinic locations. This model again confirms that trigger PSA, doubling time, and pathologic staging are prognostic of a patient remaining disease free after salvage radiation therapy and that seminal vesicle involvement, Gleason score 8 to 10, and pre-radiotherapy PSA (treated as a continuous variable) are predictors of treatment failure (Buskirk et al, 2006).

In a third model, derived from 211 patients, factors predictive of biochemical failure included a PSADT of less than 12 months (HR, 3.88; $P = .032$), seminal vesical invasion in the surgical specimen (HR, 3.22; $P = .08$), pathologic grade (HR, 1.58; $P = .23$), and the PSA value at the time of salvage radiotherapy (HR, 1.29; $P = .04$) (Ward et al, 2004).

At what point should the odds of "predicted" success or failure justify recommending treatment is controversial, with the recognition that external-beam radiation therapy can, under the appropriate circumstances, offer at least a potential for disease eradication.

Risk of Developing Metastatic Disease

A corollary to distinguishing between which patients will benefit from salvage radiation therapy and which have micrometastatic disease is to model the risk and timing of developing radiographically evident metastases. Pound and colleagues (1999) observed a cohort of men who underwent radical prostatectomy, had biochemical relapse, and were observed without therapy until symptomatic or metastases

Table 108–1.

Models to Predict Clinically Significant Events in Patients with a Rising PSA Value after Definitive Local Therapy

STUDY	NO. PATIENTS	EVENT PREDICTED	Prognostic Variables				
			PSADT	MARGIN	GLEASON	PSA	OTHER
Leventis et al, 2001	49	Biochemical relapse-free survival after salvage RT	Treated as continuous, HR 0.30 (0.11-0.83; $P = .02$)	NA	NA	Pre-RT PSA treated as continuous, HR 3.22 (1.16-8.93, $P = .025$)	NA
Stephenson et al, 2004 (updated and validated in Stephenson et al, 2007)	501	PSA progression after salvage RT	≤10 mo, HR 1.7 (1.2-2.2; $P = .001$)	Negative margin HR 1.9 (1.4-2.5, $P < .001$)	Gleason 8-10, HR 2.6 (1.7-4.1; $P < .001$)	Pre-RT PSA > 2, HR 2.3 (1.7-3.2; $P < .001$)	SVI, HR 1.4 (1.1-1.9; $P = .02$)
Ward et al, 2004	211	PSA progression after salvage RT	≤12 mo, HR (3.88; $P = .032$)	SVI, HR (3.22; $P = .023$)	Pathologic grade (HR 1.58; $P = .023$)	2-fold increase (HR 1.29; $P = .04$)	NA
Pound et al, 1999	5079	Metastasis-free survival	≤10 mo, poor prognosis (Gleason ≤ 7 only)	NA	Gleason 8-10, poor prognosis	NA	≤2 years to biochemical failure, poor prognosis
Zagars and Pollack, 1997	841	Metastasis-free survival	≤8 mo, poor prognosis	NA	NA	NA	NA
Roberts et al, 2001	587	Metastasis-free survival	<0.5 yr, RR 62; 0.5-0.9 year; RR 9.1; 1-9.9 yr, RR 4.1	NA	NA	NA	NA
Zelefsky et al, 2005	381 (all patients)	Metastasis-free survival	Continuous, HR 0.59 (0.49-0.71); $P = .001$	NA	Gleason 7-10, HR 1.0 (1.2-3.3; $P = .007$)	NA	NA
Zelefsky et al, 2005	229 (no neoadjuvant ADT)	Metastasis-free survival	Continuous, HR 0.54 (0.41-0.70)	NA	Gleason 7-10, HR 2.7 (1.4-5.2; $P = .002$)	NA	T3 or T4, HR 2.0 (1.2-3.6; $P = .01$)
Kwan et al, 2004	1786	Overall survival (disease-specific survival is also included)	NA	NA	Grouped by overall risk category, $P < .001$	Any evidence of biochemical failure, $P < .001$; absolute PSA level, $P = .168$	T stage, $P = .033$ PSA
Lee et al, 1997	151	Disease-specific survival and overall survival	NA	NA	$P = .004$ (disease specific) or .03 (overall)	NA	NA
Sandler et al, 2000	154	Cause-specific survival	Relative PSA rise and log of slope of rise ($P < .001$ and .007)	NA	NA	NA	NA
D'Amico et al, 2002	94	Cause-specific death and all-cause death	≤12 mo ($P = .03$ cause specific; $P = .05$ all causes)	NA	NA	NA	NA
D'Amico et al, 2003	1451	Cause-specific mortality	<3 mo, HR 19.6 (12.5-30.9)	NA	NA	NA	PSADT ≥3 mo (continuous) HR 0.78 (0.74-0.82)
Trock et al, 2008	635	Cancer-specific mortality	<6 mo, HR 0.36 ($P < .001$)	Not significant	8-10 HR 1.77, $P = .003$	Trigger PSA of 2 ng/mL, HR 0.27	NA

ADT, androgen-deprivation therapy; HR, hazard ratio; NA, not applicable (either not analyzed or not statistically significant in a multivariate model); PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time; RR, relative risk; RT, radiation therapy; SVI, seminal vesicle invasion.

were found radiographically. As one would anticipate, high-grade disease, short time to biochemical relapse (≤2 years vs. >2 years), and a PSADT of less than 10 months versus 10 months or more predicted for a shorter time to radiographic progression. An updated analysis has been presented based on 8801 men who underwent prostatectomies, in 774 of whom the disease biochemically relapsed, and who were observed for a median of 8 years. In this updated cohort, patients could be stratified by doubling times of less than 3, 3 to 9, 9 to 15, and 5 or more months, by Gleason score (≥8 vs. <8), and by time to relapse (>3 vs. ≤ 3 years). Median time to metastatic disease was 10 years for the entire group, but, underscoring the heterogeneity of this disease state, those with the shortest doubling times developed metastatic disease at a median of 1 year (95% CI, 0 to 1 year), whereas those with a 15-month or more doubling time did not develop metastases for 10 years (95% CI, 9 to 15 years) after biochemical relapse (Antonarakis et al, 2009).

In numerous studies, PSADT is the dominant factor used to assess the risk of developing metastasis-free survival (Roberts et al, 2001; Valicenti et al, 2006). In one study, a PSADT of 6 months or less was associated with a 5-year progression-free survival of 64% versus 93% of patients who had a longer PSADT (Roberts et al, 2001). In the Mayo Clinic series, metastases were detected at 5 and 10 years, respectively, in 10% and 29% of patients with a PSADT of 12 months or less versus 0% and 17% for those with a longer PSADT. The estimation was based on a total of 23 metastatic events representing 10% (23 of 211) of the population studied (Ward et al, 2004). In a series of 1650 patients treated with external-beam radiation therapy at MSKCC, 381 (23%) developed biochemical recurrence, of whom 98 (26%) developed distant metastases at an incidence of 10%, 21%, and 29% at 1, 3, and 5 years, respectively. In a multivariate competing-risk regression model, PSADT ($P < .001$), clinical T stage ($P = .001$), and Gleason score ($P = .007$) from the time of diagnosis were the only independent variables that predicted for distant metastases. At 3 years, patients with a PSADT of 0 to 3, 3 to 6, 6 to 12, and 12 months or more had a frequency of metastasis of 49%, 41%, 20%, and 7%, respectively ($P < .001$), at a relative risk of 7.0-, 6.6-, and 2.8-fold higher than those with a more than 12-month doubling time. The median follow-up time was 92 months from the completion of radiation therapy.

Concerns regarding the use of PSADT are that at present there is no consensus regarding the optimal number of PSA values that should be used, the time interval over which they should be determined, whether these values need to be consecutive, and whether these values should be separated by a minimum period of time. Complicating the issue further is that PSA values can fluctuate independent of treatment. Most calculations are based on a first-order kinetics assumption that

$$PSA(t) = PSA(0)e^{at}$$

where "a" is the relative velocity of PSA. Published reports are inconsistent, but in the authors' experience a minimum of 3 (ideally 4 or 5) measurements are required. Given this, upwards of one third of the PSA profiles in this patient population follow higher-order kinetics; therefore the equation does not represent the kinetics for upwards of 30% of patients (Carter et al, 1992; Patel et al, 1997). Higher-order mathematical methods may better describe the PSA profiles for these men.

Another confounder in calculating PSADT is the effect of neoadjuvant or adjuvant hormonal therapy administered during radiation therapy. Rapid testosterone recovery may induce a rapid PSA rise, which may not reflect disease kinetics. Such a patient may not be at a significant risk of developing metastatic disease despite a seemingly rapid doubling time, because if he was observed long enough for the testosterone level to stabilize the rate of rise in PSA level could plateau or at least slow.

Risk of Disease-Specific and All-Cause Risk of Death

Data exist that demonstrate an association between PSADT and disease-specific survival after radiation therapy (Lee et al, 1997; Zagars and Pollack,1997; Sandler et al, 2000; D'Amico et al, 2002, 2003a, 2003b) and between a post-treatment PSADT and time to prostate cancer–specific mortality and all-cause mortality (all P[Cox] < .001). These data are illustrated in Figure 108–2. In this, the hazard ratio for death from prostate cancer for a patient with a PSADT of less than 3 months after surgery or radiation therapy was 19.6, with a 95% CI of 12.5 to 30.9 (D'Amico et al, 2003b, 2004b). **It is therefore reasonable to incorporate PSADT when considering whether any salvage strategy is worth applying, whether systemic therapy is more appropriate, and whether such systemic options should be applied early or should be deferred.**

In what is perhaps the largest series, Freedland and colleagues (2005) evaluated 5096 patients who underwent surgery at an urban tertiary care hospital between 1982 and 2000, with a mean and median follow-up of 6 and 5 years, respectively. Of these, 979 (19%) developed a biochemical recurrence and 379 (7.6%) who were deemed to have systemic as opposed to local progression had a minimum of two PSA values to estimate the doubling times. Sixty-six patients (1.3% of the entire group) died of prostate cancer during follow-up. Overall, 6% had a doubling time of less than 3 months and 15% of less than 6 months. Considering the entire cohort, the 5-, 10-, and 15-year cause-specific survival from the time of biochemical recurrence was 93% (95% CI, 90% to 96%), 73% (95% CI, 66% to 79%), and 55% (95% CI, 41% to 67%), respectively. Patients were stratified into high-risk and low-risk categories using the Gleason score from the radical prostatectomy specimen, time from surgery to PSA relapse, and PSADT. In one example, the median survival of the 23 patients with a PSADT of less than 3 months was 6 years; for the 15 patients with a PSADT of less than 3 months, biochemical recurrence of 3 years or less, and pathologic Gleason score of 8 to 10, the median survival was only 3 years. This contrasted to a 100% 15-year cause-specific survival for those with a PSADT of 15 months or more and a biochemical recurrence of more than 3 years after surgery. Using different combinations of these same variables, cohorts of patients with 15-year survivals ranging from 94% to less than 1% could be derived.

In an attempt to define what factors at the time of surgery might independently predict for developing a rapid PSADT after biochemical relapse, Teeter and colleagues (2008) examined data from 856 men listed in the Shared Equal Access Regional Cancer Hospital Database. PSA (OR, 2.20; 95% CI, 1.52 to 3.19), Gleason score greater than or equal to 8 (OR, 4.70; 95% CI, 2.11 to 10.43) or 7 (OR, 2.11; 95% CI, 1.09 to 4.08), and stage pT3a or worse disease (OR, 2.08; 95% CI, 1.48 to 3.91) were all predictors of developing a PSADT of 9 months or less.

These analyses share certain limitations: they were retrospective; the imaging modalities used to detect disease were not the same, nor were they performed at fixed intervals; and the numbers of events on which the models are based were often quite small.

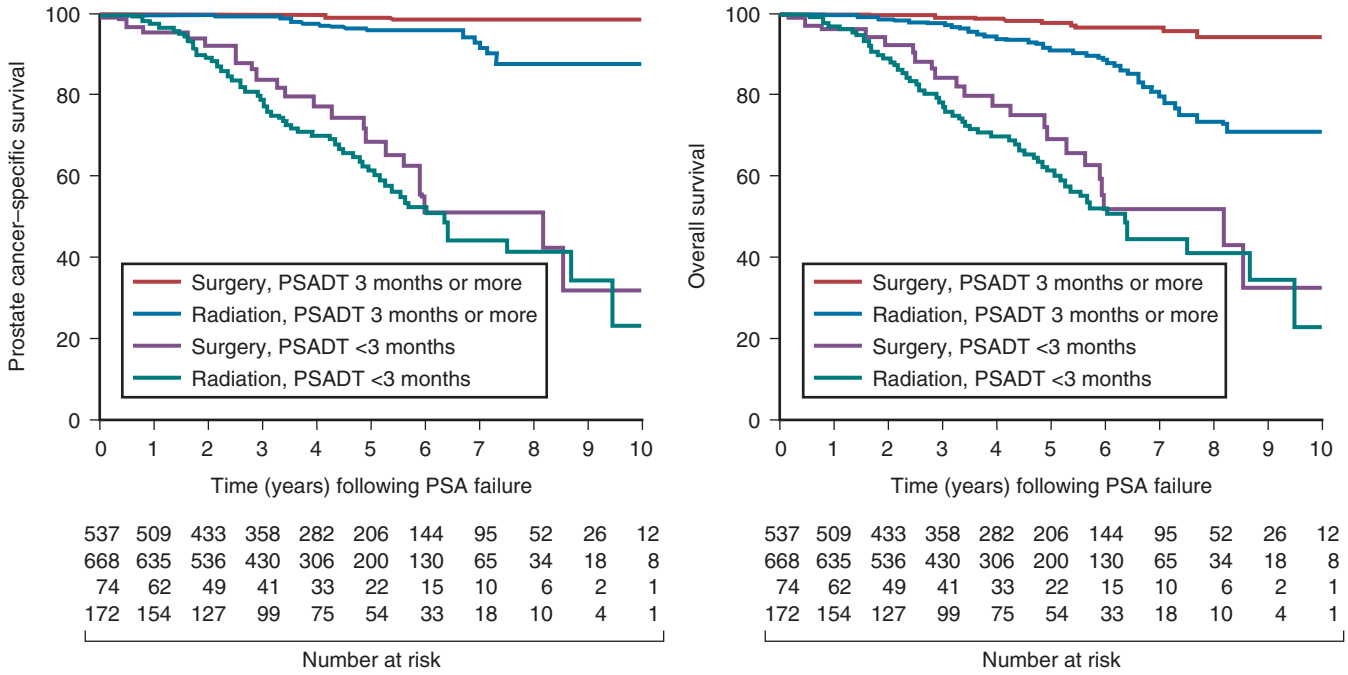


Figure 108–2. Prostate-specific antigen doubling time (PSADT) can be used to predict disease-specific *(left)* or all-cause *(right)* mortality for patients who have a rising PSA. In the model shown, patients are stratified on the basis of primary therapy and PSADT. Such models exist to predict for developing radiographically evident metastases as well and are crucial for rational clinical decision making and clinical trial design. (From D'Amico AV, Moul JW, Carroll PR, et al. Surrogate end point for prostate cancer–specific mortality after radical prostatectomy or radiation therapy. J Natl Cancer Inst 2003;95[18]:1376–83.)

Consequently, the confidence limits around the estimated survival probabilities are large. Despite these limitations the models, and in particular the PSADTs, do provide prognostic information. They do not, however, represent surrogate markers for metastatic progression or survival because they were not derived from prospective randomized comparisons in which a beneficial effect of treatment was shown.

TREATMENT STRATEGIES FOR THE PATIENT WITH A RISING PSA VALUE

It is essential to recognize that treatments given to patients with a low risk of a clinically significant event can be harmful in ways not traditionally assessed in clinical trials. In fact, few studies have systematically and prospectively assessed the compromises in patients' cognitive function and emotional well-being, overall quality of life, sexual health, cardiovascular risk, or bone integrity as primary end points. Those studies that have been performed suggest that hormonal therapy can be detrimental in all of these areas (Herr and O'Sullivan, 2000; Berruti et al, 2002; Green et al, 2004; Shahinian et al, 2005; Keating et al, 2006; Saigal et al, 2007; Tsai et al, 2007).

These potential drawbacks of hormonal therapy must be at the forefront of practitioners' minds when making decisions about this patient population, given that there are no prospective randomized data comparing any hormonal approach against no treatment for this group of patients. **Deferring treatment, especially for low-risk patients, may indeed be in the patient's interest, difficult as it may be for both patient and clinician to observe the patient's disease "progress" by a rising marker.** Indeed, the American Society of Clinical Oncology Clinical Practice Guidelines formally argue against an "early" treatment policy, with the caveat that patients preferentially should be entered into clinical trials (Loblaw et al, 2004, 2007).

Adding to this conundrum is that clinicians have no data regarding the optimal PSA value at which to initiate treatment, even for patients who are at high risk of suffering or dying of their disease. Some practitioners have advocated that androgen deprivation be started at the time of biochemical relapse, or at arbitrarily established thresholds, such as when the PSA level reaches 10 or 20 ng/mL. Such thresholds are based on data indicating that the risk of developing radiographically evident metastases increases as the PSA level rises. However, guidelines based on absolute PSA levels generally do not account for the rate of PSA level rise, Gleason score, or pretreatment PSA level, all of which have been shown, as described earlier, to be important prognosticators of time to metastatic disease, progression-free survival, and overall survival. Therefore, contemporary models that determine an individual patient's risk of metastatic progression and death from disease should be used as the basis for risk assessment in this population. What level of risk is tolerable in a given time frame is a decision to be made after a thorough discussion between the patient and his physician.

Neither clinicians nor patients, however, are immune to the impact of a significant body of literature suggesting that early hormonal therapy has the potential to confer a survival advantage in selected patients relative to hormonal therapy that has been deferred until metastases are radiographically evident. Most are randomized trials of androgen deprivation applied before, during, and after radiation therapy for variable amounts of time (from 6 months to continuously), which show improvements in disease-free and overall survival compared with either no hormonal therapy or hormonal therapy that has been deferred until diagnosis of metastatic disease (Lawton et al, 2001; Bolla et al, 2002; Pilepich et al, 2003, 2005; D'Amico et al, 2004a, 2008; Horwitz et al, 2008).

Table 108–2.

Prospective Randomized Studies of Deferred Versus Early Hormones*

STUDY	NO. PATIENTS	STAGE	THERAPY	FOLLOW-UP (yr)	OVERALL SURVIVAL (%)
RTOG 85-31 (Pilepich et al, 2005)	977	T3 or any T/N1	None vs. goserelin indefinitely	8	39 vs. 49; $P = .002$
EORTC 22863 (Bolla et al, 2002)	415	T1-2 (WHO grade 3)/ N1-N2 or T3-4/N0-1/M0	None vs. goserelin × 3 yrs	5	62 vs. 78; $P = .0002$
D'Amico et al, 2008	206	T1b-T2b + unfavorable risk factor	None vs. LH-RH/ flutamide	8	HR 1.8; $P = .01$
Messing et al, 1999, 2003, 2006	98	Node + after RRP	Goserelin or orchiectomy vs. observation	12	64 vs. 45; $P = .001$ (HR 1.84; $P = .04$)
EORTC 30891 (Studer et al, 2006)	985	T0-4N0-2M0	Immediate vs. deferred ADT	8	48 vs. 43; HR 1.25 (noninferiority $P > .1$)

*None addresses the rising prostate-specific antigen population directly, but using the results of these trials and the models in Table 108–1 can help the clinician decide whether a given patient would benefit from early hormonal therapy.

ADT, androgen-deprivation therapy; HR, hazard ratio; LH-RH, luteinizing hormone–releasing hormone; RRP, radical retropubic prostatectomy.

These trials are summarized in Table 108–2. Most of these trials are underpowered and do not consider recent trials supporting a deferred or intermittent therapy approach. In addition, the problem with using these trials as a basis for deciding on early hormonal therapy for patients with a rising PSA level is that patients with localized disease are not directly comparable to patients whose treatments have failed and who are now at risk of developing radiographically apparent metastases as the next point in the natural history of their disease.

As a result, one cannot assume that patients with a rising PSA value will derive the same benefits demonstrated in trials with patients occupying other clinical states. Hence, to the strictest and most orthodox adherents of evidence-based medicine, the standard of care for these patients should be observation or registration to a clinical trial. Such practitioners argue that there are no clinical data to demonstrate that hormones applied at biochemical relapse make patients live longer than hormones applied at the time of metastatic disease and that early hormonal therapy subjects such patients to a risk of impotence, gynecomastia, depression, weight gain, osteoporosis, fatigue, anemia, or other hormone-related disorders, with no proven benefit.

Some practitioners have treated these patients with antiandrogen monotherapy, based on results of the Early Prostate Cancer trial. In this series of studies, 8113 men with T1-4, Any N, M0 disease (although eligibility mandated N0 status in one study) were randomized to receive either 150 mg of bicalutamide or placebo in addition to standard care, which was either surgery, radiation, or observation. No difference in survival between the two study arms was seen in the overall population (HR, 1.03; 95% CI, 0.92 to 1.15; $P = 0.582$), although the patients with localized disease on observation appeared to have a survival decrement if they received bicalutamide (HR, 1.23; 95% CI, 1 to 1.5; $P = .05$) (Iversen et al, 2004; Wirth et al, 2004; McLeod et al, 2006). The use, however, of a non–testosterone-lowering form of androgen deprivation as adjuvant or primary therapy cannot be extrapolated to using testosterone-lowering therapy in a group of patients with a rising PSA level whose primary tumors have been treated. Single-agent bicalutamide has been studied in patients with either metastatic or locally advanced disease in two trials, but again neither study directly addressed the population at hand (Boccardo et al, 2002; Tyrrell et al, 2006).

Moul and colleagues (2004) retrospectively examined data collected from the Center for Prostate Disease Research Multicenter National Database (a Department of Defense program) on 1352 patients who had undergone a prostatectomy in the PSA era and who had experienced biochemical relapse. Various PSA cut points relative to when these patients were started on androgen deprivation therapy were examined, as were Gleason scores and other prognostic indicators. Interestingly, initiating hormonal therapy early did not appear to impact time to metastatic disease, which was the primary end point examined, in the overall population studied. On the other hand, time to metastatic disease was delayed in patients with Gleason score 8 to 10 tumors and those with PSADTs of 12 months or less (HR, 2.12; $P = .01$) if hormones were started at a PSA level of 5 ng/mL or less as opposed to 10 ng/mL or less. Unfortunately, these data do not inform the clinician as to whether early hormones in this population prolong survival but the data strongly suggest that the clinician should carefully select the patients he or she ultimately subjects to such therapy.

Once the decision is made to administer treatment the questions that arise are the same as those relating to the use of hormonal therapy in patients with clinical metastases (Wirth et al, 2004): Can intermittent hormones mitigate the side effects of androgen deprivation and improve the period of time of sensitivity to androgen withdrawal? Is total androgen blockade superior to orchiectomy or gonadotropin-releasing hormone monotherapy? Does high-dose bicalutamide prolong overall survival or shorten it (as in patients with localized disease)? These questions are the source of great discussion and debate. A recently completed phase III trial has done much to establish intermittent hormonal therapy as a standard of care in the rising PSA population (Klotz et al, 2011). In this study, men with a rising PSA >3 ng/mL who biochemically relapsed in excess of 1 year after radiation therapy were randomized to either intermittent hormones or continuous androgen deprivation. The primary endpoint was demonstrating noninferiority of the two arms in regard to overall survival, with secondary endpoints of time to castration-resistant disease, quality of life, and various endocrinologic parameters. A total of 1386 patients were randomized, with a median follow-up of 6.9 years. The two arms did indeed have no significant difference in overall survival (HR, 1.02 with a P for noninferiorrity of .009). Time to castration resistance was improved in the intermittent hormonal therapy arm (HR, 0.80; $P = .024$), and while more deaths from disease were seen in the intermittent hormones arm, there were fewer unrelated deaths in the intermittent arm as well. This trial therefore allows the clinician to consider intermittent hormones to be a standard, if not the standard, of care in the rising PSA population.

CLINICAL CONSIDERATIONS REGARDING LOCAL TREATMENTS

Patients who have demonstrable disease in the prostate bed may be considered for salvage radiation therapy and/or hormonal therapy specifically for the purposes of local control (rather than cure) and for preservation of pelvic functionality. Although there is uncertainty as to when these symptoms might occur, patients with local tumor masses are at risk for bowel and urinary obstruction, pain, and bleeding, and the avoidance of these events is critical to preserving quality of life. Whether this is best achieved with androgen deprivation alone is uncertain.

Patients who are anticipated to survive longer than the median duration of androgen deprivation (which generally is no longer than 2 years) may fare better with salvage radiation therapy in addition to or instead of hormonal therapy. In one analysis of 42 patients with a rising PSA level after prostatectomy with palpable cancer on digital rectal examination, patients who underwent salvage radiation therapy had a median rate of remaining free of recurrent local disease of 94%, despite the fact that only 27% of patients were free of biochemical progression (Macdonald et al, 2003).

In another investigation of 35 patients with locally recurrent disease that was clinically evident by biopsy or physical examination, the 8-year clinical relapse-free survival rate was 80% (vander Kooy et al, 1997). Although patients with clinically evident locally recurrent disease may have a worse overall prognosis than patients with a rising PSA alone (in one study, median survival was 78% vs. 96%, respectively; $P = .02$) (Macdonald et al, 2004), salvage radiation therapy may be an important tool in preserving quality of life.

However, the majority of patients in this clinical state will not have clinically evident disease in conjunction with a rise in PSA value. It is for these patients that models were developed to help assess the likelihood of durable PSA control after salvage radiation therapy. In the model of Stephenson and colleagues (2007) favorable outcomes were associated with long PSADTs and lower Gleason scores. In addition, a low PSA level at the start of radiation therapy ("trigger PSA") was associated with a favorable outcome, because 48% of patients who had a trigger PSA of 0.5 ng/mL had a 6-year progression-free survival, compared with 26% for those treated with higher trigger PSA values. Finally, late time to relapse (>2 years) and positive surgical margins were favorable prognostic indicators.

In contrast, 635 men who experienced biochemical relapse after radical prostatectomy and received salvage radiation therapy at Johns Hopkins Hospital were retrospectively analyzed by Trock and colleagues (2008) for disease-specific survival. In the overall population studied, patients who underwent salvage radiation therapy were significantly less likely to die of prostate cancer at 5 and 10 years than those who did not (0.96 and 0.86 vs. 0.88 and 0.62, respectively, $P < .001$), regardless of whether hormones were used with the radiation therapy. Many of the elements of this model disagree with those of the model of Stephenson and colleagues. In the analysis of Trock and colleagues, patients with short PSADTs (<6 months) who had salvage radiation therapy died at a significantly lower rate than their counterparts who did not receive salvage therapy, with a reduction in risk of prostate cancer–specific mortality of more than 75%. Men with longer PSADTs appeared not to benefit from salvage radiation therapy. In addition, receiving radiation therapy within 2 years of surgery and at a trigger PSA level of 2 ng/mL or less predicted for longer disease-specific survival. It should be noted that the models of Stephenson and Trock and their colleagues differ in end points—the former used progression-free survival whereas the latter used disease-specific survival—and the databases differ as well; nonetheless, contrasting these analyses gives the clinician pause and generates uncertainty as to who should be referred for salvage radiation therapy. It is the authors' practice to err on the side of potentially increasing survival by over-referring patients for radiation therapy rather than under-referring them. Certainly, however, the health status of the patient and the potential for rectal and urinary toxicities should lessen the temptation to simply refer all patients for salvage radiation therapy.

CLINICAL TRIAL CONSIDERATIONS

Patients and Agents

The rate of referrals to trials of neoadjuvant and adjuvant therapy has historically been low, in spite of the possibility that systemic therapy may be more effective in the earliest stages of the disease. Systemic therapy that confers only modest benefits in the latest phases of disease has been shown, in colorectal, thoracic, and breast malignancies, to be more effective in patients with early disease and is now the standard of care in those malignancies. But despite the fact that the response proportions with chemotherapy in prostate cancer are equivalent to or exceed those of the diseases just cited, neoadjuvant and adjuvant trials in prostate cancer have been slow to accrue, owing to both physician and patient reluctance to join such studies.

By contrast, patients who have a rising PSA level are ideal candidates for a clinical trial. They are highly motivated to join studies, especially when they see by the rising marker that they have unequivocally experienced relapse; and their risk of developing metastases and dying of their disease can be estimated with relative accuracy. In particular, high-risk patients, who may develop metastatic disease within a few years of presentation and die of their disease within a decade, are frequently eager to aggressively pursue early treatments, as may be their physicians. Given that there is no true standard of care for patients in this clinical state and there have been no definitive studies demonstrating that either the type or timing of hormonal therapies impacts survival, patients should most appropriately be referred to a clinical trial for treatment.

Patients can be divided into three groups based on prognosis: low-risk patients are unlikely to develop metastases or symptoms or die of their disease and should be managed expectantly; intermediate-risk patients receive androgen deprivation or can be considered for investigational approaches designed to slow the disease to the point where the patient dies of other causes (tantamount to cure); and high-risk patients (those with PSADTs of ≤9 months) can be considered for androgen deprivation or, ideally, enrolled in a clinical trial.

A significant challenge for the treating urologist or oncologist, or even the clinical investigator, is matching the right therapy with the appropriate patient population. Decades of research on the biology underlying prostate cancer tumorigenesis, growth, and resistance to treatment has increased the number and types of compounds available for evaluation. This presents to both

patients and physicians the dilemma of having too many choices. These choices include vaccine-based approaches, which aim to stimulate an immunologic response that results in an antitumor effect, and classes of agents being tested that target the metastatic cascade or the bone microenvironment. Pathways that impact angiogenesis, growth, differentiation, and apoptosis are also under study.

High-risk patients both medically warrant and will accept therapies with higher treatment burdens and side effect profiles, in hopes of disease eradication rather than control. In the spring of 2004, docetaxel was approved by the FDA for the treatment of patients with metastatic prostate cancer that was progressing in spite of castrate levels of testosterone. This approval was supported by a 20% to 25% reduction in the risk of death of such patients registered to two separate clinical trials, TAX327 and SWOG9916, relative to the previous chemotherapy standard of care: mitoxantrone and prednisone. Given the limited prognosis of such patients, this risk reduction translated into only a modest overall survival benefit of 2 to 3 months (Petrylak et al, 2004; Tannock et al, 2004). The overall survival benefit is commensurate with taxane-based and other treatments in patients with advanced solid tumors that are already refractory to previous systemic therapy (Nabholtz et al, 1999; Saltz et al, 2000; Shepherd et al, 2000). There are numerous examples in oncology in which seemingly modest survival benefits in advanced disease translate into increased cure rates when applied early. It is the authors' view that patients with unfavorable PSA kinetics who are at high risk of developing metastases or dying of their disease are a group who not only need systemic therapy but are also most likely to benefit from it.

Currently, the only phase 3 clinical trial to address the needs of high-risk postprostatectomy patients with a rising PSA value is TAX3503, which targets patients with a PSADT of 9 months or less, correlating to a metastasis-free survival of 4 to 5 years and overall survival of 9 to 10 years. Patients are randomized to 18 months of androgen deprivation, either alone or with 10 cycles of docetaxel. The primary end point is progression-free survival and is powered to demonstrate the hypothesis that progression-free survival can be improved from 50% to 65% for a minimum 36 months after the beginning of treatment. Progression-free survival is defined as no detectable PSA in the context of testosterone levels having recovered to noncastrate levels. Controlling for testosterone levels is novel, ensures that patients are not declared to be disease free during the period in which they were simply responding to hormones, and was integral to regulatory acceptance that such patients were indeed truly free of evidence of disease. This trial is nearly entirely accrued at the time of this writing.

Outcome Measures for the Patient with a Rising PSA Value

There are several useful end points for trials in this clinical state. The most immediate of these is the post-therapy change in PSA. The attraction of measuring serial PSA levels is that these assays can be obtained simply and frequently, with minimal inconvenience to the patient. The definition of a favorable post-treatment PSA alteration will depend on the type of agent tested. Examples of such changes are seen in Figure 108–3. Rapid post-treatment PSA declines, with or without escape, are seen with hormonal therapy and chemotherapy (see Fig. 108–3A and B). An example of a study using such end points is a phase 2 study of docetaxel, estramustine, and androgen deprivation for patients with a rising PSA value and no metastases after surgery or irradiation. A complete response was considered to be a post-treatment PSA decline below the assay's level of detectability. The primary end point was time to biochemical progression, with a variable definition depending on whether the patient underwent surgery or radiation therapy as his primary treatment (Taplin et al, 2006). Similarly, TAX3503, discussed earlier, compares androgen deprivation therapy with and without docetaxel in postprostatectomy patients with high-risk doubling times and utilizes as a primary end point duration of time that a patient's PSA value achieves a nadir of no measurable amount, with a confirmed detectable PSA level representing a treatment failure.

In "broken arrow" post-treatment PSA alterations (see Fig. 108–3C, D, F, and G) such changes might be seen in static agents, biologic therapy, or immune agents, with either immediate effects (see Fig. 108–3C) or delayed effects (see Fig. 109–3D). The clinical significance of these post-treatment PSA alterations, however, is entirely unknown. As a result, such changes are a difficult yardstick by which to assess whether a drug should be advanced to phase 3 trials or abandoned. PSA kinetics can be particularly vexing in this context, because simply measuring the PSA level on a regular fixed basis on study can result in an altered rate of rise relative to pretreatment PSA kinetics measured by the schedules typical in routine clinical practice, even if a patient is not receiving active therapy. In one randomized study comparing treatment with a biologic agent versus a placebo in 106 patients, 40% of men in the placebo group and 38% of men in the treatment group had a post-treatment PSADT greater than or equal to 150% of the baseline PSADT (Smith et al, 2004).

Because of these vagaries and the lack of prospective, validated data associating a post-treatment PSA alteration with clinical outcome, PSA-based end points are not surrogates for survival. A surrogate end point is an outcome variable that can substitute for a definitive end point and does not directly alter the treatment effect. Several investigators have proposed that post-therapy PSA changes be used as surrogates for clinical benefits, such as time to metastases or prostate cancer–specific mortality in different clinical states (D'Amico et al, 2003b, 2004b; Kelloff et al, 2004). **The demonstration of an association does not equate with surrogacy, and a large proportion of the association between PSA-based metrics and clinical outcomes has yet to be unexplained.** An additional consideration is that surrogacy cannot be "proven" in the absence of a prospective randomized trial that demonstrates the superiority of one regimen over another. **It is therefore both unsurprising and appropriate that post-therapy PSA changes have not been adopted by the FDA as an intermediate end point that can be used for an accelerated approval in this patient group.**

Other outcome measures independent of PSA, such as metastasis-free survival, delaying the onset of symptoms, or death from disease, must be considered in the context of the risk/reward ratio of intervention versus no intervention. Trials with an end point of clinical progression may be problematic because patients will not remain on observation until the clinically significant event occurs if the PSA value continues to rise, making the risk-reward ratio difficult to quantitate. In practice, the proportion of patients who remain on study without metastatic disease, who receive secondary therapy before the end point of metastatic disease, and who develop metastatic disease should be recorded separately. Finally, assessing quality of life is essential, particularly when the morbidity of the therapy may outweigh the survival benefit and

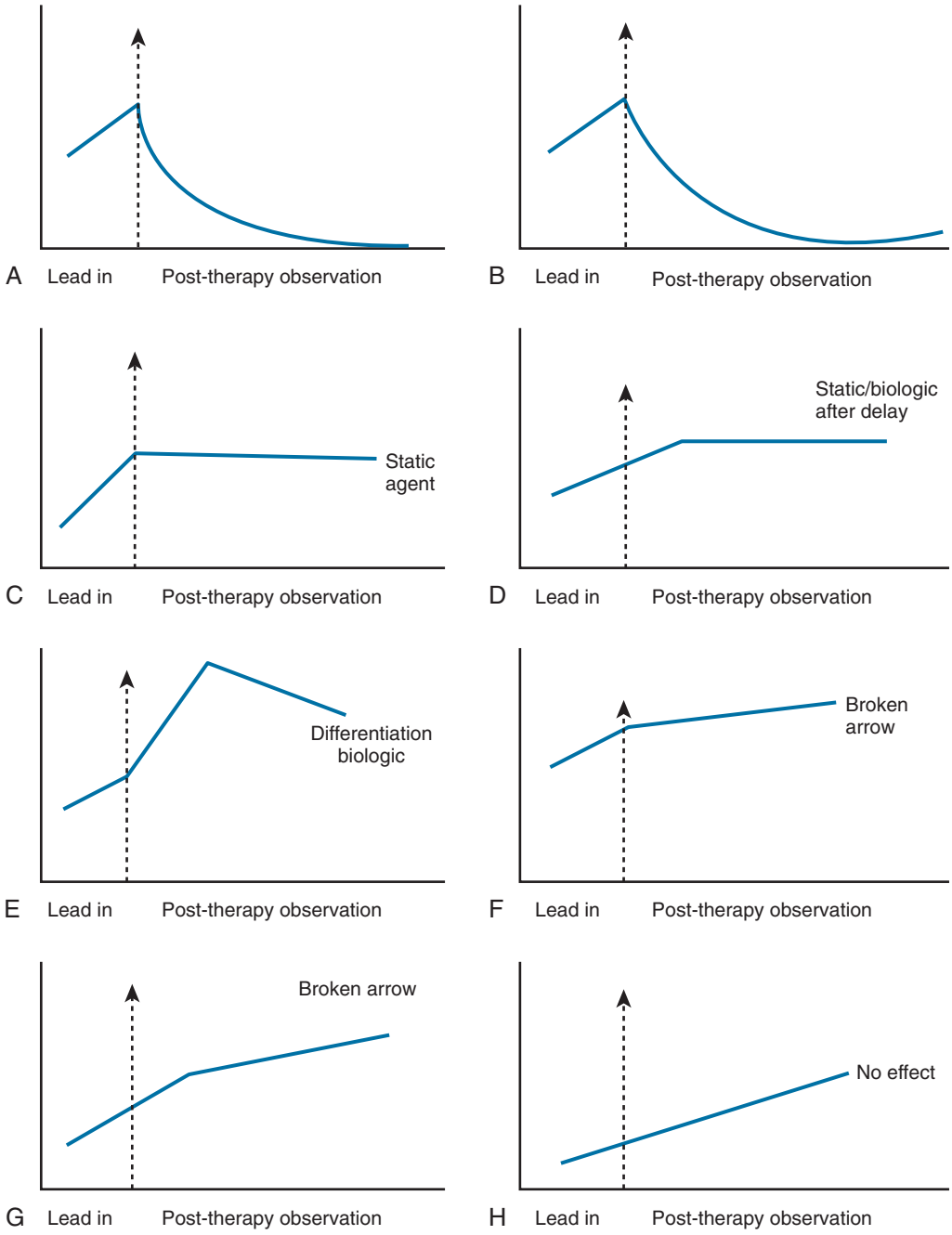


Figure 108–3. **A** to **H**, End points in clinical trials of the rising prostate-specific antigen (PSA) population vary by the type of agent being tested, as shown. The end point must match the mechanism of the drug, although no post-treatment PSA alteration should be used to presume that a clinical benefit has been demonstrated. (From Scher HI, Eisenberger M, D'Amico AV, et al. Eligibility and outcomes reporting guidelines for clinical trials for patients in the state of a rising prostate-specific antigen: recommendations from the Prostate-Specific Antigen Working Group. J Clin Oncol 2004;22[3]:537–56.)

the therapy is administered early in the disease process. Symptom-induced distress, sense of well-being, and self-assessed quality of life should be evaluated, using utilities that yield a quality-adjusted survival time metric or a sensitive measure of symptom frequency, intensity, and duration. A complete discussion of these issues can be found in a recent consensus report by experts in the field (Scher et al, 2004).

SUMMARY

The widespread implementation of PSA screening has created a new disease state, which now includes a group of patients with prostate cancer that is second in size only to those with localized disease. The state of rising PSA value is unique in that patients are characterized by an absence of symptoms, radiographic findings,

Key Points

- The clinical state of rising PSA level defines the second largest group of prostate cancer patients.
- This clinical state refers to biochemical failure after definitive local therapy, in the absence of findings of metastatic disease on standard imaging studies. It does not include patients treated with hormones alone and no definitive treatment to the primary tumor.
- The value of the PSA that defines biochemical failure is contingent on the type of primary therapy (surgery vs. irradiation), the testosterone recovery rate after neoadjuvant or adjuvant hormone therapy, and the sensitivity of the PSA assay used.
- Prognostic models can and should be used to determine the likelihood that a rising PSA level signifies local or systemic recurrence. Therapeutic decision making should be guided accordingly.
- Prognostic models can and should be used to stratify patients for metastasis-free survival, disease-specific survival, and overall survival. Decisions about the timing and type of systemic therapy applied should be guided accordingly.
- Although there are many different models, most have shown that PSADT and Gleason score are highly prognostic for clinical outcome.
- There is no standard of care for patients who occupy this clinical state. Clinical trials are highly appropriate for these patients and generally use risk-adapted strategies to match patients who face a given clinical risk with treatments of appropriate intensity and mechanism of action. Indirect and highly derivative data suggest that early androgen deprivation may be of benefit to high-risk patients.
- Trial designs for these patients, who have no measurable disease and who face highly variable clinical risks, are unique. Efforts to standardize the elements of these studies are under way and have been published as a consensus report.

or pathologic findings—standard measures of treatment effects. Although there is no definitive standard of care for these patients, risk-stratifying models can be used to distinguish patients who are at high risk of developing metastatic disease or of death. The PSADT is one of the most common elements for stratifying patients. High-risk patients should be treated on clinical trials and in the absence of such should be considered for androgen-ablative therapies. A wide range of new therapies are available for testing, from traditional cytotoxic drugs to novel agents that target specific pathways. Alternatively, patients whose predicted risk of metastatic disease is low may benefit from local salvage therapies.

SUGGESTED READINGS

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chapter
109

Hormone Therapy for Prostate Cancer

Joel B. Nelson, MD

Historic Overview
Molecular Biology of Androgen Axis
Sources of Androgen
Mechanisms of Androgen Axis Blockade
Response to Androgen Blockade
General Complications of Androgen Ablation
Combination Therapy
Timing of Therapy
Economic Considerations
The Future of Hormone Therapy

HISTORIC OVERVIEW

The response of prostate cancer to androgen ablation is among the most reproducible, durable, and profound of any systemic therapy for a solid tumor. The early and frequent descriptions of immediate relief of bone pain from metastatic prostate cancer after castration do not diminish the marvel of observing this phenomenon first hand. As is the case with many paradigm-shifting observations, endocrine therapy was based on a simple hypothesis. Described as a "biological syllogism," the idea had a major premise—"In many instances a malignant prostatic tumor is an overgrowth of adult epithelial cells," a minor premise—"All known types of adult prostatic epithelium undergo atrophy when androgen hormones are greatly reduced in amount," and a conclusion—"Therefore, significant improvements should occur in the clinical condition of patients with far advanced prostate cancer subjected to castration" (Huggins, 1947).

It had been known for at least a century that prostatic epithelium undergoes atrophy after castration (Hunter, 1840). The breakthough in Huggin's hypothesis was the recognition that benign prostatic epithelium and prostate carcinoma were biochemically analogous and they would respond in a similar fashion to androgen ablation. Emphasizing the importance of basic observations—"The evidence for the facts which represent the premises was obtained entirely in the laboratory" (Huggins, 1944)—studies on acid phosphatase provided the crucial link between benign and malignant prostate cells. Large amounts of acid phosphatase were found in the prostate glands of men and monkeys (Kutscher and Benjamin, 1935) and in primary and metastatic prostate cancer (Gutman et al, 1936), and the levels increased with androgen administration (Gutman and Gutman, 1938a). Serum levels of acid phosphatase were increased in men with disseminated prostate cancer (Barringer and Woodard, 1938; Gutman and Gutuman, 1938b). With localization of the enzyme to prostatic epithelial cells and primary and metastatic prostatic cancer cells (Gomori, 1939), the stage was set for Charles Huggins, R. E. Stevens, and Clarence V. Hodges to test the hypothesis in men with prostate cancer.

Despite negative results of castration in two men with prostate cancer reported by Young (1936), a series of 21 consecutive patients with locally advanced or metastatic prostate cancer underwent surgical castration at the University of Chicago. "A noticeable improvement occurred in the clinical status of all but three patients" with weight gain, resolution of anemia, and improvement in pain (Huggins et al, 1941). Other reported consequences of castration—a large appetite for food, loss of sexual desire and penile erections, and hot flashes—remain the common side effect profile of androgen ablation therapy today. **Although this report was the first to describe the benefits of androgen ablation in the treatment of prostate cancer it also created a new disease state: androgen-refractory prostate cancer.**

In considering these "failure cases" (Huggins, 1942), it was found that those with small testes at the time of castration had a poor prognosis, the first description of a more ominous prostate cancer arising in the hypogonadal man. After castration, rises in the levels of urinary 17-ketosteroids, a major metabolite of the adrenal gland, led to the hypothesis that adrenal androgens contributed to subsequent disease progression. The first reports of bilateral adrenalectomies for the treatment of castration-resistant disease (Huggins and Scott, 1945) are described later in a somewhat defensive manner (Scott, 1954), owing, perhaps, to the lack of response and high perioperative mortality. Hypophysectomy and pituitary irradiation (Murphy and Schwippert, 1951) were also investigated. Unfortunately the benefits of surgical castration were soon equaled by the tenacity and inevitable progression of androgen independence, a state still synonymous with the lethal form of the disease. Even in accepting the Nobel Prize for this work in 1966, Charles Huggins admitted "Despite regressions of great magnitude, it is obvious that there are many failures of endocrine therapy to control the disease" (Huggins, 1972).

Direct ablation of the source of androgen, like surgical castration, is only one of the perturbations of the hypothalamic-pituitary-gonadal axis developed to treat prostate cancer. **The first central inhibition of the axis exploited the potent negative feedback of estrogen on luteinizing hormone (LH) secretion: it is now known that estradiol is a 1000-fold more potent at suppressing LH and follicle-stimulating hormone (FSH) secretion by the pituitary compared with testosterone** (Swerdloff and Walsh, 1973). The effects of estrogen on the male phenotype, namely, regression of androgen-sensitive tissues, have been exploited, historically, to produce the effects of castration without surgical removal of the testes. For example, capons (neutered roosters) were produced by placing estrogen pellets in the neck of the bird rather than by castration (Scott, 1954). Among the various estrogenic compounds diethylstilbestrol (DES) has been most widely studied and used. Early studies indicating improved survival in men treated with both surgical castration and continuous DES (Nesbit and Baum, 1951) have not held up under further scrutiny, but the equivalence of DES compared with castration has. Indeed, given the effectiveness of the considerably less expensive estrogenic compounds it is unfortunate the associated cardiovascular toxicity has limited their widespread use.

The first isolation of luteinizing hormone–releasing hormone (LH-RH) by Schally and colleagues (1971, 1992) required the hypothalami of 165,000 pigs to obtain 800 μg of the 10 amino acid peptide. This 1977 Nobel Prize–winning work led to the development of synthetic LH-RH analogues, peptides generated by substituting D-amino acid residues at certain locations in the natural compound, creating both LH-RH agonists and LH-RH antagonists. **After an initial surge in LH release (and testosterone levels) in response to LH-RH agonists the loss of phasic pituitary stimulation results in plummeting LH levels. In the absence of LH, Leydig cell production of testosterone drops to castrate levels.** Initially, the clinical utility of these agents was hampered by their short half-lives, requiring daily injections to maintain suppression of the hypothalamic-pituitary axis. The generation of long-acting depot preparations, lasting several months, has established LH-RH agonists as the dominant treatment in hormone therapy for prostate cancer. Recently, direct LH-RH antagonists have been developed for clinical use. Lacking agonist action, these agents do produce the surge in LH and testosterone. It is interesting that both classes of compounds were developed within a few years of the discovery of LH-RH and yet it took decades to develop clinically useful agents.

Moving beyond strategies targeting the hypothalamic-pituitary axis, interruption of ligand-receptor interaction with antiandrogenic compounds is another way to reduce androgen action in prostate cancer. **All antiandrogens inhibit androgen action by binding to the androgen receptor in a competitive fashion and are classified as either steroidal or nonsteroidal.** The steroidal antiandrogen cyproterone acetate is a derivative of 17-hydroxyprogesterone and suppresses LH release (and testosterone production) through its central progestational inhibitory effects. Therefore steroidal antiandrogens block androgen action at the cellular level and also reduce circulating testosterone levels, leading to the classic side effects of the hypogonadal state such as loss of libido and erectile dysfunction. On the other hand, **the nonsteroidal antiandrogens have no antigonadotropic effects and simply block androgen receptors, including those in the hypothalamic-pituitary axis. By blocking the normal inhibiting feedback of testosterone the antiandrogens produce a paradoxic increase in LH and testosterone.** Although this maintenance of testosterone preserves potency, the peripheral conversion of this excessive testosterone to estrogen can lead to painful gynecomastia.

MOLECULAR BIOLOGY OF ANDROGEN AXIS

The androgen receptor (AR) is a member of the nuclear receptor superfamily, which includes the sex steroids (androgen, estrogen, progestin), adrenal steroids (mineralocorticoids, glucocorticoids), thyroid hormones, vitamin D, and retinoids. These receptors act as ligand-inducible transcription factors, meaning that they cause transcription of target genes within specific cells after ligands (e.g., testosterone) bind to them. **All current forms of androgen-deprivation therapy (ADT) function by reducing the ability of androgen to activate the AR, whether through lowering levels of androgen or by blocking AR binding** (Fig. 109–1). Therefore the AR is not directly affected by ADT, leading many to hypothesize that castration-resistant prostate cancer is a result of reactivation of AR-mediated pathways.

There are a variety of molecular mechanisms implicated in this process of androgen independence (Fig. 109–2). First, the AR pathway can become hypersensitive through a variety of molecular alterations and be activated by even lower levels of androgen (Linja et al, 2004). In androgen-refractory tumors, approximately one third of patients will show evidence of *AR* gene amplification, meaning many more copies of the *AR* gene are present (Koivisto et al, 1997; Linja et al, 2001). Second, the promiscuity of the AR for ligands other than androgen has been widely recognized. Mutations of the *AR* gene can also increase receptor activity (Tilley et al, 1996; Gottlieb et al, 1998; Taplin et al, 1999; Marcelli et al, 2000; Balk, 2002). Third, in an outlaw AR model, growth factor peptides, such as epithelial growth factor and insulin-like growth factor type 1 increase AR transcriptional activity in the absence of androgen (Culig et al, 1994). The cytokine interleukin-6 can activate AR, as can protein kinases A and C (Nazareth and Weigel, 1996; Lin et al, 2001). If these ligands can reactivate AR signaling in the absence of androgen, then prostate cancer can still progress in the castrate state. Increased expression of AR coregulators, proteins involved in the complex that binds to DNA, has been found in hormone-refractory prostate cancer, suggesting autonomous activation of the pathway (Yeh et al, 1999; Fujimoto et al, 2001; Gregory et al, 2001). Fourth, in a bypass AR model, activation of parallel or alternative survival pathways allows otherwise androgen-dependent prostate cancer cells to survive in the absence of androgen (Feldman and Feldman, 2001). Finally, in a lurker cell model, a small population of possible epithelial stem cells is preexistent in the prostate and androgen deprivation selects for the outgrowth of these androgen-independent cells. Rather than an acquired alteration, this model suggests an inherent quality of the prostate gland.

Even when prostate cancer progresses despite castrate levels of androgen it is rarely resistant to androgen action. In 87% of patients with androgen-refractory prostate cancer, the administration of exogenous androgen results in symptomatic tumor flare (Fowler and Whitmore, 1982). Therefore the term *androgen independent* is not completely precise: such a cancer is no longer dependent on androgen (and thus may be considered independent), but since it remains responsive to androgen it is not wholly independent of the influence of androgen. The term *androgen refractory* is more precise, indicating a disease state in which the cancer is able to progress in the absence of androgen but is neutral about a

Drug Class	Drugs	Site of Action	Mechanism of Action	Comments/Risks
Gondatropin-Releasing Hormone (GnRH) Agonists	Leuprolide Goserelin	Anterior Pituitary Gland	Decreases Release of LH Through Down-regulation of GnRH Receptors	Testosterone Surge
GnRH Antagonists	Abarelix*	Anterior Pituitary Gland	Directly Inhibits GnRH Receptors	Anaphylaxis
Adrenal Ablating Drugs	Ketoconazole	Adrenal Gland	Decreases Androgen Synthesis From Steroid Precursors Through Inhibition of Cytochrome P450 Enzymes	Administration Requires Steroid Supplementation to Prevent Adrenal Insufficiency
Androgen Receptor Antagonists	Flutamide Bicalutamide Nilutamide	Prostate Gland	Inhibits Androgen Receptor Ligand-Binding Domain Through Competitive Binding	Gynecomastia, Increased Liver Transaminases, and Mastodynia
5α-Reductase Inhibitors	Finasteride	Prostate Gland	Decreases Conversion of Testosterone to DHT Through Inhibition of 5α-Reductase	No Defined Role in Standard Care of Prostate Cancer

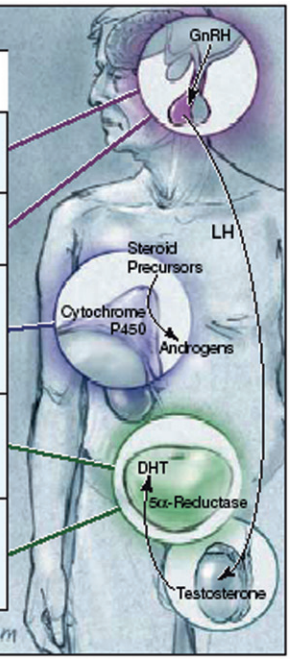


Figure 109–1. Hormonal interventions and endocrine axis in prostate cancer. DHT, dihydrotestosterone; LH, luteinizing hormone. *Abarelix is no longer available for new patients in the United States. (From Sharifi N, Gulley JL, Dahut WL. Androgen deprivation therapy for prostate cancer. JAMA 2005;294:238–44.)

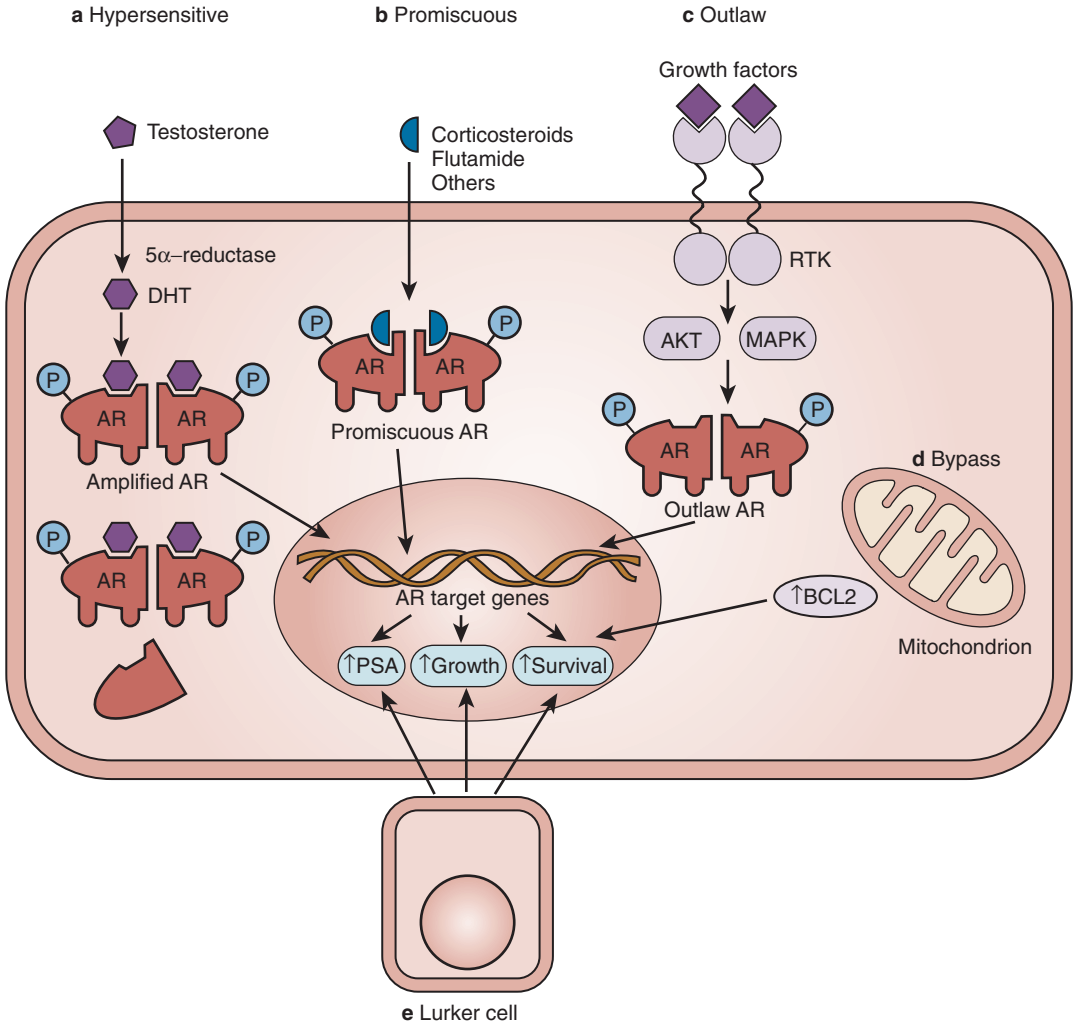


Figure 109–2. Five *(a to e)* possible pathways to androgen independence. AR, androgen receptor, DHT, dihydrotestosterone; MAPK, mitogen-activated protein kinase; P, phosphorylated; PSA, prostate-specific antigen; RTK, receptor tyrosine kinase. (From Feldman BJ, Feldman D. The development of androgen-independent prostate cancer. Nat Rev Cancer 2001;1:34–45.)

Table 109–1.

Major Circulating Androgens

SOURCE	ANDROGEN	AMOUNT PRODUCED PER DAY (mg)	RELATIVE POTENCY	RELATIVE POTENCY/ AMOUNT PRODUCED
Testes	Testosterone	6.6	100	15.2
Testes and peripheral tissues	Dihydrotestosterone	0.3	160-190	533-633
Adrenal	Androstenedione	1.4	39	27.9
Adrenal	Dehydroepiandrosterone	29	15	0.5

Table 109–2.

Therapeutic Approaches to Androgen-Deprivation Therapy: Several Agents Have Multiple Sites of Action

ABLATION OF ANDROGEN SOURCES	INHIBITION OF ANDROGEN SYNTHESIS	ANTIANDROGENS	INHIBITION OF LH-RH OR OF LH
Orchiectomy	Aminoglutethimide	Cyproterone acetate	DES
	Ketoconazole	Flutamide	Leuprolide
	Abiraterone	Bicalutamide	Goserelin
		Nilutamide	Triptorelin
		MDV3100	Histrelin
			Cetrorelix
			Abarelix
			Degarelix

DES, diethylstilbestrol; LH, luteinizing hormone; LH-RH, luteinizing hormone–releasing hormone.

responsive to androgen. Likewise, the word "hormone" is quite broad and includes the host factors defining the field of endocrinology. Therefore the term *hormone independent* is vague, as evident from the therapeutic response to secondary hormonal manipulation, estrogens, and glucocorticoids; and androgen-refractory prostate cancer is not actually independent of hormone action. The terms *hormone independent* and *hormone refractory* should be reserved for the rare cancers that are completely non-responsive to any hormonal agent (Chang et al, 2005). **Although hormone refractory prostate cancer is widely used to describe a state of progressive disease despite androgen-deprivation therapy, the term *castration-resistant prostate cancer* is more clinically precise and relevant** (Scher et al, 2004, 2008).

SOURCES OF ANDROGEN

Testosterone is the major circulating androgen, with 90% produced by the testes. Over half of testosterone is bound to sex-binding globulin and 40% is bound to albumin. Only 3% of testosterone remains unbound, and this is the functionally active form of the hormone. After passive diffusion through the cell membrane into the cytoplasm, testosterone undergoes conversion to dihydrotestosterone (DHT) through the action of the enzyme 5α-reductase. Although the relative potency of testosterone and DHT are similar (as defined by the ability to cause half-maximal response in a prostate regrowth model), if the conversion of testosterone to DHT is blocked by the 5α-reductase inhibitor finasteride, 13-fold more testosterone is required for the same effect (Wright et al, 1999). Both testosterone and DHT exert their biologic effects by binding to the AR in the cytoplasm, promoting the association of AR coregulators. The complex then translocates to the nucleus and binds to androgen response elements in the promoter regions of target genes (Heinlein and Chang, 2004).

Androgens produced by the adrenal gland—androstenedione and dehydroepiandrosterone—are stimulated by adrenocorticotropic hormone (ACTH) released by the pituitary gland in response to corticotropic-releasing factor (CRF). Adrenal androgens negatively feed back on ACTH secretion: cortisol acts as the feedback signal. **Adrenal androgens are relatively weak compared with testosterone and DHT and are almost entirely bound to albumin** (Table 109–1). Adrenal androgens remain normal in men who have undergone orchiectomy (Walsh and Siiteri, 1975), and adrenal androgens are insufficient to maintain prostatic epithelium in such men.

MECHANISMS OF ANDROGEN AXIS BLOCKADE

There are four therapeutic approaches for androgen axis blockade in current clinical use: (1) ablation of androgen sources, (2) inhibiting androgen synthesis, (3) antiandrogens, and (4) inhibition of LH-RH and/or LH release (Table 109–2).

Ablation of Androgen Sources

Bilateral orchiectomy quickly reduces circulating testosterone levels to less than 50 ng/dL, which, based on this procedure, is considered the castrate range. Within 24 hours of surgical castration, testosterone levels are reduced by greater than 90% (Maatman et al, 1985). **The Veterans Administration Cooperative Urological Research Group (VACURG) conducted a series of larger clinical trials, demonstrating the clinical effectiveness of surgical castration in reducing pain and performance status in men with advanced disease** (Veterans Adminstration, 1967; Byar, 1973; Byar and Corle, 1988).

Scrotal (Simple) Orchiectomy

A straightforward outpatient procedure, the simple scrotal orchiectomy, can be performed with the patient under local anesthesia. At the level of the external ring, each spermatic cord is grasped and infiltrated with 10 mL of 1% lidocaine without epinephrine. This cord block can be performed before the formal skin preparation and draping. After infiltration of the skin overlying the median raphe with 1% lidocaine, a 6- to 8-cm incision is made directly over the median raphe. After the skin incision, electrocautery is used exclusively to transect the other tissue layers, reducing the risk of scrotal hematoma formation. The incision is directed into one hemiscrotum where the tunica vaginalis is divided and the testis delivered through the wound. The cord is mobilized above the testis but below the level of the external ring. After dividing the cord structures into two or three equal components, the cord is ligated with nonabsorbable sutures. The author prefers double ligating the proximal cord with two sutures, one of which is a suture ligature. The cord is transected relatively close to the ligatures, to limit the amount of nonviable tissue distal to the ligature. Care is taken to examine for any bleeding, because a scrotal hematoma after scrotal orchiectomy can be dramatically large. The identical procedure is performed on the contralateral side. The dartos is then reapproximated in the midline, closing each semiscrotal incision at the same time in one layer. The skin is closed with interrupted absorbable sutures. Drains are not used for clean scrotal wounds. Scrotal supports are used for the first several days after surgery and ice is applied for symptomatic relief.

Subcapsular orchiectomy has been advocated as a technique of ADT that avoids the psychologic consequences of an empty scrotum (Desmond et al, 1988). **Because this approach relies on the complete removal of all intratesticular tissue and Leydig cells it is more dependent on technique than a simple orchiectomy to achieve ADT. In a properly performed operation, however, the hormonal and cancer responses are indistinguishable from a simple, complete orchiectomy** (Zhang et al, 1996).

Antiandrogens

Cyproterone Acetate

The classic steroidal antiandrogen with direct AR blocking effects, cyproterone acetate, also rapidly lowers testosterone levels to 70% to 80% through its progestational central inhibition (Jacobi et al, 1980; Goldenberg and Bruchovsky, 1991; Barradell and Faulds, 1994). An oral agent, the recommended dose is 100 mg, two to three times per day. Side effects are consistent with the hypogonadal state and include loss of libido, erectile dysfunction, and lassitude. **Severe cardiovascular complications can occur in up to 10% of patients, limiting the use of this agent** (deVoogt et al, 1986). Gynecomastia occurs in less than 20% of men. Rare cases of fulminate hepatotoxicity have been reported (Parys et al, 1991). Cyproterone acetate has been used at doses of 50 to 100 mg/day for the treatment of hot flashes (Goldenberg and Bruchovsky, 1991).

Nonsteroidal Antiandrogens

By blocking the testosterone feedback centrally the nonsteroidal antiandrogens cause LH and testosterone levels to increase. Testosterone levels reach about 1.5 times the normal levels of hormonally intact men (Neri, 1977). This allows antiandrogen activity without inducing hypogonadism: potency therefore can be preserved (Brufsky et al, 1997). However, in clinical trials specifically examining erectile functioning and sexual activity in men on flutamide monotherapy, long-term preservation of those domains was only 20%, not much different than men undergoing surgical castration (Schröder et al, 2000). The peripheral aromatization of increased testosterone to estradiol has been demonstrated after antiandrogen administration (Knuth, 1984), leading to the widely recognized gynecomastia and mastodynia associated with these agents. **Gastrointestinal toxicity, and most notably diarrhea, is more common with flutamide than the other nonsteroidal antiandrogens** (Han and Nelson, 2000). **Liver toxicity, ranging from reversible hepatitis to fulminate hepatic failure, is associated with all nonsteroidal antiandrogens and requires periodic monitoring of liver function tests** (Lund and Rasmussen, 1988; Wysowski et al, 1993; Dawson et al, 1997; Thole et al, 2004).

Antiandrogen Withdrawal Phenomenon

Patients treated with a combination of an antiandrogen and an LH-RH agonist can experience a decline in the prostate-specific antigen (PSA) value and even objective responses with the withdrawal of the antiandrogen from the combination. Based on this response, it appears the antiandrogen is actually exerting agonistic activity on prostate cancer cells. This phenomenon, first described with flutamide (Kelly and Scher, 1993), has now been demonstrated with all antiandrogens, including cyproterone acetate, as well as with DES and progestational agents (Kelly et al, 1997). Declines in PSA are seen within 4 weeks with flutamide withdrawal and within 6 weeks with bicalutamide and nilutamide withdrawal (Nieh, 1995). **Between 15% and 30% of patients may have PSA level declines of greater than 50% after antiandrogen withdrawal with a median duration of 3.5 to 5 months** (Scher and Kelly, 1993; Small and Srinivas, 1995). Objective, measurable tumor responses are observed less commonly. Overall survival has not been shown to be increased in those demonstrating the antiandrogen withdrawal phenomenon compared with those who have not (Small and Srinivas, 1995). Clinical trial designs of novel agents must take this phenomenon into consideration, given the possible confounding effects (Scher and Kelly, 1993). Prospective criteria to predict who will demonstrate this response have not been established, but it has been recognized that those with rapid PSA responses after androgen ablation have higher rates of antiandrogen withdrawal phenomenon.

It has been postulated that mutations in the AR may underlie this phenomenon, allowing the antiandrogen to behave as an activator of the AR (Taplin et al, 1995). The widely used prostate cancer cell line LNCaP expresses an AR with a specific point mutation that causes cell proliferation in the presence of hydroxyflutamide; the identical mutation was found in human tumor samples from patients who had remarkable declines in PSA levels after antiandrogen withdrawal (Suzuki et al, 1996). Similar point mutations in the AR have been described for bicalutamide to act as an agonist (Hara et al, 2003), with the structural basis of this mutation resolved by x-ray crystallography demonstrating the ability of bicalutamide to bind to the mutant AR in a fashion similar to DHT to the wild-type AR (Bohl et al, 2005).

Flutamide

A nonsteroidal antiandrogen, flutamide was the first "pure" antiandrogen (Neri et al, 1967). Because of the short half-life (6 hours) of the active metabolite, 2-hydroxyflutamide, this oral agent is given in a dose of 250 mg three times a day. Elimination of

hydroxyflutamide is via renal excretion. Unlike the steroidal antiandrogens there are no associated side effects of fluid retention or thromboembolism (Dalaere and Van Thillo, 1991). In a randomized, double-blind study comparing flutamide to DES (3 mg/day) in metastatic prostate cancer, overall survival was significantly shorter with flutamide (28.5 months) compared with DES (43.2 months) (Chang et al, 1996).

Bicalutamide

A nonsteroidal antiandrogen with a long serum half-life (6 days), bicalutamide has a once-per-day dosing schedule and therefore likely better compliance. It is the most potent of the nonsteroidal antiandrogens (Kolvenbag and Nash, 1999) and the best tolerated (Kolvenbag and Blackledge, 1996; Schellhammer and Davis, 2004; Fradet, 2004). The pharmacokinetics of bicalutamide are not affected by age, renal insufficiency, or moderate hepatic impairment (Mahler et al, 1998). The R-isomer of bicalutamide has about a 30-fold higher binding affinity to the AR compared with the S-isomer and functionally processes the antiandrogen activity (Mukherjee et al, 1996). As with the other antiandrogens, bicalutamide is associated with maintenance of serum testosterone levels: in the majority of patients these remain within the normal range (Denis and Mahler, 1996; Tay et al, 2004).

Bicalutamide as monotherapy has been most extensively studied and, as with flutamide monotherapy's inferiority to DES, bicalutamide monotherapy at a 50-mg/day dose was inferior to castration in survival of men with metastatic disease (Kaisary et al, 1995; Bales and Chodak, 1996; Kolvenbag and Nash, 1999). **At higher dose of 150 mg/day, however, bicalutamide monotherapy appears to have equivalent efficacy to medical or surgical castration** (Tyrrell et al, 1998; Iversen et al, 2000; Anderson, 2003; Iversen et al, 2004; Wirth et al, 2004, 2005; McLeod et al, 2005) in men with metastatic or locally advanced disease. In these large phase 3 studies, bicalutamide monotherapy (150 mg/day) had significantly better quality of life in the domains of sexual interest and physical capacity (Iversen, 2003). There was, however, a high rate of gynecomastia (66.2%) and breast pain (72.8%) (Iversen, 2003). Of more concern, **in men with low-risk, localized prostate cancer, bicalutamide was associated with significantly worse overall survival compared with those on "watchful waiting"** (see later).

Nilutamide

The plasma half-life of nilutamide is 56 hours, and elimination is via hepatic clearance employing the cytochrome P450 system. Because steady-state plasma levels are achieved in 14 days on once-daily dosing (Creaven et al, 1991), dosing recommendations are a single 300-mg daily dose for the first month of treatment followed by a single 150-mg daily dose (Mahler et al, 1998). **About one fourth of men on nilutamide therapy will note a delayed adaptation to darkness after exposure to bright illumination** (Creaven et al, 1991). Nilutamide is also associated with interstitial pneumonitis in approximately 1% of patients, which can progress to pulmonary fibrosis (Pfitzenmeyer et al, 1992). The early effects are usually reversible with cessation of nilutamide. In a small study there was a suggestion of a role for nilutamide as an effective secondary hormonal agent (Desai et al, 2001).

MDV3100

This small molecule is an AR antagonist, but, unlike bicalutamide, MDV3100 inhibits AR function by blocking nuclear translocation and DNA binding and has no agonist activity when AR is overexpressed. It is being evaluated in phase 1/2 clinical trials in men with castration-resistant prostate cancer. Early results indicate the PSA level declines in the majority of patients (Scher et al, 2008).

Inhibition of LH-RH

LH-RH Agonists

The LH-RH agonists exploit the desensitization of LH-RH receptors in the anterior pituitary after chronic exposure to LH-RH, thereby shutting down the production of LH and, ultimately, testosterone. **The clinical utility of the current LH-RH agonists is based on the creation of analogues of native LH-RH by amino acid substitutions, particularly position 6 in the peptide, increasing their potency and half-lives** (Table 109–3). Pharmacologic depot preparations and osmotic pump devices allow dosing to extend from 28 days to 1 year, respectively (Table 109–4) (Ahmann et al, 1987). **In a review of 24 trials, involving more than 6600 patients, survival after therapy with an LH-RH agonist was equivalent to that of orchiectomy** (Seidenfeld et al, 2000).

The initial exposure to more potent agonists of LH-RH results in a flare of LH and testosterone levels (Waxman et al, 1985). **This phenomenon is seen with all available LH-RH preparations and can result in a severe, life-threatening exacerbation of symptoms.** The flare, associated with up to a 10-fold increase in LH, may last for 10 to 20 days (Weckerman and Harzmann, 2004). Fortunately, **the coadministration of an antiandrogen functionally blocks the increased levels of testosterone** (Labrie et al, 1987; Kuhn et al, 1989; Schultz and Senge, 1990). Although it had been argued that the administration of the antiandrogen should precede the administration of the LH-RH agonist by a week, others have found no differences in PSA levels with the simultaneous administration of both agents (Tsushima et al, 2001). Given the predictable length

Table 109–3.

Structure of LH-RH and Therapeutic Analogues

	Amino Acid Number									
	1	2	3	4	5	6	7	8	9	10
Native LH-RH	(pyro)Glu-	His-	Trp-	Ser-	Try-	Gly-	Leu-	Arg-	Pro-	Gly-NH_2
Leuprolide	(pyro)Glu-	His-	Trp-	Ser-	Try-	D-Leu-	Leu-	Arg-	Pro-	Ethylamide
Goserelin	(pyro)Glu-	His-	Trp-	Ser-	Try-	D-Ser(tBu)-	Leu-	Arg-	Pro-	Gly-NH_2
Triptorelin	(pyro)Glu-	His-	Trp-	Ser-	Try-	D-Trp-	Leu-	Arg-	Pro-	Gly-NH_2
Histrelin	(pyro)Glu-	His-	Trp-	Ser-	Try-	D-His(Imbzl)	Leu-	Arg-	Pro-	N-Et-NH_2

LH-RH, luteinizing hormone–releasing hormone.

Table 109–4.

Luteinizing Hormone–Releasing Hormone Agonists Approved for the Treatment of Prostate Cancer

GENERIC NAME	TRADE NAME	DOSE (mg)	ROUTE	DOSING INTERVAL (days)
Leuprolide acetate for depot suspension	Lupron Depot	7.5	IM	28
		22.5		84
		30		112
Goserelin acetate implant	Zoladex	3.6	SC	28
		10.8		84
Triptorelin pamoate injectable suspension	Trelstar Depot	3.75	IM	28
	Trelstar LA	11.25		84
Leuprolide acetate for injectable suspension	Eligard	7.5	SC	28
		22.5		84
		30		112
Leuprolide acetate implant	Viadur	65	SC	365
Histrelin acetate implant	Vantas	50	SC	365

IM, intramuscular; SC, subcutaneous.

of the flare phenomenon, antiandrogen coadministration is required for only 21 to 28 days.

LH-RH Antagonists

The LH-RH antagonists bind immediately and competitively to the LH-RH receptors in the pituitary, reducing LH concentrations by 84% within 24 hours of administration (Weckerman et al, 2004). **The direct antagonistic activity eliminates the LH and testosterone flare, which is the major therapeutic advantage of these agents: there is no need for antiandrogen coadministration.** Hormonally naive patients with impending spinal cord compression or severe bone pain for whom surgical castration is not appropriate may uniquely benefit from this class of agents: clinical response has been observed with the LH-RH antagonist cetrorelix (Gonzalez-Barcena et al, 1995).

In clinical trials of the LH-RH antagonist abarelix, testosterone levels dropped very quickly, with 34.5%, 60.5%, and 98.1% of men chemically castrated at 2, 4, and 28 days, respectively (Tomera et al, 2001). Compared with an LH-RH agonist and an antiandrogen, abarelix monotherapy was equally effective in achieving castrate levels of testosterone (Trachtenberg et al, 2002). Ninety-percent of men with symptomatic prostate cancer treated in an open-label fashion had improvements in pain and/or disease-related problems (Koch et al, 2003).

Many of the first- and second-generation antagonists induced significant histamine-mediated side effects, complications not as often observed in third- and fourth-generation agents (Weckerman et al, 2004). Nevertheless, **severe allergic reactions can occur with abarelix, even after previously uneventful treatment** (Koch et al, 2003). Abarelix is approved in the United States for the treatment of advanced prostate cancer in patients who cannot take other hormonal therapies and have refused surgical castration. Given the rare but serious allergic reactions, patients must be monitored for at least 30 minutes after administration.

FSH levels are only partially suppressed by LH-RH agonists and are significantly elevated after surgical castration given the loss of inhibitory feedback. LH-RH antagonists reduce both LH and FSH levels. In an androgen-insensitive prostate cancer xenograft model, cetrorelix significantly reduced tumor growth (Lamharzi et al, 1998), suggesting other factors stimulate tumor growth. In men with disease progression after surgical castration, treatment with abarelix reduced FSH levels by nearly 90% but did not meet criteria for PSA response (Beer et al, 2004a).

A new LH-RH antagonist, degarelix, has completed phase 2 and phase 3 studies in prostate cancer (Gittelman et al, 2008; Klotz et al, 2008). **Unlike with abarelix there were no systemic allergic reactions with degarelix.** In the phase 3 study, degarelix was compared with leuprolide: at 1 year of treatment degarelix was not inferior to leuprolide, and, based on this result, it has been approved for use in the United States.

Inhibition of Androgen Synthesis

Aminoglutethimide

Aminoglutethimide inhibits the conversion of cholesterol to pregnenolone, an early step in steroidogenesis (Cash et al, 1967; Blankenstein and Bakker, 1985). **Given its inhibition of a very proximal step in adrenal function, aminoglutethimide blocks production of aldosterone and cortisol. As the medical version of a total adrenalectomy, the use of this agent requires replacement of cortisone and fludrocortisone.** Side effects include anorexia, nausea, rash, lethargy, vertigo, hypothyroidism, and nystagmus. Clinical responses have been observed in a subset of patients with androgen-refractory prostate cancer treated with aminoglutethimide plus cortisone (Sanford et al, 1976; Ponder et al, 1984). In the PSA era, 37% of patients had greater than a 50% decline in the PSA level with treatment with aminoglutethimide (1000 mg/day) and hydrocortisone acetate (40 mg/day), with median response times lasting 9 months (Kruit et al, 2004).

Ketoconazole

An orally active, broad-spectrum azole antifungal agent, ketoconazole interferes with two cytochrome P450–dependent pathways: by inhibiting 14-methylation the conversion lanosterol to cholesterol is blocked, and it also blocks 17,20-desmolase, impacting on the conversion of C21 to C19 steroids. Based on the observation that some patients taking the drug developed gynecomastia, investigations on its effects on steroid synthesis demonstrated loss of adrenal steroid synthesis (Pont et al, 1982b) and testosterone synthesis by Leydig cells (Pont et al, 1982a). The effects were rapid, with testosterone levels dropping to the castrate level within 4 hours of administration in some cases (Trachtenberg et al, 1983); the effects were also immediately reversible, indicating dosing must be continuous to maintain low testosterone levels (400 mg every 8 hours).

Early experience with ketoconazole in the treatment of prostate cancer showed this agent to be tolerable, durable, and effective (Trachtenberg and Pont, 1984) and was palliative for those who had failed first-line androgen-ablation therapy (Pont, 1987). **Although effective in rapidly bringing testosterone levels into the castrate range, with continuous treatment with ketoconazole in the otherwise hormonally intact individual (no other surgical or chemical ADT), testosterone levels begin to rise and can reach low-normal ranges within 5 months of therapy** (Vanuytsel et al, 1987). Therefore currently, ketoconazole is used for men with castration-resistant prostate cancer, often as the first or second agent in so-called secondary hormonal manipulation (Small et al, 2004). In addition to gynecomastia (caused by alterations in testosterone-estradiol ratios [Pont et al, 1985]),

ketoconazole is associated with lethargy, weakness, hepatic dysfunction, visual disturbance, and nausea (Wilkinson and Chodak, 2004; Scholz et al, 2005). Because of the adrenal suppression, ketoconazole is usually given with hydrocortisone (20 mg twice daily). Patients with higher levels of the adrenal androgen androstenedione had a improved survival in response to ketoconazole compared with those with lower levels, suggesting ketoconazole is less effective in patients with low levels of androgen at baseline (Ryan et al, 2007).

Abiraterone

Unlike the less potent ketoconazole, which inhibits several cytochrome P pathways, abiraterone is a potent, selective and irreversible inhibitor of cytochrome P17, a key enzyme in androgen synthesis (Chan et al, 1996). Specifically, abiraterone inhibits 17α-hydrolase, resulting in excess synthesis of aldosterone and its precursors and causing a suppression of cortisol with a compensatory rise in ACTH. Abiraterone also inhibits C17,20-lyase, resulting in suppression of testosterone to levels of less than 1 ng/mL (significantly < 50 ng/ml, castrate levels) (O'Donnell et al, 2004; Attard et al, 2005). Based on the hypothesis that castration-resistant prostate cancer remains driven by low levels of androgens, abiraterone is undergoing clinical testing in this state of disease. In a phase 1 clinical trial, abiraterone was well tolerated, with toxicities associated with the expected effects of mineralocorticoid excess, namely, hypertension, hypokalemia, and lower-extremity edema (Attard et al, 2008). Declines in PSA level and measurable tumor response were observed and supported by preliminary phase 2 results (de Bono et al, 2008). Phase 3 studies are underway.

RESPONSE TO ANDROGEN BLOCKADE

After the initiation of ADT the vast majority of prostate cancer patients will show some evidence of clinical response: the magnitude and rapidity of that response remain the best predictors of its durability. Assuming ADT effectively targets the androgen-sensitive population of prostate cancer cells, an incomplete or sluggish response is evidence of a significant androgen-refractory population. Early in the clinical use of PSA as a biomarker of prostate cancer it was recognized that declines in PSA could predict response (Hudson et al, 1989; Aria et al, 1990; Cooper et al; 1990). For example, **patients who had more than an 80% drop of PSA within 1 month of initiating ADT had a significantly longer disease-free progression rate** (Aria et al; 1990). Likewise, the nadir PSA predicted the progression-free interval (Matzkin et al, 1992; Benaim et al, 2002a), as did pretreatment testosterone levels (Imamoto et al, 2001). **A rise in PSA level, which is evidence of the emergence of castration-resistant disease, preceded bone metastatic progression by several months, with a mean lead time of 7.3 months** (Cooper et al, 1990; Miller et al, 1992).

More recent studies of PSA response to ADT have confirmed and amplified those observations. The odds ratio for progressing to castration-resistant progression with 24 months of starting ADT was almost 15 times higher for patients who did not achieve an undetectable PSA level (Benaim et al, 2002a). For each unit increase in Gleason score, the cumulative hazard of castration-resistant progression was nearly 70% (Benaim et al, 2002b). In one cohort of Asian men the nadir PSA was the most accurate predictor of disease progression and was independently prognostic of survival; achieving a PSA level of 1.1 ng/mL or less at 6 months after initiating ADT was the most sensitive and specific predictor of progression at 2 years (Kwak et al, 2002). **In men with newly diagnosed metastatic prostate cancer (stage D2) started on ADT the absolute PSA level after 7 months of ADT was a strong, independent predictor of survival** (Hussain et al, 2006). Median survival of men achieving a PSA level less than or equal to 0.2 ng/mL was 75 months, compared with 13 months for men whose nadir was more than 4 ng/mL (Fig. 109–3). Considering the kinetics of PSA rise before ADT compared with

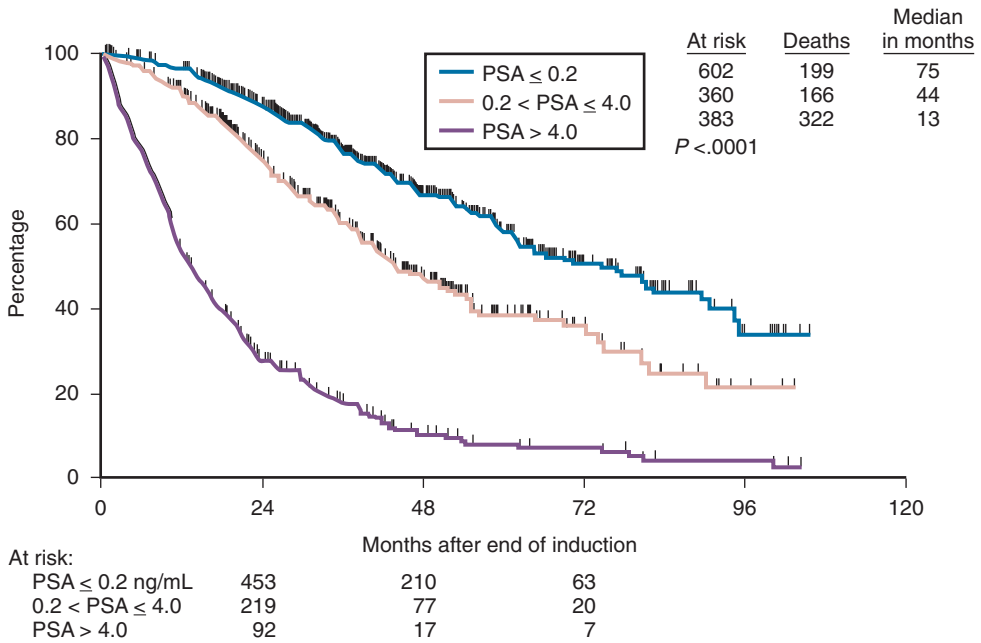


Figure 109–3. Overall survival by prostate-specific antigen (PSA, ng/mL) status at the end of induction with androgen-deprivation therapy. (From Hussain M, Tangen CM, Higano C, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). J Clin Oncol 2006;24:3984–90.)

the rate of PSA decline after ADT also predicted outcome, specifically prostate cancer–specific mortality (D'Amico et al, 2005). If the pre-ADT PSA rise was rapid and the decline after ADT was slow the cancer-specific mortality was significantly worse compared with those with slow rises in PSA before ADT and rapid declines after ADT (D'Amico et al, 2004a, 2004b).

Almost without exception those no longer responding to ADT (androgen-refractory) remain on ADT. Therefore factors influencing survival in that disease state should be considered in this discussion. In most cases, available data are based on pre- or post-treatment responses to other systemic treatments (Galsky and Kelly, 2003). Consistently predictive variables (by both univariate and multivariate analysis) of survival in this state include performance status; serum lactate dehydrogenase (LDH), serum alkaline phosphatase, and hemoglobin levels; and PSA response to secondary therapy (Smalez et al, 2002). The survival of men treated on seven sequential chemotherapy protocols at one institution provided an early experience in developing predictive measures (Kelly et al, 1993). A 50% decline in PSA value in response to chemotherapy was one of the most significant variables predicting survival. A nomogram, based on a larger groups of patients, finds the presence of visceral disease, Gleason score, performance status, baseline PSA value, LDH and alkaline phosphatase levels, and hemoglobin level were useful in modeling prognosis (Smalez et al, 2002; Halabi et al, 2003).

GENERAL COMPLICATIONS OF ANDROGEN ABLATION

Osteoporosis

The increased number of men being placed on androgen ablation therapy much earlier in the course of their disease allows the chronic manifestations of the hypogonadal state to emerge. **Widespread androgen ablation therapy applied to an increasing aging population, already predisposed to loss of bone mineral density (BMD), has created an epidemic of osteopenia and osteoporosis.** Fragile bones increase the risk of skeletal fracture. **More than half of men meet the BMD criteria for osteopenia or osteoporosis—defined as more than 2.5 standard deviations below an age-specific reference mean—before the initiation of ADT** (Wei et al, 1999; Conde et al, 2004). The longer a man remains on ADT, the greater the risk of fracture (Daniell et al, 2000; Krupski et al, 2004). After 5 years on ADT, 19.4% of men experienced fractures compared with 12.6% of controls (Shahinian et al, 2005): over 15 years, cumulative incidence of fractures was 40%, compared with 19% in noncastrate controls (Melton et al, 2003). **It has been estimated that 4 years of ADT will place the average man in the osteopenic range** (Wei et al, 1999). Prostate cancer was associated with an increased odds ratio (95% confidence intervals) for hip fractures of 3.7 (3.1 to 4.4) in a large Danish population-based study (Abrahamsen et al, 2007). Rarely discussed even 10 years ago, skeletal health is now becoming a major concern of patients and their physicians (Chen et al, 2002).

Treatment of osteoporosis begins with recognition. BMD of the hip, as measured by dual-energy x-ray absorptiometry, should be considered on all men who are anticipated to be on long-term ADT (Bae and Stein, 2004; Diamond et al, 2004). Smoking cessation, weight-bearing exercise, and vitamin D and calcium supplementation can help improve BMD. **Daily supplementation of calcium and vitamin D is recommended by the National Institutes of Health at doses of 1200 to 1500 mg/day and 400 IU/day, respectively** (Michaelson et al, 2008). Supplementation decreases the incidence of nonvertebral fractures in men and women older than 65 years of age (Dawson-Hughes et al, 1997). Prevention of osteoporosis in men receiving ADT has been demonstrated in controlled studies using the bisphosphonate pamidronate (Smith et al, 2001). **In a randomized prospective study, once-weekly oral alendronate reversed bone loss associated with ADT and improved bone density; this benefit continued with ongoing treatment, suggesting chronic treatment is beneficial** (Greenspan et al, 2007, 2008). BMD also increased in men on ADT using the considerably more potent bisphosphonate zoledronic acid (Smith et al, 2003a). Bisphosphonate therapy should be considered in any man with evidence of osteopenia or osteoporosis (Bae and Stein, 2004). Transdermal estradiol also increases BMD in men with prostate cancer (Ockrim et al, 2004). Not surprisingly, serum testosterone and estradiol levels were much lower on men receiving LH-RH agonists compared with those on nonsteroidal antiandrogen therapy; interestingly, markers of bone turnover were significantly higher in men taking LH-RH agonists compared with those on nonsteroidal antiandrogen therapy, suggesting the nonsteroidal antiandrogens may help maintain BMD (Smith et al, 2003b).

Hot Flashes

For more than 100 years, hot flashes (also called hot flushes, vasomotor symptoms) have been recognized as a side effect of androgen ablation: in 1896 Cabot mentioned "uncomfortable flushes of heat, similar to those experienced by women at the time of menopause" in men undergoing castration for prostatic enlargement (Cabot, 1896; Stearns, 2004). **Described as a subjective feeling of warmth in the upper torso and head followed by objective perspiration, hot flashes are not life threatening but are among the most common side effects of androgen ablation, affecting between 50% and 80% of patients** (Moyad, 2002; Spetz et al, 2003; Nishiyama et al, 2004). Occurring both spontaneously and precipitated by changes in body position, ingestion of hot liquids, or changes in environmental temperature, the exact etiology of hot flashes remains undefined. Among the proposed mechanisms include increases in hypothalamic adrenergic concentrations and alterations in β-endorphins and calcitonin gene–related peptides acting on the thermoregulatory center in the hypothalamus (Yuzurihara et al, 2003). Hot flashes generally decrease both in frequency and intensity over time but often persist in some men (Holzbeierlein et al, 2004).

Treatment of hot flashes should be reserved for those who find them bothersome. Just as hot flashes are a consequence of alterations in the hormonal milieu the mainstay of treatment has been based on efforts to influence that milieu (Kouriefs et al, 2001). In a double-blind, placebo-controlled, crossover study, the progestational agent megestrol acetate (20 mg, twice per day) significantly reduced the frequency of hot flashes (Loprinzi et al, 1994). The dose can be reduced to 5 mg twice daily, which may help reduce the appetite-stimulating effect of this agent. The efficacy of cyproterone acetate is based on its progestational effects (Cervenakov et al, 2000). Dosing should start at 50 mg/day and be titrated to 300 mg/day. Estrogenic compounds, such as low-dose DES and transdermal estradiol, appear to be the most effective treatment, with up to 90% partial or complete

resolution of symptoms (0; Smith, 1994; Gerber et al, 2000). With estrogen compounds, however, the cure may be worse than the disease; painful gynecomastia and thromboembolic effects have limited the utility of this approach. Clonidine, a centrally acting α agonist that decreases vascular reactivity, has been used with mixed results: in a placebo-controlled study, transdermal clonidine did not significant decrease hot flashes (Loprinzi et al, 1994). Antidepressant agents, particularly the selective serotonin reuptake inhibitor venlafaxine (12.5 mg, twice daily), have reduced hot flashes in more than 50% of men (Quella et al, 1999; Loprinzi et al, 2004). In a phase 3 randomized, double-blind, placebo-controlled trial, the antiseizure agent gabapentin decreased hot flashes to a moderate degree (Loprinzi et al, 2009).

Sexual Dysfunction (Erectile Dysfunction and Loss of Libido)

The effects of ADT on sexual function are profound, as first described by Huggins and associates (1941): "Sexual desire and penile erections were absent in all cases following castration." **Loss of sexual functioning is not inevitable, however, with up to 20% of men on ADT able to maintain some sexual activity** (Rousseau et al, 1988; Clark et al, 2001). Specifically, between 10% and 17% of men undergoing ADT can maintain an erection adequate for intercourse (Tomic, 1983; Potosky et al, 2001). **Libido is more severely compromised, with approximately 5% of men maintaining a high level of sexual interest with ADT** (Potosky et al, 2001). Sexual desire is inversely related to the duration of androgen deprivation (Basaria et al, 2002). Loss of penile volume, penile length, nocturnal penile tumescence, and, for those undergoing medical ADT, testicular volume is common (Marumo et al, 1999; Higano, 2003).

Treatment for loss of libido is extremely difficult—if not impossible—for those on ADT. Likewise, medical treatments, such as oral phosphodiesterase type 5 inhibitors, or local treatments, such as intracavernosal injections of alprostadil, can still be effective in selected patients but may not be used over the long term. If there is any fairness in the negative effects of ADT on sexual function it is the decline in both libido and erectile functioning: despite no erections or desire, the majority of patients have little to no problem with their lack of sexual functioning (Potosky et al, 2001).

Cognitive Function

There is a strong suggestion that ADT is linked to subtle but significant cognitive declines in men with prostate cancer (Nelson et al, 2008). In both men and women the hypogonadal state is associated with declines in cognitive functioning (Gouchie and Kimura, 1991; Sherwin and Tulandi, 1996). Testosterone supplementation improves verbal fluency (Alexander et al, 1998) whereas other controlled studies have found no effect of such supplementation on memory (Sih et al, 1997). In one small study, men with prostate cancer randomized to ADT performed worse in cognitive studies compared with men with prostate cancer under surveillance (Green et al, 2002); the declines were associated with tasks requiring complex information processing (Green et al, 2004). Compared with tests for other cognitive domains, tests for spatial ability uniquely declined in men on intermittent hormone therapy (Cherrier et al, 2003). In men on neoadjuvant ADT before radiotherapy, cognitive functioning declined (Jenkins et al, 2005). Unfortunately, the studies examining the effects of ADT on cognitive functioning have been small and underpowered. Not surprisingly, given many side effects of ADT, quality of life worsens, specifically in men receiving flutamide in addition to castration, compared with placebo, in the domain of emotional functioning (Moinpour et al, 1998). A short course of ADT (36 weeks) increased depression and anxiety scores on formal neuropsychologic evaluations (Almeida et al, 2004); major depressive disorder was prevalent in 12.8% of men on ADT, 8 times greater than the national rate and 32 times the rate of men older than 65 years of age (Pirl et al, 2002). Finally, psychologic distress accounted for approximately one third of declines in fatigue severity scale in men undergoing ADT (Stone et al, 2000).

Changes in Body Habitus

A loss of muscle mass and increase in percent fat body mass are common in men undergoing ADT, and these changes are most pronounced with the initiation of ADT (van Londen et al, 2008). **After 1 year of ADT the mean overall weight increases from 1.8% to 3.8%, which translates into about 5 lb for a 200-lb man** (Smith et al, 2002; Berruti et al, 2002; Smith, 2004). One study found weight increased a median of 6 kg (13.2 lbs), with a range of 3 to 15 kg (6.6 to 33 lb) (Higano et al, 1996). Because lean body mass usually decreases by the same magnitude, the weight gain is largely due to an increase in fat mass (Levy et al, 2008). The average increase in fat mass ranges from 9.4% to 23.8% (Berruti et al, 2002; Smith et al, 2002; Smith, 2004). As noted by Huggins and colleagues (1941), ADT is associated with an increase in appetite and a low testosterone level is associated with increased insulin levels and abdominal girth (Seidell et al, 1990).

The Cancer Prevention Studies I and II (1959-1972 and 1982-1996, respectively) were large population-based studies of obesity and the risk of cancer mortality. In both studies the risk of death from prostate cancer in obese men was 34% (study I) and 36% (study II) when compared with men of normal weight (Rodriguez et al, 2001; Calle et al, 2003). Furthermore, men older than the age of 65 who engaged in vigorous exercise more than 3 hours per week had a 70% reduction in prostate-cancer specific death (Giovannucci et al, 2005). The body composition changes associated with ADT may portend a worse prognosis for men with prostate cancer. Regular vigorous exercise may help patients limit the accumulation of fat and even prevent prostate cancer progression.

Diabetes and Metabolic Syndrome

Given the changes in body habitus, it is not surprising that metabolic syndrome, a clustering of specific cardiovascular disease risk factors related to insulin resistance, is present in more than 50% of men undergoing long-term ADT (Braga-Basaria et al, 2006). Unlike classic metabolic syndrome, however, characterized by visceral fat accumulation, ADT preferentially increased subcutaneous fat: furthermore, high-density lipoprotein cholesterol concentrations were increased (Smith et al, 2008a). Short-term ADT affected serum lipid and hemoglobin A1c independent of statin therapy (Yannucci et al, 2006). In a small but carefully controlled prospective study, ADT significantly decreased insulin sensitivity in men with prostate cancer (Smith et al, 2006). These findings were supported by a larger observational study (73,196 men with prostate cancer) in which there was a significant risk of developing diabetes with ADT (Keating et al, 2006). In a subset analysis of a phase 3 trial of the selective estrogen-receptor modulator toremifene for

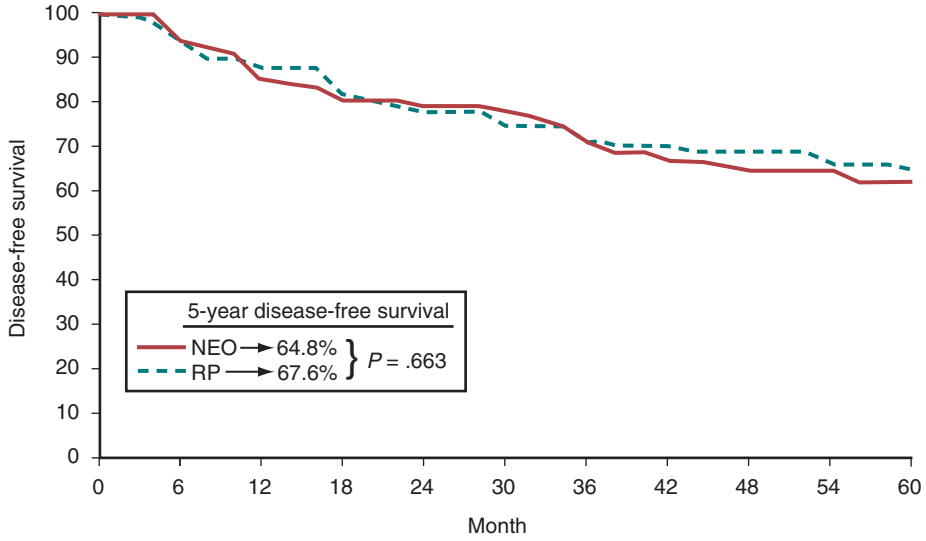


Figure 109–4. Biochemical failure rate in prostatectomy only (RP) and neoadjuvant androgen ablation plus prostatectomy (NEO) groups. (From Soloway MS, Pareek K, Sharifi R, et al. Neoadjuvant androgen ablation before radical prostatectomy in cT2bNxM0 prostate cancer: 5-year results. J Urol 2002;167:112–6.)

the prevention of osteoporosis in men undergoing ADT, placebo-treated patients had increases in low-density lipoprotein cholesterol and triglycerides, which were significantly decreased with toremifene (Smith et al, 2008b).

Cardiovascular Morbidity and Mortality

Given the generally adverse effects of ADT on body habitus, glucose metabolism, and lipid profiles, it is not surprising that studies have found that ADT is associated with increased cardiovascular morbidity and mortality. The effects appear to be most pronounced in men with lower-risk prostate cancer treated with ADT. In a large (22,816 subjects), population-based registry, newly diagnosed prostate cancer patients who received ADT for at least 1 year had a 20% higher risk of cardiovascular morbidity compared with similar men who did not receive ADT (Fig. 109–4) (Saigal et al, 2007). In men older than the age of 65 undergoing radical prostatectomy who also received ADT, the cumulative incidence of cardiovascular death was 5.5% over 5 years compared with 2.0% in those not receiving ADT (Tsai et al, 2007). On the other hand, in men with locally advanced prostate cancer treated with radiation therapy and ADT there was not an increase in cardiovascular mortality compared with men receiving radiation therapy alone (Efstathiou et al, 2008).

Gynecomastia

Depending on the agents used in ADT, alterations in breast tissue are common. **Gynecomastia, an increase in breast tissue, and mastodynia, or breast tenderness, may occur together or independently.** Estrogenic compounds, such as DES, induce gynecomastia in 40% of patients (Smith, 1996). Likewise, **the peripheral conversion of testosterone to estradiol associated with the antiandrogens induces gynecomastia at high rates: 66.3% of men taking 150 mg bicalutamide developed gynecomastia and 72.7% developed mastodynia.**

Prophylactic radiation therapy (10 Gy) has been used to prevent or reduce painful gynecomastia (Payne et al, 2002) as a result of DES or antiandrogen therapy. Radiation has no benefit once gynecomastia has begun. Liposuction and subcutaneous mastectomy have been used to treat established gynecomastia (Higano, 2003). The selective estrogen receptor modulator tamoxifen has been used to treat mastodynia (Serels and Melmann, 1998).

Anemia

The anemia associated with ADT is normochromic, normocytic, and very common: 90% of men receiving combined androgen blockade experienced declines in hemoglobin concentration of at least 10% (Strum et al, 1997). Although anemia can be further complicated by tumor growth in the marrow space, compromising hematopoiesis, even in men with nonmetastatic prostate cancer experience anemia with ADT (Choo et al, 2005). Unfortunately, anemia (defined as hemoglobin < 12 g/dL) is associated with a shorter survival in those anemic before initiation of ADT (Beer et al, 2004b). Declines in hemoglobin begin within 1 month of ADT initiation (Strum et al, 1997) and continue for 24 months (Choo et al, 2005). Compensatory mechanisms limit the symptomatic effects of anemia to a small subset (13%) of men (Strum et al, 1997).

The etiology of anemia is thought to be secondary to lack of testosterone stimulation of erythroid precursors and a decrease in erythropoietin production. In an animal model, however, erythropoietin levels increased after ADT (Voegeli et al, 2005). Whatever the etiology, clinically, patients respond to recombinant human erythropoietin. The anemia is reversible after stopping ADT but may take up to a year (Strum et al, 1997).

COMBINATION THERAPY

The advent of nonsurgical, reversible hormone therapy coupled with its profound effects on prostate cancer have led to a broad investigation of the combination of ADT with nearly every other treatment applied at prostate cancer. In some cases, most notably external-beam radiotherapy, the combination clearly improves the

Table 109–5.
Randomized, Prospective Studies of Neoadjuvant Androgen-Deprivation Therapy (ADT) before Radical Prostatectomy: No Significant Difference in Biochemical (Prostate-Specific Antigen) Progression

AUTHOR	DESIGN	NO. PATIENTS	FOLLOW-UP	BIOCHEMICAL FAILURE RATE
Schulman et al, 2000	3 mo ADT*+RRP	192	4 yr	26.4%
	RRP alone	210		32.5%
Soloway et al, 2002	3 mo ADT†+RRP	138	5 yr	35.2%
	RRP alone	144		32.4%
Aus et al, 2002	3 mo ADT‡+RRP	63	7 yr	50.2%
	RRP alone	63		48.5%
Klotz et al, 2003	3 mo ADT§+RRP	112	6 yr	37.5%
	RRP alone	101		33.6%

*Goserelin and flutamide.
†Leuprolide and flutamide.
‡Triptorelin.
§Cyproterone acetate.

outcomes: in others, most notably radical prostatectomy, there is no obvious benefit.

With Radical Prostatectomy

In nonrandomized clinical trials of ADT before radical prostatectomy the effects on the final surgical specimen were dramatic. Positive surgical margin rates fell from nearly 50% in hormonal intact patients to 15% in ADT patients (Lee et al, 1997). Glands with no evidence of malignancy (P0) were not uncommon. There was a nonsignificant trend toward improved biochemical outcome with neoadjuvant ADT. Based on these findings and a perception that neoadjuvant ADT reduced blood loss and rendered the procedure easier to perform, randomized prospective studies of 3 months of ADT following by radical retropubic prostatectomy were compared with radical retropubic prostatectomy alone (Witjes et al, 1997; Soloway et al, 2002; Klotz et al, 2003) (Table 109–5). **In both short (15 month mean follow-up) and longer (4 to 7 years) follow-up there was no significant difference in PSA progression between the groups** (see Fig. 109–4). The lack of improved biochemical recurrence in these three, randomized, prospective trials using 3 months of neoadjuvant ADT before RRP argues strongly that this combination is not indicated in the treatment of prostate cancer. Studies comparing longer term (8 months) to 3 months of ADT are underway, but at a 3-year interim analysis there is no difference in biochemical recurrence between the groups (Gleave et al, 2003).

With Radiation Therapy

Unlike the lack of long-term improved cancer-specific progression with the combination of ADT and radical prostatectomy there have been several phase 3 clinical trials that have shown a benefit with the combination of ADT and external-beam radiation therapy in overall survival, cancer-specific survival, or freedom from disease progression. The benefit appears to be in men with locally advanced disease and/or those with high-grade, high-risk disease.

A phase 3 study comparing radiation therapy alone to the combination of radiation therapy and orchiectomy in men undergoing pelvic lymph node dissection was closed owing to high frequency of progression in those receiving only radiation therapy (Granfors et al, 1998). A report at 9.3 years of median follow-up, based on 91 men randomized in this study demonstrated a significant difference in clinical progression (61% vs. 31%), overall mortality (61% vs. 38%), and prostate cancer–specific mortality (44% vs. 27%), after treatment by radiation therapy alone versus radiation therapy and orchiectomy, respectively (Granfors et al, 1998). This observation was supported by another study, randomizing men with locally advanced prostate cancer to radiation therapy alone versus radiation therapy combined with goserelin for 3 years (Bolla et al, 1997). The significant disease-free and overall survival advantage of the combination was confirmed at a long-term analysis of the trial (Fig. 109–5) (Bolla et al, 2002). **Clearly, in locally**

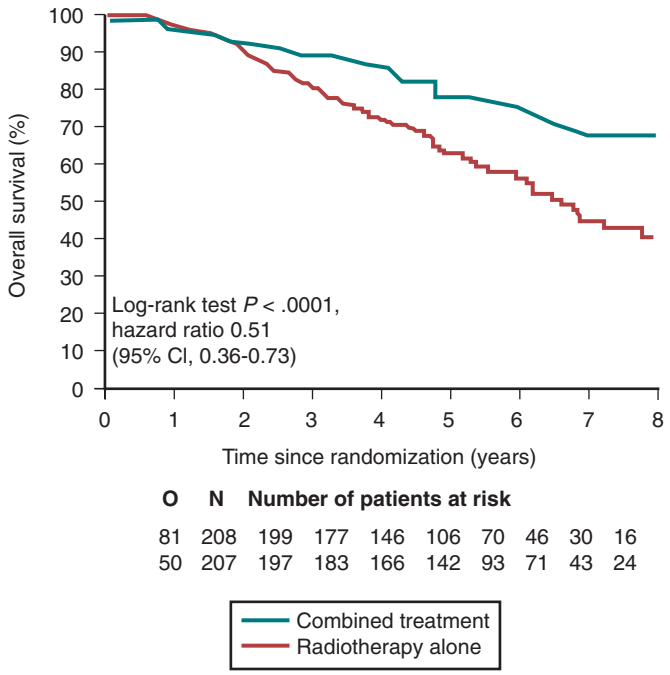


Figure 109–5. Kaplan-Meier estimates of overall survival by treatment group: 3 years of goserelin combined with external-beam irradiation versus external-beam irradiation alone for locally advanced prostate cancer. (From Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomized trial. Lancet 2002;360:103–8.)

Table 109–6.

Phase 3 Randomized, Prospective Trials Comparing Primary Radiation Therapy (RT) Alone to a Combination with Androgen-Deprivation Therapy (ADT), or 3 versus 8 Months of ADT with Radiation Therapy

TRIAL (SOURCE)	TREATMENT ARMS	NO. PATIENTS	5-YEAR OVERALL SURVIVAL	5-YEAR CANCER-SPECIFIC SURVIVAL	5-YEAR PSA PROGRESSION
EORTC 22863 (Bolla et al, 1997, 2002)	Goserelin 3 yr vs. none	208 vs. 207	78% vs. 62%	94% vs. 79%	76% vs. 45%
RTOG 85-31 (Pilepich et al, 1997, 2005; Lawton et al, 2001)	Goserelin lifetime adjuvant vs. none until relapse	477 vs. 468	75% vs. 71%*	91% vs. 87%*	54% vs. 21%
RTOG 86-10 (Pilepich et al, 2001; Shipley et al, 2002)	Goserelin + flutamide 4 mo (2 mo neoadjuvant, 2 mo concurrent) vs. none	226 vs. 230	72% vs. 68%†	85% vs. 80%	28% vs. 10%
RTOG 92-02 (Hanks et al, 2003)	Goserelin 2 yr adjuvant vs. none	761 vs. 753	80% vs. 78.5%†	91.2% vs. 94.6%	28% vs. 55.5%
DFCI 95096 (D'Amico et al, 2004)	Goserelin or leuprolide + flutamide 6 mo vs. none	102 vs. 104	88% vs. 78%		
Granfors et al, 2006‡	Orchiectomy vs. none	45 vs. 46			
Canadian Multicenter (Crook et al, 2009)	Goserelin + flutamide 3 mo vs. 8 mo, neoadjuvant	184 vs. 194	81% vs. 79%†	94% vs. 93%†	58% vs. 65%†

*The 5-year overall survival and cancer-specific survival differences between the two study arms were not significant. At 10 years of follow-up, however, the combination of adjuvant goserelin and RT compared with RT alone was significantly different: for overall survival, 49% vs. 39%, respectively; for cancer-specific survival, 84% vs. 78%, respectively.

†Difference not significant.

‡During 14 to 19 years of follow-up, 87% of subjects in RT-only arm and 76% of those in the RT + orchiectomy arm died (log rank $P = .03$); prostate cancer mortality was 57% and 35%, respectively (log rank $P = .02$).

PSA, prostate-specific antigen.

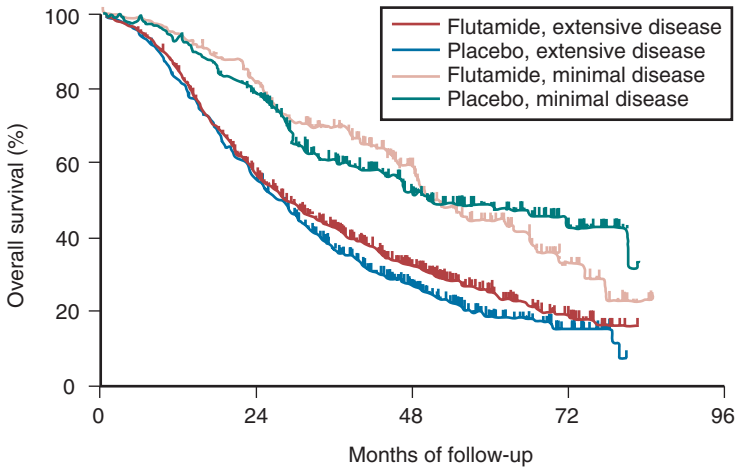
advanced, high-risk disease the combination of radiation therapy with ADT is certainly better than radiation therapy alone. A number of trials have been designed to address the timing of ADT (length, neoadjuvant, adjuvant) (Crook et al, 2004): some of the results are summarized in Table 109–6 and in several review articles (D'Amico, 2002; Lawton, 2003). Changes in the dose and field of the external-beam radiation therapy make direct study to study comparisons difficult: unlike the uniformity of radical prostatectomy (complete ablation of the prostate), the optimum irradiation technique remains undefined.

Combined Androgen Blockade

Among all the efforts to improve the efficacy of ADT, none has been as widely studied as combinations of the various forms of hormone therapy, particularly if mechanistically nonredundant. For example, ablation of the source of androgen (castration) coupled with inhibition of LH-RH with DES was one of the first combinations studied clinically to suggest improved survival (Nesbit and Baum, 1951); on closer scrutiny in the first VACURG trial the survival advantage of this combination was lost (Blackard et al, 1973). Likewise, an early experience with an LH-RH analogue and an antiandrogen in 30 patients suggested improved outcomes compared with standard treatment (Labrie et al, 1983); **on extensive scrutiny in a meta-analysis of 27 prospective, randomized, international clinical trials of the combination of an antiandrogen with either castration or an LH-RH agonist the collective result was clinically insignificant** (Prostate Cancer Trialists' Collaborative Group, 2000).

The concept of adding an antiandrogen to surgical castration or LH-RH agonists is based on the idea that, after the elimination of testicular androgens through surgical or medical castration, adrenal androgens still contribute to prostate cancer progression (Labrie et al, 1988; Miyamoto et al, 1998; Miyamoto and Chang, 2000). The fact that serum testosterone does not drop to zero after surgical or medical castration is clear evidence for additional sources of androgen (Geller, 1985; Sandlow et al, 1988). The idea of trying to eliminate all sources of endogenous androgen in treating prostate cancer is not new: bilateral surgical adrenalectomy was performed with failure far outweighing success (Huggins, 1945). Also referred to, somewhat presumptuously, as total androgen blockade or maximum androgen blockade—as if such a state is actually achieved—the term *combined androgen blockade* is more appropriate. **The antiandrogens are nonspecific in blocking the binding of androgens to the AR: both testicular and adrenal androgens are affected. In concept, the approach is sensible and some clinical trials showed prolonged survival in patients treated with combined androgen blockade with advanced prostate cancer compared with standard ADT** (Crawford et al, 1989; Dijkman et al, 1997; Denis et al, 1998).

One study showing a survival advantage to combined androgen blockade compared the antiandrogen flutamide (250 mg, three times per day) in combination with daily leuprolide—a formulation not currently used—to placebo plus daily leuprolide in men with metastatic prostate cancer (Crawford et al, 1989). The combination therapy resulted in a significantly longer progression-free survival and longer overall median survival (35.6 vs. 28.3 months) when compared with the placebo-treated controls. In a hypothesis generating subset analysis, the authors found those with minimal metastatic disease (defined as the absence of metastases in the skull, ribs, long bones, and non-nodal soft tissue) enjoyed the largest survival benefit compared with similarly defined men receiving placebo. Another positive study compared orchiectomy plus the antiandrogen nilutamide to orchiectomy plus placebo



No. of patients at risk					
Flutamide, extensive disease	556	310	120	20	0
Placebo, extensive disease	539	295	101	16	0
Flutamide, minimal disease	141	115	58	13	0
Placebo, minimal disease	146	114	51	16	0

Figure 109–6. Overall survival among eligible patients with follow-up, according to treatment assignment and extent of disease: orchiectomy plus placebo versus orchiectomy plus flutamide. (From Eisenberger MA, Blumenstein BA, Crawford ED, et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med 1998;339:1036–42.)

(Dijkman et al, 1997): at 8.5 years of follow-up the combined androgen blockade group had significantly longer median time to progression (21.2 vs. 14.7 months) and higher overall survival (37 vs. 29.8 months). Finally, a study of depot goserelin combined with flutamide was compared with orchiectomy and showed increased survival in the combined androgen blockade group (Denis et al, 1998).

Against the backdrop of these positive studies are a host of randomized trials showing no significant survival advantage for combined androgen blockade. A landmark randomized clinical trial comparing surgical castration alone to surgical castration combined with flutamide in men with metastatic prostate cancer showed no significant survival advantage for those undergoing combined therapy (Eisenberger et al, 1998). **Unlike the previous study suggesting an advantage of combined androgen blockade in men with minimal metastatic disease, stratifying outcome by disease burden (defined prospectively) was not significant** (Fig. 109–6).

In a clinical trial, when the variability in a possible outcome is large and the effect being studied may be small, confidence in the interpretation of the result is dependent on the size of the study. When several studies testing the same idea in presumably the same patient population demonstrate both positive and negative results, concerns about the existence of a real treatment effect increase. Such is the case with many of the studies of combined androgen blockade: when the study consists of only a few hundred men or is based on subset analysis of a larger study there is a risk that chance and not an antiandrogen drive the survival outcomes. Those favoring a role of combined androgen blockade in prostate cancer management point to the selected studies supporting their point of view, only to be met by those against combined androgen blockade who bring forth the negative studies that support their point of view.

Fortunately, the idea of combined androgen blockade has been very extensively studied: since the early 1980s, 27 randomized studies including 8275 men have been conducted, providing the basis for a meta-analysis comparing combined androgen blockade to standard ADT (Prostate Cancer Trialists' Collaborative Group, 2000). In these studies, 88% of patients had metastatic disease; the remainder had locally advanced disease. Interestingly, **in studies recording specific cause of death, 20% died of causes other than prostate cancer: not everyone with metastatic prostate cancer die of their disease.** In this meta-analysis the 5-year survival with combined androgen blockade was 25.4% compared with 23.4% with standard ADT, a nonsignificant gain in favor of ADT of 1.8% (Fig. 109–7). Studies including the steroidal antiandrogen cyproterone acetate had a slightly worse outcome of the combined androgen blockade study arms (5-year survival of 15.4% vs. 18.1% for ADT alone), suggesting increased non–prostate cancer deaths in those receiving cyproterone acetate. **When studies examining the outcomes of the nonsteroidal antiandrogens flutamide or nilutamide were considered independent of those with cyproterone acetate, the 5-year survival improved from 24.7% (standard ADT) to 27.6% for combined androgen blockade. This 2.9% improvement was significant, but the meta-analysis had a 0% to 5% range of uncertainty about the true size of the benefit.**

TIMING OF THERAPY

The timing of the initiation of ADT, although not as extensively studied as combined androgen blockade (CAB), remains one of the

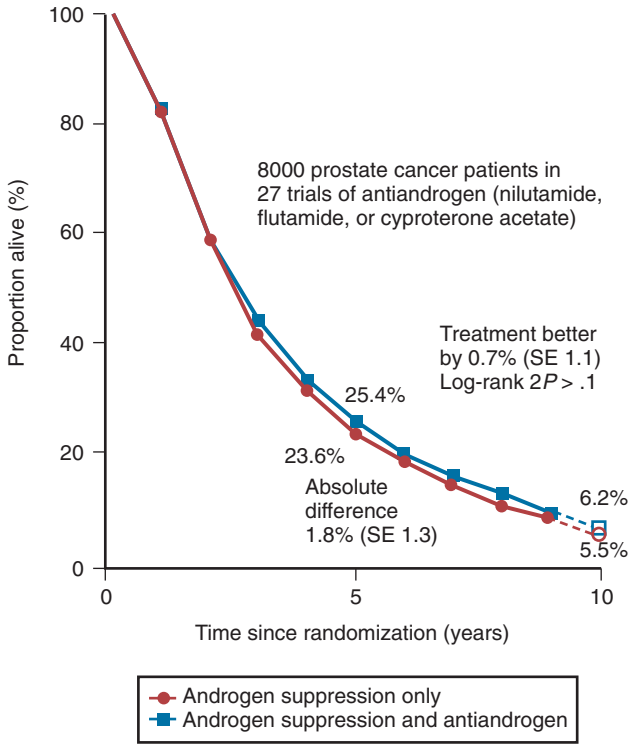


Figure 109–7. Meta-analysis of maximal androgen blockade versus testicular androgen suppression alone in 27 randomized trials and 8275 patients, with an average follow-up of about 5 years. Overall survival curves are for all men irrespective of the antiandrogen used. (From Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of randomized trials. Lancet 2000;255:1491–8.)

most contested areas of prostate cancer management. The spectrum of opinions range from ADT initiation at the first sign of primary prostate cancer failure (early) to ADT initiation only with objective evidence of distant metastatic disease (late) (Reese, 2000; Walsh et al, 2001; Loblaw et al, 2004; Miyamoto et al, 2004; Sharifi et al, 2005). Unfortunately, the clinical data to support the various perspectives are limited and it is not uncommon for proponents of a particular opinion to extrapolate data from one clinical state to another for which data do not exist. **There is no question that early ADT delays biochemical and clinical disease progression, but the effects of early ADT on survival remain unclear** (Ryan and Small, 2005). Likewise there is no question that ADT is indicated in symptomatic, metastatic disease. For the sake of this discussion ADT will be considered continuous, from initiation until death; intermittent ADT will be discussed in a subsequent section. Additionally, the focus of this discussion is on overall and prostate cancer–specific survival resulting from ADT.

It is useful to consider some facts about ADT and prostate cancer progression. First, the natural history of prostate cancer progression, even in the hormonally intact individual, is protracted. In a cohort of 304 men with a biochemical recurrence after radical prostatectomy, the median time from recurrence to metastasis was 8 years and from metastasis to death it was 5 years (Pound et al, 1999). In updates of this study the median time to prostate cancer–specific mortality had, initially, not been reached after 16 years of follow-up but was subsequently found to be 168 months (14 years) (Freedland et al, 2005; Makarov et al, 2008). Therefore, even in the absence of ADT, men with progressive prostate cancer live for a long time. **Second, despite dramatic clinical responses, men undergoing ADT will either die of a non–prostate cancer cause (estimated at 20% based on the combined androgen blockade meta-analysis) or will eventually demonstrate evidence of castration-resistant disease and die of prostate cancer.** In the randomized prospective study of orchiectomy with or without the antiandrogen flutamide, only 7% of men were still alive at 10 years after the initiation of ADT (Tangen et al, 2003). In a study using a 5% national random sample of Medicare beneficiaries undergoing ADT for prostate cancer, the median overall survival after the initiation of ADT was 4.4 years and after 8 years only 4.5% of the population was still alive (Krupski et al, 2004). **Third, ADT is not an innocuous therapy: beyond the quality of life side effects discussed earlier, in a global sense men on ADT age more rapidly; the natural extension of more rapid aging is earlier death.** Therefore the long natural history of prostate cancer progression coupled with the inevitability of its progression after ADT initiation in a population with a growing risk of death from all causes should temper enthusiasm to indiscriminately apply this therapy to all men with progressive prostate cancer.

The questions about the timing of ADT are not new. In 1973 the results of a large (more than 1900 men) study performed by the then Veterans Administration of early versus late hormonal therapy were reported (Byar, 1973). **In men with metastatic disease, death from prostate cancer occurred in 48% of men treated early versus 47% of men treated late. In men with locally advanced disease, death from prostate cancer occurred in 14% of men treated early versus 17% of patients treated late.** The lack of a survival benefit in men treated early coupled with the known side effects of therapy support the recommendations that hormonal therapy should be instituted in men with symptomatic disease. Since that time, several randomized studies have applied ADT at different times in the natural history of prostate cancer; the results of those studies must be considered within the context of when ADT is used and the circumstances of the study.

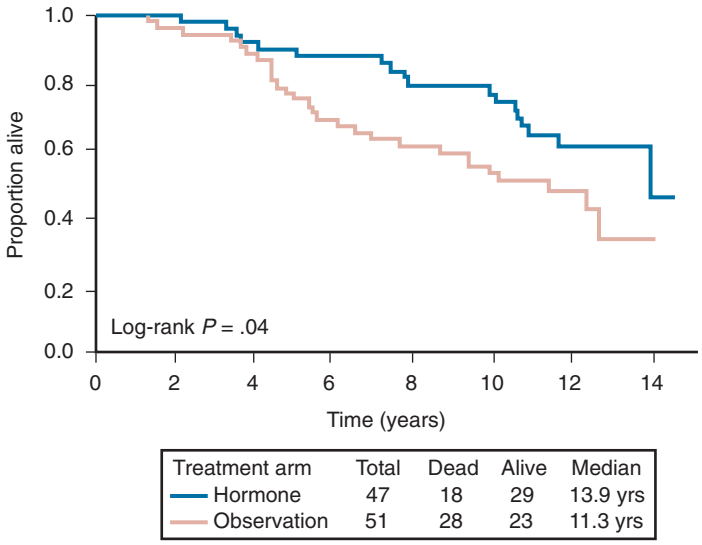
Immediate versus Delayed Androgen-Deprivation Therapy in Clinically Localized Disease

In the bicalutamide Early Prostate Cancer (EPC) program, men were randomized to bicalutamide 150 mg or placebo in addition to standard for care (See et al, 2003). End points of these trials include overall survival, progression-free survival, and tolerability. **In the subset of men with clinically localized disease the overall survival was significantly worse in those undergoing ADT with 150 mg bicalutamide compared with placebo** (Iversen, 2004). No specific cause for this decline in overall survival with ADT was identified, but it appeared to be the result of increased deaths from non–prostate cancer causes for those on bicalutamide. It is unlikely the excessive death rate in the bicalutamide study arm in those with clinically localized disease will lose significance with longer follow-up.

In a community-based cohort study (Prostate Cancer Outcomes Study), men with localized prostate cancer treated with primary ADT within 1 year of diagnosis had a 91% cancer-specific survival but only a 66% overall survival at 5 years (Graff et al, 2007). A larger study of 19,271 men 66 years or older with localized prostate

cancer who did not receive definitive local therapy found that primary ADT was associated with lower 10-year prostate cancer-specific survival compared with those on conservative management (Lu-Yao et al, 2008). Although this finding could be the result of more aggressive prostate cancers requiring immediate primary ADT, there was no increase in 10-year overall survival with primary ADT. The authors conclude "primary ADT is not associated with improved survival in the majority of elderly men with localized prostate cancer when compared with conservative management" (Lu-Yao et al, 2008). Finally, in a retrospective, matched cohort study of adjuvant ADT (within 90 days of node-negative, radical prostatectomy) compared with those who did not have ADT there was a 3% improved prostate cancer–specific survival (98% vs. 95%, respectively, $P = .009$) but no improvement in overall survival (83% in both groups) (Siddiqui et al, 2008).

These observations are important for several reasons. First, these observations resoundingly answer the claim that "ADT can't hurt, so why not use it early." **In the EPC study, men *without* ADT had significantly better survival.** Second, when ADT is applied in situations when the risk of death from prostate cancer is already low, demonstration of a prostate cancer–specific survival benefit from that therapy will be very difficult. If ADT itself increases overall mortality compared with no ADT, then a demonstration of a prostate cancer–specific benefit will be nearly impossible. Third, men with localized, low-risk prostate cancer should not be treated with ADT without first being informed of these findings. Avoidance of prostate cancer progression and death may come at the expense of a higher overall death rate. These data support the hypothesis that the more rapid aging associated with ADT will bring men with low-risk prostate cancer more quickly to their deaths.



Treatment arm	Total	Dead	Alive	Median
Hormone	47	18	29	13.9 yrs
Observation	51	28	23	11.3 yrs

Figure 109–8. Long-term overall survival of man randomized to immediate hormone therapy compared with observation after radical prostatectomy with pelvic lymphadenectomy in men with node-positive prostate cancer: at median 11.9 year follow-up, overall survival in the immediate hormone therapy group was 64% (30/47) compared with 45% (23/51) in the observation group ($P = .04$, log-rank). (From Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol 2006;7:472–9.)

Immediate versus Delayed ADT in Lymph Node Metastatic Prostate Cancer

A randomized prospective study of immediate ADT compared with delayed ADT was performed in men with histologic evidence of metastatic prostate cancer in regional lymph nodes after radical prostatectomy by the Eastern Cooperative Oncology Group (ECOG). At the time of the initial report, **at 7.1 years of median follow-up, overall survival significantly ($P < .02$) favored the immediate ADT group compared with the delayed ADT group: in the immediate ADT group, only 3 of the 7 deaths were due to prostate cancer compared with 16 of the 18 cancer-specific deaths in the delayed ADT group** (Messing et al, 1999). In an updated report, median overall survival was significantly longer in the immediate ADT compared with the delayed ADT group, 13.9 versus 11.3 years, respectively (Fig. 109–8) (Messing et al, 2003, 2004). Eight of 18 men in the immediate ADT group died of prostate cancer compared with 25 of 28 in the delayed ADT group. Given the previous discussion of the increased non–prostate cancer death rate with 150 mg bicalutamide, it is interesting that there have been proportionally more non–prostate cancer deaths in the immediate ADT group (55%) compared with the delayed therapy group (11%). Nevertheless, **based on this randomized, prospective trial, there appears to be a benefit to immediate ADT in those with histologic evidence of lymph node metastases at the time of radical prostatectomy.**

There have been several criticisms of this study (Eisenberger and Walsh, 1999). First, the study was designed to enroll 240 patients yet only enrolled 100. When a large difference in outcome is found in a small study there is a risk of a type I error (assuming a treatment has an effect when in reality it does not). There was no evidence for an imbalanced randomization, but unrecognized prognostic factors can influence outcomes in smaller studies. Second, Gleason grading was not centralized and the absence of a correlation between histologic grade and survival suggests an imbalance may exist. This concern was partially addressed by a central pathologic review in a blinded fashion of a subset (51%) of the initial specimens. Based on this reanalysis there was no significant difference in outcomes by treatment arm. Third, those on delayed ADT experienced disease progression and death from prostate cancer that was much more rapid than would have been expected from contemporary series of node-positive patients (Zincke et al, 1992; deKernion et al, 1990; Cadeddu et al, 1997). In contrast to the ECOG study, an observational study of 731 men with node-positive prostate cancer after radical prostatectomy between 1991 and 1999 found no significant difference in overall survival in those who received adjuvant ADT (within 120 days of surgery, $n = 209$) compared with those who did not (Wong et al, 2008).

The magnitude of the difference observed in the ECOG study has not been in seen in larger similar, but not identical, patient populations. A European Organization for the Research and Treatment of Cancer (EORTC) trial of immediate versus delayed ADT in pN1-3M0 patients without local treatment of the primary tumor was performed in 302 patients, of which 115 were randomized to delayed ADT and 119 to immediate ADT (Schröder et al, 2004). At a median follow-up of 13 years, the median overall survival on immediate ADT was 7.6 years (95% CI, 6.3 to 8.3 years) versus 6.1 years (95% CI, 5.7 to 7.3 years) in the delayed ADT group. The 10-year cumulative incidence of death from prostate cancer was 55.6% in the delayed ADT group versus 52.1% in

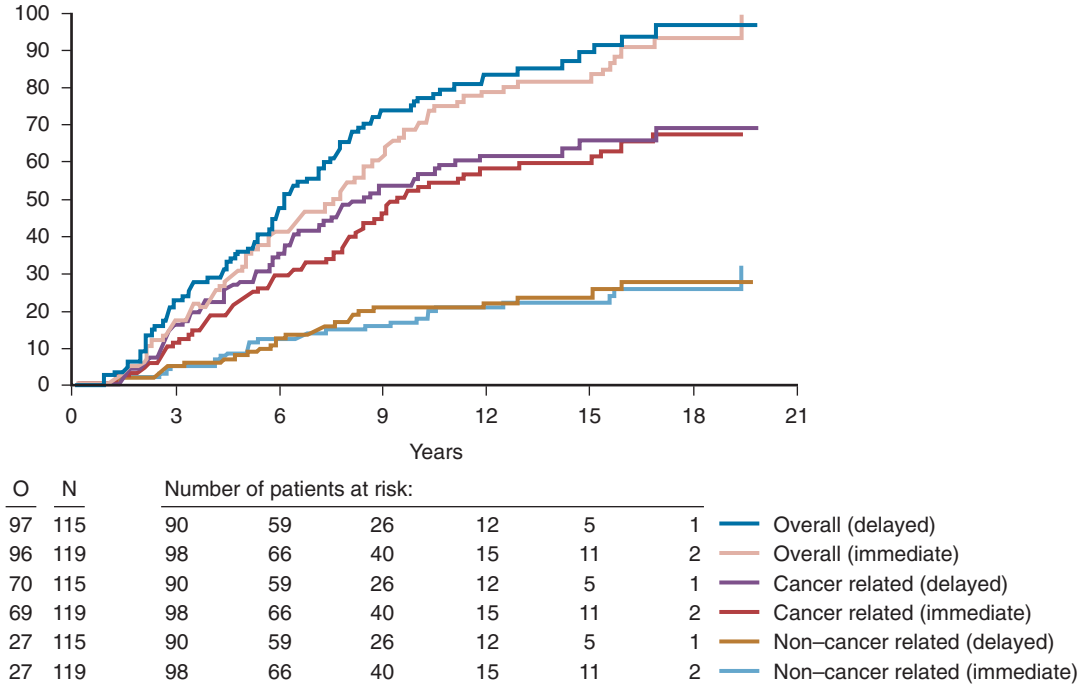


Figure 109–9. Overall mortality, cancer-related mortality, and non–cancer-related mortality in early versus delayed androgen-deprivation therapy in men with T2-T3pN1-3M0 prostate cancer without local treatment of the primary tumor. (From Schröder FH, Kurth KH, Fossa SD, et al. Early versus delayed endocrine treatment of T2-T3 pN1-3 M0 prostate cancer without local treatment of the primary tumor: final results of European Organisation for the Research and Treatment of Cancer Protocol 30846 after 13 years of follow-up [a randomized controlled trial]. Eur Urol 2009;55[1]:14–22.)

the immediate ADT group (Schröder et al, 2009) (Fig. 109–9). **Based on these data, 20.8 patients would need to be treated with immediate ADT to spare one life at 5 years and 28.6 would need to be treated to spare one life at 10 years.**

Immediate versus Delayed ADT in Locally Advanced, Asymptomatic Metastatic Disease or Disease Not Suitable to Local Treatment

A trial of immediate versus delayed ADT in men with locally advanced or asymptomatic prostate cancer was conducted by the Medical Research Council (MRC) Prostate Cancer Working Group Investigators Group (1997). A total of 934 men were included (500 M0, 261 M1, and 173 Mx), with 469 randomized to immediate ADT and 465 randomized to delayed ADT. **As originally reported there was a significant survival advantage in the M0 group; on longer follow-up the overall survival advantage is not significant** (Kirk, 2004). Overall, men in the delayed ADT arm died significantly more often from prostate cancer and had significantly more symptoms related to disease progression. Based on these data the benefits of immediate ADT would seem to support its use.

There have been many criticisms of the MRC trial. First, 6% (29/465) of men in the delayed ADT arm "died from prostate cancer before treatment could be started," meaning they died without ever receiving ADT. Delayed ADT is not the same as no ADT. Second, 173 of subjects included in the study were not staged (Mx). When nearly one in five men could have been incorrectly randomized, the impact on the study's outcome could be significant. Third, almost 10% of men in the delayed group were treated only when they had developed spinal cord compression or pathologic fractures. The emergency implementation of hormonal therapy is a rare event in patients followed closely; it certainly should not occur in 10% of patients. Finally, the lack of a standardized follow-up protocol—follow-up and management were otherwise according to the participating clinician's normal practice—may provide meaningful "real world" result but likely introduces major deviations from rigorous clinical trial design.

Because the majority of men in the MRC study have died (92.5% in immediate ADT, 93.6% in delayed ADT), the data are now mature and unlikely to change significantly in the future (Kirk, 2004). **Time to death from prostate cancer remains significantly in favor of the immediate ADT group (P = .019), whereas time to death from any cause is not significantly different between the groups (P = .0914).** The total difference in prostate cancer–specific deaths was 46 men: 241 died of prostate cancer in the immediate ADT study arm, 287 in the delayed ADT arm (Kirk, 2004); the impact of the 29 men in the delayed ADT group who never received ADT on this result is unknown but could reasonably be considered significant. Unlike the increased overall mortality for immediate ADT found in the EPC study of bicalutamide 150 mg for localized, low-risk disease, no similar increase was observed in immediate ADT in the MRC study of a higher-risk cohort.

Immediate versus delayed ADT was studied in another group (n = 935) of men not suitable for local treatment (refused local treatment, had decreased life expectancy, advanced local tumor stage and/or severe comorbidities) (Studer et al, 2006). Unlike the MRC study, immediate ADT resulted in a significant, albeit small improvement in overall survival but no difference in prostate cancer–specific mortality or overall symptom-free survival. Interestingly, **in the delayed ADT study arm, 25.6% died without ever needing treatment.**

Immediate versus Delayed ADT: Integrating the Data

With the emerging data from ongoing clinical trials and the recently published results of new studies, it is possible to consider the timing of ADT from the perspective of the natural history of the disease.

1. **There is no survival benefit to immediate ADT in low-risk, localized prostate cancer.** In fact, from the perspective of overall survival, men treated in this fashion do significantly worse than those spared ADT in this setting.
2. **In locally advanced, asymptomatic metastatic and clinically present but undefined prostate cancer treated in a community setting with limited disease monitoring, immediate ADT results in significantly better prostate cancer–specific survival but not better overall survival. On the other hand, in men deemed not suitable for local treatment, immediate ADT improved overall survival but not prostate cancer–specific survival.**
3. **In node-positive disease without primary treatment there is no significant advantage to immediate ADT, although on balance there is a 1.5-year median survival advantage. In node-positive disease with radical prostatectomy there is a significant survival advantage favoring immediate ADT, with a 2.6-year difference in median overall survival.**

In Figure 109–10, conceived and developed by Iversen, one can see the relative gain and loss in survival from adjuvant ADT based on the stage of the disease. In low-risk disease the toxicity of ADT exceeds any prostate cancer–specific benefit, so there is an overall net loss in survival. For locally advanced disease, particularly in combination with local treatment directed at the primary tumor, ADT provides a net gain in survival. As the disease progresses the inevitability of castration-resistant progression and prostate cancer-specific death limits the magnitude of the nonetheless real benefit of ADT. **Because life is more than simply survival, discussions about ADT should include the expected impact on quality of life.**

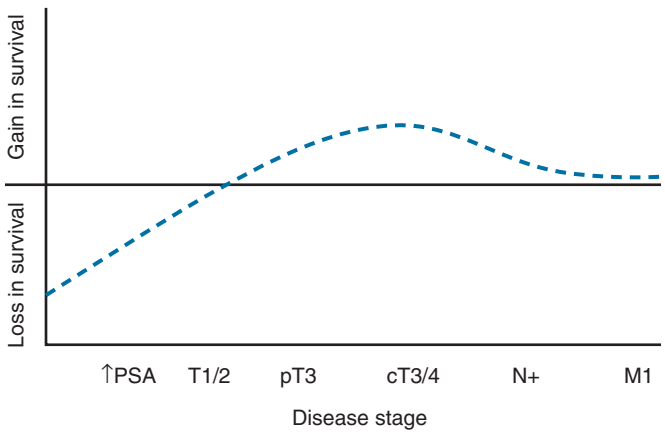


Figure 109–10. Based on available clinical trial data, the hypothetical gain or loss in overall survival based on the time in the natural history of the disease that ADT is instituted, as demonstrated by the *dotted line*. (Concept and figure courtesy of P. Iversen.)

ECONOMIC CONSIDERATIONS

In the United States, the cost of drug therapy for ADT (LH-RH agonists) in the Medicare Program was $761 million in 1997 and rose to $1.2 billion in 2003 (Holtgrewe et al, 2000; Shahinian et al, 2006). Indeed, in 2003, LH-RH agonists were the second highest Medicare Part B expenditure. This expense is not unique to the United States: in 1997, the annual cost of these agents in Sweden was $17 million and in Germany the annual cost was $142 million. In a study of 96 men undergoing ADT for prostate cancer over a 10-year period the cost of LH-RH agonists ranged from greater than 10.7 to 3.2 times the cost of bilateral orchiectomy and the cost of combined androgen blockade was 17.3 to 20.9 times greater (Mariani et al, 2001). **Clearly the cost of ADT, as currently being delivered, is extraordinary.**

Although DES is associated with increased cardiovascular toxicity, from a strictly cost point of view, it is the least expensive form of ADT, particularly at the 1-mg/day dose, with no prophylactic breast irradiation (Mariani et al, 2001). **There is no significant survival advantage of LH-RH agonists over orchiectomy, so from an economic perspective LH-RH agonists would only be more cost effective than orchiectomy if a patient only lived for a few months after initiation of ADT. The 3-month formulations of leuprolide acetate and goserelin become more expensive than orchiectomy on the administration of a second 3-month depot;** specifically, the break-even rate for leuprolide acetate is 4.2 months and that of goserelin is 5.3 months compared with orchiectomy (Mariani et al, 2001).

Combined androgen blockade is the most expensive form of ADT. Although there is no significant benefit of this treatment over orchiectomy alone (Eisenberger et al, 1998), some patients may experience a large benefit. Assuming a cost-effectiveness threshold of $100,000—meaning the expense of combined androgen blockade minus the expense of orchiectomy—for each quality of life year, combined androgen blockade would need to decrease the risk of disease progression by 20% compared with orchiectomy to be considered cost effective (Seidenfeld et al, 1999). **The earlier medical ADT is initiated, the more expensive it becomes: in models examining the cost-effectiveness, ADT was most cost effective if initiated after patients became symptomatic from prostate cancer metastases** (Bayoumi et al, 2000). In this model, LH-RH agonists, nonsteroidal antiandrogens or combined androgen blockade, had higher costs and lower quality-adjusted survival than orchiectomy.

If orchiectomy is just as effective and so much less expensive, why is it not more widely used? In two studies that offered orchiectomy versus medical therapy for ADT, 70% of patients chose medical therapy (Iversen et al, 1998). Clearly, patients (and physicians) choose medical ADT for reasons other than efficacy or expense. Indeed, the use of ADT in all-stage prostate cancer has increased significantly between 1989 to 2001: for example, primary ADT rose from 32.8% to 48.2% in men with high-risk disease (Cooperberg et al, 2003). **Avoiding the largely psychologic quality of life issues unique to orchiectomy (disfigurement, permanence) comes at an expense that would seem disproportionate to the risk, and yet society has chosen to accept this expense.**

Perhaps most sobering about the costs of ADT is the significant variability with which ADT is used by urologists. In a study of 61,717 American men with prostate cancer from 1992 until 1999,

the total variance in the use of ADT attributable to the urologist was approximately 21%, which was significantly more than that attributable to tumor characteristics (approximately 9%) or patient characteristics (approximately 4%). In other words, "the urologist who sees the patient may be a more important determinant of whether that patient will receive androgen deprivation than the characteristics of the tumor (e.g., stage or grade) or the patient (e.g., age and comorbidity)" (Shahinian et al, 2006). The challenge for urologists is to offer this expensive form of treatment to those who need it and to avoid ADT in those who do not (Schellhammer, 2006).

THE FUTURE OF HORMONE THERAPY

Intermittent Androgen-Deprivation Therapy

The use of intermittent ADT is being studied in at least seven large randomized phase 3 clinical trials (Boccon-Gibod et al, 2007). The rationale for intermittent ADT is based on two complementary ideas. First, in preclinical animal models (Shionogi breast cancer tumor, LNCaP prostate cancer tumor) exposure to androgen deprivation on a intermittent, rather than continuous, basis lengthened the time to the emergence of androgen-refractory cancer growth (Akakura et al, 1993; Sato et al, 1996). Because androgen-refractory prostate cancer is synonymous with lethal prostate cancer, any manipulation of the hormonal milieu that can delay progression into this state would be welcomed. Second, many patients (and their physicians) have increasingly questioned the real benefit of continuous ADT, given the profound and often debilitating side effects associated with its use. With readily reversible ADT, recovery of normal testosterone levels should occur when androgen ablation is stopped. In theory, the quality of life side effects of ADT on intermittent treatment should be some fraction of those side effects when ADT is used continuously.

There are several reasons to await the results of the randomized trials of intermittent ADT before it is adopted as a standard treatment for advanced prostate cancer (Bhandari et al, 2005). **There is no evidence cycling androgen levels in men with prostate cancer will delay the emergence of androgen-refractory disease:** indeed, preclinical models using the Shionogi tumor strongly predicted neoadjuvant ADT would benefit men undergoing radical prostatectomy (Gleave et al, 1997) and yet the clinical trials resoundingly rejected this hypothesis. One could make a compelling argument why return of normal androgen levels associated with intermittent ADT would actually accelerate cancer progression, recalling the 87% tumor flare associated with testosterone administration (Fowler et al, 1982) or the exacerbations of symptoms with initial use of LH-RH agonists (Waxman et al, 1985). Quality of life should improve, but at what cost? The studies of intermittent ADT may bring the balance between quantity and quality of life into fuller view but not necessarily into clearly focus. Finally, based on a lack of adequate initial response to ADT, men with the most advanced prostate cancer (high PSA [mean 834 ng/mL], high alkaline phosphatase level, more frequent T4 stage, poorly differentiated tumors, and more than five skeletal metastases) are much less likely to be eligible for intermittent ADT (Salonen et al, 2008).

Key Points

- Androgen deprivation is one of the most effective therapies against any solid tumor; unfortunately, with time almost all prostate cancers will become androgen refractory.
- All current forms of androgen-deprivation therapy (ADT) function by either lower levels of circulating androgens or blocking the binding of androgen to the androgen receptor.
- All most all androgen-refractory prostate cancer remains sensitive to androgen; therefore ADT should be continued in castration-resistant disease.
- Relative to testosterone and dihydrotestosterone, the adrenal androgens are weak.
- There are four general forms of ADT: (1) ablation of androgen sources; (2) inhibition of androgen synthesis; (3) antiandrogens; and (4) inhibition of LH-RH and/or LH.
- Bilateral orchiectomy reduces testosterone by 90% within 24 hours of surgery.
- Nonsteroidal antiandrogens cause LH and testosterone levels to increase.
- Serious liver toxicity is a possible side effect of all antiandrogens.
- Antiandrogens can act agonistic on some tumors; antiandrogen withdrawal results in PSA declines in 15% to 30% of patients.
- Bicalutamide 150 mg monotherapy appears to have equivalent efficacy to medical or surgical castration for locally advanced or metastatic prostate cancer.
- All LH-RH agonists induce a testosterone increase on initial exposure. Coadministration of an antiandrogen functionally blocks the effects of testosterone.
- The magnitude and rapidity of the initial response to ADT are strong predictors of the durability of that response.
- The side effects of ADT include osteoporosis, hot flashes, sexual dysfunction, cognitive function alterations, changes in body habitus, gynecomastia, and anemia. These side effects can be progressive but are responsive to other treatments.
- There is no evidence 3 months of neoadjuvant ADT before radical prostatectomy improves biochemical outcomes.
- There is considerable evidence that ADT combined with external-beam radiation therapy improves overall survival, cancer-specific survival, and freedom from disease progression. The optimal timing and duration of ADT in this combination remains undefined.
- Based on a large meta-analysis of many clinical trials, combined androgen blockade with nonsteroidal antiandrogens provides about a 3% survival benefit at 5 years compared with standard ADT.
- The natural history of prostate cancer progression is protracted. Many men with evidence of disease will never require ADT.
- The use of ADT in low-risk, localized prostate cancer significantly increases overall (non–prostate cancer) mortality.
- In lymph node metastatic prostate cancer ADT improves overall survival if the primary tumor is removed but has no significant effect if the primary tumor is not removed.

SUGGESTED READINGS

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The complete reference list is available online at www.expertconsult.com.

chapter
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Treatment of Castration-Resistant Prostate Cancer

Emmanuel S. Antonarakis, MD • Michael A. Carducci, MD • Mario A. Eisenberger, MD

Clinical Considerations
Cytotoxic Chemotherapy
Palliative Management
Novel Approaches
Conclusions

During the past several decades, endocrine manipulations developed to inhibit hormone-dependent prostate cancer growth and differentiation have constituted the basic strategy for the systemic control of prostate cancer. **Suppression of gonadal testosterone is the central principle of androgen-deprivation therapy (ADT), and this represents one of the most effective systemic palliative treatments known for solid tumors. Although it is extremely effective initially, virtually all patients eventually develop clinical evidence of treatment resistance. The outcomes with endocrine therapy have not changed significantly during the past few decades. Progression-free and overall survival figures of patients with metastatic disease with various methods of ADT have ranged from 12 to 20 months and 24 to 36 months, respectively** (Leuprolide Study Group, 1984; Crawford et al, 1989; Denis et al, 1993; Eisenberger et al, 1998). **Whereas somewhat longer survival times are reported in the more recent studies, this is most likely due to a "lead time" effect observed in contemporary populations of patients. The development of hormone resistance (i.e., cancer progression despite castrate levels of serum testosterone) is virtually a universal issue that affects all patients treated with ADT. Undoubtedly, further improvement in the outcome of patients with metastatic castration-resistant prostate cancer (CRPC) rests on the use of nonhormonal approaches that can effectively control the growth of the disease.**

During recent years, clinical investigations testing nonhormonal approaches have shown that systemic chemotherapy improves survival and quality of life in patients with castration-resistant (i.e., hormone-refractory) disease. Advances in the understanding of the biology of prostate cancer and characterization of key molecular pathways have added an important new dimension for treatment and the opportunity to design disease-specific targeted treatment approaches. Evolving data suggest that targeted approaches may play an important role in treatment of prostate cancer that may improve the outcome of our patients.

Progress in cell and molecular biology during the past decade has also enhanced our understanding of the mechanisms involved in the progression of prostate cancer, and this may provide the opportunity for rational planning of the appropriate timing of systemic therapeutic intervention with the objective of preventing or delaying progression of disease to lethal proportions. **Cancer cells demonstrating the castration-refractory phenotype can be identified during early stages of development of prostate cancer. Somatic alterations of the androgen receptor are frequently observed in patients with evidence of disease progression after androgen deprivation. It has also been demonstrated that during cancer progression, in the absence of androgens, a molecularly altered androgen receptor can still undergo ligand-dependent activation by other hormones such as estrogens and progestational agents and non–ligand-dependent activation by growth factors and cytokines** (Feldman and Feldman, 2001; Gelmann, 2002; Nelson WG et al, 2003). **The observation that the androgen receptor can still be activated even after long-term gonadal ablation suggests that it continues to play an important role in prostate cancer growth and may indeed be a reasonable target for treatment in patients with androgen-independent disease.**

In the presence of androgens, prostatic cancer growth is based on a cell proliferation rate that exceeds that of cell death (Isaacs et al, 1992). Androgen ablation primarily affects the cell death rate by inducing a swift apoptotic cascade. **As the tumor progresses the threshold of apoptosis progressively rises to a point at which cell proliferation exceeds cell death** (Berges et al, 1995). This results in the accumulation of endocrine-independent cells that eventually dominate the biologic behavior of prostate cancer in late stages.

Preclinical data suggest that the relatively low growth fraction expressed by adenocarcinoma of the prostate (compared with other common tumor types) may be a determining factor to explain the relative insensitivity to conventional cytotoxic chemotherapy. The proliferation rate of prostate cancer cells, which is directly proportional to the growth fraction, appears to increase with tumor progression especially after androgen ablation. Cell proliferation antigens, such as Ki-67 expressed by cycling cells (Cattoretti et al, 1992), may have important prognostic and therapeutic implications because most conventional cytotoxic chemotherapeutic agents available are usually more effective

in tumors with high proliferative rates such as lymphomas, small cell lung carcinomas, and germ cell tumors of the testis.

Changes in differentiation pathways in prostate cancer have been increasingly emphasized, particularly in the form of neuroendocrine/anaplastic cells (diSant'Agnese, 1995). Evolving experience with cytotoxic chemotherapy suggests that this aggressive clinical entity may be responsive to treatment regimens frequently employed for comparable tumors at other sites with similar phenotypic characteristics, such as small cell carcinoma of the lung. There is strong evidence to support the relationship between prostate cancer growth and various peptide growth factors (Djakiew et al, 1991; Steiner, 1993; Hofer et al, 1995; Sherwood et al, 1998; Kaplan et al, 1999; Nelson WG et al, 2003). Peptide growth factors may also exert their effects through the activation of the androgen receptor. Androgens are capable of inducing stromal production of various growth factors that could replace the androgen requirements for cell growth and differentiation (Lee, 1996). In addition, cytokines released primarily by stromal cells, such as interleukin-6, may also be important in the pathogenesis of prostate cancer. Indeed, small molecule inhibitors and other modalities of treatment (e.g., monoclonal antibodies) are being actively designed to target intracellular pathways associated with the expression of various growth factors and their receptors. Such strategies have involved inhibition of receptor tyrosine kinase activity and other intracellular molecular pathways of signal transduction as well as other critical pathways of cell growth and survival.

CLINICAL CONSIDERATIONS

Disease Assessment and Treatment Selection

Conventional staging criteria, such as the TNM staging system, do not describe the extent of disease beyond a simple anatomic classification. Treatment practices result in the creation of different disease states as described by Scher and colleagues (2008). **This system allows classification of patients in a more clinically applicable fashion and is increasingly being used throughout the literature.** Figure 110–1 **illustrates the natural history of prostate cancer relative to treatment practices and identifies the various paradigms according to the response status to different therapies.** Throughout this chapter prognostic and therapeutic considerations are largely based on the concepts proposed by this classification. A complete disease evaluation is required to estimate the outcome and to make therapeutic decisions. Critical baseline components include extent of disease, mode and site of progression (rising prostate-specific antigen [PSA] level alone, new bone metastasis, visceral and nodal metastasis), presence or absence of symptoms, and response to prior endocrine treatment. Regular monitoring with serial bone scintiscans and serum PSA levels during hormone treatment provides important information in patients demonstrating evidence of disease progression while they are receiving hormone therapy. Table 110–1 describes the postprogression survival of patients with distant metastatic disease who demonstrated progression of disease while on hormone therapy in a large prospective trial (Eisenberger et al, 1995). The data shown in this table illustrate the broad range in postprogression survival according to the mode of progression (PSA only vs. bone scintiscan progression) and according to the extent of bone metastases. This observation highlights the importance of establishing precisely the predominant mode of progression in these patients and underlines the need for serial determinations of all laboratory, clinical, and radiologic data. It also provides critical information for the interpretation of subsequent clinical trials with regard to time-dependent outcomes, such as time to disease progression and survival. Usually the first manifestation of disease progression after hormone therapy is a rising serum PSA level. In patients with metastatic disease, a rise in serum PSA level precedes evidence of advancing disease in the bone scintiscan, and during this time patients may remain relatively asymptomatic (Eisenberger et al, 1995). Routine evaluation of serum testosterone levels may provide important information for the choice of treatment. This is especially important when there are reasons to suspect treatment noncompliance

Table 110–1.

Metastatic Castration-Resistant Prostate Cancer: Survival According to Mode of Progression

MODE OF PROGRESSION	MINIMAL DISEASE, MEDIAN SURVIVAL	EXTENSIVE DISEASE, MEDIAN SURVIVAL
PSA only	40 months	18 months
PSA + bone scintiscan	23 months	11 months

Data from Eisenberger M, Crawford E, McLeod D, et al. The prognostic significance of prostate specific antigen in stage D2 prostate cancer: interim evaluation of Intergroup 0105. Proc Am Soc Clin Oncol 1995;14:abstract 613.

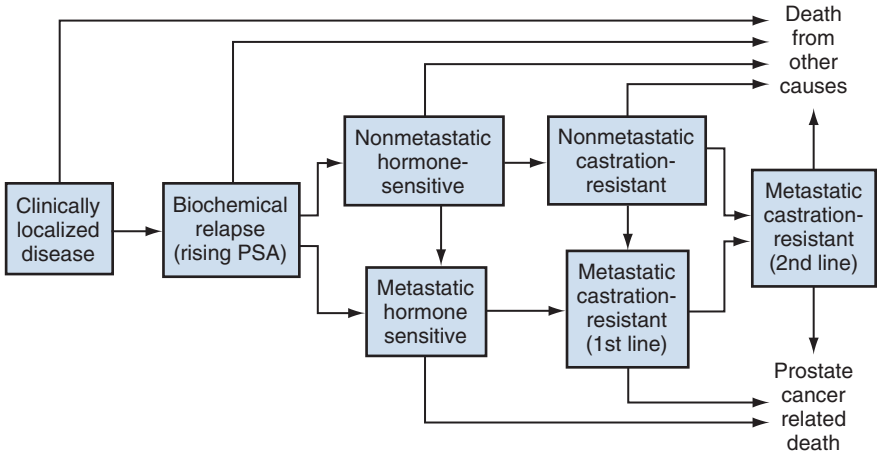


Figure 110–1. Prostate cancer clinical states. PSA, prostate-specific antigen. (Modified from Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26:1148–59.)

or if the choice of prior treatment involved regimens known not to result in a sustained suppression of serum testosterone to castrate levels (e.g., monotherapy with nonsteroidal antiandrogens, low-dose estrogens, or 5α-reductase inhibitors).

For several years it has been postulated that discontinuation of androgen suppression in nonorchiectomized patients may adversely influence the outcome of disease in terms of progression and survival (Taylor et al, 1993). **Similarly, it has been shown that administration of exogenous testosterone and its derivatives may indeed produce a significant clinical flare that results in severe pain and neurologic, urologic, and coagulation complications in a small proportion of patients** (Fowler and Whitmore, 1981; Manni et al, 1988). **In a retrospective analysis of 205 patients with castration-resistant disease treated with chemotherapy, various prognostic variables including orchiectomy were evaluated by Hussain and associates** (1994). **A multivariate analysis failed to indicate a significant correlation between prior orchiectomy and improved time to disease progression and survival. In these patients all medical forms of androgen deprivation were discontinued at least 4 weeks before initiation of chemotherapy and, contrary to that suggested by Taylor and colleagues** (1993), **this did not significantly affect outcomes. Until this issue is resolved the general consensus is to maintain all patients on luteinizing hormone–releasing hormone (LH-RH) agonists indefinitely, even during the course of chemotherapy.**

Another important management aspect relates to antiandrogen withdrawal effects (Scher and Kelly, 1993; Small and Srinivas, 1995; Small et al, 2004). **Discontinuation of antiandrogens (both steroidal and nonsteroidal) can result in short-term clinical responses expressed by decreases in PSA levels, symptomatic benefits, and, less frequently, objective improvements in soft tissue and bone metastasis in a small proportion of patients.** Because of this, it has been recommended that in patients treated with antiandrogens in combination with other forms of androgen deprivation (e.g., LH-RH agonists) the first step should involve the discontinuation of these agents and careful observation including serial monitoring of PSA levels for a period of 4 to 8 weeks before embarking on the next therapeutic maneuver.

The next step is to determine which modality of treatment should be employed first, either administration of second-line hormonal manipulation or cytotoxic chemotherapy. There is an increasing body of data on second-line endocrine therapies suggesting that there may be a role for this approach before institution of chemotherapy (Small and Vogelzang, 1997; Small et al, 2004; Ryan 2006; Ang et al, 2009). Although initial response rates range between 20% and 60%, the median duration of such responses is short ranging, between 2 and 4 months. Agents that have been reported to produce some benefit in this setting include diethylstilbestrol (Smith et al, 1986), aminoglutethimide (Sartor and Myers, 1995), ketoconazole (Small et al, 2004), as well as corticosteroids (Storlie et al, 1995). **In view of the potential higher toxicity profile associated with cytotoxic chemotherapy, a sequential hormonal approach may be a reasonable alternative for those patients with relatively limited metastatic disease who remain asymptomatic at the time of disease progression (e.g., rising serum PSA value without other clinical manifestations).**

Another important consideration is the initial clinical assessment of the potential biologic behavior of these tumors. **Evolving data evaluating the role of PSA dynamics suggest that the PSA doubling time (PSADT) predicts for the rapidity of bone scintiscan progression and survival** (D'Amico et al, 2005; Armstrong et al, 2007; Robinson et al, 2008). **Patients with PSADTs shorter than 3 months have a particularly rapid clinical course and should be considered for more aggressive management approaches.** In addition, poorly differentiated and anaplastic/neuroendocrine tumors usually have a low likelihood of significant and durable responses to androgen deprivation. The anaplastic/neuroendocrine phenotype is rare and requires special therapeutic considerations. It has been suggested that systematic biopsies of disease sites in patients with clinically aggressive disease and relatively low serum PSA levels may demonstrate evidence of a neuroendocrine component by immunostaining, which may be of prognostic and therapeutic significance (see later). The usefulness of systematic biopsies in all patients with extensive metastasis and relatively low PSA levels, however, needs to be better defined before routine clinical application.

Nonmetastatic Castration-Resistant Disease

The extraordinary stage migration that has affected all stages of prostate cancer has profoundly modified the spectrum of clinical presentation of patients with castration-resistant disease. An increasing number of patients now begin androgen deprivation at very early stages of their disease course, often at the first sign of a rising PSA, before clinical and radiologic evidence of metastasis is present. This group of patients, termed the M0 (nonmetastatic) castrate-resistant subset, is now seen in increasing proportions in the clinic. Given the changes in treatment practices with early initiation of androgen deprivation, it is conceivable that these numbers will continue to increase. At this time data on the natural history of these patients are evolving.

A number of clinical trials using second-line hormonal manipulations and noncytotoxic interventions (bone-targeted treatments) focusing on time to development of bone metastasis are providing some useful information. A report of 201 patients from a prospective clinical trial comparing the effects of the bisphosphonate zoledronate and placebo in biochemically progressing (M0), castrate-resistant disease suggests that the time to bone scintiscan positivity may be very long. At 2 years, only 33% of these patients had evidence of bone metastasis, with a median time to bone metastasis in this group of 30 months. The baseline PSA level (>10 ng/mL) and the PSA velocity independently predicted time to bone metastasis and survival (Smith et al, 2005). In a retrospective review of a similar group of patients prescribed ADT before the development of metastatic disease the median time to clinical metastasis was 9 months. The pretreatment PSA level and the PSA nadir on ADT predicted this outcome (Dotan et al, 2005). The wide difference observed with these two reports (30 months vs. 9 months for time to bone scan metastasis) underscores the heterogeneity of this group of patients and the need for careful prospective evaluation. Their outcome is dependent on various factors, among which are pre-ADT characteristics (pretreatment PSA level, PSADT, initial stage, Gleason score), as well as response to hormonal treatment. The rate of progression may be estimated by PSA constructs such as PSADT and PSA velocity.

At present there is no consensus on the most appropriate management for these patients, although the sequential endocrine approach is the most commonly employed therapeutic modality.

A trial investigating the relative efficacy of a second-line endocrine manipulation versus a docetaxel-based chemotherapy regimen in nonmetastatic disease was closed prematurely because of poor accrual. More data are needed to characterize the natural history and to define the best treatment approach of the M0 castrate subset, which represents an important evolving new paradigm.

Metastatic Castration-Resistant Disease

Patients with metastatic CRPC represent a heterogeneous group with respect to their clinical status at the time of disease progression (Fig. 110–2). **Metastatic adenocarcinoma of the prostate has an overwhelming predilection to involve the bone.** Although the explanation for this unique metastatic pattern has not been completely elucidated it probably reflects the combination of various biologic factors starting at the time of metastatic spread. Circulating prostatic adenocarcinoma cells are arrested in the cortical and medullary bone spaces, where they subsequently adhere to bone surfaces through specific receptors for moieties such as integrins, collagens, laminin, and other bone-derived proteins. Cell growth is subsequently promoted by various factors such as hormones, growth factors, and stromal-epithelial biologic interactions, most of which operate in the bone marrow. Expansion of tumor from the bone may cause pain, compression, or pathologic fractures, and extensive bone marrow replacement may cause impairment in hematologic function.

Clinical involvement of visceral sites is relatively uncommon even in patients with widespread castration-resistant disease. Table 110–2 illustrates the distribution of metastatic sites reported in selected chemotherapy phase 2 and phase 3 trials. These figures suggest that clinical evidence of visceral metastasis is observed in less than 10% of patients, whereas about 20% have demonstrable soft tissue nodal disease. Because the majority of tumor burden in metastatic prostate cancer is found in bone, responses to treatment (e.g., tumor shrinkage) in soft tissue sites alone (e.g., nodal or visceral sites) may not reflect a major treatment benefit because it represents only a small proportion of the overall disease burden.

Patients with metastatic CRPC may present with a range of hematologic problems caused primarily by the disease or by its treatment. Anemia is the most common hematologic abnormality, which can be explained by a variety of factors, such as anemia of chronic disease, bone marrow invasion, blood loss, and rarely secondary to a microangiopathic hemolytic anemia usually associated with a consumption coagulopathy (disseminated intravascular coagulation). **A decrease in the red blood cell count of patients with advanced CRPC commonly results from a combination of factors, such as prior treatment with local irradiation of bone marrow, systemic use of radiopharmaceuticals, long-term androgen deprivation, and systemic chemotherapy, as well as from extensive bone marrow invasion by tumor resulting in substantial decrease in bone marrow reserves.** The use of erythropoietin can be effective, especially in patients with a history of long-term androgen suppression, and repeated administration may require the use of iron preparations. However, erythropoietin-stimulating agents should be used with caution, because evidence is now emerging that these agents may increase mortality in cancer patients (Bennett et al, 2008). **Granulocytopenia and thrombocytopenia are most commonly a complication of extensive radiation therapy or systemic chemotherapy.** Rarely, rapidly growing tumors with bone marrow involvement result in pancytopenia. Thrombocytosis is also a nonspecific manifestation associated with various neoplastic conditions, including prostate cancer. Clotting complications associated with thrombocytosis are rarely seen in patients with prostate cancer, and treatment is not usually necessary.

Among the most important urologic sequelae in patients with advanced prostate cancer is the

Table 110–2.

Typical Distribution of Metastatic Sites in Patients with Castration-Resistant Prostate Cancer Entered in Clinical Trials

STUDY	NO. PATIENTS	Metastatic Site			
		Bone	Lung	Liver	Soft Tissue–Nodal
Hudes et al, 1992	36	36 (100%)	0 (0%)	2 (6%)	7 (19%)
Pienta et al, 1994	42	42 (100%)	3 (7%)	5 (12%)	13 (31%)
Sella et al, 1994	39	36 (92%)	3 (8%)	3 (8%)	9 (23%)
Moore et al, 1994	27	22 (81%)	2 (9%)	2 (7%)	10 (37%)
Eisenberger et al, 1995	109	108 (99%)	6 (6%)	4 (4%)	15 (14%)
Tannock et al, 2004	1006	915 (91%)			
Petrylak et al, 2004	674	579 (86%)	67 (10%)	57 (8%)	168 (25%)

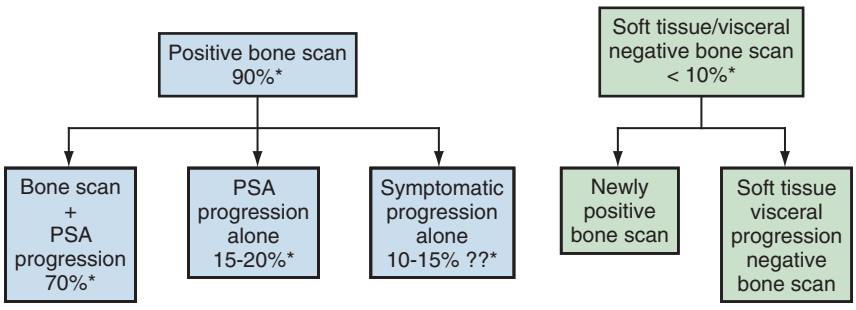


Figure 110–2. Clinical heterogeneity of castration-resistant prostate cancer. Subpopulations according to their type of progression after androgen deprivation. PSA, prostate-specific antigen. *The percentages illustrated represent an estimation based on the distribution reported in multiple trials reviewed by the authors.

development of obstructive uropathy. This complication, related to the primary disease, can be devastating in terms of quality of life and may even have major therapeutic implications. Besides an increased incidence of infection and pain, obstructed kidneys may critically impair renal function to a point where various chemotherapeutic agents (which depend largely on renal mechanisms for their clearance) cannot be safely employed. In general, patients who are otherwise candidates for treatment with cytotoxic drugs are best first managed by relief of obstruction either with placement of internal stents or by percutaneous nephrostomies.

One of the greatest emergencies in oncology is the development of epidural spinal cord compression (Sorensen et al, 1990). Because of the frequent involvement of vertebral bodies by metastatic prostate cancer, the incidence of cord compression is of particular concern (see later).

Key Points: Clinical Considerations

- Evaluate the extent and aggressiveness of the disease.
- Realize that the critical issues are presence or absence of metastases, clinical versus biochemical relapse, presence of symptoms (e.g., pain), and PSA kinetics (e.g., PSA doubling time, PSA velocity).
- Consider secondary hormonal manipulations before initiation of cytotoxic chemotherapy.

CYTOTOXIC CHEMOTHERAPY

Evaluation of Treatment Efficacy

The evaluation of chemotherapy based on uncontrolled clinical trials in patients with metastatic prostate cancer is usually confounded by significant methodologic challenges. The most common metastatic site is bone (nonmeasurable disease), manifested by diffuse osteoblastic lesions that cannot be measured reliably by current methods to allow assessments of therapeutic benefits. Soft tissue or visceral metastatic sites (measurable disease) that allow serial measurements are uncommon (see Table 110–2) and represent only a small fraction of the total burden of the disease. Selection of bi-dimensionally measurable disease sites to assess therapeutic efficacy with serial "tumor measurements" has been the subject of significant criticism. Patients with soft tissue metastasis (especially visceral disease) are considered by many a subgroup with biologic and clinical features distinct from those of the usual patient with prostate cancer who presents with bone metastasis only. A number of prognostic models evaluating baseline and post-treatment characteristics have been developed (Smaletz et al, 2002; Halabi et al, 2003; Armstrong et al, 2007). Among various clinical and laboratory parameters with consistent prognostic significance are baseline functional status (performance status), presence of pain, and pretreatment hemoglobin levels (cutoffs range from 10 to 12 g/dL). Other possible parameters are the baseline PSA level, extent of bone scintiscan involvement (number of lesions or pattern/distribution of bone involvement), and presence of visceral disease. Semi-quantitative methods to evaluate PSA mRNA expression in circulating cells (using reverse transcriptase/polymerase chain reaction) and various PSA constructs (e.g., PSADT and PSA velocity) are among the post-treatment parameters most likely to be of prognostic significance (Kantoff et al, 2001; Scher et al, 2004; Armstrong et al, 2007).

Preclinical observations have suggested that several drugs may reduce PSA secretion without affecting tumor growth (Larocca et al, 1991; Eisenberger and Nelson, 1996; Seckin et al, 1996). Whereas these laboratory observations are likely to be clinically relevant, assays used to evaluate a separate drug effect on PSA secretion still require careful validation. A PSA consensus meeting developed by several leading investigators in the field generated initial guidelines with regard to the use of the PSA test for clinical trials in patients with CRPC (Bubley et al, 1999). These guidelines were recently updated and now also provide a consensus on the use of radiologic end points as well as clinical end points (e.g., pain) for the evaluation of men with CRPC (Scher et al, 2008). The use of serum acid phosphatase and alkaline phosphatase has not been proven beneficial. Undoubtedly, new biomarkers are needed to enhance our ability to rapidly identify active treatments for CRPC. Evolving noncytotoxic and targeted therapies may require a new set of end points and identification of drug-specific intermediate biomarkers that reflect mechanism-specific biologic activity.

Clinical Trials

Most of the chemotherapeutic agents available in oncologic practice have been employed in patients with CRPC, either as single agents or in various combinations. Examples have included cyclophosphamide, 5-fluorouracil, estramustine, vinorelbine, etoposide, cisplatin, carboplatin, doxorubicin, mitoxantrone, paclitaxel, and docetaxel (Eisenberger, 1988). With the exception of docetaxel and perhaps mitoxantrone, most other cytotoxic agents are no longer being used with frequency because they have not been associated with either symptomatic improvements or extension of survival. Evolving data with selected chemotherapy during the new millennium suggest that the survival of patients with advanced CRPC is now somewhere between 16 and 18 months (Petrylak et al, 2004; Tannock et al, 2004) as opposed to 6 to 12 months as previously described (Eisenberger, 1988).

A first step forward in the chemotherapeutic management of CRPC came with mitoxantrone. This agent, a semi-synthetic anthracycline, had previously shown modest symptomatic benefits but with minimal evidence of objective antitumor activity (Osborne et al, 1983; Rearden et al, 1995). In addition, mitoxantrone appeared to have its maximal palliative effect in combination with low-dose corticosteroids (Moore et al, 1994). In two seminal prospective randomized trials of mitoxantrone plus prednisone versus prednisone alone (Tannock et al, 1996) or mitoxantrone plus hydrocortisone versus hydrocortisone alone (Kantoff et al, 1999), the combination resulted in significant improvements of various quality of life parameters, including pain, but survival was not significantly improved in either trial. These studies provided the justification for the approval in 1997 by the U.S. Food and Drug Administration (FDA) of the combination of mitoxantrone and prednisone for *symptomatic* metastatic prostate cancer.

The next significant advance in the use of chemotherapy for CRPC came with docetaxel, a member of the taxane family. This agent acts by inducing apoptosis in cancer cells through TP53-independent mechanisms that are thought to be due to inhibition of microtubule depolymerization and blockade of antiapoptotic signaling. The induction of microtubule stabilization intracellularly through β-tubulin interactions causes guanosine triphosphate (GTP)-independent polymerization and cell cycle arrest at G_2M. In addition, docetaxel has been found to induce BCL2 phosphorylation in vitro, a process

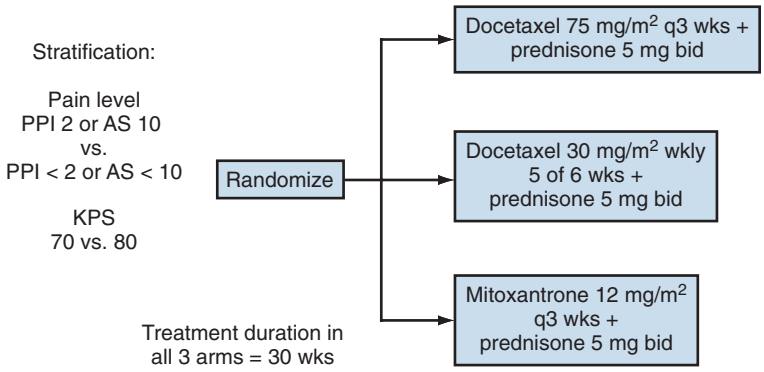


Figure 110–3. TAX 327 study design. AS, analgesic score; KPS, Karnofsky performance status score; PPI, present pain intensity score.

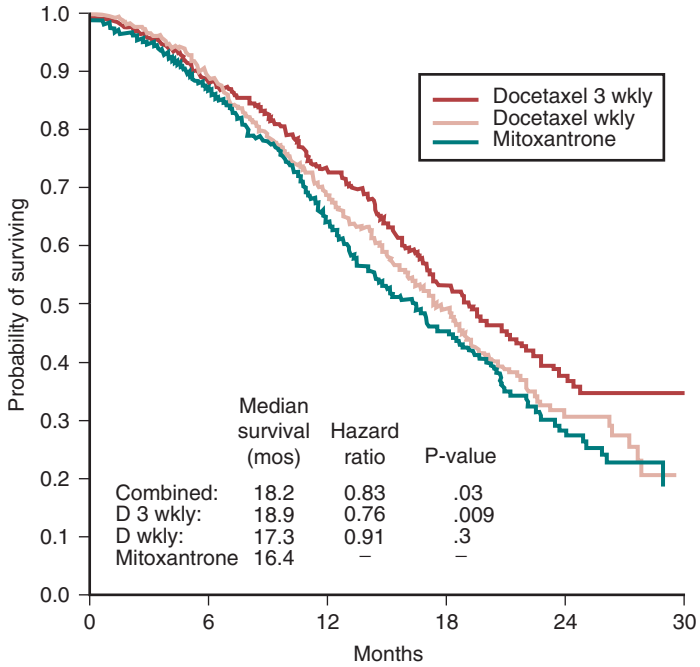


Figure 110–4. Overall survival, TAX 327.

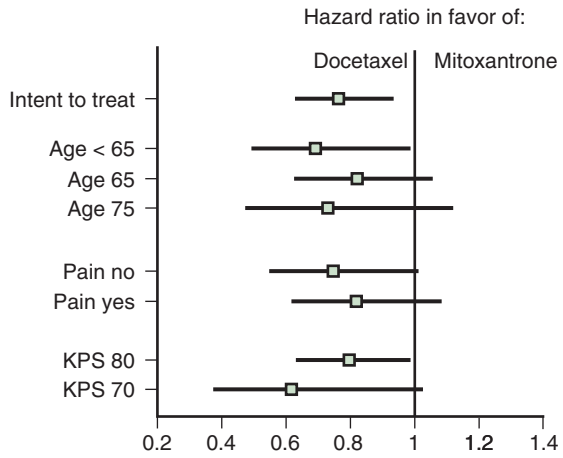


Figure 110–5. Survival in subgroups, docetaxel every 3 weeks versus mitoxantrone. KPS, Karnofsky performance status score.

that has been correlated with caspase-3 activation and loss of its normal antiapoptotic activity. Unable to inhibit the pro-apoptotic molecule BAX, phosphorylated BCL2 may also induce apoptosis through this alternate pathway. However, additional mechanisms may also be important, such as CDKN1B (formerly p27) induction and repression of BCL-XL. Data with docetaxel monotherapy previously suggested that this compound has significant activity as a single agent (Friedland et al, 1999; Picus and Schultz, 1999; Beer, 2004).

As of 2004, docetaxel has become the agent of choice for treatment of metastatic CRPC on the basis of a large phase 3 randomized trial, TAX 327 (Figs. 110–3 to 110–5 and Tables 110–3 to 110–5), **which demonstrated superiority over the previous standard, mitoxantrone and prednisone** (Tannock et al, 2004). TAX 327 enrolled 1006 patients with no prior chemotherapy and stable pain scores to one of three study arms (all with concomitant prednisone at 5 mg orally twice daily): mitoxantrone, 12 mg/m^2 intravenously every 21 days; docetaxel, 75 mg/m^2 intravenously every 21 days; or docetaxel, 30 mg/m^2 intravenously every 7 days. Patients remained on

Table 110–3.

TAX 327: Secondary Objectives (Response Rates)

	DOCETAXEL (THREE TIMES A WEEK)	DOCETAXEL (WEEKLY)	MITOXANTRONE
Pain Response Rate*			
N, evaluable	153	154	157
PSA response rate (%)	35	31	22
P value (vs. mitoxantrone)	.01	.07	
PSA Response Rate*			
N, evaluable	291	282	300
Response rate (%)	45	48	32
P value (vs. mitoxantrone)	.0005	<.0001	
Tumor Response Rate*			
N, evaluable	141	134	137
Response rate (%)	12	8	7
P value (vs. mitoxantrone)	.10	.50	

*Determined only for patients with pain or PSA ≥ 20 ng/mL or measurable disease at baseline, respectively.
PSA, prostate-specific antigen.

Table 110–4.

TAX 327: Quality of Life Response (>16 Points FACT-P Score Compared with Baseline)

	DOCETAXEL (THREE TIMES A WEEK)	DOCETAXEL (WEEKLY)	MITOXANTRONE
No. of evaluable patients	278	270	267
Response (%)	22	23	13
95% CI	17-27	18-28	9-18
P value (vs. mitoxantrone)	.009	.005	

Table 110–5.

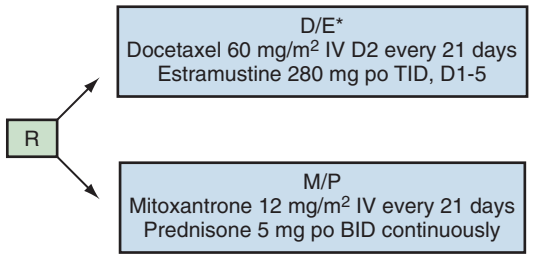
TAX 327: Grade 3-4 Hematologic Toxicity (%)

	DOCETAXEL (THREE TIMES A WEEK)	DOCETAXEL (WEEKLY)	MITOXANTRONE
No. treated	332	330	335
Anemia	5%	5%	2%
Neutropenia	32%	2%	22%
Neutropenic infection	3%	0%	1%
Febrile neutropenia	3%	0%	2%
Septic death	0%	0.3%	0.3%

gonadal suppression (e.g., LH-RH agonists) but had all other hormonal agents discontinued. Treatment duration was 30 weeks in all study arms, or a maximum of 10 cycles in the every-3-week study arms, with more patients completing treatment in the every-3-week docetaxel group than in the mitoxantrone group, mostly because of differences in disease progression (46% vs. 25%). **After a median follow-up of 20.7 months, overall survival in the every-3-week docetaxel group was 18.9 months (with a pain response rate of 35% and a PSA response of 45%), contrasted to weekly docetaxel at 17.3 months (and 31% and 48%), respectively. This translated into a 24% relative reduction in the risk of death (95% confidence interval [CI], 6% to 48%; *P* = .0005) with 3-weekly docetaxel** (see Fig. 110–4). **Patients on the mitoxantrone arm had a median survival of 16.4 months, a pain response of 22%, and a PSA response of 32%.**

Toxicity in the 3-weekly versus weekly docetaxel groups was notable for more hematologic toxicity in the every-3-week group (3% neutropenic fever vs. 0%; 32% grade-3/4 neutropenia versus 1.5%) (see Table 110–5) **but slightly lower rates of nausea and vomiting, fatigue, nail changes, hyperlacrimation, and diarrhea. Neuropathy was slightly more common in the every-3-week group (grade 3/4 in 1.8% vs. 0.9% in the weekly treated group). Quality of life responses as measured by the FACT-P scores did not differ significantly among the docetaxel schedules but were more favorable than in the mitoxantrone group.**

The Southwest Oncology Group (SWOG) 9916 study was a second large phase 3 trial (Figs. 110–6 to 110–8) (Petrylak et al, 2004) **in which 770 patients with progressive CRPC were randomly assigned to oral estramustine (280 mg three times daily) plus docetaxel (60 mg/m²**



* Coumadin 2 mg PO daily + ASA 325 mg PO daily was added
Docetaxel and mitoxantrone doses could be increased to 70 mg/m² and 14 mg/m², respectively, if no grade 3 or 4 toxicities were seen in cycle 1

Figure 110–6. SWOG 9916 study design. D/E, docetaxel plus estramustine; M/P, mitoxantrone plus prednisone.

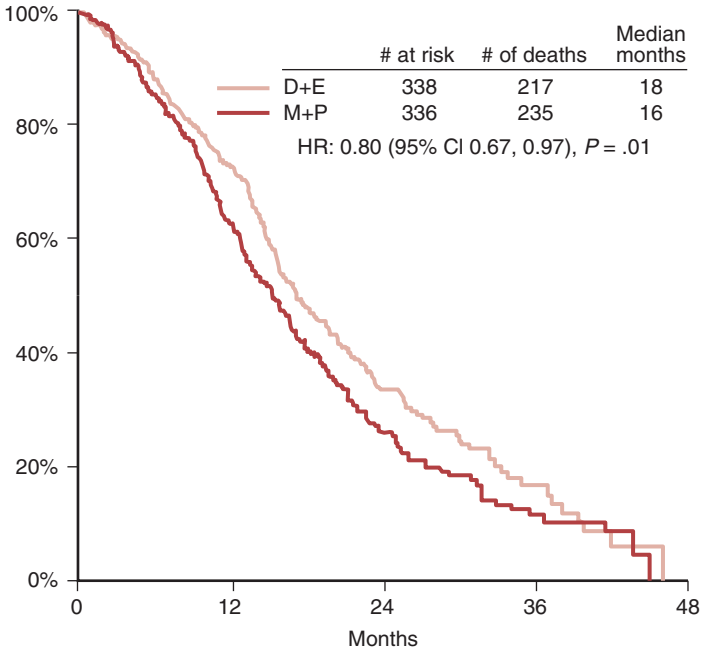


Figure 110–7. Overall survival, SWOG 9916. D+E, docetaxel plus estramustine; M+P, mitoxantrone plus prednisone.

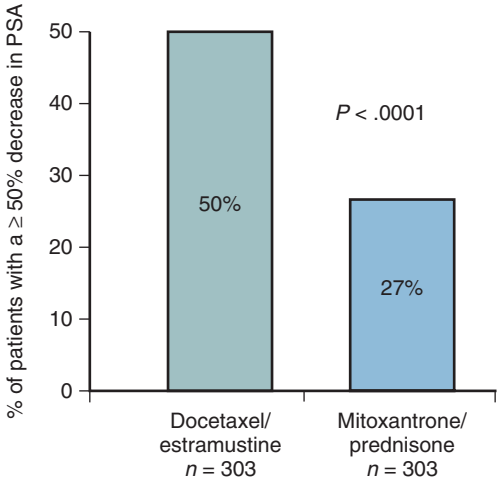


Figure 110–8. SWOG 9916 prostate-specific antigen (PSA) response rate.

every 21 days) versus mitoxantrone (12 mg/m² every 21 days) plus prednisone. In this study, median overall survival was longer in the docetaxel-estramustine group than in the mitoxantrone-prednisone group (17.5 vs. 15.6 months, $P = .02$), with a corresponding hazard ratio (HR) for death of 0.80 (95% CI, 0.67 to 0.97). Because of the high rate of thromboembolic events with estramustine, prophylactic low-dose warfarin and aspirin were added to that study arm, which did not reduce the incidence of thromboembolism. Similarly, 20% and 15%, respectively, of patients in the docetaxel-estramustine arm had grade 3/4 gastrointestinal and cardiovascular toxicities. **Although comparisons between the docetaxel arms across these two seminal trials may not be appropriate because of differences in schedule, patient populations, and docetaxel dosing (60 mg/m² in SWOG 9916 and 75 mg/m² in TAX 327), it may be concluded that estramustine is unlikely to add significantly to the activity of single-agent docetaxel.**

Until recently, effective life-prolonging therapies for men with docetaxel-refractory prostate cancer were lacking. This changed in 2010, when the FDA approved a second chemotherapy agent, cabazitaxel, for the treatment of metastatic CRPC. Cabazitaxel (Jevtana, Sanofi-aventis, Paris, France) is a novel tubulin-binding taxane that differs from docetaxel and paclitaxel due to its poor affinity for P-glycoprotein, the ATP-dependent drug efflux pump (Paller and Antonarakis, 2011). In preclinical studies using cancer cell lines and mouse xenograft models, cabazitaxel was shown to be active in both docetaxel-sensitive tumors as well as those with primary or acquired docetaxel resistance (Attard et al, 2006).

The first hint of cabazitaxel's safety and efficacy in men with prostate cancer came during phase I testing, where cabazitaxel was administered by intravenous infusion every 3 weeks at escalating doses of 10 to 25 mg/m² (Mita et al, 2009). In that study, the principal dose-limiting toxicity was neutropenia. Given the lack of cross-resistance to this agent with docetaxel, and early reports of responses in men with CRPC from this phase 1 trial, a phase 3 trial was launched to evaluate efficacy.

The safety and efficacy of cabazitaxel in patients with advanced prostate cancer was definitively evaluated in a pivotal randomized phase III trial (TROPIC) conducted in 146 institutions across 26 countries, and recruited 755 men with metastatic CRPC who had progressed during/after docetaxel-based chemotherapy (de Bono et al, 2010). Of these, 377 patients were randomized to receive mitoxantrone 12 mg/m² intravenously every 3 weeks (with oral prednisone 10 mg daily), and 378 patients were assigned to receive cabazitaxel 25 mg/m² intravenously every 3 weeks (plus prednisone). This study was the basis of the FDA's approval of cabazitaxel with prednisone for the second-line treatment of docetaxel-refractory metastatic CRPC in June 2010.

After a median follow-up of 12.8 months, overall survival in men receiving cabazitaxel was 15.1 months compared to 12.7 months in men receiving mitoxantrone (HR, 0.70; $P < .0001$) (de Bono et al, 2010). Compared to mitoxantrone, cabazitaxel also significantly lengthened progression-free survival (2.8 months vs. 1.4 months; $P < .0001$), extended time to PSA progression (6.4 months vs. 3.1 months; $P = .001$), increased radiographic tumor response rates (14.4% vs. 4.4%; $P = .0005$), and increased PSA response rates (39.2% vs. 17.8%; $P = .0002$). There were no differences between the two treatment arms with respect to pain responses, or time to pain progression.

In subset analyses, the survival advantage of cabazitaxel persisted regardless of whether patients had measurable disease or pain, or whether progression had occurred while receiving docetaxel or following a treatment holiday. In addition, cabazitaxel's survival benefit was most pronounced for men with ECOG performance status 0-1 (vs. 2), and for patients with disease progression within <3 months of docetaxel initiation (vs. ≥3 months of docetaxel initiation) (de Bono et al, 2010). The last observation implies that cabazitaxel may be effective even in men with truly docetaxel-refractory disease.

The most common serious adverse events related to cabazitaxel were hematological, including grade ≥3 neutropenia in 82% of patients (febrile neutropenia in 8%) (de Bono et al, 2010). This degree of myelosuppression begs the question of whether a lower dose of cabazitaxel (e.g., 20 mg/m²) may have been more appropriate, and a randomized trial comparing the safety and efficacy of these two doses (25 mg/m² vs. 20 mg/m²) is now being conducted. Use of growth factor support should be strongly considered, as reflected in several national guidelines (Mohler et al, 2010). Other nonhematologic toxicities included grade ≥3 diarrhea (6%) and grade ≥3 fatigue (5%). Encouragingly, although peripheral neuropathy (all grades) was observed in 14% of patients receiving cabazitaxel, only 1% developed grade 3 neuropathy.

Key Points: Cytotoxic Chemotherapy

- Docetaxel is the standard treatment for metastatic castration-resistant prostate cancer. It prolongs progression-free and overall survival, ameliorates pain, and improves quality of life.
- Toxicity of docetaxel includes myelosuppression, fatigue, edema, moderate to modest neurotoxicity, hyperlacrimation, and changes in liver function.
- No other chemotherapy regimen has shown a survival advantage in CRPC, but mitoxantrone has been approved to palliate symptoms associated with metastatic disease.
- Cabazitaxel has recently emerged as a treatment option for patients with metastatic CRPC who have experienced progressive disease during or after docetaxel treatment.

The Neuroendocrine/ Anaplastic Subtype

Laboratory and clinical evidence indicates that alterations in the differentiation pathway of prostate cancer can be seen in a small proportion of patients with advanced disease, giving rise to a neuroendocrine/anaplastic transformation (diSant'Agnese, 1995; Nelson et al, 2007). The therapeutic implications of this finding are of significance because tumors demonstrating this phenotype usually represent an inherently endocrine-resistant subtype and, in view of their different clinical and biologic properties compared with the usual adenocarcinoma of the prostate, these tumors usually require different treatment strategies.

Such tumors express a number of biologic characteristics unique to neuroendocrine tumors that can also arise from other organs, most commonly the lung. Among these are the expression of receptors to various neuroendocrine peptide growth factors, such as somatostatin, chromogranin A, and serotonin, as well as parathyroid hormone–related protein (PTHrP) and *TP53* mutations. These tumors have an uncharacteristic clinical behavior (compared with the usual metastatic prostate cancer), reflected by frequent visceral involvement and rapidly growing soft tissue metastases. Patients

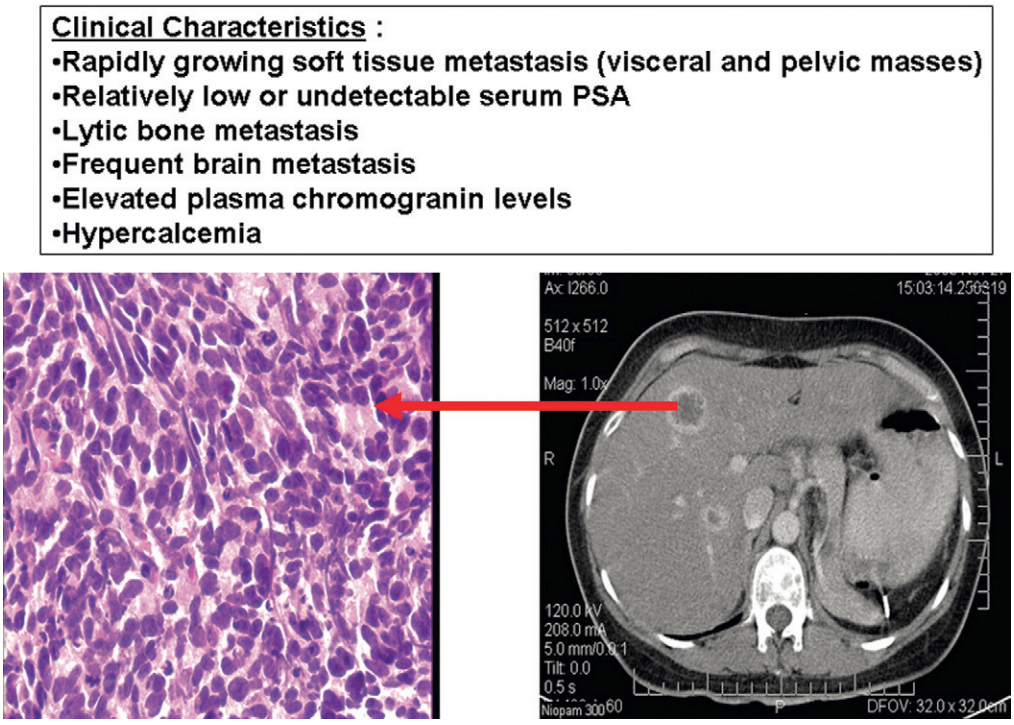


Figure 110–9. Neuroendocrine/anaplastic carcinoma of the prostate. PSA, prostate-specific antigen.

frequently present with subacute and often dramatic changes in their disease pattern characterized primarily by a rapidly growing soft tissue mass (frequently involving the primary site but also with retroperitoneal masses), rapid development of visceral (lung and liver) infiltration, osteolytic (as opposed to osteoblastic) bone metastasis, and a high incidence of parenchymal brain involvement (Fig. 110–9). **Histologic evaluation of areas demonstrating rapid growth is strongly encouraged. This frequently culminates with demonstration of a small cell variant or a poorly differentiated neoplasm on pathology and the presence of neuroendocrine markers on immunostaining** (diSant'Agnese, 1995; Nelson et al, 2007). **Interestingly, patients with this tumor phenotype either stop expressing PSA in the presence of major tumor progression or even have undetectable PSA levels at the time of this transformation.**

Treatment is usually similar to that of patients with other neuroendocrine tumors (e.g., small cell carcinoma of the lung) and includes combinations of cisplatin (or carboplatin) and etoposide (Frank, 1995), **paclitaxel, docetaxel, and topotecan. Doxorubicin-containing combinations have been reported to be moderately effective by one group** (Papandreou et al, 2002). **Radiation therapy is effective and should be considered in cases with bulky disease, with brain metastasis, or when local disease control in critical areas may have a positive impact on quality of life (pain, potential pathologic fractures, and bladder outlet obstruction). A combined chemotherapy and radiation therapy approach is frequently necessary to accomplish maximal disease control. Despite high initial response rates with chemotherapy and radiation treatment, the prognosis of these patients remains poor and is dependent on various factors, including extent and location of metastases.**

Key Points: The Neuroendocrine/Anaplastic Subtype

- Rapidly growing disease with the following clinical characteristics should prompt evaluation for the neuroendocrine/anaplastic phenotype: pelvic masses, visceral involvement, osteolytic metastasis with hypercalcemia (associated with high serum PTHrP), and brain metastasis.
- PSA is most commonly undetectable (or levels are low/declining) despite evidence of rapid disease progression. Serum chromogranin A and urine serotonin metabolites may be detected.
- These tumors are invariably unresponsive to hormonal manipulations but highly sensitive to radiation therapy and platinum-etoposide combinations.

PALLIATIVE MANAGEMENT

Pain and Epidural Cord Compression

As in other disseminated malignant neoplasms, palliation of symptoms and maintenance of adequate levels of quality of life represent the most important objectives in the management of advanced prostate cancer.

Cancer-related pain is undoubtedly the most debilitating symptom associated with metastatic prostatic carcinoma. **Prompt recognition of the various pain syndromes associated with this disease is critical to accomplish effective control of this devastating symptom.** The most common pain syndromes and their respective therapeutic considerations are described in Table 110–6.

Focal bone pain in patients with castration-refractory disease can be well controlled by external-beam localized radiation therapy. In general, it is also recommended that painful areas

Table 110–6.

Common Pain Syndromes in Metastatic Castration-Resistant Prostate Cancer

PAIN SYNDROME	INITIAL MANAGEMENT	OTHER THERAPEUTIC ALTERNATIVES
Localized bone pain	Pharmacologic pain management Localized radiotherapy (special attention to weight-bearing areas, lytic metastasis, and extremities)	Surgical stabilization of pathologic fractures or extensive bone erosions Epidural metastasis and cord compression should be evaluated in patients with focal back pain. Radiopharmaceuticals should be considered if local radiation therapy fails.
Diffuse bone pain	Pharmacologic pain management "Multi-spot" or widefield radiotherapy Radiopharmaceuticals	Corticosteroids Bisphosphonates Calcitonin Chemotherapy
Epidural metastasis and cord compression	High-dose corticosteroids Radiation therapy Surgical decompression and stabilization should be indicated in high-grade epidural blocks, extensive bone involvement, or recurrence after irradiation.	Pharmacologic pain management
Plexopathies caused by direct tumor extension or prior therapy (rare)	Pharmacologic pain management Radiation therapy (if not previously employed) Neurolytic procedures (nerve blocks)	Tricyclic antidepressants (amitriptyline) Anticonvulsants
Miscellaneous neurogenic causes: postherpetic neuralgia, peripheral neuropathies	Careful neurologic evaluation Pharmacologic pain management Discontinuation of neurotoxic drugs: paclitaxel, docetaxel, *Vinca* alkaloids, platinum compounds	Tricyclic antidepressants (amitriptyline) Anticonvulsants
Other uncommon pain syndromes: extensive skull metastasis with cranial nerve involvement, extensive painful liver metastasis or pelvic masses	Radiation therapy Pharmacologic pain management Corticosteroids (cranial nerve involvement)	Chemotherapy Intrathecal chemotherapy may ameliorate symptoms of meningeal involvement; regional infusions may be considered.

shown to be abnormal on bone scintigraphy should be evaluated with plain radiographs to exclude the presence of osteolytic lesions or pathologic fractures. Such considerations become even more important when the painful areas affect extremities and weight-bearing sites.

Epidural metastasis is a fairly common and potentially devastating complication of systemic cancer. In view of the propensity for prostate cancer to metastasize to the vertebrae and paravertebral region, the incidence of epidural cord compression is particularly high in this disease. Early diagnosis and treatment of epidural metastasis is critical in preserving ambulation and bowel and bladder function and aids in the management of back pain (Grossman and Lossignol, 1990; Gabriel and Schiff, 2004). Epidural cord compressions arising from vertebral bodies account for the majority of spinal cord compression; only less frequently is it associated with soft tissue masses involving the paravertebral region. Most patients have abnormalities on bone scintiscans and abnormal findings on radiography at the time of diagnosis. However, an abnormality on neurologic examination may be the only finding in patients who have soft tissue epidural metastasis in the paravertebral region.

Spinal magnetic resonance imaging (MRI) is routinely used to exclude the possibility of significant epidural disease, and it has almost entirely replaced other methods such as computed tomographic myelography and conventional myelography. The first therapeutic intervention should include the administration of high doses of intravenous glucocorticoids. **Dexamethasone at doses ranging from 16 to 100 mg daily is most commonly employed. Most frequently, patients are given an intravenous "loading dose" of 10 mg of dexamethasone followed by 4 to 10 mg every 6 hours; the optimal dose remains relatively undefined.** On improvement of symptoms, which can be accomplished promptly with corticosteroids, the corticosteroid dose may be tapered during a 2- to 3-week period.

Radiation therapy is often the main modality of definitive treatment. However, recent reports suggest that surgery followed by radiation therapy may be superior to radiation therapy alone (Patchell et al, 2005). **Surgery should be considered in patients who present with evidence of progressive signs and symptoms during radiation therapy, develop or present with unstable pathologic fractures, or have recurrence after radiotherapy. Clearly, the overall prognosis of the underlying disease should be taken into consideration during treatment selection. Chemotherapy is rarely used to treat epidural cord compressions.**

Bone-Targeted Approaches

The pathogenesis of bone metastases in prostate cancer remains a subject of major study (Galasko, 1986). Alterations in the normal process of bone absorption and formation, which usually follows an orderly and sequential basis, appear to be a key determining factor in the development of bone metastasis associated with most malignant neoplasms (Roodman, 2004). Under normal physiologic conditions the process of bone remodeling is initiated by an increase in osteoclastic activity followed by an increase in osteoblastic differentiation and maturation, which results in the

formation of new bone and repair of the initial absorption caused by osteoblasts. Bone loss associated with prostate cancer can result from an enhanced osteoclastic activity associated with long-term androgen suppression, which in turn will cause excessive resorption of bone mineral and organic matrix. Tumor cells may also cause mineral release and matrix resorption in the areas involved by metastatic disease (Galasko, 1986). In addition, various cytokines, growth factors, tumor necrosis factors, and bone morphogenic proteins have been shown in preclinical studies to play a major role in the induction of both osteoclastic and osteoblastic activity (Reddi and Cunningham, 1990). In prostate cancer, bone metastases are predominantly blastic, which reflects a predominance of osteoblastic activity in the process of bone remodeling (Roodman, 2004). This phenomenon may be due to specific growth factor secretion that is responsible for the induction of osteoblasts. Hypercalcemia is rare in metastatic prostate cancer. In fact, a significantly elevated serum calcium concentration is most frequently due to the neuroendocrine prostate cancer phenotype and is mediated through PTHrP, as discussed earlier (diSant'Agnese, 1995; Nelson et al, 2007).

Bisphosphonates

Bisphosphonates have become an integral part of the management of metastatic prostate cancer to the bones (Van den Wyngaert et al, 2009). These compounds reduce bone resorption by inhibiting osteoclastic activity and proliferation. Zoledronate is a potent intravenous bisphosphonate first approved for the treatment of hypercalcemia and decreased bone mineral density in postmenopausal women (Green and Rogers, 2002). In patients with progressive castration-refractory disease and bone metastases zoledronate was shown to reduce the incidence of skeletal-related events (e.g., pain, fractures) compared with placebo in a prospective randomized trial of 422 patients (Saad et al, 2004). In addition, zoledronate and pamidronate have also been shown to increase mineral bone density in patients with nonmetastatic prostate cancer receiving long-term androgen deprivation (Smith et al, 2001, 2003). At present, zoledronate is indicated for the treatment of patients with progressive prostate cancer with evidence of bone metastasis, and it is administered at a dose of 4 mg intravenously repeated at intervals of 3 to 4 weeks for several months. Side effects of this agent include fatigue, myalgias, fever, anemia, and mild elevation of the serum creatinine concentration. Hypocalcemia has been described, and concomitant use of oral calcium supplements (1500 mg/day) and vitamin D (400 units/day) is often recommended. **An unusual complication of zoledronate is the development of severe jaw pain associated with osteonecrosis of the mandibular bone.** The etiology of this effect is not well understood. However, it is most frequently seen in patients undergoing dental work or those with a history of poor dentition and chronic dental disease. Zoledronate should not be administered to patients with these problems. Other bisphosphonates have also been evaluated in prostate cancer, including alendronate, etidronate, ibandronate, and clodronate; however, their benefit has not been conclusively established in prospective randomized clinical trials (Berry et al, 2006; Van den Wyngaert et al, 2009).

RANKL Inhibitors

Interactions between tumor cells and the bone marrow microenvironment have been postulated as an additional important mechanism in the pathogenesis of bone metastasis. Tumor-associated cytokines have been shown to induce the expression of RANKL (the receptor activator of nuclear factor κB ligand), which binds and activates RANK, which is found in osteoclasts (Brown et al, 2001). Inhibition of the RANKL system has recently been the focus of much research and represents an evolving bone-targeted strategy. Among the approaches employed are monoclonal antibodies to RANKL and the use of recombinant osteoprotegerin (the natural decoy receptor of RANKL), both of which significantly inhibit osteoclastic function in vitro and in vivo (Schwarz and Ritchlin, 2007). Denosumab, a fully human monoclonal antibody against RANKL, has entered clinical trials in prostate and breast cancers. In a phase 2 randomized study evaluating 50 patients with metastatic prostate cancer, denosumab (180 mg subcutaneously every 4 weeks) produced a reduction in bone resorption over that of zoledronate, as indicated by a lowering of urinary *N*-telopeptide levels, and also resulted in less skeletal-related events (Fizazi et al, 2009). Following from these encouraging results, a pivotal multicenter phase III double-blind randomized study was conducted comparing denosumab against zoledronate for the prevention of skeletal-related events in patients with bisphosphonate-naïve metastatic CRPC. In that trial of 1904 patients, compared to men receiving zoledronate (n = 951), men receiving denosumab (n = 950) had an improved time to first skeletal-related events (20.7 vs. 17.1 months; P = .008) and longer time to first-and-subsequent skeletal-related events (HR, 0.82; P = .004) (Fizazi et al, 2011). Notably, there was no difference in overall survival or progression-free survival between study arms. Based partially on the results of this study (and partially on two other large randomized studies in metastatic breast cancer and other solid metastatic tumors), the FDA approved denosumab (Xgeva, Amgen, Thousand Oaks, CA) in November 2010 for the prevention of skeletal-related events in patients with bone metastases from solid tumors. Common toxicities of denosumab include fatigue, nausea, hypophosphatemia, hypocalcemia (5% grade ≥3), and osteonecrosis of the jaw (2%), and prophylactic calcium and vitamin D supplementation is strongly encouraged. Therefore denosumab is a reasonable alternative to zoledronate for the prevention of skeletal-related events in patients with metastatic CRPC, and also has the advantage that it does not require dose adjustment or monitoring for renal impairment. The recommended dose of denosumab is 120 mg given by subcutaneous injection every 4 weeks.

Radiopharmaceuticals

The introduction of "bone-seeking" radiopharmaceuticals has provided a useful resource for the management of diffuse bone pain from widespread prostate cancer metastases (Pandit-Taskar et al, 2004). Among the most commonly used compounds are strontium-89 (^{89}Sr) (Porter et al, 1993) and samarium-153 (^{153}Sm) (Sartor et al, 2004). Rhenium-186 has also been used (Kucuk et al, 2000). Initial studies with ^{89}Sr have shown palliation of bone pain in 25% to 65% of patients with castration-refractory disease and diffuse pain (Jager et al, 2000). The pharmacokinetics of ^{89}Sr vary considerably according to the extent of bone involvement, but the half-life is generally 4 to 5 days. The retention of the isotope is significantly longer in patients with diffuse osteoblastic metastases compared with those with relatively limited bone involvement. It is important to recognize this factor because it will undoubtedly affect the degree and duration of myelotoxicity associated with this radioactive compound (its most significant side effect). **The clinical experience with ^{153}Sm suggests that this isotope is associated with a lower incidence of severe myelotoxicity, probably because of**

its shorter half-life of 2 days. Encouraging results were reported by Sartor and colleagues (2004) in a phase 3 trial comparing radioactive ^{153}Sm and nonradioactive ^{152}Sm, indicating that a dose of ^{153}Sm of 1 mCi/kg is both safe and effective palliation for patients with castration-refractory disease and severe bone pain. One study reported encouraging synergism with ^{89}Sr and doxorubicin, a known and well-studied radiosensitizer (Tu et al, 2001). Randomized studies evaluating the synergism of various chemotherapeutic agents, including taxanes, and radiopharmaceuticals are being done.

Key Points: Palliative Management

- Patients with back pain and a history of bone metastasis should be aggressively evaluated for epidural cord compression. The clinical syndrome often has at least one of the following signs and symptoms: back pain, focal neurologic findings (leg weakness, sensory levels), or changes in bladder or bowel control.
- Initial management of suspected cord compression includes immediate magnetic resonance imaging of the spine and high-dose intravenous corticosteroid therapy.
- Definitive therapy should include surgical decompression, radiation therapy, or both.
- Zoledronic acid and denosumab are both reasonable treatment options for the prevention of skeletal-related events in patients with castration-resistant bone metastases.

NOVEL APPROACHES

Rational Target Overview

An understanding of the basic biology involved of pathogenesis of prostate cancer provides the opportunity to identify potential targets that predict the clinical outcome of the disease. The first opportunity is the demonstration of a mutation or functional dysregulation of the target. Simply targeting overexpressed proteins has been less efficient than the specific targeting of mutations that drive the bulk of the tumor growth. The second goal is identifying target causality, indicating the importance of the target alone or in combination with other mutations in reproducing the phenotypic findings of prostate cancer. Finally, there should be evidence from preclinical models that inhibition of the target leads to tumor regression or quiescence. In prostate cancer, the androgen receptor is one potential target although there are many others. Various molecular changes in the androgen receptor have been shown to parallel disease progression in castrate patients and in some situations may provide the explanation for the responses associated with some therapeutic maneuvers (antiandrogen withdrawal syndrome, responses to secondary endocrine manipulations with compounds designed to bind to the receptor). Despite this, a precise role of the androgen receptor in the pathogenesis of disease progression remains to be better elucidated. Given the molecular complexity of the prostate cancer cell pathways and relatively poor understanding of the role of individual pathways in the process of disease-specific progression, the simultaneous inhibition of multiple pathways remains a common strategy to induce sustained and clinically meaningful responses in prostate cancer.

The major biologic processes under therapeutic investigation in prostate cancer involve growth and survival, chemotherapy and hormone therapy resistance, extragonadal androgen production, modulation of the androgen receptor, angiogenesis, the bone interface, epigenetic regulation, immune surveillance and escape, and stem cell renewal. This section provides an overview of these pathways as they pertain to prostate cancer rational targets and the approaches that are currently being developed for therapeutic purposes (Table 110–7).

Targeted Treatments

Although a prostate cancer stem cell has yet to be conclusively demonstrated, prostate cancer clearly progresses from an androgen-dependent tumor with features similar to the luminal

Table 110–7.

Targeted Therapies for Castration-Resistant Prostate Cancer (CRPC): Selected Ongoing Clinical Trials

TARGET	AGENT	PHASE	SUMMARY OF TRIAL
PI3K/mTOR	Everolimus	2	Docetaxel + everolimus for first-line metastatic CRPC
EGFR/HER2	Lapatinib	2	Single-agent lapatinib for nonmetastatic CRPC
PDGFR	Imatinib	2	Docetaxel ± imatinib for first-line metastatic CRPC
Vitamin D	Calcitriol	3	Docetaxel ± calcitriol for first-line metastatic CRPC
HDAC	Vorinostat	2	Single-agent vorinostat for second-line metastatic CRPC
	Panobinostat	2	Single-agent panobinostat for second-line metastatic CRPC
Endothelin receptor	Atrasentan	3	Docetaxel ± atrasentan for first-line metastatic CRPC
	Zibotentan	3	Docetaxel ± zibotentan for first-line metastatic CRPC
RANK ligand	Denosumab	3	Denosumab vs. zoledronate for palliation in metastatic CRPC
VEGF	Bevacizumab	3	Docetaxel ± bevacizumab for first-line metastatic CRPC
VEGF receptor	Sorafenib	2	Docetaxel + sorafenib for first-line metastatic CRPC
	Sunitinib	2	Docetaxel + sunitinib for first-line metastatic CRPC
	Vatalinib	2	Single-agent vatalinib for nonmetastatic CRPC
CYP17	Abiraterone	3	Single-agent abiraterone for second-line metastatic CRPC
Androgen receptor	MDV3100	1/2	Single-agent MDV3100 for nonmetastatic/metastatic CRPC
Immunotherapy	Sipuleucel-T (Provenge)	3	Sipuleucel-T vs. placebo for first-line metastatic CRPC
	GVAX	3	GVAX vs. docetaxel for first-line metastatic CRPC
			Docetaxel ± GVAX for first-line metastatic CRPC
CTLA-4	Ipilimumab	3	Ipilimumab vs. placebo for second-line metastatic CRPC

differentiated glands of the prostate to a castration-refractory tumor that has features of adult stem cells, including antiapoptotic mechanisms, chemotherapy resistance, and reliance on nonhormonal signaling pathways. **Candidate pathways currently evaluated include hedgehog signaling, epidermal growth factor receptor (EGFR) signaling, phosphatidylinositol 3-kinase (PI3K)/Akt signaling, mitogen-activated protein kinase (MAPK) signaling, and others** (see Table 110–7). Activation of the hedgehog developmental pathway has been demonstrated in prostate cancer metastases and in preclinical models, and inhibition of this pathway has led to antitumor effects and significant inhibition of prostatic epithelial regeneration after androgen withdrawal. Inhibitors of this pathway, such as cyclopamine analogues and other agents, are in preclinical development.

PI3K/Akt/mTOR Pathway

In advanced prostate cancer, loss of the tumor suppressor *PTEN* (phosphatase and tensin homologue deleted on chromosome 10) occurs in more than 50% of metastatic lesions and in approximately 20% of locally advanced lesions (McMenamin et al, 1999; Graff, 2002). **Loss of *PTEN* correlates with advanced Gleason sum, stage, chemotherapy resistance, and other features of advanced prostate cancers** (McMenamin et al, 1999). ***PTEN* is a negative regulator of the PI3K/Akt survival pathway, and advanced prostate cancers frequently have elevated levels of phosphorylated (activated) Akt** (Gera et al, 2004). The Akt pathway is involved in signal transduction from multiple cell surface receptors, including the insulin receptor, epidermal growth factor receptor, insulin-like growth factor receptor, platelet-derived growth factor receptor, and interleukin-6 receptor, and it is likely to function as a cellular sensor for nutrient and growth signals (Vivanco and Sawyers, 2002). In addition to promoting cell survival through the inhibition of apoptosis, the Akt pathway regulates cell growth, proliferation, and angiogenesis through the mammalian target of rapamycin (mTOR) pathway and the facilitated translation of signals such as c-*MYC*, cyclin D, and vascular endothelial growth factor (Gera et al, 2004). Restoration of functional *PTEN* activity or inhibition of mTOR activity can block the growth of $PTEN^{-/-}$ prostate cancer xenografts and restore chemotherapy and possibly hormonal sensitivity (Neshat et al, 2001; Podsypanina et al, 2001; Grunwald et al, 2002).

Rapamycin is a natural compound derived from soil samples containing the bacterium *Streptomyces hygroscopicus*. It was initially discarded as an antifungal agent because of its immunosuppressive properties but later revived as a potent immunosuppressive agent for use in solid organ transplantation. Its antiproliferative properties and antitumor activity in cell lines led to its clinical development in cardiology as a means of preventing stent restenosis and in oncology, in which a wide variety of tumors were found to exhibit sensitivity to this agent and its analogue temsirolimus (Hidalgo and Rowinsky, 2000; Bjornsti and Houghton, 2004). Toxicities with rapamycin and its analogues have been predictable and often not dose related; they include maculopapular rash, hypertriglyceridemia, hyperglycemia, allergic reactions, pedal edema, mucositis, and thrombocytopenia (Hidalgo and Rowinsky, 2000; Atkins et al, 2004; Raymond et al, 2004). The combination of these agents with docetaxel is attractive, given their ability to induce apoptosis when they are given in combination with chemotherapy in patients who have demonstrable activation of the Akt pathway as a result of *PTEN* mutation or loss or other genetic alterations. For example, a new mTOR inhibitor, everolimus (RAD001), is being evaluated in combination with docetaxel as first-line treatment for metastatic CRPC in a phase 1/2 trial (Ross et al, 2008).

EGFR and PDGFR Pathways

The rapid development in the past several years of small molecules that inhibit tyrosine kinases has yielded encouraging results in a host of cancers. Demonstration of tumor response has usually correlated with mutation in the target tyrosine kinase, such as epidermal growth factor receptor (EGFR), BCR-ABL, and c-KIT. In these cases the target mutation has played a central role in the pathogenesis of these tumors. In prostate cancer, no such mutation has been identified, and early trials of tyrosine kinase inhibitors in prostate cancer have been disappointing.

EGFR is overexpressed in 40% to 80% of prostate cancer cells, and overexpression may be more common in African-American men with prostate cancer (Shuch et al, 2004). Furthermore, preclinical data suggested a correlation of EGFR expression with Gleason sum and androgen independence (Syed, 2003). In a phase 2 study of approximately 100 patients with castrate-resistant disease evaluating the EGFR tyrosine kinase inhibitor gefitinib, minimal activity and no PSA responses were reported (Moore et al, 2002; Schroder and Wildhagen, 2004). Gefitinib resistance may be related to overactivity of the PI3K/Akt pathway in prostate cancer, and thus combinations of agents that target multiple pathways may be more beneficial (She et al, 2003). Further trials of combination EGFR or dual kinase inhibitors with chemotherapy or other novel agents are in development.

Prostate cancer cells express high levels of platelet-derived growth factor receptor (PDGFR), and this signaling pathway uses the PI3K/Akt pathway, which has been implicated in prostate cancer progression. Single-agent activity with imatinib has been disappointing; however, encouraging results in combination with weekly docetaxel have been reported. A phase 2 randomized trial of this combination compared with docetaxel alone is in progress.

Another potential target in this family of receptors is the HER2/neu tyrosine kinase, whose expression has been shown to increase androgen receptor activation leading to prostate cancer growth and survival (Gregory et al, 2005). However, phase 2 studies using the anti-HER2 monoclonal antibody trastuzumab showed minimal efficacy in CRPC, perhaps owing to a low frequency of HER2 overexpression (Ziada et al 2004). Studies using the dual EGFR/HER2 small molecule inhibitor lapatinib for asymptomatic CRPC are now being conducted.

Vitamin D Analogues

Vitamin D analogues may have differentiation, antiproliferation, and chemosensitizing properties, and epidemiologic studies have shown an increased risk of prostate cancer in those with relative vitamin D deficiency. A phase 2 trial of weekly docetaxel and high-dose calcitriol demonstrated PSA responses in 30 of 37 patients (80%) and measurable responses in 8 of 15 (53%), with a median time to progression of 11.4 months and median survival of 19.4 months (Beer et al, 2005). **A randomized study with a total of 250 patients (125 per study arm) comparing the combination with docetaxel alone resulted in more than 50% decline of PSA level in 63% of the patients receiving the combination treatment compared with 52% with docetaxel alone (P = .07). However, interestingly, the authors reported a survival difference in favor of the**

combination (23.4 vs. 16.4 months; *P* = .03). These results led to the design of a large phase 3 placebo-controlled trial in metastatic CRPC evaluating docetaxel chemotherapy with or without calcitriol, with power to detect a survival benefit as the primary end point. However, early reports from this trial have shown that the primary end point was not met and that mortality was increased in the calcitriol groups, leading to premature closure of the study (Novacea, Inc., 2007).

Bone Interface

Preclinical studies suggest that endothelin A receptors are overexpressed in prostate cancer, and higher plasma endothelin levels in patients with prostate cancer have been shown to correlate with tumor stage, grade, and metastases. Endothelin-1 is a potent vasoconstrictor, and antagonists have been developed for the treatment of pulmonary hypertension. In oncology, endothelin is likely to be involved in the paracrine signals between osteoblasts and prostate cancer cells that regulate the development of bone metastases and have been shown to influence cell growth and proliferation, regulate osteoblast activity, and inhibit apoptosis. These preclinical observations suggest that this pathway may be a rational target for the interference of tumor-stromal interactions (Nelson JB et al, 2003; Carducci et al, 2002; Yin et al, 2003).

Atrasentan is a highly selective endothelin A receptor antagonist and has been extensively tested in prostate cancer. In preliminary phase 2 trials, a 10-mg dose of atrasentan was found to prolong time to progression compared with placebo in men with metastatic CRPC (196 vs. 129 days, respectively; *P* = .02) (Carducci et al, 2003). **Adverse events with atrasentan were mild and related to vasomotor reactions, including headache, rhinitis, flushing, and peripheral edema. In addition, favorable effects were seen in markers of bone deposition and resorption.** However, in a placebo-controlled double-blind phase 3 trial involving 809 patients with metastatic CRPC, oral atrasentan (10 mg/day) did not reduce the risk of disease progression (*P* = .14), despite evidence of biologic affects on PSA and bone alkaline phosphatase (Carducci et al, 2007). A second phase 3 trial in nonmetastatic CRPC that randomized 467 men to atrasentan and 474 to placebo also failed to improve time to metastatic progression (*P* = .29) or overall survival (Nelson et al, 2008). A large cooperative group phase 3 clinical trial evaluating docetaxel plus or minus atrasentan as first-line therapy for metastatic CRPC is in progress.

A novel small molecule endothelin receptor inhibitor, zibotentan (ZD4054), has shown initial promising results. In a phase 2 trial of zibotentan versus placebo in men with metastatic CRPC, this agent did not improve time to disease progression (the primary study end point; *P* = .55); however, overall survival was longer in the zibotentan group (*P* = .01) (James et al, 2009). Although survival was a secondary end point, this has led to the design of several ongoing placebo-controlled phase 3 clinical trials evaluating zibotentan either alone or in combination with docetaxel in patients with metastatic CRPC.

Angiogenesis Targets

Tumor angiogenesis is likely to be an important biologic component of prostate cancer metastasis, and elevated levels of the potent angiogenic molecule vascular endothelial growth factor (VEGF) have been shown to correlate with advanced clinical stage and survival (Duque et al, 1999; George et al, 2002).

In a retrospective study of archived serum samples, VEGF levels were independently associated with survival from prostate cancer (George et al, 2001). Similarly, antibodies to VEGF have slowed prostate xenograft growth rates, especially in combination with chemotherapy (Fox et al, 2002; Sweeney et al, 2002). These findings led to the phase 2 CALGB 90006 trial, which added bevacizumab to docetaxel and estramustine in men with metastatic CRPC. Among 79 treated patients in this study a decline of more than 50% in PSA level was seen in 65% of men, median time to progression was 9.7 months, and overall median survival was 21 months (Picus et al, 2003). Other phase 2 trials combining docetaxel and bevacizumab have also shown promising results (Ryan et al, 2006; Di Lorenzo et al, 2008). These favorable trials have led to the design of a phase 3 randomized study (CALGB 90401) evaluating docetaxel 75 mg/m^2 every 3 weeks and prednisone 10 mg daily plus either bevacizumab 15 mg/kg or placebo given every 3 weeks. The primary end point of this trial is overall survival, and accrual of 1020 patients with metastatic CRPC has been completed.

Thalidomide was originally developed in the 1960s for treatment of morning sickness and subsequently linked to teratogenic effects resulting in phocomelia and dysmelia. Whereas the exact mechanism of teratogenesis is unproven, the metabolites of thalidomide have been shown to inhibit angiogenesis through multiple potential mechanisms, including inhibition of proangiogenic signals such as VEGF, basic fibroblast growth factor (bFGF), interleukin-6, and tumor necrosis factor-α (Bartlett et al, 2004; Franks et al, 2004). Preclinical studies suggest that thalidomide has T-cell costimulatory activity and immunomodulatory properties as well. Phase 1/2 studies with high doses of thalidomide as a single agent have yielded low response rates on the order of 20% for PSA declines (Figg et al, 2001; Franks et al, 2004). However, in a randomized phase 2 trial of weekly docetaxel and low-dose thalidomide versus docetaxel alone, PSA responses, time to disease progression, and overall survival were greater in the combination therapy group (Dahut et al, 2004). Although this trial was underpowered to detect a difference from the standard study arm, the clinical activity and manageable toxicity of this agent have led to the development of more potent thalidomide analogues for combination therapy, and these are currently undergoing clinical evaluation. In a recent phase 2 trial using a three-drug combination of docetaxel, thalidomide, and bevacizumab, PSA responses were seen in approximately 80% of patients (Ning et al, 2008). However, neurotoxicity was a significant side effect with this regimen.

Toxicities with thalidomide include deep venous thrombosis, sedation, neuropathy, constipation, and fatigue. Newer thalidomide analogues with immunomodulatory features have been developed that lack the neurotoxicity of thalidomide but retain many of the T-cell modulatory functions, antiangiogenic properties, and even direct pro-apoptotic functions (Bartlett et al, 2004). Lenalidomide and CC-4047 are second-generation compounds with much more potent tumor necrosis factor-α inhibition than the parent compound, and clinical testing with these agents has begun. For example, several phase 1 and 2 studies have revealed PSA responses and partial radiologic responses with lenalidomide, both when used alone and when combined with ketoconazole or docetaxel (Dreicer et al, 2007; Moss et al, 2007; Garcia et al, 2008). Phase 3 trials using thalidomide or lenalidomide in CRPC have not yet been conducted.

There has been a recent interest in the evaluation of tyrosine kinase inhibitors (TKIs), agents that block angiogenic growth factor targets such as the VEGF and PDGF receptors. The drug

sorafenib is an oral inhibitor of RAF kinase, VEGFR, and PDGFR, which has been approved for use in metastatic renal cell carcinoma. In phase 2 studies using sorafenib in men with metastatic CRPC, this agent was shown to prevent radiologic progression and cause regression of bone metastases in some patients, but without affecting PSA levels (Dahut et al, 2006; Aragon-Ching et al, 2008).

To conclusively evaluate the efficacy and safety of abiraterone, a pivotal multicenter placebo-controlled blinded randomized phase III trial (COU-AA-301) was conducted in men with docetaxel-pretreated ketoconazole-naïve metastatic CRPC (de Bono et al, 2011). This trial randomized men (2:1) to receive either abiraterone 1000 mg daily plus prednisone 10 mg daily (n = 797) or placebo plus prednisone (n = 398). The trial met its primary endpoint, demonstrating a median overall survival of 14.8 months in the abiraterone arm and 10.9 months in the placebo arm (HR, 0.65; P < .0001). In addition, when compared to placebo, abiraterone prolonged radiographic progression-free survival (5.6 vs. 3.6 months; P < .0001), improved time to PSA progression (10.2 vs. 6.6 months; P < .0001), and produced more PSA responses (38% vs. 10%; P < .0001). Notably, the overall survival duration seen here (14.8 months) is similar to that of cabazitaxel/prednisone (15.1 months) in this second-line population with similar baseline characteristics, while the survival of men treated with prednisone alone was slightly inferior to that of mitoxantrone/prednisone in the TROPIC trial (10.9 vs. 12.7 months). Based on the results of the COU-AA-301 trial, the FDA approved abiraterone acetate (Zytiga, Janssen Biotech, Horsham, PA) in April 2010 for the treatment of patients with metastatic CRPC who have received prior docetaxel chemotherapy. The recommended dose of abiraterone is 1000 mg daily by mouth. A second randomized phase III trial (COU-AA-302) targeting men with docetaxel- and ketoconazole-naïve CRPC has completed accrual of over 1000 patients. Given the comfort level and safety of using this and other hormonal agents in prostate cancer patients prior to chemotherapy, it is very likely that abiraterone will be used clinically in both the predocetaxel and postdocetaxel settings.

CYP17 System

It has recently been recognized that the androgen receptor and ligand-dependent androgen receptor signaling commonly remain active and upregulated in men with castrate levels of testosterone (i.e., <50 ng/dL) (Debes and Tindall, 2004). Standard hormonal therapies inhibit gonadal androgenesis but do not affect androgen synthesis from adrenal or other extragonadal sources that may account for 5% to 10% of total androgen production. It has also been suggested that CRPC itself may produce intratumoral androgens autonomously (Mostaghel et al, 2007). In addition, overexpression of CYP17 has been demonstrated in tumors of men with CRPC (Stigliano et al, 2007). The novel agent abiraterone acetate is an oral selective inhibitor of the microsomal enzyme cytochrome P17 (17,20-lyase and 17α-hydroxylase) that is a key regulator of adrenal androgen synthesis. Phase 1/2 studies using abiraterone in men with CRPC (both before and after docetaxel) have shown a substantial number of PSA responses (PSA declines ≥ 50%) and also some partial radiologic responses in men with bony and visceral metastases (Attard et al, 2008; Danila et al, 2008). Common side effects of this agent include hypokalemia, hypertension, and pedal edema. These effects are explained by a syndrome of secondary mineralocorticoid excess, which improves with use of the mineralocorticoid receptor antagonist eplerenone. Phase 3 randomized studies of abiraterone plus docetaxel in first-line metastatic CRPC, and abiraterone used alone in the docetaxel-refractory setting, are being conducted.

Androgen Receptor Modulation

A slightly different androgen receptor (AR)-directed approach has focused on the development of second-generation antiandrogens that have advantages over the established agents in this class (bicalutamide, nilutamide, flutamide). One such drug is MDV3100, a potent oral nonsteroidal AR antagonist (Chen et al, 2009). Importantly, MDV3100 remains a potent antagonist of the AR in the castration-resistant state, even in the setting of overexpressed or constitutively activated AR (Watson et al, 2010). In addition, unlike other antiandrogens that may also function as partial AR agonists, MDV3100 does not exhibit any measurable agonistic activity and is able to prevent AR nuclear translocation with resultant tumoricidal (not cytostatic) activity (Tran et al, 2009). Notably, recent studies have demonstrated the emergence of ligand-independent AR splice variants in CRPC, some of which may also be inhibited by MDV3100.

A pivotal placebo-controlled double-blind phase III study (AFFIRM), randomizing 1170 patients with docetaxel-pretreated ketoconazole-naïve CRPC to MDV3100 160 mg daily (n = 780) or placebo (n = 390), has now completed accrual. A second randomized phase III trial (PREVAIL) investigating the same treatment arms in men with chemotherapy-naïve CRPC is currently underway. One advantage of MDV3100 over agents such as abiraterone is the lack of requirement for concurrent corticosteroid administration. However, the optimal sequencing of this agent, if approved, with immunotherapies and other emerging hormonal therapies will need to be defined through future clinical trials.

A phase I/II study of oral MDV3100 in men with chemotherapy-naïve (n = 65) or taxane-pretreated (n = 75) metastatic CRPC has recently been published (Scher et al, 2010). In that trial, ≥50% PSA declines were seen in 62% and 51% of chemotherapy-naïve and taxane-pretreated patients, respectively; objective tumor responses were observed in 36% and 12% of men, respectively. Radiographic progression-free survival was 6.7 months in the docetaxel-pretreated patients and >17 months in chemotherapy-naïve patients. Side effects of MDV3100 are generally mild and include fatigue (27%) and nausea (9%). Rare seizures (3/140 patients) have also been reported, perhaps mediated by a direct effect of AR antagonism on central nervous system GABA-A receptors.

Epigenetic Approaches

Histone deacetylases (HDACs) are key regulators of histone acetylation status, which is critical for AR-mediated transcriptional activation of genes implicated in the regulation of cell survival, proliferation, differentiation, and apoptosis. Vorinostat is a potent oral HDAC inhibitor that has shown antitumor activity in prostate cancer cell lines and animal models (Welsbie et al, 2009). This agent has previously been approved for the treatment of cutaneous T-cell lymphoma. However, a phase 2 study of vorinostat in the second-line treatment of men with CRPC that had progressed on docetaxel did not show significant PSA or radiologic responses and was associated with a high frequency of grade 3/4 adverse events, which included fatigue, nausea, anorexia, vomiting, diarrhea, and weight loss (Bradley et al, 2008). A novel oral HDAC inhibitor, panobinostat (LBH589), is currently in phase 1 development as an adjunct to docetaxel in first-line CRPC (Rathkopf et al, 2008).

Immunotherapy

Entraining the immune system to overcome tumor-induced tolerance is the goal of nearly every cancer vaccine program, and

active immunotherapy with vaccination against tumor antigens has been pursued in many different cancer models. A variety of approaches have been employed, including dendritic cell-based therapies; novel adjuvants such as bacille Calmette-Guérin (BCG), granulocyte-monocyte colony-stimulating factor (GM-CSF), and viral carriers; single-antigen or whole cell vaccines; and genetically modified tumors. More recently, combination therapies using costimulatory molecules, CTLA-4 blockade, Toll-like receptor agonism, and intracellular viral or bacterial mediators have been developed (Pardoll, 1992; Blattman et al, 2002; Mapara and Sykes, 2004; Harzstark and Small, 2009).

In prostate cancer, several immunologic strategies have been under clinical development. The most important of these include the sipuleucel-T (Provenge) autologous prostatic acid phosphatase (PAP)-loaded dendritic cell vaccine, the GVAX allogeneic recombinant whole cell vaccine, and CTLA-4 inhibitory approaches. Less successful strategies have included the Prostvac-VF recombinant pox viral PSA vaccine and the BLP25 MUC1 liposomal vaccine, among many others. Each of these vaccines is designed to stimulate the immune system to recognize a previously tolerance-inducing tumor in a cancer-specific way (Webster et al, 2005).

Sipuleucel-T

Sipuleucel-T (Provenge) is a vaccine derived from CD54+ dendritic cells, the major antigen-presenting cells, which are apheresed from individuals and processed with the recombinant fusion protein PAP and GM-CSF. PAP was chosen on the basis of its prostate cell membrane localization and the success of preclinical models using it to generate prostate-specific immune responses and autoimmune prostatitis. Modest activity was reported in phase 2 trials in patients with CRPC. In a randomized phase 2/3 trial comparing sipuleucel-T against placebo in 127 asymptomatic men with metastatic CRPC (PAP positive), the investigators reported no significant differences in time to disease and pain progression ($P = .052$), which corresponded to the main study end point (Small et al, 2006). Patients randomized to placebo were crossed over to receive the active vaccine at the time of progression, whereas those initially randomized to receive the active vaccine were treated at their physician's discretion at the time of progression. This postprogression management period was not part of the study and not prospectively controlled. Whereas the study as designed was negative, a 3-year update suggested a statistically significant improvement in survival for those randomly assigned to receive the active vaccine initially ($P = .01$). It is highly probable that survival differences were due to postvaccine treatments. Post hoc analyses also suggested that the benefits of sipuleucel-T may be limited to the subgroup of men with tumor Gleason sums of 7 or lower. Although preparation and production of large-scale quantities of individually tailored vaccine can be challenging, this vaccine was well tolerated with minimal infusion-related fevers and rigors being the predominant adverse events (Small et al, 2006).

A second phase 2/3 trial that randomized 98 men with asymptomatic CRPC to either sipuleucel-T or placebo also failed to show a statistically significant improvement in time to progression (the primary end point) but, unlike the previous study, did not demonstrate an overall survival advantage at 3 years ($P = .33$) (Dendreon, Inc., 2005). A post-hoc pooled analyses of these two trials ($n = 225$) did show an overall survival advantage, with median survival being 18.9 months in the placebo group and 23.2 months in the sipuleucel-T group (HR, 1.5; $P = .01$) (Dendreon, Inc., 2005). However, because overall survival was not the primary end point in either trial, the FDA did not grant approval of this treatment.

In an effort to satisfy FDA requirements, a pivotal multicenter double-blind placebo-controlled randomized phase III trial (IMPACT) was conducted in men with asymptomatic or minimally symptomatic metastatic CRPC (Kantoff et al, 2010), leading to the FDA-approval of this agent in April 2010. In this trial, 512 patients were randomized (2:1) to sipuleucel-T or placebo and the study was powered to detect an overall survival advantage. Notably, this study did not enroll men with visceral metastases or those taking narcotics for cancer pain, and most patients (85%) were chemotherapy-naïve. Impressively, median overall survival was 25.8 months in the sipuleucel-T group versus 21.7 months in the placebo group (HR, 0.78; $P = .03$), despite 64% of patients on placebo crossing over to receive salvage sipuleucel-T. In the subset of patients with prior chemotherapy exposure, overall survival trended in favor of sipuleucel-T, but this effect was not statistically significant. Therefore, although this immunotherapy is approved for all patients with asymptomatic or minimally symptomatic CRPC, it will likely have its largest impact in the prechemotherapy setting.

Similar to previous studies with sipuleucel-T, the IMPACT study found no difference in progression-free survival or PSA/radiographic response rates between the two treatment arms. Some investigators attribute the discordance between progression-free and overall survival to a possible class effect of immunotherapy agents, relating to their mechanism of action which is distinct from cytotoxic therapies. Problematic endpoints such as progression-free survival in CRPC (which may be confounded by bone scan flare or delayed-onset effects) may perhaps be better addressed by revised guidelines using outcomes that are tailored to immunologic agents (Hoos et al, 2010).

GVAX

Prostate GVAX is based on the demonstration in mouse melanoma models of improved tumor rejection when the irradiated tumor vaccine expressed the cytokine GM-CSF compared with other cytokine adjuvants (Dranoff et al, 1993; Dranoff, 2003). This form of immunotherapy uses inactivated allogeneic prostate cancer cell lines (PC3 and LNCaP) that have been modified through adenoviral transfer to secrete GM-CSF and irradiated to prevent further cell division (Ward and McNeel, 2007). The advantage with this approach is that the vaccine can be manufactured in large quantities and that multiple tumor antigens can be targeted simultaneously. However, because of the relative weakness of individual antigens, repeated intradermal dosing is necessary.

Two uncontrolled single-arm phase 2 studies in men with asymptomatic metastatic CRPC have shown antitumor effects of prostate GVAX, one demonstrating an overall survival of 26.2 months ($n = 34$) and the other showing an overall survival ranging from 20.0 to 29.1 months ($n = 80$) depending on dosing regimen (Small et al, 2007; Higano et al, 2008). In both studies the proportion of patients who generated an antibody response to one or both cell lines increased with the dose of vaccine given, and no dose-limiting or autoimmune toxicities were seen. The most common adverse events in both studies were injection-site erythema, fatigue, malaise, myalgias, and arthralgias.

Based on these promising findings, two large randomized phase 3 studies of GVAX immunotherapy (VITAL-1 and VITAL-2) were designed. VITAL-1 involved 626 men with asymptomatic chemotherapy-naive CRPC and randomized them to GVAX or docetaxel/prednisone, with the primary end point being overall survival. VITAL-2 was planned initially to enroll 600 patients with

symptomatic metastatic CRPC, randomizing them to docetaxel/prednisone or docetaxel/GVAX. Both trials were terminated early because of data observed at the time of interim analyses, suggesting that the survival improvements initially hypothesized were unlikely to be observed if the trials were to be continued (Higano et al, 2009). Moreover, in the VITAL-2 study, mortality was higher in patients on the experimental arm receiving docetaxel/GVAX (Small et al, 2009).

CTLA-4 Inhibition

Due to ongoing host immunologic pressures on evolving tumors, cancers have developed mechanisms to escape immune surveillance, effectively inducing a state of immune tolerance (Drake et al, 2006). One way to inhibit immunologic evasion by tumor cells is through blockade of the immune checkpoint molecule CTLA-4 (cytotoxic T lymphocyte-associated antigen-4), thus preventing the normal attenuation of antitumor T-cell responses (Hodi, 2007). In murine prostate cancer models, CTLA-4 inhibition has been shown to potentiate T-cell effects and induce tumor rejection.

Several clinical trials using the monoclonal anti-CTLA-4 antibody, ipilimumab, have been conducted in men with metastatic CRPC. These include phase I and II studies of ipilimumab monotherapy or in combination with radiation (Small et al, 2007), as well as a phase I study combining ipilimumab with GM-CSF (Fong et al, 2009). Encouragingly, ≥50% PSA reductions have been observed in about 20% of patients, and radiologic tumor responses were seen in about 5% of men, which is particularly noteworthy given that PSA and tumor responses were rarely reported in the immunotherapy trials with sipuleucel-T or other therapeutic vaccines. Common side effects of ipilimumab include fatigue (42%), nausea (35%), pruritus (24%), constipation (21%), and rash (19%). In addition, because CTLA-4 normally serves to attenuate autoimmunity, immunologic toxicities resulting from an unchecked immune response may occur. Such immune-related adverse events include colitis (8%), adrenal insufficiency (2%), hepatitis (1%), and even hypophysitis (1%) (Dillard et al, 2010). Ipilimumab is now in placebo-controlled phase 3 testing in the postdocetaxel setting in men with CRPC following a palliative and perhaps immune-stimulatory dose of radiation to a metastatic site, with the intent to demonstrate a survival advantage over radiation alone. A second predocetaxel placebo-controlled study is also underway.

Key Points: Novel Approaches

- Sipuleucel-T is the first therapeutic vaccine to be FDA-approved for the treatment of any cancer and is indicated for use in men with asymptomatic or minimally symptomatic metastatic CRPC.
- Abiraterone acetate is a novel androgen biosynthesis inhibitor that has gained FDA approval for the treatment of patients with metastatic CRPC who have previously received docetaxel chemotherapy.

CONCLUSIONS

With more drugs at our fingertips for the treatment of metastatic CRPC than ever before, and an increasing number of novel therapeutic targets being discovered every day, we are still left with several challenges and unanswered questions. First, we must determine how these approved and experimental therapies should ideally be sequenced in individual patients with CRPC. For example, should sipuleucel-T routinely be given prior to chemotherapy or abiraterone with prednisone? Should abiraterone be reserved only for docetaxel-resistant patients? How should we treat cabazitaxel-refractory patients? Second, we will need to develop strategies to optimally combine these drugs in a rational manner, taking advantage of our understanding of negative feedback loops and alternative pathway activation to overcome resistance to monotherapies. Ultimately, only prospective trials incorporating biomarker-driven hypotheses will be able to address these key clinical questions. Thus the collection of tumor specimens or correlative samples may be essential in identifying novel targets or developing enrichment strategies for future study of these agents. Third, we must design smarter trials with the goal of quickly yet reliably identifying agents that do not hold promise, while enabling those that do to move swiftly to registrational studies. For example, in the clinical development of MDV3100 and cabazitaxel, pivotal phase III trials were designed directly following the initial phase I/II studies that demonstrated significant drug activity in men with CRPC. Finally, we must select our patients more carefully based on clinical or molecular characteristics, in order to identify the subset most likely to benefit from a particular therapy. For example, in men with significant pain, perhaps sipuleucel-T is not appropriate systemic therapy given the prolonged onset of action and lack of palliative benefits; additionally, immune-based biomarkers may shed light on which men may obtain a greater degree of benefit from immunotherapies. Several active agents are currently in phase III development, and some of these therapies are also likely to further expand our therapeutic arsenal for men with metastatic CRPC in the near future.

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chapter 111

Normal Development of the Genitourinary Tract

John M. Park, MD

Kidney Development

Bladder and Ureter Development

Genital and Reproductive Tract Development

The study of embryology provides a useful foundation for the understanding of definitive human anatomy and various congenital disease processes. During the past few decades, a torrent of molecular information and novel experimental techniques has revolutionized the field of embryology, and the knowledge base continues to expand at an exponential rate. From the urologic surgeon's perspective, however, the classic, descriptive aspects of anatomic embryology continue to serve as an important reference point from which various congenital problems are solved clinically. The aim of this chapter is to provide a concise presentation of the essential facts of normal genitourinary system development, clarifying the important anatomic features and supplementing them with updated molecular information. Deliberate efforts have been made to separate the ever-expanding molecular information from that of the descriptive, anatomic embryology to keep the main "story" of genitourinary system development clear and understandable from a surgical point of view (Fig. 111–1). To help with visualization of the key events, various schematic drawings are provided. The goal of this chapter is not to provide potential explanations for every congenital defect that might occur in the genitourinary system but to select pertinent examples highlighting the fundamental concepts and principles.

KIDNEY DEVELOPMENT

Early Events

Mammals develop three kidneys in the course of intrauterine life. The embryonic kidneys are, in order of their appearance, the *pronephros,* the *mesonephros,* and the *metanephros.* The first two kidneys regress *in utero,* and the third becomes the permanent kidney. **Embryologically, all three kidneys develop from the intermediate mesoderm.** As the notochord and neural tube develop, the mesoderm located on either side of the midline differentiates into three subdivisions: *paraxial (somite), intermediate,* and *lateral mesoderm* (Fig. 111–2). As the embryo undergoes transverse folding, the intermediate mesoderm separates away from the paraxial mesoderm and migrates toward the intraembryonic coelom (the future peritoneum). At this time there is a progressive craniocaudal development of the bilateral longitudinal mesodermal masses, called *nephrogenic cords.* Each cord is seen bulging from the posterior wall of the coelomic cavity, producing the *urogenital ridge.*

Pronephros and Mesonephros

The mammalian *pronephros* is a transitory, nonfunctional kidney, analogous to that of primitive fish. In humans, the first evidence of pronephros is seen late in the third week, and it completely degenerates by the start of the fifth week. The pronephros develops as five to seven paired segments in the region of the future neck and thorax (Fig. 111–3A). Development of the pronephric tubules starts at the cranial end of the nephrogenic cord and progresses caudally. As each tubule matures it immediately begins to degenerate along with the segment of the nephric duct to which the tubules are attached.

The second kidney, the *mesonephros,* is also transient, but in mammals it serves as an excretory organ for the embryo while the definitive kidney, the *metanephros,* begins its development (see Fig. 111–3B and C). There is a gradual transition from the pronephros to the mesonephros at about the 9th and 10th somite levels. Development of the *nephric ducts* (also called the wolffian ducts) precedes the development of the mesonephric tubules. The nephric ducts can be seen as a pair of solid longitudinal tissue condensations at about the 24th day, developing parallel to the nephrogenic cords in the dorsolateral aspect of the embryo. Its blind distal ends grow toward the primitive cloaca and soon fuse with it at about the 28th day. As the ducts fuse with the cloaca they begin to form a lumen at the caudal end. This process of canalization then progresses cranially in a reverse direction, transforming the solid tissue condensations into the definitive nephric ducts with excretory capability. Soon after the appearance of the nephric ducts during the 4th week, mesonephric vesicles begin to form. Initially, several spherical masses of cells are found along the medial side of the nephrogenic cords at the cranial end. This differentiation progresses caudally and results in the formation of 40 to 42 pairs of mesonephric tubules, but only about 30 pairs are seen at any one time because the cranially located tubules start to degenerate starting at about the 5th week. By the 4th month, the human mesonephros has almost completely disappeared, except for a few elements that persist into maturity as part of the reproductive tract. **In males, some of the cranially located mesonephric tubules**

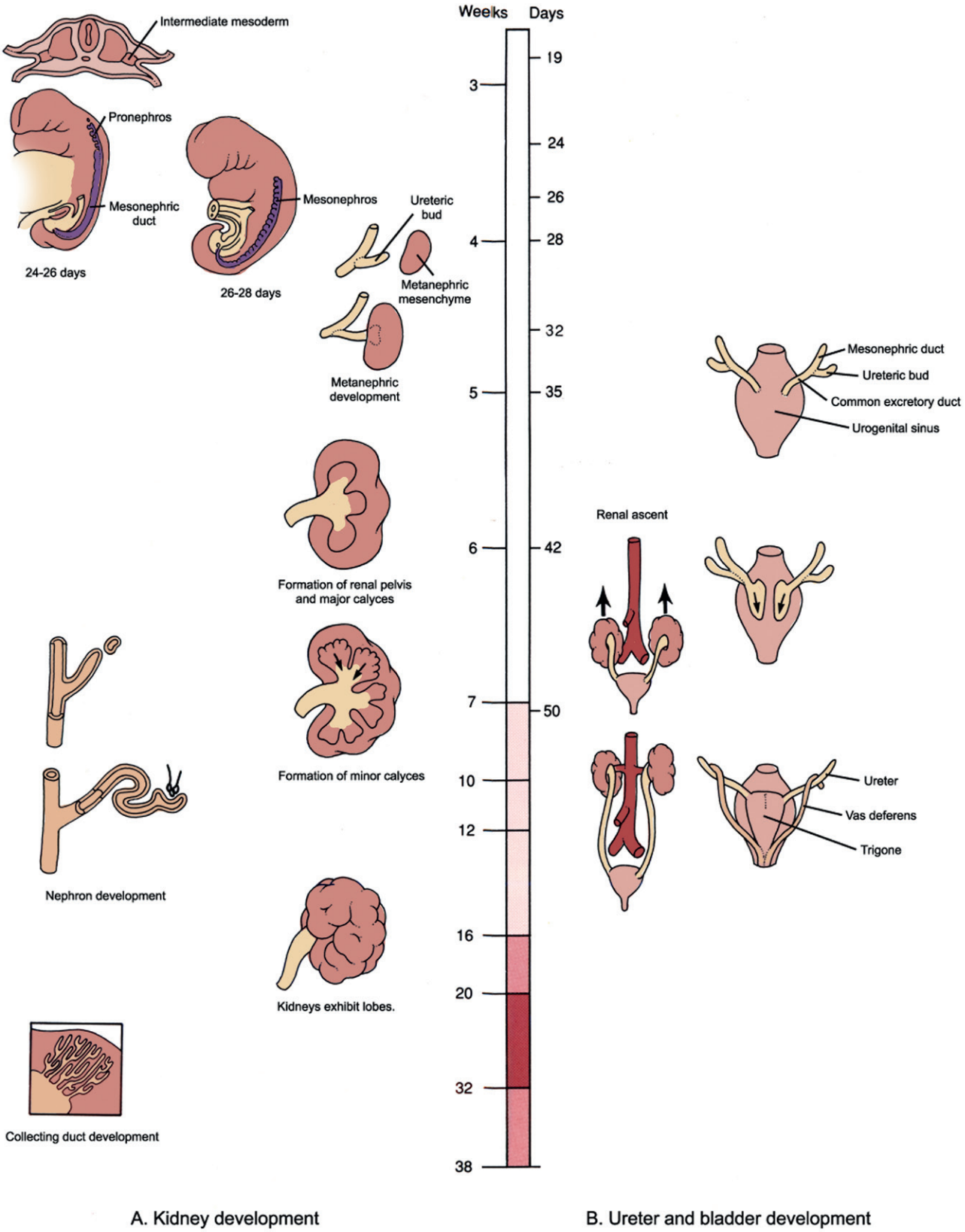
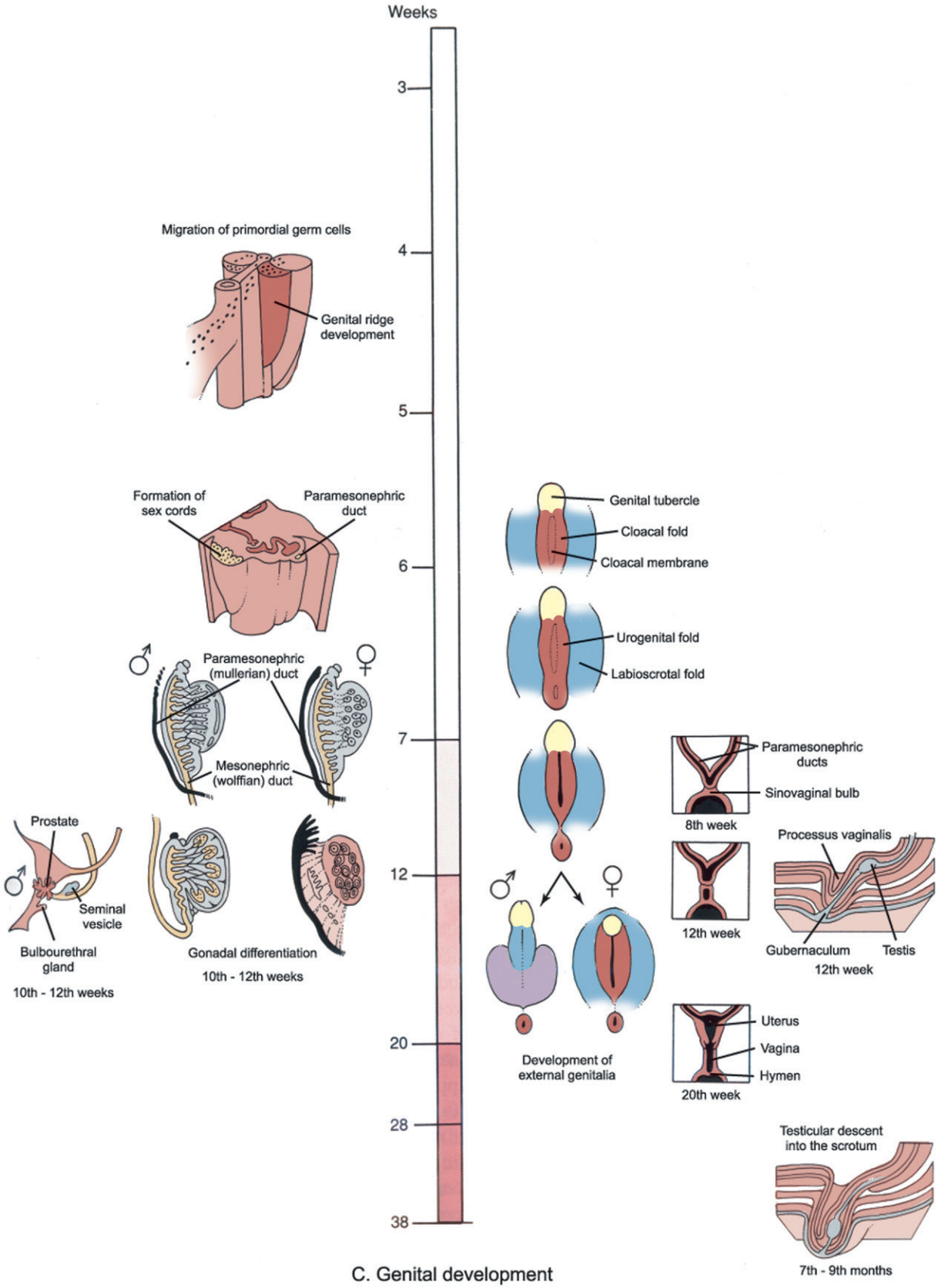


Figure 111–1. **A** to **C,** Time line and overview of genitourinary system development. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)



C. Genital development

Figure 111–1, cont'd.

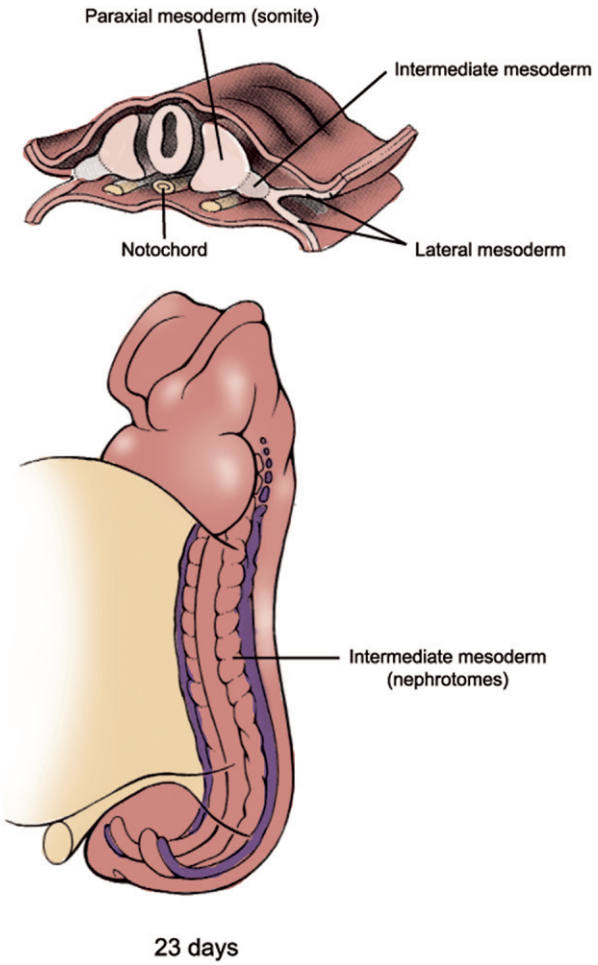


Figure 111–2. The intermediate mesoderm gives rise to paired, segmentally organized nephrotomes from cervical to sacral region. Cervical nephrotomes are formed early during the fourth week and are collectively referred to as the pronephros. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

become the efferent ductules of the testes. The epididymis and vas deferens are also formed from the nephric (wolffian) ducts. In females, remnants of cranial and caudal mesonephric tubules form small, nonfunctional mesosalpingeal structures termed the *epoöphoron* and *paroöphoron.*

The mesonephric tubules differentiate into excretory units that resemble an abbreviated version of an adult nephron. Shortly after the cell clusters are formed they develop lumens and take the shape of vesicles. As the vesicle elongates, each end curves in an opposite direction to form an S-shaped tubule. The lateral end forms a bud that connects with the nephric duct. The medial end lengthens and enlarges to form a cup-shaped sac, which eventually wraps around a knot of glomerular capillaries to form a renal corpuscle. The tuft of glomerular capillaries originating from a branch of the dorsal aorta invades the developing glomerulus while an efferent arteriole empties into a subcardinal sinus.

Metanephros

The definitive kidney, or the *metanephros,* forms in the sacral region as a pair of new structures, called the *ureteric buds,* sprout from the distal portion of the nephric duct and come in contact with the condensing blastema of *metanephric mesenchyme* at about the 28th day (Fig. 111–4). The ureteric bud penetrates the metanephric mesenchyme and begins to divide dichotomously. The tip of the dividing ureteric bud, called the *ampulla,* interacts with the metanephric mesenchyme to induce formation of future nephrons via mesenchymal-epithelial interaction. As the ureteric bud divides and branches, each new ampulla acquires a caplike condensation of metanephric mesenchyme, thereby giving the metanephros a lobulated appearance (Fig. 111–5).

The ureteric bud and metanephric mesenchyme exert reciprocal inductive effects toward each other, and the proper differentiation of these primordial structures depends on these inductive signals (see Molecular Mechanism of Kidney Development, later). The

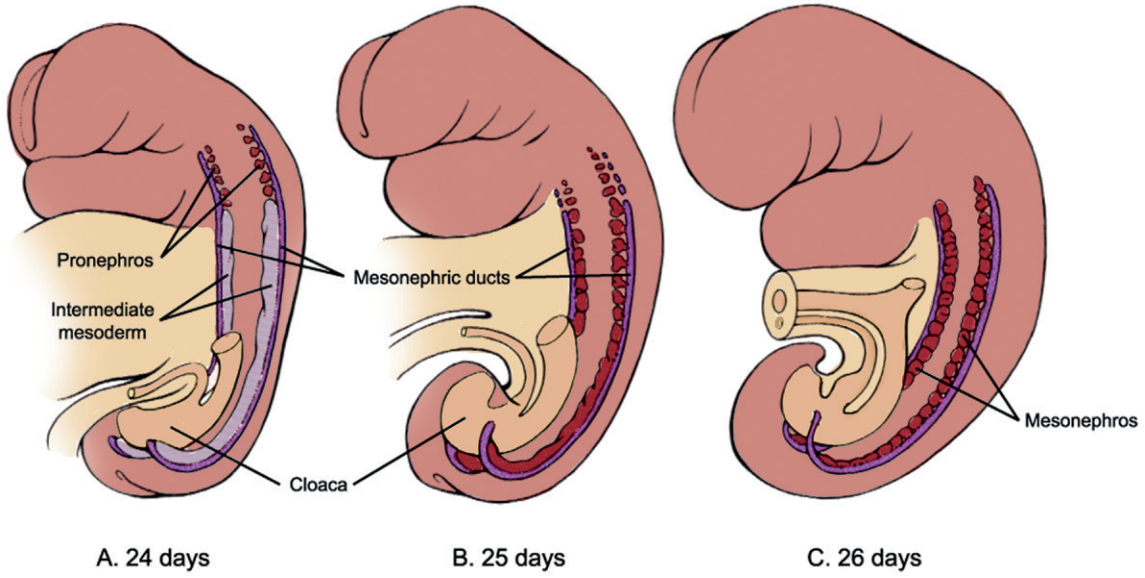


Figure 111–3. Development of pronephros and mesonephros. **A**, Pronephros develops in each of five to seven cervical segments, but this primitive renal structure degenerates quickly during the fourth week. The (meso)nephric ducts first appear on day 24. **B** and **C**, Mesonephric vesicles and tubules form in a craniocaudal direction throughout the thoracic and lumbar regions. The cranial pairs degenerate as caudal pairs develop, and the definitive mesonephros contains about 20 pairs confined to the first three lumbar segments. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

metanephric mesenchyme induces the ureteric bud to branch and divide, and, in turn, the ureteric bud induces the metanephric mesenchyme to condense and undergo mesenchymal-epithelial conversion. **The nephron, which consists of the glomerulus, proximal tubule, loop of Henle, and distal tubule, is thought to derive from the metanephric mesenchyme, while the collecting system, consisting of collecting ducts, calyces, pelvis and ureter, is formed from the ureteric bud** (Fig. 111–6).

In principle, all nephrons are formed in the same way and can be classified into fairly well-defined developmental stages (Larsson et al, 1983) (Fig. 111–7). The metanephric mesenchyme first condenses to form a four- to five-cell layer condensate around the ampulla of the advancing ureteric bud. Near the interface of the ampulla and its adjacent ureteric branch, a cluster of cells separates from the condensate and forms an oval mass, called a *pretubular aggregate*. An internal cavity forms within the pretubular aggregate, at which point the structure is called a *renal vesicle* (stage I). Cells of the stage I renal vesicle are tall and columnar and are stabilized by their attachments to the newly formed basement membrane. It has not yet established a contact with the ampulla of the ureteric bud, but it subsequently forms a luminal connection. Multipotential precursors residing in renal vesicles ultimately give rise to all the epithelial cell types of the nephron (Herzlinger et al, 1992). Nephron segmentation into glomerular and tubular domains is initiated by the sequential formation of two clefts in the renal vesicle (stage II). Creation of a lower cleft, termed the *vascular cleft,* precedes formation of a comma-shaped body. Generation of an upper cleft in the comma-shaped body precedes formation of an S-shaped body. At this stage, the cup-shaped glomerular capsule is recognized in the lowest limb of the S-shaped tubule. Epithelial cells lining the inner wall of this cup will comprise the visceral glomerular epithelium, or podocyte layer. Cells lining the outer wall of the cup will form parietal glomerular epithelium, which lines the Bowman capsule. The glomerular capillary tuft is formed via recruitment and proliferation of endothelial

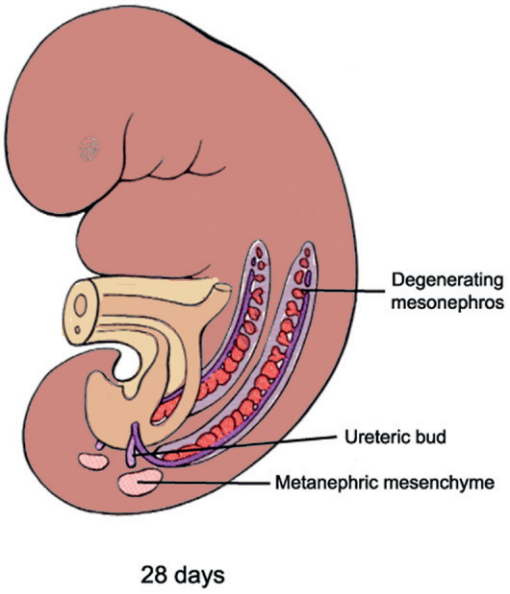


Figure 111–4. Metanephric mesenchyme condenses from the intermediate mesoderm during the early part of the fifth week and comes into contact with the ureteric bud, an outgrowth of the nephric duct, while the cranial mesonephros continues to degenerate. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

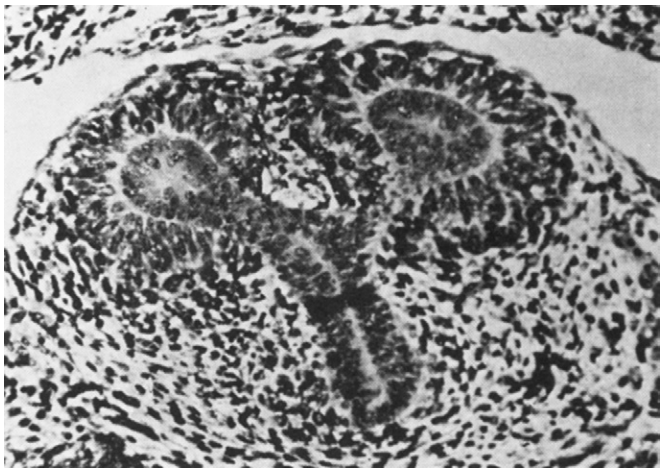


Figure 111–5. The ureteric bud divides to form enlarged tips, called ampullae, around which the metanephric mesenchyme condenses and begins nephron differentiation. The remaining mesenchymal cells remain stromal and continue to interact with tubular mesenchymal cells and dividing ureteric bud epithelial cells. (From Potter EL. Normal and abnormal development of the kidney. Chicago: Year Book Medical Publishers; 1972.)

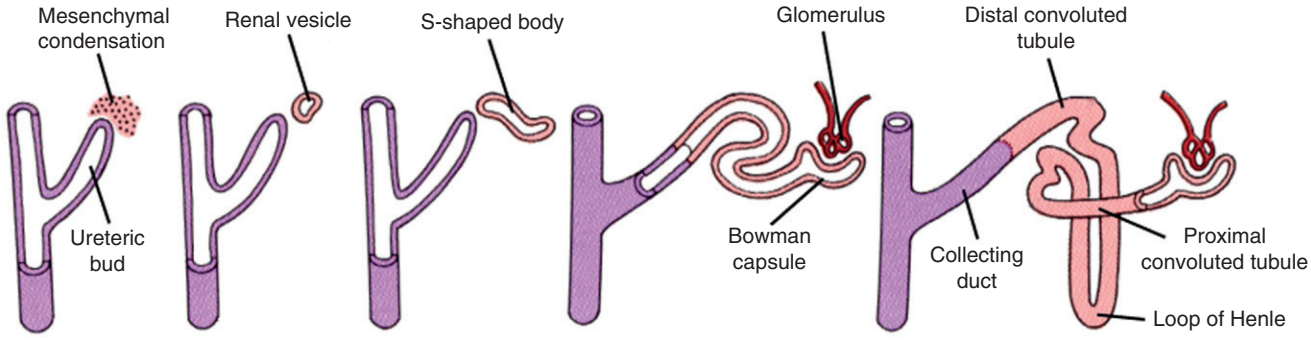


Figure 111–6. Development of the renal collecting ducts and nephrons. The tip of the dividing ureteric bud induces the metanephric mesenchyme *(in pink)* to condense, which then differentiates into a renal vesicle. This vesicle coils into an S-shaped tubule and ultimately forms a Bowman capsule as well as the proximal convoluted tubules, distal convoluted tubules, and loops of Henle. The ureteric bud *(in purple)* contributes to the formation of collecting ducts. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

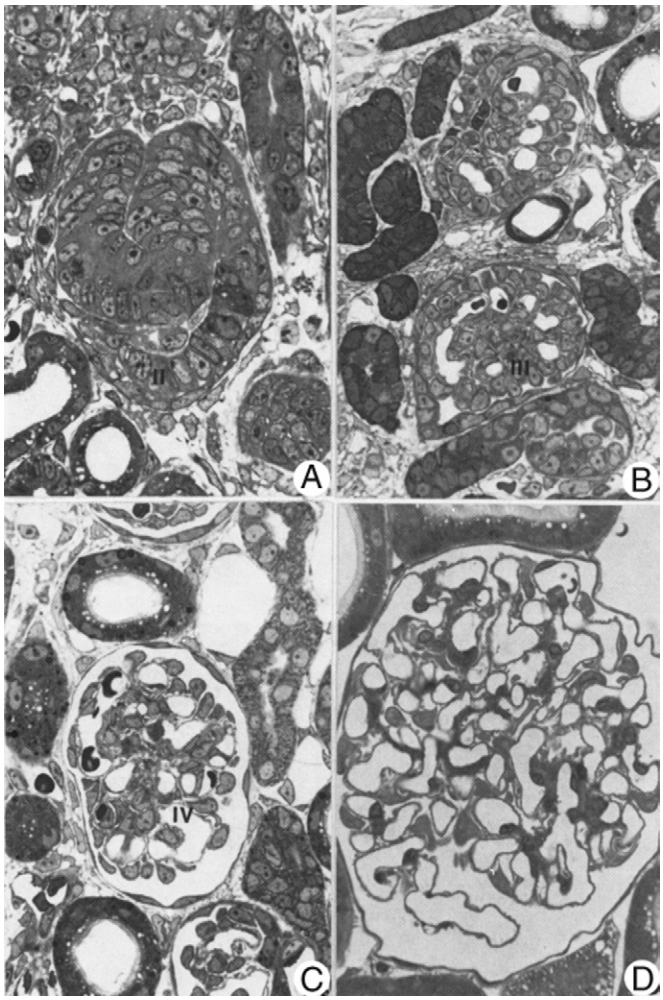


Figure 111–7. Nephron development as seen from a renal cortex of a 3-day-old rat. **A,** A developing nephron with S-shaped body (II). **B,** An oval glomeruli (III). **C,** Nephron now resembles that of mature tubules and glomeruli (IV). **D,** Mature superficial glomerulus from adult rat kidney. (Reproduced from Larsson L, Maunsbach AB. The ultrastructural development of the glomerular filtration barrier in the rat kidney: a morphometric analysis. J Ultrastruct Res 1980;72:392.)

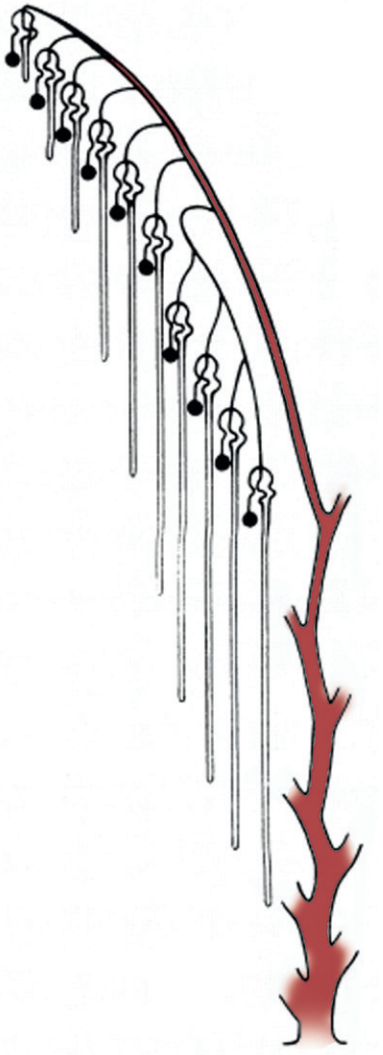


Figure 111–8. Schematic representation of progressive nephron differentiation. Older, more differentiated nephrons are located in the inner part of the kidney near the juxtamedullary region and newer, less differentiated nephrons are found at the periphery. (Reproduced from Potter EL. Normal and abnormal development of the kidney. Chicago: Year Book Medical Publishers; 1972.)

and mesangial cell precursors. The rest of the S-shaped tubule develops into the proximal tubule, the loop of Henle, and the distal tubule. When the cup-shaped glomerular capsule matures into an oval structure the nephron has now passed into stage III of development. Now the nephron can be divided into identifiable proximal and distal tubules. The stage IV nephron is characterized by a round glomerulus that closely resembles the mature renal corpuscle. The morphology of the proximal tubule resembles that of a mature nephron, whereas the distal segments are still primitive. In some species, such as rodents, all stages of nephron development are present at birth, whereas in others, such as humans, all nephrons at birth are in varying steps of stage IV. Mesenchymal cells that do not become tubular epithelium give rise to interstitial stromal cells, which differentiate into a diverse population including fibroblasts, lymphocyte-like cells, and pericytes. **Overall, these events are reiterated throughout the growing kidney so that older, more differentiated nephrons are located in the inner part of the kidney near the juxtamedullary region and newer, less differentiated nephrons are found at the periphery** (Fig. 111–8). **In humans, although renal maturation continues to take place postnatally, nephrogenesis is completed before birth at around 32 to 34 weeks of gestation.**

Collecting System

The dichotomous branching of the ureteric bud determines the eventual pelvicalyceal patterns and their corresponding renal lobules (Cebrian et al, 2004) (Fig. 111–9). In humans, the first nine branch generations are formed by approximately 15 weeks' gestation. By 20 to 22 weeks, ureteric bud branching is completed. Thereafter, collecting duct development occurs by extension of peripheral branch segments. Between 22 and 24 weeks of human fetal gestation the peripheral (cortical) and central (medullary) domains of the developing kidney are established. The renal cortex, which represents 70% of total kidney volume at birth, becomes organized as a relatively compact, circumferential rim of tissue surrounding the periphery of the kidney. The renal medulla, which represents 30% of total kidney volume

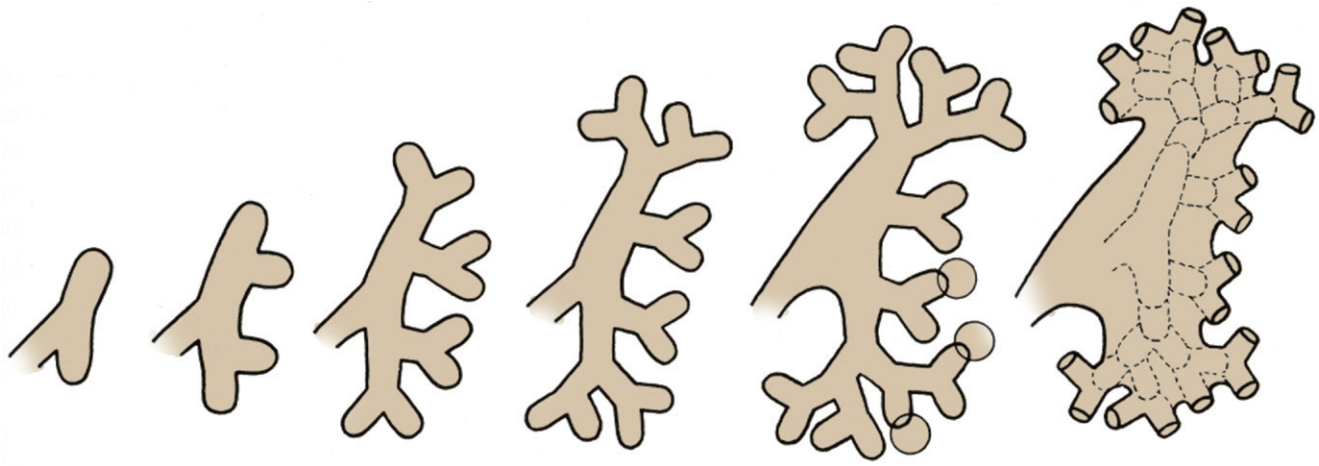


Figure 111–9. Dichotomous branching of the ureteric bud and subsequent fusion of the ampullae to form the renal pelvis and calyces. *Circles* indicate possible sites of infundibular development between the third, fourth, or fifth generations of branches and their subsequent expansions to give rise to the calyces. (Reproduced from Potter EL. Normal and abnormal development of the kidney. Chicago: Year Book Medical Publishers; 1972.)

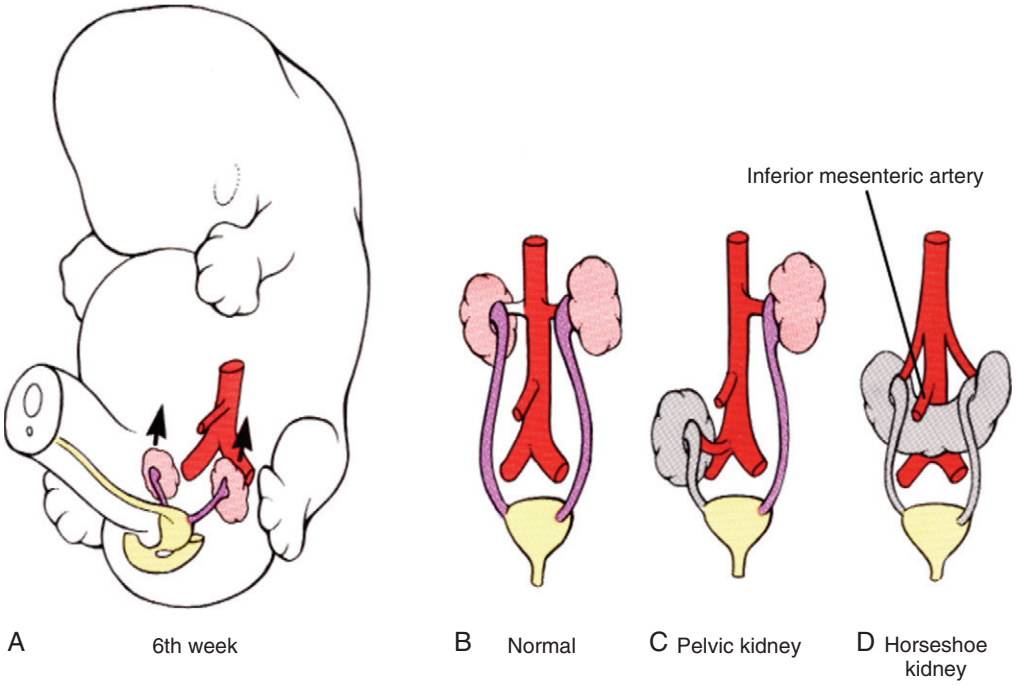


Figure 111–10. Normal and abnormal ascent of the kidneys. **A** and **B,** The metanephros normally ascends from the sacral region to its definitive lumbar location between the sixth and ninth weeks. **C,** Rarely, a kidney may fail to ascend, resulting in a pelvic kidney. **D,** If the inferior poles of the kidneys fuse before ascent, the resulting horseshoe kidney does not ascend to a normal position owing to entrapment by the inferior mesenteric artery. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

at birth, has a modified cone shape with a broad base contiguous with cortical tissue. The apex of the cone is formed by convergence of collecting ducts in the inner medulla and is termed the *papilla.* Distinct morphologic differences emerge between collecting ducts located in the medulla compared with those located in the renal cortex. Medullary collecting ducts are organized into elongated linear arrays that converge centrally in a region devoid of glomeruli. In contrast, collecting ducts located in the renal cortex continue to induce metanephric mesenchyme. The most central segments of the collecting system, formed from the first five generations of ureteric bud branching, undergo remodeling by increased growth and dilatation of these tubules to form the pelvis and calyces.

Renal Ascent

Between the sixth and ninth weeks the kidneys ascend to a lumbar site just below the adrenal glands (Fig. 111–10). The precise mechanism responsible for renal ascent is not known, but it is speculated that the differential growth of the lumbar and sacral regions of the embryo plays a major role. As the kidneys migrate they are vascularized by a succession of transient aortic sprouts that arise at progressively higher levels. These arteries do not elongate to follow the ascending kidneys but instead degenerate and are replaced by successive new arteries. The final pair of arteries forms in the upper lumbar region and becomes the definitive renal arteries. Occasionally, a more inferior pair of arteries persists as

accessory lower pole arteries. When the kidney fails to ascend properly its location becomes ectopic. If its ascent fails completely it remains as a pelvic kidney. **The inferior poles of the kidneys may also fuse, forming a horseshoe kidney that crosses over the ventral side of the aorta. During ascent the fused lower pole becomes trapped under the inferior mesenteric artery and thus does not reach its normal site.** Rarely, the kidney fuses to the contralateral one and ascends to the opposite side, resulting in a cross-fused ectopy.

Molecular Mechanism of Kidney Development

The details of inductive interactions among metanephric mesenchyme, ureteric bud epithelia, and, more recently, the stroma, are becoming clearer and provide insights into the complex regulatory mechanisms underlying renal development. **Formation of renal tubules and collecting system occurs sequentially and requires dynamic interactions among epithelial, mesenchymal, and stromal cells.** Many of the early events in embryonic kidney development were first elucidated by manipulating lower vertebrate embryos and by utilizing a mammalian in-vitro organ culture system. Clifford Grobstein's pioneering work in the 1950s led to an organ culture technique (Grobstein, 1956) whereby the metanephric mesenchyme is separated from the ureteric bud during the early part of kidney development and grown in vitro on a filter. An inducer tissue, such as ureter or spinal cord, cultured on the opposite side of the filter then provides the inductive signal (Fig. 111–11). This ingenious experimental approach has established the kidney as a model system for studying the role of epithelial-mesenchymal interaction in organ development. The development of many other organs, including lung, salivary glands, gonads, prostate, and bladder, also require epithelial-mesenchymal interaction for the controlled differentiation and proliferation of tissues.

Formation of Nephric Ducts

The first recognizable event in renal development may be the formation of nephric ducts within the region of the intermediate mesoderm. The molecular signals responsible for this early event, in which seemingly unorganized mesenchymal cells aggregate to become an epithelial duct, remain essentially unknown, but details are beginning to emerge. The early intermediate mesoderm destined to become nephric ducts is distinguished by expression of the transcription factors LIM1, PAX2, and SIM1, but only LIM1 appears to be absolutely essential for nephric duct formation (Shawlot and Behringer, 1995). PAX2 may be important for maintaining other marker gene expression in the nephric ducts (Torres et al, 1995). Available data suggest a model in which few opposing secreted factors from the surrounding tissues cumulatively restrict LIM1 expression to the intermediate mesoderm. LIM1 then

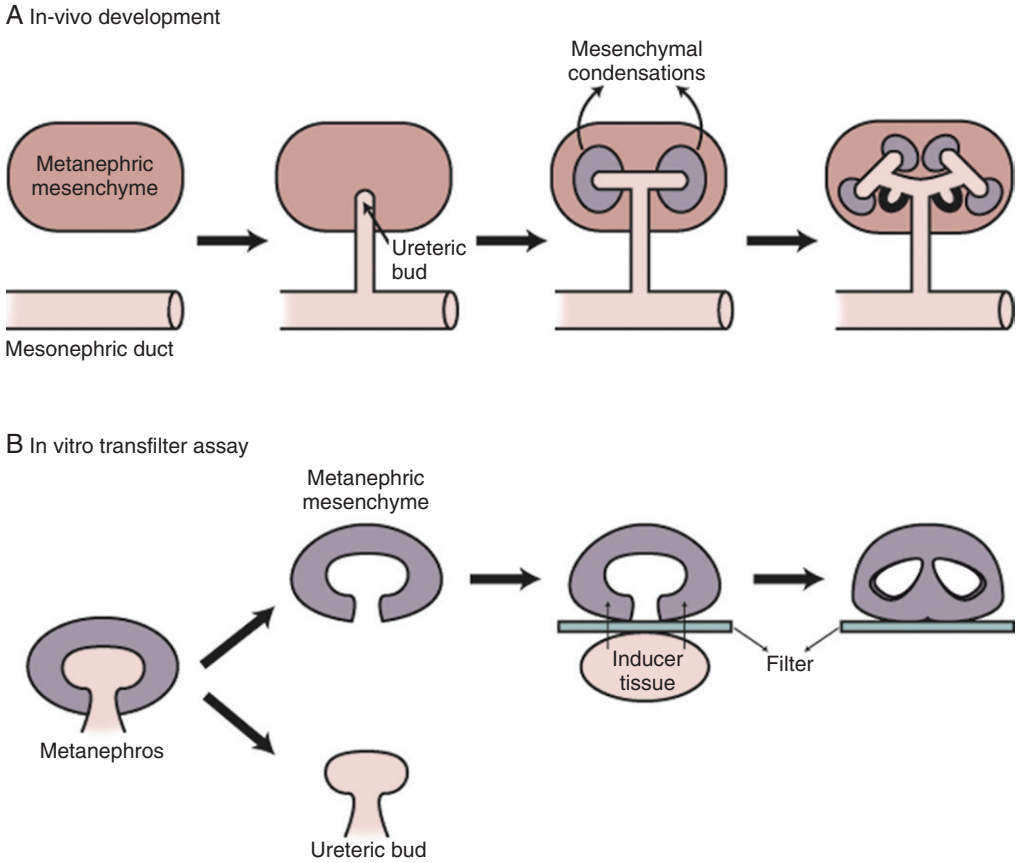


Figure 111–11. Schematic representation of in-vivo kidney development **(A)** and an in-vitro transfilter organ culture system of Grobstein **(B)**. At an early stage of renal development, the metanephric mesenchyme is separated from the ureteric bud and cultured on a filter. If there is an inducer tissue grown on the opposite side of the filter, such as ureter and spinal cord, the metanephric mesenchyme will continue to differentiate into nephron structures. In the absence of inducer tissue, the metanephric mesenchyme will degenerate via apoptosis. (Modified from Vainio S, Muller U. Inductive tissue interactions, cell signaling, and the control of kidney organogenesis. Cell 1997;90[6]:975.)

activates PAX2 expression to further orchestrate the formation of nephric ducts.

Ureteric Bud Outgrowth toward Metanephric Mesenchyme

The outgrowth of the ureteric bud from the nephric duct and its invasion into the condensing blastema of metanephric mesenchyme is a crucial initiating event in the development of the adult kidney *(metanephros).* Many candidate genes have been identified to play a critical role in this process (see http://golgi.ana.ed.ac.uk/kidhome.html). In particular, **several lines of experimental evidence have revealed a crucial role of the RET-GDNF-GFRα1 pathway in the ureteric bud outgrowth** (Fig. 111–12). Glial cell line–derived neurotrophic factor (GDNF) is a secreted peptide expressed in the metanephric mesenchyme that activates the RET receptor, which is expressed along the nephric duct. GDNF activation of RET requires the glycosylphosphatidylinositol (GPI)-linked protein GFRα1, which is expressed in both metanephric mesenchyme and nephric duct. Gene knockout mutations in *Ret, GDNF* (Moore et al, 1996; Pichel et al, 1996; Sanchez et al, 1996), and *GFRα1* (Cacalano et al, 1998) inhibit ureteric bud outgrowth. In organ culture systems, recombinant GDNF is sufficient to induce ectopic ureteric bud outgrowth (Sainio et al, 1997) (Fig. 111–13). However, the competence of the nephric duct to respond to GDNF is restricted along the anteroposterior axis. This anteroposterior restriction might be mediated by suppressors of RET signaling within the surrounding tissue, such as bone morphogenetic protein-4 (BMP4). Mice that are deficient for BMP4 show more broadened ureteric buds and/or secondary anterior buds, suggesting that full BMP4 activity is required to limit RET signaling to the caudal aspect adjacent to the developing metanephric mesenchyme (Miyazaki et al, 2000). Similarly, in organ culture, BMP4 can suppress the activity of GDNF to induce ectopic ureteric bud formation (Brophy et al, 2001). Proper positioning of the ureteric bud is also controlled by the localized expression of GDNF within the metanephric mesenchyme. Both positive and negative regulators have been described for GDNF localization. Homozygous mutation of a transcription factor Eya1 causes failure of ureteric bud outgrowth, and its metanephric mesenchyme lacks GDNF expression, suggesting that Eya1 regulates GDNF expression (Xu et al, 1999). In humans, haploinsufficiency of Eya1 results in a dominantly inherited disorder called branchio-oto-renal syndrome, which involves kidney and urinary tract anomalies (Abdelhak et al, 1997). Expression of PAX2 in the metanephric mesenchyme is also required for GDNF activation (Brophy et al, 2001). GDNF expression is also suppressed at the anterior boundary of the metanephric mesenchyme through the concerted action of the FoxC1 and FoxC2 transcription factors (Kume et al, 2000). Mutations in either Fox gene result in an expansion of GDNF expression and the formation of ectopic ureteric buds. Most FoxC1 homozygous mutants have duplex kidneys, in which the upper ureter is dilated and connects aberrantly to ectopic nephric duct derivatives in males such as seminal vesicles and vas deferens. In the developing kidneys, *Slit2* is primarily expressed in the nephric duct whereas *Robo2* is expressed in the metanephric mesenchyme (Piper et al, 2000). Mice deficient in *Slit2* or *Robo2* exhibit ectopic ureteric bud formation, multiple ureters and hydroureter, and anterior expansion of GDNF expression (Grieshammer et al,

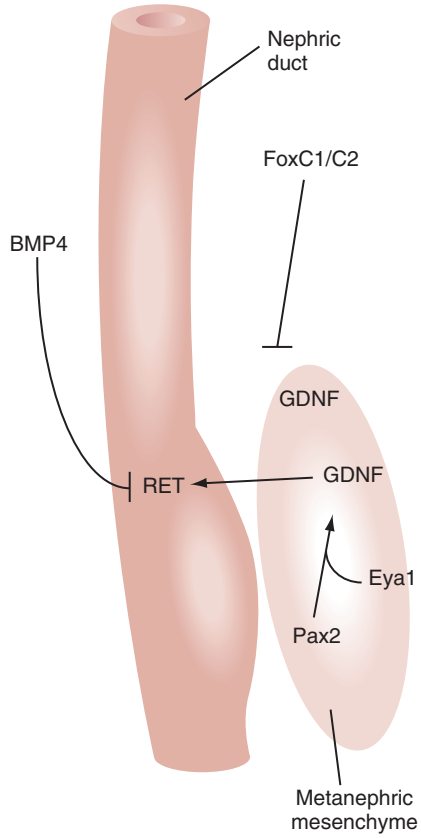


Figure 111–12. Inductive interactions during early kidney development. Glial cell line–derived neurotrophic factor (GDNF) is secreted from the metanephric mesenchyme and activates the RET receptor tyrosine kinase in the ureteric bud epithelium. The expression and localization of GDNF are positively regulated by Eya1 and Pax2 and negatively by FoxC transcription factors. The inducibility of nephric ducts to GDNF signaling is restricted by the action of BMP4. (Modified from Dressler GR. Tubulogenesis in the developing mammalian kidney. Trends Cell Biol 2002;12:390–5.)

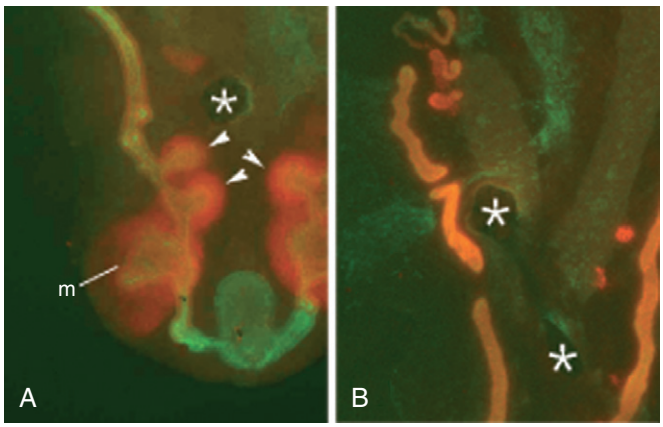


Figure 111–13. **A,** Stimulation of ectopic ureteric buds by GDNF. To determine whether GDNF is sufficient to promote outgrowth of nephric duct epithelial cells, heparin acrylamide beads preadsorbed with recombinant GDNF *(asterisks)* were placed between two nephric duct organ cultures. The native metanephros (m) is seen anteriorly. GDNF alone induces multiple ectopic ureteric buds in the posterior nephric ducts *(arrowheads).* **B,** However, the effect of GDNF is suppressed when Bmp4 is also added to the beads *(asterisks).* Cultures were stained with anti-cytokeratin *(green)* and anti-Pax2 *(red)* antibodies. (From Dressler GR. Tubulogenesis in the developing mammalian kidney. Trends Cell Biol 2002;12:390–5.)

2004). SPRY1 negatively regulates GDNF-RET signaling. Loss of SPRY1 function in mice results in renal malformations, including multiple ureters, duplex kidneys and hydroureter, and increased expression of GDNF in the metanephric mesenchyme (Basson et al, 2006). The data therefore suggest that multiple factors regulate, both positively and negatively, the precise timing and localization of GDNF, which then functions as a guidance cue to activate RET.

Ureteric Bud Branching

Once the ureteric bud has contacted the condensing metanephric mesenchyme it undergoes a dichotomous branching morphogenesis (Cebrian et al, 2004). **Many of the same factors that regulate the initial outgrowth of the ureteric bud also appear to be essential for the subsequent branching of the ureteric bud.** Ureteric bud branching is positively regulated by genetic and nutritional factors. PAX2, a paired-box type transcription factor that is mutated in humans with renal coloboma syndrome, is a positive regulator of ureteric bud branching. During renal development, *Pax2* is expressed in the nephric duct, ureteric bud, and metanephric blastema induced by ureteric bud branch tips. Mice with *Pax2* mutation exhibit decreased ureteric bud branching and renal hypoplasia (Porteous et al, 2000). Ureteric branching is also positively regulated by vitamin A and its retinoic acid receptor signaling, which promote Ret expression. Rarα and Rarβ2 are expressed in stromal cells surrounding Ret-expressing ureteric bud branch tips. Mice deficient in these receptors exhibit a decreased number of ureteric bud branches and diminished expression of Ret (Batourina et al, 2001). Certain markers such as Wnt11 might already be compartmentalized to opposing poles of the dilated bud tips, even before a morphologic branch point is evident (Pepicelli et al, 1997). In mice deficient for the homeobox gene *Emx2* (Miyamoto et al, 1997), ureteric bud outgrowth into the metanephric mesenchyme appears normal but the leading edge never dilates and branching is suppressed. Thus ureteric development is arrested before the first branching event, and the resulting metanephric mesenchyme does not express any markers for induction. Similarly, mice with mutation of *Sall1* exhibit developmental arrest just after ureteric bud outgrowth and before dilation of the leading edge (Nishinakamura et al, 2001). In normal murine embryos, *Sall1* is expressed in the metanephric mesenchyme. Thus *Sall1* might control mesenchyme-derived signals that are necessary for ureteric bud dilation and the early branch point determination. Clearly, the pattern of ureteric bud branching and the expression of ureteric bud–specific genes are influenced by the metanephric mesenchyme. Indeed, the heterologous mesenchyme derived from lung primordia can not only change the pattern of ureteric bud branching to that of lung epithelia but also induce the ureteric bud tissues to express lung-specific genes (Lin et al, 2001). Recent studies demonstrate that BMP/activin-like kinase-2 (ALK3) signaling negatively regulates early ureteric bud branching in vivo (Hartwig et al, 2008). The cell surface receptor ALK3 binds BMP2 and BMP4 with high affinity and is expressed in the nephric duct. Inactivation of ALK3 changes the pattern of primary ureteric bud branching from bifid to trifid and increases the number of first- and second-generation branches. These defects are associated with decreased formation of subsequent branch generations, resulting in a decreased complement of collecting ducts. These observations suggest that the pattern of early ureteric bud branching is a critical determinant of subsequent branching morphogenesis. **Thus ureteric bud epithelial branching morphogenesis is controlled by both intrinsic and extrinsic factors working in concert to generate a kidney-specific branching pattern.**

Tubulogenesis

Classic tissue recombination experiments focused almost exclusively on the relationship between metanephric mesenchymal cells and ureteric bud epithelial cells**. It is now clear that at least three cell types are involved in the control of renal development: the ureteric bud tip cells, the condensed mesenchymal cells, and the stromal or interstitial mesenchymal cells** (Fig. 111–14). It is not known whether the mesenchyme is a homogeneous cell population before its interaction with the ureteric bud. It is clear, however, that once induced by the ureteric bud the metanephric mesenchyme patterns itself into at least two different cell populations, a tubular one and a stromal one. The tubular cell population is thought to derive from mesenchymal cells in direct contact with the ureteric bud ampulla (Vainio et al, 1989; Stark et al, 1994; Torres et al, 1995), whereas the stromal cell population surrounds the tubular cells (Hatini et al, 1996). Once the mesenchyme has been patterned, the cells in the tubular zone undergo morphogenesis to become renal

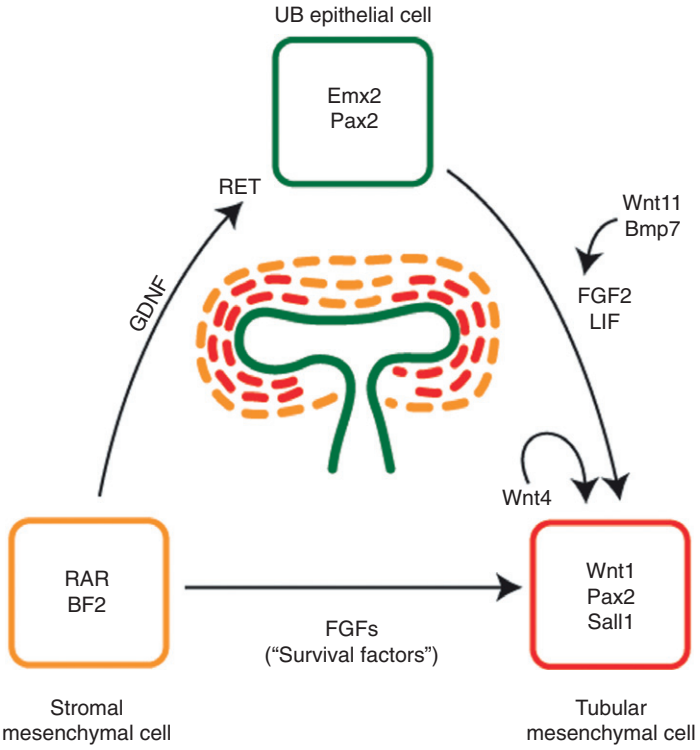


Figure 111–14. Cell-cell interactions promote nephrogenesis. Three major cell types—ureteric bud (UB) epithelial cells, condensing tubular mesenchymal cells, and stromal mesenchymal cells—are thought to play a critical role. At the UB tips, cells express unique markers such as Emx2 and Pax2. The stromal cell lineage is marked by expression of retinoic acid receptors (RAR) and BF2. Presence of Pax2, WT1, and Sall1 appear to be important for continued branching morphogenesis of the UB. Wnt4 is activated in the tubular mesenchymal cells by the invading UB and stimulates the development of polarized epithelium in an autocrine fashion. Finally, fibroblast growth factors (FGFs), such as FGF2, along with LIF, may be critical as survival factors for the developing renal tubular epithelial cells. (Modified from Dressler GR. Tubulogenesis in the developing mammalian kidney. Trends Cell Biol 2002;12:390–5.)

tubular epithelial cells. There is evidence that this process is dependent not only on signals from the ureteric bud but also on signals from the mesenchyme itself. One of these autocrine signals may be Wnt4, whose expression is induced in cells of the tubular zone on interaction with the ureteric bud. In *Wnt4* gene knockout mice the ureteric bud forms and invades the metanephric mesenchyme but subsequent development of epithelial tubules is abolished (Stark et al, 1994). This suggests that two signals are essential for renal tubule formation—initial ureteric bud derived signals activating Wnt4 expression in the metanephric mesenchyme and Wnt4 itself as a mesenchymal autocrine signal. Signals from the stromal cell population also contribute to tubule formation as well, because tubulogenesis is perturbed in *Bf2* gene knockout mice (Hatini et al, 1996). The discovery that Wnt4 acts as a downstream signal during the induction cascade leading to renal tubulogenesis leads to the question regarding the nature of the initial ureteric bud–derived signals. In-vitro data suggest a role for fibroblast growth factor-2 (FGF2) and other uncharacterized factors secreted by the ureteric bud (Karavanova et al, 1996). Candidate molecules that may cooperate with FGF2 are Wnt11 and BMP7 (Kispert et al, 1996; Vukicevic et al, 1996). Localization of RET protein to the ureteric bud tips is reinforced by both GDNF (Pepicelli et al, 1997) and signals emanating from surrounding stromal cells. For example, retinoic acid receptors are expressed in the stromal cells and are required for stromal cell–mediated signaling to maintain high levels of RET expression in the bud tips (Mendelsohn et al, 1999; Batourina et al, 2001). Consistent with the role of retinoic acid receptors in maintaining RET expression in the dividing ureteric bud, rats suffering from vitamin A deficiency have smaller kidneys and fewer nephrons (Lelievre-Pegorier et al, 1999). The cellular crosstalk among stromal, mesenchymal, and ureteric bud cells is further highlighted by gain- and loss-of-function experiments involving FGFs and BMPs. *Fgf7* null mutant mice have fewer branch points and correspondingly fewer nephrons, whereas ectopic FGF7 in organ culture can stimulate branching (Qiao et al, 1999). FGF1 and FGF10 affect elongation of the ureteric bud stalk before the branch-point decision is made (Qiao et al, 2001). Null mutations in *Bmp7* are associated with even more severe phenotypic anomalies, exhibiting limited branching morphogenesis and complete renal developmental arrest. Yet it is difficult to assess how FGFs and BMPs exert their collective effects on branching given the interplay among all the cell types present in the early kidney (Dudley et al, 1999). In addition to the proteins just mentioned, a growing list of growth factors, secreted peptides, and their receptors have been implicated in the control of branching morphogenesis, most by using a variety of in-vitro model systems (Pohl et al, 2000; Davies, 2001). For many of these factors, however, genetic studies have not proved conclusive in assigning specific functional roles during ureteric bud branching in vivo, either because of potential redundancies or embryonic lethalities before the onset of kidney development. Nevertheless, the role of these factors in the renal development must be considered.

Mesenchymal-Epithelial Conversion

The inductive signals emanating from the ureteric bud promote condensation of the metanephric mesenchymal cells around the ureteric bud tips and subsequent tubulogenesis. Mice with null mutations of *Pax2* or *Wt1* fail to exhibit ureteric bud outgrowth and, in both cases, the metanephric mesenchyme does not respond to induction even when recombined with strong inducers in vitro (Kreidberg et al, 1993; Brophy et al, 2001). The establishment of glomerular versus tubular cell fates is dependent on negative feedback between Wt1 and Pax2 (Ryan et al, 1995). During early kidney development, the expression domain of Pax2 is complementary to that of Wt1 in S-shaped bodies. Wt1 expression is restricted to glomerular epithelial precursors (Pelletier et al, 1991), whereas Pax2 expression is restricted to the portion that gives rise to tubular epithelial precursors of the proximal and distal nephron segments and later repressed in differentiated tubular epithelium (Dressler and Douglass, 1992). Evidence in support of Wnt proteins as mesenchyme inducers has been gained from in-vitro induction assays using Wnt-expressing cell lines (Herzlinger et al, 1994; Kispert et al, 1998). Of the *Wnt* mutants examined to date, only *Wnt4*, which is expressed in the mesenchyme and not the ureteric bud, is crucial for propagation of the inductive signals. Although *Wnt4* mutant mesenchyme is able to aggregate in response to ureteric bud contact, these mutant aggregates do not form polarized epithelia. Rat ureteric bud cells secrete tubulogenic factors, such as leukocyte-inhibitory factor (LIF), which, together with FGF2, appears to stimulate growth and tubulogenesis in vitro (Plisov et al, 2001). Once induced to form aggregates, metanephric mesenchyme becomes polarized into an early renal vesicle. This vesicle is closely associated with the branching ureteric bud and will eventually connect to the ureteric bud epithelium to form a continuous tubule. Profound changes take place in the expression of cell adhesion molecules such as cadherins. Shortly after induction, metanephric mesenchyme expresses R-cadherin, cadherin-6, and E-cadherin, along with suppression of the mesenchyme-specific cadherin-11. Both R-cadherin and cadherin-6 mutants show defects in the rate of mesenchymal condensation and polarization (Mah et al, 2000; Dahl et al, 2002). Some renal vesicles in cadherin-6 mutants also fail to fuse to the ureteric bud epithelia, resulting in "dead end" tubules and a subsequent loss of nephrons.

Renal Vascular Development

The origin of intrarenal vasculature is not completely understood. Until recently it was thought that renal vasculature derived exclusively from branches off the aorta and other pre-existing extrarenal vessels ("angiogenic" hypothesis). There is evidence, however, that the renal vessels may originate in situ, within the embryonic kidney from vascular progenitor cells ("vasculogenic" hypothesis) (Loughna et al, 1996; Tufro et al, 1999). Using antibodies to Flk-1, a vascular endothelial growth factor (VEGF) receptor present in angioblasts and mature endothelial cells, it was demonstrated that endothelial cell precursors were already present in the prevascular rodent kidneys before any vessels were discernible from a morphologic standpoint. When embryonic kidneys are cultured at the usual atmospheric oxygen concentration, vessels do not develop. However, if the explants are cultured in a hypoxic atmosphere containing 5% oxygen, capillary sprouts develop within and outside the glomeruli, an effect that is inhibited by anti-VEGF antibodies (Tufro-McReddie et al, 1997). Depending on the developmental potential of the cells involved, both angiogenesis and vasculogenesis may play a role in the development of renal vasculature (Abrahamson et al, 1998).

BLADDER AND URETER DEVELOPMENT

Formation of Urogenital Sinus

At the third week of gestation the cloacal membrane remains a bilaminar structure composed of endoderm and ectoderm. During the fourth week the neural tube and the tail of the embryo grow

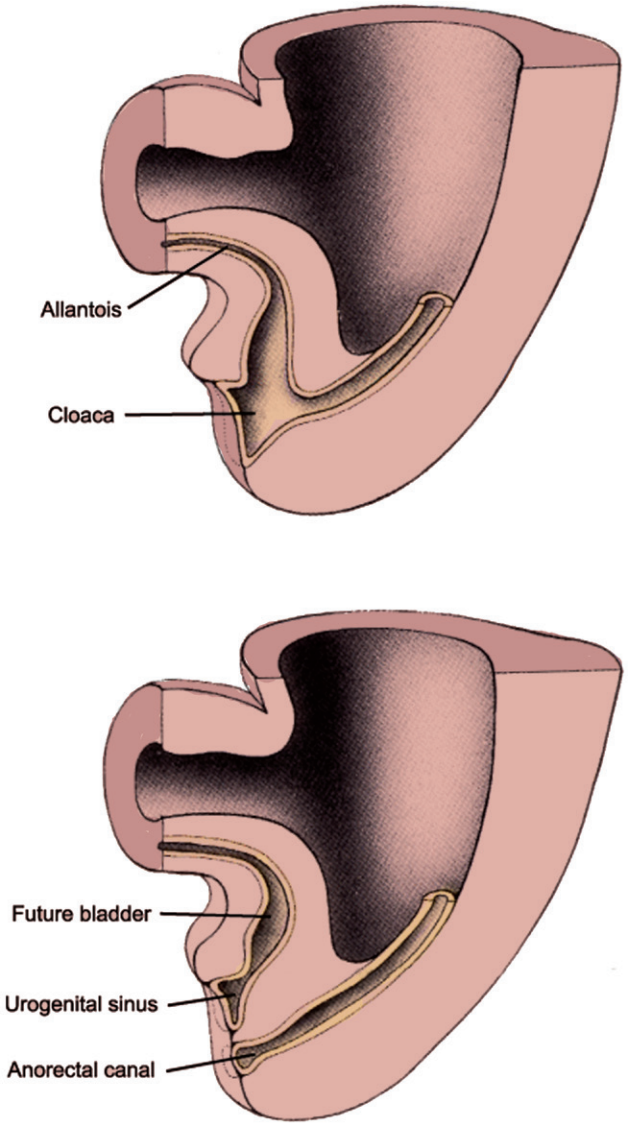


Figure 111–15. Development of the urogenital sinus. Between the fourth and sixth weeks the cloaca is divided into an anterior urogenital sinus and a posterior anorectal canal. The superior part of the urogenital sinus, continuous with the allantois, forms the bladder. The constricted narrowing at the base of the urogenital sinus forms the pelvic urethra. The distal expansion of the urogenital sinus forms the vestibule of the vagina in females and the penile urethra in males. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

dorsally and caudally, projecting itself over the cloacal membrane; and this differential growth of the body results in embryo folding. The cloacal membrane is now turned to the ventral aspect of the embryo, and the terminal portion of the endoderm-lined yolk sac dilates and becomes the *cloaca* (Fig. 111–15). According to the embryonic theories of Rathke and Tourneux, the partition of the cloaca into an anterior urogenital sinus and a posterior anorectal canal occurs by the midline fusion of two lateral ridges of the cloacal wall and by a descending urorectal septum. This process is thought to occur during the fifth and sixth weeks, and it is culminated by the fusion of this urorectal septum with the cloacal membrane. Recently, however, some investigators have challenged this classic view with evidence that there is neither a descending septum nor fusing lateral ridges of the cloacal wall (van der Putte, 1986; Kluth et al, 1995). There is further evidence that the urorectal septum never fuses with the cloacal membrane (Nievelstein et al, 1998). According to these observations the congenital cloacal and anorectal malformations, which were previously thought to occur due to a failure of septum formation and its fusion with the cloacal membrane, may in fact occur from an abnormal development of the cloacal membrane itself (Nievelstein et al, 1998) (Fig. 111–16).

The nephric (wolffian) duct fuses with the cloaca by the 24th day and remains with the urogenital sinus during the cloacal separation. **The entrance of the nephric duct into the primitive urogenital sinus serves as a landmark distinguishing the cephalad vesicourethral canal from the caudal urogenital sinus. The vesicourethral canal gives rise to the bladder and pelvic urethra, whereas the caudal urogenital sinus forms the phallic urethra for males and distal vaginal vestibule for females.**

Formation of Trigone

By day 33 of gestation, the *common excretory ducts* (the portion of nephric ducts distal to the origin of ureteric buds) dilate and connect to the urogenital sinus. The formation of these final connections involves apoptosis, which enables the ureters to disconnect from the nephric ducts, and fusion, in which the ureteral orifice inserts into the urogenital sinus epithelium at the level of the trigone (Batourina et al, 2005). **According to the classic view** (Weiss 1988), **the right and left common excretory ducts fuse in the midline as a triangular area, forming the primitive trigone, structurally different from bladder and urethra.** The ureteral orifice extrophies and evaginates into the bladder by day 37 and begins to migrate in a cranial and lateral direction within the floor of the bladder. During this process the nephric duct orifice diverges away from the ureteral orifice and migrates caudally, flanking the paramesonephric (müllerian) duct at the level of the urogenital sinus. This is the site of the future verumontanum in males and vaginal canal in females. Recent studies, however, have challenged this classic mechanism of trigone development. Using the cell lineage studies in mice, the trigone was found to form mostly from bladder smooth muscle cells with only a minor contribution from the ureters (Viana et al, 2007).

The embryonic pattern of ureteral orifice incorporation into the developing bladder is inferred primarily from clinical observations of duplex kidneys. The upper pole ureteral orifice rotates posteriorly relative to the lower pole orifice and assumes a more caudal and medial position. Weigert and Meyer recognized the regularity of this relationship between upper and lower pole ureteral orifices, which has come to be known as the *Weigert-Meyer rule*. **According to this concept, an abnormally lateral lower pole ureteral orifice may result from a ureteric bud arising too low on the nephric duct, therefore resulting in premature incorporation and migration within the developing bladder.** In such a ureteral orifice, vesicoureteral reflux is more likely to occur due to an inadequate intramural tunnel. **In contrast, an abnormally caudal upper pole ureteral orifice may result from a ureteric bud arising too high on the nephric duct.** It may drain at the bladder neck and verumontanum or remain connected to the nephric (wolffian) duct derivatives such as the vas deferens in males (Mackie and Stephens, 1977; Schwarz and Stephens, 1978). In females, the ectopic upper pole ureter may insert into the remnants of the nephric ducts (e.g., Gartner duct cyst) or vaginal vestibule (Fig. 111–17).

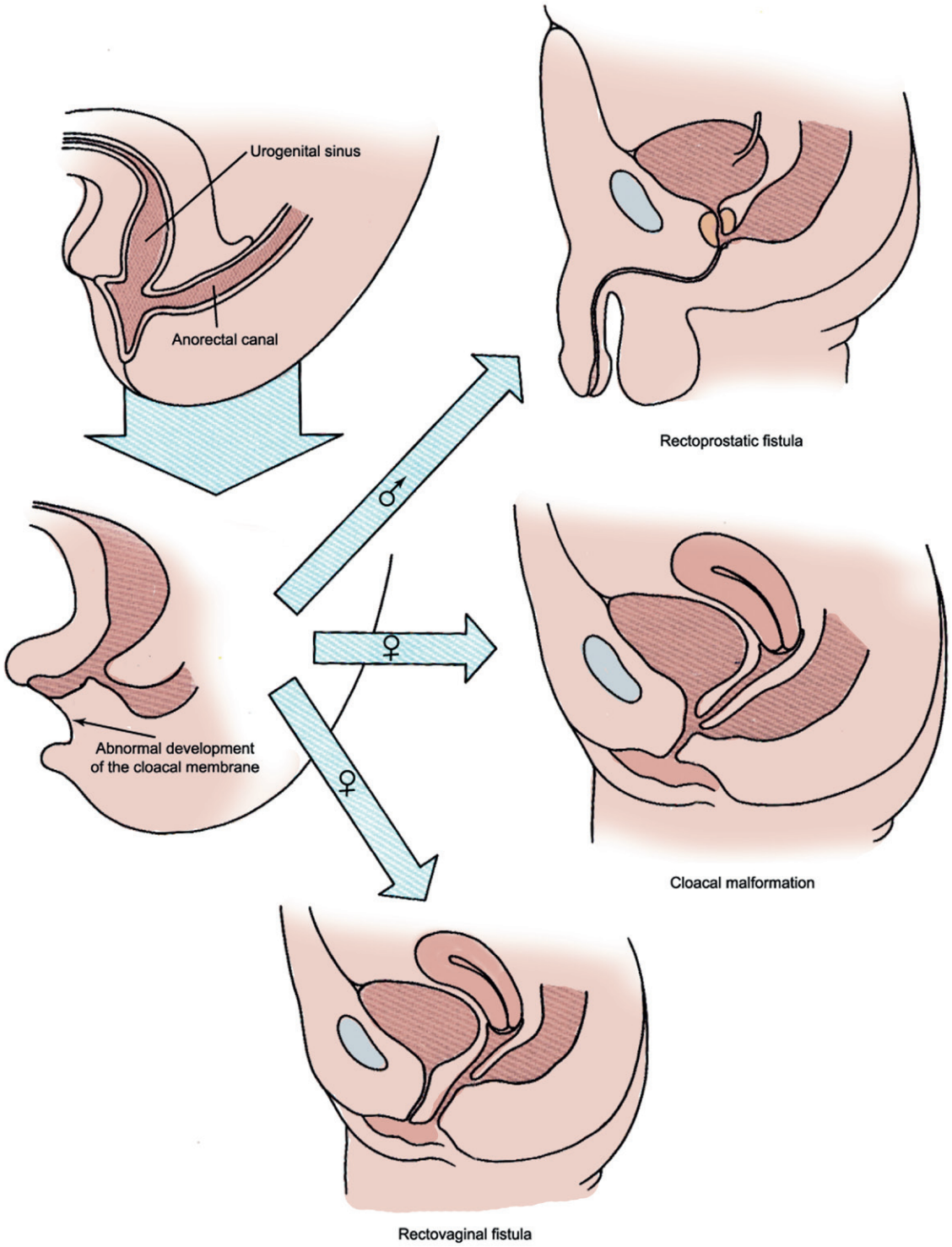


Figure 111–16. Abnormal development of cloacal membrane results in characteristic anomalies of the urogenital and lower gastrointestinal tract. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

Anomalous development of the common excretory duct may lead to an ectopic vas deferens. In certain clinical situations the vas deferens is connected to the ureter rather than the verumontanum, so that both the ureter and vas drain into a common duct. This situation may occur when the ureteric bud arises too high on the nephric duct and the subsequent common excretory duct becomes too long, resulting in incomplete absorption into the developing bladder. This anomaly, although rare, should be kept in mind when evaluating males with recurrent epididymitis and ipsilateral hydronephrosis.

Development of the Ureter

In contrast to the previous discussion regarding the molecular aspects of renal development, little is understood at the molecular level concerning the events of ureteral development. There is only

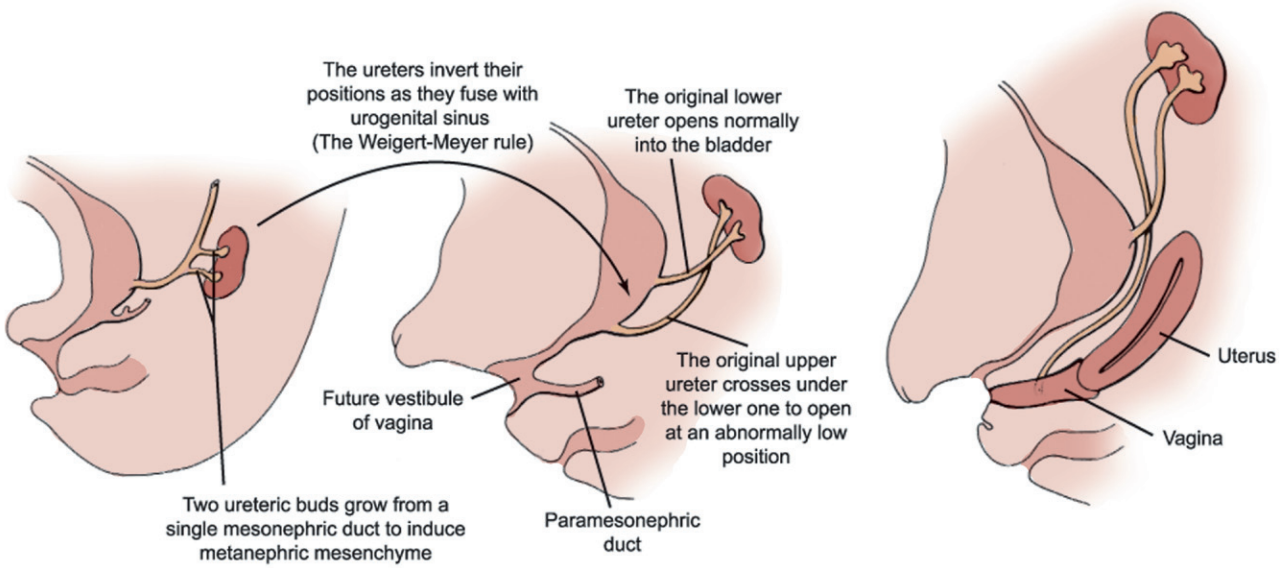


Figure 111–17. Development of an ectopic upper pole ureter draining into the vagina. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

a small amount of descriptive information and speculative theories regarding the molecular mechanism of smooth muscle cell and urothelial differentiation. Morphologically, the ureter begins as a simple cuboidal epithelial tube surrounded by loose mesenchymal cells that acquires a complete lumen at 28 days of gestation in human. It was suggested that the developing ureter undergoes a transient luminal obstruction between 37 and 40 days' gestation and subsequently recanalizes (Alcaraz et al, 1991). It appears that this recanalization process begins in the midureter and extends in a bidirectional manner both cranially and caudally. In addition, another source of physiologic ureteral obstruction may exist as the Chwalla membrane, a two-cell-thick layer over the ureteral orifice that is seen between 37 and 39 days' gestation. In humans, urine production is followed by proliferative changes in the ureteral epithelium (bilaminar by 10 weeks of gestation). The epithelium attains a transitional configuration by 14 weeks. The first signs of ureteral muscularization and development of elastic fibers are seen at 12 weeks of gestation. In both rat and human the ureteral smooth muscle phenotype appears later than that of the bladder. Smooth muscle differentiation is first detected in the subserosal region of the bladder dome and extends toward the bladder base and urethra, whereas smooth muscle differentiation of the ureter occurs later within the subepithelial region in the ureterovesical junction, ascending toward the intrarenal collecting system (Baker and Gomez, 1998). In the embryonic ureter and bladder it is likely that epithelial-mesenchymal interactions are important in the development of urothelium, lamina propria, and muscular compartments, but the exact nature of this induction process is unknown. Before 10 weeks of gestation elastic fibers are few in number, poorly developed, and randomly arranged. After 12 weeks these fibers become more numerous throughout the ureter and are seen with specific orientation (Escala et al, 1989).

Although more than 30 genes are found to be involved in the development of mammalian kidneys, only a few genes have been thus far demonstrated to concurrently cause both kidney and ureteral anomalies—*Agtr2, Bmp4, FoxC1, Pax2,* and *Eya1* (see Molecular Mechanism of Kidney Development, earlier). A mutation of *PAX2* gene has been identified in a human family carrying renal coloboma syndrome, a rare autosomal dominant syndrome characterized by optic nerve coloboma, renal anomalies, and vesicoureteral reflux (Sanyanusin et al, 1996). *EYA1* is mutated in patients with dominantly inherited disorder, branchio-oto-renal syndrome, which includes a duplex collecting system, renal hypoplasia/dysplasia, and renal agenesis (Abdelhak et al, 1997). Pax2 is required for the growth and elongation of nephric ducts prior to ureteric bud formation, whereas Eya1 appears to regulate the GDNF expression, which is a prerequisite for ureteric bud outgrowth. Bmp4 and FoxC1 appear to play a suppressive role in the ureteric bud outgrowth.

The renin-angiotensin system is present and active during fetal life. It is generally thought that the major role of this system in the fetus is to maintain fetal glomerular filtration and to ensure an adequate urine production (Lumbers, 1995). There is growing evidence, however, that the renin-angiotensin system is also important for normal growth and development of the kidney and ureter. The kidney is able to produce all components of this system, and thus the local (intrarenal) production of angiotensin II may play a critical role in this regard. Renin mRNA is detectable in the human mesonephros at about 30 days of gestation and in the metanephros at about 56 days of gestation (Schutz et al, 1996). A similar profile of expression is seen for angiotensinogen and angiotensin-converting enzyme (ACE). Mutant mice lacking ACE are found to have abnormal renal vasculature and tubules as well as increased renin synthesis in interstitial and perivascular cells (Hilgers et al, 1997). Pharmacologic inhibition of ACE in the neonatal rat produces irreversible abnormalities in renal function and morphology (Guron et al, 1997), supporting that an intact renin-angiotensin system is crucial for normal kidney development and maturation. In addition to the high rate of fetal loss, infants born to human mothers treated with ACE inhibitors during pregnancy have increased rates of oligohydramnios, hypotension, and anuria (Shotan et al, 1994; Sedman et al, 1995).

Both subtypes of angiotensin II receptors, AT1 and AT2, are expressed in the developing mesonephros and metanephros. AT2 expression predominates in the undifferentiated mesenchymal cells that surround the nephric duct at the time of ureteric bud outgrowth and declines with maturation, and this pattern of

expression suggests AT2's role in embryonic renal development. AT1 is expressed in more differentiated structures and may be involved in modulating later stages of renal vascular development and acquisition of classic angiotensin II–mediated effects of vasoconstriction and sodium reabsorption. The function of AT2 receptor is not defined completely, but when its gene, *Agtr2,* was inactivated genetically in mice these mutants demonstrated a significant incidence of anomalies in the kidney and urinary tract. Abnormal phenotype in these mice mimicked all the key features of human congenital anomalies of the kidney and urinary tract, such as ureteropelvic junction obstruction, hypoplastic kidney, vesicoureteral reflux, megaureter, and duplicated collecting system (Nishimura et al, 1999).

Because of its embryonic expression pattern, it was initially speculated that AT2 might play a role in regulating the initial outgrowth of the ureteric bud. Analysis of whole tissue sections showed that ectopic ureteric budding occurred in *Agtr2*-deficient mutant mice (Oshima et al, 2001). It was thus postulated that similar to Bmp4, AT2 might have a role in directing the site of ureteric bud outgrowth through its inhibitory effect. In other words, a defect in this process may lead to an abnormal timing and location of the ureteric bud outgrowth, resulting in congenital ureteral anomalies.

Recent evidence suggest that BMPs control formation of smooth muscle in the proximal ureter and pelvis. BMP4, expressed in the caudal mesenchyme cells, induces ureteral morphogenesis including smooth muscle differentiation and urothelial development (Brenner-Anantharam et al, 2007). Consistent with such a role, *Bmp4*- and *Bmp5*-mutant mice display hydronephrosis and hydroureter (Miyazaki et al, 2003).

Development of the Bladder and Continence Mechanism

By the 10th week of gestation the bladder is a cylindrical tube lined by a single layer of cuboidal cells surrounded by loose connective tissue. The apex tapers as the urachus, which is contiguous with the allantois. By the 12th week the urachus involutes to become a fibrous cord, which becomes the *median umbilical ligament.* The bladder epithelium consists of bilayered cuboidal cells between the 7th and 12th weeks, and it begins to acquire mature urothelial characteristics between the 13th and 17th weeks. By the 21st week it becomes four- to five-cell layers thick and demonstrates ultrastructural features similar to the fully differentiated urothelium. Between the 7th and 12th weeks the surrounding connective tissues condense and smooth muscle fibers begin to appear, first at the region of the bladder dome and later proceeding toward the bladder base. Collagen fibers first appear in the lamina propria and then later extend into the deeper wall between the muscle fibers (Newman and Antonakopoulos, 1989).

Bladder compliance is thought to change during development. When studied in whole organ preparation using fetal sheep bladders, bladder compliance is very low during early gestation and increases gradually thereafter (Coplen et al, 1994). The mechanism of these changes in bladder compliance is not known but may involve alterations in both smooth muscle tone and connective tissue composition. This phenomenon is also observed in developing human bladders (Kim et al, 1991). During gestation the bladder wall muscle thickness increases and the relative collagen content decreases. The ratio of thick-to-thin collagen fibers also decreases, whereas the amount of elastic fibers increases. These changes in compliance seem to coincide with the time of fetal urine production, suggesting a possible role for mechanical distention (Baskin et al, 1994). Using fetal mouse bladders as organ culture explants, bladder distention promoted a more orderly development of collagen fiber bundles within the lamina propria in comparison to decompressed bladder explants, suggesting that mechanical factors from accumulating urine may play a role during bladder development (Beauboeuf et al, 1998).

Similar to other organ development, the epithelial-mesenchymal inductive interactions appear to be necessary for orderly differentiation and proper development of the bladder. A modified Grobstein technique was applied to study the mechanism of bladder smooth muscle cell differentiation (Baskin et al, 1996). Undifferentiated rat bladder epithelial and mesenchymal rudiments were separated before bladder smooth muscle cell differentiation and then recombined to grow within the immunologically compromised host (athymic nude mouse). In the presence of epithelial cells, the mesenchymal cells differentiated into smooth muscle cells with sequential expression of appropriate smooth muscle markers, whereas in the absence of epithelial cells they involuted with evidence of apoptosis.

No functional study has been done to assess fetal continence mechanism. Only a handful of ontogenic descriptions are available using human fetal specimens, providing a basis for speculative theories. A mesenchymal condensation forms around the caudal end of the urogenital sinus after the division of the cloaca and the rupture of the cloacal membrane. Striated muscle fibers can be seen clearly by the 15th week. At this time the smooth muscle layer becomes thicker at the level of bladder neck and forms the inner part of the urethral musculature. The urethral sphincter, composed of central smooth muscle fibers and peripheral striated muscle fibers, develops in the anterior wall of the urethra (Bourdelat et al, 1992). Beyond this point, sexual dimorphism develops in conjunction with the formation of the prostate in males and the vagina in females (Tichy, 1989). The urethral sphincter muscle fibers extend to the posterior wall of the urethra. In males these fibers project to the lateral wall of the prostate, whereas in females the muscle fibers attach to the lateral wall of the vagina.

GENITAL AND REPRODUCTIVE TRACT DEVELOPMENT

Formation of Genital Ridges and Paramesonephric Ducts

During the fifth week, primordial germ cells migrate from the yolk sac along the dorsal mesentery to populate the mesenchyme of the posterior body wall near the 10th thoracic level (Fig. 111–18). **In both sexes the arrival of primordial germ cells in the area of future gonads serves as the signal for the existing cells of the mesonephros and the adjacent coelomic epithelium to proliferate and form a pair of *genital ridges* just medial to the developing mesonephros** (Fig. 111–19). During the sixth week the cells of the genital ridge invade the mesenchyme in the region of future gonads to form aggregates of supporting cells called the *primitive sex cords*. The primitive sex cords will subsequently invest the germ cells and support their development. The genital ridge mesenchyme containing the primitive sex cords is divided into the cortical and medullary regions. Both regions develop in all embryos, but after the sixth week they pursue different fates in the male and female.

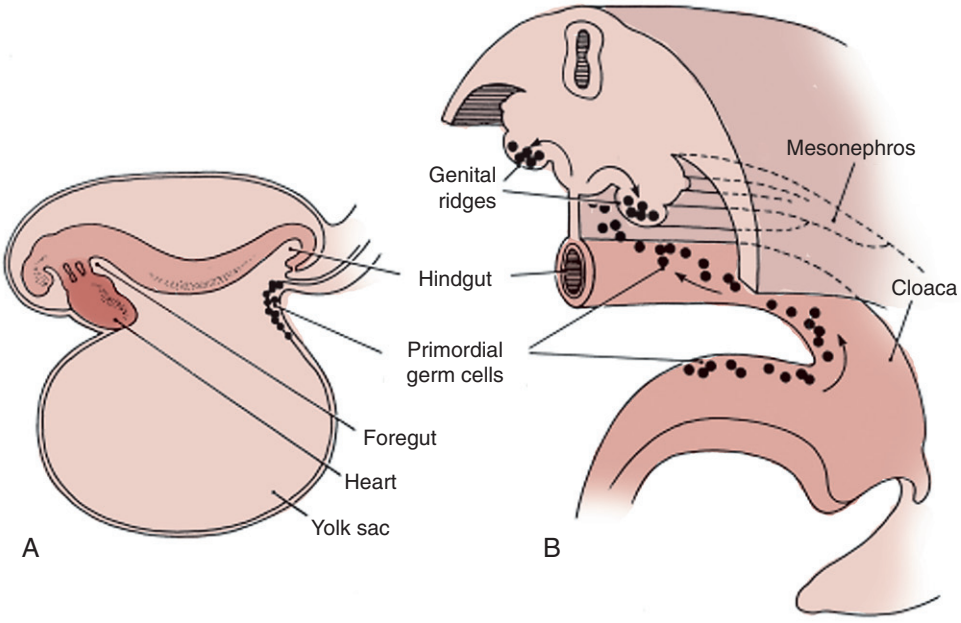


Figure 111–18. **A,** The site of the primordial germ cell origin in the wall of the yolk sac in a 3-week-old embryo. **B,** Migratory path of the primordial germ cells along the wall of the yolk sac and dorsal mesentery into the developing genital ridges. (Modified from Sadler TW. Langman's medical embryology. Baltimore: Williams & Wilkins; 1985.)

During this time a new pair of ducts, called the *paramesonephric (müllerian) ducts,* begins to form just lateral to the nephric ducts in both male and female embryos (Fig. 111–20). These ducts arise by the craniocaudal invagination of thickened coelomic epithelium, extending all the way from the third thoracic segment to the posterior wall of the developing urogenital sinus. The caudal tips of the paramesonephric ducts adhere to each other as they connect with the urogenital sinus between the openings of the right and left nephric ducts. The cranial ends of the paramesonephric ducts form funnel-shaped openings into the coelomic cavity, which is the future peritoneum.

Development of Male Genital Structures

Under the influence of *SRY* (the *S*ex-determining *R*egion of the *Y* chromosome), cells in the medullary region of the primitive sex cords begin to differentiate into *Sertoli cells,* while the cells of the cortical sex cords degenerate. Sex cord cells differentiate into Sertoli cells only if they contain the SRY protein; otherwise the sex cords differentiate into ovarian follicles. During the seventh week, the differentiating Sertoli cells organize to form the *testis cords*. At puberty these testis cords associated with germ cells undergo canalization and differentiate into seminiferous tubules. Direct cell-to-cell contact between developing Sertoli cells and primordial germ cells is thought to play a key role in the proper development of male gametes. This interaction occurs shortly after the arrival of the primordial germ cells in the presumptive genital ridge. The testis cords distal to the presumptive seminiferous tubules also develop lumen and differentiate into a set of thin-walled ducts called the *rete testis*. Just medial to the developing gonad the tubules of rete testis connect with 5 to 12 residual tubules of nephric ducts, called *efferent ductules*. The vas deferens also develops from the nephric duct. At this time the testis begins to become round, reducing its area of contact with the surrounding mesonephros. As the testis continues to develop the degenerating cortical sex cords become separated from the coelomic (peritoneal) epithelium by an intervening layer of connective tissue called the *tunica albuginea* (see Fig. 111–20).

As the developing Sertoli cells begin their differentiation in response to the SRY protein they also begin to secrete a glycoprotein hormone called *müllerian-inhibiting substance* (MIS). MIS causes the paramesonephric (müllerian) ducts to regress rapidly between the 8th and 10th weeks. **Small müllerian duct remnants can be detected in the developed male as a small tissue protrusion at the superior pole of the testis, called the *appendix testis,* and as a posterior expansion of the prostatic urethra, called the *prostatic utricle.*** In female embryos, MIS is absent; therefore the müllerian ducts do not regress. Occasionally, genetic males have persistent müllerian duct structures (uterus and fallopian tubes), a condition known as *hernia uteri inguinale*. In these individuals either MIS production by Sertoli cells is deficient or the müllerian ducts do not respond to normal MIS levels.

During the 9th and 10th weeks, Leydig cells differentiate from mesenchymal cells of the genital ridge in response to the SRY protein. These endocrine cells produce testosterone. At an early stage of development testosterone secretion is regulated by placental chorionic gonadotropin, but eventually the pituitary gonadotropins assume control of androgen production. Between the 8th and 12th weeks, testosterone secretion by Leydig cells stimulates the nephric (wolffian) ducts to transform into the vas deferens. The cranial portions of the nephric ducts degenerate, leaving a small remnant of tissue protrusion called the *appendix epididymis,* and the region of nephric ducts adjacent to the presumptive testis differentiate into the epididymis. During the 9th week, 5 to 12 nephric ducts in the region of the epididymis make contact with the sex cords of the future rete testis. It is not until the third month, however, that these tubules actually establish communication with the rete testis as the efferent ductules. Meanwhile, the nephric duct–derived tubules near the inferior pole of the developing testis degenerate, sometimes leaving a remnant of tissue protrusion called the *paradidymis*.

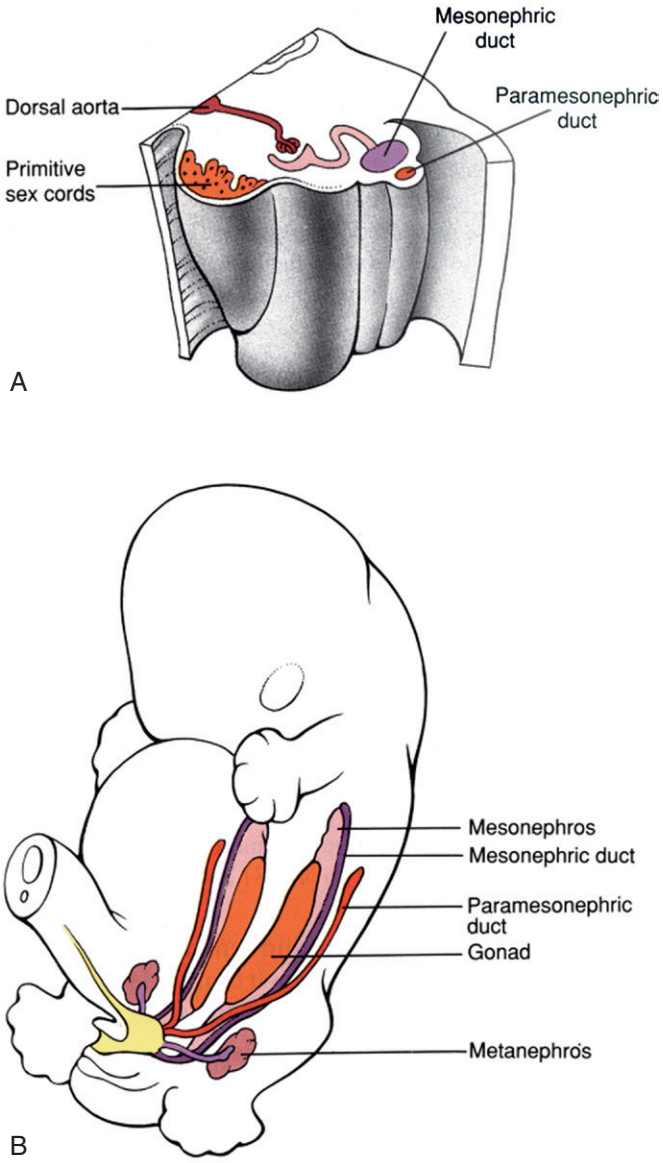


Figure 111–19. Formation of genital ridges and paramesonephric ducts. **A,** During the fifth and sixth weeks the genital ridges form in the posterior abdominal wall just medial to the developing mesonephros. The primordial germ cells induce the coelomic epithelial cells lining the peritoneal cavity and the cells of the mesonephros to proliferate and form the primitive sex cords. **B,** During the sixth week, the paramesonephric ducts develop lateral to the mesonephros. The caudal tips of the paramesonephric ducts fuse with each other as they connect with the urogenital sinus. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

Prostate and Seminal Vesicle Development

The seminal vesicles sprout from the distal nephric ducts, whereas the prostate and bulbourethral glands develop from the urogenital sinus (Fig. 111–21). They therefore have different embryologic origins. **The initial event in prostatic development is an outgrowth of solid epithelial cords from the urogenital sinus epithelium into the surrounding mesenchyme during weeks 10 to 12 of gestation.** This prostatic bud growth and subsequent branching morphogenesis occur in a specific spatial pattern that eventually establishes the lobar subdivisions of the mature prostate gland (Sugimura et al, 1986; Timms et al, 1994). The solid prostatic ducts are subsequently canalized from their urethral connections, proceeding distally toward the ductal tips. As the solid epithelial cords canalize, the epithelium organizes itself into two distinct cell types—luminal and basal cells (Hayward et al, 1996). At this time the prostatic mesenchyme differentiates into a layer of smooth muscle cells that surround the prostatic ducts (Hayward et al, 1996). At puberty, corresponding to a rise in circulating testosterone, the prostate size increases rapidly, along with functional cytodifferentiation of luminal cells, as evidenced by the expression of prostate-specific secretory proteins (Hayward et al, 1996).

Circulating androgens produced by fetal testes play a critical role in the development of the prostate. Cellular responses to circulating androgens are mediated by nuclear androgen receptors that are activated by either testosterone or dihydrotestosterone (DHT). The evidence for the requirement of androgens in establishing the prostate specificity of the urogenital sinus comes primarily from the absence of prostate development in mice and humans that lack functional androgen receptors (Lubahn et al, 1989; He et al, 1991), as well as from the development of the prostate in the female urogenital sinus exposed to androgens (Takeda et al, 1986). In the urogenital sinus, testosterone could activate androgen receptors by directly binding to the receptor and also through a local conversion of circulating testosterone into the more potent DHT by the enzyme 5α-reductase (Russell and Wilson, 1994). DHT has a 10-fold greater affinity for the androgen receptor than testosterone (Deslypere et al, 1992). When 5α-reductase is deficient, the urogenital sinus is specified to become the prostate but the overall prostatic growth and development are severely compromised (Andersson et al, 1991). Tissue recombination and grafting experiments using testicular feminization mice that lack functional androgen receptor have shown that **the presence of androgen receptors in the urogenital sinus mesenchyme is required for prostate specification and differentiation** (Cunha and Lung, 1978). The fact that mesenchymal but not epithelial androgen receptors are required for prostate-specific ductal growth and branching suggests that paracrine signals from the urogenital sinus mesenchyme mediate the action of androgens on the epithelium. Prostate development appears to be affected by the levels of estrogenic compounds as well (vom Saal et al, 1997; Timms et al, 1999), but their specific role has not been fully elucidated.

Prostate development requires inductive and reciprocal interactions between the urogenital sinus epithelium and mesenchyme. In addition to mediating the effect of androgens to the developing prostatic epithelium, paracrine signals from the urogenital sinus mesenchyme also appear to direct lobe-specific patterning of juxtaposed epithelium (Timms et al, 1995). The urogenital sinus mesenchyme when combined with either embryonic or adult bladder epithelium (also a derivative of endodermal cloaca) will stimulate formation of prostatic ducts. In contrast, the urogenital sinus mesenchyme combined with epithelia of other anatomic origins, such as seminal vesicle (a mesodermal derivative), salivary gland, or esophagus, forms tissues with epithelial characteristics that resemble the anatomic origin of the partnering epithelium (Cunha et al, 1987). **These observations suggest that prostate development is spatially restricted by prostate-inducing paracrine signals from the urogenital sinus mesenchyme and that epithelial potential to respond to signals from the urogenital sinus mesenchyme is restricted to the endodermal epithelia of similar**

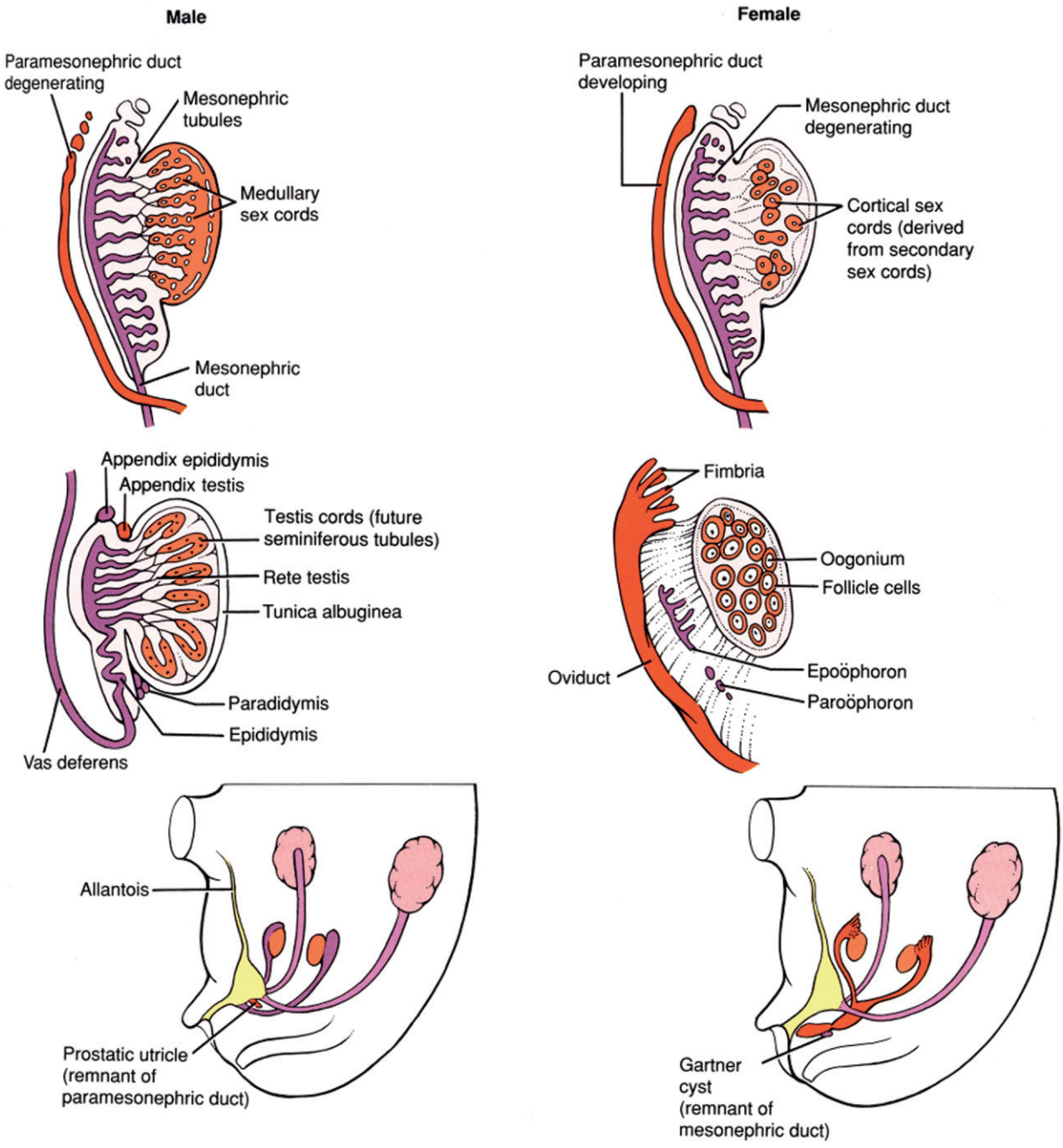


Figure 111–20. Male and female gonad and genital development. The male and female genital structures are virtually identical through the seventh week. In males, SRY protein produced by the Sertoli cells causes the medullary sex cords to become presumptive seminiferous tubules and causes the cortical sex cords to regress. Müllerian-inhibiting substance (MIS), a glycoprotein hormone produced by the Sertoli cells, then causes the paramesonephric ducts to regress, leaving behind appendix testis and prostatic utricle as remnants. Appendix epididymis and paradidymis arise from the mesonephric ducts. In females, cortical sex cords invest the primordial germ cells and become the ovarian follicles. In the absence of MIS, the mesonephric ducts degenerate and the paramesonephric ducts give rise to the fallopian tubes, uterus, and the upper vagina. The remnants of the mesonephric ducts are found in the ovarian mesentery as the epoöphoron and paroöphoron, and in the anterolateral vaginal wall as the Gartner's duct cysts. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

embryonic origin as the prostate. The interactions between epithelium and mesenchyme are reciprocal. The presence of prostate epithelium plays a critical role in the differentiation of mesenchymal cells into the periductal smooth muscle cells (Hayward et al, 1998).

Several candidate genes have been implicated in the prostate development, but the nature of paracrine mesenchymal factors that drive urogenital sinus epithelial transformation into prostatic ducts remains unknown. Furthermore, the precise relationship and the embryologic sequence of these candidate molecules have not been clearly defined. The *Hox* family of homeobox genes may be involved in the proper differentiation of male accessory sex glands, including the prostate (Podlasek et al, 1997, 1999b). In particular, Hoxa-13 and Hoxd-13 transcription factors are expressed in both urogenital sinus and nephric ducts, and the loss of function mutation of these genes in mice results in agenesis of

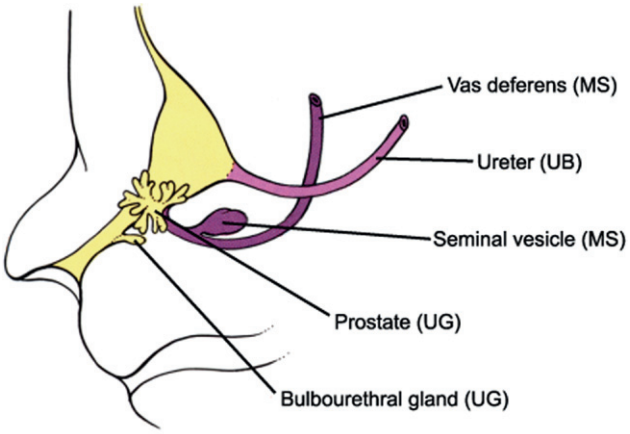


Figure 111–21. Development of male accessory sex glands. During the 10th week, the seminal vesicles sprout from the distal mesonephric ducts in response to testosterone whereas the prostate and bulbourethral glands develop from the urethra in response to dihydrotestosterone. Thus the vas deferens and seminal vesicle derive from the mesonephric ducts (MS) while prostate and bulbourethral glands develop from the urogenital sinus (UG). UB, ureteric bud. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

bulbourethral glands and defective morphogenesis of the prostate and seminal vesicles. Two members of the FGF family of secreted proteins, FGF7 and FGF10, are expressed in the urogenital sinus mesenchyme. In-vitro organ culture experiments have shown that exogenous FGF7 and FGF10 can stimulate proliferation and branching of developing prostate tissue, but these factors do not appear to be androgen responsive (Thomson and Cunha, 1999). There is also evidence that secreted factor activin-A and its antagonistic binding protein follistatin may be important in the regulation of prostate epithelial development (Cancilla et al, 2001). Activin-A is expressed in both urogenital sinus epithelium and mesenchyme, whereas its receptors are found in the epithelium. Follistatin, an activin-A antagonist, is expressed in the urogenital sinus epithelium. Prostatic ductal growth and branching might therefore be a result of balanced interplay between activin-A and follistatin. Other implicated molecules in prostate development include Bmp4 (Lamm et al, 2001), growth hormone receptor (Ruan et al, 1999), insulin-like growth factor-1 (Ruan et al, 1999), Nkx3.1 (Bhatia-Gaur et al, 1999), sonic hedgehog (Podlasek et al, 1999a), P63 (Signoretti et al, 2000), prolactin (Steger et al, 1998), hyaluronan (Gakunga et al, 1997), fucosyltransferase-1 (Marker et al, 2001), and urokinase plasminogen activator (Elfman et al, 2001).

Development of Female Genital Structures

In female embryos the primitive sex cords do not contain the Y chromosome, do not elaborate SRY protein, and therefore do not differentiate into Sertoli cells. In the absence of Sertoli cells and SRY protein, therefore, MIS synthesis, Leydig cell differentiation, and androgen production do not occur. Consequently, male development of the genital ducts and accessory glands is not stimulated and female development ensues. In females the primitive sex cords degenerate and the mesothelium of the genital ridge forms the secondary cortical sex cords. These secondary sex cords invest the primordial germ cells to form the ovarian follicles. The germ cells differentiate into oogonia and enter the first meiotic division as primary oocytes. The follicle cells then arrest further germ cell development until puberty, at which point individual oocytes resume gametogenesis in response to a monthly surge of gonadotropins.

In the absence of MIS and androgens, the nephric (wolffian) ducts degenerate, and the paramesonephric (müllerian) ducts give rise to the fallopian tubes, uterus, and upper two thirds of the vagina. The remnants of nephric ducts are found in the mesentery of the ovary as the *epoöphoron* and *paroöphoron* and near the vaginal introitus and anterolateral vaginal wall as *Gartner duct cysts*. The distal tips of the paramesonephric ducts adhere to each other just before they contact the posterior wall of the urogenital sinus. The wall of the urogenital sinus at this point forms a small thickening called the *sinusal tubercle*. As soon as the fused tips of the paramesonephric ducts connect with the sinusal tubercle the paramesonephric ducts begin to fuse in a caudal to cranial direction, forming a tube with a single lumen. This tube, called the *uterovaginal canal,* becomes the superior portion of the vagina and the uterus. The unfused, superior portions of the paramesonephric ducts become the fallopian tubes (oviducts), and the funnel-shaped superior openings of the paramesonephric ducts become the infundibula.

While the uterovaginal canal is forming during the third month, the endodermal tissue of the sinusal tubercle in the posterior urogenital sinus continues to thicken, forming a pair of swellings called the *sinovaginal bulbs*. These structures give rise to the lower third of the vagina. The most inferior portion of the uterovaginal canal becomes occluded transiently by a block of tissue called the *vaginal plate*. The origin of the vaginal plate is not clear; it may arise from the sinovaginal bulbs, from the walls of the paramesonephric ducts, from the nearby mesonephric ducts, or from a combination of these tissues. The vaginal plate elongates between the third to fifth month and subsequently becomes canalized to form the inferior vaginal lumen (Fig. 111–22).

As the vaginal plate forms, the lower end of the vagina lengthens, and its junction with the urogenital sinus migrates caudally until it comes to rest on the posterior wall of definitive urogenital sinus (future vestibule of the vagina) during the fourth month. An endodermal membrane temporarily separates the vaginal lumen from the cavity of the definitive urogenital sinus. This barrier degenerates partially after the fifth month, but its remnant persists as the vaginal *hymen*. The mucous membrane that lines the vagina and cervix may also derive from the endodermal epithelium of the definitive urogenital sinus.

Development of External Genitalia

Unlike the rest of the developing embryo the cloacal membrane, along with the oropharyngeal membrane (future oral cavity), is a bilayered structure, in which the outer ectoderm remains in close contact with the underlying endoderm without the intervening mesoderm. Initially, the cloacal membrane represents an elongated midline structure, which extends from the root of the umbilical cord to the future site of perineum distally. During the subsequent development **this bilayered cloacal membrane "retracts" into the perineum as a result of cranial and medial migration of mesodermal cells into the anterior body wall between the ectoderm and the endoderm layers of the cloacal membrane.** This mesenchymal migration brings about the closure of the inferior part of the anterior abdominal wall and causes the caudal portion of the cloacal

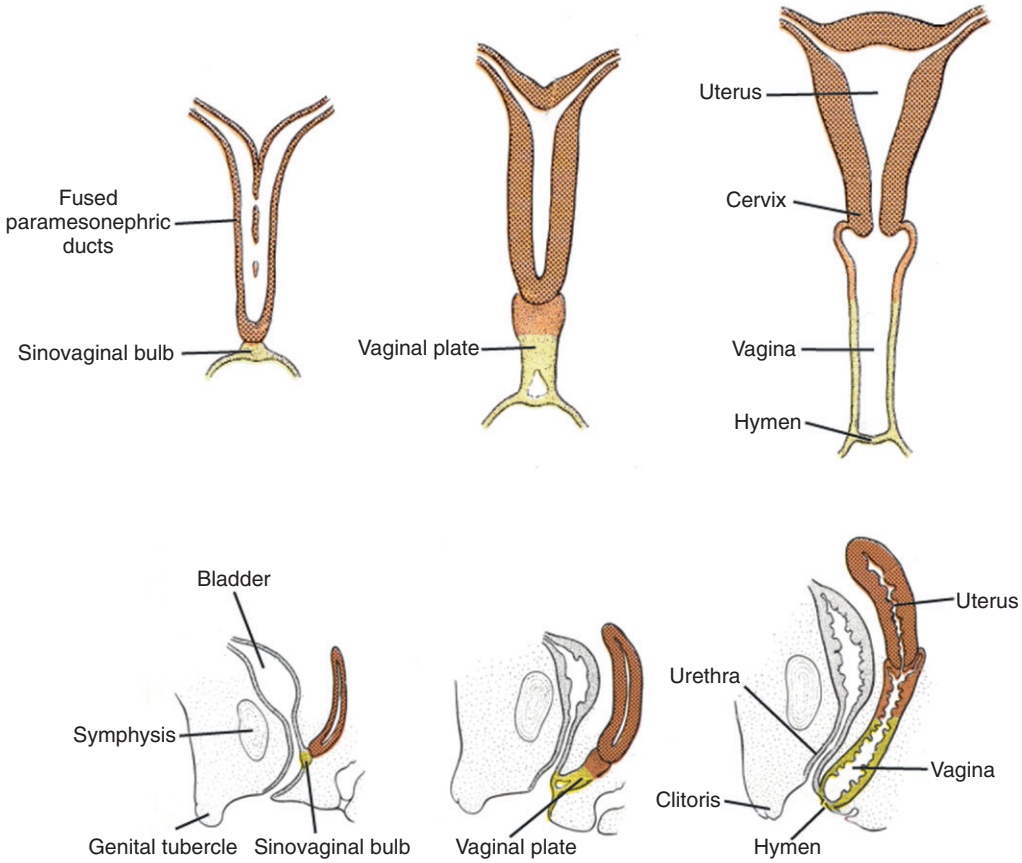


Figure 111–22. Development of uterus and vagina. During the 10th week the paramesonephric ducts fuse at their caudal ends to establish a common channel and come into contact with a thickened portion of the posterior urogenital sinus called the sinovaginal bulb. This is followed by development of the vaginal plate, which elongates between the third to fifth months and becomes canalized to form the inferior vaginal lumen. (Modified from Sadler TW. Langman's medical embryology. Baltimore: Williams & Wilkins, 1985.)

membrane to position itself in the perineal region. These migrating mesodermal cells give rise to the musculature of the medial portion of the anterior abdominal wall, the mesenchymal portion of the anterior bladder wall, the pubic symphysis, and the rudiments of the external genitalia (Vermeij-Keers et al, 1996). Failure of migration of these mesodermal cells into the midline results in bladder exstrophy and other associated genital defects (Langer, 1993; Vermeij-Keers et al, 1996).

The early development of the external genitalia is similar in both sexes. Migrating mesenchymal cells spread themselves around the cloacal membrane and pile up to form swellings. Early in the fifth week, a pair of swellings called *cloacal folds* develops on either side of the cloacal membrane. These folds meet just anterior to the cloacal membrane to form a midline swelling called the *genital tubercle* (Fig. 111–23). During the cloacal division into the anterior urogenital sinus and the posterior anorectal canal the portion of the cloacal folds flanking the opening of the urogenital sinus becomes the *urogenital folds* and the portion flanking the opening of the anorectal canal becomes the *anal folds*. A new pair of swellings, called the *labioscrotal folds,* appears on either side of the urogenital folds.

The most popular hypothesis of external genital and urethral development is based on work performed in the early part of the 20th century. Most embryology texts today quote the mechanism of urethral development proposed by Glenister (1954). As the genital tubercle elongates in males, a groove appears on its ventral aspect (called the *urethral groove*) during the sixth week. In both

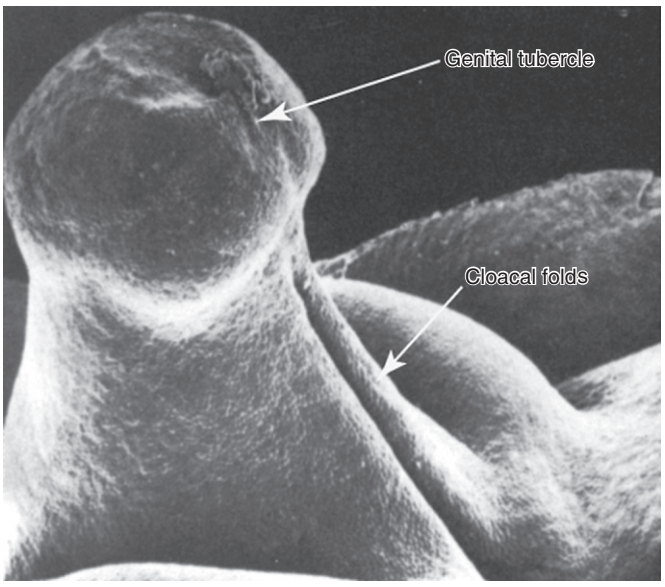


Figure 111–23. The early stages of cloacal fold development. (Reproduced from Hamilton WJ, Mossman HW. Human embryology prenatal development of form and function. New York: Macmillan; 1976; and from Waterman RE. Human embryo and fetus. In: Hafez ESE, Kenemans P, editors. Atlas of human reproduction. Hinghman [MA]: Kluwer Boston; 1982.)

sexes an ectodermal *epithelial tag* is present at the tip of the genital tubercle. The urethral groove is defined laterally by urethral folds, which are continuations of the previous urogenital folds surrounding the urogenital membrane. Initially, the urethral groove extends only part of the way distally along the shaft of the elongating genital tubercle. The distal portion of the urethral groove terminates in a solid epithelial plate called the *urethral plate* that extends into the glans penis. The solid urethral plate canalizes and thus extends the urethral groove distally toward the glans. The urethral groove is thought to be lined by endoderm. Likewise, the solid urethral plate, the distal precursor of the urethral groove, is also believed to derive from the endodermal source. **Clearly, fusion of the urethral folds is the key step in the formation of penile urethra.** A prerequisite of urethral fold fusion is the canalization of solid urethral plate and formation of the urethral groove bounded on each side by the urethral folds. If the urethral groove and urethral fold formations are abnormal, then the urethral fold fusion is likely to be impaired as well (Figs. 111–24 and 111–25).

The formation of the distal glanular urethra may occur by a combination of two separate processes—the fusion of urethral folds proximally and the ingrowth of ectodermal cells distally. It is generally thought that the stratified squamous epithelium of the fossa navicularis results from an ingrowth of surface ectoderm as far proximally as the valve of Guérin. The lacuna magna (also known as the sinus of Guérin), which can give symptoms of hematuria and dysuria in some boys, may form as a result of dorsal extension of this ectodermal ingrowth. It was suggested recently that the entire penile urethra might differentiate from the fusion of the endodermal urethral groove via the mechanism of epithelial-mesenchymal interactions (Kurzrock et al, 1999).

The molecular basis of the sexual dimorphism in genital development is based on the presence or absence of the signaling via the androgen receptor. As the fetal testis produces testosterone, cells within the fetal external genitalia express the enzyme 5α-reductase, which converts testosterone to DHT. Androgen receptors are present in cells of the developing external genitalia and prominently expressed in the genital tubercle mesenchymal cells. The action of DHT acting via androgen receptors masculinizes the developing external genitalia. The key role of androgen in sexually dimorphic development of the external genitalia has been corroborated through many experimental studies. In-utero exposure of rodents to antiandrogenic compounds reduces the size of the genital tubercle and prevents the development of the scrotum. Likewise, in-utero exposure of rats to 5α-reductase inhibitors leads to the development of hypospadias. Mice and humans with functional loss of androgen receptors via mutations demonstrate a complete feminization of the external genitalia.

The elongating phallus is covered externally by ectoderm that gives rise to the penile skin, whereas most of the substance of the penis is derived from mesodermal cells forming the corporeal bodies, connective tissue, and dermis. Corporeal tissue is first recognized as distinct dense mesenchymal condensations within the shaft of the developing penis. Little is known regarding the molecular regulatory mechanisms of the differentiation of penile mesenchyme into its various derivatives, but it is likely that this process is dependent on epithelial-mesenchymal interactions.

In the female, owing to absence of androgen receptor signaling via DHT, the primitive perineum does not lengthen and the labioscrotal and urethral folds do not fuse across the midline. The phallus bends inferiorly, becoming the clitoris, and the ostium of the urogenital membrane becomes the vestibule of the vagina. The urethral folds become the labia minora, and the labioscrotal folds become the labia majora. The external genitalia develop in a similar manner in genetic males who are deficient in 5α-reductase and therefore lack DHT.

Gonadal Descent

Morphologically, the human urogenital ridge is identical in both sexes at 7 to 8 weeks of gestation. **Before gonadal differentiation, the testis lies near the developing kidney, loosely held in place by two ligamentous structures. The dorsal ligament is referred to as the *cranial suspensory ligament* (CSL), whereas the ventral ligament later develops into the *gubernaculum*** (Fig. 111–26). Between 10 and 15 weeks, the testis remains close to the future inguinal region during the enlargement of the abdominal cavity while the ovary moves more cranially. **The testis is anchored near the inguinal region by enlargement of the gubernaculum and regression of the CSL.** As early as the 1700s, enlargement of the gubernaculum in males was observed to tether the testis near the groin while the kidney migrated cranially (Wyndham, 1943; van der Schoot, 1993). In females, the CSL continues to develop, keeping the ovary close to the kidney while the gubernaculum involutes. In males, androgen induces resorption of the CSL while the gubernaculum enlarges to become a plump ligamentous body, "holding" the testis close to the inguinal region. Starting in the seventh month, the gubernaculum begins to bulge beyond the external inguinal ring and descends to the scrotal location, while simultaneously it is hollowed out by the evaginating peritoneal diverticulum called the *processus vaginalis* (Heyns, 1987). The processus vaginalis allows the intra-abdominal testis to exit the abdominal cavity. The bulky distal end of the gubernaculum (known as the *bulb*) is resorbed in humans after completion of inguinoscrotal migration.

Caudal enlargement of the gubernaculum during the early relative transabdominal movement of the testis is known as the "swelling reaction" or "gubernacular outgrowth." The proximal gubernacular cord appears to shorten during this process, as it becomes incorporated into the enlarging bulb (Wensing, 1986). Shortening of the cord may be an important mechanism to position the testis over the inguinal ring to permit abdominal pressure to push the testis out of the abdomen (Quinlan et al, 1988; Attah and Hutson, 1993; Husmann and Levy, 1995). Transection of the gubernacular cord can lead to either accidental testicular descent into the contralateral inguinal canal or aberrant intra-abdominal location (Frey and Rajfer, 1984; Beasley and Hutson, 1988; Attah and Hutson, 1993).

Although intra-abdominal pressure may not be a factor during the initial transabdominal descent, it is thought to be important during transit through the inguinal canal and the subsequent scrotal migration. Inguinoscrotal descent requires migration of the gubernaculum over a considerable distance, along with an increase in the length of the processus vaginalis. The force for movement may come from the intra-abdominal pressure, transmitted directly and indirectly to the testis via the lumen of the processus vaginalis and the gubernacular cord, respectively.

Although patients with defective androgen production or metabolism show varied manifestations of cryptorchidism, the exact role of androgen in testicular descent still remains unclear. During intra-abdominal testicular descent, androgen appears to

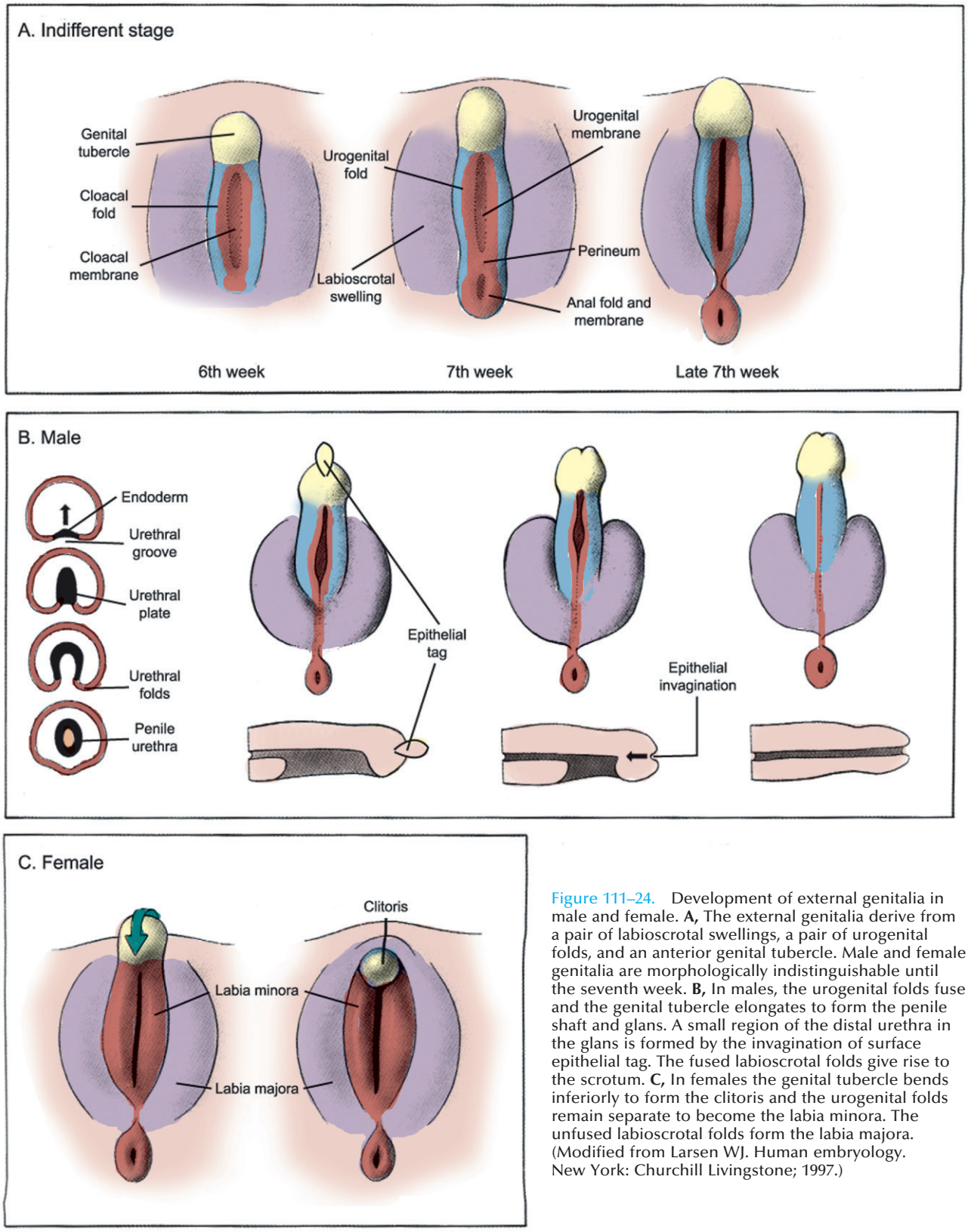


Figure 111–24. Development of external genitalia in male and female. **A,** The external genitalia derive from a pair of labioscrotal swellings, a pair of urogenital folds, and an anterior genital tubercle. Male and female genitalia are morphologically indistinguishable until the seventh week. **B,** In males, the urogenital folds fuse and the genital tubercle elongates to form the penile shaft and glans. A small region of the distal urethra in the glans is formed by the invagination of surface epithelial tag. The fused labioscrotal folds give rise to the scrotum. **C,** In females the genital tubercle bends inferiorly to form the clitoris and the urogenital folds remain separate to become the labia minora. The unfused labioscrotal folds form the labia majora. (Modified from Larsen WJ. Human embryology. New York: Churchill Livingstone; 1997.)

play a role in the regression of the CSL (van der Schoot, 1992). Gubernacular enlargement, in contrast, seems to occur independent of androgen activity, because it occurs in androgen-resistant mice and humans normally, being able to keep the testis close to the inguinal region (Hutson, 1985). The second migratory step—the inguinoscrotal phase—is thought to be more androgen dependent. Migration of the gubernaculum beyond the inguinal region is absent in gonadotropin-deficient mice (Grocock et al, 1988) and those with complete androgen resistance (Hutson, 1986). Regression of the gubernacular bulb after the completion

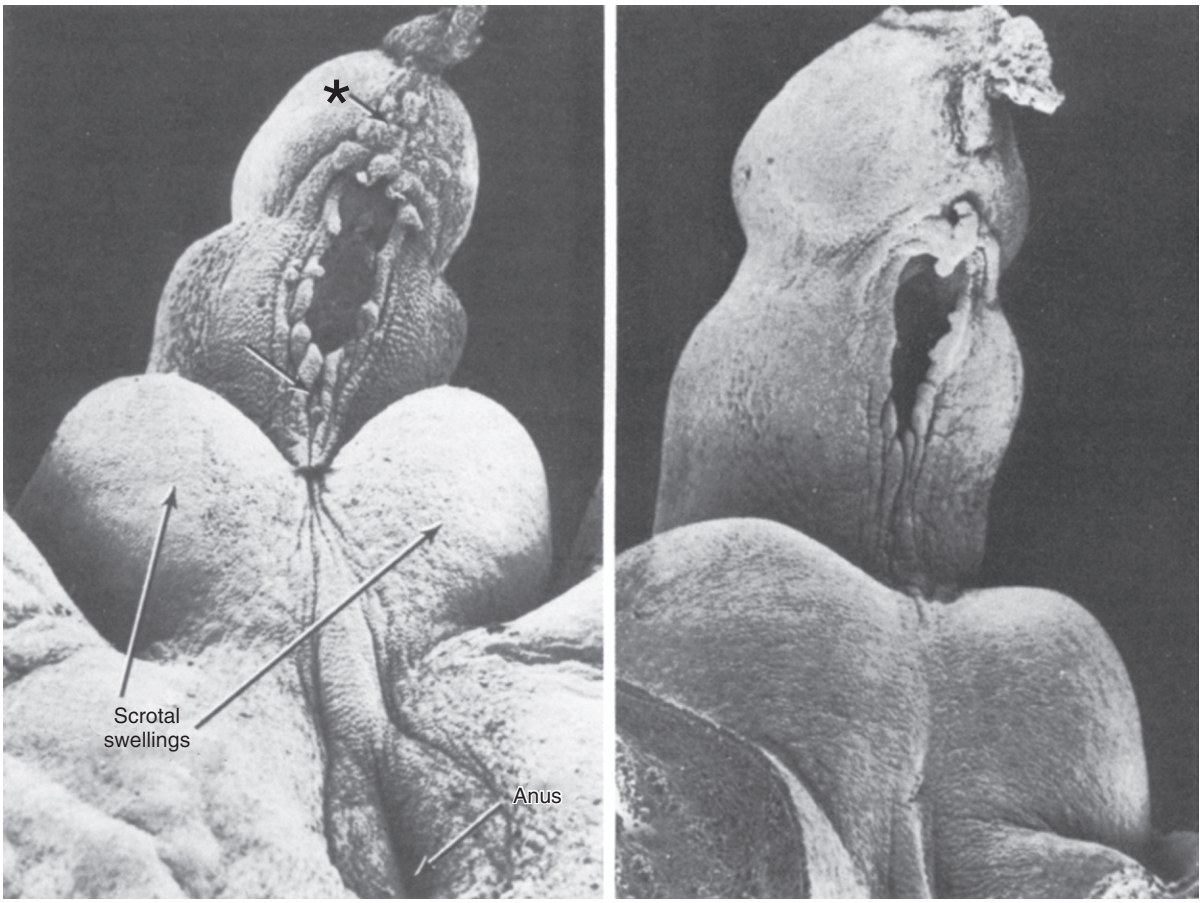


Figure 111–25. The epithelial tag *(asterisk)* and fusing urethral folds *(arrows)* in the developing male external genitalia. (Reproduced from Waterman RE. Human embryo and fetus. In: Hafez ESE, Kenemans P, editors. Atlas of human reproduction. Hinghman [MA]: Kluwer Boston; 1982.)

of scrotal descent also appears to be androgen dependent because in humans with androgen resistance the gubernaculum remains enlarged (Hutson, 1986).

Müllerian-inhibiting substance is a glycoprotein produced and secreted by Sertoli cells and is responsible for regression of the müllerian ducts (Josso et al, 1993; Lee and Donahoe, 1993). Evidence for the role of MIS in testicular descent is conflicting. Some clinical observations support the role of MIS, including patients with persistent müllerian duct syndrome caused by genetic defects of MIS or its receptor gene (Josso et al, 1983). In this clinical scenario the testes are undescended and the gubernaculum is thin and elongated. Transgenic mice with MIS deficiency show a variable testicular position depending on their androgenic status: those with normal androgen receptors have normally descended testes whereas those with androgen resistance have completely undescended testes (Behringer et al, 1994). A recent study on MIS-receptor knockout mice, however, failed to show any defect in gubernacular development and testicular positions (Bartlett et al, 2002).

INSL3 was identified as a novel gene product of the Leydig cells in 1993 (Adham et al, 1993). INSL3 is similar in structure to the peptide hormones relaxin or insulin and is expressed in both fetal and adult Leydig cells in a differentiation-dependent manner (Balvers et al, 1998). **Mice lacking a functional *Insl3* gene demonstrate intra-abdominal cryptorchidism but otherwise no obvious defects in other male reproductive organs. More importantly, early surgical correction of the cryptorchidism in these mice can restore normal fertility potential** (Nef and Parada, 1999; Zimmermann et al, 1999). These are important findings because they reflect the phenotype most commonly observed in classic cryptorchidism in humans. Recently, a G protein–coupled receptor—LGR8—has been cloned with binding and functional response to INSL3 in transfected cells (Hsu et al, 2002; Kumagai et al, 2002). Moreover, mutations in this receptor in mice can lead to the development of cryptorchidism and have been linked to a case of cryptorchidism in the human (Overbeek et al, 2001; Gorlov et al, 2002). Treatment of rat gubernacular explant with exogenous INSL3 leads to a rapid growth of the ligament, an effect that synergizes with androgen treatment (Kubota et al, 2002). It was also demonstrated that LGR8 was expressed in the rat gubernaculum (Kubota et al, 2002). Although INSL3 appears to be a good candidate for a responsible gene for cryptorchidism, to date no causative mutations have been identified in the human *INSL3* gene. Furthermore, because INSL3 is expressed in a differentiated testis, any factor that influences Leydig cell differentiation may also affect INSL3 expression and thereby cause cryptorchidism.

Treatment of pregnant mothers with diethylstilbestrol as a hormonal support during pregnancy was abandoned owing to a high rate of cryptorchidism and other genital defects (Stillman, 1982). The effect of environmental xenoestrogenic compounds has also been linked to the recent rise in cryptorchidism in humans (Toppari and Skakkebaek, 1998). In one study, mice were treated with diethylstilbestrol to induce cryptorchidism in male neonates

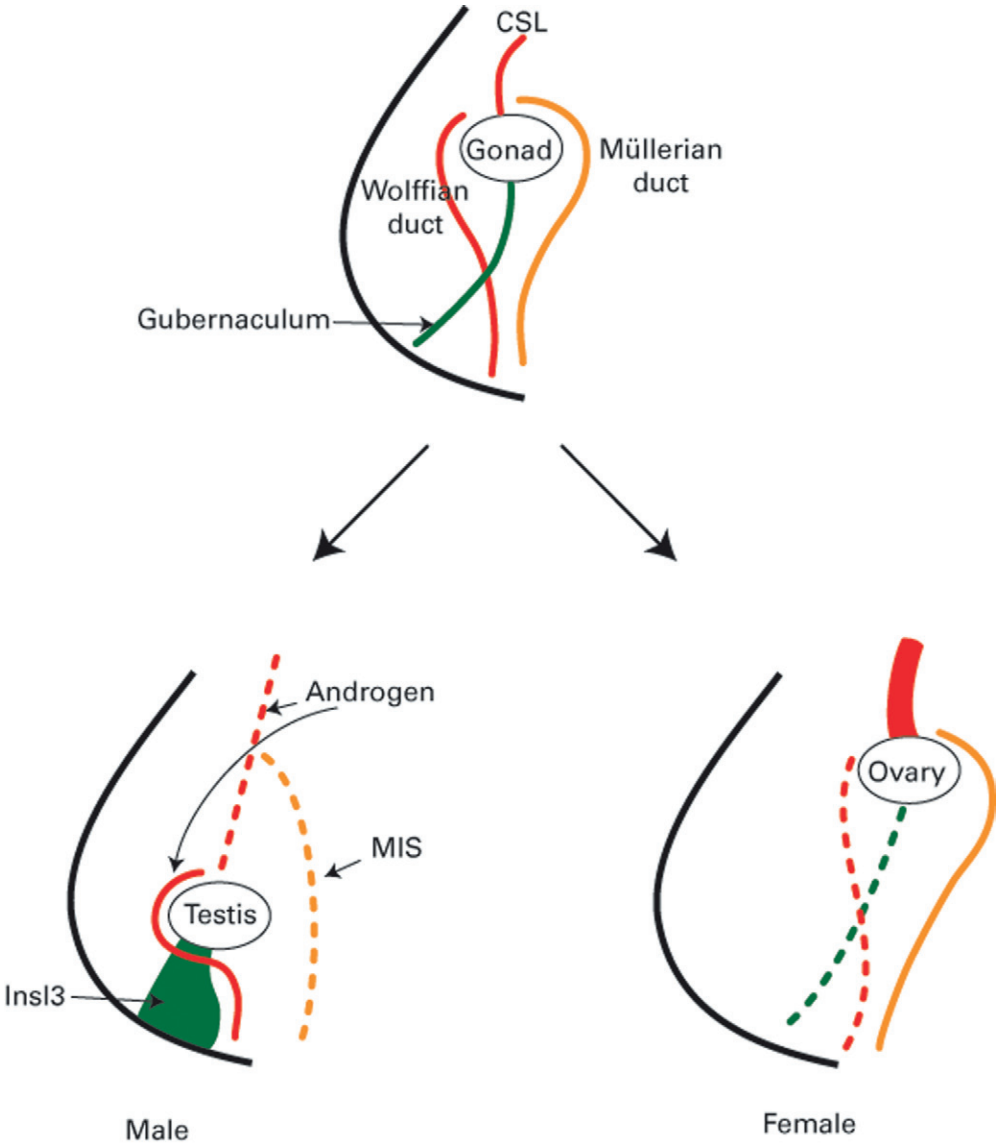


Figure 111–26. Mechanism of gonadal descent. The undifferentiated gonad is initially located high in the abdomen, anchored by the cranial suspensory ligament (CSL). In males, Insl3 will cause the swelling and enlargement of gubernaculum to pull the developing testis toward the inguinal region, whereas androgens will cause an involution of CSL. Owing to the action of müllerian-inhibiting substance (MIS), müllerian ducts will regress while androgens continue to stimulate the development of wolffian ducts into male genital ductal structures. In females, CSL persists due to the absence of androgens and the gubernaculum remains thin due to the absence of Insl3 activity, thereby keeping the ovary well within the pelvis.

(Emmen et al, 2000; Nef et al, 2000). Interestingly, the treated animals demonstrated a complete suppression of testicular *Insl3* expression on embryonic days 16 and 18.

The male knockout mice for the transcription factor *Hoxa-10* gene are viable but infertile. While they are normally virilized, they are bilaterally cryptorchid with severely underdeveloped gubernaculum. Fetal localization studies have shown that *Hoxa-10* is expressed in the gubernaculum, as well as in the kidneys, but not in other reproductive tissues. Although its function and role are not yet established, it appears to be another candidate regulatory gene for gubernacular development and testicular descent.

The spinal nucleus of the genitofemoral nerve (GFN) is located at L1-2 in the spinal cord and is sexually dimorphic (Goh et al, 1994). Transection of GFN produced cryptorchidism (Lewis, 1948), and the initial thought—now proven faulty—was that the cremasteric muscle paralysis caused by denervation led to an abnormal traction of the testis through the inguinal canal. When this observation was revisited many years later it was speculated that androgens may act via the GFN (Beasley and Hutson, 1987). The GFN innervates the gubernaculum from its posterior and caudal surface, so that distal transection would cause denervation of the gubernaculum (Tayakkanonta, 1963). Additional supporting evidence for the role of the GFN comes from the analysis of patients with spina bifida and animals with spinal cord transection (Hutson et al, 1988). In more than 300 boys with spina bifida, 23% had cryptorchidism, with a higher incidence found in those whose defect was higher than L4. In rats with neonatal spinal cord transection, approximately 40% had cryptorchidism when the lesions were midlumbar. Anatomic studies of the GFN identified calcitonin gene–related peptide (CGRP) as the primary neurotransmitter (Goh et al, 1994). The effect of CGRP on the rodent gubernaculum has been studied extensively. In male neonatal rats under

anesthesia the gubernaculum, which has not yet reached the scrotum, contracts rhythmically, and this is enhanced by increased intra-abdominal pressure and direct application of exogenous CGRP (Park and Hutson, 1991). In organ culture, neonatal rat gubernaculum responds to CGRP in a dose-dependent manner but not to other neuropeptides (Park and Hutson, 1991). Although these findings are raising a strong speculation for the role of CGRP, its significance in human testicular descent remains uncertain.

The ovaries also descend and become suspended within the broad ligaments of the uterus. As in males, the female embryos develop a gubernaculum-like structure extending initially from the inferior pole of the gonad to the subcutaneous fascia of the presumptive labioscrotal folds. This "female gubernaculum" later penetrates the abdominal wall as part of a fully formed inguinal canal and becomes the *round ligament*. In females, although the gubernaculum does not shorten like that in males, it still causes the ovaries to descend during the third gestational month (by anchoring the ovaries in the pelvis) and places them into a peritoneal fold (the *broad ligament* of the uterus). This translocation of ovaries appears to occur during the seventh week when the gubernaculum becomes attached to the developing paramesonephric (müllerian) ducts. As the paramesonephric ducts fuse together in their caudal ends they sweep out the broad ligaments and simultaneously pull the ovaries into these peritoneal folds. In the absence of androgens, the female gubernaculum remains intact and grows in step with the rest of the body. The inferior gubernaculum becomes the round ligament of the uterus and attaches the fascia of the labia majora to the uterus, while the superior gubernaculum becomes the ligament of the ovary, connecting the uterus to the ovary. As in males, the processus vaginalis of the inguinal canal is normally obliterated, but occasionally it remains patent to become an indirect inguinal hernia.

Molecular Mechanism of Sex Development

Mammalian sex development involves a complex interplay of multiple cell types, which occurs in a narrow window of time. Thus it is important to understand the temporal and spatial pattern of gene expression as well as the anatomic sequence of tissue movement and differentiation. In both sexes, before the expression of the male-determining gene *SRY,* a number of factors appear to play a role in urogenital ridge specification (Fig. 111–27). Because the urogenital ridge is the primordium for gonad, kidney, and reproductive tract, multiple organs are affected simultaneously by mutations of these genes.

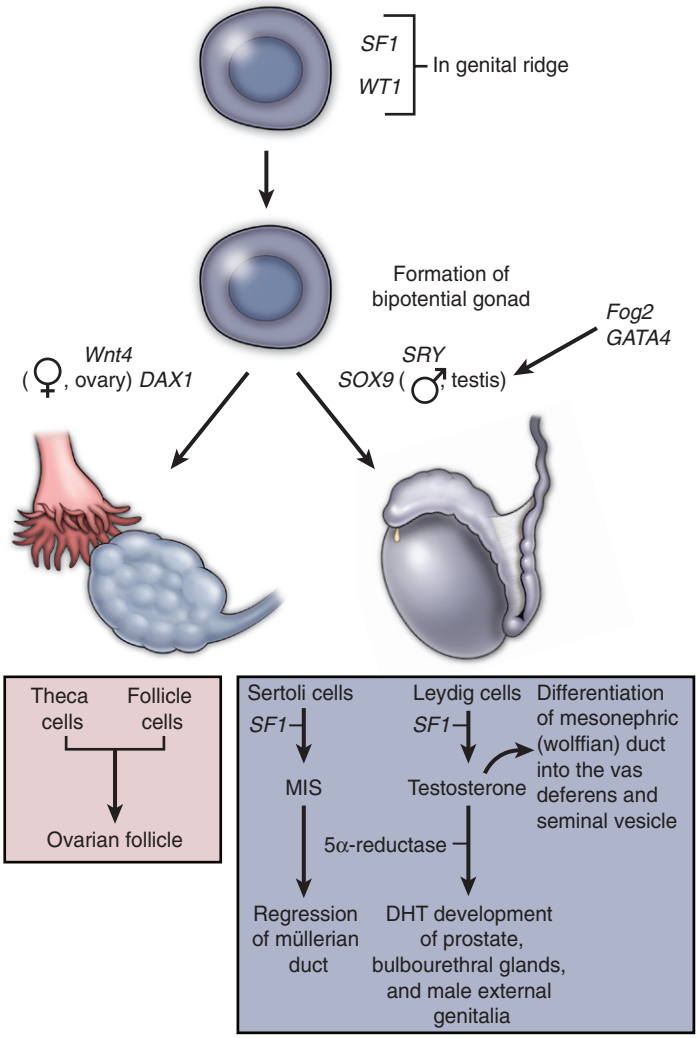


Figure 111–27. Molecular mechanism of male and female genital development. *SF1* and *WT1* expression is critical for genital ridge specification. *SRY* and *SOX9,* influenced by GATA4 and Fog2, are important factors for specifying the differentiation of Sertoli cells. *SF1* is also critical in the regulation of müllerian-inhibiting substance (MIS) and other genes involved in androgen synthesis. No specific female factors have been identified, but *Wnt4* and *DAX1* are expressed with unique female patterns. DNT, dihydrotestosterone.

In the mouse gonad, *Wt1* is expressed early, suggesting a role in specifying coelomic epithelial cells in the development of urogenital ridge. The *Wt1* homozygous knockout mice do not form kidney, adrenal, or gonad cells (Kreidberg et al, 1993). Humans heterozygous for mutations in *WT1* exhibit abnormalities of the genital system in addition to abnormalities in renal development, including WAGR syndrome, Denys-Drasch syndrome, and Frasier syndrome. *WT1* appears to function upstream of *SF1* (steroidogenic factor 1) and *DAX1* (*d*osage-sensitive sex reversal, *a*drenal hypoplasia congenita, *X* chromosome) (Wilhelm and Englert, 2002). *Wt1* and *Sf1* enhance transcription of mouse *MIS* gene, whereas *Dax1* appears to suppress this interaction (Nachtigal et al, 1998). *SF1* also regulates the expression of other genes involved in male differentiation, steroidogenesis, and reproduction (Achermann et al, 2001). Although *SF1* stimulates *DAX1* transcription (Ikeda et al, 1996), *DAX1* in turn acts as a transcriptional repressor of *SF1*-regulated genes (Ito et al, 1997). In *Sf1* knockout mice, neither XX nor XY animals form gonads, and cells in gonadal remnant undergo apoptosis, suggesting that *SF1* is a necessary survival factor for early progenitors of a developing gonad (Luo et al, 1994). Data suggest that *SF1* and *DAX1* are both independently important for normal male gonadal differentiation. Other candidate genes have also emerged based on mouse gene deletion models and embryonic expression studies, although their functional significance in gonadal development is not fully elucidated yet, and they include *M33, Lhx9, Pod1, Dmrt1, Mro, Pn1,* and *Vn1* (Park and Jameson, 2005).

Mammalian embryos remain sexually undifferentiated until the time of sex determination. When the Y-linked master regulatory gene, called *SRY* (the *s*ex-determining *r*egion of the *Y* chromosome), is expressed in the male, the epithelial cells of the primitive sex cords

differentiate into Sertoli cells, and this critical morphogenetic event triggers subsequent testicular development. Once the testes are established they produce androgens to give rise to the male phenotype. In the female gonads no morphologic change is observable at the time of *SRY* expression. It follows from this general picture that in mammals, sex determination is synonymous with testicular development, with the differentiation of Sertoli cells being the key event (McLaren, 1991). After 3 decades of search for the elusive mammalian testis-determining gene, the *SRY* gene was discovered in 1990 by Sinclair and colleagues. Since then, research has focused on identifying the putative regulatory mechanism operating downstream of *SRY* and the genetic control of *SRY* expression.

Although it has been known since 1921 that human males have an X and Y chromosome, the role of these "sex" chromosomes in human sex development was not elucidated until 1959. This question was answered by the examination of two individuals with unique chromosome abnormalities: one female with Turner syndrome (45,XO karyotype) and one male with Klinefelter syndrome (47,XXY karyotype). By 1966, analysis of many structurally aberrant Y chromosomes in humans led to the conclusion that the information necessary to initiate the male phenotypic development was present on the short arm of the Y chromosome. The identity of the protein encoded by the testis-determining region of the Y chromosome proved elusive. In the mid 1980s, the DNA of sex-reversed males with 46,XX karyotype was examined. The genome in these individuals was found to contain small amounts of Y chromosome that had been translocated onto the X chromosome. Analysis of this DNA narrowed the location of the *SRY* to a relatively small region within the short arm of the chromosome. The role of *SRY* in human sex development has been further supported by studies using mice (Greenfield and Koopman, 1996). The comparable genetic locus in mice *(Sry)* is activated and expressed in the genital ridge 11.5 days after coitus, just before the initiation of testicular development. Moreover, when the DNA of female XY mouse chromosomes was analyzed with specific DNA probes for *Sry*, this locus was absent. Most importantly, it has been demonstrated that insertion of *Sry* into one of the X chromosomes of genetically female mouse embryos converted these mice to phenotypic males (Koopman et al, 1991). These transgenic "female" mice exhibited testes, vas deferens, and an absence of the female reproductive tract. It was thought that identification of the SRY protein would rapidly lead to the identity of downstream elements regulating male sexual development. However, the binding of SRY protein to other genes or factors has not been demonstrated, and the molecular mechanism by which genes interact to determine sex remains speculative. Deletions of the *SRY* gene in humans cause XY male-to-female sex reversal, whereas *SRY* translocations to the X chromosome lead to XX female-to-male sex reversal (Harley et al, 2003). In the mouse, *Sry* expression occurs in a narrow temporal window in the developing Sertoli cells. The central region of the gonad demonstrates *Sry* expression first, followed by cephalad to caudal progression along the entire length of the gonad (Bullejos and Koopman, 2001). A closely related gene, *SOX9,* is the other definitive male-determining gene identified thus far. *SRY* and *SOX9* expression overlap in cells of the Sertoli lineage. As the *SRY* expression diminishes, *SOX9* expression increases in the male. *SOX9,* which is weakly expressed in the undifferentiated gonad, is downregulated in the female (Sekido et al, 2004). Transgenic expression of *Sox9* in XX mice is sufficient to induce female-to-male sex reversal and male differentiation (Vidal et al, 2001). Heterozygous human *SOX9* mutation leads to campomelic dysplasia, a severe skeletal disorder with defective cartilage development, and many of these patients have dysgenetic gonads (Foster et al, 1994). These individuals possess a normal *SRY* but may exhibit completely feminized genital structures. *Sox9* knockout mouse embryos have elevated levels of *Sry* expression, suggesting a possible negative feedback regulatory loop that downregulates *Sry* (Chaboissier et al, 2004). *GATA4* and *Fog2* are important in cardiac development but also appear to affect gonadal development as well. *GATA4* mutation eliminates expression of male differentiation markers *Sox9* and MIS. *Fog2* knockout mice have decreased expression of *Sry,* loss of *Sox9, MIS*, and *desert hedgehog,* but persistence of female gonad marker *Wnt4* (Tevosian et al, 2002). Similarly, triple mutants for insulin receptor, insulin-related receptor, and Igf-1 receptor have low *Sry* and *Sox9* expression and exhibit male-to-female sex reversal, implicating a role for an insulin signaling pathway (Nef et al, 2003).

Proliferation of Sertoli progenitor cells is an important event in male gonad development, a process driven by *SRY* expression (Schmahl et al, 2000). One paracrine factor linked to this proliferation is FGF9. *Fgf9* knockout mice demonstrate varying degrees of male-to-female sex reversal (Colvin et al, 2001). In addition, FGF9 is a candidate male gonad-specific chemoattractant paracrine signal that induces migration of cells from the mesonephros (endothelial and peritubular myoid cells) into the gonad (Martineau et al, 1997). Migration of these cells is critical for the development of testis cord formation (Buehr et al, 1993) as well as *SOX9* expression (Tilmann and Capel, 1999). Such migration is absent in females, presumably owing to absence of chemoattractants.

Once sex determination has occurred the subsequent phenotypic differentiation depends mostly on the production of androgens. As bipotential gonad differentiates into testis, Sf1 expression becomes restricted to Leydig cells and mediates expression of several gene-encoding enzymes that are required for testosterone biosynthesis, including StAR, Cyp11a1, Cyp17, and 3βHSD. Factors for Leydig cell determination are not known, and, moreover, Leydig cell origin, whether from immigrant mesonephric cells or progenitors within the gonad, remain speculative. There is evidence that Leydig cell fate is dependent on paracrine signals (Yao et al, 2002; Brennan et al, 2003).

Relatively few genes have been shown to exhibit a female-specific pattern of gene expression early in gonadal development. Thus far, no female-determining gene has been identified. The *DAX1* gene was initially suggested as a pro-ovarian (or antitestis) candidate gene because its duplication on an XY background was associated with impaired testicular development (Bardoni et al, 1994; Swain et al, 1998). However, loss of *DAX1* in XX background does not prevent ovary development (Yu et al, 1998). A growing list of genes demonstrates an ovary-specific expression patterns, including *Fst* and *Stra8* (Park and Jameson, 2005). There has been a postulate for a "Z-factor" that suppresses protesticular events in both XX and XY backgrounds (McElreavey et al, 1993). According to this hypothesis, the Z-factor, which normally suppresses testicular determination, is repressed by *SRY* in males, and in females, owing to absence of *SRY,* it will inhibit testicular development. Loss of Z-factor in XX background will result in female-to-male sex reversal, but gain-of-function in XY background may or may not result in male-to-female sex reversal, depending on whether the Z-factor can override the suppression effect of *SRY*-driven signaling. One candidate for such Z-factor is *Wnt4.* XX mice deficient for *Wnt4* develop testis-like differentiation and nephric (wolffian) duct derivative (Vainio et al, 1999). Curiously, their external genitalia remain female. Furthermore, *Wnt4* is downregulated in males whereas its expression remains strong in females (Yao et al, 2004).

Key Points

- The genitourinary system develops from three embryonic sources: intermediate mesoderm, mesothelium of coelomic (future peritoneum) cavity, and endoderm of the urogenital sinus.
- The urinary system begins its development before the genital system development becomes evident. With the formation of nephric ducts, embryonic kidneys develop sequentially in the order of pronephros, mesonephros, and metanephros.
- The permanent kidney, the metanephros, develops as a result of inductive interactions involving ureteric bud (an outgrowth of nephric duct), condensing blastema of metanephric mesenchyme, and stromal cells. The renal tubulogenesis occurs via mesenchymal-epithelial conversion, whereas dichotomous branching of the ureteric bud leads to the formation of the collecting system.
- The bladder and urethra develop from the endodermal urogenital sinus, which is an anterior portion of the cloaca after it becomes separated from the posterior anorectal canal.
- Morphologically, the genital development takes place about 3 weeks after the start of the urinary system development. Sexual dimorphism begins to take shape at about the seventh gestational week. Primordial germ cells migrate from the wall of the yolk sac to invade the posterior mesenchyme to establish the gonadal ridge.
- In males, driven by the *SRY* gene of the Y chromosome, mesenchymal cells of the developing testis differentiate to become the Sertoli cells. Sertoli cells produce müllerian-inhibiting substance (MIS) to cause degeneration of female müllerian ductal structures, while stimulating the development of testosterone-producing Leydig cells. Under the influence of testosterone, male external genitalia develop, as well as prostate and other male accessory sex glands.
- Both gonads descend to pelvic location by the third month, but the testis descends into the scrotum with the aid of the gubernaculum at about the seventh month.

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chapter
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Renal Functional Development and Diseases in Children

Lane S. Palmer, MD, FAAP, FACS ● Howard Trachtman, MD

Transition from the Fetus to the Infant
Principles of Fluids and Electrolytes
Hematuria
Proteinuria
Glomerular Disease
Renal Tubular Disorders
Urolithiasis and Hypertension
Acute Kidney Injury
Chronic Kidney Disease
Renal Replacement Therapy
Summary

Nephrology and urology are the two disciplines—one medical, the other surgical—devoted to the care of patients with kidney disease. This distinction between the two is often cast in sharp relief as if to imply that they are nonoverlapping fields. However, this misconception is exposed in pediatrics in which the close integration between nephrology and urology is displayed on a nearly daily basis in the wide spectrum of disorders resulting from congenital abnormalities of the genitourinary tract and the complicated impact of these malformations on all aspects of kidney function. The goal of this chapter is to review areas of shared focus with a primary emphasis on clinical aspects, rather than on the basic sciences, and on specific problems to facilitate a productive working collaboration between pediatric urologists and nephrologists.

TRANSITION FROM THE FETUS TO THE INFANT

All aspects of renal function are of limited capacity in the fetus compared with the adult. This is especially true in infants born before 34 weeks' gestation, in whom nephrogenesis is incomplete.

The glomerular filtration rate (GFR) at birth is 10% to 15% of the normal adult value. The decrease in function is caused by three factors: lower intraglomerular perfusion pressure, decreased ultrafiltration coefficient of the filtration barrier, and diminished filtration surface area. Of these three factors the final one is quantitatively the most important and is due to a combination of decreased number and perfusion of the cortical nephrons (Spitzer, 2003). Increased circulating levels of vasoactive hormones such as vasopressin and plasma renin activity and reduced synthesis of vasodilatory factors such as nitric oxide mediate the reduced glomerular blood flow. The reduction in filtration surface is exacerbated in very low–birth-weight infants delivered at 25 to 28 weeks' gestation because the premature delivery curtails the normal process of nephron development and glomerulogenesis (Ichikawa et al, 2002). **In utero obstruction interferes with normal glomerular development and triggers tubular atrophy and interstitial fibrosis.** This is associated with release of profibrotic cytokines such as transforming growth factor-β, macrophage infiltration, and epithelial-to-mesenchymal transformation (Bascands and Schanstra, 2005; Grande and Lopez-Novoa, 2009). Using experimental murine models, in which unilateral ureteral obstruction is created before completion of nephrogenesis, reversal of the obstruction leads to an increased tubular repair, reduced macrophage number, and less collagen accumulation (Cochrane et al, 2005). This suggests that correction of obstructive lesions prenatally could restore normal renal growth and preserve renal function.

Renal sodium handling is impaired in the fetus and infant. This is reflected in a higher fractional excretion of sodium (FE_{Na}) in low-birth-weight infants and even full-term neonates. In part this reflects increased permeability of the proximal and distal tubule. In addition, the response of the distal nephron to antinatriuretic hormones such as aldosterone is impaired. The urinary concentrating capacity is diminished in fetal life and in infants owing to reduced GFR and delivery of filtrate to the diluting segment of the nephron, shorter loops of Henle, and limited response of the collecting tubule to vasopressin. The renal acidification is limited in neonates because of lower sodium-hydrogen exchange in the proximal tubule, decreased bicarbonate reabsorption in the proximal tubule secondary to relative expansion of the extracellular fluid compartment, and reduced expression and activity of the Na^+,K^+-ATPase pump that drives hydrogen ion secretion. **The alterations in sodium and hydrogen balance result in compromised potassium secretion into the final urine.** The potassium retention in neonates is due to an absence of apical secretory potassium channels in the distal tubule and a predominance of the H^+,K^+-ATPase in the apical membrane that mediates potassium reabsorption (Gurkan et al, 2007). The inability to excrete potassium is also the

consequence of reduced number of renal outer medullary potassium (ROMK) channels and diminished potassium recycling in the loop of Henle.

In addition to the short-term impact of premature delivery and low birth weight, these two factors may have important long-term ramifications for kidney health. Beginning in the mid 1980s, reports appeared in the literature indicating that **low-birth-weight infants were at higher risk of developing hypertension and secondary renal diseases such as diabetic nephropathy in adulthood compared with infants of normal weight.** These epidemiologic linkages were strengthened by the detection of a lower number of nephrons in adults with hypertension who died in early adulthood after sudden unexpected accidents. The adverse outcomes have been attributed to the long-term consequences of being born with a diminished number of nephrons—sustained hyperfiltration and glomerular hypertrophy (Barker et al, 2006). The situation is analogous to the case of infants born with a solitary kidney who can develop proteinuria and focal segmental glomerulosclerosis (FSGS) at a relatively young age. The long-term implications of reduced nephron number at birth continue to be a subject of ongoing study (Vikse et al, 2008) and may represent a combined effect of both low birth weight and prematurity. There is uncertainty whether the consequences of low nephron number apply to both boys and girls and to all racial and ethnic groups. Finally, recent data suggest that impaired postnatal growth may exacerbate the maladaptive response to low birth weight (Bacchetta et al, 2009).

The evaluation of kidney function in infants is difficult because of technical problems collecting timed urine samples noninvasively or by bladder catheterization. Thus GFR is generally assessed based on changes in serum creatinine concentration, with the caveat that creatinine concentration in the first few days of life reflects maternal renal function. There are limited data about GFR based on infusion of clearance markers such as iothalamate or iohexol or measurements of serum cystatin C concentration. Tubular sodium handling can be assessed based on the following:

$$FE_{Na} = [\text{Urinary sodium/plasma sodium}] \div [\text{urinary creatinine/serum creatinine}]$$

This determination can be made using a spot urine sample collected at the time of collection of a blood sample. The normal value in neonates and infants is 1% to 3% and can be even higher in very low–birth-weight premature infants. The fractional excretion of potassium is also lower in infants compared with older children. Acid-base status is usually not evaluated with direct tests of function. Instead there is reliance on measurements of serum bicarbonate concentration and pH determinations in venous or arterial blood samples. Because of the physiologic limitations on acidification in infants, the normal serum bicarbonate concentration is lower, 15 to 18 mmol/L in infants.

The clinical manifestations of the reduced renal function in fetal life and the early transition to postnatal conditions include inability to excrete drugs that are cleared by the kidney. The ability of the infant to tolerate large infusions of isotonic fluids and blood products is also limited compared with older children. Similarly, the inability to maximally dilute the urine results in hyponatremia if infants are given excessive quantities of hypotonic fluids. The diminished capacity to reduce sodium excretion in response to dietary restrictions can lead to hyponatremia and impaired growth and hyperkalemia. The developmental defect in acidification can lead to mild renal tubular acidosis (RTA) and lower somatic growth rates.

Key Points: Transition from Fetus to Infant

- Nephrogenesis is complete by 34 weeks' gestational age in the fetus.
- GFR is dependent on gestational age and doubles in the first 2 weeks of life.
- GFR at birth is 15% to 20% of normal adult values.
- Sodium handling is impaired in the neonate with a higher FE_{Na}.
- Urine concentrating ability is reduced owing to the lower GFR.
- Renal acidification is reduced.
- Alterations in sodium and hydrogen balance as well as absence of potassium channels lead to potassium retention.
- Low-birth-weight infants are at increased risk of developing hypertension and secondary renal diseases in adulthood.

PRINCIPLES OF FLUIDS AND ELECTROLYTES

The key difference in body fluids between pediatric and adult patients is the larger percentage of body weight composed of water and the larger extracellular fluid (ECF) compartment size. **Thus, in infants and children, water makes up nearly 80% of body weight, with even higher values in premature infants of extremely low birth weight.** As children grow older and with increased adipose tissue in girls, the total amount of water falls to the normal value of 60% to 67%.

The composition of the two major body water compartments—ECF and intracellular fluid (ICF)—varies greatly. In the ECF the principal cation is sodium and the major anions are chloride and bicarbonate. In the ICF, in contrast, potassium is the major cation and proteins and phosphate comprise the bulk of the anions. However, in both compartments there is electroneutrality and an equal number of osmotically active solutes. The major factor leading to the differential distribution of solutes between the ECF and ICF is the Na^+,K^+-ATPase pump, which actively extrudes sodium from the cells. Because sodium is confined to the ECF, disturbances in the ECF volume reflect abnormalities in external sodium balance. Thus, if intake of sodium exceeds output, then the patient will have ECF volume expansion with clinical symptoms such as hypertension, pulmonary edema, and peripheral edema. If sodium losses are not counterbalanced by sufficient dietary intake, then the patient will develop intravascular volume contraction, manifesting as tachycardia, hypotension, and impaired peripheral perfusion. **Serum osmolality is the primary determinant of the normal distribution of water between the ECF and ICF in a 1:2 ratio.** Hyperosmolality causes ICF contraction, and hypo-osmolality causes ICF expansion. The major clinical consequences of changes in the ECF:ICF ratio occur because of altered cerebral volume and brain dysfunction, leading to irritability, lethargy, somnolence, and seizure (Trachtman, 1991).

From a clinical perspective, fluid and electrolyte management requires independent assessment of ECF volume status and tonicity. The former is a clinical judgment based on physical findings such as pulse rate, blood pressure, change in weight, skin turgor, urine output, and presence of peripheral edema. The degree of volume contraction is considered mild, moderate, or severe if the change in body weight is estimated as less than 3%, 3% to 6%, or

more than 6%. There is poor correlation between this clinical evaluation and most laboratory parameters such as blood urea nitrogen, serum creatinine, or bicarbonate concentration. In difficult cases, direct measurement of ECF status may be necessary, relying on invasive techniques such as insertion of a central venous or pulmonary artery catheter.

Intravenous fluid therapy should be considered a form of drug treatment and should be instituted only if there are appropriate clinical indications. These include inability to tolerate enteral fluids, severe ongoing losses, medical need to avoid oral intake, and acute kidney injury in which close monitoring of fluid intake may be necessary. Under these circumstances, maintenance fluids are provided to supply sufficient amounts of water, sodium, and potassium to account for normal urinary and gastrointestinal losses and insensible losses through the skin and respiratory tract. These quantities are best calculated based on surface area, although calculations based on body weight, a more accessible measurement, are generally reliable. Maintenance fluids need to be adjusted upward in children with fever, tachypnea, or dermatologic diseases that disrupt the skin barrier. For example, premature infants have increased insensible losses because of their thin skin and require increased free water intake to prevent hypernatremia. The maintenance fluid requirements are generally provided as a hypotonic solution of sodium chloride containing approximately 50 mmol/L. Recently, controversy has arisen about the appropriate composition of parenteral maintenance fluids. There are those who advocate routine administration of isotonic saline (0.9% or NaCl 154 mmol/L) to prevent hospital-acquired hyponatremia (Moritz and Ayus, 2003). Others suggest that the standard fluid should continue to be a hypotonic solution with recognition that modification may be necessary in seriously ill children who may be at risk of altered vasopressin release and hyponatremia (Holliday et al, 2004). Absent clinical trials, clinicians are advised to be aware of the risks of parenteral therapy in hospitalized children and to monitor the effects of prescribed fluid treatment.

Children with severe intravascular volume contraction should receive rapid infusion of isotonic saline to stabilize cardiovascular status, regardless of the serum sodium concentration. **In the majority, in which there is isotonic dehydration, the deficit can be repaired steadily over 24 hours. In patients with hyponatremia or hypernatremia the fluid deficit should be reversed more slowly over at least 48 hours to prevent adverse consequences** of cerebral cell swelling in patients with hypernatremia or cerebral cell shrinkage in patients with hyponatremia. In children with hypernatremia it is important to infuse hypotonic fluids but at a slow rate to enable gradual normalization of hyperosmolality (Banister et al, 1975). Children with nephrogenic diabetes (see later) are prone to excessive free water loss and hypernatremia (Adrogue and Madias, 2000). Similarly, patients with obstructive uropathy and pseudohypoaldosteronism are prone to develop hyponatremia, especially if they have a concurrent urinary tract infection. These disturbances need to be taken into account when formulating fluid regimens.

For patients with hyponatremia the sodium deficit can be calculated according to the following formula:

$$\text{Na deficit} = 0.6 \times \text{Body weight} \times [130 - \text{Serum Na concentration}]$$

For patients with hypernatremia the free water deficit can be calculated according to the following formula:

$$\text{Free water deficit} = 0.6 \times \text{Body weight} \times [\text{Serum sodium concentration}/140 - 1]$$

Patients with clinically manifest intravascular volume expansion require treatment with dietary sodium restriction and diuretics. In severe cases, dialysis may be required on an urgent basis to alleviate hypertension and/or pulmonary edema.

HEMATURIA

Isolated hematuria is a very common problem, the treatment of which is often shared by nephrologists and urologists. Studies done in a wide range of countries around the world indicate that the frequency of detecting blood in the urine in pediatric patients ranges from 0.5% to 3% (Hogg, 2009). **Most of the time the problem is self-limited, resolves spontaneously, and is not a sign of underlying disease.** Thus although mass screening of urine samples in pediatric patients is common in several Asian countries, there is a movement away from this practice. In 2007 the American Academy of Pediatrics revised its clinical recommendations and no longer suggests performing a urinalysis routinely at any age during childhood.

The majority of cases of hematuria are microscopic. The differential diagnosis (Table 112–1) in patients with gross hematuria is no different than in those with microscopic hematuria (Youn et al, 2006; Greenfield et al, 2007). The key difference is that patients with gross hematuria are more likely to be referred for urgent assessment and the likelihood of finding an underlying cause. **In studies of children with gross hematuria, nearly 60% have nonglomerular causes, 25% have a glomerular etiology, and the remainder have no established cause.**

Epidemiology

Studies of hematuria in children have been conducted by screening healthy children or by retrospective analyses of children with hematuria. Vehaskari (1979) estimated the prevalence of hematuria in children to be 1.1% (excluding those with transient hematuria): 74% of the 8954 children had hematuria in only one sample, 83 of the remaining 131 children with persistent hematuria had isolated hematuria most commonly due to urinary tract infection (7%), whereas 59 had associated proteinuria; this study was conducted before hypercalciuria was identified as a common cause of hematuria. Hisano (1991) found 251 of 160,000 screened

Table 112–1.

Causes of Hematuria in Children

GROSS	MICROSCOPIC
Hypercalciuria	Transient
Cystitis	Hypercalciuria
IgA nephropathy	Thin basement membrane nephropathy
Alport syndrome	Lupus
Poststreptococcal glomerulonephritis	Henoch-Schönlein purpura
Benign urethralgia	Idiopathic factors
Wilms tumor	Vasculitis
Bladder tumors	Exercise
Polycystic kidney disease	Nephrolithiasis
Exercise	Hematologic disorders
Coagulopathy	Drugs
Lupus	Trauma
Trauma	Interstitial nephritis
Renal vein thrombosis	Cystitis or pyelonephritis
Papillary necrosis	
Nutcracker syndrome	

junior high school students had isolated microscopic hematuria with an identifiable cause in 115: menses (35%), urinary tract infection (5.6%), hypercalciuria (2%), Henoch-Schönlein purpura (1.2%), and hydronephrosis (1.2%). Approximately 25% of children had resolution of hematuria, less than 1% had proteinuria, and none developed renal insufficiency. Turi (1989) reported a retrospective analysis of 341 children, ages 2 to 12 years with persistent, isolated hematuria of at least 6 months' duration followed for 2 to 17 years. Hematuria was isolated microscopic in 31%, macroscopic in 28%, or both in 41%. Persistent hematuria was documented monthly in 40%. Renal biopsy in 47 children for development of a nephritic urine sediment or proteinuria demonstrated mesangial proliferative glomerulonephritis and hereditary nephritis most commonly. Twenty percent of subjects had hypercalciuria and/or nephrolithiasis. The remaining 226 children had isolated hematuria, which resolved in 163 children. These studies support the concept that **isolated asymptomatic hematuria is a relatively benign condition after exclusion of children with easily identifiable causes by history and physical examination, family history, urine microscopy, renal imaging, urine culture, urinary calcium excretion, and renal biopsy, if indicated.**

Evaluation

Persistent microscopic hematuria lasting at least 6 months or gross hematuria warrants investigation. The evaluation of hematuria includes a proper history, physical examination, and laboratory and radiographic studies (Fig. 112–1). The history should include questions regarding the timing of the presence of the hematuria as an isolated or recurrent event; hematuria that occurs throughout voiding is more likely to be glomerular, whereas terminal hematuria is more likely to be nonglomerular. Benign **urethrorrhagia** presents as postvoid droplets of blood from the meatus after a grossly clear void (Kaplan and Brock, 1982). Glomerular hematuria is often described as urine that is tea or cola colored, whereas urine of nonglomerular hematuria is more likely to be red. Certain diagnoses may be suspected based on the presence of associated symptoms such as dysuria, urgency, frequency, abdominal pain, prior respiratory infection, lower

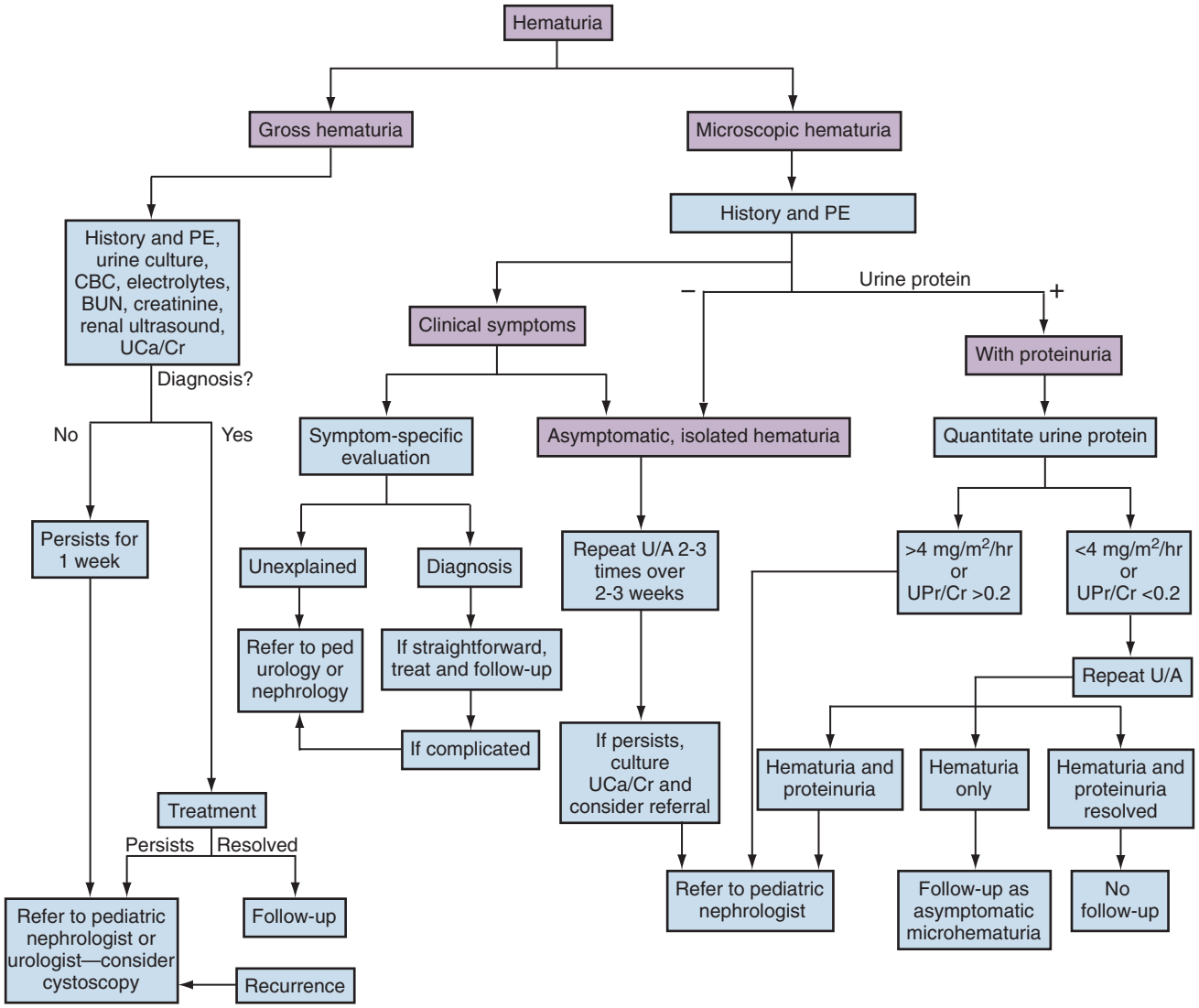


Figure 112–1. Algorithm for the treatment of hematuria. BUN, blood urea nitrogen; CBC, complete blood cell count; PE, physical examination; U/A, urinalysis; UCa/Cr, urinary calcium:creatinine ratio; UPr/Cr, urinary protein:creatinine ratio.

extremity swelling, or symptoms of hypertension (headaches, blurred vision), joint pain, fevers, weight loss, rash, or antecedent streptococcal infection. A patient or family history of sickle cell disease or trait, deafness, hematuria, or renal disease should be sought. The physical examination should assess for blood pressure with a proper-sized sphygmomanometer cuff, abdominal tenderness or masses, costovertebral angle tenderness, ecchymosis, rashes, periorbital or lower extremity swelling, and signs of trauma on the flank, pelvis, or genitalia.

A fresh urine sample should be collected for analysis and culture. Hematuria is defined as the presence of five or more red blood cells per high-power microscope field (Fitzwater and Wyatt, 1994). Hematuria is detected by dipstick via a reaction of a peroxidase with hemoglobin; however, the dipstick test may be falsely positive in the presence of hemoglobinuria or myoglobinuria. Fresh-spun urine should also be screened for protein, glucose, nitrates, leukoesterase, bilirubin, specific gravity, and pH. The key diagnostic test is a microscopic examination of the urine sediment. Patients with glomerular hematuria will have red blood cell casts and dysmorphic erythrocytes (irregular shape and size with distorted contours) in their sample, whereas children with nonglomerular hematuria have eumorphic red erythrocytes (uniform in size resembling circulating red blood cells) without red blood cell casts. This distinction can usually be made reliably by examining the urine directly (Trachtman, 2006). A 2- to 4-hour delay in urine inspection can cloud the distinction between nonglomerular and glomerular bleeding. If prompt examination of freshly voided urine samples is not feasible in a specific clinic setting, the addition of Cellfix, a formaldehyde-based fixative, allows preservation of red cell morphology for at least 24 hours and can enhance the diagnostic value of the microscopy portion of the urinalysis (Komarova et al, 2003). Phase contrast microscopy has been touted to enhance accuracy. In addition, some clinicians have recommended measurement of red cell size with Coulter counter devices used in hematology clinics. Patients with dysmorphic red cells in the urine will have smaller erythrocyte volume and greater scatter in cell size compared with patients with nonglomerular hematuria. Microscopic evaluation of the specimen should be performed to qualify and quantify the extent of the hematuria and the presence of crystals (uric acid, cystine) and casts (red or white cell).

Symptomatic children and those with persistent or recurrent microscopic or gross hematuria require additional evaluation. A second urinalysis devoid of red cells indicates transient microscopic hematuria. In the other children, urine should be cultured in the presence of symptoms of cystitis or pyelonephritis or if the urinalysis is indicative of infection. Urine calcium to creatinine ratio of greater than 0.21 suggests hypercalciuria, which needs confirmation by a 24-hour collection (>4 mg/kg/day). Serum studies should include electrolytes, blood urea nitrogen (BUN), creatinine, calcium, phosphorus, liver function tests, complete white cell count with differential, antinuclear antibodies, streptozyme and antistreptolysin O antibody titers, and C3, C4, and total complement only in patients who have other signs of renal disease in addition to hematuria, such as hypertension, proteinuria, or edema. Hematuria may occur with or without proteinuria. Large numbers of red blood cells may suggest proteinuria on the dipstick. Quantification of urinary protein aids in diagnosing isolated hematuria versus hematuria with proteinuria. Several contaminants can produce red urine without hematuria, including several drugs (rifampin and ibuprofen) and foods (beets and blackberries).

A renal and bladder ultrasound evaluation will screen for possible renal parenchymal or bladder causes of the hematuria. Computed tomography best defines renal masses, stones, and nutcracker syndrome, in which there is extrinsic compression on the aberrantly located renal vein. Additional information may be gleaned by magnetic resonance imaging (MRI). These modalities would be used to better characterize any abnormalities identified by ultrasonography. Voiding cystourethography is reserved for children with culture-positive infection or to further evaluate any abnormal ultrasound findings in the bladder. There is no role for cystoscopy in the evaluation of microscopic hematuria (Feld et al, 1998) if the sonogram is normal. Small tumors may be missed but are benign (Kaplan, 1985). Cystoscopy for gross hematuria can be useful if bleeding occurs at the time of the study. If bloody effluent is observed from both ureteral orifices, a glomerular source is more likely. If bloody urine is observed from only one ureteral orifice, unilateral urinary tract or vascular disease may be present and retrograde pyelography or ureteroscopy may be indicated.

Hypercalciuria

Hypercalciuria can present as isolated microscopic hematuria, dysuria, or recurrent gross hematuria. Gross hematuria secondary to hypercalciuria can be distinguished from that due to glomerular diseases by the potential presence of dysuria, clots in the urine, and rapid resolution of the hematuria within 24 hours. It should be noted that hypercalciuria can also cause dysuria and mimic a urinary tract infection in which the urine culture shows no bacterial growth. Finally, hypercalciuria can be the major factor leading to urolithiasis. Numerous dietary factors such as increased intake of sodium and magnesium influence tubular reabsorption of calcium and can cause hypercalciuria (Bonny et al, 2008). Hypercalciuria may have a genetic component, accounting for the clustering of kidney stones in family pedigrees. For example, specific polymorphisms in the calcium-sensing receptor gene are associated with a gain-of-function and increased susceptibility to idiopathic hypercalciuria (Vezzoli et al, 2007). The diagnosis of hypercalciuria is best made based on a 24-hour urine collection in which the calcium excretion exceeds 4 mg/kg/day. Because of logistic issues involved in collecting 24-hour collections, clinicians often rely on the calcium-to-creatinine ratio in a spot sample. **The normal calcium-to-creatinine ratio value declines with age, and in children older than 4 years old the ratio should be less than 0.2.** There are a number of secondary causes of hypercalciuria, including RTA, hyperparathyroidism, malignancies, immobilization, and sarcoidosis. However, in most cases it is idiopathic. In the past, effort was directed at discriminating between hyperabsorption of calcium from the gut versus renal leak of calcium as the basis for hypercalciuria. However, this distinction is no longer considered clinically relevant because it does not influence the diagnostic workup or patient management. In addition to these renal manifestations, idiopathic hypercalciuria predicts bone loss. Studies have demonstrated an association between the degree of hypercalciuria and bone density of the femoral neck in adult men and women (Asplin et al, 2006). The long-term implications of this finding require ongoing study. Treatment of hypercalciuria by increasing fluid intake should be started on all diagnosed children, with thiazide administration reserved for symptomatic children unresponsive to conservative measures or those with high urinary levels or active stone disease.

Key Points: Hematuria

- Isolated microhematuria (≥five red blood cells per high-powered field) in children is usually a benign self-limited condition whereas recurrent hematuria or microhematuria of 6 months' duration warrants investigation.
- Gross hematuria in children with normal urinary tract imaging rarely indicates cystoscopic examination unless it is persistent and nonglomerular in origin (60%).
- Hypercalciuria is a common cause of both macroscopic and microscopic hematuria in children and is defined as a calcium-to-creatinine ratio of greater than 0.2 in children older than age 4 years.
- Hematuria in the presence of significant proteinuria often indicates glomerular disease requiring percutaneous renal biopsy.
- A family history of renal disease or renal stones may help to guide the diagnostic evaluation of hematuria in children.

PROTEINURIA

The filtration mechanism of the glomerulus aims to limit the passage of macromolecules, such as protein, from the blood into the urine. The pores in the slit diaphragm between the foot processes have a 40-Å diameter, which allows passage of low-molecular-weight molecules (α_1 and β_1 microglobulins) that are reabsorbed by the proximal tubule and therefore not detected in the urine in the absence of tubular damage (Tomlinson, 1992). The negative charge of the glomerular capillary wall provided by heparin sulfate and proteoglycans repel other negatively charged molecules, such as albumin. The loss of the negative charge or breakdown of the size barrier can lead to proteinuria. A third factor involved in filtration is the presence of hydrostatic and oncotic forces as blood traverses the glomerulus. Proteinuria can arise from hyperfiltration when a reduction of functioning nephrons occurs (e.g., from nephrectomy). Recent studies have created controversy about the pathophysiologic basis of glomerular proteinuria—excessive leak due to a primary disturbance in glomerular barrier function or failure to reabsorb the filtered load in the proximal tubule (Russo et al, 2007).

Abnormal urinary protein excretion is defined as greater than 4 mg/m^2/hr (Nephrotic syndrome in children…, 1979) in an overnight urine collection or a protein-to-creatinine (mg/mg) ratio greater than 0.2 in a first morning urine sample. Proteinuria is prevalent in 5% to 15% of children (McKenzie et al, 1964) and is associated with increasing age with a peak incidence of 13 years in girls and 16 years in boys (Wagner et al, 1968). It is common to find isolated proteinuria, but persistent proteinuria indicates renal disease and warrants evaluation (Vehaskari and Rapola, 1982). Proteinuria is important because it may reflect progressive renal disease (Kannel et al, 1984; Williams and Coles, 1994) and lead to hypocholesterolemia and hypertriglyceridemia, which pose a higher cardiovascular risk (Sytkowski et al, 1990). Similarly, medications aimed at reducing proteinuria can delay progressive renal failure (Remuzzi et al, 2004).

Proteinuria is first detected by urinary dipstick testing, which primarily detects albumin (Fig. 112–2). The colorimetric reaction between albumin and tetrabromophenol blue results in variable shades of green, depending on the approximate concentration of protein in the urine: trace indicates approximately 15 mg/dL; 1+, 30 mg/dL; 2+, 100 mg/dL; 3+, 300 mg/dL; and 4+, 2000 mg/dL or

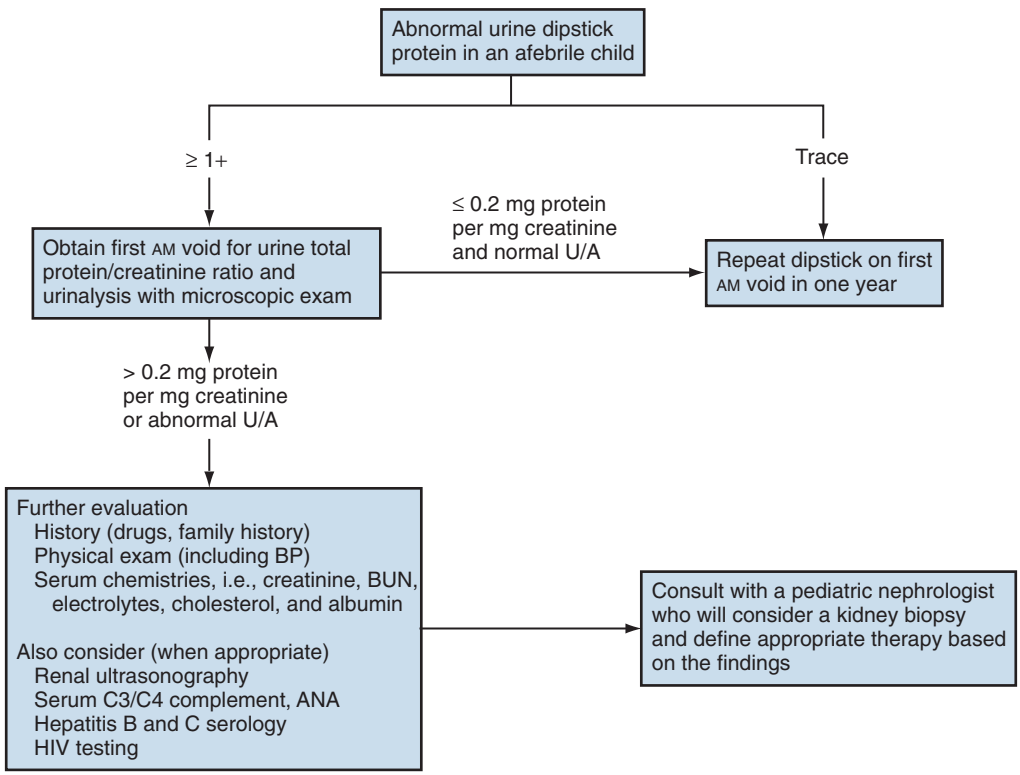


Figure 112–2. Evaluation of persistent proteinuria in children/adolescents. ANA, antinuclear antibody; BP, blood pressure; BUN, blood urea nitrogen; HIV, human immunodeficiency virus; U/A, urinalysis.

more. False-positive urine protein levels may be caused by alkaline urine, antiseptic cleanser, radiocontrast agents, or a highly concentrated sample. False-negative urine protein levels may be found in very dilute urine. Significant proteinuria is indicated by a urine sample with a dipstick reading of 1+ and a specific gravity of at least 1.015. Confirmation of the level of proteinuria may be performed using sulfosalicylic acid, which uses protein precipitation and turbidity to estimate the level of proteinuria (Hogg et al, 2000). In the absence of other signs or symptoms of renal or urinary tract disease, including systemic disease, the urinalysis may be repeated in several weeks on the first morning specimen to confirm proteinuria.

Quantification of the proteinuria is best performed from a 24-hour urine collection. Normal urine protein excretion in children is less than 4 mg/m^2/hr (<100 mg/m^2/24 hr). **Protein excretion rate greater than 4 mg/m^2/hr is abnormal, and greater than 40 mg/m^2/hr is nephrotic-range proteinuria.** Urinary creatinine value should be measured (normal is 15 to 20 mg/kg/day in girls and 20 to 25 mg/kg/day for boys) to confirm the adequacy of the collection. However, timed urine collection can be difficult to accomplish and therefore inaccurate, particularly in the incontinent child (Hogg et al, 2000). Moreover, it is not useful in establishing the diagnosis of orthostatic proteinuria, a variant of normal. A random urine protein-to-creatinine ratio correlates well with 24-hour quantification. The normal values are less than 0.5 for children 6 to 24 months of age and less than 0.2 for children older than 2 years; a ratio above 3.5 is considered in the nephrotic range. **In a first morning sample, protein-to-creatinine values greater than 2.0 indicate nephrotic range proteinuria.**

Children with 1+ or more protein by dipstick on more than one occasion have persistent proteinuria and deserve further evaluation. Inquiry should be made into the presence, severity, and duration of recent illnesses, rashes, arthralgias, edema, weight loss, fatigue, or changes in urine output or urine color; a family history of renal disease, vesicoureteral reflux, deafness, or hypertension should be sought. The complete physical examination should include weight, height (with comparisons made to standard growth charts), blood pressure measurements, then a search for the presence of edema and ascites. **Laboratory studies should include a first morning urine sample to measure the protein-to-creatinine ratio followed by a 24-hour urine collection to quantify the protein in the presence of an elevated ratio.** Serum studies including determination of electrolyte, BUN, and creatinine levels plus those of cholesterol, albumin, and triglycerides as well as serology aimed at detecting glomerular diseases (C3, C4, fluorescent antinuclear antibody, antistreptolysin O, and hepatitis B or C titers) should be done if there is persistent proteinuria for 76 months or if there are suggestive symptoms and signs. Renal ultrasonography should be performed and voiding cystourethrography should be ordered in the presence of ultrasound findings suggestive of vesicoureteral reflux.

Significant proteinuria can occur secondary to glomerular or tubulointerstitial diseases, but it is generally due to glomerulopathies. Proteinuria may be categorized as transient, orthostatic, or fixed/persistent. Transient proteinuria is present in 30% to 50% of children with proteinuria and may be associated with fever, stress, dehydration, and exercise. Transient proteinuria associated with a fever rarely exceeds 2+ on the dipstick and abates with the fever. Exercise-induced proteinuria increases with age (Poortmans et al, 1996), is related to the vigor of exercise and not duration, (Poortmans, 1985), rarely exceeds 2+ on dipstick, and resolves within 48 hours of rest. **Postural (or orthostatic) proteinuria is common (60% of asymptomatic children)** (Norman, 1987) **in which protein excretion is normal while supine but becomes abnormal when erect.** Children are asymptomatic, and the only abnormal laboratory finding is an elevated urine protein level after being upright. Postural proteinuria may be documented by collecting two timed urine samples and finding no proteinuria while the child is recumbent (sleeping) and proteinuria while the child is upright. The 24-hour urinary protein excretion in children with orthostatic proteinuria should not exceed 1000 mg/day. Persistent proteinuria (up to 6% of school-aged children (Vehaskari and Rapola, 1982; Yoshikawa et al, 1991) is diagnosed after confirming proteinuria on two dipstick tests with at least 1+ at least 1 week apart and excluding postural proteinuria. Its etiology can be divided as either glomerular where there is increased permeability of the glomerulus or as tubular from decreased protein reabsorption. The glomerular type is more common and can be selective (molecules smaller than albumin) or nonselective (molecules larger than albumin).

The differential diagnosis for isolated proteinuria includes rare cases of minimal change nephrotic syndrome, FSGS, membranous nephropathy, or IgA nephropathy. Although FSGS is more frequent in African-American children, IgA nephropathy is much more common in white children (Nair and Walker, 2006). Membranous nephropathy is a rare disease across the entire pediatric age range (Chen et al, 2007). Obstructive uropathy is thought to be a common cause of tubular proteinuria, but it usually presents as other signs and symptoms. The measurement of microalbuminuria is generally confined to the management of diabetic nephropathy. Tests to measure selectivity of proteinuria or to quantitate low-molecular-weight proteins are not routinely available and of uncertain value. Unlike the situation in adult patients, the long-term implications of microalbuminuria on general health and the incidence of cardiovascular disease is unknown in pediatric patients. In fact, because of the high prevalence of orthostatic proteinuria in adolescents, testing the early morning sample is both more appropriate and more feasible than measuring proteinuria in a 24-hour collection. The diagnosis of the cause of proteinuria usually requires performance of a kidney biopsy. In 70% of children with isolated proteinuria, the urinary abnormality spontaneously resolves within 12 months (Trachtman et al, 1994). **Therefore criteria for performing a kidney biopsy are (1) persistent subnephrotic proteinuria for at least 12 months or (2) nephrotic-range proteinuria that persists for 3 to 4 months or rising levels of proteinuria in patients who are being followed after the initial**

Key Points: Proteinuria

- Asymptomatic, isolated proteinuria is a common finding on urinalysis screening examinations in children.
- Quantification of urinary protein excretion is the most important diagnostic test with more than 4 mg/m^2/hr considered abnormal and more than 40 mg/m^2/hr considered nephrotic range.
- Children with 1+ proteinuria on more than one occasion without other associated symptoms are likely to have transient or postural proteinuria.
- Presence of hematuria, edema, hypertension, or systemic disease increases the suspicion of a glomerulopathy, making the diagnostic evaluation more urgent.

detection of isolated proteinuria. However, these standards are likely to vary from center to center reflecting the pattern of disease regional and at each institution. In general, renal biopsies done under ultrasonographic guidance are a safe and well-tolerated procedure (Gauthier et al, 1993). The presence of both hematuria and proteinuria suggests the need for a more comprehensive and urgent evaluation.

GLOMERULAR DISEASE

Nephrotic Syndrome

***Nephrotic syndrome* is defined as edema, hypoalbuminemia, hyperlipidemia, and heavy proteinuria.** The amount of proteinuria considered to be nephrotic is an excretion greater than 40 mg/m^2/hr or a random urine protein-to-creatinine ratio of greater than 2.0 to 3.0 (Hogg et al, 2000). Nephrotic syndrome may be subdivided into congenital, primary (from any type of glomerulonephritis), or secondary (systemic disease, malignancy, allergic reaction or nephrotoxin). The incidence of primary nephrotic syndrome is 2 to 4 cases per 100,000 children younger than 19 years old and is most commonly due to minimal change disease (65% to 80%). In general, nephrotic syndrome is a disease of the glomerular podocyte, with the identification of genetic disorders of podocyte proteins providing the basis for this understanding.

Hypoalbuminemia occurs from the urinary loss of albumin causing a reduced plasma colloid oncotic pressure and a fluid shift from the intravascular to the interstitial space. This translates clinically into the development of edema as the serum albumin level falls below 2.5 g/dL. The rapid intravascular volume loss leads to compensatory reabsorption of sodium and water by the kidney, which aggravates the edema. In addition to underfilling of the intravascular space, nephrotic edema occurs because of primary sodium retention and overfilling of the circulation (Schrier and Fassett, 1998). While albumin synthesis increases, it is insufficient to replace the ongoing albumin losses, poor dietary protein intake, and increased catabolism of albumin.

Serum cholesterol is high (usually exceeding 400 mg/dL), triglycerides levels are variable, and total lipids are elevated (low-density lipoproteins, very-low-density lipoproteins, and apoproteins). Lipids accumulate in renal tubular cells, especially in the proximal tubule; these cells can slough into the urine, appearing as "oval fat bodies" in the sediment and having a typical Maltese cross pattern under the polarizing microscope.

Nephrotic Syndrome in Infants

All infants with primary nephrotic syndrome have proteinuria, hypoalbuminemia, hyperlipidemia, hypogammaglobulinemia, and usually normal renal function. Edema is present at birth or develops over several weeks in concert with increasing proteinuria. Hematuria is uncommon. The leading causes of nephrotic syndrome in infants include congenital nephrotic syndrome–Finnish type (CNF), diffuse mesangial sclerosis (DMS), minimal change nephrotic syndrome (MCNS), and focal sclerosis glomerulonephritis (FSGS). Family history, outcome, and corticosteroid response may be the only ways to secure the diagnosis. MCNS is rare in early infancy, responds to corticosteroids, does not progress to end-state renal disease, shows minimal changes on biopsy, and has a negative family history. FSGS is rare and may respond to corticosteroids. The rarity of MCNS and FSGS and the increased risk of severe infection in infants with CNF preclude starting corticosteroids in the first 3 months of age in the absence of a definitive diagnosis. DMS is rare and clinically indistinguishable from CNF occurring in siblings, is resistant to corticosteroids, and progresses to end-stage renal disease (ESRD) before age 3 years. Early in the disease DMS can be distinguished from CNF on biopsy by its mesangial matrix expansion without hypercellularity, thickened glomerular basement membrane (GBM), crowding of the capillary lumens, and eventual glomerulosclerosis, leaving a contracted sclerotic mass in a dilated Bowman space. DMS is the lesion associated with the glomerulopathy of Denys-Drash syndrome and may occur secondary to mutations in the Wilms tumor-1 *(WT1)* gene (Chiang et al, 2008).

CNF, the most common form of nephrotic syndrome in infants, is an autosomal recessive disorder with a mutation of the gene coding for nephrin on chromosome 19q13.1. Nephrin is a transmembrane protein of the slit diaphragm of the glomerular podocyte. The incidence in Finland is 0.9 per 10,000 births, but most affected patients in North America lack Finnish ancestry. Two mutations, Fin-major and Fin-minor, account for the disease in nearly 90% of all affected Finnish patients. CNF may be suspected in utero by elevated amniotic fluid and maternal serum levels of α-fetoprotein and confirmed postnatally by specific genetic testing. Histopathologies of fetal kidney show foot process effacement and diffuse epithelial podocyte proliferation. Infants with CNF are small for gestational age and born prematurely. Edema is present at birth in more than 50% of patients and by 3 months in 100%. Proteins that are lost in the urine include immunoglobulins leading to hypoimmunoglobulinemia and a higher risk of bacterial infection, thyroxine causing hypothyroidism, transferrin and iron causing anemia, and protein-bound 25-hydroxyvitamin D causing vitamin D deficiency. Severe chronic nephrotic syndrome is associated with a hypercoagulable state that places these children at risk for thromboembolic events. Failure to thrive and malnutrition from excessive protein loss and anorexia occur in all affected infants. Renal function, initially normal, progresses to end-stage renal disease (ESRD) by age 3 to 8 years. Poor responders to aggressive medical management may require bilateral nephrectomy and dialysis even before ESRD. Early aggressive treatment including dialysis and renal transplantation offers good long-term survival (80%), whereas untreated infants die by age 4 years. Catch-up growth and development are common after transplantation, but CNF recurs in many (25%) patients owing to antinephrin antibody production.

Minimal Change Nephrotic Syndrome

MCNS is the most prevalent lesion throughout childhood, but the frequency declines from 85% to 90% in preschool-aged children to 50% in adolescents. **Most children with proteinuria between 1 and 10 years of age who respond to oral corticosteroids have minimal change disease.** Because most children who respond to corticosteroids with resolution of proteinuria do not undergo biopsy, the actual pathologic diagnosis is often unknown. However, the most important prognostic feature is remission of the disease with corticosteroid therapy.

Most children with MCNS present with edema, even ascites, but most children otherwise appear well. The diagnosis of MCNS is made by demonstrating nephrotic-range proteinuria, a serum albumin level below 2.5 g/dL, and elevated plasma cholesterol and/or triglyceride levels. Most children are normotensive and have normal BUN and creatinine concentrations. Microscopic evaluation of the urine demonstrates the presence of fatty casts and oval fat bodies but minimal hematuria and no cellular casts.

Once the presumptive diagnosis is made, high-dose (60 mg/m^2/day) daily treatment with oral prednisone is started (Mendoza and Tune, 1992). This regimen is continued for at least 4 weeks, followed by an additional 4 weeks of 40 mg/m^2/day on alternate days and then a gradual taper using alternate-day dosing. To simplify management, the daily dose can be 2 mg/kg and the alternate day dose 1.5 mg/kg (Gipson et al, 2009). Most children respond with remission of proteinuria within 4 weeks (negative or trace protein on dipstick for 3 consecutive days). Dietary salt restriction is another important component of treatment. Approximately two thirds of children will experience relapse, which is treated with high daily doses of corticosteroids until remission and then the dosage is tapered. Cytotoxic agents (cyclophosphamide or chlorambucil) or cyclosporine are used in some children if relapses are frequent or unsustainable without corticosteroids. In cases in which renal biopsy is performed, light microscopy demonstrates normal renal tissue or demonstrates a mild, focal increase in mesangial cellularity and matrix. On electron microscopy, effacement of epithelial cell foot processes, normal glomerular basement membrane thickness, and small paramesangial electron-dense deposits can be seen. These lesions fail to stain or stain slightly positive for IgM.

Children with MCNS are at heightened risk for infections owing to the urinary loss of opsonins, with particular risk for spontaneous bacterial peritonitis. The acute nephrotic syndrome is characterized by a relatively hypercoagulable state, and these children may develop venous thromboses during relapse. Therefore, placement of central venous catheters or femoral venipuncture is to be avoided. **Renal insufficiency rarely presents as an acute or late complication of MCNS.**

Focal Segmental Glomerulosclerosis

Focal segmental glomerulosclerosis (FSGS) is the second most common cause of primary nephrotic syndrome in children (Bonilla-Felix et al, 1999), accounting for 10% to 20% of cases. Its incidence may be increasing in all ethnic groups, perhaps related to the epidemic of obesity and the metabolic syndrome. **FSGS is more common among older children and African-American children and is much less likely to respond to corticosteroid therapy.** FSGS has many causes but no clear pathophysiology. Whereas 15% to 25% of children with primary nephrotic syndrome have biopsy-proven FSGS, 20% of patients with FSGS have asymptomatic proteinuria. Microscopic hematuria is present in over 50% of affected children, but gross hematuria is rare. Renal tubular dysfunction (glucosuria, aminoaciduria, RTA, Fanconi syndrome) and concentrating defects are risk factors for progression to chronic renal failure.

Early in the disease the renal lesions are focal and mainly located in the juxtamedullary glomeruli. The focal nature may lead to false-negative biopsies and delayed diagnosis. By light microscopy the glomeruli are enlarged, but affected glomeruli may have segmental sclerosis or segmental capillary loop collapse and increased mesangial matrix. Foam cells are associated with the segmental lesions. Tubulointerstitial disease is almost always present. IgM and C3 are detected by immunofluorescence in the mesangium or focally along the GBM of affected capillaries. Electron microscopy demonstrates endothelial cell swelling, effacement of epithelial podocytes, sclerosis, and scattered immune deposits.

Despite the suboptimal response to corticosteroids, evidence-based analyses still advocate their use as first-line therapy. Regardless of timing of the positive biopsy, only 20% of children initially have a complete response to prednisone. Twenty to 30 percent of nonresponders progress to ESRD within 5 years, and 60% do so by 10 years. Cyclosporine, tacrolimus, and mycophenolate mofetil have been used as single agents or in combination with corticosteroids with variable success. Pulse intravenous methylprednisolone for 8 to 12 weeks along with alternate-day oral prednisone with or without cyclophosphamide or chlorambucil has demonstrated sustained remission in 80% of patients. Disease progression is anticipated in the presence of persistent nephrotic syndrome and an increase in globally sclerotic glomeruli on follow-up biopsies. FSGS recurs in up to 30% after a first renal transplant and in 80% of subsequent transplants. The administration of high-dose cyclosporine, alone or in combination with plasmapheresis, has led to remission of nephrotic syndrome and allograft salvage.

Membranous Glomerulonephritis

Membranous nephropathy accounts for 1% to 3% of biopsies performed for the evaluation of nephrotic syndrome in childhood and for 10% to 20% of those performed in adolescents. Primary (idiopathic) membranous glomerulonephritis (MGN) occurs in two thirds of cases and secondary MGN from systemic diseases (systemic lupus erythematosus [SLE], chronic hepatitis B) in the others. **MGN may present months to years before the associated disorders.** Symptoms arise gradually, and MGN is commonly (two thirds) diagnosed during the evaluation for edema and nephrotic syndrome or after detecting proteinuria on screening urinalysis (one third). Hypertension (found in 30%) is not a prognostic indicator. Hematuria is nearly universal as microscopic (80%) or gross (20%). Renal function and serum C3 value are usually normal initially; the C3 may be low in SLE- and hepatitis B–associated MGN. Idiopathic MGN progresses slowly, with renal failure developing within 10 years in 10% of children younger than 10 years old and in 20% of adolescents. Spontaneous remission of proteinuria occurs in up to 30% of children.

The pathogenesis of MGN is not well known but may be due to (1) circulating antibodies that react with endogenous GBM antigens forming in-situ immune complexes or (2) deposition of circulating preformed immune complexes to the GBM induced by autoimmune reactions, infection, drugs, or toxins. Stages I to IV of MGN are classified by the progressive thickening of the GBM and larger coalescing subepithelial deposits of immune complexes (IgG and often C3) on light and electron microscopy. Stage V represents a regressive healing stage. Different stages may be observed on the same biopsy specimen. No clear correlation exists between the stage of MGN and the severity or duration of disease, and lesions may remain stable over several years.

Because of its rarity in children, controlled trials in children are lacking and management has been extrapolated from experience in adults. Angiotensin-converting enzyme I and/or angiotensin type II receptor antagonist administration is aimed at reducing proteinuria, intraglomerular hypertension, and progression to renal failure. Treatment of poorly controlled nephrotic syndrome includes use of corticosteroids possibly supplemented by chlorambucil, cyclophosphamide, or cyclosporine. Spontaneous remission is common in hepatitis B–associated MGN, allowing for initial observation. MGN associated with syphilis is effectively treated with penicillin. MGN associated with drugs or toxins may resolve after several months of withdrawal.

Membranoproliferative Glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN) accounts for only 2% to 10% of cases of primary nephrotic syndrome in childhood. Most children present between age 8 and 20 years without

a gender preference with persistent hypocomplementemia. MPGN is a chronic disease that may be idiopathic or due to other systemic diseases (SLE, malignancies) or infections (chronic hepatitis C). A hereditary component is suggested by its association with inherited deficiency of several complement components, haplotypes (HLA-B8, DR3, SC01, GL02) and predilection for siblings. Although many cases are identified after routine screening urinalysis, most children have microscopic or gross hematuria at onset and almost all have proteinuria: primary nephrotic syndrome in about 50%, asymptomatic proteinuria in 25%, and nephritis with hematuria and proteinuria in 25%. Three subtypes of MPGN can be identified by microscopy. Type I shows enlarged glomeruli, obliterated capillary lumina, marked mesangial proliferation, and positive immunofluorescent staining for IgG and C3 in the mesangium and subendothelial deposits. Type II is similar to type I with less mesangial proliferation, very dense material in the GBM, but with positive immunofluorescent staining for C3 only outlining the GBM and the dense deposits in the mesangium and only sparsely in the subendothelial and subepithelial spaces. Type III disease demonstrates extensive GBM disruption with mesangial, subendothelial, subepithelial, and transmembranous deposition of IgG and C3.

The natural history of MPGN is progression to ESRD (50% by 10 years), but a few patients have spontaneous durable remission. Poor prognostic indicators include a presenting serum creatinine concentration over 2 mg/dL, hypertension, gross hematuria, and unremitting nephrotic syndrome with edema. Corticosteroids are the mainstay of treatment. Renal transplantation is successful, but recurrence of type I (30%) and type II (60%) MPGN in the allograft is reported; the progression to graft loss is slow.

Diffuse Mesangial Proliferative Glomerulonephritis

Diffuse mesangial proliferative glomerulonephritis (DMPG) is uncommon (5%) among children with primary nephrotic syndrome. Children are likely to have microscopic hematuria (90%), hypertension (50%), and renal compromise (25%). Renal biopsy specimens demonstrate diffuse mesangial hypercellularity with or without mesangial electron-dense deposits (IgM). The significance of these IgM deposits is unknown. The prognosis is good despite initial corticosteroid resistance in 35% to 70% of patients. Some children undergo spontaneous remission of nephrotic syndrome, and progressive renal failure and ESRD occurs in fewer than 10%. DMPG recurs in up to 40% of patients after renal transplantation.

Postinfectious Glomerulonephritis

Children with resolving postinfectious glomerulonephritis will have had an upper respiratory infection with or without confirmed pharyngitis in the recent past, and this is the most common cause of acute glomerulonephritis in children. There is a latency period of 7 to 21 days after a group A β-hemolytic streptococcal infection and the acute phase of glomerulonephritis. At the time of presentation with cola-colored urine the children are well without hypertension, edema, or proteinuria. In these children, confirmation of the diagnosis is contingent on resolution of the hematuria, which may take up to 2 years after the acute episode. **The diagnostic studies include a positive antistreptolysin O or streptozyme titer and a decreased serum complement (C3) concentration.** However, there is an ongoing paradigm shift in obtaining serologic studies in suspected cases in that there may be no value in routinely measuring the C3 levels because the temporary fall in level during the acute phase of the illness has generally passed and an isolated elevation in antibody titers to streptococcal-related antigens has no diagnostic value (Srisawat et al, 2006). Provided the hematuria gradually resolves, it is thought that the long-term prognosis of the patients is no different than that of healthy controls (Blyth et al, 2007). Complete recovery of renal function can be expected in more than 90% of cases, even in those who have a protracted clinical course requiring dialysis.

The acute phase lasts approximately 2 weeks and is characterized by fluid retention, hypertension, significant hematuria (often macroscopic), and proteinuria. Varying degrees of acute renal insufficiency with oliguria, even anuria requiring intermittent dialysis, may be seen. **Control of hypertension, management of electrolyte and fluid balance, and treatment of renal functional impairment are necessary during the acute phase of the illness.** Microscopic hematuria and minimal proteinuria may persist for 3 to 6 months. C3 concentrations usually become normal within 2 months after disease onset. Proteinuria that persists for 12 months after disease onset may require a renal biopsy to assess the degree of renal histologic damage, otherwise biopsy is not required for diagnosis. The characteristic findings on biopsy are marked cellular proliferation within the glomerulus due to infiltration of polymorphonuclear leukocytes and monocytes and the associated stimulation and proliferation of endothelial and mesangial cells. Electron microscopy in classic cases demonstrates humplike dense deposits.

IgA Nephropathy

IgA nephropathy (Berger disease) is more prevalent in the second decade of life and is more common in boys compared with girls. It is usually heralded by recurrent episodes of painless gross hematuria without clots synchronous with upper respiratory tract infections (Davin and Weening, 1999). The gross hematuria takes 3 to 4 days to gradually return to normal; however, some children and adolescents have persistent isolated microscopic hematuria as the sole manifestation of IgA nephropathy. It is important to distinguish IgA nephropathy in which systemic manifestations are uncommon from Henoch-Schönlein purpura, which also can cause nephritis but, unlike IgA nephropathy, be associated with distinctive urologic problems such as acute scrotal swelling (Ha and Lee, 2007). Recent studies have suggested that IgA nephropathy may be the result of abnormal galactosylation of IgA1 molecules (Buck et al, 2008). This triggers the synthesis of autoantibodies, formation of immune complexes, and deposition in the glomerular mesangium (Suzuki et al, 2009). Serology will demonstrate elevated antistreptococcal titers and normal C3 levels. The decision on whether to perform a kidney biopsy to make the diagnosis is individualized in each case; however, in the absence of proteinuria and/or hypertension and in light of the lack of proven therapies for IgA nephropathy, biopsies are less likely to be performed in children with microscopic hematuria versus those with recurrent gross hematuria. The biopsy specimen will demonstrate variable degrees of mesangial cell proliferation and IgA deposits on immunofluorescent staining.

Wyatt (1995) reported that 15% of patients will reach ESRD after 10 years and 30% will do so after 20 years. Alternatively, nearly half of patients experience a disease-free state at some point, but the silent nature of the disease in adults warrants long-term follow-up. Treatment is based on the severity of disease at diagnosis and includes renoprotective agents such as angiotensin-converting enzyme (ACE) inhibitors, corticosteroids, and mycophenolate mofetil.

Hereditary Nephritis (Alport Syndrome)

Hereditary nephritis also manifests clinically in childhood with either persistent microscopic hematuria or recurrent episodes of gross hematuria during upper respiratory infections. **The key clinical step in distinguishing IgA nephropathy from hereditary nephritis is the absence of a family history of significant kidney disease in the former while there is a clear history of ESRD and hearing loss in first-order relatives of a child with potential hereditary nephritis.** Hereditary nephritis spans a spectrum of entities all of which are the result of genetic mutations in type IV collagen genes that are constituents of the GBM (Kashtan, 2004). In benign familial nephritis or familial thin basement nephropathy the genetic mutation is in the α3 or α4 chains of type IV collagen, which are on chromosome 2 (Kashtan, 2004). In the heterozygous state the renal involvement is mild and the sole manifestation of disease is persistent microscopic hematuria. The risk of progressive loss of kidney function is generally low in these cases. In contrast, Alport syndrome, the most severe variant of hereditary nephritis, is caused by mutations in the α5 chain of type IV collagen on the X chromosome. This accounts for the more severe disease in males. The phenotype is more variable in females because of the Lyon hypothesis and random inactivation of an X chromosome in each cell. There are autosomal dominant and recessive forms of Alport syndrome linked to mutations in the α3 and α4 chains of type IV collagen. There are extrarenal manifestations of Alport syndrome (eye, platelets, smooth muscle) that can facilitate the diagnosis but, in general, the diagnosis is made based on characteristic ultrastructural changes in the GBM—splitting and lamellation on electron microscopic examination. Immunohistochemical staining for the various α chains of type IV collagen at the dermal-epidermal junction in a skin biopsy specimen can show alterations that are diagnostic of the various categories of hereditary nephritis (Kashtan, 2004). The use of genetic testing for Alport syndrome is becoming more accessible but is still not considered a routine procedure that can replace a kidney biopsy because identification of the unique mutation in most families is a costly and time-consuming procedure.

Henoch-Schönlein Purpura

Henoch-Schönlein purpura is a systemic vasculitis with a peak age for presentation of 4 to 6 years of age. The most common features include the characteristic palpable purpuric rash, abdominal pain with gastrointestinal bleeding, and arthritis with refusal to bear weight. Renal involvement, if present, is usually not evident until several weeks after the initial symptoms. Henoch-Schönlein purpura is an acute glomerulonephritis, and the renal biopsy specimen may demonstrate segmental necrosis of glomeruli or crescent formation. Children without renal involvement or only isolated hematuria or proteinuria can be managed with supportive care. Those children with more aggressive disease including nephrotic or nephritic syndromes are at higher risk for developing chronic renal disease, particularly girls, and should receive more aggressive therapy, including corticosteroids, renoprotective agents, and immunosuppressive drugs. There is the potential for affected members within the same family to have either Henoch-Schönlein purpura or IgA nephropathy and for an individual with Henoch-Schönlein purpura to have the disease evolve into IgA nephropathy.

Lupus Nephritis

The major renal manifestation of SLE is glomerular disease. **The primary symptoms leading to the diagnosis of renal disease in children with SLE are proteinuria, microscopic hematuria, hypertension, and mild renal insufficiency** (Cameron, 1994). SLE is an autoimmune disease with the potential to affect numerous organ systems. Children with SLE are more likely than adults to have renal involvement. The peak age at onset is 14 years, around the time of puberty, and females are more likely to be affected than males (M:F = 4.4:1). Half of children with lupus nephritis have nephrotic syndrome and/or renal insufficiency at diagnosis. SLE is divided into classes based on histopathology (the prevalence of each from several biopsy series in children is given in parentheses): class I, normal (6%); class II, mesangial proliferative (19%); class III, focal endocapillary proliferative (23%); class IV, diffuse endocapillary proliferative (43%); and class V, membranous (9%). Both C3 and C4 are commonly decreased during acute illness. Abnormalities common at presentation in children with lupus nephritis are fever (78%), arthralgia (75%), rash (68%), weight loss (40%), Coombs-positive anemia (48%), leukopenia (47%), thrombocytopenia (25%), coagulopathy (27%), and renal disease (82%).

Primary therapy for lupus nephritis is based on the class or severity at diagnosis and usually consists of corticosteroids plus additional cytotoxic drugs. Although no clinical trials have been performed in children, therapy is based on adult data, showing that the best long-term renal preservation for class IV nephritis is achieved with cyclophosphamide plus corticosteroids. Monthly pulses of cyclophosphamide are given during the 6-month induction phase followed by every-3-month doses up to 2 years. More recently, mycophenolate mofetil has been shown to have equal efficacy at 2 years compared with cyclophosphamide. Renoprotective therapy is a common adjunct in lupus nephritis, and many children require more than one antihypertensive medication during therapy. Long-term follow-up studies of childhood-onset lupus nephritis are lacking. From the case series at Guy's Hospital in London, of 78 children, 15% had progressed to ESRD, 6% were dead, 27% had remission of renal disease (some still on treatment), and 36% continued to have signs of renal disease on therapy (follow-up ranged from 1 to 26 years).

Hemolytic Uremic Syndrome

Hemolytic uremic syndrome is defined by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal insufficiency. In children, hemolytic uremic syndrome may be the typical form, which is associated with diarrhea, or an atypical form (Pickering et al, 1994; Loirat and Taylor, 2004). This discussion will focus on the typical diarrhea-associated hemolytic uremic syndrome, which in North America is secondary to primary infection with enterotoxic *Escherichia coli*. The enteropathic *E. coli* infection is usually contracted through ingestion of food contaminated with bovine feces: ground beef, water supplies, or vegetables/fruits. Person-to-person spread is also possible. Specific serotypes of *E. coli* (O157:H7) produce a verotoxin that binds to enterocytes and gains access to the microcirculation. After endocytosis into vessels the toxin causes endothelial injury, particularly in the kidney, by inhibition of protein synthesis by the endothelial cell. Platelet-fibrin thrombi within glomeruli cause ischemia of glomerular capillaries associated with mesangiolysis. Severe forms are also characterized by cortical necrosis as larger arterioles may become involved.

The diagnosis of hemolytic uremic syndrome is based on clinical features at presentation, because renal biopsies are not usually performed in the classic, diarrhea-associated hemolytic uremic syndrome. **The prodrome consists of enterocolitis, typically bloody diarrhea (70% of cases) along with vomiting and fever, followed by transient improvement; 4 to 7 days later the onset of pallor (anemia), general malaise, oligoanuria, fluid overload, and hypertension occurs.** Serious neurologic sequelae (i.e., seizures, encephalopathy, and coma) may be present in 20% of cases. The severity of renal involvement is related to the severity of the gastrointestinal prodrome but not related to the severity of anemia. Efforts to isolate *E. coli* O157:H7 from stool of affected children should be made, and recovery is better when samples are obtained within 6 days from onset of diarrhea. Cases are reported to the state health department.

Treatment of diarrhea-associated hemolytic uremic syndrome is supportive. Antibiotic therapy for *E. coli*-associated enterocolitis is discouraged because there may be increased risk to develop hemolytic uremic syndrome possibly owing to release of the bacterial toxin. Antimotility agents may increase the risk of toxic megacolon. Plasma exchange seems to be an effective option for these patients, except when caused by *Streptococcus pneumoniae*. Careful attention must be paid to fluid balance and to electrolyte disturbances. Hyperkalemia, which occurs because of increased release of potassium during red blood cell lysis, is further complicated by acidosis and decreased GFR. Therapy with packed red blood cell transfusions is indicated when the hemoglobin drops to less than 7 g/dL, but platelet transfusions are discouraged. Dialysis may be required during the oliguric phase, but early dialysis does not appear to improve outcome. Mortality associated with hemolytic uremic syndrome is 1% to 2%, and irreversible renal failure occurs in 5%. Late sequelae of hemolytic uremic syndrome including proteinuria, hypertension, and renal insufficiency have been reported in as many as 30% of survivors. Late sequelae are more likely in individuals with anuria for more than 1 week or who require more than 2 weeks of dialysis.

Other, non–diarrhea-associated forms of hemolytic uremic syndrome that may occur in children but are not discussed in this brief review include *Streptococcus pneumoniae*-associated hemolytic uremic syndrome, complement factor H deficiency, abnormal von Willebrand protease inhibitor, abnormalities of vitamin B_{12} metabolism, calcineurin inhibitor–associated hemolytic uremic syndrome, and post–bone marrow transplant–associated hemolytic uremic syndrome.

Key Points: Glomerular Disease

- *Nephrotic syndrome* is defined as edema, hyperlipidemia, hypoalbuminemia, and heavy proteinuria (>40 mg/m^2/hr).
- Renal biopsy histology and immunohistochemistry, when indicated, allow for proper diagnosis and direct management and prognosis.
- Congenital nephrotic syndrome–Finnish type is the most common cause of nephrotic syndrome in infants and is due to a mutation of the gene coding for nephrin (slit diaphragm protein).
- Minimal change disease, the most common cause of nephrotic syndrome, is the presumptive diagnosis when proteinuria responds to a course of corticosteroids.
- FSGS is more common among African-American children and is often corticosteroid resistant.
- Acute glomerulonephritis most commonly occurs 7 to 21 days after an upper respiratory infection and presents as cola-colored urine in an otherwise well child. A full recovery occurs in 90%.
- Alport syndrome can be distinguished from IgA nephropathy by a family history of significant renal disease and hearing impairment in first-order relatives.
- Henoch-Schönlein purpura has variable effects on the kidneys several weeks after the onset of the typical syndrome symptoms.
- Hemolytic uremic syndrome consists of hemolytic anemia, thrombocytopenia, and acute renal insufficiency that typically occurs after enterocolitis from *E. coli* (O157:H7).

RENAL TUBULAR DISORDERS

The renal tubule is responsible for absorption or secretion of various substances after the process of glomerular filtration. Each portion of the tubule—proximal convoluted portion, loop of Henle, distal convoluted portion and collecting duct—has specific absorptive and/or secretive responsibilities. The proximal tubule transports sodium, chloride, glucose, phosphorus, ketoacids, low-molecular-weight proteins (<50 kD), and water. The loop of Henle is involved in sodium, chloride, calcium, and potassium movement. The distal tubule is limited to sodium and chloride transport, whereas the collecting ducts move sodium, chloride, potassium, and protons. Tubular disorders reflect disorders of active or passive transport mechanisms causing solute loss into the urine (Table 112–2). Active transport mechanisms require energy from adenosine triphosphate (ATP) hydrolysis and therefore a favorable sodium gradient created by the basolateral Na^+,K^+-ATPase. Disorders of tubular function may be genetic (or congenital) or acquired and specific for a solute or generalized. They are organized according to the portion of the renal tubule most affected (Gregory and Schwartz, 1998).

Proximal Tubular Disorders

Fanconi syndrome is not a specific disorder but a generalized dysfunction of the proximal tubule. The causes of Fanconi syndrome are usually primary inherited disorders

Table 112–2.

Molecular Basis of Common Pediatric Tubular Disorders

DISEASE	ABNORMAL PROTEIN
Renal tubular acidosis	Protein pump: H^+-ATPase
	WNK4
Nephrogenic diabetes insipidus	Vasopressin receptor: V2 receptor
	Aquaporin water channel: AQP2
Dent disease	Chloride channel: ClCN5
X-linked hypophosphatemia	Endopeptidase: PHEX
Gitelman syndrome	Na^+ transport: Na^+,Cl^- cotransporter
Bartter syndrome	Na^+ transport: Na^+,K^+,Cl^- cotransporter
	Chloride channel: ClCKb
	Potassium channel: ROMK
	Membrane channel: barttin

(Chesney, 2004; Jones and Chesney, 2004) (mutations of metabolic enzymes or mitochondrial DNA) but may be sporadic or due to intoxication of heavy metals and outdated tetracycline, gentamicin, cyclosporine, tacrolimus, and ifosfamide. The typical features include glucosuria, aminoaciduria, phosphaturia, proximal RTA, low-molecular-weight proteinuria, hypokalemia and hypomagnesemia, hypouricemia, and mild to moderate renal insufficiency (Chesney, 2003; Kaplan, 2004). Children usually present with polyuria, muscle weakness and pain (hypokalemia), signs of dehydration including constipation, bone pain and bowing from rickets (hypophosphatemia, calcitriol deficiency), or growth failure (acidosis). Treatment consists of electrolyte replacement (primarily sodium and phosphorus), correction of the acidosis, and active vitamin D (calcitriol) administration.

There are other rarer forms of proximal tubular dysfunction, including familial glucosuria (benign and confused with diabetes mellitus), bicarbonaturia (proximal RTA), phosphaturia (often X-linked causing rickets), and aminoaciduria (cystine).

Distal Tubular Disorders

Renal Tubular Acidosis

RTA represents the clinical syndrome that occurs when the renal acidification capacity is compromised. In general, the kidney serves two functions in maintaining acid-base homeostasis: reclamation of the filtered load of bicarbonate and regeneration of bicarbonate consumed in the titration of nonvolatile acid produced in daily metabolism. Reclamation is a large bulk process that occurs in the proximal tubule. It links H^+ secretion at the apical via the Na^+,H^+ antiporter to bicarbonate reabsorption across the basolateral membrane via the sodium bicarbonate symporter. The replacement of bicarbonate lost in normal metabolism, which amounts to 1 to 3 mmol/kg/day in a healthy adult, occurs in the distal tubule. Infants and growing children have a greater daily acid production because deposition of bone during skeletal growth is an acidogenic process. Net acid removal occurs via H^+-dislocating ATPase pumps.

RTA can occur in three basic varieties: type I or distal, type II or proximal, or type IV due to aldosterone deficiency. In proximal RTA the threshold for bicarbonate reabsorption is depressed and the serum bicarbonate is lowered to the threshold level. It can be an isolated problem or be a manifestation of broad proximal tubule dysfunction, termed *Fanconi syndrome*. In the latter case the RTA is accompanied by glycosuria, phosphaturia, hypokalemia, and aminoaciduria. The cause of proximal RTA can be idiopathic or secondary to a wide range of metabolic disorders that compromise the bioenergetic state in the proximal tubule. The most common cause is cystinosis; but other less frequent causes include galactosemia, hereditary fructose intolerance, tyrosinemia, and glycogen storage disease type I.

In distal RTA (type I), the defect in acidification reflects either a reduction in the activity of the H^+-ATPase pumps or an inability of the distal tubule to maintain a normal H^+ gradient. The cause of distal RTA can be idiopathic. Secondary causes include disorders that interfere with the structure and function of the distal tubule, including sickle cell anemia, SLE, transplant rejection, calcineurin nephrotoxicity, and reflux nephropathy.

In type IV RTA there is reduced biosynthesis of aldosterone or tubular hyporesponsiveness to the hormone. Aldosterone plays a pivotal role in acid-base balance by increasing the expression of Na^+,K^+-ATPase along the basolateral membrane and enhancing the activity of apical H^+ pumps. Aldosterone synthesis is compromised in a number of genetic disorders of corticosteroid synthesis. It can also be reduced as a consequence of hyporeninemia in patients with diabetes mellitus. Failure to respond to aldosterone is a characteristic feature of children and adults with obstructive uropathy.

Patients with RTA usually present with failure to thrive. Along with diabetes insipidus (see later) and chronic kidney disease, it represents one of the three "pure" renal causes of impaired growth. Other presentations include asymptomatic hypercalciuria, nephrocalcinosis, or kidney stones. Patients may also have episodes of diarrhea and dehydration. Rickets is present in some patients (Evan et al, 2007) and was initially thought to be more prevalent in distal RTA and be a consequence of bone buffering of retained H^+.

The diagnosis of RTA requires the presence of hyperchloremic metabolic acidosis. The bicarbonate level measured in a venous blood gas specimen is approximately 5 mmol/L higher than in a routine serum sample and provides a more accurate estimate of acid-base status (Adedoyin et al, 2003). The value of the urine pH is very limited in making the diagnosis. However, in a child with acute metabolic acidosis, urinary anion gap measurement can be a useful gauge of distal tubule acidification capacity. Under these circumstances, a normal child will enhance excretion of the cation ammonium (NH_4^+), and the urine anion gap ($[Na^+] + [K^+]) - [Cl^-]$ will be a negative number (Kim et al, 1996). The serum potassium concentration will be normal or low at presentation in type I and II RTA whereas it is high in type IV RTA. The classic method was to assess urinary acidification after infusion of ammonium chloride. However, it often is difficult to get access to this compound and it can cause gastrointestinal upset. A recent report described the efficacy of combined administration of furosemide and fludrocortisone simultaneously to stimulate acid secretion, with a positive test based on urine pH less than 5.5. This procedure was easier to perform, better tolerated, and as accurate as an ammonium chloride challenge in adult patients with RTA (Walsh et al, 2007).

The treatment of RTA involves primarily oral bicarbonate administration, and adequate therapy should result in growth normalization. The dose for type I RTA is usually in the range of 1 to 3 mmol/kg/day to neutralize nonvolatile acid production. The amount required may be higher among patients ingesting a high-protein diet or in younger children who are growing because bone growth utilizes bicarbonate in bone crystal formation. The daily bicarbonate dose is usually much higher in type II RTA because it is difficult to sustain a normal bicarbonate concentration in these children with a diminished reabsorptive threshold. In operational terms, the requirement for a large bicarbonate dose to sustain growth is indirect confirmation of a proximal RTA diagnosis. In these children, potassium supplementation may be required after the initiation of bicarbonate supplementation because the anion lowers the luminal voltage in the distal tubule and promotes a kaliuresis. There are a number of available bicarbonate preparations, including sodium bicarbonate, sodium citrate, and sodium/potassium citrate, that come in liquid or tablet formulations, allowing the choice of the one that is best tolerated by the child. In children with secondary RTA, treatment of underlying disease will lead to RTA resolution and obviate the need for bicarbonate supplementation.

Bartter Syndrome

Bartter syndrome is a group of transport disorders characterized by hypokalemia, metabolic alkalosis, polyuria, and growth failure

(Rodriguez-Soriano, 1998). The primary defect is potassium and chloride loss. Volume depletion stimulates the renin-angiotensin-aldosterone axis, which leads to further potassium and hydrogen ion loss, aggravating hypokalemia (often < 2 mEq/L) and acidosis. Hypercalciuria may lead to nephrocalcinosis. Treatment centers on correcting the volume depletion and hypokalemia, with indomethacin (prostaglandin synthetase inhibitor) being useful in some children.

Antenatal Bartter syndrome, or hyperprostaglandin E syndrome, is an autosomal recessive disorder with severe polyuria and salt wasting and is associated with polyhydramnios (Chesney, 2003; Kaplan, 2004), offspring of consanguineous progeny, sensorineural deafness, and chronic renal failure. Mutations have been identified in the loop $Na^+,K^+,2Cl^-$ cotransporter or in the luminal potassium channel (ROMK).

Classic Bartter syndrome is due to a mutation in the basolateral membrane chloride channel protein A or B (CLCKA, CKCKB) and presents within the first 2 years of life (not necessarily from birth). Features include polyuria, salt craving, constipation (dehydration), muscle weakness/cramping, and failure to thrive. Facial features include a drooping mouth, large batlike ears, and a triangular face. Serum studies demonstrate hypokalemia and hypochloremic and metabolic alkalosis whereas hypomagnesemia is found in 20% to 50% of patients; urine studies demonstrate loss of sodium and potassium. The associated volume depletion protects against developing hypertension.

Gitelman Syndrome

Gitelman syndrome, more common among adolescents and young adults, arises from mutations in the distal tubule Na^+,Cl^- cotransporter (Chesney, 2004; Jones and Chesney, 2004; Kaplan, 2004). The effect is a clinical syndrome that resembles the effects of thiazide-like diuretics. The clinical features of Gittelman syndrome include hypokalemia, metabolic acidosis, hypocalciuria (which distinguishes this from Bartter syndrome), and hypomagnesemia, leading to muscle weakness or tetany, vomiting with dehydration, abdominal pain, and fever. Treatment consists of potassium and magnesium repletion.

Collecting Tubule Disorders: Diabetes Insipidus

The ability to concentrate urine depends on (1) an intact concentration gradient in the renal medulla and (2) functioning water channels located in the collecting tubule. The binding of antidiuretic hormone (ADH) to the vasopressin receptor (V2) found on the basolateral membrane leads to the insertion of aquaporin-2 (water channel) into the apical membrane of the collecting tubule and subsequent movement of water.

Nephrogenic diabetes insipidus (NDI) results from resistance of the collecting tubules to ADH. NDI is divided into two major categories: primary or genetic and secondary or acquired (Deen et al, 2000; Sasaki, 2004). The most common causes of acquired NDI in children are obstructive uropathy, drugs, metabolic disturbances, and miscellaneous conditions. Patients with hydronephrosis have downregulation of the vasopressin receptor in the collecting duct and impaired concentrating capacity, which is reversed with obstruction relief (Shapiro et al, 1978). Genetic defects in the V2 receptor can present as congenital hydronephrosis and lead to occasional confusion in determining cause and effect in patients with NDI and hydronephrosis (McDill et al, 2006). Lithium and amphotericin are two commonly prescribed drugs leading to NDI in children. Lithium downregulates the AQP2 channel in the renal medulla. Hypercalcemia and hypokalemia are the most frequent metabolic causes of NDI. Finally, diseases that disrupt the tubulointerstitium such as sickle cell anemia and Sjögren syndrome can cause NDI (Ren et al, 2008).

In hereditary NDI, loss-of-function mutations in the V2 receptor gene on the X chromosome account for nearly 90% of cases (Sasaki, 2004). The functional consequences of the genetic alterations run the gamut from impaired membrane insertion to inability to activate adenyl cyclase (Rosenthal et al, 1993). Most female V2 mutations carriers are asymptomatic, but some may have mild polyuria and polydipsia. Contrary to expectation, the clinical spectrum of disease severity in female carriers does not correlate with the inactivation level of the normal X-chromosome (Satoh et al, 2008). Most of the remaining cases are due to changes in the gene for AQP2, which is present on chromosome 12. Both recessive and dominant forms of AQP2-related disease have been identified. Although most cases of autosomal recessive NDI occur in cases of consanguineous marriages, homozygous mutations have been documented in a child born to unrelated parents (Bircan et al, 2008). Other proteins such as AQP1 may also cause NDI.

The majority of cases of nephrogenic diabetes insipidus are diagnosed in the first year of life. **The characteristic features include massive polyuria, polydipsia, hypernatremia, and the inability to concentrate the urine due to a defect in the renal tubular response to vasopressin.** The most common signs and symptoms include vomiting, failure to thrive, fever, constipation, polydipsia that suppresses the appetite, dehydration, along with developmental delay and behavioral abnormalities. The water deprivation test secures the diagnosis by demonstrating urine osmolality (Uosm) (<200 mOsm/kg water) that remains below plasma osmolality (Posm) after dehydration *and* no change to either Uosm or Posm after ADH administration. When this test is inconclusive, the presence of normal plasma ADH levels after hypertonic saline administration distinguishes nephrogenic from central diabetes insipidus. The hypernatremia associated with NDI can cause failure to thrive and even intracranial calcifications (Bindu et al, 2007). However, the long-term neurocognitive outcome is surprisingly good (Hoekstra et al, 1996), probably because of parental diligence in ensuring adequate water intake.

Key Points: Renal Tubular Disorders

- Fanconi syndrome refers to a generalized dysfunction of the proximal tubule.
- Polyuria, polydipsia, and poor growth are common presenting complaints in children with tubular diseases.
- Type I (distal) RTA is due to disturbed management of H+ whereas type II RTA (proximal) is due to bicarbonate malabsorption.
- Type IV RTA is due to reduced aldosterone production or response and associated with hyperkalemia.
- Hypokalemia is common to both Bartter syndrome and types I and II RTA; however, Bartter syndrome is characterized by alkalosis.
- Nephrogenic diabetes insipidus presents as polyuria, polydipsia, hypernatremia, and an inability to concentrate urine and is managed by administration of free water.

The mainstay of treatment is provision of adequate free water with special attention to adjusting for fever and intercurrent illnesses. Second-line therapy is to modestly lower the solute load with avoidance of excessive protein and sodium intake. If these measures are ineffective at lowering the daily urine volume, then the use of diuretics such as hydrochlorothiazide alone or in combination with amiloride can improve quality of life (Knoers and Monnens, 1990; Kirchlechner et al, 1999). Nonspecific prostaglandin inhibitors such as ibuprofen or more selective cyclooxygenase-2 inhibitors also decrease solute free water excretion (Monn, 1981; Soylu et al, 2005). As children grow, management becomes a bit easier because their ability to express thirst and ensure access to free water becomes less problematic compared with infants. The urologic complications of hydroureteronephrosis, urinary retention, and nocturnal enuresis are related to the massive urinary flow rate.

UROLITHIASIS AND HYPERTENSION

Urolithiasis

Kidney stones (Fig. 112–3) have been considered primarily a health problem affecting middle-aged men between 20 to 50 years of age. In adults, kidney stones are not a cause of mortality but are associated with considerable morbidity and financial burden resulting from medical care costs and lost work productivity during peak employment years (Coe et al, 2005). In general there is consistent evidence of increasing prevalence of urolithiasis over the past 3 decades and the age at initial diagnosis has fallen (Sowers et al, 1998; Stamatelou et al, 2003; Lieske et al, 2006). This epidemiologic trend may vary by gender in certain geographic regions and has been attributed to dietary changes such as increased ingestion of fructose-containing beverages, increasing incidence of obesity, higher ambient temperatures due to global warming, and higher prevalence of urologic abnormalities (Taylor et al, 2005). For all of these reasons, urolithiasis often is seen as a rare childhood condition. However, recent single-center studies indicate **that the incidence of urolithiasis in children has nearly tripled in the past 10 years and that the problem can be manifest in the first decade of life** (VanDervoort et al, 2007).

The signs and symptoms of stone disease are less discrete in children compared with adults and include irritability, abdominal pain, vomiting, diarrhea, and hematuria. As children get older they are more likely to present with the classic picture of unilateral colicky pain and gross hematuria. The diagnosis of urolithiasis in children requires a high index of suspicion, especially in children with a positive family history.

The etiology of urolithiasis spans a spectrum from structural anomalies that interfere with regular drainage of the urinary tract and lead to urinary stasis to metabolic abnormalities that enhance the likelihood of crystal formation in the urine. Urologists play a more pivotal role in children with neuroanatomic defects such as posterior urethral valves or neurogenic bladder. **The most common factor leading to urolithiasis is hypercalciuria, which can be sporadic or familial.** Other factors that can cause stones due to excessive levels in the urine are oxalate, uric acid, and cystine. Hyperoxaluria can represent a rare genetic disorder in oxalate metabolism or be secondary to altered diet or gastrointestinal absorption of oxalate. Hyperuricosuria can be secondary to dietary factors, metabolic disease, or malignancy.

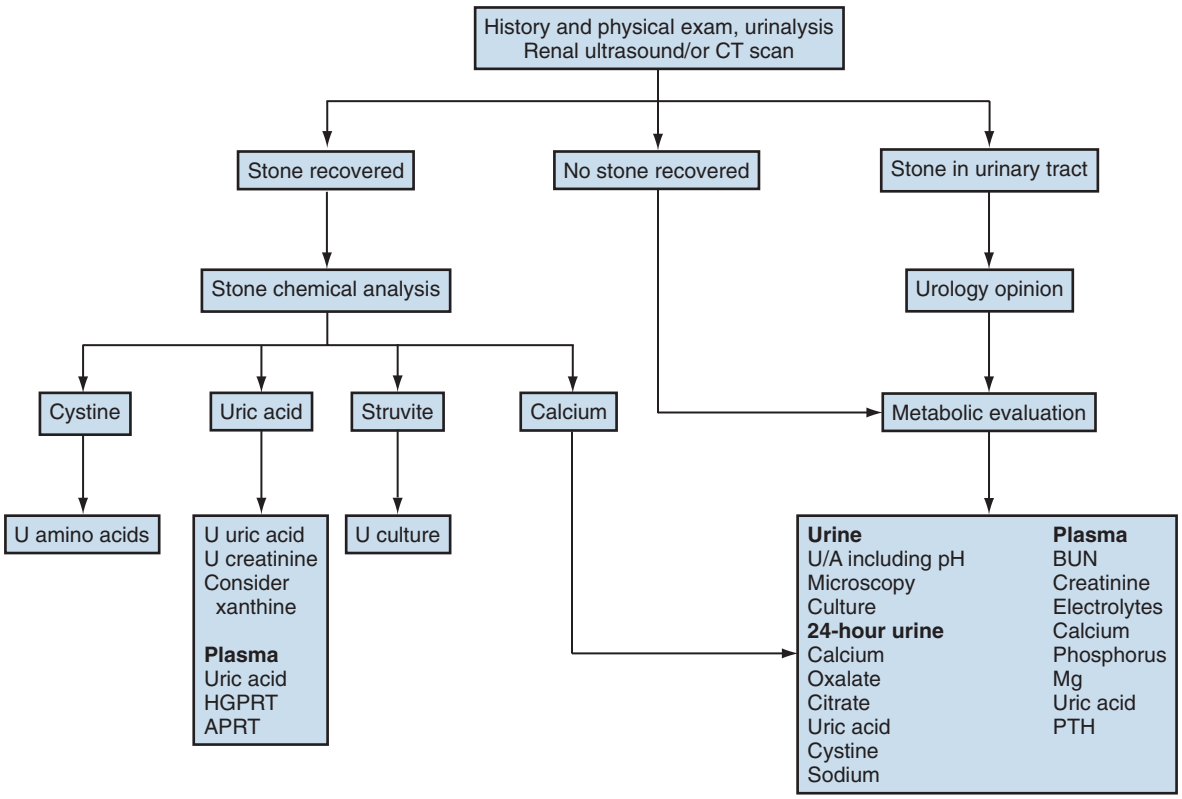


Figure 112–3. Algorithm for the evaluation of renal stones in children. APRT, adenine phosphoribosyl transferase; BUN, blood urea nitrogen; CT, computed tomography; HGPRT, hypoxanthine guanine phosphoribosyl transferase; PTH, parathyroid hormone; U/A, urinalysis.

Cystinuria is a genetic defect in dibasic amino acid transport. Among the factors that inhibit stone formation in the urine, the most prominent is citrate. Together with hypercalciuria, hypocitraturia is among two most common causes of urolithiasis in most studies of pediatric patients (VanDervoort et al, 2007). Recent studies suggest that these two factors are linked and that the urinary calcium-to-citrate ratio may be the most effect measurement to predict the occurrence of urolithiasis (Srivastava et al, 2009). Although some of the constituents of the urine can be quantitated based on spot urine with normalization to creatinine, most are best assessed based on 24-hour urine collections with reference to pediatric ranges for normal excretion of each solute.

The foundation of treatment is increased fluid intake, modest restriction in animal protein intake, and increased ingestion of fruits and vegetables. In patients with hypercalciuria, avoidance of extremes in calcium intake and use of thiazide diuretics can be implemented in patients with recurrent stone disease. Because patients with idiopathic calcium oxalate stones that may be linked to hypercalciuria demonstrate increased gastrointestinal absorption of oxalate, it may be beneficial to limit dietary intake of oxalate. Patients with hypocitraturia can be prescribed on citrate supplements. In certain high-risk populations, such as children with seizure disorders who are placed on a ketogenic diet, empirical treatment with potassium citrate without screening for hypercalciuria or hypocitraturia can achieve urinary alkalinization and reduce the incidence of kidney stones nearly sevenfold from 6.7% to 0.91% (McNally et al, 2009). Patients with hyperoxaluria can avoid excessive intake of high oxalate foods—chocolate, tea, rhubarb. However, there are data that these patients do not absorb oxalate excessively and only high oxalate-containing foods may need to be restricted (Sikora et al, 2008). A potentially exciting new development in the treatment of primary hyperoxaluria is the use of oxalate-utilizing bacteria *Oxalobacter formigenes* to diminish the gastrointestinal burden of oxalate (Kaufman et al, 2008). Long-term safety and efficacy studies are needed to validate the usefulness of this therapy. Those with cystinuria are placed on tiopronin and alkalinization of the urine to prevent recurrent stones. Extended follow-up is necessary for all children who have a kidney stone to monitor for recurrent stones that occur in 30% to 40% of patients and to assess the efficacy and need for any drug therapy. This is especially true in patients with an underlying genetic abnormality.

Hypertension

Blood pressure is influenced by a number of clinical factors, including age, gender, height, and patient posture. The range of normal values varies widely, and identification of hypertension requires consultation with reference tables of normative data collected in standardized pediatric cohorts (Feld and Corey, 2007). Based on the 2003 report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Chobanian et al, 2003), which lowered the systolic and diastolic blood pressure levels required for a diagnosis of hypertension in adults, it became apparent that prevailing norms were unacceptable. Some blood pressure levels in pediatric patients that were considered normal for children adolescents were labeled prehypertensive or abnormal in adults. As a consequence, there was a reformulation of normal blood pressure readings to bring the definitions of hypertension in children and adolescents more in line with adult guidelines, as outlined in Table 112–3 (National High Blood Pressure Education Program…, 2004).

Table 112–3.
Pediatric Definitions of Hypertension

Normal	SBP or DBP < 90th percentile for age and gender
Prehypertensive	SBP or DBP from 90th to <95th percentile *or* BP > 120/80 even if <90th percentile up to 95th percentile
Stage 1 hypertension	SBP or DBP 95th to 99th percentile + 5 mm Hg
Stage 2 hypertension	SBP or DBP > 99th percentile + 5 mm Hg

DBP, diastolic blood pressure; SBP, systolic blood pressure.

Measurement of blood pressure is not nearly as straightforward in infants and children as it is in adults. The child should be calm and sitting in a chair or a parent's lap with the arm in the right position. Older children should have their feet on the floor if possible. An appropriate size cuff that covers at least two thirds of the distance from the acromion to the olecranon should be applied to the right arm (Sala et al, 2005). Normative data for pediatric patients are based on auscultatory measurements. However, use of oscillometric devices is becoming more widespread in outpatient and emergency settings. In general, the two methods yield comparable values in children, with slightly lower systolic and slightly higher diastolic levels on oscillometric measurement.

The recommendation has been made to rely on 24-hour ambulatory blood pressure monitors (ABPMs) as the gold standard for the diagnosis of hypertension in children because the results of ABPM are more specific than home or clinic blood pressure measurements in hypertension diagnosis (Wuhl et al, 2004). There are normative data that facilitate the interpretation of 24-hour blood pressure monitoring for patients from ages 5 to 20 (Wuhl et al, 2002). In contrast to adults, for whom home blood pressure measurements are close to daytime ABPM, home measurements for pediatric patients are significantly lower than the results of 24-hour ABPM readings during waking hours (Stergiou et al, 2004). Additional benefits of ABPM include the ability to identify masked hypertension (high daytime ABPM but normal office blood pressure readings)—an entity that has the same prognosis as essential hypertension (Lurbe et al, 2005). In addition, ABPM in patients with secondary causes of hypertension including chronic kidney disease can be used to detect abnormalities in the circadian blood pressure rhythm with lack of a nocturnal dipping pattern (Seeman et al, 2005) and in blunting of ultradian rhythms that occur over intervals less than 24 hours (Wuhl et al, 2005).

There are data suggesting a trend toward rising blood pressure in children and adolescents during the past 2 decades related to an increased prevalence of childhood obesity (Munter et al, 2004; Robinson et al, 2004). A survey of blood pressure and lipid levels in 1717 eighth graders in Texas, California, and New York found that 24% had high blood pressure, a higher percentage than was seen in previous national surveys in which subjects were less overweight (Jago et al, 2006). However, a recent meta-analysis of 14 large population-based surveys of blood pressure conducted during the past few decades did not demonstrate an increase in blood pressure in children and adolescents despite the ongoing epidemic of pediatric obesity (Chiolero et al, 2007). Defining the epidemiology of hypertension in children is complicated by the observation that prehypertension and hypertension are frequently underdiagnosed in the pediatric population (Hansen et al, 2007). In a cohort study of 14,187 children and

adolescents aged 3 to 18 years who were observed at least three times for well-child care, only 26% of those with hypertension (n = 507) and 11% of those with prehypertension (n = 485) had the diagnosis documented in the electronic medical record. A large meta-analysis including data from diverse populations indicates that the strength of blood pressure tracking increases with baseline age, decreases with the duration of follow-up, and did not vary across ethnic groups (Chen and Wang, 2008). These findings indicate that although pediatric blood pressure levels do track into adulthood the correlation is not that high to preclude interventions designed to alter long-term outcomes. The role of low birth weight and reduced nephron number in the pathogenesis of essential hypertension is a contentious subject that is the focus of numerous conflicting studies (Huxley et al, 2002; Keller et al, 2003; Schreuder et al, 2007).

The secondary causes of hypertension can be divided into six categories:

1. Renal parenchymal diseases (e.g., reflux nephropathy, polycystic kidney disease, primary glomerulopathies, and obstructive uropathy)
2. Renal vascular diseases (e.g., fibromuscular dysplasia, neurofibromatosis)
3. Aortic coarctation
4. Endocrine disorders (e.g., hyperthyroidism, hyperaldosteronism)
5. Malignancy (e.g., Wilms tumor, neuroblastoma, pheochromocytoma)
6. Miscellaneous (e.g., drugs, immobilization, Guillain-Barré syndrome)

Although there are published reports that secondary disease is more common in pediatric patients, with more widespread measurement of blood pressure in routine clinical practice, most children and adolescents have primary or essential hypertension (National High Blood Pressure Education Program…, 2004).

The current recommended workup of a child with newly identified hypertension includes a complete serum biochemical panel, fasting lipid profile, urinalysis, renal ultrasonography, and an echocardiogram (National High Blood Pressure Education Program …, 2004, Nguyen et al, 2007). Use of a 24-hour ABPM is becoming more widespread and is likely to improve the accuracy and validity of hypertension assessment in children older than age 10. Additional testing including plasma renin activity, retinal examination, renal arteriography, serum cortisol, aldosterone, thyroid hormone levels, and urinary catecholamine excretion should be guided by the specific clinical circumstances in each case. A renal arteriogram is advised for patients with severe hypertension or in situations in which one drug cannot control the blood pressure because this test enables diagnosis and potential cure of the underlying renovascular cause for the hypertension (Shahdadpuri et al, 2000). However, the extensive list of tests outlined previously may not be cost effective. In a study of 200 children referred for outpatient evaluation of hypertension, only three tests yielded abnormal finding more than 10% of the time: ABPM, echocardiogram, and fasting lipid profile (Wiesen et al, 2008). This suggests that more extensive testing should be limited to those with more severe hypertension, clinical symptoms, or abnormalities in one of the three tests just listed.

The majority of pediatric patients in all ethnic groups, including whites and African-Americans, with an elevated blood pressure have essential hypertension. These patients are usually asymptomatic, have a positive family history of hypertension, tend to be obese, and are more prone to hypertensive responses to stressful events. In a study of 2816 young adults aged 20 to 35 who were not being treated with antihypertensive medications, every 10 mm Hg increment in blood pressure in response to video game and star tracing tasks was associated with a 24% increase risk of coronary artery calcification at follow-up (Matthews et al, 2006). Newly identified risk factors for essential hypertension in children and adolescents in addition to obesity (Munter et al, 2004; Robinson et al, 2004; Jago et al, 2006) include inactivity (Gidding et al, 2006), sleep apnea (Ievers-Landis and Redline, 2007), and neonatal nephrocalcinosis (Kist-van Holthe et al, 2007). Recent studies suggest that essential hypertension may not be a silent disease in pediatric patients. A survey of 409 children aged 7 to 18 with new-onset hypertension revealed that 64% of the patients reported various symptoms such as headaches, difficulty sleeping, and daytime tiredness compared with 26% of healthy normotensive controls (Croix and Feig, 2006). More serious target organ complications can also occur in this population. Children with uncontrolled essential hypertension experience cardiovascular load with resultant left ventricular hypertrophy in more than 40% of hypertensive children (Brady et al, 2008). The frequency of left ventricular hypertrophy is the justification for including echocardiograms as a standard part of the evaluation of a child with hypertension. Repeat imaging is advisable after 6 to 12 months to assess resolution of left ventricular hypertrophy with appropriate blood pressure management. Diastolic filling abnormalities were noted in 36% of patients (n = 55) with essential hypertension, changes that were more prominent in those with concentric hypertrophy (Border et al, 2007). Finally, subtle neurocognitive deficits such as reduced digit span, block design, and mathematics scores were documented in a cohort of 5077 children aged 6 to 16 who were included in the National Health and Nutrition Examination Survey III (Lande et al, 2003).

The treatment of acute severe hypertension usually requires parenteral therapy (Table 112–4). Current drug options include labetalol 0.25 to 0.5 mg/kg/dose or nicardipine 0.1 to 0.5 µg/kg/min. The goal of therapy is to lower the mean pressure by 20% (Calhoun and Oparil, 1990). Long-term management of severe hypertension can include drugs from various classes including diuretics, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, β-adrenergic blockers, and direct vasodilators. In response to the U.S. Food and Drug Administration Modernization Act of 1997 there are available data from controlled clinical trials involving children and adolescents for representative medications for most of the drug classes except diuretics and direct vasodilators (Flynn, 2003).

In patients with presumed essential hypertension, a trial of nonpharmacologic therapy including regular exercise, weight reduction, modest sodium restriction, smoking cessation, and relaxation/meditation techniques is warranted before resorting to drug treatment. The effectiveness of nonpharmacologic interventions should be reassessed after 3 to 6 months and

Table 112–4.

U.S. Food and Drug Administration–Approved Drugs for Use in Pediatric Patients

CLASS	DRUG
Angiotensin-converting enzyme inhibitors	Enalapril, lisinopril, ramipril
Angiotensin receptor blockers	Losartan, candesartan
Calcium channel blockers	Amlodipine
β-Adrenergic blockers	Metoprolol, bisoprolol

pharmacologic intervention should be instituted if normalization has not occurred by the end of the observation period (National High Blood Pressure Education Program …, 2004).

Key Points: Urolithiasis and Hypertension

- Renal stones may present in childhood as a manifestation of hypercalciuria or hypocitraturia but may be due to genetic disorders.
- Metabolic evaluation and treatment is warranted in children with nephrolithiasis.
- Proper technique, equipment, and patient cooperation are vital in measuring accurate blood pressure in children.
- Hypertension should be diagnosed using ambulatory blood pressure monitors and recently revised reference tables.
- Serum hormonal studies and angiography should be reserved for children with hypertension that is severe or fails to respond to medical therapy.
- Essential hypertension is most common and asymptomatic and related to obesity and inactivity.

ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is the new term that has been proposed to replace acute renal failure in patients with sudden decline in kidney function. It is preferred because it represents a less concrete nomenclature that allows coverage for the wide range in kidney damage and dysfunction that occur in clinical practice. In recognition of the numerous definitions that have employed in the past in studies of the epidemiology, cause, treatment, and outcome of AKI, new standards, called the RIFLE criteria (Risk, Injury, Failure, Loss, End-stage renal disease), have been adopted to classify AKI. These criteria incorporate changes in urine output and serum creatinine concentration over time in an integrated scheme to define risk, injury, and long-term damage in the spectrum of AKI.

AKI is characterized by a sudden reduction in GFR and the inability of the kidney to properly regulate fluids and electrolytes. Serum markers of renal function (BUN and creatinine) are elevated, although they may be insensitive measurements under several circumstances. **In children with normal renal function, GFR may fall by 50% before producing an increase in creatinine concentration; large changes in creatinine level are seen for small changes in GFR in children with chronic renal injury** (Doolan et al, 1962; Bennet and Porter, 1971). Creatinine levels also reflect the child's muscle mass whereas BUN is affected by hydration status and conditions that raise urea production (e.g., gastrointestinal bleeding, high protein intake) or lower urea production (e.g., severe liver disease, protein malnutrition).

The incidence of AKI ranges from 8% to 24% of neonates and is higher among hospitalized children, many with pre-existing kidney disease (Martin-Ancel et al, 1995; Mogal et al, 1998; Nolan and Anderson, 1998; Gouyon and Guignard, 2000). Genetic risks factors may predispose neonates to AKI such as polymorphisms of the ACE gene or the angiotensin receptor (Nobilis et al, 2001), tumor necrosis factor-α, interleukin (IL)-1β, IL-6, and IL-10 genes (Treszl et al, 2002). Certain causes of AKI have predilection for certain age groups, such as cortical necrosis and renal vein thrombosis in neonates, hemolytic uremic syndrome in young children, and rapidly progressive glomerulonephritis in older children.

Pathophysiology

The induction of and recovery from AKI is multifactorial, and some of the involved cellular and molecular mechanisms have been clarified. Early or mild hypoperfusion leads to activation of the adrenergic nerves causing diffuse vasoconstriction aimed at sustaining systemic blood pressure and perfusion. This compensatory response increases renal vascular resistance and decreases glomerular blood flow (Badr and Ichikawa, 1988; Tack and Perlman, 1988; Hricik and Dunn, 1990; van Bel, 1991; Schlondorff, 1993). When renal perfusion is compromised, renal vascular resistance decreases by afferent arteriolar vasodilation and the intrarenal production of prostaglandins (van Bel, 1991; Schlondorff, 1993). The renin-angiotensin-aldosterone axis is stimulated by hypovolemia and hypoperfusion: angiotensin II (AT2) production increases efferent arteriolar constriction, which in turn increases the glomerular filtration pressure (Steiner, 1979; Tucker and Blantz, 1983; Blantz, 1998) and also produces aldosterone, which stimulates salt and water reabsorption by the distal tubule. The cumulative affect is increased filtration fraction and maintenance of GFR. Administering ACE inhibitors under these conditions can precipitate AKI. Persistent or progressive hypoperfusion overwhelms the compensatory mechanisms, leading to excessive vasoconstriction, decreased glomerular blood flow, and decreased GFR (Badr and Ichikawa, 1988). The role of the renin-angiotensin system in AKI is uncertain because injury can be reduced by diuresis with mannitol or loop diuretics (neither affects intrarenal renin) or in animals immunized against renin-angiotensin, treated with ACE inhibitors, or infused with an AT2 antagonist.

ATP levels are depleted by ischemia in vivo (Karlowicz and Adelman, 1995), and inhibition of ATP production causes cellular injury in vitro. The medullary thick ascending limb (Brezis, 1984) and the straight segment of the proximal tubule (Donohoe et al, 1978) are susceptible to hypoxic injury. The marks of hypoxic injury can be averted or reversed by increasing oxygen delivery (Brezis and Rosen, 1995). Early ischemia leads to brush border sloughing; and further ischemia leads to either lethal (denuding of basement membrane epithelium) or sublethal injuries (swelling, cellular morphology disruption, mitochondrial condensation) with subsequent intratubular obstruction and tubular fluid backleak (Donohoe et al, 1978; Myers et al, 1979) largely by the loss of integrins (Gailit, 1993). Reactive oxygen molecules (hydroxyl radical, superoxide anion) play a role in local postischemia reperfusion injury (Andreoli, 1991) whereas hypochlorous acid and hydrogen peroxide can cause distant injury owing to their long half-lives and ability to cross cell membranes (McKelvey et al, 1988). These reactive molecules can cause functional protein loss by amino acid oxidation and membrane damage by lipid and lipoprotein peroxidation. Elevated intracellular calcium levels may be primary in cell injury or secondary to cell death (Weinberg, 1991). A role for apoptosis is unclear, although endonuclease activation has been identified in hypoxic and ischemic tubules (Liberthal and Levine, 1996). Cell membrane disruption occurs from the detergent affect of the degradative products, or endogenous phospholipase activation and ATP depletion may limit new phospholipids production (Humes et al, 1989; Chen et al, 1995). Redistribution of membrane lipids and proteins alters cell polarity and impairs certain cell functions (Molitoris, 1991).

Several factors influence recovery from AKI. In the first few minutes of reperfusion, ATP levels regain 50% to 70% of their loss depending on ischemia time and the pool of available adenine nucleotides (Weinberg, 1991). Over the next several hours ATP is produced from salvage pathways and from precursors provided

during reperfusion (also dependent on the ischemia time (Donohoe et al, 1978; Molitoris, 1991). ATP-$MgCl_2$ (stimulates purine synthesis) (Gaudio et al, 1982) and thyroxine (stabilizes mitochondrial adenine nucleotide transporter) (Boystun, 1995) hasten ATP recovery. Atrial natriuretic factors (Nakamoto et al, 1987) increase afferent arterial dilation and efferent arterial constriction, promoting salt and water excretion, renal blood flow, and GFR. Injured tubule cells regain polarity, perhaps through the 70-kD heat shock proteins (Emami et al, 1991). Postischemic infusion of several growth factors improves GFR, diminishes morphologic injury, increases thymidine incorporation into DNA, and increases survival (Fine et al, 1992).

Etiology

The classification of AKI into prerenal, renal, and postrenal causes with subsequent division of renal into glomerular and tubular causes is still broadly applicable to children (Table 112–5). Glomerular causes of kidney injury have key clinical signs and symptoms such as gross hematuria, hypertension, and edema that facilitate recognition and treatment.

Table 112–5.
Causes of Acute Renal Injury

Prerenal Injury
Decreased true intravascular volume
- Gastrointestinal losses
- Salt-wasting disease: renal or adrenal
- Diabetes insipidus: central or nephrogenic
- Third-space losses: sepsis, trauma, nephrotic syndrome

Decreased effective intravascular volume
- Congestive heart injury

Intrinsic Renal Disease
Acute tubular necrosis
- Ischemic-hypoxic insults
- Drugs: aminoglycosides, intravenous contrast, cisplatin, nonsteroidal anti-inflammatory drugs
- Exogenous toxins: ethylene glycol, methanol
- Endogenous toxins: myoglobin and hemoglobin

Uric acid nephropathy and tumor lysis syndrome
Interstitial nephritis
- Drug induced: antibiotics, anticonvulsants
- Idiopathic

Glomerulonephritis
- Postinfectious glomerulonephritis
- Membranoproliferative glomerulonephritis
- Systemic lupus erythematosus nephritis
- Chronic infection
- Henoch-Schönlein purpura
- Anti–glomerular basement membrane glomerulonephritis
- Idiopathic rapidly progressive glomerulonephritis

Vascular lesions
- Hemolytic uremic syndrome
- Cortical necrosis
- Renal artery thrombosis
- Renal venous thrombosis

Infectious causes
- Sepsis
- Pyelonephritis

Obstructive Uropathy
Obstruction in a solitary kidney
Bilateral ureteral obstruction
Urethral obstruction

Postrenal injury can generally be identified by history and physical examination, and the diagnosis is readily confirmed by ultrasonography in most cases. Urinary parameters are frequently used to help distinguish the category of AKI (Table 112–6).

Prerenal Injury

Prerenal causes are the most common etiology of AKI (60%). Hypoperfusion results from volume contraction after hemorrhage or dehydration from diabetes insipidus, gastrointestinal losses, salt-wasting diseases, increased insensible losses, or reduced effective blood volume (e.g., congestive heart injury, cardiac tamponade, hepatorenal syndrome). Because these kidneys are intrinsically normal, restoring renal perfusion restores renal function.

The tubules respond appropriately to renal hypoperfusion by conserving sodium and water. Thus urine osmolality is high (>400-500 mOsm/L), urine sodium is low (<10-20 mEq/L), and FE_{Na} is low (less than 1%). Infants are vulnerable to prerenal AKI because immature kidneys cannot maximally concentrate urine or conserve salt and water and their large body surface area increases insensible water loss. Neonates with immature tubules and children with pre-existing renal disease may have urinary indices suggestive of acute tubular necrosis (ATN). Nonoliguric AKI in children with concentrating defects make salt and water loss difficult to recognize. During polyuria, other indicators of free-water loss (e.g., weight loss, increased BUN, hypernatremia, increased hematocrit) should be used.

Intrinsic Renal Disease

The distinction between prerenal and true renal injury remains clinically challenging. Prerenal azotemia is a functional state in which there is reduced renal and glomerular hypoperfusion and which can be readily reversed by restoration of blood pressure and/or intravascular volume. As mentioned earlier, reliance on serum BUN and creatinine may be inaccurate and reliance on changes in serum creatinine may delay diagnosis and implementation of effective therapy. A number of new urinary biomarkers are

Table 112–6.
Urinary Values That Distinguish Categories of Acute Renal Injury

TEST	PRERENAL	INTRINSIC RENAL	POSTRENAL
BUN/Cr ratio	>20	10-20	10-20
Urine specific gravity	>1.020	~1.010	<1.010
Urine osmolality	>350	~300	~300
Urine sodium	<20	>30	>40
FE_{Na}	<1%	>2%	>3%
Urine microscopy	Normal	ATN: dark granular casts, renal epithelial cells/casts	Normal
	Hyaline casts	GN: RBCs, RBC casts, WBCs, proteinuria	Hyaline casts
		AIN: urine eosinophilia, WBCs, hyaline casts	

AIN, acute interstitial nephritis; ATN, acute tubular necrosis; BUN, blood urea nitrogen; Cr, creatinine; FE_{Na}, fractional excretion of sodium; GN, glomerulonephritis; RBCs, red blood cells; WBCs, white blood cells.

under investigation for early identification of AKI. These include neutrophil gelatinase-associated lipocalcin (NGAL), IL-18, and kidney injury molecule-1 (KIM-1). Of these three candidate biomarkers NGAL appears the most promising. A commercial kit is available to rapidly perform this measurement in urine samples, and it is being studied in clinical trials in wide variety of age groups and clinical settings to validate the diagnostic accuracy of the measurement. It is possible that optimal diagnosis of AKI will rely on dipstick testing with reagents to detect a panel of biomarkers.

Renal artery thrombosis is associated with use of an umbilical artery line and a patent ductus arteriosus. Infants present with hypertension, hematuria, and thrombocytopenia. AKI may occur in cases of a solitary kidney or massive thromboemboli (Bauer et al, 1975). The initial ultrasound image may appear normal or have minor abnormalities, whereas little or no blood flow is seen on a renal scan. Treatment aims at limiting clot extension by removing the umbilical catheter; anticoagulant or fibrinolytic therapy can be considered, particularly if the clot is large (Ellis et al, 1997).

Renal venous thrombosis (RVT) is more common and occurs after sepsis, perinatal asphyxia, hypovolemia, shock, maternal diabetes, or polycythemia in infants and from severe dehydration or hypercoagulable states in older children. RVT presents as gross hematuria, thrombocytopenia, hypertension, decreased urine output, and elevated BUN and creatinine levels. Ultrasonography reveals an enlarged kidney, and the renal scan shows reduced blood flow and function. Thrombectomy is rarely indicated or possible.

Acute glomerulonephritis is more common in schoolaged children who present with edema, hypertension, and hematuria. Postinfectious glomerulonephritis is most common and associated with mild to moderate AKI whereas other glomerulonephritides (Goodpasture syndrome) often present as AKI. Active lesions in biopsy specimens portend functional recovery. Immunosuppressive therapy might reverse renal injury (Michel and Kelly, 1998).

ATN can evolve from prerenal injury. The urinalysis may demonstrate low-grade proteinuria and granular casts, whereas urine indices of tubular function demonstrate an inability to conserve sodium and water. Serum creatinine concentration usually increases by 0.5 to 1.0 mg/dL/day. Ultrasonography reveals normal-sized kidneys with loss of corticomedullary differentiation, whereas the renal scan shows normal or slightly decreased renal blood flow with delayed tracer uptake in the parenchyma and absence of excretion in the collecting system. The prognosis of ATN is good except when the insult causes vasculature injury, microthrombi, and cortical necrosis. The mortality and morbidity is poorer in children with multiorgan injury (Stapleton et al, 1987; Bunchman et al, 2001). In those who recover, renal function returns to normal within days to weeks. There may be a diuretic phase when the recovering tubules cannot appropriately reabsorb solute and water. Fluid and electrolyte balance is important to promote recovery; however, a period of dialysis is often required. Children who do recover may later develop chronic renal disease and ESRD.

Several drugs are associated with AKI. Aminoglycoside nephrotoxicity, perhaps related to lysosomal dysfunction of proximal tubules, is related to drug dosing, therapy duration, and pretreatment renal function. Children present with nonoliguric AKI with minimal urinary abnormalities. Although the course is reversible, the serum creatinine level may rise for several days after drug discontinuation owing to ongoing tubular injury from high parenchymal levels. **Once-daily dosing of aminoglycosides decreases the incidence of nephrotoxicity without compromising efficacy** (Barza et al, 1996). Intravascular contrast media, particularly in patients with dehydration, diabetes, or preexisting renal disease may precipitate AKI. The risk can be reduced by using nonionic, low-osmolality (Rudnick et al, 1995) or isoosmolar, dimeric nonionic contrast media (Aspelin et al, 2003).

Nephrotoxic agents, exogenous or endogenous, may induce AKI. Ingestion of compounds (ethylene glycol, methanol) in their native state or after metabolism to breakdown products may be nephrotoxic. Hemolysis and rhabdomyolysis can induce tubular injury due to vasoconstriction, intra-tubular pigment precipitation, and/or heme protein–induced oxidant stress (Andreoli, 1991). Renal injury can be lessened by prompt fluid resuscitation followed by diuresis (mannitol or loop diuretics) to increase urine flow that prevents intratubular precipitation of heme proteins and by urine alkalization to increase hemoglobin and myoglobin solubility (Vanholder et al, 2000).

Malignancy or its treatment may induce AKI. Renal function can be affected by parenchymal infiltration of leukemic or lymphomatous cells or by uric acid crystal precipitation in the tubules, obstructing urine flow, or in the microvasculature, obstructing renal blood flow (Stapleton et al, 1988). More commonly, AKI results from tumor lysis syndrome associated with chemotherapy (Jones et al, 1995). Elevated levels of serum potassium, BUN, purine metabolite products, and phosphorus (with hypocalcemia) may require dialysis. Allopurinol limits uric acid excretion but increases xanthine (Andreoli et al, 1986) and other less soluble uric acid precursors. AKI is transient with expected full recovery of renal function.

Acute interstitial nephritis, perhaps from a hypersensitivity reaction to tubular basement membrane antigens, results from a drug reaction (e.g., methicillin, cimetidine, sulfonamides, rifampin, nonsteroidal anti-inflammatory drugs) or may be idiopathic. Children present with AKI, rash, fever, arthralgias, eosinophilia, and pyuria with or without eosinophiluria (Hawkins et al, 1989). The ultrasound image shows large echogenic kidneys, and the renal biopsy demonstrates an eosinophilic interstitial infiltrate. Treatment includes drug discontinuation and corticosteroids.

Postrenal Injury

Although urinary tract obstruction rarely causes AKI, children with chronic obstructive uropathies are vulnerable by either hypoxic-ischemic or nephrotoxic insults.

Management

Effective treatment of AKI, without dialysis, requires restoring adequate renal blood flow, avoiding agents that are nephrotoxic or interfere with renal compensatory mechanisms, and maximizing renal perfusion before using such agents. Increasing urine output makes fluid management easier, aids in maintaining electrolyte balance, and simplifies addressing nutritional needs.

Several vasodilatory agents have been used to maintain renal blood flow in AKI. "Renal-dose" dopamine (0.5 to 5.0 μg/kg/min) can increase renal blood flow and improve urine output by promoting natriuresis but may not decrease the need for dialysis or increase survival (Chertow et al, 1996; Denton et al, 1996). Fenoldopam mesylate (a selective dopamine-1 receptor agonist) may improve renal hemodynamics in animals and increase renal perfusion, urine flow, and sodium and potassium excretion in hypoxemic adults (Murphy et al, 2001). Atrial natriuretic peptide increases GFR by dilating afferent arterioles and constricting

efferent arterioles (Rahman et al, 1994) but failed to improve the overall dialysis-free survival rate in adults (Allgren et al, 1997).

Diuretic agents can stimulate urine output and allow safer administration of medications and nutrition; however, **converting oliguria to nonoliguria does not increase GFR or alter the course of AKI** (Shilliday et al, 1997; Kellum, 1998). Diuresis may exacerbate AKI in prerenal or contrast-induced azotemia. Mannitol (0.5 to 1.0 g/kg) may increase intratubular urine flow, limiting tubular obstruction. Furosemide (1 to 5 mg/kg/dose) acts similarly but also inhibits Na^+,K^+-ATPase to reduce oxygen consumption in damaged tubules. Loop diuretics do not alter the need for dialysis or mortality (Kellum, 1998), and high-dose furosemide can be ototoxic.

AKI may present as hypovolemia, euvolemia, or hypervolemia. Oliguria or anuria commonly presents as hypervolemia and requires fluid restriction and/or acute fluid removal. Euvolemia can be maintained by correcting insensible water losses (skin, respiratory and gastrointestinal tracts) and excess water loss from diarrhea or fever. Urine losses may be replaced milliliter for milliliter with the appropriate fluid (assessed by urine electrolytes). Nonoliguric renal injury is commonly associated with nephrotoxic insult and carries less morbidity and mortality than oliguric AKI (Mogal et al, 1998).

Hypertension is related to fluid overload and/or to increased vascular tone. Diuretic agents should be used first in cases of volume overload, but dialysis or hemofiltration may be necessary. Antihypertensive agents may be used in the form of intravenous sodium nitroprusside, labetalol, diazoxide, enalapril, and nicardipine for severe hypertension and intravenous hydralazine or sublingual nifedipine for less severe cases. Once the blood pressure is controlled, oral long-acting agents can be used.

Malnutrition associated with catabolism delays recovery, but studies in children supporting an improved outcome with nutritional supplementation are lacking. Dilute formula of increasing concentration is given to maintain calories. Hyperalimentation is used if enteral feeds are not possible. Children with oliguria/anuria may require dialysis because fluid balance may not be achievable while providing calories.

The purpose of acute renal replacement therapy is to remove endogenous and exogenous toxins and to maintain fluid, electrolyte, and acid-base balance until renal function returns. Renal replacement therapy may be provided by peritoneal dialysis, intermittent hemodialysis, or continuous renal replacement therapy

Sodium Disturbances

Mild hyponatremia may be due to dehydration, but fluid overload with dilutional hyponatremia is more common. If the serum sodium level exceeds 120 mEq/L, fluid restriction or dialytic water removal will increase the sodium level. When the serum sodium level is below 120 mEq/L, the infusion of hypertonic saline over several hours to raise the sodium level to 125 mEq/L reduces the risk of seizures.

Potassium Disturbances

Hyperkalemia is common and potentially life threatening by inducing arrhythmias. Serum potassium levels may increase owing to decreased filtration, impaired tubular secretion, acidosis-induced shifting to the extracellular compartment, and release of intracellular potassium during catabolic state. Each 0.1-unit reduction in arterial pH increases the serum potassium level by 0.3 mEq/L. The serum potassium level may be falsely elevated by hemolysis (during the blood draw) or an increased white blood cell (WBC) or platelet count (Rodriguez-Soriano, 1995). Hyperkalemia depolarizes the cardiac conduction pathway that is potentiated by hypocalcemia. The electrocardiographic findings include tall, peaked T waves followed by PR interval prolongation, flattening of P waves, and widening of the QRS complex with ventricular tachycardia and fibrillation possible. Symptoms include malaise, nausea, and progressive muscle weakness. Therapy options include intravenous calcium (stabilizes cell membranes reducing the arrhythmia risk without changing serum potassium levels), glucose and insulin or bicarbonate (shifts potassium into the intracellular space), or enteric exchange resins (sodium polystyrene sulfonate [Kayexalate]).

Acid-Base Disturbances

Acidosis is related to increased metabolic rate. Hyperventilation may partially correct the acidosis unless the child is obtunded, in which case the acidosis may become severe. Severe acidosis can be treated with intravenous or oral sodium bicarbonate or citrate solutions, but dialysis may be required. Balancing the acidosis may decrease ionized calcium levels, precipitating tetany and/or seizures; the total and ionized calcium levels must be known before starting therapy.

Calcium and Phosphate Disturbances

Kidneys excrete large amounts of ingested phosphorus, hence dietary restriction should be started and oral calcium compounds that bind phosphorus (preventing gastrointestinal absorption) may be added. Dialysis effectively removes phosphorus. Hypocalcemia may result from hyperphosphatemia, inadequate renal production of 1,25-dihydroxyvitamin D impairing adequate gastrointestinal calcium absorption, and skeletal resistance to parathyroid hormone. When severe, hypocalcemia should be treated with 10% calcium gluconate with continuous electrocardiographic monitoring. Less severe cases may be treated by oral calcium salts.

Outcome and Prognosis

Simple AKI without other underlying illness carries a 7% to 23% mortality rate, whereas children with AKI as a component of multisystemic injury have a much higher mortality rate (Goldstein, 2001) related to associated conditions. Recovery of renal function depends on the underlying cause. Children with acute interstitial nephritis and ATN typically recover normal renal function and are at low risk for any late complications. Children with substantial nephron loss or rapidly progressive glomerulonephritis are at risk for later developing renal injury. Hyperfiltration of the remnant nephrons may eventually lead to progressive glomerulosclerosis (Brenner et al, 1996). **Life-long renal function monitoring,**

Key Points: Acute Kidney Injury

- Serum BUN and creatinine may be insensitive markers of AKI.
- AKI reflects the kidneys' inability to regulate fluids and electrolytes in response to a sudden drop in GFR.
- Aminoglycoside nephrotoxicity can be reduced by once-daily dosing schemes.
- Effective treatment of AKI requires restoring renal blood flow, correcting fluid, electrolyte, and acid-base disturbances, and avoiding further insults. Dialysis is used as needed.
- Substantial nephron loss during AKI warrants life-long monitoring for progression to chronic renal disease.

blood pressure monitoring, and urinalysis in these patients is necessary to detect the harbingers of renal injury (i.e., hypertension, proteinuria, and eventually elevated BUN and creatinine levels).

CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) refers to a state of irreversible kidney damage that may remain stable or progress to ESRD, at which point renal replacement (dialysis or transplantation) is required. Children account for about 1% of the total ESRD population in the United States (U.S. Renal Data System, 2008). The causes of CKD in pediatric patients are fairly evenly divided between congenital/hereditary and acquired causes. The exact percentages vary depending on the country of origin for the registry-based data of children with renal disease. In the very young child, congenital anomalies are the most common cause (North American Pediatric Renal Trials and Collaborative Studies, 2008; U.S. Renal Data System, 2008) whereas glomerulopathies are more common in older children (Foreman, 1988). Gender is a factor only in obstructive uropathy (more common in boys) and reflux nephropathy (more common in girls).

The classification system devised by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) has been widely used since 2002 (Table 112–7) (National Kidney Foundation, 2001). The system is based on renal function in children older than the age of 2 years and with at least 3 months of kidney disease. CKD is considered present when the GFR falls below 60 mL/min/1.73 m^2. Stages 1 and 2 require evidence of kidney damage to exclude children with reduced GFR due to nonrenal causes (e.g., solitary kidneys, malnutrition). Kidney damage is defined as structural (on biopsy) or functional (e.g., proteinuria, hypertension, or abnormal imaging).

GFR measurement requires quantification of creatinine from timed urine collection or can be estimated by the Schwartz formula. Timed urine collection from children can be unreliable and inaccurate, especially in incontinent children. Factors that affect GFR include age, gender, and body size. GFR matures over the first 2 years of life after correction for 1.73 m^2 body surface area (Heilbron et al, 1991). GFR may be reliably calculated by the Schwartz equation:

$$\text{GFR (mL/min/1.73 m}^2) = 0.413 \times \text{height (cm)/serum Cr (mg/dL)}.$$

This latest iteration of the Schwartz formula differs from the prior one in that a single constant value for all ages has been instituted rather than age-based constants (Schwartz et al, 2009).

Table 112–7.

Classification of Chronic Kidney Disease for Children Older than Age 2 Years

STAGE	DEFINITION	GFR (mL/min/1.73 m^2)
1	Normal or ↓ GFR (with kidney damage)	≥90
2	Mild ↓ GFR (with kidney damage)	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	<15 or dialysis

GFR, glomerular filtration rate.

The long-term outcome for preservation of kidney function is related to the extent of in-utero damage to the kidney. Urologic procedures are important to ensure regular voiding, adequate emptying of the urinary tract with as little manipulation as possible, and prevention of urinary tract infections. However, surgery does not materially influence the time when patients reach stage 5, that is, a GFR less than 15 mL/min/1.73 m^2.

Early detection of renal disease (with prenatal ultrasonography or determination of microalbuminuria) and treatment of the effects of CKD including proteinuria (with an ACE inhibitor or angiotensin type 1 receptor antagonist), hypertension, anemia, malnutrition, electrolyte and acid-base disturbances, and renal osteodystrophy may delay CKD progression (Wuhl and Schaefer, 2008). Practically, most patients present while in the throes of renal disease and treatment is aimed at staving off progression to glomerulosclerosis. Reversing renal injury requires shifting the balance of synthesis/degradation; however, new glomeruli cannot be generated after term in humans. High doses of an ACE inhibitor or angiotensin type 1 receptor antagonist regress existing glomerulosclerosis by decreased extracellular matrix synthesis with decreased transforming growth factor-β and increased extracellular matrix degradation with a decrease of plasminogen activator inhibitor type 1 (Fogo, 2001). A low-protein diet and ACE inhibitor attenuated glomerulosclerosis in rats (Marinides et al, 1990).

Sodium Disturbances

Children with congenital anomalies (e.g., cystic dysplasia, obstructive uropathy, cystinosis) tend to have dehydration and need to have sodium and water losses corrected (Rodriguez-Soriano et al, 1986; Parekh et al, 2001). In contrast, the sodium and fluid retention associated with acquired chronic glomerulonephritis or nephrotic syndrome is treated by restricting dietary sodium and fluid and administering loop diuretics (Rees et al, 2007).

Potassium Disturbances

Hypokalemia occurs in potassium-wasting tubular diseases (e.g., cystinosis, Fanconi syndrome, Bartter syndrome) or as a side effect of thiazide or loop diuretics and can be managed by providing oral potassium. Hyperkalemia may occur as the kidney inadequately excretes potassium; treatment starts with dietary potassium restriction, correction of acidosis, and discontinuation of ACE inhibitors or angiotensin receptor–blocking agents. Managing severe hyperkalemia is discussed in the section on acute renal failure.

Acid-Base Disturbances

Progressive metabolic acidosis is common among children with CKD because the kidneys cannot adequately excrete acid produced by cellular metabolism and growth and reabsorb bicarbonate by renal tubules. In CKD stages 3 and 4, an anion-gap acidosis results from reduced excretion of inorganic (e.g., sulfates, phosphates) and organic acids. A non–anion gap acidosis occurs with tubular bicarbonate loss from tubular injury or from RTA. Uncorrected metabolic acidosis retards linear growth (Wallia et al, 1986; Chiu et al, 2009) because bone is used to buffer the excess hydrogen ions (Salusky et al, 2004). The acidosis can often be managed with oral alkaline agents (e.g., sodium bicarbonate, citrate, or acetate) (National Kidney Foundation, 2000; Chiu et al, 2009).

Renal Osteodystrophy

Rickets, osteopenia, and secondary hyperparathyroidism are bone diseases related to CKD known as renal osteodystrophy, a disorder that can lead to linear growth failure, avascular necrosis, skeletal

fractures, and deformities. The pathophysiology starts with decreased renal synthesis of calcitriol (1,25-dihydroxyvitamin D), which reduces calcium absorption in the gut, causing hypocalcemia and secondary hyperparathyroidism aimed at replacing serum calcium. Vitamin D deficiency reduces available substrate for calcitriol synthesis (National Kidney Foundation, 2005). Hyperphosphatemia from poor renal clearance exacerbates hypocalcemia and secondary hyperparathyroidism, stimulating fibroblast growth factor production (Levin et al, 2007), which further suppresses renal calcitriol production (Gutierrez et al, 2005). The treatment of osteodystrophy includes raising serum parathyroid hormone levels with active vitamin D sterol administration (calcitriol or paracalcitol) and dietary phosphate restriction and administration of calcium-based or sevelamer-based phosphate binders (Coladonato, 2005; National Kidney Foundation, 2005) to reduce hyperphosphatemia. Aluminum salts are no longer used because of their toxicity (Andreoli et al, 1984).

Nutrition and Growth

Nutrition is often impaired (Martin, 1973) owing to poor appetite and limited food options (e.g., sodium, potassium, and phosphorus restrictions). The management of these children includes provision of adequate calories and protein to support growth without exacerbating azotemia. Caloric intake should provide at least the recommended daily recommended intake for age (Rees and Shaw, 2007). However, if insufficient caloric intake affects the child's height and weight, specially formulated supplements should be provided. Most children can be fed by mouth, and reliance on enteral tube feedings should be restricted to infants and children who cannot tolerate oral feeding. Nocturnal infusion of formula can supplement caloric intake when oral intake of nutrients during the day is insufficient. **Although accelerated progression of renal failure may occur with increased protein intake** (Meyer et al, 1987), **limiting dietary protein intake does not prevent CKD progression in children; proteinuria and hypertension are more reliable predictors of progression** (Uauy et al, 1994; Wingen et al, 1997). Peritoneal dialysis clears protein in the dialysate; these children require increased protein intake. Growth failure and short stature from acidosis, renal osteodystrophy, and growth hormone resistance (Kiepe et al, 2001; Tonshoff et al, 1997) may occur despite optimal nutrition. Those children who fail to grow despite provision of adequate calories will double their growth rate if placed on recombinant human growth hormone. The dosage needs to be higher than in children with normal kidney function who are being treated for short stature. This reflects relative resistance to recombinant human growth hormone in children with CKD (Fine et al, 1994).

Anemia

Anemia is nearly universal in children with CKD and largely results from reduced renal production of erythropoietin and/or iron deficiency (McGonigle et al, 1984; Koshy and Geary, 2008). The evaluation includes serum measurements of hemoglobin, hematocrit, reticulocyte count, and serum iron studies (e.g., serum iron, ferritin, transferrin or total iron-binding capacity, and percent transferrin saturation). Treatment includes the subcutaneous administration of erythrocyte-stimulating agents such as recombinant erythropoietin. The frequency of injections can be reduced by administering glycosylated forms of erythropoietin that have a prolonged half-life and an extended duration of action (Warady, 2006). A poor therapeutic response may reflect iron deficiency, which can be supplemented orally (National Kidney Foundation, 2006b).

Hypertension

Hypertension is an independent predictor for CKD progression (Wingen et al, 1997; Mitsnefes, 2003; Wuhl and Schaefer, 2008) and blood pressure should be maintained below the 90th percentile for age, gender, and height. Hypertension from fluid overload can be treated with dietary sodium and fluid restriction plus a loop diuretic or vasodilator such as a calcium channel blocker (e.g., nifedipine, amlodipine). Second-line agents include β-adrenergic blockers (e.g., propranolol, atenolol) and central-acting agents (e.g., clonidine). Renin-mediated hypertension is best treated with an ACE inhibitor (e.g., captopril, enalapril, lisinopril, ramipril) or angiotensin type 1 receptor antagonist (e.g., losartan, candesartan, valsartan). However, these agents may induce hyperkalemia and worsen renal function in CKD stages 4 and 5. Antihypertensive agents preserve glomerular function and structure by reducing systemic blood pressure and other nonhemodynamic effects (Dworkin, 1991; Fogo and Kon, 1996). ACE inhibitors reduce glomerular pressure, halting glomerular destruction in animals (Kasiske, 1993), and maintain normal GFR and decrease proteinuria in normotensive human diabetics (Marre et al, 1987; Mathiesen et al, 1991). Either ACE inhibitors or angiotensin type 1 receptor antagonists retard progression in patients with diabetic nephropathy and hypertension (Lewis et al, 1993, 2001; Brenner et al, 2001). Calcium antagonists are protective in animal models of diabetes, renal ablation, and hypertension (Dworkin, 1991) owing to afferent arteriole vasodilation, augmenting immunosuppression and antiproliferative effects (Cianciaruso, 1994). Combining ACE inhibitors and calcium channel blockers may be synergistic by decreasing both angiotensin II and calcium-mediated effector mechanisms linked to vascular injury (Lüscher et al, 1995).

Uremia

Uremic symptoms (e.g., bleeding, pericarditis, encephalopathy) are uncommon until CKD stage 4. Acquired platelet dysfunction

Key Points: Chronic Kidney Disease

- The staging system for CKD applies to children older than age 2 years and with reduced GFR from renal causes.
- Management principles includes electrolyte and acid-base balance, calcium homeostasis to avoid osteodystrophy, proper nutrition to foster growth, hemoglobin maintenance, and treatment of hypertension.
- Limiting proteinuria can be protective against CKD progression when induced by ACE inhibitors or angiotensin type 1 receptor antagonists but not by dietary protein restriction.
- Peritoneal dialysis is the preferred mode of renal replacement therapy in children because of its reliability, convenience, and efficacy.
- Peritonitis, the most common complication of peritoneal dialysis, is diagnosed by finding more than 100 WBCs/mm^3 and 50% neutrophils in the effluent and is treated by intraperitoneal administration of antibiotics.
- Omentectomy is performed by many to avoid occlusion and possible peritoneal dialysis catheter removal.

leads to prolonged bleeding (Boccardo, 2004). Pericarditis occurs only in undialyzed or insufficiently dialyzed stage 5 patients (Renfrew et al, 1980; Alpert and Ravenscraft, 2003). The signs and symptoms of uremic encephalopathy may be subtle (poor school performance) or present as obtundation and seizures (Lawry et al, 1994). All children, including infants and young children, should be assessed regularly.

RENAL REPLACEMENT THERAPY

In certain circumstances renal insufficiency is so severe that renal replacement is needed to sustain life processes or to clear accumulated electrolytes that pose a risk to the patient, such as acidosis and hyperkalemia. The options for these children include peritoneal dialysis, hemodialysis, and renal transplantation. Each modality has its indications and can be effective in meeting these goals. Of course, each modality similarly has its associated complications and impact on quality of life.

Peritoneal Dialysis

The options for managing ESRD are renal transplantation, peritoneal dialysis (PD), or hemodialysis (HD). In 1918, Blackfan and Maxcy described successful intraperitoneal injection of saline in dehydrated infants. Subsequently, PD evolved as the preferred mode of renal replacement therapy in children with the development of disposable nylon catheters (Maxwell et al, 1959), "permanent" catheters (Tenckhoff et al, 1966), and automated dialysate delivery systems (Boen et al, 1964). In the most recent report from the North American Pediatric Renal Trials and Collaborative Studies (2008), the first treatment among children with ESRD was home PD (50%), whereas 25% underwent pre-emptive transplantation 25% began chronic HD.

PD can be performed in any child with an intact peritoneal cavity allowing diffusion (e.g., movement of solutes down a concentration gradient) and convection (e.g., transport of a fluid flux largely determined by the ultrafiltration rate) to occur. PD is preferred over HD in the first few days of life (Neu et al, 2002) and may be done by manual fluid exchange or with an automatic cycler. In acute renal failure, PD effectively clears rapidly rising levels of potassium, phosphate, and other solutes. In children with ESRD, PD should be started when the creatinine clearance falls below 14 mL/min/1.73 m^2 regardless of serum BUN or creatinine levels. **The only absolute contraindication to PD is an inadequate peritoneal cavity** (e.g., omphalocele, diaphragmatic hernia, gastroschisis). PD can be performed after abdominal surgery in the absence of draining wounds, in children with vesicostomies, urinary diversions, or other stomas, (Alexander and Lubischer, 1982; Alexander, 1983; Flynn, 2002) and after renal transplantation if the graft is placed extraperitoneally.

A reliable catheter placed percutaneously or surgically is mandatory for successful PD. Bedside placement of a percutaneous catheter, using the Seldinger technique under local anesthesia, is reasonable in infants or children at high risk for general anesthesia (Borzotta et al, 1983). These catheters historically carried high rates of peritonitis (Day and White, 1977), but long periods of infection-free use are reported (Bunchman, 1996). Conversion to a surgically placed catheter can proceed when the child is stable and prolonged dialysis is confirmed.

The permanent Tenckhoff catheter is made of soft material, with intraperitoneal and extraperitoneal portions. The intraperitoneal portion, with holes to allow passage of peritoneal fluid, is either straight or curled; the curled design causes less pain and is less likely to suffer omental occlusion. The extraperitoneal portion has one or two Dacron cuffs (the first cuff positioned at the entrance to the peritoneum and the second cuff placed 1 cm from the skin tunnel exit site) that prevent fluid leaks and bacterial migration and fix the catheter's position to the abdominal wall. The catheter exit site is positioned as far from a stoma as possible (even to the chest) to prevent infection (Chadha et al, 2000). Omental occlusion of the catheter is the leading cause of revision (Warady et al, 1997); however, routine omentectomy is not universal (Neu et al, 1995).

The PD prescription specifies dialysate composition, exchange volume, inflow, dwell, and drain times of each exchange and the number of exchanges per 24 hours. Commercially available dialysate comes in dextrose concentrations of 1.5%, 2.5%, and 4.25% and electrolyte composition of sodium, 132 mEq/L; chloride, 102 mEq/L; lactate, 35 mEq/L; magnesium, 1.5 mEq/L; and calcium, 3.5 mEq/L. Warming the dialysate to body temperature before infusion prevents sudden hypotension. Continuous ambulatory peritoneal dialysis implies four to five daily exchanges with a long overnight dwell. Initially, exchange volumes are small but increased over the next 5 to 10 days. Initial stabilization often requires several days of 30- to 60-minute exchanges, but, once stabilized, PD can continue indefinitely.

Complications

Peritonitis is the most common complication of PD (Warady et al, 1984; Verrina et al, 2000), occurring once per 4.7 patient months (Neu et al, 2002) and more commonly in children younger than age 1 year. The most common organisms are gram positive (50%), gram negative (20%), and then fungal (2.3%). **Patients have cloudy dialysate with abdominal pain, fever, vomiting, or diarrhea, but the diagnosis is made by documenting greater than 100 WBCs/mm^3 with at least 50% neutrophils in the effluent.** Treatment relies on intraperitoneal administration of broad-spectrum antibiotics for 14 to 21 days and is changed according to sensitivity results. Gram-negative bacterial and fungal infections that require PD catheter removal are associated with peritoneal scarring and peritoneal membrane failure and may potentially require a change to hemodialysis (Warady et al, 2000).

Blood-tinged dialysate is common early in PD and clears after a few exchanges. Heparin can avert catheter obstruction by small clots. Detection of an injured organ or large vessel may be difficult based on dialysate color. Using ultrasound can minimize this risk during percutaneous catheter placement. Ultrasonography may also prevent bladder perforation, which may occur in an incompletely empty bladder, especially in infants and children with neuropathic or obstructed bladders. The injury may not be noted until there is a suprapubic mass, polyuria, gross hematuria, and glycosuria.

PD should be a painless procedure for children. Pain during inflow may reflect peritonitis, cold dialysate, local reaction to the low pH of the dialysate, local irritation from rapid inflow, omental or adhesion trapping of the catheter, and abdominal distention. Rectal or suprapubic pain occurs when the catheter tip is between the bladder and the rectum. Subdiaphragmatic air leads to shoulder pain.

Dialysate leakage is common in the first few days if initial exchange volumes are too large or the catheter is frequently manipulated or placed on traction. Leakage is less likely when use of a new catheter is delayed for 24 hours. When possible,

temporary suspension of PD may be needed or the catheter replaced with a larger one.

Adequate inflow but poor outflow leads to abdominal distention and fluid overload. Catheter occlusion by omentum is the most common cause; other causes include constipation, intraperitoneal adhesions, fibrin, blood clots, faulty position, and tube kinks. Drainage can occasionally improve by flushing with heparinized saline or instilling urokinase or tissue plasminogen activator (Shea et al, 2001; Stadermann, 2002). Surgical replacement and omentectomy may be necessary.

Respiratory distress may occur from increased intraperitoneal pressure from excessive or retained dialysate. Symptoms include dyspnea, hypoxemia, and respiratory failure, especially in small infants. Hydrothorax due to a diaphragmatic hernia or diaphragmatic eventration must be considered.

Sclerosing encapsulating peritonitis is a rare but serious problem after receiving PD for more than 5 years (Warady, 2000). It is characterized by continuous, intermittent, or recurrent bowel obstruction associated with gross thickening of the peritoneum (Warady et al, 2000). Peritoneal calcifications on CT in association with ultrafiltration failure suggests the diagnosis and may result in withdrawal of PD.

Hemodialysis

HD is best performed in specialized dialysis units equipped with appropriate pediatric dialysis equipment and personnel capable of providing adequate psychosocial, educational, and dietary support to children and their families. The child's vasculature is accessed and the blood travels to the dialyzer where accumulated toxins or solutes are extracted by perfusion across a semipermeable membrane driven by diffusion and convection, and the blood is then returned to the patient. Vascular access is gained by creating an arteriovenous fistula (AVF) or implanting an arteriovenous graft (AVG) in children who are larger than 20 kg and expected to require HD for longer than 12 months (National Kidney Foundation, 2006a). AVFs are created by anastomosis of an artery to a vein, most commonly in the wrist (radiocephalic) or the antecubital fossa (brachial artery to cephalic vein). The venous portion expands over time to a size large enough for safe needle placement—a minimum of 4 weeks but preferably 3 to 4 months (National Kidney Foundation, 2001) and may require 4 to 6 months in small children (Bourquelot et al, 1990). AVGs are made of polytetrafluoroethylene tubing connecting an artery to a vein that can be used after 4 weeks when the luminal portion endothelializes (National Kidney Foundation, 2001). One-, 3-, and 5-year AVF and AVG survival rates in children are similar (90%, 60%, and 40%, respectively). AVGs have higher thrombosis and surgical intervention rates (Sheth et al, 2002). Temporary HD catheters should be placed with the tip in the right atrium to allow adequate blood flow preferably through the internal jugular site, which has a lower incidence of venous thrombosis than the subclavian vein. The catheter should be placed on the side contralateral to a planned AVF or AVG (National Kidney Foundation, 2001). Acute HD is accomplished through a temporary, uncuffed dual-lumen catheter placed in the femoral, internal jugular, or subclavian vein. Two separate single-lumen venous catheters may be needed for infants. Besides for acute renal failure, acute HD may be needed in tumor lysis syndrome and in hyperammonemia in children with inborn errors of metabolism and drug ingestions.

AVF complications include development of venous collateral vessels, arterial inflow stenosis with poststenotic aneurysm formation, and thrombosis caused by stenosis of the venous outflow tract (Swedberg et al 1989; Kanterman et al, 1995). The most common complications of HD catheters include infection (tunnel or line), kinking of the catheter, and thrombosis. Despite heparin packing, catheter thrombosis is a significant problem that is treated by instilling tissue plasminogen activator into the catheter or by intraluminal clot extraction. Gram-positive organisms, especially *Staphylococcus* species, are the most common organisms. Because HD cannot be interrupted, catheter infections are treated with antibiotics alone. Catheters should be removed in the presence of repeated symptomatic bacteremia (high fever, rigors, chills, hypotension), intractable infections, or fungal infections. The median longevity of a dual-lumen HD catheter in children is 204 to 280 days (Goldstein et al, 1997, Sharma et al, 1997; Sheth et al, 2001).

Renal Transplantation

Preparation for transplant is key in the management of CKD stage 5 in pediatric patients. The ultimate goal in these children is to proceed directly to transplantation and avoid dialysis if at all possible. Patients with congenital uropathies represent ideal transplant candidates because there is no risk of recurrent disease. It is important to have the children undergo a full imaging and urodynamic evaluation and to perform any procedures before transplantation that will be needed to ensure that urine flow and drainage will be normal after transplantation. If dialysis is necessary, PD is preferred in younger children unless there is an anatomic contraindication to the procedure.

The sources of kidneys for pediatric transplantation are either living (related or unrelated) or deceased. Although transplants with living related kidneys historically carried the highest survival rates, **the 1-year graft survival of deceased donor kidneys (93.5%) currently approaches that of living related kidneys (95.4%)** owing to advances in immunotherapy (Wuhl and Schaefer, 2008). Contraindications to kidney transplantation include active malignancy or remitted disease for less than 2 years, human immunodeficiency virus infection, positive T-cell crossmatch, and history of poor compliance or noncompliance with medical management (Davis et al, 1998). Children undergoing transplantation for FSGS, hemolytic uremic syndrome, or primary oxalosis are at significant risk of disease recurrence that may place the graft at risk for failure (Cameron, 1993; First and Peddi, 1999; Hariharan et al, 1999).

The pretransplant urologic evaluation assesses the need for native nephrectomy and to assess the fittingness of the bladder to accept the transplanted kidney without placing its survival at risk. This evaluation includes a history for urologic disease and operations on the urinary tract as well as bladder function. The physical examination includes noting the location of scars and stomas that may interfere with transplantation. A urinalysis and urine culture as well as ultrasound evaluation of the kidneys and bladder (including a postvoid image) should be performed. Voiding cystourethrography is indicated if a recent status of vesicoureteral reflux is unknown. This can be included during the urodynamic evaluation in children with a history of posterior urethral valves, triad syndrome, bladder exstrophy, or neurogenic bladder. When the bladder is unacceptable for safely accepting the graft (poor compliance) despite maximal medical management, augmentation cystoplasty may be needed to improve the success of the renal transplant. Clean intermittent catheterization should be continued after transplantation. The indications for native nephrectomy before renal

transplantation include severe uncontrollable hypertension, uncontrolled significant proteinuria, recurrent pyelonephritis, grade 4 or 5 hydronephrosis, persistent severe vesicoureteral reflux, previously infected or symptomatic polycystic kidneys or those extending below the iliac vessels, and persistent anti–GBM antibody levels.

SUMMARY

The value of the collaboration between pediatric urologists and nephrologists cannot be overestimated. In this chapter many of the entities whose evaluation and management overlap between the two specialties were reviewed and several clinical problems primarily seen by pediatric nephrologists were discussed. Some of these latter clinical conditions may not always involve urologists, but an appreciation for their features broadens the scope of knowledge and interest and can only strengthen an already solid working relationship.

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chapter
113

Congenital Urinary Obstruction: Pathophysiology and Clinical Evaluation

Craig A. Peters, MD, FACS, FAAP ● Robert L. Chevalier, MD

Clinical Context
Patterns of Congenital Obstructive Nephropathy
Growth and Differentiation
Fibrosis
Functional Integration
Reversal of Congenital Renal Obstruction
Approach to Clinical Cases
Clinical Evaluation
Imaging
Prognosis and Management Strategies

CLINICAL CONTEXT

The spectrum of urinary obstruction in children is one of the most common conditions affecting the urinary tract and has substantial health consequences. Obstructive nephrouropathies constitute the single largest entity leading to renal insufficiency in male children younger than 1 year of age and are the largest single cause of renal failure requiring transplantation, occurring in about 23% of children who undergo renal transplantation (Seikaly et al, 2003). A large number of children are affected by lesser degrees of obstruction that induces concern, leading to ongoing imaging to monitor renal function and the status of the obstruction.

The wide spectrum of obstructive changes constitutes one of the major challenges in the clinical management of these conditions in that there is no definitive dividing line between obstruction that warrants intervention from that which does not (Peters, 1995). The presence of an obstructive lesion is readily determined with current imaging, but the criteria for intervention are highly controversial. This is largely because of a lack of information regarding the natural history of differing degrees of obstruction and the absence of effective markers of the pattern and progression of obstruction (Chevalier, 2004). We are left with few guideposts along the spectrum of obstruction by which clinical decisions may be made.

The current state of knowledge regarding the pathophysiology of congenital urinary obstruction, how it may be correlated with clinical scenarios, and its distinction from postnatal obstruction are reviewed here. It is anticipated that with increasing understanding of the mechanisms involved in congenital urinary obstruction we will become better able to discriminate between children requiring therapeutic interventions and those in whom this would be unnecessary.

Clinical Presentation of Obstruction

Prenatal ultrasonographic diagnosis has radically altered the clinical presentation of obstructive conditions, and today most of these conditions are detected before birth and many have no apparent clinical signs. Those that present as clinical manifestations are often severe obstructive conditions, such as posterior urethral valves or massive hydronephrosis. Children are still found with clinical signs of obstruction, usually infection or pain and, rarely, hypertension. In the child with obstruction of the entire urinary tract, even when the obstruction is relieved the functional abnormalities inform urologists of the effects of obstruction on developing kidneys. Reduced filtration function as manifest by a rising serum creatinine concentration is associated with glomerular injury, acidosis is due to tubular injury, and nephrogenic diabetes insipidus is secondary to collecting duct abnormalities. In extreme cases these may all be present, but on occasion they are noted in isolation and will often persist after correction of the obstruction (Hutcheon et al, 1976). Obstructive hypertension appears to be renin mediated (Riehle and Vaughan, 1981; Urata et al, 1985; Mizuiri et al, 1992) and may be reversible with surgical repair (de Waard et al, 2008).

The pathologic correlates of these functional alterations have been described in the congenitally obstructed kidney to varying degrees (Elder et al, 1995; Stock et al, 1995; Han et al, 1998; Poucell-Hatton et al, 2000; Zhang et al, 2000; Huang et al, 2006). The pathologic changes associated with lesser degrees of obstruction have been less thoroughly investigated, and a spectrum of qualitatively similar alterations have been described. In the absence of overt functional alterations and in unilateral conditions, determining the state of the affected kidney becomes a

clinical challenge. This challenge is often tied to the question of whether surgical intervention is appropriate, and much controversy has emerged from this question. Clinical imaging studies are currently the only widely used modality to make this assessment, and their interpretation is not uniform. The natural history of many conditions in the spectrum of obstruction is not well described yet is the essence of the question. It should be clearly seen that the spectrum of obstruction is wide, involves conditions that do not require intervention as well as others that produce profound renal injury, and may change with age and persistence of the condition.

Progressive Renal Dysfunction

A major concern regarding obstructive conditions in the urinary tract is the potential for a progressive situation leading to ever more loss of renal function. Progression may be seen in two forms, one with the uncorrected partially obstructive lesion (i.e., ureteropelvic [UPJ] obstruction) and the second with the previously obstructed but corrected obstruction that has produced some degree of renal damage (i.e., posterior urethral valves). In the first, renal function may initially appear intact on imaging tests yet in time there will be progressive loss of absolute and relative function of the kidney affected by the obstruction. If this were known prospectively, intervention would be appropriate and should be performed early. The challenge is in predicting this situation, and few markers are available to do this. The frequency of progressive deterioration in unilateral obstruction likely ranges from 20% to 40%, but duration of follow-up will significantly affect this rate. Every prospective study of obstructive conditions has documented the potential for progressive loss (Palmer et al, 1998; Parkhouse et al, 1988; Koff and Campbell, 1992; Koff, 2000).

The second situation reflects the fact that the damaged kidney does not have the functional reserve of a normal kidney by which it may maintain its absolute function over time. These kidneys will demonstrate a steady decline in function over time, and this is usually evident in bilateral obstruction. The mechanism may be hyperfiltration of remnant renal units, and clinically this is most often seen with posterior urethral valves (Parkhouse et al, 1988; Nguyen and Peters, 1999). These children may show very adequate renal function early in life yet demonstrate a delayed and inexorable progression into renal failure in adolescence (Fig. 113–1). Whether earlier intervention would have protected their renal function is uncertain, but that possibility cannot be neglected.

Predictors of ongoing progression of renal injury secondary to either ongoing or prior renal obstruction are of critical importance, yet there are few to rely on. The most evident one is altered absolute renal function, as clinically indicated by a creatinine clearance or serum creatinine value. This is relatively insensitive in early stages of progression. Radionuclide imaging may be helpful in some cases, but there is no gold standard as to the best interpretation of potentially progressive disease.

Definition of Obstruction

Although it may not be difficult to diagnose the potentially obstructed urinary tract, usually by ultrasonographic identification of hydronephrosis, the determination of whether this particular condition requires surgical intervention to protect renal function and development is much more difficult. The frequently quoted definition of congenital obstruction (Koff, 1987), which is "a condition producing a restriction of urinary flow that will lead to deterioration in renal function," is too limited. In the growing child, renal function is expected to increase markedly, initially in excess of body mass and subsequently in parallel to it. If this increase in function does not occur, renal functional potential is lost, which may be of greater consequence than losing absolute function. Therefore **the impairment of renal functional development should be considered as a determinant of obstruction that warrants intervention** (Peters, 1995).

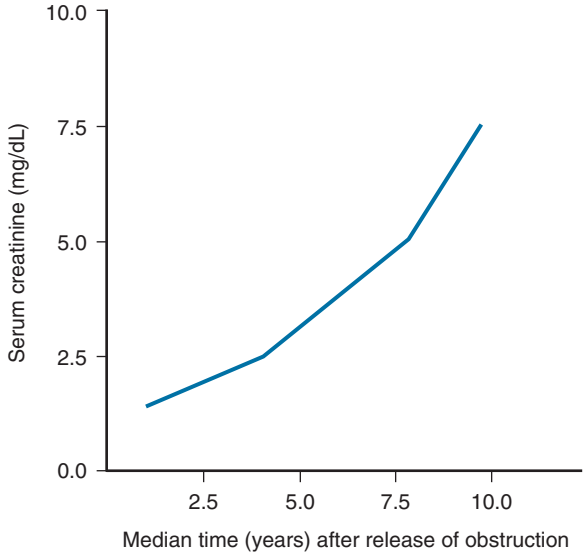


Figure 113–1. Graph depicting the progressive deterioration in renal function as indicated by a rising serum creatinine concentration in patients with posterior urethral valves despite surgical relief of obstruction. (From Roth KS, Carter WH Jr, Chan JCM. Obstructive nephropathy in children: long-term progression after relief of posterior urethral valve. Pediatrics 2001;107:1004–10.)

If this is the case, then an obstructive or hydronephrotic condition that has already resulted in less than normal function should be considered as obstructive and warranting intervention. The child with significant hydronephrosis with a kidney contributing significantly less than the anticipated 50% on a radionuclide renal scan has already suffered an impairment of functional potential and should perhaps be considered as having sufficient obstruction to warrant intervention to limit further impairment.

A critical element of congenital urinary obstruction is the recognition that it is distinct from acquired obstruction in the mature animal (or mature kidney). The fact that obstruction develops at the same time the kidney is in the process of formation creates an entirely different paradigm for congenital urinary obstruction as compared with obstruction of the mature kidney (Peters, 1997). The patterns of renal development are affected by obstruction, and this produces the ultimate functional effects. The mechanisms for these alterations are therefore wholly distinct from mature obstruction. Although there is likely to be some overlap in the critical mechanisms of change, many will be different. It cannot be assumed that the principles relevant to mature obstruction are applicable to congenital obstruction. This will clearly impact the interpretation of experimental data in the postnatal and mature animal, as well as the selection and application of experimental systems.

One of the frustrations in the management of clinical congenital obstruction is the dichotomy between therapeutic options, which are currently limited to either observation or surgery. Although the surgical options have expanded somewhat, the large

gap between these divergent options creates a great deal of tension in the minds of the patient and family as well as physicians. The absence of any medical or pharmacologic therapy to ameliorate or prevent the complications of obstruction has been a major factor in the controversy between those who choose to correct a problem and those who believe it is better to await spontaneous resolution or unambiguous evidence of obstructive injury. The horizon holds promise for medical therapies that might prevent renal injury in various ways, but it will be essential to more completely understand the nature of congenital urinary obstruction to permit such specific treatment.

Key Points: Clinical Context

- Obstruction is the single largest entity leading to renal insufficiency in boys younger than 1 year of age and the largest single cause of renal failure requiring transplantation.
- Progression of obstructive renal dysfunction may be seen in two forms, one with an uncorrected, partially obstructive lesion and the other with a previously obstructed, but corrected lesion that has produced some degree of renal damage.
- The second situation reflects the fact that the damaged kidney does not have the functional reserve of a normal kidney by which it may maintain its absolute function over time.
- Elevated creatinine concentration indicates altered absolute renal function but is relatively insensitive in the early stages of progression.

PATTERNS OF CONGENITAL OBSTRUCTIVE NEPHROPATHY

General Observations

In an attempt to understand the pathophysiology of congenital urinary obstruction, examination of obstructed renal tissues has shown disorganization of structure with primitive forms of renal tissues—dysplasia. Although the definition of *dysplasia* is not universally agreed on, evidence of altered renal development in association with obstruction is frequently reported (Bernstein, 1971; Matsell, 1998; Tarantal et al, 2001; Matsell et al, 2002; Matsell and Tarantal, 2002). Dysplasia is often considered to be an embryonic process and irreversible, yet this is not proven. It is clear that some dysplasias are due to very early abnormalities of renal development (Winyard and Chitty, 2008), unrelated to obstruction, but it is equally clear that obstructive processes can produce dysplasia. Whether there are subtle differences between these patterns is unclear, but it should not be difficult to understand that several underlying causes may produce similar outcomes when renal developmental patterns are disrupted.

In some cases, however, usually in lesser degrees of obstruction, there is no dysplasia (Bonsib, 1998; Zhang et al, 2000). In such cases the mechanisms of obstructive effect may be similar but to a lesser degree or they may be entirely different. It is important to recognize the variability of the patterns of response to obstruction.

If obstruction can produce dysplasia or abnormal developmental patterns, the particular mechanisms of obstructive effects may be identifiable. These include the fundamental processes of development, and by examining these specifically we may be able to understand the critical mechanisms of obstructive nephropathy. **Development is the controlled process of growth and differentiation of tissues in the formation of an organ or tissue. The forces that regulate these processes are likely targets of obstructive effects.**

Structural alterations with obstruction are obviously evident with hydronephrosis, but this is largely a distortion of normal architecture and relative alterations in the amounts of elements of renal tissues. There may be subtle changes, however, that are functionally important. Other alterations include fibrosis and increased interstitial tissues, as well as the presence of abnormal tubules and glomeruli. The normal layered organization of the kidney with the cortical and medullary areas with inner and outer stripes is often distorted or absent (Zhang et al, 2000). Less obvious will be changes in the differentiation of the individual renal cell types that make up the nephron (Huang et al, 2006). Cells are unlikely to perform their normal functions, including communicating with neighboring cells in an integrated fashion. Function will therefore be disrupted.

Closely tied with these altered patterns of structure are distortions of normal growth regulation with either increased or decreased growth of specific structures. In some cases, obstructed kidneys are markedly smaller than normal and in a developmental context this does not represent atrophy but hypoplasia. The distinction is important in that renal tissue mass has not been lost but has never been formed. This is growth failure not atrophy, and the mechanisms are likely distinct.

These observations are supported by both clinical and experimental work. Several biopsy studies have shown patterns indicative of altered differentiation and growth in various levels of obstruction, including both upper (UPJ obstruction) (Elder et al, 1995; Stock et al, 1995; Zhang et al, 2000; Huang et al, 2006) and lower (posterior urethral) valves (Poucell-Hatton et al, 2000; Haecker et al, 2002). These variations are not well explained, and correlation with clinical parameters is often imperfect. Experimental studies, however, have shown similarly that obstruction during development will produce changes in patterns of renal differentiation and in growth regulation (Beck, 1971; Steinhardt et al, 1988; Gonzalez et al, 1990; Peters et al, 1992; Wen et al, 2002; Cachat et al, 2003; Mure et al, 2006b). These can be seen to vary depending on the time of onset in experimental models, as well as the severity of obstruction (Fig. 113–2) (Chevalier et al, 1988, 1999c; Thornhill et al, 2005). The latter is difficult to measure accurately. The validity of any of these model systems must be challenged, however, until we have more definite correlations. Nonetheless it is clear that induced obstruction can produce such severe abnormalities of differentiation as to be considered dysplasia and to produce clear disruptions of growth regulation (Peters et al, 1992). It is therefore reasonable to examine the specific patterns observed and the potential mechanisms of those changes, all of which are likely contributing factors in the development of obstructive nephropathy.

Patterns of Effect

The effects of obstruction on the developing kidney may be summarized as producing alterations in the regulation of growth, tissue differentiation, extracellular matrix (ECM), and fibrosis and in altering the functional integration of the kidney (Fig. 113–3). The latter is largely a result of the first three major factors and refers to the mechanisms

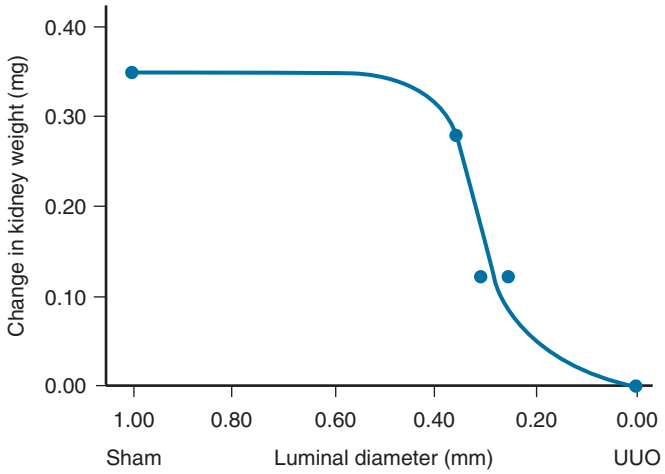


Figure 113–2. Interval change in kidney weight between 2 and 4 weeks of age in rats subjected to experimental unilateral ureteral obstruction (UUO) at birth. The sharp drop in weight with decreasing luminal diameter of the ureter suggests a threshold effect on the obstructive effects on renal growth regulation. (Modified from Thornhill BA, Burt LE, Chen C, et al. Variable chronic partial ureteral obstruction in the neonatal rat: a new model of ureteropelvic junction obstruction. Kidney Int 2005;67:42–52.)

Key Points: Patterns of Congenital Obstructive Nephropathy

- Impairment of renal functional development should be considered a determinant of obstruction that warrants intervention.
- Congenital urinary obstruction is distinct from acquired obstruction in a mature kidney.
- Obstructed renal tissues show disorganization of structure with primitive forms of renal tissues, called dysplasia.
- Structural alterations caused by obstruction are evident in hydronephrosis as a distortion in normal architecture and relative alterations in the amount of renal tissue elements. Subtle changes are functionally important and include fibrosis and increased interstitial tissue, as well as abnormal tubules and glomeruli.
- The effects of obstruction on the developing kidney vary with the time of onset, as well as the severity of obstruction.
- Obstruction of a developing kidney produces alterations in the regulation of growth, tissue differentiation, and ECM and fibrosis, as well as alterations in functional integration of the kidney.

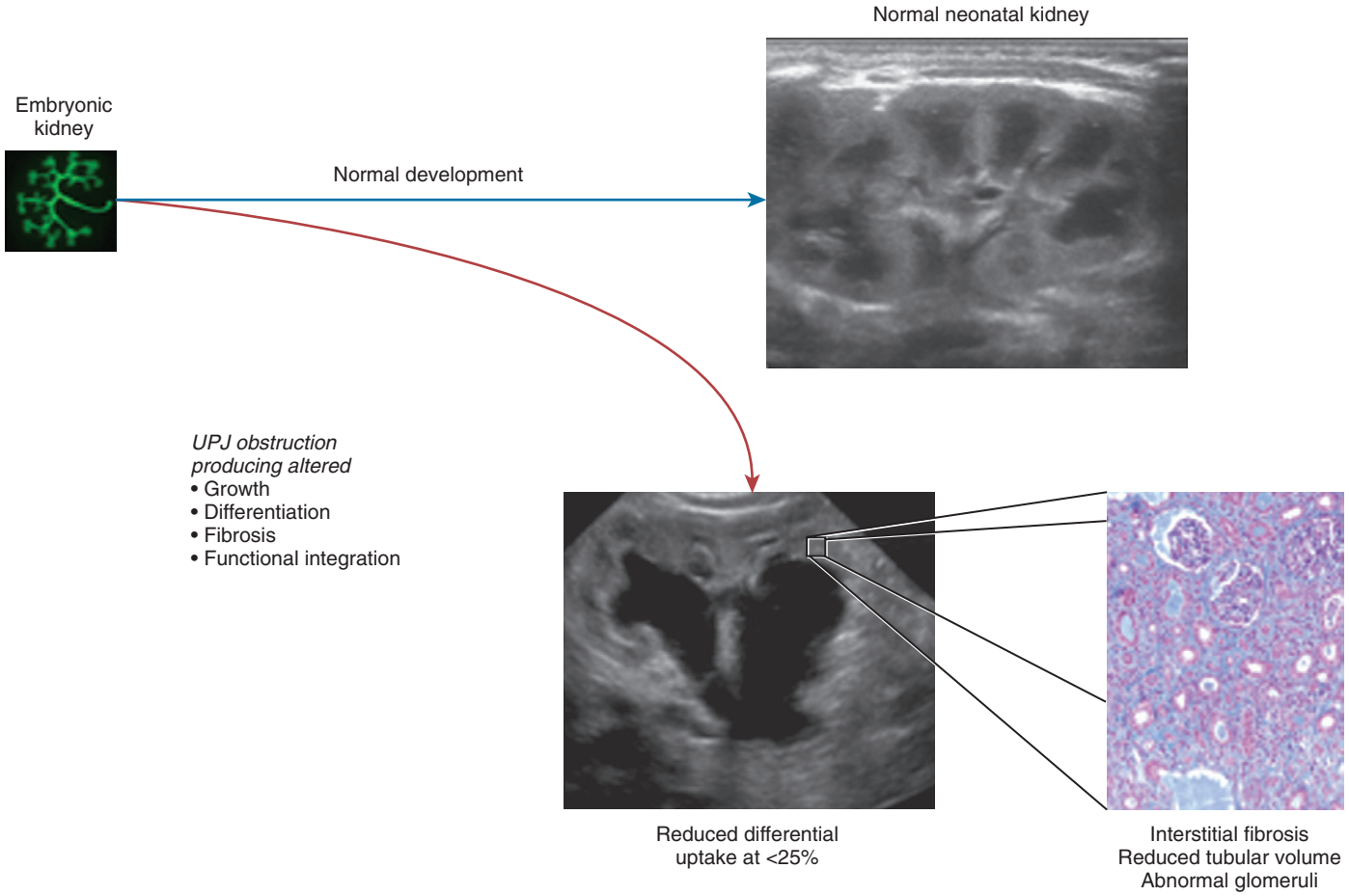


Figure 113–3. Diagram of the key patterns of effect due to obstruction during fetal life. UPJ, ureteropelvic junction.

producing vascular, neural, and humoral homeostasis and in the regulation of inflammatory cascades. Understanding the mechanisms by which these systems are dysregulated by obstruction will permit a better understanding of the outcomes of obstruction, which should improve our diagnostic, prognostic, and therapeutic abilities.

GROWTH AND DIFFERENTIATION

Growth

Growth regulation is a critical part of development, and the obstructed kidney may evidence impaired or accelerated growth. It is important to recognize that the small, obstructed kidney is not atrophic, as might be seen in the adult, but is hypoplastic. The growth it should have experienced never occurred. This can be readily seen on prenatal ultrasound evaluation and has been shown repeatedly experimentally (Peters et al, 1992; Mandell et al, 1994). This seems usually to be a generalized impairment of all parts of the kidney, with both reduced numbers of nephrons as well as smaller nephrons. Differential growth impairment within the nephron segments may be present as well (Cachat et al, 2003; Huang et al, 2006). The functional effects of significant growth impairment are obvious because there are fewer and smaller nephron units. There may be compensatory responses to these changes, and it is difficult to assess their long-term impact. Reduced renal mass can be associated with hypertension as well as reduced filtration function, and loss of tubular mass will affect electrolyte and acid-base homeostasis, as well as water balance.

Growth acceleration can be seen in the larger than normal hydronephrotic kidney, although this is difficult to prove in humans, because few of those kidneys are removed. In animal experiments, fetal partial obstruction can increase renal mass (Gobet et al, 1999a; Ayan et al, 2001). This is not seen with dysplastic changes and is not a product of edema, because the total protein and DNA are increased as well. The factors that predict altered growth appear to be the severity of obstruction and timing of the obstructive effect, although the latter is difficult to ascertain in human situations. The functional consequences of accelerated growth are not known, and this may correlate with the occasional hyperfunction measured on renal scans that is seen in some patients with hydronephrosis (Moon et al, 2003; Maenhout et al, 2005). Compensatory effects with obstruction may not be benign; growth enhancement of the glomeruli occurs in early diabetes and is later associated with glomerular sclerosis.

Growth Regulation

Regulation of renal growth is extremely complex and dynamic through development. A variety of growth factors are known to influence kidney growth at various stages of renal development and act at different loci of the nephron. Obstructive conditions have been shown to alter expression of growth-regulatory genes as well as the presence of the proteins coded by these genes (Chevalier, 1996). Some of the factors known to be altered in renal obstruction (not all in early or fetal models) are listed in Table 113–1. Epidermal growth factor (EGF) has been shown to reduce some of the growth effects of obstruction when administered exogenously (Kennedy et al, 1997; Chevalier et al, 1998, 1999a). Many studies have focused on specific growth factors, but it is evident from the complexity of renal development and growth regulation that the interactions of multiple factors and their signaling pathways will be of greater relevance.

Apoptosis Regulation

A critical component of growth in the developing kidney is apoptosis—regulated cell death. The early fetal kidney is extremely active in terms of new cell formation as well as turnover (Carr et al, 1995). **This permits remodeling during development, as well as providing a control system over unregulated growth.** Small increases in the rate of apoptosis, even with normal ongoing growth, would lead to significant reductions in renal mass over time. The role of apoptosis in congenital obstruction has become more firmly established in recent years, including cellular patterns characteristic of apoptosis and enhanced expression of apoptosis-regulating molecules (Yang et al, 2001; Yoo et al, 2006; Eskild-Jensen et al, 2007a; Campbell et al, 2008) (see Table 113–1). The changes may be seen heterogeneously, and the precise means by which these alterations occur remain incompletely defined, although apoptotic activity is regulated by cytokines (Cohen et al, 2007; Campbell et al, 2008) as well as mechanical factors (Nguyen et al, 2000; Hsieh and Nguyen, 2005). Inappropriate apoptosis may also be related to interstitial fibrosis as well (Docherty et al, 2006a). An important aspect of understanding the role of apoptosis in congenital obstruction is that the mediators may be measurable in the urine or blood, and they may permit therapeutic manipulation (Mizuguchi et al, 2008).

Differentiation

Differentiation is the process of cells attaining specific functional traits to permit specialized functions and organization into tissues. It is the basis for renal function, in its many aspects. Obstruction affects these finely tuned patterns, as can be seen histologically in a severely obstructed kidney with dysplasia. More subtle effects may require assessment of tubular or glomerular function, but all are a result of altered differentiation. Disruption of differentiation may begin as early as induction of the nephron or later in development with injury to renal collecting duct cells that regulate urinary concentrating ability. Some of these changes may be reversible, but it is usually presumed that many are not, in that some cells will undergo terminal differentiation, and if that does not occur at a particular time point in development there will not be another opportunity for it to occur. Disruption of normal differentiation of renal elements is unique to congenital obstruction and does not occur in a major way in adult obstruction. Abnormal epithelial-mesenchymal transformation (EMT) is one alteration in differentiation that does occur in the adult and can be reversible (Hay and Zuk, 1995; Yang et al, 2005; Docherty et al, 2006b; Forino et al, 2006; Higgins et al, 2007; Ivanova et al, 2008). A variety of mediators of EMT have been described, including transforming growth factor-β (TGF-β), plasminogen (Zhang et al, 2007), and leukocytes (Lange-Sperandio et al, 2007), as well as inhibitors, such as hepatocyte growth factor (HGF) (Yang et al, 2005) (Fig. 113–4). It is likely to be an important factor in fetal obstruction as well, although little is known about its role. Most adult cells may be injured and lose their differentiated capacity, but the cell types rarely change their behavior once differentiated. Understanding the patterns of altered differentiation and its regulators is critical to understanding congenital obstructive nephropathy.

Induction Process

Renal differentiation begins with induction and from then on is exquisitely sensitive to various outside effects that may disrupt the

Table 113-1.

Key Factors in Congenital Urinary Obstruction

Growth	**Apoptosis Activation**		**Apoptosis Inhibition**	
	Factor	Sources	Factor	Sources
	TGF-β1	Medjebeur et al, 1997; Ayan et al, 2001	BMP7, HGF	Liu, 1999; Klahr and Morrissey, 2003
	Angiotensin AT1 receptor	Eskild-Jensen et al, 2007a	Angiotensin AT2 receptor	
	TNF-α/NFκB	Misseri et al, 2005; Meldrum et al, 2006	STAT6	Yukawa et al, 2005a
	BAD, Bax	Liapis et al, 2000	BCL2	
	Reactive oxygen species (ROS)	Ricardo et al, 1997	Catalase, SOD	
	DAPK	Yukawa et al, 2004	CD44	Rouschop et al, 2004
	Tubular stretch	Nguyen et al, 2000; Cachat et al, 2003	EGF	Chevalier et al, 1999
	p53 caspases	Choi et al, 2001; Nguyen et al, 2006	P21	Silverstein et al, 2003
	FAS	Choi et al, 2000	HB-EGF	Nguyen et al, 2000
			IGF	Kiley et al, 2003
			Osteopontin	Yoo et al, 2006
			PAX2	Cohen et al, 2007
			SS-31	Mizuguchi et al, 2008
Differentiation	**EMT Induction**		**EMT Inhibition**	
	TGF-β1/Smad 2/Smad3	Inazaki et al, 2004; Chevalier, 2008	BMP7	Klahr and Morrissey, 2003
	Snail-1	Yoshino et al, 2007		
	PAI-1	Zhang et al, 2007		
	Leukocytes	Lange-Sperandio et al, 2007		
	Angiotensin	Topcu et al, 2007		
Fibrosis	**Profibrotic**		**Antifibrotic**	
	TIMPs	Ayan et al, 2001; Mure et al, 2006b	MMPs	Gobet et al, 1999
	TGFβ-1→ALK5 receptor	Moon et al, 2006	HGF, BMP	Mizuno et al, 2001; Klahr and Morrissey, 2003; Yang et al, 2003
	Smad2/Smad3	Inazaki et al, 2004	Smad7	Lan et al, 2003, Fukasawa et al, 2004; Chung et al, 2009
	Angiotensin AT1 receptor	Manucha et al, 2004	Angiotensin AT2 receptor, bradykinin B2 receptor	Vari et al, 1993; Yoo et al, 1997
	Ischemia, hypoxia, ROS	Cachat et al, 2003	iNOS, eNOS	Chang et al, 2002; Ito et al, 2004
	TNF-α	Meldrum et al, 2007		
	Osteopontin	Yoo et al, 2006		
	PAI-1	Zhang et al, 2007		
	PDGF, CTGF	Liapis et al, 1994; Seseke et al, 2004; Yokoi et al, 2004		
	DAPK	Yukawa et al, 2005b		
Inflammation	**Proinflammatory**		**Anti-inflammatory**	
	MCP-1	Silverstein et al, 2003; Pittock et al, 2005	Heme oxygenase-1 (HO-1)	Kim et al, 2006
	NFκB	Seseke et al, 2004	IκB	Tashiro et al, 2003
	Classically activated macrophage	Liu et al, 2008	Alternatively activated macrophage	
	TNF-α/NFκB	Meldrum et al, 2006	Adenosine A2A receptor/PDE4	Lange-Sperandio et al, 2005
	Krox 24	Silverstein et al, 2003		
	Integrins, selectins, ICAM-1	Lange-Sperandio et al, 2006		
	CCR1, CCR2	Eis et al, 2004; Kitagawa et al, 2004		

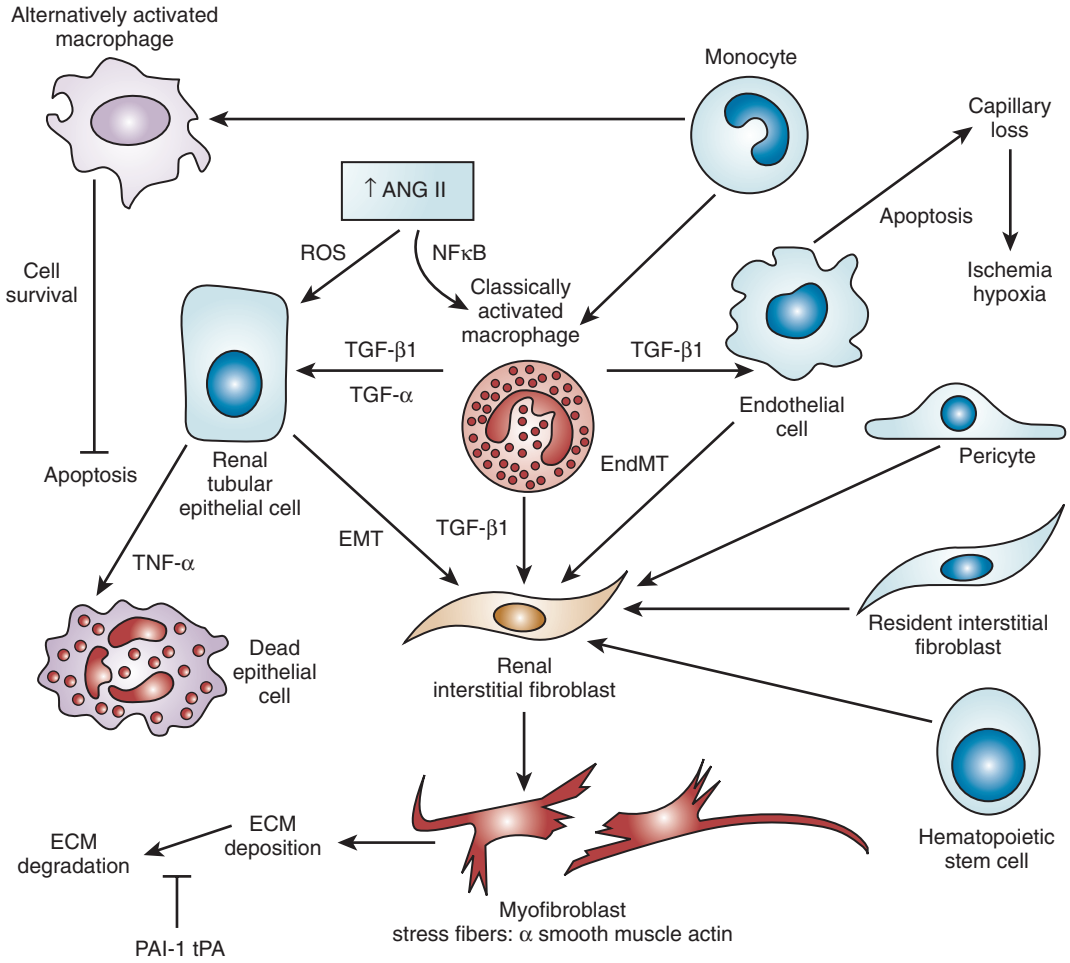


Figure 113–4. Renal cellular interactions in obstructive nephropathy. The interstitium is infiltrated by monocytes, which are "classically" activated to macrophages, which release cytokines such as transforming growth factor (TGF)-β1 and tumor necrosis factor (TNF)-α. In turn, TGF-β1 promotes a phenotypic response of tubular epithelial cells either to undergo apoptosis (leading to tubular atrophy) or to undergo epithelial-mesenchymal transition (EMT), becoming fibroblasts that migrate to the interstitium. Angiotensin II (ANG II), produced by the activation of monocytes, stimulates the production of nuclear factor kappa B (NFκB), which leads to the recruitment of more macrophages, as well as to the production of reactive oxygen species (ROS), which aggravates renal tubular injury. In contrast, alternatively activated macrophages can enhance tubular cell survival and proliferation. Endothelial cells can undergo endothelial-mesenchymal transition (EndMT) or apoptosis, which leads to capillary loss and secondary renal ischemia and hypoxia. Resident pericytes and infiltrating hematopoietic stem cells can also differentiate into fibroblasts. Under the stimulus of cytokines such as TGF-β1 produced by macrophages or other cells, fibroblasts synthesize stress fibers and undergo further differentiation to become myofibroblasts. The myofibroblasts are contractile and augment the deposition of extracellular matrix (ECM), leading to progressive interstitial fibrosis. This process is augmented by a decrease in ECM degradation, mediated by plasminogen activator inhibitor-1 (PAI-1) and tissue-type plasminogen activator (tPA). (From Chevalier RL, Forbes MS, Thornhill BA. Ureteral obstruction as a model of renal interstitial fibrosis and obstructive nephropathy. Kidney Int 2009;75:1145–52.)

normal sequence of cellular changes that results in a kidney. When these may be disturbed by obstruction is unclear, but it can be presumed that some of the variation in the spectrum of obstruction is due to different times of onset of the obstructive effect and to different degrees of severity. The pattern of effect is likely to reflect the time of onset and be reflected in the number of nephron generations and the degree of dysplastic transformation. Controversy remains as to whether obstruction can produce dysplasia, and it is often stated that if dysplasia is present, then it was due to abnormal induction and not obstruction. Abnormal induction and nephrogenesis may be produced by various factors, including genetic ones, or due to cellular disruption from mechanical forces with subsequent cellular responses. The study of Maizels and Berman is often cited to indicate that dysplasia in the chick kidney (a mesonephric kidney) was only produced with mechanical disruption of the mesenchyme and not hydronephrosis. The production of "obstruction" in that elegant study was by necessity rather crude, and several of the preparations were not obstructed. It is unclear whether they all were to a sufficient degree. It also suggests that mechanical forces can, in fact, disrupt nephronogenesis enough to produce dysplasia, and there is no inherent reason to believe that this cannot be from obstruction as well. Later mammalian studies in fetal sheep have shown dysplastic changes produced by obstruction (Steinhardt et al, 1988; Peters et al, 1992; Matsell et al, 1996), and this has also been shown in rodent studies (Thomasson et al, 1970).

The critical determinant of dysplasia in animal studies has been complete obstruction early in gestation. In the fetal sheep this was only seen when the obstruction was induced before 50% of gestation (70 days in most sheep species, which have a gestation from 140 to 145 days). Obstruction induced after that point only produces hydronephrotic changes, albeit severe ones (Beck, 1971).

Partial obstructions produced hydronephrosis only, without apparent disruption of the renal architecture. The reason for this is presumably altered sensitivity of the developing nephrons to obstructive effects at this point. Alternatively, the particular signaling systems that are active in the early phases of renal development begin to fade away with ongoing development. It is possible that the pathways sensitive to obstruction that would inherently alter the pattern of development have run their course of expression and activity by mid gestation. Expression of recognized mediators of renal development have been shown to be affected in models of fetal obstruction, including WT1 (Liapis, 2003), the *Wnt* gene family (Nguyen et al, 1999), and PAX2 (Attar et al, 1998; Mure et al, 2006b; Cohen et al, 2007).

One of the histologic hallmarks of renal dysplasia is fibromuscular collars surrounding tubular structures, so-called primitive ducts. These have a characteristic appearance, and the smooth muscle surrounding the tubules stains for α-smooth muscle actin (α-SMA) (Fig. 113–5). This pattern suggests an abnormality in the regulation of EMT (Butt et al, 2007; Baum et al, 2008). The mesenchymal structures of the primitive nephrogenic blastema and the epithelium of the ureteral bud processes interact, and there is differentiation from an epithelial to mesenchymal phenotypes and the reverse. It is uncertain whether the presence of the primitive tubules suggests persistence of mesenchyme that should have transformed to epithelium or inappropriate EMT. Understanding the signaling pathways involved in these processes will directly impact our understanding of obstructive processes (Roberts et al, 2006; Bani-Hani et al, 2008). Persistent expression of α-SMA can be seen in partial obstruction without dysplastic patterns and thus may be important at several levels of severity (Gobet et al, 1999; Mure et al, 2006a). α-SMA expression is regulated by TGF-β1, linking these two proteins to growth as well as to fibrotic changes.

Development of the glomerulus is a tightly regulated process that involves interaction of the mesenchyme and epithelium with a very specific pattern of growth and formation of intermediate structures such as the S-shaped body. In general, primitive glomeruli are not evident in obstructive changes but markedly abnormal glomeruli are seen as well as hypoplastic glomerular structures (Matsell et al, 2002). In some cases, glomeruli may be enlarged in obstruction, suggestive of the changes seen in hyperfiltration that lead to glomerulosclerosis. Dissociation of the glomerulus from the tubules can be seen in early neonatal rodent obstruction (Thornhill et al, 2007), suggesting severe disruption of the developmental program.

Key Points: Growth and Differentiation

- The effect of growth impairment includes fewer nephron units and delayed nephron maturation.
- Obstructive conditions have been shown to alter the expression of growth-regulating genes, as well as the presence of proteins coded by these genes.
- Congenital obstruction increases apoptosis and cellular patterns characteristic of apoptosis, with enhanced expression of apoptosis-regulating molecules.
- The ultimate cellular effects of such stimuli, however, depend on the summation of competing pro-apoptotic signals and antiapoptotic signals, as well as growth stimulation.
- Alteration in the differentiation of cells is unique to congenital obstruction and does not occur in a major way in adult obstruction.
- The critical determinant of dysplasia in animal studies has been complete obstruction early in gestation.

FIBROSIS

A universal characteristic of obstructive nephropathy appears to be renal fibrosis, although it is a nonspecific pattern seen in a variety of pathologic conditions

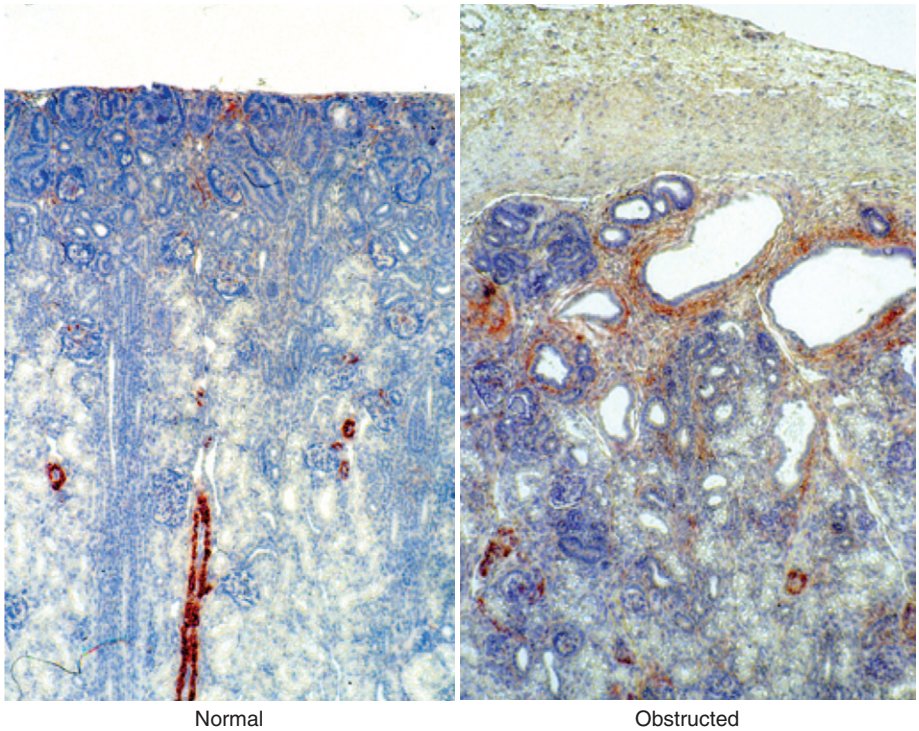


Figure 113–5. Histologic views of the kidneys of normal and obstructed full-term sheep showing the abnormal structural pattern, increased interstitial fibrosis and cells, as well as abnormally persistent α-smooth muscle actin *(brown stain)*. (From Gobet R, Bleakley J, Cisek L, et al. Fetal partial urethral obstruction causes renal fibrosis and is associated with proteolytic imbalance. J Urol 1999;162:854–60.)

affecting the kidney (Eddy, 2000). **It is seen as infiltration of the interstitium with abnormal amounts of ECM, including collagens, fibronectin, and other connective tissue proteins.** Their presence disrupts the normal interconnections between cells that permit functional integration of the renal tissues. Tubular cells may be disrupted and inadequately regulated. Cell–cell signaling by direct connection or paracrine messengers may be disrupted. Tissue oxygenation may be impaired. Fibrosis is a histopathologic hallmark of many renal diseases.

The ECM is essential to normal function of the kidney as well, in terms of providing structural integrity and contributing to normal signaling systems. When abnormally expressed, however, it becomes detrimental. ECM homeostasis is a complex balance of synthesis and breakdown. Synthetic regulation is controlled by various mechanisms, including growth factors and signaling systems that are just being discerned. Mechanical forces contribute to these signals in various conditions, including hypertension and hydronephrosis. ECM breakdown is tightly regulated and represents the product of degradative enzymes, the matrix metalloproteinases (MMPs), and their endogenous inhibitors, the tissue inhibitors of metalloproteinases (TIMPs). This product is the proteolytic balance and is regulated by various cytokines, hormones, and mechanical forces. This balance has been studied vigorously in renal disease and to a limited degree in congenital obstruction (Engelmyer et al, 1995; Ayan et al, 2001; Mure et al, 2006a). The interaction of these systems is complex, and various compensatory pathways are likely to be present (Kim et al, 2001).

Modulation of renal fibrosis may be a significant potential target for managing obstructive nephropathy, but the delicate balance of these factors needs to be understood to a greater degree than at present (Eddy, 2005).

Evidence and Patterns

Increased interstitial connective tissue is a hallmark of various renal pathologic processes (Eddy, 1996), **including obstruction. Although it is unclear if the mechanisms of fibrotic change are universal, they are believed to interfere with intercellular signaling and thus with functional integration** (Fig. 113–6). The most likely causes of excessive connective tissue include abnormal accumulation due to imbalance of synthesis and breakdown. It may also represent abnormal inductive signaling that produces excessive conversion of epithelium to mesenchymal tissue and connective tissues (Bascands and Schanstra, 2005; Burns et al, 2007; Zhang et al, 2007). These processes may be normal developmental sequences that persist due to the obstructive effect.

Abnormal accumulation may represent simply excessive synthesis with no change in ECM breakdown. Increased collagen synthesis has been shown by upregulation of collagen gene expression in obstructive models (Liapis et al, 1994; Fu et al, 2006). Collagen synthesis is regulated in part by various cytokines, including TGF-β and the renin-angiotensin system (RAS). Reduced fibrosis may be seen when angiotensinogen activity is downregulated in an obstructed system (Fern et al, 1999; Kellner et al, 2006). Similar approaches have been demonstrated in nonobstructive fibrosis as well.

The role of TGF-β is complex and context dependent, yet inhibition of activity will produce less fibrosis as well (Isaka et al, 2000; Miyajima et al, 2000; El Chaar et al, 2007). There is evidence that TGF-β interacts and regulates the activity of the RAS, as well as regulating cellular growth dynamics. Fetal obstruction induces

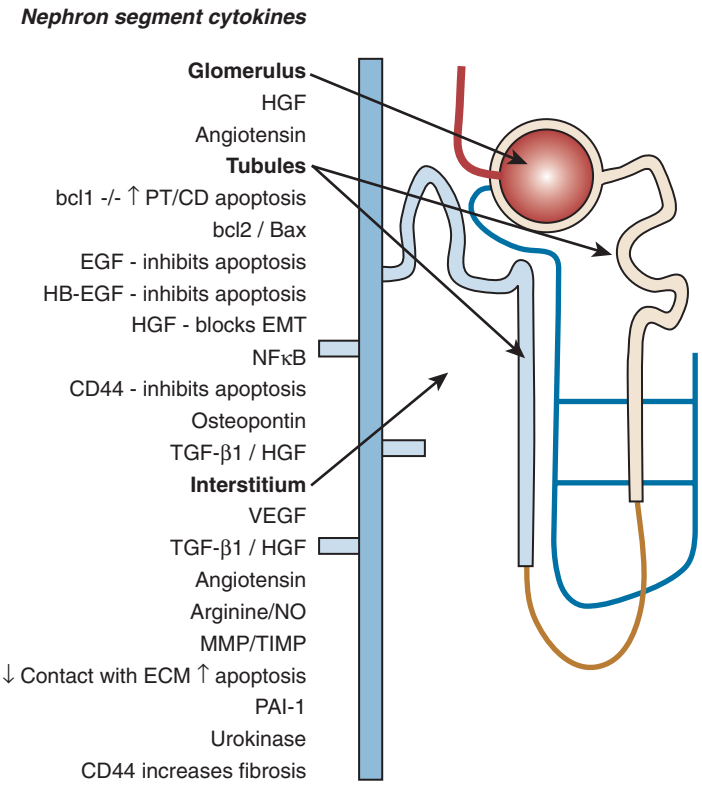


Figure 113–6. Diagram illustrating the various cytokines with reported effects on specific nephron segments. See text for details and references.

increased expression of TGF-β1 (Medjebeur et al, 1997; Ayan et al, 2001). As reviewed earlier, TGF-β1 regulates EMT, thereby contributing to renal dysplasia (Yang et al, 2000). There is considerable interest in the role of TGF-β1 in promoting EMT of differentiated renal tubular epithelial cells in response to chronic ureteral obstruction. As shown in Figure 113–4, renal interstitial fibroblasts, through transformation to myofibroblasts, play a pivotal role in the deposition of ECM in a hydronephrotic kidney. There is growing evidence that, in addition to proliferation of resident interstitial fibroblasts and transformation of hematopoietic stem cells, renal tubular epithelial cells can undergo EMT and migrate to the interstitium to contribute to the pool of fibroblasts (Iwano et al, 2002). Many of the steps involved in the transformation of tubular epithelial cells are regulated by TGF-β1; these steps include loss of cell adhesion, expression of α-SMA, disruption of tubular basement membrane, and cell migration to the interstitium (Liu, 2004). Signaling by TGF-β1 is mediated in part by Smads, which are both profibrotic (Smad2 and Smad3) and inhibitory (Smad7). Thus targeted deletion of Smad3 reduces apoptosis and fibrosis in mice with ureteral obstruction, whereas gene therapy with Smad7 also reduces fibrosis (Lan et al, 2003; Sato et al, 2003). TGF-β1 also acts through downregulation of transcriptional corepressors of the Smads: SnoN and Ski (Yang et al, 2003b). In contrast, HGF blocks EMT by blocking Smad2 and Smad3 and gene therapy with HGF reduces fibrosis in rats with ureteral obstruction (Gao et al, 2002; Yang and Liu, 2003). HGF also acts by upregulating the Smad corepressors SnoN and Ski, countering the action of TGF-β1 (Yang et al, 2005). These complex networks of counterbalancing factors provide many potential opportunities for therapeutic intervention to prevent the progression—or even promote the reversal—of interstitial fibrosis resulting from obstructive nephropathy (Fogo, 2003).

Nitric oxide has also been shown to regulate the development of obstructive fibrosis in postnatal animals and may play a similar role prenatally (Huang et al, 2000; Felsen et al, 2003). Increased nitric oxide generation reduces the degree of interstitial fibrosis (Ito et al, 2004), and in animals without the gene to produce nitric oxide synthase, unilateral obstruction produces a greater degree of fibrosis than in those animals with this enzyme intact (Hochberg et al, 2000). Data suggest a greater potential role for nitric oxide derived from endothelial nitric oxide synthase (eNOS) than inducible nitric oxide synthase (iNOS) (Huang et al, 2000; Chang et al, 2002).

Hypoxia may be a factor in the development of tissue fibrosis as well, in response to induction of hypoxia-inducible factors-1 and 2 (HIF-1, HIF-2) (Higgins et al, 2008). In-vitro stimulation of renal epithelia with HIF-1 increases EMT, known to induce fibrosis. Genetic models that do not express HIF-1α develop less fibrosis and inflammatory infiltration in response to ureteral obstruction in postnatal models (Higgins et al, 2007). The role in prenatal obstruction remains undefined but potentially relevant.

Altered regulation of ECM breakdown, the proteolytic balance, is a potential mechanism for interstitial fibrosis of obstruction as well, although less explored. Connective tissue breakdown is controlled by the MMPs, of which there are at least 15 having specific activity toward particular connective tissue proteins. MMP-1, for instance, is a collagenase (Pardo and Selman, 2005), whereas MMP-2 specifically degrades gelatin. Their expression and activity are both subject to close regulation, because it is crucial to appropriate ECM homeostasis. Too much activity will degrade the tissues, whereas too little permits accumulation of abnormal amounts of ECM. These pathologic alterations have been described in a variety of disease states, including arthritis and pulmonary fibrosis (Corbel et al, 2002; Vincenti and Brinckerhoff, 2002). One of the means by which their activity is regulated is through endogenous TIMPs. These are less varied and may have less specific activity over the MMPs in their environment and serve to check the degradative activity of the MMPs. Their expression and activity are closely regulated and their net activity is the proteolytic balance. The role of the proteolytic balance in a wide variety of disease states has been the subject of active research (Diamond et al, 1998; Vincenti, 2001).

Altered activity and regulation of the MMPs and TIMPs have been studied in the kidney (Eddy, 1996) in several conditions, and it is clear that they are important regulators of the state of the ECM. Their expression has been shown in the developing kidney as well, and in postnatal obstruction they are altered in activity. In prenatal obstruction increased expression (Ayan et al, 2001; Mure et al, 2006a) and activity (Gobet et al, 1999a) have been shown, as well as in congenital reflux-related fibrosis (Gobet et al, 1998). The precise regulators of the MMPs and TIMPs in development and obstruction are not well defined but are likely to be an important element in the development of pathologic fibrosis. There also is some evidence of regulation by the RAS and TGF-β, which opens therapeutic options for the treatment of fibrosis (Diamond et al, 1998; Ding et al, 2005; Bolbrinker et al, 2006; Yang et al, 2007).

Fibrosis is clearly a major component of the pathophysiology of congenital obstruction. Understanding the role and activities of the various components of this system may permit more specific diagnosis through urinary biomarkers reflecting the elements of the system. These elements may also be relevant targets of therapeutic intervention to modulate ECM homeostasis.

Key Points: Fibrosis

- One of the histologic hallmarks of renal dysplasia is the presence of fibromuscular collars around tubular structures, so-called primitive ducts.
- A universal characteristic of obstructive nephropathy appears to be renal fibrosis.
- Breakdown of ECM is tightly regulated and represents the product of degradative enzymes (matrix metalloproteinases [MMPs] and their endogenous inhibitors (tissue inhibitors of metalloproteinases [TIMPs]).

FUNCTIONAL INTEGRATION

Renal function is regulated at numerous levels, including vascular, neural, and hormonal factors, and this may be significantly affected by inflammatory processes. **Congenital obstruction alters both the ongoing functional integration of the kidney as well as the development of the mechanisms that are intrinsic to this regulation. It can change the regulatory mechanisms themselves.** For example, hypertension is well recognized as a potential consequence of obstruction and may have effects beyond the kidney. More subtle effects on the normal regulatory systems of the kidney may be more difficult to detect.

Inflammation appears to be a common consequence of obstruction in the postnatal human or animal model. Much attention has been paid to this in acquired obstruction, but it is surprisingly absent in congenital obstruction. Biopsies of human kidneys with obstruction but no history of infection have sparse inflammatory infiltrates (Huang et al, 2006). Models of fetal obstruction have little evidence of inflammation (Peters et al, 1992). The reason for this marked difference is unclear but suggests fundamentally distinct mechanisms. It is another indication that congenital obstruction is distinct in many ways from postnatal acquired obstruction.

Vascular Development

The developing vascular tree plays a critical role in renal development, and any disruption could be associated with a wide variety of abnormalities, ranging from lack of development of the glomerulus to aberrant regulation of renal blood flow. Sensitivity to humoral and neural regulation of blood flow may be altered as well, which may be a permanent effect.

Expression of renal renin is increased in the obstructed kidney (el-Dahr et al, 1993; Gobet et al, 1999b; Ayan et al, 2001) and decreased in the contralateral kidney. Renin-secreting renal cortical cells appear to be recruited with obstruction as well (Norwood et al, 1994). Expression of receptors for the RAS is altered in specific patterns in neonatal obstruction. Angiotensin I, which mediates vasoconstriction (as well as growth alterations) (Chung et al, 1995; Yoo et al, 1998) increases whereas the levels of angiotensin II, which acts in a contrary manner, are decreased. These alterations suggest a role for a local renal RAS in obstruction-mediated vasoconstriction and that are independent of the systemic RAS.

Altered sensitivity of both kidneys to renin-mediated vasoconstriction has been shown to occur with unilateral obstruction. Interaction with nitric oxide has been seen to be important in regulation of both glomerular and tubular function in early obstruction (Eskild-Jensen et al, 2007b). After release of obstruction, sensitivity to angiotensin II–mediated vasoconstriction was

reduced in the obstructed kidney but increased in the contralateral kidney (Chevalier and Gomez, 1988). These observations indicate the sensitivity of renal vascular regulation to obstruction as well as the importance of recognizing the interaction of the two developing kidneys. The role of renal counterbalance in obstruction has been recognized but only investigated to a limited degree. A possible mechanism for these observations is through neural regulation of renin expression (Chevalier and Thornhill, 1995a).

Neural Development

Renal innervation is an important regulator of vascularity and perfusion and is associated with expression of renin in the kidney (el-Dahr et al, 1991). Sympathetic denervation, both mechanical and chemical, has been shown to reduce the expected increase in renin expression in the setting of obstruction (Chevalier and Thornhill, 1995b). A more primitive pattern of renin gene expression appears to persist with congenital obstruction and may cause a persistence of fetal patterns of neural and vascular regulation.

Hormonal Development

The major hormones regulating renal functional development are in the RAS, and these are significantly affected by congenital urinary obstruction. This has a variety of effects, including growth alterations and fibrosis, as well as altered blood flow. The sensitivity of the kidney to elements of the RAS changes during development, presumably to permit transition from a fetal state with reduced oxygen tension and limited need for renal perfusion, to the postnatal environment. Postnatally, all filtration must be through the kidneys rather than the placenta as it is prenatally. This is thought to be related to the shift in expression of the angiotensin receptors as one aspect of this system. In fetal life, angiotensin receptor type 2 (AT2) is predominant in expression and has a vasodilating effect and may promote growth whereas type 1 (AT1) is less active until postnatally to permit regulation of renal perfusion in the postnatal environment (Robillard et al, 1995). Altered developmental regulation of these receptors has been induced with fetal obstruction as well (Gobet et al, 1999a). Activity of the RAS is balanced in the developing kidney by nitric oxide, and alterations in this balance have been demonstrated in the developing kidney subjected to obstruction (Bogaert et al, 1996), perhaps explaining the observed preservation of renal blood flow despite ongoing fetal bladder obstruction (Bogaert et al, 1995; Nguyen and Kogan, 1998). In contrast, with complete fetal unilateral ureteral obstruction, renal blood flow was not maintained, indicating thresholds of obstructive severity for certain renal responses (Mure et al, 2006a). Targeting these specific alterations may provide information as to the impact of obstruction as well as having possible therapeutic value (Topcu et al, 2007). Improved diagnostics may be developed if imaging can be linked to hormonal activity that has distinct patterns in obstruction. For example, if congenital urinary obstruction induces a balance of the RAS that favors the more fetal pattern of receptor subtypes, perfusion renography or imaging coupled with pharmacologic inhibition or stimulation of this system, as in a captopril renogram, may permit identification of this pattern (Bajpai et al, 2002). It is essential to recognize that the integrity of the RAS is critical to normal renal development and inhibition may produce negative effects on normal renal function or even exacerbate obstructive effects (Coleman et al, 2007).

Aldosterone may be a potentially useful target for therapy, because it has been shown to contribute to cardiac and renal fibrosis in various pathologic situations (Xu et al, 2008; Ku and Campese, 2009; Lea et al, 2009). Inhibition using spironolactone, a receptor antagonist, has been shown experimentally to limit the amount of interstitial fibrosis in a juvenile rodent model of complete obstruction (Trachtman et al, 2004). This raises the potential for therapeutic interventions using familiar pharmacologic tools yet also indicates the complexity of interaction in the kidney's responses to obstruction.

Tubular Function

Although glomerular filtration and renal plasma flow are the most commonly measured elements of renal function, renal tubular function is equally important yet often ignored in urinary obstruction. Tubular function regulates acid-base homeostasis, electrolyte balance, and urinary concentration as well as vitamin D homeostasis. When obstruction is bilateral, defects in these various functions are major clinical problems; when obstruction is unilateral, they are often compensated by the contralateral kidney and are therefore difficult to measure accurately and noninvasively. There are reports of persisting tubular dysfunction in various congenital obstructions (Hutcheon et al, 1976), but it is uncommon for this to be a clinical problem.

Congenital obstruction can be shown experimentally to produce several functional effects on the renal tubules, including acid-base, sodium, and water homeostasis. Specific downregulation of sodium transporters (Norregaard et al, 2005) in the tubules as well as reduction in the expression and protein levels of the aquaporins has been demonstrated in neonatal obstruction in rats and juvenile piglets (Frokiaer et al, 1997, 2003; Eskild-Jensen et al, 2006; Jensen et al, 2006). Downregulation of acid-base transporters in tubular epithelium has been demonstrated in juvenile rats (Wang et al, 2009). Although these defects may be compensated for by a normal contralateral kidney, limiting their clinical impact, alterations in urinary levels of these protein may serve as markers for significant obstructive effects.

The mechanisms of injury are likely to be a combination of the previous described effects, and therapeutic interventions targeted to those mechanisms may limit tubular dysfunction. Measuring abnormal tubular function may be possible using more sensitive measures and imaging technology.

Inflammatory Mediators

Although inflammatory changes do not appear to be a major factor in early postnatal congenital urinary obstruction (Misseri et al, 2004), it is likely that they begin to play a greater role with age. It will be necessary to confirm the pattern and role of these factors in congenital urinary obstruction in humans, because many animal systems demonstrate significant inflammation postnatally, although fetal systems do not (Peters et al, 1992). Human pathologic material has not shown large amounts of inflammation (Huang et al, 2006), except when complicated by infection (Bartoli et al, 2000; Kiratli et al, 2008). If there is a subset of patients with inflammatory changes in the presence of obstruction, it would seem an important target for investigation to improve both diagnostic and therapeutic capability (Meldrum et al, 2006, 2007). The various inflammatory cascades that have been investigated postnatally can be manipulated pharmacologically, and this may permit important therapeutic regulation of renal injury (Cale et al, 2000). Inflammatory mediators such as monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-α (TNF-α), regulated on activation normal T-cell expressed and secreted (RANTES), and

others may be measurable in the urine as well, as has been shown in experimental systems (Crisman et al, 2001; Silverstein et al, 2003).

Key Points: Functional Integration

- Angiotensin is a key modulator of many of the inflammatory responses to ureteral obstruction.
- Expression of renal renin is increased in the obstructed kidney and decreased in the contralateral one. Renin-secreting renal cortical cells appear to be recruited with obstruction as well.
- The activity of the renin-angiotensin system is altered with obstruction, which affects renal functional development by a variety of changes, including growth, fibrosis, and blood flow.

REVERSAL OF CONGENITAL RENAL OBSTRUCTION

An important element in the understanding of congenital obstruction is the potential for reversal of renal functional and developmental impairment with correction of the obstructive lesion. This is clinically relevant when making decisions regarding the utility of intervention either postnatally or prenatally. In the latter, the potential for reversal has great significance in determining whether the risks associated with fetal intervention are warranted. Improvement in function is also important in the expectation of response to relief of obstruction.

In the fetal obstructed kidney, Glick and colleagues (1984) **showed that the functional salvageability of a unilaterally obstructed kidney was dependent on the duration of obstruction and gestational age.** A direct relationship between progression of nephronogenesis and reversibility can be demonstrated (Edouga et al, 2001). Similar observations have been made in early postnatal models, with the recognition that complete reversal of the damage is seldom achieved (Claesson et al, 1987; Chevalier et al, 1988, 1999a, 1999b, 2002; Eskild-Jensen et al, 2003; Shi et al, 2004; Dissing et al, 2008). Mediators of improvement have not been explored. The severity of obstruction is also a critical determinant (Bussieres et al, 1993), but it is challenging to measure in any meaningful way. Biomarkers of salvageability have been developed and were first used clinically in accordance with the work of Glick and Adzick in obstructed fetal sheep (Adzick et al, 1985). From these basic parameters emerged the clinical prognostic factors currently used, with modification, in fetal obstruction (Harrison et al, 1982; Glick et al, 1985). **Measures of urinary sodium, chloride, osmolarity, and calcium have correlated with fetal renal functional potential** (Muller et al, 1993; Johnson et al, 1995; Dommergues et al, 2000; Biard et al, 2005). **When fetal urine approaches the character of serum, irreversible damage appears to have been done to the developing kidney.** Other markers have been explored in the fetus, including α_1-microglobulin in amniotic fluid and β_2-microglobulin in urine and serum (Burghard et al, 1987; Freedman et al, 1997; Nicolini and Spelzini, 2001; Craparo et al, 2007).

The mechanisms of functional recovery may be similar to the mechanisms of injury, but they may also be unique and the potential may exist for enhancing recovery if these mechanisms can be understood and used. In part, the pathway of recovery includes normal developmental pathways that had been impaired because of obstruction (Chevalier et al, 1988). **As a consequence of urinary tract obstruction, nephron injury is heterogeneous, with some nephrons undergoing adaptive growth and hyperfiltration and others being destroyed. Thus, 1 month after relief of 5 days of unilateral ureteral obstruction in the neonatal rat, the glomerular filtration rate (GFR) of the postobstructed kidney was normal despite a 40% reduction in the number of glomeruli** (Chevalier et al, 1999c). **However, 1 year after relief of the obstruction the GFR of the postobstructed kidney had decreased by 80%** (Chevalier et al, 2000). Even though there had been no further loss of nephrons during this interval the remaining glomeruli had undergone progressive sclerosis (Chevalier et al, 2000). Although relief of temporary unilateral ureteral obstruction did not lead to nephron loss in the adult rat, there was a reduction in glomeruli after this relief in the period immediately after nephrogenesis, as well as during nephrogenesis (Chevalier et al, 2002). This underscores the susceptibility of the developing kidney to obstructive injury not only during nephrogenesis but also during subsequent nephron maturation.

Key Points: Reversal of Congenital Renal Obstruction

- The functional salvageability of a unilateral obstructed fetal kidney is dependent on the duration of obstruction and gestational age.
- Measures of urinary sodium, chloride, osmolarity, and calcium have been correlated with fetal renal functional potential.
- When fetal urine approaches the character of serum, irreversible damage appears to have been done to the developing kidney.

APPROACH TO CLINICAL CASES

General Approach

The clinical challenge of congenital urinary obstruction reflects the clinical spectrum of the condition itself. A determination must be made as to which patients need intervention to protect renal functional development. Some will clearly need such intervention, whereas many others will do well without. Given the wide spectrum it is extremely difficult to determine a clinically practical dividing line between those in whom intervention is appropriate and those in whom it is not needed. This question is relevant to the largest number of patients with some form of congenital urinary obstruction. The ultimate determination of the need for intervention may come as a single diagnostic test or be based on a pattern of change or lack thereof over time. In this situation we wish to be sensitive but will accept being less specific. We would rather not miss a large number of patients with congenital urinary obstruction needing intervention, recognizing that some patients may undergo further evaluation or intervention when they might not have needed it.

The second challenge is with the patients at the extreme end of the spectrum in whom renal functional impairment has already occurred and poses the threat of permanent and progressive renal insufficiency. In the presence of obstruction, what is our best approach to preserve the maximal amount of renal function? Even with successful surgical intervention, we are often confronted with

an inexorable progression to renal failure in these children, yet it would seem reasonable to ask if we can prevent renal demise. As yet there has been no clinically applicable approach, but as our understanding of the pathophysiologic mechanisms of congenital urinary obstruction improve, we may be able to specifically alter critical components of the system to better regulate the mechanisms affecting renal response to obstruction.

Diagnosis

The challenge to be able to diagnose "obstruction" has been made more difficult owing to disagreement as to the definition of *obstruction*. Although the concept that obstruction is an "impairment of urine flow that will produce a reduction in function if left uncorrected" is logical, it misses several important elements in the context of congenital obstruction. One is that the developing kidney should be increasing its function, not remaining static. It also does not provide any insight into the interpretation of a kidney that has reduced function when diagnosed. Strictly interpreted, this kidney is already affected by having had its normal potential function limited, and, by definition, is "obstructed." This interpretation has not been widely used, however, and it is only on prospective follow-up that a decrease from normal is thought to be indicative of "obstruction." A more useful definition might be any condition that has or will limit ultimate functional potential should be considered clinically significant obstruction. It should also be recognized that obstruction does not mean surgical therapy is required. Obstruction may be mild and clinically insignificant. The exclusion of these patients from the diagnosis of obstruction has tended to force people to create convoluted descriptions of hydronephrotic kidneys.

Ultimately, a determination of the potential risk to a kidney will have to be made clinically and a judgment made as to whether a particular child would benefit from intervention. It would seem reasonable and cautious to assume that any hydronephrotic kidney is obstructed until proven otherwise and to assess the degree of risk. Understanding the pathologic mechanisms of obstructive nephropathy will permit more specific examination of the kidney to determine its response. It should be the renal response primarily that is used to make the determination of obstructive effect. The fluid dynamics of the upper urinary tract, while obviously relevant to the renal effect, should not be the primary focus. This may be why many drainage studies, including diuretic renography and pressure-perfusion tests, are imperfect predictors of the renal response. We have seen that the obstructed kidney is undergoing altered growth regulation, abnormal differentiation and increased fibrosis, all mediated through a variety of molecular, cellular and renal homeostatic mechanisms. These patterns of change are likely to be reflected in altered expression of proteins and chemicals, which may be assayed in the urine. There may be systemic alterations that are detectable in the blood as well. The search for these biomarkers has been active, yet few have been firmly linked to the pathologic progression of obstructive nephropathy (Chevalier, 2006).

Biomarkers of renal obstruction may reflect the response of the kidney in a direct manner, such as expression of growth factors that contribute to fibrosis or are associated with increased apoptosis in renal epithelium. They may also be downstream effects reflecting specific alterations mediated by other cytokines and in themselves not directly relevant but more indicative of the level and pattern of the obstructive effect. A broad approach that is emerging uses assessment of changes in overall protein expression in the urine—proteomics. Normal developing kidneys have an evolving protein fingerprint, which can be defined (Lee et al, 2008) and which is altered with obstruction. If particular elements of the alteration can be identified and associated with clinical outcomes, these patterns may be diagnostic of functionally significant obstruction. Such patterns may reflect a single protein, which may be an element of a response pattern, or a downstream consequence. It may be that a particular pattern of protein expression involving several factors will be the best indicator of obstruction (Decramer et al, 2006, 2008). Such studies will require development in animal systems and validation in humans. It will be necessary to set limits for what is and is not clinically significant "obstruction" and correlate this with clinical and functional outcomes of relevance. These changes also will need to be correlated with histopathologic changes in the developing kidney because our ability to measure some functional alterations remains imperfect.

An alternative approach to diagnosis may be to assess response to stimulus. This is the basis of the captopril renogram, in which radionuclide uptake in the presence of obstruction is reduced when the RAS is inhibited by the angiotensin-converting enzyme inhibitor captopril but not in the dilated, nonobstructed system (Bajpai et al, 2002). The underlying rationale for this test is that, in the obstructed kidney, function is dependent on increased activity of the RAS, as suggested earlier. By reducing the capacity of this system to support function by administration of captopril, a decrease is detected in the post-captopril study. The concept is reasonable, but problems with definitions of true "obstruction" continue to thwart its broad applicability. Alternative pharmacologic manipulations are needed to more specifically address one or more functional factors in the potentially obstructed kidney. The production of various cytokines in the presence of a stimulus may be able to distinguish the kidney at risk for injury from the kidney not at risk.

At present we are limited to the conventional imaging modalities of ultrasonography, diuretic renography, and, increasingly, magnetic resonance imaging (MRI).

Key Points: Approach to Clinical Cases

- Congenital urinary obstruction may best be defined as urinary flow impairment that has limited or may potentially limit normal renal development.
- Not all hydronephrosis represents obstruction that requires surgical correction.
- Biomarkers for renal obstruction should reflect changes in normal development, as well as specific alterations due to obstruction.
- Although most clinical cases of congenital obstruction are asymptomatic, cases in children are still detected due to pain, a mass, hematuria, and hypertension.

CLINICAL EVALUATION

The mode of presentation of obstructive uropathy will often determine the clinical management. Those presenting with symptoms will require a careful anatomic and functional assessment and, likely, surgical intervention. Those in the less discrete category, including ureteropelvic junction (UPJ) obstruction and ureterovesical

junction (UVJ) obstruction, presenting without symptoms are more challenging. If posterior urethral valves, ureterocele, or ectopic ureter is detected, even if asymptomatically, intervention is almost always appropriate. Patients with very mild versions might be considered candidates for an observational approach if no evidence of bladder or renal dysfunction is present.

Symptomatic presentation of UPJ and UVJ obstruction almost always can be managed with surgical intervention. Although it is unknown when such a symptom episode might recur, the likelihood is high, although it has never truly been determined. Infection is uncommon with UPJ obstruction but not with UVJ obstruction, and these children can become very ill due to the combination of infection and obstruction. It seems as if the severity of the obstruction may be exacerbated by the reaction to the infection. Marked increases in hydronephrosis have been reported in association with an acute infectious episode, likely owing to the effect of bacterial toxins (Pais and Retik, 1975). Subsequent resolution should not falsely suggest an insignificant process.

Stone development is another form of clinical presentation, often presenting as hematuria or pain. Although the two conditions are linked, it cannot be assumed that a treatable metabolic disorder is not possible (Husmann et al, 1996). Appropriate evaluation is warranted. Conversely, a stone impacted in the UPJ can create the appearance of a congenital UPJ obstruction on routine imaging.

The classic presentation of acute episodes of flank pain and nausea due to UPJ obstruction is termed a *Dietl crisis* when bilateral (Dietl, 1864). **It can occur more often unilaterally and is often thought to be a gastrointestinal disorder with subsequent misdirected evaluation** (Alagiri and Polepalle, 2006). These children can present at any age, although it is rarely recognized in early childhood. The pattern is often one of increasingly frequent and severe episodes of acute-onset abdominal or flank pain with nausea and vomiting. These episodes may last for minutes to several hours and often occur in the evening. Only occasionally is the episode obviously triggered by fluid intake. Some children will report that leaning over a chair can help reduce the discomfort. Little can reduce their discomfort otherwise, yet when the episode has passed they seem fully recovered. The repetitive and consistent nature of the episodes, particularly with a nonrevealing gastrointestinal workup, should prompt consideration of a renal cause and performance of an ultrasound evaluation. Diagnoses given to these episodes before being accurately identified have included abdominal migraines, food allergies, musculoskeletal problems, and emotional disturbances. In a most extreme example a girl had ongoing diagnoses of more and more food allergies while her kidney became progressively nonfunctional as a result of having had an early evaluation that was misinterpreted.

IMAGING

To define both the nature and extent of any potentially obstructive condition it is necessary to obtain an anatomic and functional assessment of the kidneys, ureters, bladder, and urethra. Performing this in a logical sequence will usually permit an appropriately selective workup.

Anatomic Assessment

Ultrasonography

The most widely useful initial imaging study for many obstructive conditions is renal and bladder ultrasonography. Although essentially a structural evaluation, functional information can also be gained. The characterization of hydronephrosis is straightforward with ultrasonography, and seldom is there a real need for any other imaging to define the degree of hydronephrosis. **Any indication of hydronephrosis on ultrasonography must be qualified by a description of the laterality, severity, and associated alterations in the renal parenchyma.**

Some consider hydronephrosis to be present only with calyceal dilation, so it is best to use the terms *pelviectasis* and *caliectasis* to describe these entities, along with a qualifier as to severity. Because the degree of pelvic and calyceal dilation is not always the same, distinct description is important. Indeed, the situation in which the renal pelvis is not markedly dilated yet there is marked caliectasis may even suggest a process distinct from UPJ obstruction, such as infundibulopelvic stenosis. A very dilated pelvis, with minimal to no caliectasis, suggests a functionally milder obstruction than the degree of dilation might indicate. The most widely used grading system is the Society for Fetal Urology scale (Fig. 113–7), which divides hydronephrosis into four grades (Fernbach et al, 1993). This is a useful communication tool but is limited in its description of the more severe degrees of dilation, which are combined into one grade with very wide inclusion. It still provides more information than a report simply stating "hydronephrosis."

The condition of the renal parenchyma is reflected to some degree in its ultrasound appearance. With increasingly abnormal development, kidneys are more echogenic. This may be due to more tissue-urine interfaces to reflect the sound waves; and although it is not proof of "dysplasia," which is a pathologic diagnosis, it is suggestive. The thickness of the renal parenchyma is often described, and the effect of hydronephrosis may be referred to as cortical thinning or cortical atrophy, although some of these kidneys have intact uptake on nuclear scans (Erickson et al, 2007). The kidney can undergo a significant amount of stretching without being markedly affected functionally, probably as a compensatory mechanism. This should not be used as an indicator of a nonsalvageable kidney in the absence of functional testing.

Direct Imaging

In some cases, specific imaging of the anatomy of the urinary collecting system may be important in determining management. This is usually when the ultrasound appearance is atypical or with a duplicated system. The intravenous pyelogram was often able to provide these anatomic insights and on occasion may still be useful. Magnetic resonance imaging (MRI) can often provide this level of detail even in small children. Retrograde pyelography performed during cystoscopy can demonstrate ureteral and pelvic anatomy very clearly and can ensure the localization of the obstructive area. This is often in preparation for operative intervention. It is important to recognize the risk of infection if the kidney is not going to be decompressed after the study, whether by stent or definitive surgery.

Antegrade imaging can be useful if a percutaneous nephrostomy has been placed. This is usually in the setting of an ill infant with bilateral obstruction or a solitary obstructed kidney or for severe pain.

In the initial evaluation of most infants with hydronephrosis, voiding cystourethrography is performed to determine whether reflux may be present. The occurrence of both reflux and obstruction can be a very challenging clinical situation. In particular this is difficult when

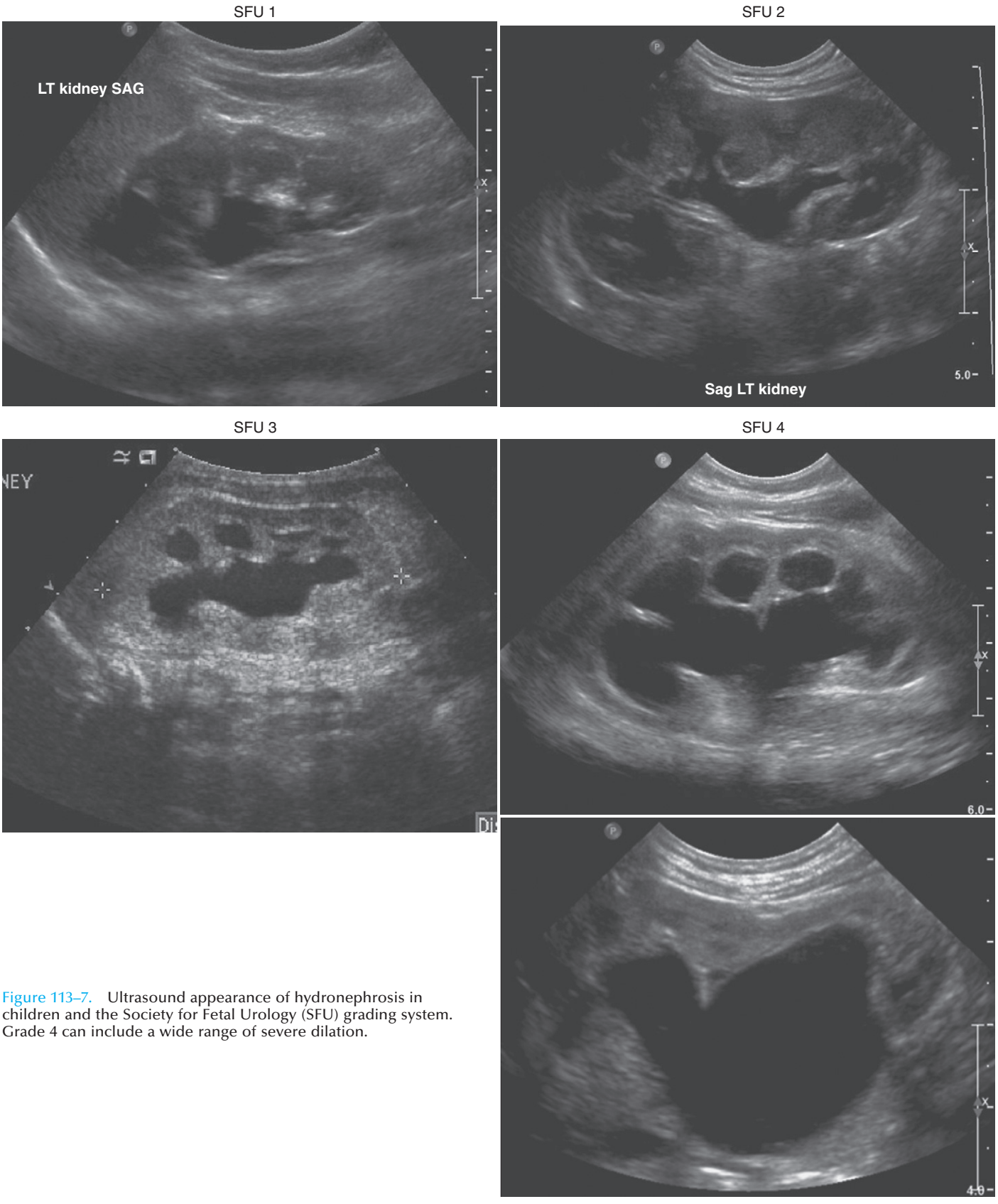


Figure 113–7. Ultrasound appearance of hydronephrosis in children and the Society for Fetal Urology (SFU) grading system. Grade 4 can include a wide range of severe dilation.

high-grade reflux may produce a very dilated pelvis, and this may create impaired drainage due to ureteral tortuosity. Whether there is a true UPJ obstruction in addition to the reflux is unclear. The decision as to which process to correct, if surgical intervention is appropriate, is difficult (Stauss et al, 2003). If there is significant ureteral tortuosity, correction of the reflux first can allow for improvement of the UPJ obstruction, but close monitoring is required (Hollowell et al, 1989).

Functional Assessment

Although anatomic assessment is a critical element of clinical diagnosis of obstruction, so, too, is a functional assessment; yet we remain limited by technology in the accuracy and utility of these methods. **At present, diuretic renography is the "gold standard" for functional imaging of congenital obstruction; yet questions must be raised as to its prognostic value and true role in clinical management.** These uncertainties are based on a poor correlation with renal pathology, variability in interpretation, and lack of reproducibility in individual patients. Attempts have been made to standardize testing protocols (the well-tempered renogram) (Conway and Maizels, 1992), but none has been validated with any method other than diuretic renography. There is still utility to the diuretic renogram when interpreted judiciously, and the emergence of MR technology for obstructive uropathy holds great, yet unfulfilled, promise. An integral part of any utility will be studies that validate imaging observations with both functional assessment by other means, pathologic correlations, and clinical outcomes.

Diuretic Renography

Diuretic renography is based on the ability to measure the rate and location of uptake of a radiolabeled organic molecule that is handled by the kidney in a specific way. The most commonly used tracer is ^{99m}Tc-mercaptoacetyltriglycine (MAG3). This tracer is taken up by the renal tubules and is largely excreted by the tubules into the tubular lumen. There is relatively little glomerular filtration. The early pattern of uptake is roughly equivalent to renal plasma flow and is parallel to GFR. Unlike dimercaptosuccinic acid (DMSA), it is not bound to the tubules and is rapidly cleared, permitting assessment of drainage from the collecting system. Another agent, diethylenetriaminepentaacetic acid (DPTA), was less avidly taken up, resulting in higher levels of background tracer, making initial functional assessment less precise. MAG3 has a very high signal-to-noise ratio during the first 1 to 2 minutes, during which time relative uptake is assessed.

Function. **What is often referred to as "function" from a diuretic renogram is relative uptake of tracer during the first 1 to 2 minutes after injection and, again, is roughly equivalent to GFR. It is expressed as differential function between the two kidneys and always adds up to 100%. It should always be borne in mind that if both kidneys are abnormal a 50% measurement is not "normal" function.** With one healthy kidney, the relative uptake of the affected unit reflects current GFR and is a reasonably good overall assessment of function. The estimated differential uptake is generally believed to be accurate to plus or minus five percentage points. It is not a direct reflection of tubular function, acid-base handling, concentrating ability, or hormonal function, but it is useful. Changes over time are a valuable clinical parameter, again with the caveat that one kidney must be normal. Attempts have been made to assess absolute function by determining an extraction factor that reflects true renal clearance (Heyman and Duckett, 1988; Cartwright et al, 1992). This may be useful in some extreme cases but has limitations on utility and is not often used clinically.

In the assessment of hydronephrosis, several aspects may affect interpretation of relative uptake. In very young infants, relative uptake is not as avid and the signal-to-noise ratio is decreased with higher background levels. Subtracting these levels can be operator dependent yet will be critical in determining uptake. For the right kidney the overlap with the liver may further confound an accurate assessment. The dilation of the parenchyma of the kidney moves it further away from the camera and the retained urine may quench some of the radioactivity, further reducing accuracy. It remains unclear how the immature obstructed kidney responds to the obstruction as noted earlier, and the compensating kidney may show relatively normal uptake yet still be abnormal. This was demonstrated in the observation of normal relative uptake in kidneys with significant histologic abnormalities in unilateral UPJ obstruction (Huang et al, 2006). Relative hyperfunction may also be seen, and it remains controversial what this actually represents (Steckler et al, 1994; Capolicchio et al, 1999; Moon et al, 2003, Maenhout et al, 2005). It may be a healthy kidney that is actually hypertrophied from the obstruction, or it may be a compensatory response that ultimately will be detrimental over time (Capolicchio et al, 1999, Oh et al, 2001). This is not a common occurrence and has not been carefully studied (Ozcan et al, 2006).

Despite these limitations a well-performed diuretic renogram provides a reasonable measure of relative uptake and "function" of the hydronephrotic kidney. It is best used as a serial marker to be followed to determine deterioration or improvement (Fig. 113–8) (Eskild-Jensen et al, 2005). When relative uptake is reduced, it is rarely recoverable despite successful surgery. Reports of spontaneous increases in uptake are difficult to interpret, because they seem rare in experience and may equally represent systematic underassessment of uptake in younger children, owing to background assessment differences (Ulman et al, 2000; Onen et al, 2002).

Drainage. The ability to assess drainage from a hydronephrotic kidney differentiates the MAG3 renogram from the DMSA. As a measure of the degree of obstruction, the time required to clear half of the accumulated tracer from the renal pelvis after reaching its peak and being stimulated by administration of furosemide, the washout half-life has become a measure of obstructive severity. **When it is over 20 minutes it is generally considered "obstructed"; less than 10 minutes is considered normal, and in between is considered uncertain** (O'Reilly et al, 1978; Koff, 1982; Abramson et al, 1983). **These parameters have been broadly used, although the clinical validation is lacking. There has been no truly effective assessment of their predictive utility in children** (Eskild-Jensen et al, 2005). Several studies have shown that the washout time did not predict functional changes over time, nor the development of symptoms (Ulman et al, 2000; Thorup et al, 2003, Koff, 2008). Washout time correlated poorly with renal histology in a biopsy study (Huang et al, 2006). Again, the value of the washout time, until better indicators become available, is in serial follow-up. There can be variability of uncertain etiology, but if a consistent trend can be demonstrated, either improving or worsening drainage, clinical decisions may be aided.

Several factors can contribute to the variability and interpretation of the washout time (Eskild-Jensen et al, 2004). Most centers will use a bladder catheter to make the assessment of washout times to eliminate bladder filling as a factor in upper tract drainage (Conway and Maizels, 1992). Although some have criticized this

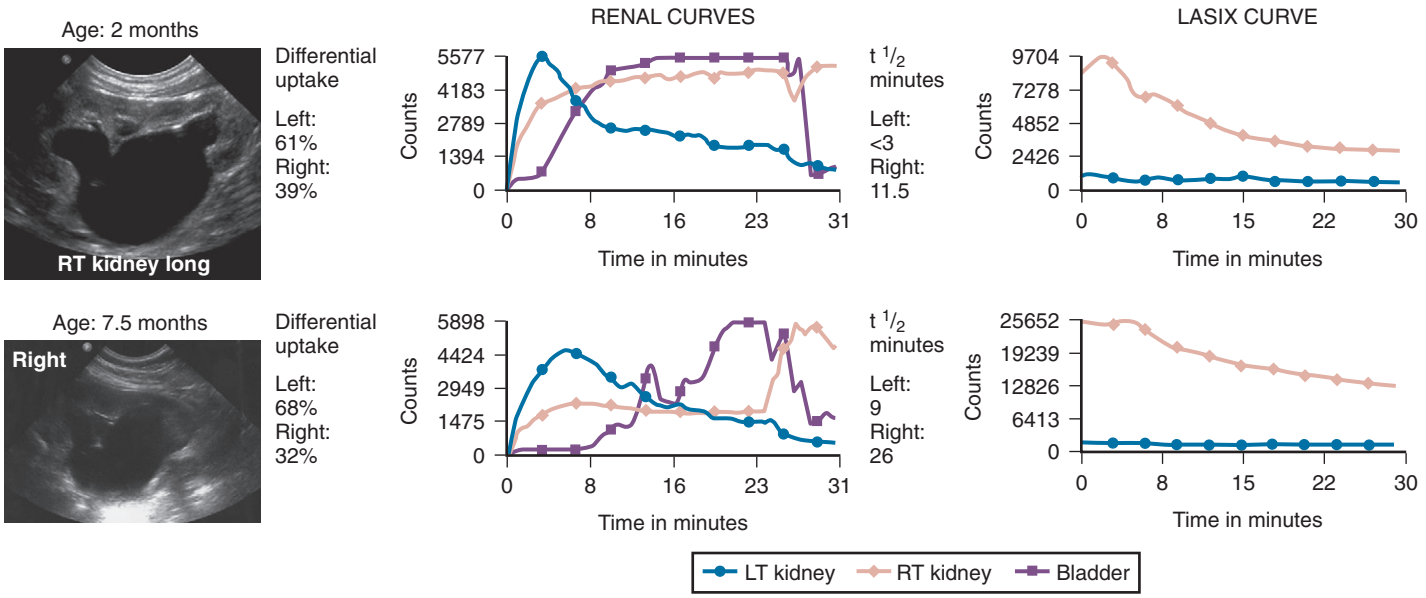


Figure 113–8. Example of the use of diuretic renography using 99mTc-mercaptoacetyltriglycine in the clinical follow-up of an infant with right ureteropelvic junction obstruction. Severe hydronephrosis (grade 4) was present and did not significantly change. Initial renography showed relative uptake of the right kidney at 39% and at ½ washout time of 11.5 minutes, which increased to 26 minutes associated with a decrease in relative uptake to 31% by age 7½ months.

as nonphysiologic, it permits standardization and in the pre–toilet-trained child is preferable. The means by which the washout time is calculated can be variable and dependent on the curve of tracer drainage. Some systems will have a brief and limited drainage, and if that initial phase of the curve is used to extrapolate the washout time it will be falsely normal. Some curves appear to be slow in initial drainage, then rapidly draining, perhaps due to delayed effect of the diuretic agent.

Some authors have attempted to modify the technique and to make it more efficient by administering the diuretic before or simultaneous with the tracer. These are termed the *F–15* or *F zero diuretic renograms* (Upsdell et al, 1992; Donoso et al, 2003; Liu et al, 2005). Although they may be equally effective, they have not been validated against a uniform standard of clinical outcome.

The time required for the tracer to move through the renal parenchyma into the collecting system is the cortical transit time and is analogous to the delay for calyceal filling in the intravenous pyelogram showing a persisting nephrogram. With severe obstruction cortical transit is prolonged, although it is uncommonly used for clinical assessment (Schlotmann et al, 2008, 2009). It is not very useful for subtle distinctions; but if it is elevated well above the normal 2 to 3 minutes, consideration for significant obstructive effect should be given.

For the present, diuretic renography is the most robust means to assess congenital obstruction, particularly of the upper tracts. Its interpretation requires judgment, and simply "going by the numbers" without inspecting the appearance of the kidneys and the uptake and washout curves is inadequate.

Magnetic Resonance Imaging

MRI holds the promise of integrating both anatomic detail with functional assessment of the kidney and urinary tract. In pediatric obstruction it has not yet been fully validated in this regard, but progress is being made and it is likely that MRI will be the modality of choice for evaluating hydronephrosis in the near future. The benefits of MRI include absence of ionizing radiation, detailed anatomic definition of the entire urinary tract, functional assessment comparable to current diuretic renography, and the potential for more specific functional assessment based on tissue characteristics and metabolic factors. Current limitations include cost, limited availability of experienced imaging professionals, need for sedation, and limited validation with clinically relevant outcomes. All of these issues are potentially solvable.

The current status of MRI in hydronephrosis in children is well outlined in several recent review articles (Cerwinka et al, 2008; Grattan-Smith and Jones, 2008) and demonstrates the ability to accurately provide data comparable to diuretic renography with the detailed imaging well known for MRI. Protocols for imaging are being established and validated with diuretic renography, the de facto gold standard. Validation against renal developmental patterns, based on histology or long-term clinical outcomes, remains to be done. At present, MRI in children can provide an accurate assessment of differential renal function, comparable to differential uptake on radionuclide imaging, and a more precise measure of obstruction, including renal transit time, cortical to medullary crossover time, ureteral filling time, and several subjective indicators of obstruction.

Relative function is expressed both as the fraction of total renal function (differential uptake), as well as an estimate of GFR. This is based on one of two methods. The first is relative volume determination (vGFR), in which the functional volume of the kidney is measured and compared with the opposite kidney. These measurements have been correlated with differential uptake on diuretic renography (Perez-Brayfield et al, 2003; Martin et al, 2008). It remains to be seen how well this method will correlate with uptake in the severely hydronephrotic kidney. It is somewhat counterintuitive that function is directly proportional to renal volume, because there are many kidneys with large volume that do not function well. The second method uses Patlak curves of tracer extraction to estimate an index of individual kidney GFR (pGFR), which has also been correlated with radionuclide methods. This can permit more accurate estimates in bilateral diseases or

with scarring. As with radionuclide imaging, the limitations of these studies include the fact that this measures GFR, an important indicator but not the only indicator of renal "function," and cannot estimate other aspects of renal function, such as acid-base, sodium, and water handling. These measures cannot accommodate for renal functional compensation as discussed earlier, and they have not been correlated with renal histology.

The second aspect of MRI is to assess the drainage function of the individual renal unit. This is performed using several parameters reflecting the passage of tracer (gadolinium) through the kidney. In some ways these differing measures probably reflect similar processes, and they do correlate with conventional diuretic renography washout times (Jones et al, 2004). Renal transit time (RTT) is the time required from first visualization in the renal parenchyma of the tracer until it is first seen in the collecting system. Normal values are reported to be up to 245 seconds, intermediate values are from 245 to 490 seconds, and "obstructed" values are over 490 seconds (Jones et al, 2004; Grattan-Smith et al, 2008). These numbers are largely based on conventional diuretic renography, and it has been recognized that this may not be accurate or reflective of relevant clinical outcomes. Calyceal transit time (CTT) has also been used, particularly when the contralateral kidney is normal, permitting comparison of symmetry (Grattan-Smith et al, 2008). Similar to RTT is the corticomedullary crossover point, which is the time required to develop sufficient signal intensity in the medulla to equal that in the cortex (Jones et al, 2005). This is comparable to RTT in that it measures rate of passage of tracer through the renal vasculature and tubules, presumably responding to increased tubular pressures from obstruction. The time until tracer is seen in the ureter is also a reflection of obstructive effect but is probably much less sensitive in the moderately severe degrees of hydronephrosis, which are the ones of most clinical uncertainty. Clinical studies of MR urography in children with hydronephrosis have been limited and have largely been attempts to correlate with diuretic renography. These indicate adequate correlation, and it has been recognized that further assessment with more clinically important parameters is required (Grattan-Smith et al, 2003; Perez-Brayfield et al, 2003; Teh et al, 2003; McDaniel et al, 2005; Martin et al, 2008). A lack of standardized protocols has been suggested as a potential basis for the limited accuracy and reproducibility of clinical reports, and a recent review indicates that routine clinical usage is not yet justified (Grenier et al, 2008).

A further potential benefit from MRI that has been utilized in other areas, and suggested in pediatric urinary imaging, is to use the exquisite sensitivity of MRI to alterations in the metabolic context of tissues. Oxygen tension (Textor et al, 2008; Edlund et al, 2009), sodium levels (Maril et al, 2006), and energy consumption (von Elverfeldt et al, 2007) in the kidney are all potentially measurable by MRI and, coupled with anatomic detail, may provide the critical information to indicate patterns of cellular response that may lead to functional impairment or loss as described earlier. These studies are yet to be conducted in the developing kidney.

There has been recent concern regarding the safety of gadolinium with regard to renal function. A pattern of systemic fibrosis associated specifically with gadolinium has been reported (Wiginton et al, 2008; Graziani et al, 2009; Perazella, 2009). This has been largely restricted to patients with impaired renal function, but it is unlikely that this is a risk to an individual kidney with reduced function due to obstruction. Continued caution is appropriate.

Clinically, MR urography is particularly useful in situations with complex anatomy that cannot be resolved with ultrasonography (Fig. 113–9) and has been used to evaluate chronic hydronephrosis when diuretic renography is ambiguous. It is not yet validated as a "gold standard" but ultimately will become this.

Intravenous Pyelography

It is rare in current usage to require a conventional intravenous pyelogram, but the simplicity of the test is occasionally of benefit. Because it can convey both anatomic and functional information,

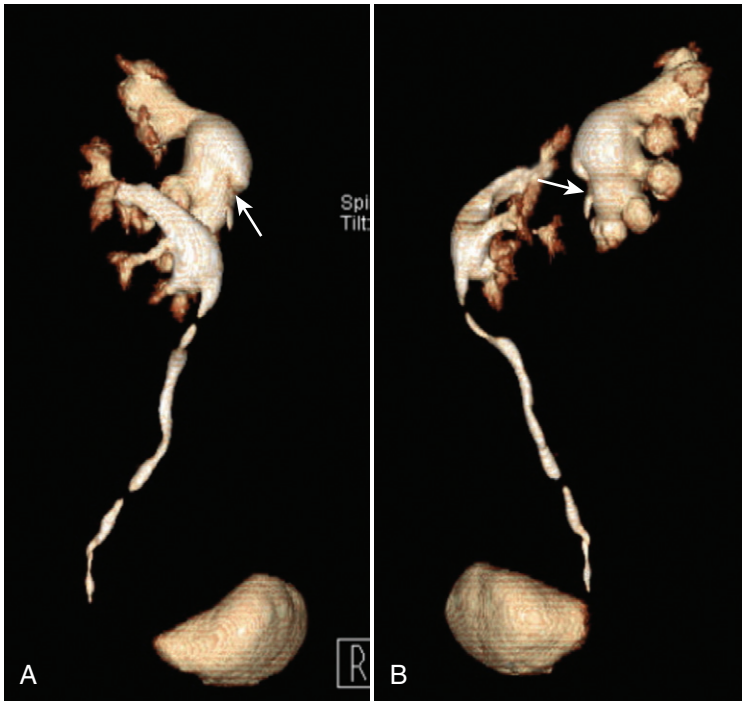


Figure 113–9. Example of the use of MR urography with three-dimensional reconstruction, with two views (**A** and **B**) demonstrating the presence of a crossing vessel causing intermittent pain and obstruction in a boy with a horseshoe kidney. The *arrows* indicate the impression of the vessel on the proximal ureter. Hydronephrosis is mild to moderate, but pain was relieved with surgical repair.

it provides a less precise and nonquantitative version of what MRI promises. Its use has become limited, and some centers no longer perform the test. The authors have found it useful in complex anatomic cases, particularly with duplication anomalies combined with hydronephrosis in which it may provide preoperative data to indicate the appropriate surgical approach. It is also useful in the postoperative situation with persisting hydronephrosis when it is uncertain if there is high-grade obstruction and a renal scan may not be needed. The intravenous pyelogram can show that the kidney is functioning and, although draining slowly, is safe for further observation to demonstrate improvement. In these cases a simple three-image study can be perfectly adequate. As MRI evolves further, and shorter scan times become routine, the intravenous pyelogram will become obsolete, but it can still play a role in selected situations.

Key Points: Imaging for Congenital Obstruction

- To define both the nature and extent of any potentially obstructive condition it is necessary to obtain an anatomic and functional assessment of the kidneys, ureters, bladder, and urethra.
- The most widely useful initial imaging study for many obstructive conditions is renal and bladder ultrasonography.
- Any indication of hydronephrosis on ultrasonography must be qualified by a description of the laterality, severity, and associated alterations in the renal parenchyma.
- In the initial evaluation of most infants with hydronephrosis, voiding cystourethrography is performed to determine whether reflux may be present. The occurrence of both reflux and obstruction can be a very challenging clinical situation.
- What is often referred to as "function" from a diuretic renogram is relative uptake of tracer during the first 1 to 2 minutes after injection and is roughly equivalent to GFR.
- Differential function on a radionuclide study represents the relative contribution of each kidney to total uptake and always adds up to 100%. If both kidneys are abnormal, a 50% measurement is not "normal" function.
- When the diuretic washout time is more than 20 minutes, it is generally considered "obstructed"; less than 10 minutes is normal, and in between that time frame it is considered uncertain.
- MRI holds the promise of integrating both anatomic detail with functional assessment of the kidney and urinary tract. In pediatric obstruction it has not yet been fully validated in this regard.

PROGNOSIS AND MANAGEMENT STRATEGIES

The assessment of possible outcome for an obstructed kidney is important in terms of determining the value of an intervention and in providing clinical prediction of possible failure of the kidney. These predictions will serve to guide therapy and assess the risk-benefit balance in treatment. As yet there are few studies to suggest any accuracy either in unilateral obstruction or bilateral obstruction. Use of renal biopsies in obstruction has shown some loose correlations but none that is clinically practical. It is likely that this ability will follow from more accurate diagnostic ability.

Can any of our current incomplete understanding of congenital urinary obstruction be used in developing a clinical management strategy for these patients? Several factors seem to emerge from the many conflicting and incomplete studies of congenital obstruction. Obstruction can be very harmful to the developing kidney, to an extent far beyond that seen in the mature kidney. The effects of obstruction may not be reversible, owing to alteration of the actual structure and functional characteristics of the kidney, which does not occur in the mature kidney. There seems to be a limited time window to permit reversal of obstruction and anticipate clinically relevant recovery of functional potential. It is clear that the developing kidney, as with the mature kidney, is able to compensate in the presence of obstruction and appear to be healthy. Yet most biologic compensation mechanisms are ultimately limited in the ability to maintain homeostasis and may mask eventual significant functional derangements. The clinical threshold for intervention may therefore be better set lower than in the mature patient.

The response to obstruction in the developing kidney is extremely complex, and multiple factors are involved in various aspects of this response. Although this may seem to be a significant impediment to understanding and clinically managing these problems, it should be seen as providing multiple opportunities to develop biomarkers of these responses that may eventually facilitate decision making.

It is clear that not all children with dilated kidneys will suffer ill effects from this condition; it is equally evident that the potential for obstructive nephropathy is significant and has severe clinical implications. As the understanding of these conditions and the mechanisms of renal response to obstruction in development improves, determination of those kidneys at risk for developmental impairment will become more accurate.

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chapter
114

Perinatal Urology

Richard S. Lee, MD ● Joseph G. Borer, MD

Fetal Imaging
Fetal Diagnosis
Specific Diagnoses
Antenatal Management of Fetal Uropathies
Postnatal Management of Antenatally Detected Urologic Renal Abnormalities
Summary

FETAL IMAGING

The increased use of maternal-fetal ultrasound has led to the development of the field of perinatal urology. **Antenatal hydronephrosis** (ANH) is identified in 1% to 3% of all pregnancies and is one of the most common birth defects detected (Livera et al, 1989; Blyth et al, 1993; Gunn et al, 1995; Sairam et al, 2001). In addition to hydronephrosis, renal cystic disease, renal agenesis, stones, and tumors have been diagnosed prenatally as well. For the urologist, these prenatal findings have created numerous challenging clinical and scientific dilemmas.

Ultasonography continues to be the mainstay of fetal imaging. With experience, this modality provides intricate detail and diagnostic capability that is similar to that of ultrasonography in the neonate. Ultrasound evaluation facilitates screening large numbers of fetuses with no radiation exposure and is near universally available. The potential advantages of three-dimensional ultrasonography in imaging of urologic diagnoses are unclear.

Fetal magnetic resonance imaging (MRI) is a valuable adjunct in those instances in which further delineation of anatomic detail is believed to be necessary to optimize diagnosis and/or management strategy (Estroff, 2009). As with ultrasonography there is no radiation exposure. Utilization of complementary computed tomography is controversial, because the additive information may not outweigh the added risk of fetal and maternal radiation exposure.

The discussion here centers on the diagnosis of prenatal urologic abnormalities and the postnatal implications, the rationale behind prenatal intervention, and clinical experience in managing children with prenatal urologic abnormalities. Further detailed discussion regarding evaluation and management of many of these entities when they occur beyond the perinatal period is presented in other chapters in this textbook.

FETAL DIAGNOSIS

Previously, a large prospective study of 11,986 Swedish women done between 1978 and 1983 identified renal anomalies in 0.28% of fetuses, of which over two thirds of the anomalies were hydronephrosis (0.18%) (Helin and Persson, 1986). Similarly, a British prospective screening study of 6292 pregnant women at 28 weeks' gestation demonstrated hydronephrosis in 1.40% of cases, with postnatal confirmation in 0.65% (Livera et al, 1989). These authors defined ANH as an **anteroposterior diameter** (APD) of the renal pelvis greater than 5 mm but noted the lack of consensus on the definition of ANH (Scott and Renwick, 1993, 1999; Scott et al, 1995). **With the rapid improvement of ultrasound technology the incidence of detection of renal anomalies may be changing.** In a more recent prospective cohort study (1999-2003), a 0.76% incidence of urinary tract abnormalities was detected that was increased as compared with an earlier cohort from the same institution (0.3%, 1989-1993) (Mallik and Watson, 2008). However, many variations in the definition and management of ANH exist in the literature and clinical practice, including method and frequency of in-utero testing, radiographic documentation, classification, or postnatal management (Benacerraf et al, 1990; Corteville et al, 1992; Fernbach et al, 1993; Adra et al, 1995; Thompson and Thilaganathan, 1998; Chudleigh et al, 2001; Lee et al, 2006). This variability may significantly alter the incidence reported within the literature.

Regardless, when an abnormality of the urinary tract is determined by antenatal ultrasonography several questions should be raised by the ultrasonographer and consulting urologist. Combinations of specific findings direct the differential diagnosis and permit a more accurate prognosis and tailoring of postnatal evaluation. The principal findings and their implications are listed in Table 114–1.

Diagnostic Findings

Kidney

There are critical elements to an antenatal ultrasound examination that may help identify urologic pathology. A constellation of aberrations may indicate pathology, particularly when placed in context with other clinical findings. Specific details of the examination need to be reported to assist antenatal counseling. **The ultrasound evalution of the kidney should comment on number, location, size, duplication, renal parenchyma (echogenicity), pelvic dilation, calyceal dilation, urothelial thickening, and cystic disease.**

Kidneys should be appropriate size for gestational age and relatively symmetrical (Chitty and Altman, 2003). Large differences in size may indicate contralateral compensatory growth. Absence of the kidney in the normal location may represent ectopia or agenesis/dysplasia. **The normal kidney should be elliptical**

Table 114–1.

Elements of Prenatal Urologic Ultrasonographic Diagnosis

PARAMETER	COMMENT	POSSIBLE CAUSES
Hydronephrosis	Variable severity; may include pelviectasis and/or caliectasis	Obstruction, reflux
Caliectasis	Intrarenal dilation; more indicative of significant pathologic process	Obstruction, reflux
Pelvic anteroposterior diameter	Measured in the coronal plane, variable; in extremes may predict clinical outcome; caution should be exercised in overreliance on these measurements	Increased in obstruction, reflux
Renal parenchyma	Echogenicity should be less than that of liver or spleen; lucent medullary pyramids should be seen	Increased echogenicity in dysplasia, obstruction, ARPKD
Urothelial thickening	Increased thickness of pelvic lining	Variable dilation as with reflux or occasionally obstruction
Duplication	Separation of renal pelvic sinus echoes when no hydronephrosis seen	Possible associated reflux or obstruction; look for dilated ureter and ureterocele
Cystic structures, renal	Simple cysts rare	MCDK, ADPKD
Cystic structures, intravesical	May be very large and fill bladder; thin walled	Ureterocele
Urinoma	Fluid collection around kidney; perinephric or subcapsular	Obstruction
Bladder filling	Fill and void cycles may be demonstrated over time	Urine production
Bladder wall thickness	Must be interpreted in context of bladder filling	Obstruction, neurogenic dysfunction
Keyhole sign	Dilated posterior urethral; difficult to image	Posterior urethral valves
Oligohydramnios	Markedly reduced amniotic fluid; usually considered as no pocket of fluid > 2 cm	Poor urine output because of obstruction and/or renal failure

ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; MCDK, multicystic dysplastic kidney.

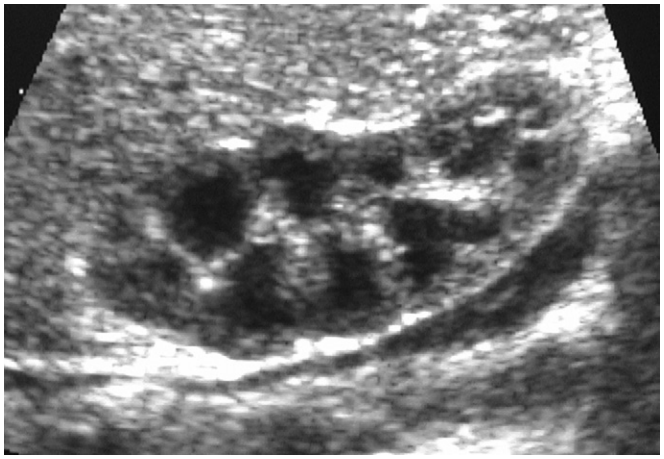


Figure 114–1. Ultrasound appearance of normal fetal kidney with echolucent medullary pyramids distinguishable from the more echogenic cortical parenchyma. The cortical parenchyma should be of lower echogenicity than adjacent liver or spleen.

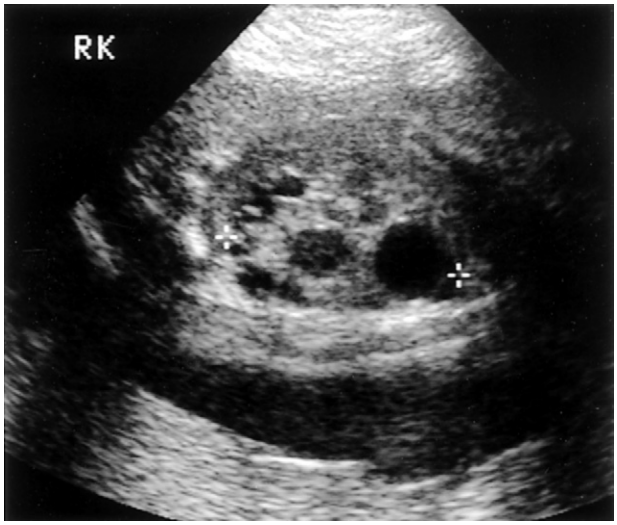


Figure 114–2. Multicystic dysplastic kidney with large, multiple, variable-sized cysts without a central large cystic area. As here, most cases show virtually no parenchyma.

and have distinctive internal echolucency, representative of normal medullary pyramids (Fig. 114–1). **The appearance of the medullary pyramids should not be confused with renal calyceal dilation.** The echogenicity of the kidney should be slightly less than the corresponding spleen or liver. Abnormalities of echogenicity with or without hydronephrosis may indicate renal disease. Isolated increased echogenicity has been associated with renal parenchymal disorders, but it has also been shown to be of no clinical significance (Carr et al, 1995). When seen with hydronephrosis it may indicate renal dysplasia, particularly if there is accompanying decreased amniotic fluid (Kaefer et al, 1997b).

Renal cystic disease can be seen in utero. Autosomal-recessive polycystic kidney disease (ARKPD) may appear as large, bright or echogenic kidneys, because the numerous small renal cysts cannot be resolved by ultrasonography. In contrast, a multicystic dysplastic kidney (MCDK) typically presents as a large noncommunicating macrocyst (Fig. 114–2). A single cyst may represent a dilated renal calyx or diverticulum, an atypical MCDK, severe hydronephrosis, or a nonrenal structure.

Ureter, Bladder, and Urinoma

In addition to kidney-specific findings, ureteral dilation, bladder filling and emptying, bladder wall thickness, intravesical cystic structures, dilation of the posterior urethra (keyhole sign), urinoma, amount of amniotic fluid, intra-abdominal/pelvic mass, and external genitalia should be noted. **Hydroureter is best**



Figure 114–3. Fetal ultrasonography showing a dilated, tortuous ureter *(arrow)*. These may be associated with reflux, valves, ectopic ureters, ureteroceles, and ureterovesical junction obstruction. In this case the ureter is associated with a dilated upper pole indicating an ectopic ureter or ureterocele.

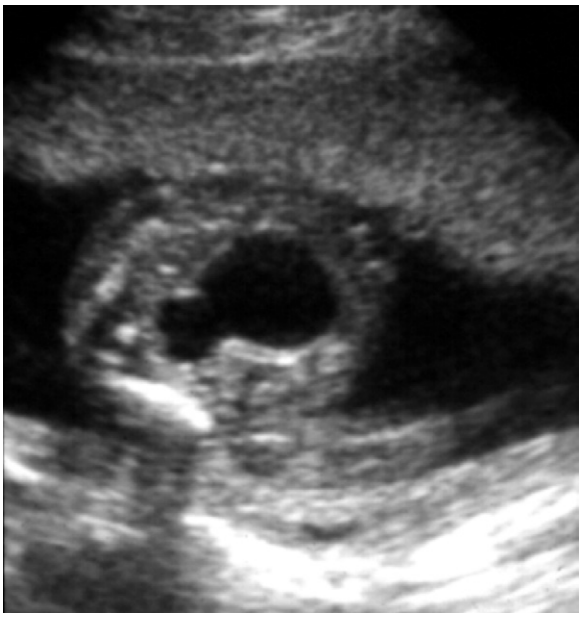


Figure 114–4. Fetal ultrasonography at 22 weeks' gestation of a male with posterior urethral valves. The bladder is thick walled and has a dilated posterior urethra (keyhole sign). There was also bilateral hydronephrosis, echogenic renal parenchyma, and a perinephric urinoma.



Figure 114–5. Appearance of a fetal perinephric urinoma associated with posterior urethral valves.

seen in cross section of a full bladder but is often difficult to detect (Fig. 114–3). Duplication and ureteral ectopia may also make this a difficult diagnosis.

Although the bladder is sometimes difficult to image well, visualization of the bladder can be very informative, because a full bladder implies renal function. **Inability to identify the bladder on repeat studies should raise the question of bladder exstrophy. Increased bladder wall thickness may indicate outlet obstruction, and dilation of the posterior urethra (keyhole sign) is strongly suggestive of posterior urethral valves** (Fig. 114–4). In duplex systems, ureteroceles may present as an intravesical cystic structure and a dilated upper pole.

Perirenal urinoma may indicate an obstructive condition (Yerkes et al, 2001) (Fig. 114–5). Typically it will have the appearance of an anechoic structure around the kidney or be in a subcapsular location. **When identified, a urinoma or urinary ascites is often associated with cases of severe bladder obstruction, or posterior urethral valves, in which the urinoma may indicate a popoff mechanism.** The popoff mechanism may be renal protective (Adzick et al, 1985). A urinoma also may be associated with a unilateral hydronephrotic/obstructed kidney (Mandell et al, 1994).

Amniotic Fluid

Critical to the evaluation of the urinary tract is the assessment of the amniotic fluid level and changes during pregnancy. **After 16 weeks, amniotic fluid production shifts from placental transudate to fetal urine; and by 20 to 22 weeks the vast majority of amniotic fluid is fetal urine** (Takeuchi et al, 1994). Consequently, **reduced amniotic fluid or oligohydramnios identified after 18 to 20 weeks' gestation may be a result of urinary tract obstruction or poor renal development** (Stiller et al, 1988).

External Genitalia

Proper identification of the external genitalia also can be very valuable in cases of gender-specific diagnoses, such as posterior urethral valves. **In cases of virilization (e.g., congenital**

adrenal hyperplasia), a clitoris may appear as a small phallus; therefore the presence of scrotal testes is critical for male gender assignment (Benacerraf et al, 1989; Bromley et al, 1994; Mandell et al, 1995). Megalourethra, or a dilated, elongated penile urethra, may be an isolated anomaly or associated with prune-belly syndrome (Dillon et al, 1994) (Fig. 114–6). **A female fetus with bilateral renal obstruction and bladder outlet obstruction would suggest a cloacal anomaly** (Cilento et al, 1994; Ohno et al, 2000; Taipale et al, 2004) (Fig. 114–7).

Hydronephrosis

Hydronephrosis, or dilation of the renal pelvis, is the most common urologic abnormality found on ultrasound evaluation. Numerous grading systems have been developed; however, there is no consensus on the best and most consistent method of reporting ANH (Fig. 114–8) (Fernbach et al, 1993). Measurement of the APD has been used widely, but there have been no formal studies to determine the interobserver and intraobserver reproducibility of ANH measurement. **One of the disadvantages of the APD can be the failure to describe pelvic configuration, calyceal dilation, and the laterality of findings, which should be included.** The APD can be affected by gestational age, hydration status of the mother, bladder hypertonicity, and degree of bladder distention. Because the dimensions of the renal pelvis may normally increase with gestational age, most investigators have adjusted threshold APD values for early and later gestational age. Unfortunately, a simple threshold APD value that separates normal from abnormal does not exist, because even severe cases of ANH have the potential to resolve without incident, whereas mild degrees of ANH have the potential to progress (Pates and Dashe, 2006).

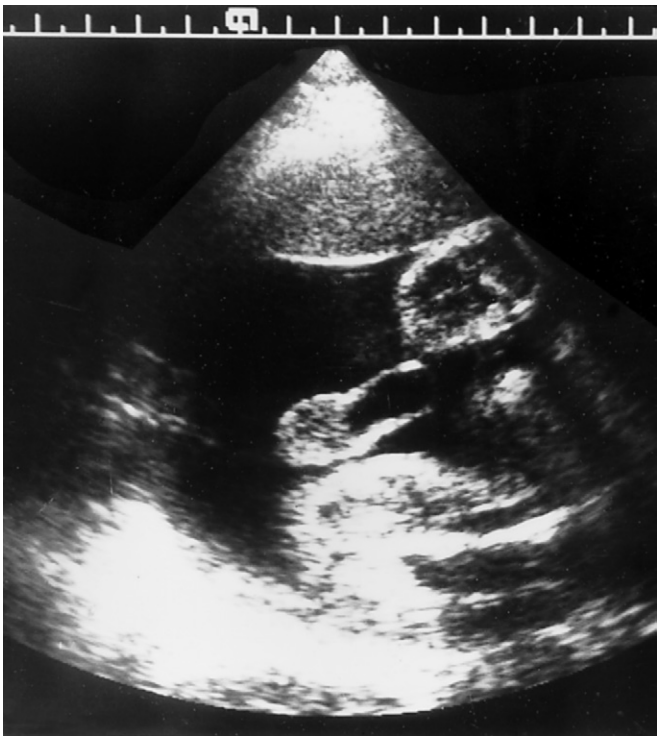


Figure 114–6. Fetal ultrasound appearance of a male with a dilated and patulous urethra typical of a megalourethra. This may be seen in prune-belly syndrome as well as in isolation. This child also had marked vesicoureteral reflux.

Varying the minimal APD threshold can significantly alter the specificity and sensitivity of APD as a measure of ANH and postnatal pathology. To date there is no consensus on the optimal APD threshold for determining the need for postnatal follow-up. An APD cutoff of 15 mm for determining obstruction yielded a

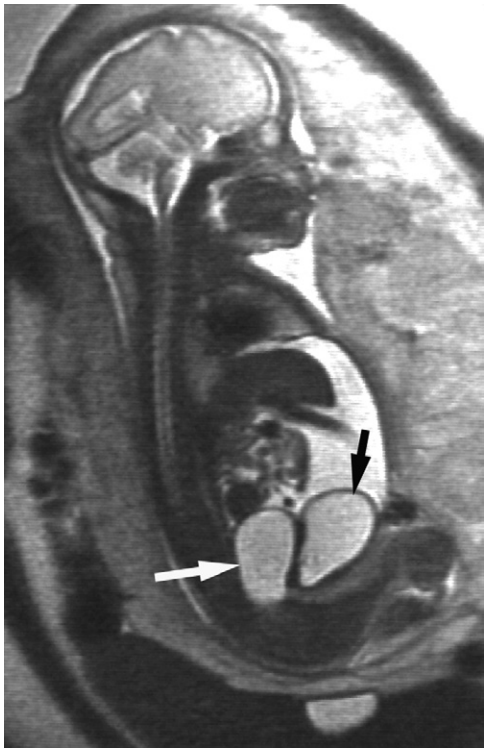


Figure 114–7. Fetal MR image illustrating severe bladder dilation *(black arrow)* and a separate dilated pelvic structure behind the bladder *(white arrow)* in a female fetus at 22 weeks' gestation. The kidneys were bilaterally and symmetrically dilated with ureteral distention. This pattern can be seen with oligohydramnios and represents a urogenital sinus malformation with bladder outlet obstruction caused by vaginal distention from urine flowing into the urogenital sinus.



Figure 114–8. Severe fetal hydronephrosis with diffuse calyceal dilation arrayed around the markedly dilated renal pelvis. The renal parenchyma is stretched over the dilated collecting system, but this does not mean loss of functional potential. Corticomedullary differentiation is difficult to see in this configuration.

postnatal sensitivity of 73% and specificity of 82% (Coplen et al, 2006). A late gestational age APD cutoff of 10 mm would detect aproximately 23% of abnormal kidneys, whereas a cutoff of 7 mm detected 68% (Ismaili et al, 2003). One large systematic review estimated that only 11.9% of total pathology presented with late gestational age APD less than 9 mm, whereas 39% of total pathology was noted at APD levels less than 15 mm (Lee et al, 2006). Nearly identical results have been demonstrated by other investigators (Wollenberg et al, 2005). What appears certain is that lower cutoffs will be more sensitive in detecting postnatal pathology but will incur a higher false-positive rate.

Categorizing ANH by APD. There is near agreement that APD greater than 15 mm represents severe or significant hydronephrosis, and some would also agree that a lower threshold of 4 to 5 mm is an appropriate value for considering APD to be abnormal (Feldman et al, 2001; Ahmad and Green, 2005; Wollenberg et al, 2005; Lee et al, 2006; Coelho et al, 2007, 2008). Taking these limitations into consideration, we define ANH in the second and third trimesters using APD thresholds for which the best available evidence provides prognostic information; along with these definitions the estimated distribution of the ANH based on the previous defined definition of APD is outlined in Table 114–2.

Diagnostic Accuracy

As both ultrasound and MRI technology improve, more accurate radiographic information is obtainable (Laifer-Narin et al, 2007). However, determining accurate postnatal diagnosis and prognosis remains challenging. Regardless of the diagnosis, early intervention is uncommon except in the potential case of severe obstruction or posterior urethral valves. In the vast majority of other cases, early detection of ANH may be an impetus for future postnatal evaluation.

The ability to determine definitive postnatal pathology based on antenatal findings is difficult. As an example, a recent systematic review of the ANH literature attempted to determine the risk of a pathologic diagnosis for patients with varying severity of ANH (Lee et al, 2006). The review included 1308 patients who were identified with ANH and sufficient postnatal radiographic follow-up. The degree of ANH was defined by APD identified in a particular trimester. Approximately 36% of the patients had a postnatal pathologic diagnosis, and the overall risk for any pathologic process increased with increasing degree of ANH (Table 114–3). **However, the risk of vesicoureteral reflux (VUR) remained consistent regardless of the degree of ANH, thereby implying that ANH is not an appropriate indicator for VUR.**

Similarly, previous literature suggests that obstruction location can be determined prenatally in 88% of the cases; many others have reported a high false-positive rate (9% to 22%) (Hobbins et al, 1984; Scott and Renwick, 1993). The majority of false-positive findings in these studies were nonobstructive causes of hydronephrosis, such as high-grade reflux, large, nonobstructed extrarenal pelves, or transient hydronephrosis.

Early and accurate diagnosis of posterior urethral valves is critical; however, it can be difficult. The hallmark signs of an in-utero diagnosis of posterior urethral valves have been described (e.g., oligohydramnios, dilated posterior urethra, thickened bladder, and hydroureteronephrosis). Other findings such as increased renal echogenicity and decreased amniotic fluid have also been suggested to be indicative of obstructive conditions (Kaefer et al, 1997b). Regardless, there are very few studies that have prospectively examined the clinical urologic implications of these findings alone or in combination (Lee et al, 2006). In one series of 22 fetuses, the false-positive rate was as high as 58% (Abbott et al, 1998), and in a population-based series the sensitivity in detecting valves was as low as 23% (Scott and Renwick, 1993).

Regardless of the degree or severity of the finding, with any antenatal detection of a urinary tract anomaly

Table 114-2.

Definition of Antenatal Hydronephrosis by Anterior Posterior Diameter and Estimated Severity Percentage Range

	Anteroposterior Diameter		
DEGREE	Second Trimester	Third Trimester	SEVERITY
Mild	4 to <7 mm	4 to <9 mm	56.7%-88%
Moderate	7 to ≤10 mm	9 to ≤15 mm	10.2%-29.8%
Severe	>10 mm	>15 mm	1.5%-13.4%

Data from Feldman et al, 2001; Ahmad and Green, 2005; Wollenberg et al, 2005; Lee et al, 2006; and Coelho et al, 2007, 2008.

Table 114-3.

Risk of Pathology by Degree of Antenatal Hydronephrosis

	Degree of Antenatal Hydronephrosis [% (95% CI)*]					
POSTNATAL PATHOLOGY	Mild (*N* = 587)	Mild-Moderate (*N* = 213)	Moderate (*N* = 235)	Moderate-Severe (*N* = 179)	Severe (*N* = 94)	TREND *P* VALUE†
Any pathology	11.9 (4.5, 28.0)	39.0 (32.6, 45.7)	45.1 (25.3, 66.6)	72.1 (47.6, 88.0)	88.3 (53.7, 98.0)	<.001
Ureteropelvic junction obstruction	4.9 (2.0, 11.9)	13.6 (9.6, 18.9)	17.0 (7.6, 33.9)	36.9 (17.9, 61.0)	54.3 (21.7, 83.6)	<.001
Vesicourethral reflux	4.4 (1.5, 12.1)	10.8 (7.3, 15.7)	14.0 (7.1, 25.9)	12.3 (8.4, 17.7)	8.5 (4.7, 15.0)	.10
Posterior urethral valves	0.2 (0.0, 1.4)	0.9 (0.2, 3.7)	0.9 (0.2, 2.9)	6.7 (2.5, 16.6)	5.3 (1.2, 21.0)	<.001
Ureteral obstruction	1.2 (0.2, 8.0)	11.7 (8.1, 16.8)	9.8 (6.3, 14.9)	10.6 (7.4, 15.0)	5.3 (1.4, 18.2)	.025
Other‡	1.2 (0.3, 4.0)	1.9 (0.7, 4.9)	3.4 (0.5, 19.4)	5.6 (3.0, 10.2)	14.9 (3.6, 44.9)	.002

Modified from Lee RS, Cendron M, et al. Antenatal hydronephrosis as a predictor of postnatal outcome: a meta-analysis. Pediatrics 2006;118(2):590.

*Pointwise 95% confidence intervals were estimated by logistic regression with robust standard errors based on generalized estimating equations with a working independence correlation structure to adjust for clustering by study for all degrees of antenatal hydronephrosis except mild to moderate. Because only one study had subjects with mild-to-moderate antenatal hydronephrosis, the pointwise 95% confidence intervals had to be estimated using logistic regression with unadjusted standard errors.

†Testing for trend in risks with increasing degree of antenatal hydronephrosis using logistic regression with robust standard errors based on generalized estimating equations with a working independence correlation structure.

‡Includes prune-belly syndrome, VATER syndrome, solitary kidney, renal mass, and unclassified causes.

a thorough fetal survey must be conducted. Amniocentesis and karyotype should be considered if intervention or a major anomaly is suspected, because the incidence of concurrent chromosomal anomalies is relatively high in fetuses with concomitant urologic anomalies (Callan et al, 1990; Nicolaides et al, 1992a, 1992b; Snijders et al, 1995).

Key Points: Prenatal Diagnostic Findings

- Ultrasonography is the mainstay of prenatal imaging. Selective use of fetal MRI may further delineate anatomic details and help with diagnosis and management.
- The normal kidney should be elliptical and have distinctive internal echolucency, representative of normal medullary pyramids.
- The appearance of the medullary pyramids should not be confused with renal calyceal dilation.
- Inability to identify the bladder on repeat studies should raise the question of bladder exstrophy.
- Dilation of the posterior urethra (keyhole sign) is strongly suggestive of posterior urethral valves.
- Reduced amniotic fluid or oligohydramnios identified after 18 to 20 weeks' gestation may be a result of urinary tract obstruction or poor renal development.
- Hydronephrosis, or dilation of the renal pelvis, is the most common urologic abnormality found on ultrasonography and is typically measured by the anteroposterior diameter (APD) of the renal pelvis.
- The APD fails to describe pelvic configuration, calyceal dilation, and the laterality of findings.
- A threshold APD value that separates normal from abnormal does not exist.
- The risk of VUR per degree of ANH is similar, implying that ANH is not an appropriate indicator of VUR.
- Antenatal detection of any urinary tract anomaly should prompt a thorough fetal survey.

SPECIFIC DIAGNOSES

Ureteropelvic Junction Obstruction

The basic features of ureteropelvic junction (UPJ) obstruction in the fetus include dilation of the renal pelvis and collecting system with no evidence of ureteral dilation. Lee and associates (2006) demonstrated that increasing severity of ANH increased the likelihood of identifying postnatal UPJ obstruction. However, the threshold for recommending postnatal follow-up is largely arbitrary and currently there are no long-term prospective studies to determine the degree of postnatal evaluation, particularly for mild and moderate cases of ANH. Nevertheless, **in the case of significant unilateral hydronephrosis there is little rationale for in-utero intervention or early delivery.** In a few cases with massive dilation, therapeutic aspiration has been recommended for prevention of dystocia. In the case of bilateral UPJ obstruction the efficacy of in-utero intervention is difficult to assess. Severe forms of UPJ obstruction may be associated with urinary ascites or perinephric urinomas, which may be a predictor of nonfunction of the kidney (Mandell et al, 1994).

Ureterovesical Junction Obstruction

Less common than UPJ obstruction, ureterovesical junction (UVJ) obstruction is characterized by ureteral dilation along with varying degrees of renal pelvic and calyceal dilation. The best way to detect ureteral dilation is at the level of the bladder, preferably in the transverse view. It is not uncommon for the distal ureter to be more dilated as compared proximally. **The causes of this appearance may be primary obstruction of the UVJ, ectopic ureter inserting into the bladder neck, or high-grade VUR.** Typically, the differentiation is made postnatally.

Cystic Kidneys

The distinction between severe unilateral hydronephrosis and MCDK occasionally may be unclear. **The findings of multiple noncommunicating cysts, minimal or absent renal parenchyma, and the absence of a central large cyst are diagnostic of MCDK** (Bearman et al, 1976; Sanders and Hartman, 1984). **The appearance of noncommunicating cysts is essential to the diagnosis and should be distinguished from severe hydronephrosis** (see Fig. 114–2). Real-time examination of the kidneys to help determine the communication of the calyces is essential. Doppler ultrasonography of the renal vasculature pulse pattern has also been reported to help make the distinction (Kaminopetros et al, 1991).

An MCDK may be present in any ectopic location but typically is in the normal position. In addition, **MCDK can be present in a duplex kidney, typically the upper pole.** If detected early in the pregnancy, the MCDK will involute over a period of time either prenatally or postnatally (Mandell et al, 1994).

Bilaterally enlarged echogenic kidneys without renal cystic disease, particularly if associated with hepatobiliary dilatation or oligohydramnios, suggest ARPKD (Smedley and Bailey, 1987; Townsend et al, 1988) (Fig. 114–9). Typically this is identified before 20 weeks' gestation, but later development has been reported (Zerres et al, 1988; Edwards and Baldinger, 1989; Mandell et al, 1991). Genetic testing is possible in some cases, thereby allowing for early diagnosis and the option for early termination because postnatal mortality and morbidity is high (Wilson, 2004; Zerres et al, 2004). A more challenging finding are normal-sized, diffusely echogenic kidneys that are not associated with other urologic lesions. A series of 19 cases (14 bilateral) included 10 patients with normal function who survived and 4 with ARPKD who died (Carr et al, 1995).

Macrocystic disorders include the rare congential multilocular cystic nephroma, which is characterized by segmental involvement of the kidney with variable macrocysts (Eble and Bonsib, 1998); cystic Wilms tumor, which typically has larger amounts of functioning parenchyma; and ADPKD, which has heterogeneous cysts in size, location, and number (Reeders et al, 1986; McHugo et al, 1988; Ceccherini et al, 1989; Edwards and Baldinger, 1989; Novelli et al, 1989).

Nonrenal cystic diseases are confused for MCDK; however, these cystic anomalies are typically not in the renal fossa and unlikely to be confused in the presence of two normal kidneys. These include mesenteric duplication cysts (Barr et al, 1990), neurenteric cysts (Uludag et al, 2001), bronchogenic cysts (Bagolan et al, 2000), extrathoracic pulmonary sequestration (Carpentieri et al, 2000), and cystic neuroblastoma (Granata et al, 2000).

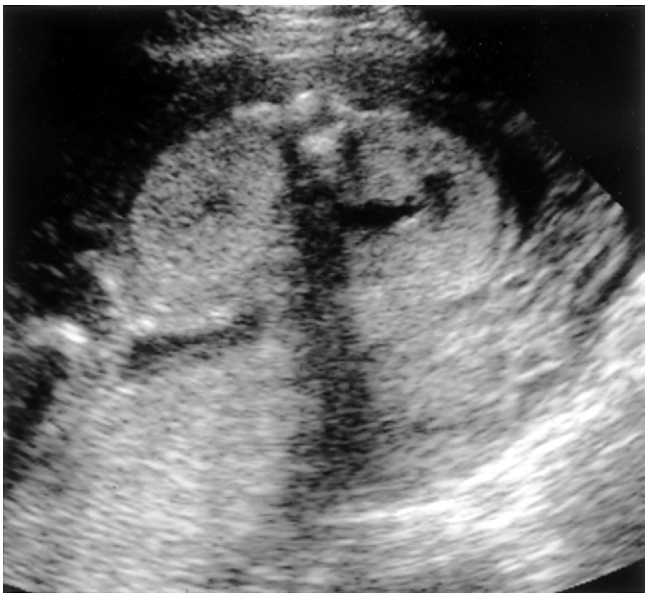


Figure 114–9. Bilaterally enlarged, echogenic kidneys without grossly apparent cysts are typical of autosomal recessive polycystic kidneys. This appearance usually, but not always, becomes apparent by 22 weeks of gestation. In early-onset cases, oligohydramnios is seen.

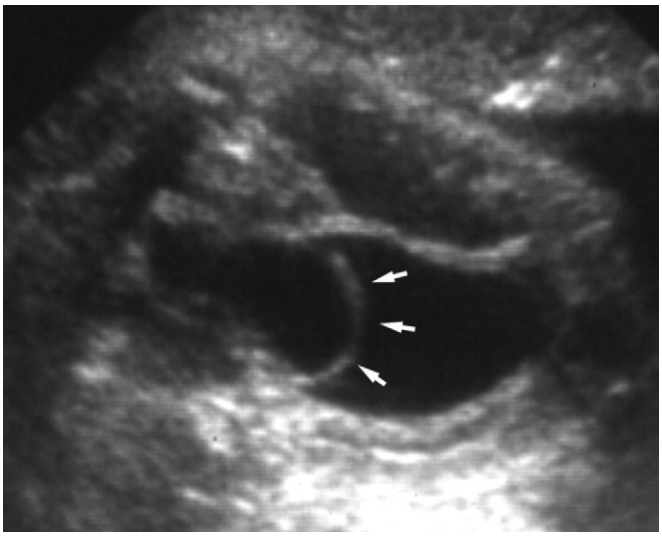


Figure 114–10. Fetal ultrasonography showing an intravesical ureterocele. The ureterocele is indicated by the *arrows* and partially fills the bladder. With this finding the ultrasonographer should examine the upper tracts to determine whether there is hydronephrosis in the entire affected kidney or only the upper pole, as shown in Figure 114–3.

Duplication Anomalies and Ureteroceles

Duplication anomalies are often recognized on the basis of upper pole hydroureteronephrosis, associated with either an obstructing ureterocele within the bladder or ectopic ureter inserting outside the bladder (Vergani et al, 1999). Ureteroceles are identified as an intravesical, thin-walled cystic structure near the base of the bladder (Fig. 114–10). **In cases of a very large ureterocele the ureterocele may be mistaken for the bladder.** Alternatively, in the setting of an ureterocele the upper pole may not always present with hydronephrosis. **The upper pole may appear as a cystic dysplastic unit without hydronephrosis and a concomitant ureterocele. This is often termed *ureterocele disproportion*** (Share and Lebowitz, 1989). Additionally, single-system ureteroceles are more likely to occur in boys and have variable degrees of hydronephrosis of the entire kidney.

Lower pole hydronephrosis may be present as a result of VUR (Fig. 114–11) or more rarely a lower pole UPJ obstruction. Occasionally, lower pole dilation is due to obstruction of both the upper and lower pole ureter by a large ureterocele. Similarly, bilateral hydronephrosis may be secondary to an element of bladder outlet obstruction from prolapse of the ureterocele into the bladder neck (Sozubir et al, 2003).

In the absence of a ureterocele, upper pole hydroureteronephrosis suggests an obstructed ectopic ureter (Abuhamad et al, 1996). The dilated ectopic ureter can be mistaken for an ureterocele because of the impression that it creates on the back wall of the bladder. However, typically the ectopic ureter is much thicker than an ureterocele. **Bilateral single-system ectopic ureters are uncommon but typically present as echogenic renal parenchyma, cystic disease, minimal bladder volume, and low amniotic fluid levels.**

Vesicoureteral Reflux

Vesicoureteral reflux cannot be definitively diagnosed on prenatal ultrasonography, although intermittent or varying degrees of hydronephrosis or hydroureter are suggestive of the diagnosis. Several studies have demonstrated that a high incidence of VUR is associated with prenatally detected hydronephrosis; however, the true incidence of VUR in children with a history of ANH is difficult to determine based on the variability of postnatal diagnostic management in the literature (Lee et al, 2006). **In two systemic reviews of the ANH literature a 10% to 15% incidence of VUR was identified regardless of the degree of ANH** (Lee et al, 2006; van Eerde et al, 2007), **indicating that the severity of ANH is not indicative of VUR and may not be the appropriate trigger for postnatal evaluation.** In a neonate with prenatally detected hydronephrosis, the importance of diagnosing VUR remains controversial, because VUR diagnosed on postnatal evaluation for ANH is associated with earlier resolution of VUR (Estrada et al, 2009a).

Posterior Urethral Valves

Perhaps the most important diagnosis to be made prenatally is that of posterior urethral valves in the male fetus. The finding of posterior urethral valves, at the very least, mandates prompt postnatal intervention, and, in some cases, prenatal intervention may be warranted. **Fetal ultrasound findings include bilateral hydroureteronephrosis, a thick-walled bladder with dilated posterior urethra, and, in more severe cases, dysplastic renal parenchymal changes with perinephric urinomas and urinary ascites** (see Fig. 114–5) (Bellinger et al, 1983; Reuter and Lebowitz, 1985; Barakat et al, 1991; Dinneen et al, 1993; Hutton et al, 1994; Gunn et al, 1995; Kaefer et al, 1997b; Abbott et al, 1998; Peters, 1998). Massive bladder dilation

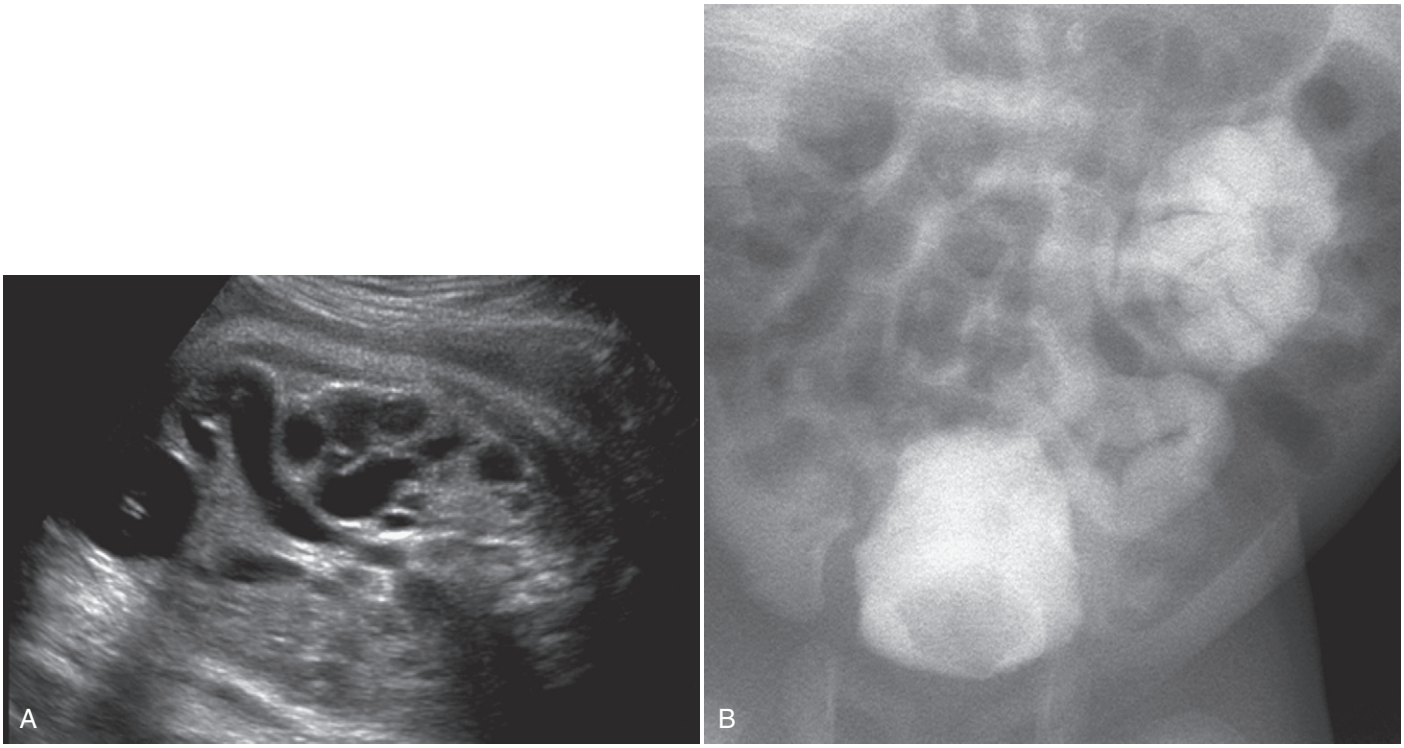


Figure 114–11. **A,** Image of a 28-week gestational age fetus with left lower pole hydronephrosis, hydroureter, and an ureterocele. **B,** Postnatal voiding cystourethrogram demonstrating lower pole vesicourethral reflux and the ureterocele.

can be seen to occupy a good proportion of the abdomen (Fig. 114–12). With progression of the pregnancy, the bladder may become more thick walled with increasing posterior urethral dilation (see Fig. 114–4). **When characteristic ultrasound findings are present the differential diagnosis includes prune-belly syndrome (with or without urethral atresia), massive VUR, and certain cloacal anomalies (in genetic females)** (Kaefer et al, 1997a; Oliveira et al, 2000).

Bladder Exstrophy

Bladder exstrophy is a congenital abnormality affecting development of the lower abdominal wall, lower urinary and reproductive tracts, and musculoskeletal system. Prenatal diagnosis can be made with reasonable certainty using ultrasonography. **Common observations in the fetus with bladder exstrophy include nonvisualization of the fetal bladder, a lower abdominal wall mass immediately inferior to a low-lying umbilicus, and diminutive genitalia** (Gearhart et al, 1995). Patience and expertise in the ultrasonographer are important for recognition of the consistent negative finding on fetal imaging—absence of bladder filling—that is critical in making the diagnosis of bladder exstrophy. **Other findings that may be evident to the experienced observer include normal kidneys in orthotopic position, normal vertebrae and spinal cord, abnormal symphyseal diastasis, and anteriorly displaced anus** (Fig. 114–13).

Prenatal diagnosis of bladder exstrophy provides an opportunity for discussion of bladder exstrophy, complex reconstruction as a neonate, follow-up care and outcomes, other organ system normality, and options of termination versus continuation of the

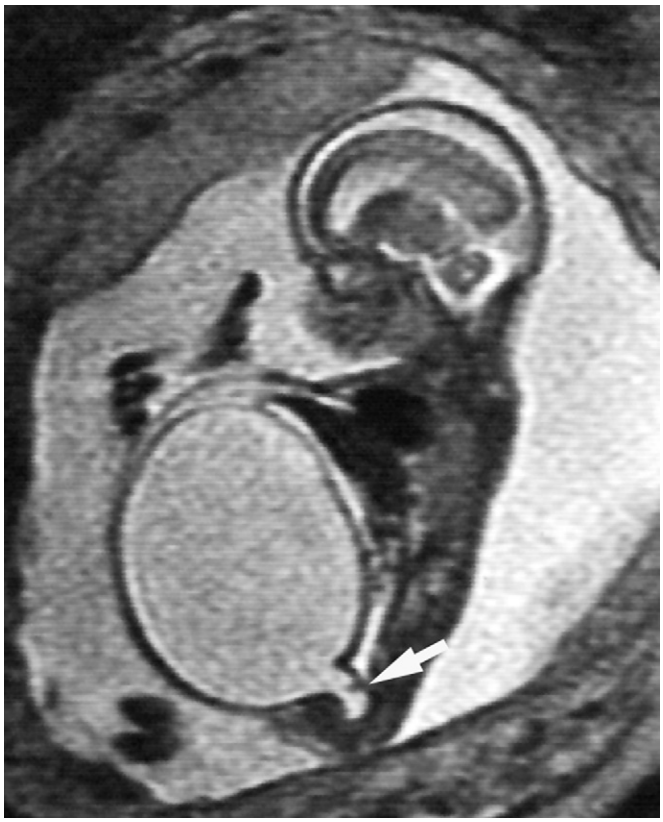


Figure 114–12. Fetal MR image showing massive bladder distention from posterior urethral valves. The dilated posterior urethra is seen below the bladder and indicated by the *arrow*.

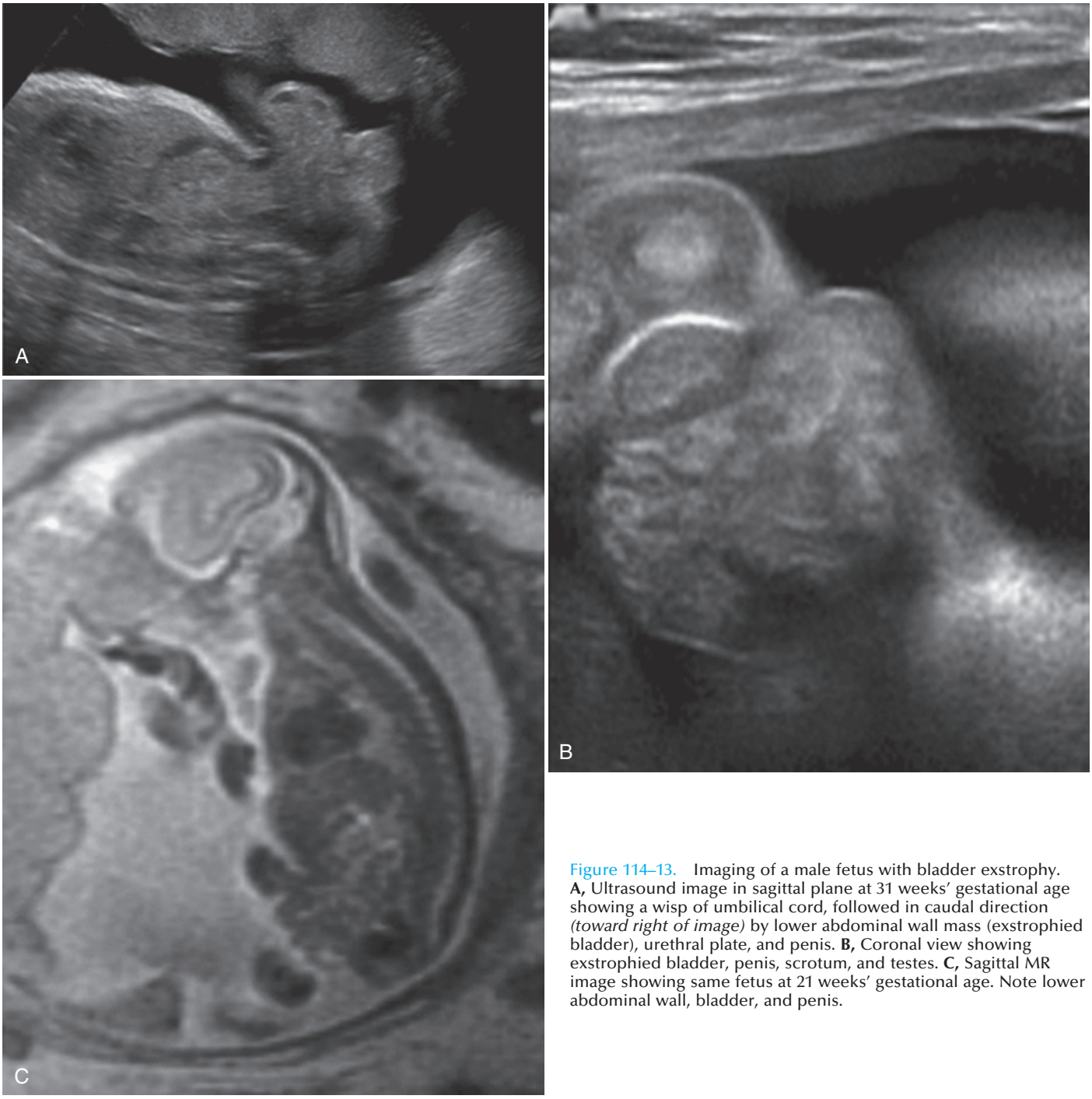


Figure 114–13. Imaging of a male fetus with bladder exstrophy. **A,** Ultrasound image in sagittal plane at 31 weeks' gestational age showing a wisp of umbilical cord, followed in caudal direction *(toward right of image)* by lower abdominal wall mass (exstrophied bladder), urethral plate, and penis. **B,** Coronal view showing exstrophied bladder, penis, scrotum, and testes. **C,** Sagittal MR image showing same fetus at 21 weeks' gestational age. Note lower abdominal wall, bladder, and penis.

pregnancy (Cacciari et al, 1999). The increasing ability to accurately diagnosis this and other complex diagnoses may have led to an increase in termination (Cromie et al, 2001).

Increasingly, the initial management of the newborn with bladder exstrophy is, perhaps, believed not to present an emergency state, and prenatal diagnosis may be helpful for several reasons. For example, at a center of excellence, expectant parent(s) who are interested may be offered advanced obstetric care, interaction with the pediatric urologic team, introduction to the pediatric hospital's support services, familiarity with the pediatric hospital itself, and interaction with parents of a child with bladder exstrophy.

Cloacal Exstrophy

Cloacal exstrophy (OEIS: Omphalocele, Exstrophy, Imperforate anus, Spinal abnormality) **is the most severe manifestation of the exstrophy-epispadias complex spectrum, carrying all of the findings associated with bladder exstrophy and renal, spinal, and bowel involvement in the form of a lateral enterovesical fistula.** Cloacal exstrophy describes a rare grouping of component malformations. The etiology is unknown but likely heterogeneous. Although postnatal identification of its associated gastrointestinal, spinal, and genitourinary systems delineates the extent and natural history of OEIS complex,

prenatal findings may provide additional information regarding early detection, possible causative factors, and outcome. The association of twinning and OEIS complex suggests that abnormal developmental step(s) may occur as early as blastogenesis (Keppler-Noreuil, 2001; Keppler-Noreuil et al, 2007). Based on fetal ultrasound findings Casale and colleagues (2004) raised a possible role of blighted conjoined twinning as a cause of cloacal exstrophy variants.

The prenatal diagnosis of cloacal exstrophy should be suspected with findings of nonvisualization of the bladder in association with a low-lying umbilicus, lower abdominal wall mass—typically omphalocele—and kidney (number, location, and/or appearance) and lumbosacral spine abnormalities (Fig. 114–14). Austin and colleagues (1988) reviewed 22 patients with prenatal ultrasound studies and cloacal exstrophy and identified relatively common "major" criteria for prenatal diagnosis of cloacal exstrophy of nonvisualization of the bladder, a large midline infraumbilical anterior wall defect, omphalocele, and lumbosacral anomalies and less frequently observed "minor" criteria including lower extremity defects, renal anomalies, ascites, widened pubic arches, hydrocephalus, and one umbilical artery. Additional ultrasound findings suggestive of cloacal exstrophy in the fetus include an elephant trunk–like image of the protruding bowel (Hamada et al, 1999) and/or hemivertebrae (Wax et al, 2008).

The differential diagnosis in the setting of a fetus with an abdominal wall mass includes omphalocele, gastroschisis, bladder exstrophy, and cloacal exstrophy. The latter two diagnoses would be entertained when nonvisualization of the urinary bladder is also noted. A study of 41 cases involving fetal abdominal wall mass from the database of the Centre of Fetal Care at Queen Charlotte's and Chelsea Hospital in London from 2000 to 2005 revealed that 25 cases were omphalocele (61%), 9 were gastroschisis (22%), 6 were body stalk anomaly (15%), and 1 case was cloacal exstrophy (2%). Seventeen cases (41%) were associated with other major malformations (Arnaoutoglou et al, 2008).

Cloacal Malformation

Abnormal early development in the fetus may result in lack of separation of the urinary, reproductive, and intestinal tracts resulting in persistent cloaca (also known as cloaca or cloacal malformation) in the female. Direct communication of these three tracts deep to the skin surface results in single perineal opening. **Persistent cloaca should be considered in any female fetus presenting as hydronephrosis and a large cystic mass arising from the pelvis as assessed by ultrasonography and/or MRI** (Cilento et al, 1994; Suzumori et al, 2009). Chaubal and colleagues (2003) have found calcified meconium to be an important sign in the prenatal sonographic diagnosis of cloacal malformation. Other authors have found that the prenatal ultrasound and MRI findings of fetal ascites, multicystic pelvic mass, bilateral hydronephrosis, and oligohydramnios are highly suggestive of the cloacal malformations associated with meconium peritonitis (Shono et al, 2007).

Similar to the fetus shown in Figure 114–15, Liu and colleagues reported MRI findings of hydrocolpos with septate vagina and massive urinary ascites due to cloacal malformation (Liu and Chen, 2009), and prenatal diagnosis of cloaca associated with esophageal atresia and tracheoesophageal fistula has also been reported (Mori et al, 2007). When present in the fetus with cloaca, urinary ascites develops from retrograde flow of urine from bladder into vagina(s), passing through cervix, uterus, and finally fallopian tube(s). The clinician should be suspicious of associated esophageal atresia and tracheoesophageal fistula with the finding of polyhydramnios in the fetus with suspected cloaca.

As with fetal diagnosis of other complex malformations, prenatal diagnosis of cloaca allows for parental counseling and planning of the delivery at a tertiary center that is well equipped with a neonatal intensive care unit and pediatric surgical and urologic expertise (Warne et al, 2002; Suzumori et al, 2009).

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) due to deficiency of 21-hydroxylase is a disorder of the adrenal cortex characterized by cortisol deficiency, with or without aldosterone deficiency, and androgen excess. The severe classic form occurs in one in 15,000 births worldwide, and the mild nonclassic form is a common cause of hyperandrogenism. **Neonatal screening for CAH and gene-specific prenatal diagnosis are now possible** (Merke and Bornstein, 2005). Clinical management of patients with CAH involves treating hormonal deficiencies, addressing issues related to genital ambiguity, avoiding morbidities, and communicating with the family about risk of CAH in other members. Screening for CAH can reduce adrenal crises, avoid incorrect sex assignments, lower mortality (especially in males), and avoid inappropriate somatic growth and precocious puberty (Speiser, 2007).

The most common form of CAH is 21-hydroxylase deficiency (21-OHD). In its severe form, 21-OHD causes prenatal virilization of external female genitalia. Through molecular genetic analysis of fetal DNA, defects in 21-OH synthesis can be diagnosed in utero. **Genital ambiguity in females can be reduced or eliminated with prenatal dexamethasone treatment, which successfully suppresses fetal androgen production.** Current data from large human studies show that prenatal diagnosis and treatment are safe in the short term for both the fetus and the mother. Preliminary data from long-term studies support these results (Nimkarn and New, 2007). Nimkarn and New (2009) also reported safety over the long term, but recommend that all subjects exposed to dexamethasone treatment during fetal life have all aspects of their development followed closely.

Megalourethra/Prune-Belly Syndrome Association

Congenital megalourethra is a rare genital anomaly characterized by dilatation of the penile urethra with or without evidence of proximal or distal urethral obstruction (Fig. 114–16). Reports of the prenatal diagnosis of this condition in the literature are limited. However, there are reports of spontaneous resolution (Nijagal et al, 2004) and also reports of associated bilateral echogenic kidneys and pregnancy termination and universal poor perinatal outcome secondary to pulmonary hypoplasia in those fetuses carried through pregnancy (Sepulveda et al, 2005). Some authors have reported cases with prune-belly syndrome–like features (Fisk et al, 1990; Wu et al, 1995). The clinician must also consider an anterior urethral valve in the differential diagnosis when a dilated penile urethra is identified in a male fetus.

Myelomeningocele

Prenatal screening with α-fetoprotein and ultrasonography have allowed the prenatal diagnosis of neural tube

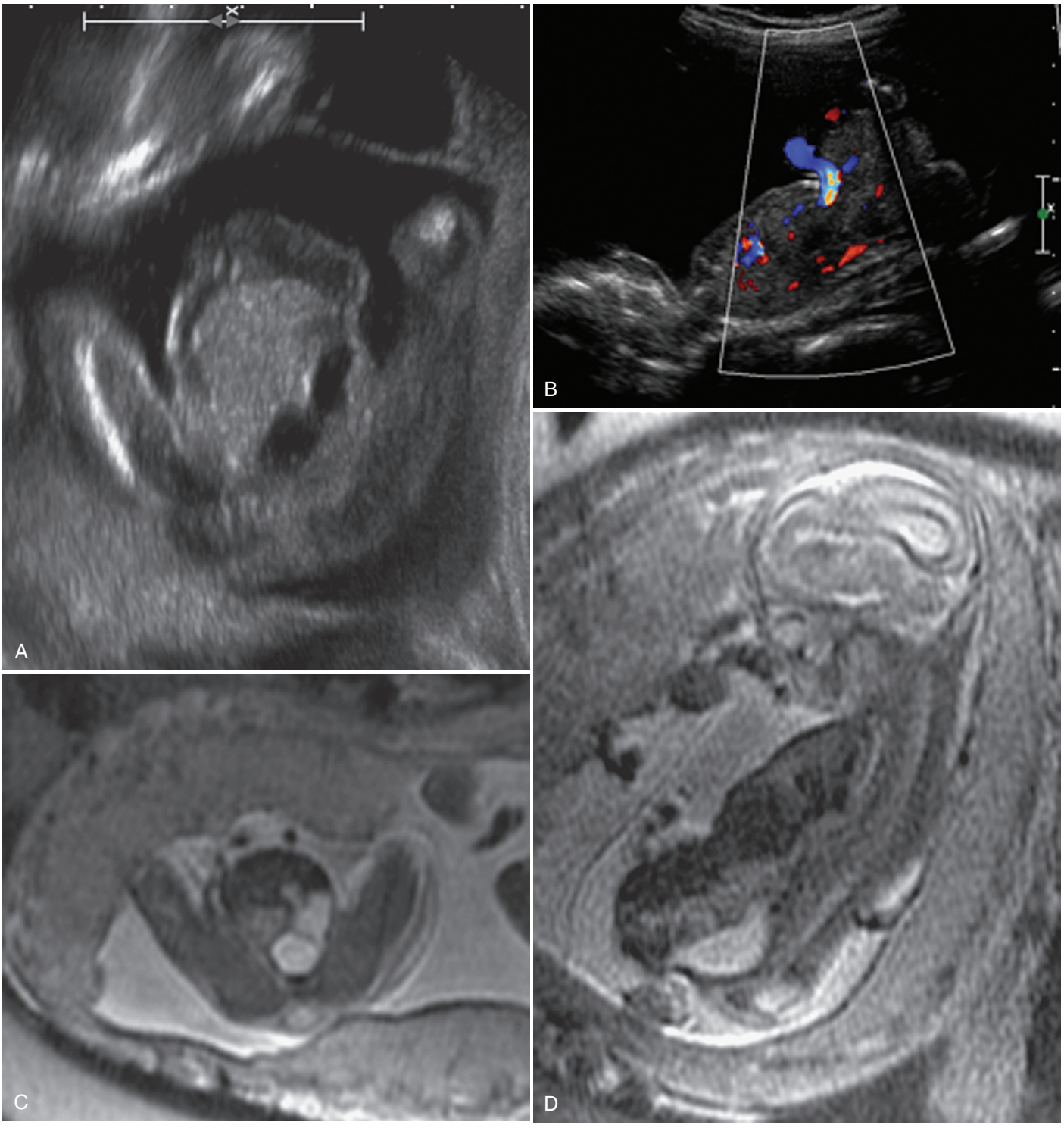


Figure 114–14. Appearance of cloacal exstrophy on imaging of a 19-week gestational age male fetus. **A,** Transverse ultrasound image through lower abdomen showing abdominal wall mass and consistent nonvisualization of the urinary bladder. **B,** Sagittal ultrasound view showing umbilical blood flow and lower abdominal wall mass immediately caudal to the umbilicus. **C,** Transverse MR image showing omphalocele with liver and dilated distal left ureter. **D,** Sagittal MR image with omphalocele, ureter, and terminal myelocystocele evident.

defects in current obstetric care, and the finding of open spina bifida in a fetus has been considered an indication for potential in-utero surgical treatment. D'Addario and colleagues (2008) evaluated the diagnostic accuracy of ultrasonographic signs that may be looked for in fetuses with spina bifida. They confirmed the usefulness of evaluation of the posterior fossa in the diagnosis of spina bifida, particularly in cases of small spinal defects that may be missed at ultrasound evaluation, noting that in 49 fetuses reviewed a small cerebellum was found in 96%, an effaced cisterna magna in 93%, and a small posterior fossa in 96%. Ventriculomegaly was present in 40 of 49 (81%) cases. With the finding of these associated features the spinal defect was identified in all but

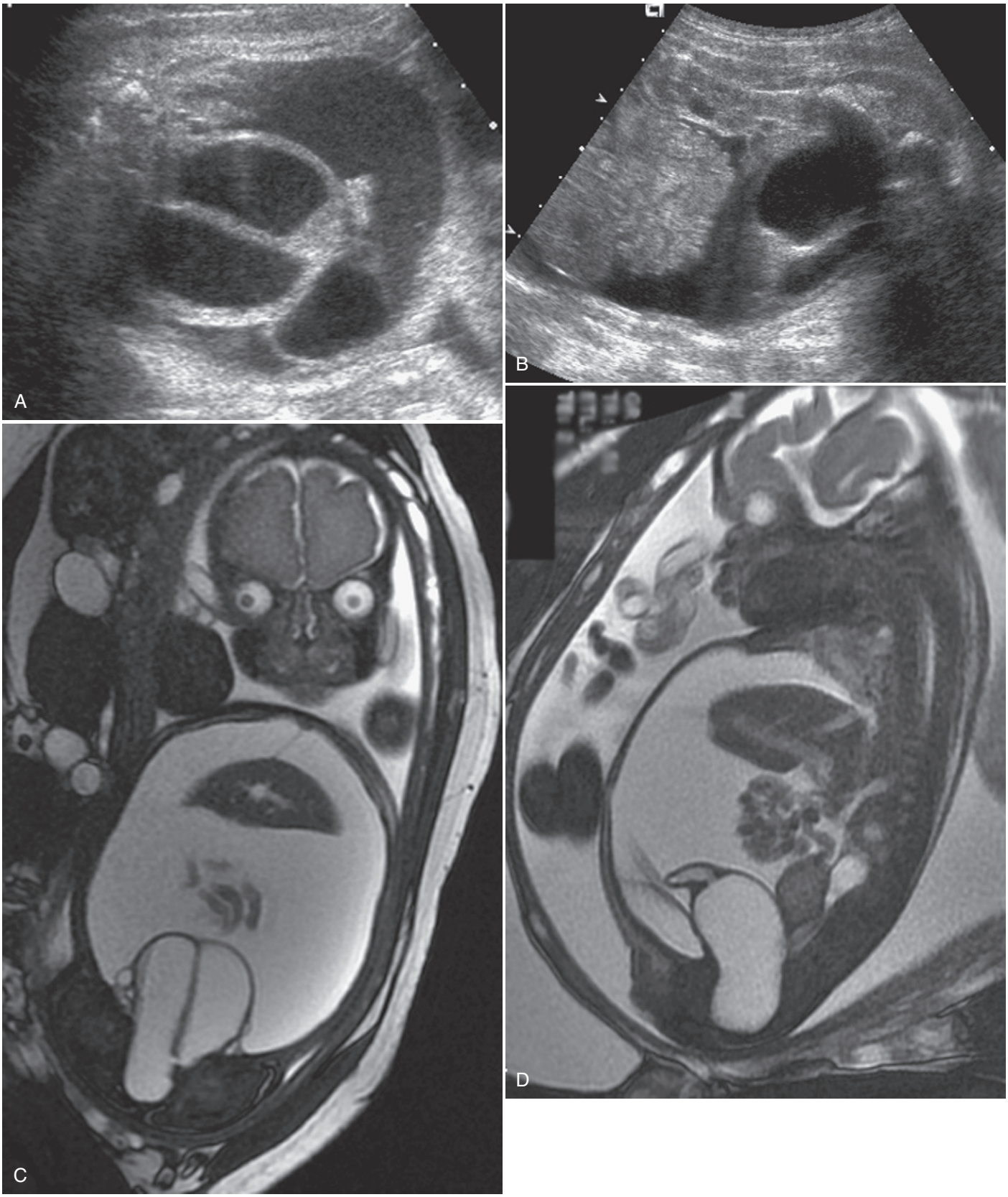


Figure 114–15. Imaging of a 30-week gestational age female fetus with cloaca. **A,** Transverse ultrasound view of abdomen showing dilated duplicate vagina, urinary bladder, and urinary ascites consistent with cloaca. **B,** Sagittal ultrasound image showing bladder, markedly distended vagina, kidney with mild hydronephrosis, and urinary ascites outlining bowel and liver. **C,** Coronal MR image showing duplicate vagina and urinary ascites. **D,** Sagittal MR image of bladder, distended vagina, cervix, uterus, and intra-abdominal organs outlined by urinary ascites.

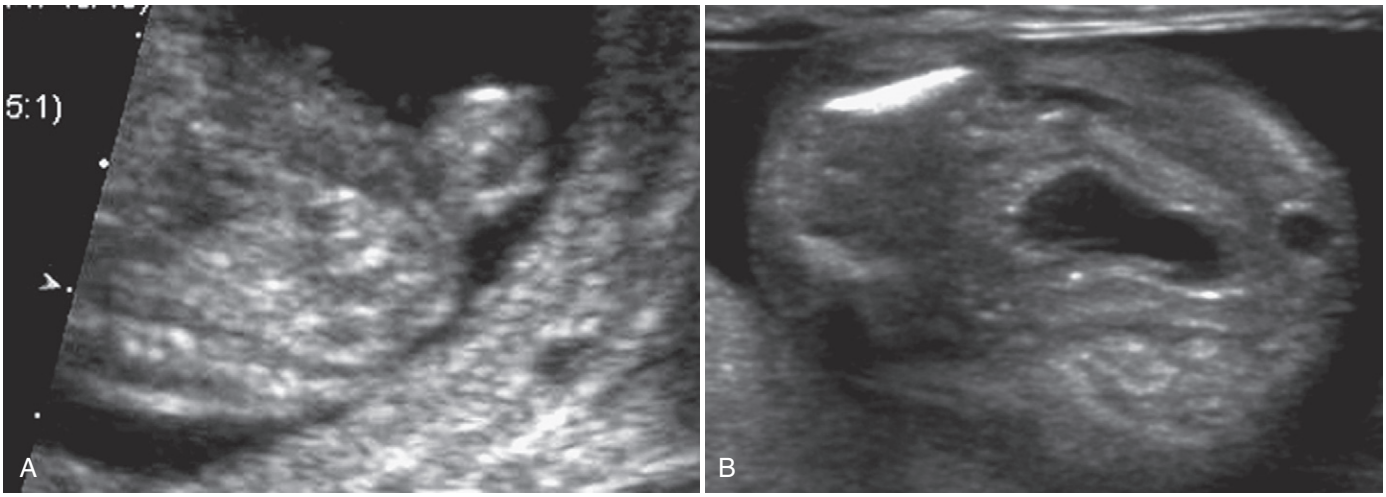


Figure 114–16. Ultrasound image of megalourethra in a 15-week gestational age male fetus. **A,** Sagittal view of dilated penile urethra. **B,** Transverse view showing thick-walled bladder and dilated posterior urethra in perineum.

one fetus. Miller and colleagues (2006) studied the impact of prenatal MRI on diagnosis and neurosurgical treatment. Between 1999 and 2003 they reviewed 320 fetal MRI studies that were performed at a single institution. Twenty-four fetuses were found to have central nervous system abnormalities. The diagnoses included spinal anomalies (e.g., scoliosis, myelomeningocele, and closed spinal dysraphism) and brain anomalies (e.g., ventriculomegaly with or without hemorrhage, intracranial cyst, craniosynostosis, and encephalocele). Fourteen of the 24 fetuses underwent surgery based on findings of prenatal MRI, and in 7 cases the pregnancy was terminated.

Fetal intervention for myelomeningocele (MMC) may improve hydrocephalus and hindbrain herniation associated with the Arnold-Chiari type II malformation and may reduce the need for ventriculoperitoneal shunting. As of now there is little evidence that prenatal repair of MMC improves neurologic function. MMC is the first nonlethal disease under consideration and study for fetal surgery. As a result, potential improvements in outcome must be balanced with maternal safety and well-being, in addition to that of the unborn patient (Hirose and Farmer, 2009).

Renal Mass

Although congenital mesoblastic nephroma (CMN) is a rare benign congenital renal tumor it is the most common solid renal tumor in the neonatal period. Prenatal diagnosis of CMN previously has been made on the basis of the findings of ultrasonography in the third trimester, and MRI-based diagnosis has also been reported. Chen and colleagues (2003) reported a case of prenatally diagnosed classic-type CMN diagnosed at 22 weeks of gestation based on the findings of ultrasonography and MRI. A vascular "ring" sign—an anechoic ring surrounding the tumor—has been described for CMN (Kelner et al, 2003).

Rhabdoid tumor of the kidney is relatively rare but a highly lethal malignancy of infancy. Prenatal detection of a renal rhabdoid tumor with mesoblastic components has been diagnosed in a 27-week fetus (Fuchs et al, 2004). The tumor presented as a large mass in the left renal area, and there was concomitant massive polyhydramnios. Ultrasound features alone did not distinguish the tumor from a benign lesion, but aggressive growth of the tumor indicated malignancy. Amniotic fluid cytology was performed but failed to confirm the diagnosis.

Leclair and colleagues (2005) reviewed outcome in 28 patients from 20 institutions with prenatally diagnosed renal tumors. The diagnosis was congenital mesoblastic nephroma in 26 patients and Wilms tumor in 2 patients. One or more complications were identified in 20 of the 28 cases (71%) during the perinatal period. Polyhydramnios was observed in 11 fetuses (39%), 2 presented with hydrops fetalis, and 7 presented in acute fetal distress requiring emergency cesarean section, of which 1 died in utero before delivery. Median gestational age of the 27 neonates born alive was 35 weeks (range 29 to 39), including 13 (46%) who were born before term. Complications at birth included hemodynamic instability in 3 neonates, respiratory distress syndrome in 8 (30%), and hypertension in 6 (22%). Surgical complications occurred in 7 patients (26%), including tumor rupture in 1 and intraoperative bleeding with postoperative death in 1. At median follow-up of 42 months, 26 of the 27 children were in complete remission. Leclair and colleagues concluded that prenatally diagnosed renal tumors have an excellent oncologic outcome but a high risk of perinatal complications. Prenatal diagnosis should allow planning the delivery at a pediatric tertiary care center to avoid a potentially life-threatening condition in early neonatal life.

Renal Vein Thrombosis

Renal vein thrombosis (RVT) is a rare event. The incidence varies from 0.5 per thousand of admissions in neonatal intensive care units to 0.5% in autopsy findings. Clinical presentation in infants includes a flank mass, hematuria, and thrombocytopenia. Antenatal ultrasound findings include an enlarged kidney, loss of corticomedullary differentiation, and branching hyperechoic vessels (Fig. 114–17). Often, an inferior vena cava thrombus can be seen with decreased or no flow in the affected renal vein (Fig. 114–18). Diallo and colleagues (1998) reported a case of RVT that was diagnosed at 34 weeks of gestation by ultrasonography in a fetus showing signs of fetal distress. The typical pattern of renal enlargement, loss of the corticomedullary differentiation, echogenic streaks, lack of definition of renal sinus echoes, and loss of venous flow in the effected kidney by Doppler imaging was observed.

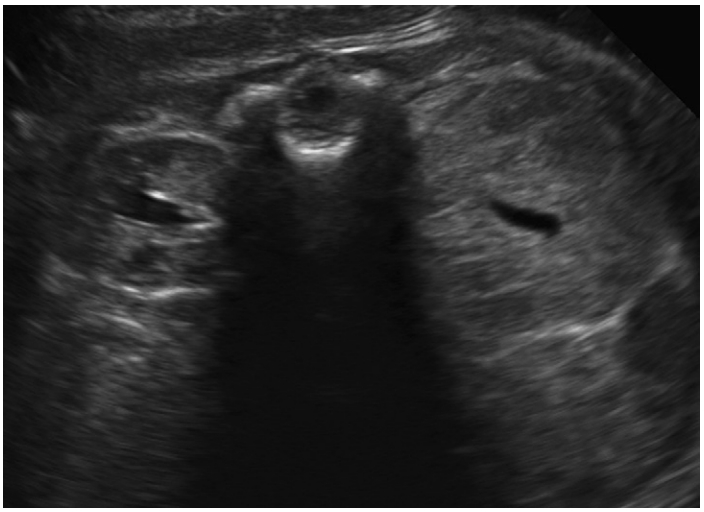


Figure 114–17. Antenatal ultrasound image at 38 weeks' gestation demonstrates an enlarged left hyperechoic kidney with loss of corticomedullary differentiation.



Figure 114–18. Antenatal ultrasound image at 36 weeks' gestation shows a left renal vein thrombosis extending into the inferior vena cava. Note the mural calcification of the inferior vena cava.

After cesarean section, full recovery at 1 week and a normal evolution at 1 month of life was reported.

Adrenal Mass

The differential diagnosis of prenatally diagnosed adrenal masses includes neuroblastoma, adrenal hemorrhage, adrenal and cortical renal cysts, adrenal adenoma and carcinoma, subdiaphragmatic pulmonary sequestration, Beckwith-Wiedemann syndrome, duplication of the renal system, Wilms tumors, congenital mesoblastic nephroma, and mesenteric and enteric duplication cysts. According to Sherer and colleagues the worldwide annual incidence of childhood adrenal cortical neoplasms ranges between 0.3 and 0.38 per 1 million children younger than 15 years. These neoplasms are even more unusual among infants, suggesting spontaneous resolution in some lesions, with only 23 cases reported in the literature (Sherer et al, 2008).

Curtis and colleagues (1997) developed an algorithm that facilitates the correct diagnosis of the suprarenal masses subdiaphragmatic extralobar pulmonary sequestration and neuroblastoma, making the correct diagnosis prenatally in 95% of patients. Based on literature review, the authors identified distinguishing features of the two lesions and created an algorithm on the basis of these distinctions. Typical findings on prenatal ultrasonography for subdiaphragmatic extralobar pulmonary sequestration include an echogenic mass that is left sided and can often be identified during the second trimester. Neuroblastoma is most often cystic, right sided, and identified in the third trimester.

Fang and colleagues (1999) reported adrenal hemorrhage confirmed in a neonate after first detection by ultrasonography at 21 weeks' gestational age. The echogenic right suprarenal mass became larger and hypoechoic on follow-up postnatal ultrasonography. With difficulty differentiating the lesion from cystic neuroblastoma, the authors performed a surgical exploration when the patient was 2 months old, and adrenal hemorrhage was confirmed, thus suggesting that adrenal hemorrhage can occur as early as the second trimester. Characteristic imaging features on ultrasonography, color Doppler imaging, and MRI help differentiate adrenal hemorrhage from neuroblastoma (Gocmen et al, 2005).

Adrenal Hemorrhage

Adrenal hemorrhage is a relatively common condition and is estimated to occur in 1% to 2% of healthy infants. More small adrenal hemorrhages are being detected with routine perinatal ultrasonography with unclear long-term significance. **Predisposing factors include prolonged labor, birth trauma, and large birth weight. RVT may be associated** (Suga et al, 2000). An association with the Beckwith-Weidemann syndrome has been reported in several cases (Anoop and Anjay, 2004; Merrot et al, 2004; Gocmen et al, 2005). Clinically, the neonate with adrenal hemorrhage may have anemia, shock, and an abdominal mass. Gross hematuria is unusual. Ultrasonography is the most efficient diagnostic measure and usually reveals an echogenic suprarenal mass (Rubenstein et al, 1995; Schwarzler et al, 1999; Lee and Lin, 2000; Velaphi and Perlman, 2001). This may appear similar to a neuroblastoma, and further evaluation, particularly with MRI, may be necessary. Scrotal hemorrhage may also be a presenting sign of adrenal hemorrhage (Avolio et al, 2002; Duman et al, 2004). The imaging characteristics of an adrenal hemorrhage evolve with time, often providing a definitive diagnosis as the mass involutes. Calcifications may later develop, reportedly as soon as 1 week (Smith and Middleton, 1979). **The late appearance of an adrenal hemorrhage is that of peripheral eggshell calcifications in contrast to stippled calcifications of neuroblastoma.** Management is almost always supportive and expectant, with a rare need for intervention.

Renal Artery Thrombosis

Hypertension and hematuria in a neonate should suggest the possibility of renal artery thrombosis (Roth et al, 2003). The clinical setting is usually suggestive in that umbilical artery catheterization is the most common cause of this condition. Renal insufficiency may be a clinical feature of this condition, as well as proteinuria and congestive heart failure (Andreoli, 2004; Cachat et al, 2004). Thrombotic involvement of the aorta may be present as well. Ultrasound examination usually reveals the diagnosis and the

extent of the thrombus. Management is dependent on the clinical setting, and unilateral involvement is best managed expectantly, although thrombolytic therapy may be appropriate (Ellis et al, 1997; Kavaler and Hensle, 1997). Control of hypertension is the most important aspect of management and occasionally requires removal of a nonfunctional kidney.

Key Points: Specific Diagnoses

- Antenatal ultrasound findings suggestive of UPJ obstruction include dilation of the renal pelvis and collecting system with no evidence of ureteral dilation.
- The findings of MCDK include multiple noncommunicating cysts, minimal or absent renal parenchyma, and the absence of a central large cyst.
- Antenatal detection of ARPKD often presents as bilaterally enlarged echogenic kidneys without obvious renal cystic disease. Concomitant hepatobiliary dilatation or oligohydramnios further suggests the disease.
- Duplication anomalies are often recognized on the basis of upper pole hydroureteronephrosis in association with either an obstructing ureterocele or an ectopic ureter.
- Very large ureteroceles can be mistaken for the bladder.
- VUR cannot be definitively diagnosed on antenatal ultrasonography, although intermittent or varying degrees of hydronephrosis or a hydroureter is suggestive of the diagnosis.
- Antenatal findings of posterior urethral valves include bilateral hydroureteronephrosis, a thick-walled bladder with dilated posterior urethra, renal dysplasia, and/or perinephric urinomas and urinary ascites.
- Fetal characteristics of bladder exstrophy include nonvisualization of the fetal bladder, lower abdominal wall mass immediately inferior to a low-lying umbilicus, and diminutive genitalia.
- Antenatal findings of exstrophy in combination with omphalocele and with kidney and lumbosacral spine abnormalities suggest cloacal exstrophy.
- A female fetus presenting with hydronephrosis and a large cystic mass arising from the pelvis suggests a persistent cloaca.

ANTENATAL MANAGEMENT OF FETAL UROPATHIES

Up to 3% of all pregnancies have fetal urinary tract anomalies. The vast majority of anomalies are associated with hydronephrosis. Severe obstruction that might warrant antenatal intervention is less than 5% of all detected anomalies.

The primary role for the perinatal urologist is to provide education and counseling for prospective parents in an objective manner. Often the patient is referred to the urologist after much information has been provided to the family. **The counseling urologist should provide (1) reassurance and dispel misconceptions, (2) a reasonable differential diagnoses, (3) information of the natural history of the disease, (4) antenatal recommendations, and (5) a postnatal management plan,** which will be discussed further. The need for continued antenatal evaluation is debatable and unclear, particularly in the cases of mid and late trimester mild and moderate hydronephrosis. In the setting of severe unilateral or bilateral hydronephrosis more regular follow-up is reasonable. **If there is a suspicion of bladder outlet obstruction, regular follow-up is needed.** In addition to normal fetal growth parameters, amniotic fluid volume, renal appearance (echogenicity, degree of hydronephrosis, cystic changes), and extrarenal fluid collections should be monitored closely.

Rationale for Fetal Intervention

Overall, the need to consider in-utero intervention for obstruction is uncommon. However, in the specific cases in which it should be considered, the rationale for antenatal treatment of hydronephrosis is to maximize normal development of renal and pulmonary function. These two aspects of fetal development are closely linked because urine comprises greater than 90% of amniotic fluid volume by the 16th week of gestation and oligohydramnios during the second trimester is usually associated with a lethal postnatal outcome secondary to pulmonary hypoplasia.

Before prenatal surgical intervention for obstructive uropathy it is critical to assess the risk-benefit ratio. The time of onset of oligohydramnios has been shown to be an important determinant of outcome (Mahony et al, 1985; Mandell et al, 1992). In fetuses in which adequate amniotic fluid was documented at up to 30 weeks' gestation in association with a urologic abnormality, pulmonary outcomes were satisfactory and postnatal clinical problems were related to renal disease. Therefore **in the setting of late-onset oligohydramnios there appears to be limited utility of urinary tract decompression or early delivery for pulmonary reasons.** It is also unclear whether early delivery, to permit earlier postnatal urinary decompression, is beneficial. If early delivery is considered, maternal corticosteroid administration for pulmonary development should be considered. Neonatology colleagues should also be involved in any early delivery decision process.

The most widely accepted indicator of salvageable renal function is analysis of fetal urine. When the urinary sodium value is less than 100 mg/dL, urine chloride value is less than 110 mmol/L, and urine osmolarity is less than 200 mOsm/dL, renal function appears to be salvageable with in-utero intervention (Table 114–4) (Glick et al, 1985). The accuracy of these predictors has been challenged (Wilkins et al, 1987; Elder et al, 1990) and, more recently, **serial aspirations of fetal urine have been reported to yield more valuable results** (Johnson et al, 1995). Guez and coworkers (1996) reported 10 fetuses who underwent multiple urine samplings and in whom severe obstruction reduced sodium and calcium reabsorption. They concluded that fetal urinary chemistries were reasonably predictive of severe but not moderate postnatal renal impairment. Other investigators have suggested the use of fetal urinary β_2-microglobulin as an indicator of tubular damage. Including this parameter, poor renal outcome has been predicted with a specificity of 83% and sensitivity of 80% (Tassis et al, 1996).

Clinical Experience

The ability to diagnose severe prenatal hydronephrosis and advances in fetal intervention has helped develop prenatal surgery for obstructive uropathy. In 1982, Harrison and colleagues (1982b) described the initial report of fetal surgery in a 21-week-old fetus with bilateral hydroureteronephrosis secondary to posterior urethral valves. After the 1986 report of the International Fetal

Table 114–4.

Indications and Conditions for In-Utero Urinary Decompression

INDICES	COMMENT
Evidence of bladder outlet obstruction	Dilated bladder, hydroureteronephrosis
Normal karyotype	By amniocentesis
No systemic anomalies	For example, central nervous system, cardiovascular
Male fetus	
Singleton	
Oligohydramnios	Early onset: <25 weeks
Noncystic kidneys	Degree of echogenicity is subjective; cysts are poor prognostic sign
Favorable urinary indices	Na < 100 mg/dL, Cl < 110 mg/dL, Osm < 210 mOsm/dL; or serial samplings trending toward normal; β_2-microglobulin in < 10 to 20
Informed consent	Risks of partial treatment must be included

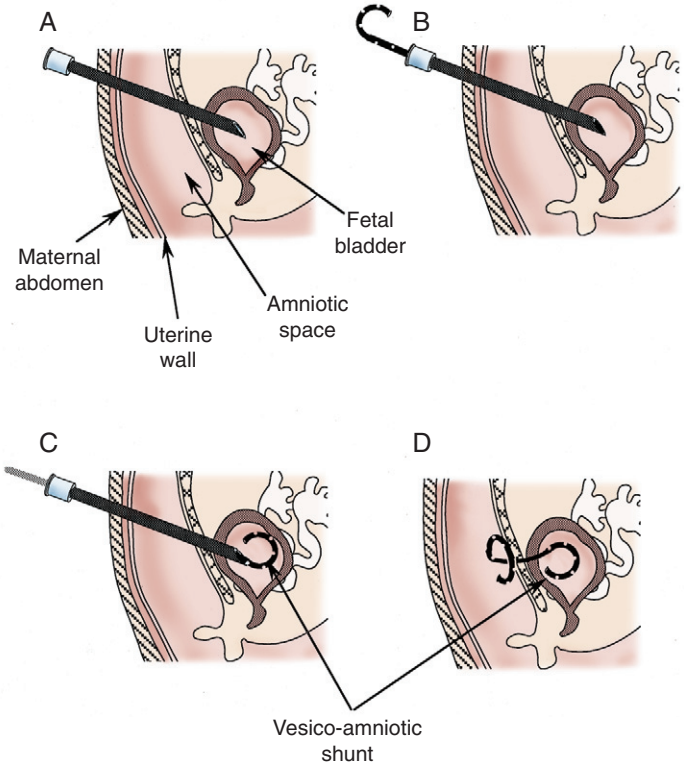


Figure 114–19. Diagram showing technique of fetal vesicoamniotic shunt placement. The fetal bladder is initially reached by needle, and a large-bore introducing sheath is passed into the bladder **(A).** Within this sheath, the shunt is passed **(B** and **C).** It is a double pigtail shunt with holes at each end allowing free drainage between the bladder and amniotic space **(D).** (From Peters CA. Surgical management of fetal uropathies. In: Marshall FF, editor. Textbook of operative urology. Philadelphia: WB Saunders; 1996. p. 1063.)

Surgery Registry in which outcomes did not seem to justify risk, a de facto moratorium on in-utero urinary tract shunting evolved (Manning et al, 1986).

More recently, with improved technology and renewed interest in fetal shunting, most cases have been referred to a small number of highly specialized centers actively engaged in prenatal surgery. **The initial method of decompression with open surgery has largely been replaced by in-utero shunt placement.** The technique of shunt placement emerged from the University of California, San Francisco (UCSF) group (Harrison et al, 1982a). **The shunt is placed under ultrasound guidance using a Seldinger technique through a trochar** (Fig. 114–19). Current practice uses the Rodeck shunt, which lies flat against the abdomen to minimize shunt dislodgment. This method has been complicated by technical problems of shunt dislodgment and, in the case of the double-J shunt, bowel herniation (Robichaux et al, 1991). Amnioinfusion may be needed to improve visualization for shunt placement; however, this may lead to excessive fetal movement. Occasionally the fetus needs to be paralyzed for accurate placement. Very large bladders may cause the shunt to be placed too high in the abdomen, resulting in dislodgment from the bladder after it decompresses.

Because of these complications some investigators have explored the use of fetoscopic methods for direct intervention to provide prolonged bladder drainage; others have attempted direct endoscopic valve ablation (Estes et al, 1992; Luks et al, 1994; Kohl et al, 1997; Luks et al, 1997; Quintero et al, 2000). **Experience with fetoscopic/endoscopic valve ablation is currently at the case report and experimental level, and long-term outcomes are unknown.** There are no studies to determine if this method of decompression is adequate in the presence of significant bladder dysfunction.

The indications and contraindications for intervention in prenatal obstructive uropathy are outlined in Table 114–4. Currently, **serial bladder sampling over 3 days has been used to help determine if the fetus is a viable candidate.** The serial nature of the procedure allows one to see the subsequent trend of urine osmolality and electrolyte composition as a reflection of fetal kidney response (Johnson et al, 1995). The principal reason for considering vesicoamniotic shunting is to prevent early neonatal pulmonary insufficiency and death. The risks that one accepts with intervention include induction of premature labor, perforation of fetal bowel and bladder, fetal loss, and fetal and/or maternal hemorrhage and infection.

More recently, the ability to influence renal outcome in male patients with posterior urethral valves but without oligohydramnios has been suggested as a possible indication for in-utero intervention. In this setting the principal goal of intervention is not to prevent pulmonary hypoplasia and deaths but to prevent or delay end-stage renal failure. Although some reports have shown promise in the ability to distinguish those fetuses with likely early renal failure from those with later-onset failure, the specificity and accuracy of methods using a combination of ultrasound and urinary chemistries (sodium, β_2-microglobin, and calcium) has not been well defined (Muller et al, 1993; Clautice-Engle et al, 1995; Dommergues et al, 2000). **In summary, precise identification of those situations in which intervention may benefit the fetus with obstructive uropathy remains unclear.**

Clinical Outcomes

To date, the reported long-term outcomes of antenatal intervention for severe obstructive uropathy (e.g., posterior urethral valves, prune-belly syndrome, urethral atresia) are mixed (Crombleholme et al, 1990; Johnson et al, 1994; Coplen et al, 1996; Freedman et al, 1999; Holmes et al,

2001; McLorie et al, 2001; Clark et al, 2003; Biard et al, 2005; Salam, 2006). Significant variability in patient selection and assessment of outcome within these studies has limited the ability to determine if prenatal intervention has altered the postnatal course. A large systematic review of the prenatal intervention for obstructive uropathy showed a statistically significant perinatal survival advantage with shunting (Clark et al, 2003). Of the studies that have reported long-term outcomes of in-utero vesicoamniotic shunting, many of the children have renal insufficiency (57%) and growth impairment (86%) (Freedman et al, 1999; Holmes et al, 2001; Biard et al, 2005). Biard and associates (2005) reported on long-term follow-up (5.8 years) of patients who have survived in-utero shunting. They noted acceptable renal function in 44%, mild impairment in 22%, and renal failure in 33%. Patients with prune-belly syndrome had the best renal outcome (57%), followed by those with posterior urethral valves (43%), and then urethral atresia (25%).

Overall, it appears that in-utero intervention for the appropriate patient may reduce the risk of neonatal mortality and may potentially improve renal function. Currently, a European-based multicenter randomized clinical trial (PLUTO: Percutaneous Shunting for Lower Urinary Tract Obstruction) is being conducted to help answer these questions. The trial is attempting to enroll 150 singleton pregnancies with ultrasound evidence of lower urinary tract obstruction to evaluate the safety and effectiveness of in-utero shunting compared with conservative management. In addition to this trial, **more sensitive and specific markers to better identify which fetus will benefit from in-utero shunting need to be defined.**

Key Points: Antenatal Management of Fetal Uropathies

- Up to 3% of all pregnancies have a urinary tract anomaly.
- The primary role for the perinatal urologist is to provide education and counseling for prospective parents in an objective manner.
- The need to consider in-utero intervention for obstruction is uncommon.

POSTNATAL MANAGEMENT OF ANTENATALLY DETECTED UROLOGIC RENAL ABNORMALITIES

A child with a prenatal diagnosis of a urologic renal abnormality such as ANH should be carefully evaluated and followed by a pediatric urologist from birth. The vast majorities of these children appear entirely healthy and in the absence of prenatal ultrasound findings would not have any indications for regular urologic follow-up. **Parental anxiety is common and should be addressed directly with prenatal counseling and education.**

Unilateral Hydronephrosis

The presence of prenatally detected unilateral dilation of the kidney warrants postnatal evaluation in a timely but nonurgent fashion (3 to 8 weeks of life) with an ultrasound evaluation (Clautice-Engle et al, 1995). The most common diagnoses associated with this finding are UPJ obstruction, VUR, and UVJ obstruction/megaureter. Early ultrasound evaluation is unlikely to miss a significant abnormality. A normal postnatal ultrasound examination indicates that obstructive uropathy is not present; however, it does not determine whether the child has VUR (Tibballs and De Bruyn, 1996). **It is important to keep in mind that a postnatal ultrasound evaluation performed within the first 48 hours of life may not yet demonstrate hydronephrosis or may underestimate the degree of hydronephrosis secondary to physiologic oliguria in the newborn.**

The decision to perform voiding cystourethrography (VCUG) or initiate prophylactic antibiotics in the neonatal period is unclear. Although some groups advocate postnatal VCUG in any child with a history of antenatal hydronephrosis, others have questioned the value of this approach (Yerkes et al, 1999). Infants with severe ANH should be placed on a prophylactic antibiotic (amoxicillin, 10 to 25 mg/kg/day) and undergo VCUG. Severe ANH may be associated with an increased risk of febrile urinary tract infection (Song et al, 2007). As for mild ANH, a recent prospective study of 192 infants with ANH noted that the majority of patients with mild ANH had no significant events during infancy (Coelho et al, 2007). Conversely, it is suggested that female infants with a history of ANH and postnatal uropathy had a higher risk of febrile urinary tract infection (Coelho et al, 2008). In a much larger study of 1514 patients with a history of ANH and persistent postnatal Society of Fetal Urology grade II hydronephrosis, of the patients who were screened (76%, 1150), VUR was identified in 28% and urinary tract infection in 1.6% (Estrada et al, 2009b). Of those not screened, the number who developed a febrile urinary tract infection and VUR was significantly higher than expected (febrile urinary tract infection: 4.4%, odds ratio 8.9) as compared with the screened group. These two studies suggest that infants with a history of ANH and persistent postnatal hydronephrosis may warrant further investigation by VCUG in the early postnatal period. However, to date, no appropriate prospective studies with coordinated and comprehensive postnatal follow-up have examined this question in a rigorous fashion to provide consensus guidelines (Lee et al, 2006; van Eerde et al, 2007).

At the authors' institution, children with moderate or severe ANH are placed on a prophylactic antibiotic at birth. These children undergo renal bladder ultrasonography and VCUG postnatally. Diuretic renography is reserved for those with persistent moderate or severe postnatal hydronephrosis not related to VUR. Infants with persistent mild hydronephrosis on serial ultrasound evaluation or no postnatal hydronephrosis are observed and followed clinically. Infants with any degree of antenatal or postnatal ureteral dilation undergo ultrasonography, VCUG, and possibly diuretic renography (with ^{99m}Tc-mercaptoacetyltriglycine) if clinically indicated.

Perhaps the most challenging aspect of managing ANH is determining if and when postnatal surgical correction for obstruction is appropriate (Ransley et al, 1990). Some have suggested that regardless of the degree of ANH, moderate or severe postnatal hydronephrosis with evidence of decreased renal function should be an indication for surgical intervention (Chertin et al, 2006). Despite the improved anatomic detail afforded by real-time ultrasonography and the increasing experience with functional nuclear medicine studies, no radiographic or clinical gold standard for physiologically significant obstruction exists. Over time, hydronephrosis has been seen to improve whereas other kidneys appear to lose function. The natural history of ANH is not clearly defined.

The debate over the appropriate management of infants with unilateral ANH continues and may ultimately be determined by a combination of epidemiologic, radiographic, and new innovative biomarker discoveries. More accurate and reproducible prenatal and postnatal radiographic documentation of the degree of hydronephrosis and function combined with appropriate natural history data are needed to better categorize these infants. Finally, new serum or urine biomarkers indicative of ongoing renal damage will be critical in helping to further define which infants are truly at risk.

Bilateral Hydronephrosis

Infants with bilateral hydroureteronephrosis may have posterior urethral valves, bilateral VUR, bilateral UPJ or UVJ obstruction, or a combination of these findings. **For the child with bilateral hydroureteronephrosis suggestive of bladder outlet obstruction, an ultrasound evaluation and VCUG should be performed promptly.** In boys, posterior urethral valves is the most important diagnosis to be ruled out. In girls, an obstructing ectopic ureterocele would be the most likely cause for bladder outlet obstruction. In the event that an obstructive lesion is discovered, it should be corrected promptly. For children with suspected lower urinary tract obstruction (e.g., posterior urethral valves), prompt bladder decompression and antibiotic prophylaxis (amoxicillin 10 to 25 mg/kg/day) should be initiated before radiographic intervention.

Renal Agenesis, Renal Ectopia, and Unilateral Multicystic Dysplastic Kidney

Infants born with solitary kidneys (renal agenesis), renal ectopia, or unilateral multicystic dysplasia should be evaluated postnatally by ultrasonography and VCUG. Functional studies such as with dimercaptosuccinic acid (DMSA) are occasionally needed to confirm the diagnosis. The need for further screening with VCUG is controversial. It has been reported that of infants with a solitary kidney, 30% have VUR, 11% UPJ obstruction, and 7% UVJ obstruction (Atiyeh et al, 1993; Cascio et al, 1999). Similarly, those with renal ectopia (simple or crossed fused ectopia) may also be at risk for VUR in the ectopic or contralateral kidney (30%) (Gleason et al, 1994; Guarino et al, 2004; Arena et al, 2007). However, there are others that report a very low incidence of associated urologic anomalies and do not recommend screening (Calisti et al, 2008).

An MCDK is primarily unilateral, isolated, and associated with a good prognosis. **If at birth the ultrasound findings are not absolutely diagnostic of a classic MCDK, a DMSA study can be used to confirm the diagnosis with the absence of uptake.** Patients with MCDK are often thought to be similar to those born with a solitary kidney. Additionally, patients with MCDK have an increased frequency of VUR and UPJ obstruction in the contralateral normal kidney (Kaneko et al, 1995; Miller et al, 2004).

Key Points: Postnatal Management of Antenatally Detected Urologic Renal Abnormalities

- Infants with antenatal unilateral hydronephrosis should undergo an ultrasound evaluation in 3 to 8 weeks after birth.
- Postnatal ultrasonography performed with 48 hours of life may underestimate the degree of hydronephrosis.
- An infant with bilateral hydroureteronephrosis consistent with bladder outlet obstruction should undergo ultrasound evaluation and VCUG promptly.

SUMMARY

With the increased use of maternal-fetal ultrasound, more genitourinary abnormalities are being detected prenatally. Although advances in imaging have increased the detection and characterization of these abnormalities, further work is needed to identify which abnormalities are clinically significant. Research directives should focus on identifying which infants require postnatal diagnostic imaging and intervention. Developments in the fields of imaging, proteomics, and genomics may provide the necessary information to not only detect the abnormality but also prognosticate which ones require further testing and medical intervention.

Acknowledgment

The authors acknowledge the assistance of Drs. Beryl R. Benacerraf, Bryann Bromley, Carol E. Barnewolt, Susan A. Connolly, and Judy A. Estroff for providing many of the fetal ultrasound images.

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chapter 115

Evaluation of the Pediatric Urology Patient

Douglas A. Canning, MD ● Sarah M. Lambert, MD

Chief Complaint and History of Present Illness
Past Medical and Surgical History
Medications and Allergies in the Pediatric Patient
Pediatric Urologic Examination
Pediatric Laboratory Evaluation
Pediatric Radiographic Evaluation
Pediatric Urodynamic and Biofeedback Evaluation
Office Surgical Procedures
Summary

Pediatric urology encompasses a spectrum of disorders from complex congenital anomalies, such as bladder or cloacal exstrophy, to more routine but nevertheless important problems such as daytime wetting in a school-aged child. This chapter focuses on the history and physical examination of the pediatric urology patient. We have placed particular emphasis upon clinical entities, examination techniques, and adjunct investigations that are unique to the pediatric population. The evaluation and treatment of pediatric urologic patients are often complex. The reader may find further details about specific conditions in other chapters within this text. The following information is an introduction to the nuances of the pediatric urologic evaluation.

CHIEF COMPLAINT AND HISTORY OF PRESENT ILLNESS

In most cases, the initial contact with the child and family will be through a referring phone call from the parent, pediatrician, family practitioner, or, if prenatal evaluation is desired, the obstetrician. In many cases, the child's family is calling from a distance and the urologist will need to decide with the referring clinician whether the child is healthy enough to be transferred or must first have his or her condition stabilized. Usually, even in remote areas, skilled general pediatric support is available. With coaching from the accepting team, most clinicians will be able to manage even complex problems in the stabilization phase of the triage process. A thorough understanding of the chief complaint, history of the present illness, and past medical history is essential to appropriate management of all pediatric urologic patients.

An important first question when beginning the history in the pediatric patient with a urologic problem is **"why is the child here?" In some cases, the child can begin to answer these questions, and it is worthwhile early in the interview to ask the child a few questions directly. This shows respect for the child, who may be an excellent historian despite young age.** As soon as the child realizes that the interview is directed to him or her, rather than to the parent, he or she will concentrate on the examination. If future therapy requires behavioral training that involves cooperation from the child, he or she may be more receptive. Additionally, it is often helpful to interview adolescents separately from their parents when asking sensitive questions.

Abdominal Complaints

Children with acute abdominal pain should be seen immediately. An accurate history of the character of the pain may be the best indicator of the source of the pain. Details about the character of the pain, timing, acuteness of onset, radiation, and migration are important and should, if possible, be elicited directly from the child. Associated loss of appetite, nausea, vomiting, or a change in bowel pattern may help to distinguish gastrointestinal from genitourinary sources. Causes of abdominal pain in children vary widely and are often unique to the pediatric population. As urologists, we suspect pyelonephritis, renal colic, or cystitis, but the differential diagnosis includes many nonurologic etiologies. Intra-abdominal causes in children include pyloric stenosis, midgut volvulus, appendicitis, and intussusception. Non-abdominal sources, such as sickle cell crisis, streptococcal pharyngitis, or pneumonia, should also be considered. In addition to a thorough abdominal examination designed to rule out surgical abdominal disease, these children should be evaluated for urinary tract infection (UTI), constipation, and spermatic cord torsion. Usually an acute abdominal series is ordered, which will show considerable amounts of stool throughout the colon if constipation is the problem. Occasionally, some children with spermatic cord torsion complain of abdominal pain and have surprisingly few complaints referring to the scrotum. **Most abdominal masses originate in genitourinary organs and should be evaluated immediately** (Chandler et al, 2004) (Table 115–1). The most common malignant abdominal tumor in infants is neuroblastoma, followed by Wilms tumor (Golden and Feusner, 2002). Children with neuroblastoma typically relate a history of more constitutional symptoms than children with Wilms tumor. If an abdominal mass is suspected, an abdominal ultrasound evaluation

Table 115–1

Distribution of Abdominal Masses of 280 Patients in the Neonatal Period*

TYPE	NO.
Kidney (65%)	
Hydronephrosis (UPJ obstruction, UVJ obstruction, ureterocele, etc.)	80 (28%)
Multicystic kidney	63 (22%)
Polycystic kidney disease	18
Renal vein thrombosis	5
Solid tumor	13
Ectopy	4
TOTAL	183
Retroperitoneum (9%)	
Neuroblastoma	17
Teratoma	3
Hemangioma	1
Abscess	4
TOTAL	25
Bladder (1%)	
Posterior urethral valves	2
Female Genital System (10%)	
Hydrocolpos	16
Ovarian cyst	13
TOTAL	31
Gastrointestinal (12%)	
Duplication	17
Giant cystic meconium ileus	4
Mesenteric cyst	3
Ileal atresia	2
Volvulus (ileum)	2
Teratoma (stomach)	1
Leiomyosarcoma (colon)	1
Meconium peritonitis with ascites	1
Ascites	1
TOTAL	32
Hepatic or Biliary (3%)	
Hemangioma (liver)	3
Solitary cyst (liver)	2
Hepatoma	1
Distended gallbladder	1
Choledochal cyst	1
Adenomatoid malformation of the lung	1
TOTAL	9

*Distended bladder, hepatomegaly, and splenomegaly were excluded in most series.

UPJ, ureteropelvic junction; UVJ, ureterovesical junction.

Data from Griscom, 1965; Emanuel and White, 1968; Raffensperger and Abousleiman, 1968; Wedge et al, 1971; Wilson, 1982.

should be ordered. If the mass is solid, computed tomography (CT) is almost always required.

Scrotal Symptoms

A child with acute scrotal pain must be presumed to have spermatic cord torsion regardless of age until proven otherwise. However, in some cases, an accurate history may save the child an unnecessary surgical exploration. It is particularly important to interview the child as well as the parent. The differential diagnosis of the acute scrotum includes testicular torsion, torsion of the appendix testis or epididymis, epididymitis/orchitis, hernia/hydrocele, trauma, sexual abuse, tumor, idiopathic scrotal edema, dermatitis, cellulitis, and vasculitis, such as Henoch-Schönlein purpura (Gatti and Murphy, 2007). Gradual onset of the pain is more consistent with epididymitis, whereas abrupt pain suggests spermatic cord torsion or torsion of one of the testicular appendices. Associated scrotal wall swelling, erythema, or superior displacement of the testis with an absent cremasteric reflex is suggestive of spermatic cord torsion. Yet, the absence of edema or erythema or the presence of a cremasteric reflex does not rule out the possibility of acute testicular torsion, especially if the onset of pain was recent. The classic presentation of testicular torsion is the sudden onset of severe, unilateral pain that is often associated with nausea and emesis. A history of similar intermittent episodes may suggest intermittent testicular torsion. Traditionally, significant ischemic damage is believed to occur after 4 to 8 hours. Therefore testicular torsion represents a true surgical emergency. Patients presenting after 8 hours should still be explored, because the viability of the testis is difficult to predict (Beard et al, 1977; Bartsch et al, 1980).

If there is history of inguinal or scrotal pain, infants and children with an inguinal hernia or a hydrocele that changes in volume should be seen within 24 hours or sooner. Not all of these children will need emergency surgery, but a few will require surgical intervention within a short period. If there is a history of scrotal or inguinal pain, the child's parents should be taught to recognize the signs of an incarcerated inguinal hernia and instructed to go to the emergency department if symptoms occur before the planned surgical correction. **Infants with asymptomatic hydrocele rarely require surgery initially.** In most cases, the hydrocele will resolve in the first year of life. The authors make an exception if the hydrocele is particularly large or palpable in the inguinal region. A large hydrocele with a palpable inguinal component or one that is enlarging may indicate the presence of an abdominoscrotal hydrocele. These do not spontaneously resolve and usually enlarge. These should be corrected, usually at 6 to 12 months through an initial scrotal incision that will decompress the hydrocele (Luks et al, 1993; Belman, 2001).

Boys with undescended testes are one of the most common referrals to the pediatric urologist. Undescended testes are present in 30% of preterm neonates and are present in 3% of full-term male infants at birth (Ghirri et al, 2002; Boisen et al, 2004). Undescended testes do not represent a surgical emergency. **We operate on patients with undescended or absent testes at about 6 months of age. Very few of these testes will descend after 3 months of age** (Berkowitz et al, 1993). Some infants with impalpable testes may require laparoscopic evaluation, and this examination may be done at 6 months as well. In prepubertal boys, concerns of an undescended testis often reflect a retractile testis that results from a brisk cremasteric reflex and does not require surgical intervention. A retractile testis must be differentiated from an ascending testis, which may require an orchidopexy.

Varicoceles are uncommon in prepubertal boys and increase in incidence to around 15% by 15 years of age (Schiff et al, 2005). We normally try to document the size of the testis with an ultrasound examination. From the three-dimensional measurements on ultrasonography, the relative testicular volumes may be calculated and used to guide further treatment (Diamond et al, 2000). Varicoceles are 90% left-sided and 10% right-sided (MacLellan and Diamond, 2006). A right-sided varicocele in the absence of a left-sided varicocele should prompt an evaluation for a retroperitoneal process.

Testicular masses should be evaluated immediately. Prepubertal testicular and paratesticular tumors should

be considered in the differential diagnosis of a scrotal mass. Although much less common than epididymal cysts or spermatoceles, a complaint of a painless testicular or paratesticular mass should be addressed urgently. A physical examination and scrotal ultrasonography should determine if the mass is concerning for neoplasia. In a contemporary series from a tertiary center, the most common prepubertal testis tumor was a teratoma, followed by rhabdomyosarcoma, epidermoid cyst, yolk sac tumor, and germ cell tumor, respectively (Metcalfe et al, 2003). This histologic distribution was corroborated by a multicenter review, including four tertiary pediatric hospitals, demonstrating that 74% of tumors were benign, with 48% being teratomas (Pohl et al, 2004). Testicular tumors occur in the newborn and in early childhood as well as after adolescence. It is important to recognize that the peak incidence of testicular tumors in young children and infants occurs at age 2. In this population, yolk sac tumors are most common, and approximately 75% of tumors are malignant (Levy et al, 1994; Ciftci, 2001). Tumors of nontesticular origin, such as leukemia and lymphoma, must also be considered in the pediatric population.

Male Penile or Urethral Symptoms

Boys with painful priapism must be evaluated immediately. Pain may suggest ischemia of the corporeal bodies, which may progress to corporeal fibrosis if untreated. **Children with sickle cell anemia are especially at risk for priapism,** with 75% of patients experiencing their first episode by the age of 20 years (Mantadakis et al, 1999; Adeyoju et al, 2002). Outpatient treatment with penile aspiration and epinephrine irrigation has successfully been used in the treatment of this condition (Mantadakis et al, 2000).

Paraphimosis also requires immediate attention and manual reduction. In children, this procedure may require some level of sedation. Conversely, phimosis is physiologic in young infants and attempts to manually retract the foreskin in boys less than 2 years of age should be avoided. Phimosis in older children is typically treated with one or two courses of low-dose steroid cream and circumcision if necessary (Ashfield et al, 2003).

Boys with hypospadias are seen routinely. Normally, we initiate the evaluation as a newborn because most parents of with a child with a birth defect, even a relatively minor one such as hypospadias, desire an early opportunity to speak with a specialist.

We evaluate children who have developed a complication after circumcision at the convenience of the family as long as there is no active bleeding, the child is voiding normally, and there is no injury to the penile shaft or shaft skin. Narrowing of the preputial ring after circumcision may result in a trapped penis (Casale et al, 1999; Gillett et al, 2005). These infants can usually be managed with application of petroleum jelly to the penis for 4 to 6 weeks as healing continues. As long as voiding remains normal during this period, the revision of the circumcision may be postponed until age 4 to 6 months when an outpatient surgical procedure can be performed. A more common complication, urethral meatal stenosis, may be present as early as 6 months of age in circumcised infants (Upadhyay et al, 1998; Ahmed et al, 1999). This problem may be easily corrected in the office (Smith and Smith, 2000).

Female Genital Symptoms

Infant girls with introital masses commonly present to the pediatric urologist's outpatient office. Vaginal masses may be palpable or may protrude from the introitus. The differential diagnosis of these masses includes benign periurethral cysts, skin tags, urethral prolapse, imperforate hymen, prolapsed ureterocele, or, rarely, malignancies such as a rhabdomyosarcoma. **Bladder outlet obstruction may result from a prolapsed ureterocele.** The majority of these lesions are differentiated by physical examination, but historical information, such as pain, bleeding, or voiding difficulties, help solidify the diagnosis.

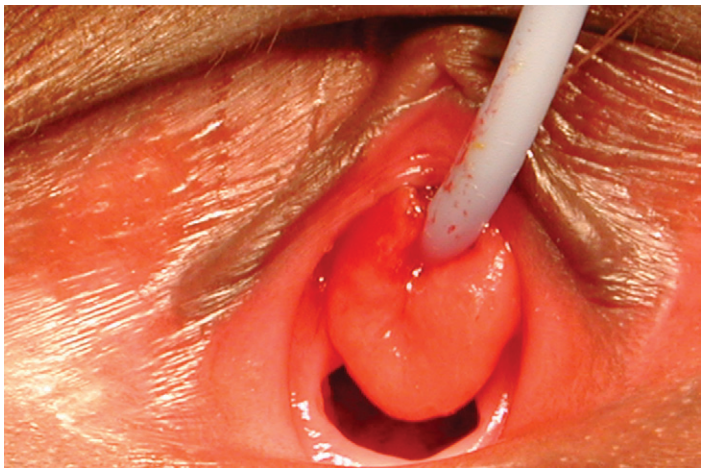


Figure 115–1. Urethral prolapse. (Courtesy of Pasquale Casale, MD.)

Urethral prolapse is relatively common, particularly in young African-American girls. Figure 115–1 demonstrates urethral prolapse in a young girl. A urethral catheter demonstrates the circumferential prolapsed urethral tissue. The prolapse is through the meatus, forming a hemorrhagic, often sensitive mass that bleeds with palpation or when in contact with the undergarments. Girls may have difficulty with urination depending on the size of the prolapse and whether it compromises the urethral meatus. Urethral prolapse may respond to topical application of estrogen and may be managed expectantly as long as voiding is normal (Redman, 1982).

Benign and malignant tumors of the vagina should be considered when vaginal bleeding occurs in young girls. A broad spectrum of entities ranging from capillary hemangioma, rhabdomyosarcoma, or carcinoma may be associated with vaginal bleeding. Labial masses may be associated with hernia or hydrocele of the canal of Nuck (Kizer et al, 1995). **Adhesions of the labia minora are common.** In most cases, they are not symptomatic. Occasionally, a girl with labial adhesions will complain of vaginal irritation from pooled urine. In this case, if the labial adhesions are not separated, the irritation may progress to irregular voiding that may exacerbate the problem of frequency and urgency. In some girls, a short course of estrogen cream applied to the labia may be effective. In many, however, separation of the adhesions in the office with local anesthetic cream may be required. Labial fusion may be associated with congenital adrenal hyperplasia (CAH), gonadal dysgenesis, or cloaca (Powell et al, 1995). A genitosinogram may be indicated in cases where the urethra cannot be distinguished from the vaginal orifice and a urogenital sinus is suspected.

The authors evaluate adolescent girls who have not menstruated and in whom there is concern about a ureteral or vaginal anomaly within 3 days. Patients with complete androgen insensitivity (CAIS) can also present with primary amenorrhea. Many of these girls have an imperforate hymen or uterine anomaly that results in poor uterine drainage that may be uncomfortable. If left

untreated, retrograde drainage of the uterus may place these patients at risk of endometriosis and infertility (Rock et al, 1982). Pelvic ultrasonography or magnetic resonance imaging (MRI) can further delineate the anatomy and guide intervention if necessary.

Voiding Symptoms

Like most teams, we see a large number of children of both sexes with voiding complaints and incontinence. Incontinence is classified as diurnal (daytime), nocturnal (nighttime) or both. If a child has never been dry, the incontinence is primary. If the child is wet after a dry interval greater than 6 months, the incontinence is secondary. **The ability to place children in categories based on the voiding history will help to focus the rest of the evaluation and guide further therapy.** The time and duration of the voiding disorder must be identified early in the interview. A thorough history obtained from both the parents and the child is important to determine the actual pattern of voiding, which may differ from parental perceptions. Did symptoms begin before or after potty training? Is wetting associated with pain, urgency, or frequency? What is the character of the voiding? Is the urinary stream steady from beginning to end or is it a "staccato" or stop and start pattern suggestive of dysfunctional voiding? Are the symptoms worse at a particular time of the day? Does the child void frequently during the day yet sleep through the night without wetting? Is wetting confined to the night, suggestive of primary nocturnal enuresis? Additionally, behavioral signs can be used to further understand the etiology of functional incontinence. Episodes of urgency in children are often suggested by holding maneuvers, such as squatting, crossing legs, and sitting on heels (Ellsworth et al, 2008). Poor potty habits may result in incomplete voiding or vaginal voiding. Giggle incontinence is encountered in young girls and describes large-volume incontinence that occurs only with laughter. In this situation, the incontinence is associated with a complete emptying of the bladder and should be distinguished from stress urinary incontinence in adults because the treatment differs significantly (Berry et al, 2009).

The voiding history is incomplete without a record of the child's eating and drinking pattern. Does the child consume small amounts of water during the day and large amounts of alternative liquids, such as soft drinks and juices, which tend to be laden with salt and sugar and low in free water? What is the stooling pattern? Does the child have firm, chunky, or pebble-like bowel movements suggestive of a retentive pattern of stooling, or does the child have soft, well-formed bowel movements more suggestive of a normal stooling pattern? Very few children hold the urine and not the stool. Conversely, children who retain stool nearly always retain urine. All of these are indicators of a dysfunctional voiding pattern, which may lead to UTI. Referencing a standardized stool chart, such as the Bristol stool form scale (http://en.wikipedia.org/wiki/Bristol_Stool_Scale; Lewis and Heaton, 1997) may be helpful to further clarify the stooling pattern (Koh et al, 2010).

Children with day or nighttime wetting are evaluated routinely in the absence of other complicating problems. The care of children with nocturnal enuresis is individualized. Although some recommend treatment in children after age 5, the authors often wait to treat until the child seems bothered by the problem. If the child does not perceive nighttime wetting as a problem, there is usually little advantage to treatment with medications or alarms. In our experience, only a few children younger than age 6 or 7 are bothered emotionally by nocturnal enuresis. Wetting during the day causes more concern and may indicate incomplete or infrequent voiding. Incomplete or infrequent voiding may lead to UTI, which may exacerbate wetting.

Although the majority of voiding symptoms are secondary to voiding habits, it is important to remember that more serious pathophysiology may present with similar complaints. After a careful history, any concerns regarding a structural etiology for voiding dysfunction should be investigated. Continuous leakage in between normal voiding patterns in a girl should raise concerns of an ectopic ureter. Symptoms suggestive of detrusor-sphincter dyssynergia may represent occult spinal dysraphism. Urinary retention and stranguria may be caused by posterior urethral valves in a boy or a bladder mass, such as a polyp, ureterocele, or rhabdomyosarcoma, in either sex. Uroflow, postvoid residual urine, and ultrasound studies are usually appropriate first steps in the evaluation of voiding dysfunction and investigation of potential structural anomalies. Additional testing may include a voiding cystourethrogram (VCUG), retrograde urethrogram, spinal MRI or ultrasound (USG), and an urodynamic evaluation.

Sexual Abuse

Although genital injuries may be accidental, the possibility of physical or sexual abuse must be considered in all cases of genital trauma in females or males. **Sexual abuse is surprisingly common and includes any activity with a child before the age of legal consent that is for sexual gratification of an adult or a significantly older child.** Sexual intercourse includes vaginal, oral, or rectal penetration, which is defined as entry into an orifice with or without tissue damage. Sex acts perpetrated by young children are learned behaviors and are associated with experiencing sexual abuse or exposure to adult sex or pornography. In 2007, there were more than 740,000 reported cases of child maltreatment. Included in this number were 56,460 victims of sexual abuse in the United States. Of these children, 18% were less than 4 years of age, 23% were 4 to 7 years of age, 24% were 8 to 11 years of age, and 35% were 12 to 15 years of age. The perpetrators of the sexual abuse are most commonly a friend or neighbor, followed by a relative or daycare worker (U.S. Department of Health and Human Services, 2009). In a recent review, the peak incidence of sexually transmitted diseases was seen in the 10- to 14-year age group (Pandhi et al, 2003). In one study of women presenting to an urban sexual assault clinic, 43% were adolescents (Jones et al, 2003). Pelvic inflammatory disease rates are highest in females age 15 to 25 with 33% of those infections in females younger than age 19 (Jenkins, 2000). Any pediatric patient with a sexually transmitted infection should be evaluated for sexual abuse. Although the mode of transmission of human papillomavirus (HPV) and herpes simplex virus (HSV) is often unclear, *Neisseria gonorrhoeae* or *Chlamydia trachomatis* infections in a prepubertal child should be reported to child protective services (Bechtel, 2010).

The possibility of sexual abuse should be considered a result of associated physical symptoms, including (1) vaginal, penile, or rectal pain, discharge, or bleeding or (2) chronic dysuria, enuresis, constipation, or encopresis. In one study, 74% of pediatric patients with documented sexually transmitted diseases had histories or signs of abuse (Pandhi et al, 2003). Sexual abuse should be considered when the vaginal mucosa is bruised or injected, the vaginal opening is dilated, or the hymen is damaged, showing a V-shaped notch or cleft (Walker, 1998). Despite these guidelines, the diagnosis of sexual abuse is

often made by the history and not by the physical examination. In a review of 506 girls with a history of penetrative abuse referred to a sexual abuse clinic, only 11% had examination findings suggestive of sexual abuse (Anderst et al, 2009). Investigating the possibility of sexual abuse requires supportive, sensitive, and detailed history taking. Many hospitals have a sexual abuse team that can be consulted if sexual abuse is suspected. The key is to be aware of the possibilities when they might exist and to invite the team in early. The pediatric urologist will likely be asked to evaluate the abdomen and perineum (Johnson, 2000). If abuse is suspected, it must be reported to the police. Furthermore, if the perpetrator is a caregiver of the child, or a parent, the state child welfare team must be contacted.

Urinary Tract Infection

Febrile UTIs in the newborn are treated emergently, because newborns are particularly susceptible to significant renal damage if the infection is not treated promptly. A urine culture should be obtained, and these infants require intravenous antibiotics as early as possible after a urine culture has been obtained, because they have a higher prevalence of concomitant bacteremia (10% to 22%) (Pitteti and Choi, 2002). Appropriate antibiotic therapy administered without delay has been shown to reduce the incidence of scarring (Ransley and Risdon, 1981; Hiraoka et al, 2003). Some authors suggest this decreased incidence of scarring reflects a decreased likelihood of renal involvement rather than a true prevention of scar formation (Doganis et al, 2007).

Febrile UTIs in children older than newborns should be treated acutely. Children of all ages with a severe urinary tract infection may be subject to renal scarring (Ransley and Risdon, 1981; van der Voort et al, 1997) and should be seen within 24 hours or sooner. **Children older than newborns with nonfebrile UTI should be seen semiurgently.** In practice, many of these patients are seen by their pediatrician and are seen in follow-up by the pediatric urologist. Nearly all children with culture-proven UTI should be evaluated with ultrasonography and VCUG, although some groups are re-evaluating the role of renal nuclear scans in these children.

The evaluation for UTI is completed at the parent's convenience after the initial infection has been treated. In most cases, radiologic studies after UTI in a child include VCUG to detect vesicoureteral reflux. However, a substantial number of cortical defects on dimercaptosuccinic acid scintigraphy (DMSA) scan occur in the absence of identifiable reflux (62% to 82%) (Majd and Rushton, 1992; Benador et al, 1997; Ditchfield and Nadel, 1998; Biggi et al, 2001; Ditchfield et al, 2002). This has led to a re-evaluation of the role of VCUG as the initial investigation in a child with a UTI. It is important to recognize that infants less than 6 months of age and uncircumcised male infants are at increased risk for recurrent UTI (Wiswell and Roscelli, 1986).

Hematuria

A practical approach to the evaluation of hematuria in children is presented in Chapter 112. The authors' recommendation for patients with microscopic hematuria with unrelated clinical symptoms is to treat the affiliated illness (e.g., pulmonary or immunologic conditions, glomerular and interstitial disease, lower urinary tract disease, stones, tumors, vascular disease, or acute abdominal conditions) and ignore hematuria until the treatment for the underlying illness is underway. Transient microhematuria is also common in healthy children (Vehaskari et al, 1979). **The large majority of children with microscopic hematuria are evaluated, and the source of the hematuria is never identified** (Diven and Travis, 2000). Notably, the most commonly identified etiology of asymptomatic microhematuria and gross hematuria in children is hypercalciuria (Parekh et al, 2002; Bergstein et al, 2005). Microscopic hematuria in the absence of other symptoms is not an emergency in children.

Gross hematuria in children is less common than microscopic hematuria, with an estimated prevalence of 1.3 per 1000 (Ingelfinger et al, 1977). The most common diagnoses are UTI (26%), perineal irritation (11%), trauma (7%), meatal stenosis with ulceration (7%), coagulation abnormalities (3%), and urinary tract stones (2%). The most common glomerular causes of gross hematuria in children are poststreptococcal glomerulonephritis and IgA nephropathy. An antecedent sore throat, pyoderma, edema, or red blood cell casts suggest glomerulonephritis. IgA nephropathy can cause recurrent gross hematuria with flank or abdominal pain and may be preceded by an upper respiratory tract infection (Meyers, 2004). Adenoviral infection, hypercalciuria, and hyperuricosuria are other sources to consider. In peripubertal boys, benign urethrorrhagia can present with terminal gross hematuria. The authors perform ultrasonography of the kidneys, ureters, and bladder in children with gross hematuria, although the yield is low (Fernbach, 1992). In contrast with the adult patient, cystoscopic examination in children rarely reveals a cause for hematuria but should be performed when bladder pathology is a consideration.

Gross hematuria in the newborn is an emergency because it may indicate renal venous thrombosis or renal arterial thrombosis. Both may be life-threatening. Renal venous thrombosis affects boys twice as often as girls, with a left-sided predominance. These infants require resuscitation and, occasionally, anticoagulant or operative therapy (Kuhle et al, 2004). **Gross hematuria outside the newborn period, although not life-threatening, should be evaluated without delay.** Many children have an easy-to-recognize source such as UTI, urethral prolapse, trauma, and meatal stenosis with ulceration, coagulation abnormalities, or urinary tract stones. Less obvious sources include acute nephritis, ureteropelvic junction obstruction, cystitis cystica, epididymitis, or tumor (Diven and Travis, 2000; Meyers, 2004). As with adult patients, a thorough history including a specific description of the color of the urine, the presence of clots, and timing of hematuria, such as terminal hematuria or hematuria upon initiation of micturition, should facilitate the diagnostic process. A directed history should include medications, exercise habits, propensity for bleeding diathesis, and a travel history to rule out exposure to infectious diseases such as schistosomiasis or tuberculosis.

Renal Trauma

The pediatric trauma patient usually presents to the emergency department and is evaluated by the emergency medicine and trauma teams, often with the assistance of the urology service. Blunt force trauma is the primary mechanism for major renal trauma (Mohamed et al, 2010). The pediatric kidney is particularly susceptible to trauma due to the limited visceral adipose tissue, limited chest wall protection, relatively increased renal size, and increased mobility of the kidney (Brown, 1998). The mechanism of injury should be determined and a thorough history obtained from the patient and caregivers or observers. **Epidemiologic data demonstrate that the majority of renal injuries**

result from motor vehicle accidents, falls, or high-velocity activities, such as sledding, skiing, all-terrain vehicle accidents, and skateboarding (Margenthaler et al, 2002; Rogers, 2004). Therefore injuries of this nature should alert the clinician to potential renal damage. The history should include any congenital renal anomalies, such as an ureteropelvic junction obstruction, a solitary kidney, or renal ectopia. Finally, evaluation of associated injuries must be undertaken. Any abdominal injury in a toddler or young child without an antecedent history of blunt force trauma should be evaluated for physical abuse (Barnes et al, 2005).

Blunt force renal trauma represents a urologic emergency that requires immediate attention but does not necessarily require operative intervention. It is well accepted that low-grade blunt renal injuries are managed conservatively. More recently, the conservative treatment of high-grade blunt renal injuries have been successfully described in children. A consecutive series of 101 patients from The Children's Hospital of Philadelphia (CHOP) with blunt renal injury demonstrated that a nonoperative management strategy was advantageous and successful in 94.7% of pediatric blunt renal injuries (Nance et al, 2004). The children with high-grade injuries at risk for failure of conservative management include those with major vascular avulsion or extensive urinary extravasation, especially in the setting of ureteropelvic junction disruptions (Henderson et al, 2007). These patients deserve close urologic observation and repeated examinations. The authors recommend conservative management and recognize that a complete evaluation is necessary to accurately determine which patients require further intervention.

Ambiguous Genitalia

Infants with ambiguous genitalia also require immediate evaluation. Many will require direct transfer from a referring hospital. **Because CAH may result in salt wasting, which may be life threatening, infants with ambiguous genitalia must be evaluated quickly and stabilized** (Forest, 2004). **If CAH is suspected, the infant should not be discharged home from the nursery before appropriate testing is complete.** In some cases, a genotypic female neonate with CAH may be incorrectly identified as a male neonate. The correct diagnosis should be made as quickly as possible to establish the appropriate sex of rearing. Infants with ambiguous genitalia may also have other syndromes and may require further evaluation (Tables 115–2 and 115–3). A history of a discordant karyotype from an amniocentesis and infant phenotype should prompt an evaluation. The parents should be asked about a family history of infertility, amenorrhea, and infant mortality. The complete evaluation of infants with ambiguous genitalia should include urology, neonatology, endocrinology, genetics, and radiology.

Antenatal Hydronephrosis

In neonates with prenatally detected hydronephrosis and a normal bladder, the authors begin the postnatal evaluation of the hydronephrosis within the first few days of life. Families are usually concerned about the diagnosis and anxious to establish a management plan. The postnatal evaluation can be scheduled at the family's convenience for most infants. This classification includes infants with a history of prenatal hydronephrosis who are not suspected of having bladder outlet obstruction on the postnatal ultrasonography. Additionally, the ultrasonogram must not demonstrate bilateral hydronephrosis, a solitary kidney, or a thickened bladder wall. The infant must be thriving and have normal electrolytes and normal blood urea nitrogen (BUN) and creatinine levels.

The postnatal history should also include the sex of the infant, laterality of the hydronephrosis, the level of obstruction (i.e., ureteropelvic junction [UPJ], ureterovesical junction [UVJ], urethra), the presence or absence of oligohydramnios, and any other associated anomalies. The additional tests to be scheduled can include a repeat ultrasonogram, a renal scan, or a voiding cystourethrogram to evaluate the relative drainage and percentage of function of the kidneys, as well as to evaluate for vesicoureteral reflux. Until this postnatal evaluation is completed, most infants are maintained on amoxicillin prophylaxis. The utility of specific testing remains controversial. The differential diagnosis for antenatal hydronephrosis most commonly includes UPJ obstruction, vesicoureteral reflux, ectopic ureter, ureterocele, megaureter (UVJ obstruction), multicystic dysplastic kidney, posterior urethral valves, prune-belly syndrome, and megacystis microcolon syndrome.

Certain conditions require more immediate intervention, especially when bladder outlet obstruction is present. If posterior urethral valves are considered, the bladder should be drained with a feeding tube and a VCUG performed at an appropriate interval. Conversely, if prune-belly syndrome is considered, urethral catheterization should be avoided, if possible, to minimize the risk of urinary tract infection. Additionally, a ureterocele may obstruct the bladder outlet and result in bilateral upper tract dilatation. This situation can be ameliorated by placement of a urinary catheter.

An increasing number of **pregnant mothers carrying a fetus with hydronephrosis seek prenatal evaluation with the urologist. These visits are scheduled within the week unless the following conditions exist: (1) there is bilateral hydronephrosis or hydronephrosis in a single system kidney, (2) there is oligohydramnios, and (3) there is evidence of significant cystic renal disease in a fetus younger than 22 weeks' gestation.** In certain circumstances, termination of pregnancy may be considered. Conversely, fetal intervention may be indicated. These difficult decisions are often precipitated by oligohydramnios and the risk of severe pulmonary and renal insufficiency. The decision for discontinuation of the pregnancy is dependent on the gestational age of the fetus; thus prompt evaluation may be required.

Congenital Anomalies in the Neonate

Patients with major abdominal defects, such as bladder or cloacal exstrophy, require direct admission to the neonatal nursery for stabilization and surgical planning. In many cases, a team is assembled and provides orthopedic, general surgical, and urologic care during the surgery (Jeffs, 1978; Lattimer et al, 1979; Gearhart, 1999). Patients with imperforate anus and variants, such as a cloacal anomaly, require decompression of the intestinal tract, usually within the first 24 to 48 hours (Chen, 1999). At the time of the colostomy, the urologist may evaluate the perineum and perform endoscopy to further assess the urinary anomalies. Procedures to correct these major defects must be planned by surgeons who are familiar with the potential risks and complications associated with the reconstruction of the urethra, vagina, and colon. The anesthesia team must be skillful in the management of the complex metabolic changes that may occur in infants who are under anesthesia for long periods. The neonatologists must be expert in the management of infants who have undergone major surgical procedures.

Table 115–2

Syndromes Associated with Multisystemic Disease

SYNDROME	INHERITANCE	RENAL ANOMALIES	GENITAL ANOMALIES	ANOMALIES IN OTHER SYSTEMS
Aarskog-Scott			Shawl scrotum, cryptorchidism	Broad facies, short stature
Beckwith-Wiedemann		Wilms tumor		Macroglossia, gigantism, hepatoblastoma
Carpenter	AR		Small genitalia	Acrocephaly, polydactyly
Caudal regression		Hydronephrosis, renal agenesis	Vaginal and uterine agenesis	Imperforate anus, LS spine abnormality
Cerebro-oculofacial	AR	Renal agenesis	Cryptorchidism	Arthrogryposis, microcephaly, cataracts
CHARGE			Small genitalia	Coloboma, heart defects, ear anomalies
Cornelia de Lange			Small genitalia, cryptorchidism	Micromelia, bushy eyebrows
Curran		Renal agenesis		Acral anomalies
Donohue			Enlarged penis or clitoris	Hirsutism, elfin face, thick lips, low-set ears
Drash		Wilms tumor, glomerulonephritis	Mixed gonadal dysgenesis	
Dubowitz	AR		Hypospadias, cryptorchidism	Eczema, small stature, peculiar facies
Ehlers-Danlos	AR	Hydroureter		Skin hyperextensibility, poor wound healing
Fraser			Hypospadias, cryptorchidism	Cryptophthalmos
G			Hypospadias	Esophageal defect, low-set ears, abnormal facies
Holt-Oram		Renal anomalies		Defects of upper limb
Laurence-Moon-Biedl			Small genitalia	Obesity, retinal pigmentation, polydactyly
Marfan	AD	Renal duplication, hydroureter	Cryptorchidism	Aortic aneurysm, arachnodactyly
Mayer-Rokitansky		Renal agenesis	Duplex uterus, vaginal atresia	
Meckel-Gruber	AR	Renal cysts	Ambiguous genitalia, cryptorchidism	Microcephaly, polydactyly
Menkes		Hydronephrosis, reflux	Cryptorchidism	Kinky hair, CNS abnormality
Ochoa		Neurogenic bladder, hydronephrosis	Cryptorchidism	Aortic aneurysm, arachnodactyly
Opitz	AR		Hypospadias, cryptorchidism	Hypertelorism, mental retardation
Prader-Willi			Cryptorchidism	Hypotonia, obesity, mental retardation
Prune-belly		Hydronephrosis	Cryptorchidism	Hypoplastic abdominal muscle
Robert	AR	Hydroureter	Hypospadias, large penis, cryptorchidism	Hypomelia, growth retardation
Robinow	AD		Small genitalia, cryptorchidism	Flat face, short forearms
Rubenstein-Taybi	AR		Chordee	Hypoplastic maxilla, broad thumbs and toes
Rudiger	AR	Hydroureter	Small penis	Bicornuate uterus, coarse facies, stub nose
Russell-Silver	AR	Nonspecific renal anomalies	Small penis, hypospadias, cryptorchidism	Short stature, café-au-lait spots, skeletal asymmetry
Seckel	AR		Small genitalia, cryptorchidism	Small head, beak nose
Smith-Lemli-Opitz	AR		Hypospadias, cryptorchidism	Pernicious anemia, mental retardatic syndactyly, microcephaly
VATER		Hydronephrosis, renal dysplasia	Hypospadias	Vertebral anomalies, anal atresia, VSD, TE fistula, radial dysplasia
von Hippel-Lindau		Renal cyst, renal tumor		Pancreatic cyst, cerebral tumor, ichthyosis
Wolfram	AR	Hydroureter		Optic atrophy, deafness, diabetes
Zellweger	AR	Hydroureter	Hypospadias, cryptorchidism	Hypotonia, hepatomegaly

AD, autosomal dominant; AR, autosomal recessive; CHARGE, coloboma, heart anomaly, choanal atresia, retardation, and genetic and ear anomalies; CNS, central nervous system; LS, lumbosacral; TE, tracheoesophageal; VATER, vertebral, anal atresia, tracheoesophageal, renal; VSD, ventriculospetal defect.

Data from Barakat AY, Seikaly MG, Perkaloustian VM. Urogenital abnormalities in genetic disease. J Urol 1987;136:778–85; Walker RD. Familial and genetic urologic disorders in childhood. AUA Update Series 1987;6:1–6; Mininberg D. The genetic basis of urologic disease. AUA Update Series 1992;9:218–23.

Table 115–3

Chromosomal Syndromes Associated with Genitourinary Anomalies

CHROMOSOME NUMBER	CLINICAL FEATURES	RENAL ANOMALIES	GENITAL ANOMALIES
4 Autosome	Microcephaly	Hydronephrosis	Hypospadias
Wolf-Hirschhorn syndrome	Hemangiomas		Undescended testis
4p Trisomy	Hypertelorism		
4q	Cleft lip/palate		
	Low-set ears		
8 Autosome	Large, square head	Hydronephrosis	Hypospadias
Trisomy 8	Prominent forehead	Horseshoe kidney	Undescended testis
	Widely spaced eyes	Reflux	
	Slender body and limbs		
9 Autosome	Small cranium	Renal hypoplasia	Hypospadias
9p Trisomy, 9p tetrasomy	Strabismus	Pancake kidney	Undescended testis
9p Monosomy	Large nose		Infantile male genitalia
	Webbed neck		
10 Autosome	Microcephaly	Cystic kidney	Undescended testis
10q Syndrome	Oval, flat face	Hydronephrosis	Small penis
10p Syndrome	Microphthalmia		
	Short neck		
11 Autosome		High forehead	
		Micropenis	
11q Syndrome	Flat nose		
	Wide glabella		
	Cleft lip/palate		
13 Autosome	Microcephaly	Horseshoe kidney	Undescended testis
Patau syndrome	Hypertelorism	Hydronephrosis	
Trisomy 13	Polydactyly	Cystic kidney	
	Congenital heart disease		
15 Autosome	Obesity		Hypogonadism
Monosomy 15q	Hypotonia		Cryptorchidism
Prader-Willi syndrome	Retardation		
18 Autosome	Micrognathia	Horseshoe kidney	Undescended testis
Trisomy 18	Hypertonia	Hydronephrosis	Small penis
Edwards' syndrome	Congenital heart disease		
20 Autosome	Round face	Hydronephrosis	Hypospadias
20p Syndrome	Short nose	Polycystic kidney	
	Dental abnormalities		
	Vertebral abnormalities		
21 Autosome	Brachycephalic skull		Undescended testis
Trisomy 21	Congenital heart disease		Small penis
Down syndrome	Nasal hypoplasia		
	Broad, short hands		
22 Autosome	Microcephaly		Undescended testis
Trisomy 22	Preauricular skin tags		Small penis
	Low-set ears		
	Beaked nose		
	Cleft palate		
Cat's eye syndrome	Coloboma	Renal agenesis	
Possibly from both 13 and 22 autosomes	Anal atresia	Horseshoe kidney	
	Low-set ears	Reflux	
	Hemivertebrae		
	Congenital heart disease		
Sex chromosome Y	Elongated legs		Small penis
Klinefelter syndrome	Gynecomastia		Small testes
XXY, XXXY	Eunuchoid body build		
XXXXY	Sparse body hair		
Sex chromosome	Short stature	Horseshoe kidney	Infantile genitalia
X Turner syndrome	Primary amenorrhea		
XO	Webbed neck		
	Broad chest		
	Coarctation of aorta		

Data from Barakat AY, Seikaly MG, Derkaloustian VM. Urogenital anomalies in genetic diseases. J Urol 1986;136:778–85; Walker RD: Familial and genetic urologic disorders in childhood. AUA Update Series 1987;6:1–6; and Mininberg D. The genetic basis of urologic disease. AUA Update Series 1992;9:218–23.

Table 115–4

Developmental Milestones

AGE (mo)	GROSS MOTOR	FINE MOTOR	SOCIAL SKILLS	LANGUAGE
3	Supports weight on forearms	Opens hands spontaneously	Smiles appropriately	Coos, laughs
6	Sits momentarily	Transfers objects	Shows likes and dislikes	Babbles
9	Pulls to stand	Pincer grasp	Plays pat-a-cake, peek-a-boo	Imitates sounds
12	Walks with one hand held	Releases an object on command	Comes when called	1-2 meaningful words
18	Walks upstairs with assistance	Feeds from a spoon	Mimics actions of others	At least 6 words
24	Runs	Builds a tower of six blocks	Plays with others	2-3 word sentences

From Haslam RHA. Neurological examination. In: Behrman R, Kliegman R, Jenson H, editors. Nelson textbook of pediatrics. 16th ed. Philadelphia: Elsevier; 2000.

Today, **many newborns with spinal dysraphisms are diagnosed in utero** (Babcook et al, 1995). These infants are referred by direct admission to the neonatal intensive care nursery. Most of these children are not in urinary retention initially, but many develop spinal shock after neurosurgery in the newborn period and have a transient period of overflow urinary drainage. As soon as possible after closure of the spinal defect, a baseline renal and bladder ultrasonogram is performed to evaluate for evidence of bladder or upper tract abnormalities. Initial urodynamics investigation is performed after resolution of the spinal shock to ensure that bladder storage pressures are not excessive (McGuire et al, 1977, 1983; Bauer, 1998; Tarcan et al, 2001). High-risk infants (those with a detrusor leak-point pressure greater than 40 cm H_2O or detrusor-sphincter dyssynergia) are started on anticholinergic therapy and intermittent catheterization (Snodgrass and Adams, 2004). Even those infants with normal urodynamic findings require close follow-up due to the risk for subsequent neurourologic deterioration resulting from spinal cord tethering (Tarcan et al, 2001).

Key Points: Chief Complaint and History of Present Illness

- Pediatric diagnoses should be triaged into categories: emergent, urgent, semiurgent, and routine.
- Acute scrotal pain must be evaluated emergently due to the risk of spermatic cord torsion, regardless of age.
- Neonates with bilateral hydronephroses or hydronephrosis in a solitary kidney should be evaluated immediately after birth while in the newborn nursery.
- If congenital adrenal hyperplasia is suspected, evaluation should be completed prior to hospital discharge.
- If sexual abuse is suspected the sexual abuse team should be immediately consulted and appropriate interventions initiated.

PAST MEDICAL AND SURGICAL HISTORY

A patient's past medical and surgical history are always germane to the patient history and often provide insight into the current condition. Many pediatric congenital syndromes include urologic anomalies (see Tables 115–2 and 115–3), and the pediatric urologist should be aware of these associations. Additionally, an assessment of the child's developmental progress may impact their urologic development, especially in the context of potty training and enuresis. A brief description of developmental milestones is provided in Table 115–4.

Other pediatric conditions impact the timing of surgical intervention and affect the level of risk from anesthesia. In healthy children, a recent history of a respiratory illness or asthma increases the risk of reactive airway disease and therefore the risk of general anesthesia (Schreiner et al, 1996; Parnis et al, 2001). Preterm infants are also at increased risk of anesthetic complications and postoperative apnea. As a result, many of these infants require postoperative cardiopulmonary monitoring. Neonates with a history of apnea are at highest risk (Murphy et al, 2008). A history of recent upper or lower respiratory tract infection increases the risk of reactive airway disease and anesthetic-related complications (Stasic, 2004). Infants with significant cardiac anomalies may benefit from a pediatric anesthesiologist with cardiac experience. Although the pediatric anesthesiology team will assess the child for anesthetic risk, the pediatric urologist should be aware of these conditions as well. Finally, all bleeding dyscrasias, such as von Willebrand disease, should be evaluated by pediatric hematology prior to operative intervention.

MEDICATIONS AND ALLERGIES IN THE PEDIATRIC PATIENT

Medications are typically dosed based upon weight, such as milligrams per kilogram. Therefore an accurate weight must be obtained prior to prescribing most medications to pediatric patients. Additionally, many adult medications are contraindicated in children, and pediatric guidelines should be consulted. For example, **aspirin has been associated with Reye syndrome in children and adolescents and is not recommended for the treatment of fever in children.** Acetaminophen (10 to 15 mg/kg every 4 hr) and ibuprofen (5 to 10 mg/kg every 6 hr) are not associated with significant adverse effects. However, overdoses of acetaminophen can lead to hepatic failure. Trimethoprim-sulfamethoxazole is contraindicated in preterm infants and full-term infants less than 2 to 3 months of age due to the risk of hyperbilirubinemia and kernicterus. Sulfonamide medications can be initiated after 2 to 3 months of age (Fefer and Ellsworth, 2006).

Allergies should be recorded for all patients and be clearly documented. In the pediatric urology population, children with myelomeningoceles are at increased risk for latex allergies, and latex precautions should be instituted in these patients. Children with an increased number of operations and operative intervention in the neonatal period are associated with an increased risk of latex sensitivity in this population (Pires et al, 2002).

Key Points: Past Medical and Surgical History, Medications, and Allergies in the Pediatric Patient

- Congenital urologic anomalies are often associated with known syndromes, and the pediatric urologist should be aware of concurrent conditions.
- Pediatric pulmonary conditions directly impact the anesthesia risk and should be evaluated prior to surgical intervention.
- Aspirin is associated with Reye syndrome and should be avoided in children.
- Patients with myelomeningoceles are at greater risk for latex sensitivity and latex precautions should be used.

PEDIATRIC UROLOGIC EXAMINATION

General Examination

In most cases, the primary care provider has identified a problem that requires review by the pediatric urologist. However, because other processes may coexist, the urologist must be alert for evidence of disease in other organ systems. Although few children are severely ill when evaluated in the urologist's office, it is important to develop the skills to recognize an infant or child who requires hospitalization. The ability to determine when an infant requires an inpatient admission is particularly important, because the metabolic reserve is less abundant in the newborn (Park, 2000). **Observation of the child and a careful history from the parent may be more important than the vital signs or the physical examination when attempting to determine the severity of illness, particularly in the infant or small child.** The child's color (pale or cyanotic), level of alertness, response to the parent's comforting, quality of interaction with the examiner, and the quantity of tearing while crying may provide considerable information about mental status and level of hydration. If the child's response in any of these areas suggests severe illness, the child should be transferred to the emergency department, where appropriate resuscitation can be delivered while the diagnostic evaluation continues. In the acute emergency department setting, a full general and urologic examination must be performed by the evaluating medical team. Patients with hemodynamic instability must be emergently addressed.

In the office, the authors record vital signs on every new patient, and in children with history of renal anomalies or vesicoureteral reflux, on all subsequent visits. Because **the blood pressure and heart rate change as a function of age,** reference ranges for blood pressure and pulse rates for boys and girls should be posted in the clinic near where the vital signs are taken (Bernstein, 2000). Assistants taking the blood pressure should all be aware of the variation with age and should notify the team of blood pressure readings greater than the 90th percentile. Upon entering the room, a clinician can address both the child and parent to encourage the child to participate in the examination process. Physical examination in young children can prove challenging and the clinician must attempt to create a favorable environment. Examining a child on his or her mother's lap can be useful in comforting a frightened child. Additionally, sitting or kneeling near a young child facilitates interaction at the child's level.

Abdominal Examination

When examining the abdomen, the examiner's hand should be placed behind the flank to help palpate the kidney on either side. If the abdomen is supple, the approximate size and location of each kidney may be determined with deep palpation. An attempt should be made to feel the liver edge and spleen as well as the colon, particularly the descending colon. In the newborn, the liver may be palpable, sometimes as much as 2 cm below the ribs on the left. When examining the left lower quadrant, an estimate should be made of the volume of stool in the descending colon. In infants, a large amount of gas may be present within the gastrointestinal tract. The abdominal wall is normally weak, especially in premature infants. An abdominal examination can be performed on a crying infant during inspiration when the anterior abdominal muscles are relaxed. Separation of the rectus muscles and umbilical hernias are common in the newborn. The abdominal wall is lax and protuberant in boys with prune-belly syndrome. Occasionally, children with other types of bladder outlet obstruction or profound antenatal hydronephrosis will also have considerable laxity of the abdominal muscles. The abdomen should be inspected for other abnormalities, such as ventral hernia, flaring of the rib cage, umbilical leakage, mass, or hernia. Unusual masses should be investigated immediately with ultrasonography.

Renal pathology is the source of up to two thirds of neonatal abdominal masses (Pinto and Guignard, 1995). **Cystic abdominal masses include hydronephrosis, multicystic dysplastic kidneys, adrenal hemorrhage, hydrometrocolpos, intestinal duplication, and choledochal ovarian omental or pancreatic cysts. Solid masses include neuroblastoma, congenital mesoblastic nephroma, hepatoblastoma, and teratoma.** A solid flank mass may be due to renal venous thrombosis, which becomes apparent with signs of hematuria, hypertension, and thrombocytopenia. Renal venous thrombosis in infants is associated with polycythemia, dehydration, diabetic mothers, asphyxia, sepsis, and coagulopathies such as antithrombin-3 or protein C deficiencies. In neonates, transillumination of the abdomen may assist in distinguishing between solid and cystic lesions.

Abdominal distention at birth or shortly afterward suggests either obstruction or perforation of the gastrointestinal tract, often due to meconium ileus. Later distention suggests bowel obstruction, sepsis, or peritonitis. Abdominal wall defects may be present either through the umbilicus (omphalocele) or lateral wall (gastroschisis). Omphaloceles are associated with other anomalies and syndromes, such as Beckwith-Wiedemann syndrome, conjoined twins, trisomy 18, meningomyelocele, and imperforate anus (Hassink et al, 1996; Chen et al, 1997; Kallen et al, 2000). In bladder exstrophy, the posterior bladder wall is visible through a midline defect in the abdominal wall and a pubic diastasis is appreciated. In addition, a bifid clitoris or epispadias is present. In cloacal exstrophy, an omphalocele is superior to the cecal plate and lateral bladder halves with prolapsed ileum typically in the midline. Additionally, a bifid clitoris or penis, imperforate anus, and spinal abnormalities are present.

Many patients presenting with blunt force renal trauma will have associated extrarenal injuries, such as other solid organ injuries, a pneumothorax, pelvic fractures, and bladder or urethral injuries. Therefore complete physical examination in trauma patients is essential (Margenthaler et al, 2002; Mohamed et al, 2009). During examination for renal trauma, the urine should be

assessed for gross hematuria. A urethral catheter should be postponed in the setting of gross hematuria until the lower urinary tract is assessed by the urology team.

Genital Examination

Scrotal Examination

To begin the scrotal examination, the inguinal canal should be inspected on each side for signs of asymmetry or mass. To begin the examination, the examiner's left hand closes the internal inguinal ring (Fig. 115–2). This maneuver prevents an intracanalicular testis from migrating into the abdomen. The inguinal canal is then palpated to identify a fullness or mass suggestive of a hernia or hydrocele of the spermatic cord. The examiner may feel a "silk glove" sign suggestive of a thickened patent processus vaginalis that may be present if a hernia is intermittent. The examiner's right hand is then brought down to the scrotal area, and the testis is then palpated. The testis should be examined with consideration of the anatomy of the testis, the epididymis, and the vas deferens, which can be palpated even in some newborns. Particular attention to the symmetry of the examination is important, if intersex conditions are thought to exist. **In the infant with a possible disorder of sexual differentiation, a symmetrical gonadal examination (gonads palpable on each side or impalpable on both sides) suggests a global disorder, such as CAH or androgen insensitivity. Asymmetry in the gonadal examination suggests a localized problem, such as mixed gonadal dysgenesis or ovotesticular disorder of sexual differentiation.**

The acute scrotum should be examined carefully to determine the true etiology. Testicular torsion may present with varied clinical findings, but the involved testis often demonstrates signs, such as riding higher in the hemiscrotum, a transverse orientation, an anterior epididymis, absent cremasteric reflex, and tenderness of the testis and epipdidymis. In addition, the testis with torsion is often very hard to palpation if significant time has elapsed prior to presentation. In contrast, torsion of the appendix testis or epididymis often results in localized tenderness at the superior pole of the testis or caput epididymis and is often associated with a reactive hydrocele. Additionally, in boys with thin scrotal skin, the "blue dot" sign can be seen reflective of a necrotic appendix. Epididymitis classically has a gradual onset and is not associated with nausea or emesis (Gatti and Murphy, 2007).



Figure 115–2. Clinical examination of male groin.

The normal newborn scrotum is relatively large. Its size may be increased with the trauma of breech delivery or by a newborn hydrocele that can be distinguished from hernia by palpation and transillumination as well as from the absence of a mass in the inguinal canal. In the absence of volume changes within the hydrocele, the processus vaginalis is usually not patent, and the newborn hydrocele resolves by 1 year of age without surgery. Persistence of a hydrocele beyond 12 to 18 months, even in the absence of volume changes, usually indicates a patent processus vaginalis and is an indication for surgical ligation of the processus vaginalis and incision of the scrotal component of the hydrocele. Neonatal extravaginal testicular torsion can also occur prenatally, resulting in a firm, enlarged, nontender mass in the hemiscrotum that is usually associated with dark discoloration of the overlying skin. A normal scrotal examination at birth and subsequent development of erythematous, tender, edematous hemiscrotum suggests postnatal extravaginal testicular torsion and should be addressed immediately with surgical intervention if the neonate is clinically stable.

Undescended testes can be palpated if they are in the scrotum or outside the external inguinal ring. Occasionally, the testis in a newborn can be palpated if it is in the inguinal canal, but, in many cases, the testis will move in and out of the canal into the abdomen, which makes palpation of the testis inconsistent. Retractile testes may in some cases be difficult to distinguish from a low, undescended testis. Pressure on the femoral artery may sometimes help to relax the cremasteric reflex in boys older than 2 years of age. Placing the child in a squatting or legs-crossed position will sometimes relax the reflex and facilitate palpation of the testis. A testis is descended if it can be manipulated to the base of the scrotum and remains there after release, at least for a moment. Testes that feel tethered during manipulation and cannot be manipulated to the base of the scrotum are at risk for becoming ascending testes. If doubt exists, a second examination 6 to 18 months later may be helpful to distinguish a retractile testis from a tethered testis. As the child ages, an ascending or tethered testis (both cryptorchid testes) will be more and more difficult to manipulate into the bottom of the scrotum (Eardley et al, 1994; Clarnette and Hutson, 1997; Davey, 1997).

Scrotal masses can be transilluminated to determine if the component is primarily fluid, such as a tense hydrocele, or solid, such as a testicular tumor. If a firm intratesticular mass is palpated, a thorough examination of the lymph nodes should be performed to evaluate for lymphoma, leukemia, or metastatic disease. Patients with a nontender testicular mass and signs of precocious puberty should be evaluated for a Leydig cell tumor or, less commonly, a Sertoli cell tumor (Agarwal and Palmer, 2006). Epididymal cysts and spermatoceles can present as extratesticular masses but are characteristically smooth, round, and located within the epididymis. A scrotal ultrasonogram can further differentiate these physical examination findings.

Varicoceles (varicosities of the internal spermatic vein) almost always occur on the left side and are bilateral in about 10%. Varicoceles are palpable when the boy is standing but drain when supine. If only the right side is involved or if the varicocele does not decompress when the boy is supine, there exists a possibility that a retroperitoneal tumor is present and compressing the vein.

Penile Examination

In the newborn, the foreskin is adherent to the glans. These glanular adhesions should not be separated, and the glans need not be inspected if the parents do not desire a circumcision. Glanular preputial adhesions usually separate before the age of 4 but may persist in some boys for longer periods. **In the absence of balanitis or UTI, the prepuce should not be retracted but allowed to separate naturally** (Imamura, 1997). If symptoms do develop, topical corticosteroids have successfully been used as an alternative to circumcision in some boys with adherent foreskin (Chu et al, 1999; Monsour et al, 1999; Orsola et al, 2000; Elmore et al, 2002).

The position of the urethral meatus is almost never abnormal in the uncircumcised penis with a circumferential foreskin. If the ventral foreskin is short, or absent, or if there is a ventral or dorsal curvature, the boy should not be circumcised in the nursery by the obstetrician or the pediatrician and should be re-examined as soon as possible by the specialist if hypospadias or epispadias correction may need to be performed. The presence of a midline dimple on the ventral penile shaft should lead one to suspect a diagnosis of hypospadias, despite a normal-appearing foreskin. The severity of hypospadias is based on the position of the urethral meatus, the presence or absence of penile curvature, and the degree of ventral penile shaft skin coverage. Occasionally, when the foreskin is pulled back before a circumcision, the distal urethra and urethral meatus are enlarged. If a megameatus is identified before a newborn circumcision, the circumcision should be canceled. The foreskin may be removed at the time of the urethral repair. However, because normal spongiosum is present on the ventral surface of the penis, repair of the urethra is not usually difficult even after a circumcision has been performed (Duckett and Keating, 1989).

Stretched penile length and girth should be measured. If the penis in a term infant is less than 1.9 cm, micropenis should be suspected and a karyotype should be performed and the hypothalamic-pituitary-testicular axis should be assayed. **The penis should be examined in relation to the scrotum for evidence of penile concealment, buried penis, or webbed penis.** In these conditions, the penis is of normal size but buried or concealed beneath a prominent pubic fat pad; trapped by a narrowed, more proximal preputial ring; or tethered to the scrotum. If the penile shaft skin is shortened, correction may require a rotational flap of inner preputial skin to provide additional coverage for the ventrum of the penis after release of the narrowed preputial ring. If a newborn clamp circumcision is performed, more penile shaft than indicated is often removed, resulting in a scar and sometimes a secondary trapped penis. If there is encroachment of the scrotum onto the penile shaft, circumcision should be deferred until it can be done freehand under a general anesthesia, usually at 4 to 6 months (Casale et al, 1999; Williams et al, 2000).

Female Perineal Examination

Examination of the perineum in female infants and young children should include examination of the urethral meatus, vaginal introitus, and anus. An easy way of examining the perineum is to gently grasp the labia majora and pull inferiorly (Fig. 115–3).

This maneuver tends to better define the various perineal folds and provide for a consistent examination in nearly all cases (Redman, 1982). The female genital examination video (available on the Expert Consult website) demonstrates this efficient maneuver. The clitoris is examined for evidence of hypertrophy that may be suggestive of a disorder of sexual differentiation. Additionally, any introital masses should be examined for site of origin, laterality, symmetry, and signs of infection or irritation. Placing a small feeding tube into the urethral meatus can help distinguish between an asymmetrical prolapsed ureterocele or the circular edema and congestion associated with urethral prolapse. Skene duct cysts are paraurethral in location, with a bulging whitish mass superior to the vagina, and may present with signs of maternal estrogen effects, such as breast enlargement and edema of the vaginal introitus (Soyer et al, 2007). An imperforate hymen in infancy generally appears as a midline, bulging, pearly white membrane.



Figure 115–3. Female perineal examination. (Courtesy of Pasquale Casale, MD.)

In an adolescent girl, the examination may be performed with the mother present if the adolescent is in agreement. In general, bimanual examination in an adolescent girl is best performed in the operating room in the dorsolithotomy position. In the office, the girl can be examined in a frog-leg position. Gently spreading the labia majora in an inferior direction will allow inspection of the clitoral area and usually of the introitus. The vestibule is assessed for any evidence of discharge. The hymen should be inspected as well as the introitus. **An imperforate hymen may result in hydrometrocolpos and a lower abdominal mass.** In older girls, a small speculum may be used to evaluate the cervix and vaginal canal. Palpation of the vaginal walls and cervix and bimanual examination of the uterus completes the examination. A Valsalva maneuver may allow adequate assessment of the introital vaginal area. Vaginal discharge can be associated with vaginal voiding and is particularly common in children who hold urine and subsequently dribble urine into the vagina. Treatment of dysfunctional voiding results in reduced vaginal drainage. Vaginal bleeding in the preadolescent may result from foreign bodies, such as wadded toilet paper trapped in the vagina. Occasionally, other foreign bodies may have been inserted intentionally or accidentally.

Additional Physical Examination

In addition to the abdominal and perineal examination, an examination of the back should be performed. The lower back should be examined for any evidence of presacral dimpling or other cutaneous markers of occult spinal dysraphisms. **An "atypical"**

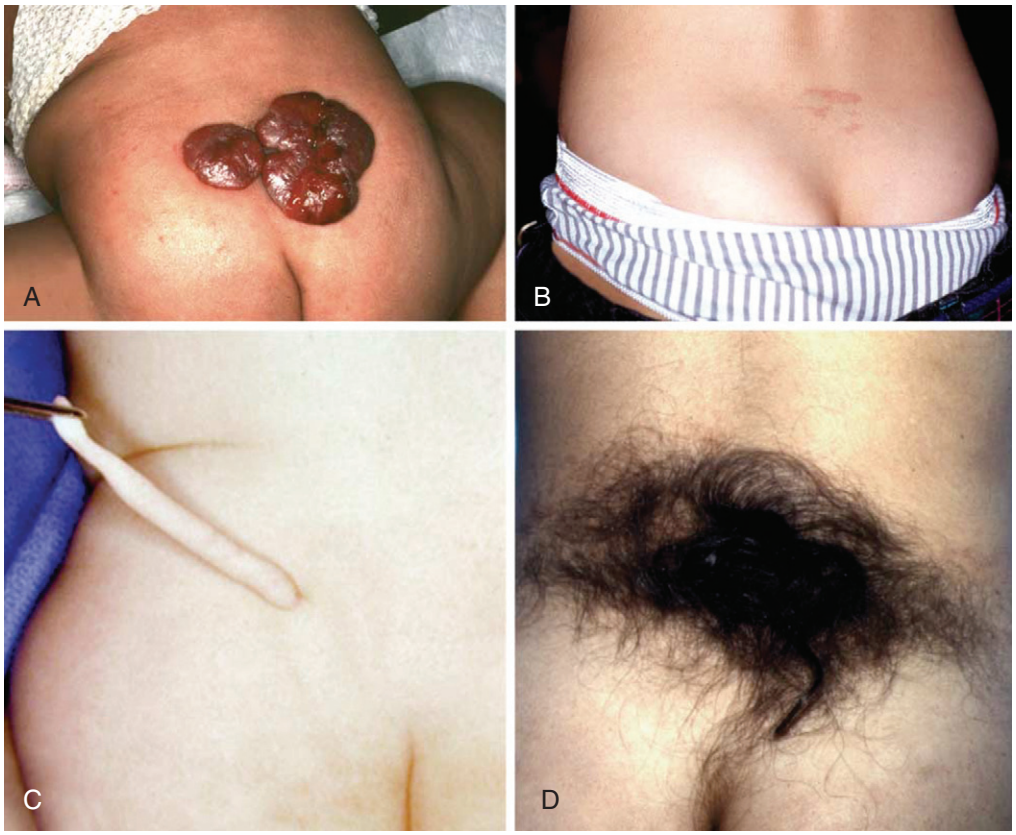


Figure 115–4. Clinical aspects of congenital median lumbosacral cutaneous lesions. **A,** Ulcerated hemangioma centered on a dermal sinus and deviation of the gluteal furrow. **B,** Isolated port-wine stain. **C,** Human tail. **D,** Faun tail. (From Guggisberg D, Hadj-Rabia S, Viney C, et al: Skin markers in occult spinal dysraphism: a review of 54 cases. Arch Dermatol 2004;140:1109–15.)

presacral dimple may indicate spina bifida or cord tethering if the dimple is off center, more than 2.5 cm from the anal verge at birth, or deeper than 0.5 cm (Soonawala et al, 1999). In a series of 207 neonates with sacral and presacral cutaneous stigmata, 40% of patients with atypical dimples were found to have occult spinal dysraphism (Kriss and Desai, 1998). Other skin markers to suggest occult spinal abnormalities include subcutaneous lipomas, dermal sinuses, tails, and localized hypertrichosis (Fig. 115–4). A combination of two or more of these congenital midline skin lesions is the strongest marker of occult spinal dysraphism (Guggisberg et al, 2004). We recommend an ultrasonogram of the lumbosacral spine in the newborn if any of these conditions exists (Unsinn et al, 2000; Hughes et al, 2003). For equivocal ultrasound studies and in older children, the authors order MRI for a complete evaluation. A brief evaluation of the upper and lower extremities and of the back is performed for any evidence of asymmetry, length discrepancy, or misalignment of the spine.

If a neurologic examination is indicated, the examination should begin with observation of the child at the outset of the visit. Often, delays in development (see Table 115–4) are identified by simple observation. A note is made of the level of alertness of the pediatric patient. Factors affecting the alertness of a newborn include the time of the last feeding, room temperature, and the gestational age. One should suspect an underlying metabolic or infectious cause in cases of decreased alertness. Identification of a sensory level in association with a spinal cord lesion can be very difficult in the infant. Differences in color or temperature can sometimes be observed, with the skin drier and cooler below the level of the cord lesion. Children older than 4 to 5 years of age are often capable of detailed sensory testing; however, success depends on the ingenuity and patience of the examiner. A child with a low spinal cord lesion may have a patulous anus and absence of contraction of the anal sphincter when stimulated in the anal region by a sharp object (anal wink). Changes in bladder function, such as new-onset urinary incontinence, may indicate a spinal cord lesion.

Often, the urologist may encounter signs of nonurologic or systemic illnesses during physical examination. In the infant, generalized edema may occur with prematurity or hypoproteinemia. Localized edema suggests a congenital malformation of the lymphatic system. **When confined to one or more extremities, edema may be a presenting sign of coarctation of the aorta in association with Turner syndrome.** Vasomotor instability and decreased peripheral circulation are revealed by red or purple color in a crying infant. Scattered **petechiae** in the infant may be present in the scalp and face after a difficult delivery. **Café-au-lait spots** are uniformly hyperpigmented, sharply demarcated macular lesions, the hues of which vary within the normal degree of pigmentation of the individual. These may be dark brown in African-American children. They may vary in size and may be large, covering a significant proportion of the trunk or limb. One to three lesions are common in normal children. Approximately 10% of normal children have café-au-lait macules. They may be present at birth or develop during childhood. **If there are five or more spots, each more than 5 mm in diameter, in prepubertal patients or six or more spots, more than 15 mm, in postpubertal children, neurofibromatosis type 1 (von Recklinghausen disease) should be suspected.**

An exceptionally large head suggests hydrocephaly, a storage disease, achondroplasia, cerebral gigantism, neurocutaneous syndromes, or inborn errors of metabolism, or it may be a familial condition. Dysmorphic features, such as **broadened epicanthal folds, widely spaced eyes, micrognathia, and low-set ears are often associated with congenital syndromes that may suggest a genitourinary problem.** Preauricular sinuses and pits may be the result of imperfect fusion of the tubercles of the first and second branchial arches. These anomalies may be unilateral or bilateral, may be a familial condition, are more common in females and African-Americans, and at times are associated with other anomalies of the ears and face. Preauricular pits are present in bronchio-oto-renal dysplasia, an autosomal-dominant disorder that consists of external ear malformations, bronchial fistulas, hearing loss, and renal anomalies. **Macroglossia can be associated with Beckwith-Wiedemann syndrome, which also includes hepatosplenomegaly, nephromegaly, and hypoglycemia secondary to pancreatic β-cell hyperplasia in a large gestational age infant.** These children are predisposed to a specific subset of childhood neoplasms, including Wilms tumor and adrenocortical carcinoma. Webbing of the neck in a female infant suggests intrauterine lymphedema in Turner syndrome, as do the widely spaced nipples with a shield-shaped chest (Stoll and Kliegman, 2000).

The skin, hair, and nails should be evaluated with special focus on congenital or metabolic problems that may be associated with brittle or abnormal hair and nails or abnormal skin dryness (see Tables 115–2 and 115–3). Supernumerary nipples may occur in a unilateral or bilateral distribution along a line from the anterior axillary fold to the inguinal area. They are more common in African-American infants (3.5%) than white (0.6%) children. Accessory nipples may not have an associated areola and may be mistaken for congenital nevi. They may be excised if desired to improve appearance. Associated renal or urinary tract anomalies may be present.

Key Points: Pediatric Urologic Examination

- Renal pathology is the source of up to two thirds of neonatal abdominal masses.
- Performing a scrotal examination in the legs-crossed position facilitates palpation of the testes.
- The inner preputial skin is adherent to the glans in infants and should not be forcibly retracted in the absence of balanitis or UTI.
- The lower back should be examined for evidence of cutaneous markers suggestive of occult spinal dysraphisms.

PEDIATRIC LABORATORY EVALUATION

The urine specimen may be obtained in a number of different ways. In the child who is not potty trained, a bagged specimen, although the most susceptible to contamination, is the easiest and least invasive to obtain. To minimize contamination with fecal or skin flora, a hole is cut in the diaper and the perineal bag is brought through the hole in the diaper. A parent is instructed to watch the bag, and as soon as urine is noted (which can be easily seen because the bag is visible coming through a hole in the diaper), the bag should then be removed. If the specimen is collected in the office, the bag is immediately drained and the urine plated and sent to the laboratory for culture. Using this method, the skin contamination of the urine specimen is minimized, and the trauma of catheterization is avoided (Falcao et al, 1999). However to be reliable, positive cultures must still be confirmed with catheterized specimens. In most cases, we push for catheterized specimens for the diagnostic reliability they provide.

Older children generally provide a clean midstream urine specimen. Most studies have failed to show any benefit to formally cleansing the introitus before obtaining the specimen. Once a midstream urine specimen is collected, it is sent to the laboratory for urinalysis and culture. **Pyuria is defined as more than 5 white blood cells per high-powered field for girls and more than 3 white blood cells per high-powered field for boys.** Infection can occur without pyuria and, conversely, pyuria may be present without UTI. Consequently, pyuria as an isolated finding is more confirmatory than diagnostic for UTI. Nitrate and leukocyte esterase assays are usually positive in infected urine. However, if the urine has not remained in the bladder for more than 1 hour, the conversion of nitrates to nitrites may not be complete, and the chemical strip may read negative despite the presence of nitrogen-splitting bacteria in the bladder.

If the culture grows greater than 100,000 colonies of a single pathogen or if there are 10,000 colonies and the child is symptomatic, we consider a UTI to be present. **White blood cell casts and urinary sediment suggest renal involvement,** but these are rarely identified. If the child is not symptomatic and the urinalysis is normal, it is unlikely that the urine is infected. However, if the child is symptomatic, a UTI is possible regardless of the results of the urinalysis (Bonadio, 1987). Microscopic hematuria is common in acute bacterial as well as viral cystitis. Gross hematuria may be present in viral cystitis but is less common in acute bacterial cystitis. If the child is symptomatic, the urinalysis is suggestive of UTI, and the culture grows more than one organism or fewer than 100,000 colonies, the clinician has the option of treating with an antibiotic that is effective based on the sensitivities or repeating the culture. The authors repeat the culture but start the child on a treatment dose of antibiotic at that time. If a second catheterized culture is negative, then the antibiotics are discontinued and close follow-up is provided. This is particularly important in infants who may not demonstrate the usual signs and symptoms of infection that would be present in an older child.

Microscopic hematuria is common in children. Routine office screening with urinalysis for urinary abnormalities is no longer recommended. Thus the actual time of onset for microscopic hematuria is often unknown. Normally, the first indicator is a positive urine strip test for blood. Most strips can detect concentrations of 5 to 10 intact red blood cells/mL. This concentration corresponds to 2 to 5 red blood cells per high-powered field. Improper interpretation of the dipstick, such as delayed reading or cross-contamination of urine from other chemically impregnated pads, may result in false-positive results. The urine should be dipped, the excess urine tapped off, and the strips should be read immediately at the recommended time. **Confirmation of microscopic hematuria after a positive dipstick examination requires a microscopic examination of the urine for the presence of red blood cells.** Microscopic hematuria may be defined as more than 5 red blood cells per high-powered field in at least two of three urinalyses over 2 to 3 weeks. An absence of red blood cells in the urine with a positive dipstick result suggests hemoglobinuria or myoglobinuria. A positive dipstick on a single specimen with microscopic confirmation should be viewed as an indication for further urine testing rather than as diagnostic until persistence is confirmed on subsequent studies.

PEDIATRIC RADIOGRAPHIC EVALUATION

Ultrasonography

Ultrasonography of the kidneys, ureters, and bladder is an extension of the physical examination. Ultrasonography provides a noninvasive evaluation that does not require sedation, ionizing radiation, or contrast injection and can be performed at the bedside in critically ill children. Additionally, the body habitus of young children allow for accurate imaging. Older children or children with significant skeletal abnormalities, such as severe scoliosis or kyphosis, often require other imaging modalities to accurately assess the kidneys and collection system. Palpable masses within the abdomen can be localized and even diagnosed with the aid of ultrasonography performed by a uroradiologist with an interest in pediatrics. The examination should evaluate not only the genitourinary system but also adjacent organs, such as the adrenal gland, liver, and spleen. The image of the parenchyma of the liver and spleen should be used for comparison when assessing the parenchyma of the right and left kidney, respectively. The density of the kidney and of the renal medullary pyramids, as well as the wall thickness and configuration of the collecting system, the presence or absence of caliectasis, pelviectasis, or ureterectasis are all important indicators of renal and ureteral pathophysiology (Hulbert et al, 1992). The luminal diameter of the ureters, thickness of the bladder wall, and the volume of the bladder both before and after voiding should be recorded (Palmer, 2006). If hydronephrosis or ureterectasis is present before voiding, the kidneys and ureters should be rescanned after voiding. A skillful ultrasonographer can provide anatomic detail about the insertion of the ureters and the degree of dilation of the ureter and can identify the jet of urine as it enters the bladder (Kirby and Rosenberg, 1992; Cvitkovic et al, 2001). Ultrasonography is the first radiographic test used in the evaluation of suspected urolithiasis. Ultrasonography may also be used to accurately measure postvoid residual urine (Coombes and Millard, 1994). Increased thickness of the bladder wall may be suggestive of bladder outlet obstruction from posterior urethral valves or urethral atresia. Trabeculation within the bladder, bladder diverticulum, and ureteral duplication or ureterocele are all easily identified with ultrasonography. Children presenting with a febrile UTI are evaluated with ultrasonography to determine if a structural anomaly is present (Giorgi et al, 2005). **Ultrasonography in the absence of comparison studies or appropriate history cannot by itself distinguish obstructive from nonobstructive hydronephrosis.** Therefore a functional study such as a renal scan is usually required for diagnosis. Ultrasonography is also sensitive in detecting solid renal masses, particularly those that measure at least 1.5 cm in the largest dimension. For smaller renal masses, the ultrasound findings should be considered preliminary and should be confirmed with CT or MRI (Jamis-Dow et al, 1996).

Ultrasonography is also frequently used to examine the scrotum, such as in cases of boys with varicoceles (Diamond et al, 2000). It may also be used to assess blood flow if spermatic cord torsion is suspected, as well as to distinguish between epididymitis and torsion of the appendix testis in cases in which tenderness is localized to the upper pole of the testis. In the setting of acute scrotal pain, ultrasonography has been reported to have a sensitivity of 78.6% and specificity of 96.9% in diagnosing surgical and nonsurgical scrotal conditions (Blask et al, 2002) Therefore it is important to remember that false-negative ultrasonograms can occur and must be confirmed by a careful physical examination. The authors have also found it useful in distinguishing a hernia from a hydrocele or identifying abdominoscrotal hydroceles (Finkelstein et al, 1986). Additionally, scrotal masses are evaluated by ultrasonography.

When used as a first-line test in suspected occult spinal dysraphism, optimal timing of the spinal ultrasonography is earlier than 6 months of age. Ossification of the posterior elements after 6 months of age prevents an acoustic window. Agreement between ultrasonography and MRI is good, particularly for the detection of the low-lying cord (90%) (Hughes et al, 2003).

Ultrasonography is also performed during routine prenatal care. The kidneys and bladder can be visualized at 15 weeks of gestation. Further details, including the renal pelvis and corticomedullary differentiation, are detectable after 20 weeks of gestation (Sty and Pan, 2006). Hydronephrosis remains one of the most common abnormalities detected by prenatal sonography. After delivery, repeat renal and bladder ultrasonography is performed to further assess the collecting system and determine the appropriate evaluation and treatment if necessary.

Voiding Cystourethrography

VCUG is used to identify vesicoureteral reflux (VUR), to evaluate the anatomy of the bladder outlet (bladder neck and posterior urethra) during bladder filling and voiding, and to assess the presence of residual urine after micturition. Additional information regarding trabeculation of the bladder, bladder diverticula, and presence or absence of urachal abnormalities may be identified with a fluoroscopic VCUG (Fernbach, 2000; Goldman et al, 2000; McDonald et al, 2000). The VCUG begins with a plain film, followed by placement of a feeding tube rather than a Foley catheter. The balloon on a Foley catheter may obscure the anatomy of the bladder neck and trigone, particularly at the beginning of the study. The percentage of bladder filling when the reflux is first identified may also be an indicator of potential resolution of VUR. On subsequent examinations, improvement in VUR may be assumed if a smaller percentage of total bladder volume is refluxing into the ureter or if the reflux occurs at a greater percentage of total bladder filling (Mozley et al, 1994). On the plain film, abnormalities of the spine, ribs, and pelvis and the presence or absence of stones within the kidney, ureter, or bladder should be noted. The gas pattern and volume of stool is particularly important in infants and in children with dysfunctional voiding in whom constipation may be an important part of the clinical pattern. Gas should normally be present in the rectum on plain film by 24 hours of age. The bladder should be drained, and contrast medium should be gently infused. In children in whom an ureterocele is suspected, the first few images during filling of the bladder best demonstrate the ureterocele. The bladder is then filled slowly, and the child voids.

Voiding views must be obtained in all cases, but particularly if bladder outlet obstruction such as a posterior urethral valve is suspected. In children in whom VUR is suspected or in patients with an ectopic ureter, cyclic VCUG must be performed in which at least two voiding cycles are completed. In some cases, the ectopic ureter that is draining to the bladder neck must empty for additional contrast material to reflux. If a second voiding cycle is not performed, one might miss reflux into the ectopic system (Hellstrom and Jacobsson, 1999; Polito et al, 2000). It is important to image the bladder neck during voiding in the female as well as the male. The presence of a "spinning top urethra" in a

school-aged girl may be an important indicator of dysfunctional voiding (Saxton et al, 1988; Soygur et al, 2004). Vaginal voiding and subsequent emptying (or failure to empty) of the vagina should also be noted, which may be seen on the postvoid views.

In patients with a urogenital sinus, contrast VCUG may be modified to image the urethra and vagina simultaneously. In this study, the urogenital sinus is intubated with a blunt-tipped catheter (which can be made by trimming the cone-shaped end of a feeding tube) and placed against the perineal opening. Contrast medium is injected retrograde to identify the point where the vaginal introitus meets the urethra to form the urogenital sinus. The study will also aid in differentiating a cervical dimple from a prostatic utricle. If a cloaca is present, the sinogram will provide detail about the position of the rectum, vagina, and urethra and about the point of confluence and the distance to the perineum (Shaul and Harrison, 1997; De Filippo et al, 1999). The distances of these structures will help determine the approach required during surgery (Pena et al, 2004).

Nuclear Medicine Renal Scan

A radionuclide renal scan is measured in two phases: the cortical imaging and tubular imaging phase. Most radionuclide agents will demonstrate renal tubular as well as renal cortical binding. Radionuclide studies are best suited to demonstrate changes in tubular or cortical transit that result from abnormalities of renal perfusion, secretion, and filtration. In most cases, the radionuclide study is inferior to CT, MRI, or ultrasonography for demonstration of anatomic alterations. **Technetium-99m mercaptoacetyltriglycine (MAG-3)** is secreted, in part, by renal tubular function and may also be used to approximate relative renal plasma flow. The MAG-3 renal scan assists in differentiating obstructive versus nonobstructive dilatation of the urinary tract. Proper interpretation of the information obtained from this study requires detailed knowledge of the factors affecting drainage of the upper urinary tract (Shulkin et al, 2008). If detailed imaging of the renal cortex is required to identify renal scarring, **technetium-99m dimercaptosuccinic acid (DMSA)** may be given and the kidneys imaged 3 to 4 hours after the injection (Piepsz et al, 1999).

Renal scintigraphy scans using gallium-67– or indium-111–labeled leukocytes may be helpful to diagnose and localize the site of urinary tract infections (Yen et al, 1999; Velasco et al, 2004). These techniques may be used to identify and guide therapy for children with focal segmental bacterial pyelonephritis in whom the duration of therapy is uncertain. In a prospective study by Yen and associates (1999), gallium-67 renal scans were more sensitive than DMSA scans in the diagnosis of acute pyelonephritis, especially in differentiating new lesions from old ones. These are particularly useful in patients with abnormal renal anatomy or in patients with diminished renal function in whom the DMSA scan may be less specific.

Computed Tomography

Computed tomography (CT) is used judiciously in specific pediatric clinical settings due to the ionizing radiation required. CT is rarely used in neonates or infants, with the exception of evaluation of a retroperitoneal or pelvic mass. Conversely, CT with intravenous (IV) contrast is the current imaging modality of choice for evaluation of pediatric abdominal trauma. **Ultrasonography provides effective evaluation for most suspected cases of pediatric stone disease and should be used as a first-line test due to the absence of ionizing radiation. Spiral CT has in most cases replaced the intravenous pyelogram (IVP) as a confirmatory study in children with complex stone disease. A recent study documented 76% sensitivity and 100% specificity of ultrasonography in comparison with CT in the diagnosis of pediatric urolithiasis** (Passerotti et al, 2009). In addition, CT with or without contrast medium enhancement is particularly important as an adjunct in children with suspected focal segmental bacterial pyelonephritis. CT is also particularly important in the diagnosis and staging of solid tumors of the chest and abdomen. Contrast medium–enhanced CT is particularly useful in cases of nephroblastomatosis, in which ultrasonography shows little displacement of the renal capsule. One must be reminded that radiation doses from CT are cumulative over the life of an individual (Frush et al, 2003). With sufficient clinical information, the radiologist may be able to recommend other imaging modalities (e.g., ultrasonography, MRI) that do not use ionizing radiation.

Magnetic Resonance Imaging

Although still expensive as an individual radiologic study, **magnetic resonance urography (MRU) may provide the best information of the anatomy and function of the genitourinary tract from a single study.** Advantages of MRU include the avoidance of ionizing radiation, its use in patients with impaired renal function, and higher-quality contrast and spatial resolution in any plane relative to other imaging modalities (Fig. 115–5) (Wille et al, 2003; Grattan-Smith, 2008). If obstruction of the urinary tract is suspected, gadolinium followed by furosemide can be administered. Notably, MRI with gadolinium should not be performed earlier than 2 months of age in a full-term infant. Antenatal MRI is used to diagnose ureteropelvic junction

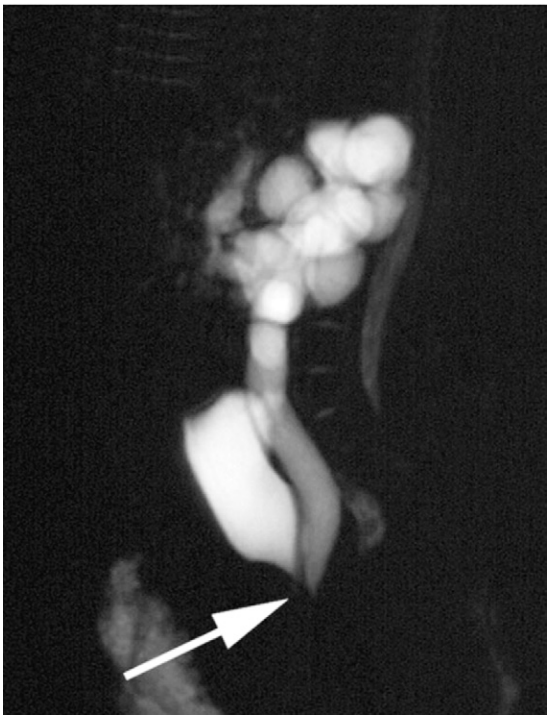


Figure 115–5. Magnetic resonance urogram of a megaureter on the left side in the sagittal plane with narrowing of the distal ureter *(arrow)*. (From Wille S, Knobloch R, Klose KJ, et al. Magnetic resonance urography in pediatric urology. Scand J Urol Nephrol 2003;37:16–21.)

obstructions, ectopic ureters, abnormal ureteral buds associated with renal agenesis, and cloacal exstrophy in the fetus (Maas et al, 1997; Matsuki et al, 1998; Wille et al, 2003). When antenatal ultrasonography is equivocal, antenatal MRU provides additional anatomic detail, especially in the diagnosis of ureteral pathology (Kajbafzadeh et al, 2008). The limitations of MRU, at this time, include its high costs and the requirement for sedation/anesthesia in most young patients. Although not routine, MRI is used more frequently now in the evaluation and identification of the impalpable testis (Yeung et al, 1999; Lam et al, 2001). In the workup of suspected renovascular hypertension, gadolinium-enhanced MR angiography (MRA) is a noninvasive modality with comparable accuracy to digital subtraction angiography (Hacklander et al, 2004). In the presence of renal insufficiency, however, caution must be exercised in the use of gadolinium contrast due to the risk of nephrogenic systemic fibrosis (Penfield, 2008).

Intravenous Pyelography

Despite the newer imaging techniques that are now available, the intravenous pyelogram (IVP) is useful in selected cases. The plain film of the abdomen should be inspected for calculi, spinal abnormalities, and an abnormal intestinal gas pattern. The nephrogram phase of the IVP identifies mass effects within the kidney and the presence or absence of scarring after pyelonephritis. Subsequent views can sequentially assess the anatomy of the renal cortex, calyces, fornices, renal pelvis, ureters, bladder, and urethra (Smellie, 1995). Subtle anatomic variations in normal anatomy of the renal calyces or of the ureteropelvic junction that may be confusing on ultrasonography or CT may be clarified with the IVP.

Key Points: Pediatric Laboratory and Radiographic Evaluation

- Microscopic hematuria diagnosed on dipstick evaluation should be confirmed with microscopic examination of the urine.
- Ultrasonography cannot definitively distinguish obstructive for nonobstructive upper tract urinary dilatation.
- A VCUG should include multiple voiding cycles with images of voiding views.
- Nuclear medicine evaluation is increasingly used in the evaluation of patients with vesicoureteral reflux.
- CT should be used judiciously in children due to the risks of ionized radiation.
- MR urography provides functional and anatomic information about the entire urinary tract.

PEDIATRIC URODYNAMIC AND BIOFEEDBACK EVALUATION

The well-equipped urology office will have a urodynamic suite as part of the overall complex. Modern urodynamic systems allow accurate measurements of the intravesical pressures before, during, and after bladder contraction. From these measurements, estimates of bladder compliance, as well as the bladder outlet resistance, may be made. With this information, the pediatric urologist may assess whether the bladder stores at pressures low enough to prevent renal damage and empties well enough to prevent UTI. The addition of fluoroscopic monitoring of the bladder and upper tracts during urodynamics greatly adds to the information garnered from the urodynamic study. However, videourodynamic suites must be located within a lead-lined room, which may preclude placement in every office.

Biofeedback training designed to help the child to improve bladder emptying may also be performed in the office. Biofeedback sessions should be done in a room that is separate from the urodynamic suite, because, in most cases, a different population of patients requires biofeedback training than will undergo urodynamic study (Yamanishi et al, 2000; Schulman, 2004). Biofeedback, if done properly, is time consuming. The child must be relaxed and motivated for the session to be effective. Awareness of the pelvic floor muscle and urinary sphincter is a key factor to achieve successful biofeedback treatment. Biofeedback incorporating interactive computer games is available, with success rates approaching 90% after a mean of 4.9 sessions (Herndon et al, 2001).

OFFICE SURGICAL PROCEDURES

Successful outpatient surgery with a local anesthetic depends on cooperation from the parent as well as the child. Parents must believe that the convenience of having the procedure in the office outweighs the advantages of a general anesthetic in the main operating room. We believe many infants weighing less than 10 pounds may easily undergo an office circumcision with an anesthetic cream combined with an injected local anesthetic (Hoebeke et al, 1997). However, in a recent meta-analysis by Brady-Fryer and colleagues (2004), dorsal penile nerve block was the most effective at reducing circumcision pain compared with a eutectic mixture of local anesthetics (EMLA) and placebo. The authors rarely provide for office circumcision in older children. Infants older than 3 months are too big to be easily restrained, and the risk of bleeding postoperatively, if the skin edges are not sutured, is considerable.

A number of techniques may be used in the clinic for circumcision, including a Plastibell, Mogen, and Gomco clamp. We use the Gomco clamp, which is a three-component device that includes a bell that fits over the glans of the penis and separates the glans from the inner preputial skin (Guazzo, 1999; Amir et al, 2000; Wan, 2002). The clamp is applied, and the foreskin is trimmed away from the clamp. If the clamp is left in place for a considerable amount of time (usually about 10 minutes), then there is very little separation of the skin postoperatively. If desired, a small nonstick bandage is placed beneath a transparent adhesive dressing. The bandage is removed the next day. The boy's parents are instructed to apply petroleum jelly to the incision during the healing period.

Complications after neonatal circumcision include bleeding, wound infection, meatal stenosis, and secondary phimosis resulting from removal of insufficient foreskin or removal of insufficient inner preputial skin. Potentially serious complications include death, sepsis, amputation of distal part of the glans, removal of excessive foreskin, and urethrocutaneous fistula (Baskin et al, 1997; Hutcheson, 2004). After a circumcision, the cut edge of the preputial surface may occasionally graft to the inflamed glans tissue forming a preputial-glanular bridge that may be incised in the office with application of local anesthetic cream and subsequent injection of local anesthetic. After injection, the skin bridge is clamped, the clamp is removed, and the skin bridge is sharply incised. No suturing is required in most cases. This procedure is easy and virtually

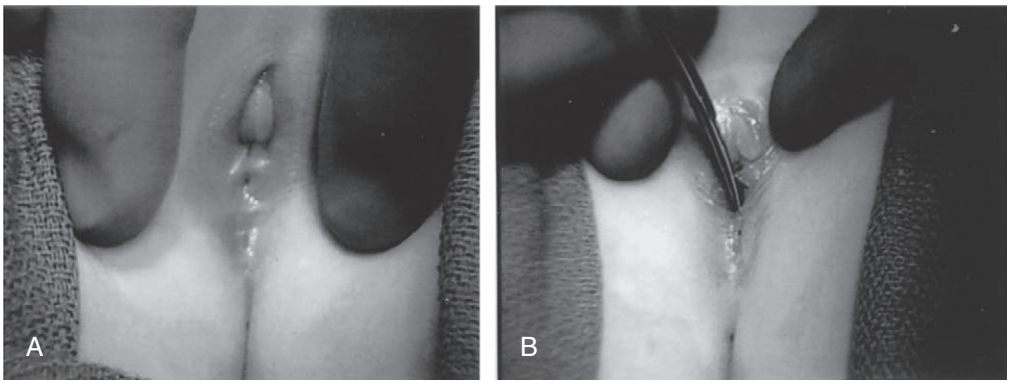


Figure 115–6. Outpatient lysis of labial adhesions. **A,** Dense labial adhesions. **B,** Adhesions clamped and incised. (From Nurzia MJ, Eickhorst KM, Ankem MK, Barone JG. The surgical treatment of labial adhesions in prepubertal girls. J Pediatr Adolesc Gynecol 2003;16:21–3.)

painless. After the procedure, the parents apply petroleum jelly to the incised edges to prevent them from readhering.

Meatal stenosis is common after circumcision. It may result from contraction of the meatus after healing of the inflamed, denuded glans tissue that occurs after retraction of the foreskin or from damage to the frenular artery at the time of circumcision (Persad et al, 1995; Upadhyay et al, 1998). If the narrowing is pronounced enough to cause deflection of the urinary stream or dysuria, a meatotomy is indicated.

To perform a meatotomy in the office, an anesthetic cream is applied. After 45 minutes, lidocaine with 1% epinephrine is injected with a 26-gauge needle to provide a small wheal at the ventrum of the urethral meatus. The ventral edge of the urethral meatus is clamped, and a small wedge of the scarred tissue is crushed with a straight hemostat and sharply excised. After the procedure, the parents are advised to apply a fine petrolatum ointment to the cut edges of the urethral meatus. A small meatal dilator is used twice a day for 4 to 6 weeks. Postoperatively, these children are seen 2 to 3 months later to assess the result.

If a VCUG is required, or if dysuria associated with vaginal pooling of urine contributes to a dysfunctional voiding pattern, we have occasionally separated labial adhesions in the office. These membranous adhesions are easy to separate on the midline with a probe or the tip of a curved hemostat (Fig. 115–6). A local anesthetic cream is applied to the labia in hope of easing the discomfort, which is minimal. After lysis of the adhesions, the child's parent must separate the labia and apply a barrier cream, such as petroleum jelly, at least twice a day for 4 to 6 weeks while the labial tissue matures. With diligent postoperative care, recurrence is rare.

Key Points: Pediatric Urodynamic Evaluation, Biofeedback Evaluation, and Office Surgical Procedures

- A well-equipped urology office will have a urodynamics and biofeedback training suite.
- Most infants weighing less than 10 pounds may easily undergo an office circumcision with an anesthetic cream combined with injected local anesthesia.
- Petroleum jelly is applied after circumcision, urethral meatotomy, or lysis of labial adhesions to prevent complications.

SUMMARY

The final goal of the surgical care of children is to assure as normal an adult life as possible. The pediatric urologist should continue to act as consultant, even after the child enters adulthood, for boys with prune-belly syndrome or posterior urethral valves and for children of either sex born with bladder or cloacal exstrophy. **As children grow into adults, the pediatric team must develop a liaison with a skilled, interested adult team. Using this method, a lifetime plan of care may be designed and carried out to ensure well-coordinated urologic therapy that is capable of addressing the complicated problems unique to this special group of boys and girls.**

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter 116

Infection and Inflammation of the Pediatric Genitourinary Tract

Linda Marie Dairiki Shortliffe, MD

Epidemiology of Pediatric Urinary Tract Infections
Pathogenesis of Urinary Tract Infection in Children
Diagnosis of Urinary Tract Infection
Management of Pediatric Urinary Tract Infections
Prophylactic Antimicrobial Agents
Imaging Evaluation
Specific Imaging Techniques
Risks of Ionizing Radiation and Responsible Imaging
Sequelae of Urinary Tract Infection
Management of Special Urinary Tract Infections and Common Associated Problems
Other Genitourinary Tract Infections and Syndromes
Genitourinary Tract and Nosocomial Infections
Bacteriologic Ecology and Antimicrobial Resistance
Considerations in Treating Children with Urinary Tract Infection

Bacterial urinary tract infection (UTI) is the most common cause of childhood urinary tract inflammation. Beginning with bacterial adherence to host epithelial cells at the portal of entry, bacterial clonal studies now clearly support the fecal-perineal-urethral route and subsequent retrograde ascent of bacteria that cause UTI (Tullus et al, 1986; Mitsumori et al, 1997; Yamamoto et al, 1997). In UTI, both bacterial virulence factors and the human immune system (innate and adaptive) interact, and both are critical in understanding UTI pathogenesis. The practitioner must consider the human microbiome, moreover, as a community when managing difficult and recurrent UTI. We need to understand issues of (1) prenatal fetal anatomy, (2) issues of infection prevention versus treatment, and (3) medical globalism.

Recognition that bacteriuria can cause renal parenchymal and functional loss has prompted recommendations for rapid diagnosis and evaluation of UTI with genitourinary imaging techniques and tests. In infants, UTI is a common cause of fever and may be the most common cause of renal parenchymal damage and loss. For this reason, the goal of managing childhood UTI is based upon identifying and modifying, if possible, factors that increase risk of renal damage from the time of the index infection forward. With improved diagnosis based upon imaging and improved antimicrobial agents, some of these risks may have shifted. This chapter focuses upon host and bacterial mechanisms by which bacteria gain access to the bladder and kidney, management and evaluation of first and recurrent urinary tract infections, possible short- and long-term complications of urinary tract infection, and potential factors that identify a child who may risk bacteriuria or its potential complications.

EPIDEMIOLOGY OF PEDIATRIC URINARY TRACT INFECTIONS

Only during the first year of life do males get more UTIs than females (Asscher et al, 1973; Winberg et al, 1974), and during that year, the risk of UTI in **uncircumcised boys is about ten times that of circumcised boys** (Rushton and Majd, 1992a; Wiswell and Hachey, 1993). By age 1 year, 2.7% of boys and 0.7% of girls have had bacteriuria (Wettergren et al, 1980). Although this incidence declines to less than 1% in school-age boys (ranging from 0.03% to 1.2%), it rises to 1% to 3% in school-age girls (Asscher, 1975; Savage, 1975; Bailey, 1979), with sexually active females having more UTIs than sexually inactive ones (Kunin and McCormack, 1968).

Data from the U.S. Healthcare Cost and Utilization Project (HCUP) show that UTI causes about 51 per 100,000 children per year to be hospitalized and 174 per 100,000 infants (children younger than 3 months); about 18 to 20 per 100,000 of these cases are coded as pyelonephritis (Freedman, 2004). Overall, girls were hospitalized 2.5 times more than boys. UTI accounts for 2.4% to 2.8% of physician visits for children with commercial insurance or Medicaid; the National Ambulatory Medical Care Survey shows that UTIs are 0.7% of all pediatric office visits, thus documenting a heavy burden of childhood ambulatory UTI visits (Freedman, 2004). Given an average of 40,000 admissions for UTI per year (HCUP data) and a mean cost of $4500 per child for each UTI admission (Freedman, 2004), the financial cost for hospitalization of children with UTI alone is $180 million per year, without

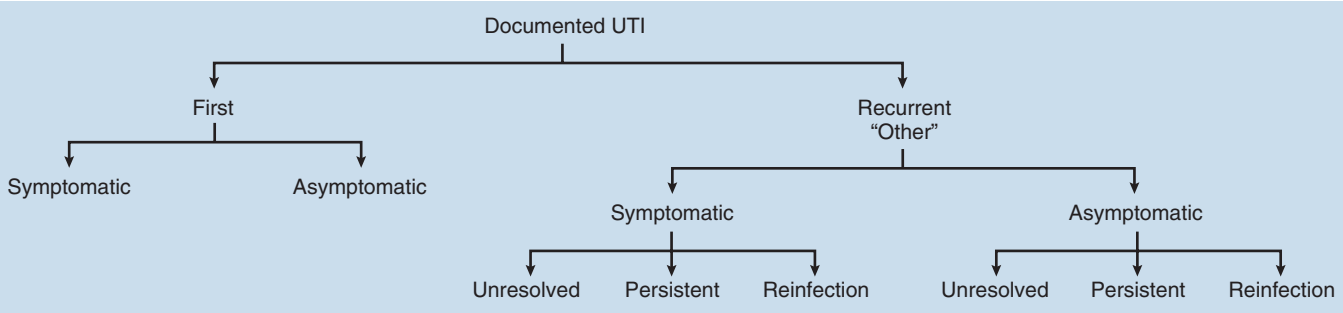


Figure 116–1. Functional classification of urinary tract infections (UTI) in children.

including ambulatory visits that account for much of UTI treatment in this country (Freedman, 2004).

Definition of Infection

What constitutes a "significant" clinical UTI is controversial. The urinary tract is normally sterile. Whether "colonization" of the urinary tract occurs (benign bacteriuria) or whether colonization is true infection is debatable. Specimen contamination can occur, and specimens are often difficult to interpret.

Urinary collection is important for the reliability of UTI diagnosis (Fig. 116–1).

Classification of Urinary Infections

UTI is classified in many ways: complicated versus uncomplicated, upper versus lower tract, persistent infection versus reinfection, and symptomatic versus asymptomatic. For practical purposes pediatric UTI can be divided into two categories: first infections and recurrent or other infections.

Recurrent infections may be (1) unresolved during initial therapy, (2) persistent (from an anatomic site) and/or (3) reinfection from a separate microorganism (Stamey, 1975). As will be discussed, first childhood UTIs are complicated because of evaluation and management implications and considerations.

A UTI may not resolve because it is treated with a drug to which the bacterium is resistant, the antimicrobial levels are too low for physiologic reasons of poor renal concentrating ability or gastrointestinal malabsorption, or the infection is polymicrobial. When proper culture and antimicrobial sensitivity results are available, usually unresolved UTIs are treated successfully.

UTI imaging evaluation reveals most sources of bacterial persistence early in childhood. The discovery of surgically correctable sources of bacterial persistence is obviously important so that these sites can be removed (Table 116–1). The majority of recurrent UTIs are not surgically correctable, because they result from reinfection from the same or a different gut microorganism. Screening urinary culture when a child is being examined for reasons unrelated to urinary symptoms, may diagnose an asymptomatic or covert UTI (Savage, 1975); these UTIs will be discussed.

Table 116–1.

Surgically Correctable Causes of Bacterial Persistence in Children

Infection stones
Infected nonfunctioning or poorly functioning kidneys or renal segments
Infected ureteral stumps after nephrectomy
Vesicointestinal or urethrorectal fistula
Vesicovaginal fistula
Infected necrotic papillae in papillary necrosis
Unilateral medullary sponge kidney
Infected urachal cyst
Infected urethral diverticulum or periurethral gland

Bacteria

Some bacteria appear to have a special affinity for causing UTI. The most common bacteria infecting the urinary tract are the gram-negative Enterobacteriaceae, usually *Escherichia coli*. Specific cell wall O-antigens that are identified by serotyping, such as *E. coli* serotypes 01, 02, 04, 06, 07, and 075, commonly cause pediatric UTI (Kunin et al, 1964; Bergström et al, 1972; Winberg et al, 1974), and many of these are now called UPEC (uropathogenic *E. coli*) or are included among ExPEC (extraintestinal *E. coli*) (Russo and Johnson, 2000). Experimental findings suggest that current *Enterococcus faecalis* with multidrug resistance may have a specific affinity for the kidney (Kau et al, 2005).

Bacterial surface structures, pili or fimbriae, may increase uropathogenicity. The bacterial fimbriae mediate bacterial adherence to uroepithelial cells and agglutinate red blood cells. Red blood cell agglutinating characteristics of *E. coli,* called hemagglutination, are blocked by different sugars (Duguid et al, 1978; Svanborg Edén and Hanson, 1978). Using this characteristic, Källenius and associates (1981) discovered that pyelonephritic *E. coli* cause mannose-resistant hemagglutination (MRHA) of human red blood cells. The terminal glycolipid of the human red cell P blood group antigen is a receptor that binds the P fimbriae on these *E. coli*. Therefore **two important markers for *E. coli* virulence are MRHA characteristics and P blood group–specific adhesins** (P fimbriae or P pili) (Källenius et al, 1981; Väisänen et al, 1981).

Most *E. coli* strains causing pediatric clinical pyelonephritis have both MRHA and P fimbriae (MRHA 91% [29/32], P fimbriae 81%) (Väisänen et al, 1981). P fimbriae are absent on less virulent strains. Källenius and associates (1981) found P fimbriae on 94% (33/35) of *E. coli* causing acute pyelonephritis, 19% (5/26) of *E. coli* causing acute cystitis, 14% (5/36) of *E. coli* causing asymptomatic bacteriuria, and on 7% (6/82) of *E. coli* from the feces of healthy children.

Two virulence factors appear to subvert the urinary tract immune system: one found in UPEC strains that acts by inhibiting Toll-like receptor (TLR) signaling (Cirl et al, 2008) and another that is a secreted autotransporter toxin (serine protease

autotransporter) that damages tight junctions in epithelial cells (Guignot et al, 2007).

Other less well-characterized virulence factors are hydrophobic *E. coli* properties and the iron-binding capability of the bacteria associated with aerobactin production (Jacobson et al, 1988, 1989b). Genes with three specific uropathogenic proteins (USP, a *Vibrio cholerae* zot gene homologue; IrgA homologue adhesin Iha, a nonhemagglutinating adhesin; IroN(*E. coli*), a catechole siderophore receptor homologue) are associated with factors that cause UTI and pyelonephritis (Bauer et al, 2002).

Organisms that cause covert or asymptomatic UTI may lack such virulence characteristics, be self-agglutinating, and lack fimbriae.

PATHOGENESIS OF URINARY TRACT INFECTION IN CHILDREN

The natural course of UTI in children is unpredictable. Although risk factors and bacterial virulence influence this course, these factors alone are unhelpful in predicting who gets pyelonephritis, renal scarring, or parenchymal and functional loss from a single or recurrent UTI. Of the 3% of girls and 1% of boys who get a prepubertal UTI (Winberg et al, 1974), 17% or more will get infection-related renal scarring. Of those with scarring, 10% to 20% may become hypertensive, and only a rare child acquires progressive renal dysfunction culminating in end-stage renal disease. The course of UTI in adults and children differs, and studies on UTI in children are reported without regard for age and other child-specific factors (Shortliffe and McCue, 2002). For this reason, much of the course of pediatric UTI remains elusive.

Cystitis and Pyelonephritis

The bladder's normal lack of susceptibility to bacteria is a complex interplay between bacterial virulence factors and the innate immune responses at the level of the uroepithelial cell. Because adaptive immune systems are incapable of immediate response to continual bacterial challenge at the urethral portal of entry, the initial response must be innate and reflexive for the host who is at times sitting in fecal microbiota (i.e., diapers). For this reason, the role of the fecal flora and human microbiome transitions—for reasons of diet, geography, pharmacotherapy, or epidemic and endemic contacts—must not be underestimated (Hällgren et al, 2005; Manges et al, 2008; Moreno et al, 2008; Smith et al, 2008) (Fig. 116–2).

Bacterial genetic clonal studies confirm that entry into the urinary tract occurs through the suspected fecal-perineal-urethral route with subsequent retrograde ascent of periurethral bacteria (Kaijser and Larsson, 1982; Tullus et al, 1984; Mitsumori et al, 1997; Yamamoto et al, 1997). Bacteria overcome urethral defenses of urethral washout, epithelial shedding, and paraurethral glandular secretion, all of which vary by gender, age, and individual, causing variable likelihood for bacterial ascent and establishment of UTI (Kunin, 2002). At the molecular level, **microbial polysaccharides may**

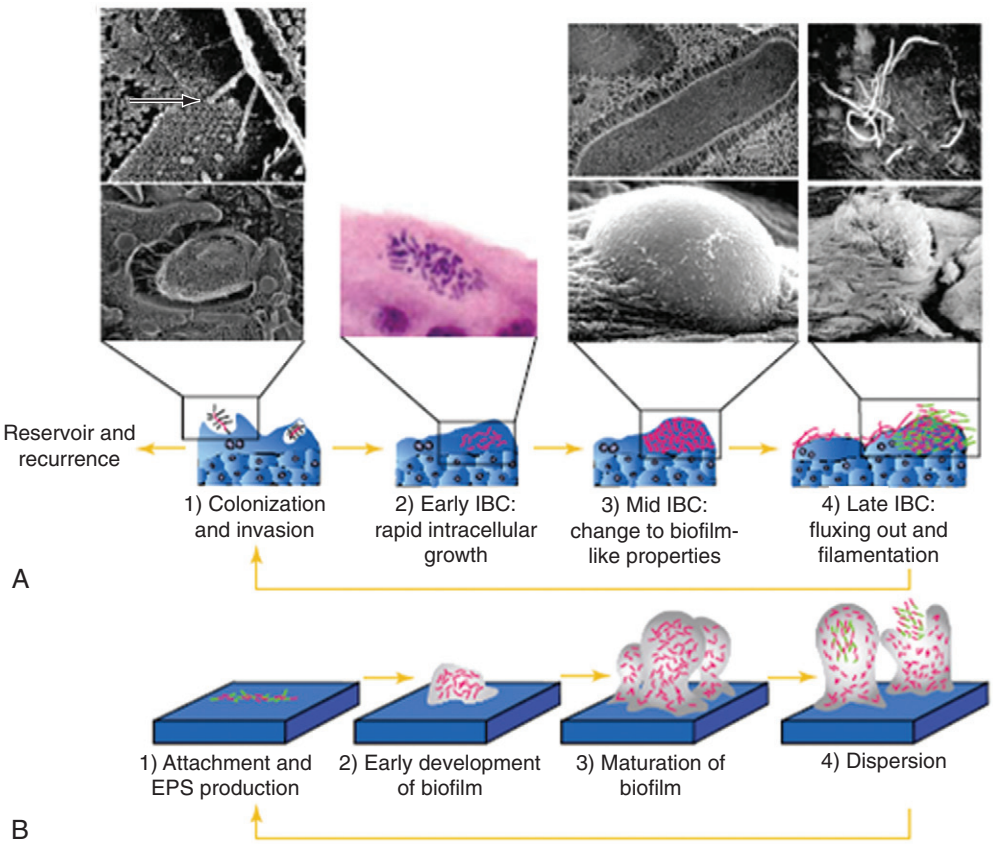


Figure 116–2. **A,** The stages of bacterial invasion of uropathogenic *Escherichia coli* attaching to uroepithelial cell and subsequent formation of pod and dispersion. **B,** The similar stages compared with previously known biofilm formation on inert surfaces such as urethral catheters. EPS, extracellular polymeric substances; IBC, intracellular bacterial communities. (From Kau A, Hunstad D, Hultgren SJ. Interaction of uropathogenic *Escherichia coli* with host uroepithelium. Curr Opin Microbiol 2005;8:54; Fig. 2.)

trigger urothelial receptors (Toll-like receptors) that activate the local immune system (Akira and Takeda, 2004). Tamm-Horsfall protein (THP) a common urinary protein, moreover, adheres specifically to type 1 fimbriated uropathogenic *E. coli* to participate in the host defense by helping to wash out bacteria during voiding (Bates et al, 2004; Raffi et al, 2005; Säemann et al, 2005) and may decrease inflammation during injury (El-Achkar et al, 2008).

Rodent and murine models have revealed the potential bacterial and uroepithelial interactions through which UTI occurs, and the models explain a new paradigm for acute and recurrent UTI. Superficial bladder umbrella cells are unique slow-cycling cells that renew only every few months. These cells contain special two-dimensional hexagonal crystals of 16-nm uroplakin particles that normally allow these superficial cells to flatten, expand, and allow normal bladder surface activity (Kong et al, 2004). A genetically altered uroplakin-deficient mouse has major urinary tract abnormalities.

Although the **initial event in infection is attachment between the uroepithelial cell and bacteria through factors such as type 1 pili and P fimbriae, this attachment initiates a molecular interaction in which the adhesin-receptor complexes trigger a series of events that causes uptake of the bacteria into the bladder surface umbrella cells** (Kau et al, 2005). In response, the host response rapidly sheds the uroepithelial cells (Mulvey et al, 1998). The bacteria then enter the bladder epithelial cells, interacting with lipid rafts and uroplakins and forming intracellular bacterial communities. These bacterial communities develop, and the organisms transform into an organized biofilm and have a more coccoid form. As these communities enlarge, they form cellular "pods" that protrude from the surface and may detach. These may then retransform into their rodlike motile form and disseminate through the urinary tract (Anderson et al, 2003). The intracellular bacterial "pod" may defend bacteria from normal host cellular immune and antimicrobial effects (Justice et al, 2004). **These biofilms appear to allow microbial adaption to variable environments and then allow aggregate detachment that will cause systemic infection, antimicrobial resistance through plasmid exchange, endotoxin production, and overall increased resistance to host immune systems** (Donlan, 2002). Simultaneously, however, the bacteria also attach to uroepithelial cell receptors (Toll-like receptors) and initiate a dramatic immune response with release and activation of proinflammatory cytokines and chemokines (IL-1, IL-6, IL-8) that signal and direct neutrophil transmigration across the epithelial barrier and into the urinary tract lumen, creating the clinical symptoms and signs of bladder and urinary tract infection. The balance between these processes determines whether UTI occurs.

Once bacteria are in the bladder, host immunity, impaired ureteral peristalsis, vesicoureteral reflux, and the specific organism uropathogenicity affect possible retrograde ascent. Under normal circumstances, nonspecific mechanisms, such as cytokine release, may play a role (Davidoff et al, 1997).

Although hematogenous dissemination of bacteria may occur, this appears to be relatively uncommon and may primarily involve infants with incompletely developed immunity, staphylococcal skin or systemic infections with organism dissemination, or systemic infection, such as tuberculosis. In these situations, renal, perirenal, or epididymal abscesses can occur.

Pyelonephritis is important because of the clinical severity of the illness and the potential renal damage that may occur. Bacterial infection of the urinary tract also causes bladder and ureteral inflammation with tissue changes that alter dynamics of the entire urinary tract (Hinman, 1971; Boyarsky and Labay, 1972; Issa and Shortliffe, 1992; Johnson et al, 1992). Animal studies have shown that UTI causes abnormally elevated renal pelvic pressures even if (or especially if) vesicoureteral reflux is absent (Issa and Shortliffe, 1992; Angell et al, 1998), thus giving increased pressure and poor smooth muscle compliance as a further explanation for ureteral dilation observed in patients with acute pyelonephritis and otherwise normal upper collecting systems (Mårild et al, 1989).

Determining the point of clinical progression from cystitis to pyelonephritis or differentiating between these entities is impossible, because simple techniques with which to localize the level and extent of urinary tract bacteria are lacking. Although ureteral catheterization with sequential cultures is the gold standard for localizing upper and lower tract bacteria, this requires cystoscopy and is an impractical invasive way of following the course of infection (Stamey, 1980). Moreover, localizing the site of bacteria does not show the extent of renal inflammation. The Fairley bladder washout localization technique requires urethral catheterization during acute infection and subsequent bladder irrigation and washing with sterile water to localize bacteria to bladder (found in the first bladder culture) or above the bladder (found in cultures taken after the washing). **Clinical symptoms correlate poorly with the results of localization studies using the Fairley or ureteral catheterization techniques. In one study comparing clinical symptoms with Fairley results, fewer than half the patients (mainly children) with fever and flank pain had upper tract bacteria (34/73) on Fairley test, and almost 20% (83/473) who were asymptomatic had upper tract bacteria** (Busch and Huland, 1984).

Key Points: Urinary Tract Infection Pathogenesis

- The first year of life is the only year during which males have more UTIs than females.
- Each year about 50 per 100,000 children are hospitalized for UTI; the rate is greater than 3 times this number in infants (children younger than 3 months).
- In children, discovering surgically correctable sources of bacterial persistence is important.
- Bacterial pili or fimbriae increase uropathogenicity.
- Approximately 17% or more of children who have pyelonephritis acquire renal scarring.
- Clinical symptoms correlate poorly with bacterial localization within the urinary tract.
- Bacterial clonal studies confirm the fecal-perineal-urethral retrograde ascent of periurethral bacteria causing UTI.
- Microbial lipopolysaccharides may trigger urothelial receptors (Toll-like receptors) to activate the innate local immune system—cytokines, chemokines, and neutrophils.
- Intracellular bacterial biofilms allow microbial adaption to variable environments and allow aggregate detachment causing systemic infection in a way that increases bacterial resistance to the host immune system.

Risk Factors for Bacteriuria and Renal Damage

Although we are unable to alter bacterial pathogenicity at this time, it is worth reviewing characteristics that alter risk of UTI

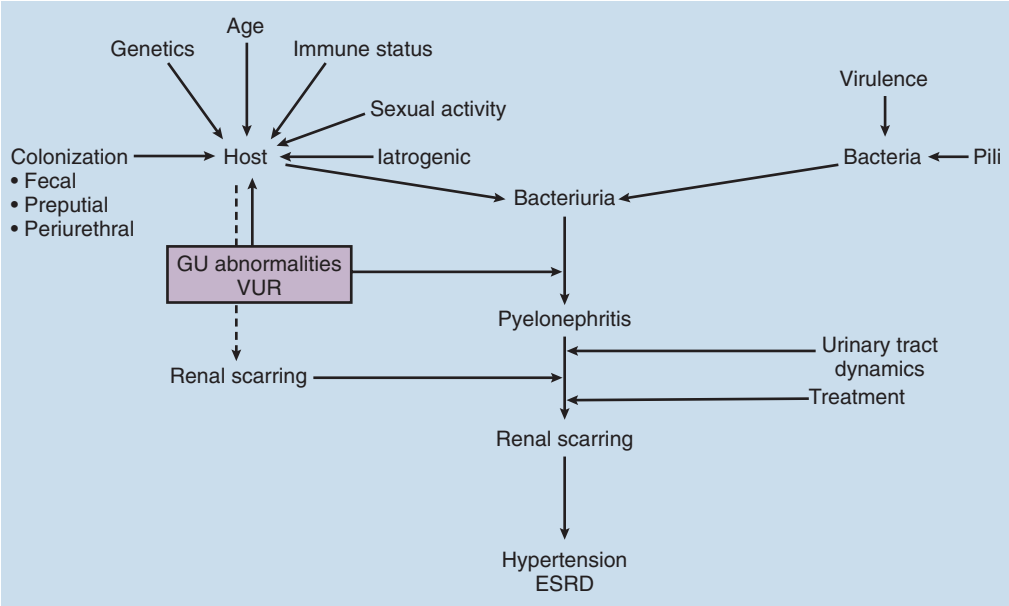


Figure 116–3. Factors that affect the development of bacteriuria and subsequent pyelonephritis, renal scarring, hypertension, and end-stage renal disease (ESRD). Urinary tract urodynamics reflect urinary tract pressures and related factors. GU, genitourinary; VUR, vesicoureteral reflux.

and renal damage and that may be therapeutically altered (Fig. 116–3).

Age

The prevalence of UTI is age dependent. **Bacteriuria is more common at the extremes of life—in neonates and the elderly** (Shortliffe and McCue, 2002). As already discussed, the prevalence of UTI for both males and females younger than 1 year is higher than at other times during childhood. There may be many factors causing this age-dependent relationship, some of which involve interactions with other host factors, such as periurethral colonization, breast-feeding, or immature immune status. Although none of these factors appears to be independent, the importance of the various factors may be age related. Others have discussed major factors creating risk for UTI in females, for instance, sexual intercourse, contraceptive usage (diaphragm/spermicidal), antimicrobial usage, previous history of UTI, estrogen status, and postvoid residual (Stamm and Raz, 1999). The degree to which these factors contribute is more or less dependent upon the subject's age and previous history.

Genetics

Multiple host genetic factors that affect risk have been identified. Individuals who have childhood UTI continue to be at risk for adult UTI whether or not they have vesicoureteral reflux (Beetz et al, 2002). Obviously, issues related to gender, race, or ethnicity have specific genetic links and will be discussed separately.

Both alteration of bacterial–uroepithelial attachment related to bacterial virulence, which depends upon microorganism specificity, and alteration of the host immune response affect periurethral colonization. Children who originally had primary vesicoureteral reflux that resolved are commonly still susceptible to recurrent UTI, although symptoms are confined to the lower tract (Mansfield et al, 1995; Beetz et al, 2002). Clinical histories support a familial risk for UTI. On screening, sisters of girls who have recurrent UTI have a higher incidence of significant bacteriuria cultures than expected for the normal population (Fennell et al, 1977; Stauffer et al, 2004). **Notably, two distinct risks for recurrent UTI in young women (age 18 to 30 years) are age at first UTI (less than age 15 years; odds ratio [OR] = 3.9) and UTI in the mother (OR = 2.3)** (Scholes et al, 2000). The possible genetic relationship of renal scarring and UTI is discussed in the section Renal Scarring.

In the early 1980s, when bacterial P fimbriae were identified as a virulence factor, glycolipids characterizing the P blood group antigens were found on host uroepithelial cells and found to act as bacterial receptors. Because hosts with these receptors (i.e., P blood group phenotype) were suspected to have increased susceptibility for infection, children with recurrent infections were tested for this P blood group phenotype. **The P1 blood group phenotype was found in 97% (35/36) of girls with recurrent pyelonephritis with minimal (grade I) or no reflux** and was found in 75% (63/84) of controls without UTI (Lomberg et al, 1983). They found, moreover, that bacteria binding to glycolipid receptors (bacteria with P fimbriae) were more likely to be found in the girls with the P1 blood group without reflux than in those with the P1 blood group having reflux, suggesting that vesicoureteral reflux is more likely to contribute to ascent of the bacteria once UTI occurs than would the UTI itself.

Other blood group antigens on the urothelial surface (ABO, Lewis, and secretor phenotypes) influence UTI susceptibility. Adult women with Le (a–b–) and Le (a+b–) blood phenotypes are 3 times more likely to have a recurrent UTI than Le (a–b+) women, and epithelial cells from nonsecretors have more bacterial receptors than cells from secretors (Sheinfeld et al, 1989). Similarly, in children with UTI, the frequency of Le (a–b–) phenotype is higher, and the relative risk of infection in these children is 3.2 (Jantausch et al, 1994). Analysis of children with various anatomic abnormalities (e.g., ureteropelvic junction obstruction, vesicoureteral reflux, ureteroceles, and primary obstructive lesions) suggests that children with these abnormalities and a presumed nonsecretor phenotype (minimal or undetectable ABO and Le^b immunoreactivity) are more likely to have had a history of UTI (16/17, 94.1%) (Sheinfeld et al, 1989, 1990). More

recently, the nonsecretor status of ABH blood type antigens (ABH Ag) was found to be associated with ^{99m}Tc-dimercaptosuccinic acid (DMSA)–defined focal renal scarring in children with vesicoureteral reflux (Kanematsu et al, 2005).

Predisposition for pyelonephritis correlates with decreased expression of IL-8 receptors (CXCR1) on peripheral neutrophils (Frendéus et al, 2001; Lundstedt et al, 2007; Ragnarsdóttir et al, 2008) **and polymorphisms of cytokine interleukin-8 (IL-8) regardless of vesicoureteral reflux status** (Artifoni et al, 2007). Genetic polymorphisms, such as of intercellular adhesion molecule-1 (ICAM-1), which modulates the inflammatory infiltration into the surrounding tissues (Gbadegesin et al, 2006), and of transforming growth factor-β1 (TGF-β1) (Yim et al, 2007), which may affect other parts of the inflammatory and scarring process, are also associated with children who develop UTI-associated renal scarring. Other, separate gene polymorphisms of TLR correlate with UTI (TLR2 with both symptomatic and asymptomatic UTI [Tabel et al, 2007]; TLR4 with UTI and asymptomatic UTI [Karoly et al, 2007; Ragnarsdöttir et al, 2007] and vascular endothelial growth factor [VEGF] [Yim et al, 2007]).

In summary, it appears that **host genes separate from those associated with vesicoureteral reflux increase urinary tract susceptibility to infection and/or to pyelonephritis and renal scarring**. Further investigation should improve our identification of these individuals.

Gender

As discussed earlier, the ratio of UTI by sex in the white population shows a preponderance of UTI in boys during the first year of life, but, thereafter, more girls than boys have UTI. Although many factors, including urethral length, prostate, hormones, and foreskin, are hypothesized to account for this finding, the complete explanation is unclear.

Race and Ethnicity

Although UTIs occur in all races, epidemiologic studies show varying prevalence and complications of UTIs in different races. These factors are incompletely studied. In one comparative study of children less than 2 years old, including white, Hispanic, and African-American children, UTIs were most prevalent in white, then Hispanic, and finally African-American girls, but, in boys, UTIs were most common in Hispanic, white, and African-American boys, in that order. Circumcision status confounds these data (Bachur and Harper, 2001a, 2001b). **Several studies show that African-Americans have fewer UTIs, lower incidence of vesicoureteral reflux, and perhaps less likelihood of reflux nephropathy than Hispanics or whites** (Kunin and McCormack, 1968; Kunin, 1970; Lohr et al, 1994; Hoberman and Wald, 1997; Pinto, 2004). Interestingly, it has been reported that in Chinese children, UTI, vesicoureteral reflux (VUR), and renal scarring are more common in boys than girls; however, the ages are unreported, and these findings could be confounded by age and circumcision status (Howard et al, 2001; Williams et al, 2001a).

Renal Scarring

Renal scarring correlates with later UTI complications, such as hypertension, renal insufficiency, progressive renal scarring, and renal functional deterioration (Berg, 1992). **Clinical studies that examine the association of recurrent bacteriuria and new renal scarring or progressive renal scarring** support the notion that **renal scarring begets renal scarring** (Newcastle Asymptomatic Bacteriuria Research Group, 1975; Savage, 1975; Cardiff-Oxford Bacteriuria Study Group, 1978; Newcastle Covert Bacteriuria Research Group, 1981). Long-term follow-up has also shown that kidneys that were initially normal after UTI tend to remain normal, while those that were initially scarred appear to be more likely to suffer subsequent damage (Smellie, 1991; Smellie et al, 1998).

Angiotensin-converting enzyme (ACE) gene polymorphisms that are associated with increased renin-angiotensin activity are implicated in renal scarring. Increased DD genotype polymorphism is associated with increased risk of progressive renal failure in IgA nephropathy, diabetic nephropathy, autosomal-dominant polycystic kidney disease, focal glomerulosclerosis, and in children with congenital urologic abnormalities who have evidence of renal parenchymal damage and reflux nephropathy (Brock et al, 1997, 1998; Ozen et al, 1999). Genetic polymorphisms that relate to the immune response, such as those of ICAM-1, which modulates the inflammatory infiltration into the surrounding tissues (Gbadegesin et al, 2006), and of TGF-β1, which may affect other parts of the inflammatory and scarring process (Yim et al, 2007), are associated with children who develop UTI-associated renal scarring.

A systematic review and meta-analysis concluded that **primary vesicoureteral reflux is a weak predictor of renal scarring in children *hospitalized* with UTI** (Gordon et al, 2003). Using a definition of UTI as fever, positive urinary culture, and a DMSA scan showing photopenia during acute illness, another meta-analysis concluded that the rate of renal scarring after acute pyelonephritis is 36% to 41.6%, and those children with VUR have a 2.8 times greater risk of renal scarring (Faust et al, 2009). Although both meta-analyses found that children with VUR were more likely to have scarring than those without, the severity of illness differed and might account for the differing conclusions.

Colonization

Periurethral Colonization

The incidence of UTI in infants is higher during their first few weeks to months of life than at any subsequent time in the next few years. During this time, the periurethral area of healthy girls and boys is colonized massively with aerobic bacteria (especially *E. coli,* enterococci, and staphylococci) (Bollgren and Winberg, 1976b). This colonization decreases during the first year and is unusual in children who do not get recurrent infections after age 5 years. After this period, only those women and children who suffer repeated UTI remain more colonized by periurethral gram-negative bacteria than those who do not get infections (Stamey and Sexton, 1975; Bollgren and Winberg, 1976a, 1976b). Times and conditions of increased periurethral colonization are therefore associated with increased risk of UTI.

Preputial Skin

During the first few months of life, foreskin, periurethral, and preputial bacterial colonization and UTI appear to correlate. This association between the foreskin and neonatal UTI has caused controversy regarding the advantages and disadvantages of circumcision (Hallett et al, 1976). This has resulted in numerous editorials and recommendations by the American Academy of Pediatrics (King, 1982; Cunningham, 1986; Roberts, 1986; Lohr, 1989; Schoen et al, 1989; Winberg et al, 1989; Poland, 1990; Schoen, 1990; American Academy of Pediatrics [Task Force on Circumcision], 1999b), and more recently, the controversy has expanded to include sexually transmitted infection.

In a group of mainly uncircumcised normal boys, Bollgren and Winberg (1976b) documented that preputial aerobic bacterial colonization is highest during the first months after birth, decreases after 6 months, and is uncommon after age 5 years. Subsequently, Wiswell and associates (1988) **compared the periurethral bacterial flora (using intraurethral and glanular cultures) during the first year of life in circumcised and uncircumcised boys and found that, for the first 6 months, periurethral uropathogenic organisms were cultured more frequently from the uncircumcised than circumcised boys.** They and others concluded that the foreskin is responsible for this finding (Hallett et al, 1976; Glennon et al, 1988; Wiswell et al, 1988).

Although the reasons for neonatal bacterial colonization of the foreskin are multifactorial, including immature immune status, unusual nosocomial colonization, breast-feeding (Winberg et al, 1989), and other characteristics mediating bacterial adherence (Fussell et al, 1988), this high colonization is associated with a greater number of neonatal UTIs. In a series of retrospective reviews of 55 worldwide U.S. Army hospitals, Wiswell and Roscelli (1986) examined the incidence of UTI diagnosed by catheterization or suprapubic aspirate in male infants hospitalized during 1974 to 1983. **They found that the incidence of infections in circumcised male infants was 0.11% (193/175,317); that in uncircumcised infants was 1.12% (468/41,799); and that in female infants was 0.57%** (1164/205,212). Because these numbers are from hospitalized children in Hawaii, they may underestimate UTI; others report higher overall incidence of UTI in infant boys of 2.2% to 4.1%, with the majority (70% to 86%) occurring in uncircumcised infants (Wiswell et al, 1985; Schoen et al, 2000; Wiswell, 2000).

Uncircumcised male infants, moreover, have an increased relative risk of UTI of 3.12 when compared with circumcised boys, but this risk decreases from 3.7 at age 1 year to 3.0 at age 3 years (Wiswell and Hachey, 1993; To et al, 1998; Wiswell, 2000). The majority of infections occurred during the first 3 months of life. When the UTI incidence of the first and the final years of the study are compared, the total number of UTIs increased as the circumcision rate decreased, leading Wiswell to conclude that UTIs are more frequent in uncircumcised boys (Wiswell and Roscelli, 1986; Wiswell et al, 1987).

Using case-control methodology, circumcised boys in a population with a high rate of uncircumcised boys (Australia) were compared with a population of circumcised boys. Craig and associates (1996) concluded that circumcision was still associated with a lower rate of UTI before and past the first year of life. Although there may be difficulties with these data related to retrospective analysis and selection bias, periurethral colonization is associated with increased risk of UTI in girls and women also.

Others found no difference in pre- and postoperative rates of UTI **whether or not circumcision is performed at the time of ureteroneocystotomies** (Kwak et al, 2004). At this time, there is no way of predicting whether a male infant with a normal urinary tract who gets a UTI has a genetic or familial predisposition for infection. Because few infant boys who suffer a neonatal UTI risk a recurrent UTI after 1 year if they remain UTI free in the interim, prophylactic antibiotics for 6 months may be helpful in these boys.

There is some evidence that circumcision in hospitalized (neonatal intensive care) premature boys may decrease risk of recurrent UTI during the neonatal period (Cason et al, 2000). UTI treatment in uncircumcised infant boys also tends to be more expensive to treat, because these children are more likely to be hospitalized, especially during the first 3 months of life (Schoen et al, 2000). The cause for this is unknown, but it is reported that the organisms involved in these uncircumcised boys are more virulent and appear more similar to the strains causing pyelonephritis and urosepsis in adults (Bonacorsi et al, 2005). After meta-analysis, one group has calculated that circumcision decreases risk of UTI with an odds ratio of 0.13, yet UTI is rare enough in boys and common circumcision complications high enough so that only boys having recurrent UTI or high risk for recurrent UTI may benefit from circumcision (Singh-Grewal et al, 2005).

Although a full discussion of sexually transmitted infections (STI) are beyond the scope of this chapter, recent literature focuses upon a relationship between STI and circumcision status. A systematic meta-analysis of literature evaluating studies that examine sexually transmitted urethritis and genitourinary ulcerative diseases concluded that circumcised males may be more likely to acquire urethral STI (primarily *Chlamydia*), whereas uncircumcised males may be more likely to acquire ulcerative diseases (primarily chancroid) without a difference between rates of gonococcal infection (Van Howe, 2007). As might be expected, however, interstudy diversity makes definitive conclusions difficult. Other recent studies suggest that specific groups of circumcised males have lower rates of human papilloma viral penile and urethral infection and reduced HIV prevalence, but again, the conclusions relate to special populations and may not be generalizable (Auvert et al, 2009; Nielson et al, 2009; Sobngwi-Tambekou et al, 2009; Warner et al, 2009).

Current data do not support routine neonatal circumcision for UTI prevention in neonates or children, although some evidence exists that boys with recurrent UTI may benefit (American Academy of Pediatrics [Task Force on Circumcision], 1999b; Singh-Grewal et al, 2005). Although there appears to be evidence that specific STI may be increased in specific populations, STI (e.g., *Chlamydia,* gonorrhea, syphilis, nonspecific urethritis, genital herpes or warts) rates, when adjusted for socioeconomic status and sexual behavior, show no significant difference based on neonatal circumcision status in developed countries (Dickson et al, 2008). Opinions on this differ (Thiruchelvam and Cuckow, 2005). Some reports document slightly higher UTI incidence following ritual circumcision, which may reflect surgical technique (Liora et al, 2002).

Fecal Colonization

Because most UTIs result from fecal-perineal-urethral ascent of bacteria, fecal colonization is an important consideration. The human fecal flora is dependent upon the surrounding microbial ecology, native immunity, and microbial-altering drugs and foods. Studies showing that fecal colonization with specific pyelonephritic bacteria may occur in a neonatal nursery or hospital, with subsequent bacteriuria or pyelonephritis occurring several months later, emphasizing the importance of abnormal fecal colonization (Tullus et al, 1986). **Bacterial clonal studies also associate fecal and urinary bacteria with community outbreaks** (Manges et al, 2006, 2008; Smith et al, 2008) and show household members may share rectal flora (Johnson et al, 2008a).

The creation and selection of resistant organisms in the gut by antimicrobial usage is well recognized. **Because the fecal flora is commonly responsible for perineal and periurethral colonization, the importance of responsible antimicrobial usage should not be underestimated.** In one study, antibiotic treatment of school girls with phenoxymethylpenicillin

for intercurrent nonbladder infections, usually otitis media, caused colonization and bacteriuria with strains more likely to be symptomatic (Hansson et al, 1989b).

Immune Status and Infancy

Compromised native immunity is associated with increased risk of infection. In children, the immune status varies with normal development, with transmission either natural or acquired (e.g., vaccination, breast-feeding, illness), and with congenital or acquired immunodeficiencies. UTIs are common in infants and children with immature immune systems. For instance, serum IgG is lowest from age 1 to 3 months (Robbins, 1972) when periurethral colonization is high in normal children. Secretory IgA is an important human immunoglobulin at the secretory and mucosal surface, and it is transferred to the newborn in colostrum if the child is breast-fed. Serum IgA is found in diminished concentrations for the first several months and is either absent or almost absent at the secretory surfaces of the nasopharynx, gut, and urothelium during this period (Svanborg Edén et al, 1985; Fliedner et al, 1986; Yoder and Polin, 1986) and undetectable in the urine at birth. Urinary secretory IgA and total IgA increase during the first year and are higher in children who are breast-fed (James-Ellison et al, 1997). The role that urinary IgA plays in childhood UTI has not been investigated extensively. In children with acute UTI or pyelonephritis, urinary excretion of IgA is higher than in those without UTI, yet levels are exceeded in normal adults (Svanborg Edén et al, 1985; James-Ellison et al, 1997).

Urinary IgA in infants, moreover, is in the monomeric rather than the secretory form normally found in adults, suggesting that urinary IgA in infants may be systemic immunoglobulin excreted as a result of infection-related tubular dysfunction rather than secretory. Children with recurrent UTI have lower urinary secretory IgA concentrations than those without (Fliedner et al, 1986). The benefits of breast milk are unclear (Hanson, 1998; Committee on Breast Feeding, 2005). **Case-control studies suggest that breast-feeding confers a protective effect against UTI during the first 6 months of life.** These studies show the duration of breast-feeding is shorter in children who have UTI (9 vs. 16 weeks in children who had exclusive breast-feeding) (Mårild et al, 1989), but that full or partial breast-feeding may confer a protective effect against UTI for the first 6 months of life (Pisacane et al, 1990, 1992). Although the mechanism of the protection is unknown, the oligosaccharide content of the mother's breast milk and urine are the same as in the breast-fed infant. Some hypothesize that the oligosaccharides inhibit the adherence of pathogenic *E. coli* to the uroepithelium (Coppa et al, 1990). Other **studies show that exclusive breast-feeding for 4 or more months protects against single or recurrent otitis media in children** or infants with cleft palate (Duncan et al, 1993; Paradise et al, 1994).

As expected, children with specific immune deficiency syndromes have altered immunity and commonly have an increased risk of infection and its dissemination. About 20% of human immunodeficiency virus (HIV)-infected children have bacterial UTI with both common and opportunistic organisms (Grattan-Smith et al, 1992), and others have associated UTI and HIV; specifically, in HIV-seropositive women, UTI was associated with high viral load (OR = 1.82) (Park et al, 2002). Specific deficiencies of the immune response associated with genetic polymorphisms that involve the TLR and cytokine-associated responses are discussed in the section Genetics.

Sexual Activity

Epidemiologic studies show that sexual activity is a risk factor for UTI. Sexually active females have more UTIs than inactive females (e.g., nuns) (Kunin and McCormack, 1968). This association has caused some to suggest that **UTI is a marker for teenage sexual activity** (Nguyen and Weir, 2002). Whether this relationship stems from colonization or other factors is unclear.

Genitourinary Anatomic Abnormalities

UTI has been a marker for pediatric genitourinary tract anatomic abnormalities; hence, the reason UTI evaluation consists of imaging. This maxim was reaffirmed when investigators followed children with prenatally detected renal pelvic dilation of 5 mm or greater at 28 weeks' gestation, and found the children had increased risk of UTI (Coelho et al, 2008). Genitourinary abnormalities, in particular, nonfunctioning segments can serve as niduses of infection causing bacterial persistence because of renal inability to achieve urinary antimicrobial concentrations adequate to eradicate bacteria in these segments. Similarly, genitourinary partial obstruction or renal functional impairment may create increased risk of renal damage because of poor or inadequate antimicrobial penetration. A sequela of chronic UTI and inflammation, xanthogranulomatous pyelonephritis, may also occur in children with obstruction and UTI in renal segments (Stamey et al, 1977; Zafaranloo et al, 1990; Cousins et al, 1994; Hammadeh et al, 1994).

Vesicoureteral Reflux

Vesicoureteral reflux is discussed in Chapter 122. Reflux is common in children with UTI, but no correlation between reflux and susceptibility to UTI is evident (Winberg et al, 1974). At least one group has shown no difference in occurrence of recurrent UTI between children who have reflux and those who do not (Garin et al, 2006). Surveys show that 21% to 57% of children who have bacteriuria have vesicoureteral reflux when evaluated (Kunin et al, 1964; Abbott, 1972; Asscher et al, 1973; Newcastle Asymptomatic Bacteriuria Research Group, 1975). Although vesicoureteral reflux raises risk of pyelonephritis associated with bacteriuria, it correlates poorly with UTI-induced renal scarring (Gordon et al, 2003).

Peripubertal Girls with Persistent Vesicoureteral Reflux (Pregnancy)

The question of whether girls approaching puberty who have persistent vesicoureteral reflux should have their reflux corrected because of the potential for future pregnancy is problematic. If primary vesicoureteral reflux persists as a girl approaches puberty, it becomes statistically less likely each year to resolve spontaneously. For this reason, some advocate that all girls approaching puberty undergo correction of reflux to avoid the risks of pyelonephritis during future pregnancies. Whether a female with persistent vesicoureteral reflux who has never had a UTI and demonstrates no increased susceptibility for UTI should undergo routine correction of reflux is controversial; moreover, whether a female with persistent vesicoureteral reflux who has demonstrated increased susceptibility for UTI should undergo correction is also controversial. Although the prevalence of bacteriuria in pregnant women is the same as in nonpregnant women (Shortliffe and Stamey, 1986b; Shortliffe, 1991), **the likelihood that bacteriuria may progress to pyelonephritis is greatly increased. Thirteen and a half to 65 percent of pregnant women who are bacteriuric on a screening urinary culture will develop subsequent pyelonephritis during pregnancy if**

untreated (Sweet, 1977), **whereas pyelonephritis is rarely the consequence of uncomplicated cystitis in a nonpregnant woman.**

The reasons for this increased likelihood of pyelonephritis during pregnancy are unknown, but they may relate to hormonal and hydrodynamic changes of pregnancy. There is increased bladder and urinary tract compliance and bladder enlargement, and an enlarging uterus may cause anatomic displacement of the bladder and ureters (Hsia and Shortliffe, 1995). There are no data to suggest that pregnancy causes vesicoureteral reflux (Shortliffe and Stamey, 1986b). When 321 women had a single-film voiding cystourethrogram during the third trimester of pregnancy or immediately postpartum, only 9 (2.8%) had vesicoureteral reflux (Heidrick et al, 1967). Although 6.2% (20/321) of these women had asymptomatic bacteriuria, only 1 of these 20 women had vesicoureteral reflux. Therefore in contrast to the pediatric situation, few pregnant women who develop pyelonephritis have reflux. Of the 9 women who had reflux, 3 developed pyelonephritis during a pregnancy.

In another series, 21 of 100 pregnant women (27 refluxing renal units in 21 patients) with asymptomatic bacteriuria evaluated postpartum had vesicoureteral reflux, mostly of low grade (67% into the ureter only), and 17% of these women had renal scarring (Williams et al, 1968). Although some use these data to justify correction of all pubertal reflux in girls, this renal scarring is unlikely to be the result of UTI during pregnancy. This rate of scarring is similar to that found in children with screening bacteriuria and renal scarring (Asscher et al, 1973; Newcastle Asymptomatic Bacteriuria Research Group, 1975; Savage, 1975). Because these women had no imaging before pregnancy, it is most likely that any renal scarring found post partum was present beforehand and occurred in childhood.

These data suggest that postpubertal females who have vesicoureteral reflux and a predisposition for frequent urinary tract infections will continue to have this predisposition for infections into adulthood and pregnancy. Moreover, those women who were susceptible to UTI before pregnancy will continue to be more likely to develop UTI during and after pregnancy, whether or not they have vesicoureteral reflux (Mansfield et al, 1995; Bukowski et al, 1998; Beetz et al, 2002).

Even though correction of vesicoureteral reflux, spontaneously or by intervention, may decrease the likelihood of developing ascending pyelonephritis from bladder bacteriuria under normal circumstances, during pregnancy the nonrefluxing orifice does not appear to offer the expected protection from pyelonephritis. Unless a surgically corrected ureterovesical junction better protects the kidney against the pyelonephritis of pregnancy than nature's normal nonrefluxing ureteral junction does, intervention cannot be justified. Therefore both persistent reflux and a patient's susceptibility to UTI should be assessed before surgical correction of reflux. **If vesicoureteral reflux is corrected in a girl with recurrent UTI, these females should be told that pyelonephritis during pregnancy is still possible. When these females become pregnant, bacteriuria screening is essential.**

Pregnant Women with Renal Insufficiency

When a practitioner counsels a woman with known reflux nephropathy and renal insufficiency about pregnancy, renal function needs evaluation. With physiologic pregnancy—renal hyperperfusion and resulting hyperfiltration—a blood urea nitrogen (BUN) greater than 14 mg/dL and serum creatinine greater than 0.9/dL may indicate pre-existing renal insufficiency (Vidaeff et al, 2008). **Though outcomes data for pregnancy are sparse, when there is moderate or severe renal insufficiency (moderate, initial serum creatinine, 1.4 to 2.4 mg/dL; severe, 2.5 mg/dL or greater), even though infant survival may be greater than 90%, maternal and obstetrical complications are high** (Bear, 1976; Davison and Lindheimer, 1978; Jones and Hayslett, 1996). In these high-risk women, 43% had a pregnancy-related deterioration in creatinine clearance of at least 25% that occurred during pregnancy (20%) or immediately postpartum (23%). In the majority, this pregnancy-related deterioration in renal function was irreversible (Epstein, 1996; Jones and Hayslett, 1996). This accelerated renal insufficiency was associated with increased hypertension and high-grade proteinuria. Almost 60% of these pregnancies ended in preterm delivery with cesarian section, and the majority of infants were below the 50th percentile in birth weight (Jones and Hayslett, 1996). **These data have been interpreted to indicate that when the serum creatinine exceeds 2.0 mg/dL in a pregnant woman, she has a 1 in 3 risk of progressing to end-stage renal disease either during or just after delivery** (Epstein, 1996).

The effect of a maternal UTI on the fetus has been controversial. Analyses of National Collaborative Perinatal Project (NCCP) data from the 1970s and Medicaid data from the 1990s (both representative of women of low socioeconomic status) show an association between third-trimester maternal UTI and fetal mental retardation or developmental delay; and NCPP data, furthermore, associates third-trimester UTI with increased chance of fetal death (McDermott et al, 2001). Others have documented infant low birth weight and prematurity (Naeye, 1979). **With mild to moderate renal insufficiency, fetal survival is only slightly diminished** (Vidaeff et al, 2008).

Neurogenic and Bowel-Augmented Bladders

Children who have neurogenic bladders with abnormally elevated bladder pressures risk increased renal damage. Risk of UTI is also increased secondary to increased instrumentation common with the neurogenic bladder (intermittent catheterization). Increased pressure within the neurogenic system combined with the physiologic effects of UTI that create increased pressure creates a greater likelihood for subsequent renal parenchymal damage (Hansen et al, 2003). Chronically or intermittently elevated bladder pressures may cause secondary vesicoureteral reflux from decompensation of the ureterovesical junction from the elevated pressure (Hutch, 1952). If this does not occur, the elevated bladder pressures associated with a neurogenic bladder may also cause effective ureterovesical obstruction. This obstruction increases the risk of renal damage associated with urinary tract infections (Cowan and Shortliffe, 1998), and as discussed earlier in this chapter, intermittent elevations in bladder pressure associated with physiologic bladder dynamics in the immature bladder may exacerbate the effects of vesicoureteral reflux and UTI.

When untreated, children with neurogenic bladders that empty or fill at abnormally high pressures will be more likely to risk the effects of UTI and renal damage, because of inability to spontaneously clear bacteria. Clean intermittent catheterization programs are useful for emptying the neurogenic bladder, but these

catheterizations introduce bacteria. **Although conclusions from previous studies involving clean intermittent catheterization in children are limited because they combined sexes, wide age ranges, different types of neurogenic bladders, short follow-up, different prophylactic regimens, and differing definitions of bacteriuria, they all agree that bacteriuria and even pyuria occurs in most children.**

Forty to 80 percent of the urinary specimens sampled had bacteriuria and/or pyuria (Taylor et al, 1985; de la Hunt et al, 1989; Joseph et al, 1989; Gribble and Puterman, 1993; Johnson et al, 1994; Schlager et al, 1995, 1998), and most were asymptomatic (Geraniotis et al, 1988; Joseph et al, 1989; Schlager et al, 1995). However, this catheter-associated asymptomatic bacteriuria appears to lack morbidity much of the time. Notably, even though a majority of these children have asymptomatic bacteriuria, most may undergo urodynamic studies without complications (Shekarriz et al, 1999).

Even though prophylactic antibiotics administered during clean intermittent catheterization may delay and possibly decrease bacteriuria in the short term (Johnson et al, 1994), long term there appears to be no proven efficacy and may cause increased microorganism resistance (Clarke et al, 2005). **Meta-analysis of data on the use of sterile versus nonsterile, single versus multiple use, and lubricated versus nonlubricated catheters document no benefits among the alternatives in reducing UTI** (Schlager et al 2001; Moore et al, 2007). **Thus neither sterile, single-use lubricated catheters nor antimicrobial prophylaxis is recommended for long-term bladder management.** The natural history of clean intermittent catheterization programs deserves further study.

Novel management for those with neurogenic bladders who acquire frequent symptomatic recurrent UTI is to induce asymptomatic UTI using previously identified strains from individuals with asymptomatic UTI (Trautner et al, 2008; Prasad et al, 2009). These studies are preliminary at this time.

Little investigation of the bacteriuria of bowel-augmented bladders exists. In a prospective study, those who have bladder substitution were found to have greater bacteriuria than those without, and there was a substantial local IgA antibody response to the resident bacteria and increased IgG response from the bladder or upper tracts (Iwakiri et al, 2002). Whether this local response contributes to asymptomatic UTI or is protective is unknown.

Iatrogenic Factors

The urinary tract is the most common site of nosocomial infection. Although there are no good data on risk of catheter-induced infections in children, in adult women the incidence of catheter-induced UTI ranges from 1% to 20% depending upon the circumstances of catheterization (Stamey, 1980). It has been documented that nosocomial UTI frequently complicates hospitalization in children, especially when urethral catheterization is performed (Dele Davies et al, 1992; Lohr et al, 1994), and this may be a reason to consider giving antimicrobial prophylaxis. On this basis, children who have hospital-acquired UTI, have urinary tract abnormalities, have recently been instrumented, or have had recent antimicrobial treatment are more likely to have infections caused by unusual and more antibiotic-resistant organisms (Ashkenazi et al, 1991).

When urethral catheters remain indwelling for longer than 4 days, bacteriuria is almost inevitable, because bacteria attach to the device surface and form biofilms of extracellular polymers, making these bound organisms resistant to routine antimicrobial treatment (Donlan, 2001). **Because the urinary tract is second only to the mouth as the source of bacterial endocarditis, the American Heart Association recommends bacterial endocarditis antimicrobial prophylaxis before urethral catheterization in individuals with a known urinary infection.** Cost-outcome analysis for bacterial endocarditis prophylaxis of febrile children with moderate cardiac lesions in an emergency room being evaluated for UTI shows no cost-benefit value (Caviness et al, 2004).

Endocarditis antimicrobial prophylaxis is not recommended, however, when urine is sterile. It is noteworthy that the British Society for Antimicrobial Chemotherapy revised their guidelines in 2006 and continue to recommend prophylaxis for prevention of enterococcal endocarditis for cystoscopy, urethral dilation, and transurethral procedures, whereas the American Heart Association in 2007 no longer recommended routine prophylaxis for gastrointestinal or urologic procedures with "uninfected tissues" (Pediatric Care Online, 2007; Wilson et al, 2007; Shanson, 2008).

In school-age boys, urethral self-manipulation with water injection or self-instrumentation can cause UTI (Labbé, 1990). About 25% of children who are victims of sexual abuse may complain of dysuria and urinary frequency, but these children rarely have UTI (Klevan and DeJong, 1990).

Key Points: Urinary Tract Infection Pathogenesis and Risk Factors

- Risk factors for bacteriuria and subsequent renal damage are distinct for individual hosts.
- Bacteriuria is most common at the extremes of life—infancy and old age.
- Blood group phenotypes found on the urothelial surface influence risk of UTI.
- Two risks for recurrent UTI in young women are age at first UTI of less than 15 years and UTI in the mother.
- Renal scarring is a risk factor for future renal scarring.
- Host genetic polymorphisms affect both UTI and scarring susceptibility.

DIAGNOSIS OF URINARY TRACT INFECTION

Rapid diagnosis of UTI is essential to initiating rapid antimicrobial treatment and preventing renal damage. In children who have no alternative fever source from history or physical findings, UTI accounts for greater than 5% of fevers (American Academy of Pediatrics, 1999a). In febrile infants (younger than 8 weeks), UTIs account for 13.6% of these fevers with the majority occurring in males (Lin et al, 2000). Young children may show only signs of generalized illness—fever, irritability, poor feeding, vomiting, and diarrhea. In a busy children's hospital emergency room, the **overall prevalence of UTI in febrile infants younger than 12 months and girls younger than 2 years with fever greater than 38.5° C and without other cause was 3.3%,** with higher prevalence in whites, girls, and uncircumcised boys; white girls had a UTI prevalence of 16.1% (Shaw et al, 1998a, 1998b).

Symptoms

UTI is a common cause of pediatric bacterial infection (Crain and Gershel, 1990; Bonadio et al, 1993; Hoberman et al, 1993). Fever accounts for about 20% of pediatric office visits (Eggli and Tulchinsky, 1993), and UTI causes 4.1% to 7.5% of these febrile episodes (American Academy of Pediatrics, 1999a).

Infants

In seriously ill infants and young children, one must suspect UTI and obtain a urinary specimen, even if signs may point elsewhere. Especially in febrile infants, from birth to 8 to 10 weeks, neither clinical symptoms nor laboratory tests will predict a presumptive UTI. Even if clinical symptoms suggest other sites of infection, this does not eliminate the likelihood of a UTI (Crain and Gershel, 1990).

The prevalence of UTI in febrile infants (younger than 8 weeks) is about 13.6%, with the majority occurring in males (Lin et al, 2000). **It is important to note that febrile infants not suspected of having a urinary source of infection are as likely of having a urinary source as those who are suspected of having a urinary source (5.1% vs. 5.9%). In infants with another possible fever source, such as otitis media, 3.5% also had a UTI** (Hoberman et al, 1993).

Young Children

As in infants, children less than 2 years old have UTI symptoms that are vague and generalized—fever, irritability, poor feeding, vomiting, diarrhea, and ill appearance (Ginsburg and McCracken, 1982) (Tables 116–2 and 116–3). **If one uses a clinical decision rule to decide which febrile young girls should be cultured for UTI, the presence of two of the following five variables may be useful: (1) age less than 12 months, (2) white race, (3) absence of other fever source, (4) fever greater than 39° C, and (5) fever of 2 days or more. Using these parameters, one can predict UTI with a sensitivity of 95% and specificity of 0.31 while avoiding 30% of unnecessary cultures** (Gorelick and Shaw, 2000).

Older Children

The older toilet-trained, talking child may indicate signs that better localize to the urinary tract, such as dysuria, suprapubic pain, voiding dysfunction, incontinence, or flank and/or abdominal pain. Many of these children still do not describe urinary tract symptoms, however. In children without localizing signs or with symptoms only vaguely referable to the urinary tract, suspicion must still be high to avoid missing the diagnosis.

Adolescents

Adolescents with lower urinary tract symptoms should not be treated as large children or young adults. Although *E. coli* is still the most common UTI in female adolescents, the second most common is *Staphylococcus saprophyticus,* and it may be associated with sexual activity and recurrent UTI (Huppert et al, 2007). In adolescent males, UTI may be associated with structural abnormalities and lower urinary tract symptoms with voiding dysfunction (unfortunately labeled prostatitis IIIb—noninflammatory, nonbacterial) (Li et al, 2006). Adolescent females with dysuria and frequency should be evaluated for both UTI and sexually transmitted infection (STI). **There are estimates that 50% of high school students have had at least one sexual encounter. The prevalence of *Chlamydia* is 13% to 26% and *Neisseria gonorrhea* is about 2% to 10% in this population.** For this reason, considering STI in this group (age 16 to 24 years) may be just as important, or more important, in considering UTI for the differential diagnosis (Claudius, 2000; Pimenta et al, 2000). A suggested marker for teenage sexual activity is UTI (Nguyen and Weir, 2002).

Sexually active adolescent females with urinary symptoms need evaluation for both UTI and STI with clean catch urinalysis, culture, and *Chlamydia* and *N. gonorrhea* testing (vaginal swab), because they can occur together. The U.S. Preventive Services recommends screening for chlamydial infection using urinary or vaginal swab nucleic acid amplification testing in sexually active young women age 24 years and younger, whether pregnant or nonpregnant. Individuals who have had previous chlamydial infection, other sexually transmitted infections, sex work, and inconsistent condom usage are at increased risk (U.S. Preventive Services Task Force, 2007). *N. gonorrhea* and *Trichomonas* (wet mount for *Trichomonas,* urinary nucleic acid amplification testing for *N. gonorrhea*) tests should be performed upon symptoms and the presence of urinary leukocytes, because these infections cause sterile pyuria that will not be discovered until cultures are negative days later. Although wet-mount microscopic examination for *Trichomonas* was available in the past, many practitioners have lost laboratory access due to regulation; so, *Trichomonas* culture or antigen tests may need to be ordered (Huppert et al, 2007). Rescreening in 3 months is recommended for patients in whom

Table 116–2.

Host Factors Affecting Bacteriuria

Age
Gender
Colonization
Periurethral
Periputial
Fecal
Genetics (uroepithelial receptors)
Renal scarring
Immune status (innate and adaptive)
Sexual activity
Genitourinary abnormalities
Vesicoureteral reflux
Pregnancy
Neurogenic bladder
Iatrogenic factors

Table 116–3.

Symptoms of Urinary Tract Infection in 100 Infants with Acute Urinary Tract Infections

SYMPTOM	PERCENTAGE
Fever	67
≥38° C	100
≥39° C	57
Irritable	55
Poor feeding	38
Vomiting	36
Diarrhea	36
Abdominal distention	8
Jaundice	7

Modified from Ginsburg CM, McCracken GHJ. Urinary tract infections in young infants. Pediatrics 1982;69:409–12.

testing is positive for *Chlamydia* or *Trichomonas* due to high risk for asymptomatic reinfection (Peterman et al, 2006). There are insufficient data to recommend screening in adolescent males (U.S. Preventive Services Task Force, 2007).

In this group of teenage females, untreated STI can progress to pelvic inflammatory disease in 10% to 40% with 12% infertility and an even greater possibility of chronic pelvic pain. One study documents that differentiating between females with culture UTI and those with STI on the basis of symptoms is not possible (Claudius, 2000); moreover, some had both infections (Huppert et al, 2007).

Physical Examination

There are no specific symptoms or signs for UTI in the infant. If there is a gross genitourinary anatomic abnormality, a renal mass may be palpable, as in children with xanthogranulomatous pyelonephritis or infected severe hydronephrosis. Palpation in the suprapubic and flank areas may cause pain in the older child, but generalized abdominal or upper quadrant pain may also be present. Perineal examination will rarely show an ectopic ureteral opening, ureterocele, or urethral discharge in girls. Signs such as back scars, sacral fat pads, or sacral dimples or pits may suggest a neurogenic bladder and may require further investigation. In boys, the testes are abnormal if affected by epididymitis or epididymo-orchitis.

Diagnostic Tests

Urinary Specimens

Good urinary specimens with which to make the diagnosis of UTI are hard to obtain in children, and diagnostic reliability depends upon the quality of the specimen. Routinely, four types of urinary specimens are obtained from children. **In order of least to most reliable for UTI diagnosis** (Hardy et al, 1976), **the specimen types are (1) a plastic bag attached to the perineum—a bagged specimen, (2) midstream void, (3) catheterized specimen, or (4) suprapubic bladder aspirate.**

Even after extensive skin cleansing, a plastic bag specimen usually reflects perineal and rectal flora and often leads to indeterminate results. Although an individual midstream-voided specimen in a circumcised boy, older girl, or older uncircumcised boy who can retract his foreskin can be reliable, such specimens obtained in young girls and uncircumcised boys usually reflect periurethral and preputial organisms and cells. A catheterized specimen is reliable if the first portion of urine, which may contain urethral organisms, is discarded, and the specimen is taken from later flow through the catheter. Catheterization has the disadvantages of being traumatic and potentially introducing urethral organisms into a sterile bladder (Dele Davies et al, 1992; Lohr et al, 1994).

Suprapubic bladder aspiration is the most reliable method. This procedure is performed safely in children and even premature infants with a full bladder. After cleaning the skin, a 21- or 22-gauge needle is introduced 1 to 2 cm above the pubic symphysis until urine is obtained by aspirating into a sterile syringe (Barkemeyer, 1994). Although unnecessary in most instances, in infants and young children, ultrasound guidance of suprapubic aspiration may aid the procedure (Buys et al, 1994), and also the use of topical and local anesthesia.

Because urine does not cross the urethra in the aspirated specimen, urethral or periurethral organisms are absent; skin contamination should be nil. **Organisms present in a suprapubic aspirate are pathognomonic of bacteriuria, and low bacterial counts are routine** (Buys et al, 1994). The main drawback of suprapubic aspiration is that needle aspiration may be distasteful and/or inconvenient to the older child, parent, or even physician, and these considerations are important (Kramer et al, 1994).

Generally, if a UTI is suspected in a child who is not yet toilet-trained, only a catheterized or needle-aspirated specimen is acceptable for diagnosis, because bagged urinary specimens have an unacceptably high false-positive rate. Under special collection circumstances, when the perineum is cleaned well and the bag removed and processed promptly after voiding, a bagged specimen, or even a diaper specimen, that shows no growth is useful in eliminating bacteriuria as a diagnosis (Ahmad et al, 1991; Whiting et al, 2005). **Plastic bag specimens are unreliable and unacceptable for *diagnosis* of UTI in high-risk populations and infants younger than 2 months** (Crain and Gershel, 1990).

Urinalysis

Four determinations from the urinalysis are advocated to support a UTI diagnosis: (1) microscopic urinary examination for white blood cells (WBCs)—pyuria, usually defined as greater than 5 white blood cells/high-power field (WBC/HPF) in a centrifuged specimen, (2) microscopic urinary examination for bacteria, defined as any bacteria per HPF in the unstained centrifuged urinary sediment, (3) urinary leukocyte esterase, and (4) urinary nitrite. The finding of red and white cell casts in the urinary sediment is unreliable.

Sensitivity of routine urinalysis for UTI is calculated to be 82% and is independent of age in children less than 2 years old, and the probability of a UTI with a negative urinalysis is based upon the patient-specific prevalence of UTI (Shaw et al, 1998b; Bachur and Harper, 2001b). The prevalence depends upon the child's age, race, sex, and temperature. Urinalysis findings that do not support a UTI, however, decrease the likelihood of a UTI fivefold (Bachur and Harper, 2001b).

Microscopic Examination

Although there are many confounding factors, the microscopic identification of bacteria in the urine is more sensitive and specific for diagnosing UTI than identification of pyuria (Hallender et al, 1986; Lohr, 1991). **Identification of bacteria under high dry magnification (450 to 570× magnification) represents about 30,000 bacteria per mL.** In a meta-analysis of screening tests, microscopic identification of any bacteria on Gram stain of uncentrifuged urine had the best combination of sensitivity and false-positive rates (Gorelick and Shaw, 1999). However, each of these tests separately has such low sensitivity in this high-risk population that neither is reliable.

In febrile children younger than 2 years, Hoberman and associates (1997) found that catheter-collected specimens had a positive predictive value for UTI diagnosis of 84.6% when microscopic examination showed bacteria (any bacteria on 10 oil-immersion fields in a Gram-stained specimen) and greater than or equal to 10 WBC/mm^3 (on enhanced urinalysis—not per HPF) (Hoberman and Wald, 1997). Although these two parameters offer predictive value, the office practitioner cannot perform either of these tests easily and rapidly without further instruction (enhanced

quantitative WBC count and Gram-stained bacteria on unspun specimen). **These investigators emphasize that UTI in these children is still best defined by a urinary leukocyte count of greater than or equal to 10/mm^3 and greater than or equal to 50,000 colony-forming units (CFU)/mL on culture** (Hoberman et al, 1994; Hoberman and Wald, 1997).

Urinary Leukocyte Esterase, Nitrite, and Other Chemical Tests

Several other "quick" tests that may be performed on urinalysis have been popular for trying to predict UTI. Urinary leukocyte esterase detects urinary enzymes produced by the breakdown of white cells in the urine and, as such, is dependent upon the presence of white cells that may or may not be present with the infection. The test may be less reliable in infants (Hoberman et al, 1994). **Dietary nitrates that are reduced to nitrite by many gram-negative urinary bacteria are measured by the urinary nitrite test. The fact that first morning-voided urinary specimens should be used for this test, because bacterial reduction of nitrate can take several hours and many gram-positive bacteria do not perform this reduction, are serious drawbacks.** Urinary catalase, an enzyme commonly produced by bacteria infecting the urinary tract, although sensitive, has too high a false-positive rate to be reliable (Waisman et al, 1999). Although these tests are rapid and efficient, they are even less reliable when the bacterial count is less than 100,000 CFU/mL. In a general pediatric population, when urinary specimens are properly collected and promptly processed, **the combination of positive leukocyte esterase and nitrite testing, and microscopic confirmation of bacteria, has almost 100% sensitivity for detection of UTI. When all (or leukocyte esterase and nitrite tests) are negative, the negative predictive value approaches 100%** (Wiggelinkhuizen et al, 1988; Lohr et al, 1993; Whiting et al, 2005). The arguments for and against relying upon urinalysis characteristics for presumptive diagnosis of a UTI are well summarized (Lohr, 1991; American Academy of Pediatrics, 1999a; Gorelick and Shaw, 1999; Whiting et al, 2005). Moreover, presumptive treatment when the dipstick shows at least 2+ leukocyte esterase or positive nitrite while the culture is obtained appears to be most cost effective as well (Shaw et al, 1998b). Although there is no test or combination of urinary tests that meets gold standard of culture, combinations of these tests may help suggest patients in whom culture will be positive and in whom presumptive treatment can be started.

Urinalysis cannot replace urinary culture. A risk-benefit analysis, based on the current literature about febrile children 3 to 24 months old, shows that one needs both urinalysis and culture to optimize prevention of end-stage renal disease and hypertension, (Kramer et al, 1994). A negative microscopic examination of urinary sediment for bacteria and white cells, negative leukocyte esterase, and negative nitrite are probably sufficient evidence to avoid culture (Whiting et al, 2005).

Serum Tests Indicating Urinary Tract Severity

Complete blood counts (Kramer et al, 1993), erythrocyte sedimentation rates (ESR), C-reactive protein (CRP), urinary concentrating ability (Åbyholm and Monn, 1979), urinary tubular enzymes (Johnson et al, 1990; Tomlinson et al, 1994), antibody-coated bacteria, urinary antibodies, and interleukins 6 and 8 (IL-6, IL-8) (Benson et al, 1994; Sheu et al, 2008; Zaki, 2008) have been examined as possible simple and noninvasive markers of renal infection (Buyan et al, 1993), but none are in widespread use.

C-reactive protein greater than 7 mg/dL has been associated with serious bacterial infection in febrile children age 1 to 36 months (Pulliam et al, 2001). Although the host urinary tract responds to bacterial infection with the production of cytokines, and IL-6 and IL-8 are secreted in response to *E. coli* attachment to the Toll-like receptors, it appears that this local response is then followed by a systemic increase in CRP and fibrinogen, temperature, and ESR (de Man et al, 1991). Some recommend that children who have UTI and fever longer than 2 days and CRP greater than 66.4 mg/L, or fever less than 2 days and CRP greater than 27.3 mg/L, should be treated for presumptive acute pyelonephritis if no DMSA scan is available (Huang et al, 2007). Recent examination of children diagnosed to have acute pyelonephritis has shown that both serum and urinary IL-6 and IL-8 are elevated when there is "upper tract" involvement and that elevated urinary IL-8 may be useful as a marker for pyelonephritis (Tullus et al, 1994; Sheu et al, 2006; Artifoni et al, 2007; Zaki, 2008).

Serum procalcitonin, a hormonally inactive precursor of calcitonin produced in the thyroid, is elevated in sepsis and appears to be in the systemic circulation only during severe inflammation. **Elevation of serum procalcitonin is reported to correlate better than ESR or CRP with pyelonephritis and to predict risk of renal scarring** and may be particularly useful in infants (Pecile and Romanello, 2007; Bressan et al, 2009; Kotoula et al, 2009). Still, this is a nonspecific systemic marker for severe infection.

Reduced urinary concentrating ability is associated with pyelonephritis, but this appears to be unassociated with the acute febrile response in pyelonephritis and is probably not a reliable sign for early detection of pyelonephritis (de Man et al, 1991). Unfortunately, none of these tests is reliable enough for early UTI detection or to differentiate between upper and lower tract infections or severity of infection for routine use.

Urinary Culture

The gold standard for the diagnosis of UTI is quantitative urinary culture. This requires that a known quantity of urine is plated onto a culture plate, and the number of bacterial colony-forming units that grow is counted and determined as CFU/mL. The interpretation of the culture results defining a UTI diagnosis, however, is debatable and dependent upon specimen quality. Because it may take 24 or more hours before bacterial colony-forming units grow and the culture is complete, indirect urinary tests that may be performed with routine urinalysis to detect the presence of bacteria or byproducts have been sought for a more rapid diagnosis.

Although greater than or equal to 100,000 CFU/mL of voided urine is the traditional definition for a clinically significant UTI (Kass and Finland, 1956), other studies have shown that less than or equal to 10,000 or fewer organisms on a voided specimen may indicate a significant UTI (Stamm et al, 1982; Bollgren et al, 1984). In febrile children younger than 2 years, Hoberman and associates (1994) showed that greater than or equal to 50,000 CFU/mL in catheterized specimens constitutes a significant UTI. Occasionally, even lower numbers of bacteria may justify diagnosis of a significant UTI, especially when the specimen is obtained by suprapubic needle aspiration, circumstances under which any number of organisms might be significant. Cultured colony-forming units per milliliter may be low because of hydrational dilution, frequent

voiding that prevents bacterial multiplication in the bladder, and bacterial growth characteristics.

Acute and Focal Pyelonephritis (Lobar Nephronia or Focal Bacterial Nephritis)

Symptoms and Signs

Children with pyelonephritis may have classic symptoms of fever, chills, and unilateral or bilateral flank pain with or without accompanying lower tract symptoms of dysuria, frequency, and urgency. They may complain of nonspecific abdominal discomfort and not complain of flank pain. Physical examination reveals fever usually accompanied by abdominal discomfort and pain over the costovertebral area.

The urine is usually cloudy and malodorous. Urinary sediment usually shows pyuria, white blood cell casts, and red blood cells. Bacterial rods are often present. Bacterial infection of the urinary tract causes bladder, ureteral, renal pelvic, and renal inflammation that alter urinary tract urodynamics and causes ureterectasis, elevated renal pelvic pressures, and renal inflammatory changes that may be associated with renal swelling (Hinman, 1971; Boyarsky and Labay, 1972; Issa and Shortliffe, 1992; Johnson et al, 1992).

Radiologic Findings

The discoveries that early renal cortical lesions from pyelonephritis can be detected by ^{99m}Tc-dimercaptosuccinic acid (DMSA) nuclear scan, and that these lesions correlate with histopathologic areas of acute renal inflammation in animal models, have advanced knowledge of the natural history of urinary tract bacteriuria (Wikstad et al, 1990; Rushton and Majd, 1992b; Giblin et al, 1993). Radiologic findings in acute pyelonephritis depend upon the imaging modality used. When intravenous urography was the main urinary tract imaging modality, the majority of patients had normal studies. Other modalities show renal enlargement related to inflammation and edema, focal renal enlargement (acute lobar nephronia or focal bacterial pyelonephritis), impaired or delayed excretion, and dilation of the urinary collecting system, findings that are commonly associated with acute infection. These acute changes affect renal and collecting system dilation and size, making the interval between the UTI and imaging evaluation an important consideration when a clinician evaluates renal size or shape. What appears to be a kidney of normal, or even enlarged, size and shape may be a scarred small one later (Hansen and Shortliffe, 1998).

Focal or general renal enlargement or swollen kidneys may be found in acute pyelonephritis. Renal ultrasonography, nuclear scans, and computed tomography (CT) may show generalized renal enlargement or focal hypo- or hyperechoic areas representing focal pyelonephritis (lobar nephronia). The latter represents a localized, severe nonliquefactive infection of one or more renal lobules (Greenfield and Montgomery, 1987; Klar et al, 1996; Wallin et al, 1997; Uehling et al, 2000). Other findings on ultrasonography include thickening of the renal pelvis, hypoechogenicity and focal or diffuse hyperechogenicity, and ureteral dilation (Mårild et al, 1989; Morin et al, 1999). **CT or power Doppler may show areas of decreased perfusion** (Dacher et al, 1996). High-resolution renal ultrasonography has been suggested to be almost as sensitive as DMSA scanning for diagnosing renal involvement in pyelonephritis (Dacher et al, 1996; Morin et al, 1999).

When DMSA-defined lesions are the standard for diagnosing acute pyelonephritis, about 50% to 86% of children (about 60% of kidneys) with febrile UTI and other clinical signs have renal involvement or pyelonephritis (Verber and Meller, 1989; Rushton and Majd, 1992b; Benador et al, 1994; Jakobsson et al, 1994). About half (38% to 75%) of these lesions persist on DMSA scans performed 2 months to 2 years later (Rushton and Majd, 1992b; Benador et al, 1994; Stokland et al, 1996), with fewer lesions persisting at longer intervals of follow-up. This suggests that as many as 40% to 50% of young children who have febrile UTI suffer renal scarring. In children older than age 1 year with first-time symptomatic UTI, 38% have DMSA-defined evidence of renal damage after 1 year, and almost half of these (47%) have reflux. **Children who have elevated CRP, fever, and dilating reflux have a 10-fold higher risk of renal damage than children with UTI who have a normal or slightly elevated CRP, no or mild fever, and no vesicoureteral reflux** (Stokland et al, 1996; Yen et al, 1999).

Pyonephrosis

Pyonephrosis is characterized by accumulation of purulent debris and sediment in the renal pelvis and urinary collecting system. Children with pyonephrosis have symptoms similar to acute pyelonephritis but have additional structural obstructive hydronephrosis. This situation usually implies bacterial infection and obstruction; so, rapid diagnosis and treatment is essential to avoid sepsis and parenchymal loss. Renal ultrasonography is usually diagnostic. The majority of obstructed pyonephrotic kidneys are either nonfunctioning or poorly functioning. **The renal sonogram may show shifting fluid-debris levels with changes in the patient's position, persistent echoes from the lower collecting system, air in the collecting system, or weak echoes secondary to pus in a dilated poorly transonic renal collecting system** (Coleman, 1985). If performed, retrograde pyelography shows ureteral obstruction and irregular renal pelvic filling defects caused by purulent sediment. When it is possible to pass a ureteral catheter past the obstruction, drainage becomes both diagnostic and therapeutic. The treatment for pyonephrosis is administration of appropriate antimicrobial drugs and prompt drainage of the infected pelvis by either retrograde catheterization or nephrostomy placement. When the acute infection is treated and the patient is on appropriate antimicrobial agents, further evaluation to identify and treat the obstruction may be necessary.

Perinephric or Renal Abscess

Improvements in imaging of the genitourinary tract and widespread use of powerful antimicrobial agents have changed the evaluation and natural history of perinephric and renal abscesses (Shortliffe and Stamey, 1986a). In the past, the high mortality rate from perinephric abscesses related, in part, to diagnostic delay. Perinephric and renal abscesses are uncommon in children. These abscesses arise from either hematogenous seeding from extragenital sites of infection or renal extension of ascending urinary infections. **Since the introduction of broad-spectrum and powerful antimicrobial agents in the 1940s, the percentage of perirenal abscesses caused by staphylococci decreased from 45% before 1940 to 6% after 1940, and those attributed to *E. coli* and *Proteus* rose from 8% to 30% and 4% to 44%, respectively** (Thorley et al, 1974). This large decrease in perirenal and renal abscesses caused by staphylococci may relate to the advent of antimicrobial agents discovered to treat skin and wound abscesses (Thorley et al, 1974;

Shortliffe and Stamey, 1986a). Children with renal and perirenal abscesses have severe pyelonephritis—fever, flank pain, leukocytosis, and occasionally sepsis. With the frequent use of renal ultrasonography for evaluation of such symptoms and characteristic findings, diagnosis is now easier and earlier. Because most abscesses have a fluid component, perinephric collections usually appear sonolucent, and diagnostic aspiration of this area usually carries minimal morbidity. Computed tomography will assess the extent and may show perirenal fluid or gas, renal distortion, and involvement of the retroperitoneum (Hoddick et al, 1983). **Although *Staphylococcus aureus* with antecedent skin lesions may have been the most common cause of renal abscesses in children and adults more than 2 decades ago** (Rote et al, 1978), **gram-negative organisms (*E. coli*) are now the most common cause.** These are more likely associated with retrograde extension of ascending infection in relation to severe pyelonephritis and genitourinary anomalies (Rote et al, 1978; Steele et al, 1990; Barker and Ahmed, 1991; Vachvanichsanong et al, 1992). Anaerobic bacteria may cause perinephric or renal abscesses in association with previous abdominal surgery, renal transplant, malignancy, and oral or dental infection (Brook, 1994).

Current systemic antimicrobial agents allow successful treatment of some abscesses with antimicrobial therapy alone without surgical intervention. In many cases, however, percutaneous or surgical drainage combined with appropriate antibiotic therapy is required (Rote et al, 1978; Steele et al, 1990; Vachvanichsanong et al, 1992).

Key Points: Urinary Tract Infection Diagnosis

- Febrile infants unsuspected of having a UTI are as likely of having a UTI as those who are suspected to have a UTI.
- In adolescents, UTI is a possible marker for teenage sexual activity, and they should be evaluated for STI.
- Any organisms present in a suprapubic urine aspirate are pathognomonic of bacteriuria; low bacterial counts are routine.
- Plastic bag specimens are unreliable and unacceptable for UTI diagnosis in high-risk populations and infants.
- Identification of bacteria under high dry microscope field represents about 30,000 bacteria/mL.
- C-reactive protein greater than 7 mg/dL is likely to be associated with serious bacterial infection in febrile children to age 3 years.
- In acute pyelonephritis, focal or general renal swelling may be found in imaging tests.
- Children with elevated CRP, fever, and dilating reflux have 10 times the risk of renal damage than those with these elements absent.
- Gram-negative organisms are now the most common cause of renal abscesses, in contrast to *S. aureus* being the most common 3 decades ago.

MANAGEMENT OF PEDIATRIC URINARY TRACT INFECTIONS

The therapeutic strategy in managing pediatric UTI is first to minimize renal damage during the acutely diagnosed UTI and second to minimize risk of future renal damage from subsequent infections. Rapid recognition of a UTI and rapid, appropriate antimicrobial treatment are crucial to preventing renal damage. As discussed earlier, clinical and experimental data show that early antimicrobial treatment appears to be the most effective means of preventing renal scarring and subsequent complications.

Treatment of Acute Urinary Tract Infections

Infants (Children Younger Than 90 Days)

In UTI treatment, infants and children younger than 90 days are treated differently than older children. Children younger than 90 days are more likely to have their course of disease change rapidly because of their physiology and incompletely developed immune system. There have been documented studies that emphasize immune deficiencies or alterations in neonatal T, B, and antigen-presenting cells compared with adult cell behavior (Adkins et al, 2004). Moreover, infants have vague and nonspecific symptoms of illness that are difficult to interpret. Most commonly, children are seen with growth failure, diarrhea, irritability, lethargy, malodorous urine, fever, oliguria, or polyuria.

Because UTIs are a common cause of fever in infants, with a prevalence of 5% to 11%, consideration of UTI diagnosis and management is important. In these children with "occult" serious bacterial infection, C-reactive protein (Pulliam et al, 2001), absolute neutrophil count greater than 10.6×10^9/L (Isaacman and Burke, 2002), and asymptomatic jaundice (Garcia and Nager, 2002) may be present. **It is recommended that testing for UTI be part of the evaluation of asymptomatic jaundice that occurs in an infant younger than 8 weeks, especially with onset after 8 days of life** (Garcia and Nager, 2002). Other risks for infantile UTI are lack of circumcision, female sex, and fever lasting longer than 24 hours (Newman et al, 2002). For febrile infants younger than 90 days, UTI (67%) is one of the common causes of serious bacterial infection (Byington et al, 2003). Although those younger than 1 month are commonly hospitalized for treatment, those between age 30 to 90 days have been managed as outpatients. Although antibiotic prophylaxis against group B *Streptococcus* during pregnancy has decreased serious neonatal infections with this organism, in many communities increasing numbers of pathogens are ampicillin resistant. In one study from Utah Children's Hospital, **ampicillin-resistant gram-negative bacteria are the most common cause of serious bacterial infection in infants younger than 3 months** (Byington et al, 2003). This resistance must be taken into consideration for judicious and effective treatment.

Treatment depends upon the child's age and severity of illness. In the child younger than 2 to 3 months, particularly 30 days or younger with a presumptive serious bacterial infection and possibly a UTI, consideration must be given to antimicrobial coverage of *Listeria monocytogenes* (perinatally acquired) and *Enterococcus* (usually postnatally acquired) in which ampicillin gives coverage, thus making ampicillin and gentamicin recommended in this age group (Brown et al, 2002).

Others recommend that, for children younger than 60 days, a third-generation cephalosporin may replace ampicillin with or without gentamicin unless meningitis or gram-positive UTI is suspected, because of the unlikelihood of *Listeria* and the high resistance rate of other gram-negative organisms. **However, because *Enterococcus* UTI still occurs in this group, this is not appropriate when UTI is suspected** (Sadow et al, 1999). Other young children who are suspected to have UTI and are severely systemically ill (or have a fever and flank or abdominal

Table 116–4.

Potentially Useful Antibacterial Drugs for Urinary Tract Infection (UTI)

UTI SEVERITY	ADULT DOSAGE*	PEDIATRIC DOSAGE†	MODE
Urinary Tract Sepsis			
THIRD-GENERATION CEPHALOSPORIN ± AMINOGLYCOSIDE			
Cefotaxime (Claforan)		50-180 mg/kg/day (q4-6h)	
Ceftriaxone (Rocephin)		50-75 mg/kg/day (q12-24h)	
Ceftazidime (Fortaz, Tazicef, Tazidime)		90-150 mg/kg/day (q8-12h)	
PENICILLIN GROUP (E.G., ENTEROCOCCUS SUSPECTED) ± AMINOGLYCOSIDE		50-100 mg/kg/day (q4-8h)	
Ticarcillin/clavulanate (Timentin)	200-300 mg/kg/day	50-200 mg/kg/day (q4-8h)	
Aminoglycosides			
Gentamicin		7.5 mg/kg/day (q8h)	
Tobramycin			
Amikacin		7.5 mg/kg/day (q8h)	
Aztreonam (Azactam)		90-120 mg/kg/day (q6-8h)	
Vancomycin *(if penicillin allergy)*	2 g/day (q6h)	10 mg/kg/dose (q6h)	
Acute Uncomplicated Pyelonephritis			
Fluoroquinolones			
Ciprofloxacin (Cipro)	500-1500 mg/day (q12h)	20-40 mg/kg/day (q12h)‡	PO
Amoxicillin/clavulanate (Augmentin)		20-40 mg/kg/day (q8h)	PO
Third-generation cephalosporin			PO
Uncomplicated UTI			
Trimethoprim (TMP)-sulfamethoxazole			
Generic (400 mg/80 mg)	4 tablets/day (q12h)	8 mg/kg/day (TMP) (q12h)	PO
Double strength (DS) (800 mg/160 mg)	2 DS tablets/day (q12h)		PO
Amoxicillin/clavulanate (Augmentin)		20-40 mg/kg/day (q8h)	PO
Cephalosporin			
Cephalexin (Keflex)	1-4 g daily (q6-12h)	25-50 mg/kg day (q6-12h)	PO
Cefixime (Suprax)	400 mg/day	8 mg/kg/day (q12-24h)	PO
Nalidixic acid	4 g/day (qid)	55 mg/kg/day (qid)	PO
Fluoroquinolones			
Ciprofloxacin (Cipro)	500-1500 mg/day (q12h)	20-40 mg/kg/day (q12h)‡	PO
Nitrofurantoin			
Nitrofurantoin (generic, Macrodantin)	200-400 mg/day (q6h)	5-7 mg/kg/day (q6h)	PO
Macrobid	200 mg/day (q12h)	>12 yr 200 mg/day (q12h)	PO

*Dosage may need to be adjusted for renal or hepatic insufficiency.
†Safety indications and dosage should be checked for children younger than 3 months, and dosage may need adjustment for renal or hepatic insufficiency.
‡Not to exceed 750 mg/dose even in children weighing >51 kg.
Adapted from Abramowicz M. Drugs for bacterial infection. Med Lett 2010;8:43–55; and Lindert KA, Shortliffe LMD. Evaluation and management of pediatric urinary tract infections. Urol Clin North Am 1999;26:719–28.

pain), are unable to take fluids, and are immune compromised, should be treated with parenteral broad-spectrum antimicrobial agents (e.g., aminoglycoside and ampicillin, third-generation cephalosporin, aminoglycoside, and cephalosporin) (Table 116–4), with aminopenicillin/clavulonic acid used because of widespread ampicillin resistance (Prelog et al, 2008). Whether this child requires hospitalization or outpatient parenteral or oral treatment depends upon the clinical status.

Children and Outpatient Therapy

In appropriate infants and young children with presumptive febrile UTI who are taking fluids, who have cooperative and reliable parents, and with whom daily contact is possible, some of the newer third-generation cephalosporins, such as **ceftriaxone, allow once-daily outpatient parenteral therapy** (Baskin et al, 1992; Gordon, 1991). Most of these third-generation cephalosporins have a broad spectrum, treat *Enterobacter* species and some *Pseudomonas aeruginosa,* and conveniently require only once- or twice-daily dosing. It must be emphasized that ***Enterococcus is still resistant to most third-generation cephalosporins.*** **Meta-analysis of available randomized evidence recommends adoption of a once-daily dosing of aminoglycosides in children; this minimizes cost, may improve efficacy and safety, and allows day or potentially outpatient treatment** (Contopoulos-Ioannidis et al, 2004). It may be that efficacy of once-daily dosing for treatment of urinary tract infections stems from the fact that serum aminoglycoside drug levels so often targeted in treatment of bacteremia are unnecessary in the treatment of urinary tract infections without associated sepsis. As the drugs are concentrated during excretion in the kidney and urine to levels many times those achieved in the serum, lower serum levels may be achieved with treatment efficacy. There is little evidence that gentamicin is likely to permanently affect those with reduced residual renal function (Baker et al, 2003).

Because the antimicrobial spectrum varies slightly for each of these drugs, the environment and local ecology (e.g., community-acquired outpatient versus hospital-acquired UTI)

should determine drug selection. National and local antimicrobial resistance to common organisms that commonly infect the urinary tract must be considered in the selection of both the agent for initial treatment and that for prophylaxis. Generally, parenteral treatment continues for 2 to 4 days until fever is gone, the child is able to take adequate fluids, and bacterial sensitivities are available to allow treatment with an oral drug with a narrow spectrum.

The clinical response to treatment also depends upon the severity and rapidity of treatment. In children age 2 years or younger (median 5.6 months) who were hospitalized with a diagnosis of febrile UTI, **89% (of 288 children) were afebrile 48 hours after parenteral antimicrobial agents were started even if bacteremia or significant genitourinary abnormality was found** (Bachur, 2000). **The median time to attain a normal temperature was 13 to 16 hours.**

Although the duration of treatment is debatable, in most studies involving treatment of febrile UTI in young children, total duration of therapy has extended from 7 to 10 days. When culture and sensitivity information are available, the antimicrobial agent should be re-evaluated and changed if necessary, and treatment continued for 7 to 10 days. In most cases, an oral drug with a narrower spectrum, but to which the organism is sensitive, can be selected. **Analysis has shown that no follow-up urinary culture after 48 hours is required, if organisms are sensitive to the antibiotic selected** (Currie et al, 2003)**.**

Less-ill older infants and young children who have presumptive febrile UTI and are capable of taking fluids and oral medicines may be treated with an antimicrobial agent that has a broad spectrum for genitourinary pathogens. Although the newer oral cephalosporins have good gram-positive and gram-negative treatment spectra and need only once- or twice-daily dosing, many *Enterococcus, Pseudomonas,* and *Enterobacter* species may be resistant to treatment (Fennell et al, 1980; Ginsburg et al, 1982; Ginsburg and McCracken, 1982; Dagan et al, 1992; Stutman, 1993). **In a recent multicenter randomized clinical trial, oral cefixime appeared as effective as initial intravenous cefotaxime in children with febrile UTI at age 1 to 24 months** (Hoberman et al, 1999).

In adults, the quinolones are useful because of their broader antimicrobial spectrum and special activity against *Pseudomonas aeruginosa,* but in children, usage of this drug has been limited because of studies showing quinolone-induced cartilage toxicity in young animals. With careful monitoring, limited quinolone usage has shown no cartilage-related toxicities. In situations such as an abnormal urinary tract with upper tract *Pseudomonas aeruginosa*, there may be good indication for usage (Schaad, 1991). In 2005, the quinolones were not yet approved for the treatment of pediatric UTI, but clinical trials are examining pediatric safety and efficacy issues, and they are more widely used in children. In adult women, amoxicillin-clavulanate is less effective than ciprofloxacin for treatment of uncomplicated cystitis for the possible reason that ciprofloxacin is more likely to eradicate vaginal *E. coli* (Hooten et al, 2005). Because young children are less likely to be sexually active, vaginal colonization may be less important in the pathogenesis.

As with other effective antimicrobial agents, resistance to quinolones is rising. In one report from Spain in 1995, 6.4% of *E. coli* UTIs were resistant to ciprofloxacin (Ena et al, 1995). Risk for resistance was related to urinary tract abnormalities, previous quinolone treatment, urinary catheterization, and being age 65 years or older. In Colorado, 9% quinolone resistance was reported with risks for resistance being hospitalization and previous levofloxacin exposure (Johnson et al, 2008b). Quinolone resistance in other organisms unrelated to UTIs has led to the U.S. withdrawal of approval for addition of these drugs in animal feed in 2005.

School-Age Children

In school-age children who do not appear systemically ill and have a "clinically uncomplicated bladder infection," many oral broad-spectrum antimicrobial agents that are well tolerated will cure the "uncomplicated" UTI in a course of 3 to 5 days; there are no clinical advantages to longer therapy (Lohr et al, 1981; Copenhagen Study Group of Urinary Tract Infections in Children, 1991; Jójárt, 1991; Gaudreault et al, 1992). In some of these children, single-dose treatment, particularly with intramuscular aminoglycoside, may be curative and cause less fecal antimicrobial resistance (Grimwood, 1988; Khan, 1994), but, **in unselected children, single doses may not be quite as effective as 3 to 5 days of treatment** (Madrigal et al, 1988; Khan, 1994). Although these trials appear to show that shorter therapy of 3 to 5 days may be as effective as 7 to 14 days, a **meta-analysis of trials involving 3- to 5- versus 7- to 10-day therapy shows that longer therapy is more effective. They attribute their findings to the fact that in children, unlike adults, urinary tract abnormalities or vesicoureteral reflux may require longer treatment** (Keren and Chan, 2002).

"Switch Therapy"

"Switch therapy," intravenous therapy followed by oral therapy, is commonplace in adults and becoming common in children. **A large series of children age 3 months to 5 years had successful treatment of febrile UTI with intravenous gentamicin 5 mg/kg/day once-daily until afebrile (2 to 4 days) given in a day treatment center of a tertiary-care hospital, followed by oral antibiotic for a total of 10 days** (Gauthier et al, 2004). Similar findings were reported in a randomized trial between once-daily intravenous treatment with ceftriaxone for 3 days versus 10 days followed by oral cefixime for 15 days (Benador et al, 2001).

Antimicrobial Agent Selection

Common uropathogens are increasingly resistant to trimethoprim-sulfamethoxazole and ampicillin. This should be considered when prescribing initial antimicrobial therapy for UTI. The prevalence of uropathogen resistance to trimethoprim-sulfamethoxazole has increased from 8% in 1992 to greater than 16% in 1996 (Gupta et al, 1999), with *E. coli* resistance as high as 32% (range of 0% to 46%) in the western United States (Talan et al, 2000). Resistance to ampicillin is reported to range from 25% to 45% in recent years (Dyer et al, 1998; Gupta et al, 1999, 2001). **Predictors of situations in which uropathogens will be more likely resistant to commonly used agents are diabetes, recent hospitalization, recent use of antibiotics (especially trimethoprim-sulfamethoxazole)** (Wright et al, 1999), **and presence of urinary malformations, urethral catheters, and antimicrobial prophylaxis** (Ashkenazi et al, 1991).

Nitrofurantoin attains high urinary concentrations and low serum concentrations, and, as such, is a poor choice to treat any severe systemic or renal infection but is ideal for treating a bladder UTI when there is a normal urinary tract. **Resistance rates to nitrofurantoin have changed little over the past decade** (Kashanian et al, 2008). **After the therapeutic regimen for acute UTI, the child may be started on a daily prophylactic antimicrobial agent until radiologic evaluation of**

the urinary tract can be performed in the next days to weeks.

PROPHYLACTIC ANTIMICROBIAL AGENTS

Giving daily antimicrobial agents to prevent recurrent urinary tract infections in children who have a 30% to 40% chance of recurrence within a year is rational if this prevents significant morbidity and renal damage; however, no definitive trials to examine efficacy of UTI prevention using this management for vesicoureteral reflux and hydronephrosis have been performed. Antimicrobial prophylaxis to prevent UTI was originally suggested for women and girls who had a history of recurrent (two or more UTIs within 6 to 12 months); it was not intended for individuals who had never had UTI (e.g., prenatally diagnosed vesicoureteral reflux or hydronephrosis) or for those with a single UTI. Nonetheless, retrospective data show that reflux nephropathy is less likely in children with high-grade vesicoureteral reflux who present without UTI (Sweeney et al, 2001). Review of the few trials of randomized studies of children involving prophylactic antibiotics offer inadequate data to definitively support prophylaxis (Le Saux et al, 2000; Thompson et al, 2001; Williams et al, 2001a, 2001b; Wheeler et al, 2003; Fanos and Cataldi, 2004; Conway et al, 2007). **A systematic review and meta-analysis of studies in 2006, concludes, moreover, that data are of low quality and do not give definitive evidence that prophylaxis prevents recurrent symptomatic UTI** (Williams et al, 2006). **Two randomized prospective studies published since the meta-analysis, including one of children with and without vesicoureteral reflux, also found no preventive benefit from prophylactic antimicrobial agents** (Garin et al, 2006; Roussey-Kesler et al, 2008). In children, antimicrobial prophylaxis is most commonly used to prevent UTI in the situations listed in Table 116–5. Although urinary tract prophylaxis has been used and shown to decrease infections over a limited period in select groups of children with vesicoureteral reflux (Hansson et al, 1989d), long-term efficacy compared with adequate patient supervision, (Cascio et al, 2001) surveillance, and education has not been studied with randomization and proper patient stratification (Bollgren, 1999; Thompson et al, 2001). In some situations, such as partially obstructive hydronephrosis, the efficacy of prophylaxis is not established.

The use of antimicrobial prophylaxis with clean intermittent catheterization is controversial, and some of the considerations are discussed in the section Neurogenic and Bowel-Augmented Bladders. The use of nightly urinary tract antibiotic prophylaxis in children without known urinary tract abnormalities who suffer recurrent UTI is often successful in decreasing symptomatic UTI, and so is postintercourse prophylaxis in teens who suffer apparent postcoital "induced" UTI (Pfau and Sacks, 1994; Vosti, 2002).

It has been suggested that circumcision be performed to remove bacterial colonization of the prepuce (uncircumcised penis) in infant boys with vesicoureteral reflux and severe hydronephrosis, because one report states antibiotic prophylaxis is ineffective: Periurethral swabs grew uropathogens in 37% of boys (mean 2.5 years) taking prophylaxis (Cascio et al, 2001). Although periurethral colonization is a risk factor for UTI, it is unclear how prophylaxis was managed and unlikely that the only role of prophylaxis is in clearing the periurethral area of organisms (Cascio et al, 2001). Moreover, benefits of prophylactic circumcision are controversial.

Once urinary tract antimicrobial prophylaxis is initiated, duration is unclear. Prophylaxis may be stopped when resolution of the urinary tract abnormality occurs (e.g., spontaneous or surgical resolution of vesicoureteral reflux or obstruction).

When resolution does not occur within a few months to years, however, the time for stopping prophylaxis becomes indeterminate. Because evidence exists that renal scarring in girls with pyelonephritis may be less likely after 5 to 6 years of age, and may occur less frequently until age 15 to 16 years (see Renal Scarring), it is reasonable to try stopping prophylaxis when a patient reaches age 5 to 8 years or older, especially when he or she has no history of UTI and no renal scarring. Although select groups of children have been followed for a few years after stopping prophylaxis, and they have generally done well without evidence of urinary tract infections or new scars, these studies are limited by lack of randomization, short follow-up, and/or small numbers (Cooper et al, 2000). Although many antimicrobial agents treat UTI, the efficacy, microbiology, and pharmacology of few antimicrobial agents used for prophylactic effect have been examined in children.

The ideal prophylactic agent should have low serum and high urinary concentrations, minimal effect on the normal fecal flora, be easily administered and tolerated, and be cost effective. The potency of these antimicrobial agents is based upon the general susceptibility of most fecal Enterobacteriaceae to these agents at urinary levels. Because these agents are generally concentrated in the urine, the urinary drug levels should be much higher than the drug levels found simultaneously in serum, gut, or tissue, and, if sufficiently low, antimicrobial resistance patterns should not develop in the gut. In some instances, this characteristic of the prophylactic antimicrobial agents may be dose related, so that inappropriately high dosing for prophylaxis is less effective rather than more effective, because bacterial resistance is created (Martinez et al, 1985).

A difficulty in determining prophylaxis efficacy is dose selection. Although adequate urinary levels are required for bactericidal activity, how many hours per day these levels must persist is unknown. In an unusual urinary bioassay study of pediatric prophylaxis, after a single prophylactic evening dose, cotrimoxazole and cefixime sustained bactericidal effect for about 60% of a 24-hour day, with much shorter effects for nalidixic acid and cephalexin (Pomeranz et al, 2000). It is unclear, however, whether a shorter-lived, lower urinary concentration would achieve better prophylaxis with less likelihood of creating bacterial resistance. There is also evidence that commonly selected antibiotics may have different absorption and metabolism patterns in children than in adults (Rylance et al, 1985; Hoppu, 1987; Pomeranz et al, 2000).

Table 116–5.

Indications for Urinary Tract Antimicrobial Prophylaxis

Vesicoureteral reflux
Unstable urinary tract abnormality (e.g., partial urinary tract obstruction)
Normal urinary tract but frequent reinfections
After acute UTI awaiting radiologic evaluation
Urethral instrumentation
Immunosuppressed or immunocompromised status
Infants with first UTI before 8-12 weeks of age
Clean intermittent catheterization and vesicoureteral reflux (?)

UTI, urinary tract infection.

In any case, the parent who doubles or triples the dose of prophylactic antimicrobial agent each time their child develops the slightest symptom or cold may be destroying the prophylactic value of the agent and creating greater bacterial resistance with a higher likelihood of a break-through infection with a resistant organism. Another consideration is that long-term patient compliance with daily prophylaxis may be difficult (Smyth and Judd, 1993).

Because urinary prophylaxis is usually initiated following treatment of an infection for which long-term (10 days) high-dose treatment was given, the fecal flora is usually resistant to the treatment drug and many of the prophylactic agents. The child who is very susceptible to urinary infections is likely to become reinfected with an organism resistant to the prophylactic agent before the gut is repopulated with more normal flora. This accounts for frustrating "break-through" infections that occur when the child is on prophylactic antimicrobial agents or after treatment of other frequent infections such as otitis media. **The period of greatest risk of recurrent infection is usually the first few weeks after any full-dose treatment. This is the reason why the therapeutic antimicrobial agent should not be the prophylactic agent.** In children with normal urinary function, useful agents for urinary prophylaxis are nitrofurantoin, cephalexin, and trimethoprim-sulfamethoxazole (Brendstrup et al, 1990). In toilet-trained children, urinary tract prophylactic antimicrobial drugs may be best given once nightly, when they will be excreted into and remain in the urine overnight.

The long-term effects of prophylactic agents on the child and their microbial ecology are incompletely examined. A literature review of nitrofurantoin and trimethoprim-sulfamethoxazole prophylaxis in children supports long-term safety (Karpman and Kurzrock, 2004). A question relating antibiotic usage and breast cancer in women was raised following an epidemiologic study of the two entities; however, data relating the two entities are equivocal, and further exploration of this information is needed before a clear conclusion can be drawn (Sørensen et al, 2004; Velicer et al, 2004). Although there is some evidence that antibiotics that lack systemic absorption and are excreted only in the urine may result in less overall bacterial resistance and change to human microbial ecology than systemic agents, long-term studies are lacking (Gribble and Puterman, 1993; Johnson et al, 1994; Sandock et al, 1995; Schlager et al, 1998).

Nitrofurantoin

Nitrofurantoin is an effective urinary prophylactic agent because its serum levels are low, urinary levels high, and it produces minimal effect upon the fecal flora (Winberg et al, 1973). Its effect is based upon urinary excretion of the antimicrobial once daily and is found to be effective in girls at doses of 1.2 to 2.4 mg/kg given each evening (Lohr et al, 1977). When renal function is less than half of normal, the efficacy of nitrofurantoin may also be reduced.

The majority of nitrofurantoin drug reactions occur in adults; it has caused acute allergic pneumonitis, neuropathy, and liver damage (Holmberg et al, 1980). Long-term treatment has been associated with rare cases of pulmonary fibrosis. **Children with glucose-6-phosphate dehydrogenase deficiencies should not take nitrofurantoin, because it is an oxidizing agent that can cause hemolysis.** About 10% of African-Americans, Sardinians, non-Ashkenazi Jews, Greeks, Eti-Turks, and Thais may have a glucose-6-phosphate deficiency, and in these persons, regeneration of glutathione, which is partially responsible for maintaining red blood cell integrity, is impaired by the enzyme deficiency. When nitrofurantoin is given, it oxidizes the hemoglobin to methemoglobin, which is degraded (Thompson, 1969).

E. coli resistance to nitrofurantoin at one institution was 2.3%, whereas resistance to the quinolones was about 24% (Kashanian et al, 2008).

Cephalexin

Cephalexin was studied in adults as a prophylactic agent (Martinez et al, 1985). **Although fecal Enterobacteriaceae resistance has developed in many patients taking full-dose cephalexin (500 mg 4 times daily), patients taking low-dose (one quarter to one eighth the adult daily dose, 250 to 125 mg/day) do not appear to develop resistance.** Cephalexin at one quarter or less of the treatment dose per weight may be a useful pediatric prophylactic agent.

Trimethoprim-Sulfamethoxazole

Trimethoprim-sulfamethoxazole has been a successful combination drug in the treatment of UTI and useful for prophylaxis at a dose of approximately 2 mg/kg of trimethoprim (Grüneberg et al, 1976; Stamey et al, 1977). The trimethoprim has the unusual characteristic of diffusing into the vaginal fluid and therefore decreasing vaginal bacterial colonization in the female (Stamey and Sexton, 1975). **Because the trimethoprim-sulfamethoxazole combination contains a sulfonamide, it probably should not be used in the first few months of life; sulfonamides may compete for bilirubin binding sites on albumin and cause neonatal hyperbilirubinemia and kernicterus.** As previously mentioned, there has been a significant increase in the bacterial resistance rate seen for this drug over the past decade, making it less useful than previously.

Trimethoprim

Initial studies performed in adult women found trimethoprim (dose approximately 2 mg/kg once nightly) to be as effective as trimethoprim-sulfamethoxazole and nitrofurantoin in preventing recurrent UTI (Stamm et al, 1980). In contrast, other studies show rapid emergence of significant trimethoprim-resistant *E. coli* during either treatment or prophylaxis (Huovinen and Toivanen, 1980; Brogden et al, 1982; Murray et al, 1982; Murray and Rensimer, 1983; Brumfitt et al, 1985; Brendstrup et al, 1990).

Studies examining emergence of resistance are controversial. In one study after 14 days of trimethoprim 200 mg daily, 96% of the trimethoprim-resistant *E. coli* isolated from the fecal flora were resistant to at least four other antimicrobial agents (Murray et al, 1982), emphasizing the need for concern regarding resistance and spread of multidrug resistance. **A clinical trial in children examined the efficacy of nitrofurantoin and trimethoprim prophylaxis in preventing recurrent UTI and showed nitrofurantoin to be more effective as prophylaxis when used in association with urinary tract abnormalities or vesicoureteral reflux** (Brendstrup et al, 1990). Nitrofurantoin prophylaxis did not change the resistance pattern in uropathogens causing subsequent UTI, whereas those on trimethoprim prophylaxis developed a breakthrough UTI with an organism resistant to the drug in 76%.

With the recent distribution of liquid trimethoprim approved for treatment of acute otitis media in children and possible wider

usage, judicious use may prevent a repetition of previous antimicrobial resistance.

Nalidixic Acid

Nalidixic acid was used to treat children before the advent of more powerful quinolones; however, testing of the newer quinolones (e.g., norfloxacin, cinoxacin, ciprofloxacin) showed these drugs to cause cartilage erosion in weight-bearing joints and arthropathy in immature animals. In limited groups of children treated with quinolones, there have not been these problems (Schaad, 1991). A study examining quinolones in children was performed, but the results are unknown at this time.

Probiotic and Naturopathic Treatments

Study of human infectious disease requires understanding of the normal human microbiota—the microorganisms living on and within the human body. The combination and interplay between these microorganism genomes and the human genome (together called the microbiome) requires a complex interchange and balance in which the "normal" microbiota forms part of normal bodily function. Microbial imbalance or invasion with abnormal organisms creates infection or disease (Turnbaugh et al, 2007).

Concerns about the growing rate of bacterial resistance and possible antimicrobial therapy–associated conditions, such as childhood allergy, has stemmed interest in dietary, probiotic, and alternative therapies to routine antimicrobial agents for UTI treatment and potential prevention. Because the rectal bacterial flora is the bacterial reservoir for UTI, investigators have attempted to manipulate the organisms. As such, **probiotic therapy refers to a concept in which live organisms are given to patients for therapeutic benefit, often as food or dietary supplements**.

Although the entire mechanisms of action of most probiotic organisms are undiscovered, they are generally nonpathogenic and nontoxigenic organisms. They are characterized by their ability to survive transit through the gastrointestinal system by adherence to gut epithelium or mucus. These microorganisms protect against pathogenic organisms by competitive exclusion, secretion of adhesion or growth-inhibitory products that have antimicrobial effects, alteration of the host immune status, or contribution to host nutritional status (Vanderhoof and Young, 2002; Macfarlane and Cummings, 2002; Kontiokari et al, 2004; Servin, 2004; Jones and Versalovic, 2009; Lim et al, 2009). Yeast, bacilli, *E. coli*, enterococci, bifidobacteria, and *Lactobacillus* trials have had variable success.

Investigation has shown that certain undigested portions of food, usually nondigestible carbohydrates (oligosaccharides), may be consumed by certain gut microbiota, especially probiotic organisms, and encourage their growth. These molecules are **prebiotics** (Chen and Walker, 2005; Hord, 2008).

Both prebiotic and probiotic agents have been used to alter allergic reactions, infectious or postantibiotic diarrhea, infant necrotizing enterocolitis (Lin et al, 2005), urinary tract infections (Czaja et al, 2007), and adult female vaginosis (Reid, 2008). In the area of UTI, probiotic lactobacilli have been used to prevent necrotizing enterocolitis in infants, catheter-related infections in spinal cord–injured patients or in children with a neurogenic bladder, and to prevent recurrent UTI in women. There are studies showing that probiotics may have a place in decreasing recurrent UTI, and also ongoing studies. At this time, results are variable and appear to be dependent upon bacterial strain, preparation, dosage and regimen, and administrative route. A randomized trial in premature infants using *Lactobacillus* GG showed no protective probiotic effect for UTI or necrotizing enterocolitis (Dani et al, 2002; Lin et al, 2008). A combination vaginal suppository of *L. rhamnosus* and *L. reuteri* has treated bacterial vaginosis in adult women (Reid, 2008), and others have shown that *L. crispatus* vaginal suppositories can establish vaginal colonization, particularly when the vaginal microbiota is abnormal (Czaja et al, 2007). **Because there are no evidence-based data related to UTI treatment or prevention with *Lactobacillus* or specific regimens and dosing, and variable drug formulation and activity are found** (Michail et al, 2006), **a recommendation cannot be made at this time.**

It is notable that risks of probiotic *Lactobacillus* usage are recognized in premature neonates or individuals with immune deficiency, chronic disease, or extreme debilitation in whom probiotic usage–associated instances of bacterial sepsis and death have occurred (Land et al, 2005; Boyle et al, 2006).

Microorganisms have also been used to create a "protective" interference bacteriuria using organisms with nonvirulent features. The theory is that these strains will competitively inhibit more virulent or pathogenic organisms. Trautner and associates have introduced genetically engineered *E. coli* that caused asymptomatic bacteriuria in another patient into neurogenic bladders of patients on intermittent catheterization (Trautner et al, 2007, 2008; Prasad et al, 2009). Although bacteriuria occurred and symptomatic UTI decreased in this population, the study sample size was too small for conclusions. This approach offers a novel form of intervening in recurrent UTI.

There is public interest in alternative dietary or food supplements that may decrease the likelihood of UTI. There is evidence that cranberry products inhibit fimbriated *E. coli* adherence and seem to decrease bacterial biofilms, perhaps thus decreasing recurrent UTI (Kontiokari et al, 2005). Reviews of randomized control studies in adult women show that cranberry products reduced the incidence of UTI during a period of a year; however, side effects and subsequent study-patient dropout was high. Because controls regarding formulation and dosing were variable, the optimal methods of administration, dosage, and timing are unclear from these studies (Jepson and Craig, 2007a, 2007b).

Studies on cranberry-product usage in children has focused upon use in children with a neurogenic bladder, and benefit in these groups is not supported at this time (Schlager et al, 1999; Jepson and Craig, 2007a, 2007b).

Future Treatments

At this time, the most powerful therapies for acute UTI are antimicrobial agents. Vaccine trials to prevent mucosal adherence of uropathogenic *E. coli* in animals by using common bacterial antigens or the FimH subunit of type 1 pili (Langermann et al, 1997; Thankavel et al, 1997; Uehling et al, 1999), and use of preventive *Lactobacillus* variants are ongoing, but there are no acceptable long-term preventive interventions at this time.

IMAGING EVALUATION

Imaging studies are basic to urinary tract evaluation for infection. Guidelines for optimal imaging are changing as data emerge. Some imaging evaluation data are mixed with data related to imaging for potential risk of UTI, so interpretation is complex. With multiple imaging modalities available, however, the most efficient and

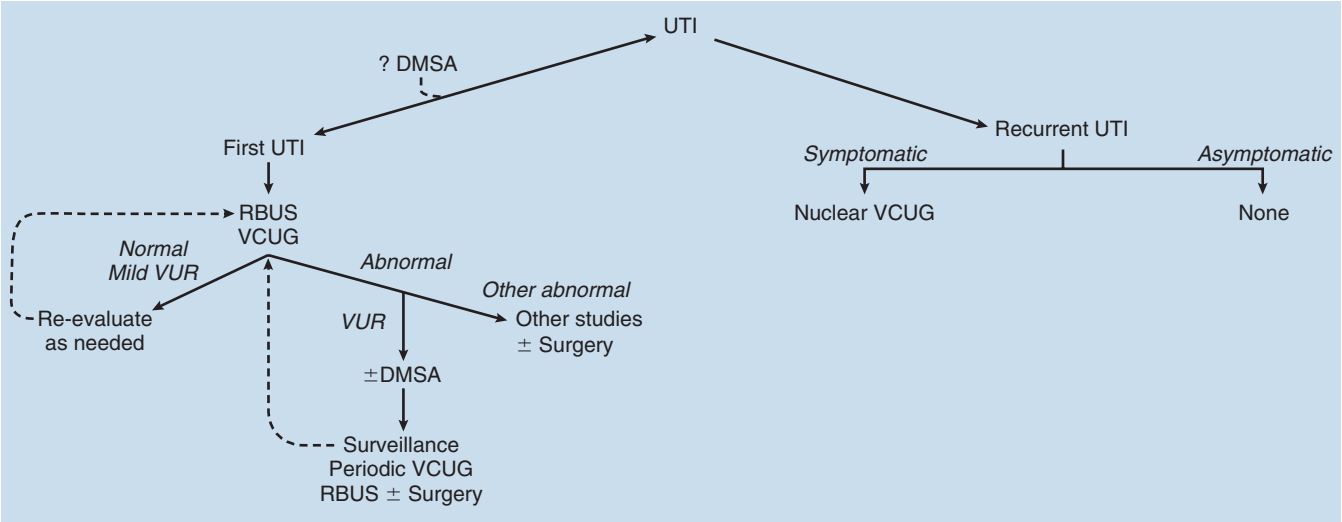


Figure 116–4. Flow diagram of imaging studies used to evaluate and manage urinary tract infections (UTI) in infants and children using the functional classification of UTI from Figure 116–1. DMSA, technetium-99m dimercaptosuccinic acid renal scanning; RBUS, renal and bladder ultrasonography; VCUG, voiding cystourethrogram; VUR, vesicoureteral reflux.

rational order and selection of studies must be made with a goal of minimizing damage from the acute and future UTI. **Radiologic imaging can be used to (1) evaluate and localize the acute urinary infection, (2) detect renal damage from the acute infection, (3) identify genitourinary anatomy that increases risk of future renal damage from infection, and (4) evaluate change in the urinary tract over time.** Deciding which studies are necessary in a child with a presumptive or diagnosed UTI should depend on whether potential radiologic findings would change a child's clinical management (Fig. 116–4).

Acute Imaging

Early urinary tract imaging is important in a seriously ill and/or febrile child in whom the site of infection is unclear or who has unusual circumstances. Circumstances such as newly diagnosed azotemia; a poor response to appropriate antimicrobial drugs after 2 to 3 days; an unusual infecting organism (e.g., tuberculosis or urea-splitting organism such as *Proteus*); known partial obstruction, such as a ureterocele, ureteropelvic junction obstruction, and megaureters; nonfunctioning or poorly functioning renal units; or history of diabetes, papillary necrosis, or a neuropathic bladder, warrant acute or early upper and lower tract urinary tract imaging. If treatment depends upon localizing the infection to the kidney, an acute imaging study can be performed. This is particularly important in the severely ill hospitalized child who improves on initial parenteral treatment, but urinary cultures are inadequate or indeterminate for bacterial infection. An acute DMSA scan may show if acute renal inflammation is present and justifies treatment. If, on the other hand, UTI appears highly likely, and antimicrobial treatment will be started regardless of radiologic findings, early DMSA scintigraphy is probably unnecessary. This has been confirmed recently by Hoberman and associates (Gorelick et al, 2003; Hoberman et al, 2003).

Acute imaging (ultrasonography) is recommended by the United Kingdom National Institute for Health and Clinical Excellence Guidelines when a child does not respond to antimicrobial treatment within 48 hours or if the UTI is "atypical" (defined as a child being seriously ill), has poor urinary flow, an abdominal mass, elevated creatinine, or has an infection with a non–*E. coli* organism (Baumer and Jones, 2007).

Definition of Renal Morphology and Identification of Urinary Tract Abnormalities

Because UTI in infants and young children may serve as a marker for anatomic abnormalities, after the initial UTI has been adequately treated, the child may be maintained on antimicrobial prophylaxis, and radiologic studies may be performed to delineate the urinary tract. Although there is controversy whether studies should be performed after the first or recurrent episode, if obstructive lesions are found in 5% to 10% of children and reflux occurs in 21% to 57% (Kunin et al, 1964; Abbott, 1972; Asscher et al, 1973; Newcastle Asymptomatic Bacteriuria Research Group, 1975), early detection of these abnormalities merits imaging attention.

It is of interest that VUR is diagnosed more frequently in children than in neonates. One study of the first UTI in neonates shows that VUR occurred at a rate of 20% in both girls and boys, yet the rate of UTI occurrence was sixfold greater in infant boys versus girls (Cleper et al, 2004). **Urinary tract imaging evaluation consists of some form of renal and upper collecting system evaluation (usually renal and bladder ultrasonography [RBUS]) and at times voiding cystourethrogram (VCUG).** As prenatal ultrasonography reveals many genitourinary abnormalities, the need for performing postnatal UTI imaging evaluation has been questioned. In one multicenter study examining children after their first UTI, however, no cases of grade V vesicoureteral reflux, obstructive lesions, and few cases of grade IV reflux were detected, although 39% of children scanned had mild to moderate vesicoureteral reflux (Hoberman et al, 2003). Another study demonstrated that in their population RBUS may be disregarded with a normal prenatal ultrasonography

(US) (Miron et al, 2007). Because this study occurred under circumstances of universal health care with a high physician to patient ratio, this recommendation may not apply to all populations.

Need for the VCUG in children less than 2 years old who have a UTI, a renal ultrasonography without evidence of urinary tract dilation, and a DMSA scan without scarring 3 months later has also been questioned (Hansson et al, 2004). In a retrospective study of children with UTI who are less than 2 years old, in which children who had suspected obstruction were eliminated, VUR grade III or higher correlated with presence of renal lesions, and 26% of children had evidence of renal scarring on DMSA scan. Although a normal DMSA scan and dilating grade III VUR were present in seven children, after 2 years, VUR resolved spontaneously in five children, one improved, and one developed a scarred kidney. Forty-six percent of infants without VUR had DMSA-defined scarring and 20 of 44 (45%) of children with grade I to II VUR had scarring (Hansson et al, 2004). Had the children with a normal DMSA scan and grade I to III VUR been undetected and untreated with prophylaxis, as suggested by these authors, the outcome would be unclear.

The United Kingdom National Institute of Clinical Excellence guidelines have limited imaging recommendations. Although they recommend RBUS for children during acute atypical UTI, as noted earlier, RBUS is ultimately performed only when UTI is recurrent or the child is less than 6 months old. VCUG is recommended only for children younger than 6 months or those from 6 months to 3 years with non–*E. coli* UTI, if there is poor urinary flow, if ultrasonography shows urinary tract dilation, or there is a family history of vesicoureteral reflux. It must be emphasized, however, although the guidelines restrict earlier imaging, they recommend a DMSA nuclear scan 4 to 6 months after the UTI, whenever the UTI is recurrent, and after an atypical UTI if the child is less than 3 years old (Baumer and Jones, 2007). Others recommend performing a VCUG only when an acute DMSA scan is positive (Preda et al, 2007).

Although the American Academy of Pediatrics practice parameters limited the original recommendations for first UTI imaging evaluation of the upper and lower urinary tract to children between 2 months and 2 years old (American Academy of Pediatrics, 1999a), others support such evaluation in even younger infants (Goldman et al, 2000). These recommendations are under revision and are likely to reflect more selective imaging, except in children with recurrent UTI.

Acute studies of the kidney may cause overestimation of renal size resulting from initial edema or lack of appreciation of renal scarring, because mature renal scars may take up to 2 years to be seen by certain imaging techniques (Filly et al, 1974; Troell et al, 1984; Gordon, 1986; Conway, 1988; Johansson et al, 1988a, 1988b; Conway and Cohn, 1994). As a result, later studies may show smaller or scarred kidneys that may be misinterpreted and cause inappropriate changes in patient management. **It is reported that the risks of missing renal scars by performing ultrasonography alone ranges from 0.4% (school-age children) to 11.1% (infants with recurrent upper tract UTI)** (Christian et al, 2000), but it should be emphasized that this is age dependent so that further evidence associated with the risk is needed. Obviously, obstruction and other anatomic abnormalities demonstrated by radiologic evaluation may require other evaluation(s) specific to their diagnosis before definitive management is decided. These situations need to be evaluated and treated individually.

Follow-up Imaging Evaluation

When a child who has a UTI has no abnormality found after urinary tract radiologic evaluation, they need no further studies. If the collecting systems are normal, but one or both kidneys show massive generalized or focal edema with areas of possible hypoperfusion during the acute infection, a subsequent study may be performed to examine the kidney for signs of renal scarring or shrinkage. The situations under which the United Kingdom National Institute for Clinical Excellence recommends a DMSA scan at 4 to 6 months after recurrent UTI are described in greater detail in the section Acute Imaging (Baumer and Jones, 2007). A DMSA scan will identify children who need monitoring for recurrent infections, hypertension, and renal dysfunction. **If a child has recurrent symptomatic pyelonephritis and no reflux found on previous fluoroscopic voiding cystourethrogram (VCUG), a nuclear VCUG may be more sensitive at revealing reflux, although less likely to define it** (Kogan et al, 1986; Macpherson and Gordon, 1986).

SPECIFIC IMAGING TECHNIQUES

Imaging techniques that are useful for evaluating children with UTI consist of an upper tract modality and limited use of a lower tract one that evaluates for vesicoureteral reflux. The radiologic follow-up of children diagnosed to have vesicoureteral reflux is discussed elsewhere. Details related to the use of each of these modalities are discussed in relation to each specific study.

Voiding Cystourethrography (VCUG, Fluoroscopic versus Nuclear)

The VCUG is the most important examination in assessing for vesicoureteral reflux in children, and, as such, is important when one wants to diagnose reflux. The VCUG may be performed either with fluoroscopy and iodinated contrast medium or with nuclear imaging agents (usually technetium-99m pertechnetate) using similar techniques (direct radionuclide cystography), but these studies give different information. The traditional fluoroscopic VCUG can show urethral and bladder abnormalities and vesicoureteral reflux.

The radionuclide VCUG may be more sensitive for reflux detection, but offers poorer spatial resolution so that details of the urethra and collecting system and degree of reflux may not be seen. **Vesicoureteral reflux detection by either fluoroscopic or radionuclide VCUG is dependent upon the child voiding** and the technical performance (e.g., bladder filling volume) of the study (Fairley and Roysmith, 1977; Lebowitz, 1986; Macpherson and Gordon, 1986). When a single nuclear VCUG shows no vesicoureteral reflux if performed for reflux follow-up, a year later 30% of patients may show reflux. Whether this discrepancy relates to previously missed reflux, recurrent reflux, or technical variation is unclear (Neel and Shillinger, 2000).

The main advantage of radionuclide VCUG has been the lower radiation exposure of 1 to 5 mrad or 1 mSv (ovarian dose) compared with 27 to 1000 mrad or 0.8 to 1.6 mSv from VCUG (reported ovarian exposure depends upon equipment) (Cleveland et al, 1992; Lebowitz, 1992). With modern imaging technology and a tailored examination, however, the fluoroscopic VCUG has been done with 1.7 to 5.2 mrad (Kleinman et al, 1994) and, if available, may offer advantages of anatomic resolution compared

with the radionuclide VCUG. Fluoroscopic radiation from modern equipment claiming low-dose radiation at four different children's hospitals may produce a wide exposure range—from 34 to 2230 mrads/minute—and pulsed fluoroscopy with optimization for pediatric image produces the best image quality per exposure (Brown et al, 2000).

The radionuclide VCUG may be most useful for periodic reflux re-evaluation (Lebowitz, 1992) or for screening siblings who have low risk of reflux. **In first infections, in infants or young boys in whom risk of genitourinary abnormality is high and urethral visualization important, or in any child in whom high-resolution imaging of the lower urinary tract is important, the radionuclide VCUG should not be used.**

Indirect radionuclide VCUG is performed as part of a renal imaging study. The radionuclide is injected intravenously and the study performed when the kidneys and upper collecting systems are cleared of the radiopharmaceutical agent and the bladder is filled maximally with it. The child then voids. Although this method avoids catheterization, when compared with the direct radionuclide VCUG, there is increased radiation exposure and decreased resolution because of body radionuclide background. Because it detects only about 60% of the reflux compared with the direct VCUG, there are few reasons to perform this test (Eggli and Tulchinsky, 1993).

VCUG may be performed as soon as the urine is sterile and voiding is normal; patient compliance may be greater when performed within a week of the diagnosis. Studies have shown that UTI does not cause reflux, and there is no reason to wait 3 to 6 weeks to perform the study as long as voiding and bladder volumes have returned to normal (Lebowitz, 1986; McDonald et al, 2000). Whether the VCUG is done during antimicrobial therapy, immediately after, or a few weeks afterward is not important so long as the child has normal renal function, has normal voiding, responds rapidly to antimicrobial treatment with urinary sterilization, and/or is maintained on prophylactic antimicrobial treatment to keep urine sterile in the interval between the herald infection and the radiologic evaluation.

If the VCUG is the initial radiologic study, subsequent imaging may be directed by VCUG results (Hellström et al, 1989). If the VCUG is normal, shows a ureterocele, or vesicoureteral reflux, an ultrasound examination of the kidney and bladder will usually demonstrate other urinary tract structural abnormalities or anomalies, such as dysplasia or obstruction, should they exist. In general and commonly, renal and bladder ultrasonography may be the initial study and will detect children who may need urgent urologic intervention (Alon et al, 1986, 1989; Honkinen et al, 1986; Lindsell and Moncrieff, 1986; Macpherson and Gordon, 1986). If, however, vesicoureteral reflux appears to be the primary diagnosis, DMSA scintigraphy with single-photon emission computed tomography (SPECT) or three-dimensional renal magnetic resonance imaging (MRI) may be the most useful studies with which to detect renal scars when desired (Fig. 116–5).

Renal and Bladder Ultrasonography (RBUS)

Renal ultrasonography has replaced intravenous pyelography as the standard for evaluating the pediatric urinary tract after UTI. Because this modality is not dependent upon renal function, ultrasonography will detect both gross and subtle abnormalities of the urinary tract, including those that involve poorly functioning or nonfunctioning renal units. **Routine renal ultrasonography is not as sensitive as CT, MRI, or DMSA scintigraphy at detecting changes associated with acute UTI** (Verboven et al, 1990, Björgvinsson et al, 1991; Eggli and Tulchinsky, 1993; MacKenzie et al, 1994; Mucci and Maguire, 1994)**.**

When performed at the time of acute inflammation, ultrasonography may show enlarged swollen kidneys, focal enlargement from edema and inflammation that may create a masslike effect (focal pyelonephritis or lobar nephronia), and ureteral widening (Silver et al, 1976; Hellström et al, 1987; Conway, 1988; Johansson

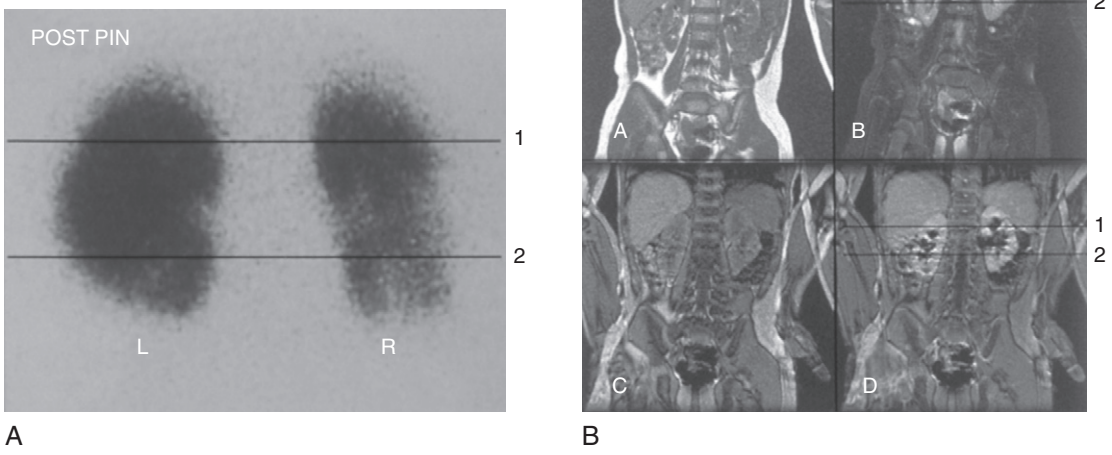


Figure 116–5. Dimercaptosuccinic acid (DMSA) renogram with single-photon emission computed tomography (SPECT) **(A)** and magnetic resonance imaging (MRI) **(B),** showing renal scars in a 3-year-old girl with reflux nephropathy. Comparative coronal levels of DMSA **(A)** and MRI **(B)** are shown. (From Rodriguez L, Spielman D, Herfkens R, Shortliffe L. Magnetic resonance imaging [MRI] for the evaluation of hydronephrosis, reflux, and renal scarring in children. J Urol 2001;166:1023–27.)

et al, 1988a, 1988b). High-resolution power and color Doppler ultrasonography may also detect small areas of inflammation and hypoperfusion detected by DMSA scintigraphy (Dacher et al, 1996; Morin et al, 1999). As noted previously, renal pelvic debris and sediment levels are diagnostic of pyonephrosis. Although renal inflammatory masses are usually easily differentiated from other masses based on symptom context, sometimes imaging with CT or MRI is needed (Cheng et al, 2004).

RBUS is, moreover, more likely to detect perinephric fluid collections or anatomic abnormalities, especially those involving urinary tract dilation, than either DMSA scanning or intravenous urography (MacKenzie et al, 1994). Pediatric RBUS is probably more dependent upon the skill and experience of the ultrasonographer with children than is DMSA scintigraphy (Patel et al, 1993). **Even with careful examination for vesicoureteral reflux, however, RBUS is notoriously poor at detecting or predicting vesicoureteral reflux** (Mahant et al, 2002).

Nuclear Renography

Because nuclear scintigraphy can detect areas of acute renal inflammation and chronic scarring, this test has improved detection of renal inflammation in pediatric UTI over the past 10 years. **Because approximately 60% of injected ^{99m}Tc-DMSA is bound to the proximal renal tubular cells and is excreted slowly in the urine, it is a good cortical imaging agent** (Jakobsson et al, 1992).

Radionuclide technology using pinhole images and high-resolution computed tomography (single-photon emission computed tomography [SPECT]) gives greater renal anatomic detail, resolution, and scar detection (Eggli and Tulchinsky, 1993). DMSA scintigraphy with SPECT is the benchmark for renal scars, and is the study used when cortical definition alone is needed (Björgvinsson et al, 1991; Eggli and Tulchinsky, 1993).

Because ^{99m}Tc-glucoheptonate, on the other hand, is partially concentrated, excreted, and partially bound to the renal tubule, both collecting system visualization and cortical definition is observed. Similarly, ^{99m}Tc-mertiatide (MAG3), a tubular renal imaging agent primarily used to assess renal parenchymal flow, function, and drainage, also has renal cortical imaging characteristics (planar or SPECT). MAG3 or ^{99m}Tc-glucoheptonate is almost as effective as DMSA in detecting changes of acute pyelonephritis (Traisman et al, 1986; Sreenarasimhaiah and Alon, 1995; Sfakianakis and Georgiou, 1997; Laguna et al, 1998). MAG3 has advantages over DMSA, because it is more rapid, gives a lower radiation dose to most organs, including the urinary bladder and gonads, and evaluates urinary tract drainage (Sfakianakis and Georgiou, 1997).

The findings of pyelonephritis detected by renal nuclear scintigraphy (i.e., DMSA with SPECT) differ depending upon the timing of the scan. Acutely, the renal studies will usually show either uptake defects or renal swelling (Wallin and Bajc, 1993; Wallin et al, 1997). The uptake defects may appear as wedge-shaped polar or lateral renal defects or as scattered uptake defects within the kidney. For this reason, DMSA may differentiate focal pyelonephritis, lobar nephronia, the column of Bertin, and neoplasm, although CT and MRI are generally more detailed. **After the acute episode heals, scans may show (1) a normal pattern, (2) generally diminished uptake and small kidney volume, (3) diminished uptake in the medial kidney, or (4) polar defects with diminished uptake in the renal poles** (Wallin and Bajc, 1994).

DMSA scintigraphy is clearly more sensitive than routine renal ultrasonography, or even intravenous urography, at detecting renal scarring, but newer high-resolution ultrasonography is nearly as sensitive as DMSA scintigraphy in diagnosing acute renal involvement (Morin et al, 1999). Because recurrent pyelonephritis appears to occur in the same areas as scarring, however, it may be difficult to differentiate between new and old or progressive renal scarring unless serial studies are performed (Björgvinsson et al, 1991; Rushton and Majd, 1992b). **Attempts to distinguish between congenital and acquired reflux nephropathy cite generalized decreased renal uptake relating to congenital and dysplastic changes, whereas focal defects are usually acquired** (Polito et al, 2000). These distinctions are important if one believes acquired lesions are preventable. In children in whom severe renal scarring has occurred and the glomerular filtration rate (GFR) may need to be estimated, the radionuclide renogram gives an accurate estimate of GFR even in young children (Gates, 1982; Shore et al, 1984; Rehling et al, 1989).

Intravenous Urography (IVU)

Although the traditional means of evaluating the upper urinary tract and documenting renal scarring was intravenous urography with renal tomography, in most situations DMSA scintigraphy has replaced the role of intravenous urography. DMSA scintigraphy is more sensitive for detecting renal scars but shows less resolution in defining the scars. An IVU still defines collecting system abnormalities in more detail than either DMSA scintigraphy or ultrasonography. It is probably most useful in defining the collecting system in patients with confusing situations or in whom calyceal detail may be important.

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

Although seldom used to evaluate acute renal inflammatory processes unless unusual or complicating anatomic configurations occur on ultrasonography, CT or MRI reveal detailed and sensitive signs of acute renal inflammation. These modalities are often able to differentiate and distinguish between inflammatory, neoplastic, and other renal masses seen on other imaging techniques.

For CT and MR evaluation all four stages of renal enhancement following contrast delivery—renal vascular (10 to 15 seconds), corticomedullary nephrographic (20 to 45 seconds), parenchymal nephrographic (45 seconds to 2 minutes), and excretory phase when the contrast appears in the collecting system (2 to 3 minutes)—should be examined for changes related to inflammation.

Acute inflammatory changes of the kidney may be described as (1) unilateral or bilateral, (2) focal or diffuse, (3) with or without focal swelling, and (4) with or without renal enlargement. Other features that may be seen during the various phases are cortical hypoattenuation, wedge defects, and poor corticomedullary differentiation during the cortical and parenchymal nephrographic phases, and linear bands of alternating hyper- and hypoattenuation parallel to the tubules and collecting ducts, creating a striated effect during the excretory phase. Scans delayed 3 or more hours may help to differentiate renal abscess from hypofunctioning parenchyma in severe pyelonephritis (Kawashima et al, 1997). It should be noted that acute focal pyelonephritis (or lobar nephronia) on CT has been misinterpreted as renal abscess, because of an appearance of acute decreased perfusion, and, at times, MRI- or

CT-guided needle aspiration may be needed to clarify the clinical situation. As the mass effect of focal pyelonephritis may take months to resolve, more remotely these may need to be differentiated from neoplasm.

In direct comparison studies of MRI, DMSA planar, and SPECT for detection of renal scars, single-series coronal fat-saturated T1W MRI is judged as able to replace DMSA, avoiding the need for injection and ionizing radiation (Kavanagh et al, 2005). For routine evaluation of UTI, neither CT nor MRI is cost effective, but in children with complicated anatomy and UTI, either CT or MRI can be highly useful for defining renal abnormalities and extent of disease, when other modalities are inconclusive. Because MRI may determine function, anatomy, and vesicoureteral reflux while avoiding the significant ionizing radiation of CT, MRI becomes a preferable imaging modality (Rodriguez et al, 2001).

RISKS OF IONIZING RADIATION AND RESPONSIBLE IMAGING

Recommendations for imaging evaluation after UTI have changed, in part, from greater knowledge of the epidemiology of UTI and, in part, from developing imaging technologies. Although technology has wrought newer imaging modalities with improved tissue and organ resolution, some progress occurs at the cost of significant increased patient radiation exposure. **Use of CT imaging is the main cause in one country for increased exposure to medical ionizing radiation by almost 25% (1.59 to 1.98 mSv per capita) from 1994 to 2002** (Shannoun et al, 2006). Others have noted that a few procedures, such as CT, angiography, and gastrointestinal and genitourinary contrast studies with fluoroscopy, account for almost 80% of total collective ionizing radiation dosage given to the public (Wall, 2004). With the growing ease and rapidity of CT scanning, moreover, abdominal-pelvic CT usage in children increased 92% at one U.S. institution from 1996 to 1999 (Brenner et al, 2001).

Increased recognition of the increased risks of lifetime cancer from relatively low-dosage radiation to children and fetuses has emerged from studies of children and fetuses who survived the atomic bomb in Nagasaki and Hiroshima, Japan. **These studies give evidence for a linear increase in excess lifetime solid cancer and leukemia risk for radiation exposure of 1 to 150 mSv and is highest for those exposed as children** (Preston et al, 2003, 2008).

Concern specifically relates to childhood radiation exposure because (1) childhood radiation has a longer time span during which effects may become manifest, (2) developing cells have greater potential of developing direct damage from radiation exposure, and (3) medical and diagnostic procedure radiation appropriate for adults is often unadjusted for children, causing disproportionately high-radiation exposure.

The measure of effective radiation dose is the millisievert (mSv), which is used to refer to a radiation dosage averaged over the entire body, accounting for the relative differences in the exposed tissues in a way that is comparative to natural background radiation (ICRP [International Commission on Radiological Protection], 1998). Most common background radiation is from cosmic rays at ground level, primordial radionuclides, or ingested potassium. Average background radiation is estimated to be 3 mSv per year (American College of Radiology and Radiological Society of North America, 2009), and estimated procedural radiation exposure of common pediatric urologic procedures is shown in Table 116–6. **A CT scan with and without contrast in a child, using pediatric parameters, will give an effective radiation dose of 6 to 10 mSv—almost 3.5 years of equivalent background radiation** (Gaca, 2008), **and the estimated lifetime cancer mortality from an abdominal pediatric CT in a 1-year-old child is 0.18%** (Brenner et al, 2001).

Radiation exposure risks to young developing infants and children must be considered carefully as practitioners consider individualized evaluation of UTI. Radiation risk to children may be limited in two ways: (1) decreased exposure through technologic imaging advance and (2) practitioner decision analysis in which imaging studies with risk of ionizing radiation exposure are selected only when information that may give advantage to treatment or management is obtained. Radiologists have adopted the concept of radiation exposure termed "as low as reasonably achievable" (ALARA) (Strauss and Kaste, 2006), and technical adjustments and improvements allow decreased exposure through such changes as pediatric-specific settings and pulsed and digital fluoroscopy.

Table 116–6.

Relative Radiation Exposure

EXAMINATION	AVERAGE EFFECTIVE DOSE (mSv)	EQUIVALENT CHEST RADIOGRAPHS	EQUIVALENT BACKGROUND RADIATION
Background radiation in a year	3	150	1 year
U.S. coast to coast airline flight	0.03	1.5	3.6 days
Chest radiograph	0.1	1	10 days
Abdomen radiograph	1.0	50	125 days
VCUG infant	0.8	40	90 days
VCUG (5-10 years)	1.6	80	180 days
Intravenous urogram (IVU)	1.6	80	180 days
Abdomen/pelvis CT (pediatric parameters)	3-5	250	1 year 260 days
Abdomen/pelvis CT with and without contrast (pediatric parameters)	6-10	500	3 years 155 days
Abdomen/pelvis CT (adult parameters)	15-20	750-100	5-6 years
Renal scan ^{99m}Tc-DMSA	1	50	125 days

CT, computed tomography; 99mTc-DMSA, technetium-99m dimercaptosuccinic acid; VCUG, voiding cystourethrogram.

Data from Gaca AM. Radiation protection and safety in pediatric imaging. Pediatr Ann 2008;37:383–7; American College of Radiology and Radiological Society of North America. Radiation exposure in x-ray examinations. Oak Brook (IL): RSNA; 2009. Smith T, Gordon I, Kelly J. Comparison of radiation dose from intravenous urography and 99Tcm DMSA scintigraphy in children. Br J Radiol 1998;71:314–9.

Ionizing radiation exposure in imaging studies for UTI evaluation occurs with CT, IVU, VCUG, and DMSA scintigraphy (1 mSv) (Smith et al, 1998). High-quality ultrasonography has generally replaced IVU, and digital and pulsed fluoroscopy limit exposure from performance of VCUG to low or negligible (in the opinion of some) (Perisinakis et al, 2006; Sulieman et al, 2007). In complex situations in which greater clarity or detail of the urinary tract is needed, MRI is increasingly useful, even though it may require sedation.

These changes, however, do not mitigate the urologist's role in choosing whether a child requires radiation exposure. Because we have advanced past using IVU and VCUG with fluoroscopy as primary imaging technologies with which we evaluate the urinary tract, and we have alternatives limiting or eliminating ionizing radiation, such as renal and bladder ultrasonography, nuclear VCUG, and magnetic resonance imaging, it is incumbent on the practitioner to make judicious and knowledgeable selection for imaging evaluation and use of fluoroscopy. Further limitations to ionizing radiation exposure need to be considered in vesicoureteral reflux evaluations.

SEQUELAE OF URINARY TRACT INFECTION

Chronic Pyelonephritis—Renal Scarring and Dysfunction

Coarse renal scarring seen radiologically as calyceal deformity and renal parenchymal thinning over localized or multiple calyces is known as "reflux nephropathy." Because it is now clear that such scarring occurs with or without reflux, the phenomenon would be better termed "pyelonephritic scarring." **The pediatric kidney appears to be at greater risk of scarring from bacterial pyelonephritis than the mature kidney.** Many factors, such as intrarenal reflux, urinary tract pressures, host immunity, age, genetic polymorphisms, and treatment appear to contribute to this.

Rolleston and associates (1974) found that areas of renal scar were associated with intrarenal foci of reflux (pyelotubular backflow) observed on voiding cystourethrography in children less than age 4 years who had vesicoureteral reflux. Calyces allowing reflux contained papillae fused with adjacent papillae, which caused the papillary ducts to open at right angles rather than at oblique angles that are more resistant to reflux (Ransley and Risdon, 1974). **These compound papillae are at the renal poles, the areas in which clinical renal scarring is observed most commonly clinically** (Hannerz et al, 1987)**.** Common patterns of scarring are seen (Fig. 116–6).

In pigs with vesicoureteral reflux and even intrarenal reflux, however, renal scarring occurs only when both vesicoureteral reflux and bacteriuria are present (Ransley and Risdon, 1978). Reflux without bacteriuria resulted in renal scarring only when the urethra was partially obstructed, causing abnormally high voiding pressures (Hodson et al, 1975; Ransley et al, 1984). Experimentally, therefore, the "water hammer" (back pressure) effect of vesicoureteral and intrarenal reflux alone causes renal scarring only when associated with abnormally high bladder and renal pressures.

In the neonate, however, the kidney may respond to urinary back pressure, or the "water-hammer" effect at different thresholds and in different ways than the adult kidney. Autopsy studies on normal neonates (younger than 1 month) reveal that intrarenal reflux into compound calyces occurs at low pressures of 2 mm Hg, whereas the same reflux in a child 1 year old occurs at 20 mm Hg. At autopsy, furthermore, at 50 mm Hg pressure, intrarenal reflux occurs in all calyces, even simple ones, in children less than 12 years old (Funston and Cremin, 1978).

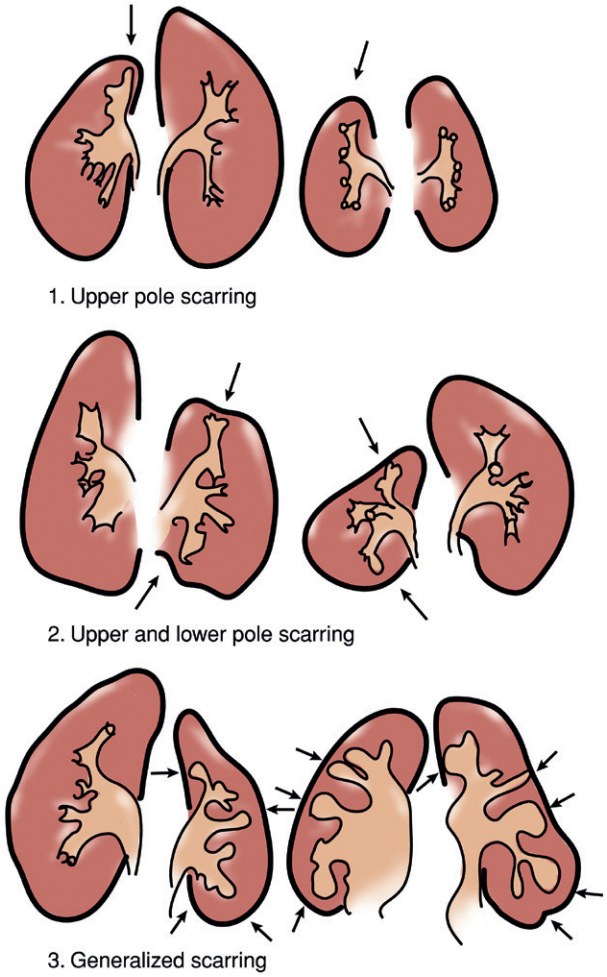


Figure 116–6. The common areas of renal scarring, characterized by parenchymal thinning over a deformed calyx, as examined from intravenous pyelograms. The extent of scarring was related to single polar scars; multiple areas of upper, lower, and medial scars; or generalized scarring, as depicted. (From Hodson CJ. Natural history of chronic pyelonephritic scarring. Br Med J 1965;2:191–4.)

This suggests that physiologically normal urinary intrapelvic pressures in adults or older children could have a different response in neonates. This effect could be augmented by increases in renal pelvic pressures that may result from ureteral and pelvic smooth muscle dysfunction in infection. Animal models with bacterial urinary infection show that infection elevates renal pelvic pressures whether or not reflux is present, and, in fact, renal pelvic pressures may even be higher when reflux is absent. This may also account for further parenchymal damage with severe infection (Issa and Shortliffe, 1992; Angell et al, 1998). Young children have incompletely developed immune and neurologic systems. A depressed or incompletely mature immune system may allow easier bacterial colonization of the bladder and kidney because of decreased local and systemic defenses, and it may eliminate bacteria even less efficiently once bacteriuria occurs. Immature

bladder activity associated with increased contractions may also contribute to dynamic change in the upper tracts, even in the apparently normal child (Koff and Murtagh, 1984). As a result, bacteriuria combined with reflux may result in greater susceptibility to renal damage.

Neonatal symptoms of urinary infection and pyelonephritis are often vague and nonspecific, resulting in delayed or inadequate treatment. During this period of delay, bacterial invasion of the kidney creates an inflammatory response characterized by vascular granulocytic aggregation and hypoperfusion with subsequent scarring and loss of renal parenchyma (Winberg et al, 1974). Finally, genetic polymorphisms associated with the immune system and renin angiotensin system may make some individuals more susceptible to renal scarring from pyelonephritis, as previously discussed.

One must not confuse small, scarred kidneys with congenitally small, dysplastic, poor, or nonfunctioning kidneys, however. This distinction, one that is difficult and sometimes impossible to make radiologically, is important because dysplastic kidneys are histologically abnormal. Dysplastic kidneys and atrophic, scarred kidneys are histologically distinct. Although gross renal changes may be detected radiologically, lesser lesions associated with vesicoureteral reflux and infection insult, such as cortical pitting, global renal shrinkage, or hypoplasia, may not be detected by routine imaging tests and yet may affect renal histology and function (Chang et al, 2007; Wong et al, 2009).

Using pyelographic techniques before DMSA scintigraphy, about 17% of school-age children with screening bacteriuria (cultures performed for screening rather than for symptoms) are diagnosed with renal scarring (Asscher et al, 1973; Newcastle Asymptomatic Bacteriuria Research Group, 1975; Savage, 1975). This correlates with the observation of Winberg and associates (1974) that 4.5% of children had radiologic renal scars after their first symptomatic UTI, and 17% had scars after the second symptomatic UTI. Although the percentage of scars using these earlier techniques may underestimate scarring, because some studies using DMSA scintigraphy suggest the incidence of scarring after symptomatic UTI could be almost twice this rate, these data emphasize that a child with both covert and symptomatic UTI has significant risk for renal scarring. Although by definition, the natural history and pathogenesis of scarring in covert or asymptomatic bacteriuria is unknown, these scars probably reflect injury from previous undiagnosed bacteriuric episodes.

In most children with UTI in whom renal scars are found (and who have normal voiding) on the first set of imaging studies, the scarring does not improve or worsen irrespective of the child's future clinical course (Verber and Meller, 1989). It has been hypothesized that the young kidney may be more prone to damage, and, as such, the initial UTI in the neonate or young child less than 4 or 5 years old causes whatever renal damage that will occur, and this initial response determines the kidney's future course ("big bang theory"). This theory is supported by the higher prevalence of early cortical DMSA-defined defects observed in children less than 2 years old who have UTI, compared with those greater than 2 years old (Ditchfield et al, 1994). One retrospective study links individuals with scars found on DMSA scanning with a greater likelihood of breakthrough UTI and less likely spontaneous resolution of their vesicoureteral reflux (Mingin et al, 2004). Although older children appear to have less risk of scarring from UTI than children less than 5 years old, vulnerability for scarring persists until puberty (10 to 15 years old). Studies link new or progressive renal scarring after early childhood diagnosis to uncontrolled recurrent UTI and persistent vesicoureteral reflux (Filly et al, 1974; Smellie et al, 1985; Shimada et al, 1989). Filly and associates (1974) found that in girls less than 10 years old who had recurrent UTI and vesicoureteral reflux, renal scars progressed (i.e., developed clubbing or scarring in previously normal areas) in 43% of kidneys (17/40), and 2 of 16 normal kidneys developed new scars. Some of these scars took up to 2 years from the episode of pyelonephritis to maximally evolve.

Investigators who have used DMSA scanning routinely to detect renal scars have also found that new or progressive renal scarring is more common than previously thought. Up to 7.3% of children with recurrent or persistent bacteriuria and reflux have progressive scarring, and almost all young children with recurrent pyelonephritis suffer renal scarring (Shimada et al, 1989; Verber and Meller, 1989; Jakobsson et al, 1994).

Conversely, imaging evaluation of girls with reflux grades II to IV/V (International Reflux Grading) without further UTI show no progressive renal damage when followed up to 10 years (Holland et al, 1990). This supports earlier animal and clinical data that given normal urinary tract urodynamics, vesicoureteral reflux alone (sterile reflux) does not cause renal damage or impair renal growth (Ransley and Risdon, 1978; Smellie et al, 1981; Ransley et al, 1984). If no infections occur, no association between the severity of vesicoureteral reflux and impaired renal growth has been demonstrated in an otherwise normal urinary tract.

Furthermore, adults who have acute nonobstructive pyelonephritis and normal urinary tracts rarely develop focal renal cortical scarring, papillary and/or calyceal distortion, or measurable generalized renal shrinkage (Davidson and Talner, 1978). In all these studies, however, wedge-shaped polar renal scars or grossly small kidneys were the markers, rather than renal mass or size. Others have examined renal mass and found that children with UTI and VUR have smaller kidneys (not grossly small) without signs of gross cortical scars (Chang et al, 2007). This implies that renal scarring is not the most sensitive measure of renal UTI damage.

Renal infection stimulates both innate (immediate) and more specific (delayed) immune responses. In rat models of pyelonephritis, maximal renal suppuration and exudation with an inflammatory infiltration occurs 3 to 5 days after the infection starts, and collagen infiltration and scarring follows (Glauser et al, 1978; Miller et al, 1979; Miller and Phillips, 1981; Shimamura, 1981; Slotki and Asscher, 1982). During the acute inflammatory cell infiltrate, granulocytic aggregation may cause vascular occlusion and ischemia with renin elevation (Kaack et al, 1986; Ivanyi and Thoenes, 1987). Bactericidal activity of the neutrophils and release of enzymes, superoxide, and oxygen radicals may cause the renal tubular damage observed in pyelonephritis (Roberts et al, 1981, 1982).

Advanced understanding of the innate "reflex" and specific immune responses to bacterial infection at a molecular and cellular level has increased knowledge of this process in UTI. UTI susceptibility is a complex interplay between factors of bacterial virulence and the immune response at the level of the uroepithelial cell. The uroepithelial cells have receptors (Toll-like receptors [TLRs]) that recognize structural molecules from microbes. When triggered by the microbial molecules, these TLRs activate proinflammatory cytokines and chemokines (IL-1, IL-6, IL-8) that signal and direct neutrophil transmigration across the epithelial barrier and into the urinary tract lumen, creating the clinical symptoms and signs of bladder and urinary tract infection. TLR4 is present on bladder uroepithelial cells; TLR5 is primarily in the bladder, with some expression in the kidney; and TLR11 is primarily in the kidney (Zhang et al, 2004).

Type 1 fimbriated bacterial attachment to bladder TLR initiates this cascade. Uroepithelial TLR4 appears to signal cytokine and chemokine production by either a NF-kβ pathway or a faster pathway involving 3′,5′-cyclic adenosine monophosphate (cAMP), both of which create an inflammatory response with the goal of shedding the infecting microbes and inhibiting bacterial invasion (Song et al, 2007; Ragnarsdóttir et al, 2008; Song and Abraham, 2008).

Discovery of genetic immune system deficiencies that cause more frequent UTI and pyelonephritis in mouse knockout models has given investigators clues to discovering human genetic polymorphisms associated with increased effects of UTI. Investigators have predicted and found groups of individuals with increased susceptibility for pyelonephritis associated with cytokine abnormalities, suggesting that aberrant immune response pathways may be associated with increased UTI susceptibility (Frendéus et al, 2001; Godaly et al, 2001; Artifoni et al, 2007; Ragnarsdóttir et al, 2008; Svensson et al, 2008). Measurement of the proinflammatory cytokines in serum or urine (e.g., IL-6, IL-8) also offer means of detecting or monitoring renal inflammation in acute pyelonephritis, and, as such, detection of elevated IL-6 and IL-8 has been proposed to diagnose acute pyelonephritis and renal scarring (Gürgöze et al, 2005; Sharifian et al, 2008; Sheu et al, 2008).

This inflammatory response causes proximal and distal tubular dysfunction and abnormal reduction in urinary concentrating ability (Berg, 1981), increased fractional sodium excretion, decreased phosphate reabsorption, and increased low-molecular-weight protein excretion (Tulassy et al, 1986). More recently, animal models examining bacterial attachment to renal collecting duct cells have shown that this process causes deregulation in vasopressin hormonal release and may affect TLR4 and innate immune activity (Chassin et al, 2007).

Decreased renal concentrating capacity correlates with evidence of severity of renal scarring (bilateral worse than unilateral) (Åbyholm and Monn, 1979). Other investigators correlate elevated urinary retinol binding protein (RBP, a tubular protein giving evidence of tubular dysfunction) excretion with the type and severity of renal scarring, and they link elevated *N*-acetyl-β-D-glucosaminidase (NAG, an excretory protein indicating tubular damage) and albumin excretion to children with bilateral scarring. These data suggest that tubular dysfunction occurs before glomerular dysfunction and commonly occurs in children with bilateral renal scarring (Tomlinson et al, 1994).

If antimicrobial treatment starts within the first days of infection, the acute suppurative response to the bacteria may be minimized, and renal scarring may be decreased or prevented (Glauser et al, 1978; Miller and Phillips, 1981; Shimamura, 1981; Slotki and Asscher, 1982). Inhibition of superoxide production may decrease renal inflammation and tubular damage (Roberts et al, 1982). Other animal studies suggest that supplementing antimicrobial treatment with anti-inflammatory agents, such as ibuprofen, decreases neutrophil chemotaxis and blocks the cyclooxygenase pathways, or that any other glucocorticoid anti-inflammatory agent may decrease renal scarring (Huang et al, 1999; Pohl et al, 1999).

Clinically, larger cortical defects correlate with longer delay in treatment and longer length of illness (Jakobsson et al, 1992). The likelihood of renal scarring directly correlates, moreover, with the number of UTI occurrences (Jodal, 1987; American Academy of Pediatrics, 1999a) (Fig. 116–7).

Certain recent studies have questioned these premises, however. In one study, hospitalized children less than 12 months old who were treated with intravenous antibiotics 1 to 8 days from the time of fever onset had more limited renal involvement when treated within the first 24 hours. No difference in scarring occurred when treated early or late though (Doganis et al, 2007). Another study examined children less than 7 years old with first episodes of pyelonephritis and concluded that early treatment had no effect on later renal scarring, but this study excluded children who were found to have "renal and/or urologic abnormalities" (Hewitt et al, 2008). Because the typical child with a first febrile UTI may not be hospitalized for intravenous antimicrobial drugs or have knowledge of their urologic abnormalties prior to diagnosis, the clinical implications of these kinds of studies are unclear.

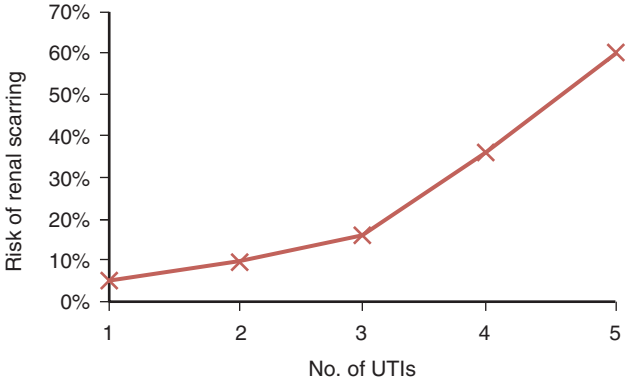


Figure 116–7. The relationship between risk of renal scarring and number of urinary tract infections (UTIs). (From American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. Pediatrics 1999a;103:845.)

Xanthogranulomatous Pyelonephritis (XGP)

Under certain circumstances, chronic bacterial pyelonephritis and obstruction are associated with a distinct severe inflammatory process known as xanthogranulomatous pyelonephritis (XGP). Although this occurs in only about 1% of cases and recently is diagnosed more frequently with imaging (Malek and Elder, 1978; Zugor et al, 2007), it is important because the entity has been confused with childhood renal tumors (e.g., Wilms tumor, multilocular cystic nephroma, congenital mesoblastic nephroma, malignant rhabdoid tumors, and clear cell sarcoma). Although the ***cause is unknown,*** the process is usually associated with both infection and obstruction. XGP affects mainly adults, but children also have the entity. Symptoms in children are similar to those in adults with flank pain, fever, chills, and chronic bacteriuria (*E. coli* and *Proteus* are most common) and associated with more vague symptoms of malaise, malnutrition, weight loss, and failure to thrive. Lower tract irritative symptoms are uncommon. Symptoms are often chronic with the majority, with XGP being symptomatic for greater than a month (Brown et al, 1996; Zugor et al, 2007). **The most common infecting organisms are *Proteus* and *E. coli*.** Urinalysis usually shows pus and protein, and blood counts often show anemia, reflecting the chronic nature of the disease. The process is usually unilateral and may involve pericalyceal tissue alone (focal) or the kidney diffusely (diffuse), with extension into the perinephric fat, and even the retroperitoneum with encasement of the great vessels (Malek and Elder, 1978; Eastham et al, 1994). The clinical presentation in children differs

from adults**. In children XGP often affects those less than 8 years old and is of the focal renal rather than diffuse renal form (17% to 25% of cases in children). Boys are affected more frequently** (Brown et al, 1996), **and contralateral renal hypertrophy may occur** (Quinn et al, 1999). Although obstructive calculi occur in both children and adults, obstruction may involve congenital genitourinary abnormalities in children. On the other hand, focal XGP seldom occurs with obstruction.

Radiologic findings include renal calculi in 38% to 70% of patients, nonfunctioning renal segments in 27% to 80%, and a mass in as many as 62% (Anhalt et al, 1971; Malek and Elder, 1978). Ultrasonography may show an enlarged kidney with hypoechoic areas that represent areas of necrosis and pus-filled calyces. Computed tomography with contrast shows areas of low attenuation that do not enhance and may show extension of the mass into the perinephric fat. The "bear paw" sign with areas of low-attenuation nonenhancing dilated calyces and abscesses within areas of high-attenuation enhancing renal parenchyma may be present (Cousins et al, 1994; Goodman et al, 1998). No radiologic feature of XGP is diagnostic, but in recent reports, magnetic resonance imaging (MRI) or computed tomography (CT) has allowed correct preoperative diagnosis and planning in some patients.

Grossly, the kidney shows yellow-white nodules and evidence of pyonephrosis. **The histologic diagnostic feature is the xanthoma cell, a foamy lipid-laden histiocyte that may simulate the renal carcinoma cell.** These xanthoma cells may also appear in other conditions of chronic inflammation and obstruction, such as obstructive pneumonia (Moller and Kristensen, 1980). If one makes a preoperative diagnosis of XGP, partial nephrectomy will treat localized disease, but diffuse and extensive disease associated with a nonfunctioning kidney usually requires removal of the involved kidney and perinephric fat. Medical treatment of focal XGP is successful, and rare instances and some instances of remote amyloidosis occurring in the remaining kidney are reported (Brown et al, 1996; Quinn et al, 1999).

Pyelonephritic Hypertension

The childhood incidence of hypertension is between 1% to 11%, depending upon age and sex. Renal-related hypertension is most common (Dillon, 1979). **Children with gross pyelonephritic nephropathy (reflux nephropathy) have at least a 10% to 20% risk of future hypertension** (Holland et al, 1975; Wallace et al, 1978; Smellie and Normand, 1979; Jacobson et al, 1989a), with risks of later progressive deterioration in renal function and other complications of hypertension. Wallace and associates (1978) found that 12.8% of 141 patients with urinary infections and surgically corrected vesicoureteral reflux developed hypertension during the first 10 years of follow-up. Of those with renal scarring, 17% became hypertensive during follow-up. In another series, Smellie and Normand (1979) followed 83 children with scars, of whom 11(13%) had initial hypertension, 6 (7%) had malignant hypertension, and another 14 (17%) became hypertensive during the next 4 to 20 years, making a total of 37% who developed infection-related hypertension. In Sweden, Jacobson and associates (1989a) found that 7 of 30 (23%) children with focal renal scarring developed hypertension after 27 years, and of these, 10% developed end-stage renal disease. Eleven of the children followed by Smellie and Normand had hypertension initially, and none of Wallace's or Jacobson's did, probably indicating that the group followed by Smellie and Normand had more severe initial renal damage. In both series, however, **hypertension occurred whether renal scarring was segmental, focal, unilateral, or bilateral, and it was therefore independent of the degree of scarring.** An examination of ambulatory blood pressure measurements (24-hour ambulatory blood pressure measurement) suggests that hypertension measured in this way correlates directly with degree of reflux nephropathy. Nocturnal hypertension was the most sensitive indicator, but whether this is predictive of daytime hypertension is not confirmed (Patzer et al, 2003).

The etiology of pyelonephritic hypertension is poorly understood. It is likely that the renin-angiotensin system is involved. In 1978 at Great Ormond Street in London, the plasma renin activity was measured in children with reflux nephropathy who had been corrected surgically 1 to 10 years earlier (Savage et al, 1978). In all 15 children who were hypertensive when studied, plasma renin activities were above the normal mean, with 9 having levels above normal for their age, whereas in 8 of 100 children who were normotensive after the surgery, the plasma renin levels were elevated above the normal range for their age. When 85 of these 100 children were traced 5 years later, 4 had developed serious hypertension, and 4 others had borderline hypertension. A single elevated plasma renin activity level in 1978 did not, however, predict hypertension 5 years later, and by 1987 19% (16 of 85) of the children had elevated plasma renin activity. In this study, moreover, the normal tendency for the plasma renin activity to decrease with increasing age was not seen, and instead the opposite was observed; plasma renin activity increased with age, and the standard deviation increased. Almost 10 years later, the percentage of children with elevated peripheral plasma renin activity continued to increase in teenagers older than age 15 years, but elevation appeared to plateau by age 25 years, and blood pressure had leveled by age 15 years (Goonasekera et al, 1996). Peripheral plasma renin elevation did not predict future hypertension during the 15 years of follow-up. The value of selective renal vein renin measurements in the management of children with hypertension from reflux nephropathy is controversial (Holland et al, 1975; Stecker et al, 1977; Bailey et al, 1978; Bailey et al, 1984a, 1984b; Dillon et al, 1984), even though segmental renal vein renin has been useful in some for localizing sources of renin production (Dillon et al, 1984). Further indirect evidence for the role of renin in pyelonephritic nephropathy has been the successful treatment of hypertension with agents specifically aimed at blocking the renin-angiotensin system. In those children who have been examined with renal arteriography, normal main renal arteries are found to progress to scarred kidneys with vascular changes limited to small interlobular arterial branches (Holland et al, 1975; Stecker et al, 1977).

Progressive Renal Dysfunction

Although renal failure associated with acute pyelonephritis occurs rarely after recurrent pyelonephritis, especially that associated with pyelonephritic nephropathy, some children develop delayed hypertension and progressive renal dysfunction without further known UTI. **Generally, when measured years after UTI, overall renal function is well preserved, but individual GFR of scarred kidneys is decreased; this decrease correlates inversely with the original degree of vesicoureteral reflux when associated with reflux (higher-grade reflux, lower GFR)** (Jacobson et al, 1989a; Wennerström et al, 2000). As might be expected with long-term follow-up, those with small kidneys, whether scarred or not, had a lower GFR than those

with normal kidneys, and those with bilaterally small or scarred kidneys had the lowest GFR (Berg, 1992). **Most long-term studies emphasize that early detection of complications of renal scarring, such as hypertension, renal insufficiency, and proteinuria, is useful in minimizing progressive deterioration in renal function** (Jacobson et al, 1989a; Berg, 1992; Martinell et al, 1996; Smellie et al, 1998; Wennerström et al, 2000).

When renal scarring is found in children or bilateral renal scarring is found in adults with a history of UTI, it seems to be a risk factor for further decreasing renal function. As confirmed by Smellie and associates (1998), on long-term follow-up (mean, 27 years) of children with reflux and recurrent UTI (who were carefully managed to prevent UTI), those who had complications as adults had extensive renal scarring in childhood, while those who had no scarring in childhood did well as adults.

For over a decade, glomerular lesions and progressive proteinuria have been observed in patients who have renal scarring (Kincaid-Smith, 1975; Torres et al, 1980). Significant proteinuria (greater than 1 g/24 hr) has been a routine finding in patients with vesicoureteral reflux and progressive deterioration in renal function (Torres et al, 1980). Certain investigators, moreover, have found glomerular sclerosis in the nonscarred, radiologically normal kidney in cases of unilateral reflux nephropathy (Kincaid-Smith, 1975, 1984; Bailey et al, 1984a, 1984b). Two theories, one involving progressive renal damage from hyperfiltration of remaining nephrons, and the other involving progressive immunologic damage to the kidney, have been postulated to cause this. Micropuncture studies of rat renal tubules have allowed measurement of single-nephron glomerular filtration rates. These investigations have shown that removal of a kidney or loss of a majority of functioning nephrons results in hyperfiltration in the remaining nephrons and increased glomerular plasma flow. From rat studies in which one kidney and two thirds of the other kidney were removed (a five-sixths nephrectomy model), increases in glomerular plasma flow, mean net glomerular transcapillary hydraulic pressure, and single-nephron glomerular filtration rates were measured in the remnant nephrons. Later, as an apparent consequence, these rats developed focal segmental glomerulosclerosis (FSGS) (Hostetter et al, 1981, 1982). The glomerulosclerosis was felt to result from vascular injury caused by renal hyperfiltration. Rats maintained on a low-protein diet failed to show the pressure or pathologic changes, and indeed, rats maintained on a high-protein diet had greater degrees of glomerular sclerosis and more rapid renal death than those on normal diets (Brenner et al, 1982). **FSGS has been found in children with reflux nephropathy and proteinuria, even when renal function (measured by glomerular filtration rate) is relatively preserved.** In these children, glomerular involvement correlates with degree of proteinuria. Because most children who suffer renal scarring and loss of parenchyma have adequate renal function, the glomerular and vascular changes may be an evolving response to hyperfiltration injury (Morita et al, 1990).

Another explanation for the progressive renal dysfunction involves a chronic inflammatory response that develops into an autoimmune phenomenon. Tamm-Horsfall protein (THP) is produced in the renal tubular cells of the loop of Henle and distal convoluted tubules and is secreted into the urine. Whether it has any specific physiologic role is unknown, but it does appear to affect bacterial adherence to the mucosa and may serve some protective role (Duncan, 1988; El-Achkar et al, 2008) (see section on Cystitis and Pyelonephritis).

Although Tamm-Horsfall protein is usually found only in the urine and on the luminal side of the tubules, both clinically and experimentally, the protein has been detected in interstitial deposits in kidneys that have been subject to infection or reflux and has been associated with mononuclear cell infiltrates and renal scarring (Andriole, 1985). Also, even though antibodies (autoantibodies) to Tamm-Horsfall protein are widespread, the immunologic response to Tamm-Horsfall protein after a UTI may be disturbed in children with renal scarring (Fasth et al, 1980). This protein may account for findings of renal dysfunction or scarring associated with urinary vesicoureteral reflux without known infections, and the autoimmune response related to it may also provide a reason why chronic or progressive renal damage occurs long after cessation of reflux or active infections (Andriole, 1985).

End-Stage Renal Disease (ESRD)

Although end-stage renal disease caused by UTI alone is rare, end-stage renal disease related to reflux nephropathy is commonly associated with UTI and is estimated to account for 7% to 17% of ESRD worldwide, but it is only about 2% in the United States (Craig et al, 2000). This retrospective analysis of reflux nephropathy–associated ESRD does not show that treatment of vesicoureteral reflux with long-term antimicrobial prophylaxis or surgery has improved the natural history of reflux nephropathy. However, the proportion and incidence of children with ESRD with diagnosis of reflux nephropathy has decreased from 32.5% (1967 to 1971) to 7.2% (2002 to 2006) (Orr et al, 2009). The extent to which this finding is confounded by diagnoses of congenital renal dysplasia or hypoplasia associated with antenatal vesicoureteral reflux, rather than postnatal pyelonephritic scarring, is unclear. Notably, in Sweden in the 1990s, no child was recorded to have ESRD related to pyelonephritic scarring, and according to the Swedish Registry of Uremia, the incidence of pyelonephritic scarring–related ESRD is now only 6% to 7% (Wennerström et al, 2000).

MANAGEMENT OF SPECIAL URINARY TRACT INFECTIONS AND COMMON ASSOCIATED PROBLEMS

Urinary Tract Abnormalities

A reason for imaging to be part of the UTI evaluation in children comes from historical information of the close association of UTI and genitourinary malformations. These data appear two ways: (1) data examining the imaging findings after first UTI and (2) data examining genitourinary malformations and citing the proportion diagnosed by UTI evaluation. Earlier data have shown that imaging evaluation of children with UTI reveal that 5% to 10% of children have obstructive urinary tract lesions, and an additional 21% to 57% have vesicoureteral reflux (Kunin et al, 1964; Abbott, 1972; Asscher et al, 1973; Winberg et al, 1974; Newcastle Asymptomatic Bacteriuria Research Group, 1975). Because these data were collected prior to the widespread usage of both routine and prenatal ultrasonography and prophylactic antimicrobial usage in infants identified to have many genitourinary abnormalities, current practice confounds these associations in more recent reports. Although many countries now use prenatal screening and discover many genitourinary abnormalities for special management, thus removing children who may otherwise have had UTI, recent statistics

using imaging evaluation triggered by febrile UTI still reveal significant numbers of genitourinary abnormalities. A more recent retrospective examination of imaging results obtained from children in Taiwan after a first febrile UTI showed 56.1% to have abnormalities (all vesicoureteral reflux, 29.5%; grades III to V vesicoureteral reflux, 17%; renal hypodysplasia, 2%; hydronephrosis, 34% [grades I to II, 32%; grades III to IV, 2%]; hydroureter, 3%) (Lee et al, 2009).

From the side of the genitourinary abnormality, at one institution in Nigeria in which 28 boys were diagnosed to have posterior urethral valves (the majority of whom had prenatal ultrasonography), 50% of 28 boys were diagnosed only after UTI with urosepsis (Ikuerowo et al, 2008). Although renal scarring and hypoplasia are not considered correctable urinary tract abnormalities, they are abnormalities found after evaluation of UTI. In febrile UTI in children less than 5 years old (excluding those with obstructive lesions), 45% had acute DMSA-defined lesions (29% of kidneys). Two years later, 27% of these children (24% of kidneys) still had kidney scars independent of the presence of vesicoureteral reflux (Ditchfield et al, 2004).

Recurrent Urinary Tract Infection with a Normal Genitourinary System

Children who have no anatomic genitourinary problems but have recurrent UTI are common, and the condition is frustrating to parents and physician. Because host uroepithelial characteristics are independent of gross urinary tract abnormalities or reflux, **recurrent UTI will occur in about 20% of patients, the majority being girls, regardless of whether the urinary tract is normal** (Bratslavsky et al, 2004). Recurrent UTIs are common, and Winberg and associates (1974) have nicely documented the natural history. **Of boys who are infected before they are 1 year old, 18% develop a recurrent infection, but recurrences more than a year after the initial infection are rare. In contrast, if the initial infection occurs in an older boy, 32% become reinfected, suggesting that risk for neonatal UTI differs from that in older children.**

About 26% of girls who have an initial neonatal infection have a recurrence, and similar to infant boys, recurrences 1 year after the neonatal infection are less frequent. Girls who have their first infection after the neonatal period have a 40% recurrence rate, with the majority of recurrences occurring within the first 3 months after the hallmark UTI and two thirds occurring within the first year. Although the risk of recurrent infection in these girls drops with each subsequent infection-free year, 8% had their first recurrence more than 4 years after their original UTI; so, the risk never totally disappears.

For a girl who has a UTI, Winberg and associates (1974) calculated the risk of another UTI occurring within a year of the previous UTI to be proportional to the number of previous infections (i.e., the more UTIs a girl has, the more likely she is to get another). His data showed that this risk is greater than 25% with one previous UTI, greater than 50% with two previous UTIs, and almost 75% after three previous UTIs (Bergström et al, 1967; Winberg et al, 1974). This rate did not change whether the initial infection was symptomatic or asymptomatic, or if there was pyelonephritis or cystitis; in fact, about a third of the recurrences were asymptomatic. Data using polymerase chain reaction analysis of UTI *E. coli* isolates suggest that more recurrent UTIs in infants may be endogenous relapses (i.e., reinfection with same organism from the bowel) rather than new organism reinfections (Jantunen et al, 2002).

The lower rate of recurrent UTI in neonates and young boys and higher rate for older girls supports the importance of variable host and bacterial factors that create risk for bacteriuria in any individual. Unfortunately, there are no routinely available tests that can predict which children with a normal urinary tract have a biologic predisposition for UTI; polymorphisms discovered so far are part of research studies. Routine bacterial biotyping and sensitivity data obtained from cultures, moreover, do not give data relating to bacterial virulence. For this reason, management of the possibility of recurrences in these patients depends upon the child's age and severity of symptoms.

In the majority of children with normal urinary tracts who have mainly bladder irritative symptoms with their UTI (so-called uncomplicated infections), there is evidence that 3 to 5 days' treatment with an appropriate antimicrobial agent to which the organism is sensitive (Lohr et al, 1981; Madrigal et al, 1988; Copenhagen Study Group of Urinary Tract Infections in Children, 1991; Jójárt, 1991), or even a single dose of a parenteral antimicrobial agent (e.g., an aminoglycoside), is an effective treatment (Principi et al, 1977; Vigano et al, 1985; Grimwood, 1988). Longer antimicrobial courses of 10 to 14 days have not been proven to be more effective in these cases and may cause increased side effects and antimicrobial resistance in the fecal bacteria (Hansson et al, 1989a, 1989b, 1989c; Copenhagen Study Group of Urinary Tract Infections in Children, 1991). If the child has frequent recurrent infections (two or more during a 6-month period), a urinary prophylactic antimicrobial treatment during a limited period may be worthwhile, because the child has then established herself or himself to have susceptibility for infections. Antimicrobial agents taken at a prophylactic dosage will usually successfully decrease the rate of infections during the period of prophylaxis. When the antimicrobial agent is stopped, however, the child may extend into a period of remission from infection, but often eventually returns to an increased basic susceptibility for urinary infections (Winberg et al, 1974; Kraft and Stamey, 1977). Results from a questionnaire given to women with urinary frequency and painful bladder syndromes (e.g., interstitial cystitis) have associated childhood recurrent urinary infections and dysfunctional voiding symptoms in these individuals (Peters et al, 2009); however, there are no prospective or biologic studies confirming this.

Voiding Dysfunction and Constipation

Symptoms of nocturnal and diurnal incontinence are common in children with recurrent UTI. Epidemiologic investigations showed that monosymptomatic nocturnal enuresis is not associated with UTI, but diurnal enuresis or a combination of diurnal and nocturnal enuresis, even if as infrequent as once a week, may be associated with pediatric UTI (Hansson, 1992). Interestingly, **this study also revealed that 7-year-old girls who were greater than 3 years old when they had their first UTI were more likely to have symptoms of voiding dysfunction than those who were less than 3 years old at the time of the first UTI;** this may indicate an age-related phenomenon of this syndrome. Others, who compared children with UTI who were less than 2 years old to children without UTI, were unable to associate dysfunctional elimination syndrome with either UTI or VUR if the children were assessed again when they were 7 years

old (Shaikh et al, 2003). **Of note, almost 20% of children who had a recurrent UTI developed new diurnal enuresis that, starting with the onset of the UTI, persisted as long as 12 months, even when they remained free of UTI during the follow-up interval** (Sørensen et al, 1988).

Urodynamic testing in neurologically normal children with recurrent urinary infections and incontinence has shown abnormal cystometry and voiding patterns (Kass et al, 1979; Koff et al, 1979; Bauer et al, 1980; Koff, 1982; Kondo et al, 1983; Qvist et al, 1986; Hansson, 1992; Passerini-Glazel et al, 1992; vanGool et al, 1992). In 35 such children, Bauer and associates (1980) found 12 (34%) had normal filling cystometry, 9 (26%) had large hypotonic bladders, 9 (26%) had small capacity hypertonic bladders with increased intravesical filling pressure and sustained uncontrolled detrusor contraction at a low volume, and 5 (14%) had hyper-reflexic bladders showing uninhibited detrusor contractions during filling (Bauer et al, 1980). Voiding dysfunction has also been described with staccato (interrupted) urinary flows during voiding, showing increased pelvic floor activity during voiding with resulting incomplete bladder emptying (Bauer et al, 1980; Hansson, 1992; Passerini-Glazel et al, 1992; vanGool et al, 1992; Kjølseth et al, 1993). One group has shown that paradoxic pelvic floor activity may respond to biofeedback (de Jong et al, 2007). Notably, voiding dysfunction defined as increased pelvic floor activity causing elevated voiding pressures that lead to renal damage is probably unusual, whereas voiding patterns of extraordinary frequency, urgency with detrusor instability, infrequency, and incontinence are common (Hellerstein and Linebarger, 2003).

In addition to voiding dysfunction, children with recurrent UTI have frequent constipation. When 47 girls with normal urinary tracts, but who had recurrent UTI (with or without incontinence) and cystometry-proven bladder instability, were studied by digital rectal examination and rectal manometry, all had signs of functional constipation (O'Regan et al, 1985). Diurnal and nocturnal urinary incontinence (29% and 34%, respectively) and UTI (11%) were found in children greater than 5 years old who had chronic constipation (as defined by stool retention on rectal examination) and encopresis at least once a week (Loening-Baucke, 1997). Importantly, these findings were present even when constipation or encopresis was denied.

Others have not found constipation or daytime incontinence to be predictive of recurrent UTI (Bratslavsky et al, 2004). Although these findings do not establish causality between UTI, constipation, and voiding dysfunction, it can be seen that UTI may initiate symptoms of bladder and sphincter (urethral and rectal) dysfunction with variable persistence (Chase et al, 2004). **Girls with recurrent UTI are more likely to have a family history of UTI, infrequent voiding, poor fluid intake, and stool retention** (Stauffer et al, 2004). In some situations, treatment of constipation and/or voiding abnormalities has resulted in decreased UTI, and this possible relationship should be considered in the management of vesicoureteral reflux as well (Koff et al, 1998; Upadhyay et al, 2003), even though the association is unclear (Chen et al, 2004). These data suggest that bacteriuria or constipation may provoke abnormal detrusor-sphincter activity, or vice versa.

Covert or Asymptomatic Urinary Tract Infection

When covert or asymptomatic infections are diagnosed on screening urinary cultures, children often have symptoms related to the lower urinary tract upon careful interviews. They may have nocturnal and/or diurnal enuresis, squatting, and urgency, and at least 20% have a history of previous urinary tract infection (Kunin et al, 1962; Savage, 1975); however, these symptoms were not the reason they had the urinalysis or culture. About 50% of these children have normal urinary tracts defined by intravenous urography and voiding cystourethrogram.

Jodal (1987) found that a majority of infants who have covert bacteriuria may clear their bacteriuria without treatment; others state that only about 30% of asymptomatic school-age girls with asymptomatic UTI clear their bacteriuria spontaneously (without treatment) (Verrier-Jones et al, 1975; Lindberg et al, 1978). Whether treated or not, the majority of these girls will acquire persistent infection or reinfection. Whether the UTI is symptomatic or asymptomatic may not be important for the first UTI; the UTI marks host susceptibility. Thus this first UTI should be treated similar to any other first UTI. However, once the urinary tract has been evaluated and found to be normal or abnormal, treatment or screening for subsequent asymptomatic or covert UTI is debatable and probably unnecessary; obtaining routine cultures or urinary screening cultures are not supported (Shortliffe, 1995; Narchi, 2004).

Because covert bacteriuria may not be totally asymptomatic in school-age children, if symptoms such as incontinence are elicited by history, they should be treated. Treatment of the infection alone, however, may not obviate symptoms of voiding dysfunction. **Controlled studies involving older children with treated and untreated covert bacteriuria show that treatment makes little difference in the rate of future reinfection; over half will have recurrent infection whether treated or not, and the risk of any renal damage in these older children is very low** (Lindberg et al, 1975; Savage, 1975; Verrier-Jones et al, 1975; Jodal, 1987).

Furthermore, women with type 2 diabetes mellitus and asymptomatic bacteriuria have increased risk of getting a symptomatic UTI (Geerlings et al, 2001a, 2001b). Therefore there is little evidence that the natural history of asymptomatic UTI is changed by therapy, and the UTI event, symptomatic or asymptomatic, marks a susceptible host. This is now supported by long-term follow-up of women with symptomatic bacteriuria and prospective studies of those with asymptomatic bacteriuria (Hooten et al, 2000; Vosti, 2002). However, not all share this conclusion and the management implications (Bensman, 2002).

In several series in which girls with urinary tract infections were randomized between antimicrobial treatment and no treatment, subsequent renal scars rarely occurred when the kidney was free of scars at first imaging; conversely, new or increased scarring usually occurred in previously scarred kidneys in which vesicoureteral reflux was present. This was independent of antimicrobial therapy (Newcastle Asymptomatic Bacteriuria Research Group, 1975; Savage et al, 1975; Cardiff-Oxford Bacteriuria Study Group, 1978; Newcastle Covert Bacteriuria Research Group, 1981).

There is evidence that *E. coli* causing covert bacteriuria may be strains of *E. coli* that show self-agglutination, loss of surface antigens, inability to develop an epithelial cell IL-6 response, and less overall pathogenicity (Lindberg et al, 1975, 1978; Hansson et al, 1989a; Mabbett et al, 2009). Some studies have suggested that urinary tract colonization with a strain of *E. coli* causing asymptomatic bacteriuria may prevent colonization with an *E. coli* causing symptoms, and that treatment may actually lead to later acute symptomatic pyelonephritis (Hansson et al, 1989a, 1989b, 1989c). Other evidence points to a host deficit, with an impaired

mucosal TLR4 inflammatory response causing decreased symptoms (Ragnarsdöttir et al, 2007). For this reason, in difficult cases of recurrent asymptomatic infection without other urinary tract abnormalities or pregnancy, follow-up without further antimicrobial treatment should be considered seriously.

Incontinence Associated with Urinary Tract Infection and Normal Urinary Tracts

When symptoms of voiding dysfunction accompany recurrent UTI, it is probably worth observing the child on prophylactic antimicrobial agents to observe any change in voiding pattern while the urine is sterile. If symptoms of incontinence persist, addition of an anticholinergic agent, such as oxybutynin, and/or bladder rehabilitation that includes timed voiding and biofeedback techniques may help to improve incontinence and decrease the frequency of UTI.

In addition, **if constipation is found or even suspected, there may be an improvement in voiding and reduction in UTI if this is treated.** With the acute onset of bowel and bladder dysfunction in a child, the possibility of a tethered cord or other neurologic abnormalities must be eliminated.

OTHER GENITOURINARY TRACT INFECTIONS AND SYNDROMES

Bacteria and other organisms that grow under fastidious conditions and cannot be cultured without special growth media may cause UTI and pyelonephritis, especially in association with abnormal urinary tracts and renal insufficiency. Organisms such as *Haemophilus* associated with UTI in abnormal urinary tracts (Hansson et al, 2007) and *Trichomonas, Chlamydia,* microaerophilic microorganisms, and viruses will not grow in ordinary cultures; so, one must be suspicious of organisms other than those causing tuberculosis if evaluating sterile pyuria.

Inflammatory Acute Hemorrhagic Cystitis (Viral Cystitis)

Acute hemorrhagic cystitis accompanied by frequency, urgency, and dysuria in children has been associated with UTI caused by adenovirus 11 (Manolo et al, 1971; Mufson et al, 1973; Numazaki et al, 1968, 1973) and, occasionally, *E. coli* (Loghman-Adham et al, 1988-1989). **Adenovirus is the most common cause of viral acute hemorrhagic cystitis in children.** In a series of 69 infants and children with acute hemorrhagic cystitis, adenovirus 11 was recovered from the urine of 10 (14.5%), adenovirus 21 was in the urine of 2 (2.9%), and *E. coli* was present in 12 (17.4%), but the remainder (greater than 60%) had no infectious agents isolated from the urine (Mufson et al, 1973). Polyomaviruses have caused both hemorrhagic and nonhemorrhagic cystitis in children.

Viral cystitis has been commonly associated with bone marrow transplantation and other immunosuppressed conditions. Severe adenovirus in these children has caused fatalities as high as 50% to 80% without successful treatment, although recent ribavirin usage has been reported (Gavin and Katz, 2002). **BK, a DNA virus of the polyomavirus genus, has been found in the urine of bone marrow transplantation and other immunosuppressed patients having hemorrhagic cystitis (0.5 to 5 months after transplantation), causing both symptomatic (hematuria and dysuria), and asymptomatic infections** (Apperley et al, 1987; Bedi et al, 1995). It is hypothesized that immunosuppression may relate to reactivation of BK virus. In several series, hemorrhagic cystitis was associated with persistent BK viruria the majority of the time, and shedding of BK virus was usually correlated with onset of hemorrhagic cystitis.

Because routine viral cultures are infrequently done, children with symptoms of acute hemorrhagic cystitis most often have no growth on routine urinary culture. Although no antimicrobial treatment is indicated in healthy individuals with viral cystitis, renal and bladder ultrasonography or other imaging should still be performed to eliminate other causes for hematuria. It has been suggested that ribavirin may be useful for adenovirus cystitis after bone marrow transplantation (Cassano, 1991). Chemically induced hemorrhagic cystitis is not discussed in this section.

Interstitial Cystitis

Although individuals with interstitial cystitis often have a history of possible UTI, and some patients recall childhood symptoms (Peters et al, 2009), there is no evidence that it results from infection. Initial symptoms of frequency—suprapubic pain, nocturia, and urgency—may be confused with UTI but must be differentiated in children with either voiding dysfunction or urinary frequency syndrome. When strict diagnostic criteria of interstitial cystitis, such as Hunner ulcers, pain on bladder filling relieved with emptying, suprapubic pain, and urinary urgency or frequency are applied, this is a rare condition in children (Farkas et al, 1977; Close et al, 1996). This is primarily a diagnosis of exclusion, but the diagnosis is usually based upon finding bladder glomerulations on cystoscopy and decreased compliance on cystometrogram. Urodynamic findings of instability and involuntary bladder contractions are incompatible with this diagnosis (Close et al, 1996). When culture and sensitivity information are available, the antimicrobial agent should be re-evaluated and changed, if necessary, with treatment continuing for 7 to 10 days.

Epididymitis, Epididymo-orchitis, and Orchitis

Epididymitis is an important clinical syndrome because of its differential diagnosis and management. Although prepubertal epididymitis was diagnosed rarely in earlier series (Anderson and Giacomantonio, 1985), more **recent series using newer imaging modalities have diagnosed epididymitis almost as frequently as acute testicular torsion.** In 2000, according to the HCUP data, children were rarely hospitalized with orchitis—1.6 hospitalizations per 100,000 (Freedman, 2004). **Epididymitis is often difficult to distinguish from other pediatric acute scrotal processes, especially acute testicular torsion, and occurs almost as frequently (15% to 45%)** (Caldamone et al, 1984; Knight and Vassy, 1984; Mendel et al, 1985; Yazbeck and Patriquin, 1994). Although the differential diagnosis and evaluation of the acute scrotum is discussed in Chapter 132, the etiology and evaluation of epididymitis is related to UTI in some of these cases.

Although there is overlap, pediatric epididymitis occurs in a somewhat bimodal age distribution. **It usually occurs in very young and postpubertal boys** (Gierup et al, 1975; Knight and

Vassy, 1984; Anderson and Giacomantonio, 1985; Likitnukul et al, 1987; Siegel et al, 1987; Melekos et al, 1988; Anderson et al, 1989). This is a useful distinction clinically, because the etiologies and management differ.

Symptoms and Signs

The symptoms and signs of acute epididymitis cannot be differentiated from those of any acute scrotal condition and may also be the reactive result of early torsion of the testes or appendix testes. Characteristics that may be useful for comparison with acute torsion of the testes are history of more gradual onset, dysuria, urethral discharge, and history of urethral manipulation; recent urinary tract surgery (hypospadias, ureteral reimplantation); catheterization; neurogenic bladder; imperforate anus; or known lower tract genitourinary anatomic abnormalities (ureteral or vasal ectopia, bladder exstrophy) (Mandell et al, 1981; Knight and Vassy, 1984; Umeyama et al, 1985; Siegel et al, 1987; de la Hunt et al, 1989; Stein et al, 1994). The scrotum is usually inflamed and swollen (Doolittle et al, 1966); there may be localized epididymal pain; 18% to 33% of boys have fever (Doolittle et al, 1966; Gierup et al, 1975; Knight and Vassy, 1984; Siegel et al, 1987); and 24% to 73% have pyuria (Doolittle et al, 1966; Gislason et al, 1980; Knight and Vassy, 1984; Anderson and Giacomantonio, 1985; Siegel et al, 1987; Anderson et al, 1989). Although these symptoms are more likely to be associated with epididymitis than acute testicular torsion or torsion of the appendix testes, none is diagnostic. Pyuria and bacteriuria are rarely found in torsion.

When a boy has an acute scrotum, scrotal color flow Doppler ultrasonography and testes scintigraphy help confirm or follow epididymitis, and may at times confirm torsion of the appendix testes (Mendel et al, 1985; Mueller et al, 1988; McAlistar and Sisler, 1990; Atkinson et al, 1992; Yazbeck and Patriquin, 1994). Ultrasonography may show an enlarged epididymis of mixed echogenicity surrounded by reactive fluid. Color flow Doppler sonography usually shows increased testicular flow, except when there is such extensive swelling that ischemia may occur. However, most changes, including those from viral or mumps orchitis or epididymo-orchitis, are nonspecific (Tarantino et al, 2001). Nuclear scintigraphy, similarly, will usually show increased perfusion and increased radiotracer deposition in the affected side of the scrotum. Although nuclear scintigraphy may be more sensitive in detecting flow, especially in prepubertal boys, sonography has better anatomic resolution and may reveal epididymal or testicular abscesses (McAlistar and Sisler, 1990; Atkinson et al, 1992).

Pathogenesis

In young boys and infants, epididymitis is more likely to be related to genitourinary abnormalities (abnormal connections) or systemic hematogenous dissemination than in older males (Williams et al, 1979). **Urethral and urinary cultures from the prepubertal male are likely to show either nothing or gram-negative organisms and thus are referred to as "nonspecific epididymitis," whereas, in postpubertal sexually active boys, the cause may involve sexually transmitted organisms (*N. gonorrhea, Chlamydia trachomatis*).** Similar to the pathogenesis of renal abscess, data support two means of bacterial access to the epididymitis and testes: hematogenous dissemination and urinary tract–related infection. In young boys and infants, hematogenous pathogenesis is supported by reports in which *Haemophilus influenzae* type b have been cultured from epididymal abscesses concurrent with other sites of infection, such as otitis media, while the urinalysis remains normal, and associated positive viral titers may be found in others with acute inflammation (Weber, 1985; Greenfield, 1986; Lin et al, 1988; Somekh et al, 2004). Because organisms such as *Haemophilus influenzae* may require special culture techniques that may not ordinarily be used for urinary cultures, this may also account for the 40% to 84% of cultures from boys diagnosed to have epididymitis without an identifiable organism (Knight and Vassy, 1984; Cabral et al, 1985; Likitnukul et al, 1987). The fact that ascending UTI or bacteria sometimes causes epididymitis and epididymo-orchitis is supported by the observation that these boys who have pyuria and bacteriuria are more likely to have a urinary tract abnormality and may be diagnosed at a young age (Siegel et al, 1987).

Management

Epididymitis should be treated for the presumptive causative organism. Specifically, in the young child who has pyuria and possible bacterial epididymitis, initial broad-spectrum antimicrobial coverage similar to that used to treat a UTI in an ill child should be used. Once the culture results and antimicrobial sensitivities are available, the most specific and cost-effective agent (with few side effects) that achieves good tissue and urinary levels should be selected. Clearly, those children who are thought to have epididymitis on the basis of viral infection, reaction to torsion of the appendix testes, trauma, or other nonbacterial etiology should not be given antimicrobial agents; treatment with analgesics and nonsteroidal anti-inflammatory agents is more appropriate.

During or after treatment of the acute bacterial urinary and epididymal infections, radiologic evaluation of the urinary tract should be performed as with any UTI. Two studies report a high probability of genitourinary anatomic abnormalities, in particular abnormal connections between the urinary tract and bowel or genital duct system when a child has bacterial epididymitis and a UTI (Siegel et al, 1987; Anderson et al, 1989). In both studies, boys with negative urinary cultures had normal urinary tracts. Whether all boys with epididymitis, including those with negative urethral and urinary cultures, need a full radiologic evaluation of the urinary tract is unclear from current data. It does appear prudent, however, to perform a voiding cystourethrogram and renal and bladder ultrasonography on prepubertal boys with documented urinary infections, and perhaps those in whom epididymal abscesses are found, although the latter may be related to hematogenous spread.

Epididymitis Associated with Unusual Organisms

Whenever scrotal masses are considered, tuberculous epididymitis must also be considered as the most common form of urogenital tuberculosis (Cabral et al, 1985). Whereas this form of epididymitis is more likely to be confused with a malignancy rather than a cause of an acute scrotal mass, because it usually involves painless swelling, this can be an important cause of epididymitis when dealing with patients from areas in which tuberculosis may be endemic. Although there is evidence for both local urinary spread and hematogenous spread of tuberculosis to the epididymis, in the reported pediatric cases of tuberculous epididymitis, there are usually other signs of hematogenous involvement, and the urine may or may not be positive for the organism (Cabral et al, 1985).

Funguria

Fungal UTI is an increasing health care–associated infection, especially in individuals who have received antimicrobial agents and have urinary drainage catheters (Kauffman et al, 2000). **Candidemia in one neonatal intensive care unit increased more than 11-fold between 1985 and 1995** (Kossoff et al, 1998). In children, predisposing factors may include antimicrobial therapy, prematurity, and intravenous or umbilical artery catheterization, parenteral nutrition, and immunocompromised status (Keller et al, 1977). The urinary tract may serve both as a primary portal of entry and as a site of disseminated infection. **Prophylactic usage of oral nystatin or fluconazole in very low–birth-weight babies (<1000 to 1500 g) has been reported to be useful in preventing colonization and invasive fungal infection** (Sims et al, 1988; Kaufman et al, 2001; Kicklighter et al, 2001). In children and adults with disseminated candidiasis, the kidney is the most commonly involved organ (Keller et al, 1977). ***Candida* species are the most common cause of fungal UTI, with *Candida albicans* being the most common of these and responsible for about half of these. The second most common is *Torulopsis glabrata* (also known as *Candida glabrata*), an important species to recognize because of its common resistance to fluconazole** (van't Wout, 1996; Kauffman et al, 2000). Fungal bezoars may form in the renal pelvis, causing obstruction and anuria in infants with bilateral involvement (Keller et al, 1977; Eckstein and Kass, 1982; Robinson et al, 1987; Bartone et al, 1988; Rehan and Davidson, 1992; Hitchcock et al, 1995). For this reason, renal ultrasonography may be helpful in evaluating the extent of fungal infection when funguria is persistent. Although urinary alkalinization and oral or intravenous antifungal chemotherapy may dissolve some of these fungal balls, in infants these balls may totally obstruct the small urinary tract, requiring percutaneous or surgical removal of the bezoars or drainage so that both local irrigation and systemic therapy can be given. Streptokinase was reported to rapidly dissolve a fungal ball in one infant (Kabaalioglu et al, 2001). **Deciding when asymptomatic funguria related to an indwelling urethral catheter should be treated remains controversial, and a surveillance study involving 861 patients has shown that progression to disseminated candidemia is relatively uncommon** (Kauffman et al, 2000). When repeated cultures grow to concentrations greater than 10,000 to 15,000 CFU/mL, treatment is usually recommended (Wise, 1998). Although stopping unnecessary antimicrobial agents, changing or removing the indwelling catheter, and urinary alkalinization may be helpful, these means do not clear many cases of funguria. Recent prospective studies with intravesical amphotericin B bladder irrigation and oral fluconazole appear to show that both may clear funguria, although fungal recurrences are common (Gubbins et al, 1994, 1999). Optimal dosages, length of treatment, and delivery (intermittent vs. continuous) for amphotericin are indeterminate and controversial, but amphotericin B (50 mg/L) infused continuously at 42 mL/hr for 72 hours is effective (Trinh et al, 1995; Nesbit et al, 1999). Fluconazole has been used successfully in children, although unapproved for those less than 6 months old (Hitchcock et al, 1995; Zia-ul-Miraj and Mirza, 1997). Fungal bezoars in the collecting system require treating obstruction, when present, with a percutaneous nephrostomy tube for drainage and potential local irrigation. In these situations, both local and systemic therapy with amphotericin B and/or oral fluconazole may be useful for management. Should the fungal balls persist, surgical removal is necessary.

GENITOURINARY TRACT AND NOSOCOMIAL INFECTIONS

Surgical-Site Infections and Surgical Prophylaxis

There is scant literature on surgical-site infection for the urinary tract in children (Grabe et al, 2001). In 1992, the Centers for Disease Control and Prevention (CDC) changed the term for surgical procedure–associated infections to surgical-site infections: incisional superficial (skin and subcutaneous tissue) and deep (deep soft tissue, muscle, fascia), organ, and spaces manipulated during an operation. The organisms associated with such infections relate to the organs and orifices entered. When the gastrointestinal, genitourinary, or respiratory tracts have not been entered, the most common pathogen is *Staphylococcus aureus*.

Data from the U.S. National Nosocomial Infections Surveillance System show the **incidence of surgical-site infections are higher in infants younger than 2 months than in older children** (Richards et al, 1999). Other data support the view that prepubertal children, except neonates, have lower incidence of surgical-site infections than older children and adults, but these data are difficult to compare. One report on genitourinary infections in children and adolescents reports that shaving the surgical site in the operating room, rather than the night before, is associated with decreased wound infections (McCray et al, 1986).

The most recent published CDC guidelines related to surgical-site infections were published in 1999 and summarized by Nichols and associates (Nichols, 2001; Nichols and Florman, 2001). None are specific for children or include genitourinary operations (Bratzler et al, 2005). **These guidelines recommend (1) not removing hair unless it will interfere with the operation and, if removed, clipping immediately before the operation; (2) identifying and treating all remote infections; (3) maintaining as short a hospitalization as possible; (4) administering antimicrobial agents only when indicated, based upon published recommendations for a specific operation; (5) administering antimicrobial agents intravenously to ensure bactericidal serum and tissue levels when the incision is made (60 minutes before incision with most agents and 120 minutes before incision with vancomycin) and maintaining these levels for a few hours after closure, with discontinuation no later than 24 hours after surgery, even if drainage catheters are left in place** (Botto et al, 2001); **(6) preparing the bowel for elective operations with mechanical bowel preparation, including enemas and cathartic agents and nonabsorbable oral antimicrobial agents the day before surgery, in addition to the intravenous drugs; and (7) withholding routine vancomycin usage** (Zanetti et al, 2005). In situations in which the value of antibiotic prophylaxis is unproven, a single-dose systemic-appropriate cephalosporin given during the immediate preoperative period may be indicated. Although the CDC website lists the preceding guidelines as of 2009, augmentation cystoplasty in children and ileal conduit urinary diversion has been performed without mechanical and antibiotic preparation,

and without increased morbidity (Gundeti et al, 2006; Tabibi et al, 2007). Others perform small and large bowel surgery without bowel preparation.

Nosocomial Urinary Tract Infections

Catheter-associated UTIs are the most common hospital-acquired infections, usually associated with urethral instrumentation or chronic indwelling catheterization (Shortliffe, 1997). The risk of UTI increases with the duration of catheterization, and the acute nosocomial UTI is usually asymptomatic. **In one study, 20% of childhood bacteremia was caused by UTI or prior urinary tract manipulation with introduction of pathogens** (Dupont and Spink, 1969). Other infectious complications associated with catheterization and UTI are acute epididymitis-orchitis, pyelonephritis, periurethral abscesses, and struvite and renal calculi. Cultures taken from urethral catheter tips show little correlation with urine cultures (Gross et al, 1974a, 1974b).

When urethral catheters are placed, the patient risks urethral injury and bacteremia from catheter manipulation. As a result, **any individual with a cardiac problem who risks endocarditis must receive antimicrobial prophylaxis before catheter manipulation.** The incidence of UTI directly relates to the duration of the indwelling catheterization. There are no studies examining the rate of bacteriuria in children, but adult studies show that **in 95% of open drainage systems, bacteriuria occurs within 4 days** (Kass and Finland, 1956), **and with closed drainage systems, 5% to 10% become bacteriuric each day** (Warren et al, 1978).

Catheter-associated UTI originates from (1) periurethral organisms, (2) organisms infecting the collecting bag or device, and (3) organisms entering the system with breaks in the closed drainage system or lack of a closed system. **Recommendations for indwelling catheter care are (1) genital washing once or twice daily with water and soap without antiseptics or antimicrobial agents, (2) regular emptying of the collection bag, and (3) ongoing prophylactic antimicrobial drug therapy to prevent infection during insertion or while indwelling, but it is not recommended unless the patient is at risk for endocarditis or is neutropenic** (Daschner et al, 2001; Warren, 2001). There is no need for irrigation with antibacterial substances, antimicrobial agent instillation into the collecting bag, special antibacterial-coated catheters, or routine change of the catheter. None of these procedures can prevent catheter-associated UTI permanently.

Asymptomatic bacteriuria associated with catheter drainage need only be treated before any urinary tract manipulation or when the drainage tube is removed; the resident organisms should then be treated and the urine sterilized prior to removal (Botto et al, 2001; Warren, 2001). **If the catheter has been left in for 4 or more days, the practitioner should assume that the urine is infected. (See earlier section [Neurogenic and Bowel-Augmented Bladder] on management of the neurogenic bladder for information on clean intermittent catheterization programs.)**

BACTERIOLOGIC ECOLOGY AND ANTIMICROBIAL RESISTANCE

The development of more powerful antimicrobial agents allows improved and less morbid treatment of UTI, specifically pyelonephritis. At the same time, however, infecting organisms are becoming more and more resistant to routine antimicrobial agents and more problematic to treat, with fewer agents from which to select. In 1993, Calvin Kunin referred to this problem as a "worldwide calamity" resulting from bacterial genetic change causing resistance and population mobility (Kunin, 1993). The situation has not improved in the last 15 years.

The widespread usage of antimicrobial agents was thought to create the pressure that creates and selects for most resistant organisms. However, using techniques of DNA fingerprinting, electrophoretic pattern characterization, serotyping, and virulence identification, **certain clones of multidrug–resistant *E. coli* have been shown to behave with characteristics of an "epidemic outbreak."** For instance, an outbreak of *E. coli* 015:K52:H1 caused a community-acquired cystitis, pyelonephritis, and sepsis in London from 1987 to 1988 with epidemic-like spread, and the outbreak caused endemic *E. coli* urinary infections in Spain. In another instance, a single, previously unidentified multidrug–resistant *E. coli* clonal group A isolate (with resistance to trimethoprim-sulfamethoxazole) was discovered to cause 11% of community-acquired UTI in women seen in a California university health service during a 4-month period and to account for about 50% of the resistant isolates. The same clonal group appeared to cause almost 40% of resistant infections in cohort groups in Michigan and Minnesota (Manges et al, 2001). In another evaluation of this resistant *E. coli* clonal group A organism in a large public health system in Denver, Colorado, the **risk of having UTI with the resistant organism was associated with those younger than age 3 years, Hispanic ethnicity, recent travel outside the United States, and prior UTI.** Almost 15% of groups had trimethoprim-sulfamethoxazole–resistant organisms (Burman et al, 2003). The source of these clonal epidemic-like occurrences is unclear, but some evidence implicates food and or contact with food sources that may have had antimicrobial agent contact (Drexler, 2002).

This resistance is global; in 1999 in Israel, community-acquired UTI organisms were resistant to trimethoprim-sulfamethoxazole (31%), to cephalexin (37%), and to ampicillin (70%) (Prais et al, 2003). In Canada, from 1992 to 1994, examination of 1636 consecutive isolates of *E. coli* causing UTI found antimicrobial resistance occurrence was 45% for ampicillin, 31.4% for trimethoprim-sulfamethoxazole, with combined resistance to both at 22.2%; 1.7% of organisms were resistant to both ampicillin and gentamicin. Case-control examination of those with trimethoprim-sulfamethoxazole–resistant organisms showed that children who were given antimicrobials for more than 4 weeks in the previous 6 months were 23 times more likely to have resistance; children with genitourinary abnormalities (e.g., genitourinary tract abnormalities, spina bifida, vesicoureteral reflux) were 2.4 times more likely to have resistance; and children with previous hospital admissions had an OR of 2.3 if one admission and an OR of 3.2 if there was more than one admission. Also the OR was 0.3 in those less than 2 years old compared with those 2 to 6 years old (Allen et al, 1999) (Table 116–7).

To attempt any control of this global problem, we must prescribe antimicrobial agents in a socially conscious manner. Recommendations by the Infectious Disease Society of America (IDSA) include **(1) optimal use of antimicrobial agents, (2) restriction of classes or specific agents, (3) rotational or cyclic usage, and (4) use of combination antimicrobial therapy to decrease resistance** (Shlaes et al, 1997).

Table 116–7.

Factors Associated with Trimethoprim-Sulfamethoxazole Resistance

FACTOR	ODDS RATIO
Antibiotics taken for >4 weeks in past 6 months	23.4
Genitourinary tract abnormality	2.4
Number of hospital admissions in past year	
0 (reference)	1.0
1	2.3
≥2	3.2
Age in years	
<2	0.3
2-6 (reference)	1.0
>6	0.5

Modified from Allen U, McDonald N, et al. Risk factors for resistance to "first-line" antimicrobials among urinary tract isolates *of Escherichia coli* in children. CMAJ 1999;160:1436–40; Table 4.

CONSIDERATIONS IN TREATING CHILDREN WITH URINARY TRACT INFECTION

Rational treatment of infants and children with UTI is based upon an understanding of bacterial and host risk factors with rapid detection of UTI and evaluation of potential risks to modify them when possible. Moreover, judicious use of antimicrobial agents allows effective treatment and limits organism selection and bacterial resistance. We should consider the inevitable emergence of antimicrobial resistance with widespread usage of any antimicrobial agent and that future virulence targets for drugs are limited (Lee et al, 2003).

Antimicrobial usage should be limited to the shortest effective duration and narrowest spectrum. When a child with UTI and renal scarring has been identified, their management should minimize their chances of future bacteriuria and assess potential risk factors to prevent further infection-related renal damage. In some instances, knowledge of predisposing risk factors may help select children for urinary tract antimicrobial prophylaxis or further evaluation. In others, anatomic knowledge may allow consideration of lack of antimicrobial treatment. When renal scarring is identified, the child and parents should be educated about potential future hypertension, proteinuria, and progressive nephropathy. In moderate to severe renal scarring with renal insufficiency, early nephrologic consultation for evaluation and surveillance for hypertension, proteinuria, acid-base imbalance, and counseling and management may improve or stabilize renal function and improve growth. In particular, the young female with renal insufficiency from "pyelonephritic nephropathy" and recurrent UTI may desire pregnancy counseling related to future renal insufficiency.

Although full genetic screening for UTI, renal scarring, and vesicoureteral reflux susceptibility is not yet available, or perhaps practical, families in whom a member has vesicoureteral reflux, renal insufficiency, and/or renal scarring should be made aware of potential risk for vesicoureteral reflux, UTI, and consequences of UTI, as appropriate, and the need for early diagnosis, treatment, and evaluation of UTI in family members. Future research should help direct more selective identification of those children at high risk of renal damage from UTI.

Key Points: Urinary Tract Management

- No follow-up urinary culture after 48 hours of treatment is required if organisms are sensitive to the antibiotic selected.
- Risk factors for acquiring antimicrobial-resistant uropathogens are diabetes, recent hospitalization, recent antibiotic usage (especially trimethoprim-sulfamethoxazole), urinary malformations, urethral catheters, and antimicrobial prophylaxis.
- Radionuclide VCUG should not be used to evaluate first infections in infants, young boys, or those in whom risk of genitourinary abnormality is high and urethral visualization is important.
- VCUG performed for purposes of UTI evaluation may be performed when the urine is sterile, bladder volume is normal, and bladder irritability is no longer present.
- The pediatric kidney is more likely to scar than the mature adult kidney.
- Focal segmental glomerulosclerosis is found in children with reflux nephropathy and proteinuria, even when renal function is relatively preserved.
- Epididymitis in children is difficult to distinguish from testicular torsion and occurs almost as frequently.
- Antimicrobial agents must be prescribed in a responsible way to avoid and decrease antimicrobial agent resistance.
- Benefits of antimicrobial prophylaxis for children with general vesicoureteral reflux and hydronephrosis are unclear.
- Benefits of probiotic microorganisms are unclear.

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The complete reference list is available online at www.expertconsult.com.

chapter 117

Anomalies of the Upper Urinary Tract

Ellen Shapiro, MD ● Stuart B. Bauer, MD ● Jeanne S. Chow, MD

Anomalies of Number
Anomalies of Ascent
Anomalies of Form and Fusion
Anomalies of Rotation
Anomalies of Renal Vasculature
Anomalies of the Collecting System

Congenital anomalies of the upper urinary tract comprise a group of abnormalities, ranging from complete absence to aberrant location, orientation, and shape of the kidney as well as aberrations of the collecting system and blood supply. These diverse entities are among the most common malformations in newborns. Historically, developmental biology of the urinary tract was based on observations in animal models and human fetuses. The mechanism and timing of various congenital anomalies were extrapolated from the normal process of organogenesis. Technical advances in molecular genetics have provided the opportunity to hypothesize complex mechanisms of normal and abnormal development.

ANOMALIES OF NUMBER

Bilateral Renal Agenesis

Of all the anomalies of the upper urinary tract, bilateral renal agenesis (BRA) has the most profound effect on the fetus. Fortunately, it occurs infrequently when compared with other renal abnormalities. Although BRA was first recognized in 1671 by Wolfstrigel, it was not until Potter's extensive description of the constellation of associated defects that the full extent of the syndrome could be appreciated and easily recognized (Potter, 1946a, 1946b, 1952). Subsequently, many investigators have attempted to explain the syndrome by employing a single unifying etiology (Fitch and Lachance, 1972). However, we are learning that there is probably no single etiology as we begin to unravel the myriad of complex molecular events that are required for normal renal development.

The incidence of BRA is rare, with only about 500 cases reported in the literature. Potter (1965) estimated that BRA occurs once in 4800 births, but in British Columbia the incidence is 1 in 10,000 births (Wilson and Baird, 1985). Davidson and Ross (1954) noted a 0.28% incidence in autopsies of infants and children, whereas Stroup and colleagues (1990) detected an incidence of 3.5 per 100,000 in the Centers for Disease Control Birth Defects Monitoring Program. A recent study using prenatal ultrasonography in 8500 pregnancies in Poland reported an incidence of 0.25% (Forys et al, 2003). There is significant male predominance, with almost 75% of individuals being male. Increasing maternal age appears to be a risk factor (Bianca et al, 2003), but specific complications of pregnancy or any maternal disease do not appear to consistently influence the incidence of BRA (Davidson and Ross, 1954; Ruhland et al, 1998). The anomaly was reported in three infants of an insulin-dependent diabetic mother (Novak and Robinson, 1994). It has been observed in several sets of siblings (Rizza and Downing, 1971; Dicker et al, 1984) and in monozygotic twins (Thomas and Smith, 1974; Cilento et al, 1994). In four pairs of monozygotic twins, one sibling was anephric while the other had normal kidneys (Kohler, 1972; Mauer et al, 1974; Cilento et al, 1994; Klinger et al, 1997). It has been suggested that an autosomal-recessive inheritance pattern exists (Dicker et al, 1984). There is a genetic predisposition to this syndrome with a high level of penetrance (Stella, 1998). **When siblings and parents of an index child with BRA were screened, 4.5% had unilateral renal agenesis** (Roodhooft et al, 1984) and 3.5% had BRA (McPherson et al, 1987). This is 1000 times higher than in the general population (Stroup et al, 1990). Other investigators have suggested that this is an autosomal-dominant trait with variable penetrance (Kovacs et al, 1991; Murugasu et al, 1991; Moerman et al, 1994; Stella, 1998). Recently, McPherson (2007) evaluated renal anomalies in families of individuals with congenital solitary kidneys that included renal agenesis or a very poorly functioning kidney due to dysplasia/hypoplasia. The empiric risk of 7% for offspring, 4% for parents, and 2.5% for siblings may be an underestimation, because not all relatives underwent ultrasound screening. The incidence of BRA in offspring of congenital solitary kidney probands was ≈1%, which is significantly greater than the risk found in the general population but less than that for families with a history of BRA. Ultrasound screening has been recommended for parents and siblings of infants born with either unilateral or bilateral renal agenesis or dysgenesis (Roodhooft, 1984). McPherson (2007) has recommended prenatal ultrasound examination when either parent has a congenital solitary kidney. Ultrasound screening is also recommended for first-degree relatives of persons with congenital solitary kidney.

Syndromic Associations. BRA has been detected in higher-than-expected proportions in esophageal atresia (Saing et al, 1998) and several syndromes, including cryptophthalmos or Frazer syndrome (Fryns et al, 1997), Klinefelter syndrome (Barroeta et al, 2004), and Kallmann syndrome (Colquhoun-Kerr et al, 1999).

Renal Embryology. The **intermediate kidney, or mesonephros, develops and then regresses except for the mesonephric tubules** (Constantini and Shakya, 2006; Schedl, 2007; Uetani and Bouchard, 2009). In the male, these are the efferent ductules that serve as a link between the gonad and the mesonephric or wolffian duct (WD) structures (the body and tail of the epididymis and vas deferens). In the female, the mesonephric tubules link the ovary through the fimbriated end of the fallopian tube to the reproductive tract. The WD elongates caudally and fuses with the anterior cloaca. **The definitive kidney differentiates from the metanephric blastema, which is a specialized region of the intermediate mesoderm termed the metanephric mesenchyme (MM).**

This process requires the reciprocal induction between the metanephric blastema and the ureteral bud (UB). The metanephric blastema sends signals to the WD to initiate UB formation between the fifth and seventh weeks of gestation. As a result, the ureter is induced from the caudal end of the WD. The UB evaginates and invades the metanephric blastema and branches repeatedly in a characteristic pattern to form the collecting duct system. The ureteral tips induce nephron differentiation in the adjacent mesenchyme, forming the mature metanephros (Airik, 2007; Uetani and Bouchard, 2009). The absence of a nephrogenic ridge on the dorsolateral aspect of the coelomic cavity or the failure of a UB to develop from the WD will result in renal agenesis. Therefore in order for BRA to occur, there must be an alteration in normal molecular development or a mutation that causes renal or ureteral maldevelopment on both sides of the midline (see Molecular Mechanisms of Mammalian Kidney Organogenesis).

Relationship of the Wolffian Duct to Müllerian Duct Formation. **A review of the relationship of the WD to müllerian duct (MD) development is necessary to understand the genitourinary phenotype of individuals with renal anomalies or more specifically, renal agenesis** (Kobayashi and Behringer, 2003). The cellular mechanisms involved in MD formation have been partially unraveled only recently. Gene fate mapping and lineage tracing experiments show that the WD does not contribute cells to the MD, and the MDs are derived from the coelomic epithelium (Guioli et al, 2007; Orvis and Behringer, 2007). **A three-phase model of MD development has recently been proposed** (Guioli et al, 2007; Orvis and Behringer, 2007). In the first phase, cells of the coelomic epithelium in the cervical region of the intermediate mesoderm are specified to become MD cells and have been noted to express *Lim1* (Kobayashi et al, 2005; Orvis and Behringer, 2007; Masse et al, 2009) (Fig. 117–1). After the process of specification is complete, the second phase is heralded by *Wnt4* expression from the mesonephros or coelomic epithelium, which induces these cells that are destined to become the MDs to invaginate (Kobayashi et al, 2004, 2005; Orvis and Behringer, 2007). The second phase of MD development is WD independent and ends when the MD extends caudally and contacts the WD (Carroll, 2005; Kobayashi et al, 2005; Orvis and Behringer, 2007). The third phase involves elongation of the MDs posteriorly until they are joined at the urogenital sinus. This process is WD dependent, requiring the MD epithelium at its posterior end to be in close physical contact with the WD epithelium, while the MDs are separated from the coelomic epithelium by only a basement membrane (Orvis and Behringer, 2007). This intimate relationship between the WD and MD is emphasized in experiments that interrupt the formation of the WD at a specific point and show that the MD could not grow beyond that point to complete its formation (Gruenwald, 1941).

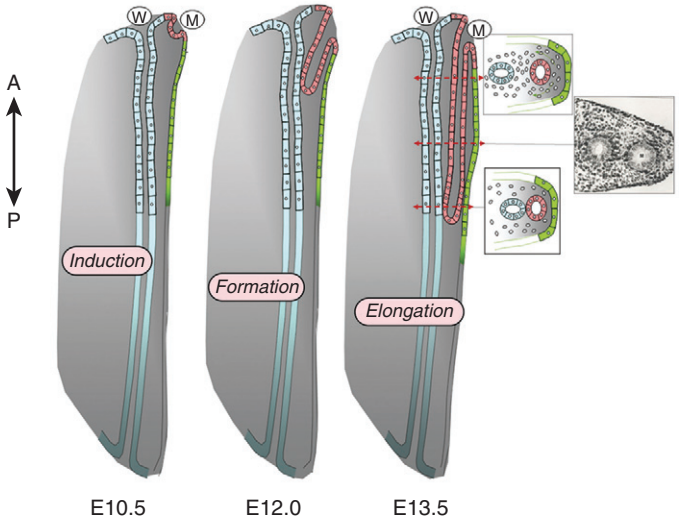


Figure 117–1. Model for müllerian duct development. At E11.75, after a subset of coelomic epithelium cells (represented in green) are specified, they invaginate in the intermediate mesoderm. Then, the invaginating cells form the müllerian duct (*M*, represented in pink). Anteriorly, the funnel is opened in the abdominal cavity, and caudally, the growing tip extends to and contacts the wolffian ducts (*W*, represented in blue) at E12.0. A phase of elongation allows the müllerian duct to elongate posteriorly in very close contact with the wolffian duct. As soon as the müllerian duct growing tip has deposited cells and elongated caudally, the physical contact between the ducts is lost by the appearance of mesenchymal cells around the müllerian duct epithelium. At E13.5, the two müllerian ducts reach the urogenital sinus and fuse together. Developmental stages indicated in this figure correspond to mouse stages. (From Masse J, Watrin T, Laurent A, et al. The developing female genital tract: from genetics to epigenetics. Int J Dev Biol 2009;53:411–24.)

Lim1 in the WD is critical for WD maintainance. Loss of *Lim1* in the WD by inactivation leads to WD loss. Because the MD is dependent upon the WD in this third phase, the MDs are again incompletely formed (Kobayashi et al, 2005). This third phase is also dependent upon the *Pax2* gene; mice mutants for this gene show cellular invagination but no elongation because the WDs have degenerated (Torres et al, 1995; Miyamoto et al, 1997). Studies have also shown that the WD not only acts as a physical guide but also plays a role in MD elongation through paracrine signaling. More specifically, *Wnt9b* is expressed by the WD epithelium, and gene inactivation results in incomplete formation of the MDs (Carroll et al, 2005). Loss of *Wnt9b* expression did not affect the WD, per se, or the first two phases of MD development but did affect the caudal extension and elongation of the MDs, suggesting that WD signaling by *Wnt9b* is one of the critical factors in directing MD formation (Carroll et al, 2005). For a clinical correlation, see Anomalies in the Female (Unilateral Renal Agenesis section).

Molecular Mechanisms of Mammalian Kidney Organogenesis. **Several genes play a critical role in WD development, including *Pax2/8, Gata3, and Lim1*.** Many of the same genes affecting renal development will also affect internal duct development. If there is gene inactivation of *Pax2/8, Gata3,* or *Lim1,* there will be no formation of the kidneys (BRA), ureters, or genital tract (Uetani and Bouchard, 2009). The pathway for mammalian kidney development is regulated by reciprocal epithelial-mesenchymal inductive signaling between the UB epithelium and the MM (Yu et al, 2004). Ureteral bud formation and the induction of its branching require glial cell line–derived neurotrophic factor

(GDNF), a secreted growth factor expressed in the MM (Michos et al, 2007). The GDNF ligand activates the RET receptor, which is expressed in the WD epithelium and then around the UB tips as branching proceeds. *Gdnf* expression and localization are positively regulated by *Eya1* and *Pax2* (Michos, 2009). GDNF activation of RET requires the glial cell line–derived neurotrophic factor family receptor α1 (GFRα1) and is essential for induction of UB formation and initiation of outgrowth and branching (Chi, 2009). Most genes that are thought to be essential for UB formation are also regulators of *Gdnf* or *Ret* expression. Studies of murine kidney development show that *Gdnf* –/– mice have renal agenesis, while *Ret*–/– mice have renal agenesis or dysplastic kidneys (Pichel et al, 1996; Schuchardi et al, 1996, Glassberg, 2002).

Skinner and colleagues (2008) examined the association between abnormal kidney development and mutations of *RET, GDNF,* and *GFRα1* in 29 stillborn fetuses with BRA or unilateral renal agenesis (URA). Mutations in *RET* were found in 7 of 19 fetuses with BRA and 2 of 10 fetuses with URA. A mutation in *GDNF* was found in 1 fetus with URA who also had mutations in *RET*. No *GFRα1* mutations were observed. These data suggest that congenital renal agenesis results from *RET* mutations that prevent or impede the embryonic development of *RET*-dependent structures.

After the GDNF/GFRα1 complex binds to RET, the *Wnt11* gene is activated in the epithelial tips of the UB and is associated with UB branching (Majumdar et al, 2003). *Wnt11* is a member of the *Wnt* gene family, which is composed of structurally related genes encoding secreted signaling proteins. These proteins are likely involved in several processes, including regulation of cell fate and patterning during embryogenesis. WNT11 signaling is required for the propagation of mesenchymal GDNF signaling, which establishes the autoregulatory epithelial-mesenchymal GDNF/WNT11 feedback signaling loop that controls the progression of metanephric branching morphogenesis after initiation of UB outgrowth (Majumdar et al, 2003; Michos et al, 2007).

Bone morphogenetic protein-4 (BMP4), a member of the transforming growth factor-α family, is expressed in the periureteral mesenchyme and is essential for morphogenesis (Glassberg, 2002; Miyazaki et al, 2000, 2003; Michos et al, 2007). In wild-type mouse embryos, BMP4 is expressed by the mesenchyme surrounding the WD and UB. Mesenchymal cells that express BMP4 inhibit UB formation, in part by inhibiting *Wnt11* expression. BMP4 migrates to ectopic sites, thereby preventing ectopic UB formation. The BMP4 mesenchymal cells act in a similar fashion during UB branching by inhibiting side branching and permitting stems to lengthen. Mesenchymal cells that are devoid of BMP4 surround the tip, where further branching proceeds. Mice heterozygous for a null mutation in BMP4 (+/–) manifest anomalies, including hypoplastic/dysplastic kidney, hydroureter, ectopic ureter, ureteral duplication, megaureter, ureterovesical junction obstruction, and reflux (Miyazaki et al, 2000, 2003).

Mammalian Kidney Organogenesis: New Advances. Gremlin 1 (GREM1) is an extracellular BMP antagonist that is expressed in the meso- and metanephric mesenchyme (Michos et al, 2004) (Fig. 117–2). GREM1 is upregulated in the mesenchyme around the origin of the UB prior to initiation of its outgrowth. BMP activity, at this time, is reduced locally. In the *Grem1*-deficient mouse embryo, metanephric development is disrupted at the stage of UB outgrowth initiation, resulting in bilateral renal agenesis. This inhibition of UB outgrowth causes progressive loss of *Gdnf* expression, resulting in apoptosis of the MM.

To further examine the relationship of these various ligands and their effects on epithelial-mesenchymal interactions, Michos and colleagues (2007) cultured early *Grem1*-deficient mutant mouse kidney rudiments in medium supplemented with recombinant GREM1. The addition of GREM1 restored UB outgrowth and induced supernumerary epithelial buds that invaded the MM and initiated branching morphogenesis. At the molecular level, GREM1 replacement activated *Wnt11* expression in the epithelial buds and upregulated *Gdnf* expression in the mesenchyme. Because genetic suppression of BMP4 activity in a *Grem1*-deficient mouse model completely restored kidney development, the local reduction of BMP4 activity by GREM1 was presumed to be critical to the initiation of UB outgrowth and kidney organogenesis.

Because BMP4 signaling by the mesenchyme surrounding the WD prevents formation of supernumerary epithelial buds, successful initiation of UB outgrowth most likely requires both antagonism of BMP4 by GREM1 in mesenchyme and signaling by GDNF from the MM to RET in the ureteric epithelium (Michos et al, 2007). In addition, autoregulatory feedback signaling between GDNF in the mesenchyme and WNT11 in the epithelial tips regulates branching morphogenesis. *Grem1* is essential for both upregulation of *Wnt11* in the ureteric epithelium and *Gdnf* expression in the mesenchyme and the establishment of epithelial-mesenchymal feedback signaling.

Gross Pathologic Description of Retroperitoneal Findings

In an extensive autopsy analysis by Ashley and Mostofi (1960), **the kidneys were completely absent on gross inspection of the entire retroperitoneum.** Occasionally, there was a small mass of poorly organized mesenchymal tissue containing primitive glomerular elements with only minute vascular branches from the aorta. Complete absence of the renal vessels was observed in about 25% of specimens with BRA in this series. **Complete ureteral atresia was observed in 39 of the 42 cases of BRA, and partial ureteral absence was noted in 3.** Only small projections with no demonstrable lumen alongside the bladder were noted. With complete absence of the ureter, a rudimentary kidney was discovered in only a few instances, supporting the concept of reciprocal induction.

The adrenal gland may appear flattened on ultrasonography but is rarely malpositioned or absent (Davidson and Ross, 1954; Hoffman et al, 1992). A normally located adrenal gland is expected, because the adrenal cortex develops from primitive mesoderm medial to the urogenital ridge and the medulla develops from ectodermal neural crest cells, while the metanephros is derived from the intermediate mesoderm.

Fused and/or horseshoe-shaped glands have been noted on prenatal ultrasound screening (Strouse et al, 2002). Potter (1965) noted that fused glands were often found in the presence of spinal anomalies. In a small number of autopsies, the gonads were

Key Points: Bilateral Renal Agenesis

- Forty percent of the affected infants are stillborn.
- Most of the children who are born alive do not survive beyond 48 hours due to respiratory distress associated with pulmonary hypoplasia.
- The characteristic Potter facies and the presence of oligohydramnios are pathognomonic.
- The ureters are almost always absent, and the bladder is either absent or hypoplastic.
- The adrenal glands are usually positioned normally.
- Müllerian duct anomalies are commonly observed.

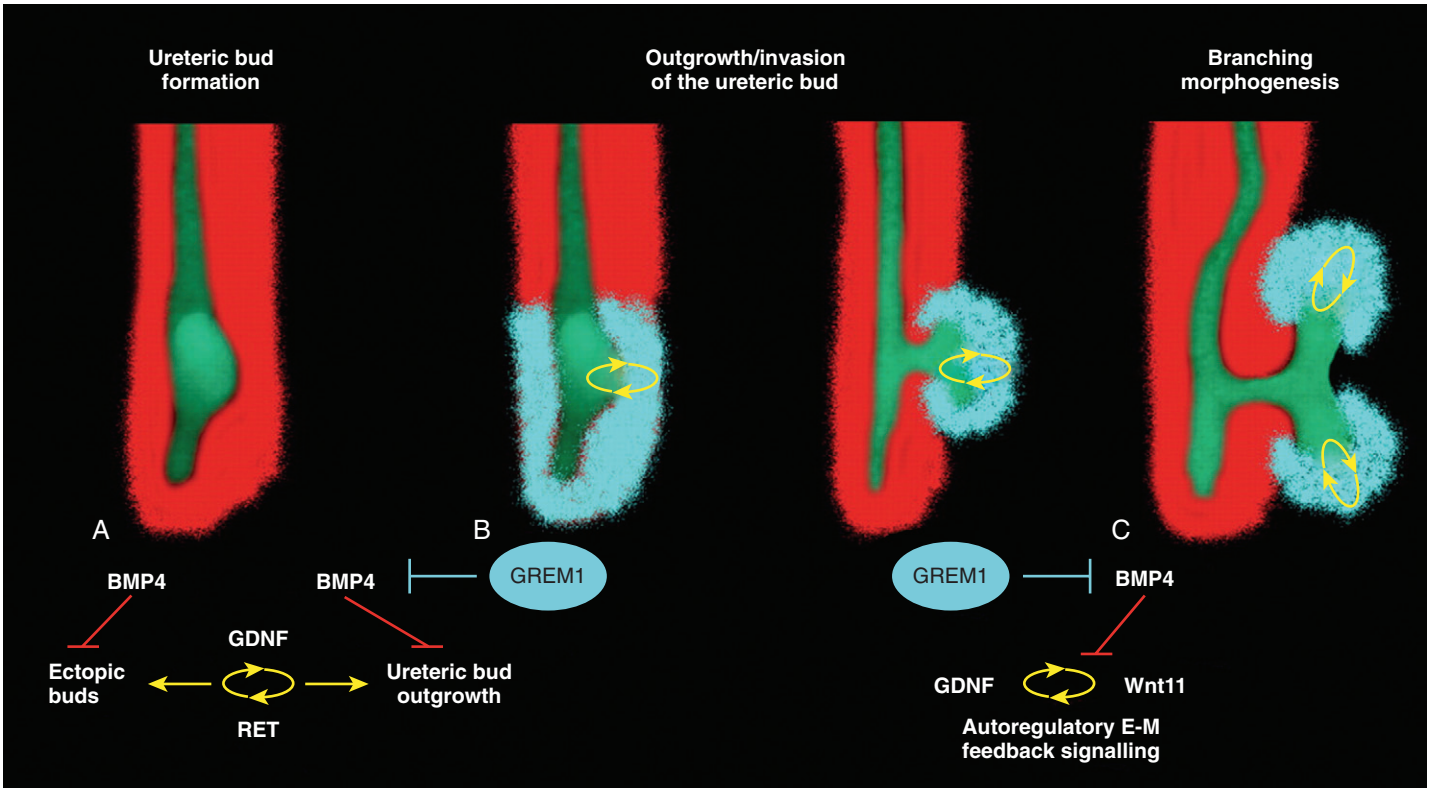


Figure 117–2. Reduction of BMP4 activity by gremlin 1 in the mesenchyme around the ureteric bud is essential to enable ureteric epithelial outgrowth, GDNF-RET– and WNT11-mediated epithelial-mesenchymal (e-m) feedback signaling, and branching morphogenesis. **A,** In mouse, the ureteric bud forms in the caudalmost part of the wolffian duct under the influence of GDNF-RET signaling. During this inductive period, *Bmp4* is expressed by the mesenchyme enveloping the wolffian duct. High levels of mesenchymal BMP4 activity inhibit the formation of ectopic epithelial buds and epithelial branching at this stage (prior to E11.0). At this early stage, only low levels of *Grem1* transcripts are detected (not shown). **B,** Expression of the BMP antagonist *Grem1 is* upregulated in the mesenchyme around the nascent ureteric bud, thereby locally reducing BMP4 signal transduction (around E11.75-11.0). This reduction of BMP4 activity by GREM1 enables initiation of ureteric bud outgrowth and its invasion into the metanephric mesenchyme. **C,** GREM1 is required to maintain and propagate expression of *Wnt11* in the ureteric epithelial tip(s) and *Gdnf* in the mesenchyme by e-m feedback signaling. (From Michos O, Goncalves A, Lopez-Rios J, et al. Reduction of BMP4 activity by gremlin 1 enables ureteric bud outgrowth and GDNF/WNT11 feedback signaling during kidney branching morphogenesis. Development 2007;134:2397–405.)

absent, indicating the abnormality or insult occurred before the fifth week and affected the overall development of the urogenital ridge (Carpentier and Potter, 1959).

In the Ashley and Mostofi series (1960), **about 50% of cases of complete ureteral atresia showed complete absence of the bladder, and in the remainder of cases, a hypoplastic bladder was found consisting only of a muscular tube with a minute lumen.** In Potter's series (1965), the bladders were also hypoplastic and lacked ureteral orifices. A normally closed urachus was observed.

Abnormal development of the bladder is thought to be due to the lack of stimulation by fetal urine production, which starts at 10 to 12 weeks of gestation. Alternatively, it has been postulated that UB and WD structures migrating into the ventral cloacal region are needed to initiate normal bladder development. The absence of the UB, and not the *lack* of urine, may arrest bladder development (Levin, 1952; Katz and Chatten, 1974). This theory is supported by the fact that despite absence of bladder filling in bladder exstrophy, many of these bladders are functional following surgical closure alone, while the bladders associated with bilateral ureteral ectopia almost invariably require augmentation (Jayanthi et al, 1997, Gearhart and Matthews, 2007).

Phenotypic Features. Phenotypic features associated with BRA have been extensively described by Potter. These infants have low birth weights, ranging from 1000 to 2500 g, and intrauterine growth retardation due in part to low iron stores in the liver (Georgieff et al, 1996). At birth, oligohydramnios (absent or minimal amniotic fluid) is present. **The characteristic facial appearance and deformity of the extremities distinguishes these children from normal newborns.** The infants look prematurely senile and have "a prominent fold of skin that begins over each eye, swings down in a semi-circle over the inner canthus and extends onto the cheek" (Potter, 1946a, 1946b). This facial feature is a sine qua non of nonfunctioning renal parenchyma and suggests that its absence confirms the presence of at least one kidney (Fig. 117–3). The nose is blunted, and a prominent depression exists between the lower lip and chin. The ears appear to be low set, are drawn forward, and are often pressed against the side of the head, making the lobes seem unusually broad and exceedingly large. The ear canals are not dislocated, but the appearance of the ear lobes gives the impression that the ears are displaced downward. Periauricular pits and tags have been noted (Wang et al, 2001). The skin can be excessively dry and appears too loose for the body. This may be secondary to severe dehydration or lack of subcutaneous fat. The hands are relatively large and clawlike. The legs are often bowed and clubbed, with excessive flexion at the hip and knee joints (Saing et al, 1998; Carbillon et al, 2001; Das et al, 2002). Occasionally, the lower extremities are completely fused as seen with sirenomelia (Liatsikos



Figure 117–3. An anephric child who lived 2 days has the typical Potter facial appearance. **A,** Note the prominent fold and skin crease beneath each eye, blunted nose, and depression between lower lip and chin. **B,** The ears give an impression of being low set because lobes are broad and drawn forward, but actually the ear canals are located normally.

et al, 1999). A lumbar meningocele with or without the Arnold-Chiari malformation and hydrocephalus is often observed (Davidson and Ross, 1954; Ashley and Mostofi, 1960). In Potter's series (1965), anomalies of the gastrointestinal tract were found in 60% of fetuses.

Anomalies of the external genitalia include absence of the scrotum and clitoral hypertrophy. Penile development is usually normal, but in a few cases, penile agenesis or a rudimentary penis and scrotum have been reported (O'Connor et al, 1993; Potter, 1965). Hypospadias is rare and does not appear to be related to the presence or absence of the testes. **The testes are undescended in 43% of cases** (Carpentier and Potter, 1959). Ashley and Mostofi (1960) found testicular agenesis in 10%. The vas deferens is normal in most cases, implying that the factor responsible for the renal agenesis influenced the UB *only after* it formed from a completely elongated WD or that the insult affected the induction of the MM.

There is a relatively high incidence of anomalies of the MD structures and ovaries (Carpentier and Potter, 1959). The ovaries are frequently hypoplastic or absent. The uterus is usually rudimentary or bicornuate but occasionally absent. The vagina is a short, blind-ending pouch or completely absent.

Role of Amniotic Fluid Production and Pulmonary Development. **The characteristic facial abnormalities and limb features may result from deformations rather than malformations of structures due to the lack of "cushioning" from amniotic fluid** (Fitch and Lachance, 1972; Thomas and Smith, 1974). This observation was confirmed by an experiment in nature in which one twin with BRA did not have the characteristic Potter facies because it shared the same amniotic sac with the second twin who had an adequate volume of amniotic fluid (Klinger et al, 1997). Fetal renal urine is the major source of amniotic fluid, accounting for more than 90% of its volume by the third trimester (Thomas and Smith, 1974; Chevalier and Roth, 2007), but the skin, gastrointestinal tract, and central nervous system also contribute small amounts, particularly before urine production begins at 10 to 12 weeks.

Pulmonary hypoplasia and a bell-shaped chest are common associated findings that were originally thought to be due to uterine wall compression of the thoracic cage as a result of oligohydramnios (Bain and Scott, 1960). Subsequently, it was postulated that the amniotic fluid alone was responsible for pulmonary development (Fitch and Lachance, 1972). However, this theory was rejected when they observed a significant reduction in the number of airway generations as well as a decrease in acini formation in these fetuses (Hislop et al, 1979). Pulmonary airway branching occurs between the 12th and 16th weeks of gestation (Reid, 1977). A reduction in the number of branches implies interference with this process before the 16th week of gestation. Hislop and colleagues (1979) suggested that the anephric fetus fails to produce proline, which is a prerequisite for collagen formation in the bronchiolar tree. The kidney is the primary source of proline (Clemmons, 1977). Thus pulmonary hypoplasia may result from the absence of renal parenchyma and not from diminished amniotic fluid. This hypothesis is supported by the finding of normal lungs in two infants with prolonged leakage of amniotic fluid beginning at a time when pulmonary hypoplasia would have been expected if the amniotic fluid alone were responsible for the defect (Perlman et al, 1976; Cilento et al, 1994).

Peters and colleagues (1991a) **proposed a two-step process in pulmonary development, with a primary "renal growth factor" influencing early lung development and an amniotic fluid volume-dependent phase influencing later gestational lung growth.** Smith and colleagues (2006) studied early lung development using a murine knockout model of renal agenesis/dysgenesis and anuria. They found that pulmonary development occurred early in embryogenesis, and fetal anuria and hypoplastic lung development preceded oligohydramnios. These observations support the two-step model proposed by Peters (1991a). Alternatively, oligohydramnios due to experimentally induced urinary obstruction is associated with pulmonary hypoplasia in fetal sheep, with initially normal renal function (Peters et al, 1991a, 1991b). Restoring amniotic fluid volume only partially restores lung growth. **Therefore uropathy-associated pulmonary hypoplasia appears to be a result of oligohydramnios rather than renal dysfunction** (Peters, 1991b).

Prenatal and Postnatal Diagnosis. **BRA is being diagnosed by prenatal ultrasonography in the second and third trimesters, when severe oligohydramnios is noted and no renal parenchyma can be identified** (Forys et al, 2003). Termination of the pregnancy has been considered when the diagnosis is certain (Rayburn and Laferla, 1986). Additional diagnostic findings include small lung volumes and chest diameter and abnormal adrenal gland appearance (Latini et al, 1998; Sepulveda et al, 1998; Heling et al, 2001; Strouse et al, 2002). **The characteristic Potter facies and the presence of oligohydramnios are pathognomonic.** Amnion nodosum—small, white, keratinized nodules on the surface of the amniotic sac—have been considered a placental hallmark of prolonged, severe, oligohydramnios. Recently, oligohydramnios was diagnosed in only 22% of cases of amnion nodosum, suggesting that it may not be a reliable sign of oligohydramnios. Nevertheless, the finding portends a very poor prognosis (Adeniran and Stanek, 2007).

Ninety percent of newborns void during the first day of life (Sherry and Kramer, 1955). In a study of 500 infants, every infant voided within the first 24 hours of life, regardless of the gestational age (Clarke, 1977). After the first 24 hours, anuria without distention of the bladder suggests BRA (Williams, 1974). However, most neonates with BRA who are born alive experience severe respiratory distress within the first 24 hours of life. When this becomes the focus of attention, the anuria may be initially unnoticed.

Postnatal Radiographic Evaluation. **Renal ultrasonography is the most efficient way to identify the kidneys and bladder and confirm the presence or absence of urine production.** The advent of power Doppler ultrasonography has been highly accurate in determining the status of the renal arteries, even in fetuses with oligohydramnios and suspected BRA (Sepulveda et al, 1998). The finding of a flattened adrenal gland in its normal location supports the diagnosis of an absent kidney (Hoffman et al, 1992). If abdominal ultrasonography is inconclusive, renal scintigraphy can be performed using ^{99m}Tc-dimercaptosuccinic acid (DMSA). The absence of uptake of the radionuclide in both renal fossae above background activity or in an ectopic location confirms the diagnosis of BRA. Historically, umbilical artery catheterization and an aortogram were performed when other modalities were not diagnostic.

Prognosis. **About 40% of the affected neonates are stillborn. Of those neonates who are born alive, most do not survive beyond the first 24 to 48 hours due to respiratory distress associated with pulmonary hypoplasia.** Survival subsequently depends on the rate at which renal failure develops. The longest-surviving child lived 39 days (Davidson and Ross, 1954).

Unilateral Renal Agenesis

Complete absence of one kidney occurs more frequently than BRA but is not easily detected from findings on physical examination. An isolated single umbilical artery has been associated with renal anomalies, including unilateral renal agenesis (URA) (Dursun et al, 2005). More recently, the largest study to date of neonates with an isolated single umbilical artery did not find an increased incidence of URA or other malformations and concluded that postnatal renal ultrasonography was not routinely warranted (Deshpande et al, 2009).

URA may remain undetected unless examination of the external genitalia and/or radiographic evaluation of the female or male pelvis for other reasons reveal an anomaly associated with renal agenesis. **Over the past two decades, prenatal ultrasound examinations have been performed more routinely, and URA is being detected with increased frequency** (Sipek et al, 1997). **These imaging studies have also revealed that a substantial number of cases thought to be URA were a dysplastic or multicystic dysplastic kidney (MCDK) that had undergone involution prior to birth** (Mesrobian et al, 1993; Hitchcock and Burge, 1994; Dell'Acqua et al, 2002; Hiraoka et al, 2002). **A plain film of the abdomen supports this diagnosis if the splenic or hepatic flexure of the bowel is in its normal location and not in the ipsilateral renal fossa, suggesting that a dysplastic kidney or MCDK may have formed in the renal fossa before involuting.** Curvilinear calcifications on a plain radiograph or computed tomography (CT) scan are another sign of a prior MCDK (Nakano et al, 1996). A flattened adrenal or the spleen (on the left) may be mistaken for a kidney in the 20-week structural ultrasound study, but at later gestational weeks, the diagnosis of URA becomes more apparent (Woolf and Hillman, 2006).

Incidence. **Most autopsy series suggest that unilateral renal agenesis occurs once in 1100 births** (Doroshow and Abeshouse, 1961). In an historical survey of excretory urograms, the incidence ranged between 1 in 1500 (Longo and Thompson, 1952) to 1 in 5000 (Wilson and Baird, 1985). Ultrasound screening of 280,000 school children in Taipei revealed the incidence of URA to be 1 in 1200 (Shieh et al, 1990). A similar incidence was found on prenatal screening in the Czech Republic (Sipek et al, 1997).

The high male predominance of BRA is not nearly as striking in the unilateral condition, with a **male to female ratio of 1.8:1** (Doroshow and Abeshouse, 1961). **Absence of a kidney occurs somewhat more frequently on the left side. A familial tendency has been noted** (Arfeen et al, 1993; Selig et al, 1993; Cascio et al, 1999). Siblings within a single family and even monozygotic twins have been affected (Kohn and Borns, 1973; Uchida et al, 1990). In a study of several families, McPherson and colleagues (1987) concluded the inheritance of URA was autosomal dominant with a 50% to 90% penetrance. This inheritance pattern has been confirmed by others who evaluated families with more than one affected individual (Biedel et al, 1984; Roodhooft et al, 1984; Battin et al, 1993). For screening recommendations, see the section Incidence under Bilateral Renal Agenesis.

Genetic/Syndromic Associations. An absent kidney has been noted in a number of genetic disorders in which there is a deletion of several chromosomal loci: 8q13.3 (Pierides et al, 2002), 18q22.2 (Dowton et al, 1997), 22q11 (Anonymous, 1998; Stewart et al,

1999), as well as in X-linked and sporadic cases of Kallmann syndrome (Colquhoun-Kerr et al, 1999; Zenteno et al, 1999; Quinton et al, 2001). Several syndromes have been associated with URA, including Turner syndrome, Poland syndrome (Mace et al, 1972), Frazer syndrome (Fryns et al, 1997), BOR (brachio-oto-renal) syndrome (Pierides et al, 2002), DiGeorge anomaly (when associated with insulin-dependent diabetes mellitus in the mother) (Wilson et al, 1993; Novak and Robinson, 1994), dysmorphogenesis, and Kallmann syndrome. Abnormalities of the *KAL1* locus at Xp22 in the X-linked autosomal-dominant disorder have a 40% incidence of URA (Say and Gerald, 1968; Colquhoun-Kerr et al, 1999; Zenteno et al, 1999; Quinton et al, 2001). Similarly, Townes-Brock syndrome with *SALL1* deletions is associated with a high incidence of URA (Salerno et al, 2000; Nishinakamura et al, 2001; Sato et al, 2003, 2004). Twenty to 30 percent of children with the VACTERL association (*V*ertebral, imperforate *A*nus, *C*ardiac, *T*racheo-*E*sophageal atresia, *R*enal, and *L*imb anomalies) have URA (Barry and Auldist, 1974; Kolon et al, 2000). Children with supernumerary nipples (Urbani and Betti, 1996) and disorders of the ears with hearing loss, especially if it is congenital (Huang et al, 2001), and preauricular pits (Pierides et al, 2002) have been thought to have an increased incidence of URA. Recently, studies have not shown a significant relationship between preauricular pits, minor ear tags, and URA (Arora and Pryce, 2004; Deshpande and Watson, 2006). Nonetheless, a screening renal ultrasonogram is recommended when these ear anomalies are found in the presence of other malformations. In addition, when more than one anomaly is present (e.g., ventricular septal defect [VSD] and an undescended testis) a screening renal ultrasonogram is prudent, but when specific complexes of anomalies associated with renal agenesis are present (for example, VACTERL-associated anomalies), a comprehensive radiographic review of all organ systems is mandatory.

Embryology. The embryologic basis for URA and BRA are thought to be similar. **The etiology is most likely due to the UB, because increased *RET* mutations occur in humans with renal agenesis** (Skinner et al, 2008). Complete absence of a bud or aborted ureteral development prevents reciprocal induction, which is critical for the development of the metanephric blastema into the definitive adult kidney. **The metanephros is likely not to be responsible for the majority of cases, because the ipsilateral gonad (derived from adjacent mesenchymal tissue) is rarely absent, malpositioned, or nonfunctioning** (Ashley and Mostofi, 1960). **The high incidence of absent or malformed proximal WD structures in the male and anomalies of the MD structures in the female suggest that the embryologic insult affects the UB primarily in its early development and influences the development of WD derivatives.** The abnormality most likely occurs no later than the fourth or fifth week of gestation, when the UB forms and the WD begins to develop into the ejaculatory duct, seminal vesicle, and vas deferens. The MD in the female begins its medial migration at this time, crossing over the WD (sixth week) during its differentiation into the fallopian tube, uterine horn and body, and proximal vagina (Woolf and Allen, 1953; Semmens, 1962; Yoder and Pfister, 1976).

Magee and colleagues (1979) **proposed an embryologic classification to explain the association of URA and MD anomalies** (Fig. 117–4). In type I URA, the insult occurs before the fourth week, and there is nondifferentiation of the urogenital ridge structures, including the MD and WD. If unilateral, a uterus consisting of a single MD (unicornate uterus) will form and will be associated with contralateral renal agenesis. In type II URA, the insult occurs early in the fourth week of gestation, affecting both the WD and the UB. Because it is critical that the MD maintains close contact with the WD for MD elongation and subsequent fusion, maldevelopment of the WD affects renal development, MD elongation, contact with the urogenital sinus (UGS), and subsequent fusion. Therefore a didelphys uterus will form with obstruction of the horn and vagina on the side of the URA. Finally, in type III URA, the insult occurs after the fourth week, and the WD and MD elongation and differentiation proceed normally. In this case, only the UB and metanephric blastema are affected, thereby resulting in isolated URA.

Associated Genitourinary and Adrenal Anomalies. **The ipsilateral ureter is completely absent in about 60% of the cases** (Fortune, 1927; Collins, 1932; Ashley and Mostofi, 1960). In the Ashley and Mostofi series, 19 of 232 with URA had only a portion of the lower end of the ureter present. There were no normally developed ureters reaching the level of the normal kidney. In most cases of complete absence of the ureters, the bladder showed no evidence of a ureteric orifice with failure of ipsilateral trigone development (Ashley and Mostofi, 1960). Cell lineage studies using a murine model show that the trigone has a urogenital sinus origin and should form normally (Viana et al, 2007; Mendelsohn, 2009). The trigone may not be distinguishable from the surrounding detrusor when the intramural ureter is absent. Therefore the

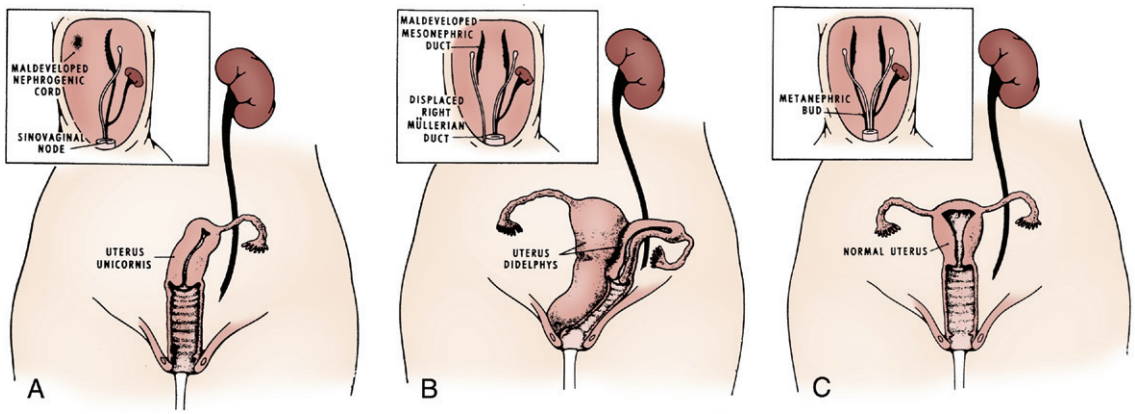


Figure 117–4. **A** to **C,** A proposed categorization of genital and renal anomalies in females. See text for details. (From Magee MC, Lucey DT, Fried FA. A new embryologic classification for urogynecologic malformations: the syndromes of mesonephric duct induced müllerian deformities. J Urol 1979;121:265.)

endoscopic appearance of the trigone in this setting has lead to the probable misnomer in the case of the "hemitrigone" (in association with complete ureteral agenesis) or "asymmetrical trigone" (in the presence of a partially developed ureter). Segmental ureteral atresia on one side has been associated with contralateral ureteral or renal ectopia (Limkakeng and Retik, 1972). Except for ectopia or malrotation, anomalies of the contralateral kidney are infrequent (Longo and Thompson, 1952; Chow et al, 2005) (Fig. 117–5). **However, abnormalities of the contralateral ureter are not uncommon, including ureteropelvic and ureterovesical junction obstruction in 11% and 7%, respectively** (Cascio et al, 1999), **and reflux in 30%** (Atiyeh et al, 1993; Cascio et al, 1999). Other urologic abnormalities are found in 65% with URA (Kaneyama et al, 2004).

Although the ipsilateral adrenal gland may be flattened (Hoffman et al, 1992), **adrenal agenesis occurs in**

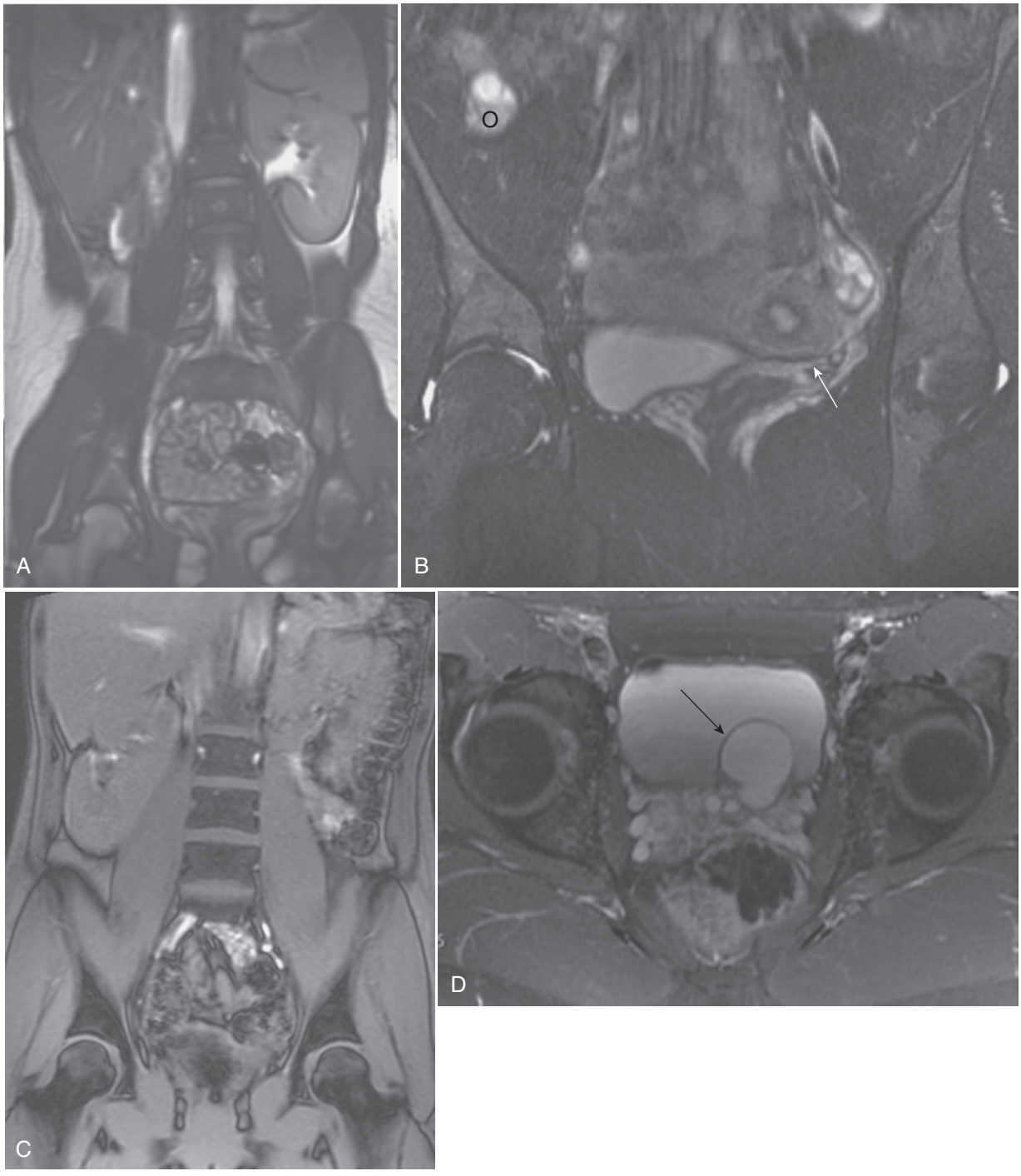


Figure 117–5. Magnetic resonance imaging (MRI) showing **(A)** coronal scout image of right renal agenesis with the bowel occupying the right renal fossa. **B,** Coronal T2 fat-saturated images show left unicornuate uterus *(arrow)*, absent right cornua, and superior location of right ovary *(o)*. **C,** Coronal scout image demonstrates left renal agenesis with bowel occupying the left renal fossa and right renal malrotation. **D,** Transverse T2 fat-saturated image of male pelvis shows left seminal vesicle cyst *(arrow)*.

fewer than 10% of autopsy reports (Fortune, 1927; Collins, 1932; Ashley and Mostofi, 1960) **and in 17% of individuals with URA undergoing a CT scan** (Kenney et al, 1985).

Genital anomalies are much more frequently observed. The incidence of a reproductive tract malformation for both sexes varies from 20% to 40% (Smith and Orkin, 1945; Doroshow and Abeshouse, 1961; Thompson and Lynn, 1966). **Despite the predominance of males with URA, reproductive tract abnormalities in females occur in at least 25% to 50% compared with 10% to 15% in males. Regardless of sex, both gonads are usually normal. Therefore the different phenotypes that occur with URA may result from a primary urogenital ridge defect, which explains the finding of gonadal and adrenal agenesis in the minority of cases, or a primary defect in development of the UB and WD, which leads to the more common cases of URA and frequently observed abnormalities of the WD, MD, and their derivatives.**

Anomalies in the Male. **The testis and head of the epididymis, which contain the efferent ductules derived from the mesonephric tubules, are invariably present; all structures proximal to that point, which develop from the WD (the body and tail of the epididymis, vas deferens, seminal vesicle, ampulla, and ejaculatory duct), are absent in almost 50%** (Radasch, 1908; Collins, 1932; Charny and Gillenwater, 1965; Ochsner et al, 1972). Donohue and Fauver (1989) reported 79% of adult males with an absence of the vas deferens have an absent ipsilateral kidney; left-sided lesions predominated with a ratio of 3.5 : 1. However, bilateral absence of the vas has been noted with URA (McCallum et al, 2001). Occasionally, the WD structures are rudimentary or ectopic rather than absent (Holt and Peterson, 1974). Ipsilateral cryptorchidism rarely occurs. In 1914, Zinner reported a seminal vesicle cyst in association with ipsilateral renal agenesis (Pereira et al, 2009). Seminal vesicle cysts secondary to obstruction of the ejaculatory duct are currently diagnosed with increasing frequency as pelvic ultrasound examinations are performed more often (Lopez-Garcia et al, 1998; Kaneyama et al, 2004). Six cases (5%) were noted among 119 boys who were found to have URA during ultrasound screening of schoolchildren (Shieh et al, 1990). A pelvic ultrasonogram or magnetic resonance imaging (MRI) in boys diagnosed with URA may demonstrate a seminal vesicle cyst (Van den Ouden et al, 1998, Seo et al, 2009) (see Fig. 117–5). In cases of seminal vesicle cysts and URA, the ureter may insert into the prostatic urethra or seminal vesicle. Cystic dysplasia of the rete testis, a rare benign condition, is often associated with ispsilateral renal anomalies, most commonly URA (Wojcik et al, 1997; Camassei et al, 2002).

In males, **the diagnosis of URA should be suspected during a physical examination when the vas deferens or body and tail of the epididymis are impalpable. This may be more common in adults undergoing evaluation for infertility.** In infants and young boys, URA should be considered when vasal and/or epididymal anomalies are incidentally found at the time of orchiopexy.

Anomalies in the Female. A variety of anomalies may result in the female from incomplete MD formation because of alterations in normal WD development. **Approximately one fourth to one third of women with URA have an abnormality relating to WD development** (Thompson and Lynn, 1966; Heinonen, 2004). Conversely, 43% of women with genital anomalies have URA (Semmens, 1962; Heinonen, 1997). The most common MD anomalies are a true unicornuate uterus with complete absence of the ipsilateral horn and fallopian tube or a bicornuate uterus with rudimentary development of the horn on the affected side (Candiani et al, 1997) (see Fig. 117–5). The fimbriated end of the fallopian tube, however, is usually fully formed and is analogous to the head of the epididymis in the male (Shumacker, 1938). Partial or complete midline fusion of the MD may result in a double (didelphys) or septate uterus with either a single or a duplicated cervix (Radasch, 1908; Fortune, 1927). Complete duplication or separation of the vagina, proximal vaginal atresia associated with a small introital dimple, and complete absence of the vagina have been reported (Woolf and Allen, 1953; D'Alberton et al, 1981). **Obstruction of one side of a duplicated system is not uncommon, and unilateral hematocolpos or hydrocolpos associated with a pelvic mass and/or pain has been described in pubertal girls** (Weiss and Dykhuizen, 1967; Vinstein and Franken, 1972; Gilliland and Dick, 1976; Wiersma et al, 1976; Yoder and Pfister, 1976). **Smith and Laufer** (2007) **suggested the acronym OHVIRA to classify the syndrome of *O*bstructed *H*emivagina and *I*psilateral *R*enal *A*nomaly.** In rare instances, this anomalous condition has been mistaken for a large or infected Gartner duct cyst. Sometimes a true Gartner duct cyst has been found in a prepubertal girl in association with an ectopic ureter that is blind ending at its proximal end or one that is connected to a rudimentary kidney (Currarino, 1982). Six percent of girls with URA were found to have a Gartner cyst on mass screening of schoolchildren (Shieh et al, 1990). Infertility occurs in as many as 33% of affected women with renal agenesis and unicornuate uterus (Heinonen, 1997). When specific anomalies of the uterus, including congenital absence of the uterus, unicornuate uterus, and didelphic uterus, are found on ultrasonography or MRI, radiologic investigation of the urinary tract often demonstrates URA or other renal anomalies (Bryan et al, 1949; Phelan et al, 1953; Thompson and Lynn, 1966; Candiani et al, 1997; Heinonen, 1997, Govindarajan et al, 2008; Reichman and Laufer, 2010).

Another important anomaly often associated with URA is the Mayer-Rokitansky-Kuster-Hauser syndrome (MRKH), which is a complex of malformations occurring in 1 in 5000 newborn females (Guerrier et al, 2006). This syndrome not only includes renal anomalies but also genital tract anomalies ranging from upper vaginal atresia to total müllerian agenesis in an otherwise phenotypically normal female with a normal 46, XX karyotype. There are two subtypes reported. Type I is the typical form characterized by the finding of only symmetrical muscular buds or müllerian remnants and normal fallopian tubes. Type II, which is the more common but considered the atypical form, is characterized by asymmetrical hypoplasia of one or two buds with or without dysplasia of the fallopian tubes. Most importantly, the atypical form is often associated with renal anomalies, primarily URA or ectopia of one or both kidneys and horseshoe kidney in about 40% to 60% (Guerrier et al, 2006). In addition, there can be cervico-thoracic anomalies, auditory defects, and digital anomalies. Duncan and colleagues (1979) reported on the most severe constellation of malformations and referred to this as the MURCS association or *MÜ*llerian duct aphasia (96%), *R*enal aphasia or ectopic (86%), and *C*ardiothoracic *S*omite dysplasia (two to four anomalous vertebrae between C5-T1 (80%).

Anomalies of Other Organ Systems. **Anomalies of other organ systems are found frequently in affected individuals. The more common sites involve the cardiovascular (30%), gastrointestinal (25%), and musculoskeletal (14%) systems** (Emanuel et al, 1974) (Fig. 117–6). They include septal and valvular cardiac defects, imperforate anus and anal or esophageal strictures or atresia, and vertebral or phalangeal abnormalities

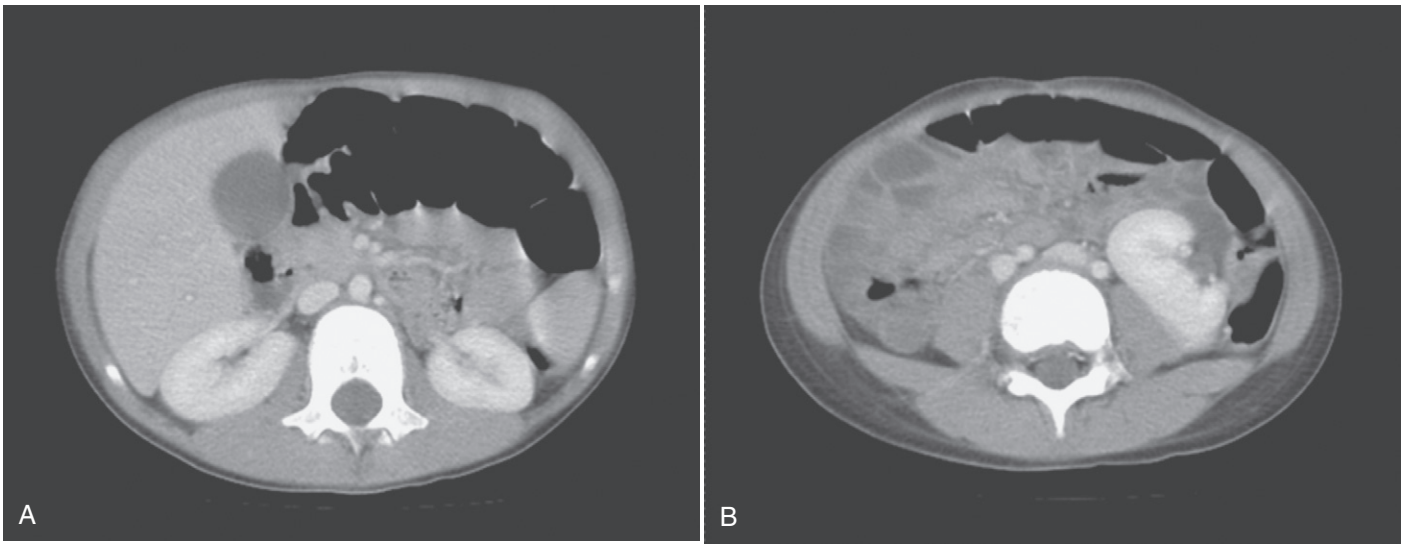


Figure 117–6. Contrast CT scan showing **(A)** right and left orthotopic kidneys. **B,** Right midabdominal malrotated supernumerary kidney.

(Jancu et al, 1976; Wheeler and Weaver, 2001; Rai et al, 2002). Dursun and colleagues (2005) found that 44% of individuals with a congenital solitary kidney, most of whom had URA, had various nonurologic anomalies, but they detected lower incidences of these problems (cardiovascular, 15%; gastrointestinal, 9%; neurologic, 3%; and hematologic, 6%) than previously reported by Emanuel. Chow and colleagues (2005) reported a similar incidence of 42%.

Key Points: Unilateral Renal Agenesis

- Unilateral agenesis occurs once in 1100 births.
- Males predominate with a ratio of 1.8:1.
- Absence of one kidney occurs somewhat more frequently on the left side.
- The ipsilateral ureter is completely absent in about half of the patients.
- Despite the predominance of males with URA, müllerian duct abnormalities occur in 25% to 50% of cases of females with URA compared with wolffian duct anomalies in 10% to 15% of males with URA.
- Approximately one fourth to one third of women with müllerian duct anomalies are found to have URA.
- Anomalies of other organ systems are found frequently in affected individuals. The more common sites involve the cardiovascular, gastrointestinal, and musculoskeletal systems.

Diagnosis and Radiographic Evaluation. **There are no specific symptoms that suggest an absent kidney. Previously, most reports were compiled from autopsy series, but now prenatal screening is detecting URA. The solitary kidney may begin to undergo compensatory hypertrophy in utero** (Mandell et al, 1993; Hill et al, 2000). Recently, prenatal ultrasonography was used to determine compensatory hypertrophy in cases of fetal unilateral empty renal fossa (Cho et al, 2009). These investigators retrospectively measured the ratio of the anteroposterior (AP) and transverse (TR) diameters of the contralateral normal kidney in a set of patients: 12 with URA, 6 with MCDK, and 6 with pelvic kidneys, and these patients were compared with 20 normal controls. They found that when using 0.9 as the discriminating value of the ratio, there was 100% sensitivity, specificity, and accuracy.

Once URA is diagnosed, a retroperitoneal ultrasonogram with color Doppler will show absence of the kidney and ipsilateral renal vessels. A plain film of the abdomen showing the gas pattern of the splenic flexure in the left renal fossa suggests left renal agenesis, ectopia, or crossed ectopia (Mascatello and Lebowitz, 1976), whereas the gas pattern of the hepatic flexure positioned in the right renal fossa suggests congenital absence of the right kidney (Curtis et al, 1977). The diagnosis of URA usually can be confirmed with a DMSA scan showing absent uptake of the isotope on one side, with the contralateral kidney often showing compensatory hypertrophy (Hynes and Watkin, 1970; Cope and Trickey, 1982). A DMSA scan will also detect an ectopic (usually pelvic) or a crossed ectopic kidney in cases where the nonvisualized orthotopic kidney is thought to be absent (Volkan, 2003). In some cases, crossed fused ectopia may be difficult to distinguish from a congenital solitary kidney that has undergone compensatory hypertrophy or a solitary complete duplication. A small dysplastic kidney or MCDK may be misdiagnosed as URA when a kidney is not seen on ultrasonography (Mesrobian, 1993). In these cases, the colonic gas pattern will not be observed in the renal fossa. In addition, calcifications in the renal fossa may suggest an involuted MCDK (Nakano et al, 1996).

Ultrasonography, radionuclide scintigraphy, and MRI have replaced arteriography in diagnosing URA. When a fetus with other suspected organ anomalies undergoes MRI, an absent kidney can be confirmed (Dell'Acqua et al, 2002). URA has also been found incidentally during fluoroscopic monitoring of the renal fossa at the end of a cardiac catheterization or at the end of an echocardiogram. **When URA is diagnosed, a voiding cystourethrogram should be performed, because there is a 28% incidence of contralateral reflux** (Cascio et al, 1999; Kaneyama et al, 2004).

Special Considerations. **The most common question many parents ask is "Will having only one kidney affect my**

child's life, and will there be any restrictions on their activities?" Several North American studies examine the risks of injury to the pediatric kidney through sports. Psooy (2006, 2009) summarizes the results of these studies, which suggest that motor vehicle accidents as passenger and pedestrian result in more renal trauma than sports activities. In addition, bicycling, sledding, downhill skiing/snowboarding, and equestrian activities are the more common causes of high-grade renal trauma. These activities have a more than fivefold relative risk for head injury compared with renal injury. Psooy (2009) notes that children are not generally restricted from these activities on the basis of having "only one head." **Rice and the Council on Sports Medicine and Fitness of the American Academy of Pediatrics** (2008) **advise that each athlete needs individual assessment for their particular sport and that wearing protective padding may reduce the risk of injury to the solitary kidney, thus allowing participation in most sports.**

Prognosis. **In the past, there was no definitive evidence that a solitary kidney predisposes to increased susceptibility to other diseases** (Shapiro et al, 2003). Reviews conducted in the preantibiotic era reported a high incidnce of glomerulonephritis, stones, and tuberculosis. The advent of antibiotics has reduced the incidence of morbidity and mortality for individuals with URA. In the Ashley and Mostofi series (1960), only 15% of the patients died because of renal disease. Renal trauma resulted in death for 5%; some patients in this group might have survived had there been two kidneys. However, because the source of the autopsy material included many military personnel, the potential risk of injury was accentuated. Therefore URA with a normal contralateral kidney is thought to be compatible with normal longevity and the contralateral kidney is not predisposed to greater than normal risks (Gutierrez, 1933; Dees, 1960).

In more contemporary studies, Rugui and colleagues (1986) found an increased occurrence of hypertension, hyperuricemia, and decreased renal function but no proteinuria in a small group of patients with congenital absence of one kidney. Only one patient had a renal biopsy showing focal glomerulosclerosis. This finding has been confirmed in other patients and is similar to observations in the remaining kidney in the hyperfiltration syndrome noted after unilateral nephrectomy (Kiprov et al, 1982; Nomura and Osawa, 1990; Brenner et al, 1996). Oldrizzi and colleagues (1991) reported on URA and progressive renal damage in 39 individuals with a mean age of 33 years. They found prevalence rates of 40% for hypertension, 46% for proteinuria, and 15% for impaired renal function. The limitation of this study is that it was composed of symptomatic patients, and there was no age-matched asymptomatic control population with URA.

Argueso and colleagues (1992) **assessed 157 individuals with congenital URA with a mean age of 37 (age 2 to 84) at diagnosis and noted hypertension, proteinuria (>50 mg/day), and mild renal insufficiency in 47%, 19%, and 13%, respectively.** Only 32 patients actually had their glomerular flow rate (GFR) measured. Of the 13 patients in their seventh to ninth decade, the mean GFR was 65 mL/minute per 1.73 m^2, and the 4 who had renal insufficiency had a GFR between 32 to 53 mL/minute per 1.73 m^2. Six of the 43 deceased patients in this study died from chronic renal failure. Only about 25% of patients had their proteinuria quantified, and less than a third had blood pressure measured. Recognizing these study deficiencies, **the authors concluded that survival was not impaired in this group, because the overall patient survival curve was similar to the general population.** In addition, others have reported that the ability of the kidney to excrete increased loads of protein was not impaired, even in patients with renal insufficiency or proteinuria (DeSanto et al, 1997).

In another study of 206 women with uterine abnormalities, 33 (16%) had URA and 19 had been pregnant and delivered (Heinonen, 2004; Heinonen, 1997). The control group was composed of 44 age-matched women with similar parity and similar uterine malformations but who had two normal kidneys. Eight (42%) of the 19 women with a uterine anomaly and URA (in at least one pregnancy) had gestational hypertension, pre-eclampsia, or gestational proteinuria, compared with only 8 (18%) of the women with two kidneys. The relative risk of gestational hypertension, pre-eclampsia, or gestational proteinuria was significantly higher in women with URA (RR = 2.3). Perinatal outcomes were similar in both groups, with no patient having proteinuria or chronic renal disease, but 2 of the 19 women (11%) with URA were started on long-term antihypertensive medication.

Current Concepts Regarding Prognosis in Adults with Unilateral Renal Agenesis. **There is now evidence that subtle defects in UB branching can cause a reduced nephron number, which may lead to renal disease later in life** (Brenner and Mackenzie, 1997; Costantini and Shakya, 2006; Chevalier, 2009). In humans, there is an eightfold range in normal variation in the number of glomeruli, that is, from 200,000 to 1.8 million (Hughson, 2003). Therefore it is more likely for an individual with nephron numbers at the lower end of the spectrum to be at greater risk for renal insufficiency at any age and from any etiology.

In the past, studies of the renal survival in children with *C*ongenital *A*nomalies of the *K*idney and *U*rinary *T*ract (CAKUT) have been difficult to perform because they involve decades of follow-up and the phenotypes of these disorders are not uniform (Pope et al, 1999; Kerecuk et al, 2008; Zaffanello et al, 2009). Recently, Sanna-Cherchi and colleagues (2009) evaluated the long-term functional outcomes in individuals with CAKUT, including those with URA from a single pediatric nephrology center. Three hundred and twelve patients with CAKUT who had a known defect of the number or size of at least one kidney were followed up to 20 years. Patients with isolated vesicoureteral reflux and duplications were excluded. Dialysis-free survival was evaluated, taking into consideration reflux, age at diagnosis, hypertension, proteinuria, and serum creatinine. Six subgroups were examined, including URA, unilateral and bilateral hypodysplasia, posterior urethral valves, multicystic dysplastic kidney, and horseshoe kidney. These investigators found that by 30 years of age, 19% of all patients were on dialysis, most of whom had posterior urethral valves, bilateral renal hypoplasia, or URA. **Further analysis showed that patients with a solitary kidney had a 50% probability of requiring dialysis by 30 years of age.** Notably, most of the patients with URA in this study were diagnosed during adolescence and had a normal creatinine level at the time of diagnosis. Interestingly, the patients diagnosed at birth had a slightly elevated creatinine level (0.68 mg/dL). These and other studies point out the fundamental differences in individuals with URA and adults who undergo unilateral nephrectomy. The number of nephrons in children with URA may be abnormally low, and those with fewer nephrons may be at greater risk to developing focal glomerulosclerosis.

Current suggestions for children with a normal-appearing single kidney include annual assessments of blood pressure and proteinuria, the hallmarks of a progressive decrease in glomerular filtration rate (Hegde and Coulthard, 2009). Laboratory evaluation, including a blood urea nitrogen and serum creatinine level, can be performed periodically unless abnormalities are denoted. If there is hypertension, proteinuria, and/or impaired renal function,

a pediatric nephrologist should be consulted. They may suggest dietary changes, including limiting salt and avoiding excessive protein intake, depending on the age of the patient. Treatment with an angiotensin-converting enzyme inhibitor may also be indicated (Puddu et al, 2009).

Supernumerary Kidney

Parenchymal development was thought to be controlled by an unidentified substance that limited the amount of functioning renal tissue. Nature has created, albeit rarely, a condition in which three separate kidneys can form. In this condition, the two main kidneys are usually normal and equal in size, whereas the third is small. **The supernumerary kidney is truly an accessory organ with its own collecting system, blood supply, and distinct encapsulated parenchymal mass.** It may be either totally separate from the normal kidney on the same side or connected to it by loose areolar tissue (Geisinger, 1937). The ipsilateral ureters may be bifid or completely duplicated. The condition is not analogous to a single kidney with ureteral duplication in which the collecting systems drain portions of one parenchymatous mass surrounded by a single capsule.

Incidence. The true incidence of this anomaly cannot be determined, because it occurs very infrequently. **About 100 cases have been reported since it was first described in 1656** (Sasidharan et al, 1976; MacPherson, 1987). It affects males and females equally but has a higher predilection for the left side (N'Guessan and Stephens, 1983). Four cases of bilateral supernumerary kidneys have been reported (Campbell, 1970; Oto et al, 2002).

Embryology and Molecular Mechanisms. A second UB or a branching from the initial UB appears as a necessary first step. Next, the nephrogenic anlage may divide into two metanephric tails, which separate entirely when induced to differentiate by the separate or bifid UBs (N'Guessan and Stephens, 1983). The two metanephroi develop only after being penetrated by the bifid or separate UBs. N'Guessan and Stephens do not accept that this condition is the result of widely divergent bifid or separate UBs. Geisinger (1937) proposed that the separate kidneys developed by fragmentation of a single metanephros or by linear infarction producing separate viable fragments that develop only when a second UB is present.

Kidney development is initiated when a single UB forms from the WD in response to GDNF secreted by the adjacent MM. Posterior restriction of *Gdnf* expression is critical for the development of a UB in the normal position, while another intercellular signaling system, including SLIT2 or its receptor ROBO2, is also important in ensuring that a single UB forms in the appropriate location. Grieshammer and colleagues (2004) showed that mutant mice lacking either SLIT2 or its receptor ROBO2 develop supernumerary UBs that are correlated with abnormal maintenance of *Gdnf* expression in anterior MM. The SLIT2/ROBO2 intercellular signaling system restricts, directly or indirectly, the extent of the *Gdnf* expression and plays a critical role in precisely positioning the site of kidney induction.

Description. The supernumerary kidney is a distinct mass of renal parenchyma that may be either completely separate or only loosely attached to the major kidney on the ipsilateral side. In about 60% of cases, it is located caudad to the dominant kidney, which is in its orthotopic position in the renal fossa. When a separate and distinct ureter is present, the supernumerary kidney is more likely to be cranial to the dominant kidney but caudal to the adrenal (Bernik et al, 2001). Occasionally, the supernumerary kidney lies either posterior or superior to the main kidney, or it may even be a midline structure anterior to the great vessels and loosely attached to each of the other two kidneys (see Fig. 117–6). The supernumerary kidney may become wedged between the lower poles of a right and left kidney, leading to the radiographic appearance of a "pseudohorseshoe" kidney (Macpherson, 1987). A pelvic supernumerary kidney has also been reported (Eberle et al, 2002).

Key Points: Supernumerary Kidney

- The supernumerary kidney is a definitive accessory organ with its own collecting system, blood supply, and distinct encapsulated parenchyma.
- The supernumerary kidney may be either completely separate or loosely attached to the kidney on the ipsilateral side.
- The ureteral inter-relationships on the side of the supernumerary kidney can be variable.

The supernumerary kidney is reniform but generally smaller than the main ipsilateral kidney. In about one third of cases, the kidney or its collecting system is abnormal. In almost half of the reported cases, the collecting system is severely dilated with thin parenchyma suggesting obstruction.

The ureteral interrelationships on the side of the supernumerary kidney can be variable (Kretschmer, 1929). Convergence of the ipsilateral ureters distally to form a common stem and a single ureteral orifice occurs in 50% of the cases (Exley and Hotchkiss, 1944; N'Guessan and Stephens, 1983), which suggests "a bud off of a bud" situation. Two completely independent ureters, each with its own entrance into the bladder, are seen in the other 50% of cases. The Weigert-Meyer principle (see Chapter 111) usually is followed, but in 10%, the caudal kidney has a ureter that does not follow the rule and enters the trigone below the ipsilateral ureter (Tada et al, 1981) (Fig. 117–7). Rarely, the supernumerary kidney has a completely ectopic ureter opening into the vagina or introitus (Rubin, 1948; Carlson, 1950). Individual case reports have described calyceal communications between the supernumerary and the dominant kidney, or fusion of the dominant kidney's ureter with the pelvis of the supernumerary kidney (Kretschmer, 1929) to create a single distal ureter that then enters the bladder (Fig. 117–8). The vascular supply to the supernumerary kidney is anomalous and depends on its position in relation to the major ipsilateral kidney. Most investigators believe that the blood supply to the individual parenchymal masses should be separate to consider this a true supernumerary kidney (Kaneoya et al, 1989).

Associated Anomalies. Usually, the ipsilateral and contralateral kidneys are normal. Except for an occasional ectopic orifice from the ureter draining the supernumerary kidney, no genitourinary abnormalities are present in any consistent pattern. A few of the case reports describe anomalies of other organ systems (Janda et al, 2009).

Symptoms. Although this anomaly is present at birth, it is rarely symptomatic but may become symptomatic in early adulthood. The average age at diagnosis was 36 years. Pain, fever, hypertension, and a palpable abdominal mass are the usual presenting complaints. Urinary infection or obstruction, or both, are the major conditions that lead to an evaluation. Ureteral ectopia from the supernumerary kidney may produce urinary

incontinence, but this is extremely rare (Shane, 1942; Hoffman and McMillan, 1948).

A palpable abdominal mass secondary to development of carcinoma in the supernumerary kidney has been described in two patients. In 25% of all reported cases, the supernumerary kidney remains completely asymptomatic and is discovered only at autopsy (Carlson, 1950).

Diagnosis. If the supernumerary kidney is normal and asymptomatic, it is usually diagnosed when abdominal ultrasonography, CT, or MRI is performed for other reasons. The kidney may be inferior and distant enough from the ipsilateral kidney so that it does not alter the position of the normal kidney (Conrad and Loes, 1987). If it is in close proximity, it may displace the predominant kidney or its ureter very slightly.

A supernumerary kidney may become symptomatic from hydronephrosis due to obstruction or stone formation (Koureas et al, 2000). In this case, ultrasonography may demonstrate distortion of the normal ipsilateral kidney and ureter. If the collecting system is bifid, the dominant kidney on that side will usually be involved in the same disease process. If the ureters are separate, the ipsilateral kidney may show the effects of an abnormal supernumerary kidney. Voiding cystourethrography, ultrasonography, or MR urography, and even retrograde pyelography may be needed to help delineate the anomaly. Radionuclide imaging provides information about relative function in the supernumerary and the normal kidneys (Conrad and Loes, 1987). Cystoscopy reveals one or two ureteral orifices on the ipsilateral side, depending on whether the ureters are completely duplicated. Ureteral ectopia may exist in or outside of the bladder. Occasionally, a supernumerary kidney is not accurately diagnosed until the time of surgery or at autopsy, or it may mimic a duplication (Kaneoya et al, 1989).

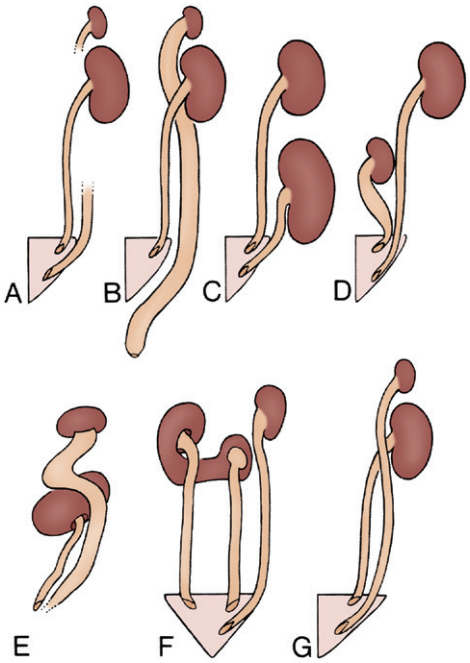


Figure 117–7. **A** to **G,** Various patterns of urinary drainage of supernumerary and ipsilateral kidneys when ureters are completely separated. All kidney positions are relative only and are depicted on the left side for ease of interpretation. *Dashed lines* indicate that detail was not defined. (From N'Guessan G, Stephens FD. Supernumerary kidney. J Urol 1983;130:649.)

ANOMALIES OF ASCENT

Simple Renal Ectopia

When the mature kidney fails to reach its normal location in the "renal" fossa, the condition is known as *renal ectopia.* The term is derived from the Greek words *ek* ("out") and *topos* ("place") and literally means "out of place." It is to be differentiated from renal ptosis, in which the kidney initially is located in its proper place (and has normal vascularity) but moves downward in relation to body position. The ectopic kidney has never resided in the appropriate location. An ectopic kidney can be found in one of the following positions: pelvic, iliac, abdominal, thoracic, and contralateral or crossed (Fig. 117–9).

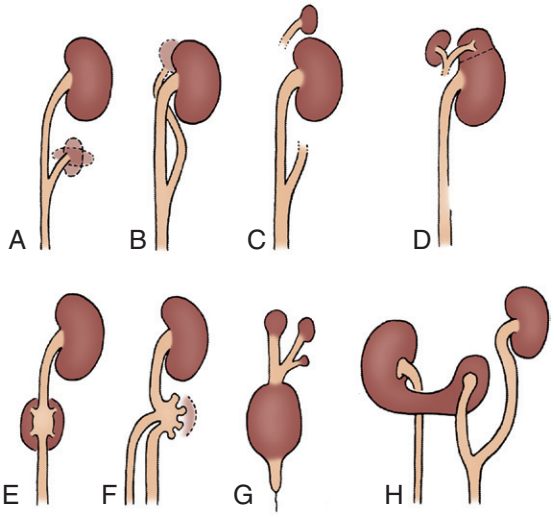


Figure 117–8. **A** to **H,** Various patterns of urinary drainage when ureters form a common stem. All kidney positions are relative only and are depicted on the left side for ease of interpretation. *Dashed lines* indicate that detail was not defined. (From N'Guessan G, Stephens FD. Supernumerary kidney. J Urol 1983;130:649.)

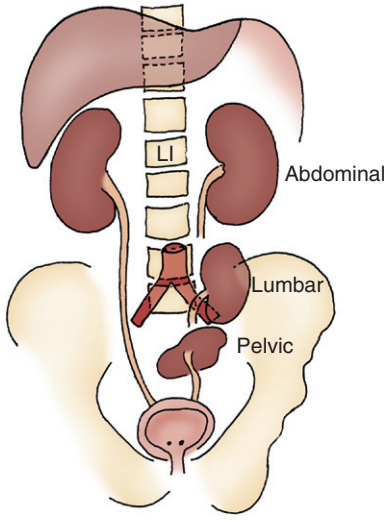


Figure 117–9. Incomplete ascent of kidney. The kidney may halt at any level of its ascent from the pelvis. (From Gray SW, Skandalakis JE. The kidney and ureter. In: Gray SW, Skandalakis JE, editors. Embryology for surgeons. Philadelphia: WB Saunders; 1972.)

Incidence. Renal ectopia has been known to exist since it was described by 16th century anatomists, but it did not achieve clinical interest until the mid-19th century. Recently, with improved imaging, simple renal ectopia has been noted with increasing frequency.

The actual incidence among autopsy series varies from 1 in 500 (Campbell, 1930) **to 1 in 1200** (Stevens, 1937; Thompson and Pace, 1937; Anson and Riba, 1939; Bell, 1946a), **but the average occurrence is about 1 in 900** (Abeshouse and Bhisitkul, 1959). With increasing clinical detection, the incidence among hospitalized patients has approached the autopsy rate (Abeshouse and Bhisitkul, 1959). Autopsy studies reveal no significant difference in incidence between the sexes. A recent review of prenatal ultrasonograms detected an incidence of 0.003% in India, but this likely under-represents its true occurrence (Sanghvi et al, 1998). Clinically, renal ectopia is more readily recognized in females; they undergo uroradiologic evaluation more frequently than males because of their higher rate of UTI and/or associated genital anomalies (Thompson and Pace, 1937).

The left side is favored slightly over the right. Pelvic ectopia has been estimated to occur in 1 of 2100 to 3000 autopsies (Stevens, 1937). A solitary ectopic kidney occurs in 1 of 22,000 autopsies (Stevens, 1937; Hawes, 1950; Delson, 1975). By 1973, only 165 cases of a solitary pelvic kidney had been recorded (Downs et al, 1973). Bilateral ectopic kidneys are even more rarely observed and account for only 10% of all patients with renal ectopia (Malek et al, 1971) (Fig. 117–10).

Embryology. The UB, arising from the WD at the end of the fourth week, grows craniad toward the urogenital ridge, acquiring a cap of metanephric blastema by the fifth week. The developing metanephric tissue and UB migrate cephalad, rotating medially on its long axis. The entire process is completed by the eighth week of gestation. Factors that may prevent the orderly ascent and rotation of kidneys include UB maldevelopment (Campbell, 1930), defective metanephric tissue that fails to induce ascent (Ward et al, 1965), genetic abnormalities, and maternal illnesses or teratogenic causes (Malek et al, 1971). A vascular barrier that prevents upward migration secondary to persistence of the fetal blood supply has also been postulated (Baggenstoss, 1951), but the existence of an "early" renal blood supply does not prevent the affected kidney's movement to its ultimate position. Most probably, this is the end result, not the cause, of renal ectopia.

Description. The classification of ectopia is based on the position of the kidney within the retroperitoneum: The pelvic kidney opposite the sacrum and kidneys below the aortic bifurcation are the most common sites of ectopia; the lumbar kidney resides near the sacral promontory in the iliac fossa and anterior to the iliac vessels; and the abdominal kidney is above the iliac crest and adjacent to the second lumbar vertebra (see Fig. 117–10).

The ectopic kidney is usually smaller, and it may not conform to the usual reniform shape, due to the presence of fetal lobulations. The axis of the kidney is slightly medial or vertical, but it may be tilted as much as 90 degrees laterally so that it lies in a true horizontal plane. **The renal pelvis is usually anterior (instead of medial) to the parenchyma, because the kidney has incompletely rotated. As a result, 56% of ectopic kidneys have a hydronephrotic collecting system. Half of these cases are due to obstruction of the ureteropelvic or the ureterovesical junction (70% and 30%, respectively), 25% from reflux grade III or greater, and 25% from the malrotation alone** (Gleason et al, 1994). Overall, vesicoureteral reflux has been found in 30% of children with ectopic kidneys (Guarino et al, 2004).

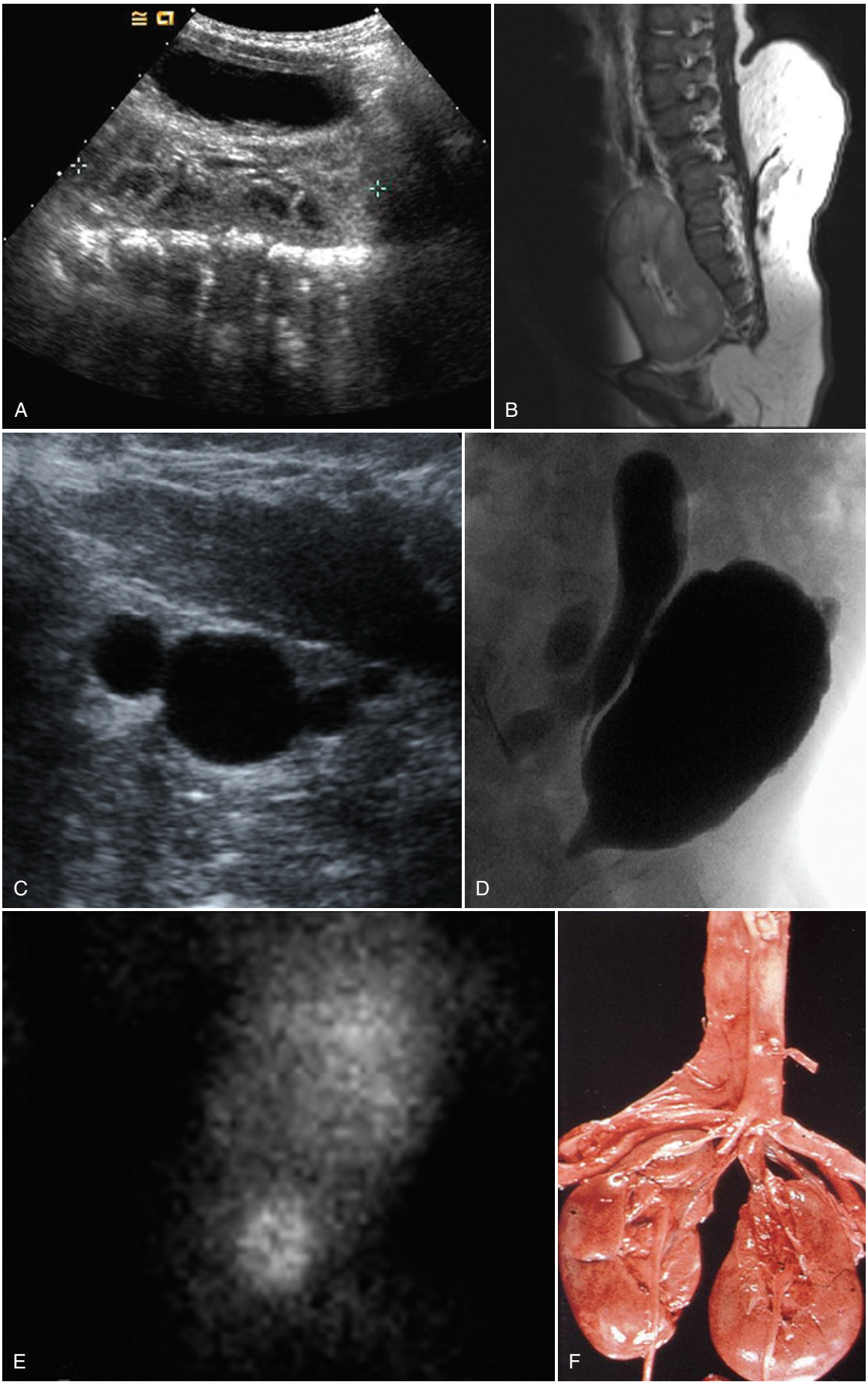
The length of the ureter usually conforms to the position of the kidney, but occasionally, it is slightly tortuous. It is rarely redundant, in contrast to the ptotic kidney, in which the ureter has achieved its full length before the kidney drops. **The ureter usually enters the bladder on the ipsilateral side with its orifice positioned normally, except for those unusual cases with ectopic ureters.** The arterial and venous network is anomalous and its vascular pattern depends on the ultimate position of the kidney (Anson and Riba, 1939). There may be one or two main renal arteries arising from the distal aorta or from the aortic bifurcation, with one or more aberrant arteries emanating from the common or external iliac or even the inferior mesenteric artery. The kidney may be supplied entirely by multiple anomalous branches, none of which arises from the aorta. In no instance has the main renal artery arisen from the level of the aorta that would be its proper origin if the kidney were positioned normally.

Associated Anomalies. Although the contralateral kidney is usually normal, it is associated with a number of congenital defects. **Malek and colleagues** (1971) **and Thompson and Pace** (1937) **reported the incidence of contralateral agenesis to be rather high** (Chow et al, 2005). Bilateral ectopia occurs infrequently (10%) (see Fig. 117–10). Hydronephrosis secondary to obstruction or reflux may be seen in as many as 25% of nonectopic contralateral kidneys (Gleason et al, 1994).

Key Points: Simple Renal Ectopia

- The left side is affected slightly more than the right.
- Pelvic ectopia has been estimated to occur in 1 of 2100 to 3000 autopsies.
- Fifty-six percent of ectopic kidneys have a hydronephrotic collecting system. Half of these cases result from obstruction at the ureteropelvic or the ureterovesical junction (70% and 30%, respectively), 25% from reflux grade III or greater, and 25% from the malrotation alone.
- Vesicoureteral reflux has been found in 30% of children with ectopic kidneys.
- The incidence of genital anomalies in the patient with ectopia is about 15%.
- Most ectopic kidneys are clinically asymptomatic, except in cases of associated ectopic ureter.

Figure 117–10. One-day-old boy with a right retrovesical pelvic kidney demonstrated on **(A)** transverse ultrasonogram of right pelvis. **B,** Sagittal MRI. Vertebral abnormalities and a portion of a lipomyelomeningocele are also observed. **C,** Longitudinal ultrasonogram of left multicystic dysplastic pelvic kidney. **D,** Voiding cystourethrogram shows reflux into dilated, tortuous right megaureter. **E,** Flow study of dimercaptosuccinic acid shows early activity only in the region of the right pelvic kidney and no uptake on the left. **F,** Postmortem specimen from a different case showing bilateral pelvic ectopia, anterior orientation of renal pelves, and anomalous blood supply from the aortic bifurcation. (**C,** Courtesy of Dr. Sara Milla; **F,** from Weiss MA, Mills SE. Atlas of genitourinary tract disorders. Philadelphia: JB Lippincott; 1988.)


A
B
C
D
E
F

The most striking feature is the association of genital anomalies and ectopia. The incidence varies from 15% (Thompson and Pace, 1937) **to 45%** (Downs et al, 1973), depending on how carefully the patient is evaluated. Twenty to 66 percent of females have one or more of the following abnormalities of the reproductive organs: bicornuate or unicornuate uterus with atresia of one horn (McCrea, 1942), rudimentary or absent uterus and proximal and/or distal vagina (Tabisky and Bhisitkul, 1965; D'Alberton et al, 1981), and duplication of the vagina. Among male patients, 10% to 20% have a recognizable associated genital defect; undescended testes, duplication of the urethra, and hypospadias are the most common (Thompson and Pace, 1937). Fourteen percent of patients with a cloacal malformation have an ectopic kidney (Warne et al, 2002; Dursun et al, 2005).

Rarely is the adrenal gland absent or abnormally positioned. Twenty-one percent of individuals have anomalies of other organ systems (Downs et al, 1973); most involve the skeletal or cardiac systems.

Diagnosis. With the increasing use of various imaging modalities, the incidence of an asymptomatic ectopic kidney is increasing. **Most ectopic kidneys are asymptomatic.** Vague abdominal complaints or ureteral colic secondary to an obstructing stone are the most frequent symptoms leading to the diagnosis of an ectopic kidney. The abnormal position of the kidney results in a pattern of direct and referred pain that is atypical for colic and may be misdiagnosed as acute appendicitis or as pelvic inflammatory disease in female patients. Symptoms rarely occur due to adjacent organs to the ectopic kidney. Renal ectopia may also present with a UTI or a palpable abdominal mass. Seven cases of concomitant renal and ureteral ectopia presenting with urinary incontinence have been reported (Borer et al, 1993, 1998). The difficulty in diagnosing this condition is related to the poor function of these ectopic kidneys. The kidneys may be very small and/or dysplastic with essentially no function leading to the misdiagnosis of URA. DMSA scanning or MR urography may both be necessary to diagnose these unusual cases (Borer et al, 1998; Leitha, 1998; Pattaras et al, 1999) (see Fig. 117–10).

Malposition of the colon as observed with renal ageneisis will be observed in cases of ectopic lumbar or pelvic kidney. The diagnosis is made when the renal ultrasonogram fails to reveal a kidney in its orthotopic location. Many of these kidneys were not visualized in the past on an excretory urogram because they overlie the bony pelvis, which obscures the collecting system and leads to a misdiagnosis. With a carefully performed power color Doppler study, the main renal artery and intrarenal vasculature can be more easily delineated. Ultrasonography of the pelvic ectopic kidney demonstrated absence of renal sinus echoes, a normal finding associated with the extrarenal position of the pelvis and calyces (Barnewolt and Lebowitz, 1996).

Cystoscopy, if performed, will demonstrate ureteral orifices that are invariably normal unless the ureteral orifice is also ectopic. If surgery is indicated on an ectopic kidney, MR arteriography can be performed preoperatively to define the anatomy of the renal vasculature, which is especially important in cases of solitary ectopia.

Prognosis. **The ectopic kidney is no more susceptible to disease than the normally positioned kidney, except for the development of hydronephrosis or urinary calculus formation** (Gleason et al, 1994; Benchekroun et al, 2002). This may be due to the anteriorly placed pelvis and malrotation of the kidney, which may lead to impaired drainage of urine from a high insertion of the ureter to the pelvis or an anomalous vasculature that partially obstructs one of the major calyces or the upper ureter. In addition, there may be an increased risk of injury from blunt abdominal trauma, because the low-lying kidney is not protected by the rib cage.

Renovascular hypertension secondary to an anomalous blood supply has been reported, but a higher-than-normal incidence is yet to be proved. A recent study by van den Bosch and colleagues (2010) examined the urologic and nephrologic consequences of both simple and crossed renal ectopia. They found no adverse effects on blood pressure or kidney function during childhood. They did note that although global renal function of these kidneys was normal, the relative function of the ectopic kidney on dimercaptosuccinic acid scan (^{99m}Tc-DMSA) was 38% (interquartile range [IQR] 33% to 43%).

Anderson and Harrison (1965), in a review of pregnant women with renal ectopia, found no increased occurrence of difficult deliveries or maternal or fetal complications related to the ectopic kidney (Anderson and Harrison, 1965; Delson, 1975). Dystocia from a pelvic kidney is a very rare finding, but when it does occur, early recognition is mandatory and cesarean section is indicated. Although three cases of cancer in an ectopic kidney have been reported, there does not appear to be an increased risk for malignancy. No deaths have been directly attributable to the ectopic kidney, but in at least five instances, a solitary ectopic kidney has been mistakenly removed, because the kidney was thought to represent a pelvic malignancy (Downs et al, 1973). This should not happen with the current armamentarium of imaging techniques available to accurately diagnose this condition.

Cephalad Renal Ectopia

The kidney may be positioned more craniad than normal when there is an omphalocele (Pinckney et al, 1978). When the liver herniates into the omphalocele with the intestines, the kidneys continue to ascend until their ascent is arrested by the diaphragm. In all reported cases, both kidneys were affected and were positioned immediately beneath the diaphragm at the level of the 10th thoracic vertebra. The ureters are excessively long but otherwise normal. A color Doppler ultrasonogram or MR arteriography demonstrates that the origin of each renal artery is more cephalad than normal, and no other abnormality of the vascular network is present. Patients with this anomaly usually have no symptoms referable to the malposition, and urinary drainage is not impaired.

Thoracic Kidney

The rarest form of renal ectopia exists when the kidney is positioned considerably higher than normal. **Intrathoracic ectopia denotes either a partial or a complete protrusion of the kidney above the level of the diaphragm into the posterior mediastinum** (Fig. 117–11). **Fewer than 5% of all patients with renal ectopia have an intrathoracic kidney, with an incidence of 1:13,000 at autopsy** (Campbell, 1930). This condition must be differentiated from a congenital or traumatic diaphragmatic hernia in which other abdominal organs, as well as the kidney, have advanced into the chest cavity.

Incidence. Before 1940, this condition was only noted at autopsy (DeCastro and Shumacher, 1969). Since that time, **at least 200 patients with a thoracic kidney have been reported** in the literature (Donat and Donat, 1988; Lacasta Garcia et al, 1999), 4 of whom had bilateral thoracic kidneys (Berlin et al, 1957; Hertz and Shahin, 1969; Lundius, 1975; N'Guessan and Stephens, 1984; Liddell et al, 1989). There appears to be a slight left-sided predominance of 1.5:1, and the sex ratio favors males

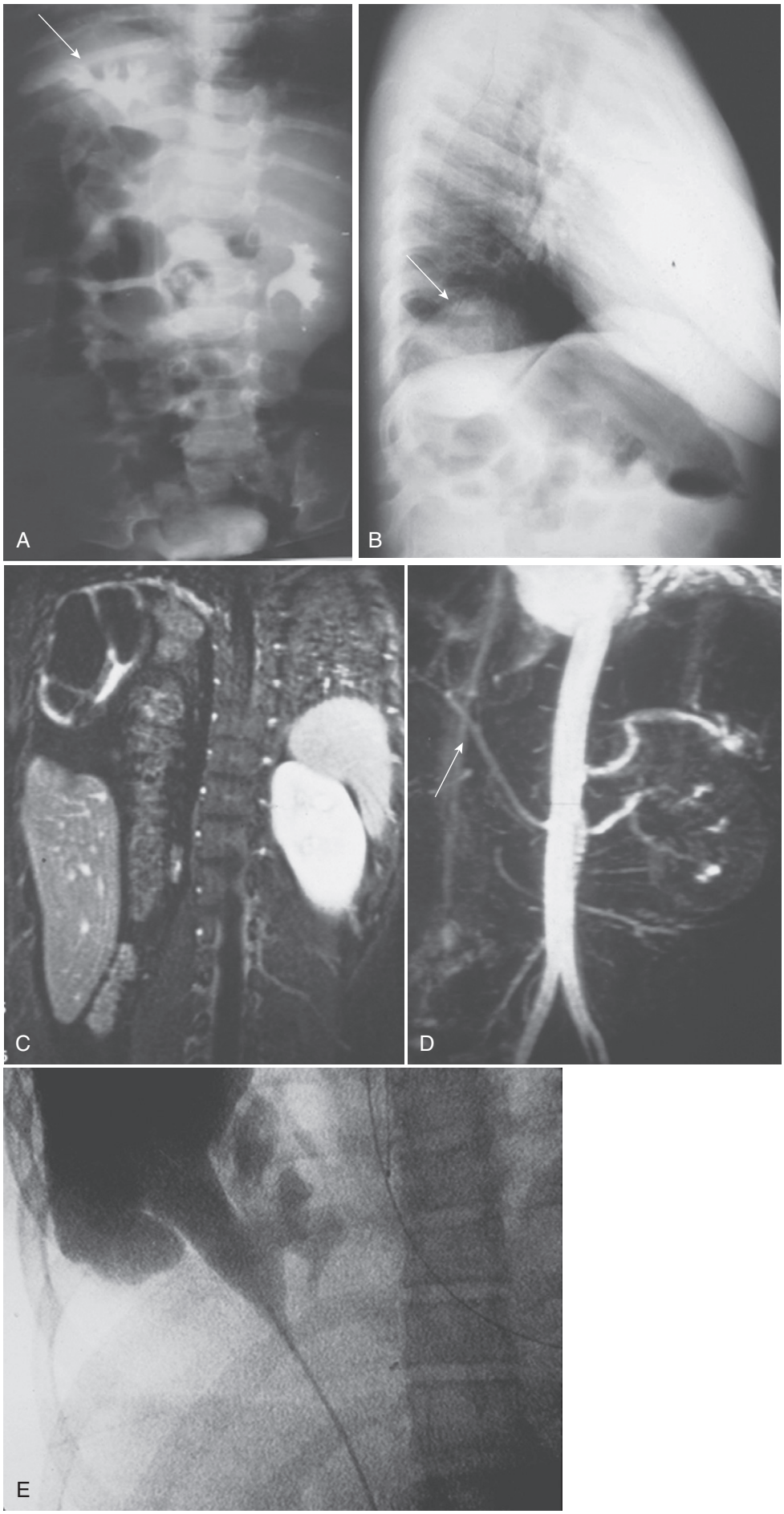


Figure 117–11. One-year-old girl with febrile urinary tract infection (UTI). **A,** Intravenous pyelogram shows a right thoracic kidney *(arrow)* and left orthotopic kidney. She was found to have bilateral vesicoureteral reflux and underwent bilateral ureteral reimplants. At age 16, she developed right back pain and chest tightness. **B,** Chest radiograph demonstrates right diaphragmatic eventration and a right intrathoracic kidney *(arrow)*. **C,** MR urogram shows coronal T1 fat-saturation after contrast images of poorly functioning right hydronephrotic kidney located superior to the liver and inferior to the right lung with absence of the posterior right hemidiaphragm, permitting the colon to enter the right hemithorax. **D,** Angiographic sequence demonstrating right renal artery *(arrow)* arising from the aorta at the normal level of the left renal artery coursing superiorly to enter the right renal hilum. **E,** Intraoperative right retrograde pyelogram shows narrowing at the ureteropelvic junction. (**A,** Courtesy of Dr. Terry Hensle.)

by 2:1 (Lozano and Rodriguez, 1975). This entity has been found on prenatal ultrasonography (Masturzo et al, 2001) and in all age groups, from a neonate (Shapira et al, 1965) to a 75-year-old man evaluated for prostatic hypertrophy (Burke et al, 1967), but it is most commonly detected in adults undergoing chest radiography for other reasons (Drop et al, 2003) (see Fig. 117–11).

Embryology. **The kidney reaches its adult location by the end of the eighth week of gestation.** At this time, the diaphragmatic leaflets are formed as the pleuroperitoneal membrane separates the pleural from the peritoneal cavity. Mesenchymal tissues associated with this membrane eventually form the muscular component of the diaphragm. It is uncertain whether delayed closure of the diaphragmatic anlage allows for protracted renal ascent above the level of the future diaphragm or whether the kidney overshoots its usual position because of accelerated ascent before normal diaphragmatic closure (Spillane and Prather, 1952; Burke et al, 1967; N'Guessan and Stephens, 1984). Delayed involution of mesonephric tissue has been proposed as a causative factor (Angulo et al, 1992), because intrathoracic kidneys occur in only 0.25% of patients with a diaphragmatic hernia (Donat and Donat, 1988). Renal angiography has demonstrated either a normal site (Lundius, 1975) or a more cranial origin (Franciskovic and Martincic, 1959) for the origin of the renal artery from the aorta supplying the thoracic kidney (see Fig. 117–11).

Description. **The kidney is situated in the posterior mediastinum and usually has completed the normal rotation process.** The renal contour and collecting system are normal. The kidney usually lies in the posterolateral aspect of the diaphragm in the foramen of Bochdalek. At this point, the diaphragm thins out and a flimsy membrane surrounds the protruding portion of kidney. Therefore the kidney is not within the pleural space (N'Guessan and Stephens, 1984). The lower lobe of the adjacent lung may be hypoplastic secondary to compression by the kidney mass. The renal vasculature and the ureter enter and exit from the pleural cavity through the foramen of Bochdalek.

Associated Anomalies. **The ureter is elongated to accommodate the excessive distance to the bladder, but it never enters ectopically into the bladder or other pelvic sites.** N'Guessan and Stephens (1984) analyzed 10 cases and determined that the **adrenal gland typically occupies its normal location** in most patients. In unilateral cases, the contralateral kidney is usually normal. No consistent anomalies have been described in other organ systems.

Symptoms. **The vast majority of affected individuals are asymptomatic.** Pulmonary and urinary symptoms are exceedingly rare. One case of a pyeloplasty in a thoracic kidney with ureteropelvic junction (UPJ) obstruction and presenting with flank pain has been reported (Hampton and Borden, 2002). A case depicted in Figure 117–11 shows severe hydronephrosis of a previously normal thoracic kidney, presumably due to intermittent obstruction by the muscular fibers of the diaphragm (Shapiro, personal communication).

Diagnosis. **The diagnosis is most commonly made after a routine chest radiograph shows the affected hemidiaphragm slightly elevated.** A smooth, rounded mass is seen extending into the chest near the midline on an anteroposterior film and along the posterior aspect of the diaphragmatic leaflet on a lateral view (see Fig. 117–11). A thoracic kidney may be found at the time of thoracotomy for a suspected mediastinal tumor (DeNoronha et al, 1974). Historically, excretory urography or renal scintigraphy (Williams et al, 1983) provided the diagnosis, while CT or MR urography is currently the imaging modality of choice. Rarely, cardiac or pulmonary arteriography reveals a thoracic kidney (Fusonie and Molnar, 1966).

Prognosis. Neither autopsy series nor clinical reports suggest that a thoracic kidney will usually cause serious urinary or pulmonary complications.

ANOMALIES OF FORM AND FUSION

Crossed Renal Ectopia with and without Fusion

When a kidney is located on the side opposite from that in which its ureter inserts into the bladder, the condition is known as *crossed ectopia*. Ninety percent of crossed ectopic kidneys are fused to their ipsilateral mate. Except for the horseshoe anomaly, they account for the majority of fusion defects. Fusion anomalies are usually diagnosed in children as part of a constellation of malformations, in young adults during evaluation for delayed menarche, and in the elderly as incidental findings (Glodny et al, 2008).

Fusion anomalies of the kidney were first logically categorized by Wilmer (1938), but McDonald and McClellan (1957) refined and expanded that classification to include crossed ectopia with fusion, crossed ectopia without fusion, solitary crossed ectopia, and bilaterally crossed ectopia (Fig. 117–12). The fusion anomalies have been designated as (1) unilateral fused kidney with inferior ectopia; (2) sigmoid, or S-shaped; (3) lump or cake; (4) L-shaped, or tandem; (5) disc, shield, or doughnut; and (6) unilateral fused kidneys with superior ectopia (Fig. 117–13). Although

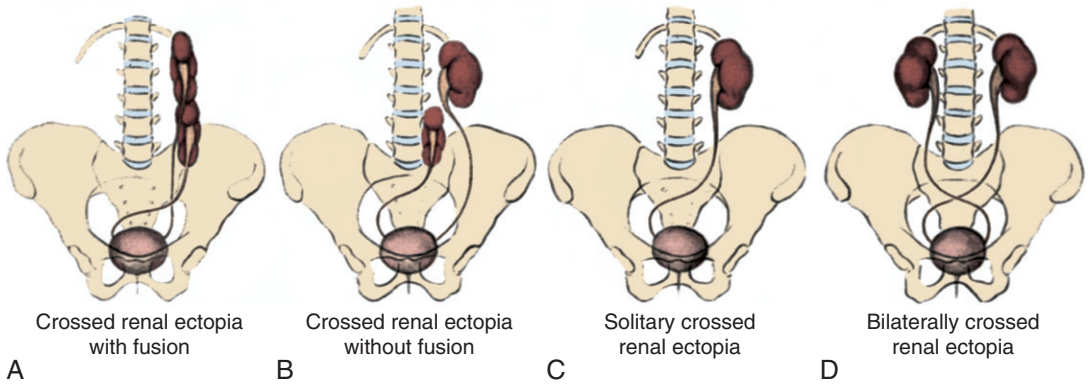


Figure 117–12. **A** to **D,** Four types of crossed renal ectopia.

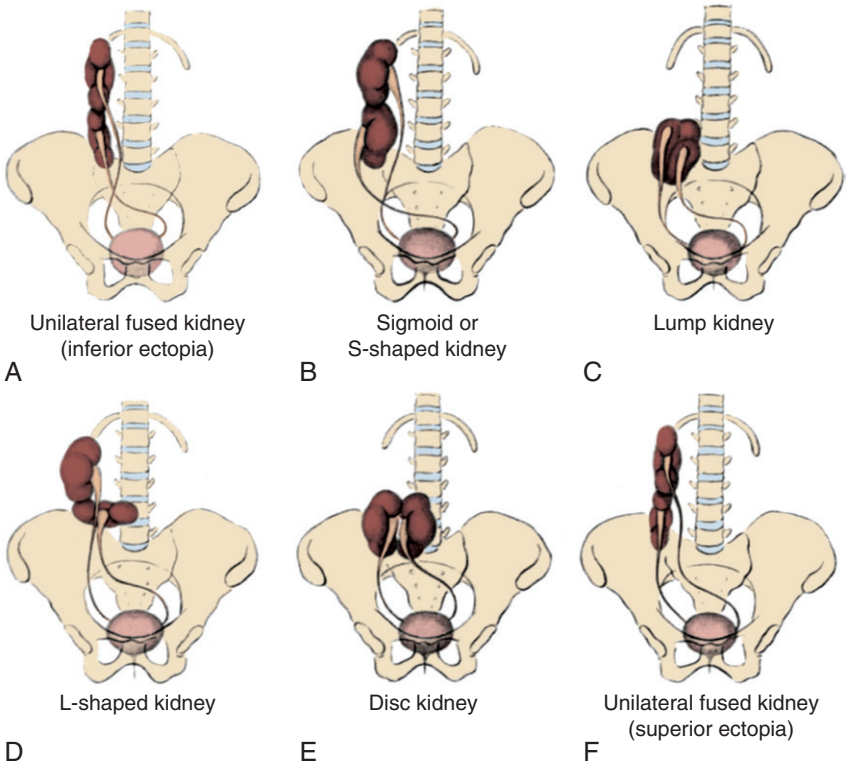


Figure 117–13. **A** to **F,** Six forms of crossed renal ectopia with fusion.

this classification has little clinical significance, it does provide insights into the embryology of renal ascent and rotation.

Incidence. The first reported case of crossed ectopia was described by Pamarolus in 1654. Abeshouse and Bhisitkul, in 1959, conducted the last significant review of the subject and reported 500 cases of crossed ectopia with and without fusion that presented primarily with clinical symptoms. Glodny and colleagues (2008) reported on 24 crossed fused ectopia found on a CT scan performed for nonurologic indications.

Sixty-two patients with crossed ectopia without fusion have been reported (Diaz, 1953; Winram and Ward-McQuaid, 1959). This represents approximately 10% of all crossed ectopic kidneys (Lee, 1949). The anomaly occurs more commonly in males with a ratio of 2:1, and left-to-right ectopia is seen three times more frequently than right-to-left ectopia (Lee, 1949).

Solitary crossed ectopia has been reported in 34 patients (Miles et al, 1985; Gu and Alton, 1991). Males predominate with a ratio of 2:1. The crossed ectopia involves migration of the left kidney to the right side with absence of the right kidney, rather than the reverse, with a ratio of almost 2:1 (Kakei et al, 1976). In most cases, the kidney fails to ascend and rotate completely. The left to right crossed kidney is rarely a multicystic dysplastic kidney. Bilateral crossed renal ectopia has been described in five patients (McDonald and McClellan, 1957; Abeshouse and Bhisitkul, 1959) and is considered the rarest form. Abeshouse and Bhisitkul (1959) compiled 443 reports of crossed ectopia with fusion and estimated its occurrence at 1 in 1000 live births. This figure varies with the type of fusion anomaly; **the unilaterally fused kidney with inferior ectopia is the most common variety, whereas fusion with superior ectopia is the least common.** The autopsy incidence has been calculated at 1 in 2000 (Baggenstoss, 1951). There is a slight male predominance (3:2), and a left-to-right crossover occurs somewhat more frequently than its counterpart.

Embryology. The UB enters the metanephric blastema adjacent to the anlage of the lumbosacral spine. During the next 4 weeks, the developing kidney comes to lie at the level of the L1-L3 vertebrae. Because the mechanisms responsible for normal complete ascent of the kidney during gestation are unknown, **the cause of crossed ectopia is also unknown.** Wilmer (1938) suggested that crossover occurs as a result of pressure from abnormally placed umbilical arteries that prevent cephalad migration of the renal unit, which then follows the path of least resistance to the opposite side.

Potter (1952) and Alexander and colleagues (1950) theorized that crossed ectopia is strictly a ureteral phenomenon, with the developing UB wandering to the opposite side and inducing differentiation of the contralateral nephrogenic anlage. Ashley and Mostofi (1960) deduced that strong but undetermined forces are responsible for renal ascent and that these forces attract one or both kidneys to their final place on the opposite side of the midline. Cook and Stephens (1977) postulated that crossover is the result of malalignment and abnormal rotation of the caudal end of the developing fetus, with the distal curled end of the vertebral column being displaced to one side or the other. As a result, either the cloaca and WD structures lie to one side of the vertebral column, allowing one ureter to cross the midline and enter the opposite nephrogenic blastema, or the kidney and ureter are transplanted to the opposite side of the midline during "normal" renal ascent (Hertz et al, 1977; Maizels and Stephens, 1979).

Kelalis and colleagues (1973) implicated teratogenic factors after they noted an increased incidence of associated genitourinary and other organ system anomalies. Finally, genetic influences may play a role, because familial inheritance of crossed renal ectopia has been reported (Greenberg and Nelsen, 1971; Hildreth and Cass, 1978; Rinat et al, 2001).

Fusion of the metanephric masses may occur when the renal anlagen are still in the true pelvis before or at the

start of cephalad migration, or it may occur during the latter stages of ascent. The extent of fusion is determined by the proximity of the developing renal anlagen to one another. After fusion, advancement of the kidneys toward their normal location is impeded by midline retroperitoneal structures, the aortic bifurcation, the inferior mesenteric artery, and the base of the small bowel mesentery (Joly, 1940).

Description. **Fusion of a crossed ectopic kidney is related to the time at which it comes in contact with its mate.** The crossed kidney usually lies caudad to its normal counterpart on that side. It is likely that migration of each kidney begins simultaneously, but ascent of the ectopic renal unit lags behind because of crossover time. **Therefore it is the superior pole of the ectopic kidney that usually joins with the inferior aspect of the normal kidney. Ascent continues until either the uncrossed kidney reaches its normal location or one of the retroperitoneal structures prevents further migration of the fused mass. The final shape of the fused kidneys depends on the time and extent of fusion and the degree of renal rotation that has occurred.** No further rotation is likely once the two kidneys have joined. Therefore the position of each renal pelvis may provide a clue as to the chronology of the congenital defect. An anteriorly placed pelvis suggests early fusion, whereas a medially positioned renal pelvis indicates that fusion probably occurred after rotation was completed.

Ninety percent of crossed ectopic kidneys are fused with their mate. When they are not fused, the uncrossed kidney usually resides in its normal dorsolumbar location with proper orientation, while the ectopic kidney is inferior and in either a diagonal or a horizontal position with an anteriorly placed renal pelvis. The two kidneys are usually separated by a variable distance, and each is surrounded by its own capsule of Gerota fascia. In every case of crossed ectopia without fusion, the ureter from the normal kidney enters the bladder on the same side, and that of the ectopic kidney crosses the midline at the pelvic brim and enters the bladder on the contralateral side (Fig. 117–14).

In cases of solitary crossed ectopia, the kidney is usually located somewhat low but in the opposite renal fossa at the level of L1-L3 and is oriented anteriorly, having incompletely rotated on its vertical axis (Alexander et al, 1950; Purpon, 1963). When the kidney remains in the pelvis or ascends only to the lower lumbar region, it may assume a horizontal lie with an anteriorly placed pelvis because it has failed to rotate fully (Trabrisky and Bhisitkul, 1965). The ureter crosses the midline above the S2 vertebra and enters the bladder on the opposite side (Gu and Alton, 1991). The contralateral ureter, if present, is often rudimentary (Caine, 1956).

Key Points: Crossed Renal Ectopia with and without Fusion

- When a kidney is located on the side opposite from that in which its ureter inserts into the bladder, the condition is known as crossed ectopia.
- Ninety percent of crossed ectopic kidneys are fused with their mate; the superior pole of the ectopic kidney usually joins with the inferior aspect of the normal kidney.
- In all the types of fusion anomalies, the ureter from each kidney is usually orthotopic.
- The highest incidence of associated anomalies occurs in children with solitary renal ectopia and involves both the skeletal system and genital organs.

The patient with bilateral crossed ectopia may have perfectly normal-appearing kidneys and renal pelves, but the ureters cross the midline at the level of the lower lumbar vertebrae (Abeshouse and Bhisitkul, 1959).

Inferior Ectopic Kidney. Two thirds of all unilaterally fused kidneys involve inferior ectopia. The upper pole of the crossed kidney is attached to the inferior aspect of the normally positioned mate. Both renal pelves are anterior, so fusion probably occurs relatively early.

Sigmoid, or S-Shaped, Kidney. The sigmoid, or S-shaped, kidney is the second most common anomaly of fusion. The crossed kidney is inferior, with the two kidneys fused at their adjacent poles. Fusion of the two kidneys occurs relatively late, after complete rotation on the vertical axis has taken place. Therefore each renal pelvis is oriented correctly, and they face in opposite directions from one another. The lower convex border of one kidney is directly opposite the outer border of its counterpart, creating an S-shaped appearance to the entire renal outline. The ureter from the normal kidney courses downward anterior to the outer border of the inferior kidney, and the ectopic kidney's ureter crosses the midline before entering the bladder.

Cake or Lump Kidney. The cake or lump kidney is a relatively rare form of fusion (Fig. 117–15). Extensive fusion has taken place over a wide margin of maturing renal anlage, resulting in one mass. The total kidney is irregular and lobulated. Usually, ascent progresses only as far as the sacral promontory, but in many instances, the kidney remains within the true pelvis. Both renal pelves are anterior, and they drain separate areas of parenchyma. The ureters do not cross. Only nine cases of pelvic cake kidney drained by a single ureter have been reported (Schwartz, 2010). Recently, a case of cake kidney drained by a single ureter associated with a unicornuate uterus, and another associated with bilateral absence of the vas deferens, have been reported (Rosenkrantz et al, 2010; Schwartz et al, 2010).

L-Shaped Kidney. The L-shaped, or tandem, kidney occurs when the crossed kidney assumes a transverse position at the time of its attachment to the inferior pole of the normal kidney. The crossed kidney lies in the midline or in the contralateral paramedian space anterior to the L4 vertebra. Rotation about the long axis of the kidney produces an inverted or a reversed pelvic position. The ureter from each kidney enters the bladder on its respective side.

Disc Kidney. Disc, shield, doughnut, or pancake kidneys are kidneys that have joined at the medial borders of each pole to produce a doughnut- or ring-shaped mass. More extensive fusion along the entire medial aspect of the kidneys creates a disc or shield shape. The lateral aspect of each kidney retains its normal contour. This type of fusion differs from the lump or cake kidney in that the reniform shape is better preserved owing to a less extensive degree of fusion. The pelves are anteriorly placed, and the ureters remain uncrossed. The collecting system drains each respective half of the kidney and does not communicate with the opposite side.

Superior Ectopic Kidney. The least common variety of renal fusion is the crossed ectopic kidney that lies superior to the normal kidney. The lower pole of the crossed kidney is fused to the upper pole of the normal kidney. The renal units retain a fetal orientation, with both pelves lying anteriorly, suggesting that fusion occurred very early.

Regardless of the type of fusion encountered, the vascular supply to the kidneys is variable and unpredictable. The crossed ectopic kidney is supplied by one or more branches from the aorta or common iliac artery (Rubinstein et al, 1976). The normal kidney frequently has an anomalous blood supply, with multiple

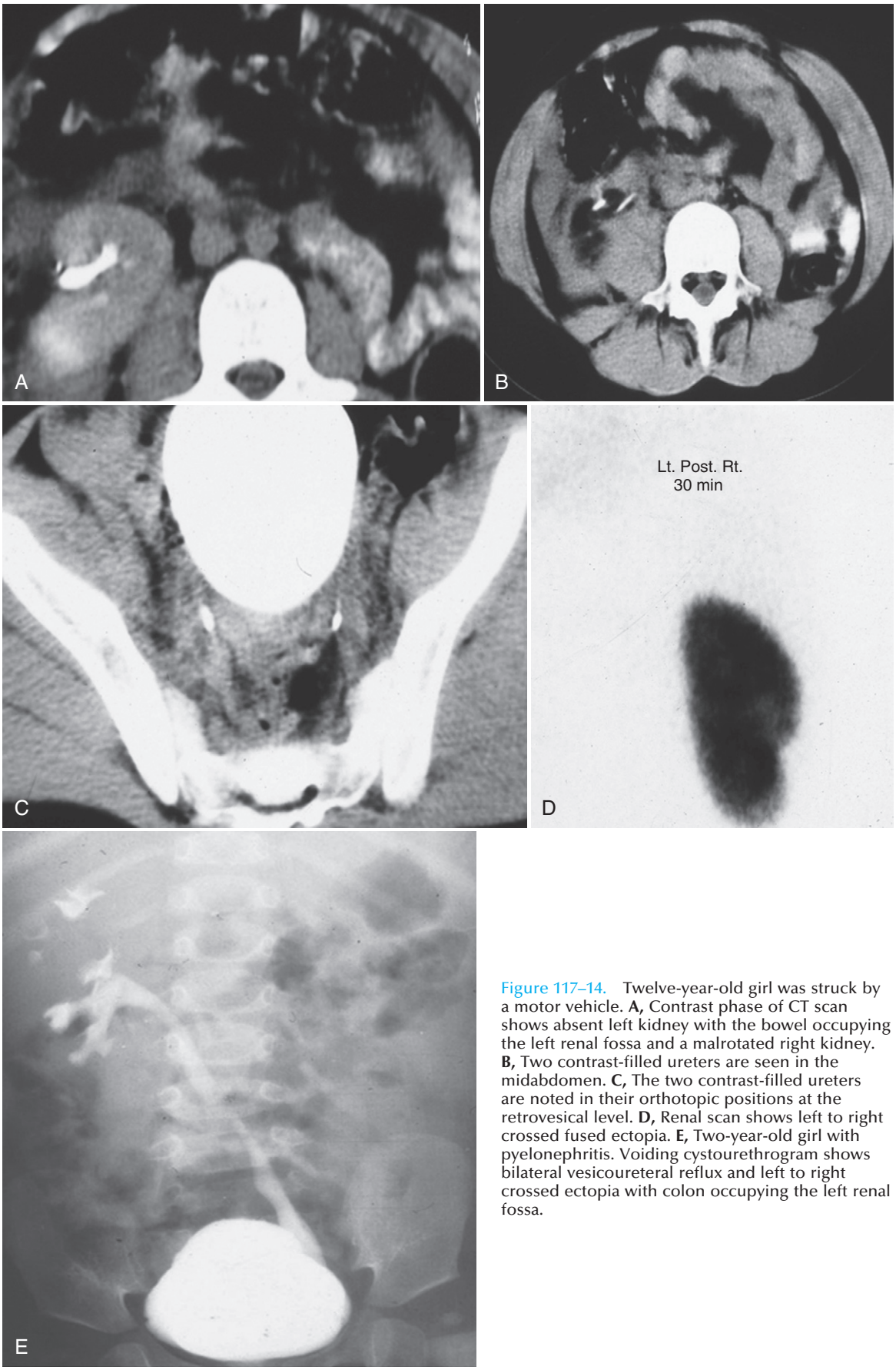


Figure 117–14. Twelve-year-old girl was struck by a motor vehicle. **A,** Contrast phase of CT scan shows absent left kidney with the bowel occupying the left renal fossa and a malrotated right kidney. **B,** Two contrast-filled ureters are seen in the midabdomen. **C,** The two contrast-filled ureters are noted in their orthotopic positions at the retrovesical level. **D,** Renal scan shows left to right crossed fused ectopia. **E,** Two-year-old girl with pyelonephritis. Voiding cystourethrogram shows bilateral vesicoureteral reflux and left to right crossed ectopia with colon occupying the left renal fossa.

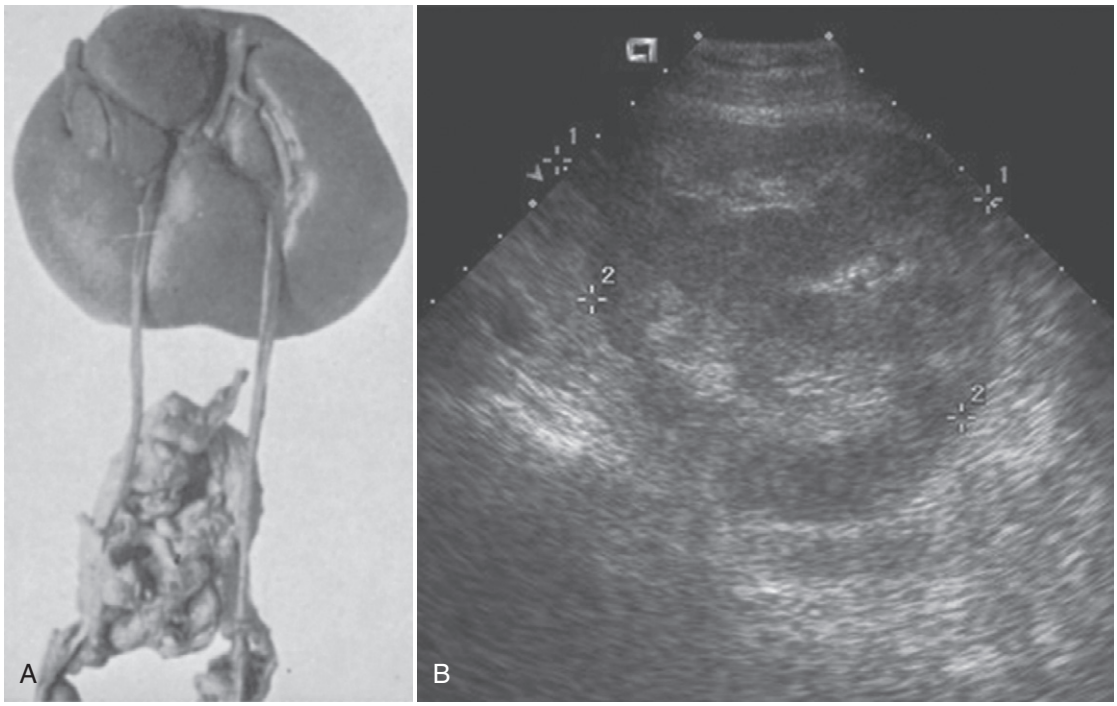


Figure 117–15. **A,** Lump or cake kidney showing the unusual anatomy, with the anterior blood supply coming from above and the ureters leaving from below. **B,** Ultrasonogram of cake kidney in sagittal view (space between calipers denotes renal length). (**A,** Courtesy of Dr. H.S. Altman; **B,** courtesy of Dr. Shpetim Telegrafi.)

renal arteries originating from various levels along the aorta. In one rare instance, Rubinstein and colleagues (1976) discovered that one renal artery crossed the midline to supply the tandem ectopic kidney. The solitary crossed ectopic kidney generally receives its blood supply from the aorta or iliac artery on the side which it is positioned (Tanenbaum et al, 1970).

Associated Anomalies. **In all the types of fusion anomalies, the ureteral orifice associated with each kidney is usually orthotopic.** Except for solitary crossed ectopia, most patients with crossed ectopia have a normal trigone (Magri, 1961; Tanenbaum et al, 1970; Yates-Bell and Packham, 1972). The incidence of an ectopic ureteral orifice from the crossed renal unit is about 3% (Abeshouse and Bhisitkul, 1959; Magri, 1961; Hendren et al, 1976). Occasionally, the ureter from the uncrossed renal segment of a fusion anomaly has an ectopic orifice (Hendren et al, 1976). Malek and Utz (1970) discovered a case of an ectopic ureterocele associated with the uncrossed kidney. Vesicoureteral reflux is noted in 20% of crossed ectopia and in 71% of bilateral crossed ectopia (Kelalis et al, 1973; Guarino et al, 2004) (see Fig. 117–14). Currarino and Weisbruch (1989) reported 10 cases of midline renal fusion in which a single ureter divided into two pelves that stretched across the midline to drain one respective half of the total parenchymatous mass. In 4 of the 10 cases, a second ureter was present that drained a separate duplex system on either the right or left side. Most of the affected individuals had an imperforate anus or abnormal vertebrae, or both.

Most orthotopic renal units are normal. If an abnormality exists, it usually involves the ectopic kidney and consists of cystic dysplasia, UPJ obstruction (29%), reflux (15%), or carcinoma (Abeshouse and Bhisitkul, 1959; Gerber et al, 1980; Caldamone and Rabinowitz, 1981; Macksood and James, 1983; Nussbaum et al, 1987; Gleason et al, 1994). Only four tumors have been reported, all of which were renal cell carcinomas (Stimac et al, 2004).

The highest incidence of associated anomalies occurs in children with solitary renal ectopia and involves both the skeletal system and genital organs (Miles et al, 1985; Gleason et al, 1994). This may be related more to renal agenesis than to the ectopic anomaly, per se. Fifty percent and 40% of solitary crossed renal ectopia have a skeletal or genital abnormality, respectively (Gu and Alton, 1991). **The most common genital abnormality in the male is cryptorchidism or absence of the vas deferens; in the female, it is vaginal atresia or a unilateral uterine abnormality** (Yates-Bell and Packham, 1972; Kakei et al, 1976). An imperforate anus has also been observed in 20% with solitary crossed ectopia.

In general, the occurrence of an associated anomaly in crossed renal ectopia, excluding solitary crossed ectopia, is low; the most frequent conditions are imperforate anus (4%), orthopedic anomalies (4%), skeletal abnormalities, and septal cardiovascular defects.

Symptoms. **Most individuals with crossed ectopic anomalies have no symptoms.** The defects are often discovered incidentally at autopsy, during routine perinatal ultrasound screening, or after bone scanning. When symptoms occur, they usually develop in the third or fourth decades of life and include vague lower abdominal pain, pyuria, hematuria, and urinary tract infection (UTI) (Gleason et al, 1994). It is believed that the abnormal kidney position and the anomalous blood supply may impede drainage from the collecting system, creating a predisposition to UTI and calculus formation (Collura et al, 2004). Romans and colleagues (1976) observed that when a stone in a crossed ureter causes colic, the pain is lateralized to the anephric side or the side of the embryonic origin of the ureter, while when there is pyelonephritis or obstruction at the UPJ in the crossed kidney, the lumbar pain is on the side of the kidneys. These observations suggest ureteral, not renal, migration as a causative factor in crossed ectopia.

An asymptomatic abdominal mass is the presenting sign in one third of cases (Abeshouse and Bhisitkul, 1959; Nussbaum et al, 1987). Hypertension occasionally leads to the finding of an ectopic fusion anomaly (Abeshouse and Bhisitkul, 1959), and in one case, hypertension was attributable to a vascular lesion in one of the anomalous vessels (Mininberg et al, 1971).

Diagnosis. **In the past, the usual method of detection was by excretory urography, but currently, ultrasonography and radionuclide scintigraphy using ^{99m}Tc-DMSA have revealed more asymptomatic cases** (Volkan et al, 2003).

Multidetector three-dimensional (3D) CT urography is excellent for delineating the renal parenchyma, collecting system, ureters, and vascular supply of the fused kidneys. The main limitation of this modality is the increased risk of significant radiation exposure, which is especially problematic for pediatric patients, pregnant women, and individuals requiring repeat examinations (Türkvatan et al, 2009). Magnetic resonance urography (MRU) and magnetic resonance arteriography (MRA) should be performed in children undergoing extensive surgery on an ectopic kidney. Cystoscopy and retrograde pyelography can be useful in mapping the collecting system and pattern of drainage.

Prognosis. **Most individuals with crossed renal ectopia have normal longevity.** However, those with an obstructive-appearing collecting system are at risk for development of UTI or renal calculi, or both (Kron and Meranze, 1949). Boatman and colleagues (1972a) noted that one third of their symptomatic patients required a pyelolithotomy for an obstructing stone. More recently, extracorporeal shock wave lithotripsy therapy and percutaneous nephrolithotomy have rendered most patients stone free (Semerci et al, 1997; Desai and Jasani, 2000). A rare case of renal cell carcinoma was recently reported in a solitary crossed ectopic kidney (Grotas and Phillips, 2009).

Horseshoe Kidney

The horseshoe kidney is the most common of all renal fusion anomalies. It should not be confused with asymmetrical or off-center fused kidneys, which may give the impression of being horseshoe shaped. The anomaly consists of two distinct renal masses lying vertically on either side of the midline and connected at their respective lower poles by a parenchymatous or fibrous isthmus that crosses the midplane of the body. It was first recognized during an autopsy by Da Carpi in 1522, but Botallo, in 1564, presented the first extensive description and illustration of a horseshoe kidney (Benjamin and Schullian, 1950).

Incidence. **Horseshoe kidney occurs in 0.25% of the population, or about 1 in 400 persons** (Dees, 1941; Nation, 1945; Bell, 1946b; Glenn, 1959; Campbell, 1970). A recent review of more than 15,000 radiologic imaging studies revealed an incidence of 1 in 666 individuals (Weizer et al, 2003). Horseshoe kidney is found more commonly in males with a ratio slightly greater than 2:1 (Basar et al, 1999; Weizer et al, 2003). The abnormality has been discovered in all age groups, ranging from fetal life to 80 years. In autopsy series, it is more prevalent in children (Segura et al, 1972). This early age prevalence is related to the high incidence of multiple congenital anomalies associated with the horseshoe kidney, some of which are incompatible with long-term survival (Scott, 2002).

Horseshoe kidneys have been reported in identical twins (Bridge, 1960) and among several siblings (David, 1974). It is doubtful that this anomaly represents a particular genetic predisposition, but it may be the result of a genetic expression with a low degree of penetrance (Leiter, 1972).

Embryology. The abnormality occurs between the fourth and sixth week of gestation, after the UB has entered the renal blastema. In view of the ultimate spatial configuration of the horseshoe kidney, the entrance of the UB had to have taken place before rotation and considerably before renal ascent (Fig. 117–16). Boyden (1931) described a 6-week-old embryo with a horseshoe kidney, the youngest fetus ever discovered with this anomaly. He postulated that at the 14-mm stage (4.5 weeks), the developing metanephric masses lie close to one another; any disturbance in this relationship might result in the masses joining at their inferior poles. A slight alteration in the position of the umbilical or common iliac artery could change the orientation of the migrating kidneys, leading to contact and fusion. It has been postulated that an abnormality in the formation of the tail of the embryo or another pelvic organ accounts for the fusion process (Cook and Stephens, 1977). Domenech-Mateu and Gonzales-Compta (1988), after studying a 16-mm human embryo, suggested that posterior nephrogenic cells migrate abnormally to form an isthmus, or connection, between the two developing kidneys to create the horseshoe shape.

Recently, Tripathi and colleagues (2010) investigated the role of axial structures, including the notochord and floor plate of the neural tube in metanephric kidney development. The notochord, which is replaced by the vertebral column in higher vertebrates, is essential for the formation of the floor plate. In addition, the sonic hedgehog *(Shh)* gene exists in these structures and is thought to affect renal development. Using a murine model, these investigators disrupted the notochord and neural plate, which resulted in kidney fusions. Then they only inactivated *Shh* in the notochord and floor plate, which also resulted in kidney fusion. **These findings suggest that the notochord is *not* necessary for nephrogenesis but *is required* for correct positioning of the metanephric kidney, while the axial SHH signal is critical for kidney positioning along the mediolateral axis. These studies provide insights into the molecular basis for horseshoe kidney formation and provide an explanation for the increased incidence of horseshoe kidneys in children with vertebral and neural tube defects (see Associated Anomalies).**

Description. There are several variations in the basic shape of the horseshoe kidney. **In 95% of cases, the kidneys join at the lower pole, which occurs before the kidneys have rotated on their long axes.** The pelves and ureters of the horseshoe kidney are usually anteriorly placed, crossing ventrally to the isthmus (see Fig. 117–16). Very rarely, the pelves are anteromedial, suggesting that fusion occurred after some rotation occurred. **In a small subset, an isthmus connects both upper poles** (Love and Wasserman, 1975). In addition, migration is usually incomplete, with the kidneys lying lower in the abdomen than normal. It is presumed that the inferior mesenteric artery prevents full ascent by obstructing the movement of the isthmus.

Generally, the isthmus is bulky and consists of parenchymatous tissue with its own blood supply (Glenn, 1959; Love and Wasserman, 1975). Occasionally, it is just a flimsy midline structure composed of fibrous tissue that tends to draw the renal masses close together. The isthmus is located adjacent to the L3 or L4 vertebra just below the origin of the inferior mesenteric artery from the aorta, resulting in the paired kidneys lying lower than normal in the retroperitoneum. The isthmus most often lies anterior to the aorta and vena cava, but it has been reported to pass between the inferior vena cava and the aorta or

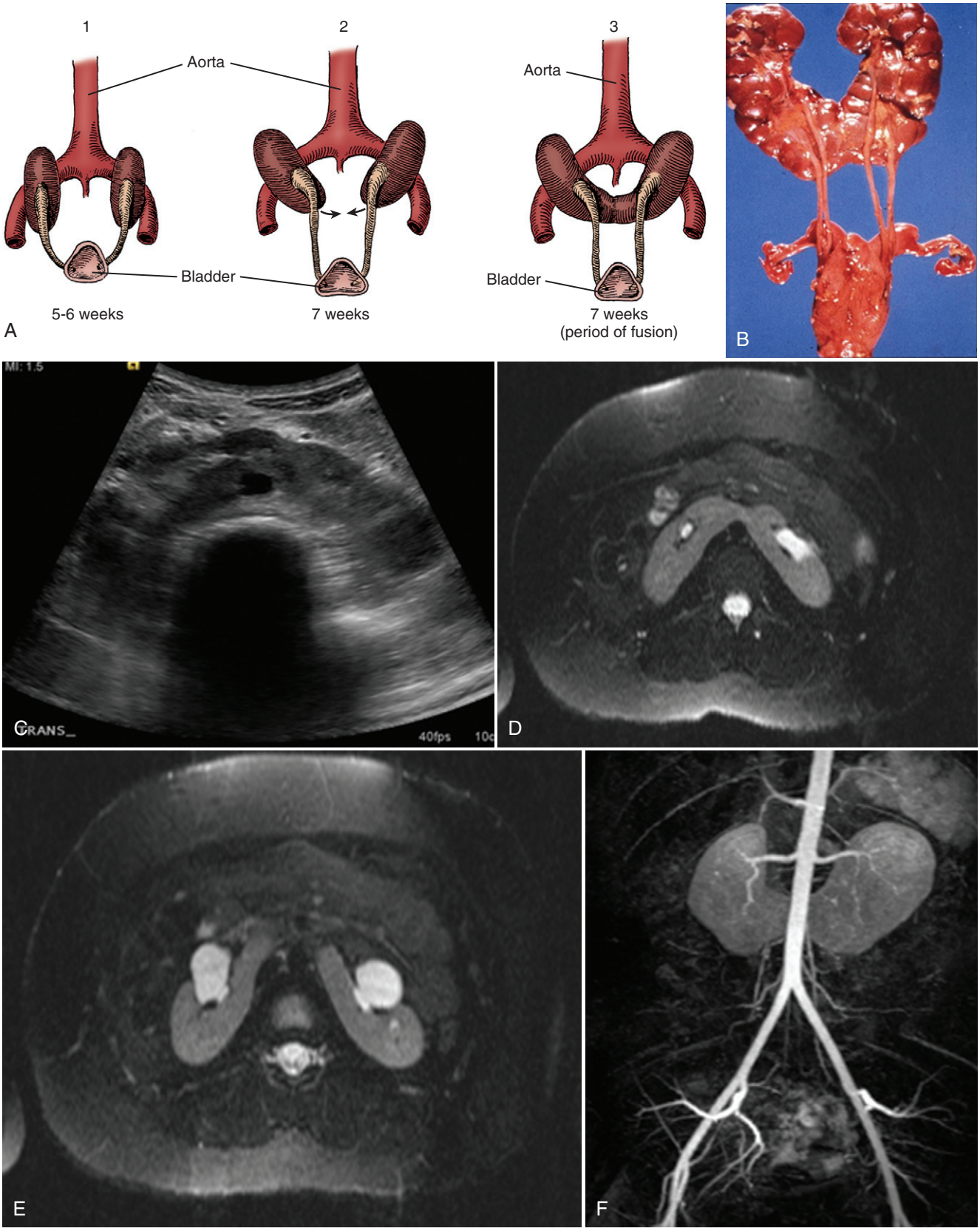
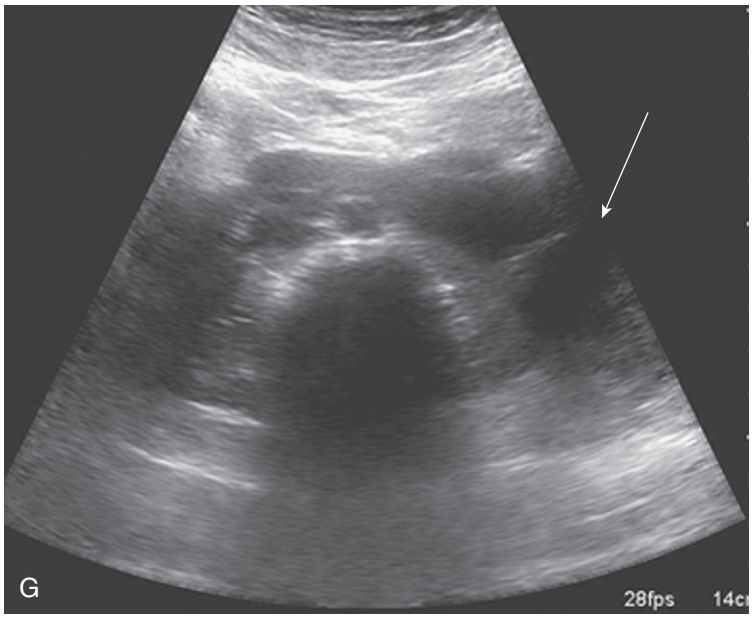


Figure 117–16. **A,** Embryogenesis of horseshoe kidney. The lower poles of the two kidneys touch and fuse as they cross the iliac arteries. Ascent is stopped when the fused kidneys reach the junction of the aorta and inferior mesenteric artery. **B,** Postmortem specimen showing horseshoe kidney with bilateral duplicated ureters. **C,** Ultrasonogram of horseshoe kidney at the level of the isthmus. **D,** MR urogram shows axial T2 fat-saturated image at the level of the isthmus. **E,** Axial T2 fat-saturated image demonstrates extrarenal pelves. **F,** Angiographic sequence shows variable blood supply to the kidney.



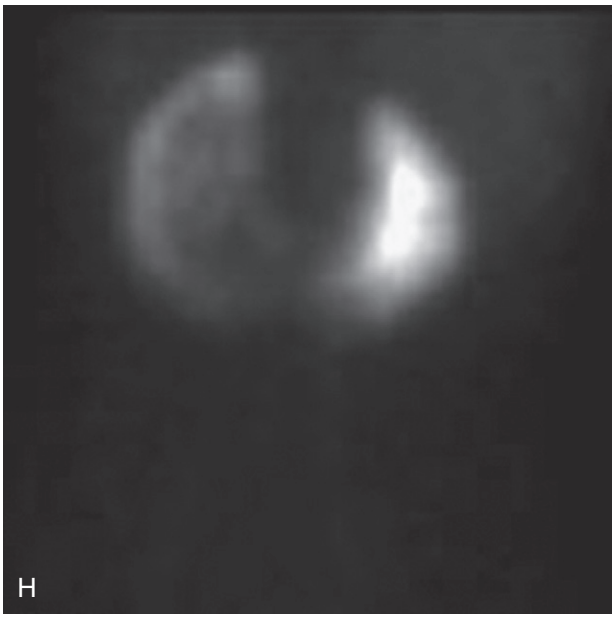




Figure 117–16, cont'd. **G,** Transverse ultrasonogram of 14-year-old girl with left flank pain found to have marked left hydronephrosis in a horseshoe kidney *(arrow)*. **H,** MAG3 scan demonstrates left ureteropelvic junction obstruction. **I,** Coronal T2 images of MR urogram show the isthmus *(arrow)* and severe left hydronephrosis. (**A,** From Benjamin JA, Schullian DM. Observation on fused kidneys with horseshoe configuration: the contribution of Leonardo Botallo [1564]. J Hist Med Allied Sci 1950;5:315, after Gutierrez, 1931; **B,** from Weiss, MA, Mills, SE. Atlas of genitourinary tract disorders. Philadelphia: JB Lippincott; 1988.)

even behind both great vessels (Jarmin, 1938; Meek and Wadsworth, 1940; Dajani, 1966). In some instances, the anomalous kidneys are very low, anterior to the sacral promontory or even in the true pelvis behind the bladder (Campbell, 1970). A similar finding of fused pelvic kidneys is observed in the *Foxd1* mouse mutant. These pelvic kidneys also show defects in UB branching and nephron formation (Levinson et al, 2005).

The calyces are normal in number and are atypical in orientation. Because the kidney fails to rotate, the calyces point posteriorly, and the axis of each pelvis remains in the vertical or obliquely lateral plane (on a line drawn from lower to upper poles). The lowermost calyces extend caudally or even medially to drain the isthmus and may overlie the vertebral column (Strauss et al, 2000).

The ureter may insert high on the renal pelvis and lie laterally, probably as the result of incomplete renal rotation. It courses downward and has a characteristic bend as it crosses over and anterior to the isthmus, a deviation that is proportionate to the thickness of the midline structure (Strauss et al, 2000). Despite upper ureteral angulation, the lower ureter usually enters the bladder normally and rarely is ectopic.

The blood supply to the horseshoe kidney can be quite variable. In 30% of cases, it consists of one renal artery to each kidney (Glenn, 1959) (see Fig. 117–16). Duplicate, or even triplicate, renal arteries may supply one or both kidneys. The blood supply to the isthmus and lower poles is also variable. The isthmus and adjacent parenchymal masses may receive a branch from each main renal artery, or they may have their own arterial supply from the aorta originating either above or below the level of the isthmus. Not infrequently, this area is supplied by branches from the inferior mesenteric, common or external iliac or sacral arteries (Boatman et al, 1971; Kolln et al, 1972). Three cases of retrocaval

ureter and isthmus have been reported (Eidelman et al, 1978; Hefferman et al, 1978). A horseshoe kidney drained by a single circumcaval ureter has also been reported (Knutson and Hawas, 2004).

Associated Anomalies. **The horseshoe kidney is frequently associated with other congenital anomalies.** Boatman and colleagues (1972b) reported that almost one third of the 96 cases studied had at least one other abnormality. Many newborns and young infants with multiple congenital anomalies have a horseshoe kidney. The autopsy incidence of other anomalies is greater in children who die at birth or in early infancy than in those who reach adulthood (Zondek and Zondek, 1964; Scott, 2002). This implies that a horseshoe kidney occurs more often in association with other serious congenital anomalies. The organ systems most commonly affected include the skeletal, cardiovascular (primarily ventriculoseptal defects [Voisin et al, 1988]), and central nervous system. Horseshoe kidney is found in 3% of children with neural tube defects (Whitaker and Hunt, 1987). Anorectal malformations are frequently encountered in these patients. Horseshoe kidney is seen in approximately 20% of patients with trisomy 18, in 60% of females with Turner syndrome (Smith, 1970; Lippe et al, 1988), and with Townes-Brock syndrome in those who have a *SALL1* transcription factor defect (Salerno et al, 2000).

Key Points: Horseshoe Kidney

- Horseshoe kidney occurs in 0.25% of the population, or about 1 in 400 persons.
- The isthmus is bulky and consists of parenchymatous tissue.
- The calyces, normal in number, are atypical in orientation. Because the kidney fails to rotate, the calyces point posteriorly, and the axis of each pelvis remains in the vertical or obliquely lateral plane.
- The blood supply can be quite variable.
- Horseshoe kidney is frequently found in association with other congenital anomalies.
- UPJ obstruction, causing significant hydronephrosis, occurs in as many as one third of individuals with horseshoe kidneys.
- Sixty percent of patients with horseshoe kidneys remained asymptomatic for an average of 10 years after discovery.

Boatman and his colleagues (1972b) **also discovered an increased occurrence of other genitourinary anomalies associated with a horseshoe kidney.** Hypospadias and undescended testes occurred in 4% of males, and a bicornuate uterus or septate vagina or both were noted in 7% of the females.

Duplication of the ureter occurs in 10% of cases (Zondek and Zondek, 1964; Boatman et al, 1972b); in some cases this has been associated with an ectopic ureterocele (see Fig. 117–16). Vesicoureteral reflux has been noted in more than half of affected individuals (Segura et al, 1972; Pitts and Muecke, 1975; Cascio et al, 2002). UPJ dilation has been seen in over 20%, but on diuretic radionuclide scintigraphy, less than 20% have an obstructive pattern (Cascio et al, 2002; Kao et al, 2003). Cystic disease, including multicystic dysplasia in one half (the upper pole) of one side (Novak et al, 1977; Boullier et al, 1992) and the lower pole of one side (Shapiro, personal communication), and adult polycystic kidney disease, have been reported with horseshoe kidney (Gutierrez, 1934; Campbell, 1970; Pitts and Muecke, 1975; Correa and Paton, 1976). DMSA scanning in 22 patients revealed asymmetrical function in 63% (Kao et al, 2003). **Stone formation has been commonly seen in horseshoe kidney.** Metabolic stone evaluation in 11 of 37 of these stone formers revealed at least one abnormality in all cases, with an average of 2.68 abnormalities per 24-hour urine collection. Hypovolemia, hypercalciuria, and hypocitraturia were the most common metabolic defects (Raj et al, 2004). Because stone formation in the horseshoe kidney is likely due to an anatomic and metabolic etiology, metabolic evaluation should be performed to reduce the risk of recurrent calculus formation.

Symptoms. With increased ultrasound screening for renal anomalies, it is likely that at least 50% with horseshoe kidneys are asymptomatic rather than the 33% incidence previously reported (Glenn, 1959; Kolln et al, 1972). In most instances, the anomaly is an incidental finding at autopsy (Pitts and Muecke, 1975). Symptoms are typically related to hydronephrosis, infection, or calculus formation. The most common symptom is vague abdominal pain that may radiate to the lower lumbar region. Gastrointestinal complaints may also be present. The Rovsing sign is used to elicit right lower quadrant pain of appendicitis when pushing on the left lower quadrant by stretching the peritoneum. It is also used to describe patients with horseshoe kidney who have abdominal pain, nausea, and vomiting on hyperextension of the spine. UTIs occur in 30% of patients, and calculi have been noted in 20% to 80% (Glenn, 1959; Kolln et al, 1972; Pitts and Muecke, 1975; Evans and Resnick, 1981; Sharma and Bapna, 1986; Benchekroun et al, 1998). Five to 10 percent of horseshoe kidneys are confirmed after palpation of an abdominal mass (Glenn, 1959; Kolln et al, 1972).

Previously, up to one third of individuals with horseshoe kidney had hydronephrosis secondary to UPJ obstruction (Whitehouse, 1975; Das and Amar, 1984) (see Fig. 117–16). The high insertion of the ureter into the renal pelvis, its abnormal course anterior to the isthmus, and the anomalous blood supply to the kidney may individually or collectively contribute to this obstruction. **In the modern era, horseshoe kidneys are frequently discovered incidentally, and their apparent hydronephrosis often shows a nonobstructed pattern on radionuclide scanning.** Horseshoe kidneys have been detected after angiography for evaluation of an abdominal aortic aneurysm (Huber et al, 1990; deBrito et al, 1991).

Horseshoe kidneys are also incidentally observed on ^{99m}Tc bone scan as a result of renal uptake and excretion of the isotope (O'Brien et al, 2008).

Diagnosis and Radiographic Appearance. The horseshoe kidney does not by itself produce symptoms (Grandone et al, 1985). The clinical features from a diseased horseshoe kidney are often vague and nonspecific. In the absence of a palpable mass, the anomaly is not suspected until an imaging study is obtained. Prenatal ultrasonography is detecting most horseshoe kidneys (Sherer and Woods, 1992; Van Every, 1992). **The classic radiologic features on a plain film of the abdomen include kidneys that are somewhat low lying and close to the vertebral column and have a vertical or outward axis with the lower poles being more medial than in the normal kidney** (O'Brien et al, 2008). The kidneys may be observed by the delineation of the perinephric fat. Ultrasonography detects the isthmus joining the two lower poles of the kidneys in the midline. This may not always be observed, because the isthmus may be only a thin fibrous band. Ultrasound diagnosis is easily made by scanning horizontally along the midline in a craniocaudal direction, especially in children and thin patients. Radionuclide

scanning demonstrates the abnormal axis of a horseshoe kidney. A continuous band across the midline is observed if the isthmus contains functioning parenchyma. CT and MRU can also be used to evaluate the horseshoe kidney. Both studies characterize the isthmus. MR angiography will accurately delineate the vascular anatomy for preoperative planning (O'Brien et al, 2008).

Prognosis. Although Smith and Orkin (1945) believed that horseshoe kidneys are almost always associated with disease, **Glenn** (1959) **observed patients with horseshoe kidneys for an average of 10 years after discovery and found that almost 60% of these remained asymptomatic.** Only 13% had persistent urinary infection or pain, and 17% developed recurrent calculi. When stone disease is present, extracorporeal shock wave lithotripsy and percutaneous nephrolithotomy yields stone-free rates of 68% and 87.5%, respectively (Kupeli et al, 1999; Raj et al, 2003). In Glenn's series, no patients benefited from division of the isthmus for relief of pain; as a result, this idea has now been largely repudiated (Glenn, 1959; Pitts and Muecke, 1975).

Many disease processes have been described with a horseshoe kidney, but this likely reflects the relative frequency of the congenital defect. **Kidney cancers have been reported in about 150 individuals with horseshoe kidney** (Buntley, 1976; Hohenfellner et al, 1992; Schubert et al, 1998, Stimac et al, 2004). **Renal cell carcinoma accounts for about half of these cases, although the incidence is no greater than that in the general population.** Two cases of bilateral tumors have been reported (Romics et al, 2002). Renal pelvic tumors and Wilms tumor each accounted for about 25% of the total, with sarcoma and carcinoids occurring much less frequently. Overall, 41 of 8617 (0.48%) Wilms tumors in the National Wilms Tumor study occurred in horseshoe kidneys, mostly on the left side, rarely in the isthmus, and practically all with favorable histology (Neville et al, 2002). **This incidence of Wilms tumor in horseshoe kidneys is 1.76 to 7.93 times higher than that expected in the general population** (Mesrobian et al, 1985). Thirty-seven percent of these Wilms tumors were initially inoperable. However, with preoperative chemotherapy, most patients were salvaged, yielding a 75% preservation rate of renal parenchyma (Neville et al, 2002). Wilms tumor may originate in the isthmus (Beck and Hlivko, 1960), creating a very bizarre radiologic picture (Walker, 1977). Except for renal pelvic tumors, a surprisingly high number of renal cancers arise in the isthmus (Blackard and Mellinger, 1968). For this reason, it has been suggested that teratogenic factors are responsible for abnormal migration of nephrogenic cells to form an isthmus, which then leads to the horseshoe shape and the predisposition for the development of cancer in this portion of the kidney (Domenech-Mateu and Gonzales-Compta, 1988; Hohenfellner et al, 1992).

It has been suggested that the increased occurrence of chronic infection, obstruction, and stone formation explains the higher-than-expected incidence of renal pelvic tumors because the incidence exceeds that of the general population (Shoup et al, 1962; Castor and Green, 1975; Dische and Johnston, 1979). Survival from these tumors is related to the pathology and stage of the tumor at diagnosis and not to the renal anomaly (Murphy and Zincke, 1982). Surveillance for tumors in symptomatic horseshoe kidneys may be prudent.

Because a horseshoe kidney is located above the pelvic inlet, it should not adversely affect pregnancy or delivery (Bell, 1946b). Glomerulocystic disease has been reported in children younger than 1 year of age but does not appear to be related specifically to the horseshoe anomaly (Craver et al, 1993). The development of renal failure associated with adult polycystic kidney disease is not any greater in the presence of a horseshoe kidney (Correa and Paton, 1976). According to the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS, McDonald et al, 2000) and the Department of Health and Human Services 2000 Annual Report (U.S. Department of Health and Human Services, U.S. Scientific Registry of Transplant Recipients and the Organ Procurement and Transplantation Network, 2000) no individual with a horseshoe kidney received a renal transplant. A worldwide review from the Netherlands noted that 23 whole and 57 split horseshoe kidneys have been transplanted with initial failure rates of only 4.3% and 13.4% for en bloc and for split transplants, respectively. An overall 80% graft survival rate has been reported at 5 years (Stroosma et al, 2001).

ANOMALIES OF ROTATION

The kidney, as it assumes its final position in the "renal" fossa, orients itself so that the calyces point laterally and the pelvis faces medially. When this alignment is not exact, the condition is known as *malrotation* and is often described in conjunction with other renal anomalies, such as ectopia with or without fusion or horseshoe kidney. This discussion centers on malrotation as an isolated renal entity.

Incidence. The true incidence of this developmental anomaly cannot be accurately calculated, because minor degrees of malrotation are not reported. Campbell (1963) found renal malrotation in 1 of 939 autopsies, and Smith and Orkin (1945) noted 1 case per 390 hospital admissions. **It is frequently observed in association with Turner syndrome** (Gray and Skandalakis, 1972b). Males are affected twice as often as females, but there does not appear to be any predilection for one side or the other.

Embryology. It is thought that medial rotation of the collecting system occurs simultaneously with renal migration. The kidney starts to turn during the sixth week, just when it is leaving the true pelvis, and it completes this process by rotating 90 degrees toward the midline by the time ascent is complete at the end of the ninth week of gestation.

In 1912, Felix postulated that rotation is actually the result of unequal branching of successive orders of the budding ureteral tree, with two branches extending ventrally and one dorsally during each generation or division. Each ureteral branch then induces differentiation of the metanephrogenic tissue, surrounding it to encase it as a cap. More parenchyma develops ventrally than dorsally, and the pelvis seems to rotate medially. Weyrauch (1939) accepted this theory of renal rotation as the result of excessive ventral versus dorsal branching of the ureteral tree and concluded that the fault of malrotation lies entirely with the ureter. A late-appearing UB may insert into an atypical portion of the renal blastema, leading to a lessened propensity for the developing nephric tissue to shift. Late appearance of the UB is almost always associated with an aberrant origin from the WD; this translates

Key Points: Anomalies of Rotation

- The kidney and renal pelvis normally rotate 90 degrees ventromedially during ascent so that the calyces point laterally and the pelvis faces medially. When this alignment is not exact, the condition is known as malrotation.
- It is frequently associated with Turner syndrome.

into ureteral ectopia at the level of the lower urinary tract. Mackie and colleagues (1975), however, did not describe any malrotation anomalies in their study of renal ectopia. The renal blood supply does not appear to be the cause or a limiting factor in malrotation but rather follows the course of renal hyporotation, hyper-rotation, or reverse rotation.

Description. **The kidney and renal pelvis normally rotate 90 degrees ventromedially during ascent.** Weyrauch (1939), in a detailed study, categorized the various abnormal phases of medial and reverse rotation according to the position of the renal pelvis (Fig. 117–17).

Ventral Position. The pelvis is ventral and in the same anteroposterior plane as the calyces, which point dorsally because they have undergone no rotation at all. This is the most common form of malrotation. Very rarely, this position may represent excessive medial rotation in which a complete 360-degree turn has occurred. In a case reported by Weyrauch (1939), the vasculature had rotated with the kidney and passed around dorsally and laterally to it before entering the anteriorly placed hilus.

Ventromedial Position. The pelvis faces ventromedially because of an incompletely rotated kidney. Excursion probably stops during the seventh week of gestation when the kidney and pelvis normally reach this position. The calyces thus point dorsolaterally.

Dorsal Position. Renal excursion of 180 degrees occurs to produce this rarest position. The pelvis is dorsal to the parenchyma, and the vessels pass behind the kidney to reach the hilum.

Lateral Position. When the kidney and pelvis rotate between 180 degrees to 360 degrees, or when reverse rotation of up to 180 degrees takes place, the pelvis faces laterally and the kidney parenchyma resides medially. The renal vascular supply provides the only clue to the actual direction of excursion. Vessels that course ventral to the kidney to enter a laterally or dorsolaterally placed hilum suggest reverse rotation, whereas a path dorsal to the kidney implies excessive ventral rotation. Both types of anomalous turning were cited in Weyrauch's series (1939).

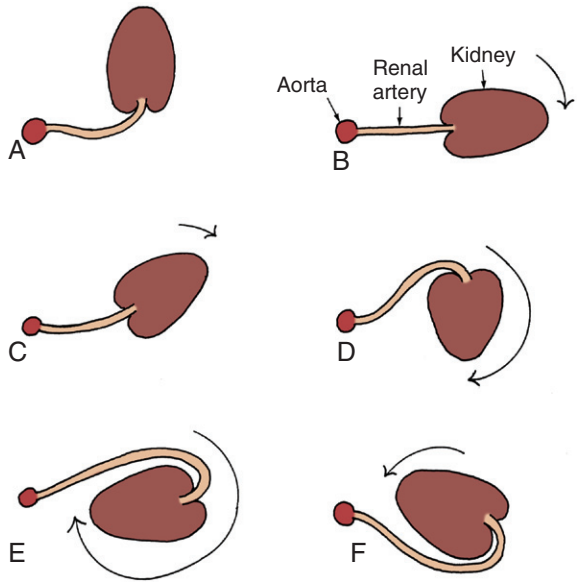


Figure 117–17. Rotation of the kidney during its ascent from the pelvis. The left kidney with its renal artery and the aorta are viewed in transverse section to show normal and abnormal rotation during its ascent to the adult site. **A,** Primitive embryonic position; hilus faces ventrad (anterior). **B,** Normal adult position; hilus faces mediad. **C,** Incomplete rotation. **D,** Hyper-rotation; hilus faces dorsad (posterior). **E,** Hyper-rotation; hilus faces laterad. **F,** Reverse rotation; hilus faces laterad. (From Gray SW, Skandalakis JE. Embryology for surgeons. Philadelphia: WB Saunders; 1972.)

In cases of isolated malrotation, other characteristic features may be present. The kidney shape may be discoid, elongated, oval, or triangular, with flattened anterior and posterior surfaces. Fetal lobulations are invariably present and accentuated beyond normal limits. A dense amount of fibrous tissue encases the hilar area, possibly even distorting and fixing the pelvis. The UPJ may be distorted as well. The upper ureter initially courses laterally, and it, too, may be encased in this fibrous matting. The pelvis is elongated and narrow, and calyces, especially the superior calyx, may be stretched. The blood supply may vary widely, depending on the direction and degree of rotation. The vasculature may consist of a single vessel with or without multiple additional branches entering the parenchyma along the course of the renal artery. Also, there may be a polar vessel in conjunction with the main renal artery. The vascular orientation around the kidney provides the only clue to the type and extent of renal rotation.

Symptoms. Rotation anomalies, per se, do not produce any specific symptoms. The excessive amount of fibrous tissue encasing the pelvis, UPJ, and upper ureter, however, may lead to varying degrees of upper tract obstruction. Vascular compression from an accessory or main renal artery or distortion of the upper ureter or UPJ may contribute to impaired drainage. Symptoms of obstruction may occur during periods of increased urine production. Hematuria associated with hydronephrosis, infection, and calculus formation may also occur secondary to poor urinary drainage.

Diagnosis. The diagnosis should be considered when a renal calculus is detected in an abnormal location, but confirmation should be obtained from a renal ultrasonogram, CT, MRU, or retrograde pyelogram. These studies reveal the abnormal orientation of the renal pelvis and calyces, a flattened and elongated pelvis, a stretched superior calyx with blunting of the remaining calyces, and a laterally displaced upper third of the ureter. Bilateral malrotation is not uncommon and may lead to the diagnosis of a horseshoe kidney. However, careful inspection for an isthmus and observation of the lower pole renal outline should distinguish the two entities.

Prognosis. No abnormality of function of the kidney has been detected secondary to malrotation. Hydronephrosis resulting from impaired urinary drainage may lead to infection and calculus formation.

ANOMALIES OF RENAL VASCULATURE

Aberrant, Accessory, or Multiple Vessels

Knowledge of the anatomy of the renal blood supply is essential for good outcomes following renal surgery. The advent of aortography in the 1940s and 1950s spearheaded a systematic understanding of vascular anomalies (Graves, 1954, 1956; Anson and Kurth, 1955; Merklin and Michele, 1958; Anson and Daseler, 1961; Geyer and Poutasse, 1962).

The kidney is divided into various segments, each supplied by a single "end" arterial branch that usually courses from one main renal artery. *Multiple renal arteries* is the correct term to describe any kidney supplied by more than one vessel. The term *anomalous vessels* or

***aberrant vessels* should be reserved for those arteries that originate from vessels other than the aorta or main renal artery. The term *accessory vessels* denotes two or more arterial branches supplying the same renal segment.**

Incidence. **Between 71%** (Merklin and Michele, 1958) **and 85%** (Geyer and Poutasse, 1962) **of kidneys have one artery that supplies the entire renal parenchyma.** A slightly higher percentage of right-sided kidneys have a single renal artery compared with left-sided organs (Geyer and Poutasse, 1962). True aberrant vessels are rare, except in cases with renal ectopia, with or without fusion, and in individuals with a horseshoe kidney (Degani et al, 2010).

Embryology. **The renal arterial tree is derived from three groups of primitive vasculature that coalesce to form the mature vascular pattern for all retroperitoneal structures.** The cranial group consists of two pairs of arteries dorsal to the suprarenal gland that shift dorsally to form the phrenic artery. The middle group is made up of three pairs of vessels that pass through the suprarenal area and retain the same lateral position, becoming the adrenal artery. Finally, the caudal group of four paired arteries cross ventral to the suprarenal area and become the main renal artery. Sometimes they are joined by the most inferior pair from the middle group (Guggemos, 1962). It is believed that during renal migration this network of vessels selectively degenerates, and the remaining adjacent arteries assume a progressively more important function. By a process of elimination, one primitive renal arterial pair eventually becomes the dominant vessel, the completed process being dependent on the final position of the kidney (Graves, 1956). Polar arteries or multiple renal arteries to the normally positioned kidney represent a failure of complete degeneration of all primitive vascular channels. The multiple vessel pattern that has been described for renal ectopia should be considered as an arrested embryonic state for that particular renal position (Gray and Skandalakis, 1972a).

Description. **On the basis of vascular supply, the renal parenchyma is divided into five segments: apical, upper, middle, lower, and posterior.** The main renal artery divides initially into an anterior and posterior branch. The anterior branch almost always supplies the upper, middle, and lower segments of the kidney. The posterior branch invariably supplies the posterior and lower segments (Sampaio and Aragao, 1990a). The vessel to the apical segment has the greatest variation in origin; it arises from (1) the anterior division (43%), (2) the junction of the anterior and posterior divisions (23%), (3) the main stem renal artery or aorta (23%), or (4) the posterior division of the main renal artery (10%) (Graves, 1954). Rarely, the upper segment is supplied from a branch totally separate from the main renal artery (Merklin and Michele, 1958). The artrial and venous tree of the kidney and its relationship to the collecting system was beautifully depicted in endocasts by Sampaio and Aragao (1990a, 1990b). These investigations showed that the least likely areas to encounter vessels when entering the collecting system, either endourologically or with open surgery, is directly end-on through a fornix or inferiorly on the posterior aspect of the pelvis. Shoja and colleauges (2008) studied the perihilar (extraparenchymal) branching patterns and morphologies of the renal artery. A "fork" pattern with a common branching point (usually duplicated) was the most commonly observed extrarenal division and branching pattern of the main renal artery. They conclude that perihilar branching of the main renal artery was highly variable, with predictable patterns in the majority of kidneys. This information is very useful for the transplant surgeon when interpreting radiodiagnostics of the renal hilum.

The lower renal segment, however, is often supplied by an accessory vessel (Fig. 117–18). This vessel is usually the most proximal branch when it arises from the main renal artery or its anterior division (Graves, 1954). However, it may originate directly from the aorta near the main renal artery, or it may be aberrant, arising from the gonadal vessel. Merklin and Michele (1958) performed an extensive study of the variant renal and suprarenal blood supply. The venous drainage of the kidney has been studied by Sampaio and Aragao (1990b), who noted a close association between the inferior branch to the main renal vein and the anterior inferior aspect of the renal pelvis in 40% of kidneys. Although an endourologic incision for UPJ obstruction is

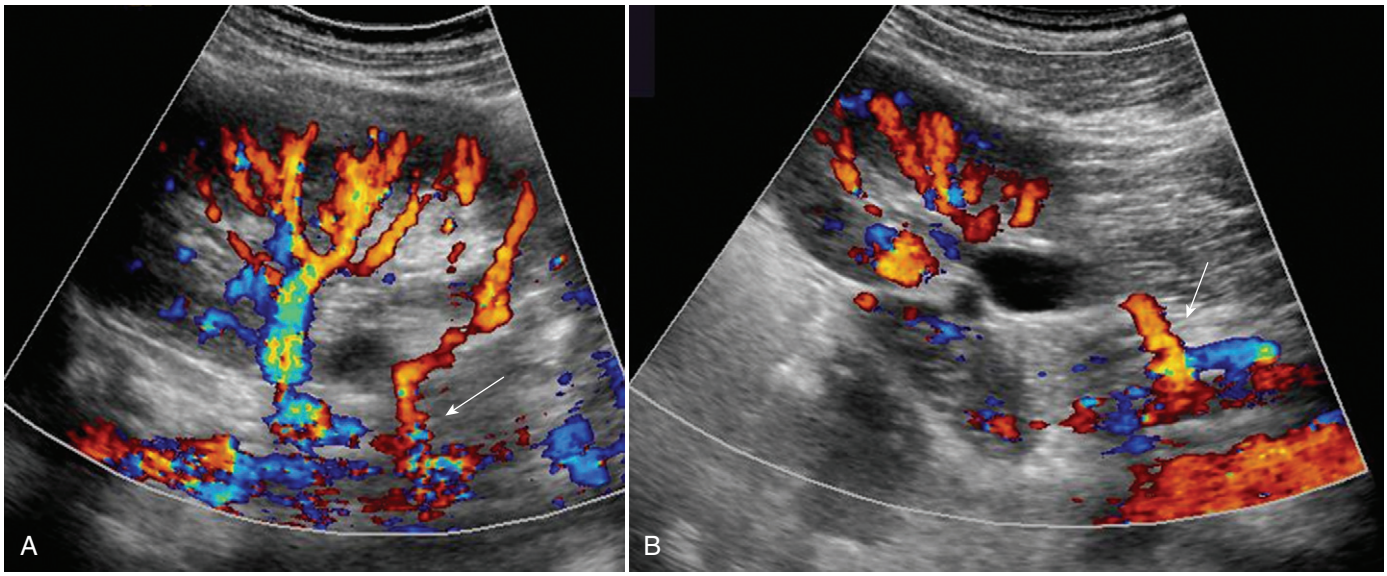


Figure 117–18. Nine-year-old girl with intermittent left flank pain, nausea, and vomiting. **A,** Color Doppler ultrasound study shows normal left renal artery and lower pole accessory vessel. **B,** Oblique sagittal view showing left lower pole accessory vessel supplying the lower pole of the kidney, causing intermittent left ureteropelvic junction obstruction.

now infrequently used, it should be performed laterally and posteriorly instead of anteriorly to avoid injury to this vessel.

Symptoms. Symptoms attributable to renal vascular anomalies are those that might result from inadequate urinary drainage. Multiple, aberrant, or accessory vessels may constrict an infundibulum, a major calyx, or the UPJ (Yen et al, 2004). Pain and hematuria secondary to hydronephrosis, UTI, or calculus may result.

Diagnosis. Historically, excretory urography would reveal multiple renal vessels or an aberrant artery (1) when a filling defect in the renal pelvis is consistent with an anomalous vascular pattern; (2) when hydronephrosis is noted along with a sharp cutoff in the superior infundibulum (Fraley, 1966, 1969); (3) when UPJ obstruction is seen in association with an angulated ureter near the renal pelvis and a kidney whose pole-to-pole axis is more vertical than normal; or (4) when differences are noted in the timing and concentration of one renal segment or in the entire kidney when compared with the opposite side (especially when hypertension is present). Renal angiography has been the gold standard for defining the vascular tree of the kidney, but less invasive imaging studies, including 3D power Doppler ultrasonography, CT, and MRI, provide precise anatomic resolution of vascular variants and associated disease states (Textor and Canzanello, 1996; Salcarga et al, 1999; Park et al, 2003; Degani et al, 2010).

Prognosis. None of these variations in the vascular tree, with the exception of a lower pole crossing vessel, increases the kidney's susceptibility to disease. Hydronephrosis secondary to a vascular anomaly is a very rare finding, especially when one considers the relative frequency of all renal vascular variations. Hypertension is no more frequent in patients with multiple renal arteries than in those with a single vessel (Geyer and Poutasse, 1962).

Renal Artery Aneurysm

Aneurysmal dilation was the first disease process of the renal artery to be recognized (Poutasse, 1957); it was considered a rare occurrence until selective renal angiography became widely available. **Since then, the overall incidence has been calculated to be between 0.1% and 0.3%.** Abeshouse (1951) classified renal artery aneurysms as follows: saccular, fusiform, dissecting, and arteriovenous. The saccular aneurysm, a localized outpouching that communicates with the arterial lumen by a narrow or wide opening, is the most common type, accounting for 93% of all aneurysms (McKeil et al, 1966; Stanley et al, 1975; Hageman et al, 1978; Zinman and Libertino, 1982). Renal artery aneurysms have been associated with autosomal-dominant polycystic kidney disease (Schievink, 1998). When the aneurysm is located at the bifurcation of the main renal artery and its anterior and posterior divisions or at one of the more distal branchings, it is considered to be congenital in origin and is called the fusiform type (Poutasse, 1957). The presence of similar aneurysms at branching points in the vasculature of other organ systems attests to this possible origin (Lorentz et al, 1984). Acquired aneurysms may be located anywhere and may result from inflammatory, traumatic, or degenerative factors. A localized defect in the internal elastic tissue and the media allows the vessel to dilate at that point. It is a true aneurysm, because its walls are composed of most of the layers that make up the normal artery (Poutasse, 1957). The outpouchings may vary in size from 1 to 2 cm up to 10 cm (Garritano, 1957), but 90% are smaller than 2 cm. There is no absolute predilection for side, but the right appears to be favored, and bilateral aneurysms are seen in 15% (Pfeiffer et al, 2003).

Almost half of renal artery aneurysms are silent, especially in children (Sarker et al, 1991). Some produce symptoms at a later age, because the size of the aneurysm increases with time. Pain (15%), hematuria (microscopic and macroscopic) (30%), and hypertension (55%) secondary to compression of adjacent parenchyma or to altered blood flow within the vascular tree can occur (Glass and Uson, 1967; Bulbul and Farrow, 1992). The hypertension is renin-mediated and secondary to relative parenchymal ischemia (Lorentz et al, 1984). Thirteen cases of hydronephrosis secondary to an adjacent renal vessel aneurysm was noted (Miyagawa et al, 2001).

The diagnosis is suspected when a pulsatile mass is palpated in the region of the renal hilum or when a bruit is heard on abdominal auscultation. A wreathlike calcification in the area of the renal artery or its branches (30%) is highly suggestive (Silvis et al, 1956), but this finding is often missed on a plain abdominal radiograph (Bulbul and Farrow, 1992). Color Doppler imaging (Bunchman et al, 1991) will demonstrate decreased flow. Selective renal angiography (Cerny et al, 1968), digital subtraction angiography, color Doppler ultrasonography (Okamato et al, 1992), or MR angiography (Takebayashi et al, 1994) confirms the diagnosis.

Many asymptomatic renal artery aneurysms come to light during a workup of hypertension. Fifty percent are diagnosed when a renal arteriogram is performed for other reasons (Zinman and Libertino, 1982). CT also readily detects the lesion (Miyagawa et al, 2001; Nishimura et al, 2002). Generally, excision is recommended if (1) the hypertension cannot be easily controlled; (2) incomplete ringlike calcification is present; (3) the aneurysm is larger than 2.5 cm (Poutasse, 1975; Pfeiffer et al, 2003); (4) the patient is female and of child-bearing age, because rupture during pregnancy is a likely possibility (Cohen and Shamash, 1987); (5) the aneurysm increases in size on serial angiograms; or (6) an arteriovenous fistula is present. More than 30 cases of a ruptured aneurysm during pregnancy have been reported (Lacroix et al, 2001), so any aneurysm larger than 1.0 cm in younger women should be repaired (Henke and Stanley, 2003). The likelihood of spontaneous rupture (about 10%), with its dire consequences, dictates attentive treatment in the foregoing situations. Recent advances in endovascular techniques dictate early prophylactic treatment (Yamamoto et al, 1998).

Key Points: Renal Artery Aneurysm

- The overall incidence has been calculated to be between 0.1% and 0.3%.
- Most renal artery aneurysms are silent, especially in children. Many asymptomatic renal artery aneurysms are diagnosed during an evaluation of hypertension.
- The diagnosis may be suspected with a pulsatile mass in the region of the renal hilum or when an abdominal bruit is heard. A wreathlike calcification in the area of the renal artery or its branches (30%) is highly suggestive.

Renal Arteriovenous Fistula

Although rare, renal arteriovenous fistulas (AVFs) have been diagnosed with increasing frequency since they were first described by

Varela in 1928. **Two types exist, congenital and acquired** (Maldonado et al, 1964), **with the latter (secondary to trauma, inflammation, renal surgery, or percutaneous needle biopsy) accounting for the recent increased incidence.** Only the congenital variant is discussed here.

Fewer than 25% of all AVFs are congenital, with only 91 reported cases (Takaha et al, 1980). **They are identifiable by their cirsoid configuration and multiple communications between the main or segmental renal arteries and venous channels** (Crummy et al, 1965; Cho and Stanley, 1978). Although congenital, they rarely present clinically before the third or fourth decade. Women are affected three times as often as men, and the right kidney is involved slightly more often than the left (Cho and Stanley, 1978; Ishikawa et al, 2004). The lesion is usually located in the upper pole (45% of cases), but not infrequently, it may be found in the midportion (30%) or in the lower pole (25%) of the kidney (Yazaki et al, 1976).

The condition is thought to be either present at birth or results from a congenital aneurysm eroding into an adjacent vein (Thomason et al, 1972). The pathophysiology involved in the shunting of blood, which bypasses the renal parenchyma and rapidly joins the venous circulation and returns to the heart, results in a varied clinical picture. The symptoms are based on the age and size of the AVF (Messing et al, 1976).

The hemodynamic derangement often produces a loud bruit in 75% of cases. Diminished perfusion of renal parenchyma distal to the fistulous site leads to relative ischemia and renin-mediated hypertension in approximately 50% (McAlhany et al, 1971). The increased venous return and high cardiac output with concomitant diminution in peripheral resistance may result in left ventricular hypertrophy and subsequent high-output cardiac failure in 50% of cases (Maldonado et al, 1964). Macroscopic and microscopic hematuria occurs in more than 75% of affected individuals due to the proximity of the collecting system (Messing et al, 1976; Cho and Stanley, 1978; Montoya et al, 2004). Although flank or abdominal pain may be present, a mass is rarely palpable (10%).

In the past, excretory urography revealed diminished or absent function either in one segment or in the entire portion of the involved kidney (DeSai and DeSautels, 1973), an irregular filling defect in the renal pelvis or calyces (secondary to either clot or encroachment by the fistula), or calyceal distortion or obstruction distal to the site of the lesion (Gunterberg, 1968). Despite these specific radiographic features, an abnormality had been noted in only 50% of excretory urograms in the past. **Three-dimensional Doppler ultrasonography and MR angiography are accurate and noninvasive tests** (Mohaupt et al, 1999; Ishikawa et al, 2004), **but selective renal arteriography or digital subtraction angiography is the most definitive method for diagnosing the lesion.** A cirsoid appearance with multiple small, tortuous channels; prompt venous filling; and an enlarged renal, and possibly gonadal, vein are pathognomonic for arteriovenous malformation (AFM) (DeSai and DeSautels, 1973).

The symptomatic nature of this lesion, which causes progressive alterations in the cardiovascular system, often dictates surgical intervention. The congenital variant rarely behaves like its acquired counterpart, which may disappear spontaneously after several months. Nephrectomy, partial nephrectomy, vascular ligation (Boijsen and Kohler, 1962), selective embolization (Bookstein and Goldstein, 1973), and balloon catheter occlusion (Bentson and Crandalls, 1972) have been used to obliterate the fistula.

ANOMALIES OF THE COLLECTING SYSTEM

Calyceal Diverticulum

A calyceal diverticulum is a cystic cavity within the kidney that is lined by transitional epithelium and communicates with a calyx or less commonly with the renal pelvis through a narrow isthmus (Estrada et al, 2009). This abnormality, first described by Rayer in 1841, may be multiple, with the upper calyx most frequently affected.

In the past, an incidence of 4.5 per 1000 excretory urograms had been reported (Timmons et al, 1975). A similar incidence was noted in both children and adults, with no predilection for either side or sex. Most diverticula, labeled type I, occur adjacent to an upper or, occasionally, a lower pole calyx. Type II diverticula are larger, communicate with the renal pelvis, and tend to be symptomatic (Wulfsohn, 1980).

Congenital and acquired factors have been suggested to explain the formation of calyceal diverticula. The similar incidence in children and adults is consistent with an embryologic etiology (Abeshouse, 1950; Mathieson, 1953; Devine et al, 1969; Middleton and Pfister, 1974). At the 5-mm stage of the embryo, ureteral branches of the third and fourth generation, which ordinarily degenerate, may persist as isolated branches, resulting in the formation of a calyceal diverticulum (Lister and Singh, 1973).

A localized cortical abscess draining into a calyx has also been postulated as an etiologic factor. Other proposed causes include obstruction from stones or infection within a calyx, progressive fibrosis of an infundibular stenosis, renal injury, achalasia, and spasm or dysfunction of one of the supposed sphincters surrounding a minor calyx (Amar, 1975; Patriquin et al, 1985; Siegel and McAlister, 1979). Vesicoureteral reflux has also been thought be an etiologic factor. Amar (1975) postulated that calyceal tubular backflow of infected urine could result in abscess formation and parenchymal injury leading to diverticular formation. **Small diverticula are usually asymptomatic and are found incidentally by ultrasonography, CT, or MRI.** These diverticula tend to progressively distend with trapped urine (Amar, 1975; Patriquin et al, 1985; Siegel and McAlister, 1979). Infection, milk of calcium (i.e., crystallization of calcium salts without actual stone formation) (Patriquin et al, 1985), or true stone formation are complications of stasis or obstruction that can produce symptoms (Lister and Singh, 1973; Siegel and McAlister, 1979) (Fig.

Key Points: Calyceal Diverticulum

- A calyceal diverticulum is a cystic cavity within the kidney that is lined by transitional epithelium and communicates with a calyx or, less commonly, with the renal pelvis through a narrow isthmus.
- The incidence based on excretory urography is about 4.5 per 1000.
- The diagnosis is best made by CT or MR urography.
- Laparocopy by a retroperitoneal approach for marsupialization of the diverticulum, fulguration of the epithelial lining, and percutaneous marsupialization/ablation are treatment options.

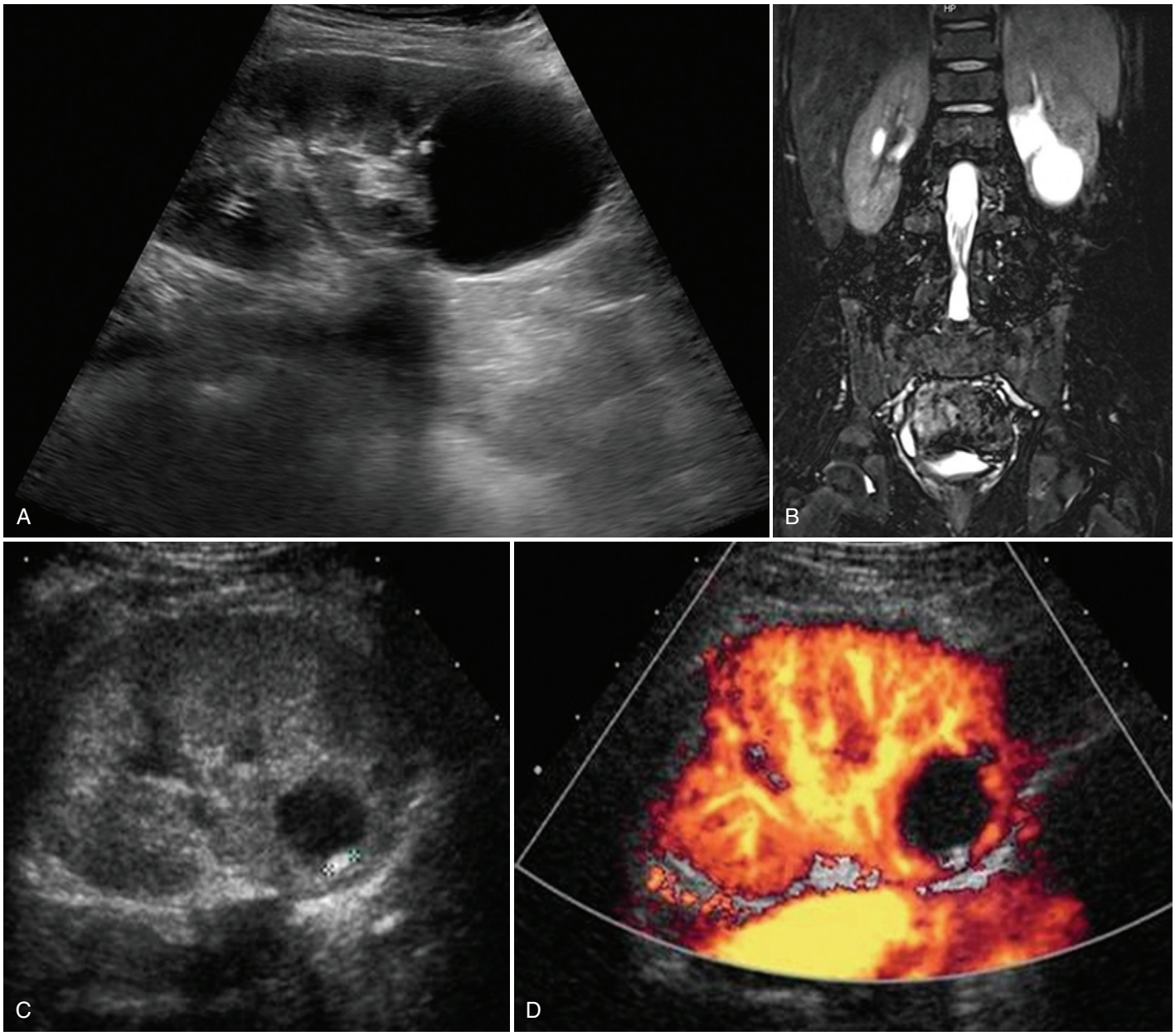


Figure 117–19. Lower pole calyceal diverticulum. **A,** Sagittal ultrasonogram. **B,** Sequence of coronal T2 images. **C,** Sagittal ultrasonogram shows small stone within a diverticulum. **D,** Color Doppler ultrasonogram demonstrates absence of flow. (**B,** Courtesy of Dr. Sara Milla; **C** and **D,** courtesy of Dr. Shpetim Telegrafi.)

117–19). **Hematuria, pain, and UTI may be seen in the presence of stones, which may be present in almost 40% of patients.** In the Mayo Clinic series (Timmons et al, 1975), 39% of patients with calyceal diverticula had calculi.

The diagnosis is suggested on ultrasonography but confirmed on CT scan and MR urography (Ellis et al, 1990; Estrada et al, 2009) (see Fig. 117–19). Delayed films demonstrate pooling of contrast material in the diverticulum. Retrograde pyelography and delayed imaging CT with contrast medium enhancement and MR urography are used to diagnose and define the precise anatomy. Ultrasonography delineates a fluid-filled area more centrally located near the collecting system than a simple renal cyst (see Fig. 117–19). When it is filled with microcalculi, ultrasonography characteristically demonstrates a layering effect, within the diverticulum, between clear fluid above and echo-dense debris without shadowing below (Patriquin et al, 1985). Ultrasonography will image the milk of calcium within the diverticulum as the patient changes position.

Patients who are asymptomatic do not require treatment but should be followed periodically with ultrasonography. Estrada and colleagues (2009) reported 10 of 23 calyceal diverticula (43%) that required treatment at a mean of 27 ± 25 months after initial treatment. Most commonly, these children presented with febrile UTI. The indications for surgery included enlargement of the diverticulum associated with pain or infection, abscess formation, urosepsis, and symptomatic calculus formation. Percutaneous ablation of the communication and fulguration of the diverticular lining was used until 1995. Although percutaneous ablation remains a viable treatment alternative, the availability of pediatric laparoscopic equipment has led to

the retroperitoneal laparoscopic approach for marsupialization of the diverticulum and fulguration of the epithelial lining (Estrada et al, 2009). Ureteroscopy with enlargement of the diverticular communication and removal of the stones has also been reported (Baldwin et al, 1998).

Hydrocalycosis

Hydrocalycosis is a very rare cystic dilation of a major calyx with a demonstrable connection to the renal pelvis (Fig. 117–20). It may be caused by a congenital or acquired intrinsic obstruction, such as a parapelvic cyst.

Dilation of the upper calyx due to obstruction of the upper infundibulum by vessels or stenosis has been described (Fraley, 1966; Johnston and Sandomirsky, 1972). Cicatrization of an infundibulum may result from infection or trauma. Conversely, hydrocalycosis has been reported to occur without an obvious cause (Williams and Mininberg, 1968). It has been postulated that achalasia of a ring of muscle at the entrance of the infundibulum into the renal pelvis causes a functional obstruction (Moore, 1950; Williams and Mininberg, 1968).

Mild upper calyceal dilation caused by partial infundibular obstruction is relatively common but usually asymptomatic. Although the most frequent presenting symptom is upper abdominal or flank pain, hydrocalycosis may be detected on prenatal ultrasonography (see Fig. 117–20). On occasion, a mass may be palpated. Stasis can lead to hematuria or urinary infection, or both.

Hydrocalycosis must be differentiated from multiple dilated calyces secondary to ureteral obstruction, calyceal clubbing as a result of recurrent pyelonephritis or medullary necrosis, renal tuberculosis, a large calyceal diverticulum, and megacalycosis. These entities can be differentiated by a combination of radiographic studies, surgical findings, histology, and cultures of the tissue.

Hydrocalycosis due to vascular obstruction is usually treated by dismembered infundibulopyelostomy. If the cystic dilation is caused by an intrinsic stenosis of the infundibulum, an intubated infundibulotomy or partial nephrectomy has been performed (Lang, 1991). Although clinical improvement is apparent in most instances, the radiologic appearance often is not altered significantly.

Megacalycosis

Megacalycosis is defined as nonobstructive enlargement of calyces resulting from malformation of the renal papillae (Fig. 117–21). It was first described by Puigvert in 1963. The calyces are generally dilated and malformed and may be increased in number (12 to 20) (Gittes, 1984; Pieretti-Vanmarcke et al, 2009). The renal pelvis is not dilated, nor is its wall thickened, and the UPJ is normally funneled without evidence of obstruction. The cortical tissue around the abnormal calyx is normal in thickness. The medulla, however, is underdeveloped and assumes a falciform (crescent) or semilunar appearance instead of its normal pyramidal shape. The collecting tubules are not dilated but are definitely shorter than normal, and they are oriented transversely rather than vertically from the corticomedullary junction (Puigvert, 1963). A mild disorder of maximal concentrating ability has been reported (Gittes and Talner, 1972), but acid excretion is normal after an acid load (Vela-Navarrete and Garcia Robledo, 1983). Other functions of the kidney-glomerular filtration, renal plasma flow, and isotope uptake also are not altered (Gittes, 1984).

Megacalycosis is congenital and has been diagnosed prenatally (Vidal Company et al, 2001). **It occurs predominantly in males with a ratio of 6:1 and has been found only in whites. Bilateral disease has been seen almost exclusively in males, whereas segmental unilateral involvement occurs only in females** (Cacciaguerra et al, 1996), suggesting an X-linked partially recessive gene with reduced penetrance in females (Gittes, 1984). Except for one report of two affected brothers, the entity has not been thought to be familial (Briner and Thiel, 1988).

It was theorized by Puigvert (1964) and endorsed by Johnston and Sandomirsky (1972) that there is transient delay in the recanalization of the upper ureter after the branches of the UB hook up with the metanephric blastema. This produces transient obstruction when the glomeruli start producing urine. The fetal calyces may dilate and retain their obstructed appearance, despite the lack of evidence of obstruction in postnatal life (Gittes and Talner, 1972). **The increased number of calyces may be an aborted response by the branching UB to the obstruction.**

The abnormality is usually diagnosed during radiographic evaluation of a UTI or other congenital anomalies (Arambasic et al, 2003). Adults frequently present with hematuria secondary to renal calculi.

The calyces are dilated and usually increased in number, but the infundibuli and pelvis may not be enlarged. Although the UPJ does not appear obstructed, there may be segmental dilation of the distal third of the ureter (Kozakewich and Lebowitz, 1974). Megacalycosis associated with an ipsilateral segmental megaureter was described in 12 children (Mandell et al, 1987), mostly boys, and predominantly left-sided. A normal-caliber ureter was interposed between the two entities. This anatomic picture may be mistaken for congenital ureteropelvic, ureterovesical junction obstruction, or infundibular stenosis (Redman and Neeb, 2005; Pieretti-Vanmanrcke et al, 2009). Diuretic renography reveals a normal pattern for uptake and washout of the isotope (Gomez Tellado et al, 1997). **Long-term follow-up of these patients does not reveal progression of the anatomic derangement or functional impairment of the kidney** (Gittes, 1984).

Key Points: Megacalycosis

- Megacalycosis is a nonobstructive enlargement of calyces resulting from malformation of the renal papillae.
- It occurs predominantly in males with a ratio of 6:1. Bilateral disease has been seen almost exclusively in males, whereas segmental unilateral involvement occurs only in females.
- Long-term follow-up of patients with this anomaly does not usually reveal progression of the anatomic or functional status of the kidney.

Unipapillary Kidney

The unipapillary kidney is a rare anomaly with only 18 cases reported (Neal and Murphy, 1960; Sakatoku and Kitayama, 1964; Harrison et al, 1976; Morimoto et al, 1979; Toppercer, 1980; Kaneto et al, 1997). This anomaly is present not uncommonly in monkeys, rabbits, dogs, marsupials, insectivores, and monotremes. The cause is thought to be a failure of progressive branching after the first three to five generations (which create the pelvis) of the UB (Potter, cited by Harrison et al, 1976). The solitary calyx drains a ridgelike papilla. Nephrons attach to fewer collecting tubules,

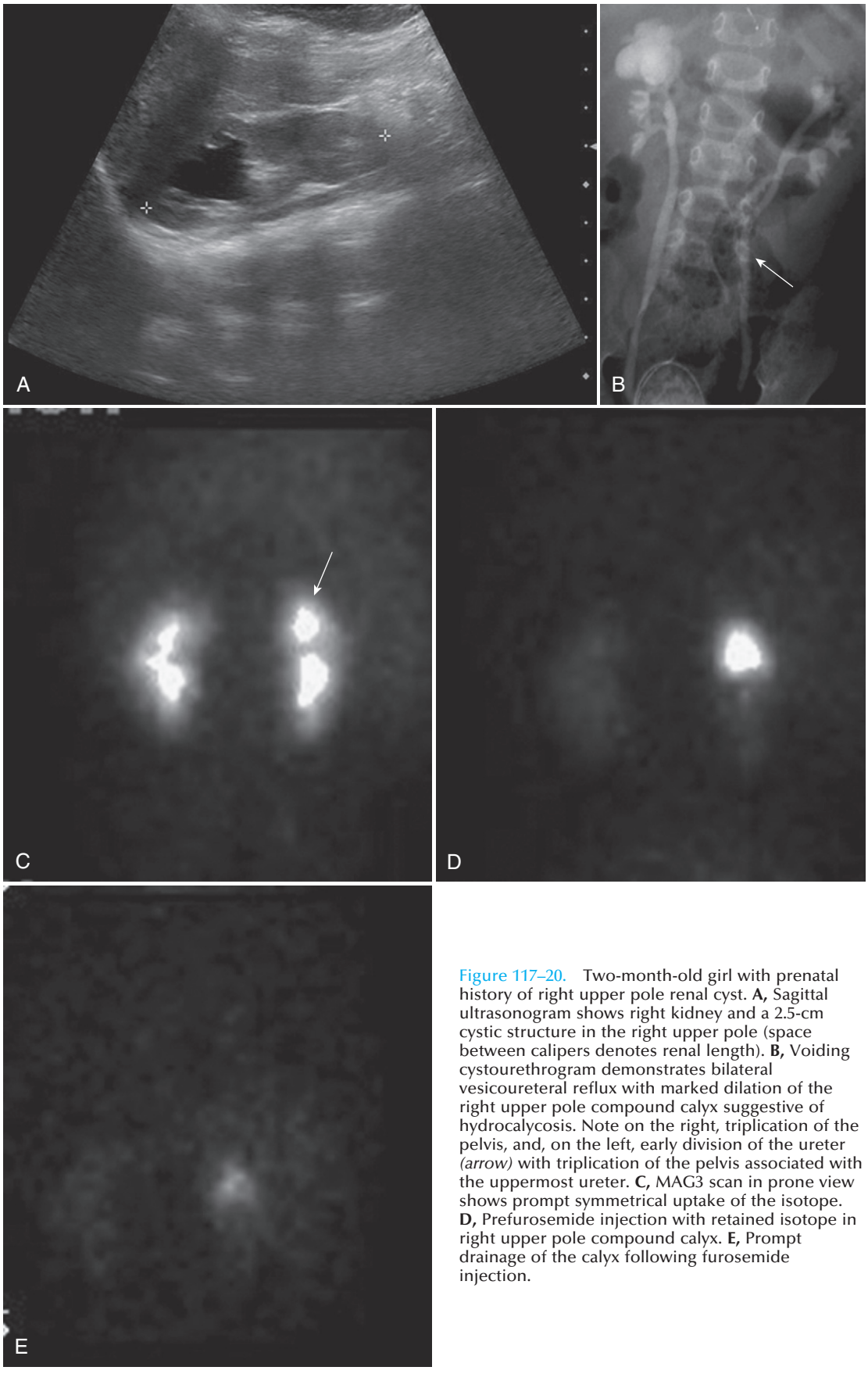


Figure 117–20. Two-month-old girl with prenatal history of right upper pole renal cyst. **A,** Sagittal ultrasonogram shows right kidney and a 2.5-cm cystic structure in the right upper pole (space between calipers denotes renal length). **B,** Voiding cystourethrogram demonstrates bilateral vesicoureteral reflux with marked dilation of the right upper pole compound calyx suggestive of hydrocalycosis. Note on the right, triplication of the pelvis, and, on the left, early division of the ureter *(arrow)* with triplication of the pelvis associated with the uppermost ureter. **C,** MAG3 scan in prone view shows prompt symmetrical uptake of the isotope. **D,** Prefurosemide injection with retained isotope in right upper pole compound calyx. **E,** Prompt drainage of the calyx following furosemide injection.

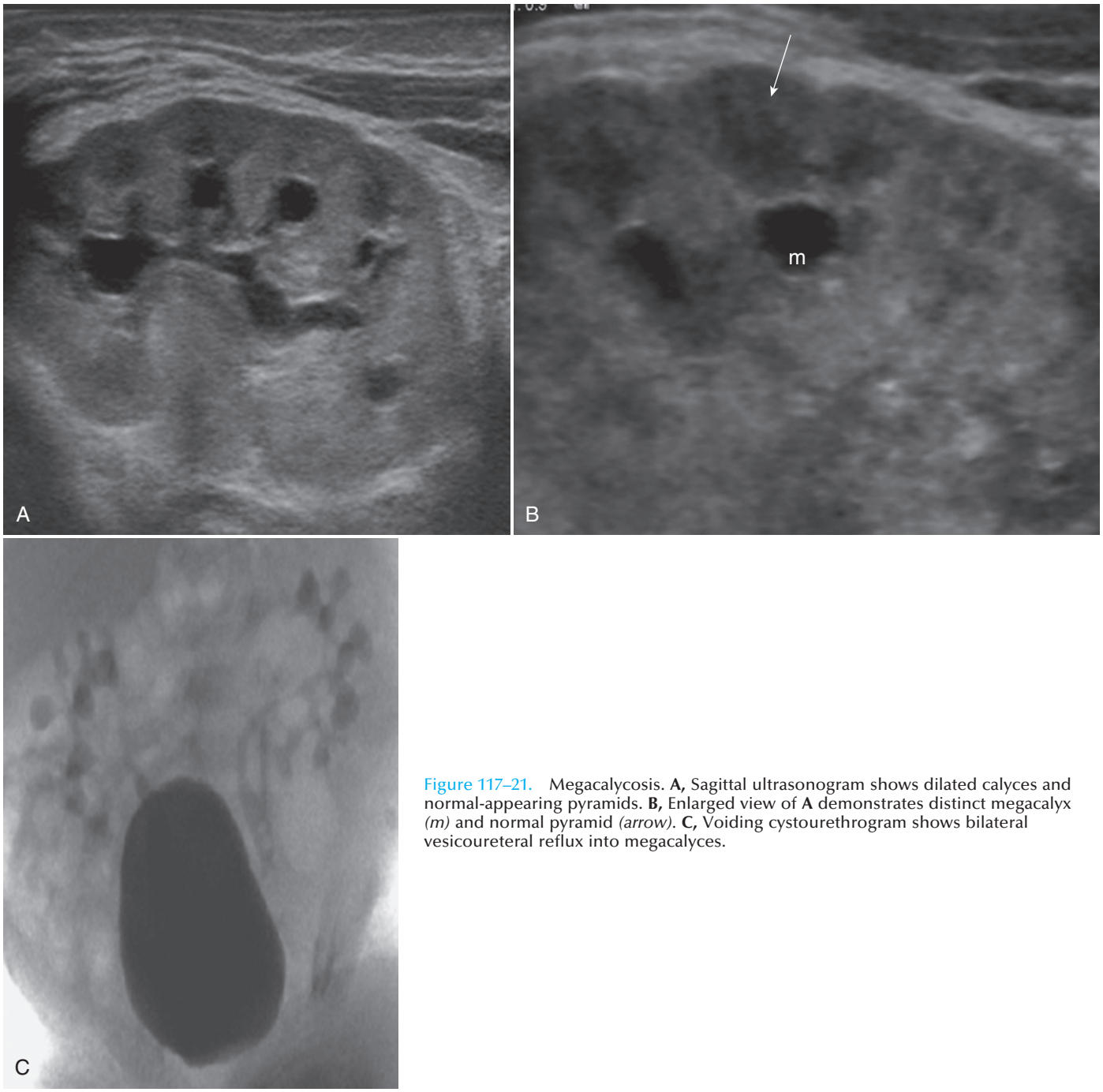


Figure 117–21. Megacalycosis. **A,** Sagittal ultrasonogram shows dilated calyces and normal-appearing pyramids. **B,** Enlarged view of **A** demonstrates distinct megacalyx *(m)* and normal pyramid *(arrow)*. **C,** Voiding cystourethrogram shows bilateral vesicoureteral reflux into megacalyces.

which then drain directly into the pelvis. Biopsies of these kidneys reveal glomerulosclerosis, tubular atrophy, and increased fibrosis (Bischel et al, 1978).

The kidney is smaller than normal, often with reduced function, but usually is in its correct location (Smith et al, 1984; Kaneto et al, 1997). The sparse arterial tree has a normal configuration. **The contralateral kidney is frequently absent.** Genital anomalies are often present. The condition is frequently asymptomatic. Often there are abnormalities of the proximal ureter (i.e., megaureter, reflux, or ectopic insertion), suggesting an underlying UB defect as the cause (Smith et al, 1984; Kaneto et al, 1997).

Extrarenal Calyces

Extrarenal calyces are an uncommon congenital anomaly in which the major calyces and the renal pelvis are outside the parenchyma of the kidney, with only about 20 cases reported in the literature (Nataraju et al, 2009). This entity was originally reviewed by Eisendrath in 1925 and then more extensively by Malament and colleagues in 1961. The kidney is usually discoid, with the pelvis and the major and minor calyces located outside the renal parenchyma. The calyces may be blunted. The renal vessels have an anomalous distribution into the kidney,

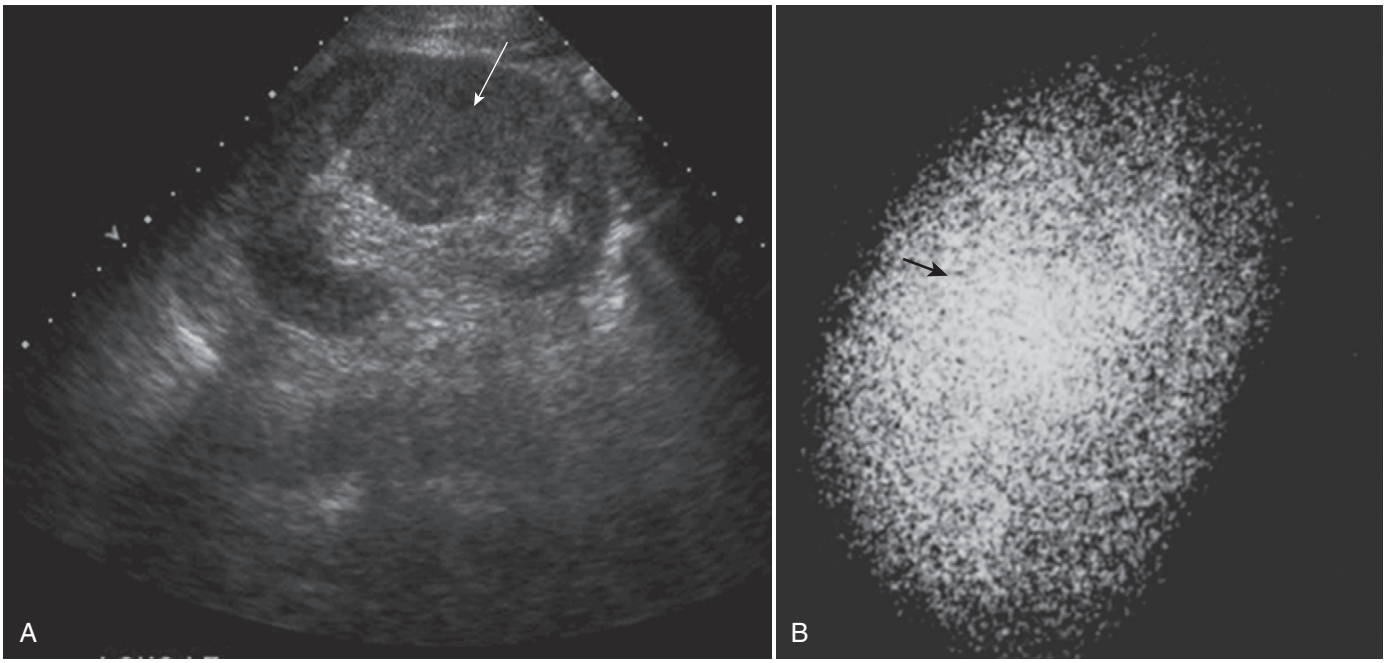


Figure 117–22. Column of Bertin. **A,** Ultrasonogram shows sagittal view of left kidney and possible midpolar mass. **B,** DMSA scan demonstrates normal uptake in the area of the mass *(arrow),* suggesting the pseudotumor, but it is actually a hypertrophied column of Bertin. (**A,** Courtesy of Dr. Shpetim Telegrafi.)

usually at the circumferential edge of the flat, widened hilus. Malament considered this condition to be the result of abnormally slow development of the nephrogenic anlage or a too early and rapidly developing UB, both resulting in abnormal coalescence of the collecting system with the nephrogenic mass. Extrarenal calyces have been associated with ectopic and horseshoe kidneys and renal dysplasia. They usually do not produce symptoms, although hydronephrosis with impairment of normal drainage may lead to stasis, infection, and calculi, requiring surgical intervention (Nataraju et al, 2009).

Anomalous Calyx (Pseudotumor of the Kidney)

A number of normal variants of the pyelocalyceal system in the kidney have been described. **One such entity manifests as a localized mass, usually situated between the infundibula of the upper and middle calyces, and is called a hypertrophied column of Bertin** (Fig. 117–22). The column may be sufficiently large to compress and deform the adjacent pelvis and calyces, suggesting a mass or "pseudotumor." The individual calyces, however, are normally shaped and developed.

It is important to differentiate this calyceal anomaly from true disease of the calyx and from a parenchymal tumor. **A renal ultrasound study shows a normal echogenic pattern of parenchyma in the area in question, and a renal scan shows normal uptake of the radioisotope in this area** (Parker et al, 1976).

Infundibulopelvic Stenosis

Infundibulopelvic stenosis most likely forms a link between cystic dysplasia of the kidney and the grossly hydronephrotic organ (Kelalis and Malek, 1981; Uhlenhuth et al, 1990). This condition includes a variety of radiographically dysmorphic kidneys with varying degrees of infundibular or infundibulopelvic stenosis that may be associated with renal dysplasia (Fig. 117–23). The first case involving the entire pelvis and all the infundibuli of both kidneys was reported by Boyce and Whitehurst in 1976. Rayer had described a focal form of the disease in 1841, and several reports noting narrowing of one or two infundibuli appeared between 1949 and 1976 (Uhlenhuth et al, 1990). These authors tried to link the focal form to cystic dysplasia secondary to obstruction, in which multicystic kidney disease is the severest form in the spectrum. Uhlenhuth and colleagues (1990) believed that this phenomenon is the result of extensive dysgenesis of the pyelocalyceal system but with preservation of renal function. Reflux is not commonly observed in these patients.

Key Points: Infundibulopelvic Stenosis

- Infundibulopelvic stenosis most likely forms a link between cystic dysplasia of the kidney and the grossly hydronephrotic kidney.
- Infundibulopelvic stenosis is usually bilateral and is commonly associated with vesicoureteral reflux, suggesting an abnormality of the entire UB.

Infundibulopelvic stenosis is usually bilateral and is commonly associated with vesicoureteral reflux, suggesting an abnormality of the entire UB (Kelalis and Malek, 1981). Patients usually present with urinary infection, hypertension, or flank pain. Sometimes, an asymptomatic child with multiple anomalies is found to have this condition. Despite extensively dysmorphic kidney features, the function is either normal or only slightly affected (Kelalis and Malek, 1981). In Husmann's study of 21 patients with the longest follow-up to date (median of 11 years), 90% had bilateral renal disease (Husmann et al, 1994). Ten patients had bilateral infundibulopelvic stenosis, 6 had a contralateral dysplastic renal unit, and 3 had contralateral URA. Renal insufficiency or end-stage renal disease developed in 8 (37%), all

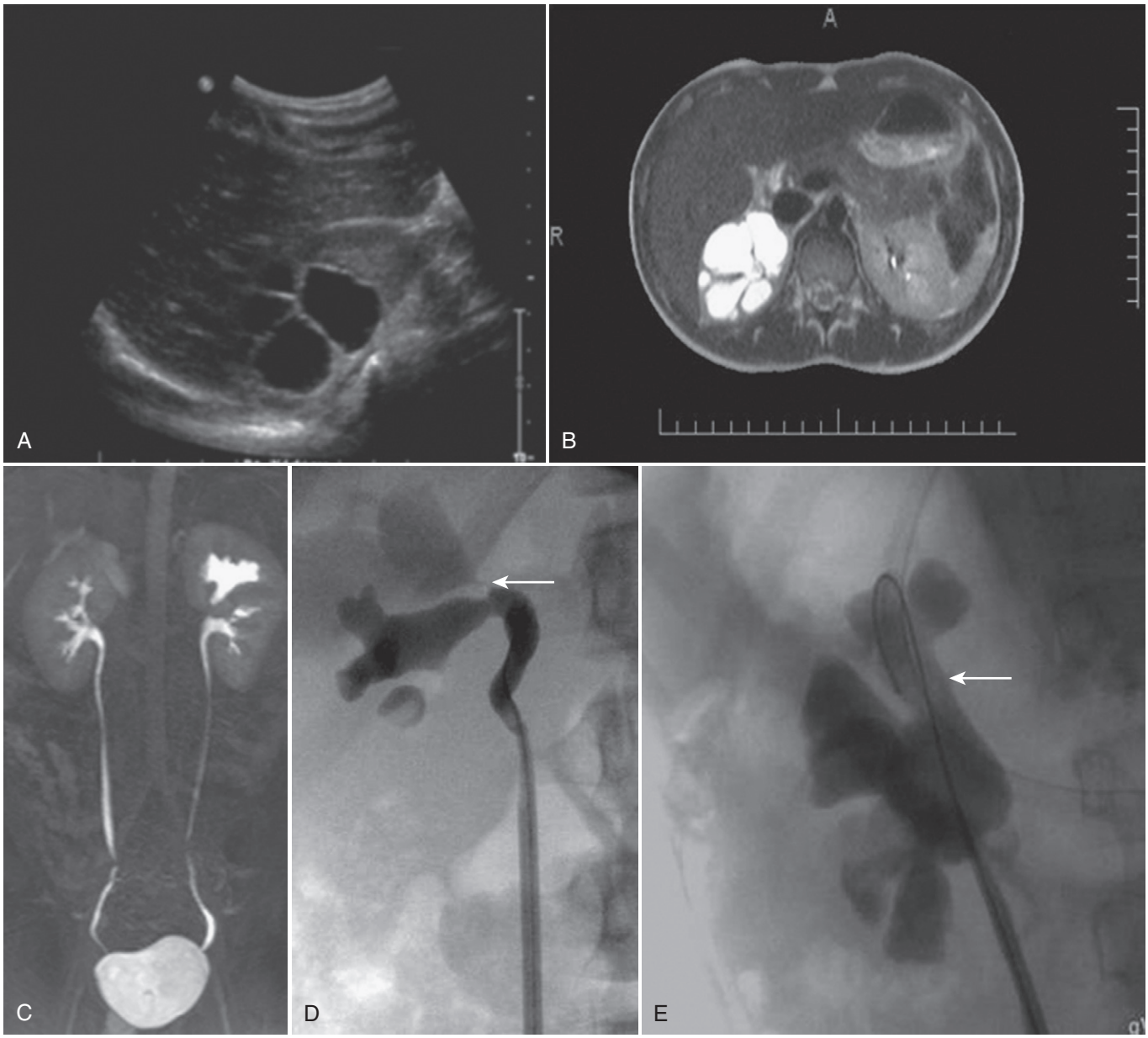


Figure 117–23. Infundibular stenosis of right upper pole calyx. **A,** Sagittal ultrasonogram. **B,** Axial T2 images. **C,** Coronal MR urogram. **D,** Right retrograde pyelogram shows no filling of the stenotic infundibulum *(arrow)*. **E,** Right retrograde pyelogram following laser incision and balloon dilation of the infundibulum *(arrow)*. (Courtesy of Dr. Pasquale Casale.)

of whom had bilateral kidney anomalies. Renal biopsies in those with end-stage renal disease demonstrated renal dysplasia proximal to the stenotic infundibuli and varying degrees of glomerulosclerosis of the glomeruli that were not involved in the regions with dysplasia. They proposed that the decreased total functional renal tissue leads to hyperfiltration injury. They suggested that routine infundibulotomy should not be performed, but endoscopic or percutaneous surgery should be considered for increasing hydronephrosis (see Fig. 117–23). More recently, Nurzia and colleagues (2002) recommend monitoring of renal function to include a baseline and yearly serum creatinine level, estimation of glomerular filtration rate, and urinalysis. Prevention of hyperfiltration injury with calcium channel blocking agents, angiotensin-converting enzyme inhibitors, and dietary restriction of protein should be considered when a decline in renal function with azotemia, proteinuria, or hypertension occurs (Paddu et al, 2009).

Pelvis

Extrarenal Pelvis

An extrarenal pelvis is of clinical importance only when drainage is impaired and may be associated with malposition and malrotation that predispose to urinary stasis, infection, and calculous disease. UPJ obstruction causing dilation of only the renal pelvis and not the calyces has been reported (Johnson, 1999).

Bifid Pelvis

Approximately 10% of normal renal pelves are bifid, the pelvis dividing first at or just within its entrance to the kidney to form two major calyces. A bifid pelvis should be considered a normal variant. When there is an incomplete duplication and a bifid pelvis, a ^{99m}Tc-mercaptoacetyltriglycine or MAG3 scan may

show the "yo-yo" effect of urine ascending one limb after descending from another, which is thought, but not proven, to infrequently cause flank pain and UTI (Chu et al, 2003). If further division of the renal pelvis occurs, triplication of the pelvis may result, but this is extremely rare (see Fig. 117–20).

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chapter 118

Renal Dysgenesis and Cystic Disease of the Kidney

John C. Pope IV, MD

Overview of Genetics
Renal Agenesis and Dysplasia
Hypoplasia and Hypodysplasia
Cystic Diseases of the Kidney
Autosomal Recessive (Infantile) Polycystic Kidney Disease
Autosomal Dominant (Adult) Polycystic Kidney Disease
Juvenile Nephronophthisis/Medullary Cystic Disease Complex
Multiple Malformation Syndromes with Renal Cysts
Multicystic Dysplastic Kidney
Benign Multilocular Cyst (Cystic Nephroma)
Simple Cysts
Medullary Sponge Kidney
Acquired Renal Cystic Disease
Calyceal Diverticulum (Pyelogenic Cyst)
Parapelvic and Renal Sinus Cysts


An expanded version of this chapter is available online at www.expertconsult.com.

Congenital and acquired renal malformations constitute a wide spectrum of clinical entities. Ectopia and fusion anomalies are covered in another chapter. This chapter is devoted to those disorders that lead to dysgenesis of the kidney, cystic lesions of the kidney, or, in some cases, a combination of both.

Many of these conditions are related to maldevelopment of the kidney and urinary tract and are thus the result of anomalous genetic mechanisms, some of which are understood, others of which are not. A basic knowledge of molecular genetics is required to better understand normal renal development, absence of renal development, and the effects of genetic mutations and abnormal signaling proteins on renal maldevelopment and cystic diseases. Within this chapter, the relevant genetic processes will be discussed as they relate to specific disease processes. Further discussion on the specific genes involved with renal development appears in Chapter 111 and in an article by Glassberg in 2002.

OVERVIEW OF GENETICS

Genetic direction of kidney and urinary tract development results when a gene from a specific chromosomal area produces a protein product that then signals certain actions to occur within an individual cell or group of cells. This cellular differentiation is then responsible for the particular action of those cells. In general, when a gene is normal, its protein product is normal as well. When a gene is abnormal, it produces an abnormal protein that can lead to maldevelopment or disease. Obviously, with complex organogenesis, the process is not always this simple. Often, **more than one gene can be responsible for a specific disease. For example, an abnormality of one of two genes is responsible for the entity tuberous sclerosis. One tuberous sclerosis gene, *TSC1,* is located on chromosome 2 and the second, *TSC2,* on chromosome 16.**

Each gene within a cell is one of a set of two; each is called an allele. One defective allele may be the carrier for the defect**. In Knudson's** (1991) **two-hit theory, the first hit is an inherited mutation that is found in all cells of an individual (i.e., a germline mutation). The second hit occurs when the wild-type, normal allele spontaneously mutates within a specific organ, although it may be a different mutation than in the primarily affected allele** (Knudson, 1991). For example, the typical somatic cells in the kidney and all other cells of a patient with von Hippel-Lindau (VHL) disease typically are heterozygous for the *VHL* gene located on chromosome 3; that is, the mutant *VHL* allele is inherited and its mate is the normal wild-type allele. However, the configuration of wild-type *VHL* makes it prone to spontaneous mutation. If the wild-type allele develops a defect within the cells of a specific organ, those cells no longer are able to produce normal pVHL (VHL protein) with its suppressor properties. That organ then has the propensity to develop a tumor. The variability in manifestations of autosomal dominant polycystic kidney disease (ADPKD) may be related to a two-hit phenomenon as well. For example, ADPKD is a

heterozygous condition in which one allele of the *PKD1* or *PKD2* set is responsible for the genetic transmission of the disease but may not be enough for cystogenesis. A spontaneous mutation of the wild-type allele may be responsible for cystogenesis or for other manifestations of the disease. Qian and colleagues (1996) suggested that the *PKD1* gene has an unusual genomic structure that makes it readily mutable for a second hit, and the timing of this second hit may account for the phenotypic variability within one family. The second hit itself may occur only in a few cells, possibly accounting for the fact that less than 1% of nephrons in ADPKD eventually develop cysts (Qian et al, 1996). Within a cyst, many but not all of the lining cells have lost their heterozygosity (Brazier and Henske, 1997; Qian et al, 1999).

RENAL AGENESIS AND DYSPLASIA

There are many terms that can be used to describe anomalous development of the kidney. These terms are often used interchangeably and can result in great confusion. The definitions as adopted in 1987 by the American Academy of Pediatrics (AAP) Section on Urology (Glassberg et al, 1987) will be employed in this chapter.

Renal Agenesis

Renal agenesis, or absent kidney development, can result from anomalous development of the wolffian duct, ureteric bud, and/or metanephric blastema. Bilateral agenesis occurs in 1 of every 4000 births and has a male predominance (Potter, 1965). Fetal demise occurs secondary to the lack of fetal urine production and subsequent oligohydramnios. Affected infants are born with immature lungs and pneumothorax, Potter facies (hypertelorism, prominent inner canthal folds, and recessive chin), and orthopedic defects secondary to intrauterine compression. Most cases of bilateral agenesis are sporadic, and many are associated with other congenital anomalies, including urogenital sinus defects.

Unilateral agenesis is more common, with an incidence of 1 in 450 to 1000 births (Kass and Bloom, 1992). Again, a wolffian duct abnormality is often the cause, and associated other wolffian and müllerian abnormalities may also be present, such as malformation of the ipsilateral uterine horn, fallopian tube or ovary in the female, or absence of the ipsilateral testis, vas deferens, or seminiferous tubules in the male. Mayer-Rokitansky-Küster-Hauser syndrome refers to a group of associated findings that include unilateral renal agenesis or renal ectopia, ipsilateral müllerian defects, and vaginal agenesis. Of men with unilateral or bilateral congenital absence of the vas deferens, 26% or 11%, respectively, had renal agenesis. Congenital bilateral agenesis of the vas deferens is also an expected finding in male patients with cystic fibrosis.

Unilateral renal agenesis can also be associated with other urologic abnormalities in 48% of patients, including primary vesicoureteral reflux (28%), obstructive megaureter (11%), and ureteropelvic junction obstruction (3%) (Cascio et al, 1999)**. These findings are similar to those associated with unilateral multicystic kidney disease, suggesting the possibility that some absent kidneys represent involuted multicystic dysplastic kidneys.**

Additional reading on renal agenesis may be found in Chapter 117.

Key Points: Renal Agenesis

- Bilateral renal agenesis is associated with oligohydramnios and Potter facies (hypertelorism, prominent inner canthal folds, and recessive chin).
- Unilateral agenesis is often associated with other genitourinary anomalies, and these patients should be appropriately screened.

Dysplasia

Definition

Renal dysgenesis is defined as maldevelopment of the kidney that affects its size, shape, or structure. It is composed of two primary subtypes, the first of which is dysplasia. The term dysplasia, while literally and most simply is defined as "abnormal tissue," specifically, as it relates to the kidney, it can only truly be defined on the basis of histopathology. **Dysplasia is a histologic diagnosis made by the presence of embryonic, immature mesenchyme, and primitive renal components** (Fig. 118–1). Ericsson and Ivemark (1958) considered these primitive ducts to be the sine qua non finding of all dysplasia. Cysts may or may not be present. The etiology for the development of dysplasia appears to be twofold: (1) a primary, inherent abnormality in the differentiation of the nephron and collecting duct, often with an underlying genetic cause, and (2) a secondary cause resulting from congenital urinary tract obstruction.

Key Points: Dysplasia

- The hallmark of dysplasia is the "primitive duct," a duct encircled by a collar of fibromuscular cells.
- Dysplasia in its truest form is a histopathologic definition, not a clinical one.
- Dysplasia often is associated with ureteric bud anomalies and/or urinary tract obstruction.

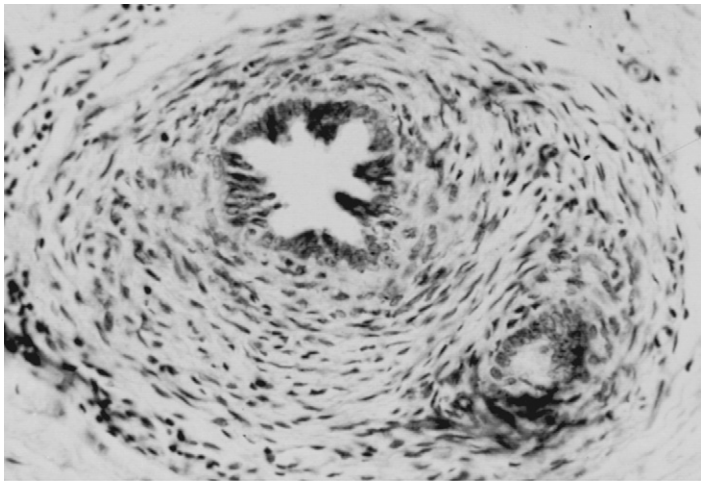


Figure 118–1. Primitive duct lined with columnar epithelial cells. Note concentric arrangement of spindle mesenchymal cells around the duct. Special staining is required to demonstrate smooth muscle cells.

Etiology

Renal dysplasia is the primary cause of childhood end-stage renal disease and two main theories have been considered in its pathogenesis: (1) a primary failure of ureteric bud activity and (2) a disruption in renal development produced by fetal urinary outflow impairment (obstruction).

Currently, there is no direct experimental evidence to prove that an abnormal ureteric bud site leads to ureteric bud penetration at a peripheral area of the blastema. However, there is much data to support the idea that defects in genetic and apoptotic pathways can affect ureteric bud formation, branching morphogenesis within the metanephric blastema, and normal nephrogenesis (e.g., RET, RAR, BMP4, SLIT2-ROBO2, COX-2, AT2) (Mendelsohn et al, 1994; Norwood et al, 2000; Pope et al, 2001; Grieshammer et al, 2004; Thomas et al, 2005). The genetic defect at each point may be the same, but the downstream pathway associated with the defect may vary for each process.

Animal studies of fetal urinary tract obstruction generate some but not all of the anatomic and histopathologic features of human renal dysplasia. Findings in these animal studies include dilatation at various segments of the nephron and collecting duct, inhibition of nephron development in the nephrogenic zone, architectural disorganization, and the appearance of primitive glomeruli as well as S-shaped bodies and cysts. At times, obstruction in these animal models can even lead to dedifferentiation of certain cells. An example is the conversion of renal epithelial cells back into mesenchymal cells and even of mesenchymal cells into myofibroblasts (Peters et al, 1992; Nguyen et al, 1999; Matsell and Tarantal, 2002). Dysplasia arising from obstruction typically appears at the periphery of the kidney, at the nephrogenic zone, and frequently with subcapsular cysts. This type usually develops later in gestation, such as in the case of posterior urethral valves (PUVs) (Fig. 118–2).

Ultrasonographically, dysplastic kidneys have a distinct appearance. The kidney is typically small and is hyperechogenic when compared with the liver. There is loss of the typical corticomedullary differentiation, and there is minimal distinction of the renal parenchyma and the perirenal fat (Fig. 118–3A). Cysts can be seen in conjunction with parenchymal dysplasia (Fig. 118–3B). These cysts can also develop from either abnormal development of the metanephric blastema or from distal obstruction. Again, the exact etiology of the cyst formation can be unclear. The important point is that not all cysts are a result of dysplasia and not all dysplasia is associated with cysts.

HYPOPLASIA AND HYPODYSPLASIA

Renal Hypoplasia

Another form of renal dysgenesis is hypoplasia, which is defined as the underdevelopment of a tissue or organ, and is usually due to a deficiency in the number of cells. Renal hypoplasia is a condition in which there is a reduction in the size of the functioning renal mass. Use of the term *hypoplasia* should be restricted to kidneys that have less than the normal number of calyces and nephrons but are not dysplastic or embryonic. These are kidneys that are morphologically normal but have either a reduced number of nephrons or smaller nephrons, although a hypoplastic kidney may have a normal nephron density despite its small size.

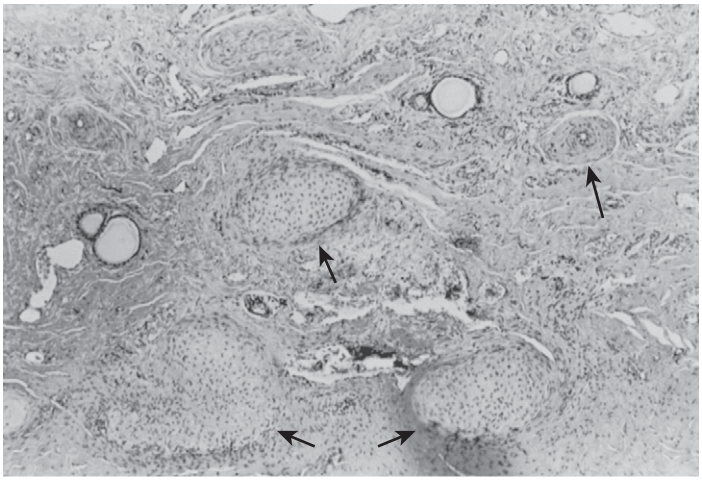


Figure 118–2. Histologic specimen of a nonfunctioning reflux kidney in a patient with posterior urethral valves. Note presence of nests of cartilage *(short arrows)*. Primitive ducts are scattered throughout the specimen *(long arrow)* (100×). The findings are compatible with dysplasia.

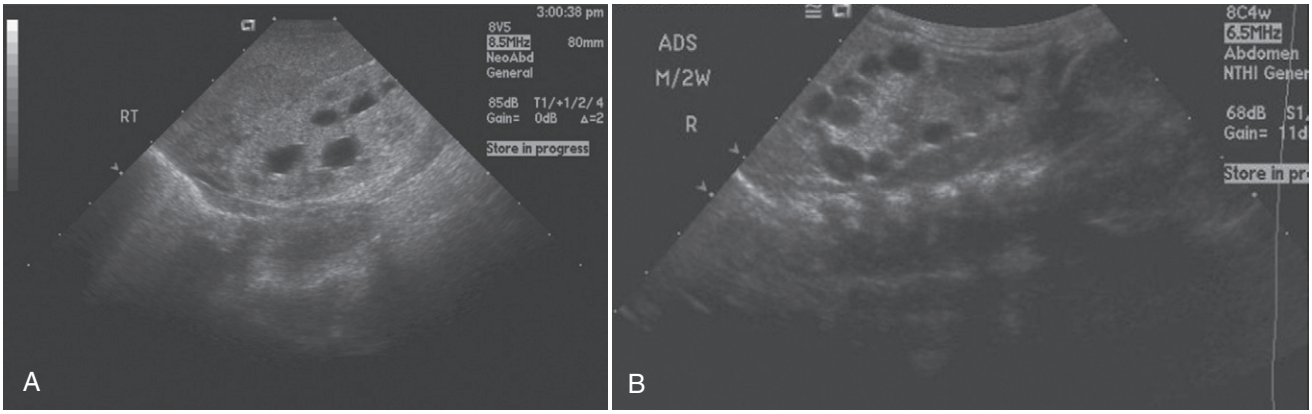


Figure 118–3. Ultrasonographic appearance of renal dysplasia. **A,** Classic dysplasia with hyperechogenic appearance of the kidney relative to the liver, a loss of normal corticomedullary differentiation, and dysmorphic calyces. **B,** Renal dysplasia accompanied by cysts. (Courtesy of Marta Hernanz-Schulman, MD.)

Hypoplasia may be bilateral or unilateral. In unilateral cases, the other kidney usually shows greater compensatory growth than is characteristic in patients with renal atrophy caused by acquired disease. A common cause of renal hypoplasia is vesicoureteral reflux, although the term *reflux nephropathy* is now used to describe the renal changes associated with reflux.

Hypodysplastic kidneys most often occur in conjunction with ectopic ureteric orifices, with the extent of dysplasia correlating with the degree of ectopia (Schwarz et al, 1981). However, hypodysplastic kidneys are seen in a few patients with normal ureteric orifices. In such cases, obstruction may or may not be present.

All forms of hypoplasia can be assessed by ultrasonography with measurement of the kidneys. The size will be reduced in all forms. Dilated calyces may also be seen. The collecting systems will be demonstrated by excretory urography if renal function is not sufficiently impaired to prevent this. Renal function is assessed biochemically and, if there is unilateral hypoplasia, by radionuclide studies.

Oligomeganephronia

First described in 1962 (Habib et al, 1962; Royer et al, 1962), oligomeganephronia is a type of renal hypoplasia that results from a quantitative defect of the renal parenchyma with a reduced number of nephrons and hypertrophy of each nephron. It may occur as a sporadic defect or in association with a number of syndromes. It is usually a bilateral condition, although a few instances of unilateral oligomeganephronia associated with contralateral renal agenesis have been reported (Griffel et al, 1972; Lam et al, 1982; Forster and Hawkins, 1994). Oligomeganephronia results from arrested development of the metanephric blastema at 14 to 20 weeks' gestation, with subsequent hypertrophy of glomeruli and tubules in the kidney. This hypertrophy and hyperfiltration results in further nephron injury and sclerosis. Eventually, this progressive loss of nephrons leads to end-stage renal disease (ESRD). Although oligomeganephronia is associated with some genetic syndromes, most cases are sporadic. Vascular abnormalities and accidents have been associated with this type of renal hypoplasia. The cause of most oligomeganephronia cases is unknown.

Oligomeganephronia is a noninheritable congenital disorder, and boys appear to be affected more often than girls. It frequently is associated with low birth weight (2500 g). The condition is usually discovered within the first 2 years of life. In neonates, kidney disease is often suspected with spontaneous pneumothorax, feeding problems, or laboratory abnormalities. Oligomeganephronia typically presents with anorexia, vomiting, dehydration, intense thirst, polyuria, and failure to thrive. It may also be incidentally diagnosed when renal anomalies are discovered in the evaluation of another illness. Oligomeganephronia is a progressive disorder and many patients go on to renal failure in the second decade.

Meticulous histologic examination of the kidney is the only way to establish an absolute diagnosis of oligomeganephronia (Fig. 118–4). Proteinuria is often the first laboratory manifestation of oligomeganephronia and precedes decline in renal function by several years. Other laboratory manifestations of renal failure are frequently present, including elevated BUN and creatinine levels, hyponatremia, and metabolic acidosis. Treatment is generally supportive and directed at maintaining normal biochemical balance, hemoglobin, and growth. High fluid intake and correction of salt loss and acidosis are the initial steps. Daily dietary protein should be limited to 1.5g/kg during the stable phase (Royer et al, 1962). In addition, angiotensin-converting enzyme inhibitors may be of benefit in slowing progression of renal failure, even if the patient has a normal blood pressure. End-stage renal disease is managed by dialysis and transplantation. The allograft may come from a living related donor because the disease is not familial.

Ask-Upmark Kidney (Segmental Hypoplasia)

In 1929, Erik Ask-Upmark, a Swedish physician, described distinctive small kidneys in eight patients, seven of whom had malignant hypertension; six of these patients were adolescents. Subsequently, this problem was described histologically as focal renal hypoplasia resulting in a segmental renal scar. Segmental renal hypoplasia, or Ask-Upmark kidney, is an extremely rare anomaly, and the patients (usually young women and girls) most frequently present with hypertension. The lesions found in these kidneys are most likely acquired, possibly representing chronic atrophic pyelonephritis due to vesicoureteral reflux, although some appear to be congenital. Segmental vascular (arterial) anomalies have also been cited as a possible cause for these lesions.

Most patients are 10 years of age or older at diagnosis. The disease is associated with severe hypertension, sometimes with headaches, either alone or together with hypertensive encephalopathy (Rosenfeld et al, 1973) and with retinopathy in half of the patients (Royer et al, 1971). Proteinuria and some degree of renal insufficiency may be present if the disease is bilateral. Approximately half of the patients in the series described by Royer and colleagues (1971) had these signs at diagnosis. The disorder is usually unilateral, producing a small kidney with deep, narrow, segmental scars (slit-scar) found in the midzone. These slit scars are the classic radiographic finding.

The Ask-Upmark kidney is smaller than normal—12 to 35 g (Royer et al, 1971). Its distinctive feature is one or more deep grooves on the lateral convexity, underneath which the parenchyma consists of tubules resembling those in the thyroid gland. Usually, the hypoplastic segments are easily distinguished from adjacent areas (Fig. 118–5).

Abnormal renin secretion has been proposed as the cause of the hypertension; however, nephrectomy has been shown to normalize blood pressure regardless of plasma renin activities (Babin et al, 2005). In patients with unilateral disease, partial or total nephrectomy may control the hypertension (Royer et al, 1971; Meares and Gross, 1972). Failure of this measure suggests an unrecognized scar or generalized arteriosclerosis in the remaining kidney (Arant et al, 1979). Bilateral disease with renal insufficiency usually is managed medically, although dialysis and transplantation may be needed. Correction of reflux may prevent further renal damage but probably will have no effect on the hypertension.

Renal Hypodysplasia

Hypodysplasia may be associated with a wide spectrum of urologic diseases, such as primary obstructive megaureter and ureteropelvic junction obstruction, ureterocele, urethral obstruction, or prune-belly syndrome, to name a few. It has been previously mentioned that abnormal ureteric budding leads to abnormal renal development that often is manifested as hypodysplasia. Lateral ureteral ectopia usually leads to vesicoureteral reflux and its associated forms of hypodysplasia—be it a developmental anomaly, the result of chronic pyelonephritis, or a combination of both. Medial ureteral ectopia, with or without the presence of an ureterocele, can often result in hypodysplasia as well. The renal cortex may be thin,

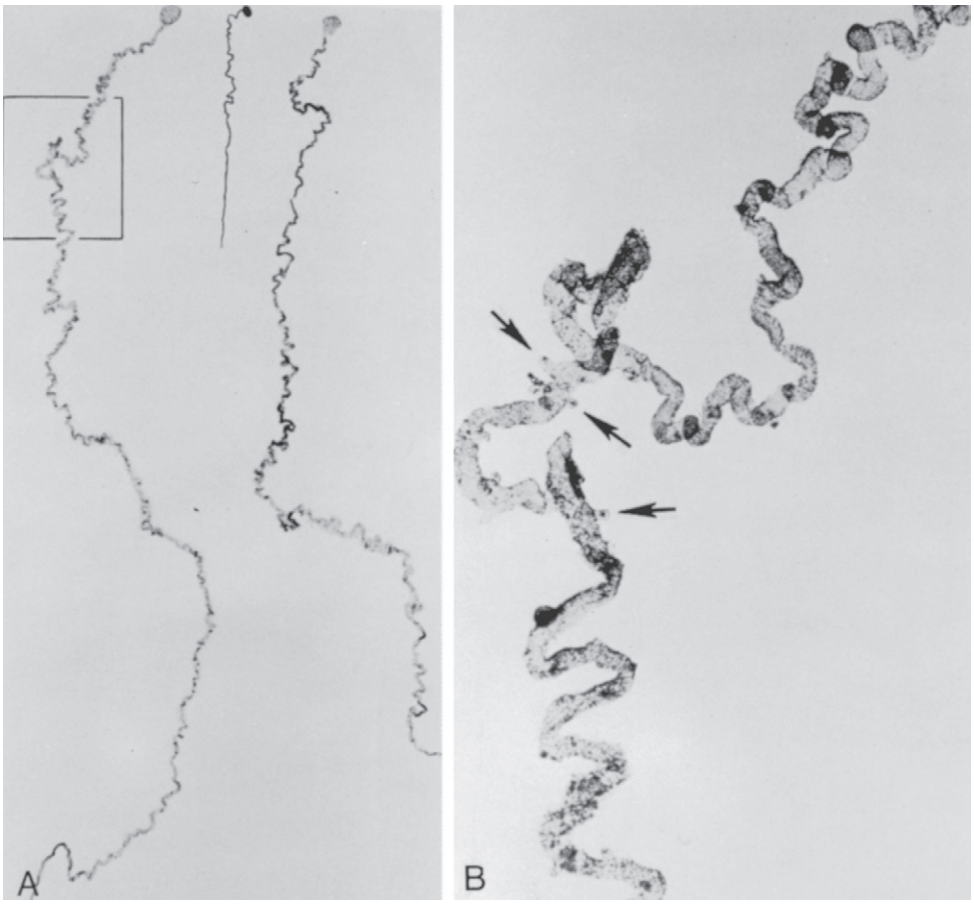


Figure 118–4. **A,** Mosaic photograph of two typical proximal tubules dissected from the kidney of a patient with oligomeganephronia. The silhouette in the top center is a diagrammatic representation to scale of an average proximal tubule from a kidney of an age-matched control. **B,** Enlargement of the *inset* in **A** showing the diverticula along the course of the nephron *(arrows).* (From Fetterman GH, Habib R. Congenital bilateral oligonephronic renal hypoplasia with hypertrophy of nephrons [oligomeganephronia]. Am J Clin Pathol 1969;52:199–207.)

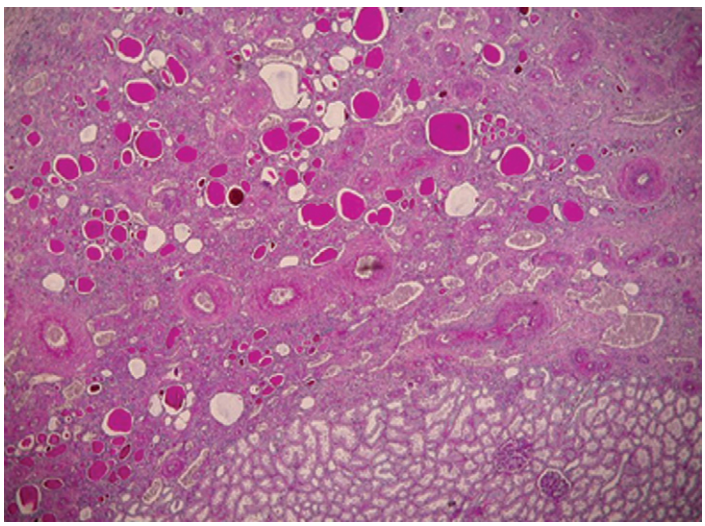


Figure 118–5. Typical microscopic pattern of segmental hypoplasia affecting the cortex with thyroid-like tubules, thick-walled arteries, and the absence of glomerulus. Note the sharp delineation from the surrounding normal kidney *(bottom).* Periodic acid–Schiff stain. (From Babin J, Sackett M, Delage C, Lebel M. The Ask-Upmark kidney: a curable cause of hypertension in young patients. J Hum Hypertens 2005;19:315–6.)

secondary to hydronephrosis, or severely dysplastic, and perhaps with numerous small cysts.

According to Osathanondh and Potter (1964), posterior urethral valves may be associated with two types of renal hypodysplasia. In the less severe form, there are small, usually subcapsular cysts and nearly normal renal function. In the second form, the cysts are larger and more widely distributed, and numerous islands of cartilage are present. This form usually is associated with earlier onset and more severe obstruction and reflux (see Fig 118–2).

The features of the prune-belly syndrome (absent abdominal musculature, triad syndrome) include grossly deformed kidneys, which may have various degrees of hypodysplasia. The ureters are wide and tortuous, often with large and laterally placed orifices. Urethral obstruction or atresia may be present in the most severe cases, but usually there is no lower urinary tract obstruction.

CYSTIC DISEASES OF THE KIDNEY

The kidney is one of the most common sites in the body for cyst formation. Renal cystic diseases encompass a broad spectrum of sporadic and genetically determined congenital or acquired conditions that have in common the presence of cysts in one or both kidneys. These diseases often require a multidisciplinary approach to evaluation and treatment.

Renal cysts are cavities derived primarily from tubules and are composed of a layer of partially dedifferentiated epithelial cells enclosing a cavity filled with urine-like liquid or semisolid material. They may develop in any tubular segment between the Bowman capsule and the tip of the renal papilla, depending on the nature of the underlying disorder. Some cysts are saccular or fusiform structures that resemble diverticula. Other cysts may or may not communicate with a glomerulus, tubule, collecting duct, or calyx, or they may initially have communicated only to become isolated later. **Multicystic dysplasia is an exception in that it arises before formation of the nephron, from abnormal induction of metanephric development, from a primary abnormality of the nephrogenic blastema, or from obstruction occurring early in renal development. Another exception, benign multilocular cyst, represents a neoplastic growth.**

Key Points: Hypoplasia and Hypodysplasia

- Hypoplasia and hypodysplasia often are associated with ectopic orifices and sometimes with obstruction.
- Oligomeganephronia is a condition with a reduced number of nephrons and hypertrophy of each nephron.
- Ask-Upmark kidneys have segmented dysplasia, are seen most frequently in association with reflux, and are often the cause of severe hypertension.

The fundamental processes that are essential for the development and progressive enlargement of renal cysts include (1) proliferation of epithelial cells in segments of renal tubule, (2) accumulation of fluid within the expanding tubule segment, and (3) disturbed organization and metabolism of the extracellular matrix (Fig. 118–6).

An imbalance of the secretory and absorptive properties in proliferating epithelial cells leads to a net accumulation of fluid

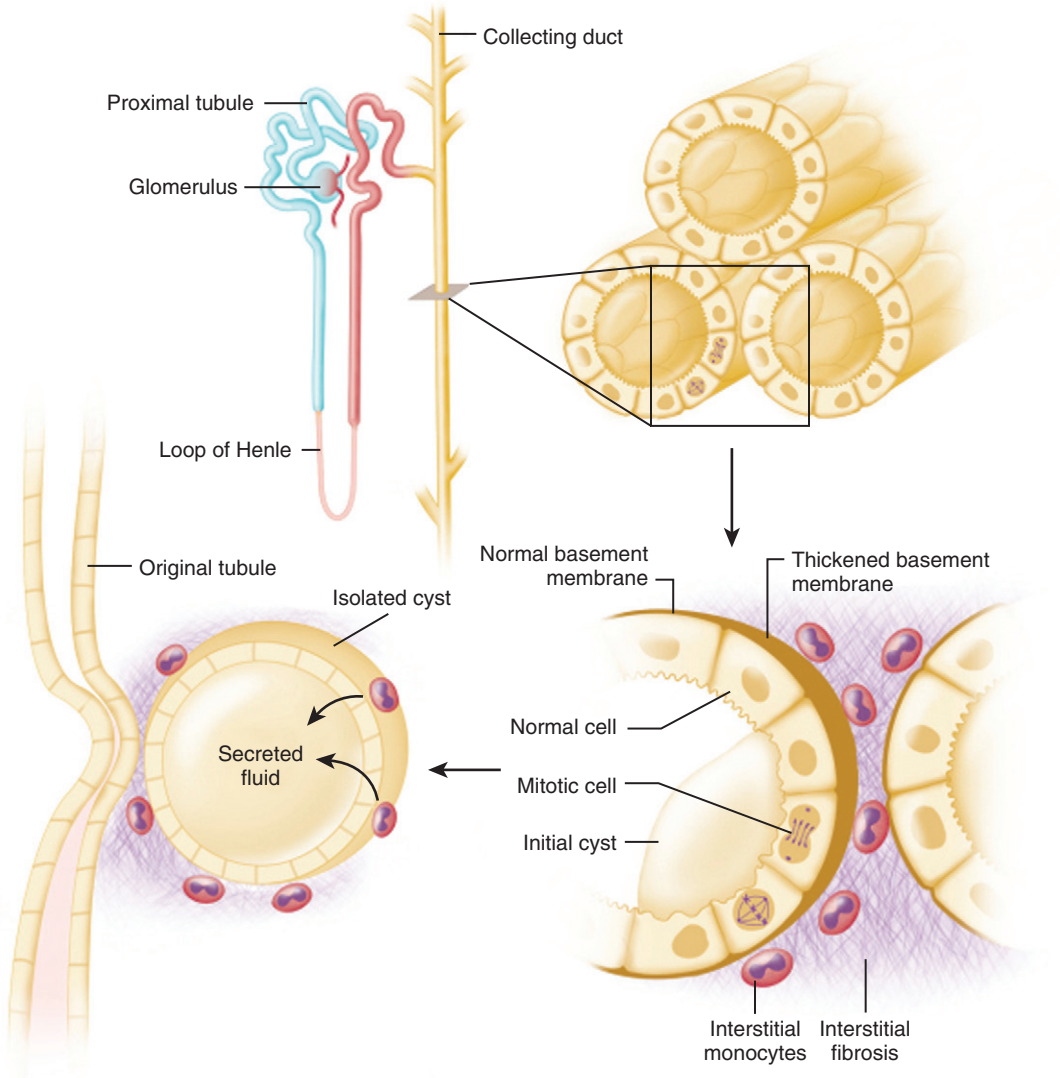


Figure 118–6. Evolution of cysts from renal tubules. Abnormal proliferation of tubule epithelium begins in a single cell after a "second-hit" process disables the function of the normal allele. Repeated cycles of cell proliferation lead to expansion of the tubule wall into a cyst. The cystic epithelium is associated with thickening of the adjacent tubule basement membrane and with an influx of inflammatory cells into the interstitium. The cystic segment eventually separates from the original tubule, and net epithelial fluid secretion contributes to the accumulation of liquid within the cyst cavity. (From Brenner BM, editor. Brenner and Rector's the kidney. 8th ed. Philadelphia: WB Saunders; 2007. p. 1428.)

in otherwise normal renal tubules. Recent evidence indicates that, beyond the loop of Henle, tubule cells have the capacity to secrete solutes and fluid on stimulation with 3′,5′-cyclic adenosine monophosphate (cAMP) (Wallace et al, 2001). This secretory flux operates in competition with the more powerful mechanism by which sodium (Na^+) is absorbed through apical epithelial Na^+ channels (ENaC). Under conditions in which Na^+ absorption is diminished, the net secretion of sodium chloride (NaCl) and fluid occurs.

Abnormalities of the extracellular matrix in and about renal cysts are seen in all cystic disorders. In the early stages of renal cyst development, changes in expression of collagen I and IV, metalloproteinase activators and inhibitors, integrins, and β-catenin may forecast a vital role for extracellular matrix remodeling in the pathogenesis of renal cysts. Recently, a hypomorphic mutation in the mouse laminin α5 gene was found to cause polycystic kidney disease (PKD) (Joly et al, 2006; Shannon et al, 2006).

Until recently, the mechanisms responsible for the abnormal differentiation and functional behavior of the epithelial cells that give rise to the cysts were largely unknown. Evidence now strongly suggests that a long-neglected structure, the primary cilium, is essential in maintaining epithelial cell differentiation. Structural and functional defects in the primary apical cilia of tubular epithelia may have a central role in determining cyst development and the abnormal differentiation and behavior of the cystic epithelium, and in various forms of human and rodent cystic diseases (Torres, 2008).

Cystic kidneys of different etiologies may appear morphologically similar, whereas the same etiologic entity may cause a wide spectrum of renal abnormalities. For example, in ADPKD, tuberous sclerosis, von Hippel-Lindau (VHL) disease, and acquired renal cystic disease (ARCD), the cysts have a hyperplastic lining, sometimes with nodules of hyperplasia or polyps that project into the cyst lumen. However, these hyperplastic conditions are very different from each other. Another example of such similarities is the ectatic collecting ducts seen in two very different clinical entities, autosomal recessive polycystic kidney disease (ARPKD) and medullary sponge kidney.

Classification

In this chapter, the classification of renal cystic disease as outlined in 1987 by the Committee on Classification, Nomenclature, and Terminology of the AAP Section on Urology is used. **The primary distinction is between genetic ("inheritable") and nongenetic ("noninheritable") disease**. Table 118–1 gives an overview of characteristics associated with the various forms cystic disease.

The terms *multicystic* and *polycystic* should not be confused, even though both terms literally mean "many cysts." *Multicystic* typically refers to a dysplastic kidney resulting from aberrant renal development. *Polycystic* refers to renal units that developed in a normal fashion, all of which have no dysplasia and have nephrons throughout the kidney. The term *polycystic kidney disease* traditionally is used in reference to two conditions: ARPKD and ADPKD. Many of the polycystic kidney disease entities progress to renal failure as the nephrons become more diseased. In other conditions, such as tuberous sclerosis and VHL disease, there are hyperplastic cysts, and the individual nephrons are normal. Only occasionally do the nephrons become compressed by the cysts or by associated tumors, and only in such situations does renal failure ensue.

Table 118–1

Cystic Diseases of the Kidney

Inheritable
Autosomal recessive (infantile) polycystic kidney disease
Autosomal dominant (adult) polycystic kidney disease
Juvenile nephronophthisis/medullary cystic disease complex
Juvenile nephronophthisis (autosomal recessive)
Medullary cystic disease (autosomal dominant)
Congenital nephrosis (familial nephrotic syndrome) (autosomal recessive)
Familial hypoplastic glomerulocystic disease (autosomal dominant)
Multiple malformation syndromes with renal cysts (e.g., tuberous sclerosis, von Hippel-Lindau disease)
Noninheritable
Multicystic kidney (multicystic dysplastic kidney)
Benign multilocular cyst (cystic nephroma)
Simple cysts
Medullary sponge kidney
Sporadic glomerulocystic kidney disease
Acquired renal cystic disease
Calyceal diverticulum (pyelogenic cyst)

Among the noninheritable cystic diseases, benign multilocular cysts, cystic renal cell carcinoma, and other variants are considered neoplasms. Medullary sponge kidney is a disease principally of dilated ectatic collecting ducts, with cysts playing a lesser role, although the size of the ducts by definition makes them cysts. The nephrons initially are normal.

Inheritable Cystic Disease

Genetic (inheritable) cystic diseases can be classified based on their mode of transmission: autosomal dominant, autosomal recessive, X-linked, among others. Some of these disorders are caused by a single gene defect, some by an X-linked gene defect, and others by chromosomal defects. The modes of inheritance of these diseases and the specific gene or gene locus, where identified, are summarized in Table 118–2.

AUTOSOMAL RECESSIVE (INFANTILE) POLYCYSTIC KIDNEY DISEASE

Autosomal recessive polycystic kidney disease (ARPKD) is typified by relatively rapid, symmetrical, and bilateral enlargement of the kidneys in infants secondary to collecting duct cysts. It is invariably associated with some degree of congenital hepatic fibrosis (Zerres et al, 1988; Guay-Woodford and Desmond, 2003; MacRae Dell and Avner, 2003). ARPKD has been referred to as the "infantile" form in the past; however, the disease can present in adolescents and young adults, although significantly less frequently. **ARPKD has a spectrum of severity, with the most severe forms appearing earliest in life. If it is not apparent at birth, the disease will become apparent later in childhood (up to age 13 years or, rarely, up to age 20 years).**

The reported incidence of ARPKD varies from 1 in 10,000 to 50,000 live births (Zerres et al, 1988; Kaplan et al, 1989a). However, as many as 50% of affected newborns die in the first few days of life, making for a significantly lower incidence among children who live for at least 1 year. Of those infants who survive the neonatal period, approximately 50% are alive at 10 years of age (Kaplan et al, 1989a).

Table 118–2

Characteristics of Major Inheritable and Noninheritable Cystic Kidney Diseases

Inheritable

DISEASE ENTITY	CHROMOSOMAL DEFECT	RENAL FINDINGS	EXTRARENAL MANIFESTATIONS
Autosomal recessive polycystic kidney disease (ARPKD)	Chromosome 6	In newborn usually large, homogeneous, echogenic kidneys	Congenital hepatic fibrosis; biliary dysgenesis
Autosomal dominant polycystic kidney disease (ADPKD)	*PKD1:* chromosome 16 *PKD2:* chromosome 4 *PKD3;* not mapped	Renal cysts scattered throughout parenchyma; large kidneys	Diverticulitis; liver, spleen, pancreatic cysts; mitral valve prolapse; intracranial (berry) aneurysms
Juvenile nephronophthisis/ medullary cystic disease complex	Chromosome 2; not mapped	Cysts of corticomedullary junction; develop after onset of renal failure; always thickened tubular basement membrane	Retinitis pigmentosa (16%; also known as Senior-Løken syndrome); rarely skeletal abnormalities, hepatic fibrosis, Bardet-Biedl syndrome, ocular motor apraxia, and other neurologic defects
Juvenile nephronophthisis (autosomal recessive)		Cysts of corticomedullary junction; develop before onset of renal failure; tubular basement membrane may NOT be thickened	None
Medullary cystic disease (autosomal dominant)			
Tuberous sclerosis (autosomal dominant)	*TSC1:* Chromosome 9 *TSC2:* Chromosome 16	Cysts and angiomyolipomas throughout kidney; cysts even present in utero; 3% incidence of RCC	Adenoma sebaceum; epilepsy; mental retardation; cranial tumors
von Hippel-Lindau disease (autosomal dominant)	Chromosome 3	Cysts, adenomas, and clear cell RCC (35%-38% of cases)	Cerebellar hemangioblastomas; retinal angiomas; pheochromocytomas; cysts of pancreas and epididymis

Noninheritable

DISEASE ENTITY	RENAL FINDINGS	EXTRARENAL MANIFESTATIONS
Multicystic dysplastic kidney	Renal maldevelopment with diffuse cysts and remnants of early metanephros; minimal, if any, nephron development; most frequent renal cystic disease in newborns	Unusual
Benign multilocular cyst	Benign cystic neoplasm of the kidney; remainder of kidney has normal nephrons that may be compromised by growing mass; present more often in males when less than 4 years of age and females when greater than 30 years of age	None
Simple cysts	Single or multiple cysts; normal nephrons throughout kidney; very common in normal kidneys with increasing age	None
Medullary sponge kidney	Ectatic collecting ducts; nephrons usually normal	None
Acquired renal cystic disease	Diffuse cysts; adenomas; occasionally RCC; increases with duration of ESRD	None

ESRD, end-stage renal disease; RCC, renal cell carcinoma.

Genetics

Once the diagnosis of ARPKD is strongly suspected, referral for genetic evaluation and counseling is appropriate. A detailed history should be taken of at least three generations. **Because the disease is transmitted as an autosomal recessive trait, siblings of either sex have a 1 in 4 chance of being affected.**

Despite the clinical variability of ARPKD, it appears that only mutations of a single gene, named *PKHD1* and located on chromosome 6 (6p12), are responsible for the disease. The gene produces a protein called fibrocystin (also known as polyductin) (Onuchic et al, 2002; Ward et al, 2002). This protein is a member of a larger family of proteins involved in regulation of cell proliferation and of cellular adhesion and repulsion.

Clinical Features

Affected children typically present in utero with enlarged, echogenic kidneys. Oligohydramnios is common because of the lack of normal urine production by the fetus. The infant often displays Potter facies and deformities of the limbs and may have respiratory distress as a consequence of pulmonary hypoplasia. The affected newborn usually has enormous, kidney-shaped, nonbosselated flank masses that are hard and do not transilluminate. In some cases, the kidneys are large enough to impede delivery. The infant's serum creatinine and BUN concentrations are those of the mother's at birth but soon begin to rise. Thirty to 50 percent of the affected individuals die shortly after birth as a result of uremia or respiratory failure (Kaplan et al, 1989c; Capisonda et al, 2003; Guay-Woodford, 2003). The earlier the age at which the disease is identified, the more severe the disease. **No matter what the severity of the renal disease, all patients with ARPKD have liver involvement in the form of congenital hepatic fibrosis and vary in the degree of biliary ectasia and periportal fibrosis** (Habib and Bois, 1973; Kissane and Smith, 1975).

Patients who survive the neonatal period have a milder form of the disease and are likely to survive into adulthood. Some diagnosed as neonates can live beyond age 3 or 4 years before going into renal failure (Cole et al, 1987; Avni et al, 2002).

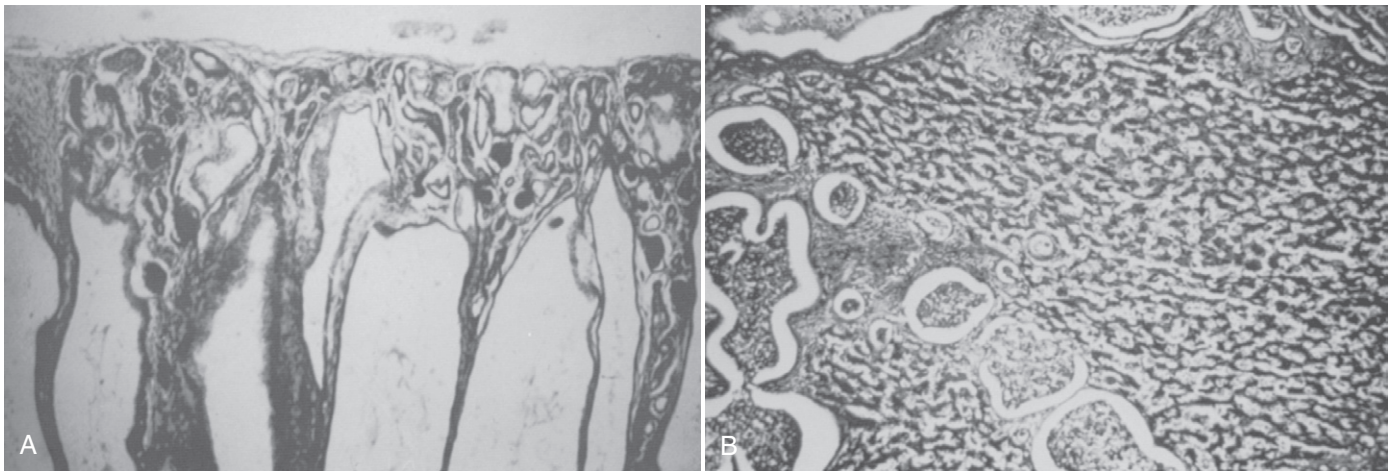


Figure 118–7. Newborn with abdominal mass and pulmonary hypoplasia. Neither parent had a history of renal cysts. **A,** Renal histology demonstrates dilated ducts radiating out to the periphery of the kidney. **B,** On liver histology, ectatic biliary ducts are seen in the left half of the figure, and periportal fibrosis is seen at the upper edge. These findings confirm the diagnosis of autosomal recessive polycystic disease.

Hypertension and renal insufficiency are the major manifestations in surviving children, with liver disease becoming more prevalent in older patients.

Patients whose disease appears later in life develop renal failure and hypertension more slowly. In general, their clinical problems are the consequence of liver disease rather than the renal disease, with hepatic fibrosis leading to portal hypertension, esophageal varices, and hepatosplenomegaly. Hepatocellular function is rarely abnormal, with liver enzymes typically remaining normal. The kidneys in these patients are often normal in appearance.

No association of ARPKD with renal neoplasms has been reported to date.

Histopathology

The kidneys are symmetrically enlarged (up to 20 times their normal size) and retain a reniform configuration. The parenchyma exhibits small subcapsular cysts, representing generalized fusiform dilations of the collecting tubules radiating from the medulla to the cortex with their long axis perpendicular to the renal surface (Bisceglia et al, 2006). Almost 100% of collecting ducts are affected in the most severe cases. The cortex is crowded with minute cysts (Fig. 118–7A). The renal pedicle is normal, as are the renal pelvis and ureter.

ARPKD affects both the kidneys and the liver in approximately inverse proportions (Torres, 2008). The disease may be viewed as a spectrum ranging from severe renal disease and mild liver changes at one extreme to mild renal damage and severe liver disease at the other. The form with severe renal disease is the most common and the one typically seen at or near the time of birth. The form with less severe renal disease and more significant liver damage is present in older children. **All children with ARPKD have lesions in the periportal areas of the liver** (Habib and Bois, 1973; Kissane and Smith, 1975) (Fig. 118–7B).

Evaluation

The diagnosis may be suspected from in utero ultrasound examination and may be associated with oligohydramnios, a finding secondary to low urinary output. **In both fetus and newborn, ultrasonography identifies bilateral, very enlarged, diffusely echogenic kidneys, especially when compared with the echogenicity of the liver** (Fig. 118–8A)**. The increased echogenicity is due to the presence of numerous microcysts (created by tightly compacted, dilated collecting ducts) that result in innumerable interfaces. Compared with normal newborn kidneys, in ARPKD, the pyramids are hyperechogenic because they blend in with the rest of the kidney, and the kidneys typically have a homogeneous appearance** (see Fig. 118–8A). In ADPKD, the cysts, if apparent in newborns, are usually diffuse and large (Fig. 118–8B). Also included in the differential diagnosis is severe bilateral hydronephrosis (the kidneys are enlarged with hypoechogenic calyces), multicystic kidney (hypoechogenic cysts lie within a nonreniform mass that has very little parenchyma), sporadic glomerulocystic kidney disease, bilateral mesoblastic nephroma, Wilms tumor, and bilateral renal vein thrombosis. If the diagnosis is in doubt, computed tomography is valuable because it is more sensitive to inhomogeneity (and therefore to tumor) within abdominal masses.

Considerable overlap in clinical presentation and imaging findings can occur between ADPKD and ARPKD. Occasionally, a newborn with severe ADPKD can also have enlarged, homogeneously hyperechogenic kidneys. Age at onset can overlap, and typically, when ADPKD manifests at birth, cysts are apparent on the sonographic image. Macrocysts are rare in newborns with ARPKD but do increase in frequency as the child gets older, sometimes producing an appearance similar to that of the dominant disease. Cysts less than 1 cm appear more often than large cysts (Avni et al, 2002) (Fig. 118–9). Hepatic fibrosis can rarely occur in patients with ADPKD, as can brain aneurysms with ARPKD (Cobben et al, 1990; Neumann et al, 1999). The correct diagnosis of ARPKD depends on the overall clinical data: positive family history with a recessive mode of inheritance, a positive liver biopsy, and the lack of the extrarenal malformations often associated with other renal cystic diseases.

Treatment

No cure has been found for ARPKD. Respiratory care can ease or extend the child's life. Severely affected neonates may require unilateral or bilateral nephrectomy, because of respiratory and nutritional compromise. Patients who survive may require treatment for hypertension, congestive heart failure, and renal and

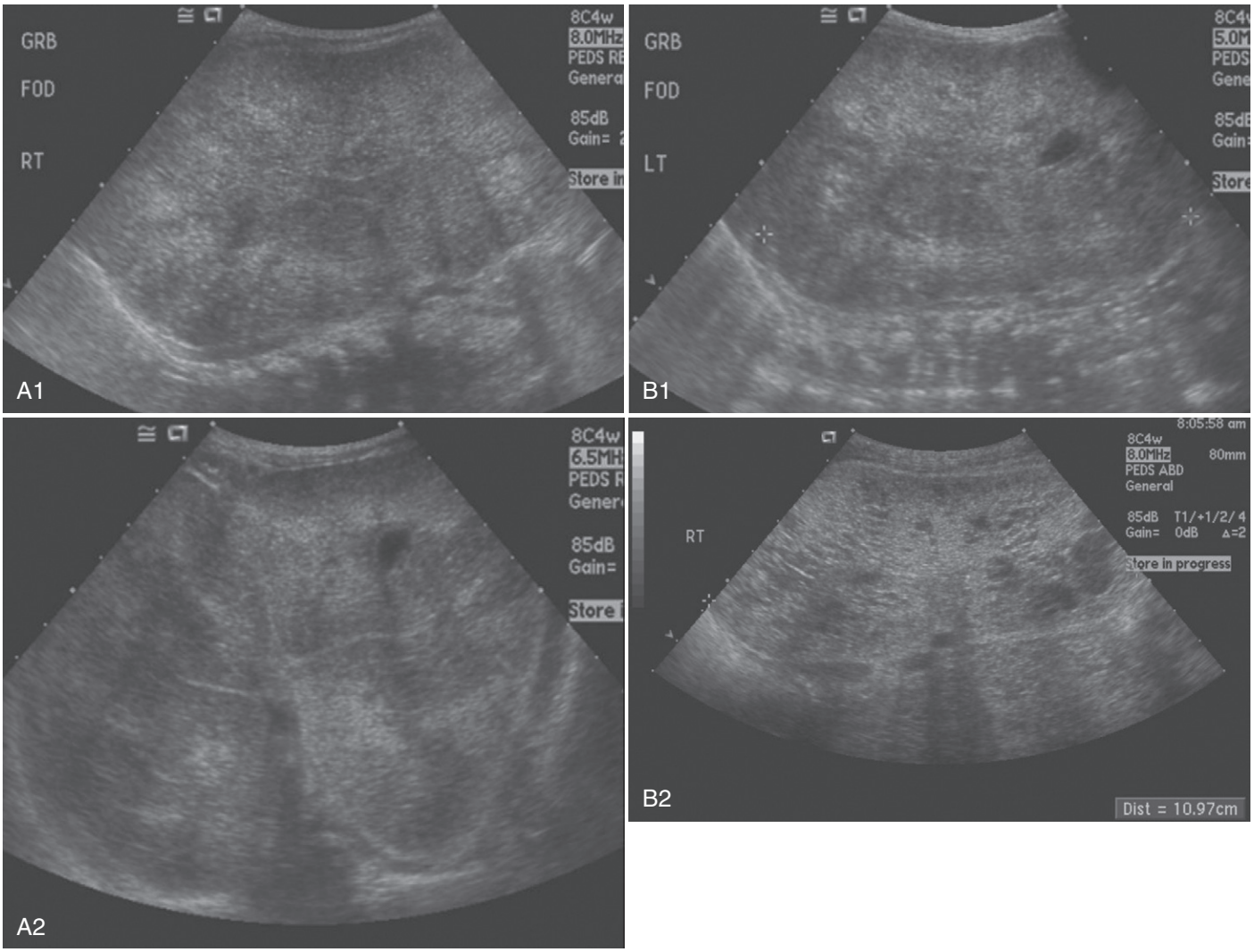


Figure 118–8. Ultrasonographic appearance of the kidneys in neonates with autosomal recessive polycystic kidney disease (ARPKD) and autosomal dominant polycystic kidney disease (ADPKD) can be similar. **A1** and **A2,** Newborn with ARPKD. **A1,** Note the large size and hyperechogenic, homogeneous appearance of the renal parenchyma. **A2** is a cross-sectional cut of the baby's abdomen showing both kidneys to be quite large and occupying a large portion of the abdominal cavity. **B1** and **B2,** Newborn with ADPKD. Again note the abnormal renal architecture and the hyperechogenic appearance of the kidneys. The parenchyma consists of multiple tiny cysts, with some being slightly larger than others. (Courtesy of Marta Hernanz-Schulman, MD.)

hepatic failure. Portal hypertension may be dealt with by decompressive procedures such as a splenorenal shunt. Esophageal varices may be managed, at least temporarily, by gastric section and reanastomosis. Endoscopic sclerotherapy is widely employed in pediatric and adults with bleeding varices. Hemodialysis and renal transplantation must eventually be considered in many patients.

AUTOSOMAL DOMINANT (ADULT) POLYCYSTIC KIDNEY DISEASE

Autosomal dominant polycystic kidney disease is by far the most common inheritable form of renal cystic disease, with an incidence of approximately 1 in 400 to 1000 live births (Iglesias et al, 1983; Grantham, 1996). It is an important cause of renal failure, accounting for 7% to 15% of patients who receive hemodialysis (Hildebrandt, 1995; Grantham, 1996; Wilson, 2004). The trait theoretically has a 100% penetrance, and, on average, because it is transmitted in an autosomal dominant fashion, 50% of an affected individual's offspring will likewise be affected. Although a positive family history is one of the major criteria for the diagnosis of ADPKD, 10% of cases occur sporadically. Ninety-six percent of affected persons will manifest the disease clinically by age 90 years (Gabow, 1991).

Although most cases are identified between the fourth and fifth decades of life, the condition has been reported in newborns and infants (Proesmans et al, 1982). All affected individuals manifest the disease (although not necessarily symptomatically) if they live long enough, but renal failure is seldom seen before the age of 40 years, unless the disease manifests during infancy, in which case it is much more aggressive.

A number of associated anomalies are common, including cysts of the liver, pancreas, spleen, and lungs; aneurysms of the circle of Willis (berry aneurysms); colonic diverticula; aortic aneurysms; and mitral valve prolapse (Table 118–3).

Table 118–3

Comparison of Autosomal Recessive and Autosomal Dominant Polycystic Kidney Disease

	AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE	AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE
Gene defect	Chromosome 6	Chromosome 4 and 16
Incidence	1: 5000-40,000	1: 500-1100
Usual age at clinical presentation	Perinatal	Third to fifth decades
Typical ultrasonographic appearance of kidneys	Symmetrically enlarged, homogeneous, hyperechogenic	Large, cystic kidneys, sometimes asymmetrical
Histology	Collecting duct ectasia; cysts derived principally from collecting duct	Microcysts and macrocysts derived from the entire nephron
Liver	Always with congenital hepatic fibrosis but of varying severity	Cysts, mostly in adults
Other organ system(s) involvement	None	Intracranial (berry) aneurysms, colonic diverticuli; mitral valve prolapse; cysts of other organs (seminal vesicle, arachnoid membrane, pancreas)

Key Points: Autosomal Recessive Polycystic Kidney Disease

- ARPKD is secondary to a mutation of the *PKHD1* gene on chromosome 6.
- The severe form presents in utero or in infancy; milder cases can present later in childhood and rarely into the early 20s.
- All affected individuals have some degree of congenital hepatic fibrosis.
- When it manifests early, it is associated most often with very large kidneys that are homogeneously hyperechogenic.
- Discrete cysts appear more often as the child gets older.
- Renal ultrasonography reveals bilateral, very enlarged, diffusely echogenic kidneys, and the increased echogenicity is due to the presence of numerous microcysts (created by tightly compacted, dilated collecting ducts) that result in innumerable interfaces.
- Considerable overlap in clinical presentation and imaging findings can occur between ADPKD and ARPKD.

Genetics

There are two major genetic forms of ADPKD caused by mutation in the genes *PDK1* and *PDK2* (Reeders et al, 1985; Breuning et al, 1987; Ryynanen et al, 1987; Pieke et al, 1989). *PDK1* has been localized to the short arm of chromosome 16, with its gene product being polycystin-1. Mutations in the *PDK1* gene account for 85% of ADPKD cases. These patients typically have a more rapidly progressive form of the disease, with cysts usually developing by the age of 20 years (64% of children have cysts by the age of 10 years and 90% by the age of 20 years) and ESRD occurring in their 50s (Chakraborty and McHugh, 2005). The *PKD2* gene has been mapped to the long arm of chromosome 4 (Peters et al, 1992), and it encodes the protein polycystin 2. *PDK2* mutations account for about 15% of ADPKD cases, and in these patients, the disease progresses more slowly. ESRD usually does not occur until these patients are in their 70s (Hateboer et al, 1999). The presence of a third locus *(PKD3)* is now accepted as the cause of disease in a very small percentage of patients who have been found to have neither a *PKD1* nor a *PKD2* gene defect (Dauost et al, 1993). **When either the *PKD1* or the *PKD2* gene is abnormal, cystic kidneys can develop.** Because defects of *PKD1* and *PKD2* manifest similarly, it has been suggested that the gene product of each is involved in the same pathway and that an abnormality of either product results in similar manifestations of the disease (Qian et al, 1996).

Every cell of the nephron and collecting duct has the *PDK1* or *PDK2* mutation; however, only 1% to 2% of these glomerular units are affected by cyst formation. Only those nephrons that undergo a disruption of a second allele undergo cystic enlargement. This is the "second hit" of the Knudson theory, which has been proposed to explain the focal nature of the cysts (Knudson, 1991).

Occasionally, the classic ADPKD phenotype is seen in conjunction with tuberous sclerosis. This association is a classic example of a "contiguous gene syndrome," which is a disorder due to deletion of multiple gene loci that are adjacent to one another. Contiguous gene syndromes are characterized by multiple, apparently unrelated, clinical features caused by deletion of the multiple adjacent genes. Due to the fact that the *PDK1* gene is immediately adjacent to the *TSC2* gene (the most important gene in tuberous sclerosis) on chromosome 16, large deletions in this area can involve both the *PDK1* and *TSC2* genes. Thus these patients have the classic features of tuberous sclerosis in addition to the renal cystic phenotype of ADPKD.

Pathogenesis

The PDK1 and PDK2 proteins, polycystin 1 (PC1) and polycystin 2 (PC2), are transmembrane proteins that in all likelihood form a functional complex. When working properly, PC1 and PC2 inhibit cell proliferation by several pathways. Polycystin 1 functions as a mechanoreceptor located on the primary cilium of renal tubular cells. These cilia project from the surface of the cell into the lumen of the ducts and tubules. Mutations that block the assembly of these cilia are known to cause many cystic diseases of the kidney. The products of the *ADPKD, ARPKD,* and nephronophthisis genes are at least partially localized to these primary cilia. Polycystin 1 is linked to polycystin 2, which contains a calcium (Ca^{++}) channel. When the mechanoreceptor of polycystin 1 is stimulated by calcium-containing urine flowing through the tubule, the calcium channel of polycystin 2 opens and calcium enters the cell (Nauli et al, 2003; Braun, 2009). This process regulates the proliferative state of the renal tubular cells through a

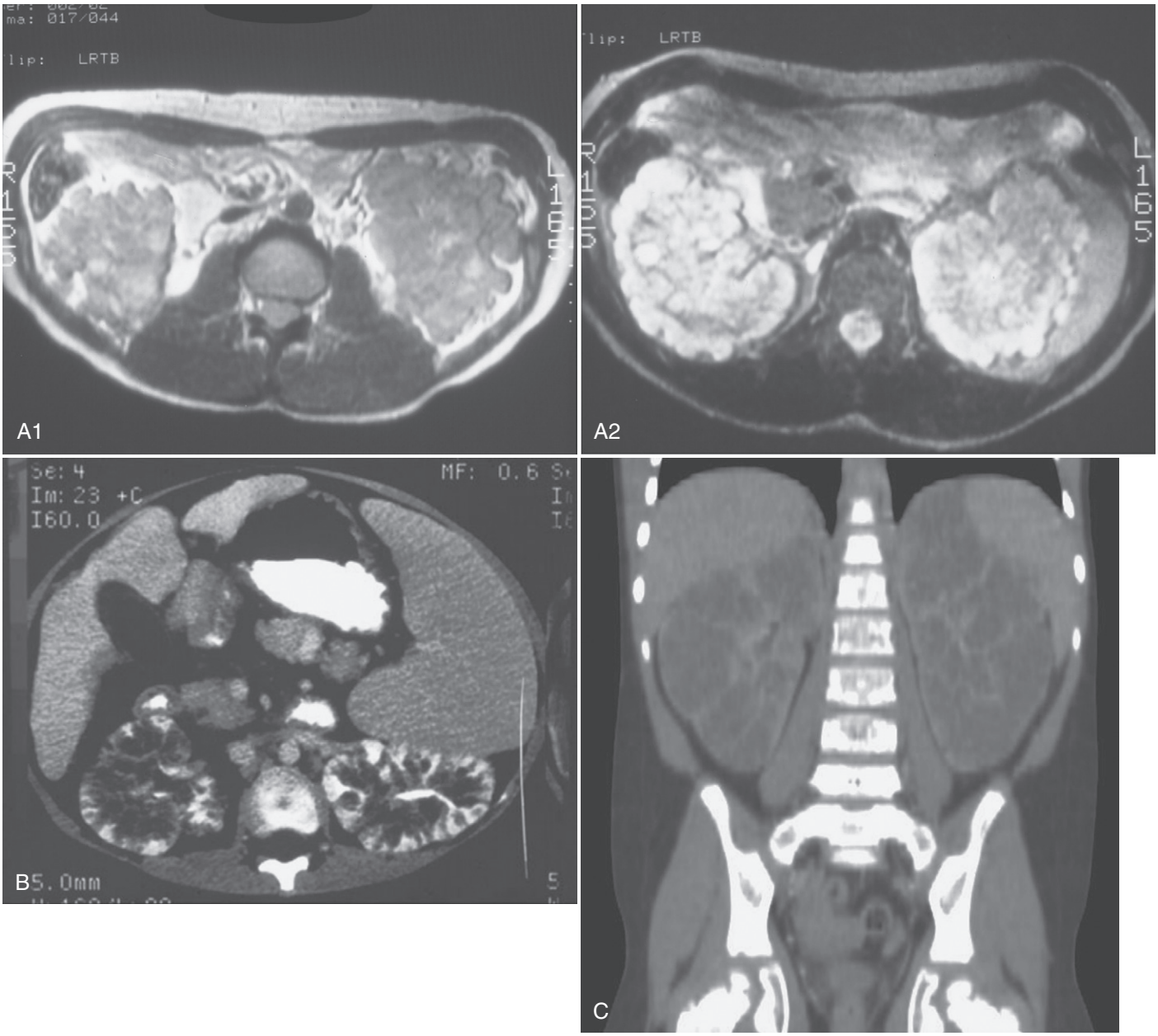


Figure 118–9. **A1** and **A2**, MR images of an 8-month-old child with autosomal recessive polycystic kidney disease (ARPKD) demonstrating multiple renal cysts. **A1**, On T1-weighted image, fluid content of cysts appears dark. **A2**, On T2-weighted image, the fluid content appears white. **B**, CT scan of a child with ARPKD. Horizontal cuts showing contrast puddling in collecting ducts. **C**, Coronal cut. Note the kidneys are enlarged, and the enhancing renal parenchyma is effaced by nonenhancing cysts and represents the progression/normal history of the disorder. (**A**, Courtesy of Walter Berdon, MD. **B**, Courtesy of Marta Hernanz-Schulman, MD.)

variety of signaling pathways (cAMP, extracellularly regulated kinase [ERK], mammalian target of rapamycin [mTOR], etc.). The cilia likely serve as organization centers for this signal transduction (Pazour, 2004).

In ADPKD, the polycystins do not function properly, and these proliferative pathways are unopposed and cyst formation occurs to varying degrees.

Increased levels of cAMP have been noted in multiple animal models of ADPKD, and biochemical processes that alter cAMP appear to affect the presence and size of renal cysts. For example, cAMP is broken down by phosphodiesterases. Caffeine and methylxanthine products, such as theophylline, interfere with phosphodiesterase activity, raise cAMP in epithelial cell cultures from patients with ADPKD, and increase cyst formation in canine kidney cell cultures (Mangoo-Karim et al, 1989; Belibi et al, 2002). Upregulation of the vasopressin V2 receptor has also been shown to increase cAMP levels. Vasopressin receptor antagonists have been shown to decrease cAMP and ERK, to prevent or reduce renal cysts, and to preserve renal function (Gattone et al, 2003; Wang et al, 2005).

Clinical Features

Phenotypes associated with ADPKD are highly variable in penetrance. This variability related to the severity of renal disease can range from fetal demise and neonatal death to adequate renal

function into old age. Characteristics of the associated liver disease and extrarenal manifestations can also be quite variable. *PDK1* and *PDK2* gene mutations are obviously critical, but intrafamilial variability also indicate that genetic background and environmental factors can also affect ultimate clinical expression of the disease (Rossetti and Harris, 2007).

Typically, signs or symptoms first occur between the ages of 30 and 50 years (Glassberg et al, 1981). These include microscopic and gross hematuria, flank pain, gastrointestinal symptoms (perhaps secondary to renomegaly or associated colonic diverticula), renal colic (secondary either to clots or stones), and hypertension. Microscopic or gross hematuria is seen in 50% of patients, and, in 19% to 35%, it is the presenting symptom (Milutinovic et al, 1984; Delaney et al, 1985; Zeier et al, 1988; Gabow et al, 1992). Because patients with ADPKD have increased renal mass, erythropoietin levels are increased, making anemia unusual even when ESRD is present (Gabow, 1993).

Pain (flank and/or abdominal) is the most common presenting symptom in adults. This results from a number of possible factors: mass effect (cysts impinging on abdominal wall or neighboring organs), bleeding into the cysts, urinary tract infection (including infected cysts), and nephrolithiasis. Twenty to 30 percent of patients with ADPKD develop stones (Fick et al, 1994), and these are treated by conservative means if possible (i.e., urine alkalinization, spontaneous stone passage, extracorporeal shock wave lithotripsy). Uric acid stones and calcium oxalate stones are equally prevalent. The finding of hydronephrosis, which helps make the diagnosis of stones, may not be as useful in ADPKD patients because of the number of cysts camouflaging the findings (Choyke et al, 1995). Urinary tract infections are more frequent in female patients. Cyst aspiration for both diagnostic and therapeutic reasons should be considered in the setting of suspected cyst infection.

As blood pressure screening has become more widespread, hypertension has become a very common form of presentation (Zeier et al, 1988). Hypertension is present in roughly 50% of patients 20 to 35 years old having ADPKD with normal renal function. Virtually 100% of patients with ESRD will have hypertension (Kelleher et al, 2004). The hypertension seems to be renin mediated, secondary to stretching of the intrarenal vessels around cysts, causing distal ischemia (Gabow, 1993). Diagnosis and treatment of this hypertension is critical to slow the progression of renal failure, as well as to decrease morbidity and mortality from heart disease and cerebral aneurysms.

The development of renal failure is highly variable. Renal function is usually maintained, despite increasingly rapid cyst growth, until the fourth to sixth decade of life. Risk factors for earlier onset of ESRD include *PKD1* gene mutation, male gender, first episode of hematuria before age 30 years, onset of hypertension before age 35 years, hyperlipidemia, and sickle cell trait (Yium et al, 1994; Johnson and Gabow, 1997). There is a strong relationship between the decline in renal function and the size of the kidneys and cyst volumes. As the cysts, and thus the kidneys, become larger, the renal function declines proportionately (Gabow et al, 1990a). Hypertension and vascular remodeling secondary to cyst expansion also contribute to progressive renal failure.

Extrarenal Manifestations

Hepatic cysts, usually identified incidentally by ultrasonography, are the most common extrarenal manifestation of ADPKD. These cysts are associated with *PKD1* and non-*PKD1* genotypes. They are rare in children, and their frequency increases with age. They are present in virtually all ADPKD patients by the age of 50 years (Bae et al, 2006). Hepatic cysts are more prevalent and their size greater in females (Fick et al, 1994). Several studies have shown an estrogen effect on hepatic cyst growth (Gabow et al, 1990b; Sherstha et al, 1997). Hepatic cysts are usually asymptomatic but can occasionally cause symptoms due to mass effect or from complicating infection or hemorrhage. In rare instances, enlargement of hepatic cysts leads to portal hypertension and bleeding esophageal varices (Campbell et al, 1958). When secondary portal hypertension appears, differentiating ADPKD from ARPKD can be difficult. In ARPKD, portal hypertension is seen much more frequently and is always secondary to congenital hepatic fibrosis. However, congenital hepatic fibrosis, on very rare occasions, may accompany ADPKD as well, particularly when the diagnosis is made perinatally.

Intracranial aneurysms (ICAs)—predominately aneurysms of the circle of Willis (berry aneurysm)—occur in 10% to 30% of patients, and approximately 9% of these patients die because of subarachnoid hemorrhages (Hartnett and Bennett, 1976; Grantham, 1979; Wakabayashi et al, 1983; Sedman and Gabow, 1984; Ryu, 1990). The most common symptom of subarachnoid hemorrhage is the sudden onset of a severe headache, frequently associated with nausea and vomiting. When this occurs, immediate medical evaluation is obviously imperative. Morbidity and mortality from these aneurysms are strongly influenced by positive family history and the *PDK1* genotype. Now, with MRI, even small berry aneurysms can be detected. These aneurysms, when diagnosed, average only 6.1 mm. Although small aneurysms (1 cm) have a lower risk of rupture, patients with small aneurysms have a greater risk of rupture when there is a positive family history of ruptured ICAs or the presence of ADPKD (Huston et al, 1993). Control of hypertension is critical to minimize the risk of aneurysm rupture. **In some patients with ADPKD, hemorrhage follows the rupture of *intracerebral* arteries, which is the usual type of intracranial hemorrhage seen in patients with hypertension who do not have ADPKD.**

Cysts may also occur in the seminal vesicles (40%), arachnoid membrane (8%), and pancreas (5%). Seminal vesicle cysts rarely cause infertility; however, many of these men may have problems with sperm motility. Arachnoid membrane and pancreatic cysts are typically asymptomatic. Other abnormalities associated with ADPKD are mitral valve prolapse and colonic diverticulosis (Scheff et al, 1980; Hossack et al, 1986; Kupin et al, 1987). Patients who have diverticulosis are more likely to have hepatic cysts and symptomatic berry aneurysms (Kupin et al, 1987).

Association with Renal Cell Carcinoma

The incidence of renal adenomas is almost as high in ADPKD as in ARCD associated with ESRD (i.e., one in four to five patients). However, whereas ESRD is associated with an increased incidence of renal cell carcinoma (RCC), especially when associated with ARCD (3 to 6 times the incidence seen in the general population), **the incidence of RCC in patients with ADPKD is no higher than that in the general population**. However, there are certain findings considered typical of a predisposition to RCC that are seen more frequently in patients with ADPKD than in the general population. For example, RCC in ADPKD is often diagnosed at a younger age, is more often concurrently bilateral (12% vs. 1% to 5% in the general population), multicentric (28% vs. 6%), and sarcomatoid in type (33% vs. 1% to 5%) (Keith et al, 1994). The diagnosis of RCC in the context of

ADPKD can be quite difficult, because tumor may be masked by the complex cystic appearance of the kidney. In addition, cystic hemorrhage, degenerating blood clots, proteinaceous debris, and infection can also complicate the diagnosis.

Histopathology

ADPKD kidneys typically maintain their reniform shape, and their size can range from minimally enlarged in early disease to massive enlargement in more advanced disease. Both kidneys are usually equally affected, and the cysts range from a few millimeters to a few centimeters in diameter and appear diffusely throughout the cortex and medulla with communications at various points along the nephron (Kissane, 1974). The cysts appear to begin as focal tubular outpouchings, and, as they enlarge, they usually become detached from their tubule of origin. The first pathologic finding in fetuses is focal tubular dilatation, which may occur anywhere along the nephron (Choyke et al, 1995) (Fig. 118–10).

Epithelial hyperplasia or even adenoma formation in the cyst wall is common, and the basement membrane of the wall is thickened. Arteriosclerosis is present in more than 70% of patients with preterminal or terminal renal failure; and interstitial fibrosis, with or without infiltrates, is common (Zeier et al, 1988). This fibrosis may be secondary to infection or to an inflammatory reaction set off by spontaneously rupturing cysts.

Evaluation

To make the diagnosis, it is important to have at least three generations of the patient's family history. Questions should be asked about renal disease, hypertension, and strokes. Patients and families should be counseled before any imaging or other testing is undertaken. Genetic testing can be used when the imaging results are equivocal and when a definite diagnosis is required. Benefits of testing include making a diagnosis that may affect family planning, early detection and treatment of disease complications, and selection of genetically unaffected family members for living donor–related renal transplantation. Disadvantages to testing include discrimination in terms of insurability and employment associated with a positive diagnosis, as well as the psychologic stress of impending organ failure.

Abdominal ultrasonography may reveal renal cysts (Fig. 118–11) as well as cysts in other organs**. Ultrasonographic diagnostic criteria for individuals at 50% risk for the disease include at least two unilateral or bilateral cysts in individuals younger than 30 years of age, two cysts in each kidney in individuals 30 to 59 years of age, and four cysts in each kidney in individuals 60 years of age or older** (Ravine et al, 1994). The sensitivity of these criteria is nearly 100% for individuals 30 years or older and for younger individuals with *PKD1* mutations but only 67% for individuals with *PKD2* mutations younger than 30 years (Nicolau et al, 1999). When there is no family history to support a diagnosis of ADPKD, a presumptive diagnosis can be made if bilateral renal cysts are present and two or more of the following symptoms are present as well: bilateral renal enlargement, three or more hepatic cysts, cerebral artery aneurysm, and a solitary cyst of the arachnoid, pineal gland, pancreas, or spleen (Grantham, 1993).

CT or MRI (or both) may be helpful in some cases and often is superior to ultrasonography for detecting cysts in organs other than the kidney (Fig. 118–12A). CT is helpful in making the diagnosis of hemorrhage within a cyst. More acute hemorrhage has a higher density (50 to 90 Hounsfield units [HU]) than old hemorrhage (Choyke et al, 1995). MRI also may be helpful, particularly in patients with compromised renal function, because no contrast agent is needed (Fig. 118–12B).

When ADPKD is manifested in utero or in infancy, 50% of affected kidneys are large with identifiable macrocysts (Pretorius et al, 1987). However, the kidneys may appear identical to those

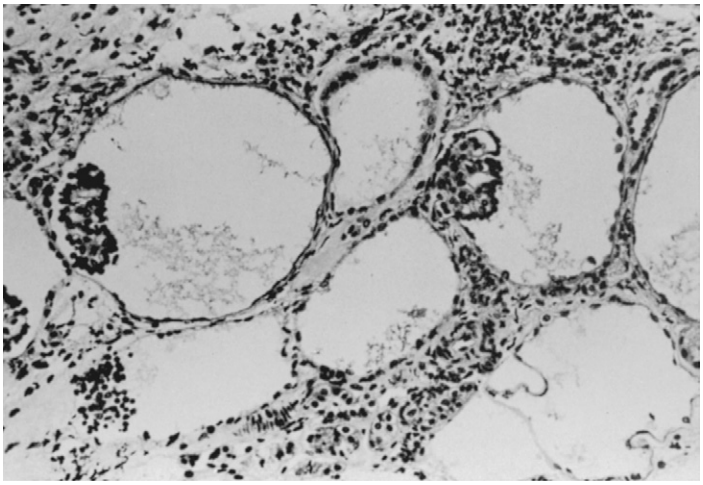


Figure 118–10. Glomerular cysts with a pattern compatible with autosomal dominant polycystic kidney disease in early childhood (190×). (From Bernstein J, Gardner KD Jr: Cystic disease and dysplasia of the kidneys. In: Murphy WM, editor. Urological pathology. Philadelphia: WB Saunders; 1989. p. 483–524.)

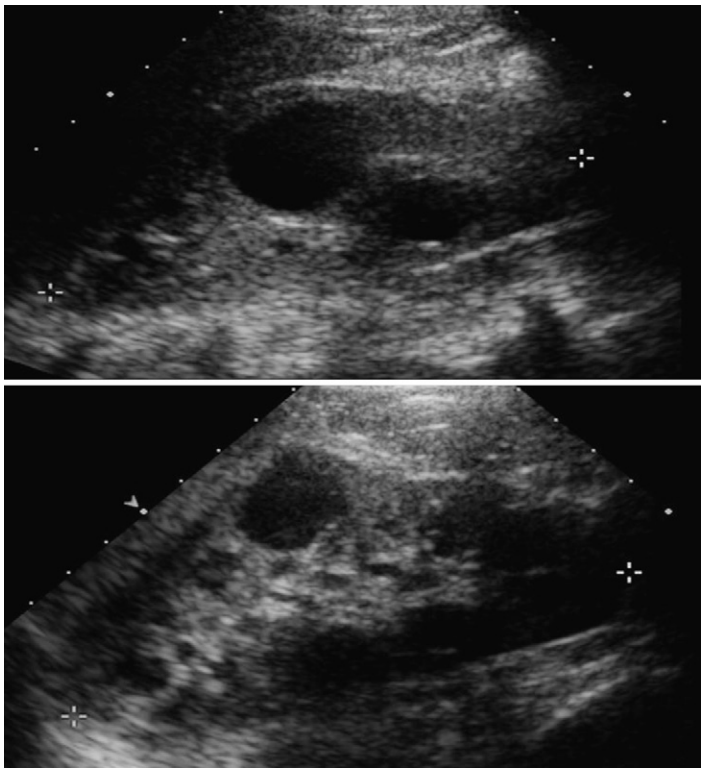


Figure 118–11. Renal ultrasonogram of 20-year-old patient newly diagnosed with autosomal dominant polycystic kidney disease. Note the presence of multiple cysts in both kidneys. (Courtesy of Marta Hernanz-Schulman, MD.)

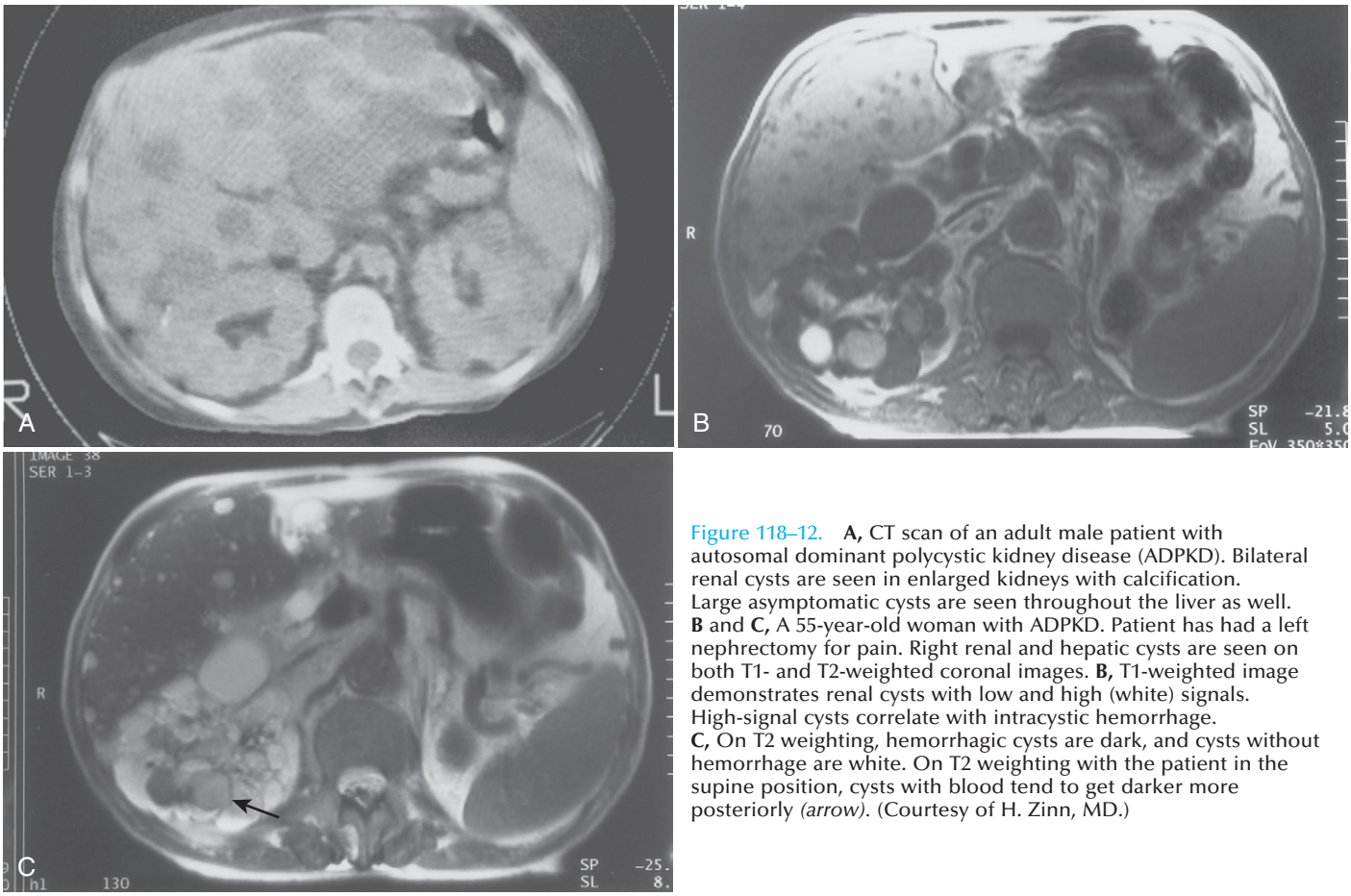


Figure 118–12. **A,** CT scan of an adult male patient with autosomal dominant polycystic kidney disease (ADPKD). Bilateral renal cysts are seen in enlarged kidneys with calcification. Large asymptomatic cysts are seen throughout the liver as well. **B** and **C,** A 55-year-old woman with ADPKD. Patient has had a left nephrectomy for pain. Right renal and hepatic cysts are seen on both T1- and T2-weighted coronal images. **B,** T1-weighted image demonstrates renal cysts with low and high (white) signals. High-signal cysts correlate with intracystic hemorrhage. **C,** On T2 weighting, hemorrhagic cysts are dark, and cysts without hemorrhage are white. On T2 weighting with the patient in the supine position, cysts with blood tend to get darker more posteriorly *(arrow)*. (Courtesy of H. Zinn, MD.)

seen in ARPKD, having no apparent macrocysts and showing only enlargement and homogeneous hyperechoic features. In such situations, one must look for a parent with ADPKD to confirm the diagnosis. With time, cysts often larger than 1 cm will develop in most children (Avni et al, 2002).

Treatment and Prognosis

Current therapy is directed toward lessening the complications of ADPKD and delaying the onset of ESRD. There is no known cure at this time. More than 60% of patients with ADPKD who do not yet have renal impairment have hypertension (Gabow et al, 1984), which can worsen renal function, cause cardiac disease, and predispose the patient to intracranial hemorrhage. **The complications of ADPKD can be reduced significantly by controlling the blood pressure**. There is no proven antihypertensive agent of choice; however, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor antagonists would seem to be logical first-line choices.

Chronic pain must be evaluated and entities such as infection, stone, and tumor treated accordingly. The use of chronic nephrotoxic analgesics (nonsteroidal anti-inflammatory diseases [NSAIDs]) must be avoided. The use of narcotic analgesics should be limited to acute pain episodes, because patient dependence on narcotics is a significant risk in this patient population. When conservative measures fail, surgical management must be considered. Ultrasonography- or CT-guided cyst aspiration is a straightforward procedure and may be both diagnostic and therapeutic. Surgical unroofing of multiple or very large cysts can potentially alleviate symptoms of pain and can be performed either laparoscopically or through open flank or dorsal lumbotomy incisions (Elzinga et al, 1992; Lee and Lee, 2003; Lee and Clayman, 2004). The effect of laparoscopic unroofing in those patients with hypertension was quite variable. Surgical intervention appears to only improve symptomatology and does not appear to either accelerate the decline of renal function or preserve declining renal function. Nephrectomy is indicated for symptomatic patients with ESRD.

Upper urinary tract infections are common in patients with ADPKD, especially women, and must be treated appropriately. If a patient with suspected pyelonephritis does not respond to an appropriate antibiotic, one must consider whether the infection may be present in a noncommunicating cyst (Gabow, 1993). Actual cyst infections can be quite challenging to treat due to poor cyst penetration of many antibiotics. Lipophilic antibiotics, such as trimethoprim-sulfamethoxazole, chloramphenicol, and fluoroquinolones, are the best choices (Schwab et al, 1987; Bennett et al, 1990). If appropriate antibiotic therapy fails, percutaneous or surgical drainage of infected cysts may be required. Complicating factors, such as urinary tract obstruction, renal or perinephric abscess, or urolithiasis, must be excluded.

Screening for asymptomatic berry aneurysms is not currently recommended UNLESS the patient has a family history of aneurysm or subarachnoid hemorrhage, previous aneurysm rupture, need for screening in preparation for major elective surgery, high-risk occupation (e.g., airline pilot), or a high anxiety level over the possibility

of ICA (Pirson et al, 2002). CT and MR angiography are the imaging studies of choice, although the former requires intravenous contrast. Aneurysm rupture occurs most often in people with larger aneurysms and/or poorly controlled high blood pressure. Screening of low-risk patients is not recommended because aneurysms are rare in this group, and most aneurysms that are found have a low risk of rupture. Conservative management is usually recommended for ADPKD patients with small (<7 mm) aneurysms detected by presymptomatic screening. Aneurysms that are greater than 7 to 10 mm in size have a higher risk of rupture (up to 2% per year for larger aneurysms). Cerebral aneurysms of this size and those that cause symptoms may be corrected with open surgical clipping or with endovascular procedures, placing a coil within the aneurysm. Smaller aneurysms that do not cause symptoms are much less likely to rupture and are not routinely corrected, except in patients with a history of a bleeding aneurysm.

Emerging Therapeutics

New studies are underway to better investigate the value of inhibition of the renin angiotensin system (RAS) in patients with ADPKD. New therapeutic approaches have also been undertaken to reduce the levels of cAMP in the kidneys of ADPKD patients.

Key Points: Autosomal Dominant Polycystic Kidney Disease

- ADPKD is the most common inheritable form of renal cystic disease.
- ADPKD most often becomes clinically apparent after age 30 years but may present at any age, including in utero.
- Ninety-nine percent of affected individuals have a mutation either of the *PKD1* gene on chromosome 16 or, less often, of the *PKD2* gene on chromosome 4.
- The protein products of *PKD1* and *PKD2* are polycystin-1 and polycystin-2, and they inhibit cell proliferation through several pathways.
- Cysts can be identified sonographically before age 20 years in almost all affected individuals.
- ADPKD is associated with a high incidence of liver cysts that increases with age.
- Signs or symptoms first occur between the ages of 30 and 50 years and include hematuria, flank pain, gastrointestinal symptoms, renal colic, and hypertension.
- Hepatic cysts occur in virtually all patients with ADPKD by the age of 50 years and are rarely symptomatic.
- ICAs of the circle of Willis (berry aneurysm) occur in 10% to 30% of patients, and approximately 9% of these patients die because of subarachnoid hemorrhages.
- The incidence of RCC in ADPKD patients is no higher than that of the general population.

JUVENILE NEPHRONOPHTHISIS/ MEDULLARY CYSTIC DISEASE COMPLEX

Juvenile nephronophthisis (NPH) (first described by Fanconi and colleagues in 1951) and medullary cystic disease (MCKD) (first reported by Smith and Graham in 1945) describe a group of genetic (inheritable) disorders with both similar and unique characteristics. Similarities include the gross and histopathologic appearance of the kidneys, with the hallmark being interstitial fibrosis. Distinguishing features are the mode of inheritance, the age of onset of ESRD, and the type of extrarenal organ involvement. Juvenile nephronophthisis is the more common condition and is responsible for 10% to 20% of cases of renal failure occurring in children and 1% to 5% of all patients undergoing dialysis or transplantation (Cantani et al, 1986).

Although either condition can occur sporadically, **juvenile nephronophthisis usually is inherited as an autosomal recessive trait.** It is genetically heterogeneous, and six responsible genes have been identified for various forms of NPH (Hildebrandt et al, 1997; Saunier et al, 1997; Olbrich, 2003; Mollet et al, 2005; Otto et al, 2003, 2005; Sayer et al, 2006). The majority of patients are homozygous for an *NPHP1* deletion (Konrad et al, 1996). *NPHP1*, *NPHP4*, *NPHP5*, and *NPHP6* mutations may be associated with the Senior-Løken syndrome (a combination of NPH and retinitis pigmentosa). **Medullary cystic disease usually is inherited in an autosomal dominant fashion** (50% of all offspring will have the disease) caused by mutations in either the *MCKD1* or *MCKD2* genes.

Juvenile nephronophthisis and medullary cystic disease both cause polydipsia and polyuria in more than 80% of cases, but not to the extent observed in patients with diabetes insipidus (Gardner and Evan, 1984; Cantani et al, 1986). The polyuria is caused by a renal tubular urinary concentrating defect that leads to salt wasting, and this process is resistant to vasopressin. Subsequently, a large dietary salt intake frequently is necessary. One major difference in the two entities is the presence of hypertension. There is no hypertension associated with juvenile nephronophthisis, while patients with medullary cystic disease can have significant hypertension. Renal failure usually ensues 5 to 10 years after initial presentation (Cantani et al, 1986). Another important difference between the two entities is that renal failure develops in patients with NPH at a mean age of 13 years and almost always before 25 years (Neumann et al, 1997). MCKD is a milder disease when it presents in early adulthood, but it will manifest in all patients by 50 years of age (Bernstein and Gardner, 1979). ESRD in patients with MCKD most often develops in the third or fourth decade.

Twenty percent of juvenile nephronophthisis families have extrarenal manifestations, while MCKD usually only affects the kidneys (Neumann et al, 1997). Sixteen percent of patients with juvenile nephronophthisis have associated **retinitis pigmentosa** (Hildebrandt et al, 1993). When the two entities coexist, the condition is referred to as renal-retinal or Senior-Løken syndrome.

Pathologically, NPH and MCKD are similar. Grossly, the kidneys are small to normal in size with multiple cysts at the corticomedullary junction. Histologically, there is a characteristic triad present that includes (1) irregular thickening and disintegration of the tubular basement membrane, (2) marked tubular atrophy with cyst development, and (3) interstitial cell infiltration with fibrosis.

Evaluation

Diagnosis of NPH/MCKD can be difficult early in its onset due to the relative vagueness and nonspecificity of symptoms; thus a high index of suspicion is required. Excretory urography and ultrasonography frequently fail to detect cysts because they are small (Chang and Udupa, 1989; Ala-Mello et al, 1998). Cysts may be seen on imaging studies if they are large enough (Rosenfeld et al, 1977), but, early in the disease, cysts are rarely visible. The parenchyma may also appear hyperechogenic secondary to

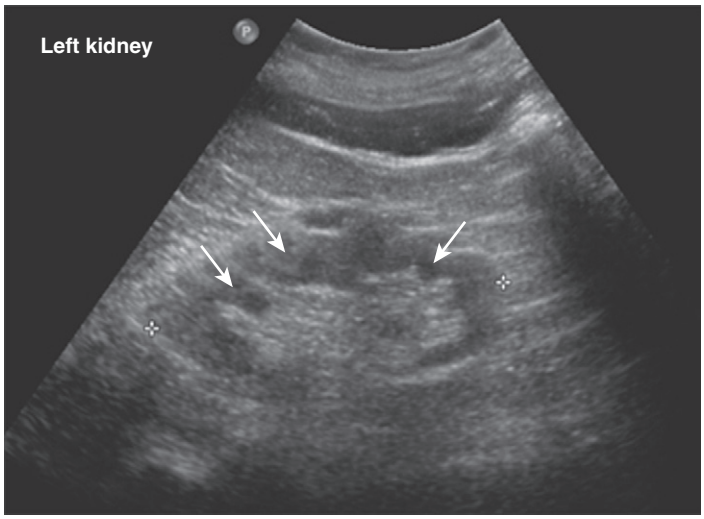


Figure 118–13. Features of medullary cystic kidney disease. Ultrasonogram demonstrating corticomedullary cysts, some of which are indicated by *arrows*. The hyperechogenicity is secondary to the tubulointerstitial fibrosis. (From Simms RJ, Eley L, Sayer JA. Nephronophthisis. Eur J Hum Gen 2009;17:406–16.)

tubulointerstitial fibrosis (Resnick and Hartman, 1990) (Fig. 118–13). Contrast-enhanced CT and MRI scans are more sensitive for detecting small corticomedullary and medullary cysts, but failure to detect cysts does not exclude the diagnosis.

Treatment

The treatment of NPH is supportive. Because of the tendency to sodium wasting, volume contraction, and renal azotemia, sodium replacement is indicated early in the course of the disease, and unnecessary sodium restriction or use of diuretics should be avoided. Later, dialysis and transplantation must be considered.

Key Points: Juvenile Nephronophthisis/Medullary Cystic Disease Complex

- Juvenile nephronophthisis, an autosomal recessive disease, is responsible for 10% to 20% of cases with renal failure in children and leads to early ESRD (early teens).
- Medullary cystic disease, an autosomal dominant disease, manifests in early adulthood.
- Polyuria, polydipsia, and hypertension are clinical hallmarks of these disease entities.
- Both have almost identical histology, with severe interstitial nephritis; many demonstrate cysts at the corticomedullary junction.

MULTIPLE MALFORMATION SYNDROMES WITH RENAL CYSTS

Renal cysts are a feature of several syndromes characterized by multiple malformations (see Table 118–2). Tuberous sclerosis and VHL disease are autosomal dominant disorders and are the ones most likely to be encountered by urologists. Meckel syndrome, Jeune asphyxiating thoracic dystrophy, and Zellweger cerebrohepatorenal syndrome are some of the more common autosomal recessive syndromes. Many of these conditions involve glomerular cysts, and some have cystic dysplasia as a feature.

Tuberous Sclerosis Complex (TSC)

Bourneville described tuberous sclerosis in 1880. It is usually an autosomal dominant neurocutaneous disorder with an incidence of up to 1 in 6000 individuals (Webb et al, 1991; O'Hagan et al, 1996). It is characterized by benign growths called hamartomas, which can develop in nearly every organ of the human body.

Classically, tuberous sclerosis has been described as the triad of *Bourneville phakomatosis* (epilepsy) (80% of cases), mental retardation (60% of cases), and adenoma sebaceum (facial angiofibromata) (75% of cases) (Lagos and Gomez, 1967; Pampigliana and Moynahan, 1976). Adenoma sebaceum are firm, discrete, red or brown telangiectatic papules located in the nasolabial folds, chin, and cheeks. They usually appear after the age of 2 years, gradually become more prominent with time and persist throughout life. An earlier skin lesion that is a white papule in the shape of an "ash leaf" is sometimes identified (Shepherd et al, 1991). An examination of the skin with ultraviolet light may reveal cutaneous lesions earlier and should be part of a diagnostic evaluation.

Definitive diagnosis, however, is no longer dependent on this triad but rather on the presence of certain major and minor clinical features (Roach et al, 1998). The diagnosis of TSC requires two major features (renal angiomyolipoma, facial angiofibromas or forehead plaques, nontraumatic ungual or periungual fibroma, three or more hypomelanotic macules, shagreen patch, multiple retinal nodular hamartomas, cortical tuber, subependymal nodule, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioleiomyomatosis) or one major plus two minor features (multiple renal cysts, nonrenal hamartoma, hamartomatous rectal polyps, retinal achromic patch, cerebral white matter radial migration tracts, bone cysts, gingival fibromas, "confetti" skin lesions, multiple enamel pits).

The kidneys of these patients may be free of lesions (Stillwell et al, 1987) or may display cysts, angiomyolipomas, or both (Figs. 118–14 and 118–15).

Genetics

Although it is transmitted as an autosomal dominant trait in 25% to 40% of cases, in the remainder, tuberous sclerosis occurs either sporadically or as an example of the genetic condition with variable or incomplete penetrance. Because it is a heterogeneous genetic disorder with variable manifestations, it usually is referred to as tuberous sclerosis complex (TSC). It is caused by mutations in one of two genes. ***TSC1* is located on chromosome 9 (9q34) and encodes the protein hamartin, and *TSC2* is on chromosome 16 (16p13) and encodes the protein tuberin** (Jones et al, 1999; Dabora et al, 2001; Sancak, 2005). Both of these genes are characterized as tumor suppressor genes, and the loss of function of either gene leads to hamartoma formation. Both hamartin and tuberin function as a complex to inhibit the mTOR (mammalian target of rapamycin) pathway. This pathway serves to modulate cell signaling pathways that are important in the regulation of cell growth and migration, as well as cell number and organ size. Therefore a mutation of either gene will lead to similar clinical manifestations.

Clinical Features

Renal involvement in TSC is second only to central nervous system abnormalities and includes predominately

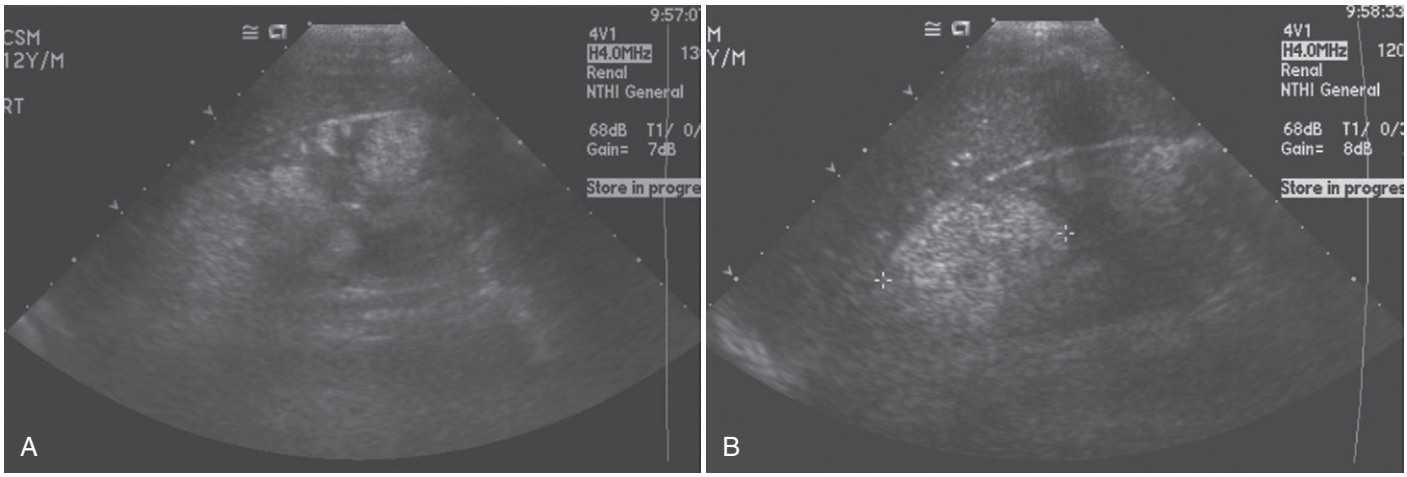


Figure 118–14. **A** and **B,** Renal ultrasonogram of 13-year-old patient with tuberous sclerosis. Multiple hyperechoic lesions of varying size are visible, consistent with angiomyolipomas. (Courtesy of Marta Hernanz-Schulman, MD.)

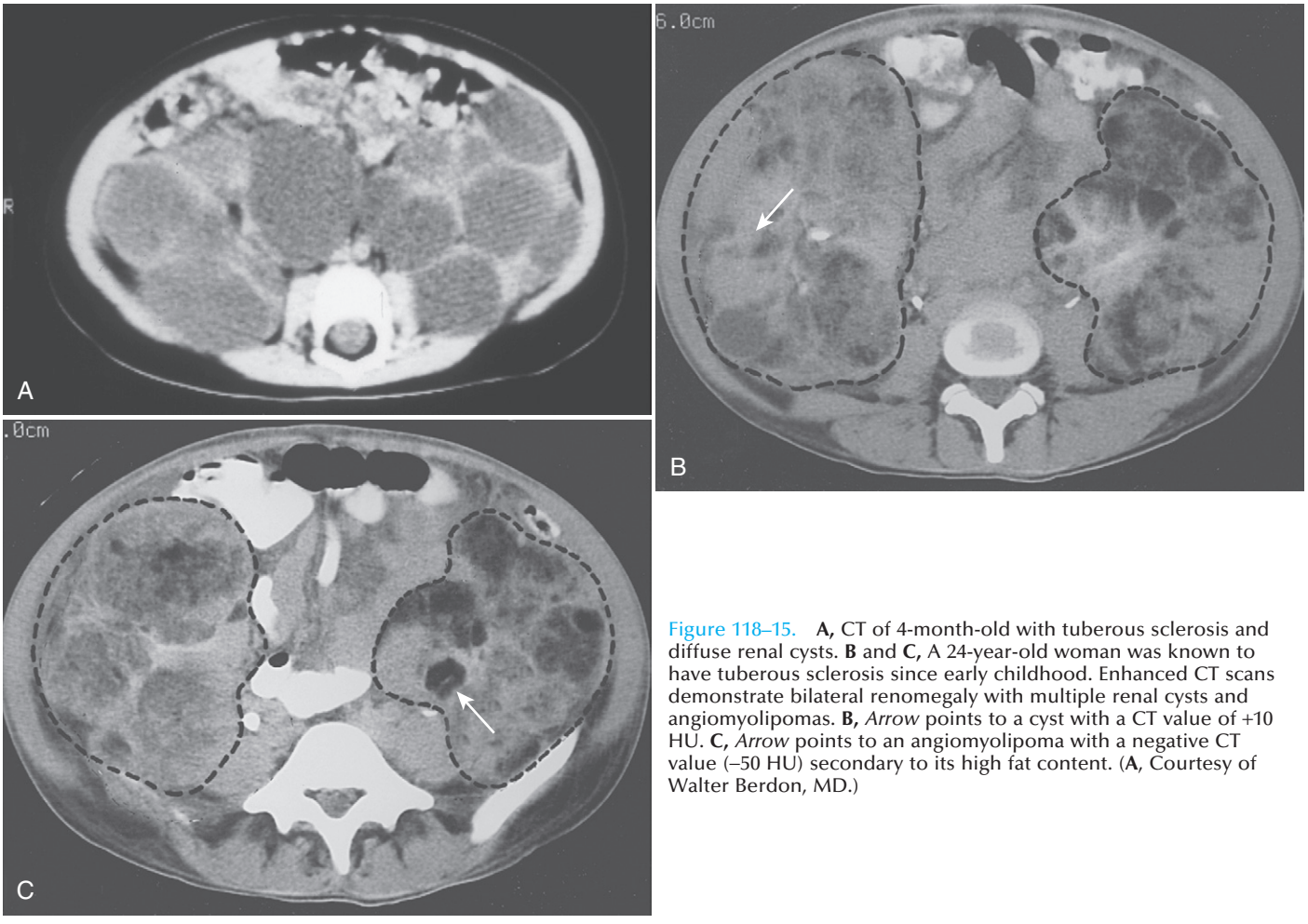


Figure 118–15. **A,** CT of 4-month-old with tuberous sclerosis and diffuse renal cysts. **B** and **C,** A 24-year-old woman was known to have tuberous sclerosis since early childhood. Enhanced CT scans demonstrate bilateral renomegaly with multiple renal cysts and angiomyolipomas. **B,** *Arrow* points to a cyst with a CT value of +10 HU. **C,** *Arrow* points to an angiomyolipoma with a negative CT value (–50 HU) secondary to its high fat content. (**A**, Courtesy of Walter Berdon, MD.)

angiomyolipoma (AML), renal cysts, and RCCs. AMLs are extremely common in TSC and are usually bilateral, multiple, and affect both genders, whereas in the general population, they are uncommon, usually single, and are found mainly in middle-age women. **Renal angiomyolipomas occur in 40% to 80% of patients with TSC** (Chonko et al, 1974; Gomez, 1979). They are rarely identified before the age of 6 years but are common after age 10 years (Bernstein et al, 1986). The primary risk of these lesions relates to their potential for to hemorrhage or mass effect. Abdominal or flank mass and tenderness, hypertension, and renal insufficiency can

also occur as a result of these lesions. By themselves, these lesions probably do not cause renal failure (Okada et al, 1982; Bernstein et al, 1986). Also, belying their aggressive histologic appearance, which is characterized by pleomorphism and mitoses, no evidence of metastases has been presented.

Unlike angiomyolipomas, renal cysts may be present in the first year of life, and cystic disease may be the presenting manifestation of TSC. **Renal cysts develop in approximately 20% of patients and most often manifest before 3 years of age; one third of children are younger than 1 year of age at presentation.** Patients with large cysts or polycystic kidney disease may be identified by in-utero ultrasonography or may present with an abdominal mass and distended abdomen in the first year of life. Most patients with renal cysts do not develop any serious renal compromise, but when the disease is more widespread within the kidney and large cysts are present, renal failure may develop in the milder form with polycystic kidney disease. If any renal failure develops, it is uncommon before the fourth decade (Glazier et al, 1996).

TSC2 and *PKD1* lie adjacent to each other in a tail-to-tail orientation on chromosome 16 at 16p13.3. Deletions inactivating both genes are associated with polycystic kidneys diagnosed during the first year of life or early childhood (*TSC2/PKD1* contiguous gene syndrome) (Brook-Carter et al, 1994; Sampson et al, 1997). Therefore TSC should be considered in children with renal cysts and no family history of PKD. Rarely, *TSC2/PKD1* contiguous gene syndrome can be diagnosed in adults (Martignoni et al, 2002). Patients with the contiguous gene syndrome usually reach ESRD at an earlier age than that of patients with ADPKD alone. Patients with *TSC1* or *TSC2* mutations without the contiguous gene syndrome also have an increased frequency of renal cysts. The combination of cystic kidneys and angiomyolipomas has been said to be virtually pathognomonic for tuberous sclerosis.

Association with Renal Cell Carcinoma

The numerous reports of RCC in patients with tuberous sclerosis make it clear that this association is more than coincidental and may be as frequent as 2% (Bernstein et al, 1986; Bernstein, 1993). However, the incidence of RCC is considerably less than that seen in VHL disease and ARCD of chronic renal failure. Compared with sporadic RCCs, there is a female predominance, earlier age of presentation, and increased bilaterality. Early detection is essential. RCC should be suspected in cases of enlarging lesions without demonstrable fat and in the presence of calcifications within the lesions.

Radiographic Evaluation

Sometimes both renal cysts and angiomyolipomas can be identified by ultrasonography in tuberous sclerosis, the former lesions being sonolucent and the latter having a fluffy, white appearance. When renal cysts are present without angiomyolipomas, the ultrasonographic appearance of the kidneys in tuberous sclerosis is very similar to that in ADPKD. Therefore it is not that unusual for a patient with cysts identified as typical of ADPKD to be diagnosed as having ADPKD, only to develop the stigmata of tuberous sclerosis a few years later. To help make the diagnosis, abdominal CT can be useful in demonstrating angiomyolipomas that may be present in the kidney or other organs (findings that are compatible with tuberous sclerosis) and in revealing cysts in other organs (compatible with ADPKD) (see Fig. 118–15). MRI or CT of the head may demonstrate the classic cranial calcifications associated with tubers or gliosis (Okada et al, 1982).

Treatment

Because more patients with tuberous sclerosis now survive their central nervous system lesions than in the past, the urologist is more likely to be asked to manage the renal problems (Stillwell et al, 1987). Shepherd and colleagues (1991) found that renal disease was the leading cause of death in these patients (11 of 40 deaths). Of these 11 patients, 2 died of metastatic RCC, 2 of massive hemorrhage associated with renal angiomyolipomas, and 6 of renal failure secondary to the cysts, angiomyolipomas, or both.

AMLs are benign lesions that usually are asymptomatic and do not require treatment. Large angiomyolipomas are more likely to bleed. Van Baal and colleagues (1994) have recommended careful monitoring of the size of angiomyolipomas and prophylactic embolization or surgical excision if they enlarge to greater than 4 cm. Annual surveillance with renal ultrasonography (RUS) or CT are necessary to assess for growth of the lesions and to detect the development of other complications. Renal-sparing surgery is indicated for symptoms such as pain and hemorrhage, growth of the lesions to the point it compromises renal function, and the inability to exclude RCC. Reports of hemorrhagic complications during pregnancy have led to the recommendation that patients with multiple or large AMLs be warned about the potential risk of pregnancy and estrogen administration.

Hypertension and renal failure must also be treated accordingly. Bilateral nephrectomy should be considered prior to transplantation due to the risk of life-threatening hemorrhage and the development of RCC.

Finally, in rodent models of TSC, treatment with rapamycin before the onset of disease reduces the development of renal tumors without affecting the number of precursor lesions (Kenerson et al, 2005). Phase I/II clinical trials of the mTOR inhibitor rapamycin have demonstrated reduction in the size of tuberous sclerosis–associated renal, lung, and brain tumors. Larger scale randomized control trials of mTOR inhibitors are currently underway (Clark and Cookson, 2008; Sampson, 2009).

von Hippel-Lindau Disease

In 1904, Eugene von Hippel, a German ophthalmologist, first described retinal angiomatosis—angiomatous lesions of the retina that caused blindness in association with similar cerebellar tumors. One of his patients developed renal cancer, and this was reported in 1921. In 1926, Arvid Lindau, a Swedish pathologist, published a series about patients with retinal and cerebellar tumors, with four of his patients also having renal cysts and renal cancer. He was also the first to propose these lesions had an inherited origin.

VHL disease is an autosomal dominant syndrome manifested by cerebellar and retinal hemangioblastomas; cysts of the pancreas, kidney, and epididymis; epididymal cystadenoma; pheochromocytoma; and clear cell RCC. It is found in all ethnic groups, both sexes are affected, and it has an incidence ranging from 1 in 30,000 to 1 in 50,000 individuals. It has over 95% penetrance by the age of 65 years in affected individuals. It is grouped with the phakomatoses (Sturge-Webber-Krabbe syndrome, TSC, and neurofibromatosis), because they all have a common inheritance pattern and propensity for neoplasm.

Etiology

VHL disease is caused by a germline mutation in the tumor suppressor gene known as *VHL*, located on

chromosome 3 (3p25) (Latif et al, 1993; Lesho, 1994; Kondo and Kaelin, 2001). A tumor suppressor gene is one in which both copies of the gene must be disabled for a cancer to develop. Seventy percent of patients will have a mutation of one *VHL* allele. As long as one copy of the *VHL* gene is producing functional VHL protein in each cell, tumors do not form. If a mutation occurs in the second copy of the *VHL* gene during a person's lifetime (another example of a "second hit" as proposed by Knudson's two-hit hypothesis (Knudson, 1991), the cell will have no working copies of the gene and will produce no functional VHL protein. A lack of this protein allows tumors characteristic of von Hippel-Lindau syndrome to develop. The discovery and characterization of the *VHL* gene, and its role in cell regulation, is a prime example of how discoveries in the basic science arena can revolutionize treatment of human disease (Clark and Cookson, 2008).

Clinical Features

The mean age at presentation is 35 to 40 years (Neumann et al, 1997). There is no sex preference for the disease or for RCC development. Sporadic RCC in individuals without VHL disease occurs more often in males and usually after age 50 years. **Renal cysts, the most common and often earliest manifestation, are seen in 76% of patients** (Levine et al, 1982). The cysts are bilateral in 75% of affected persons and multifocal in 87% (Reichard et al, 1998). RCC occurs in approximately 50% of affected persons. The renal cysts, as well as the tumors, usually are asymptomatic, although large tumors may cause pain or a mass. Hematuria may occur after rupture of the tumor into the pelvicalyceal system. When cysts are present, typically they are large. Only rarely do images demonstrate ADPKD, and, even less often, do cysts cause renal failure.

Pheochromocytoma occurs in 10% to 17% of affected persons and appears to be confined to specific families (Horton et al, 1976; Levine et al, 1982). Patients may present with seizures or dizziness secondary to hemangioblastomas of the central nervous system. **Cerebellar hemangioblastomas** usually become symptomatic between 15 and 40 years of age (Jennings and Gaines, 1988). These lesions are the most frequent, characteristic, and clinically specific tumors seen in VHL (Zbar et al, 1996; Shehata et al, 2008). Although benign tumors, they often result in major morbidity and mortality. They cause a mass effect because of their location, and, due to their vascular nature, they tend to rupture and bleed. **Retinal angiomas** (hemangiomas) frequently manifest early. Bleeding may cause blurred vision, retinal detachment, and blindness. Early diagnosis is important, because these tumors respond to laser therapy or cryotherapy. The pancreas is commonly involved with either cysts or true neoplasms. **Pancreatic cysts** can occur in up to 70% of patients with VHL but are usually asymptomatic and benign. Islet cell tumors occur in approximately 12% of VHL patients, and metastatic RCC of the pancreas is not unusual (Cheng et al, 1997; Kogire et al, 2000). Other clinical findings in patients with VHL can include **endolymphatic sac tumor, which is a papillary tumor of the petrous bone and can cause hearing loss; papillary cystadenomas of the epididymis; and the female counterpart, cystadenoma of the broad ligament** (Zbar et al, 1996; Shehata et al, 2008).

Because of the high incidence of RCC in patients with VHL disease, the urologist's primary role is careful surveillance so that small tumors can be identified and treated before they metastasize. Although central nervous system hemangioblastomas account for more than half of the deaths in these patients, metastatic RCC is also a major cause of mortality and, in some accounts, is the leading cause of death in this population (Maher et al, 1990; Reichard et al, 1998). Accordingly, annual or perhaps biannual CT examinations are advised.

Table 118–4

Classification of von Hippel-Lindau Disease

Type: Clinical Characteristic
1: Without pheochromocytoma
2: With pheochromocytoma
2A: Without renal cell carcinoma or pancreatic cysts
2B: With renal cell carcinoma and pancreatic cysts
2C: Familial pheochromocytoma without hemangioblastomas and clear cell renal cell carcinoma

Classification

Patients with VHL are subdivided into groups based on disease presentation, and each group has a specific *VHL* gene aberration. VHL type 1 is the most common form of the disease and is characterized by a tendency to develop tumors in the eyes, brain, spinal cord, kidney, and pancreas. VHL type 2 is less common. VHL type 2 differs from type 1 in that affected family members are at high risk to develop pheochromocytomas. VHL type 2 is further divided into types 2A, 2B, and 2C. Individuals in families with VHL type 2A develop pheochromocytomas but have a low risk for RCC (this type of VHL is uncommon). Those with VHL type 2B develop pheochromocytomas and have a high risk for RCC. Patients with type 2C VHL have familial pheochromocytoma without hemangioblastomas and clear cell RCCs (Zbar et al, 1996; Shehata et al, 2008) (Table 118–4).

Histopathology

When present, renal cysts and tumors often are multiple and bilateral. The cysts usually simulate simple benign cysts, with flattened epithelium that some investigators consider precancerous. In VHL patients, cysts larger than 2 cm are more likely than smaller cysts to have components of RCC (Poston et al, 1993). Frank cancer usually appears between the ages of 20 and 50 years (Jennings and Gaines, 1988). Others found that the hyperplastic cells lining cysts frequently resembled the clear cell type of RCC, the most common type in these patients (Loughlin and Gittes, 1986). Ibrahim and colleagues (1989) studied the cysts adjacent to carcinomas and found, much as in tuberous sclerosis, that the karyotype resembled that of the tumors. This similarity is evidence that the hyperplastic cells of the cyst lining are precursors of the carcinomas.

Solomon and Schwartz (1988) believed that a spectrum of pathology is found within the kidneys of patients with VHL disease. At one extreme is a simple cyst with a single layer of bland epithelium. The next step is a typical proliferative cyst with layers of epithelial cells. In the ensuing step, there are complex neoplastic projections into the cyst lumen. If one agrees with the arbitrary distinction between adenoma and carcinoma on the basis of size, the next stage would be adenoma. Finally, there is the full-blown RCC. All of these stages may be found within a single kidney (Solomon and Schwartz, 1988).

Evaluation

In patients with a known family history of VHL, the diagnosis can be made based on the presence of a single retinal or cerebellar hemangioblastoma, RCC, or pheochromocytoma (Melmon and

Rosen, 1964; Couch et al, 2000). In such families, germline mutations may be present without clinical manifestations, and the patient should be screened for this mutation. For those patients who do not have a family history, the diagnosis requires two or more cardinal manifestations, such as retinal or cerebellar hemangioblastomas, or a single hemangioblastoma and an additional characteristic lesion.

Ultrasonography is useful in diagnosing the typical benign renal cystic features of VHL disease: absence of internal echoes, well-defined margins, and acoustic enhancement. On CT, sharp thin walls are seen around homogeneous contents without enhancement after contrast medium injection. Because multiple lesions (cysts, tumors, or both) are often present, CT frequently is more useful than ultrasonography. CT often is useful in examining the adrenal glands for pheochromocytomas.

When the lesions are small, it is impossible to distinguish tumors from cysts. In such cases, patients should have regular CT scans with narrow-screen collimation (Levine et al, 1982). With larger lesions, and whenever RCC is suspected, renal angiography with magnification or subtraction is advisable. This type of study helps to reveal any additional tumors and indicates the appropriateness of conservative surgery (Kadir, 1981; Loughlin and Gittes, 1986). Intra-arterial administration of epinephrine is sometimes helpful, because it causes vasoconstriction of the normal vessels but has no effect on tumor neovascularity.

MRI has not been very useful for small tumors of the kidney, unless the shape of the kidney is altered. The lesions on MRI have a signal intensity that is similar to that of normal renal parenchyma on T1- and T2-weighted images. However, gadolinium is useful because it enhances RCC. The heterogeneous nature of the larger tumors makes them more readily diagnosed (Rominger et al, 1992).

Table 118–5

Screening Protocol for Patients and Families with von Hippel-Lindau Disease

STUDY	AFFECTED PERSONS	RELATIVES AT RISK
Physical exam	Annual	Annual
24-hour urine collection for metanephrins and normetanephrins	Annual	Annual
Fundoscopy	Annual	Annual (age 10-60 years)
Gadolinium MRI brain scan (or CT)	Every 3 years from age 10-50 years; every 5 years thereafter	Every 3 years from age 15-40 years then every 5 years until age 60 years
Abdominal evaluation	Annual renal US with abdominal CT scan every 3 years (more frequently if multiple renal cysts present)	Annual renal US with abdominal CT scan every 3 years from age 20-65

CT, computed tomography; MRI, magnetic resonance image; US, ultrasonogram.
From Maher ER, Yates JR, Harris R, et al: Clinical features and natural history of von Hippel-Lindau disease. QJ Med 1990;7:1151–63.

Screening

The genetic nature of VHL disease mandates careful screening. However, because of molecular genetic advances, the screening process for the disease in family members can now be more selective. Previously, asymptomatic relatives required routine ophthalmoscopic examination to rule out retinal angiomas, as well as frequent abdominal CT scans. Now only genetically affected family members require screening (Table 118–5).

Treatment

The treatment of patients with VHL requires a multidisciplinary approach, because the involvement of multiple organ systems and numerous medical problems are inherent to this disease. Because the tumors that characterize VHL disease are frequently multiple, bilateral, and recurrent, the goals of treatment for patients who have VHL disease are not as straightforward as the goals of treatment for patients who have sporadic tumors. Close surveillance and minimization of surgical procedures constitute the mainstay of treatment. **For patients who have VHL disease, and all patients who have hereditary cancer syndromes, the goal of treatment is cancer control, not cancer cure, and preservation of functional parenchyma to avoid the morbidity associated with renal or adrenal loss.** In patients who have VHL disease, surgical resection is performed with the understanding that microscopic disease probably is left behind. At present, open nephron-sparing surgery should be considered the standard of care for treating low-grade RCC in the setting of VHL disease. Patients with high-grade disease are still probably best served with bilateral nephrectomy. With the objective of sparing as much renal parenchyma as possible and preventing metastasis of the lesions already present, it is not curative surgery (Reed and Parekh, 2009). Although this approach does not reduce the risk of recurrence, reported to be 75% to 85%, the 10-year disease specific survival rates are quite high (81% to 94%) (Malek et al, 1987; Steinbach et al, 1995; Roupret et al, 2003; Ploussard et al, 2007). Classically, the survival rate after nephrectomy has been only 50%. Because most of these tumors are low grade, a nephron-sparing approach provides very good survival rates while avoiding the diminished quality of life that comes with bilateral nephrectomy and subsequent dialysis/transplantation. Laparoscopic and percutaneous image-guided ablative techniques, such as radiofrequency ablation and cryoablation, have also been used and are currently under investigation.

Given the high risk of multiple and bilateral pheochromocytomas in patients who have VHL disease, bilateral adrenalectomy can lead to the loss of all adrenal function. Preservation of normal adrenocortical function should be a primary surgical goal, because medical replacement therapy is associated with decreased quality of life (Telenius et al, 1989). Partial adrenalectomy can preserve normal adrenal function and avoid this morbidity. Identification of small pheochromocytomas may enable laparoscopic preservation of adrenal function and maintain quality of life in these complicated patients. The small size and lack of function of these tumors make them ideal for partial adrenalectomy; however, recurrences may develop in 15% of patients (Walther et al, 1999a, 1999b).

Papillary cystadenomas (PCs) of the epididymis can be unilateral or bilateral and occur in approximately 10% to 26% of men who have VHL disease (Horton et al, 1976; Lamiell et al, 1989). They seem to have no malignant potential. Surgery is not performed for these lesions unless the patient experiences severe pain.

Key Points: Multiple Malformation Syndromes

- Tuberous sclerosis complex is an autosomal dominant condition that includes the triad of epilepsy, mental retardation, and adenoma sebaceum. It is associated with renal cysts (20% of patients), renal angiomyolipoma (40% to 80%), and RCC (2%).
- There are two different gene mutations associated with tuberous sclerosis: *TSC1* on chromosome 9 and *TSC2* on chromosome 16.
- von Hippel-Lindau (VHL) disease is an autosomal dominant syndrome associated with cerebellar and retinal hemangioblastomas; cysts of the pancreas, kidney (76%), and epididymis; pheochromocytoma (10% to 12%); and clear cell RCC (50% incidence and 30% to 40% of death).
- VHL disease is associated with an inherited mutation of the *VHL* gene on chromosome 3.
- *VHL* is a tumor suppressor gene involved in regulation of hypoxia-inducible factor (HIF) target genes, including *VEGF*; abnormal or absent VHL leads to increased tissue levels of specific growth factors and, in particular, VEGF, the most prominent growth factor in RCC.

MULTICYSTIC DYSPLASTIC KIDNEY

Multicystic dysplastic kidney is a developmental anomaly resulting in multiple cysts of varying sizes, without identifiable normal renal parenchyma. These kidneys have no function by definition, and usually the contralateral kidney is normal and exhibits compensatory hypertrophy. Only unilateral involvement is compatible with life. The kidney often does not have a reniform appearance, and they are typically associated with an atretic ureter with no connection between glomerulus and calyces. Typically, the kidney has the appearance of "a bunch of grapes," with little stroma between the cysts (Fig. 118–16). Renal size is highly variable, ranging from a small nubbin of tissue to a very large mass that fills most of the abdomen. In fact, MCDK is the second most common cause of an abdominal mass in a newborn, after hydronephrosis.

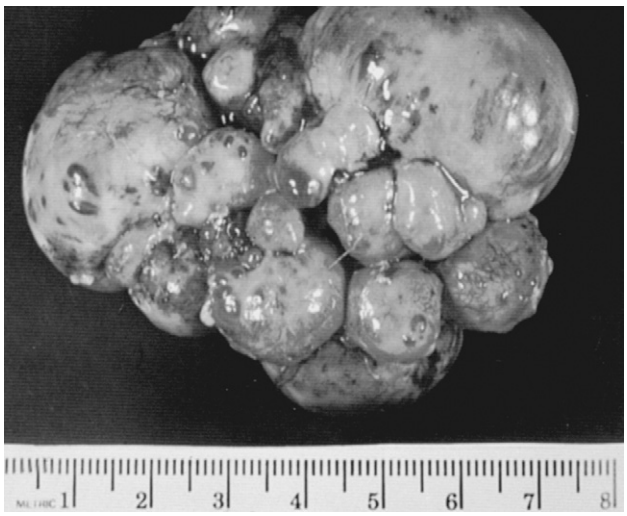


Figure 118–16. A typical multicystic dysplastic kidney having the appearance of a bunch of grapes. The kidney was composed almost entirely of cysts with very little stroma.

MCDK can be of two types: the infundibulopelvic type, with the atresia involving both the renal pelvis and the ureter, and the less common hydronephrotic type, where only the upper ureter is atretic (Felson and Cussen, 1975). In both cases, the ureters are absent or atretic, and the renal vessels are hypoplastic. MCDK can also rarely be secondary to ureteroceles that have caused complete obstruction. It can rarely be seen in one half of a duplex kidney (usually the upper pole associated with an ectopic ureter) or in other abnormalities such as a horseshoe kidney.

Etiology

Many theories have been offered to explain the etiology of MCDK. Clearly, it is a result of an error in renal development. Some have proposed that the multicystic kidney is an extreme form of obstructive hydronephrosis that occurs secondary to atresia of the ureter or renal pelvis. The fact that the left kidney is the one more often affected supports this view, because this is the kidney more often associated with primary obstructive megaureter (Glassberg, 1977) and ureteropelvic junction obstruction (Johnston et al, 1977). Several investigators have attempted to establish an animal model of MCDK by ligating the ureter at various points in gestation (Beck, 1971; Tanagho, 1972; Fetterman et al, 1974). This approach is not effective in middle or late gestation; early ligation of the fetal lamb ureter produces renal dysplasia but not multicystic dysplasia (Beck, 1971). Similarly, other investigators have been able to induce dysplasia, but no one as yet has been able to induce a multicystic dysplastic kidney.

Another theory stems from the "ureteric bud theory" as proposed by Mackie and Stephens (1975). This theory hypothesizes that MCDK may result from abnormal interaction between the ureteric bud and metanephric mesenchyme. Mutations in genes such as *EYA1, SIX1, WNT, WT-1, GNF, AT2,* and *PAX2* are known to have important roles in ureteric bud development and have been identified in multiple human syndromes with renal dysplasia (Pope et al, 1999). These studies linking genetic mutations with renal dysplasia support the ureteric bud theory in the pathogenesis of MCDK and may also explain its frequent association with other urinary tract anomalies (Hains et al, 2009). In addition, Hildebrandt (1894) suggested that failure of the union between the ureteric bud and the metanephric blastema leads to cystic dilatation in the latter; this hypothesis, like the obstructive view, is supported by the high incidence of concomitant ureteral atresia.

Although the ureteric bud theory and the obstruction theory may at some level go hand in hand, there is no question that there are several gene-mediated processes that go awry in the process of making a developmentally abnormal MCDK. These genes and their proteins are currently potential targets for both therapeutic intervention and research to further elucidate the mechanism that cause MCDK.

Clinical Features

Multicystic dysplasia is the most common type of renal cystic disease and is the second most common cause of an abdominal mass in infants (Longino and Martin, 1958; Melicow and Uson, 1959; Griscom et al, 1975). Most cases in the current era are diagnosed by prenatal ultrasonography, and the incidence is 1 per 1000 to 4000 live births (Kalyoussef et al, 2006). There is a male preponderance (55% to 70%), and studies conflict as to whether MCDK is more common on the right or left side.

The contralateral system frequently is abnormal. For example, contralateral ureteropelvic junction obstruction is found in 3% to 12% of infants with MCDK, and contralateral vesicoureteral reflux is seen in 18% to 43% of infants (Heikkinen et al, 1980; Atiyeh et al, 1992; Flack and Bellinger, 1993; Wacksman and Phipps, 1993; Al-Khaldi et al, 1994).

The natural history of MCDK is benign; the incidence of complications is extremely rare; and approximately 40% of MCDKs will spontaneously involute. Although anecdotal case reports exist, available large series data indicate that MCDK is not associated with an increased risk for hypertension or neoplasm (Wacksman and Phipps, 1993; Tilemis, 2003; Truong et al, 2003; Rabelo et al, 2004; Farnham et al, 2005; Narchi, 2005a, 2005b; Onal and Kogan, 2006). Although hypertension is a rare but recognized sequela of MCDK, it is reasonable to follow patients with MCDK conservatively. The primary care provider should monitor patients with multicystic dysplastic kidney for hypertension, abdominal mass, and urinary tract infection.

Histopathology

Multicystic kidneys with large cysts tend to be large with little stroma, whereas those with small cysts generally are smaller and more solid. Likewise, the blood supply is variable, ranging from a pedicle with small vessels to no pedicle at all (Parkkulainen et al, 1959). Usually the ureter is partly or totally atretic, and the renal pelvis may be absent. Griscom and colleagues (1975) referred to the form without a renal pelvis as "pyeloinfundibular atresia" and reported finding no evidence of communication between the cysts. However, others have shown distribution of contrast medium among the cysts by means of connecting tubules (Saxton et al, 1981). Microscopically, the cysts are lined by low cuboidal epithelium, are surrounded by collars of spindle cells, and are filled with proteinaceous or sanguinous fluid. They are separated by thin septa of fibrous tissue and primitive dysplastic elements, especially primitive ducts. Immature-appearing cartilage is often present in the tissue. Frequently, immature glomeruli are present, and, on occasion, a few mature glomeruli are seen (Fig. 118–17).

Key Points: Multicystic Dysplastic Kidney

- Multicystic dysplastic kidney is a developmental anomaly resulting in multiple cysts of varying sizes, is without identifiable normal renal parenchyma, is associated with active expression of genes involved with nephrogenesis, and has a changing morphology.
- Kidneys usually get smaller or disappear from view on imaging studies (i.e., renal aplasia), very occasionally increase in size, and, very rarely, are associated with Wilms tumor.
- There is no clear indication for removal of the kidney, unless an increased amount of solid tissue is identified.
- Large series data indicate that MCDK is not associated with an increased risk for hypertension or neoplasm.
- Fifteen percent of patients have associated contralateral reflux, and debate exists regarding whether or not to obtain a voiding cystourethrogram in all or only in those with some degree of fullness in the contralateral collecting system.

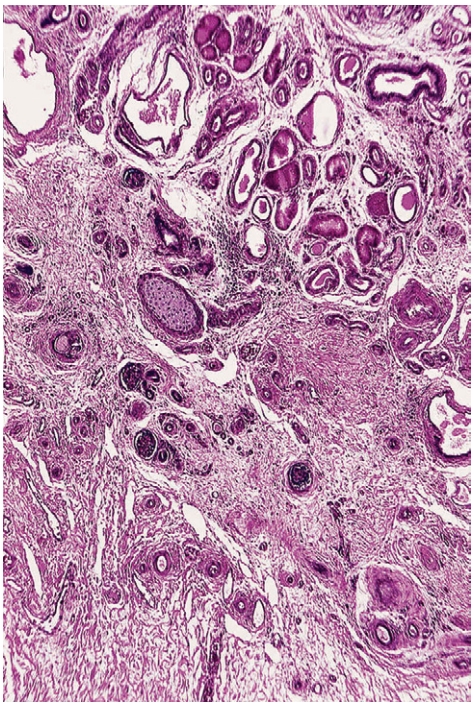


Figure 118–17. Disorganized development of kidney consistent with multicystic dysplastic kidney showing primitive glomeruli, tubules, and mesenchyme. (From Ordonez NG, Rosai J. Urinary tract. In: Rosai and Ackerman's surgical pathology. 9th ed. Edinburgh: Mosby; 2004.)

Evaluation

MDCK is most often identified by prenatal ultrasonography, and, in newborns, ultrasonography is usually repeated (one within the first few days of life and another one month later) to confirm the diagnosis and to evaluate the contralateral kidney and bladder. In a few cases, it is difficult to differentiate multicystic kidney disease from severe hydronephrosis (Gates, 1980; Hadlock et al, 1981). **In general, the multicystic kidney has a haphazard distribution of cysts of various sizes without a larger central or medial cyst and without visible communications between the cysts. Frequently, very small cysts appear between the large cysts. By comparison, in ureteropelvic junction obstruction, the cysts or calyces are organized around the periphery of the kidney; connections usually can be demonstrated between the peripheral cysts and a central or medial cyst that represents the renal pelvis; and there is an absence of small cysts between the larger cysts** (Fig. 118–18).

In these difficult cases, radioisotope studies may be helpful. **Hydronephrotic kidneys usually show some function on a dimercaptosuccinic acid (DMSA) or technetium-99m mercaptoacetyltriglycine (^{99m}Tc MAG3) scan, whereas renal uptake is seldom seen in multicystic kidneys** (Fig. 118–19). Angiography reveals an absent or small renal artery in the multicystic kidney, but this study is rarely indicated. Cystoscopy may reveal a hemitrigone and absent ureteric orifice on the affected MCDK side; however, more often an orifice is present, but retrograde urography demonstrates ureteral atresia. Again, this study is seldom performed. As mentioned previously, voiding cystourethrography (VCUG) is usually indicated in the workup, because of the high incidence of reflux into the contralateral single

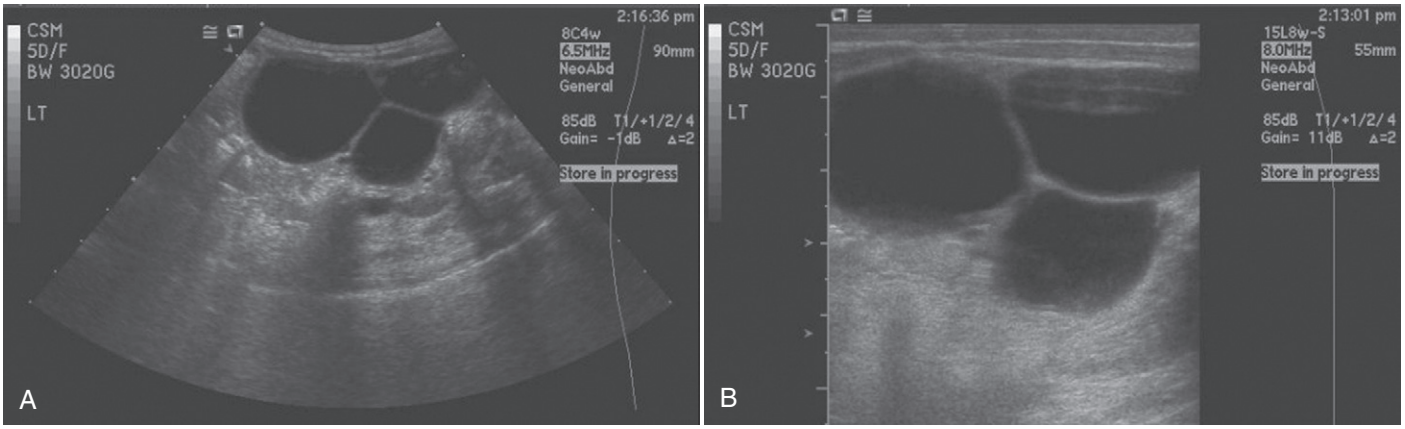


Figure 118–18. **A** and **B,** Renal ultrasonogram of large left multicystic dysplastic kidney. There are multiple large cysts. No definite renal cortex is seen.

functioning kidney. Some authors, however, have started to advocate that VCUG is of little value if serial high-quality ultrasound findings are consistent with MCDK and demonstrate a normal bladder and contralateral kidney. A VCUG is not necessary unless clinically indicated later in life (Ismaili et al, 2005; Welch and Wacksman, 2005; Onal and Kogan, 2006).

Treatment and Prognosis

It has often been stated that the multicystic kidney can be ignored unless its bulk is inconvenient (Pathak and Williams, 1964; Griscom et al, 1975), and attention should be directed instead to identifying any abnormalities of the contralateral urinary tract. Large MCDKs are known to interfere with respiratory and digestive function simply due to their mass effect. Intervention for these large masses may need to be undertaken to relieve these problems. Nephrectomy for MCDK may also be necessary to correct the rare cases of associated hypertension or if a cyst has ruptured spontaneously or secondary to trauma (to relieve pain or hemorrhage).

A nonfunctioning hydronephrotic kidney could be mistaken for a multicystic kidney, although complete nonfunction on a nuclear medicine study is unusual in kidneys affected by ureteropelvic junction obstruction. Fortunately, if the correct diagnosis is missed in such a case, there are unlikely to be significant consequences, because a totally nonfunctioning hydronephrotic kidney is rarely salvageable and probably will cause no problems other than a predisposition to infection or hypertension.

The probability of malignant transformation is estimated to be extremely low and believed by many to be nonexistent (Avni et al, 1987; Gordon et al, 1988; Wacksman and Phipps, 1993; Narchi, 2005b). Less than 15 cases of malignant degeneration have been reported in MCDK. Roughly half have been identified as RCC, half as Wilms tumor, and there has been one reported mesothelioma. Recommendations for addressing this risk range from early nephrectomy of the MCDK to minimal follow-up with no imaging and only periodic abdominal examination by the primary care physician (PCP). Many pediatric urologists will do ultrasound surveillance every 3 to 12 months, but there has been no conclusive evidence that this is beneficial or cost effective (Perez et al, 1998; Onal and Kogan, 2006).

There has also been much debate in contemporary series regarding hypertension in MCDK. The various case reports and small series that were reviewed offer conflicting data on the issue. An additional confounding factor is that MCDK is often associated with contralateral abnormalities, such as ureteropelvic junction (UPJ) obstruction and reflux. Thus groups have had difficulty determining if hypertension is associated with contralateral abnormalities or with MCDK. Several small series have reported patients with MCDK and hypertension who were cured with nephrectomy (Javadpour et al, 1970; Susskind et al, 1989; Angermeier et al, 1992; Webb et al, 1997; Snodgrass, 2000). Although these reports demonstrate that hypertension can occur with MCDK, most large series support the rarity of hypertension in association with MCDK. Several studies, including the report from the Multicystic Kidney Registry in 1993, have demonstrated the incidence of hypertension in patients with MCDK and long-term follow-up to be less than 1% (Wacksman and Phipps, 1993; Gough et al, 1995; Perez et al, 1998; Farnham et al, 2005). One study, however, demonstrated a much higher incidence of hypertension than the other MCDK series (Seeman et al, 2001). This could be due to the more stringent measurement of blood pressure applied, although these patients were examined at a much later age than in other series, which may also have contributed to the higher detected incidence of hypertension. Two of those four patients with hypertension had concomitant abnormalities; thus it was concluded that increased blood pressure is mainly associated with contralateral kidney damage regardless of the presence or absence of the dysplastic kidney (Seeman et al, 2001). In summary, hypertension is a rare but recognized sequela of MCDK. However, there is a suggestion that with more diligent monitoring, its incidence would increase. Therefore it is reasonable to follow patients with MCDK conservatively, realizing that hypertension can exist and should be assessed periodically. Because hypertension can be discovered on an examination by the primary care physician, the potential for this problem does not require urologic follow-up, only an informed primary care physician and family (Farnham et al, 2005).

BENIGN MULTILOCULAR CYST (CYSTIC NEPHROMA)

Benign multilocular cyst (multilocular cystic nephroma) is a multilocular cystic neoplastic lesion in the kidney that falls in a spectrum of diseases along with multilocular cyst with partially differentiated Wilms tumor, a multilocular cyst with nodules of Wilms tumor, or cystic Wilms tumor (Fig. 118–20). These four lesions form a spectrum, with benign multilocular cyst at the most benign extreme and

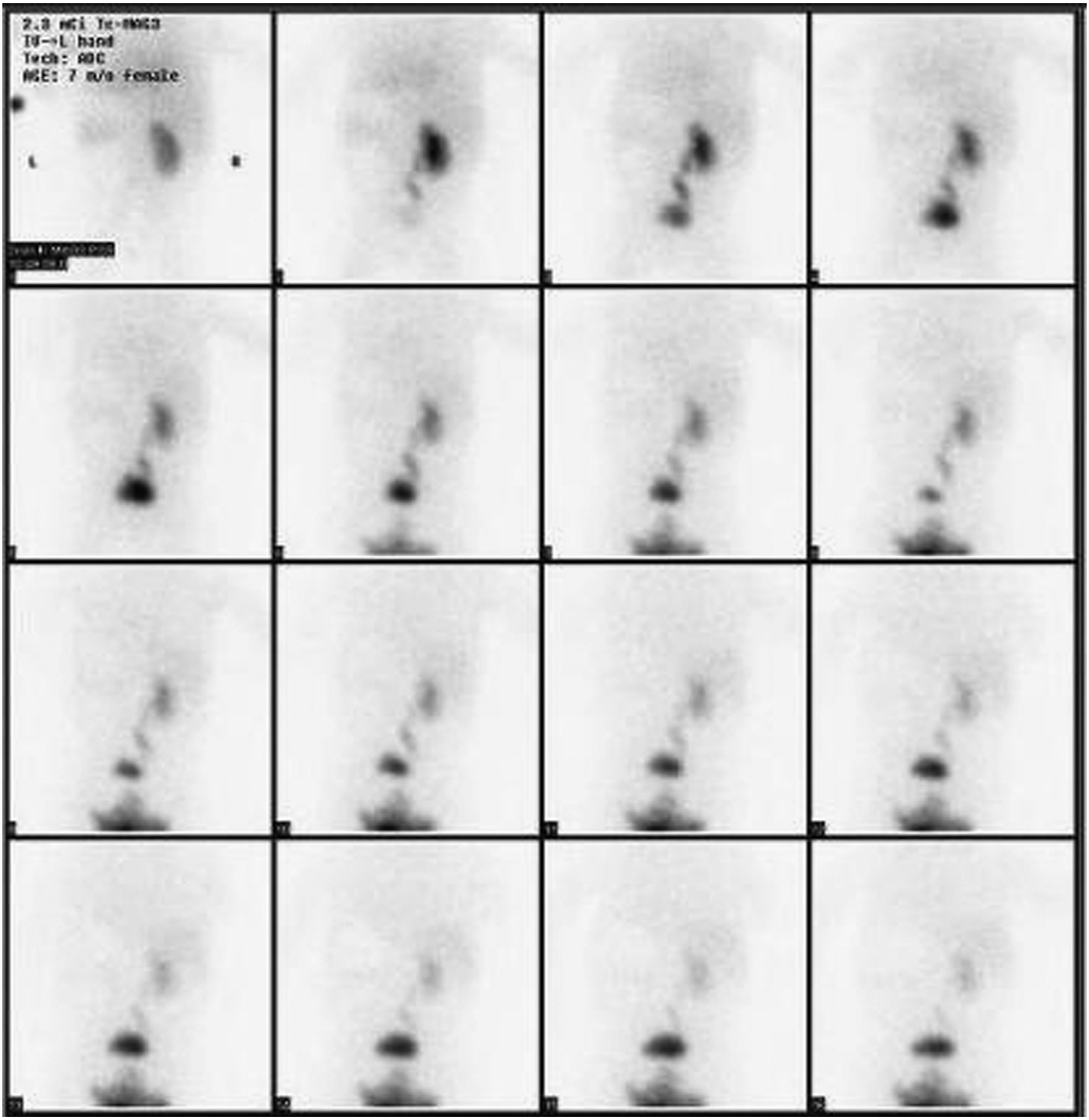


Figure 118–19. MAG3 renogram revealing a normally functioning right kidney and no function on the left, which is consistent with a left multicystic dysplastic kidney.

cystic Wilms tumor at the most malignant extreme. There has been some debate as to whether these lesions represent a spectrum of one disease with a common etiology.

A multilocular cyst is not a renal segment affected by multicystic kidney disease; these conditions differ clinically, histologically, and radiographically. However, controversy continues about whether the multilocular cyst is a segmental form of renal dysplasia (Powell et al, 1951, Osathanondh and Potter, 1964; Johnson et al, 1973), a hamartomatous malformation (Arey, 1959), or a neoplastic disease (Boggs and Kimmelsteil, 1956; Christ, 1968; Fowler, 1971; Gallo and Penchansky, 1977). The confusion arises in part from the variability of the histologic picture: the appearance of the primitive stroma; the maturity of tubular, and, even on occasion, of muscle elements; and the degree of epithelial atypical that differs not only from patient to patient but also within the same lesion.

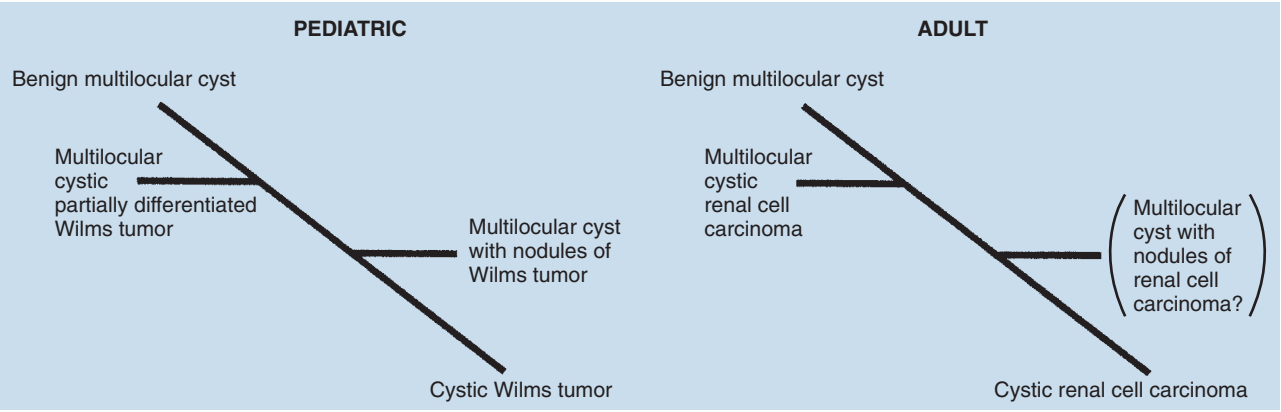


Figure 118–20. The spectrum of multilocular cystic lesions in children and adults. There is no evidence that one lesion can convert into the other. Benign cystic, partially differentiated Wilms tumor and multilocular, cystic renal cell carcinoma act as benign lesions. When nodules of tumor are present, the lesion should be considered malignant, although the prognosis of this lesion, as well as cystic Wilms tumor and cystic renal cell carcinoma, seems to be better than that of the corresponding solid lesions. It is not clear whether clinical examples of "multilocular cyst with nodules of renal cell carcinoma" actually exist, but this entity is placed in the spectrum for consideration. For simplicity, the multilocular-appearing lesions of other cystic tumors (e.g., cystic oncocytoma, cystic hamartoma of the renal pelvis) are not included in the figure.

Clinical Features

The great majority of patients (95%) present before the age of 4 years or after 30 years. If less than 4 years of age, the patient is 2 times as likely to be male; if older than 30 years of age, the patient is 8 times as likely to be female (Eble and Bonsib, 1998).

The signs and symptoms differ according to the age at presentation. **In children, an asymptomatic flank mass is the most common finding, whereas most adults present with either a flank mass, abdominal pain, or hematuria.** The bleeding is felt to be secondary to herniation of the cyst through the transitional epithelium into the renal pelvis (Uson and Melicow, 1963; Aterman et al, 1973; Madewell et al, 1983).

Seven cases of bilateral benign multilocular cysts of the kidney have been described (Castillo et al, 1991), and recurrence after excision has been rarely described (Geller et al, 1979). There are also at least two instances in which multilocular cysts arose in kidneys known to have been normal previously (Uson and Melicow, 1963; Chatten and Bishop, 1977). Such cases support a neoplastic theory of the origin of this lesion.

Histopathology

These lesions are bulky and are circumscribed by a thick capsule. Normal renal parenchyma adjacent to the lesion frequently is compressed by it. The lesion may extend beyond the renal capsule into the perinephric space or renal pelvis. The loculi, which range from a few millimeters to centimeters in diameter, do not communicate. They contain clear, straw-colored or yellow fluid and are lined by cuboidal or low columnar epithelial cells. In some cases, eosinophilic cuboidal cells project into the cyst lumen, creating a hobnail appearance (Madewell et al, 1983). The septa of a benign multilocular cyst are composed of fibrous tissue in which well-differentiated tubules may be present, but poorly differentiated tissues and blastemal cells are not present (Joshi and Beckwith, 1989).

In children, although there may be a continuum from benign multilocular cyst to cystic Wilms tumor, and although all of these lesions may be derived from similar cells or tissues, no evidence suggests that one entity transforms into another. Furthermore, **none of the genetically determined conditions associated with Wilms tumor (e.g., hemihypertrophy, aniridia) has accompanied a benign multilocular cyst** (Banner et al, 1981).

In adults, there also is a spectrum of multilocular cystic lesions. Multilocular cystic RCC in adults falls in the spectrum between a benign multilocular cyst and a cystic malignant tumor, such as a **multilocular cystic RCC, a cystic RCC, a cystic oncocytoma, or a cystic hamartoma of the renal pelvis** (Eble and Bonsib, 1998; Kirsh et al, 1999). The cystic component of the tumor at the carcinomatosis end of the spectrum in both children and adults (i.e., cystic Wilms tumor and cystic RCC) improves the prognosis of the malignant lesion (Kirsh et al, 1999). In adults, as in children, there is no evidence that one lesion can convert into another (Fig. 118–21).

Key Points: Benign Multilocular Cyst

- A benign multilocular cyst is a benign, nondysplastic, neoplastic lesion that occurs most commonly either before the age of 4 years, most frequently in males, or after the age of 30 years, predominantly in females.
- The only way to determine the diagnosis of a multilocular cystic lesion identified on imaging studies, in either a child or adult, is by surgical excision.
- Benign multilocular cyst is thought to fall at the benign end of a spectrum of the same disease process that also includes multilocular cyst with partially differentiated Wilms tumor, multilocular cyst with nodules of Wilms tumor, or cystic Wilms tumor at the most malignant end of the spectrum.

Evaluation

A number of tests may be useful, including ultrasonography, CT, MRI, cyst puncture with aspiration and double-contrast cystography, and arteriography. **Ultrasonography and CT can**

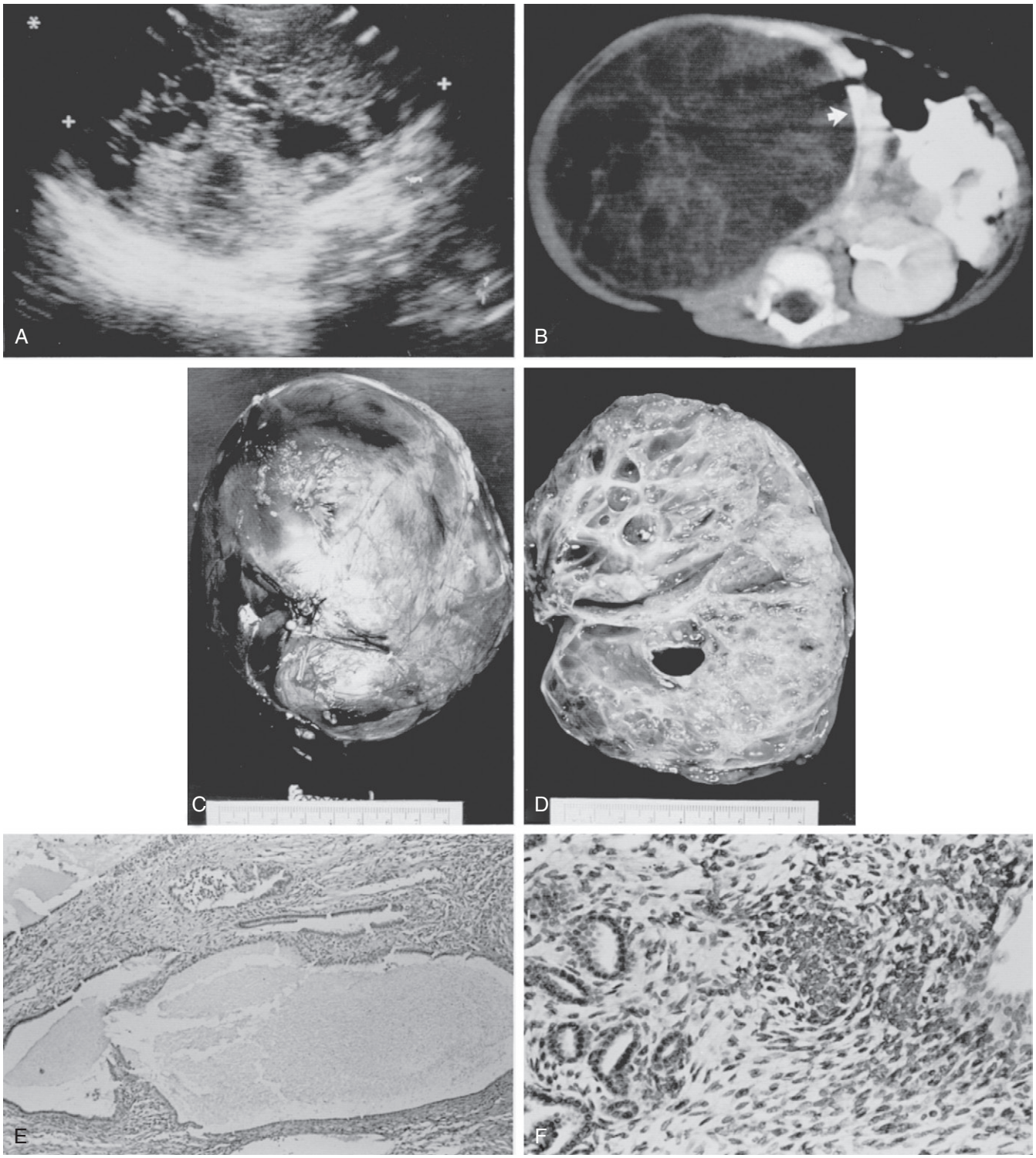


Figure 118–21. A 4-year-old girl with a right-sided abdominal mass. **A,** Renal ultrasonogram shows multiple cysts throughout the left kidney. **B,** On contrast medium–enhanced CT scan, a large, smoothly outlined left renal mass is seen with fine septa throughout the mass. Residual preserved parenchyma and the pelvicalyceal system are compressed medially and pushed to the contralateral side *(arrow)*. **C,** Uncut gross specimen reveals a smooth-walled, encapsulated renal mass. **D,** Cross section of mass reveals multiple noncommunicating loculations. **E,** On histology, a hypocellular cystic area is seen with monotonous stroma (100×). **F,** Between loculi, nests of blastemal cells are visualized along with tubular elements *(left),* making the diagnosis of multilocular cyst with partially differentiated Wilms tumor (200×).

distinguish multicystic kidneys from multilocular cysts, but neither study is sufficiently reliable to distinguish between multilocular cysts, multilocular cysts with foci of Wilms tumor or adenocarcinoma, mesoblastic nephromas, cystic Wilms tumors, and clear cell sarcomas. Typically, the septa are highly echogenic with sonolucent loculi, although, if there is debris in a loculus, it may appear more solid. On CT, the septa are less dense than normal parenchyma. Calcification is rarely visible in such lesions in children (Madewell et al, 1983).

Treatment

The treatment for any multilocular cystic lesion, even the most benign variant, is nephrectomy. If the lesion is localized enough and there is well-preserved normal tissue, excision of the lesion or partial nephrectomy is feasible. Children who have a multilocular cyst with nodules of Wilms tumor or a cystic Wilms tumor should be treated as for Wilms tumor, according to the National Wilms Tumor Study (NWTS) recommendations for the appropriate stage of disease, recognizing the generally favorable outlook. Similarly, cystic RCC in adults should be managed as a malignant lesion, however, again recognizing its better prognosis. In adults, benign multilocular cysts more often are associated with larger amounts of normal renal tissue, making partial nephrectomy more often feasible.

If enucleation or partial nephrectomy is chosen, recurrence is possible. However, with more Wilms tumors being treated by local excision, the case for enucleation or partial nephrectomy combined with close follow-up by ultrasonography and CT is stronger, even if malignancy is found within the lesion. By comparison, if a clear cell sarcoma is found after enucleation, the remaining ipsilateral renal tissue should be removed, because of the aggressiveness of this cancer. The recurrence of a multilocular cyst not containing malignancy probably reflects inadequate excision of the initial lesion.

SIMPLE CYSTS

Simple cysts are the most common cystic lesions found in the human kidney. They are usually oval to round, may be solitary or multiple, unilateral or bilateral, and are filled with plasma-like clear or straw-colored fluid (Nahm and Ritz, 2000; Terada et al, 2002). They are not connected to any part of the nephron, although they may originate initially from a portion of the nephron.

Simple cysts may manifest at any time in utero and have been diagnosed as early as 14 weeks of gestation. Ultrasonography done on 29,984 fetuses in succession revealed 0.09% of 11,000 pregnancies to have renal cysts (Blazer et al, 1999). Between birth and 18 years of age, the incidence of simple renal cysts is fairly stable, ranging from 0.1% to 0.45%, with an average incidence of 0.22% (McHugh et al, 1991). However, in adults the frequency rises with age, with an incidence of 20% by age 40 years and as high as 50% after age 60 years (Kissane and Smith, 1975; Laucks and McLachlan, 1981). Most reports show no gender predilection; however, in at least two studies, men were affected more frequently than women (Bearth and Steg, 1977; Tada et al, 1983).

Clinical Features

In both children and adults, cysts rarely call attention to themselves. Instead, they are discovered incidentally on ultrasonography, CT, or urography. However, cysts can produce an abdominal mass or pain, hematuria secondary to rupture into the pelvicalyceal system, and hypertension secondary to segmental ischemia (Rockson et al, 1974; Lüscher et al, 1986; Papanicolaou et al, 1986). Cysts can cause calyceal or renal pelvic obstruction as well (Wahlqvist and Grumstedt, 1966; Evans and Coughlin, 1970; Hinman, 1978; Barloon and Vince, 1987). They may or may not increase in size with time.

Cysts can rupture into the pelvicalyceal system, maintain a communication, and become a pseudocalyceal diverticulum. The reverse is also possible: Closure of the communication of a diverticulum can create a simple cyst (Mosli et al, 1986; Papanicolaou et al, 1986). These two sequences of events can be distinguished only by histologic examination. Theoretically, diverticula should have linings of transitional epithelium, whereas simple cysts should be lined by a single layer of flattened or cuboidal epithelium.

Key Points: Simple Cysts

- Simple cysts are seldom seen in children; in adults, simple cysts are seen increasingly more frequently with age.
- To diagnose a benign simple cyst on ultrasonography, it should (1) have no internal echoes, (2) have a sharply defined, thin, distinct smooth wall, (3) be spherical or oval with no internal echoes, and (4) have good transmission of sound waves with acoustic enhancement behind the cyst. When these criteria are not met, CT with contrast enhancement must be performed.
- Relevant guidelines for determining when to explore or remove a complex cyst are often based on the Bosniak CT classification (Table 118–6).

Evaluation

Most simple cysts are identified incidentally. One can safely make the diagnosis of a classic benign simple cyst by ultrasonography when the following criteria are met: **(1) absence of internal echoes, (2) presence of a sharply defined, thin, distinct wall with a smooth and distinct margin, (3) good transmission of sound waves through the cyst with consequent acoustic enhancement behind the cyst, and (4) a spherical or slightly ovoid shape** (Goldman and Hartman, 1990). If all of these criteria are satisfied, the chance that malignancy is present is negligible (Fig. 118–22) (Lingard and Lawson, 1979; Livingston et al, 1981).

Table 118–6

Bosniak's Classification of Simple and Complex Cysts

Category I
Simple benign cyst with (1) good through-transmission (i.e., acoustic enhancement), (2) no echoes within the cyst, (3) sharply, marginated smooth wall; requires no surgery

Category II
Looks benign with some radiologic concerns, including septation, minimal calcification, and high density; requires no surgery

Category II F
Although calcification in wall of cyst may even be thicker and more nodular than in category II, the septa have minimal enhancement, especially those with calcium; requires no surgery

Category III
More complicated lesion that cannot confidently be distinguished from malignancy, having more calcification, more prominent septation of a thicker wall than a category II lesion; more likely to be benign than malignant; requires surgical exploration and/or removal

Category IV
Clearly a malignant lesion with large cystic components, irregular margins; solid vascular elements; requires surgical removal

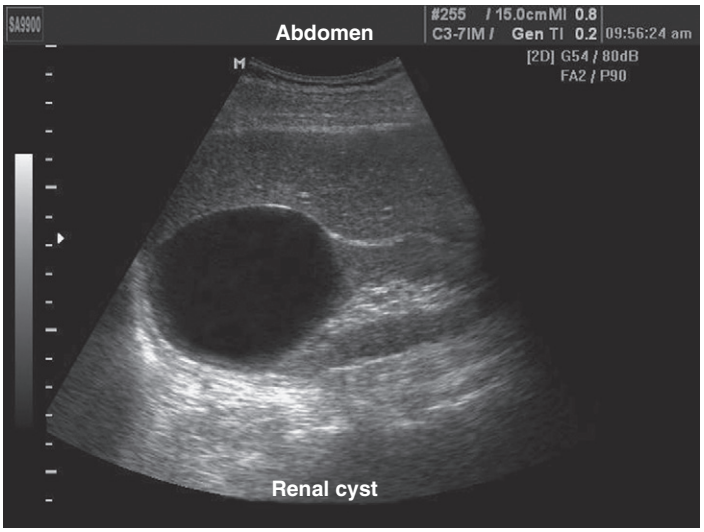


Figure 118–22. Ultrasonographic appearance of a 4-cm simple renal cyst. Note this meets the definition of a true simple cyst: (1) absence of internal echoes; (2) sharply defined, thin, distinct wall with a smooth and distinct margin; (3) good transmission of sound waves through the cyst with consequent acoustic enhancement behind the cyst; and (4) spherical or slightly ovoid shape.

When some of these criteria are not met (e.g., when there are septations, irregular margins, calcifications, or suspect areas), further evaluation by CT, or perhaps needle aspiration or MRI, is indicated (Bosniak, 1986). A cluster of cysts is another indication for further study, because they may be hiding a small carcinoma. CT is better than ultrasonography in defining such a camouflaged lesion (Bosniak, 1986). Peripelvic cysts often require CT confirmation, because they frequently are interspersed between structures of the collecting system and hilum, which can create artificial echoes (Bosniak, 1986).

The CT criteria for a simple cyst are similar to those used in ultrasonography: (1) a sharp, thin, distinct, smooth wall and margin, (2) a spherical or ovoid shape, and (3) homogeneous content. When these criteria are respected, the accuracy of diagnosis of a simple cyst by CT approaches 100% (Fig. 118–23) (McClennan et al, 1979). The density ranges from –10 to +20 HU, similar to the density of water, and no enhancement should occur after the intravenous injection of contrast medium.

When the cyst fluid is hyperdense (i.e., between 20 and 90 HU), it still is likely to be a simple cyst if no enhancement occurs when intravenous contrast agent is injected

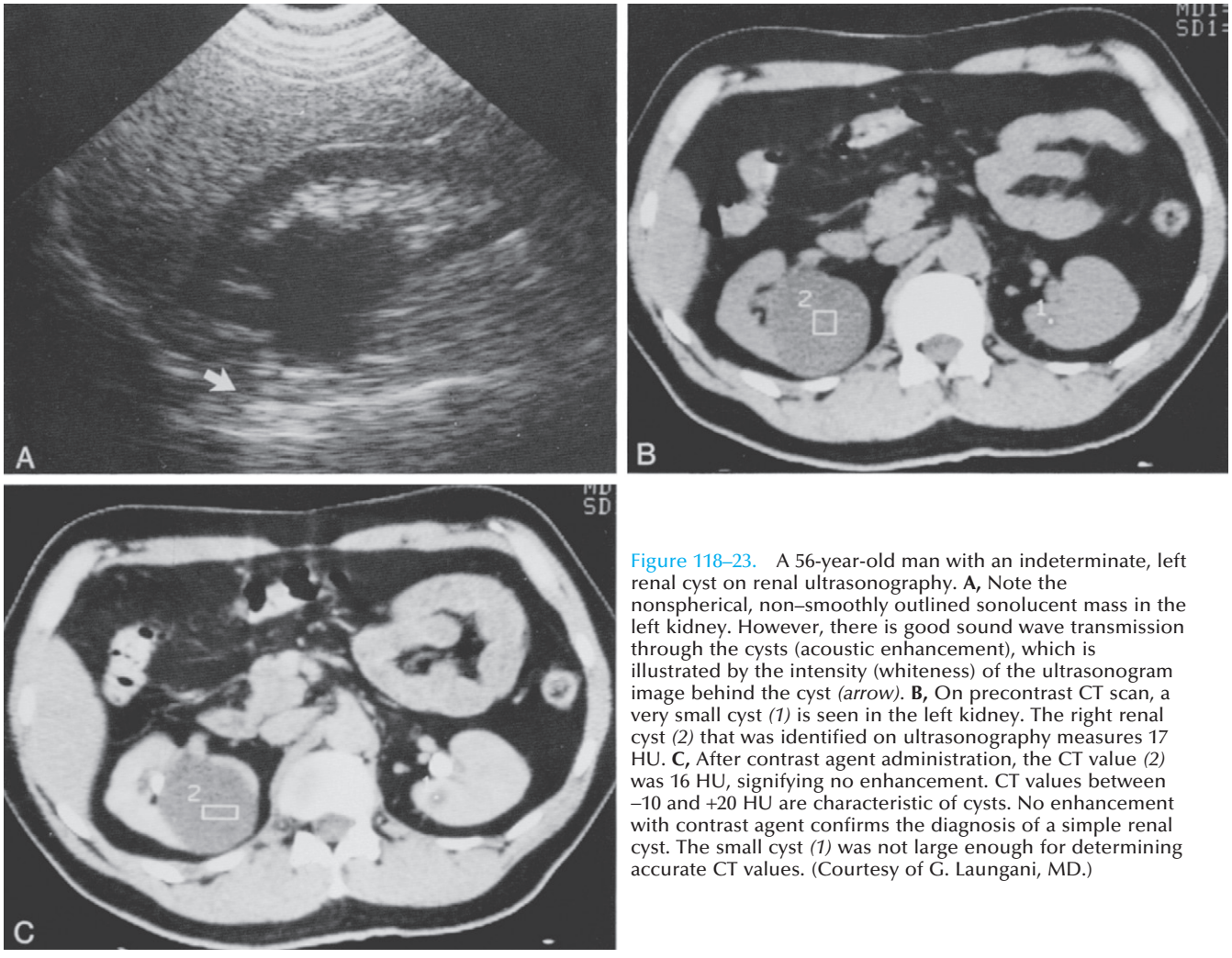


Figure 118–23. A 56-year-old man with an indeterminate, left renal cyst on renal ultrasonography. **A,** Note the nonspherical, non–smoothly outlined sonolucent mass in the left kidney. However, there is good sound wave transmission through the cysts (acoustic enhancement), which is illustrated by the intensity (whiteness) of the ultrasonogram image behind the cyst *(arrow)*. **B,** On precontrast CT scan, a very small cyst *(1)* is seen in the left kidney. The right renal cyst *(2)* that was identified on ultrasonography measures 17 HU. **C,** After contrast agent administration, the CT value *(2)* was 16 HU, signifying no enhancement. CT values between –10 and +20 HU are characteristic of cysts. No enhancement with contrast agent confirms the diagnosis of a simple renal cyst. The small cyst *(1)* was not large enough for determining accurate CT values. (Courtesy of G. Laungani, MD.)

and if the other criteria of CT and ultrasonography are met. Hyperdense cysts must be evaluated with narrow window settings to make sure that they are homogeneous. Other criteria that must be met to avoid further evaluation of hyperdense cysts (e.g., cyst puncture or exploration) include size (the lesion should be 3 cm or smaller) and location (at least one fourth of the cyst's circumference should extend beyond the renal contour so that the smoothness of a good portion of the cyst can be evaluated) (Bosniak, 1991; Hartman et al, 1992). **Because cysts have no blood vessels and do not communicate directly with nephrons, they should not enhance; enhancement therefore implies vascular tissue or contrast medium mixing with fluid.** Enhancement of the lesion with contrast is taken as proof of vascularity within the lesion, and thus there should be a high index of suspicion for neoplasm.

When ultrasonographic or CT criteria are not met, conditions other than a simple cyst must be considered, such as complicated cysts (i.e., those containing blood, pus, or calcification) and cystic neoplasms. Cyst puncture and aspiration with or without contrast medium injection has been popular in the past, but with current imaging modalities, the need for cyst puncture is very rare. The remaining indications for cyst puncture are (1) suspected infection, in which case puncture may be therapeutic as well as diagnostic, (2) the presence of low-level echoes on ultrasonography but a classic cyst on CT, and (3) a borderline lesion in a poor surgical candidate.

Two percent of simple cysts and 10% of RCCs contain calcium deposits, but calcification in simple cysts appears to be peripheral, whereas in tumors it is more central. When the cysts are numerous and bilateral, differentiation from ADPKD may be difficult if liver cysts are not also found. Because of the obvious implications, it is important to avoid a diagnosis of ADPKD in questionable cases, unless a familial history consistent with autosomal dominant transmission can be documented or the diagnosis confirmed by genetic testing.

MRI offers little information beyond that available from ultrasonography and CT, although it is more specific in identifying the nature of the cyst fluid. Marotti and colleagues (1987) found that if the fluid has low signal intensity (similar to that of urine) on T1-weighted images, the cyst is benign even if the wall is thick or septa are present. If this report is substantiated by additional studies, MRI may prove valuable in deciding which indeterminate cysts are benign and which should be considered for exploration. The T2-weighted images identify bloody fluid with an extremely bright image.

Classification

In an attempt better categorize surgical and nonsurgical cysts in the kidney, Bosniak suggested a classification in 1986 that was clarified further in 1997 and modified by Israel and Bosniak in 2003 (see Table 118–6).

Category I cysts are the typical benign cysts. Category II cysts are benign cystic lesions that are minimally complicated, such as by septations, small calcifications, infection, or high density, and do not require surgery. For example, when all the criteria for a simple cyst are met, except that a fine line of calcification or a short segment of slightly thickened calcification is seen in the wall or septa, the lesion should be considered a benign cyst, and exploration is not required. Another example is the cyst with fine traversing strands, perhaps containing calcium. In this case, exploration is not required unless the septa are numerous, irregular, or thick.

Category II F cysts (Israel and Bosniak, 2003) are complex cysts that cannot be classified either as category II or III. These lesions may contain increased calcification. The calcification may even be thicker and nodular, but although the septa may have minimal enhancement those septa with calcium do not enhance. Calcification seems to represent a less significant finding in making a lesion suspicious as a malignancy than previously thought. More focus is placed on tissue enhancement. There is little concern if calcification increases with time but much concern if the wall or septa becomes thicker or irregular. **Category II F does not require surgical exploration** (Israel and Bosniak, 2003) (Fig. 118–24).

Category III cysts are more complicated lesions with radiologic features that are also seen in malignancy. One example is the lesion with more extensive calcification, especially if the wall is not pencil-point thin or is irregular. Other category III cysts are those with septations, suggesting a multilocular cystic lesion, or chronic infection with a thickened wall. These lesions are more problematic and require a surgical approach that is individualized. In some cases, one might consider violating the Gerota fascia to expose the kidney for examination of the lesion or partial nephrectomy.

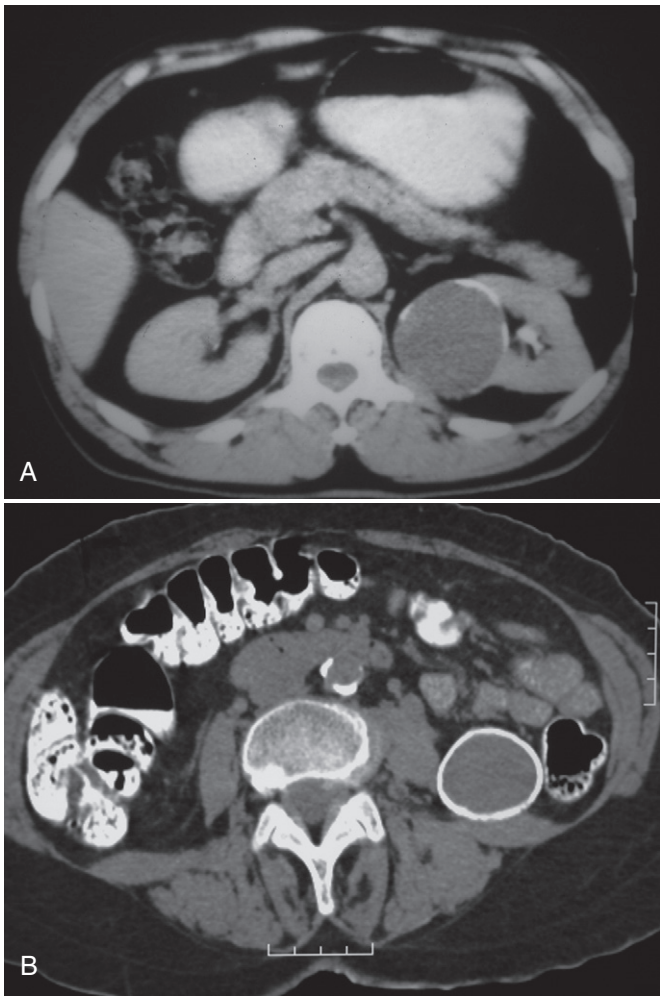


Figure 118–24. **A** and **B,** Two examples of Bosniak category II F cysts with diffuse calcification but no enhancement of septa on CT. (Courtesy of Jeffrey Newhouse, MD.)

Bosniak category IV lesions are cystic malignant tumors and are dealt with as such, namely, by radical nephrectomy.

Treatment and Prognosis

Once malignancy has been ruled out, surgical intervention for an asymptomatic cyst is not indicated (Gordon et al, 1979; Bartholomew et al, 1980; Ravden et al, 1980; Siegel and McAlister, 1980). Large renal cysts may cause abdominal or flank pain, although this pain may be caused by a coexisting problem (i.e., nephrolithiasis), and other sources of pain should be ruled out. Other symptoms that may arise as a result of simple cysts are pain resulting from hemorrhage into the cyst or calyceal or infundibular obstruction due to cyst impingement. In rare cases, hypertension may occur, presumably from cyst compression causing segmental renal ischemia of the surrounding renal parenchyma. Cyst infection is a rare but potentially severe complication, with patients presenting with fever, flank pain, and, often, a sympathetic pleural effusion (Torres, 2008). Most of these patients are women, the most common pathogen is *Escherichia coli,* and urine cultures can often be negative.

Treatment of the simple cyst must thus be directed to the symptomatology. When a benign simple cyst causes pyelocalyceal obstruction or hypertension, the problem may be corrected either surgically, by unroofing the cyst, or percutaneously, by aspirating the fluid and perhaps injecting a sclerosing agent, particularly if fluid has reaccumulated after an earlier aspiration. Several sclerosing agents have been used, including glucose, phenol, iophendylate (Pantopaque), bismuth phosphate, and absolute ethanol, but none has been sufficiently impressive for its use to become dominant (Holmberg and Hietala, 1989). Infected cysts must be drained and appropriate antibiotics given. Percutaneous resection, intrarenal marsupialization (Hubner et al, 1990; Hulbert and Hunter, 1990; Meyer and Jonas, 1990), and laparoscopic unroofing (either transperitoneally or retroperitoneally) are all reasonable options for the treatment of symptomatic simple cysts.

Unilateral renal cystic disease is characterized by cysts of varying size appearing side by side, often more numerous at one pole. Except for its unilateral location, no extrarenal cyst formation, and the fact that these patients show no genetic background or progressive deterioration in **renal** function, the gross and histologic findings of are indistinguishable from those of asymmetrical ADPKD (Lee et al, 1978; Kossow and Meek, 1982). It is important not to overdiagnose unilateral simple cyst disease, because the entity itself is rare, and when first identified in an individual, it is more likely to represent a unilateral asymmetrical presentation of ADPKD. Because the entity seems to represent nothing more than multiple simple cysts lying side by side within a kidney, it seems reasonable to consider it as a variation of the presentation of simple cysts. Now that genetic studies are becoming available for ADPKD, tuberous sclerosis, and VHL disease, the diagnosis of unilateral renal cystic disease can more readily be confirmed (Fig. 118–25).

MEDULLARY SPONGE KIDNEY

The condition known as medullary sponge kidney (also known as precalyceal canalicular ectasia) was recognized by Beitzke in 1908, and its radiographic features were described by Lenarduzzi in 1939. The name of this disorder dates from a 1949 publication by Cacchi and Ricci. **It is characterized by tubular dilatation of the distal portion of the collecting ducts with numerous associated cysts and diverticula strictly confined to the medullary pyramids.** These dilated ducts have the appearance of the bristles on a brush and often are more ectatic and filled with calcifications, giving an appearance suggestive of a "bouquet of flowers" (Fig. 118–26).

Clinical Features

Medullary sponge kidney is usually a benign process, and it may remain asymptomatic and undetected for life. Clinical presentation usually occurs after age 20 years, with the most common presentation being renal colic (50% to 60%), followed by urinary tract infection (20% to 33%) and gross hematuria (10% to 18%) (Kuiper, 1976). The incidence of medullary sponge kidney in stone formers differs widely in the reported series, ranging from 2.6% to

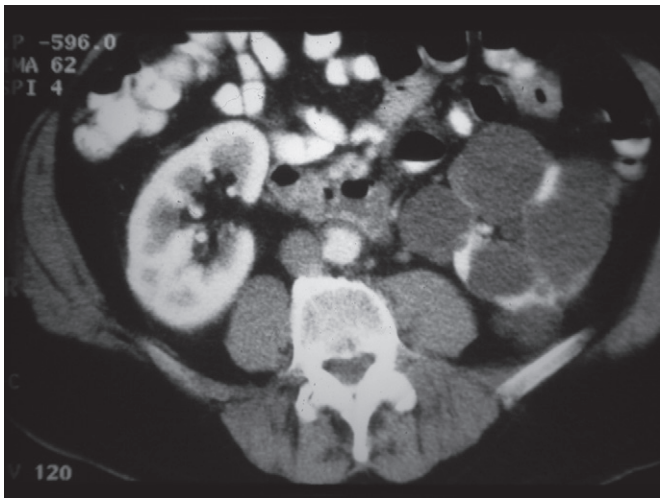


Figure 118–25. Unilateral renal cystic disease. Diffuse simple cysts were evident in one kidney. There was no discrete mass or evidence of multiple malformation syndrome. (Courtesy of Jeffrey Newhouse, MD.)

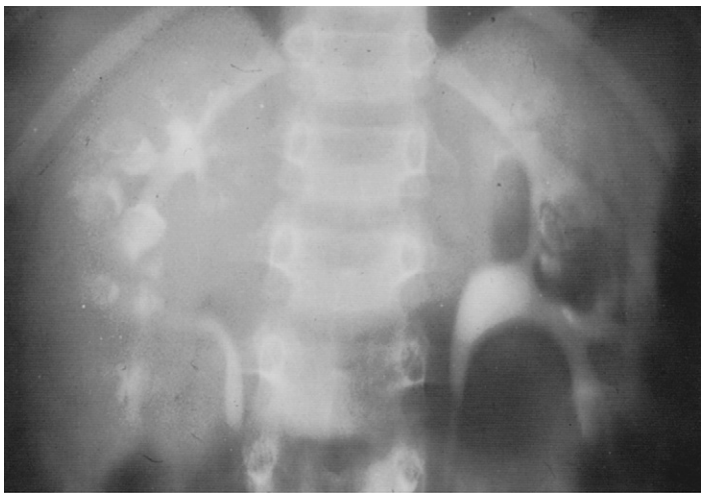


Figure 118–26. Intravenous urogram of a 9-year-old girl with hematuria. Characteristic puddling of contrast medium in the ectatic papillary collecting ducts makes the diagnosis of medullary sponge kidney. (From Glassberg KI, Hackett RE, Waterhouse K: Congenital anomalies of the kidney, ureter and bladder. In: Kendall AR, Karafin L, editors. Goldsmith's practice of surgery: urology. New York: Harper & Row; 1981. p. 1–82.)

Key Points: Medullary Sponge Kidney

- Medullary sponge kidney is usually a nonheritable condition associated with dilated collecting ducts that appear as bristles on a brush on intravenous pyelography, and the ducts are sometimes filled with calcifications.
- There is a high incidence of renal colic (50% to 60%), urinary tract infections (20% to 33%), gross hematuria (10% to 18%), and hypercalciuria (33%).

21%. The incidence appears to be higher in female than in male stone formers (Palubinskas, 1961; Lavan et al, 1971; Parks et al, 1982; Sage et al, 1982; Wikstrom et al, 1983; Vagelli et al, 1988; Yendt, 1990). Urinary tract infections, likewise, seem to be more common in female patients with medullary sponge kidney (Parks et al, 1982).

One third to one half of the patients with medullary sponge kidney has hypercalciuria (Ekstrom et al, 1959; Harrison and Rose, 1979; Parks et al, 1982; Yendt, 1990). Incomplete distal renal tubular acidosis may be found in as many as 30% to 40% of these patients (Torres, 2008). In the absence of infection, the stones passed by patients with medullary sponge kidney are composed of calcium oxalate, either alone or in combination with calcium phosphate. Medullary sponge kidney has also been reported in association with rare congenital anomalies, such as hemihypertrophy, Beckwith-Wiedemann syndrome (macroglossia, omphalocele, and gigantism), Ehler-Danlos syndrome, anodontia, and Caroli disease.

Diagnosis

In general, intravenous urography is more sensitive than CT in detecting mild cases of medullary sponge kidney. **The urographic features of the disorder are as follows: (1) enlarged kidneys, sometimes with calcification, particularly in the papillae; (2) elongated papillary tubules or cavities that fill with contrast medium; and (3) papillary contrast blush and persistent medullary opacification** (Gedroyc and Saxton, 1988). Calcium deposits within the tubules may appear as renal calculi or nephrocalcinosis.

Treatment and Prognosis

It is the complications of medullary sponge kidney, calculus formation and infection, that require management. In addition to liberal fluid intake, **thiazides are effective for lowering hypercalciuria and limiting stone formation. If thiazides cannot be used, inorganic phosphates may be appropriate;** however, they should not be used in patients with urinary tract infections caused by urease-producing organisms, because of the risk of struvite stones. **For those patients with renal lithiasis, thiazides should be administered even if hypercalciuria is not present.**

Because infections are not unusual in patients with medullary sponge kidney, especially if stones are present, cultures should be obtained frequently, and long-term prophylaxis should be considered in some cases. Infections by coagulase-positive staphylococci are common in patients with stones and should be treated even when the colony count in the cultures is less than 100,000/mL (Yendt, 1990). Repeated investigations for hematuria should be avoided. In cases where stones require surgical therapy, standard procedures, such as extracorporeal lithotripsy and percutaneous nephrolithotomy, may be employed.

ACQUIRED RENAL CYSTIC DISEASE

Acquired renal cystic disease (ARCD), also known as acquired cystic kidney disease (ACKD), is defined as bilateral cystic renal change in patients with end-stage renal disease due to causes other than inherited renal cystic disease. A minimum of three cysts in each kidney is required for diagnosis. This disease entity was first described in 1977 in **patients receiving hemodialysis; however, it soon became apparent that the disorder is almost as common in patients receiving peritoneal dialysis** (Dunhill et al, 1977; Thomson et al, 1986). It is now known that dialysis is not a prerequisite of ARCD, and it is likely that the uremic state causes the pathologic changes seen; dialysis merely prolongs patient survival and the amount of time available for the cystic changes to occur (Fisher and Horvath, 1972; Ishikawa et al, 1980; Kutcher et al, 1983; Miller et al, 1989; Truong et al, 2003).

The prevalence and severity of this disease increase with the duration of azotemia and the subsequent need for dialysis. Acquired cysts are found in roughly 10% of patients with ESRD prior to dialysis. The incidence increases to 44% within 3 years after beginning dialysis, to 60% at 5 years after beginning dialysis, and to greater than 90% if the patient is on dialysis for 10 or more years. ARCD is 3 times more common in men than in women and is generally thought to be unrelated to age or the cause of renal failure. African-Americans, and perhaps Japanese, are more prone than Americans of European descent to develop ARCD (Reichard et al, 1998). **ARCD can occur in children as well (an incidence of ≈23% has been reported)** (Hakim et al, 1994). A successful renal transplant was previously thought to delay or even reverse the cystic changes, but this is not supported by more recent data (Heinz-Peer et al, 1995; Doublet et al, 1997; Kliem et al, 1997).

Etiology

Several etiologic theories have been proposed for ARCD, although the exact cause has not been identified. One theory suggests that tubular obstruction resulting from fibrosis, oxalate crystals, vascular occlusion, or ischemia leads to cyst formation. A number of other findings suggest a role for toxins. First, the cysts, adenomas, and carcinomas usually are multiple and bilateral, as are the carcinomas induced experimentally in rats by toxins. Second, there is often a regression of the cysts after successful transplantation (Ishikawa et al, 1983), suggesting that some cystogenic or carcinogenic toxin of uremia is being eliminated by the allograft. Third, if transplantation fails and dialysis is resumed, the cysts return even in chronically rejected transplanted kidneys. Another hypothesis suggests that the accumulation of growth factors, such as epidermal growth factor (EGF), and other stimulatory chemicals (present with uremia) lead to the development of cysts (Bisceglia et al, 2006). Yet another theory suggests that loss of functioning renal tissue leads to the production of renotrophic agents that induce hyperplasia of remaining glomeruli, cyst development, and, in extreme cases, renal tumors (Harris et al, 1983; Yamamoto et al, 1983).

Clinical Features

Most patients with ARCD are asymptomatic. **The majority of clinical manifestations result from spontaneous**

Key Points: Acquired Renal Cystic Disease

- Acquired renal cystic disease is associated with chronic renal failure and is most often seen in patients on long-term hemo- and peritoneal dialysis.
- Acquired renal cystic disease consists of hyperplastic renal cysts and frequently adenomas; either can progress to RCC.
- The incidence of renal malignancy in dialysis patients is 5 to 50 times greater than in the general population. If RCC develops, it mostly does so before 10 years of dialysis.
- The cysts usually regress with transplantation, and even when this occurs, there still is some suggestion that the risk of developing RCC still persists, but at a much lower incidence.

bleeding into one or more of the cysts, making the most common presentation loin pain, hematuria, or both conditions. Bleeding occurs in as many as 50% of patients (Levine, 1996). When significant bleeding occurs, it may cause a subcapsular or retroperitoneal hematoma and may be secondary to renal cysts or to RCC. This bleeding may be complicated by coagulation defects induced by uremia or heparinization during dialysis. Other much less common complications are cyst infection, urolithiasis, and a rapid rise in hematocrit, which is probably related to increased renal synthesis of erythropoietin (Shalhoub et al, 1982; Ratcliffe et al, 1983; Mickisch et al, 1984).

Renal neoplasms, principally adenomas, occur in 10% of patients receiving chronic hemodialysis, and, when ARCD is present, the incidence of neoplasms is even higher, ranging from 20% to 25% (Gardner and Evan, 1984). The overall prevalence of RCC in hemodialysis patients is approximately 1%. Carcinoma is 3 times more likely in the presence of ARCD and 6 times more common in large cystic kidneys than in small cystic kidneys (Torres, 2008). **Overall, the incidence of renal malignancy in dialysis patients is 5 to 50 times greater than in the general population** (Resseguie et al, 1978; Port et al, 1989; Levine et al, 1991; Ishikawa, 1993; Truong et al, 1995).

Compared with the sporadic form, RCC associated with ARCD is characterized by younger patient age, male predominance, frequent multicentricity and bilaterality, and less aggressive behavior (Gronwald et al, 1999; Denton et al, 2002; Truong et al, 2003). Approximately 20% of ARCD-associated RCC metastasizes versus 50% for sporadic RCC. **The risk factors for tumor development include male gender, duration of dialysis, and kidney weight, but not type of dialysis.** Children on dialysis can also develop RCC, despite its rarity in the general pediatric population. Most tumors (86%) are asymptomatic, and the symptomatic ones are related mostly to bleeding from tumor. Many manifest exclusively as persistent hematuria and are not seen by any available imaging techniques. Nephrectomy is recommended for tumors larger than 3 cm or for smaller ones that are associated with persistent hematuria or rapid growth (Ishikawa, 2000; Truong et al, 1995).

Histopathology

Both kidneys are usually smaller than normal, and the cysts are multiple and bilateral. The cysts develop predominantly in the cortex, although the medulla may be affected, especially later in the disease process (Fig. 118–27). The cysts average 0.5 to 1.0 cm in diameter, but some have been reported to reach 5.0 cm (Miller et al, 1989). Larger cysts, a frequent feature of ADPKD, are rare. The cysts are unilocular and contain clear, straw-colored, or gelatinous fluid, with frequent bleeding and/or neoplastic transformation.

Most cysts are lined by a single layer of epithelium composed of flat nondescript cells, cells with abundant cytoplasm and hyaline droplets, or small cuboidal cells resembling those from distal tubules or collecting ducts. Cysts usually show secondary changes, including luminal deposition of degenerated blood, hemosiderin, or calcium oxalates (Hughson et al, 1986; Ishikawa, 1991; Truong et al, 1995). The nuclei of the epithelial cells in these cases are round and regular, without prominent nucleoli (Hughson et al, 1980).

Differentiating renal tumors into adenomas and carcinomas is arbitrary at times. Most renal nodules that are smaller than 1 cm in diameter are adenomas, and most that are larger than 3 cm in diameter are carcinomas. Tumors between 1 and 3 cm in diameter must be considered equivocal. It is not clear whether renal adenomas undergo malignant transformation. It is believed that atypical hyperplastic epithelium occurs even without cyst formation and that these cells are the precursors of both atypical cysts and adenomas (Hughson et al, 1986). It is thus possible that either hyperplastic cysts or adenomas can become RCCs. Therefore one must not ignore the native kidney left in situ during a renal transplantation. Hyperplastic cyst epithelium has also been considered a possible precursor of RCC in other cystic diseases (VHL disease and tuberous sclerosis) (Fayemi and Ali, 1980).

Evaluation

Ultrasonography is the most common modality used to diagnose and monitor patients with ARCD. CT and MRI identify more cysts, and MRI is probably better at demonstrating and characterizing small lesions in particular (Heinz-Peer et al, 1998). Ultrasonography usually shows small, hyperechoic kidneys with cysts of various sizes. Cyst wall calcification may be visible, but it is more readily seen on CT. CT with and without contrast is better for distinguishing kidneys with a few simple cysts from those with multiple acquired cysts and is the most useful for detecting neoplasms. In patients with ESRD not yet on dialysis, however, the use of CT contrast should be avoided for fear of causing further deterioration of renal function. Ultrasonography and MRI with gadolinium enhancement are better alternatives to contrast-enhanced CT in these patients. **A word of caution, however: Nephrogenic systemic fibrosis (NSF) is a rare but serious and life-threatening disorder observed in patients with renal impairment, and is associated with the infusion of gadolinium as a MRI contrast agent in patients with ESRD. Caution should be used when using gadolinium in this patient population.**

In uremic patients with fever, one should consider the diagnosis of ARCD and the possibility of an infected cyst (Bonal et al, 1987). Infection should be suspected if ultrasonographic examination shows internal echoes or a thickened wall. Cyst puncture can be used to confirm the diagnosis and to identify the infecting microorganism. CT examination may identify cyst wall thickening in cases with infection.

In the differential diagnosis of ARCD, the etiology of the renal failure must be considered and, in particular, the possibility of ADPKD. Usually, patients with ARCD have smaller kidneys and



Figure 118–27. Bilateral multiple renal cysts and diffuse calcification in enlarged kidneys in a patient undergoing chronic hemodialysis. The findings simulate those of ADPKD. However, cystic disease was not the cause of the uremia, and the diagnosis of acquired renal cystic disease was made. (Courtesy of D. Gordon, MD.)

smaller cysts and are free of the extrarenal manifestations of ADPKD. In patients receiving hemodialysis, kidneys affected by ARCD usually are less than 300 g; ADPKD kidneys usually are larger than 800 g (Feiner et al, 1981).

Treatment

Bleeding episodes are often treated conservatively with bed rest and symptom control. Persistent bleeding and pain, however, may require nephrectomy or renal embolization. If heparinization is associated with hematuria during hemodialysis, peritoneal dialysis may be substituted. Because the risk of undetected RCC is high in patients with retroperitoneal hemorrhage, nephrectomy is recommended in those cases in which carcinoma cannot be ruled out. If a few larger cysts are associated with flank pain, percutaneous aspiration (with cytologic examination) is a reasonable temporizing measure, because ARCD may regress after successful renal transplantation (Torres, 2008). For an infected cyst, percutaneous drainage may be effective. When it is not, surgical drainage or nephrectomy should be considered.

Although small renal tumors may metastasize, it is known that those less than 3.0 cm in diameter rarely do so (Bell, 1935; Talamo and Shonnard, 1980). Thus it is currently recommended that renal masses larger than 3 cm detected in ACKD be treated by surgical excision. For tumors smaller than 3 cm, some advise nephrectomy for the acceptable surgical candidate, whereas others recommend annual CT follow-up with resection only if the tumors enlarge.

It has been recommended that patients who have been receiving hemodialysis for longer than 3 years be screened by ultrasonography and CT and then monitored by ultrasonography every 6 months if the kidneys are without cysts and tumors or by both ultrasonography and CT on the same schedule if cysts or tumors smaller than 2 cm are identified (Sarasin et al, 1995).

A number of investigators have found that the cysts of ARCD regress after renal transplantation (Ishikawa et al, 1983; Kutcher et al, 1983; Thomson et al, 1986). Therefore it was considered that the incidence of RCC might fall after transplantation as well. Unfortunately, 18% of patients developed new cysts after transplantation, and renal carcinoma can occur in the native kidney 3 to 8 years after transplantation (Ishikawa, 1991; Levine and Gburek, 1994). It appears that the malignant potential of ARCD may persist for many years after transplantation, especially in older transplantation patients and in men (Heinz-Peer et al, 1995). Finally, it must be remembered that immunosuppression, in and of itself, makes these patients vulnerable to carcinoma. Native kidneys account for 4.5% of all malignancies in renal transplantation recipients (Penn, 1979).

CALYCEAL DIVERTICULUM (PYELOGENIC CYST)

A calyceal diverticulum is an outpouching of the collecting system into the corticomedullary region of the kidney, and it usually arises from the fornix of a calyx. It is a transitional epithelial-lined, smooth wall, spherical cavity that communicates with the pelvicalyceal system by a thin channel or neck, typically in the upper or lower pole. It is sometimes known as a pyelogenic cyst, especially if it arises from the renal pelvis. The size of such lesions can range from a few millimeters to several centimeters. Most diverticula are presumed to be congenital; however, similar lesions may occur due to blunt renal trauma or obstruction of a calyceal infundibulum. Diverticula are usually asymptomatic but may occasionally develop calculi. The calculi may be a single larger stone or multiple tiny stones. Occasionally, milk of calcium may be present. Passage of a stone through the narrow channel into the calyx may cause pain and hematuria.

Radiographically, these diverticula are seen as a spherical collection of contrast medium adjacent to a papilla on intravenous pyelography (IVP); however, the connecting channel is often too narrow to be demonstrated. On upright films, the urine and contrast media form a fluid level. Calyceal diverticula can also be seen on CT, MRI and ultrasonography, but the distinction between an obstructed calyx and a renal cyst may be difficult unless contrast is administered (Fig. 118–28).

This entity is discussed in more depth in Chapter 117.

PARAPELVIC AND RENAL SINUS CYSTS

Parapelvic cysts, renal sinus cyst, peripelvic cyst, pelvic cyst, parapelvic lymphatic cysts, hilus cysts, cysts of the renal hilum, and parapelvic lymphangiectasia are all terms used to describe cysts that are adjacent to the renal pelvis or within the hilum. Although some "peripelvic" cysts are simple cysts that arise from the renal parenchyma and impinge upon the renal pelvis, true cysts derived from the renal sinus have no parenchymal etiology. Thus the terms *parapelvic* and *peripelvic* are terms better used to describe the location of parenchymal cysts, while the term *renal sinus cyst* more accurately describes all other cysts in the hilum that are not derived from the renal parenchyma but rather from the other structures of the renal sinus, such as arteries, lymphatics, and fat. These are all benign lesions found in 15% to 2% of patients at autopsy. With modern imaging techniques, they can easily be distinguished from more serious lesions of the renal pelvis or renal parenchyma (Fig. 118–29).

The predominant type of renal sinus cyst appears to be due to dilation of lymphatics; however, the mechanism responsible for these changes is not known. Most often these cysts are

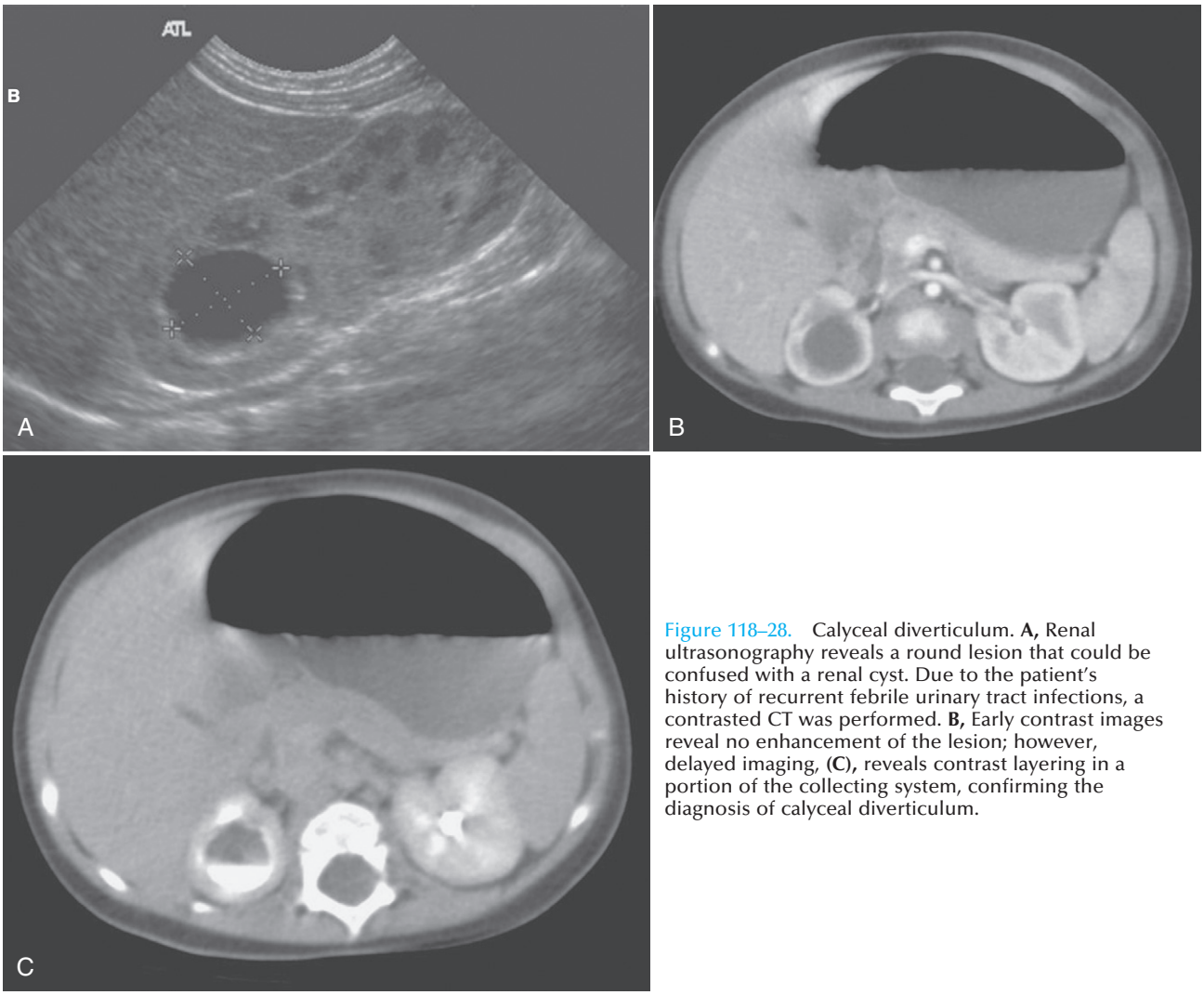


Figure 118–28. Calyceal diverticulum. **A,** Renal ultrasonography reveals a round lesion that could be confused with a renal cyst. Due to the patient's history of recurrent febrile urinary tract infections, a contrasted CT was performed. **B,** Early contrast images reveal no enhancement of the lesion; however, delayed imaging, **(C),** reveals contrast layering in a portion of the collecting system, confirming the diagnosis of calyceal diverticulum.

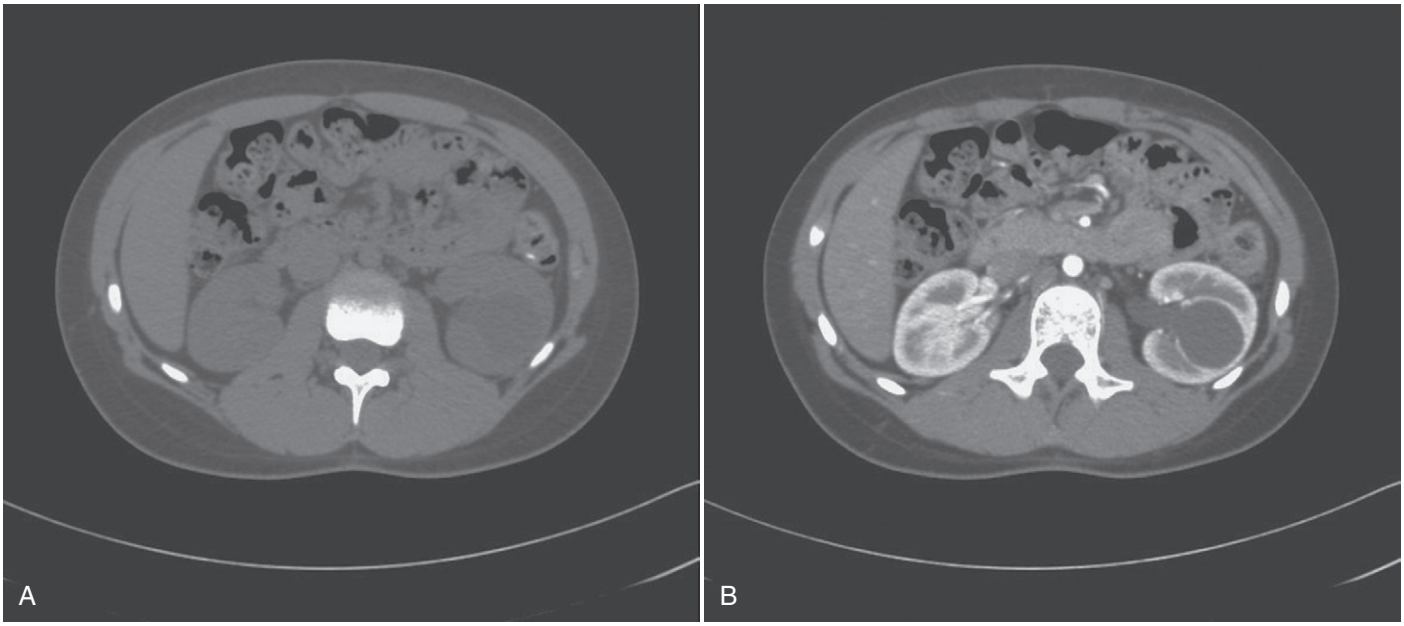


Figure 118–29. Parapelvic cyst. **A,** A hypoechoic, well-circumscribed, round focus in the peripelvic region of the kidney. **B,** There is no delayed enhancement following the administration of intravenous contrast. There is no hydronephrosis or hydroureter. Note contrast within the ureter on the contrasted images.

multiple, and often they are bilateral. Other renal sinus cysts are due to fluid replacing adipose tissue in the renal sinus as the kidney becomes affected by local vascular disease and atrophy.

Patients are usually in their fifth or sixth decades and are almost always asymptomatic. These cysts are usually discovered incidentally in the course of evaluation for other conditions, such as urinary tract infections, nephrolithiasis, hypertension, and prostatism. There are rare instances of obstruction of a collecting system from these cysts. Ultrasonography will show multiple echo-free areas in the region of the renal sinus. Differentiation from hydronephrosis may be difficult. A diagnosis of hydronephrosis is established without question when dilated calyces are seen to communicate with a dilated renal pelvis. On CT, renal sinus cysts have the attenuation value of water, and they can often be seen within the renal sinus as they displace the calyces peripherally. On nonenhanced scans, multiple renal sinus cysts resemble a dilated renal pelvis and thus mimic hydronephrosis. Differential diagnosis should include renal sinus lipomatosis (fat density), lymphoma, hemorrhage, and urinoma. The therapeutic approach to renal sinus cysts should be conservative.


Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter 119

Core Principles of Perioperative Management in Children

Carlos R. Estrada, Jr., MD ● Lynne R. Ferrari, MD

Growth and Maturation
Perioperative Fluids
Pediatric Anesthesia and Analgesia
Surgical Preparation
Intraoperative Considerations
Postoperative Care

The maxim "children are not small adults" is a critically important concept that must be remembered when contemplating surgical intervention in the pediatric population. Children have unique anatomy, physiology, and emotional and psychologic needs, all of which vary with the child's age. In addition, we are increasingly involved in prenatal counseling and care, and therefore an understanding of fetal development and physiology is necessary. This chapter reviews the core principles of pediatric perioperative care with which any pediatric surgeon must be familiar to ensure optimal surgical outcomes.

GROWTH AND MATURATION

Prematurity and Intrauterine Growth Restriction

A baby born before 37 weeks' gestation is considered premature. The severity of prematurity may be indicated by the birth weight, although these two factors are not necessarily related. Infants weighing 2500 g or less at birth are considered low birth weight (LBW) in prematurity, but in an infant born full term, this weight would indicate intrauterine growth restriction (IUGR). This is an important distinction, because full-term neonates with IUGR usually have different problems than premature infants. In the United States, approximately 30% of LBW infants are born after 37 weeks' gestation. Premature infants weighing 1500 to 2500 g are referred to as moderately low birth weight (MLBW); those less than 1500 g are referred to as very low–birth-weight (VLBW) infants; and infants who weigh less than 1000 g are considered extremely low–birth-weight (ELBW) infants. MLBW infants account for 82% of premature infants, VLBW 12%, and ELBW 6%. In 2006, 12.8% of live births in the United States were premature, and 8.3% were LBW. Between 1996 and 2006, the rate of premature births in the United States increased more than 16%. With respect to race, the rate of prematurity in the United States is highest for black infants (18.3%), followed by Native Americans (14.1%), Hispanics (12.1%), whites (11.6%), and Asians (10.7%). **The clinical implications of prematurity are profound, and premature infants accounted for 16.6% of all infant deaths in the United States in 2005.** These implications are especially relevant to the VLBW and ELBW infants, who are surviving in increasing numbers due to remarkable advances in neonatal critical care. These infants account for a large proportion of neonatal deaths and long-term disability, and because of their extreme prematurity are predisposed to hyaline membrane disease, leading to chronic lung disease, retinopathy of prematurity, intraventricular hemorrhage, and necrotizing enterocolitis (Teitelbaum and Coran, 2003b; Pierro, 2006; Eichenwald and Stark, 2008; Goldenberg et al, 2008).

IUGR is defined on prenatal ultrasonography as a fetus whose estimated weight is below the 10th percentile for its gestational age. At term, the birth weight below 2500 g is considered IUGR. Approximately 70% of infants with a birth weight that qualifies for IUGR are constitutionally small, and in the remaining 30%, the cause of IUGR is pathologic. IUGR can be limited to intrauterine development, resulting in a normal-sized baby at birth. General causes of IUGR include placental insufficiency, chronic maternal disease, abnormal placentation, genetic disorders, malformations, immunologic diseases, maternal infections, metabolic diseases, maternal substance abuse, and multiple gestations. IUGR is typically classified as symmetrical or asymmetrical. Symmetrical IUGR describes a fetus whose entire body is proportionally small, and is considered the more severe form (Styne, 2004). Asymmetrical IUGR is related to processes that require the fetus to direct its energy to the maintenance of vital organs, usually the heart and brain. Therefore the fetus with asymmetrical IUGR typically has a normal head circumference but small abdominal circumference, small limbs, reduced skeletal muscle mass, and decreased subcutaneous and abdominal fat. Infants with asymmetrical IUGR more frequently exhibit catch-up growth than their symmetrical IUGR counterparts. However, of all infants with IUGR, 10% to 30% will have short stature as adults. Given the wide variety of causes, the management of IUGR is individualized, and often complex decisions are required, weighing elective preterm delivery and the risks of prematurity against the risks associated with IUGR (Teitelbaum, 2003b; Pierro, 2006; Alberry and Soothill, 2007; Goldenberg et al, 2008).

Intrauterine Growth and Lung Development

Proper intrauterine growth and development are dependent on presence of normal amniotic fluid volume. Of particular relevance to urologists is lung development, which is dependent on amniotic fluid. Early in pregnancy, the placenta produces amniotic fluid. **At 10 to 12 weeks' gestation, the fetal kidneys begin to produce urine, which comprises the majority of amniotic fluid.** Lung development is a highly complex orchestration of molecular processes, and is divided into three stages: embryonic, fetal, and postnatal or alveolar stages.

The embryonic stage begins with a ventral bud from the foregut at 3 weeks' gestation, which divides into the primordial segments that give rise to all lung tissue (Teitelbaum, 2003b; Wilson, 2006). **The fetal stage of lung development begins at 7 weeks' gestation and proceeds to term.** This stage is further subdivided into three phases: pseudoglandular (7 to 17 weeks), canalicular (16 to 25 weeks), and saccular (25 weeks to term). The pseudoglandular phase is of particular interest, because its timing coincides with the replacement of placenta-derived amniotic fluid with fetal urine-derived amniotic fluid. **By the end of the 16th week of gestation, all lung branching occurs, resulting in the terminal bronchial airways.** After this time, the only further growth that occurs is elongation and widening of existing airways. **A large body of experimental data indicates that these early and critical events in lung development are dependent on lung fluid dynamics, and any restrictive process, including tracheal occlusion (e.g., atresia) or oligohydramnios, results in pulmonary hypoplasia, which can be fatal at birth.** The severity of the restrictive process is proportional to the degree of hypoplasia (Teitelbaum, 2003b; Wilson, 2006).

The postnatal stage continues for one year after birth. This stage is characterized by maturation of the terminal saccules into alveoli. At birth, the lung contains approximately 20 million saccules, and at approximately 5 weeks postnatal, these begin to develop into the 300 million alveoli expected to be present by 8 years of age. The most robust development of the alveoli occurs before 4 years of age. After 8 years of age, lung volume increases because of increase in alveolar size, not from an increase in alveolar number (Teitelbaum, 2003b; Wilson, 2006).

Postnatal Considerations

In the postnatal period, growth and development in children occurs at a rapid pace, especially in early childhood. A full-term newborn grows at a rate of 25 to 30 g/day over the first 6 months of life, leading to a doubling of the birth weight during this period. In the first 12 months of life, an infant's birth weight is typically tripled. By 3 years of age, birth weight is expected to quadruple, and by 10 years of age it will increase 20-fold from the birth weight. Body length increases by approximately 50% in the first year of life, and by threefold by 10 years of age (Teitelbaum and Coran, 2003c).

Cardiovascular

A detailed description of pediatric cardiovascular physiology and management is beyond the scope of this chapter, but a few principles are important for the urologist to consider. These include the basic differences between pediatric and adult cardiovascular physiology and an understanding of the common congenital heart defects that may affect urologic patients.

The neonatal and pediatric myocardium is stiffer and less compliant compared with the adult heart. This results in diminished preload capacity, so that increases in end-diastolic ventricular volume and increases in right ventricular pressure result in decreased cardiac output at lower levels than in adult patients. In addition, infants and children have relatively higher resting heart rates. **As a result, cardiac output in children is heart rate dependent, because the stroke volume is relatively fixed. Decreases in heart rate in infants and children will result in decreases in cardiac output to a greater extent than a similar decrease in heart rate in an adult patient.** A reduction of a child's heart rate to that of a typical adult would result in marked decrease in cardiac output. Finally, the pediatric heart is significantly less responsive to inotropic agents, because it has reduced intramyocardial calcium release (Hirschl, 2003a; Rocchini, 2006).

Congenital heart defects are very common, occurring in approximately 1 of every 120 live births. In general, they are classified as hypoplastic, septal, cyanotic, or obstruction defects. The septal defects are the most common, of which ventricular septal defect (VSD) is most prevalent. Most infants with septal defects have no symptoms during the first month. However, after 4 to 6 weeks of life, pulmonary resistance reaches normal levels, and thus during the second month of life, congestive heart failure can occur. Hypoplasia of the heart is rare, but is the most serious form of congenital heart disease. These defects typically result in the failure of either the right ventricle or the left ventricle to develop adequately, leaving only one side of the heart capable of pumping blood to the body and lungs. In hypoplastic left heart syndrome, the presence of a patent ductus arteriosus is critical for the infant's ability to survive until emergency surgery can be performed. Without this pathway, blood cannot circulate to the body. In hypoplastic right heart syndrome, a patent foramen ovale serves the same function. Obstruction defects occur when heart valves, arteries, or veins are abnormally narrow or blocked. Common obstruction defects include pulmonary valve stenosis, aortic valve stenosis, and coarctation of the aorta, with other types, such as bicuspid aortic valve stenosis and subaortic stenosis, being comparatively rare. Any narrowing or blockage can cause enlargement of the heart or hypertension. Cyanotic heart defects are named thus because they result in cyanosis. These defects include persistent truncus arteriosus, total anomalous pulmonary venous connection, tetralogy of Fallot, transposition of the great vessels, and tricuspid atresia. From a noncardiac surgery perspective, it is important to remember that many children with complex cardiac anomalies are on medications, such as aspirin and sildenafil, that predispose them to bleeding. In addition, certain types of surgically induced circulation—for instance, induced by the Fontan procedure—purposely increase systemic venous pressure, which can be problematic for postoperative bleeding. Careful consideration of these variables and planning with a pediatric cardiac anesthesiologist is obligatory (Hirschl, 2003a; Rocchini, 2006).

Immunologic

Neonates have increased susceptibility to bacterial infections, which is predominantly due to deficiencies in neonatal host defense mechanisms. Premature infants are at even higher risk. This susceptibility is due to several factors related to the immaturity of neonatal leukocytes, including neutrophils, monocytes, T and B lymphocytes, and NK cells, and also with deficiencies in the complement activation system.

Although the number of neutrophils is near the adult level at term (approximately 60% of circulating leukocytes), neonates have a relative inability to increase their circulating levels in response to stress or infection. This is thought to be due to a decreased neutrophil storage pool and to increased margination of neutrophils. Premature infants have the added problem of having a significantly lower neutrophil count at birth. Neonatal neutrophils are also less adhesive to activated endothelium, a process that is critical to chemotaxis and migration to sites of inflammation and infection. This may be due to decreased neonatal neutrophil expression of L-selectin and β_2 integrin. In addition, neonatal serum is deficient in opsonins, which are necessary for neutrophil phagocytosis. Therefore even though neonatal neutrophils are fully competent to kill bacteria, they may do so less efficiently. Unlike a decreased neutrophil storage pool, the number of monocytes in neonates is equal to or greater than in adults. For unclear reasons, however, the migration of monocytes to sites of inflammation and infection is significantly delayed (Hirschl, 2003b; Upperman, 2006).

T-lymphocyte function is also impaired in neonates, despite having a significantly greater number of circulating T cells compared with adults. In addition, unlike adults, there is a greater proportion of CD4+ T cells than CD8+ T cells. The impaired function is believed to be related to their naive phenotype that is due to their lack of exposure to foreign antigens and because they produce relatively limited amounts of key inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interleukin (IL)-3, IL-4, IL-5, and IL-10. B-lymphocyte function is also impaired in neonates, which is due to their inability to differentiate into immunoglobulin (Ig)G- or IgA-secreting plasma cells. They are able to differentiate into IgM-secreting plasma cells but rely on maternal placental transfer for essentially all IgG. This reliance continues until the third or fourth month of life, after which time the proportion of neonatal IgG overtakes maternal IgG. Although maternal IgG is adequate for protection against most infections, strains of bacteria, such as *Escherichia coli* and *Salmonella,* can elicit a different immunoglobulin subtype, leaving the fetus and neonate with suboptimal immune protection. Premature infants are at even greater risk, because they are born without sufficient levels of maternal IgG (Hirschl, 2003b; Upperman, 2006).

Another lymphocytic deficiency in neonates involves the natural killer (NK) cells, which play an important role in protection against intracellular pathogens by targeted cell lysis. At term, the proportion of NK cells is similar to that in adult circulation, but they are functionally and phenotypically immature. For unclear reasons, their lytic potential is only 50% of adult NK cells, and it is not until late infancy that they reach their full functional potential (Hirschl, 2003b; Upperman, 2006).

The relative deficiency of immunoglobulins in neonates results in the increased reliance on the alternative, that is, antibody-independent pathway of complement activation. However, in neonates there are a reduced number of classic and alternative complement activation pathway factors. Specifically, the level of C9 is diminished, which is critical for protection against gram-negative bacteria. Breast-feeding is believed to partially compensate for these intrinsic neonatal immunologic deficiencies. Human milk contains immunoglobulins, including IgG, IgM, and secretory IgA; lymphocytes; macrophages; polymorphonuclear leukocytes; and components of the complement cascade. Because of these and other benefits, the American Academy of Pediatrics recommends continuing breast-feeding for the first 12 months of life. **Although the neonatal period presents the highest risk of infection for children, the immune system is not fully competent until approximately 8 years of age** (Hirschl, 2003b; Upperman, 2006).

Renal

A detailed discussion of renal development can be found in Chapter 112 of this text, and therefore this section represents a very brief synopsis. Renal function begins in utero, with the first functional nephrons appearing at 8 weeks' gestation. Nephrogenesis is complete by 34 weeks. Urine production begins between 10 and 12 weeks' gestation, coinciding with the start of glomerular filtration. In utero, renovascular resistance is high, limiting renal blood flow. Immediately following birth, the distribution of renal cortical blood flow changes, with increased perfusion of the outer cortex and increased reactivity of the renal vascular bed. Consequently, the glomerular filtration rate (GFR) rises quickly despite renal blood flow remaining unchanged. In addition, water and electrolyte homeostasis is difficult to predict. **GFR and tubular function double by 1 month of age** (Kaskel et al, 1987), **and over the first 3 months of life, renovascular resistance continues to decrease, which results in further rises in GFR. Following this relatively rapid rise, GFR continues to increase more slowly toward adult levels, which are reached by 12 to 24 months of life.** The maturation of renal tubular function lags behind the maturation of glomerular function, and therefore the neonate can concentrate urine to only approximately 50% of adult capability (Greco, 2002; Teitelbaum and Coran, 2003a; Pierro, 2006).

Key Points: Growth and Maturation

- Infants with a history of prematurity and/or IUGR are at risk for adverse events and account for a large proportion of neonatal deaths and long-term disability.
- Proper intrauterine growth and development are absolutely dependent on the presence of normal amniotic fluid volume, the majority of which is composed of urine after 10 to 12 weeks' gestation.
- Lung development, in particular, depends on fluid dynamics, and processes such as oligohydramnios result in pulmonary hypoplasia.
- Neonatal and pediatric myocardium is stiffer and less compliant than in an adult, resulting in significant differences in physiologic responses and cardiovascular care.
- Many children with complex cardiac anomalies are on medications, such as aspirin and sildenafil, that predispose them to bleeding. In addition, certain types of surgically induced circulation, for instance, induced by the Fontan procedure, purposely increase systemic venous pressure, which can be problematic for postoperative bleeding.
- Neonates have increased susceptibility to bacterial infections due to deficiencies in host defense mechanisms, and the immune system is not fully competent until 8 years of age.
- The normalization of renal function is a rapidly evolving process at birth, and adult-level GFR is not reached until 12 to 24 months of life.

PERIOPERATIVE FLUIDS

Maintenance of hydration is a fundamental and critically important concept in pediatric care. For the pediatric urologist,

administration of fluids is usually for maintenance therapy in the postoperative period or for deficit therapy in the setting of postoperative dehydration. Appropriate intraoperative fluid therapy is critical to simplify postoperative fluid management and optimize the postoperative course. This is increasingly important given the increase in ambulatory surgery and the shorter length of hospital stays. **Perioperative fluid therapy begins with an estimation of fluid deficit by the anesthesia team.** If possible, urine output should be carefully monitored for the duration of surgery, and in the setting of an open lower urinary tract, the urologist should provide feedback to the anesthesiologist to ensure that the patient remains well hydrated.

Maintenance fluid replaces two losses: insensible, or evaporative, losses and urinary losses. In the perioperative period, insensible losses can vary widely with the presence or severity of several variables, including fever, tachypnea, and other conditions. Insensible losses represent loss of free water and generally account for one third of maintenance fluids. Urine losses are calculated as 280 to 300 mOsm/kg of water with a specific gravity of 1.008 to 1.015, but this concentration can vary depending on the patient's ability to concentrate urine. Urinary losses account for two thirds of total maintenance fluids. **The total requirements for maintenance fluids can be calculated using the Holliday-Segar formula as shown in** Table 119–1 (Holliday and Segar, 1957). **After calculating the fluid requirement, children usually receive either 5% dextrose (D5) ¼ normal saline (NS) + 20 mEq/L potassium chloride (KCl) or D5 ½ NS + 20 mEq/L KCl.** Children who are younger than 6 months are generally given the solution with ¼ NS because of their high water needs per kilogram. Children 6 months and older, however, should receive the solution with ½ NS (Greenbaum, 2007).

In the setting of postoperative dehydration, the severity is determined as described in Table 119–2 (Siker, 2002). **Generally, deficit replacement should begin with a balanced salt solution, such as lactated Ringer (LR) solution or normal saline, to increase intravascular volume.** Typically, a bolus of 10 to 20 mL/kg is used, but a rate of up to 40 mL/kg during the first 1 to 2 hours is well tolerated (Carvajal, 1994). The type of fluid deficit can be estimated from the patient's history, physical examination findings, electrolyte values, and serum tonicity. Types of dehydration include isotonic (serum osmolarity 270 to 300 mOsm/L, serum sodium [Na^+] concentration 130 to 150 mEq/L), hypotonic (serum osmolarity < 270 mOsm/L, serum Na^+ concentration < 130 mEq/L), or hypertonic (serum osmolarity > 310 mOsm/L, serum Na^+ concentration > 150 mEq/L). Patients with hypertonic dehydration require careful consideration of fluid type and rate, because complications, such as cerebral edema, may occur during rehydration (Friedman, 2005; Greenbaum, 2007).

Table 119–1.

Daily Maintenance Fluid Requirements

WEIGHT (kg)	DAILY REPLACEMENT	HOURLY REPLACEMENT
0-10	100 mL/kg/day	4 mL/kg/hr
11-20	1000 mL/day + 50 mL/kg/day	40 mL/hr + 2 mL/kg/hr
>20	1500 mL/day + 25 mL/kg/day	60 mL/hr + 1 mL/kg/hr

From Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. Pediatrics 1957;19:823–32.

Table 119–2.

Estimation of Fluid Deficit

DEFICIT	CLINICAL FINDINGS
Mild (1%-5%)	Dry mucous membranes, poor skin turgor, irritability, decreased urination
Moderate (6%-10%)	No tears, tenting of skin, lethargy, oliguria
Severe (≥11%)	Sunken eyes and fontanelles, cold skin, anuria, tachycardia and tachypnea, hypotension, coma

Modified from Siker D. Pediatric fluids, electrolytes, and nutrition. In: Gregory GA, editor. Pediatric anesthesia. New York: WB Saunders; 2002.

Key Points: Perioperative Fluids

- Maintenance of appropriate hydration is a fundamental and critically important concept in pediatric care.
- Fluid therapy must begin with an assessment of fluid deficit.
- Replacement fluids should begin with a balanced salt solution such as LR or NS.
- Maintenance fluids can be calculated using the Holliday-Segar formula.
- For maintenance fluids, children usually receive either D5 ¼ NS + 20 mEq/L KCl or D5 ½ NS + 20 mEq/L KCl, depending on their age and weight.

PEDIATRIC ANESTHESIA AND ANALGESIA

Psychologic and Emotional Preparation

The psychologic state of a child and family, as well as the clinical state of each child, must be thoroughly understood before anesthesia and surgical intervention. If the child is not treated in an age-appropriate manner, the entire perioperative experience will likely be compromised. Conversely, if the psychologic and emotional aspects of a child's condition distract caregivers from the primary medical and surgical concerns, a successful outcome may be compromised. Therefore it is imperative that the entire health care team find the ideal balance between these two considerations (Ferrari, 2008).

It is well known that significant preoperative anxiety is associated with a difficult and often prolonged anesthetic induction (Kain et al, 1996a, 1996b). Factors including the temperament and age of the child, as well as the situational distress of the parent and the outcome of previous medical experiences, will affect the child's anxiety level. For many children, the immediate postoperative course is a mirror of the induction experience. Children who go to sleep peacefully generally awaken in the same manner and are known to have fewer difficulties in the postanesthetic care unit (PACU). It is therefore necessary to take the time to prepare the child for the anesthetic experience in an age-appropriate manner. There is consensus among anesthesiologists regarding the need for the treatment of a child's anxiety before surgery (McCann and Kain, 2001). The development of coping skills is considered the most effective preoperative intervention, followed by modeling, play therapy, an operating room (OR) tour, and printed material (Kain et al, 1996a; O'Byrne et al, 1997; Moynihan and Kurkar, 1999; Ferrari, 2008).

The level of maturity affects a child's understanding of and response to illness (Moynihan and Kurkar, 1999). **Infants fear separation from their primary caregivers and exhibit stranger anxiety; therefore it is important that parental involvement in the perioperative experience be maintained. Toddlers fear loss of control, so enabling a child to make choices, such as asking if the child has a color preference for his or her hospital gown, will diminish anxiety. Preschool-age children fear injury; they may fear, for example, that a blood draw may result in not enough blood being left in their bodies.** They tend to think in concrete terms and therefore may take statements literally, so one must be cautious when choosing the language used with this age group. **The school-age child typically fears that he or she may not meet the expectations of adults.** They may nod with understanding and listen intently, despite not grasping what the adult is saying. They are reluctant to ask questions for fear that they should already know the answer. It is therefore imperative that expectations are clearly explained. **Adolescents fear death and usually do not understand bodily functions.** They are often panic-stricken preoperatively but try to not show any sign of this. As a result, they might remain very quiet. It is the responsibility of the care team to anticipate this anxiety and reassure the adolescent without prompting (Ferrari, 2008).

Risk of Anesthesia

Most parents will express that they experience more anxiety about the anesthetic than the risks of the surgery. Fear of anesthesia among parents originates largely from a lack of information regarding modern anesthesia practice rather than from a high probability of risk. For many families, it may be helpful to discuss specific risks of anesthesia for their child (Olsson and Hallen, 1984; Ferrari, 2008). **For a healthy child undergoing uncomplicated surgery, the risk of an adverse event is approximately 1 in 200,000** (Eichhorn, 1993). The risk of death under anesthesia is the most feared complication. This risk is 1 in 10,000 for all patients of any age undergoing any surgical procedure (Keenan and Boyan, 1985; Tiret et al, 1986; Holzman, 1994). **However, the risk of death directly attributable to the anesthetic approaches zero, although the risk of cardiac arrests due to anesthesia remains approximately 4.5 in 10,000** (Gobbo Braz et al, 2006). The incidence of anesthetic-related complications and death is highest during the first year of life at 43:10,000, but this decreases dramatically during the second year of life to 5:10,000 (Tiret et al, 1988). **Anesthetic risks increase by a factor of 6 during emergency procedures in all age groups** (Ferrari, 2008; Holzman, 2008).

Basic Preoperative Preparation

A complete medical history is always the first step in a thorough preoperative assessment. The history should include the prenatal course and neonatal period, because events during pregnancy and delivery may influence the child's current state of health (Means, 1997). Any prior hospital admissions should be noted. A complete review of systems is performed to evaluate for medical comorbidity that could influence the choice or outcome of anesthesia (Cote, 2001). The presence of cough, asthma, or a recent upper respiratory infection (URI) might predispose the child to bronchospasm, atelectasis, or pneumonia. New-onset heart murmur, cyanosis, hypertension, exercise intolerance, or a history of rheumatic fever can suggest an evolving issue that could be exacerbated by an anesthetic or with a surgical procedure. Parents should be queried for the presence of vomiting, diarrhea, malabsorption, black stools, gastroesophageal reflux, or jaundice to interrogate for electrolyte imbalance, dehydration, hypoglycemia, anemia, or the need for a rapid-sequence induction. A history of seizures, head trauma, or difficulty swallowing may indicate a metabolic derangement, increased intracranial pressure, or sensitivity to muscle relaxants. Urinary tract abnormalities may impact the state of hydration and renal function, and the urologist should clearly communicate the significance of these. Abnormal development, alterations in serum glucose levels, or a history of chronic steroid use may indicate an endocrinopathy, diabetes mellitus, hypothyroidism, or adrenal insufficiency. Lastly, a history of anemia, bruising, or excess bleeding may suggest a transfusion requirement or coagulopathy (Ferrari, 2008).

The family history should be obtained with particular attention to anesthesia-related events. Specifically, a history of liver problems in family members after anesthesia is important to elicit, because certain anesthetic agents are known to rarely cause liver damage. Malignant hyperthermia (MH) is always a concern in the pediatric population. Although most pediatric anesthesiologists refrain from routinely using succinylcholine, a family history of prolonged paralysis or mechanical ventilation after general anesthesia should be obtained. Finally, families should be asked if there is a history of unexpected death, sudden infant death syndrome, genetic defects, or familial conditions, such as muscular dystrophy, cystic fibrosis, sickle cell disease, bleeding tendencies, or human immunodeficiency virus infection (Ferrari, 2008).

Obtaining a complete medication history is essential. This includes prescription medications, nonprescription medications, and herbal or alternative therapies. Many over-the-counter cold remedies contain aspirin, nonsteroidal anti-inflammatory drugs, or other compounds that may interfere with coagulation. Herbal and alternative therapies are known to have significant deleterious interactions with certain prescription medications and must be considered prior to administration of anesthesia and proceeding with surgery (Cupp, 1999).

The practice of body piercing is becoming increasingly common in adolescents and young adults. Metal objects in the skin during surgery and anesthesia increase the risk of burn injury if there is an intraoperative electrocautery malfunction. In addition, metal objects can become caught on equipment in the OR, resulting in tears of the skin and subcutaneous tissue. Tongue piercing may interfere with laryngoscopy and make securing the airway unnecessarily challenging. Therefore patients should be counseled to remove all metal objects and disclose any body piercing that cannot be seen during the preoperative interview (Ferrari, 2008).

The physical examination of children must begin with simple observation from a distance, because the infant or child may become frightened when approached directly. A great deal can be learned about relevant physical findings without touching the child. The color of the skin, including the presence of pallor, cyanosis, rash, jaundice, unusual markings, or prior surgical scars, may reveal the presence of organ system dysfunction. Because congenital anomalies often occur in association with others, abnormal facies may indicate additional anomalies. The respiratory system examination should specifically address any signs of an URI. The cardiovascular examination specifically addresses the presence of heart murmurs, which must be accurately diagnosed as innocent versus pathologic. Lesions in which bacterial endocarditis prophylaxis or protection from paradoxic air embolism are required must be documented (Wilson et al, 2007; Ferrari, 2008).

Routine diagnostic testing in preparation for surgery is rarely indicated in healthy children, and studies that are ordered should be selected based on the general medical health of the patient and the procedure being performed. In general, measurement of hemoglobin/hematocrit in a healthy child undergoing elective surgery is unnecessary (Steward, 1991). **A hemoglobin/hematocrit should be measured if significant blood loss is anticipated or if the child is younger than 6 months or was born prematurely.** Neither the routine measurement of a coagulation profile nor a history of "easy bruising" is reliable in predicting surgical bleeding (Burk et al, 1992). A history of a prior hematoma and excessive bleeding following circumcision or large bruises should prompt an appropriate hematologic evaluation. Routine preoperative urinalysis is not indicated in children, and serum chemistries should only be performed when an abnormality is suspected. Children who are treated with anticonvulsants should have these medication levels checked, and an electrocardiogram or chest radiograph should only be ordered if the general medical condition warrants. Routine pregnancy testing is controversial, and the policy of one's medical facility should be followed (Ferrari, 2008).

None per Os (NPO) Guidelines

It is no longer advisable or safe to restrict children to "NPO after midnight" (Cote, 1990). This outmoded restriction increases the child's chance of undergoing induction of anesthesia when dehydrated, hypoglycemic, and cranky, all of which lead to a suboptimal situation. The risk of pulmonary aspiration of gastric contents in healthy children undergoing elective surgery is only 0.04% (Warner et al, 1999). The American Society of Anesthesiologists (ASA) has proposed practice guidelines that may be followed when determining NPO restrictions in children (Practice guidelines, 1999). **The ASA recommends fasting from clear fluids for 2 hours prior to anesthesia.** Clear liquids consist of water, nonparticulate juices (e.g., apple, white grape), Pedialyte, and Popsicles. **Fasting from breast milk for 4 hours and formula for 6 hours is recommended. The suggested fasting period for solid food is 6 hours for regular meals and 8 hours for fat-containing meals.** However, a large survey of pediatric institutions recommends fasting from all solids for at least 8 hours in all children (Ferrari et al, 1999). However, individual institutions may have specific practice guidelines that differ from the above.

Immunizations

The timing of vaccinations in the perioperative period has been a controversial topic. It is known that both anesthesia and surgery exert immunomodulatory effects, and some believe that these effects may exert additive or synergistic influences on vaccine efficacy and safety (Siebert et al, 2007). This risk, however, is theoretic and there are no guidelines that address the issue. Based on an exhaustive review of the literature, Siebert and colleagues (2007) concluded that the immunomodulatory influence of anesthesia during elective surgery is both minor and transient, lasting about 48 hours, and that the current evidence does not provide any contraindication to the immunization of healthy children scheduled for elective surgery. **However, respecting a minimal delay of 2 days (inactivated vaccines) or 14 to 21 days (live attenuated viral vaccines) between immunization and anesthesia may be useful to avoid the risk of misinterpretation of vaccine-driven adverse events as postoperative complications**. Of utmost importance is the distinction between postvaccine and postoperative temperature elevation.

Special Circumstances

Child with an Upper Respiratory Infection

Whether to proceed with an elective operation in a child with an active URI is one of the most difficult and fundamental questions in pediatric anesthesia (Hinkle, 1989). Children typically experience three to nine URI episodes per year, and the majority occur during the winter months (Van der Walt, 1995). The classic signs and symptoms include fever, irritability, restlessness, sneezing, nasal discharge, nasal obstruction, headache, malaise, and anorexia (Tait and Malviya, 2005). Children between the ages of 3 months and 3 years also have fever early in the course of the illness, and, in general, younger children have more severe infections than older children. It is likely that during the winter months a child *has* a cold, is just *recovering* from a cold, or is *about to catch* a new cold (Tait and Malviya, 2005; Ferrari, 2008).

A cough is a sign of lower respiratory involvement and should be evaluated for origin (upper airway or bronchial) and quality (wet or dry). Most children will have clear breath sounds when auscultated during quiet respirations. It is during coughing and crying that rales and rhonchi will be best detected (Ferrari, 2008).

Definitive criteria for canceling surgery have not been established, and the decision is often subjective. **Criteria that suggest that cancellation should be considered, including the necessity for endotracheal intubation, parental observation that the child is acutely ill on the day of surgery, the presence of nasal congestion and cough, a history of secondary smoke exposure, and active sputum production** (Cohen and Cameron, 1991; Parnis et al, 2001). Decisions to cancel surgery should be made collaboratively between the anesthesiologist and surgeon and based on the type of procedure, the urgency of the procedure, and the child's overall medical condition. **Most authors agree that surgery may be scheduled after the acute symptoms have resolved and no sooner than 3 to 4 weeks after the initial evaluation** (Ferrari, 2008). A suggested algorithm is provided in Figure 119–1 (Tait and Malviya, 2005; Zuckerberg, 2009).

Asthma

Asthma is one of the most common chronic pediatric illnesses and is characterized by bronchoconstriction, hypersecretion of mucous, mucosal edema, and desquamation of inflammatory cells. The hyperactive airways are very sensitive to stimulation, and endotracheal intubation is one of the most noxious stimulants resulting in bronchoconstriction in the susceptible airway. In preparing children with asthma for surgery, it is important to note if a child is on maximal medical therapy and if wheezing persists despite this. **All asthma medications, both inhaled and oral, should be administered up to and including the morning of surgery.** If children are not on maintenance therapy and only require treatment during acute exacerbations, this therapy should be administered for the 48 hours prior to anesthesia even if the child is asymptomatic. If performed, recent pulmonary function test (PFT) results should be available, and children as young as 5 years can cooperate with PFT (Ferrari, 2008).

Former Premature Infant

Advances in neonatology have resulted in an increasing number of premature infants surviving. These infants generally have

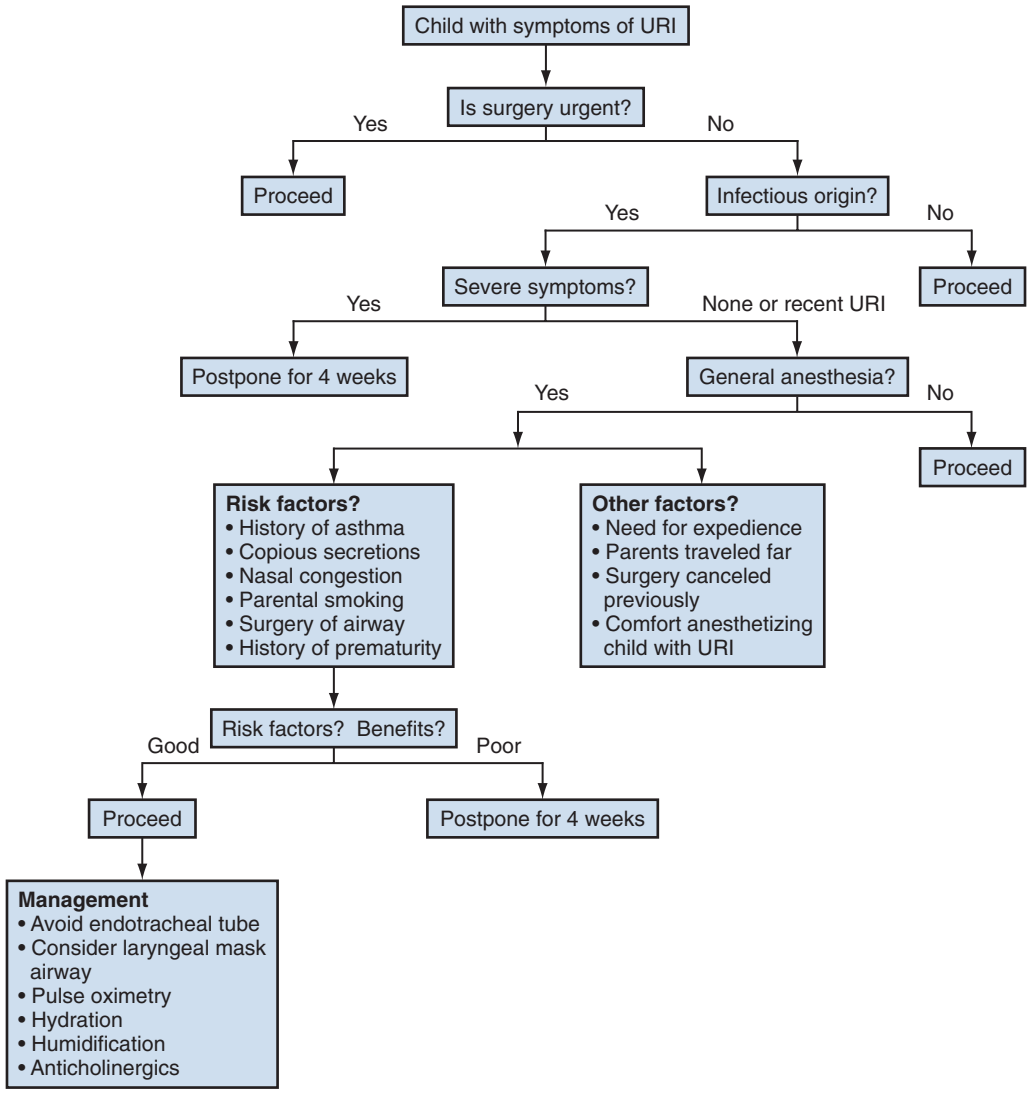


Figure 119–1. Preoperative decision making in children with upper respiratory infection symptoms (URI). (From Tait AR, Malviya S. Anesthesia for the child with an upper respiratory infection: still a dilemma? Anesth Analg 2005;100:59–65.)

complex medical issues and often require surgery for a variety of reasons. Urgent urologic surgery in these babies, however, is rare. From a perioperative perspective, the major issue with these infants is the risk of apnea. Apnea is usually central and is the result of brainstem immaturity, which predisposes these infants to more significant apnea during the postoperative period (Kurth et al, 1987). This risk is less than 1% in a 35-week former premature infant if surgery is delayed until after 54 weeks postconceptual age (Cote et al, 1995). If surgery cannot wait, then postanesthetic apnea monitoring is required for 24 hours. Postanesthetic apnea has also been reported in full-term infants younger than 4 weeks of age, and therefore similar monitoring is required (Noseworthy et al, 1989). **In addition, a hematocrit less than 30 is associated with an increased risk of postanesthetic apnea in the former preterm infant, and therefore a preoperative hematocrit is warranted in all premature infants undergoing surgery** (Welborn et al, 1991; Ferrari, 2008).

Spina Bifida

Spina bifida is one of the most common birth defects, and urologists should be involved in the care of these patients beginning immediately after birth. The average incidence of spina bifida in the United States is 0.7 per 1000 live births. The incidence is higher on the East Coast than on the West Coast, and higher in whites (1 case per 1000 live births) than in blacks (0.1 to 0.4 cases per 1000 live births) (Lemire, 1988). These children are frequent visitors to the OR and require careful preoperative preparation, given their frequent comorbidities. **There is a high incidence of sensitivity to latex-containing products, so all patients with spina bifida should be regarded as having a latex allergy.** A significant number of children with spina bifida have ventriculoperitoneal (VP) shunts to manage the hydrocephalus. At Children's Hospital Boston, we have a mandatory protocol for elective surgery preparation in children with VP shunts to ensure that they are functional prior to administration of anesthesia (Fig. 119–2).

Children with Cancer

Children with a current or prior malignancy should have all chemotherapy documented. Anthracyclines (doxorubicin [Adriamycin]) can cause myocardial dysfunction, and others such as mitomycin C and bleomycin can cause pulmonary dysfunction. Children who have been treated with anthracycline agents require echocardiography if the cumulative dose is greater than 150 mg

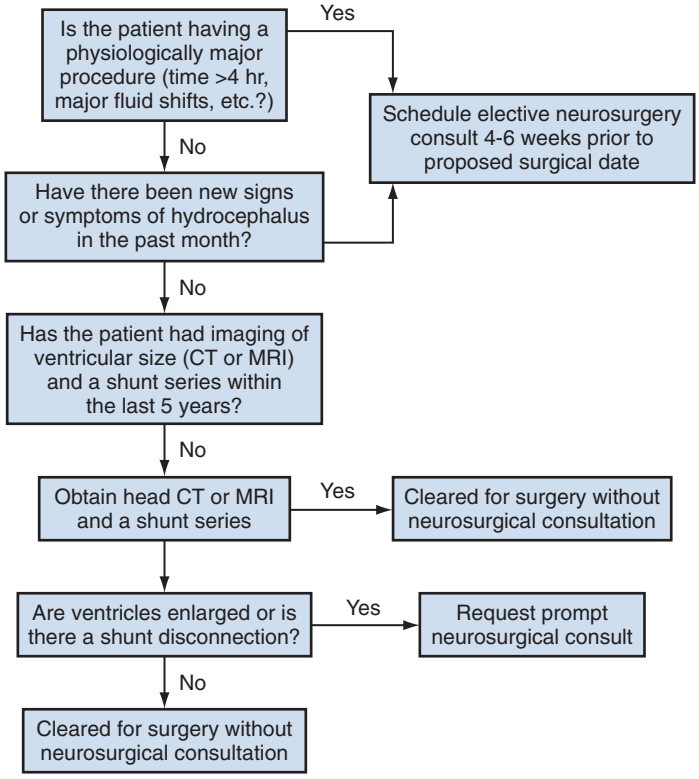


Figure 119–2. Preoperative assessment of patients with shunted hydrocephalus. (From Children's Hospital Boston, copyrighted 2008.)

per m^2 (Lipshultz et al, 1991). Any child with a history of congestive heart failure, who has not had a postanthracycline echocardiogram or an echocardiogram within 2 years before the time of anesthesia, requires a preoperative echocardiogram (Ferrari, 2008).

Child of a Jehovah's Witness

Jehovah's Witnesses refuse blood transfusions because of the belief that the "life force" resides in their blood. Although adult Jehovah's Witness patients may choose to refuse lifesaving blood transfusions, pediatric patients, as minors, do not have that same right. It is therefore imperative that the surgical and anesthesia teams define a plan with the parents in the event that blood is required. Perioperative volume expanders, such as albumin, and hemodilution and blood banking are acceptable to some individuals, depending on their interpretation of biblical passages (Benson, 1989). **Most medical care providers agree that in an emergency it is unacceptable for a parent to make a conscious decision that could result in the loss of a minor child's life; in such cases, appropriate medical therapy, including transfusion of blood products, is administered against the wishes of the family** (Swartz, 1985). In most circumstances, the courts have intervened to allow blood transfusions over the religious objections of the parents. No child of Jehovah's Witness parents should die for lack of transfused blood without a physician seeking a court order to do so (Waisel, 2001). Consultation with a pediatric hematologist may be helpful to optimize the preoperative preparation, which may include oral iron therapy 2 to 3 weeks before surgery.

Congenital Adrenal Hyperplasia

Patients with congenital adrenal hyperplasia (CAH) are frequently treated by pediatric urologists, and their condition requires careful perioperative preparation. The most common form of CAH is 21-hydroxylase deficiency, which results in an excess of progesterone and 17-hydroxyprogesterone. These hormones are then peripherally converted to androgens, which result in virilization of affected girls. Approximately 75% of these patients are also salt-wasters, because of impaired mineralocorticoid production. In addition, adrenal catecholamine production is deficient in patients with CAH. The cornerstone of medical management of CAH is lifelong hormonal replacement. Children are given hydrocortisone, and salt-wasting patients also require fludrocortisones and sodium chloride supplementation. **Perioperatively, it is critical to be clear on the nature of the child's CAH and how well and stably it is medically managed.** Baseline parameters, including hydration status, blood pressure, and electrolytes are determined. The usual doses of hydrocortisone are inadequate to cover the physiologic stress of surgery, and thus CAH patients are typically given 100 mg/m^2 hydrocortisone in four divided intravenous doses for the first 24 hours and then slowly tapered (Zuckerberg, 2009). A clear perioperative plan for hormonal supplementation should be developed in conjunction with the child's endocrinologist.

Regional Anesthesia

There has been increased interest in regional anesthesia in children mainly due to two general factors: decreased general anesthetic requirement and improved postoperative pain management. At Children's Hospital Boston, the authors routinely use two related types of regional anesthesia: single-shot caudal blocks and epidurals. Caudal blocks are typically used in patients undergoing bilateral groin surgery, open ureteroneocystostomy, and neonatal patients in whom we would like to limit the administration of narcotics. Epidural anesthesia is generally used in children undergoing renal surgery or extensive pelvic surgery.

Single-shot caudal blocks are one-time injections of local anesthetic agents into the epidural space, and can provide analgesia in the T10 to S5 dermatome region. The most common local anesthetic used is bupivacaine 0.125% to 0.25%, with epinephrine administered in volumes of 0.5 to 2 mL/kg (not to exceed toxic doses measured in mg/kg) (Kraemer and Rose, 2009). **The addition of clonidine, 1 to 2 μg/kg to a maximum of 30 μg, may enhance the duration and intensity of the caudal block** (Constant et al, 1998). In addition to the one-time injection, an angiocatheter may be left in place in the caudal region for additional postoperative local anesthetic administration. One of the most frequent complications with caudal blocks is the inadvertent needle placement into the vasculature, intrathecal space, or even bone in very young children; however, this rate is low (0.7 per 1000) (Kraemer and Rose, 2009).

Continuous epidural analgesia (CEA) provides excellent perioperative analgesia in infants and children undergoing thoracic, abdominal, pelvic, and perineal surgery. The epidural space may be accessed at any level, but is most frequently approached at the lumbar or caudal region in children. If the epidural needle touches the spinal cord, a patient who is awake will react, and spinal cord injury can be thereby avoided. However, the vast majority of epidural catheters in children are placed under general anesthesia, because it is generally considered safer to place epidurals in children who are not moving. The risk of neurologic injury with lumbar epidural catheter placement is exceedingly low, but thoracic placement does carry a higher risk of spinal cord injury should the needle be advanced too far. As such, direct thoracic placement under general

anesthesia should be performed only by very experienced personnel and with careful consideration of the potential risks and benefits (Greco, 2002). In selected cases, catheters can be advanced to the thoracic level from a lumbar or caudal route under fluoroscopic guidance. The location of the catheter tip can be confirmed with a contrast epidurogram (Greco, 2002). Epidural drug selection is individualized and varies with site of surgery, location of the epidural, and patient-specific factors. In general, local anesthetics are infused in combination with opioids, clonidine, or both. Clonidine is used because of the same benefits as discussed for single-shot caudal blocks, and is used preferentially over opioids, if possible, because it does not cause adverse effects typical of opioids, including pruritus, nausea, ileus, urinary retention, or respiratory depression (Greco, 2002; Hirschl, 2003c). The risk of local anesthetic toxicity is one of the main concerns that require continuous monitoring during CEA. Hospitals should have a dedicated team of anesthesiologists and nurses immediately available to manage any emergent problems with pain control or adverse effects with CEA. The epidural site should be evaluated daily for signs of infection. Protocols and CEA order sets should include patient monitoring parameters and neurologic assessment every 4 hours (Kraemer and Rose, 2009).

A related topic is the use of local anesthetic drugs for peripheral sensory nerve blockade, an approach commonly used in pediatric urology with the dorsal penile block. This technique is routinely used for penile surgery including circumcision, circumcision revision, and hypospadias repair. **It has been shown to be simple, safe, and effective, and provides equivalent analgesia to a one-shot caudal block** (Cyna and Middleton, 2008). The most commonly used drug is bupivacaine (0.25%) in volumes of 1 mL/kg. Compared with lidocaine, it has a longer onset time but also significantly longer duration. However, it has greater potential for cardiotoxicity if inadvertently injected intravascularly. A newer alternative is ropivacaine (0.75%), which has an onset time and duration of action comparable with bupivacaine but is associated with less toxicity (Ecoffey, 2005). However, ropivacaine has theoretical vasoconstrictive properties and has been associated with a case of penile ischemia (Burke et al, 2000). The safest technique is to inject the appropriate volume of the local anesthetic bilaterally just below the pubis. This avoids the midline, where the dorsal penile vessels are located, thereby reducing the risk of hematoma formation and provides the most direct route to the dorsal penile nerves located lateral to the midline in the Buck fascia. In addition, the authors prefer to inject half of the allotted dose of the local anesthetic at the beginning of the case and half at the completion of surgery, because this has been shown to provide significant improvement in postoperative pain control (Chhibber et al, 1997).

Postoperative Pain Management

It is incumbent upon pediatric care providers to make every attempt possible to assess their patients' pain, which may be very challenging given the limited cognition and language skills of infants and children. Pain assessment tools are well established and widely available, but assessing pain in neonates, infants, and nonverbal or developmentally delayed children is still limited (Kraemer and Rose, 2009). In general, the younger the child, the less likely he or she can clearly delineate between levels of pain using pain scales. **In general, however, children 8 years and older can reliably report pain on the visual analog scale used for adults. Children between the ages of 3 and 7 years can better report pain using a faces scale that uses a series of drawings depicting increasing levels of distress** (Kraemer and Rose, 2009). Table 119–3 provides examples of some routinely used pediatric pain scales. In addition to the child, parents are very often an excellent source of information regarding their child's pain.

Table 119–3.
Pediatric Pain Scales

SCALE	TYPE	AGES	SCORING INDICATORS
PIPP	Behavioral and physiologic parameters Procedural pain	Term and preterm infants	Gestational age Behavioral state Heart rate, SpO_2 Facial expression
CRIES	Behavioral and physiologic parameters Postoperative pain	32-60 weeks	Crying, increased O_2 Increased vital signs Expression Sleeplessness
FLACC	Behavioral parameters	<3 years or unable to self-report	Face, legs, activity, cry, consolability
FACES	Self-report	3-12 years	Happy face to saddest face yield numeric 0-10 score
VAS	Self-report	>7 years	0 = no pain 10 = maximum pain

CRIES, crying, increased O_2, increased vital signs, facial expression, sleeplessness; FLACC, face, legs, activity, cry, consolability; PIPP, premature infant pain profile; VAS, visual analog scale.

Modified from Kraemer FW, Rose JB. Pharmacologic management of acute pediatric pain. Anesthesiol Clin 2009;27:241–68.

Based on severity, pediatric pain management involves targeting several of the complex elements of pain transduction, transmission, modulation, and perception (Kraemer and Rose, 2009). Common multimodal plans include nonsteroidal anti-inflammatory drugs (NSAIDs) acting on the periphery; regional block of peripheral nerves, nerve roots, or spinal cord; and/or opiates acting centrally. Such a balanced approach can minimize the adverse effects of each modality and work synergistically to best manage acute pain.

For children who undergo nonambulatory surgery and who do not have CEA, patient-controlled analgesia (PCA) is an excellent option for treating moderate to severe pain. **Children as young as 5 years old have successfully used PCA with proper education and guidance, but PCA is routinely used in children age 7 years and older** (McDonald and Cooper, 2001). The use of PCA mandates institutional/departmental monitoring requirements that include respiratory rate, pulse oximetry, heart rate, blood pressure, pain assessment, and level of consciousness. When used with appropriate monitoring, PCA is safe, effective, and highly reliable. In younger children or those unable to reliably control their PCA, nurse- or parent-controlled analgesia can be used with similar success and efficacy.

Oral pain medications include nonopioid and opioid analgesics. Nonopioid options include acetaminophen and NSAIDs. **Acetaminophen is the most widely used antipyretic and analgesic medication in pediatrics and is commonly combined with opioids for patients with moderate to severe pain.** When dosed appropriately, acetaminophen can be used safely in neonates. It is normally metabolized in the liver primarily by glucuronidation and sulfation. Neonates and infants primarily conjugate by sulfation, and the mature ratio of glucuronidation/

Table 119–4.
Acetaminophen Dosing

ROUTE OF ADMINISTRATION	PRETERM INFANTS (28-32 WEEKS)	PRETERM INFANTS (>32 WEEKS)	FULL-TERM INFANTS AND CHILDREN <52 kg	CHILDREN >52 kg, ADOLESCENTS, AND ADULTS
Oral	12.5 mg/kg q6h PRN for 72 hours	12.5 mg/kg q4h PRN for 72 hours	12.5 mg/kg q4h PRN for 72 hours	325-975 q4h PRN for 72 hours
Rectal	20 mg/kg q12h PRN for 72 hours	15 mg/kg q8h PRN for 72 hours	15-20 mg/kg q4h PRN for 72 hours	325-975 q4h PRN for 72 hours
Maximum dose	50 mg/kg/day	90 mg/kg/day	90 mg/kg/day (up to 4 g/day)	4 g/day

Based on Children's Hospital Boston formulary.

sulfation is reached at approximately 12 years of age. **The concerning feature of acetaminophen is that overdose can lead to liver necrosis and failure.** This is because supranormal doses of acetaminophen are metabolized by the oxidative cytochrome P450 pathway, which results in a highly hepatotoxic metabolite. Acetaminophen is available in several formulations, including drops (80 mg/0.8 mL), elixir (160 mg/5 mL), chewable tablets (80 mg and 160 mg), dissolvable tablets (160 mg), tablets (325 mg and 500 mg), and suppositories (80 mg, 120 mg, 325 mg, and 650 mg). Intravenous acetaminophen preparations do exist but are currently not available in the United States. The suggested dosing of acetaminophen is provided in Table 119–4.

NSAIDs are commonly used for postoperative pain, because they provide excellent analgesia and are well tolerated. **A review of short-term ibuprofen use in a large cohort of children revealed no increase in renal or gastrointestinal adverse effects compared with acetaminophen** (Lesko and Mitchell, 1995). NSAIDs are more similar than they are different. Adult clinical trials, outcome studies, and systematic reviews indicate that no NSAID possesses uniquely greater analgesic effect than others and that the oral, rectal, and parenteral routes of administration are equally effective (Greco, 2002). Like acetaminophen, ibuprofen is available in several preparations, including drops (50 mg/1.25 mL), elixir (100 mg/5 mL), chewable tablets (50 mg and 100 mg), and tablets (200 mg, 400 mg, 600 mg, and 800 mg). Intravenous ibuprofen is available in the United States, but has not been approved for use in pediatric patients for the treatment of pain. Ibuprofen should be used routinely in children age 6 months and older. For analgesia, a single dose of 15 mg/kg can be used. However, if repeated doses are anticipated or planned, dosing should be 4 to 10 mg/kg/dose every 6 to 8 hours, with a maximum daily dose of 40 mg/kg/day.

Ketorolac is the only parenteral NSAID (15 mg/mL and 30 mg/mL) available for in the United States to treat pediatric pain, and it has been used as an adjuvant to opioids and a single agent for the treatment of postoperative pain. The authors routinely use ketorolac in children at least 6 months of age, but it is approved for use in children 2 years or older. **The authors have found that in addition to excellent analgesia, ketorolac significantly reduces the incidence and severity of bladder spasms** (Park et al, 2000), **and the authors routinely use ketorolac following bladder surgery.** However, significant adverse effects have been reported, including acute renal failure, prolongation of bleeding times, and hypersensitivity reactions, and therefore caution is warranted (Kraemer and Rose, 2009). Because of this, the authors do not use ketorolac in patients with renal insufficiency, renal scarring, a solitary kidney, NSAID sensitivity, or a patient in whom a risk of significant postoperative bleeding is feared. Dosing of ketorolac is 0.25 to 0.5 mg/kg every 6 hours, with no loading dose requirement.

Table 119–5.
Opioid Dosing

OPIOID	ROUTE/AGE GROUP	DOSE/INTERVAL
Morphine	**Intravenous bolus:**	
	Full-term neonate	10-25 µg/kg every 2-4 hr
	Preterm neonate	25-50 µg/kg every 3-4 hr
	Infants and children	50-100 µg/kg every 3-4 hr
	IV infusion:	
	Preterm neonate	2-5 µg/kg/hr
	Full-term neonate	5-10 µg/kg/hr
	Infants and children	15-30 µg/kg/hr
Codeine	Oral	0.5-1 mg/kg every 4 hr
Oxycodone	Oral	0.05-0.15 mg/kg every 4 hr

Modified from Kraemer FW, Rose JB. Pharmacologic management of acute pediatric pain. Anesthesiol Clin 2009;27:241–68.

Opioids are commonly used for moderate to severe pain, and for the vast majority of children, provide excellent analgesia with a wide margin of safety. They affect analgesia by central nervous system neuronal inhibition. The commonly used opioids in the pediatric population are mu_1 agonists and include morphine, hydromorphone, methadone, fentanyl, codeine, oxycodone, and hydrocodone (Table 119–5). Opioids can be administered through several routes, including oral, intravenous, intramuscular, subcutaneous, rectal, transdermal, or transmucosal. Oral administration is usually the easiest route and provides relatively constant drug plasma levels. **Despite their general efficacy, there is substantial individual variation in opioid dose requirements. The adequate opioid dose is that which provides pain relief but does not result in excessive somnolence or respiratory depression.** Morphine is the standard opioid to which all others are compared (Greco, 2002; Kraemer and Rose, 2009). It is metabolized in the liver, and the elimination half-life is longer and the clearance is decreased in newborns. This difference is even more substantial in preterm neonates. Within 2 months of age, however, the elimination half-life and clearance reach adult levels. There is no established optimal morphine plasma concentration, and therefore the appropriate dose needs to be established for each patient, while carefully monitoring for respiratory depression.

Codeine is available in elixir form and is the most common orally administered opioid in young children. It is often combined with acetaminophen (acetaminophen 120 mg with codeine 12 mg/5 mL), and, in this form, is more effective. Dosing of codeine is 0.5 to 1 mg/kg every 4 hours, but the dose of acetaminophen needs to be carefully considered to avoid

acetaminophen toxicity. The maximum dose based on acetaminophen content for children weighing less than 45 kg is acetaminophen 90 mg/kg/day, and for children weighing more than 45 kg it is acetaminophen 4 g/day. **Codeine itself is a relatively weak opioid, given its extremely low affinity for opioid receptors, and most of its analgesic effect is due to the 10% that is metabolized to morphine.** The metabolism to morphine is predominantly by *O*-demethylation by the cytochrome P450 enzyme CYP2D6, which is known to show genetic polymorphism (Williams et al, 2001). **Therefore variations in CYP2D6 will result in variable abilities to metabolize codeine.** In this way, individuals may be classified as poor metabolizers or ultrarapid metabolizers, depending on the phenotype of their CYP2D6 enzyme. **Three percent of whites and 40% of people of North African descent are ultrarapid metabolizers, resulting in dangerously high plasma levels of morphine** (Gasche et al, 2004). **Conversely, 7% to 10% of whites are poor metabolizers of codeine, and receive little or no analgesia from codeine administration** (Kraemer and Rose, 2009). The disastrous consequences of CYP2D6 variability is highlighted by the recent report of the death of a 2-year-old child who was given codeine at home following a routine tonsillectomy (Ciszkowski et al, 2009). Genotyping of the patient revealed duplication of the CYP2D6 allele (ultrarapid metabolizer), and the plasma concentration of morphine was 32 ng/mL (>20 ng/mL results in respiratory depression). **Because of this risk, the authors generally prefer oxycodone, which appears to have less variable metabolism.**

Oxycodone is available in tablet and liquid form and is also commonly combined with acetaminophen. The combined preparation is commonly used in children and is available in solution (oxycodone 5 mg and acetaminophen 325 mg/5 mL) and in tablet form (oxycodone 2.5 to 10 mg and acetaminophen 300 to 650 mg). The initial dose is based on the oxycodone content, but the maximum daily dose is based on the acetaminophen content. Based on pain severity, the initial oxycodone dose is 0.05 to 0.3 mg/kg/dose. The maximum dose based on acetaminophen content for children weighing less than 45 kg is acetaminophen 90 mg/kg/day and for children weighing more than 45 kg is acetaminophen 4 g/day.

Key Points: Pediatric Anesthesia and Analgesia

- Surgical preparation is a multifaceted endeavor that involves consideration of medical and psychological needs of children and their families, all of which vary with the child's age and developmental status.
- The risks associated with anesthesia in a healthy child undergoing uncomplicated surgery are extremely low.
- Routine diagnostic testing for surgery is rarely indicated in healthy children, and studies that are ordered should be selected based on the general health of the patient and the procedure being performed.
- Children should not be kept "NPO after midnight"; the ASA has provided guidelines to optimize patient hydration and minimize risk.
- URI is very common in childhood; elective surgery should be scheduled after the acute symptoms have resolved and no sooner than 3 to 4 weeks after the initial evaluation.
- Children with VP shunts should undergo evaluation to ensure proper shunt function prior to major surgery.
- Regional anesthesia plays an important role in several urologic surgeries, and the most commonly performed are the single-shot caudal block and continuous epidurals.
- Based on severity, pediatric pain management involves targeting several of the complex elements of pain transduction, transmission, modulation, and perception.
- Acetaminophen is the most widely used analgesic in pediatrics; ibuprofen is also commonly used, and children are unlikely to experience renal or gastrointestinal adverse effects.
- Opioids are used for moderate to severe pain, and there is substantial variation in individual opioid dose requirements.
- Codeine has highly variable efficacy due to genetic polymorphism of the CYP2D6 liver enzyme; patients may be poor metabolizers, resulting in little or no analgesia, or rapid metabolizers, resulting in dangerous plasma levels of postmetabolism opioid.

SURGICAL PREPARATION

Antimicrobial Prophylaxis

Because there are no available guidelines from any of the pediatric urologic or surgical societies, whether to use prophylactic antibiotics in children undergoing surgery remains an individual and non–evidence-based decision. This decision is generally not controversial for major surgery when surgical antimicrobial prophylaxis (SAP) is routinely administered, but it is for minor procedures, such as orchidopexy, herniorrhaphy, and circumcision. The Centers for Disease Control and Prevention (CDC) provided guidelines for SAP (Mangram et al, 1999), but these were broad and general and did not specifically address urologic surgery. In 2001, the European Association of Urology published urology-specific guidelines, but pediatric procedures were not specifically addressed. Recently, the Japanese Urological Association published comprehensive SAP guidelines that included pediatric procedures (Matsumoto et al, 2007), but these were not evidence based and were formulated based on the opinions and practice patterns of academic pediatric urologists. The CDC surgical wound classification system of clean (class I), clean-contaminated (class II), contaminated (class III), and dirty/infected (class IV) can be applied to pediatric urologic procedures, and examples are provided in Table 119–6. **In general, SAP is recommended for (1) all surgery in neonates less than 72 hours of age because of possible exposure to maternal pathogens and, particularly, compromised immunologic capacity, (2) major class II surgery, and (3) all class III and IV surgical procedures** (Antimicrobial prophylaxis for surgery, 2004). Antibiotic use in class I and minor class II operations has not been studied, and remains based on individual surgeon's preference. Recommendations for SAP are provided in Table 119–7. **The timing of SAP administration is critically important, and the first dose should be given 30 minutes to 3 hours prior to incision to achieve bactericidal levels of the antibiotic at the site of incision.**

Thromboembolism Prophylaxis

Venous thromboembolic events (VTEs) in children are rare when compared with adults. The incidence of VTEs in

children is estimated to be 0.07 to 0.14 per 10,000 in the general population and 5.3 per 10,000 for pediatric hospital admissions (Andrew et al, 1994; van Ommen et al, 2001). In general, the frequency of VTEs in children is one tenth that of adults (Levy et al, 2004), and several factors are believed to contribute to this difference. These include lower levels of thrombin in childhood, enhanced levels of thrombin inhibitors in children, and significantly lower levels of various clotting factors at different times in childhood (Jackson and Morgan, 2008). Despite the rare incidence, it is believed to be increasing, most likely owning to increased awareness and diagnosis and improved life expectancy of children with serious prothrombotic diseases, such as congenital heart disease, cancer, and extreme prematurity (Jackson and Morgan, 2008). **The incidence of VTE in the pediatric population is bimodal, occurring most often in infants aged less than 1 year and in adolescents.** These two age groups account for more than 70% of VTEs. Risk factors in infants include diminutive blood vessels, a unique hemostatic system, and the use of central venous catheters (CVCs). Risk factors in adolescents include smoking, contraception, and obesity (Sandoval et al, 2008). In general, the greatest risk factor is the presence of a CVC. There are no clear guidelines in pediatric surgery for the use of thromboprophylaxis, and typically individual institutions develop local policy. In general, for pediatric noncancer urologic surgery, the authors use thromboprophylaxis in the postpubertal period, because it is assumed that the adult risk of VTE develops after sexual maturation. **The extent of thromboprophylaxis, which can include compression stockings and/or sequential compression devices (SCDs) plus or minus subcutaneous enoxaparin, is made on a case-by-case basis, depending on the assessment of an individual child's risk factors.**

Table 119–6.

Wound Classification in Pediatric Urologic Surgery

WOUND CLASSIFICATION	PROCEDURES
Clean	Nephrectomy, adrenalectomy, retroperitoneal tumor resection, orchidopexy, herniorrhaphy
Clean-contaminated	Nephroureterectomy, partial nephrectomy, pyeloplasty, ureteral reimplant, other intravesical procedures, exstrophy closure, partial cystectomy, hypospadias repair, other genital surgery, cystoscopy, transurethral incision of ureterocele, transurethral ablation of posterior urethral valves
Contaminated	Bladder enterocystoplasty, continent urinary diversion
Dirty	Open trauma of the urinary tract, operations for infected kidney, ruptured bladder augmentation

Modified from Yamamoto S, Shima H, Matsumoto T. Controversies in perioperative management and antimicrobial prophylaxis in urologic surgery. Int J Urol 2008;15:467–71.

Hair Removal

Peripubertal children and postpubertal adolescents may have a significant amount of hair at the sites of urologic procedures. The questions of appropriate timing and method of hair removal have been debated because they are thought to significantly impact the development of surgical-site infections (SSIs). The most recent data indicate that there is a higher risk of SSI when hair is removed on the day or night prior to surgery and also with the use of razors. **Lower rates of SSI are achieved by using clippers or depilatory agents immediately prior to surgery** (Tanner et al, 2007)**.** Based on this, the authors' policy is to remove hair, using clippers, at the time of immediate presurgical preparation in the operating room. Razors are no longer available in our operating rooms.

Table 119–7.

Recommendations for Surgical Antimicrobial Prophylaxis

OPERATION	LIKELY PATHOGENS	PROPHYLACTIC ANTIBIOTICS	PREOPERATIVE DOSE
Neonatal (<72 hr old) Surgery	Group B streptococci, enteric gram-negative bacilli, enterococci	Ampicillin + gentamicin	50 mg/kg ampicillin 2.5-3 mg/kg gentamicin
Class I (clean)	*Staphylococcus epidermidis, Staphylococcus aureus,* streptococci, gram-negative enteric bacilli	Cefazolin or Vancomycin (if MRSA or MRSE likely)	25 mg/kg 10 mg/kg
Class II (clean-contaminated)	Enteric gram-negative bacilli, enterococci	Cefazolin or Ampicillin + gentamicin	25 mg/kg 50 mg/kg ampicillin 2.5-3 mg/kg gentamicin
Class III (contaminated)	Gram-negative enteric bacilli, enterococci, anaerobes	Cefoxitin or Cefotetan	40 mg/kg 40 mg/kg
Class IV (dirty/infected)	Gram-negative enteric bacilli, enterococci, anaerobes	Cefoxitin or Cefotetan ± gentamicin or Gentamicin + clindamycin	40 mg/kg 40 mg/kg (±2 mg/kg gentamicin) 2 mg/kg gentamicin + 10 mg/kg clindamycin

MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*.

Modified from McInerny TK, Adam HM, Campbell DE, et al, editors. American Academy of Pediatrics textbook of pediatric care. Elk Grove Village (IL): American Academy of Pediatrics; 2009.

INTRAOPERATIVE CONSIDERATIONS

Blood Loss and Transfusion Requirement

Blood volume in children varies with age, but can be estimated as 70 to 80 mL/kg (Linderkamp et al, 1977). In general, transfusion of packed red blood cells (PRBCs) is indicated for a hematocrit of less than 24% with signs and symptoms of anemia in the perioperative period or blood loss of more than 15% of the blood volume (Roseff et al, 2002). In cases of blood loss less than 15% of the blood volume, volume replacement with crystalloids is usually adequate. Massive bleeding involving the loss and replacement of one blood volume in 24 hours can lead to serious complications, and the mortality rate associated with this situation is approximately 40% (Radel, 2009). In an extreme situation, non–cross-matched O Rh-negative blood may be used, but all efforts should be made to use blood type–specific blood products. In general, platelet transfusion is reserved for a platelet count of less than 50,000/μL. Fresh frozen plasma (FFP) is used if the prothrombin time (PT) or partial thromboplastin time (PTT) is more than 1.5 times normal (Radel, 2009). **In the authors' experience, complete primary repair of bladder exstrophy in the newborn has been the pediatric urologic surgical case most likely to require transfusion of PRBCs, with 75% of boys and 29% of girls requiring intraoperative transfusion** (Borer et al, 2005).

The risks associated with transfusion are minimal but are a consistent source of worry for parents. The elimination of paid donors, more thorough donor screening, and increasingly sophisticated donor blood testing have led to a significant decrease in the incidence of infection transmitted by transfusion (Zuckerberg, 2009). **The incidence of transfusion-associated hepatitis B is 1:63,000, and the risk of transfusion-transmitted hepatitis C is 1:103,000** (Schreiber et al, 1996). **The risk of transfusion-transmitted human immunodeficiency virus (HIV) is estimated to be between 1:450,000 and 1:600,000** (Schreiber et al, 1996). In addition to the risk of transmission of infection, transfusion reactions occur in 2% to 3% of cases. Of these, 41% are febrile and nonhemolytic, 58% are urticarial, and 1% are delayed hemolytic (American Medical Association, 1985).

Thermoregulation

Infants and children experience heat loss as a result of convection, conduction, and evaporation. As a result, they are more susceptible than adults to changes in ambient temperature due to a relatively large body surface to mass ratio; less insulating tissue, such as fat or hair; and limited energy reserves. Neonates are especially sensitive to cold exposure, because they are unable to shiver and rely on brown adipose tissue for generation of heat. **Maintaining normal body temperature intraoperatively is important, because hypothermia increases the incidence of intraoperative and postoperative complications, including bleeding, acidosis, impaired immune function, and delayed wound healing.** During anesthesia, children are exposed to all the factors of heat loss: convection, radiation, evaporation, and conduction. Measures including humidification and warming of inspired air, warmed fluids for intravenous administration, and the use of warming devices, such as the BAIR Hugger (Arizant, Eden Prairie, MN), may be used as needed (Pierro, 2006; Wetzel, 2007).

Key Points: Surgical Preparation and Intraoperative Considerations

- In general, SAP is recommended for (1) all surgery in neonates less than 72 hours of age, because of possible exposure to maternal pathogens and particularly compromised immunologic capacity, (2) major class II surgery, and (3) all class III and IV surgical procedures; antibiotic use in class I and minor class II operations remains based on the individual surgeon's preference.
- The timing of SAP administration is critically important, and the first dose should be given 30 minutes to 3 hours prior to incision.
- VTEs in children are rare, but the incidence is believed to be increasing and is bimodal, occurring most often in infants less than 1 year of age and in adolescents.
- Lower rates of SSI are achieved by using clippers of depilatory agents immediately prior to surgery for hair removal.
- Blood volume in children varies with age but can be estimated as 75 to 80 mL/kg.
- The risks associated with blood transfusion are very low; the incidence of transmission of hepatitis B is 1:63,000; for hepatitis C it is 1:103,000; and for HIV it is 1:450,000 to 1:600,000.
- Infants and children are more susceptible than adults to changes in ambient temperature, because they have a relatively large body surface to mass ratio; less insulating tissue, such as fat or hair; and limited energy reserves.
- Maintaining normal body temperature intraoperatively is important, because hypothermia increases the incidence of intraoperative and postoperative complications, including bleeding, acidosis, impaired immune function, and delayed wound healing.

POSTOPERATIVE CARE

A majority of pediatric urologic operations are performed as outpatient procedures, and there continues to be a push to expand the number of these. Routine outpatient urologic procedures include orchidopexy, herniorrhaphy, circumcision, laparoscopic procedures for maldescended testes, and hypospadias repair. Some groups are also performing operations once performed exclusively as inpatient surgery, such as unilateral extravesical ureteral reimplants, in this manner (Palmer, 2008). Certainly, outpatient surgery has many advantages, including cost savings, lessened psychologic trauma, fewer nosocomial infections, and faster recovery (Yaster et al, 1994). However, adequate perioperative patient and family education are vital to obtaining good outcomes and requires collaborative efforts from the surgeon, anesthesiologist, and nursing staff.

Complications

The vast majority of children who undergo urologic surgery are healthy, and in this population, the incidence of serious complications is less than 1% (Hannallah, 1987). A detailed discussion of complications specific to various urologic procedures is beyond the scope of this chapter, but broad postoperative complications will be addressed instead.

Although not a surgical complication, per se, postoperative nausea and vomiting (PONV) is the most common early complication associated with the administration

Table 119–8.

Common Causes of Postoperative Fever

SITE	ETIOLOGY	TIME	INCIDENCE	SIGNS/SYMPTOMS	THERAPY
Wind	Atelectasis	24-48 hours	Very common	Cough, shortness of breath, retractions	Cough, deep breathing, incentive spirometry
Wound	Surgical-site infection	<24 hours–7 days	Rare	Pain, erythema, induration	Antibiotics, open drainage, and debridement
Water	Urinary tract infection	3-5 days	Very rare	Dysuria, hematuria	Remove indwelling catheter as early as possible, antibiotics
Walking	Deep vein thrombosis	>3 days	Extremely rare	Swelling, lower extremity pain, superficial venous congestion, palpable cord	Bed rest, elevation, anticoagulation, thrombolytics

Modified from Maxwell LG. Postoperative care. In: McInerny TK, Adam HM, Campbell DE, et al, editors. American Academy of Pediatrics textbook of pediatric care. Elk Grove Village (IL): American Academy of Pediatrics; 2009. p. 552–63.

of anesthesia (Maxwell, 2009). PONV is the most common cause of delayed discharge from the postanesthesia care unit (PACU) and unscheduled hospitalization following outpatient procedures, representing the cause of almost 25% of unplanned admissions (Patel and Hannallah, 1988; Blacoe et al, 2008). The cause of PONV is multifactorial, but some procedures are known to be associated with higher rates, including orchidopexy, which has been associated with a greater than 50% incidence of PONV (Maxwell, 2009). Another significant contributing factor is the use of opioids in the perioperative period. Several measures can be taken to limit PONV, including avoiding opioids if possible, using antiemetics perioperatively, providing adequate intravenous hydration with glucose supplementation, and limiting oral intake postoperatively (Maxwell, 2009). Avoidance of nitrous oxide in the intraoperative period may also help to decrease the incidence of PONV. The commonly used antiemetics include benzamides (metoclopramide [Reglan]), serotonin antagonists (ondansetron [Zofran]), phenothiazines (prochlorperazine [Compazine]; promethazine [Phenergan]), and antihistamines (diphenhydramine [Benadryl]). The authors most commonly use ondansetron, because it is the only antiemetic drug for children that does not routinely result in sedation. Ondanstron is contraindicated in children taking serotonin reuptake inhibitors for migraine headaches. The use of promethazine (Phenergan) in children is strongly discouraged, given the U.S. Food and Drug Administration warning issued in 2006 warning that it should not be used in children less than 2 years of age because of the potential for fatal respiratory depression and used with caution in children 2 years of age and older. In general, children in the PACU should not be forced fluids, and their administration should be based on the child's request. In the setting of PONV, forced fluids to encourage timely discharge will most likely be counterproductive.

Postoperative fever is a very common early surgical problem, and its etiology is taught in the first days of medical school surgery clerkships as the four Ws: wind, wound, water, and walking. "Wind" refers to atelectasis, "wound" to a surgical-site infection (SSI), "water" to an infection in the urinary tract (UTI), and "walking" to fever caused by deep vein thrombosis (DVT) in the lower extremities. **Fever, defined as greater than 38.5° C rectal temperature, is common within 24 hours of surgery and is usually caused by atelectasis.** Pulmonary toilet with deep breathing, coughing, and ambulation is usually effective in otherwise healthy children. In patients too young to participate in pulmonary toilet, measures such as blowing bubbles can be effective. The other causes, SSI, UTI, and DVT, are rare to extremely rare in the pediatric population. These common causes are summarized in Table 119–8. In addition, other common causes of fever in children should be considered, including upper respiratory infections, gastroenteritis, and otitis media.

Postoperative SSIs were traditionally characterized as incisional (superficial) or deep, but this fails to consider the total operative site. **The Centers for Disease Control and Prevention has modified the definition of SSIs, which now are reported as incisional SSI–superficial versus deep or organ/space SSI** (Ashcroft, 2005; Ziegler, 2003). **It is critically important to diagnose early and intervene promptly to avoid morbidity and even mortality.** The wound is examined for classic signs of infection and inflammation, including erythema, edema, tenderness, and warmth. If there appears to be a SSI, a Gram stain and culture should be obtained with a sterile swab. Treatment should be tailored according to the extent of the infection and may include oral or parenteral antibiotics, incision and drainage, or extensive debridement. **The incidence of SSIs varies from 1% to 11% in clean wounds and from 6% to 21% in contaminated wounds** (Ashcroft, 2005). **In general, most SSIs occur between the 5th and 10th postoperative days.** The rare exceptions are β-streptococcal, *Clostridium difficile,* and *Clostridium perfringens* (welchii) infections, which produce SSIs that can become clinically apparent within 24 to 48 hours postoperatively. **Clostridial and streptococcal infections may be life threatening, and children with these develop high, spiking fevers (39° C to 41° C), become irrational, and may develop jaundice** (Maxwell, 2009). Table 119–9 provides a summary of SSIs.

Significant postoperative bleeding is rare in pediatric urology. Persistent bleeding at the surgical incision for more than 6 to 8 hours postoperatively usually indicates inadequate hemostasis and is usually due to a superficial skin artery. The two most common postoperative bleeding situations encountered in pediatric urology involve circumcisions and scrotal hematomas following herniorrhaphy/hydrocelectomy or orchidopexy, with rates of persistent bleeding of approximately 1% to 2% and 2% to 11%, respectively (Caruso et al, 2000; Brisson et al, 2002; Cathcart et al, 2006). Persistent bleeding following circumcision usually responds to direct digital pressure, and reoperation is exceedingly rare. Scrotal hematomas are usually self-limited, and generally resolve during a period of 4 to 6 weeks. However, fever, erythema of the overlying scrotal skin, tenderness, and progressive enlargement may indicate close monitoring and surgical re-exploration. In patients with thrombocytopenia, prophylactic platelet transfusion is prudent for platelet counts below 50,000/μL (Gmur et al, 1991).

Table 119–9.

Postoperative Surgical-Site Infections

ONSET (POSTOPERATIVE DAY)	USUAL PATHOGENS	WOUND APPEARANCE	OTHER SIGNS
1-3	*Clostridium welchii*	Brawny, hemorrhagic, cool Occasional gaseous crepitance Putrid dishwater exudate Intense local pain	High standard fever (39° C–40° C) Irrational behavior Leukocytosis (WBC count > 15,000/mL) Occasional jaundice
2-3	*Streptococcus*	Erythematous, warm, tender Occasionally, hemorrhagic with blebs Serous exudate	High, spiking fever (39° C–40° C) Irrational at times Leukocytosis (WBC count > 15,000/mL) Rare jaundice
3-5	*Staphylococcus*	Erythematous, warm, tender Purulent exudate	High, spiking fever (39° C–40° C) Irrational at times Leukocytosis (WBC count 12,000-20,000/mL)
>5	Gram-negative rods	Erythematous, warm, tender Purulent exudate	Sustained low-grade to moderate fever (38° C–40° C) Rational behavior Leukocytosis (WBC count 10,000-16,000/mL)
>5	Symbiotic (usually anaerobes plus gram-negative rods)	Erythematous, warm, tender Focal necrosis Purulent, putrid exudate	Moderate to high fever (38° C–40° C) Leukocytosis (WBC count > 15,000/mL) Occasional jaundice Mentation variable

Modified from Maxwell LG. Postoperative care. In: McInerny TK, Adam HM, Campbell DE, et al, editors. American Academy of Pediatrics textbook of pediatric care. Elk Grove Village (IL): American Academy of Pediatrics; 2009. p. 552–63.

Key Points: Postoperative Care

- PONV is the most common early complication associated with the administration of anesthesia.
- Certain procedures are associated with high rates of PONV; the rate approaches 50% following orchidopexy.
- Fever, defined as greater than 38.5° C rectal temperature, is common within 24 hours of surgery and, as in adults, is usually caused by atelectasis.
- In cases of SSI, it is critically important to diagnose early and intervene promptly to avoid morbidity and even mortality.
- The incidence of SSIs varies from 1% to 11% in clean wounds and from 6% to 21% in contaminated wounds; most SSIs occur between the 5th and 10th postoperative days.

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The complete reference list is available online at www.expertconsult.com.

chapter
120

Anomalies and Surgery of the Ureter in Children

Michael C. Carr, MD, PhD ● Pasquale Casale, MD

Evidence
Etiology
Megaureters
Symptoms/Presentation
Surgical Repair
Outcome and Complications
Procedures for Recurrent Ureteropelvic Junction Obstruction
Conclusions

There is ongoing debate as to whether a hydronephrotic kidney is obstructed, primarily because the tools we use to measure or define obstruction are less than precise. A ureteropelvic junction (UPJ) obstruction can be considered a restriction to flow of urine from the renal pelvis to the ureter, which, if left uncorrected, will lead to progressive renal deterioration (Whitaker, 1975; Koff et al, 1986; Koff, 1990). The same notion occurs when one considers a ureterovesical junction (UVJ) obstruction, in which both the renal pelvis and ureter are dilated with the restriction occurring within the distal portion of the ureter. The response to UPJ obstruction is the development of renal pelvic hypertrophy, in which the kidney compensates to maintain adequate urinary flow. Eventually, there are further changes to the renal pelvis and pressure-induced injury that lead to irreversible renal damage.

This chapter considers congenital UPJ and UVJ obstruction along with those unusual situations in which midureteral strictures or ureteral polyps exist. The focus of this chapter will be on surgical repair, with consideration of open repair along with the continually evolving minimally invasive repairs. Increasingly, robotic-assisted repairs are supplanting the open procedures that many pediatric urologists consider among their favorite procedures. Other conditions that delay drainage of the proximal urinary tract and secondarily affect the UPJ are discussed elsewhere in this text.

EVIDENCE

UPJ obstruction occurs in all pediatric age groups, but there tends to be a clustering in the neonatal period because of the detection of antenatal hydronephrosis and again later in life because of symptomatic occurrence. Once, about 25% of cases were discovered within the first year of life (Williams and Kenawi, 1976), but today the majority of cases are identified and diagnosed in the perinatal period (Brown et al, 1987). **UPJ obstruction is the most common cause of significant dilation of the collecting system in the fetal kidney,** accounting for 48% of all dilation of the collecting system and far exceeding the incidence of multicystic dysplastic kidney (Colodny et al, 1980; Brown et al, 1987). Those kidneys with an anteroposterior (AP) diameter of greater than 20 mm seen prenatally are certainly at greater risk for requiring surgery postnatally (Dhillon, 1998). The problem existing today is that the diagnosis of UPJ is "made" at the time of prenatal ultrasonography so that expectant parents are often informed their fetus will most likely require surgical intervention as a neonate. This contributes to ongoing anxiety and altered parental enjoyment during pregnancy (Harding et al, 1999).

Beyond the neonatal period, UPJ obstruction is seen during childhood and adolescence but to a lesser degree. Often, the cause is an aberrant lower pole parenchymal vessel that crosses over the UPJ (Lowe and Marshall, 1984). **Obstruction occurs more commonly in boys than in girls** (Williams and Karlaftis, 1966; Kelalis et al, 1971; Johnston et al, 1977), especially in the newborn period, where the ratio exceeds 2:1 (Robson et al, 1976; Williams and Kenawi, 1976; Johnson et al, 1977). Left-sided lesions predominate, particularly in the neonate (approximately 67%). Bilateral UPJ obstruction is present in 10% to 40% of cases (Nixon, 1953; Uson et al, 1968; Robson et al, 1976; Williams and Kenawi, 1976; Johnson et al, 1977; Lebowitz and Griscom, 1977), with both synchronous and asynchronous occurrences. This tends to occur in infants younger than 6 months of age (Perlmutter et al, 1980; Snyder et al, 1980), and it has been known to affect members of more than one generation (Cohen et al, 1978).

ETIOLOGY

The precise cause of UPJ obstruction remains elusive despite investigation along a number of lines: embryologic (Osathanondh and Potter, 1963; Allen, 1973; Ruano-Gil et al, 1975), anatomic (Nixon, 1953; Johnston, 1969), functional (Whitaker, 1975), and histologic (Murnaghan, 1958; Notley, 1968; Hanna et al, 1976). A narrowing of the UPJ is often found (Allen, 1973; Lebowitz and Griscom, 1977), but whether this is a result of developmental arrest (Osathanondh and Potter, 1963; Allen, 1973) or of an incomplete recanalization of the ureter (Ruano-Gil et al, 1975) is not yet known.

Megaureter is simply a descriptive term that indicates a dilated ureter. The underlying pathophysiology remains to be defined, as ureters can become dilated due to obstruction, reflux, or a combination of both. What has been observed is that all dilation of the urinary tract does not necessarily equate with a physiologically significant obstructive process with renal functional implications despite the anatomic distortion of the collecting system that it represents. Prudent observation, rather than hasty surgical solutions, has shown that improvement can occur in many situations.

Intrinsic

The typical finding on pyeloplasty is a narrowed segment of the ureter at the UPJ that is probe patent (Fig. 120–1). This finding may be the result of an interruption in the development of the circular musculature of the UPJ (Murnaghan, 1958) or an alteration of collagen fibers and composition between and around the muscle cells (Notley, 1968; Hanna et al, 1976; Hanna, 2000). **The muscle fibers become widely separated and attenuated, leading to a functional discontinuity of the muscular contractions and ultimately to insufficient emptying.** Further characterization of the UPJ by Starr and colleagues (1992) noted a significant increase in the lamina muscularis and in the number of inner longitudinal muscular bundles of the UPJ complex of obstructed kidneys in infants younger than 1 year of age compared with age-matched normal infants. These findings suggest a dramatic response by the muscular layers to obstruction. Further work has shown that the expression of transforming growth factor-β (TGF-β) is increased in the pelvis of partially obstructed kidneys (Seremetis and Maizels, 1996), which may help explain some of the histologic and electron microscope findings that were described by Notley and Hanna and their colleagues.

Other causes of intrinsic UPJ obstruction include valvular mucosal folds (Maizels and Stephens, 1980), **persistent fetal convolutions** (Leiter, 1979), **and upper ureteral polyps** (Colgan et al, 1973; Gup, 1975; Williams and Kenawi, 1976; Williams et al, 1980; Thorup et al, 1981). Congenital folds are a common finding in the upper ureter of fetuses after the fourth month of development and may persist until the newborn period. Such folds are mucosal infolds with an axial offshoot and adventitia that do not flatten when the ureter is distended or stretched. The epithelial folds are secondary to differential growth rates of the ureter and the body of the child, with excessive ureteral length occurring in early gestation. This provides a "length reserve" for the ureter, which traverses a shorter distance in the newborn period than in the adult (Östling, 1942). Östling thought that these folds were a precursor of UPJ obstruction, because they frequently were discovered in babies who had contralateral UPJ obstruction. This concept has evolved, and "Östling folds" are now considered folds that are not obstructive and disappear with a person's linear growth (Leiter, 1979) (Fig. 120–2). They are rarely seen in an older child or adult. On the other hand, persistent fetal folds containing muscle and high insertion of a valvular leaflet at the UPJ may become obstructive (Maizels and Stephens, 1980). This type of obstruction sometimes can be relieved by dissections of the folds and elimination of the kinking (Johnston, 1969), but, more commonly, the ureteral portion containing the valve must be excised.

Extrinsic

An aberrant, accessory, or early-branching lower-pole vessel is the most common cause of extrinsic UPJ obstruction (Fig. 120–3). These vessels pass anteriorly to the UPJ or proximal ureter and contribute to mechanical obstruction. Nixon (1953) reported that 25 of 78 cases of UPJ obstruction were secondary to vascular compression; other reported incidences have varied between 15% and 52% (Ericsson et al, 1961; Williams and Kenawi, 1976; Johnston et al, 1977; Stephens, 1982; Lowe and Marshall, 1984). This a major cause of UPJ obstruction in adults. **Whether the**

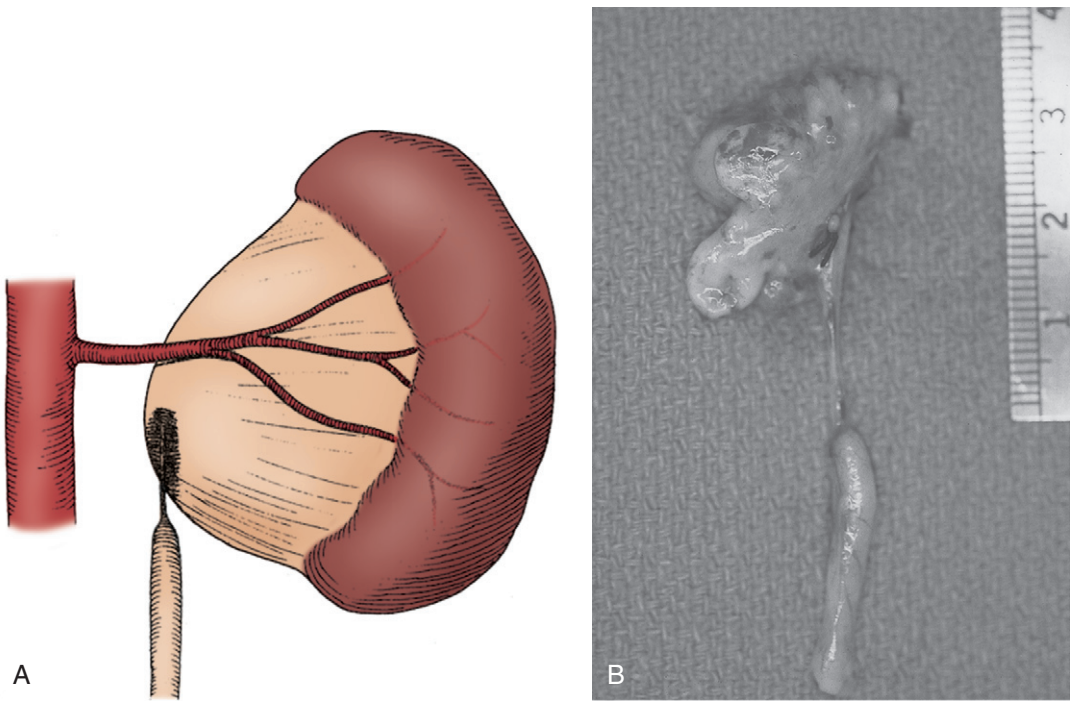


Figure 120–1. **A,** Intrinsic narrowing of upper ureter contributing to ureteropelvic junction obstruction. **B,** Surgical specimen of nonfunctioning kidney with significant proximal ureteral narrowing.

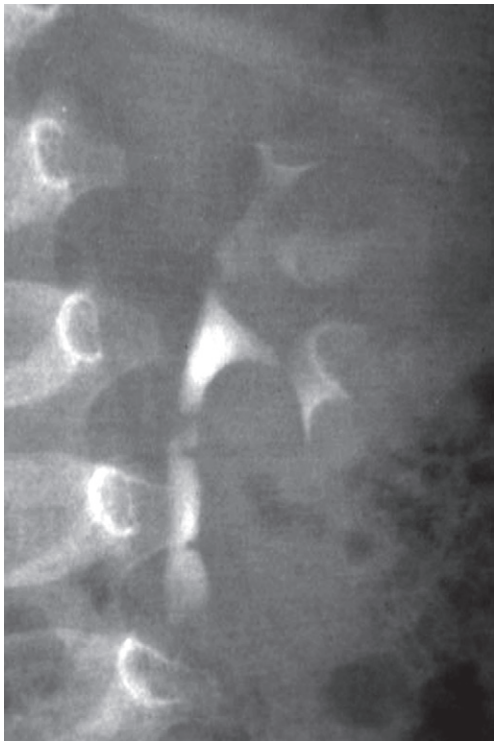


Figure 120–2. Early image of left kidney from intravenous urogram of 4-month-old girl with prenatal hydronephrosis depicting Östling's folds.

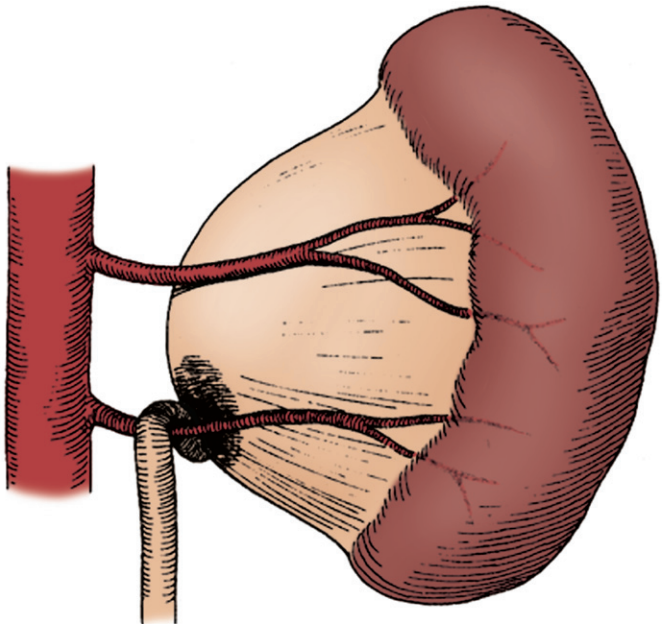


Figure 120–3. A lower pole–crossing vessel contributes to significant kinking at the ureteropelvic junction and resultant intermittent obstruction. Often, when the ureter is mobilized, no evidence of intrinsic narrowing is found. Insertional anomaly and peripelvic fibrosis may also be present as secondary obstructive factors.

aberrant vessel causes the obstruction or is a covariable that exists along with intrinsic narrowing is unclear. Stephens (1982) theorized that when an aberrant or accessory renal artery to the lower pole of the kidney is present and the ureter courses behind it, the ureter may angulate at both the UPJ and the point at which it traverses over the vessel as the pelvis fills and bulges anteriorly. Further angulation of the ureter occurs as it becomes adherent to the UPJ secondary to an inflammatory process. A two-point obstruction ensues, with kinking of the ureter at the UPJ and at the point where the ureter drapes over the vessel. Stephens (1982) could find no evidence of stricture or fibrosis at these points when the ureter was freed of its adhesions and lifted off the vessel. However, he suggested that, over time, these areas may become ischemic, fibrotic, and finally stenotic.

Secondary Ureteral Pelvic Junction Obstruction

UPJ obstruction may also be seen with severe vesicoureteral reflux (VUR); these conditions coexist in 10% of cases. **The ureter elongates and develops a torturous course in response to the obstructive element of reflux. A kink may develop in the UPJ area, a point of relative fixation, and may cause an obstruction secondarily** (Lebowitz and Blickman, 1983). In such a situation, the obstructive lesion needs to be corrected initially, even though the VUR contributed to the initial problem (Fig. 120–4). With the advent of injectable biomaterials, such as Deflux (Q-Med, Uppsala, Sweden) and Macroplastique (Uroplasty, Inc., Minneapolis, MN), consideration should be given to correcting the proximal obstruction, as well as the distal reflux, by an endoscopic approach.

Lower Pole Ureteral Pelvic Junction Obstruction

Lower pole ureteral pelvic junction obstruction can occur in kidneys with an associated incomplete renal duplication. Hydronephrosis of the lower pole moiety can be delineated with a well-performed ultrasonogram. Such a finding can suggest the presence of a lower pole ureteropelvic junction obstruction, which is an unusual finding. The incidence of renal duplication is predicted to be 0.3% to 6%. Incomplete duplications are found approximately 70% of the time in comparison with complete duplications (Privett et al, 1976). The anatomy of lower pole UPJ obstruction is either a short bifurcating ureteral segment distal to the ureteropelvic junction or a longer bifurcating ureteral segment. Such a long ureteral segment lends itself to a typical dismembered pyeloplasty, whereas the short ureteral segment is better handled by opening the renal pelvis, excising the stenotic ureteral bifurcation, and performing an end-to-side pyeloureterostomy (Fig. 120–5) (Joseph et al, 1989).

Associated Anomalies

Congenital renal malformations are commonly seen in association with UPJ obstruction. Other urologic abnormalities may be found in 50% of affected infants (Uson et al, 1968; Robson et al, 1976; Lebowitz and Griscom, 1977). **UPJ obstruction is the most common anomaly** encountered in the opposite kidney; it occurs in 10% to 40% of cases. Renal dysplasia and multicystic kidney are the next most frequently observed contralateral lesions (Williams and Karlaftis, 1966). In addition, unilateral renal agenesis has been noted in almost 5% of children (Robson et al, 1976; Williams and Kenawi, 1976; Johnston et al, 1977). UPJ obstruction may also occur in the lower or, very rarely,

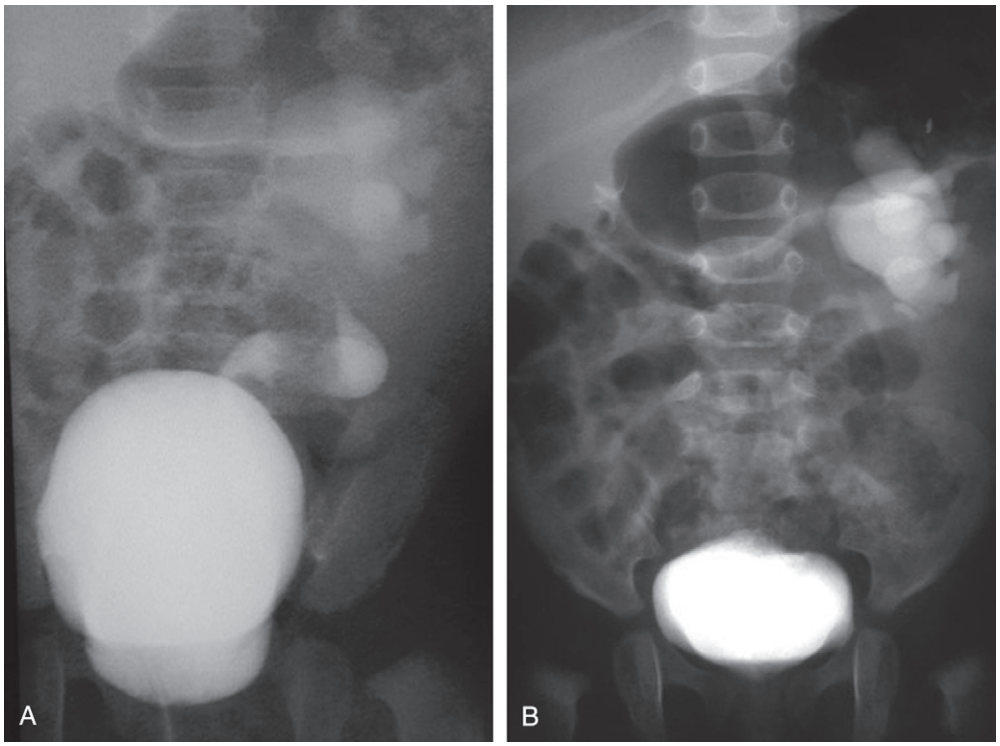


Figure 120–4. **A,** Voiding cystourethrogram demonstrating left vesicoureteral reflux. Note dilutional effect of contrast in renal pelvis. **B,** Postvoid view demonstrating right grade II vesicoureteral reflux and significant retained contrast in left renal pelvis. Patient developed worsening left hydronephrosis, which was observed on subsequent ultrasound imaging, and underwent a left dismembered pyeloplasty. There was evidence of a lower pole–crossing vessel contributing to intermittent kinking of the ureter.

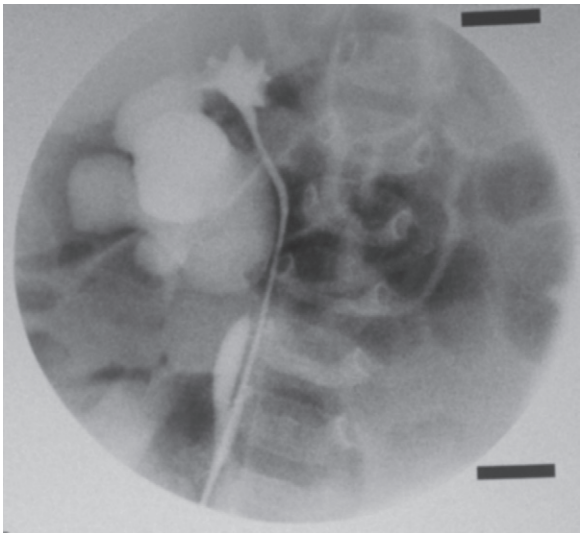


Figure 120–5. Retrograde pyelogram demonstrating anatomy of right incomplete renal duplication with lower pole–ureteropelvic junction obstruction.

the upper segment of a duplicated collecting system (Amar, 1976; Joseph et al, 1989) (see Fig. 120–5) or of a horseshoe or ectopic kidney (Fig. 120–6).

UPJ obstruction was noted in 21% of children with the VATER (*V*ertebral defects, imperforate *A*nus, *T*racheoesophageal fistula, and *R*adial and *R*enal dysplasia) association (Uehling et al, 1983), whereas a more recent review showed a 9% incidence of ureteropelvic junction obstruction, along with the majority of patients having some degree of hydronephrosis but no obstruction or reflux and solitary renal kidneys, or a small percentage may have multicystic dysplastic kidneys (Kolon et al, 2000).

VUR has been found in as many as 40% of affected children (Williams and Kenawi, 1976; Juskiewenski et al, 1983; Lebowitz and Blickman, 1983). This degree of reflux is often low grade, not contributing to upper urinary tract obstruction, and with a high likelihood of spontaneous resolution. In certain situations, high-grade VUR can have a profound effect on the UPJ, as previously noted. Anomalies of other organ systems are frequently observed but without any consistent pattern of inheritance.

MEGAURETERS

Megaloureter is a term introduced by Caulk to describe a dilated ureter. The condition was felt to be similar to large atonic dilatation of the colon. Ultimately the condition became known as megaureter, which referred primarily to two gross pathologic types: (1) megaureter caused by massive vesicoureteral reflux (either or primary or secondary to a distal obstruction, such as posterior urethral valves) and (2) obstructive megaureter from segmental narrowing of the terminal ureter or aperistalsis. In both types, the ureter can be very dilated and tortuous. Finally, a minority of megaureters can be a composite of the two above-described types with evidence of reflux and obstruction.

A normal ureteral diameter is rarely greater than 5 mm (Cussen, 1971), whereas ureters wider than 7 to 8 mm can all be considered megaureters (Hellström et al, 1985). This measurement is subject to variability owing to the imaging modality and concomitant insults, such as infection or inflammation (Hellström et al, 1987). An international classification dating back to the 1970s has become the basis for today's designations and categorization for management. Thus **a megaureter may be obstructed,**



Figure 120–6. **A,** Intravenous urogram (10-minute image) showing delayed uptake and excretion of contrast from left kidney. **B,** Thirty-minute image demonstrating horseshoe kidney and wisp of contrast in proximal left ureter. Patient was found to have high insertion and intermittent kinking of the ureter, which was contributing to periodic abdominal pain. He presented with gross hematuria after being struck by a soccer ball.

refluxing, both refluxing and obstructed, or unobstructed and not refluxing, either from a primary (idiopathic cause intrinsic to the ureter or secondary to specific pathophysiologic processes, such as outlet obstruction, neurogenic dysfunction, polyuria, or infection). This practical division is of diagnostic and therapeutic importance and underscores the effects that the bladder can have on ureteral anatomy and pathophysiology. Secondary causes should always be sought, because management would be directed at the specific problem rather than dealing with the consequence of the problem. In the same way that it can be difficult to define a ureteropelvic junction obstruction, a ureterovesical junction obstruction may be even more problematic. The treatment of a megaureter needs to be geared to preventing renal damage and, ultimately, irreversible loss of function rather than reacting to a worrisome radiographic finding.

Key Points: Megaureter

- Megaureter (MGU) is a nonspecific term implying a spectrum of anomalies associated with pathologically excessive ureteral diameter.
- Primary (at the UVJ; adynamic segment) or secondary (e.g., bladder malfunction) origins influence management and must therefore be differentiated.
- Indications for correction are often driven by serially increasing pelvicalyceal dilation, increasing ureteral diameter, or pyelonephritis and ureteral pyuria.
- Antibiotic prophylaxis should be used to protect the dilated ureter regardless of cause.
- Many cases of antenatally diagnosed MGU will resolve spontaneously. If there is improvement in degree of hydroureteronephrosis, but not resolution, imaging at puberty is advised.

SYMPTOMS/PRESENTATION

The dichotomy of presentation in infants and children with UPJ obstruction is that **most infants are asymptomatic, and most children are discovered because of their symptoms.** Previously, infants were discovered to have UPJ obstruction because of a palpable mass (Williams and Karlaftis, 1966; Robson et al, 1976; Johnson et al, 1977). Now, the almost universal use of prenatal sonography has made discovery of UPJ obstruction a common occurrence. It has changed our approach to evaluation, because now we are attempting to prove that a problem exists in an otherwise asymptomatic infant. Occasionally, there are still infants who present with failure to thrive, feeding difficulties, sepsis secondary to urinary tract infection, or pain or hematuria related to nephrolithiasis. Urinary tract infection is the presenting sign in 30% of affected children beyond the neonatal period (Snyder et al, 1980).

In the older child, episodic flank or upper abdominal pain, sometimes associated with nausea and vomiting due to intermittent UPJ obstruction, is a prominent symptom (Kelalis et al, 1971; Williams and Kenawi, 1976) (Fig. 120–7). This is clearly less often seen with an obstructive megaureter. At other times, **cyclic vomiting alone is caused by intermittent UPJ obstruction.** The pathology may be manifested only during the episode of cyclic vomiting and/or abdominal pain. Hematuria, which is seen in 25% of children, may occur after minor abdominal trauma (Kelalis et al, 1971; Williams and Kenawi, 1976). This hematuria is believed to be caused by disruption and rupture of mucosal vessels in the dilated collecting system (Kelalis et al, 1971). In the young adult, episodic flank or abdominal pain, particularly during diuresis, is a common

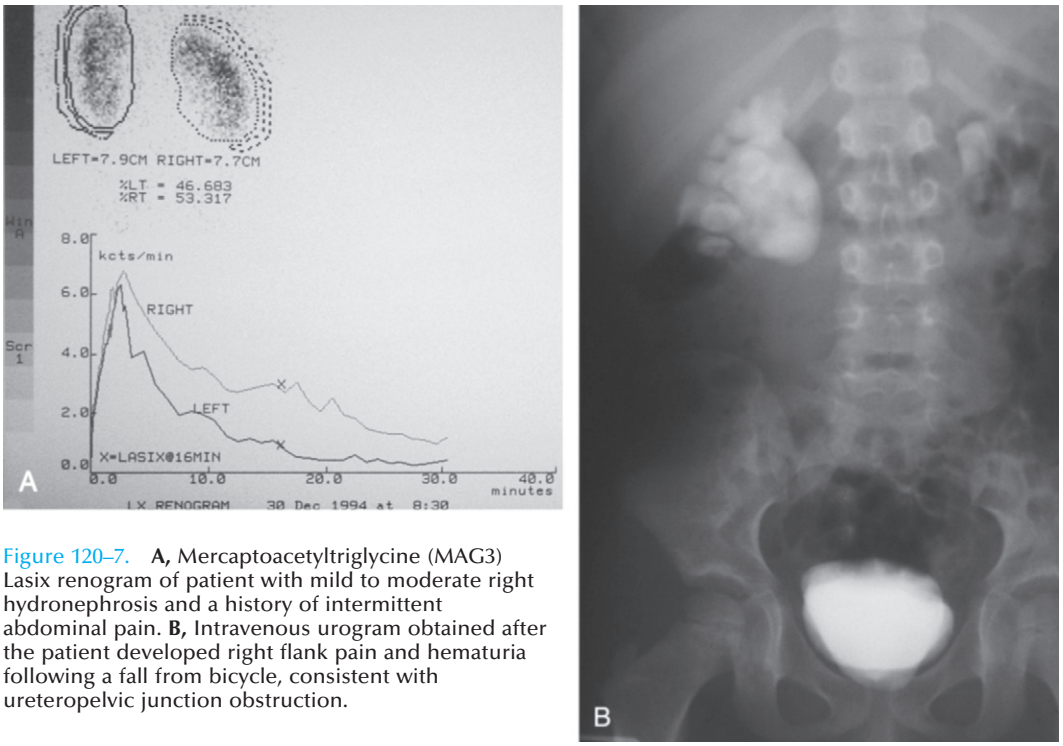


Figure 120–7. **A,** Mercaptoacetyltriglycine (MAG3) Lasix renogram of patient with mild to moderate right hydronephrosis and a history of intermittent abdominal pain. **B,** Intravenous urogram obtained after the patient developed right flank pain and hematuria following a fall from bicycle, consistent with ureteropelvic junction obstruction.

manifestation. Occasionally, a patient with the UPJ obstruction presents with hypertension (Squitieri et al, 1974; Johnson et al, 1977; Munoz et al, 1977; Grossman et al, 1981). The pathophysiology is thought to be a functional ischemia with reduced blood flow caused by the enlarged collecting system that produces a renin-mediated hypertension (Belman et al, 1968).

SURGICAL REPAIR

The evolution in the surgical correction of UPJ obstruction and obstructive megaureter has occurred on a number of fronts, with **open surgical techniques yielding way to endoscopic, laparoscopic, and robotic-assisted approaches.** The open techniques that have had the greatest applicability can be classified into three main groups: the flap type, the incisional-intubated type, and the dismembered type. The Anderson-Hynes pyeloplasty (1949) has become the most commonly employed "open" surgical procedure for the repair of UPJ. This repair had as its underpinnings both the Foley Y-V plasty (1937) and the Davis intubated ureterotomy (1943).

The Foley operation was designed for the correction of UPJ with a high ureteral insertion (Fig. 120–8). As such, this technique cannot be used in conjunction with transposition of a lower pole vessel, nor does it allow for any significant reduction of the renal pelvic size. The Davis intubated ureterotomy depends on secondary epithelialization from the incised ureter. It is applicable when multiple or extensive strictures of the proximal ureter are present but cannot be bridged by a pelvic flap (Fig. 120–9). Its use requires maintenance of ureteral continuity on at least one side and the presence of an indwelling ureteral stent for 6 weeks, the time needed for full circumferential regeneration of all layers of the ureter.

The spiral flap described by Culp and DeWeerd (1951) is created from the renal pelvis, which is used to repair the defect at the UPJ. Such a flap is able to bridge the gap between the pelvis and healthy ureter over a distance of several centimeters (Fig. 120–10). Scardino and Prince (1953) described a vertical flap that can be used in the situation of a dependent UPJ with a large, square-shaped extrarenal pelvis (Fig. 120–11). The rare cases of giant hydronephrosis that may be associated with a completely atretic ureter can be corrected by reconstructing the entire ureter using redundant pelvic tissue (Kheradpir, 1983).

Dismembered Pyeloplasty

The technique of dismembering the ureter was borne out of necessity in the repair of a retrocaval ureter (Anderson and Hynes, 1949) (Fig. 120–12). This technique was embraced by English surgeons in the repair of UPJ obstruction, but there was reluctance on the part of surgeons elsewhere because of concerns about severing the neural continuity between pelvis and ureter. Later work, however, demonstrated that the bolus of urine is the peristaltic stimulus. Furthermore, injection studies (Douville and Hollingshead, 1955) demonstrated that the arborization of blood vessels in the renal pelvis would ensure appropriate healing even with dismembering.

The principal reasons for the universal acceptance of the dismembered pyeloplasty are (1) broad applicability, including preservation of lower pole or crossing vessels, (2) excision of the pathologic UPJ and appropriate repositioning, and (3) successful reduction pyeloplasty. This operation is generally easy to perform and can be accomplished by a number of surgical approaches, including anterior subcostal, flank, and posterior lumbotomy.

A dismembered pyeloplasty may be problematic if there is inadequate ureteral length. A spiral flap from the renal pelvis can overcome this problem. Alternatively, excision of all scar tissue along with a dismembered technique is often possible when the kidney is completely mobilized and brought down as a "reverse" nephropexy. This can provide an additional 5 cm of length,

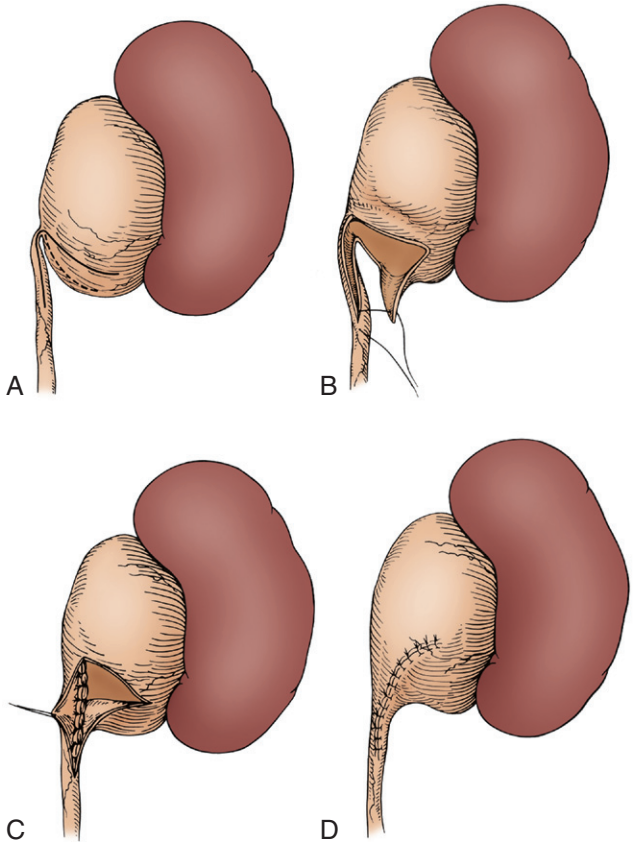


Figure 120–8. **A,** A Foley Y-V plasty is best applied to a ureteropelvic junction obstruction associated with a high insertion of the ureter. The flap is outlined with tissue market or stay sutures. The base of the V is positioned on the dependent, medial aspect of the renal pelvis and the apex at the ureteropelvic junction. The incision from the apex of the flap, which represents the stem of the Y, is then carried along the lateral aspect of the proximal ureter well into an area of normal caliber. **B,** The flap is developed with fine scissors. The apex of the pelvic flap is brought to the most inferior aspect of the ureterotomy incision. **C,** The posterior walls are approximated using interrupted or running fine absorbable sutures. **D,** The anastomosis is completed with approximation of the anterior walls of the pelvic flap and ureterotomy.

avoiding such maneuvers as bowel interposition, ureterocalicostomy, or autotransplantation.

The age and size of the patient and the position of UPJ are factors that must be considered when choosing a surgical approach. **A posterior lumbotomy affords good exposure in the neonate but may not be a good choice in a muscular adolescent.** The position of the UPJ can be determined from an intravenous urogram, but most surgeons now perform renal scans instead. Therefore retrograde pyelography can be used for making this determination. Cockrell and Hendren (1990) noted the benefits of performing retrograde pyelography at the time of pyeloplasty. Findings included a discrete area of narrowing, a long segment of narrowing, tortuosity of the upper ureter, more than one area of narrowing, high insertion of the ureter on the renal pelvis, and compression of the ureter by the lower pole of the kidney. Rushton and colleagues (1994) noted that their surgical findings confirmed obstruction at the UPJ in all patients. Undiagnosed distal ureteral obstruction was not seen, and therefore routine retrograde pyelography was deemed unnecessary.

The actual repair for the modified Anderson-Hynes dismembered pyeloplasty, as performed through an anterior subcostal incision, is as follows:

1. The anterior subcostal incision is a muscle-splitting incision that is made with the patient supine and a roll placed transversely beneath the patient to elevate the flank (Fig. 120–13).
2. Each muscle layer encountered is split in the direction of the muscle fibers until the Gerota fascia is identified by sweeping the peritoneum medially. The fascia is then incised posteriorly over the lateral aspect of the kidney.
3. The renal pelvis is identified by medial retraction of the peritoneum and lateral traction of the kidney. If the renal pelvis is significantly dilated, an angiocatheter can be inserted to decompress the pelvis and facilitate identification of the UPJ.
4. Anterior exposure is usually better when a dismembered pyeloplasty is being performed. **Once the ureter and UPJ are identified, a traction suture is displaced anteriorly through the proximal ureter** to minimize subsequent handling.
5. The area of UPJ is dissected free to allow for a clear area in which to perform the anastomosis. **Traction sutures** of 6-0 Prolene may be placed in the renal pelvis superiorly, medially, laterally, and inferiorly to the UPJ. Once adequate ureteral length is confirmed and the pathology of UPJ identified, the ureter can be transected at the UPJ. If the ureter is short, the kidney is completely mobilized to determine whether it can be brought down sufficiently to allow for a primary tension-free anastomosis.
6. After transection of the UPJ, the renal pelvis may not spontaneously drain until it is incised. This should be done after the site for anastomosis is chosen.
7. The **ureter is spatulated on the side opposite to the traction suture** using Potts tenotomy scissors. The distance over which the ureter is opened is variable, until healthy ureter is encountered, which springs open when forceps are placed into it.
8. A **portion of pelvis is excised,** usually a diamond-shaped segment that is present within the traction sutures that were placed in the renal pelvis. It is better to leave too much renal pelvis than too little, especially when resecting along the medial aspect of the renal pelvis. Infundibula can be encountered if one is not careful (Fig. 120–14).
9. The ureter and renal pelvis are aligned to ensure that the anastomosis can be accomplished without tension. If a nephrostomy tube is to be used, it is placed at this time. An inferior calix is chosen, preferably where the overlying parenchyma is not too thick. A Malecot catheter works well and is positioned away from the repair to minimize the chance of the catheter causing urinary blockage through the reconstructed UPJ.
10. The anastomosis is started by placing the first 7-0 Maxon (Davis and Geck, Norwalk, CT) suture at the apex of the "V" in the ureter and into the tip of the inferior pelvic flap. As the suture is tied down, the ureter and renal pelvis are brought together to minimize tension on the repair. A small feeding tube is placed into the ureter; it can be used to stabilize the ureter during the anastomosis. **A "no-touch" technique is employed with the ureter to minimize trauma** and edema to the ureteral tissue. Either interrupted sutures or a running closure may be used, depending on the surgeon's preference. The inferior

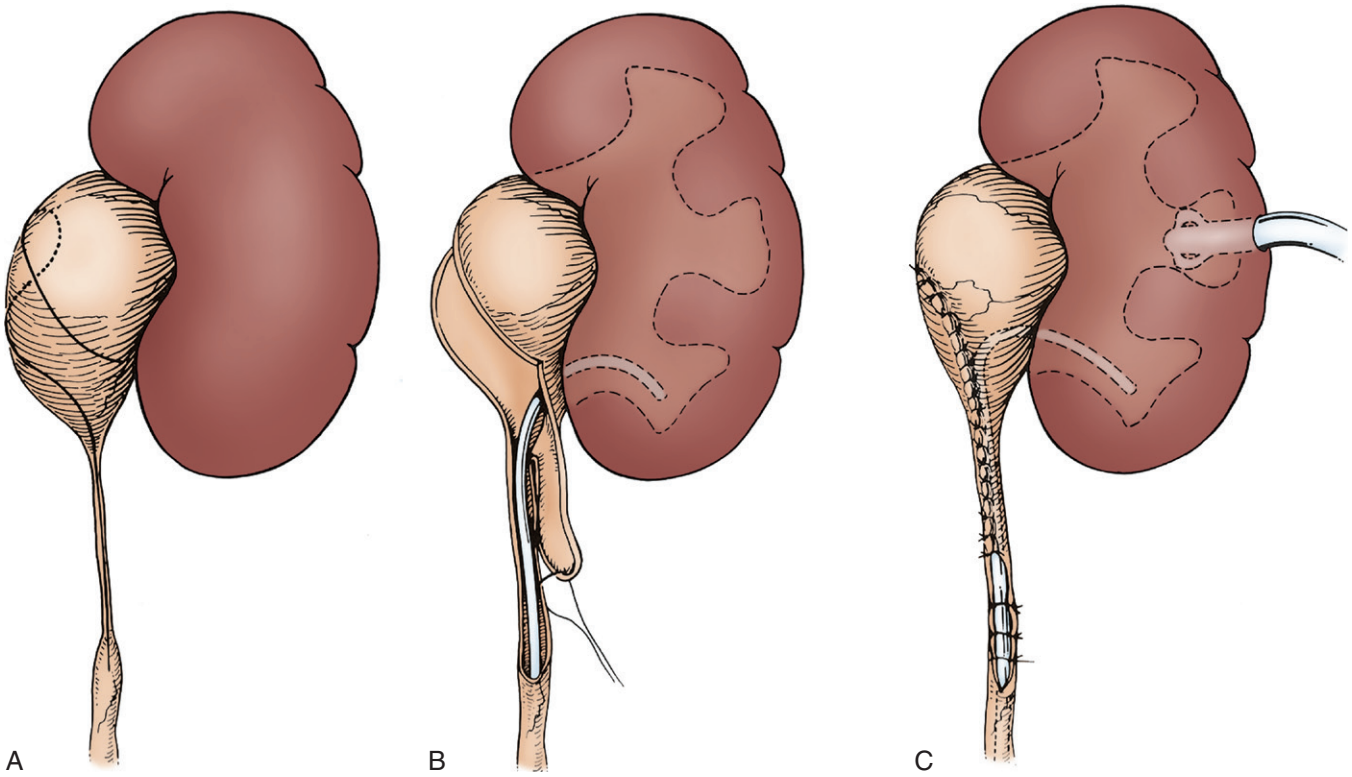


Figure 120–9. **A,** The intubated ureterotomy may be of value when a ureteropelvic junction obstruction is associated with extremely long or multiple ureteral strictures. A spiral flap is outlined and developed as described in Figure 120–10. The ureterotomy incision will be carried completely through the long strictured area or through each of the multiple areas of stricture. **B,** The flap is developed, taking care to use minimal dissection of the ureter to preserve its blood supply. In contrast to uncomplicated repairs, nephrostomy tube drainage is used routinely. A self-retaining, soft, inert internal ureteral stent is placed and positioned proximally in the renal pelvis or lower infundibulum and distally in the bladder. The apex of the flap is brought as far down as possible over the stent on the ureterotomy. The flap is closed with interrupted or running absorbable sutures. **C,** The distal aspect of the ureterotomy is left open to heal secondarily by ureteral regeneration. A few fine absorbable sutures may be placed loosely to keep the sides of the ureter in apposition to the stent.

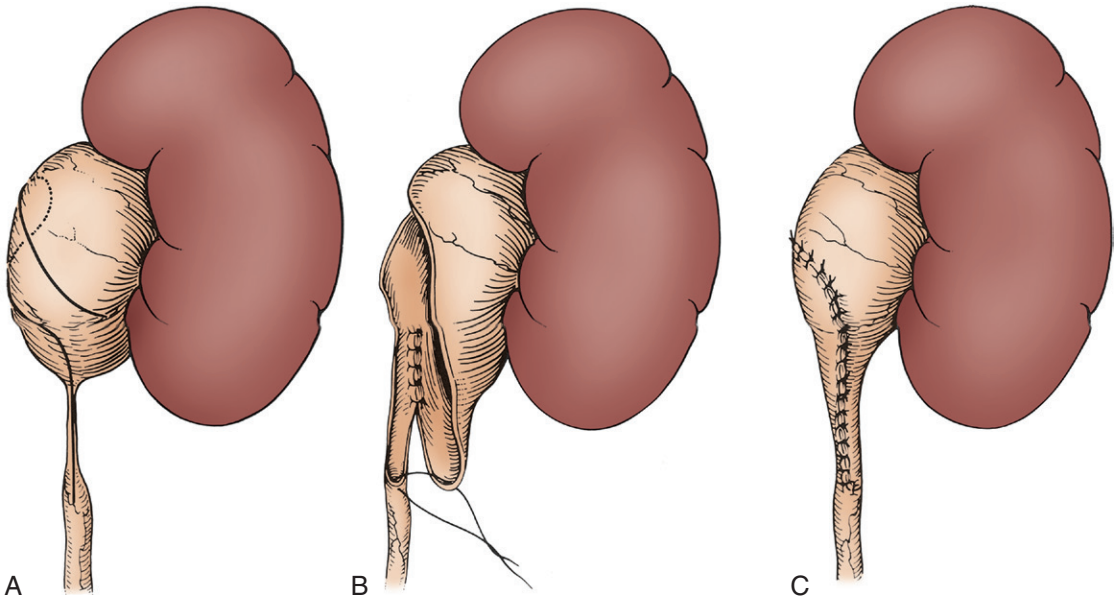


Figure 120–10. **A,** Spiral flap may be indicated for relatively long areas of proximal ureteral obstruction when the ureteropelvic junction is already in a dependent position. The spiral flap is outlined with the base situated obliquely on the dependent aspect of the renal pelvis. The base of the flap is positioned anatomically lateral to the ureteropelvic junction between the ureteral insertion and the renal parenchyma. The flap is spiraled posteriorly to anteriorly, or vice versa. The anatomically medial line of incision is carried down completely through the obstructed proximal ureteral segment into normal-caliber ureter. The site of the apex for the flap is determined by the length of the flap required to bridge the obstruction. The longer the segment of proximal ureteral obstruction, the farther away is the apex because this will make the flap longer. To preserve vascular integrity to the flap, however, the ratio of flap length to width should not exceed 3 to 1. **B,** Once the flap is developed, the apex is rotated down to the most inferior aspect of the ureterotomy. **C,** The anastomosis is completed, usually over an internal stent, using fine absorbable sutures.

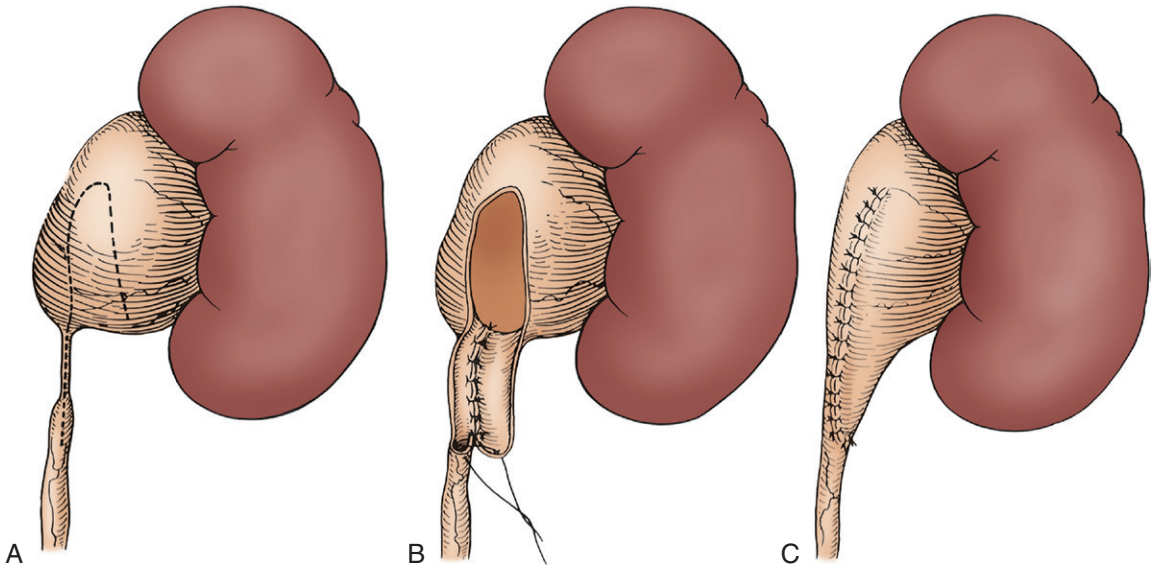


Figure 120–11. **A,** Vertical flap technique may be used when a dependent ureteropelvic junction is situated at the medial margin of a large, box-shaped extrarenal pelvis. In contrast to the spiral flap, the base of the vertical flap is situated more horizontally on the dependent aspect of the renal pelvis, between the ureteropelvic junction and the renal parenchyma. The flap itself is formed by two straight incisions converging from the base vertically up to the apex on either the anterior or posterior aspects of the renal pelvis. As for the spiral flap, the position of the apex determines the length of the flap, which should be a function of the length of proximal ureter to be bridged. The medial incision of the flap is carried down the proximal ureter completely through the strictured area into normal-caliber ureter. **B,** The apex of the flap is rotated down to the most inferior aspect of the ureterotomy. **C,** The flap is closed by approximating the edges with interrupted or running fine absorbable sutures.

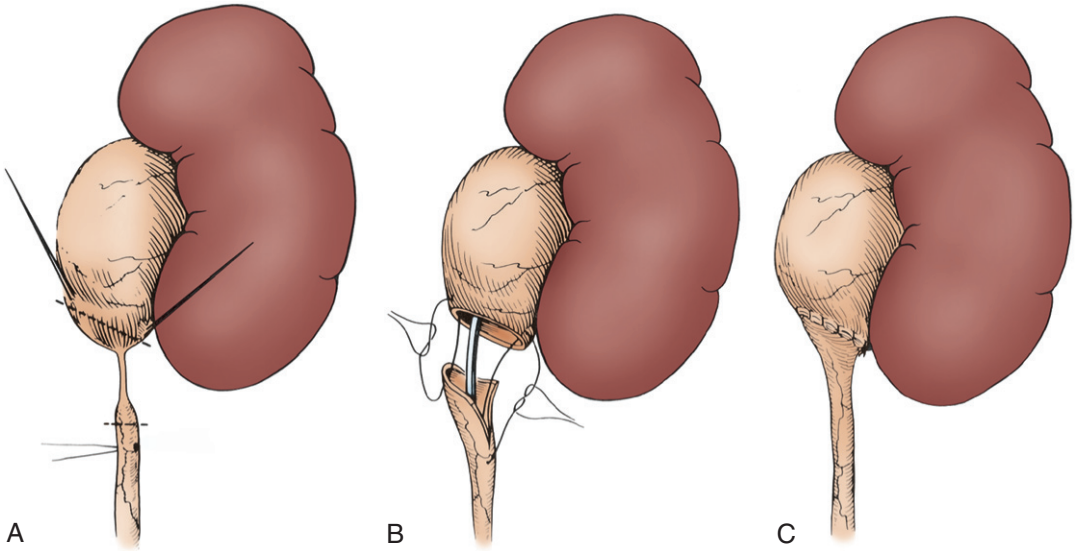


Figure 120–12. Anderson-Hynes dismembered pyeloplasty. **A,** Traction sutures are placed on the medial and lateral aspects of the dependent portion of the renal pelvis in preparation for dismembered pyeloplasty. A traction suture is also placed on the lateral aspect of the proximal ureter below the level of the obstruction. This suture will help maintain proper orientation for the subsequent repair. **B,** The ureteropelvic junction is excised. The proximal ureter is spatulated on its lateral aspect. The apex of this lateral, spatulated aspect of the ureter is then brought to the inferior border of the pelvis while the medial side of the ureter is brought to the superior edge of the pelvis. **C,** The anastomosis is performed with fine interrupted or running absorbable sutures placed full thickness through the ureteral and renal pelvic walls in a watertight fashion. In general, the authors prefer to leave an indwelling internal stent in adult patients. The stent is removed 4 to 6 weeks later.

aspect of the anastomosis at the vertex of the spatulation is critical to ensuring a watertight closure.

11. Before the repair is completed, the renal pelvis is irrigated to remove any blood clots or debris that could obstruct the UPJ. If an indwelling double-J ureteral stent is employed, it should be placed now, with care taken to place the stent into the bladder and renal pelvis without kinking it.
12. A Penrose drain is placed adjacent to the repair and brought out through a separate stab wound.
13. The kidney is returned to its native position, and perinephric fat, if available, is placed over the anastomosis.
14. Closure of the three fascial layers is readily accomplished, followed by closure of the Scarpa fascia and subcuticular skin.

15. A Foley catheter, which was placed at the beginning of the procedure, may be left in place for 24 to 48 hours postoperatively. The Penrose drain usually can be removed before discharge or, if left in place, it can easily be removed in the office 7 to 10 days postoperatively.

Posterior Lumbotomy

The patient is placed in a prone position with a roll under the chest, pelvis, and knees (Fig. 120–15). After the skin incision, the Scarpa fascia is sharply incised and a vertical incision is made through the lumbodorsal fascia (posterior lamella). The lateral edge of the lumbodorsal fascia is elevated, and the sacrospinalis muscle is medially retracted. An incision is made through the middle and anterior lamella of the lumbodorsal fascia, taking care not to injure the iliohypogastric nerve. The quadratus lumborum muscle is retracted, exposing the Gerota fascia beneath the paranephric fat, and then this fascia is opened. The renal pelvis is



Figure 120–13. A 3-month-old male with left ureteropelvic junction obstruction positioned for anterior subcostal approach to dismembered pyeloplasty. The tip of the 11th and 12th ribs are marked, and the patient is placed on a gel roll for elevation of flank.

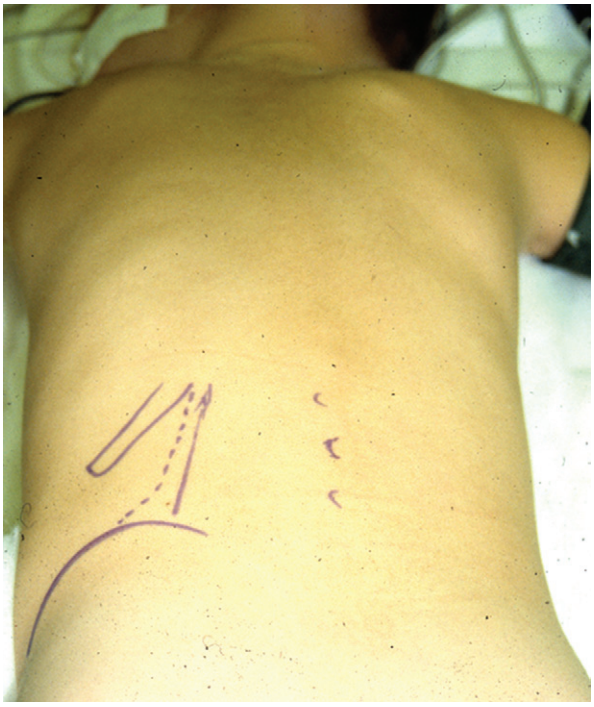


Figure 120–15. Positioning of patient for left posterior lumbotomy incision. An oblique incision is made from the angle of the 12th rib down to the iliac crest at a point one third of the distance from the anterior superior iliac spine to the spinal processes.

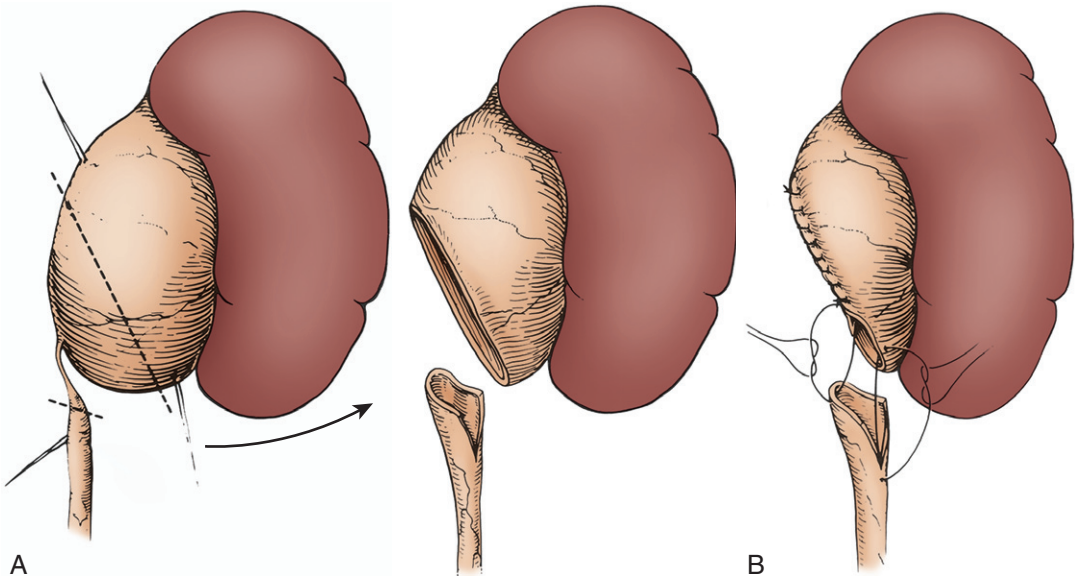


Figure 120–14. **A,** For a large or redundant pelvis, a reduction pyeloplasty is performed by excising the redundant portion between traction sutures. **B,** The cephalad aspect of the pelvis is then closed with running absorbable sutures down to the dependent portion. The dependent aspect of the pelvis is anastomosed to the proximal ureter as described in Figure 120–12.

identified, and several holding stitches are placed in the pelvis. The ureter is identified, a holding stitch is placed in the ureter, and the surgeon proceeds with the dismembered pyeloplasty.

Flank Approach

The patient is placed over the kidney rest in a flank position; the kidney rest is elevated; and the operating room table is flexed. The skin incision is made off the tip of the 12th rib, or, if necessary, a supracostal 12th rib incision is made. The external oblique and latissimus dorsi muscles are divided. Next the internal oblique and serratus posterior inferior muscle are divided. The transversalis muscle is often thin and can be divided with digital dissection. The peritoneum is identified and retracted medially. The Gerota fascia is then encountered and opened longitudinally to gain exposure to the perinephric space. After identification of the renal pelvis and the ureter, a dismembered pyeloplasty can be performed as described earlier.

Minimally Invasive Techniques

Minimally invasive approaches in the repair of UPJ obstruction include endoscopic approaches and pyeloplasties performed laparoscopically (Schuessler et al, 1993; Chen et al, 1998; Tan, 1999) or with the assistance of the da Vinci robotic system (Intuitive Surgical, Sunnyvale, CA).

Endoscopic Approaches

The endoscopic approach to the UPJ has been successful in both an antegrade and retrograde fashion. The initial attempts at balloon dilation (Tan et al, 1995) have been superseded by the use of an Acucise device (ureteral cutting balloon catheter, 5 Fr; Applied Medical, Rancho Santa Margarita, CA) (Bolton et al, 1994). Postoperative stenting is required for 6 weeks, with a 100% success rate being reported in a small series of patients. In a much larger series of adult patients, Kim and colleagues (1998) reported an overall success rate of 78%. Two patients required angiographic studies and embolization of lower pole branching arteries because they developed gross hematuria after Acucise endopyelotomy.

Antegrade endopyelotomy can readily be accomplished in both adults and preadolescent or adolescent patients. Figenshau and Clayman (1998) recommended this procedure for any patient with a reasonably functioning kidney, mild to moderate hydronephrosis, and no evidence of a crossing vessel. Computed tomography or magnetic resonance imaging (MRI) can be used for preoperative assessment of a crossing vessel, or endoluminal ultrasonography can be performed before the procedure. **Antegrade endopyelotomy requires access to the kidney by a midpole posterior calix.** Direct visualization of UPJ obstruction allows use of a cold knife, electrocautery, and even a contact laser fiber to achieve the endopyelotomy (Renner et al, 1998). After fluoroscopic documentation of successful incision and/or dilation of the UPJ, a double-pigtail ureteral stent is placed under direct vision in the renal collecting system and fluoroscopically positioned into the bladder.

The need for fluoroscopy for urologic intervention, along with two and sometimes three anesthetics for preoperative stent placement (nephrostomy tube placement), endopyelotomy, and subsequent stent removal, must be weighed against the more invasive open dismembered pyeloplasty. Older pediatric patients may be managed with the less invasive procedures, with the expectation of good results (80% to 85% success) and improved postoperative convalescence. In one of the largest pediatric experiences to date, endopyelotomy in children ranging in age from 4.5 to 17 years was successful 89% of the time (Tallai et al, 2004); yet, use of this method in children is rare. Endopyelotomy was considered an option in the case of a failed pyeloplasty, because the UPJ should be in a dependent location (Fig. 120–16). A nephrostomy tube may already be in place, and a stricture or stenosis is most likely to be encountered at the UPJ. After a successful endopyelotomy, a double-pigtail ureteral stent is maintained for 6 weeks. Unlike the adult endopyelotomy stent (14 Fr/7 Fr), a pediatric endopyelotomy stent does not exist. The ideal stent would be a biodegradable stent that would not require removal (Lumiaho et al, 2000). Despite early optimistic reports, endopyelotomy for either primary or secondary UPJ obstruction appears to have limited utility.

Laparoscopic Pyeloplasty

Laparoscopic pyeloplasty was introduced in adults in 1993 (Kavoussi and Peters, 1993; Schuessler et al, 1993). In the initial report of five cases, the operative time ranged from 3 to 7 hours. The procedure has gained in popularity, and more recent series have reported a success rate of greater than 95% (Ben Slama, 2000). Laparoscopic pyeloplasty in children has followed the same evolution as nephrectomy. The procedure was first described using a transperitoneal approach. Tan (1999) reported the first pediatric series of transperitoneal laparoscopic dismembered pyeloplasty in 18 children aged 3 months to 15 years. Mean operative time was 89 minutes. Two patients with persistent obstruction underwent repeat laparoscopic pyeloplasty.

Yeung and colleagues (2001) have reported their initial experience with retroperitoneal dismembered pyeloplasty in 13 patients, one of whom required open conversion. The mean operative time was 143 (range 103 to 235) minutes. The longer time needed for the retroperitoneal approach is probably related to the limits of the working space that renders suturing more difficult.

Robotic-assisted surgery may be ideally suited for a pyeloplasty, allowing one to overcome the difficulties encountered with laparoscopic suturing. Peters (2004) presented the first preliminary results of robotic-assisted laparoscopic transperitoneal pyeloplasty in children. Olsen and Jorgensen (2003, 2004) reported their unique experience of retroperitoneal robotic-assisted pyeloplasty. They compared a group of 8 children operated by the robotic-assisted procedures with a previous group of 15 children operated by the standard procedure laparoscopic procedure. The median operative time with the robot was lower than with standard equipment (172 vs. 210 minutes); the shortest operative time with robot was 110 minutes. This early experience has been corroborated by a number of centers, including the authors', demonstrating that advanced laparoscopic reconstructive surgery is feasible. The concern, though, is that the skill set needed for laparoscopic surgery is not being achieved before advancing to a robotic-assisted surgery. The opinion has been voiced that if a robotic malfunction occurs, the more difficult skills of laparoscopic suturing would be needed.

Soulie and colleagues (2001) compared retroperitoneal laparoscopic versus open pyeloplasty with a minimal incision in 53 consecutive nonrandomized adults. The mean operating time (165 vs. 145 minutes) was similar in both groups. Incidence of complications, hospital stay, and functional results were equivalent for both groups, but the return to painless activity was more rapid with laparoscopy in younger patients. Bauer and colleagues (1999) did a similar study, with no difference in the postoperative outcome between laparoscopic and open pyeloplasty. Comparisons between laparoscopic and robotic-assisted anastomoses have begun to define the improvements observed (Franco et al, 2007).

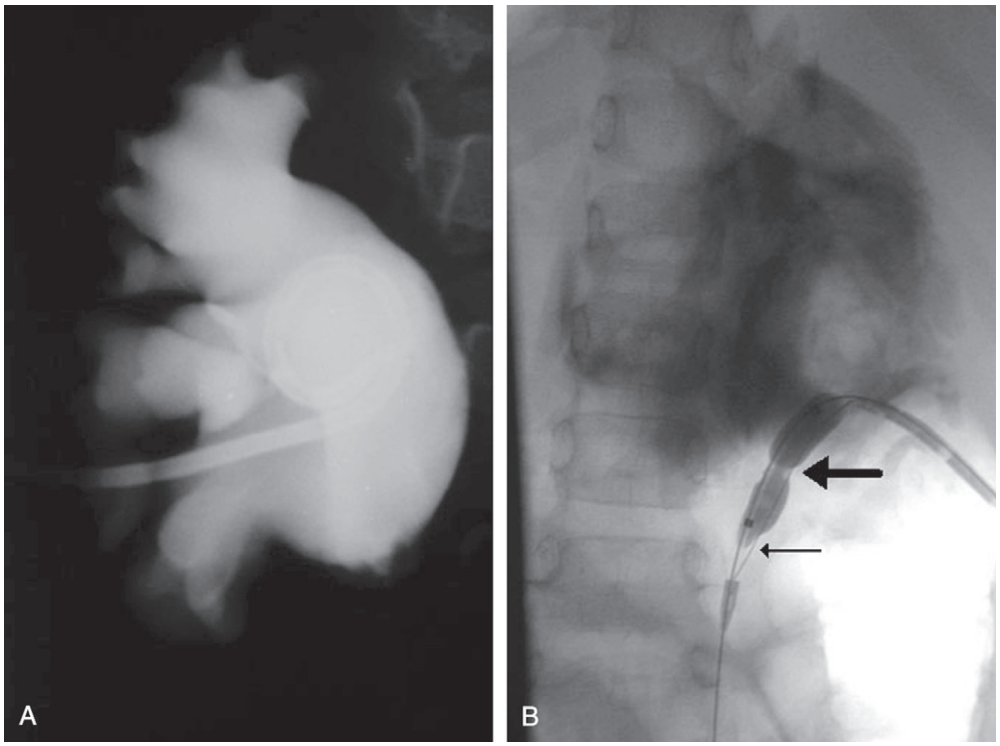


Figure 120–16. **A,** Right antegrade nephrostogram performed 2 months after dismembered pyeloplasty, demonstrating persistent obstruction at the ureteropelvic junction. A nephrostomy tube was placed 2 weeks after surgery, after the patient developed flank pain, fever, and *Staphylococcus aureus* urinary tract infection. **B,** Acucise balloon being inflated across the ureteropelvic junction narrowing. Note waist present in balloon *(upper arrow)* and cutting wire positioned laterally *(lower arrow)*.

The authors' experience thus far encompasses over 300 minimally invasive procedures, thus providing a unique perspective on the learning curve for the minimally invasive approach. The authors' operative times decreased steadily at a rate of 26 minutes, on average with a 35 case interval in between each major time decrease until just over 100 procedures were performed. The attending surgeon's operative time in the first 30 cases lasted, on average, 155 minutes, and now all operative times are less than 90 minutes from incision to skin closure completion. A similar learning curve is seen with trainees, with an extension of the operative times to be 35 minutes on average. Proficiency with instrumentation and suture manipulation is paramount in training. These tasks are accomplished outside the operating arena using surgical simulation tasks with a laparoscopic trainer.

In performing robotic pyeloplasty, one must take into account that a small work space can cause collision of the robotic arms and could be a limiting factor while performing complex manipulative procedures, such as suturing and anastomosis between the renal pelvis and ureter in a restricted space (Thakre, 2008). Robotic pyeloplasty is technically possible but a challenging procedure in small infants. For this reason, the authors' current practice is to perform open pyeloplasties in those infants younger than 6 months. Either a posterior lumbotomy or an anterior subcostal incision is well tolerated in this age group, and the benefits of a laparoscopic approach are more apparent in those patients who are slightly older.

Instruments and Supplies

Typically, an open access technique is used for the camera port. The camera port is placed in the superior aspect of the umbilicus. The abdomen is insufflated with CO_2 at a pressure of 8 to 15 mm Hg with a flow rate of 3 to 10 liters per minute. **The rule is to use enough insufflation to see the relevant anatomy using as little pressure and flow as possible.** Two additional working trocars are usually inserted, typically, 8 or 5 mm for robotics and 5 mm for conventional laparoscopy. A fourth trocar can be placed for additional grasping and retraction, but the space is limited in tiny children, especially infants. The techniques and technology have evolved, allowing identical results and using 5-0, 6-0, and 7-0 suture as in open surgeries. The authors typically use 6-0 monofilament absorbable suture, but one can use any 5-0 or 6-0 suture, depending on the size of the patient.

Surgical Technique

General Procedures. The patient is placed in a modified flank position with a 40- to 60-degree elevation of the flank (Fig. 120–17). **The patient is placed as close to the edge of the bed as possible, and secured with towels and silk tape.** The urethral catheter can be introduced in the sterile operative field for intraoperative access, allowing instillation of saline with or without an indicator for verification of reaching the bladder during the antegrade double-pigtail ureteral stent placement, as described below.

In prepubertal children and teenagers, the ports are placed in the umbilicus for the camera port, along with two working ports in the midclavicular line above and below the umbilicus. On the other hand, in infants, the upper working port should be placed subxyphoid in the midline and the lower working port as lateral as possible to the rectus muscle and close to the inguinal region (Fig. 120–18). For robotics, it is helpful after the port placement to visualize the organ site and decide whether any rotation or reposition of the patient is necessary because it is impossible to



Figure 120–17. The patient is placed in a modified 40- to 60-degree decubitus position. The ipsilateral arm is typically placed along the patient's side as shown in the figure. The authors find this arm configuration to be less obstructive to the laparoscopic field, especially when robotics is employed. It is important to note that with the use of robotics, the entire patient positioning, including bed rotation, must be done prior to docking the robot. Once the robot is docked, any change in patient or bed position requires undocking it.

make such changes after robotic docking without first undocking.

The choice of the transperitoneal or retroperitoneal approach depends on the surgeon's experience. The UPJ is exposed transmesenterically on the left (Fig. 120–19) or by slightly mobilizing the colon on the right, as described below. If one chooses colonic mobilization on the left, it must be taken medially over the aorta. A precise dissection of the UPJ is required to evaluate the cause of UPJ obstruction (UPJO), including lower pole–crossing vessels, additional small arterial branches, or small lumber or gonadal veins crossing the ureter (Rassweiler, 2008) and the renal pelvis. Any crossing vessels should be completely isolated. The ureter also should be free from surrounding structures, such as crossing vessel or periureteral bands. After exposure of UPJO, a hitch stitch is passed through the abdominal wall to elevate and stabilize the pelvis, if so desired. We use a hitch stitch if a pyelolithotomy is necessary. **The choice of dismembered** (Fig. 120–20) **or nondismembered pyeloplasty** (Fig. 120–21) **depends on the surgeon's experience or the anatomy of the renal pelvis and ureter, such as the presence of crossing vessels,** as described below in detail. After the pelvis is incised, the ureter is spatulated laterally, and the anastomosis is performed using a running suture (Fig. 120–22). A double-pigtail ureteral stent is placed after the posterior wall closure is completed (Fig. 120–23). This affords visualization of the anterior wall closure and prevents twisting of the ureter. The double-pigtail ureteral stent placement is performed by placing a 14- or 16-gauge angiocatheter through the anterior abdominal wall. A guidewire is then placed in an antegrade fashion, and the stent is passed over the guidewire. One can fill the bladder with saline or methylene blue to observe the efflux of urine, once there is access into the bladder by the stent. The stent can also be placed retrograde, using a dangling string to allow removal in the office.

Transperitoneal or Retroperitoneal Approach. Recently, several reports have demonstrated the usefulness of conventional retroperitoneoscopic pyeloplasty for children. Canon and colleagues (2007) reported their comparison study of transperitoneal and retroperitoneal approaches in children. They showed no major difference between the two approaches for correcting UPJO, although the average operative time for the retroperitoneoscopic approach was significantly longer than for the transperitoneal approach. Metzelder and colleagues (2006) concluded that no disadvantage was attributable to the transperitoneal approach in children.

Robotic pyeloplasty can be also performed using the transperitoneal or retroperitoneal approach, but there have been no large-scale randomized, prospective studies comparing the approaches. The authors choose a transperitoneal approach because they find that the working space is not limiting and are more comfortable with this approach. **Robotic pyeloplasty using retroperitoneal approach remains a technically challenging procedure in children. This is due to the difficult manipulation within the limited retroperitoneal space, particularly prior to opening the Gerota fascia.** In fact, there are only two reports on the experiences of pediatric robotic pyeloplasty using a retroperitoneal approach (Olsen et al, 2007). This difficulty may be overcome with improvement in operative skill and advancement of robotic technology.

Retrocolic or Transmesenteric Access. Traditionally, a transperitoneal laparoscopic approach to UPJO has been performed in retrocolic fashion by reflecting the colon and its mesentery medially to expose the renal pelvis and ureter; however, **transmesenteric access to the retroperitoneum is a better option for left transperitoneal laparoscopic pyeloplasty, because it allows direct access to a left UPJ with little or no bowel manipulation and shorter operative time** (Lee et al, 2006). The authors also prefer to perform robotic left pyeloplasty for children by transmesenteric access.

Procedures: Dismembered or Nondismembered Robotic Pyeloplasty. The surgical procedures of robotic and laparoscopic dismembered pyeloplasty follow the same steps as the open Anderson-Hynes technique. The stenotic segment is excised and, if necessary, reduction of the renal pelvis accomplished. Position stay sutures should be used with caution to avoid recurrent UPJO, because they may leave the renal pelvis and the ureter in an unfavorable position once released and allowed to fall back (Olsen and Rawashdeh, 2008).

On the other hand, nondismembered pyeloplasty includes the "Fenger-plasty using the Heinecke-Miculicz principle" of a longitudinal incision of the UPJO and vertical suturing, "Y-V plasty" with a V-shaped incision of the renal pelvis, an additional incision of the stenosis including spatulation of the ureter (Y-shaped), and a subsequent closure as a V-flap and "bypass pyeloplasty" with side-to-side anastomosis between the dilated portion of the ureter just distal to the UPJO and the lower and dependent portion of the hydronephrotic renal pelvis (Mesrobian, 2009). Bypass pyeloplasty may be a more physiologic procedure in patients with mid- to high insertion of the ureter. The Heinecke-Mikulicz principle has been abandoned due to inferior long-term success rates. Y-V plasty is better suited for a high insertion of the ureter into the pelvis or for small extrarenal pelvis (Casale et al, 2004). The authors have recently performed a robotic-modified bypass

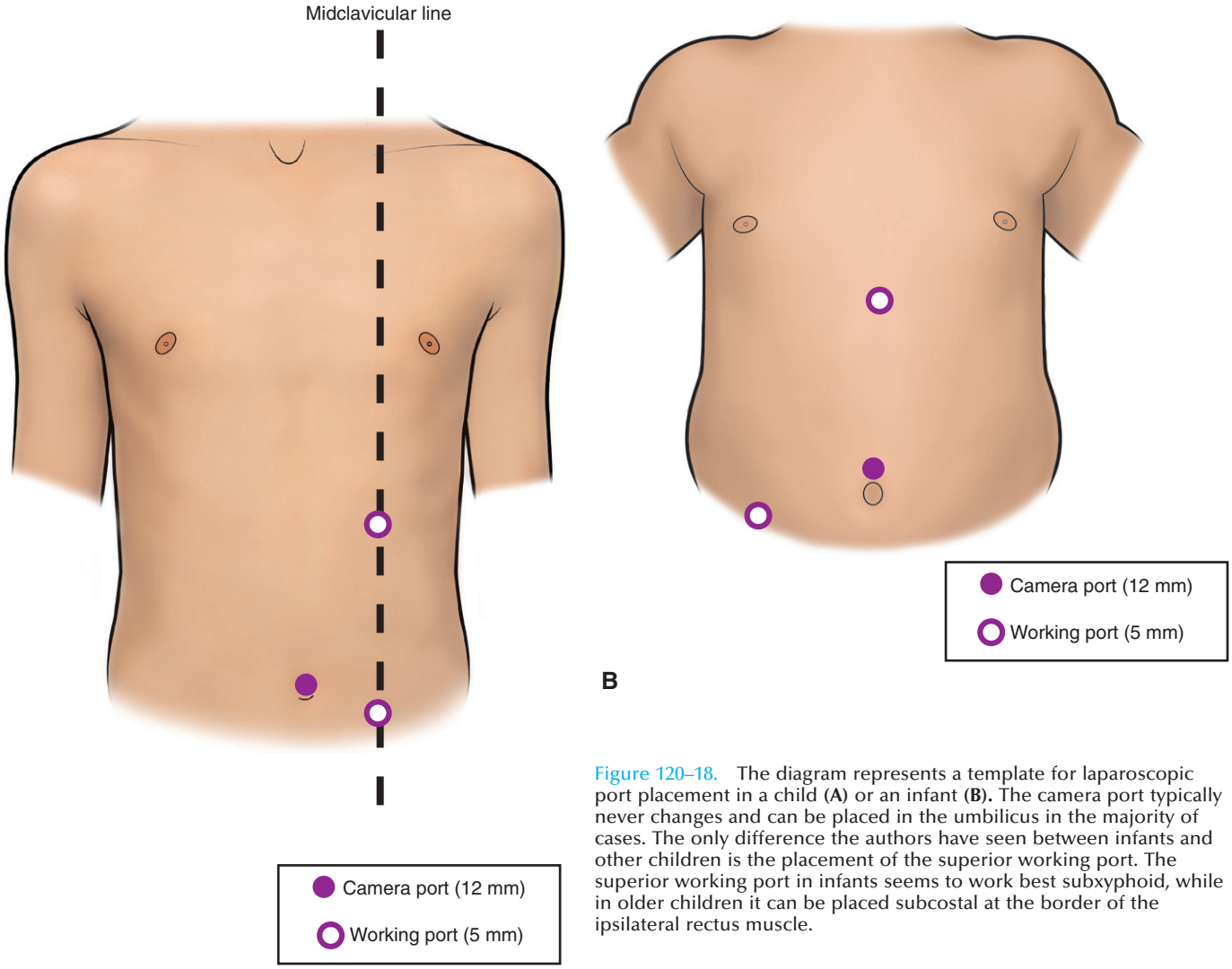


Figure 120–18. The diagram represents a template for laparoscopic port placement in a child **(A)** or an infant **(B)**. The camera port typically never changes and can be placed in the umbilicus in the majority of cases. The only difference the authors have seen between infants and other children is the placement of the superior working port. The superior working port in infants seems to work best subxyphoid, while in older children it can be placed subcostal at the border of the ipsilateral rectus muscle.

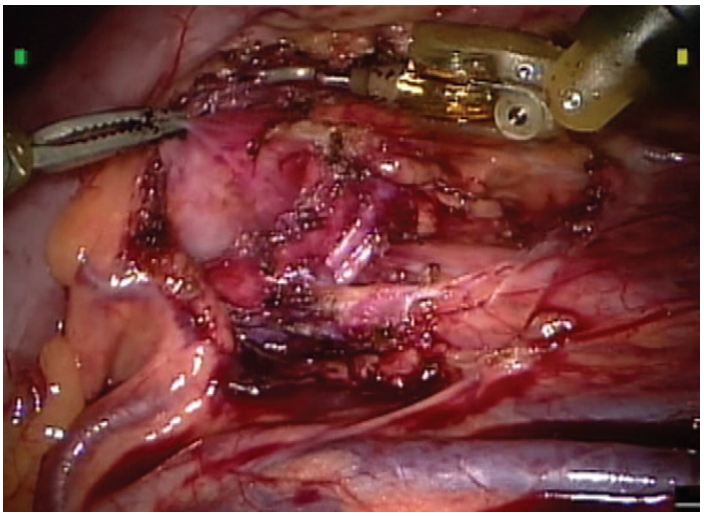


Figure 120–19. Intraoperative laparoscopic view of a transmesenteric approach to the left kidney. Note the crossing vessels seen at the level of the ureteropelvic junction.

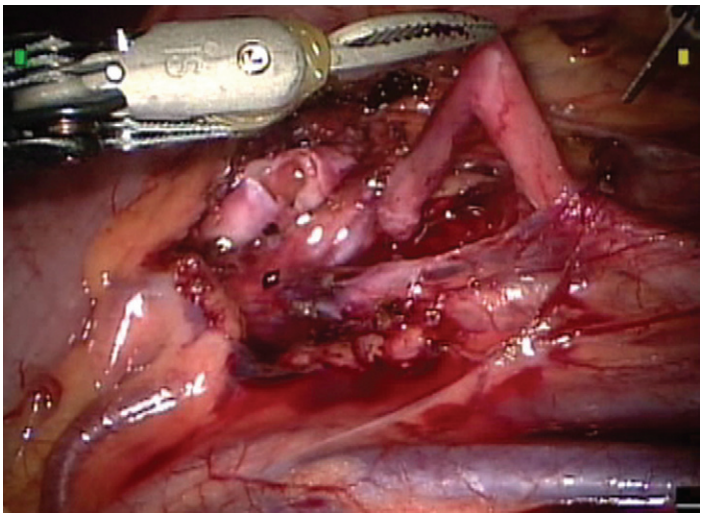


Figure 120–20. Intraoperative laparoscopic view of a transected ureter from the renal pelvis with lower pole–crossing blood vessel pathology. The ureter is then slid out from underneath the vessels with manipulation of the adventitia only.

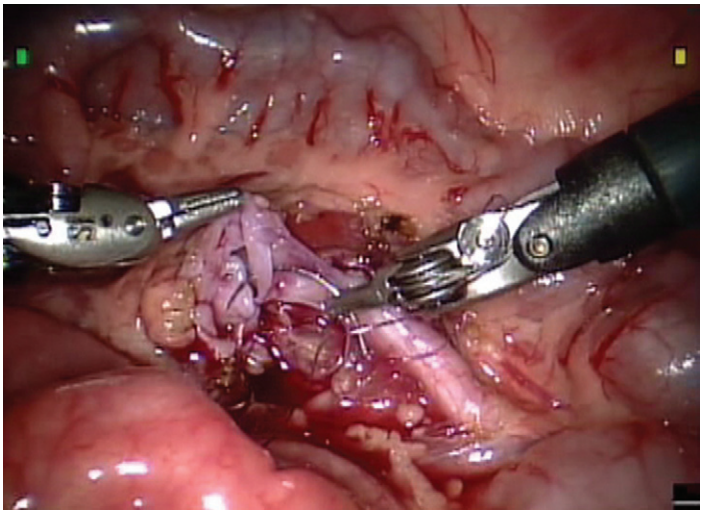


Figure 120–21. Laparoscopic view of a nondismembered pyeloplasty using a side-to-side ureteropyelostomy technique described as a "bypass pyeloplasty." It is imperative that the dependent new ureteropelvic junction be within 1 cm of the lower pole parenchyma.

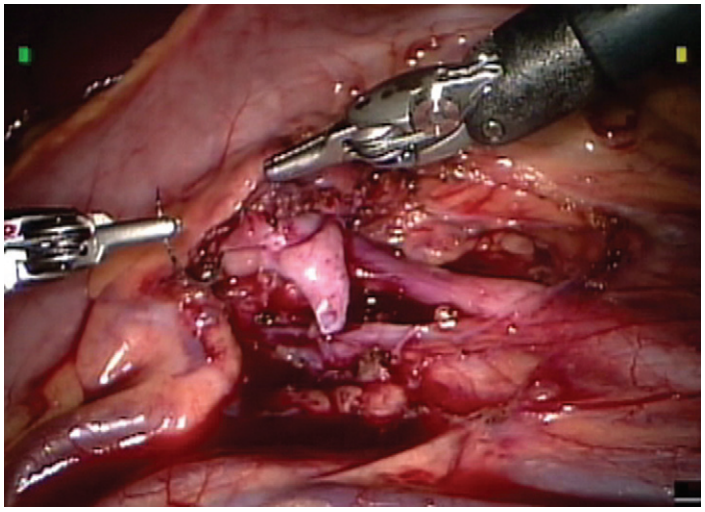


Figure 120–22. Laparoscopic view of the posterior anastomosis of the pyeloplasty. A 6-0 or 5-0 absorbable suture is used in a running fashion.

pyeloplasty for children without crossing vessels, which involves an extended longitudinal incision on the lateral side from the renal pelvis to ureter through the stenotic segment of UPJ. A side-to-side anastomosis between the renal pelvis and ureter is accomplished with a running suture (Fig. 120–24).

One can argue that **an advantage of dismembered pyeloplasty is the complete excision of a stenotic segment of UPJ. Conversely, nondismembered pyeloplasty is technically easier because the ureter is not completely transected from the renal pelvis, facilitating tension-free suturing,** especially with placement of the first stitch (Casale et al, 2004). Maintaining the stenotic segment helps prevent twisting of the ureter and reduces suturing time. A comparison study may be required to clarify which procedure is more suitable in children, although the choice between these types of procedures basically depends on the surgeon's experience along with the anatomy of the renal pelvis and ureter.

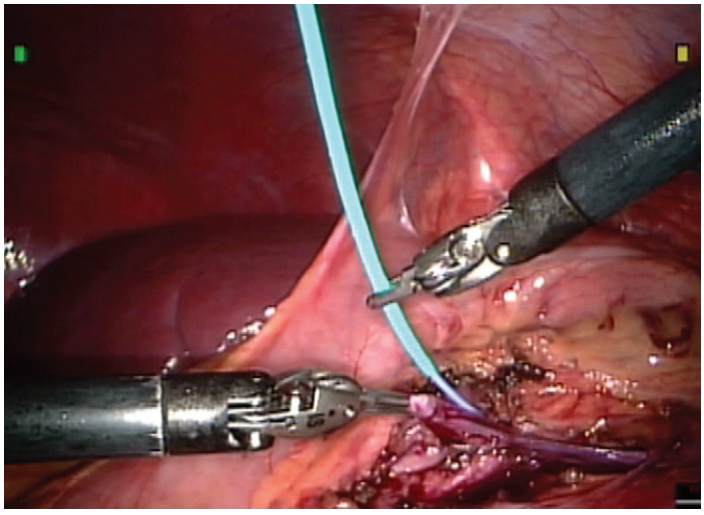


Figure 120–23. Antegrade placement of a double-pigtail catheter after the posterior anastomosis is completed. A 16-gauge angiocatheter is placed percutaneously through the abdominal wall just over the site of the pyeloplasty. A guidewire is then passed with the stent on the wire as one unit traversing the ureter to the bladder. It is important to allow 5 cm of wire to extrude from the stent so that the stent will not get caught at the ureteral orifice below. The bladder catheter can be clamped at the beginning of the posterior anastomosis as to allow bladder filling to allow verification of stent placement into the bladder or dilute methylene blue instilled in the bladder to allow for efflux of blue once the stent enters bladder.

OUTCOME AND COMPLICATIONS

Open Pyeloplasty

Adherence to sound surgical principles, minimal handling of the ureter at the time of repair, and judicious use of internal stenting or nephrostomy tube drainage ensure a successful outcome (Austin et al, 2000). Success is defined as improvement in hydronephrosis and stabilization or improvement in function on renal scan along with a decrease in washout time. In those situations in which symptomatic presentation occurred, resolution of flank/abdominal pain or vomiting should also occur.

Imaging of the kidneys postoperatively depends on whether a nephrostomy tube has been used. A nephrostogram performed 10 to 14 days after surgery allows visualization of the anastomosis. Others have simply clamped the nephrostomy tube for 24 hours and checked the residual in the renal pelvis. If the residual is less than 15 mL, then the nephrostomy tube is removed (Flint et al, 1998). If a double-pigtail ureteral stent is left indwelling, it is removed 2 to 6 weeks after the initial procedure. A renal ultrasonogram is obtained 6 to 8 weeks after pyeloplasty or after stent removal to ensure that the hydronephrosis (pelvocaliectasis) is improving or at least remaining stable. A renal scan may be obtained 1 year after the pyeloplasty to provide a relative assessment of the overall renal function. This is particularly helpful if the initial renal scan showed diminished renal function to the affected kidney. A new baseline is then established, which may be helpful for long-term outcome. On the other hand, if the renal function was not significantly affected at the time of surgery, an overall decrease in the degree of pelvocaliectasis over time is a good indication that the obstruction has been relieved. Long-term imaging at 3 to 5 years may be obtained to look for that

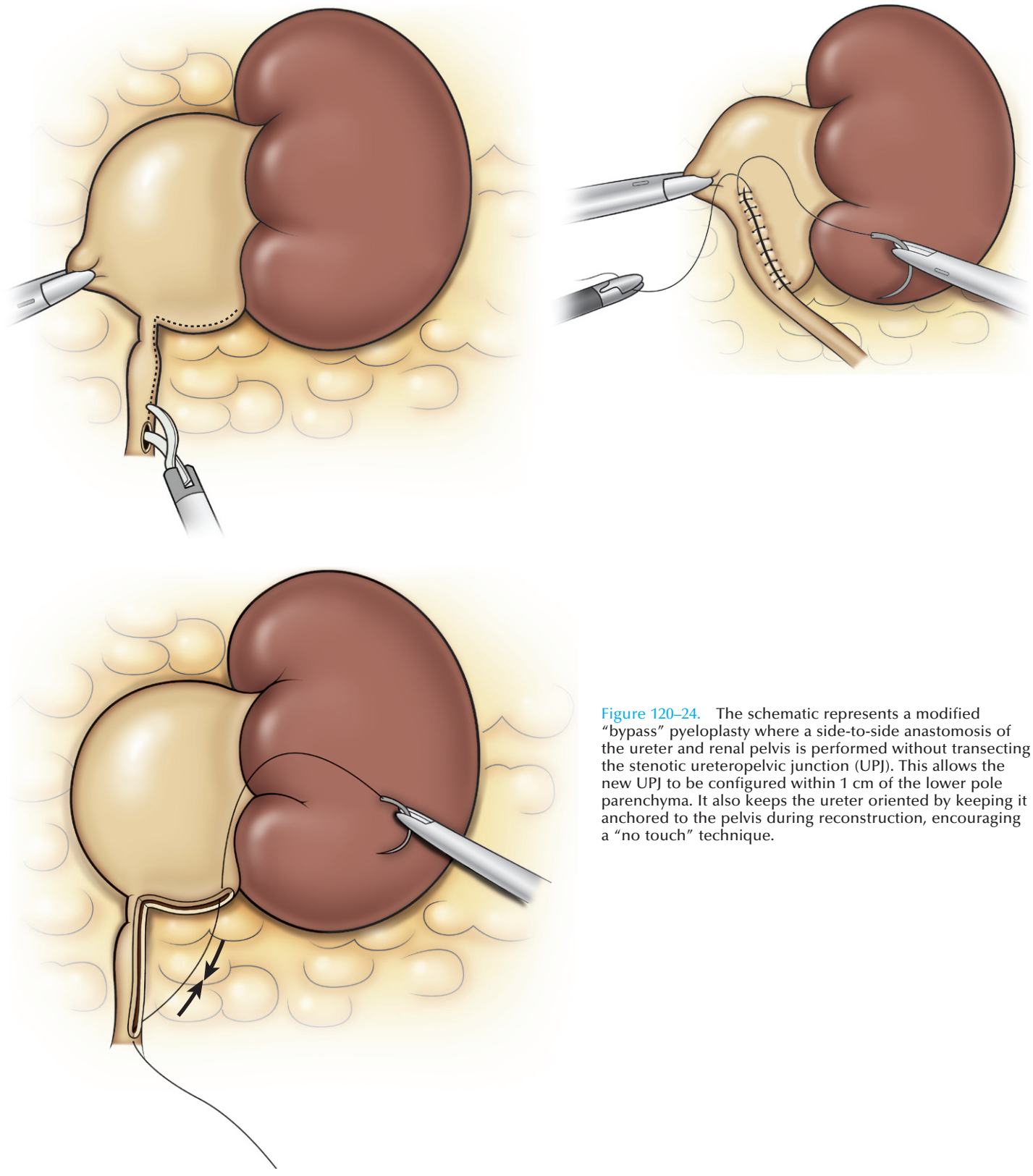


Figure 120–24. The schematic represents a modified "bypass" pyeloplasty where a side-to-side anastomosis of the ureter and renal pelvis is performed without transecting the stenotic ureteropelvic junction (UPJ). This allows the new UPJ to be configured within 1 cm of the lower pole parenchyma. It also keeps the ureter oriented by keeping it anchored to the pelvis during reconstruction, encouraging a "no touch" technique.

rare situation of delayed cicatrization and restenosis of the UPJ. Generally, once the trend of improved pelvocaliectasis is documented postoperatively and confirmed with an evaluation 1 year following surgery, further imaging is not needed. Table 120–1 lists the results from a number of contemporary series of pyeloplasties.

Early complications of pyeloplasty are uncommon and usually involve prolonged urinary leakage from the Penrose drain. Depending on the amount of drainage, observation is generally the best approach. If it persists beyond 10 to 14 days, placement of a retrograde ureteral stent can often rectify the situation. Spontaneously delayed opening of the anastomosis has

Table 120–1.

Results from a Number of Contemporary Series of Pyeloplasties

AUTHOR AND YEAR	PATIENTS/KIDNEYS	SUCCESS (%)
Poulsen et al, 1987	35	100
O'Reilly, 1989	30	83-93
MacNeily et al, 1993	75	85
Shaul et al, 1994	32/33 (2 months old)	97
	30/33 (>2 months old)	93
Salem et al, 1995	100	98
McAleer and Kaplan, 1999	79	90
Austin et al, 2000	135/137	91
Houben et al, 2000	186/203	93
Casale et al, 2004*	19	94
Bonnard et al, 2005†	20	96

*Transperitoneal laparoscopic.
†Retroperitoneal laparoscopic.

occurred as late as several months after the repair. If a patient presents postoperatively with fever, flank pain, and significant hydronephrosis, a nephrostomy tube may be necessary to decompress the kidney. Lack of drainage for a prolonged period would necessitate further imaging with repeat antegrade nephrostogram and consideration of retrograde pyelography as well.

Minimally Invasive Procedures

Complications of the pediatric minimally invasive surgery (MIS) pyeloplasty series published to date include prolonged drainage (Atug et al, 2005) and ileus (Yee et al, 2006), conversion to an open procedure, postoperative nephrectomy, urinary tract infection, hematuria, and displaced double-pigtail ureteral stents (Olsen et al, 2007). Potential intra- and postoperative complications are basically similar to those with conventional laparoscopic procedures as noted below.

Intraoperative Complications

Potential intraoperative complications with MIS pyeloplasty include bleeding requiring transfusion, trocar damage to viscera or vessels, and thermal damage to tissues or organs (Canon et al, 2007). A rare, but significant, complication is bowel injury, the risk of which might be higher if a transperitoneal or even a transmesenteric access is used. Diligent inspection of the viscera at the end of every procedure may help identify an injury (Moore et al, 1995). In some cases, a double-pigtail ureteral stent cannot be advanced into the bladder and urethroscopic repositioning of the stent might become necessary. Technical problems during a robotic pyeloplasty, such as robotic failure, can lead to a conventional laparoscopic conversion.

Postoperative Complications

Potential postoperative complications include hernia internally or at the port site, wound infection, persistent urine leakage and urinary tract infection. Postoperative ileus is a complication with the transperitoneal approach due to leakage of urine from the anastomosis. **Postoperatively, a child should make steady, consistent progress in the first few hours after surgery and dramatically day by day over the first week.** Prompt action should ensure assessing the child and minimizing adverse outcomes (Atug et al, 2005; Canon et al, 2007).

PROCEDURES FOR RECURRENT URETEROPELVIC JUNCTION OBSTRUCTION

Although open laparoscopic and robotic pyeloplasties have favorable outcomes with success rates exceeding 90%, recurrent UPJO sometimes occurs in all procedures. Factors such as young age at initial surgery (less than 6 months), prolonged urinary diversion (dry anastomosis), missed anatomic findings at the first intervention (crossing vessels or long ureteral segment narrowing), and lack of retrograde pyelogram have been related to pyeloplasty failure (Thomas et al, 2005; Braga at al, 2008). Second-line therapies have previously been shown to fail at a higher rate than the initial therapeutic procedure (Atug et al, 2005). It is a serious complication for which treatment remains challenging, because of the extensive scarring and fibrosis from the prior procedure. Patients with recurrent UPJO sometimes present a treatment dilemma to pediatric urologists.

Open or Minimally Invasive Surgery (MIS) Redo Pyeloplasty

Usually, repeat dismembered pyeloplasty has been successful in correcting the problem. An anteriorly elongated flank incision facilitates exposure; a transperitoneal approach avoids some of the dense scarring that often occurs; and a nephrostomy tube postoperatively is recommended (Rohrmann et al, 1997). Alternatively, MIS redo pyeloplasty is reported to be a safe and effective option in the treatment of these challenging patients (Passerotti et al, 2007; Hemal et al, 2008). Basically, the procedure is performed as described for the primary MIS pyeloplasty. Although both dismembered and nondismembered pyeloplasties are possible, for cases in which scarring prevents extensive mobilization of the renal pelvis and ureter to allow dismembered pyeloplasty, Y-V plasty is an excellent option when crossing vessels were not missed the first time around (Passerotti et al, 2007).

Careful preoperative planning is mandatory before embarking upon the redo surgery. **The location and the extent of the diseased segment is assessed with preoperative imaging, including antegrade, retrograde, or intravenous urography and nuclear renography or magnetic resonance urography to assess renal function and location.** The available options for management of recurrent UPJO are balloon dilation, endopyelotomy, open, or MIS pyeloplasty. Braga and colleagues (2007) compared retrograde endopyelotomy, using a holmium laser or cautery/balloon dilation, with redo pyeloplasty through a flank incision or laparoscopy for the treatment of failed pyeloplasty in children. They demonstrated that retrograde endopyelotomy had a significantly lower success rate (39%) than redo pyeloplasty (100%) for correction of recurrent UPJO (Braga et al, 2007). Piaggio and colleagues (2007) assessed the feasibility of pediatric redo conventional laparoscopic pyeloplasty in comparison with redo open pyeloplasty and demonstrated that the success rate was the same in both groups (80%). However, surgical time for redo conventional laparoscopic pyeloplasty was longer than for redo open pyeloplasty. Redo conventional laparoscopic pyeloplasty is technically more challenging than primary conventional laparoscopic pyeloplasty with longer operative times. Because the most time-consuming part of the operation is the laparoscopic exposure and suturing for recurrent UPJO, robotic procedures, such as redo pyeloplasty and ureterocalicostomy, for these children can be alternative options.

Dissection of the UPJ area may be one of the most technically difficult parts of performing redo MIS pyeloplasty. Because of the presence of scar tissue, care must be taken to avoid injury to the ureter or major vessels. The magnification and dexterity afforded by the robot might allow more precise dissection (Atug et al, 2006). The degree of adhesion and fibrosis is highly variable, which may be secondary to healing factors of the patients as well as to technical problems in the primary operation, such as incomplete or unfavorable position of the anastomosis between the renal pelvis and ureter or urinoma (Brito et al, 2007). Crossing vessels that may have been missed during the primary operation must be identified, because it can be a cause of recurrent UPJO (Rehman et al, 2001). The ureter should be free from surrounding structures and spatulated clearly enough to encounter healthy tissue. Passerotti and colleagues (2007) reported redo robotic pyeloplasty for 6 children with uniform success and no complications. Hemal and colleagues (2008) reported their experience of redo robotic pyeloplasty for 5 children younger than 15 years as a salvage procedure, and all children had improvement of obstruction.

Key Points: Pyeloplasty

- Ureteropelvic junction obstruction is typically due to either an intrinsic narrowing in which the ureteral segment has an interruption in the development of the circular musculature of the ureteropelvic junction, an alteration in collagen fibers in and around the muscular cells, or an extrinsic obstruction that is seen in association with aberrant, accessory, or an early branching lower pole vessel that passes anteriorly to the UPJ or proximal ureter and contributes to mechanical obstruction.
- Congenital renal malformations can be commonly seen in association with a ureteropelvic junction, with a contralateral UPJ obstruction being the most common anomaly, followed by renal dysplasia and multicystic dysplastic kidneys.
- The surgical approach favored in the repair of a ureteropelvic junction obstruction is the dismembered pyeloplasty, which has been shown to be effective because of its broad applicability, means of allowing excision of the pathologic segment question, and facilitation of a reduction pyeloplasty when necessary.
- Laparoscopic pyeloplasties provide excellent visualization of the anatomy, enhance cosmesis, and duplicate the results of open pyeloplasties with short-term follow-up. The technical challenges of this approach have been facilitated by the use of a robotic-assisted procedure that improves the anastomotic repair.
- Complications from a pyeloplasty include prolonged urinary drainage postoperatively, lack of improvement in renal function or improvement in washout, and, occasionally, worsening hydronephrosis and diminished renal function postoperatively. Such a situation may lend itself to a repair using ureterocalicostomy or a redo dismembered pyeloplasty.

Open, Robotic, or Laparoscopic Ureterocalicostomy

In performing a ureterocalicostomy, key points include amputating the lower pole of the kidney; preserving all periureteral tissue and blood supply; creating a widely spatulated, tension-free, mucosa to mucosa anastomosis; and adequate internal stenting. Retroperitoneal fat can be placed around the anastomosis, but closing the lower pole capsule over the renal parenchyma should be avoided (Matlaga et al, 2005) (Fig. 120–25).

Laparoscopic ureterocalicostomy is a potential option not only in patients with failed pyeloplasty but also in patients with UPJO and significant lower pole calicectasis and a minimal pelvis, or in patients with an exaggerated intrarenal pelvis (Casale et al, 2008). If the pelvis is not readily accessible, robotic ureterocalicostomy will be a better choice than redo robotic pyeloplasty. The colon is reflected, exposing the massively dilated kidney. The ureters are transected and ligated with absorbable sutures at the level of the renal pelvis or crossing vessels. The ureter is spatulated before transection (Fig. 120–26). The most dependent lower pole calyx is amputated with a hot shears. There is a minimal amount of bleeding from the thinned parenchyma of the lower pole system, and the electrocautery of the hot shears easily controls any bleeding. The posterior anastomosis is performed with 5-0 absorbable suture in a running fashion (Fig. 120–27). The ureteral stent is then placed in the same fashion as for a robotic pyeloplasty, as described above. The anterior anastomosis is performed in an interrupted manner, allowing visualization and approximation of the renal collecting system to the ureteral mucosa without placing tension on the renal parenchyma. The anterior sutures are then tied in groups so that the last few suture placements are unobstructed and precise. The stent is removed at 6 weeks after surgery with a retrograde ureteropyelogram to visualize the anastomosis. The authors performed robotic ureterocalicostomy for nine patients with UPJO (mean age 6.5 years). Mean operative time was 168 minutes and mean hospital stay was 21 hours (Casale et al, 2008). There was no evidence of obstruction after operation in any patient.

Key Points: Minimally Invasive Surgery

- Use enough insufflation pressure to afford visualization without compromising venous return and pulmonary performance. Typically, 10 mm Hg is sufficient in children.
- Postoperatively, a child should make steady, consistent progress in the first few hours after surgery and dramatically day by day over the first week. If this sequence does not occur, then one must be wary of a missed injury or incomplete or failed anastomosis.

Megaureter

The decision to repair a megaureter is dependent on the clinical presentation, because megaureters, much like hydronephrotic kidneys, can be detected at the time of prenatal ultrasonography. Experience has shown that many, in fact **the majority of megaureters, can be successfully managed by a nonoperative approach.** Megaureters that have been deemed nonobstructed often will show gradual improvement over time (Keating et al, 1989; Baskin et al, 1994; McLellan et al, 2002). It is helpful to document resolution with periodic ultrasonography. **Megaureters that improve but do not resolve warrant a follow-up ultrasound evaluation around the time of puberty, because the authors have several patients return with worsening but asymptomatic hydroureteronephrosis**

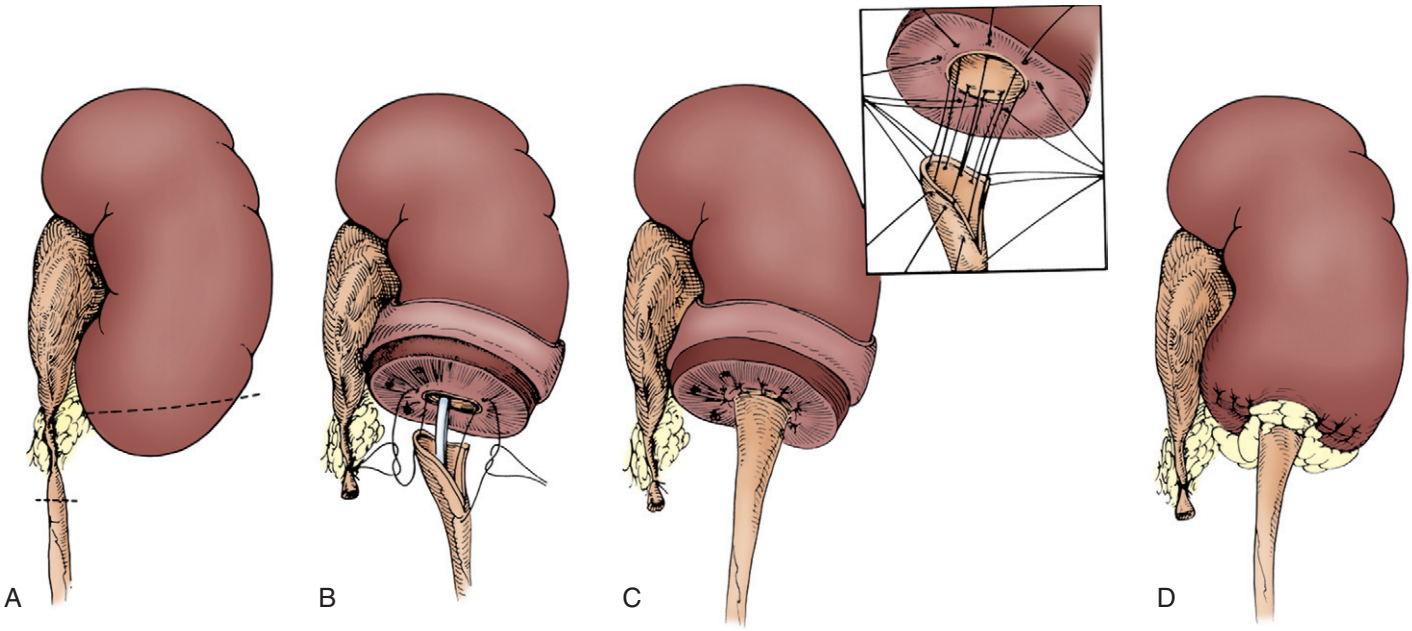


Figure 120–25. **A,** The ureter is identified in the retroperitoneum and dissected proximally as far as possible. The kidney is mobilized as much as necessary to gain access to the lower pole and to subsequently perform the anastomosis without tension. A lower pole nephrectomy is performed, removing as much parenchyma as necessary to widely expose a dilated lower pole calyx. **B,** The proximal ureter is spatulated laterally. The anastomosis should subsequently be performed over an internal stent and consideration given to leaving a nephrostomy tube. The initial suture is placed at the apex of the ureteral spatulation and the lateral wall of the calyx, with another suture placed 180 degrees from that. **C,** The anastomosis is completed in an open fashion, placing each suture circumferentially but not securing them until the anastomosis has been completed. **D,** The renal capsule is closed over the cut surface of the parenchyma whenever possible. However, the capsule should not be closed close to the anastomosis itself because that may compromise the lumen by extrinsic compression. Instead, the anastomosis should be protected with a graft of perinephric fat or with a peritoneal or an omental flap.

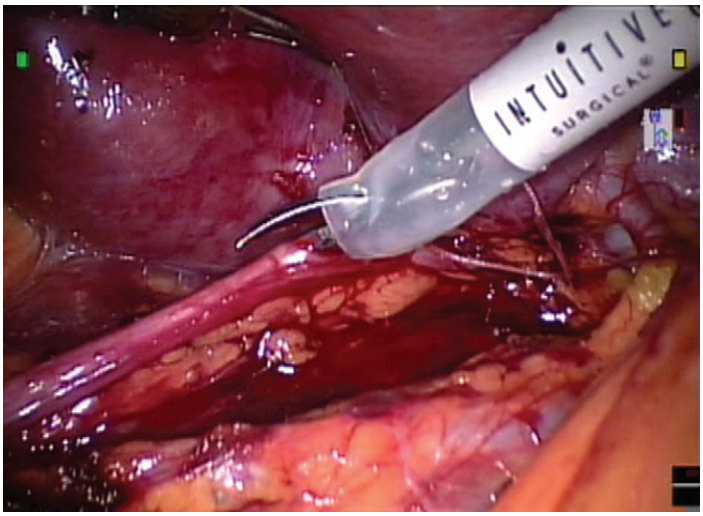


Figure 120–26. Laparoscopic view of ureteral spatulation before transaction of the ureter from the renal pelvis during a robotic ureterocalicostomy for an exaggerated intrarenal pelvis with giant hydronephrosis.

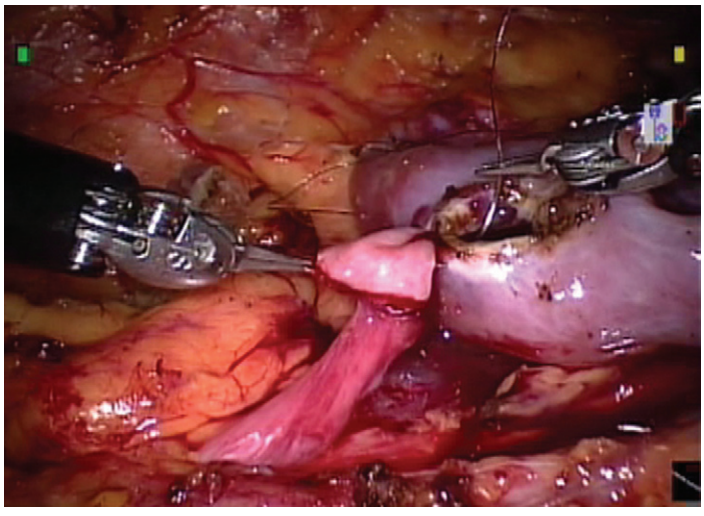


Figure 120–27. Intraoperative laparoscopic view of a robotic ureterocalicostomy. After the most dependent lower pole calix is amputated with a hot shears, the posterior anastomosis is performed with 5-0 absorbable suture in a running fashion.

(Shukla et al, 2005). Dilatation of the urinary tract does not necessarily equate to a physiologically significant obstructive process with renal functional impairment despite the anatomic distortion of the collecting system.

Surgical Management

The repair of a megaureter, whether obstructed, refluxing, refluxing and obstructed, involves a narrowing of the ureteral caliber (tapering or plication) so that an adequate length-to-diameter ratio can be achieved and resection of the obstructive segment. This narrowing allows successful coaptation of the ureteral walls and aids effective peristalsis. Once the obstruction is relieved and distal tortuosity corrected, proximal ureteral dilation improves. Previously, megaureters were approached distally, and then, several months later, proximal narrowing was performed. This was found not to be necessary when the patient demonstrated significant improvement once distal obstruction was relieved (Hendren, 1969).

Two methods can be used to remodel a megaureter. **Plication or infolding** (Kaliciński et al, 1977; Starr, 1979) **is reserved for a moderately dilated ureter.** Ureteral vascularity is preserved, and the repair can be reversed if vascular compromise is suspected (Bakker et al, 1988). **Excisional tapering is reserved for a more severely dilated ureter or a ureter that is markedly thickened, avoiding reimplantation of a bulky ureter** (Hendren, 1969). Plication of ureters greater than 1.75 cm in diameter has been associated with more complications (Parrott et al, 1990). Options for reimplantation included a standard intravesical technique in addition to extravesical repairs (Perovic, 1994, DeFoor et al, 2004). The success with reimplantation of remodeled megaureters, regardless of the technique, is not as high as nondilated ureters; yet, a 90% to 95% success rate may be anticipated (Hendren, 1969; Retik et al, 1978; Parrott et al, 1990). A review of Dr. Hendren's megaureter cases until 1993 demonstrated greater initial success with obstructed (93%) versus refluxing (83%) megaureters and clearly greater success in those patients with normal bladders (91%) versus abnormal bladders (81%, posterior urethral valves, neuropathic, ureteroceles, prune belly syndrome (Hendren, personal communication).

Another approach to an infant with a markedly dilated megaureter is early diversion by an end-cutaneous ureterostomy as a temporizing measure, with subsequent ureteral reimplantation. Successful decompression of significant hydroureteronephrosis, in addition to bladder growth, can allow for a straightforward reimplantation at 15 to 18 months of age, often avoiding additional ureteral plication (Kitchens et al, 2007). Alternatively, a primary obstructive megaureter can be converted to a temporary refluxing system by anastomosing the ureter proximal to the obstruction to the dome of the bladder (Lee et al, 2005). Reimplantation is performed 12 to 15 months later following successful improvement in ureteral size, again obviating the need for ureteral plication prior to reimplantation.

Just as laparoscopic pyeloplasties and robotic-assisted pyeloplasties have become surgical options in the management of UPJ obstruction, ureteral reimplantations are increasingly being performed in a minimally invasive fashion. Robotic-assisted plication of ureters can be accomplished by an extravesical approach, and even formal excisional tapering of the ureter can be done as well. To date, just a handful of institutions are performing such surgery.

Description of the Surgical Technique

After making a Pfannenstiel incision, the bladder is opened in the midline and the ureter is dissected from its intravesical and extravesical attachments (Fig. 120–28). In some instances, the ureter can be adequately mobilized by staying within the bladder. In such cases, the approach for a reimplantation by either the Cohen or the Politano-Leadbetter method is repeated after ureteral tailoring. However, when very large ureters are being tapered, it is advisable to work outside the bladder, as well in order to better define and preserve the blood supply.

If a method of reimplantation similar to the Politano-Leadbetter technique is chosen, a new hiatus should be created prior to moving extravesically. The hiatus is widened with a right angle clamp, and the peritoneum is swept from the base of the bladder using either a lighted suction tip or Senn retractors or a right angle clamp. The clamp is incised upon and spread at an appropriate superior-medial location for the new hiatus. A red rubber catheter or vessel loop, which helps guide the ureter through its new hiatus, is engaged and carried extravesically and then back into the bladder, where it is snapped.

Dissection outside the bladder is begun by sweeping the lateral peritoneal attachments superiorly with a Kittner dissector. A right angle clamp is used to pass the ureteral cuff stitch through the old hiatus to the perivesical space, and the ureter is brought extravesically.

The adventitia and blood supply to the lower ureter, which usually emanate medially, are carefully preserved. When working outside the bladder, it is helpful to divide the obliterated hypogastric (umbilical artery) to aid in the dissection and to eliminate it as a possible source of obstruction. Excessive mobilization plus removal of proximal kinks is unnecessary.

After excision of any obstructive distal ureter or excessive length, ureteral tailoring is done over a 10-Fr red rubber catheter (8 Fr in an infant) unless the ureter is already snug over the catheter, in which case revision is unnecessary. Tailoring is achieved by one of the following methods: In the tapering method (Fig. 120–29), the technique used is similar to that originally described by Hendren (1969). Baby Allis clamps are placed laterally to define redundant ureter while preserving the medial vascular supply. Atraumatic clamps are applied around the catheter and excess ureter is excised. Excessive narrowing of the lumen should be avoided, and the more proximal ureter should be left slightly wider to create a funneled configuration. A running, locking 6-0 polydioxanone suture is used to reapproximate the proximal two thirds of the tapered ureter. Interrupted sutures complete the repair and allow for any shortening that may be necessary. The proximal portion of the tailored ureter must remain outside the bladder after completion of the reimplantation with either tapering or plication. Secondary obstruction is likely if the entire tailored segment is located within the intravesical tunnel.

Starr Plication. Ureteral redundancy is again defined by briefly applying atraumatic clamps to mark the extent of plication and preserve the best-vascularized portion of the ureter. Starting proximally, the ureter is plicated with interrupted 5-0 polydioxanone sutures placed in Lembert fashion along the clamp impressions (Fig. 120–30) (Starr, 1979).

Kaliciński Plication. Two 6-0 polydioxanone sutures are placed along the clamp impressions, one at the proximal extent of the proposed revision and the other at the new meatus. The ureter is divided longitudinally by weaving one suture through the ureter in running fashion along the clamp impression, thus creating two lumens. The ureter is then reduced by folding its nonfunctional portion over the catheterized lumen (Fig. 120–31) (Kaliciński, 1977).

The reimplantation is completed with either the cross trigonal, Politano-Leadbetter, or extravesical technique. It is often helpful to secure the repair with a psoas hitch, especially in smaller children, patients who require a long submucosal tunnel, and cases in which the surgeon is particularly concerned about angulation of the tailored ureter as it enters the bladder. Tapered ureters are stented for 5 to 7 days. A feeding tube can simply be left in place and is brought out through the anterior abdominal wall or, alternatively, a double-J stent can be placed, which requires removal in 4 weeks. Stentograms are not necessary to look for leaks but can confirm that drainage will occur once the stent is removed.

Results and Complications

Reimplantations of megaureters is associated with the same complications (i.e., persistent reflux and obstruction) as reimplantation of nondilated ureters but at increased rates. Complications can occur regardless of whether excisional tapering or a folding technique is used (Ehrlich, 1985; Daher et al, 1999; Fretz et al,

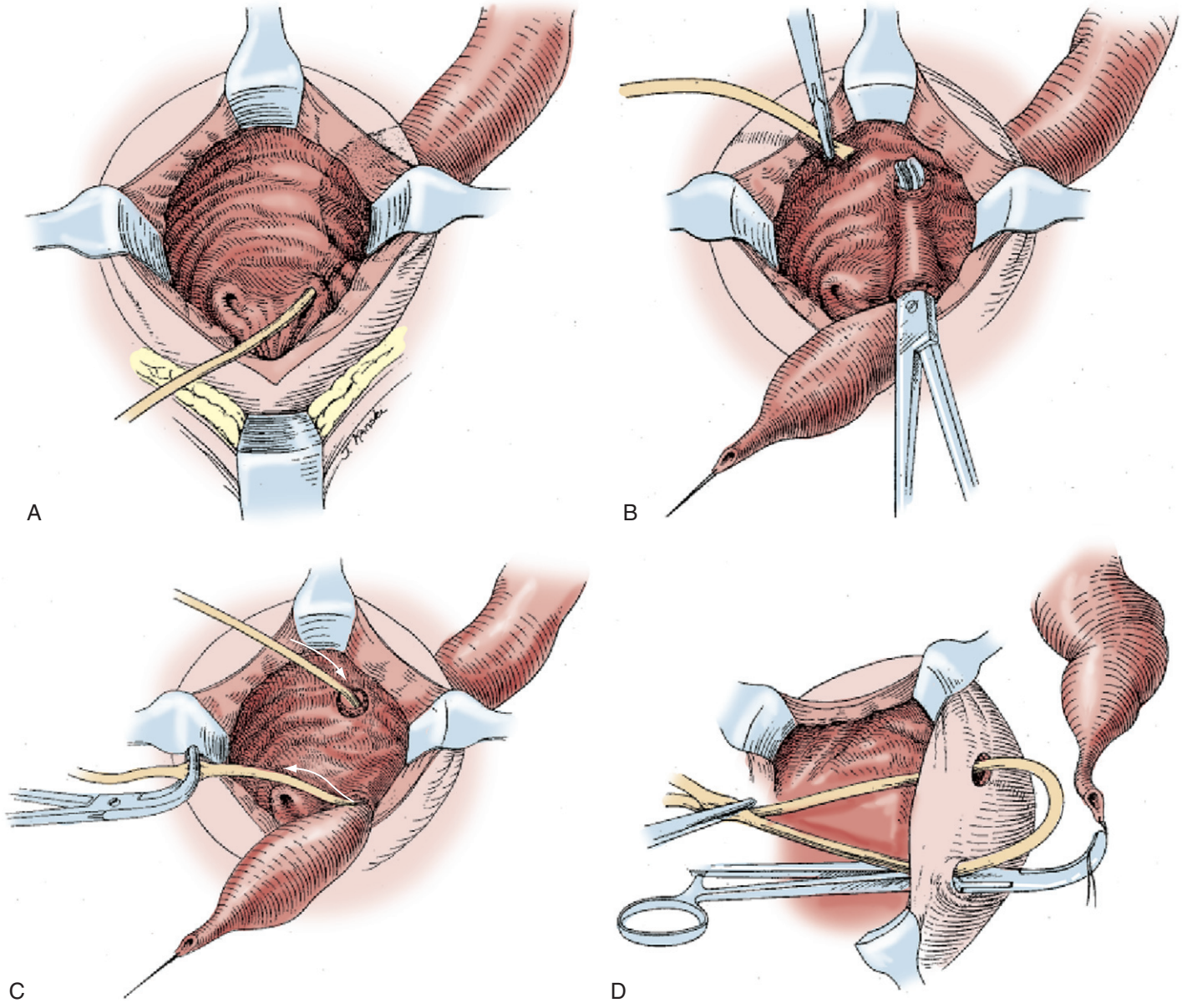


Figure 120–28. Technique for repair of megaureter. **A,** A 5-Fr feeding tube typically passes up a normal-caliber intravesical segment of primary obstructive megaureter. **B,** After the megaureter is freed from its intravesical and extravesical attachments, a blunt right angle clamp is used to clear the peritoneum from the posterior and base of the bladder. If extravesical dissection is necessary, it is advisable to make the new hiatus before moving outside the bladder. A right-angle clamp is incised upon and spread. **C,** A fine red rubber catheter marks the new hiatus by being pulled from within the bladder to the outside and then through the old hiatus. **D,** A right angle clamp is guided from within the bladder to the perivesical space, where it is identified and incised upon. The ureter is brought extravesically by grasping the traction suture in the ureter.

2004). Perdzyński and Kaliciński (1996) cited good results in 52 (93%) of 56 megaureters. Two cases of stenosis and two cases of reflux occurred in failures. Some authors have noted better results with obstructive megaureters and higher rates of unresolved reflux after tailoring of refluxing variants (Johnston and Farkas, 1975; DeFoor et al, 2004), a finding that could be explained by the previously mentioned studies of Lee and colleagues (1998, 2005) in which **abnormal collagen deposition in the refluxing variants could cause an intrinsically stiffer ureter and lessen surgical success.** This has been attributed to a higher incidence of bladder dysfunction associated with the latter and to more significant abnormalities in their musculature. It has been suggested that extravesical reimplantation and excisional tapering can be performed with a high success rate in patients with primary obstructive megaureters and that intravesical reimplantation can be reserved as a better option for children with voiding dysfunction or associated vesicoureteral reflux (DeFoor, 2004). Postoperative success is often documented with the use of follow-up voiding cystourethrogram (VCUG) studies in refluxing megaureters and nuclear renal scans in addition to renal ultrasonography. Improvement or resolution of hydroureteronephrosis is not always the case. **Male patients, those operated on at a younger age, and those with a lower preoperative grade of hydronephrosis are more likely to demonstrate improvement or**

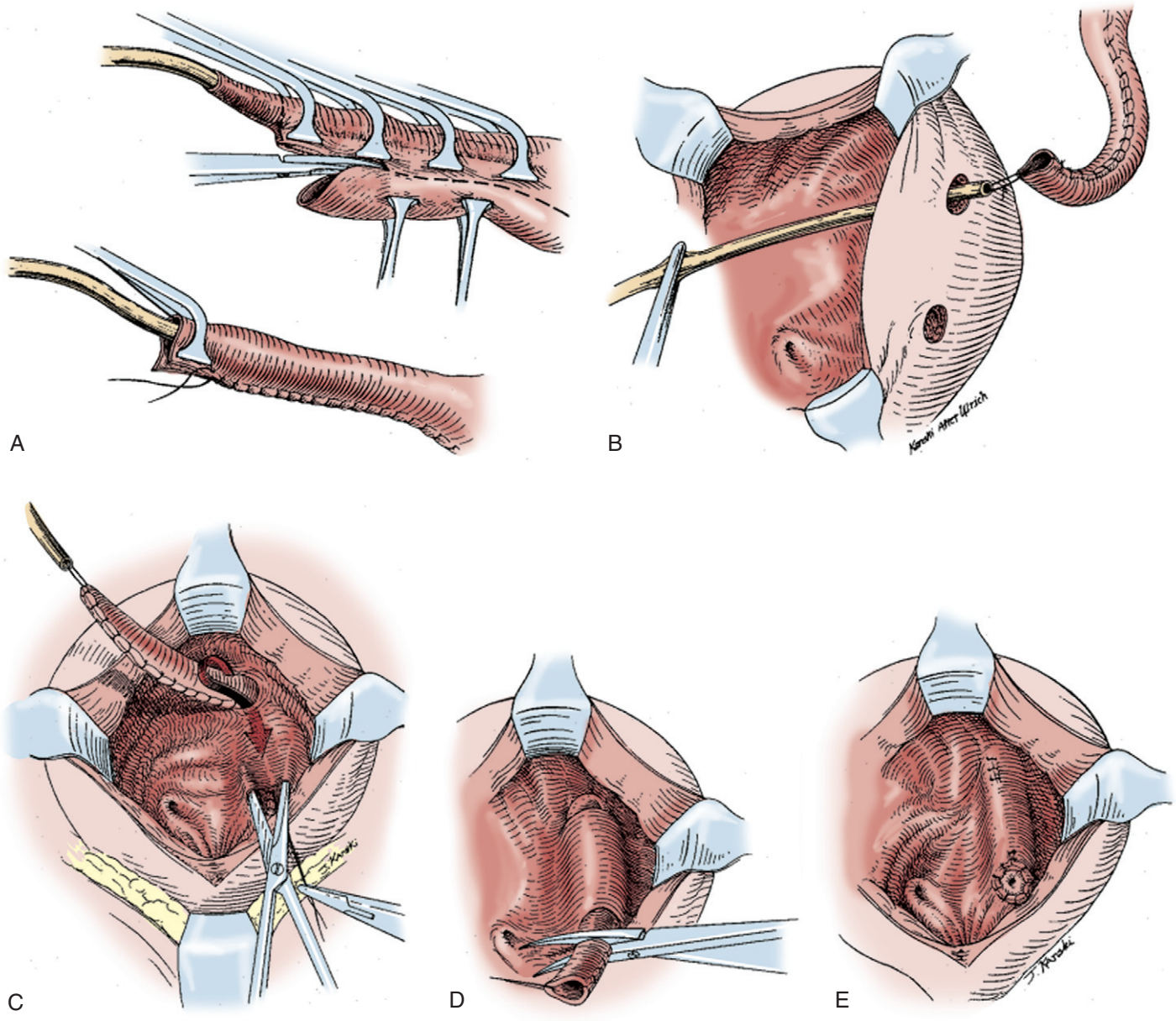


Figure 120–29. **A,** Ureteral tailoring is completed. Tapering is done over an 8-Fr red rubber catheter in infants or a 10-Fr catheter in older children and adults. After vascularity is defined, special atraumatic clamps are placed over the catheter. Baby Allis clamps help retract the portion of ureter to be resected, which is usually lateral. It is important to not resect too much ureter. Running 5-0 polydioxanone or chromic suture is used to reapproximate the proximal two thirds of the ureter. Its distal third is closed with interrupted sutures to allow for shortening. **B,** The tailored ureter is brought back into the bladder through the new hiatus. **C,** After closing the original hiatus, a new submucosal tunnel is made to the new hiatus. **D,** The distal portion of ureter is resected to match the length of the tunnel. **E,** The revised ureter is anastomosed to the bladder with fine interrupted sutures.

resolution of hydronephrosis. Thus it is not uncommon to see persistent hydroureteronephrosis following excisional tapering and reimplantation of megaureters in children (Link et al, 2007).

On rare occasions, reflux persists despite ureteral tunnels deemed adequate intraoperatively by both tapered and normal-sized ureters. Postoperative vesicoureteral reflux can occur in a higher percentage of patients than with normal-caliber ureters (Hendren, 1969; Peters et al, 1989; Fretz et al, 2004). The possibility of dysfunctional voiding patterns should be considered. Mild cases may improve with time. When associated with complications (e.g., recurrent episodes of pyelonephritis), surgical correction is indicated. Even though the experience is limited, subureteric injection therapy may be considered initially. Selected cases may proceed to open surgery, with the difficulties imposed by scarring and a potentially limited blood supply. If severe, the rigid distal ureter is incapable of normal peristalsis or appropriate coaptation during bladder contractions, because of the intrinsic ureteral dysfunction caused by transmural scarring. Transuretero-ureterostomy is ideal for unilateral disease (Mure et al, 2000). Bilateral cases can be approached by excising the scarred distal ureter and creating an exaggerated ureteral tunnel length whose diameter-to-length ratio may exceed 10:1. In-situ tailoring is

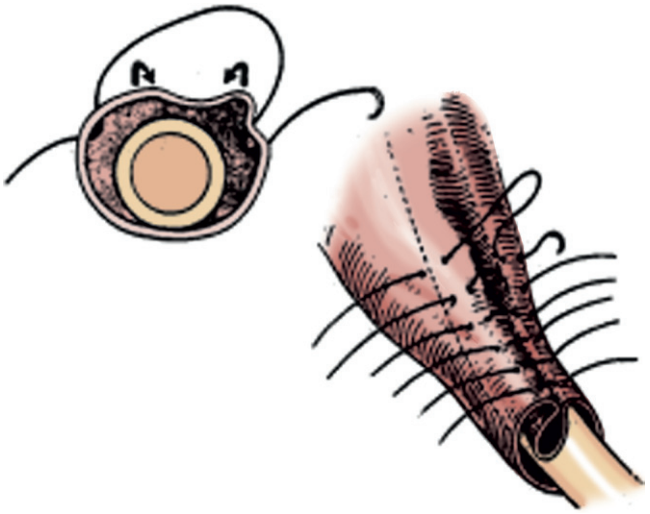


Figure 120–30. Ureteral plication is performed over the appropriate catheter, with interrupted 5-0 polyglycolic sutures placed in Lembert fashion (after Starr). (From Keating MA, Retik AB. Management of failures of ureteroneocystostomy. In: McDougal WS, editor. Difficult problems in urologic surgery. Chicago: Year Book Medical; 1989. p. 131.)

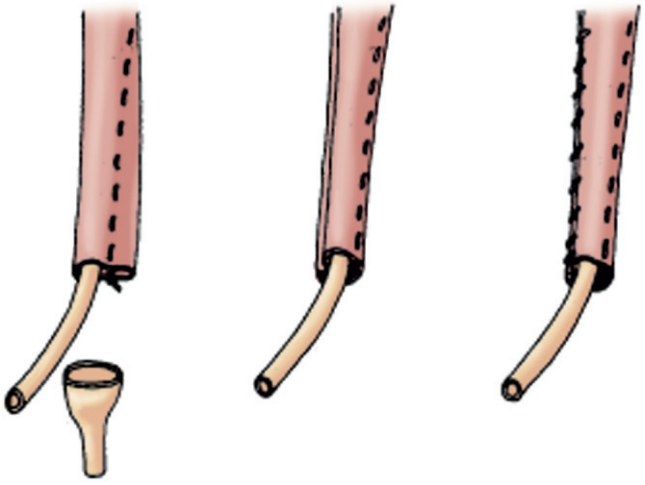


Figure 120–31. Ureteral folding technique. A running suture is longitudinally woven through the megaureter to create two lumens. This isolates the best-vascularized portion as a functional ureter (catheter within) and excludes redundancy. The redundant portion is then folded, and the two are tacked together with interrupted sutures. (From Kalicinski ZH, Kansy J, Kotarbinska B, et al. Surgery of megaureters: modification of Hendren's operation. J Pediatr Surg 1977;12:183.)

another option for dilated ureters that continue to reflux after initial reimplantation. Vascularity is preserved and injury to the contralateral ureter avoided in unilateral cases (Diamond and Parulkar, 1998).

Ureteral obstruction is related to postoperative edema in many cases, and the edema generally resolves with time (up to 8 weeks) and requires temporary diversion most commonly with a percutaneous nephrostomy tube or antegrade double-J stenting. If persistent, the usual cause is ureteral ischemia, which requires revision and excision of the ischemic segment followed by reimplantation. Given our changing notions with vesicoureteral reflux, it is certainly better to have a child with low-grade reflux than one who has an obstructed ureter.

Special Situations

Midureteral Stricture

Rare situations exist in which proximal ureteral dilation is present due to a midureteral stricture. In a series of seven patients who were found to have midureteral strictures, five of seven patients had prenatal hydronephrosis. Retrograde pyelography in all seven patients led to an accurate diagnosis of midureteral narrowing. Six patients were managed with excision of the narrowed area, along with primary ureteroureterostomy of the dilated proximal ureter to the normal caliber distal ureter. The excised segments were funnel-shaped, leading to a stenotic zone that was generally less than 0.1 cm in internal diameter. Significant acute or chronic inflammation, fibrosis, hemosiderin, and vasculopathy were not identified at the sites of ureteral stenosis. Ureteral valves or folds were not identified either grossly or microscopically in any of the patients who underwent surgical repair (Hwang et al, 2005).

Ureteral Polyps

Ureteral polyps are an unusual cause of obstruction, both at the ureteral pelvic junction and within the ureter. A strong index of suspicion is necessary to make this diagnosis, along with exquisite imaging to detect a polyp(s). The use of intravenous urography, ultrasonography, and enhanced CT imaging may allow a preoperative diagnosis. Children often present with hematuria and/or flank pain. Polyps tend to be one of two types: filiform, which are multiple or single, or bilobed and of varying sizes (Niu et al, 2007). Occasionally, the polyps are discovered at the time of ureteroscopy for ureteral stones. Ureteroscopy and laser ablation or urethroscopic snaring of the polyps has been an effective treatment. Recently, the authors have had several patients with multiple ureteral polyps who were discovered at the time of laparoscopic pyeloplasties. Subsequent ureteroscopy was used to remove the residual polyps at the time that the double-J stents were removed.

Ureteral Stricture

Finally, there is the rare occurrence of ureteral damage that obviates the use of the ureter. In such a situation, ureteral replacement has been accomplished with the use of ileum. Ileoneoureters can bypass the abnormal ureter but tend to be rather redundant. The Yang-Monti principle for creation of a catheterizable channel of narrow caliber is ideally suited for ureter replacement therapy (Kamat and Khandelwal, 2007). Two segments can be anastomosed if a long ureteral substitution is needed. Stenting of the ileoneoureter is needed for several weeks. This technique has been used in isolated cases, but long-term follow-up is needed to ensure durability.

CONCLUSIONS

Future progress will be made in understanding the underlying factors that contribute to the formation of UPJ and UVJ obstruction, along with continuing improvements in successful surgical approaches. There will continue to be debate as to what constitutes surgical obstruction. The tools that are used to define and measure the problem are imprecise. Newer modalities, such as magnetic resonance urography, may shed light on the problem and help surgeons in their decision-making process. In the end,

however, it is an assimilation of radiographic studies, the patient's history, and the surgeon's experience that collectively guide the therapy.

Minimally invasive surgery is revolutionizing reconstructive renal and ureteral surgery in children. The advent of robotic surgery enables further advancement for pediatric urologic surgery with enhanced visualization and dexterity. MIS pyeloplasty for adults has been established as one of the most suitable urologic operations. Although further outcome studies and prospective randomized comparison studies with open surgery are needed, conventional pediatric laparoscopic and robotic pyeloplasty and ureteral reconstruction should become an established alternative in the near future.

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chapter
121

Ectopic Ureter, Ureterocele, and Ureteral Anomalies

Craig A. Peters, MD, FACS, FAAP • Richard N. Schlussel, MD • Cathy Mendelsohn, PhD

Classification and Anatomic Description
Clinical Presentation
Clinical Decision Making Summary
Other Ureteral Anomalies
Anomalies of Position
Other Anomalies of Position

CLASSIFICATION AND ANATOMIC DESCRIPTION

General Patterns

Abnormalities of ureteral development including ectopic ureters and ureteroceles represent a large component of clinical urology and continue to challenge clinical management, despite their wide recognition and well-defined surgical strategies. The wide spectrum of involvement and the variable patterns of presentation underlie the clinical challenge and require a thorough understanding of both normal and abnormal embryology of the lower urinary tract. This chapter presents the embryology, clinical manifestations, pathology, evaluation, and management strategies for ectopic ureters and ureteroceles, as well as other less common ureteral anomalies of formation. Obstructive ureteral pathologies including ureteropelvic junction (UPJ) obstruction and ureterovesical junction obstruction are reviewed in Chapter 120.

Although ectopic ureter and ureterocele are typically presented as distinct entities, they apparently share many common features and may well have the same underlying developmental mechanisms with slight variations that induce the obvious differences in their appearances. In many ways, they may be approached in a similar manner, with slight variation in management due to their particular differences. It is also apparent that clinical cases may represent manifestations that lie between the two entities, suggesting a continuum of embryologic maldevelopment.

Ectopic Ureter

By definition, an ectopic ureter is any ureter, single or duplex, that does not enter the trigonal area of the bladder (Glassberg et al, 1984). **In a duplex system this is inevitably the upper pole ureter, presumably due to its budding from the mesonephric duct later than the lower pole ureteral bud.** If it is simply near the bladder neck, it is not technically ectopic, which requires entry at the level of the bladder neck or distal. **In females the ectopic ureter may enter anywhere from the bladder neck to the perineum and into the vagina, uterus, and even rectum** (Weight et al, 2006). It may be associated with a cyst of Gartner duct, the remnant of the wolffian duct from which the ureter buds, and may include cystic dilation of the duct. The duct typically runs parallel to the vagina (the müllerian structure) and with rupture of the cystic ductal structure, communication with the vagina is established (Weiss et al, 1984; Rosenfeld and Lis, 1993). This is the basis for incontinence, the frequent presentation of an ectopic ureter in females. **In males the ectopic ureter always enters the urogenital system above the external sphincter or pelvic floor and usually into the wolffian structures including vas deferens, seminal vesicles, or ejaculatory duct.** These may be associated with cystic dilation, presumably due to continued urine production. Males do not present with incontinence but with infection and pain of the affected organs (testicles and epididymis).

Single-system ectopic ureters may present in a similar fashion but may also be associated with an apparently absent kidney. This usually reflects an inability to identify the kidney on typical imaging and has led to the use of computed tomography (CT) imaging with contrast to detect small poorly functioning renal units associated with an ectopic ureter (Borer et al, 1998). Either single or duplex systems with an ectopic ureter may present with severe hydronephrosis reflecting distal obstruction. This may have impaired normal renal development to the point that the affected segment is nonfunctional, which needs to be clinically assessed.

A rare entity of bilateral single-system ectopic ureters occurs and may be associated with a hypoplastic bladder and bilateral renal abnormalities, typically dysplasia (Noseworthy and Persky, 1982; Johnin et al, 2007). Some of these children may be considered to have bladder agenesis due to the absence of a recognizable bladder structure, presumably due to the absence of bladder filling and emptying in utero (Weight et al, 2006).

Ureterocele

Ureteroceles may be seen to represent a version of the ectopic ureter with a cystic dilation of the distal aspect of the ureter that is located either within the bladder or spanning the bladder neck and urethra. Studies in mouse

Key Points: Ectopic Ureter

- An ectopic ureter is any ureter, single or duplex, that does not enter the trigonal area of the bladder.
- In a duplex system the ectopic ureter is inevitably the upper pole ureter due to its budding from the mesonephric duct later (more cephalad) than the lower pole ureteral bud.
- In females the ectopic ureter may enter anywhere from the bladder neck to the perineum and into the vagina, uterus, and even rectum. One of the classic symptoms is continuous wetting.
- In males the ectopic ureter always enters the urogenital system above the external sphincter or pelvic floor, and usually into the wolffian structures including vas deferens, seminal vesicles, or ejaculatory duct.

models suggest that ureteroceles may reflect defective ureteral maturation, the process by which the developing ureteric bud detaches from the mesonephric duct and moves to the bladder (see later) (Mendelsohn, 2009). As with the ectopic ureter, ureteroceles may be associated with a single or duplex system and in duplex systems they are associated with the upper pole. Ureteroceles can extend into the urethra but do not form entirely within the urethra, nor do they attach to the wolffian ductal structures.

Several classification systems exist for ureteroceles, but the most useful one for clinical practice separates intravesical from extravesical ureteroceles. The intravesical ureterocele is entirely within the bladder and above the bladder neck. This would include a "simple" ureterocele that may be seen in the adult with minimal dilation and mild to no upper tract dilatation. This term, however, should be discouraged and the term *single intravesical ureterocele* used instead (Glassberg et al, 1984). An ectopic ureterocele includes those "in which some portion of the ureterocele is situated permanently at the bladder neck or urethra" (Glassberg et al, 1984). The orifice may be in the bladder, at the bladder neck, or in the urethra. This should be distinguished from an intravesical ureterocele that prolapses into the urethra with voiding.

Further descriptive subdivision of ureterocele types has been published, particularly by Stephens (Stephens, 1971; Stephens et al, 1996). These include cecoureterocele, stenotic, sphincteric, sphincteric-stenotic, blind, and nonobstructed ureteroceles (Figs. 121–1 and 121–2). **From a clinical perspective, the most important subgroup to recognize is the cecoureteroceles. In these cases the orifice of the affected ureter is within the bladder, but the cavity of the ureterocele extends beyond the bladder neck into the urethra.** These may not be readily identified preoperatively (Smith and Parrott, 1994) and their complexity may create surgical challenges, particularly with endoscopic incision (see later).

An unusual but diagnostically challenging ureterocele variant is the so-called "nonobstructive" ureterocele with duplication (Bauer and Retik, 1978) or "ureterocele disproportion" (Share and Lebowitz, 1989). These are associated with a duplex kidney, but the affected upper pole is nondilated and typically dysplastic to such a degree that it is not readily detected on most imaging and the affected ureter is not dilated beyond the bladder. A typical-appearing ureterocele is seen in the bladder, but the ipsilateral kidney appears normal.

There is some association of ureterocele type with outcomes of various therapeutic measures, but these have not proven to be as predictable as initially reported. Churchill and colleagues (1992) proposed a classification system on the basis of the impact of the ureterocele on the upper urinary tract including all renal units. This functional system separates those in which the upper pole only is in jeopardy, from those in which an entire ipsilateral kidney is threatened, to those in which the contralateral system is also at risk due to reflux or bladder outlet obstruction. The latter group comprised 26% of the reported cases.

Embryology and Etiology

The specific mechanisms responsible for ectopic ureters and ureteroceles remain undefined, but our emerging understanding of normal and abnormal ureterotrigonal development, along with new investigational tools, are likely to provide valuable insights (Mendelsohn, 2009). Although these molecular mechanisms will be of scientific importance, they will also permit potential separation between variants of these conditions that are likely to have therapeutic relevance, as well as perhaps ultimately permitting

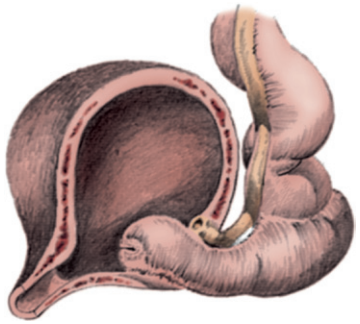


Figure 121–1. The orifice of a stenotic ectopic ureterocele may be located at the tip or at the superior or inferior surface of the ureterocele.

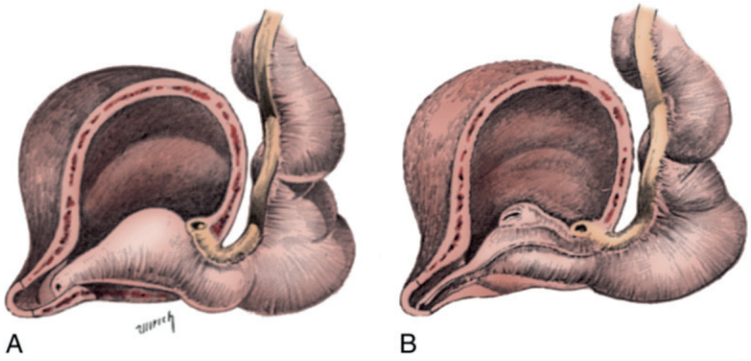


Figure 121–2. **A,** Sphincterostenotic ectopic ureterocele. **B,** Cecoureterocele lumen extends distal to the orifice as a long tongue beneath the ureteral submucosa. The orifice communicates with the lumen of the bladder and is large and incompetent.

Key Points: Ureterocele

- Ureteroceles represent a version of the ectopic ureter with a cystic dilation of the distal aspect of the ureter that is located either within the bladder or spanning the bladder neck and urethra.
- Several classification systems exist for ureteroceles, but the most useful one for clinical practice separates intravesical from extravesical ureteroceles.
- The most important subgroup to recognize is the cecoureterocele.
- In a cecoureterocele the orifice of the affected ureter is within the bladder, but the cavity of the ureterocele extends beyond the bladder neck into the urethra.

early detection (i.e., in utero) and intervention. The latter is a distant but not implausible horizon. At present experts remain uncertain as to fundamental mechanisms and yet need to know which ureteroceles and ectopic ureters may be associated with bladder neck and trigonal maldevelopment sufficient to cause incontinence. These children will require more aggressive therapy to achieve continence. Early identification may permit earlier and more effective surgical therapies.

Clinical Relevance

Understanding the potential relationships of the abnormal ureter associated with ectopia or a ureterocele, which is based on aberrations in normal development of the wolffian and müllerian ducts, ureteral bud, urogenital sinus (UGS), and bladder, can facilitate clinical interpretation of these conditions. Knowledge of the sites of ectopic insertion may be useful in planning imaging and in surgical correction. Recognition of the possible effects of abnormal ureteral development on bladder and urethral development is essential in determining reconstructive strategies, and an awareness of the possible coexistence of ureteral and müllerian abnormalities is important.

Ureteral-Trigonal-Renal Development

The pathogenesis of ureteral ectopia with or without a ureterocele rests in ureterotrigonal and renal development. This involves the common nephric duct (CND), ureteral budding, ureterometanephric interactions, and bladder and trigone development. Ectopic ureters can arise due to abnormal timing or location of the primary ureteral budding from the mesonephric ducts, or abnormalities at the stage of ureter. That temporospatial location will determine both the character of the ureter incorporated into the emerging bladder, as well as the development of the trigone and kidney. **Ureter maturation occurs after the ureteric bud sprouts from the mesonephric duct when the posterior nephric duct segment (the common nephric duct, CND) expands and is absorbed into the bladder where the CND undergoes apoptosis. At this point, ureteral cells merge with bladder epithelia and undergo a second wave of apoptosis, generating a new ureteral orifice, which is now in the bladder neck. Growth and expansion of the bladder moves the ureteral orifice, which is now inserted in the bladder epithelium, farther away from the mesonephric duct to the final position.** Of course, these elements can all be affected with both ureteral ectopia and ureterocele.

Classical understanding of uretero-trigonal development has indicated that the trigone originates from the mesodermal CND, as does the ureter, and is distinct from the endodermal origin of the bladder. According to this model, the CND expands, moving the ureter away from the mesonephric duct, and is incorporated into the primitive bladder, repositioning the ureter orifice at the bladder neck (Wesson, 1920; Tanagho and Pugh, 1963; Woodburne, 1965). Normal regulation of ureter remodeling permits fusion of the ureter and the UGS, as well as separation of the ureter and the wolffian duct (Mendelsohn, 2009; Tanaka et al, 2010).

However, the observation that the CND degenerates during ureter maturation suggests that it may not give rise to the trigone as previously thought (Batourina et al, 2002, 2005; Viana et al, 2007; Chi et al, 2009; Mendelsohn, 2009; Uetani et al, 2009; Tanaka et al, 2010). Consistent with this, **lineage studies and tissue recombination studies in mice suggest that the trigone is formed by bladder mesoderm/muscle and muscle surrounding the intravesical ureter. One possibility is that intersection between ureteral fibers and bladder muscle give the trigonal region its distinct morphology.**

A revised model of ureteral bud–trigonal maturation based on these studies requires coordinate expansion and subsequent apoptosis of the CND between the developing ureter and wolffian duct. Expansion of the CND permits correct alignment of the ureter with the UGS and may be seen to determine the position of the attachment of the ureter to the bladder and trigone. In contrast to the classic model, however, in which the CND forms the trigone, the revised model includes regression of the CND in the normal animal through apoptosis (Batourina et al, 2002, 2005; Viana et al, 2007; Chi et al, 2009) (Fig. 121–3).

The revised model of ureteral maturation provides possible mechanisms for ureteral ectopia and ureterocele formation. Abnormal apoptosis may maintain the connection between the ureter and the wolffian duct and prevent incorporation of the ureter and the UGS. This defect would produce a ureter attached to the wolffian remnants in girls (Gartner duct) or to the vas deferens or ejaculatory system in boys. Abnormal timing of ureteral budding may be one cause of this dysregulated apoptosis and would explain the occurrence of these defects with duplicated systems, particularly the upper pole (later budding) ureter. A lesser defect, either by timing or completeness of the defect, might explain the ectopic ureter to the urethra distal to the bladder neck in girls. Specific defects in the signaling molecules, as seen in knockout mouse models, may produce isolated defects, but by disruption of the normal sequence both temporally and spatially, could produce a range of downstream abnormalities. Similar phenotypes may be caused by multiple mechanisms, with more subtle variation among individuals. This may explain some of the variation seen in both ectopic ureters and ureteroceles.

The expansion of the CND that permits normal alignment of the developing ureter appears to be in response to contact with the UGS (Batourina et al, 2005) and must be coordinated with later apoptosis of the CND, as well as being regulated by local factors and CND cellular responsivity. Impaired expansion may produce ectopia due to delayed or limited movement of the ureter relative to the UGS, whereas unregulated expansion may prevent normal communication of the ureter with the UGS and perhaps

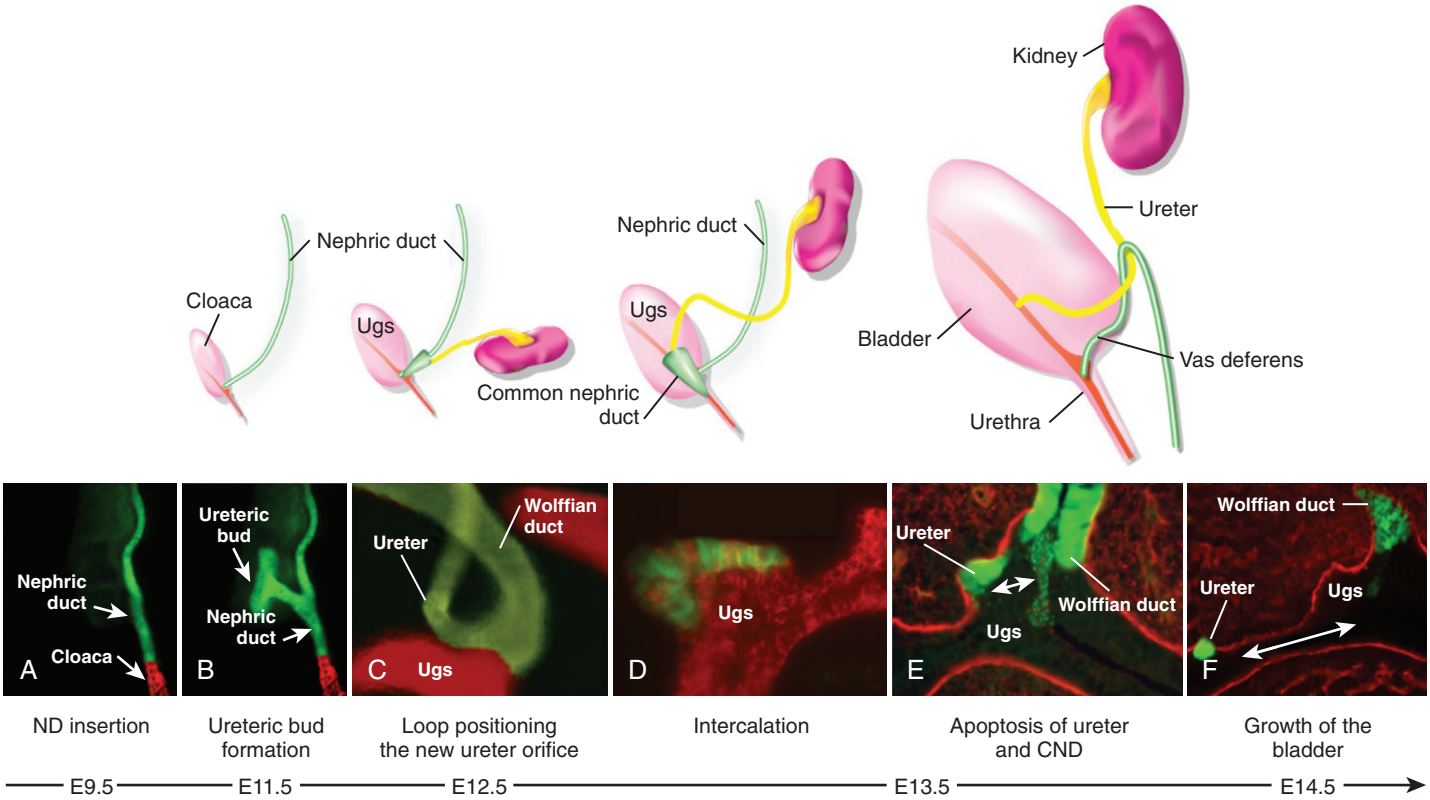


Figure 121–3. *Top:* schematic showing a revised model of ureter maturation. *Bottom:* images of Hoxb7-Gfp expressing embryos showing different stages of urinary tract morphogenesis. In the lower urinary tract, the Hoxb7-Gfp transgene is localized in the ureter, mesonephric (wolffian) duct, and common nephric duct (CND) (Srinivas et al, 1999). **A,** Whole mount urogenital tract from an E9 Hoxb7-Gfp embryo counterstained with E-cadherin to reveal the mesonephric duct *(green)* inserting into the primitive bladder *(red)*. **B,** A whole mount urogenital tract from an E11 Hoxb7-Gfp embryo counterstained with E-cadherin *(red)*. The CND lies below the primary ureteric bud branch, which at this stage has invaded the kidney blastema (not visible). **C,** Whole mount urogenital tract from an E12 Hoxb7-Gfp embryo *(green)* stained with cytokeratin *(red)*. Apoptosis of the CND has brought the caudal-most ureter into close contact with the bladder, where it aligns, setting the position of the future ureteral orifice. **D,** A vibratome section from an E13 Hoxb7-Gfp urogenital tract stained with E-cadherin *(red)*. Cells from the most distal ureter epithelium have now merged with the bladder epithelium, where they will undergo apoptosis, creating a new ureteral bud connection. **E,** A whole mount urogenital tract from an E13.5 Hoxb7-Gfp embryo stained with Laminin to reveal the basement membrane of the bladder epithelium *(red)*. The ureter orifice is now inserted in the epithelium and is separated from the mesonephric duct by a short distance. **F,** Expansion and elongation of the bladder has moved the ureter orifice farther away from the mesonephric (wolffian) duct. Ugs, urogenital sinus.

be the initiation of terminal ureteral expansion as seen in ureteroceles. Tanagho (1976) postulated that ureteroceles resulted from the distal ureter being inappropriately exposed to the factors inducing expansion of the UGS and bladder. Nearly all growth during development is the result of balanced stimulatory and inhibitory factors, regulated by temporal and spatial gradients, proximity, and cofactors that are, in turn, regulated by similar mechanisms. Altered timing and coregulation of these systems are likely the basis of altered development.

The classic explanation of ureterocele formation is that of Chwalle (1927), postulating that distal ureteral expansion is produced by failure of rupture of a distal membrane at the ureteral orifice (Chwalle membrane). Obstruction is unlikely to be a major and certainly not the only factor producing ureteral dilation, as seen with ureteroceles. Ureteroceles with large orifices and no apparent obstruction are well recognized clinically. Ectopic ureters with insertion into the bladder neck are dilated but do not have the disproportionate distal dilation characteristic of the ureterocele. Obstruction plays some role in ureterocele pathophysiology, however, as is evident in the frequent occurrence of decompression with ureterocele puncture. Whether this is determined by the degree of muscularization of the ureterocele is undefined. Recent studies support the idea that degeneration of Chwalle membrane is important for generating a patent connection between the ureter orifice and the bladder. These studies suggest that Chwalle membrane, which has been thought to form from the UGS, may in fact be derived from luminal cells in the ureter that undergo apoptosis at a relatively late stage, before the onset of renal function, which may be important for generating a patent connection between the distal ureter and bladder.

Relationship with Embryonic Ductal Structures

The embryologic relationships of the developing ureter and the metanephric (wolffian) and müllerian ducts are important to understand the possible sites of ectopic ureteral insertion. Because the ureteral bud derives from the wolffian duct, the ectopic ureter will not insert directly into the müllerian structures (i.e., vagina, cervix, uterus) but will be associated with them through the remnant of the wolffian duct, Gartner duct, that

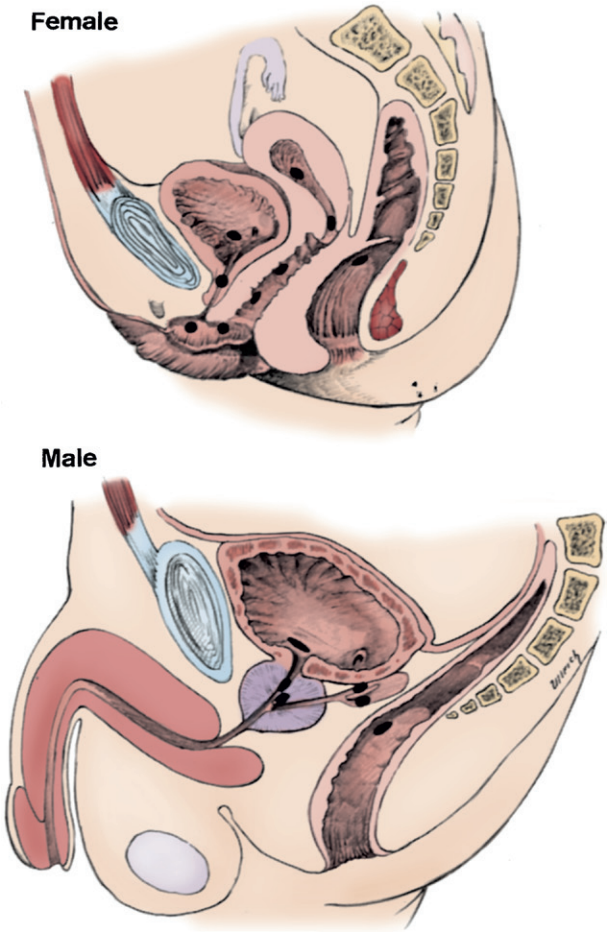


Figure 121–4. Sites of ectopic ureteral orifices in the male and female.

runs alongside the mature müllerian structures. Communication into these structures is likely due to rupture of Gartner duct or of a cyst of Gartner duct into the vagina (see later).

The possible sites of ectopic ureteral insertion are shown in Figure 121–4, including the common locations that are associated with normal wolffian duct development; however, more aberrant locations have been reported. It is unclear what the embryologic mechanisms of these locations, including rectum, might be, but they probably reflect more diffusely deranged overall development. Given that the wolffian duct in the male is never associated with any structures below the pelvic floor and sphincter, males do not present with urinary incontinence, as is seen in females. Abnormal bladder function is recognized in children with ureteroceles and is characterized by larger than normal bladders with inadequate emptying (Abrahamsson et al, 1998). This is potentially consistent with not only the obstructive effect the ureterocele can have on the bladder outlet, but also abnormal bladder and trigone development.

Patterns Associated with Duplication

As the developing ureteral buds incorporate into the developing UGS, the lowest bud, associated with the lower pole of the kidney, is incorporated first and migrates more laterally. The upper pole ureter is later to be incorporated and thereby is closer to the bladder neck. The Weigert-Meyer rule (Fig. 121–5) (see also Chapter 111) **describes the inverse relationship of the duplex ureteral orifices, in which the ectopic ureter or ureterocele associated with the upper pole is caudal to the lower pole ureteral orifice.** The association of the upper pole ureter and renal segment with the abnormally developed distal ureter further supports the principle that ectopic ureters and ureteroceles result from aberrant temporo-spatial signaling as the CND merges with the UGS.

Key Points: Embryology

- In contrast to the classic model in which the common nephric duct (CND) forms the trigone, the revised model includes regression of the CND in the normal animal through apoptosis and formation of the trigone from the endoderm, as is the bladder.
- The classic explanation of ureterocele formation is that of Chwalle, postulating that distal ureteral expansion is produced by failure of rupture of a distal membrane at the ureteral orifice (Chwalle membrane).
- Because the ureteral bud derives from the wolffian duct, the ectopic ureter will not insert directly into the müllerian structures (i.e., vagina, cervix, uterus) but will be associated with them through the remnant of the wolffian duct, Gartner duct, that runs alongside the mature müllerian structures.
- The Weigert-Meyer rule describes the inverse relationship of the duplex ureteral orifices, in which the ectopic ureter or ureterocele associated with the upper pole is caudal to the lower pole ureteral orifice.

CLINICAL PRESENTATION

Imaging

Prenatal Detection

The majority of ureteroceles and ectopic ureters are detected through prenatal ultrasound (US) imaging, even if the specific diagnosis is not made. The abnormality prompts postnatal imaging, which will invariably determine the specific cause, induce further studies, and permit an adequate characterization of the condition. The prenatal imaging patterns are identical to those seen postnatally on US imaging yet may be misinterpreted. These are described in Chapter 114, but several elements should be emphasized here.

The identification of a duplex system prenatally may be difficult except when one of the moieties is dilated. The report of an upper pole "cyst" in a fetus should be interpreted as being upper pole hydronephrosis until proven otherwise. Minor degrees of hydronephrosis may not be as readily identified, although changes over time may prompt recognition. The expected ureteral dilation may not be readily detected but can be traced to the bladder. The bladder must be inspected in all such cases to identify a ureterocele, but it may be required to await bladder filling to make this observation. A large ureterocele can fill a bladder and mask its own presence.

The character of the renal parenchyma of the upper pole should be noted, both thickness and echogenicity. This should never be

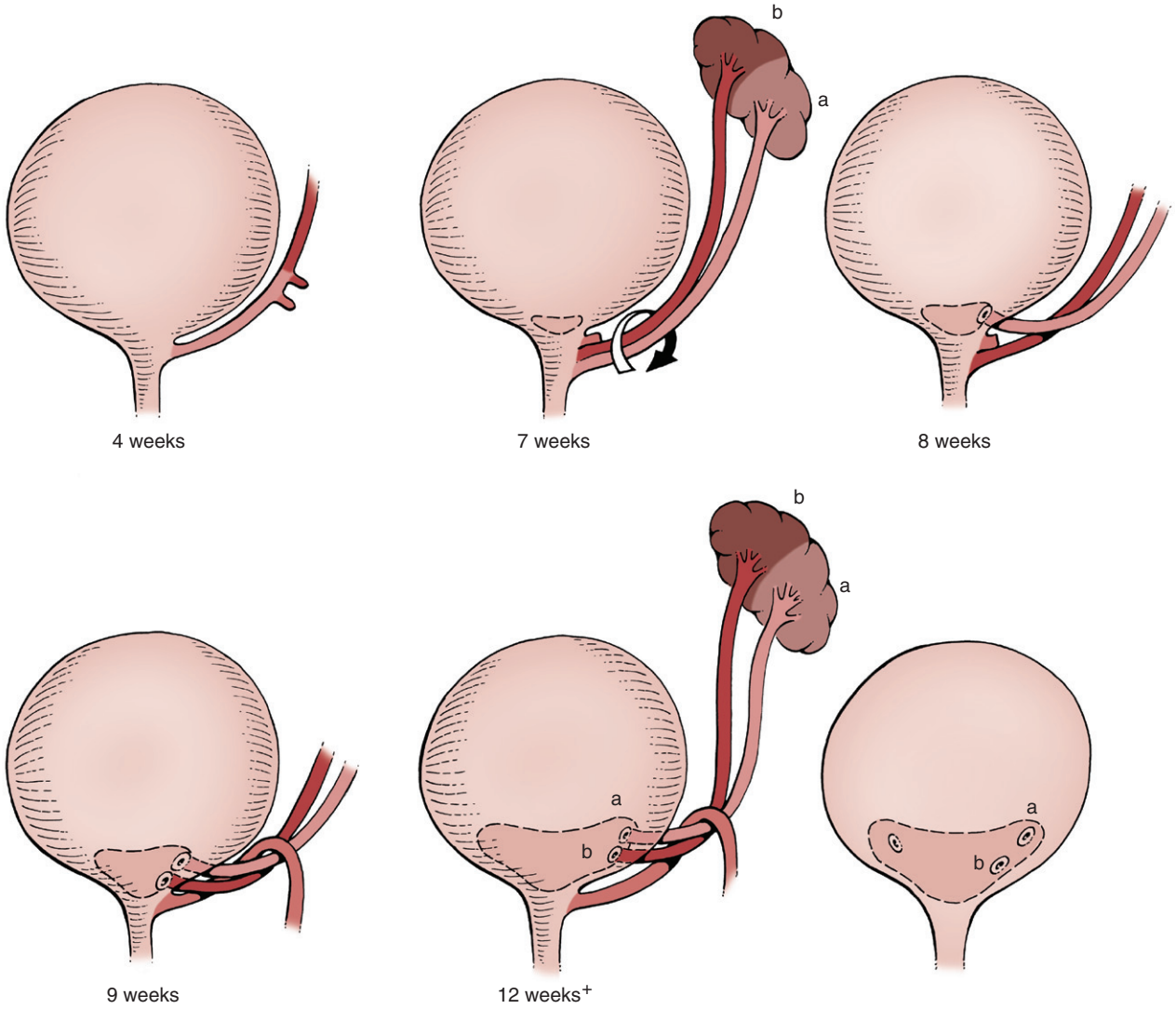


Figure 121–5. The Weigert-Meyer rule is depicted. The upper pole ureter and the lower pole ureter rotate on their long axes to yield an upper pole orifice *(b)* that is medial and caudal to the lower pole orifice *(a)*.

used alone to determine salvageability of the upper pole but may be useful in making clinical decisions.

The ectopic ureter can appear identical to a ureterocele with a dilated upper pole, tortuous ureter, but no intravesical component. On occasion, a large ectopic ureter may impinge on the bladder and appear as an intravesical structure, termed a *pseudoureterocele* (Sumfest et al, 1995). These patterns are identical to those seen postnatally but do require an experienced maternal-fetal ultrasonographer to recognize.

With a tentative diagnosis of a ureterocele or ectopic ureter made, careful evaluation of the other renal units and bladder should be made. Ipsilateral lower pole or contralateral dilatation suggests reflux or less commonly obstruction from the ureterocele or the dilated ectopic ureter. Bladder outlet obstruction by a ureterocele can occur and present with hydronephrosis of all renal units. It is unusual to identify bladder obstruction to the extent to produce oligohydramnios, but this has been reported (Gloor et al, 1996; Crane, 2000) including in-utero decompression (Quintero et al, 2001; Ashmead et al, 2004). Contralateral renal dysplasia may be evident and associated with reduced amniotic fluid. The need for prenatal intervention or early delivery is exceptional and unlikely to provide any significant benefit.

A single system ureterocele or ectopic ureter will be evident with dilatation of the entire kidney and ureter. It may be impossible to differentiate this from an obstructive megaureter or severe reflux, but this will have little immediate prenatal clinical impact.

Incidental

When significant hydronephrosis is present with either an ectopic ureter or ureterocele, an incidental diagnosis will occasionally be made. In some cases, however, this may result from a search for an explanation of general abdominal pain that was not considered to be due to a renal cause. It is also possible that the dilated ureter may not be recognized as such, and cases of presumed ovarian cysts that were actually markedly dilated ureters have been seen (Fig. 121–6).

Infection

Infection remains a significant reason for clinical presentation of both ectopic ureters and ureteroceles, and these may be at any age and have a highly variable pattern.



Figure 121–6. Magnetic resonance urogram of 15-year-old girl with intermittent abdominal pain attributed to ovarian cysts but, in fact, caused by an ectopic ureter. The association with the upper pole of the left kidney and the insertion just below the bladder neck are evident on this image.

Clinical Patterns

Although there is great variability in the presentation of either ectopic ureter or ureterocele, several patterns may be anticipated. In either case, generalized urosepsis may be the presenting clinical scenario and a renal bladder US will usually provide the diagnosis. It has been reported that an acute US study is unnecessary if a child presents with a febrile urinary tract infection (UTI) and has a history of a normal prenatal US after 30 to 32 weeks (Hoberman et al, 2003). The extreme variability in quality of prenatal imaging makes this recommendation tenuous, and it would seem prudent that an US be obtained in all children with urosepsis. In those with a febrile UTI, there is rarely urgency if they are clinically responding. The value of early detection is the potential for early treatment, which may be a simple drainage procedure. If the child is recovering rapidly, imaging may be elective.

In the acute setting, with evidence of an ectopic ureter or ureterocele, the initial clinical response to antibiotic therapy will determine the timing of intervention and is discussed later. Certainly the septic child who is not responding rapidly to appropriate therapy may require urgent transurethral incision (TUI) of an infected ureterocele or percutaneous or open drainage of an ectopic ureter. Open drainage in this setting is often an end ureterostomy, as described later.

Ectopic ureters will frequently present with a less acute pattern evidenced by ongoing low-grade fever with periodic spikes. In some cases, urine cultures will be negative because the infected ectopic system is not draining into the bladder. Parents may describe a purulent discharge from the perineum. This clinical pattern should prompt an US study, which will usually reveal a dilated upper pole or entire system. It is rare for the unobstructed ectopic ureter to present with infection, but it is associated with incontinence.

In the male, a similar subacute pattern of infection may be present, but more often, these boys present with epididymitis. Although this may be an unusual subset of young boys with an acute scrotum, they will have a true bacterial epididymitis and may or may not have infected urine. In the setting of a suspicion for epididymitis in a young boy, it is prudent to perform a brief US of the upper tracts to ensure no abnormality. Older males will also present in this manner, although it is unclear why it may be so delayed. Some have had recurrent episodes of epididymitis or scrotal abscess before the underlying cause is detected. Xanthogranulomatous pyelonephritis in the upper pole segment of an infant has been reported as well (Perez et al, 1999).

Incontinence

Clinical Patterns

Urinary incontinence may be due to an ectopic ureter in a girl but not in a boy. Untreated ureteroceles are rarely associated with incontinence. The toilet-trained girl with verified continuous urinary leakage must be evaluated for an ectopic ureter. Imaging studies may not immediately detect this condition because the affected renal moiety may not be dilated, and the level of suspicion must be guided by a careful history and occasionally physical examination. Before toilet training it may be difficult to detect continuous incontinence, although some parents will note persistent dribbling during diaper changing. In early training, the wetting may be falsely attributed to lack of motivation. Persistence will usually prompt evaluation, and the characteristic history can be obtained. This is usually one of persistent low-volume dampness at all times. When asked if the child can be dry for 30 to 60 minutes, the parent will usually say no. It is important to be cautious in questioning because some parents with a child who wets for other reasons may state "she is always wet," when in fact the child can be dry for periods of time. The dampness associated with an ectopic ureter typically occurs throughout the day and does not relent, yet the children have normal sensation of bladder filling, no urgency or frequency, and empty completely. It may seem to be worse with activity in some. In rare cases it is intermittent, perhaps due to intermittent leakage through a membrane of Gartner duct. This pattern has been seen only in adolescents.

In older children in whom the diagnosis has not been recognized, attribution of the symptoms may be due to dysfunctional voiding, laziness, and even sexual abuse (Heidemeier et al, 2007). During the history taking, signs of typical voiding dysfunction such as voiding postponement, posturing, and constipation should be sought to assess the likelihood of these being an explanation for the wetting.

Pain

Pain is uncommonly associated with either an ectopic ureter or ureterocele. The exceptions are acute infection, as well as episodic obstruction of the ectopic ureter or bladder pain due to an obstructing ureterocele. Occasional cases of intermittent drainage of an ectopic ureter in older children have been experienced and are characterized by abdominal pain followed by perineal drainage of urine or purulent material. It is presumed that this reflects accumulation of urine in a system that is obstructed at the level of the orifice with subsequent drainage and relief of symptoms. One such

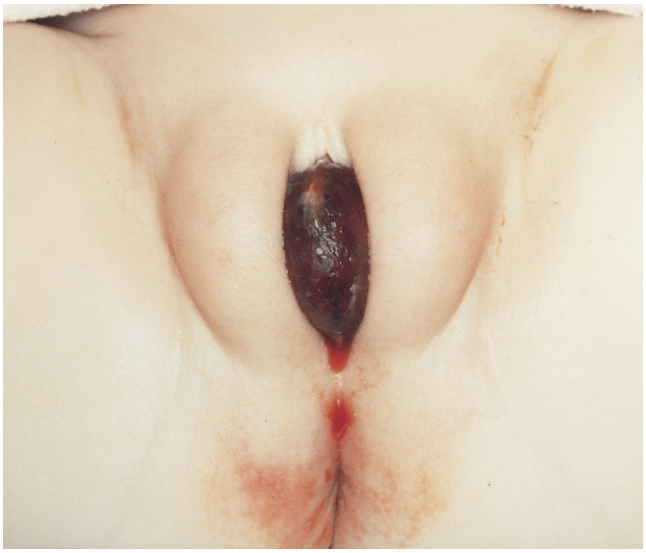


Figure 121–7. A prolapsed ureterocele presented as an interlabial mass in a 3-week-old girl.

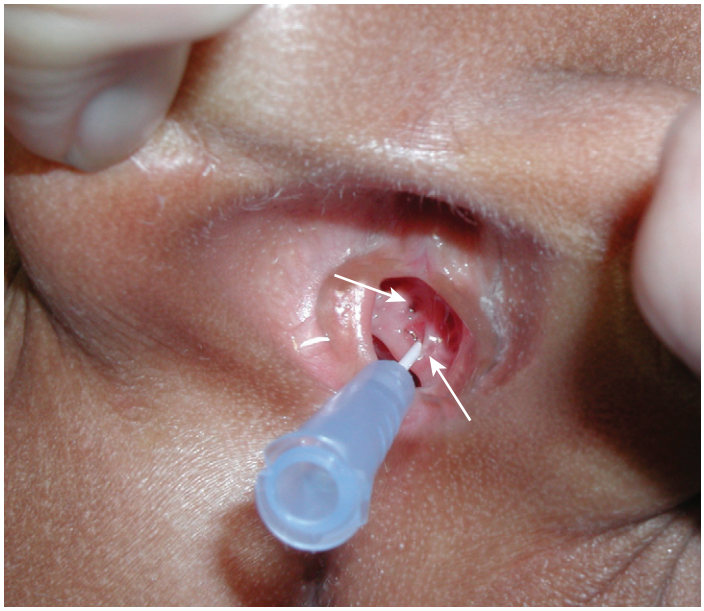


Figure 121–8. Perineal ectopic ureteral orifice *(bottom arrow)* cannulated with an angiocatheter, situated between the urethral orifice *(top arrow)* and the vagina, just to the left of midline.

case was attributed to an ovarian cyst, supported by the finding of a large cystic structure in the pelvis, which was in fact a dilated ureter.

Prolapse

Ureterocele prolapse is an unusual but distinctive presenting sign that may still confuse the clinician. These are usually smooth, congested, mucosa-covered intralabial masses, and the child may be experiencing difficulty voiding. The mass protrudes from the urethra, distinct from the vagina, and is not circumferential as a urethral prolapse will be (Fig. 121–7). It is not lobulated as a sarcoma botryoides appears. An US of the bladder will usually confirm the diagnosis, and kidney images will further support this.

Key Points: Clinical Presentation

- The majority of ureteroceles and ectopic ureters are detected through prenatal US imaging, even if the specific diagnosis is not made.
- Ectopic ureters will frequently present with a less acute pattern evidenced by ongoing low-grade fever with periodic spikes. In some cases, urine cultures will be negative because the infected ectopic system is not draining into the bladder.
- In the male a similar subacute pattern of infection may be present, but more often, these boys present with epididymitis.
- Urinary incontinence may be due to an ectopic ureter in a girl but not in a boy. The toilet-trained girl with verified continuous urinary leakage must be evaluated for an ectopic ureter.
- Ureterocele prolapse is an unusual but distinctive presenting sign; these are usually smooth, congested, mucosa-covered intralabial masses, and the child may be experiencing difficulty voiding.

Evaluation

Management of ectopic ureter or ureterocele is based on a thorough assessment of the affected anatomy and the functional implications of the condition. This may usually be obtained readily but in some cases will require more involved imaging such as magnetic resonance (MR) urography.

Anatomic Assessment

Physical Examination

With both ectopic ureter and ureterocele, physical findings may facilitate diagnosis. The prolapsed ureterocele is diagnostic and dramatic but unusual. Further study of the anatomy is necessary. It is unusual to be able to detect an ectopic perineal ureteral orifice in a child, but this will provide much information as to the character of the situation and best treatment (Fig. 121–8). A search for the perineal orifice in a child with continuous wetting or a known leaking ectopic ureter is worthwhile. Rarely, the dilated Gartner duct cyst may be detected on careful perineal examination (Fig. 121–9). These orifices or cystic structures may then be imaged by injection of contrast. Continuous dripping or pooling of urine may be seen in the introitus of females. Visualizing the actual orifice in the introitus is difficult due to the many mucosal folds. However, absence of dripping of urine does not exclude the diagnosis of ectopic ureter. The ectopic ureter may be connected to renal tissue so dysplastic that it rarely produces urine.

The dilated upper pole of either an ectopic ureter or ureterocele may be palpable in the relaxed infant, but this is difficult in the older child.

Ultrasound

The US image will usually provide the anatomic diagnosis and permit inference of functional assessment. The typical findings are as with the prenatal imaging of a

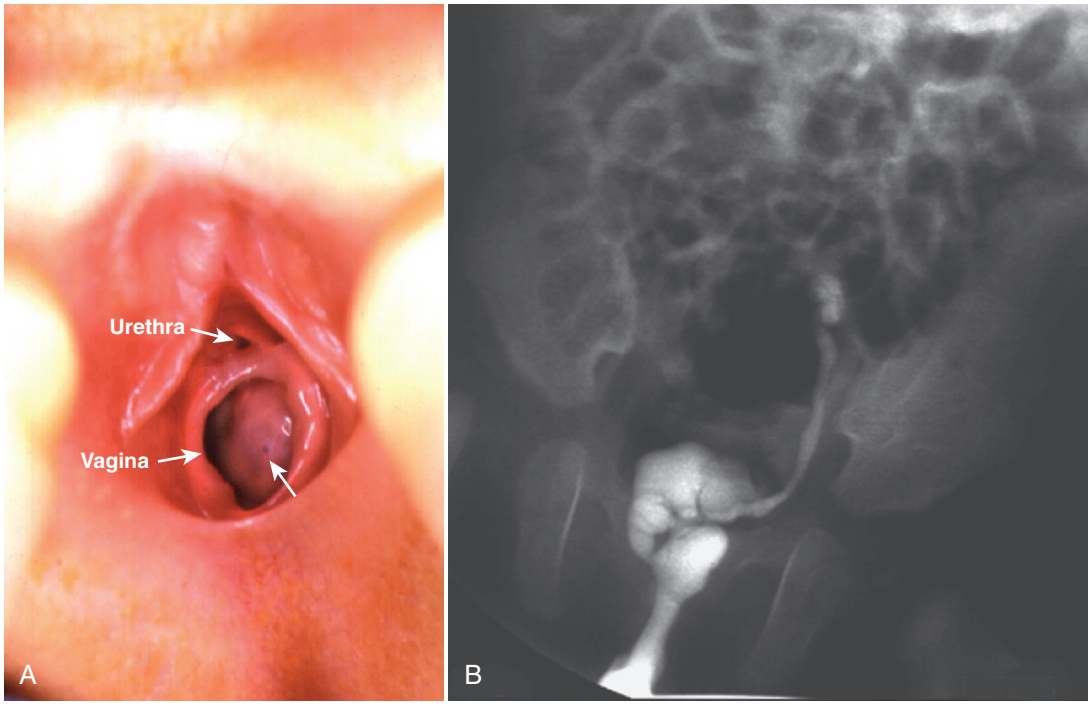


Figure 121–9. **A,** Gartner duct cyst *(bottom right arrow)* in newborn with a left multicystic dysplastic kidney. **B,** Injection of the cyst communicated with the ureter and dysplastic kidney.

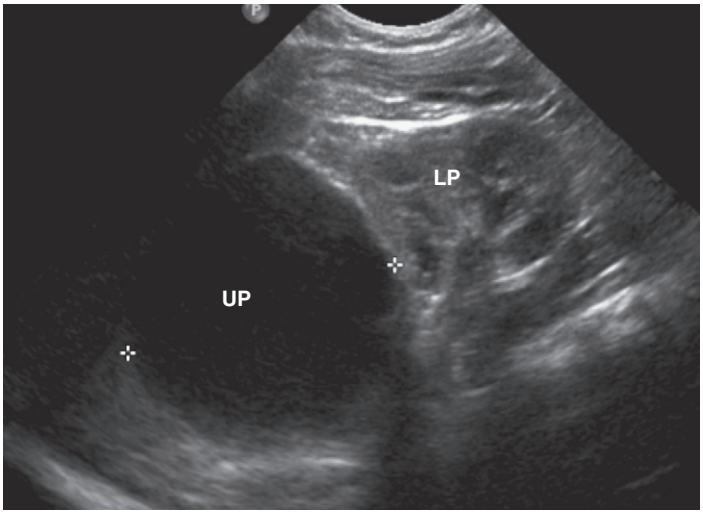


Figure 121–10. Ultrasound image of dilated upper pole (UP) associated with a ureterocele, demonstrating limited renal parenchyma (same patient as Fig. 121–30). LP, lower pole.

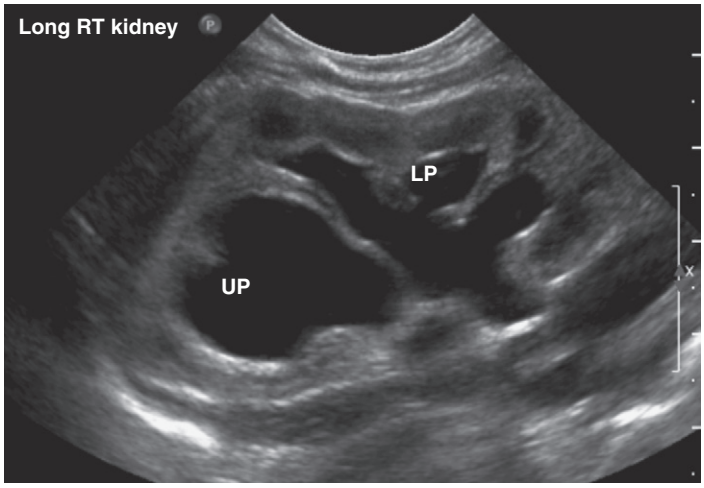


Figure 121–11. Ultrasound demonstrating dilated upper pole (UP) and lower pole (LP) associated with a ureterocele. The upper pole has evident renal parenchyma. The lower pole is dilated due to compression of the dilated upper pole ureter on the lower pole system, creating a partial obstruction.

dilated upper pole with ureteral dilation or a dilated single system (see Fig. 121–9). The character of the renal parenchyma will be more readily seen postnatally, and if it appears healthy, the true need for functional upper tract imaging can be questioned. Depending on the chosen treatment algorithm, it may be argued that this is unnecessary because it will not change treatment. The difference between functioning upper poles and those with little to no function are usually apparent (Figs. 121–10 and 121–11).

No characteristics permit differentiation between a dilated ectopic ureter and ureterocele above the bladder. The bladder images therefore become critically important because management is different.

Bladder views should be diagnostic to differentiate ureterocele from ectopic ureter (Fig. 121–12). **The ureterocele is characterized by a thin-walled, cystic dilation within the bladder and not extending beyond its walls.** The laterality of the ureterocele is usually apparent but may appear midline if large. A lobulated ureterocele may appear as two structures, but careful examination should show communication. It is difficult to visualize extension of a cecoureterocele into the bladder neck, so nonvisualization is not diagnostic.

Several US patterns may produce confusion in diagnosis. **A large ureterocele may completely fill a bladder with no urine in the bladder itself. A full bladder with an effaced ureterocele may be mistakenly considered an ectopic**

ureter. Observation of the bladder over time will usually avoid these errors. A ureterocele may also evert and has been seen outside the bladder and mistakenly diagnosed as a diverticulum. **A dilated ectopic ureter may produce an impression on the bladder and appear as a ureterocele** (the previously noted "pseudoureterocele") as noted in fetal diagnosis, **but the wall will be clearly bilaminar and much thicker than typically seen with a ureterocele. Further, the lumen of the ectopic ureter will extend well outside the bladder walls** (Fig. 121–13).

Magnetic Resonance Imaging

MR urography can provide the most detailed images of an affected urinary tract as a whole along with functional information yet is rarely useful to provide more data than may be obtained with less expensive methods not requiring sedation. Eventually, however, MR imaging (MRI) is likely to become the modality of choice. **At present the value of MRI rests with cases in which other imaging cannot define complex anatomy.** This may occur with massive dilation in which the existence of duplication may be uncertain or in which anatomic relationships are significantly distorted (Fig. 121–14). Not all ectopic ureters are massively dilated, and the MR can also be helpful in identifying a small, dysplastic upper pole and its ectopic ureter that was unrecognized on US. If this type of anatomic delineation is necessary, MR offers the addition of functional information that is an equally important aspect of evaluation. The ability to integrate detailed anatomic assessment of MR with functional assessment can be useful in the detection of the occult ectopic ureter causing incontinence with minimal function (Fig. 121–15).

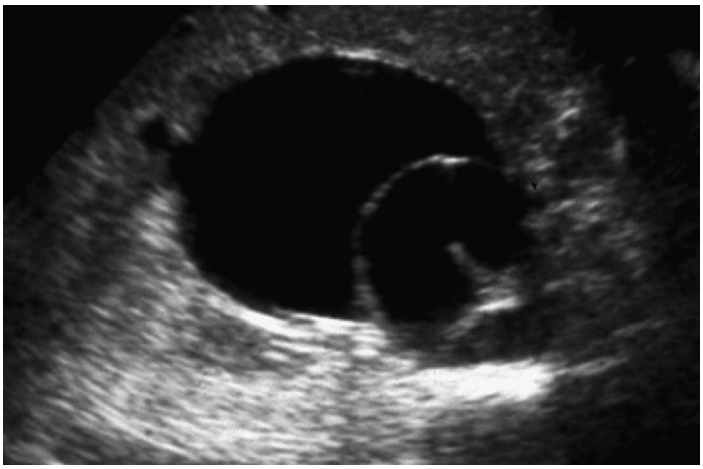


Figure 121–12. Ultrasound image of an intravesical ureterocele at the bladder level.

Functional Assessment

Functional urinary assessment in association with an ectopic ureter or ureterocele is the foundation for both initial management and postoperative care. Both renal and bladder function are affected by the developmental abnormalities of abnormal ureteral formation and may ultimately require complex surgical interventions.

Renal Function

Nuclear Imaging

Radionuclide renal imaging remains the gold standard for renal functional assessment, and this is usually best provided by dimercaptosuccinic acid (DMSA) imaging. The function of the affected upper pole is the principal

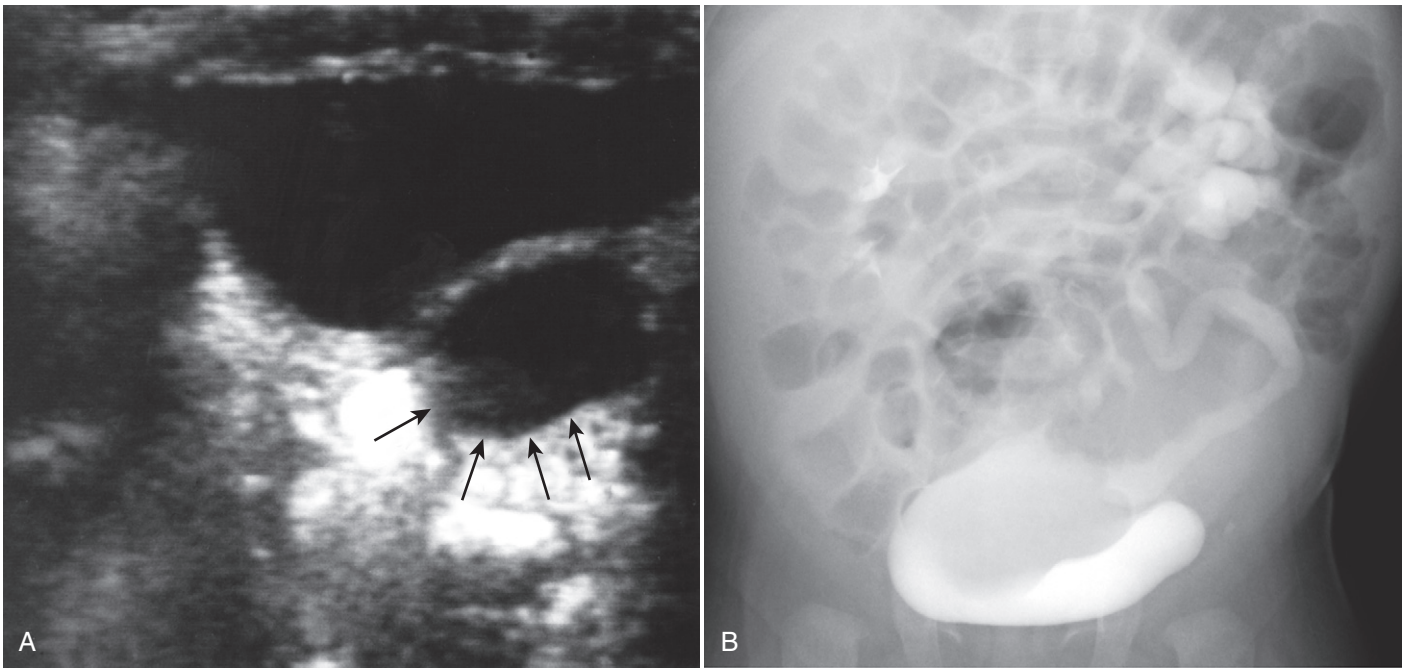


Figure 121–13. **A,** Ultrasound image of bladder in a child with an ectopic ureter extending into the bladder. The wall of the ureter is thicker than a ureterocele, and the lumen of the ureter extends well outside the bladder lumen, indicating that this is an ectopic ureter rather than a ureterocele. **B,** Voiding cystourethrogram of a large ectopic ureter pushing inward on the back of the bladder and appearing as a filling defect in the bladder (pseudoureterocele). (**B,** Courtesy of Dr. Jeanne Chow, Assistant Professor of Radiology, Harvard Medical School and Children's Hospital Boston.)

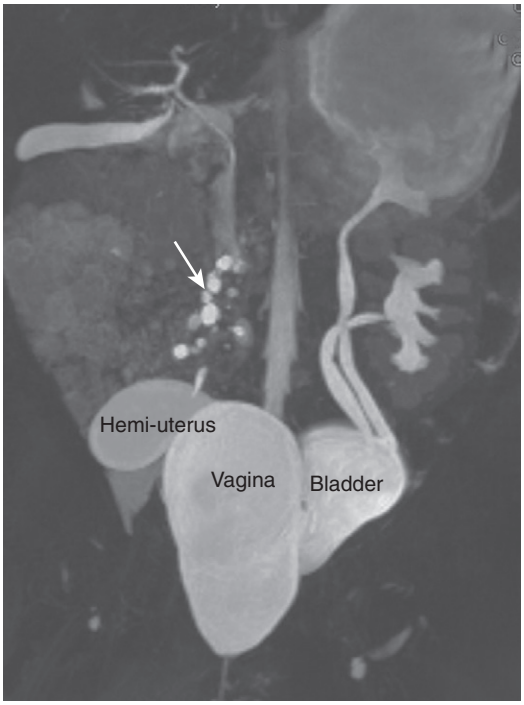


Figure 121–14. Use of magnetic resonance imaging to define the complex anatomy of a child with an ectopic ureter associated with a right dysplastic, cystic kidney *(arrow)* draining into an obstructed hemi-vagina and producing urinary dilation of the right hemi-uterus. Initial therapy constituted creating a distal window between the two vaginae. Subsequently she underwent right nephrectomy.

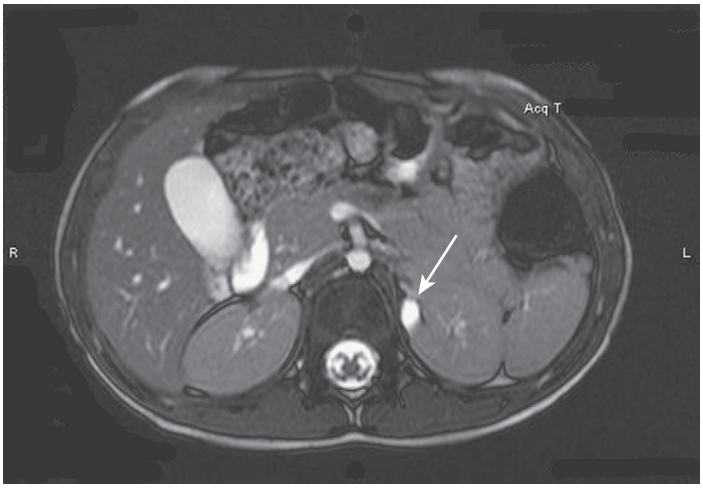


Figure 121–15. Magnetic resonance urography demonstrating the presence of an occult upper pole associated with an ectopic ureter producing incontinence. The left upper pole ureter is marked by the *arrow* at the level of the lower pole pelvis.

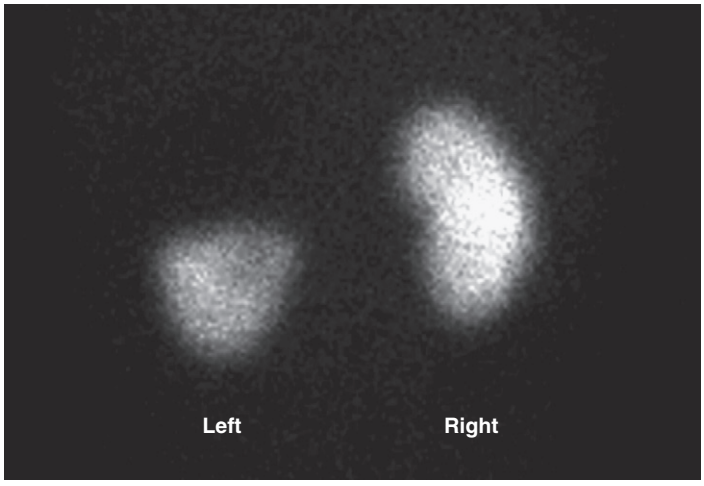


Figure 121–16. Dimercaptosuccinic acid renal scan in a child with a left ureterocele demonstrating no function in the affected upper pole.

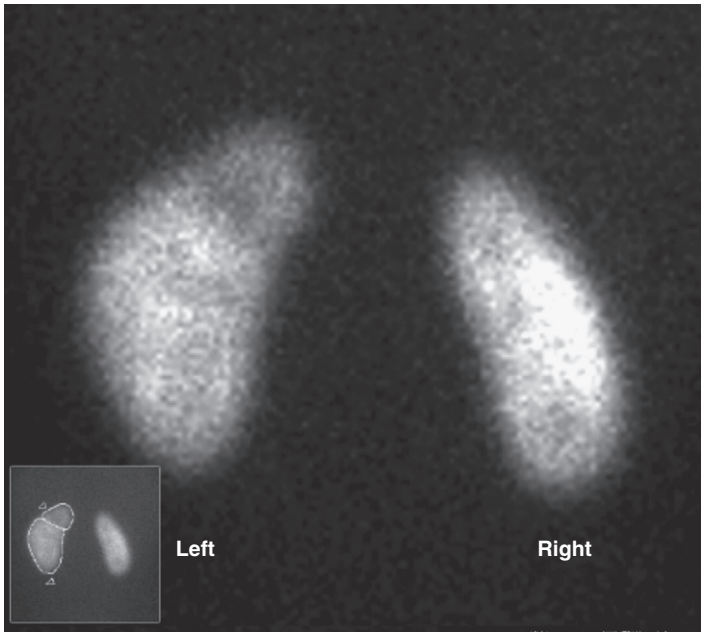


Figure 121–17. Dimercaptosuccinic acid renal scan in a child with a ureterocele with evidence of upper pole function after transurethral incision to decompress the ureterocele. The upper pole was separately assessed as contributing approximately 18% of total renal function.

focus, but the health of the other renal moieties must be determined as well, particularly if there is lower pole reflux or hydronephrosis of any unit. Although there have been some attempts to define what the "normal" function of an upper pole associated with an ectopic ureter or ureterocele should be, there are no criteria to define this. The clinical impact comes with the decision to preserve the upper tract or not, yet there are no objective parameters to determine what level of functional contribution should be preserved. The functional assessment therefore offers the dichotomy of "some function" versus "no function," and this may or may not determine clinical management (see later) (Figs. 121–16 and 121–17). In general, this is clear, but there will always be ambiguous cases. Preoperative assessment is further confused by the lack of ability to predict the effect of decompression.

The assessment of drainage function is rarely of practical utility in that a purely observational approach is only rarely entertained and usually not on the basis of functional parameters. There are no guidelines as to the level of obstructive effect that will cause a clinical problem, particularly infection, although this has been used as a selection tool for nonoperative management (Han et al, 2005).

Intravenous Pyelogram

In unusual situations the intravenous pyelogram (IVP) may offer adequate functional information with anatomic delineation without the complexities of MRI. Because the quantitative measure of upper pole function is rarely necessary with any precision, the IVP can offer an efficient means to complete the renal functional assessment (Fig. 121–18). The IVP may be of particular value in the ectopic ureter without ureteral or upper pole dilation.

Bladder Function

Although the bladder is not usually the focus of clinical attention in the evaluation of the ectopic ureter or ureterocele, the potential for impaired bladder function cannot be ignored. This may be due to bladder outlet obstruction from a ureterocele or impaired continence due to inadequate bladder neck function with an ectopic ureter or ureterocele. In the extreme case of bilateral single-system ectopic ureters, bladder development may be severely impaired due to the absence of developmental bladder filling.

Ultrasound Imaging Interpretation

A simple bladder US image may be useful in completing the functional evaluation of these patients. This requires some patience to wait for bladder filling and emptying yet will yield information on bladder capacity, emptying efficiency, trabeculation, and bladder wall thickness (indicative of possible outlet obstruction). The character, location, and size of the ureterocele can usually be assessed as well (see Fig. 121–12). In some cases the ectopic nature of a dilated ureter may be identified ultrasonographically (see Fig. 121–13A). At times, the distinction between a ureterocele and ectopic ureter may be difficult, as discussed earlier.

Voiding Cystourethrogram

The voiding cystourethrogram (VCUG) provides the most definitive evaluation of the bladder and distal ureters, as well as the urethra, and is an obligate imaging test. This should almost always be performed before any intervention to define the baseline situation. The unusual situation in which a VCUG may not be obtained would be where decompression of a ureterocele producing bladder outlet obstruction or severe bilateral upper tract obstruction is urgent. It is unlikely that the findings on VCUG would alter treatment in that unusual case, which would nearly always be transurethral puncture.

Reflux

The presence of reflux may determine initial treatment for some practitioners and is an important parameter in clinical management after initial decompression of the ureterocele. Lower pole reflux may be of any degree and can often be associated with a massively dilated ureter (Fig. 121–19). In the setting of an ectopic ureter, ipsilateral lower pole reflux is unlikely to resolve spontaneously and will determine definitive treatment options.

Following endoscopic incision of a ureterocele, the presence of reflux either ipsilaterally or contralaterally will be critical in therapeutic decision making.

Ureterocele and Bladder Outlet

The appearance of the bladder base with filling and voiding demonstrated on VCUG will also be useful in therapeutic decisions because massive eversion indicates a weak trigonal floor that may be more likely to require surgical repair. Prolapse of a ureterocele into the urethra and demonstration of a cecoureterocele are important factors in planning and performing a TUI. These factors may be more

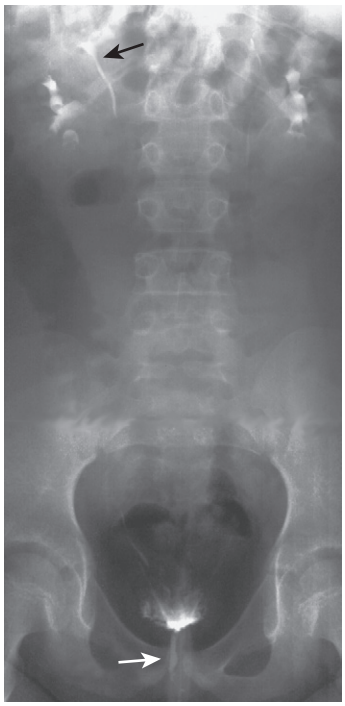


Figure 121–18. Intravenous pyelogram image of a 10-year-old child with life-long wetting and evidence of ureteral duplication *(black arrow—upper pole)* with no hydronephrosis. The distal ureter *(white arrow)* can be seen passing by the bladder and bladder neck and inserting into the urethra near the perineum.



Figure 121–19. Voiding cystourethrogram image of child with a ureterocele appearing as a filling defect within the bladder and massive ipsilateral lower pole reflux.

predictive of the subsequent need for secondary surgery. The usual descriptive terms in the context of a ureterocele include effacement or flattening of the ureterocele with bladder filling; prolapse, which is movement of the ureterocele into the urethra; eversion; diverticulum-like protrusion of the bladder base and trigone with filling and voiding (Fig. 121–20); and intussusception, or protrusion of the ureterocele into its ureter (Fig. 121–21).

Although it is difficult to predict continence at initial presentation, the ureterocele or ectopic ureter associated with a patulous bladder neck may be complicated by later urinary incontinence. Cecoureteroceles are of particular risk (Fig. 121–22), but we have also observed bladder neck ectopic ureters with wide-open bladder necks and later incontinence after resection of the distal ectopic ureter and external bladder neck reinforcement. These patients may benefit from more aggressive bladder neck tightening at the time of definitive resection of the ureterocele or ectopic ureter, but this entails some risk of disturbing what may be normal bladder neck function. Video-urodynamic evaluation may be helpful in such cases.

Endoscopic Evaluation

The final element of evaluation of a ureterocele or ectopic ureter can be endoscopic. Although this is not always essential, most cases of both ureterocele and ectopic ureter will come to operative intervention and concurrent endoscopic evaluation is important, if not essential. Certainly when endoscopic incision is to be performed, this is a critical element and should be performed thoroughly before incision to permit selection of the most effective site.

Endoscopy should take note of the character of the urethra, bladder neck, and trigone relative to the ureterocele or ectopic ureter. The location of other ureteral orifices should be documented. The orifice of the affected ureter should be sought but may not be identified. The urethra is examined carefully for the orifice if not seen in the bladder. **The appearance of the ureterocele will vary with bladder filling, and it is best to start with little filling and slowly increase bladder volume** (Fig. 121–23). The

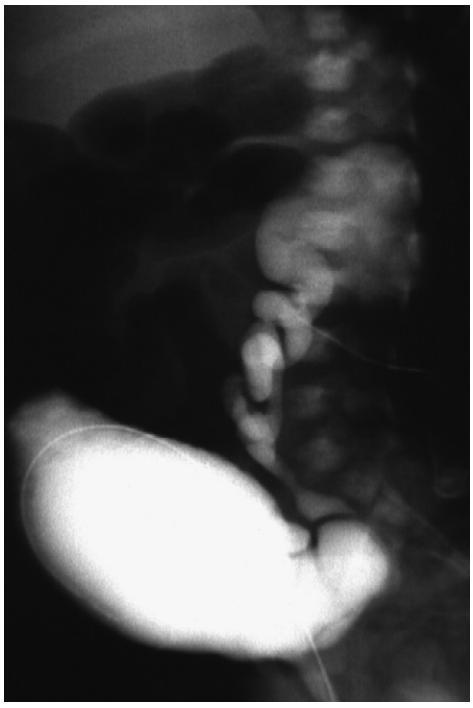


Figure 121–21. Voiding cystourethrogram in a child with a ureterocele and evidence of ureterocele eversion with voiding. The apparent diverticulum is the ureterocele extending outside the bladder wall with increased intravesical pressure. This pattern may be seen with the ureterocele everting or intussucepting into its dilated ureter. There is lower pole reflux as well.

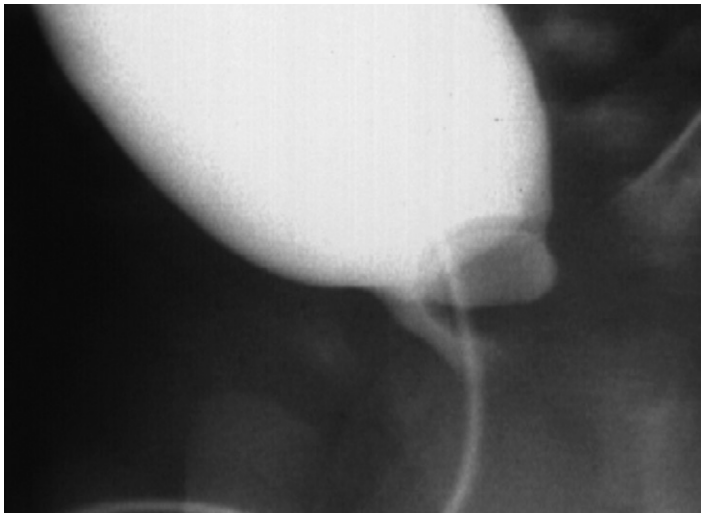


Figure 121–20. Voiding cystourethrogram of child with ureterocele and evidence of prolapse of the ureterocele into the bladder neck with voiding. This is distinct from a cecoureterocele where the ureterocele is part of the urethra. This pattern of prolapse can cause bladder outlet obstruction.

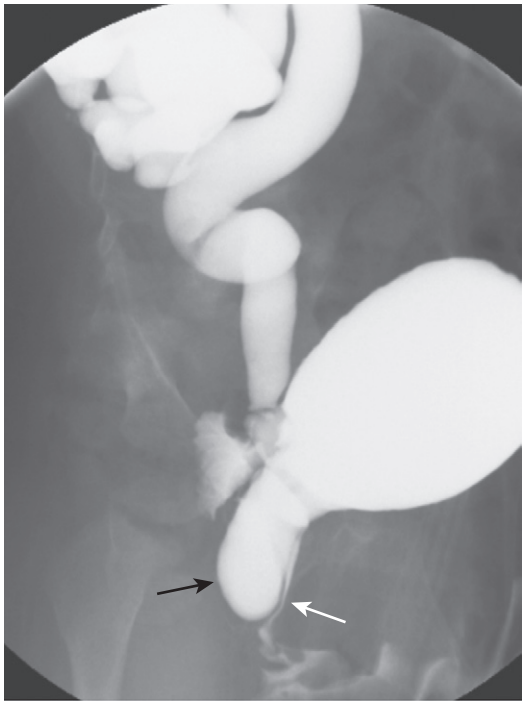


Figure 121–22. Voiding cystourethrogram image of a cecoureterocele where the ureterocele *(black arrow)* is attached to the urethra *(white arrow)* and the lumen extends into the urethra. These are the most challenging ureteroceles due to the involvement of the bladder neck and urethra.

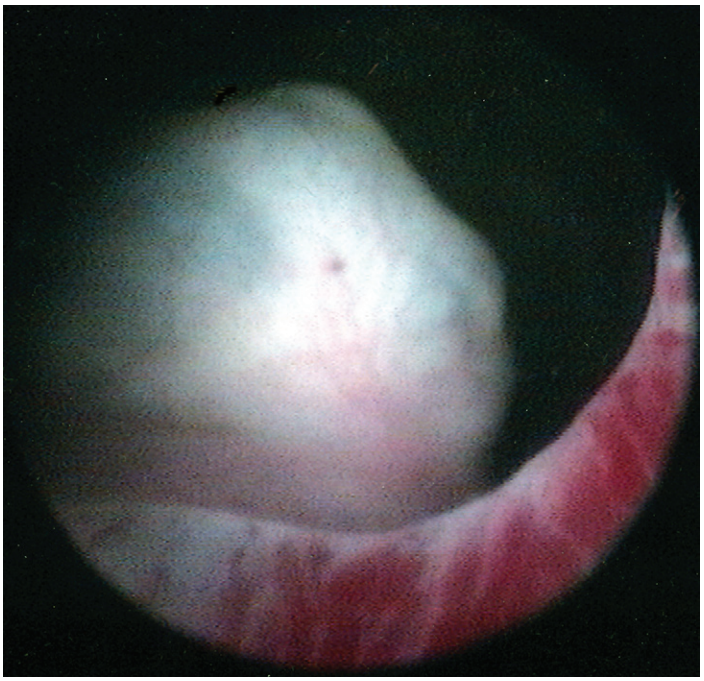


Figure 121–23. Endoscopic image of an intravesical ureterocele just inside the bladder neck.

ureterocele will be seen to slowly flatten. Its true limits are best appreciated with limited bladder filling, and this will provide the lowermost portion, which is probably the best site for incision. Extension of the ureterocele into the urethra, indicative of a cecoureterocele, may be detected and this would indicate the need to make sure this section does not cause obstruction with incision. Retrograde contrast injection can confirm the presence of ureterocele disproportion because there will be only a narrow proximal ureter and no filling of an upper pole segment (Fig. 121–24). Unusual connections with the genital ducts may also be demonstrated, as in the example of a boy with a ureterocele and communication among the ureter, vas deferens, and seminal vesicles (Fig. 121–25).

An ectopic ureteral orifice may be difficult to find endoscopically, but if in the bladder neck it is often patulous (Fig. 121–26). The anatomic connections of the ectopic ureter may be demonstrated using retrograde contrast studies. The authors have identified ectopic ureters that appear to have a thin layer of tissue separating it from the urethra, looking much more like a ureterocele than ectopic ureter (Fig. 121–27A). These may be associated with defects in the bladder neck and incontinence (Fig. 121–27B). Consideration for more extensive removal of these patulous segments with reconstruction of the bladder neck may be part of the clinical decision, and their endoscopic appearance can facilitate this decision.

Clinical Management

Management Goals

It should once again be stressed that, before any surgical intervention for ectopic ureters or ureteroceles, the surgeon must obtain as much information as possible regarding the patient's altered anatomy and physiology. Only then can a rational treatment plan be devised. Although specific and definitive management for ectopic ureters and ureteroceles differs in some individuals, the



Figure 121–24. Ureterocele disproportion demonstrated via retrograde pyelography. Note the disparity between the large ureterocele and the thin ureter and nondilated collecting system.

Key Points: Evaluation

- The US image will usually provide the anatomic diagnosis of an ectopic ureter or ureterocele and permit an inference of function.
- The typical findings are of a dilated upper pole with ureteral dilation or a dilated single system.
- The ureterocele is characterized by a thin-walled, cystic dilation within the bladder and not extending beyond its walls.
- A dilated ectopic ureter may produce an impression on the bladder and appear as a ureterocele.
- Radionuclide renal imaging remains the gold standard for renal functional assessment, and this is usually best provided by DMSA imaging.
- The function of the affected upper pole is the principle focus, but the health of the other renal moieties must be determined as well.
- VCUG provides the most definitive evaluation of the bladder and distal ureters, as well as the urethra.
- The appearance of the bladder base with filling and voiding demonstrated on VCUG will also be useful in therapeutic decisions because massive eversion indicates a weak trigonal floor that may be more likely to require surgical repair.
- Endoscopy should take note of the character of the urethra, bladder neck, and trigone relative to the ureterocele or ectopic ureter.

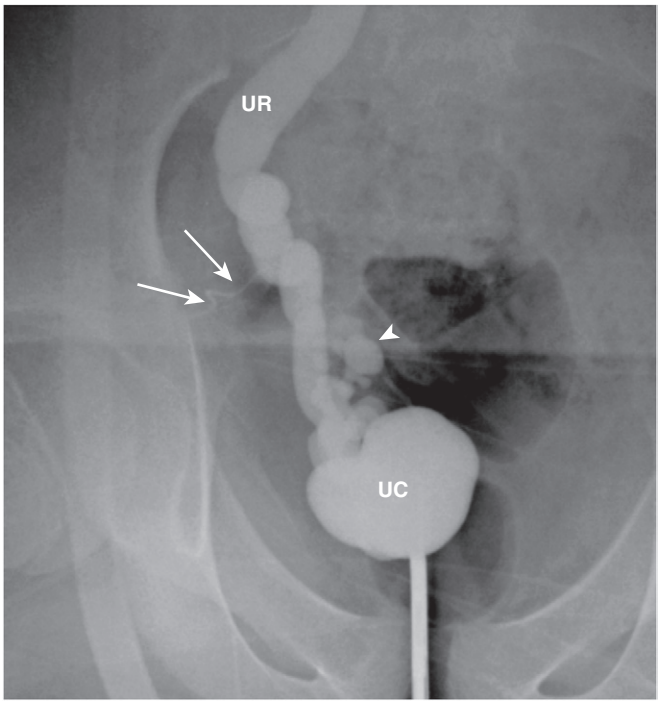


Figure 121–25. Retrograde injection study of a boy with abdominal pain and a ureterocele associated with a hypoplastic right kidney. The intravesical ureterocele (UC) is being injected and demonstrates communication with the right seminal vesicle *(arrowhead)* and vas deferens *(arrows)* with the ureter (UR) leading to the dysplastic kidney. At surgical resection, the ureter and vas joined just above the seminal vesicles.

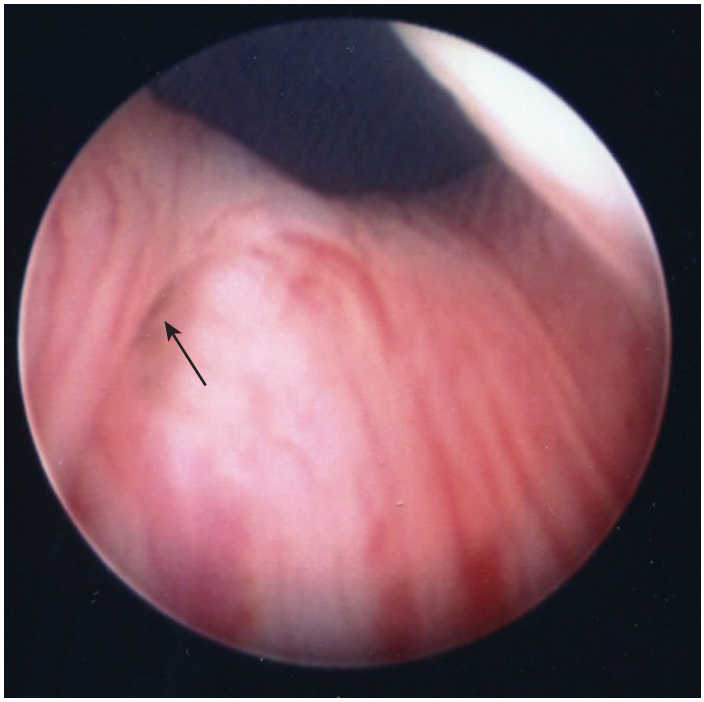
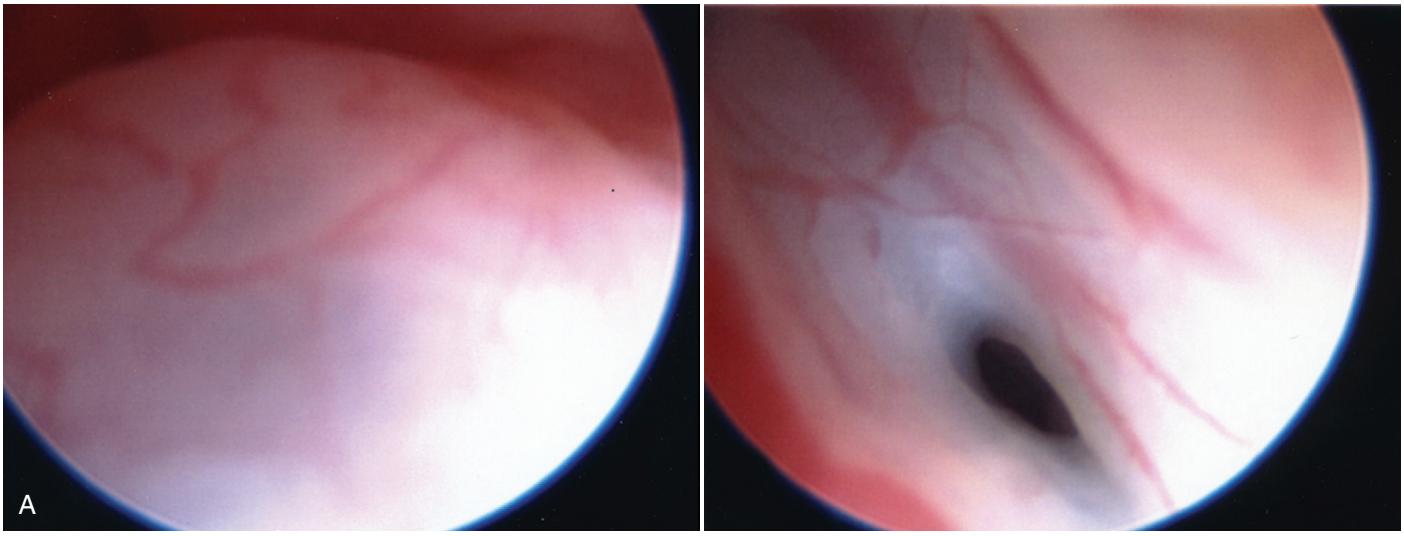


Figure 121–26. Endoscopic views of the bladder neck and the ectopic ureteral orifice marked by the *arrow*. Bladder neck ectopic ureteral orifices are often patulous but do not always reflux.



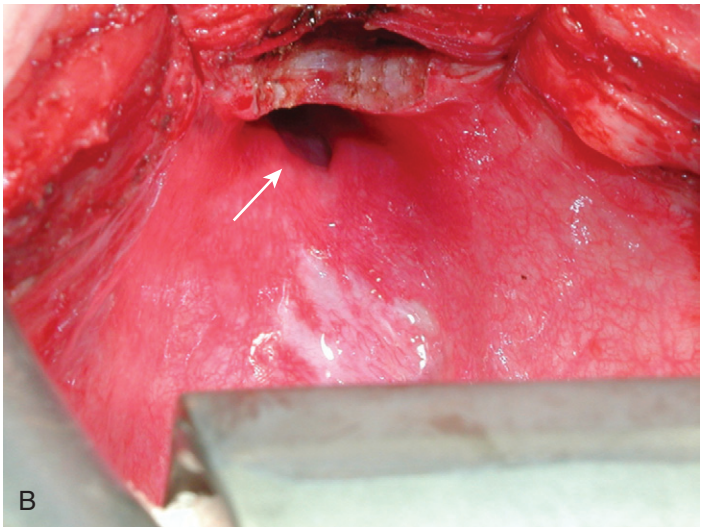


Figure 121–27. **A,** Endoscopic images of the bladder neck orifices of an ectopic ureter with an appearance similar to that of a ureterocele without the dilated intravesical portion. The membrane overlying the orifice was thin and fluttered with irrigation, just as a ureterocele would. **B,** At open surgery, these bladder neck ectopic ureters can have the appearance of a defect in the bladder neck *(arrow)* and be associated with incontinence. It remains unclear how these ectopic ureters are related to ureteroceles.

goals of management are the same and, in many cases, the approaches are identical.

The goals of therapy should be clearly defined and factored into the clinical decisions. These goals are preservation of renal function; elimination of infection, obstruction, and reflux; and maintenance of urinary continence. Minimizing surgical morbidity is a goal that must be included in this consideration. Although the goals of treatment could certainly generate a consensus, the means to achieving those goals have not necessarily been agreed on. One area of at least partial agreement is that early institution of daily prophylactic antibiotics can reduce the risk of urinary tract infections in those cases in which there is significant hydronephrosis.

Preservation of Renal Function

For both ectopic ureter and ureterocele associated with a duplicated system, a primary concern is the preservation of functional renal parenchyma if at all possible. This goal is achieved by correcting obstruction and preventing reflux with its risks of renal parenchymal damage from infection. At times it is necessary to balance one against the other because relieving the obstruction of an ectopic ureter or ureterocele may induce reflux in either or both poles of the involved kidney. In other instances the same action may cause existing lower pole reflux to resolve. Several means of achieving these goals are available.

For an ectopic ureter, this can mean common sheath reimplantation or ureteroureterostomy, either low or proximal near the renal pelvis. For a ureterocele, this can be accomplished by TUI, as well as ureterocele excision and common sheath reimplantation or ureteroureterostomy. In both cases, acute decompression may be necessary due to sepsis and the age of the child. For the ectopic ureter, acute decompression is best achieved with an end ureterostomy near the bladder, whereas for a ureterocele, TUI is usually effective.

The decision making for renal parenchymal preservation is largely empirical, and there are few objective criteria to indicate how much residual function is worth preserving. As noted earlier, this is a subjective determination. The presence of vesicoureteral reflux (VUR) into either of the ureters must be considered as well, and every effort to correct this with the drainage procedure should be made.

Ectopic ureters and ureteroceles are overwhelmingly dealt with postnatally. Although one might reason that a prenatal diagnosis could lead to earlier relief of obstruction and presumably a greater chance of recovery of upper pole function, the evidence in the literature seems to show that there is a limited recovery of function, even with early decompression. The observations by Tank using early endoscopic puncture demonstrated function that had not been detected before drainage (Tank, 1986). Impaired function of the upper pole occurs equally in those diagnosed prenatally and postnatally (Upadhyay et al, 2002). In most instances the upper pole contributes little to overall renal function, but as discussed earlier, there are no criteria for what should be normal upper pole function.

Upper Pole Ablation and Lower Tract Reconstruction

Partial Nephrectomy. The goal of elimination of infection and reflux may be achieved through removal of the abnormal segment associated with either a ureterocele or ectopic ureter, which has been the traditional means of "definitive" surgical intervention. It may need to be accompanied by reimplantation of the lower pole ureter combined with ureterocele excision or removal of the distal ectopic ureter. This can be accomplished in a single-stage procedure, often with two incisions, or in a conditional or planned staged procedure.

The technique of upper pole nephrectomy for nonfunctioning upper poles due to ureteroceles is the same technique as that for ectopic ureters (Fig. 121–28). Upper pole nephrectomy can be performed laparoscopically even in children younger than 12 months.

Ureterocele Excision and Reimplantation. In the case of a ureterocele, excision at the bladder level with reimplantation of the affected ureter and its lower pole mate can be accomplished to both relieve obstruction and eliminate reflux. As described later, this is a complex procedure in which the upper pole ureter may need to be tapered for reimplantation and there are risks of injury to the vagina and bladder neck.

Observational Management

Coplen and Austin (2004) described a subset of patients with ureteroceles and multicystic dysplastic kidneys in the associated upper tract segment. This group had either low-grade or no reflux and no ureteral dilatation. These prenatally diagnosed patients were managed nonoperatively and had a benign clinical course. Other groups have reported nonoperative management of ureteroceles meeting criteria of no obstruction of the ipsilateral lower pole or contralateral kidney, as well as limited reflux to the lower pole (≤grade 3) (Shankar et al, 2001; Direnna and Leonard, 2006), no function of the upper pole, or no obstruction on diuretic renography (Han et al, 2005). Clearly, some children will do well for a period of time without intervention and in some cases, resolution of upper pole dilation and lower pole reflux has been reported. It is challenging to know how to counsel families regarding this approach because the potential for later, unpredictable acute presentation is real. For that individual, even if with a low statistical incidence, it is clinically significant. The long-term risk and relative balance of morbidities of this strategy, as well as the robustness of clinical predictors, has yet to be determined.

Key Points: Clinical Management—Goals of Treatment

- The goals of therapy are preservation of renal function; elimination of infection, obstruction, and reflux; and maintenance of urinary continence.
- Minimization of overall procedural morbidity is also a goal of treatment.
- For both ectopic ureter and ureterocele associated with a duplicated system, a primary concern is the preservation of functional renal parenchyma.
- Decision making for renal parenchymal preservation is largely empirical, and there are few objective criteria to indicate how much residual function is worth preserving.
- For an ectopic ureter, this can mean common sheath reimplantation or ureteroureterostomy, either low or proximal near the renal pelvis.
- For a ureterocele, this can be accomplished by TUI, as well as ureterocele excision and common sheath reimplantation or ureteroureterostomy.

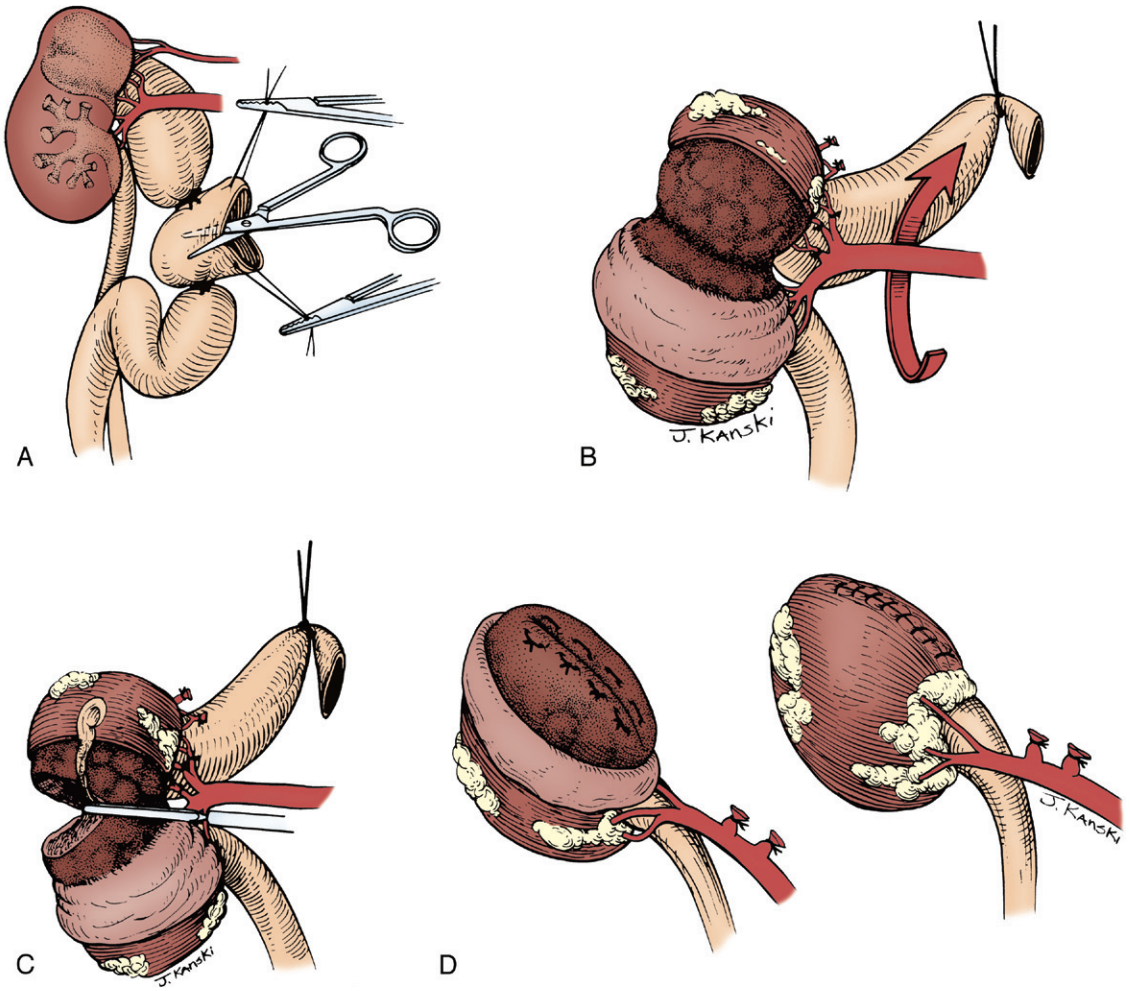


Figure 121–28. Technique of upper pole nephrectomy. **A,** The upper pole ureter is usually dilated and tortuous and can be identified readily at the lower pole of the kidney. It is separated carefully from the lower pole ureter, divided, and used to improve access to the upper pole moiety. **B,** The upper pole ureter is passed beneath the hilar renal vessels and retracted upward. Small feeding vessels to the upper pole are individually ligated and divided. Any larger vessels that may be supplying the upper pole can be temporarily clamped to determine the extent of their distribution. The capsule of the upper pole is bluntly stripped away, exposing the often coarse and cystic parenchyma of the upper pole. This can usually be distinguished from the smooth texture of the normal lower pole. Often, an indented demarcation is seen between the two poles. **C,** While traction is applied to the lower pole ureter, the upper pole is excised with the use of electrocautery. Vascular control is achieved by temporary clamping of the lower pole vessels. This may also be accomplished by gentle finger compression of the lower pole. Individual vessels are identified and ligated during this part of the procedure. **D,** The parenchyma of the lower pole is approximated at the site of removal of the upper pole with the use of broad mattress sutures. The redundant capsule is then brought over the site of repair and sewn together with a running suture.

Procedural Descriptions

Transurethral Incision of Ureterocele

The authors' preferred method of incising the ureterocele is similar to the one described by Rich and colleagues (1990): a transverse incision through the full thickness of the ureterocele wall using the cutting current. Making the incision as distally on the ureterocele and as close to the bladder floor as possible lessens the chance of postoperative reflux into the ureterocele. One can either use a Bugbee electrode or an angled tip wire. The authors favor the latter instrument because it has a finer tip and allows for more precision, and the angle allows for easier manipulation. In older children the resectoscope with the Collins hot knife may be used to make the incision. Laser incision has been reported with equivalent results (Marr and Skoog, 2002; Jankowski and Palmer, 2006). Cold-knife incision has been used as well.

The ureterocele should be incised deeply because ureteroceles may be thick walled. Adequacy of ureterocele incision is confirmed by either the escape of a jet of urine from the ureterocele or viewing the urothelium of the inside of the ureterocele (Fig. 121–29). For the ectopic ureterocele that extends into the urethra, adequate drainage may be achieved by either a longitudinal incision that extends down from the intravesical portion into the urethral portion or two separate punctures, one in the intravesical portion of the ureterocele and one in the urethral portion of the ureterocele.

No bladder catheter is left in place, and most children are treated as outpatients. A follow-up US is performed in 4 to 6 weeks to assess the degree of decompression. Most series have reported greater than 90% decompression (Fig. 121–30), and it is uncommon to require a second incision. A voiding cystogram is performed in 2 to 3 months to determine the status of lower pole

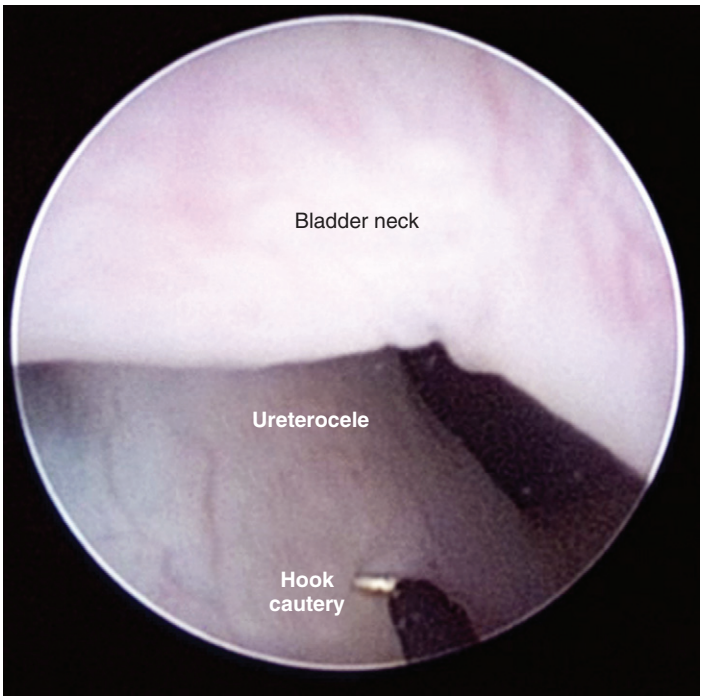


Figure 121–29. Endoscopic image of a ureterocele about to be incised with a hook cautery. The incision should be made inferior and medial to limit the risk of reflux, but the key goal is decompression. The ureterocele should be incised with the bladder partially filled, but not so much as to efface the ureterocele.



Figure 121–31. Voiding cystourethrogram demonstrating reflux into the upper pole of a duplex system after ureterocele incision. This type of reflux will rarely resolve spontaneously, Although the clinical risk is uncertain, the reflux is most often repaired.

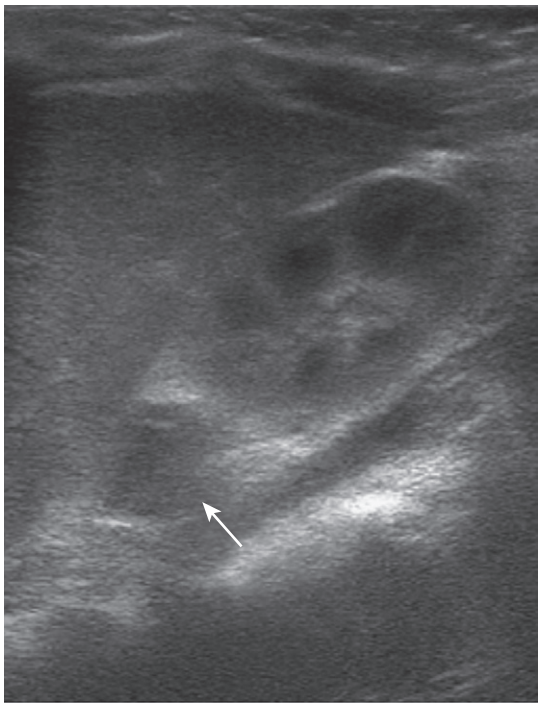


Figure 121–30. Appearance of the decompressed upper pole from Figure 121–10, following endoscopic incision of the ureterocele.

reflux and whether new reflux has been created into the ureterocele (Fig. 121–31).

The reported incidence of new reflux ranges from 0% to 50% and may depend on the method used for incision (Tank, 1986; Rich et al, 1990; Blyth et al, 1993; Jelloul et al, 1997; Dahm and King, 1998; Husmann et al, 1999; Jayanthi and Koff, 1999; Shekarriz et al, 1999; Cooper et al, 2000; Singh and Smith, 2001; Upadhyay et al, 2002; Chertin et al, 2007). Some authors favor puncture instead of incision, but no data are available to demonstrate a clear difference. **The type of ureterocele is a clear determinant of the outcomes of TUI with intravesical ureteroceles having the highest likelihood of achieving all therapeutic goals with only the incision. Decompression with no reflux can be expected to be achieved in 70% to 80% of cases. Extravesical ureteroceles, however, are more likely to have persisting or new reflux and may require secondary surgery on the basis of the presence of reflux in 70% by some series.** In the meta-analysis by Byun and Mergurian (2006), the presence of lower pole reflux and the location of the ureterocele are similar in their impact on outcomes. In this analysis, the relative risk of reoperation was 1.74 times greater in the presence of reflux as without and 2.78-fold times higher if extravesical. These factors did not seem to be additive, suggesting they represented similar underlying causes. In comparison with an open approach of any modality, however, the simplicity of ureterocele incision coupled with the potential for definitive cure, even if not in a large fraction, is appealing. TUI also acts to better prepare the patient for a secondary major surgery if necessary, by decompressing dilated ureters.

Ureterostomy for Ectopic Ureter

The ectopic ureter presenting with sepsis or with massive dilation in a neonate may be best managed with a temporary end ureterostomy (el Ghoneimi et al, 1996). **This has the advantage of permitting acute decompression to manage sepsis and permit later assessment of any**

function in the affected renal unit before definitive management. By performing an end ureterostomy, the ureter can decompress and it is in position to be reimplanted if the renal unit is felt to be salvageable. No resection of redundant ureter is performed because this will shorten in time and some length will be necessary to perform the reimplantation. The stoma should be positioned at what would be the lateral end of a Pfannenstiel incision. Percutaneous ureterostomy has been reported as well (Bilen et al, 2006). Assessment of functional status is performed shortly before definitive surgery, usually in 4 months or after age 6 months. DMSA scanning is probably the most efficient means, but differential urine collection is an option as well. If there is no function appreciable, partial or total nephrectomy is performed with removal of the entire ureter to the stoma.

Ureteroureterostomy and Pyeloureterostomy

When the upper pole of either an ectopic ureter or ureterocele is to be maintained due to function or surgeon preference, pyeloureterostomy or ureteroureterostomy may be carried out. Both proximal and distal approaches may be used, and these have been described with open and laparoscopic techniques.

Open. **Ureteroureterostomy can be performed distally to create an anastomosis between the upper pole ureter to the lower pole ureter in an end-to-side fashion.** This can be done at the distal ureter via an inguinal, open approach (Huisman et al, 1987; Lashley et al, 2001; Chacko et al, 2007; Prieto et al, 2009). It is critically important in this type of procedure to correctly identify the recipient lower pole ureter, and it is strongly recommended to cystoscopically place a stent into the lower pole ureter at the start of the procedure. In the authors' experience, many of these reconstructive procedures have resulted in decreased dilatation of the upper urinary tract and improved function.

Other options to achieve this goal are the proximal anastomotic techniques of ureteroureterostomy or ureteropyelostomy. This results in the upper pole system's draining into the lower pole system. **Such high anastomoses may be preferable to a distal ureteroureterostomy with a dilated upper pole because the latter may have more urinary stasis with a distal anastomosis.** Whether the "yo-yo" phenomenon is clinically significant remains uncertain, but the authors prefer a proximal anastomosis when there is a significant mismatch in ureteral size.

When performing upper tract anastomoses, dissection should be limited to an absolute minimum, especially medially, to prevent disruption of either ureter's blood supply. The upper pole ureter may be considerably larger than the lower pole ureter. A generous longitudinal pyelotomy or ureterotomy made in the lower pole ureter is performed to overcome such disproportion, and the anastomosis is performed in an end-to-side fashion. The distal portion of the upper pole ureter should be aspirated with a feeding tube to decompress it. The distal upper pole ureter is resected as far inferiorly as possible, with care taken to stay directly on this ureter's wall and avoid the vasculature of the adjacent lower pole ureter. If there is no reflux, the resection is taken as distally as possible and the remnant lower portion of ureter may be left open. If reflux is present in an ectopic ureter, it should be taken as close to the bladder neck as possible. If associated with a ureterocele, it may be possible to avoid resection of the ureterocele as long as it is well decompressed.

Laparoscopic. Both ureteroureterostomy and pyeloureterostomy can be readily performed laparoscopically (Gonzalez and Piaggio, 2007; Steyaert et al, 2009), which is aided with robotic control (Kutikov et al, 2007; Smith et al, 2009). The author prefers stenting across the anastomosis, but others have indicated that this may not be necessary and only to stent the recipient ureter.

Key Points: Transurethral Incision of Ureterocele and Drainage Procedures

- The reported incidence of new reflux following TUI of a ureterocele ranges from 0% to 50% and may be dependent on the method used for incision.
- The type of ureterocele is a clear determinant of the outcomes of TUI with intravesical ureteroceles having the highest likelihood of achieving all therapeutic goals with only the incision.
- TUI also acts to better prepare the patient for a secondary major surgery, if needed, by decompressing dilated ureters.
- Persisting reflux into the upper or lower poles is typically an indication for ureterocele excision and reimplantation.
- It has not been generally possible to predict with any accuracy in an individual how they might respond to a TUI based upon clinical parameters.
- The ectopic ureter presenting with sepsis or with massive dilation in a neonate may be best managed with a temporary end ureterostomy.
- Ureteroureterostomy can be performed distally or proximally to create an anastamosis between the upper pole ureter to the lower pole ureter in an end-to-side fashion.

Upper Pole Partial Nephrectomy

Upper pole removal, using a partial nephrectomy or heminephrectomy of a duplex system, is typically the preferred treatment when there is clearly no function in the upper pole and if there is concern about how effective a drainage procedure may be due to massive dilation. There are numerous series advocating one or another approach with variable results dependent upon factors such as degree of reflux, age, and underlying pathology, but there are no clear data to indicate that one approach is so definitively better as to be the universal choice.

The surgical methods for partial nephrectomy have been described and remain useful and similar whether being used with open surgery, conventional laparoscopy or robotic laparoscopy. These apply to both ectopic ureters and ureteroceles in duplex systems.

Open Partial Nephrectomy or Heminephrectomy

Heminephrectomy is a standardized procedure, with relatively little recent evolution (Mor et al, 1994), but several technical points deserve emphasis (Fig. 121–28). A flank approach for heminephrectomy usually offers better exposure to the upper pole vessels. The procedure may be performed through a dorsal lumbotomy approach, which is both effective and less morbid than a muscle-dividing flank incision. In older children this exposure can become less effective, however.

In an upper pole nephrectomy, the primary concern is to avoid damaging the viable lower pole. The kidney should be retracted gently so as not to cause any vascular injury through traction and spasm of small vessels. Transecting the upper pole ureter and placing a traction stitch on the proximal portion of this ureter affords the surgeon a good method of retraction and

manipulation of the upper pole. Once at the pedicle, dissection of the ureter both below and above the vessels allows for easier, safer freeing of the ureter. The ureter is passed behind the main renal vessels. The dissection around the renal vessels should be done carefully to avoid damage to the lower pole. The upper pole vessels (most often two to three in number) are sequentially ligated. Demarcation of the upper pole parenchyma becomes apparent after the upper pole vessels are ligated. Stripping the capsule off the upper pole in continuity allows it to be used in the closure. Several mattress sutures incorporating a pedicle of retroperitoneal fat are used for closure.

During upper pole nephrectomy, atraumatic clamping of the renal pedicle can be used, enabling work in a bloodless field. Administration of an intravenous osmotic diuretic (e.g., mannitol) moments before and after clamping of the pedicle helps prevent acute tubular necrosis. Topical vasodilating agents (e.g., papaverine) should be available in case vasospasm occurs. In general, vascular control is not essential in upper pole partial nephrectomy as the polar vessels may be identified and controlled. Resection of the upper pole renal tissue can then be carried out with electrocautery or other cutting device.

When performing the upper pole ureterectomy, it is of utmost importance to maintain the dissection immediately on the wall of the upper pole ureter as much as possible to preserve the blood supply to the remaining lower pole ureter.

If, in addition to obstruction, there is concomitant reflux into the ectopic ureter, some recommend a second incision (i.e., a Gibson incision) to resect the ureter in its entirety. Care must be taken to avoid injury to the vas deferens in male patients. As mentioned previously, dissection should be performed strictly along the wall of the upper pole ureter. To prevent complications that may arise from dissection within a common sheath of two ureters (especially distally), the back wall of the upper pole ureter can be left attached to the lower pole ureter. The remainder of the upper pole ureter should be removed (Fig. 121–32). Such a maneuver prevents damage to the lower pole ureteral blood supply, which courses between both ureters. Resection is carried out to the level of the bladder, where several vesicle sutures are placed to close the upper pole ureteral hiatus.

Other surgeons are comfortable ligating the distal refluxing ureteral stump and leaving it in situ with few subsequent problems attributed to the small volume of reflux into that stump (Cain et al., 1998; Kim et al., 2001). The refluxing, obstructed ectopic ureter raises the most concern regarding a later infection and as much of the ureter should be removed as is possible without injury to the bladder neck.

A Penrose drain (brought through a separate stab wound or at the edge of the incision) is placed in such a fashion as to drain the renal fossa and the area of the ureteral dissection. **Postoperative evaluation is best performed with a Doppler sonogram to demonstrate normal postoperative anatomy, absence of a urinoma, and normal blood flow to the lower pole.** Optionally, a functional study such as a nuclear renal scan may be performed if there is concern regarding viability of the lower pole.

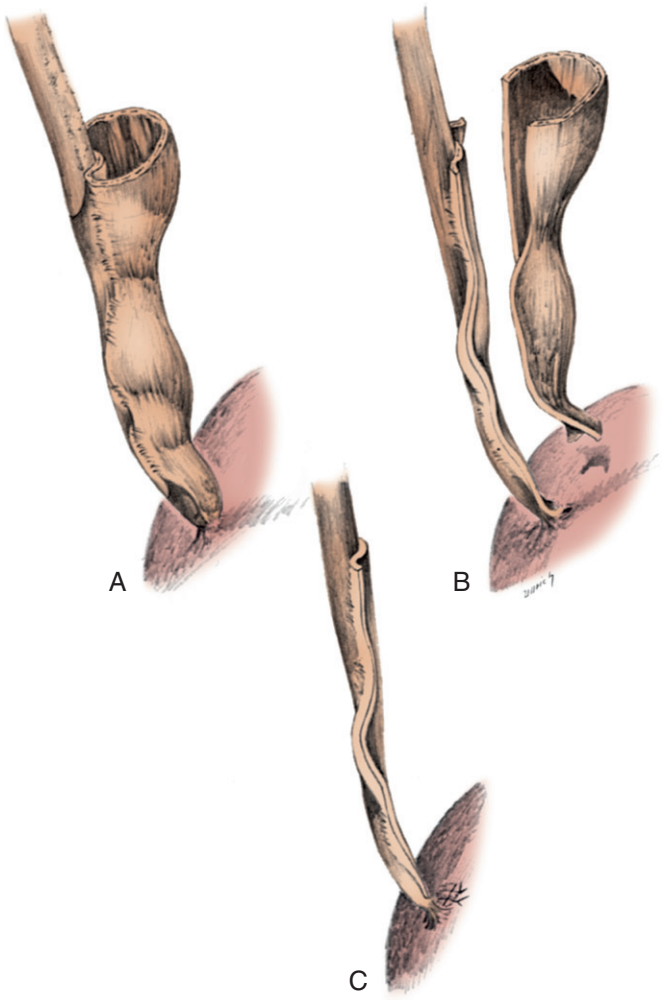


Figure 121–32. Surgical management of the refluxing ureteral stump. **A,** It is difficult to completely separate the distal 2 to 3 cm of the upper pole ureter from the lower pole ureter. The ectopic ureter is excised to this point. **B,** The outer wall of the ectopic ureter is excised to the bladder level. **C,** A transfixing suture obliterates its lumen, with care being taken not to injure the orthotopic ureter.

Laparoscopic Partial Nephrectomy

Another surgical option is laparoscopic nephrectomy or heminephrectomy. This can be done by either a transabdominal or a retroperitoneal approach, and robotic assistance is now available. Laparoscopic procedures may offer reduced morbidity with less postoperative pain, earlier return of gastrointestinal function, earlier discharge home, and presumably a quicker return to work for the parents (Jordan & Winslow, 1993; Janetschek et al, 1997; El-Ghoneimi et al, 1998; Wang et al, 2004; Lee et al, 2005; Wallis et al, 2006; Lee et al, 2009; You et al, 2009). Other advantages include enhanced visualization and increased magnification of the operative field, improved cosmesis, and avoidance of a second incision that is often needed for the distal ureterectomy of a nephroureterectomy.

Laparoscopic heminephrectomy can be performed in very small infants, and the operative time has decreased as experience and skill have increased (El-Ghoneimi, 2003; Wang et al, 2004; Sydorak and Shaul, 2005; Piaggio et al, 2006). Equipment such as the LigaSure device (Valleylab, Boulder, CO) and the Harmonic Scalpel (Ethicon EndoSurgery, Cincinnati, OH) allow for resection of the upper pole in a bloodless field.

Some authors believe that cystoscopic placement of a ureteral catheter allows for easier identification of the ureter at the time of laparoscopy (Yao & Poppas, 2000). The authors have not felt this to be essential given the usual marked size difference in the ureters.

Laparoscopic heminephrouretectomy begins similarly to the open procedure in that the pathologic ureter is grasped as a handle and dissected closely to its wall to avoid compromise of the blood supply to the normal ureter. The upper pole ureter is passed behind the vessels and used to facilitate dissection of the upper pole. The polar renal vessels are then ligated with clips or divided with electrocautery; this allows for a more discernible demarcation of the affected upper pole (Fig. 121–33A). The plane between the upper pole collecting system and the upper parenchyma of the lower pole is developed bluntly to facilitate identifying and transecting the upper pole attachments to the lower pole (Fig. 121–33B). After the polar element is removed with electrocautery, one can check for collecting system leakage with intravenous injection of methylene blue (Yao and Poppas, 2000). Janetschek and colleagues place fibrin glue and hemostatic agents on the cut surface and then cover it with Gerota fascia to aid in hemostasis (Janetschek et al, 1997). The authors have not used these agents, but have closed the defect over a pedicle of local fatty tissue (Fig. 121–33C).

When performing a partial nephrectomy, robotic-assisted laparoscopy offers advantages over standard laparoscopy (Lee et al, 2009). The magnification is augmented and the dexterity of the robotic instruments allows for greater precision when working around the renal pedicle and controlling the upper pole vessels, as well as the visual advantages of a 3-dimensional image. Patient and port positioning is the same as for pyeloplasty. Vascular control may be by absorbable or metal clips or even with suture ties. The latter may be preferable by reducing the risk of avulsing a clip during later dissection. The defect is usually closed with a tongue of retroperitoneal fat laid into the defect, which is then closed with 2 or 3 mattress sutures of 3-0 PDS or Vicryl.

Laparoendoscopic single-site ("LESS") nephrectomy has been described for a single-system ectopic ureter. This technique represents the newest horizon for minimally invasive surgery as only one 22-mm multitrocar port site (recessed in the umbilicus) is used to perform the entire surgery (Park et al, 2009).

Outcomes

Results of upper pole removal for ectopic ureters and ureteroceles are generally very good, but this must be integrated with the overall clinical decision making. This is rarely any problem with ectopic ureters, as the residual stump is rarely problematic. In cases of ureteroceles in which lower pole reflux is present, resolution may be expected in up to 20% (Husmann et al, 1999), **and new reflux may be seen in 15% to 50% of those where no reflux was present preoperatively.** The overall secondary

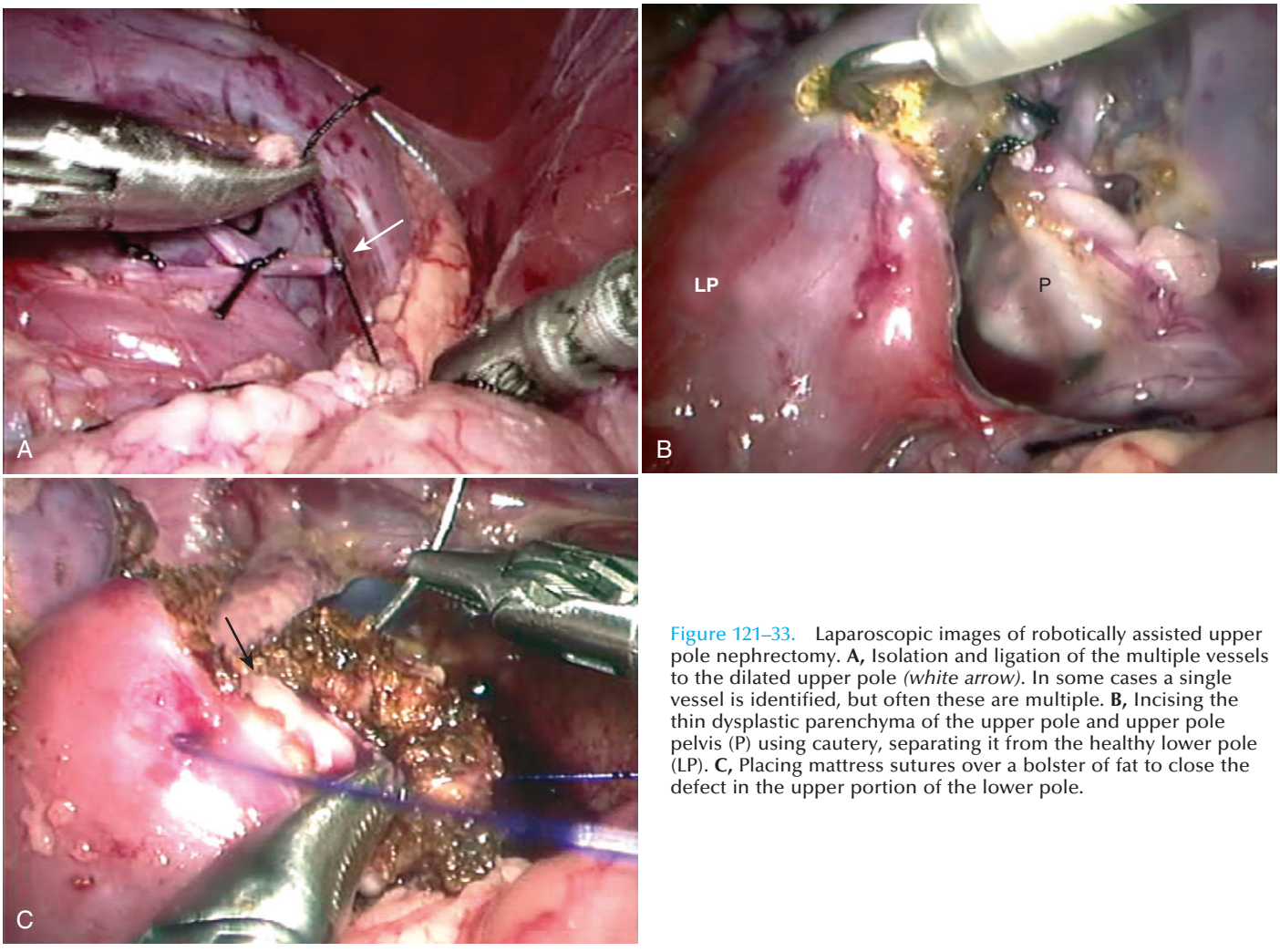


Figure 121–33. Laparoscopic images of robotically assisted upper pole nephrectomy. **A,** Isolation and ligation of the multiple vessels to the dilated upper pole *(white arrow)*. In some cases a single vessel is identified, but often these are multiple. **B,** Incising the thin dysplastic parenchyma of the upper pole and upper pole pelvis (P) using cautery, separating it from the healthy lower pole (LP). **C,** Placing mattress sutures over a bolster of fat to close the defect in the upper portion of the lower pole.

surgery rate after primary upper pole nephrectomy for ureterocele is between 35 and 45% based on the literature. The difficulty in interpreting the literature rests in variable indications for secondary surgery. In some, reflux was simply followed and within the short follow-up did not cause any problems, while in others it was felt that removal of a nonfunctioning upper pole was necessary. Neither of these approaches has been validated by long-term data.

Complications

Complications related to heminephrectomy include loss of lower pole function (Mandell et al, 1980; Wallis et al, 2006; You et al, 2009) and development of postoperative upper pole urinomas (Valla et al, 2003; You et al, 2009). Loss of function may be a long-term issue and may not be recognized immediately. Clinical signs of fever, increasing pain, and hematuria may be evident in the first week after surgery. Urinomas have been reported mostly in series in which there is no formal closure of the polar defect. Whether these urinomas are due to injury to the lower pole or remnant upper pole is unclear. Urinomas, if causing no symptoms and not expanding, can be observed. Other less common problems can include inferior vena cava laceration, duodenal perforation and total nephrectomy, and peritoneal tears (if done via the retroperitoneum).

Key Points: Upper Pole Nephrectomy

- In an upper pole nephrectomy, the primary concern is to avoid damaging the viable lower pole.
- Postoperative evaluation is best performed with a Doppler sonogram to demonstrate normal postoperative anatomy, absence of a urinoma, and normal blood flow to the lower pole.
- Definitive cure by partial nephrectomy for ectopic ureters is generally successful because the residual stump is rarely problematic.
- In ureteroceles in which lower pole reflux is present, resolution may be expected in up to 20%, and new reflux may be seen in 15% to 50% of those where no reflux was present preoperatively.
- Complications related to heminephrectomy include loss of lower pole function and development of a postoperative upper pole urinoma.
- Separation of the duplicated ureters during intravesical dissection should be discouraged because it can lead to injury of the common blood supply running longitudinally between the two ureters.

Ureterocele Excision and Common-Sheath Reimplantation

The intravesical approach to the ureterocele begins with a transverse incision of the ureterocele between two stay sutures (Figs. 121–34 and 121–35A). Proximally, a plane is obtained between the ureterocele wall and the wall of the bladder. The ureterocele is dissected off the bladder to the point at which it joins the lower pole ureter. Then the two ureters are dissected as a unit, the upper pole ureter is tapered as needed, and both ureters are reimplanted submucosally. Amar (1978) advocated submucosal saline injection to facilitate creation of the submucosal tunnel. The distal portion of the ureterocele is dissected in the same plane (Fig. 121–35B) to the level of the bladder neck, where it is resected. The detrusor muscle is plicated if it is attenuated, and it appears that it may offer insufficient backing. Bladder mucosal flaps are raised to cover the area of the removed ureterocele (Fig. 121–35C).

Once again, several technical points regarding ureterocele excision and common sheath reimplantation deserve mention. **Separation of the duplicated ureters during intravesical dissection should be discouraged because it can lead to injury of the common blood supply running longitudinally between the two ureters.** Plication of the detrusor muscle underlying the ureterocele may be necessary to reinforce any areas of muscle deficiency. Furthermore, **the distal portion of the ureterocele may extend below the bladder neck. Extreme care must be taken in this part of the dissection to avoid injury to the sphincter mechanisms. If the entire ureterocele cannot be excised, it can be fulgurated carefully and closed over with two layers.**

Cecoureteroceles present a unique challenge in ureterocele excision and reimplantation in that the distal aspect of the ureterocele can create an obstructive flap-valve with voiding, acting as a "wind sock" behind the urethra. Options include resection by gentle retraction of the ureterocele if it is not large, closure of the opening with two layers of tissue, or fulguration of the lumen to cause collapse and closure. Careful postoperative assessment is necessary in any case to identify what can be progressive voiding dysfunction if the remnant cecoureterocele creates obstructive voiding (Fig. 121–36).

An alternative approach to ureterocele resection is that of marsupialization in which the thin intravesical aspect is removed and the edge is sutured. No attempt is made to reinforce the back wall on the basis of empirical observation that this is not always necessary. Reported results have been satisfactory (Scherz et al, 1989; Lewis et al, 2008). Although this eliminates the need to dissect out the ureterocele and avoids injury to the underlying vagina, it is the authors' impression that this approach has inherent risks that can be avoided by a controlled and predictable surgical approach of trigonal reconstruction. A major problem with marsupialization may be rare, but it seems preferable to definitively correct the anatomic and functional defect on the first open operation when necessary.

Reported results of ureterocele excision and common sheath reimplantation are good, although persisting reflux can be an issue in 5% to 10% of cases. This may be more common when ureteral tapering is necessary. Although in some reports it is claimed that these patients do not require surgery, persisting reflux in this context must be viewed with caution.

Total Reconstruction

Total reconstruction of both upper and lower tracts has been advocated by some authors as being the most definitive procedure for ureteroceles (Hendren and Mitchell, 1979; Kroovand and Perlmutter, 1979). **Upper pole nephrectomy with ureterocele excision and reimplantation of the lower pole ureter is definitive, but is an extensive operation performed with two incisions.** Although the reported success rates are good, it remains uncertain if this is appropriate in most children when long-term relief from obstruction and reflux may be achieved in one or at most two lesser procedures. No clear clinical situations have been reported to be such that two procedures are always

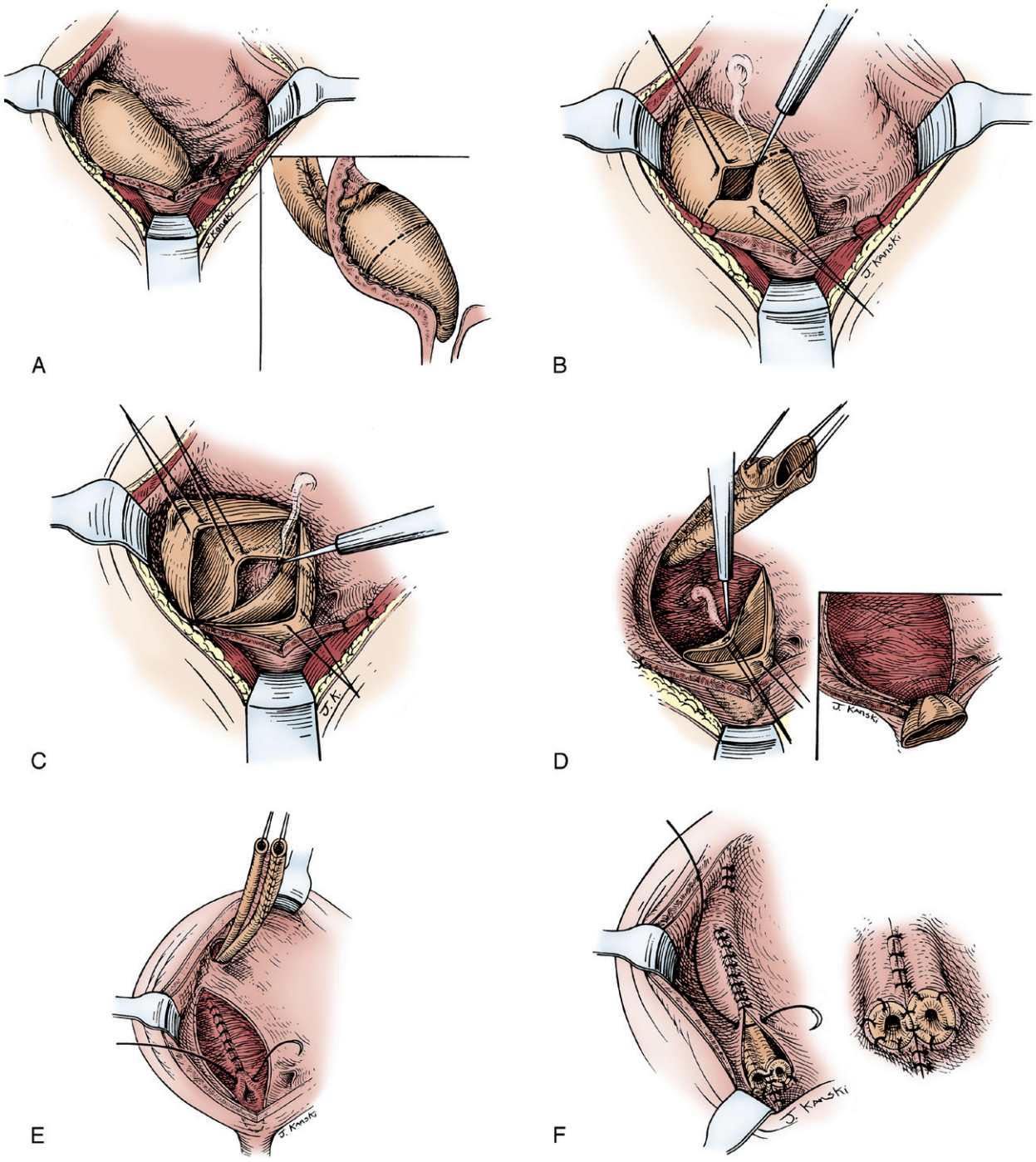


Figure 121–34. Technique for excision of ectopic ureterocele and common sheath reimplantation of upper and lower pole ureters. **A,** Appearance of right-sided ureterocele with open bladder, viewed from below. Note proximity of the contralateral ureteral orifice. *Inset,* Cutaway side view demonstrating the close association of the two polar ureters with a common vascular supply. The *dotted line* indicates the planned initial incision of the ureterocele. **B,** After stay sutures are placed, the ureterocele is incised with electrocautery in a transverse direction, exposing the inner cavity of the ureterocele. **C,** The posterior mucosal wall of the ureterocele is incised transversely, revealing the often thinned posterior muscular wall of the bladder. This incision will then be continued around the bladder mucosal edge of the ureterocele including the orifice of the lower pole ureter. Stay sutures are important to provide adequate exposure. **D,** The upper and lower pole ureters have been mobilized and are retracted into the bladder. The distal aspect of the ureterocele is being mobilized in a similar fashion. The bladder mucosal surface will also be incised around the edge of the ureterocele to permit complete removal of the ureterocele. *Inset,* The fully mobilized distal ureterocele is retracted caudally, revealing its narrowing attachment at the bladder neck. **E,** The dilated upper pole ureter associated with the ureterocele has been tapered and remains in continuity with the lower pole ureter. Both have been brought into the bladder through a newly formed muscular hiatus to provide adequate tunnel length for the ureteral reimplantation. The thinned-out posterior bladder wall has been repaired with multiple interrupted sutures to provide adequate muscular backing for the ureters. The bladder mucosa surrounding the ureterocele defect has been mobilized to permit covering of the ureters. **F,** *Left,* the ureters have been reimplanted into the new ureteral tunnel, have been sutured distally after spatulation, and are being covered with bladder mucosa. The lower pole orifice is medial. *Right,* Final appearance of the ureteral tunnel after completion of the reimplantation.

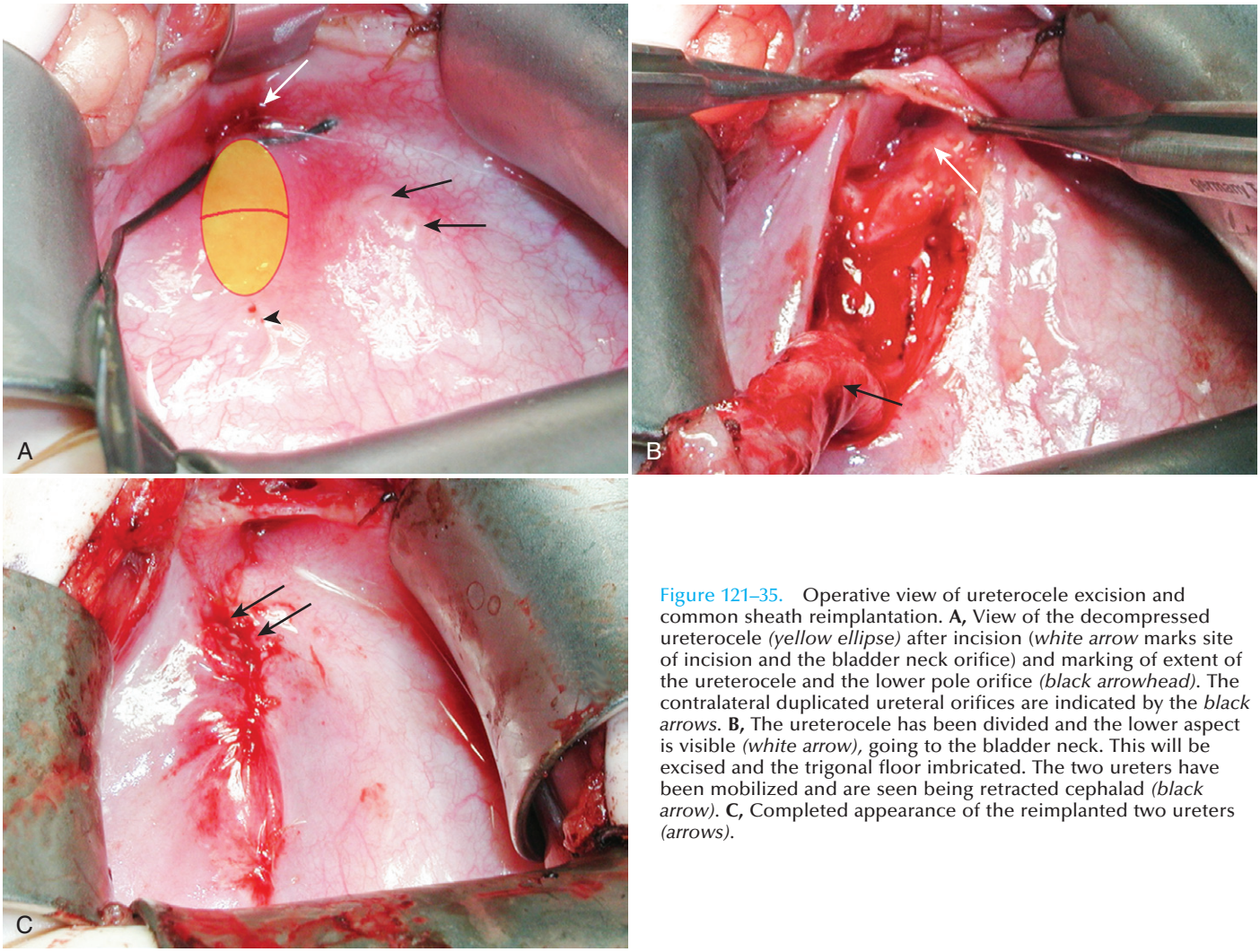


Figure 121–35. Operative view of ureterocele excision and common sheath reimplantation. **A,** View of the decompressed ureterocele *(yellow ellipse)* after incision (*white arrow* marks site of incision and the bladder neck orifice) and marking of extent of the ureterocele and the lower pole orifice *(black arrowhead)*. The contralateral duplicated ureteral orifices are indicated by the *black arrows*. **B,** The ureterocele has been divided and the lower aspect is visible *(white arrow)*, going to the bladder neck. This will be excised and the trigonal floor imbricated. The two ureters have been mobilized and are seen being retracted cephalad *(black arrow)*. **C,** Completed appearance of the reimplanted two ureters *(arrows)*.

Key Points: Ureterocele Excision and Reimplantation

- Cecoureteroceles present a unique challenge in ureterocele excision and reimplantation in that the distal aspect of the ureterocele can create an obstructive flap-valve with voiding, acting as a "wind sock" behind the urethra.
- An alternative approach to ureterocele resection is that of marsupialization in which the thin intravesical aspect is removed and the edge is sutured.
- Results of ureterocele excision and common sheath reimplantation are good, although persisting reflux can be an issue in 5% to 10% of cases.
- Total reconstruction including upper pole nephrectomy with ureterocele excision and reimplantation of the lower pole ureter is definitive but is an extensive operation performed with two incisions.

required, and if TUI is the first procedure, it is not comparable with either an upper or lower tract procedure. The older child with a massive ureterocele and no function of an upper pole with significant lower pole reflux might be reasonably treated with upper pole nephrectomy, ureterocele excision, and bladder reconstruction. At present, the partial nephrectomy would be reasonably performed laparoscopically with a lower Pfannenstiel incision for the bladder reconstruction and reimplantation. This is an unusual clinical scenario.

CLINICAL DECISION MAKING SUMMARY

For ectopic ureters, clinical decision making is much more straightforward than for ureteroceles and rests on whether to maintain the upper pole of a duplex system. If this is chosen, then the surgical approach depends on the presence of reflux in the lower pole; if present, a common sheath reimplantation or a lower pole reimplantation with distal upper to lower pole ureteroureterostomy is performed. If there is no lower pole reflux, either proximal or distal ureteroureterostomy is performed. If the degree of function is ambiguous, a temporary end ureterostomy can be used to permit assessment out of the acute setting, particularly with a massively dilated ureter. Also, if reflux is present, the need for lower surgery to correct the reflux may influence the choice to avoid upper tract surgery. If removal of the upper pole is chosen on the basis of the degree of dilation or the preference for removal of nonfunctioning, dysplastic tissue, an upper pole nephrectomy is performed.

For the single-system ectopic ureter, preservation or removal is also based on degree of function and surgeon preference. No objective outcome data are available to advocate clearly for one or another approach.

For a ureterocele in a duplex system, the availability of endoscopic incision creates more options (Table 121–1) (Fig. 121–37). It is important to recognize that although TUI is an "operation," it is of a totally different nature than either an upper pole nephrectomy or a lower tract reconstruction. It is inappropriate to equate them as an "operation" in a comparative manner. **It has not been generally possible to predict with any accuracy in an individual how they might respond to a TUI on the basis of clinical parameters.** Because in some cases, significant lower pole reflux and upper tract dilation may be treated with a brief outpatient procedure with documented long-term results, it would seem reasonable to offer that option before moving directly to a more complex upper or lower tract reconstruction. **Even if half of those cases may need subsequent surgery, it can be safely deferred until the child is older. There is also the further appeal of TUI in that it may make a subsequent surgical procedure less complex by decompressing a dilated upper pole ureter.** Reimplantation may be much more effective and not require excisional tapering. This lessens overall morbidity, another goal of management. The appeal of TUI

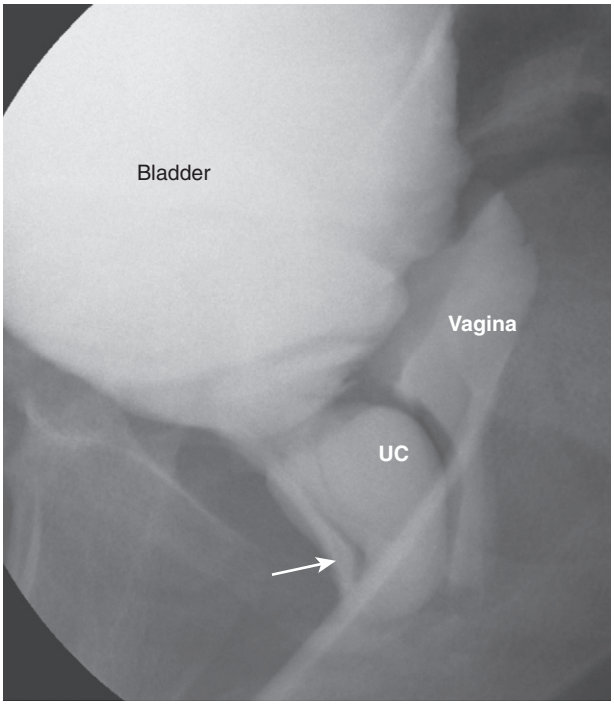


Figure 121–36. Voiding cystourethrogram appearance of a large cecoureterocele (UC) extending down the urethra and causing bladder outlet obstruction with voiding. The ureterocele fills, acting like an obstructive wind sock. The lumen of the urethra is marked with the *arrow*.

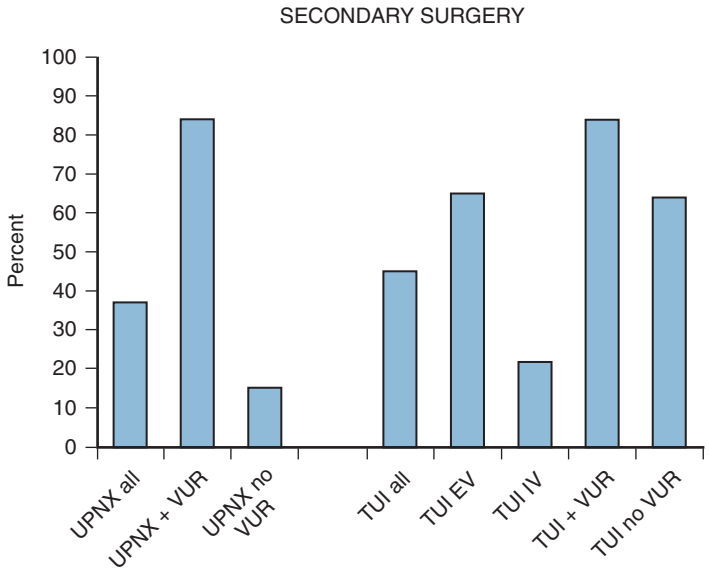


Figure 121–37. Chart showing incidence of secondary major surgery for patients with ureterocele following either transurethral incision or partial nephrectomy. The specific incidences are also shown when reflux is present or absent. Data are based on multiple reports as indicated in Table 121–1. EV, extravesical; IV, intravesical; TUI, transurethral incision; UPNX, upper pole nephrectomy; VUR, vesicoureteral reflux.

Table 121–1.

Options for Ureterocele Management

PROCEDURE	IDEAL INDICATIONS	ADVANTAGES	LIMITATIONS
Transurethral incision	Infant Large ureterocele with VUR	Outpatient procedure, effective decompression Occasionally definitive	May produce reflux into ureterocele segment, requiring bladder surgery
Upper pole nephrectomy	Older patient Large nonfunctioning upper pole No VUR	May be definitive Removes pathology Avoids bladder level surgery	May not be definitive Significant surgery Risk to lower pole May still require lower surgery in bladder
Ureteroureterostomy or ureteropyelostomy	Older patient Functioning upper pole No VUR	Drains obstructed segment with little risk of obstruction or UTI	Leaves ureterocele in bladder May develop reflux
Ureterocele excision and common sheath reimplantation	Reflux Functioning upper pole without significant dilation	Eliminates obstruction and reflux, removes ureterocele No renal risk	Complex surgery Risk to vagina and bladder neck May require ureteral tapering

UTI, urinary tract infection; VUR, vesicoureteral junction.

may therefore be less in the older child presenting with a massive upper pole in whom removal may be preferable and definitive surgery can be performed at diagnosis.

OTHER URETERAL ANOMALIES

Anomalies of Number

Bifid Ureters

Ureteral duplication may be associated with ectopia or a ureterocele but is also compatible with a normally functioning renal system if both ureters enter orthotopically or if there is partial duplication. Ureteral duplication is a common condition, described in approximately 1 in 125 (0.8%) people on the basis of autopsy series, which tend to be less selective (Nation, 1944). There is a slightly higher incidence in females, estimated to be approximately 1.6:1. Duplication is unilateral six times more than it is bilateral; however, **it is clinically prudent to carefully look for contralateral duplication when unilateral duplication is documented.** This may be critical in the setting of nonhydronephrotic upper poles and ureteral ectopic causing incontinence. Right and left sides appear to be affected similarly with unilateral duplication (Table 121–2).

A bifid renal pelvis includes only a single ureter, but confluence of the upper and lower ureters lower than the UPJ constitutes partial duplication of the ureter or bifid ureter.

An increased incidence of ureterorenal pathology has been documented with duplication anomalies. The clinical implication of duplication depends largely on the ureteral insertion. A useful clinical rule is to consider that **conditions that routinely affect the single-system kidney are those that affect the lower pole including UPJ obstruction and VUR. The upper pole is more likely affected by conditions due to abnormal ureteral formation including ectopia and ureterocele,** as previously discussed.

Lower pole UPJ obstruction (UPJO) evaluation and management are similar to a single-system UPJO. Lower pole UPJO may be identified with partial and complete ureteral duplication. Recognition of the presence of the duplication may be challenging with massive hydronephrosis, but in most cases the normal upper pole will be identified on functional imaging such as a renal scan, even if not detected on US. MRI can help clarify the anatomy in these cases. Lower pole UPJO may resolve spontaneously, just as a single system with comparable severity of dilation. Repair may be optionally accomplished using a pyeloureterostomy of the dilated renal pelvis of the lower pole to the normal upper pole ureter (Ulchaker et al, 1996; VanderBrink et al, 2009).

Upper pole UPJO has been reported including in association with lower pole UPJO but is exceptionally rare (Jain et al, 2008).

Hydronephrosis of the lower pole moiety may also represent VUR, and this is often of high grade. The presence of a dilated ureter on ultrasonographic evaluation will usually be present. This rarely represents ureterovesical obstruction and more often indicates VUR. Lower pole VUR is often associated with significant functional reduction in the lower pole, which is usually congenital but may also be associated with prior infection. Evaluation and management are similar to reflux into a single system, but spontaneous resolution may be more delayed (Afshar et al, 2005). Common sheath ureteral reimplantation and endoscopic injection are surgical options, as well as low ureteroureterostomy of the refluxing lower pole ureter to the upper pole ureter. Lower pole reflux associated with severe hydronephrosis and scant lower pole function may necessitate lower pole nephrectomy.

Triplication

Triplication of the ureter, either complete or partial, is rare. These conditions typically have presented with infection or wetting. The classification by Smith, in which triplex ureters are divided into four types, remains useful (Smith, 1946). Type 1 constitutes three entirely separate ureters with unique attachment to the bladder or distally and accounts for 35% of triplications. Type 2 is an incomplete separation with two ureteral orifices, occurring in 21%. Type 3 is a trifid ureter with a single ureteral orifice, seen in 31%, and type 4 describes two ureters with three orifices. This occurs with an inverted Y bifurcation. The positioning of the ureteral orifices generally follows the Weigert-Meyer law (Zaontz and Maizels, 1985).

The ureters may be associated with ureteroceles (Park, 2008) and may be ectopic to the bladder neck, urethra, or vagina (Engelstein et al, 1996; Patel et al, 2001). Lower and midpole (Sivrikaya et al, 2007) ureteropelvic junction obstruction may be present, as well as ureterovesical obstruction (Merlini, 1983). VUR is also described (Ander et al, 1997), as well as contralateral duplication (Srivastava et al, 1996). Fusion anomalies may be present in some (Pode et al, 1983; Golomb and Ehrlich, 1989).

Quadruple Ureters

Even more rare is ureteral quadruplication with only eight cases reported. Most have been in adults, but three recent cases included four ureters draining into a large ureteral cyst and connecting to the bladder through a single ureter (Klinge et al, 2001; Vicentini et al, 2007; Koszutski et al, 2008). One report of a young adult presenting with incontinence defines three of the four ureters merging and entering the bladder orthotopically and the fourth ureter drained to the perineum. This ectopic ureter was associated with the lower midcalyx, contrary to what the Weigert-Meyer law would predict.

Fibroepithelial Polyps

Polyps of the ureter may present clinically with flank pain, hematuria, or by incidental detection of hydronephrosis. The most common site of attachment is at the UPJ, although polyps may originate from any part of the ureter. As a cause of UPJ obstruction, they are uncommon, reported as 0.5% of all UPJ cases undergoing pyeloplasty (Adey et al, 2003). A large majority were male (89%) and on the left side (78%). They are uncommonly bilateral, but this has been reported with clinical effects on both kidneys (Bartone et al, 1990; Lavelle et al, 1997; Bhalla et al, 2002; Adey et al, 2003). In a recent series, two of nine patients had bilateral clinically obstructive UPJ polyps. They may also be multiple. The authors have seen one case in which the polyp protruded from the urethra and produced severe voiding symptoms. The polyp was ultimately found to originate from the proximal third of the ureter.

Smaller polyps may not be evident on modern imaging, and in a recent series they were detected in 22% of cases preoperatively for UPJ obstruction (Adey et al, 2003). They would usually be seen on intravenous pyelography but may be mistaken for ureteral blood clots, particularly in the setting of hematuria (Fig. 121–38). Filling defects on retrograde pyelography in anticipation of a pyeloplasty should trigger a search for the polyps. It is unlikely that this would alter the surgical approach unless the polyp was significantly distal to the UPJ.

Table 121–2.

Ureteral Duplication: Clinical, Radiographic, and Autopsy Studies

STUDY	DATABASE		NO. DUPLICATIONS PARTIAL	F	M	UNILATERAL	BILATERAL	COMPLETE	PARTIAL	UNILATERAL/ COMPLETE PARTIAL	BILATERAL COMPLETE/ PARTIAL	BILATERAL MIXED
Archangelskj, 1926	110	R	619			502 (80%)	117 (20%)					
		A	3 (2.7%)									
Colosimo, 1938	1500	X	50 (3.3%)	88 (6.8%)								
Nation, 1944	16,000	A	109 (0.68%)	*(63%)	*							
		C	121	88 (73%)	33	177 (77%)	53 (23%)	102 (44%)	118 (51)	78 (44%)/99 (56%)	35 (45%)/19 (36%)	10 (4.3%)
Nordmark, 1948	4744	X	138 (2.8%)			119 (86%)	19 (14%)	70 (51%)	65 (47%)	59/60	11/5	3 (2.1%)
Payne, 1959		C	141	87 (62%)	54	120 (85%)	21 (15%)	45	78 + 18 bifid pelvis			
	5000	X	83									
Johnston, 1961		C	73					63 (77%)	19 (33%)			
		A	9	57 (70%)	25							
Kaplan and Elkin, 1968	(Partial duplications only)	X	51	33 (65%)	18	43 (84%)	8 (16%)					
Campbell, 1970	51,880 (19,046 children) (32, 834 adults)	A	342 (0.65%) 61 (0.32%) 281 (0.85%)			293 (85%)	53 (15%)	101 (30%)			4	"1 in 5 cases"
Timothy et al, 1971		C	46	39 (85%)	7			24 (52%)	16 (35%)	13/15	11/1	6 (13%)
Privett et al, 1976	5196 (1716 children; 3480 adults [2896 male; 2300 female])	X	91 (1.8%)	63 (66%)	32	79 (85%)	16 (15%)	33 (29%) (but 21 not known)	57 (52%)			

*See text.

A, autopsy; C, clinical; R, review; X, x-ray.

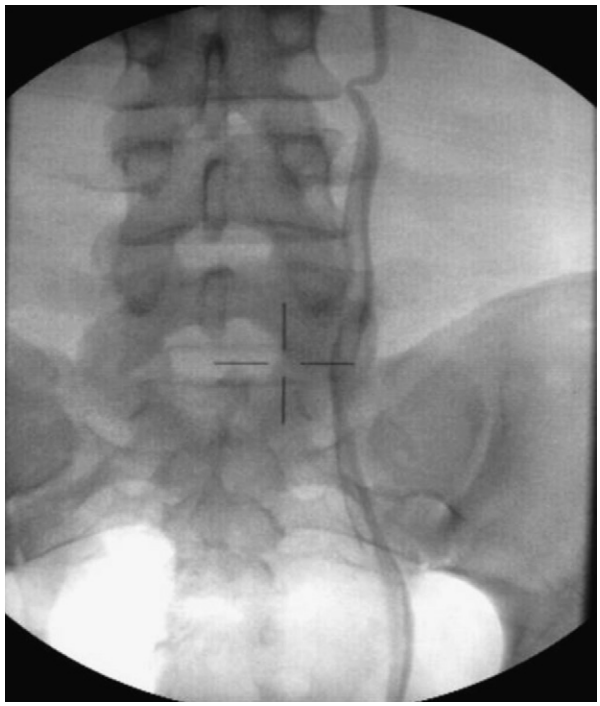


Figure 121–38. Retrograde ureterogram of adolescent with a history of hematuria, dysuria, and a fleshy mass protruding from her urethra. The distal segment had been resected by an outside physician. The long-filling defects are typical of fibroepithelial polyps but may be confused for blood clots.

Key Points: Other Ureteral Anomalies

- Ureteral duplication is compatible with a normally functioning renal system if both ureters enter orthotopically or if there is partial duplication.
- It is clinically prudent to look for contralateral duplication when unilateral duplication is documented.
- An increased incidence of ureterorenal pathology has been documented with duplication anomalies.
- Conditions routinely affecting a single-system kidney are those that affect the lower pole including UPJ obstruction and VUR. The upper pole is more likely affected by conditions due to abnormal ureteral formation including ectopia and ureterocele.
- Polyps of the ureter may present clinically with flank pain, hematuria, or by incidental detection of hydronephrosis.
- The most common site of attachment of fibroepithelial polyps is at the ureteropelvic junction, although they may originate from any part of the ureter.
- UPJ polyps are best treated with pyeloplasty, although the question of whether endoscopic resection might suffice is not settled.
- Ureteroscopic removal of ureteral polyps is the recommended therapy away from the UPJ.

The etiology of fibroepithelial polyps is unclear, although progressive traction due to ureteral peristalsis may promote edema and growth. The senior author has seen one in which the ureter was being intussuscepted into itself due to traction on the polyp in the midureter. Histologically, they are considered benign neoplasms with fibroepithelial and vascular elements, with overlying normal to hypertrophied urothelium. There is usually a fibrovascular core with significant stromal edema. Little inflammation is seen.

Management of the polyp is dictated by the presentation and location. **For polyps at the UPJ, most have undergone pyeloplasty, although the question of whether simple endoscopic resection might suffice is not settled because there are too few cases. Ureteroscopic removal of ureteral polyps is the recommended therapy away from the UPJ on the basis of combined adult and pediatric reports** (Minevich et al, 2005; Childs et al, 2009). Earlier reports advocated sleeve resection and reanastomosis of the ureter to prevent recurrence, yet the persisting success with ureteroscopic resection would suggest that to be unnecessary. Even earlier reports recommended nephrectomy, which cannot be justified.

ANOMALIES OF POSITION

Vascular Anomalies Involving the Ureter

A variety of vascular lesions can cause ureteral obstruction. With these lesions, the vascular system rather than the urinary system is anomalous. With the exception of accessory renal blood vessels, all of these lesions are relatively uncommon, although all have clinical relevance.

Preureteral Vena Cava

Anatomy

This anomaly is commonly known to urologists as circumcaval or retrocaval ureter, terms that are anatomically descriptive but misleading in regard to development (Lerman et al, 1956; Dreyfuss, 1959). **The term *preureteral vena cava*** emphasizes that the circumcaval ureter results from altered vascular, rather than ureteral, development. This is the more accurate term.

This disorder involves the right ureter, which typically deviates medially behind (dorsal to) the inferior vena cava, winding about and crossing in front of it from a medial to a lateral direction, to resume a normal course, distally, to the bladder. The renal pelvis and upper ureter are typically elongated and dilated in a J or fishhook shape before passing behind the vena cava. The collecting system is not inevitably obstructed. Circumcaval ureters can be classified into two clinical types (Bateson and Atkinson, 1969; Kenawi and Williams, 1976): (1) the more common type 1 has hydronephrosis and a typically obstructed pattern demonstrating some degree of fishhook-shaped deformity of the ureter to the level of the obstruction and (2) type 2 has a lesser degree of hydronephrosis or none at all. Here, the upper ureter is not kinked but passes behind the vena cava at a higher level, with the renal pelvis and upper ureter lying almost horizontal before encircling the vena cava in a smooth curve. In type 1, the obstruction appears to occur at the edge of the iliopsoas muscle, at which point the ureter deviates cephalad before passing behind the vena cava.

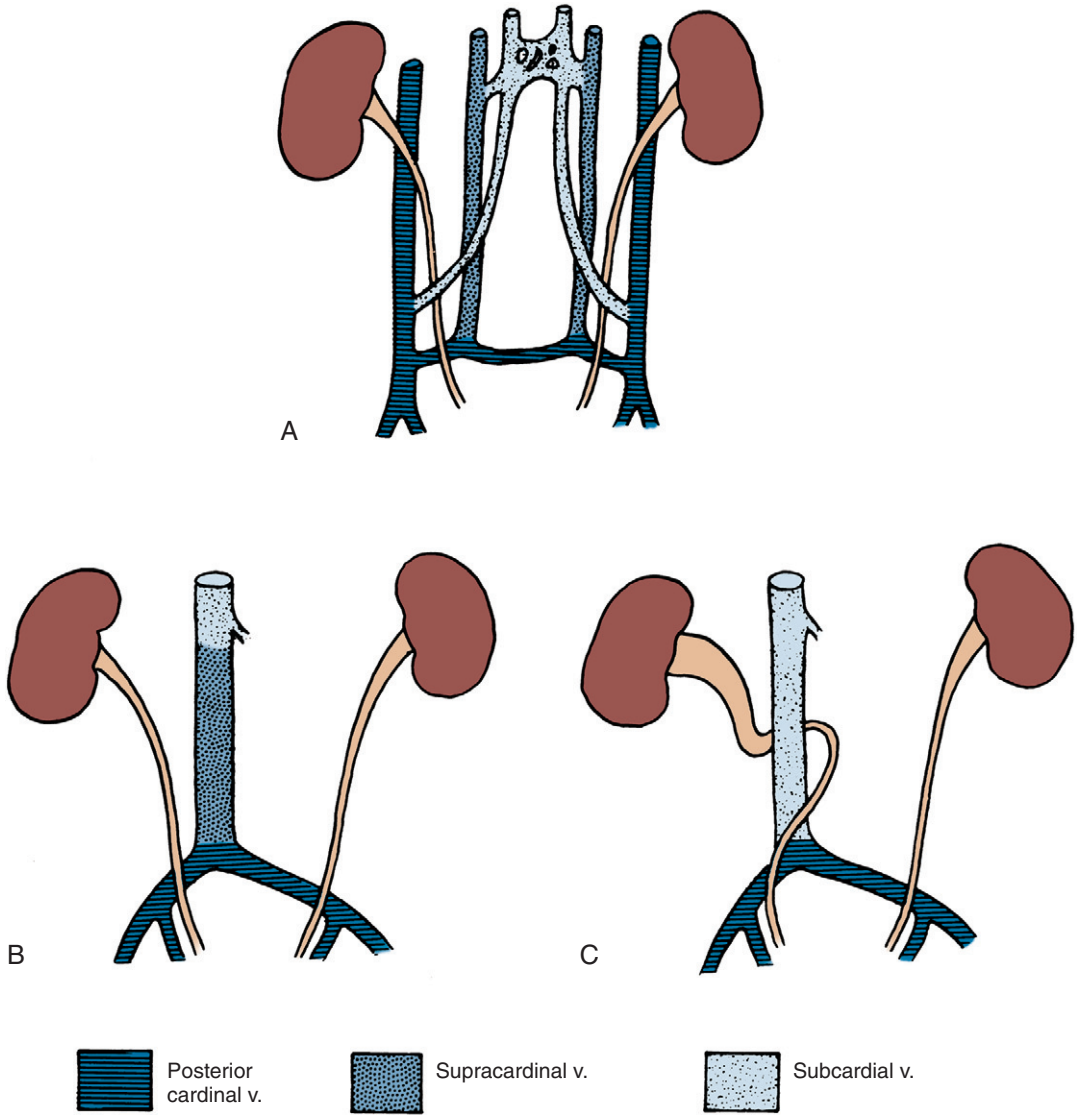


Figure 121–39. Fetal venous ring **(A)**, normal vena cava **(B)**, and preureteric vena cava **(C).** (Redrawn from Hollinshead WH. Anatomy for surgeons, vol 2. New York: Hoeber Medical Division of Harper and Row; 1956.)

Embryology

The definitive inferior vena cava develops on the right side from a plexus of fetal veins (Fig. 121–39). Initially, the venous retroperitoneal pathways consist of symmetrically placed vessels, both central and dorsal. The posterior cardinal and supracardinal veins lie dorsally, and the subcardinal veins lie ventrally. These channels, with their anastomoses, form a collar on each side through which the ascending kidneys pass. Normally, the left supracardinal veins and the lumbar portion of the right posterior cardinal vein atrophy. The subcardinal veins become the internal spermatic veins. The definitive right-sided inferior vena cava forms from the right supracardinal vein. **If the subcardinal vein in the lumbar portion fails to atrophy and becomes the primary right-sided vein, the ureter is trapped dorsal to it.**

When the definitive vena cava forms normally and the ventral portion of the primitive ring also persists, a double right vena cava is formed because of the persistence of both the right subcardinal vein dorsally and the right subcardinal vein ventrally. This double vena cava traps the right ureter between its limbs (Sasai et al, 1986).

Although bilateral vena cava or left-sided vena cava can occur (Clements et al, 1978; Mayo et al, 1983), a bilateral circumcaval ureter has been described in a case of situs inversus (Brooks, 1962). In cases of bilateral vena cava associated with a circumcaval ureter, the circumcaval ureter has been reported only on the right side, denoting that the right vena cava developed abnormally from a persistent subcardinal vein, whereas the left vena cava developed from the left supracardinal vein but otherwise normally (Pick and Anson, 1940).

Incidence

The incidence of preureteral vena cava at autopsy is about 1 in 1500 (Heslin and Mamonas, 1951), and the anomaly is three to four times more common in male than female cadavers. A literature review reported a ratio of 114:41 males to females (2.8:1) (Kenawi and Williams, 1976).

The symptoms of preureteral vena cava are those of obstruction. **Although the lesion is congenital** (Soundappan and Barker, 2004; Acharya et al, 2009)**, most patients do not present until the third or fourth decade of life** (Kenawi and Williams, 1976).

Diagnosis

Clinically, patients may present with symptoms of flank or abdominal pain or infection or the disorder may be discovered incidentally during other radiologic tests. Excretory urography often fails to visualize the portion of the ureter beyond the J hook (i.e., extending behind the vena cava), but retrograde ureteropyelography demonstrates an S curve to the point of obstruction with the retrocaval segment lying at the level of L3 or L4 (Kenawi and Williams, 1976). Cavography is no longer a necessary diagnostic test.

US (Murphy et al, 1987) and CT or MRI have also been useful in defining the vascular malformation. CT urography may be the procedure of choice to confirm the diagnosis and avoid retrograde ureteropyelography (Sasai et al, 1986; Kellman et al, 1988). Nuclear renal furosemide scanning can categorize the anomaly as obstructed or nonobstructed (Pienkny et al, 1999). **MRI can demonstrate the course of a preureteral vena cava and may be a more detailed and less invasive imaging modality when compared with CT and retrograde pyelography** (Uthappa et al, 2002).

Treatment. Surgical correction involves ureteral division, with relocation and ureteroureteral or ureteropelvic reanastomosis, usually with excision or bypass of the retrocaval segment, which can be aperistaltic. It is important to be mindful of the ureter's blood supply from the renal artery and aorta superiorly and the iliac vessels inferiorly. As stated earlier, the preferred approach for the obstructed ureter is ureteral division and relocation. Laparoscopic (Miyazato et al, 2002; Ramalingam and Selvarajan, 2003; Tobias-Machado et al, 2005; Fernandez-Fernandez and Pachano-Arenas, 2008) and robotic (Gundeti et al, 2006; Smith et al, 2009) reconstruction of the ureter in a preureteral vena cava has been described both via the transperitoneal and retroperitoneal approaches in children.

OTHER ANOMALIES OF POSITION

Several instances of horseshoe kidney have been reported (Cukier et al, 1969; Cendron and Reis, 1972; Heffernan et al, 1978; Taguchi et al, 1986). Anomalies include a variety of left renal anomalies such as agenesis, hydronephrosis, malrotation, and hypoplasia (Kenawi and Williams, 1976). An obstructing branch of the right spermatic vein and a lumbar vein have mimicked circumcaval ureteral obstruction (Dreyfuss, 1959; Psihramis, 1987), as has an anomalous tendon of the iliopsoas muscle (Guarise et al, 1989).

Key Points: Preureteral Vena Cava (Circumcaval Ureter, Retrocaval Ureter)

- This disorder involves the right ureter, which typically deviates medially behind (dorsal to) the inferior vena cava, winding about and crossing in front of it from a medial to a lateral direction, to resume a normal course to the bladder.
- If the subcardinal vein in the lumbar portion fails to atrophy and becomes the primary right-sided vein, the ureter is trapped dorsal to it.
- Patients may present with symptoms of flank or abdominal pain or infection, or the disorder may be discovered incidentally.
- Surgical correction involves ureteral division, with relocation and ureteroureteral or ureteropelvic reanastomosis, usually with excision or bypass of the retrocaval segment, which can be aperistaltic.

Preureteral Iliac Artery (Retroiliac Ureter)

A ureter coursing behind the common iliac artery is rare (Corbus et al, 1960; Seitzman and Patton, 1960; Hanna, 1972; Radhkrishnan et al, 1980). Either side can be involved; in two cases, the condition was bilateral (Hanna, 1972; Radhkrishnan et al, 1980). Obstruction occurs at the level of L5 or S1 as the ureter is compressed behind the artery. Coexisting anomalies are common (Nguyen et al, 1989), particularly vasal anomalies (Seitzman and Patton, 1960; Radhkrishnan et al, 1980).

Like the preureteral caval, the preureteral iliac artery is considered to be of vascular origin without definitive proof. Normally, the primitive ventral root of the umbilical artery is replaced by development of a more dorsal branch between the aorta and distal umbilical artery. Persistence of the ventral root as the dorsal root fails to form traps the ureter dorsally.

Ureteral or mesonephric duct ectopia is often present (Nguyen et al, 1989). The case of Seitzman and Patton involved an ectopic ureter that emptied, along with the ipsilateral vas deferens, via a persistent common mesonephric duct into the proximal posterior urethra (Seitzman and Patton, 1960). In the case of Radhrishnan and colleagues, bilateral retroiliac ureters also involved bilateral ectopic termination of the vasa deferentia into the ureters (Radhkrishnan et al, 1980). Iuchtman and colleagues (1980) described ectopic vaginal termination of the involved ureter, with urometrocolpos from an imperforate hymen.

Taibah and colleagues (1987) reported the unusual finding of left ureteral obstruction from a retrointernal iliac artery ureter in an otherwise normal young woman.

Vascular Obstruction of the Distal Ureter

Obstruction of the distal ureter from uterine, umbilical, obturator, and hypogastric vessels close to the bladder has been described (Campbell, 1936; Young and Kiser, 1965; Scultety and Varga, 1975). However, it is not always clear that vascular impressions on a dilated ureter are the cause of the obstruction. At times, these findings may be an artifact, as when a dilated ureter from an intrinsic obstruction is secondarily compressed against the adjacent vessel. Judging from the paucity of contemporary reports describing this lesion, it is likely that primary terminal ureteral obstruction by vascular lesions is a rare occurrence.

Herniation of the Ureter

Herniation of the ureter is another extremely rare condition. Dourmashkin (1937) searched the literature and tabulated a series of inguinal, scrotal, and femoral herniations of the ureter. Most of these were paraperitoneal (i.e., a loop of herniated ureter extended alongside a peritoneal hernial sac). Only a minority were extraperitoneal (i.e., with no hernial sac present). In paraperitoneal ureteral hernias, the ureteral loop is always medial to the peritoneal sac. Of six scrotal hernias, four did not have peritoneal sacs. When the ureter extended into the scrotum, it was more likely to be dilated, causing upper tract obstruction.

In children, herniated ureters have presented with hydronephrosis, associated with megaureters and persistent hydronephrosis after posterior urethral valve ablation (Jewett and Harris, 1953; Powell and Kapila, 1985; Burgu et al, 2009).

Internal hernias of the ureter are even more exceptional. Reports have been published of a sciatic hernia containing a ureter (Oyen et al, 1987; Witney-Smith et al, 2007; Tsai et al, 2008; Hsu et al, 2010), herniation between the psoas muscle and iliac vessels (Page, 1955), and lumbar triangle herniation (Cabello et al, 2008). Ureteral herniation with obstruction has been reported as a rare complication of renal transplantation (Ingber et al, 2007).

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chapter 122

Vesicoureteral Reflux

Antoine E. Khoury, MD, FRCSC, FAAP ●
Darius J. Bägli, MDCM, FRCSC, FAAP, FACS

Historical Perspective

Vesicoureteral reflux (VUR) represents the retrograde flow of urine from the bladder to the upper urinary tract. VUR is a common clinical entity. Its clinical challenges arise from the fact that it is usually asymptomatic. When it is not, however, it is responsible for pyelonephritic scarring and can be associated with congenital renal dysmorphism. There are many unresolved issues regarding the etiology, diagnosis, and management of VUR. This chapter attempts to reconcile some of these areas by interpreting the best available information in the literature. Some areas, however, will continue to await more rigorous study. Some may remain unresolved for quite some time.

HISTORICAL PERSPECTIVE

VUR has a unique distinction of having evolved from an anatomic curiosity around the first century AD into one of the most contentious and complex areas of urology today. Galen and da Vinci made the first references to VUR by Western Medicine when they alluded to the ureterovesical junction (UVJ) as a mediator of unidirectional flow of urine from the kidneys to the bladder. Although VUR was first demonstrated to be a normal finding in dogs and rabbits (Semblinow, 1907), it was a gynecologic misadventure. It revealed that VUR in human adults may not be a normal state (Pozzi, 1893). Sampson, in 1907, suggested that the oblique course of the ureter through the bladder wall created a locking mechanism at the UVJ and was also the first to imply that VUR might lead to renal infection. Although it was not possible to uniformly demonstrate VUR in all people in cadaveric studies (Young, 1989), it was not until the UJV had been more clearly dissected that it was realized the incidence of VUR varied with the length of the ureter's obliquity in the bladder and the formation of the trigone (Gruber, 1929).

Pivotal discoveries occurred when Hutch (1952) reported on a relationship between VUR and chronic pyelonephritis in paraplegic patients and Hodson (1959) observed that urinary tract infection (UTI) and renal scarring carried a high likelihood of VUR in children.

Two seminal bodies of work defined the modern era of VUR. The first, the work of Ransley and Risdon (1979), defined the pathophysiology of reflux nephropathy by demonstrating the relationship among infection, reflux, and pyelonephritic scarring. Secondly, these observations complemented the clinical studies of Smellie (1991) and colleagues, who galvanized the related concepts inherent in clinical UTI, bacterial pyelonephritis, renal scarring, and VUR. In 1985 a consensus system for the grading of reflux was published by Lebowitz and colleagues (1985) on the basis of the International Reflux Study Group's deliberations.

Until recently, the virtues of medical therapy to avert infections and surgical therapy to correct reflux itself have been evenly debated for more than 20 years. However, the recent introduction of the biodegradable cross-linked polysaccharides dextranomer and stabilized hyaluronic acid for use in injectable endoscopic correction of reflux, as well as re-examination of the basis for medical therapy and the risks of reflux, have initiated a re-examination of virtually all aspects of reflux. From the age-related impact of reflux, through use of antibiotics for medical prophylaxis, invasiveness of cystography, and traditional indications for surgery, the impact of reflux and its management are being openly explored. Although the fundamental biologic importance of reflux disease is not in question, many facets of how reflux diagnosis and management are approached may take new shape in the coming decade.

Demographics

Prevalence

The tendency for VUR to resolve spontaneously on the one hand or persist beyond its natural resolution rate due to abnormal bladder dynamics makes it difficult to confidently generalize the true prevalence of reflux from a given population. In one meta-analysis of studies of children undergoing cystography for various indications (Sargent, 2000), the prevalence of reflux was estimated to be approximately 30% for children with UTI and 17% without infection. **In contrast, reflux may be present in up to 70% of infants who present with UTI** (Baker et al, 1966). In a population of 157 adults investigated for incidental hypertension without any evidence of renal abnormality, the prevalence of VUR was estimated to be 19%, with high-grade reflux in more than half of the refluxing group (Barai et al, 2004). Reflux is relatively uncommon in adult males (Chapple et al, 1990). In asymptomatic infants followed up for antenatal hydronephrosis, the prevalence of reflux ranges from 15% in infants with absent or mild hydronephrosis on postnatal ultrasound (Phan et al, 2003) to 38% in a group of neonates with various postnatal upper tract sonographic anomalies including hydronephrosis, renal cysts, or renal agenesis (Zerin et al, 1993).

Gender

Differences in reflux rates between males and females may suggest a sexual dichotomy in the function of the lower urinary tract, bladder outlet, and urethra. In one study of 117 infants assessed for reflux following fetal upper tract dilation, 76% of refluxing infants were male (Ring et al, 1993). In later life, the likelihood of having reflux if presenting with a UTI is higher if male than female

(Shopfner, 1970), even though the great majority (85%) of prevailing reflux in older children is in females. A confounding factor in understanding true gender differences in reflux between males and females is the gender-driven predisposition to UTI. Uncircumcised male infants show a 12-fold greater risk for UTI than circumcised males, as well as a greater propensity for harboring periurethral uropathogenic flora (Wiswell et al, 1988; Wiswell and Hachey, 1993). The greater incidence of UTI will necessarily invite more frequent evaluation and therefore detection of VUR in this population. It is not known whether the incidence of reflux detection would rise in females if they were to be incidentally evaluated for reflux as often as infant males. In a related finding, only 10% of patients entered into the International Reflux Study in Children from the United States were boys compared with 24% entered from Europe. The circumcision rate in the latter group was only 5% compared with 62% in the U.S. group ($P < .001$) (Weiss et al, 1992b).

Reflux in the Fetus

Most studies of fetal reflux do not in fact detect reflux per se in the fetus but relate fetal hydronephrosis parameters to reflux in the neonatal period. However, fetal hydronephrosis is common, often resolves, and has low specificity for postnatal VUR. Nevertheless, fetal hydronephrosis is commonly associated with postnatally detected reflux. Zerin described a 38% detection rate of reflux in 130 neonates with prenatal hydronephrosis (Zerin et al, 1993). In 19% the reflux was bilateral. It is suggested that the lower the threshold for defining hydronephrosis (in millimeters of pelvic diameter) in the fetus, the more often reflux will be detected postnatally (Anderson et al, 1997). This leads to speculation as to whether reflux is a normal variant in the population but becomes clinically relevant only in some because of a predisposition to UTI, a conclusion supported by the observation that reflux without infection is of questionable clinical significance. Boys appear to harbor postnatal reflux more commonly—a 6:1 male-to-female ratio was reported in one study of 27 cases (Marra et al, 1994). The highest grades of reflux are most commonly associated with renal scintigraphic abnormalities. In many cases, even in the absence of any infection history from birth, the presence of a small kidney with globally reduced scintigraphic function may indicate that such renal scintigraphic abnormalities may be associated with a developmental ureteral bud abnormality associated with high-grade reflux or secondary to the reflux itself (Oliveira et al, 1998; Stock et al, 1998).

Age

As stated previously, because the natural history of reflux involves spontaneous resolution over time, it is self-evident that less primary reflux would be prevalent in older children compared with infants (Table 122–1). Even in the presence of infection or asymptomatic bacteriuria, reflux is more common in younger patients (Smellie, 1991).

Table 122–1.

Incidence of Reflux in Patients with Urinary Tract Infections

AGE (yr)	INCIDENCE (%)
<1	70
4	25
12	15
Adults	5.2

From Baker R, Maxted W, Maylath J, et al. Relation of age, sex, and infection to reflux: data indicating high spontaneous cure rate in pediatric patients. J Urol 1966;95:27.

Race

Little is known about racial predisposition to reflux worldwide because reflux studies have generally been restricted to western countries. **One difference established over several studies is the relative 10-fold lower frequency of reflux in female children of African descent** (Skoog and Belman, 1991; Chand et al, 2003). In addition, reflux resolved sooner in this population ($P < .005$). In a series of non-Caucasian children with a 4:1 male-to-female ratio, 58% of whom were younger than 1 year of age presenting with UTI (72%), voiding difficulties (10%), or other malformations (14%), reflux was present in only 10% (West and Venugopal, 1993). Even in follow-up of antinatal hydronephrosis, reflux was found in 17.6% of 51 nonblack versus 0% of 58 black infants (Horowitz et al, 1999). Such differences may involve a delay in maturation of the antireflux mechanism in Caucasian patients as the race-associated frequency of reflux becomes equal regardless of race after 10 years of age (Melhem and Harpen, 1997).

Inheritance and Genetics

Sibling Reflux

A recent meta-analysis of sibling reflux studies suggests the prevalence of VUR in siblings to be approximately 32% (Hollowell and Greenfeld, 2002). However, the prevalence may be as low as 7% in older siblings (Connolly et al, 1996) or as high as 100% in identical twin siblings (Kaefer et al, 2000). **The latter finding undeniably supports the notion that VUR can be an inherited condition** and that the genetic mode of transmission may be autosomal dominant. Although a heightened prevalence of reflux exists in siblings of refluxing index patients, the natural history of reflux would suggest that siblings who are older harbor reflux less often compared with relatively younger siblings because of spontaneous reflux resolution (Connolly et al, 1996). However, none of the existing sibling studies rigorously state whether the prevalence of sibling reflux is dependent on whether the sibling is younger or older than the index patient herself. By virtue of its detection by screening, sibling reflux is usually asymptomatic at the time of diagnosis. Furthermore, the tendency for reflux to have resolved before any renal changes such as focal scarring detected by imaging can be reliably ascribed to the reflux itself further complicates the management of reflux in siblings. These clinical features underscore the difficulties inherent in formulating meaningful recommendations for the management of sibling reflux detected by screening.

Much of the concern for sibling reflux detected by screening stems from reports of renal abnormalities detected by ultrasound or nuclear scintigraphy in these patients.

In one retrospective study of 123 screened siblings, 44 (36%) demonstrated VUR on voiding cystography (Houle et al, 2004). Thirty-seven of these patients underwent renal imaging. Ultrasound was abnormal in 30% and renal scintigraphy, when used, was abnormal in 28%. However, in siblings older than 2 years, renal scintigraphic abnormalities were twice as common as in the entire group of siblings. The authors concluded that renal damage is therefore progressive in the older siblings and proposed earlier screening of siblings of refluxing index patients. However, this study fails to address the fact that renal damage or aberrant formation may have occurred very early and over time (beyond 2 years of age), renal growth may have exaggerated the appearance of such scintigraphic abnormalities. Scintigraphic results may become

exaggerated by normal cortical growth surrounding a scarred region that has failed to grow or by compensatory hypertrophy of a contralateral kidney. **The missing link is a prospective scintigraphic or sonographic follow-up of asymptomatic refluxing infant sibling children from birth onward.** Finally, the reporting of scintigraphic results by many sibling reflux studies is confounded by failing to differentiate between aberrant renal development often associated with higher grades of reflux and true scarring secondary to infection and inflammation. Moreover, the ability to modulate the course of the processes that mediate congenital dysplasia is not possible presently, as it is with scarring. In the absence of such data and faced with the invasive nature of the gold standard test for reflux, the cystogram, one is left with the following questions.

Is asymptomatic reflux in a sibling of clinical concern? If the propensity for UTI itself, with or without VUR, could reliably be determined to be genetically regulated, it would strengthen the case for screening for reflux in a sibling. Because biologic infection propensity cannot be reliably determined in either an index patient or his or her sibling, the mere likelihood of developing a UTI cannot be used to support screening siblings for reflux. Therefore one must rely on the aggregate clinical information available for the sibling in question. **Because it is renal consequences of reflux that are at issue, rather than reflux itself, siblings may be better served by noninvasively screening for cortical abnormalities first, before screening for reflux itself.** The intensity of renal assessment, using ultrasound for general screening or a nuclear scan for highest accuracy, could then be tempered by clinical factors including family history, patient and family compliance with follow-up, blood pressure, a history of UTIs and fevers, and voiding dysfunction. The absence of renal structural abnormalities would allow the clinician to conclude that reflux, if present, has not yet been of any renal consequence.

Should screening depend on sibling age? Because the risk for new renal scarring following pyelonephritis is lower in children older than 5 years of age, older siblings would likely suffer fewer consequences from a recent reflux-induced pyelonephritis and therefore stand to benefit less from confirming a diagnosis of reflux and instituting antibiotic prophylaxis than an infant or younger sibling. Nevertheless, a history of untreated febrile infections would support a decision to consider renal assessment or even obtain a cystogram in an older sibling.

Thus by imaging the kidneys first followed by assessing the integrity of the ureterovesical junctions, a rational top-down approach to sibling reflux screening emerges. Such an approach helps to strike a balance between the invasive nature of reflux detection and classic commitment to prophylaxis versus first detecting existing renal cortical abnormalities that might be the result of past or ongoing reflux. If consideration of age and renal integrity is combined, a possible graded approach to screening can be developed for siblings older or younger than 5 years of age, with or without renal structural abnormalities. The proximate urologic and voiding history must also play a deciding role in whether a sibling is ultimately screened by cystography for VUR. Thus in siblings 5 years or older with normal kidneys, little would be gained from detecting reflux that could not be addressed by responding to a febrile UTI in the usual fashion as for the general pediatric population. Indeed, the knowledge that the index patient has VUR might heighten the attention to family or self-reporting regarding urinary symptoms in the older sibling. In siblings 5 years or older with renal abnormalities, the suggestion would be of past or continuing reflux. Ruling the diagnosis in or out by cystography could then depend on prevailing voiding habits and proximate urologic history. The sibling younger than 5 years of age with normal kidneys would be managed on the basis of clinical judgment regarding likelihood for infection rather than an immediate need to diagnose reflux. The sibling younger than 5 years with cortical renal defects would have the most to lose by a febrile infection in the face of reflux and attendant risk of additional cortical loss following reflux-induced pyelonephritis triggered by an infection. In this case, knowledge of the potentially higher prevalence of reflux in siblings would logically support obtaining a screening cystogram. In any sibling, if reflux is diagnosed, the indications for reflux correction remain the same as for the general refluxing pediatric population.

Genes Involved

In addition to sibling reflux, a prospective screen of progeny of refluxing patients revealed a 66% rate of reflux in the offspring (Noe et al, 1992), which further strengthens the notion of an autosomal dominant component to the genetic mechanism of reflux. The substantially higher rate of reflux in siblings and progeny of index patients than in the general population defines these patients as susceptible to renal morbidity. Segregation and linkage analyses have implicated a number of loci in the pathogenesis of VUR, though no specific gene product or functional role for these loci in reflux has yet been identified (Chapman et al, 1985; Feather et al, 2000). Several studies have used a morphogenetic approach to search for candidate genes, which may underlie VUR. The original ureteral budding studies of Mackie and Stephens (1975), which correlate the position of ureteral budding from the mesonephric (wolffian) duct with that of the final ureteral orifice (UO), provide a modern basis for a genetic interpretation of VUR. Several genes have been observed to regulate these developmental processes and, by extension, are believed to serve as potential regulators of ureterovesical junction integrity. Indeed, genetic misregulation of ureteral budding is believed to underlie many congenital anomalies of the kidney and urinary tract (often referred to as CAKUT) (Miyazaki and Ichikawa, 2003). *PAX2* is a transcription factor regulating kidney, central nervous system, and ocular development in mice. It is necessary for ureteric budding in mice (Keller et al, 1994). *PAX2* is located on human chromosome 10q, and mutations have been reported in human syndromes involving colobomas and renal anomalies including hypoplasia, dysplasia, glomerulonephritis, and VUR (Sanyanusin et al, 1995). However, *PAX2* has not been shown to be a major determinant of primary VUR (Choi et al, 1998; Cunliffe et al, 1998). Glial-derived neurotrophic factor (Gdnf) and its receptor RET show strong involvement in ureterovesical junction formation in mice (Yu et al, 2004). Overexpression of RET in mice leads to abnormal placement of the ureteral bud and is associated with a 30% incidence of VUR at birth compared with 4% in wild-type mice. Nevertheless, the Gdnf RET signaling complex has not been found to mediate VUR in humans (Shefelbine et al, 1998). Another fascinating animal model of VUR is observed following depletion of the uroplakin III gene (Hu et al, 2000). However, no structural uroplakin III gene alterations have been noted in human cohorts with VUR (Giltay et al, 2004; Jiang et al, 2004). One explanation for this current finding may be that major uroplakin mutations are developmentally lethal in humans. Finally, members of the renin-angiotensin family of proteins have been implicated in several renal and ureteral developmental anomalies including ureteropelvic junction (UPJ) obstruction and megaureter (Hohenfellner et al, 1999). Although associations between angiotensin receptor-2 (Agtr2) (Yoneda et al, 2002) and angiotensin-converting

enzyme (ACE) (Liu et al, 2004) genes with VUR have been sought, no definitive etiologic link with VUR has been found. Notwithstanding an observed pattern of autosomal dominant inheritance in some families, the failure to identify any strong genetic mechanism in primary VUR in humans despite the presence of convincing animal genetic models of reflux argues for a more complex polygenetic mechanism of disease in humans.

Embryology of the Ureterovesical Junction

A full discussion of the embryology of the trigone and ureteric orifice is found elsewhere in the text. In brief, two events proceed simultaneously to govern the ultimate position and integrity of the UVJ. At one point, the embryonic ureter buds from the mesonephric or wolffian duct to define the metanephric duct or early fetal ureter. The wolffian duct (early vas deferens) and early ureter can be thought of as forming the two upper arms of a Y with the distal mesonephric duct as the stem of the Y. While budding is occurring, the distal mesonephric duct is being drawn and incorporated into the region of the urogenital sinus, which later becomes the bladder. Incorporation continues until the entire stem is absorbed, leaving the two arms of the Y to enter the bladder separately: one as the ureter and the other as the vas and ejaculatory duct in the male prostatic urethra (or the vestigial Gartner duct in the female vagina). The two arms of the Y also rotate relative to each other once they contact the urogenital sinus (UGS)/bladder wall resulting in the UO being proximal to the ejaculatory duct orifice. If the ureteral bud reaches the UGS too soon (believed to be due to early budding), over-rotation draws it high and lateral in the bladder wall, leading to inadequate incorporation, insufficient intramural length in the bladder wall, and reflux (Mackie et al, 1975). If the ureteral bud reaches the UGS too late (due to budding late), insufficient rotation occurs, resulting in an ectopic ureter that is drawn distally and medially, often obstructing in the bladder neck region or elsewhere. Furthermore, early or late budding is also thought to mistarget the contact between bud epithelium and the metanephros, leading to renal malformations, dysplasia, hypoplasia, or even agenesis.

Functional Anatomy of the Antireflux Mechanism

The phenomenon of vesicoureteral reflux represents a balance of several factors. Abnormality in any of these factors alone or in combination will allow or cause the retrograde flow of urine from the bladder up the ureter and ultimately to the renal pelvis and tubules. These factors include the functional integrity of the ureter, the anatomic composition of the ureterovesical junction (UVJ), and the functional dynamics of the bladder.

First, for purposes of reflux prevention, the ureter represents a dynamic conduit, which adequately propels the urine presented to it in a bolus fashion, antegrade, by neuromuscular propagation of peristaltic activity. In so doing, reflux is actively opposed. Moreover, if reflux were to occur, depending on its degree and timing, antegrade flow might be expected to keep refluxing urine from reaching the renal pelvis. The second component is the anatomic design of the UVJ. At the heart of this unique mechanism lies an intramural portion of ureter that travels within the detrusor muscle as it traverses the bladder wall (Fig. 122–1) (Elbadawi, 1972). At the extravesical bladder hiatus, the three muscle layers of the ureter separate. The outer ureteral muscle merges with the outer detrusor muscle to form Waldeyer sheath. The latter contributes to formation of the deep trigone. The intramural ureter remains passively compressed by the bladder wall during bladder filling, preventing urine from entering the ureter. Adequate intramural length and fixation of the ureter between its extravesical and intravesical points is required to create this antirefluxing

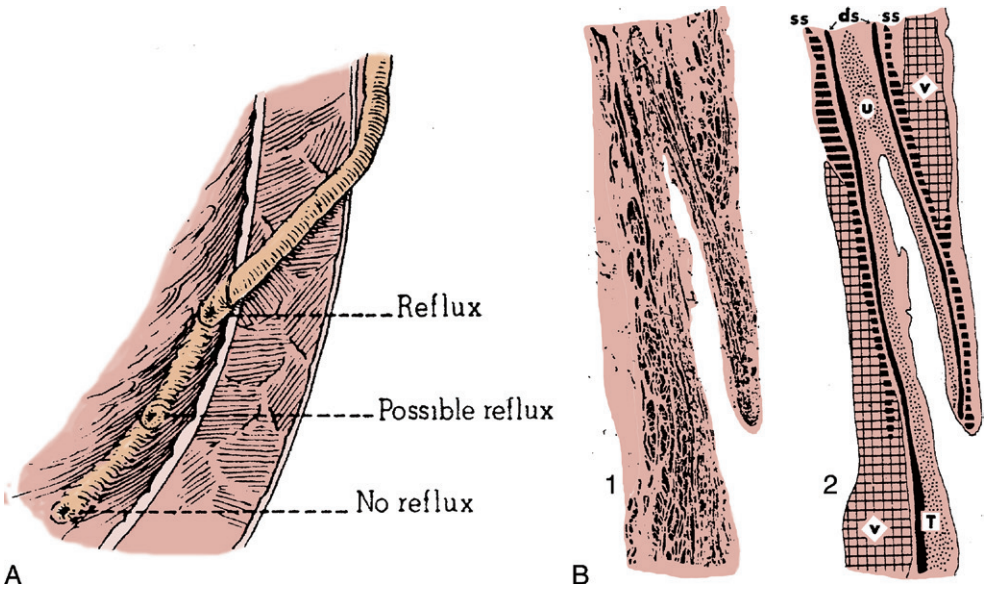


Figure 122–1. **A,** A refluxing ureterovesical junction has the same anatomic features as a nonrefluxing orifice, except for inadequate length of the intravesical submucosal ureter. Some orifices with marginal submucosal tunnels may reflux intermittently. **B,** Ureterovesical junction in longitudinal section. 1, Photomicrograph; 2, diagrammatic representation. The ureteral muscularis (u) is surrounded by superficial (ss) and deep (ds) periureteral sheaths that extend in the roof of the submucosal segment and continue beyond the orifice into the trigonal muscle (t). The relationship of the superficial sheath to the vesical muscularis (v) is clearly seen. Transverse fascicles in the superior lip of the ureteral orifice belong to the superficial and deep sheaths. No true space separates ureter from bladder. (**A,** From Glenn J, editor. Urologic surgery. 2nd ed. New York: Harper & Row; 1975; **B,** from Elbadawi A. Anatomy and function of the urethral sheath. J Urol 1972;107:224.)

Table 122–2.

Mean Ureteral Tunnel Length and Diameter in Normal Children

AGE (yr)	INTRAVESICAL URETERAL LENGTH (mm)	SUBMUCOSAL URETERAL LENGTH (mm)	URETERAL DIAMETER AT THE URETEROVESICAL JUNCTION (mm)
1-3	7	3	1.4
3-6	7	3	1.7
6-9	9	4	2.0
9-12	12	6	1.9

From Paquin AJ. Ureterovesical anastomosis: the description and evaluation of a technique. J Urol 1959;82:573.

compression valve. Paquin's early dissections of the UVJ in children revealed an approximately 5:1 ratio of tunnel length to ureteral diameter in nonrefluxing junctions compared with a 1.4:1 ratio in refluxing UVJs (Paquin, 1959) (Table 122–2). Intravesically, the inner muscle of the ureter merges with detrusor muscle to contribute to the superficial trigone. Some of these inner ureteral fibers pass medially to contribute to the intraureteric ridge (Mercier bar). The cellular and molecular details that characterize normal and refluxing UVJs are still unknown. However, it is likely that in addition to architectural deficiencies of tunnel length, abnormalities in UV smooth muscle and extracellular matrix composition and neural function may contribute to reflux (Oswald et al, 2004).

Opening of the UVJ is achieved by active contraction of the longitudinal muscles within the tunnel. This draws the extravesical and intravesical points of the intramural ureter closer together, shortening and widening the tunnel, and allows passage of the urine bolus into the bladder. Indeed, when viewed cystoscopically, a lateral displacement of the UO accompanies the classic jet of urine into the bladder. Although such lateral displacement is functionally normal and necessary to permit urine to pass, permanent lateral displacement by virtue of a constitutively short tunnel characterizes the cystoscopic position of the refluxing UO. Closure of the UVJ results both from compression of the intramural ureter and a return to its full tunnel length as the ureteral muscle relaxes. Thus active and passive mechanisms dynamically reconfigure the tunnel as needed to allow antegrade passage of urine while preventing retrograde flow. Finally, the existence of local efferent and afferent neuromuscular coordination between the UVJ and the periureteric bladder wall is suggested by neurophysiologic studies that induce elevation or decrease in intraluminal UVJ pressure during bladder filling (Shafik, 1996).

Etiology of Vesicoureteral Reflux

As mentioned previously, the occurrence of VUR represents a balance of several factors. The degree to which each contributes to the pathology largely defines whether reflux is considered primary or secondary. In general, **reflux is considered primary if the main reason for it is a fundamental deficiency in the function of the UVJ antireflux mechanism while remaining factors (bladder and ureter) remain normal or relatively noncontributory. Secondary reflux, then, implies reflux caused by overwhelming the normal function of the UVJ. Bladder dysfunction of a congenital, acquired, or behavioral nature is often the root cause of secondary reflux.** It is also accepted that reflux is often considered secondary if its absence was documented at some point before its detection.

Primary Reflux

As stated earlier, primary reflux represents a congenital defect in the structure and therefore function of the UVJ. Reflux occurs despite an adequately low pressure urine storage profile in the bladder. The length-to-diameter ratio of the intramural ureteral tunnel is almost always less than that described by Paquin. Although inadequate tunnel length rather than excessive ureteral diameter usually underlies primary reflux, the dilated ureter often poses a challenge when a nonrefluxing ureterovesicostomy is required. This has traditionally prompted both long tunnels (>5 cm) or reduction of ureteral diameter by tapering or plication, or both, to reconstruct a successful antireflux mechanism. On the other hand, construction of a new tunnel with a full 5:1 length-to-diameter ratio may not be absolutely required to correct reflux.

Secondary Reflux

Any number of obstructing bladder pathologies can create hostile and excessive storage and emptying pressures that eventually overwhelm a normal antirefluxing intramural flap-valve mechanism. Such abnormalities can be functional or anatomic.

The natural history of reflux to resolve suggests the length-to-diameter ratio gradually evolves toward functional competency. Given that there is likely a range of tunnel lengths that can protect against reflux, as well as a spectrum of obstructional voiding etiologies in the refluxing population, it is reasonable to assume some degree of secondary reflux may coexist with primary reflux.

The most common anatomic obstruction of the bladder in the pediatric population is posterior urethral valves (PUVs). Reflux is present in 48% to 70% of PUV patients (Reuter and Lebowitz, 1985; Puri and Kumar, 1996; Hassan et al, 2003; Priti et al, 2004). Relief of PUV obstruction appears responsible for resolution of reflux in about one third of the patients. In one of these series, 78% of reflux resolved within 6 months of valve ablation (Priti et al, 2004). Such observations argue for the secondary nature of reflux due to elevated voiding pressures in PUV bladders. Even prostatic enlargement and its relief are associated with VUR and its resolution, respectively (Morita, 1987). In females, anatomic bladder obstruction is rare. The most common structural obstruction is from a ureterocele, which prolapses into the bladder neck (Merlini and Lelli Chiesa, 2004). In such cases, reflux in a contralateral ureter is likely due to the ensuing outlet obstruction and often resolves with decompression of the ureterocele. In general, then, if relief of the obstruction results in rapid reflux resolution, the reflux was likely secondary.

In contrast to anatomic obstruction, neurofunctional etiologies of elevated bladder pressures also predispose to VUR. In particular, neurogenic bladder associated with spina bifida is at risk for reflux (Bauer et al, 1982). This fact must be borne in mind during evaluation of the child with UTI. Special attention to the potential for occult spinal dysraphism including sacral dimple or hairy patch, gluteal cleft abnormality, diminished rectal tone, or significant constipation or encopresis should prompt consideration of investigation for coexistent spinal cord abnormalities.

Urodynamic extremes that predispose to reflux in the absence of overt neurologic pathology may also exist. Some studies suggest that a secondary aspect to neonatal reflux is a peculiarity of male infants. In a study by Yeung and colleagues (1998), 22 of 24 refluxing infants showing urodynamic evidence of instability (overactivity), inadequate, or obstructive voiding patterns were male. Normal or immature voiding patterns were observed in all infants in the nonrefluxing control group, of which 16 of 21 were male. In infants, higher voiding pressures are associated with reflux,

particularly in boys (Chandra et al, 1996), and may contribute to the male preponderance of reflux in infants. Urodynamic evaluation suggests these elevated infant bladder pressures may be due to inadequate sphincter relaxation (Chandra and Maddix, 2000) during this stage of development. However, detrusor activity in such infants is largely normal during filling, with slightly diminished bladder capacities in some (Podesta et al, 2004), though uninhibited activity during filling has been observed, again predominantly in male infants (Yeung et al, 1998). Considering that the high prevalence for reflux in infants coexists with urodynamic evidence of elevated voiding pressures, these observations suggest that infant voiding patterns may be a part of normal development. Thus even though the UVJ matures with age, infant voiding patterns predispose to a form of secondary reflux that resolves with normalization of urodynamic parameters as these infants grow older.

In older children, acquired abnormalities in voiding parameters commonly known as *dysfunctional voiding* or *dysfunctional elimination* have been associated with reflux. The precise cause of voiding dysfunction is variable but may evolve from a persistence of the expected early attempts to suppress bladder contractions during the toilet training months by volitional contraction of the external sphincter (Allen, 1985). If this behavior becomes prolonged or intensifies, often driven by the child's overwhelming desire for continence, bladder voiding pressures increase. Continence is gradually exchanged for incomplete emptying, resulting in a higher UTI risk. Although investigation of UTI might necessarily diagnose some subjects with persistence of primary reflux, the elevated bladder pressures gradually distort bladder and UVJ architecture and may create (secondary) reflux (Koff and Campbell, 1992). Structural failure of the UVJ is likely a critical determinant because high voiding pressures of approximately 100 cm of water are common in normal bladders and structurally intact nonrefluxing UVJ. Indeed, with structural failure of the UVJ, reflux occurs easily and at low voiding pressures or during early filling and is a poor prognostic factor for reflux resolution (Koff and Campbell, 1992; Hinman et al, 2002). Uninhibited bladder contraction is the most common urodynamic abnormality associated with reflux in neurologically normal children. In one study of 37 girls with "primary" reflux, 75% had uninhibited contractions (Taylor, 1982). However, the observation that treatment of such patients with oxybutynin can virtually eliminate reflux in up to 80% of refluxing ureters strongly argues that an overactive bladder can frequently be responsible for reflux, either by causing secondary reflux or perpetuating primary reflux (Koff and Murtagh, 1983; Homsy et al, 1985; Seruca, 1989). **Thus it is apparent that primary and secondary reflux may not always be mutually exclusive or that what is perceived as primary reflux in some children may, in fact, be secondary to abnormal voiding patterns.**

Clinical Correlates

The previous discussion clearly suggests that multiple opportunities exist for modifying the course of reflux if secondary causes are appreciated, identified, and treated. Van Gool and coworkers (1992) identified that 18% of children enrolled in the European arm of the International Reflux Study in Children harbored voiding dysfunction associated with more frequent UTI and greater persistence of reflux compared with those subjects without voiding dysfunction. Similar findings were reported from the recent Swedish Reflux Trial in which a cohort of children 1 year of age to younger than 2 years of age with grade 3 and 4 reflux were assessed and followed for 2 years for lower urinary tract dysfunction prevalence and type (Sillen et al, 2010). Twenty percent of children harbored some form of dysfunction at entry. This dysfunction prevalence increased to 34% at 2 years of follow-up. A negative correlation was found between dysfunction at follow-up and reflux improvement (P = .002). In addition, scintigraphic renal abnormalities (defined in Brandström et al, 2010a) at study entry and at follow-up were also associated with dysfunction (P = .001). Failure to address voiding abnormalities can also adversely affect outcome of antireflux surgery (Koff et al, 1998).

Indeed, compelling meta-analytic evidence recently compiled by the American Urological Association (AUA) Panel on VUR Guidelines now suggests that bladder and bowel dysfunction (BBD) is by far one of the most critical and modifiable variables that affect VUR management and attendant UTIs. Composite study analysis now indicates that **BBD is associated with a higher incidence of UTIs while on antibiotic prophylaxis, as well as after surgical correction of VUR, with less VUR resolution at 24 months from diagnosis and with reduced success of endoscopic surgery. In the studies selected by the Panel that qualified as having acceptable levels of evidence, BBD did not appear to reduce the success of open surgical reflux correction** (Fig. 122–2).

Thus although dysfunctional elimination syndromes are discussed in detail elsewhere in the text, a thorough evaluation of the toilet-trained child with reflux must recognize dribbling, urgency, or incontinence as signs of coexisting voiding disorders. Girls will also exhibit procrastination about voiding or demonstrate curtsying behavior, and boys may squeeze the penis, in attempts to suppress bladder contractions. The close proximity of the bladder and anal outlets often leads to sympathetic contraction of the anal sphincter as well, resulting in the frequent association of constipation and encopresis with reflux and UTI, in what is probably a mutually aggravating pattern (O'Regan and Yazbeck, 1985; O'Regan et al, 1986; Chase et al, 2004). **Constipation must be recognized and eliminated as much as possible in order to establish optimal conditions for successful spontaneous or surgical resolution of reflux.** The initial report of McGuire and colleagues (1981) suggested that pressures in excess of 40 cm of water measured at full capacity is associated with reflux and upper tract deterioration. Treatments to maintain pressures below this value result in significant reflux resolution (Flood et al, 1994).

Lower Tract Urinary Tract Infection and Reflux

Reflux is not a general cause of UTI. In the absence of bladder symptoms or inflammation, reflux is most readily considered a clinical accelerant of bacteriuria, by mechanically delivering infected urine to the renal pelvis. Infection-related cystitis is expected to incite bladder irritability and dysuria, upsetting the voiding pattern and lowering the threshold for reflux in a given UV junction. However, animal studies differ on whether infection itself can perpetuate UV reflux. In primate studies, surgically created reflux followed by introduction of pathogenic bacteria into the bladder was associated with reflux persistence (Roberts et al, 1988), compared with spontaneously occurring primary reflux in the presence of chronic infection (Lewis and Roberts, 1986), where infection did not delay reflux resolution.

Significant hydroureter and hydronephrosis associated with high-grade reflux could, in theory, act as a reservoir for the repeat

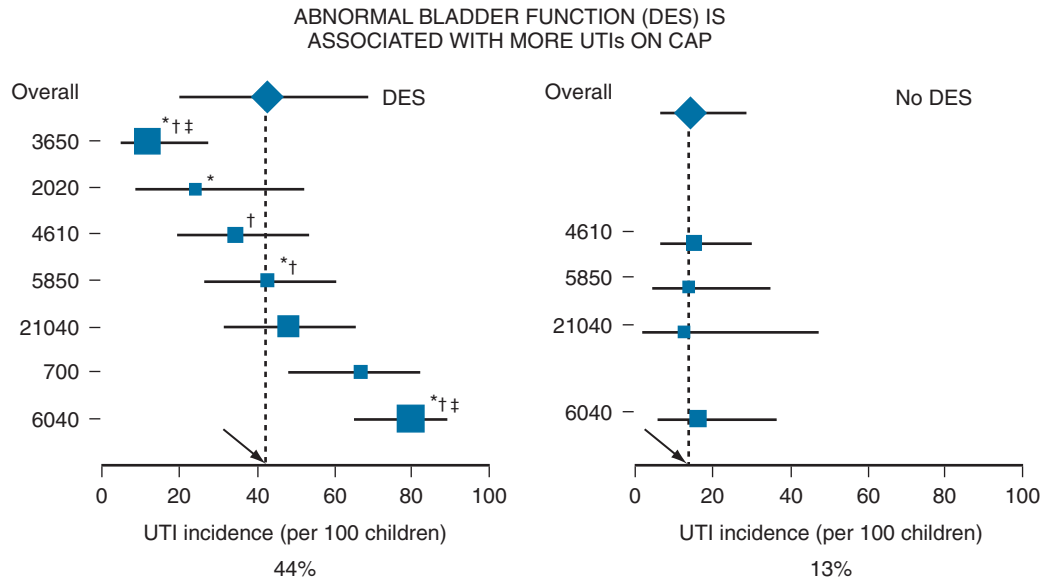


Figure 122–2. Dysfunctional elimination syndrome (DES) and urinary tract infection (UTI). CAP, continuous antibiotic prophylaxis. (From Peters CA, Skoog SJ, Arant BS, et al. Summary of the AUA Guideline on Management of Primary Vesicoureteral Reflux in Children. J Urol 2010;184:1134–44.)

antegrade reintroduction of pathogenic organisms to the bladder. Colonized urine might then cyclically reflux retrograde to the upper tracts. Similarly, ureteral atony secondary to the effects of endotoxin could fail to expel infected urine from the upper tracts, but this does not appear to reduce the ultimate resolution of reflux (Roberts and Riopelle, 1978). Indeed, the dilated upper tracts seen in high-grade reflux explored in the Swedish Reflux randomized prospective controlled trial were associated with a higher rate of recurrent febrile UTI in patients on surveillance without antibiotic prophylaxis (57%) (Brandström et al, 2010b). Reflux correction or antibiotic prophylaxis reduced the recurrent infection rate to approximately 20% (P = 0.0001). Interestingly, the finding was restricted to girls, which may reflect an anatomic predisposition to bacterial colonization of the bladder in girls versus boys; the febrile nature of the infection was likely due to reflux washing of bacteria to the upper tracts and renal parenchyma.

Grading of Reflux

Grading systems generally exist to help prognosticate the behavior of the disease they classify. In 1981 the International Reflux Study Committee proposed a system of five grades of reflux that remains in current use today in North America (Duckett and Bellinger, 1982; Lebowitz et al, 1985). **Five grades of reflux are currently used to depict the appearance of the ureter, renal pelvis, and calyces as seen on the radiographic contrast images generated by the voiding cystourethrogram** (Table 122–3 and Fig. 122–3). Using such a system serves several purposes. Grading standardizes the description of the degree of reflux for clinical management of the individual patient, as well as for grouping research subjects in the design of clinical studies and trials. Grading facilitates documenting the natural history of the reflux process in the individual patient. It also permits establishing quantitative associations between reflux and other clinical parameters, in order to determine whether such associations hold multivariate clinical relevance. Most importantly, description of initial grade in primary reflux is the most significant parameter associated with prediction of reflux resolution (see later).

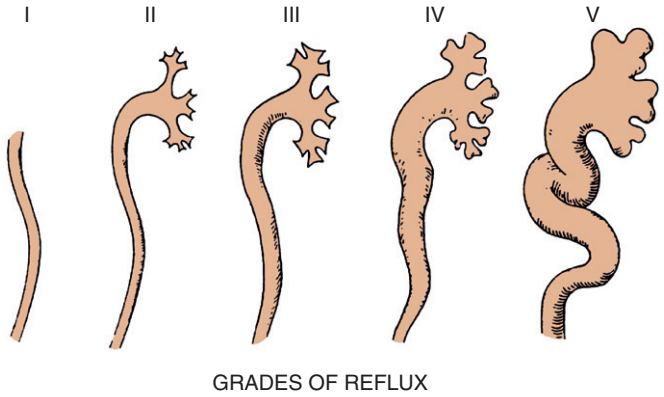


Figure 122–3. International classification of vesicoureteral reflux.

Table 122–3.

International Classification of Vesicoureteral Reflux

GRADE	DESCRIPTION
1	Into a nondilated ureter
2	Into the pelvis and calyces without dilatation
3	Mild to moderate dilatation of the ureter, renal pelvis, and calyces with minimal blunting of the fornices
4	Moderate ureteral tortuosity and dilatation of the pelvis and calyces
5	Gross dilatation of the ureter, pelvis, and calyces; loss of papillary impressions; and ureteral tortuosity

Despite the widespread use of the five-point grading system, several shortcomings exist. For example, the expected concordance between ureteral and calyceal dilation does not always occur (Fig. 122–4). Either the ureter or the calyces may demonstrate dilation out of proportion to the calyces or ureter, respectively. Whether this reflects an anomaly in the biomechanical tissue properties or peristaltic activity of the excessively dilated structure, as compared with the typical refluxing upper tract is unknown. Nevertheless, such anatomy is difficult to grade using



Figure 122–4. A refluxing ureter with significant dilatation of the lower segment but no distortion of the collecting system may be different from the typical system with grade 2 reflux.

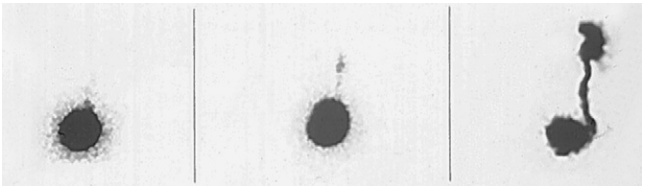


Figure 122–5. Nuclear voiding cystography showing right-sided reflux. Radionuclide tracer can be quantitated (from left to right) as grade 1 (grade I of the international grading system), grade 2 (grades II to III of the international grading system), and grade 3 (grades IV to V of the international grading system).

the current system. Similarly, it is unknown whether the propensity to either scarring in the face of infection or reflux resolution is altered in such systems.

Attempts have also been made to grade reflux using radionuclide cystography (RNC). Because RNC does not provide discrete images of the ureteral and calyceal architecture required to assign reflux grade, classifying reflux by RNC is difficult. Alternative RNC grading has been proposed (Zhang et al, 1987). This provides reasonable concordance to the objectives of the classic grading system by collapsing grades 2 and 3, as well as grades 4 and 5, into low-grade and high-grade reflux, respectively (Fig. 122–5). The impact of the reduction in grading detail from five grades (1 to 5) to two (low and high) on understanding reflux pathophysiology and on the design of clinical studies has yet to be determined.

Although grading is purely a classification of the appearance of contrast in the upper tract, ascribing an absolute value to the grade has the potential to cast the reflux in unequivocal terms, to the exclusion of other factors that modulate reflux at the time the images are acquired. Inherent bladder dynamics, the bladder outlet, and even ipsilateral UVJ obstruction all influence the degree of reflux at any given assessment (Lebowitz, 1992). Grade, reflux detection, and reflux resolution are all interrelated and are influenced by the degree of bladder filling, the voiding cycle, the number of filling cycles during the contrast cystogram, and whether the reflux occurs during filling or only during voiding. None of these parameters is built into the grading system for reflux used currently. However, given the principal role of a reflux grading system is to help prognosticate reflux resolution, future incorporation of other parameters may provide additional clinical acumen. Finally, it must be remembered that reflux grade is still presently determined by an imaging study that requires invasion of a sensitive anatomic region. For a given reflux grading result, the aforementioned variables of bladder dynamics, filling, and voiding cannot necessarily be replicated with certainty in a given patient each time he or she is studied. It is reasonable to speculate that reflux grade could easily vary up or down by at least one grade if sequential studies were performed in a given patient. Thus the entire reflux literature itself, which historically reports results in terms of five separate grades, must be considered with some circumspection because the veracity of grade at the time of the contrast study may be, to some extent, arbitrary.

Diagnosis and Evaluation of Vesicoureteral Reflux

Confirmation of Urinary Tract Infection

Because preventable reflux nephropathy is predicated on the combined effects of UTI and reflux, confirming and documenting true UTI is paramount in the appropriate management of the patient with reflux. Many variables are responsible for the accurate assessment and interpretation of UTI in the context of reflux. These include clinical history and presence of fever; age of the patient; circumcision status; method of urine specimen collection, storage, and delivery; and the results of urine dipstick and microscopic analyses. Although confirming true pyuria by dipstick or microscopic analysis, in addition to the presence of bacteriuria, will help to differentiate infection from colonization, colonization alone in the presence of reflux may still pose a threat to the upper tracts. Attention to these details cannot be overemphasized because major management decisions including operative intervention for correction of reflux often rest solely on a diagnosis of UTI. Conversely, confirming microbial growth in a urine specimen is of little value if the mode of collection is highly suspect and likely to harbor contamination. Confirmation of UTI begins with collection of the urine specimen. If storage is necessary, specimens should be maintained at 4° C until transfer to the laboratory.

In infants, specimen collection will often entail the placement of an adhesive urine collection bag over the genitalia. Although topical cleansing of the area is reasonable to reduce contamination and false-positive cultures, care must be taken to avoid introducing the disinfection agent into the specimen. Unfortunately, routine practice is so variable that such guidelines are often difficult to follow or confirm and **microbial contamination of bagged specimens is common. Conversely, this method is most useful if the resulting urine culture is negative.** Although fevers are common in infants, UTI comprises only 5% of children presenting with fever (Hoberman and Wald, 1997). Thus the ability to easily rule out a UTI in the febrile infant with reflux facilitates management. If there is a high clinical suspicion for UTI in an infant, the more accurate method is to obtain a catheterized specimen. Even this method may prove suspect in the uncircumcised infant male whose preputial skin is not yet

retractable to easily reveal the urethral meatus. In this and other instances where the urethral route is difficult or compromised in patients of any age, a suprapubic needle aspiration of bladder urine provides the most accurate method of obtaining a urine sample. In the younger child, however, repeated catheterization for specimen acquisition and radiographic assessment (see later) should be considered carefully. This hitherto routine practice is coming under greater scrutiny as the long-term sequelae of this invasive maneuver become appreciated (Stashinko and Goldberger, 1998) and could become a factor in patient compliance with follow-up (and therefore management decisions for reflux).

In patients who can void spontaneously, a clean voided midstream catch specimen is preferred. The initial urine is discarded because it is rich in periurethral organisms.

The previously mentioned guidelines pertain to patients with both unknown and known reflux status. In the former, the decision to look for reflux will depend on the propensity for acquired reflux nephropathy in the individual patient. In the patient known to have reflux, the prevailing propensity for acquired reflux nephropathy and compliance with proper voiding habits, antibiotic prophylaxis, and timely reporting will influence further management (see later).

Evaluating Urinary Tract Infection

Numerous factors support a search for reflux in the patient with UTI. The probability of finding VUR in children with a UTI is 29% to 50% (Anonymous, 1981). Furthermore, in some patients, higher grades of reflux may be associated with various degrees of existing renal parenchymal maldevelopment (see embryology section earlier) (Nakai et al, 2003). In addition, because reflux tends to resolve over time, it is reasonable that UTI is more commonly associated with reflux in younger patients (Smellie et al, 1981b), whose renal parenchyma is at more risk for scarring following a given pyelonephritis, compared with the older child. Smellie also suggests that the presence of reflux does not usually provide any unique clinical features in the patient with a UTI. Thus as with the search for sibling reflux, radiologic investigation of the patient with UTI is tailored to those patients who are placed at greatest renal functional risk from the presence of VUR. For this reason, **radiographic investigation for VUR has generally been directed to children younger than 5 years old, all children with a febrile UTI, and any male with a UTI regardless of age or fever, unless sexually active.**

The high repeat UTI rate after a first UTI has prompted a recommendation for some form of VUR work-up (Fig. 122–6). However, the current state of the VUR debate makes it difficult to know which patients, by such evaluations, might harbor clinically significant reflux, given how common UTI is in children. Some reassurance can be provided if a voiding study is negative for VUR. However, the parental concern over the invasiveness of the cystogram may first limit the evaluation to ultrasonography only, to rule out any existing gross structural defects. As such, taking the appropriate voiding, fever, and family histories into account, a sonographic study of the bladder and kidneys can be considered a reasonable minimum evaluation in the infant or child following a UTI, if a cystogram is deemed overly aggressive by the family or treating physician. Even the detection of reflux following treatment for UTI could be of questionable significance if the child is older and/or no fever accompanies the UTI. On the other hand, the presence of structural renal anomalies or significant asymmetry would support proceeding with a cystogram. More recent studies of racial predilection for reflux have supported a lower prevalence in children of African origin (Askari and Belman, 1982; Horowitz et al, 1999), but the prevalence in children of Hispanic origin (Pinto, 2004) is similar to that of Caucasians.

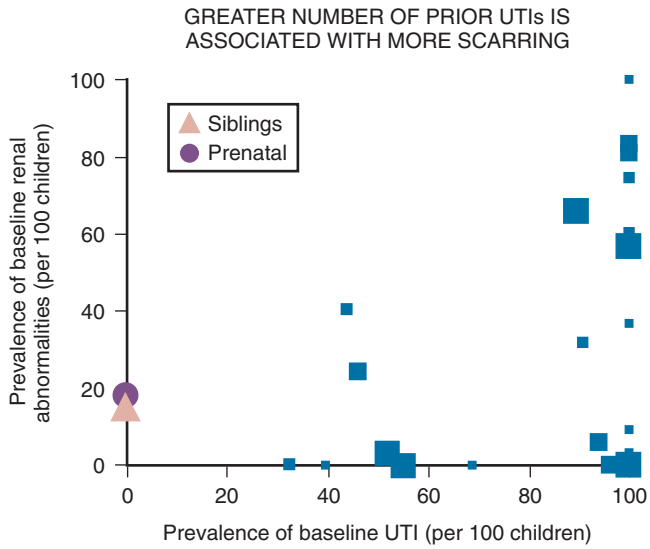


Figure 122–6. Urinary tract infection (UTI) history. (From Peters CA, Skoog SJ, Arant BS, et al. Summary of the AUA Guideline on Management of Primary Vesicoureteral Reflux in Children. J Urol 2010;184:1134–44.)

The advent of prenatal ultrasound has likely augmented the detection of asymptomatic reflux in newborns, as a result of mass surveillance for persistent postnatal hydronephrosis and the ensuing performance of cystography in these infants. It must be remembered that the sonographic finding of hydronephrosis is generally much more common than hydronephrosis due to a renal moiety actively refluxing at the time of the sonogram. Indeed, there is little correlation between the degree of antenatal hydronephrosis and the existence of reflux (Farhat et al, 2000). A corollary study also demonstrated normal postnatal ultrasounds in 25% of patients with VUR and antenatal hydronephrosis (Lebowitz, 1993).

Assessment of the Lower Urinary Tract

Cystographic Imaging

The basis of reflux detection lies in demonstrating the retrograde passage of an imaging contrast material from the bladder to the ureter and renal pelvicalyceal system. The currently available methodologies require a source of contrast agent in the bladder. Two approaches, the so-called *indirect* and *direct cystograms,* can be performed depending on whether the contrast enters the bladder indirectly following excretory urography or directly, usually by urethral catheterization. Indirect cystography, although avoiding the invasive nature of urethral catheterization, is prone to false-positive interpretation due to contrast that does not originate from the bladder, remaining in the ureter or pelvis after filtration and antegrade passage, and false-negative results in lower grades of reflux (Conway et al, 1975). However, it has been suggested that the value of indirect cystography may lie in ruling out the presence of VUR (Carlsen et al, 1986).

The voiding cystourethrogram (VCUG) and radionuclide cystogram (RNC) therefore are the two common forms of direct cystography and constitute the present-day gold standard approaches to reflux detection. More recently, to eliminate the need for ionizing radiation, some studies have demonstrated a growing interest in sonographic detection of reflux using either color Doppler imaging (Haberlik, 1997; Oak et al, 1999; Galia et al, 2004) or

echo-enhancing contrast agents (Berrocal et al, 2001; Darge et al, 2001; Darge and Troeger, 2002; McEwing et al, 2002; Tasic and Todorovska, 2003; Valentini et al, 2004; Vassiou et al, 2004; Darge et al, 2005). Direct imaging of reflux is affected by several parameters. These include bladder contraction during voiding, the fluid volume instilled into the bladder, and presence of infection and therefore inflammation of the UVJ mucosa. Reflux may occur during filling or only during the active bladder contraction associated with voiding. Consequently, if a patient is unable to void in the artificial setting of the radiography suite, false-negative results may ensue. More importantly, even during voiding, reflux may not be demonstrated on a single filling-voiding cycle. Several studies have demonstrated a roughly 12% to 20% greater detection rate for VUR if a cyclic study is performed (Paltiel et al, 1992; Papadopoulou et al, 2002; Novljan et al, 2003). A cyclic VCUG involves a second or third cycle of bladder filling and emptying under fluoroscopic observation. A similar cyclic strategy is commonly employed for the RNC as well (Fettich and Kenda, 1992). Reflux may also be demonstrated during catheter filling of the bladder. Because filling assumes far lower intravesicle pressure than that of voiding, reflux during filling, or passive reflux, is generally considered a poor prognostic sign for reflux resolution and suggests the presence of a fixed decompensation of the UVJ. This is a common finding in patients with acquired or neurogenic voiding dysfunction, wherein high-resistance voiding gradually remodels the bladder wall and UVJ, leading to complete failure of the latter's antireflux mechanism, and immediate reflux at virtually any volume of the filling phase (Koff, 1992). This is in contrast to reflux that only occurs during the higher-pressure milieu of bladder emptying and contraction. Thus technical inconsistencies in the ratio of instilled volume-to-bladder capacity during the radiographic technique can lead to variations in rates of reflux detection: if the bladder is overfilled or underfilled for a given degree of progressive UVJ incompetency, reflux may be overdetected or underdetected, respectively.

One difficult dilemma in the performance of voiding studies involves cystography during active infection. On one hand, some UVJs maintain only borderline antireflux mechanisms, which are competent in a sterile milieu but become incompetent from edema and inflammation associated with mucosal inflammation during cystitis. Such patients may have VCUG studies negative for reflux in the absence of infection but suffer from repeated pyelonephritic episodes. Cystograms in such patients may demonstrate reflux if obtained during active infection. On the other hand, evoking reflux during an active cystitis, by definition, will transmit bacteria to the upper urinary tract and renal pelvis and risks iatrogenic pyelonephritis. Nevertheless, the general consensus has been to delay the voiding study for at least a week or longer to allow for adequate recovery from the acute infection episode (Craig et al, 1997). Only if it is imperative to make the diagnosis of reflux in children with a history of recurrent pyelonephritis and repeatedly negative voiding studies in the intercurrent periods should cystography during UTI be considered.

The VCUG is a fluoroscopic study that provides information on both the functional dynamics and structural anatomy of the urinary tract. The detailed technique of the VCUG is discussed more fully elsewhere in the text. Bladder contrast is instilled by gravity following urethral catheterization. Bladder capacity is recorded when contrast influx ceases. Static images record bladder contour, presence of diverticula or ureteroceles, grade of reflux, configuration and blunting of calyces, and intrarenal reflux. Passive or active reflux is demonstrated dynamically during fluoroscopy while filling and voiding, respectively. In addition, bladder neck anatomy, funneling or dilation, and urethral patency are parameters derived from the VCUG. **Delayed or postvoid films are crucial in documenting clearance of contrast from the upper tracts because retained contrast, particularly with dilated pelvicalyceal systems, could signify the presence of a concomitant UPJ obstruction (UPJO)**, either primarily or secondarily due to distortion of the UPJ by massive retrograde filling of the pelvis by the reflux (Hollowell et al, 1989). **If both the UPJ and UVJ meet criteria for operative repair, the UPJ should be repaired first to avoid the incipient obstruction that may ensue if resistance is added to the UVJ when reflux is corrected** (Hollowell et al, 1989). With care, both processes may be repaired simultaneously when it is clear that they are independent significant problems.

The RNC has historically enjoyed a reputation for requiring approximately 1% the radiation exposure generated by the VCUG (Blaufox et al, 1971; Diamond et al, 1996a). Presently, the reduced radiation requirements of modern digital techniques have significantly narrowed the difference between fluoroscopy and RNC. Although little anatomic detail is afforded by the RNC, it is ideal as both a screening modality and for monitoring the natural history or surgical follow-up of reflux. In contrast to the VCUG, the instilled bladder contrast material, usually Technetium Tc99 pertechnetate, is itself the radiation source. Reflux is detected on scintigraphic gamma camera images (Fig. 122–7). **Lack of confounding imaging densities typical of fluoroscopy, as well as the ability to obtain prolonged exposures, allow for greater sensitivity of the RNC in grade 2 to 5 reflux.** Ironically, **grade 1 reflux into the distal ureter is often poorly detected due to the overlying exposure generated by contrast within the bladder itself.** Thus RNC and VCUG imaging can be used complementarily, balancing radiation exposure with the need for dynamic information and anatomic detail. Notwithstanding the forgoing discussion, modern digital fluoroscopic equipment has further reduced the radiation exposure of conventional fluoroscopy, thereby narrowing the difference in radiation exposure between the two modalities.

Another modality gaining popularity in some centers is ultrasonic cystography to detect reflux. Modern transducers coupled with the use of echo-enhancing contrast agents can image reflux well in older children (Novljan et al, 2003; Riccabona et al, 2003; Tasic and Todorovska, 2003; Galia et al, 2004), but the technique remains of limited use in neonates (McEwing et al, 2002).

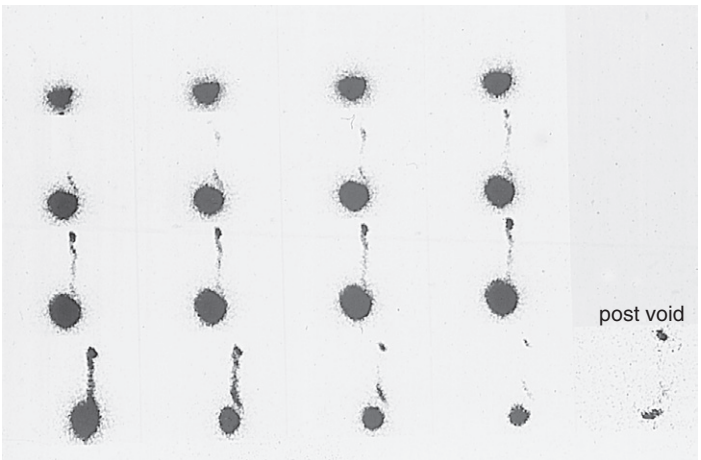


Figure 122–7. Radionuclide cystogram showing right-sided reflux that worsens with bladder filling. The upper collecting system drains fully with voiding.

Furthermore, while radiation exposure is eliminated, bladder catheterization remains a necessary feature with this approach.

Diagnostic Controversies: Challenging the Assessment of Reflux

The well-recognized distress of the family and patient associated with urethral catheterization, particularly in children, coupled with the advent of low-morbidity outpatient correction of reflux using endoscopic approaches appears to be challenging conventional reflux management and therapy. All aspects of VUR including modern incidence of renal scarring and failure, peak ages of renal susceptibility, and indications for reflux correction, including the assumption that permanent correction of reflux is an absolute necessity, are coming under scrutiny. This has given rise to added pressure to avoid bladder catheterization. The cystogram can have traumatic aftereffects in young patients (Stashinko and Goldberger, 1998; Elder, 2005) and must be approached with sensitivity and awareness of the developmental stage of the patient. Sedation (Stokland et al, 2003), topical urethral anesthetic (Gerard et al, 2003), and more recently hypnosis (Butler et al, 2005) have all been effective in mitigating the deleterious psychologic effects of cystography. Nevertheless, it is clear that **parental perception of the nature of the medical modalities involved in reflux management will influence their choice of therapy** for their children (Ogan et al, 2001). **This should in no way be construed as license for the abandonment of conventional observational therapy including antibiotic prophylaxis and periodic cystography in favor of immediate reflux correction in all patients** (Aaronson, 2005). Rather, the evolution of less invasive imaging modalities for reflux detection and reduced morbidity of reflux correction should be encouraged in parallel.

Uroflowmetry

Evaluation of the lower urinary tract during clinical assessment of VUR cannot rely solely on imaging. Because reflux is a dynamic phenomenon, the prevailing functional status of the bladder must also be considered. Although full pressure-volume urodynamic studies of the bladder are not required in all reflux patients, a minimal survey of bladder emptying characteristics can be obtained by uroflowmetry. The details of uroflowmetry technique are discussed elsewhere in the text. In refluxing patients, it is important to establish whether the bladder outlet is functioning relatively normally or harbors more resistive characteristics that are highly prevalent in younger patients. Elements of the uroflow such as lack of smoothness of the flow-velocity curve suggest incomplete relaxation of the bladder outlet during voiding. This implies the existence or development of relatively higher pressures during voiding, which could delay the natural history of reflux resolution or even perpetuate reflux. An increased postvoid residual volume may be a risk factor for UTI. In the setting of passive reflux, carrying infected postvoid residual urine can also lead to ascending infection and pyelonephritis.

Top-Down Approach

The top-down approach is an interesting concept based on the notion that only clinically relevant reflux with potential to cause renal injury is worthy of uncovering. Only a dimercaptosuccinic acid (DMSA) renal scan is obtained following a febrile UTI, with cystography reserved only for patients with abnormal scintigraphy. Children with a negative DMSA require no further evaluation unless they develop recurrent UTI, in which case a VCUG should be obtained.

Hansson and colleagues (2004) retrospectively reviewed 303 children younger than 2 years of age who had undergone evaluation by DMSA and VCUG within 3 months of their first UTI. Although 82% of these infections were febrile, VUR was found in only 26% of the children (80/303), 66% of whom had abnormal DMSA scans, while no abnormalities were detected in the remaining 27 patients. An approach based on identifying renal cortical abnormalities before obtaining a VCUG would have identified the 66% of children with VUR presumably at risk for further scarring, and it would have excluded 120 children (40%) without VUR or renal abnormalities from an unnecessary VCUG.

Implementation of a top-down approach would obviously not have detected 34% (27/80) of the cases of VUR. However, the patients in Hanson's study did receive prophylaxis as the top-down approach was being studied only from a theoretic viewpoint. In applying the top-down approach, these infants would not have been started on antibiotic prophylaxis and potentially might have been at risk to develop recurrent UTI. However, in 74% (27/80) of these patients, VUR was low grade and the remaining seven cases (grade 3 to 5 VUR) either resolved or improved significantly during a 2-year follow-up period with one of them developing a renal scar on repeat DMSA scintigraphy.

In a follow-up study from the same institution, Preda and colleagues (2007) prospectively confirmed these observations in 290 children younger than 1 year of age with UTI (79% febrile) with VCUG and DMSA renal scans. Fifty-one percent of the patients had positive scans including 85% (44/52) of the children later found to have VUR. Seven of the eight cases of VUR with normal DMSA scans were low grade, the remaining boy having grade 3 VUR with no acquired renal scars in follow-up despite an episode of breakthrough UTI.

The potential ability to detect those children with significant VUR who are at risk for renal scarring while avoiding invasive evaluation and unnecessary treatment of those who are not is clearly appealing. These data underscore the importance of further prospective analysis with longer follow-up to establish the validity and safety of the top-down approach.

National Institutes for Clinical Excellence Guidelines

In an attempt to streamline the investigations and treatment in infants and children presenting with UTI, the National Institutes for Clinical Excellence (NICE) in the United Kingdom proposed a set of guidelines aimed at reducing morbidity, antibiotic usage, and cost. Investigations are limited to an ultrasound of the urinary tract with cystography reserved for infants younger than 6 months and in older infants when dilation is observed by ultrasound. They do not recommend early DMSA renal scans to confirm or exclude renal involvement and rely solely on ultrasound in the sicker patients to determine the need for further investigation. Hence the major criticism to this approach lies in the poor correlation between the appearance of the kidneys on ultrasound and the presence of renal parenchymal changes or the presence and grade of VUR. The NICE committee did not provide any clinical outcomes to validate these guidelines and until confirmation of the safety of this approach is established prospectively, it cannot be recommended for general clinical use.

Cystoscopy and the Positioning of the Installation of Contrast Cystogram

Modern management of reflux does not include routine cystoscopy. It is rare for cystoscopy to add any information that will alter management of a patient with reflux, either at the time of

initial diagnosis or during follow-up. Its routine use, especially in children with UTI or reflux, should be considered an anachronism. Similarly, the appearance and configuration of the UOs and intramural tunnel length that are afforded by cystoscopy and once considered useful parameters have over time provided little correlation with either the diagnosis or grade of reflux (Duckett, 1983). Cystoscopy can provide useful information immediately before open surgery, such as confirmation of orifice position and duplication and the proximity of diverticula to the orifice, and clarify urethral patency if indicated. Similarly, such cystoscopic parameters will become immediately available in all patients at the time of endoscopic reflux correction.

A recently developed, although still controversial (Elder, 2005), cystoscopic modality termed the *PIC technique* (*P*ositioning of the *I*nstillation of *C*ontrast at the UO) purports to detect reflux under general anesthesia in patients with a history of febrile UTIs but a normal VCUG. The technique of PIC cystography (Edmondson et al, 2006) involves cystoscopy using a 9.5-Fr or 14-Fr rigid cystoscope. With the bladder empty, the cystoscope beak is positioned close to and facing the UO. Contrast is instilled at the UO using the irrigation port of the cystoscope from a height of 1 meter above the bladder. Fluoroscopic spot imaging is done simultaneously with the instillation. PIC-VUR is confirmed if retrograde flow of contrast into the ureter/kidney pelvis is observed. The bladder is emptied before the procedure is repeated on the contralateral side.

It is conceivable that antireflux mechanisms may be barely functional in some patients with recurrent UTI. The unique but unphysiologic nature of the PIC technique may then reveal reflux in such cases. Furthermore, PIC cystography does not allow for age-adjusted instillation pressures; some pressures may be too high in younger patients and may be creating iatrogenic reflux rather than unmasking relevant, physiologically borderline reflux.

A multi-institutional study by the PIC Cystography Group (2008) examined the clinical significance of reflux discovered by PIC in 118 children with a history of febrile UTIs and negative VCUGs. VUR diagnosed by PIC was treated by surgery (endoscopic injection in 104, reimplantation in 3) or by antimicrobial prophylaxis (11). In the 98 evaluable patients, VUR grade was 1-3 and was unilateral in 34 patients and bilateral in 64 patients. Treating occult VUR identified by PIC cystography, with either antibiotics or surgery, reduced the incidence rate of febrile UTI by 20-fold (from 0.161 per patient per month before PIC-VUR treatment to 0.008 per patient per month after treatment).

It is generally believed that VUR does not cause UTI; however, in this nonrandomized study (with the patients acting as their own controls), PIC cystography provides seductive evidence and rationale for antireflux therapy in a new subset of patients, particularly because endoscopic correction could theoretically and easily follow the fluoroscopy at the same time. However, **the urologist must exercise caution in this approach until prospective studies randomizing patients with PIC-VUR to treatment or observation confirm its clinical importance.**

Assessment of the Upper Tract

Rationale for Serial Assessment of Upper Tracts

The known effects of VUR on the upper tracts are largely what direct the need for reflux diagnosis and correction. Pyelonephritis propagated by reflux causes renal scarring, impedes attainment of full renal growth potential, and increases risk of renovascular hypertension. Therefore imaging of the upper tracts is directed at assessing renal structure and function with attention to the aforementioned parameters. A fundamental goal in upper tract imaging with VUR is to ascertain whether abnormalities are due to ongoing or resolved reflux and differentiate them from intrinsic developmental disturbances, medical renal disease, or antegrade flow resistance. Almost always, particularly in the youngest patients in whom VUR has the greatest potential to adversely effect renal function, these goals are best achieved through serial imaging of the kidneys over a period of months to years.

However, a meta-analysis of 63 studies assessing the value of routine diagnostic imaging after initial UTI in children for the prevention of renal damage found no accurate evidence to support this practice (Dick and Feldman, 1996). Many observational studies raised concern for the sequelae of UTIs and highlighted the potential for successful intervention. **The reason to image the upper tracts following a UTI may occur with or without knowledge of the reflux status of the lower tract. Reflux status may be known, suspected, or completely unknown. These three considerations, coupled with the age of the patient, gender, race, family history of reflux, and bladder functional status serve as a guide to selective imaging, which attempts to balance intensity of imaging studies with propensity for renal damage.**

Renal Sonography

The mainstay of renal imaging in VUR management is ultrasonography. As a nonionizing, noninvasive imaging platform, coupled with its ability to assess renal vasculature, it is ideally suited to serial follow-up of renal growth and development. Ultrasonography has supplanted routine excretory urography as the imaging modality of choice to monitor renal status over time.

Ultrasound lends itself well to quantitative assessment of renal dimensions (Rodriguez et al, 2001; Chen et al, 2002), which can then be used to follow renal growth over time. Renal growth can be referenced to standard renal growth curves. In reflux diagnosed in the neonatal period, baseline renal dimensions are obtained and appropriate renal growth can be monitored over time. The impact of any intercurrent febrile urinary infection can be gauged by observing the effects on renal growth. Similarly, if the UTI history between follow-up visits for reflux is unclear, serial assessment of renal dimensions can help the urologist advise on the need for further assessment of renal function by scintigraphy or on the need for reflux correction. Indeed, in the presence of reflux, modern postnatal renal sonography provides excellent correlation between renal length and scintigraphic hypoplasia (Farhat et al, 2002a).

Ultrasonography also images the degree of corticomedullary differentiation in the kidney. Loss of corticomedullary differentiation, or an increase in the overall echogenicity of the kidney, is associated with some degree of renal functional impairment. In neonates in particular, these parameters can be useful in assessing overall status of a renal unit in the context of higher grades of reflux, even before any history of UTI or pyelonephritis has occurred. Coupled with a relatively smaller ipsilateral kidney, loss of corticomedullary differentiation or increased echogenicity suggests a degree of intrinsic renal dysplasia that developmentally accompanies high-grade reflux. In the neonate with no infection history, such findings should not be confused with renal scarring, which is the direct sequela of inflammation and infectious pyelonephritis. In general, the routine sonogram is noninvasive, performed relatively quickly, and does not require intravenous access for contrast agents. From a practical point of view, it is virtually

an extension of the urologic physical examination and is still commonplace in urologists' offices. As such, just as serial documentation of height, weight, and blood pressure are basic components of most pediatric encounters, most urologists commonly perform serial sonography every 6 to 24 months during follow-up of reflux, if only to confirm that renal growth is proceeding normally.

Notwithstanding the value of renal sonography, it must be remembered that a single ultrasound study cannot reliably diagnose VUR. Although it is tempting to speculate on the presence of reflux in the presence of postnatal hydronephrosis on sonography, particularly of higher grades, there is no significant correlation between a normal ultrasound and the absence of reflux (Farhat et al, 2000; Zamir et al, 2004). Similarly, renal sonography is limited in its ability to visualize renal cortical abnormalities. Sonography is better suited to the noninvasive detection of larger cortical defects or renal size asymmetry (Merguerian et al, 1999).

Modern enhancements in ultrasound technology permit imaging of perfusion abnormalities in tissue. In reflux nephropathy using color Doppler ultrasound, renal resistive index measurements derived from blood flow in interlobar and arcuate arteries are significantly increased in higher grades of reflux and correlate positively with scintigraphic findings from the same renal unit (Radmayr et al, 1999). Resistive indices are also higher in patients with bona fide pyelonephritis confirmed by nuclear scintigraphy compared with patients with lower UTI alone (Ozcelik et al, 2004). Animal studies have also demonstrated that contrast-enhanced harmonic ultrasound can detect histologically confirmed regions of reflux-induced pyelonephritis with great sensitivity and more than 80% positive and negative predictive value (Farhat et al, 2002b).

Renal Scintigraphy

The gold standard for imaging functioning renal parenchyma is scintigraphy using ^{99m}Tc-labeled DMSA. The radiotracer is taken up only by functioning proximal tubular tissue mass, where it binds for several hours. The uptake of DMSA provides a good proportional representation of glomerular filtration (Taylor et al, 1982). Because pyelonephritis impairs tubular uptake of radiotracer, these areas will fail to radioemit photons and appear as unexposed or underexposed regions in the resultant renal cortical images (Fig. 122–8). Although many such affected areas in the kidney resolve, especially if prompt medical treatment is possible (Fernández-Menéndez et al, 2003), when they persist, irreversible renal damage or scarring is said to have occurred (Rushton and Majd, 1992). In a study of 79 children followed for 1 to 4 years, DMSA scanning provided a 98% sensitivity and 92% specificity for scar detection (Merrick et al, 1980). Although Rushton's study suggested that subsequent scarring was independent of the presence or absence of VUR (Rushton and Majd, 1992), a more recent meta-analysis found that reflux conferred an approximately threefold increased risk of detecting renal cortical abnormalities after infection (Faust et al, 2009). Indeed, considering the overall incidence of pyelonephritis in children, VUR is present in 22% to 39% of such patients (Hoberman et al, 2003; Lin et al, 2003). Nonetheless, the importance of VUR lies in the realization that it remains a spontaneously resolving or surgically treatable etiology for this ascending group of renal infections (Majd et al, 1991).

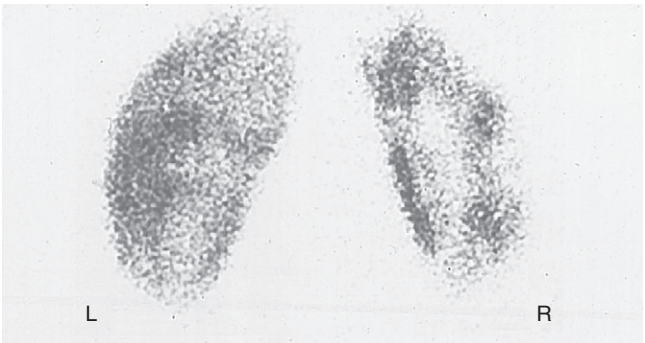


Figure 122–8. Dimercaptosuccinic acid renal scintigraphy. Pinhole images show a normal left kidney and a right kidney with multiple cortical defects.

One advance in nuclear scintigraphy of the kidneys is SPECT imaging (single-photon emission computed tomography). This approach reconstructs three-dimensional images of the renal cortical architecture, which can be viewed in any aspect in 360 degrees of rotation. Although SPECT images provide slightly higher sensitivity for detection of cortical defects, they do not add appreciably to standard pinhole DMSA images in the clinical management of reflux (Majd et al, 1996).

Much has been written in the literature on the role of DMSA scanning in the management of VUR, as an indirect entrée to the diagnosis of reflux itself, for the detection of reflux-associated renal damage and acute pyelonephritic changes, and for follow-up of reflux. However, no consensus exists on the precise use of DMSA scanning in reflux management. For example, growing concerns over the nature and frequency of voiding studies has prompted some to propose cystography after UTI only in those children with persistent postinfection renal lesions on DMSA scan, citing that only a minority of post-UTI cystograms are positive for reflux (Hansson et al, 2004). DMSA and ultrasound are often used complementarily, particularly when knowledge of relative renal function is desired (Riccabona et al, 1993). As a general rule, the utility of scintigraphy can best be appreciated in the context of the data it provides relevant to reflux: imaging cortical defects and relative renal function. The usefulness of this information will depend on which associated clinical and radiology data are at hand. If reflux and infection history are unclear or unknown in a new patient referred for evaluation after UTI, scintigraphy can provide the gold standard for demonstration of cortical defects for any reason and help with counseling on additional studies. If the significance or febrile nature of a potential pyelonephritis is unclear, particularly in a younger patient, a follow-up DMSA scan 4 to 6 months post-UTI can rule out subsequent scarring, particularly if a normal scan exists from a prior evaluation. DMSA scanning can be particularly useful if the diagnosis of pyelonephritis is unclear during an acute infection. Confirmation of photopenic radioemission and acute pyelonephritis can help to ensure that adequate antimicrobial therapy is provided. If surgical intervention is planned and significant renal asymmetry exists on ultrasound, quantification of relative function by scintigraphy can help to decide between reflux correction and nephrectomy.

DMSA scanning has also demonstrated that congenital cortical maldevelopment can exist, particularly in high-grade reflux, even in the absence of any history of UTI or outlet obstruction (Nguyen et al, 2000; Wallin and Bajc, 1994). This underscores the fact that cortical defects detected by DMSA scanning are not always the byproduct of infection; all DMSA defects are not necessarily scars. The distinction is an important one in the design of clinical studies and interpretation of the reflux literature, where congenital cortical defects may be erroneously construed and evaluated as if they were due to postinfection scarring. One corollary to this observation is that scintigraphic renal defects detected for the first

time in a child in whom the reflux history from birth cannot be confidently known could be secondary to reflux-associated pyelonephritic scarring, even though the reflux has resolved by the time of the study. Failure to appreciate that reflux often resolves in early childhood before scanning detects cortical defects for the first time makes it difficult to know whether these defects were or were not associated with reflux.

Cortical Defects

Congenital Defects versus Acquired Scar

The term *scar* is defined as fibrous tissue replacing normal tissues destroyed by injury or disease. In a renal context, the term is most accurately used to describe the fibrous, contracted regions of the kidney that have been destroyed by infection. These areas of scar tissue often appear smaller and photopenic by scintigraphy or hyperechoic and shrunken on sonographic images. The importance of such scars lies in the realization that they are the preventable complication of pyelonephritis, the latter being directly influenced by VUR in the presence of a bladder infection.

However, VUR, particularly of higher grades, may result in renal maldevelopment that often appears scintigraphically or sonographically identical to postinfection pyelonephritic scars. Thus over time in the literature and in clinical practice, the terminology of scarring, which is ideally defined to describe an end product of infection, has become contaminated by the inclusion of reflux-associated congenital dysmorphism. However, until such time that primary reflux can be averted prenatally (Gobet et al, 1998) or during the early postnatal phase of continued renal development, dysmorphism will remain the nonpreventable developmental sequela of reflux. Failure to appreciate this important distinction has tainted and confused study design and interpretation in the reflux literature.

Reflux-Associated Renal Dysmorphism

The association of renal maldevelopment with the highest grades of reflux is expected by the theory of Mackie and Stephens (1975), which suggests that an abnormal origin of the ureteral bud will interact suboptimally with the metanephric blastema (Fig. 122–9). The latter process is currently believed to be the likely cause of renal dysmorphism associated with reflux. Several studies have confirmed the association between VUR and a smaller than normal ipsilateral kidney, an overall reduced relative renal function, and global (Najmaldin et al, 1990; Burge et al, 1992) or focal (Risdon, 1993) areas of poor uptake by scintigraphy. These infants tend to be male, and the preponderance of refluxing renal units are grade 4 or 5 (Marra et al, 1994, 2004) (Table 122–4 and Fig. 122–10). Indeed, boys tend to be spared an infectious etiology of reflux-associated scarring because they have a lower incidence of recurrent UTIs (Wennerstrom et al, 2000).

Renal dysplasia is not unique to primary isolated VUR but may also occur in a variety of urologic settings. Duplex renal moieties (Mackie et al, 1975), prune-belly syndrome (Manivel et al, 1989), and posterior valves may all exhibit reflux-associated renal dysmorphism, particularly when the grade of reflux has been high.

Requirement for Urinary Microorganisms

It is now firmly established that nephropathy from primary VUR requires the colonization of urine with pathogenic bacteria, in the face of normal voiding dynamics. Indeed, the basis of current expectant medical management of reflux is to maintain urinary sterility while allowing reflux to resolve naturally. In the absence of infection, sterile urinary reflux is insufficient to cause renal damage. This concept has been most definitively demonstrated by the elegant series of experiments by Ransley and Risden. Reflux was induced experimentally in a pig model by unroofing the intravesicle ureteral tunnel. Only if the urine was subsequently infected could pyelonephritis and reflux nephropathy be induced. Without urine infection, no nephropathy could be created (Ransley and Risden, 1981). Large clinical studies have also reiterated these experimental findings, demonstrating new reflux-associated scarring only in children with recurrent UTIs (Smellie et al, 1975; Huland and Busch, 1984). These observations conflict somewhat with earlier animal studies by Hodson and colleagues (1975), which induced reflux with sterile urine. However, bladder outflow obstruction was also included in this model, leading to a finding of atrophic pyelonephritis similar to obstructive nephropathy. Scarring was nevertheless intensified by the presence of urinary microorganisms. Thus abnormal hydrodynamic bladder characteristics may modulate even sterile reflux, but reflux is unlikely to be of any clinical significance in the absence of infection with relatively normal bladder function. These earlier observations of Hodson, however, underscore the importance of normalizing bladder and bowel function while awaiting reflux resolution.

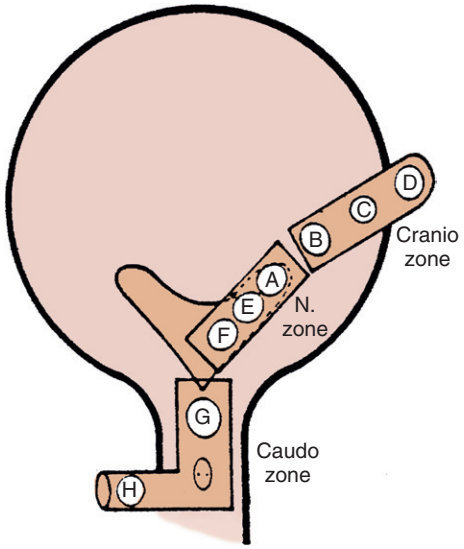


Figure 122–9. Classification of ureteral orifice position. Obstruction usually occurs in the caudo zone, and ureters positioned in the cranio zone are likely to result in reflux. Ureters positioned in the normal (N) zone are associated with normal kidneys. Because of ureteral bud abnormality, renal dysplasia occurs with ureters projecting from both abnormal positions. (From Mackie GC, Stephens FD. Duplex kidneys: a correlation of renal dysplasia with position of the ureteral orifice. J Urol 1975;114:274.)

Table 122–4.

Congenital Renal Scarring

GRADE OF VESICOURETERAL REFLUX	NO. OF PATIENTS NORMAL	SLIGHT DAMAGE	SEVERE DAMAGE
1-3	13 (100%)	—	—
4	8 (53%)	5 (34%)	2 (13%)
5	2 (15%)	5 (38%)	6 (46%)

Modified from Marra G, Barbieri G, Dell'Agnola CA, et al. Congenital renal damage associated with primary vesicoureteric reflux. Arch Dis Child Fetal Neonatal Ed 1994;70:F147.

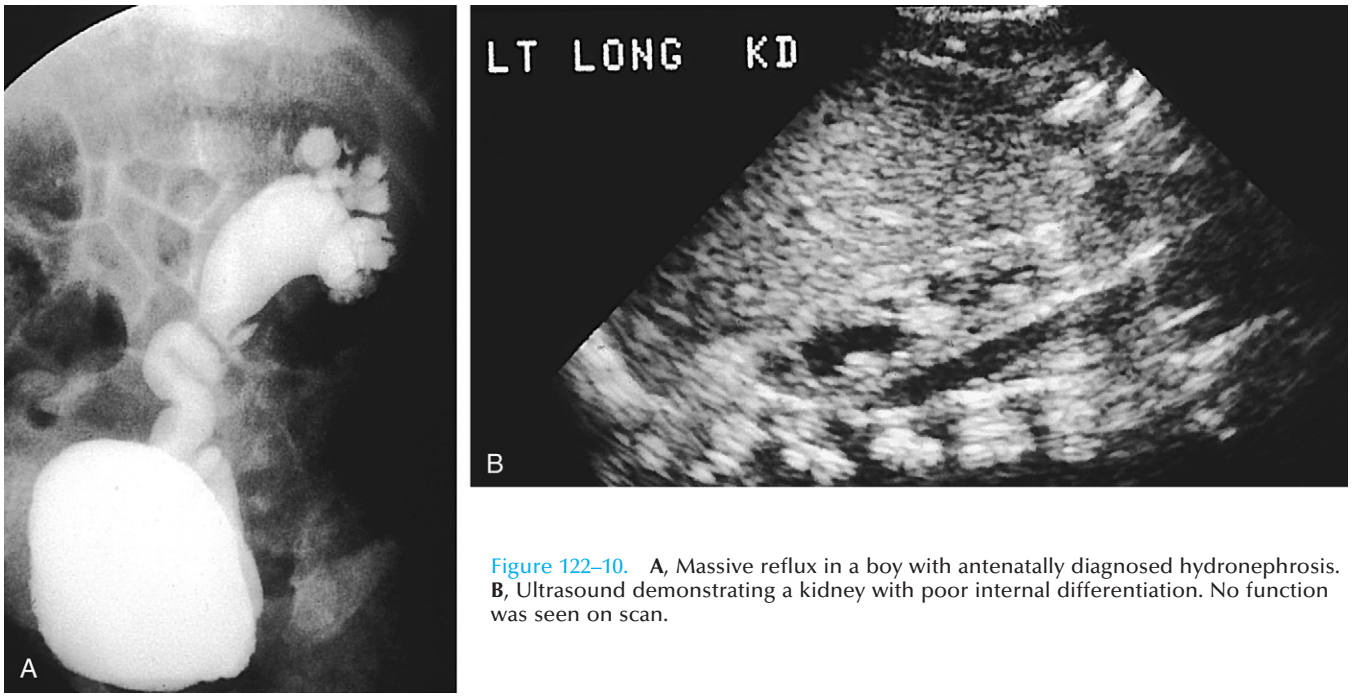


Figure 122–10. **A**, Massive reflux in a boy with antenatally diagnosed hydronephrosis. **B**, Ultrasound demonstrating a kidney with poor internal differentiation. No function was seen on scan.

Pathophysiology of Acquired Scarring

Renal scarring is a sequela of infectious pyelonephritis. A full discussion of the pathophysiology of renal scarring is covered elsewhere in the text. However, VUR exploits several conditions that predispose to scarring. Most importantly, **reflux provides a mechanical hydrodynamic mechanism that facilitates the ascension of microorganisms from the bladder to the kidneys. As such, reflux may be considered an accelerant for renal tissue infection, following bacterial colonization of the bladder.** This principle has been confirmed by studies showing an increased incidence of pyelonephritis in higher-grade reflux compared with lower-grade reflux (Majd et al, 1991). Furthermore, the frequency of scarring itself appears to be directly proportional to the grade of reflux with which it is associated (Winter et al, 1983; Weiss et al, 1992a). This principle is also supported by observations following reflux correction. In one study of 74 patients in whom preoperative and postoperative scintigraphy studies were available, more than 90% of renal units corrected for reflux showed no new scars during a mean follow-up period of 19 months, despite asymptomatic bacteriuria in 47% of the patients during follow-up (Choi et al, 1999).

Age. **The kidney's predilection for postpyelonephritic scarring is inversely proportional to age. This point is a guiding principle, which must be considered in all decisions regarding reflux diagnosis and choice of therapy. The greatest risk for postinfectious renal scarring occurs within the first year of life** (Winberg, 1992). Similarly, patients younger than 4 years are more prone to developing scarring after a single UTI than older children (Smellie and Normand, 1985), though scarring may still occur beyond 5 years of age (Smellie and Normand, 1985; Benador et al, 1997). Indeed, while younger patients are the most vulnerable to scarring, scarring in older children is often the result of late diagnosis, delayed or inadequate treatment of infection, and social factors that often interfere with patient management. Thus in older children with reflux in whom a consideration to relinquish care from the urologist back to the family physician is being considered, it is vital that fundamental principles of an adequate clinical index of suspicion for UTI and prompt UTI management be reiterated before transfer.

The seminal studies of **Ransley and Risdon (1981) proposed a "Big Bang" theory for the origin of scars following infant pyelonephritis. They observed that most of the scarring to which the kidney is ultimately susceptible occurs after the initial bout of pyelonephritis and that further scarring in the absence of repeated pyelonephritic episodes is unlikely to occur.** Consequently, the assumption is that little change in the initial scarring pattern is to be expected in follow-up scintigraphic imaging. **However, the uncertainties introduced by such factors as (1) the weakly substantiated assumption that a relatively greater scarring propensity exists in younger kidneys, (2) the reports of new follow-up scarring in the landmark reflux studies (see later), (3) the failure to differentiate between postpylonephritic imaging defects due to infection versus intrinsic developmental dysmorphism associated with reflux, (4) the changing appearance of such imaging defects with renal growth over time, and (5) the limited ability to compare disparate imaging modalities in the reflux literature (urograms vs. nuclear scans) together must challenge the notion that the greatest postinfection parenchymal loss occurs following the first infection.**

Papillary Anatomy. Another factor governing renal susceptibility to scarring is the configuration of the papillae as their ducts open to the calyces. Papillae with a concave architecture (compound papillae) present their ducts at right angles, whereas more convex papillae possess ducts that end obliquely, producing a valvular effect that guards against backflow of urine into the medullary collecting ducts (Fig. 122–11). The more polar calyces are composed preferentially of compound papillae compared with the middle calyces. The former are more commonly the site of intrarenal reflux (reflux into the ducts) and are the prime regions of susceptibility to scarring. Furthermore, necropsy studies have

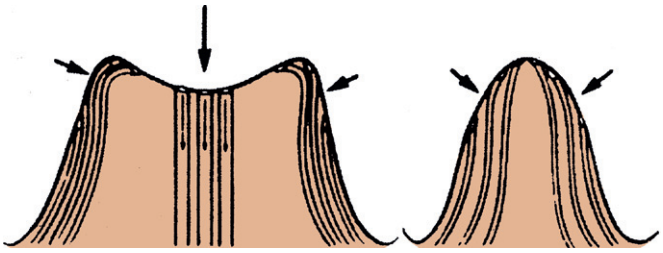


Figure 122–11. Papillary configuration in intrarenal reflux. A convex papilla *(right)* does not reflux because the crescentic or slitlike openings of its collecting ducts open obliquely onto the papilla. In contrast, a concave *(left)* or flat papilla refluxes because its collecting ducts open at right angles onto a flat papilla. (From Ransley PG, Risdon RA. Reflux and renal scarring. Br J Radiol 1978;14[Suppl.]:1.)

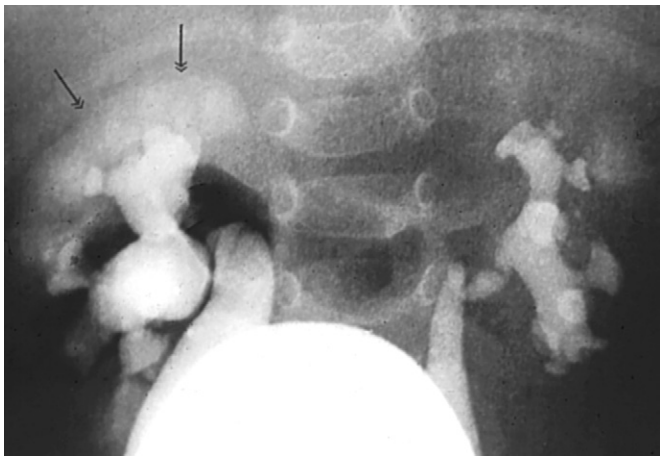


Figure 122–12. Intrarenal reflux (*arrows*) shown on a voiding cystourethrogram.

determined that reflux into compound papillae occurs at lower pressures than into simple papillae (Funston and Cremin, 1978). Intrarenal reflux can occur with as little as 2 mm Hg pressure in the neonate (Fig. 122–12). By 1 year of age, the pressure required is one order of magnitude greater (Funston and Cremin, 1978) and helps to explain the relative infrequency of intrarenal reflux in older children.

Bacterial Virulence. Bacteria possess phenotypes that provide infective advantage when exposed to the lumen of the urinary tract. Chief among these is the ability to adhere to uroepithelium. Adherence is mediated by interaction between specific molecules or ligands located on bacterial fimbriae and with specific receptors on host uroepithelial cells. A full discussion of the mechanism of action of uropathogenic bacteria is found elsewhere in the text. Once bacteria bind to host epithelium, specific biologic responses are activated in both the microorganism and host cell. Bacterial responses are designed to facilitate their survival and proliferation, as well as inhibit host defenses. These include release of endotoxin and reduction of ureteral peristalsis, which may lead to urinary stasis and reduced antegrade flow of urine. The host inflammatory response perpetuates the classic symptoms of UTI. Although a more systematic understanding of bacterial-host interactions in the propensity for reflux-associated renal scarring is not yet available, it appears that bacteria responsible for postpyelonephritic scars in the presence of reflux often express fewer than three virulence factors (Lomberg et al, 1984). Ironically, then, less virulent bacteria are most often sufficient to produce scarring in the presence of reflux.

Host Susceptibility and Response. Nonhematogenous bacterial access to the urinary tract rests essentially with periurethral organisms. Thus the type and number of vaginal and preputial organisms will determine individual propensity for bladder colonization. Local factors such as hygiene and bowel habits will also influence the bacterial load presented to the perineal surface from the intestinal tract, the latter being the principal repository for organisms that infect the urinary tract. The functional diversity of the host receptors for bacterial adherence also plays a role in the success or failure of bacteria to gain entry to the bladder. In one study, girls with recurrent UTI harbored far heavier periurethral colonization than a control group of girls who were infection free, suggesting a variation in the function of antibacterial defenses in susceptible females (Bollgren and Winberg, 1976a). Furthermore, such factors may exhibit both gender- and age-related dimorphism (Bollgren and Winberg, 1976a). The great majority of UTIs in both sexes younger than 6 months old is confined to uncircumcised boys (Rushton et al, 1992) and is consistent with the observation that *Escherichia coli* colonization is dense in infant boys but sparse in girls (Bollgren and Winberg, 1976b).

Perhaps the greatest tangible factor in promoting susceptibility to UTI is urinary dwell time. The postvoid urine volume is traditionally singled out as being suspect in providing sanctuary for ascending urethral organisms. Perhaps more important, however, is the overall dwell time between voids, which provides the greatest advantage to bacterial proliferation. **When the average doubling time for *E. coli* is measured in minutes, it is self-evident that a quantity of micoroorganisms sufficient for clinical infection can easily incubate exponentially in a bladder that is not emptied for several hours.**

Recent advances have also been made in understanding the renal epithelial response to pathogens. The classic components of the innate immune response to infection include activation of the complement system; recruitment of neutrophils and macrophages with scavenging ability; and production of a variety of cytokines, chemokines, and defensins (antimicrobial peptides). One family of receptors, the Toll-like receptors (TLR), respond to highly constant antigens expressed in bacteria (Chowdhury et al, 2004). The best studied of these, TLR4, detects lipopolysaccharide (LPS). A breakthrough in understanding renal infection came with the demonstration that mutations encoding the TLR4 gene were responsible for LPS hyporesponsiveness (Hoshino et al, 1999). Nevertheless, molecules accessory to TLR4 are important to its response to LPS. Similarly, molecules such as CXCR1 and CXCR2 are receptors for interleukin-8, the principle renal epithelial secreted chemokine responsible for neutrophil migration (Godaly et al, 2000). Deficiencies of CXCR expression and function may underlie human susceptibility to pyelonephritis (Frendeus et al, 2000, 2001). Such advances placed into the context of VUR provide interesting and powerful opportunities to modify the natural history of the condition.

As well as orchestrating the assembly of the phagosome for bacterial clearance, **the fallout of these renal epithelial processes that is the inflammatory response leads to local tissue damage and scarring.** Hallmarks of the response include capillary congestion, ischemia and reperfusion injury, and free oxygen radical and inflammatory cytokine release (Roberts, 1990, 1992). Microabscess formation later coalesces into scar tissue typical of the histologic changes of chronic pyelonephritis

(Roberts, 1995). Although limiting the inflammatory response to reduce scarring may appear logical, no specific pyelonephritis anti-inflammatory pharmacotherapy is yet available. Traditional non-specific anti-inflammatory agents, both steroidal and nonsteroidal, are not currently indicated in the treatment of pyelonephritis; in their current formulations the latter poses a threat to renal function (Schaller and Kaplan, 1998). Nevertheless, the concept has been demonstrated experimentally in animals (Huang et al, 1999). A full understanding of the specific pathways involved in reflux-associated pyelonephritis could provide key strategies to limiting specific renal inflammatory fallout without limiting bacterial clearance. Until then, antimicrobial prophylaxis instituted in a timely fashion, usually within 24 to 48 hours, is the single most effective pharmacologic strategy to date to limit the scarring consequences of pyelonephritis in both young and older children (Smellie et al, 1985; Ransley and Risdon, 1981).

Hypertension. VUR has long been held as the primary cause of significant hypertension in children. Arterial derangements in the renin-angiotensin system and sodium-potassium adenosine triphosphatase activity (Goonasekera and Dillon, 1998) may be involved, though the precise pathophysiology is not clear. Although methodologic flaws (Farnham et al, 2005) taint many studies of hypertension in the pediatric urology population, one study using continuous ambulatory blood pressure monitoring revealed some correlation between progression to hypertension and more severe reflux nephropathy in children (Lama et al, 2003). A recent adult review of 157 patients with hypertension, but no evidence of abnormal renal parameters, discovered by cystography that latent VUR was present in 20% of the subjects, demonstrating that a significant association between reflux and hypertension exists in adulthood (Barai et al, 2004). The striking association between VUR diagnosed for the first time only in adulthood and arterial hypertension continues to underscore the importance of remaining vigilant about untreated infections in the reflux population (Kohler et al, 1997). Nevertheless, it remains unclear whether it is the nephropathy associated with postinfection scarring, congenital dysmorphism associated with reflux, or some combination of both that predisposes to hypertension (Wolfish et al, 1993). This latter observation questions, then, whether prevention of postinfection scarring per se in the management of VUR will specifically help to offset future hypertensive risk in those cases where congenital renal dysmorphisms are already present. There is obvious potential for the etiology of reflux-associated hypertension to rest with deranged renal microvascular mechanisms associated with parenchymal defects. This suggests that successful correction of reflux alone is unlikely to ameliorate blood pressure (Wallace et al, 1978). Indeed, removal of renal segments verified by selective renal vein sampling of arteriolar or segmental vessel renin levels has provided durable normalization of blood pressure in carefully selected patients (Tash et al, 2003). On occasion, complete removal of a small unilateral congenitally dysmorphic or globally scarred and shrunken kidney may also correct renovascular hypertension (Dillon and Smellie, 1984) because such kidneys are clearly not amenable to partial nephrectomy for any discrete segment.

Renal Growth. Several studies have attempted to demonstrate that correction of reflux will restore retarded renal growth associated with reflux, particularly when the growth defect is in a unilaterally affected kidney. However, reflux correction is a poor predictor of catch-up upgrowth in such kidneys (Hagberg et al, 1984; Shimada et al, 1988). A significant factor governing growth of an ipsilateral kidney is the function of its contralateral mate. Although forestalling infection in the presence of VUR will maintain the normal trajectory of renal growth in most cases (Smellie et al, 1981a), it must be remembered that compensatory hypertrophy of the contralateral kidney will magnify the perceived impact of infection on renal growth because the contralateral developing kidney will assume the required renal function whenever the ipsilateral kidney is unable to contribute optimally to function. When reflux correction has been associated with improved renal growth, it is likely this is due to removal of the propensity for ascending infection rather than the elimination of the reflux per se (Willscher et al, 1976a, 1976b).

Renal Failure and Somatic Growth. Today, renal failure due to primary VUR-associated infection should be an anachronism, although it is still seen. This is largely due to the virtual paradigm shift in reflux management championed by Smellie and colleagues during their pivotal studies of reflux and infection in children during the 1970s and 1980s. Over the past 30 years, chronic pyelonephritis as a primary cause of end-stage renal disease has fallen from 15% to 25% (The 12th Report of the Human Renal Transplant Registry, 1975) to less than 2% (Committee, 2004). Reflux nephropathy in all its forms, however, was the fourth most common primary diagnosis in nonblack pediatric transplant recipients (Committee, 2004). The medical renal disease (Hinchliffe et al, 1994) that accompanies renal scarring can include hyperfiltration, concentrating defects, proteinuria, microalbuminuria (Lama et al, 1997), renal tubular acidosis (Guizar et al, 1996), and increased fractional excretion of sodium and magnesium. Although all of these parameters are likely the direct result of tubular and parenchymal damage or dysmorphism, concentrating defects and increased concentrations of tubular enzymes (Carr et al, 1991) have been reported in the presence of sterile reflux, independent of any history of infection per se (Walker et al, 1973). The concentrating defect is proportional to reflux grade and improves following reflux cessation. These observations have suggested that a relative flow resistance may be created by retrograde nature of reflux and raises the possibility of a functionally obstructive parameter in reflux pathogenesis. However, the precise relationship between antegrade flow, retrograde flow, and bladder dynamics in this theoretic mechanism has not been more fully articulated.

One of the best global parameters of renal function in children is the somatic growth curve. Many children with VUR fall below the normal age-adjusted growth curve, particularly in patients with bilateral reflux and some degree of renal damage. Furthermore, successful suppression of pyelonephritis through either medical prevention of infection or surgical correction of reflux itself can result in catch-up growth, both for height and weight (Polito et al, 1996, 1997). Although a clear superiority has yet to be demonstrated between medical and surgical therapy to affect growth improvement or subsequent renal scarring following an initial pyelonephritic insult, surgical correction of reflux can benefit somatic growth when recurrent breakthrough infection indicates failure of antibiotic prophylaxis (Sutton and Atwell, 1989).

Associated Anomalies and Conditions

Ureteropelvic Junction Obstruction

VUR and ureteropelvic junction obstruction are two of the most common pathologic conditions in pediatric urology. Thus it is not unusual that these two conditions coexist. Whether the concomitant presence of these two conditions is a random event or

is causally related remains unclear. It has been speculated that a developmental ureteral bud anomaly may be responsible for the imperfect formation of both the UVJ and the UPJ (Bomalaski et al, 1997a).

The incidence of VUR associated with UPJO ranges from 9% to 18% (Lebowitz and Blickman, 1983; Maizels et al, 1984; Hollowell et al, 1989; Bomalaski et al, 1997a; Kim et al, 2001). When the two conditions were primarily present, most of the patients in these studies had reflux that was coincidentally discovered, was of low grade, and resolved spontaneously with time. Such patients typically exhibited a significant discrepancy between the minimal degree of ureteral dilatation and the significantly dilated renal pelvis. Thus the apparent grade of reflux may be overestimated, and management decisions based on the grade of reflux are inaccurate at best.

Conversely, the incidence of UPJO in patients with reflux ranges from 0.75% to 3.6% (Lebowitz and Blickman, 1983; Bomalaski et al, 1997a), with **high-grade reflux being five times more likely to be associated with UPJO than lower grades of reflux** (Lebowitz and Blickman, 1983; Bomalaski et al, 1997a). Indeed, in one study of children with reflux and hydronephrosis, 50% of high-grade sonographic hydronephrosis, commonly associated with the highest grades of reflux, showed an obstructive pattern on lasix scintigraphy (Stauss et al, 2003).

Three radiology signs might suggest the existence of UPJO in the setting of reflux. First, if the pelvis shows little or no filling, while the ureter is dilated by contrast, this may indicate a point of kinking secondary to reflux or from a primary UPJO itself (Fig. 122–13). Secondly, contrast that does enter the pelvis may be poorly visualized due to dilution in a large pelvic volume and

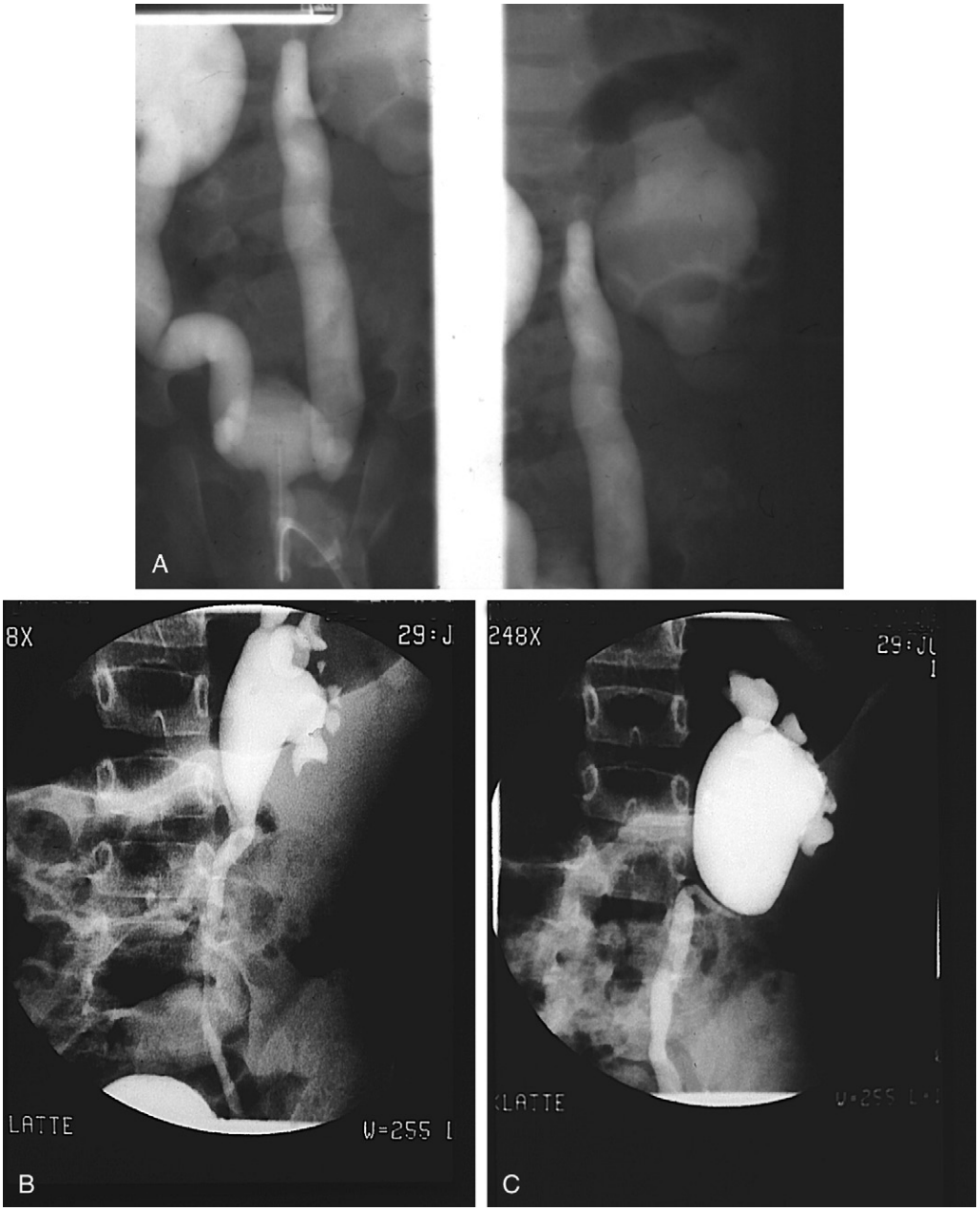


Figure 122–13. Reflux and ureteropelvic junction (UPJ) obstruction. **A,** Significant reflux fills the left ureter to the level of the UPJ. Minimal filling of the pelvis can be a sign of obstruction at this level. **B,** In a different patient, reflux is seen as the bladder fills. **C,** Significant kinking of the UPJ occurs with voiding.

exhibits a markedly reduced radiodensity compared with the ureter or bladder. Finally, a large pelvis that fails to exhibit prompt drainage but retains contrast is also suggestive of UPJO.

Radiographic studies of UPJO associated with VUR may indicate true anatomic obstruction or simply dilation associated with pelvic-ureteral dilation from higher grades of reflux. Hollowell and colleagues (1989) referred to three clinical categories of concomitant obstruction and reflux. Group 1 had primary UPJO and incidental low-grade reflux, and group 2 had secondary UPJO from high-grade reflux. These two groups represent true anatomic obstruction for which pyeloplasty is recommended. Group 3 represents only significant dilation of the upper tracts, which is confirmed by documenting good drainage images by cystography or renal scintigraphy.

The etiology of secondary UPJO is unclear. Several factors are thought to predispose or even aggravate a potential narrowing at the level of the UPJ. High-grade reflux may result in kinking of the upper ureter and adjacent pelvic junction. The chronic effects of reflux may also stretch the renal pelvis so that atonicity and an inability to propel urine through the UPJ may occur (Whitaker, 1973). In the setting of UTI propagated to the upper tracts by reflux, inflammation and ureteritis can also contribute to transient or chronic obstruction at the UPJ.

The convergence of two ureteral anomalies in the same patient raises additional management questions where treatment of one anomaly may affect the natural history of the other. **Nevertheless, the guiding therapeutic principle is the preservation of renal function. Although sterile reflux may be observed, obstruction even in the absence of infection may jeopardize renal function. Therefore in the presence of reflux, if scintigraphy with catheter drainage confirms obstruction, pyeloplasty should be performed.** The secondary insult to the UPJ from reflux is an evolving process that cannot be efficiently or adequately corrected by surgical repair of the reflux itself. Furthermore, reflux correction alone risks amplifying upper tract dilation during the phase of postoperative edema in the lower ureter, as well as risks introducing infection to a renal pelvis still harboring obstruction at the UPJ.

The simultaneous open correction of UPJO and reflux has always raised a concern over surgical manipulation of both the upper and lower ureter at the same time, as well as its potential negative impact on ureteral vascularity. However, the advent of endoscopic injection raises the possibility of correcting reflux at the time of pyeloplasty for secondary or primary UPJO. The indications for reflux correction are being re-evaluated since the advent of endoscopic therapy and are discussed in the section on endoscopic management later.

Ureteral Duplication

VUR is the most common abnormality associated with complete ureteral duplications. The embryologic origin of the duplicated ureter supports the observation that reflux occurs most commonly into the lower pole. This relationship is based on the studies of Weigert (1877) and Meyer (1946), who documented the more lateral and proximal insertion of the lower pole ureter associated with a shorter intramural ureter at the UVJ (Fig. 122–14).

The incidence of reflux is increased in patients with complete ureteral duplication (Privett et al, 1976). Earlier studies provide a limited view of whether reflux in a duplex moiety carries increased patient risk due to lack of control groups, arbitrary patient selection, and short follow-up. There has been some tendency to correct reflux on the basis of the existence of the duplication anomaly itself. Even in the absence of obstruction from a ureterocele or ureteral ectopia, duplication with low-grade reflux may take longer to resolve than in single-system reflux (Estrada et al, 2009), though it carries no increased risk of increasing grade, breakthrough infection, or scarring (Ben-Ami et al, 1989; Husmann and Allen, 1991). The most recent series supports this finding in low-grade reflux but notes that high-grade reflux into lower pole ureters in females is more prone to breakthrough infection and scarring and therefore may warrant more aggressive management (Afshar, 2005; Estrada et al, 2009).

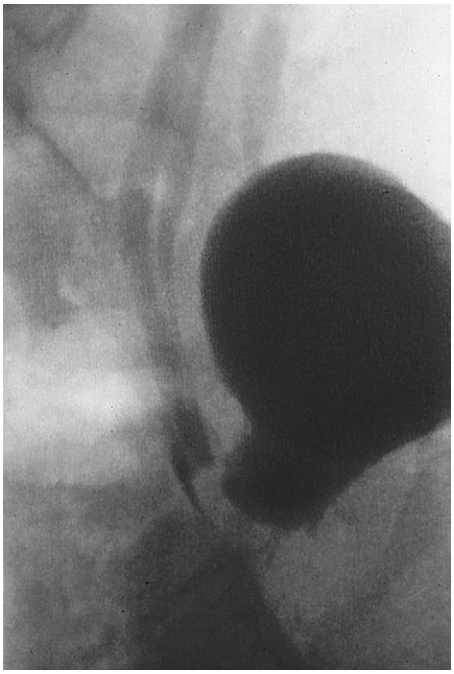


Figure 122–14. Reflux into both ureters of a complete duplication, as shown here, is less common than reflux into the lower pole ureter alone.

Bladder Diverticula

A full discussion of bladder diverticula is found elsewhere in the text. The outpouching of mucosa between detrusor muscle bundles, which lacks any true muscle backing itself, commonly defining a bladder diverticulum, has the theoretic potential to affect the natural history of VUR in two ways. Most commonly, if the UVJ is distorted by the so-called paraureteral diverticulum, which shares an anatomic point of origin at or near the UVJ, it is theoretically possible that the configuration of the diverticulum could compromise the antireflux configuration of the UVJ to cause reflux (Fig. 122–15). Secondly, and more rarely, a large paraureteral diverticulum could expand within Waldeyer fascia to cause ureteral obstruction or project forward into the bladder to obstruct the bladder outlet, much as a ureterocele, and incite secondary reflux (Boechat and Lebowitz, 1978). Although the latter would require cystoscopic confirmation, neither cystoscopy nor imaging is predictive of whether paraureteral diverticula truly compromise the resolution of reflux, as has been commonly believed. Hutch (1961) was the first to recognize that bladder diverticula were congenital abnormalities that occurred primarily in smooth-walled normal bladders in children. A 40-year review of the literature from 1966-2004 fails to provide any objective case control or cohort studies to support the routine repair of reflux where the

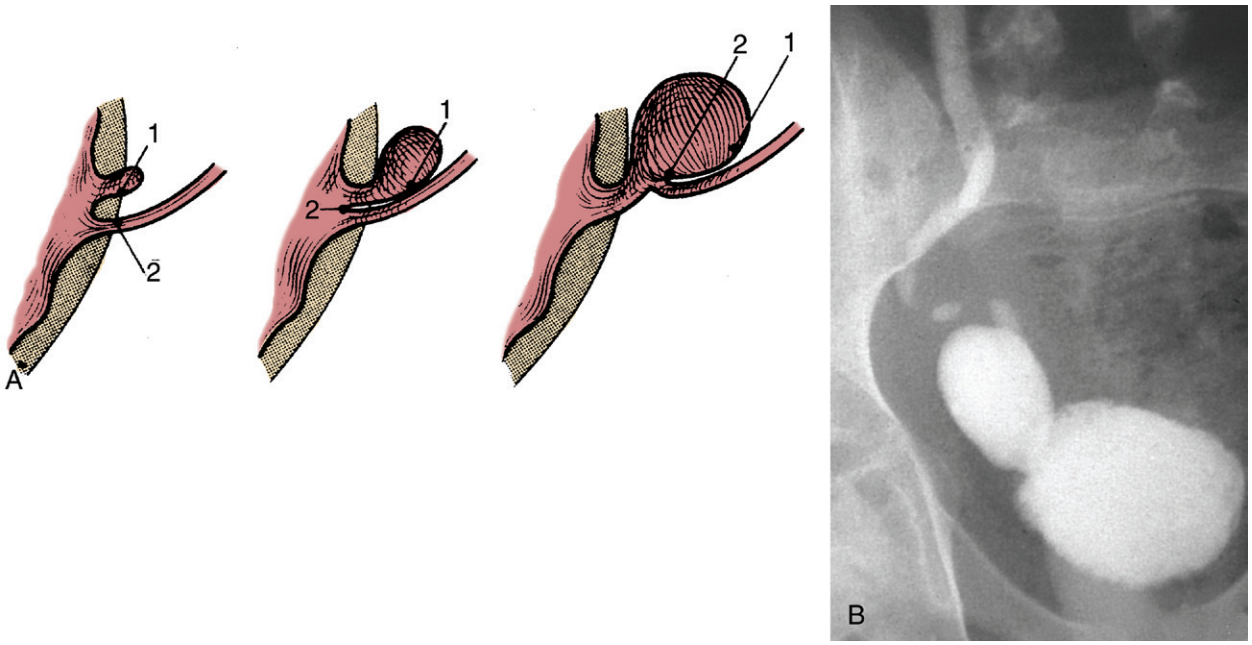


Figure 122–15. **A,** Schematic representation of a bladder diverticulum. A small amount of mucosa initially herniates through a congenital defect in the bladder musculature. The defect enlarges with voiding. Finally, the ureteral orifice is incorporated into the diverticulum. **B,** Reflux into a right-sided paraureteral diverticulum and ureter seen on voiding cystography. (**A,** From Hernanz-Schulman M, Lebowitz RL. The elusiveness and importance of bladder diverticula in children. Pediatr Radiol 1995;15:399–402.)

sole indication was the presence of a paraureteral or Hutch diverticulum. However, a contemporary retrospective cohort analysis of 84 patients with paraureteral diverticula and reflux showed no significant difference in spontaneous resolution rates (60%, 39%, and 22% for grades 1 to 2, 3, and 4 to 5 reflux with paraureteral diverticulum vs. 52%, 28%, and 33% in a matched control group of 95 refluxing patients without diverticulum). Rates of UTI and scarring were similar in both groups. Multivariate analysis revealed reflux grade to be the only predictor of resolution in both groups (Afshar, 2005). Thus **reflux associated with paraureteral diverticula resolves at rates similar to primary reflux and should be managed according to the prevailing indications for the reflux itself, irrespective of the diverticulum.** However, when a refluxing ureter enters a diverticulum, the latter is no longer paraureteral. With no muscular support to the UVJ, reflux is not expected to resolve. In a given patient, indications for repair require the combined consideration of the potential impact of unresolved reflux, if any, along with whether the diverticulum itself is of sufficient size or conformation to incite complications.

Renal Anomalies

By definition, primary reflux represents a dysfunction of the ureterovesical junction. Because the development of both the UVJ and the kidney itself are linked to the origin and fate of the ureteral bud, it is reasonable to consider the existence of reflux whenever an anomaly of renal form or number is present. **The cardinal renal anomalies associated with reflux are multicystic dysplastic kidney (MCDK) and renal agenesis, and the presence of either condition mandates a VCUG.** In the largest series to date, 75 patients with MCDK showed a prevalence of contralateral reflux of 26% (19 patients) and half of these were low grade (1 to 2) (Miller et al, 2004). Spontaneous resolution occurred in a mean of 4.4 years, regardless of grade. Only one patient had reflux corrected surgically. In a small series of ureteral ectopia, one patient with MCDK had the contralateral ureter enter into the ductus deferens (Wunsch et al, 2000), further underscoring the importance of documenting the contralateral kidney's ureteral conformation in patients with MCDK. Although contralateral renal growth often displays compensatory hypertrophy, one study observed somewhat less compensatory hypertrophy by 1 year of age (Zerin and Leiser, 1998) than may be expected if contralateral reflux is absent (5.1 cm vs. 6.2 cm median renal lengths, $P < .001$).

Renal agenesis is associated with an even higher prevalence of contralateral VUR. In a retrospective study of 46 children with solitary renal agenesis, the rate of contralateral renal pathology was 46%. VUR was by far the most common contralateral defect (28%) (Cascio et al, 1999) with UVJ and UPJO seen in 11% and 7%, respectively. Both UPJ and reflux were present in 1 patient. In another study, 19 cases of contralateral reflux were observed in 51 patients with ipsilateral renal agenesis (Song et al, 1995). Reflux repair or persistence was documented in nine and seven patients, respectively, with spontaneous resolution observed in only three patients. Whether renal agenesis represents one extreme on a continuum that includes MCDK is unclear. Nevertheless, these data suggest that contralateral reflux associated with renal agenesis may show less tendency to spontaneous resolution than that associated with MCDK.

Megacystis-Megaureter Association

Massive bilateral VUR can cause a gradual remodeling of the entire upper urinary tract. The gross inefficiency of the bladder that expels urine to both the exterior and the upper tracts results in gradual bladder dilation as the refluxed urine returns to the bladder. This perpetuates marked ureteral dilation leading to the radiographic appearance of massive hydroureter and a thin-walled enlarged bladder (Burbige et al, 1984). The phenomenon is referred to as the megacystis-megaureter association or syndrome. This configuration is even discernable in utero (Mandell et al, 1992). It

is more frequent in males, and the differentiation from posterior valves is crucial (Kaefer et al, 1997). Although the latter is due to an obstructive lesion, megacystis-megaureter is a nonobstructive condition akin to cardiac dilation by regurgitation from incompetent valves. Voiding studies will readily demonstrate an open posterior urethra and differentiate megacystis-megaureter from posterior valves or prune-belly syndrome. The persistent large residual urine volume is a significant risk factor for recurrent UTI. Vesicostomy can temporize by eliminating the residual urine volume and establishing safe drainage of the upper tracts until ureteral reimplantation can be performed. Given the propensity for reflux to exacerbate the effects of bacteriuria and the fact that ureterovesical junction dysfunction is the primary factor perpetuating the syndrome, surgical correction for the reflux is indicated. Treatments aimed at improving an already patent bladder outlet are contraindicated, risk infection, and fail to correct the primary etiology. A period of bladder rehabilitation by strict attention to emptying in the postoperative period (Koefoot et al, 1981) will usually result in a return to normal bladder volume and contractile behavior. This suggests that potentially normal underlying bladder physiology can be realized if the propensity for reflux is corrected.

Other Anomalies

VUR has also been described in association with a number of congenital conditions and syndromes. No precise common genetic insult has been determined to explain such associations. A complete survey of the Online Mendelian Inheritance in Man Database developed by Johns Hopkins University, maintained by the of the National Center of Biotechnology Information, reveals more than 40 different syndromes where VUR has been described (http://www.ncbi.nlm.nih.gov/Omim/getmap.cgi?l193000). These include the VACTERL association (*V*ertebral, *A*nal, *C*ardiac, *T*racheo*E*sophageal, *R*enal, and *L*imb anomalies), CHARGE syndrome (*C*oloboma, *H*eart disease, *A*tresia choanae, *R*etarded development, *G*enital hypoplasia, and *E*ar anomalies), and imperforate anus. In cases where VUR is anticipated, a VCUG is the initial study of choice to disclose both dysfunction at the UVJ, as well as overall bladder and bladder outlet anatomy.

Pregnancy and Reflux

The morphology of the urinary tract is altered with the onset of pregnancy and increases throughout gestation (Beydoun, 1985). **Bladder tone decreases because of edema and hyperemia, changes that predispose the patient to bacteriuria. In addition, urine volume increases in the upper collecting system as the physiologic dilatation of pregnancy evolves.** The slower drainage that results can enhance the growth of organisms and increase the propensity to develop pyelonephritis. It seems logical to assume that during pregnancy the presence of VUR in a system already prone to bacteriuria would lead to increased morbidity. A number of studies have been conducted to examine this relationship.

The presence of active reflux appears to present a risk factor for the affected mother. In 1958 Hutch described a higher incidence of pyelonephritis during pregnancy in 23 women with a history of reflux and recurrent bacteriuria. Heidrick and colleagues (1967) evaluated 321 women with cystography either during the last trimester or within 30 hours after delivery. The incidence of pyelonephritis was 33% in women with reflux compared with less than 5% in women without reflux. Finally, cystograms performed 4 to 6 months postpartum in 100 women with a history of asymptomatic bacteriuria during pregnancy showed reflux in 21%. Bacteriuria was easier to clear in patients without reflux (67%) than in those with reflux (33%) (Williams and Hulme-Moir, 1970).

Maternal history also becomes a factor if past reflux, renal scarring, or a tendency to UTIs is included. Martinell and colleagues (1990) compared the outcome of pregnancy in matched controls with that in 41 women with and without renal scarring after childhood UTIs. They found that women with a history of prior infections had a high incidence of bacteriuria during pregnancy, whereas those with renal scarring and persistent reflux were more prone to develop acute pyelonephritis. In a similar study, the outcome of pregnancy was assessed in 88 women with previous bacteriuria. Women with known scars had a 3.3-fold increased incidence of hypertension, a 7.6-fold increased risk of preeclampsia, and a higher rate of obstetric interventions. Women with normal kidneys and reflux also had an increased risk of hypertension during the last trimester (McGladdery et al, 1992). Pregnant women with bilateral renal scars were also shown to have a higher incidence of pre-eclampsia than those with unilateral scarring (24% vs. 7%, respectively) (El-Khatib et al, 1994), and those with creatinine elevation are also at risk (Jungers et al, 1987). In a large study of 158 women with reflux nephropathy, pregnancy was uneventful in patients with normal blood pressure and renal function, whereas the risks of fetal demise and accelerated maternal renal disease were increased in women with impaired renal function (Jungers et al, 1996).

The implications of reimplantation surgery were studied by Austenfeld and Snow (1988), who found an increased risk of UTI and fetal loss in 31 women who had undergone ureteral reimplantation as children, despite correction of the anomaly. In a follow-up study comparing these patients with a new cohort of historical controls, women with UTIs and reflux who underwent reimplantation (suggesting an initially higher degree of reflux and increased renal scarring) were still at significant risk of UTI during pregnancy (Mansfield et al, 1995). However, they were not at a higher risk of miscarriage than the general population. In a larger study of 77 pregnancies in 41 women whose ureters had been reimplanted, Bukowski (1998) and colleagues reported that the incidence of pyelonephritis during pregnancy was slightly higher than in the general population but that the fetus and mother were at significant risk when renal scarring or hypertension was present. Although these studies may at first suggest a limited benefit to reimplantation during a subsequent pregnancy, several factors must be borne in mind. None of these studies document any associated BBD in these women, which may have existed in childhood and continued unrecognized into the fertility years. Also, the bladder dynamics change during pregnancy as a result of increasing uterine size (see elsewhere). Although it is assumed that reflux remains absent during pregnancy following correction in childhood, radiologic verification that the surgically corrected UVJ remains competent (reflux free) is not feasible, and such data are not available. Finally, it is not known whether formerly refluxing renal units in such adult patients carry a latent predisposition or heightened susceptibility to pyelonephritis during the pregnancy as a consequence of previous postinfection damage during childhood and/or any inherent reflux-associated dysmorphism (both of which would persist despite surgery at the bladder level). When combined with the known physiologic renal and bladder changes during pregnancy, it is reasonable to speculate that such kidneys may carry a heightened predisposition to pyelonephritis.

In summary, the majority of studies examining the effects of VUR on pregnancy suggest that women with a history of reflux have increased morbidity during pregnancy because of

infection-related complications, whether the reflux has been corrected or not. **Women with hypertension and an element of renal failure are particularly at risk.** Those with uncorrected reflux appear to be particularly at risk and should have their reflux corrected before pregnancy to minimize maternal and fetal morbidity. The morbidity during pregnancy of women with persistent reflux without renal scarring remains poorly defined, but the tendency to UTI seems to be increased. Because of the difficulty in predicting an outcome for this subset of patients, most clinicians recommend surgical correction for girls with reflux that persists beyond puberty, although there has been a trend toward discontinuation of prophylactic antibiotics in older girls with active reflux. Long-term follow-up studies of these patients through puberty are unavailable (see later discussion).

Natural History and Management

Spontaneous Resolution

The one feature of VUR that provides the greatest relief to parents and caregivers but at the same time creates confusion in reflux study design and literature interpretation is spontaneous resolution. Indeed, the basis of contemporary medical therapy is predicated on an expected rate of spontaneous resolution. At birth, the probability of spontaneous resolution of primary reflux is roughly inversely proportional to the initial grade. If a patient is encountered at a later age, resolution from any point in time forward will depend on initial grade of reflux, if it is known, and age at presentation. For example, unilateral grade 3 reflux at birth should resolve in 70% of cases by age 5. However, if a 6-year-old with normal bladder function presents with grade 3 reflux, it is much less likely to resolve. However, given a growing tendency among some clinicians to reassess females for persistent reflux and possible endoscopic correction following a "holiday period" of nonfollow-up (between 5 years and the teenage years), it is possible new information remains to be learned about reflux resolution. Reflux likely resolves spontaneously due to remodeling of the UVJ over time, with progressive elongation and consolidation of the intravesical ureter and antireflux mechanism, as well as stabilization of bladder dynamics. Conversely, failure of the latter likely accounts for reflux persistence beyond the statistical norms in many patients. Indeed, inability to strictly understand bladder dynamics may have skewed earlier determinations of absolute reflux resolution rates but in doing so provided a "real-world" picture of spontaneous resolution.

Resolution by Grade

Most cases of low-grade reflux (grade 1 and 2) will resolve. Several studies have documented this high rate of spontaneous resolution. However, the variance in reported resolution rates for low-grade reflux was 63% of grade 2 (Duckett, 1983); 80% of grade 2 (Arant, 1992); and 85% of grade 2 (Edwards et al, 1977). This belies the fact that lower urinary tract dynamics may also play a role in mitigating spontaneous resolution.

Grade 3 reflux will resolve in approximately 50% of cases (Duckett, 1983; McLorie et al, 1990). Very few cases of higher-grade reflux (grades 4 and 5, and bilateral grade 3) will resolve spontaneously. Analyses from several sources including the International Reflux Study in Children support a uniformly low prevalence of resolved high-grade reflux with no more than 25% (Weiss et al, 1992b) and as little as 9% (Skoog et al, 1987) of patients demonstrating spontaneous resolution. It is possible no real difference exists in resolution rates in high-grade reflux (Tamminen-Mobius et al, 1992). When one considers the fact that any given reflux grade is assigned on the basis of a dynamic voiding study, the possibility for variability by at least one grade, especially in assigning higher grades to reflux, is quite real. Thus attempting to discriminate true differences in resolution rates for grades 3 and higher reflux may not be particularly clinically relevant.

Resolution by Age

The age at which reflux begins or is first encountered will play a more potent role in the management of the patient with reflux than the grade itself. It is self-evident that if reflux is a congenital disorder with an inherent tendency to resolve spontaneously over time, it will (1) be most prevalent in neonates and young children, and (2) will demonstrate the greatest tendency to resolve in this group. Conversely, in any analysis, if reflux is truly primary and encountered in an older child where it has been present since birth, it has already demonstrated a propensity to persist and therefore is self-selected for reflux, which is unlikely to resolve (Skoog et al, 1987). The 1997 AUA Guidelines data provide a synthesis of large numbers and reasonable statistical estimates of resolution rates segregated by age and grade (Elder et al, 1997) (Fig. 122–16). Interpretation of more recent follow-up studies

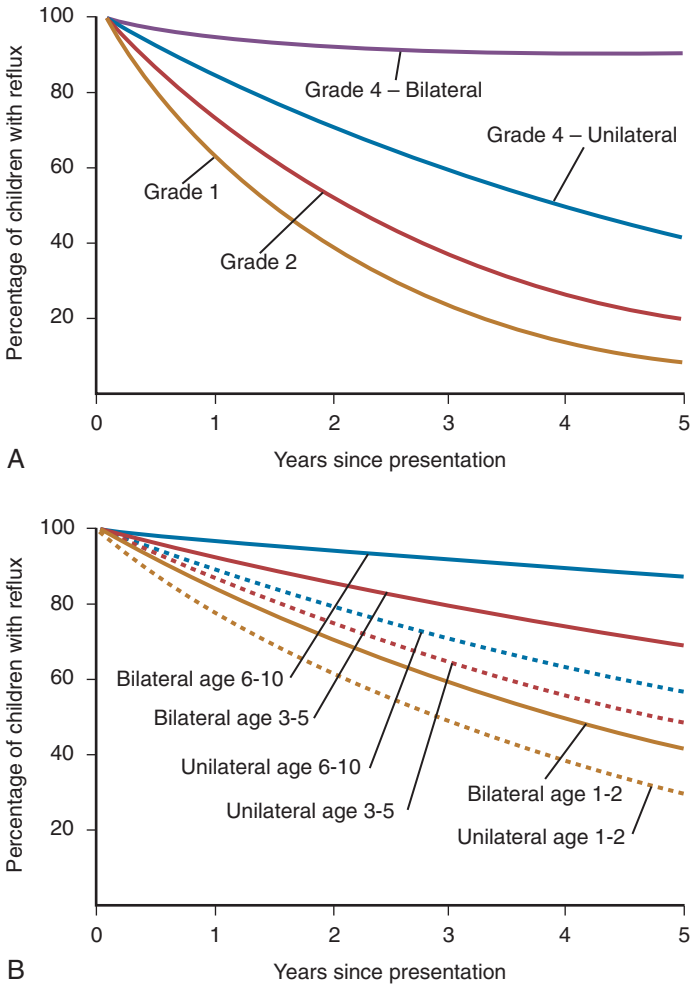


Figure 122–16. **A,** Percent chance of persistence of grades 1, 2, and 4 reflux for 1 to 5 years after initial evaluation. **B,** Percent chance of persistence of grade 3 reflux by age for 1 to 5 years after initial evaluation. (From American Urological Association. Report on the Management of Vesicoureteral Reflux in Children. Baltimore: American Urological Association, Pediatric Vesicoureteral Reflux Clinical Guidelines Panel; 1997.)

(Connolly et al, 2001) suggest that diagnosis at age 5, as well as in infancy, is associated with a similar resolution rate (20% per year), regardless of age. However, as stated at the outset, it must be remembered that resolution 5 years after age 5 implies reflux has required 10 years to resolve versus resolution 5 years after birth. Moreover, the observation by McLorie and colleagues (1990) that high-grade reflux in patients presenting after birth showed no difference in resolution rates between subjects younger and older than 1 year of age may reflect the generally poor resolution rate of high-grade reflux to begin with. Thus persistence in early life will imply persistence when older. These principles likely underlie the observation that when reflux resolves, it often does so within the first few years of life. The study by Skoog and colleagues (1987) observed that 30% to 35% of subjects resolved their reflux each year. Younger patients (<12 months old) resolved more quickly (1.44 vs. 1.85 years, $P < .02$), with grade 3 requiring slightly more time than grade 2 to resolve (1.56 vs. 1.97 years, $P < .04$).

The traditional period of observation for resolution is 5 years, probably because the greatest proportion of growth and anatomic remodeling of the UVJ is complete. In the McLorie and coworkers study (1990), 92% of resolved grade 3 reflux occurred within 4 years. There is a tendency to ascribe a benefit to the observation of interval reduction in grade. Such a finding could herald progression to resolution, but in the end it still carries the same risk of escalating a UTI to pyelonephritis and so should be interpreted with caution when counseling families. The resolution rates for VUR followed into the teenage and adult years remain unknown. **Clearly then, what constitutes reflux resolution depends on the period over which resolution is sought.**

Principles of Management

The medical and surgical therapy for reflux has purported to offer similar benefit to patients (Table 122–5). This has fueled the debate between fundamental choices of therapy for decades. The tension embedded in decision making for reflux management stems from the almost perfect results attainable by surgical correction of reflux, now commonly successful in more than 98% of cases. However, traditional practice in reflux management has held that the end does not justify the means: Reflux correction is not indicated merely because it can be corrected easily and reliably. As stated earlier, almost 80% of low-grade and half of grade 3 reflux will resolve spontaneously. Walker (1994) summarized the essential tenants of reflux management as follows:

1. Spontaneous resolution of reflux is very common.
2. High-grade reflux is less likely to resolve spontaneously.
3. Sterile reflux is benign.
4. Extended use of prophylactic antibiotics is benign.
5. Success of (open) surgical correction is very high.

Table 122–5.

Outcomes of Medical and Surgical Therapy for Children with Primary Vesicoureteral Reflux and Renal Scarring

REGISTRANT	NO. OF PATIENTS	NEW SCARS	THINNING
Europe			
Medical	155	19 (12%)	11 (7%)
Surgical	151	20 (13%)	15 (10%)
United States			
Medical	66	14 (20%)	9 (13%)
Surgical	64	16 (25%)	2 (3%)

Rather than providing strict guidelines for treatment, these principles provide ample room to individualize treatment on the basis of the particular preferences and tolerances of physicians, families, and patients for the various burdens each of the principles entails. **The classic approach has been to offer daily low-dose prophylactic antibiotic suppression of infections as the first line of treatment under the principle that every case of reflux should be offered time to resolve spontaneously, despite grade.** Clearly, age at presentation and grade will factor into predicting when and if resolution is likely to occur. In addition, in patients diagnosed after one or more episodes of pyelonephritis, the presence of scarring on renal scintigraphy may temper a decision for extended prophylaxis and observation, particularly if scarring is extensive, the reflux is high grade, renal function is already globally depressed, or congenital dysmorphism of one or both kidneys is present. In such cases, tolerance for yet another infection despite the presence of prophylaxis may be low, or simple disquiet with the notion of ongoing reflux may invite strong consideration for reflux correction.

As stated previously, it is not clear how long to wait for reflux resolution in the individual patient. In newborn patients, it is reasonable to wait until approximately 5 years of age assuming no intercurrent breakthrough infections occur. Beyond this age, it is commonly believed that the kidneys become less prone to scarring after pyelonephritis (Olbing et al, 2003), although the previously mentioned limitations in the interpretation of imaging inherent in the reflux literature should be remembered. Thus some practitioners are withdrawing prophylaxis as the child approaches the age of 5. After this age, boys with asymptomatic reflux will require little or no formal follow-up as long as lifelong attention to good bladder habits is reinforced, and they are counseled to seek prompt medical attention if a pyelonephritis were to occur in the future, as well as reassessment of their reflux status. Nevertheless, there would remain disagreement whether to correct asymptomatic bilateral high-grade reflux with normal renal parenchyma and function in an older boy despite the belief that sterile reflux is benign. Girls have traditionally undergone open surgical correction, even for asymptomatic reflux that fails to resolve by the age of 5, on the premise that it will reduce maternal and fetal morbidity during a future pregnancy. Using the rationale of antibiotic withdrawal in the older child, one study demonstrated that less than 10% of patients will subsequently develop recurrent febrile UTIs mandating surgical correction of reflux (Cooper et al, 2000), albeit with limited clinical follow-up and using only ultrasound imaging to assess renal health. Clinical guidelines for reflux management in children are presented in Table 122–6.

Adult patients who present with nonobstructive flank pain, febrile UTIs, or pyelonephritis and are found to have VUR have traditionally been offered antireflux surgery. Endoscopic correction of uncomplicated adult reflux should also be possible (Arce et al, 2009).

Emerging Role for Endoscopic Correction of Reflux. Endoscopic management is discussed in greater detail later. In North America the relative ease and low morbidity of endoscopic correction has begun to transform the indications for unresolved reflux correction in females. Indeed, although open antireflux surgery is more technically demanding, as well as more taxing on the older female patient, endoscopic correction can be easily performed well into the teenage years and beyond. Between the age of 5 and mid-to-late teens, girls with asymptomatic reflux may be treated in the same fashion as boys and have their antibiotic prophylaxis withdrawn and follow-up imaging suspended for several years, in the absence of any febrile UTI. This will also afford the opportunity

Table 122–6.

Treatment Recommendations for Boys and Girls with Primary Vesicoureteral Reflux*

VUR GRADE AND LATERALITY	CLINICAL MANIFESTATION AGE (yr)	INITIAL (ANTIBIOTIC PROPHYLAXIS OR OPEN SURGICAL REPAIR) GUIDELINE	FOLLOW-UP† (CONTINUED ANTIBIOTIC PROPHYLAXIS, CYSTOGRAPHY, OR OPEN SURGICAL REPAIR) PREFERRED OPTION	REASONABLE OPTION	GUIDELINE	PREFERRED OPTION	NO CONSENSUS‡
For Children without Scarring at Diagnosis							
1-2, unilateral or bilateral	<1	Prophylaxis					Boys and girls
	1-5	Prophylaxis					Boys and girls
	6-10	Prophylaxis					Boys and girls
3-4, unilateral or bilateral	<1	Prophylaxis			Bilateral: surgery if persistent§	Unilateral: surgery if persistent§	
	1-5	Unilateral: prophylaxis	Bilateral: prophylaxis			Surgery if persistent§	
	6-10		Unilateral: prophylaxis Bilateral: surgery	Bilateral: prophylaxis		Surgery if persistent§	
5, unilateral or bilateral	<1		Prophylaxis		Surgery if persistent§		
	1-5		Bilateral: prophylaxis Unilateral: prophylaxis	Bilateral: prophylaxis Unilateral: surgery	Surgery if persistent§		
	6-10	Surgery					
For Children with Scarring at Diagnosis							
1-2, unilateral or bilateral	<1	Prophylaxis					Boys and girls
	1-5	Prophylaxis					Boys and girls
	6-10	Prophylaxis					Boys and girls
3-4, unilateral	<1	Prophylaxis			Girls: surgery if persistent§	Boys: surgery if persistent§	
	1-5	Prophylaxis			Girls: surgery if persistent§	Boys: surgery if persistent§	
	6-10		Prophylaxis		Surgery if persistent§		
3-4, bilateral	<1	Prophylaxis			Surgery if persistent§		
	1-5		Prophylaxis	Surgery	Surgery if persistent§		
	6-10	Surgery					
5, unilateral or bilateral	<1		Prophylaxis	Surgery	Surgery if persistent§		
	1-5	Bilateral: surgery	Unilateral: surgery			Surgery if persistent§	
	6-10	Surgery					

*Recommendations were derived from a survey of preferred treatment options from 36 clinical categories of children with reflux. The recommendations are classified as follows:
Guidelines: treatments selected by 8 or 9 of 9 panel members, given the strongest recommendation language.
Preferred Options: treatments selected by 5 to 7 of 9 panel members.
Reasonable Alternatives: treatments selected by 3 to 4 of 9 panel members.
No Consensus: treatment selected by no more than 2 of 9 panel members.
†For patients with persistent uncomplicated reflux after extended treatment with continuous antibiotic therapy.
‡No consensus was reached regarding the role of continued antibiotic prophylaxis, cystography, or surgery.
§See the text regarding the length of time that clinicians should wait before recommending surgery.
From American Urological Association. Report on the management of vesicoureteral reflux in children. Baltimore: American Urological Association, Pediatric Vesicoureteral Reflux Clinical Guidelines Panel; 1997.

for a new cohort of older patients to provide longer-term resolution rates on a systematic basis. Girls may then return for a final cystogram. If reflux is still present, endoscopic injection is performed followed by a postinjection cystogram. Formal prospective trials of this proposition will be required to validate the principle.

Moreover, studies of parental preference in reflux management are revealing that endoscopic treatment may sometimes be preferred over either antibiotic prophylaxis or open surgery depending on the perceived duration for reflux resolution (Ogan et al, 2001; Capozza et al, 2003). However, such studies must be interpreted with caution in that any therapy that combines low morbidity and technical ease can become a seductive choice, especially since endoscopic therapy was preferred despite an acknowledged lower success rate than open surgery and potential for more than one anesthetic. Alternatively, others may tolerate only definitive open surgical correction.

Notwithstanding the ethical considerations of proffering endoscopic treatment for reflux correction, endoscopic indications have a wider theoretic potential than open surgery. For example, even if the durability of endoscopic correction is not indefinite, recognizing that the prime age for postpyelonephritic scarring is younger than 5 years, one could conceive of temporary reflux correction by endoscopy for the early years, obviating the need for several years of prophylaxis in either males or females. Beyond 5 years, postinjection recurrence of asymptomatic reflux in males, were it to occur, would be of little clinical consequence. Males would require re-evaluation only if pyelonephritis were to occur anytime after the age of 5 years. In females, demonstration of durability of injection therapy extending from infancy to at least the end of the childbearing years would be required. One recent long-term study documents only a 5- to 7-year durability of 80% (Dodat et al, 2004); thus in one fifth of patients, reflux recurs. Moreover, these results represent the brand of injectable agent called Macroplastique. Similar data are as yet unavailable for Deflux. Nevertheless, regardless of the substance injected and the uneven durability reported to date compared with open reflux correction, the endoscopic approach to reflux management has gained favor over the past several years in both Europe (Puri et al, 2003; Lendvay et al, 2006) and the United States.

Medical Management: Watchful Waiting

Although some reports have suggested the existence of "water-hammer" renal damage from high-grade reflux of sterile urine against the renal papillae (Hodson et al, 1975; Hagen and Klevmark, 1991), no such clinical entity has been predictably demonstrated. Because it is not reflux per se that is actually being managed, **the hallmark of observational therapy in reflux disease can be more accurately termed "watchful waiting" while maintaining urinary sterility through the judicious use of single daily low-dose antimicrobial prophylaxis.** Often, antibiotics are given as oral suspensions once per day and preferably at night. **Nighttime dosing allows for antibiotic concentration in the bladder urine over the longest period of expected physiologic retention, when infection is most likely to develop.** For children younger than 2 months of age, the most commonly used medications are trimethoprim and amoxicillin. **Children younger than 2 months of age possess relative hepatic immaturity and are unable to clear sulfamethoxazole efficiently; the drug displaces fetal bilirubin and leads to jaundice.** After 2 months of age, the antibiotic of choice becomes trimethoprim-sulfamethoxazole (TSX, Septra, Bactrim). Like virtually any drug, some mild side effects should be kept in mind and include gastrointestinal upset and allergy. Although transient leucopenia has been reported with TSX, it is rare, resolves with discontinuation of the drug, and is not believed to be significant enough to warrant regular monitoring of white blood cell counts in all children taking the drug. The other drug most commonly used is nitrofurantoin (Macrodantin). Nitrofurantoin may minimize the development of resistance to fecal organisms, the latter being the largest reservoir for urine infectivity. This drug is known to cause pulmonary fibrosis and, rarely, interstitial pneumonia. However, oral tolerance is less than with TSX due to taste, and gastrointestinal symptoms are subjectively worse. A recent comprehensive literature review of the use of these drugs by Karpman and Kurzrock (2004) in children revealed a low incidence of significant hepatic (five patients) or pulmonary (nine patients) involvement, almost always associated with full-dose rather than once-a-day low-dose therapy. Finally, a growing literature on the use of probiotics (live microorganisms such as strains of *Lactobacillus,* which may displace and suppress the growth of uropathogenic bacteria) is addressing UTI prophylaxis in children (Bruce and Reid, 2003; Reid and Devillard, 2004; Salvini et al, 2004). The mechanisms that underlie the demonstrated benefit of probiotic use are now emerging (Reid, 2006; Storm, 2011). Further studies will be required to define the use of this attractive approach in the medical treatment of patients with reflux.

Breakthrough febrile UTIs or pyelonephritis while on antibiotic prophylaxis are generally considered an indication for termination of watchful waiting and correcting the reflux. However, individual documentation and verification of true breakthrough infection varies widely. As such, it is likely that instances of premature reflux correction (false positive) and failure to proceed with reflux correction (false negative) are to be expected. This possibility underscores the importance of proper antibiotic dosing, patient and parental acceptance and compliance with the chosen therapy, and meticulous attention to proper collection and handling of urine culture specimens (see earlier). Although the interaction between host defenses and bacterial virulence factors is what ideally dictates breakthrough infection, **Smellie has provided useful interpretations surrounding practical causes of breakthrough infection: 1. If the organism is sensitive to the prescribed prophylactic antibiotic, the child or parent has likely not been compliant or the dose is too low, 2. If the organism is resistant to the prescribed antibiotic, either the residual bladder volume is too high too often or the dose is too high** (Smellie, 1991). Indeed, many referrals for definitive reflux correction result from breakthrough UTI following full-dose antibiotic usage for extended periods.

Once the radiographic resolution of reflux has been documented, antibiotic prophylaxis is terminated, usually a few days after the cystogram. **However, because reflux resolution will likely herald a tapering off or discharge from regular urologic follow-up, this also is the precise time for reinforcing a lifelong adoption of good toileting and bladder behaviors.**

Landmark Studies

The efficacy of medical management rests with a few key studies that came to define and establish watchful waiting as a cornerstone of therapy for reflux disease. Smellie and colleagues led a series of studies that repeatedly demonstrated the ability of low-dose prophylactic antibiotics to prevent infection and renal scarring while reflux resolved in a significant majority of children (Edwards et al, 1977). Since then two additional large-scale

prospective studies validated this approach and helped to further define the natural history of VUR.

International Reflux Study in Children. The International Reflux Study in Children was a North American (Weiss et al, 1992a) and European (Tamminen-Mobius et al, 1992) cooperative study that randomized children younger than 9 years old with high-grade reflux to watchful waiting with prophylaxis or corrective open surgery (see Table 122–5). **Although surgery was complicated by temporary postoperative obstruction in some patients, it was more effective than prophylaxis in reducing, but not eliminating, the occurrence of pyelonephritis. Nevertheless, the incidence of UTI (38%) was the same with both modalities. Furthermore, both modalities were equally effective in reducing, but not eliminating, new scar formation.** Only the European arm stratified data for the effect of dysfunctional voiding behaviors (18%) (van Gool et al, 1992). **When untreated, voiding dysfunction was associated with more UTIs, more persistent cases of reflux, and greater grade variation during follow-up.**

Birmingham Reflux Study. Medical and surgical management was prospectively compared in a randomized cohort of 104 patients with high-grade reflux (Birmingham-Reflux-Study-Group, 1987) over a 5-year period. Again, the incidence of new scars was the same using either treatment modality. Although more than half the patients continued to reflux at 5 years, all cases of new scarring occurred within the first 2 years, consistent with the "Big Bang" concept of postinfectious renal injury mentioned previously.

Additional Prospective Studies. Medical management alone was assessed in 59 patients (84 refluxing ureters, grades 1 to 3) by the Southwest Pediatric Nephrology Group (Arant, 1992). Resolution occurred in 67%, breakthrough infection in 33%, and new scarring in 10% of the low-grade and 28% of the grade 3 patients. Scholtmeijer (1993) demonstrated resolution in 57% of 47 cases of grade 3 to 4 reflux followed by watchful waiting and prophylaxis for 5 years. Interestingly, 15 cases underwent surgical correction after breakthrough infection and 6 of these subsequently developed new scars, whereas 2 of the patients managed medically developed new scars.

RIVUR Study. Despite the long-standing standard of care regarding medical management of VUR using prophylactic antibiotics, there exist mounting countervailing concerns over the long-term use of low-dose antimicrobials. These concerns are likely fueled at least in part by the documented abundant use of antibiotics both within the medical arena and in the food chain, as well as the rising incidence of antimicrobial resistance (Cheng et al, 2008; Alam et al, 2009). Furthermore, newer prospective studies are beginning to question the ability of daily antibiotic prophylaxis to reduce the incidence of UTI (see later). Reflux management is being further challenged by discordant and seemingly random recommendations variously for watchful waiting with or without antibiotic prophylaxis or first-line endoscopic, laparoscopic, or open correction of the reflux, depending on the individual consultant. The lack of appropriate (placebo) controls or observational arms in prior retrospective reflux studies has further called their conclusions into question. If daily low-dose antimicrobial prophylaxis is to maintain any position as a first-line treatment, its true efficacy will require greater scrutiny. One major study addressing this question is termed the RIVUR study (*R*andomized *I*ntervention for the Management of *V*esico*U*reteral *R*eflux). RIVUR is a National Institutes of Health multicenter, double-blind, randomized, placebo-controlled trial designed to evaluate the effectiveness of antimicrobial prophylaxis in children found to have reflux after an initial UTI. Fifteen collaborating centers have enrolled approximately 600 children with grade 1 to 4 reflux following an initial febrile UTI. Study participants have been randomized to oral placebo versus oral trimethoprim-sulfamethoxazole antibiotic prophylaxis. The primary outcome measure is the development of recurrent febrile or symptomatic UTI (Chesney et al, 2008; Greenfield et al, 2008; Keren et al, 2008; Matthews et al, 2009).

Antibiotic Controversies and Potential New Approaches

The principal rationale for antibiotic use in the management of reflux is in the prevention of urinary infection, principally febrile pyelonephritis, which may lead to permanent postinfection renal scarring. Driving this rationale in part is the belief that the *first* febrile UTI, in the presence of reflux, will create the greater proportion of clinically significant postinfection scarring, despite the fact that this concern is based on models of postinfection scarring in experimentally induced reflux in animals with a priori **normal** renal development (Torres et al, 1985). This belief, in turn, spawned the now routine and widespread sonographic follow-up of prenatal hydronephrosis for evidence of postnatal hydronephrosis, which, if present, then triggers the documentation of reflux by cystography in order to prevent the first febrile UTI by instituting immediate antibiotic prophylaxis if reflux is found.

However, several recent prospective studies have brought into question the ability of chronic low-dose antibiotic prophylaxis to prevent UTI in children. For example, in children with grade 2 to 4 reflux, following an initial UTI, randomization of 50 patients each to antibiotic prophylaxis versus no treatment groups showed no difference in the rate of subsequent UTI or renal scarring (Pennesi et al, 2008). One multicenter trial of 225 children with reflux aged 1 to 3 years, randomizing subjects to antibiotic prophylaxis versus no treatment, found no statistical overall reduction in UTI incidence with prophylaxis, although subset analysis did suggest some benefit in boys with grade 3 reflux (Roussey-Kesler et al, 2008). As a corollary, patients with ongoing reflux in whom prophylactic antibiotics have been withdrawn have not suffered any increased incidence of UTI when compared with age-matched refluxing control patients who remain on prophylaxis (Leslie et al, 2009). Similarly, patients who have failed endoscopic reflux correction and remain uncorrected fail to show any increased incidence of UTI whether they remain on prophylaxis or not (Moore et al, 2009).

Such studies are plagued with a host of important shortcomings including small patient numbers, high dropout rates, inaccurate urine collection methods (i.e., bags), no placebo controls, routine screening rather than evaluation in response to symptoms including screening bagged sample collections in uncircumcised infants, and lack of distinction between febrile and febrile UTIs. Many of these shortcomings are being addressed in the large RIVUR study mentioned earlier. Nevertheless, despite their limitations, these studies have succeeded in casting new doubt on the true and precise effectiveness and role of antibiotic prophylaxis in reflux management. However, in the recent Swedish Reflux trial (Brandström et al, 2010c) girls 1 to 2 years old with grade 3 to 4 VUR prospectively randomized to antibiotic prophylaxis had a significantly lower incidence of new renal scars compared with those randomized to surveillance (no antibiotics) and endoscopic treatment. New scars were more prevalent following febrile UTIs (11/49 or 22%). In contrast, only 3% (4/152) of nonfebrile

UTIs were associated with new renal damage ($P < .0001$). The rate of new renal damage was low in boys (observed in 2 of 75 males enrolled). These data support the use of antibiotic prophylaxis in girls younger than 2 years of age with grade 3 to 5 VUR.

Endoscopic correction of VUR did not reduce the incidence of new renal scars or febrile UTIs. However, the relatively low success rate of endoscopic treatment in this study (54% complete resolution with an additional 17% downgraded to grades 1 to 2) may have negated any potential benefit of endoscopic correction.

When added to the underlying concern for the long-term use of antibiotics in general, studies that bring into question the efficacy of antibiotic prophylaxis are giving rise to reflux management alternatives. Where low-dose antibiotic prophylaxis may be of questionable value, the effectiveness of appropriate full-dose antibiotic treatment of UTI by eliminating fever and symptoms of acute illness, as well as eradicating the infection, is not in question. Therefore one alternative is close observation for UTI symptoms without prophylaxis, coupled with precise treatment of culture-proven UTI. However, two recent pediatric nephrology studies of UTI (Doganis et al, 2007; Hewitt et al, 2008) suggest that early (within 24 hours) versus later (within 4 to 7 days) antibiotic treatment does not necessarily reduce the incidence of postpyelonephritic scarring if the kidneys become involved in the UTI, though early treatment may reduce initial renal involvement (Doganis et al, 2007). Moreover, in both studies, reflux was not found to be a significant variable affecting scarring incidence. In both studies, limitations such as precise knowledge of timing of UTI onset and the previously mentioned limitations of DMSA scanning in differentiating pre-existing renal dysmorphism from true postinfection renal scarring (none of the foregoing study subjects had preinfection scans) remain.

With regard to endoscopic correction of reflux, the aforementioned chemoprophylaxis and invasive imaging concerns, the ease of endoscopic therapy, and parental preference for endoscopic correction despite knowledge of a lower success rate versus open surgery (Ogan et al, 2001) may be among the factors driving the resurgence and ever-increasing use of endoscopic correction of reflux. If this trend continues without rigorous prospective analysis, it could erode equipoise, to potentially position this technique as another first-line therapy following reflux diagnosis. Although studies of primary endoscopic therapy are emerging from South America and Europe (Nortes Cano et al, 2008), no North American studies endorsing this as a primary approach for low-grade reflux management are yet available. One uncontrolled retrospective study has suggested that endoscopic correction may reduce incidence of subsequent UTI, similar to the conclusion of the International Reflux Study, though endoscopic correction was not primary therapy (Wadie et al, 2007). More importantly, the durability of endoscopic reflux correction is in question, with two recent studies documenting 20% and 27% delayed recurrence of reflux following initial successful reflux correction (Sedberry-Ross et al, 2008; Holmdahl et al, 2010). Thus the indications for primary endoscopic correction of reflux will require carefully designed prospective randomized trials taking into account patient age and concomitant stage of renal development and renal susceptibility to scarring. In addition, other patient factors known to modify surgical outcomes such as pre-existence or subsequent onset of elimination dysfunction must be considered. Finally, given the high incidence of incidental and clinically silent reflux in the normal population, as well as the high propensity for reflux to resolve over time, primary endoscopic correction of reflux without knowing which patients will benefit physiologically and clinically will likely result in both unnecessary correction of reflux destined to resolve naturally and/or correction of reflux with no clinical benefit.

Antibiotic prophylaxis is not a panacea—this approach is destined to fail without adequate teaching and periodic review of perineal hygiene techniques, timely bladder emptying habits, and anticonstipation measures. Similarly, family compliance with the antibiotic administration and follow-up visits for imaging may vary widely (Wan et al, 1996). Careful discussion of obligations and expectations should take place to assess whether watchful waiting is appropriate in each case. Given the need for strict compliance with such an approach, alternative regimens such as alternate-day dosing of prophylactic antibiotics, or early aggressive treatment of UTI with full-dose antibiotics with no prophylaxis otherwise, while conceptually attractive, will be at risk for decreasing compliance, especially when new opportunities for relaxing a daily routine and awareness are introduced into the management profile. If families or patients are willing but unable to maintain all the elements of a watchful waiting treatment regimen, then consideration for open or endoscopic correction of VUR may be relatively indicated.

Surgical Management

Starting with Hutch's initial report on the successful correction of VUR in seven out of nine paraplegic patients (Hutch, 1952), multiple surgical techniques have been described to effectively correct VUR. Currently, the principles from these techniques have been incorporated into a handful of procedures with excellent results. The choice of procedure is individualized according to the surgeon's experience and the patient's condition.

Surgical Principles of Reflux Correction

The principles of surgical correction of reflux include the following:

- Exclusion of causes of secondary VUR
- Adequate mobilization of the distal ureter without tension or damage to its delicate blood supply
- Creation of a submucosal tunnel that is generous in caliber and satisfies the 5:1 ratio of length to width recommended by Paquin (1959)
- Attention to the entry point of the ureter into the bladder (hiatus), the direction of the submucosal tunnel and the ureteromucosal anastomosis to prevent stenosis, angulation, or twisting of the ureter
- Attention to the muscular backing of the ureter to achieve an effective antireflux mechanism
- Gentle handling of the bladder to reduce postoperative hematuria and bladder spasms

The surgical procedures can be classified on the basis of the approach to the ureter as *intravesical, extravesical* or *combined*. Furthermore, they can be classified on the basis of the position of the submucosal tunnel in relation to the original hiatus into *suprahiatal* or *infrahiatal*.

The following components apply to all of the various surgical techniques. The surgeon is free to select the appropriate components tailored to the patient's anatomy to achieve a successful ureteral reimplant. Prophylactic antibiotics may be administered with induction of anesthesia. The patients are generally admitted the morning of the surgery unless there are specific reasons requiring preoperative admission. Enemas are only reserved for select cases because all issues related to dysfunctional elimination should be addressed when the diagnosis of VUR is made.

Cystoscopy

Historically, many centers performed cystoscopy following the diagnosis of VUR with the premise that it offers a predictive assessment of the likelihood of spontaneous resolution of VUR. Parameters such as shape (except for the golf hole orifice associated with high-grade reflux) and location of the ureteral orifice and the submucosal tunnel length were subsequently found not to have a predictive value (Duckett and Bellinger, 1982). Therefore cystoscopy in the course of conservative management of VUR is only indicated to confirm or manage abnormalities found on other imaging modalities (Ferrer et al, 1998).

Some surgeons choose to perform cystoscopy at the time of ureteral reimplantation surgery following the induction of anesthesia. This is helpful in identifying subtle anomalies not detected on preoperative imaging, particularly if an extravesical technique is employed and the bladder is not opened. Preoperative cystoscopy may uncover inflammatory changes, trabeculation, duplication anomalies, or anatomic anomalies at the ureterovesical junction such as small ureteroceles or diverticula.

The bladder should be examined as it is distending because a paraureteral diverticulum may not be apparent until the bladder is moderately to fully distended. Some authors have suggested the use of hydrodistension of the ureteral orifice (Kirsch et al, 2004), particularly of the contralateral ureter, as a predictor of which ureters will develop contralateral reflux after surgery. PIC cystography (Rubenstein et al, 2003) has also been recommended for the detection of occult reflux in children who have had febrile UTI and a negative VCUG. In both of these techniques the tip of the cystoscope is positioned at the ureteral orifice and the irrigating fluid flow (with or without radiographic contrast) is directed at the ureter. The elevation of the anterior wall of the ureter, allowing visualization of the ureteral lumen, and/or the retrograde flow of contrast detected by fluoroscopy is considered to be indicative of an incompetent UVJ that might reflux during a UTI or following contralateral surgery but remains to be validated.

At the completion of cystoscopy the bladder is left half full if an intravesical technique is contemplated. If an extravesical technique will be used, a Foley catheter connected to a three-way adapter can be inserted to allow bladder distension to facilitate the dissection of the detrusor flaps.

Positioning

The child is positioned supine. To facilitate exposure of the bladder, especially in older children and adolescents, a rolled towel may be placed at the level of the upper sacrum or a slight break in the table is used to raise the lower pelvis and hips. All pressure points are appropriately padded, and a wide surgical prep is performed. The hips are abducted slightly to allow access to the urethra in girls if required; in boys the penis is prepped and draped in the field.

Incision

A Pfannenstiel skin incision, along a skin crease, is made about 2 cm above the symphysis pubis to the lateral edges of the rectus muscles. If the child is exceptionally overweight, the classic Pfannestiel can be extended. The anterior rectus fascia is opened in a transverse fashion and elevated superiorly to just below the umbilicus and inferiorly to the symphysis pubis. The pyramidis muscles attach between the pubic bone and the anterior rectus sheath. Thus they should not be separated from the rectus sheath. The bellies of the recti are then separated in the midline exposing the bladder. Alternatively, after the skin and Scarpa fascia are incised, the skin can be mobilized off the anterior rectus sheath and the linea alba can be opened in the midline vertically.

Intravesical Procedures

Approaching the Ureters

The peritoneum is gently swept off the dome of the bladder. This is easier with a moderately full bladder. The bladder is opened in the midline down to about 2 cm proximal to the bladder neck. Figure-of-eight stay sutures, using 3-0 Prolene, are placed at the junction of the lateral edges with the bladder dome and at the inferior apex of the incision to prevent extension of the incision into the bladder neck. A Dennis-Brown retractor provides excellent exposure. Saline-soaked sponges are folded and gently packed into the dome of the bladder and also placed along the lateral edges of the bladder incision. Three blades of the retractor are used to retract the lateral walls of the bladder and the dome. The retractor blades should be placed with the utmost care, and minimal touching, suctioning, or rubbing of the bladder mucosa are recommended to prevent edema or inflammation of the mucosa, which can lead to bleeding and difficult mucosal dissection and may aggravate the bladder spasms in the postoperative period.

Intravesical Mobilization of the Ureter

The ureter(s) is cannulated with a 3- or 5-Fr Silastic feeding tube that is sutured to the bladder mucosa at the inferior edge of the ureteral orifice with 5-0 Prolene. This serves to maintain orientation of the ureter during all phases of the procedure and is used to handle the ureter and apply gentle traction. Before ureteral mobilization, some surgeons inject epinephrine 1:200,000 submucosally to reduce the bleeding. Using needlepoint cautery, a circumscribing incision is made in the bladder mucosa about 1 to 2 mm away from the ureteral orifice. With gentle traction on the feeding tube, the ureter can now be mobilized into the bladder. Mobilization of the ureter is best started at the 6 o'clock position by spreading the blades of the tenotomy scissors gently in a posterior direction initially. Once the correct plane is entered, the dissection is carried out circumferentially. The adventitia of the ureter must not be violated to prevent ischemic injury to the ureter. The ureter is freed from its attachments to the bladder using a fine right-angle clamp and electrocautery. This is aided by gentle traction on the feeding tube. Dissection of the ureter is continued until it can reach the contralateral bladder wall without tension. At that point the surgeon is ready to develop the submucosal tunnel using the same ureteral hiatus or a suprahiatal technique depending on experience and preference.

Suprahiatal Tunnels

Politano-Leadbetter Technique

The principle behind this technique, which was originally described by Politano and Leadbetter (1958), is to bring the ureter in through a new hiatus superior to the original insertion. A submucosal tunnel is created in the direction of the trigone, medial to the original orifice. The advantage of this technique is that a long tunnel can be created, which is valuable in the higher grades of reflux. This antireflux mechanism can also be further supported by a psoas hitch.

Technique

After completion of the ureteral mobilization intravesically, the location of new hiatus is selected in a **straight line superior to the original orifice** (Fig. 122–17). With the bladder open

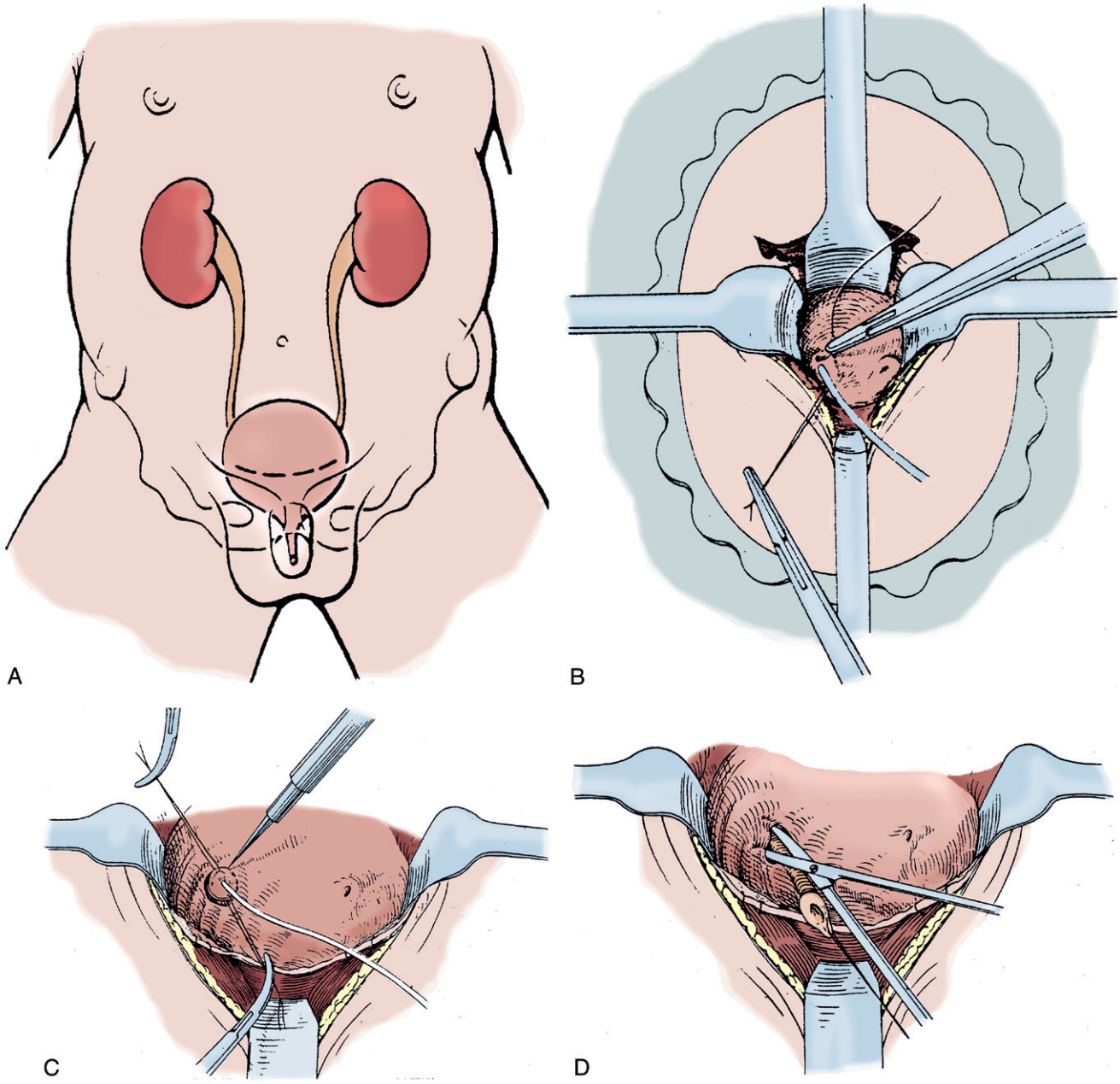


Figure 122–17. Politano-Leadbetter technique. **A,** Typical approach to the bladder for reimplantation. A transverse, lower abdominal incision is made along a skin crease one or two fingerbreadths above the symphysis pubis. **B,** Fine sutures are placed above and below the ureteral orifice for handling. A feeding tube in the ureter aids in the initial dissection. **C,** A needle-tip cautery outlines a circumferential incision around the orifice. **D,** Tenotomy scissors initially establish the plane of dissection inferiorly, where ureteral damage can be avoided. The plane is then carried around the ureter.

Continued

and the lateral walls retracted, the inexperienced surgeon might be inclined to position the new hiatus too laterally on the posterior wall. Once the bladder is closed and full, the ureter enters on the anterolateral wall and then hooks back posteriorly toward the trigone, creating the classic "hooking," which is an important cause for postoperative ureteral obstruction. In the original description of the Politano-Leadbetter technique, the new hiatus was created blindly by passing a right-angle clamp from the original hiatus behind the bladder to puncture through the posterior wall of the bladder at the new hiatal opening. This blind maneuver must be discouraged because it is the cause of significant complications that may be associated with this procedure such as routing the ureter intraperitoneally, injury to bowel, vas deferens, vagina, or other nearby structures. The current approach is to retract the superior lip of the original hiatus with a stay suture or a vein retractor and to clear the back wall of the bladder bluntly under direct vision. A right-angle clamp is then used to create a new hiatus through which the ureter enters the bladder. The submucosal tunnel is created in the direction of the trigone, medial to the original orifice. The length of the tunnel depends on the diameter of the ureter. A 5:1 ratio (length to width) as suggested by Paquin is a helpful guide. It is important to lift the mucosa off the detrusor at the point of entry of the ureter into the bladder so that the mucosa can be closed properly over the new hiatus. The

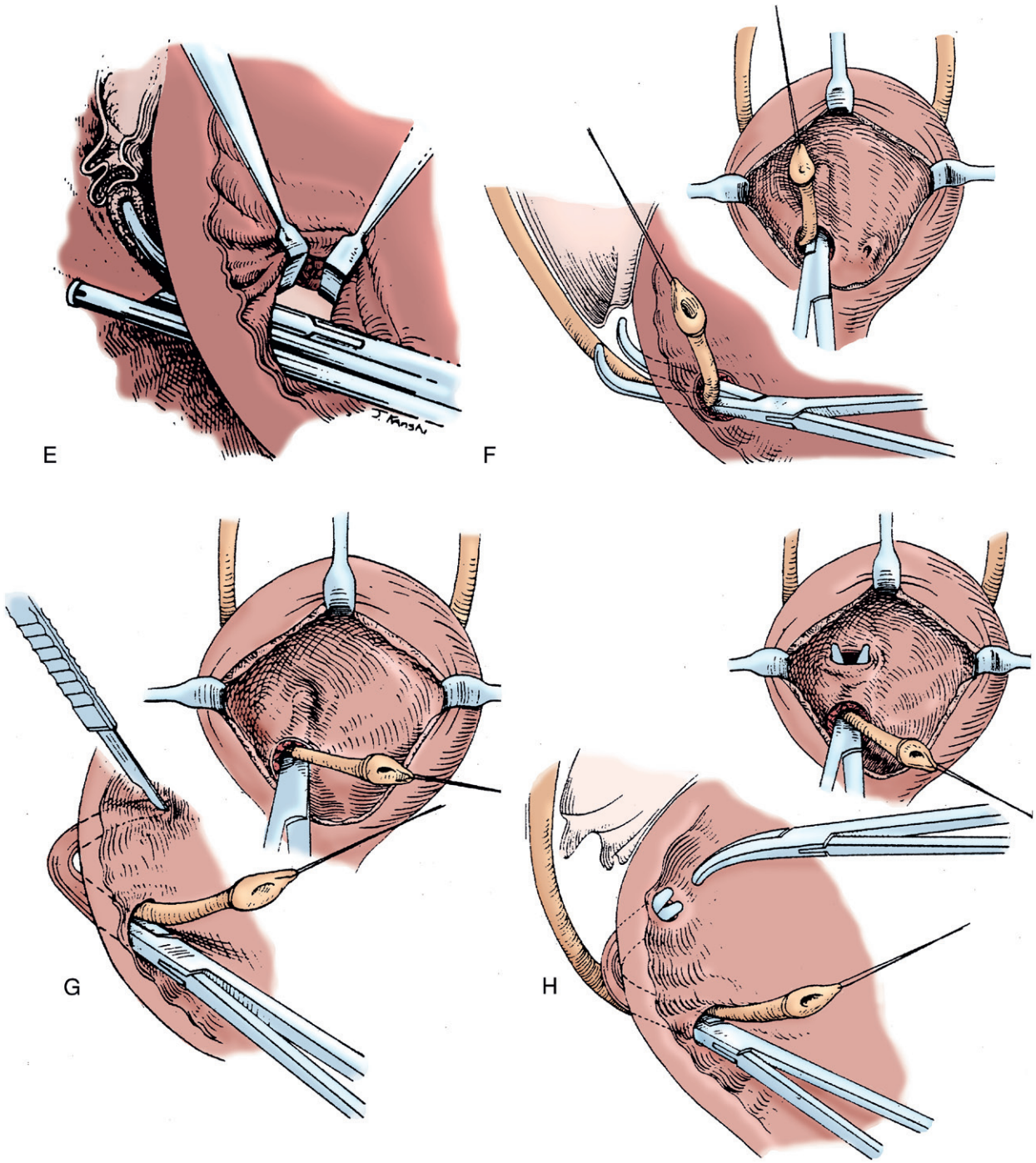


Figure 122–17, cont'd. **E,** With the aid of a lighted suction tip and two Senn retractors, a fine gauze dissector is used to sweep the peritoneum from the posterior bladder wall. **F,** After sweeping the peritoneum away, a blunt right-angle clamp indents the bladder from behind at a new hiatus approximately 2.5 cm superior and somewhat medial to the original hiatus. **G,** The clamp is incised on from within and generously spread to make certain that the new hiatus is wide enough. **H,** A second right-angle clamp follows the first from within the bladder to the original hiatus.

tunnel should be capacious enough to prevent constriction of the ureter. The ureter is pulled through the tunnel, and the feeding tube is removed.

Ureteral Anastomosis. The ureter is spatulated ventrally (at the 6 o'clock position), and the edges are freshened if necessary. Three interrupted sutures of 5-0 polyglactin placed relatively close to each other anchor the ureter to the trigone by suturing it to the bladder muscle and mucosa. The anchoring sutures should be placed carefully because the apex of the spatulation is the narrowest point of the ureter. The remainder of the ureteral anastomosis is carried out with interrupted 5-0 polyglactin sutures at the 3, 9, and 12 o'clock positions. The 12 o'clock suture may also be used to evert the anterior wall of the ureter, thus creating a small cuff. Although a 5-Fr feeding tube passed up the ureter confirms patency and absence of kinks, the most reassuring sign that the ureteral reimplant is not obstructed is to see the jet of urine emerging from the orifice. It is thus important to communicate to the anesthesiologist the importance of adequate fluid

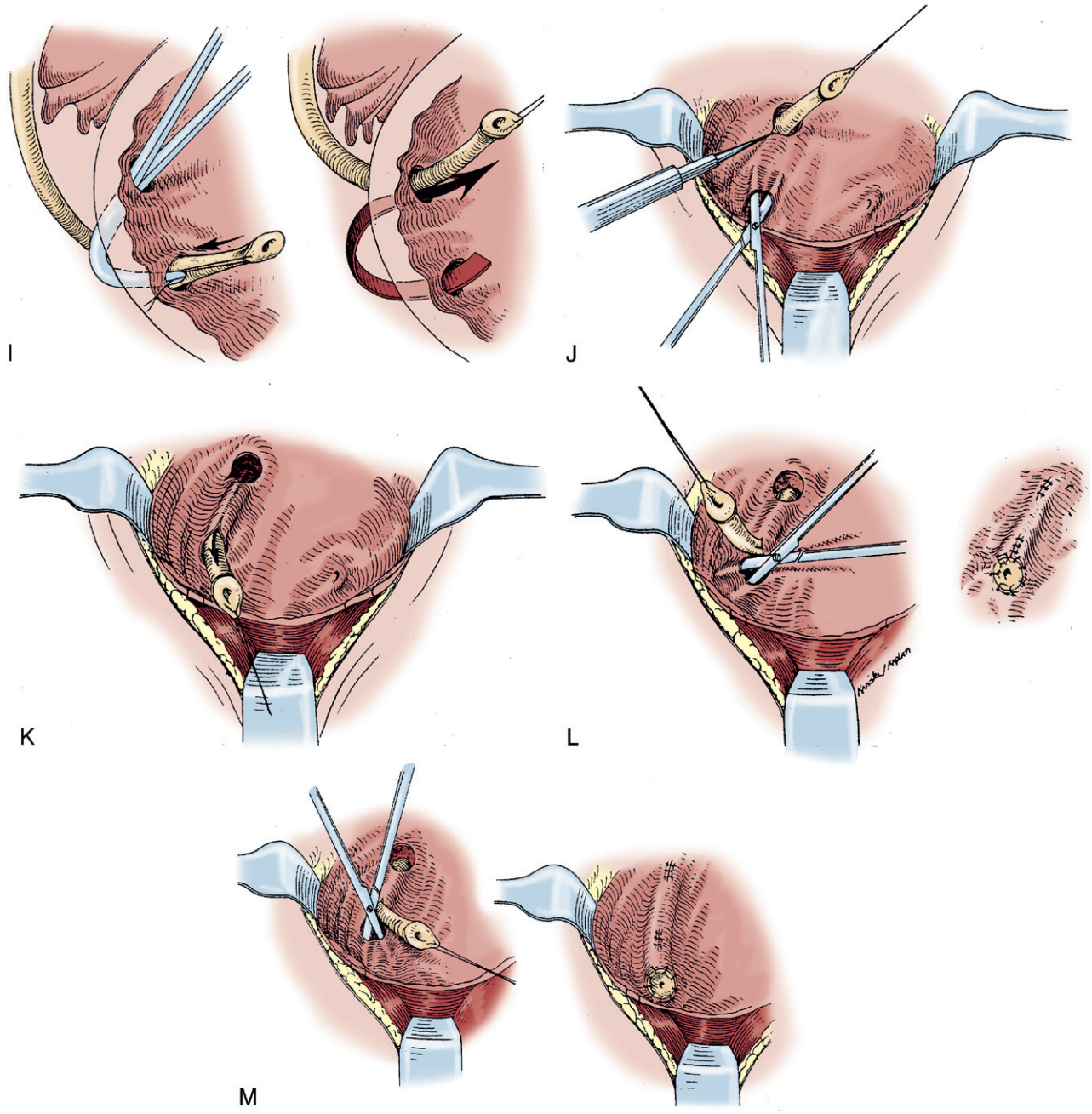


Figure 122–17, cont'd. **I,** The right-angle clamp grasps the stay suture, and the ureter is pulled through the new hiatus. **J,** The inferior lip of muscle at the new hiatus is divided for a few millimeters to eliminate any ureteral angulation at its entrance to the submucosal tunnel that is created with scissors. **K,** The ureter is brought through the new tunnel to the original hiatus. **L,** The ureter is anastomosed to the original hiatus in the classic Politano-Leadbetter technique. Proximal mucosa can be closed over the ureter to give the tunnel additional length. **M,** Ureteral advancement is also helpful, especially if the original hiatus is laterally positioned. A second submucosal tunnel can be created toward the bladder neck to place the new orifice in a more inferior position and gain additional length for the reimplant. (**A** to **D** and **F** to **M,** From Retik AB, Colodny AH, Bauer SB. Pediatric urology. In: Paulson DF, editor. Genitourinary surgery, vol. 2. New York: Churchill Livingstone; 1984. p. 757–63; **E,** from Keating MA, Retik AB. Management of failures of ureteroneocystostomy. In: McDougal WS, editor. Difficult problems in urologic surgery. Chicago: Year Book; 1989. p. 121.)

administration throughout the case. The mucosa overlying the new hiatus is closed with a running 5-0 polyglactin suture. The bladder is closed in two layers using a 3-0 polyglactin suture. A Foley catheter is used to drain the bladder for 48 hours; drains and stents are only employed for the more complex cases.

Paquin Technique

Paquin described this combined extravesical/intravesical technique in 1959 (Paquin, 1959). The new ureteral hiatus is created from outside the bladder, thus avoiding the difficulties associated with this maneuver in the Politano-Leadbetter technique. As with most of the other open techniques, a success rate greater than 95% for primary VUR is achieved with this method (Woodard and Keats, 1973).

The ureter in the Paquin technique can be approached extravesically (see Extravesical Mobilization of the Ureter) before opening the bladder. A right-angle clamp is applied at the ureterovesical junction, the ureter is divided, and a 3-0 polyglactin suture

is used to suture ligate the original hiatus. The bladder is then opened in the midline, and a new hiatus is created, located cephalad to the prior position. The peritoneum is carefully cleared off the back wall of the bladder at the site of the new hiatus. A right-angle clamp is passed from inside the bladder under direct vision, and one end of a 5-mm Penrose drain is pulled into the bladder. A mosquito snap is applied to the Penrose drain, which acts as a holder and facilitates the creation of the submucosal tunnel. The mucosa is dissected off the detrusor circumferentially at the new hiatus. The length of the submucosal tunnel is governed by the diameter of the ureter, and a 5:1 ratio is usually achievable. In more complex cases a psoas hitch may be required to achieve a longer tunnel length. The tunnel is developed by carefully lifting the mucosa off the detrusor using tenotomy scissors. Countertraction on the mucosa is helpful, especially in redo cases and when the bladder wall is trabeculated. Once the tunnel is developed the remainder of the reimplants is similar to the Politano-Leadbetter procedure.

The modified Paquin technique is particularly suited for dilated ureters and complex (El-Sherbiny et al, 2002) and failed reimplants (Mesrobian et al, 1985) because of the versatility offered by the combined extravesical/intravesical approach to the ureter and the ability to achieve longer submucosal tunnel lengths.

Infrahiatal Tunnels

Glenn-Anderson Technique (Fig. 122–18)

In 1967 Glenn and Anderson described their technique of ureteral reimplantation (Glenn and Anderson, 1967). By using the same hiatus and advancing the ureter distally toward the bladder neck, the potential complications associated with the Politano-Leadbetter technique, specifically kinking of the ureter, are avoided. The ureter is mobilized as described earlier. A submucosal tunnel is created toward the bladder neck using tenotomy scissors. The distance from the hiatus to the bladder neck limits the length of the tunnel. Glenn later described a modification that allows creation of a longer tunnel by incising the detrusor proximally at the original hiatus (Glenn and Anderson, 1978). The detrusor edges are then reapproximated distal to the ureter. With advancement of the ureter toward the bladder neck, the distal anastomosis of the ureter could be challenging with this technique. As with the other procedures, the results with this technique are excellent with a 98% success rate (Gonzales et al, 1972).

Cohen Cross-Trigonal Technique

Cohen's technique (1975) overcomes the limitation of the tunnel length in the Glenn-Anderson technique by directing the tunnel across the trigone toward the contralateral bladder wall (Figs. 122–19 and 122–20). The difficulty with the distal anastomosis in the Glenn-Anderson technique is also eliminated.

Cohen's technique is particularly suited for small bladders or thick-walled bladders (PUV or neuropathic) because the ureteral advancement across the back wall of the bladder rarely results in kinks or obstruction. The cross-trigonal reimplant is also the procedure of choice in conjunction with bladder neck reconstructive procedures because the superior displacement of the ureters provides room for adequate elongation of the bladder neck.

As a result of its simplicity and reliable results (up to 99% [Glassberg et al, 1985; Kennelly et al, 1995; McCool and Joseph, 1995; El-Ghoneimi et al, 1999]), Cohen's procedure has become the most commonly employed intravesical reimplant.

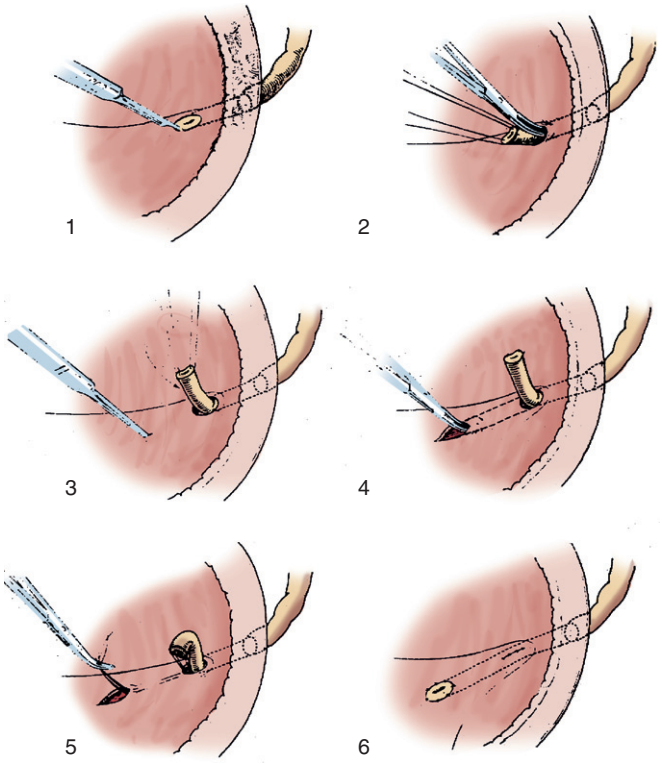


Figure 122–18. Glenn-Anderson technique. The ureter is mobilized and advanced beneath a new submucosal tunnel. (From Glenn JF, Anderson EE. Distal tunnel ureteral reimplantation. J Urol 1967;97:623.)

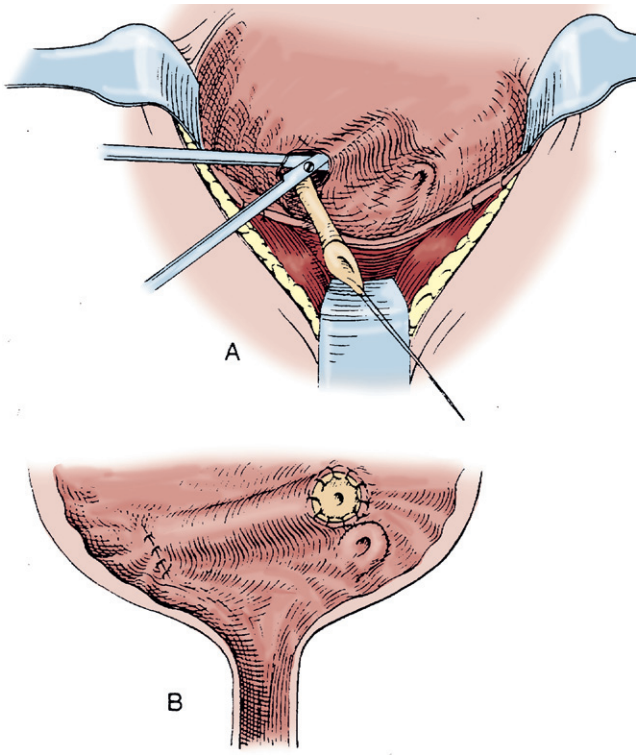


Figure 122–19. Cohen cross-trigonal technique, unilateral reimplantation. After the ureter is freed **(A),** a submucosal tunnel is made, with the new mucosal hiatus just above the contralateral ureteral orifice **(B).** (From Retik AB, Colodny AH, Bauer SB. Pediatric urology. In: Paulson DF, editor. Genitourinary surgery, vol. 2. New York: Churchill Livingstone; 1984. p. 764.)

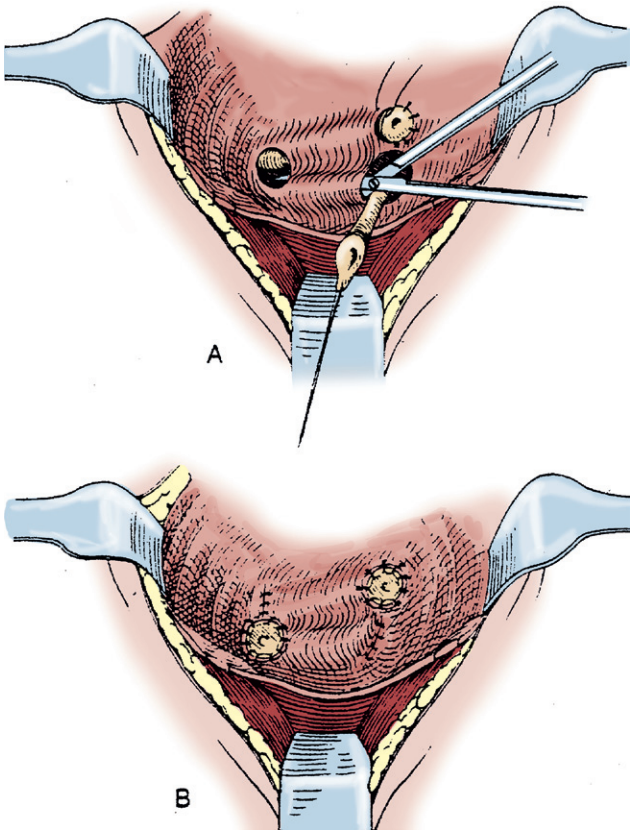


Figure 122–20. Cohen cross-trigonal technique, bilateral reimplant. **A,** The more superior ureter is tunneled transversely, with its new orifice just above the contralateral orifice. **B,** The other ureter is tunneled inferiorly, with its new orifice located at the inferior-most portion of the contralateral hiatus. (From Retik AB, Colodny AH, Bauer SB. Pediatric urology. In: Paulson DF, editor. Genitourinary surgery, vol. 2. New York: Churchill Livingstone; 1984, p. 765.)

Critics of this technique cite the difficulty of retrograde catheterization of the superolaterally positioned ureteral orifice for radiographic studies, insertion of stents, and management of ureterolithiasis as significant disadvantages. Suggested approaches to overcome this include suprapubic cystotomy by trocar (Lamesch, 1981) or 14-gauge 5-cm intravenous cannula in conjunction with cystoscopy to direct the ureteral catheter into the ureter or by using a curved tip vascular access catheter and an angle-tipped glide wire with a torque device (Wallis et al, 2003) or the use of a flexible ureteroscope.

Method

1. The technical methods of the Cohen and Glenn-Anderson procedures are similar in many aspects.
2. The ureter is approached and mobilized using the standard intravesical approach.
3. A hiatal groove may be created on the medial side of the ureter to reduce the angulation of the ureter as it crosses transversely, especially when the bladder wall is thickened. If the hiatus is excessively patulous, it can be reapproximated with one or more interrupted 3-0 polyglactin sutures to avoid diverticulum formation (Ahmed and Tan, 1982). The hiatus should easily accommodate the tips of a large right-angle clamp alongside the ureter to avoid obstruction of the ureter.
4. The submucosal tunnel is developed using the tenotomy scissors as previously described. When only one ureter is reimplanted, the tunnel is directed superior to the contralateral ureteral orifice. If both ureters are reimplanted, the tunnel for the more laterally displaced ureter is directed superior to the contralateral orifice. The second tunnel is directed toward the inferior edge of the orifice of the laterally displaced ureter. A common submucosal tunnel has been used successfully for bilateral reimplants (Androulakakis et al, 2003).
5. The ureter is spatulated and anastomosed to the bladder mucosa as described in the Politano-Leadbetter technique. The mucosa over the old hiatus is closed with 5-0 polyglactin sutures.
6. Alternatively, the mucosal cuff of the ureteral orifice may be preserved and anastomosed to the bladder mucosa without spatulation.
7. The ureter is catheterized with a 5-Fr feeding tube to ensure patency, although the continuous efflux of urine from the orifice provides the best assurance of patency.
8. Closure of the bladder and drainage is completed as described previously.

Extravesical Procedures

Lich and colleagues (1961) in the United States and Gregoir (1964) in Europe independently described the extravesical approach to ureteral reimplantation (Fig. 122–21). The technique became more popular following the modifications described by Daines and Hodgson (1971), and Zaontz and colleagues (1987) popularized anchoring the ureter with advancement sutures. These modifications allow for a combined advancement of the ureter and lengthening the tunnel proximally. In addition, anchoring sutures fix the ureter distally and thus maintain stability of the tunnel. The advantage of the extravesical technique is that the bladder is not opened; thus postoperative hematuria and bladder spasms are minimized. The technique is simple to learn and is readily taught.

The main concern with this technique has been the development of transient voiding inefficiency that is seen in up to 20% (Fung et al, 1995; Lapointe et al, 1998; Lipski et al, 1998; Barrieras et al, 1999; Marotte and Smith, 2001) of children who undergo bilateral extravesical reimplants. The mechanism is thought to be due to disruption of the nerves to the bladder bilaterally possibly due to excessive use of cautery during the detrusorotomy. The population most at risk appears to be boys younger than 3 years of age with bilateral high-grade reflux (Barrieras et al, 1999).

Leissner and colleagues (2001) used human cadavers to study the topography of the pelvic plexus in an effort to understand the mechanism of injury to the plexus resulting from extravesical reimplant surgery. They demonstrated that the main portion of the pelvic plexus is located approximately 1.5 cm to 2 cm dorsal and medial to the UVJ in adult cadavers. Smaller branches travel along the medial aspect of the ureter, outside the thin layer of tissue (the mesoureter) that surrounds the ureter. On the basis of their anatomic description, injury to the branches of the pelvic plexus is avoided if dissection of the distal ureter is carried out between the mesoureter and ureteral adventitia. Yucel and Baskin (2003) further refined the description of the neuroanatomy of the distal ureter and UVJ using immunohistochemical analysis and three-dimensional imaging techniques in normal human fetuses (21 to 40 weeks' gestation). They confirmed the localization of the nerves along the medial aspect of the ureter just outside the Waldeyer sheath. At the UVJ the nerves surround the ureter in a

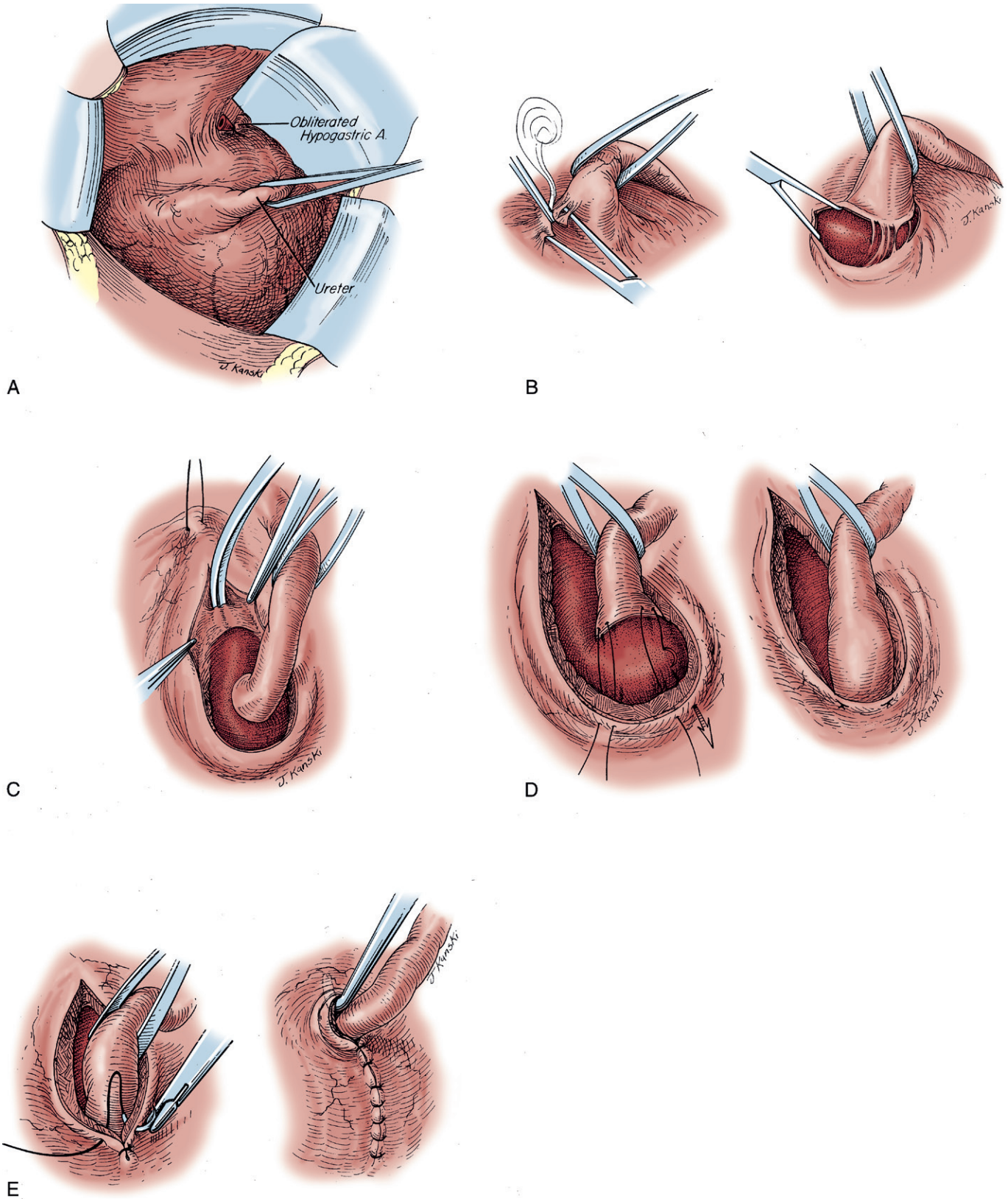


Figure 122–21. Modified Lich-Gregoir/detrusorrhaphy technique. **A,** The ureter is identified and gently grasped after ligation of the obliterated hypogastric artery. **B,** The ureter is circumferentially mobilized at its intersection with the bladder by incising the detrusor at the level of the ureteral hiatus. **C,** The serosal and muscular layers of the bladder (4 to 5 cm) are opened along a straight course cephalad and lateral from the ureterovesical junction to create the trough for reimplantation. A tacking suture aids in orientation. **D,** The bladder mucosa is elevated off muscle wall, and vest-type sutures are placed from the detrusor at the distal limit of dissection to the proximal ureteral adventitia and back again through same tissue planes. Tying of the vest sutures advances and anchors the ureter onto the trigone. **E,** Reapproximation of the detrusor creates a long submucosal tunnel and completes the repair. (From Peters C, Retik AB. Ureteral reimplantation including megaureter repair. In: Marshall FF, editor. Textbook of operative urology. Philadelphia: WB Saunders; 1996. p. 868–70.)

network-like fashion; distally, once the ureter enters the bladder, the nerves localize on the detrusor muscle distal and lateral to the ureter. From these two studies it is suggested that the incidence of voiding inefficiency observed after bilateral extravesical reimplants depends on the surgical technique. The injury is limited to the smaller nerve branches rather than the actual pelvic plexus, which is located medially and posteriorly. The neural damage may be due to transection of the nerves, electrocautery, or neuropraxia caused by surgical trauma. Injury to the nerves may be prevented by limiting the dissection to the correct plane, just outside the ureteral adventitia, reducing the use and power of electrocautery, restricting the incision of the detrusor distal to the UVJ, and gentle handling of the tissues (David et al, 2004).

Patients who develop urinary retention, requiring insertion of a Foley catheter or intermittent catheterization, are able to void within 1 to 2 weeks (Minevich et al, 1998a; Barrieras et al, 1999) indicating the reversibility of the neurologic lesion.

Approaching the Ureters

A Pfannensteil incision is used as described earlier. It is best to have the bladder somewhat distended to this point to facilitate dissection of the peritoneum of the lateral bladder wall. The obliterated umbilical artery is identified. The ureter crosses medial to the point of origin of the obliterated umbilical artery from the internal iliac artery. This is an excellent anatomic reference point for identification of the distal ureter. Dividing the obliterated umbilical artery facilitates dissection and mobilization of the ureter. Some authors were concerned that the injury to the bladder innervation occurs when the obliterated umbilical artery is divided. However, Lipski and colleagues (1998) demonstrated that there was no difference between two groups of patients whether the obliterated umbilical artery was divided or not. The peritoneum is meticulously reflected off the anterior surface of the ureter. In order to avoid injury to any of the branches of the pelvic plexus, it is recommended that the surgeon stay right on the ureter during its dissection being careful not to injure blood vessels running in the ureteral adventitia. A vessel loop is passed around the ureter and used as a handle. Dissection and mobilization of the ureter is carried distally to the point where it tunnels under the detrusor muscle.

Creation of the Extravesical Tunnel

With the bladder in its normal anatomic position, the course of the ureter along the posterior wall of the bladder is identified and marked for a distance of 5 cm. The bladder is reflected medially; a Dennis Brown retractor is quite helpful for this procedure. The outlined course of the ureter is inspected. The peritoneal reflection may need to be gently lifted off the wall of the bladder. With the bladder retracted, the tunnel direction will appear to be pointing toward the anterior abdominal wall. It is important to have the bladder full and somewhat tense but not overstretched. The detrusor is incised using low current electrical cautery (15 watts) to create the new submucosal tunnel. Following that, tenotomy scissors are used to divide the detrusor fibers along the same line of the initial incision down to the bladder mucosa. Care should be taken to incise the detrusor fibers along one line, without wandering sideways, in order to facilitate lifting the detrusor off the mucosa with minimal disruption to the detrusor muscle and its innervation. Blood vessels are easily seen as one incises the detrusor fibers, and these are cauterized selectively with bipolar cautery. It is critical that all detrusor muscle bundles are divided before elevation of the detrusor flaps. When the last detrusor bundles have been divided, a **uniform** mucosal dome bulges out. This provides the surgeon with an excellent point of reference that the tunnel has been established in the correct plane.

The detrusor is dissected off the mucosa on either side of the incision, for a width slightly larger than the circumference of the ureter. This dissection is best carried out from proximal to distal, leaving the dissection around the ureter as the final step of the tunnel creation.

There is a definite **avascular** plane between the muscle and the mucosa. The most efficient method to realize this dissection is to have the assistant grasp the detrusor bundles closest to the mucosa with two forceps elevating the muscle off the mucosa. The surgeon gently depresses the mucosal bulge with one hand and uses the tenotomy scissors to sharply separate the muscle bundles off the mucosa, on either side, along the length of the tunnel. Injury to the mucosa during dissection of the tunnel is quite avoidable unless the bladder is thick walled and trabeculated. Inadvertent injury to the mucosa could be closed with a 6-0 polyglactin figure-of-eight suture. It is not necessary to create a wide tunnel unless the ureter is very dilated.

Particular attention is necessary when dissecting around the ureter. The detrusor fibers attached to the ureter are carefully divided, staying close to the ureter to avoid injury to any of the terminal nerve branches entering the bladder. The dissection is carried out along the lateral and medial attachments of the ureter but is not extended distally.

The original modification described by Zaontz and colleagues (1987) for the extravesical procedure included incision of the detrusor distal to the ureteral orifice for 5 to 10 mm with advancement of the ureter using two vest sutures. Leissner and colleagues (2001) demonstrated that this particular aspect of the procedure may be responsible for injury to the bladder innervation at the trigonal area and may be the lead cause of urinary retention in bilateral extravesical reimplants. Therefore in order to avoid damage to the nerves, this maneuver should be avoided unless there is a paraureteral diverticulum that requires repair simultaneously (Jayanthi et al, 1995). In those cases, dissection of the detrusor distal to the ureter should be carried out in a limited fashion.

Once creation of the submucosal tunnel is complete, the bladder is decompressed before reapproximation of the detrusor. The ureter is positioned in the new tunnel, and the detrusor reapproximated using interrupted 3-0 polyglactin sutures. To achieve alignment of the tunnel, it is best to place the most proximal suture first at the new ureteral hiatus and to leave it untied and tagged on a mosquito snap. Tension applied to this suture straightens and elevates the detrusor flaps, allowing the surgeon to reapproximate the detrusor without risk of injury to the ureter or the mucosa. The suturing commences at the most distal portion. The adventitia of the ureter may be incorporated in one or two of these sutures to stabilize the tunnel and prevent a diverticulum from forming at the most distal or proximal portion of it. At the completion of the suture line, the caliber of the hiatus should be tested with a right-angle clamp to ensure absence of any constriction or compression of the ureter.

The bladder is refilled and the retractor is removed. The course of the ureter is reinspected to ensure absence of any kinks in the retroperitoneum or any bulging of the mucosa at either end of the tunnel.

A Foley catheter is left for 24 to 48 hours; some authors recommended not leaving a catheter at all (Marotte and Smith, 2001). If an epidural caudal catheter is inserted for postoperative analgesia, it should be discontinued 6 to 12 hours before removal of the Foley catheter.

If the child is observed to void without problems, he or she is discharged, to return for a follow-up ultrasound and a VCUG usually 3 months postoperatively.

Postoperative Evaluation

In expert hands the success rate for ureteroneocystostomy in patients with low-grade primary VUR approaches 100%. As a result of these outstanding outcomes, several centers have evaluated the need for postoperative invasive imaging. Most agree that an ultrasound is necessary at 6 to 12 weeks postoperatively. In a large study by Barrieras and colleagues (2000), 723 renal units were evaluated. At 1 year postoperatively there was a significant difference between children who had undergone surgery for low-grade primary VUR (99% resolution) versus those with high-grade reflux (94%). Thus in patients who initially had low-grade primary reflux, in whom the preoperative and postoperative ultrasound was normal and do not have voiding dysfunction or recurrent UTIs (Lavine et al, 2001), the success rate with uncomplicated ureteroneocystostomy approaches 100% (Bisignani and Decter, 1997; Bomalaski et al, 1997b; El-Ghoneimi et al, 1999; Barrieras et al, 2000; Grossklaus et al, 2001). On the basis of these reports, it has been suggested that the postoperative VCUG can be avoided in this group of patients. This recommendation should be individualized on the basis of the family situation and the expertise of the center performing the surgery. Some families have followed reflux for several years and are anxious to know with certainty that the reflux has resolved. In other families, the children are quite reluctant to undergo another VCUG, and in this situation it may be reasonable not to perform a postoperative study unless the child has a dysfunctional bladder or develops postoperative hydronephrosis or UTIs. However, the lower success rate for high-grade reflux would still support complete postoperative studies in most cases.

Following ureteroneocystostomy, the presence of minimal ureteral dilatation and low-grade hydronephrosis on early postoperative ultrasound is not unusual (Barrieras et al, 2000; Bomalaski et al, 1997b). Indeed, this common finding should argue against performing such studies too early after surgery. On the other hand, persistence of this dilatation beyond 3 months or its progression should be further investigated (Aboutaleb et al, 2003). Additionally, the development of new renal scars on late follow-up ultrasound, a discrepancy in renal growth, or recurrent UTIs may warrant complete radiologic re-evaluation of the patient.

As discussed previously, children with renal scarring should have their blood pressure measured at every visit with their family physician.

Complications of Ureteral Reimplantation

Early Complications

Persistent Reflux. Early reflux following ureteroneocystostomy is usually not a significant clinical problem and commonly resolves by 1 year on repeat cystography. In the report by Barrieras and colleagues (2000), 49 out of 723 renal units had reflux at 3 months, 11 of which were contralateral. At 12 months' follow-up, reflux resolved spontaneously in 20 of the 38 ipsilateral and in 8 of the 11 contralateral ureters. Persistent reflux at 1 year was more common in patients who had high-grade reflux preoperatively. In their study 30% of patients undergoing surgery had high-grade reflux. Two thirds of those with persistent reflux at 1 year (12/18) were from that group. Thus the majority of low-grade postoperative reflux detected in the initial VCUG at the 3-month follow-up point disappeared spontaneously, likely due to the resolution of the bladder inflammation and improvement in bladder dysfunction that may be present in the early postoperative period.

Contralateral Reflux. The issue of contralateral reflux has been the subject of several reports in the literature over the past 15 years, most of which are retrospective. Minevich and colleagues (1998b) and Burno and colleagues (1998) noted a low incidence of contralateral reflux after unilateral extravesical detrusorrhaphy in 5.6% and 11.6% of their patients, respectively. Diamond and colleagues (1996b), in a multicenter trial of 141 patients, reported an 18% incidence of contralateral VUR. These patients were analyzed according to grade of initial reflux, presence of a Hutch diverticulum or duplex system, and the surgical technique employed to correct the reflux. There was no difference noted among the various surgical techniques, but there was a significant trend toward development of contralateral reflux with the higher grades of ipsilateral corrected reflux and correction of reflux in duplex systems. They concluded that the distortion of the contralateral hemi-trigone was not a responsible factor for contralateral reflux but rather the severity (grade 5) of reflux, and the presence of a duplex system put patients at risk for development of contralateral reflux postoperatively. Conversely, Kumar and Puri (1997) reported on 495 children with unilateral reflux who had undergone subureteral Teflon injections. New contralateral reflux was diagnosed in only 37 children (7%). They were unable to find any correlation between the grade of preoperative ipsilateral reflux and postoperative contralateral reflux and suggested that low incidence of new contralateral VUR may be due to a relative noninterference with the contralateral trigone afforded by endoscopic compared with open reflux correction. They refuted the existence of the pop-off mechanism accounting for new contralateral reflux in their series because the risk of new contralateral reflux did not correlate with the preoperative reflux grade (grades 4 and 5). Sparr and colleagues (1998) reviewed a series of 143 patients on conservative management and initially diagnosed with unilateral reflux but subsequently developed metachronous contralateral reflux. Contralateral reflux appeared in 33%, suggesting a different etiology for the appearance of contralateral reflux unrelated to surgical correction. They speculated that the contralateral reflux was in fact synchronous (i.e., bilateral) but missed on initial cystogram or that the natural history of unilateral or bilateral reflux may involve intermittent appearance and disappearance of VUR on one side.

Prophylactic bilateral reimplantation for unilateral reflux, to avoid contralateral reflux, is not warranted on the basis of the high spontaneous resolution rates (Burno et al, 1998). Recommendations for management of contralateral reflux range from observation in the majority of cases to intervention for control of clinical pyelonephritis episodes. In asymptomatic children, younger than 4 to 5 years of age, prophylactic antibiotics are warranted for postoperative contralateral reflux, particularly if one is to be consistent with the medical therapy for the previous ipsilateral reflux. If the child remains asymptomatic and infection free, repeat VCUGs may not be necessary because contralateral reflux resolves spontaneously in the majority of children. In girls around the age of puberty, controversy persists as to whether a VCUG and correction of reflux at that point become necessary.

Obstruction. It is not unusual to detect a mild to moderate degree of hydronephrosis in the early postoperative period by ultrasound (see earlier). This should resolve spontaneously with time. Acute postoperative obstruction may be related to technical issues such as twisting or kinking of the ureter in its new tunnel,

intramural blood clots, or extramural compression by submucosal hematoma or edema at the site of anastomosis. Progressive, significant obstructions usually become apparent in the first 2 weeks after surgery. The children typically present with symptoms of acute ureteral obstruction including acute abdominal pain, nausea, and vomiting. Although infection is less common, if it occurs it is quite significant in the obstructed system. The diagnosis is readily made on ultrasound where the severe hydroureteronephrosis is confirmed by delayed function and excretion on renal scintigraphy. In the more significant cases, drainage of the system either by retrograde insertion of a double-J stent or a percutaneous nephrostomy tube may be necessary. The nephrostomy tube should be internalized as early as possible to avoid a dry reimplant. Many of these cases resolve without requiring additional surgery.

Long-Term Complications

Obstruction

Progressive dilatation of the ureter and kidney following reimplantation surgery can be due to several factors and can be classified on the basis of the location of the obstructive lesion:

Suprahiatal—twist of the ureter or ischemia due to poor handling of the ureter are the most common causes of suprahiatal obstruction.

Hiatus—at the point of entry into the new hiatus angulation of the ureter, most commonly due to a hiatus that is positioned too lateral or anterior such that when the bladder fills, the ureter becomes carried laterally and anteriorly, resulting in the "high reimplant" phenomenon. These ureters drain better when the bladder is empty. This situation may resolve spontaneously but on occasion requires stenting or redo surgery.

Tunnel—A submucosal tunnel that is not adequately developed can lead to compression of the ureter causing obstruction within the tunnel. The submucosal tunnel is obviously more difficult to develop in an abnormal bladder such as the valve or neuropathic bladder. Developing a smooth, capacious, submucosal tunnel can be quite challenging because of the irregularities created by the muscular hypertrophy, trabeculation, and cellule formation. Ischemia to the ureter and the submucosal tunnel is another important factor that results from improper handling of the ureter, leading to its devascularization. Significant obstruction in the submucosal tunnel can be overcome by balloon dilatation and stenting for a period of time. If conservative measures are unsuccessful, redo reimplantation is required.

Orifice—The anastomosis of the ureter to the bladder and the new hiatal position is an important technical aspect of the reimplant procedure. The most vulnerable point for obstruction is the apex of the ureteral spatulation. The apical sutures must be placed with the utmost of care to ensure an adequate orifice caliber. Stenosis can also occur as a result of ischemic changes. Isolated obstruction of the orifice can be managed by dilatation and stenting. If the submucosal tunnel is of adequate length, endoscopic unroofing of the distal few millimeters including the orifice may relieve the obstruction while maintaining the antireflux mechanism.

Recurrent or Persistent Reflux

Failure of antireflux procedures in primary low-grade reflux is extremely rare. Most failures are due either to high-grade reflux or to an inadequate ratio of tunnel length to ureteral diameter. Development of a short tunnel and failure to taper the excessively wide ureter are obvious important factors. Another significant cause of persistent or recurrent reflux is due to failure to recognize secondary reflux, especially associated with neurogenic bladders and posterior urethral valve bladders. **Reflux in these situations is secondary to the poor storage or emptying characteristics of the bladder. These issues need to be addressed and optimized before reimplant surgery is attempted.** In most situations improving bladder storage and/or emptying with a combination of an anticholinergic and intermittent self-catheterization results in spontaneous resolution of secondary reflux (Agarwal et al, 1997). Proceeding with reimplantation surgery in the presence of an abnormal bladder only results in worsening of the ureteral dilatation and deposition of scar tissue in the pelvis, which would render future attempts at correcting the reflux even more difficult.

Redo Reimplantation

Redo reimplantation is technically more challenging and requires careful attention to detail and meticulous surgical technique. Dissection of the ureter and extensive mobilization is required in order to achieve an adequate submucosal tunnel. Careful dissection of the ureter is best accomplished by a combination of extravesical and intravesical mobilization as needed. The ureter should be carefully evaluated and ischemic segments excised. Free bleeding from the divided distal end should be observed in addition to peristaltic activity, assuring normal musculature and blood supply. It is preferable to create a new hiatus and submucosal tunnel. If the ureter is shorter, a psoas hitch (Fig. 122–22) can be used to facilitate the creation of the antireflux mechanism. The psoas hitch should be carried out with nonabsorbable suture before creation of the submucosal tunnel. The bladder is fixed to the psoas muscle sheath on either side of the iliac vessels, providing a stable posterior bladder wall. In children, the bladder can be mobilized sufficiently to bring it up almost to the bifurcation of the common iliac vessels. This may provide adequate bridging for a distal ureteral defect. A psoas hitch can be achieved only on one side. Attempting a psoas hitch on both sides will not provide adequate length on either side and thus should be avoided. If both

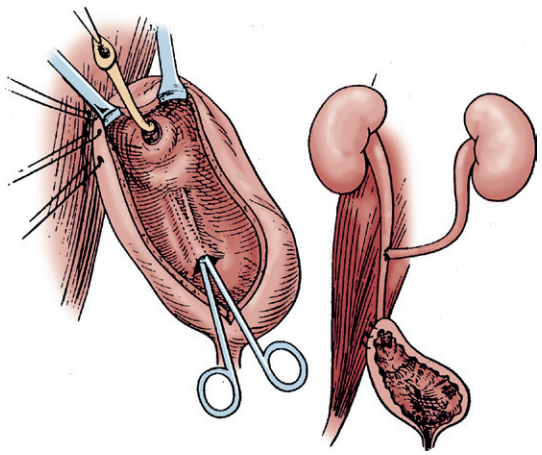


Figure 122–22. A psoas hitch can be used to effectively bridge significant ureteral defects. Its combination with transureteroureterostomy is ideal when both ureters are addressed in a reoperative setting. (From Keating MA, Retik AB. Management of failures of ureteroneocystostomy. In: McDougal WS, editor. Difficult problems in urologic surgery. Chicago: Year Book; 1989. p. 140.)

ureters are shortened, consider a psoas hitch on one side to achieve a satisfactory antireflux mechanism with a transureteroureterostomy for the other ureter.

Other techniques to consider for the short ureter include the Boari flap, where a flap extending from the dome to the anterior wall of the bladder based on the posterior wall can be rotated proximally. The flap should be wide enough to allow creation of a submucosal tunnel and tubularization of this flap. In the short ureter a nipple valve can be created in association with a short submucosal tunnel. The nipple valve is particularly useful in dilated ureters and is fashioned by spatulating the ureter and folding it back onto itself.

In situations where the ureter is significantly foreshortened, it can be replaced using a reconfigured segment of bowel as described by Pope and Koch (1996). The colon or ileum is reconfigured similar to the Monti procedure. This technique offers important advantages over the classic tapered ileal ureter, allowing a long tube to be created from a short segment of colon without tapering, thus eliminating the metabolic consequences; additionally, the mesentery is in the center of the tube, which facilitates creation of the submucosal tunnel.

Endoscopic Treatment of Vesicoureteral Reflux

Matouschek (1981) first described the injection of polytetrafluoroethylene (PTFE) paste at the ureteral orifice to correct VUR. It was O'Donnell and Puri (1986) who popularized the technique when they published their initial report on the successful endoscopic correction of primary VUR in 103 ureters with a success rate of 75% after one injection. They coined the term STING (*S*ubureteric *T*eflon *I*njection). This procedure became popular in many countries but never achieved widespread use in the United States because of lack of U.S. Food and Drug Administration (FDA) approval over concerns regarding the potential migration of PTFE particles (Malizia et al, 1984a, 1984b; Aaronson et al, 1993). The ability to correct reflux in a large proportion of patients (the more recent studies report success rates approaching 90% after one injection of Deflux in low-grade primary reflux [Kirsch et al, 2004]) on an outpatient basis using a simple procedure with minimal morbidity prompted the search for safer materials. One caveat when evaluating the results of the reported results of endoscopic correction is to interpret with caution those reports in which the authors regard downgrading of reflux to grade 1 or 2 (Sweden) as a successful outcome. Because this would not be acceptable to most surgeons carrying out open surgery, the definition of success should be applied uniformly.

Due to the minimal morbidity of the procedure, the benefit of endoscopic injection in newly diagnosed patients has been evaluated using computer modeling with a view to reduce the morbidity and cost of repeated VCUGs and long-term antibiotics (Kobelt et al, 2003). Rigorous comparisons of various treatment approaches need to be undertaken and **until the outcome of such studies are available, the indications for correction of reflux should remain unchanged whether reflux is corrected by open surgery, endoscopy, or laparoscopy.**

Two key challenges with endoscopic treatment of reflux are reproducibility and durability of the results. Long-term follow-up will determine whether endoscopic therapy, with the currently available materials, will stand the test of time or if open surgery with its 95% to 99% success rate will remain the most cost-effective way of **permanently** correcting reflux.

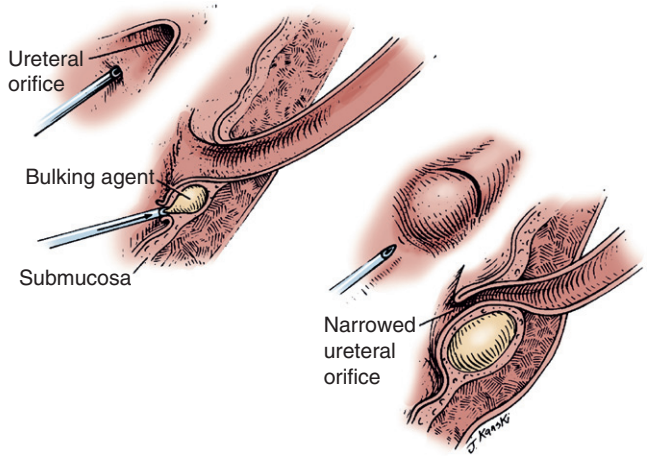


Figure 122–23. Principle of endoscopic treatment of reflux. A bulking agent is injected beneath the ureteral orifice with a needle. The buttress that is provided helps coapt the distal end of the ureter.

Technique of Endoscopic Injection

The classic STING technique was described by O'Donnell and Puri (1984) (Fig. 122–23). Prophylactic antibiotic is usually administered with induction of anesthesia. A cystoscopy should be carried out before opening the materials in case the procedure is cancelled due to inflammatory changes in the bladder. If a rigid needle is used, an offset lens injection scope should be used. If a flexible needle is used, a standard 0- or 30-degree lens cystoscope can be used. The size of the needle varies depending of the viscosity of the material and ranges from 3.7 Fr to 5 Fr. The viscosity of the material also determines whether injecting the material can be carried out using a regular syringe or requires a ratcheted metal syringe holder. A 3-Fr ureteric catheter may be introduced to lift up the anterior wall of the ureter and identify the axis of the tunnel. The needle is inserted with the bevel facing up at the 6 o'clock position. The original description by O'Donnell and Puri suggested entering the mucosa 2 to 3 mm distal to the ureterovesical junction and advancing the needle in the submucosal plane for a distance of 4 to 5 mm. For high-grade reflux and ureters without submucosal tunnel, the Dublin group suggested inserting the needle directly inside the ureter to increase the length of the intravesical ureter (Chertin et al, 2002, 2003). Kirsch and colleagues (2004) popularized this approach (submucosal implantation within the intramural ureter) and reported improved results with all grades of reflux compared with the classic technique (92% vs. 79% of ureters).

The accuracy of the needle entry point and needle placement are important components for success of the procedure (Fig. 122–24). An improper puncture may not result in the desired mound formation and thus may not provide adequate support for the UVJ. If the needle requires repositioning, the implanted material may leak out of the first puncture site, resulting in failure of the procedure.

Injection should be carried out slowly. If the needle is positioned in the submucosal plane, the mound becomes apparent with the initial injection of 0.1 to 0.2 mL. This is a key point in the procedure; unsatisfactory mound formation and location after this initial injection is an indicator that the tip of the needle is not in the proper position. Repositioning of the needle by withdrawing it slowly and then advancing it while injecting, in addition to rotating the bevel gently (depending on the lateral location

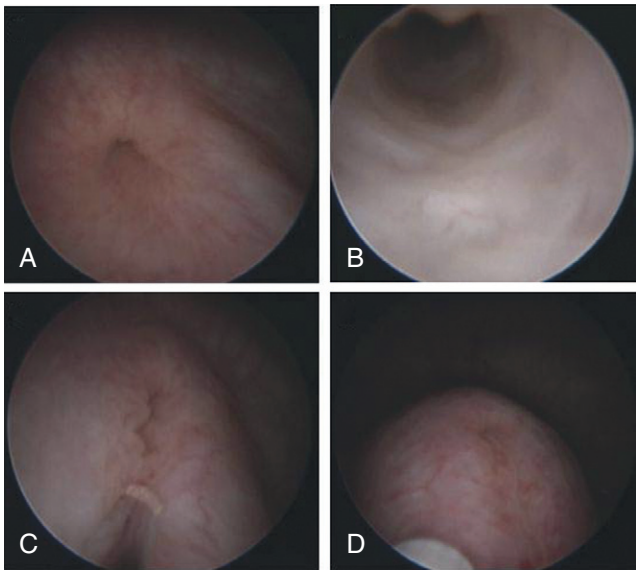


Figure 122–24. The classic STING technique. **A,** Appearance of the orifice before hydrodistention **(B). C,** The entry point of the needle is 2 mm distal to the 6 o'clock position. **D,** Appearance of the mound after completion of the injection.

of the mound), should help achieve the desired effect. Once a volcano appearance with the ureteral meatus on top of the mound is achieved, additional volume is injected until the ureteral orifice becomes crescent or slit shaped. The shape of the achieved mound was found to be a significant predictor of a successful outcome. Achieving a volcano-shaped mound was associated with an 87% success rate, whereas other morphologies were only associated with a 53% successful rate (Lavelle et al, 2005). For most materials, the needle should be kept in place for 1 minute at the end of the injection to reduce extrusion of the material at the injection site. With Deflux this step is not essential. The bladder is emptied, and the mound is inspected with an empty and a full bladder to ensure that adequate support of the ureter is persistent. Rarely, bleeding occurs at the puncture site. This is best dealt with by emptying the bladder and applying gentle pressure with the tip of the scope until the bleeding stops. Cauterizing the area is not advisable because it results in sloughing of the mucosa and extrusion of the injected material. At the end of the procedure lidocaine gel may be instilled in the urethra; catheter drainage is not necessary. In general the child spends a brief amount of time in the recovery room followed by discharge. All activities can be resumed immediately.

There is a significant learning curve with endoscopic correction of VUR (Kirsch et al, 2003). In a study by Herz and colleagues (2001), the importance of the learning curve was highlighted. In the first 6 months of their study the success rate was 46% in 18 children with 28 refluxing ureters. In the remaining 18 months of that study, the overall correction rate was 93% in 56 children with 84 refluxing ureters after a single endoscopic injection. Although the technique is quite simple once learned, there are some technical nuances and details that require specific attention.

Follow-up

The child is maintained on antibiotics for 3 months when a follow-up ultrasound and VCUG are obtained. If reflux is persistent, a repeat injection can be considered 6 months after the initial injection. If there is still no resolution, then open surgery is recommended.

Table 122–7.

Agents used for Endoscopic Correction of Vesicoureteral Reflux

Nonautologous Materials
Polytetrafluoroethylene (PTFE)
Cross-linked bovine collagen
Polydimethylsiloxane
Dextranomer hyaluronic copolymer (Deflux)
Coaptite
Autologous Materials
Chondrocytes
Fat
Collagen
Muscle

Most reports to date have not indicated any additional difficulty with open surgery following endoscopic correction using Deflux (Herz et al, 2001; Lackgren et al, 2001), but some have experienced difficulty with other substances. At open surgery the injected material is either not seen at all or is found well encapsulated but in a wrong plane or wrong location inside or outside the bladder. The material is easily removed en bloc, and the open reimplant procedure carried out without difficulty.

Materials Used for Endoscopic Correction of Reflux

In order for an injectable biomaterial to be ideal, it must be nontoxic and stable without migration to vital organs. It should cause minimal local inflammation, while at the same time be well encapsulated by normal fibrous tissue and fibrocytes. The material should be easy to inject through a long needle that passes easily through most standard endoscopic instruments. It must be viscous enough to prevent leakage from the puncture site and maintain its injected volume and the mound shape after the normal process of exchange and excretion of any carrier molecules.

Several agents have been used for endoscopic correction of VUR. These materials can be classified as **particulate** or **degradable and autologous or nonautologous** (Table 122–7).

The concern with the particulate agents is **migration** and with degradable agents is **durability.** Distant migration can occur by two mechanisms. The first is expansion of the injected bolus, which may lead to disruption of the small vessels in the area of the distal ureter and trigone, resulting in the material gaining intravascular access. Particles smaller than 50 µm may bypass the pulmonary vascular bed and thus access the systemic circulation and reach other organs in the body. The second migration mechanism is by phagocytosis of the injected particles by tissue macrophages or blood-borne monocytes. The particle size determines whether phagocytosis can occur, as it is generally agreed that phagocytosis requires a particle less than 80 µm in diameter.

Nonautologous Materials

Polytetrafluoroethylene Paste (Teflon Paste)

PTFE has been in use as a component of many biomaterials and injectable agents for many years. It has been used for the manufacturing of vascular grafts, cardiac valves/implants, surgical sutures, cosmetic surgery, and patches for hernia repairs (Monaghan and Meban, 1991; Godin et al, 1995; Sayers et al, 1998; Briguori et al, 2001). Teflon paste was also used as an injectable agent for

embolization of vessels (Weingarten and Kauffman, 1977) and for injection of vocal chords (Kasperbauer, 1995) and as a bulking agent for urinary incontinence (Politano, 1992).

Matouschek (1981) first reported on the use of Teflon paste as a bulking agent for correction of reflux. O'Donnell and Puri (1984) and Chertin and Puri (2002) popularized this technique and reported on its use in hundreds of patients with long-term follow-up (Puri, 1995; Chertin and Puri, 2002). A large European multicenter survey reported on 6216 ureters and 4166 children with 10 years' follow-up and demonstrated a cure rate of 86% after one to four injections (Puri et al, 1995). The longest follow-up is available from Dublin; 247 patients treated with Teflon paste with 11 to 17 years of follow-up demonstrated a sustained success rate of 95% with a 5% recurrence rate (Chertin and Puri, 2002).

Teflon paste is relatively inexpensive; it is viscous and requires a ratcheted syringe for injection. Despite its widespread use in Europe, Teflon paste never gained FDA approval in the United States because of concerns regarding distant migration of the PTFE particles. Malizia demonstrated in experimental studies that the particles can migrate to regional lymph nodes and to distant organs including the lung and the brain (Malizia et al, 1984a, 1984b). Malizia's findings were substantiated by several clinical reports confirming particle migration (Claes et al, 1989; Aaronson et al, 1993; Dewan and Fraundorfer, 1996; Steyaert et al, 2000). Particle migration is thought to be related to the small size of the Teflon paste particles that range from 4 to 100 μm with 90% of the particles less than 40 μm.

With the availability of other, presumably, safer injectable agents, PTFE has fallen totally out of favor and been all but abandoned.

Cross-Linked Bovine Collagen

Apart from concerns regarding allergy to bovine collagen in 3% of the population, this material is otherwise safe and causes minimal local inflammatory changes (Leonard et al, 1990). It is easily injectable through a 25-gauge needle with standard endoscopic equipment. The downside to cross-linked collagen is the fact that the results are not durable because of the variable degree of ingrowth of native fibroblasts and replacement of the injectable collagen with native collagen (Leonard et al, 1990, 1991; Frey et al, 1992). Despite the odd report of sustained effect (Reunanen, 1995), the inconsistency, and questionable durability of cross-linked collagen (Haferkamp et al, 2000a, 2000b), most centers have abandoned its use for correction of reflux.

Polydimethylsiloxane (Macroplastique)

Polydimethylsiloxane (PDS) is a solid silicone elastomer that has been used as a soft tissue bulking agent. The injectable material is composed of soft, flexible, highly textured implants of heat-vulcanized PDS suspended in a bioextractable carrier gel. The carrier gel is a water-soluble low-molecular-weight polyvinylpyrrolidone hydrogel (Povidone). The carrier gel is absorbed and replaced with host fibroblasts that subsequently deposit collagen, encapsulating the implant. The implant retains its size and shape. To minimize the risk of migration, PDS is engineered to create an elastomer, instead of the less cross-linked silicone gels or non–cross-linked silicone oils. Although 76% of particles are greater than 100 μm in diameter, **7% are less than 50 μm in diameter.** The smaller particles (Henley et al, 1995) and possible intramuscular injection of the agent are responsible for migration of particles to the lungs, kidneys, brain, and lymph nodes demonstrated in animal models. Unlike Teflon paste, Macroplastique does not cause an intense local inflammatory response. In patients requiring open surgery after failed injection with Macroplastique, the injectable bolus was found encapsulated and easily removed without adherence to the ureter or bladder (Herz et al, 2001). Histologic examination of the bladder muscle biopsies and pelvic lymph nodes at the time of open surgery revealed a mild inflammatory reaction with no evidence of PDS particle migration in either the wall of the bladder or the draining lymph nodes.

The efficacy of PDS as a bulking agent for correction of reflux is well documented. Dodat and colleagues (2004) reported on the long-term outcomes of Macroplastique injections for correction of VUR. Results in 590 refluxing ureters in 389 patients who were injected with a minimum follow-up of 5 years revealed a sustained success rate of 79.4%. Herz and colleagues (2001) demonstrated a reflux resolution rate of 81% after a single injection and 90% after a second injection with a 12-month follow-up. Similarly, van Capelle and colleagues (2004) reported an 82.3% success rate in 311 ureters in 195 children over a 10-year period from two European centers.

The main advantage of PDS is that it is a permanent material that remains well encapsulated, causing minimal local inflammatory changes. Although it has a demonstrated long-term track record, PDS has yet to achieve FDA approval for correction of VUR in the United States, possibly because of concerns regarding migration, particularly particles that are smaller than 80 μm, and the negative connotations associated with silicone implants.

Dextranomer/Hyaluronic Copolymer (Deflux)

Dextranomer/Hyaluronic Copolymer (DX/HA) is formed of cross-linked dextranomer microspheres (80 to 250 μm in diameter) suspended in a carrier gel of stabilized sodium hyaluronate. DX/HA is biodegradable, the carrier gel is reabsorbed, and the dextranomer microspheres capsulated by fibroblast migration and collagen ingrowth. DX/HA loses about 23% of its volume beyond 3 months of follow-up (Stenberg and Lackgren, 1995).

Deflux was first introduced by the Swedish group of Stenberg and Lackgren (1995) and received FDA approval in 2001. Since then there have been several clinical reports from Europe and the United States documenting success rates ranging from 68% to 89% (Lackgren et al, 2001; Puri et al, 2003; Kirsch et al, 2004; Lavelle et al, 2005). The 89% success rate was achieved by Kirsch and colleagues (2004) using the intraureteral injection technique. In a long-term follow-up study by Lackgren and colleagues (2001), 68% of 221 children followed for a mean of 5 years maintained grade 1 VUR or less at the last VUCG. No significant long-term adverse effects were noted. In patients who fail endoscopic treatment with Deflux and proceed to open surgery, the bulking agent is noted to have completely disappeared. Whether this represents a technical error in the injection technique or is due to complete reabsorption of the injectable agent remains unproven.

The appeal of Deflux is that it is a natural product that is easily administered without a ratcheted syringe through a smaller-gauge needle. It is currently the preferred agent for endoscopic correction in most centers; however, the durability of correction of VUR with Deflux remains to be proven.

Coaptite

Calcium hydroxyl apatite is synthetic bone material. The particles have a uniform spherical shape and range in size from 75 to 125 μm. The material injects easily through a 21-gauge needle without the need for a ratcheted syringe. At the AUA meeting in 2002, Mevorach and colleagues presented the initial results in a clinical trial including 98 patients and 155 ureters with grade 2 to 4 reflux (Mevorach et al, 2002). Reflux resolved in 67% of the

patients and 75% of the ureters. There are no published reports at this point, and the FDA is currently evaluating the clinical trials.

Autologous Materials

Fat, collagen, muscle, and chondrocytes have all been evaluated as bulking agents. The key advantage of these agents is that they are not foreign materials, but the obvious disadvantage is the observed volume loss (up to 100% in the case of fat [Matthews et al, 1994]) that they need to be harvested and expanded (in the case of chondrocytes and muscle) before injection. Autologous materials behave as a free graft at the injection site, so reabsorption of the material is worrisome and may be responsible for the inconsistent results.

Chondrocytes

Atala and colleagues (1993, 1994) described the harvesting and expansion of chondrocytes in vitro and successful correction of VUR in animal models. Subsequently, human trials using chondrocytes harvested from the posterior auricular cartilage were conducted (Diamond et al, 1999; Caldamone and Diamond, 2001). The chondrocytes were grown in culture for 6 weeks, quantitated, concentrated, and then suspended in a mixture of sodium alginate and calcium sulfate solution for injection. At 3 months' follow-up, reflux was corrected in 55% (27 of 47) of the ureters. This improved to 86% after one or two repeat injections. At 1-year follow-up, reflux correction was maintained in 70% (32 of 46) of the ureters and 60% of the patients (19 of 29). At subsequent endoscopy, failures were attributable to volume loss and shifting of the subureteral mounds.

Recurrence of Vesicoureteral Reflux Following Endoscopic Correction

The **true incidence** of recurrent VUR after successful endoscopic correction with any specific material is difficult to determine because a repeat VCUG is not obtained beyond the initial negative study except in the context of a research protocol.

Only a handful of series have reported long-term follow-up with repeat VCUG beyond the initial negative study. Chertin and colleagues (2002) reported a 5% recurrence rate using Teflon paste with follow-up up to 17 years. A 13% recurrence rate with Deflux is reported by Lackgren and colleagues (2001) 2 to 5 years after an initial negative VCUG. The higher rate with Deflux, an absorbable agent, is not unexpected. In the absence of UTIs, the significance of confirming the long-term absence of VUR is less important. Furthermore, even if absorbable bulking materials were to lose volume or reabsorb completely over time, VUR resolution may be maintained by growth of the child and maturation of the UVJ. The injectable agent may just have bought time for this process to conclude. The implication of recurrent reflux in young adulthood for these patients is inadequately defined at present. More recent evidence suggests that children undergoing endoscopic correction with a preinjection history of multiple febrile UTIs, BBD, and renal scarring are at a higher risk for recurrent infections and late recurrence of VUR despite initial negative VCUG (Sedberry-Ross et al, 2008).

Laparoscopy as Applied to Correction of Reflux

The laparoscopic approach to ureteral reimplantation should theoretically provide the success rate and durability of open surgery while avoiding its morbidity. Three procedures have been attempted laparoscopically: the extravesical reimplant, the Gil-Vernet procedure, and the Cohen cross-trigonal reimplant.

In addition to the long operative times and steep learning curve, the initial experience with laparoscopic reimplantation identified significant technical challenges in the creation of the submucosal tunnel while maintaining an intact bladder urothelium and with the suturing aspects of the procedures. Although the robot may assist with the suturing aspect, the current port size required is still not ideal for smaller children. The continued refinement of open reimplantation surgery, more recently dispensing with the use of both postoperative bladder catheters and the need for overnight hospital stays, will place even greater onus on the proponents of the laparoscopic approach to better define the ideal conditions for this minimally invasive technique.

Laparoscopic Surgical Procedures

Gil-Vernet Procedure

In this procedure the trigonal mucosa is incised vertically and the two ureters are approximated into the midline with a single submucosal suture. This procedure has been accomplished laparoscopically transvesically with limited success. Okamura and colleagues (1999) and Cartwright and colleagues (1996) reported success rates of 59% and 62.5%, respectively. The recurrence of reflux is thought to be due to splitting of the trigone and lateral displacement of the ureters.

Laparoscopic Extravesical Reimplant. This is likely the most commonly reported procedure for laparoscopic correction of reflux. The technique has a steep learning curve; initial experiences described challenges with exposure of the ureter, trauma to the ureter, and difficulty developing the extravesical tunnel without injuries to the urothelium in addition to long operative times.

Separation of the urothelium from the detrusor is difficult laparoscopically because the adequately distended bladder protrudes into the limited pelvic working space and hinders the laparoscopic dissection. Additionally, the ability to adequately retract the incised detrusor edges to create a wider trough is limited because of the exposure and the angles at which the instruments enter the abdomen.

Several modifications of the technique have been described by Lakshmanan and Fung (2000), leading to a more effective procedure with shorter operative time and results that approximate those of open surgery.

Trocar Placement. A 5-mm, 0-degree laparoscope is inserted through the umbilicus. Three additional working ports are inserted in the lower abdomen along the lines of a Pfannenstiel incision in the middle and on either end.

Ureteral Dissection. The ureter is best identified at the pelvic brim and followed distally. The overlying peritoneum is incised transversely. Ureteric catheters placed cystoscopically may aid in identification of the ureter in the older patient. Once the ureter is identified, it can be grasped with Babcock forceps and freed from the surrounding tissues. In the male the incision of the peritoneum should be carried out caudal to the vas deferens so that the vas can be reflected with the peritoneum in a cephalad direction. A vessel loop or a Diamond-Flex retractor can be passed around the ureter and used as a holder.

Creation of the Tunnel. It is important to mark the direction of the tunnel with electrocautery while the bladder is semidistended in its normal position. A 4-0 Prolene traction suture is applied at the proximal end of the detrusor tunnel. This suture is passed through the abdominal wall on a straight needle and used to hitch

the bladder, and then the needle is passed out again providing external control to achieve the desired tension and elevation of the detrusor. The incision of the detrusor is carried out starting from proximal to distal. The serosa is scored with cautery, but most of the dissection should be carried out using scissors to prevent injury to the bladder innervation as described in the open extravesical reimplant earlier in the chapter. Elevation of the detrusor flaps is more difficult in the laparoscopic procedure, and therefore a trough as wide as that developed with open surgery may not be achievable. The incision is continued distally around the ureter, leaving the distal attachments intact. The mucosal bulge is also not as obvious as in open surgery because the bladder is not as distended and is also compressed by the peritoneal insufflation.

Closure of the Myotomy (Detrusorrhaphy). The ureter is placed in the new tunnel, and a 3-0 polyglactin suture is placed at the most proximal end to stabilize the ureter and facilitate reclosure of the detrusor with interrupted sutures starting at the ureteral orifice distally. Anchoring sutures are not required because the distal attachments of the ureter are left intact.

After completion of the detrusorrhaphy, the bladder retraction suture is released and the bladder is filled. The ureter is observed in its new tunnel to confirm the absence of angulation or kinking. A catheter may be left in the bladder for 12 to 24 hours postoperatively.

The largest published series is that of Lakshmanan and Fung (2000) in which 71 ureters were reimplanted laparoscopically. Early on in that series, three ureteral injuries required open reimplantation in two and stenting in one to drain a urinoma. The remaining patients are free of reflux and obstruction. More recently, Casale and colleagues (2008) reported a 97.6% success rate in 41 patients using a transperitoneal robotic-assisted approach.

Endoscopic Cross-Trigonal Reimplant

In order to avoid transgressing the peritoneum and the challenges associated with the small pelvis in the child, other groups have developed a transvesical approach, similar to the Cohen cross-trigonal reimplant, using carbon dioxide insufflation of the bladder (pneumovesicum).

Yeung and colleagues (2005) initially described the procedure using standard laparoscopic instruments. Peters and Woo (2005) followed with a report describing a robotically assisted technique to facilitate the creation of the submucosal tunnel and the ureteral anastomosis.

Port Placement. The patient is positioned supine with the legs separated to allow access to the urethra for cystoscopy and bladder catheterization intraoperatively. Cystoscopy is carried out, and the bladder is distended with saline. A traction suture is passed percutaneously at the level of the bladder dome under cystoscopic vision to anchor the bladder wall to the abdomen and prevent it from pulling away when the camera port incision is made at the dome. Following that, a 5-mm port is inserted under cystoscopic vision. The cystoscope is removed, and a urethral catheter is inserted. CO_2 insufflation to 10-mm mercury pressure is started, and a 5-mm 30-degree lens is inserted. Two additional 3-mm working ports are inserted on either side of the bladder under direct vision.

Dissection of the Ureter. A 5-cm segment of a 5-Fr feeding tube is inserted in the ureter and secured with a 4-0 Prolene suture. The catheter facilitates handling and dissection of the ureter as described in the open Cohen procedure. The ureteral mobilization begins with the usual circumscribing incision using the hook electrocautery. The 3-mm endoscopic scissors are used to develop the plane of dissection starting on the distal aspect of the ureter. The dissection is carried out circumferentially for a distance of 2 to 3 cm. The muscular defect in the ureteral hiatus is repaired using 4-0 absorbable sutures.

Creation of the Submucosal Tunnel. An incision is made using the hook cautery at the site of the new ureteral orifice across the back wall of the bladder. The submucosal tunnel is started from the old hiatus toward the new hiatus using fine endoscissors. A fine grasper is then inserted through the new hiatus, and the feeding tube is used to pull the ureter through the tunnel.

Ureteral Neocystostomy. The ureter is spatulated at the 6 o'clock position and anastomosed at the new location using 6-0 interrupted sutures. Peters and Woo (2005) described using the robot to facilitate the delicate suturing laparoscopically and improve the efficiency of the procedure. The port sites in the bladder are closed, and an indwelling urethral catheter is maintained for 24 hours. Reflux resolution was demonstrated in 15 of 16 patients in Yeung's series (2005) and in five of six patients in Peters' series (2005). Providing a detailed description of the nuances of the vesicoscopic technique, Jayanthi and Patel (2008) reported a 94% success rate in a larger series of 103 patients, 10 of whom had failed endoscopic injection. Three patients were converted to open surgery early in their experience. Of the 77 patients who have undergone postoperative cystograms, reflux resolution was confirmed in 72 of 77 (94%). The failures were all in the first 30 patients of the series with no reported failures in the last 47 patients.

Although open surgical correction of reflux is still the gold standard against which the endoscopic and laparoscopic approaches are compared, the technical advances and improved results achieved using minimally invasive techniques are gradually becoming more enthusiastically endorsed.

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chapter
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Prune-Belly Syndrome

Anthony A. Caldamone, MD, MMS, FAAP, FACS • John R. Woodard, MD

Genetics
Embryology
Clinical Features of Prune-Belly Syndrome
Presentation
Evaluation and Management
Long-Term Outlook

Prune-belly syndrome (PBS) represents a constellation of anomalies with variable degrees of severity. The three major findings are a deficiency of the abdominal musculature, bilateral intra-abdominal testes, and an anomalous urinary tract. The urinary tract is characterized by variable degrees of hydronephrosis, renal dysplasia, dilated tortuous ureters, an enlarged bladder, and a dilated prostatic urethra. Additional associated anomalies involve the respiratory tract, gastrointestinal tract, cardiac system, and musculoskeletal system. There is a broad spectrum of severity of the syndrome, with some children not surviving the newborn period and others being minimally affected. The single most important determinant of survival is usually the severity of the urinary tract anomaly, in particular, the degree of renal dysplasia.

The characteristic abdominal wall was first described by Frolich in 1839, and the full triad of anomalies by Parker in 1895. Osler's vivid description of the abdominal wall of an infant with the characteristic findings led to the term *prune-belly syndrome* (Osler, 1901). Other names that have been applied to this syndrome include *triad syndrome, Eagle-Barrett syndrome,* and *abdominal musculation syndrome* (Eagle and Barrett, 1950; Greskovich and Nyberg, 1988).

The incidence of PBS has been reported to be 1 in 29,000 to 1 in 40,000 live births, similar to that of bladder exstrophy (Williams and Burkholder, 1967), **with 95% occurring in males** (Wheatley et al, 1996). Females with PBS have the abdominal wall deficiency and urinary tract dysmorphism without any gonadal anomaly (Rabinowitz and Schillinger, 1977; Reinberg et al, 1991b). A higher incidence is noted in twins, blacks, and children born to younger mothers. The incidence appears to be declining, possibly because of prenatal diagnosis and a decision to terminate the pregnancy.

GENETICS

The high male-to-female ratio, occasional occurrence in male siblings and cousins, and increased occurrence in twins suggest a genetic basis for PBS. Yet most cases are sporadic and have a normal karyotype. One in 23 children with PBS is the product of a twin pregnancy (Ives, 1974). However, the majority of reported twins have been discordant for PBS, evidence against a genetic etiology. It has been suggested that the etiology in twins may be due to an uneven distribution of mesenchymal tissue at a critical time of primitive streak development during the third week of embryogenesis (Coplen et al, 1996). There is a reported association with Turner syndrome, monosomy 16, trisomy 13, and trisomy 18 (Amacker et al, 1986; Hoagland and Hutchins, 1987). A variety of inheritance patterns have been proposed including X-linked recessive (Frydman et al, 1993), a two-step autosomal dominant mutation (Riccardi and Grum, 1977), and polygenetic transmission (Garlinger and Ott, 1974; Lockhart et al, 1979; Adeyokunnu and Familusi, 1982). A report by Ramasamy and colleagues (2005) suggested a sex-influenced autosomal recessive mode of inheritance in familial PBS. The consensus, however, remains that an associated chromosomal abnormality is the exception rather than the rule because most have a normal karyotype. Other reports have noted an association between PBS and Beckwith-Wiedemann syndrome (Silengo et al, 2002; Sinico et al, 2004).

EMBRYOLOGY

Several theories about the embryogenesis of PBS have been proposed. However, because there is no experimental model that can be used to test these theories, the exact mechanism remains elusive. The four chief theories are (1) early in utero posterior urethral obstruction resulting in severe dilation of urinary tract and possible fetal ascites and oligohydramnios (Strumme, 1903; Pagon et al, 1979; Wheatley et al, 1996; Beasley et al, 1988); (2) primary defect in the lateral plate mesoderm, which is the precursor of the ureters, bladder, prostate, urethra, and gubernaculum (Ives, 1974; Gonzalez et al, 1990); (3) an intrinsic defect of the urinary tract leading to ureteral dilation and fetal ascites (Symonds and Driscoll, 1974; Monie and Monie, 1979; Smythe, 1981; Nakayama et al, 1984; Cazorla et al, 1997); and (4) a yolk sac defect (Stephens, 1983; Stephens and Gupta, 1994). None of these theories have universal acceptance, and there is some overlap between them.

CLINICAL FEATURES OF PRUNE-BELLY SYNDROME

Genitourinary Anomalies

Kidneys

A spectrum of renal abnormalities extends from normal renal parenchyma to dysplasia (Fig. 123–1). The more severely dysplastic kidneys are generally associated with bladder outlet obstruction

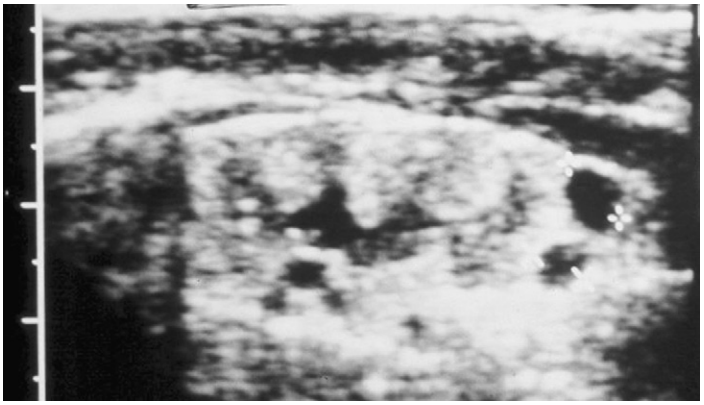


Figure 123–1. Ultrasound scan of a kidney of a newborn with prune-belly syndrome demonstrating markedly echogenic renal parenchyma and cortical cysts indicative of renal dysplasia.

in which there has not been decompression through a patent urachus (Potter, 1972). **Dysplasia is present in 50% of cases; however, it may vary in degree and laterally** (Rogers and Ostrow, 1973; Stephens, 1983). **Renal dysplasia in PBS of the Potter type II and IV varieties is seen.** The Potter type II variety with few nephrons and parenchymal disorganization is more indicative of a renal mesenchymal defect, whereas the Potter type IV with cortical and tubular cysts is associated with outlet obstruction (Wigger and Blanc, 1977).

The renal collecting system is characteristically dilated, often to a severe degree. The degree of dilation, however, does not correlate with the degree of renal dysplasia. Calyceal morphology may be well preserved, even in the presence of massively dilated ureters and renal pelves (Berdon et al, 1977). Ureteropelvic junction obstruction can occur on a primary or secondary basis; however, nonobstructive hydronephrosis is the rule (Woodard and Parrott, 1978b). It is renal infection rather than obstruction that poses the greatest risk to renal function.

Ureters

The ureters are typically dilated, tortuous, and redundant (Fig. 123–2). The proximal (upper) portions of the ureters are usually less abnormal than the distal segments, although massive dilation and stenosis can occur at all levels. Histologic sectioning demonstrates a lack of smooth muscle cells and an increase in fibrous connective tissue. Generally there are more normal-appearing smooth muscle cells in the proximal segments (Palmer and Tesluk, 1974; Stephens, 1983). This fact is critical when ureteral reconstruction is undertaken. The ratio of collagen to smooth muscle cells in prune-belly ureters has been noted to be elevated, especially in refluxing ureters (Gearhart et al, 1995). A decreased number of thick and thin myofibrils noted on ultrastructural examination is thought to contribute to the poor peristalsis (Berdon et al, 1977; Stephens, 1983).

Vesicoureteral reflux is present in 75% of children with PBS (Berdon et al, 1977; Fallat et al, 1989) (Fig. 123–3). Obstruction is not common but has been reported at both the ureteropelvic and ureterovesical junctions (Wigger and Blanc, 1977; Moerman et al, 1982; Manivel et al, 1989).

These large ureters may have ineffective peristalsis because of poor ureteral wall coaptation. The ureteral conduction wave reaches a reduced smooth muscle cell population of poor contractile potential related to reduced myofibrils, often separated by patches of collagen with a resulting bolus of urine reaching more dilated ureteral segments as it progresses toward the bladder (Woodard and Smith, 1998). This can be seen fluoroscopically as ineffective peristalsis, resulting in upper tract stasis, which may lead to infection (Nunn and Stephens, 1961; Williams and Burkholder, 1967).

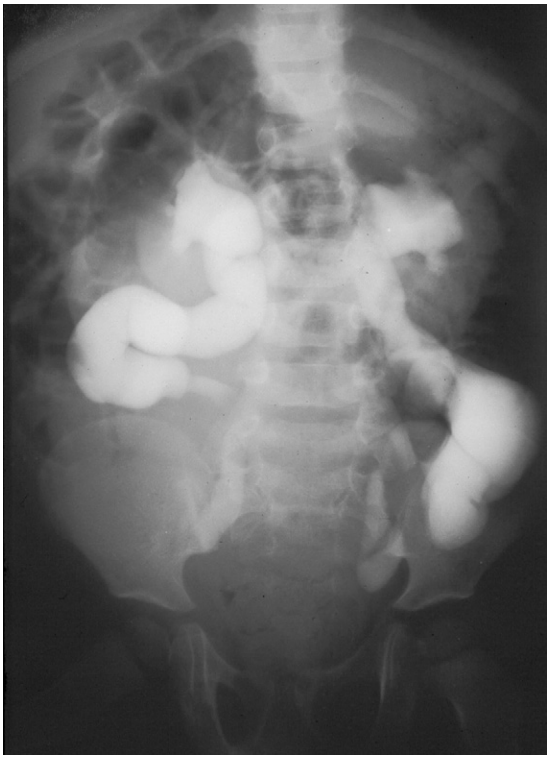


Figure 123–2. Excretory urogram of a patient with prune-belly syndrome; note ureters displaced laterally and calyces relatively well preserved.

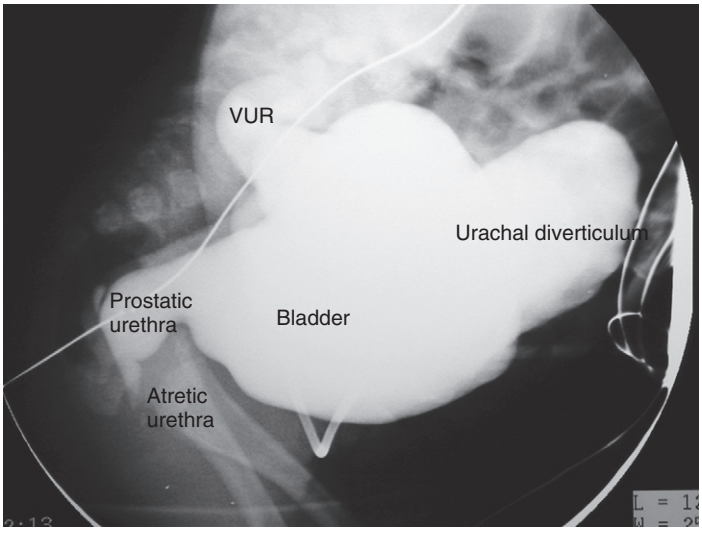


Figure 123–3. Voiding cystourethrogram of a child with prune-belly syndrome demonstrating urethral atresia, urachal diverticulum, and vesicoureteral reflux (VUR).

Bladder

The bladder usually appears massively enlarged with a pseudodiverticulum at the urachus (Fig. 123–4). **The urachus is patent at birth in 25% to 30% of children**

Key Points: Clinical Features

- Hydroureteronephrosis is often to a severe degree; however, the calyceal morphology may be well preserved.
- The proximal portion of the ureters has more normal muscle than the distal portions.
- The bladder is large with a pseudodiverticulum at the urachus and a wide bladder neck opening into a dilated prostatic urethra.

(Lattimer, 1958; Wigger and Blanc, 1977; Stephens and Gupta, 1994). **Histologically, the bladder has an increased ratio of collagen to muscle fibers in the absence of obstruction** (Workman and Kogan, 1990). The wall is smooth, unlike that seen in obstructed bladders. The pelvic distribution of ganglion cells has been shown to be normal (Nunn and Stephens, 1961; Burke et al, 1969). Smooth muscle hypertrophy is seen, however, in the obstructed prune bladder (Perlmutter, 1976). Stephens demonstrated that the trigone is splayed with the ureteral orifices displaced laterally and superiorly, possibly contributing to the high incidence of reflux (Williams and Burkholder, 1967).

On voiding, the bladder neck opens widely into a dilated prostatic urethra (see Fig. 123–4). Urodynamic assessment generally shows normal compliance; however, there is a delayed first sensation to void and large capacity (Snyder et al, 1976). The ability to empty the bladder is variable, with some emptying well and others carrying a significant postvoid residual. This is thought to be due to a relative outlet obstruction and the ability of the bladder to generate sufficient pressure with a detrusor contraction. When the relative outflow resistance prevents effective bladder emptying, the term *unbalanced voiding* is used (Snyder et al, 1976; Kinahan et al, 1992). **Despite these limitations, about 50% of prune-belly patients void spontaneously with normal voiding pressures, normal flow rates, and low postvoid residuals** (Nunn and Stephens, 1961; Kinahan et al, 1992). However, as Kinahan and colleagues (1992) demonstrated, deterioration of balanced voiding can occur, resulting in significant postvoid residuals, emphasizing the need for periodic assessment.

Prostate and Accessory Sex Organs

The dilation of the posterior urethra is due to prostatic hypoplasia, probably related to abnormal mesenchymal-epithelial development (Stephens and Gupta, 1994). Histologically, there are few prostatic cellular elements with a reduction of both epithelial and smooth muscle cells and an increase in connective tissue cells (Moerman et al, 1982; Popek et al, 1991; Stephens and Gupta, 1994). Various obstructive lesions of the distal posterior urethra have been described—urethral atresia, valves, urethral stenosis, urethral membrane, and urethral diverticulum—and are thought to occur in 20% of cases (Hoagland and Hutchins, 1987). Stephens (1983) described an angulation of the urethra during voiding, referred to as *type IV valves,* which results from lack of prostatic parenchymal tissue. Prostatic hypoplasia, the etiology of which is controversial, is thought to be a factor in the ejaculatory failure of PBS patients (Volmar et al, 2001). **The vas deferens and seminal vesicles are often atretic, although either may be dilated or thickened** (Stephens and Gupta, 1994). **The epididymis may be poorly attached to the testis, as is seen commonly in abdominal undescended testes. There may also be lack of continuity between the efferent ductules and the rete testis.** Ejaculation is usually in a retrograde fashion because of an incompetent bladder neck.

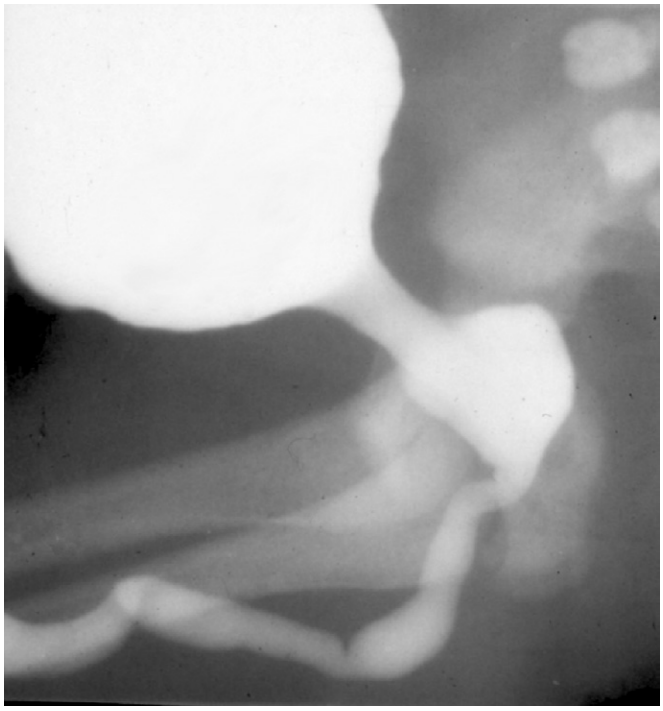


Figure 123–4. Voiding cystourethrogram of a child with prune-belly syndrome demonstrating prostatic urethral enlargement related to a hypoplastic prostate.

Anterior Urethra

Although the anterior urethra of the PBS child is usually normal, several anomalies of the anterior urethra have been reported, the most common being urethral atresia and megalourethra (Kroovand et al, 1982; Perrotin et al, 2001). **Unless it is associated with a patent urachus, urethral atresia is often lethal** (see Fig. 123–3). It has been postulated that urethral atresia or microurethra occurs because the urethra is unused rather than malformed. Spontaneous bladder rupture with fistula formation has also been reported (Reinberg et al, 1993).

PBS is associated with two variations of megalourethra (Shrom et al, 1981; Mortensen et al, 1985). **The fusiform type is a deficiency of the corpus cavernosum, as well as the spongiosum, and the scaphoid variety is a deficiency of the spongiosum only with preservation of the glans and corpora cavernosa** (Fig. 123–5). **With the scaphoid variety, the ventral urethra dilates with voiding, whereas with the fusiform variety the entire phallus dilates with voiding.** The fusiform variety is thought to result from a mesenchymal deficiency of the urethral folds, whereas the scaphoid variety results from a mesenchymal deficiency of the urethral supportive tissues (Dorairajan, 1963). Megalourethra is more commonly seen in PBS than any other syndrome (Appel et al, 1986). Transient in utero obstruction of the junction between the glanular and penile urethra has been proposed to cause megalourethra.

Testes

Bilateral intra-abdominal testes lying over the iliac vessels are the most typical findings. Although mechanical forces such as a distended bladder and intra-abdominal pressure have been

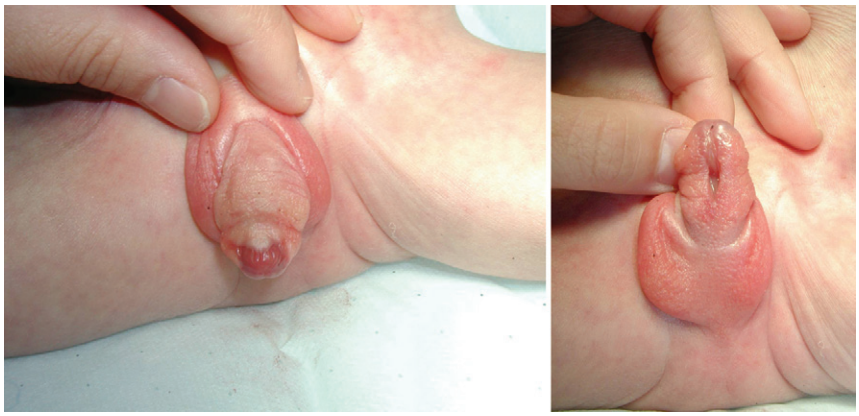


Figure 123–5. Scaphoid megalourethra with hypospadiac orifice of prune-belly syndrome. (Courtesy of C. Peters.)

implicated in maldescent of the testes (Kaplan et al, 1986; Hutson and Beasley, 1988), the fact that some patients with the typical urinary tract and abdominal musculature anomalies (termed *pseudoprune patients*) may have descended testes raises some doubt about pure mechanical factors.

Pak and colleagues (1993) compared the histology of the testes in PBS patients with that of non–prune-belly intra-abdominal testes and that of age-matched control subjects. **They found no difference in germ cell counts, Ad spermatogonia, and Leydig cells between PBS testes and non-PBS intra-abdominal testes. However, because germ cell counts in PBS patients younger than 1 year are similar to those of age-matched controls, the implication is that the environmental state of the abdomen is a major factor in their later spermatogenic potential** (Nunn and Stephens, 1961; Coplen et al, 1996). This mirrors findings of Nunn and Stephens (1961) of normal germinal epithelium of fetal and newborn PBS testes. Alternatively, Orvis and colleagues (1988) noted decreased numbers of spermatogonia and Leydig cell hyperplasia in fetal PBS testes, implying an intrinsic testicular abnormality. Azoospermia was found in adult PBS patients, and no PBS patient has been reported to have fathered a child (Woodhouse and Snyder, 1985). More recently, Ross and colleagues (1998) have documented paternity in three adults with classic PBS, achieved by sperm retrieval techniques and intracytoplasmic sperm injection. The infertility is thought to be due to a combination of testicular histologic abnormalities, structural defects of the ducts, and prostatic abnormalities (Tayakkanonta, 1963).

Three cases of testis tumor have been reported (Woodhouse and Ransley, 1983; Sayre et al, 1986; Massad et al, 1991; Parra et al, 1991). Massad and colleagues (1991) described histologic testicular patterns similar to those in intratubular germ cell neoplasia in three infants. Although the risk of malignancy may be relatively low considering the lack of germinal epithelium (Uehling et al, 1984), it is clear that placement of the testis in the scrotum and long-term follow-up are necessary to reduce the risk of testicular malignancy and enhance detection.

Extragenitourinary Abnormalities

Of all children with PBS, 75% have non–urinary tract abnormalities (Geary et al, 1986). After the obvious abdominal wall defect, the most common are cardiac, pulmonary, and orthopedic (Table 123–1).

Table 123–1.
Extragenitourinary Abnormalities

Cardiac	Patent ductus arteriosus
	Ventricular septal defect
	Atrial septal defect
	Tetralogy of Fallot
Pulmonary	Lobar atelectasis
	Pulmonary hypoplasia
	Pneumothorax
	Pneumomediastinum
Gastrointestinal	Intestinal malrotation
	Intestinal atresias or stenosis
	Omphalocele
	Gastroschisis
	Hirschsprung disease
	Imperforate anus
	Hepatobiliary anomalies
Orthopedic	Pectus excavatum, pectus carinatum
	Scoliosis
	Sacral agenesis (partial)
	Congenital hip subluxation or dislocation
	Genu valgum
	Talipes equinovarus
	Severe leg maldevelopment
Miscellaneous	Splenic torsion
	Adrenal cystic dysplasia

Modified from Woodard JR, Smith EA. Prune-belly syndrome. In: Walsh PC, Retik AB, Vaughan Jr ED, Wein AJ, editors. Campbell's urology. 7th ed. Philadelphia: WB Saunders; 1998. p. 1991.

Abdominal Wall Defect

The appearance of the abdominal wall gives PBS of newborns their most characteristic feature (Fig. 123–6). Although in some cases the musculature of the abdominal wall may be totally absent (Manivel et al, 1989), most commonly there is uneven involvement with the medial and inferior muscular typically most deficient (Mininberg et al, 1973; Randolph, 1977). The appearance at birth is that of wrinkled, redundant skin with an abdomen that bulges in the flanks. One may be able to discern intra-abdominal organs through the thinned abdominal wall. **The most severely affected areas may have skin, subcutaneous fat, and a single fibrous layer on the peritoneum** (Mininberg et al, 1973; Baird and Sadovnick, 1987). **Randolph conducted electromyographic mapping and demonstrated the inferior**



Figure 123–6. Wrinkled abdomen of a newborn with prune-belly syndrome. (Courtesy of C. Peters.)

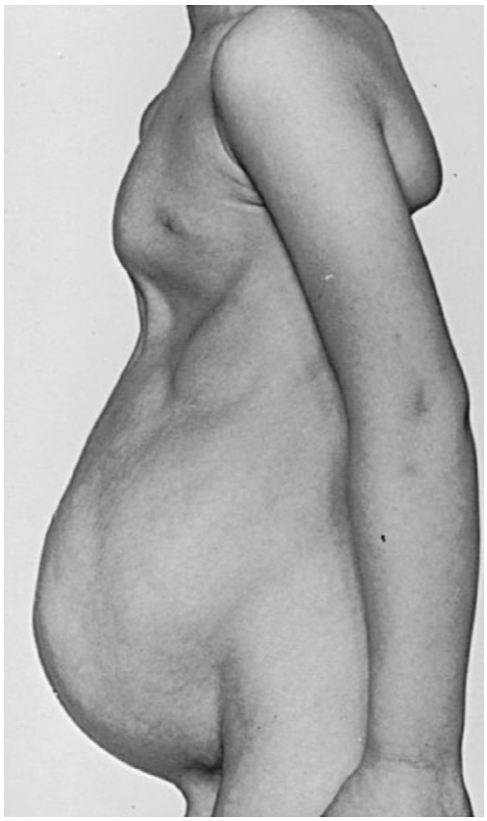


Figure 123–7. Older child with prune-belly syndrome, showing the absence of wrinkling, the "potbelly" appearance, and the consequent deformity of the lower ribs.

and medial segments to be most consistently affected (Randolph et al, 1981a). Electron microscopy has demonstrated a nonspecific pattern of myofilament disarray, Z-line disorganization, and mitochondrial proliferation (Afifi et al, 1972; Randolph et al, 1981b; Woodard and Smith, 1998). The fact that normal spinal anterior horn cells have been shown rules out a neuropathic etiology for the muscular deficiency (Nunn and Stephens, 1961). The muscular deficiency, however, is typically inconsistent and patchy.

As the child grows older, the abdomen becomes less wrinkled and takes on more of a pot-bellied appearance (Fig. 123–7). Gait is usually not affected, although it may be delayed, and the children tend to roll to their side and use their arms to sit from a supine position. The poor support of the lower chest wall results in flaring of the costal margin (Woodard and Smith, 1998). These children are more vulnerable to respiratory illness because their cough effectiveness is compromised. In spite of these abdominal wall issues, Woodard and Smith (1998) reported good wound healing without a tendency toward infections or incisional hernias.

Cardiac Anomalies

Cardiac anomalies such as patent ductus arteriosus, atrial septal defect, ventricular septal defect, and tetralogy of Fallot occur in 10% of children with PBS (Adebonojo, 1973). Cardiac abnormalities at birth may take precedence over urologic issues.

Pulmonary

Pulmonary difficulties can be observed at any age in patients with PBS. **Pulmonary hypoplasia can result from severe oligohydramnios related to renal dysplasia or severe bladder outlet obstruction and may result in newborn demise. In addition, pneumothorax and pneumomediastinum can be seen with or without pulmonary hypoplasia** (Skoog, 1992). **Significant pulmonary difficulties have been reported in 55% of PBS survivors** (Geary et al, 1986). **The lack of ability to generate significant intra-abdominal pressure may contribute to pneumonia and lobar atelectasis** (Alford et al, 1978; Ewig et al, 1996). Acute respiratory illnesses or an anesthetic procedure can easily lead to respiratory insufficiency in the PBS patient, who may have underlying chronic bronchitis from repeated respiratory illnesses. Many patients demonstrate significant restrictive lung disease secondary to musculoskeletal abnormalities such as scoliosis, rib cage abnormalities, and compromised abdominal musculature (Coplen et al, 1996).

Gastrointestinal Abnormalities

In at least 30% of cases, gastrointestinal anomalies are observed. The majority of the anomalies result from incomplete rotation of the midgut giving way to a wide mesentery, which results in increased bowel mobility with intestinal malrotation, volvulus, atresias, and stenosis (Silverman and Huang, 1950; Wright et al, 1986). Splenic torsion related to abnormal mesenteric fixation has also been reported (Heydenrych and Du Toit, 1978; Teramoto et al, 1981). Omphalocele, gastroschisis, and anorectal abnormalities have been reported (Petersen et al, 1972; Morgan et al, 1978; Wilbert et al, 1978; Short et al, 1985; Walker et al, 1987). With a limited ability to generate intra-abdominal pressure, constipation becomes a lifelong problem and leads to acquired megacolon (Woodard and Smith, 1998).

Orthopedic

Orthopedic abnormalities, ranging in incidence from 30% to 45%, are second in frequency to those of the genitourinary tract and abdominal wall. Many of these abnormalities result from the compressive effects of oligohydramnios. Some think the musculoskeletal defects result from the abnormal mesenchymal development at 6 weeks of gestation (Loder et al, 1992). Green and colleagues (1993), however, pointed out that because many of the deformities are unilateral, oligohydramnios is the most likely etiology. Dimpling of the lateral aspect of the knees is a common finding in

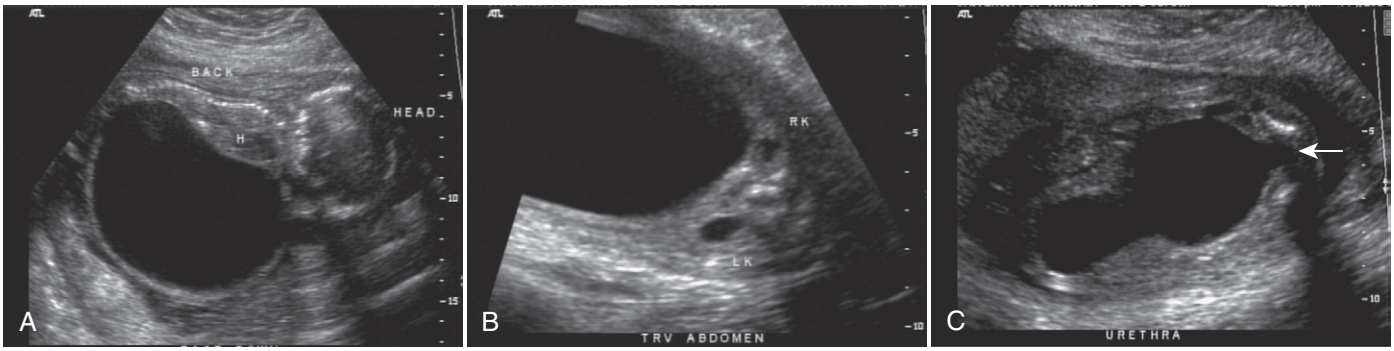


Figure 123–8. Prenatal ultrasound of a fetus with prune-belly syndrome **A,** Massively dilated bladder filling most of the abdominal cavity. Note the lack of amniotic fluid. **B,** The cephalic portion of the bladder reaching the level of both kidneys with hydronephrosis and renal parenchyma noted. **C,** A dilated bladder with a urachal diverticulum *(arrow)* and an elongated and dilated posterior urethra. (Courtesy of C. Peters.)

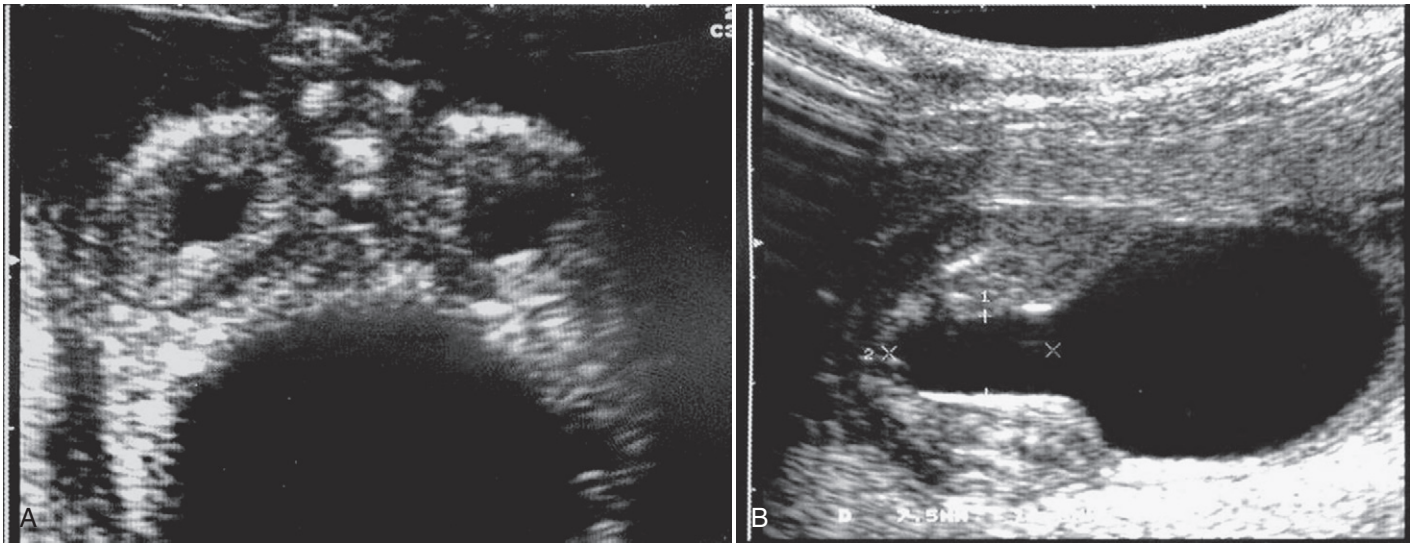


Figure 123–9. **A,** Fetus with prune-belly syndrome demonstrating distended bladder with hydronephrotic echogenic kidneys. **B,** Distended bladder with dilated prostatic urethra indicative of outlet obstruction from urethral atresia. (Courtesy of E. Ruiz.)

oligohydramnios. Oligohydramnios may also result in talipes equinovarus (26%), hip dysplasia (5%), and congenital scoliosis (4%) (Woodard and Smith, 1998). It has been proposed that a distended bladder that may impinge on the external iliac vessels may compromise the blood supply to the lower extremities and in severely affected cases result in lower extremity hypoplasia, absence, or amputation (Smith, 1913; Green et al, 1993).

PRESENTATION

Prenatal Diagnosis and Management

Prenatal ultrasonography has played a major role in the identification of congenital genitourinary abnormalities. Fetal hydronephrosis can be diagnosed accurately in the second trimester and is present in approximately 1% of all pregnancies. However, the etiology of the hydronephrosis cannot be accurately determined in all cases. Elder (1990) estimated that the accuracy of determining the etiology of fetal hydronephrosis varies from 30% to 85%.

In particular, PBS presents prenatally with findings similar to those of other causes of bladder outlet obstruction (Fig. 123–8), **as in posterior urethral valves, or megacystis megaureter syndrome** (Kramer, 1983). **Although an accurate diagnosis of PBS has been made as early as 11 to 14 weeks of gestation** (Shimizu et al, 1992; Yamamoto et al, 2001) (Fig. 123–9), **the classic findings of hydroureteronephrosis, a distended bladder, and an irregular abdominal circumference are not consistently seen at 30 weeks** (Okulski, 1977; Bovicelli et al, 1980; Christopher et al, 1982; Shih et al, 1982). Early fetal ascites has been suggested to correlate with PBS (Scarbrough et al, 1988). It is imperative to remember that the majority of patients with PBS do not have demonstrable urinary obstruction and that the degree of hydroureteronephrosis does not correlate with the postnatal renal function (Gadziala et al, 1982).

Whereas some have recommended in utero intervention for relief of urinary tract dilation and oligohydramnios (Gadziala et al, 1982; Glazer et al, 1982; Nakayama et al, 1984; Scarborough et al, 1988; Estes and Harrison, 1993; Leeners et al, 2000), others have recommended termination of pregnancy (Pescia et al, 1982). **It is difficult to justify the advocacy of pregnancy termination in light of our inability to diagnose precisely the etiology of prenatal hydronephrosis and inability to predict postnatal renal function on the basis of the**

degree of urinary tract dilation, except in rare cases of early and severe oligohydramnios. Prenatal intervention has been applied to PBS with no proven benefit in terms of postnatal renal function (Elder et al, 1987; Sholder et al, 1988; Freedman et al, 1999; Biard et al, 2005; Blaicher et al, 2005). The only circumstances in which prenatal intervention may be justified are the rare situations of urethral atresia with progressive oligohydramnios (Steinhardt et al, 1990; Reinberg et al, 1993; Perez-Brayfield et al, 2001) or cases in which decompression of the urinary tract is necessary to prevent dystocia (Gadziala et al, 1982).

Neonatal Presentation

The appearance of the abdominal wall immediately suggests the diagnosis of PBS (see Fig. 123–6) whether or not the diagnosis was suspected prenatally. It should be remembered that other associated abnormalities such as cardiac or pulmonary often should take precedence over the urinary tract because in the absence of true bladder outlet obstruction, as seen with urethral atresia, the hydroureteronephrosis is not life threatening.

Spectrum of Disease

With the number of variable anomalies present in PBS, it is understandable that there is a wide spectrum of clinical presentations. There are three major categories of presentation in the neonatal period as described by Woodard (1985) (Table 123–2).

Category I consists of neonates who have experienced marked oligohydramnios as a result of renal dysplasia or severe bladder outlet obstruction with resultant pulmonary hypoplasia and skeletal abnormalities. Most infants with urethral atresia fall in this category. The exceptions to this are patients with urethral atresia and a patent urachus (Rogers and Ostrow, 1973). Those in this category who are not stillborn commonly succumb within a few days of life to pulmonary hypoplasia or later to renal failure. Approximately 20% of newborns with PBS die in the perinatal period (Woodard and Parrott, 1978b; Burbige et al, 1987; Fallat et al, 1989). It would be unusual for any urologic intervention in this category of patients to alter the course of events. Simple catheter drainage is all that is justifiable.

Category II demonstrates the full spectrum of the disorder with moderate or unilateral renal insufficiency and moderate to severe hydroureteronephrosis. Pulmonary hypoplasia is not a prominent feature of this group of patients. The clinical course is that of stabilization of renal function at or somewhat below normal or progressive azotemia. It is in this group of patients that significant controversy over management exists (Waldbaum and Marshall, 1970; Randolph, 1977; Woodard and Parrott, 1978b).

Category III consists of patients with mild features of the triad or incomplete forms of PBS. This category comprises the majority of PBS patients in whom hydroureteronephrosis is present to some degree but renal function is well maintained (Woodhouse et al, 1982; Woodard, 1998). **There is no evidence of pulmonary insufficiency.** There is little controversy that urologic intervention in the group is reserved for patients who demonstrate repeated urinary tract infections, probably related to urinary stasis or vesicoureteral reflux, or development of upper tract deterioration (Woodard and Smith, 1998). As previously noted, there is poor correlation between the extent of abdominal wall deficit and the degree of hydronephrosis or renal dysplasia, or both. This is also apparent in other variants of the syndrome. Some children have markedly dilated urinary tracts with minimal or no dysplasia and therefore normal renal function. Therefore the appearance of the abdominal wall or the degree of hydronephrosis may have little bearing on the long-term prognosis of children with PBS.

Table 123–2.

Spectrum of Prune-Belly Syndrome

CATEGORY	CHARACTERISTICS
I	Renal dysplasia Oligohydramnios Pulmonary hypoplasia Potter features Urethral atresia
II	Full triad features Minimal or unilateral renal dysplasia No pulmonary hypoplasia May progress to renal failure
III	Incomplete or mild triad features Mild to moderate uropathy No renal dysplasia Stable renal function No pulmonary hypoplasia

Incomplete Syndrome

These are male patients who may not have all the features of the triad syndrome but share other features. **Most typically, these incomplete forms of the syndrome would lack the typical abdominal wall features but have the common uropathy and cryptorchidism. Many of these patients may go on to experience renal failure and therefore require close observation, monitoring, and selective intervention.** Bellah reported a relatively high (8/15) tendency to progressive renal failure in his population of pseudoprune patients. This may be partially attributed to a delay in diagnosis in the absence of the obvious abdominal musculature deficiency and therefore a tendency to present with recurring urinary tract infections (Bellah et al, 1996).

Adult Presentation

Patients with incomplete forms of PBS and specifically those who lack the abdominal wall features may present as late as adulthood with symptoms of renal failure and hypertension (Lee, 1977; Kerbl and Pauer, 1993). Although there have been isolated reports of adults with no history of urinary tract infections, most others who present in adulthood eventually develop urinary tract infections from the chronic urinary stasis associated with the syndrome (Culp and Flocks, 1954).

Female Syndrome

Five percent of PBS patients are female, most of whom have the abdominal wall deficiency and the abnormal urinary tract (Reinberg et al, 1991b). Rabinowitz and Schillinger (1977) reported female patients with the typical abdominal wall deficit and a normal urinary tract. In the series of Reinberg and colleagues (1991b), bladder outlet obstruction was commonly seen along with a 40% occurrence of anorectal anomalies similar to the statistics for the male; 40% did not survive the newborn period.

EVALUATION AND MANAGEMENT

The initial evaluation of the newborn with PBS requires a team consisting of a neonatologist, a nephrologist, and a urologist. As dictated, other specialists, particularly a cardiologist, may be indicated. Early orthopedic evaluation is also warranted. The major initial concern is that of management of cardiac and respiratory issues. An immediate chest radiograph is necessary to exclude commonly associated pulmonary abnormalities such as pneumothorax, pneumomediastinum, and pulmonary hypoplasia, which is commonly a result of oligohydramnios (Perlman and Levin, 1974). Early urologic intervention is indicated only for neonates with evidence of bladder outlet obstruction, in whom a percutaneous suprapubic tube can be inserted in the neonatal intensive care unit.

Initial evaluation of renal function and the urinary tract status is important but must be tempered by transitional neonatal physiology. Although an initial creatinine level is important in establishing a baseline, it may be more reflective of the mother's renal function, and therefore the trend in creatinine levels over the course of the early postnatal days or weeks is much more predictive of long-term renal function.

Key Points: Initial Management

- A team consisting of neonatology, nephrology, urology, and other specialties such as cardiology is necessary.
- A voiding cystourethrogram (VCUG) is indicated in the neonatal period if there is renal insufficiency or evidence of bladder outlet obstruction and only after antibiotic prophylaxis.
- A chest radiograph to evaluate for pneumothorax, pneumomediastinum, and pulmonary hypoplasia is necessary.
- Baseline assessment of renal function should include renal and bladder ultrasonography, blood urea nitrogen (BUN), creatinine, and electrolytes.
- Circumcision is advisable in the absence of a structural penile abnormality.
- Early intervention is indicated for evidence of bladder outlet obstruction and preferably with a percutaneous suprapubic tube.

Serum, blood urea nitrogen, and electrolytes are necessary to assess for the potential systemic acidosis and electrolyte imbalances that may be seen in renal insufficiency. It has been shown in multiple reports that a baseline creatinine level of less than 0.7 mg/dL is predictive of adequate renal function through childhood, in the absence of repeated insults from pyelonephritis (Geary et al, 1986; Reinberg et al, 1991a; Noh et al, 1999).

Early renal and bladder ultrasonography, once the newborn is stabilized, is necessary to assess the renal parenchyma for its thickness, density, and presence or absence of cortical cysts and degree of urinary tract dilation (see Fig. 123–1).

Avoidance of urinary tract infection is essential in light of the urinary stasis and often compromised baseline renal function. Circumcision is advisable in the absence of a structural penile abnormality to reduce the risk of infant urinary tract infections. Similarly, prophylactic antibiotic therapy is recommended, especially before urinary tract instrumentation, including the initial voiding cystourethrogram (VCUG). Although instrumentation without a defined purpose that may alter management should be avoided, a VCUG to assess the bladder outlet and bladder emptying ability, especially in the presence of renal insufficiency, is warranted (Woodard and Smith, 1998). The VCUG is necessary in neonates with renal insufficiency to rule out bladder outlet obstruction as the etiology versus urinary stagnation. In up to 70% of children with PBS, vesicoureteral reflux is diagnosed (Berdon et al, 1977; Fallat et al, 1989). Any instrumentation should be carried out with strict attention to sterile technique to reduce the risk of inoculation of a static urinary system. One can avoid an early VCUG in the presence of normal renal function and evidence of adequate bladder drainage per urethra or a patent urachus.

As noted, neonates can be categorized on the basis of their spectrum of disease (see Table 123–1). There is little disagreement on the management of category I PBS patients. There is no evidence that anything beyond supportive care is justifiable; in particular, intervention in the urinary tract is not indicated beyond simple bladder drainage because their fate cannot be altered (Woodard and Smith, 1998).

At the other end of the spectrum, category III patients rarely require urologic intervention for the urinary tract because they are in a balanced state of hydronephrosis with good, if not normal, renal function. Early in infancy their cryptorchidism requires correction. Children in this category require regular monitoring of urinary tract dilation (ultrasonography) and renal function (serum creatinine).

Category II patients require individualization of evaluation and management on the basis of the fact that within this category there are variable degrees of severity of each facet of PBS. There is, however, much controversy over their management. Evaluation of renal function or renal drainage, or both, is required in those with renal insufficiency. Excretory urography, while providing dramatic images of the urinary tract (see Fig. 123–2), does not provide sufficient information on comparative function. Renal parenchymal function is best assessed by a technetium-99m (^{99m}Tc) dimercaptosuccinic acid (DMSA) renal scan at 4 to 6 weeks of age to prevent difficulties in interpretation related to transitional neonatal physiology. Renal outflow obstruction is best assessed by ^{99m}Tc mercaptoacetyltriglycine (MAG3), which also provides an assessment of comparative renal function with massive hydronephrosis and resultant stasis. In the presence of poor renal function, assessment of renal outflow obstruction by nuclear scan techniques may be limited; therefore selective use of the Whitaker antegrade perfusion test may be helpful.

Controversies in Management of Category II Prune-Belly Syndrome

Aggressive surgical intervention was initially derived from early observations of the poor prognosis for category II infants as a group. Compilation of the cases reported in the literature between 1950 and 1970 by Waldbaum and Marshall (1970) revealed that 86% of the 56 accurately traceable patients had died, with or without surgical intervention. The obvious implication was that a more aggressive approach was necessary to improve the fate of the infant with PBS. **With the recognition that infection and progressive renal insufficiency are the factors that most often pose the greatest threat to quality of life and survival, surgical reconstruction to normalize the anatomy and function of the genitourinary tract was advocated.**

Early retailoring of the urinary system to reduce stasis and eliminate reflux or obstruction has included ureteral shortening, tapering, and vesicoureteral reimplantation and reduction cystoplasty. Reconstruction is best delayed until the child is at least 3 months of age to allow for pulmonary maturation. This approach has been successful in achieving anatomic and functional improvement as evidenced by stable radiographic studies, stable creatinine values, and a reduced occurrence of infection (Waldbaum and Marshall, 1970; Jeffs et al, 1977; Woodard and Parrott, 1978b; Randolph et al, 1981b). In the personal reconstructive experience of one of the authors (JW), 15 patients have maintained a normal creatinine level and only 2 have demonstrated moderate renal insufficiency, with follow-up ranging from 2 to 27 years.

An alternative approach of limited surgical intervention has also been applied. Proponents advocate close surveillance with medical management of bacteriuria and surgical intervention only in patients with proven obstruction or intractable infection. Opinions vary about the management of vesicoureteral reflux in the PBS population, although there is no reason to believe that reflux in this population is any less important, and correction of high-grade reflux seems prudent. Success with minimal surgical intervention has been reported (Woodhouse et al, 1979; Duckett et al, 1980; Tank and McCoy, 1983; McMullin et al, 1988). Woodhouse and colleagues (1979) reviewed a series of patients with PBS managed conservatively. Nine of these 11 patients, who were monitored from infancy, remained well except for a few urinary tract infections for periods of up to 24 years. They were said to have normal voiding patterns and normal renal function. Certainly, patients in category III are candidates for this type of management.

The paucity of long-term data for category II patients, the probable variation in assignment of disease severity in treatment groups, and the variable natural history of the disease make comparisons of these retrospective studies difficult. **Spontaneous improvement in ureteral appearance and function may occur with normal growth and elongation of the ureters** (Duckett et al, 1980). **Also, some patients with gross abnormalities of the urinary collecting system have survived decades without medical attention** (Asplund and Laska, 1975; Lee, 1977; Texter and Koontz, 1980). **Yet progressive uropathy is also well known to occur, and many patients with PBS ultimately require renal transplantation** (Reinberg et al, 1989). Controversy will persist over category II patients until accurate application of a medical or surgical approach is possible on the basis of distinct clinical features. Dénes and colleagues (2004) emphasize the individualization of care in their 17-year experience with 32 patients.

Surgical Management of the Prune-Belly Syndrome Patient

Surgical management of children with PBS can be divided into three categories: urinary tract reconstruction, abdominal wall reconstruction, and orchidopexy. Urinary tract reconstruction is generally reserved for children with progressive or severe hydronephrosis, recurrent upper tract infections, true obstructive uropathy, and progressive renal failure. Temporary urinary diversion also has a role in the very young or the very ill child.

Supravesical Urinary Diversion

In certain instances the occurrence of repeated upper tract infections or deterioration of renal function dictates temporary urinary diversion. Although cutaneous vesicostomy usually provides adequate upper tract drainage and decompression, in rare instances more proximal diversion is indicated because of ureteropelvic or ureterovesical junction obstruction. Here a cutaneous pyeloplasty is advocated rather than proximal ureterostomy because it provides the best upper tract drainage and avoids sacrificing a normal proximal ureter that might be useful in later reconstruction.

Cutaneous Vesicostomy

Urinary diversion may be necessary as a temporary measure in children with acute renal failure, urinary sepsis, or bladder outlet obstruction from urethral atresia with limited patency of the urachus (Fig. 123–10) (Teramoto et al, 1981; Joseph, 1999). **When temporary urinary diversion is indicated, a cutaneous vesicostomy is the procedure of choice. This is best done by the Blocksom technique as described by** Duckett (1974, 1986) and colleagues. If there is a large urachal diverticulum, it

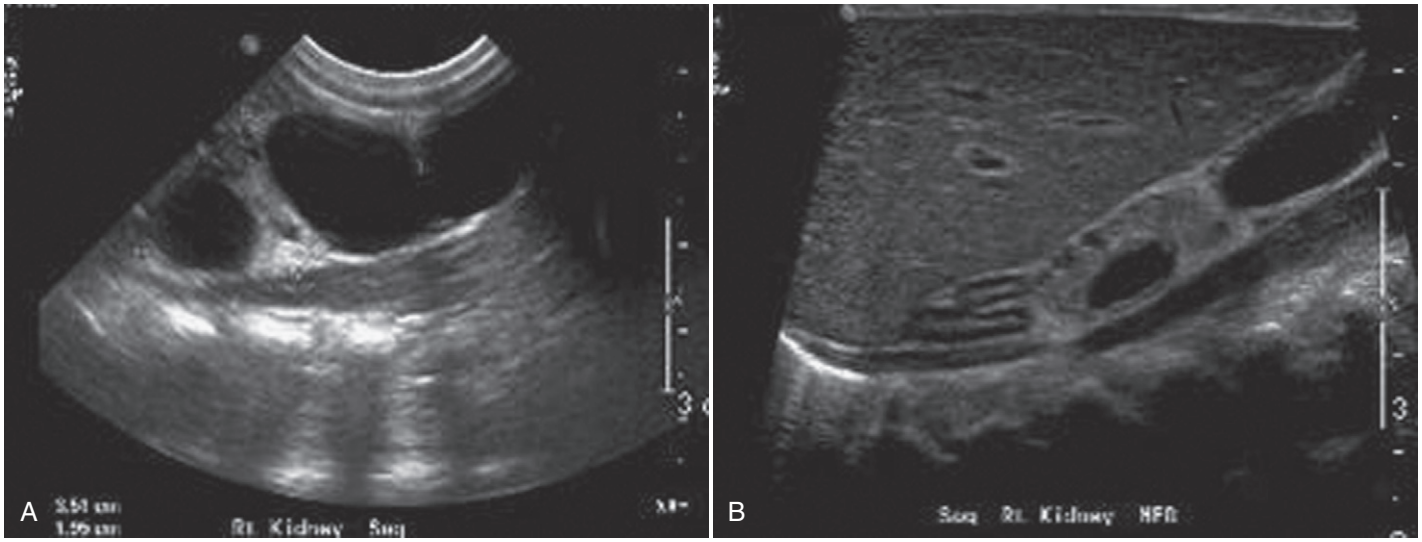


Figure 123–10. **A,** Prevesicostomy ultrasound of the right kidney demonstrating massive hydronephrosis with echogenic parenchyma. **B,** Postvesicostomy ultrasound demonstrating a decompressed kidney with echogenic parenchyma and cortical cysts. (Courtesy of C. Peters.)

can be excised at that time. It is advisable to create a larger than normal stoma in the PBS patient because stenosis is common, probably because of the decreased intra-abdominal pressure (Snow and Duckett, 1987).

Internal Urethrotomy

In the absence of urethral atresia, true anatomic obstruction of the urethra is rare in PBS. However, the normal resistance of the urinary sphincter has been implicated in "unbalanced" urethrovesical function contributing to large postvoid residuals. Snyder and Cukier proposed lowering urethral resistance by internal urethrotomy to improve bladder emptying (Snyder et al, 1976; Cukier, 1977). In patients studied by urodynamic flow rate profilometry, improved flow rates with reduced residual urine and improvement in the radiographic appearance of the upper tracts were found (Snyder et al, 1976; Woodhouse et al, 1979). Although sustained long-term success has not been demonstrated, internal urethrotomy should be considered in PBS children with high postvoid residuals, increasing hydroureteronephrosis, or vesicoureteral reflux with recurrent upper tract infections. Williams (1979) advocated using an Otis urethrotome achieving a No. 24- to 30-Fr caliber with one or two incisions made anteriorly or anterolaterally; however, direct visual urethrotomy would seem preferable and should be performed at the distal end of the prostatic urethra (Smith and Woodard, 2002). It is interesting to note that internal urethrotomy does not result in incontinence in this population.

Reduction Cystoplasty

In many PBS patients, poor bladder contractibility leads to incomplete and infrequent emptying from the complicating urinary stasis and vesicoureteral reflux issues. This leads to the concept of reducing the size of the bladder and remodeling it into a more spherical shape to better direct the contractible forces (Perlmutter, 1976). A variety of approaches have been proposed, from simple excision of the urachal diverticulum to the excision of redundant mucosa with the creation of overlapping between flaps to improve contractibility (Williams and Parker, 1974; Woodard and Trulock, 1986). Over time, however, high bladder capacity and residual volumes seem to recur (Bukowski and Perlmutter, 1994). It seems therefore that reduction cystoplasty would be justified only to remove the larger urachal diverticulum or as part of a more extensive internal reconstruction. Intermittent catheterization through the urethra or through an appendicovesicostomy channel is likely to afford better long-term bladder emptying with reduction of residual urinary volumes (Joseph, 1999).

Anterior Urethral Reconstruction

On one end of the spectrum of urethral maldevelopment is urethral atresia, sometimes referred to as *microurethra* (see Fig. 123–3). Passerini-Glazel and colleagues (1988) reported on progressive gentle urethral dilation with good success. This technique may be used in situ or through and through in cases in which a vesicostomy has been performed (Fig. 123–11). As reported by Reinberg and colleagues (1993), however, this technique is not uniformly successful and one may require a more formal urethroplasty with skin flaps or grafts, or both.

Megalourethra in PBS may be either fusiform or scaphoid (Appel et al, 1986). This is best approached with a circumferential subcoronal incision and penile degloving (Fig. 123–12A-F). The redundant urethra can be excised, and the urethra reconstructed over an appropriately sized catheter. Alternatively, some of the urethra can be used to reinforce the urethroplasty because in either form of megalourethra the spongiosum is deficient.

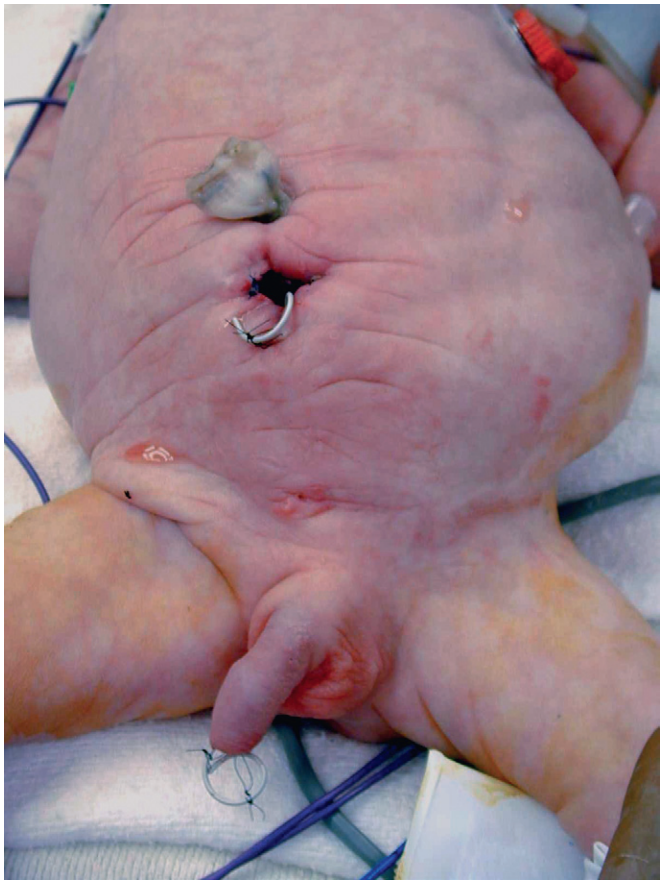


Figure 123–11. Prune-belly syndrome patient with urethral atresia. Note vesicostomy and double-J stent through the urethra for urethral progressive dilation.

Ureteral Reconstruction

Ureteral remodeling remains controversial. It is best undertaken in children who demonstrated repeated nonsuppressible upper urinary tract infections or those with progressive upper tract deterioration. The goal of remodeling is to reduce urinary stasis. The key to success relies on meticulous surgical technique and preservation of the upper few centimeters of proximal ureter for reconstruction. Ureteral reimplantation into the abnormal bladder can be difficult in that the creation of a submucosal tunnel can be challenging (Woodard and Trulock, 1986). Woodard and his colleagues have demonstrated excellent success in this population when these procedures were performed in the neonatal period or in the older child (Woodard and Parrott, 1978b; Woodard and Zucker, 1990). They no longer, however, recommend such extensive reconstructive surgery before the age of 3 to 6 months. Dénes and colleagues (2004) have reported excellent results of reconstruction of the prune upper and lower urinary tracts in a large group of patients, with an experience of more than 17 years.

Orchidopexy

The timing of orchidopexy is dictated by our current understanding of the need for early treatment of the undescended testis in non-PBS patients along with individual PBS patients' needs for either temporary or reconstructive surgery. Although the fertility

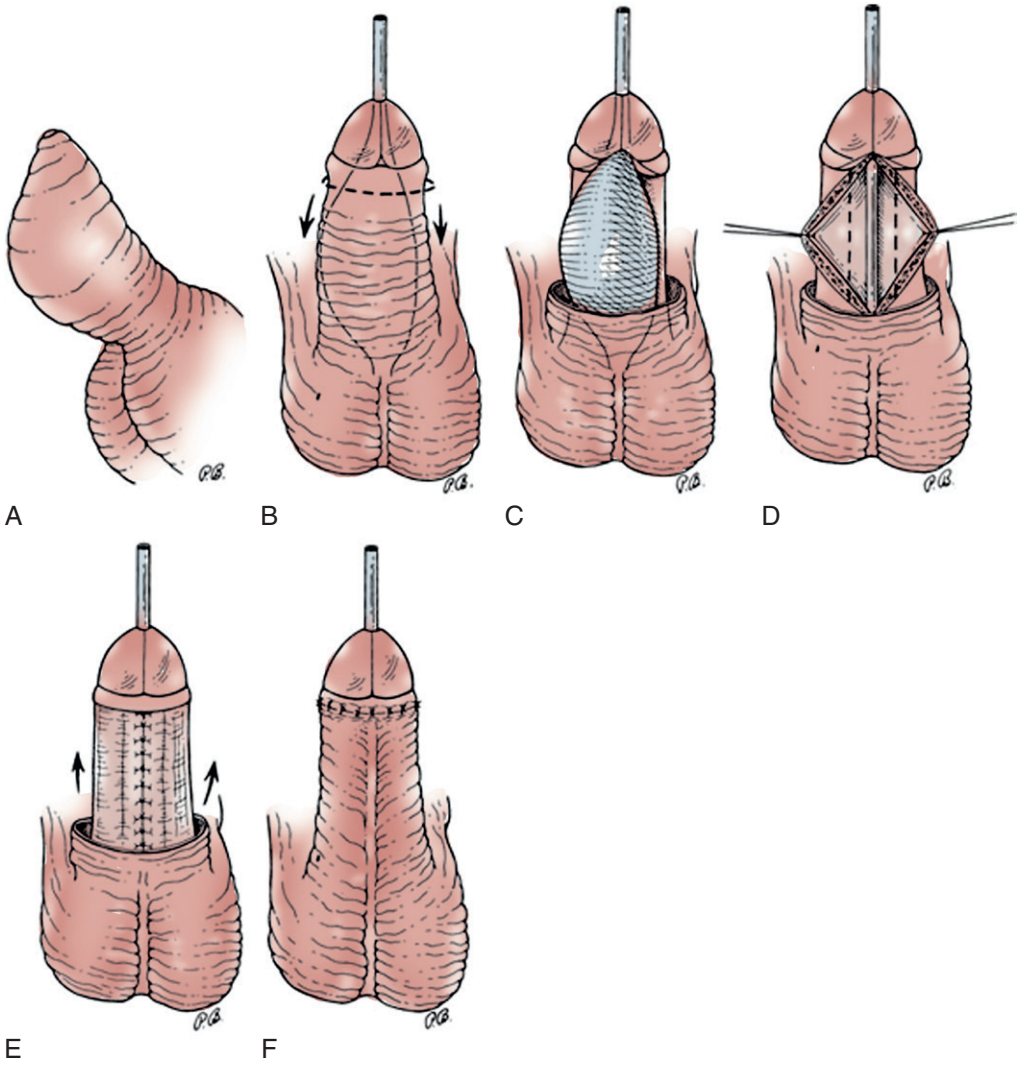


Figure 123–12. **A,** The prepuce is reduced, and a circumcising incision is made, preserving a mucosal collar. **B,** With a catheter in place to assist with identification of the urethra, the penis is degloved along the subdartos plane. **C,** The involved segment of the urethra is opened longitudinally, and the redundant urethral wall is excised to allow tapering of the urethra over a catheter of appropriate size. **D,** The urethra is closed with absorbable running sutures and is bolstered with a second layer of sutures placed in an interrupted fashion if possible. **E,** The penile skin is brought forward, the excess foreskin is removed with a second circumferential incision, and the penile shaft skin is approximated to the mucocutaneous border **(F).**

Key Points: Surgical Reconstruction

- Upper urinary tract reconstruction is controversial but clearly indicated for evidence of declining renal function in the presence of hydronephrosis, recurrent upper tract infections, or progression of the hydroureteronephrosis.
- Orchidopexy is best performed early in life because this affords the most likely prospect of a successful single-stage procedure.
- Abdominal wall reconstruction has demonstrated improved bladder emptying, a more effective cough, and improved defecation in addition to psychosocial benefits.

potential of the PBS patient is known to be compromised, germ cells are present in the testes of infants with PBS. In addition, the prognosis for normal hormonal function at puberty is excellent. These factors, along with the potential risk of testicular carcinoma (Uehling et al, 1984; Massad et al, 1991), would justify early orchidopexy. Because the testes are uniformly located in the abdomen, most commonly on a broad mesorchium overlying the iliac vessels (Coplen et al, 1996), standard inguinal approaches are not usually successful in achieving a satisfactory scrotal position. Four alternative approaches may be considered.

Transabdominal Orchidopexy. Woodard, Parrott, and other researchers noted that if an orchidopexy is done in the neonatal period and up to 6 months of age by a transabdominal approach, adequate spermatic vessel mobilization can usually be achieved for scrotal placement (Woodard and Parrott, 1978a, 1978b; Randolph et al, 1981a; Fallat et al, 1989). **Transabdominal bilateral orchidopexy at about 6 months of age is currently considered the approach of choice.** This approach is often used in conjunction with other abdominal surgeries, either a vesicostomy, urinary tract reconstruction, or abdominal wall reconstruction. In the absence of need for other abdominal surgeries, this can be accomplished laparoscopically.

Spermatic Vessel Ligation. When successful transabdominal orchidopexy cannot be accomplished in the first few months of life, the other options that may be considered

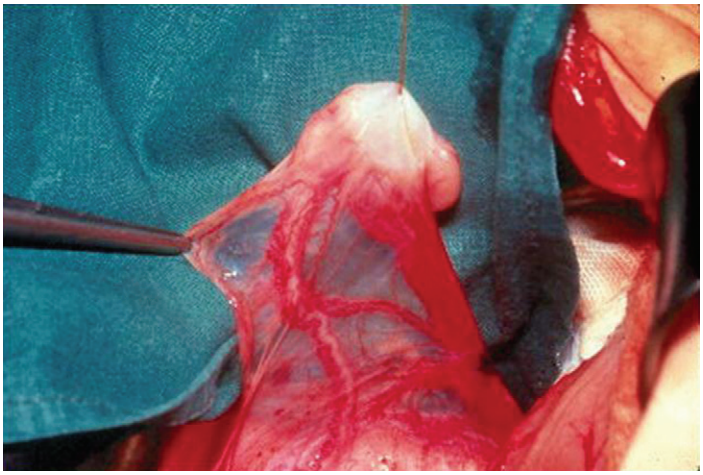


Figure 123–13. Operative photograph showing increased vacularity along vas deferens 4 months after first stage Fowler-Stephens orchidopexy.

are (1) Fowler-Stephens orchidopexy (Fowler and Stephens, 1959; Gibbons et al, 1979; Boddy et al, 1991; Kirsch et al, 1998), **(2) staged Fowler-Stephens orchidopexy** (Fig. 123–13) (Ransley et al, 1984; Bloom, 1991; Caldamone and Amaral, 1994; Docimo, 1995; Yu et al, 1995), **and (3) microvascular autotransplantation** (MacMahon et al, 1976; Wacksman et al, 1980; Boddy et al, 1991). A meta-analysis report by Docimo (1995) indicated comparative success rates of 67% and 77% for standard and staged Fowler-Stephens techniques, respectively. In a multi-institutional report of laparoscopic orchidopexy, Baker and colleagues (2001) noted a success rate of 81% for a standard Fowler-Stephens approach compared with 90% for a staged approach. In a long-term follow-up report, Patil and colleagues (2004) reported a satisfactory outcome in PBS with a one- or two-stage Fowler-Stephens orchidopexy. Some authors have recommended several technical adjustments during laparoscopic orchiopexy in children with PBS, particularly port placement because there is little resistance to cannula placement in these children (Saxena and Brinkmann, 2007).

Reconstruction of the Abdominal Wall

Children with mild degrees of abdominal muscular deficiency may show improvement in the abdominal wall laxity as they mature. However, most others with moderate to severe degrees of abdominal wall laxity are left with a potentially psychologically crippling defect (Ehrlich et al, 1986; Parrott and Woodard, 1992). An elasticized corset can improve the external appearance when they are fully clothed; however, it is quite inconvenient to use. There is general agreement about the cosmetic benefit of abdominal wall reconstruction. However, whether it improves bladder, bowel, and pulmonary function is controversial (Smith et al, 1998; Woodard, 1998). Smith and colleagues demonstrated improved bladder emptying following abdominal wall reconstruction; however, some of their reconstructed patients underwent concomitant urinary tract remodeling as well. Potential effects include a more effective cough and improvement in defecation. The timing of abdominal wall reconstruction should be dictated by the need for other surgical interventions, particularly if upper urinary tract remodeling is necessary. If upper tract remodeling is not anticipated, the abdominal wall can be addressed at any time and has been done as young as 6 months of age along with transabdominal orchidopexy (Smith and Woodard, 2002). However, if the procedure is done in infancy, one must be prepared to place the infant on a respirator postoperatively for a period of time. Of the following techniques, the consensus currently is that the Monfort and Ehrlich techniques provide the best functional and cosmetic results.

Randolph Technique

Randolph and colleagues (1981) first popularized a technique for abdominal wall reconstruction based on electromyographic mapping, which indicated that the most severely affected area of the abdomen is the infraumbilical regions and the lateral and supraumbilical regions are generally least affected. This technique makes a transverse incision from the 12th rib to the pubic symphysis to the opposite 12th rib with a full-thickness removal of the skin, lower abdominal musculature, and peritoneum. The healthy fascia is then approximated to the anterior iliac spines, pubic tubercle, and inferior fascia. Although this technique is successful in establishing a waistline, lateral abdominal bulging often persists. Of the 16 patients reported, 9 had excellent cosmetic results and there was some residual protuberance in 7 (Fallat et al, 1989).

Ehrlich Technique

The technique described by Ehrlich used a vertical midline incision and allows preservation of the umbilicus on a vascular pedicle from the inferior epigastric artery (Ehrlich et al, 1986; Ehrlich and Lesavoy, 1993). The skin and subcutaneous tissues are elevated off the muscle and fascial layers, and an overlapping, pants over vest advancement of each side to the contralateral flank is performed, preserving the less affected lateral muscles and fascia.

Monfort Technique

Monfort described a technique that is vertically oriented similar to that of Ehrlich's approach; however, an elliptically oriented incision is used to isolate the redundant skin (Monfort et al, 1991). The incision extends from the tip of the xiphoid to the pubis. A second incision is made around the umbilicus to preserve it in situ (Fig. 123–14). The skin and subcutaneous tissue are dissected off the attenuated fascia and muscle with the dissection extending laterally to the anterior axillary line. Vertical fascial incisions are made lateral to the superior epigastric arteries, leaving a central fascial bridge. If intra-abdominal surgery is necessary, excellent exposure to the urinary tract or abdominal testes is afforded through these lateral fascial incisions. The lateral fascial is then advanced over the central fascial bridge from both sides, alleviating the redundancy and increasing the thickness of the abdominal wall (Figs. 123–15 and 123–16).

Furness and colleagues (1998) described a modified midline approach with less abdominal wall dissection that avoids entering the peritoneum, which may be useful if intra-abdominal surgery is not planned. A modification of the Monfort technique uses laparoscopy to protect the abdominal contents (Franco, 2005).

LONG-TERM OUTLOOK

The nadir creatinine value during infancy has proved to be a useful predictor of long-term renal function. If the nadir value is less than 0.7 mg/dL, renal function tends to be stable during childhood unless there is further renal compromise by pyelonephritis (Geary et al, 1986; Reinberg et al 1991b; Noh et al 1999). The importance of urinary tract monitoring by periodic cultures and prompt treatment of urinary tract infections cannot be overemphasized. Unfortunately, the risk of infection is constant in the setting of urinary

tract dilation and stasis. Up to 30% of patients, generally those with impaired renal function at initial evaluation, develop chronic renal failure during childhood or adolescence (Geary et al, 1986). Renal transplantation is necessary for these patients to ensure normal growth and development, and success with transplantation in PBS patients can be expected to equal that in other age-matched groups (Reinberg et al, 1989). Fusaro and colleagues (2004) have reported on five boys with PBS who underwent renal transplantation. The 5-year graft survival rate was 66.7%, with all maintaining their native urinary tracts. Normal growth can be expected in most of the patients with normal renal function, although growth retardation in the absence of renal compromise was observed in one third of patients in one series (Geary et al, 1986). A normal pattern of secondary sexual development can be expected (Woodhouse and Snyder, 1985). Although primary fertility is not expected in the PBS population, fertility with assisted reproductive techniques may be feasible in those having had successful early orchidopexy.

The overall outlook for the PBS patient, both for survival and for quality of care, has improved considerably, largely through advances in medical, surgical, and urodynamic management. The key to management of the PBS patient is individualization of care because some require major urologic reconstruction, and others require little if any reconstruction. Long-term surveillance of the urinary tract is essential because functional dynamics can change over time.

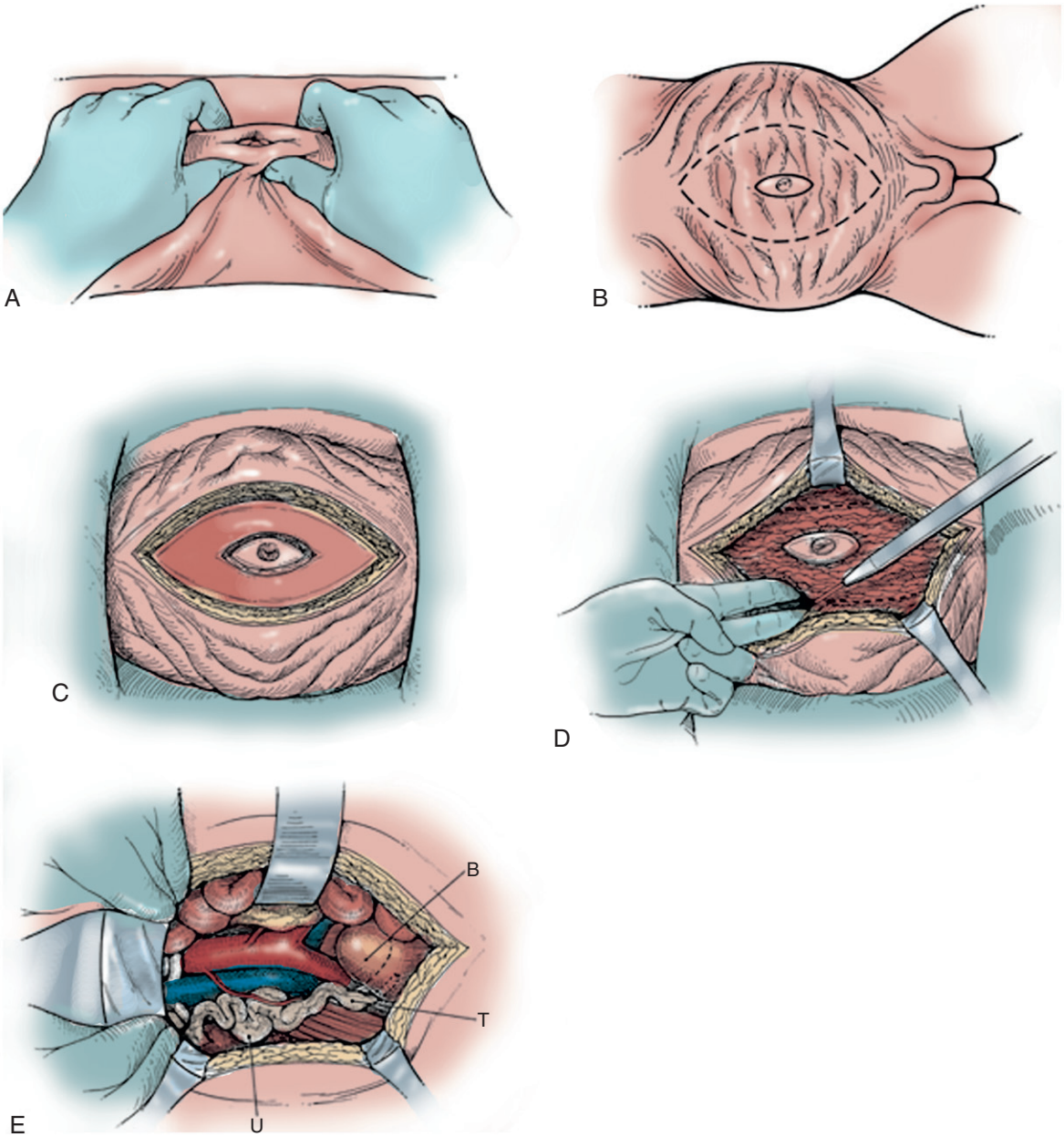


Figure 123–14. Surgical technique for Monfort abdominoplasty and concomitant reconstruction of prune-belly uropathy. **A,** Delineation of redundancy by tenting up abdominal wall. **B,** Skin incisions are outlined with a separate circumscribing incision to isolate the umbilicus. **C,** Skin (epidermis and dermis only) is excised with electrocautery. **D,** Abdominal wall central plate is incised at the lateral border of the rectus muscle on either side, from the superior epigastric to the inferior epigastric vessels, creating a central musculofascial plate. **E,** Adequate exposure is provided for concomitant transperitoneal genitourinary procedures.

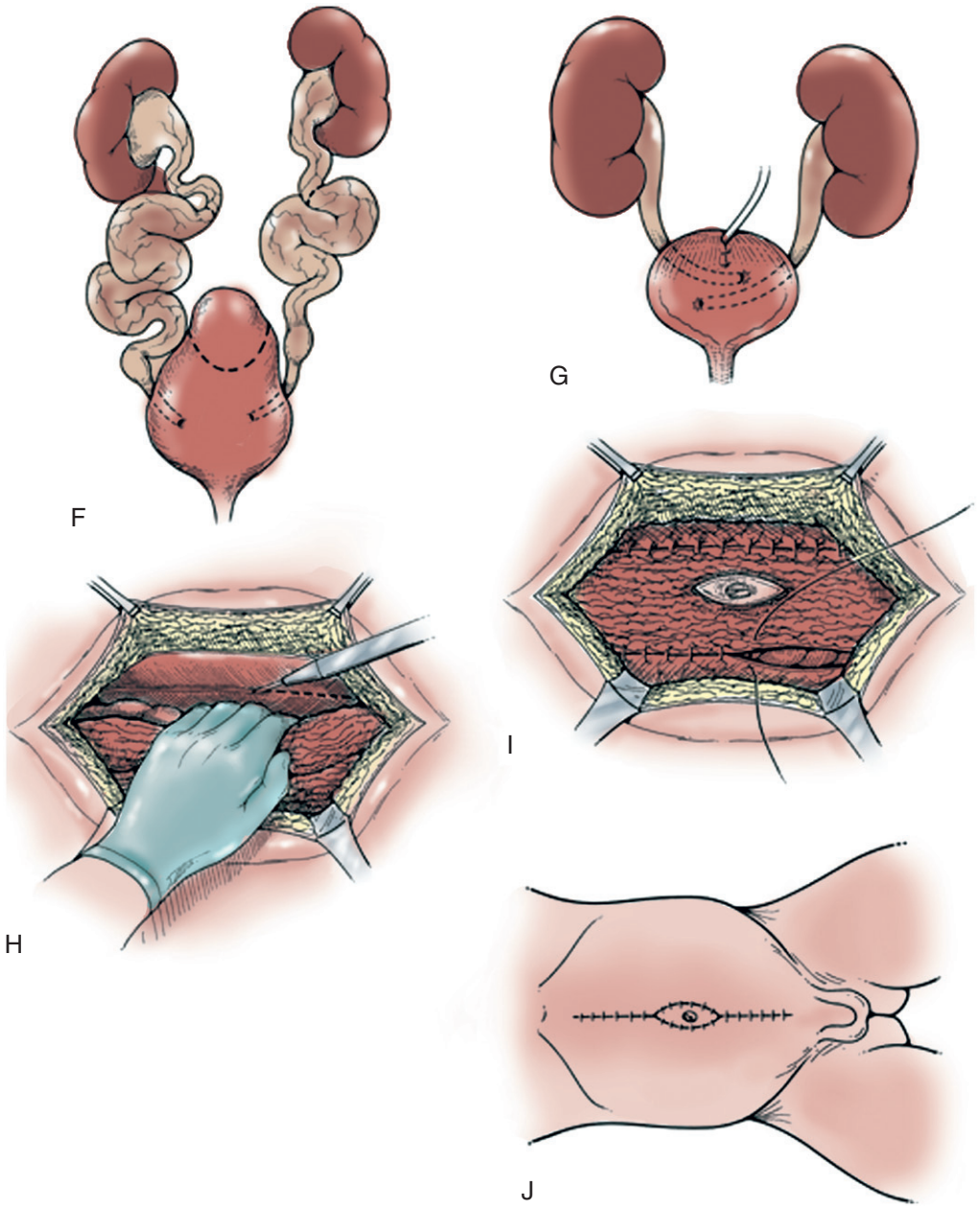


Figure 123–14, cont'd. **F,** Only the more normal proximal ureter is preserved for vesicoureteral reimplantation, and the urachal diverticulum is excised. **G,** Transtrigonal ureteral reimplantation is performed with or without ureteral tapering as needed. The bladder is closed in two layers, and ureteral stents (not shown) and a cystostomy tube are employed. **H,** Completion of abdominoplasty by scoring of the parietal peritoneum overlying the lateral abdominal wall musculature with electrocautery. **I,** The edges of the central plate are sutured to the lateral abdominal wall musculature along the scored line. **J,** Lateral flaps are brought together in the midline, with closed suction drains placed between the lateral flaps and the central plate. Skin is brought together in the midline, enveloping the previously isolated umbilicus. B, bladder; T, testis; U, ureter. (From Woodard JR, Perez LM. Prune-belly syndrome. In: Marshall FF, editor. Operative urology. Philadelphia: WB Saunders; 1996.)

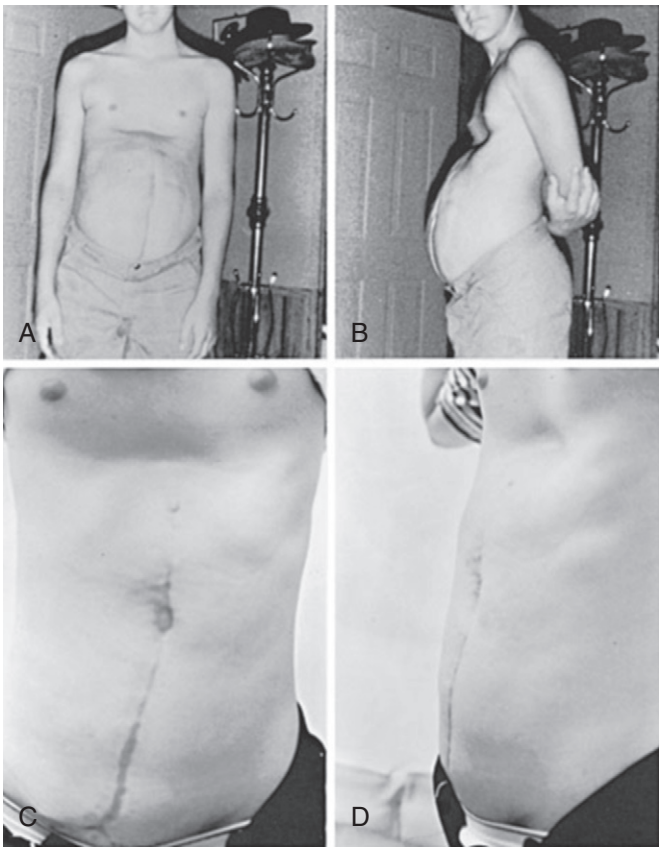


Figure 123–15. **A** and **B,** Anterior and lateral views of the abdomen of a 14-year-old boy who underwent major surgical remodeling of the urinary tract during early infancy with good results. Note typical abdominal configuration. **C** and **D,** Anterior and lateral views of the same boy 1 month after undergoing abdominoplasty with the technique described by Monfort.

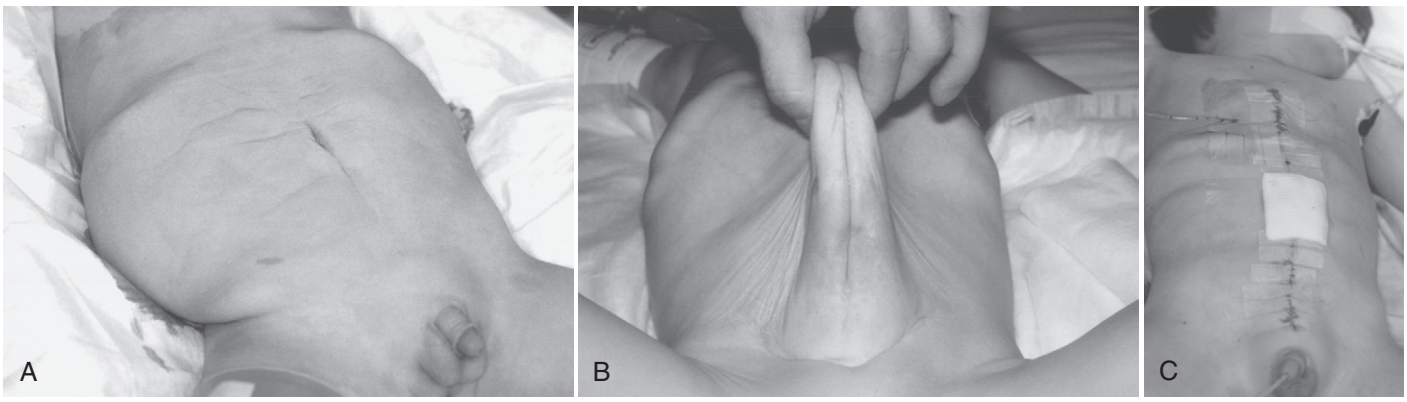


Figure 123–16. Prune-belly syndrome patient demonstrating preoperative appearance of abdominal wall **(A),** estimated extent of abdominal wall resection **(B),** and immediate postabdominoplasty appearance **(C).**

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chapter 124

Exstrophy-Epispadias Complex

John P. Gearhart, MD ● Ranjiv I. Mathews, MD

Exstrophy-Epispadias Complex
Classic Bladder Exstrophy
Surgical Reconstruction of Bladder Exstrophy
Modern Initial Repair of Bladder Exstrophy: Outcomes and Results
Other Modern Exstrophy Repairs: Continence Outcomes
Exstrophy Reconstruction Failures
Cloacal Exstrophy
Surgical Reconstruction of Cloacal Exstrophy
Long-Term Issues in Cloacal Exstrophy
Epispadias
Adolescents and Adults with Exstrophy
Sexual Function and Fertility in the Exstrophy Patient
Long-Term Adjustment Issues

EXSTROPHY-EPISPADIAS COMPLEX

The exstrophy-epispadias complex of genitourinary malformations can be as simple as a glanular epispadias or as overwhelming as a multisystem defect such as cloacal exstrophy (Fig. 124–1). This chapter provides a comprehensive overview of the entire spectrum of the exstrophy-epispadias-cloacal exstrophy defects. In addition, all modern methods of exstrophy management, their complications, and outcomes are discussed.

Historical Aspects

In older texts, the first account of bladder exstrophy was ascribed to Assyro-Babylonian sources dating from the first and second millennia BC. At that time, birth anomalies in both humans and animals were carefully recorded on tablets for their importance as omens on the basis of their interpretation by divination experts. Feneley and Gearhart (2000) examined Assyro-Babylonian descriptions of congenital anomalies from cuneiform texts at the British Museum in London. Although references to anomalies involving the external genitalia were frequent (e.g., hermaphroditism, absence of external genitalia, unilateral and bilateral undescended testes), references to renal and bladder anomalies were few and difficult to interpret medically. Duplication and laterality of anomalies were described in detail owing to their distinct significance, but malformations in combination were not recorded. On the basis of these studies performed with a prominent Assyriologist, a definitive description of bladder or cloacal exstrophy was not corroborated. **The first recorded case of epispadias is attributed to the Byzantine Emperor Heraclius** (AD 610-641) and the first description of bladder exstrophy to Schenck in 1595 (Feneley and Gearhart, 2000).

Incidence and Inheritance

The incidence of bladder exstrophy has been estimated as between 1 in 10,000 and 1 in 50,000 (Lattimer and Smith, 1966) live births. However, data from the International Clearinghouse for Birth Defects monitoring system estimated the incidence to be 3.3 cases in 100,000 live births (Lancaster, 1987). The male-to-female ratio of bladder exstrophy derived from multiple series is 2.3:1 (Shapiro et al, 1985). However, two series reported a 5:1 to 6:1 male-to-female ratio of exstrophy births (Ives et al, 1980; Lancaster, 1987).

The risk of recurrence of bladder exstrophy in a given family is approximately 1 in 100 (Ives et al, 1980). Shapiro and colleagues (1985) conducted a questionnaire of pediatric urologists and surgeons in North America and Europe and identified the recurrence of exstrophy and epispadias in only 9 of approximately 2500 indexed cases. Lattimer and Smith (1966) cited a set of identical twins with bladder exstrophy and another set of twins in whom only one child had exstrophy. Shapiro's series identified five sets of male and female nonidentical twins in whom only one twin was affected with exstrophy; five sets of male identical twins in whom both twins were affected; one set of identical male twins in whom only one twin was affected; and three sets of female identical twins in whom only one twin had the exstrophy anomaly (Shapiro et al, 1985). Evidence by Reutter and colleagues has demonstrated six families with two occurrences of exstrophy-epispadias complex, one in which the proband was the product of a consanguineous union and four discordant twin pairs. Also, Boyadjiev and colleagues (2004a) found four multiplex families (2.7%) in a cohort of 151 families with the exstrophy-epispadias complex. There were three twin pairs, two of which were monozygotic, and concordance was

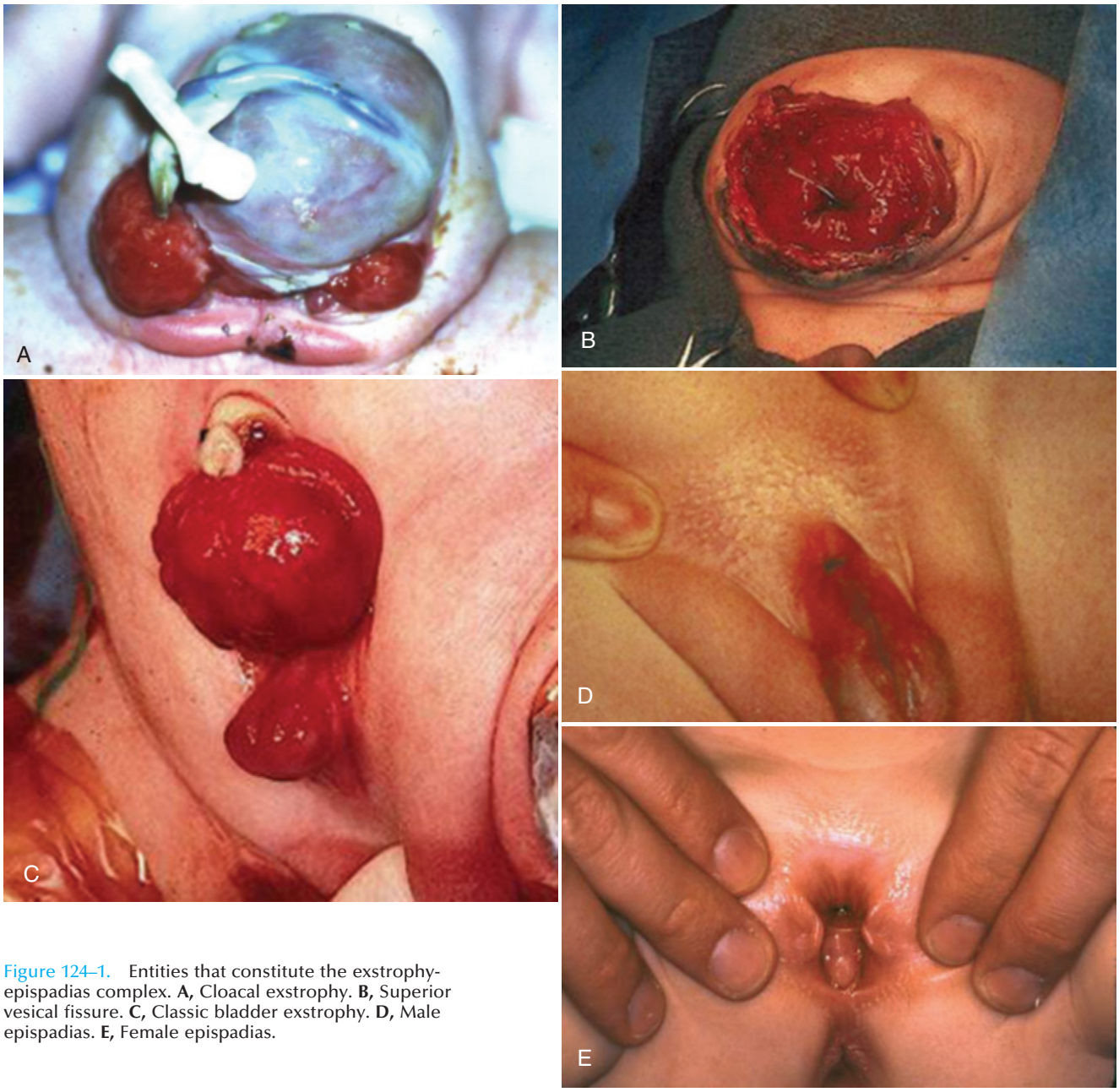


Figure 124–1. Entities that constitute the exstrophy-epispadias complex. **A,** Cloacal exstrophy. **B,** Superior vesical fissure. **C,** Classic bladder exstrophy. **D,** Male epispadias. **E,** Female epispadias.

present in only one of the twin pairs. Consanguinity was present in one family. Bladder exstrophy or epispadias was not reported until the 1980s in the offspring of parents with the exstrophy-epispadias complex. Shapiro and colleagues (1985) described two women with complete epispadias who gave birth to sons with bladder exstrophy. They also reported that another woman with bladder exstrophy gave birth to a son with bladder exstrophy. The inheritance of these three cases of bladder exstrophy was identified in a total of 225 offspring (75 boys and 150 girls) produced by individuals with bladder exstrophy and epispadias. **Shapiro and colleagues** (1985) **determined that the risk of bladder exstrophy in the offspring of individuals with bladder exstrophy and epispadias is 1 in 70 live births, a 500-fold greater incidence than in the general population.** Boyadjiev and colleagues (2004a) studied sibling data from 200 families and found 259 unaffected children in addition to the probands with exstrophy. Twenty-six probands had first-, second-, or third-degree relatives with congenital anomalies unrelated to the exstrophy-epispadias complex, most of which were midline defects and oral clefts. Four probands had a total of seven biologic children that were unaffected. In a multinational review of exstrophy patients (Lancaster, 1987), two interesting trends were found: (1) Bladder exstrophy tends to occur in infants of younger mothers, and (2) an increased risk at higher parity is observed for bladder exstrophy but not for epispadias. Boyadjiev's (2004a) data, however, differ from these trends, indicating that the average maternal age was 34 years and the average paternal age was 32 years. In addition, 49% of probands were born from first pregnancies. This change may represent societal changes, indicating advancing maternal age for first pregnancies and

increasing utilization of assisted reproductive techniques in first pregnancies.

Exploration of possible etiologies for the exstrophy-epispadias complex continues. A report from Israel indicated a 10-fold increase in exstrophy births to mothers who had received large doses of progesterone in the early part of the first trimester. Wood and colleagues (2003) reported on a sizable series of children with exstrophy conceived using assisted reproductive techniques. A 7.5-fold increase in incidence was noted when in vitro fertilization was used. These two reports indicate a role for hormonal changes in the etiology of the exstrophy-epispadias complex. In a large series of 214 females, no association of parental age, maternal reproductive history, or periconceptual material exposure to alcohol, drugs, radiation, or infections was found (Gambhir et al, 2008). However, periconceptual maternal exposure to smoking was significantly more common in patients with cloacal exstrophy than in the combined group of patients with classic exstrophy/epispadias. Periconceptual use of folic acid offered no protection to this anomaly (Gambhir et al, 2008).

Genetic studies to identify a genetic locus for the exstrophy-epispadias complex are under way. Boyadjiev and colleagues (2004b) have reported finding a breakpoint disruption in the 5′ region of the *CASPR3* gene on chromosome 9. This observation is the first to suggest a possible genetic basis for development of the exstrophy-epispadias complex. In another recent study by Ludwig and colleagues (2009), risk loci for the exstrophy spectrum were found in seven separate chromosomes with susceptibility genes in several regions.

Embryology

Bladder exstrophy, cloacal exstrophy, and epispadias are variants of the exstrophy-epispadias complex (see Fig. 124–1). The cause of this complex is thought to be the failure of the cloacal membrane to be reinforced by ingrowth of mesoderm (Muecke, 1964). The cloacal membrane is a bilaminar layer situated at the caudal end of the germinal disk that occupies the infraumbilical abdominal wall. Mesenchymal ingrowth between the ectodermal and endodermal layers of the cloacal membrane results in formation of the lower abdominal muscles and the pelvic bones. The cloacal membrane is subject to premature rupture, and, depending on the extent of the infraumbilical defect and the stage of development during which the rupture occurs, bladder exstrophy, cloacal exstrophy, or epispadias results (Ambrose and O'Brien, 1974).

After mesenchymal ingrowth occurs, the urorectal septum grows in a caudal direction and divides the cloaca into a bladder anteriorly and a rectum posteriorly (Fig. 124–2). Distally, the septum meets the posterior remnant of the bilaminar membrane, which eventually perforates and forms the urogenital and anal openings. The paired genital tubercles migrate medially and fuse in the midline, cephalad to the dorsal membrane before perforation.

The theory of embryonic maldevelopment in exstrophy held by Marshall and Muecke (1968) is that the basic defect is an abnormal overdevelopment of the cloacal membrane, which prevents medial migration of the mesenchymal tissue and proper lower abdominal wall development. The timing of the rupture of this defective cloacal

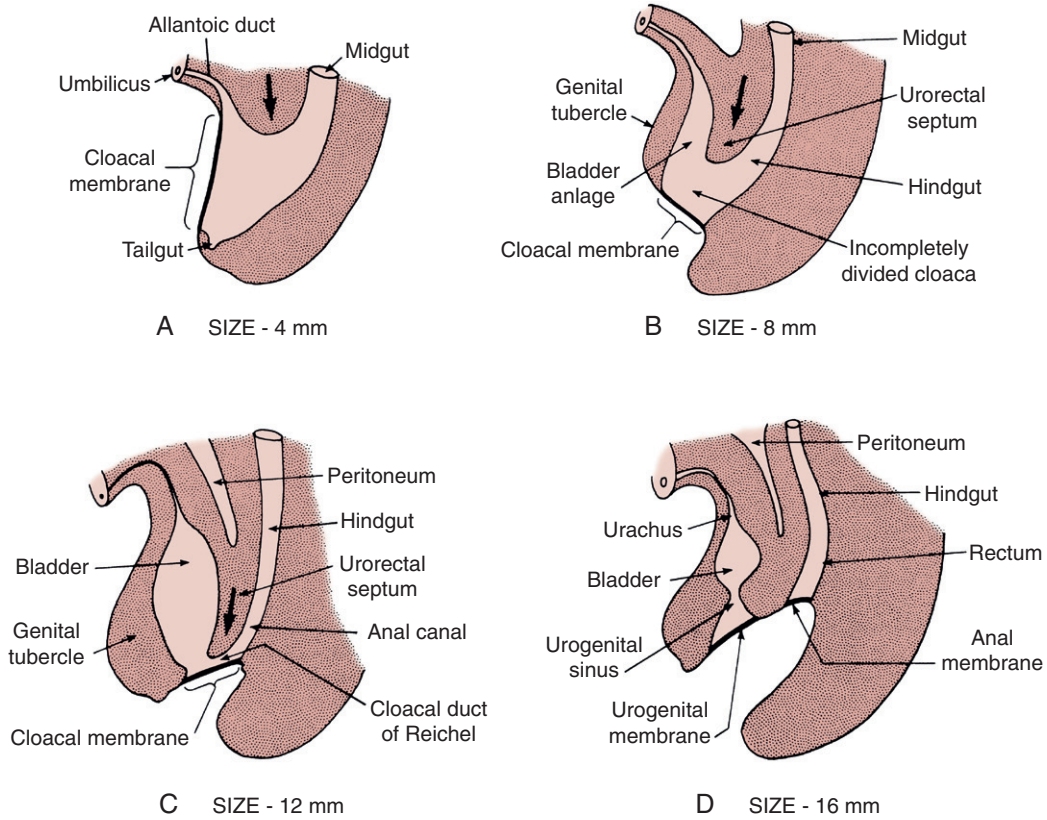


Figure 124–2. Development of the cloaca and cloacal membrane in the 4- to 16-mm embryonic stages. Caudal growth of the urorectal septum leads to separation of the anterior urogenital sinus from the posterior rectum.

membrane determines the variant of the exstrophy-epispadias complex that results. This theory is supported by Muecke's work in the chick embryo and by the high incidence of expected central perforations, resulting in the preponderance of classic exstrophy variants. Classic exstrophy accounts for more than 50% of the patients born with this complex (Muecke, 1964; Marshall and Muecke, 1968). Martinez-Frias and colleagues (2001) using epidemiologic factors of low birth weight, twinning, single umbilical artery, and associated defects postulated that cloacal exstrophy and exstrophy of the bladder are two different expressions of a primary developmental field defect with cloacal exstrophy being an early defect. New theories have been offered regarding the origins of these ventral body wall defects. It has been postulated that failure of one or both of the lateral body wall folds to move far enough ventrally to meet its counterpart in the midline (Sadler and Feldkamp, 2008). The associate defect results in one or more of the internal organs protruding through the defective region. Thus if closure fails in the abdominal and pelvic region, cloacal exstrophy results. If in the pelvis alone, only classic exstrophy occurs.

Other plausible theories concerning the cause of the exstrophy-epispadias complex exist. Abnormal development of the genital hillocks caudal to the normal position, with fusion in the midline below rather than above the cloacal membrane, has been embraced by other investigators (Patton and Barry, 1952; Ambrose and O'Brien, 1974). Another interesting hypothesis that remains controversial describes an abnormal caudal insertion of the body stalk, which results in a failure of interposition of the mesenchymal tissue in the midline (Mildenberger et al, 1988). As a consequence of this failure, translocation of the cloaca into the depths of the abdominal cavity does not occur. A cloacal membrane that remains in a superficial infraumbilical position represents an unstable embryonic state with a strong tendency to disintegrate (Johnston and Kogan, 1974). The lack of ability of the Meucke hypothesis to explain the absence of the ileocecal region of the digestive system and the superior mesenteric blood supply of the exstrophied intestinal region has led to a suggestion that there may be involvement of the allantois in the development of cloacal exstrophy (Zarabi and Rupani, 1985). Absence of migration, ascent, or alignment of the allantois with the yolk sac with its persistence at the dome of the cloaca can be used to explain the bowel abnormalities noted in cloacal exstrophy. Maldevelopment of the bony pelvis rather than soft tissue defects has been suggested to be the inciting issue for the development of exstrophy. Beaudoin and colleagues (1997) have suggested that lack of "rotation" of the pelvic ring primordium prevents structures attached to the pelvic ring from joining in the midline, allowing herniation of the bladder to occur. The cause of this inadequate rotation remains elusive. Stec and colleagues (2003) were able to demonstrate that the anatomic microstructure of the pelvic ring in exstrophy was similar to that in age-matched control subjects.

CLASSIC BLADDER EXSTROPHY

Anatomic Considerations

Exstrophy of the bladder is part of a spectrum of anomalies involving the urinary tract, the genital tract, the musculoskeletal system, and sometimes the intestinal tract. In classic bladder exstrophy, most anomalies are related to defects of the abdominal wall, bladder, genitalia, pelvic bones, rectum, and anus. Because of the involved nature of this defect, the deficits are described here as they affect each system.

Skeletal Defects

Formerly, classic bladder exstrophy was thought only to show the characteristic widening of the pubic symphysis caused by malrotation of the innominate bones in relation to the sagittal plane of the body along both sacroiliac joints. In addition, there was an outward rotation or eversion of the pubic rami at their junction with the iliac bones. More recently, Sponseller and colleagues (1995), using computed tomography (CT) of the pelvis with three-dimensional (3D) reconstruction, have further characterized the bone defect associated with both classic bladder exstrophy and cloacal exstrophy. **In reviewing a large group of patients with exstrophy of the bladder, using pelvic CT scans and age-matched controls, Sponseller and colleagues (1995) found that patients with classic bladder exstrophy have a mean external rotation of the posterior aspect of the pelvis of 12 degrees on each side, retroversion of the acetabulum, and a mean 18 degrees of external rotation of the anterior pelvis, along with 30% shortening of the pubic rami, in addition to the previously described diastasis of the symphysis pubis** (Fig. 124–3). In long-term follow-up there was a foot progression angle of 20 to 30 degrees of external rotation beyond the normal limits seen in early childhood, but this rotation improved with age. Likewise, patients with cloacal exstrophy not only had pelvic deformities to a greater degree but also had asymmetry of the preceding parameters between the right and left sides of the pelvis, malformation of the sacroiliac joints, and occasional dislocations of the hip (Sponseller et al, 1995).

Data from Stec and colleagues (2001a) using 3D models from CT scans have provided further insight into the bone defect of children born with classic bladder exstrophy. Using age-matched controls, they found that the sacroiliac joint angle (before closure) was 10 degrees larger in the exstrophy pelvis, being 10 degrees more toward the coronal plane than the sagittal (Fig. 124–4). Also, the bony pelvis in exstrophy has 14.7 degrees more inferior rotation than in healthy patients. Lastly, the sacrum in exstrophy patients has a 42.6% larger volume and 23.5% more surface area than in controls. These new findings will help with planning better osteotomies and better reduction of both the pubic diastasis and pubic long-term undergrowth in these patients.

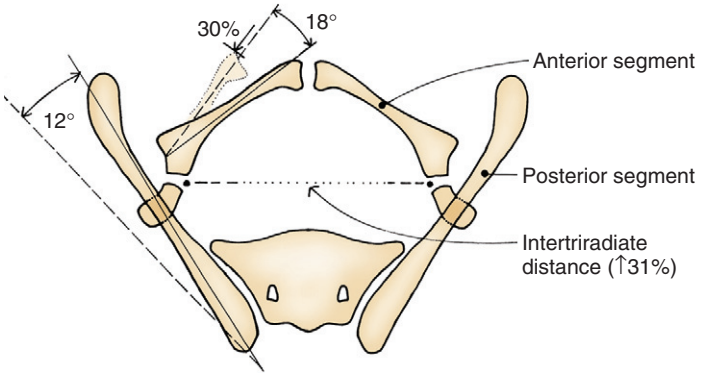


Figure 124–3. Pelvic bone abnormalities noted in classic bladder exstrophy. The posterior bone segment is externally rotated (12 degrees mean on each side), but the length is unchanged. The anterior segment is externally rotated (18 degrees mean on each side) and shortened by 30%. The distance between the triradiate cartilage is increased by 31%.

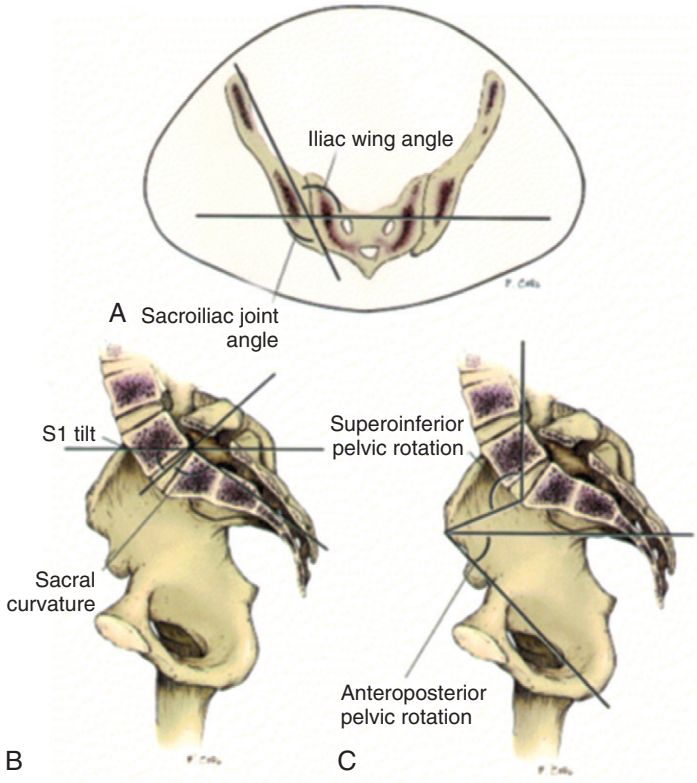


Figure 124–4. **A** to **C,** Sacroiliac joint angles before closure in children with classic exstrophy 10 degrees larger than normal controls. The bony pelvic has 14.7 degrees inferior rotation compared with normal controls. (From Stec AA, Pannu HK, Tadros YE, et al. Evaluation of the bony pelvis in classic bladder exstrophy using 3D CT—further insights. Urology 2001;58:1030.)

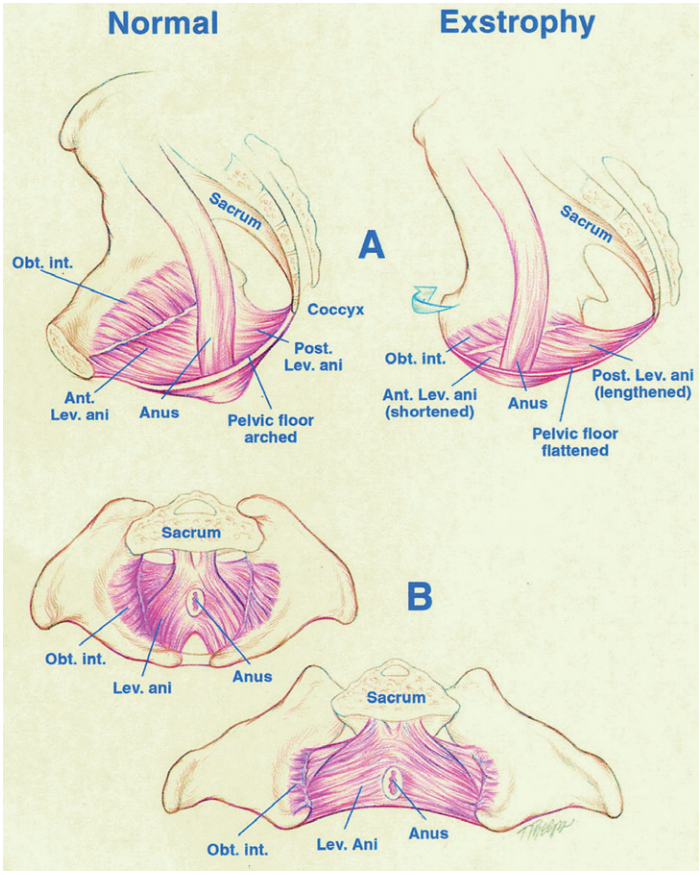


Figure 124–5. Pelvic floor changes in the patient with exstrophy; levator ani group is positioned more posteriorly (68% located posterior to the rectum) compared with normal controls.

These rotational deformities of the pelvic skeletal structures contribute to the short, pendular penis seen in bladder exstrophy. Outward rotation and lateral displacement of the innominate bones also account for the increased distance among the hips, waddling gait, and outward rotation of the lower limbs in these children, which in itself causes little disability and usually corrects to some degree over time. Data from Sponseller and colleagues (2001) show an increased incidence of premature osteoarthritis of the hip in adult patients who were closed without an osteotomy. Although these findings do not affect function, periodic radiologic evaluation of the pelvis and lumbosacrum should be performed in adult life. The 30% shortage of bone in exstrophy pelvis has largely gone unexplained. Data by Stec and colleagues (2003) using sections from the bony pelvis in fetal exstrophy and normal aborted fetuses found that the ultrastructure, bone development, microscopic growth patterns, and endochondrial ossification were absolutely the same. Thus restoration of the physiologic shape of the pelvis would likely lead to more normal gross bone growth, decreases in shortage of bone, and a more appropriate distribution of the mechanical and development forces on a more closed normally functioning pelvic ring.

Spinal abnormalities have frequently been noted in children with cloacal exstrophy, but incidence in bladder exstrophy has not been studied. A study of 299 children with bladder exstrophy indicated spinal variations without clinical significance (spina bifida occulta, lumbarization or sacralization of vertebrae) in 11%, uncomplicated scoliosis in 2.7%, and spinal dysraphism in 4% including myelomeningocele, lipomeningocele, scimitar sacrum, and hemivertebrae, but only one patient demonstrated any evidence of neurologic dysfunction (Cadeddu et al, 1997). Thus although present in classic bladder exstrophy, symptomatic spinal anomalies appear rare.

Pelvic Floor Defects

Stec and colleagues (2001b), using 3D models created from CT scans of children with classic bladder exstrophy and normal age-matched controls, found that the puborectal slings were supporting two times more body cavity area than normal. The levator ani group is positioned more posteriorly in exstrophy patients, with 68% located posterior to the rectum and 32% anterior (vs. 52% posterior and 48% anterior in healthy controls) (Fig. 124–5). The levators are also rotated outward 15.5 degrees, and in the coronal aspect the levators are 31.7 degrees more flattened than normal. This deviation from normal makes the exstrophy puborectal sling more flattened than its normal conical shape. There was no significant difference in the length or thickness of these muscles between patients with exstrophy and normal controls.

These new insights further elucidate the entire exstrophy defect, especially in regard to pelvic reconstruction. Interest in development of continence after primary closure in some patients has led to further investigation of the pelvic floor anatomy. Differences in orientation and anatomy of the pelvic floor musculature may directly affect development of continence following closure alone. The successful application of 3D magnetic resonance imaging (MRI) in anorectal anomalies has led to its use for the anatomic definition of the pelvic floor musculature in exstrophy. A

comparison of 3D MRI in children with exstrophy before closure and in normal controls indicated that the levator ani group was less dome shaped and more irregular in those with exstrophy (Williams et al, 2004). Also, there was no relationship between the amount of pubic diastasis and the extent of disproportionate curvature of the levator ani group. In addition, Halachmi and colleagues (2003) reported on the postoperative appearance of the pelvic floor with 3D MRI. In two patients who had some degree of continence, the intrasymphyseal distance was noted to be shortest, the angle of the levator ani divergence sharpest, and the bladder neck most deeply positioned in the pelvis. Gargollo and colleagues (2005), reporting on a series of patients who had MRI before and after exstrophy closure, noted that the puborectalis angle in those with dry intervals was decreased compared with that before closure. These two studies correlate well with earlier findings of Gearhart and colleagues (1993c) showing that in the adult patients who were dry, the puborectalis angle was less than 65 degrees. These data reinforce the necessity for aggressive dissection and posterior placement of the posterior urethra and bladder and the role for osteotomy and pelvic fixation.

Abdominal Wall Defects

The triangular defect caused by the premature rupture of the abnormal cloacal membrane is occupied by the exstrophy bladder and posterior urethra. The fascial defect is limited inferiorly by the intrasymphyseal band, which represents the divergent urogenital diaphragm. This band connects the bladder neck and posterior urethra to the pubic ramus on anatomic study. The anterior sheath of the rectus muscle has a fanlike extension behind the urethra and bladder neck that inserts into the intrasymphyseal band. Investigations into the relationship of the rectus muscle and fascia to the urogenital diaphragm (Wakim and Barbet, 2002) have found no gross or histologic evidence of the presence of the striated sphincter. However, clear evidence of bladder musculature extending laterally to the pubis was found where it interdigitates with fibers from the rectus fascia forming the fibrous urogenital diaphragm (Wakim and Barbet, 2002). Gearhart and colleagues (1991) have shown the importance of radical incision of these fibers lateral to the urethral plate down to the level of the inferior pubic ramus and levator hiatus for the bladder and posterior urethra to be placed in a deep pelvic position. Data from failed exstrophy closures show these fibers to be intact in many patients at the time of reclosure.

At the upper end of the triangular fascial defect is the umbilicus. In bladder exstrophy, the distance between the umbilicus and the anus is always foreshortened. Because the umbilicus is situated well below the horizontal line of the iliac crest, there is an unusual expanse of uninterrupted abdominal skin. Although an umbilical hernia is usually present, it is usually of insignificant size. The umbilical hernia is repaired at the time of the initial exstrophy closure. Omphaloceles, although rarely seen in conjunction with bladder exstrophy, are frequently associated with cloacal exstrophy. Omphaloceles associated with classic bladder exstrophy-epispadias complex are usually small and can be closed at the time of bladder closure.

The frequent occurrence of indirect inguinal hernias is attributed to a persistent processus vaginalis, large internal and external inguinal rings, and lack of obliquity of the inguinal canal. Connolly and colleagues (1995), **in a review of 181 children with bladder exstrophy, reported inguinal hernias in 81.8% of boys and 10.5% of girls.** At the time of closure of the bladder exstrophy, these hernias should be repaired by excision of the hernial sac and repair of the transversalis fascia and muscle defect to prevent recurrence or a direct inguinal hernia. The contralateral side should also be explored because the incidence of synchronous or asynchronous bilaterality is high.

Anorectal Defects

The perineum is short and broad, and the anus is situated directly behind the urogenital diaphragm; it is displaced anteriorly and corresponds to the posterior limit of the triangular fascial defect. The anal sphincter mechanism is also anteriorly displaced and should be preserved intact in case internal urinary diversion is required in future management.

The divergent levator ani and puborectalis muscles and the distorted anatomy of the external sphincter contribute to varying degrees of anal incontinence and rectal prolapse. Anal continence is usually imperfect at an early age. In rare patients, the rectal sphincter mechanism may never be adequate to control the liquid content of the bowel. Rectal prolapse frequently occurs in untreated exstrophy patients with a widely separated symphysis. It is usually transient and easily reduced. Prolapse virtually disappears after bladder closure or cystectomy and urinary diversion. The appearance of prolapse in an infant is an indication to proceed with definitive management of the exstrophied bladder. **If rectal prolapse occurs at any time after exstrophy closure, posterior urethral/bladder outlet obstruction should be suspected and immediate evaluation of the outlet tract by cystoscopy should be performed** (Baker and Gearhart, 1998).

Male Genital Defect

The male genital defect is severe and is probably the most troublesome aspect of the surgical reconstruction, independent of the decision whether to treat with modern staged closure, combined closure, or a form of urinary diversion (Fig. 124–6). Formerly, it was thought that the individual corpora cavernosa were of normal caliber but appeared shorter because of the wide separation of the crural attachments, the prominent dorsal chordee, and the shortened urethral groove. **However, Silver and colleagues** (1997b) **described the genital defect for the first time in bladder exstrophy in greater detail. MRI was used in adult men with bladder exstrophy and compared with results for age- and race-matched controls. They found that the anterior corporal length of male patients with bladder exstrophy was almost 50% shorter than that of normal controls** (Fig. 124–7). However, although the posterior length of the corporal body was the same as in age-matched controls, the diameter of the posterior corporal segment was greater than in normal controls. It was also found on MRI that the diastasis of the symphysis pubis increased the intrasymphyseal and intercorporal distances, but the angle between the corpora cavernosa was unchanged because the corporal bodies were separated in a parallel fashion. Therefore the penis appears short not only because of the diastasis of the pubic symphysis, as thought in the past, but also because of marked congenital deficiency of anterior corporal tissue (Silver et al, 1997b). In a recent surgical anatomic study by Perovic and Djinovic (2007), precise description of the penile defect included (1) corporal bodies separated and triangular in shape; (2) a long convex ventral surface and a short wedge-shaped dorsal surface; and (3) neurovascular bundle length determined by its lie on the individual corporal bodies.

A functional and cosmetically pleasing penis can be achieved when the dorsal chordee is released, the urethral groove lengthened, and the penis somewhat lengthened by mobilizing the crura in the midline.



Figure 124–6. Newborn male with classic bladder exstrophy. Note the dorsal chordee, short urethral plate, and flattening of the scrotum.

In a study by Gearhart and colleagues (1993c), 13 adult men born with bladder exstrophy were evaluated with MRI of the pelvis to evaluate the size and configuration of the prostate and sex accessory organs. The volume, weight, and maximum cross-sectional area of the prostate appeared normal compared with published control values (Fig. 124–8). However, in none of the patients did the prostate extend circumferentially around the urethra, and the urethra was anterior to the prostate in all patients. Except for studies to document the presence of the prostate gland or its size, data do not exist concerning the function of the prostate gland in the patient with exstrophy. Silver and colleagues (1997a) reported free and total prostate-specific antigen levels for a group of adult men with bladder exstrophy. Although they were measurable, they were below the upper limits of established age-specific reference ranges for normal men. The vas deferens and ejaculatory ducts are normal in the exstrophy patient, provided they are not injured iatrogenically. Also, the mean seminal vesicle length in men with exstrophy was normal compared with published controls. Additional evaluation of the puborectalis muscle group was undertaken, and these muscles were found to be widely separated and provided lateral support of the prostate with a narrower puborectalis angle in those who were continent and had undergone prior iliac osteotomy.

Autonomic innervation of the corpus cavernosum is provided by the cavernous nerves. These autonomic nerves are displaced laterally in patients with exstrophy (Schlegel and Gearhart, 1989). These nerves are preserved in almost all exstrophy patients because potency is preserved after surgery. However, retrograde ejaculation may occur after bladder closure and later bladder neck reconstruction.

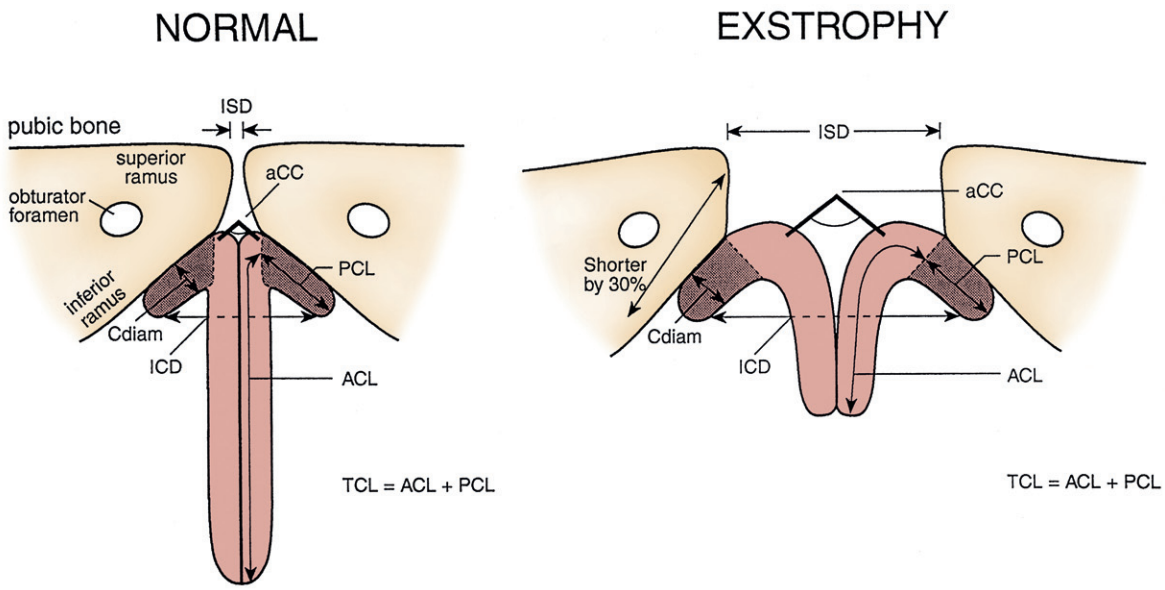


Figure 124–7. Separation of the pubic bones in men with classic exstrophy combined with the congenital deficiency of the anterior corporal tissue leads to the shorter appearance of the penis. aCC, corpora cavernosa sustended angle; ACL, anterior corporal length; Cdiam, corpus cavernosum diameter; ICD, intercorporal distance; ISD, intersymphyseal distance; PCL, posterior corporal length; TCL, total corporal length.

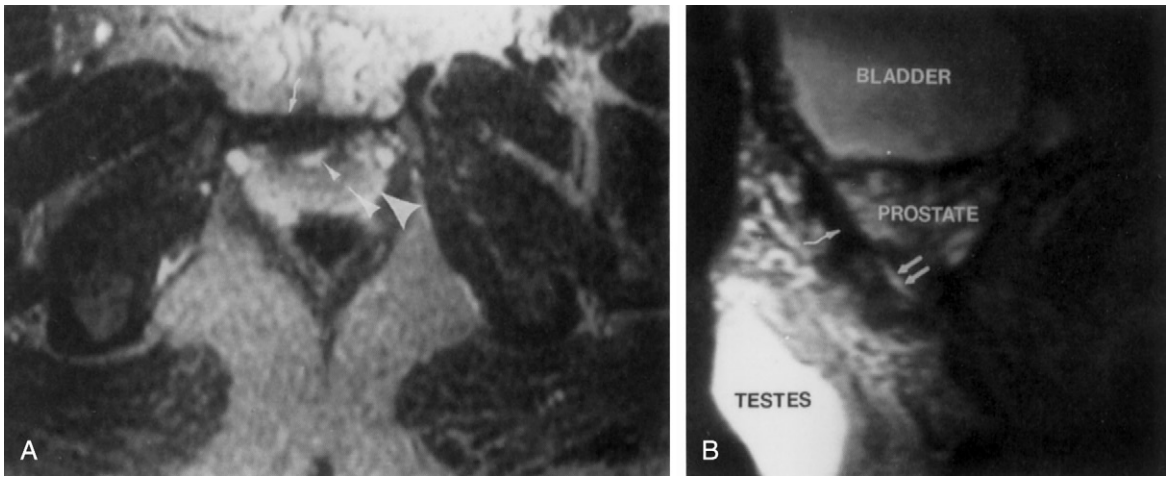


Figure 124–8. **A,** Axial T2-weighted image of the midprostate in a 20-year-old continent patient with bladder exstrophy. *Small arrowhead,* lumen of the urethra; *medium arrowhead,* transitional zone; *large arrowhead,* peripheral zone. *Curved arrow,* fibrous band of the intersymphyseal bar. **B,** Sagittal T2-weighted image through the midprostate gland shows anterior urethra *(double arrows)* and posterior prostate gland. Intersymphyseal fibrous band *(curved arrow)* extends along the entire length of the prostate.

Testis function has not been studied in a large group of postpubertal exstrophy patients, but it is generally believed that fertility is not impaired by testicular dysfunction. The testes frequently appear undescended in their course from the widened separated pubic tubercles to the flat, wide scrotum. Most testes are retractile and have an adequate length of spermatic cord to reach the scrotum without the need for orchiopexy.

Female Genital Defects

Reconstruction of the female genitalia presents a less complex problem than in the male (Fig. 124–9). **The vagina is shorter than normal, hardly greater than 6 cm in depth, but of normal caliber. The vaginal orifice is frequently stenotic and displaced anteriorly, the clitoris is bifid, and the labia, mons pubis, and clitoris are divergent. The uterus enters the vagina superiorly so that the cervix is in the anterior vaginal wall. The fallopian tubes and ovaries are normal.** The clitoral halves should be joined, and the two ends of the labia minora joined to make a fourchette at the time of primary closure. Vaginal dilatation or episiotomy may be required to allow satisfactory intercourse in the mature female. The defective pelvic floor may predispose mature females to the development of uterine prolapse, making uterine suspension necessary. This usually occurs after childbirth but can occur even in the nulliparous patient. When studied in a large adult female population, 10 of 56 women developed uterine prolapse at a mean age of 16 years. Six patients had been managed with reconstruction that included a posterior iliac osteotomy (Mathews et al, 2003). Mean age at the time of osteotomy was 2.1 years. The use of the modern combined anterior innominate and vertical iliac osteotomy early in life may lead to reduction in the incidence of later prolapse.

Urinary Defects

At birth, the bladder mucosa may appear normal; however, ectopic bowel mucosa, an isolated bowel loop, or more commonly a hamartomatous polyp may be present on the bladder surface. If the bladder mucosa is not frequently irrigated with saline and protected from surface trauma by the interposition of some form of protective membrane before closure, cystic or metaplastic changes in the mucosal surface of the bladder may occur.



Figure 124–9. Newborn girl with classic bladder exstrophy. Notice the open urethral plate, bifid clitoral halves, and anterior displacement of the vaginal orifice.

The size, distensibility, and neuromuscular function of the exstrophied bladder, as well as the size of the triangular fascial defect to which the bladder muscles attach, affect the decision to attempt repair. In the past several years, multiple basic science studies that further delineate the exact nature of the exstrophied bladder in the newborn have been published. **One of the first papers to characterize the neuromuscular function of the bladder was published by** Shapiro and colleagues (1985). **In their work, muscarinic cholinergic receptor density and binding affinity were measured in control subjects and in patients with classic bladder exstrophy. The density of the muscarinic cholinergic receptors in both the control and exstrophy groups was similar, as was the binding affinity of the muscarinic receptor.** Therefore it was thought by the authors that the neurophysiologic composition of the exstrophied bladder is not grossly altered during its anomalous development. Studies have investigated both the neural innervation of the newborn exstrophy bladder and its muscle and collagen content. Lee and colleagues (1996) looked at bladder biopsies obtained from 12 newborns with bladder exstrophy, compared with age-matched controls, and found an increase

in the ratio of collagen to smooth muscle in the newborns with bladder exstrophy. In addition, using anticollagen antibodies, they evaluated various types of collagen in these bladders. Compared with normal control bladders, there was no statistical difference in the amount of type I collagen in the bladders of newborns with exstrophy at initial closure, but there was a threefold increase in type III collagen. Peppas and colleagues (1999) studied patients who gained adequate bladder capacities and were awaiting bladder neck reconstruction and found that the ratio of collagen to smooth muscle decreased markedly after a successful closure and infection-free follow-up. Lais and colleagues (1996) reported similar findings, but they measured the ratio of smooth muscle to collagen and found it increased after a successful closure.

In an extension of the studies just cited, Mathews and colleagues (1999b) **looked at the number of myelinated nerves per field in the newborn bladders of normal subjects and those with exstrophy. The average number of myelinated nerves per field was reduced in the exstrophy bladders compared with controls, and the difference was statistically significant. This reduction in nerve fibers appears to be the result of a lack of small fibers with preservation of larger nerve fibers. In light of the findings already mentioned, it is believed that bladder exstrophy in a newborn probably represents an earlier stage in bladder development.**

In a large study by Rosch and colleagues (1997) **from Germany, multiple immunocytochemical and histochemical markers were examined in patients with epispadias or classic bladder exstrophy. These studies involved indirect immunocytochemistry for vasoactive intestinal polypeptide (VIP), neuropeptide Y (NPY), substance P (SP), calcitonin gene–related product (CGRP), protein gene product (PGP) 9.5, and nicotinamide adenine dinucleotide phosphate diaphorase (NADPHd). No evidence of bladder muscle dysinnervation was found morphologically in any cases of classic bladder exstrophy.** Cases of bladder exstrophy after failed reconstruction had muscle innervation deficiencies that increased subepithelial and intraepithelial innervation. Therefore although a newborn with bladder exstrophy may have a maturational delay in bladder development, these bladders have the potential for normal development after a successful initial closure.

When the bladder is small, fibrosed, inelastic, and covered with polyps, functional repair may be impossible (Fig. 124–10). Novak and colleagues (2005) investigated the pathology and malignant potential of the polyps found in these small bladders. Two types of polyps were observed, with some overlap in findings: fibrotic and edematous. Both were associated with overlying squamous metaplasia in approximately 50% of cases. Varying degrees of von Brunn nests, cystitis cystica, and cystitis glandularis were noted. Cystitis glandularis was noted in a higher percentage of secondary closures. Because of the potential risk of adenocarcinoma associated with cystitis glandularis, future surveillance of these patients with urine cytology and cystoscopy as they enter adulthood is recommended. The more normal bladder may be invaginated, or it may bulge through a small fascial defect, indicating the potential for satisfactory capacity after successful initial closure. **Also, not until examination under anesthesia can the true defect be adequately evaluated because bladders that appear small in the nursery may have a good bit of bladder sequestered below the fascial defect. The depth of this extension often cannot be appreciated unless the infant is totally relaxed under anesthesia.**



Figure 124–10. Small inelastic bladder template covered with polyps, unsuitable for primary closure.

Bladder function was assessed in a group of continent exstrophy patients with normal reflexive bladders. Normal cystometrograms were obtained in 70% to 90% of cases (Toguri et al, 1987). Diamond and colleagues (1999), looking at 30 patients with bladder exstrophy at various stages of reconstruction, found that 80% of patients had compliant and stable bladders before bladder neck reconstruction. After bladder neck reconstruction, approximately half of the patients maintained normal bladder compliance and a lesser number maintained normal stability. The authors believed that compliance and stability were impaired after bladder neck reconstruction and that 25% of patients with exstrophy may maintain normal detrusor function after reconstruction. In an earlier paper by Hollowell and colleagues (1993), 13 of 21 children revealed involuntary contractions and only 4 revealed stable bladders before bladder neck reconstruction. Also, 7 of 21 had increased pressures (>10 cm H_2O), suggesting decreased compliance. The difference in findings between these two urodynamic studies is difficult to explain from an experimental perspective. However, standardized methods of bladder neck repair do not exist, and these differences may be reflected in the different urodynamic findings after bladder neck repair in these two groups of patients.

Several interesting aspects of the microstructure of the bladder in children with bladder exstrophy were noted by Mathews and colleagues (2004) using specimens obtained from children with bladder exstrophy at various stages of reconstruction (newborn bladder closure, bladder neck reconstruction, augmentation cystoplasty). At the cellular level, important differences were noted. Caveoli, which are important intracellular structures involved in cell-cell signaling, were found to be normal in the patients with a successful closure and improvement in bladder capacity and significantly lacking in the patients who required eventual augmentation cystoplasty (Fig. 124–11). In addition, the ultrastructure of cells in the patients in whom closure failed was noted to be abnormal.

The urinary tract is usually normal, but anomalous development does occur. Horseshoe kidney, pelvic kidney, hypoplastic

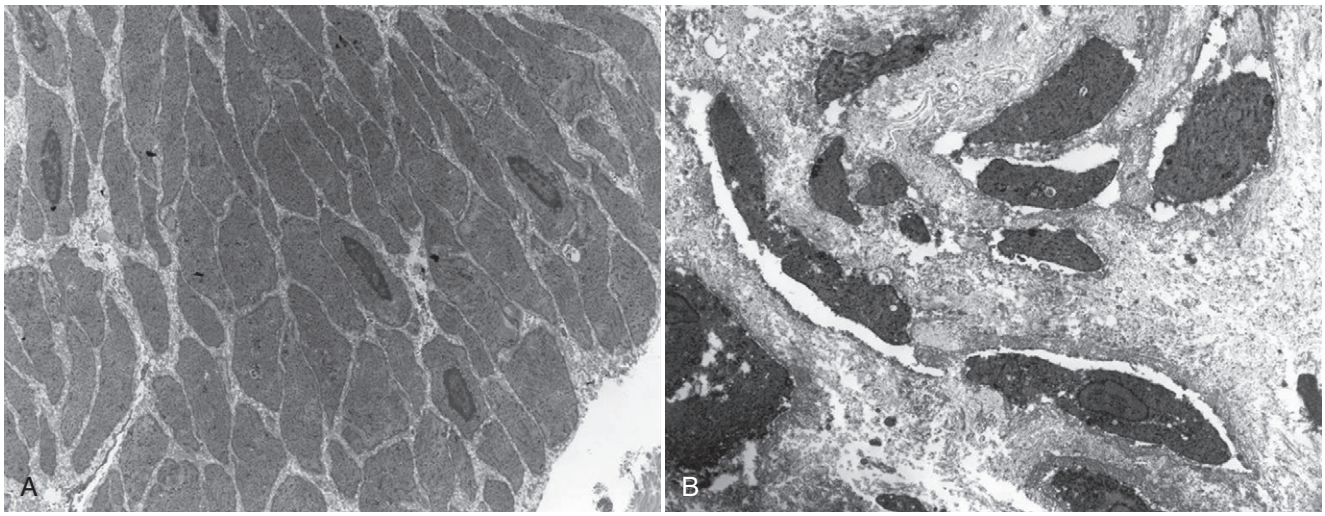


Figure 124–11. Ultrastructural changes noted in the exstrophic bladder. **A,** Normal muscle and nerve profiles in the newborn bladder. **B,** Following failure of prior closure, significant deterioration is noted with increased intercellular collagen and degenerating muscle and few nerve profiles. (From Matthews RI, Wills M, Perlman E, et al. Neural innervation of the newborn exstrophy bladder: an immunohistological study. J Urol 1999;162:506.)

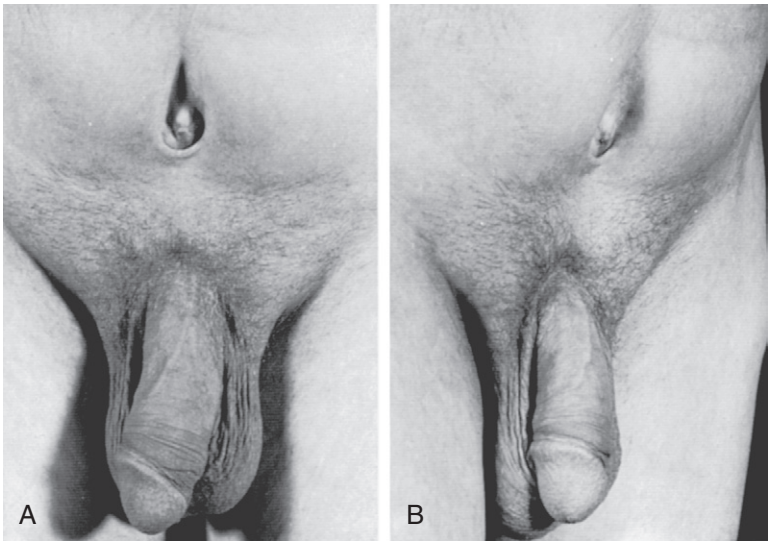


Figure 124–12. **A** and **B,** Pseudoexstrophy in an adult male patient. Musculoskeletal deformity characteristic of the exstrophy complex is present, but the urinary tract is intact.

kidney, solitary kidney, and dysplasia with megaureter are all encountered in these patients. The ureters have an abnormal course in their termination. The peritoneal pouch of Douglas between the bladder and the rectum is enlarged and unusually deep, forcing the ureter down laterally in its course across the true pelvis. The distal segment of the ureter approaches the bladder from a point inferior and lateral to the orifice, and it enters the bladder with little or no obliquity. **Therefore reflux in the closed exstrophy bladder occurs in 100% of cases, and subsequent surgery is usually required at the time of bladder neck reconstruction. If excessive outlet resistance is gained at the time of either initial closure or combined epispadias and bladder exstrophy closure and recurrent infections are a problem even with suppressive antibiotics, ureteral reimplantation or Deflux injection is required before bladder neck reconstruction.**

Exstrophy Complex and Variants

Exstrophy complex includes a spectrum of anomalies ranging from epispadias to cloacal exstrophy. Many variations in anatomy and types of defects have been noted. Because there is probably a common embryologic origin for all of these defects, they all share many or some of the defects noted in the three major components of the complex—skeletal, urinary, and genital. The presence of a characteristic musculoskeletal defect of the exstrophy anomaly with no major defect in the urinary tract has been named "pseudoexstrophy" (Marshall and Muecke, 1968). Predominant characteristics include an elongated, low-set umbilicus and divergent rectus muscles that attach to the separated pubic bones (Fig. 124–12). In this variant, the mesodermal migration has been interrupted in its superior aspect only, thus wedging apart the musculoskeletal elements of the lower abdominal wall without obstructing the formation of the genital tubercle.

In the superior vesical fissure variant of the exstrophy complex, the musculature and skeletal defects are exactly the same as those in classic exstrophy; however, the persistent cloacal membrane ruptures only at the uppermost portion, and a superior vesical fistula that actually resembles a vesicostomy results. Bladder extrusion

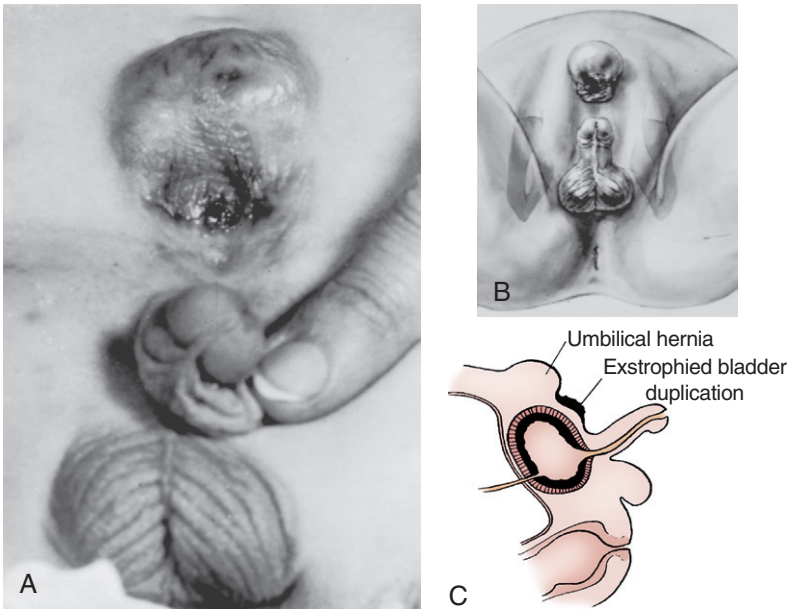


Figure 124–13. **A** to **C,** Duplicate exstrophy in a boy with an intact lower urinary tract.

is minimal and is present only over the normal umbilicus (see Fig. 124–1B).

In a large review of an exstrophy database of more than 815 patients, Lowentritt and colleagues (2005) reported 25 exstrophy complex variants, 6 of which were cloacal exstrophy variants. Continence rates after bladder neck repair were compatible with classic exstrophy (Fig. 124–13). Three cases were reported by Arap and Giron (1986) in which the patients had classic musculoskeletal defects, and two of the three were continent. Of the two male patients, one had an associated complete epispadias and the other had a completely normal penis. Therefore the external genital manifestations in duplicate exstrophy can be quite variable.

In addition to pseudoexstrophy, superior vesical fissure, and duplicated exstrophy, isolated occurrences of a fourth entity, "covered exstrophy," have been reported (Cerniglia et al, 1989). This has also been referred to as *split symphysis variant*. A common factor in these patients is the presence of musculoskeletal defect associated with classic exstrophy but no significant defect of the urinary tract. Chandra and colleagues (1999) reported a covered exstrophy with incomplete duplication of the bladder. However, in most cases of covered exstrophy (Narasimharao et al, 1985; Cerniglia et al, 1989), there has been an isolated ectopic bowel segment present on the inferior abdominal wall near the genital area, which can be either colon or ileum with no connection with the underlying gastrointestinal tract and only epispadias in the male. A patient seen at our institution had the standard appearance of most split symphysis variants, and one could actually see the bladder through a thin membrane of lower abdominal skin. Although all of the classic musculoskeletal defects of exstrophy were present, there was no isolated ectopic bowel segment present on the lower abdominal wall (Fig. 124–14). These patients should all undergo formal exstrophy closure at birth.

There are two different forms of duplication, anteroposterior duplication and side-by-side duplication. The first form is considered a duplicate exstrophy with a patch of everted bladder mucosa on the anterior abdominal wall with a second bladder lying in the pelvis. The ureters attach to the closed bladder, rendering the

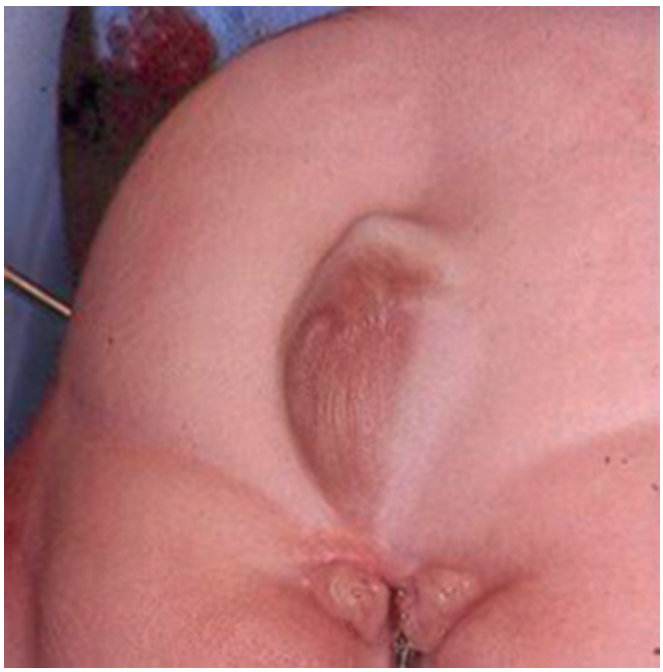


Figure 124–14. Skin-covered exstrophy in a female patient. Note urethral sound in the bladder and the subcutaneous position below the skin of the abdominal wall. No bowel is sequestered on the abdominal wall, as has been reported in some patients with this variant.

superficial mucosa dry (see Fig. 124–13). The mainstay of treatment has been resection of the ectopic mucosa and closure of the abdominal wall defect. The other form of duplication involves patients who have two separately formed bladder halves in a left-right orientation with a midline septum between the bladders containing muscle. Each bladder has its own ureter and an intact sphincter. Oftentimes there is diastasis of the pubis and rectus muscle.

Cloacal Exstrophy Variants—Covered Cloacal Exstrophy and Duplicate Bladder. Cloacal exstrophy usually includes an open and

everted intestinal segment situated between two hemibladders, an omphalocele and a blind ending tailgut with an imperforate anus. The pubic symphysis and the rectus muscles are widely separated. The phallus is bifid, and the scrotum or labia are split and laterally displaced. In girls the vagina is bifid with two uteri. Given that cloacal exstrophy encompasses abnormalities of the genitourinary, gastrointestinal, and musculoskeletal systems, and often the neurologic system, it is not surprising that a wide range of variants from the classic presentation have been reported. The treatment of cloacal exstrophy has evolved from palliation of an almost universally fatal disorder into complex genitourinary and gastrointestinal reconstruction and a near-normal life span.

Of six cases reported by Lowentritt and colleagues (2005) with cloacal variants, five were covered by skin and one involved duplication of the bowel and hemibladders. Cases of cloacal exstrophy are challenging in their surgical management, and the variations of the complex add to the difficulties of initial diagnosis and management. Only by using a combination of genitograms, retrograde ureterograms, and bowel continence studies was it possible to understand the complex anatomy of the patients in these groups. Interestingly, three patients had no spinal abnormalities and one had spina bifida occulta. Three patients in this group had innervation of the pelvic floor, enabling successful Pena procedures in two, with the third patient awaiting the procedure.

The epispadias-bladder/cloacal exstrophy complex has a wide range of presentations. Variants are rare, but it is important to recognize the different appearances at birth because the initial treatment will greatly influence the long-term outcome. Two patient groups had better outcomes than those with classic presentations—superior vesical fissure and skin-covered cloacal exstrophy. Because the sphincter is intact, patients with superior vesical fissure went through regular toilet training and became continent without the need for a later bladder neck procedure. Many reports of exstrophy variants include these patients, leading to the wrong belief that all patients with variants perform better than those with bladder exstrophy. Lowentritt (2005) suggests that other than superior vesical fissure, all variants should be managed with formal exstrophy closure at birth and followed in the same manner as their classic presentations. Duplicated organs can be useful in later reconstruction. Cloacal variants have a lower incidence of spinal abnormalities and a higher rate of fecal continence compared with their classic presentations. Overall, these patients had a low incidence of severe comorbid conditions. Therefore appropriate treatment of these genitourinary malformations can significantly impact and improve the quality of life.

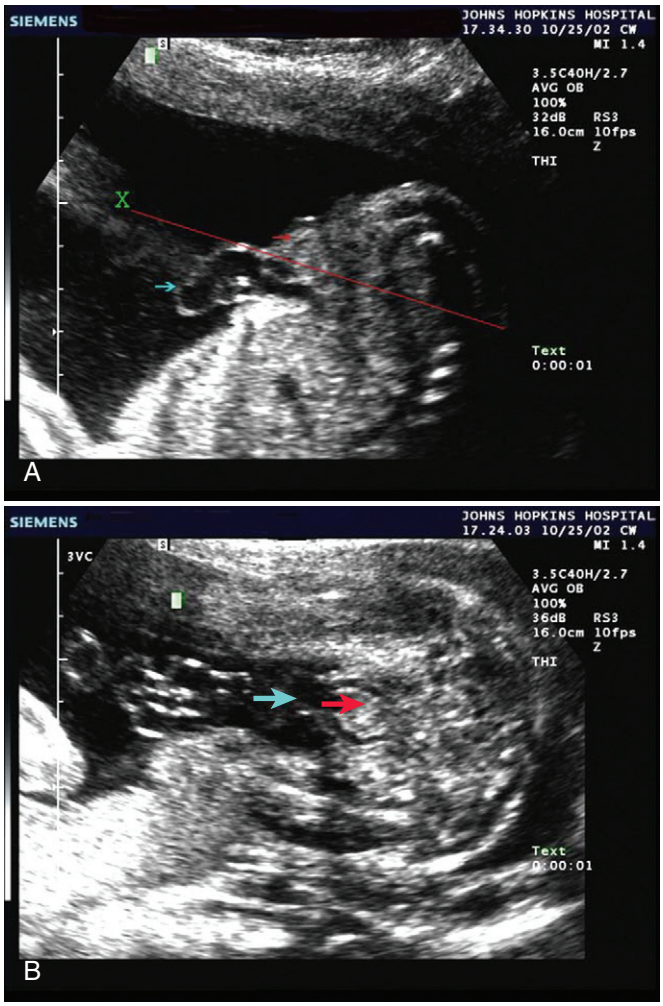


Figure 124–15. Prenatal ultrasound scan demonstrating bladder exstrophy. **A,** Longitudinal view showing the low-set umbilicus *(cyan arrow),* lack of intra-abdominal bladder, and lower abdominal mass *(red arrow).* **B,** Transverse view through the plane (X) in **A** shows presence of the umbilicus *(cyan arrow)* and the upper edge of the bladder plate that appears hyperechoic *(red arrow).*

Prenatal Diagnosis

Currently, the prenatal diagnosis of bladder exstrophy is difficult to delineate. Often, a diagnosis of omphalocele or gastroschisis is made and the exstrophy condition is overlooked. Ultrasound evaluation of the fetus, by means of high-resolution real-time units, allows a thorough survey of the fetal anatomy, even during routine obstetric ultrasound examinations (Gearhart et al, 1995a). Several groups have outlined important criteria for the diagnosis of classic bladder exstrophy prenatally. In these reviews, the absence of a normal fluid-filled bladder on repeated examinations suggested the diagnosis, as did a mass of echogenic tissue on the lower abdominal wall (Mirk et al, 1986; Verco et al, 1986). **In a review of 25 prenatal ultrasound examinations with the subsequent birth of a newborn with classic bladder exstrophy** (Gearhart et al, 1995a), several observations were made: (1) absence of bladder filling, (2) a low-set umbilicus, (3) widening pubis ramus, (4) diminutive genitalia, and (5) a lower abdominal mass that increases in size as the pregnancy progresses and as the intra-abdominal viscera increases in size (Fig. 124–15).

The application of 3D ultrasonography and fetal MRI has improved the antenatal diagnosis of bladder and cloacal exstrophy. In the authors' practice, fetal MRI is reserved for patients in whom 3D ultrasound is not sufficient to differentiate satisfactorily between classic and cloacal exstrophy or when other severe anomalies are suspected. The main reason for the prenatal diagnosis of bladder exstrophy is so that the parents can be counseled regarding the risks and benefits and other aspects of the condition. After appropriate counseling, arrangements can be made for delivery of the baby in a specialized exstrophy center where immediate reconstruction of the exstrophy can occur. Presentations from various centers have shown that the sooner the bladder is closed, the more likely it is that the bladder will grow and will not require augmentation. Delivery in a specialized exstrophy center allows the parents to be exposed to the expertise of multiple disciplines including the all-important psychologic support these young parents need when a child with a birth defect of this magnitude is delivered.

SURGICAL RECONSTRUCTION OF BLADDER EXSTROPHY

Sweetser and colleagues (1952) initially described a staged surgical approach for bladder exstrophy. Four to 6 days before bladder closure, bilateral iliac osteotomies were performed. Epispadias repair was performed as a separate procedure. The continence procedure was limited to freeing the fibers from the intrasymphyseal band and wrapping this band around the urethra at the time of closure to increase outlet resistance.

The initial staged approach to functional bladder closure included three separate stages: bladder, abdominal wall, and posterior urethral closure; bladder neck reconstruction and antireflux procedure; and later epispadias repair. This approach was recommended for most cases of exstrophy reconstruction beginning in the early 1970s (Cendron, 1971; Jeffs et al, 1972; Williams and Keaton, 1973; Gearhart and Jeffs, 1989b). **Although this procedure was successful, it has been significantly modified to include bladder, abdominal wall closure, and posterior urethral closure well onto the penis in the newborn period with bilateral innominate and vertical iliac osteotomy, if indicated; epispadias repair at 6 months to 1 year of age; and bladder neck reconstruction along with antireflux procedure at age 4 to 5 years, when the child has achieved an adequate bladder capacity for bladder neck reconstruction and is motivated to participate in a postoperative voiding program** (Gearhart and Jeffs, 1998).

Other methods of treatment of the newborn with bladder exstrophy have been offered. Grady and Mitchell (1999) proposed combining bladder exstrophy closure with epispadias repair in the newborn period. Baka-Jakubiak (2000) recommended newborn exstrophy closure alone and combined bladder neck reconstruction and epispadias repair when the child reaches a satisfactory age for participation in a voiding program. Kelly (1995) and colleagues have recommended a staged repair in which no osteotomy is used and supplanted by a second-stage "radical soft tissue mobilization" before later urethral repair. Schrott and colleagues (1984) recommended bladder closure, ureteral reimplantation, epispadias repair, and bladder neck reconstruction in the newborn period. Lastly, Stein and colleagues (1999) recommended ureterosigmoidostomy in the newborn period with abdominal wall and bladder closure. This chapter offers a comprehensive look at all of these repairs, their outcomes, and most importantly overall complications and those specific to the different types of repairs.

Evaluation and Management at Birth

At birth, although the bladder mucosa is usually smooth, pink, and intact, it is also sensitive and easily denuded. In the delivery room the umbilical cord should be tied with 2-0 silk close to the abdominal wall so that the umbilical clamp does not traumatize the delicate mucosa and cause excoriation of the bladder surface. The bladder can then be covered with a nonadherent film of plastic wrap (e.g., Saran Wrap) (Fig. 124–16) to prevent sticking of the bladder mucosa to clothing or diapers. In addition, each time the diaper is changed the plastic wrap should be removed, the bladder surface irrigated with sterile saline, and clean plastic wrap placed over the bladder surface area.

The distraught parents need reassurance at this stage. Counseling of the parents and decisions regarding eventual therapy should begin prenatally if the condition is diagnosed by prenatal ultrasonography. The parents should be educated by a surgeon with a special interest and experience in managing cases of bladder or cloacal exstrophy. An exstrophy support team should be available and should include a pediatric orthopedic surgeon, pediatric anesthesiologist, social workers, nurses with special interest in bladder exstrophy, and a child psychiatrist with expertise and experience in genital anomalies. The Association of Bladder Exstrophy Children, based in La Salle, MI, has a website for parents and family members to obtain further information about this condition. In addition, should the parents desire, websites are available in some major exstrophy centers for further information.



Figure 124–16. Use of plastic wrap to keep bladder plate moist before closure.

Although it is true that parents need to be educated as fully as possible about the exstrophy condition, this is especially true regarding the sex of rearing males with bladder exstrophy. We have seen several families who were made even more distraught by being told that their child had ambiguous genitalia in addition to bladder exstrophy and that the child would need a change of gender. The need for changing the sex of rearing in classic bladder exstrophy is almost nonexistent in the male infant.

Cardiopulmonary and general physical assessment measures can be carried out in the first few hours of life. Radionuclide scans and ultrasound studies can provide evidence of renal structure, function, and drainage, even in the first few hours of life before the patient undergoes closure of the exstrophy defect.

Circumstances may be less than ideal at birth. A thorough neonatal assessment may have to be deferred until transportation to a major children's medical center can be arranged. In these days of modern transportation, no child is ever more than a few hours away from a neonatal center with full diagnostic and consultative services. During travel the bladder should be protected by a plastic membrane, as in the nursery, to prevent damage to the delicate newborn bladder mucosa.

Selection of Patients for Immediate Closure

Successful treatment of exstrophy with functional closure demands that the potential for success in each child be carefully considered at birth. The size and functional capacity of the detrusor muscle are important considerations for the eventual success of functional closure. Correlation between apparent bladder size and the potential bladder capacity must not be confused. In minor grades of exstrophy that approach the condition of complete epispadias with incontinence, the bladder may be small yet may demonstrate

acceptable capacity, either by bulging when the baby cries or by indenting easily when touched by a sterile gloved finger in the operating room with the child under anesthesia. **Sometimes a good bit of previously unappreciated bladder can be discovered behind the fascia under examination with anesthesia** (Gearhart and Jeffs, 1998). Once the bladder is relieved of surface irritation and repeated trauma, the small bladder can enlarge and increase in capacity with the absence of sphincter activity and with minimal outlet resistance. The exstrophied bladder that is estimated at the time of birth to have a capacity of 5 mL or more and demonstrates elasticity and contractility can be expected to develop useful size and capacity after successful bladder, posterior urethral, and abdominal wall closure with early epispadias repair (Gearhart and Jeffs, 1998).

Small Exstrophy Bladder Unsuitable for Newborn Closure

A small, fibrotic bladder patch that is stretched between the edges of the small triangular fascial defect without elasticity or contractility cannot be selected for the usual closure procedure (Gearhart and Jeffs, 1998) (see Fig. 124–10). **Examination with the patient under anesthesia may at times be required to assess the bladder adequately, particularly if considerable edema, excoriation, and polyp formation have developed between birth and the time of assessment. Decisions regarding the suitability of bladder closure or the need for waiting should be made only by surgeons with a great deal of experience in the exstrophy condition** (Gearhart and Jeffs, 1998). Neonatal closure, even when the bladder is small, can allow assessment of bladder potential, provides an initial step in genital reconstruction, and is helpful in reassuring the family. Some conditions preclude primary closure, including penoscrotal duplication, ectopic bowel within the extruded bladder (a relative contraindication), a hypoplastic bladder, and significant bilateral hydronephrosis.

In a recent review by Lakshmanan and colleagues (2008) of cases at our institution, it was found on initial judgment that the bladder was too small for closure in 34 patients evaluated at birth. There were 27 males and 6 females who underwent delayed closure at a mean age of 13.2 months. Osteotomy was performed on 29 (85%). All had a successful delayed primary closure. Eleven (41%) of the boys had a simultaneous epispadias repair. Sixty one percent developed sufficient capacity for bladder neck reconstruction and 39% are continent. Compared with newer data by Novak and colleagues (2010), these rates are over double the continence rates seen in bladder neck repair after failed primary closure and successful secondary closure.

Thus waiting for the bladder template to grow for 6 to 12 months in the child with a small bladder is not as risky as submitting a small bladder template to closure in an inappropriate setting, resulting in dehiscence and allowing the fate of the bladder to be sealed at that point. If the bladder does not grow to sufficient size after 6 to 12 months, other options include excision of the bladder and a nonrefluxing colon conduit or ureterosigmoidostomy. Another alternative involves urinary diversion with a colon conduit and placing the small bladder inside to be used later for the posterior urethra in an Arap-type procedure. Lastly, if the bladder is small and the presentation is for late primary closure, bladder augmentation, ureteral reimplantation, and an outlet procedure, in addition to a continent urinary stoma, can be considered.

Osteotomy

Children born with bladder exstrophy have an exposed bladder and a wide diastasis of the pubic rami, resulting in an open pelvic ring. The musculoskeletal function appears to be normal throughout childhood; the gait is characterized by external foot progression, which lessens with growth, even if osteotomy is not performed.

Several types of pelvic osteotomies have been developed to help close the pelvic ring, decrease the stress on the abdominal wall during initial exstrophy closure, and improve the outcome of future genitourinary reconstruction. Shultz was the first researcher known to the authors to describe bilateral posterior iliac osteotomy as part of a two-stage repair of bladder exstrophy. This early osteotomy was shown to lower rates of wound dehiscence and help obtain a more secure and better genitourinary reconstruction than was formerly obtained with reconstruction without osteotomy. The success in achieving continence has been reported to be related to the reduction in the diastasis and has been thought to result from better approximation of the muscles of the pelvic floor around the urethra.

Patients may undergo pelvic osteotomy at any stage of exstrophy repair if the diastasis prevents attainment of these urologic goals. In general, the authors rarely perform osteotomy on newborns unless the diastasis is over 4 cm because the laxity of the sacroiliac ligaments allows closure of the defect without undue tension.

Types of osteotomies that have been used include bilateral osteotomy of the superior pubic ramus, diagonal osteotomy of the iliac wing, and anterior innominate osteotomy with or without posterior iliac osteotomy. The combined anterior innominate and vertical osteotomy was developed for several reasons. The osteotomy is performed with the patient in the supine position as is the urologic repair, thus avoiding the need to turn the patient. The anterior osteotomy also allows placement of an external fixator under direct vision. A greenstick-type closing-wedge osteotomy of the ilium is also performed adjacent to the sacrum in most patients, creating two large bony fragments that are easily movable.

Following failure of initial closure and in children with significant pubic diastasis, as seen in cloacal exstrophy, osteotomy is also required. Pubic approximation may not be possible in a single step at the time of abdominal closure when the diastasis is extensive. The use of staged closure of the pelvis following osteotomy has been used successfully in this circumstance. This technique has been used with great success for the treatment of children presenting with extreme diastasis, even in younger patients.

Pelvic osteotomy performed at the time of initial closure confers several advantages including (1) easy approximation of the symphysis with diminished tension on the abdominal wall closure and elimination of the need for fascial flaps; (2) placement of the posterior vesicourethral unit deep within the pelvic ring, enhancing bladder outlet resistance; and (3) bringing the large pelvic floor muscles near the midline, where they can support the bladder neck and aid in eventual urinary control (Fig. 124–17). After pubic approximation with osteotomy, some patients show the ability to stop and start the urinary stream, experience dry intervals, and in some cases become completely continent (Gearhart and Jeffs, 1991a). In a review of a large number of patients referred to our institution after failed exstrophy procedures, it was found that a majority of the patients who had partial or complete dehiscence of the bladder or major bladder prolapse had not undergone a prior osteotomy at the time of

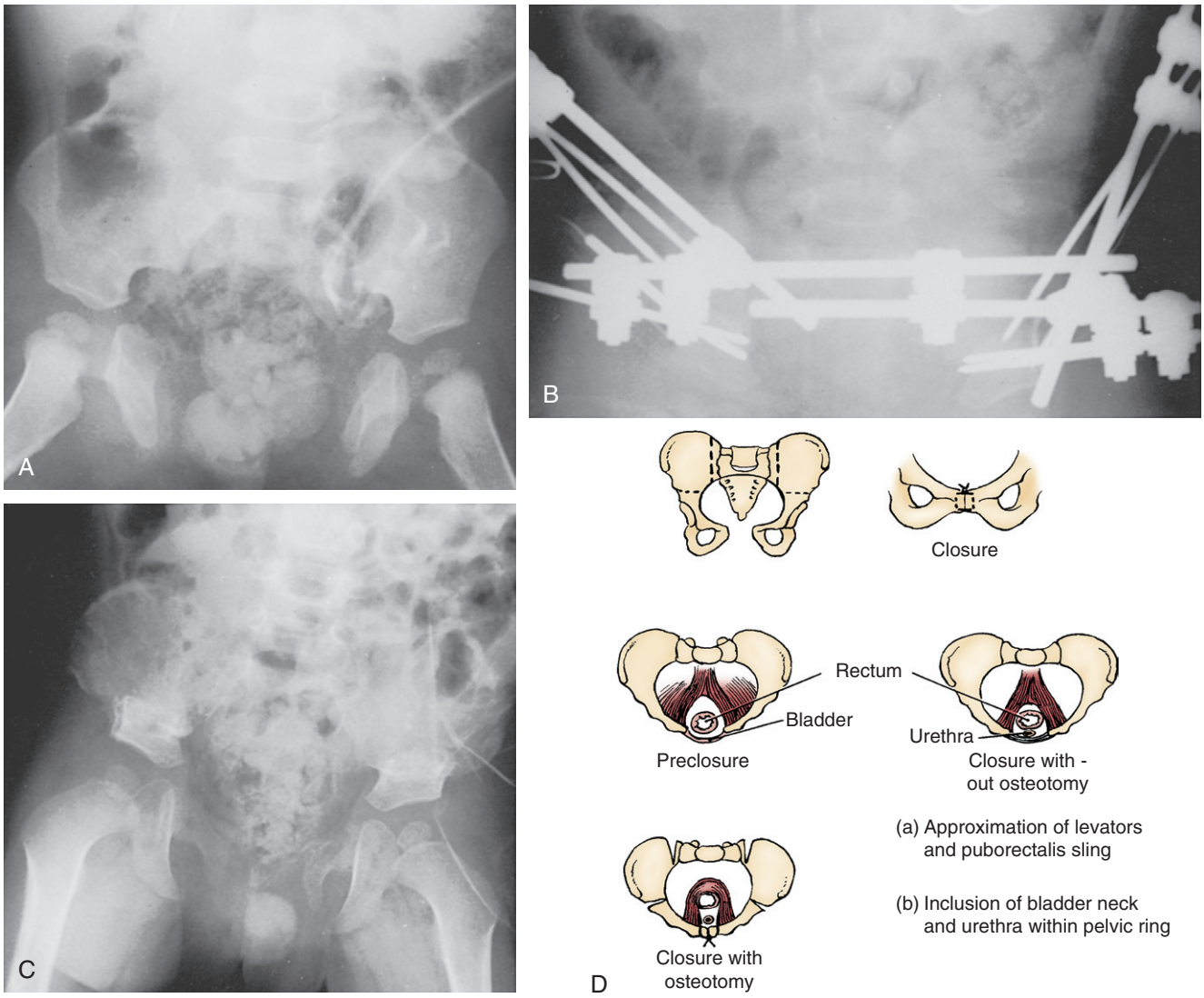


Figure 124–17. **A,** Eight-month-old patient with classic bladder exstrophy closed at birth without osteotomy with complete dehiscence. Patient was initially seen at 8 months of age. **B,** Patient after having undergone anterior innominate and vertical iliac osteotomy and placement of intrafragmentary pins and external fixator. **C,** The same patient 4 months after removal of external fixator and pins. Successful closure was achieved. **D,** The technique of combined osteotomy showing incision sites.

initial bladder closure (Gearhart et al, 1993b). The authors recommend performing bilateral transverse innominate and vertical iliac osteotomy when bladder closure is performed after 72 hours of age (Fig. 124–18). In addition, if the pelvis is not malleable or if the pubic bones are more than 4 cm apart at the time of initial examination under anesthesia, osteotomy should be performed, even if closure is done before 72 hours of age. A well-coordinated surgery and anesthesia team can perform osteotomy and proceed to bladder closure without undue loss of blood or risk of prolonged anesthesia in the child. However, it must be realized that osteotomy together with posterior urethral and bladder closure and abdominal wall closure is a 5- to 7-hour procedure in these infants.

If the patient is younger than 72 hours old and examination under anesthesia reveals that the pubic bones are malleable and able to be brought together easily in the midline by medial rotation of the greater trochanters, the patient can undergo closure without osteotomy. However, no chances should be taken with a decision of this magnitude. If there is any doubt, an osteotomy should be performed.

The most frequently used osteotomy today is the bilateral anterior innominate and vertical iliac osteotomy, popularized by Gearhart, Sponseller, and colleagues in 1996 (Gearhart et al, 1996b). This approach improves the ease of symphyseal approximation in the patient with exstrophy compared with posterior approaches, which require turning the patient. In our experience, this osteotomy is superior to the pubic mobilization seen with simple bilateral transverse anterior innominate osteotomy or even pubic ramotomy. With the ease of approximation obtained with this combined osteotomy, tension on the midline abdominal closure is lessened and the rates of bladder dehiscence and bladder prolapse are markedly decreased (Gearhart and Jeffs, 1998). In addition, pelvic closure allows approximation of the levator ani to strengthen the puborectalis sling, with positioning of the bladder neck and posterior urethra deep within the pelvic ring and improved continence rates. **Besides the ease of approximation, combined osteotomy was developed for three reasons: (1) Osteotomy is performed with the patient in the supine position, as is the urologic repair, thereby avoiding the need to turn the patient; (2) the anterior**

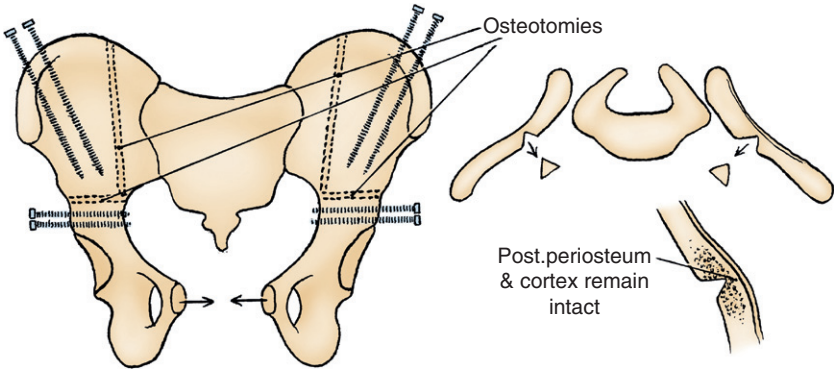


Figure 124–18. Depiction of the new combined transverse innominate and vertical iliac osteotomy indicated intrafragmentary pin placement sites and bone approximation.

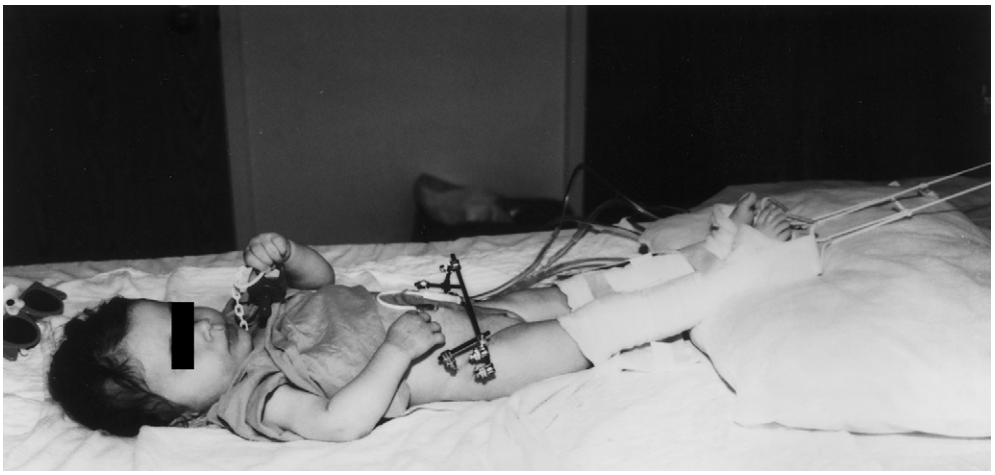


Figure 124–19. Fifteen-month-old patient following reclosure of bladder exstrophy with external fixator in place and modified Buck traction.

approach to this osteotomy allows placement of an external fixator device and intrafragmentary pins under direct vision; and (3) the cosmetic appearance of this osteotomy is superior to that of the posterior iliac approach (Gearhart et al, 1996b).

In the posterior approach there was occasional malunion of the ileum, the blood loss was greater in the posterior approach, and the need to turn the patient intraoperatively from the prone to the supine position was always worrisome. The results of the combined horizontal transverse innominate osteotomy and vertical iliac osteotomy are so satisfactory that the approach is now being used in all primary closures of bladder exstrophy that require pelvic osteotomy (Gearhart et al, 1996b).

Combined osteotomy is performed by placing the patient in the supine position, preparing and draping the lower body below the costal margins, and placing soft absorbent gauze over the exposed bladder. The pelvis is exposed from the iliac wings inferiorly to the pectineal tubercle and posteriorly to the sacroiliac joints. The periosteum and sciatic notch are carefully elevated, and a Gigli saw is used to create a transverse innominate osteotomy exiting anteriorly at a point halfway between the anterior-superior and anterior-inferior spines (see Fig. 124–18). This osteotomy is created at a slightly more cranial level than that described for a Salter osteotomy in order to allow placement of external fixator pins in the distal segments. In addition to the transverse osteotomy, the posterior ileum may be incised from the anterior approach in an effort to correct the deformity more completely. This is important because anatomic studies have shown that the posterior portion of the pelvis is also externally rotated in patients with exstrophy, and as patients age they lose elasticity of the sacroiliac ligaments. For this part of the osteotomy, an osteotome is used to create a closing wedge osteotomy vertically and just lateral to the sacroiliac joints. The proximal posterior iliac cortex is left intact and used as a hinge (see Fig. 124–18). This combination osteotomy easily corrects the abnormalities in both the anterior and posterior segments of the pelvis.

Two fixator pins are placed in the inferior osteotomized segment, and two are placed in the wing of the ileum superiorly. Radiographs are obtained to confirm pin placement, soft tissues are closed, and the urologic procedure is performed (see Fig. 124–17). At the end of the procedure, the pelvis is closed with a suture between the two pubic rami. The external fixators are then applied between the pins to hold the pelvis in a correct position. In a newborn with less than optimal amounts of cancellous bone, only one pin is placed inferiorly and superiorly in the wing of the ileum, whereas older children have two pins in each bone wing.

Radiographs are taken 7 to 10 days after surgery to look for complete reduction of the symphyseal diastasis. If this diastasis has not been completely reduced, the right and left sides can be gradually approximated by means of the fixator bars over several days. Longitudinal skin traction is used to keep the legs still (Fig. 124–19). The patient remains supine in traction for approximately 4 weeks to prevent dislodgement of tubes and destabilization of the pelvis. The external fixator is kept on for 4 to 6 weeks, until adequate callus is seen at the site of the osteotomy (see Fig. 124–15B and C). Postoperatively, in newborns who undergo



Figure 124–20. Newborn closure without osteotomy with patient in modified Bryant traction.

closure without osteotomy in the first 48 to 72 hours of life, the baby is immobilized in modified Bryant traction in a position in which the hips have 90 degrees of flexion. When modified Bryant traction is used, the traction is employed for 4 weeks (Fig. 124–20). A horizontal mattress suture of No. 2 nylon is placed between the fibrous cartilage of the pubic rami and tied anteriorly to the pubic closure at the time of bladder closure. **Evidence obtained by** Sussman and colleagues (1997) **from biomechanical testing in an intact piglet pelvic model revealed that all methods of pubic approximation were weak compared with the intact symphysis. However, the best technique with the strongest load-to-failure ratio was a No. 2 nylon horizontal mattress suture.** Should this suture work loose or cut through the tissues during healing, the anterior placement of a knot in the horizontal mattress suture ensures that it will not erode into the urethra and interfere with the bladder or urethral lumen.

Complications of Osteotomy and Immobilization Techniques

Complications of immobilization can include failure of the closure and skin breakdown with resultant ulceration. Meldrum and colleagues (2003) reviewed a series of 86 patients in whom initial exstrophy closure failed. Most had been immobilized with a "mummy wrap" or spica cast. Successful closure was noted in 97% of those immobilized with an external fixator and modified Buck traction. In addition, in those failing initial closure, six had severe skin ulcerations from the mummy wrapping or spica cast and two of these children required later skin grafting.

Sponseller and colleagues (2001) reported on a total of 86 combined bilateral anterior innominate and vertical iliac osteotomies performed in 88 children. Ten of these children had cloacal exstrophy, and 72 had bladder exstrophy with at least 2 years of clinical follow-up (mean 4.8 years). Complications included seven cases of transient left femoral nerve palsy, which resolved fully by 12 weeks after surgery. There were no cases of right femoral nerve palsy, although the same surgeon performed the same technique on both sides. Patients with transient femoral nerve palsy were on bed rest for the first 6 to 8 weeks; use of a knee immobilizer was necessary for the remaining 6 weeks until resolution. Other complications included three cases with delayed ileal union, one case of superficial infection of the ileal femoral incision that required irrigation and débridement, one case of transient right thigh abductor weakness, one infection of the ileum around a pin site requiring irrigation and débridement, and one case of transient right peroneal palsy. Almost all patients had skin inflammation around the pins, particularly those in the proximal (iliac crest) segments. This was always controlled with the use of oral antibiotics. In a recent paper by Satsuma and colleagues (2006), comparisons were made between patients who underwent posterior iliac or the combined osteotomy. Pubic approximation was better, and the mean recurrence far less in the combined transverse innominate and posterior iliac osteotomy. Thus the combined approach corrected and maintained the pelvic ring with fewer complications than a post-pelvic osteotomy.

Whichever type of osteotomy is used, pelvic ring closure not only allows midline approximation of the abdominal wall structures but also allows the levator ani and puborectalis muscles to lend potential support to the bladder outlet, thus increasing resistance to urinary outflow (see Fig. 124–17D) (Sponseller et al, 1991; Gearhart et al, 1993b, 1996b; Schmidt et al, 1993; McKenna et al, 1994). Furthermore, a continence procedure can be performed later on the bladder neck and urethra deep within the closed pelvic ring at a distance from the surface without independent movement of the two halves of the pubis. The urethra and bladder neck are set more deeply in the true pelvis, in a more normal relationship than when acutely angulated.

When good callus formation is seen on radiography, the fixating device and pins are removed with the patient under light sedation. The age of the patient plays a role in the amount of correction of the diastasis that is maintained over time. On review of the previously described types of osteotomy, both classic and cloacal exstrophy patients gained approximation, although the former group gained greater correction toward normal (Gearhart et al, 1996b). Greater postoperative diastasis, as well as less optimal bone density in the newborn, contributes to the greater difficulty in obtaining and maintaining closure of the pelvic bone deformity over time.

The authors' impression is that partial recurrence of diastasis in classic exstrophy occurs by two mechanisms. First, the pelvis may partially derotate owing to early loosening of pins before the time of osteotomy healing; this is seen mostly in infants. In the older child, increased bone density allows more rigid external fixation and thus better maintenance of the corrected position. Second, there is long-term undergrowth of the ischiopubic segment, which has been shown to be 33% smaller than normal in the adult with exstrophy, as the pelvis grows. Pubic diastasis increases with growth in the patient with uncorrected exstrophy. Therefore even with some loss of approximation, significant correction remains in comparison with the unoperated state. The authors regard the main role of osteotomy to be relaxation of tension on the bladder, posterior urethra, and abdominal wall repair during healing. Therefore they use osteotomy rarely in newborns and young infants because ligament laxity allows the pelvis to be closed without tension. However, it becomes essential in the older child with a failed exstrophy repair, in the patient with cloacal exstrophy, and in a newborn with a wide diastasis and excellent bladder template. **In patients undergoing combined exstrophy closure and epispadias repair, osteotomy allows the pubis to be joined, making it easier for the corpora to be brought over the closed proximal urethra** (Gearhart et al, 1998). In a recent large series of failed exstrophy reclosures, 56 patients were found who underwent repeat pelvic osteotomy (Nelson et al, 2006). All of the reclosures were successful, and 95% had a normal gait after reoperative osteotomy. There were no femoral or sciatic nerve palsies and only five local pin site

infections, which were easily treated. Thus even repeat pelvic osteotomy is safe in experienced hands.

Surgical Options in the Newborn with Classic Bladder Exstrophy

Although the modern staged repair of exstrophy (MSRE) currently enjoys widespread popularity, other methods have been described for the primary reconstruction of exstrophy. This section discusses the other types of repair, their use, and application. The outcomes and complications are discussed in separate sections because many are similar and their correction the same.

Warsaw Approach

First described by Baka-Jakubiak in 2000, this procedure involved closing the bladder, posterior urethra, pubis, and abdominal wall at the time of primary closure with or without osteotomy but always with appropriate immobilization. Osteotomy is used in all patients older than 72 hours or in any with a diastasis greater than 5 cm. A spica cast is used for 3 weeks and an elastic bandage for 3 further weeks. When the bladder had achieved suitable capacity (>70 mL) and the child was interested in continence, bladder neck repair was performed along with epispadias repair. Baka-Jakubiak has used this approach in more than 100 with classic exstrophy and complete epispadias. The intersymphyseal band is routinely divided to allow better visualization of the bladder neck and posterior urethra region. An additional proposed benefit of this procedure is that the bladder neck and posterior urethral unit is straighter at the second procedure and this allows easier catheterization and cystoscopy following reconstruction. A 10% complication rate, mainly urethral fistula or stricture, was noted in this procedure.

Kelly Repair

The radical soft tissue mobilization procedure was developed by Kelly in the late 1980s and early 1990s as a means to improve on the technique described by Ansell and to obviate pelvic osteotomies that were often required to obtain a tension-free closure. It is a multistaged repair that includes (1) closure of the bladder dome and hernia repair at birth, followed at age 3 to 6 months by (2) reconstruction of the proximal urethra with associated sphincteric tissue with penile lengthening and creation of a penoscrotal urethrostomy in males; and (3) repair of the resulting penoscrotal hypospadiac around 3 years of age. The unique aspects relate to the second stage, where a more radical mobilization of the pelvic floor muscles is performed. Specifically, the dissection includes the periosteum of the ischium and pubis where one encounters the attachment of the voluntary and involuntary sphincter muscles, as well as the pudendal nerves and vessels. The muscles are then wrapped around the reconstructed proximal urethra in an attempt to provide a continence mechanism. The neourethra itself is constructed from the urethral plate on the dorsum of the penis after it is dissected from the corporal bodies, much as in the penile disassembly technique. However, unlike the penile disassembly technique, the meatus is always brought to the penoscrotal junction and later brought distally.

Complete Repair

Developed by Mitchell, the complete repair combines the standard bladder closure with the "penile disassembly" technique for epispadias repair in an effort to decrease the number of procedures required for reconstruction and potentially provide continence without the need for formal bladder neck reconstruction (Grady and Mitchell, 1999). The urethral plate is dissected from the corporal bodies, and the urethra and bladder plate are moved posteriorly into the pelvis. Mitchell emphasizes the importance of dissecting the perineal membrane from the pubis, allowing the bladder and posterior urethra to be set deep into the pelvis. This feature is common to all properly performed exstrophy reconstructions and helps ensure success. The dissection of the urethral plate from the corpora leaves 60% to 75% of patients with hypospadias (Hafez and El-Sherbiny, 2005), and 50% of children require ureteral reimplantation in the first year of life (Grady and Mitchell, 1999).

Mainz Repair

Hohenfelner and colleagues first began using ureterosigmoidostomy for both failed exstrophy patients and for patients with small bladder templates, which led to its use as a technique in primary exstrophy closures. Beginning in 1964, this was begun in all newborns with exstrophy irrespective of bladder template size at birth. At the age of 2, ureterosigmoidostomy is performed. Some of the remnant bladder is made into a small seminal receptaculum, and the penis is reconstructed during the same procedure. In girls, the external genitalia are reconstructed and anterior fixation of the uterus is performed. In both boys and girls, cosmetic correction is usually necessary later. However, this usually means only one further operation. In 1996 Fisch and Hohenfelner modified this technique with the introduction of the Mainz Sigma pouch. This was designed to reduce intracolonic pressure and to maintain better fecal continence. Most of the patients are immediately started on oral alkalinization.

Erlangen Approach

This approach is clearly the most involved of any of the primary closure techniques. In the Erlangen approach developed by Schrott and popularized by Roesch, if the bladder template is deemed of adequate size, the "total" repair is done at 8 weeks of age. If the template is too small at birth, the bladder only is closed with bilateral groin exploration, closure of the pubis, epispadias repair, and no osteotomy. In the classic Erlangen "total repair," the bladder is closed along with bilateral reimplantations, bladder neck plasty, bilateral groin exploration, epispadias repair, pubic closure, no osteotomy, and an epidural catheter for 5 days. Osteotomy is only done in cloacal exstrophy and reoperative closures. Thus the Erlangen repair is truly a "complete repair" encompassing all phases of exstrophy repair in one setting (Ebert et al, 2010).

Regardless of the modern method of reconstruction chosen for the newborn, certain surgical principles remain: (1) radical mobilization of the bladder and posterior urethra from surrounding tissue; (2) combined closure with epispadias repair in only carefully selected patients; (3) tension-free closure of the abdominal wall and pelvic bones with adjunctive osteotomy if needed; and (4) definition of strict criteria for selection of patients to undergo newborn closure.

Modern Reconstruction of Bladder Exstrophy

The primary objective in functional closure is to convert the bladder exstrophy into a complete epispadias with the urethra well onto the penis with completion of the epispadias in only highly select patients. The resultant incontinence with balanced posterior outlet resistance not only preserves renal function but also stimulates bladder growth. Typically, epispadias repair is now performed around 6 months of age, after testosterone stimulation. Bladder

neck repair usually occurs when the child is 4 to 5 years of age, has an adequate bladder capacity, and, most importantly, is ready to participate in a postoperative voiding program. Many repairs such as the Erlangen, Kelly, and complete primary repair of exstrophy (CPRE) were purported to establish continence without the need for bladder neck repair, but recent reports have shown the need for an outlet procedure in most patients (Gearhart et al, 2007; Shoukry et al, 2009).

Bladder, Urethral, and Abdominal Wall Closure

Various steps in primary bladder closure are illustrated in Figure 124–21. A strip of mucosa 2 cm wide, extending from the distal trigone to below the verumontanum in the male and to the vaginal orifice in the female, is outlined for prostatic and posterior urethral reconstruction in the male and adequate urethral closure in the female. The male urethral groove may be adequate, in which case no transverse incision of the urethral plate need be performed for urethral lengthening (see Fig. 124–21A). The authors tend to not incise a urethral plate unless the length of the urethral groove from the verumontanum to the urethral glans is so short that it interferes with eventual penile length and produces dorsal angulation. If so, the urethral groove is lengthened after the manner of Johnston (1974) or Duckett (1977). The drawings in Figure 124–21B and C show marking of the incision just above the umbilicus, down the junction of the bladder and paraexstrophy skin, to the level of the urethral plate.

An appropriate plane is entered just above the umbilicus, and a plane is established between the rectus fascia and the bladder (see Fig. 124–21D). The umbilical vessels are doubly ligated and incised and allowed to fall into the pelvis. The peritoneum is taken off the dome of the bladder at this point so that the bladder can be placed deep into the pelvis at the time of closure. The plane is continued caudally down between the bladder and rectus fascia until the urogenital diaphragm fibers are encountered bilaterally. The pubis is encountered at this junction, and a double-pronged skin hook can be inserted into the bone at this time and pulled laterally to accentuate the urogenital diaphragm fibers. This helps the surgeon radically incise these fibers among the bladder neck, posterior urethra, and pubic bone (see Fig. 124–21E). Gentle traction on the glans at this point shows the insertion of the corporal body on the lateral inferior aspect of the pubis. These urogenital diaphragm fibers are taken down sharply with electrocautery down to the pelvic floor in their entirety (see Fig. 124–21F). If this maneuver is not performed adequately, the posterior urethra and bladder will not be placed deeply into the pelvis, and when the pubic bones are brought together, the posterior vesical unit will be brought anteriorly into an unsatisfactory position for later Cantwell-Ransley epispadias repair. If the urethral plate is left in continuity, it must be mobilized up to the level of the prostate in order to create as much additional urethral and penile length as possible. Further urethral lengthening can be performed at the time of epispadias repair.

Penile lengthening is achieved by exposing the corpora cavernosa bilaterally and freeing the corpora from their attachments to the suspensory ligaments on the anterior part of the inferior pubic rami. **However, because Silver and colleagues (1997b) showed that there is a 50% shortage of length of the corporal bodies in exstrophy versus normal controls, any penile length that is obtained is more correction of chordee and change in angulation of the penis rather than true penile lengthening.** The wide band of fibers and muscular tissue representing the urogenital diaphragm is detached subperiosteally from the pubis bilaterally (see Fig. 123–21F). Reluctance to free the bladder neck and urethra well from the inferior ramus of the pubis moves the neobladder opening cephalad should any separation of the pubis occur during healing, thus increasing the chance of bladder prolapse. The mucosa and muscle of the bladder, bladder neck, and urethra are then closed well onto the penis in the midline anteriorly (see Fig. 123–21G). This should be tapered over a 10- to 12-Fr sound comfortably. The size of the opening should allow enough resistance to aid in bladder adaptation and to prevent prolapse but not enough outlet resistance to cause upper tract changes. The posterior urethra and bladder neck are buttressed with a second layer of local tissue if possible. If a CPRE is performed, a penile disassembly is done with many of the patients being made hypospadiac. The bladder is drained by a suprapubic non-latex Malecot catheter for a period of 4 weeks. The urethra is not stented in order to avoid necrosis with accumulation of secretions in the neourethra. Stents provide drainage during the first 10 to 14 days after closure because swelling caused by the pressure of closure of a small bladder can obstruct the ureters and give rise to obstruction and transient hypotension. If there are no problems with the stents during healing, the authors leave the stents in as long as 2 to 3 weeks.

When the bladder and urethra have been closed and the drainage tubes placed, pressure over the greater trochanters bilaterally allows the pubic bones to be approximated in the midline. Horizontal mattress sutures are placed in the pubis and tied with a knot away from the neourethra (see Fig. 123–21H). Often, it is possible to use another stitch of No. 2 nylon at the most caudal insertion of the rectus fascia onto the pubic bone. This maneuver adds to the security of the pubic closure. A V-shaped flap of abdominal skin at a point corresponding to the normal position of the umbilicus is tacked down to the abdominal fascia, and a drainage tube exits this orifice. The method described by Hanna (1986) is our most commonly performed procedure. Before and during the procedure, the patient is given broad-spectrum antibiotics in an attempt to convert a contaminated field into a clean surgical wound.

If the decision is made at this point that the urethral groove is to be transected, the groove is cut distal to the verumontanum with continuity maintained between the thin, mucosal, non–hair-bearing skin adjacent to the posterior urethra and bladder neck and the skin and mucosa of the penile skin and glans. Flaps in the area of the thin skin are subsequently moved distally and rotated to reconstruct the urethral groove, resurfacing the penis dorsally. The corporal bodies are not brought together at this juncture because later Cantwell-Ransley repair is planned.

Combined Bladder Closure and Epispadias Repair

The modern staged repair of bladder exstrophy has yielded consistently good cosmetic and functional results, and the utilization of osteotomy has improved the potential for successful initial closure and later continence. **In an effort to decrease costs, decrease the morbidity associated with multiple operative procedures, and possibly affect continence, there has been interest in performing single-stage reconstruction or combining procedures in appropriately selected patients.** This technique was first described by Lattimer and Smith (1966) but was abandoned in the 1970s because of high complication and failure rates. The technique was revisited by Gearhart and Jeffs (1991a) for failed exstrophy closures and more

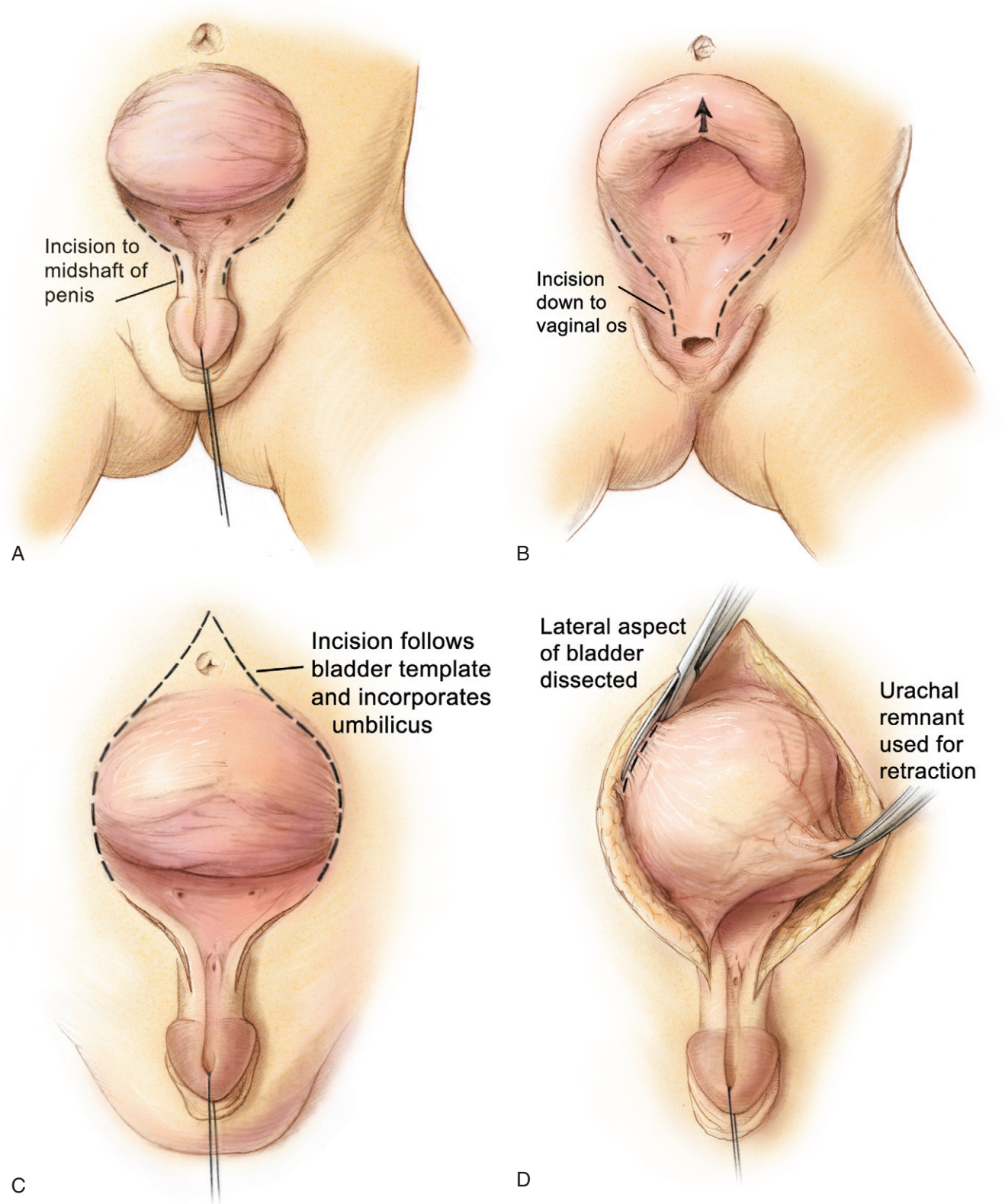


Figure 124–21. Steps in the initial closure of the bladder and posterior urethra with or without osteotomy. The bladder plate is dissected off the anterior abdominal wall. **A,** Initial incision around the bladder plate in the male. **B,** Initial incision around the bladder plate in the female. **C,** Incision follows the bladder template and includes the umbilicus. **D,** Dissection of the lateral aspect of the bladder from the abdominal wall.

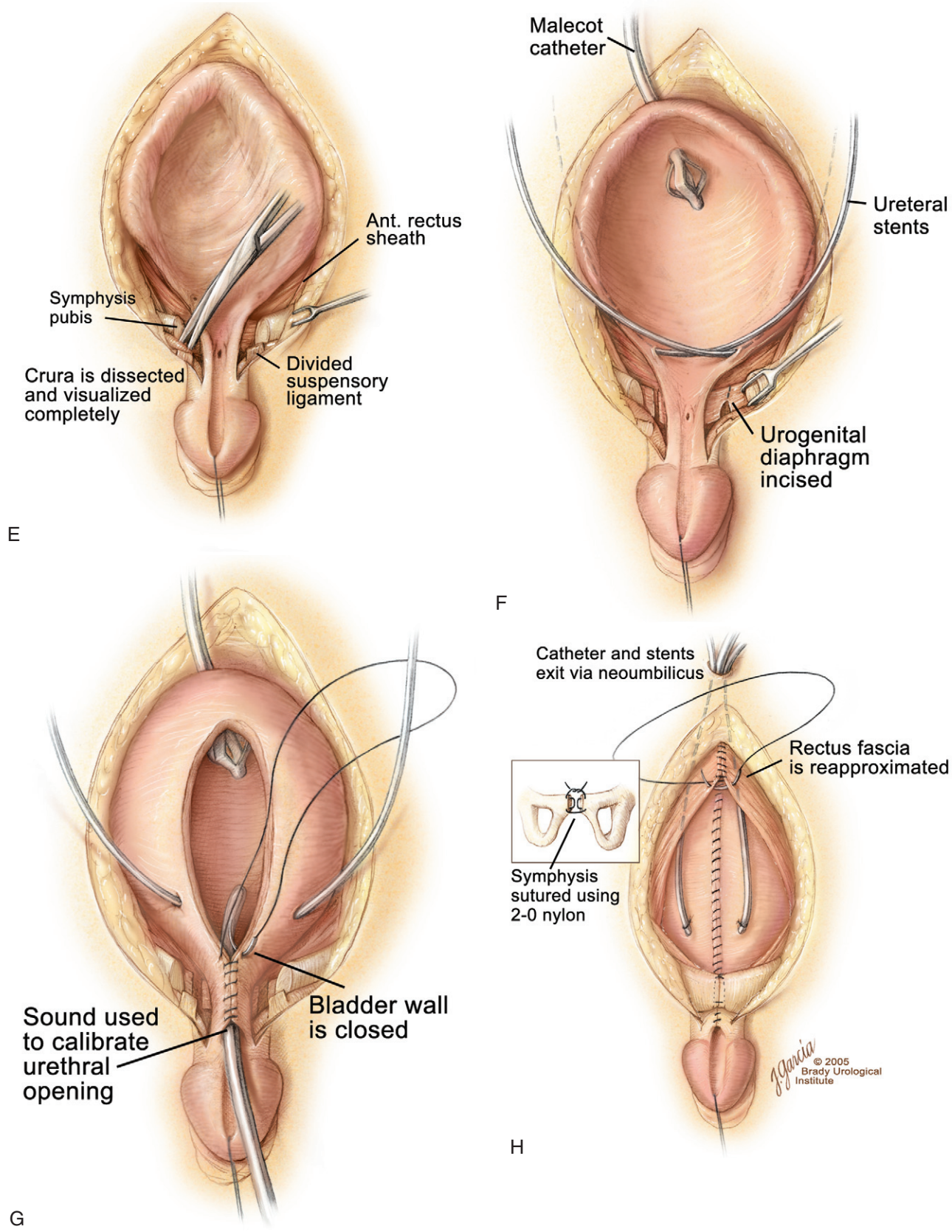


Figure 124–21, cont'd. **E,** Dissection of the crura from the symphysis pubis. **F,** Division of the urogenital diaphragm fibers. Note stents and suprapubic tubes in place in the bladder. **G,** Initial layer of the bladder closure. Urethral meatus is calibrated to 14-Fr size. Stents are brought out of the bladder. **H,** Pubic approximation is performed with No. 2 nylon mattress suture (see inset). Abdominal wall closure is completed. Suprapubic tube and stents are brought out through the neoumbilicus. (© Brady Urological Institute.)

recently by Grady and Mitchell for newborn patients (1999). In the combined exstrophy and epispadias repair, bladder closure is combined with the modified Cantwell-Ransley epispadias repair (Gearhart et al, 1998; Baird et al, 2005c). This technique can be applied to both delayed primary closure and failed closures. As with the complete repair, many require early ureteral reimplantation, but none were made hypospadiac.

Results have now emerged in groups of boys undergoing single-stage reconstruction (bladder closure and epispadias repair) in infancy (Gearhart et al, 1998; Baird et al, 2005c). In our opinion, this technique should be limited to boys of older age (older than 4 to 6 months) because of evidence indicating that potential complication of these combined procedures is significant loss of penile and corporal tissue that makes further reconstruction problematic (Husmann and Gearhart, 2004). Patients should be carefully selected, and utilization of these extensive procedures by the occasional exstrophy surgeon is not recommended. **Selection should take into account phallic size and length, depth of the urethral groove, and size of the bladder template in those with delayed primary closures, as well as perivesical and urethral scarring in those who have undergone a prior failed closure** (Gearhart and Jeffs, 1991a; Gearhart et al, 1998; Baird et al, 2005c).

Management after Primary Closure

The initial step of the MSRE converts a patient with exstrophy into one with penile epispadias and incontinence. **Before removal of the suprapubic tube, 4 weeks after surgery, the bladder outlet is calibrated by a urethral catheter or a urethral sound to ensure free drainage. A complete ultrasound examination is obtained to ascertain the status of the renal pelves and ureters, and appropriate urinary antibiotics are administered because all patients have reflux after closure.** Residual urine is estimated by clamping the suprapubic tube, and specimens for culture are obtained before the patient leaves the hospital and at subsequent intervals to detect infection and ensure that the bladder is empty. If the initial ultrasound examination shows good drainage, upper tract imaging by ultrasonography is repeated 3 months after discharge from the hospital and at intervals of 6 months to 1 year during the next 2 to 3 years to detect any upper tract changes caused by reflux, infection, or obstruction. Prophylactic antibiotics should be continuous because all patients with bladder exstrophy, once closed, have vesicoureteral reflux. If a useful continence interval has resulted from the initial closure, a further operation for incontinence may not be required; however, this situation is quite unusual. In the authors' experience with more than 85 primary closures, this has occurred in three patients, all of whom were girls. After the conversion from exstrophy to complete epispadias with incontinence, the bladder gradually increases in capacity as inflammatory changes in the mucosa resolve.

Cystoscopy and cystography at yearly intervals are used to evaluate the degree of reflux noted in almost 100% of patients and to provide an estimate of bladder capacity (Gearhart and Jeffs, 1998). Even in a completely incontinent patient, bladder capacity gradually increases to a point at which the bladder can be distended at cystography to its true capacity. This must be done under anesthesia in young children because the values obtained differ markedly from those obtained when trying to fill the bladder of a crying, squirming infant on an x-ray table (Gearhart and Jeffs, 1998). If the bladder has not achieved a capacity of at least 30 mL by 1 to 2 years, concern must be voiced to the parents about the overall ability of the bladder to undergo a continence procedure. Currently, the only parameters available to predict overall success are the size of the bladder template at birth and a successful primary closure with absence of infections.

Should bladder outlet resistance be such that urine is retained within the bladder and reflux and ureteral dilatation develop with infected urine, it may be necessary to dilate the urethra or to begin intermittent catheterization (Baker et al, 1999). Sometimes the posterior urethral obstruction can be such that it requires a transurethral incision of the stricture to maintain an adequate posterior urethral outlet. If bladder outlet resistance persists and infections continue, an antireflux procedure may be required as early as 6 months to 1 year after initial closure (Mathews and Gearhart, 2003). After primary closure with the CPRE repair, 50% will require ureteral reimplantation in the first year after closure. Because of this problem, some units are trying ureteral reimplantation at the time of bladder closure but the numbers of patients treated in this fashion is small (Braga et al, 2008a). If severe upper tract changes occur, surgical revision of the bladder outlet by advancing skin flaps into the orifice or even patching the stricture may be necessary to prevent scarring and further obstruction. As mentioned previously, transurethral incision of the urethral stricture to obtain a balanced outlet should be tried before surgical revision. Judgment is required to know when to avoid attempts at functional closure and to know when to return to urinary diversion as a means to preserve renal function. This change of plan is seldom necessary if an adequate outlet has been constructed at the initial closure and if careful attention has been paid to the details of follow-up of the bladder and posterior urethra. An important caveat is that if there are recurrent urinary tract infections (UTIs) and if the bladder is distended on ultrasonography, cystoscopy should be performed and the posterior urethra should be carefully examined anteriorly for erosion of the intrapubic stitch, which may be the cause of the recurrent infections (Baker et al, 1999). If the intrapubic stitch is seen in the posterior urethra, a small suprapubic incision should be made and the stitch should be removed, or, if it can be grasped, it should be removed transurethrally. Husmann and colleagues (1990) have shown acceptable levels of upper tract function after primary closure as long as prophylactic antibiotics were used after initial closure and elevated urinary residuals were kept below 50 mL.

Selected Technical Aspects of Other Methods of Closure

Kelly Repair

In the first stage of the Kelly repair the bladder is closed up to the level of the posterior urethra with no attempt to bring the pubic bones into apposition. The second step of the Kelly repair, which differs from other types of repair, is the "radical soft tissue mobilization." This is accomplished by making an incision around the old bladder closure and by making parallel incisions on the urethral plate extending proximally to halfway between the ureteric orifices and the verumontanum. This maneuver helps expose the corpora laterally as they move over toward their insertion onto the pubis. The mucosa lateral to the urethra is excised, as well as some of the mucosa of the bladder (Fig. 124–22A and B). The initial lateral extension of the incision exposes the dorsal nerves of the penis and the attachment of the corpora to the pubis (Fig. 124–22B). The urethral plate is mobilized from the corporal

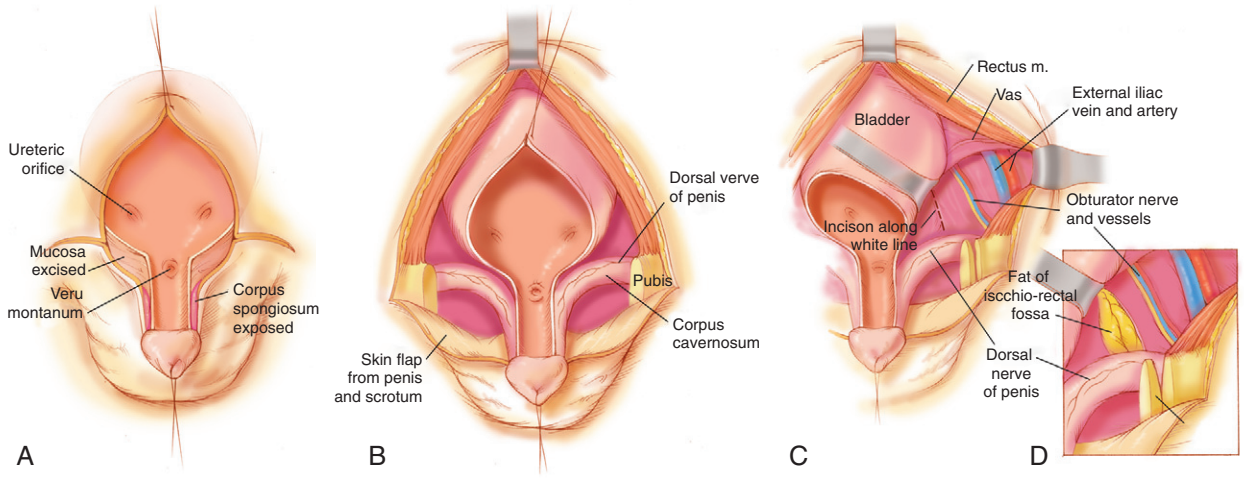


Figure 124–22. Kelly repair. **A,** The penis has been degloved and pulled down over the scrotum. The corpora are exposed with their attachments to the pubis. The dorsal nerves of the penis are identifed emerging from the pelvis superior to the attachment of the corpus to the pubis (redrawn from Kelly with permission). **B,** The extraperitoneal plane behind the left rectus muscle has been opened.The vas is identified and retracted with peritoneum. The external iliac vessels and obturator vessels and nerves are identified. The initial incision into the pubis to create a flake of bone, taking care only to go down to the level of the emergence of the dorsal nerve of the penis (redrawn from Kelly with permission). **C,** The pelvic floor is opened, and the bladder and rectum retracted medially. An incision is made through the levator medial to the white line. This incision is taken out to the wall of the pelvis, so the attachment of the levator to the back of the pubis will be moved with the bone flake. **D,** Further deeper, the ischio rectal fossa is encountered where the pudendal vessels are identifed and freed up. Once the vessels and bone flake are totally free, the tissues of the penis, bladder neck, and urethra are reconstructed.

bodies and moved to below them to create a penoscrotal hypospadias.

Laterally the extraperitoneal space behind the rectus is entered and the vas retracted (Fig. 124–22C). An incision is made in the superior aspect of the pubis downward, creating a "flake" to which the corpora of the penis and remnants of the urogenital diaphragm are medically attached (Fig. 124–22D). The incision is then taken deeper to the superior aspect of the levator ani. The incision is carried through the levator muscles both deeply and anteriorly to where the levators insert on the back of the pubis. The pudendal vessels and nerves are freed from any attachments, and when it appears the entire course has been determined, the "flake" of the pubis is incised totally and the urethral, bladder neck area and muscles are brought together without tension.

Mitchell Repair

The Mitchell repair, as in all closures, is best performed in the newborn period. The closure technique is much the same as in all methods of closures as far as preoperative evaluation and postoperative care. The main difference is that the urethra is separated from its attachments to the underlying corporal bodies and pelvic diaphragm. Mitchell purports that this allows better posterior positioning of the bladder neck and posterior urethra into the pelvis. This combined bladder closure with epispadias repair was originally thought to be sufficient for the patient to achieve urinary continence, but this has been found not to be the case in that most of these patients require bladder neck repair (Shoukry et al, 2009).

The closure is begun in the standard fashion, but the incision is carried out onto the urethral plate taking care to preserve its blood supply and avoid corporal injury. The penis is then disassembled into three components: (1) right corpus; (2) left corpus; and (3) urethral wedge (Fig. 124–23A). The dissection moves cranially, and the intersymphyseal band is incised. This is also accomplished as in the MSRE by going medial to the inferior aspect of the pubis and cutting these fibers from their posterior urethral attachment all the way to the levator hiatus (Gearhart et al, 2007). After standard closure of the bladder, the urethra is closed and an attempt to move the urethra to the tip of the penis is made (Fig. 124–23B). If it does not reach the tip of the penis, the urethra is taken to the base of the penis in a hypospadiac position in a majority of patients (Fig. 124–23C).

The repair is similar in the female patient with care taken to mobilize the bladder neck, urethra, and vagina as a single unit. Unlike the Kelly repair but similar to the MSRE repair, an osteotomy is used in both sexes if the child is older than 3 days or the diastasis is judged to be excessive (Gearhart, 2002).

Penile and Urethral Closure in Exstrophy

Epispadias Repair

Historically, bladder neck reconstruction was performed before penile and urethral reconstruction. However, an increase in bladder capacity in patients with extremely small bladder capacities after epispadias repair prompted a change in the management program (Gearhart and Jeffs, 1989a) (Fig. 124–24A and B). In a group of patients with a small bladder capacity after initial closure, there was a mean increase of 55 mL in males in only 22 months after epispadias repair. However, with MSRE, the epispadias repair is now performed at about 6 months of age in all patients. With this modification, possibly all patients can achieve an appropriate capacity at the time when they are ready physically and mentally to undergo bladder neck reconstruction. Because most boys with exstrophy have a somewhat small penis and a shortage of available penile skin, all patients undergo testosterone stimulation before urethroplasty and penile reconstruction (Gearhart and Jeffs, 1987).

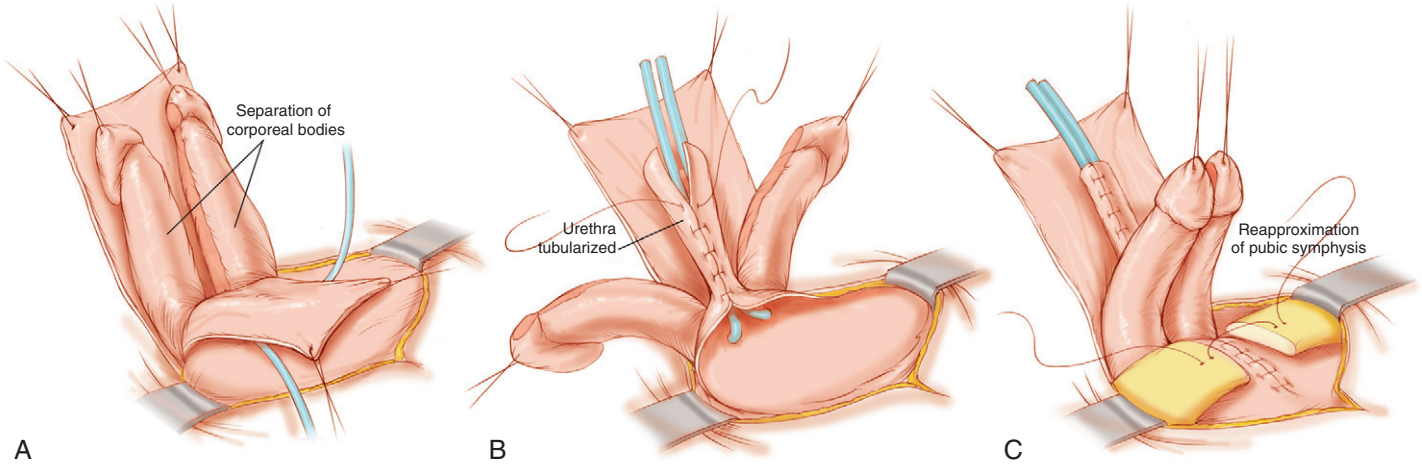


Figure 124–23. **A,** Corporal separation with dissection of urethral plate to complete penile disassembly (redrawn from Grady with permission). **B,** Urethral plate tubularization done with interrupted sutures in an attempt to lengthen it (redrawn after Grady with permission). **C,** Reapproximation of pubic symphysis with medial rotation of the corpora and placement of tubularized urethra underneath corpora either on or below glans in a hypospadiac position. (Redrawn from Grady with permission.)

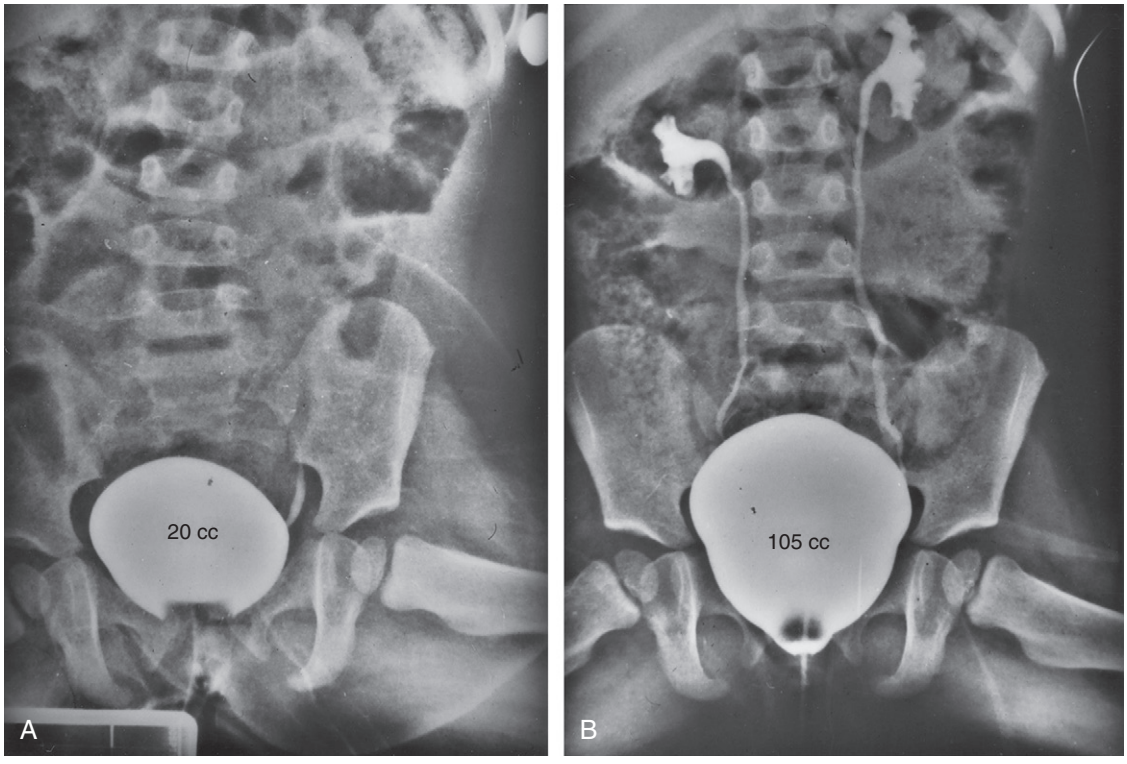


Figure 124–24. **A,** Initial cystogram under anesthesia showing small bladder capacity after bladder closure. **B,** Improvement in bladder capacity noted following urethroplasty.

Many techniques have been described for reconstruction of the penis and urethra in patients with classic bladder exstrophy. Current methods of epispadias repair in bladder exstrophy are the Cantwell-Ransley repair (1989), the modified Cantwell-Ransley repair (1992, 1995), and the penile disassembly technique described by Mitchell and Bagli (1996).

Regardless of the surgical technique chosen for reconstruction of the penis in bladder exstrophy, four key concerns must be addressed to ensure a functional and cosmetically pleasing penis. These concerns are (1) correction of dorsal chordee, (2) urethral reconstruction, (3) glanular reconstruction, and (4) penile skin closure.

Although it is possible to achieve some penile lengthening with release of chordee at the time of initial closure, it is often necessary to perform formal penile elongation with release of chordee at the time of urethroplasty in exstrophy patients. Data of Silver and colleagues (1997b) clearly showed that this is more an apparent lengthening of the penis than a true lengthening because the anterior corporal bodies in exstrophy patients have 50% less length than those of age-matched controls in adult life. Certainly,

all remnants of the suspensory ligaments and old scar tissue from the initial bladder closure must be excised. Also, further dissection of the corpora cavernosa from the inferior pubic ramus can be achieved. It is often surprising how little is accomplished in freeing the corporal bodies from the pubis at the time of initial exstrophy closure (Gearhart, 1991).

Lengthening of the urethral groove is also essential. Whether or not paraexstrophy skin flaps are used at the time of bladder closure, further lengthening is necessary. This can range from something as simple as Cantwell's original procedure to transection of the urethral plate and replacement of the genital tissue. However, in modern techniques of epispadias repair, replacement of the urethra is not typically performed. In the penile disassembly technique described by Mitchell and Bagli (1996), the urethral plate is dissected completely from the glans; in more than 70% of patients it is not long enough to reach the tip of the penis, and as a result hypospadias is present with further reconstruction needed at another setting (Hafez and El-Sherbiny, 2005). **The authors believe that because of the marked length disparity in male children with exstrophy compared with normal males, complete detachment of the urethra from the glans is an unnecessary step in light of the small amount of length that is obtained with this maneuver and the near certainty of creating hypospadias that, with the paucity of skin in this condition, can be difficult to repair and many end up with a coronal urethral opening.**

Chordee

Besides lengthening of the urethral groove, dorsal chordee must be addressed. To release dorsal chordee, one may lengthen the dorsomedial aspect of the corpora by incision and anastomosis of the corpora themselves (Gearhart et al, 1992). Also, length can be gained by placement of a dermal graft to allow lengthening of the dorsal aspect of the corpora (Woodhouse, 1986). Another technique to improve dorsal chordee before urethroplasty is shortening or medial rotation of the ventral corpora (Koff and Eakins, 1984). However, most of these techniques, especially grafting, are reserved for patients who are seen in adolescent and adult years for epispadias surgery with the need for some increased penile length and correction of residual chordee.

Urethral Reconstruction

Urethral reconstruction is an important aspect of external genital reconstruction in exstrophy. This can be accomplished by many previously reported methods. Tubularization of the dorsal urethral groove as a modified Young urethroplasty has been abandoned in the authors' practice because of the high incidence of urethrocutaneous fistula and the less than optimal cosmetic appearance of the penis (Lepor et al, 1984). In the past, interposition of a free graft of genital or extragenital skin, or even bladder mucosa, has been used (Hendren, 1979). In addition, ventral transverse island flaps and double-faced island flaps have been used with some success for urethral reconstruction in exstrophy patients (Thomalla and Mitchell, 1984; Monfort et al, 1987). However, modern techniques of epispadias repair associated with bladder exstrophy use tubularization of the urethral plate, moving the urethral plate under the corporal bodies after closure to lessen the incidence of urethrocutaneous fistula and also to give the penis a more downward deflection and more easily catheterizable urethral channel (Surer et al, 2001a). With the penile disassembly technique, interrupted sutures are often used to try and get the urethra to the tip of the penis again after it is completely detached with resultant hypospadias in many.

Penile Skin Closure

If skin closure continues to be a problem in genital reconstruction, owing to the paucity of skin associated with this condition, a Z-plasty incision and closure at the base of the penis prevents skin contraction and upward tethering of the penis. The ventral foreskin can be split in the midline and brought to the dorsum as lateral preputial flaps for coverage of the penile shaft. If the flaps are a bit asymmetrical, a staggered dorsal suture line results, with less upward tethering. Alternatively, a buttonhole can be created in the ventral foreskin and simply transposed to the dorsum for additional penile skin coverage.

Modified Cantwell-Ransley Repair

The authors' preference for urethroplasty and penile reconstruction, if the urethral groove has adequate length, is the modified Cantwell-Ransley repair (Gearhart et al, 1992, 1995c, 2004) (Fig. 124–25). Currently, in the modern applications of the staged reconstruction of bladder exstrophy, epispadias repair is performed when the child is 6 months to 1 year of age. The modified Cantwell-Ransley procedure is begun by placing an island stitch through the glans as a traction stitch. Incisions are made over two parallel lines marked previously on the dorsum of the penis that outline an 18-mm-wide strip of urethral mucosa, extending from the prostatic urethral meatus to the tip of the penis (see Fig. 124–25A). For this procedure, a deep vertical incision is made in the urethral plate distally. The incision is then closed with 6-0 polyglycolic sutures in a transverse fashion (see Fig. 124–25B to D). This procedure flattens the distal urethral plate and advances the urethra to the tip of the phallus so that it will be in excellent glanular position when the glanular wings are closed over the reconstructed urethra. Glanular mucosal areas of the dorsal glans are excised adjacent to the urethral strip, and thick glandar flaps are constructed bilaterally (see Fig. 124–25F). Lateral skin flaps are mobilized and undermined. A Z-incision of the suprapubic area permits wide exposure and division of the suspensory ligaments and old scar tissue from initial exstrophy closure (see Fig. 124–25F).

Ventral penile skin is taken down to the level of the scrotum (see Fig. 124–25E). Care is taken to preserve the mesentery to the urethral plate, which arises proximally and extends upward between the corporal blood supply to the urethral plate. Dissection of the corpora is begun ventrally with dissection on the surface of Buck fascia covering the corporal bodies. The plane is followed closely until one exits on the dorsum of the penis between the corpus spongiosum and the corporal body, first on one side and then on the other (see Fig. 124–25F and G). The loops are placed around the corporal bodies, and the dissection is extended proximally on the corpora to dissect the urethral plate free from the corporal bodies up to the level of the prostate. Although one might expect difficulties when dissecting proximally where the paraexstrophy skin flaps had been sutured to the urethral plate, this has not been encountered in the authors' experience, and dissection is kept just on the corporal bodies while proceeding proximally. The urethral plate is also dissected distally past the level of the junction of the glans with the corporal bodies. In this manner, adequate mobilization is obtained, and it is not difficult to bring the corporal bodies over the urethra at the level of the corona. This almost separates the penis into three components: the two corpora and the urethral plate (see Fig. 124–25F). Complete penile disassembly is not undertaken, and the distalmost 1-cm attachment of the mucosa plate to the glans is left intact (Surer et al, 2001a; Gearhart et al, 2004).

The neurovascular bundles, situated between Buck fascia and the corporal wall, are typically left intact in young patients if rotation of the corporal bodies over the urethra effectively straightens the penis. If not, the neurovascular bundles are dissected free from the corporal bodies, with vessel loops being placed around these structures so that the neurovascular bundles will not be compromised when incisions are made in the corpora and the corpora are rotated medially over the neourethra (see Fig. 124–25H). After the corporal bodies are incised or rotated over the urethra, the urethral strip is closed in a linear manner from the prostatic opening to

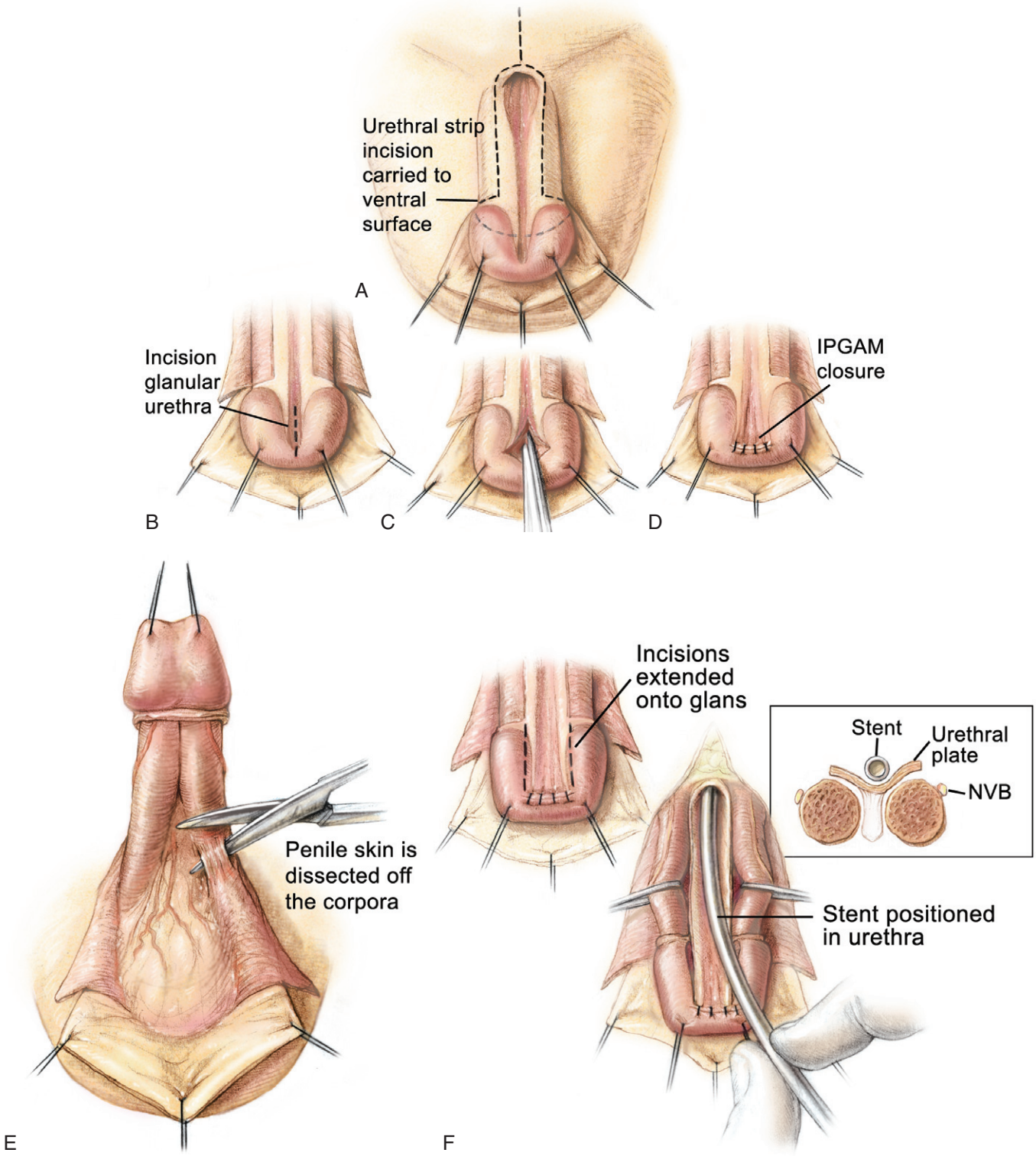


Figure 124–25. Modified Cantwell-Ransley epispadias repair. **A,** Initial incision line extending around the urethral plate and the coronal sulcus. **B** to **D,** Performance of the reversed meatal advancement and glanuloplasty procedure to bring the urethral meatus to the tip of the glans. **E,** Dissection of the foreskin on the ventral aspect of the penis. **F,** The corpora are dissected off the urethral plate, and parallel incisions are made into the glans to create glans wings. Note the lateral position of the neurovascular bundles (NVB) (*inset*).

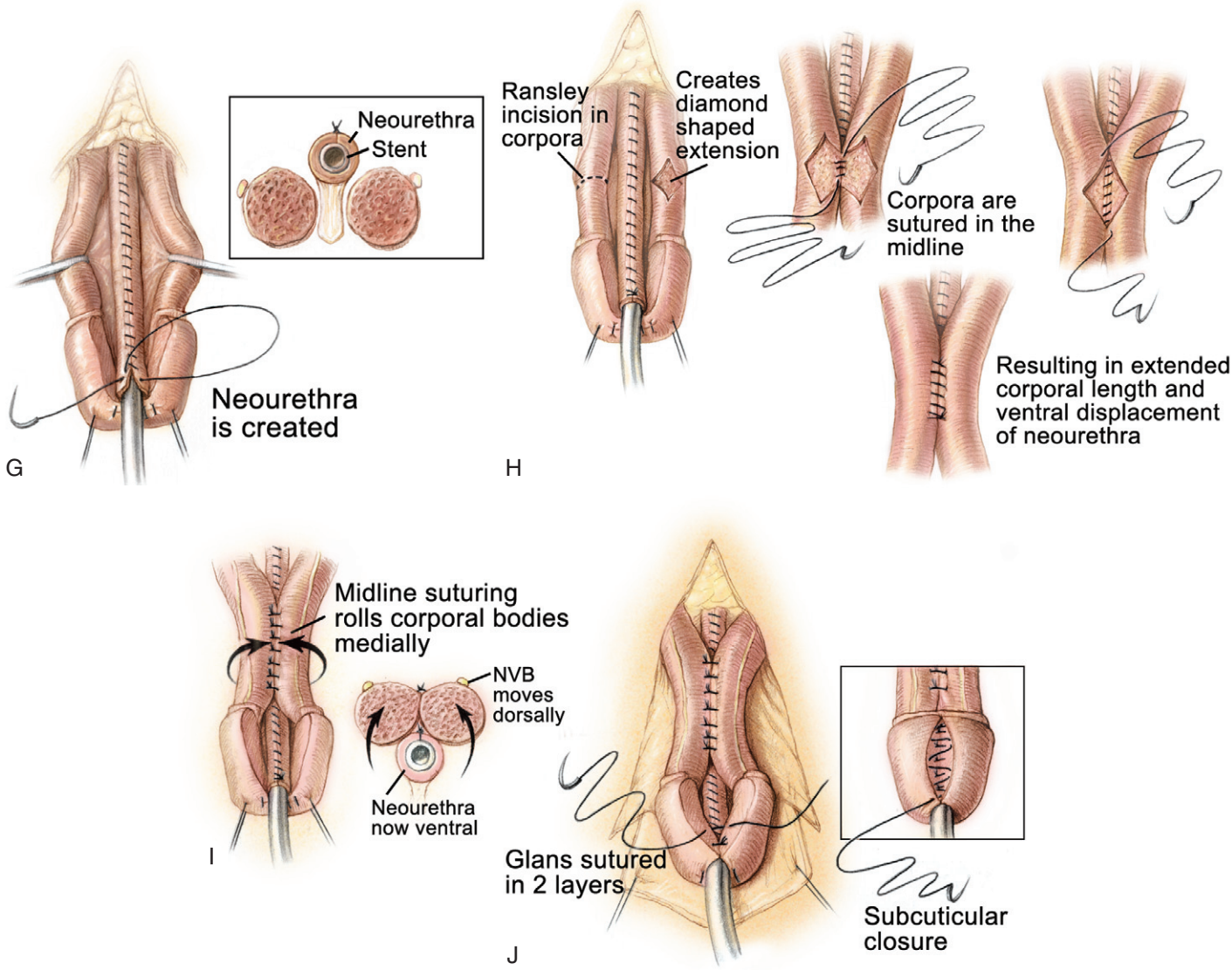


Figure 124–25, cont'd. **G,** The urethra is tubularized using a continuous running suture. **H,** Approximation of the corpora using the incisions in the corpora if indicated. **I,** Corpora approximated above the urethra to provide an anatomically ventral location of the urethra (see inset). **J,** Glans is reconstructed in two layers. *Continued*

the glans over an 8-Fr silicone stent with 6-0 polyglycolic sutures. After this is accomplished, incisions are made in the corporal bodies at the point of maximum curvature, opening a diamond-shaped effect in the erectile tissue (see Fig. 124–25H). The corpora are then closed over the neourethra with two running sutures of 5-0 polydiaxone, and the diamond-shaped defects in the adjacent area of the corpora are sutured to each other. This procedure effectively displaces the urethra ventrally in a normal position. This not only causes the downward deflection of the penis but also allows some additional length by dorsal rotation and approximation of the corporal bodies over the neourethra. After the urethra has been transferred to the ventrum, further sutures of 4-0 polyglycolic acid are placed between the corporal bodies to bury the urethra further, especially at the level of the junction of the glans and the corporal bodies at the corona (see Fig. 124–25I).

The glans wings are then closed over the glanular urethra using subcuticular sutures of 5-0 polyglycolic acid, and the glans epithelium is closed with 6-0 polyglycolic acid sutures (see Fig. 124–25I). The ventral skin is then brought up and sutured to the ventral edge of the corona, and the flaps are fashioned to provide adequate coverage and lengthening of the dorsum of the penis. The skin is reapproximated with interrupted 5-0 or 6-0 polyglycolic sutures (see Fig. 124–25K to M). A Z-plasty at the base of the penis is closed with interrupted 5-0 or 6-0 polyglycolic acid sutures. A silicone stent is left indwelling in the neourethra to provide drainage for 10 to 12 days (see Fig. 124–25N).

Postoperative Problems

Postoperative pain and bladder spasms after extensive external genital reconstructive surgery require a combined effort of the pediatric anesthesia pain service and the surgical service. Controlling bladder spasms is paramount because they are associated with urinary extravasation and fistula formation. All of our patients have a caudal epidural catheter placed at the time of surgery to help with postoperative pain control and bladder spasms. In addition, oxybutynin is started immediately after surgery to decrease the incidence of bladder spasms and enhance the patient's comfort. At the time of discharge, the plastic dressing on the penis is left intact and the child is discharged with narcotics, antispasmodics, and appropriate broad-spectrum antibiotic coverage.

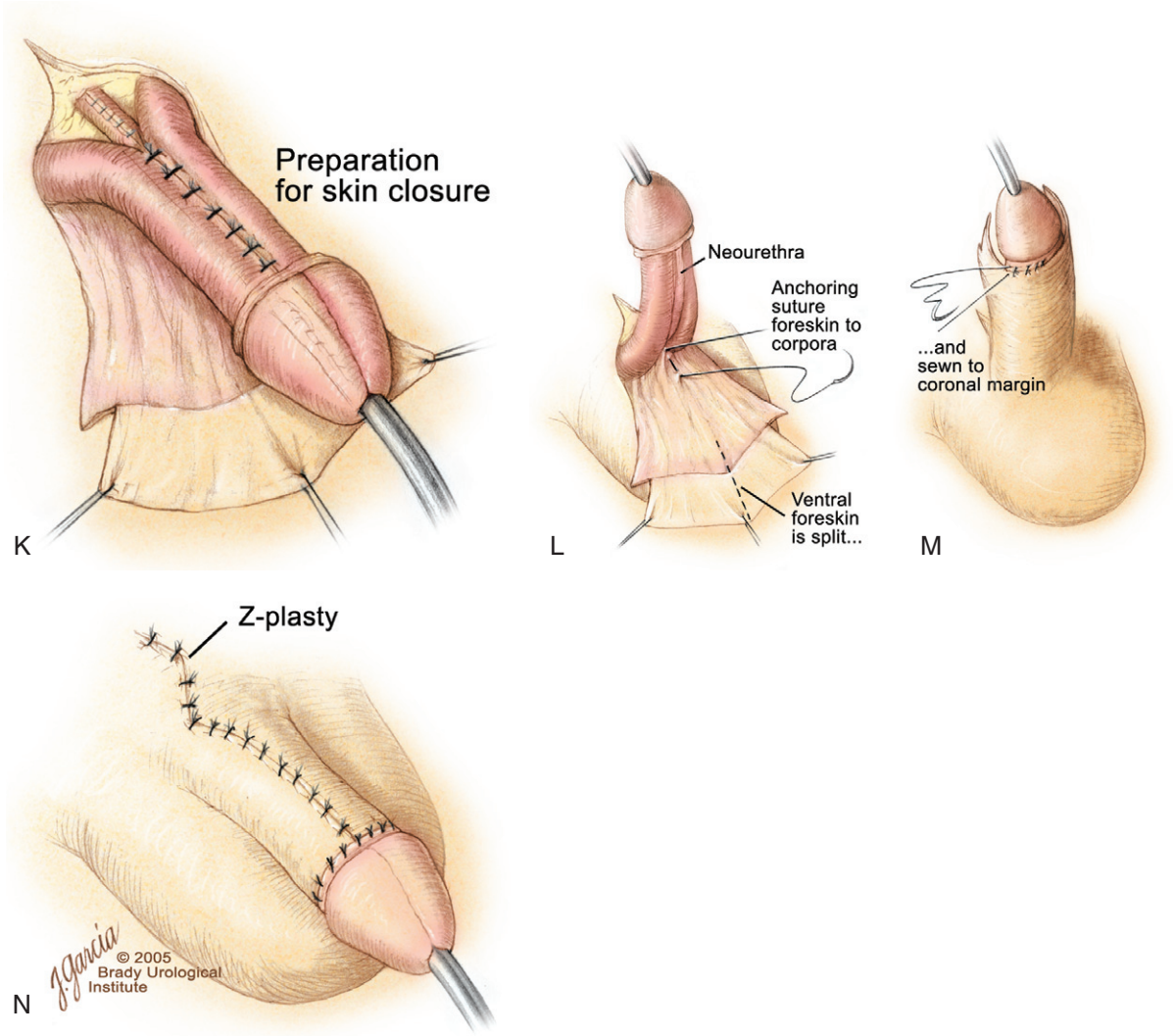


Figure 124–25, cont'd. **K,** Preparation for skin closure. **L,** Suture is placed at the base of the penis to locate the foreskin on the shaft of the penis, as well as to provide an area of distinction between the penis and the scrotum. **M,** Foreskin is sewn to the coronal sulcus. **N,** Completion of the repair with resurfacing of the penis and use of a proximal Z-plasty incision to provide downward penile deflection. (© Brady Urological Institute.)

Penile Disassembly Epispadias Repair

This technique of epispadias repair was developed by Mitchell and Bagli (1996). It has now been incorporated in the CPRE exstrophy repair for primary closure in the newborn. The authors feel this approach better recapitulates the anatomy of the penis and allows better placement of the bladder/urethra into the pelvis.

The penis is dissected into three components—the right and left corpora with their associated hemiglans and the urethral wedge (urethral plate with its associated spongiosa) (see Fig 124–23). The dissection as in the Cantwell-Ransley repair begins on the ventral aspect of the penis. The dissection moves medially just above Buck fascia but is taken down to the tunica albuginea of the corpora. Care is taken to preserve the spongiosum with the urethral wedge, and this dissection is carried posteriorly to the area of the bladder neck. The penis is then separated into the three previously mentioned components. Several authors have found problems getting the reconstructed urethra back to the tip of the glans and have recommended interrupted suturing of the urethral plate or leaving the most distal part of the urethral plate attached to the glans as in the Cantwell-Ransley repair. Others have found the need to make the patients hypospadiac and then perform a later hypospadias repair due to a shortened urethral plate. The rate of hypospadias created has been reported to be from 30% to 70% of cases. If the urethra can be brought up to each hemiglans, an orthotopic meatus is configured. The glans is brought together using interrupted mattress sutures of PDS followed by horizontal mattress sutures of 7-0 nonfilament sutures to bring the glanular epithelium together. The urethra is matured to the glans with interrupted sutures of 7-0 braided polygalactin sutures. The corpora are then brought over the reconstructed urethra with interrupted sutures. Skin closure is similar to that of standard hypospadiac with fine absorbable sutures. If concomitant exstrophy closure is to be done, the dissection then moves proximally into the pelvis to be able to move the structures into the pelvis (see section on CPRE repair).

Female Exstrophy

The principles of repair of both female and male exstrophy are similar. However, in the female the authors recommend the following: (1) radical dissection of the bladder and urethra from surrounding structure; (2) dissection of the lateral aspects of the

posterior vesicourethral and vaginal unit from their attachments to the pelvic floor; (3) tension-free closure of the abdomen, bladder/urethra, and external genitalia; and (4) judicious use of osteotomy and proper immobilization of the pelvis and extremities.

As in the male, if the pelvic bones are separated more than 4 cm or are not malleable under anesthesia, an osteotomy is then performed. The transverse innominate osteotomy along with vertical iliac osteotomy is commonly used in our practice. Intrafragmentary pins are placed, and the fixator is applied after the soft tissue surgery has been completed. An interesting finding in more than 928 exstrophies in the authors' database is that even with a large bladder template the diastasis tends to be narrower than in males. Thus female exstrophy patients are easier to close and do not require an osteotomy as commonly as males.

The vagina is prepped with an iodine prep so that if it is violated during the dissection, it can simply be closed. In the closure, the authors start their dissection along the medial aspect of the clitoral/corporal halves and move deeply into the pelvis. Pinpoint electrocautery at a low setting is used to limit both bleeding and tissue injury. The dissection of the vagina proceeds laterally and posteriorly. The urethrovaginal septum is left intact to preserve its blood supply. As in the male, the dissection proceeds posterior and downward until the levator hiatus is reached with the urogenital diaphragm fibers lateral and posterior to the vesicourethral plate and vaginal incision. This maneuver allows placement of the unit deeply into the pelvis, and more importantly it keeps it from being displaced anteriorly when the pelvic bones are brought together.

The bladder is closed with a single figure-of-eight layer of 3-0 polygalactin suture to maximize postclosure bladder volume. The urethra is closed with a single layer of 4-0 to 5-0 polygalactin depending on the thickness of the tissue. An indwelling suprapubic tube is brought out through the dome of the bladder along with two small feeding tubes, which act as stents and are left in place for 4 full weeks and exit the neoumbilicus. No tubes are brought out through the neourethra because this can be associated with wound infection and prolapse or dehiscence. A No. 2 nylon suture in a horizontal mattress fashion is used to bring the pubic bones into apposition. Once the pubic bones are brought together, a routine subcutaneous and skin closure is performed. A mons plasty is then performed, and the subcutaneous tissues of the clitorides are brought together with 5-0 polygalactin and the epithelium with 6-0 polygalactin sutures. If needed, a Y-V labioplasty is performed for better exteriorization of the vaginal introitus.

If an osteotomy has been performed, the external fixator is then placed and a pelvic radiograph obtained. If pin and fixator placement are optimal, then the infant is placed in modified Buck traction for 4 weeks. If an osteotomy was not performed, the infant is placed in Bryant traction for 4 weeks. Postoperative care is the same as in the male with excellent pain control delivered by an indwelling epidural catheter and bladder spasms controlled by both the epidural and oral oxybutinin.

Continence and Antireflux Procedure

Although some modern exstrophy repairs claim to establish suitable continence without formal bladder neck repair, many patients are referred to our unit still incontinent after only prior newborn repair or after newborn repair and multiple injections of various substances into the bladder neck area. Likewise, other groups have reported their outcomes with newborn repair and most recommended some sort of outlet procedure. In our unit each child has a cystoscopy and gravity cystogram under anesthesia yearly after newborn closure to assess bladder growth. Prior data by Gearhart and Jeffs (1989b) have shown that after newborn exstrophy closure there should be an average increase in bladder capacity by 54 mL in 24 months. Recently, Purves and colleagues (2009b) found that, in selected exstrophy patients who underwent closure, epispadias repair, and bladder neck reconstruction at the authors' institution, a median bladder capacity of 100 mL was more common in the group that was completely dry after bladder neck reconstruction. Most of these children were 4 to 5 years of age and were ready emotionally, maturationally, and intellectually to participate in a postoperative voiding program. Continence and antireflux procedures performed at the authors' institution are illustrated in Figure 124–26. The bladder is open through a transverse incision at the bladder neck with a vertical extension. The later midline closure of this incision is the width of the bladder neck and enlarges the vertical dimension of the bladder, which in exstrophy is often short (see Fig. 124–26A). A Cohen transtrigonal ureteral reimplantation or a cephalotrigonal reimplantation is performed to move the ureter across the bladder, above the trigone, or to direct the ureter cephalad up onto the edge of the trigone (see Fig. 124–26B and C) (Canning et al, 1992). In addition, if the ureters are low on the trigone, there is a need to move the ureteral hiatus higher on the trigone. The hiatus is simply cut in a cephalad direction, and cross-trigonal reimplants are performed at the upper aspect of the trigone (see Fig. 124–26C).

The continence procedure is begun by selecting a posterior strip of mucosa 15 to 18 mm wide and 30 mm long that extends distally from the midtrigone to the prostate or posterior urethra (see Fig. 124–26D). Bladder muscle lateral to the mucosal strip is denuded from the mucosa. It is often helpful at this juncture to use one or two epinephrine-soaked sponges to aid in the control of bleeding and the visualization of the denuded area. Tailoring of the denuded lateral muscle triangles is aided by multiple small incisions on the free edge bilaterally that allow the area of the reconstruction to assume a more cephalad position (see Fig. 124–26E). **These muscle flaps are not only smaller but also not incised transversely at their cephalad extent as described in the original Young-Dees procedure. The authors believe that, if these flaps are incised medially at the cephalad border only where they join the floor of the bladder, there is a significant risk of denervation and ischemia that will harm the bladder neck repair. The basic premise is to create a mucosa-lined tube inside a muscular funnel that narrows from its junction with the floor of the bladder that extends caudally.** The edges of the mucosa and underlying muscle are closed with interrupted sutures of 4-0 polyglycolic acid (see Fig. 124–26F). The adjacent denuded muscle flaps are overlapped and sutured firmly in place with a 3-0 polydiaxone suture to provide reinforcement of the bladder neck and urethral reconstruction (see Fig. 124–26G to I). An 8-Fr urethral stent may be used as a guide during urethral reconstruction, but it is removed after the bladder neck reconstruction is completed. After the bladder neck repair is completed, the repair is suspended to the rectus fascia (see Fig. 124–26J; see inset).

Very radical dissection of the bladder, bladder neck, and posterior urethra is required, not only within the pelvis but also from the posterior aspect of the pubic bar to provide enough mobility for the bladder neck reconstruction. This maneuver allows adequate bladder neck narrowing and tightening of the bladder neck repair and subsequent anterior suspension of the newly created posterior urethra and

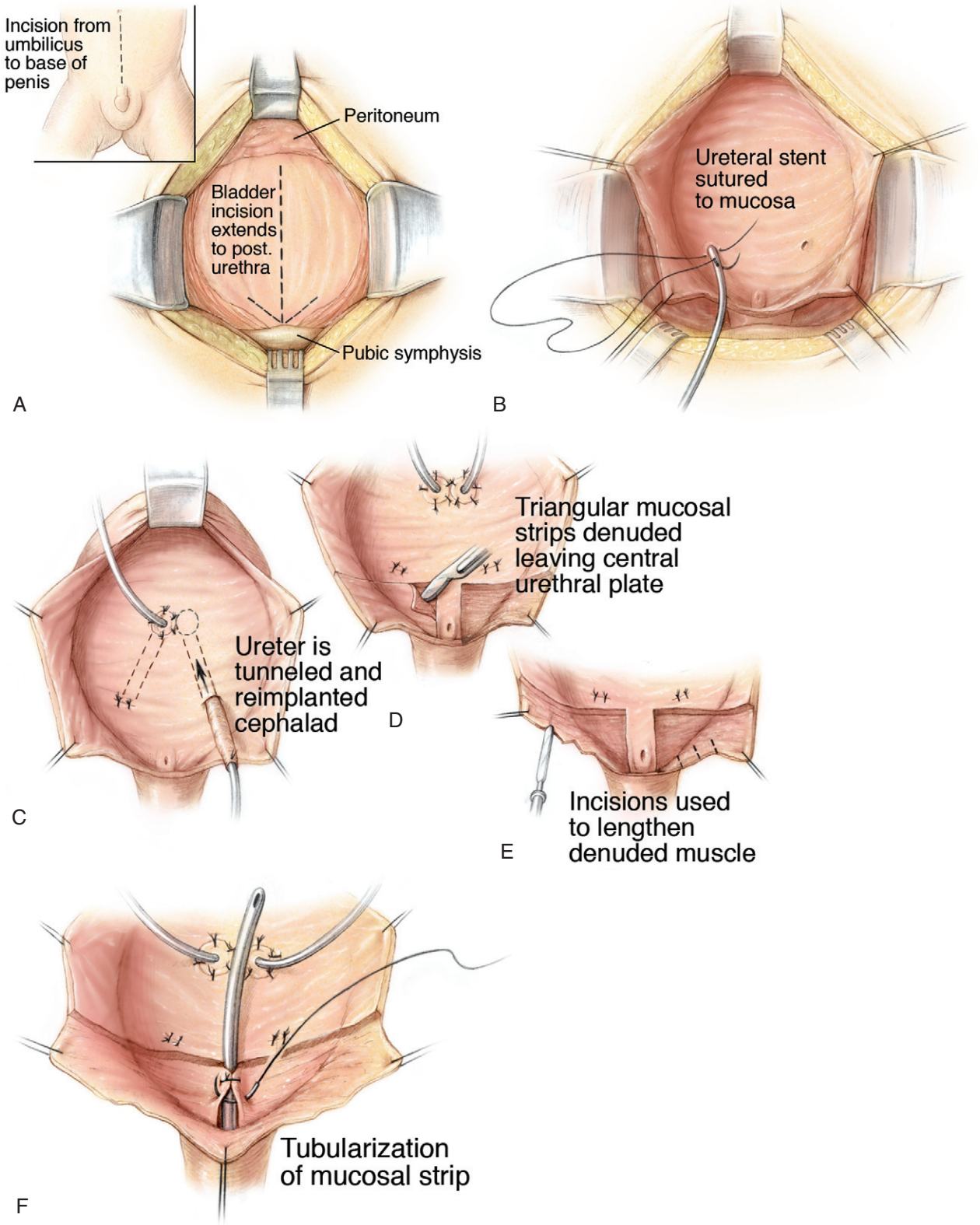


Figure 124–26. Modified Young-Dees-Leadbetter bladder neck reconstruction. **A,** Vertical bladder incision with distal transverse extension where the bladder and posterior urethra are under the pubic bar. **B** and **C,** Ureters are identified, mobilized, and reimplanted in a cephalotrigonal position. **D** and **E,** Segments of mucosa are excised from either side of a median strip (1.5 cm × 3 cm) that will form the neourethra. Short incisions in the muscle will permit extension of the bladder neck. **F,** Urethra is tubularized using a continuous running suture.

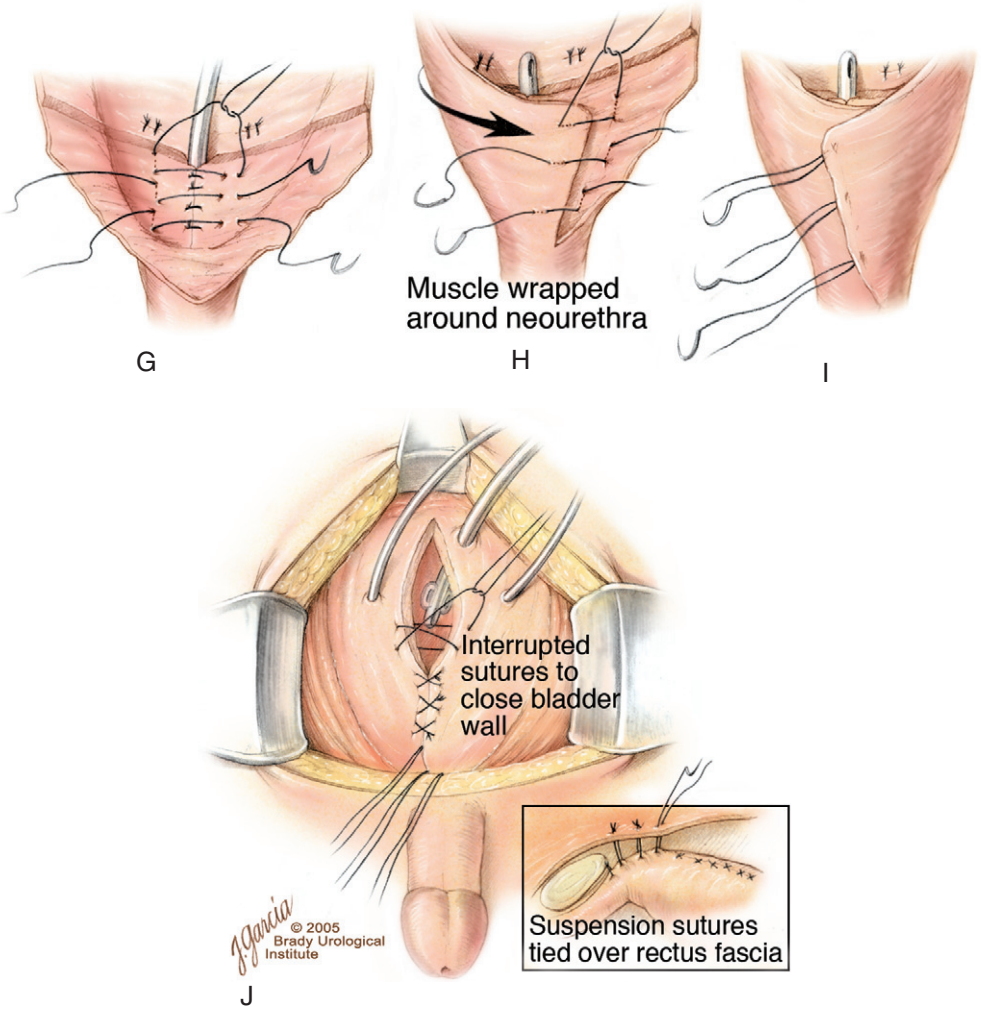


Figure 124–26, cont'd. **G,** Posterior urethra and bladder neck are reconstructed. **H** and **I,** Bladder muscle is brought together in a double-breasted fashion over the neourethra. **J,** Bladder closure is completed, and the distal suspensory sutures are tied over the abdominal wall (see inset). Suprapubic tube and stents are left in place; however, the urethra is left unstented. (© Brady Urological Institute.)

bladder neck. In patients who present after CPRE repair in the newborn period and who had a vesicocutaneous fistula after closure, great care must be taken anteriorly during mobilization of the bladder neck because the tissues are more adherent to the back of the intrasymphyseal bar than in those who underwent bladder neck tailoring as typically seen in that repair. If visualization of the posterior urethra is problematic, the intrasymphyseal bar can be cut, thus providing a widened field of exposure. The intrasymphyseal bar is approximated with 2-0 sutures of polydioxanone. If the intrasymphyseal bar is cut, mobility of the child should be restricted in the postoperative period to allow proper healing of the intrasymphyseal bar.

Postoperative Care

Ureteral stents are placed in the reimplanted ureters and brought out through the wall of the bladder, and the bladder is drained by suprapubic tube, which is left indwelling for a 3-week period. **At the end of 3 weeks the suprapubic tube is clamped, and the patient is allowed to attempt to void. Initially, the tube should not be clamped for more than 1 hour. If voiding does not occur, the child is given an anesthetic and an 8-Fr Foley catheter is placed.** This is left in place for 5 days and removed, and then another voiding trial is begun. This part of the postoperative period is most demanding on the patient, family, and surgeon. Some children require several catheter placements before voiding is initiated. If the child can empty the bladder satisfactorily, the suprapubic tube is removed. Frequent bladder and renal ultrasound examinations are required in the first few months after bladder neck repair.

MODERN INITIAL REPAIR OF BLADDER EXSTROPHY: OUTCOMES AND RESULTS

The use of functional reconstruction in bladder exstrophy has resulted in dramatic improvement in the success of reconstruction. Several recent series (Purves et al, 2008, 2009b; Grady and Mitchell, 1999) have demonstrated the success and applicability of early newborn closure with or without pelvic osteotomy to bladder exstrophy. Other important but older series have shown acceptable continence rates with preservation of renal function in a majority of patients treated in early life (Table 124-1).

Two of the most reliable predictors of eventual urinary continence are the size of the bladder template at birth and a successful primary closure. Regardless of the technique used, a complication-free newborn closure of the abdomen, pelvis, bladder, and proximal/complete urethra paves the way for an optimal

Table 124–1.

Urinary Continence after Functional Bladder Closure

SERIES	NO. OF CLOSURES EVALUATED	PATIENTS CONTINENT
Perlmutter et al (1991)	15	77%
Mollard et al (1994)	73	69%
McMahon et al (1996)	33	70%
Lottmann et al (1998)	57	67%
Purves et al (2008)	67	70%

long-term result. A large series by Surer and colleagues (2001b) has demonstrated in a large group of exstrophy patients who underwent early closure with importance of a successful primary closure. Sixty-eight patients (57 males and 11 females) were referred for bladder neck reconstruction after primary closure at many other centers. Twenty percent had concomitant pelvic osteotomy at the time of closure. The majority of patients were closed within the first 72 hours of life. Mean capacity at the time of bladder neck repair was 121 mL. Eighty-three percent are continent and voiding per urethra. This application of early successful closure and follow-up reconstruction by a second surgeon shows convincingly that a successful primary closure is one of the most important determinants of eventual bladder capacity and compliance regardless of who originally performed the repair.

Initial Closure

Long-term data on all modern types of exstrophy repair can be difficult to obtain. Nonetheless, this section deals with what has been gleaned from the recent literature. Most data come from the MSRE and CPRE groups. In a large series reported by Purves and colleagues (2008), 189 patients who had undergone primary closure between 1988 and 2004 were extracted. The records of 131 patients (95 males) who underwent MSRE with a modified Cantwell-Ransley repair by a single surgeon in 1988-2004 were reviewed with a minimum of 5-year follow-up. Complications from bladder closure and additional procedures to correct these complications are presented in Table 124–2. The importance of a successful initial closure is emphasized by Oesterling and Jeffs (1987) and Husmann and colleagues (1989), who found that the onset of continence was quicker and the continence rate higher in those who underwent a successful primary closure with or without osteotomy. In addition, Novak and colleagues (2010) reported on patients with bladder exstrophy who underwent more than one attempt at primary closure. If a patient underwent two closures, the chance of having an adequate bladder capacity for bladder neck repair was 60% and the chance of voided continence was 17% overall. Patients who underwent three closures had only a 50% chance of an adequate capacity and less than 16% chance of voided continence. In an evaluation of this select group it was found that at the time of primary closure, 80% of patients had no form of pelvic osteotomy. Thus the chance of obtaining an adequate bladder capacity and eventual continence after more than one exstrophy closure is markedly diminished. These poor results underline the paramount importance of a secure abdominal, bony pelvis, and posterior vesicourethral unit with or without epispadias repair in the newborn exstrophy.

Also, compared with many of the other repairs, data are available from several units on their results with the CPRE repair. In a recent series by Shnorhavorian and coworkers (2008) there were

Table 124–2.

Urologic/Orthopedic/Neurologic Complications in 185 Primary Bladder Closures

UROLOGIC COMPLICATIONS	NO. OF PATIENTS
Bladder prolapse/dehiscence	6
Post-outlet obstruction	4
Suprapubic tube removal	2
Intrapubic stitch erosion	4
Febrile urinary tract infection	6
Wound infection	3
Bladder calculi	5
Orthopedic Complications	
Nonunion osteotomy	2
Leg length inequity	1
Persistent joint pain	1
Pelvic osteomyelitis	1
Pinsite infection	3
Pressure sore	1
Neurologic Complications	
Femoral nerve palsy	4

2 instances of dehiscence of the fascia, and 9 of 37 developed a vesicocutaneous fistula. Complications seen in the CPRE repair are much as those seen in the MSRE. However, some that are particular to this repair have been seen. A large series of vesicocutaneous fistula was reported from a single institutional study, in which some patients had an osteotomy and others did not (Shoukry et al, 2009). In addition, several series have reported the need for early ureteral reimplantation after closure and the occurrence of significant upper tract changes in many patients (Grady and Mitchell, 1999). This has prompted the call for ureteral reimplantation at the time of exstrophy closure by one group (Braga et al, 2008a).

Although most published series are not large, the incidence of bladder prolapse and dehiscence is reported to be small. In a recent series of primary CPRE repairs by Shoukry and colleagues (2009), the incidence of major prolapse and dehiscence was 15.8% even with the use of osteotomy. In this author's series, we have seen a number of referred patients with complete dehiscence and major bladder prolapse after newborn CPRE repair. However, the complicating factors we have seen, along with the previously mentioned factors, have been significant losses of soft tissue including partial or complete loss of the glans in nine patients and the loss of the urethrovaginal septum in two. In a series by Hammouda (2003), 5 of 42 patients had ischemic loss of glans tissue after CPRE repair. Thus the complications of closure between the CPRE and MSRE are similar but more serious if soft tissue loss occurs.

Data from Baka-Jakubiak (2000) and colleagues from Warsaw involved 100 primary closures. Complete dehiscence occurred in 31 patients, of whom 24 had no osteotomy and 7 a posterior iliac osteotomy only. Of those who were closed at less than 72 hours ($n = 47$) and no osteotomy performed, dehiscence occurred in 13 patients. All were immobilized with a modified spica "chair" cast for 3 weeks and then an elastic bandage for 3 weeks. The authors currently recommend osteotomy for all newborns with a diastasis greater than 5 cm and in those closed after 72 hours.

In a recent publication of the Erlangen repair by Rosch and colleagues (1997) of 100 closures, the complications were generally mild with urethrocutaneous fistulae in 2. Minimal hydronephrosis occurred in 20%, and 3% had severe hydronephrosis requiring further surgery. There were no incidents of bladder

prolapse or dehiscence. Osteotomy was not used in any patient, but a sophisticated coaptation technique involving the obturator foramen was used in all patients. In a recent report by Kelly and colleagues (2008) of 26 patients, there was a reported incidence of bladder prolapse requiring treatment in 25%. Soft tissue loss of glanular tissue was noted in 2 of 26 patients.

Interest in the outcomes of exstrophy closure has expanded to interest in the economic outcomes of the treatment of this major birth defect and who should be doing these types of operations in the newborn. In a paper by Nelson and colleagues (2005), high-volume hospitals (those closing more than five exstrophies per year) had lower overall costs per patient than low-volume hospitals (fewer than five exstrophies per year). In addition, Nelson and colleagues (2005) found that successful newborn closure had overall markedly less costly inflation-adjusted hospital charges than reclosures due to shorter operating times and shorter length of stay.

A corollary to these papers was one from Meldrum and colleagues (2005), who found that when exstrophy closures failed and had to be reclosed, the success rates and ultimate continence were better among fellowship-trained pediatric urologists rather than other surgeons (general urologists, non–fellowship-trained pediatric urologists, and general pediatric surgeons).

In the evaluation of this group of selected exstrophy patients, it was found that at the time of initial closure 19 of 23 patients had no form of osteotomy. Six of the patients had obtained bladder capacity suitable for bladder neck reconstruction; three were dry, and three were incontinent. Bladder size was inadequate in nine patients after being monitored for bladder growth. The chance of obtaining an adequate bladder capacity and eventual continence after more than one closure attempt is markedly diminished. These less than satisfactory results underline the paramount importance of a secure abdominal wall, posterior urethra, and bladder closure in these complex cases. Lastly, the importance of early initial closure was emphasized by data from Husmann and colleagues (1989) showing that only 10% of the patients who undergo bladder closure before 1 year of age but 40% of those who have the procedure at a later age require eventual augmentation.

Epispadias Repair

Although urinary incontinence remains the most significant problem for patients with classic bladder exstrophy and epispadias, anxiety about inadequate and unattractive genitalia still poses the greatest concern to male patients. The authors began using the modified Cantwell-Ransley repair in patients with classic exstrophy or epispadias in 1988 and have reported their early experience (Gearhart et al, 1992, 1995c, 2004).

Since 1988, the modified Cantwell-Ransley repair has been performed for 129 male patients with either classic bladder exstrophy (97 patients) or epispadias (32 patients) (Baird et al, 2005b). At the time of surgery, the patients' age ranged from 1 to 18 years with an average age of 19 months. Of the 97 patients with bladder exstrophy, 31 had a short urethral groove requiring paraexstrophy skin flaps for penile lengthening at the time of initial bladder exstrophy closure. Of the 32 epispadiac patients, 26 had penopubic and 6 had penile epispadias at presentation.

This technique was used for primary urethroplasty in 106 patients with bladder exstrophy and 32 with epispadias. The modified Cantwell-Ransley repair was used as a secondary procedure after failed urethroplasty in 15 patients with exstrophy and 8 with epispadias and was combined with reclosure of bladder exstrophy in 18 patients. Early epispadias repair was performed when the patients were 6 months to 1 year of age. However, because of concerns about getting the urethra deeper under the corpora at the glanular level, beginning in 1994 we further modified the Cantwell-Ransley repair by detaching the mucosal plate from the corona except for the distal 0.5 to 1 cm of the plate. Intramuscular testosterone enanthate in oil was given to all children at a dose of 2 mg/kg at approximately 5 weeks and again at 2 weeks before surgery.

One hundred twenty patients had a horizontal or downward-angled penis while standing. The incidence of urethrocutaneous fistula in the immediate postoperative period was 16%, and at 3 months it was 12%. Nine patients developed a urethral stricture of the proximal anastomotic site, and 12 had minor skin separation of the dorsal skin closure. Cystoscopy with catheterization in 120 patients revealed an easily negotiable channel in all. Eight patients required further penile-straightening surgery. Fifteen patients older than 16 years had engaged in satisfactory intercourse, and all reported orgasms and ejaculation with a straight penis on erection. One patient reported that his penis was shorter following surgery.

Modern penile reconstructive techniques should create a straight and functional penis with a glanular meatus, an easily catheterizable neourethral channel (if needed), and an acceptable cosmetic appearance. Many adolescents considered their odd-appearing genitalia with a short, widened penis that deviated upward to be a greater psychosocial problem than incontinence, and therefore every effort should be made to restore the penis to a normal condition. In 1989, Ransley and colleagues introduced a concept to release dorsal chordee by incision and anastomosis of the dorsomedial aspect of the corpora over the urethra and urethral meatotomy at the distal end of the glans, to move the meatus to a more normal position and secure good direction of the urinary stream (IPGAM). Ransley's group reported their long-term experience with 95 patients in whom the modified Cantwell-Ransley repair was used: Fistula occurred in only 4% of patients, and a urethral stricture in only 5% (Kajbafzadeh et al, 1995).

Dissection of the urethral strip to inside the glans penis provides a ventral position of the urethra and the glans and submerges the urethra well below the corpora at the glans level. This approximation of raw surface of glanular tissues dorsally over the urethra is clearly why the incidence of fistula in the area of the corona is rare compared with the Young repair. Fistulae in the authors' patients usually appear at the base of the penis, where the urethra comes up proximally between the corporal bodies. In modern exstrophy reconstructive techniques, most surgeons try to preserve the urethral plate at the time of exstrophy closure. Interestingly, the authors do not find a significant difference for fistula formation between those in whom paraexstrophy skin flaps were used at the time of initial closure and those in whom they were not. Despite the positive findings with regard to fistula formation, the use of paraexstrophy skin flaps has been noted to be associated with the development of strictures. Use of these flaps is therefore limited to selected patients in whom penile lengthening cannot be achieved with standard techniques.

Papers from several institutions have reported their results with the Mitchell-Bagli penile disassembly technique. Complications are similar to other methods of epispadias repair (i.e., fistula and urethral stricture) (Zaontz et al, 1998; Kibar et al, 2009a). Although not a complication, a high percentage is made hypospadiac as the completely dissected urethral plate fails to reach the tip of the glans. The rate of being made hypospadiac has been reported from 38% to 83% (Mitchell and Bagli, 1996; El-Sherbiny and Hafez, 2005). As mentioned in the section on exstrophy closure, reports

of ischemic loss of the glans, urethral plate, and corpora have been reported by Hammouda (2003) and Husmann and Gearhart (2004). Repair of the hypospadias in these patients has been reported by the Seattle group as not difficult or associated with major complications. However, data from Hafez and colleagues (2005) and Gearhart and Baird (2005) show difficulties that can be associated with these repairs. In an attempt to deal with the issues and prevent them, El-Sherbiny and Hafez (2005) have modified the Mitchell repair as with the modified Cantwell-Ransley repair (Gearhart and Baird, 2005) to keep the urethral plate attached to the distal glans to obviate the need for making the child hypospadiac at the time of isolated epispadias repair or when associated with CPRE.

In the authors' opinion, none of the current epispadias repairs offers any significant gain in penile length by removal of the entire urethral plate from the glans or even the use of a free graft. Data reported by Silver and colleagues (1997b) clearly showed that, although anterior corporal length is significantly less in patients with exstrophy, the posterior corporal length is normal. These findings suggest that penile lengthening procedures at the time of epispadias repair improve apparent penile length and straighten the penis but do not transfer additional tissue (i.e., length) to the corporal bodies. The authors have observed that the modified Cantwell-Ransley repair effectively corrects corporal chordee and adds some penile length. It can be hoped that dorsal penile curvature, which is often seen during the growth spurt at puberty, will be resisted. After significant experience with adolescent exstrophy males with significant dorsal chordee, the authors agree that movement of the neurovascular bundles along with incision and grafting of the resultant defect gives better results long term than incision and corpora cavernostomy. In the patients in whom corporal rotation is used without corporal incision and anastomosis, the neurovascular bundle is left intact and not dissected from its bed. However, if incision and anastomosis are necessary, mobilization of the neurovascular bundle is required. Typically in the authors' experience, incision and rotation are used only for older patients with marked chordee. Although review of findings reveals that almost all penises are straight or deflected downward, many of these patients are still young children. The long-term assessment of penile and urethral reconstruction in exstrophy patients by the modified Cantwell-Ransley repair has shown that in patients with bladder exstrophy and epispadias there is some increase in penile length, and a relatively straight penis with an adequate urethral caliber, which is adequate to void and ejaculate through, can be achieved with minimal morbidity. Long-term reports with the penile disassembly technique have also demonstrated a reasonably straight penis (Grady et al, 2003).

Bladder Neck Repair

Bladder neck reconstruction results in the exstrophy population have been reported by several groups. Some large experiences have come from the European groups in Lyon and Paris. Mouriquand and colleagues (2003) reported on 80 children with bladder exstrophy and 25 with incontinent epispadias. Follow-up ranged from 1 to 11 years. Forty-five percent of the group with exstrophy and 52% of those with epispadias had a dry interval greater than 3 hours. Although the continence rate was low, many of the exstrophy patients were not closed until 6 to 12 months of age. Also, many had their epispadias repair after bladder neck reconstruction, a factor known to influence both eventual capacity and continence. Lottmann and colleagues (1998) presented a long-term follow-up study of Cendron's exstrophy patients who underwent complete reconstruction. With the Young-Dees repair they achieved urinary continence in 71% of male patients and 53% of females. Overall continence was 65% with a mean follow-up of 12 years after bladder neck repair. Series from North America using mainly the classic Young-Dees-Leadbetter repair reported continence rates ranging from 60% to 82% (Husmann et al, 1989; Mergurian et al, 1991; Perlmutter et al, 1991; Franco et al, 1994; McMahon et al, 1996; Chan et al, 2001; Cole et al, 2003) (see Fig. 124–2). **The most important long-term factor gleaned from a review of all these series is the fact that bladder capacity at the time of bladder neck reconstruction is an important determinant of eventual success.**

Records of 95 patients who underwent all stages of MSRE by a single surgeon at our institution between 1988 and 2004 were reviewed by Purves and colleagues (2008). Sixty-seven patients with bladder neck reconstruction and minimum 5-year follow-up were available for analysis. The current voiding status of each patient was obtained from parental or patient interview or direct observation by the nursing and physician staff. The patients were categorized as spontaneous voiding not on intermittent catheterization and were assigned a status of (1) completely dry day and night; (2) socially continent, being dry at least 3 hours during the day with occasional wet nights; or (3) wet being dry for less than 3 hours during the day and wet at night (Table 124–3).

Of the 67 male patients who underwent bladder neck repair, the mean age for primary closure was 4 months (range 6 hours to 4 months). The mean age at bladder neck repair was 4.8 years (range 40 to 60 months), and these patients had a mean bladder capacity before repair of 98 mL (range 75 to 185 mL). Of the 67 patients, 47 (70%) are continent and voiding urethrally without the need for augmentation or intermittent catheterization. Seven patients (10%) had social continence with occasional wet nights. The renal units of all patients who underwent bladder neck repair were evaluated by intravenous pyelography or ultrasound postoperatively on multiple occasions to assess preservation of renal function after the outlet procedure. One patient had reflux and hydronephrosis after the outlet procedure and bilateral reimplantation and developed left pyelonephritis with resultant mild scarring. DMSA revealed nearly normal bilateral function. Conservative follow-up revealed resolution of the reflux with time. One patient developed ureteral obstruction and required reoperative reimplantation. Prolonged outlet obstruction required cystoscopy and placement of an 8-Fr catheter in 19 patients, and prolonged suprapubic drainage was required in 13 patients. Thirteen (19%) failed bladder neck repair completely, six underwent continent diversion, and seven awaited further surgery. The mean time to daytime continence was 14 months (range 4 to 23 months), and the mean time to nighttime dryness was 23 months (range 11 to 34 months).

Table 124–3.

Urinary Continence after 67 Initial Bladder Neck Reconstructions

RESULT	AVERAGE DRY INTERVAL	NO. OF PATIENTS	% OF PATIENTS
Continent	3 hr	47	70%
Social continence (dry daytime, occasional wet nights)	3 hr	7	10%
Wet	<3 hr	13	19%

No correlation was found between age at bladder neck reconstruction and age at achieving continence.

The findings in this series were that continence was more likely in patients who underwent primary exstrophy closure before 72 hours of age or after 72 hours of age with an osteotomy. These results coincide with those of Husmann and colleagues (1989) who found that patients who underwent delayed closure without osteotomy showed a continence rate of only 10%. There was another revealing factor in this study. Bladder capacity at the time of bladder neck repair gave a strong indication of not only who would be dry but also who would be dry sooner. If the patients were divided into those with a preoperative bladder capacity greater than or less than 100 mL, results showed that the group with the larger capacity had a high rate of continence (42/50 dry and voiding versus 5/17 in the lower-capacity group). In addition, the mean time to dryness in the higher- and lower-capacity group was 10 months and 21 months, respectively (14 months in the group overall).

In a similar series by Purves and Gearhart (2008), the results in females mirrored those of the male group with a slightly higher continence rate of 74% (dry day and night) and social continence again in 10%. Again, patients with capacity greater than 100 mL had better outcomes. In a phenomenon not seen in the males, six patients (20%) became continent after bladder and pelvic closure alone.

A continence procedure should be delayed until the bladder reaches a capacity of 100 mL, and the child is motivated to be dry and participate in a postoperative voiding program. The onset of continence is an interesting phenomenon in these patients. The vast majority achieve daytime dryness within 12 months after bladder neck repair. A few patients gain a longer daytime dry interval during the second year after their outlet procedure. However, patients who are not dry within 2 years are considered incontinent and failures. The onset of nighttime continence varies but takes longer than the time needed for daytime continence and can be 2 to 3 years. Caione and colleagues (1999) showed that use of desmopressin acetate (DDAVP) can increase the onset and number of dry nights in these patients. In the series by Purves and Gearhart (2008), 25% of patients required either DDAVP or oxybutynin to establish nighttime dryness.

Urodynamic evaluation by Dave and colleagues (2001) showed that patients with good continence after bladder neck repair had high cystometric bladder capacity and compliance compared with those who were incontinent. However, unstable contractions were seen in both groups. Also, higher-end filling pressures were reported and those patients had a high incidence of nonobstructive hydronephrosis. These findings in addition to those of Bolduc and colleagues (2002) indicate that careful lifelong follow-up is essential in these patients after successful childhood reconstruction.

OTHER MODERN EXSTROPHY REPAIRS: CONTINENCE OUTCOMES

Warsaw Approach

The long-term reported outcomes of this repair include 36 patients with classic exstrophy and 37 with epispadias. Eighty-nine percent of patients with epispadias were continent during the day, but more than 40% were still wet at night. Seventy-five percent of patients with classic exstrophy had daytime continence, but nine had occasional wet nights. Eleven boys required short-term intermittent catheterization, which was easily performed by the patient and family. All but two began voiding within 3 to 5 months, and only two have continued with intermittent catheterization. Complications in seven boys included two urethrocutaneous fistulas and five urethral strictures (Baka-Jakubiak, 2000). All of these responded to urethral dilatation or endoscopic incision. There were no instances of abdominal wall dehiscence or glanular or corporal loss. Ureteral reimplantation was not performed at the time of bladder neck reconstruction and epispadias repair, but many patients required later reimplantation for gradually worsening hydronephrosis.

Compared with this experience, Mathews and Gearhart (2003) reported on a group of patients who had ureteral reimplantation performed at the time of bladder neck reconstruction and epispadias repair. None of these patients developed reflux or worsening hydronephrosis. Baka-Jakubiak (2000) recommends performance of this combined procedure if the bladder capacity is documented to be above 100 mL and the penis is large enough for epispadias repair. Follow-up urodynamic studies demonstrated the presence of normal detrusor function in most, although some patients developed high voiding pressures and some had poor detrusor contractility. If poor detrusor contractility was noted, prolonged intermittent catheterization was required and high voiding pressures were managed with anticholinergic therapy. Most patients were managed later in life, and the standard addition of ureteral reimplantation at the time of reconstruction should probably be universally performed.

Erlangen Approach

In a recent review by Ebert and colleagues (2010), who have reported on 100 patients, using this technique has occurred in both newborns and failed closures. Ninety-one children with exstrophy (69 boys and 22 girls) and nine with complete epispadias (7 boys and 2 girls) have had this procedure performed. The complete single-stage repair was performed in 47 children and included pelvic closure without osteotomy, bladder neck reconstruction, an antireflux procedure, and epispadias repair using the Cantwell-Ransley technique. An additional 53 patients had primary reconstruction elsewhere and then had bladder neck reconstruction and epispadias repair performed. Continence was defined as dryness for more than 3 hours and no nocturnal enuresis. Partial continence was defined as dry for 1 to 3 hours or longer with occasional stress incontinence or wet nights. Patients dry for less than 1 hour were considered incontinent. Among the patients undergoing single-stage repair, 72% (34 of 39) are dry voiding per urethra, 2 on clean intermittent catheterization (CIC), and 3 on CIC following augmentation. Four patients are partially continent, and two are dry on desmopressin. Four patients are incontinent, and three have had continent diversion. Of 53 patients who had primary closure elsewhere, 55% are continent and 7 have been augmented. Fourteen are partially continent and 10 are incontinent, 4 of whom have had continent diversion. The authors have emphasized the superiority of this repair for primary rather than failed closures.

Complete Repair

Various series have been published about outcomes including the need for ureteral reimplantation in the first year of life, the number of patients requiring hypospadias repair after this procedure, and the complication rates of this procedure. However, little has been published about the long-term continence results of the need for bladder neck reconstruction in this group of patients. Borer and

colleagues (2005) reported that ultimately 65% to 70% of patients undergoing CPRE in the newborn period will require a bladder outlet procedure. In an update series, Borer and colleagues (2005) found that four of six patients with long-term follow-up have suitable continence after bladder neck repair. In a large series by Hafez and colleagues (2005), some of whom were delayed or failed primary closures, 84% of males and 50% of females required bladder neck repair to be dry. Some of these require concomitant bladder augmentation to be dry. In another large series by Shoukry and colleagues (2009), none were continent after CPRE alone and most required augmentation to be dry. More importantly, early dry intervals did not translate into later continence.

New data from Shnorhavorian and coworkers (2008) reviewed their total experience with the CPRE repair. This was a total of 39 patients since 1989. Daytime voided continence was achieved in 74% of males and females with 4 years of follow-up. However, only 20% and 43% of boys and girls, respectively, achieved continence without the need for bladder neck repair. Eighteen percent achieved dryness with bladder neck injection only. In a recent series of CPRE patients referred for reclosure or after successful closure for bladder neck reconstruction, the results were interesting (Gearhart et al, 2007). All patients were operated on by an experienced senior surgeon who does not routinely do newborn CPRE repairs. None of the 14 patients who underwent successful CPRE in the newborn period was continent for any appreciable interval after closure. Of the 19 patients who underwent bladder neck reconstruction after complications with their newborn closure, only 25% were voiding from the urethra and continent. In the group with a successful primary closure ($n = 14$), 57% were dry day and night and 28% were dry during the day only (Purves et al, 2009a). Of interest, all patients who were dry after bladder neck reconstruction had a successful primary closure with pelvic osteotomy and hypospadias repair before 1 year of age. None required ureteral reimplantation before bladder neck repair. These data clearly show that in the majority of cases, "complete repair" patients will need to undergo bladder neck repair. However, as in all of the major repairs, in a successful primary closure with fewer bladder violations with interval surgeries, the chance for voided continence, although reasonable, still needs to be improved.

Other methods have combined epispadias repair with bladder exstrophy in the male patient. In a series of 38 boys with classic exstrophy, Baird and colleagues (2005c) evaluated patients with either failed or delayed primary closures. The complications were those seen with routine exstrophy repairs including urethrocutaneous fistula and urethral strictures. Three boys were dry with combined closure alone. Nineteen boys went on to modified Young-Dees-Leadbetter bladder neck repair. During both day and night, 12 of 19 were totally dry. These data, as well as the data of Mitchell and Grady, clearly show that epispadias repair and exstrophy closure can be combined with acceptable results. However, the complications are real and can portend the loss of any chance at volitional voiding and should only be performed by experienced exstrophy surgeons and not the occasional surgeon.

Kelly Repair

There are not many papers with long-term follow-up of the Kelly technique. However, a recent presentation by the Melbourne group gives the best and most current results that can be found with this repair. Data was collected in children older than 4 years. Complete continence was defined as dry for more than 3 hours day and night (with two or fewer wet nights per months). Partial continence was dry for 2 or more hours during the day and three or more wet nights per month and/or stress incontinence. Twenty-four of 31 Kelly patients voided spontaneously, and 17 of 31 voided in an unaided fashion (without IC or augmentation). Overall continence was 71% with 3 of 17 (18%) who voided in an unaided fashion enjoying complete continence, Nine of 17 (53%) had partial continence. The 18% dry and voiding rate compares favorably with that recently reported by Shnorhavorian and colleagues (Jarzebowski et al, 2009).

EXSTROPHY RECONSTRUCTION FAILURES

Failed Closure

After any form of repair, failures can manifest as complete bladder dehiscence, bladder prolapse, neourethral stricture and obstruction, and soft tissue loss. Meldrum and colleagues (2005) reported on a select group of children who failed exstrophy reconstruction before referral to a tertiary care facility. In the cohort of 101 children, 51 had primary surgical management performed by a fellowship-trained pediatric urologist, 18 by a general urologist, 6 by a pediatric surgeon, and 9 by an unknown surgeon. Following successful reclosure, 38 patients eventually developed adequate bladder capacity for bladder neck reconstruction, and only 26% (10) eventually achieved dryness. These data emphasize the need for initial successful reconstruction and suggest that individuals undertaking this reconstruction should be comfortable with the complexity of repair. It is prudent for the surgeon who may see only a few patients with this condition to consider referral of these complex management situations to a center where special expertise and experience exist.

In a recent large series by Schaeffer and colleagues (2008), 185 patients who underwent closure by one of two surgeons were reviewed for both major and minor complications (see Table 124–2). Sixty-three underwent osteotomy at the time of primary closure. There were 14 major complications (11%) and 27 minor complications (14%). Major urologic complications included bladder prolapse or dehiscence in six male patients (3%), all which were successfully reclosed. Major orthopedic complications including nonunion in two patients, leg length inequality in one, and persistent joint pain in one developed in 4 of 63 patients (6%) who underwent osteotomy. Major neurologic complications included femoral nerve palsy in four patients (2%). There were 21 minor urologic complications (11%) including posterior bladder outlet obstruction in four cases, urethrocutaneous fistula in two, suprapubic tube removal in two, intrapubic stitch erosion in four, febrile UTI in six, and surgical site infection in three. Six patients (3%) had minor orthopedic complications including pelvic osteomyelitis in one, pin site infection in three, and a pressure sore from immobilization in one.

Dehiscence, which may be precipitated by incomplete mobilization of the pelvic diaphragm and inadequate pelvic immobilization postoperatively, wound infection, abdominal distention, or urinary tube malfunction, necessitates a 6-month recovery period before a second attempt at closure can be made (Gearhart and Jeffs, 1991a; Gearhart et al, 1993b) (Fig. 124–27A). Dehiscence and prolapse have also been reported following the CPRE and may be associated with glandar, corporal, urethral plate, and other major soft tissue loss (Fig. 124–27B). Tension-free reclosure with osteotomy and immobilization are important factors in initial and subsequent closures. Unfortunately, the chance of obtaining adequate bladder

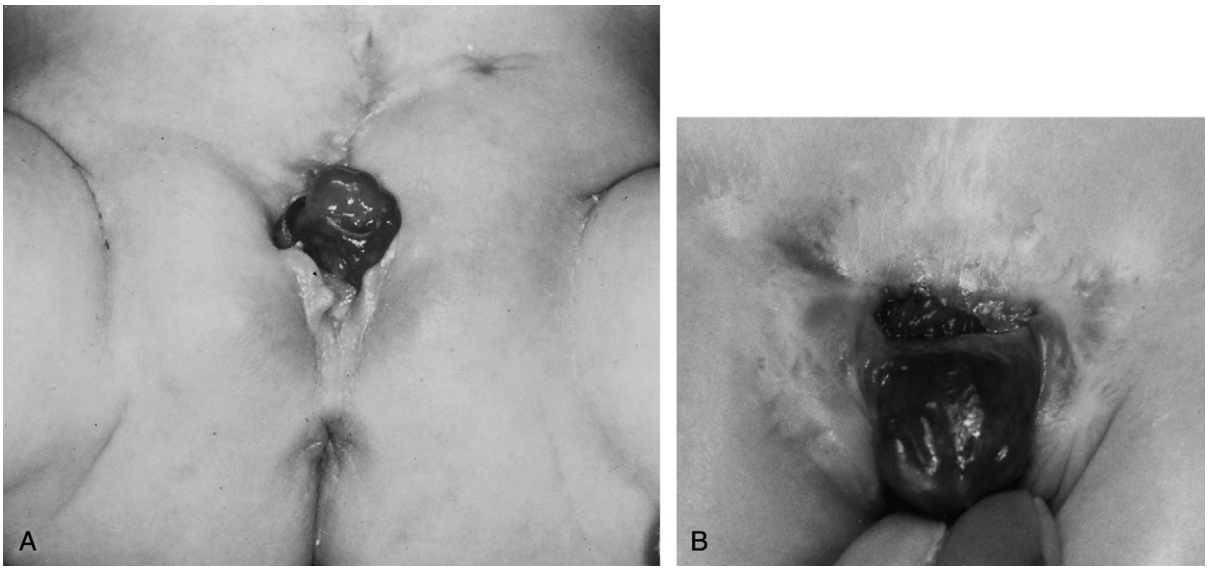


Figure 124–27. **A,** Complete dehiscence of bladder closure in a child who had reconstruction without osteotomy. **B,** Dehiscence of a patient who had bladder closure using the complete reconstruction technique.

capacity for bladder neck plasty and eventual continence after multiple closures is markedly diminished (Gearhart et al, 1996a). Similarly, bladder prolapse is considered a failure and requires bladder reclosure or revision. In a recent series from a single institution of 122 patients who underwent reclosure with a mean follow-up of 14 years, the voided continence rate was 16% (Novak et al, 2010). In a patient with significant bladder prolapse or dehiscence, at the time of secondary closure the authors combine epispadias repair with bladder, posterior urethra, and abdominal wall closure (Gearhart et al, 1998). The patient is given testosterone enanthate intramuscularly 5 weeks and 2 weeks before surgical repair and undergoes an osteotomy with concomitant bladder, urethral, and abdominal wall closure. Major soft tissue loss that is seen following CPRE requires extensive preoperative planning and may require use of buccal mucosal or full-thickness grafts or tissue expansion (Gearhart and Baird, 2005).

Gearhart and Baird (2005) reported on 38 boys undergoing combined exstrophy closure and epispadias repair along with osteotomy, and 30 had failed prior reconstruction. Complications in this group were limited to urethrocutaneous fistulae and urethral strictures. Although the results after reclosure are not as good as those obtained with a successful primary closure, they are respectable and may obviate the need for bladder augmentation.

Erosion of the intrapubic stitch into the posterior urethra during the healing process can present as a UTI, increasingly dry diapers, or high residual urine in the immediate postoperative state before removal of the suprapubic tube. In any of these cases or if any hydronephrosis is seen on postoperative ultrasound, immediate cystoscopy should be performed to rule out obstruction. If the stitch has eroded into the urethra and the child is older than 4 months, it can be removed easily through a small suprapubic incision. If it occurs early, the authors usually leave the postoperative tube for 8 to 12 weeks before stitch removal.

Neourethral stricture is often associated with paraexstrophy skin flap use, pubic suture reaction, erosion, or the use of urethral stents. This may be somewhat subtle; however, warning signs consist of UTIs, detectable increased bladder volumes on ultrasonography, bladder stones, prolonged dry intervals, and unexplained rectal prolapse. In a review by Baker and colleagues (1999), posterior urethral obstruction was found in 41 patients. Most episodes occurred within 60 days after primary closure. If diversion was used for longer than 6 months, the ultimate fate of the bladder was augmentation. If diversion was used for less than 6 months, most reconstructions were ultimately bowel free. The authors have also seen outlet obstruction including complete obliteration after both the CPRE and Kelly repair (Hernandez et al, 2008). Whether this is due to ischemic damage to the urethral plate or technical error is unclear. Regardless, because there is a paucity of long-term data from these two repairs, the outlet must be monitored carefully as with all exstrophy patients after primary closure. Ultimately, posterior urethral obstruction after exstrophy closure markedly decreased the success of any repair. This complication presents a significant risk to the upper urinary tract and should be detected early.

Although all closed exstrophy bladders have vesicoureteral reflux, upper tract deterioration is the ultimate fate of significant outlet obstruction. At this point the management includes urethral dilation (incision), open urethroplasty, or upper tract diversion. If renal function is compromised, the choice must achieve unquestionable free drainage to allow the upper tracts and kidneys to recover fully. Further bladder neck or urethral reconstruction should not be performed until the posterior urethral stricture is clearly repaired and free drainage has been achieved. After CPRE repair, up to 50% of patients will require bilateral ureteral reimplantation during the first year following their operation because of UTIs and increasing hydronephrosis.

Despite satisfactory closure, some bladders never achieve adequate capacity to act as functional bladders. It has become clear that multiple bladder closures, bladder prolapse, dehiscence, bladder calculi, recurrent infections, and vesicostomy have a negative impact on the potential of the exstrophy bladder (Silver et al, 1997b). The authors have used transurethral injection of collagen around the bladder neck to increase outlet resistance and stimulate the bladder to grow. However, in our hands this has not been as successful as reported by Caione and colleagues (Caione et al, 1993a, 1993b) from Italy. If the bladder does not grow to a sufficient size for bladder neck reconstruction, bladder augmentation is recommended in this situation. If the bladder neck or urethra

or both are problematic, a catheterizable continent stoma with or without bladder neck plasty or transection is performed, along with augmentation (Gearhart et al, 1995b).

Failed Bladder Neck Repair

Early successful bladder closure with or without pelvic osteotomy with a good bladder template is the first step to achieve voided continence. Early epispadias repair with good bladder growth (>100 mL) is the second step in this sequence. Proper patient selection with a motivated family and, lastly, proper execution in the operating room are the final steps in this journey. Nonetheless, missteps can occur and there remains a subgroup of children with urinary incontinence after bladder neck reconstruction secondary to (1) inadequate outlet resistance; (2) a small bladder capacity (lack of growth after bladder neck reconstruction); (3) decreased compliance; and (4) a combination of these factors.

If urinary continence, defined as a 3-hour dry interval, is not achieved within 2 years after bladder neck reconstruction, failure to achieve dryness has resulted. Occasionally, the dry interval is nearly acceptable for daytime dryness (i.e., longer than 2 hours). In these situations, collagen injections into the bladder neck can move the dry interval up to 3 hours, but more than one injection may be required (Ben-Chaim et al, 1995a). Data from Lottmann with the use of dextranomer implant (Deflux) have shown improvement in the dry interval when used following partial success with bladder neck reconstruction. Some successes have been seen with repeated Young-Dees-Leadbetter repair if the bladder neck is patulous, the bladder capacity is adequate, and urodynamic evaluation reveals a stable bladder (Gearhart et al, 1991). In a series by Gearhart and colleagues (1991), only 50% of patients with a failed prior bladder neck reconstruction were candidates for reoperative surgery. In this highly select group, continence rates were acceptable after reoperative bladder neck reconstruction. All of these patients had excellent bladder capacity (>100 mL) and were stable on urodynamics before the redo repair. A majority of bladder neck failures require eventual augmentation or continent diversion. The artificial urinary sphincter has been used with some success in patients who have a good bladder capacity. However, in most of these failures the bladder capacity is small and augmentation is required. At the time of reoperative surgery, either the bladder neck is transected proximal to the prostate with a Mitrofanoff substitution or a continence procedure such as an artificial sphincter or collagen injection, or both, are performed. In the authors' extensive experience with failed bladder neck reconstructions, most of the patients have had several surgeries and need to be dry. In a recent large series of 31 patients who had undergone prior bladder neck reconstruction, studied by Novak and colleagues (2009), most patients had undergone multiple prior repairs to achieve continence. Bladder neck transaction along with enterocystoplasty was performed with initial continence achieved in 86%. Seven patients underwent further bladder neck surgery, and 90% achieve dryness by intermittent catheterization. One renal unit was lost, nonobstructive hydronephrosis developed in 8, and bladder stones formed in 30%.

Delayed urinary continence has been reported at the onset of puberty in some males and has been attributed to prostatic growth. On MRI, the prostate of exstrophy patients is clover shaped and absent anteriorly, and its mean weight and maximal cross section and volume are normal (Gearhart et al, 1992). Therefore it is doubtful that growth of this abnormally configured prostate can have much impact on later urinary continence after failed bladder neck repair.

Failed Genitourethral Reconstruction

Common complications of modern epispadias repair include urethrocutaneous fistula formation. This has been reported in as little as 4% and up to 19% of cases (Kajbafzadeh et al, 1995; Surer et al, 2001a). Urethral tortuosity with difficult catheterization or strictures is uncommon with modern epispadias repair. Since the application of the penile disassembly for epispadias reconstruction, newer, more significant complications have been noted (Hammouda, 2003). Gearhart and Baird (2004) have reported loss of the glans, corpora, or both in addition to loss of penile skin and the urethral plate. Whether this is secondary to surgical misadventure, vagaries in the blood supply of the penis, or the intrinsic difficulties in the procedure remains a topic of debate. Reconstruction of these complications has required additional techniques including tissue expansion, full-thickness skin grafting, buccal mucosal grafting, and other complex techniques. In some patients with significant losses, tissue engineering may eventually provide the material for final cosmetic reconstruction.

At an older age, unsightly penile scars and a short phallus may prompt further surgical intervention. Scar excision can be closed in a plastic fashion if enough penile skin is available. Otherwise, flaps or full-thickness skin grafts can be used. In severe cases, tissue expanders can be placed under the penile skin and gradually inflated over 6 weeks to allow more penile skin and obviate the need for grafting. Freeing all scar tissues and suspensory ligament tissue can maximize available penile length. A dorsal dermal corporal graft or ventral corporal plication or rotation may additionally help lengthen and correct any chordee. However, it must be recognized that the exstrophy penis, when compared with age- and race-matched controls, is congenitally deficient in anterior corporal tissue as assessed by MRI (Silver et al, 1997b). Therefore overly aggressive attempts at penile lengthening may result only in corporal denervation and devascularization without additional lengthening.

Alternative Techniques of Reconstruction

Not all children with bladder exstrophy are candidates for primary repair at initial evaluation because of a small bladder plate or significant hydronephrosis. Additional reasons for seeking other methods of treatment include failure of initial closure with a small remaining bladder or failure of continence surgery, or both. Excluding the patients in whom initial treatment fails, this discussion deals with options available when modern repair is not chosen by the surgeon or for other reasons has not been suitable.

Ureterosigmoidostomy

Whichever urinary diversion is chosen, the upper tracts and renal function are initially normal. This allows the reimplantation of normal-sized ureters in a reliable, nonrefluxing manner into the colon or other suitable reservoir. Historically, ureterosigmoidostomy was the first form of diversion to be popularized for patients with exstrophy. Although the initial series was associated with multiple metabolic problems, results improved markedly with newer techniques of reimplantation (Zarbo and Kay, 1986; Koo et al, 1996). Ureterosigmoidostomy is favored by some because of the lack of an abdominal stoma. **However, this form of**

diversion should not be offered until one is certain that anal continence is normal and after the family has been made aware of the potential serious complications including pyelonephritis, hyperkalemic acidosis, rectal incontinence, ureteral obstruction, and delayed development of malignancy (Spence et al, 1979; Duckett and Gazak, 1983). More recently, ureterosigmoidostomy has been proposed again as an initial treatment of bladder exstrophy with acceptable continence and renal preservation on follow-up of 10 years or longer. In a recent long-term study by Gobet and colleagues (2009) of 42 patients, 50% had their ureterosigmoidostomy in place and were fecally continent at 50 years of age. One had suffered a colonic malignancy, and 60% had normal renal function.

Stein and colleagues (1999) treated a group of 128 patients with bladder exstrophy-epispadias with the Mainz technique for ureterosigmoidostomy. The Mainz Sigma pouch is constructed, and the ureters are reimplanted in a nonrefluxing manner. The abdominal wall is reconstructed and the bladder is closed as a seminal receptacle above the prostate. The penis is then reconstructed at a later date. D'elia and colleagues (2004) reported on 26 patients with the exstrophy-epispadias complex who showed excellent continence rates with long-term upper tract preservation when compared with standard ureterosigmoidostomy. Continence was achieved in 95% of patients with a rectal reservoir. Their recommendation for treatment in a number of patients with severely impaired renal function was that a colonic conduit was the best method of choice for diversion. In the patients with a normal or slightly dilated upper tract and intact anal sphincters, a Mainz rectal reservoir was recommended. Although the group from Mainz reported no cancer in a long-term follow-up study of patients who underwent ureterosigmoidostomy, the risk for malignancy still exists and must be carefully considered in a young child. Patients who have had mixing of urine and feces at any time during reconstruction remain at high risk for the development of cancers (Smeulders and Woodhouse, 2001). Bladder exstrophy patients who have failed an initial reconstruction and have polyposis at the time of repeated closure may also be at higher risk for the later development of malignancy (Novak et al, 2005). This is especially true in today's mobile society, in which careful long-term follow-up may be difficult to guarantee.

Continent Urinary Diversion in the Exstrophy Patient

In modern pediatric urology there is usually little need for incontinent urinary diversion in the patient with bladder exstrophy. In a young child with a bladder that is too small to close, or in a failed closure where the bladder template is too small to reclose, the authors recommend a nonrefluxing colon conduit. This protects the kidneys from vesicoureteral reflux, and undiversion can be performed when clinically indicated at an older age.

Advances in the reconstruction of the lower urinary tract in the past several years have been applied to the patient with exstrophy (Cervellione et al, 2008). Most commonly, further reconstruction is required in the patient in whom bladder neck reconstruction has failed. If a patient does not meet the criteria for bladder neck reconstruction (i.e., inadequate bladder capacity or inability to conform to a voiding regimen), deferring surgery is advisable. Patients in whom bladder neck reconstruction fails are most often destined to augmentation cystoplasty and continent urinary diversion. Surer and colleagues (2003) reported on 91 patients with the exstrophy-epispadias complex who underwent continent urinary diversion. Eight patients had bladder exstrophy, eight had cloacal exstrophy, and three had complete epispadias. The majority had undergone prior failed bladder neck reconstruction ($n = 62$). Seventy-nine patients (87%) had exstrophy closure before referral, 53 had also undergone bladder neck reconstruction, and 29 patients had never reached adequate capacity for bladder neck reconstruction. Ten of the 53 patients had undergone one prior attempt, 35 had two prior attempts, and 8 had three prior attempts at bladder neck reconstruction. A combined augmentation cystoplasty, continent urinary diversion, and bladder neck closure was performed in 59 patients (65%), and reaugmentation and continent urinary diversion was performed in 18 children. Ileocystoplasty was used in 41 patients, and sigmoid cystoplasty was performed in 30 patients. The appendix was used as the continent urinary diversion in 67 patients. Continence using intermittent catheterization through the stoma was achieved in 93% of children with the most common complication reported being that of bladder stones, noted in 26%. Although low, failures can occur with continent urinary diversion in exstrophy (Frimberger et al, 2003). The most common mode of failure was a deintussusception of a nipple valve, inadequate tunnel for an appendiceal channel, or continued bladder neck incompetence. The vast majority of these complications can be successfully repaired. Equally successful outcomes have been reported by Baird and colleagues (2005a) in adolescents who had undergone a mean of eight prior procedures before their definitive repair.

Continence can be achieved in most patients with exstrophy following failure of bladder neck reconstruction. This continence is typically obtained through augmentation cystoplasty and revision of the bladder neck reconstruction or closure. If a patient is unlikely to develop adequate capacity for eventual bladder neck reconstruction, moving early to continent urinary diversion is preferable. One long-term concern has been the risk of malignancy in these patients over the long term. Recent data by Higuchi and colleagues (2010) revealed that the overall rate of malignancy is low unless associated with coexisting carcinogenic stimuli (prolonged tabacco/chronic immunosuppression) or the inherent risk associated with bladder exstrophy.

Key Points: Bladder Exstrophy—Priorities in Management

- Size and quality of bladder template
- Extent of pubic diastasis and malleability of the pelvis
- Need for osteotomy
- Length and width of urethral plate
- Penile size
- Associated anomalies

CLOACAL EXSTROPHY

Cloacal exstrophy includes a spectrum of abnormalities but is primarily an anterior abdominal wall defect. A reported incidence of 1:200,000 to 1:400,000 makes this one of the rarer urologic abnormalities (Hurwitz et al, 1987). Although prior reports have suggested a male/female ratio of 2:1 (Gearhart and Jeffs, 1998), a large study by Boyadjiev and colleagues (2004a) indicated that the sex ratio may be 1:1. Most cases are sporadic, and isolated incidences of unbalanced translocations have been reported to be potentially causative (Thauvin-Robinet et al, 2004); however, one report noted recurrence in siblings, perhaps indicating a more multifactorial etiology. Associated defects of the neurospinal axis,

intestinal tract, and urogenital and skeletal systems are frequently noted. When neurospinal defects and omphalocele coexist with cloacal exstrophy, the term *OEIS complex* (*o*mphalocele, *e*xstrophy, *i*mperforate anus, *s*pinal defects) has been used (Keppler-Noreiul, 2001). Advances in critical care of children have resulted in most patients surviving into adult life and modified the focus to improving quality of life (Mathews et al, 1998).

Anatomic Considerations

The classic constellation of anomalies that are noted in children with cloacal exstrophy includes exstrophy of the bladder, complete phallic separation, wide pubic diastasis, exstrophy of the terminal ileum between the two halves of the bladder, a rudimentary hindgut, imperforate anus, and the presence of an omphalocele (Fig. 124–28). Many children have associated spinal defects, and various lower extremity malformations may be noted (Loder and Dayioglu, 1990; Jain and Weaver, 2004). The urogenital anomalies in cloacal exstrophy are similar to those seen with classic bladder exstrophy (see earlier), although they are typically of greater severity.

Neurospinal Abnormalities

Abnormalities of the spinal cord or vertebral column, or both, have been noted in 85% to 100% of children with cloacal exstrophy (Appignani et al, 1994; McLaughlin et al, 1995). Although most patients have lumbar myelodysplasia (80%), thoracic defects may be noted in 10% with the remaining having sacral defects. In a large series of 34 patients from a single center with cloacal exstrophy and associated spinal defects, Mathews and colleagues (1998) noted lipomeningocele in 17, myelomeningocele in 8, and spina bifida and isolated cord tethering in 7 and 2 patients, respectively. The nearly universal incidence of spinal abnormalities has led some authors to suggest MRI for all patients with a diagnosis of cloacal exstrophy (Cohen, 1991). Spinal ultrasound evaluation, which is easily performed, has been noted to be comparable with MRI for the diagnosis of spinal anomalies in infants with cloacal exstrophy (Dick et al, 2001). Karrer and colleagues (1988) noted that only one in five children with spinal dysraphism noted on ultrasonography had a sacral abnormality visible on the skin surface.

The embryologic basis for the neurospinal defects associated with cloacal exstrophy has been postulated to be secondary to problems with the disruption of the tissue of the dorsal mesenchyme rather than failure of neural tube closure (McLaughlin et al, 1995). Alternatively, it has been suggested that the defects that lead to the formation of cloacal exstrophy may lead to the developing spinal cord and vertebrae being pulled apart (Cohen, 1991). Functional deficits can range from patients who have almost normal sensation of the pelvis and lower extremity to patients who are wheelchair bound. The presence of a clinically significant neurologic anomaly was found to affect negatively the development of continence (Husmann et al, 1999) and led to a significant reduction in continence when compared with patients

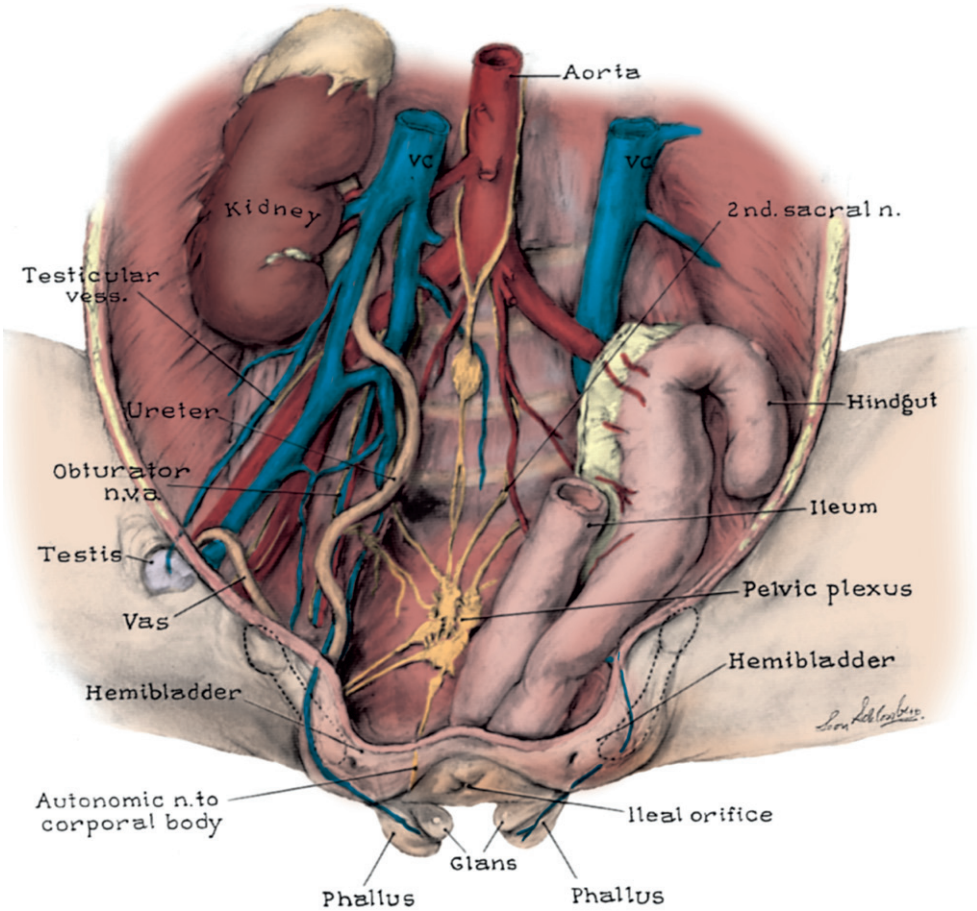


Figure 124–28. Internal view of a patient with cloacal exstrophy. Pudendal vessels, nerves, and other vessels and autonomic innervation of the corporal bodies are demonstrated. Internal structures of the pelvis along with duplication of the vena cava in this dissected specimen are also shown.

with bladder exstrophy. Only 1 of 13 neurologically impaired patients in this series developed voided continence.

The neuroanatomic dissections performed by Schlegel and Gearhart (1989) further indicate that the neuroanatomic landmarks in the infant with cloacal exstrophy are different from those in the normal newborn with the autonomic bladder innervation being derived from a more medial location (see Fig. 124–28). This potentially puts the nerve supply in jeopardy during initial bladder dissection and reconstruction and may leave the bladder neuropathic following reconstruction (Husmann et al, 1999). **Innervation to the duplicated corporal bodies arises from the sacral plexus, travels in the midline, perforates the interior portion of the pelvic floor, and courses medially to the hemibladders** (Schlegel and Gearhart, 1989). Innervation abnormalities were also noted at a histologic level in the studies by Rosch and colleagues (1997). When compared with those in patients with bladder exstrophy, the neural elements identified on immunohistochemical evaluation were found to show significant structural abnormalities.

Skeletal System Abnormalities

Anomalies of the skeletal system are universally noted in children with cloacal exstrophy (Suson et al, 2009). The pelvic defects that are seen with classic bladder exstrophy are noted with greater severity in the patient with cloacal exstrophy. Sponseller and colleagues (1995), studying patients with the exstrophy complex, noted that the posterior segment of the pelvis in children with cloacal exstrophy was angled farther posteriorly and there was a greater likelihood of asymmetry between the two sides. Similarly, the anterior segment of the pelvis had more severe degrees of external rotation. The actual length of the bone segments, however, was similar between those with cloacal and classic exstrophy. The interpubic distance (diastasis) in children with cloacal exstrophy was noted to be almost twice that of children with classic bladder exstrophy. Malformation of the sacroiliac joints and side-to-side asymmetry were also noted. These issues become of increasing importance, and most children with cloacal exstrophy require osteotomy for successful reconstruction. Stec and colleagues (2003) noted that, microscopically, the bones in children with cloacal exstrophy were similar to those in normal controls and were developing at a similar rate, indicating that the potential for growth was also similar.

Vertebral anomalies that were not associated with myelodysplasia were noted in 8 of 37 children with cloacal exstrophy (Mathews et al, 1998). Loder and Dayioglu (1990) noted vertebral anomalies in three of five children with cloacal exstrophy. Absence or shortening of limbs was also noted, as were clubfoot malformations. **Skeletal and limb anomalies were also reported by** Diamond (1990) **in 12% to 65% of cases.** The vast majority were clubfoot deformities, although absence of feet, severe tibial or fibular deformities, and congenital hip dislocations were commonly noted in this group of patients. A similar high incidence of foot abnormalities and greater than normal abduction of the hips was noted in a study by Greene and colleagues (1991).

Intestinal Tract Abnormalities

Gastrointestinal tract anomalies occur in virtually all patients with cloacal exstrophy. **In Diamond's series** (1990), **the incidence of omphalocele was 88% and a majority of all series reported an incidence of 95% or greater.** In the series reported by Mathews and colleagues (1998), 100% had an omphalocele. Omphaloceles do vary in size and usually contain small bowel or liver, or both. Immediate closure of the omphalocele defect in the newborn period is advised to prevent subsequent rupture.

Hurwitz and colleagues (1987), in a large review of cloacal exstrophy patients, reported a 46% incidence of associated gastrointestinal tract anomalies, with malrotation, duplication anomalies, and anatomically short bowel occurring with equal frequency. A hindgut remnant of varying size is also noted in most patients (Sawaya et al, 2010). Hurwitz noted a 23% incidence of short gut syndrome, which is compatible with the 25% incidence reported by Diamond (Hurwitz et al, 1987; Diamond, 1990). It now seems well accepted that short gut syndrome may occur in the presence of normal small bowel length, suggesting absorptive dysfunction and emphasizing the absolute need to preserve as much large bowel as possible. If not used for incorporation into the fecal stream, the hindgut remnant may be preserved for use in urogenital tract reconstruction (Mathews et al, 1998).

Genitourinary Abnormalities

Müllerian anomalies have been frequently noted in conjunction with cloacal exstrophy. **The most commonly reported müllerian anomaly was uterine duplication, seen in 95% of patients** (Diamond, 1990). The vast majority of these patients had partial uterine duplication, predominantly a bicornate uterus. Vaginal duplication occurred in 65% of cases, and vaginal agenesis was seen in 25% to 50% of patients. In a report by Hurwitz and colleagues (1987), cases of complete duplication of the uterus and fallopian tubes associated with both vaginal duplication and vaginal agenesis were noted. Gearhart and Jeffs (1991b) recommended preservation of all müllerian duplication anomalies for possible utilization in reconstructing the lower urinary tract.

Upper urinary tract anomalies occurred in 41% to 60% of patients in Diamond's review. The most common anomalies were pelvic kidney and renal agenesis, both occurring in up to one third of patients. Hydronephrosis and hydroureter were common, occurring in one third of patients. Multicystic dysplastic kidneys and fusion anomalies were seen less frequently. Ectopic ureters draining to the vasa in the male and into the uterus, vagina, or fallopian tubes in the female were also reported (Diamond, 1990). A similar incidence of upper tract defects was noted by Mathews and colleagues (1998). Ureteral duplication, congenital stricture, and megaureter were also reported.

Genital anomalies in the male have typically included complete separation of the two phallic halves and accompanied separation of the scrotal halves. Asymmetry of these structures can also be seen and provide additional challenges to successful reconstruction. Testes may be noted in the scrotum but are frequently noted to be undescended, and associated inguinal hernias are a common finding. Girls typically have widely divergent clitoral halves.

The lower urinary tract is typically composed of two exstrophied hemibladders flanking the exstrophied intestinal segment. Each bladder half usually drains the ipsilateral ureter and is closely related to the ipsilateral phallic segment. Variations of anatomy, however, are frequently seen and every patient has unique anatomic features.

Additional System Anomalies

Life-threatening cardiovascular and pulmonary anomalies are rarely seen in cloacal exstrophy. Reported cases included two patients with cyanotic heart disease and one with aortic duplication. A bilobed lung was reported in two patients and an atretic right upper lung in one. Also, Schlegel and Gearhart (1989) reported caval duplication in their anatomic dissection of a patient with cloacal exstrophy.

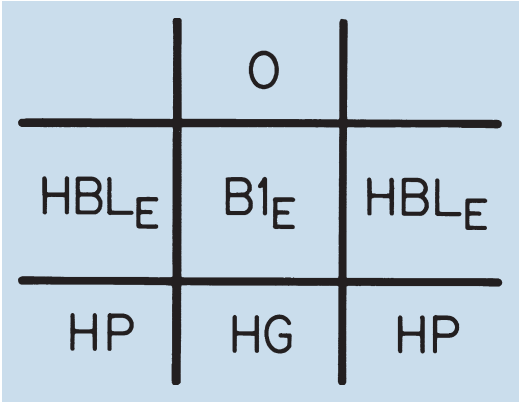


Figure 124–29. Coding grid used to describe cloacal exstrophy and its variants. O, omphalocele; HBLE, hemibladder; B1E, everted bowel; HP, hemiphallus; HG, hindgut. (From Hurwitz RS, Manzoni GA, Ransley PG, Stephen FD. Cloacal exstrophy: a report of 34 cases. J Urol 1987;138:1060.)

Because of the complexity and the multisystem nature of cloacal exstrophy, Hurwitz and coauthors (1987) have devised a grid for the clarification of anatomy in each patient and to permit planning for reconstruction (Fig. 124–29). This permits the standard form of cloacal exstrophy to be separated from variants and allows the soft tissue components of the defect to be described systematically.

Prenatal Diagnosis

Since its initial description in the early 1980s, further refinements in the prenatal diagnosis of cloacal exstrophy have occurred (Meizner and Bar-Ziv, 1985). These authors indicated that the three main criteria used to identify the diagnosis were a large midline infraumbilical anterior abdominal wall defect, lumbosacral myelomeningocele, and failure to visualize the urinary bladder. Chitrit and colleagues (1993) reported the diagnosis of monozygotic twins with cloacal exstrophy detected during antenatal ultrasound screening. Since these initial reports, there have been only occasional case reports of prenatal diagnosis of cloacal exstrophy, and only 15% of patients with this anomaly have been diagnosed by prenatal ultrasonography, according to the literature. With the marked improvements in survival of patients with cloacal exstrophy in the past 20 years and the common application of fetal ultrasonography, early diagnosis may permit appropriate prenatal counseling for parents and expedite postnatal care.

Austin and colleagues (1998) reviewed 20 patients with this abnormality, expanded on the diagnostic findings, and proposed major and minor criteria for the prenatal diagnosis of cloacal exstrophy on the basis of the frequency of occurrence rather than the severity of individual findings. A criterion was considered major if it was present in more than 50% of cases. The gestational age at diagnosis of cloacal exstrophy ranged from 15 to 32 weeks (mean, 22 weeks). Major diagnostic criteria included nonvisualization of the bladder in 91%, a large midline infraumbilical anterior wall defect or a cystic anterior wall structure in 82%, an omphalocele in 77%, and a myelomeningocele in 68%. Minor criteria included lower extremity defects in 23%, renal anomalies in 23%, ascites in 41%, widened pubic arches in 18%, narrow thorax in 9%, hydrocephalus in 9%, and a single umbilical artery in 9%. Hamada and colleagues (1999) reported a single case in which ultrasonography revealed a wavy cordlike segment of soft tissue protruding from the anterior abdominal wall of the fetus below the umbilicus. This was found to be prolapsed terminal ileum, which resembled the trunk of an elephant. The authors suggested that this sonographic image be added to the criteria described by Austin and colleagues (1998) for making a prenatal diagnosis of cloacal exstrophy.

Universal use of antenatal ultrasonography has permitted diagnosis of cloacal exstrophy to be made at a time when parental counseling may lead to possible pregnancy termination. Extensive parental counseling regarding the significant anatomic anomalies that constitute the complex is appropriate in conjunction with psychologic support.

SURGICAL RECONSTRUCTION OF CLOACAL EXSTROPHY

The initial successful reconstruction of cloacal exstrophy was reported by Rickham (1960). Survival in the 1970s remained at about 50%; however, the institution of intensive postnatal care led to improvement in survival in the 1980s to almost 100%.

Evaluation and Management at Birth

Immediate management is directed to the medical stabilization of the infant. Complete physical examination and determination of the various anatomic defects present allow short- and long-term management strategies to be created (Table 124–4). This initial planning stage should include decisions about gender assignment. The bowel and bladder segments are kept moist with protective plastic dressings as with bladder exstrophy (Gearhart and Jeffs, 1998). Presence of neurospinal abnormalities requires immediate neurosurgical evaluation. Consultations from social work, pediatric orthopedic surgery, and other disciplines should be obtained. Evaluation of the genitalia and gender assignment should be made by a gender assignment team including a pediatric urologist, pediatric surgeon, pediatrician, pediatric endocrinologist, and child psychologist or psychiatrist. Gender assignment decisions should be made in conjunction with appropriate parental counseling and involvement. In a large medical center with experience in dealing with complex malformations, these multiple consultations should be done in a short period of time. If there are medical concerns, delayed closure after initial intestinal diversion is appropriate (Mathews et al, 1998).

Gender Assignment

Because of the significant separation of the corpora of the penis and scrotum and the reduction in corporal size noted in boys with cloacal exstrophy, early reports had recommended universal gender reassignment of boys (46,XY) with cloacal exstrophy to functional females (Tank and Lindenaur, 1970). To this end, bilateral orchiectomy was combined with phallic reconstruction as a functional clitoris and early or delayed vaginoplasty. Reiner (2004) has reported on 29 males with cloacal exstrophy who had gender reassignment to female. Psychosexual evaluation indicated that all of these patients had a marked male shift in psychosexual development despite having no pubertal hormonal surges. A comparison of patients with cloacal exstrophy and other cloacal anomalies at the Great Ormond Street, however, indicated no difference in social or behavioral competence or psychologic problems. Gender assignment was not associated

Table 124–4.

Modern Functional Reconstruction of Cloacal Exstrophy

Immediate Neonatal Assessment

Evaluate associated anomalies
Decide whether to proceed with reparative surgery

Functional Bladder Closure (Soon after Neonatal Assessment)

ONE-STAGE REPAIR (FEW ASSOCIATED ANOMALIES)

Excision of omphalocele
Separation of cecal plate from bladder halves
Joining and closure of bladder halves and urethroplasty
Bilateral anterior innominate and vertical iliac osteotomy
Gonadectomy in males with unreconstructible phallus
Terminal ielostomy/colostomy
Genital revision if needed

TWO-STAGE REPAIR

First stage (newborn period)
- Excision of omphalocele
- Separation of cecal plate from bladder halves
- Joining of bladder halves
- Gonadectomy in male with unreconstructible phallus

Terminal ileostomy/colostomy
Second stage
- Closure of joined bladder halves and urethroplasty
- Bilateral anterior innominate and vertical iliac osteotomy
- Genital revision if necessary

Anti-Incontinence/Reflux Procedure (age 4-5 yr)

Bladder capacity ≥ 85 mL (small select group of patients)
- Young-Dees-Leadbetter bladder neck reconstruction
- Bilateral Cohen ureteral reimplantations
- Bowel and/or stomach segment used to augment bladder

or

- Continent diversion with abdominal/perineal stoma

Vaginal Reconstruction

Vagina constructed or augmented using colon, ileum, or full-thickness skin graft



Figure 124–30. A 46,XY child with cloacal exstrophy with a dominant right hemiphallus. This child was reconstructed and reared as male.

with childhood psychologic, emotional, or behavioral problems (Baker Towell and Towell, 2003). Schober and colleagues (2002), reporting on 14 children who had undergone early gender reassignment, indicated that although patients had masculine childhood behavior, they had a feminine gender identity. Currently, however, most authors recommend assigning gender that is consistent with karyotypic makeup of the individual if at all possible (Fig. 124–30). This policy can be supported by a report indicating that the histology of the testis at birth is normal (Mathews et al, 1999a). Furthermore, with evolution of techniques for phallic reconstruction, a functional and cosmetically acceptable phallus can now be constructed (Husmann et al, 1989).

Immediate Surgical Reconstruction

Cloacal exstrophy patients should undergo carefully planned and individualized reconstructions (Ricketts et al, 1991; Lund and Hendren, 1993; Mathews et al, 1998). For infants with spinal dysraphism and myelocystocele, neurosurgical consultation should be obtained and closure undertaken as soon as the infant is medically stable. After closure of the myelocystocele, long-term follow-up is mandatory to evaluate for subtle changes in the neurologic evaluation that could herald cord tethering. Symptomatic spinal cord tethering can be seen in up to 33% of children (McLaughlin et al, 1995).

Neonatal omphalocele closure is recommended to prevent untimely rupture and is typically combined with intestinal diversion. Formerly, initial attempts focused on ileostomy with resection of the hindgut remnant. **Since the recognition of the metabolic changes that occur in patients with ileostomy, an attempt has always been made to use the hindgut remnant to provide additional length of bowel for fluid absorption** (Husmann et al, 1989; Mathews et al, 1998). Enlargement of the hindgut remnant and increased water absorption have been noted in children who have had this segment incorporated into construction of a fecal colostomy. The hindgut segment may be anastomosed in an isoperistaltic or retroperistaltic fashion to increase motility and generate formed stool. Children who have anal stenosis and not imperforate anus may have the capability for later continence and may be treated with a pull-through procedure (Ricketts et al, 1991). If the hindgut remnant is not used for bowel reconstruction, it should be left as a mucus fistula to be used for later bladder augmentation or vaginal reconstruction (Lund and Hendren, 1993; Mathews et al, 1998). If gastrointestinal reconstruction is combined with bladder closure, approximation of the pubis, usually with osteotomies, is beneficial in reconstruction of the pelvic ring and increases the potential for successful bladder and abdominal wall closure (Mathews et al, 1998). Some authors have suggested that gastrointestinal reconstruction after initial fecal diversion be delayed for 1 to 2 years of observation (Soffer et al, 2000). After this time, radiographic evaluation is performed to determine residual colonic length. If near-normal colonic length is noted, a pull-through procedure is performed. If there is short colon but the patient is able to make solid stool, the patient may still be a candidate for pull-through procedures. Patients who are unable to make solid stool are typically managed with a permanent fecal stoma.

At the initial stage of omphalocele closure, if it is determined that bladder and abdominal wall closure may not be accomplished, the bladder halves are approximated in the midline without further dissection and the defect is converted to a bladder exstrophy (Ricketts et al, 1991; Mathews et al, 1998). This permits abdominal distention to allow enlargement of this bladder plate for later closure. If the hindgut segment is not used in the initial reconstruction of the bowel, it is left as a mucus fistula.

Urinary Reconstruction

Modern Staged Reconstruction

The staged management of the urinary tract follows that used for the management of bladder exstrophy (Gearhart and Jeffs, 1991b). Once the bladder halves have been approximated posteriorly, the lateral edges are separated from the abdominal wall and brought together in the midline. As in the patient with classic exstrophy, placement of the bladder and posterior urethra deep into the pelvis remains a key factor in the successful surgical reconstruction of the urinary tract. Inguinal hernias that are noted should be repaired at the time of closure. In genetic females and in genotypic male subjects undergoing gender reassignment, reconstruction should be performed to improve the appearance of the genitalia. Recent reports by Thomas and colleagues (2007) in a series using a staged approach found successful results in a series of seven patients all with tethered cords.

Reconstruction of the external genitalia in the immediate postnatal period is performed to make the infant appear more congruent with the gender assigned. The psychiatric studies of children who have had gender assignment have fueled interest in male gender assignment if adequate unilateral or bilateral corporal tissue is present (Reiner, 2004). Histologic studies indicate normal histology in the testes of male subjects who have had gender reassignment despite the presence of cryptorchidism (Mathews et al, 1999a). Results of phallic reconstruction in male patients with minimal or no penile tissue in the past have been disappointing. For male-to-female reassignment, initial female genital reconstruction should bring the phallic halves together in the midline as a clitoris.

However, in instances with adequate corporal tissue, either unilaterally or bilaterally, epispadias repair can be performed at around age 1 using the standards identified for the staged reconstruction. Vaginal reconstruction can be performed early in the genetic female patient. In gender-converted male patients who require reconstruction of a neovagina, delayed reconstruction is appropriate. Reconstruction may be performed by using a preserved hindgut segment or expanded perineal skin. Long-term dilatation of the neovagina may be required.

Pubic approximation permits abdominal wall closure and usually requires osteotomy and fixation with postoperative traction. External fixation and traction are typically maintained for 6 to 8 weeks to permit healing.

Role of Osteotomy

Infants who are medically stable may be considered for urinary tract reconstruction in the immediate postnatal period. Osteotomy is indicated in all children with cloacal exstrophy at the time of bladder closure because of the wide diastasis that is invariably present (Mathews et al, 1998). Osteotomy allows the pelvic ring, bladder, and abdominal wall to be closed without undue tension on the closure. Reduction in dehiscence and postoperative ventral hernias has been noted in patients treated with osteotomy. In a large series reported by Ben-Chaim and colleagues (1995c), significant complications occurred in 89% of patients who underwent closure of the cloacal exstrophy without osteotomy but in only 17% of patients who underwent osteotomy at the time of initial cloacal exstrophy closure. Interestingly, the patients who underwent osteotomy and those who did not were similar in terms of size of the omphalocele, presence of myelomeningocele, and time of primary closure. However, it is not surprising that osteotomy had no effect on eventual continence of patients with cloacal exstrophy.

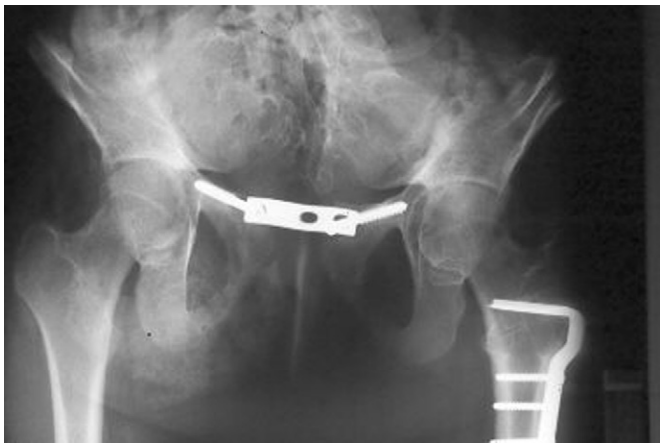


Figure 124–31. Pubic approximation and maintenance with a stainless steel plate in a child with cloacal exstrophy.

Currently, combined anterior innominate and vertical iliac osteotomies are routinely used at our institution (Silver et al, 1999). This approach does not require the patient to be repositioned on the operating table before commencing bladder and abdominal wall closure. In addition, this method obviates the use of a posterior approach and any complication of the procedure related to the spinal or back closure. **In a series of five patients with extreme pubic diastasis greater than 10 cm, Silver and colleagues (1999) described initial pelvic osteotomy and gradual pelvic closure of the fixator for 1 to 2 weeks, followed by abdominal wall closure and bladder closure.** Closure was successful in all patients without technical problems or complications. This technique of staged pelvic closure may provide reliable initial secondary repair in patients with cloacal exstrophy in whom one-stage pelvic closure is not feasible, even with pelvic osteotomy. An interpubic stainless bar has been added to permit stabilization of the pubic approximation and maintain the reduction in diastasis (Fig. 124–31) (Mathews et al, 2005). Because of the possible asymmetry that can be noted in the pelvic bones, care must be used when performing osteotomies and fixation. In patients who have lower extremity abnormalities, providing postoperative traction can also be challenging.

Single-Stage Reconstruction

Grady and Mitchell (1999) have reported using a single-stage reconstruction in cloacal exstrophy—a procedure similar to that done for bladder exstrophy. Delay in urinary tract reconstruction has also been advised by these authors if there is a large omphalocele or other medical instability. In this situation, the conversion to a bladder exstrophy and subsequent reconstruction of the bladder and penis as a single step is performed. Among the small number of patients who have had this type of management strategy, occasional patients have been reported to be able to have voided continence. As with staged reconstruction, most patients have required augmentation cystoplasty for continence.

Techniques to Create Urinary Continence

Urinary continence is possible in most children but usually requires bladder augmentation and the use of intermittent catheterization. Multiple series by Gearhart and

Jeffs (1991b), Mitchell and colleagues (1990), and Hendren (1992) have shown the applicability of modern techniques for lower tract reconstruction to help these patients achieve urinary continence. Enhancement of bladder capacity may be performed using a hindgut segment, if available; ileum; or stomach. Continence appears to be more difficult to achieve in male patients who undergo gender reassignment, and a continent stoma may be most applicable in this special group of patients (Mathews et al, 1998). In genetic female patients, successful continence has been achieved after Young-Dees-Leadbetter bladder neck reconstruction, but the vast majority of patients have required intermittent catheterization (Husmann et al, 1999). Similar findings were reported in a series by Mitchell and colleagues (1990). Husmann and colleagues (1999) reported that the success rate of Young-Dees-Leadbetter bladder neck reconstruction in the cloacal exstrophy population was closely related to the presence of coexisting neurologic abnormalities.

Urinary continence can be achieved in these individuals in many ways. An orthotopic urethra can be constructed from local tissue, vagina, ileum, stomach, or ureter. A catheterizable stoma can be constructed from ileum when enough bowel is present and fluid loss is not a problem. The bladder may be augmented with unused hindgut, ileum, or stomach. However, surgery to provide a continent urinary reservoir should be delayed until a method of evacuation can be taught and the child is old enough to participate in self-care. The choice between a catheterizable urethra and an abdominal stoma depends on the adequacy of the urethra and bladder outlet, interest and dexterity of the child, and orthopedic status regarding the spine, hip joints, braces, and ambulation. In a series by Gearhart and Jeffs (1991b) and in another series by Mitchell and colleagues (1990), multiple techniques were used to produce continence in patients with cloacal exstrophy. An innovative approach is required to find a suitable solution for each individual patient according to the patient's bladder size and function and mental, neurologic, and orthopedic status. With the advent of modern pediatric anesthesia and intensive care, the newborn survival rate is high. Improving survivorship makes reconstructive techniques applicable in a large percentage of patients born with this condition.

LONG-TERM ISSUES IN CLOACAL EXSTROPHY

Because survival has become almost universal, the focus has changed in cloacal exstrophy to improving quality of life. Improvement in functional outcomes has become the mainstay of improving the quality of life. Patients presenting with significant neurologic defects need intensive management to provide improvement in quality of life. In this population, management of the bowel with permanent diversion and using continent catheterization channels for urinary management provide independence and promote improvement in self-esteem. When neurologic issues are minimal or absent, bowel pull-through and voided continence would be ideal. Ricketts and colleagues (1991) have presented a continence score that can be used in this group of children. Using a six-point scoring system to determine bowel and bladder continence (6 = best; 0 = worst), they evaluated 12 patients who had been managed over time. They had seven patients with a continence score of 1 (colostomy and incontinent bladder) and only one patient who had a score of 5 (enema program and a continent bladder), attesting to the difficulties presented with surgical reconstruction.

Some children have required permanent ileostomy for management of their gut. Husmann and colleagues (1989) noted that patients undergoing permanent ileostomy, in comparison with terminal colostomy, had greater initial morbidity; however, bowel adaptation appeared to occur by age 3 years with resolution of the short gut syndrome in most. If patients with terminal ileostomy were aggressively managed with hyperalimentation, growth characteristics in the two groups were similar.

Attempts at phallic reconstruction in the past had minimal success because of the diminutive nature of the corpora in boys and the wide pubic separation. Modern reconstructive surgical techniques may allow some boys to have complete phallic reconstruction performed with forearm grafts. Fertility appears to be universally compromised in boys, but girls have normal fertility and pregnancy has been reported. Girls have higher degrees of cervical prolapse when compared with their counterparts with bladder exstrophy.

Summary

Evolution in management of cloacal exstrophy has permitted near-universal survival with significant improvement in cosmetic and functional outcomes. Debate continues regarding the issue of gender reassignment, and long-term data are still accruing on the best strategy for management. Continence can be achieved with appropriate reconstruction and the use of intermittent catheterization. Despite the extensive malformations noted, many patients have gone on to live fruitful lives.

Key Points: Cloacal Exstrophy—Priorities in Management

- Assure medical stabilization of infant.
- Discuss and evaluate gender assignment with parents and consulting physicians.
- Discuss with all consultants colonic functionalization and presentation.
- Assume complete separation of the bladder from the mid-gut plate.
- Evaluate the need and potential for genital reconstruction.

EPISPADIAS

Epispadias varies from a mild glanular defect in a covered penis to the penopubic variety with complete incontinence in males or females. It is most commonly noted as a component of bladder and cloacal exstrophy.

Male Epispadias

Isolated male epispadias is a rare anomaly, with a reported incidence of 1 in 117,000 males. Most male epispadias patients (about 70%) have complete epispadias with incontinence (Gearhart and Jeffs, 1998). Epispadias consists of a defect in the dorsal wall of the urethra. The normal urethra is replaced by a broad, mucosal strip lining the dorsum of the penis extending toward the bladder, with potential incompetence of the sphincter mechanism. The displaced meatus is free of deformity, and occurrence of urinary incontinence is related to the degree of the dorsally displaced urethral meatus (Gearhart and



Figure 124–32. **A,** Three-month-old boy with complete epispadias. **B,** Six-month-old girl with complete female epispadias.

Jeffs, 1998). The displaced meatus may be found on the glans, penile shaft, or in the penopubic region. All types of epispadias are associated with varying degrees of dorsal chordee. In penopubic or subsymphyseal epispadias, the entire penile urethra is opened and the bladder outlet may be large enough to admit the examining finger, indicating obvious gross incontinence (Fig. 124–32A). To a lesser extent than those with classic bladder exstrophy, patients with epispadias have a characteristic widening of the symphysis pubis caused by outward rotation of the innominate bones. This separation of the pubis causes divergent penopubic attachments that contribute to the short, pendular penis with dorsal chordee. Therefore the penile deformity is virtually identical to that observed in bladder exstrophy. The reported male-to-female ratio of epispadias varies between 3:1 (Dees, 1949) and 5:1 (Kramer and Kelalis, 1982a).

Kramer and Kelalis (1982a) reviewed their experience with 82 male patients with epispadias. Penopubic epispadias occurred in 49 cases, penile epispadias in 21, and glanular epispadias in 12. Urinary incontinence was observed in 46 of 49 patients with penopubic epispadias, in 15 of 21 patients with penile epispadias, and in no patient with glanular epispadias. The goals of the treatment of complete male epispadias include creation of normal urinary control and establishment of a straight, cosmetically acceptable penis of adequate length that is functional for normal sexual intercourse. It has been postulated that complete male epispadias is similar to classic bladder exstrophy except that in complete epispadias the bladder is closed and bladder closure procedures are not required.

Associated Anomalies

Anomalies associated with complete epispadias are usually confined to deformities of the external genitalia, diastasis of the pubic symphysis, and deficiency of the urinary continence mechanism. The only renal anomaly observed in 11 cases of epispadias was agenesis of the left kidney (Campbell, 1952). In a review by Arap and colleagues (1988), 1 case of renal agenesis and 1 ectopic kidney occurred among 38 patients.

The ureterovesical junction is inherently deficient in complete epispadias, and the incidence of reflux has been reported in a number of series to be between 30% and 40% (Kramer and Kelalis, 1982a; Arap et al, 1988). In a review by Ben-Chaim and colleagues (1995b) of a series of 15 patients with complete male epispadias treated at our institution, a lower rate of vesicoureteral reflux was noted compared with male patients with classic bladder exstrophy (100% vs. 82%, respectively); the rate of inguinal hernias (33%) was also significantly lower. A possible explanation for the lower incidence of reflux in complete male epispadias is that the pouch of Douglas is not as enlarged and deep. Therefore the distal ureter enters the bladder in a more oblique fashion than in classic exstrophy (Gearhart and Jeffs, 1998).

Surgical Management

The objectives of repair of penopubic epispadias include achievement of urinary continence with preservation of the upper urinary tracts and the reconstruction of cosmetically acceptable genitalia. The surgical management of incontinence in penopubic epispadias is virtually identical to that in closed bladder exstrophy.

Young (1922) reported the first cure of incontinence in a male patient with complete epispadias. Since this initial report, continence following surgical reconstruction has progressively improved (Burkholder and Williams, 1965; Kramer and Kelalis, 1982a; Arap et al, 1988; Mollard et al, 1998; Peters et al, 1988). In patients with complete epispadias and good bladder capacity, epispadias and bladder neck reconstruction can be performed in a single-stage operation. Urethroplasty formerly was performed after bladder neck reconstruction (Kramer and Kelalis, 1982a; Arap et al, 1988). However, improvements in bladder capacity in the small bladder associated with exstrophy (Gearhart and Jeffs, 1989a) and that associated with epispadias (Peters et al, 1988) have led us to perform urethroplasty and penile elongation before bladder neck reconstruction. A small, incontinent bladder with reflux is hardly an ideal situation for bladder neck reconstruction and ureteral reimplantation. Before bladder neck reconstruction there was an average increase in bladder capacity of 95 mL within 18 months after epispadias repair in the patients with an initial small bladder capacity and a continence rate of 87% after the continence

procedure (Peters et al, 1988). **In a series by Ben-Chaim and colleagues (1995b) composed exclusively of patients with complete male epispadias, bladder capacity increased by an average of 42 mL within 18 months after urethroplasty.** Nine (82%) of 11 patients were dry day and night after an average of 9 months.

In epispadias, as in the bladder exstrophy, bladder capacity is the predominant indicator of eventual continence (Ritchey et al, 1988). Arap and colleagues (1988) reported higher continence rates in patients who had an adequate bladder capacity before bladder neck reconstruction than in those with inadequate capacity (71% vs. 20%, respectively). In addition, in Arap's group of patients with complete epispadias, most obtained continence within 2 years, similar to results in patients with classic bladder exstrophy.

A firm intrasymphyseal band typically bridges the divergent symphysis, and an osteotomy is not usually performed. The Young-Dees-Leadbetter bladder neck plasty, Marshall-Marchetti-Krantz suspension, and ureteral reimplantation are performed when the bladder capacity reaches approximately 80 to 85 mL, which usually occurs between 4 and 5 years of age. Genital reconstruction procedures in epispadias and exstrophy are similar. The following reconstructive maneuvers must take place: release of dorsal chordee and division of the suspensory ligaments; dissection of the corpora from their attachments to the inferior pubic ramus; lengthening of the urethral groove; and lengthening of the corpora, if needed, by incision and anastomosis or grafting or by medial rotation of the ventral corpora in a more downward direction.

Urethral reconstruction in complete epispadias has been performed in many ways. A transverse island flap was used by Monfort and colleagues (1987). The urethra, once reconstructed, can be positioned between and below the corpora (Cantwell, 1895; Ransley et al, 1989; Gearhart et al, 1992, 1995c). Mitchell and Bagli (1996) reported their experience with a complete penile disassembly technique, and a multicenter experience with the technique was later reported in a total of 17 patients from four institutions (Zaontz et al, 1998). Chordee was reliably corrected, erectile function was preserved, the urethra was eventually situated in a cosmetic fashion, and satisfactory cosmesis was achieved. A recent small series by Kropp and colleagues (2008) of patients with complete epispadias showed that complications using the disassembly repair were in the acceptable range. Unlike the use of this in the exstrophy group, there was no ischemia of the glans or corpora. However, most required additional surgery because hypospadias was created in a number of patients. Ransley and colleagues reported excellent results using the modified Cantwell-Ransley procedure, saving cavernocavernostomy for patients with severe chordee and especially those in the older age group (Kajbafzadeh et al, 1995; Surer et al, 2001a). For a detailed description of the surgical reconstruction, see the previous discussion in the section on bladder exstrophy.

Achievement of urinary continence after epispadias repair in patients with isolated epispadias is summarized in Table 124–5. A majority of these patients underwent reconstruction by means of a Young-Dees-Leadbetter bladder neck plasty. Urinary continence was obtained in 82% of male patients (Ben-Chaim et al, 1995b). As in the exstrophy population, repair of the epispadiac deformity results in an increase of outlet resistance and possible increase in bladder capacity before bladder neck reconstruction. Although both complete epispadias and bladder exstrophy patients achieve improvement in bladder capacity after epispadias repair, the mean increase in overall capacity is higher in those with complete epispadias. This increase in bladder capacity may account for increased continence in this group compared with the classic bladder exstrophy population. **Clinically, these bladders are more supple, easier to mobilize, and more amenable to bladder neck reconstruction.** Ben-Chaim and colleagues (1995b) reported that the mean time to initial continence following bladder neck reconstruction was 90 days in patients with complete male epispadias compared with 110 days in those with bladder exstrophy. These results suggest that, for patients with complete epispadias, bladder capacity before reconstruction and the rate of achieving continence afterward are better than for patients with bladder exstrophy. The reason might be that the bladder is not exposed in utero and does not have any scarring from prior closure; therefore its potential for expansion is higher.

It was formerly thought that the effect of urethral lengthening and prostatic enlargement might be significant in complete epispadias by increasing outlet resistance if continence was not perfect as the child became older. Earlier in a series by Arap and colleagues (1988), the establishment of continence had no relation to puberty and usually occurred within 2 years, usually preceding puberty by several years. In the series reported by Ben-Chaim and colleagues (1995b), as stated previously, all patients obtained daytime continence at a mean of 9 months after

Table 124–5.

Urinary Continence after Bladder Neck Reconstruction (BNR) in Patients with Complete Epispadias

	BEN-CHAIM ET AL (1995b)	GEARHART ET AL (1993a)	KRAMER AND KELALIS (1982a)	ARAP ET AL (1988)	BURKHOLDER AND WILLIAMS (1965)
No. patients	15	11	53	38	27
Males					
Treated with BNR	11		32*	21	17
Surgically corrected incontinence	9		22	15	8
Percentage with surgically corrected incontinence	82		69	71	47
Females					
Treated with BNR	0	9	8	9	10
Surgically corrected incontinence	0	8	8	7	7
Percentage with surgically corrected incontinence	0	87	88	77	70

*All complete female epispadias cases.

bladder neck reconstruction, and 9 (82%) of 11 patients attained total day and night continence. All patients voided spontaneously. After a mean follow-up of 7 years, all patients maintained normal upper tracts and kidney function. All of them had cosmetically pleasing genitalia, as judged by parents, patients, and physicians, and experienced normal erections. A 36-year-old patient was married and had fathered three children. Many of the patients were younger than 16 years of age and had not yet become sexually active.

Results of urethroplasty in epispadias have been reported in a number of publications (Mesrobian et al, 1986; Ransley et al, 1989; Kajbafzadeh et al, 1995; Zaontz et al, 1998). In a modern series of modified Cantwell-Ransley repairs reported by Surer and colleagues (2001a), the incidence of postoperative fistula in the 3-month period after surgery was 19%, and the incidence of urethral stricture formation was less than 10%. Catheterization and cystoscopy could easily negotiate the neourethral channel in all patients who underwent a modified Cantwell-Ransley epispadias repair. In another modern series reported by Mollard and colleagues (1998), the continence rate was 84% and the fistula rate was less than 10%. In Mollard's series with long-term follow-up, patients had normal erections; the vast majority had regular sexual intercourse, and most had normal ejaculation or had fathered children. Most of Surer's patients were quite young, and assessment of genital reconstruction must be deferred until these patients are sexually mature and active (2001a). In a large series of Hammouda (2003) using the penile disassembly technique, 6% of boys were made hypospadiac and 1% had partial glandar loss. Although many methods of epispadias repair exist, meticulous follow-up of the urethra, selection of patients, and surgical experience remain the milestones of success. Lastly, Ransley and colleagues (Kajbafzadeh et al, 1995) obtained good results using a modified Cantwell-Ransley repair in a large number of patients with epispadias. The fistula rate was 4%, and the urethral stricture rate was 5.3%. Baird and colleagues (2005b) reported on 129 boys who underwent a modified Cantwell-Ransley repair. Of this group, 32 had penopubic epispadias. Twenty-four were primary repairs, and 8 were secondary repairs. Urethrocutaneous fistula occurred in 13% of primary and 25% of secondary repairs. A urethral stricture occurred in one patient.

In a different approach to the treatment of incontinence associated with epispadias reported by Duffy and Ransley (1998), 12 boys aged 3 to 7 years underwent endoscopic submucosal injection of plastic microspheres. All patients had undergone a modified Cantwell-Ransley epispadias repair before injection. The procedure was performed 24 times, with a total volume of 83 mL of material injected into 59 sites in the posterior urethra. Mean follow-up was 10.8 months. Three patients (25%) were rendered completely dry, the degree of incontinence was improved in six, and there was no change in three. The authors offered this as an alternative to bladder neck reconstruction in patients with primary epispadias. Ben-Chaim and colleagues (1995a) reported that submucosal injection of collagen in the bladder neck area can have a role in improving stress incontinence when the patient with complete epispadias has incomplete urinary control or as an adjunct after bladder neck reconstruction. In a recent study by Kibar and colleagues (2009b) of complete epispadias, 1 patient out of 12 was continent after bladder neck injection.

Kramer and colleagues (Mesrobian et al, 1986) reported the success of genital reconstruction in epispadias, with good long-term follow-up ending with a straight penis angled downward in almost 70% of patients, with normal erectile function. Of this group, 80% had satisfactory sexual intercourse, and of 29 married patients, 19 had fathered children. These results were mirrored in the long-term follow-up study of Mollard and colleagues (1998).

A carefully constructed and well-planned approach to the management of urinary incontinence in genital deformities associated with complete epispadias should provide a satisfactory cosmetic appearance, normal genital function, and preservation of fertility potential in most patients.

Female Epispadias

Female epispadias is a rare congenital anomaly; it occurs in 1 of every 484,000 female patients (Gearhart and Jeffs, 1998). The authors use the classification of Davis (1928), which describes three degrees of epispadias in female patients. In the least degree of epispadias, the urethral orifice simply appears patulous. In intermediate epispadias, the urethra is dorsally split along most of the urethra. In the most severe degree of epispadias, the urethral cleft involves the entire length of the urethra and sphincteric mechanism and the patient is rendered incontinent (see Fig. 124–32B). The genital defect is characterized by a bifid clitoris. The mons is depressed in shape and coated by a smooth, glabrous area of skin. Beneath this area, there may be a moderate amount of subcutaneous tissue and fat, or the skin may be closely applied to the anterior and inferior surface of the symphysis pubis. The labia minora are usually poorly developed and terminate anteriorly at the corresponding half of the bifid clitoris, where there may be a rudiment of a preputial fold. These external appearances are most characteristic: On minimal separation of the labia, one sees the urethra, which may vary considerably, as mentioned previously. The symphysis pubis is usually closed but may be represented by a narrow fibrous band. The vagina and internal genitalia are usually normal.

Associated Anomalies

The ureterovesical junction is inherently deficient in cases of epispadias, and the ureters are often laterally placed in the bladder with a straight course so that reflux occurs. The incidence of reflux is reported to be 30% to 75% (Kramer and Kelalis, 1982b; Gearhart et al, 1993a). Because there is no outlet resistance, the bladder is small and the wall is thin. However, after urethral reconstruction, the mild urethral resistance created allows the bladder to develop an acceptable capacity for potential later bladder neck reconstruction.

Surgical Objectives

Objectives for repair of female epispadias parallel those devised for male patients: (1) achievement of urinary continence, (2) preservation of the upper urinary tracts, and (3) reconstruction of functional and cosmetically acceptable external genitalia.

Operative Techniques

With the patient in the lithotomy position, the defect of the female epispadias with incontinence is apparent (Fig. 124–33A). The two halves of the clitoris are widely separated, and the roof of the urethra is cleft between the 9 o'clock and 3 o'clock positions. The smooth mucosa of the urethra tends to blend cephalad with the thin, hairless skin over the mons. The urethral incision is begun at the cephalad extent of the vertical incision at the base of the mons and is brought inferiorly through the full thickness of the urethral wall at the 9 o'clock and 3 o'clock positions (Fig. 124–33B). Sutures can be placed in the urethra to permit downward traction on the urethra so that the roof of the urethra is

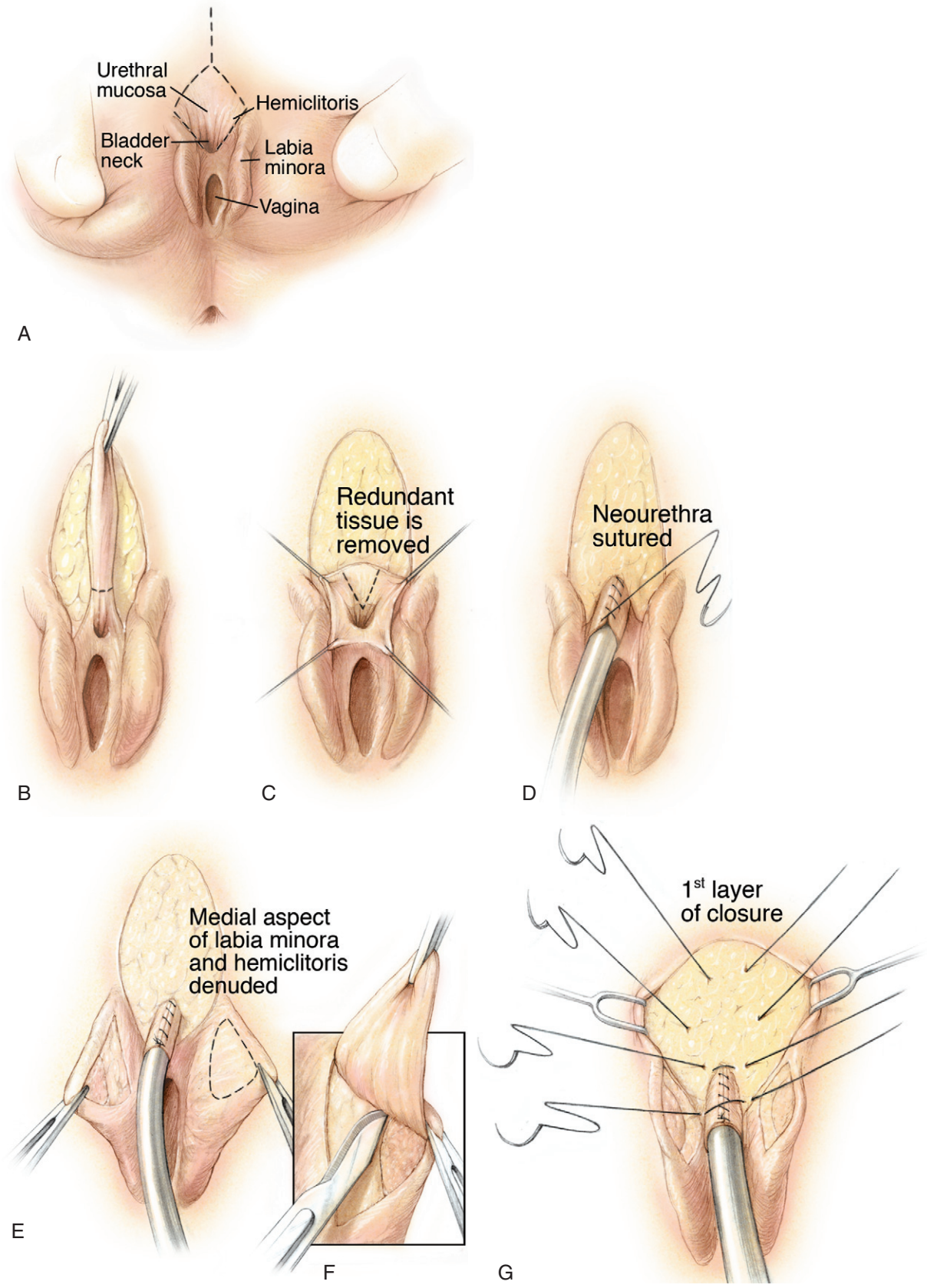


Figure 124–33. **A,** Typical appearance of female epispadias with initial incisions outlined. **B,** Excision of the glabrous skin of the mons. **C,** Tapering of the urethra with a dorsal resection of a wedge of tissue. **D,** Reconstruction of the urethra over a catheter with running suture. **E** and **F,** Medial aspect of the labia minora and clitoris. **G,** Initial layer of mons closure. *Continued*

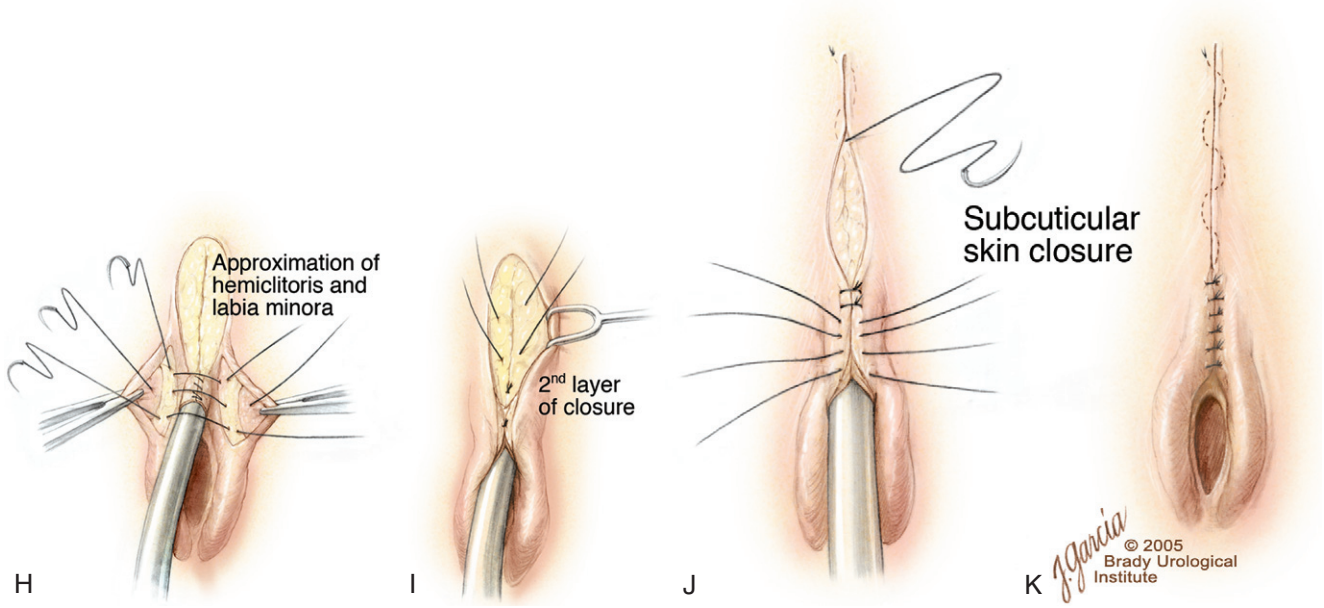


Figure 124–33, cont'd. **H,** Approximation of the labia minora over the urethral reconstruction. **I,** Second layer of mons closure. **J,** Creation of clitoral hood. **K,** Completion of mons closure. (© Brady Urological Institute.)

excised to a level near the bladder neck (Fig. 124–33C). Often, one finds the dissection proceeding under the symphysis. An inverting closure of the urethra is then performed over a 12- or 10-Fr Foley catheter. Suturing is begun near the bladder neck and progresses distally until closure of the neourethra is accomplished (Fig. 124–33D). Attention is then given to denuding the medial half of the bifid clitoris and the labia minora so that proper genital coaptation can be obtained.

After this is done, fat from the mons and subcutaneous tissue can be used to cover the suture line and obliterate the space in front of the pubic symphysis (Fig. 124–33E and F). The two halves of the clitoris and labia minora are brought together using interrupted sutures of 6-0 polyglycolic acid. The corpora may be partially detached from the anterior ramus of the pubis to aid in the urethral closure. Also, bringing these tissues together may contribute by adding resistance to the urethra. Mons closure is further aided by mobilizing subcutaneous tissue laterally and bringing it medially to fill any prior depression that remains (Fig. 124–33G). The subcutaneous layer is closed with 4-0 polyglactin suture in an interrupted fashion (Fig. 124–33H). The skin is closed with interrupted sutures of 6-0 polypropylene (Fig. 124–33I to K). A 10-Fr catheter is left indwelling for 5 to 7 days. Should the patient undergo simultaneous bladder neck reconstruction, a Foley catheter is not left in the urethra and the patient is placed in the supine position for the abdominal part of the procedure.

Achievement of a satisfactory cosmetic appearance of the external genitalia and urinary continence in the female child with epispadias represents a surgical challenge. Many operations have been reported to control continence in the epispadias group, but the results are disappointing. These procedures include transvaginal plication of the urethra and bladder neck, muscle transplantations, urethra twisting, cauterization of the urethra, bladder flap, and Marshall-Marchetti vesicourethral suspension (Stiles, 1911; Davis, 1928; Marshall et al, 1949; Gross and Kresson, 1952). These procedures may increase urethral resistance, but they do not correct incontinence or the malformed anatomy of the urethra, bladder neck, and genitalia.

The challenge of the small bladder in the female epispadias patient is comparable with a situation seen in some patients with closed bladder exstrophy. The small, incontinent bladder, with or without reflux, is hardly an ideal setting for a successful bladder neck reconstruction and ureteral reimplantation. A third of all incontinent epispadias patients have a bladder capacity of less than 60 mL, in the authors' experience and that of Kramer and Kelalis (1982b). Bladder augmentation, injection of polytetrafluoroethylene (Teflon) in the bladder neck area, and simultaneous bladder neck reconstruction and bladder neck augmentation have been offered as a solution to this challenge. However, primary closure of the epispadiac urethra in children with closed exstrophy was found to increase bladder capacity without causing hydronephrosis, and this approach has been applied to male and female patients with epispadias (Peters et al, 1988; Gearhart and Jeffs, 1989a; Ben-Chaim et al, 1995b). Although the authors typically perform urethral and genital reconstruction at about 1 year of age, they advocate delaying bladder neck reconstruction until the child is 4 to 5 years old. Not only does this delay allow the bladder to increase in capacity, it also allows the child to accept essential instructions for toilet training, which is critical to achieving satisfactory continence in the postoperative state. Data from deJong and colleagues (2000) combined a standard exterior genitoplasty plus urethroplasty with a percutaneous bladder neck suspension. The authors felt the suspension moved the bladder neck into an intra-abdominal position. In this small series one was dry and voiding, two required bladder neck bulking agents, and one was on CIC. In another small series from India, Bhat and colleagues (2008) performed a urethroplasty and the perineal musculature was double-breasted over the urethral closure from the bladder neck distally. They report impressive results with two patients totally continent, one partially continent, and one continent after bladder neck reconstruction.

Surgical Results

The continence rate of 87.5% in our female patients is comparable with that of Hanna and Williams (1972), who found a 67% continence rate in female patients with good bladder capacity, and

that of Kramer and Kelalis (1982b), who reported an 83% continence rate in patients with adequate bladder capacity. All of the authors' patients seen for primary treatment have achieved a capacity in excess of 80 mL (see Table 124–5).

Hendren (1981) and Kramer and Kelalis (1982b) showed that genitourethral reconstruction can be accomplished with satisfactory results. At our institution, patients who underwent prior urethral and genital reconstruction had a mean bladder capacity at bladder neck reconstruction of 121 mL, making the bladder suitable for the reconstruction and eventual continence without the use of augmentation cystoplasty or need for intermittent catheterization.

The time interval to achieve continence in our patients was a mean of 18 months for those who underwent genitourethral and bladder neck reconstruction in one procedure and 23 months for those who underwent preliminary urethroplasty and genital reconstruction after bladder neck reconstruction. In a series by Klauber and Williams (1974), the mean interval to acceptable continence was 2.25 years. Also, in a series by Kramer and Kelalis (1982b), some patients became continent within a short period, whereas complete continence was delayed for several years in others. The time delay for achieving continence may represent increased pelvic muscular development, as suggested by Kramer and Kelalis (1982b). In regard to the interval to continence, no advantage appears to be gained by preliminary urethroplasty. However, the authors believe that the advantage gained by increased bladder capacity at the time of bladder neck reconstruction outweighs any advantage gained by a combined approach. In the series by Bhat and colleagues (2008) and deJong and coworkers (2000), continence rates were between 40% and 60% without further bladder neck repair or injection.

Key Points: Epispadias—Priorities in Management

- The length and width of the urethral plate on the male is assessed.
- The length and width of the urethral plate and genitalia relationships in the female is assessed.
- The bladder size is measured under anesthesia by gravity cystogram.
- The bladder neck sphincter (if present) is assessed by cystoscopy.
- Any associated anomalies are assessed.

ADOLESCENTS AND ADULTS WITH EXSTROPHY

Male Concerns

The mainstay of male concerns is the length, appearance, and axis deviation (chordee) associated with exstrophy. In the typical adolescent and adult these three concerns are all intertwined. In this author's significant experience, most boys seek consultation for all of these concerns around the time they begin showering at school. More penile length can be achieved (around an inch) by degloving the penis and cutting all scar tissue and any remnants of the suspensory ligaments. A conscious decision about the appearance must be made preoperatively because the authors have found that the placement of tissue expanders and expanding the penile skin if satisfactory is superior to full-thickness skin grafting (Fig. 124–34). If the penile skin is inferior and not a good candidate to be expanded, then full-thickness grafting is a suitable alternative (Hernandez et al, 2008). Residual dorsal chordee lasting from childhood is not uncommon because the corporal anatomy is longer on the ventrum than the dorsum, and this oftentimes remains to be adequately corrected. The use of grafts (dermal grafts, tunica vaginalis, human alloderm) can be used to lengthen the dorsal aspect of the penis. The authors' preference is human alloderm because it is readily available, durable, and easy to use. Because of its anatomy, the penis must be opened dorsally for one half of its circumference as described by Perovic and Djinovic (2007) to both lengthen and straighten the penis. Early measurements and determinations from artificial erections must be adequate because after grafting, the artificial erections can leak saline through the suture lines and give misleading information about the adequacy of correction.



Figure 124–34. Tissue expander recently placed under the penile shaft on the right.

In rare cases the penis is so inadequate that a neophallus must be constructed. The authors and their pediatric plastic surgery colleagues have used a radical free-flap phalloplasty in five patients with excellent results (Gearhart and Redett, 2010).

Female Concerns

The three main female concerns are the appearance of the external genitalia, adequacy of the vaginal opening, and uterine prolapse. Although the authors correct the female external genitalia defect at birth, sometimes "touch-up" surgery needs to be performed at puberty. The three cosmetic concerns are the appearance of the lower abdominal wall, the mons veneris, and the clitorides. The authors' group has found that in females who underwent pelvic osteotomy at the time of newborn closure, the appearance of the mons veneris is more cosmetic and in less need of repair while in the patients who do not have an osteotomy the mons is thin, inelastic, and flat appearing. To repair this in adolescence, the mons flaps are raised laterally and brought to the midline and sewn to the fascia and themselves easily. In extreme cases with an extremely scarred flat mons veneris, tissue expanders are placed laterally and gradually inflated over 6 weeks. These flaps are moved medially and used to reconstruct the mons. The pseudocapsules are rolled together in the midline to give the mons a more elevated appearance. This oftentimes involves the lower abdominal wall as well. Dissection is performed laterally, the lateral flaps are mobilized, and the midline scars are all excised to improve the

appearance. This same defect is seen in the clitorides when an osteotomy is not performed at birth. They tend to be separated and scarred. Mobilizing lateral mons veneris flaps brings the clitoral halves closer to the midline and makes them easier to bring into apposition. Local estrogen cream is used three times daily for 2 weeks before any external genital surgery to soften scars, increase skin availability, and improve local vascularity. The vaginal orifice is more vertical and somewhat stenotic in exstrophy females compared with normal females. The young women appear at puberty having difficulty inserting tampons and also with intromission. These are easily repaired by an inverted U-flap of perineal skin inserted into the posterior vaginal wall, which is incised vertically (Stein et al, 1995). Beware that the cervix in exstrophy females is in the anterior vaginal wall, and sometimes opening the stenotic opening allows for uterine prolapse, which would have occurred anyway. If the patient is not sexually active, a vaginal dilator is used once daily until sexual activity occurs.

As in the genitalia and lower abdominal wall, prolapse of the uterus is more common in those who did not undergo osteotomy at birth. However, the authors have still seen it in those who did undergo pelvic closure with an osteotomy. The degree of prolapse depends on the degree of pubic bone divergence and the diameter of the opening in the levator hiatus for the vagina and rectum (Miles-Thomas et al, 2006). Because of the rarity of this condition, the average gynecologist has often never seen an adolescent or adult woman with it. The authors suspend the uterus to the sacrum with human alloderm or "pelvicoil." The suspensory substance is sewn to the uterus from the cervix and dome of the uterus so that it can be snugly suspended to the ligaments on the front of the uterus. The authors do this prophylactically in adolescents undergoing continent diversion or other major abdominal procedures (Stein et al, 1999).

SEXUAL FUNCTION AND FERTILITY IN THE EXSTROPHY PATIENT

Male Patient

Reconstruction of the male genitalia and preservation of fertility were not primary objectives in early surgical management of bladder exstrophy. **Sporadic instances of pregnancy or the initiation of pregnancy by males with bladder exstrophy have been reported.** In two large exstrophy series, male fertility was documented. Only 3 of 68 men in one study (Bennett, 1973) and 4 of 72 in another (Woodhouse et al, 1983) had successfully fathered children. In a large series of 2500 patients with exstrophy and epispadias (Shapiro et al, 1985), there were 38 males who had fathered children.

Hanna and Williams (1972) compared semen analyses in men who had undergone primary closure and ureterosigmoidostomy. A normal sperm count was found in only one of eight men after functional closure and in four of eight men with diversion. The difference in observed fertility potential is probably attributable to iatrogenic injury to the verumontanum during functional closure or bladder neck reconstruction. Retrograde ejaculation may also account for low sperm counts after functional bladder closure. **In a long-term study from our institution, Ben-Chaim and colleagues (1996) found that 10 of 16 men reported they ejaculated a few cubic centimeters of volume, 3 ejaculated only a few drops, and 3 had no ejaculation. Semen analysis was obtained in four patients: Three had azoospermia, and one had oligospermia. The average ejaculated volume of the patients who had sperm counts was 0.4 mL.** In another large series by Stein and colleagues (1994) from Germany, the authors found that none of the patients who had reconstruction of the external genitalia could ejaculate normally, nor had they fathered children. Five patients who did not undergo reconstruction had normal ejaculation, and two had fathered children. The conclusion was that male patients with genital reconstruction and closure of the urethra demonstrated high risk of infertility. In a recent large study of successful primary closure from a large exstrophy center by Ebert and colleagues (2008), sperm parameters were poor in 18 of 21 patients and FSH was increased in 25% of patients (Ebert et al, 2010).

Assisted reproductive techniques have been applied to the exstrophy population. **Bastuba and colleagues (1993) reported pregnancies achieved with the use of assisted reproductive techniques. In a small series from the Netherlands, all patients delivered a normal infant after ICSI** (D'Hauwers et al, 2008). **Regardless of the method of reconstruction of the external genitalia and bladder neck, newer techniques such as gamete intrafallopian transfer (GIFT) or intracytoplasmic sperm injection (ICSI)** can be used to assist these patients in their goal of pregnancy achievement. Use of GIFT or ICSI in 21 men with exstrophy led to successful pregnancy with no instances of exstrophy in any of the offspring in our exstrophy population.

Sexual function and libido in exstrophy patients are normal (Woodhouse, 1998). The erectile mechanism in patients who have undergone epispadias repair appears to be intact because 87% of boys and young men in the Hopkins series experienced erections after repair of epispadias (Surer et al, 2001a). Poor or absent ejaculation may occur after genital reconstruction. Complete absence of ejaculation is rare, but the emission that does occur may be slow and may occur for several hours. Milking the urethra in an antegrade fashion from proximal to distal has provided pregnancy in some cases (Woodhouse, 1999). In papers from both Woodhouse (1998) and Ben-Chaim and colleagues (1996) and Ebert and colleagues (2008), most patients reported satisfactory orgasm; half of the men and all of the women described intimate relationships as serious and long term. In the series by Ben-Chaim, the only patients who had no ejaculation were two patients who had undergone cystectomy. Overall, it seems from the experience in England, Germany, and the United States that most men with exstrophy achieve erection and have a reasonable sex life.

With better reconstructive techniques, patients with bladder exstrophy are living long and fruitful lives. The authors have recently reported a case of prostate cancer in a reconstructed male exstrophy and have seen two others in the recent past.

Female Patient

Further reconstruction of the female genitalia may be necessary during adolescent years. In our experience, the external genitalia are fully reconstructed at the time of initial exstrophy closure because with the use of osteotomy, a suitable mons pubis can be created and the bifid clitoris and labia can easily be brought together in the midline. **Vulvoplasty is sometimes indicated in patients before they become sexually active or start using tampons. In Woodhouse's experience** (1999), **most patients required vaginoplasty before intercourse could take place.** Woodhouse reported successful intercourse in all of his patients, but three found it painful. Stein and colleagues (1995) from Germany reviewed a large series of patients with exstrophy

and found that a cut-back vaginoplasty was required before intercourse in 23 patients. The authors have also seen several patients who have not had vulvoplasty, have two clitoral halves, have a normal sex life and normal orgasm, and desire no surgical repair of this condition.

Mathews and colleagues (2003) reported on a large series of girls and women with the exstrophy complex. All girls older than 18 years indicated that they had normal sexual desire, and many were sexually active. Mean age for commencement of sexual activity was 19.9 years. Although a few patients complained of dyspareunia, most indicated normal orgasms. Other studies by Baird and colleagues (2005a) and Ben-Chaim and colleagues (1996) confirmed the results of the larger study by Mathews. Some patients indicated that they restricted sexual activity because of the cosmetic appearance of their external genitalia. Mons plasty is therefore important to obtain a cosmetically pleasing appearance either in infancy or in adolescence because hair-bearing skin and fat should be used to cover the midline defect. As mentioned earlier, the authors perform this procedure at the time of initial closure. It certainly can be done in adolescence with the use of rhomboid flaps, as popularized by Kramer and Jackson (1986).

Obstetric Implications

Review of the literature reveals 45 women with bladder exstrophy who successfully delivered 49 normal offspring. The main complication after pregnancy was cervical and uterine prolapse, which occurred frequently (Krisiloff et al, 1978). Burbage and colleagues (1986) described 40 women ranging from 19 to 36 years of age who were treated in infancy for bladder exstrophy; 14 pregnancies in 11 of these women resulted in 9 normal deliveries, 3 spontaneous abortions, and 2 elective abortions. Uterine prolapse occurred in 7 of the 11 patients during pregnancy. All had undergone prior permanent urinary diversions. Spontaneous vaginal deliveries were performed in those women, and cesarean sections were performed in women with functional bladder closures to eliminate stress on the pelvic floor and to avoid traumatic injury to the urinary sphincter mechanism (Krisiloff et al, 1978). With modern reconstructive techniques, successful pregnancies have been reported in female patients who have undergone continent urinary diversion (Kennedy et al, 1993).

Woodhouse (1999) reported prolapse in a number of patients, and it was said to be a considerable problem to correct. Seven patients had total prolapse, one of whom had never had intercourse or a pregnancy. Woodhouse believes that prolapse may occur in up to half of patients after pregnancy. In a report from Mathews and colleagues (2003), vaginal prolapse and uterine prolapse were noted commonly and even quite early in life (mean age 16 years). Uterine suspension provided only modest success for the prevention of recurrent prolapse. Stein and colleagues (1995), in a large exstrophy series from Germany, found that uterine fixation was required to correct prolapse in 13 patients with long-term follow-up of more than 25 years. The anterior displacement of the vaginal os and the marked posterior displacement of the dorsorectalis sling with its deficient anterior component were postulated as reasons for prolapse. With the modern use of osteotomy with resultant recreation of the pelvic floor, the authors have seen less uterine prolapse in their series.

Regardless of the method of repair, the uterus must be anchored in such a way that it is fixated in the pelvis and less susceptible to prolapse. Some authors have advocated fixation of the uterus to the anterior abdominal wall in childhood; this, they say, prevents prolapse but still allows normal pregnancy. Woodhouse (1999) believed that, although prophylactic surgery may be helpful, once prolapse occurs, anterior fixation is insufficient to correct uterine prolapse in the exstrophy patient. The authors fix both sides of the uterus from the cervix to the top of the uterus bilaterally to the presacral ligaments.

LONG-TERM ADJUSTMENT ISSUES

Interest has increased in long-term adjustment issues in patients with bladder exstrophy. Children with exstrophy undergo multiple reconstructive surgeries and have potential problems with respect to urinary incontinence and sexual dysfunction. However, the ultimate outcome would be better measured by how these children adjust overall in society. The severe nature of the exstrophy disorder could predict that this birth defect could have substantial psychologic implications. Parental reaction to the child's medical condition may change the way the parents interact with the child. Incontinence may have a negative impact on social function and self-esteem. Multiple hospitalizations may interfere with the ability to be like other children. Concerning the potential medical and psychologic implications of this anomaly, children born with exstrophy may be at increased risk for difficulties.

Formerly, there was a limited amount of information in the literature concerning this condition and its treatment and whether or not it has a deleterious effect on children and their families. Montagnino and colleagues (1998) evaluated younger children who performed more poorly and had disturbed behavior, specifically in skills related to function in school. Children who achieved continence after the age of 5 years were more likely to have problems with acting-out behavior. There were no differences in adjustment on the basis of male or female sex, bladder versus cloacal exstrophy, type of continence strategy, or gender reassignment versus no reassignment. **The conclusions of this long-term study were that children with exstrophy do not have clinical psychopathology** (Montagnino et al, 1998). There was acting-out behavior rather than depression or anxiety, suggesting that improved outcomes may be achieved through a focus on normal adaptation rather than potential psychologic stress. In addition, earlier achievement of continence through reconstructive efforts is potentially of psychologic benefit. This work was further supported by Catti and colleagues (2006), who found in adults that quality of life was better in those who were continent with a good body image (Catti et al, 2006).

Reiner (1999) studied 42 children with exstrophy and presented preliminary results suggesting that these patients tend to have more severe behavioral and developmental problems than children with other anomalies, significant body distortion, and self-esteem problems. Reiner has recommended early intervention with the exstrophy patient and family and continuation with long-term psychiatric support into adult life. In a study from Europe, Feitz and colleagues (1994) found a more positive picture when they evaluated 11 women and 11 men with exstrophy, of whom 9 women (82%) and 10 men (91%) did not manifest any clinical levels of psychologic stress. The authors concluded that these adults had a positive attitude toward life. With the use of structured instruments and appropriate evaluation and interviews, Reiner and Gearhart (2006) indicated that all 20 patients evaluated met criteria for at least one anxiety disorder. Older patients experienced waning of anxiety associated peer discovery of incontinence following successful surgical reconstruction, and all noted intensified sexual activity with age. New data from Reiner and colleagues (2008) of a large series of male patients found that 14%

experienced suicidal ideation. As they became older, 31% experienced this phenomenon and a few attempted adolescent/early adulthood suicide. One succeeded. These findings underline the importance of screening patients as they become older for psychopathology.

In an important study by Lee and colleagues (2006), females were found to have more close friendships, fewer disadvantages in relation to healthy peers, and more partnerships than males. There were no gender differences in adjustment within educational and professional careers, which overall were good. Ebert and colleagues (2005) reviewed by questionnaire a group of 100 exstrophy adolescents. Education and social integration were high. All patients were heterosexual, and almost 50% were sexually active. Almost 60% expressed anxiety about sexual activity. The most important finding was that 94% of patients expressed an interest in psychologic assistance. These exciting new data underline the importance of early childhood intervention.

Being born with exstrophy does not result in childhood psychopathology. **Children with exstrophy exhibit some tendency toward increased problems with acting out or lack of attainment of age-appropriate adaptive behavior** (Montagnino et al, 1998; Reiner, 1999). Therefore all experts in childhood psychology tend to agree that counseling should come from the nursing and medical staff early in the exstrophy condition. Likewise, the patient and parents should be served by an experienced exstrophy support team, and psychologic support and counseling should be extended into adult life.

Acknowledgment

This chapter is dedicated to the memory of Dr. Jean Cendron (1923-2008) and Dr. Robert D. Jeffs (1924-2006), the pioneers of modern exstrophy surgery.

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chapter 125

Bladder Anomalies in Children

Dominic C. Frimberger, MD ● Bradley P. Kropp, MD, FAAP

Bladder and Urachal Development
Classification of Bladder Anomalies
Conclusion

Although anomalies of the urogenital tract are among the most commonly diagnosed antenatal malformations, the incidence of all congenital bladder anomalies is low (Carrera et al, 1995). **Additionally, bladder anomalies are often a reaction to infravesical obstruction or part of a more serious disorder rather than a true isolated structural malformation.** Bladder anomalies can be severe, cause urinary obstruction, and even lead to renal failure. Early detection and intervention are crucial to prevent future decompensation of the genitourinary tract. Anomalies can be detected prenatally or postnatally using ultrasound but often require voiding studies for definite diagnosis. This chapter reviews congenital bladder abnormalities in the prenatal and postnatal period and focuses on malformations not caused by infravesical obstruction. This chapter includes a discussion of the initial presentation, diagnosis, and current treatment options for the different entities and a classification based on the prenatal and postnatal presentations of bladder anomalies.

BLADDER AND URACHAL DEVELOPMENT

A comprehensive understanding of the embryologic development of the bladder and urachus is mandatory to correctly interpret the prenatal and postnatal findings and to counsel the parents toward the optimal management.

Between the fourth and sixth weeks of gestation, the urorectal septum divides the endodermal cloaca into a ventral urogenital sinus and a dorsal rectum. The cranial part of the urogenital sinus is continuous with the allantois and develops into the bladder and pelvic urethra. The caudal portion gives rise to the phallic urethra in males and the distal vagina in females. Unlike in males, the entire female urethra is derived from the pelvic part of the urogenital sinus. The allantois develops as an extraembryonic cavity from the yolk sac and connects with the cranioventral portion of the cloaca, the future bladder. Around the fourth to fifth month of gestation, the allantoic duct and the ventral cloaca involute as the bladder descends into the pelvis. The descent causes the allantoic duct to elongate because it does not grow with the embryo. This epithelialized fibromuscular tube continues to become narrower until it obliterates into a thick fibrous cord, the urachus (Moore, 1982). The obliterated urachus becomes the median umbilical ligament and connects the apex of the bladder with the umbilicus (Nix et al, 1958).

Normal Antenatal Sonographic Findings of the Bladder

The fetal bladder presents as an elliptical structure filled with anechoic fluid within the pelvis. It is bordered laterally by the umbilical arteries. The pubic bones mark the anterior border, and the rectosigmoid indicates the posterior border. The bladder wall thickness should not exceed 3 mm. The mucosa and musculature present with a similar echogenicity to other structures in the pelvis (McHugo and Whittle, 2001). **The bladder can be visualized in about 50% of cases in the fetal pelvis at the tenth week of gestation, concurrent with the onset of urine production** (Green and Hobbins, 1988). **The detection rate increases with fetal age to 78% at 11 weeks, 88% at 12 weeks, and almost 100% at 13 weeks** (Rosati and Guariglia, 1996). Compared with abdominal ultrasound, transvaginal ultrasound increases the quality of the obtained images and detection rate. Because the fetal bladder empties every 15 to 20 minutes, a second ultrasound in the same setting is mandatory in case of nonvisualization of the bladder. The bladder's diameter increases during the first trimester but should not be more than 6 to 8 mm.

The fetal sex, amount of amniotic fluid, and appearance of the umbilical cord become increasingly important in the interpretation and differential diagnosis of abnormal bladder findings. Fetal sex is difficult to determine before week 14 and should not be based on the presence or absence of a phallus but on the visualization of testes (Efrat et al, 1999). The measurement of amniotic fluid as an indicator of fetal urine production is a critical portion of every antenatal ultrasound. Until 16 weeks of gestation, the amniotic fluid is mainly consistent with placental transudate, at which time it changes to predominantly fetal urine (Takeuchi et al, 1994). The umbilical cord should contain two arteries and one vein without evidence of a fluid-filled urachus (Bronsthein et al, 1990).

CLASSIFICATION OF BLADDER ANOMALIES

Bladder anomalies can present as either abnormal findings during prenatal ultrasound or postnatally due to symptoms or as a part of an unrelated workup.

Classifying bladder anomalies is difficult due to the large variety of possible malformations, the relatively low incidence of the anomalies, and the common association with other congenital anomalies. Therefore it seems reasonable to classify the different presentations into two main groups:

- Prenatally detected
  - Dilated
  - Nondilated
- Postnatally detected
  - Urachal abnormalities
  - Bladder diverticulum
  - Bladder duplication
  - Other bladder anomalies

Prenatally Detected Bladder Anomalies

The fetal bladder can either appear dilated, hypoplastic, or absent on ultrasound. If the bladder is dilated, the condition can be due to obstruction or caused by incomplete empting of the bladder itself without evidence of a mechanical obstruction. In nondil ated conditions, the bladder is either completely absent or is unrecognizable as a fluid-filled structure due to incomplete formation.

Dilated Fetal Bladder

In the first trimester, the fetal bladder is considered to be dilated if larger than 7 mm on ultrasound. If, on subsequent ultrasounds, the bladder continues to retain urine and shows no evidence of urine cycling, concern regarding obstruction should be raised. If the amniotic fluid does not increase, this may indicate the progression to oligohydramnios. **Determination of the sex of the child is important because of the male gender predominance of certain diseases such as posterior urethral valves (PUVs) or prune-belly syndrome.** It can be difficult to distinguish in utero if the dilatation is due to obstruction. In a retrospective study, Kaefer and colleagues (1997) described 15 patients with marked bladder dilatation in utero, 8 with and 7 without obstruction. All of the obstructed cases presented with moderate to severe oligohydramnios and a marked increase in renal echogenicity, while all but one of the nonobstructed bladders had normal amniotic fluid levels and regular renal echogenicity (Kaefer et al, 1997). Therefore fetuses with nonobstructive dilatation appear to pass enough urine to maintain renal function and adequate amniotic fluid levels throughout the pregnancy (Mandell et al, 1992).

Dilatation Caused by Obstruction

Urethral Anomalies and External Bladder Outlet Obstruction. **Dilatations of the fetal bladder caused by anatomic obstructions are mostly due to urethral anomalies or external obstruction.** Urethral anomalies include congenital urethral strictures, anterior and posterior urethral valves, and urethral atresia. Compression of the bladder outlet region can be due to obstructing syringoceles, a sacrococcygeal teratoma or pelvic neuroblastoma, an anterior sacral myelomeningocele, a dilated vagina in a girl with a cloacal anomaly, or with rectal anomalies. The observed bladder changes are due to mechanical obstruction and affect bladder development at a critical time point, which can lead to bladder wall hypertrophy and remodeling (Pagon et al, 1979; Beasley et al, 1988; Stephens and Gupta, 1994).

Dilatation in Nonobstruction

Prune-Belly Syndrome and Neurogenic Bladder Disease. Affected patients do not demonstrate any sign of obstruction on postnatally performed voiding studies or cystoscopic evaluations, except when urethral atresia is also present. In this case the presentation is similar to posterior urethral valve patients. However, it is possible that the largely distended bladder, as in prune-belly syndrome, is caused by a transient obstruction in utero, and in some cases the presence of urethral atresia has been noted with prune-belly syndrome. Another possibility for the distention is the presence of neurologic disorders leading to an inability to empty the bladder in utero.

Congenital Megacystis

The term *megacystis* is often used to describe any condition leading to a distended fetal bladder in utero, without referring to the cause of the dilation. Historically, congenital megacystis was thought to be caused by bladder neck obstruction, leading to massive bilateral vesicoureteral reflux (VUR) and a thin bladder wall (Williams, 1957; Paquin et al, 1960). Even the describing authors recognized that surgical interventions at the bladder neck level did not change the future outcome. Harrow (1967) revisited the subject and recognized that all patients had normal urethras and complete emptying of their bladders on voiding cystourethrography. Therefore **the observed reflux is not an aftereffect of obstruction, but rather the cause of the bladder dilatation from continuous recycling of the urine between the upper tract and bladder** (Harrow, 1967). Congenital megacystis is defined currently as a dilated, thin-walled bladder with a wide and poorly developed trigone. The wide-gaping ureteral orifices are displaced laterally, causing massive reflux (Fig. 125–1). Bladder contractility is normal, although a majority of the urine refluxes into the ureters with each void. No neurogenic abnormalities are described. Most patients are recognized prenatally and should be placed on prophylactic antibiotics after birth (Mandell et al, 1992). **Correcting the reflux often restores normal voiding dynamics and should be performed after 6 months of age.** Reduction cystoplasty can be performed but is usually unnecessary (Burbige et al, 1984). Although the bladder is large enough to accommodate the tapered ureters even in a young infant, the operation can be difficult due to the bladder wall's thinness.

Congenital megacystis has been recognized in association with microcolon-intestinal hypoperistalsis syndrome. This syndrome is a rare congenital disorder characterized by a dilated, nonobstructive urinary bladder and hypoperistalsis of the gastrointestinal tract. The syndrome can be identified by antenatal ultrasound by the appearance of a largely dilated bladder. It has been reported mostly in females and is usually considered lethal (Srikanth et al, 1993; Lashley et al, 2000). So far there are only 10 patients who lived beyond the first year of life, and almost all need total parental nutrition. Once identified after birth, the distended bladder requires drainage via intermittent catheterization or vesicostomy placement. Long-term data concerning the urinary tract are not available due to the short life span of the patients (Bloom and Kolon, 2002).

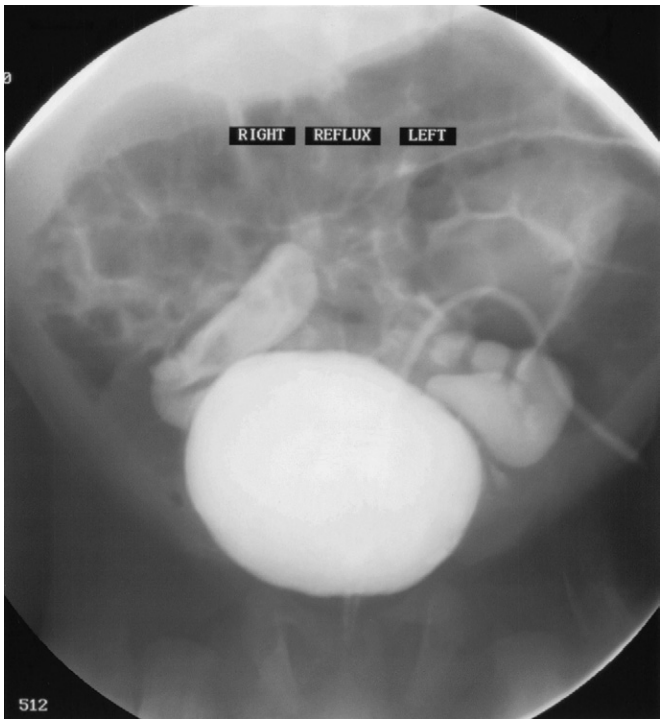


Figure 125–1. Megacystis. Vesicoureterogram image of congenital megacystis with associated reflux.

Nondilated or Absent Fetal Bladder

In order to truly diagnose an absent fetal bladder on ultrasound, the examination has to be repeated after 15 to 20 minutes to rule out that the fetus has not simply emptied the bladder.

Cloacal and Bladder Exstrophy. Bladder exstrophy conditions are characterized by the presence of a bladder template only. Therefore it can be suspected in the absence of regular bladder filling during fetal ultrasound. Bladder exstrophy can be distinguished from bladder agenesis by the bladder template on the lower abdominal wall, which, along with the amniotic fluid level, remains normal throughout the pregnancy (Mirk et al, 1986; Gearhart et al, 1995).

Bladder Hypoplasia. The bladder can be hypoplastic due to inadequate filling or storing of urine during fetal life. Although the bladder is formed during fetal development and can be detected on antenatal ultrasound throughout pregnancy, it never reaches an adequate capacity. Conditions caused by inadequate bladder outlet resistance (e.g., severe epispadias), separation defects (e.g., urogenital sinus abnormalities), abnormalities of renal development (e.g., bilateral renal dysplasia or agenesis), or urine bypassing the bladder (e.g., ureteral ectopia) can all lead to underdevelopment of the fetal bladder. Some of these bladders grow once the malformation is corrected; however, later bladder augmentation is often required to reach adequate capacity (Gearhart, 2002).

Bladder Agenesis. Embryologic development of bladder agenesis remains difficult to explain. The division of the cloaca into the urogenital sinus and the anorectum is apparently regular because the hindgut is usually normal. Therefore the defect can be due to either atrophy of the cranial part of the urogenital sinus or a failure to incorporate the mesonephric ducts and ureters into the trigone (Krull et al, 1988). The absence of the bladder is often associated with neurologic, orthopedic, or other urogenital anomalies such as renal dysplasia or agenesis or absence of the prostate, seminal vesicles, penis, and vagina (Aragona et al, 1988). It is a rare anomaly; only 16 live births have been reported out of the 45 known cases in the English literature. All but two were female (Adkes et al, 1988; Gopal et al, 1993; DiBenedetto et al, 1999). The defect is only compatible with life if the ureters drain ectopically into normally developed müllerian structures in the female or in the rectum in males. In surviving infants, the diagnosis can be confirmed by retrograde ureteronephrograms via the ectopic openings. Renal function can be preserved after creation of an ureterosigmoidostomy or external stoma (Glenn, 1959; Berrocal et al, 2002).

Key Points: Prenatally Detected Bladder Anomalies

- Prenatally detected bladder anomalies can be categorized into dilated and nondilated anomalies.
- Dilated bladders can be caused by anatomic or functional obstruction. They are commonly associated with severe anomalies, are often the cause for oligohydramnios, and can require fetal or immediate postnatal intervention to prevent fetal demise.
- Nondilated anomalies are associated with the most severe forms of congenital urologic malformations like bladder and cloacal exstrophy. Usually normal amniotic fluid levels are found.
- Bladder agenesis is only compatible with life if the ureters drain ectopically.

Postnatally Detected Bladder Anomalies

The malformations in this group can be diagnosed by antenatal ultrasound. However, most patients are diagnosed postnatally due to symptomatic disease or during workup for a nonrelated disease. Malformations listed in the prenatally detected group usually severely affect fetal development, are often associated with other malformations, and require prenatal or postnatal interventions. **Postnatal-detected defects, on the other hand, usually do not affect fetal development and generally can be treated with conservative measures or a single surgical intervention.** Bladder anomalies in the infant or child are suspected in cases of urinary tract infections, hematuria, voiding difficulties, anatomic malformations and masses, or umbilical site drainage.

Urachal Anomalies

Understanding the embryologic development of the urachus and its unique location is the key to understanding congenital urachal anomalies. The urachus is located preperitoneal in the center of a pyramid-shaped space. This space is lined by the obliterated umbilical arteries, with its base on the anterior dome of the bladder and the tip directed toward the umbilicus (Fig. 125–2). The urachal length varies from 3 to 10 cm. It has a diameter between 8 and 10 mm and can connect with one or both obliterated umbilical arteries. Microscopically, three layers can be identified. An inner layer consists of either transitional or cuboidal epithelial cells, surrounded by a layer of connective tissue. A smooth muscle layer in continuity with the detrusor muscle comprises the outer layer. Because the urachus is surrounded by the umbilicovesical fascia, disease processes usually remain contained



Figure 125–2. Urachal anatomy. (From Cullen TS. Embryology, anatomy and diseases of the umbilicus. Philadelphia: WB Saunders; 1916.)

inside the pyramid-shaped space (Hammond et al, 1941). The urachus can remain either completely open or obliterate partially, leading to the formation of cystic structures at any site throughout its course.

Ashley and colleagues (2007) examined the medical records of 176 patients diagnosed with an urachal anomaly, and urachal remnants were found in 46 children and 130 adults. Children mostly presented with umbilical drainage or on physical examination, and 74% underwent excision, while 66% of adults had hematuria or pain and underwent excision in 90%. Surgical treatment in children consisted of simple excision, whereas more than 50% of adults required partial or radical cystectomy due to malignancy. They concluded that urachal anomalies present and progress differently in pediatric and adult populations and recommended urachal excision in early childhood to prevent later problems or cancer formation. **There was no reported evidence that a persistent urachal remnant in childhood was the cause of later cancer development** (Ashley et al, 2007). Galati and colleagues (2008) reported 23 children with urachal remnants, 10 of whom underwent excision due to symptomatic problems. In their treatment protocol, asymptomatic remnants are managed with physical and sonographic examination. **They found that spontaneous resolution with nonoperative management is likely with remnants in patients younger than 6 months.** However, if symptoms persist or the remnant fails to resolve after age 6 months, they recommend excision (Galati et al, 2008). Four different urachal anomalies have been described (Fig. 125–3).

- Patent urachus (50%)
- Umbilical-urachus sinus (15%)
- Urachal cyst (30%)
- Vesicourachal diverticulum (3% to 5%)

Patent Urachus

Patent urachus is explained by nondescent of the bladder or, more commonly, failure of the epithelial-lined urachal canal to obliterate (Gearhart, 2002). Bladder obstruction during fetal development has been blamed for the urachus remaining tubular. The fact that urachal patency is often absent with severely obstructed bladders in utero, however, casts doubt on this theory. Additionally, only up to 14% of patients with a patent urachus have postnatal confirmation of in utero bladder obstruction (Schrenck and Campbell, 1972; Mesrobian et al, 1997). It seems possible that obliteration of the urachus may be independent from the level of bladder distention. Therefore retubularization, rather than primary patency, might be the cause for urinary drainage from the umbilicus. This theory is supported by reports of umbilical urinary fistulas in acquired bladder obstructions later in life (Schubert et al, 1983; Berman et al, 1988).

A patent urachus is suspected in the neonatal period by continuous or intermittent drainage of fluid from the umbilicus. The most common organisms cultured from the umbilical drainage include *Staphylococcus aureus, Escherichia coli, Enterococcus, Citrobacter,* and rarely *Proteus* species (Mesrobian et al, 1997). Additional presentations include an enlarged or edematous umbilicus and delayed healing of the cord stump (Razvi et al, 2001; Schiesser et al, 2003). The diagnosis is confirmed by demonstration of the fluid-filled canal on longitudinal ultrasound or contrast filling on retrograde fistulogram or voiding cystourethrogram (VCUG) (Fig. 125–4) (Mesrobian et al, 1997). Computed tomography (CT) scans can aid in the diagnosis but are usually dependent on the bladder's filling status. Differentiating the condition from a patent omphalomesenteric duct is important. The presences of both anomalies in the same patient are rare (Mendoza et al, 1968).

Management of an infected urachus with abscess formation includes initial drainage under antibiotic coverage. Once the infection has subsided, complete excision of the patent urachus including a bladder cuff is required (Nix et al, 1958). Removing all anomalous tissue is important. This avoids recurrences or stone formation and prevents the rare event of later transformation into a malignant adenocarcinoma (Blichert-Toft and Nielson, 1971; Sheldon et al, 1984; Goldman et al, 1988; Upadhay and Kukkady, 2003).

Traditionally, the patent urachus is surgically excised using a transverse or midline infraumbilical incision. Before surgery, a balloon catheter is used to distend the bladder. In infants, a small transverse subumbilical incision is often possible because the bladder dome is still high.

A feeding tube or small catheter is placed into the patent urachus for better intraoperative identification. The urachus can be incised circumscriptly, without removing the umbilicus for

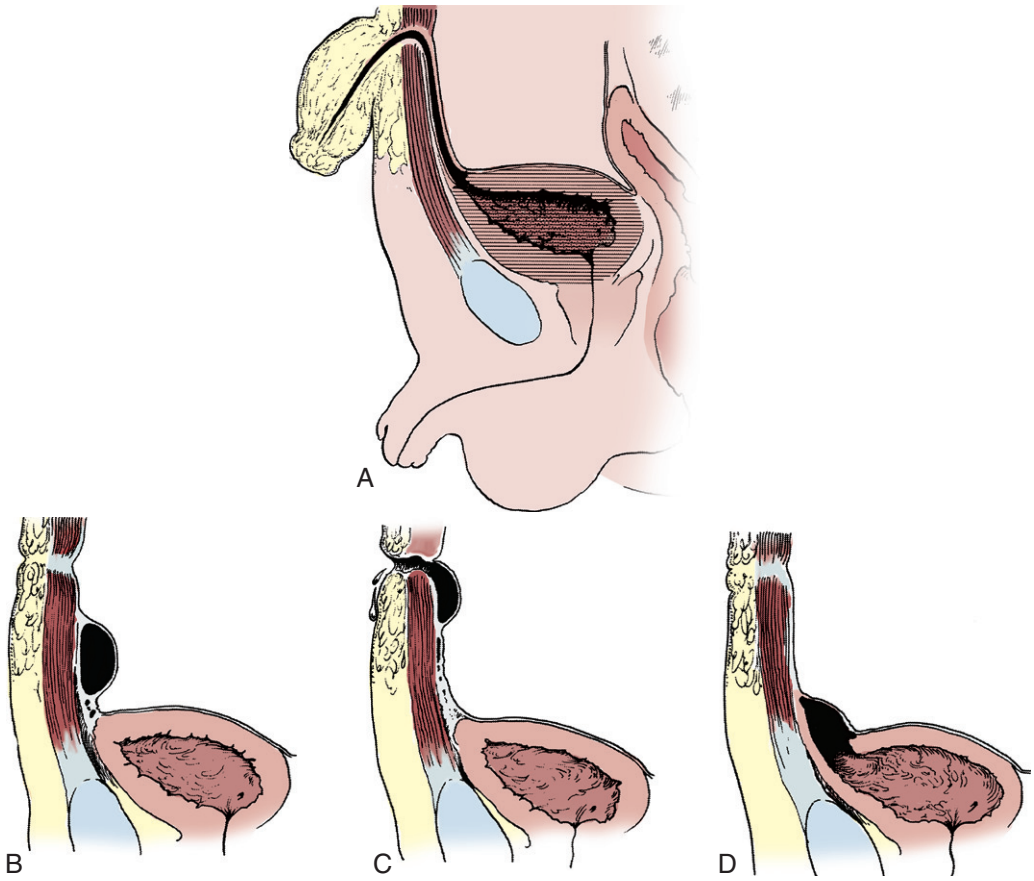


Figure 125–3. Urachal anomalies. **A,** Patent urachus. **B,** Urachal cyst. **C,** Umbilical-urachus sinus. **D,** Vesicourachal diverticulum.

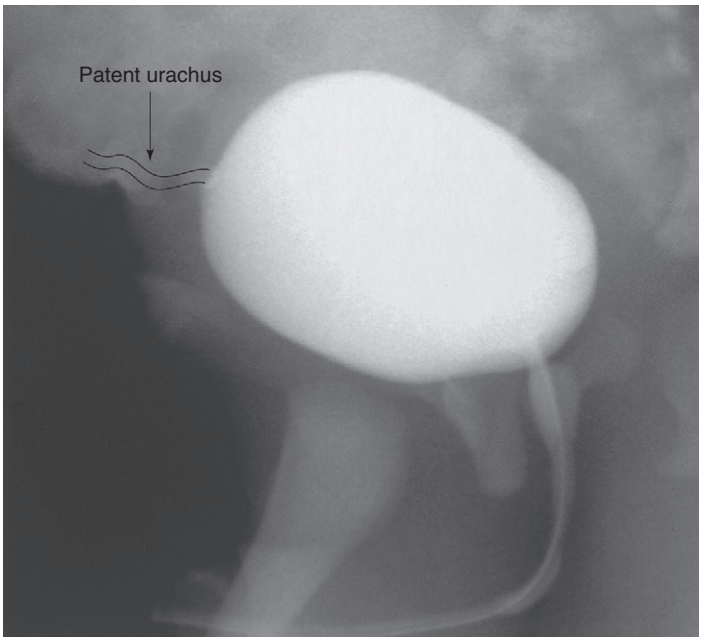


Figure 125–4. Patent urachus. Vesicoureterogram image of patent urachus in a newborn. Retrograde contrast filling of patent canal with contrast pooling in umbilicus.

cosmetic reasons. The rectus fascia is incised in a longitudinal fashion, muscles spread apart, and the dome of the distended bladder identified. The urachus is identified, isolated, and a vessel loop placed. The dissection continues extraperitoneally toward the umbilicus until the previously incised umbilical portion is free and can be pulled into the surgical field. It is then removed. A bladder cuff including the urachal insertion is marked and excised using electrocautery. The bladder is closed watertight in two layers. The catheter can be left in place overnight and removed the following morning.

Alternatively, urachal remnants can be removed laparoscopically. This can be done even in children younger than 6 months of age (Fahlenkamp et al, 1995; Cadeddu et al, 2000; Khurana and Borzi, 2002). Khurana and Borzi described their laparoscopic experience with four children between 5 months and 10 years and found the procedure to be safe in children of all ages. Technically, they suggested a three-port approach, with the camera port in the midline between the umbilicus and the xiphoid and two working ports on either site in the upper quadrant. Turial and colleagues (2007) reported 27 children with a median age of 4.7 years. Early in their series they inserted the camera port at the umbilicus with working ports into the right and left upper abdomen. Later they preferred to place the camera into the left lower abdominal wall with 2-mm working ports at the left lower and upper abdomen for better visualization of the urachus at the umbilicus. They reported no intraoperative or postoperative complications, no recurrences, and a median operating time of 35 minutes (Turial et al, 2007). The advantage of the laparoscopic technique is the

good visualization of the course of the urachus and the bladder dome. However, laparoscopic techniques require an intra-abdominal approach and pose the potential risk of spilling infected or malignant material into the abdominal cavity.

Umbilical-Urachus Sinus

In this situation the urachus obliterates at the bladder level but remains open at the umbilical site, causing a continuously draining sinus. The presentation is similar to the patent urachus. The diagnosis is made by sinogram. The caudal part of the urachus is filled with desquamated epithelial cells, and no connection to the bladder can be identified. The presence of a persistent omphalomesenteric duct must be considered. This would present as a Meckel's diverticulum connected to the umbilicus. These structures can be difficult to differentiate from an umbilical-urachus sinus because no connection to the bladder or bowel can be seen on sinogram. However, the surgical approach to both anomalies requires the complete excision of all tissue. Unlike urachal structures, omphalomesenteric remnants can show gastric or small bowel mucosa on histologic examination.

Urachal Cyst

There is no communication of the cyst with the bladder or umbilicus. However, the fluid-filled cyst can drain through the umbilicus or into the bladder intermittently. Urachal cysts are found more commonly in the distal part of the urachus and present more commonly in adults than in infants or children (Cilento et al, 1998). The cyst material consists of desquamated epithelial cells. These cells can become infected; *S. aureus* has been identified as the most common organism (Mesrobian et al, 1997).

Once infected, urachal cysts can present as umbilical abscess formation or bladder infections. Additional symptoms include localized lower abdominal pain, voiding symptoms, or even a painful and palpable mass. The diagnosis is confirmed by ultrasound, demonstrating the localized cyst between the anterior abdominal wall and the peritoneum. In a case of massive infection or difficult presentation, a CT scan can clarify the anatomy and extent of disease (Berrocal et al, 2002). If unrecognized, the infected cyst can perforate into the bladder (Maruschke et al, 2003) or peritoneal cavity. This can cause peritonitis and formation of an enteric fistula (Ohgaki et al, 2003; Quek et al, 2003). Treatment consists of draining the infected cyst, followed by complete excision of the urachal remnant structures.

Vesicourachal Diverticulum

The urachus obliterates almost completely, except at the level of bladder apex. Here it forms a diverticulum of varying size. These lesions are usually nonsymptomatic and found incidentally on nonrelated radiographic workups. Although the diverticulum can enlarge in size in case of urinary obstruction, it rarely causes problems because it tends to have a large opening and drain into the bladder well. There have been reports of stone formation and urinary infections, especially in the case of a narrowed neck causing the need for intervention.

Bladder Diverticulum

Bladder diverticula are caused by infravesical obstruction, bladder surgery (iatrogenic), or congenital defects. Independent from the cause, all diverticula develop as herniation of bladder mucosa between defects of bladder smooth muscle fibers. The neck of the resulting diverticulum depends on the size of the muscular defect. The incidence is reported to be low, with 1.7% in a selected pediatric population of children undergoing radiographic evaluation for symptomatic disease (Blane et al, 1994). In adult males the incidence tends to be much higher due to the higher occurrence of infravesical obstruction. The true incidence in children is difficult to evaluate because many of the congenital diverticula remain asymptomatic and are probably never detected.

In his landmark article, Hutch (1961) describes two kinds of diverticula at the ureteral hiatus.

- **Primary paraureteral diverticula** are seen in smooth-walled bladders, occur isolated with no other diverticula, are intermittent in presentation, and happen in children with no infravesical obstruction.
- **Secondary paraureteral diverticula** are found in trabeculated bladders as one of many diverticula in the bladder, are always present, and are caused by infravesical obstruction.

Primary diverticula arise as a localized herniation of bladder mucosa through the ureteral hiatus between the intravesical ureter and the roof of the ureteral hiatus. These primary diverticula are also known as *congenital diverticula* and are most likely caused by a congenitally deficient bladder wall (Fig. 125–5). Some authors have implied an isolated defect in Waldeyer sheet; however, congenital diverticula often occur on one side only, and a unilateral defect seems unlikely (Stephens, 1963). Congenital diverticula are often found in children with generalized connective tissue diseases such as Ehlers-Danlos, Williams Elfin-Facies, or Menkes syndrome (Babbitt et al, 1979; Daly and Rabinovitch, 1981; Levard et al, 1989). These diverticula can be resected if symptomatic; however, due to the impaired healing in patients with connective tissue disease, recurrence and wound healing complications are more common.

Secondary paraureteral diverticula are acquired and develop due to existing infravesical obstruction. The resulting increased infravesical pressure forces the bladder mucosa to bulge between the muscle fibers. These diverticula are usually just one of many "pop-off" mechanisms that can occur throughout the bladder. These diverticula can also be caused by weakening in the bladder muscle by infection (Barrett et al, 1976) or development of a muscular defect after bladder surgery (Sheu et al, 1998).

In both types of paraureteral diverticula, Waldeyer sheet eventually becomes damaged as the diverticulum expands in size. The increasing diverticulum pulls the intravesical ureter out of its anchored position, causing dysfunction of the ureterovesical junction. Eventually, the enlarged diverticulum can become responsible for ureteral obstruction. This has even been associated with renal dysplasia (Amar, 1972; Livne and Gonzales, 1985).

Key Points: Urachal Anomalies

- Urachal anomalies are usually detected postnatally due to umbilical drainage.
- Infected urachal remnants are initially treated with drainage and antibiotics, followed by surgical excision. Conservative treatment with observation is justified in asymptomatic cases due to possible spontaneous resolution.
- Imaging possibilities include ultrasound, CT, and VCUG.
- Nonresolved urachal remnants should be excised due to the increased risk of later adenocarcinoma formation.

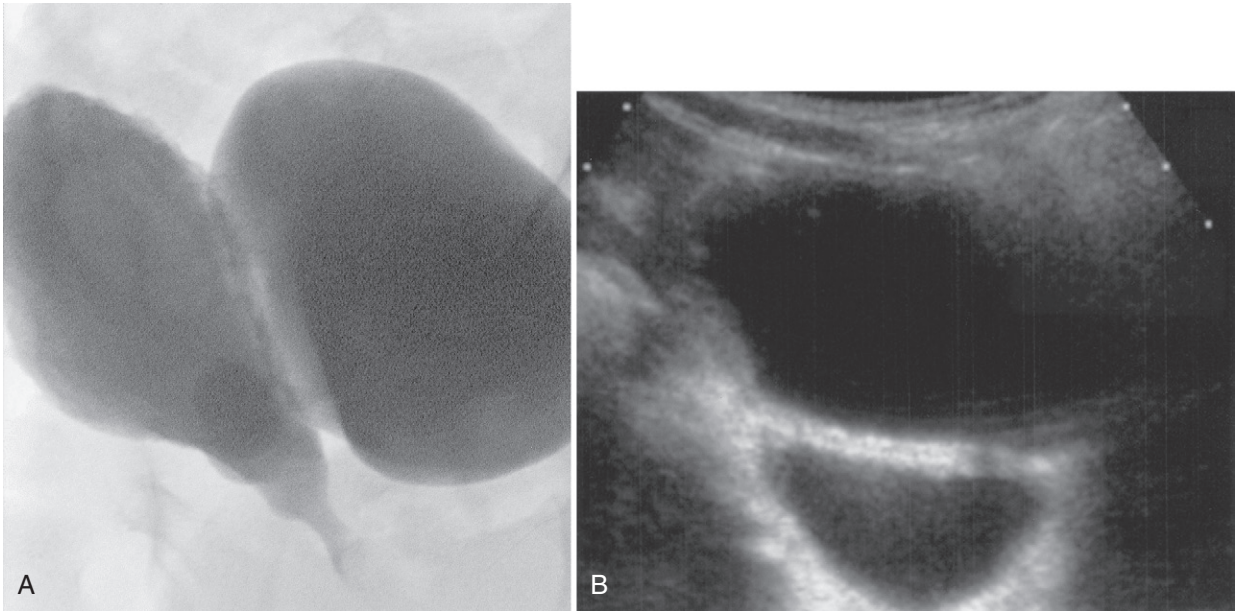


Figure 125–5. Primary paraureteral diverticulum. **A,** Vesicoureterogram image of large primary paraureteral diverticulum. **B,** Ultrasound image of the same diverticulum.

Paraureteral diverticula or diverticula located in the lower part of the bladder can become so large that they compress the bladder neck or posterior urethra. The resulting bladder outlet obstruction starts a vicious circle by continuously filling and expanding the diverticulum. This increases the obstructing and subsequently causes complete urinary retention (Sheldon and Essig, 1994; Zia-Ul-Miraj, 1999).

Bladder diverticula can be detected on prenatal ultrasound (Gaudet et al, 1999) but are mostly discovered during workup for infection, hematuria, incontinence, or obstruction. They can be suspected during ultrasound examination, especially if the bladder is viewed in different filling stages. The gold standard remains VCUG, which will reveal possible accompanying VUR. If no VUR is present, an intravenous pyelogram (IVP) with oblique views can help determine the relationship of the ureter with the diverticulum if there is hydronephrosis. Alternatively, nuclear renal studies can be used to obtain information concerning anatomy, kidney function, and ureteral obstruction. It is important to remember that congenital diverticula can have a dynamic nature and might not be present on every study. Radiographic studies may need to be repeated in cases of continuous clinical suspicion.

Small, asymptomatic congenital diverticula detected during unrelated workups can be treated conservatively with regular observation. Many surgeons tend to recommend excision of paraureteral diverticula if they are accompanied by VUR. Girls will show spontaneous resolution of their diverticula in association with VUR more frequently than boys. In his review of 304 patients with VUR, Amar (1972) confirmed the lesser resolution rate in boys. He attributed it to higher voiding pressures even without the presence of infravesical obstruction.

In acquired bladder diverticula, the infravesical obstruction has to be eliminated first. After bladder outlet resistance is normalized, the bladder can reshape and diverticulectomy might become unnecessary. If symptomatic, the diverticulum should be excised. The ipsilateral ureter should be reimplanted if it is near or included in the diverticulum. This traditionally has been performed intravesically; however, the procedure can be safely performed via an extravesical approach (Jayanthi et al, 1995; Yu, 2002). Laparoscopic excision has also been successfully performed in a 6-year-old child (Kok et al, 2000). Endoscopic subureteral injection of dextranomer/hyaluronic acid (Deflux) has been used for the correction of VUR, even in the presence of a primary paraureteral diverticulum (Perez-Brayfield et al, 2004).

Key Points: Bladder Diverticulum

- Bladder diverticula can be detected on prenatal ultrasound, but the gold standard remains VCUG, which will reveal possible accompanying VUR.
- Primary diverticula arise as a localized herniation of bladder mucosa at the ureteral hiatus and are most likely caused by a congenitally deficient bladder wall.
- Secondary paraureteral diverticula are acquired and develop due to existing infravesical obstruction.
- Symptomatic diverticula, especially in conjunction with VUR, should be treated surgically.

Bladder Duplication

Duplication of the bladder and urethra can be complete or incomplete. It can occur either in the coronal or sagittal plane. Abrahamson attempted to classify the various bladder duplication anomalies and found complete duplication in the sagittal plane the most common (Abrahamson, 1961). In incomplete duplications, the two bladder halves communicate and are usually drained by a single urethra. In complete duplications, the two bladders are fully separated entities with normal mucosa and a full-thickness musculature wall divided by a peritoneal fold (Fig. 125–6). Although the size and quality of each entity can be different, they are usually supplied

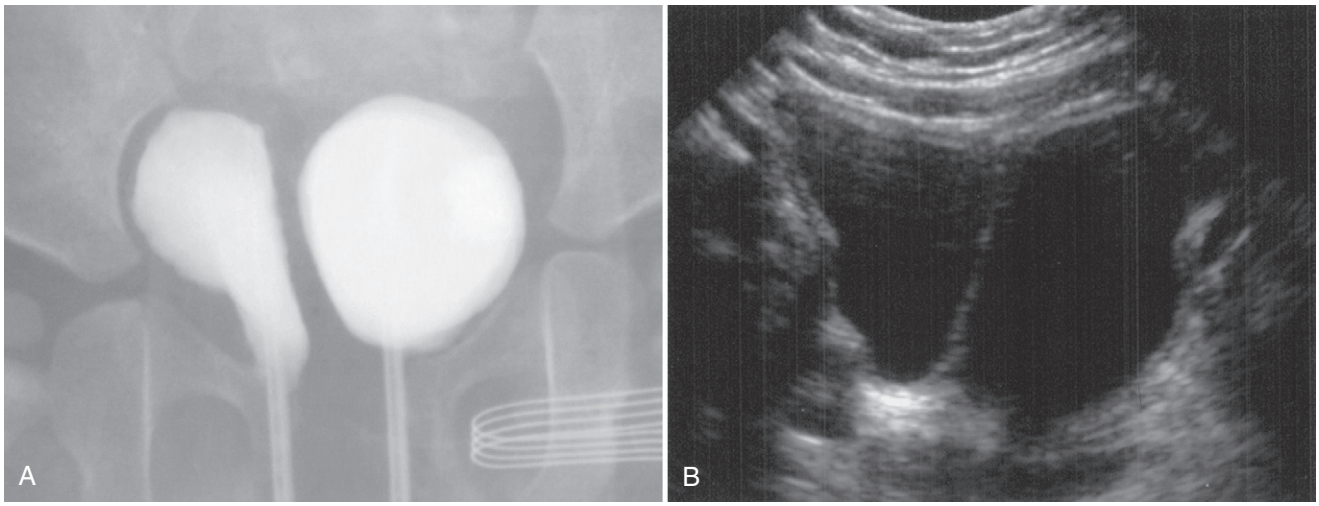


Figure 125–6. Complete bladder duplication. **A,** Vesicoureterogram image of complete bladder duplication with catheters inserted into each individual urethra. Note the size discrepancy. **B,** Ultrasound image of the same patient.

with their own ureter and are drained by an individual urethra and external meatus (Esham and Holt, 1980). In rare cases, one bladder can lack a urethra. This leads to ipsilateral renal dysplasia via complete obstruction (Cheng and Maizels, 1996). Both bladders may possess a sufficient continence mechanism, or one side is compromised, causing incontinent episodes.

Associated duplication anomalies of the external genitalia have been reported in up to 90% of cases; associated duplication anomalies of the lower gastrointestinal tract have been reported in up to 42% of cases (Kossow and Morales, 1973). Duplicated vaginas can be connected to a separate unicornuate uterus. Duplicated penises are supplied with an individual urethra. Additional urologic abnormalities such as VUR, renal ectopia, or dysplasia are commonly found. Association with other nonurologic congenital anomalies are more frequent in sagittal than in coronal duplications. Multiple manifestations have been described including gastrointestinal malformations, duplications of the spine, spina bifida conditions, and various fistula formation between the urogenital and gastrointestinal tract (Berrocal et al, 1999). In duplication variations of the classical cloacal-bladder exstrophy complex, patients present with an exstrophic bladder and urethra in addition to a closed regular intra-abdominal bladder (Perren and Frey, 1998).

The embryologic development of the various duplication anomalies remains poorly understood. Complete duplication of the bladder and hindgut is thought to occur due to partial twinning of the tail portion of the embryo (Ravitch and Scott, 1953). It is also suggested that the development of a sagittal fissure on the cloacal plate occurs when the urorectal septum separates the urogenital from the digestive sinus (Bellagha et al, 1993).

The wide range of anatomic manifestations of duplicate bladders explains the different time points and modes of presentation. With associated malformations of the gastrointestinal or external genital tract, the diagnosis is often made in the newborn period. However, many children are not diagnosed until recurrent infections or incontinence initiates a urologic workup. Although similarities exist, each case is different and warrants individual management. Complete preoperative diagnostic evaluations with karyotype, ultrasound, IVP, video-urodynamic studies, genitogram, and gastrointestinal tract imaging are useful to determine the anatomic situation. VCUG and nuclear renal scans can supply additional information regarding VUR and renal function. Complete understanding of the various anomalies can be difficult. Often the final treatment plan has to be deferred until the time of endoscopic and surgical exploration of the malformation. **Initial treatment is directed toward renal preservation and prevention of infections by relieving possibly obstructed genitourinary tracts.** Long-term goals include achieving continence and reconstructing the internal and external genitalia. Incomplete duplications may not require surgical procedures if both bladder halves are sufficiently drained by a common urethra. In complete duplications, the two bladders can be combined into one. If both sphincter complexes are competent, the distal urethras are connected. If one is incompetent, the corresponding bladder neck can be closed and the connected urethra excised. Duplicated vaginas are combined in the midline, and a vulvoplasty is performed. The urogenital duplications can also be left uncorrected if the patient is asymptomatic; Gastol and colleagues (2000) reported two successful pregnancies in a 26-year-old woman. Due to the rarity of the disease and the large variety of presentations, the surgeries must be individualized and should be performed in centers experienced in complex urogenital reconstruction.

Key Points: Bladder Duplication

- Bladder duplication is often associated with duplication anomalies of the external genitalia and lower gastrointestinal tract.
- Initial treatment is directed toward renal preservation and prevention of infections by relieving possibly obstructed genitourinary tracts.
- Long-term goals include achieving continence and reconstructing the internal and external genitalia.
- Due to the rarity of the disease and the large variety of presentations, the surgeries must be individualized.

Other Bladder Anomalies

Nephrogenic Adenoma

Nephrogenic adenoma of the urinary bladder is a rare benign tumor mostly found in adults. Sporadic case reports in children describe the lesion as a reaction to infection, lithiasis, and trauma or in response to surgery. Heidenreich and colleagues (1999) found a significant predominance of girls compared with boys (5:1), typically presenting with hematuria or irritative bladder symptoms. The diagnosis is established after cystoscopy with biopsy. Treatment consists of transurethral fulguration or resection and can be combined with long-term antibiotic prophylaxis. Although malignant transformation was not reported, tumor recurrence developed in 80% of the children with a latency period of 4 years.

Hungerhuber and colleagues (2008) reported a case of an adenocarcinoma in a 25-year-old who developed a neurogenic bladder after a car accident. He subsequently developed a nephrogenic adenoma, which was resected several times. Although the initial pathology was benign, a moderately differentiated adenocarcinoma was found after several resections. He underwent a radical cystectomy and remained tumor free.

Eosinophilic Cystitis

Eosinophilic cystitis in children is sporadically described in case reports with a predominance in boys. **The etiology remains unclear, and the histopathologic examination includes inflammatory cells with numerous eosinophils throughout all layers of the bladder wall** (Tsakiri et al, 2004). Presenting symptoms include dysuria, hematuria, suprapubic pain, and urinary retention. It can be detected on ultrasound, but the diagnosis is made by cystoscopy with transurethral biopsy of the lesion (Fig. 125–7). Immunologic diseases and allergies have been suggested to be causative for the development of the lesions. In his large review of 135 cases, van den Ouden (2000) found transurethral resection combined with corticosteroids, antihistaminics, or antibiotics to be most successful for all age groups. In neonates and young children the disease can be self-limited and observation is justified (Al-Omar et al, 2005).

Bladder Hemangioma

These benign vascular tumors are mostly seen in association with Klippel-Trenaunay syndrome and can be solitary or on multiple locations throughout the bladder. The leading symptom is macrohematuria, and the vascular tumors are found during cystoscopy. Treatment consists of Nd:YAG laser fulguration of the affected areas (Kato et al, 2000).

Bladder Hernia

In rare cases the bladder has been found in hernia sacs during a routine hernia repair. It can be suspected in an unusual large hernia sac, urine drainage during or after surgery, or the new onset of hematuria postoperatively. Manatt and colleagues (2006) reported a bladder hernia in a premature infant found during a cystogram performed due to hydronephrosis. The bladder was reduced during hernia repair, and no further problems were encountered.

CONCLUSION

Isolated congenital bladder anomalies are rare. Most published information relies on case reports of various malformations and their individualized management. Many of the detected anomalies are due to infravesical obstruction or are part of a syndrome affecting other parts of the genitourinary or nonurologic systems. Prenatal ultrasound allows early detection of bladder changes and has vastly influenced the prenatal and postnatal management of the described malformations. However, due to the rarity of the various presentations, large series with adequate follow-up are missing. Management and treatment remain individualized. Severe anomalies are often difficult to understand, and treatment should be centralized in specialized centers.

Acknowledgments

We thank Dr. Faridali G. Ramji, Associate Professor and Director of the Fellowship Program in the Department of Radiology at the Children's Hospital of Oklahoma, Oklahoma University Medical Center, for providing the figures and the Imaging Technologists

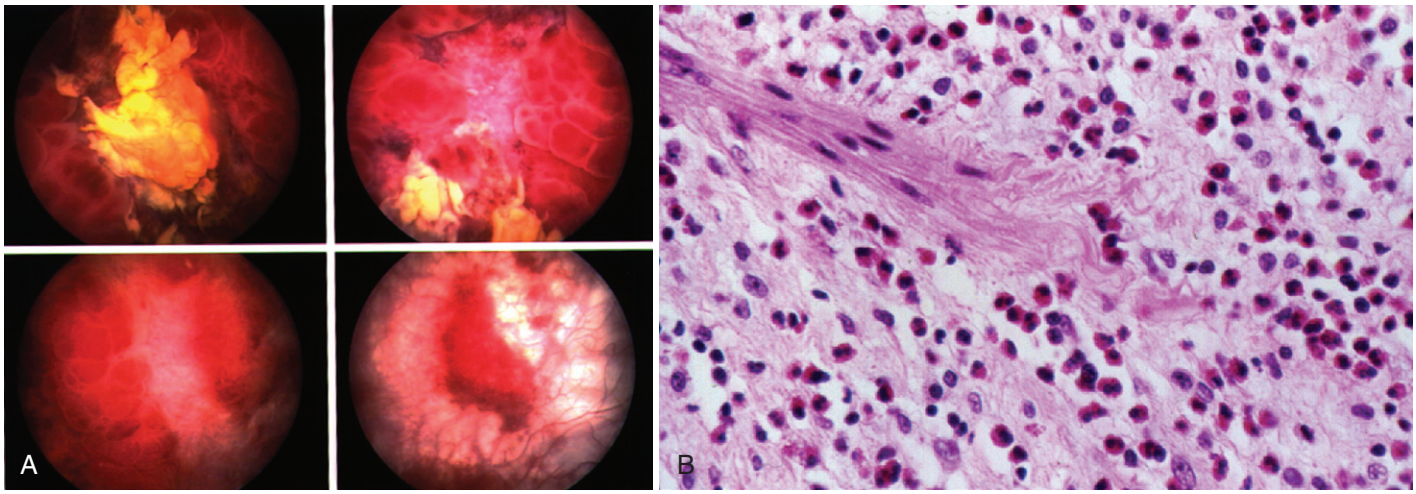


Figure 125–7. Eosinophilic cystitis. **A,** Cystoscopic views of lesion detected as mass on ultrasound in teenage male with severe dysuria and gross hematuria. **B,** Biopsy of mucosal lesion demonstrating eosinophilic infiltrate and no evidence of malignancy.

in the Department of Radiology at the Children's Hospital of Oklahoma, Oklahoma University Medical Center, for assisting with the image formatting.

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chapter 126

Posterior Urethral Valves

Anthony J. Casale, MD

Posterior Urethral Valves
Valve Bladder Syndrome
Antenatal Diagnosis and Management
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POSTERIOR URETHRAL VALVES

Description, Classification, and Embryology

Congenital obstruction of the urethra is one of the most devastating anomalies that occur in the urinary tract and is one of the few that are life threatening in the neonatal period. These lesions usually result in lifelong disabilities with incontinence and decreased renal function despite optimal medical management. The condition of posterior urethral valves is still relatively common and makes up the vast majority of congenital urethral obstructions.

Langenbeck is credited with first reporting congenital obstruction of the prostatic urethra in 1802 (Dewan et al, 1999). Despite this observation it was left for Hugh Hampton Young, over a century later, to define and name the condition as posterior urethral valves (Young et al, 1919). His remarkably accurate observations were made only with gross pathologic dissection and with the primitive cystoscopic instruments of his day. Young observed the anatomic variability of the anomaly and developed a classification that is still used almost 100 years later.

The term *valves* is unfortunate because it implies function. This obstructive membrane has no active function and is not a developmental stage in the embryology of the urethra. It is simply a passive barrier to urine flow. Young adopted this term when he found that a urethral sound would pass easily from the urethral meatus into the bladder in a retrograde manner while the same sound (or urine for that matter) would not pass antegrade out of the bladder and down the urethra. This unidirectional access through the urethra suggested to Young the function of a one-way valve, and he described the condition as such.

Posterior urethral valves occur in 1 in 8000 to 25,000 live births and make up 10% of urinary obstructions diagnosed in utero (Atwell, 1983; Thomas and Gordon, 1989; Casale, 1990). The diagnosis has been made on average in 1 in 1250 fetal ultrasound screenings (Gunn et al, 1995). There are reported cases of congenital urethral obstruction in females, but the classic posterior urethral valves occur only in males (Nesbit et al, 1964). The incidence of posterior urethral valves is dropping in some populations due to the effects of prenatal diagnosis and subsequent termination of affected fetuses. In one report, fetuses diagnosed with valves were electively terminated in 46% of cases (Cromie et al, 2001).

Despite several alternative proposals, Young's classification is still most commonly used (Dewan, 1993) (Fig. 126–1). He described three types of posterior urethral valves:

> Type I. In the most common type there is a ridge lying on the floor of the urethra, continuous with the verumontanum, which takes an anterior course and divides into two forklike processes in the region of the bulbomembranous junction. These processes are continued as thin membranous sheets, directed upward and forward, which may be attached to the urethra throughout its entire circumference. In the majority of cases of this general type the fusion of the valves anteriorly is not complete, there existing at this point a slight separation of the folds. However, in a few of the cases…the anterior fusion is complete while a cleft exists between the folds posteriorly.

Recently it has been proposed that all boys with valves originally have complete fusion along the anterior urethra, leaving only an open channel along the posterior urethral wall. The frequently observed cleft in the membrane may be iatrogenic, created by instrumentation or catheterization that erodes the valve tissue in the anterior midline and splits the valve in two leaflets (Robertson and Hayes, 1969; Dewan et al, 1992).

Young's type I valves make up 95% of all posterior urethral obstructions (Fig. 126–2).

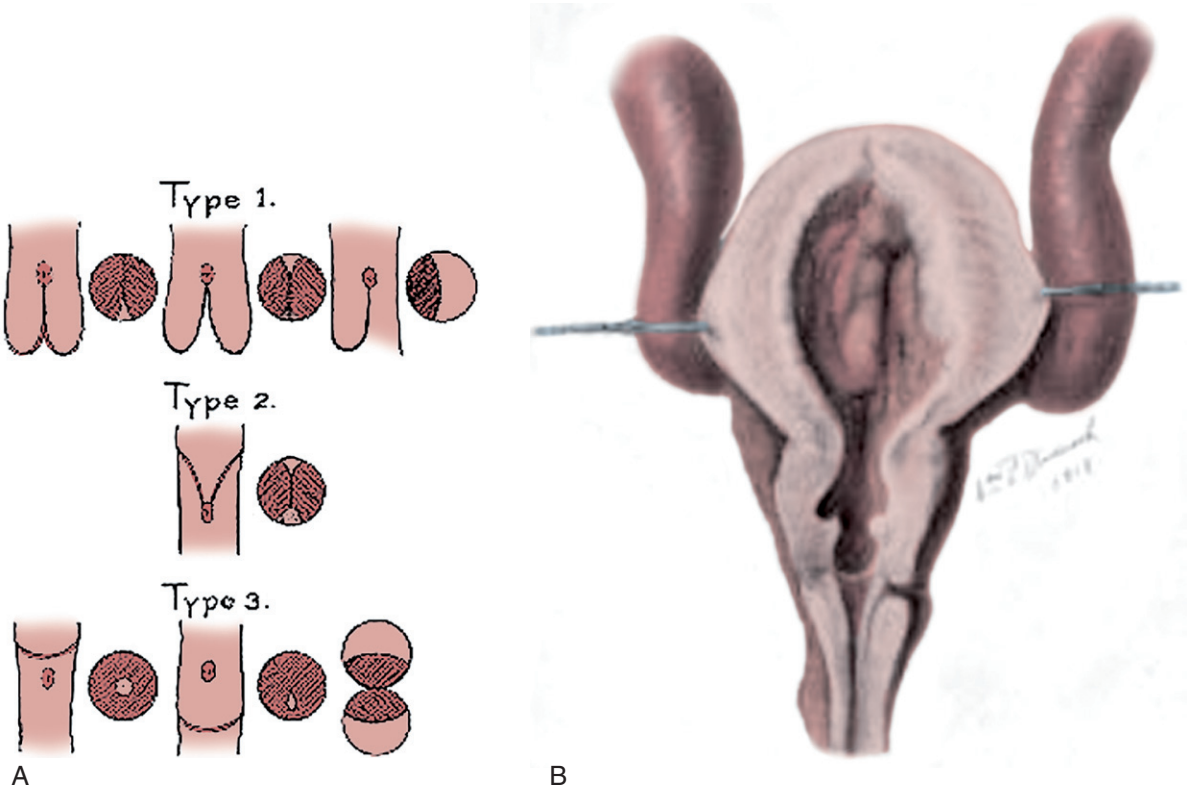


Figure 126–1. **A,** Young's original figures from his 1919 article. He described three types of posterior urethral valves and diagrammed them. **B,** William P. Didusch drew this pathologic dissection that shows the features of posterior urethral valves, the thickened bladder wall with an elevated bladder neck, and enlarged posterior urethra. The two valve leaflets of type I valves are seen. The ureters are massively dilated. (From Young HH, Frontz WA, Baldwin JC. Congenital obstruction of the posterior urethra. J Urol 1919;3:289.)

The thickness of the valves themselves varies from rigid, thick tissue to thin, almost transparent membranes. The valve itself is made of a fibrous stroma covered on each side by transitional epithelium. There is no muscle within the valve. The degree of obstruction also varies widely and, in turn, the amount of damage to the urinary tract.

The embryology of posterior urethral valves is speculative but may be related to an abnormal insertion of the mesonephric ducts into the fetal cloaca. Evidence supporting this theory lies in the fact that type I valve patients lack plicae colliculi, mucosal folds found in the normal male urethra that are believed to represent a remnant of the normal pathway of migration of the mesonephric ducts toward the verumontanum (Stephens, 1983).

Young described a type II valve as arising from the verumontanum and extending along the posterior urethral wall toward the bladder neck. This description was based on the similar appearance of these folds to the membranes found in type I. These type II folds are not obstructive and probably result from hypertrophy of muscles of the superficial trigone and prostatic urethra in response to high voiding pressure from distal obstruction. They can be seen in response to many obstructive conditions such as urethral strictures, posterior urethral valves, anterior urethral valves, and detrusor-sphincter dyssynergia. These type II folds are no longer referred to as valves.

Young described type III valves as a membrane lying transversely across the urethra with a small perforation near its center (Fig. 126–3). The membrane is distal to the verumontanum and sometimes is elongated like a wind sock reaching the bulbous urethra (Field and Stephens, 1974). Type III valves make up only 5% of the total. Young described them as follows:

> There is a third type which has been found at different levels of the posterior urethra and which apparently bears no such relation to the verumontanum as the types just considered....This obstruction was attached to the entire circumference of the urethra, there being a small opening in the center. Incomplete varieties of this type have been described, the most common being a more or less crescentic or semicircular fold crossing the urethra and being attached either to the roof or floor.

The embryologic origin of type III valves has been attributed to incomplete dissolution of the urogenital portion of the cloacal membrane. Type III valves present in the same manner and are managed in the same way as the more common type I, although there is some evidence that type III valves have a worse prognosis (Rosenfeld et al, 1994).

The inheritance of posterior urethral valves is poorly understood and may involve several genes and inheritance patterns (Livne et al, 1983; Weber et al, 2005). Valves have occurred in siblings, twins, and in successive generations (Farkas and Skinner, 1976; Hanlon-Lundberg et al, 1994; Morini et al, 2002; Maruotti et al, 2006). The timing of valve development is also speculative, but it would appear that they become obstructive during or after the eighth week of life by which time the prostatic urethra has developed from the urogenital sinus (Mitchell and Close, 1996). In a recent review of the literature, Baskin and colleagues concluded that the precise origins regarding the anatomy and embryology of posterior urethral valves remain undefined. Although theories of etiology abound, there are a limited number of modern

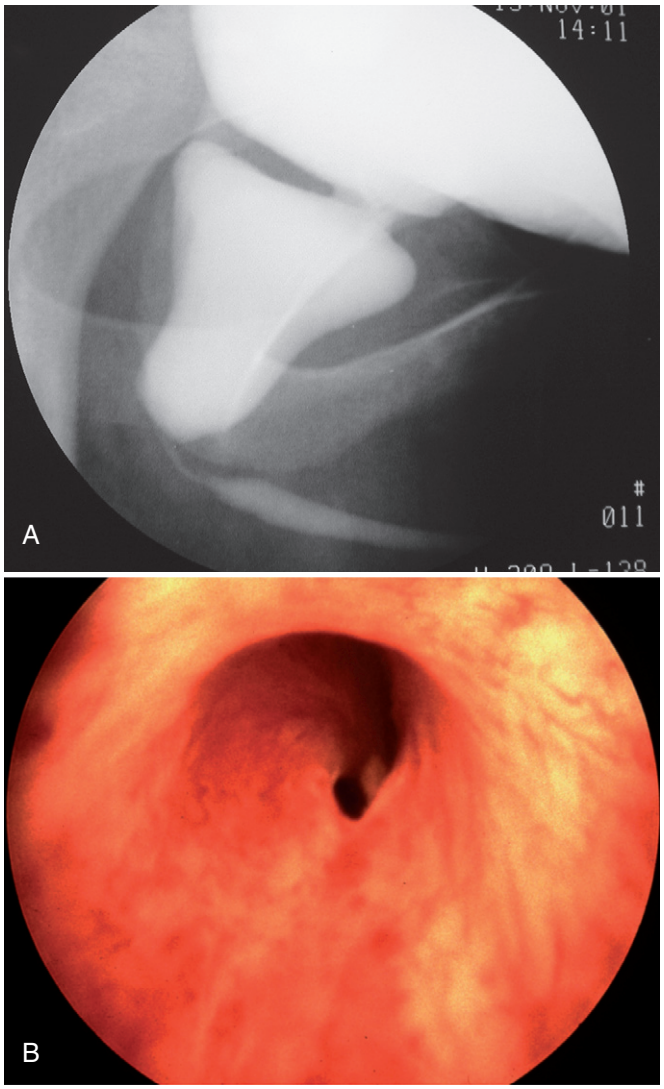


Figure 126–2. **A,** Voiding cystourethrogram demonstrates a typical type I posterior urethral valve with a dilated posterior urethra, elevated bladder neck, and valve leaflets obstructing the flow of contrast material from the bladder. **B,** This cystoscopic image from the distal urethra shows the valve leaflets forced into the lumen with the bladder full, illustrating their obstructive effect.

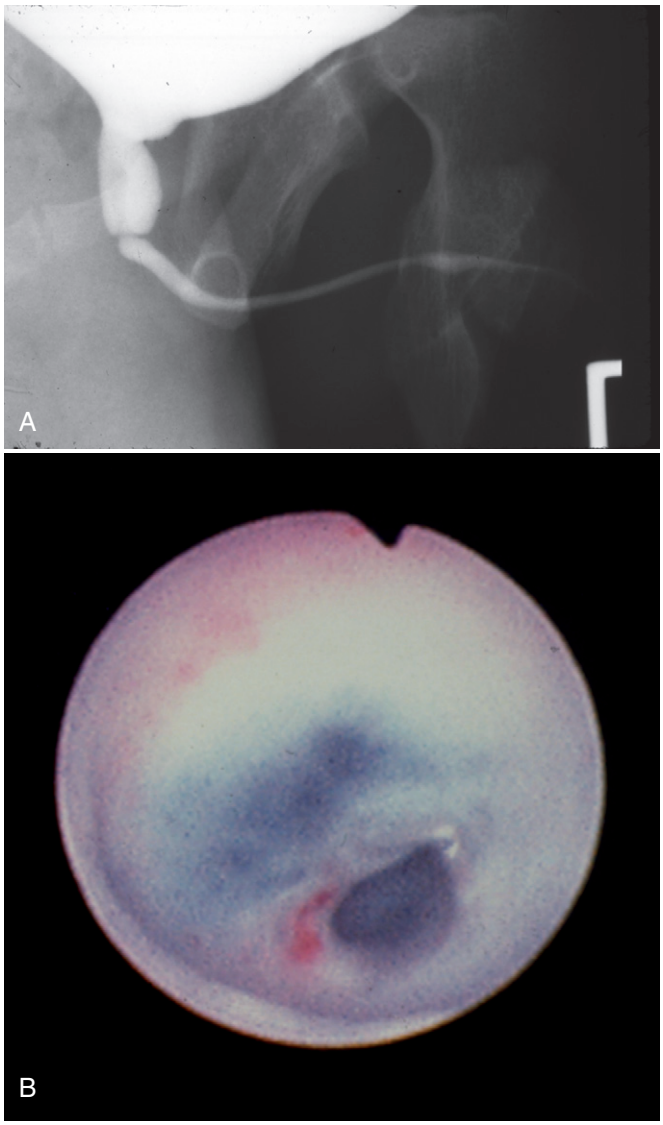


Figure 126–3. **A,** Voiding cystourethrogram demonstrates a typical type III posterior urethral valve with a transverse septum crossing the urethra at a right angle distal to the verumontanum. **B,** A cystoscopic image from the distal urethra shows the thin membrane and a small off-center opening.

methodical anatomic and histiologic studies to support them (Krishnan et al, 2006).

Pathophysiology

The effects of congenital obstruction of the urethra are reflected in the entire urinary tract above the level of obstruction (Table 126–1). Proximal urethra, prostate, bladder neck, bladder, ureters, and kidneys are all affected and suffer various forms of damage.

Lower Urinary Tract

The injury to the lower urinary tract appears to be caused by high-pressure urine storage and voiding (McConnell, 1989; Keating, 1994). Bladder histology of fetuses with posterior urethral valves shows hypertrophy and hyperplasia of the detrusor muscle along with increased connective tissue. The ratio of muscle to connective tissue is the same as in normal bladders, but there is conflicting evidence that the type of collagen within the bladder is altered (Kim et al, 1991; Ewalt et al, 1992). Some bladder findings in neonates such as wall thickness and poor compliance will improve after relief of obstruction, but the valve bladders seldom if ever achieve normal function.

High voiding pressures distend and thin the prostatic urethra. The storage capacity of the prostatic urethra sometimes exceeds that of the bladder because of the relative lack of muscle there. The verumontanum is distorted, and the ejaculatory ducts may be dilated from refluxing urine. The bladder neck is rigid and hypertrophied (Fig. 126–4). This high bladder neck was once mistaken as another cause of obstruction and was surgically incised to facilitate bladder emptying. Unfortunately, this practice often resulted in total incontinence. Today it is understood that the appearance

Table 126–1.
Damage Due to Posterior Urethral Valves

ORGAN	EFFECT	NATURAL HISTORY
Lung	Pulmonary hypoplasia	May be fatal in newborns; if infant survives, there are few long-term problems
Kidney		
Glomerular injury		
Obstructive uropathy	Reversible renal insufficiency	Usually improves with initial treatment but can recur with bladder dysfunction
Dysplasia	Irreversible renal insufficiency	Permanent level of renal damage that limits growth; leads to progressive renal failure and hypertension
Tubular injury	Inability to limit sodium and water loss	Progressive with age; nephrogenic diabetes insipidus
Bladder	Poor sensation, hypercontractility, low compliance, and eventual myogenic failure all may contribute to incontinence and poor emptying	Bladder problems are lifelong and change with age
Ureters	Poor contractility and inability to coapt and transport urine	Most will improve initially, but most have chronic hydronephrosis

of the bladder neck is a result of distal obstruction and not obstructive lesion itself. Bladder neck appearance and function usually improves after the obstructive valves are destroyed.

Upper Urinary Tract

Ureteral damage is usually severe. The appearance and function of the ureters are markedly abnormal. The ureteral wall is thickened and the lumen massively dilated. The ureter is at the mercy of the ureterovesical junction (UVJ). If this junction functions to prevent reflux, the ureter and kidney are somewhat protected from the complete force of the bladder contractions. If the junction allows reflux, the entire pressure of the thickened and hypercontractile bladder is transmitted directly to the upper tract with severe consequences. Virtually all valve patients have hydroureteronephrosis, and this can be the result of obstruction from the valves, the UVJ, or both. Although reflux is variable, hydroureteronephrosis is a constant in these patients. Severely dilated ureters coapt poorly and contract weakly, if at all (Gearhart et al, 1995). The propulsion of urine down the ureter is diminished in the infant, and this ureteral dysfunction may persist throughout life despite relief of distal obstruction.

The nature of the renal injury in boys with posterior urethral valves is complex and appears to have two distinct components. Some damage, described as obstructive uropathy, is caused by persistent high pressure. It is ongoing and can be progressive, but it is potentially reversible with relief of high pressures. Other damage, termed *renal dysplasia,* may be due to either increased pressure during the development of the kidney or abnormal embryologic development. Renal dysplasia is not reversible, and therefore the degree of dysplasia is critical in determining eventual renal function in valve patients.

Dysplasia is, in fact, a histologic diagnosis and depends on identifying a fundamental disorganization of the renal parenchyma on a cellular and tissue level. The elements of dysplasia include embryonic tubules, cartilage, cysts, and mesenchymal connective tissue. The particular type of dysplasia in valve patients is termed *microcystic* and can be observed primarily in the peripheral cortical zone of the kidney.

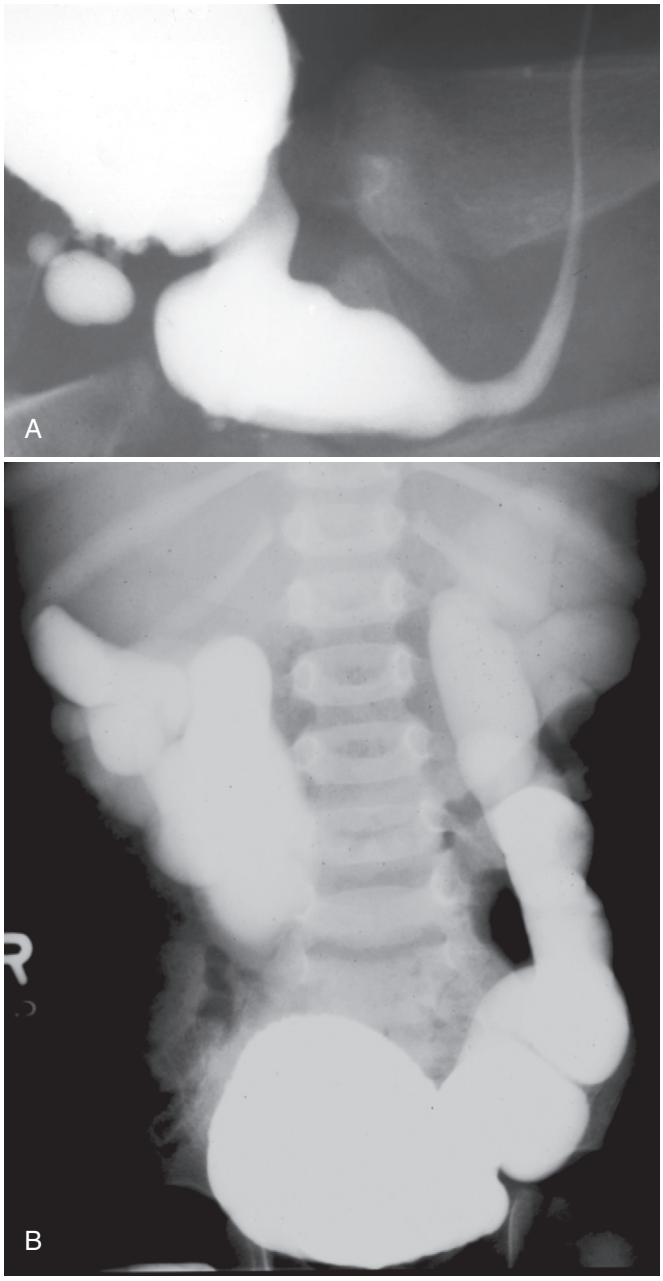


Figure 126–4. **A,** Voiding cystourethrogram shows a posterior bladder diverticulum near the base of the bladder and an extremely high bladder neck. A catheter passed blindly can fail to pass over the bladder neck and coil in the dilated posterior urethra. **B,** Massive vesicoureteral reflux in a boy with valves.

The exact cause of dysplasia is a matter of continued debate. Beck and Glick demonstrated that dysplasia could be produced by early urinary obstruction in lambs (Beck, 1971; Glick et al, 1984). Maizels and colleagues (1983) also produced a form of dysplasia in chicken embryos by obstructing the fetal urinary tract. Ample evidence indicates that a form of dysplasia can be induced by early fetal urinary obstruction and resultant high intrarenal urinary pressure.

On the other hand, Stephens and Henneberry (1980) have demonstrated that dysplasia may be found in patients who do not seem to have a history of obstruction but instead have abnormal ureteral development. In patients with severe vesicoureteral reflux, the ureteral orifice is usually in an abnormal position. These patients frequently demonstrate renal dysplasia, and the degree of dysplasia is proportional to how much the position of the ureter deviates from normal. Stephens postulated that this dysplasia was the result of a faulty ureteral bud arising in an abnormal position along the mesonephric duct. Because the ureteral bud induces the development of the kidney, it follows that an abnormal bud may induce an abnormal kidney.

Dysplasia therefore occurs in association with obstruction and with reflux, seemingly unrelated conditions. Both theories are plausible and not exclusive. **Whatever the cause, dysplasia is the defining factor in long-term renal function in most patients with valves. Because this type of renal damage is not reversible, the extent of dysplasia will ultimately determine the growth and functional potential of the infant's kidneys. A number of other related factors may contribute to declining renal function in valve patients including infection, persistent obstruction, hypertension, hyperfiltration of damaged parenchyma, and perhaps high-protein diet, but none are as important as the degree of dysplasia** (Brenner et al, 1982; Klahr, 1989; Farnham et al, 2005).

All posterior urethral valve patients have a degree of associated obstructive uropathy. Obstructive uropathy involves both glomerular injury and tubular injury. Glomerular injury occurs when high pressures result in decreased renal perfusion and filtration. These changes are partially reversible when pressures are dropped and obstruction is relieved. The potential for recovery is felt to be time sensitive, and early relief of obstruction should favor recovery. **Some degree of scarring and fibrosis within the parenchyma persists, but unlike dysplasia, obstructive uropathy usually improves with treatment.**

Tubular damage from increased urinary pressure results in failure to concentrate and acidify the urine. This occurs in up to 59% of valve patients and sometimes occurs in patients without evidence of glomerular injury (Parkhouse and Woodhouse, 1990; Dinneen et al, 1995). **Concentrating defects in the form of nephrogenic diabetes insipidus lead to increased urine output independent of the patient's state of hydration. Patients are at risk for electrolyte imbalances and dehydration due to inability to conserve sodium and water even in the face of dehydration** (Gonzales, 1978). **Pathologically large urine output also stresses the ureters and bladder and contributes to persistent hydroureteronephrosis and bladder dysfunction. Tubular damage worsens with age despite early relief of obstruction in many patients, and resultant high urine volumes contribute to the deterioration of renal and bladder function in late childhood.**

Key Points: Pathophysiology

- Posterior urethral valves damage the entire urinary tract proximal to the valve.
- Pulmonary hypoplasia is the most common cause of mortality in valve patients.
- Most renal damage occurs early in fetal life.
- Bladder dysfunction is usually a lifelong problem resulting in incontinence and poor emptying.
- Persistent hydronephrosis is common and may be due to either ureteral or bladder dysfunction.
- Reflux usually improves and often resolves after valve ablation.

Vesicourethral Reflux and Dysplasia and Pop-Off Mechanisms

Hoover and Duckett identified the relationship between valves, reflux, and dysplasia (Hoover and Duckett, 1982). **They recognized that valve infants with unilateral reflux had markedly different renal function when comparing refluxing and nonrefluxing kidneys. Reflux was consistently associated with dsyplastic and damaged kidneys. They postulated that the reflux allowed the high bladder pressures to focus on the refluxing kidney, sparing and protecting the nonrefluxing kidney.** The vesicoureteral reflux and dysplasia (VURD) relationship is found in 13% of valve patients, and interestingly the refluxing kidney is on the left side in 92%.

The proposed mechanism of this protection is that the refluxing collecting system acts as a pressure pop-off valve. The belief was that the protected kidney would ultimately lead to a better long-term prognosis compared with boys without unilateral reflux. The long-term protective effect of VURD has not been as helpful as originally thought. Longitudinal studies in VURD patients have shown that by midchildhood both serum creatinine and glomerular filtration rate (GFR) were significantly decreased compared with normal children (Cuckow et al, 1997). In addition, scarring has been observed with dimercaptosuccinic acid scanning in half of the contralateral, nonrefluxing kidneys with possible negative long-term consequences (Narasimhan et al, 2005). Other types of pop-off pressure systems include bladder diverticuli, urinomas, and urinary ascites (Rittenberg et al, 1988). The protective effect of these clinical situations is highly variable.

Clinical Presentation

In the past boys with posterior urethral valves presented with a variety of symptoms and at various ages (Hendren, 1971). **They ranged from newborns with life-threatening renal and pulmonary conditions to older children with minor voiding dysfunction.** In general, the symptoms are age dependent with the more severely affected boys presenting earlier in life (Dinneen and Duffy, 1996).

Neonates

Today, most patients with posterior urethral valves are diagnosed with prenatal ultrasound. Obstruction leads to decreased fetal urine output and results in

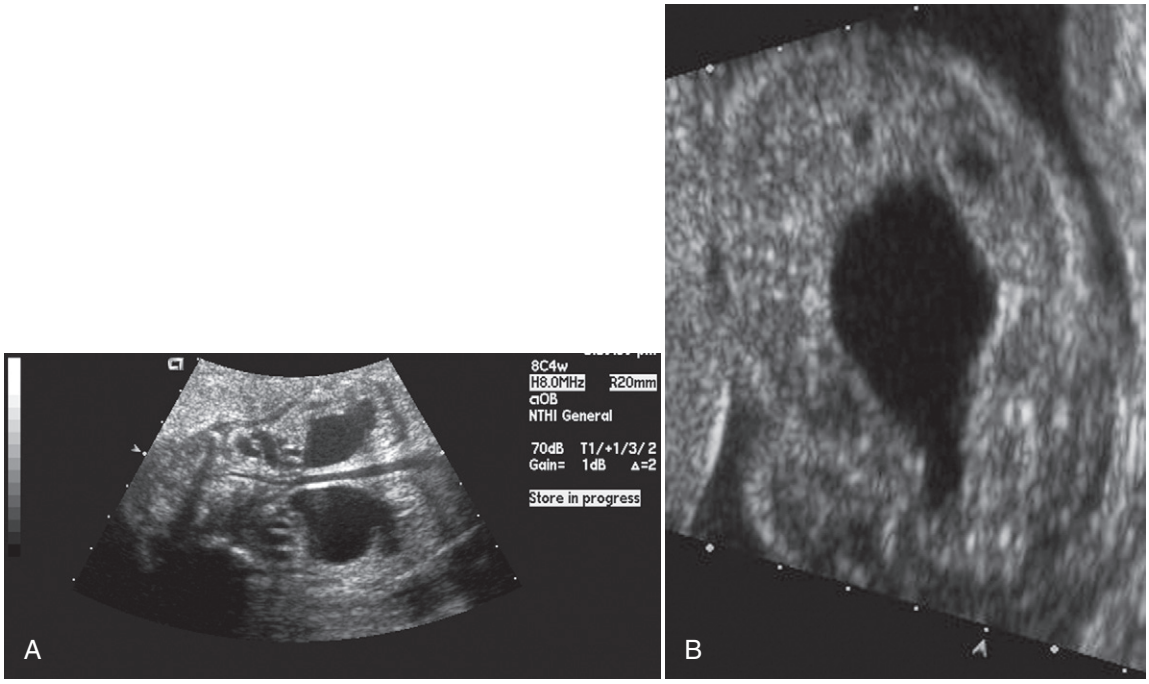


Figure 126–5. **A,** Ultrasound examination shows severe hydroureteronephrosis in a fetus with posterior urethral valves. **B,** Fetal ultrasound examination demonstrates a severely thickened bladder wall with a distended bladder and posterior urethra. These two fluid collections, a larger one above the smaller one, produce the "keyhole" sign indicative of posterior urethral valves.

oligohydramnios. The observation of marked hydroureteronephrosis, a distended bladder, and a thickened bladder wall in utero strongly support the diagnosis of valves (Fig. 126–5). Often the urologist has been consulted long before delivery, and in some cases intervention has been undertaken in utero.

Pulmonary Hypoplasia. The most severe clinical problem facing the neonate with posterior urethral valves is pulmonary hypoplasia. The infants are often cyanotic and require respiratory support at delivery. Pulmonary hypoplasia is a direct result of oligohydramnios and accounts for most of the mortality today (Churchill et al, 1990). The exact etiology of the pulmonary hypoplasia is unclear, but contributing factors include physical restriction of fetal breathing motion (Landers and Hanson, 1990). The lack of amniotic fluid to surround and buffer the fetus from intra-abdominal pressure leads to a small chest cavity and prevents chest wall breathing motion and normal musculoskeletal development. Amniotic fluid may be important in development of the fetal pulmonary tree by providing needed intraluminal pressure, volume, and flow. In addition, the amniotic fluid may provide some cellular or molecular stimulus to the developing lung. The results of oligohydramnios are often life threatening, and some infants succumb despite heroic measures. The mortality of valves has decreased significantly over the past two decades with development of better methods to manage pulmonary hypoplasia by neonatology. It is rare to have an infant die today with the quality of pulmonary support available in the newborn intensive care unit (Dejter and Gibbons, 1989; Gibbons et al, 1993).

Renal Insufficiency. In addition to pulmonary distress, the newborn with posterior urethral valves usually presents with signs of severe systemic illness such as intrauterine growth retardation, failure to thrive, lethargy, and poor feeding. The infants may be pale and have poor muscle tone. They may demonstrate the classic signs of oligohydramnios such as Potter facies and bowed and deformed limbs with pressure dimples over knees and elbows from intrauterine pressure. Examination of the abdomen may reveal masses due to hydroureteronephrosis and a distended bladder. The infant may suffer from extensive edema and urinary ascites. The caregivers may notice a diminished force of urinary stream, but this sign is not reliable to predict valves (Smith et al, 1996). If not diagnosed in utero, the most severely affected valve patients present as newborns. Often urinary tract infection or urosepsis precipitates evaluation and diagnosis.

Ascites. Forty percent of neonatal ascites is caused by urinary conditions (Fig. 126–6) (Adzick et al, 1985). Urinary ascites occurs when high intraluminal pressure forces urine to extravasate from the kidney, usually across a renal fornix. Urine then enters the retroperitoneum and travels across the peritoneum as a transudate. If aspirated from the peritoneal cavity, the ascites or extravasated urine contains electrolyte and creatinine levels similar to serum. The urine within the peritoneum is subject to the large absorptive mesothelial surface that quickly normalizes these values, masking the identity of ascitic fluid as urine. The diagnosis of urinary ascites may be difficult and may require definitive upper tract drainage in the form of nephrostomy tubes in order to establish the etiology of the ascites and allow its resolution. Urinary ascites in the case of distal obstruction may serve to lower urinary pressures and offer some protection to the developing kidneys (Conner et al, 1988).

Patel and colleagues (2003) reviewed a large group of 615 valve patients and analyzed the protective effect of ascites compared with unilateral and bilateral urinomas. The authors found that the kidney associated with a unilateral urinoma is often impaired. Bilateral urinomas are associated with good renal function, but

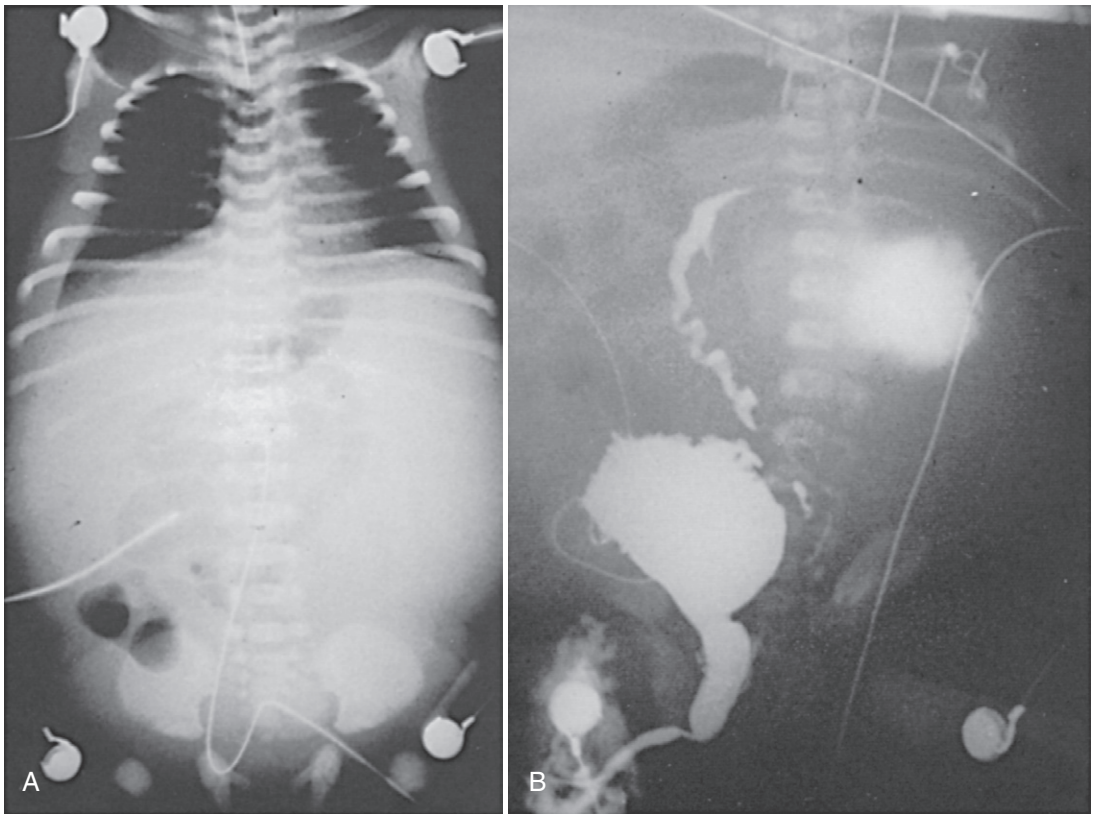


Figure 126–6. **A,** Abdominal radiograph shows the ground-glass appearance of an infant with ascites. **B,** Voiding cystourethrogram demonstrates reflux of contrast material, which is then seen extravasating into a urinoma and later flowing into the abdominal cavity as urinary ascites. (From Gonzales ED. Posterior urethral valves and other ureteral anomalies. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, editors. Campbell's urology. 8th ed. Philadelphia: WB Saunders; 2002.)

urinary ascites alone has a poorer prognosis. The GFR of patients with urinary ascites alone was 29 mL/min per 1.73 m^3 compared with 36 mL for boys with unilateral urinoma alone, 74 mL for boys with urinoma plus ascites, and 104 mL for bilateral urinomas.

Heikkila and colleagues (2008a) studied 200 patients with valves and found that the incidence of urinoma approached 15% after the introduction of ultrasound. This group included nine with perirenal urine collections, six with urinary ascites, and two with urothorax. They found initial and post-treatment serum creatinine levels, incidence of reflux, median split renal function, and risk for end-stage renal disease (ESRD) in the 17 patients with urinoma to be statistically similar to a control group of valve patients without urinoma. Their conclusion was that renal function is similar in patients with or without urinoma. Other authors have also found no association between renal function and urinoma formation in valve patients (Kleppe et al, 2006).

Older Children

The majority of boys who present later in life do so with urinary tract infection and/or voiding dysfunction. With a better understanding of functional voiding disorders, valves are now an uncommon cause of minor voiding dysfunction (Pieretti, 1993). Due to widespread prenatal ultrasound, it is now rare to see a new patient with posterior urethral valves past the neonatal period. Although boys who present later in life are generally believed to have more normal urinary tracts, this is not a uniform finding. One series reported that patients who presented at school age suffered renal insufficiency in 35% of cases (Bomalaski et al, 1999).

Initial Diagnostic Evaluation

Ultrasound

The widespread use of maternal ultrasound in the past 25 years in the United States has resulted in at least 80% of women undergoing ultrasound screening study during pregnancy. **Posterior urethral valves is the third most common antenatal genitourinary diagnosis made today and accounts for 10% of all fetal uropathy** (Thomas and Gordon, 1989). Although it was reported that two thirds of patients with valves presented on fetal ultrasound during the 1990s, this percentage has continued to rise (Greenfield, 1997). The quality and availability of ultrasound technology continues to improve, and with it the ability to image the fetus.

Ultrasound is sensitive in detecting fetal hydronephrosis, but the specific diagnosis of posterior urethral valves is more difficult. The differential diagnosis of bilateral hydronephrosis includes posterior urethral valves, prune-belly syndrome, bilateral ureteropelvic junction obstruction, bilateral high-grade vesicoureteral reflux, bilateral ureterovesical junction obstruction, congenital urethral atresia, and anterior urethral obstruction. Valves were correctly diagnosed in only 66% of 18 fetuses who were identified with hydronephrosis (Skolder et al, 1988). In a review of 42 patients with valves, only 45% were detected on antenatal ultrasound (Dinneen et al, 1993).

The timing of screening for fetal uropathy is an important factor in accuracy. There is compelling evidence that valves may be missed if the screening ultrasound is

done before 24 weeks' gestation (Jee et al, 1993; Hutton et al, 1994). In Dinneen's series, 92% of the 36 patients scanned before 24 weeks' gestation were not detected. The classic ultrasound findings in patients with valves include bilateral hydroureteronephrosis, distended bladder, dilated posterior urethra, and a thickened bladder wall. The "keyhole" sign of a dilated bladder above a dilated prostatic urethra is also helpful. Bladder wall thickness is an important diagnostic sign. The findings of an excessively thick bladder wall and a distended bladder indicate distal obstruction (Kaefer et al, 1997a).

Renal echogenicity is another parameter that may aid in the diagnosis of valves. Increased echogenicity predicted an obstructive process in a study of fetuses with bilateral hydroureteronephrosis and distended bladders (Kaefer et al, 1997b). Patients with a nonobstructive process such as megacystis-megaureter association failed to demonstrate increased echogenicity, while 87.5% of valve patients had increased echogenicity at a mean gestational age of 26 weeks. The same predictive value was found with oligohydramnios. **Any male fetus with bilateral hydroureteronephrosis, decreased amniotic fluid, and a distended bladder should be considered to have posterior urethral valves until proved otherwise.** The ultrasound findings of a neonate with posterior urethral valves are identical to those of a fetus.

Voiding Cystourethrography

The voiding cystourethrogram (VCUG) remains the most important study in diagnosing posterior urethral valves because it defines the anatomy and gross function of the bladder, bladder neck, and urethra (Fig. 126–7). **When the diagnosis of valves is in question, a VCUG should be obtained as soon as possible. On imaging the bladder and upper tracts of children with neuropathic bladder, urethral stricture, anterior urethral obstruction, and posterior urethral valves may all appear identical. Images of the urethra during voiding are necessary to make the correct diagnosis.**



Figure 126–7. Voiding cystourethrogram reveals massive vesicoureteral reflux in an infant with posterior urethral valves.

In posterior urethral valves the bladder is thickened and trabeculated. The VCUG often demonstrates bladder diverticuli and severe vesicoureteral reflux. From the lateral projection the bladder neck is elevated. The proximal urethra is quite dilated, and the actual valve structure is often visible. Vesicoureteral reflux is present in at least 50% of valve patients at the time of diagnosis (Churchill et al, 1990). The incidence of reflux has been found to be higher in neonates than in older children. Because most valve patients are now discovered in utero, the incidence of reflux may continue to increase compared with historical studies. There is an 80% incidence of reflux on the left side in patients with unilateral reflux for no apparent reason (Hoover and Duckett, 1982).

Ultrasound imaging of the posterior urethra from the perineum has been suggested as a noninvasive way to diagnose valves (Good et al, 1996). Valve leaflets can be visualized on ultrasound while bladder wall thickness and posterior urethral diameter before and during voiding is increased in valve patients. Although this application has little to add to the newborn evaluation, it can be used to evaluate older children without catheterization.

Radionuclide Renal Scan

In addition to the VCUG and renal ultrasound, the radionuclide renal scan has become an important part of the evaluation. Mercaptoacetyltriglycine (MAG-3) is the most useful agent for this imaging because it provides functional data and adequate imaging of both the parenchyma and collecting system. Scans provide differential renal function and some insight about drainage of the upper urinary tracts. **In patients with reflux the bladder must be emptied during the entire study with a catheter in order to avoid artificial enhancement of renal function by reflux of the isotope from the bladder.** If the catheter cannot keep the bladder empty through gravity, it may be necessary to aspirate it with a syringe during the study.

Laboratory Evaluation

Initial laboratory evaluation of the newborn with valves is usually misleading due to the effects of maternal renal

Key Points: Diagnosis and Evaluation

- Most cases of posterior urethral valves are diagnosed on antenatal ultrasound screening.
- The VCUG with urethral imaging is the key study in the diagnosis of valves.
- Evaluation of the infant's renal function often takes several days to allow for maternal effects on serum chemistries to resolve.
- Urodynamics are necessary in understanding bladder function throughout life.
- Nuclear renal scans and in some cases Whitaker perfusion tests are necessary in some patients to evaluate persistent hydroureteronephrosis.

function mediated through the placenta. Initial creatinine and blood urea nitrogen (BUN) levels may be artificially low, and it will take approximately 48 hours for the serum levels to accurately represent the child's intrinsic renal function. Creatinine, BUN, and electrolytes should be followed twice daily for the first few days of life until they plateau. Serum bicarbonate, sodium, and potassium are all critical factors to monitor.

Initial Management of Posterior Urethral Valves

Bladder Drainage

Initial management of all patients with posterior urethral valves requires the immediate establishment of urinary catheter drainage from the bladder. This should be performed even if the diagnosis has not been confirmed by VCUG. Neonates can be catheterized with a 3.5- or 5-Fr pediatric feeding tube. Foley catheters have been used with success, but there have also been reports that the balloon causes irritation and resultant bladder spasms. The bladder may be extremely irritable, and the presence of any catheter can cause spasms so severe as to obstruct the flow of urine into the bladder (Noe and Jerkins, 1983; Jordan and Hoover, 1985). Accurate catheter placement in the bladder must be documented either by irrigation of the catheter or by bladder imaging. Because it is difficult to pass the catheter over the elevated bladder neck and to avoid placing the catheter in the dilated prostatic urethra instead of the bladder, a one-shot cystogram is often advisable.

The ill newborn with posterior urethral valves is usually in the hands of the neonatal service for the management of the most threatening issues such as pulmonary hypoplasia and renal insufficiency. It is in these areas where improvement of medical management has decreased early mortality in valve babies (Nakayama et al, 1986). These infants may require maximal ventilatory support, extracorporeal membrane oxygenation, dialysis, parenteral nutrition, control of hypertension, and a host of other services provided by neonatology and pediatric nephrology (Gibbons et al, 1993).

Valve Ablation

After successful initial bladder drainage and when the patient's medical condition has stabilized, the next step is to permanently destroy the valves. In the past, destruction of valves was done by open surgery or patients were managed with long-term suprapubic tube drainage (Gonzalez et al, 1990). Both of these early therapies can lead to unacceptable complications such as incontinence, stones, and infection (Churchill et al, 1983).

Today a number of successful surgical techniques are available to disrupt or destroy posterior urethral valves including hooks, balloon catheters, and valvulotomes (Deane et al, 1988; Kolicinski, 1988; Cromie et al, 1994; Chandna et al, 1996; Chertin et al, 2002). One of the more common methods uses the Whitaker hook. This instrument looks like a crochet hook and has been used successfully to cut valves either blindly or with fluoroscopic control (Whitaker and Sherwood, 1986). **New, smaller pediatric cystoscopes with improved optics are favored today because of the ability to perform the procedure under direct vision. A bugbee electrode or a pediatric resectoscope with a hook or cold knife can be used to incise the valves** (Fig. 126–8). A number of authors report using a cystoscope and laser to disrupt valves (Ehrlich and Shanberg, 1988; Biewald and Schier, 1992; Gholdoian et al, 1998). Although most surgeons incise the valves from a retrograde position viewed through the urethra, others have found that an antegrade approach through a vesicostomy or suprapubic puncture of the bladder is helpful (Zaontz and Firlit, 1985).

Originally surgeons attempted to completely resect the valves. This practice produced frequent complications from urethral stricture resulting from electrosurgical and instrument damage to the urethra. Modern appropriately sized cystoscopic equipment and limited use of electrosurgery have reduced the incidence of urethral injury to 5% (Nijman and Scholtmeyer, 1991). **Today the goal is not to remove the valves but to incise them so that they are not suspended across the urethra obstructing urine flow. Well-placed incisions can disrupt their integrity and allow the valves to lie freely along the walls of the urethra when the child voids. The exact point of incision can vary; some surgeons prefer the 12**

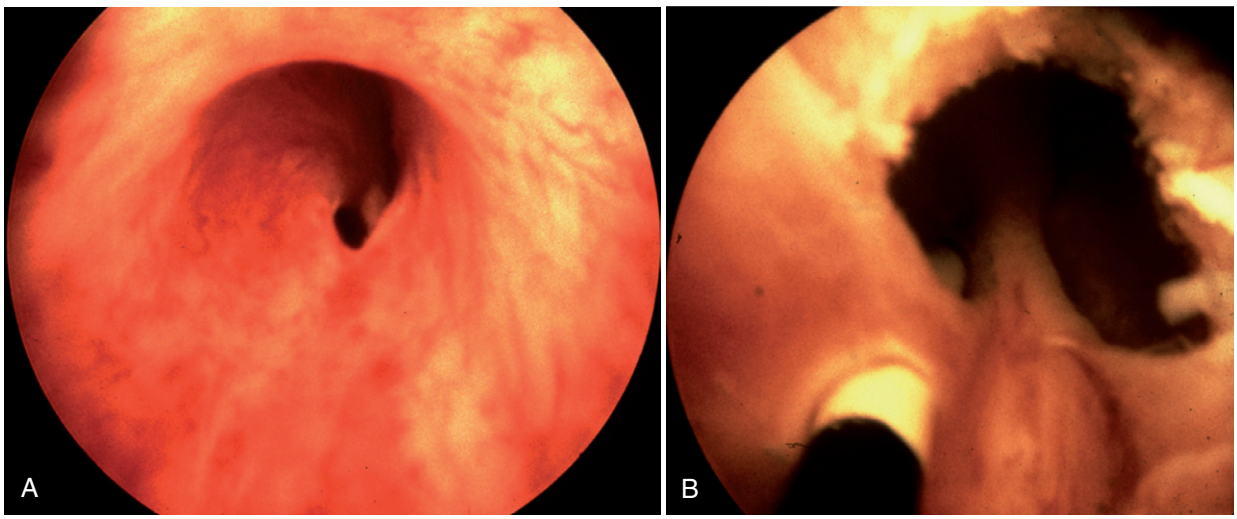


Figure 126–8. Cystoscopic photographs made from the distal urethra show the posterior urethral valves before ablation **(A)** and after ablation **(B).** The ureteral catheter has been passed through a perforation in the valve leaflet.

o'clock position, others prefer incisions at 4 and 8 o'clock, and others all three. Although most valves are quite thin and do not bleed at surgery, it is sometimes preferable to leave a catheter in place for 24 hours after incision. The valve remnants involute after incision, and there is often no evidence of them on later cystoscopic examination.

Documenting that the valve remnants are no longer obstructive after valve ablation is imperative. The timing of a postoperative VCUG is debatable, but one should be done to not only view the urethra but also evaluate bladder size and reflux. Decreased trabeculation, resolution of reflux, and a more uniform urethral diameter are all signs of successful relief of obstruction. One can measure the ratio of the diameter of the posterior urethra to that of the anterior urethra as an indicator of obstruction. A postablation urethral ratio of 2.5 to 3.0 is considered an acceptable postoperative result at 12 weeks (Gupta et al, 2009). **Evidence indicates that early valve ablation allows the bladder to cycle, thus improving compliance and bladder stability in infancy and resulting in less bladder dysfunction in older children** (Youssif et al, 2009).

Transurethral incision of the bladder neck at the time of valve incision has not been part of standard management; however, there is a report that this procedure has produced improved bladder performance with fewer inhibited contractions, lower mean maximum voiding pressures, and less need for anticholinergic medications than an age-matched control group after 4 years (Kajbafzadeh et al, 2008). Additional study of the modern use of this procedure is necessary.

Cutaneous Vesicostomy

If the infant is too small to instrument safely for valve ablation, then a cutaneous vesicostomy can be performed as a temporary measure (Fig. 126–9). Temporary vesicostomy drainage allows the urologist to incise the valves later when the patient is older and healthier. The vesicostomy has proven to be a safe and efficient treatment with long-term results in preserving renal function and somatic growth equal to primary valve ablation (Walker and Padron, 1990; Narasimhan et al, 2004). The vesicostomy provides adequate drainage of the upper tracts in more than 90% of cases (Krahn and Johnston, 1993). Vesicostomy itself is not without complication, however, and one study reported an 8.6% reoperation rate (Noe and Jerkins, 1985). Some people have questioned whether vesicostomy would cause permanent loss of bladder volume, but this has not proven to be true and vesicostomy does not significantly affect bladder capacity (Khoury et al, 1990). Some authors report that compliance may be decreased in vesicostomy bladders compared with those treated with primary ablation (Kim et al, 1996; Podesta et al, 2000). In general, primary ablation is the preferred surgical procedure to treat posterior urethral valves and vesicostomy is reserved for very small or very ill infants. Vesicostomy remains an excellent alternative treatment in these difficult situations.

Upper Tract Diversion

In the past, initial management of posterior urethral valves relied on upper tract diversion with ureterostomy or pyelostomy (Johnston, 1963). Diversion was effective in decompressing the upper tracts and controlling infection. Infants with high urinary diversion, however, often faced difficult urinary reconstructive problems later in life. In addition, high diversion produces stomas that present chronic management problems with incontinence. Even with these difficulties urinary diversion provided the best management available for valve patients for many years.

With the development of new cystoscopic equipment, Johnston demonstrated that endoscopic ablation could be performed safely and with good initial results (Johnston, 1966). Once the option of primary valve ablation was available, a long and thorough debate over the relative merits of initial upper tract diversion versus primary valve ablation followed.

Because both approaches yield good initial control of infection and adequate decompression of the upper urinary tract in most cases, the controversy focused on long-term results and measured renal function, bladder function, and somatic growth in each group. Conflicting data have been found regarding ultimate renal function and somatic growth, with Krueger and colleagues (1980) presenting data supporting ureterostomy from the large Toronto experience. He found that patients initially diverted had better eventual renal function and somatic growth. On the other hand, Reinberg, Duckett, and Hendren presented data supporting the conclusion that there was no significant difference in long-term outcomes between the two initial treatments (Hendren, 1978; Duckett and Norris, 1989; Reinberg et al, 1992a). Although more study may help clarify the situation, the current consensus is that neither initial treatment is superior in promoting renal function and somatic growth.

Despite early concerns that a bladder that is left without urine flow by proximal diversion would deteriorate from disuse, more recent data have shown that most of these bladders do not lose significant function. After upper tract diversion, urodynamics have shown that bladder capacity is preserved in 80% and compliance in 69% (Lome et al, 1972; Tanagho, 1974; Ghanem and Nijman, 2005). **Primary valve ablation may give the best chance for optimal bladder rehabilitation because of the ability of the bladder to cycle, but temporary supravesical diversion remains a reasonable alternative in the complex valve patient and usually leads to a marginal, if any, decrease in long-term bladder function** (Close et al, 1997; Podesta et al, 2002).

The current consensus is that both approaches eventually yield similar results and that infants who undergo initial upper tract diversion are at the disadvantage of needing more surgical procedures. Today upper tract diversion is usually limited to those patients who fail to respond to bladder level drainage. The specific clinical situation for upper tract diversion in posterior urethral valves today develops when bladder level drainage is insufficient to prevent infection or adequately drain the upper tracts. The decision to perform upper tract diversion relies on renal function, infection, and to a lesser extent, degree of hydronephrosis. Kidney development and growth in early life is critical, and neonatal kidneys may potentially recover function and continue to produce new cells during this period (Mayor et al, 1975; Hayslett, 1983). It is compelling to place these damaged kidneys in the best possible physiologic situation to recover, but this must be balanced with the knowledge that although upper tract diversion does initially improve renal function and drainage, there is no evidence that it offers any long-term advantage over primary ablation.

After the bladder has been adequately decompressed, the decision of whether to perform upper tract diversion is one of clinical judgment. Because hydronephrosis usually takes months to improve significantly, renal function is a better early parameter to follow. If the serum creatinine level drops below 2.0 it is safe

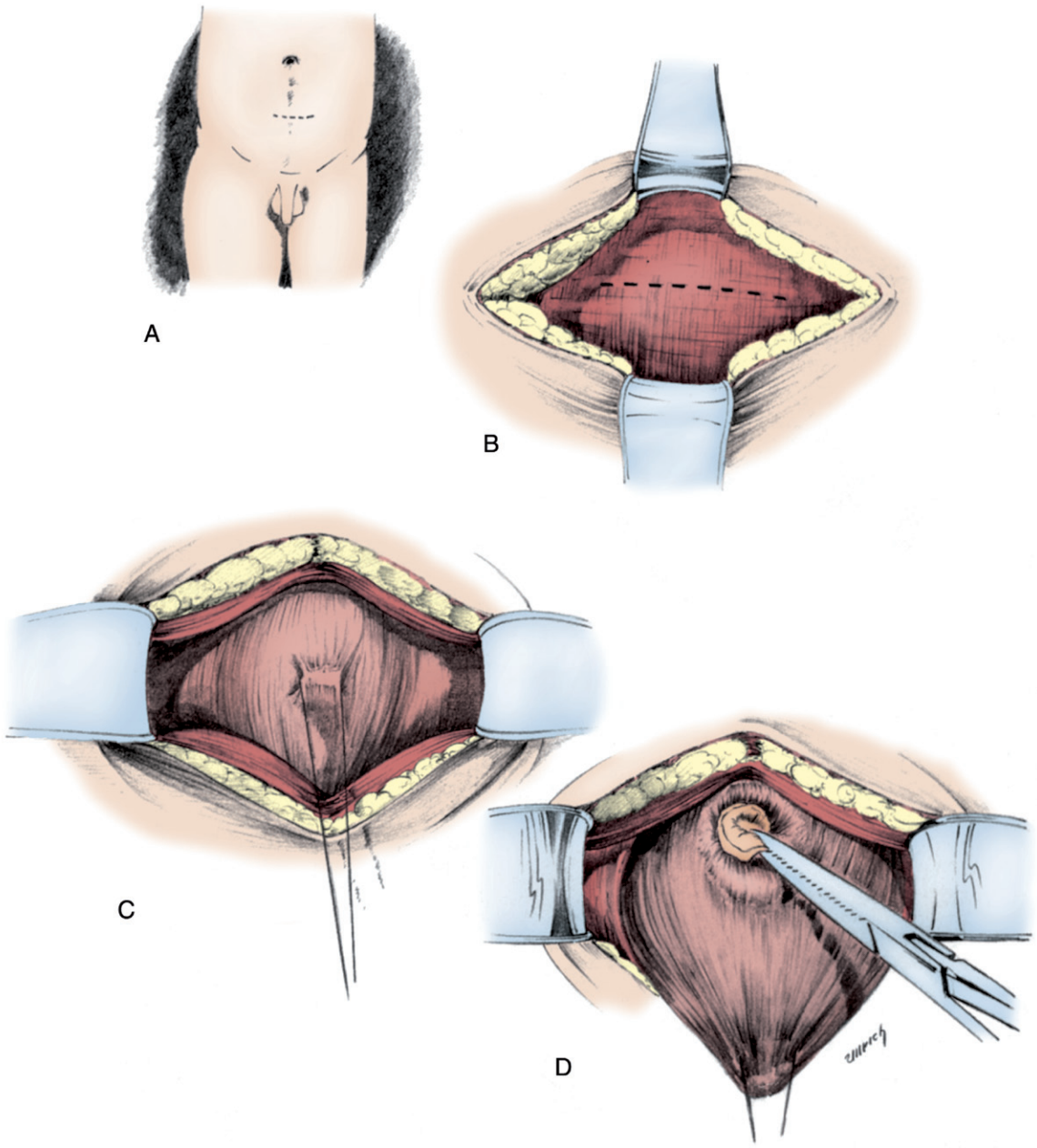


Figure 126–9. Blocksom technique for performance of cutaneous vesicostomy. **A,** After the bladder is filled, a transverse incision is made at the upper limit of the filled bladder and near the midpoint between the pubis and umbilicus. **B,** A transverse incision is made in the rectus fascia. **C** and **D,** The bladder is mobilized with a stay stitch and blunt dissection to free the peritoneum away from the bladder dome.

Continued

to rely on improved bladder drainage for additional kidney improvement. If the creatinine level remains above 2.0 after 10 days of adequate bladder decompression and if hydronephrosis is unimproved, then upper tract diversion may be considered. The type of diversion remains the surgeon's choice, and there are proponents of high loop ureterostomy, ring ureterostomy, pyelostomy, and end ureterostomy (Sober, 1972; Williams and Cromie, 1975; Kitchens et al, 2007). The type of upper tract diversion the authors prefer is a low loop ureterostomy because it provides adequate drainage, places the stoma under the diaper, and offers the most logical and simple reconstruction later.

If upper tract diversion is performed, reconstructive surgery to internalize the urinary tract should be delayed until the bladder and upper tracts have improved as much as can be expected. Practically this usually occurs between 3 and 5 years of age. If the patient is destined to reach ESRD, then reconstruction should be delayed until transplantation can be performed (Sheldon et al, 1992). It is imperative to establish an efficient method to empty the bladder, either by voiding or intermittent catheterization, before undiversion (Fig. 126–10).

Management of Vesicoureteral Reflux

Between 50% and 70% of patients with posterior urethral valves will have vesicoureteral reflux at the time of diagnosis (Fig. 126–11) (Hulbert and Duckett, 1992). Scott

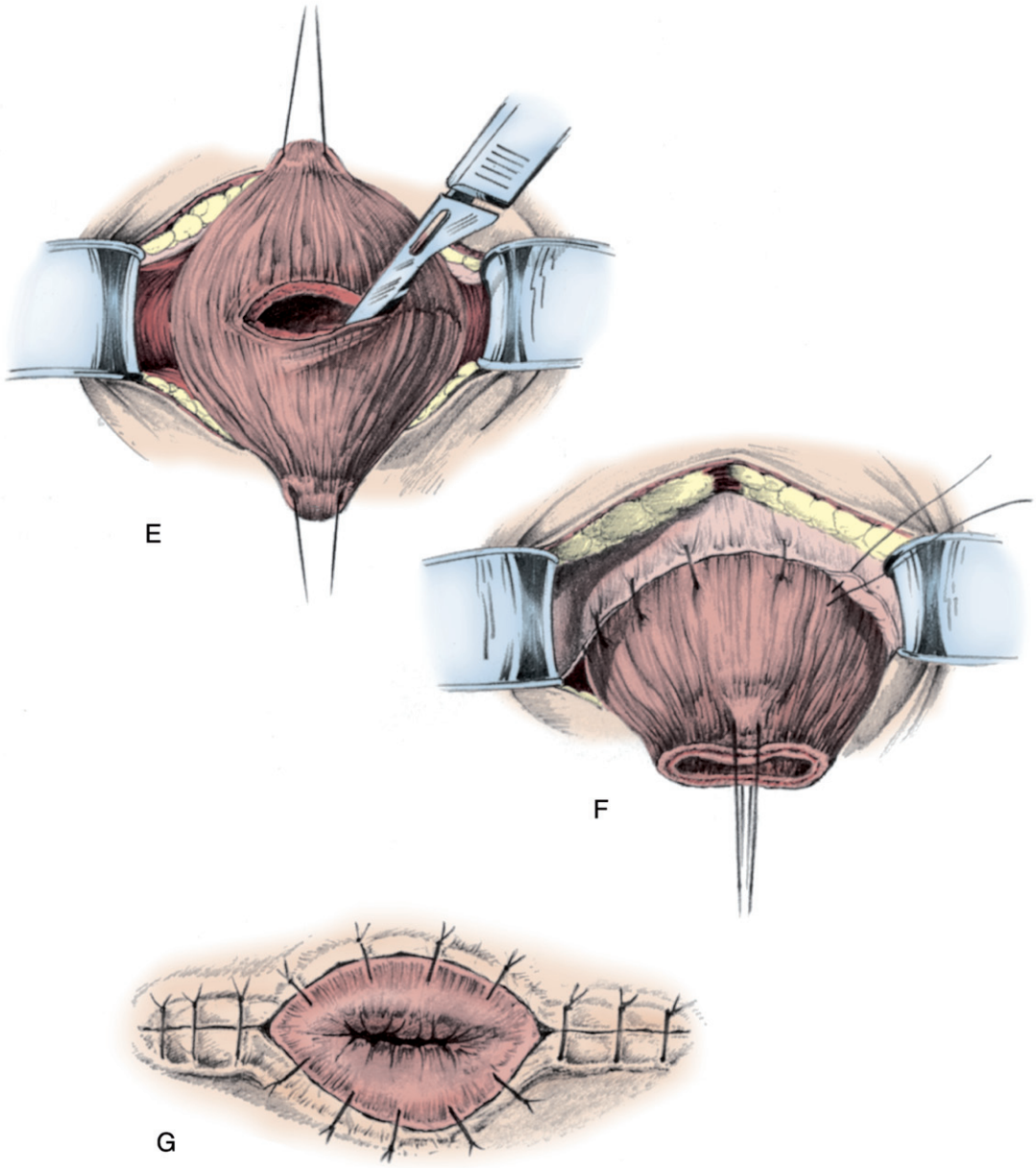


Figure 126–9, cont'd. **E,** A transverse incision is made into the bladder. **F,** The bladder is sewn to the rectus fascia, placing these sutures 1 cm away from the edge of the bladder incision. **G,** The bladder wall is sewn flush to the skin. (From Gonzales ED. Posterior urethral valves and other ureteral anomalies. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, editors. Campbell's urology. 8th ed. Philadelphia: WB Saunders; 2002.)

(1985) studied 46 affected boys with valves and found reflux in 72% of patients and in 53% of ureters. Bilateral reflux occurred in 32% of this study group.

Reflux in posterior urethral valves is considered secondary to bladder outlet obstruction so that the initial management of reflux is relief of obstruction. Reflux resolves after valve ablation in between 20% and 32% of refluxing ureters (Scott, 1985). Most reflux resolves within several months, but some can take as long as 3 years. Reflux is more likely to resolve when associated with a better functioning kidney. Hassan found that reflux resolved in only 10% of kidneys with less than 20% split renal function in a series of 73 boys with valves (Hassan et al, 2003). Children with initial bilateral reflux are more likely to have reflux resolve than those with unilateral reflux. As with all children with vesicoureteral reflux, they must be maintained on prophylactic antibiotics to prevent infection.

If persistent high-grade reflux is a clinical problem because of urinary tract infections or incontinence, then bladder function and drainage must be reviewed. Bladder dysfunction in the form of inadequate emptying and high storage pressures are the usual causes of persistent reflux. Surgery to repair reflux in valve patients must be undertaken with great care, and reimplanting ureters into a valve bladder that has not been adequately rehabilitated will lead to a high failure and complication rate (Warshaw et al, 1985; Hulbert et al, 1992; El-Sherbiny, 2002a).

The first step in evaluation of persistent reflux is to repeat the VCUG to look for persistent valve remnants. If no remnants are

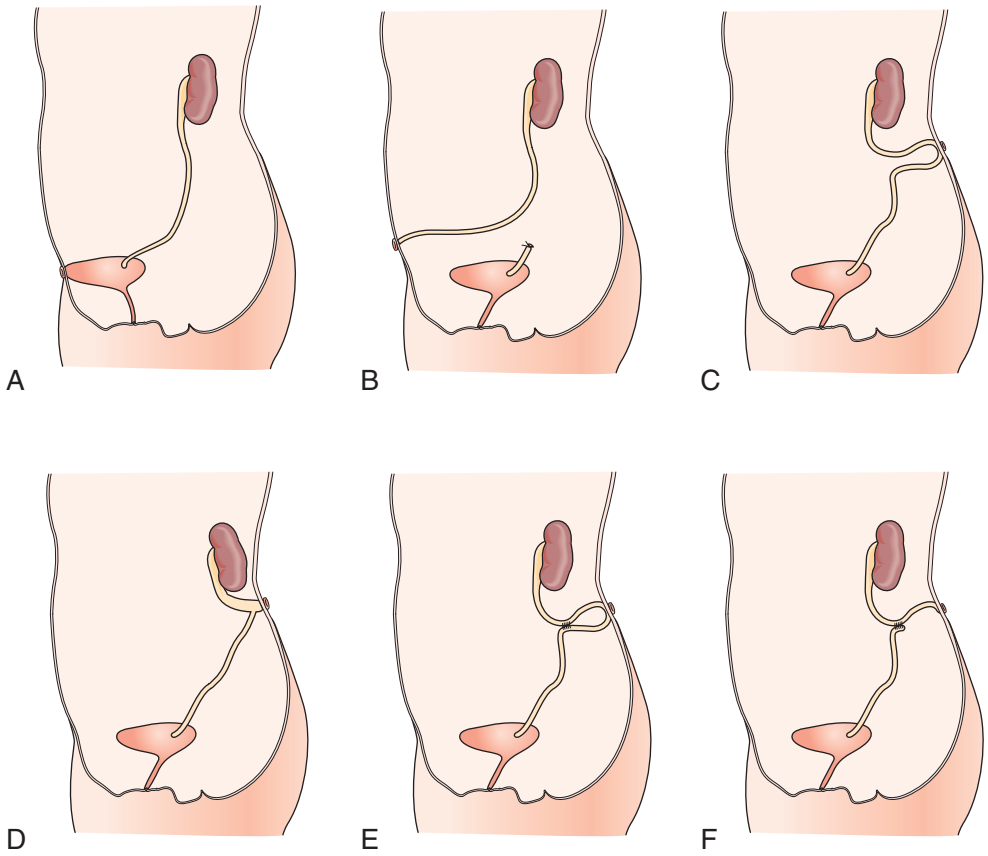


Figure 126–10. The variety of urinary tract diversions useful in posterior urethral valves. **A,** Vesicostomy. **B,** Distal ureterostomy. **C,** Proximal loop ureterostomy. **D,** Cutaneous pyelostomy. **E,** Ring ureterostomy. **F,** Sober Y ureterostomy. (From Glassberg KI, Horowitz M. Urethral valves and other anomalies of the male urethra. In: Belman AB, King LR, Kramer SA, editors. Clinical pediatric urology. 4th ed. London: Martin Dunitz; 2002. p. 899–945.)

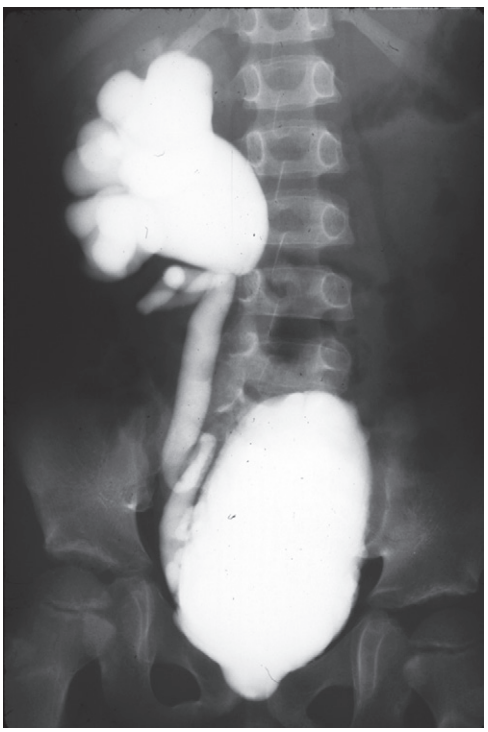


Figure 126–11. Voiding cystourethrogram shows persistent high-grade vesicoureteral reflux in a boy with posterior urethral valves. Note the large-capacity, mildly trabeculated bladder.

found, then urodynamics are necessary to evaluate the bladder. If the bladder function is adequate and persistent reflux remains a problem, surgery to correct reflux may be necessary. **Ureteroneocystostomy is usually limited to the situation where infections cannot be controlled and bladder function is adequate.**

High-grade reflux is often associated with severe dysplasia and nonfunction in the associated kidney in valve patients (Heikkila and Rintala, 2009). In the past these nonfunctional kidneys and dilated collecting systems were removed early in life. It has become evident that there is no urgency to remove these units as long as they do not lead to recurrent infection. They are best retained until the bladder has rehabilitated as much as possible. The dilated collecting system could possibly be used as a ureteral augmentation if bladder volume or pressure warrants (Bellinger, 1993). Ureter is the best material available for augmentation cystoplasty because it is lined with urothelium and the ureteral muscle will not contribute to high pressures from detrusor contractions (Landau et al, 1994). It is also possible to leave these nonfunctional units in place and successfully repair the reflux (Kim et al, 1997a). This is a reasonable alternative when faced with the need for reimplant surgery on the contralateral side.

Management of Hydronephrosis

Almost all patients with posterior urethral valves have severe hydroureteronephrosis at diagnosis. Scott found hydronephrosis in 96.5% of valve patients, and in 78% it was

bilateral (Scott, 1985). Hydronephrosis may or may not be associated with reflux. **Like reflux, hydronephrosis is a secondary phenomenon in valve patients and like reflux, it often resolves once the primary pathology, obstruction, is relieved.** Nonrefluxing hydronephrosis resolves in 49% of patients and may do so quite rapidly after valve ablation. This leaves a significant population of valve patients with persistent hydronephrosis for years despite adequate bladder emptying (Johnston and Kulatilake, 1971). Hulbert and Duckett (1988) found that 25% of valve patients have dilated upper tracts 5 to 15 years after successful valve ablation.

The majority of patients with persistent hydronephrosis do not have obstruction either at the bladder outlet or the ureterovesical junction. Whitaker developed his antegrade perfusion test specifically to examine chronic hydronephrosis in valve patients and document pressures within the upper urinary tract and across the UVJ (Whitaker, 1973). Tietjen also used the Whitaker test to evaluate 25 valve patients with persistent hydronephrosis and found only 8% of patients to have an element of obstruction at the ureterovesical junction (Tietjen et al, 1997). The majority of patients with hydronephrosis had a measured mean perfusion pressure of only 3 cm of H_2O (normal is <15 cm of H_2O). The ureterovesical junction may be functionally obstructed before ablation of the valves, but this usually resolves with bladder rehabilitation (Glassberg et al, 1982).

VALVE BLADDER SYNDROME

The *valve bladder* or *full valve bladder* are terms coined by Mitchell to describe a chronic condition in valve patients where despite successful valve ablation, intrinsic bladder dysfunction leads to deterioration of the upper urinary tracts and incontinence (Mitchell, 1982). **The combination of poor sensation, high bladder volumes, and poor compliance produce storage pressures high enough to prevent adequate drainage of the upper tracts. These boys are comfortable with large bladder volumes at high pressures. They frequently have overflow incontinence and void infrequently and incompletely.** Videourodyanmics are necessary to diagnose this condition, and there is a direct correlation of abnormal urodynamics indicating poor compliance and detrusor overactivity with poor renal function (Ghanem et al, 2004). Initial management is usually timed voiding, but if this does not successfully lower pressures and empty the bladder, α blockers or clean intermittent catheterization (CIC) can be used (Austin et al, 1999). α Blockers can be effective in reducing postvoid residual urine and improving the urinary stream. Abraham and colleagues (2009) studied 42 children with valves, and residual urine volume was significantly reduced in 95%. The mean reduction of residual volume was 85%.

Glassberg (2001) has suggested that proactive urodynamic-directed bladder management might improve long-term bladder outcome. Koff and colleagues (2002) also proposed that valve bladder syndrome is not a permanent state due to prenatal bladder damage but is an induced condition due to a combination of polyuria, impaired bladder sensation, and residual urine volume. Bladder decompensation in response to this situation results in increasing residual urine, upper tract dilation, and renal injury.

Koff proposed intermittent catheterization with continuous nocturnal bladder emptying. He found a significant improvement of hydronephrosis in 10 boys with valves treated in this manner. Nguyen also found significant improvement in frequency of urinary tract infection, upper tract dilatation, and continence in valve patients who underwent overnight bladder drainage (Nguyen et al, 2005). Holmdahl and colleagues (2003) studied 35 boys with valve bladder and found that intermittent catheterization not only improved GFR but also improved bladder compliance and capacity more than expected for age and when compared with valve patients who did not catheterize.

Glassberg and colleagues (1982) categorized the hydronephrotic upper tracts of valve patients into three types: those that drain independent of bladder volume, those that drain efficiently only with the bladder empty, and those that are obstructed independent of bladder volume. Duckett applied this classification to 100 valve patients and found only four cases of true obstruction of the upper tracts independent of bladder dysfunction, and all had undergone ureteral reimplantation (Smith and Duckett, 1996).

Evaluation of persistent hydronephrosis in valve patients is complex and may require measurement of voided volumes to evaluate the relationship between renal tubular competence and bladder function, videourodynamics to evaluate the ability of the bladder to hold and empty adequate volumes at acceptable pressures, ultrasound to evaluate degree of hydronephrosis, lasix renography to evaluate relative renal function and induced drainage, and Whitaker perfusion test to measure intrarenal pressures at a given drainage rate. Access to all of these modalities is necessary to choose proper management of the valve patient with persistent hydronephrosis. Luckily, most children with persistent hydronephrosis do not need surgical therapy outside of valve ablation and attention to bladder function.

Management of Bladder Dysfunction

Posterior urethral valves affect no organ more consistently and profoundly than the bladder. The degree of damage varies considerably, and it is the rare patient who does not suffer significant lifelong bladder dysfunction. The bladder causes two types of long-term problems for the valve patient: interference with upper tract drainage and incontinence. The bladder subjects the upper tracts to a form of obstruction at two points of life, as newborns and late in childhood. At birth the bladder is thick and trabeculated with saccules and diverticuli. It contracts with great force, and compliance is low. Although urodynamics are difficult to perform in infants, particularly in the presence of reflux and diverticuli, the bladder can be seen on imaging to undergo strong contractions. This stage of bladder dysfunction can persist for months despite successful valve ablation. Voiding pressures are high in male infants with valves but no higher than their normal peers. Furthermore, high voiding pressures are not associated with reduced kidney function (Taskinen et al, 2009). Storage pressures, compliance, and ability to empty are other key elements of bladder function in these children.

Late in childhood the bladder is less contractile but displays poor compliance, and this along with poor sensation leads to the valve bladder syndrome discussed earlier. Both the hypercontractile bladder of infancy and the rigid bladder of late childhood inhibit upper tract drainage.

Incontinence is a major problem for valve patients. A review of 100 patients revealed 81% had delayed day and night continence at age 5 years (Smith et al, 1996). **Another large series discovered that only 53% were dry by age 12** (Churchill et al, 1990). This problem improves in most by age 20, but the delay in attaining continence creates painful difficulties during adolescence (Parkhouse et al, 1988). In the past, incontinence was felt to be due to sphincter injuries and bladder neck

dysfunction, but today this problem is thought to be multifactorial and due to a combination of poor bladder sensation, poor bladder compliance, detrusor instability, and polyuria. Renal tubular damage, which progresses during childhood, leads to inability to conserve sodium and free water and can lead to nephrogenic diabetes insipidus and urine volumes up of several liters per day. These exaggerated volumes can overcome any bladder's functional ability, especially one with limited potential.

Peters identified three urodynamics patterns in valve boys: myogenic failure, detrusor hyperreflexia, and decreased compliance/small capacity (Peters et al, 1990). **Myogenic failure usually occurs in older children and leads to overflow incontinence and incomplete bladder emptying. Management includes timed voiding, double voiding, α blockers, and intermittent catheterization.** The urinary frequency and urge incontinence due to detrusor hyperreflexia is managed with anticholinergic medications. Anticholinergics may also help with those patients with small poorly compliant bladders but may not be sufficient to prevent the need for augmentation cystoplasty to provide adequate urine storage necessary for continence and upper tract drainage. Inappropriate use of anticholinergic medications may induce iatrogenic myogenic failure and therefore they should only be used with urodynamic monitoring (Misseri et al, 2002).

Holmdahl and colleagues (1995) **studied valve patients with urodynamics over many years to assess changes in bladder function. They found that the functional patterns outlined by Peters overlap in the majority of patients and that the dominant pattern changed with age. They concluded that these patterns are stages of development. In infants, poor compliance dominates; in older children instability from hypercontractility is the dominant pattern; in postpubertal boys myogenic failure becomes the norm. The valve bladder is surely one in constant transition during childhood. Urodynamics are necessary to track changes and to alter management in these patients throughout the first two decades of life** (Kim et al, 1997b).

Boys with valves who present later in childhood frequently have only voiding complaints and a more functional urinary tract. In a study of 70 children who presented at average age of 7.5 years, Schober and Dulabon (2004) found that ablation of valves will dramatically improve symptoms of urinary frequency and diurnal and nocturnal enuresis. Despite this improvement, most boys will continue to have a degree of hydronephrosis and some voiding difficulties.

In some boys with valves, bladder performance is not adequate to protect the upper tracts from the deleterious effects of high storage pressures and recurrent infection despite maximal medical management. Treatment of these children depends on their age and their ability to undergo CIC in most cases. If the boy can be catheterized, then anticholinergics and CIC will often improve the bladder environment enough to allow the bladder to rehabilitate and develop a better compliance and pressure profile. If this approach fails, then a vesicostomy is usually an excellent alternative.

After the age of toilet training the expectations change, and if anticholinergics and CIC fail to provide either a safe environment for the kidneys or the boy remains incontinent, then augmentation cystoplasty may be indicated (Kajbafzadeh et al, 1995; Bhatti et al, 2007). Although ileal augmentation is the historical norm and works well, it carries the disadvantages of mucous production, risk of rupture, stone production, and the potential for bladder cancers later in life. Because many valve patients have massive hydronephrosis and some have a unilateral nonfunctional kidney, ureteral augmentation is a somewhat popular alternative (Fisang et al, 2010). Ureteral augmentation has the advantage of leaving the bladder lined only with native urothelium and avoiding mucus, stones, and cancer. Bladder performance in 13 of 17 patients (10 with valves) after ureteral augmentation was significantly improved with a mean follow-up of 4.5 years when measured by capacity, mean end filling pressure, and compliance (Johal et al, 2008).

Augmentation in valve patients was more popular in the past before the national history of valve bladder development, and the pathophysiology of tubular damage in dysplastic kidneys was as well defined. Today it is somewhat rare and many patients are managed medically with CIC, medicine, and nighttime catheter drainage until their bladder pressures decrease and/or their renal failure is treated definitively with transplantation.

Catheterizable urinary channels are useful in many boys because the urethra is sensate and the high bladder neck often makes catheterization technically difficult (Cain et al, 1999). Appendicovesicostomy is slightly more difficult in valve patients because of the thickness and relative fibrotic bladder wall, but once accomplished it works well. This gives the boys easy access for CIC and nighttime catheter drainage. The authors perform appendicovesicostomy routinely in all older valve boys who require CIC.

In summary, management of bladder dysfunction in boys with posterior urethral valves is an intensively individualized process with close monitoring of urodynamics, urine volumes, renal function, infections, and hydronephrosis. Patients may need anticholinergics, α blockers, intermittent catheterization, continuous nocturnal bladder drainage, timed voiding, or any combination of management options. In addition, because the bladder is in transition throughout most of childhood, their management needs will change as they mature.

Management of Glomerular Injury and Renal Function

The primary goal of management in posterior urethral valves is to preserve renal function and to maximize renal growth and development. Renal injury in posterior urethral valves includes two initial glomerular insults: dysplasia and obstructive uropathy. Dysplasia is by far the most important because it is irreversible and not only produces a level of renal insufficiency at diagnosis but also limits future growth and development of the kidney. Obstructive uropathy may produce ongoing injury and is potentially reversible. It is mandatory to provide low-pressure storage and drainage of urine in order to prevent further renal damage.

Other threats to glomerular function come from persistent or progressive obstruction and infection. Hyperfiltration has been recognized in animal models as a cause of additional injury, but its importance in humans remains undocumented (Brenner et al, 1982). As somatic growth makes additional demands on the kidneys, valve patients can experience proteinuria, hypertension, and progressive loss of renal function (Tejani et al, 1986; Burbige and Hensle, 1987; Parkhouse et al, 1988; Reinberg et al, 1992a; Farnham et al, 2005). Poorly controlled hypertension also can add to renal deterioration. **Consistent and regular urologic care with monitoring of bladder**

function and infection will place the kidneys in the best position to grow and develop to their full potential.

ANTENATAL DIAGNOSIS AND MANAGEMENT

The incidence of urologic anomalies is 1 in 500 fetuses detected on ultrasounds (Colodny, 1987). **Posterior urethral valves are the most common cause of bilateral hydronephrosis in male fetuses.** Most valve patients are diagnosed by prenatal ultrasound, and the ability to image the fetus continues to improve with the technology of ultrasound. The accuracy of ultrasound diagnosis is proportional to fetal age, and valves may be missed in scans done before 24 weeks' gestation (Skolder et al, 1988; Abbott et al, 1998). **The differential diagnosis of a male fetus with bilateral hydroureteronephrosis and a distended bladder includes prune-belly syndrome and severe reflux. Bladder wall thickness is impressively increased only with valves. Fetal urine parameters may also be useful in predicting renal damage in utero. Aspirated fetal bladder urine with high sodium content and isosthenuria compared with serum values suggests poor renal function and that fetal intervention would not be helpful from a renal standpoint** (Glick et al, 1985).

Valves have emerged as the only urologic anomaly to be considered for antenatal intervention. Fetal intervention, although championed in the 1980s, has become quite rare due to a lack of objective evidence that it alters renal development (Reinberg et al, 1992b; Freedman et al, 1999). Although antenatal decompression of the urinary tract and the subsequent restoration of amniotic fluid are usually accomplished by placing a vesicoamniotic shunt, there have been reports of fetal valve ablation (Quintero et al, 1995). Restoring the volume of amniotic fluid can be a life-saving maneuver because of its effect on pulmonary function (Harrison et al, 1982). For optimal results this intervention must be performed during the appropriate stage of pulmonary development, older than 20 weeks and younger than 32 weeks. Oligohydramnios earlier than 20 weeks is usually incompatible with life due to pulmonary hypoplasia, and if diagnosed later than 32 weeks early delivery is preferable to fetal intervention. The decision to undertake fetal intervention must weigh the potential benefit for the fetus versus the risk of complications to both fetus and mother that occurred in 44% of those cases reviewed by the International Fetal Surgery Registry (Elder et al, 1987) (Fig. 126–12).

Key Points: Management of Posterior Urethral Valves

- Immediate catheter drainage is the initial management in all suspected valve patients.
- Primary valve ablation is the preferred initial surgical treatment in most valve patients.
- If the infant is too small or ill for endoscopic valve ablation, a vesicostomy is an excellent form of temporary diversion and provides drainage of the urinary tract.
- Initial management of hydronephrosis and reflux is valve ablation and observation with antibiotic prophylaxis.
- Bladder and renal function are often unstable in valve patients and usually change throughout life, requiring lifelong monitoring.



Figure 126–12. This boy had a vesicoamniotic shunt placed at 18 weeks of gestational age. The shunt has been attached to a drainage bag in the intensive care unit. The structure extending from the shunt site is herniated omentum. There is a significant risk of abdominal wall hernia at the shunt site.

PROGNOSTIC INDICATORS OF RENAL FUNCTION

Four basic predictors of renal function exist in patients with posterior urethral valves: ultrasound appearance, serum chemistries, age at diagnosis, and presence of reflux. Ultrasound, age at diagnosis, and presence of reflux can be determined at diagnosis, but serum chemistries require some time to develop.

Ultrasound appearance is a method of estimating the amount of dysplasia present in the kidneys. Dysplasia, strictly speaking, is a histologic diagnosis of tissue disorganization and includes fibrosis and cysts. This disorganization appears more echogenic on ultrasound and may be obvious by comparing the kidney to the liver and spleen as controls (Sanders et al, 1988). Kidneys that are considerably brighter than the liver usually contain significant dysplasia. Hyperechogenic kidneys diagnosed on ultrasound before 25 weeks' gestational age were predictive of renal dysplasia on postmortem examination of 24 male fetuses with urethral obstruction (Robyr et al, 2005). Loss of the normal corticomedullary junction normally visible on ultrasound has also been correlated with poor long-term renal function (Hulbert et al, 1992).

Age at diagnosis may be helpful in predicting prognosis. In the past, infants who presented younger than 1 year of age had a worse prognosis than those who presented later in life. Older boys usually present with voiding difficulty. They were long considered to represent the least affected of valve patients, but recent evidence has shown that some boys who present later in life suffer significant renal damage (Pieretti, 1993; El-Sherbiny et al, 2002b).

One study of boys who presented older than 5 years revealed that 35% had renal insufficiency and 10% reached ESRD (Bomalaski et al, 1999).

In a review of 70 boys who presented at the mean age of 7.5 years, Schober found that all had a normal serum creatinine (Schrober et al, 2004). Ansari and colleagues (2008) compared 95 patients with valves who presented before 2 years of age to 99 patients who presented after 2 years. They found that the incidence of azotemia at presentation, mean serum creatinine level, and risk for ESRD were worse in the boys who presented after age 2 years. The conflicting data in numerous studies seem to indicate that postnatal age at diagnosis alone is not a reliable factor in predicting outcome in valve patients, but it may be helpful in understanding the risks for an individual when considered with other clinical factors.

Today with most infants diagnosed antenatally and improved prenatal care, mortality of newborns with valves has decreased from almost 50% to between 3% and 10% (Williams, 1954; Churchill et al, 1990). Despite this improvement in mortality, positive effects of prenatal diagnosis on long-term renal function have been difficult to determine. Multiple authors have found that early gestational age at the time of diagnosis (before 24 weeks) is a significant negative factor in predicting long-term renal failure (Hutton et al, 1994; Sarhan et al, 2008).

Reflux in valve patients carries a poor prognosis. Johnston reviewed a series of valve patients in which the mortality was 57% in patients with bilateral reflux, 17% with unilateral reflux, and 9% with no reflux (Johnston, 1979). Many other authors have noted the grave effect of bilateral reflux on patients with posterior urethral valves (Parkhouse et al, 1988; Churchill et al, 1989). The commonly accepted explanation is that the incompetent ureterovesical junction that allows free reflux into the kidney also transmits the high pressures generated by the bladder. On the other hand, Stevens and others believe that severe reflux is associated with dysplasia primarily because the ureteric bud is abnormal and, in turn, induces an abnormal kidney.

The final prognostic factor is based on serum chemistries and relies on serial measurements of renal performance over time. **Warshaw reported that a nadir creatinine of less than or equal to 0.8 mg/dL during the first year of life predicts likely good long-term renal function** (Warshaw et al, 1985). **Other authors found the same relationship with a nadir creatinine level of 1 mg/dL during the first year of life** (Conner and Burbige, 1990; Sarhan et al, 2009; Ansari et al, 2010). Early renal function may be a helpful predictor as well. Denes reported on 32 patients with posterior urethral valves treated with immediate drainage. Serum creatinine was measured at diagnosis, after 4 days of drainage, and the nadir in the first year of life. After a mean of 10 years the authors found that patients fell into two groups, one with a GFR of greater than 70 mL/1.73 m^2 and the other with a GFR less than 70. The group with worse long-term function had initial creatinine of 3.6 mg/dL, a postdrainage creatinine of 2.4, and a nadir of 1.7. The group with better long-term renal function had initial creatinine of 1.3 mg/dL, postdrainage creatinine 0.6, and a 1-year nadir of 0.4 (Denes et al, 1997).

In a multivariate analysis of 119 valve patients seen over 30 years with approximately half presenting as newborns, DeFoor identified two independent risk factors that were statistically significant in predicting ESRD: increased nadir serum creatinine and severe bladder dysfunction. Reflux was associated with an increased risk of ESRD, but this did not reach statistical significance (DeFoor et al, 2008). Ansari studied 260 valve patients and found that nadir serum creatinine level, severe bladder dysfunction, and bilateral reflux were significant predictors of eventual ESRD (Ansari et al, 2010). The most powerful tools yet proposed in predicting outcomes in posterior urethral valves may lie at the genetic or molecular level (Woolf and Winyard, 2000).

TRANSPLANTATION IN VALVE PATIENTS

Obstructive uropathy is the most common cause of ESRD in children and accounts for 16.3% of children presenting for transplantation (Seikaly et al, 2001). **The most common condition producing this degree of dysfunction is posterior urethral valves. Up to 50% of boys with posterior urethral valves will reach ESRD in their lifetime.** Most of these will need dialysis or transplantation during the first two decades of life. Because renal transplantation allows a better quality of life and optimal somatic growth, it is the preferred method of managing ESRD in children and adolescents. The damaged bladder of valve patients presents a technical challenge for renal transplantation, and abnormal bladder function has been considered a threat to the success of transplantation.

Early transplant series in children with valves demonstrated significantly decreased success in transplant graft survival and in graft function compared with those who suffered ESRD due to reflux nephropathy (Churchill et al, 1988; Reinberg et al, 1988). The principal cause of graft failure was chronic rejection, and the relationship between bladder function and rejection was not apparent. Valve patients are known to have decreased bladder compliance and increased storage pressures, but in the absence of obstructive hydronephrosis or infection these factors can be managed successfully to protect the kidney.

More recent data have shown improved results with some series demonstrating good graft survival but a statistically significant increase in serum creatinine levels compared with controls (Bryant et al, 1991; Salomon et al, 2000). Still others have found no significant difference between valve patients and others in either graft survival or renal function (Groenewegen et al, 1993; Ross et al, 1994; DeFoor et al, 2003; Mendizabal et al, 2005; Otukesh et al, 2008). **Because the lower urinary tract is markedly abnormal in valve patients, it is not surprising that urologic complications are higher than in patients with normal bladders.** Urethral strictures, stones, and urinary retention were among the urologic complications that occurred in 19% of valve patients undergoing transplantation (Ross et al, 1994). Mochon found an increased risk of urinary tract infection in valve patients compared with others after transplantation, but this relationship may have been present before transplant and did not affect graft function (Mochon et al, 1992).

It is safe to say that renal transplantation is an important part of management of some valve patients and that success rates are high. It must be undertaken with the knowledge that urinary tract management may be more complex and complications more common than with other children undergoing transplantation. Careful urodynamic evaluation of bladder function before transplantation is vital, and the patient may need intermittent catheterization and/or augmentation cystoplasty in order to function safely with the new kidney (Zaragoza et al, 1993; Indudhara et al, 1998; Koo et al, 1999; Salomon et al, 2000; Mendizabal et al, 2005; Ozcan et al, 2006).

QUALITY OF LIFE WITH POSTERIOR URETHRAL VALVES

Although study in this area is somewhat limited, with modern management of renal insufficiency and bladder dysfunction most boys with posterior urethral valves feel they have a good quality of daily life (Hellström et al, 2006). Intermittent catheterization is seen as an obstacle in the company of friends and has required boys to develop strategies to perform this discreetly. Overall, boys with valves saw their treatment as a small part of their lives and valued friends, being able to participate in health care decisions, and having their own doctor and nurse.

The generally positive attitude toward life by valve patients can lead to their being lost from the health care system, and almost half of a group of 31- to 44-year-olds with valves had not been checked since adolescence. Among this group, a third was uremic and 40% had signs of bladder dysfunction despite being continent. The ability to father children was dependent on the presence of uremia. This study highlights the importance of lifelong follow-up care to monitor the often silent complications of valves, which ultimately affect quality of life (Holmdahl and Sillen, 2005). Boys with posterior urethral valves have a higher incidence of cryptorchidism (16%) and inguinal hernia (11%) (Heikkila et al, 2008b).

ANTERIOR URETHRAL VALVES

Anterior urethral obstruction is rare compared with posterior urethral valves. Although these obstructive structures may be called valves, they often occur in the form of a diverticulum of the urethra with one wall acting as an obstructive "valve" (Fig. 126–13) (Tank, 1987). There are also some reported cases of urethral flaps or valves in the anterior urethra (DeCastro et al, 1987; Scherz et al, 1987). The first case was reported in 1906, and the total number in the literature is small (Watts, 1906; Williams and Retik, 1969; Firlit et al, 1978).

Anterior urethral diverticuli typically occur where there is a defect of the corpus spongiosum, leaving a thin-walled urethra (Fig. 126–14). This segment of urethra balloons during voiding and causes a mass that is sometimes visible along the ventral wall of the penis. The mass resolves as urine drains from it between voids, and when full, urine can be expressed from the diverticulum by applying pressure. The distal edge of the diverticulum forms a flap that obstructs the flow of urine, and the effects of anterior urethral valves can be as damaging to the urinary tract as those of the posterior urethra. The embryology of these structures remains unclear but seems to be unrelated to the development of posterior urethral valves.

Boys with anterior urethral valves often present later in childhood with infection, straining to void, or incontinence. One third present with voiding symptoms, a third with antenatal hydronephrosis, and the remainder with a visible diverticulum (Van Savage et al, 1997). The degree of obstruction can be severe and produce pressures as high as with the posterior urethral valve. Spontaneous rupture of the fetal bladder in anterior urethral valves has been reported (Merrot et al, 2003).

Diagnosis depends on VCUG or cystoscopy. It may be difficult to pass a catheter into the bladder because the catheter often easily enters the diverticulum and becomes trapped. Treatment is similar to that of posterior urethral valves in that relief of obstruction is the most important goal. In severely ill children or young infants a vesicostomy is a good option for temporary drainage, allowing the urinary tract to decompress and delaying urethral repair until conditions are optimal (Rushton et al, 1987).

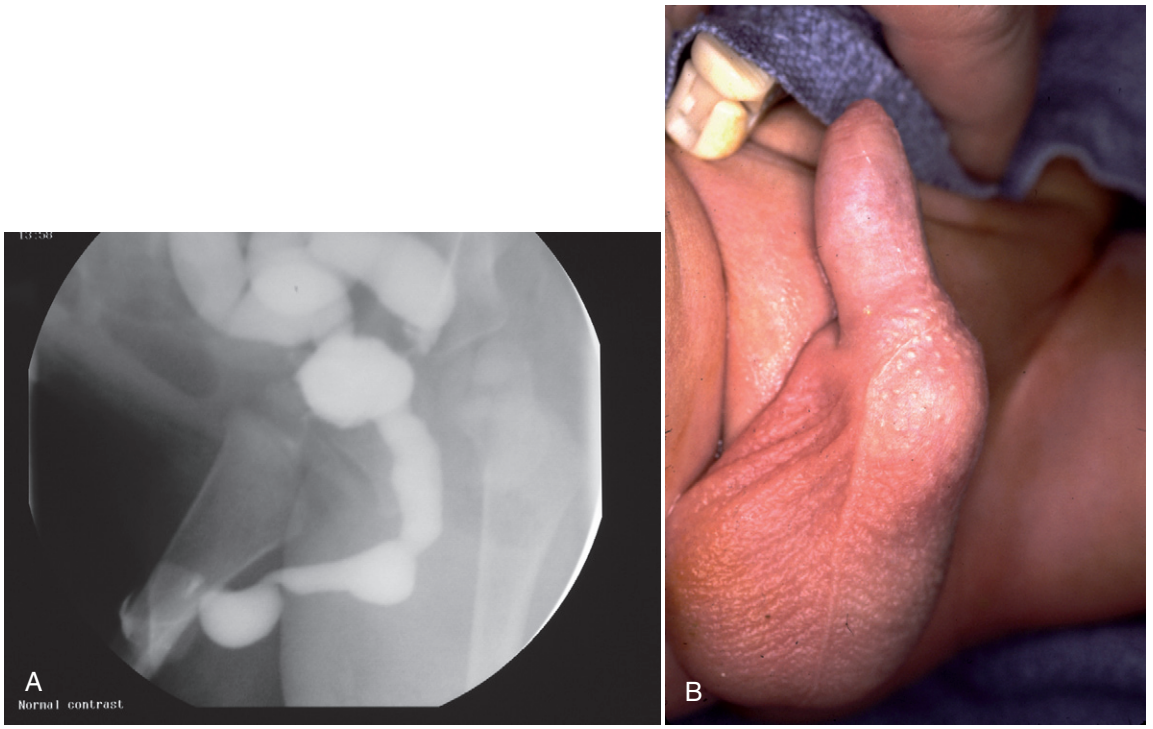


Figure 126–13. **A,** Voiding cystourethrogram shows a severe case of anterior urethral valves. The bladder is almost empty, and there is massive reflux. The valve is in the form of a diverticulum. **B,** The filled diverticulum can sometimes be seen as a mass on the penis that resolves between voids. Pressing on the mass may express urine for some time after voiding.

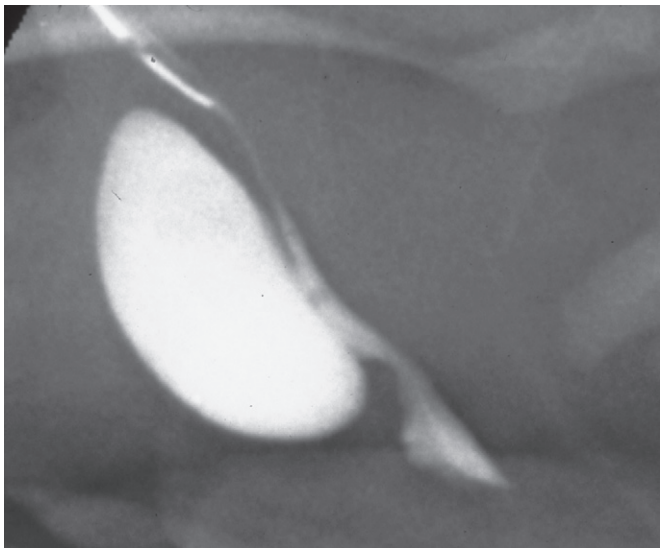


Figure 126–14. Voiding cystourethrogram demonstrates an anterior urethral diverticulum trapping urine during voiding.

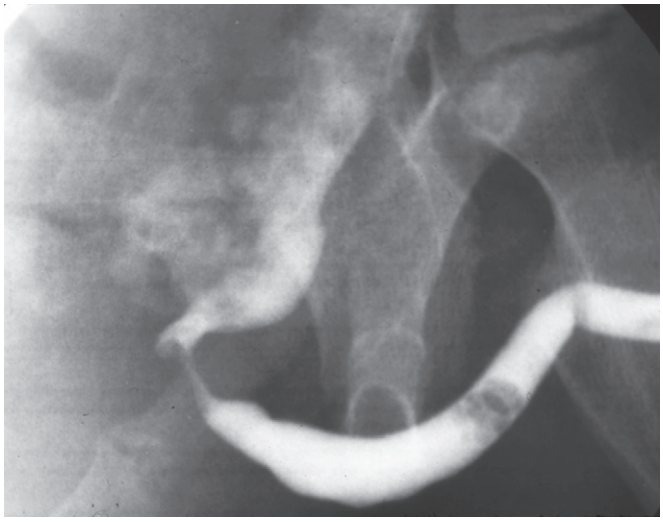


Figure 126–15. Voiding cystourethrogram shows a congenital urethral stricture. These rare conditions cause a clinical situation similar to posterior urethral valves.

Treatment of anterior urethral valves may include transurethral incision to allow free flow of urine or open urethral reconstruction. If the diverticulum is small or there is a urethral flap, transurethral incision is preferred. If the diverticulum is large, it will usually cause pooling of urine and repeated infection. The best option is an open excision of diverticulum and repair of the urethra. This can be difficult surgery and requires catheter drainage to facilitate urethral healing.

The long-term outcome of anterior urethral obstruction is similar to that of the posterior urethra. In general the severity of obstruction, degree of hydronephrosis, and incidence of renal failure is usually better in anterior urethral valves (Rawat et al, 2009). Less than 5% of patients with anterior urethral valves have reached ESRD compared with more than 30% of those with posterior urethral valves (Kaplan and Scherz, 1992).

CONGENITAL URETHRAL STRICTURE

Congenital urethral strictures are rare anomalies that produce the same pathologic and clinical problems as posterior urethral valves (Fig. 126–15) (Currarino and Stephens, 1981). They occur in the posterior urethra and lead to oligohydramnios, bilateral hydroureteronephrosis, and a distended bladder (Narborough et al, 1990). **Initial treatment in the newborn is almost always vesicostomy.** Because these strictures are usually too long to incise and too tight to dilate with sounds, they may be dilated gradually with increasingly larger catheters with good results (Passerini-Glazel et al, 1988).

URETHRAL POLYPS

Urethral polyps are rare anomalies of the male urethra (Fig. 126–16). **Patients with urethral polyps usually present with intermittent voiding complaints such as hematuria, stranguria, and dysuria** (Raviv et al, 1993; Walsh et al, 1993). Unlike urethral valves, polyps do not produce extensive damage to the urinary tract. They usually occur in the prostatic urethra near the bladder neck and may be quite mobile on a long stalk. Anterior urethral polyps have been reported (Coleman and Nense, 1991).

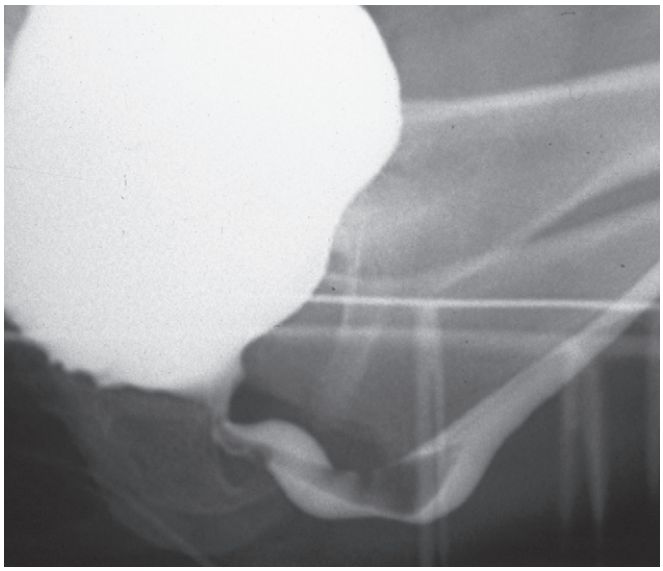


Figure 126–16. This urethral polyp is on a long stalk and caused intermittent dysuria and straining to void.

The polyps are usually diagnosed on VCUG, and the diagnosis is confirmed by cystoscopy. They are benign but may be confused with rhabdomyosarcoma of the prostate. Benign urethral polyps are usually solitary, whereas the polypoid form of rhabdomyosarcoma usually presents with multiple polyps and a mass extending beyond the bladder or prostate. Transurethral resection is curative in urethral polyps (Gleason et al, 1994).

URETHRAL DUPLICATION

Duplication of the urethra is a rare anomaly. Various types and several classification systems exist (Fig. 126–17) (Effmann et al, 1976; Woodhouse and Williams, 1979). In practice, urethral duplication is so rare that it is usually described by anatomic landmarks. Most urethral duplications occur in the same sagittal plane and can be divided into either dorsal or ventral.

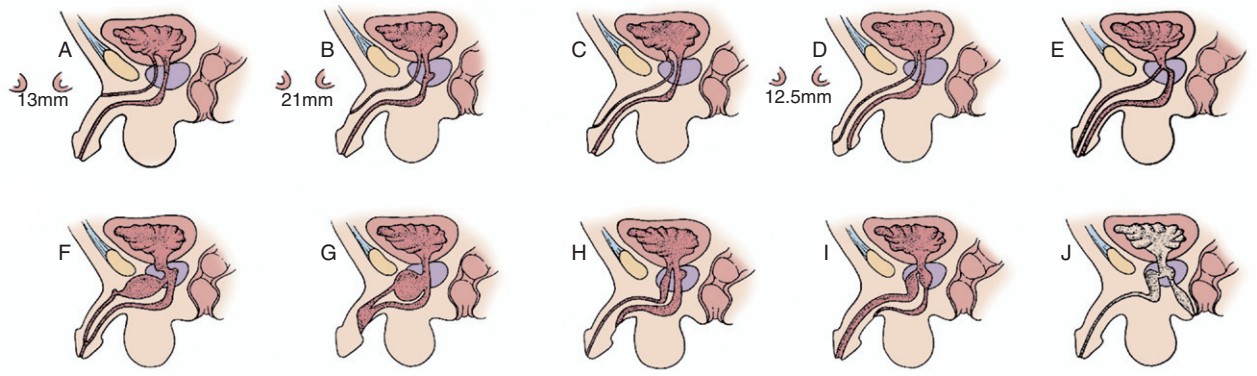


Figure 126–17. **A** to **J,** Variations of urethral duplications in the sagittal plane. Each of these drawings shows the ventral urethra as the functional one as it passes through the prostate and sphincter. (From Colodny A. Urethral lesions in infants and children. In: Gillenwater JT, Howards SS, Duckett JW, editors. Adult and pediatric urology. 2nd ed. St Louis: Mosby-Year Book; 1991. p. 2013.)

Some more rare duplications occur in the same horizontal plane, and the urethras lie next to one another, one left and one right. This horizontal type may be associated with duplicated phallus or complete bladder duplication (Woodhouse and Williams, 1979). Some patients present with incontinence or infection, but most are discovered in infancy on examination by the mother or pediatrician.

Dorsal urethral duplication occurs when there is a normal urinary meatus, dorsal chordee of the penis, and a second epispadiac meatus along the dorsal aspect of the penis. The foreskin may be incomplete dorsally, and the epispadiac meatus can occur anywhere along the midline of the penis (Sharma et al, 1987). The normal urethra is the ventral one that ends on the glans. The epispadiac duplicate urethra may be blind ending or extend to the bladder. If it communicates with the bladder, the patient may be incontinent. These patients may have a widened symphysis pubis similar to epispadias or exstrophy.

Ventral urethral duplications are extremely rare and may also be complete or incomplete with a blind-ending urethra. There may be a normally placed urethra on the glans and a second along the ventral aspect of the penis or even along the perineum. The dorsal urethra may be of normal caliber or narrow. The ventral urethra is considered the more normal because it usually passes out of the bladder neck and sphincter (Salle et al, 2000). The "Y" duplication occurs when the prostatic urethra splits into two channels with one extending to the glans and the more functional ventral one coursing to the perineum near the rectum.

Diagnosis of urethral duplication depends on the type of anomaly. If the duplication is complete, a VCUG will demonstrate both urethras during voiding (Fig. 126–18) (Hoekstra et al, 1985). If the duplication is blind ending, a retrograde injection of contrast and cystoscopy may be required to delineate the anatomy (Fig. 126–19) (Podesta et al, 1998).

Management of urethral duplication varies with symptoms and the severity of the anomaly. Some patients do not require treatment if they are free from infection and incontinence. Simple accessory duplicate urethras may be fulgurated with a bugbee and allowed to scar and close (Holst and Peterson, 1988). Others need to be excised to make the patient dry and prevent infection. If both urethras are functional and end adjacent to one another on the glans, the septum between the two can be excised at the meatus, giving the patient a single urinary meatus. The most complex "Y" fistulae may require extensive urethroplasties requiring tissue transfer such as buccal mucosa grafts (Ortolano and Nasaralloh, 1986).

URINARY FISTULA IN BOYS WITH ANORECTAL ANOMALIES

More than 80% of boys born with anorectal malformations have a fistula between the rectum and the urinary tract (Hong et al, 2002) (Fig. 126–20). **The vast majority have imperforate anus, but occasionally a congenital fistula occurs between the urinary tract and the rectum in a boy with an external anal opening (H-type fistula).** Fistulae are usually discovered by the pediatric general surgery service in their evaluation of the newborn with an anorectal anomaly and may be demonstrated with a VCUG. Because the initial treatment of most patients with anorectal anomalies is a diverting colostomy, many fistulae are diagnosed at 6 months of age with a distal colostogram. The distal colostogram is done by injecting contrast into the distal limb of the diverting colostomy before surgical repair of the anus.

Pediatric urologists are involved early in the child's life when recurrent urinary infections are a problem due to distal colostomy limb bacterial overgrowth, which leads to contamination of the bladder or urethra. This may be treated with antibiotic prophylaxis, enemas to empty the distal bowel, surgical separation of the proximal and distal limbs of the colostomy to prevent spillage, or in some cases early repair of the anus with a pull-through procedure. Upper urinary tract anomalies have been reported in up to 60% of boys with anorectal anomalies and may include vesicoureteral reflux, renal anomalies including solitary kidney, and hydronephrosis (Misra et al, 1996). Because 40% of these patients have sacral anomalies and 55% of those have severe lower urinary tract dysfunction comparable with patients with myelodysplasia, the threat of continued contamination of the urinary tract is serious (Boemers et al, 1996).

Definitive treatment of congenital recto-urinary fistulae is done at the time of anoplasty by the pediatric general surgery service. If this procedure is successful, the fistula is taken down at the time of rectal repair. Urethral injuries occur in 3% to 25% and may present immediately or in a delayed fashion (see Fig. 126–20). Fistulae may be either persistent or recurrent after rectal surgery or acquired by injuring the urethra at the time of anoplasty. In addition, a section of the rectum may be left attached to the fistula, creating a urethral diverticulum that may present with incontinence or UTI later in childhood. Rarely, the urethra may be divided or injured so severely that it causes stricturing.

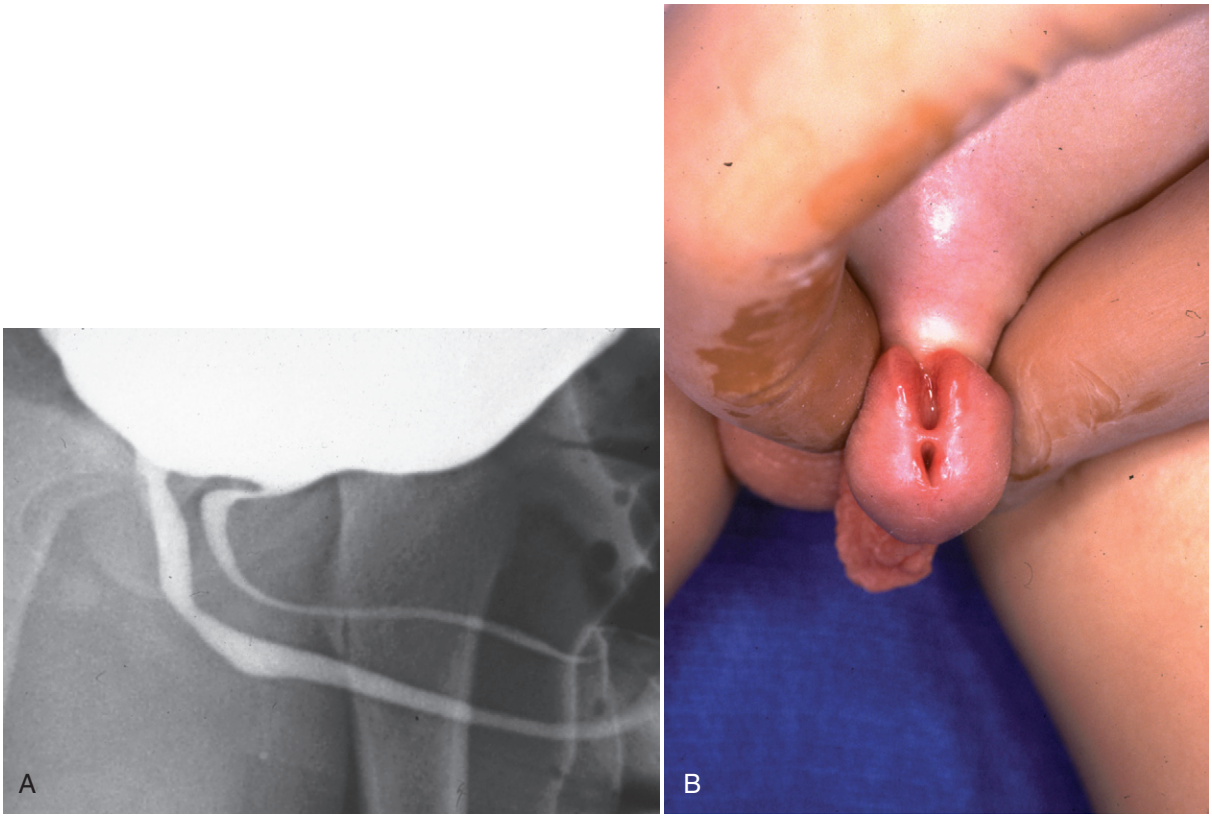


Figure 126–18. **A,** Voiding cystourethrogram shows a complete duplication of the urethra with an epispadiac dorsal segment. **B,** The ventral urethra is in the center of the glans, and the dorsal urethra ends in the dorsal glans cleft in an epispadiac location.

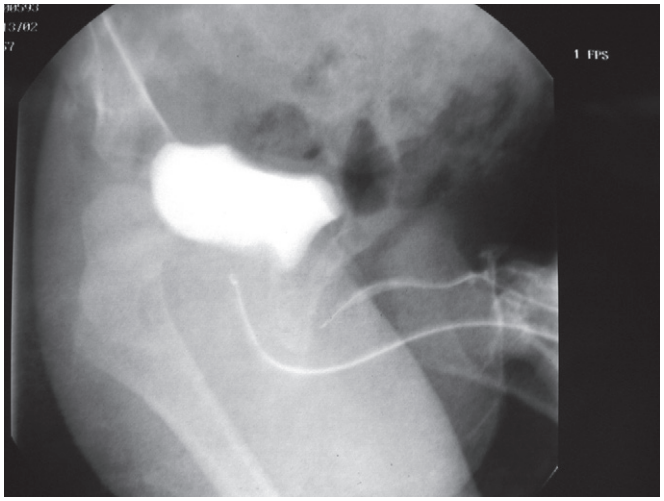


Figure 126–19. This urethral duplication has a blind-ending dorsal segment that ends under the pubis.



Figure 126–20. This voiding cystourethrogram demonstrates a posterior urethral fistula to the rectum discovered after an anoplasty. The patient presented with recurrent urinary tract infection and diarrhea due to urine passing into the rectum.

The urologist should be involved with injuries to the urethra or bladder. Cystoscopy with catheterization of the fistula and imaging will often be helpful to the surgeon, and if the urinary injury is more than a simple persistent fistula the pediatric urologist should repair the urinary tract. **Repair of fistula in infants and children follows the same set of operative rules that apply to adults. Any obstructive element of the urethra must be eliminated, the rectum and urethra (or bladder) must be adequately separated, the fistula must be ligated, and healthy tissue must be interposed between the urinary tract and gut.** Often, pediatric surgeons pull down fresh bowel at the time of revision and uninjured rectal wall opposes the urinary fistula, allowing healing. If this is not possible, it may be necessary to interpose omentum or a Dartos fascial flap as a barrier to repeat fistula (Youssef et al, 1998). The importance of having a catheter in the urethra during any rectal surgery cannot be overstated. In addition, adequate preoperative imaging with VCUG, colostogram, and magnetic resonance imaging will give the operating surgeon the best opportunity to have a successful outcome to this difficult surgical problem. Symptomatic urethral diverticuli must be excised using many of the same surgical techniques.

After any type of fistula or diverticulum repair, a urinary catheter should be left in place for at least 7 days. These children will need lifelong monitoring due to the risk of stricture, recurrent fistulae, or neurogenic bladder dysfunction.

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chapter 127

Non-Neuropathic Dysfunction of the Lower Urinary Tract in Children

C.K. Yeung, MD ● Jennifer D.Y. Sihoe, MD

Normal Bladder Function in Infants and Children
Epidemiology and Classification of Non-Neuropathic Bladder-Sphincter Dysfunction in Children
Bladder-Sphincter Dysfunction during Bladder Filling
Bladder-Sphincter Dysfunction during Bladder Emptying
Dysfunctional Elimination Syndrome, Constipation, and Bladder Dysfunction
Relationship among Bladder-Sphincter Dysfunction, Vesicoureteral Reflux, and Recurrent Urinary Tract Infections
Evaluation of Non-Neuropathic Bladder-Sphincter Dysfunction
Management of Non-Neuropathic Bladder-Sphincter Dysfunction
Nocturnal Enuresis
Summary

Our increasing understanding and recognition of non-neuropathic lower urinary tract dysfunction as a cause of various urologic disorders in childhood has had a profound influence on our management strategies over the past decade. What was known as primary or idiopathic, such as primary vesicoureteral reflux (VUR) or primary nocturnal enuresis, is often associated with underlying bladder dysfunctions evident on urodynamics and resolves with successful correction of the bladder physiology (Koff and Murtagh, 1983; Homsy et al, 1985; Watanabe et al, 1994; Yeung et al, 1998, 1999). Conversely, failure of recognition and treatment of the associated problem can result in persistence or even further deterioration.

The understanding of the spectrum of dysfunction of the bladder and even of normal bladder physiology in infants and young children is complex. Not only are the dynamics and functional disturbances of the lower urinary tract different from those in adults, but the evolution in normal bladder-sphincteric function during growth and maturation in children poses continuous changes (Yeung, 1995; Yeung et al, 1995; Sillen et al, 1996; Holmdahl, 1997). More confusingly, one type of bladder dysfunction may often progress with time and evolve imperceptibly into another, without a sharp distinction between the different stages. This is further confounded by a lack of age- and sex-specific normal reference values for various urodynamic parameters, especially for the very young age groups (Yeung et al, 1995).

Recent advances and development in the use of urodynamic techniques specially designed for infants and young children have allowed more accurate assessment of bladder function and provided much better understanding of bladder pathophysiology. This has allowed for better recognition of functional disorders, as well as to provide a scientific basis for their therapy (Hjalmas, 1988; Perez et al, 1992; Bauer, 1997; Nevéus et al, 2007). In view of the important association of bladder dysfunctions with various common urologic disorders, urologists should be acquainted with the spectrum of dysfunction and the techniques to facilitate proper diagnosis and treatment.

NORMAL BLADDER FUNCTION IN INFANTS AND CHILDREN

Anatomy of Bladder

The bladder is a unique organ of the human body in that it not only carries a dual function of both storage and emptying of urine but also has a complex innervation of voluntary and involuntary control of function. Understanding of the functional anatomy of the lower urinary tract stems from extensive postmortem studies carried out over decades (Gosling et al, 1981; Gosling, 1985; DeLancey, 1988; de Groat, 1993; Zvara et al, 1994).

The bladder is an abdominal organ, and when full it can be readily palpable in infants and young children

due to a shallow pelvis (Wiegel, 1990). The bladder wall consists of three layers: mucosa, detrusor, and adventitia. The detrusor consists of a meshwork of smooth muscle fibers arranged into a single functioning unit with an ability to elicit nearly maximum active tension over a wide range of length. This allows the bladder to fill with urine from the upper tract at low pressures (compliance) (Mattiasson, 1994). The ability of the bladder to store urine (reservoir function) is determined by the concomitant activity of the detrusor muscle and the bladder outlet (consisting of the bladder neck, proximal urethra, and striated muscle of the pelvic floor) (de Groat, 1993).

The bladder sphincter (external and internal) plays a major role in urinary continence by closure of the bladder neck and proximal urethra. The anatomy of the external urinary sphincter consists of a cylindrical structure, which is accentuated anteriorly and thinned out or actually absent posteriorly, thus giving a characteristic horseshoe or omega shape on cross section. It has an inner layer of smooth muscle and an outer layer of striated muscle, extending from the apex of the prostate to invest the length of the membranous urethra in males. In the females this is less well developed and extends from the bladder neck to the midurethra. The internal sphincter, however, has not been well delineated anatomically. It has generally been accepted that it consists of smooth muscle fibers continuing from the bladder base and trigone, which traverse inferiorly through the bladder neck to extend toward the proximal urethra. Its existence has been better delineated on radiologic and urethral pressure measurement studies. **During micturition, the bladder base, bladder neck, and proximal urethra can be shown to contract simultaneously as a unit, producing a funneling effect that opens up the bladder outlet with initiation of voiding.**

Little, too, is known about the natural course of development or maturation of the structure and function of the sphincter mechanism. **Literature suggests that immature detrusor-sphincter coordination, manifested as detrusor hypercontractility and interrupted voiding, commonly occurs in the first 1 to 2 years of life, causing some degree of functional bladder outflow obstruction** (Sillen et al, 1992; Yeung et al, 1998). In a postmortem study of the ontogeny of the external urinary sphincter in human fetuses, infants, and young children, Kokoua and Homsy found significant age-related differences in the histologic structure of the sphincter as compared with that in adults. Striated muscle fibers of the sphincter first appeared at around 20 weeks of gestation and then became arranged in a concentric pattern as a closed ring, fused posteriorly to form a tail-like structure that was directed to the perineal body. Posterior splitting of the striated sphincter, starting first caudally and progressively in a cephalad manner, then occurred during the first year of life, coinciding in parallel with gradual resorption of the "tail," to eventually giving way to a mature omega-shaped structure (Kokoua et al, 1992). As a complete closed ring of striated sphincteric muscle was present up to 1 year of age in more than 40% of cases, it may well be conjectured that this could be related to the high intravesical pressures and interrupted voiding that are commonly observed during urodynamic studies in infants (Sillen et al, 1992; Yeung et al, 1995, 1998).

Innervation of Bladder

Activation, coordination, and integration of various parts of the bladder-sphincteric complex involve both the central somatic and autonomic nervous systems through three sets of peripheral nerves: sacral parasympathetic (pelvic nerve), thoracolumbar sympathetic (hypogastric nerves and sympathetic chain), and sacral somatic nerves (primarily the pudendal nerve) (Fig. 127–1) (deGroat, 1993; Mattiasson, 1994).

Parasympathetic nerve fibers run in the pelvic nerve (S_2-S_4) to supply the pelvic and vesical plexuses before entering the bladder. Parasympathetic ganglia are found within these plexuses and in the bladder wall. Sympathetic nerves arise from segments T_{10}-L_2 of the spinal cord and go to the inferior mesenteric ganglion through the sympathetic trunk. From the inferior mesenteric ganglion the nerve fibers pass to the pelvic plexus and bladder through the hypogastric nerves. There is also sympathetic innervation originating from T_{10}-L_2 supplying the detrusor and urethral sphincter (Bradley et al, 1974). The somatic nervous system (pudendal nerve) supplies the periurethral pelvic floor musculature (Mattiasson, 1994). The sensory and motor nerves carried by all three nerves innervate both the bladder and urethral sphincter. They originate from parasympathetic ganglia located in the second, third, and fourth segments of the sacral spinal cord (Bradley et al, 1974). Within the spinal cord, information from bladder afferents is integrated with that from other viscera and somatic sources and projected to the brainstem centers that coordinate the micturition cycle (Harrison and Abrams, 1994).

Development of Normal Bladder Function and Micturition Control

Urodynamic studies on normal infant bladders have shown that bladder function in young children is different from that in adults. During the first 2 to 3 years of life there is progressive development from an initially indiscriminate infantile voiding pattern to a more socially conscious and voluntary or adult type of micturition. This is achieved through an active learning process whereby the child acquires the ability to voluntarily inhibit or initiate voiding at socially convenient times. **This natural evolution of bladder control entails an intact nervous system and depends on at least three main events occurring in parallel: (1) a progressive increase in bladder functional storage capacity; (2) maturation of voluntary control over the urethral striated muscle sphincter; and, perhaps most importantly, (3) development of direct volitional control over the bladder-sphincteric unit so that the child can voluntarily initiate or inhibit the micturition reflex.** This process can also be influenced by an awareness of the accepted social norms in families during toilet training (Yeung et al, 2010).

Change in Bladder Functional Parameters

Voiding Frequency. During the third trimester of pregnancy, the fetus is voiding at the rate of approximately 30 times every 24 hours (Goellner et al, 1981). However, immediately after birth, this drops dramatically for the first few days of life, only to increase again after the first week to reach a peak by weeks 2 to 4 to an average of once per hour. Subsequently this rate declines again to about 10 to 15 times per day between 6 and 12 months and to about 8 to 10 times per day by 2 to 3 years (Goellner et al, 1981; Yeung, 1995; Holmdahl et al, 1996). **This reduction in voiding frequency observed during the first few years of life appears to be related mainly to an increase in bladder capacity in parallel to body growth,** which is proportionately greater than simultaneous increase in urine volume

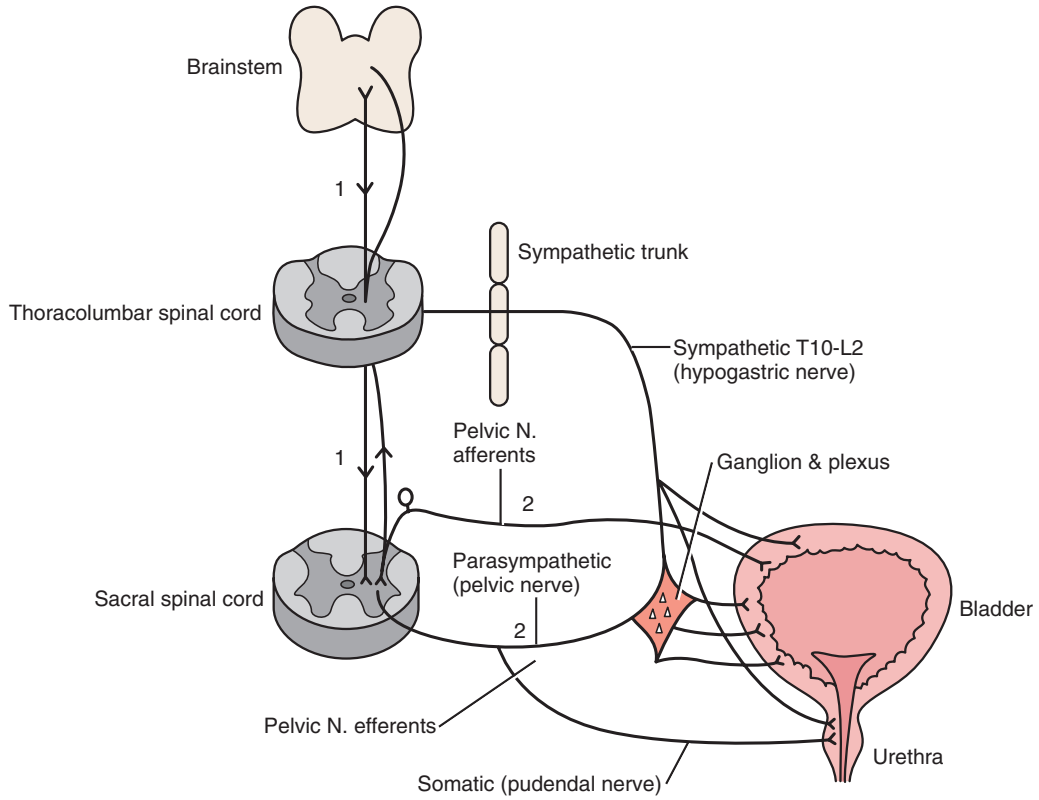


Figure 127–1. Diagram to illustrate the innervation of the bladder-sphincter complex. (From Yeung CK, Barker GM, Läckgren G. Pathophysiology of bladder dysfunction. In: Gearhart JP, Rink RC, Mouriquand PDE, editors. Pediatric urology. 2nd ed. Philadelphia: Elsevier Saunders; 2010. p. 353–65.)

production (Yeates, 1973; Koff, 1997). By the age of 12, the voiding pattern is similar to that in an adult and usually comprises 4 to 6 voids per day (Fig. 127–2).

Bladder Capacity, Voided Volume, and Emptying Efficiency. The increase in bladder capacity with the growth of the child is a crucial step in the development of bladder function and urinary continence. **An adequate reservoir function for urine storage is necessary to meet the increased rate of urine production and decreased voiding frequency in the growing child.**

Several studies have shown that functional bladder capacity at a certain age can be accurately estimated and expressed as a function of age with no difference in sex. For young infants it can be expressed as:

$$\text{Bladder capacity (mL)} = 38 + 2.5 \times \text{Age (months)}$$
(Holmdahl et al, 1996)

For older children, one of the most widely accepted formulas is the Koff formula:

$$\text{Bladder capacity (mL)} = [\text{Age (years)} + 2] \times 30 \text{ (Koff, 1983)}$$

Or similarly, the Hjalmas formula follows:

$$\text{Bladder capacity (mL)} = 30 + [\text{Age (years)} \times 30] \text{(Hjalmas, 1976, 1988)}$$

In parallel to the increase in bladder capacity, the mean voided volume of each micturition increases with age. Of note, urodynamic studies have shown that a significant proportion of infants with incomplete maturation of detrusor-sphincter coordination

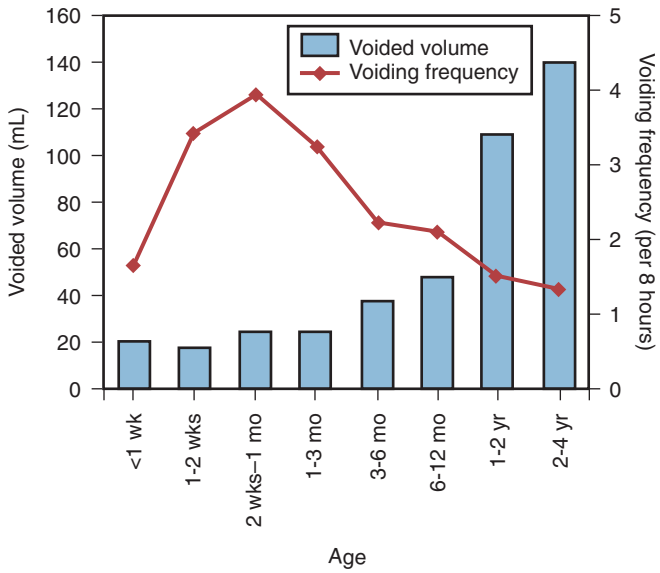


Figure 127–2. Changes in voided volume and micturition frequency from neonates to early infancy.

before the age of 1 are still able to achieve satisfactory bladder emptying (>80% efficacy) (Yeung, 1995; Yeung et al, 1995, 1998; Holmdahl et al, 1996; Bachelard et al, 1999; Sillen et al, 2000).

Detrusor Pressure at Voiding. Studies on detrusor pressures at voiding in normal infants are limited due to (1) the technical difficulties involved in performing urodynamic studies in young infants and (2) an ethical consideration in justifying doing so. From the data in a natural filling cystometric study of infants with

normal lower urinary tracts (as indicated by a normal micturating cystourethrogram) and who had undergone either dismembered pyeloplasty for pelviureteric junction obstruction or nephrectomy for dysplastic kidney, **the authors have documented significantly higher maximum detrusor pressures with micturition (Pdetmax) than in normal adults. It was also noted that male infants voided with significantly higher pressures than females (mean Pdetmax: 118 versus 75 cm H_20 respectively, $P < .03$)** (Yeung et al, 1995a, 1995b, 1998). Similar findings were reported in healthy, asymptomatic infant siblings of children with VUR (Bachelard et al, 1999).

Studies have also shown that these high detrusor pressures noted during micturition were mainly observed only during the first year of life and decreased progressively with age. Furthermore, an interrupted or "staccato" type of urinary stream was noted in more than half of the patients (Yeung et al, 1995a, 1995b, 1998). This was demonstrated by fluctuations of the detrusor pressure when it reached maximum during voiding and resumption of urinary stream in conjunction with a sharp fall in the detrusor pressure. The high detrusor pressures during voiding are thought to represent variations among individual infants in the maturation process of detrusor and sphincter coordination during the first 1 to 2 years of life (Yeung et al, 1995, 1998; Holmdahl et al, 1996; Bachelard et al, 1999; Sillen et al, 2000).

The authors have further confirmed this finding using video cystometry under fluoroscopy combined with natural fill urodynamics and perineal electromyography (EMG) in infants with a history of urinary tract infections (UTIs). Periods of increase in perineal or sphincteric EMG activities were noted during voiding and associated with a sudden cessation of urinary flow with a simultaneous isometric rise or high peak of detrusor pressure. In contrast, resumption of urinary flow was associated with relaxation of the external urinary sphincter and a paradoxical drop in detrusor pressure. Also, the detrusor pressure associated with the initiation of urinary flow was usually significantly lower than the maximal detrusor pressure during micturition (Pdetmax) and that the Pdetmax was significantly higher than those recorded in normal adults (Fig. 127–3).

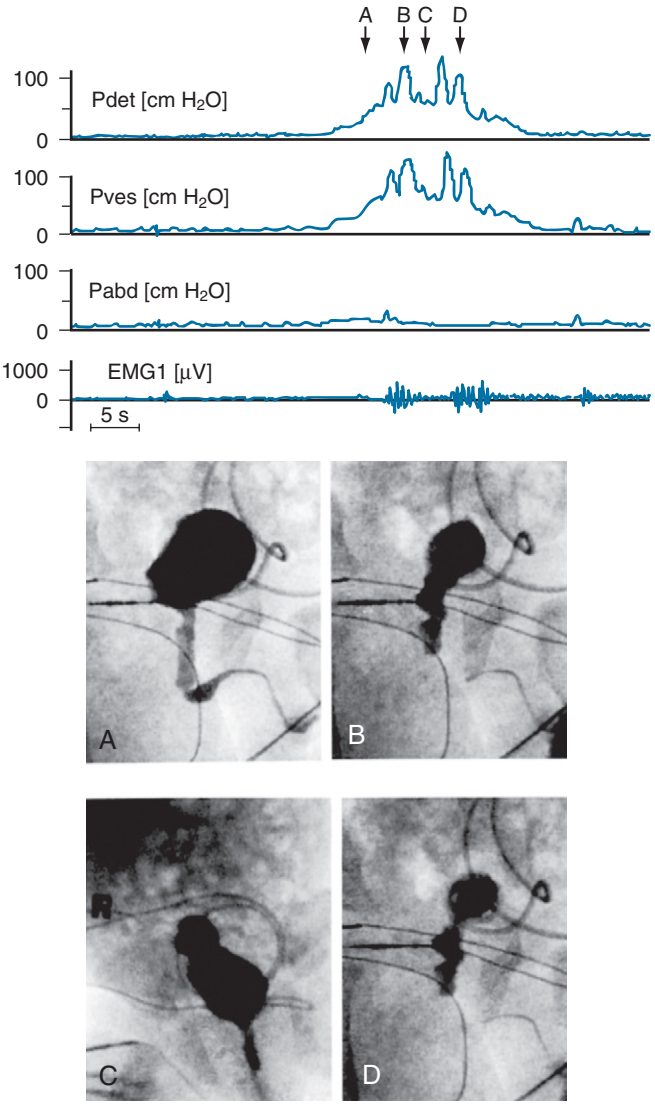


Figure 127–3. Interrupted voiding pattern due to detrusor-sphincter discoordination as revealed by urodynamic study with simultaneous perineal electromyographic (EMG) monitoring and videocystourethrography. *Arrows with letters in top graph* correspond to urethrograms at bottom. **A**, Urinary flow started. **B**, Premature sphincteric contraction and urethral closure as evidenced by the urethrogram and increase in sphincteric EMG activities, leading to a sharp spike of detrusor pressure (isometric increase) associated with a paradoxical abrupt cessation of urinary flow. **C**, Urinary flow resumed in parallel with sphincter relaxation. **D**, Repeated sphincteric contraction leading to another sharp increase in detrusor pressure and paradoxical interruption of urinary flow. P abd, abdominal pressure; Pdet, detrusor pressure; Pves, intravesical pressure. (From Yeung CK, Barker GM, Läckgren G. Pathophysiology of bladder dysfunction. In: Gearhart JP, Rink RC, Mouriquand PDE, editors. Pediatric urology. 2nd ed. Philadelphia: Elsevier Saunders; 2010. p. 353–65.)

Evolution of Normal Micturition Control

Traditionally, it has been assumed that micturition in newborns and young infants occurs automatically with a full bladder by a simple spinal cord reflex, with little or no mediation by the higher neural centers, and that with progressive maturation, voluntary inhibition of the bladder emptying reflex is achieved by adulthood. A delay in the normal maturation of bladder control was attributed to certain conditions such as primary nocturnal enuresis and hence the traditional belief that all enuretics would get better with age (Nash, 1949). However, more recent studies have indicated that this is an oversimplification of what actually occurs. **Even in full-term fetuses and newborns, it has been shown that micturition is modulated by higher centers.** Ohel and colleagues (1995) showed that intrauterine micturition almost exclusively occurs while the fetus is awake rather than randomly distributed over various behavioral (sleep/arousal) states. Furthermore, it has been observed that micturition in a full-term fetus can be elicited by vibroacoustic stimulation, all of which indicates that the micturition reflex is probably under higher neural control even at near gestational term (Zimmer et al, 1993). Further extensive modulation occurs during the postnatal period.

Studies on normal neonates using ambulatory bladder monitoring techniques in conjunction with polysomnographic recordings have shown that even in newborns, micturition does not occur during sleep (Yeung et al, 1995). During sleep the bladder is normally quiescent and stable with lack of facilitation of detrusor contractions, whereas during wakefulness marked detrusor overactivity is observed. Clear electroencephalographic (EEG) evidence of cortical arousal or actual awakening occurs in response to bladder distension, and sleeping infants are noted to wake up before bladder activity

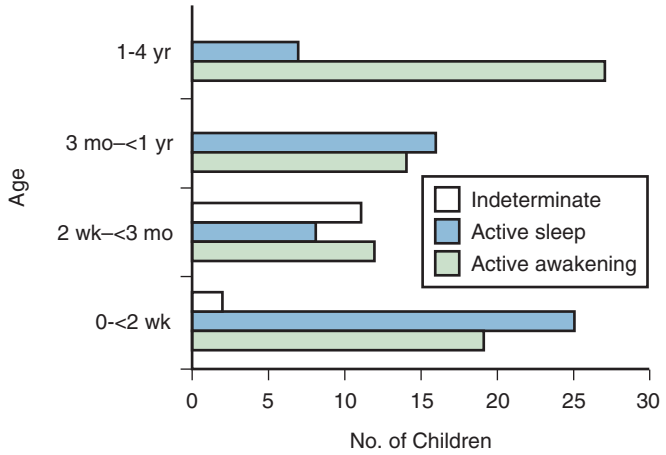


Figure 127–4. Incidence of micturition during different sleep states, according to age group.

returns and voiding occurs. However, this arousal period may often be transient with the infant crying or moving for a brief period, micturating, and then going back to sleep without being noticed to have awakened. This wakening response to bladder distension probably involves more complicated neural pathways and higher centers than has been appreciated up until now (Fig. 127–4).

These results also correlate with recent animal studies showing a sophisticated integration of preexisting central and peripheral neural pathway in micturition control at birth with remodulation occurring in the early postnatal period (Maggi et al, 1986; Thor et al, 1989). Extensive studies using experimental animals by de Groat and colleagues (1993, 1998) have indicated that early postnatal maturation of bladder function probably occurs at different levels: (1) changes in the properties of detrusor muscle; (2) developmental modifications in the peripheral innervation of the bladder; and (3) alterations in central synaptic circuitry and neuroplasticity in the parasympathetic reflex pathways to the bladder (Sugaya and de Groat, 1994; Araki and de Groat, 1997; Sugaya et al, 1997). Recordings of spontaneous activity in bladder smooth muscle in neonatal rats showed much larger amplitude and more synchronous rhythmic contractions compared with those observed in adult rats (Sugaya and de Groat, 1994). This suggests that there is a progressive reduction in intercellular communication between detrusor smooth muscle cells, resulting in less spontaneous activities and hence more efficient urine storage, during early postnatal development. In addition, peripheral and central neural mechanisms also change extensively during this period. In cats (and some other species) micturition during the newborn period is dependent on an exteroreceptive somatovesical reflex triggered when the mother licks the perineum of the kittens (de Groat et al, 1993, 1998; Araki and de Groat, 1997). This somatovesical reflex, processed in the sacral spinal cord, disappears in older animals but may reappear after spinal cord injury. Further neuroanatomic studies have indicated that spinal bladder reflexes are mediated via interneurons located immediately adjacent to, and synapsing with, the sacral preganglionic neurons (Sugaya et al, 1997). This interneuron–preganglionic neuron synaptic transmission is efficient immediately after birth but is abruptly downregulated during the third postnatal week when the mature supraspinal micturition reflexes start to appear (Araki and de Groat, 1997). Transection of the spinal cord prevents this downregulation, indicating that the higher neural centers play an important role in this synaptic remodeling, which contributes to postnatal development of micturition reflexes.

During the second or third year of life there is progressive development toward a socially conscious continence and a more voluntary or adult type of micturition control. The child becomes more aware of the sensation of bladder distension and the urge to urinate, as well as the social norm and embarrassment associated with urinary incontinence. Through an active learning process, the child acquires the ability to voluntarily inhibit and delay voiding until a socially convenient time and then actively initiate urination even when the bladder is not very full and allow it to proceed to completion. **This natural evolution of micturition control mechanisms depends on an intact neural pathway and awareness of social norms, as well as multiple factors including the gradual increase in functional bladder capacity, maturation of detrusor-sphincter coordination, and progressive development of voluntary control over the whole bladder-sphincteric-perineal complex.** The final steps are usually achieved at around the age of 3 to 4 years, when most children have developed the adult pattern of urinary control and will be dry both day and night. The child has learned to inhibit a micturition reflex, postpone voiding, and voluntarily initiate micturition at socially acceptable and convenient times and places. This development of continence and voluntary micturition is also dependent on behavioral learning and can be influenced by toilet training, which in turns depends on the cognitive perception of the maturing urinary tract. It is understandable therefore that this series of complex events is highly susceptible to the development of various types of dysfunctions.

Neurologic control of normal micturition occurs at different levels of the central nervous system (CNS), from the spinal cord with the "sacral micturition center," to the brainstem with the "pontine micturition center," the cerebellum, basal ganglia, limbic system, thalamus and hypothalamus, and cerebral cortex (Blaivas, 1982; McLorie and Husman, 1987; de Groat, 1993; Fernandes et al, 1994). It should be noted that the bladder is unique among other visceral organs in that its function is under the control of both the somatic and the autonomic nervous system. Besides acetylcholine and norepinephrine, various other neurotransmitters including prostaglandin substance P, opioid peptides, vasoactive intestinal peptide, and neuropeptide Y are involved during bladder stimulation (Fernandes et al, 1994). Simple manipulation of adrenergic and cholinergic receptors may only partially abolish the effect of neural stimulation, which explains why pharmacologic blockage of the classic neurotransmitters (acetylcholine and norepinephrine) alone may fail to elicit the expected full clinical response.

Transitory Detrusor-Sphincter Discoordination in Infancy

Studies have shown that in making the transition from an infantile to an adult pattern of micturition control, all children may transiently display some degree of abnormal bladder-sphincteric function (Koff, 1997). For instance, it has been clearly shown that a significant proportion of normal infants exhibit prominent detrusor-sphincter discoordination and interrupted voiding during the first 1 to 2 years of life. This is manifested by a discoordinated and interrupted urine flow, which may even be brought to a complete stop for 1 to 2 minutes before restarting, producing a pattern of repeated small voidings in quick succession (Yeung et al, 1995a, 1995b, 1998). **Urodynamic findings show**

association with high voiding pressures and interruption of flow but no impairment of overall bladder emptying. However, this type of dysfunction resolved with a period of successful toilet training and was only transitory or intermittent and did not persist. One must therefore be cautious in the assessment of young children with apparent voiding dysfunctions and resist the temptation to overinterpret intermittent or transient symptoms as pathologic and hence overinvestigate. However, if voiding dysfunctions are persistent well beyond the period of toilet training, especially if associated with urinary complications like recurrent urosepsis, then the possibility of underlying anatomic and neurologic causes must be considered and duly evaluated.

Key Points: Normal Bladder Function and Development in Infants and Children

- The bladder has dual function (storing and emptying) and dual innervation (central somatic and autonomic nervous systems).
- Evidence indicates that micturition is modulated by higher neural centers even in full-term fetuses and newborns and that micturition almost always occurs during wakefulness.
- In the transition from an infantile to adult bladder, detrusor-sphincteric discoordination may be a normal transient phenomenon that resolves after toilet training.
- The natural evolution of micturition control involves the gradual increase in functional bladder capacity, maturation of detrusor-sphincter coordination, and progressive development of voluntary control over the whole bladder-sphincteric-perineal complex.

EPIDEMIOLOGY AND CLASSIFICATION OF NON-NEUROPATHIC BLADDER-SPHINCTER DYSFUNCTION IN CHILDREN

Epidemiology and Prevalence

Non-neuropathic bladder-sphincter dysfunction in children is probably more common than what meets the eye, but many times it only presents to us when UTI, VUR, or urinary incontinence is manifested. It has been reported that 15% of 6-year-old children suffer this condition (Hoebeke, 2002).

Categorization of Non-Neuropathic Bladder-Sphincter Dysfunction in Children

Various conditions have been described under the category of non-neuropathic bladder-sphincter dysfunction, but it must be emphasized that these conditions should not be viewed rigidly as separate and distinct entities but rather as transitional phases of a complex sequence of events. For instance, a girl with dysfunctional voiding may start with having detrusor instability associated with sphincter and pelvic floor overactivity, then gradually evolve to develop fractionated voiding with increasing postmicturition residues, and finally develop bladder decompensation and the "lazy bladder" syndrome (van Gool et al, 1992). It must also be emphasized that **use of the term "non-neuropathic" is based purely on the fact that no obvious and identifiable neurologic lesions can be identified.** However, conditions like the urofacial syndrome complex (Ochoa syndrome) and the Hinman syndrome behave almost identically to the typical neuropathic bladder-sphincter dysfunctions. It is indeed conceivable that they do have an organic underlying neurologic cause, although the exact neuroanatomic lesion has not yet been identified. Hence the distinction between neuropathic and non-neuropathic bladder dysfunctions may not be as clear as traditionally thought.

In adults, lower urinary tract function has been well understood and standardization of terminology has been established by a committee working under the International Continence Society (ICS) since the early 1970s (Bates et al, 1976a, 1976b, 1979). In contrast, neural control over the bladder-sphincter unit in children is age dependent and is much more variable and complex. Definitions of normal versus abnormal lower urinary tract function have therefore been far less standardized. Various classifications for bladder dysfunctions in children have been described over the past few decades (Bellinger, 1996; Lapides, 1970; Wein, 1998). To avoid confusion, the classification proposed by the International Children's Continence Society in 2007, with a standardized set of terminology and definitions for different lower urinary tract dysfunctions, was adopted (Nevéus et al, 2007).

Etiologic Classification of Bladder Dysfunction

Dysfunction of the lower urinary tract in children can be secondary to derangement of nervous control, disorders of detrusor and sphincteric muscle function, structural abnormalities, and other unclassified conditions (Nevéus et al, 2007).

Derangement of Nervous Control Conditions. These include the following:

- Congenital malformations of the CNS (e.g., myelomeningocele, spina bifida occulta, caudal regression syndrome, tethered cord syndrome)
- Developmental disturbances (e.g., mental retardation, dysfunctional voiding, urge syndrome)
- Acquired conditions (e.g., cerebral palsy, progressive degenerative diseases of the CNS associated with spasticity, transverse myelitis, multiple sclerosis, vascular malformations, and trauma of the spinal cord)

Disorders of Detrusor and Sphincteric Muscle Function. These include the following:

- Congenital conditions (e.g., muscular dystrophy, neuronal dysplasia, megacolon-megacystis syndrome)
- Acquired conditions (e.g., chronic bladder distension, fibrosis of detrusor or bladder wall)

Structural Abnormalities. These include the following:

- Congenital conditions (e.g., bladder exstrophy, epispadias, cloacal anomaly, ureteroceles, posterior urethral valves and other urethral anomalies, prune-belly syndrome)
- Acquired conditions (e.g., traumatic stricture or damage to the sphincter or urethra)

Other Unclassified Conditions. These include the following:

- Giggle incontinence
- Hinman syndrome
- Ochoa syndrome (urofacial syndrome)

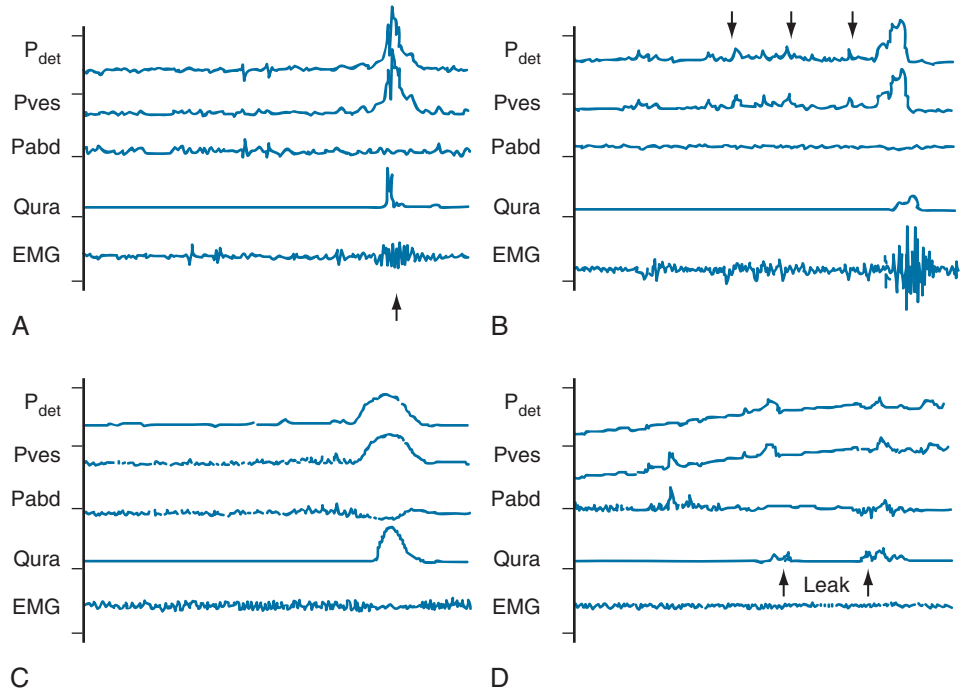


Figure 127–5. Various bladder functional patterns. **A**, Dyssynergic patterns with an increase in sphincteric electromyographic activities during micturition *(arrow),* leading to an interrupted urinary flow. **B**, Overactive bladder, characterized by frequent unstable detrusor contractions *(arrows)* during the filling phase. **C**, Normal female micturition pattern; note the pelvic floor relaxation as evidenced by a drop in abdominal pressure during micturition. **D**, Bladder with low (poor) compliance as evidenced by a rapid increase in intravesical pressure during filling, often associated with urinary leakage *(arrows)*. EMG, electromyogram; Pabd, abdominal pressure; Pdet, detrusor pressure; Pves, intravesical pressure; Qura, uroflow. (From Yeung CK, Barker GM, Läckgren G. Pathophysiology of bladder dysfunction. In: Gearhart JP, Rink RC, Mouriquand PDE, editors. Pediatric urology. 2nd ed. Philadelphia: Elsevier Saunders; 2010. p. 353–65.)

Functional Classification of Bladder Dysfunction

This is based on the functional state of the bladder-sphincteric complex with respect to detrusor activity, bladder sensation, bladder compliance and capacity, and urethral function both during the filling and the voiding phase of cystometry (Fig. 127–5) (Nevéus et al, 2007).

During the Filling (Storage) Phase

Detrusor Activity. *Normal* bladder volume increases during filling without a significant rise in detrusor pressure or involuntary phasic contractions despite provocation.

***Overactive* bladder is characterized by phasic involuntary detrusor contractions, which may occur either spontaneously or on provocation.** The exact pathogenesis for detrusor overactivity has not been resolved. Various underlying causes have been proposed: (1) failure of maturation of CNS control mechanisms; (2) low detrusor levels of inhibitory vasoactive intestinal peptide; (3) abnormal enkephalin-mediated inhibitory neurotransmission; (4) denervation hypersensitivity; and (5) alterations in the properties of the detrusor myocytes (Wein and Barrett, 1992; Harrison and Abrams, 1994; Brading, 1997). Detrusor overactivity was frequently found in children with both diurnal and nocturnal enuresis (Bauer et al, 1980; Nevéus et al, 2007). However, the precise relationship between detrusor overactivity contraction exhibited on a cystometrogram and different types of urinary incontinence is still debated (Nevéus et al, 2007). Children with an unstable bladder typically present with a sudden urge to void that can be only be partially suppressed. Often a girl with an unstable bladder will squat down on the heel of one foot, demonstrating the pathognomonic sign of Vincent curtsy.

Detrusor overactivity may also be qualified when possible according to cause into neurogenic detrusor overactivity (formerly called detrusor hyperreflexia) when there is objective evidence of a relevant neurologic disorder.

BLADDER SENSATION. This can be normal, increased (hypersensitive), reduced (diminished), or absent (no sensation).

BLADDER CAPACITY. This can be normal, high, or low.

COMPLIANCE. This can be normal, high, or low. During normal bladder filling, little or no pressure change occurs but there are no standardized reference ranges for compliance in children.

Urethral Function. *Normal* positive urethral closure pressure is maintained during filling, even in the presence of increased abdominal pressure (guarding reflex), but it decreases immediately before micturition to allow flow.

Incompetent leakage of urine occurs in the absence of detrusor contraction despite urethral closure.

During the Voiding (Emptying) Phase

Detrusor Activity

NORMAL. Voiding is achieved by voluntarily initiated detrusor contraction that is sustained and cannot usually be suppressed voluntarily until at least after the age of 4 years. Complete bladder emptying is achieved in the absence of bladder outlet obstruction.

UNDERACTIVE. Detrusor contraction is of inadequate magnitude and/or duration to effect bladder emptying with a normal time span. The term should be reserved for describing detrusor activity during micturition because it is not readily visible during the filling phase of the cystometrogram. It is often observed in the overdistended postobstructive bladder.

ACONTRACTILE. This is due to an abnormality of nervous control and denotes the complete absence of centrally coordinated contractions.

Urethral Function

NORMAL. The urethra opens to allow bladder emptying.

OBSTRUCTIVE. This may be due to sphincteric overactivity or mechanical obstruction due to obstructive urethral lesions such as congenital obstructive posterior urethral membrane or syringoceles (Dhillon et al, 1993; Dewan and Goh, 1995).

Dysfunctional Elimination Syndrome

The association of constipation with urologic pathologies has been described in the literature since the 1950s, but it was only over the past decade that clinicians have paid more attention to this relationship and recognized its existence with the term *dysfunctional elimination syndrome* (DES). This term is used to reflect the broad spectrum of functional disturbances that may affect the urinary tract, including that of functional bowel disturbances, and can be classified as follows:

- Functional disorder of filling: overactive bladder, overdistension of bladder or insensate bladder, which may be associated with fecal impaction or rectal distension with infrequent call to stool.
- Functional disorder of emptying: over-recruitment of pelvic floor activity during voiding, causing interrupted and/or incomplete emptying also associated with defecation difficulties due to nonrelaxation of pubo-rectalis, pain on defecation, or even anismus (Bower et al, 2005).

Koff and colleagues (1998) showed that the pattern of DES significantly influenced clinical outcome of ureteric reimplantation surgery for VUR in children. Children with constipation had the highest likelihood of developing a breakthrough UTI and thus required surgery. DES also had an adverse effect on the rate of spontaneous reflux resolution, with children requiring an average of 1.6 years longer to outgrow reflux than children without DES. For those requiring surgery, both the results and postoperative complications seemed to be negatively influenced by DES. Postoperative UTIs developed in 78% of children with DES. All children who had persistent reflux, recurrent reflux after 2 years, and contralateral reflux after unilateral reimplantation had DES.

Loening-Baucke (1997) looked at resolution of urinary incontinence and UTIs in children after treatment of their constipation. This study showed that after successful treatment of constipation, 89% of those with daytime incontinence and 63% with nighttime incontinence became dry. None of the children who had UTI had recurrence after treatment of constipation.

It therefore seems from these data that management of the underlying dysfunction should be given priority in the treatment protocol of children with conditions such as VUR, incontinence, and UTI because successful management may significantly improve outcome. Thus more attention should be paid to evaluate for the presence of functional bowel disturbances even in cases of urologic pathologies.

BLADDER-SPHINCTER DYSFUNCTION DURING BLADDER FILLING

Overactive Bladder, Urge Syndrome, and Urge Incontinence

Overactive bladder (OAB) is the most common term currently used in clinical medicine to describe a complex of lower urinary tract symptoms (LUTS). **Traditionally, the infant bladder has been described as unstable (replaced with OAB now) or uninhibited, but recent studies using prolonged natural filling bladder monitoring techniques have shown that to the contrary, the bladder is normally quiescent and stable even in newborns** (Yeung et al, 1995). Clinically, the condition of OAB is best exhibited by urge syndrome with or without urge incontinence. The syndrome, characterized by frequent attacks of sudden and imperative sensations of urge, due to detrusor overactivity during the filling phase, is more prevalent in girls. This burning sensation or urge to void occurs even with small bladder capacities. The unstable contractions are often counteracted by voluntary contraction of the pelvic floor muscles in an attempt to externally compress the urethra (hold maneuvers) exhibited as squatting (Vincent curtsy sign) in many cases (Vincent, 1966; van Gool and de Jonge, 1989). However, despite this move, urge incontinence can still occur with frequent urine leakage onto the underpants. Urge incontinence usually consists of small quantities of urine loss and occurs most often in the afternoon or when the child is preoccupied in play or other activities and is not alert enough to contract the pelvic floor in response to the urge sensation. Children with urge syndrome have small bladder capacities for age and often choose to drink extremely little in order to escape from the social embarrassment of frequent imperative urges to go to the toilet and from urinary incontinence, but otherwise they have complete relaxation of the pelvic floor musculature in most instances. In addition, habitual voluntary pelvic floor contraction to counteract every urge to void may often lead to inappropriate postponement of defecation, constipation, and fecal soiling (Vincent, 1966; O'Regan et al, 1986). This should not be confused with encopresis in children with behavioral problems.

Functional Urinary Incontinence

This can be defined as the involuntary loss of urine due to a failure of control of the bladder-sphincteric unit, which is frequent enough to constitute a social or hygienic problem, and in the absence of underlying anatomic causes (Nevéus et al, 2007). Apart from urge incontinence that is associated with detrusor overactivity and urge syndrome as described earlier, other forms of functional urinary incontinence exist as a result of failure of the bladder storage and/or sphincteric control mechanisms. ***Stress incontinence*** **represents the involuntary leakage of urine occurring at times when the intravesical pressure exceeds the bladder outlet or urethral resistance, in the absence of measurable detrusor contraction.** Unlike in adults and particularly in elderly women, true stress incontinence is extremely uncommon in neurologically normal children and is in general not associated with any demonstrable urodynamic abnormalities. It should therefore be differentiated from urge incontinence and detrusor overactivity. Insufficient bladder outlet or urethral resistance is usually not a main factor. Because the amount of urine leakage in most patients is usually small, the incontinence may at times be only scarcely discernible. It is possible therefore that the actual incidence of this condition may be underestimated.

Giggle Incontinence

Giggle incontinence is usually seen in girls and is characterized by involuntary and typically unpredictable wetting during giggling or laughter. In contrast to stress incontinence, it produces a much larger volume of urine leakage, often amounting to complete bladder emptying. Similar to stress incontinence, however, cystometry may be completely normal or occasionally demonstrate

some detrusor overactivity. Treatment is notoriously difficult, but sometimes a course of anticholinergic drugs may help to ameliorate the symptoms.

BLADDER-SPHINCTER DYSFUNCTION DURING BLADDER EMPTYING

Dysfunctional Voiding

Dysfunctional voiding is characterized by incomplete relaxation or overactivity of the pelvic floor muscles during micturition. It can manifest in different patterns depending on the degree of functional outflow obstruction caused, as well as the status of the detrusor activity. As outlined earlier, the underlying bladder-sphincter dysfunction may evolve progressively and change with time through a transitional phase of a complex sequence of events of bladder functional development.

Staccato and Fractionated Voiding

In staccato voiding the urinary stream is often delayed after the onset of detrusor contraction and is typically interrupted, resulting in a few small squirts of urine passed in quick succession. The interrupted voiding is caused by periodic bursts of pelvic floor muscle activities during micturition, resulting in the characteristic abrupt elevation or spikes of voiding pressures, coinciding with paradoxical cessation of urinary flow. The flow time is usually prolonged and bladder emptying is often incomplete, resulting in increased postmicturition residues and hence a predisposition to UTIs.

***Fractionated voiding* is characterized by infrequent and incomplete emptying secondary to detrusor inactivity.** Micturition occurs in several small, discontinuous fractions due to poor and unsustained detrusor contractions, leaving significant postvoid residual urine volumes. Abdominal straining is usually evident as an effort to improve bladder emptying. However, this is often paradoxically counteracted by a reflex increase in activities of the pelvic floor muscles that is triggered by an increase in intravesical pressure. The bladder capacity is usually large for age and may gradually increase as the condition further progresses. Overflow incontinence may ultimately develop.

Infrequent Voiding and Underactive Bladder Syndrome ("Lazy Bladder")

These two conditions are described together because they represent a spectrum of disease that more commonly occurs in girls. The old entity "lazy bladder" is now replaced by the term *underactive bladder.* At one end of the spectrum, the underactive bladder is generally regarded as the end point of long-standing dysfunctional voiding culminating in a fully decompensated system. **As a result of the chronic functional bladder outflow obstruction, there is a gradual deterioration in detrusor contractility and emptying efficiency.** Postmicturition residual urine and bladder capacity progressively increase, eventually developing into a large, floppy bladder with inefficient emptying. The child uses abdominal straining as the main driving force for bladder emptying, and detrusor contractions are small and unsustained with low pressures, at times being completely undetectable using conventional cystometry. **Because urge sensation is either absent or diminished, voiding is infrequent and occasionally the child may not void for 8 to 10 hours or even longer if engaged in activities.** The typical presentation of a child with *infrequent voiding syndrome* is where the mother always complains that the child never voids unless told to do so. The resultant large volume of postmicturition residual urines predispose to recurrent UTIs, which often constitute the primary complaint bringing the child to the pediatric urologist. Overflow incontinence is usually evident, which may be further associated with constipation and/or fecal soiling. Urodynamic studies typically reveal a large-capacity bladder with high compliance on filling. Detrusor contractions are noticeably absent, and voiding is associated with increased abdominal pressures, resulting in a fractionated flow pattern. Electromyography often shows increased activity in the pelvic floor muscle with each abdominal strain.

Hinman Syndrome and Occult Neuropathic Bladder

Hinman, Allen, and Dorfman first coined the terms *non-neurogenic neurogenic bladder* or *subclinical neurogenic bladder,* and later *Hinman syndrome* to describe a **presumably acquired form of bladder-sphincter dysfunction in children that was characterized by a combination of bladder decompensation with incontinence, poor emptying, and recurrent urinary infections** (Dorfman et al, 1969; Hinman and Baumann, 1973; Allen, 1977; Hinman, 1986). **Most children also have significant bowel dysfunction including encopresis, constipation, and fecal impaction.** In British literature the condition is often referred to as "occult neuropathic bladder" after the article by D. Innes Williams and colleagues (1975). The condition has all the clinical and urodynamic features typical of neuropathic bladder dysfunction, but no neurologic pathology can be demonstrated. Hinman and Baumann initially hypothesized that the condition could be ascribed to acquired psychologically abnormal behavior with voluntary discoordination between the detrusor muscle and the pelvic floor–external urethral sphincter complex during voiding (Hinman and Baumann, 1973). This notion, however, has not received strong support from later studies, and controversies still exist as to whether a subtle or occult spinal pathology can occur to account for an isolated bladder neuropathy in a child who does not exhibit other somatic neurologic deficits and has normal magnetic resonance imaging of the spinal cord. Urodynamic studies often revealed marked sphincteric overactivity and abrupt contractions of the pelvic floor as the child attempted to control incontinence from uninhibited bladder contractions. In its severe form, the bladder-sphincter dysfunction can cause full-blown bladder decompensation with day-and-night wetting, large postmicturition residual urine volumes, recurrent urinary infections, and significant damage to the upper urinary tracts (Dorfman et al, 1969; Hinman and Baumann, 1973; Williams et al, 1975; Allen, 1977; Hinman, 1986, 1997; Jayanthi et al, 1997). Imaging studies often reveal profound changes in the upper urinary tracts, with about two thirds of the children developing hydroureteronephrosis and over half having VUR. Nearly every patient has a grossly trabeculated, large-capacity bladder with a considerable volume of postmicturition residual urine. Treatment should therefore entail measures to control infection and to restore normal bladder storage and emptying function. Due to the great similarities to neuropathic bladder dysfunction, the management strategy in these children generally follows similar principles for the former condition.

Another piece of indirect evidence that a subtle or occult neurologic lesion may account for some cases of "non-neurogenic neurogenic" bladder-sphincteric dysfunction is the Ochoa

(urofacial) syndrome. **Children with this syndrome exhibit all the classical features of dysfunctional voiding including urinary incontinence, recurrent UTI, constipation, reflux and upper tract damage, but in addition have a peculiar painful or apparently crying facial expression during smiling** (Ochoa and Gorlin, 1987; Ochoa, 1992). The condition has an autosomal recessive inheritance and the gene has been located on chromosome 10. Urodynamic studies characteristically showed a sustained contraction of the external sphincter during voiding. The resulting severe bladder-sphincter dysfunction is often associated with a dismal outcome. Of the 66 children reported by Ochoa, 33% had renal functional impairment, 26% had hypertension, and 24% had end-stage renal failure. Five patients received renal transplantation and 17 were dead (Ochoa, 1992). Because the neural ganglia controlling the facial muscles are situated close to the pontine micturition center, it is tempting to speculate that a small, genetically predetermined, congenital neurologic lesion in this area may be responsible for both the peculiar facial expression and the bladder dysfunction. Further studies in this direction may help to resolve some of the continuing dilemma.

Postvoid Dribbling

Postvoid dribbling refers to involuntary leakage of urine immediately after voiding. Typically this refers to post–toilet-trained girls who dribble soon after standing up following a void and are otherwise normal with no other associated urinary symptoms. In these circumstances **it may be a result of vesicovaginal reflux whereby urine is trapped in the vagina during voiding, and once the child stands the urine begins to dribble out.** When in doubt, it can be confirmed by performing a micturating cystourethrogram. The condition is harmless and tends to resolve with age, but the child may also be taught to empty her vagina by simply voiding with her thighs apart and leaning forward after voiding before getting up.

DYSFUNCTIONAL ELIMINATION SYNDROME, CONSTIPATION, AND BLADDER DYSFUNCTION

It has long been recognized that children with dysfunctional voiding and recurrent urinary infections often have associated bowel dysfunction including constipation, fecal impaction, and encopresis. However, only recently has the term *dysfunctional elimination syndrome* been given to recognize the existence of this relationship. Studies have been performed to explain how constipation and chronic rectal dilatation may interfere with the normal function of the lower urinary tract, resulting in bladder dysfunction, reflux, and UTIs (Yazbeck et al, 1987; O'Regan et al, 1997). **The close proximity of the rectum to the posterior wall of the bladder makes it possible that any gross distension of the rectum by impacted feces can result in mechanical compression of the bladder and bladder neck leading to urinary obstruction** (Shopfner, 1968; O'Regan et al, 1997). **In addition, it has been observed that large fecal impaction may induce significant detrusor instability and other bladder dysfunctions, which in turn will result in urge syndrome, UTI, and reflux** (Shopfner, 1968; Yazbeck et al, 1987; O'Regan et al, 1997). O'Regan and colleagues have reported a high incidence of enuresis in children with urinary infection and constipation. It has been noted that in constipated enuretic children who had detrusor instability, treatment of concomitant constipation resulted in cessation or improvement of enuresis (O'Regan et al, 1985, 1986). Animal studies have also revealed an increased predisposition to bacteriuria in rats with surgically induced fecal retention (Breda et al, 1975). The evidence available so far therefore strongly suggests that there is an important relationship among constipation, detrusor instability, reflux, UTI, and enuresis. Proper attention to associated bowel dysfunction should therefore form an integral part of the overall management in children with bladder dysfunctions.

RELATIONSHIP AMONG BLADDER-SPHINCTER DYSFUNCTION, VESICOURETERAL REFLUX, AND RECURRENT URINARY TRACT INFECTIONS

Impairment in the functions of the lower urinary tract often coexists with recurrent UTIs and VUR, without any identified neurologic or other causal pathology (Koff and Murtag, 1983; Griffiths and Scholtmeijer, 1987; Sillen et al, 1992; Chandra et al, 1996; Yeung et al, 1998). Incidence of higher intravesical pressure, detrusor overactivity, detrusor-sphincter dyssynergia, or incomplete voiding have been reported in a significant proportion of children with VUR and conversely, micturating cystourethrograms (MCUs) performed in children with bladder dysfunctions often find concomitant VUR. **The most common abnormalities of the lower urinary tract found to coexist with VUR are predominantly detrusor overactivity and uncoordinated detrusor-sphincter function during micturition.** These abnormalities may occur secondary to urinary infection or can be acquired during the period when voluntary control of micturition is being established. Although the bladder instability can occur in most children with VUR, it is unlikely to have its role in initiating VUR (Koff and Murtag, 1984). However, **reflux from incompetence of the ureterovesical junction (UVJ) may be worsened by detrusor instability** (Stephens, 1979). The urethral sphincteric dysfunction or discoordination is characterized urodynamically by obstruction during voiding due to involuntary constriction of the urinary sphincter and is believed to be the normal response of the individual to an uninhibited bladder contraction while attempting not to void (Scholtmeijer and Griffifths, 1990; Koff, 1992; Homsy, 1994; Scholtmeijer and Nijman, 1994). It is considered as the most serious dysfunction because it has been reported that patients with this dysfunction often have bilateral high-grade reflux and injured upper renal tracts (Griffiths and Scholtmeijer, 1987; Orellana et al, 2004). The discoordinated bladder also regularly decompensates, and a significant number of children with moderate or severe VUR were reported to have overdistended bladder with weak contractions and high capacity (Hjalmas et al, 1994; Koff et al, 2002; Garat Barredo et al, 2004).

Previous studies showed that infants with UTI and VUR have a high prevalence of high voiding detrusor pressure (Fig. 127–6) (Sillen et al, 1992, 1996; Yeung et al, 1998). **Male refluxers are characterized by considerably higher maximum voiding pressures associated with detrusor overactivity, which may represent a more pronounced form of detrusor-sphincter dyssynergia, as compared with age-matched female refluxers and normal nonrefluxing infants.** In contrast, in the majority of female refluxing infants no detrusor

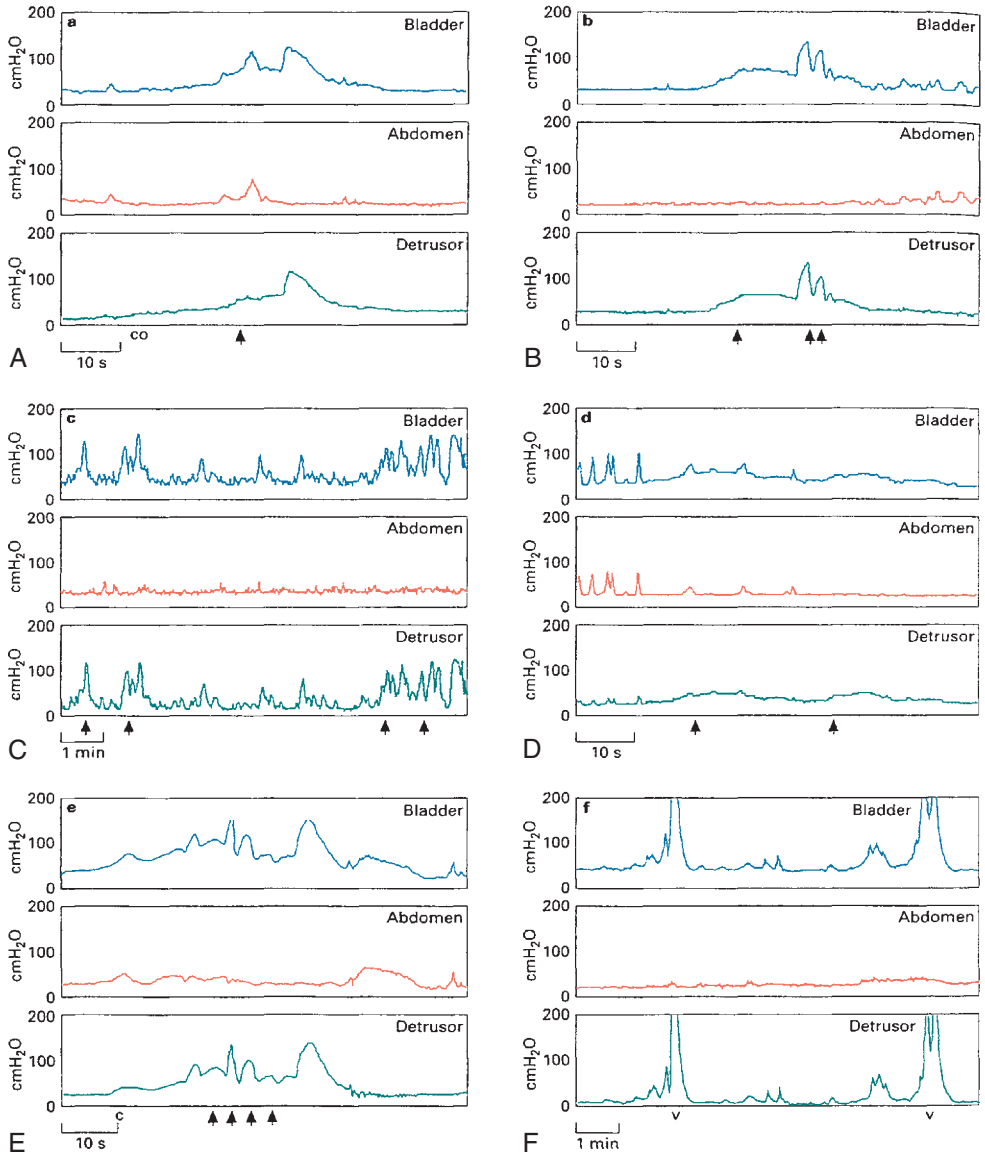


Figure 127–6. Urodynamic patterns in infants with vesicoureteral reflux. **A**, Normal: a period of low-pressure detrusor contraction (co) preceded a more formal contraction associated with the onset of urinary flow *(arrow)*. **B**, Immature: urinary flow *(arrows)* was interrupted during periods of sudden elevation of detrusor pressure. **C**, Unstable: frequent high-pressure unstable bladder contractions associated with occasional leakage of urine *(arrows)*. **D**, Inadequate: unsustained low-pressure detrusor contractions associated with the passage of small dribbles of urine *(arrows)* and a large PVR. **E**, Dyssynergic: significant interruption of urinary flow *(arrows)* associated with spikes of increase in detrusor pressure. **F**, Obstructive: note frequent voiding (v) with high detrusor pressures, greater than 20 cm H_2O. (From Yeung CK, Godley ML, Dhillon HK, et al. Urodynamic patterns in infants with normal lower urinary tracts or primary vesico-ureteric reflux. Br J Urol 1998;81:461–7.)

hypercontractility was noted and instead they often displayed a urodynamic pattern with normal voiding pressures and relatively large bladder capacity with or without emptying inefficiency and postmicturition residues. The finding of higher voiding detrusor pressure in male infants compared with female infants may be attributed to higher urethral resistance of the longer male urethra and smaller urethral meatus and anatomic difference in the configuration of external sphincter. Studies have also shown that high intravesical pressure significantly contributes to the development and severity of VUR. It was shown that infants with bilateral high-grade VUR had significantly higher voiding detrusor pressures and higher prevalence of detrusor overactivity than those with lower-grade or unilateral VUR (Chandra and Maddix, 2000).

It has been further shown that the spontaneous resolution of VUR may be delayed in the presence of abnormal dynamics of the bladder (Godley et al, 2001; Sofia et al, 2004). Bladder dysfunction was shown to have a powerful relationship with the nonresolution of high-grade infant VUR. It is generally accepted that bladder dysfunction delays the spontaneous resolution of reflux in older children (Koff and Murtag, 1984; Taylor et al, 1982). Studies have also shown that there is a strong correlation between recurrent infections and nonresolution, which probably reflects the fact that most infections were seen in infants and children with bladder dysfunction. Therefore recurrent infections can be regarded as a marker of bladder dysfunction, indicating an investigation of bladder function (Sofia et al, 2004).

Moreover, successful treatment of the underlying bladder dysfunction resulted in marked increase in the rate of spontaneous resolution of reflux and significant reduction in recurrent UTIs. Therefore early detection and proper management of underlying lower urinary tract abnormalities are crucial in the treatment of VUR in infants and children. The first step in management in those children presenting postnatally with VUR or UTI should be a detailed evaluation of bladder function to choose an appropriate treatment modality and to prevent renal deterioration.

Why do children who have VUR have such a high incidence of bladder dysfunction? The correlation of this maturational lag in the bladder function and development of the CNS is the other untouched area of investigation. A similar association between gastroesophageal reflux and cerebral palsy is now well studied; understood and effective surgical treatment protocol has evolved over the past 2 decades.

Key Points: Epidemiology and Classification of Non-Neuropathic Bladder-Sphincter Dysfunction in Children

- Bladder dysfunctions during filling include overactive bladders, urge syndrome, functional urinary incontinence, and giggle incontinence.
- Bladder dysfunctions during emptying include dysfunctional voiding, staccato voiding, infrequent voiding, Hinman syndrome, Ochoa syndrome, and postvoid dribbling.
- It is now well recognized that dysfunctional voiding often has associated bowel dysfunction, and together this is known as the dysfunctional elimination syndrome.
- VUR may be secondary to underlying bladder dysfunction, particularly in girls. Treatment should aim at correcting the voiding dysfunction before contemplating surgery.

EVALUATION OF NON-NEUROPATHIC BLADDER-SPHINCTER DYSFUNCTION

History

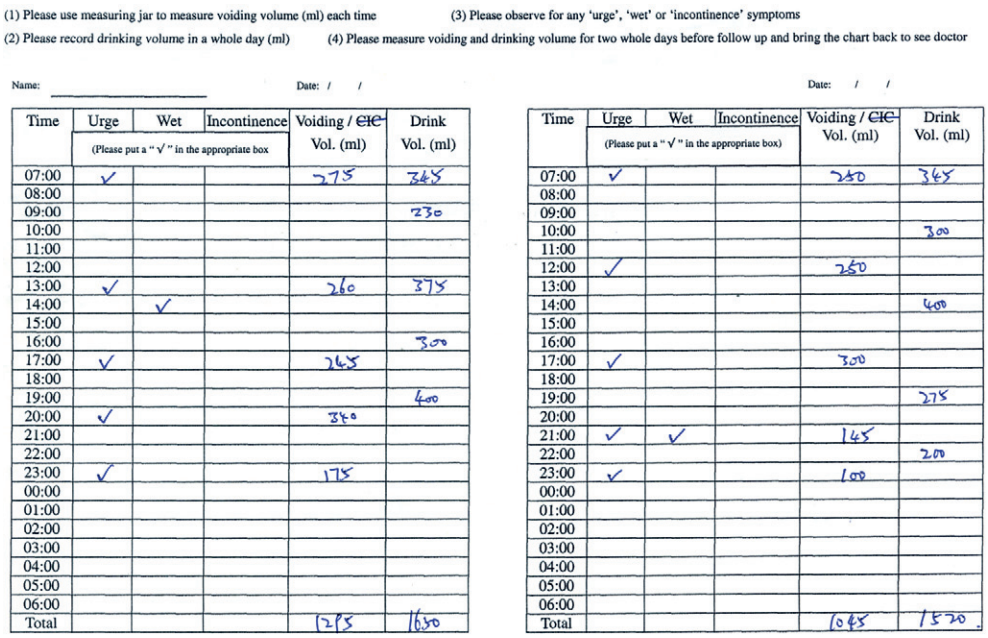
The majority of children with non-neuropathic bladder-sphincter dysfunction typically present after toilet training with symptoms of either nighttime or daytime urinary incontinence or both. Occasionally they can be recognized at an earlier age when the child presents for investigation of UTIs or VUR. In any case, it is important to obtain a detailed history from the child and guardian. This should include relevant questions to exclude neurologic and congenital abnormalities. Bowel dysfunction can coexist in the form of encopresis, constipation, and fecal impaction and should be noted during history-taking. The urinary history should focus on symptoms related to both the storage and evacuation of urine.

Voiding Diary

A voiding diary is used to record daily fluid intake and urine output at home under normal conditions. When properly filled in, it can be informative and give us clues to the underlying dysfunction. The number of voidings per day, the distribution of voids during the day, and each voided volume are recorded. It can also record any episodes of urgency and leakage. It is a useful tool to help identify those who may warrant further studies, as well as in follow-up of patients (Fig. 127–7).

Physical Examination

Physical examination is usually normal in children with non-neuropathic bladder-sphincter dysfunction, but careful examination is required to exclude those who may require further neurologic evaluation. Occasionally, in an otherwise normal child,



(1) Please use measuring jar to measure voiding volume (ml) each time (3) Please observe for any 'urge', 'wet' or 'incontinence' symptoms
(2) Please record drinking volume in a whole day (ml) (4) Please measure voiding and drinking volume for two whole days before follow up and bring the chart back to see doctor

Name: _____ Date: / /

Time	Urge (Please put a "√" in the appropriate box)	Wet	Incontinence	Voiding / ~~cic~~ Vol. (ml)	Drink Vol. (ml)
07:00	√			275	345
08:00					
09:00					230
10:00					
11:00					
12:00					
13:00	√			260	375
14:00		√			
15:00					
16:00					300
17:00	√			265	
18:00					
19:00					400
20:00	√			380	
21:00					
22:00					
23:00	√			175	
00:00					
01:00					
02:00					
03:00					
04:00					
05:00					
06:00					
Total				1295	1650

Date: / /

Time	Urge (Please put a "√" in the appropriate box)	Wet	Incontinence	Voiding / ~~cic~~ Vol. (ml)	Drink Vol. (ml)
07:00	√			250	345
08:00					
09:00					
10:00					300
11:00					
12:00	√			250	
13:00					
14:00					400
15:00					
16:00					
17:00	√			300	
18:00					
19:00					275
20:00					
21:00	√	√		145	
22:00					200
23:00	√			100	
00:00					
01:00					
02:00					
03:00					
04:00					
05:00					
06:00					
Total				1045	1520

Figure 127–7. Examples of voiding diary.

one may find a palpable bladder on abdominal examination in cases of decompensated bladders. **Abnormalities of the lower spine should be sought specifically to exclude the possibility of an occult spinal dysraphism.** Lesions such as an asymmetric gluteal fold, hairy patch, dermovascular malformation, or lipomatous abnormality of the sacral region should prompt further imaging evaluation. The external genitalia may be examined to exclude any obvious anatomic problems that can explain the urinary symptoms in question. Rectal examination may reveal fecal impaction or distended rectum in those with chronic constipation. In the absence of any positive findings on examination, further investigations may be warranted.

Laboratory Investigations

Laboratory investigations are generally not routinely required unless the child presents with complications such as UTIs. However, to complement a full workup, urinalysis may be performed to rule out bacteriuria and glucosuria. Serum and urine osmolality may be looked at in cases of nocturnal enuresis to assess renal concentrating ability.

Ultrasonography

Ultrasonography (USG) is often the first-line investigation in children with non-neuropathic bladder-sphincter dysfunction because it is a simple, readily available, and noninvasive tool that is able to provide information both on anatomic and functional problems when performed by experienced pediatric radiologists.

Ultrasonography has been increasingly used in the study of the pelvic floor musculature. In boys the external sphincter, puborectalis, and bulbocavernosus have been observed to contract during a hold maneuver on USG. In girls, lengthening of the urethra and movement of the bladder neck in the direction of the symphysis are seen. However, **in patients with non-neuropathic bladder-sphincter dysfunction, approximately one third of the children were unable to elicit movement of the pelvic floor or had paradoxical movement.** The clinical significance of this remains unclear, but when introduced to a program of urotherapy, marked improvement of symptoms was reported. Similarly, the USG had been employed in the study of bladder neck mobility. Studies have shown that in a proportion of girls with hyperlaxity of joints, coughing or straining would result in a wide opening of the bladder neck and urethra. In this group of girls, urotherapy would prove difficult and occasionally some would go on to require surgery to the bladder neck (deJong, 2005).

More recently, the ultrasound has been used to measure bladder parameters used in calculating a "bladder volume and wall thickness index" (BVWI). This BVWI can be classified into normal, thick, or thin according to the measured parameters. Studies have shown that these classification corresponded closely to urodynamic findings of underlying bladder dysfunctions and can act as a reliable tool to guide for further invasive investigations (Yeung et al, 2004).

Other Imaging Studies

Radiologic examination of the spine may be necessary to rule out any neurogenic causes of bladder-sphincter dysfunction.

A micturating cystourethrogram may be performed in patients to rule out VUR. Information on the bladder emptying efficiency may be obtained, and the status of the urethra can be assessed to exclude any outflow obstruction.

Urodynamic Studies

Urodynamic studies are employed to describe the physiologic parameters involved in the bladder mechanics during filling and voiding.

Uroflowmetry

All urodynamics should be preceded by or combined with a uroflow study. When performing uroflowmetry, the child must experience normal desire to void for it to be representative and repeated recordings should be performed. Preferably, the voiding should be observed and correct sitting or standing position ascertained. **In children, normal flow rates are different from adults and there is usually a poor correlation between maximal flow rate (Qmax) and outflow resistance as the detrusor is able to exert much stronger contractions to counteract any increased resistance.** It is therefore important to study the pattern of the flow curve in addition to the flow rates in children. The precise shape of the flow curve is determined by detrusor contractility, the presence of any abdominal straining, and the bladder outlet. The normal pattern is that of a smooth *bell* shape. A *tower*-shaped curve produced by an explosive voiding contraction is seen in overactive bladders, and a low *plateau*-shaped curve is representative of an outlet obstruction. A *staccato* pattern is seen with sphincteric overactivity during voiding with peaks and troughs throughout voiding, and an *interrupted* flow is seen in acontractile or underactive bladders. When combined with cystometry and perineal EMG studies, further information on the different spectrum of functional bladder outflow obstructions can be analyzed (Nijman, 1997).

Conventional Fill Urodynamic Studies

This involves more sophisticated instruments and becomes more invasive to the patient, requiring a bladder catheter introduced transurethrally or suprapubically. The use of suprapubic catheterization has been suggested as a better alternative to transurethral catheterization. Although it may be considered more invasive, it is much more physiologic than to try to void with a catheter in the urethra, particularly in children. Not only is it obstructive to flow, but the trauma of placing the catheter just before the investigation may cause significant discomfort. For suprapubic catheterization, a 6-Fr double-lumen catheter is placed suprapubically under sedation and left in situ for 24 hours before commencement of the urodynamic study.

The suprapubic catheter is connected to a computer system and used to measure intravesical pressure. Another catheter is placed in the rectum to measure intra-abdominal pressure surrounding the bladder. By subtracting the latter from the intravesical pressure, one can calculate the detrusor pressure. Sphincteric activity can also be measured with simultaneous perineal EMG recordings. All the measured data are directly fed into a computer for analysis and display of graphical measurements. The urodynamic study looks at both the filling and voiding phases of the bladder. Bladder filling and storage are described according to bladder sensation, detrusor activity, bladder compliance, and bladder capacity. Pressure flow studies are carried out during the voiding phase.

Traditionally, the bladder is filled artificially with water/normal saline to speed up the procedure. The child is asked to indicate his or her desire to void (if old enough to do so) and then void into a specially designed seat with a uroflowmeter attached. The investigator observing the study should also make note of any events occurring during the study (e.g., any large movements of the patient, coughing, or in particular any urinary dribbling).

By combining cystometry with fluoroscopy, video-urodynamics can be performed with fluoroscopic images of the bladder, bladder neck, and urethra captured. Conventional fill urodynamics is performed in the usual manner with the child sitting in a specially designed chair with a uroflowmetry device in the fluoroscopy suite. Fluoroscopic images are taken during filling and voiding. This has the added advantage of being able to observe the shape of the bladder during filling and voiding, observing for signs of VUR, as well as the configuration of the urethra and pelvic floor.

Natural Fill Urodynamic Studies

More recently, studies have shown that the nonphysiologic filling of the bladder during conventional fill urodynamics, even at low filling rates, can lead to misrepresentations of true bladder activity during normal situations. Therefore natural fill urodynamic studies may be performed whereby the child is asked to drink to allow the bladder to fill up on its own rate. Urodynamic studies in children with urge syndrome usually reveal detrusor overactivity associated with a small bladder capacity but may occasionally be normal with incontinence only barely perceptible, particularly if conventional fill cystometry rather than natural filling cystometry is used. It appears that the **artificial filling may inhibit the detrusor response and attenuate its maximum contractile potential, rendering detrusor instability much less pronounced and undetectable.** Therefore natural fill cystometry is the preferred technique in children, or better still, the combined use of artificial and natural filling urodynamic studies is helpful to accurately delineate the underlying bladder dysfunction (Yeung et al, 1995).

Ambulatory Urodynamic Studies

The unfamiliar hospital and urodynamic laboratory environment, as well as the presence of a urodynamics investigator, can sometimes cause significant distress, particularly to young children. To overcome this, an ambulatory urodynamic study may be performed. This study is performed with ambulatory equipment strapped to the child and relies on infrared telemetry while the investigator sits behind a one-way mirror (Yeung, 1998).

The system consists of an ambulatory urodynamic recorder with a specially designed built-in extension board that converts digital pressure signals to a modulated infrared wave. Two external infrared leads are connected to the output and fixed to the clothing of the patient (Fig. 127–8). The optimal emission from the recorder has a 10-m range and completes the circuit of the infrared on-line link by cable to the computer. Direct line of sight from the transmitter to the receiver is unnecessary because the infrared signals reflect from the walls of the room before reaching the receiver. For active and uncooperative patients, more than one receiver connected in parallel with the power unit and computer can be used at the same time to enhance signal collection. The first receiver to receive valid signals transmits the data to the computer and inhibits the other receivers simultaneously (Fig. 127–9).

During the investigation the infant can conduct normal activities, be totally mobile, and be accompanied by one or both of the parents undisturbed in a private cubicle. From an adjoining room the hidden investigator observes and records the patient's activities, including urinary dribbling and micturition, through a one-way mirror, while real-time on-line pressure signal displays are monitored continuously on the computer. Only natural fill studies are possible by this means. Overall, it allows for a continuous monitoring of bladder function under near-natural conditions for the child.

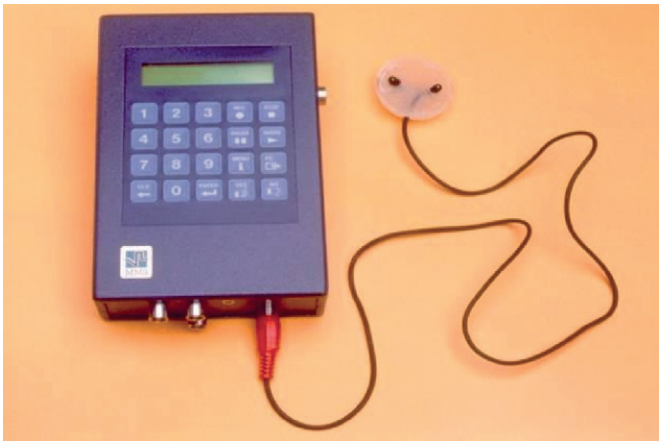


Figure 127–8. The ambulatory urodynamic recorder with the external infrared leads mounted in a plastic holder that can be attached to the patient. (From Yeung CK. Continuous real-time ambulatory urodynamic monitoring in infants and young children using infrared telemetry. Br J Urol 1998:81;76–80.)

More recently, the Bluetooth system has been introduced. This works in much the same way as the infrared system but is much less bulky for the patient to carry around. It offers even more freedom of movement with a much longer transmission range and more reliable reception. If coupled with a camera recorder in the room the child is in, there is no need for the investigator to sit behind a one-way mirror throughout the procedure. With such advances in technology, it will not be surprising if urodynamics can soon be performed in the setting of one's own home!

Key Points: Evaluation of Non-Neuropathic Bladder-Sphincter Dysfunction in Children

- An adequate history should include congenital abnormalities, voiding and wetting patterns (including a voiding diary), and assessment of bowel function.
- Abnormalities of the lower spine should be sought specifically to exclude the possibility of an occult spinal dysraphism.
- Ultrasonography is useful to assess bladder function and wall thickness, as well as pelvic floor function.
- In children, normal flow rates are different from adults and there is usually a poor correlation between maximal flow rate (Qmax) and outflow resistance.
- Urodynamic study looks at both the filling and voiding phases of the bladder.
- Artificial filling may inhibit the detrusor response and attenuate its maximum contractile potential, rendering detrusor instability much less pronounced and undetectable.

MANAGEMENT OF NON-NEUROPATHIC BLADDER-SPHINCTER DYSFUNCTION

Behavior Modification and Standard Urotherapy

Urotherapy is a nonpharmacologic and nonsurgical combination of cognitive, behavioral, and physical therapy

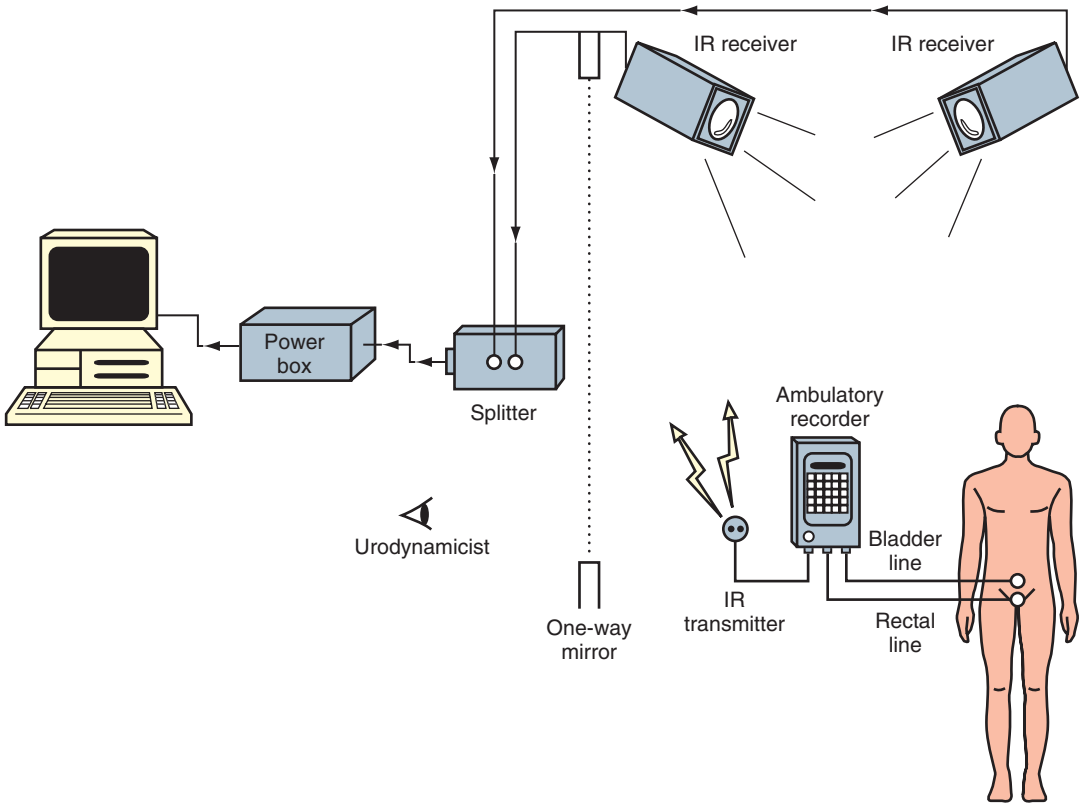


Figure 127–9. Schematic diagram to show the setup for continuous real-time ambulatory urodynamics using infrared telemetry. (From Yeung CK. Continuous real-time ambulatory urodynamic monitoring in infants and young children using infrared telemetry. Br J Urol 1998:81;76–80.)

with an aim to normalize micturition pattern and prevent further functional disturbances of the lower urinary tract. The children and their parents are educated on proper voiding mechanics, and their specific problem is explained to them to provide motivation for improvement. Specific instructions are then given as to how and when to void. Children are assessed and taught correct sitting or standing positions for voiding. They are taught how to relax the pelvic floor and avoid straining. Their drinking and voiding habits are studied and modified accordingly to include proper hydration with timed voiding. A proper assessment of their bowel function is imperative to successful management. To achieve good results, strong patient support with adequate motivation of both the child and the parents is essential.

Biofeedback and Pelvic Floor Rehabilitation

Biofeedback is based on the concept of building self-perception on detrusor contractions and pelvic floor relaxation in the patient. By combining uroflowmetry with real-time monitoring, the child is able to see how well he or she is voiding. It also helps the child understand what can be altered with voluntary control and with relaxation of the pelvic floor. Biofeedback as a treatment modality for children with dysfunctional voiding is based on this concept and has proven to be highly effective either on its own or in combination with standard urotherapy (Figs. 127–10 through 127–12).

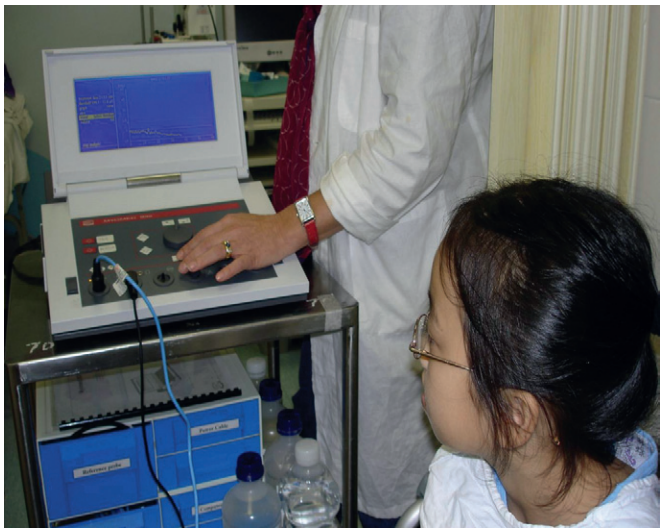


Figure 127–10. Urotherapy. Pelvic floor rehabilitation with real-time biofeedback monitoring.

Neuromodulation, Acupuncture, and Other Treatment Modalities

Recent studies reported that transcutaneous electrical nerve stimulation (TENS) is a simple, cost-effective, noninvasive treatment modality for the management of a wide variety of lower urinary tract disorders with few side effects. The mechanisms of action of

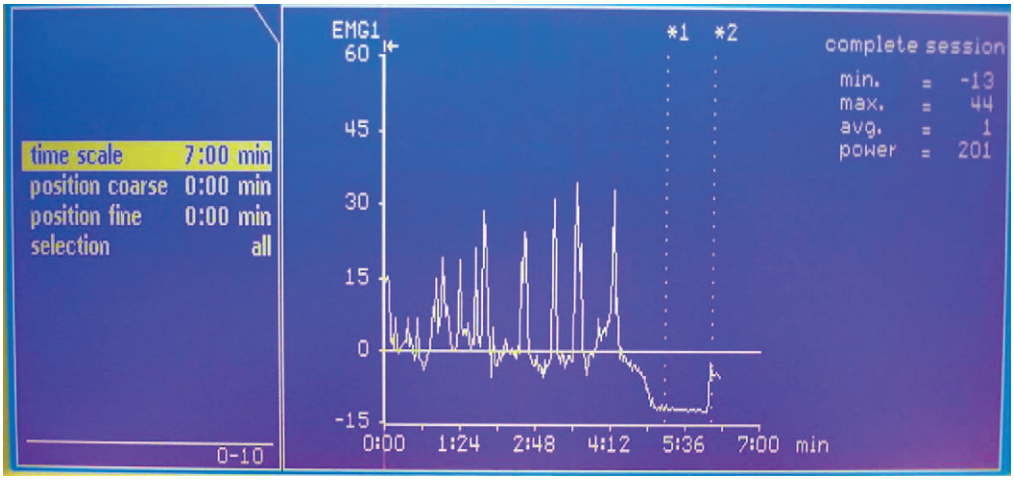


Figure 127–11. Urotherapy. Example of real-time pelvic floor rehabilitation biofeedback tracing showing voluntary contraction and relaxation of pelvic muscles.



Figure 127–12. Urotherapy. Biofeedback with real-time uroflowmetry.

the reported techniques remain unclear, but symptomatic improvements are common. Some reports indicate changes in urodynamic parameters during transcutaneous stimulation, suggesting that the TENS therapy was capable of inhibiting detrusor contractions. The beneficial effects of TENS over the sacral dermatomes (S2-S3) in patients with lower urinary tract symptoms associated with detrusor overactivity have been reported. **The use of low-frequency electrical current to inhibit detrusor activity in adults is common and appears to modulate excitatory and inhibitory components of bladder control.** Such studies provide the rationale for the application of TENS therapy to modulate detrusor function in patients with functional detrusor dysfunction.

Traditional acupuncture has also reported high efficacy in the treatment of nocturnal enuresis with low relapse rate. Reports have used acupoints innervated by sacral segments S2-S4, and stimulation involved both manual and electrostimulation. However, its use in the pediatric population remains limited by the intrinsic fear of needling in children with subsequent lack of cooperation (Bower et al, 2005).

Bowel Management

The principles of bowel management include rectal emptying of impacted stool and the maintenance of regular soft stools. A reliable bowel habit pattern can only be established when the child is able to achieve pain-free defecation of soft stool. An initial cleanout of the bowel can be achieved by oral laxatives and rectal enemas on a regular basis until there is complete disimpaction of the rectum. Occasionally, high-colonic washouts may be necessary to achieve a good result. Only when this has been achieved should the second stage of management commence. This involves prevention of further stool accumulation with continuation of regular oral laxatives and/or stool softeners, as well as dietary modification. Correct toileting posture and correct recruitment of abdominal muscles in the defecation process aids in the effectiveness of bowel emptying. However, success of a bowel management program can only be achieved with sound support from the family. Parental education is necessary in order to reinforce and encourage correct toileting habits at home.

Medications

Pharmacologic control of the lower urinary tract (LUT) can either act via the central nervous system (CNS) or peripherally. Several CNS regions have been identified to be involved with micturition control including the cortex, pontine tegmentum, medulla, and spinal structures. All these regions are modulated by several different neurotransmitters, which have become targets for drug treatment. However, **many of the drugs developed with CNS action are not sufficiently selective to affect only the lower urinary tract, increasing the possibility of these drugs causing adverse drug reactions.** Pharmacologic targets for treating bladder dysfunction may be aimed at the bladder, urethra, ganglia, or peripheral nerves. **The main targets for**

drug therapy are receptors or ion channels known to be involved in bladder contraction (muscarinic receptors, L-type calcium channels). More recently, research has been focused more on alternative neurotransmission and modulation of afferent signaling from the LUT.

Antimuscarinics

Antimuscarinics are the gold standard in treatment of overactive bladders. Muscarinic receptors are found in the human detrusor muscle, and bladder contractions are initiated by stimulation of these receptors with the release of acetylcholine from cholinergic nerves. The main action of antimuscarinics is on the M1 and M3 receptor subtypes, which are thought to be responsible for the pathogenesis of detrusor overactivity. Antimuscarinics, such as oxybutynin, **act by reducing the frequency and intensity of involuntary contractions, resulting in an increase in the functional bladder capacity.** The clinical efficacy depends on various factors such as receptor affinity, pharmacokinetics, and the specificity for the bladder. Latest developments have focused on receptor specificity and efficacy-to-side-effect ratio. **The nonselective pattern of activity and penetration of the blood-brain barrier are known to induce systemic and central side effects.**

α-Adrenergic Blockers

The body of the bladder receives relatively sparse innervation by noradrenergic nerves. The density of noradrenergic nerves increases markedly toward the bladder neck, where the smooth muscle receives a dense noradrenergic nerve supply, particularly in males. **The normal response to noradrenaline is relaxation of the detrusor and contraction of the bladder neck. α Blockers are therefore used in patients with evidence of bladder neck dysfunction for relaxation of the bladder neck.**

Other Medications

Tricyclic antidepressants such as imipramine have been found to be effective for increasing urine storage by both decreasing the detrusor contractility and increasing outlet resistance. However, the precise mechanism of action is not well explained. Its possible effect on the bladder outlet has been described by inhibition of norepinephrine reuptake producing α-adrenergic stimulation. These agents are associated with a high incidence of side effects, and their use should be judicious.

β-Adrenergic agonists can cause significant increases in bladder capacity but can cause significant cardiovascular side effects.

Parasympathicomimetics, calcium antagonists, potassium channel openers, and prostaglandin inhibitors have all been described for use with effect on the bladder, but these are rarely used in children either due to their unfavorable side effects or due to a lack of proven efficacy.

Clean Intermittent Catheterization

Clean intermittent catheterization (CIC) may become necessary in children with decompensated bladders or lazy bladder syndrome in which bladder emptying efficiency is compromised and upper urinary tract dilatation may exist. Regular emptying of the bladder to achieve low-pressure emptying improves detrusor contractility and bladder emptying function. Therefore a regular CIC program can allow for bladder retraining. Some of these children may be able to eventually wean from use of CIC.

Surgery

When conservative management with nonpharmacologic and pharmacologic treatment fails, surgical approaches should be considered. **Bladder augmentation may be performed to help produce a low-pressure system with increased bladder capacity.** Augmentation may be performed using intestinal segments such as colon, ileum, or stomach. However, the complications that may ensue must be considered including mucus production, electrolyte imbalance, and even possible metaplasia/malignancy.

Surgical means have also been employed to reduce urethral/sphincteric pressure as an alternative to α blockers. Recent studies have focused on the use of balloon dilatation of the bladder neck and botulinum A toxin injection into the urethral urinary sphincter in children with non-neuropathic bladder-sphincter dysfunction with promising results. However, these methods seem to require repeated attempts, and long-term effects and efficacy have yet to be presented.

Key Points: Management of Non-Neuropathic Bladder-Sphincter Dysfunction in Children

- Urotherapy is a nonpharmacologic and nonsurgical combination of cognitive, behavioral, and physical therapy with an aim to normalize micturition pattern and prevent further functional disturbances of the lower urinary tract.
- Biofeedback is based on the concept of building self-perception on detrusor contractions and pelvic floor relaxation in the patient.
- The use of low-frequency electrical current (TENS) to inhibit detrusor activity in adults is common and appears to modulate excitatory and inhibitory components of bladder control.
- The principles of bowel management include rectal emptying of impacted stool and the maintenance of regular soft stools.
- Many of the drugs developed with CNS action are not sufficiently selective to affect only the lower urinary tract, increasing the possibility of these drugs causing adverse drug reactions.
- Antimuscarinics are the gold standard in treatment of overactive bladders.
- α Blockers are therefore used in patients with evidence of bladder neck dysfunction for relaxation of the bladder neck.

NOCTURNAL ENURESIS

Etiologic Factors for Nocturnal Enuresis

Primary nocturnal enuresis (PNE) is a common disorder among children. Despite extensive research there is still significant controversy regarding its etiology, and it is now generally accepted that multiple pathologic factors are probably involved. Among others, a common finding is that the nocturnal urine output in many enuretic children is in excess of the bladder reservoir capacity during sleep at night (Norgaard et al, 1985; Hjalmas, 1997, 1998). **Nocturnal polyuria can be either absolute—which is usually associated with a derangement of the circadian rhythm of antidiuretic hormone (ADH) secretion—or relative, mainly due to a reduced functional bladder**

capacity during sleep at night. However, whether it is an increased urine production or a reduced bladder capacity that results in the mismatch between nocturnal bladder capacity and the amount of urine produced during sleep at night, there must be a simultaneous arousal failure in response to bladder fullness before bedwetting can occur.

Bladder-Sphincter Dysfunction in Nocturnal Enuresis

The exact role of bladder dysfunction in the pathogenesis of PNE has until recently remained largely controversial. Although some workers have observed markedly reduced functional bladder capacities among enuretic children compared with age-matched nonenuretic controls, others have previously reported that enuretic episodes were triggered by a full bladder and that bladder capacities in the enuretic children were completely normal (Starfield, 1967; Norgaard, 1989; Jarvelin et al, 1990). However, recent studies have convincingly proven that in **a significant proportion of children with severe nocturnal enuresis, especially those who were refractory to conservative treatment and failed to respond to desmopressin therapy, there was a marked reduction in functional bladder capacities when compared with age-matched normal controls** (Watanabe et al, 1994; Kirk et al, 1995; Rushton et al, 1996; Eller et al, 1998; Yeung et al, 1999). Furthermore, it has been shown that other types of bladder dysfunctions, notably dysfunctional voiding and marked detrusor overactivity with extremely high voiding pressures suggestive of an obstructive pattern, are not uncommon among enuretic children (Figs. 127–13 through 127–15) (Yeung et al, 1999).

Sleep Arousal Disturbance and Brainstem Dysfunction in Nocturnal Enuresis

More recently, the involvement of the central nervous system in the etiology of childhood nocturnal enuresis has been assessed. **Enuretic boys were shown to be more difficult to arouse than age-matched controls. The arousal inability in patients with nocturnal enuresis may relate to either elevated arousal thresholds or the presence of spontaneous uninhibited bladder contractions.**

There is also accumulating evidence that a small functional bladder capacity and detrusor overactivity may play an important role in the pathophysiology of nocturnal enuresis and can further provide reliable predictive clues to the treatment response. Most interestingly, **overnight studies in enuretic children with simultaneous sleep EEG and cystometry have revealed marked detrusor instability only after sleep at night but not during wakeful periods in the daytime** (Watanabe, 1995; Yeung et al, 1999). This per se can result in a marked reduction in the nocturnal functional bladder capacity (Watanabe, 1995; Rushton et al, 1996; Eller et al, 1998; Yeung et al, 1999). Because this pattern has not been observed in normal nonenuretic subjects even during the newborn period, one may hypothesize that this could be due to a small neurologic lesion affecting a tiny area surrounding the vicinity of the pontine micturition center, the posterior hypothalamus (responsible for secretion of ADH), and the locus coeruleus (which is thought to play an important role in the initiation of cortical arousal and release of noradrenaline) (Yeung et al, 1995, 1998, 1999).

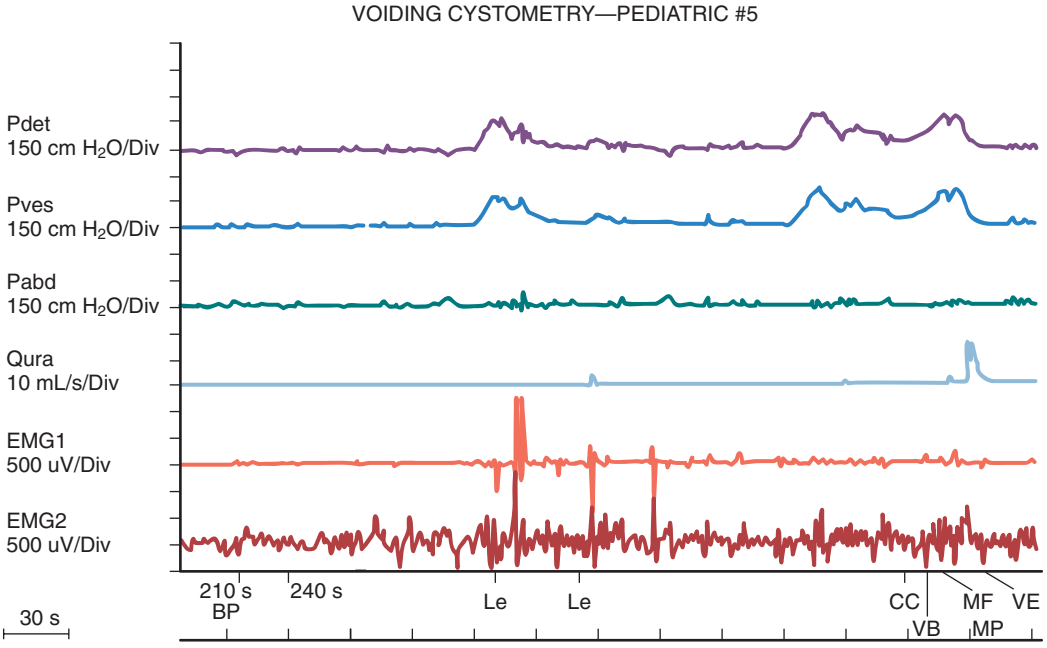


Figure 127–13. Urodynamic tracing showing primary bladder neck dysfunction characterized by a marked delay in initiation of flow after onset of detrusor contraction, often associated with high detrusor pressure but minimal pelvic electromyographic activities.

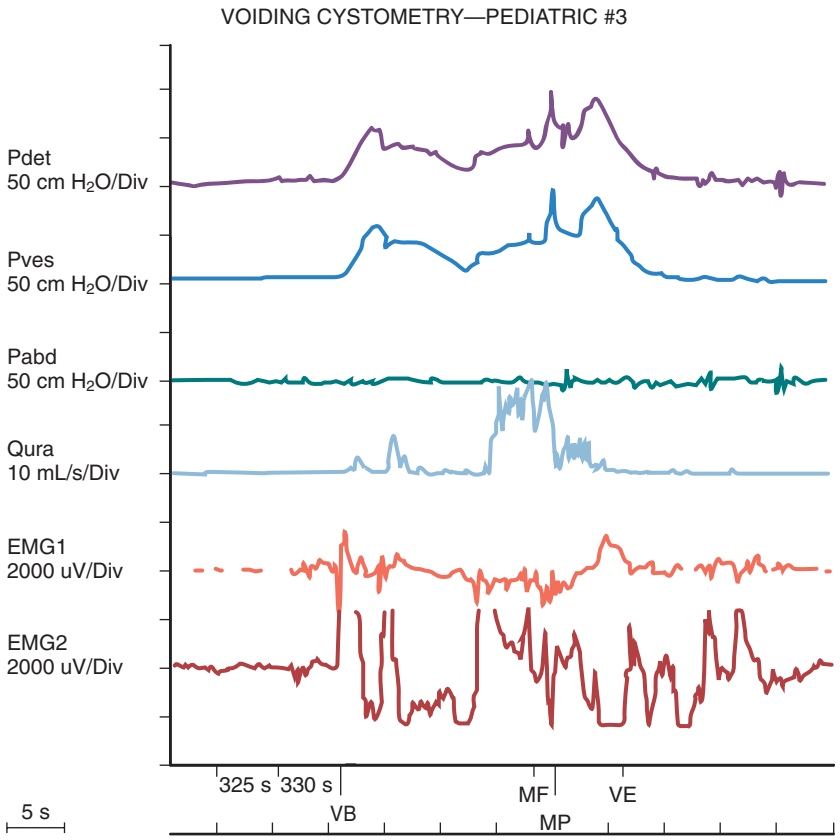


Figure 127–14. Urodynamic tracing showing detrusor-sphincter dyssynergia characterized by marked staccato or interrupted voiding, often associated with detrusor overactivity and/or evidence of increased electromyographic activities.

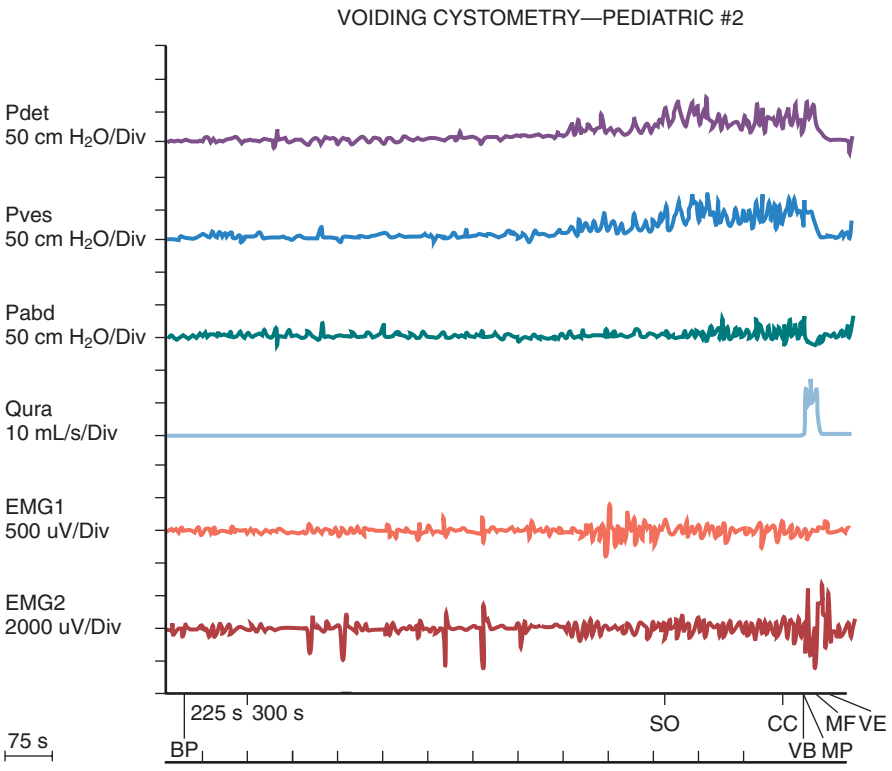


Figure 127–15. Urodynamic tracing showing dysfunctional voiding characterized by abdominal/pelvic straining (holding maneuver) immediately before initiation of micturition, often associated with detrusor overactivity and evidence of increased pelvic electromyographic activities.

It should be noted that despite the high prevalence of underlying bladder dysfunction among patients with severe, refractory PNE, many have no identifiable daytime urinary symptoms including incontinence, frequency, and urgency. A detailed urodynamic study would, however, reveal detrusor instability in 30% to 90% of patients. The authors' experience has shown that many enuretic children with reduced functional bladder capacity have learned, either consciously but more probably subconsciously, to restrain fluid intake during the daytime as an attempt to avoid the social inconvenience of urinary frequency and urge incontinence. This could often be easily spotted by a detailed home-recorded voiding diary by an extraordinarily low fluid intake and infrequent, small-volume voiding. By giving these patients a standard fluid intake and then asking them to repeat a home recording of micturition frequency and urinary volume, one could quite easily obtain a highly reliable estimation of the functional bladder capacity and hence identify those patients with reduced bladder capacities (Rittig et al, 1997; Yeung et al, 1999).

Relationship between Bladder and Brain Dysfunctions (Bladder-Brain Dialogue)

A deficiency of prepulse inhibition (PPI) of startle has been reported in enuretic children such that prestimulation 120 msec before the main stimulus resulted in significantly less inhibition of the blink reflex among enuretic children than healthy controls. Prepulse inhibition is based on an inhibition of the startle pathway by the pedunculopontine tegmental nucleus, which lies in close proximity to the pontine micturition center in the brainstem. It has been postulated that a deficient PPI and reduced ability to inhibit micturition during sleep might both originate from a common dysfunction in the pontine tegmentum. This suggests that a relationship may exist between nocturnal bladder function and brainstem functions in humans (Diao et al, 2005; Ornitz et al, 1999, 2000).

Furthermore, it has also been shown that following successful treatment of nocturnal enuresis in these children, both the sleep arousal threshold and the PPI of startle improved. This suggests that brainstem dysfunction may be a secondary effect to the underlying bladder dysfunction, further supporting the "bladder-brain dialogue" concept whereby there is a bidirectional communication between the bladder and the brain.

Key Points: Nocturnal Enuresis

- A significant proportion of children with severe nocturnal enuresis have marked reduction in functional bladder capacities.
- Most patients with nocturnal enuresis are found to have underlying bladder dysfunction.
- Studies have shown that brainstem dysfunction may be related and secondary to underlying bladder dysfunction in patients with nocturnal enuresis.
- Treatment may consist of behavioral modification, standard urotherapy, biofeedback, pelvic floor rehabilitation, neuromodulation, bowel management, drug therapy, and/or surgery.

SUMMARY

Despite extensive clinical and animal research, it is perhaps embarrassing to admit that the exact neurologic mechanisms of the development of micturition control from newborn to infancy and later childhood, as well as the pathophysiologic pathways that are involved in various types of bladder dysfunction, have as yet remained largely unclear. It is, however, certain that the bladder and the brain talk with each other all the time as early as in the fetus, and there are extremely rapid and extensive changes and modulation of micturition reflexes during the early postnatal period, leading to copious potentials for developmental errors and voiding dysfunctions. Over the past decade experts have learned that both normal and abnormal bladder function are much more dynamic than previously believed. New investigative tools and research have allowed physicians to study in much greater details and precision the various components including neurologic, muscular, urodynamic, and hormonal mechanisms that may intricately interact to produce different patterns of bladder dysfunctions, as well as their relentless, dynamic changes.

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The complete reference list is available online at www.expertconsult.com.

chapter 128

Neuropathic Dysfunction of the Lower Urinary Tract

Dawn Lee MacLellan, MD, FRCSC ● Stuart B. Bauer, MD

Urodynamic Evaluation
Neurospinal Dysraphisms
Central Nervous System Insults

Many of the clinical problems seen in pediatric urology are the result of neurologic lesions that affect lower urinary tract function. As pediatric urology developed in the latter half of the 20th century, urinary diversion initially was the mainstay of treatment for these children with either intractable incontinence or normal or abnormal upper urinary tracts (Smith, 1972). The advent of clean intermittent catheterization (CIC) in the early 1970s by Lapides and associates (1972), refinements in techniques of urodynamic studies in children (Gierup and Ericsson, 1970; Blaivas et al, 1977; Blaivas, 1979), and the development of surgical modalities in conjunction with CIC to manage incontinence dramatically changed the way this group of children was traditionally managed. Most pediatric urologic centers consider functional assessment of the lower urinary tract as an integral element in the evaluation process and almost if not as important as radiographic visualization in characterizing and managing these abnormal conditions (McGuire et al, 1981; Bauer et al, 1984). The natural outcome of early functional investigation has been the advocacy of proactive or early aggressive management in the children who are at risk for urinary tract deterioration based on specific hostile urodynamic parameters (Perez et al, 1992; Edelstein et al, 1995; Kaufman et al, 1996). This has resulted in (1) a statistically significant decrease in upper urinary tract deterioration, compared with those children followed expectantly in the past, and (2) a dramatic reduction in the need for augmentation cystoplasty (Wu et al, 1997; Kaefer et al, 1999; Bauer, 2000). Furthermore, there is now evidence that molecular changes occur intracellularly when prophylactic treatment is begun as early as possible (Park et al, 1999; Ohnishi et al, 2000). Because urodynamic testing has become such an integral part of any discussion of the subject, the testing process as it applies to children is discussed first and then various neurologic abnormalities that are prevalent in children are elaborated upon. For purposes of minimizing ambiguity the terminology used in this chapter is based on the International Continence Society (ICS) standardization of terminology documents (Abrams et al, 2002, 2003; Neveus, 2006).

URODYNAMIC EVALUATION

Before a urodynamic study is performed it is important for the child and the family to have full knowledge of the procedure. Therefore an explanation of the test is sent to each family before the appointment. Attempts are made to minimize anxiety in children by providing reasons for specific portions of the test and explaining exactly what the child will experience. Premedication is rarely given. Parents are instructed to make sure the child has a bowel movement the night before the study.

In males a topical anesthetic cream is applied to the perineum about 45 minutes before the electromyography (EMG) needle is inserted to record sphincter activity. If possible, the child is instructed to come to the urodynamic suite with a full bladder to obtain an initial representative uroflow. The time of the child's previous urination (or catheterization) is noted to calculate an average rate of urine production per unit of time. The flowmeter is located in a private bathroom that contains a one-way mirror so that voiding can be viewed unobtrusively. This allows the investigator to see what position the child assumes when voiding and whether a Credé or a Valsalva maneuver is employed by the child to help empty.

Next, the nurse reviews the test and shows the child all the equipment in an attempt to make the patient feel as comfortable as possible. The child is catheterized with either a No. 7 Fr or a No. 11 Fr triple-lumen urodynamic catheter (Cook Urological, Inc, Spencer, IN)—the smaller, the better—after a small amount of liquid lidocaine (Xylocaine) (1%) has been injected into the urethra and held in place for a moment or two. First, the intravesicular pressure is recorded. Then the bladder is drained and the residual urine is carefully measured, yielding a pressure at residual volume (Kaefer et al, 1997). Sometimes it is necessary to aspirate the catheter to get the accurate volume of residual urine, especially if the bladder is underactive (particularly if the child is taking anticholinergic medication) or has been previously augmented and secretes mucus (because it may not drain completely after insertion of a catheter).

A small balloon catheter is passed into the rectum at this time to measure intra-abdominal pressure during the cystometrogram to identify artifacts of motion and monitor increases in abdominal pressure during the filling and emptying phases of the study (Bates et al, 1970; Bauer, 1979).

Before the bladder is filled, a urethral pressure profile is sometimes obtained by infusing saline through the side-hole channel at a rate of 2 mL/min as the catheter is withdrawn at a rate of 2 mm/sec (Yalla et al, 1980). Many centers have eliminated urethral pressure profile measurements in favor of monitoring detrusor leak point pressure (the subtracted detrusor pressure at

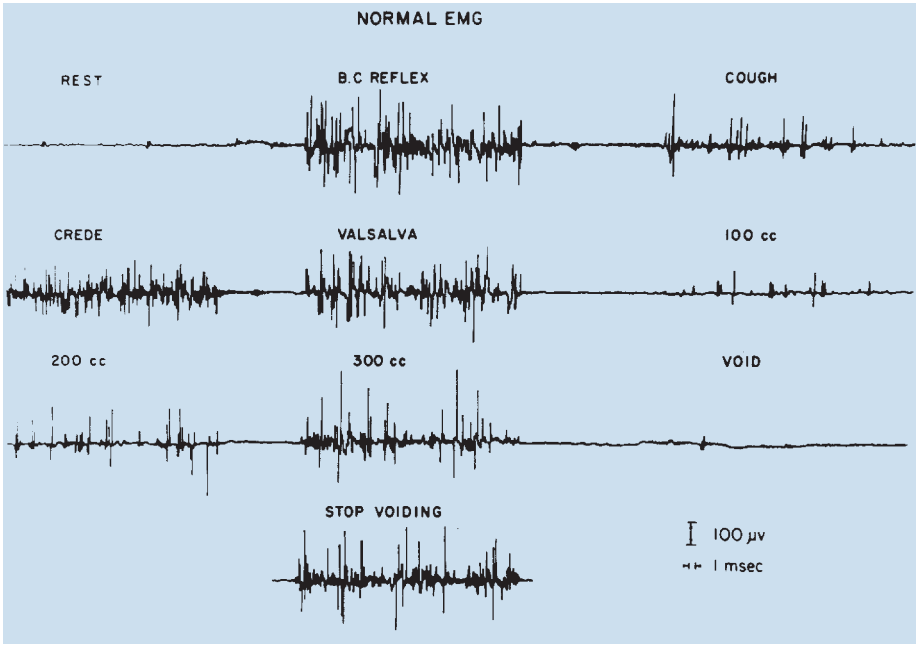


Figure 128–1. Normal reaction of the external urethral sphincter on electromyogram to all the sacral reflexes and to bladder filling and emptying. (From Bauer SB. Urodynamic evaluation and neuromuscular dysfunction. In: Kelalis PP, Kin LR, Belman AB, editors. Clinical pediatric urology. 2nd ed, vol. 1. Philadelphia: WB Saunders; 1985. p. 283–310.)

which the child leaks when the bladder is filled to its functional or maximal capacity). Abdominal leak point pressure is the abdominal pressure at which the child leaks when straining or coughing but that is not as accurate as the detrusor leak point pressure, which is a proportional reflection of outlet resistance (McGuire et al, 1996).

External urethral sphincter EMG is performed using a 24-gauge concentric needle electrode (Diokno et al, 1974; Blaivas et al, 1977b) inserted perineally in boys or paraurethrally in girls and advanced into the skeletal muscle component of the sphincter until individual motor unit action potentials are seen or heard on a standard EMG recorder. Alternatively, perineal electrodes (Maizels and Firlit, 1979) or abdominal patch electrodes (Koff and Kass, 1982) have been used to record the bioelectric activity in the sphincter muscle. Disagreements exist concerning the accuracy of these surface electrode measurements, compared with those obtained with needle electrodes, particularly during voiding. The intactness of sacral spinal cord function is easily measured with needle electrodes by (1) looking at the characteristic waveform of individual motor unit action potentials when the patient is relaxed and the bladder is empty, (2) performing and recording the responses to bulbocavernosus and anal stimulation and to Credé and Valsalva maneuvers, (3) asking the patient to voluntarily contract and relax the external sphincter, and (4) seeing the reaction of the sphincter to filling and emptying of the bladder (Fig. 128–1) (Blaivas et al, 1977a; Blaivas, 1979b).

The rate of bladder filling per minute is selected by first calculating the child's predicted or known capacity (see Chapter 127) and then dividing the result by 10 in order to fill the bladder slowly. In children with myelodysplasia, the average bladder capacity (in milliliters) fits the following formula: 24.5 × age in years + 62 (Palmer et al, 1997). It has been shown that more rapid filling rates may yield falsely low levels of detrusor compliance and may minimize an overactive detrusor (Turner-Warwick, 1975; Joseph, 1992). The bladder is filled slowly with saline warmed to 37° C to avoid this problem (Chin-Peuckert et al, 2004). When it is important to determine very mild degrees of poor compliance, even slower rates of filling are used to measure its true incidence (Kerr et al, 1994; Yeung et al, 1995; Zermann et al, 1997). Some investigators have recorded pressure at residual volume to measure natural filling pressure as the most accurate means of denoting poor compliance (Kaefer et al, 1997; Walter et al, 1998). During filling, it is helpful to try to divert the child's attention by asking unrelated questions, reading a story aloud, or showing a movie or cartoon. If the examiner wishes to elicit detrusor overactivity, the child is asked to cough (Mayo, 1978); alternatively, a cold solution may be instilled at a rapid rate. Most urodynamic parameters do not change with a child's position (sitting vs. supine). However, the sitting position is preferred for the detection of detrusor overactivity and incontinence (Lorenzo et al, 2007).

The study is not considered complete until the child urinates and voiding pressures are measured in those children who urinate on their own. The small size of the urodynamic catheter does not seem to affect micturition pressures adversely, even in very young children. The normal voiding pressure varies from 55 to 80 cm H_2O in boys and from 30 to 65 cm H_2O in girls (Blaivas et al, 1977b; Blaivas, 1979a; Gierup et al, 1979). Infants tend to have higher voiding pressures than older children. Sometimes it is difficult to get the child to void; patience and time are needed in this situation. Placing a urine collection device under the buttocks of the child when supine or dripping tepid water on the genital area often stimulates the child sufficiently to begin urinating. Once the child has voided, it is important to do the following:

1. Analyze the pressure curve to determine whether the contraction is sustained until voiding is complete.
2. Determine whether abdominal pressure has been used to facilitate the emptying process.
3. Listen to changes in EMG activity of the sphincter to determine whether it remained quiet throughout the voiding process and/or resumed prematurely before emptying was complete.
4. Note whether the flow rate curve was bell shaped, intermittent, or prolonged.
5. Measure the voided volume.
6. Calculate whether the patient voided to completion.
7. Observe whether an after-contraction occurred.

Video-urodynamics has gained popularity since its introduction in 1970 (Bates et al, 1970). Visualization of the bladder and bladder neck during filling and of the urethra during voiding has added a dimension for more accurately integrating all aspects of lower urinary tract function and characterizing an abnormality (Glazier et al, 1997). Incompetency of the bladder neck or pelvic floor or the location of any posterior urethral obstruction can be correlated with pressure measurements and external urethral sphincter EMG activity recorded simultaneously (Zerin et al, 1990). Sometimes, aberrations noted on pressure monitoring of sphincter EMG tracings can be confirmed, enhancing these findings (Passerini-Glazel et al, 1992; Weerasinghe and Malone, 1993). Ambulatory urodynamics has become available and feasible in children with the development of microtransducers mounted on small catheters positioned in the bladder (McInerney et al, 1991; Kulseng-Hanssen and Klevmark, 1996).

Often, because it is appropriate to see the effects of drug administration, studies are repeated under similar circumstances several weeks to months later. This is especially true when one is trying to treat reduced detrusor compliance or overactivity medically. To determine the maximal effect, the usual dose of most drugs is taken 2 to 3 hours before the test is performed a second time. The most commonly used drugs that affect lower urinary tract function are listed in Table 128–1, along with their appropriate dose ranges.

Table 128–1.

Drugs That Affect Lower Urinary Tract Function

TYPE	Dosage† Minimum	Dosage† Maximum
Cholinergic		
Bethanechol (Urecholine)	0.7 mg/kg tid	0.8 mg/kg qid
Anticholinergic		
Propantheline (Pro-Banthine)	0.5 mg/kg bid	0.5 mg/kg qid
Oxybutynin (Ditropan)	0.2 mg/kg bid	0.2 mg/kg qid
Glycopyrrolate (Robinul)	0.01 mg/kg bid	0.03 mg/kg tid
Hyoscyamine (Levsin)	0.03 mg/kg bid	0.1 mg/kg tid
Tolterodine (Detrol)	0.01 mg/kg bid	0.04 mg/kg bid
Trospium (Sanctura)*	10 mg/day	20 mg/day
Solifenacin (Vesicare)*	5 mg/day	10 mg/day
Darifenacin (Enablex)*	7.5 mg day	15 mg day
Propiverine (Detrunorm)*	0.1 mg/kg bid	0.4 mg/kg bid
α-Sympathomimetic		
Phenylpropanolamine	2.5 mg/kg tid	2.5 mg/kg qid
Ephedrine	0.5 mg/kg tid	1.0 mg/kg tid
Pseudoephedrine	0.4 mg/kg bid	0.9 mg/kg tid
α-Sympatholytic		
Prazosin (Minipress)	0.05 mg/kg bid	0.1 mg/kg tid
Phenoxybenzamine	0.3 mg/kg bid	0.5 mg/kg tid
β-Sympatholytic		
Propranolol	0.25 mg/kg bid	0.5 mg/kg bid
Smooth Muscle Relaxant		
Flavoxate (Urispas)	3.0 mg/kg bid	3.0 mg/kg tid
Dicyclomine (Bentyl)	0.1 mg/kg tid	0.3 mg/kg tid
Other		
Imipramine (Tofranil)	0.7 mg/kg bid	1.2 mg/kg tid

*Studies evaluating safe dosing in children have not been completed.
†Dosages based on recommendations for a 70-kg person.

NEUROSPINAL DYSRAPHISMS

Myelodysplasia

The most common cause of neurogenic bladder dysfunction in children is abnormal development of the spinal canal and internecine spinal cord. Formation of the spinal cord and vertebral column begins at about the 18th day of gestation. Closure of the canal proceeds in a caudal direction from the cephalad end and is complete by 35 days. The exact mechanism that results in closure and what produces a dysraphic state are yet to be elucidated, but numerous factors have been implicated. The incidence was reported as 1 per 1000 births in the United States (Stein et al, 1982), but there has been a definite decrease in this rate in the past 20 years (Laurence, 1989; Lary and Edmonds, 1996; CDC, 2004; Williams et al, 2005). With the advent of prenatal screening, many affected fetuses are being identified and the pregnancies terminated before 16 weeks of gestation, thereby lowering the number of children born with this disease (Palomaki et al, 1999). The addition of folate supplements to the diet of women of childbearing age has also reduced the incidence of spina bifida worldwide (Committee on Genetics, American Academy of Pediatrics, 1999). The incidence of myelodysplasia (per 1000 live births) in the general population is 1.0, for a mother with one affected child it is 20 to 50, and for a patient with myelodysplasia it is 40 (Scarff and Fronczak, 1981; Stein et al, 1982). Therefore when the disease is already present in a family, the Medical Research Council Vitamin Study Group recommends that women of childbearing age take 4000 μg (4.0 mg) of folic acid per day beginning at least 2 months before the time they plan on becoming pregnant (Committee on Genetics, American Academy of Pediatrics, 1999). There is strong evidence that folate deficiency can lead to a myelodysplastic abnormality de novo; therefore, maternal ingestion of 400 μg of folate per day in all women of childbearing age can reduce the incidence of spina bifida by 50% (Laurence et al, 1981; MRC Vitamin Study Research Group, 1991; Czeizel and Dudas, 1992; Centers for Disease Control and Prevention, 2004). It is now mandatory that enriched grain products be fortified with folic acid (U.S. Food and Drug Administration, 1996). Since these recommendations have been followed worldwide, there has been a reduction in neural tube defects in the United States (Williams et al, 2005) and elsewhere (Botto et al, 2005). In some cases, however, despite increased folic acid intake, women may still give birth to a child with spina bifida owing to antibodies that have developed in response to the increased folate ingestion, thus negating its salutary effect (Rothenberg et al, 2004).

Pathogenesis

Myelodysplasia is an all-inclusive term used to describe the various abnormal conditions of the vertebral column that affect spinal cord function. More specific labels for each abnormality include the following: a *meningocele* occurs when just the meninges but no neural elements extend beyond the confines of the vertebral canal; in a *myelomeningocele,* neural tissue, either nerve roots or portions of the spinal cord, has evaginated with the meningocele (Fig. 128–2); the term *lipomyelomeningocele* denotes that fatty tissue has developed with the cord structures and both are extending with the protruding sac. **Myelomeningocele accounts for more than 90% of all open spinal dysraphic states** (Stark, 1977). Most spinal defects occur at the level of the lumbar vertebrae, with the sacral, thoracic, and cervical areas, in decreasing order of frequency, less affected (Bauer et al, 1977) (Table 128–2).



Figure 128–2. Typical appearance of an open myelomeningocele in a neonate.

Table 128–2.
Spinal Level of Myelomeningocele

LOCATION	INCIDENCE (%)
Cervical–high thoracic	2
Low thoracic	5
Lumbar	26
Lumbosacral	47
Sacral	20

An overwhelming number of meningoceles are directed posteriorly, but on rare occasions they may protrude anteriorly, particularly in the sacral area. Usually the meningocele is made up of a flimsy covering of transparent tissue, but it may be open and leaking cerebrospinal fluid. For this reason urgent repair is necessary, with sterile precautions being followed in the interval between birth and spinal canal closure. In 85% of affected children there is an associated Arnold-Chiari malformation, in which the cerebellar tonsils have herniated down through the foramen magnum, obstructing the fourth ventricle and preventing the cerebrospinal fluid from entering the subarachnoid space surrounding the brain and spinal cord.

In the past several years, several centers in the United States have begun closing the defect in fetuses between 19 and 25 weeks of gestation in an attempt to improve the neurologic defect in these children (Adzick et al, 1998; Bruner et al, 1999; Holzbeierlein et al, 2000). Thus far, this procedure has not altered the incidence of abnormal findings in the lower extremities (Farmer et al, 2003) or on urodynamic assessment in the postnatal period (Koh et al, 2003), but, surprisingly, aqueduct obstruction and, consequently, hydrocephalus has not occurred at birth to the same incidence or extent (Johnson et al, 2003). **It is possible that leakage of cerebrospinal fluid from the open spinal column accounts for herniation of the posterior brainstem down the foramen magnum, leading to the development of hydrocephalus.**

Key Points: Neurogenic Bladder Dysfunction

- At least 25% of the clinical problems seen in pediatric urology are the result of neurologic lesions that affect lower urinary tract function.
- The most common cause of neurogenic bladder dysfunction in children is abnormal development of the spinal canal and internecine spinal cord.
- Myelomeningocele accounts for more than 90% of all open spinal dysraphic states.
- The neurologic lesion produced by this condition can be variable. The bony vertebral level provides little or no clue to the exact neurologic level or lesion produced.

The neurologic lesion produced by the myelomeningocele can be variable, depending on what neural elements, if any, have everted with the meningocele sac. The bony vertebral level often provides little or no clue to the exact neurologic level or lesion produced. The height of the bony level may differ from the highest extent of the neurologic lesion for one to three vertebrae in either direction (Bauer et al, 1977). Furthermore, there may be differences in function from one side of the body to the other at the same neurologic level and from one neurologic level to the next, owing to asymmetry of the affected neural elements. It is important to remember that no two children have the same neurourologic defect. In addition, in 20% of affected children a vertebral bony or intraspinal abnormality occurs more cephalad than the vertebral defect and meningocele, and this can affect function in those portions of the cord. Children with thoracic or upper lumbar meningoceles often have complete reconstitution of the spine in the sacral area, and these individuals frequently have intact sacral reflex arc function involving the sacral spinal roots (in the authors' series of patients with high-level lesions, 74% of neonates and 54% of older children were affected thusly) (Pontari et al, 1995). In fact, it is more likely that children with upper thoracic or cervical lesions will have just a meningocele and no myelomeningocele. Children with neurologic deficits at S1 or lower may also manifest a variety of findings on urodynamic testing, ranging from normal function to upper and/or lower motor neuron lesions involving either the bladder and/or the external urethral sphincter (Dator et al, 1992). Upper motor neuron lesions are characterized by an overactive detrusor, exaggerated sacral reflexes, absence of voluntary control over sphincter function, detrusor-sphincter dyssynergia (DSD), and no EMG evidence of denervation potentials in the sphincter (White and Klauber, 1976; Koff and DeRidder, 1977; Guzman et al, 1983; Capitanucci et al, 1997). The bladder tends to be thick walled (or trabeculated) with a closed bladder neck on voiding cystourethrography (VCUG) or ultrasonography. A lower motor neuron lesion is noted when an acontractile detrusor and partial or complete denervation of the external urethral sphincter with diminished or absent sacral reflexes may be seen. In these instances the bladder is usually small and smooth walled with an open bladder neck (Wilmshurst et al, 1999). The presence or absence of the bulbocavernosus reflex is an indicator (although not a foolproof one) of an upper or a lower motor neuron lesion, respectively (Schlussel et al, 1994). Approximately 10% of neonates with

myelomeningocele exhibit no abnormality on urodynamic testing (Tarcan et al, 2001). Finally, the differing growth rates of the vertebral bodies and the elongating spinal cord add a dynamic factor in the developing fetus that further confounds the picture (Lais et al, 1993). Twenty-four percent of children with normal lower urinary tract function at birth develop upper motor neuron changes over time (Tarcan et al, 2001). Superimposed on all this is the Arnold-Chiari malformation, which can have a profound effect on the brainstem and pontine mesencephalic center, areas that are involved in control of lower urinary tract function.

Therefore the neurologic lesion produced by this condition influences lower urinary tract function in a variety of ways and cannot be predicted just by looking at the spinal abnormality or the neurologic function of the lower extremities. Even careful assessment of the sacral area may not provide sufficient information to make a concrete inference. As a result, urodynamic evaluation in the neonatal period is now the standard of care at most pediatric centers in the United States, because it not only provides a clear picture of the function of the sacral spinal cord and lower urinary tract but also has predictive value in infants at risk for future urinary tract deterioration and progressive neurologic change (McGuire et al, 1981; Van Gool et al, 1982; Bauer, 1984b; Sidi et al, 1986). The advent of hostility scores and the reliability of urodynamic risk factors have led many clinicians to initiate prophylactic therapy in those neonates considered to be at risk for urinary tract deterioration (Perez et al, 1992). There are some, however, who do not consider urodynamic testing an important factor but rely solely on physical examination and radiologic assessment to direct their decision-making process (Hopps and Kropp, 2003), a concept not shared by many.

Neonatal Assessment

Ideally, it would be best to perform urodynamic testing immediately after the infant is born, but the risk of spinal infection and the urgency for closure have not made this a viable option. It was accomplished in one study, however, and the results showed that 1 in 30 children (3.2%) experienced a change in neurologic status as a result of the spinal canal closure (Kroovand et al, 1990). Therefore, **renal ultrasonography and measurement of residual urine are performed as early as possible after birth,** either before or immediately after the spinal defect is closed. Urodynamic studies are delayed until it is safe to transport the child to the urodynamic suite and place him or her on the back or side for the test. The initial urodynamic study should be performed within the first 3 months of life. If the infant cannot empty the bladder after a spontaneous void or with a Credé maneuver, CIC is begun even before urodynamic studies are conducted. If the Credé maneuver is effective in emptying the bladder, it is performed on a regular basis instead of using CIC until the lower urinary tract can be fully investigated. The normal bladder capacity in the neonatal period is 10 to 15 mL; therefore, a residual urine volume of less than 5 mL is acceptable. Other tests that should be performed in the neonatal period include a urinalysis and culture, serum creatinine determination, and careful neurologic examination of the lower extremities.

Once the spinal closure has healed sufficiently, a renal ultrasonogram is performed to reassess upper urinary tract architecture. Next, VCUG and urodynamic study are conducted. **These studies meet several objectives: they provide baseline information about the radiologic appearance of the upper and lower urinary tracts as well as the condition of the sacral spinal cord and the central nervous system (CNS); they provide information that can be compared with findings on subsequent assessments, so that early signs of deterioration of urinary tract function and drainage, or of progressive neurologic denervation, can be detected; they help to identify infants at risk for urinary tract deterioration as a result of a poorly compliant or overactive detrusor or outflow obstruction from DSD, which predetermines the need to initiate prophylactic measures before any deterioration in upper urinary tract architecture and function actually takes place; and they help the physician to counsel parents about the child's future bladder and sexual function** (McGuire et al, 1981; Bauer et al, 1984; Bauer, 1984a; Sidi et al, 1986; Lais et al, 1993). If an abnormality is detected on renal ultrasonography or vesicoureteral reflux is demonstrated, a dimercaptosuccinic acid (DMSA) renal scan is recommended.

Findings

Fifteen to 20 percent of neonates have an abnormal urinary tract on radiologic examination when first evaluated (Bauer, 1985); 3% have hydroureteronephrosis secondary to spinal shock, probably from the spinal canal closure (Chiaramonte et al, 1986), and 15% have abnormalities that developed in utero as a result of abnormal lower urinary tract function in the form of outlet obstruction (Bauer, 2003).

Urodynamic studies in the neonatal period have shown that 63% of infants have bladder contractions. This is also true for an equivalent number of children with upper lumbar or thoracic lesions in whom the sacral spinal cord is spared, 50% of whom have detrusor overactivity (Pontari et al, 1995). Thirty-seven percent have an acontractile detrusor with compliance during filling that is either good (20%) or poor (17%) in this subgroup (Bauer et al, 1984; Bauer, 2003). EMG assessment of the external urethral sphincter demonstrates an intact sacral reflex arc with no evidence of lower motor neuron denervation in 40% of neonates; partial denervation is seen in 24%; and complete loss of sacral cord function is noted in 36% (Lais et al, 1993; Bauer, 2003).

A combination of bladder contractility and external sphincter activity results in **three categories of lower urinary tract dynamics: synergic (26%), dyssynergic with and without poor detrusor compliance (37%), and complete denervation (36%)** (Fig. 128–3) (Bauer et al, 1984; Sidi et al, 1986; Bauer, 2003). DSD occurs when the external sphincter fails to decrease or actually increases its activity during a detrusor contraction or a sustained increase in intravesical pressure as the bladder is filled to capacity (Blaivas et al, 1986). Frequently, a poorly compliant bladder with high intravesical pressure occurs in conjunction with a dyssynergic sphincter, resulting in a bladder that empties only at high intravesical pressure (Van Gool et al, 1982; Sidi et al, 1986). Synergy is characterized by complete silencing of the sphincter during a detrusor contraction or when capacity is reached at the end of filling. Voiding pressures are usually within the normal range. Complete denervation is noted when no bioelectric potentials are detectable in the region of the external sphincter at any time during the micturition cycle or in response to sacral stimulation or a Credé maneuver.

The categorization of lower urinary tract function in this way has been extremely useful because it reveals which children are at risk for urinary tract changes, who should be treated prophylactically, who need close surveillance, and who can be monitored at shorter or longer intervals. Within the first 3 years of life, 71% of neonates

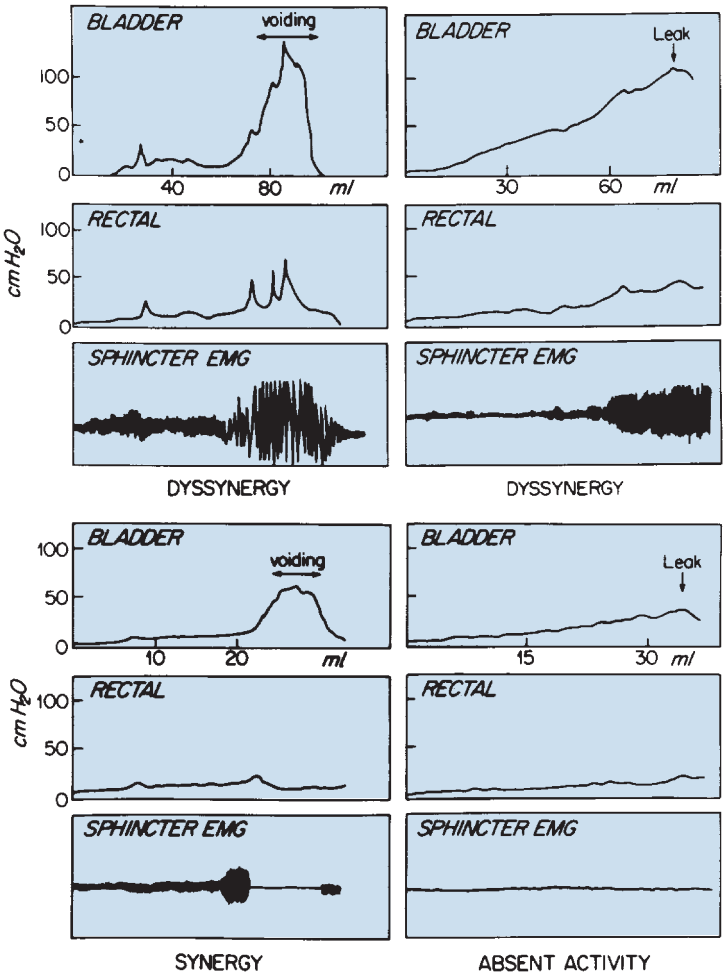


Figure 128–3. Various patterns of urodynamic findings on electromyography (EMG) in neonates with myelodysplasia. Note that a hypertonic detrusor with a nonrelaxing sphincter is also labeled dyssynergy. (From Bauer SB. Early evaluation and management of children with spina bifida. In: King LR, editor. Urologic surgery in neonates and young infants. Philadelphia: WB Saunders; 1988. p. 252–64.)

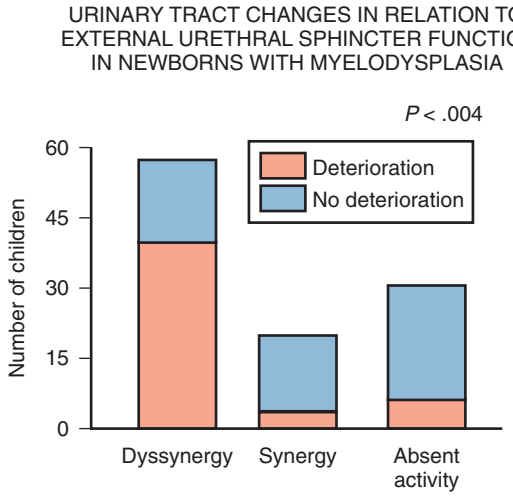


Figure 128–4. Urinary tract deterioration is related to outflow obstruction and is most often associated with dyssynergy. Children with synergy converted to dyssynergy, and patients with complete denervation developed fibrosis with a fixed high outlet resistance in the external sphincter, before any changes occurred in the urinary tract. (From Bauer SB. Early evaluation and management of children with spina bifida. In: King LR, editor. Urologic surgery in neonates and young infants. Philadelphia: WB Saunders; 1988. p. 252–64.)

Key Points: Neonatal Assessment for Neurogenic Bladder Dysfunction

- Renal ultrasonography and measurement of residual urine are performed as early as possible after birth.
- Initial evaluation can be compared with findings on subsequent assessments, so that early signs of deterioration of urinary tract function and drainage, or of progressive neurologic denervation, can be detected.
- Infants at risk for urinary tract deterioration as a result of a poorly compliant or overactive detrusor or outflow obstruction from DSD need to be identified.
- This determines the need to initiate prophylactic measures before any deterioration in upper urinary tract architecture and function take place.
- Fifteen to 20 percent of neonates have an abnormal urinary tract on radiologic examination when first evaluated.
- Three categories of lower urinary tract dynamics may be detected: synergic (26%), dyssynergic with and without poor detrusor compliance (37%), and complete denervation (36%).

with DSD had urinary tract deterioration on initial assessment or subsequent studies whereas only 17% of synergic children and 23% of completely denervated individuals developed similar changes (Fig. 128–4). Infants in the synergic group who showed deterioration did so only after they converted to a dyssynergic pattern of sphincter function. Among the infants with complete denervation, the ones who showed deterioration were those who had increased levels of urethral resistance, presumably caused by fibrosis of the skeletal muscle component of the external sphincter. Therefore, it appears that outlet obstruction is a major contributor to the development of urinary tract deterioration in these children (Fig. 128–5). Poor detrusor compliance plays an important role in this regard, especially when outlet resistance exceeds 40 cm H_2O (McGuire et al, 1981; Landau et al, 1994; Tanaka et al, 1999). Detrusor compliance seems to be worse in children with high levels of outlet resistance (Ghoniem et al, 1989). Bloom and colleagues (1990) and then Park and associates (2001) noted an improvement in compliance when outlet resistance was reduced after gentle urethral dilation in these children; however, the reasons for this change are unclear, and the long-term effect of this maneuver on ultimate continence and lower urinary tract function remains uncertain.

It may be that detrusor filling pressures need to be looked at in a more critical way to determine whether they are an important factor in upper urinary tract deterioration. **Landau and colleagues** (1994) **developed the concept of low detrusor filling pressure (<30 cm H_2O)** at specific volumes adjusted for age and not at maximal capacity. Applying this idea, they noted significantly improved sensitivity in predicting upper urinary tract deterioration. The ability to predict accurately which neonates are at risk for urinary tract deterioration prompted the initiation of prophylactic therapy with CIC and anticholinergic drugs (Geranoitis et al, 1988; Kasabian et al, 1992). Long-term success has been achieved in preventing reflux and hydronephrosis and

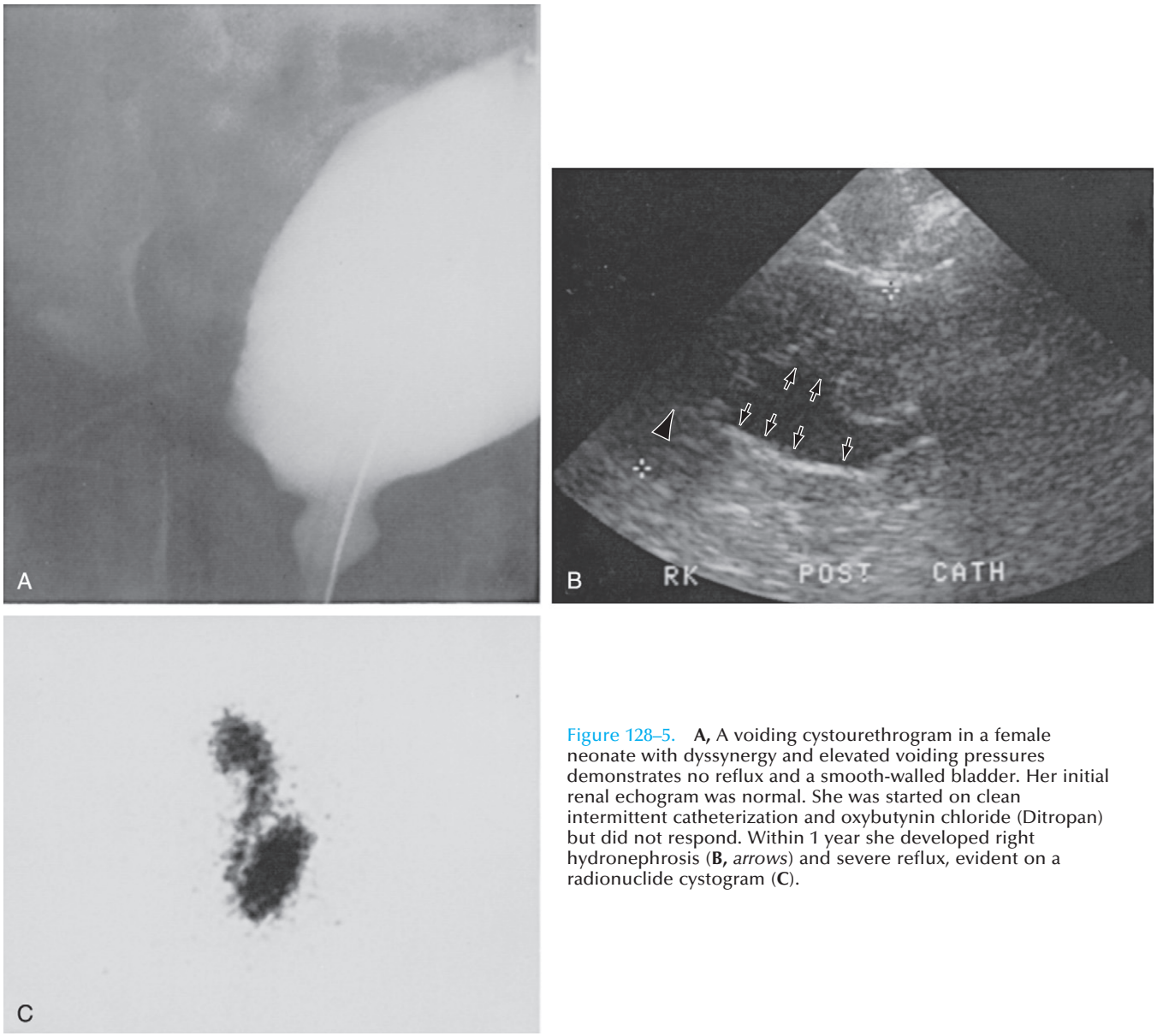


Figure 128–5. **A,** A voiding cystourethrogram in a female neonate with dyssynergy and elevated voiding pressures demonstrates no reflux and a smooth-walled bladder. Her initial renal echogram was normal. She was started on clean intermittent catheterization and oxybutynin chloride (Ditropan) but did not respond. Within 1 year she developed right hydronephrosis (**B,** *arrows*) and severe reflux, evident on a radionuclide cystogram (**C**).

in reducing the need for augmentation cystoplasty, from between 27% and 41% to between 11% and 17% (Edelstein et al, 1995; Wu et al, 1997; Kaefer et al, 1999). Others believe that aggressive observation and prompt intervention yields similar long-term results with less morbidity from catheterization (Teichman et al, 1994), but only time will delineate which avenue of treatment is most efficacious (Tanaka et al, 1999; Hopps and Kropp, 2003).

Management Principles

Because expectant treatment has revealed that infants with outlet obstruction in the form of DSD are at considerable risk for urinary tract deterioration, the idea of treating these children prophylactically has emerged as an important alternative. When CIC is begun in the neonatal period, it is easy for parents to master, even in uncircumcised boys, and for children to accept as they grow (Joseph et al, 1989). Complications such as meatitis, epididymitis, and urethral injury are rarely encountered, and urinary infections occur in fewer than 30% (Kasabian et al, 1992), although asymptomatic bacteriuria can be seen in almost 70% (Schlager et al, 2001).

CIC alone or in combination with anticholinergic agents, when detrusor filling pressures exceed 40 cm H_2O and voiding pressures are higher than 80 to 100 cm H_2O, resulted in an incidence of urinary tract deterioration of only 8% to 10% (Geranoitis et al, 1988; Kasabian et al, 1992; Edelstein et al, 1995). This represents a significant drop in the occurrence of detrimental changes compared with children observed expectantly (McGuire et al, 1981; Bauer et al, 1984; Sidi et al, 1986; Teichman et al, 1994; Wu et al, 1997). Oxybutynin is administered in a dose of 0.2 to 0.4 mg/kg divided two or three times daily with no apparent side effects. On rare occasions when an overactive or poorly compliant bladder fails to respond to these measures, augmentation cystoplasty may be needed with cutaneous vesicostomy almost never required (Duckett, 1974; Mandell et al, 1981).

Neurologic Findings and Recommendations

The neurologic lesion in myelodysplasia is a dynamic disease process in which changes take place throughout childhood (Epstein, 1982; Reigel, 1983; Venes and Stevens, 1983; Oi et al, 1990), especially in early infancy (Spindel et al, 1987) and

later at puberty (Begger et al, 1986), when the linear growth rate accelerates again. When a change is noted on neurologic, orthopedic, or urodynamic assessment, radiologic investigation of the CNS often reveals (1) tethering of the spinal cord (Fig. 128–6), (2) a syringomyelia, a dilation and fluid collection within the spinal cord, (3) increased intracranial pressure due to a shunt malfunction, or (4) partial herniation of the brainstem and cerebellum. Children with completely intact or only partially denervated sacral cord function are particularly vulnerable to progressive changes. Magnetic resonance imaging (MRI) is the test of choice because it reveals anatomic details of the spinal column and CNS (Just et al, 1990). However, it is not a functional study and when used alone it cannot provide exact information about a changing neurologic lesion.

Key Points: Management Principles

- Bladder pressures should be maintained below 30 cm H_2O as much as possible to prevent urinary tract deterioration.
- CIC alone or in combination with anticholinergic agents, when detrusor filling pressures exceed 30 to 40 cm H_2O and voiding pressures are higher than 80 to 100 cm H_2O, can reduce the incidence of urinary tract deterioration.
- The neurologic lesion in myelodysplasia is a dynamic disease process in which changes take place throughout childhood.
- Sequential urodynamic testing on a yearly basis beginning in the neonatal period and continuing until the child is 5 years old provides a means of monitoring these children.
- Vesicoureteral reflux occurs in 3% to 5% of neonates with myelodysplasia.
- The indications for antireflux surgery are not very different from those applicable to children with normal bladder function.

Sequential urodynamic testing on a yearly basis beginning in the neonatal period and continuing until the child is 5 years old provides a means of carefully monitoring these children to detect signs of change, thus offering the hope that early detection and neurosurgical intervention may help to arrest or even reverse a progressive pathologic process. Changes occurring in a group of neonates monitored in this manner involved both the sacral reflex arc and the pontine-sacral reflex interaction (Fig. 128–7) (Lais et al, 1993). Most children who experience such changes tend to do so in the first 3 years of life (Phuong et al, 2002) (Fig. 128–8). Twenty-two of 28 children in whom the neurologic picture became worse underwent a second neurosurgical procedure; 11 of them had a beneficial effect from



Figure 128–6. MR image in a 9-year-old girl who developed a tethered cord after myelomeningocele repair reveals the conus opposite the L3–4 vertebrae *(arrow)*.

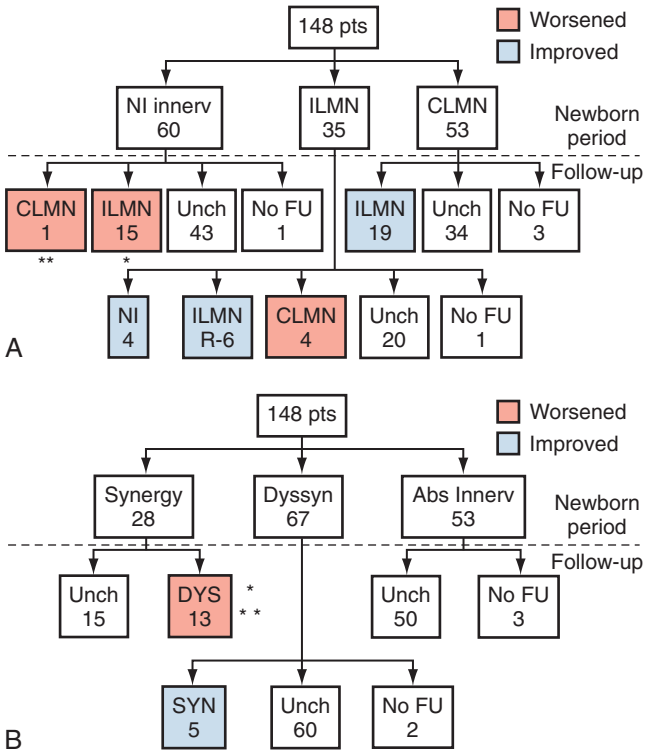


Figure 128–7. Changes in innervation of the purely sacral (**A**) and pontine-sacral (**B**) reflex arc pathways that occurred in a group of children with myelodysplasia who were monitored with sequential urodynamic studies beginning in the newborn period. ILMN, incomplete lower motor neuron lesion; CLMN, complete lower motor neuron lesion; NL, normal innervation; Unch, unchanged; FU, follow-up; DYS, dyssynergy; Syn, synergy. **A,** The *double asterisk* indicates 1 patient changed from synergy to dyssynergy and the *single asterisk* indicates 4 of 15 patients so changed. **B,** The *single asterisk* indicates 1 patient changed from normal to partial and then complete denervation, and the *double asterisk* indicates 4 patients changed from normal to partial denervation. (From Lais A, Kasabian NG, Dyro FM, et al. Neurosurgical implications of continuous neuro-urological surveillance of children with myelodysplasia. J Urol 1993;150:1879–83.)

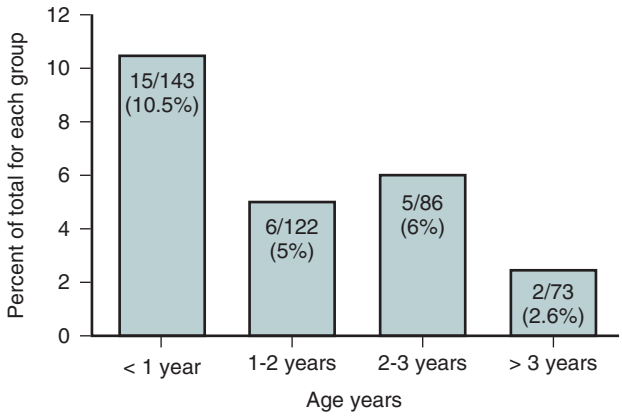


Figure 128–8. The propensity for a change in urethral sphincter innervation is greatest in the first year of life. (From Lais A, Kasabian NG, Dyro FM, et al. Neurosurgical implications of continuous neuro-urological surveillance of children with myelodysplasia. J Urol 1993;150:1879–83.)

Table 128–3.
Surveillance in Infants with Myelodysplasia*

SPHINCTER ACTIVITY	RECOMMENDED TESTS	FREQUENCY
Intact–synergic	Postvoid residual volume	q 4 mo
	US	q 12 mo
	UDS	q 12 mo
Intact–dyssynergic†	US	q 12 mo
	UDS	q 12 mo
	VCUG or RNC‡	q 12 mo
Partial denervation	Postvoid residual volume	q 4 mo
	US	q 12 mo
	UDS§	q 12 mo
	VCUG or RNC‡	q 12 mo
Complete denervation	Postvoid residual volume	q 6 mo
	US	q 12 mo

*Until age 5 years.
†Patients receiving intermittent catheterization and anticholinergic agents.
‡If detrusor hypertonicity or reflux is already present.
§Depending on degree of denervation.
US, renal ultrasonography; UDS, urodynamic study; VCUG, voiding cystourethrography; RNC, radionuclide cystography.

the surgery and showed improvement in urethral sphincter function (Lais et al, 1993). Infants with only sacral level deficits have a 47% risk of deterioration (Dator et al, 1992). Even children with normal neurourologic function at birth have a 32% risk of developing a tethered spinal cord with the development of DSD with or without detrusor overactivity (Tarcan et al, 2001).

As a result of these developments **it is recommended that all infants with myelodysplasia be monitored according to the guidelines set forth in Table 128–3.** It is not enough to look at just the radiologic appearance of the urinary tract; scrutiny of the functional status of the lower urinary tract is important as well. In addition to the reasons cited previously, it may be necessary to repeat a urodynamic study if the upper urinary tract dilates secondary to impaired drainage from a poorly compliant detrusor.

Beyond the age of 5 years renal ultrasonography every 18 months until puberty and then every 2 years thereafter is recommended. Urodynamic studies are indicated to evaluate the development of new neurologic symptoms, new hydronephrosis, or changes in continence. VCUG should be done if recurrent urinary tract infections are experienced.

Management of Reflux

Vesicoureteral reflux occurs in 3% to 5% of neonates with myelodysplasia, usually in association with poor detrusor compliance, detrusor overactivity, and/or DSD (Flood et al, 1994). It is rare to find reflux in any neonate without these urodynamic findings (Bauer, 1984b; Geranoitis et al, 1988; Edelstein et al, 1995). If left untreated, the incidence of reflux in these infants at risk increases with time until 30% to 40% are afflicted by 5 years of age (Bauer, 1984a; Seki et al, 1999). Prophylactic treatment that lowers detrusor filling and voiding pressures with anticholinergic agents and empties the bladder by means of CIC significantly reduces this rising incidence of reflux (Edelstein et al, 1995).

In children with reflux grades 1 to 3 (International Classification) who void spontaneously or have complete lesions with little or no outlet resistance and empty their bladder completely, management consists solely of prophylaxis with antibiotics to prevent recurrent infection. In children with high-grade reflux (grade 4 or 5), CIC is begun to ensure complete emptying. Children who cannot empty their bladder spontaneously, regardless of the grade of reflux, are treated with CIC to empty the bladder efficiently. Children with poor detrusor compliance with or without hydroureteronephrosis are also started on anticholinergic agents to lower intravesical pressure and ensure adequate upper urinary tract decompression (Flood et al, 1994). When reflux is managed in this manner there has been a dramatic response, with reflux resolving in 30% to 55% of individuals (Kass et al, 1981; Bauer, 1984b; Joseph et al, 1989; Flood et al, 1994; Agarwal et al, 1997; Hopps and Kropp, 2003). Although bacteriuria can be seen in as many as 56% of children on CIC it is not harmful except in the presence of high-grade reflux, because symptomatic urinary infection and renal scarring rarely occur with lesser grades of reflux (Kass et al, 1981; Cohen et al, 1990).

Credé voiding should be avoided in children with reflux, especially those with a reactive external urethral sphincter. In this circumstance, the Credé maneuver results in a reflex response in the external sphincter that increases urethral resistance and raises the pressure needed to expel urine from the bladder (Barbalais et al, 1983) (Fig. 128–9). This has the effect of aggravating the degree of reflux and accentuating its waterhammer effect on the kidneys. Vesicostomy drainage (Duckett, 1974; Mandell et al, 1981) is rarely required today but is reserved for those infants (1) who have such severe reflux that CIC and anticholinergic medication fail to improve upper urinary tract drainage, (2) whose parents cannot adapt to the catheterization program, or (3) who are not good candidates for augmentation cystoplasty (Morrisroe et al, 2005).

The indications for antireflux surgery in this group of children are not very different from those applicable to children with normal bladder function. They include recurrent symptomatic (febrile) urinary infection while receiving adequate antibiotic therapy and appropriate catheterization techniques; persistent hydroureteronephrosis despite effective emptying of the bladder and lowering of intravesical pressure; severe reflux with an anatomic abnormality at the ureterovesical junction; reflux that persists into puberty; and the presence of reflux in any child undergoing surgery to increase bladder outlet resistance. Although some clinicians do not advocate reimplanting ureters in patients with low-grade reflux who are undergoing augmentation cystoplasty to lower intravesical pressure, this concept is not universally accepted (Nasrallah and Aliabadi, 1991).

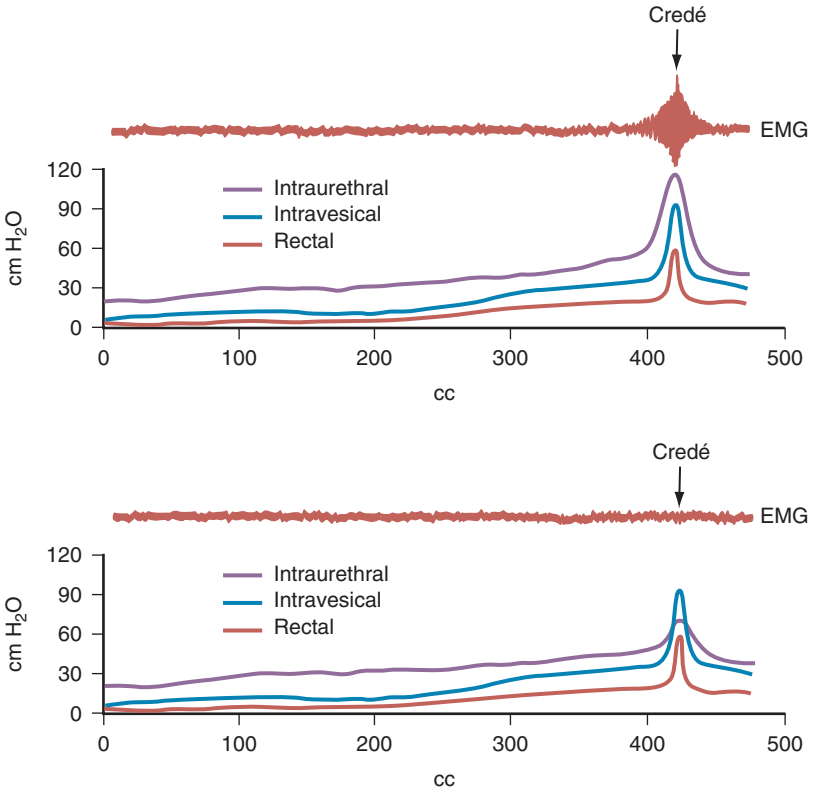


Figure 128–9. When the external sphincter is reactive *(top)*, a Credé maneuver produces a reflex increase in electromyographic (EMG) activity of the sphincter and a concomitant rise in urethral resistance, resulting in high voiding pressure. A child whose sphincter is denervated and nonreactive *(bottom)* will not have a corresponding rise in EMG activity, urethral resistance, or voiding pressure. A Credé maneuver here will not be detrimental. (From Bauer SB. Early evaluation and management of children with spina bifida. In: King LR, editor. Urologic surgery in neonates and young infants. Philadelphia: WB Saunders; 1988. p. 252–64.)

Jeffs and colleagues (1976) were the first to show that **antireflux surgery can be very effective in children with neurogenic bladder dysfunction as long as it is combined with measures to ensure complete bladder emptying.** Before this observation was made, the results of ureteral reimplantation were so dismal that most physicians treating these children advocated urinary diversion as a means of managing reflux (Smith, 1972; Cass, 1976). Since the advent of CIC, success rates for antireflux surgery have approached 95% (Kass et al, 1981; Woodard et al, 1981; Bauer et al, 1982; Kaplan and Firlit, 1983). Bilateral surgery for unilateral disease need not be done, because contralateral reflux does not occur postoperatively (Bauer, 1984a). The endoscopic injection of various materials has altered the management of reflux in children with myelomeningocele (Elder et al, 2004; Schlussel, 2004). A recent meta-analysis demonstrated that the success rate of endoscopic treatment is less in children with neurogenic bladder than those with normal bladder function (62% vs. 74%) (Elder et al, 2004). Studies comparing the effectiveness of open surgical to endoscopic management in this population show a significantly greater success rate for traditional open procedures (61% to 72.5% vs. 84.3% to 95.5%) (Engel, 1997; Granata, 1999). Thus, the endoscopic approach is a reasonable alternative to ureteroneocystotomy; however, the long-term outcomes are not defined.

Continence and Prevention of Upper Urinary Tract Deterioration

The primary goals of management for children with myelomeningocele are the attainment of social continence and preservation of normal renal function. These goals can be achieved for most children with a combination of medical and surgical therapies.

Urinary continence is becoming an increasingly important issue that demands attention at an early age. It has been shown that children who are continent have higher ratings in self-confidence and social acceptance than boys and girls who are wet; thus this issue becomes paramount as the children grow up and attend school (Moore et al, 2004). **Initial attempts at achieving continence include CIC and drug therapy designed to maintain low intravesical pressures and a reasonable level of urethral resistance** (Figs. 128–10 and 128–11). Although these measures can be initiated on a trial-and-error basis, it is more efficient to use exact treatment protocols based on specific urodynamic findings. As a result, urodynamic testing is performed if initial attempts with CIC and oxybutynin fail to achieve continence. Without urodynamic studies it is hard to know whether (1) a single drug is effective, (2) the dose should be increased, (3) a second drug should be added to the regimen, or (4) alternative methods of treatment (i.e., augmentation cystoplasty) should be contemplated.

At this point, if poor detrusor compliance and/or overactivity have not been dealt with effectively the dose of the anticholinergic drug may be increased. If this is not successful, another anticholinergic agent may be combined with or given instead of oxybutynin (see Table 128–1). A recent study in adults with neurogenic bladder has shown the addition of a second anticholinergic agent to an existing double-dose anticholinergic agent resulted in improved urodynamic parameters and continence in 85% of patients who had failed single-agent therapy with minimal adverse effects (Amend, 2008). Glycopyrrolate is the most potent oral anticholinergic drug available today, but it may have the typical belladonna-like side effects common to all these drugs. Tolterodine, a newly approved anticholinergic drug, is equally effective as oxybutynin in reducing detrusor overactivity and improving compliance, but with fewer side effects, especially constipation (Goessl et al, 2000). Hyoscyamine produces fewer side effects still, but its potency is even less. Intravesical instillation of oxybutynin has been proven to be successful in lowering detrusor pressure and has fewer side effects compared with oral administration; serum

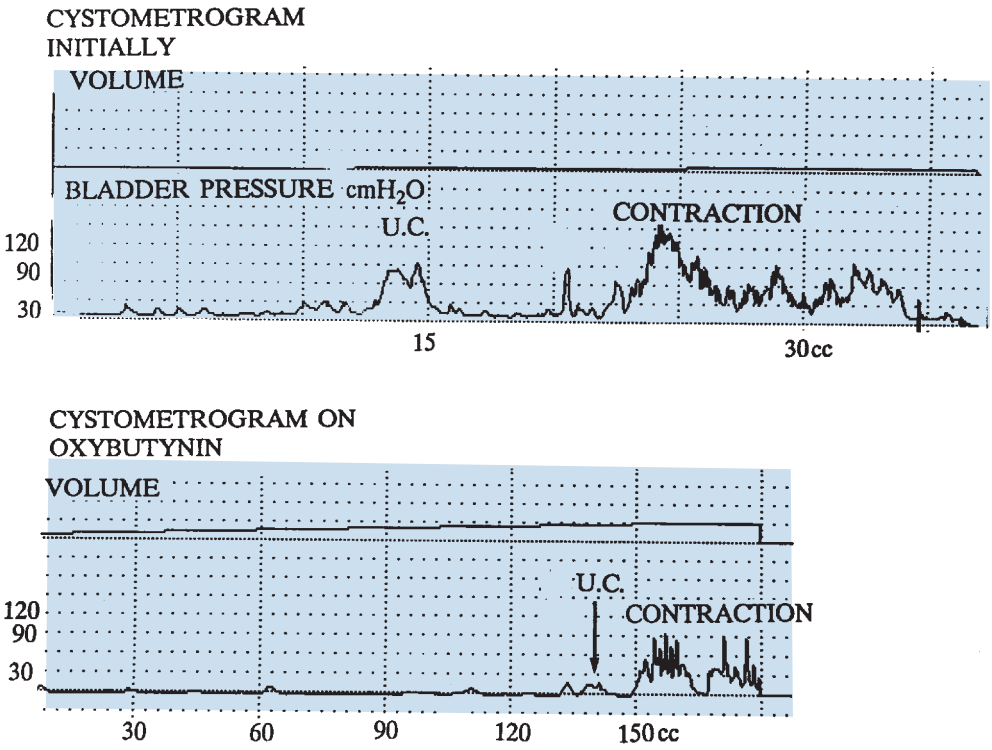


Figure 128–10. Oxybutynin is a potent anticholinergic agent that dramatically delays detrusor contractions and lowers contraction pressure, as demonstrated on these two graphs. U.C., uninhibited contraction.

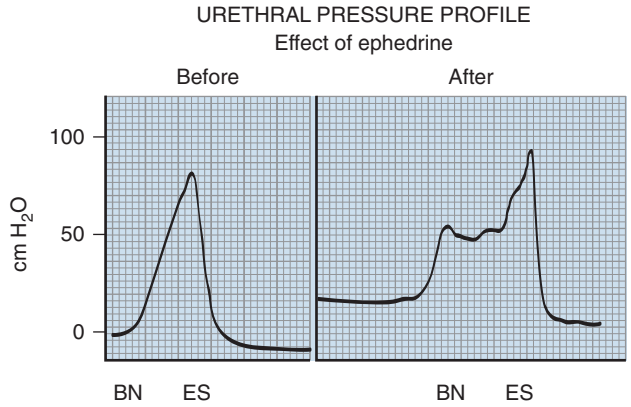


Figure 128–11. α-Sympathomimetic agents potentially have their greatest effect in the bladder neck region, where the highest concentration of α-adrenergic receptor sites exists. They can raise outlet resistance and improve continence in many individuals. BN, bladder neck; ES, external sphincter.

concentrations may reach similar levels regardless of the route of intake (Greenfield and Fera, 1991; Massad et al, 1992). Inconvenience of administration, however, seems to preclude its long-term use (Kasabian et al, 1994). Trospium chloride, a recently approved quaternary ammonium compound with antimuscarinic activity that has a high binding affinity for muscarinic receptors M_1, M_2, and M_3 but not nicotinic or cholinergic receptors holds promise because it has a more direct effect on detrusor function with fewer systemic side effects than anticholinergic agents (Rovner, 2004; Doroshyenko et al, 2005; Kim et al, 2005). Solifenacin, darifenacin, and propiverine are muscarinic receptor antagonists with high affinity for the M_3 receptor. Propiverine also has calcium channel–blocking effects. These three novel agents may reduce adverse events; however, their safety and effectiveness has not yet been established in children. If conservative management with medications and CIC fail to achieve continence or prevent upper urinary tract deterioration, more aggressive intervention is warranted. In up to 80% of children, nocturnal bladder emptying has been shown to improve hydronephrosis, bladder compliance and capacity, urinary tract infections, and continence (Koff, 2005).

If urodynamic testing reveals that urethral resistance is inadequate to maintain continence because either the sphincter fails to react to increases in abdominal pressure or its resistance drops with bladder filling, α-sympathomimetic agents

Key Points: Continence in Neurogenic Bladder Dysfunction

- Initial attempts at achieving continence include CIC and drug therapy designed to maintain low intravesical pressures and a reasonable level of urethral resistance.
- If urodynamic testing reveals that urethral resistance is inadequate to maintain continence, α-sympathomimetic agents are added.
- Overnight Foley drainage has been effective in lowering bladder filling pressure and in maintaining a stable upper urinary tract in some children at risk.
- Surgery becomes a viable option when drug therapy fails to achieve continence.
- If bladder neck or urethral resistance is insufficient to allow adequate storage capacity, several operations are available to improve this continence mechanism.
- Continent urinary diversion with closure of the bladder neck (or compression via a fascial sling) has been used to provide a better quality of life for those with intractable urethral incompetence.

are added to the regimen (see Table 128–1); phenylpropanolamine is the most effective drug in this regard.

Some children will ultimately require surgical intervention. A persistent poorly compliant or overactive detrusor may be treated either with enterocystoplasty (Mitchell and Piser, 1987; Sidi et al, 1987; Hernandez et al, 1994), autoaugmentation (Cartwright and Snow, 1989a, 1989b), or a combination thereof (Duel et al, 1998). Sigmoid, cecum, and small intestine, in that order, have been used to enlarge the bladder. The ileocecal segment is avoided in children with myelodysplasia because removing it might aggravate the bowel dysfunction in these children. Detubularization of the bowel is needed to minimize the intrinsic contractions of the intestinal segment and prevent it from causing intractable incontinence once it has been added to the bladder (Goldwasser et al, 1987; Hinman, 1988). **Concerns have surfaced about gastric segments because they can cause hyponatremic hypochloremic metabolic alkalosis** (Gosalbez et al, 1993) or the hematuria dysuria syndrome (Nguyen et al, 1996). Except for children with progressive or end-stage renal failure, gastrocystoplasty has not been recommended as a routine form of augmentation (Leonard et al, 2000; Plaire et al, 2000).

With the long view of hindsight it is becoming evident that augmentation cystoplasty with any segment of the gastrointestinal tract can lead to long-term consequences in acid-base balance, vitamin B_{12} deficiency, fat absorption, renal function, bone metabolism, growth retardation, recurrent urinary tract infection, stone formation, and even cancer risk (Gilbert and Hensle, 2005). Consequently, there is considerable interest in developing new techniques for replacing the bladder without the need for bowel substitution (i.e., tissue-engineered autologous augments; see also Chapter 19).

The well-documented development of malignancy in patients with intestinal and gastric bladder augmentation mandates careful surveillance of these patients. Most studies note a 10-year minimum lag time between the augmentation and presentation of disease. Thus, **10 years after augmentation an annual surveillance cystoscopy with site-directed biopsies at the anastomotic suture line is recommended** (Soergel et al, 2004; Castellan et al, 2007; Vemulakonda et al, 2008). Symptoms and signs such as new-onset hydronephrosis, hematuria, or bladder wall thickening warrant prompt evaluation (Castellan et al, 2007; Vemulakonda et al, 2008).

If bladder neck or urethral resistance is insufficient to allow adequate storage capacity, several operations are available to improve this continence mechanism. Bladder neck reconstruction can be undertaken in a variety of ways, including the Young-Dees or Leadbetter procedures (Young, 1919; Dees, 1949; Leadbetter, 1964) or the Kropp approach (Kropp and Angwafo, 1986), modified by Salle to make catheterization easier (Salle et al, 1994). A fascial sling procedure suspending the bladder neck and buttressing it against the undersurface of the pubis has been advocated enthusiastically by several clinicians (McGuire et al, 1986; Raz et al, 1988; Bauer et al, 1989). Artificially derived material, small intestine submucosa (SIS) (Colvert et al, 2002), and a rectus muscle "fascial" wrap around the bladder neck (Walker et al, 2000) have been as effective as rectus fascia in increasing bladder neck resistance and their effectiveness does not seem to dissipate over time (Elder, 1990; Castellan et al, 2005). Even though it is applicable to males it has not been as effective as in females (Nguyen et al, 2001; Castellan et al, 2005). Each of these operations, however, necessitates the use of CIC to empty the bladder postoperatively. It is most effective when combined with augmentation cystoplasty to ensure an adequate reservoir with good compliance (Castellan et al, 2005). The use of a bladder neck sling in conjunction with continent cutaneous catheterizable channel has been proposed to avoid bladder augmentation in some patients with neurogenic bladder. These children have a similar improvement in their continence level but may have a shorter interval between catheterization and require more anticholinergic agents than children with slings and augmentation (Snodgrass et al, 2009). However, this approach is controversial because of the potential risk of bladder deterioration related to increasing bladder pressures and lack of sufficient long-term follow-up. The artificial sphincter (Barrett and Furlow, 1982; Light and Scott, 1983; Light et al, 1983) also increases bladder outlet resistance, and its mechanism of action allows emptying at low urethral pressure. Any patient who can empty his or her bladder before the device is implanted should be able to do so afterward without the need for CIC. In fact, this is the only bladder neck procedure that allows for spontaneous voiding yet is compatible with CIC when needed (Herndon et al, 2003). However, children who have had bladder augmentation or an artificial sphincter placed before puberty are much more likely to require CIC to empty the bladder postpubertally (Catti, 2008). Poor detrusor compliance can develop postoperatively if the preoperative cystometrogram is not carefully scrutinized for signs of increased filling pressure (Woodside and McGuire, 1982; Bauer et al, 1986), and this may lead to progressive renal failure if not treated in a timely fashion with medication or augmentation cystoplasty (Bauer et al, 1993). Long-term results with the artificial sphincter have shown that it is a viable option in children with neurogenic bladder dysfunction (Bosco et al, 1991; Levesque et al, 1996; Kryger et al, 1999; Kryger et al, 2001; Herndon et al, 2003); however, device removal may be required in 9% to 20% (Lopez Pereira et al, 2006; Bauer, 2008; Catti, 2008).

An alternative, minimally invasive option to increase bladder outlet resistance is the endoscopic injection of bulking agents in the bladder neck (Ben-Chiam et al, 1995). Various bulking agents have been used. Early reports are usually promising; however, long-term results are less favorable (Perez et al, 1996; Silveri et al, 1998; Guys et al, 2001). Long-term data on newly developed injectable agents are not available (Caione and Capozza, 2002; Misseri et al, 2005).

Urinary diversion, once considered a panacea for children with myelodysplasia, has turned out to be a Pandora's box of new clinical problems (Schwarz and Jeffs, 1975; Shapiro et al, 1975). Pyelonephritis and renal scarring, calculi, ureterointestinal obstruction, strictures of the conduit, and stomal stenosis are often encountered in children who are monitored on a long-term basis. Although antirefluxing colon conduits seem to have fewer complications, they are still not ideal. In the past 15 years very successful attempts have been made to reverse a urinary tract diversion in children who probably would not have undergone the procedure today (Hendren, 1973, 1990). Few children undergo urinary diversion now; if they do, it is in association with a continent catheterizable stoma.

Continent urinary diversion with complete closure of the bladder neck (or compression via a fascial sling) has been used to provide a better quality of life for those with intractable urethral incompetence despite bladder outlet surgery or to make it easier to catheterize those individuals who cannot easily catheterize themselves via their native urethra (MacNeily et al, 2005).

Several operations have been devised, but the ones that achieved the most publicity initially were the Kock pouch in

adults (Kock, 1971; Skinner et al, 1987) and the Indiana reservoir in children (Rowland et al, 1987). **Mitrofanoff** (1980) **created a continence mechanism by tunneling one end of the vermiform appendix into the bladder, as if reimplanting the ureter to prevent reflux, with the other end being brought out through the skin as a continent catheterizable stoma. This principle has been extended to the ureter.** After the ureter is transected at the pelvic brim, a proximal transureteroureterostomy is performed and the cut end of the distal segment is brought to the skin as a stoma (Duckett and Snyder, 1986). Continence is achieved by the intramural detrusor tunnel of the ureter. Other narrow structures (e.g., fallopian tube, a rolled strip of stomach, a tapered or reconfigured ileal segment) have been implanted either into the native bladder or along the tinea of a detubularized portion of sigmoid or cecum when the latter act as a urinary reservoir (Woodhouse et al, 1989; Reidmiller et al, 1990; Bihrie et al, 1991; Montie et al, 1997). The success rate for achieving continence has been excellent, approaching 85%, primarily owing to the flap valve effect of the intramural tunnel (Hinman, 1990; Watson et al, 1995; Kaefer et al, 1997; Gerharz et al, 1998). For this reason, it is now the preferred method for continent urinary diversion (Harris et al, 2000).

An alternative option for achieving continence and improving urodynamic parameters is the intravesical injection of botulinum-A toxin, which is a neurotoxin protein produced by *Clostridium botulinum* that acts by inhibiting acetylcholine release, resulting in muscle paralysis. The commonly injected dose ranges from 5 to 12 IU/kg, with a maximum total dose of up to 360 IU. Sixty-five to 87 percent of children who have failed conservative medical management and CIC have achieved dryness with a botulinum-A injection. Improvements in urodynamic parameters include decreased maximum detrusor pressure (33% to 57%); increased maximum cystometric capacity (34% to 165%); and improved compliance (121% to 183%) (Schulte-Baukloh et al, 2002; Riccabona et al, 2004; Altaweel et al, 2006; Kajbafzadeh et al, 2006). The duration of response ranges from 6 to 10.5 months. It appears that repeated injections continue to be effective with the interval between repeated injections increasing with each series of injections (Schulte-Baukloh et al, 2005; Altaweel et al, 2006). Complete lack of a response to botulinum-A injection has been linked to the presence of botulinum-A antibodies (Schulte-Baukloh et al, 2008).

The artificial somatic-autonomic reflex pathway is a promising new therapeutic approach to restore bladder function in children with spina bifida. The procedure involves a limited laminectomy and a lumbar ventral root to S3 ventral root microanastomosis. The L5 dorsal root is left intact as the afferent branch of the somatic-autonomic reflex pathway after axonal regeneration (Xiao et al, 2005). In a series of 20 children with spina bifida, 17 developed satisfactory bladder control and continence within 12 months of the procedure. Those children with DSD and overactivity demonstrated nearly normal storage and synergic voiding on follow-up urodynamic studies (Xiao, 2005). A recent study at an independent center confirmed early favorable results with improved continence and spontaneous voiding in 30% of the spina bifida patients (median age 8 years) who underwent intradural lumbar to sacral motor root microanastomosis. Postoperative complications included prolonged wound drainage, ipsilateral footdrop, and temporary lower extremity muscle weakness (Peters et al, 2010). Thus this novel approach appears to have promising results when preformed by experts. The long-term results and general application of the procedure are yet to be determined.

Sexuality

Sexuality in this population is becoming an increasingly important issue as more individuals reach adulthood and want to marry or to have intimate relationships (Cromer et al, 1990). Investigators are looking into the concerns, fears, self-imagery, and desires of teenagers and young adults and at the ability of males to procreate and females to bear children (Bomalaski et al, 1995). However, few studies are available that look critically at sexual function in these patients. Mental disability, poor manual dexterity, lack of education regarding normal and abnormal sexual function, invasion of personal privacy, and overprotective parents often prevent independent behavior and, as a result, lead to poor understanding of sexual issues (Joyner et al, 1998; Woodhouse, 2005).

In several studies, researchers interviewed groups of teenagers and reported that **28% to 40% of them had had one or more sexual encounters and almost all of them had a desire to marry and ultimately to bear children** (Cromer et al, 1990; Palmer et al, 1999a). In one study, 72% of male subjects claimed they were able to have an erection, and two thirds of these were able to ejaculate (Decter et al, 1997). Medical therapy has been shown to be effective in this population. Sildenafil improved erectile function in 80% of men with meningomyelocele in a randomized, double-blind, placebo-controlled trial (Palmer et al, 2000). Other studies revealed that 70% to 80% of myelodysplastic women were able to become pregnant and to have an uneventful pregnancy and delivery, although urinary incontinence in the latter stages of gestation was common in many, as was delivery by cesarean section (Laurence and Beresford, 1975; Cass et al, 1986; Bomalaski et al, 1995; Arata et al, 2000). In the same studies, 17% to 39% of male subjects claimed that they were able to father children and another 25% had a good prognosis for fathering them (Laurence and Beresford, 1975; Bomalaski et al, 1995; Decter et al, 1997). It is more likely that men will have problems with erectile and ejaculatory function because the sacral spinal cord is frequently involved, whereas reproductive function in women, which is under hormonal control, is not affected. Men with neurologic lesions at S1 or lower are likely to have normal or adequate reproductive sexual function, but only 50% of those with lesions above that level have adequate function (Woodhouse, 1994, 2005). Poor semen quality (Reilly and Oates, 1992) and Sertoli cell–only histology on testis biopsy (Glass and Soni, 1999) have been reported as reasons (in addition to erectile dysfunction) for infertility in males with spina bifida.

The degree of sexuality is inversely proportional to the level of neurologic dysfunction (Joyner et al, 1998; Palmer et al, 1999b). Until recently, however, this subject has been taboo (Decter et al, 1997). Sexual identity, education, and social mores have been taken out of the realm of secrecy and are now openly discussed. **However, parents of children with spina bifida are more overprotective than parents of normal children and are less willing to grant autonomy to them for adequate peer and sexual development** (Holmbeck et al, 2002); this tends to lead to less self-assurance regarding social interaction with the opposite sex and diminished sexual identity. Boys reach puberty at an age similar to the age for normal males, whereas breast development and menarche tend to start as much as 2 years earlier than usual in myelodysplastic compared with normal girls. The cause of this early hormonal surge is uncertain, but it may be related to changes in pituitary function in girls secondary to hydrocephalus (Hayden, 1985).

Bowel Function

There is no unanimity regarding the ideal bowel management program for myelodysplastic children. The external anal sphincter is innervated by the same (or similar) nerves that modulate the external urethral sphincter, whereas the internal anal sphincter is under the influence of more proximal nerves from the sympathetic nervous system. In addition, the internal anal muscle reflexively relaxes in response to anal distention. Consequently, **bowel incontinence is frequently unpredictable and is not associated with the attainment of urinary continence;** it is often related to the consistency of fecal material and how rapidly the anal area refills after an evacuation, the degree of intactness of sacral cord sensation and motor function, and reflex reactivity of the external anal sphincter muscle (Younoszai, 1992).

A majority of pediatricians managing these children believe that a regular and efficient bowel emptying regimen is paramount and mandatory. Most programs begin at about 1 year of age, but the best method of attaining these objectives is still controversial. Usually the children are placed on diets that are intended to create formed but not severely constipated stool. Roughage in the form of fruits and bran and stool softeners (in older children) are given to achieve this goal. Suppositories that help evacuate the rectum are used on a regular basis to help train the lower bowel to fill and empty. Some physicians believe that enemas are more effective in evacuating a greater portion of the lower bowel, but one problem with them is the difficulty of retaining the solution when the anal sphincter muscle is lax. Biofeedback training programs to strengthen the external anal sphincter are no more effective than a good bowel management program in attaining fecal continence (Loening-Baucke et al, 1988). Whereas electrostimulation of the bowel has had a variable effect in fecal continence, ranging from 0% to 36% (Marshall and Boston, 1997; Palmer et al, 1997), intravesical bladder stimulation has had a more pronounced effect on bowel continence (Han et al, 2004). When a carefully constructed bowel regimen is adhered to, most children with myelomeningocele can achieve some degree of fecal continence (Myers, 1984), but the uncertainty of accidents always makes this a tenuous situation. Often the urinary incontinence is effectively managed with CIC, drugs, and/or surgery but episodes of fecal soiling remain a problem, particularly in socially minded adolescents (Hayden, 1985; Krogh et al, 2003). When diet, medications, and manual evacuation fail to achieve predictable bowel emptying without soiling, a continent cutaneous pathway from the lower abdominal wall to the cecum may be created using the vermiform appendix; this is called the ACE procedure, for *A*ntegrade *C*ontinence *E*nema (Griffiths and Malone, 1995). When the appendix is unavailable, a small segment of the bowel may be reconfigured to act as a conduit. Alternatively, a button cecostomy provides effective access for antegrade continence enemas (Duel, 1999). Enemas consisting of either Golytely, saline, or tap water, sometimes in combination with bisacodyl, are instilled daily or every other day to evacuate the colon. Cleansing the colon in this manner has resulted in complete continence in 89% of children in whom it has been tried (Squire et al, 1993; Gerharz et al 1997; Yerkes et al, 2002). Older children readily become independent in managing their bowel function, leading to improved self-esteem and sociability (Bau et al, 2001; Aksnes et al, 2002).

Key Point: Bowel Function

- Bowel incontinence is frequently unpredictable and is not associated with the attainment of urinary continence.

Table 128–4.

Types of Occult Spinal Dysraphisms

Lipomeningocele
Intradural lipoma
Diastematomyelia
Tight filum terminale
Dermoid cyst/sinus
Aberrant nerve roots
Anterior sacral meningocele
Cauda equina tumor

Lipomeningocele and Other Spinal Dysraphisms

Diagnosis

There is a group of congenital defects that affect the formation of the spinal column but do not result in an open vertebral canal (James and Lassman, 1972) (Table 128–4). They occur once in 4000 live births, but with the ease of MRI screening of children with suspected lesions the incidence of these defects is increasing (Bruce and Schut, 1979). In a recent study the incidence of lipomeningocele in families was calculated to be 0.043% (Sebold et al, 2005). These lesions can be very subtle and have no obvious outward signs, but in more than 90% of children there is a cutaneous abnormality overlying the lower spine (Anderson, 1975; Pierre-Kahn et al, 1997). This varies from a small dimple or skin tag to a tuft of hair, a dermal vascular malformation, a very noticeable subcutaneous lipoma, or an asymmetrically curving gluteal cleft (Fig. 128–12). In addition, on careful inspection of the legs, one may note a high arched foot or feet; hammer toes or claw toes; a discrepancy in muscle size, shortness, and decreased strength in one leg compared with the other, typically at the ankle; and/or a gait abnormality, especially in older children (Dubrowitz et al, 1965; Weissert et al, 1989; Jindal and Mahaptra, 2000). Absent perineal sensation, back pain, and secondary incontinence after a period of dryness are common symptoms in older children and young adults (Linder et al, 1982; Yip et al, 1985; Weissert et al, 1989). Lower urinary tract function is abnormal in 40% to 90% of affected older individuals, with the incidence of an abnormality increasing proportionately with age (Mandell et al, 1980; Koyangi et al, 1997; Pierre-Kahn et al, 1997; Sarica et al, 2003). The child may experience difficulty with toilet training, urinary incontinence after an initial period of dryness once toilet trained (especially during the pubertal growth spurt), recurrent urinary infection, and/or fecal soiling. Occasionally, some patients without an obvious back lesion escape detection until they develop urinary (66%) or lower extremity (19%) symptoms or back pain (14%) after puberty caused by delayed traction on the spinal cord (Satar et al, 1995).

Findings

When these children are evaluated in the neonatal period or early infancy, **a majority have a perfectly normal neurologic examination** (Atala et al, 1992). Urodynamic testing, however, reveals abnormal lower urinary tract function in about one third of infants younger than 18 months of age (Keating et al, 1988) (Fig. 128–13). Such studies may provide the only evidence of a neurologic injury involving the lower spinal cord (Keating et al, 1988; Foster et al, 1990; Atala et al, 1992, Satar et al, 1997; Nogueira et al, 2004). When present, the most likely abnormality is an upper motor neuron lesion characterized by an overactive

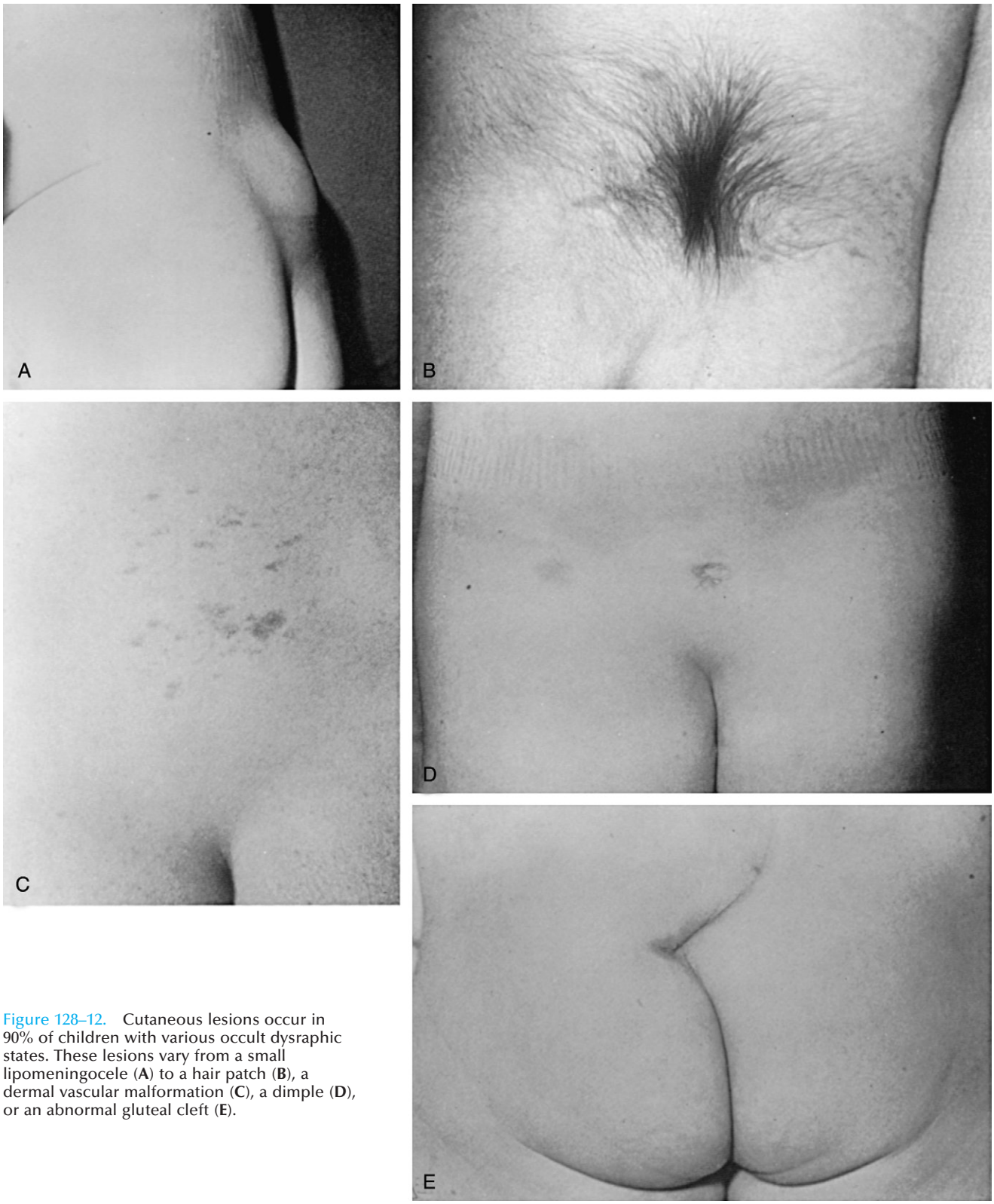


Figure 128–12. Cutaneous lesions occur in 90% of children with various occult dysraphic states. These lesions vary from a small lipomeningocele (**A**) to a hair patch (**B**), a dermal vascular malformation (**C**), a dimple (**D**), or an abnormal gluteal cleft (**E**).

detrusor and/or hyperactive sacral spinal cord reflexes (Fone et al, 1997; Pierre-Kahn et al, 1997); mild forms of DSD are rarely noted. Lower motor neuron signs with denervation potentials in the sphincter or an acontractile detrusor occur in only 10% of young children.

In contrast, practically all individuals older than 3 years of age who have not been operated on or in whom an occult dysraphism has been belatedly diagnosed have either an upper or lower motor neuron lesion or a combination thereof on urodynamic testing (92%) (see Fig. 128–13) or neurologic signs of lower extremity dysfunction (Yip et al, 1985; Kondo et al, 1986; Keating et al, 1988; Atala et al, 1992; Satar et al, 1997; Nogueira et al, 2004). When such children were observed expectantly from infancy after the diagnosis was

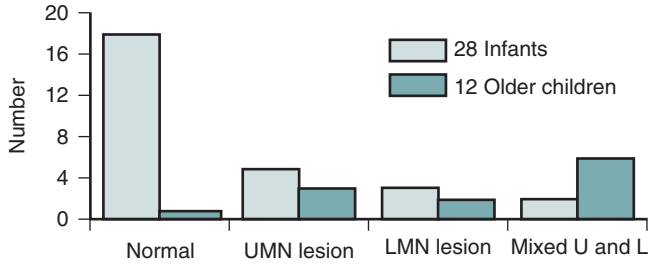
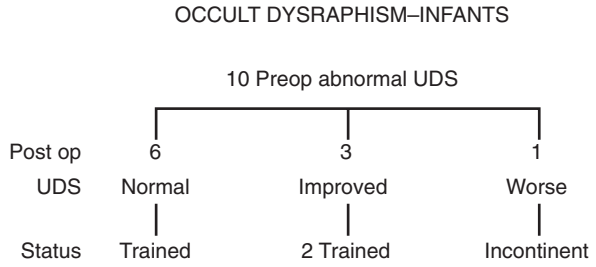


Figure 128–13. Most neonates with an occult spinal dysraphism have normal lower urinary tract function, whereas older children tend to have both upper motor neuron (UMN) and lower motor neuron (LMN) lesions.



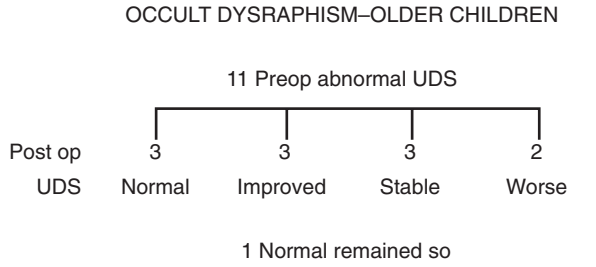


Figure 128–14. The potential for recoverable function is greatest in infants (6 of 10, 60%) and less so in older children (3 of 11, 27%). The risk of damage to neural tissue at the time of exploration to those with normal function is small (2 of 19, 11%). UDS, urodynamic study.

Key Points: Lipomeningocele and Other Spinal Dysraphisms

- There is a group of congenital defects that affect the formation of the spinal column but do not result in an open vertebral canal.
- Practically all individuals older than 3 years of age who have not been operated on or in whom an occult dysraphism has been belatedly diagnosed have either an upper or lower motor neuron lesion or a combination thereof.
- A majority of infants have a perfectly normal neurologic examination.
- Early detection and early intervention can both reverse or at least stabilize the progression of the lesion; this does not happen in older children.

made, 58% experienced deterioration of their disorder within 2 years (Andar et al, 1997; Cornette et al, 1998). There does not seem to be a preponderance of one type of lesion over another (i.e., upper vs. lower motor neuron); and often the child shows signs of both (Hellstrom et al, 1986; Kondo et al, 1986). In one study of children older than 3 years of age, 43% had denervation in the sphincter and 52% detrusor areflexia, with a total of 81% having an abnormality (Satar et al, 1995).

Pathogenesis

Various occult spinal dysraphic lesions produce different neurourologic findings. When they do cause an abnormality, lipomas of the cauda equina invariably cause an upper motor neuron lesion (70%), alone or in combination with a lower motor neuron deficit (30%) (Satar et al, 1997). The split cord syndrome results in an isolated upper or lower motor neuron lesion in 25% each or a combined lesion in 50% (Proctor et al, 2000).

The reason for this difference in neurologic findings may be related to (1) compression on the cauda equina or sacral nerve roots by an expanding lipoma or lipomeningocele (Yamada et al, 1983), **(2) tension on the spinal cord from tethering secondary to differential growth rates in the bony vertebrae and neural elements while the lower end of the cord is held in place by the lipmoa or by a thickened filum terminale** (Dubrowitz et al, 1965), **or (3) fixation of the split lumbosacral cord by an intravertebral bony spicule or fibrous band** (Pang, 1992; Pang et al, 1992; Andar et al, 1997). The overt stretching that invariably occurs when there is a forcible flexion and/or extension of the spinal cord with normal movement leads to changes in oxidation/reduction of cytochrome oxidase, most notably in the lumbosacral spinal neurons when there is no intraspinal pathologic process (Yamada et al, 2004; Henderson et al, 2005). Under normal circumstances the conus medullaris ends just below the L2 vertebra at birth and recedes upward to T12 by adulthood (Barson, 1970). When the cord does not "rise" or is fixed in place owing to one of these lesions, ischemic injury may ensue (Yamada et al, 1981, 2004). Correcting the lesion in infancy has resulted not only in stabilization but also in improvement in the neurologic picture in many instances (Koyangi et al, 1997, Cornette et al, 1998; Proctor et al, 2000) (Fig. 128–14). Sixty percent of infants with abnormal urodynamic findings preoperatively revert to normal postoperatively, with improvement noted in 30%; 10% become worse with time. In older children there is a less dramatic change after surgery, with only 27% becoming normal, 27% improving, 27% stabilizing, but 19% actually becoming worse with time (see Fig. 128–14) (Keating et al, 1988; Satar et al, 1997). Older children with an overactive detrusor tend to improve, whereas those with acontractile bladders do not (Hellstrom et al, 1986; Kondo et al, 1986; Flanigan et al, 1989). Finally, 5% to 27% of children operated on in early childhood develop secondary tethering when observed for several years, suggesting that early surgery has both beneficial and sustaining effects in patients with this condition (Pierre-Kahn et al, 1997; Satar et al, 1997; Proctor et al, 2000).

As a result of these findings, it is apparent that urodynamic testing may be the only way to document that an occult spinal dysraphism is actually affecting lower spinal cord function (Keating et al, 1988; Khoury et al, 1990; Sarica et al, 2003). The serial use of electromyography of the external urethral sphincter using a needle electrode to monitor individual motor unit action potentials provides a precise mechanism for measuring changes in innervation that may occur over time. Some investigators have

shown that posterior tibial somatosensory evoked potentials are an even more sensitive indicator of tethering and should be an integral part of the urodynamic evaluation (Roy et al, 1986). The implication of these findings lies in the fact that **early detection and early intervention can either reverse or at least stabilize the progression of the lesion, which does not happen in older children** (Yamada et al, 1983; Tami et al, 1987; Kaplan et al, 1988) and offers a degree of protection from subsequent tethering (Pierre-Kahn et al, 1997; Satar et al, 1997; Proctor et al, 2000), which seems to be a frequent occurrence when the lesion is not dealt with expeditiously in infancy (Chapman, 1982; Seeds and Jones, 1986).

Recommendations

In addition to MRI studies (Tracey and Hanigan, 1990), urodynamic testing including EMG of the external urethral sphincter should be performed in every child who has a questionable cutaneous or bony abnormality of the lower spine, especially if there is a radiologic abnormality of the spinal cord (Packer et al, 1986; Campobasso et al, 1988; Hall et al, 1988; Meyrat et al, 2003). This test provides the most accurate measure of sacral spinal cord function at diagnosis and provides a basis for comparison with subsequent studies when the children are either operated on or carefully observed. **In children younger than 3 months of age the vertebral bones have not ossified; thus a window of opportunity exists for ultrasonography to be a useful screening tool in visualizing the spinal canal** (Fig. 128–15) (Raghavendra et al, 1983; Scheible et al, 1983). **At this age there is good correlation between the ultrasound imaging and MRI findings; however, if a spinal cord abnormality is identified the latter provides for a better definition of the spinal cord lesion. Consequently, ultrasonography should not be used as the definitive imaging modality** (Hughes et al, 2003). Older children with an occult spinal cord lesion may have urologic symptoms in 20% of cases (Hsieh et al, 2006), and 50% to 60% may have abnormal urodynamic findings preoperatively (Geurra et al, 2006). Resolution of the abnormal urodynamic parameters is noted in 50% to 60% of cases after detethering (Hseih et al, 2006; Geurra et al, 2006). Therefore, urodynamic study is recommended for all children with an occult spinal dysraphism before and after spinal cord detethering procedures.

In the past, most of these conditions were treated by excising the superficial skin lesion, without dissecting further into the spinal canal to remove or repair the entire abnormality. Currently, most neurosurgeons advocate laminectomy and removal of the intraspinal process as completely as possible without injuring the nerve roots or cord to release the tether and prevent further injury with subsequent growth (Linder et al, 1982; Kondo et al, 1986; Kaplan et al, 1988; Foster et al, 1990; Atala et al, 1992; Pierre-Kahn et al, 1997; Proctor et al, 2000; Jindal and Mahapatra, 2000; Nogueira et al, 2004).

Sacral Agenesis

Sacral agenesis has been defined as the absence of part or all of two or more lower vertebral bodies. The cause of this condition is still uncertain, but teratogenic factors may play a role, because insulin-dependent diabetic mothers have a 1% chance of giving birth to a child with this disorder. Conversely, 16% or more of children with sacral agenesis have a mother who is insulin dependent with diabetes mellitus (Passarge and Lenz, 1966; Guzman et al, 1983; Wilmshurst et al, 1999). Often the mothers have only gestational insulin-dependent diabetes. The

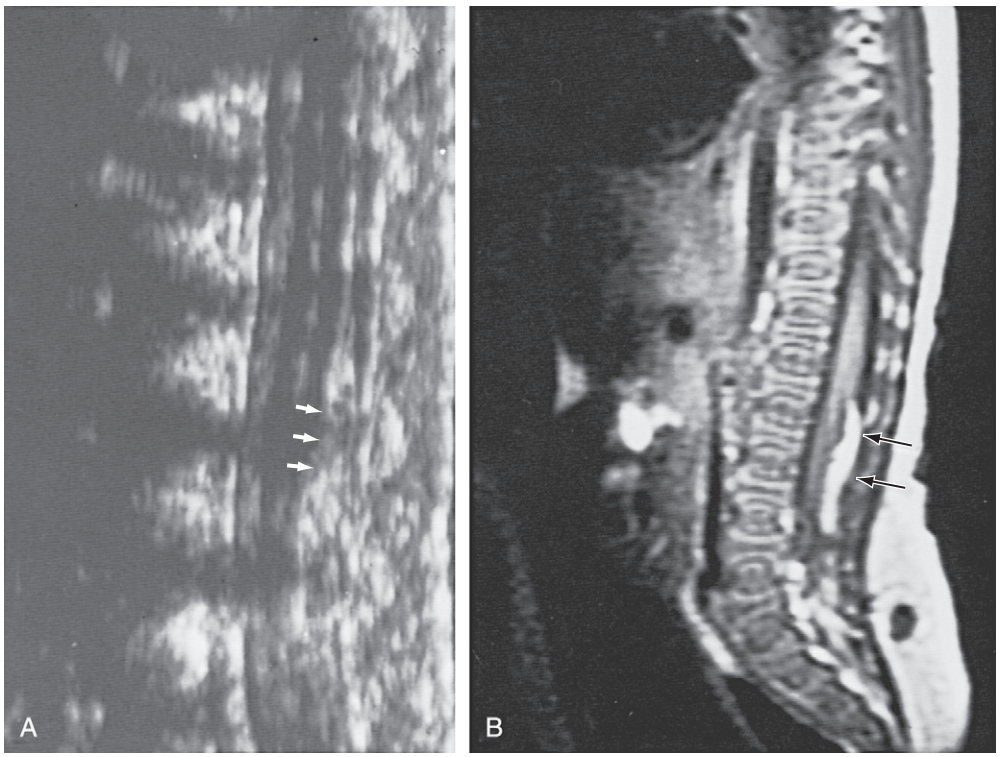


Figure 128–15. **A,** During the first few months of life, ultrasonography can clearly demonstrate intravertebral anatomy because the posterior arches have not completely ossified. Note that the spinal cord along with its central canal is displaced anteriorly *(white arrows)* beginning at L3 because of an intradural lipoma. **B,** The MR image is juxtaposed to confirm the ultrasound findings. The longitudinal white intraspinal mass *(black arrows)* is the lipoma; the longitudinal gray mass is the spinal cord.

disease has been reproduced in chicks by exposing embryos to insulin (Landauer, 1945; White and Klauber, 1976). Maternal insulin-antibody complexes have been noted to cross the placenta, and their concentration in the fetal circulation is directly correlated with macrosomia (Menon et al, 1990). It is possible that a similar cause-and-effect phenomenon occurs in sacral agenesis. There is evidence that a deletion of the seventh chromosome (7q36) leading to the absence of a transcription factor may be responsible for this anomaly (Papapetrou et al, 1999). In addition, maternal drug exposure (i.e., minoxidil) has been reported to cause sacral agenesis (Rojansky et al, 2002).

In familial cases of sacral agenesis associated with the Currarino syndrome (presacral mass, sacral agenesis, and anorectal malformation), deletions in chromosome 7 (7q) resulting in *HLXB9* genetic mutations have been found (Ross et al, 1998). A mutation in *HLXB9,* a homeodomain gene of a 403 amino acid protein that appears to be responsible for neural plate infolding, has been identified in 20 of 21 patients with familial cases and in 2 of 7 sporadic cases of Currarino syndrome (Hagan et al, 2000; Kochling et al, 2001). Heterozygote carriers within these families have also been identified (Lynch et al, 2000). Thus, sacral agenesis may represent one point on a spectrum of abnormalities that encompass sacral meningoceles and anorectal malformations (Bernbeck et al, 2004).

Diagnosis

The presentation is bimodal, with more than three fourths of the disorders being detected in early infancy and the remainder discovered between 4 and 5 years of age (Wilmshurst et al, 1999). With the increased use of prenatal ultrasonography, it is being diagnosed with increased frequency before birth. Sacral vertebral bony ossification begins at 15 weeks, so it is possible to detect the lesion after 18 weeks of gestation on an ultrasound examination and then to confirm it by fetal MRI (De Biasio et al, 2003). When not detected prenatally or at birth, the diagnosis is often delayed until failed attempts at toilet training bring the child to the attention of a physician. Sensation, including that in the perianal dermatomes, is usually intact, and lower extremity function is normal (Koff and DeRidder, 1977; Jakobson et al, 1985; Capitanucci et al, 1997). Because these children have normal sensation and little or no orthopedic deformity in the lower extremities (although high arched feet or claw toes or hammer toes may be present), the underlying lesion is often overlooked. In fact, 20% escape detection until the age of 3 or 4 years (Guzman et al, 1983). The only clue, besides a high index of suspicion, is flattened buttocks and a low, short gluteal cleft (Bauer, 1990) (Fig. 128–16). Palpation of the coccyx is helpful in detecting the absent vertebrae (White and Klauber, 1976). The diagnosis is most easily confirmed with a lateral film of the lower spine, because this area is often obscured by the overlying gas pattern on an anteroposterior projection (White and Klauber, 1976; Guzman et al, 1983) (Fig. 128–17). MRI has been used to visualize the spinal cord in these cases; its imaging reveals a sharp cutoff of the conus at T12 as a consistent finding (Pang, 1993; Diel et al, 2001) (Fig. 128–18).

Findings

On urodynamic evaluation an almost equal number of individuals manifest either an upper or a lower motor neuron lesion (35% vs. 40%, respectively); 25% have no sign of denervation (Guzman et al, 1983; Boemers et al, 1994). The number of affected vertebrae does not seem to correlate with the type of motor neuron lesion present (Boemers et al, 1994) (Fig. 128–19). The injury appears to be stable and rarely shows signs of progressive denervation as the child grows. Sacral sensation is relatively spared, even in the presence of extensive sacral motor deficits (Boemers et al, 1994; Schlussel et al, 1994). Urinary tract infection may be detected in 75% of children over time, with vesicoureteral reflux diagnosed in 37%. Reflux is most likely to occur in those with an upper (75%) (irrespective of whether they have synergy or dyssynergy) versus a lower (40%) motor neuron lesion (Schlussel et al, 1994; Wilmshurst et al, 1999).

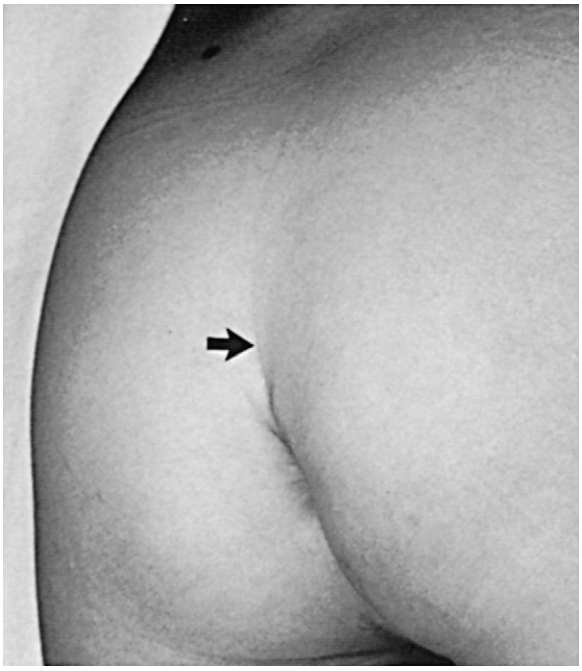


Figure 128–16. Characteristically, in sacral agenesis the gluteal crease is short and is seen only inferiorly *(below arrow)* because of the flattened buttocks.

Key Points: Sacral Agenesis

- Sacral agenesis has been defined as the absence of part or all of two or more lower vertebral bodies.
- On urodynamic evaluation an almost equal number of individuals manifest either an upper or a lower motor neuron lesion (35% vs. 40%, respectively); 25% have no sign of any denervation.
- Management depends on the specific type of neurourologic dysfunction seen on urodynamic testing.

Recommendations

Because most children who are diagnosed with this condition have a neurologic deficit, urodynamic testing is mandatory at the time of diagnosis. **Renal ultrasonography and nuclear or conventional cystography should be included as part of the evaluation process, especially if the child has a history of urinary tract infection or findings of an upper motor neuron lesion on urodynamic testing.** Additional imaging studies may be required based on the child's history and findings from baseline studies.

Management depends on the specific type of neurourologic dysfunction seen on urodynamic testing. Anticholinergic agents should be given to children with upper motor neuron findings of detrusor overactivity, whereas CIC and

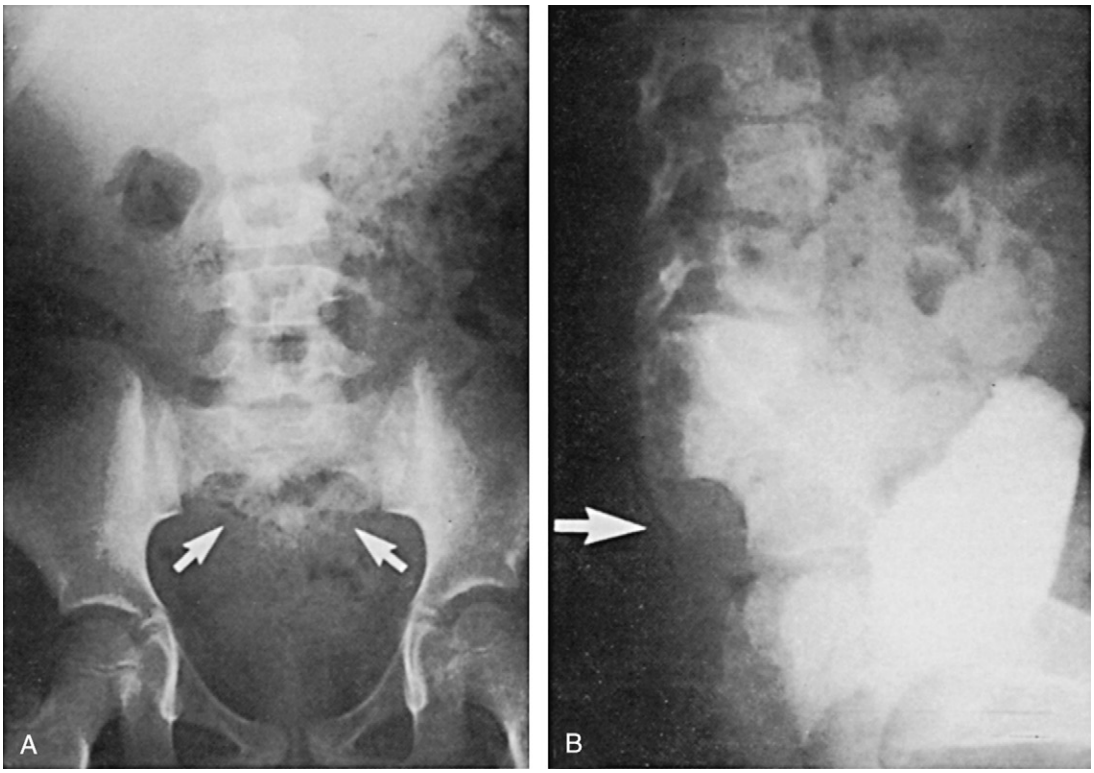


Figure 128–17. The diagnosis of partial or complete sacral agenesis *(arrows)* is easily confirmed on an anteroposterior (**A**) or lateral (**B**) radiograph of the spine if bowel gas obscures the sacral area. (From Bauer SB. Early evaluation and management of children with spina bifida. In: King LR, editor. Urologic surgery in neonates and young infants. Philadelphia: WB Saunders; 1988. p. 283–310.)

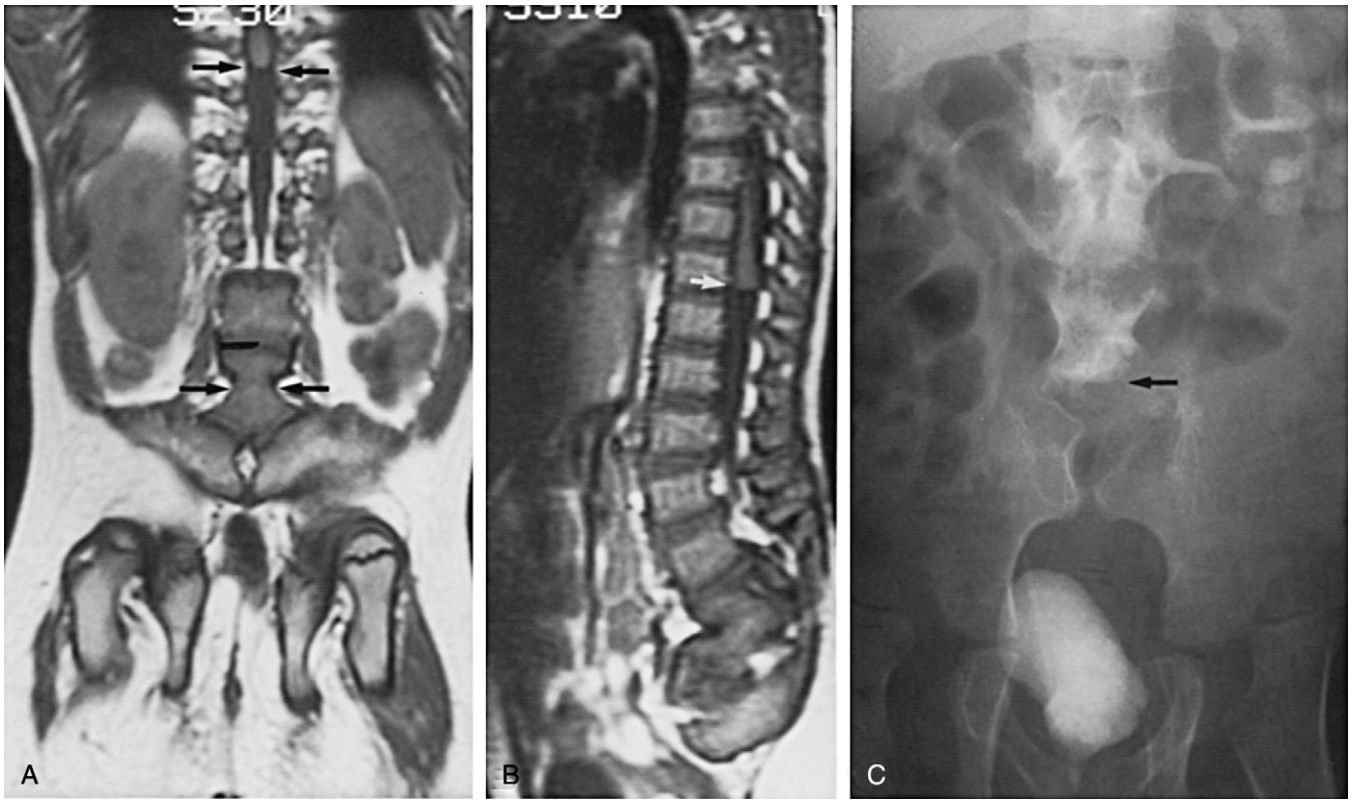


Figure 128–18. Coronal (**A**) and sagittal (**B**) MR images in a 10-year-old boy with sacral agenesis beginning at L5. Note the squared lower limit of the cord adjacent to T11 (**A,** *upper arrows;* **B,** *white arrow*) and the two sacroiliac joints (**A,** *lower arrows*), which are in the midline because of absence of the sacrum. **C,** An anteroposterior radiograph from an excretory urogram shows no vertebral bodies below L4 *(arrow)*.

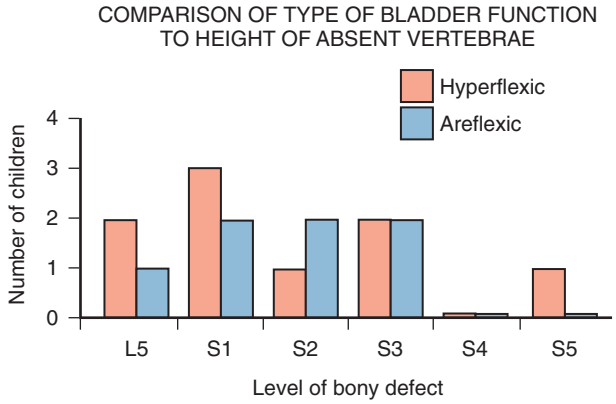


Figure 128–19. Bladder contractility is unrelated to the number of absent vertebrae. (From Bauer SB. Early evaluation and management of children with spina bifida. In: King LR, editor. Urologic surgery in neonates and young infants. Philadelphia: WB Saunders; 1988. p. 283–310.)

α-sympathomimetic medications may have to be given to individuals with lower motor neuron deficits who cannot empty their bladders or stay dry between catheterizations. When anticholinergic medication is ineffective in controlling the overactive detrusor, augmentation cystoplasty may be required to attain an adequate organ for urinary storage. Failure of α-sympathomimetic agents may require either endoscopic injection of bulking agents or even artificial urinary sphincter implantation to increase bladder outlet resistance. The bowels manifest a similar picture of dysfunction and need as much characterization and treatment as the lower urinary tract. Anorectal manometry has identified abnormalities in the internal anal sphincter and in voluntary anal sphincter squeeze pressure, leading to weakness of the muscle and concomitant fecal incontinence (Morera and Nurko, 2003). It is important to identify these individuals as early as possible so that they can become continent and out of diapers at an appropriate age, thus avoiding the social stigma of fecal or urinary incontinence.

Imperforate Anus

Imperforate anus is a condition that can occur alone or as part of a constellation of anomalies that have been called the VATER or VACTERL syndrome (Barry and Auldist, 1974). This mnemonic denotes all the regions or structures that can possibly be affected (*v*ertebral, *a*nal, *c*ardiac, *t*racheo-*e*sophageal fistula, *r*enal, *l*imb). The incidence of anorectal malformations varies between 1 in 4000 to 1 in 5000 live births (Templeton and O'Neill, 1986). There is a male predominance of 1.5:1. The majority of female patients have low lesions, whereas males tend to have high ones (Santulli et al, 1971). Several classification systems have been devised, but the most commonly used one is the Wingspread Workshop on Anorectal Malformations (Table 128–5) (Shaul and Harrison, 1997). This format attempts to divide the lesions into high, intermediate, or low, depending on whether the rectum ends above, at, or below the levator ani muscle, respectively. The relative incidence for the various levels of the defect is 36% high, 14% intermediate, 47% low, and 1% a cloacal lesion. Imperforate anus may be part of a spectrum of hindgut abnormalities that include sacral agenesis and even a presacral mass or meningocele recently labeled as Currarino syndrome (Currarino et al, 1981; Hagan et al, 2000), which has genetic implications (Ross et al, 1998).

Table 128–5.

Wingspread Classification of Anorectal Malformations

	FEMALE	MALE
High	Anorectal agenesis With rectovaginal fistula Without fistula Rectal atresia	Anorectal agenesis With rectourethral (prostatic) fistula Without fistula Rectal atresia
Intermediate	Rectovestibular fistula Rectovaginal fistula Anal agenesis without fistula	Rectovestibular urethral fistula Anal agenesis without fistula
Low	Anovestibular fistula Anocutaneous fistula Anal stenosis Cloacal malformation Rare malformation	Anocutaneous fistula Anal stenosis Rare malformation

Associated Findings

A fistulous communication with the lower urinary tract is a common occurrence, related in part to the sex of the child and the extent of the lesion: 87% of male and 79% of female infants with a high or intermediate lesion have a connection, whereas 7% of male and 10% of female children with a low lesion have such a communication (Templeton and O'Neill, 1986; Holschneider et al, 1994). Urinary tract abnormalities have been noted in 26% to 52% of affected children, with renal agenesis (primarily left-sided) and vesicoureteral reflux as the most common associated findings (Parrott, 1985). Again, the highest incidence of an abnormality is in those children with a high (70%) versus a low (infralevator) (35%) lesion (Shaul and Harrison, 1997; Emir and Soylet, 1998), with boys more prone than girls to having an anomaly (50% vs. 29%) (Metts et al, 1997). Spinal bony abnormalities range in incidence from 30% to 44%, but patients with a high lesion are more likely to be affected (48% to 54%) than those with a low lesion (15% to 27%) (Carson et al, 1984; Tsakayannis and Shamberger, 1995; Long et al, 1996). Spinal cord abnormalities including a tethered cord, thickened or fatty filum terminale, and a lipoma have been noted in 18% to 50% of patients, with the incidence varying proportionately in relation to the height of the rectal lesion (Shaul and Harrison, 1997). **Not all patients with a spinal cord abnormality have a bony defect, so intraspinal imaging is mandatory to ensure the presence of a normal spinal cord, especially in cases of high lesions** (Rivosecchi et al, 1995). On occasion, an abnormal spinal cord can be found in patients even without one of these commonly associated other anomalies. Neurogenic bladder dysfunction is a frequent finding (Kakizaki et al, 1994), usually manifesting as incontinence, but its occurrence is rare when no spinal cord malformation exists (Hulthen de Medina et al, 2004) (Fig. 128–20). It often manifests when the child is older and the parents have difficulty with toilet training. It is not certain whether the dysfunction is caused by a spinal cord defect or by trauma to the nerves supplying the lower urinary tract or the pelvic floor musculature occasioned during surgery to repair the spinal cord or rectal defect (Parrott and Woodard, 1979). With the advent of the Peña posterior sagittal midline approach, the latter etiology is less likely (Peña, 1986; Boemers et al, 1994). Despite careful dissection



Figure 128–20. **A** and **B,** A 1-year-old girl with an imperforate anus and bony vertebral abnormalities has a tethered cord and bilateral hydronephrosis on MRI. **C,** Voiding cystourethrogram reveals significant trabeculation and reflux on the left. **D,** Excretory urogram demonstrates bilateral hydronephrosis secondary to the reflux on the left and a ureterovesical junction obstruction on the right. Subsequent urodynamic study revealed poor detrusor compliance and dyssynergy.

techniques, 37% still have long-term problems with fecal incontinence (Peña and Hong, 2000).

Neonatal Assessment

Initial evaluation in the neonatal period should include a careful inspection of the perineum looking for a fistulous site from the bowel, an examination of the upper and lower extremities, and an assessment of the spine and spinal cord (Carson et al, 1984; Mosiello et al, 2003). A prone cross-table lateral image with the child held in that position for 3 minutes and a radiopaque marker placed on the perineum will help delineate the distance from the end of the rectum to the skin in order to classify the extent of the rectal defect. Gas, meconium, or a gram-negative infection in the urine strongly suggests a rectal/urinary tract fistula, which then necessitates a divided colostomy very early in the postnatal period. Once the child is stable clinically, radiologic investigation of the urinary tract is begun, first with renal ultrasonography and then with VCUG, to define the presence of an abnormality and discover any clues for possible neurogenic bladder dysfunction.

Vertebral bony anomalies, especially sacral level lesions, often signify an underlying spinal cord abnormality (Boemers et al, 1996). Thus any bony abnormality warrants ultrasonography of the spine if the child is younger than 3 months of age because the vertebral bodies have not ossified and a spinal MRI to rule out any abnormal intraspinal process (see Fig. 128–20) (Barnes et al, 1986; Tunell et al, 1987; Emir and Soylet 1998; Karrer et al, 1988; Mosiello et al, 2003). Urodynamic studies including sphincter electromyography are reserved for those children with either a bony abnormality of the spine, a spinal cord defect, or the telltale signs of dysfunction on VCUG or renal ultrasonography (Taskinen et al, 2002; Mosiello et al, 2003). These studies should be conducted early in infancy before the child has had any definitive surgery for the imperforate anus and again after a pull-through operation has been performed on the rectum to determine, respectively, the true incidence of neurogenic bladder dysfunction and any changes that might have occurred as a result of the surgery. The presence of an abnormality on urodynamic testing in early infancy may warrant either intervention at that time to correct a spinal cord defect or watchful waiting to determine whether the lesion is progressive. Urodynamic studies are repeated subsequently or performed for the first time if secondary urinary or fecal incontinence ensues (Taskinen et al, 2002).

The most common finding on urodynamic testing is an upper motor neuron lesion with an overactive detrusor and/or DSD (Boemers et al, 1994; Taskinen et al, 2002), but a lower motor neuron lesion with an acontractile detrusor and a denervated sphincter may be seen as well (see Fig. 128–20) (Greenfield and Fera, 1991; Taskinen et al, 2002). EMG assessment of the perianal musculature at this time helps determine the exact location of the future anus. In addition, it can provide precise information about the innervation to the levator ani muscle and its competence to function as a sphincter. The posterior midline approach espoused by Peña (1986) minimizes the chances of injuring the pelvic nerves that innervate the pelvic floor muscles and therefore reduces the risk of an iatrogenic cause for neurogenic bladder dysfunction.

CENTRAL NERVOUS SYSTEM INSULTS

Cerebral Palsy

Pathogenesis

Cerebral palsy is a nonprogressive injury of the brain occurring in the perinatal period that results in either a neuromuscular disability, a specific symptom complex, or cerebral dysfunction (Kuban and Leviton, 1994). Its incidence is approximately 1.5 per 1000 births, but the incidence is increasing as smaller and younger premature infants survive in intensive care units (Kuban and Leviton, 1994). The condition is usually caused by a perinatal infection (e.g., sepsis, meningoencephalitis) or by a period of anoxia (or hypoxia) that affects the CNS (Nelson and Ellenberg, 1986; Naeye et al, 1989). It most commonly appears in infants who were premature, weighed less than 2 kg at birth, had intraventricular hemorrhage, and received mechanical ventilation for a prolonged time in the postnatal period and in premature infants weighing more than 2 kg who experienced a neonatal seizure (Kim et al, 1999). Maternal urinary infection in the later stages of pregnancy increases the risk of having an affected child by four to five times (Polivka et al, 1997).

Diagnosis

Affected children have delayed gross motor development, abnormal fine motor performance, altered muscle tone, abnormal stress gait, and exaggerated deep tendon reflexes. These findings can vary substantially, from obvious to very subtle when no discernible lesion is present, unless a careful neurologic examination is performed. These abnormalities may not manifest in the postnatal period, but they do become evident over time, because myelination of axons and maturation of neurons in the basal ganglia are required before spasticity, dystonia, and athetosis become apparent (Kyllerman et al, 1982). The lesions are classified according to which extremities are involved (monoplegia, hemiplegia, diplegia, and quadriplegia) and what kind of neurologic dysfunction is present (spastic, hypotonic, dystonic, athetotic, or a combination thereof). Among the more overtly affected individuals, spastic diplegia is the most common of the five types of dysfunction that characterize this disease, accounting for almost two thirds of the cases (Kuban and Leviton, 1994).

Findings

Most children with cerebral palsy develop total urinary control. Incontinence is a feature in some, but the exact incidence has never been truly determined (McNeal et al, 1983; Decter et al, 1987). In a recent survey of questionnaires sent to over 600 families with an affected child aged 4 to 18 years, 23.5% had persistent urinary incontinence (Roijen et al, 2001). When urinary continence was achieved, its development was delayed when compared with normal children of similar age. With further analysis of the data, 80% of children with spastic diplegia, 54% with tetraplegia, and 38% with low intellectual capacity attained continence. The presence of incontinence is often related to the extent of the physical impairment, because the handicap prevents the child from getting to the bathroom on time, causing an episode of wetting (Murphy et al, 1995). A number of children have such a severe degree of mental retardation that they are not trainable. They either do not recognize the need to void or cannot relate this fact to caregivers early enough to be toileted successfully (Roijen et al, 2001). The majority, however, have sufficient intelligence to learn basic societal protocols with patient and persistent handling. When continence is achieved (usually at a later than expected age), diurnal continence is attained first with nocturnal continence occurring within the subsequent year (Roijen et al, 2001). Therefore, urodynamic evaluation is reserved for children who appear to be trainable and do not seem to be hampered too much by their physical impairment but who have not achieved continence by late childhood or early puberty.

In one review (Decter et al, 1987), urodynamic studies were performed in 57 children with cerebral palsy (Table 128–6). **Forty-nine (86%) had the expected picture of a partial upper motor neuron type of dysfunction,** with exaggerated sacral reflexes, an overactive detrusor and/or DSD (Fig. 128–21), even though they manifested voluntary control over voiding. Six (11%) of the 57 had evidence of both upper and lower motor neuron denervation with an acontractile detrusor or abnormal motor unit potentials on sphincter EMG assessment (Table 128–7). Most of the children who exhibited these latter findings were found to have an episode of cyanosis in the perinatal period when their records were analyzed on a retrospective basis (Table 128–8). Therefore, a lower motor neuron lesion may be seen in addition to the expected upper motor neuron dysfunction. Similar findings have been noted subsequently (Mayo, 1992; Reid and Borzyskowski, 1993).

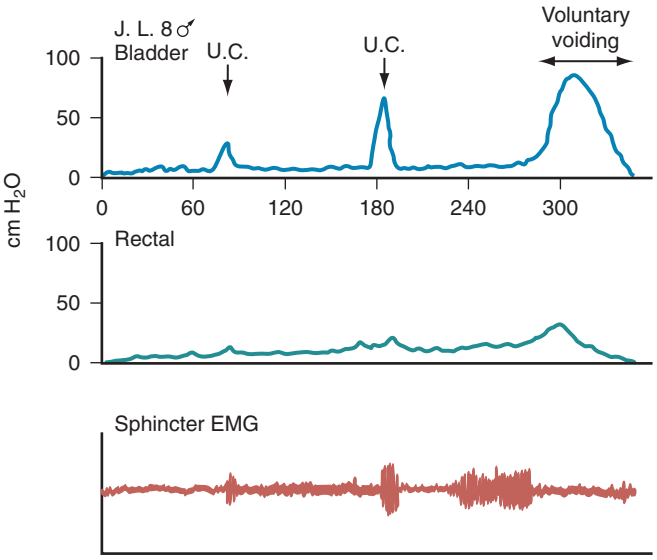


Figure 128–21. Electromyogram (EMG) of an 8-year-old boy with spastic diplegia shows a typical partial upper motor neuron type bladder with uninhibited contractions (U.C.) associated with increased sphincter activity but normal voiding dynamics at capacity. Wetting is caused by these contractions when they are unaccompanied by the heightened sphincter activity.

Table 128–6.

Lower Urinary Tract Function in Cerebral Palsy

TYPE	NO. PATIENTS	%
Upper motor neuron lesion	49	86
Mixed upper + lower motor neuron lesion	5	9.5
Incomplete lower motor neuron lesion	1	1.5
No urodynamic lesion	2	3

Adapted from Decter RM, Bauer SB, Khoshbin SJ, et al. Urodynamic assessment of children with cerebral palsy. J Urol 1987;138:1110.

Table 128–7.

Urodynamic Findings in Cerebral Palsy*

TYPE OF LESION	NO. PATIENTS
Upper Motor Neuron	
Uninhibited contractions	35
Detrusor sphincter dyssynergy	7
Hyperactive sacral reflexes	6
No voluntary control	3
Small-capacity bladder	2
Hypertonia	2
Lower Motor Neuron	
Excessive polyphasia	5
↑ Amplitude + ↑ duration potentials	4

*Some patients had more than one finding.
Adapted from Decter RM, Bauer SB, Khoshbin S, et al. Urodynamic assessment of children with cerebral palsy. J Urol 1987;138:1110.

In two more recent reviews **of 65 children with cerebral palsy undergoing urodynamic studies** (Bross et al, 2004; Karaman et al, 2005), **abnormal bladder and urethral sphincter function was found in almost all.** In the first study involving 29 (Bross et al, 2004), 23 had incontinence and/or urinary tract infection whereas 6 were asymptomatic; urodynamic studies demonstrated poor compliance in 21 of the 23 symptomatic and 2 of the 6 asymptomatic children, an overactive detrusor in all symptomatic and 5 of 6 asymptomatic children, and high leak point pressure in 16 of 23 and 4 of 6 symptomatic and asymptomatic children, respectively. VCUG revealed bladder trabeculation in 58% and reflux in 9% of symptomatic children, and trabeculation in 50% but no reflux in the asymptomatic children. In the other study (Karaman et al, 2005), 66% had dysfunctional voiding symptoms, including 47.2% with daytime incontinence and 44.4% with difficulty urinating. Neurogenic detrusor overactivity was present in 47.2%, and dyssynergy between the bladder and sphincter was noted in 11%. In a meta-analysis of all published reports of urodynamic findings in children with cerebral palsy, detrusor overactivity was seen in 80%, dyssynergy between the bladder and sphincter in 5%, and normal function in only 12% (Decter et al, 1987; Mayo and Burns, 1990; Reid et al, 1993; Bross et al, 2004; Karaman et al, 2005). From these reports it is apparent that urodynamic studies can be very revealing in all children, whether they have urinary symptoms (Bross et al, 2004), but are especially useful if frequent toileting or initial anticholinergic treatment fails to improve incontinence, the child develops urinary infection, or renal ultrasonography reveals hydronephrosis. Upper urinary tract imaging is usually normal even in children with upper motor neuron lesions (Brodak et al, 1994).

Table 128–8.

Perinatal Risk Factors in Cerebral Palsy

FACTOR	UPPER MOTOR NEURON LESION (NO. PATIENTS)	LOWER MOTOR NEURON LESION (NO. PATIENTS)
Prematurity	10	1
Respiratory distress/ arrest/apnea	9	2
Neonatal seizures	5	—
Infection	5	—
Traumatic birth	5	—
Congenital hydrocephalus	3	—
Placenta previa/abruption	2	2
Hypoglycemia ± seizures	2	—
Intracranial hemorrhage	2	—
Cyanosis at birth	1	3
No specific factor noted	15	—

Adapted from Decter RM, Bauer SB, Khoshbin S, et al. Urodynamic assessment of children with cerebral palsy. J Urol 1987;138:1110.

Key Points: Cerebral Palsy

- Cerebral palsy is a nonprogressive injury of the brain occurring in the perinatal period that results in either a neuromuscular disability, a specific symptom complex, or cerebral dysfunction.
- Affected children have delayed gross motor development, abnormal fine motor performance, altered muscle tone, an abnormal stress gait, and exaggerated deep tendon reflexes.
- Most children with cerebral palsy develop total urinary control.
- The presence of incontinence is often related to the extent of the physical impairment; abnormal bladder and urethral sphincter function was found in almost all.
- Treatment usually centers on abolishing the overactive detrusor using anticholinergic medication, but residual urine must be monitored closely to ensure complete evacuation with each void.

Recommendations

Treatment usually centers on abolishing the overactive detrusor using anticholinergic medication, but residual urine must be monitored closely to ensure complete evacuation with each void. CIC may be required for those who cannot empty their bladder. Selective dorsal rhizotomy has improved bladder capacity, reduced the detrusor overactivity, and increased compliance, thus rendering the patient more continent, in a selected group of children who failed to respond to less invasive measures (Houle et al, 1998). The risk of neurourologic deterioration from this procedure is extremely low, with less than 5% developing incontinence if careful mapping of dorsal nerve roots are identified (Huang, 1997; Steinbok and Schrag, 1998; Liu et al, 1999). Upper and lower urinary tract imaging is not recommended unless urinary tract infection has occurred (Reid and Borzyskowski, 1993).

Traumatic Injuries to the Spine

Diagnosis

Despite increased exposure to and the potential for traumatic spinal cord injuries, **such injuries are rarely encountered in children. The incidence in Sweden is 2.6 cases per million children per year** (Augutis and Levi, 2003). **The incidence tends to increase geometrically with age** (Anderson and Schutt, 1980) (Fig. 128–22). When an injury does occur, it is more likely to happen in a male than a female child, and it is usually the result of a motor vehicle or bicycle accident (24% to 52%), a fall from a high place, a gunshot wound, or a diving or sports incident (Cass et al, 1984; Hadley et al, 1988; Decter and Bauer, 1993; Brown et al, 2001; Augutis and Levi 2003; Cirak et al, 2004). The type of causative injuries varies with age, with infants more prone to an injury from a motor vehicle accident (71%), toddlers and children injured secondary to a fall (48% and 34%, respectively) and adolescents having a sports-related event (29%) (Cirak et al, 2004). An injury may also occur iatrogenically after surgery to correct scoliosis, kyphosis, or other intraspinal processes or congenital aortic anomalies or after ligation of a patent ductus arteriosus (Cass et al, 1984; Batista et al, 1995). Neonates are particularly prone to a hyperextension injury during a high forceps delivery (Adams et al, 1988; Lanska et al, 1990). Among younger children, girls are affected as often as boys (Ruge et al, 1988).

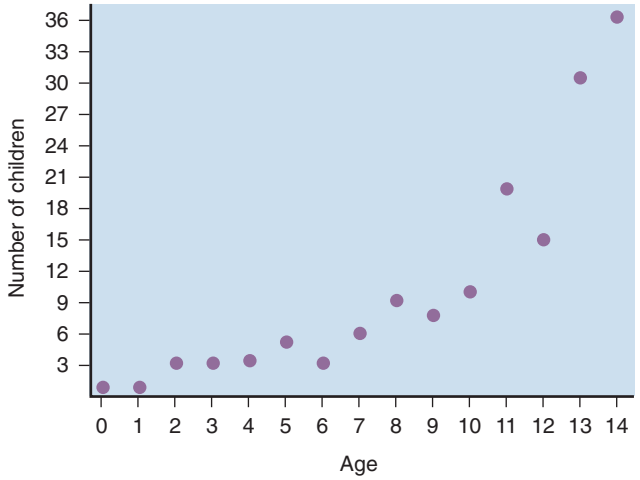


Figure 128–22. Increasing frequency of spinal injury with age. (From Anderson JM, Schutt AH. Spinal injury in children: a review of 156 cases seen from 1958 through 1980. Mayo Clin Proc 1980;55:499–504.)

Pathogenesis

Spinal cord injuries in children are intrinsically different from those in adults because of a variety of factors, including the mechanism of injury and the difference in configuration of the brainstem and spinal cord in children compared with adults. In addition, the horizontal versus vertical orientation of the facet joints in vertebral bodies that predisposes to anteroposterior subluxation in children, the delayed supportive effect of the paraspinous musculature and ligaments, and the relative heaviness of the head, which causes a fulcrum of maximal flexion of the upper cervical region in infants and young children, all contribute to a high degree of hypermobility that places the child's spinal cord at risk for ischemic necrosis (Decter and Bauer, 1993).

Key Points: Traumatic Injuries to the Spine

- The incidence in Sweden is 2.6 cases per million children per year. The incidence increases geometrically with age.
- Spinal cord injuries in children are intrinsically different from those in adults because of a variety of factors, including the mechanism of injury and the difference in configuration of the brainstem and spinal cord in children compared with adults.
- Patients with an upper thoracic or cervical lesion are likely to exhibit autonomic dysreflexia with a spontaneous discharge of α_1-stimulants during bladder filling and with contractions of the detrusor.
- Monitoring of blood pressure and availability of α-antagonists are mandatory during VCUG or urodynamic studies.
- Upper spinal cord injuries produce an upper motor neuron type lesion with an overactive detrusor and DSD. The potential danger from this outflow obstruction is obvious.

Findings

The lower urinary tract dysfunction that ensues is not likely to be an isolated event but is usually associated with loss of sensation and paralysis of the lower limbs. Radiologic investigation of the spine may not reveal any bony abnormality, although momentary subluxation of osseous structures resulting from the elasticity of the vertebral ligaments can result in a neurologic injury (Pollack et al, 1988). This condition has been seen only in children (usually younger than 8 years old) and has been labeled *s*pinal *c*ord *i*njury *w*ith*o*ut *r*adiologic *a*bnormality (SCIWORA) (Pang and Wilberger, 1982; Pang and Pollack, 1989). Overall, SCIWORA can account for up to 38% of spinal cord injuries in children (Brown et al, 2001). Myelography and computed tomography show swelling of the cord below the level of the lesion (Adams et al, 1988; Lanska et al, 1990). **Often, what appears to be a permanent lesion initially turns out to be a transient phenomenon with time.** Although sensation and motor function in the lower extremities may be restored relatively quickly, the dysfunction involving the bladder and rectum may persist considerably longer.

During the acute phase of the injury the bladder is often acontractile and the urethral sphincter nonreactive, although normal-appearing bioelectric potentials can be recorded on sphincter EMG (spinal shock). Over a variable period of time, detrusor

contractility and sphincter reactivity return as spinal cord edema subsides. With this return of function, an overactive detrusor and bladder-sphincter dyssynergy develop if the lateral reticulospinal cord pathways to and from the brainstem have been disrupted. When the lesion affects the cauda equina there is probably little to no return of bladder or urethral sphincter function. Sacral sensation and peripheral reflexes are not good indicators of ultimate lower urinary tract function (Shenot et al, 1998). Over time, the predominant urodynamic pattern in patients with a thoracic-level lesion is an overactive detrusor with DSD, high voiding pressures, eventual hydronephrosis, and vesicoureteral reflux. Often children exhibit a highly compliant bladder for a portion of bladder filling but then have C-fiber–mediated, small, ineffective rhythmic contractions of the detrusor with simultaneous waxing and waning of external urethral sphincter activity. Some urinary leakage may occur with these contractions, but in general the bladder does not empty with them. **Patients with an upper thoracic or cervical lesion are likely to exhibit autonomic dysreflexia with a spontaneous discharge of α_1-stimulants during bladder filling and with contractions of the detrusor. Monitoring of blood pressure and availability of α-antagonists are mandatory during VCUG or urodynamic studies** (Perkash, 1997; Vaidyanathan et al, 1998b).

Management

If urinary retention occurs immediately after the injury, an indwelling Foley catheter is passed into the bladder and left in place for as short a time as possible, until the patient's condition is stable and aseptic intermittent catheterization can be started safely on a regular basis (Guttmann and Frankel, 1966; Barkin et al, 1983). There is no difference in the incidence of urinary infection or in the development of stones in patients using sterile versus clean catheterization techniques to empty the bladder (Prieto-Fingerhut et al, 1997; VanHala et al, 1997). Rates of infection range as high as 60% to 80% (Biering-Sorensen et al, 1999), and stone formation occurs in 1.5% to 3% within the first 5 years after the trauma (Donnellan and Bolton, 1999; McKinley et al, 1999). When the child starts to void again, the timing of catheterization can be regulated so that it is used as a means of measuring the residual urine after a spontaneous void. Residual urine volumes of 25 mL or less are considered safe enough to allow reducing the frequency or even stopping the catheterization program (Barkin et al, 1983). After 4 to 6 weeks, if there is no improvement in lower urinary tract function, urodynamic studies are conducted to determine whether the condition is the result of spinal shock or an actual nerve root or spinal cord injury. An acontractile detrusor is not uncommon under these circumstances (Iwatsubo et al, 1985). On the other hand, EMG recording of the sphincter often reveals normal motor units without fibrillation potentials but absent sacral reflexes and a nonrelaxing sphincter with bladder filling, a sign that transient spinal shock has occurred (Iwatsubo et al, 1985). The outcome of this situation is guarded but good, because most cases resolve completely as edema of the cord in response to the injury subsides, leaving no permanent damage (Iwatsubo et al, 1985; Fanciullacci et al, 1988).

If and when bladder function returns and emptying is incomplete, it has been shown in the cat (Xiao et al, 1999) that peripheral L7 dermatome stimulation initiates a micturition reflex without DSD. In a preliminary study of 15 adults with spinal cord injury, detrusor overactivity, and DSD, the creation of an artificial somatic/CNS/autonomic reflex pathway resulted in satisfactory bladder control in 67% of patients. Follow-up urodynamic study revealed a change to almost normal storage and synergic voiding without DSD (Xiao et al, 2003). A more recent study showed satisfactory bladder control in 75% of patients with complete suprasacral spinal cord injury within 6 to 12 months. However, the mean and median time since the injury was 9 months, so the time from injury may have been a factor in this study (Lin et al, 2009). Incomplete emptying may be enhanced by the judicious use of α-sympatholytic agents (Al-Ali et al, 1999). **The goal is balanced voiding at pressures lower than 40 cm H_2O,** which reduces the 30% risk for urinary tract deterioration seen in poorly managed patients (Giannantoni et al, 1998; Kim et al, 1998). If this cannot be achieved, then CIC is continued. Anticholinergics, either orally or intravesically (Vaidyanathan et al, 1998a; Wein, 1998), or capsaicin (an inhibitor of C-fiber stimulation [Wiart et al, 1998]) have been added and are effective in reducing an overactive detrusor, but at the cost of significant side effects. Alternative treatments that have been effective to ensure complete emptying at low pressure include external urethral sphincterotomy (Kim et al, 1998), urethral stent placement (Chancellor et al, 1999), or injection of botulinum-A toxin into the external sphincter (Schurch et al, 1997, 2000; Kuo, 2003; Tai et al, 2005). In some cases, a continent catheterizable abdominal urinary stoma may be created to facilitate self-catheterization in patients with low cervical or upper thoracic lesions who cannot easily catheterize themselves, in order to minimize the embarrassment of periodic genital organ exposure when care providers need to repeatedly catheterize the bladder (Sylora et al, 1997).

Recommendations

Most permanent traumatic injuries involve either the upper thoracic or the cervical spinal cord but some affect the cauda equina region. The sacral cord injury most likely produces a lower motor neuron deficit of the striated urethral sphincter that usually leads to low pressure bladder emptying with little risk of upper urinary tract deterioration. However, it probably necessitates medical and/or surgical therapy to achieve continence. On the other hand, upper spinal cord injuries produce an upper motor neuron type lesion with an overactive detrusor and DSD. The potential danger from this outflow obstruction is obvious (Donnelly et al, 1972). Substantial residual urine volumes, high-pressure reflux, urinary infections, and their sequelae are the leading causes of long-term morbidity and mortality in patients with spinal cord injury (Giannantoni et al, 1998). Even patients who voluntarily urinate and are continent or who involuntarily but spontaneously void to completion are not immune to urinary tract changes (Decter and Bauer, 1993). Urodynamic studies are imperative to identify which patients are at risk (Barkin et al, 1983). These studies should be performed within 2 to 3 months after the injury, again 6 to 9 months later, and possibly at 2 years after the trauma to determine the stability of lower urinary tract function, the need for continued CIC, and whether adjuvant drug or surgical therapy should be added (or continued) to achieve good long-term success. When these measures are employed judiciously, effective management can be achieved (Pannek et al, 1997). Renal ultrasonography early in the course and VCUG if signs of bladder outlet obstruction are present on urodynamic testing or if recurrent urinary infection ensues are also recommended. Radionuclide cystography is indicated if the patient has repeated urinary tract infection or develops hydronephrosis (Phillips et al, 1997). Because stone formation can be insidious, periodic imaging of the kidneys and bladder is necessary. Early identification and proper management may prevent the signs and effects of bladder outlet obstruction before they become

apparent on radiographic examination of the urinary tract (Pearman, 1976; Ogawa et al, 1988; Watanabe et al, 1996).

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chapter 129

Urinary Tract Reconstruction in Children

Mark C. Adams, MD, FAAP ● David B. Joseph, MD, FACS, FAAP

The "Functional" Urinary Tract
Evaluation of the Patient
Preparation of the Patient
Antireflux
Bladder Neck Reconstruction
Augmentation Cystoplasty
Continent Urinary Diversion
Continence Mechanisms and Catheterizable Segments
Antegrade Continence Enemas
Urinary Refunctionalization
Summary

The goal of this chapter is to review techniques for lower urinary tract reconstruction in pediatric patients and the principles that guide their use. In general, such intervention is taken to reestablish or to construct anew a system that protects renal function, avoids significant infection, and eventually provides for urinary continence. Those, in simplistic terms, are functions of a "normal" urinary tract.

The scope of the chapter is large. Many specific techniques are presented in detail, particularly those used primarily in the pediatric population. When techniques have been used more extensively in adults, descriptions are brief with focus on adaptations for and results of use in children. Urinary diversion, both temporary and permanent with bowel, is discussed elsewhere in this text. Augmentation cystoplasty is reviewed in detail from preoperative evaluation and surgical techniques to long-term results and newer alternatives. In few areas of urology have intestinal segments been used more extensively than for bladder augmentation in pediatric patients. This experience with augmentation cystoplasty established the groundwork for later work with continent urinary diversions and orthotopic neobladders.

Complex patients with bladder dysfunction may have bladder neck and external sphincteric problems as well. This chapter covers techniques to increase native outflow resistance in the pediatric population. Certain techniques, such as Young-Dees-Leadbetter bladder neck repair, are presented elsewhere in this section of this text. Others (i.e., sling, collagen injection, and artificial urinary sphincter) have been used more extensively in adults; again, in that setting, the focus in this chapter is on adaptations of those procedures for children. **Perhaps the most important contribution affecting lower urinary tract reconstruction was the introduction of clean intermittent catheterization (CIC) by Lapides and colleagues** (1972, 1976). Because many pediatric patients with bladder and sphincteric dysfunction will not void adequately after reconstruction, a reliable means for easy catheterization without discomfort is an important part of their care. The work of Mitrofanoff (1980) stimulated interest in continent abdominal wall stomas within pediatric urology, and several effective techniques have since been developed. That experience serves as a nice lead into a discussion of continent urinary diversion in children because construction of an effective efferent limb that provides continence and a reliable means for catheterization is often the most challenging aspect of such diversion. "Pure" continent urinary reservoirs, such as Indiana and Kock pouches, are occasionally performed in children, and that experience is reviewed. More frequently in children, some of the patient's native urinary tract is used in the reconstruction. This is done to maintain as much urothelium-lined tissue in the urinary tract as possible, to minimize the amount of needed bowel, and, potentially at least, to minimize the morbidity to the patient. The result then is a spectrum of repairs between bladder augmentation and continent urinary diversion but rarely a continent urinary reservoir in the classic sense.

Several decades ago, many such reconstructions were performed after previous, permanent urinary diversion with use of bowel (Hendren, 1998). Today, however, few children are initially treated with permanent diversion. **Most reconstructive procedures are now undertaken primarily to correct a problem in the native urinary tract (hydronephrosis, infection, incontinence) unresponsive to medical management or after temporary diversion. Children with bladder and sphincteric dysfunction are among the most complex seen in pediatric urology; among others, patients with diagnoses such as exstrophy, persistent cloaca and urogenital sinus, posterior urethral valves, bilateral single ectopic ureters, and prune-belly syndrome may be**

involved. For most pediatric urologists, patients with myelomeningocele make up the majority of patients requiring this type of surgical intervention. Consequently, many of the results discussed herein focus on the neurogenic population.

Many children with anomalies affecting the bladder and outlet are managed so that surgical intervention is not necessary, and a primary goal of pediatric urologists is to minimize the number of children requiring many of these techniques. Once conservative, medical therapy fails, surgical reconstruction remains an important and effective tool. When reconstruction is considered, it is imperative that the patient be thoroughly evaluated. Each child is unique, and the particular pathophysiologic changes must be understood so that surgical techniques available may be used thoughtfully to optimize results while minimizing morbidity. **The most important factor influencing the outcome of urinary tract reconstruction in children is the commitment of the patient and family to achieving good care.** Determining that commitment may at times be difficult, but its importance should not be underestimated.

THE "FUNCTIONAL" URINARY TRACT

The renal pelves and ureters should empty effortlessly into the bladder without any increase in pressure or element of obstruction. The normal ureterovesical junction prevents vesicoureteral reflux. Bladder physiology can be characterized as two different dynamic phases: passive and active. During the passive storage phase the bladder functions as a reservoir, allowing an appropriate volume of urine to be stored without leakage while maintaining low pressure. In the active voiding phase the bladder contracts for elimination of urine.

Basic Bladder Function

Passive: Storage

Appropriate urinary storage requires a reservoir that is compliant and of age-appropriate capacity. Age-based capacity may be estimated by formulas proposed by Koff (1983):

$$\text{Volume (mL)} = 30(\text{age in years} + 2)$$

or by Kaefer and associates (1997c) for children younger than 2 years:

$$\text{Volume (mL)} = 32(2 \times \text{age in years} + 2)$$

and for children older than 2 years:

$$\text{Volume (mL)} = 30(\text{age in years} \div 2 + 6)$$

Compliance is defined as the change in bladder volume divided by the change in pressure. Normally, the bladder is considered a highly compliant vesicle in that it will accommodate an increasing volume of urine without a corresponding increase in intravesical pressure. Multiple factors contribute to this property. Initially, the bladder is in a collapsed state that allows the storage of urine at low pressure by simple unfolding. As it expands, detrusor properties of elasticity and viscoelasticity take effect. Elasticity allows the detrusor muscle to stretch without an increase in tension until it reaches a critical volume. This volume should be greater than the expected bladder capacity. The viscoelastic bladder property allows a subtle continuous pressure change that occurs with bladder filling. It is associated with a small rise in pressure as the bladder stretches, balanced by a corresponding rapid pressure decay (Zinner et al, 1976; Wagg and Fry, 1999). With slow natural bladder filling there should be no net change in bladder pressure until capacity is reached. This viscoelastic bladder property is also defined as stress relaxation and can be overcome when the rate of bladder filling exceeds normal parameters, resulting in a pattern consistent with poor compliance (Mundy, 1984; Finkbeiner, 1999). This artifact of testing is often noted when urodynamic assessment is performed at an excessive filling rate for the child's age or size (Bauer and Joseph,1990; Joseph, 1992). These properties of elasticity and viscoelasticity will eventually be overcome in every child, and at that point the bladder pressure rapidly rises. **Favorable dynamics for urine storage include a thin bladder wall with an appropriate composition of muscle and collagen allowing expression of normal elastic and viscoelastic properties.** Factors adversely affecting normal compliance include detrusor hypertrophy, fibrosis, outlet obstruction, and recurrent urinary tract infections (Mundy, 1984; Joseph, 1994).

Continence during urinary storage requires a closed bladder neck at times supported by a contracted external urinary sphincter. Fixed obstruction, neurogenic dysfunction, and chronic inflammation can affect any or all of these passive parameters, resulting in resting bladder hostility and clinical manifestations of poor compliance, upper tract deterioration, and incontinence (Brading, 1997).

Active: Voiding

Under normal conditions the active phase of voiding requires the bladder to contract after descent of the bladder neck (Morrison, 1997). Reflexive opening of the bladder neck and sequential relaxation of the external urinary sphincter allow low-pressure balanced voiding and complete elimination of urine. Again, obstruction, neurogenic dysfunction, and chronic infection can cause physiologic changes preventing coordinated function of the detrusor, bladder neck, and external sphincter, defined as dyssynergy (Mundy et al, 1985). A poorly functioning external sphincter from denervation fibrosis may also prevent appropriate relaxation, causing elevated voiding pressure against a fixed outlet. Finally, detrusor pathophysiologic changes may prevent a sustained, coordinated bladder contraction and full elimination of all urine.

Dysfunction

Upper Tracts

It is critical to understand the dynamics of the entire urinary tract before any major reconstructive procedure. Careful evaluation is imperative. In the presence of hydronephrosis, upper tract obstruction must be excluded. With severe and long-standing bladder problems, particularly those involving poor bladder compliance and emptying, upper tract obstruction is often secondary to the bladder abnormality. Nuclear renography with a catheter in the bladder to keep the bladder empty and at low pressure may be useful to rule out a primary upper tract problem. Antegrade perfusion studies with fluoroscopy and pressure measurement are occasionally necessary. Certainly, if upper tract obstruction is present it should be corrected at the time of bladder-sphincter reconstruction.

Much like obstruction, vesicoureteral reflux in the presence of a bladder abnormality may be primary or secondary. Differentiation between the two can be difficult. On occasion the history is helpful. If reflux was not present initially in a patient with neurogenic dysfunction but developed later, it is typically secondary to

bladder hostility. Most reflux in patients with neurogenic dysfunction requiring bladder augmentation is likely to be secondary; reflux in patients with other problems (exstrophy, prune-belly syndrome, or posterior urethral valves) may be either primary or a fixed secondary problem if it persists until the time that bladder reconstruction is necessary. Previous work has suggested that reflux truly secondary to bladder dysfunction may not need surgical correction if the bladder is adequately managed. In those reports, neurogenic bladder patients requiring augmentation did not undergo reimplantation for secondary reflux, and virtually all of the low-grade reflux resolved with augmentation alone (Nasrallah and Aliabadi, 1991; Morioka et al, 1998; Lopez Pereira et al, 2001; Soylet et al, 2004; Juhasz et al, 2008). It is interesting to speculate whether reflux is even a significant problem if a large, compliant bladder is achieved (Soylet et al, 2004). Bacteria may ascend without reflux after reconstruction (Gonzalez and Reinberg, 1987). Experience with certain forms of continent diversion has not shown an increased risk of pyelonephritis in the absence of any antireflux mechanism if the reservoir is adequate (Helal et al, 1993; Pantuck et al, 2000). Although the authors agree that most low-grade secondary reflux is likely to resolve with adequate treatment of the bladder alone, our preference is to correct reflux at the time of bladder reconstruction, unless it is low grade or clearly secondary, because the morbidity is low. After bladder reconstruction, many patients have chronic bacteriuria, particularly those who catheterize to empty, and the absence of reflux, at least theoretically, may decrease the likelihood of ascent to the kidney. Caution must be taken when the treatment of chronically dilated and scarred ureters is considered. Correction of reflux in that setting is certainly appropriate, but one must be careful not to trade reflux for more problematic obstruction. Overaggressive tapering or tunneling of such ureters may be fraught with complications.

Dysfunction in the upper urinary tract is usually manifested by hydronephrosis, pyelonephritis, or impairment of renal function. When such problems are present in patients with lower tract dysfunction, thoughtful evaluation and treatment are necessary. All problems should be addressed at reconstructive surgery to provide the best result for the patient.

Bladder Dysfunction

Bladder dysfunction is a composite of physiologic abnormalities, and it is helpful to assess each component of passive and active bladder function independently. **Elevated passive filling pressure becomes clinically pathogenic when a pressure higher than 40 cm H_2O is chronically reached** (McGuire et al, 1981; Wang et al, 1988; Weston et al, 1989). Pressures at this level sustained for a time impair ureteral drainage, which may result in pyelocalyceal changes, hydroureteronephrosis, and decreased glomerular filtration rate. In addition, persistent elevation in filling pressure can result in acquired vesicoureteral reflux (Sidi et al, 1986a; Cohen et al, 1990).

Pharmacologic management can play a role in decreasing filling pressure, particularly when hyperreflexic detrusor contractions are present. A combination of medications and intermittent catheterization has a positive impact, particularly in children with neurogenic dysfunction (Rink and Mitchell, 1984; Aslan et al, 2002; Verpoorten et al, 2008). Bladders that are poorly compliant because of irradiation or chronic inflammatory processes are not as likely to respond in a positive fashion to this form of therapy. When compliance is unaffected by medical management, augmentation cystoplasty will be required to improve the storage characteristics. It is expected that detrusor contractions resulting in effective emptying will be significantly diminished after augmentation. **With rare exceptions, intermittent catheterization should be taught to and accepted by the patient and caretaker before urinary reconstruction is contemplated.**

One of the most important contributions in the care of children with bladder dysfunction came with the acceptance of CIC described by Lapides and colleagues (1972, 1976) **based on the work of Guttmann and Frankel** (1966). The effective use of CIC has allowed the application of augmentation and lower tract reconstruction to groups of patients who had not previously been candidates. The principle of intermittent catheterization allows the reconstructive surgeon to aggressively correct storage problems by providing an adequate reservoir and good outflow resistance. Good spontaneous voiding, although a goal, is not imperative because catheterization can be used for emptying. Intermittent catheterization can maintain a physiologic state of complete emptying on a regular basis.

Urinary incontinence is a prominent sign of bladder dysfunction. Continence is based on outflow resistance generated by the bladder neck and external urinary sphincter. Outflow resistance must remain greater than resting bladder pressure during storage throughout normal daily activity. When outflow resistance is diminished because of an abnormal bladder neck and external urinary sphincter, incontinence often will occur. Pharmacologic management with α-adrenergic agents can enhance outflow resistance when needed, but operative reconstruction is more commonly required in that setting.

When incontinence occurs during the filling phase because of poor outlet resistance, it is essential to evaluate not only the bladder neck and external urinary sphincter but also the detrusor characteristics. Clinical experience has shown that once appropriate resistance is achieved at the bladder neck through operative intervention, adverse detrusor characteristics may become unmasked and result in high-pressure urinary storage or uninhibited contractions not previously documented (Bauer et al, 1986; Churchill et al, 1987; Dave et al, 2008b). For that reason, provocative urodynamic assessment with occlusion of the bladder neck is important before any bladder neck reconstruction in an attempt to identify children who will be at risk.

Normal synergistic voiding occurs when the bladder neck descends, relaxes, and opens followed by relaxation of the external urinary sphincter and subsequent detrusor contraction. The cascade results in low-pressure voiding. Dysfunctional voiding during this active bladder phase occurs from discoordinated activity of the bladder neck, external urinary sphincter, and detrusor and can result in urinary incontinence. In addition, when neurogenic dysfunction leads to detrusor-sphincter dyssynergy, high-pressure voiding results during a period of time, having a negative impact on the bladder and upper urinary tract (Mundy et al, 1982; Bauer et al, 1984). A similar clinical situation occurs with a fixed, fibrotic external sphincter. Initial treatment usually involves pharmacologic management and mechanical elimination of urine from the bladder through CIC in an attempt to bypass the abnormal voiding mechanics.

Other Considerations

Renal function should be assessed in any patient undergoing bladder reconstruction, particularly if hydronephrosis or severe renal scarring is present. **Demos** (1962) **and Koch and McDougal** (1985) **have demonstrated that urinary solutes, particularly chloride, are absorbed from urine in contact**

with the mucosa of small and large bowel. For patients with normal renal function, the kidneys are able to handle the reabsorbed load of chloride and acid without obvious difficulty. Patients with decreased renal function, however, may develop significant metabolic acidosis secondary to such reabsorption. If acidosis exists preoperatively, it will invariably worsen if urine is stored in small or large intestinal segments (Mitchell and Pizer, 1987). The first component of renal function to deteriorate after obstruction or infection is typically concentrating ability. Patients with compromised function may generate enormous volumes of urine. **The bladder volume achieved through bladder reconstruction must accommodate the patient's urinary output for an acceptable time, usually about 4 hours.** Patients with renal failure or other medical problems may conversely develop oliguria. Low urinary output may affect an augmented bladder or bowel reservoir because there is greater potential for collection and inspissation of mucus. There is also less urine for dilution and buffering of gastric secretions if stomach is used.

Abnormal function of other organ systems also influences the risk of bladder reconstruction with use of intestinal segments. Reabsorption of ammonia by large or small intestinal segments in contact with urine may be dangerous for patients with hepatic failure (McDougal, 1992a). Some medications excreted in urine may be reabsorbed by bowel mucosa (Savauagen and Dixey, 1969). Therefore, liver function tests and arterial blood gas studies may be appropriate for some patients. Careful history should be taken of the patient's preoperative bowel function; this is particularly true of adult patients who may have acquired, or secondary, gastrointestinal problems. Obviously, short-gut syndrome is a concern among patients with cloacal exstrophy, prior bowel resections, or a history of significant irradiation. A history of chronic diarrhea or fecal incontinence preoperatively should signal concern about use of the ileocecal valve in urinary reconstruction.

A critical factor to consider is the commitment of the patient and family. Urinary incontinence, at times, protects some patients from infection and upper tract deterioration. Effective storage can put the patient at risk for such problems if emptying is not accomplished on a regular basis. All must be aware of the responsibility that goes along with bladder reconstruction and urinary continence.

The timing of appropriate surgical intervention may vary dramatically among patients. It is sometimes necessary to perform early reconstruction when the upper tracts and renal function are threatened. This situation most often occurs in the presence of high outflow resistance and poor bladder compliance. More commonly, intervention may be undertaken later to achieve urinary continence. The age at which urinary incontinence becomes socially unacceptable varies among patients and families.

When appropriate, it is beneficial for the patient and family to wait for bladder reconstruction until all needs of the patient are identified. With intervention because of infection or hydronephrosis this is not always possible. When reconstruction is undertaken to achieve continence it is most efficient to identify all reconstructive issues and to address them with one operation. Good urodynamic assessment is usually necessary to determine whether a procedure to increase outflow resistance is necessary in addition to bladder augmentation or replacement. Introduction of intermittent catheterization preoperatively is mandatory in that it allows the patient to demonstrate the ability and desire to do so on a regular basis. It is also helpful in determining whether a continent abdominal wall stoma may help improve the reliability of catheterization and increase the patient's independence. Likewise, particularly in the neurogenic population, it is advantageous to identify the patient who may also benefit from an antegrade colonic enema. It is certainly better for the patient and surgeon to address all of these issues at one operative sitting rather than with sequential procedures that may add morbidity.

EVALUATION OF THE PATIENT

Each patient should have upper tract imaging before bladder reconstruction. Most patients with significant bladder problems will have had routine ultrasonography as part of their surveillance. **If hydronephrosis is present, obstruction and vesicoureteral reflux should be sought with a functional renal study and voiding cystography.** Nuclear renography with a catheter in the bladder is usually adequate to rule out a primary upper tract obstruction. Reflux should be excluded with a voiding study, although that study may be done as part of videourodynamics. In the presence of any hydronephrosis, each patient should have determinations of serum electrolytes, blood urea nitrogen, and serum creatinine. For patients with elevation of the serum creatinine concentration or significant hydronephrosis, a 24-hour urine collection for both creatinine clearance and urine volume should be obtained.

Urodynamics

Bladder Dynamics: Capacity and Compliance

Urodynamic assessment of the lower urinary tract plays an essential role in considering bladder reconstruction. It can provide reproducible results in infants and children but requires meticulous attention to detail (Joseph, 1994). Several mechanical factors may adversely influence urodynamics data, creating artifacts that can have a negative impact on the validity of the evaluation if they are not recognized. Testing is typically performed with transurethral catheter placement in this population of patients. The size of the catheter can lead to the appearance of elevated leak or voiding pressure and the inability to empty well, particularly in infants and young boys (Decter and Harpser, 1992). Suprapubic catheter placement circumvents this problem but is not practical in most cases. The testing medium and infusion rate can influence the results. Carbon dioxide is not as reliable as fluid infusion, particularly in evaluation of bladder compliance and capacity. The most common fluids used for testing are saline and iodinated contrast medium, both of which provide reproducible results (Joseph, 1993). Use of testing media at body temperature is also appropriate (Joseph, 1996). End filling pressure, and therefore bladder compliance, can be dramatically affected by simply changing the filling rate (Joseph, 1992). Bauer (1979) has suggested that cystometrography be performed at a fill rate of no more than 10% of the predicted bladder capacity per minute.

Sphincter Dynamics: Outflow Resistance

The bladder neck and external urinary sphincter work in synergy, but only one is required to maintain urinary continence. Often, neurogenic dysfunction leads to abnormalities of both the bladder neck and external urinary sphincter, resulting in diminished outlet resistance during storage or dyssynergic function with voiding. Monitoring of external urinary sphincter electrical activity is required to evaluate coordinated voiding and dyssynergic detrusor-sphincter activity. Perineal surface electrodes, abdominal wall sensors, anal plugs, vaginal monitors, electrical wires, and concentric needle electrodes have all been used for electromyography (Joseph, 1996). In children with neurogenic dysfunction, a concentric needle electrode or dual needle electrodes placed

through a 25-gauge needle increase accuracy in measuring sphincter activity (Blaivas et al, 1977; Joseph, 1996).

The functional length of the external urinary sphincter also plays a role in outflow resistance, and its measurement can be undertaken with urethral pressure profilometry. Unfortunately, the short length and small diameter of the pediatric urethra make this study technically more difficult to perform than in the adult because the mechanical pulling device is not practical for pediatric use. To assess urethral pressure profile, a constant infusion of testing medium at a rate of 2 mL/min with use of a continuous Harvard pump is required (Joseph, 1996) to eliminate pressure wave artifacts noted with the standard roller ball infusion pumps. Hand withdrawal of the catheter is done while every 5 mm is marked on the recording strip. With practice, reliable measurements can be obtained. There is limited value in comparing specific urethral pressure profile results for a patient against a standard uroflow nomogram; however, a preoperative urethral pressure profile for a given patient provides baseline information that can be beneficial in assessing the intraoperative and postoperative functional urethral length.

Some surgeons use leak point pressure to evaluate outflow resistance, the bladder pressure causing leakage per urethra, which can be determined during passive filling and Valsalva maneuver. Fluoroscopy can be informative during those events. The leak point pressure may be artifactually elevated by the urodynamics catheter in a small male urethra (Decter and Harpser, 1992). Much work remains to determine how well such measurable parameters correlate and identify which patients require a procedure on the outlet to achieve adequate continence.

Bladder Emptying

The patient's ability to empty the bladder before reconstruction should be assessed carefully. Useful parameters related to bladder emptying include synergistic relaxation of the external sphincter on electromyography, urinary flow rates, and measurements of postvoid residual urine. Neurologically normal patients who are able to empty the bladder well preoperatively are much more likely to do so after reconstruction than are patients who have neurogenic dysfunction or those who are unable to empty well preoperatively. **No test ensures that a patient will be able to void spontaneously and empty well after bladder augmentation or other reconstruction.** Therefore, all patients must be prepared to perform CIC postoperatively. The native urethra should be examined for the ease of catheterization. Ideally, the patient should learn CIC and practice it preoperatively until the patient, family, and surgeon are comfortable that catheterization can and will be done reliably. Physical and psychosocial limitations of the patient must be considered in regard to the ability to self-catheterize and to perform self-care. **Failure to catheterize and empty reliably after bladder reconstruction may result in upper tract deterioration, urinary tract infection, or bladder perforation despite a technically perfect operation.** Most patients who may catheterize per native urethra or an abdominal wall stoma will overwhelmingly prefer the latter (Horowitz et al, 1995).

PREPARATION OF THE PATIENT

Bladder and sphincter reconstructive procedures remain some of the most challenging in urology. The general status of patients should be optimized so that they have the best chance to achieve a good result with the least risk of morbidity. Each patient's general nutritional and hydration status should be determined and corrected, if necessary, before surgery. Coexisting medical problems, particularly cardiac and pulmonary, should be well managed preoperatively.

Bowel Preparation

Historically, each patient has undergone preoperative bowel preparation to minimize the potential risk of surgery if the use of any bowel is contemplated. Even when ureterocystoplasty or other alternatives are planned, intraoperative findings may dictate the need for use of a bowel segment. A clear liquid diet for 2 days before bowel preparation aids in clearing solid stool. The patient should then undergo full mechanical bowel preparation the day before surgery. Such bowel preparations have usually been done in the hospital (O'Donnell, 2007); however, recent trends find this changing to an outpatient setting. Major reconstructive procedures often require many hours of operative time with large fluid shifts. It is critical that the patient be well hydrated at the time of surgery. There should be a low threshold for the use of intravenous fluids during the preoperative day. The use of oral antibiotics in bowel preparation, once dogma, is now a matter of personal preference (Breckler et al, 2007). Special attention must be paid to the bowel preparation of patients with neurogenic dysfunction. Most of these patients have chronic constipation. Good bowel cleansing is difficult in such patients and should be done aggressively. Several days of oral cathartics and a clear liquid diet at home may be helpful. Patients with renal insufficiency should be observed carefully during bowel preparation for dehydration and electrolyte disturbances.

Theoretically, gastric contents are sterile, and parenteral antibiotics and a routine bowel preparation are not necessary before gastrocystoplasty. In one study (Gundeti et al, 2006) it was suggested that routine bowel preparation may not be necessary before ileocystoplasty in children.

Urine Culture

All patients should have a urine culture performed several days before bladder reconstruction. The bladder should not be opened with infected urine, which will spill intraperitoneally. Any patient with a positive preoperative urine culture should undergo treatment with either oral or intravesical antibiotics and have a second culture documenting sterile urine before the procedure. Many pediatric patients undergoing augmentation cystoplasty have spina bifida and a ventriculoperitoneal shunt. With a negative urine culture and good bowel preparation the incidence of shunt infection or problems should be low (Yerkes et al, 2001; Hayashi et al, 2008).

Cystoscopy

Preoperative cystoscopy may be the final step in evaluating the native bladder, outflow, or ureteral orifices in pediatric patients. Endoscopy should be performed immediately before bladder reconstruction under the same anesthetic. In adult patients with interstitial cystitis or irritative bladder symptoms requiring augmentation cystoplasty, cystoscopy should be performed well before augmentation to rule out urothelial carcinoma in situ. Bladder biopsy and cytologic examination of the urine may be helpful in excluding tumor. On the basis of history, an occasional patient may warrant endoscopic or radiographic gastrointestinal evaluation.

Key Points: Evaluation and Preparation

- Evaluation for renal function, upper tract obstruction, and vesicoureteral reflux should be performed if hydronephrosis is present, although most such changes are secondary to the bladder dysfunction.
- Careful urodynamic evaluation is critical to understand all of the problems that may contribute to the dysfunction.
- The patient is likely to require CIC after reconstruction and must be capable of doing so on a reliable basis.
- Commitment of the patient and family is essential.
- Basic preoperative preparation includes sterile urine and thorough bowel cleansing.

ANTIREFLUX

Ureteral reimplantation into a native bladder, whether the ureter is dilated or not, is a standard procedure familiar to all pediatric urologists and reconstructive surgeons. The long-term success rate is good, and complications are rare. Such reimplantation is certainly preferable and usually possible during lower tract reconstruction.

Transureteroureterostomy and Single Ureteral Reimplantation

On occasion, the urinary bladder is so small that it is inadequate for bilateral reimplantation, and alternatives must be considered. It is preferable to reimplant both ureters separately, although **if the native urinary bladder is small and adequate for only a single ureteral tunnel, transureteroureterostomy and a single reimplant may be helpful** (Fig. 129–1).

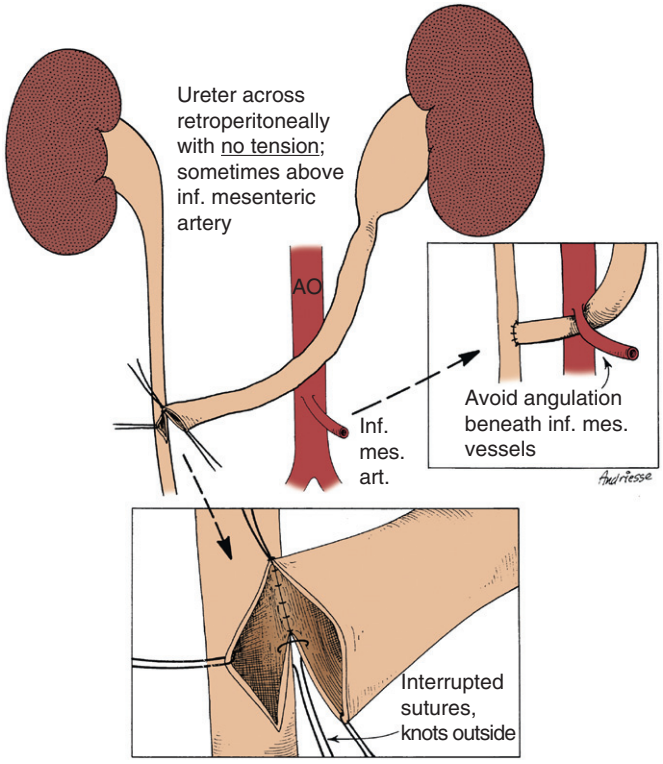


Figure 129–1. Technique for transureteroureterostomy. AO, aorta; Inf. mes. art., inferior mesenteric artery. (Courtesy of W. Hardy Hendren.)

Typically, the better ureter should be implanted into the bladder, draining the other across into it. The crossing ureter should be mobilized to swing gently across the abdomen to the recipient side in a smooth course without tension. It should be carefully mobilized with all of its adventitia and as much periureteral tissue as possible to preserve blood supply. Care must be taken not to angulate the crossing ureter immediately beneath the inferior mesenteric artery. The crossing ureter is widely anastomosed to the posteromedial aspect of the recipient ureter. The recipient is not mobilized or brought medially to meet the end of the other ureter. Transureteroureterostomy, when it is fashioned appropriately, is successful and carries minimal risk for leakage or obstruction (Hodges et al, 1963; Hendren and Hensle, 1980; Noble et al, 1997; Mure et al, 2000). A history of previous calculi remains a relative contraindication to transureteroureterostomy.

The manner in which the bladder is opened may optimize its use for a single reimplant. Rather than incision of the bladder in the anterior midline, a wide, anterior U-shaped incision based cephalad can be made. This potentially elongates the bladder as a posterior plate that can be brought to one side or the other to meet a single ureter. Incision of the bladder in this way may also be useful in placing a continent catheterizable stoma to the umbilicus when the native bladder otherwise will not reach that far. For ureteral reimplantation after such an incision, a psoas hitch of the bladder fixes the bladder in position for a long, straight ureteral tunnel.

Psoas Hitch

Fixation of the bladder to the psoas muscle allows precise control of both the length and direction of a ureteral reimplant. Securing the bladder in this manner helps the bladder reach a short ureter or development of a long tunnel when necessary. A psoas hitch should prevent any angulation of the ureter with bladder filling. Such angulation may be particularly problematic or obstructive with a dilated and scarred ureter. The bladder should be secured to the psoas muscle and fascia with nonabsorbable sutures. Those sutures must not enter the bladder lumen or stones will occur. Broad, shallow purchases of the psoas muscle and fascia should be used to hold long term without trapping the sciatic nerve. The hitching sutures should not be tied so tightly that they cut through either bladder or psoas muscle. The contralateral bladder pedicle may be divided to increase bladder mobility and the length of the hitch on occasion. In general, the ureteral reimplantation should be performed before the bladder psoas hitch (Fig. 129–2).

Antireflux with Intestinal Segments

Necessity of ureteral reimplantation into an intestinal segment may occasionally determine the segment to be used for bladder augmentation or replacement. Long experience with ureterosigmoidostomy and colon conduit diversion has established an effective means of antireflux into a colonic segment. A flap valve mechanism can be constructed by tunneling the ureter beneath a taenia. Important principles learned from ureterosigmoidostomy include a direct mucosa-to-mucosa anastomosis and a submucosal tunnel of adequate length. This technique, familiar to most urologists, has provided favorable long-term results since the 1950s (Nesbit, 1949; Goodwin et al, 1953; Leadbetter and Clarke, 1954) and is based on the initial work of Coffey (1911). Implantation may be done from inside the reservoir with the intestinal segment open or from without after the intestinal segment has been completely reconfigured and closed.

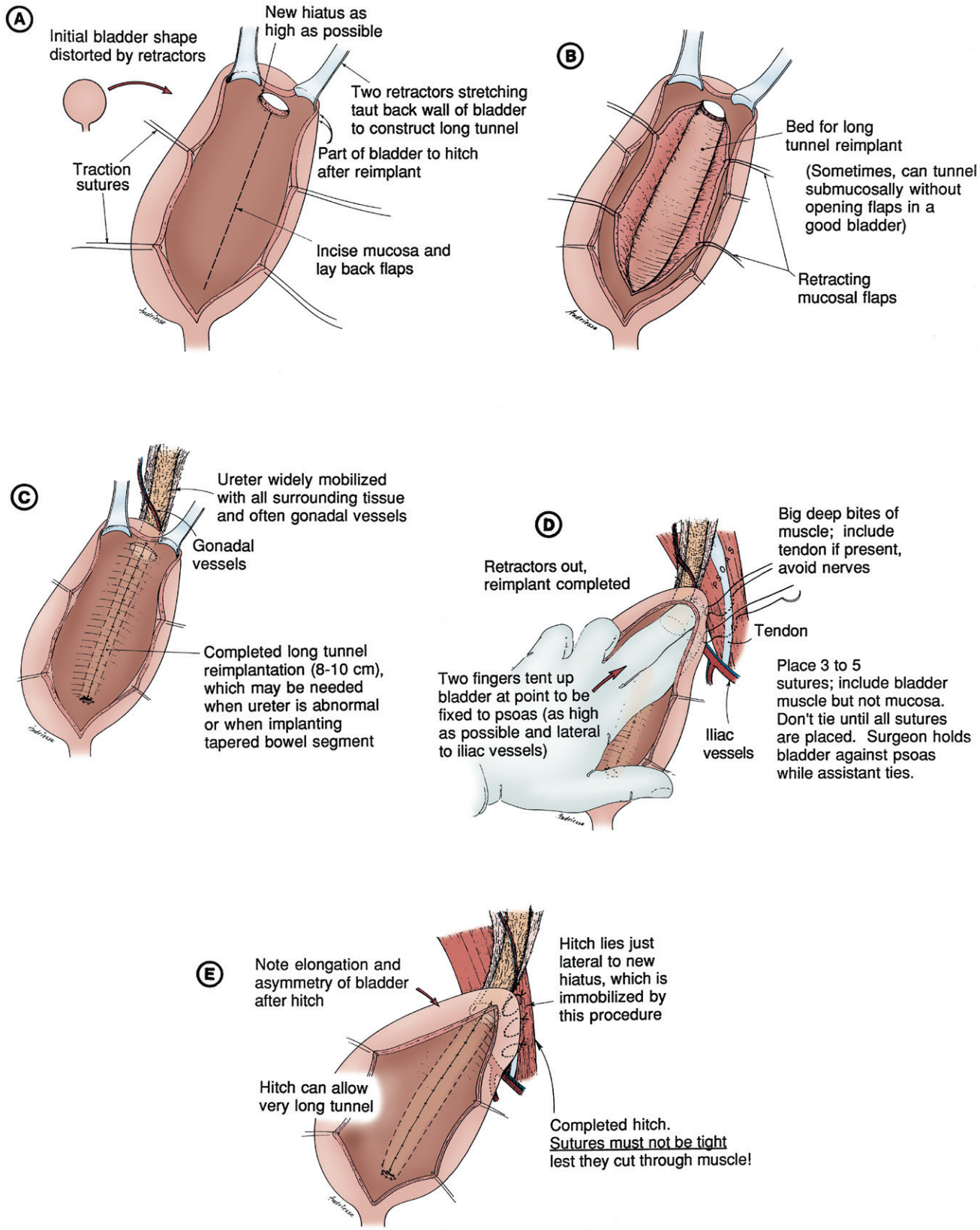


Figure 129–2. **A** to **E**, Technique for psoas hitch, which allows the construction of a long reimplantation tunnel and prevents angulation of the ureter or tapered bowel segment when the bladder fills. Monofilament nonabsorbable suture material is used to fix the bladder to psoas muscle. Care must be taken to avoid entering the bladder, which might cause stone formation on a suture. (Courtesy of W. Hardy Hendren.)

If a gastric segment is used for bladder augmentation or replacement, ureters may be reimplanted into the stomach in a manner remarkably similar to that used in the native bladder. It is easy to form a submucosal tunnel with good muscle backing. The same principles for choosing the length of tunnel relative to the width of the ureter are used as with bladder. Construction of an effective antireflux mechanism into an ileal segment is more difficult. The split-nipple technique described by Griffith may prevent reflux at least at low reservoir pressure (Turner-Warwick and Ashken, 1967; Patil et al, 1976; Stone and MacDermott, 1989; Sagalowsky, 1995). A short longitudinal incision is made in the distal ureter and the ureteral wall turned back on itself. The nipple should be at least twice as long as the width of the ureter. The cuff is stabilized by suturing the ureter to itself. The adventitia of the ureter immediately proximal to the cuff is then approximated to the full thickness of the ileal wall at the hiatus so that the cuff protrudes into the lumen. Le Duc and associates (1987) described a technique in which the ureter is brought through a hiatus in the ileal wall. From that hiatus the ileal mucosa is incised and the edges are mobilized to construct a trough for the ureter. The spatulated ureter is laid into the trough and approximated to the mucosa at the distal end. The ileal mucosa is sutured to the lateral edges of the ureter and should eventually grow over it. Long-term results with these two techniques have been conflicting but generally have not proved as reliable as a tunneled ureterocolonic anastomosis in preventing reflux (Patil et al, 1976; Le Duc et al, 1987; Rowland, 1996; Bihrle, 1997), with one exception (Lugagne et al, 1997). It is also possible to construct an antirefluxing, serosa-lined tunnel between two limbs of ileum as described by Abol-Enein and Ghoneim (1999; Soygur et al, 2005).

Reinforced nipple valves of ileum have been used extensively for antireflux with the Kock pouch (Skinner et al, 1989). After several modifications by Skinner, good long-term results have been achieved. This technique requires a relatively long segment of ileum and use of permanent staples. Attempts have been made to secure the nipple long term without staples or mesh (Hanna and Bloiso, 1987; Gosalbez and Gousse, 1998; Tsuchiya et al, 2004). Maintenance of the intussuscepted cuff is the key to a successful result. The same forces that compress the nipple to achieve antireflux or continence tend to evert or destabilize it. An ileal nipple valve may be particularly useful with short, dilated ureters; an isoperistaltic segment of ileum may be left with the nipple to replace a short ureter. Likewise, the antireflux mechanism is based on the ileal segment and not the ureter. Consequently, a very dilated ureter may be anastomosed to the ileum without tapering. In some neobladders, an isoperistaltic limb of ileum is positioned between the reservoir and ureters to discourage reflux, at least at low pressures (Studer and Zingg, 1997).

Key Points: Antireflux

- Ureteral reimplantation into native bladder is preferable when necessary; the initial bladder incision may facilitate such a procedure.
- An antireflux mechanism can be constructed with any bowel segment but is most challenging with ileum.

BLADDER NECK RECONSTRUCTION

One of the greatest technical challenges facing the surgeon in bladder reconstruction is providing adequate outflow resistance. The bladder neck may be incompetent due to neurogenic dysfunction secondary to spinal dysraphism. Other underlying pathologic conditions, such as exstrophy, bilateral ectopic ureters, and ureteroceles, are unique problems that must be considered in addressing outlet resistance. Many operative techniques have been described for bladder neck reconstruction, indicating that no single option is best for all patients (Kryger et al, 2000; Cole et al, 2003; Lemelle et al, 2006; Dave et al, 2008a). Khoury and associates (2008) have challenged the need for bladder neck reconstruction in the incontinent neurogenic patient with severe bladder trabeculation. **The necessity of preoperative evaluation and thorough knowledge of the patient's specific physiologic limitations cannot be overstated.**

The capability for a sustained bladder contraction to result in complete emptying by voiding or the absence of hyperreflexic contractions may influence the technique selected for gaining outlet resistance. Any operative technique that increases outlet resistance may do so at the expense of detrusor contractibility. For reasons not clearly defined, increasing outlet resistance can change the behavior of the detrusor into a noncompliant hostile environment (Bauer et al, 1986; Burbige et al, 1987; Churchill et al, 1987). Provocative cystometry may identify only some patients at risk, and close postoperative observation is mandatory (Kronner et al, 1998b).

A spectrum of techniques are available for repair; these encompass tightening of the bladder neck, construction of a flap valve mechanism, placement of artificial or autologous bulking agents, and the artificial urinary sphincter. **The selected option should be individualized to the patient's pathologic process, needs, and personal goals.**

An important consideration is the patient's ability to empty well before reconstruction and the likelihood that the patient can afterward. Some of these repairs may prohibit spontaneous voiding. In many patients, particularly patients with neurogenic dysfunction also requiring bladder augmentation, voiding cannot be expected and the major concern is providing adequate outflow resistance. For those with other diagnoses, especially if augmentation cystoplasty is not necessary, spontaneous voiding remains a key goal.

The following discussion covers a variety of operative techniques used to achieve urinary continence through bladder neck and external urinary sphincter reconstruction. Most of the results are based on experience in individuals with spinal dysraphism, but the techniques may be used with other pathogenic conditions. All techniques have a learning curve, which necessitates careful analysis of results and forthright reporting. An evidence-based review of operative bladder neck procedures found assessment of results to be limited by several factors, including the lack of a true, consistent definition of "success" and "continence," consideration of patients with and without concomitant bladder augmentation, and evaluation of small populations of patients with mixed pathologic conditions (Joseph et al, 2003).

Young-Dees-Leadbetter Repair

The Young-Dees-Leadbetter bladder neck reconstruction is one of the most recognized operative techniques to increase outlet resistance. The original Young procedure has evolved and remains of primary consideration in reconstruction of the exstrophic bladder neck (Ferrer et al, 2001). It has been used in patients with many diagnoses.

Technique. Young's initial description (1919) of excising a portion of the bladder neck and significantly tightening the

bladder neck over a silver probe was modified by Dees (1949), who extended the length of excised tissue through the trigone. Leadbetter (1964) followed by elevating the ureters off the trigone, placing them in a more cephalad position on the bladder floor. This allowed tubularization of the trigone and further enhanced lengthening of the urethra. A detailed description and illustrations are found in Chapter 124.

Results. Reports of success with the Young-Dees-Leadbetter bladder neck reconstruction in children with neurogenic sphincter dysfunction are limited, not only in the number of patients but also in overall improvement. Tanagho (1981) and Leadbetter (1985) independently reviewed their long-term results and showed minimal success in individuals with neurogenic dysfunction. They speculated that the lack of success was due to a lack of muscle tone and activity in the wrapped muscle related to the underlying neurogenic problem. Many patients in the early series did not undergo bladder augmentation, possibly compromising the continence achieved. Contrary to the results reported in exstrophy patients, the majority of individuals with neurogenic deficiency of the bladder neck will require bladder augmentation and intermittent catheterization. Sidi and colleagues (1987b) documented a 4-hour continence interval in 7 of 11 patients after such repair, although 10 required catheterization and 9 required augmentation. Five of the 7 needed reoperation to achieve continence. This small series represents one of the more recent long-term results of the Young-Dees-Leadbetter reconstruction in children with neurogenic dysfunction because it has largely fallen out of favor. In an attempt to enhance the Young-Dees-Leadbetter procedure, Mitchell and Rink (1983) described the addition of external support and compression achieved through the placement of a silicone sheath around the reconstructed bladder neck. This was somewhat done to establish a plane for future placement of an artificial sphincter cuff, if necessary. In place, it seemed to improve the function of the repair by either improving coaptation or by maintaining the proximal repair in a better anatomic position. Unfortunately, most of the thicker Silastic sheaths eventually eroded and disrupted the repairs (Kropp et al, 1993). Quimby and colleagues (1996) used a thinner Silastic sheath without the same risk of erosion. They also wrapped omentum between the repair and Silastic wrap. The authors reported better results for continence and thought that placement of an artificial sphincter cuff was much easier when needed.

Donnahoo and coworkers (1999) reviewed one of the largest series of the repair used in treatment of neurogenic incontinence (38 children, 25 of whom were girls). A primary repair was performed in 24 children, a secondary procedure in 6, and a primary repair in conjunction with a silicone sheath in 8. Partial continence was achieved after the initial repair in 26 children (68%). All children with the silicone sheath were initially continent, but erosion occurred in 5. More critically, 35 (92%) of the children required augmentation cystoplasty to become continent. The authors found that although continence could be achieved with this technique, it was at the expense of augmentation cystoplasty and multiple procedures. Their results are similar to those reported by Cole and associates (2003).

Fascial Sling

Sling procedures were developed in an attempt to increase resistance at the bladder neck. Both artificial and natural tissue have been used with similar technique. Resultant coaptation and elevation of the bladder neck should cause approximation of opposing epithelial surfaces and increased outlet resistance that is greater than the resting bladder pressure and the pressure achieved during stressful activity or Valsalva behavior. With sling coaptation, the bladder neck remains fixed; and although a strong detrusor contraction can establish a voiding pressure leading to urine flow, it rarely allows adequate bladder emptying in the face of anatomic or neurologic problems. The majority of pediatric patients who undergo a sling procedure must be prepared for intermittent catheterization. The resistance achieved with bladder neck slings can potentially be overcome by hyperreflexic bladder contractions or elevated pressure due to diminished bladder compliance. Therefore simultaneous bladder augmentation has again been reported in 55% to 100% of patients who achieve urinary continence after a sling procedure (Bauer et al, 1989; Elder, 1990; Decter, 1993; Kakizaki et al, 1995; Perez et al, 1996a; Dik et al, 1999, 2003; Walker et al, 2000; Bugg and Joseph, 2003; Cole et al, 2003; Godbole et al, 2003). Snodgrass and associates (2007) have reviewed their series of 30 consecutive patients with neurogenic incontinence who underwent bladder neck fascial sling only. They conclude continence can be achieved without upper tract damage and the adverse effect of enterocystoplasty. Others have cautioned taking this approach (Dave et al, 2008b). Alternatives to fascia, such as an expanded fluorocarbon polymer (Gore-Tex), have been used in a similar fashion, although early continence has not been maintained (Godbole and Mackinnon, 2004). Good early results have been noted with small intestinal submucosa and other biodegradable scaffolds (Colvert et al, 2002; Misseri et al, 2005).

Technique. The bladder neck is exposed by clearing fatty tissue overlying the bladder neck and the lateral endopelvic fascia. An incision is made within the endopelvic fascia for approximately 2 cm. The junction between the bladder neck and proximal urethra can be identified by placing a transurethral catheter into the bladder and gently pulling down on the catheter to lodge the balloon at the bladder neck. By blunt dissection, a plane between the posterior bladder neck and vagina in girls or rectal wall in boys is developed. The proper plane may be more easily developed from the cul-de-sac by dissecting behind the bladder and ureters from above (Lottmann et al, 1999; Badiola et al, 2000). If the landmarks are not easily defined, as in a secondary repair, the dissection becomes difficult. It may be appropriate to open the bladder to help prevent inadvertent dissection into the urethra or posterior structures. Storm and associates (2008) reported on a robotic-assisted laparoscopic approach for posterior bladder neck dissection and placement of the sling. This may become more appealing as robotic technology expands into bladder reconstruction. Dik and colleagues (2003) proposed a transvaginal approach, eliminating the need to open the bladder or to dissect between the bladder neck and anterior vagina.

When fascial tissue is used the technique is based on that described by McGuire and Lytton (1978) for stress urinary incontinence. Rectus abdominis fascia 1 cm in width and an appropriate length is harvested. This fascia can be taken in either vertical or horizontal fashion, depending on the initial skin incision. Fascia from other sites has been used in a similar fashion but requires a second incision. Often poor nutritional states and prior abdominal procedures limit the availability of rectus fascia, resulting in the use of alternative material such as small intestinal submucosa, cadaveric tissue, biodegradable scaffolds, and bladder wall (Colvert et al, 2002; Misseri et al, 2005; Albouy et al, 2007). All are generally secured to the anterior rectus fascia on either side. Autologous fascial tissue has been used, combining the benefits of a compressive wrap and suspension of the proximal urethra and bladder neck. Several variations of fascial placement and configuration have been described (Woodside and Borden, 1982; McGuire et al,

1986; Elder, 1990; Perez et al, 1996a; Bugg and Joseph, 2003; Dik et al, 2003). When fascial slings and wraps are used for neurogenic sphincter incontinence there is not as much concern for making a wrap or sling that is too tight because most patients are preferentially managed with CIC.

Results. Fascial slings have been used more extensively and with better results in girls with neurogenic sphincter incompetence, although some success has recently been reported in boys. Overall long-term success with fascial slings in the neurogenic population has varied greatly from 40% to 100% (Kryger et al, 2000; Castellan et al, 2005; Misseri et al, 2005; Snodgrass et al, 2007). A variation thought to contribute to a higher success includes a circumferential fascial wrap around the bladder neck. A circumferential wrap may equalize the compressive pressure over a greater surface area of bladder neck and posterior urethra (Walker et al, 1995; Strang et al, 2006). With a 360-degree wrap, simultaneous suspension has also been applied (Bugg and Joseph, 2003). Success rates have varied so much that it is difficult to determine whether any modification of the sling accounts for an increase in continence. Most patients who have undergone a fascial sling or wrap have also had simultaneous bladder augmentation. **Success of the sling, as with most repairs, appears to be improved with augmentation cystoplasty in this patient population by almost all reports** (Castellan et al, 2005). Perez and associates (1996a) reviewed the outcome of sling cystourethropexy in 39 children, 15 of whom were boys. One of four techniques was performed. When postoperative continence was evaluated on the basis of age, sex, underlying diagnosis, preoperative urodynamics, surgical technique, and enterocystoplasty, only concomitant enterocystoplasty was predictive of a successful outcome.

Contrary to the Silastic sheath, fascial sling erosion rarely occurs. Gormley and coworkers (1994) reported a revision rate with fascial slings of 15%. Placement of a fascial sling does not eliminate the possibility of later placement of an artificial urinary sphincter (Decter, 1993; Barthold et al, 1999). It is not unreasonable to consider placement of a fascial sling in a child with a marginally competent bladder neck and posterior urethra if the child is undergoing augmentation cystoplasty and already requires intermittent catheterization.

Bladder Neck Bulking Agents

Vorstman and colleagues (1985) reported one of the initial descriptions of injection therapy with a bulking agent into the bladder neck of incontinent children. The initial enthusiasm for use of polytetrafluoroethylene was quickly tempered because of concern about migration of particles to regional and distant sites including pelvic nodes, lungs, brain, kidney, and spleen found in animal models (Malizia et al, 1984). The technique remains of interest, and several alternatives to polytetrafluoroethylene have been assessed, including glutaraldehyde cross-linked collagen, dextranomer/hyaluronic acid copolymer, and polydimethylsiloxane (Leonard et al, 1990a; Guys et al, 2006; Knudson et al, 2006; Lottmann et al, 2006; Dean et al, 2007). Bovine collagen should not be used in latex-sensitive children with spina bifida because the product is not latex free (Kryger et al, 2000). In an attempt to achieve an ideal substance for injection, investigation is ongoing with autologous cartilage cells harvested from a separate site and then grown in an alginate matrix for endoscopic implantation (Bent et al, 2000). Although preliminary results have been obtained in adult women with stress incontinence, the material has not achieved an enthusiastic use in pediatrics. Whether this or other materials will be an appropriate alternative for neurogenic sphincter incontinence in children is yet to be seen.

In an attempt to alleviate the risks with injection of a foreign biologic product, alternatives to collagen and bovine have been investigated. Polydimethylsiloxane is one such agent. It is composed of sterile solid textured silicone particles, with an average size of 200 μg, suspended in a biologic hydrogen carrier. The large size of the particles should virtually eliminate lymphatic and distant migration (Beisang and Ersek, 1992; Guys et al, 1999; Halachmi et al, 2004; Guys et al, 2006). Contemporary reports favor the use of dextranomer/hyaluronic acid (Lottmann et al, 2006; Dean et al, 2007; Dyer et al, 2007).

Technique. Endoscopic exposure is used to localize the proximal urethra and bladder neck. Injection can be done directly through the working channel of the endoscope, often one with an offset lens system. Ideal placement of the material is in a subepithelial space, mobilizing the epithelium toward the lumen of the bladder neck. When it is completed in a circumferential fashion, adequate epithelial coaptation may occur that effectively raises outlet resistance. Alternatively, periurethral injection in women with a long needle placed from the perineum or through a suprapubic approach has been used. Dean and associates (2007) advocate simultaneous antegrade and retrograde endoscopic injection. Evidence is lacking whether the exact approach affects success, but accurate placement is important and transurethral injection generally preferred.

Results. The durability and success of bladder neck and proximal urethral injection remain in doubt for the pediatric population, particularly those with neurogenic dysfunction. True continence, as defined by a 4-hour dry period between voidings or catheterization, has been reported to be at most 64% and has ranged as low as 5% (Leonard et al, 1990a; Capozza et al, 1995; Bomalaski et al, 1996; Perez et al, 1996b; Sundaram et al, 1997; Silveri et al, 1998; Guys et al, 2001, 2006; Godbole et al, 2003; Halachmi et al, 2004; Lottmann et al, 2006; Dean et al, 2007). Several factors play a role in the outcome, one of which is a history of any previous operative bladder neck repair. Success is enhanced by elevation of the epithelium of the bladder neck, which may be compromised by scarring from previous operative procedures. **The concept of a minimally invasive operation used to enhance a marginal result gained from a more formal bladder neck repair is enticing; unfortunately, the data are lacking to show that bladder neck injection is of lasting value in that setting.**

Sundaram and colleagues (1997) reported on the efficacy and durability of glutaraldehyde cross-linked bovine collagen in 20 children, 12 of whom had neurogenic sphincter dysfunction. More than half of the children required two or three independent injections. Success was achieved in only 1 patient (5%), who was considered dry; 5 had some improvement, and 10 had either no change or transient improvement of only 2 to 90 days. Thus collagen therapy only delayed the ultimate need for bladder neck reconstruction.

Submucosal bladder neck injection of bovine dermal collagen was used by Perez and coworkers (1996b) in 32 patients. Continence was achieved after a single injection in only 20% of the children with neurogenic dysfunction. Complications were limited to febrile urinary infections, one episode of urinary retention, and worsening incontinence in 2 patients. The authors concluded that even though their success was limited the low morbidity and ease of placement justified submucosal injection in selected children.

Guys and associates (2006) treated 49 children with polydimethylsiloxane, 41 of whom had neurogenic bladder neck and

sphincter incontinence. The level of continence continued to deteriorate through 18 months, then stabilized. At an average follow-up of 73 months, success was achieved in 16 (33%) and 7 (14%) were improved. Godbole and colleagues (2003), Halachmi and associates (2004), and Dyer and coworkers (2007) independently came to the conclusion that regardless of the material injected (polytetrafluoroethylene, collagen, polydimethylsiloxane, dextranomer/hyaluronic acid), short-term success is not long lasting.

Kitchens and colleagues (2007) evaluated the use of dextranomer/hyaluronic acid to correct incontinence in patients who had previously undergone bladder neck reconstruction. They achieved success or improvement in 70% of select patients at 17 months, indicating this may be an alternative to other salvage therapy.

Overall, the cost of the bulking agents can be excessive and there does not appear to be any financial benefit over a formal repair (Kryger et al, 2000). **At present, bulking agents play a limited role for increasing outlet resistance and should be reserved for a select group of patients. The exact criteria that define that group have not been established.** Patients with marginal native outflow resistance are probably better candidates than are those with minimal preoperative function.

Artificial Urinary Sphincter

The artificial urinary sphincter has been recognized as a device that can result in prompt continence in select children while preserving their ability to void spontaneously. The artificial urinary sphincter was introduced by Scott in 1974. The general concept and design of the initial model have been retained; however, improvements and enhancements have evolved that have positive impact on the long-term success of the artificial urinary sphincter. The current 800 model includes a seamless, pressurized balloon reservoir, nonkink tubing, and changes in the cuff that facilitate its placement and effectiveness with coaptation of the bladder neck and proximal urethra (Light and Reynolds, 1992; Barrett et al, 1993; Lai et al, 2007). Alternatives to the AS800 model have also been explored (Vilar et al, 2004).

Technique. Placement of the cuff should be at the level of the bladder neck in all female patients and prepubertal boys (Fig. 129–3). It is also the most desirable and effective location in pubertal boys and adult men with neurogenic sphincter incompetence. The bulbar urethra can be used as an alternative site in adult men with mature spongiosum. Levesque and associates (1996) have indicated that age is not a factor in placement of the cuff around the bladder neck. They found that children do not outgrow the artificial urinary sphincter as they progress through puberty and that replacement of the cuff is not routinely necessary. The artificial urinary sphincter cuff can be positioned around intestinal segments used in total urinary reconstruction but is more susceptible to erosion there. Several authors have described the successful placement of the cuff around a bowel segment, particularly when omentum is interposed between the cuff and the segment (Burbige et al, 1987; Weston et al, 1991; Light et al, 1995).

Placement of an artificial sphincter in children is the same as that described for adults. Development of the proper plane for the cuff is virtually identical to that described for a fascial sling. The cuff should be sized snugly, but not tightly, around the bladder neck. Obviously, a sterile environment is critical in considering placement of the artificial urinary sphincter to avoid infection. For that reason, preoperative antibiotics are a necessity, and confirmation of sterile urine is required. With those precautions there is freedom to open the bladder in dissecting around the bladder neck. This will often facilitate the dissection and ensure proper placement. The AS800 model has a locking mechanism in the pump that permits the artificial urinary sphincter to be deactivated and activated without a second operative procedure. Experience has shown that leaving the unit deactivated with the cuff deflated after placement allows formation of a pseudocapsule around the cuff and decreases the risk of erosion (Furlow, 1981; Sidi et al, 1984). The noncycled artificial urinary sphincter

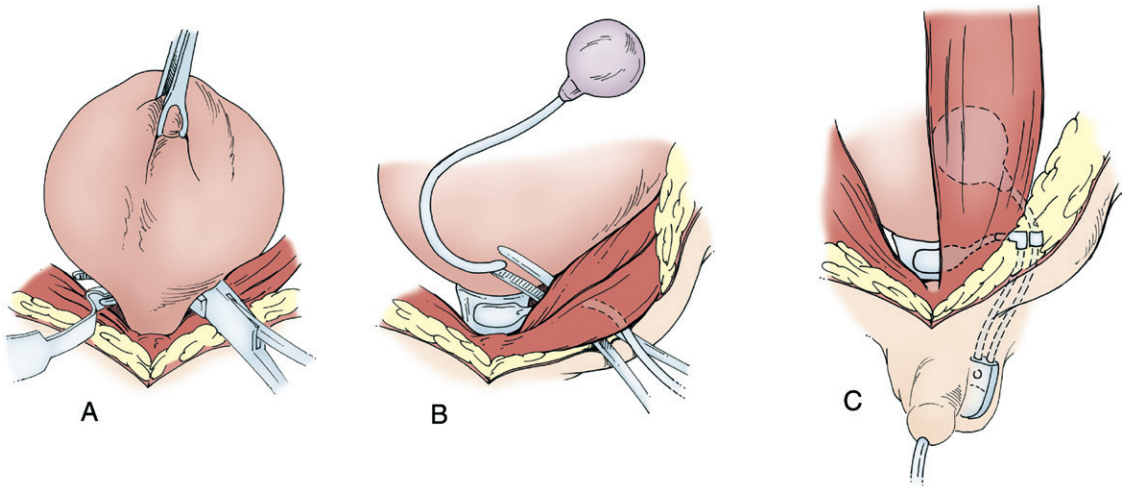


Figure 129–3. Artificial urinary sphincter placement in children. **A**, The cuff is placed around the bladder neck in prepubertal children. Dissection may be facilitated by palpation of a urethral catheter and balloon or by a posterior approach. If dissection is difficult, the bladder can be opened. **B**, The reservoir is placed beneath the rectus muscle. **C**, A tunnel is then made into the scrotum or labia for positioning of the pump on the same side as the reservoir. Tubing connections are made ventral to the rectus fascia, and the device is initially left deactivated.

occasionally may provide enough resistance for continence, eliminating the disadvantages of activation (Herndon et al, 2004a).

Results. There are substantial short- and long-term data regarding continence after placement of the artificial urinary sphincter, with the largest series presented by Herndon and associates (2003). **In investigation of continence, it must be placed in context of the cost experienced by the patient defined by mechanical malfunctions resulting in secondary operative procedures and more catastrophic complications, such as device infection and erosion.** Dramatic improvement regarding the need for secondary procedures has occurred with the technical refinements in the device. Ten- to 15-year long-term follow-up of the artificial urinary sphincter in children has been reported (Levesque et al, 1996; Kryger et al, 1999, 2001; Castera et al, 2001; Hafez et al, 2002; Herndon et al, 2003; Lopez Pereira et al, 2006; Ruiz et al, 2006). All groups report an impressive continence rate of 80% and a functioning sphincter in 95% of patients. These reports are consistent with older series in children reporting continence rates of 75% to 90% and a functioning sphincter in 85% to 97% (Nurse and Mundy, 1988; Gonzalez et al, 1989a; Bosco et al, 1991; O'Flynn and Thomas, 1991; Aprikian et al, 1992; Singh and Thomas, 1996; Simeoni et al, 1996; Catti et al, 2008). Herndon and colleagues (2003) presented the most comprehensive long-term data. They achieved overall continence in 86% of 142 patients with an average follow-up of 10 years. Age at implementation does not appear to affect continence (Kryger et al, 2001).

Whereas the artificial urinary sphincter is one of the few surgically created continence mechanisms that does not negatively affect spontaneous voiding, intermittent catheterization remains an important adjunct in approximately 75% of children with neurogenic sphincter incompetence and can be performed successfully through the cuff (Diokno and Sonda, 1981; Gonzalez et al, 1995; Levesque et al, 1996; Kryger, 1999, 2001; Castera et al, 2001; Hafez et al, 2002; Herndon et al, 2003). As boys approach puberty, spontaneous voiding may become progressively inadequate. It has been speculated that growth of the prostate causes an increase in native outlet resistance. Kaefer and associates (1997a) evaluated increases in cuff size to facilitate spontaneous voiding in boys. In their limited series, they did not find that up-sizing restored the ability to void spontaneously. Jumper and colleagues (1990) reported on prostatic development and sexual function in pubertal boys with spinal dysraphism who had been treated with the artificial urinary sphincter. They found that the artificial sphincter did not alter sexual development, prostatic growth, or morphologic features.

Herndon and associates (2003) reported device malfunction in 64% with the pre-AS800 model and 30% with the AS800. Sphincter erosion was similar for the pre-AS800 and AS800, occurring at 19% and 16%, respectively, in their experience. Fastidious attention to detail and sterile technique diminish the risk of infection but do not eliminate it. When infection occurs without erosion, the unit can be removed and later replaced (Nurse and Mundy, 1988). Infections are minimized by sterilization of the urine preoperatively, meticulous cleaning of the wound site, preoperative bowel preparation, perioperative parenteral antibiotics, and copious antibiotic wound irrigation. Newer cuff design and a 6-week delay in activation of the device help formation of a thickened pseudocapsule that substantially decreases bladder neck and proximal urethral erosion. Kryger and associates (1999) indicated that erosion can be virtually eliminated when the cuff is placed as the primary treatment for bladder neck incompetence. They and others (Aliabadi and Gonzalez, 1990; Gonzalez et al, 1995; Simeoni et al, 1996; Levesque et al, 1996; Castera et al, 2001; Hafez et al, 2002; Herndon et al, 2003) noted that the risk of erosion substantially increases after previous failed repairs but this has not been the experience of others (Ruiz et al, 2006). Identification of the correct plane between the bladder neck and vagina in female patients or rectum in male patients preserves the vascularity of the bladder neck and proximal urethra and may decrease the rate of erosion (Aliabadi and Gonzalez, 1990). Initial exposure through a posterior bladder approach as described by Lottmann and coworkers (1999) may be helpful. Shankar and colleagues (2001) suggested that there is an advantage to exposure of the bladder neck with a transperitoneal approach by decreasing the potential of bleeding from the prostatic venous plexus and improving visualization of the rectal wall.

Levesque and associates (1996) evaluated the long-term outcome of the artificial urinary sphincter on the basis of date of insertion and location of the placement. Before 1985 the artificial urinary sphincter had been inserted in 36 children. Between 1985 and 1990, an additional 18 children underwent placement. In the original group, 24 of the 36 sphincters were in place and 22 functional; 12 had required at least one revision. The mean survival of the device was 12.5 years. Success rates at 5 and 10 years were 75% and 72%, respectively. In the group implanted after 1985, 78% retained a functioning sphincter. The overall continence rate in both groups was 59%; sphincter survival probability at 10 years was approximately 70%. There was no difference found between failure rates in males and females with the exception that female patients who had previously undergone bladder neck surgery were more likely to suffer an erosion. The ability to void independently without the use of intermittent catheterization was retained in 36 children (67%). Those findings are supported by contemporary series (Levesque et al, 1996; Kryger, 1999, 2001; Castera et al, 2001; Hafez et al, 2002; Herndon et al, 2003; Lopez Pereira et al, 2006; Ruiz et al, 2006; Catti et al, 2008).

Upper urinary tract changes including hydronephrosis have been reported to occur in up to 15% of children after placement of the artificial urinary sphincter (Light and Pietro, 1986; Churchill et al, 1987; Gonzalez et al, 1995; Levesque et al, 1996; Kryger et al, 1999). In extreme cases, renal insufficiency has resulted. **It is now recognized that occlusion of the bladder neck in children with neurogenic sphincter incompetence can result in the unmasking or development of detrusor hostility manifested by a decrease in bladder compliance or increase in detrusor hyperreflexia** (Bauer et al, 1986). **Careful preoperative urodynamic assessment helps identify only some of the children who are at risk** (Kronner et al, 1998b). When hostile bladder characteristics are found preoperatively, anticholinergic medications can be beneficial for hyperreflexic contractions but augmentation cystoplasty is usually required for diminished compliance. Churchill and associates (1987) showed that favorable parameters can be maintained after placement of the artificial urinary sphincter; however, close observation is still recommended in any child undergoing bladder neck reconstruction to identify any early deterioration in bladder dynamics before upper tract changes.

Some children undergoing sphincter placement need bladder augmentation as well, and the timing of the two procedures may be questioned because of the concern for artificial urinary sphincter infection. Light and colleagues (1995) reported a 50% infection rate with simultaneous augmentation compared with 9.5% when the procedures were staged. On the contrary, a contemporary review by Miller and coworkers (1998) found that infection necessitating removal of the device occurred in only 2 of 29 such

patients (7%). This low rate is similar to that noted by others (Strawbridge et al, 1989; Gonzalez et al, 1989b). Several reports have evaluated various factors and found that the intestinal segment selected for augmentation appeared to be the only parameter affecting results; gastric augmentation was the least offensive regarding infection (Ganesan et al, 1993; Miller et al, 1998; Holmes et al, 2001). Gonzalez and associates (2002) reported an alternative technique using a seromuscular colocystoplasty and simultaneous placement of the artificial urinary sphincter. They achieved continence in 89% without the need for additional procedures and no deterioration of the upper urinary tract.

The AS800 is the subject of most reviews when the artificial urinary sphincter is discussed, but alternative devices have been reported (Lima et al, 1996; de O Vilar et al, 2004). An alternative device is a one-piece adjustable cuff connected to an injection port for inflation. The injection port is placed subcutaneously and made available for percutaneous access. This allows for adjusting the pressure within the cuff in order to achieve continence. It is particularly convenient for individuals with limited ability to actively pump the AS800. The periurethral constrictor is wider and more fluid than the AS800. It can be deactivated and reactivated by tapping the subcutaneous port.

The ultimate benefits of the artificial urinary sphincter lie in its ability to achieve a high rate of continence while maintaining the potential for spontaneous voiding. For practical purposes, when intermittent catheterization is required along with augmentation cystoplasty, use of native tissue for continence eliminates the long-term concern for infection or erosion and the risk of mechanical failure.

Urethral Lengthening

Young's original description of bladder neck reconstruction (1919) consisted of two components: excision of a segment of anterior urethral bladder neck tissue and narrowing of the adjacent remaining posterior portion. This, however, ultimately led to failure because the tubularized segment remained unsupported within the bladder. Refinements by Dees (1949) and Leadbetter (1964) maximized good muscle tone at the bladder neck and extension of the urethral tube through the trigone.

With similar principles, Tanagho (1981) described a cephalad-based anterior detrusor wall tube. Closure of the tubularized bladder neck formed circularly oriented muscle fibers that Tanagho described as a sphincter mechanism. However, he cautioned against the use of this technique in the neurogenic population. Because of potential breakdown of that tubularized bladder neck and poor results, other techniques have been developed on the basis of the concept of a flap valve mechanism for urinary retention. Kropp and Angwafo (1986) described urethral lengthening and construction of a flap valve for neurogenic bladder neck and sphincter dysfunction. The technique is based on an anterior detrusor wall tube that is kept in continuity with the urethra, tubularized, and implanted into a submucosal tunnel within the trigone. Conceptually, this is effective; however, difficulty with catheterization is a common problem and significant concern.

Technique. A Foley catheter is placed intravesically and the bladder filled to capacity. The bladder is exposed through either a midline or low transverse abdominal incision. The bladder neck is then identified with application of gentle catheter traction. A 6 × 2-cm rectangular flap based on the bladder neck and urethra is then isolated. Stay sutures are placed, and the flap is mobilized in continuity with the proximal urethra. The detrusor musculature at the bladder neck is then divided, separating the bladder and urethra, or the muscle may be left intact at the 5- and 7-o'clock positions. The anterior vaginal wall is exposed in girls; the seminal vesicles are exposed in boys. The rectangular strip based on the urethra is tubularized posteriorly around the urethral catheter with a continuous absorbable suture. The distal portion of the tubularized strip should be approximated in an interrupted fashion to facilitate excision of excessive tissue without jeopardizing the suture line. A capacious submucosal tunnel through the trigone is then developed posteriorly for the proximal neourethra (Fig. 129–4). A wide tunnel is required to prevent kinking at the level of the bladder neck, which will impede catheterization. It is important to eliminate dead space at the entrance of the urethra into the bladder, and this can be accomplished by placement of lateral anchoring sutures in the region of the bladder neck. The detrusor tube must be pulled straight through the tunnel without curve or deviation to facilitate catheterization. Waters and colleagues (1997) and Kropp (1999) have not found it necessary to reimplant all ureters in a cephalic location; they now typically reimplant only refluxing ureters (Kropp, 1999). When the bladder is closed, the lateral wings in the region of the bladder neck are approximated and incorporate adventitia of the tubularized urethra. This enhances a watertight closure and is continued for 2 to 3 cm anteriorly, often up to the area of augmentation. The tubularized neourethra should be long enough to reach the true lumen of the bladder, where it is exposed to pressure as an effective flap valve.

Because of the difficulties with catheterization, modifications of the Kropp bladder neck procedure have been described. Belman and Kaplan (1989) suggested a simplified approach. They harvested a rectangular strip from the anterior bladder wall similar to that described by Kropp. The lateral and posterior muscles at the bladder wall are not incised, however, and the proximal urethra and bladder are not separated. The flap is tubularized over an 8-Fr catheter. The epithelium on the floor of the bladder is incised, contrary to the tunnel made by Kropp. The tube is placed within the trough with the proximal meatus secured on the floor of the bladder. The epithelial edges of the trough are then secured to the lateral aspect of the tube. As in the initial description, the suture line for tubularization of the urethra is posterior against trigonal muscle. Closure of the bladder begins with reapproximation of the lateral walls of the bladder to the tube until the bladder edges meet. The remaining portion of the bladder is covered by an augmentation. Regardless of any modification to the Kropp bladder neck procedure, catheterization potentially remains problematic and therefore the patient should be prepared for a catheterizable abdominal-vesicle channel.

Results. Snodgrass (1997) examined the results in 23 children, 22 of whom had neurogenic sphincter incompetence and noted continence in more than 90% of the children. The most common complication was difficult catheterization, particularly in boys. Less than half of the boys in Snodgrass' series catheterize through the native urethra; the majority do so through an abdominal wall stoma. Postoperative vesicoureteral reflux was identified in 9 of 18 children, and Snodgrass speculated that this was due to lateral retraction of the ureters. The recommendation was made to leave the posterior bladder wall open and flat in receiving the augmentation to prevent this distortion. Kropp (1999) has not had as much problem with catheterizations in his patients and likewise has achieved a high rate of continence without a high incidence of new reflux.

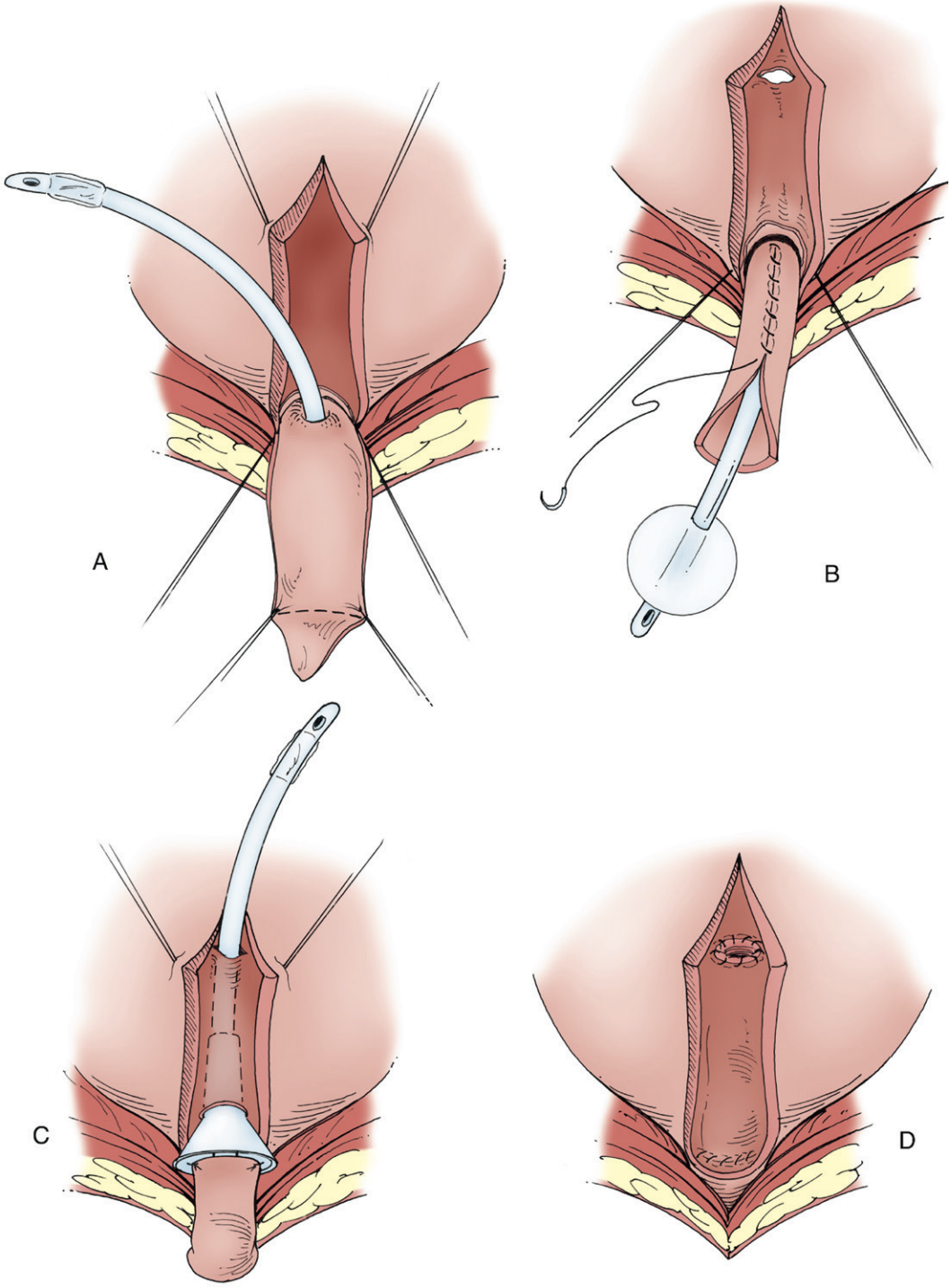


Figure 129–4. Kropp anterior detrusor tube. **A**, An anterior flap of bladder (2 cm wide × 5 to 6 cm long) is developed in continuity with the urethra. **B**, The anterior flap is tubularized over a catheter. A tunnel beneath the mucosa of the trigone is made between the ureteral orifices for the length of the tube. **C**, The tubularized flap is brought through the tunnel. **D**, The detrusor tube is secured to the floor of the trigone with interrupted absorbable suture in a straight course.

Some patients with an effective flap valve mechanism constructed by urethral lengthening will virtually never leak per urethra. This potentially puts them at risk for upper tract deterioration or bladder rupture, particularly if they do not or cannot catheterize reliably. Snodgrass (1997) thought that his modification was beneficial in that it resulted in a shorter intravesical tunnel for the neourethra, allowing leakage per urethra with overfilling.

Pippi-Salle Procedure

In an attempt to maximize the benefits of the Kropp technique and to decrease problems with catheterization, Salle (1994) **reported an anterior bladder onlay flap.** With this technique the posterior wall of the neourethra is intact, theoretically providing less potential hang-up during catheterization. Modifications have been made since the first report to

improve flap viability, to minimize fistula formation, and to extend the indications for the procedure beyond that of the neurogenic bladder (Salle et al, 1997).

Technique. An anterior, full-thickness bladder wall flap 5 × 1 cm is mobilized to the bladder neck with 0.1 cm of its epithelial edges excised to avoid overlapping suture lines. Two parallel incisions down to the level of the muscle are made in the mucosa of the trigone from the native bladder neck. The anterior flap is secured to the midline strip of trigone mucosa to form a tube of lengthened urethra with absorbable suture. The muscle on either side of the posterior epithelial strip may be incised superficially to provide an edge to which the muscle of the anterior flap may be approximated with a second layer of suture in an effort to avoid fistula (Fig. 129–5). The more lateral mucosa of the trigone is mobilized and closed over the midline urethra. Distally, the muscle of the bladder neck is wrapped fairly tightly around the urethra with closure. More proximally, the lengthened urethra should extend well into the lumen of the bladder.

Results. Initial complications of this procedure included persistent incontinence, urethrovesical fistula, and partial necrosis of the intravesical neourethra. Widening the base of the urethra at the level of the bladder neck may decrease these problems. Children who have previously undergone bladder surgery can have a secondary Salle repair if the anterior bladder flap is lateralized slightly to avoid any old midline suture line and increased potential for scarring or necrosis.

Salle and coworkers (1997) found that continence was achieved in 12 of 17 patients (70%) for more than 4 hours. Catheterization difficulties occurred in only 3 of 17 children, 1 of whom subsequently underwent an appendicovesicostomy. Fistula formation at the base of the flap between the proximal, intravesical urethra and bladder occurred in 2 children and resulted in recurrent incontinence. This problem appears to be diminished by making a wider base to the flap and generously trimming the epithelial edges. Jawaheer and Rangecroft (1999) reported a diurnal continence rate of 61% for 3 hours or longer with the Salle procedure. However, only 44% of their patients were dry through the night. Less trouble with catheterization has occurred relative to the Kropp technique, and it rarely remains a problem. Continence rates have not been quite as high in most series (Rink et al, 1994; Mouriquand et al, 1995; Cole et al, 2003).

Canales and coworkers (2006) capitalized on both the Kropp and Pippi-Salle techniques. They evaluated a miniature intravesical urethral lengthening. The primary difference relates to a diminished tunnel (3 cm) and radius of the anterior detrusor tube (8 Fr) with the intent of enhancing resistance, maintaining a popoff mechanism, limiting the use of bladder tissue, and avoiding the need for ureteral reimplantation. At follow-up of 2.5 years, 8 of 9 patients were dry, had normal upper tracts, and had an average leak point pressure of 71 cm H_2O.

Bladder Neck Division

The ultimate procedure to increase bladder outlet resistance is to divide the bladder neck so that it is no longer in continuity with the urethra. It must be accompanied by construction of a continent abdominal wall stoma and should be performed only in patients who will reliably catheterize. If effective, it prevents any leakage or popoff per urethra and potentially increases the risk for upper tract deterioration or bladder rupture if emptying is not performed. Division is seldom performed as a primary procedure but may be considered if the previously mentioned repairs fail (Khoury et al, 1999; Bergman et al, 2006).

Such a procedure effectively moves the reconstructive effort into the realm of continent urinary diversion. The bladder neck is abandoned from a physiologic standpoint, although the bladder may be used as part of the reservoir. Effective division of the bladder neck is not a simple procedure. The bladder must be aggressively mobilized away from the urethra. The bladder should be closed distally in several layers after the posterior lip of bladder neck and trigone are rolled anteriorly and widely separated from the distal urethra. Omentum has generally been interposed. Without these steps, fistulization and leakage per urethra can occur (Khoury et al, 1999; Nguyen and Baskin, 2003). With aggressive mobilization, the fistula rate should be low (Thomasch et al, 2009).

Key Points: Bladder Neck Reconstruction

- Any bladder neck repair other than placement of an artificial urinary sphincter, particularly in combination with augmentation cystoplasty, is likely to make spontaneous voiding inadequate.
- Young-Dees-Leadbetter bladder neck repair in the spina bifida population may have variable success related to the underlying neurogenic dysfunction.
- Fascial slings have been used more extensively and with better results in girls than in boys with neurogenic sphincter incompetence, although those results have varied greatly.
- Experience does not yet suggest that injection of bladder neck bulking agents has a lasting effect on severe neurogenic sphincter incompetence.
- A functioning, well-positioned artificial urinary sphincter device generally provides good outflow resistance and is best suited for patients who can empty adequately with spontaneous voiding.
- Urethral lengthening procedures construct an effective flap value mechanism for continence that disrupts any chance of spontaneous voiding and may make catheterization per urethra difficult.
- The success of most bladder neck repairs in the neurogenic population is improved when the repair is associated with bladder augmentation.
- Any bladder neck repair may unmask or result in new bladder hostility; careful follow-up is mandatory.

AUGMENTATION CYSTOPLASTY

The initial approach to the patient for augmentation cystoplasty is similar regardless of the bowel segment to be used. Cystoscopy should be performed preoperatively to identify any unsuspected anatomic abnormalities that may affect the surgery or postoperative care. If other bladder procedures, such as ureteral reimplantation, are to be performed, the bladder is left full after cystoscopy. If only augmentation is indicated, the bladder is emptied to allow easy access to the peritoneal cavity.

As a general rule, a midline incision is preferred for intestinal cystoplasty, although these procedures can be performed through a lower transverse incision if there has been no previous abdominal surgery. Laparoscopic assistance with mobilization of the intestine may allow

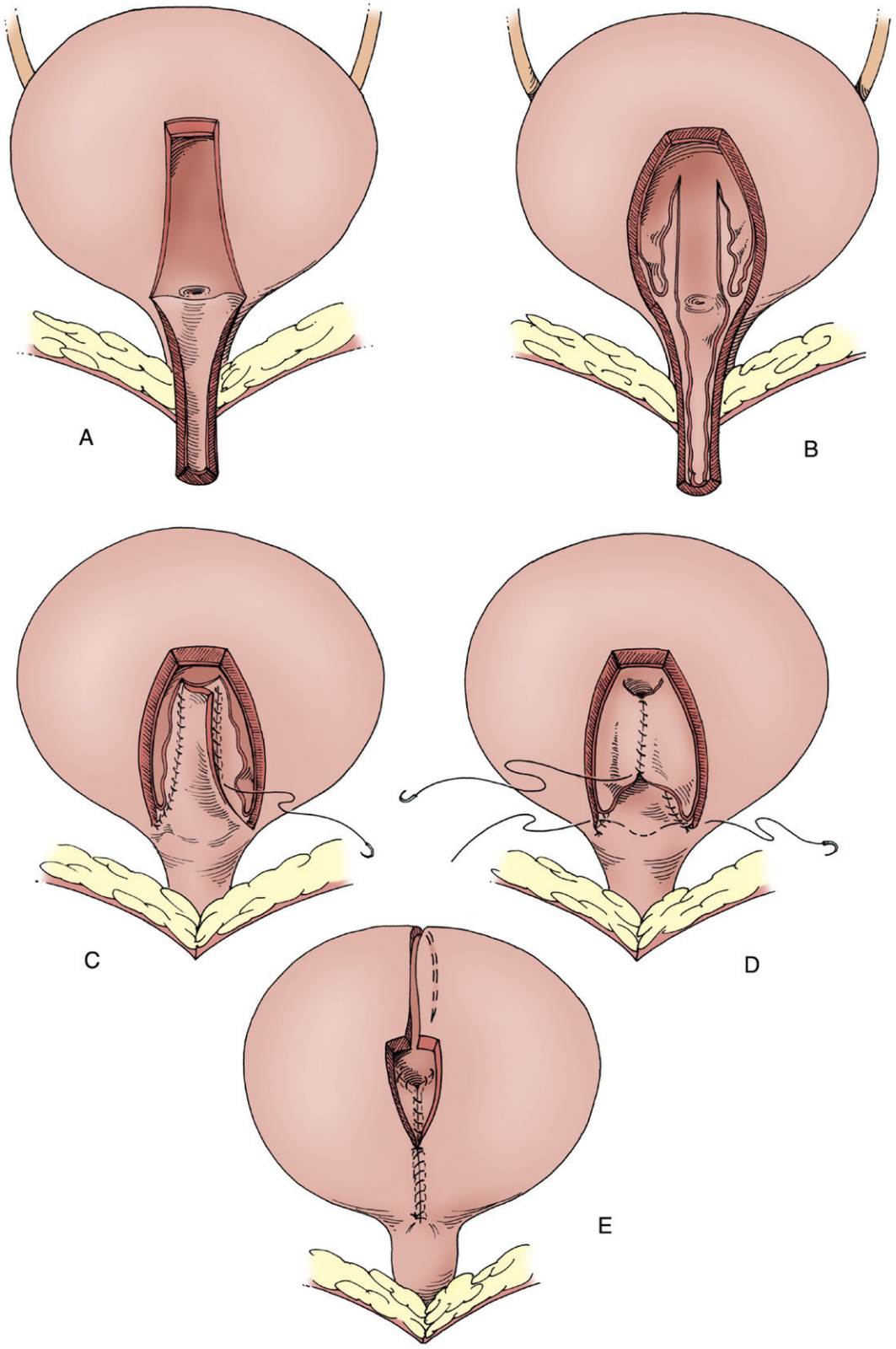


Figure 129–5. Pippi-Salle anterior detrusor tube onlay. **A**, An anterior detrusor tube (1 cm × 4 to 5 cm) is mobilized to the level of the bladder neck. **B**, A central strip on the floor of the bladder is developed by incision of the epithelium on either side. **C**, The anterior detrusor flap is secured to the strip in a two-layer fashion, approximating the epithelium with the first layer and muscle with the second. **D**, The lateral mucosa of the trigone is mobilized and secured over the lengthened urethra. Distally, the bladder is closed to itself and should incorporate a portion of the anterior detrusor flap to ensure a watertight seal. **E**, After distal closure the remaining portion of the bladder is left open if augmentation cystoplasty is necessary.

augmentation through a smaller, lower incision (Hedican et al, 1999). Augmentation cystoplasty may eventually be performed completely by laparoscopy with or without use of a robotic system (Lorenzo et al, 2007a, 2007b; Wang et al, 2007; Passerotti et al, 2008). Associated bladder procedures should be performed before the peritoneal cavity is opened to minimize third-space fluid loss. For gastrocystoplasty the incision needs to extend from the pubis to xiphoid to allow more cephalad exposure.

Management of the Native Bladder

In the past it had been recommended that the majority of the "diseased" bladder be excised in preparation for augmentation. This meant removal of the supratrigonal bladder, leaving only a small cuff of higher bladder for anastomosis to the intestinal segment. Despite the cuff, a relatively small area is left for anastomosis to the bowel segment; most of the bowel is approximated to itself. **Most surgeons now preserve the native bladder as long as it is widely opened to prevent a narrow-mouthed anastomosis, which can result in the augmentation segment's behaving like a diverticulum** (Fig. 129–6). A sagittal incision to bivalve the bladder is generally useful (Fig. 129–7). The incision is carried from a point several centimeters cephalad to the bladder neck anteriorly to a position just above the trigone posteriorly. Such an incision allows a technically easier anastomosis to the bowel segment and leaves the native bladder to add to the overall capacity. A greater circumference for the anastomosis can be provided, if needed, by opening the bladder in a stellate fashion with a second transverse incision into the two bladder halves. There have been reports of severe penile or perineal pain in sensate boys after augmentation with preservation of the native bladder (Phelps and Malone, 2004). Although four such patients required secondary excision of the bladder, similar problems have not been frequent enough to warrant routine excision at the time of augmentation.

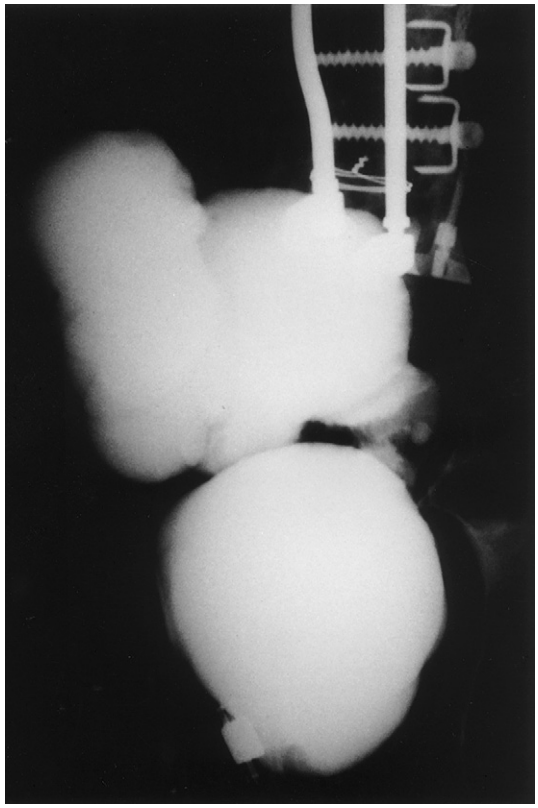


Figure 129–6. Cystogram after augmentation demonstrates a narrow anastomosis of the bowel segment to bladder. The segment behaves like a diverticulum.

Management of Intestinal Segments

Hinman (1988) and Koff (1988) have demonstrated the advantages of opening a bowel segment on its antimesenteric border, with subsequent detubularization and reconfiguration of that intestinal segment. **Reconfiguration into a spherical shape provides multiple advantages, including maximization of the volume achieved for any given surface area, blunting of bowel contractions, and improvement of overall capacity and compliance.** All intact, tubular intestinal segments have been noted to generate pressures of 60 to 100 cm H_2O with contractions, including ileum (Kock, 1969; Light and Engleman, 1985; Fowler 1988; Camey et al, 1991). Detubularization lowered the maximal contractile pressure from 63 to 42 cm H_2O in the right colon and 81 to 28 cm H_2O with use of ileum (Goldwasser et al, 1987). Furthermore, a shorter intestinal segment can be used to achieve the same capacity than when it is left in tubular form. **Detubularization and reconfiguration should always be performed during augmentation cystoplasty.**

Mathematical models based on the length and width of the bowel segment used may predict the volume needed but are cumbersome (Rink and Mitchell, 1990). Depending on the volume needed, 20 to 40 cm of ileum or approximately 20 cm of colon is generally used for cystoplasty. This somewhat depends on the volume of the native bladder being augmented. If the cystoplasty is being done on a bladder of moderate volume that generates high pressure by uninhibited contractions, less bowel is necessary than for one that is tiny in capacity. Unless it is otherwise contraindicated, the surgeon should err by making the bladder too large rather than too small. Appreciation of the patient's urinary volumes also should influence the size of the bladder required. Patients with upper tract damage, particularly to concentrating ability, may make huge volumes of urine and require a larger capacity.

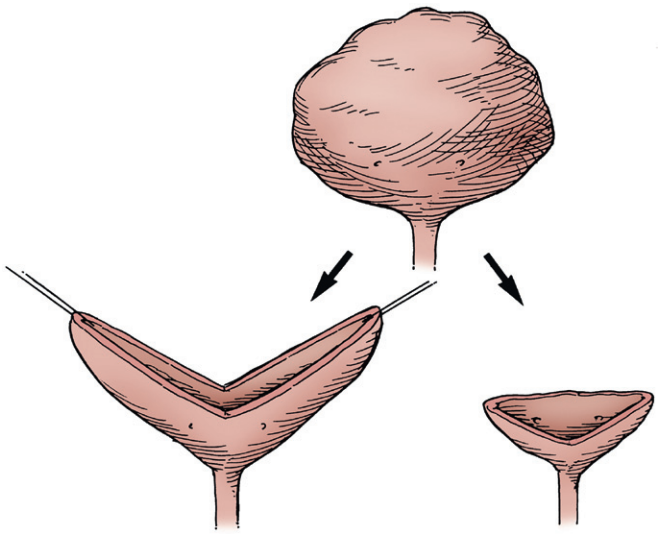


Figure 129–7. The native bladder can be managed by supratrigonal excision of the diseased bladder. More typically, the bladder is opened widely in a sagittal plane (*left*).

Ileocystoplasty

Goodwin and associates (1959) were among the first to demonstrate the numerous ways of anastomosing a patch of ileum to the native bladder after the ileum was detubularized and reconfigured to achieve the most spherical shape possible.

Technique. **A segment of ileum at least 15 to 20 cm proximal to the ileocecal valve should be selected.** The distal portion of terminal ileum is unique from a physiologic standpoint and should be avoided. The isolated segment should be 20 to 40 cm in length, depending on the patient's size, native bladder capacity, and desired final capacity. With short ureters, an extra tail of isoperistaltic ileum can be useful to reach the foreshortened ureters. This requires construction of an ileal nipple valve to prevent reflux as in the Kock or hemi-Kock pouch. This type of construction may require up to 60 cm of small intestine. **The segment to be used should have an adequate mesentery to reach the native bladder without tension.**

After selection of the appropriate segment, the mesentery is cleared from the bowel at either end for a short distance to make a window. The bowel is divided at those ends, and a hand-sewn ileoileostomy or stapled anastomosis is performed. The mesenteric window at the bowel anastomosis is closed to prevent an internal hernia. The harvested ileal segment is irrigated clear with 0.25% neomycin solution and opened on its antimesenteric border (Fig. 129–8A). **The ileum is folded in a** U **shape most commonly, although longer segments can be folded further into an** S **or** W **configuration.** The ileum is anastomosed to itself with running absorbable sutures (Fig. 129–8B). The suture line should approximate the full thickness of ileum to ileum while inverting

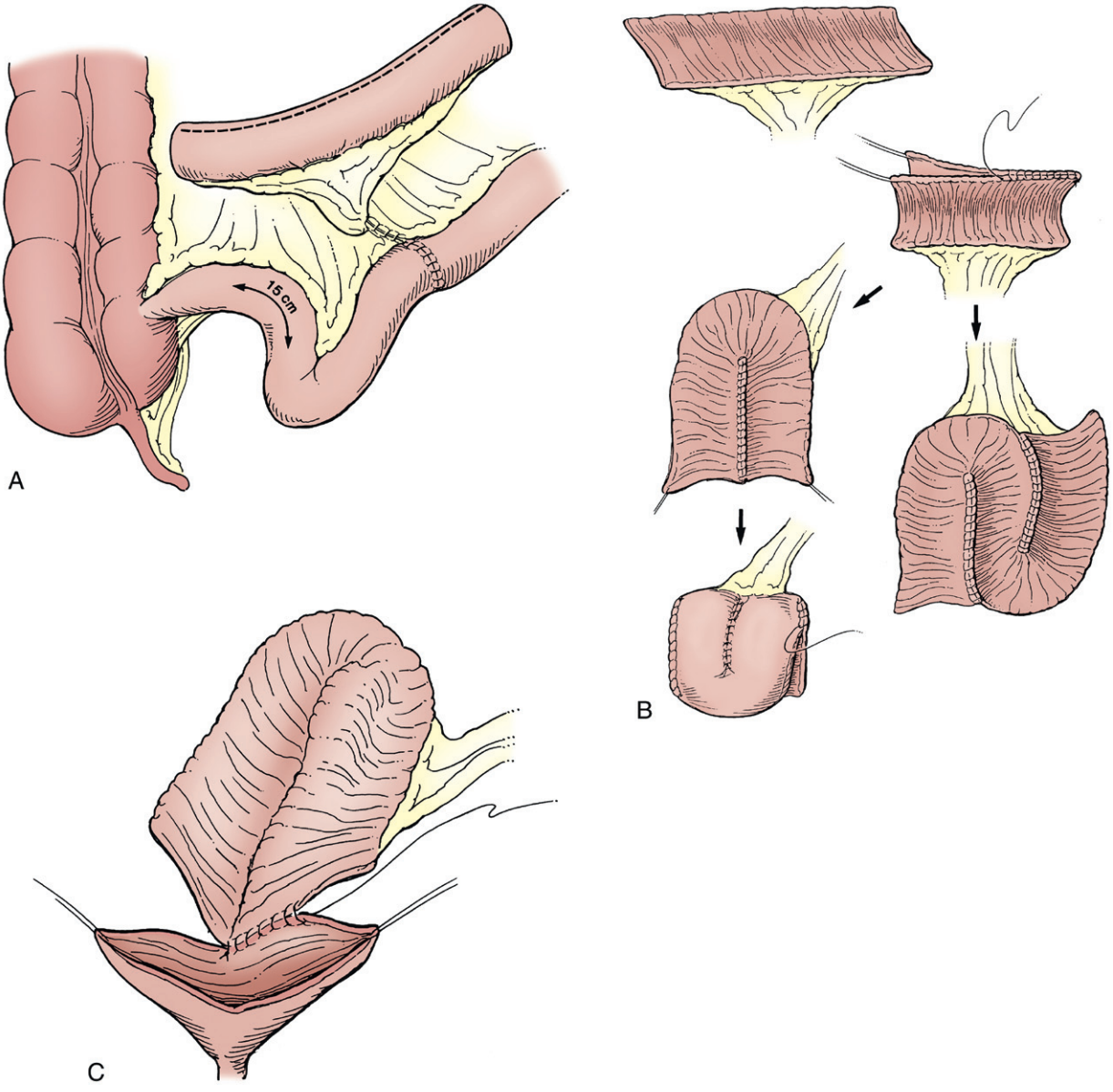


Figure 129–8. **A**, Ileocystoplasty. A 20- to 40-cm segment of ileum at least 15 cm from the ileocecal valve is removed and opened on its antimesenteric border. Ileoileostomy reconstitutes the bowel. **B**, The opened ileal segment should be reconfigured. This can be done in a U, S, or W configuration. It can be further folded as a cup patch. **C**, The reconfigured ileal segment is anastomosed widely to the native bladder.

the mucosa. If the bladder was not opened previously, it is incised in a sagittal plane. The anastomosis of the ileum to native bladder is easily done when it is started posteriorly. The anastomosis may be done in a one- or two-layer fashion, always using absorbable suture and inverting the mucosa to the lumen (Fig. 129–8C). Permanent sutures should never be used for any cystoplasty because they serve as a nidus for stone formation.

A suprapubic tube is brought out through the native bladder when possible and secured. The anterior aspect of the anastomosis is then completed. A drain is placed near the bladder and brought out of the pelvis through a separate stab incision. It should be removed promptly if it is not draining urine, particularly in neurogenic patients with a ventriculoperitoneal shunt. The wound is thoroughly irrigated and the abdomen is closed in layers.

Cecocystoplasty and Ileocecocystoplasty

Couvelaire described the use of the cecum for augmentation cystoplasty in 1950, and numerous reports of simple cecocystoplasty have appeared since then. Presently, cecocystoplasty is an uncommon operative procedure and is not discussed because it has largely been replaced by various forms of ileocecocystoplasty. With this technique, the cecum is opened, reconfigured, and used to augment the bladder alone, leaving a segment of ileum to reach the ureters or for construction of a continent abdominal wall stoma based on imbrication of the ileocecal valve and proximal ileum. Conversely, the ileal segment can be opened and used as a patch on the cecal segment before augmentation cystoplasty. Many modifications of the technique exist, but all start with mobilization of the cecum and right colon by incision of the peritoneum along the white line of Toldt up to the hepatic flexure. Fifteen to 30 cm of the terminal ileum is used. The length of the ileal segment depends on the technique employed. As with all intestinal cystoplasties, before division of the bowel segment it should be noted that it will reach the bladder without tension (Fig. 129–9A).

Technique. The isolated ileocecal segment is irrigated clear with neomycin solution and opened on its antimesenteric border through the ileocecal valve for its entire length. In the typical ileocecal augmentation the ileal and cecal segments are of equivalent length such that the borders of the open segment can be anastomosed and then folded on themselves to form a cup cystoplasty (Fig. 129–9B). The anastomosis of the reconfigured segments is done in either a one- or two-layer closure with absorbable suture. The opening should be left large enough to provide a wide anastomosis to the bivalved bladder. **If more volume is necessary, the ileal segment can be significantly longer, allowing it to be folded before anastomosis to the cecum.** The Mainz ileocecocystoplasty uses an ileal segment twice the length of the cecal segment. The opened edge of the cecal portion is anastomosed to the first portion of the ileal segment. The first and second portions of the ileal segment are next approximated. The compound ileocecal patch is then anastomosed to the bladder (Fig. 129–10). The mesenteric window is closed, and a suprapubic tube is placed through the native bladder and secured through the abdominal wall.

Appendix. One potential advantage of ileocecocystoplasty is the presence of the appendix. Particularly in children the appendix is useful in construction of a reliable continent abdominal wall stoma. The appendix may be removed with a small cuff of cecal wall and tunneled into the native bladder or a taenia of the cecal segment to provide a continence mechanism. Likewise, it may be left in situ and the base safely tunneled beneath a taenia. If the appendix is not to be used, an appendectomy is performed with standard ileocecocystoplasty.

Ileocecal Valve. The ileocecal segment has been used extensively in the adult population undergoing reconstruction and bladder replacement. It has been used less frequently so in children because the majority of patients undergoing augmentation cystoplasty do so for neurovesical dysfunction. Those patients generally have neurapraxic bowel dysfunction as well. Removal of the ileocecal valve in such children can result in intractable diarrhea (Gonzalez and Cabral, 1987; King, 1987). Use of the ileocecal valve in such

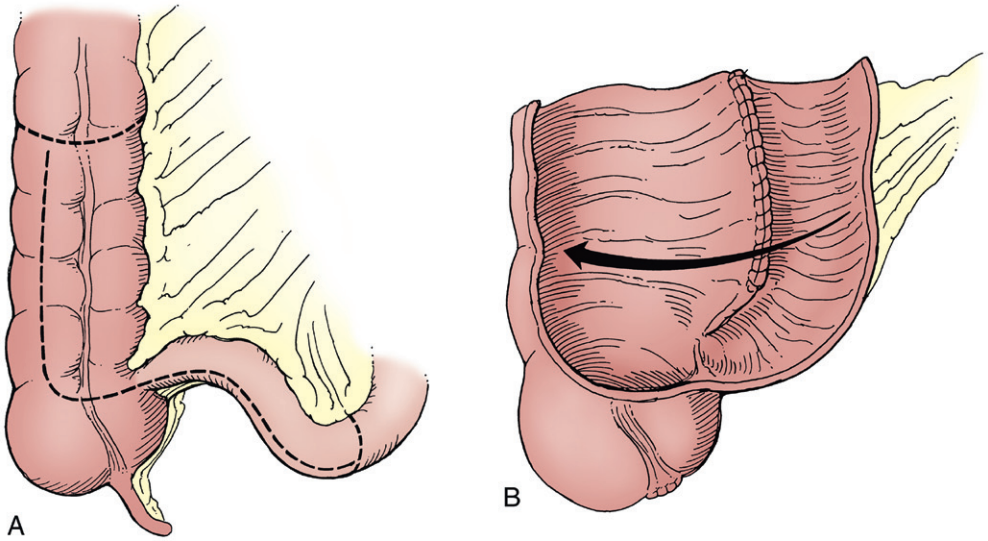


Figure 129–9. Ileocecocystoplasty. **A**, An ileocecal segment is selected. The length of segment chosen depends on the technique employed. After removal, it is opened on the antimesenteric border (*dashed lines*). **B**, The opened ileal and cecal segments are anastomosed to form a cup in the standard ileocecal cystoplasty.

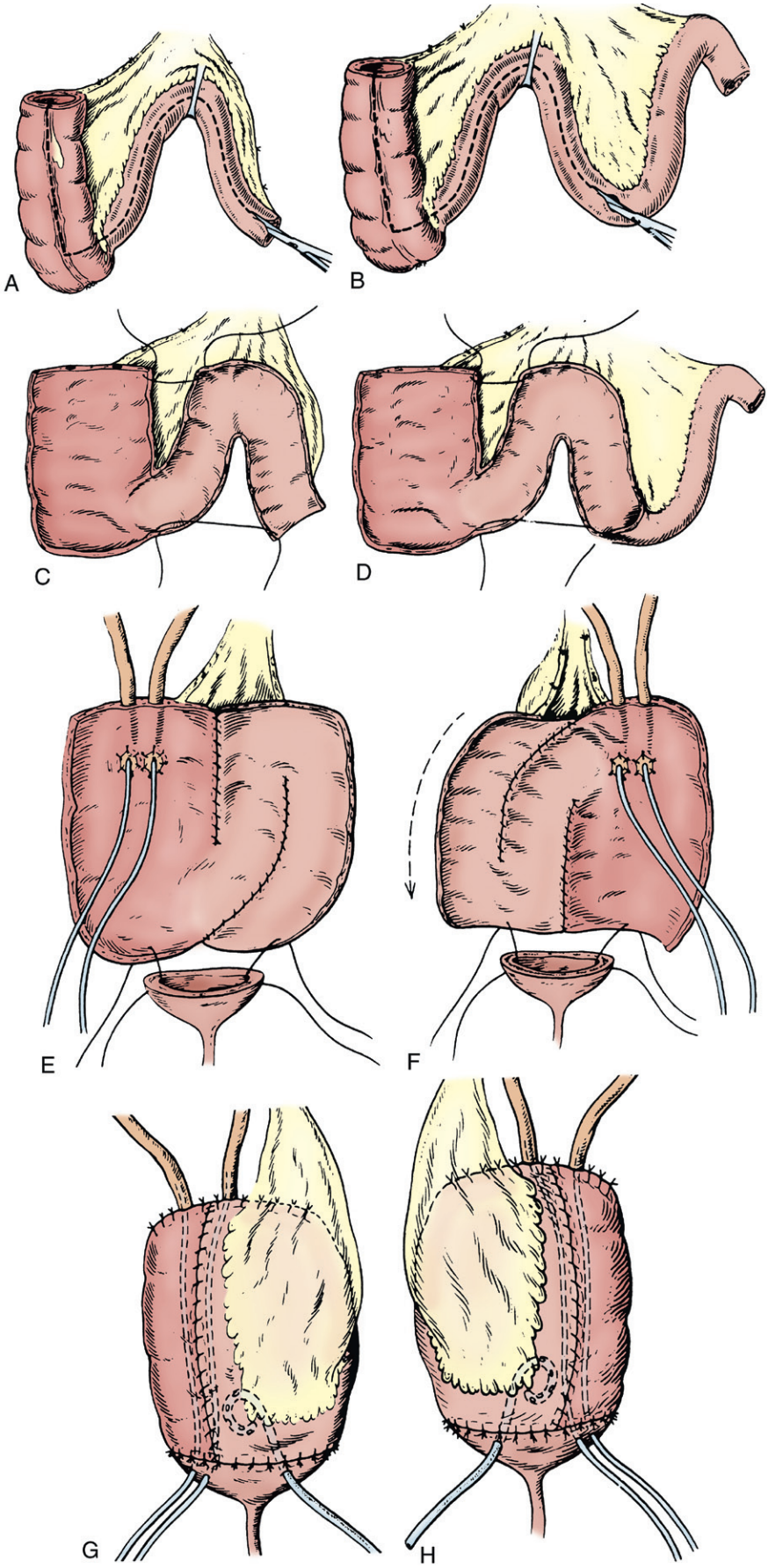


Figure 129–10. The Mainz ileocecocystoplasty. **A** and **B**, The ileal segment is twice the length of the cecal segment. **C** and **D**, It is opened on the antimesenteric border. **E** and **F**, The ureters can be reimplanted into the opened cecal segment if necessary. **G** and **H**, The ileocecal segment is anastomosed to the native bladder. (From Thuroff JW, et al. In: King LR, Stone AR, Webster GD, editors. Bladder reconstruction and continent urinary diversion. Chicago: Year Book; 1987.)

patients should be avoided unless other advantages of the segment outweigh the risk of diarrhea and fecal incontinence.

There are potential advantages to the use of the ileocecal segment. Antireflux tunnels can easily be performed into the taenia of the cecum when necessary. Again, for the short ureter, a tail of ileum can be left intact to bridge the gap and the imbricated ileocecal valve used for antireflux. The same imbrication technique can be used to construct a continent abdominal wall stoma as with the appendix. Cain and associates (Cain and Husmann, 1994; Cain et al, 1999) have proposed use of the ileocecal segment for augmentation with the plicated ileal segment brought to the abdominal wall as a catheterizable stoma as in the Indiana pouch.

Sigmoid Cystoplasty

Use of the sigmoid colon for augmentation cystoplasty was first reported by Lemoine in 1912 (Charghi et al, 1967) and continues to be used commonly. **Because of the strong unit contractions of the sigmoid, it is imperative to detubularize and reconfigure the segment to provide maximal compliance and disruption of contractions.**

Technique. Fifteen to 20 cm of sigmoid colon is identified and mobilized. The mesentery is transilluminated to identify the vascular arcade to the segment. After identification of this blood supply the surgeon must ensure that the segment can reach the bladder without tension. If so, the bowel segment is divided between clamps and a colocolostomy performed (Fig. 129–11A). The remainder of the abdominal cavity is carefully packed to prevent contamination from the open sigmoid segment. Detubularization and reconfiguration are done in a fashion determined by the surgeon's preference. The sigmoid patch is anastomosed to the bivalved bladder in a manner similar to that previously described for ileocystoplasty. Again, a large suprapubic tube is brought out through the native bladder and secured to the bladder and skin exit sites. Drains are placed as previously noted.

Reconfiguration of Sigmoid. Sigmoid colon segments are generally reconfigured in one of two ways. Mitchell (1986) suggested closing the two ends and then opening the segment longitudinally opposite its blood supply. The segment easily fits on the bivalved bladder in either the sagittal or coronal plane (Fig. 129–11B). More radical reconfiguration, and perhaps breakup of unit contractions, may be achieved by folding the sigmoid segment in a U shape similar to that described for ileocystoplasty (Sidi et al, 1987a) (Fig. 129–11C). A slightly longer segment of sigmoid may be necessary for effective reconfiguration in this manner.

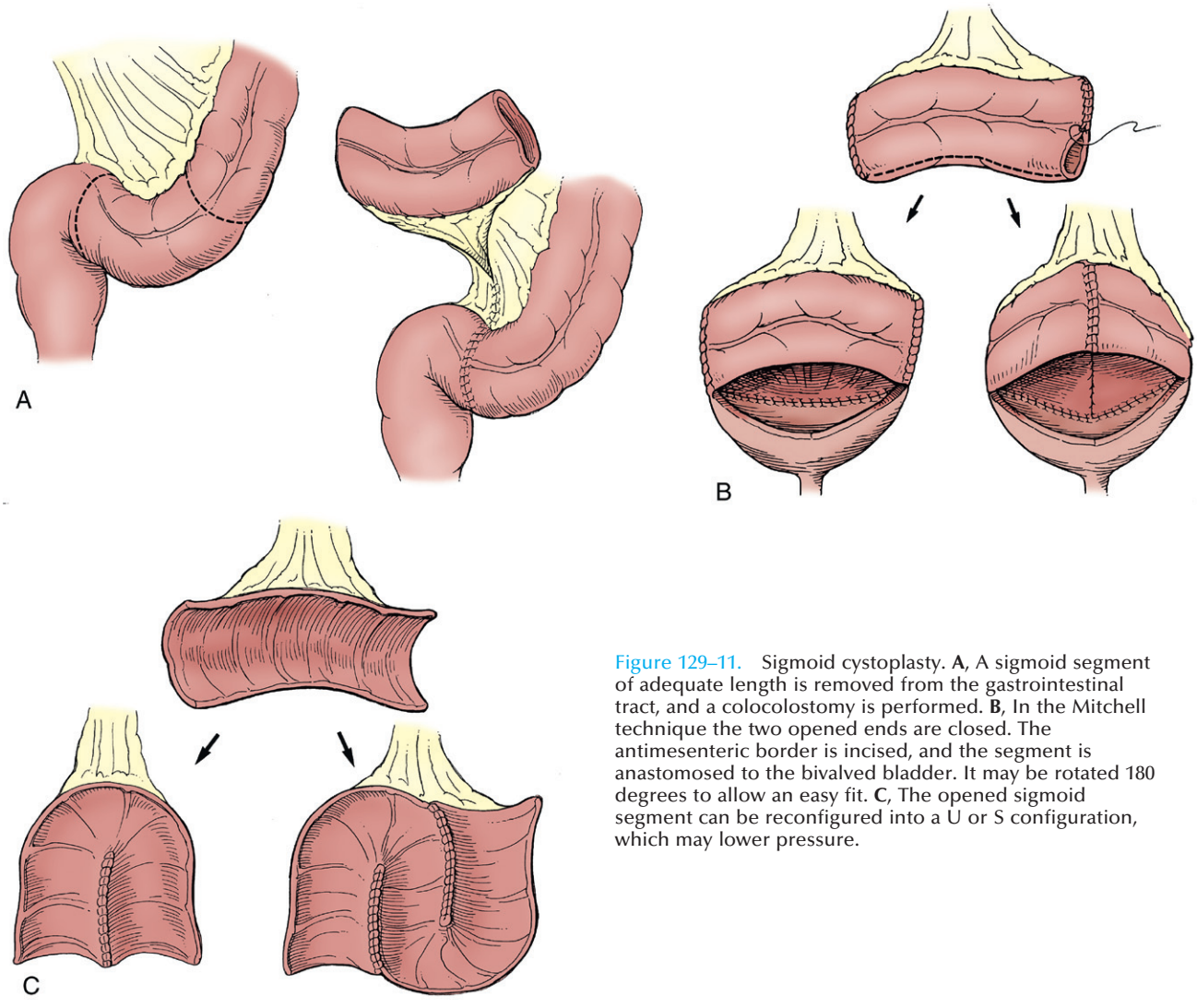


Figure 129–11. Sigmoid cystoplasty. **A**, A sigmoid segment of adequate length is removed from the gastrointestinal tract, and a colocolostomy is performed. **B**, In the Mitchell technique the two opened ends are closed. The antimesenteric border is incised, and the segment is anastomosed to the bivalved bladder. It may be rotated 180 degrees to allow an easy fit. **C**, The opened sigmoid segment can be reconfigured into a U or S configuration, which may lower pressure.

Gastrocystoplasty

Two basic techniques exist for use of stomach in bladder augmentation.

Technique with Use of Gastric Antrum. Leong and Ong (1972) described the use of the entire gastric antrum with a small rim of body for bladder replacement. With their technique the left gastroepiploic artery is always used as a vascular pedicle. If the right gastroepiploic artery is dominant and the left vessel ends high of the greater curvature, a strip of body along the greater curvature from the left gastroepiploic artery to the antrum is maintained and provides adequate blood supply (Leong, 1988). Continuity of the upper gastrointestinal tract is restored by a Billroth I gastroduodenostomy.

Technique with Use of Gastric Body. A gastric wedge based on the midportion of the greater curvature may be used (Adams et al, 1988) (Fig. 129–12A). **The gastric segment used in this technique is made up mainly of body and consequently has a higher concentration of acid-producing cells. The right or left gastroepiploic artery may be used as a vascular pedicle to this segment.** The right artery is commonly dominant and thus more frequently used. The wedge-shaped segment

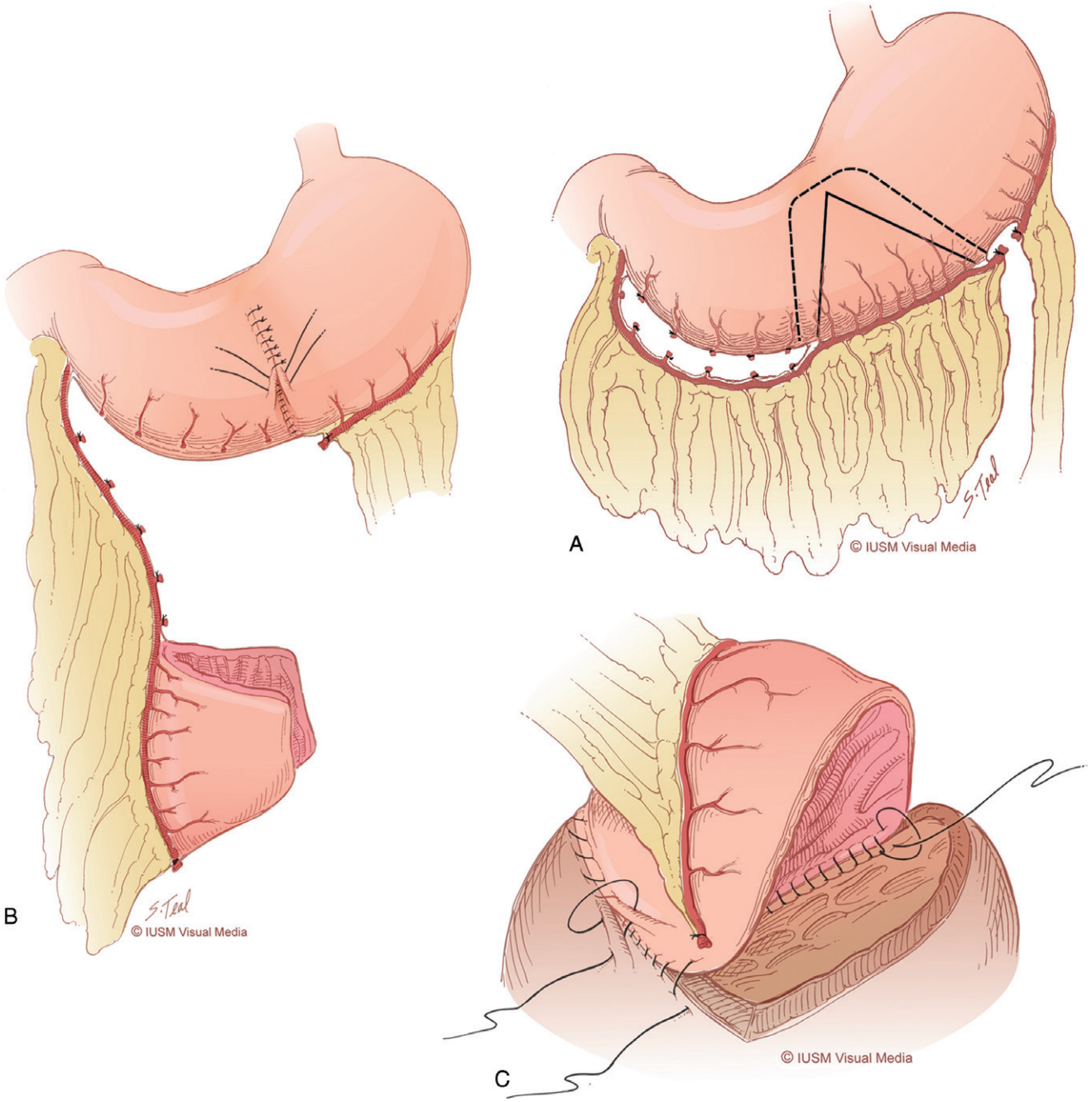


Figure 129–12. Gastrocystoplasty with use of the body. **A**, Gastric segment of body is mobilized on the right gastroepiploic artery. The left vessel may also be used; neither vessel as a pedicle should be free floating through the peritoneum. **B**, A longer gastric segment along the greater curvature with wider apex provides more surface area for augmentation. **C**, The gastric segment is anastomosed to the bivalved bladder with the mucosa inverted. (© Indiana University Medical Illustration Department.)

of stomach includes both the anterior and posterior wall. The segment used may be 10 to 20 cm along the greater curvature, depending on the patient's age and size as well as the needed volume (Fig. 129–12B). The incision into the stomach is stopped just short of the lesser curvature to avoid injury to branches of the vagus nerve controlling the gastric outlet. Branches of the left gastric artery just cephalad to the apex of this incision are suture ligated in situ before incision to avoid significant bleeding. Parallel atraumatic bowel clamps are placed on either side of the gastric incisions to avoid excessive bleeding or spillage of gastric contents. Alternatively, the stomach may be incised by use of a gastrointestinal stapling device that places a double row of staples on each side of the incision (Mitchell et al, 1992). The staple lines, however, must eventually be excised. The native stomach is closed in two layers with permanent sutures on the outer seromuscular layer.

Branches of the gastroepiploic artery to the antrum on the right or to the high corpus on the left are divided to provide mobilization of the gastroepiploic pedicle. For the eventual pedicle to be long enough to reach the bladder, the appropriate segment may be higher on the greater curvature if the right vessel is used as a pedicle or lower if it is based on the left. The vascular pedicle, with omentum, should not be free floating through the abdomen. The segment and pedicle may be passed through windows in the transverse mesocolon and mesentery of the distal ileum and carefully secured to the posterior peritoneum. Despite careful consideration for an adequate pedicle length, on occasion the gastric segment initially may not reach the bladder without tension. Either gastroepiploic artery may be mobilized closer to its origin for further length. The first few branches from the gastroepiploic artery to the isolated gastric segment may also be divided. Because of the rich submucosal arterial plexus in the stomach, devascularization of the isolated segment does not result. Rarely, it may be necessary to approximate some of the isolated gastric segment to itself in one corner. The gastric segment should be approximated to the native bladder with one or two layers of absorbable sutures, with care taken to invert the mucosa (Fig. 129–12C).

Raz and colleagues (1993) and Lockhart and associates (1993) have described the use of a much longer, more narrow segment of stomach based along the greater curvature. Use of this segment, which includes both body and antrum, somewhat narrows the lumen of the stomach along its entire length except at the fundus and pylorus. Raz and colleagues have isolated this segment with a gastrointestinal stapler so that the native stomach is never open. The segment used in both of these series is similar to that first described by Sinaiko (1956), the first surgeon to use stomach in bladder replacement. **Postoperative bladder and gastric drainage is no different from that described for intestinal cystoplasty.** Histamine-2 (H_2) blockers are often given in the early postoperative period to promote healing (Rink et al, 2000).

Postoperative Management

Early Management

Care of patients after cystoplasty is similar regardless of the gastrointestinal segment used in the procedure. Typically, **all patients have been maintained on nasogastric decompression until bowel function recovers, although in two studies** (Gundeti et al, 2006; Erickson et al, 2007) **it was suggested that nasogastric suction may not be necessary after ileocystoplasty. Attention to fluid and electrolyte management is important because third-space losses may be significant after extensive reconstructive surgery.**

Continuous drainage of the bladder is achieved by suprapubic cystostomy. Mucus production from small or large bowel may be excessive and can potentially occlude the drainage catheter. **The suprapubic tube should be irrigated at least three times daily and whenever drainage is slowed by mucus.** Extravesical drains may be removed after several days if drainage of urine is not apparent. The drains are generally removed more promptly in patients with a ventriculoperitoneal shunt to avoid potential infection. Some surgeons prefer a cystogram before discharge of the patient; others wait approximately 3 weeks for the study before clamping the suprapubic tube. All patients should begin on CIC every 2 to 3 hours during the day and one or two times at night after bladder healing is documented. The suprapubic tube is removed after catheterization is successfully under way and well tolerated. The duration between catheterizations is gradually increased during several weeks but should not exceed 4 to 5 hours during the day. Patients without neurologic impairment may eventually attempt to void spontaneously. All should check postvoid residual volumes and continue catheterizations if the residual urine amounts are significant.

Late Management

Routine radiographic surveillance of the upper urinary tract is indicated at 6 weeks, 6 months, and 1 year after augmentation cystoplasty. Most such surveillance may be done with ultrasonography. Serum electrolyte, blood urea nitrogen, and creatinine determinations along with urine cultures are performed several times in the first year after surgery. Not all positive urine cultures need to be treated in patients on CIC. Certainly, symptomatic cystitis or infections involving urea-splitting organisms should be cleared. Evaluation by ultrasonography and serum chemistries is then appropriate once a year. Eventually, yearly endoscopy for tumor surveillance may be performed. No consensus exists about the initiation or frequency of cystoscopic examination; however, we generally begin such surveillance approximately 5 years after augmentation. Husmann (2009) has suggested that surveillance may be of greater yield in patient populations at greater risk such as valve patients that are on immunosuppression after transplantation or exstrophy patients with their inherent increased risk for bladder adenocarcinoma. There is no experience demonstrating that routine endoscopy is cost effective or successful in this population.

Results and Complications

The effect of cystoplasty on the patient should be considered in two main categories. One must first consider the effect of removal of a relatively small portion of the gastrointestinal tract for use in urinary reconstruction. **Any more than rare development of gastrointestinal problems would be prohibitive, even if results were perfect from the standpoint of the urinary bladder.** Second, the effect of augmentation cystoplasty on the urinary bladder must be reviewed. The primary goal of augmentation is to provide a compliant urinary reservoir. **Therefore, the main consideration after augmentation is the storage pressure and capacity that are achieved. Any other effect on the urinary bladder is a side effect or complication that exists because bowel is not a perfect physiologic substitute for native bladder. It is clear that approximately one third of patients will require further surgery after augmentation cystoplasty because of various problems** (Metcalfe et al, 2006).

Gastrointestinal Effects

Postoperative bowel obstruction is uncommon after augmentation cystoplasty, occurring in approximately 3% of patients after augmentation (Gearhart et al, 1986; King, 1987; Mitchell and Pizer, 1987; Hollensbe et al, 1992; Rink et al, 1995a). **The rate of obstruction is equivalent to that noted after conduit diversion or continent urinary diversion** (McDougal, 1992b). Delicate handling of tissues, closure of mesenteric windows, and elimination of sites of internal herniation help avoid obstruction. Occasional series have suggested differing rates of bowel obstruction, depending on the segment used. These differences have not been consistent in most series and therefore are not likely to be significant; the incidence of bowel obstruction is low regardless of the gastrointestinal segment used and should not influence the choice of a particular segment for enterocystoplasty.

Reports of chronic diarrhea after bladder augmentation alone have been rare. Diarrhea can occur after removal of large segments of ileum from the gastrointestinal tract, although the lengths of the segments typically used for augmentation are rarely problematic unless other problems coexist. Much longer segments required for continent urinary diversion may increase the risk. The use of a typical colonic segment for augmentation only rarely results in a change in bowel function. **Removal of a segment from the gastrointestinal tract including the ileocecal valve is more likely to cause diarrhea.** Some children with neurogenic impairment depend on controlled constipation for fecal continence. Removal of the ileocecal valve from the gastrointestinal tract may significantly decrease bowel transit time. Loss of the valve can also allow bacterial backflow into the ileum, and the organisms may interfere with fat and vitamin B_{12} metabolism. Studies have noted chronic diarrhea in 10% to 23% of patients with neurogenic dysfunction after displacement of the ileocecal valve (King, 1987; Roth et al, 1995), although the risk may be lower for carefully selected patients (Husmann and Cain, 1999).

Ileum is the sole site of vitamin B_{12} absorption. **Removal of the distal ileum from the gastrointestinal tract may therefore result in vitamin B_{12} deficiency and megaloblastic anemia. Certainly, the terminal 15 to 20 cm of ileum should not be used for augmentation, although problems may arise even if that segment is preserved** (Waters et al, 1987; Steiner and Morton, 1991; Racioppi et al, 1999). Again, the risk is greater if longer segments of ileum are used as with continent diversion. Thirty-five percent of patients observed for 5 years after a Kock pouch were found to be deficient in vitamin B_{12} in one series (Akerlund et al, 1989). In general, the length of ileum used for augmentation is less than half of that used for a Kock pouch, so that vitamin B_{12} deficiency seems unlikely after routine bladder augmentation. Canning and associates (1989) evaluated 26 patients after bladder augmentation or replacement and found no patients with either fat malabsorption or vitamin B_{12} deficiency. Only 3 patients, however, were observed longer than 3 years, and longer observation is necessary because existing body vitamin B_{12} storage may last considerably longer (Stein et al, 1997a). Eventually, determination of vitamin B_{12} levels or routine injections of the vitamin may be appropriate after ileocystoplasty.

Early satiety may occur after gastrocystoplasty but usually resolves with time. Disorders of gastric emptying should be extremely rare, particularly when gastric body is used.

Bladder Compliance after Augmentation

An early lesson of past clinical experience with augmentation cystoplasty is the value of detubularization and reconfiguration of the bowel segment (Hinman, 1988; Koff, 1988). **Bowel in its native, tubular form continues to display peristalsis or mass contraction. The tubular form does not maximize the volume achieved for the surface area of bowel used.** Hinman (1988) demonstrated with a mathematical model that the maximum volume achieved for a given surface area occurs when a sphere is formed. No finished cystoplasty is a perfect sphere but should approach it as nearly as possible.

Some surgeons with extensive experience in augmentation cystoplasty and continent diversion have concluded that ileum is superior to other segments in terms of compliance after augmentation, although controlled experimental examination of similarly sized and used bowel or gastric segments is lacking (Goldwasser and Webster, 1986; Rink and McLaughlin, 1994; Studer and Zingg, 1997). On the contrary, one report has suggested superior results with colon compared with ileum (Shekarriz et al, 2000) when a longer colonic segment reconfigured into a U shape was utilized. Good results have been achieved with all segments in most cases, and it is more important to use a bowel segment well than to choose a particular bowel segment for every patient.

Most problems with pressure after augmentation cystoplasty occur from uninhibited contractions, apparently in the bowel segment. It is extremely rare not to achieve an adequate capacity or flat tonus limb unless a technical error has occurred with use of the bowel segment. On occasion, a small, scarred pelvis may prevent adequate expansion of the augmented bladder. When pressure contractions occur in the bladder after augmentation they are often noted in a rhythmic or sinusoidal pattern occasionally with increasing amplitude (Fig. 129–13). Contractions that begin at low amplitude later in filling and progress only near capacity may be of no clinical significance at all. Early contractions of higher pressure may occasionally result in persistent incontinence, delayed perforation, hydronephrosis, or vesicoureteral reflux. If patients have such clinical problems after augmentation, repeated urodynamic testing is necessary. One cannot assume the bladder is compliant after augmentation. Rhythmic contractions have been noted postoperatively with all bowel segments, although ileum seems the least likely to demonstrate remarkable urodynamic abnormalities and stomach the most likely.

After bladder augmentation or replacement, some urodynamic evaluation has suggested that colonic segments, whether cecum or sigmoid, still generate more pressure than ileum despite detubularization (Berglund et al, 1987; Jakobsen et al, 1987; Thuroff et al, 1987; Lytton and Green, 1989; Studer and Zingg, 1997). Other work has suggested that pressure contractions from the colon decrease with time (Hedlund et al, 1984; Sidi et al, 1986b). Nonetheless, Goldwasser and coworkers' review (1987) of enterocystoplasty demonstrated contractions above 15 cm H_2O in 42% of patients after ileocystoplasty versus 60% of those after colocystoplasty. Significant contractions, defined as those above 40 cm H_2O at a volume of less than 200 mL, were not noted in any of the ileal augmentations but persisted in 10% of colocystoplasties. Their work agreed with that of Berglund and colleagues (1987) and Studer and Zingg (1997) in suggesting that ileal reservoirs have lower basal pressures and less motor activity. None of these studies critically controlled for the size of the bowel segment or the technique in which it was used. In fact, a canine model of partial bladder replacement using identically sized segments failed to

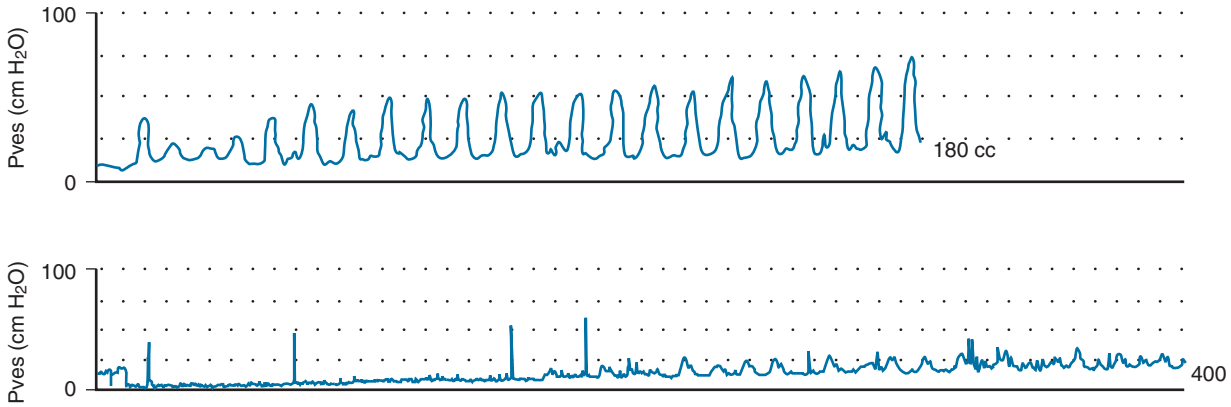


Figure 129–13. Rhythmic, sinusoidal contractions (*top*) may occur after bladder augmentation, in this case with stomach. Contractions of significant amplitude early in filling occasionally require secondary augmentation. After secondary augmentation with ileum (*bottom*), urodynamics show that contractions still occur but are much lower in pressure and occur later in filling.

demonstrate in vitro or in vivo any differences between the gastrointestinal segments (Nelson et al, 2005).

Rhythmic contractions after gastrocystoplasty have been noted in up to 62% of patients (Adams et al, 1988; Atala et al, 1993a; Gosalbez et al, 1993a; Roth et al, 2000). The segment of stomach initially described for augmentation with the body was much smaller than segments of ileum or colon commonly used for cystoplasty. Use of a slightly larger gastric segment that is longer along the greater curvature results in improved urodynamics after augmentation with less prominent contractions (Adams et al, 1995; Kurzrock et al, 1998; Koraitim et al, 1999; DeFoor et al, 2003b). Leong (1988) has suggested that an antral segment of stomach is less likely to demonstrate such contractions.

In perhaps the largest experience with pediatric bladder augmentation, Hollensbe and associates at Indiana University found that approximately 5% of several hundred patients had significant uninhibited contractions after augmentation cystoplasty causing clinical problems (Hollensbe et al, 1992). Pope and Rink (1999) found that 6% of more than 300 patients required secondary augmentation of a previously augmented bladder for similar problems in long-term follow-up. With longer follow-up, the same group has eventually performed reaugmentation in 9% of patients (Metcalfe et al, 2006). These secondary augmentations represent true failures of the primary cystoplasty, not from any side effect or complication but from failure to achieve the objective—capacity and compliance. In that series, sigmoid colon followed by stomach and then ileum were more likely to require reaugmentation. A colonic segment closed at the ends and not generally reconfigured otherwise was typically used in that experience. Other studies have suggested that stomach is more likely than colon to require secondary intervention (El-Ghoneimi et al, 1998).

Metabolic Complications

Chloride Absorption and Acidosis. **The first recognized metabolic complication related to storage of urine within intestinal segments was the occasional development of hyperchloremic metabolic acidosis after ureterosigmoidostomy** (Ferris and Odel, 1950). Patients with this metabolic derangement were noted to have fatigue, weakness, anorexia, and polydipsia. Koch and McDougal (1985) **demonstrated the mechanisms by which acid is absorbed from urine in contact with intestinal mucosa.** Resorption in the form of ammonium results in chronic acid loading. Patients with normal renal function are generally able to handle the resorbed load of chloride and acid without frank acidosis. Mitchell and Piser (1987) **noted that essentially every patient after augmentation with an intestinal segment had an increase in serum chloride concentration and a decrease in serum bicarbonate level, although full acidosis was rare if renal function was normal.** Similar trends of increased serum chloride and decreased bicarbonate have been noted with ileal conduits (Malek et al, 1971) and continent urinary reservoirs (Allen et al, 1985; McDougal, 1986; Ashken, 1987; Thuroff et al, 1987; Boyd et al, 1989). More severe acidosis and electrolyte disturbances requiring treatment have been reported despite normal renal function (Schmidt et al, 1973; Whitmore and Gittes, 1983). Such derangements may be debilitating to the patient if they are not recognized and treated, and death of patients has been reported (Heidler et al, 1979). Hall and colleagues (1991) noted that there is an increase in the urinary acid load with wasting of bone buffers even in the absence of frank acidosis. Such wasting may result in bone demineralization and could potentially cause retarded growth in children after augmentation cystoplasty (Abes et al, 2003; Hafez et al, 2003; Vajda et al, 2003). Patients with acidosis should receive bicarbonate therapy. Whether all patients with intestine in the lower urinary tract might benefit from supplemental bicarbonate is controversial. Nurse and Mundy (1989) have suggested that arterial blood gas values may be more sensitive than serum bicarbonate or chloride levels for detecting acidosis. Stein and associates (1998) thought that measurements of arterial blood gas for base deficit allowed early treatment of acidosis and avoidance of bone demineralization. In severe cases of acidosis, chloride transport can be blocked with chlorpromazine and nicotinic acid.

Although jejunum is rarely used for bladder reconstruction, storage of urine in this segment results in a unique metabolic pattern of hyponatremic, hypochloremic, and hyperkalemic metabolic acidosis. The problem is often associated with significant hypovolemia.

Gastric mucosa is a barrier to chloride and acid resorption and, in fact, secretes hydrochloric acid (Piser et al, 1987). This difference was the primary factor in the initial consideration of stomach for use in the urinary tract. This secretory nature was shown to be of benefit in azotemic animals during acid loading (Piser et al, 1987; Kennedy et al, 1988). **Serum chloride does decrease and serum bicarbonate increases slightly**

after gastrocystoplasty, whether antrum or body is used in patients with normal and impaired renal function (Adams et al, 1988; Ganesan et al, 1991; Kurzrock et al, 1998). In 21 patients with renal insufficiency, serum bicarbonate improved in all patients except one after gastrocystoplasty, and many patients requiring oral bicarbonate therapy before cystoplasty did not do so after gastrocystoplasty (Ganesan et al, 1991). A similar benefit has been noted in a smaller group of patients with renal failure (Sheldon and Gilbert, 1991).

Patient Growth. Delayed or slowed growth in some children after intestinal cystoplasty has previously been recognized (Wagstaff et al, 1991, 1992; Mundy and Nurse, 1992). A delay in linear growth was noted in 20% of almost 200 pediatric patients without any gross biochemical abnormalities. However, no control patients were included in the series, and body habitus and growth are difficult to measure and predict in children with myelodysplasia. Such patients make up the majority in most series of augmentation cystoplasty. Gros and colleagues (2000) evaluated growth in exstrophy patients. Patients requiring augmentation were matched retrospectively with a similar group not requiring bladder augmentation. Hydronephrosis was not mentioned in the patients but was unlikely with a diagnosis of exstrophy. Only 1 patient was noted to have acidosis in either group. Other factors that might affect growth, such as urinary tract infection, were not controlled. Of 17 patients with adequate measurements before and after augmentation cystoplasty, 14, or 82%, had a decline in percentile height postoperatively. The decline corresponded to a 1.5-inch decrease in expected height. The pattern of growth was significantly different between patients with and without augmentation in the series. That series is small, and no evaluation of familial growth patterns or ultimate height was possible; however, the findings are worrisome, particularly because Feng and coworkers (2002) noted similar differences in exstrophy patients. In the absence of any serum abnormalities the exact mechanism of delayed growth was not evident, although it seems likely to be related to chloride absorption and subclinical acidosis (Koch and McDougal, 1988; Bushinsky, 1989; Hochstetler et al, 1997). It should be noted that Taskinen and coworkers (2008) found no adverse effect on longitudinal growth after bladder augmentation in the exstrophy population. Three recent series did show the effect of bowel cystoplasty on bone mineral density in some patients (Abes et al, 2003; Hafez et al, 2003; Vajda et al, 2003), although Mingin and associates (2002) noted no such changes. One must be careful to determine whether any such changes are due to augmentation cystoplasty or the underlying pathologic process (Boylu et al, 2006; Taskinen et al, 2007). Better analysis of subtle metabolic alterations after enterocystoplasty may establish better understanding of the effect on growth, minimize changes, or aid in early treatment to avoid the complication (Brkovic et al, 2004).

Alkalosis. The secretory nature of gastric mucosa may at times be detrimental to the patient and can result in two unique complications of gastrocystoplasty. Severe episodes of hypokalemic, hypochloremic metabolic alkalosis that followed acute gastrointestinal illnesses have been noted in 5 of 37 patients after gastrocystoplasty (Hollensbe et al, 1992). The episodes were significant enough to require hospitalization in all cases and were recurrent in 2 patients. Three of the 5 patients suffering the complication had renal insufficiency and would not have been good candidates for augmentation with other segments because of acidosis. Ganesan and associates (1991) noted similar episodes of alkalosis in 5 of 21 patients with renal insufficiency after gastrocystoplasty. **Those patients with the primary indication for consideration of gastrocystoplasty may be the ones at greatest risk for this unusual complication.** It has been proposed that the alkalosis results from ongoing chloride loss from the gastric segment in the bladder in the presence of decreased oral intake. McDougal (1992a) suggested that the decreased ability to excrete bicarbonate from an impaired kidney may compound the problem. Gosalbez and associates (1993b) demonstrated persistently increased fractional excretion of chloride despite profound hypochloremia, suggesting that inappropriate gastric secretion is likely to be the primary mediator. One patient in their series eventually required resection of three fourths of the gastric segment in the bladder because of recurrent problems with alkalosis, and several required therapy with H_2 blockers or H^+,K^+ pump inhibitors.

All patients and families should be made aware of this potential problem because it has been reported to occur intermittently in between 3% and 24% of patients. A composite reservoir of stomach and ileum or colon may provide a more metabolically neutral reservoir (McLaughlin et al, 1995; Austin et al, 1997, 1999, 2001), although they have typically been constructed in only complex circumstances. Duel and associates (1996) have used stomach and colon together to advantage in a staged fashion for oncology patients; patients initially diverted with a colon conduit after cystectomy had a composite reservoir constructed later after cure from tumor was ensured.

Hematuria-Dysuria Syndrome

Acid secretion by gastric mucosa may result in another unique problem after gastrocystoplasty: the hematuria-dysuria syndrome. Mitchell's group has characterized this syndrome well (Nguyen et al, 1993; Plaire et al, 1999). **Virtually all patients after gastrocystoplasty with normal sensation have occasional hematuria or dysuria with voiding or catheterization beyond that which is expected with other intestinal segments** (Leonard et al, 1999). All patients should be warned of this potential problem, although these symptoms are intermittent and mild in most patients and do not require treatment. The problem has led one group to recommend avoiding gastrocystoplasty in patients with bladder exstrophy (El-Ghoneimi et al, 1998). The dysuria is certainly not as problematic in patients with neurogenic dysfunction. In the experience of Nguyen and colleagues (1993), 36% of patients have developed signs or symptoms of the hematuria-dysuria syndrome after gastrocystoplasty; 14% of patients have required treatment with medications, including 9% on a regular basis. They believe that patients who are incontinent or have decreased renal function are at increased risk. Others have noted a similar requirement for short-term and chronic medical therapy (Hollensbe et al, 1992; Adams et al, 1995). In the authors' experience and that of Nguyen and colleagues, the symptoms of the hematuria-dysuria syndrome respond well to H_2 blockers and H^+ pump blockers. Bladder irrigation with baking soda may also be effective. It has been demonstrated that urine pH may decrease remarkably after meals following gastrocystoplasty (Bogaert et al, 1995). The signs and symptoms of the hematuria-dysuria syndrome are most likely secondary to acid irritation. Recent work has suggested that *Helicobacter pylori* may play a role in this complication as it may in acid complications in the native stomach (Celayir et al, 1999). Such problems can occur but are less frequent after antral cystoplasty where there is a smaller load of parietal cells (Ngan et al, 1993).

Acid in the urine may also cause external irritation. Leong first noted glanular excoriation after gastrocystoplasty in a patient with voiding symptoms (Ngan et al, 1993). Similar meatal irritation has

been noted in other patients after gastrocystoplasty; most have had significant dysuria. Nguyen and associates (1993) noted skin excoriation in 8 of 57 patients after gastrocystoplasty; all 8 patients had some element of urinary incontinence. **It is imperative to achieve reliable urinary continence in patients undergoing gastrocystoplasty because urine leakage may result in the exposure of the skin to gastric secretions and in gastric secretions that are poorly diluted and buffered.** Such dilution is important; Reinberg and coworkers (1992) reported a perforation of a gastric segment in a defunctionalized bladder after gastrocystoplasty. They then evaluated the influence of urine on gastrocystoplasties in dogs (Castro-Diaz et al, 1992). The animals developed marked inflammation of the gastric segment and native bladder after construction of a dry gastrocystoplasty; three of nine dogs developed ulceration and perforation. Use of H_2 blockers resulted in some protection for the animals; however, such a clinical situation should certainly be avoided. Rare perforations and ulcerations have been noted clinically without defunctionalization (El-Ghoneimi et al, 1998; Mingin et al, 1999b).

Mucus

Intestinal segments continue to produce mucus after placement in the urinary tract. The proteinaceous material can potentially impede bladder drainage during voiding or CIC, particularly in pediatric patients in whom the use of small-caliber catheters is necessary. Mucus may serve as a nidus for infection or stone formation when it remains in the bladder for long periods. Mucus production often increases after cystoplasty in the presence of cystitis. Kulb and associates (1986) have shown experimentally in dogs that colonic segments produce more mucus than ileum does and that gastric segments produce the least amount. This has been noted clinically as well. Most patients do not require any routine bladder irrigations for mucus after gastrocystoplasty. Villous atrophy in the ileum has been documented after long-term placement in the urinary tract. It has been suggested that such atrophy may result in decreased mucus production (Gearhart, 1987), although laboratory demonstration of any decrease in production with time has not been evident (Murray et al, 1987). Hendren and Hendren (1990) noted a decrease in mucus production from colonic segments over years; however, others have not been impressed with such changes (Rink et al, 1995a). Glandular atrophy in colonic mucosa has not been noted histologically (Mansson et al, 1984). **Routine use of daily bladder irrigations to prevent mucus buildup may minimize complications of enterocystoplasty, such as urinary tract infection and calculi** (Hensle et al, 2004).

Urinary Tract Infection

Bacteriuria is common after intestinal cystoplasty, particularly among patients requiring intermittent catheterization (Gearhart et al, 1986; Hendren and Hendren, 1990; King, 1991). Recent experience with bowel neobladders has demonstrated that patients who are able to spontaneously void to completion frequently maintain sterile urine. **It appears that the use of CIC is a prominent factor in the development of bacteriuria in patients after augmentation cystoplasty.** Bacteriuria has been noted even when patients are maintained on daily oral antibiotics or antibiotic irrigation (Gearhart et al, 1986; Casale et al, 1999). In Hirst's (1991) experience, persistent or recurrent bacteriuria occurred in 50% of patients augmented with sigmoid colon versus 25% of those after ileocystoplasty. Hollensbe and coworkers (1992) noted bacteriuria much more commonly in patients requiring CIC regardless of the segment considered. The incidence of symptomatic cystitis after cystoplasty probably depends on the length of follow-up and the diligence with which symptoms are sought. All patients and families should be told to expect some signs or symptoms of cystitis. Recurrent episodes of symptomatic cystitis requiring treatment occurred in 23% of patients after ileocystoplasty, 17% after sigmoid cystoplasty, 13% after cecocystoplasty, and 8% after gastrocystoplasty at Indiana University (Hollensbe et al, 1992). Febrile urinary tract infections occurred in 13% of those 231 patients after augmentation. The same trend among different bowel segments was noted for febrile infections, although there was no statistically significant difference among the various segments. **The incidence of pyelonephritis after augmentation cystoplasty, as long as upper tract problems are corrected, is similar to that noted for conduit diversion, whether refluxing or not** (McDougal, 1992b). Recurrent infections resulting in deterioration of renal function in the absence of other problems have been rare after effective augmentation. Infections may occasionally be more problematic in an immunocompromised patient (Alfrey et al, 1997).

Not every episode of asymptomatic bacteriuria requires treatment in patients performing CIC. Bacteriuria should be treated for significant symptoms, such as incontinence or suprapubic pain, and perhaps for hematuria, foul-smelling urine, or remarkably increased mucus production. **Bacteriuria should be treated if the urine culture demonstrates growth of a urea-splitting organism that may lead to stone formation.** To minimize infection, patients requiring CIC must perform it on a regular basis to avoid increased reservoir pressures and work to empty the bladder completely. This process may require periodic irrigation of mucus as well as patience with the catheter in place. Special care must be taken by patients catheterizing through a continent abdominal wall stoma. Such patients may have more difficulty completely emptying the bladder from a nondependent stoma. Most can do so with effort (Ludlow et al, 1995). Although catheterization is not routinely a sterile technique, proper clean technique should be emphasized.

Calculi

Another long-term complication of augmentation cystoplasty is bladder calculus formation. In the early 1990s, several series reported calculi in 18% of patients after augmentation cystoplasty (Hendren and Hendren, 1990; Hirst, 1991). Blyth and associates (1992) noted calculus formation in 30% of such patients; they found that patients catheterizing through an abdominal wall stoma have the highest risk, probably because of incomplete emptying. Palmer and associates (1993) noted urolithiasis in 52% of patients after augmentation cystoplasty. Metcalfe and colleagues (2006) noted a 15% rate of bladder stone formation in 500 patients with long-term follow-up after enterocystoplasty; the reasons for these remarkable differences are not clear. **The majority of bladder stones in this population of patients are struvite, and bacteriuria has been thought to be an important risk factor.** Any infection with a urea-splitting organism should therefore be treated aggressively. All patients requiring CIC, particularly those who have already formed stones, should make every effort to empty the bladder completely with each catheterization. If stones are found in patients voiding spontaneously after augmentation, the adequacy of emptying should be reevaluated. The association of urinary stasis with stone formation is well established. Routine bladder irrigations to avoid buildup of inspissated mucus may remove a nidus for stone

formation. The group at Indiana University and others have stressed irrigations and asked patients and families to routinely irrigate the bladder several times a day after augmentation (Rink et al, 1995a; Hensle et al, 2004). Compliance with such irrigations may lower the frequency of stone formation.

Stones have been noted after the use of all intestinal segments, with no significant difference noted between small and large intestine. Struvite stones are less likely after gastrocystoplasty (Kaefer et al, 1998; Kronner et al, 1998a), probably because of decreased mucus production and acid that minimizes bacteriuria. Uric acid calculi have rarely been noted in the bladder after gastrocystoplasty (Kaefer et al, 1998). Clearly, any foreign body will serve as a nidus for stone formation; the use of permanent suture or staples in the urinary tract should be avoided during enterocystoplasty. Khoury and associates (1997) looked for metabolic problems in patients after augmentation and noted low urinary citrate levels in patients with and without stones. They thought that poor emptying and mucus buildup were more significant factors.

Tumor Formation

A well-recognized complication of ureterosigmoidostomy has been the development of tumors, primarily adenocarcinoma, at the ureterocolonic anastomotic site. In Husmann and Spence's (1990) review of reported tumors after ureterosigmoidostomy the latency for development of such tumors averaged 26 years and ranged from 3 to 53 years. Adenocarcinomas were the prominent tumors that developed, but benign polyps and other types of carcinoma were also found. Eraklis and Folkman (1978) estimated that the risk for development of such tumors is increased by 7000-fold over that of age-matched controls after ureterosigmoidostomy. The exact basis for the increased risk is unknown; however, *N*-nitroso compounds thought to originate from a mixture of urine and feces may be carcinogenic. These compounds have been noted in the urine of patients with conduit diversion and augmentation (Treiger and Marshall, 1991). Husmann and Spence (1990) suggested that those compounds are more likely to be enhancing agents rather than a lone cause of tumor development. It has been proposed that inflammatory reaction at the anastomotic site may induce growth factor production, which in turn increases cellular proliferation.

Filmer and Spencer (1990) **identified 14 patients who have developed adenocarcinoma in an augmented bladder, and several more have been reported since then.** Nine of those tumors occurred after ileocystoplasty and 5 after colocystoplasty. One study has noted a relatively high incidence of tumor after gastrocystoplasty (Castellan et al, 2007). **Experimental work in the rat demonstrated hyperplastic growth in the augmented bladder with use of all intestinal segments; no segment showed any particular increased risk** (Klee et al, 1990; Buson et al, 1993; Spencer et al, 1993; Little et al, 1994). The applicability of such findings to humans is uncertain. The long latency noted for tumor development after ureterosigmoidostomy suggests that short-term follow-up after augmentation cystoplasty is not adequate to evaluate tumor formation. The earliest reported tumor after augmentation was found only 4 years after cystoplasty (Carr and Hershown, 1997). **Patients undergoing augmentation cystoplasty should be made aware of a potential increased risk for tumor development. Yearly surveillance of the augmented bladder with endoscopy should eventually be performed; the latency period until such procedures are necessary is not well defined** (Vajda et al, 2002). The earliest reported tumor after augmentation was found only 4 years after cystoplasty (Carr and Herschorn, 1997). Transitional cell carcinoma, hyperplasia, and dysplasia have also been noted near the anastomosis in humans (Gregoire et al, 1993; Barrington et al, 1997; Soergel et al, 2004). Transitional cell carcinomas associated with augmentation cystoplasty have been aggressive; often the patients have metastatic disease at presentation (Metcalfe et al, 2006; Higuchi et al, 2010). Urothelium adjacent to the anastomosis has been demonstrated to be genetically unstable on biopsy in one study (Appanna et al, 2007). Urine cytology or flow cytometry may ultimately become useful in surveillance.

Delayed Spontaneous Bladder Perforation

Perhaps the most disturbing complication of augmentation cystoplasty is delayed bladder perforation. Patients presenting with spontaneous perforation after augmentation cystoplasty are generally quite ill with abdominal pain, distention, and fever. Sepsis has been common. Nausea, decreased urine output, and shoulder pain from diaphragmatic irritation have also been noted. Perforations have been found in evaluation of asymptomatic pelvic masses (Pope et al, 1999). **Patients with neurogenic dysfunction often have impaired lower abdominal sensation and present later in the course of the illness; severe sepsis and death have occurred.** Patients with perforation after gastrocystoplasty often present promptly because of acid irritation. **A high index of suspicion for perforation is necessary. Contrast cystography is diagnostic in most cases** (Braverman and Lebowitz, 1991; Rosen and Light, 1991; Bauer et al, 1992) (Fig. 129–14). Thorough technique is important to identify as many true positives as possible with cystography (Braverman and Lebowitz, 1991). Some reports of perforations have noted a significant false-negative rate on cystography (Rushton et al, 1988; Sheiner and Kaplan, 1988; Pope et al, 1999) and suggested that ultrasonography and computed tomography improve diagnostic accuracy. They recommended that one of those studies be done in any child thought to have a perforation if the initial cystogram is normal.

Etiology. **The etiology of delayed perforations within a bowel segment is unknown.** It has been suggested that perforation might be secondary to traumatic catheterization in some cases (Elder et al, 1988; Rushton et al, 1988). Perforation of a

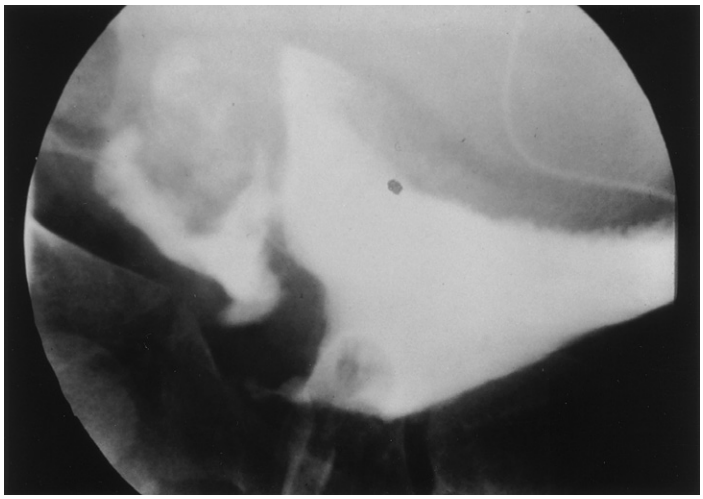


Figure 129–14. After complete filling, a sagittal view on the cystogram demonstrates a spontaneous bladder perforation on the post-drain view.

bladder not previously augmented has been recognized after CIC (Reisman and Preminger, 1989). It seems unlikely that catheterization trauma is the lone cause in most patients. The location of the perforations has been variable among patients and even in a single patient with multiple perforations. Perforations have occurred after augmentation in patients who did not catheterize at all. Others have suggested that trauma to the bowel because of fixed adhesions resulting in shearing forces with emptying and filling may result in perforation (Elder et al, 1988). Chronic, transmural infection of the bladder wall has also been proposed as a cause. **Histologic examination of bowel segments adjacent to areas of perforation has noted necrosis, vascular congestion, hemorrhage, and hemosiderin deposition compatible with chronic bowel wall ischemia** (Crane et al, 1991). **Chronic overdistention of the bladder might result in such ischemia.** Decreased perfusion in dog bowel used for augmentation can be induced experimentally with high intravesical pressure (Essig et al, 1991). Those changes were noted more prominently at the antimesenteric border of the bowel. Chronic ischemia may thus play a significant role in at least some delayed bladder perforations. Anderson and Rickwood (1991) have reported perforations occurring in bladders with significant uninhibited contractions after augmentation, as have others (Pope et al, 1998). **High outflow resistance may maintain bladder pressure rather than allow urine leakage and venting of the pressure, potentially increasing ischemia** (Martinez del Castillo et al, 2005). Hyperreflexia alone is not likely to be a solitary cause of perforation; the complication was essentially never recognized in the era before bowel detubularization and reconfiguration when persistent pressure contractions were more common after augmentation cystoplasty. **Once bowel is reconfigured, however, it may be more susceptible to ischemia if high pressure does persist.** Failure to perform CIC on a regular basis when needed to empty may exacerbate such issues (DeFoor et al, 2003a; Martinez del Castillo et al, 2005).

The majority of patients suffering perforations after augmentation cystoplasty have had myelodysplasia. The incidence of perforation has been lower in series of patients with other diagnoses requiring bladder reconstruction (Hendren and Hendren, 1990). The role of neurogenic dysfunction in the etiology of these perforations is unclear. No matter what the etiology there is likely to be some field effect on the entire segment. Once a patient has suffered a spontaneous perforation, the chance of recurrence is significant (Hollensbe et al, 1992; Martinez del Castillo et al, 2005; Metcalfe et al, 2006). One fourth of patients with ruptures in one very large series had a recurrence (Metcalfe et al, 2006). Consideration must eventually be given to removal of the original segment and replacement by another after repeated perforation.

Incidence. Early postoperative leaks from the bowel-to-bowel or bowel-to-bladder anastomoses after augmentation cystoplasty are rare and represent a technical error or problem with early healing. **Delayed perforations more commonly occur within the bowel segment itself and represent a problem with long-term storage of urine within an intestinal segment.** There may be no particular increased risk of one intestinal segment over another. At Indiana University, perforations were noted in 43 of 500 patients (8.6%) undergoing cystoplasty (Metcalfe et al, 2006) an average of 4.3 years after augmentation. Analysis of this experience suggested that the use of sigmoid colon was the only significantly increased risk. Several other large series of patients with sigmoid cystoplasty have noted a low incidence of delayed perforation (Sidi et al, 1987a; Hendren and Hendren, 1990; Shekarriz et al, 2000). At Children's Hospital Boston, the incidence of perforation after augmentation was highest in ileum (9.3%) and less frequent in ileocecal, sigmoid, and gastric segments (Bauer et al, 1992).

With inconsistent differences across multiple large series it is unlikely that any given enteric segment is at significantly increased risk for perforation and that likely multiple factors influence the risk for the complication. Pope, Rink, and the Indiana group (1999) still believe strongly from their experience that sigmoid colon has a greater risk for perforation based on a four-time higher rate than ileum there. Some other experienced surgeons think the same (Ransley, 1998). The highest rate of perforation noted has been 16.6% in one relatively small series (Martinez del Castillo et al, 2005); however, it is reasonable to present an expected risk of about 9% to patients and families based on experience at Indiana University (Metcalfe et al, 2006).

Treatment. **The standard treatment of spontaneous perforation of the augmented bladder is surgical repair, as it is for intraperitoneal rupture of the bladder after trauma.** There are reported series of conservative management for suspected perforation (Slaton and Kropp, 1994). Conservative management including catheter drainage, antibiotics, and serial abdominal examinations was successful in 87% of the patients, although only 2 of the 13 patients with suspected ruptures had x-ray documentation unequivocally identifying a perforation. Even patients who do well with conservative management during the acute episode often require eventual surgical intervention (Pope et al, 1999). Such management may be a consideration in a stable patient with sterile urine. The surgeon should certainly have a low threshold for surgical exploration and repair. The majority of patients with perforations have myelodysplasia and present late in the course of the disease because of impaired sensation. Increasing sepsis and death of the patient may result from a delay in diagnosis or treatment.

Pregnancy

Good success has been reported for female patients after bladder augmentation, bladder neck repair, or continent urinary diversion in terms of continence and upper tract preservation. Little note has been made of fertility issues. **Limited information exists regarding the outcome of pregnancy in women who have undergone augmentation cystoplasty, because many of these patients are just reaching childbearing age.** Older women undergoing bladder replacement for oncologic reasons often are rendered infertile by the nature of the disease and treatment.

Three major issues are raised in the context of pregnancy and bladder reconstruction: how the expanding uterus will affect the pedicle of the reconstruction; how to manage bacteriuria during pregnancy; and whether cesarean section is needed in all or some of these patients and, when it is performed, how to manage the pedicle of the augmentation patch.

Experience during pregnancy related to the pedicle of a prior bladder augmentation is limited. Hatch and colleagues (1991) and Schumacher and coworkers (1997) have noted that the mesenteric pedicle to bladder augmentations did not appear to be stretched at the time of cesarean section. In those cases the pedicle was not located near the exposed anterior uterus but deflected laterally. Schilling and colleagues (1996) recognized a difference between urinary diversion and augmentation. With diversion, the pedicle of the intestinal segment extended cranially and laterally away from the uterus, whereas the pedicle covered the uterus after bladder augmentation. Neither process prevented the rise of the

uterus during pregnancy. Those authors speculated that the mesentery underwent changes that enabled deflection or stretch without any adverse effect on circulation. Loss of the augmentation due to mechanical effect on the pedicle from the enlarging uterus has not been reported. Pregnancy itself has not had a reported detrimental effect on the augmentation other than temporary incontinence in some patients, particularly during the third trimester. Successful pregnancy with spontaneous vaginal delivery has been observed in a few cases with bladder augmentations (Quenneville et al, 2003) and other forms of urinary reconstruction, such as ureterosigmoidostomy and ileal conduit urinary diversion (Pedlow, 1961; Asif and Uehling, 1969). Schumacher and coworkers (1997) reviewed their experience with pregnancy and delivery in patients who had undergone continent catheterizable ileocecal diversion and found no major complications. It is likely that this would also be true for other forms of reconstruction (Wren et al, 2003). Urgency and late difficulty with catheterization have been noted with Kock continent ileostomies (Ojerskog et al, 1988) and can occur with any continent abdominal wall stoma (Greenwell et al, 2003).

Urinary tract infections may be problematic during pregnancy in women who have undergone urinary reconstruction including bladder augmentation. Ureteral dilation, increased residual urine, and diminished tone to the upper tract may all be important risk factors (Hill et al, 1990; Hatch et al, 1991). Asymptomatic bacteriuria is usually treated immediately in pregnancy women because of an increased rate of progression to symptoms and pyelonephritis and because of the potential significant consequences of pyelonephritis. Asymptomatic bacteriuria is often not treated routinely in a woman on intermittent catheterization after cystoplasty when not pregnant. There is little consensus about the role of antibiotics and the risk of asymptomatic bacteriuria in the same population once pregnant (Thomas and Adams, 2009). Antibiotics, if used, must not be teratogenic.

Patients with preexisting hydronephrosis may be at increased risk not only for infection but also for worsening hydronephrosis. Some may require stent or nephrostomy tube placement (Gitlin et al, 2002). The patients at greatest risk during pregnancy after reconstruction are those with renal insufficiency. Some may demonstrate deterioration of function or permanent failure (Jones and Hayslett, 1996). Uterine prolapse has been noted to occur at a higher rate with pregnancy, particularly in exstrophy patients (Kennedy et al, 1993). Because of such concerns, Stein and associates (1994) suggested fixation of the uterus during reconstructive surgery.

The need for cesarean section is probably not universal for all women with bladder reconstructions. Adequate progression of spontaneous vaginal delivery, however, may require flaccid, distensible pelvic tissues, which may not be present after extensive pelvic surgery. It is unknown if tissues fixed from previous operative repairs can undergo the trauma of delivery and resume the same level of function as before the pregnancy. The authors' bias would be that women having undergone extensive bladder neck repair should consider cesarean delivery, particularly if the progression toward spontaneous vaginal delivery is slowed or difficult at all. Although there are reports of spontaneous vaginal delivery in the presence of an artificial urinary sphincter (Fishman and Scott, 1993; Creagh et al, 1995), the presence of such a prosthetic device raises a concern for erosion with a long, difficult delivery.

If cesarean section is required or selected, it is imperative to protect the augmentation or continent stoma and its vascular pedicle. The anterior uterus can typically be exposed atraumatically, although some time and patience may be required to protect the bladder. Such exposure may be more difficult if multiple abdominal stomas are present. The reconstructive urologist familiar with the patient and her anatomy should be present during cesarean section to maximize safety.

Choice of Segment

The use of bowel for augmentation of the bladder was first described experimentally by Tizzoni and Foggi in 1888 and in humans by Mikulicz in 1898 (Orr et al, 1958). Extraordinary advances have been made in the use of the bowel in urinary tract reconstruction since then. Bladder augmentation is used for patients with bladder dysfunction related to a small-capacity, noncompliant reservoir. **Enterocystoplasty improves bladder capacity and compliance in most cases when medical management fails.** It is obvious from the preceding discussion that there is no one single bowel segment that is perfect for augmentation in all patients. All gastrointestinal segments have been used and continue to be used with good results. Unremitting medical problems are relatively rare after augmentation cystoplasty if used appropriately in well-selected patients. No one bowel segment has a clear advantage over another when all such problems are considered. Diagnosis, anatomy, and physiology may suggest that one bowel segment is preferable for a particular patient. Each surgeon interested in augmentation cystoplasty should be familiar with the advantages and disadvantages of each segment in different settings.

In many routine cases, any gastrointestinal segment may be chosen for cystoplasty purely on the basis of the personal preference and familiarity of the surgeon. The surgeon's experience and confidence in using a segment are important. **The authors believe that no one bowel segment is the best choice in**

Key Points: Augmentation Cystoplasty

- No matter the gastrointestinal segment used, that segment should be reconfigured and widely anastomosed to the native bladder to maximize capacity and compliance.
- Failures to achieve adequate compliance are rare (5%-10%) and are usually related to rhythmic pressure contractions.
- Gastrointestinal effects are rare, although chronic diarrhea may occur if the ileocecal segment is used in the neurogenic population.
- Ammonium resorption from urine in contact with intestinal mucosa can cause chronic metabolic acidosis, particularly among patients with renal insufficiency.
- Acid secretion after gastrocystoplasty results in two unique potential complications: hematuria-dysuria syndrome and acute metabolic alkalosis.
- Bacteriuria is common after cystoplasty and does not always require treatment.
- Bladder calculi, usually struvite, occur in 10% to 30% of patients after augmentation cystoplasty but may be minimized by routine irrigations for mucus.
- Adenocarcinoma in the intestinal segment has been reported as early as 4 years after augmentation cystoplasty but, thus far, has not occurred with the frequency noted after ureterosigmoidostomy.
- Delayed spontaneous perforation of the bowel segment can be expected in 5% of patients after augmentation. It has occurred most frequently in colonic segments used in the neurogenic population.

all patients and that optimal results are achieved when the bowel segment is chosen on the basis of the needs of the particular patient. The segment must then be used correctly. Ileum is preferred if there is no clear advantage to or reason for use of another segment. Stomach is reserved for children with renal insufficiency and acidosis, short-gut syndrome, and heavy irradiation. Sigmoid cystoplasty is used in select patients without reservation; clearly, good results can be expected for most patients with any segment if it is used properly.

Alternatives to Gastrointestinal Cystoplasty

Largely because of the complications and side effects just reviewed, alternative methods that can achieve a large-capacity, compliant reservoir remain attractive. Efforts have covered the spectrum from synthetic materials and autologous grafts to construction of a bladder diverticulum (autoaugmentation) and to various forms of neural stimulation. **Some of these alternatives appear to hold promise, but none has stood the test of time for true comparison to intestinal cystoplasty.**

An ideal tissue for increasing capacity and improving compliance would have transitional epithelium to be relatively impermeable and avoid metabolic changes. The lining would also not produce mucus and carry no increased potential for tumor development. The ability to augment the bladder without violation of the peritoneal cavity would also decrease potential morbidity. Two such alternative procedures are ureterocystoplasty and autoaugmentation. With ureterocystoplasty there is good muscle backing of transitional epithelium; collagen eventually backs the transitional mucosa of an autoaugmentation.

Ureterocystoplasty

It has been noted for years that in patients with posterior urethral valves, unilateral reflux may behave like a "popoff" valve to lower intravesical pressures and protect the contralateral upper tract (Hoover and Duckett, 1982; Rittenberg et al, 1988; Kaefer et al, 1995). In many of these patients the refluxing ureter is massively dilated, draining a poorly functioning or nonfunctioning kidney. **It was a logical extension to use this ureteral tissue to augment the bladder.**

Technique. Ureterocystoplasty may be performed through a midline, intraperitoneal incision. This incision provides access to the intestine should mobilization of the ureter for augmentation be unsatisfactory. **Bellinger** (1993), **Dewan and colleagues** (1994a), **and Reinberg and associates** (1995) **have shown that ureterocystoplasty can be done through two incisions, remaining completely extraperitoneal.** The general technique is the same. A standard nephrectomy is performed with great care to preserve the renal pelvic and upper ureteral blood supply. All adventitia and periureteral tissue is swept from the peritoneum toward the ureter during mobilization to protect the ureteral blood supply. Proximally, this blood supply typically arises medially. As the ureter enters the true pelvis the blood supply arises posterior and laterally. After mobilization of the ureter into the pelvis the bladder is opened in the sagittal plane. Posteriorly, this incision has typically been carried off-center directly into and through the ureteral orifice of the ureter used for cystoplasty. The ureter is *not* detached from the bladder but is opened longitudinally along its entire length, with care taken to avoid its main blood supply (Fig. 129–15). The incision in the bladder and distal ureter should avoid branches of the superior vesical artery that serves as an important blood supply to the mobilized ureter. The ureter is folded on itself, and the ureter-to-ureter and ureter-to-bladder anastomosis is performed with running absorbable suture. A suprapubic tube is left indwelling through the native bladder for 3 weeks during healing. After cystography documents the absence of leakage, CIC is started. Patients, particularly those without neurogenic dysfunction, may attempt to void spontaneously, although all must prove that they can empty appropriately by checking postvoid residual urine amounts.

Alternatively, the bladder incision can be stopped approximately 2 cm from the orifice and a similar length of distal ureter left in situ and intact without incision. The resulting small loop of intact ureter does not cause clinical problems or adversely affect

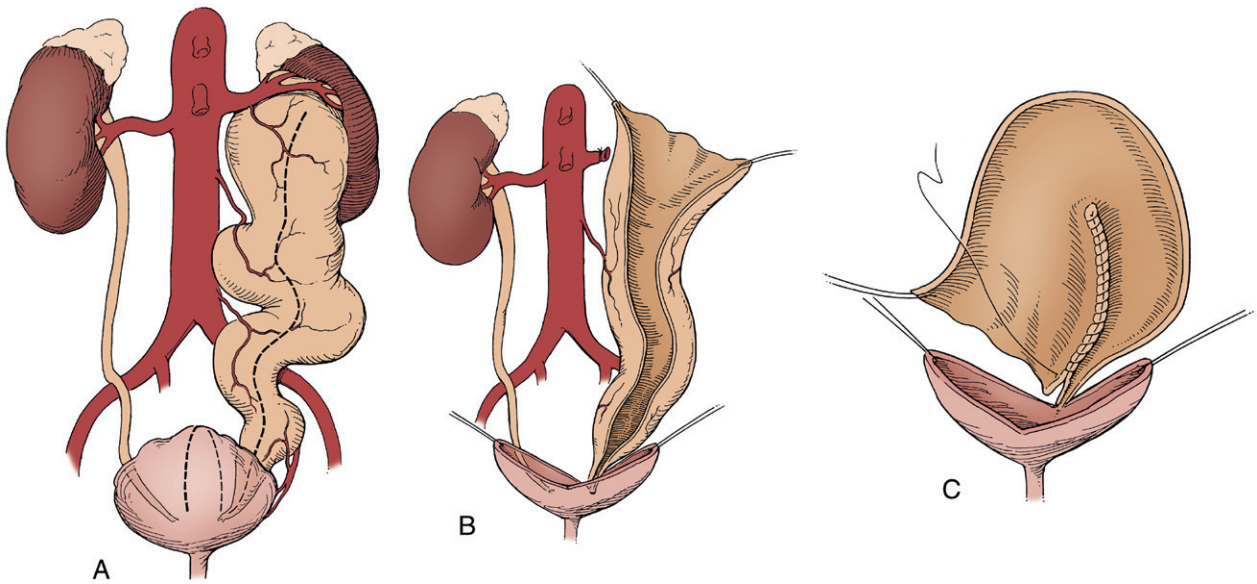


Figure 129–15. Ureterocystoplasty. **A**, After nephrectomy, the bladder is bivalved, with the posterior aspect of the incision carried off the midline to enter the ureteral orifice. The ureter is not detached from the bladder. **B**, The ureter is opened opposite its main blood supply. **C**, The ureter is reconfigured as in intestinal cystoplasty before anastomosis to the bladder.

the end volume in a significant manner (Adams et al, 1998). This modification of technique is easier and may be safer in that it avoids potential injury to the blood supply of the mobilized ureter near the ureterovesical junction.

Results. Early reports suggested that ureterocystoplasty could be achieved after nephrectomy by bivalving the bladder through the vesicoureteral junction and laying in the open ureter (Mitchell et al, 1992; Bellinger, 1993). Later reports modified and improved the procedure by noting that with meticulous care the vascularity to the entire renal pelvis could be preserved, allowing more tissue for cystoplasty (Churchill et al, 1993; Landau et al, 1994; McKenna and Bauer, 1995; Reinberg et al, 1995). As with intestinal cystoplasty, folding the ureter into a more spherical configuration maximizes the volume that can be achieved. If a massively dilated ureter drains a functioning kidney the distal ureter alone may be used for augmentation; the proximal ureter is either reimplanted into the bladder or anastomosed to the contralateral ureter (Bellinger, 1993).

Numerous series have reported good results after augmentation with use of ureter, some with follow-up as long as 8 years. The upper tracts have remained stable or improved in virtually all patients. Complications have been uncommon, with only a rare early extravasation of urine reported (Churchill et al, 1993). Landau and colleagues (1994) compared age-matched and diagnosis-matched children having ureterocystoplasty or ileocystoplasty. **The total mean bladder capacity was 470 mL in the ureterocystoplasty group and 381 mL in the ileocystoplasty group. Bladder volumes at 30 cm H_2O were 413 mL and 380 mL after ureterocystoplasty and ileocystoplasty, respectively.** Ureter effectively enhanced both volume and compliance. There was one failure in the group that occurred in a child in whom the distal ureter did not provide enough volume. Work has shown that one dilated ureter typically is enough for cystoplasty (Zubieta et al, 1999).

The main disadvantage to ureterocystoplasty is the limited population of patients with a nonfunctioning kidney draining into a megaureter. McKenna and Bauer (1995) have reported the use of a normal-sized ureter. The ultimate success of ureterocystoplasty with normal ureter requires further follow-up, particularly since Gonzalez (1999) has stated that one fourth of his patients with posterior urethral valves have failed ureterocystoplasty with a dilated ureter because of their huge urinary volume. Husmann and colleagues (2004) noted even worse results if the ureter used was less than 1.5 cm in diameter. Atala and colleagues (1994) presented an experimental technique to slowly dilate a normal ureter for later use. Work continues to develop such a technique that is clinically applicable for patients (Stifelman et al, 1998; Desai et al, 2003).

Autoaugmentation

Techniques and Results. Cartwright and Snow (1989a, 1989b) described an ingenious method to improve bladder compliance and capacity with use of native urothelial tissue. In their procedure, known as autoaugmentation, they excised the detrusor muscle over the dome of the bladder, leaving the mucosa intact to protrude as a wide-mouth diverticulum. Initially, they made a midline incision through the bladder muscle (Fig. 129–16A). With the bladder distended with saline so that mucosa bulged from the incision, the muscle was then mobilized and excised laterally in each direction (Fig. 129–16B). The lateral edges of the detrusor muscle were then secured to the psoas muscle bilaterally to prevent collapse of the diverticulum (Fig. 129–16C). The early

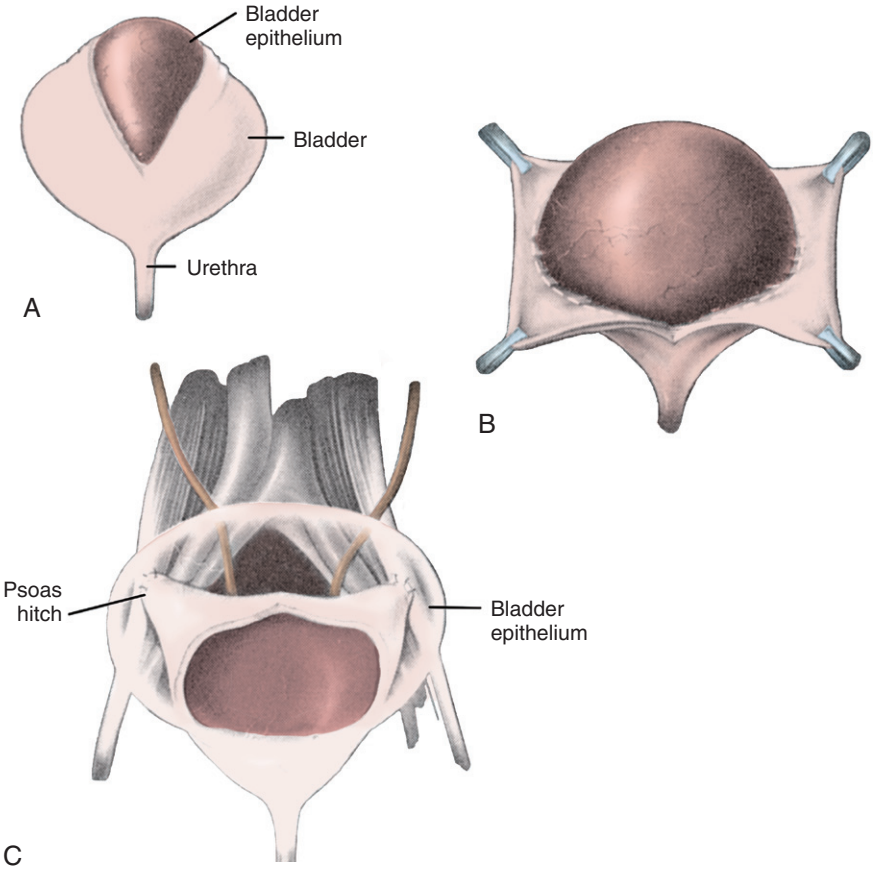


Figure 129–16. Autoaugmentation. **A**, The detrusor is incised. **B**, Detrusor is stripped and excised from mucosa. **C**, The detrusor muscle is anchored bilaterally so that the mucosa bulges with bladder filling. (From Cartwright PC, Snow BW. Bladder autoaugmentation: early clinical experience. J Urol 1989;142:505.)

experience of these investigators noted improved compliance in most, and increased capacity in some, patients (Cartwright and Snow, 1989a).

This procedure has since been modified by a number of surgeons, each providing a different name for the procedure, depending on whether the detrusor muscle is simply incised or excised to make the diverticulum. In an effort to determine if incision or excision provided superior results, Johnson and colleagues (1994) performed 16 vesicomyotomies and 16 vesicomyectomies in rabbits after previously reducing the bladder capacity. Functional bladder capacity in the animals increased by 43.5%, and there was no statistical difference between the two techniques. They then performed vesicomyotomies (incision) in 12 patients with neurogenic bladder dysfunction and demonstrated a mean increase in capacity of 40% and a mean decrease in leak point pressure of 33% (Stothers et al, 1994). They concluded that detrusor excision offered no advantage over incision. All patients demonstrated some increase in capacity (15% to 70%), and no patient in early follow-up clinically deteriorated and required enterocystoplasty.

Detrusorectomy, leaving a small cap of muscle at the dome through which a suprapubic tube can be placed, has been proposed by Landa and Moorehead (1994). **They have been concerned that although these procedures usually improve compliance, increase in volume is "modest at best," a concern shared by others** (Snow and Cartwright, 1996; Cartwright and Snow, 1998). In a report of 12 detrusorectomies, five patients were considered to have excellent results, two had acceptable results, and one was lost to follow-up. There were four failures (one hydronephrosis, two persistent incontinence, one worsening renal insufficiency); three patients have undergone gastrocystoplasty or ileocystoplasty (Landa and Moorehead, 1994). Overall, only 52% of patients had a good result with autoaugmentation; 20% had a poor outcome (Snow and Cartwright, 1996). Reoperative enterocystoplasty was not hampered by the prior detrusorectomy. The urothelial diverticulum at the time of augmentation cystoplasty was noted to be thick and fibrous, similar to a leather bag.

There are obvious advantages to autoaugmentation and its variants. Native urothelial tissue is used. It is an extraperitoneal procedure, which shortens operative time and avoids the risks of intestinal surgery and adhesions. Autoaugmentation is compatible with CIC and does not seem to complicate subsequent intestinal cystoplasty when it is necessary.

Complications from the procedures are generally uncommon. Perforation, a major concern after intestinal cystoplasty, has not been reported. Inadvertent opening of the mucosa during the procedure can make subsequent mobilization more difficult and may promote prolonged postoperative extravasation. Such extravasation usually stops with bladder drainage (Landa and Moorehead, 1994; Stothers et al, 1994). Prolonged drainage, however, may result in compromised results from collapse of the diverticulum. If concomitant ureteral reimplantation or bladder neck surgery is necessary, various authors have recommended that it be done first and the bladder then closed before detrusorectomy (Stothers et al, 1994).

Ehrlich and Gershman (1993) first reported laparoscopic myotomy (incision). A laparoscopic approach uses a smaller incision and perhaps shortens postoperative hospitalization; it may make effective fixation of the detrusor muscle in an open fashion to allow good bulging more difficult.

Concerns. **The main disadvantage of autoaugmentation is a limited increase in bladder capacity such that adequate preoperative volume may be the most important predictor of success** (Landa and Moorehead, 1994). If the maximum capacity and the volume of urine held at 40 cm H_2O are similar the patient may be better served by immediate intestinal cystoplasty. It is of note that some patients have demonstrated clinical improvement after these procedures without a significant change in urodynamics. The reason for the improvement in that setting is unknown.

In most series of autoaugmentation, no matter what the technique, it has been noted in occasional patients or concern has existed at the time of the initial procedure that adequate expansion was not achieved. In most such cases it was elected to proceed with enterocystoplasty immediately at the time (Landa and Moorehead, 1994). These patients are not included in the failure rate of autoaugmentation. The patient and surgeon must be prepared for such an event on occasion. Stohrer's group (1999) as well as Leng and associates (1999) reported good results with the technique among patients with hyperreflexia. In terms of capacity, even if adequate expansion is achieved initially, there is concern that any improvement may not persist long term (Dewan et al, 1994b). In animals the surface area of the autoaugmentation site was noted to decrease approximately 50% at 12 weeks. Progressive thickening and contracture of the site have been noted because of collagenous infiltrate (Johnson et al, 1994). Milam (2000) has noted that almost half of his adult patients with hyperreflexia who had a good early result after autoaugmentation have failed with longer follow-up. Similar delayed failures have been noted in pediatric patients (Lindley et al, 2003), including one series with very poor results (MacNeily et al, 2003).

At this point, autoaugmentation should probably be considered only in patients who have reasonable capacity but poor compliance due to uninhibited contractions. **If a significant increase in capacity is needed, autoaugmentation is unlikely to be as definitive as other techniques.**

Seromuscular Enterocystoplasty

Based on concerns about collagen deposition and contraction around autoaugmentation, efforts have been made to cover the bulging urothelium with demucosalized enteric segments. The use of enteric segments without bowel mucosa within the bladder is not new. As far back as the 1950s, seromuscular augmentation cystoplasty was performed with the serosal side of the bowel turned to the bladder lumen (Shoemaker and Marucci, 1955; Shoemaker et al, 1957). Urothelium soon covered the serosa. Gonzalez's group experienced good results with reversed seromuscular cystoplasty in rats, as did others with rabbits (Celayir et al, 1995), but contracture of the patch occurred in larger animals (De Badiola et al, 1991; Long et al, 1992). Others left the exposed submucosa facing the bladder lumen and noted reepithelialization with urothelium in animals (Oesch, 1988; Salle et al, 1990). Despite the reepithelialization, patch contracture occurred (Salle et al, 1990). Several recent series have reevaluated demucosalized augmentation in humans after taking care to preserve the submucosa. Better results have been noted (Lima et al, 1998, 2004; de Badiola et al, 1999; Dayanc et al, 1999), although regrowth of metaplastic enteric mucosa was found in the second study. Early placement of a silicone balloon or mold may help prevent contracture (Lima et al, 2004).

Techniques and Results. **To avoid contracture, a combination of autoaugmentation after detrusorectomy and coverage with a demucosalized enteric segment has now been used.** This has been done to potentially preserve the advantages of both procedures. In a similar fashion the combination has

been undertaken with both colon and stomach. Buson and colleagues (1994) used reconfigured, demucosalized sigmoid colon placed over the urothelium (seromuscular colocystoplasty lined with urothelium). They and others noted that the intestinal submucosa should be preserved to avoid contracture (Buson et al, 1994; Vates et al, 1997) (Fig. 129–17). This procedure has been performed clinically with early reports of good results in most patients (Gonzalez et al, 1994). Postoperative bladder capacity increased an average of 2.4-fold (139 to 335 mL) in 14 of 16 patients, and end filling pressure decreased from an average of 51.6 to 27.7 cm H_2O. Two patients experienced failure of the procedure and required ileocystoplasty; their urodynamic data were excluded. Two other patients developed an hourglass deformity (Gonzalez et al, 1994). Endoscopic biopsy of the segments has been interesting. Of 10 biopsies performed in the series, in 1 urothelium with islands of colonic mucosa was noted and in 2 others only colon mucosa was found. Removal of all of the enteric mucosa is important when sigmoid is used to prevent mucoceles or overgrowth of intestinal mucosa (Gonzalez et al, 1994; Lutz and Frey, 1994). Dewan and associates (1997) thought that preservation of the submucosa eventually promoted regrowth of bowel mucosa. The interaction of the two different tissues will be interesting to follow. The long-term effects on the urothelium by the seromuscular segment and vice versa are unknown. Work has shown that persistent transitional lining will protect from metabolic problems and mucus production (Denes et al, 1997).

Dewan and Byard (1993) and Close and associates (2004) alternatively used demucosalized stomach to cover an autoaugmentation, first in sheep and then in patients. Early results showed improved bladder function both clinically and by urodynamics (Horowitz and Mitchell, 1993; Dewan et al, 1994c; Horowitz et al, 1994; Robinson et al, 1994), although long-term results are not as encouraging (Carr et al, 1999). These procedures are technically more demanding than simple augmentation or autoaugmentation and are associated with more blood loss and a longer operative time (Gonzalez et al, 1994; Horowitz et al, 1994). Increased bleeding is particularly true when stomach is used. These urothelium-lined, seromuscular augmentations are theoretically attractive. Thus far, the failure and reoperation rate after such procedures remains higher than that noted for standard enterocystoplasty (Vates et al, 1997; Carr et al, 1999; Shekarriz et al, 2000). The results have been reported with colon (Shekarriz et al, 2000). Those results may be partially attributed to the learning curve with a new, complex procedure. Longer follow-up and more experience are necessary to determine whether the complication rate will decrease with experience or increase because of problems with the combination.

Bladder Regeneration

Other efforts to find alternatives to intestinal cystoplasty in the 1950s included the use of alloplastic materials for bladder substitution (Gleeson and Griffith, 1992; Kanematsu et al, 2007; Lewis et al, 2007; Yamzon et al, 2008). Early research efforts met with limited success due to foreign body complications but provided the foundation for regenerative medicine, which uses cells and biomaterials to establish regrowth of healthy tissue. This led to a focus on biodegradable, collagen-rich tissues serving as a scaffold for bladder regeneration (Kelami, 1971; Fishman et al,

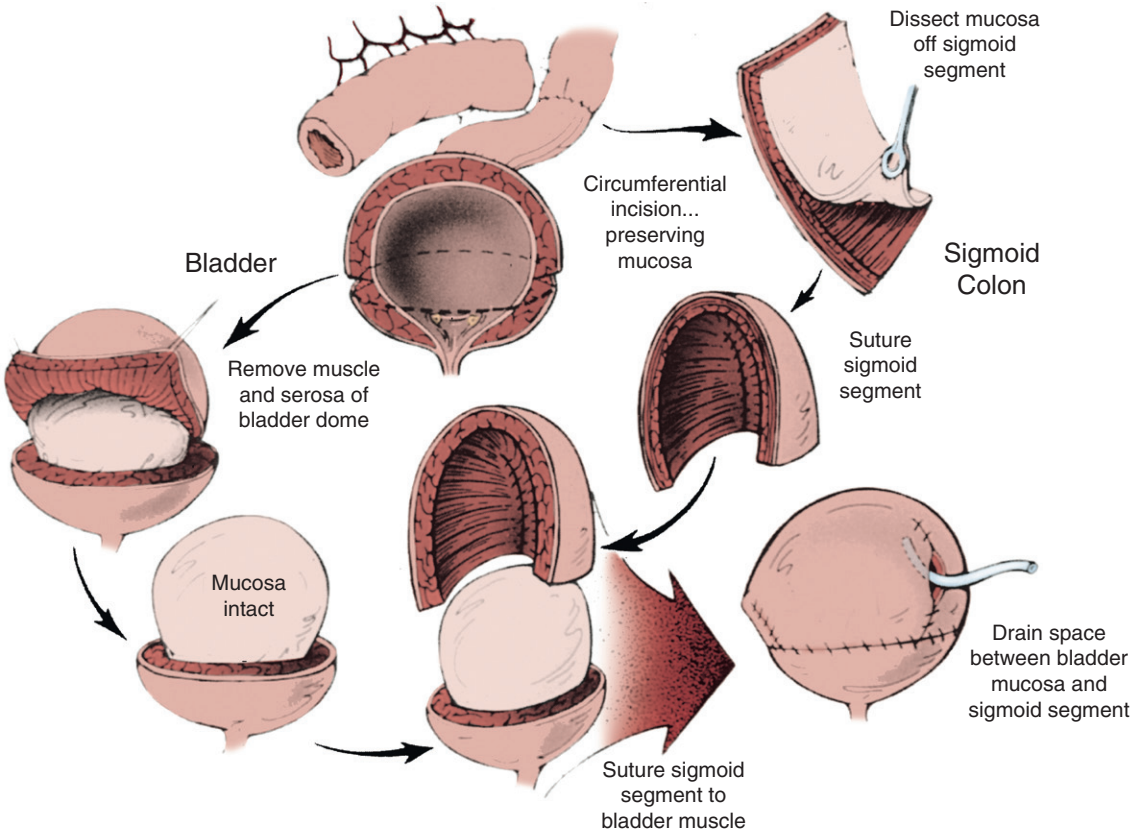


Figure 129–17. Seromuscular enterocystoplasty with use of sigmoid colon. Detrusor incision is performed as in autoaugmentation; however, the bulging mucosa is covered with a demucosalized segment of sigmoid colon. (From Buson H, Manivel JC, Dayanc M, et al. Seromuscular colocystoplasty lined with urothelium: experimental study. Urology 1994;44:745.)

1987; Kambic et al, 1992; Kropp et al, 1995a, 1995b, 2004; Zhang et al, 2004; Harrington et al, 2008). Successful regeneration using this technology has been produced in the laboratory with either "unseeded" or cell "seeded" regenerative growth. Atala and associates (2006) provide the first reported data using a seeded biodegradable construct for augmentation in the neurogenic population. Seven children underwent autologous augmentation. No major complications were reported. Encouraging subjective response to the augmentation was obtained, but uniform urodynamic improvement was not universally appreciated. This work by Atala and associates has provided the foundation for an industry-supported prospective multi-institution investigation using a neobladder construction (Joseph et al, 2009). The study enrolled 11 children, and 10 underwent neobladder augmentation. All 10 patients have completed the primary 12-month endpoint. Results similar to Atala and associates' initial findings have been encountered. Subjective improvement has been reported by some families but has not been correlated with objective urodynamic changes (Joseph et al, 2009). Although these results remain promising, to date an objective successful clinical outcome using autologous regenerative tissue for bladder augmentation is limited. Using autologous tissue from a neuropathic source may potentiate growth of abnormal tissue, but an alternative cell source for regenerative tissue such as stem cells may circumvent that concern. However, the clinical use of stem cells carries its own set of obstacles (Aboushwareb and Atala, 2008; Aitken and Bägli, 2009; Soler et al, 2009). Further investigation into the clinical applicably of regenerative tissue engineering is required. This technology remains poised to significantly alter the field of reconstructive bladder surgery (Atala et al, 1992, 1993b; Cilento et al, 1994; Kropp et al, 1995b; Oberpenning et al, 1997; Probst et al, 1997; Fauza et al, 1998; Kropp, 1998; Yoo et al, 1998; Reddy et al, 2000; Lai et al, 2002; Zhang et al, 2004; Wood and Southgate, 2008; Aitken and Bägli, 2009; Soler et al, 2009).

A Decreasing Necessity?

Although augmentation cystoplasty works well for most patients who require it, and work on alternatives to bowel cystoplasty may lower morbidity for the patient, a primary goal for every pediatric urologist is to minimize the number of patients needing cystoplasty. Newer medical regimens and neuromodulation may prove effective for some patients who presently do not respond to conservative measures (Aslan and Kogan, 2002). Xiao (2005) continues to refine an artificial somatic-autonomic reflex pathway in children with neurogenic bladder due to spinal cord injury and spina bifida. Through a limited laminectomy, the dorsal nerve root of L5 is identified and transected and an anastomosis is made with the distal end of the S3 ventral root. Scratching the dermatome supported by L5 creates reflex stimulation of the bladder initiating a contraction. Improvement in bladder compliance may occur. Other centers are exploring this technique (Peters et al, 2010). No matter what the diagnosis, earlier and more aggressive treatment of bladder dysfunction may minimize the insult to the bladder and maximize recovery as well as ultimate bladder function. Early urodynamic evaluation of boys with posterior urethral valves may identify treatable bladder problems and improve the prognosis from the standpoint of the kidneys and bladder (Misseri et al, 2002). Grady and colleagues (2003) have suggested that complete primary repair of bladder exstrophy results in early bladder cycling that improves eventual bladder function and decreases the likelihood of augmentation cystoplasty.

With perhaps the most compelling evidence to date, Kaefer and associates (1999b) found that only 17% of patients with hostile neurogenic bladder dysfunction treated immediately on diagnosis required augmentation cystoplasty compared with 41% of similar patients treated expectantly. Although the series included no collaborative urodynamic data and might be subject to lag time bias, the authors thought that there was a significant difference in the outcomes for the two groups. Because there are no prospective, randomized trials evaluating early evaluation and treatment of pediatric bladder dysfunction, recommendations that expectant treatment may lower the necessity for augmentation cystoplasty (Bauer, 2003; Mitchell, 2003) remain a personal bias rather than a scientific fact. Thus far, early bladder management has not decreased the rate of augmentation cystoplasty (Lendvay et al, 2006). Critical, prospective evaluation of such treatment is needed and will, it is hoped, demonstrate how to manage these patients. It is likely that such improvements will minimize the need for cystoplasty but not completely remove it.

Improving Quality of Life?

Reconstruction to achieve continence has been assumed to improve health-related quality of life. Early evaluation of small numbers of patients undergoing reconstruction including augmentation cystoplasty do not always show improved status on objective questionnaires compared with preoperative studies or control patients without surgery despite what generally would be considered to be good clinical results (Macneily et al, 2005; Parekh et al, 2006). Patient-reported scores also do not always correlate with those noted by their parents. Most evaluation of surgical techniques to date has focused on results and complications from the perspective of surgeons. Future evaluation should include objective, patient-reported consideration. Tools to acquire that information must be validated for longitudinal study of these patients and their disease processes.

Key Points: Alternatives to Gastrointestinal Cystoplasty

- Ureterocystoplasty avoids the complications associated with bowel segments but may not provide adequate volume if the ureter is not remarkably dilated.
- Autoaugmentation, no matter what the technique, seldom adds significant capacity and may not always improve compliance long term.
- More experience and longer follow-up with seromuscular enterocystoplasty are needed to determine its appropriate role.
- Care for the underlying bladder dysfunction should be improved to lower the need for augmentation cystoplasty.

CONTINENT URINARY DIVERSION

The frequency with which continent urinary diversion is performed in children depends on one's definition of continent diversion. In adults, total bladder replacement is not uncommon after cystectomy for transitional cell carcinoma. This has led to extensive experience with continent urinary diversion and orthotopic neobladders that allow spontaneous voiding. Tumors resulting in cystectomy among children are much less common. It is in that setting, and the occasional child in whom the bladder is

congenitally absent or so small as to be virtually useless, that a pure continent urinary diversion in the classic sense of an Indiana or Kock pouch might be performed. Very good results with continent diversion in children have been achieved, equivalent to those reported in adults (Stein et al, 2005). Orthotopic neobladders in children are performed infrequently. Neurogenic or anatomic problems at the outlet prevent spontaneous voiding in many cases. Even among patients having undergone cystectomy for tumors, irradiation can interfere with voiding. On occasion, a child with neurogenic dysfunction may be a candidate for orthotopic bladder substitution (Stein et al, 2000, 2005). It is not clear how many of those patients with neurogenic dysfunction can be expected to void adequately.

More frequently in children, a series of continent diversion have included patients undergoing a mix of the techniques discussed in this chapter. Some authors have defined combinations of bladder augmentation, continent abdominal wall stoma, and some procedure at the outlet as continent diversions (Kaefer et al, 1997b). Division and closure of the bladder neck to prevent incontinence per native urethra has typically meant inclusion. Certainly, maximal use of the native urinary tract is beneficial to the child. Much like urinary refunctionalization, these procedures typically have been performed in complex patients with multiple problems that must be addressed, often after numerous previous surgeries.

Considerations

The amount of bowel used in continent urinary diversion may vary according to the patient. Total bladder replacement requires much more intestine than simple augmentation. Typically, a 40-cm segment of small bowel is used for an ileal reservoir in a Kock pouch compared with the 20 cm often used for augmentation. Likewise, the entire right colon with the hepatic flexure may be used in an Indiana pouch with or without a patch of small intestine, whereas only 15 to 20 cm of colon is needed for colocystoplasty. Because of the potential morbidity associated with use of a larger intestinal segment the native bladder is often incorporated in children if it provides any significant volume. To do so, however, may require repair of the outlet if outflow resistance is low. Otherwise, incontinence per native urethra will result.

Imbrication of the ileocecal valve and terminal ileum has proved to be a simple and reliable means for construction of an effective efferent limb in continent diversion among adults and children. Despite reports to the contrary in select patients (Husmann and Cain, 1999), concern about fecal incontinence secondary to use of the ileocecal valve persists for patients with neurogenic dysfunction. The flap valve continence mechanism provides numerous alternatives for those surgeons with such concerns in continent diversion. The good results achieved with the appendix or tapered intestinal segments has led to their increased use in recent years.

Whereas maintenance of the native urethra for catheterization is ideal, it may not be appropriate or possible in all individuals. As indicated previously, reconstructive bladder neck procedures are often subject to difficulty with catheterization. **Children with neurogenic sphincter incompetence may have associated neurologic limitations that prevent easy access to the native urethra. This is particularly true for the wheelchair-bound child. For children without neurologic deficits, normal sensation in the native urethra can prevent compliance with a routine catheterization schedule because of discomfort. For these reasons, a continent catheterizable stoma provides an adequate and sometimes a more reliably useful alternative.**

CONTINENCE MECHANISMS AND CATHETERIZABLE SEGMENTS

Ureterosigmoidostomy and Its Variants

Ureterosigmoidostomy can be an effective form of continent urinary diversion in some patients. Its major advantage is the potential for spontaneous emptying by evacuation of urine with stool. The significant complications of hyperchloremic acidosis, infection, hydronephrosis, and the development of colonic malignant neoplasms have led to disfavor and disuse, particularly in the United States. **Although good results with standard ureterosigmoidostomy have been reported in some children, the procedure is rarely performed as originally described. The morbidity of acidosis and upper tract changes may increase with time, making those complications particularly worrisome for children with a long life expectancy. The significant risk of adenocarcinoma commits the patients to a lifetime of close surveillance for an avoidable tumor.** It is unlikely that ureterosigmoidostomy, as classically described, will regain acceptance for children.

Several modifications of ureterosigmoidostomy have been developed in an attempt to decrease the significant complication rate. **The most basic of the modifications is the sigma rectum or the Mainz II pouch.** The colon is incised along the antimesenteric border for 6 cm both proximal and distal to the rectosigmoid junction. The ureters are implanted in an antirefluxing fashion, and that portion of colon is then reconfigured and closed. This is done to create a rectosigmoid reservoir of lower pressure to protect the upper tracts. The Mainz II pouch has been used in children primarily with bladder exstrophy (Stein et al, 1997a). Continence in appropriately selected patients is good, although acidosis is still a significant problem because of exposure of the entire colon to urine (Fisch et al, 1996; Gerharz et al, 1999; Mingin et al, 1999a). The potential for development of adenocarcinoma still exists with this technique. Long-term follow-up is necessary to determine if the reconfiguration of the sigmoid in the area of ureteral implantation is truly effective for protection of the upper tracts. Stricture at the ureterocolonic anastomosis has been the most common complication in relatively short follow-up (Fisch et al, 1996).

In an effort to control the amount of colon to which urine is exposed, Kock and associates (1988) **described a colorectal valve to confine urine to the distal segment.** The intussuscepted nipple valve is stabilized with permanent staples. The distal rectal segment is opened and patched with ileum to lower pressure. With short-term follow-up, the valve is effective in that the authors noted no necessity for sodium bicarbonate or potassium citrate therapy (Kock et al, 1988), a finding duplicated by others (Mahran et al, 1999). An increased risk for tumor development probably still exists with this modification because the ureterocolic anastomoses are still exposed to an admixture of stool and urine. Urodynamic evaluation has revealed low pressure in the rectal reservoir (Kock et al, 1988). Long-term follow-up of its use in children is needed to see if it is truly less morbid in terms of infection and upper tract deterioration. If placement of a colorectal valve avoids most complications of metabolic acidosis from ureterosigmoidostomy and construction of a reservoir with lower pressure better protects the upper tracts,

then the last remaining major concern about ureterosigmoidostomy is tumor development. The concern is significant; of 94 children observed in Boston after ureterosigmoidostomy, adenocarcinoma developed in 7, of whom 4 died of the tumor (Rink and Retik, 1991). Kock and coworkers (1988), followed by Skinner and associates (1989), used a hemi-Kock pouch to augment the distal rectal segment. A colorectal valve was made to isolate urine to the distal colonic reservoir. The afferent nipple valve kept stool away from the ureteroileal anastomoses, perhaps lowering the risk for tumor development. Simoneau and Skinner (1995) reported their results with the procedure in 15 patients, including 4 children. Their complication rate, both early and late, was relatively high. This is not surprising, considering the relatively complex nature of the procedure. They did think that the pediatric patients were better suited for the procedure. Rink and Retik (1991) suggested that the rectum could be augmented with a nonrefluxing ileocecal conduit in a similar fashion.

Before any variant of ureterosigmoidostomy is considered, competence of the anal sphincter must be ensured. Tests used to assess sphincter integrity include manometry, electromyography, and practical evaluation of the ability to retain an oatmeal enema in the upright position for a time without soilage. Incontinence of a mixture of stool and urine results in foul soilage and must be avoided. Consequently, most patients with neurogenic dysfunction, who are incapable of fecal continence in the presence of diarrhea, are not candidates for these procedures. Procedures that separate the fecal and urinary streams within the rectal sphincter have been described but have not been widely used among children.

Nipple Valves

The greatest experience with nipple valves used to achieve urinary continence has been with the Kock pouch. Skinner and associates (1989) made a series of modifications to aid in maintenance of the efferent nipple. Despite experience and use of these modifications, a failure rate of 15% or higher can be expected (Benson and Olsson, 1998) (Fig. 129–18). Several authors have reported a reoperative rate of approximately 33% with the Kock pouch, most frequently related to the efferent nipple (deKernion et al, 1985; Waters et al, 1997). Equivalent results with the nipple valve and a Kock pouch have been achieved in children (Hanna and Bloiso, 1987; Skinner et al, 1988; Kaefer et al, 1997b; Abd-El-Gawad et al, 1999). The last report noted a significant incidence of hyperchloremic acidosis and new hydronephrosis, although those complications were likely due to the complex nature of the patients rather than the particular continent diversion used.

Intussuscepted nipple valves have also been used with colonic and ileocolonic reservoirs, particularly the Mainz I pouch. Again, evolution of the nipple valve in the Mainz pouch occurred over time (Thuroff et al, 1986, 1988; Hohenfellner et al, 1990; Stein et al, 1995). Most recently, the intussuscepted ileum was fixed with staples, passed through the intact ileocecal valve, and fixed again. Much as with the Kock pouch, the incidence of incontinence decreased with experience and modifications. The Mainz I pouch has been used in children with good results and low rates of incontinence with the latest modifications (Stein et al, 1995, 1997a, 2000; Steiner et al, 1998). Maintenance of normal upper tracts has been good, and metabolic problems are rare (Stein et al, 1997b). In fact, improvement of preexisting hydronephrosis has been more common than worsening. For the past several years, the group in Mainz has used a flap valve mechanism and the appendix for a continent catheterizable stoma with less incontinence (Stein et al, 1995; Gerharz et al, 1997).

Flap Valves and the Mitrofanoff Principle

Mitrofanoff (1980) described a continence mechanism with use of the appendix and ureter to make a flap valve. He recognized that any tubular structure could be implanted effectively into a low-pressure reservoir. This continence mechanism circumvents many of the secondary potential complications associated with harvesting of the ileocecal valve or use of other gastrointestinal segments.

The foundation for the success of the Mitrofanoff principle is based on construction of a submucosal tunnel for a supple, small-diameter conduit. As the reservoir fills, the rise in intravesical pressure is transmitted through the epithelium and to the implanted conduit, coapting its lumen (Fig. 129–19). **The appendix is an ideal natural tubular structure that can be safely removed from the gastrointestinal tract without significant morbidity. The small caliber of the appendix**

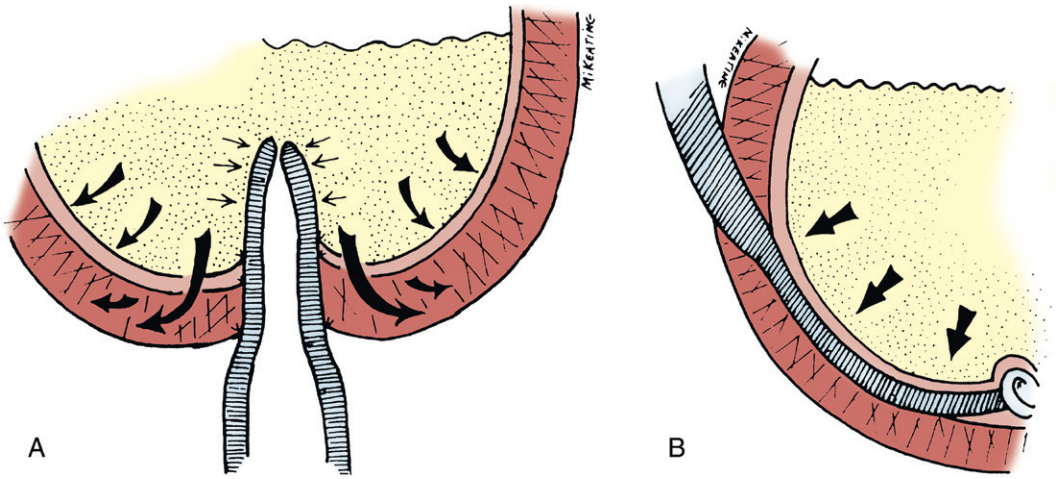


Figure 129–18. Continence mechanisms. **A**, The same pressures that create continence tend to efface nipple valves. **B**, This is not true of flap valves, which have been more reliable in pediatric reconstruction.

facilitates construction of a short functional tunnel with the bladder wall. Experience has shown that continence can be achieved with only a 2-cm appendiceal tunnel (Kaefer and Retik, 1997). Whether in a continent urinary reservoir or native bladder the appendix has been used as an efferent limb with very good results (Hampel et al, 1995; Jayanthi et al, 1995; Kaefer et al, 1997b; Mollard et al, 1997; Cain et al, 1999). The appendix has been particularly useful in children because it is relatively longer and the abdominal wall generally thinner. The flap valve is probably the most reliable of all of the surgically constructed continence mechanisms. This is good in terms of continence when the patient is catheterized reliably. Many patients with good flap valves will virtually never leak per stoma. This potentially puts them at greater risk for upper tract deterioration or spontaneous rupture of the bladder or reservoir if catheterization is not performed.

If the appendix is used in situ as a continence mechanism in a continent urinary reservoir, the reservoir by necessity will include the right colon. Duckett and Snyder (1986, 1987) used the right colon and appendix with good results in children. The mesoappendix, in most cases, allows mobilization of the appendix for use in the native bladder or virtually any reservoir.

Technique. Appropriate preoperative planning is required to position the skin incision to allow adequate mobilization of the appendix to the bladder. In most children this can be achieved through a low midline or a transverse incision. On occasion, the cecum may be high in the abdomen. Mobilization of the ascending colon along the line of Toldt may be required to gain mobilization of the appendix and its mesentery. Cadeddu and Docimo (1999) have used laparoscopy to aid in mobilization of the ascending colon and cecum. Once the cecum has been mobilized the base of the appendix is amputated, leaving a small cuff of cecum with the appendix. Use of the cuff at the stoma may decrease the risk of stenosis. The cecum is closed in a fashion similar to an open appendectomy. If the length of the appendix is marginal, then a greater portion of the cecum can be harvested, which effectively increases the functional length of the appendix (Cromie et al, 1991). A portion may be tubularized with the appendix (Bruce and McRoberts, 1998).

After harvesting, a location is selected for implantation of the appendix into the bladder. The location is based on the length of the appendix, the mobility of the bladder, and the location for the appendiceal stoma. Typically, the distal end of the appendix is tunneled into a posterolateral position within the bladder (see Fig. 129–19).

The base of the appendix is brought to the abdominal wall in a location chosen preoperatively to suit the patient. If a patient wears a supportive brace, stomal positioning must take this into account. The appendix should be brought up to reach the skin without tension, and care must be taken not to twist the pedicle or to occlude it as it passes through the abdominal wall fascia. The base of the appendix often can be hidden within the umbilicus, which allows elimination of a small but obvious abdominal stoma. Because of the small circular diameter of the appendiceal base, stomal stenosis is common; and techniques have been described to prevent this problem. Various flaps have been described as a method for avoiding stomal stenosis (Keating et al, 1993; Kajbafzadeh et al, 1995; Kaefer and Retik, 1997; Frane-Guimond et al, 2006; Berrettini et al, 2008; Landau et al, 2008). The VQZ stomaplasty and its variations have been described in an attempt to prevent exposing intestinal mucosa from the catheterizable channel and decreasing the risk of stomal stenosis (Frane-Guimond et al, 2006; Berrettini et al, 2008; Landau et al, 2008). Regardless of the technique, stomal stenosis will remain a primary complication. Chronic nighttime catheterization with a stent placed into the channel but not reaching the bladder may further decrease the risk of superficial stenosis (Mickelson et al, 2009). **For prevention of kinking and problems with catheterization it is advisable to maintain as short a conduit as possible.** Securing the appendix and bladder wall to the peritoneum beneath the fascia will help diminish the problem of conduit kinking with reservoir filling. When appendix or any catheterizable stoma is used, it is advisable to repeatedly catheterize the channel after each step in reconstruction to confirm easy passage. If the catheter does not pass easily into the reservoir, the preceding step needs to be revised. Problems with catheterization by the surgeon during the operative procedure usually result in more difficulty for the patient afterward. It is also beneficial to catheterize at variable reservoir volumes to confirm proper fixation of the reservoir and the absence of any kinking. A 6- to 10-Fr Silastic stent is typically left for 10 to 14 days within the efferent catheterizable channel during the healing process. It is advisable for the surgeon to

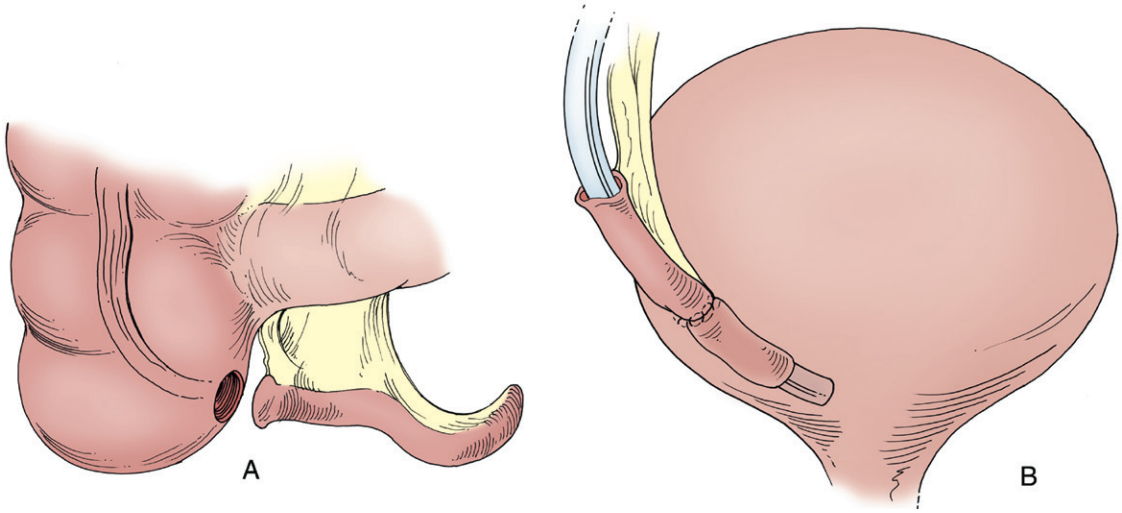


Figure 129–19. Appendicovesicostomy. **A**, The appendix is harvested with a cuff of cecum on a wide pedicle based on the appendiceal artery. A flap of cecum can be harvested in continuity with the appendix and tubularized to increase the length. **B**, The distal appendix is tunneled into the bladder to provide continence after the end is amputated. The proximal end of the appendix, the cecal cuff, is brought to the umbilicus or right lower quadrant as a catheterizable stoma.

personally catheterize the efferent limb before allowing the patient or other family members to do so. Catheterization should be repeated at least every 4 hours during the day for reservoir drainage, maintenance of patency, and minimalization of the risk of stomal stenosis.

The appendix may not be available for use in all patients because of previous appendectomy, its location or length, congenital absence, involvement with adhesions, or its use for continence enemas. Histologic abnormalities of the appendix have been reported to occur in as many as 30% of patients (Liebovitch et al, 1992) and to increase with age. They rarely are of enough clinical significance to preclude use (Mulvihill et al, 1983).

Results. Several papers have reviewed large series of patients after appendicovesicostomy (Kaefer et al, 1997b; Cain et al, 1999, Harris et al, 2000; Thomas et al, 2006; Welk et al, 2008). The populations of patients have been typical of most pediatric groups, the majority having neurogenic dysfunction. Inability to use the appendix, other than because it was needed in situ for antegrade continence enemas, has been rare. The results, in terms of continence, have been superb, usually above 95% (Gerharz et al, 1997, 1998; Kaefer and Retik, 1997d; Mor et al, 1997; Suzer et al, 1997; Gosalbez et al, 1998; Cain et al, 1999; Castellan et al, 1999; Liard et al, 2001; Thomas et al, 2006; Welk et al, 2008). **Incontinence is a rare event with the Mitrofanoff principle and may result from inadequate length of the flap valve mechanism or persistently elevated reservoir pressure.** Urodynamic evaluation is required to evaluate the cause of the incontinence. Injection of collagen or other biomaterials is a possible treatment for inadequate outflow resistance, with success reported up to 50% but long-term durability unknown (Welk et al, 2008). A more formal approach with takedown and revision of the leaking Mitrofanoff valve is usually required (Kaefer and Retik, 1997d). **The most common complication has been stomal stenosis, which has generally occurred in 6% to 10% of patients** (Thomas et al, 2006; Welk et al, 2008). Such stenosis resulting in difficult catheterization may occur early in the postoperative course and require formal revision (Harris et al, 2000). Another recognized complication has been appendiceal perforation. Most problems with stomal stenosis and creation of a false passage (perforation) occur in the first few years after reconstruction (Thomas et al, 2006). Stricture and necrosis, particularly of cecal extensions of the appendix, have occurred rarely. Abdominal stomas may be associated with a higher risk of reservoir calculi because of the potential for incomplete emptying.

Follow-up in the recent series has averaged approximately 4 years. Patients from Mitrofanoff's early experience (1980) should now have follow-up of more than 20 years, suggesting that the appendix may provide a durable alternative for pediatric patients with a long life expectancy, a finding also noted by others (Cain et al, 1999; Harris et al, 2000; Liard et al, 2001). Whereas the majority of the experience with the Mitrofanoff technique has been in children, similar outcomes with successful durable continence has been achieved in the adult population (Gowda et al, 2008; Van der Aa et al, 2009).

Alternatives

When the appendix is unavailable for use, other tubular structures can provide a similar mechanism for catheterization and continence. Mitrofanoff (1980) described a similar technique with ureter (Kaefer et al, 1997b). Care must be taken to preserve the distal blood supply to prevent ischemia. Refluxing ureters have even been used after extravesical reimplantation (Ashcraft and Dennis, 1986; Duel et al, 1996; Kaefer et al, 1997b). Stomal stenosis seems to be more problematic with use of the ureter compared with the appendix, possibly owing to compromised blood supply. In addition, distention of the ureter due to catheter passage has caused discomfort in some individuals (Duckett and Lofti, 1993).

Woodhouse and MacNeily (1994) as well as others have used the fallopian tube, which can accommodate catheterization. Stenosis again appears to be a significant problem with the fallopian tube. In addition, the effect on fertility should be considered when there is a normal ipsilateral gonad. Bihrle and associates (1991) fashioned a gastric tube mobilized on the gastroepiploic artery for implantation in continent reservoirs. Acid irritation of the skin was a problem in some patients. They then used a tapered segment of ileum as well (Adams et al, 1992). By narrowing the segment longitudinally along the mesenteric border with permanent staples in series, they were able to construct a uniform tube of adequate length that was easy to catheterize and provided good continence rates. Others (Hasan et al, 1994; Woodhouse and MacNeily, 1994) have had similar good results. It is ideal for such tubes to be long enough to reach from the reservoir to skin without tension; however, they should then be kept as short and straight as possible to facilitate easy catheterization. Any unnecessarily long catheterizable channel that is mobile within the abdomen can potentially kink and result in difficult catheterization or perforation.

Monti and colleagues (1997) **have been credited with a novel modification of the tapered intestinal segment that can be reimplanted according to the Mitrofanoff principle. Recognition should also be directed to another report of this procedure by** Yang (1993). A very short (1 to 2 cm) segment of small bowel is opened longitudinally along the antimesenteric border and then closed transversely (Fig. 129–20). By this reconfiguration, the initial circumference of the segment is converted to length, and the original length to circumference, of the reconfigured tube. A uniform tube is made with a small mesentery toward the center. The two ends are devoid of mesentery, making them easy to tunnel into bladder and bring through the abdominal wall. If the first incision is made directly at the antimesenteric border, both limbs are of equal length. By making the incision well around one side, one limb may be made much longer than the other. Experience has shown that one need not achieve a long tunnel in the bladder or reservoir to achieve continence with such a small tube, and the longer limb has typically been used to reach the skin through a thick abdominal wall.

Very good results have been achieved with the Yang-Monti tube as a catheterizable stoma, and it is certainly an efficient use of bowel (Thomas et al, 2006). Some surgeons have suggested that it may be easier to catheterize than an ileal segment tapered longitudinally because circular mucosal folds are redirected longitudinally in the direction of catheter passage. Stomas constructed with ileum may have a lower rate of stomal stenosis than those made with appendix (Kaefer et al, 1999a). The one potential disadvantage of the Yang-Monti tube is that it remains relatively short and may not reach the skin without tension in obese patients. Despite extensive use of skin flaps, such tension may lead to stomal stenosis. Two separate reconfigured tubes can be anastomosed together for better length (Kaefer and Retik, 1997). Casale (1999) has used an initial segment that was twice as long that was partially split in the middle and then opened in a spiral fashion on opposite sides to make a longer strip that could be tubularized in continuity. Narayanaswamy and colleagues (2001) noted difficulty with catheterizations through Yang-Monti

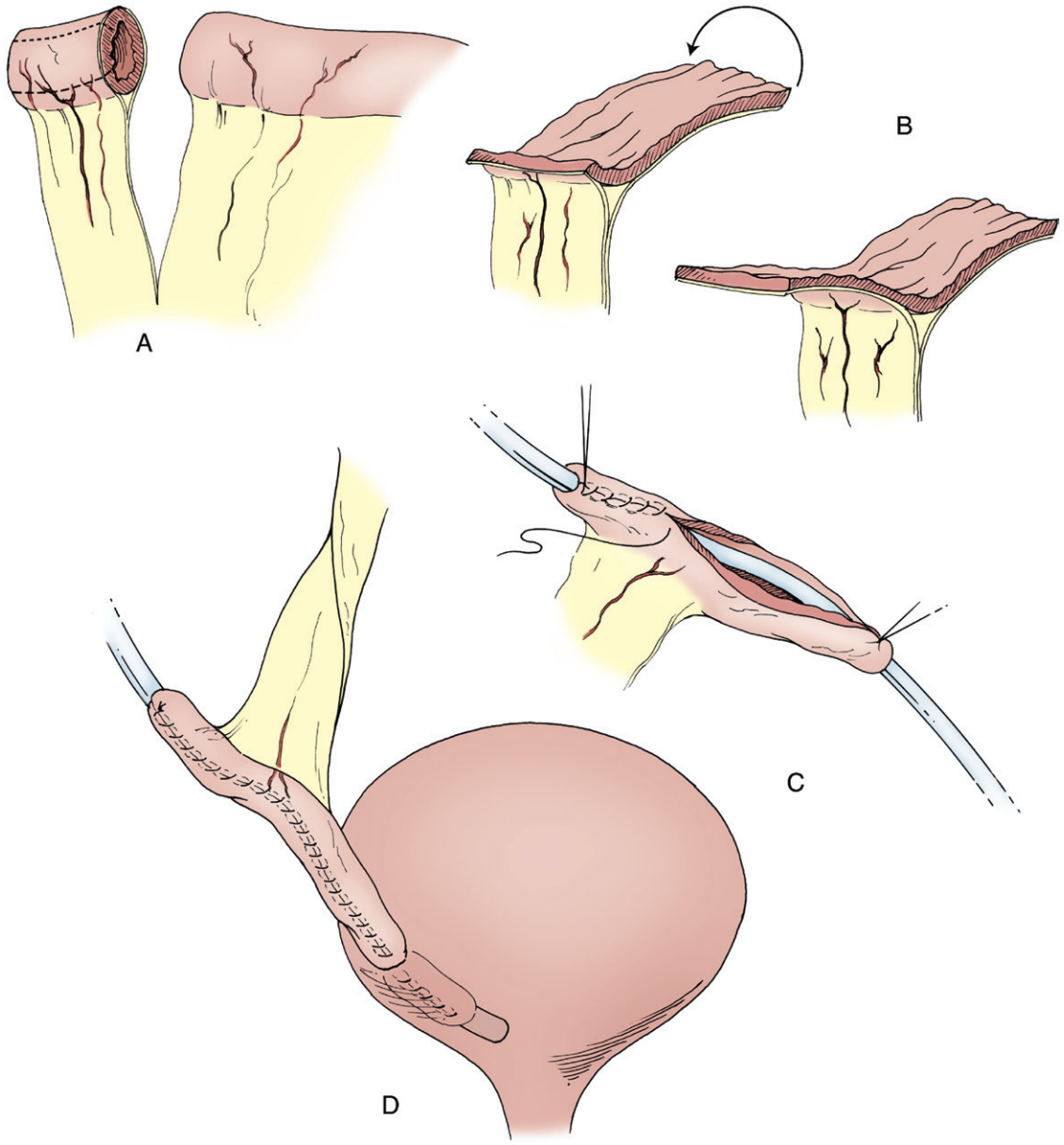


Figure 129–20. Yang-Monti technique to efficiently construct a catheterizable tube. **A**, A 2-cm length of ileum is harvested either independently or next to a segment for augmentation cystoplasty. The segment is opened horizontally and tubularized in a longitudinal fashion. **B**, If the segment is opened directly on the antimesenteric border, two equal-length limbs result with a central mesenteric pedicle. Initial incision may be made to one side to form a shorter limb for implantation in the bladder and a longer one to be brought through the abdominal wall. **C**, The reconfigured ileal segment is tubularized over a 12-Fr catheter in a two-layer technique with absorbable sutures. **D**, A continent catheterizable stoma is constructed.

channels in 28% of a large series of patients due to "pouchlike dilatation." Such a problem has been avoidable in most series.

Ileocecal Valve

Use of the ileocecal valve as a continence mechanism began with Gilchrist (1950) and was popularized by the Indiana group (Rowland et al, 1985; Bihrle, 1997). Various modifications exist. In general, a short segment of terminal ileum, whether imbricated or tailored, is used as an efferent limb. This segment should be kept as short and straight as possible to facilitate easy intermittent catheterization. Continence is based on the imbricated ileocecal valve, not the length of the efferent limb. The imbrication is usually secured with interrupted, permanent sutures, involving the very distal ileum and ileocecal valve, and the imbrication is carried well onto the cecum. The reservoir itself is constructed from reconfigured right colon up through the hepatic flexure, with or without a patch of ileum. Standard ureterocolonic anastomoses are done beneath the taenia to prevent reflux. Staplers using absorbable staples have been used for reconfiguration of the reservoir (Kirsch et al, 1996) and may shorten the operative time for reconstruction.

The Indiana pouch has been used in children with excellent results, as it has in adults. Besides the appendix, this continence mechanism is perhaps the simplest and has the shortest learning curve to achieve reliable results. Continence rates as high as 95%

have been reported with preservation of normal upper tracts (Rowland et al, 1985; Lockhart et al, 1990; Rink and Bihrle, 1990; Hensle and Ring, 1991; Rowland, 1995; Kaefer et al, 1997b). Rare reports have noted higher rates of incontinence (Canning, 1998). Husmann and Cain (1999) have used the cecal segment for bladder augmentation and the efferent limb to construct a continent catheterizable stoma with equally good results. They noted a low incidence of detrimental effect on gastrointestinal function in a select group of patients with neurogenic dysfunction.

Hydraulic Valves

Benchekroun (1982, 1989) developed an interesting hydraulic valve as a continence mechanism that was modified by Guzman and coworkers (1989). Urine from the reservoir and any pressure generated there is allowed to enter a sleeve of ileum around the catheterizable channel. Compression of the inner tube theoretically provides continence, and early results were encouraging. Initial continence rates approached 75% and then 90% with a single revision (Benchekroun et al, 1989). Others have not been able to duplicate those results (Sanda et al, 1988; Leonard et al, 1990b), and the valve has largely been abandoned.

Koff and associates (1989) added hydraulic compression to the terminal ileum of an Indiana pouch by anastomosing a segment of tubular ileum to the cecum and then wrapping it around the efferent limb. The procedure has not gained popularity, probably because of the excellent success of the standard Indiana pouch.

Continent Vesicostomy

Yachia (1997) described construction of a bladder tube fashioned from a wide flap of the anterior bladder wall. No attempt was made to produce continence at the level of the bladder. The continence mechanism was fashioned by weaving the bladder tube through the rectus muscle to produce compression and continence. Continence in the small, short-term series was reported at 100% but has not been duplicated.

Hanna and colleagues (1999) described a continence mechanism based on either a flap of bladder or intestinal tissue fashioned after prior enterocystoplasty. A rectangular flap in continuity with the bladder is tubularized over a 14- to 16-Fr catheter. The bladder is plicated around the proximal 3 cm of the tube with nonabsorbable suture to make a type of nipple similar to gastric fundoplication. No significant morbidity has been identified in a limited series of five children, and all children have remained dry on intermittent catheterization. Macedo and Srougi (2000) described a similar continence mechanism made at the time of initial augmentation. They achieved acceptable continence in eight of their first nine patients. Their technique is potentially appealing for patients requiring augmentation and having no appendix because of the simplicity; however, continence is based on a type of nipple valve that historically has been difficult to keep fixed. The same forces that create continence tend to efface the continence mechanism.

Casale (1991) has described a form of continent vesicostomy in which the continence mechanism is based on a flap valve made from a tubularized strip of bladder mucosa. It is particularly suitable when the bladder is compliant and of large capacity. An anterior detrusor strip is also used to construct a catheterizable limb.

Technique. Parallel incisions 3 cm apart are made into the anterior bladder and used to form a long rectangular flap. The abdominal wall should be measured to ensure that the strip is long enough to reach the skin without tension. The full-thickness strip is tubularized down to the bladder, typically in two layers. The muscle portion is left broad to come around without tension and provide good blood supply. The mucosa may be trimmed in width before tubularization to avoid redundancy. A strip of mucosa within the bladder, 2 to 3 cm in length and 1.5 cm in width, is incised in a direct line and in continuity with the mobilized bladder tube. The edges of this strip are mobilized until it can be tubularized along its entire length. It may be beneficial to mobilize only one edge over to the other side, which allows one to avoid overlapping suture lines. Casale (1991) originally incised the mucosa transversely at the end of the intravesical strip to be tubularized; Rink and associates (1995b) then suggested that it could be left intact (Fig. 129–21). The bladder mucosa from either side of the tube is then mobilized and closed over the mucosal tube to create a flap valve. More extensive mobilization of the side opposite that mobilized for the inner tube allows closure without overlapping suture lines, which may help avoid fistula formation and incontinence. A soft stent is usually left through the tube for 3 weeks during healing to prevent stenosis. It does tend to close if it is not catheterized regularly and may be even more susceptible than other catheterizable channels to stomal stenosis (Cain et al, 2002; Thomas et al, 2005).

Results. Continence rates have been good, as with most flap valve mechanisms (Cain et al, 1999, 2002). Stomal stenosis remains a significant problem—45% in the experience at Indiana University (Cain et al, 2002). Skin flaps and avoidance of tension to reach the skin may minimize this risk but not remove it. Advantages include avoidance of an intraperitoneal procedure and bowel anastomosis; the appendix can be reserved for use with enemas. It does use some bladder and decreases capacity, which may not be appropriate for some patients.

Results with Pediatric Continent Diversion

Continent urinary reservoirs have been performed in children with very good results, equivalent to those achieved for adults. Construction of an adequate reservoir and an antireflux mechanism has generally been straightforward. For review of issues concerning compliance of the reservoir or mechanisms by which reflux can be prevented, the reader may review earlier parts of this chapter or the information on continent urinary diversion in adults elsewhere in this textbook. The most challenging aspect of continent diversion remains construction of an efferent limb that provides reliable continence and easy catheterization. The continence mechanism most familiar to pediatric urologists is the flap valve. The appendix is simple to use, suitable for most children, and associated with very good continence rates. If the appendix is not present or is to be used for antegrade colonic enemas, tapered intestinal segments provide a nice alternative. Nipple valves are the most complex continence mechanism and therefore their creation requires a longer learning curve. Continence rates of approximately 85% can be expected with stapled nipple valves (Kaefer et al, 1997b; Benson and Olsson, 1998), even with extensive experience. With use of the other efferent limbs, continence rates above 90% and approaching 95% have routinely been reported in children (Duckett and Snyder, 1986; Hensle and Ring, 1991; Kaefer et al, 1997b; Surer et al, 2003). Those continence rates have been achieved with preservation of the upper tracts. With proper selection of patients and appropriately performed continent diversion, hydronephrosis in children is rare

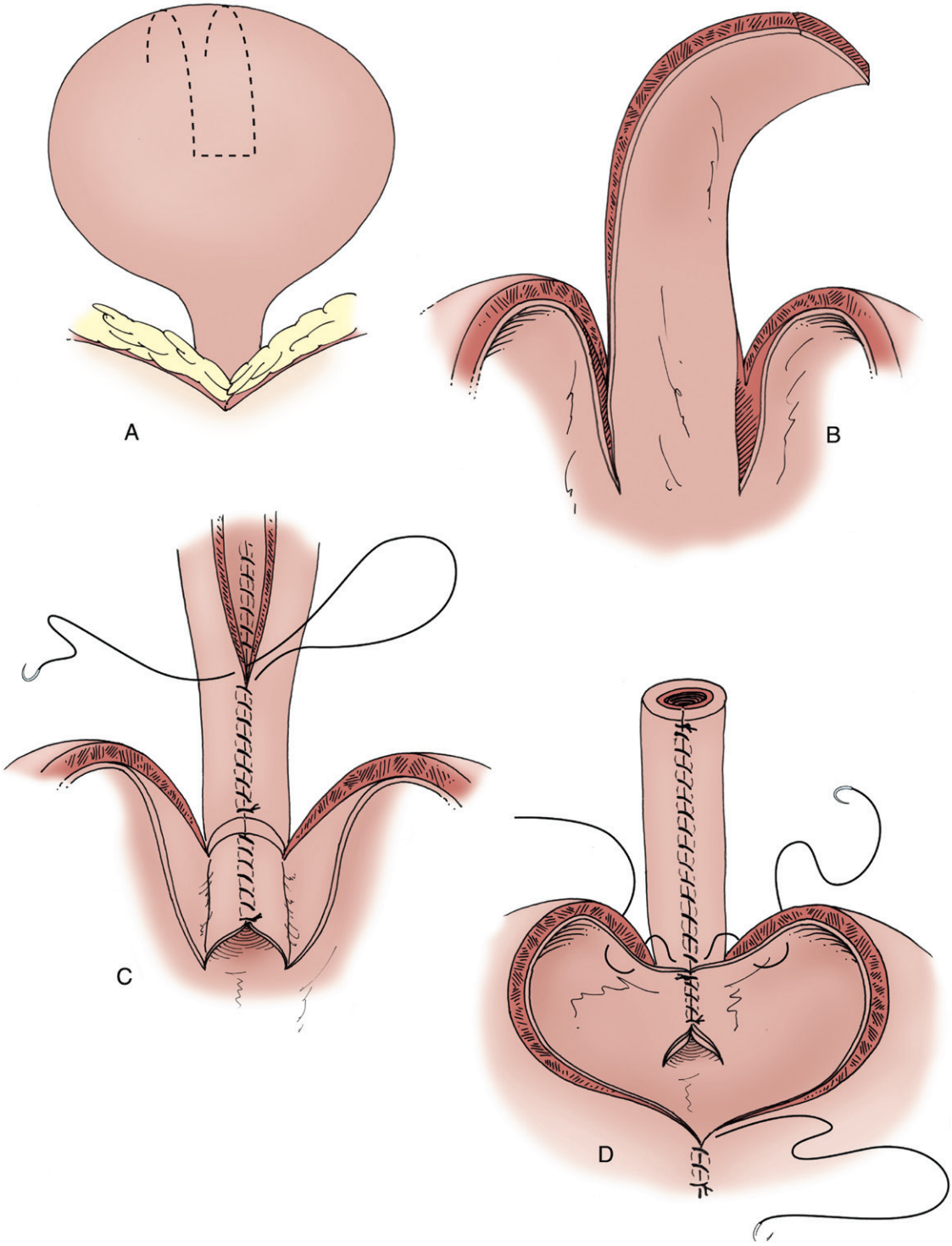


Figure 129–21. Casale continent catheterizable stoma. **A**, Parallel incisions are made in the bladder dome, forming a full-thickness bladder strip. **B**, The epithelium of the bladder is then incised for an additional 2.5 cm. The edges of the epithelium are mobilized, allowing tubularization. **C**, The epithelium is tubularized from the bladder out to the tip of the strip with an absorbable suture. The muscle of the bladder strip is then tubularized with an absorbable suture. **D**, The lateral edges of the epithelium within the bladder are reapproximated over the tubularized bladder segment with absorbable suture. The bladder is then closed with absorbable suture, incorporating the bladder tube with the initial sutures to prevent kinking.

postoperatively. Particularly if catheterization is not performed reliably, new hydronephrosis can occur (Abd-El-Gawad et al, 1999). There is no evidence that children suffer more hydronephrosis after continent diversion compared with conduit diversion (Stein et al, 2000).

Children undergoing continent diversion have a long life expectancy. The incidence of complications after continent diversion will probably increase with longer follow-up. Those patients will be subject to the same complications discussed at length for bladder augmentation. All of those complications, including

infection, hydronephrosis, calculi, spontaneous perforation, and tumor, have been reported after continent diversion in adults if not in children. These are largely a function of the use of intestine as a urinary reservoir. Because more intestine is usually required in continent diversion than in bladder augmentation, the incidence of complications may ultimately be higher than with simple augmentation as follow-up increases. Certainly, serum changes of increased chloride, decreased bicarbonate, and acidosis have been noted in some patients after continent diversion (Allen et al, 1985; Ashken, 1987; Thuroff et al, 1987; Boyd et al, 1989; McDougal, 1992a). Spontaneous perforation has occurred in up to 1.5% of patients (Mansson et al, 1997).

The most common complication in pediatric continent diversion thus far has been stomal stenosis. Such stenosis occurs more commonly at the umbilicus and when appendix is used compared with tapered ileal segments (Fichtner et al, 1997; Kaefer et al, 1999a). Various skin flaps may be placed into the terminal end of the appendix or intestinal segment to lower the rate of stenosis but do not eliminate it (Kajbafzadeh et al, 1995). Bladder calculi have also been common problems (Surer et al, 2003).

Key Points: Continent Urinary Diversion

- "Pure" continent diversions in children have been used with good results similar to those expected in adults.
- Variants of ureterosigmoidostomy may lower morbidity; however, they are rarely used in pediatric patients, and concerns about tumor development remain.
- Flap valves provide a reliable continence mechanism with appendix or reconfigured intestinal channels.
- The efferent limb should be kept short and straight to facilitate catheterization.
- Stomal stenosis is the most common complication of pediatric continent diversion.
- The appendix may be best used for antegrade continence enemas in some pediatric patients.

ANTEGRADE CONTINENCE ENEMAS

Fecal incontinence may be more socially debilitating to patients than urinary incontinence. In a sense, it has been easier to work surgically on urinary incontinence because urologists and their patients have intermittent catheterization to reliably empty. Unfortunately, that has not been the case with constipation and fecal incontinence, particularly among patients with neurogenic dysfunction. **Malone and colleagues** (1990) **have described use of the appendix for antegrade continence enemas (i.e., the MACE procedure) to control constipation and achieve fecal continence in patients with complex gastrointestinal disorders refractory to conservative management.** These enemas, usually performed once a day, provide a thorough cleansing in a short time. Patients, particularly those with neurogenic dysfunction, often will not stool again until their next enema (Curry et al, 1999). Cecostomy tubes, cecostomy buttons, and tapered intestinal segments tunneled into the cecum have been used for the enemas when the appendix is not suitable or is unavailable (Stanton et al, 2002; Kim et al, 2006a; Yagmurlu et al, 2006; Biyani et al, 2007b; Lorenzo et al, 2007b; Heshmat et al, 2008). Antegrade continence enemas as originally described by Malone have been used extensively in the neurogenic population (Koyle et al, 1995; Curry et al, 1999; Kim et al, 2006a; Vande Velde et al, 2007; Bani-Hani et al, 2008b; Sinha et al, 2008b). Enemas can be performed using saline, but tap water has been found to be equally suitable (Hyde et al, 2008). Metabolic derangements are unusual, although water treated in a softener should be avoided because it can cause hypernatremia (Yerkes et al, 2000).

Average irrigating volumes in most series have approached 650 mL but occasionally reach 1000 mL. The transit time for the enema after insertion varies among patients but averages 25 minutes and ranges from 15 minutes to an hour (Hyde et al, 2000; Hinds et al, 2004; Bani-Hani et al, 2008b). Smaller volumes and less transit time may be required for left colon antegrade enemas (Churchill et al, 2003). Additives to the irrigant may decrease the transit time in some patients (Kajbafzadeh and Chubak, 2000; Bani-Hani et al, 2008b). The enemas are begun daily as soon as bowel function returns after reconstructive surgery. The initial volume used is low and typically increased every 2 or 3 days until adequate decompression is achieved. Fecal continence until the next enema has been consistent for most patients with neurogenic dysfunction and ranges from 67% to above 90% (Hensle et al, 1998; Herndon et al, 2004b; Kim et al, 2006a; Vande Velde et al, 2007; Bani-Hani et al, 2008b; Sinha et al, 2008b). Hensle and colleagues (1998) noted occasional soilage requiring a pad in one fourth of their patients performing the enemas routinely. The majority of patients can perform the enemas independently. Almost universally, the patients and families have continued to perform the enemas on a regular basis in these series, which is good evidence that they find the results to be worth any time and effort involved (Yerkes et al, 2003; Herndon et al, 2004b). Rare patients may have severe colonic spasms with flushing that preclude use (Bau et al, 2000). They occasionally respond better to multiple flushings with smaller volumes. The most common complication, as with use of the appendix as a catheterizable stoma elsewhere, has been stomal stenosis, although stenosis may not occur as commonly as when the appendix is moved to the bladder (Kaefer et al, 2000). Some children require catheterization of the appendix twice a day to avoid contracture or a cicatrix at the skin level. Mickelson and associates (2009) have described the use of an L stent with or without steroid cream placed nightly to maintain patency. Fecal and irrigant incontinence can occur and is socially unacceptable. Reassessment of irrigating technique is important along with radiographic confirmation of irrigant transit through the colon. Endoscopic injection of a bulking agent at the junction of the catheterizable channel and the cecum can be tried (Koivusalo et al, 2006). Formal open revision and reinforcement of the catheterizable channel may be required. Perforation of the appendix has been noted with catheterization, as has false passage parallel to the appendix. Subsequent intraperitoneal injection of the enema fluid has resulted in peritonitis. Such patients require antibiotics and close observation. They do not routinely require reoperation (Brock, 2000). Kokoska and associates (2004) reported two cases of cecal volvulus among 164 patients using these enemas.

The appendix can be used easily in situ (Fig. 129–22). In review of a large experience, Bani-Hani and colleagues (2008a) have noted fewer complications after in-situ use of the appendix than with other techniques. Windows in the mesoappendix may be made and permanent Lembert sutures used to approximate the cecal wall in each window. This effectively wraps the cecum around the base of the appendix to prevent spillage. Alternatively, one taenia leading to the appendix may be incised longitudinally and reapproximated in the windows of the

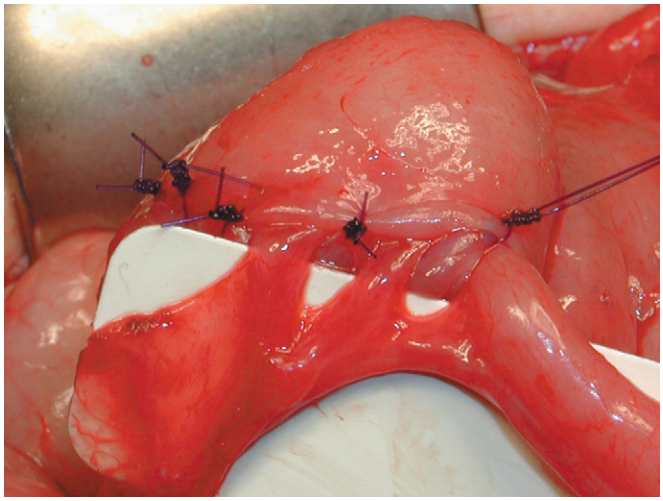


Figure 129–22. The appendix used in situ for antegrade continence enema or urinary continent catheterizable stoma. The appendix and its mesentery are mobilized without detachment from the cecum. Windows are carefully made in the mesentery between vessels to the proximal appendix. The taeniae from either side of the cecum are approximated in those windows with permanent sutures to ensure continence of the stoma. The distal end of the appendix is brought to the abdominal wall for catheterization.

mesoappendix. Others have made no attempt to construct a continence mechanism at the appendicocecal junction, particularly surgeons performing antegrade continence enemas laparoscopically (Cadeddu and Docimo, 1999; Casale et al, 2004; Nanigian et al, 2008). A left colonic catheterizable channel has been advocated especially when the appendix is not available. The results are similar to an appendicocecostomy, with continence reported to be 74% to 94% and stomal stenosis at a rate of 26% (Kim et al, 2006b; Sinha et al, 2008a). Most MACE procedures are performed by urologists at the time of a major reconstructive procedure involving the bladder (Casale et al, 2006). Their long experience with construction of continent catheterizable stomas for the urinary bladder has taught them the principles to achieve a good result, but about 15% of patients will require some revisional surgery (Bani-Hani et al, 2008a). The authors' preference is to provide some continence mechanism at the base of the appendix in this setting to avoid any spillage (Donohoe et al, 2004).

URINARY REFUNCTIONALIZATION

The clinical need for urinary refunctionalization has changed dramatically during the past several decades. Before the acceptance of CIC (Lapides et al, 1976), many children were not candidates for complex reconstructive procedures because of an inability to empty afterward. Many were initially treated with permanent urinary diversions with use of an intestinal segment with high expectations. Over time, it became clear that such diversions had significant complications, including infection, stones, and nephropathy (Smith, 1972; Richie et al, 1974; Shapiro et al, 1975; Middleton and Hendren, 1976; Pitts and Muecke, 1979). With the recognition of those complications and the routine use of CIC, urinary refunctionalization became a relatively common procedure for the reconstructive surgeon (Hendren, 1974, 1987, 1990; Perlmutter, 1980). Fewer patients now require diversion. Better anesthetic and perioperative surgical care has allowed safe definitive repair of primary problems in younger infants. The occasional diversion presently done in extreme cases is usually temporary rather than a permanent one using bowel. Consequently, urinary refunctionalization now is infrequent and typically involves closure of some urinary stoma rather than takedown of an intestinal segment.

Permanent diversions in children are now typically confined to cancer patients. When their outcome is good, they may then be candidates for urinary refunctionalization and conversion to continent urinary diversion. The Boston group has favored initial temporary diversion with a transverse colon conduit to avoid irradiated bowel when cystectomy is required. Once cure is ensured, the conduit can be converted to a continent reservoir by augmenting the colonic segment with stomach to provide an adequate reservoir and by providing a continent catheterizable efferent limb (Duel et al, 1996).

The key to urinary refunctionalization is understanding the original pathologic process that led to diversion. This may be relatively easy if the surgeon involved has cared for the patient throughout his or her course. If the original diversion was done by someone else years previously, such understanding may be difficult and require thorough investigation. Accurate understanding of the underlying disease may be made more difficult because of defunctionalization of the remaining urinary tract. It is important to review the patient's original history and studies to understand the pathophysiologic changes before any intervention. For example, failure of the urinary bladder in a patient with neurogenic dysfunction to respond adequately to anticholinergic medication and intermittent catheterization before vesicostomy diversion might well predict that it will not do so after vesicostomy closure. Special nuances in the current evaluation may also be necessary. Urodynamic evaluation of a bladder diverted for several years with a vesicostomy will virtually always show a small capacity. A repeated study after several days of bladder cycling or occlusion of the vesicostomy may be more predictive of bladder function. The bladder may respond to bladder cycling quickly (Bauer et al, 1986; McGuire, 1996). Temporary occlusion of a vesicostomy with a gastrostomy button may be informative (de Badiola et al, 1995). Occlusion of the vesicostomy during urodynamics may be necessary to achieve good bladder filling and to accurately define the adequacy of outflow resistance. Such parameters must be evaluated before urinary refunctionalization and may have changed since the time of diversion, particularly in patients with neurogenic dysfunction. Antegrade perfusion studies may be helpful and necessary in evaluation of the upper tract previously diverted by ureterostomy or pyelostomy.

Correction of Original and New Pathologic Processes. It is essential that all pathophysiologic change is appreciated, whether it is original or new. Failure to do so can result in recurrent clinical problems for the patient (i.e., renal insufficiency, hydronephrosis, infection, and incontinence) in the presence of a technically perfect operation. Once the reconstructive surgeon understands those problems the reconstructive options available for urinary refunctionalization should be assessed on an individual basis. Considerations include the length, dilation, and scarring of the ureters; the volume, compliance, and fibrosis of the native bladder; and the function of the outlet in terms of resistance for continence and synergistic relaxation for emptying. More global problems, such as renal insufficiency and neurogenic dysfunction, may influence the choices of technique as well. In patients with an existing permanent diversion involving an intestinal segment, the quality,

length, and volume of that segment should be considered to determine how it might best be used in reconstruction. An existing ileal conduit might be used as an ileal ureter, as a segment for bladder augmentation, or for tapering as a continent stoma, depending on the needs of the patient.

For examples that illustrate the potentially complex nature of many urinary refunctionalization cases, the reader is referred to Dr. Hendren's chapter on undiversion in prior editions of this text (Hendren, 1998). No one has more experience, and his cases demonstrate the total command of all surgical alternatives that is required to manage these patients well. The illustrated cases there are typical of the types of patients that historically underwent undiversion.

Results. Hendren (1998) reported a 26-year experience with urinary refunctionalization in 216 patients. Two thirds of the patients had permanent diversions, often of long duration. He noted that many of the patients had impaired renal function, either from their underlying problems or as morbidity related to the diversion. More than 10% of the patients had already required renal transplantation after undiversion, and even more were progressing toward it. With successful relief of obstruction, prevention of reflux, and provision of a compliant bladder, Hendren noted that urinary refunctionalization prolonged the time to renal failure in some patients and may have avoided it entirely in others. Urinary refunctionalization may protect renal function rather than contribute to any decline if it is properly selected and performed.

In Hendren's series, management of the bladder was relatively straightforward and effective with bladder augmentation as necessary. Inadequate outflow resistance was usually treated with Young-Dees-Leadbetter bladder neck repair. Most complications were related to the ureters: 23 patients required reoperation for persistent reflux; 10 did so for partial obstruction of the ureter. Those reoperation rates are indicative of the difficulty one faces in dealing with short, dilated, and scarred ureters that may be present after urinary diversion (Hendren, 1998). Others have had similar good success (Gonzalez et al, 1986; Mitchell and Rink, 1987) with urinary refunctionalization.

The success of many of the techniques necessary for urinary refunctionalization should be similar to the success of those done in primary reconstruction. In other words, the good results of ileocystoplasty or appendicovesicostomy should be equivalent whether they are done as part of a urinary refunctionalization or not. As noted in Hendren's cases and series, many problems may be present and multiple techniques might be required for a given patient. **The key to achieving a good result in urinary refunctionalization is to understand all of the patient's problems and to correct each. The most difficult measure of complex urinary refunctionalization, and the one most prone to complication, relates to the short, dilated, and chronically scarred ureter that may be the residual of the original problem or secondary to prior surgery including diversion.**

In occasional cases of urinary undiversion, conversion to a continent urinary reservoir is appropriate. This is true of cases in which the native bladder is congenitally absent, removed, or heavily irradiated. In those rare cases, the volume and quality of the patient's native tissue may be so poor that inclusion in the reconstruction is not warranted. **In the majority of cases of urinary refunctionalization, reconstruction of the native urinary tract is preferable to continent diversion.** Such reconstruction can minimize morbidity to the patient by utilizing more tissue line by urothelium.

Key Points: Urinary Refunctionalization

- Most urinary refunctionalization procedures now involve takedown of a urinary stoma rather than an intestinal diversion.
- It is key to understand the patient's underlying pathophysiologic process as well as any problems related to diversion.
- Chronically scarred and shortened ureters may be a challenge in these patients.

SUMMARY

Every effort should be made to treat pediatric bladder dysfunction, no matter what the etiology, early and aggressively to minimize the number of patients requiring reconstructive surgery for bladder and sphincter dysfunction. Some such surgery will still be necessary, and the patients must be carefully evaluated so that all problems are identified and addressed. The surgeon should then be flexible and prepared to use the bowel segments and techniques that best fit each patient. **Whereas a given surgeon's result with any technique may improve with experience and confidence, each patient's unique problems and anatomy may make some choices better than others. Forcing one procedure to fit every patient should be avoided.**

Preoperative evaluation should identify upper tract obstruction or vesicoureteral reflux. Such problems should be corrected at the time of surgery, although low-grade secondary reflux will usually resolve spontaneously with correction of bladder dysfunction. It is imperative to provide the patient with an adequate bladder or reservoir, one capable of holding at low pressure a urinary volume that will be produced between voidings or catheterizations. This can be accomplished by either augmentation or construction of a continent reservoir with use of any gastrointestinal segment. Each has its own set of advantages and disadvantages that should be considered. If adequate outflow resistance is lacking, it should be created at the bladder neck to prevent incontinence. Any patient undergoing reconstructive surgery for bladder or sphincter dysfunction must be prepared to perform and be capable of performing intermittent catheterization on a reliable basis; most will require it routinely. This is particularly true of those patients with neurogenic dysfunction.

As much of the patient's native urinary tract as possible should be preserved in pediatric urologic reconstruction. The urothelial lining avoids much of the morbidity associated with intestinal segments. If necessary, however, virtually any portion of the lower urinary tract may be reconstructed or replaced with intestine. Unfortunately, occasional complications do occur when intestinal segments are used in that manner. They are not perfect physiologic substitutes. Patients after reconstruction require a lifetime of follow-up, and that observation should include careful evaluation of their true quality of life. The most important factor in avoiding problems with such complex pediatric patients is the motivation of the patient and family to achieve a successful outcome. Assessment of that commitment is critical.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter 130

Hypospadias

Warren T. Snodgrass, MD

Embryology of Penile Development
Etiology
Epidemiology
Diagnosis
Associated Anomalies
Preoperative Evaluation and Management
General Aspects of Surgical Repair
Historic Background
Hypospadias Surgery
Assessing Surgical Outcomes
Urethroplasty Complications
Reoperations
Limitations of Hypospadias Literature

Hypospadias is believed to result from arrested penile development, leaving a proximal urethral meatus. It has challenged generations of reconstructive surgeons trying to extend the urethra while straightening associated penile curvature and managing ventral skin deficiency, with the goal of restoring as normal function and appearance as is possible. The current understanding of the etiology of hypospadias and current methods for its surgical correction are discussed in this chapter.

An emphasis is given to those procedures most commonly used today, and this selection inevitably omits some techniques that a minority of surgeons prefers. For example, meatoplasty and glansplasty (MAGPI) and Mathieu flip-flap are not discussed in detail, but technical aspects of these procedures have not significantly changed since their description in prior editions of this textbook.

Objective outcomes data are provided for described techniques to the extent available, usually summarized in the tables. Total complications may exceed the number of patients with complications due to multiple problems in some patients. Numbers appear only in columns designating outcomes specifically mentioned by authors.

EMBRYOLOGY OF PENILE DEVELOPMENT

The external genital anlage is initially indifferent and develops the female phenotype unless exposed to androgens during the critical gestational time period of 8 to 12 weeks. 5α-Reductase type 2 is highly expressed in mesenchymal stroma while the androgen receptor is concentrated in epithelium of the urethral plate (Kim et al, 2002). Dihydrotestosterone derived from 5α-reduced testosterone mediates the key steps in penis formation: elongation of the genital tubercle and fusion of urethral folds.

The urethral plate develops as an extension of endoderm from the cloaca along the ventral midline of the genital tubercle. Proliferating mesenchyme to either side creates urethral folds and establishes the urethral groove. Fusion of the urethral folds begins proximally and continues distally at least to the glans. Two theories are proposed for glanular urethra development: ectodermal ingrowth cannulating the glans to the urethral plate (Glenister, 1954) versus urethral plate tubularization to the tip of the glans (Kurzrock et al, 1999).

Embryo studies suggest the penis initially exhibits ventral curvature (VC) during formation, which can persist in hypospadias when normal development arrests (Kaplan and Lamm, 1975). This VC originally was ascribed to fibrous tissue bands. However, histology from both embryos and resected surgical specimens demonstrate well-vascularized tissues without fibrosis (Baskin et al, 1998; Snodgrass et al, 2000).

Preputial development begins with a cellular lamella oriented dorsally at the coronal sulcus, with ventral fusion into the frenulum delayed until after urethral formation is completed.

Neither the molecular mechanisms involved in normal penis development nor those disturbances resulting in hypospadias are currently known. In mice, Sonic hedgehog (Shh) expressed by distal urethral plate epithelium is needed for genital tubercle outgrowth, with targeted deletion resulting in penile and clitoral agenesis (Haraguchi et al, 2001). Shh regulates fibroblastic growth factor-8 (fgf8), also known as androgen-induced growth factor, which upregulates expression of fgf10 involved in glans morphogenesis. Fgf10 also is expressed in midline mesenchyme during urethral fold fusion (Haraguchi et al, 2000), and deficient mutant mice exhibit a hypospadias-like phenotype that Yucel and associates (2004) believe indicates its crucial role in distal urethral plate tubularization. Fgf receptor 2 (Fgfr2) similarly is expressed in the urethral plate and prepuce in mice, and mice lacking it manifest proximal hypospadias (Petiot et al, 2005). Androgen receptor antagonists result in loss of Fgf10 and Fgfr2 expression in the urethra and hypospadias phenotype, indicating these genes are downstream targets involved in urethral formation (Petiot et al, 2005). The B-subclass of cell-surface Ehp and ephrin molecules also plays an important role in murine urethral formation, with heterozygous mutant males demonstrating perineal hypospadias (Yucel et al, 2007).

However, extrapolation of these findings in mice to human development is currently uncertain. Although Baskin and coworkers (2004) state the murine urethra tubularizes proximally to distally by urethral fold fusion similar to humans, others describe canalization of the urethral plate without fusion of urethral folds in rats and mice (Uda et al, 2004).

ETIOLOGY

The underlying cause for nonsyndromic hypospadias in most individual cases is unknown. Based on knowledge of normal penis formation and the presumption that hypospadias represents arrested development, several causes may exist.

Genetic Factors

Familial aggregation is found in 4% to 10% of hypospadias cases, including first-, second-, and third-degree relatives (Calzolari et al, 1986; Harris and Beaty, 1993; Fredell et al, 2002; Schnack et al, 2008). A recent national registration-based study from Denmark (Schnack et al, 2008) included 1.2 million males with 5380 hypospadias cases, reporting hypospadias equally transmitted through maternal and paternal sides of the family, with recurrence risk ratios similar for twin brothers, brothers, and sons. Difficulties in establishing recurrence risks include heterogeneity in the severity of hypospadias in probands, reliance on family histories introducing recall bias, and inclusion of patients with unrecognized syndromal hypospadias (Harris and Beaty, 1993; Schnack et al, 2008). Despite these limitations, a consistent conclusion is that familial aggregation is best explained by genetic factors rather than environmental exposure (Calzolari et al, 1986; Stoll et al, 1990; Schnack et al, 2008).

Endocrinopathies

The pivotal role of androgens in normal penis development suggests endocrinopathies impacting hormone production or action may underlie hypospadias. Leydig cell dysfunction was implicated by findings of elevated basal luteinizing hormone and reduced testosterone response to human chorionic gonadotropin stimulation in prepubertal boys with hypospadias versus controls (Nonomura et al, 1984). Defects in the testosterone biosynthetic pathway, specifically, impaired 3β-hydroxysteroid dehydrogenase alone or with impaired 17,20-lyase or 17α-hydroxylase activity, were reported in proximal hypospadias (Aaronson et al, 1997) but not confirmed in subsequent studies (Feyaerts et al, 2002; Holmes et al, 2004). Although enzymatic assays for 5α-reductase type 2 activity in isolated hypospadias are normal, mutations in its coding gene *SRD5A2* on chromosome 2 were reported in 9% of patients with hypospadias not found in controls (Silver and Russell, 1999). Androgen receptor gene mutations are considered a rare cause of hypospadias (Batch et al, 1993; Hiort et al, 1994; Allera et al, 1995; Sutherland et al, 1996) but were not detected by others (Feyaerts et al, 2002).

Problems linking disturbed androgen activity to hypospadias were summarized by Holmes and associates (2004): little evidence has been found to suggest that nonsyndromic hypospadias without other genital anomalies is associated with defects in testosterone production, its conversion to dihydrotestosterone, or androgen receptor activity. Furthermore, the autosomal recessive pattern of inheritance characterizing steroidogenic enzyme disorders does not correlate with the genetics of hypospadias.

Gene Mutations

Murine studies indicating androgen receptor activity regulates *Fgf8, Fgf10,* and *Fgfr2* involved in urethral development have led to screening for defects in these candidate genes in patients with hypospadias. Among cases of nonsyndromic familial hypospadias variants have been found in *FGF8* and *FGFR2* not seen in normal controls (Beleza-Meireles et al, 2007a).

Estrogens play a role in male development, with specific nuclear estrogen receptors, predominantly ER2, found in proximity to the androgen receptor. Variants of ER2 influence serum testosterone levels and have been described in patients with hypospadias (Beleza-Meireles et al, 2007b). Further evidence implicating estrogen-related events in urethral maldevelopment was the finding that several estrogen-responsive genes are upregulated in hypospadias patients, including *ACT3, Cyr61, CTGF,* and *CADD45β* (Wang et al, 2007). Polymorphisms of *ACT3* were subsequently reported associated with hypospadias, as were less common mutations (Beleza-Meireles et al, 2008).

Endocrine Disruptors

A hypothesis that natural or synthetic compounds exerting estrogen-like and/or antiandrogen effects could result in hypospadias potentially is supported by several observations. First are reports that the incidence of hypospadias is increasing in Western nations where exposure to industrial compounds is presumed widespread. In addition, pregnant animals exposed to various chemicals in pesticides exerting estrogen-like or antiandrogen effects produce male offspring with urogenital anomalies, including hypospadias (Gray et al, 2004). Similarly, an increased risk for hypospadias has been identified in males after assisted reproduction, possibly attributable to progesterone administered to mothers. Finally, there is recognition that the estrogen receptor influences androgen activity as mentioned earlier, suggesting exposure to estrogen-like compounds may explain abnormal masculinization in the absence of demonstrated defects in testosterone production, 5α-reductase type 2 activity, or the androgen receptor.

However, although human penis development is potentially vulnerable to endocrine disruption, to date xenobiotics have not been linked to hypospadias (Baskin et al, 2001; Safe, 2005). Furthermore, the reported increase in hypospadias that suggests environmental endocrine disturbance has been challenged by recent epidemiologic studies (see later).

Syndromes with Hypospadias

Nearly 200 syndromes are associated with hypospadias (Edery, 2007).

Smith-Lemli-Opitz syndrome results from autosomal recessive mutation of the *DHCR7* gene on chromosome 11q13 coding for 7-dehydrocholesterol reductase. Affected individuals have mental retardation, facial dysmorphism, microcephaly, and syndactyly. *DHCR7* regulates Sonic hedgehog signaling, and so association of this syndrome with hypospadias potentially links to observations in mice regarding the role of Shh in penis development.

Deletion in chromosome 11q13 results in WAGR syndrome (*W*ilms tumor, *A*niridia, *G*enital anomalies, mental *R*etardation), associated with hypospadias due to altered *WT1* gene activity. One study screening for *WT1* gene defects in boys with nonsyndromic hypospadias reported no mutations (Nordenskjold et al, 1999).

Hand-foot-genital syndrome is an extremely rare autosomal dominant condition due to mutations in *HOXA13* on chromosome 7p14-15, resulting in bilateral thumb and great toe hypoplasia. Hypospadias in mice mutant for *Hoxa13* also have loss of *Fgf8* and bone morphogenetic protein-7 in the urethral plate (Beleza-Meireles et al, 2007a).

Opitz G syndrome (Opitz G/BBB syndrome) occurs from X-linked mutations in midline 1 gene or autosomal dominant deletions in chromosome 22q11. The resultant phenotype includes hypertelorism, tracheoesophageal defects, cleft lip/palate, and mild mental retardation as well as hypospadias.

Wolf-Hirschhorn syndrome derives from deletions in chromosome 4p, resulting in mental retardation, seizures, abnormal facies, and midline defects, including hypospadias.

13q deletion syndrome is characterized by mental retardation, facial dysmorphia, imperforate anus, and hypospadias with penoscrotal transposition. The critical region mediating anorectal and genital anomalies has been localized to 13q33.1-34, containing 20 annotated genes including *EFNB2* (Garcia et al, 2006). Partial loss of ephrin B-2 function altering ephrin signaling in mice is associated with hypospadias, as discussed earlier.

EPIDEMIOLOGY

Prevalence

In the 1800s both Bouisson and Rennes reported that hypospadias occurred in 1 of 300 males (Beck, 1917). Data from birth registries in the United States during the late 1960s demonstrated a similar incidence (Paulozzi et al, 1997). Subsequent studies in the 1970s and 1980s indicated an apparent doubling in hypospadias occurrence in the United States, Hungary, and England, with upward trends in Denmark, Norway, and Sweden (Paulozzi et al, 1997; Aho et al, 2000a; Toppari et al, 2001). A simultaneous increase in the ratio of severe to mild forms of the condition in the Metropolitan Atlanta Congenital Defects Program suggested the increase was due to growing incidence rather than to more frequent reporting of distal cases (Paulozzi et al, 1997). Together these data from national birth registries have been taken as evidence for the influence of environmental toxins.

However, a review of surgically treated cases versus live births in Finland from 1970 to 1986 found prevalence of hypospadias unchanged despite the apparent increase noted in the national malformation registry (Aho et al, 2000a). Further investigation suggested hypospadias was previously underreported in the Finnish national malformation registry, as well as in Swedish and Danish registries (Kallen et al, 1986). Therefore, the apparent increase in hypospadias rate in these countries may only indicate changes in reporting.

In addition, various national databases have differences in reporting requirements. For example, in Australia and Japan only cases with the urethral opening on the penile shaft, scrotum, or perineum are registered, omitting the more common coronal and glanular forms (Toppari et al, 2001). Similarly, a comparison between surgical registries and the National Congenital Anomaly System in England found significant disparity in hypospadias rates attributed to a decision in 1990 to exclude reporting of distal cases (Nelson et al, 2007). Consequently, data from such registries cannot be used to accurately determine either incidence of hypospadias or geographic variations in its occurrence.

Other Associations

Placental dysfunction in early pregnancy has been implicated in risk for offspring with hypospadias, given its role in hormone production. Significant associations have been found to low birth weight (<10th percentile), preterm birth (<37 weeks), prepregnancy maternal obesity and diabetes, and maternal hypertension (Porter et al, 2005; Nordenskjold and Frisen, 2007; Akre et al, 2008). Both decreased (<24 years) and increased (>40 years) maternal age have been reported (Porter et al, 2005; Akre et al, 2008). Males have greater risk when paired with another male, versus female, twin, but the observation that twin pregnancy is associated with hypospadias may be explained by low birth weight (Nordenskjold and Frisen, 2007).

Assisted reproduction is associated with an increased hypospadias risk, which has been attributed to hormonal manipulations during and after the procedures (Macnab and Zouves, 1991; Silver et al, 1999), as well as paternal subfertility and twin pregnancy (Wennerholm et al, 2000).

DIAGNOSIS

Hypospadias is diagnosed by physical examination, first suspected by the ventrally deficient prepuce and confirmed by the proximal meatus (Fig. 130–1). **Other**

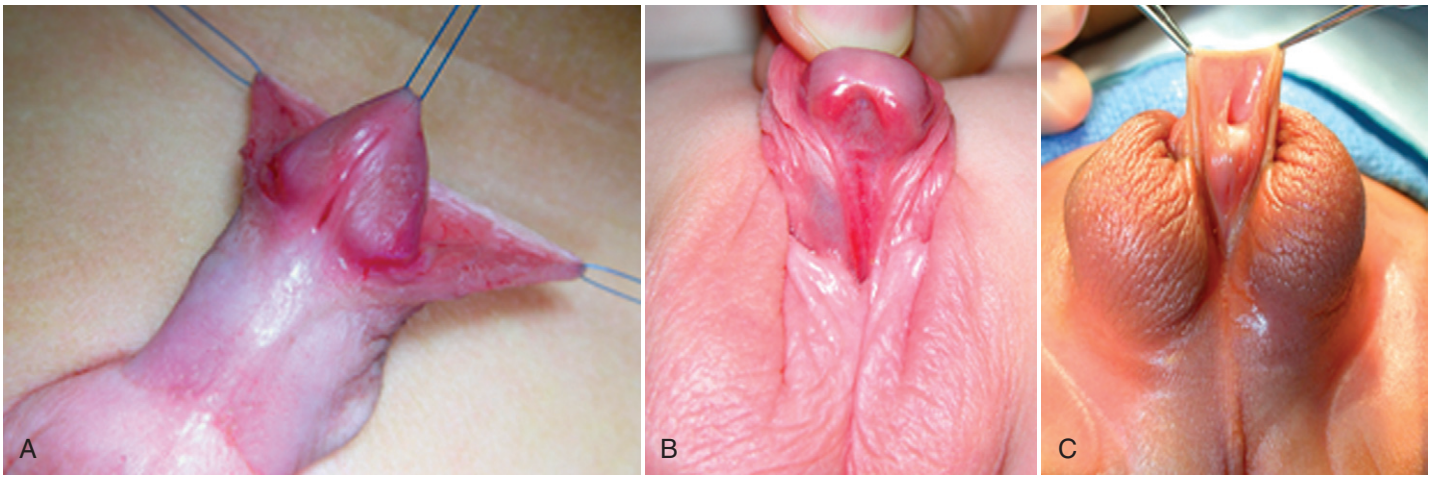


Figure 130–1. Spectrum of hypospadias. **A,** Coronal hypospadias. **B,** Penoscrotal hypospadias. **C,** Scrotal hypospadias with scrotal transposition.

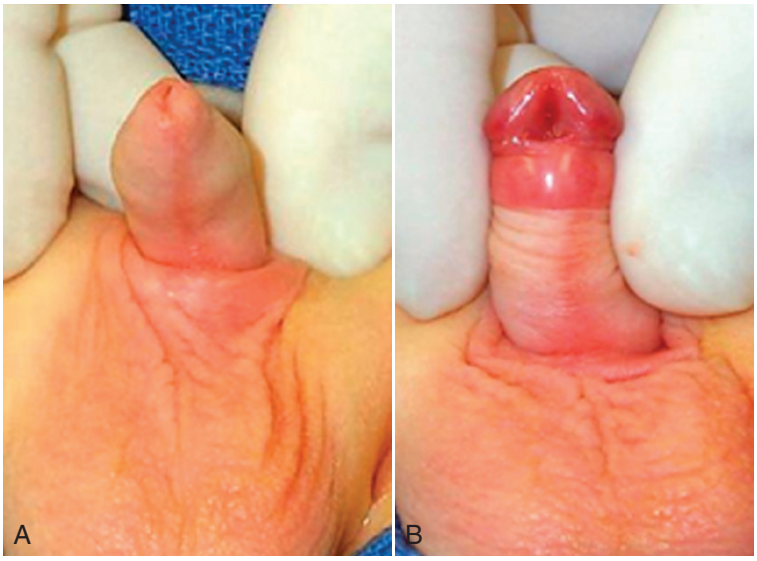


Figure 130–2. Megameatus intact prepuce hypospadias variant. **A,** Apparently normal penis with complete foreskin. **B,** Foreskin retracted, revealing coronal hypospadias.

abnormal ventral findings potentially include downward glans tilt, deviation of the median penile raphe, VC, scrotal encroachment onto the penile shaft, midline scrotal cleft, and penoscrotal transposition.

A variant subset has a normally formed foreskin concealing a glanular to distal shaft hypospadias termed *megameatus intact prepuce* (MIP) (Fig. 130–2). Diagnosis is made after elective neonatal circumcision or in later childhood when the foreskin retracts.

Patients with ventrally deficient foreskins but a normally located urethral meatus are diagnosed as having *chordee without hypospadias*. The term implies ventral penile curvature, although, in the majority, apparent downward bending is corrected by simply degloving the ventral skin. This categorization has included patients with a glanular meatus but deficient corpus spongiosum and thin distal urethra that others consider hypospadias variants. To end confusion, **boys with a hooded prepuce and bending should be diagnosed with *congenital ventral curvature* if the urethra is grossly normal or otherwise with hypospadias** (Snodgrass, 2008).

ASSOCIATED ANOMALIES

Cryptorchidism

Retrospective chart reviews (Kaefer et al, 1999; Wu et al, 2002) and a case-control study from the Danish National Patient Register (Weidner et al, 1999) report that approximately 7% of hypospadias patients also have cryptorchidism. In a series of 356 patients with hypospadias the incidence of cryptorchidism was 3.4% of 88 with distal versus 10% of 234 with proximal hypospadias (Wu et al, 2002).

Prostatic Utricle

An enlarged utricle sometimes hinders catheter placement during urethroplasty. After excluding patients with a disorder of sex development (DSD), urethrography demonstrates that enlarged utricles are uncommon in penile shaft hypospadias, with increasing incidence as severity progresses from penoscrotal to perineal cases (Devine et al, 1980; Ikoma et al, 1985).

Disorders of Sex Development

Although hypospadias is considered arrested masculinization, by convention it is distinguished from DSD. As discussed earlier, defects in testosterone production, its conversion to dihydrotestosterone, or androgen receptor activity that characterizes various disorders of sexual differentiation are uncommonly detected in isolated hypospadias.

The simultaneous occurrence of hypospadias with cryptorchidism increases the likelihood for DSD. Overall reported incidence in patients considered to have a male-appearing phenotype ranges from 0% to 30% and is greater with increasing severity of hypospadias and nonpalpable testes (Rajfer and Walsh, 1976; Kaefer et al, 1999; McAleer and Kaplan, 2001; Cox et al, 2008). Kaefer and colleagues reported DSD in approximately 50% of patients with a nonpalpable testis and hypospadias.

The most frequent finding is mixed gonadal dysgenesis, followed by ovotesticular disordered sexual differentiation. Incomplete androgen insensitivity, 5α-reductase type 2 deficiency, and testicular dysgenesis have also been reported. However, likely differences in defining male appearance versus ambiguity and failure to perform uniform genetic, biochemical, and radiologic evaluation in hypospadias patients with cryptorchidism make determination of the incidence of DSD uncertain.

Coexistence of hypospadias and cryptorchidism can be explained by other associations than DSD. For example, a case-control study examining risk factors independently for the two conditions within the same nationwide cohort in Sweden found low birth weight and prematurity positively correlated with each (Akre et al, 1999).

Malformation Syndromes

Hypospadias most often occurs in infants without additional known medical conditions. The finding of other anomalies increases the likelihood that hypospadias is part of a malformation syndrome. From the description of various syndromes just given these include developmental delay, facial dysmorphy, anorectal malformations, and other genital anomalies, including penoscrotal transposition and cryptorchidism.

Key Points: Penile Development

- Hypospadias is considered arrested penile development; the underlying etiology is unknown for most cases.
- Ventral curvature (VC) results from arrest during normal development when the penis is curved, rather than from fibrous bands previously termed *chordee*.
- Hypospadias with undescended testes may indicate a disorder of sexual differentiation, indicating need for karyotyping.
- Hypospadias with developmental delay, dysmorphic facies, and/or anorectal or scrotal malformations also suggests need for karyotyping.

PREOPERATIVE EVALUATION AND MANAGEMENT

Karyotyping

A karyotype may help categorize hypospadias as syndromic when there are other nongenital anomalies, especially developmental delay, dysmorphic facies, and/or anorectal or scrotal malformations. It may also detect gonadal DSD, especially when there is also cryptorchidism. The role for karyotyping in isolated hypospadias, even proximal cases, is unclear because most reports concern hypospadias associated with cryptorchidism (Rajfer and Walsh, 1976; Kaefer et al, 1999; McAleer and Kaplan, 2001; Cox et al, 2008) or do not state the severity of isolated hypospadias (Moreno-Garcia and Miranda, 2002).

Radiologic Studies

No prospective studies report the incidence of radiologically detected urinary tract anomalies associated with hypospadias. Initial retrospective reviews concerned intravenous pyelography, and of these the largest series found upper tract anomalies are not increased with nonsyndromic hypospadias (McArdle and Lebowitz, 1975; Lutzker et al, 1977; Cerasaro et al, 1986). Routine voiding cystourethrography to demonstrate an enlarged utricle is not necessary, because the most common clinical manifestation is difficult catheterization that can be managed intraoperatively. Imaging can be reserved for screening patients with suspected syndromic hypospadias or DSD.

Timing of Surgery

There are no data regarding optimal timing for hypospadias surgery in children, and so guidelines are derived from expert opinion. The 1996 Action Committee for the American Academy of Pediatrics Section on Urology reviewed psychological factors, anesthetic considerations, and technical aspects of hypospadias repair before recommending surgery be performed between 6 and 12 months, assuming the surgeon, anesthesiologist, and facility were experienced in the care of infants (American Academy of Pediatrics, 1996). Same-day surgery can be performed after 50 gestational weeks in otherwise healthy boys, leading the author to routinely recommend repair at 3 months of age or older for distal hypospadias and selected proximal cases with an apparently normal-sized phallus. Infants with proximal hypospadias and a small-appearing glans are reassessed at 3 months and then administered hormonal stimulation, as discussed later, before surgery at approximately 6 months of age.

Optimal timing for surgery in children presenting at an older age is uncertain. From 18 months to approximately 3 years of age has been described as a difficult period for hospitalization, leading to a recommendation that repair be postponed to age greater than 3 years (Manzoni et al, 2004). However, the American Academy of Pediatrics Action Committee observed that surgery from 30 to 65 months of age may increase the child's anxiety for physical injury. One study compared health-related quality of life assessment after hypospadias surgery done at less than 18 months of age versus more than 18 months of age and found no differences related to age at operation (Weber et al, 2008). **Preoperative sedatives, minimal separation from family, same-day surgery, anesthetic blocks that reduce early postoperative pain, dressings that fall off spontaneously, and urinary diversion into diapers all may reduce psychological stress from hypospadias repair.**

Preoperative Hormonal Stimulation

Androgenic stimulation has been advocated to increase penile size, reduce VC, and improve vascularity. Although several reports involving small numbers of patients with varied severity of hypospadias document increased penile size, glans circumference, and/or transverse length of the inner prepuce, no prospective randomized trial has determined that hormonal therapy favorably impacts objective surgical outcomes. Furthermore, no available data establish mean and standard deviations for normal glans size in children of varying ages.

One reported regimen is intramuscular testosterone enanthate 2 mg/kg given 5 and 2 weeks preoperatively (Gearhart and Jeffs, 1987; Luo et al, 2003). A comparison between a mixture of testosterone propionate and enanthate providing a dose of 2 mg/kg/wk administered twice daily topically or intramuscularly weekly found no differences in response regarding penile length or diameter. Elevated serum levels greater than 10 ng/mL only were noted after topical therapy, possibly from excessive application (Chalapathi et al, 2003).

Reported mean increases in penile length range from approximately 0.5 to nearly 3 cm, with partial to complete loss of these gains by 3 to 12 months after stimulation (Gearhart and Jeffs, 1987; Davits et al, 1993; Chalapathi et al, 2003). Side effects include pubic hair growth and aggressive behavior; accelerated linear height and bone age have not been documented (Gearhart and Jeffs, 1987; Davits et al, 1993; Chalapathi et al, 2003), but few patients have had bone age assessed after stimulation.

The author prefers two to three intramuscular injections of testosterone enanthate 2 mg/kg over a 6- to 12-week period. Hormonal stimulation has been used in less than 1% of distal repairs versus 25% of proximal to perineal cases and is recommended when the glans appears small, recognizing there are no published criteria to define normal or adequate glans diameter (Snodgrass and Yucel, 2007).

GENERAL ASPECTS OF SURGICAL REPAIR

Suture Materials

No randomized controlled trials (RCTs) compare suture materials while controlling other factors that may

Table 130–1.
Sutures and Needles for Hypospadias Repair

SUTURE SIZE AND MATERIAL	NEEDLE
7-0 polyglactin	TG 140-8
6-0 polyglactin	S 29
4-0, 5-0 polyglactin	RB
6-0 polypropylene	BV 1
6-0, 7-0 polydioxanone	BV 1
4-0, 5-0 polydioxanone	RB

influence outcomes, including severity of hypospadias, type of repair, and suturing technique. Recommendations therefore reflect the surgeon's preference. Available needles for various sutures may also influence choice and outcomes but are rarely reported in hypospadias literature. Sutures and needles preferred by the author are listed in Table 130–1.

Perioperative Antibiotics

No RCTs have been performed to determine if hypospadias surgical outcomes are influenced by preoperative intravenous antibiotics. One RCT comprising 101 patients compared intraoperative intravenous cefonicid plus postoperative oral cephalexin to intravenous cefonicid alone. There were no differences in the two groups regarding surgical complications, but both asymptomatic bacilluria (21% vs. 51%, $P < .05$) and febrile urinary tract infection (6% vs. 23%, $P < .05$) were more common without postoperative antibiotics (Meir and Livne, 2004). Postoperative antibiotics are commonly used during urinary diversion; the author prefers trimethoprim/sulfamethoxazole.

Postoperative Urinary Diversion

One RCT randomized 64 toilet-trained boys (median age 6 years, range 2 to 17) undergoing tubularized incised plate (TIP) repair by a single surgeon to postoperative bladder catheterization or not, decided at the conclusion of the procedure. There were no differences in urethroplasty complications; however, dysuria (14% vs. 45%, $P < .01$), urinary retention (0% vs. 24%, $P < .05$), and urinary extravasation (0% vs. 17%, $P < .05$) occurred significantly more often in the unstented group (El-Sherbiny, 2003).

A prospective observational study by the same surgeon involved 32 consecutive non–toilet-trained boys (mean age 18 ± 6 months) undergoing TIP repair with no urinary diversion. Urinary extravasation developed in one patient the second postoperative day resulting in catheter placement. There were no urethroplasty complications with mean follow-up of 9 months (Almodhen et al, 2008).

Another prospective study compared 36 patients undergoing Mathieu repair with catheter ($n = 17$, mean age 4.1 years) versus without diversion ($n = 19$, mean age 4.6 years) and no difference was reported in urethroplasty complications at 6 months or longer follow-up (McCormack et al, 1993).

The author prefers urinary diversion to avoid the occasional need for early postoperative catheterization due to retention or extravasation. However, should the catheter inadvertently be dislodged prematurely it is not replaced unless urinary retention or extravasation occurs. A 6-Fr bladder stent is used for all repairs in prepubertal boys regardless of age, or a 12- to 14-Fr catheter is used in patients after puberty.

Dressings

Two RCTs, one having 100 patients operated on by one surgeon (Van Savage et al, 2000) and the other comprising 120 patients and four surgeons (McLorie et al, 2001), were done to evaluate the role of postoperative bandages. In the first study patients had an adhesive film versus no dressing, whereas the second compared postoperative topical antibiotic ointment alone to an adhesive film or compressive wrap followed by topical antibiotic ointment applied after dressing removal. In both, 2% of patients were excluded from randomization owing to bleeding at the conclusion of the procedure resulting in a bandage. Parents in both studies were instructed to remove the bandage by postoperative day 2 (Van Savage et al, 2000) or when it appeared loose (McLorie et al, 2001). Neither study reported the appearance of the penis on catheter removal (e.g., extent of edema or hematoma formation). **Urethroplasty outcomes were not impacted by dressings versus no dressings.** Both studies noted greater numbers of telephone calls from parents of boys with bandages, although one did not state if these calls specifically related to the dressing.

Both these studies concluded that bandages are not needed after hypospadias repair, and when they are used they increase parental anxiety. However, in both, parental concern also might relate to instructions to remove the dressings. McLorie and colleagues (2005) specifically noted that half the parents did not remove the bandage as instructed and that 38% of boys with adhesive films and 82% with compressive wraps experienced pain with dressing removal.

The lack of benefit to compressive wrap dressings and the greater likelihood of discomfort for the child with their removal argues against their use. Otherwise, in both studies a major argument against dressings is the bother for parents in removing them. Because adhesive films nearly always fall off spontaneously, surgeons who prefer bandages might consider their use—combined with assurances that the parents need not be concerned with dressings.

HISTORIC BACKGROUND

Although it is commonly written that more than 200 repairs have been described, hypospadias urethroplasty can be summarized into three basic categories: tubularization of the urethral plate, supplementation or substitution of the urethral plate with skin flaps, or urethral plate substitution with grafts (Fig. 130–3). Of these, today the most common primary surgery is urethral plate tubularization. This is also the most recently introduced concept, given that the urethral plate—tissues extending distally from the hypospadias meatus that normally form the urethra—was only recognized as a distinct structure in the late 1980s.

Hypospadias surgery that began in the early 1800s originally focused on repair for proximal defects. VC often found in these cases was ascribed to fibrous bands, and by the 1940s the belief that these fibrous tissues represented dysplastic corpus spongiosum extending fanlike from the meatus became firmly entrenched. This "chordee tissue," now recognized as the urethral plate, was resected for straightening. Consequently, substitution urethroplasty was necessary, most often accomplished using preputial flaps. Variations of these flaps account for most of the different repairs described.

Modern hypospadias surgery dates to 1980. Duckett (1980) mobilized inner preputial flaps on a vascular pedicle away from dorsal shaft skin, providing greater flexibility to transpose them ventrally. The following year he described the meatoplasty and glanuloplasty (MAGPI) technique for glanular defects (Duckett,

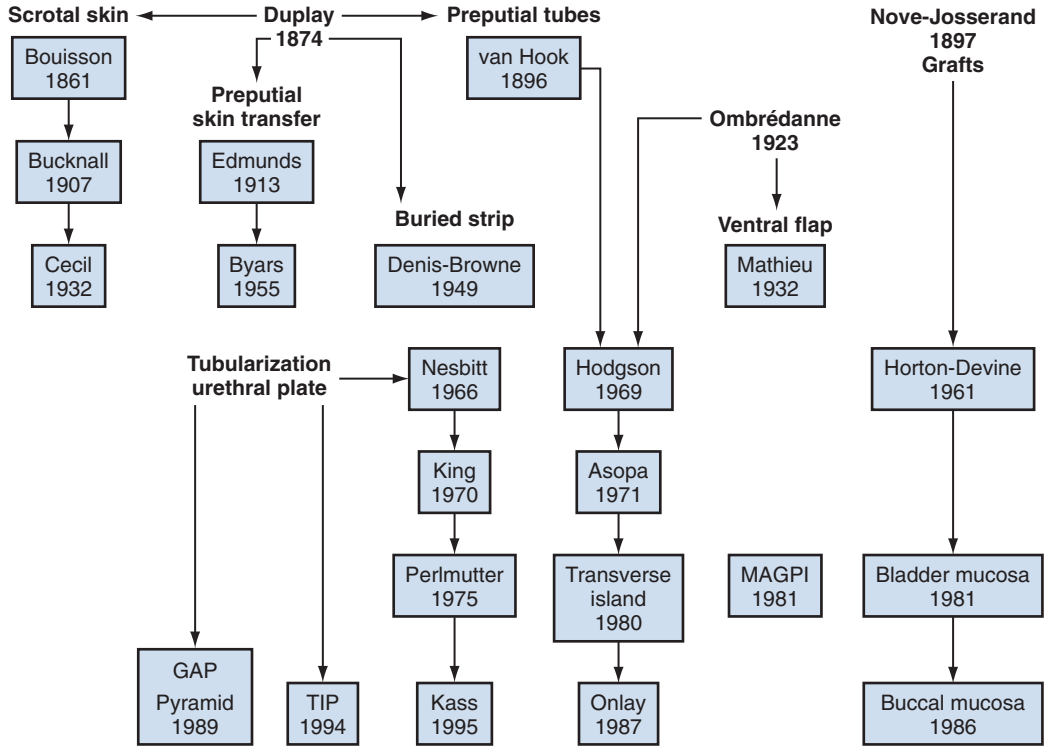


Figure 130–3. Genealogy of hypospadias urethroplasty. Duplay is considered the father of tubularized skin flaps, Ombredanne inspired ventral flaps, and Nove-Josserand pioneered grafts. The urethral plate was not recognized as a distinct structure until the late 1980s, and so procedures utilizing the plate are the most recently described. GAP, glans approximation procedure; MAGPI, meatoplasty and glansplasty; TIP, tubularized incised plate.

1981), opening the door for routine distal repair that today comprises most hypospadias surgery. It was also Duckett who defined the urethral plate and then modified his tubularized preputial flap ("transverse island") to the onlay version supplementing, rather than substituting, the plate after realizing routine "chordee" excision was not necessary (Baskin et al, 1994). By the end of the decade nearly all primary hypospadias could be repaired using MAGPI, onlay, or tubularized preputial flaps.

Although tubularization of the broad or deeply grooved urethral plate had been reported sporadically, in 1994 the midline incision was described to tubularize the narrow or flat plate without the need for supplemental skin flaps (Snodgrass, 1994). The TIP repair subsequently gained widespread use for its perceived simplicity and improved cosmetic outcomes versus flap repairs. Its application to proximal hypospadias followed increased realization that the urethral plate is not fibrous scar but well-vascularized tissues that potentially can be preserved for urethroplasty, even in some cases with VC.

HYPOSPADIAS SURGERY

Ventral Curvature

Etiology

The penis exhibits VC during normal development (Kaplan and Lamm, 1975), which implies that persistent bending in hypospadias reflects arrested development. Consequently, ventral tissues—including shaft skin, dartos, corpus spongiosum, urethral plate, and overlying tunics of the corpora cavernosa—may be shortened relative to the dorsal surface. Previous concepts that dysplastic dartos and corpus spongiosum coalesce into fibrous "chordee" tissues that require resection have been disproved by histologic studies in both embryos and surgical specimens referenced earlier (Baskin et al, 1998; Snodgrass et al, 2000).

Extent of Curvature

Prevalence and severity of VC after release of shaft skin varies by extent of hypospadias. From the author's experience since 2000, VC occurred in 50 (11%) of 440 primary distal cases undergoing artificial erection (Snodgrass et al, 2010), 12 of 40 (30%) midshaft repairs (Snodgrass and Yucel, 2007), and 57 of 70 (81%) proximal repairs (Snodgrass and Prieto, 2009). VC in all patients with distal and midshaft repairs was less than 30 degrees.

VC in consecutive proximal shaft to perineal hypospadias was less than 30 degrees in 22 patients (31%) and more than 30 degrees in 35 patients (50%). Half of these patients with proximal hypospadias either had no VC after the penis was degloved or had minor bending readily correctable with a single dorsal plication.

It is also important to consider what extent of VC impairs sexual activity. Reports concerning adult men seeking medical attention suggest bending 30 degrees or more is present before sexual dysfunction occurs (Bracka, 1989; Thiounn et al, 1998; Van Der Horst et al, 2004; Greenfield et al, 2006).

Preoperative and Intraoperative Assessment

Preoperative assessment cannot accurately predict either the extent of curvature or the means required for straightening. Apparent bending may improve or resolve as the skin is degloved, so the common maneuver of compressing penopubic and penoscrotal tissues at the base of the penis to better visualize the penile shaft may falsely suggest or exaggerate VC by traction on deficient ventral skin. The finding that skin adjacent to the meatus may retract as far as the penoscrotal junction during

degloving provides additional proof that relatively short ventral skin contributes to curvature.

Cephalad traction on the glans stay suture causes the bent (>30 degrees) penis to pivot from side to side. Such observations formed the basis for determining VC and its correction until saline corporeal injection was described by Gittes and McLaughlin in 1974. Artificial erection induced by saline injection remains the most commonly used means to assess presence and severity of VC, as well as to document successful correction. Criticisms of the technique include the potential for supraphysiologic or subphysiologic intracorporeal pressure during injection to distort findings. After ventral dissection of tissues from the tunica albuginea and/or ventral lengthening procedures for the corpora cavernosa (see later discussion), repeat erection may be difficult, owing to corporeal leakage.

Vasoactive drugs have also been injected to induce erection during hypospadias repair (Perovic et al, 1997; Kogan, 2000), with the proposed advantage being more physiologic assessment in contrast to saline injection. However, dose regimens are empirical in children, erection lasts longer than with saline irrigation unless a reversal agent is injected, and there may be increased bleeding from the prolonged erection.

It should also be noted that reported degrees of curvature, including those by this author, most likely were subjectively determined by visual estimate without direct measurement with a protractor.

Straightening Maneuvers

Curvature up to 30 degrees can be corrected by midline dorsal plication into the tunica albuginea of the corpora cavernosa directly opposite the area of greatest bending (Fig. 130–4). Baskin and colleagues (1998) reported lack of sensory nerves in this location, and straightening without corporotomy can be achieved.

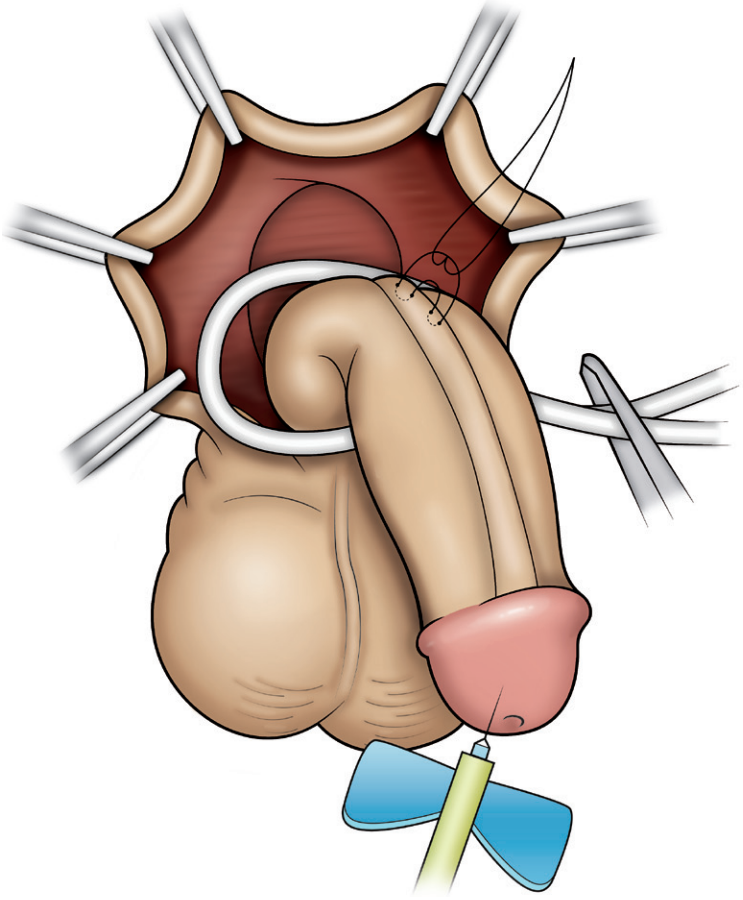


Figure 130–4. Midline dorsal plication. The surface of the corpora cavernosa is exposed in the midline opposite the region of curvature, avoiding the dorsal veins; and then polypropylene suture is placed, burying the knot.

There are few reports concerning sutures used, efficacy, or durability of plication, and assessment is complicated by lack of objective determination of intraoperative and postoperative extent of curvature. The only outcomes data for midline plication to date are found in a retrospective review of 43 prepubertal boys, 53% with VC greater than 30 degrees, whose curvature was straightened using one or two polypropylene 4-0 or 5-0 sutures. At median 16 months' follow-up, 93% of patients were thought to maintain a straight penis (Bar Yosef et al, 2004). In contrast, the author uses only a single 6-0 polypropylene suture for midline plication of bending less than 30 degrees, preferring alternative methods to multiple plications when curvature is greater.

Similarly, optimal management of VC greater than 30 degrees remains uncertain. Multiple plications using 5-0 to 4-0 polypropylene are described, although concerns for both recurrent curvature and loss of penile length increase when more than one plication is performed (Braga et al, 2008). This extent of bending after skin degloving and ventral dartos dissection is considered disproportion between the ventral and dorsal aspects of the corpora cavernosa (Baskin et al, 1994). Ventral lengthening traditionally involves transection of the urethral plate followed by transverse incision from the 3- to 9-o'clock position into the tunica albuginea to expose erectile tissues of the corpora in the region of greatest curvature. The resultant defect has been closed using dermal grafts, small intestine submucosa, or tunica vaginalis flaps or grafts (Fig. 130–5). No evidence indicates the outcome is significantly influenced by choice of materials for corporotomy repair. Most proponents of the use of small intestine submucosa have used single-layer material; use of four-layer small intestine submucosa was reported in two small series and was associated with recurrent curvature in one (2 of 12 cases) (Soergel et al, 2003) but not in another (0 of 21 cases) (Elmore et al, 2007).

Urethral plate transection to facilitate corporeal grafting requires substitution urethroplasty using preputial flaps or grafts in either one or two stages. Alternatively, the urethral plate and adjacent corpus spongiosum can be preserved and dissected from the underlying surface of the corpora cavernosa. Elevation of the plate alone has been reported to correct curvature (Mollard and Castagnola, 1994), or it can be combined with corporotomy and grafting (Kajbafzadeh et al, 2007). Dissection under the urethral plate can also be continued proximally to near the membranous junction, elevating the normal urethra from the corpora (Fig. 130–6). This maneuver was adapted from urethral stricture repair in which mobilization of the urethra combined with its inherent elasticity allows gaps to 5 cm in adults to be bridged (Warwick et al, 1997). After dissection of the urethral plate and urethra, residual VC can be corrected by dorsal plication or ventral corporotomy (Riccabona et al, 2003; Bhat, 2007; Snodgrass and Prieto, 2009). Rather than a single corporotomy with grafting, two to three transverse incisions can be made into the tunica albuginea without exposing erectile spongy tissue or need for grafting (see Fig. 130–5) (Devine, 1983; Snodgrass and Prieto, 2009). The preserved urethral plate can then be incorporated into TIP repair or onlay urethroplasty.

VC that persists despite mobilization of the urethral plate and urethra requires urethral plate transection for

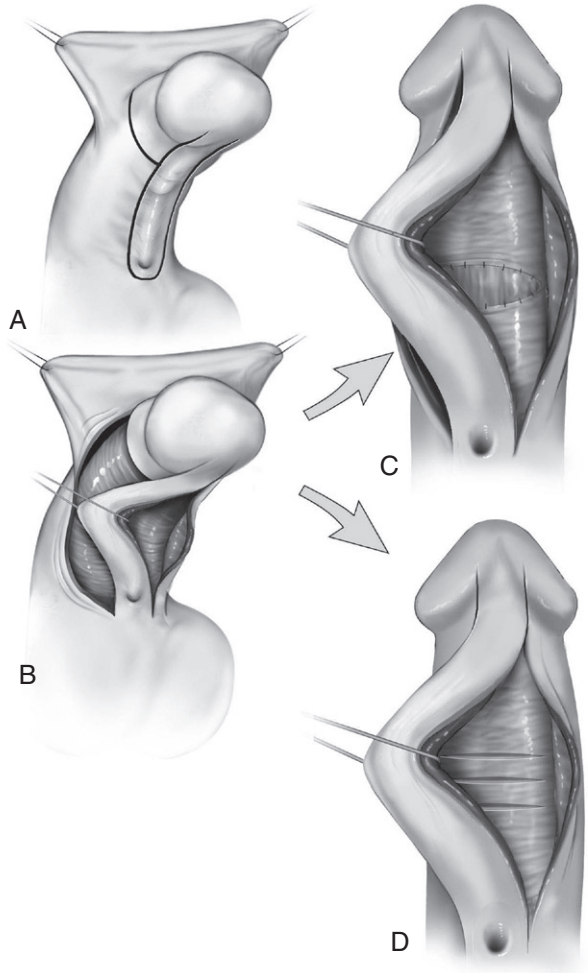


Figure 130–5. Ventral corporeal lengthening to correct ventral curvature. **A,** Ventral penile curvature showing skin incisions preserving the urethral plate. **B,** Urethral plate dissected from the corpora cavernosa. **C,** Ventral corporotomy with grafting. **D,** Multiple corporotomies without grafting.

straightening. In the author's experience 15 patients with penoscrotal to perineal hypospadias have undergone urethral plate elevation alone (3 patients) or combined with urethral mobilization (12 patients), of which 3 patients had persistent bending despite dissection to the membranous region, visibly due to tethering by a short urethral plate (Snodgrass and Prieto, 2009).

A proposed algorithm for correcting penile curvature is outlined in Figure 130–7.

Congenital Penile Curvature

Description of patients diagnosed with "chordee without hypospadias" is complicated by varying inclusion or exclusion of patients with divergent corpus spongiosum and a hypoplastic urethra. In series excluding such cases, VC is attributed most often to deficient ventral shaft skin and dartos, followed by corpora cavernosa disproportion, with a shortened urethra the least common finding (Donnohoo et al, 1998; Tang et al, 2007).

Outcomes of Straightening after Puberty

No report describes effects of pubertal growth on straightening achieved by dorsal plication. A single series comprising 16 patients, 14 with proximal hypospadias and 2 with congenital penile

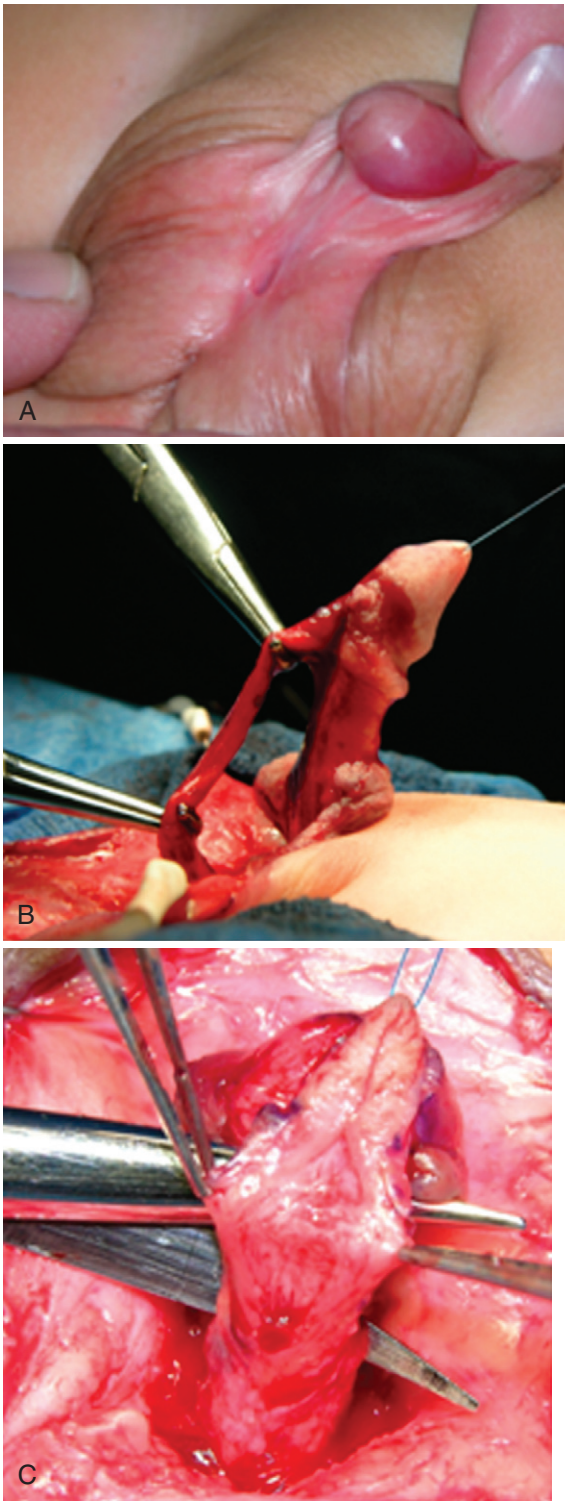


Figure 130–6. Mobilization of urethral plate and proximal urethra. **A,** Scrotal hypospadias with ventral curvature. **B,** Penis straightening included dissection of the urethral plate and proximal urethra off the corpora cavernosa. The picture shows there is no tension on the urethra after mobilization. Ventral corporeal lengthening and/or dorsal plication can also be used with this maneuver as needed to correct ventral curvature. **C,** Despite elevation of the urethral plate from the corpora, a dorsal midline incision for TIP urethroplasty can still be performed without creating separate strips. (Reprinted from Snodgrass W, Prieto J. Straightening ventral curvature while preserving the urethral plate in proximal hypospadias repair. J Urol 2009;182[Suppl. 4]:1720–5.)

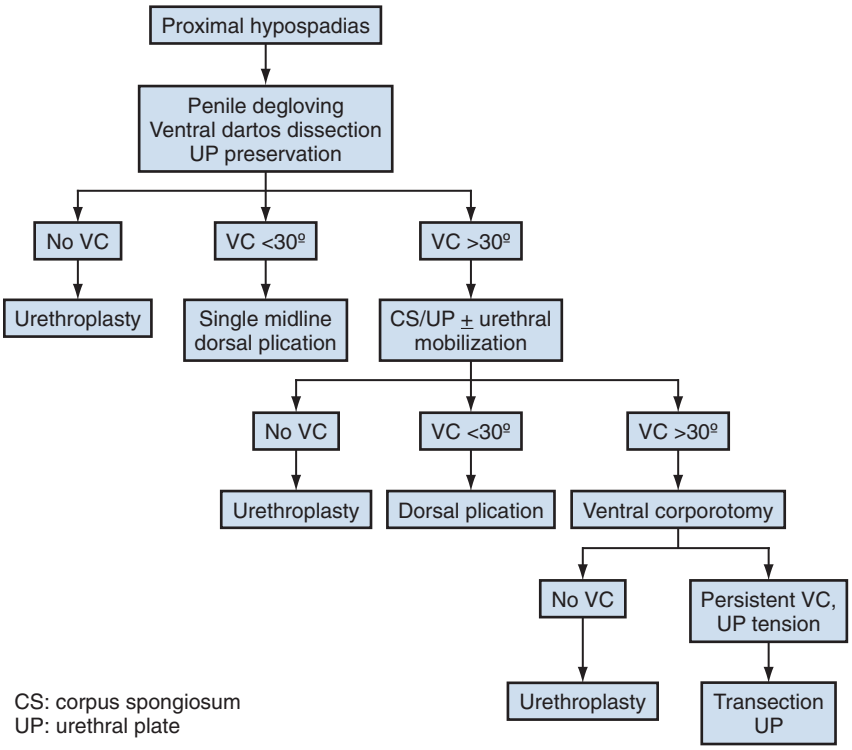


Figure 130–7. Algorithm for straightening ventral curvature (VC) with hypospadias.

curvature without hypospadias, provides information after corporotomy and dermal grafting (Badawy and Morsi, 2008). Although all patients were postpubertal at final review, only 3 were sexually active. Fifteen reported firm erection, but 1 patient undergoing repair after puberty subsequently noted impaired erection despite sildenafil, requiring intracorporeal injection for sufficient firmness. The authors reported weakness and bulging at the site of his graft.

Key Points: Ventral Curvature

- VC may resolve with ventral degloving and dartos dissection.
- VC less than or equal to 30 degrees remaining after ventral dissection can be corrected by midline dorsal plication.
- VC greater than or equal to 30 degrees after ventral dissection can be straightened by either single ventral corporeal incision with grafting or multiple ventral corporeal incisions without grafting. During these maneuvers the urethral plate and adjacent corpus spongiosum often can be maintained intact by elevating them from the corpora.
- Persistent VC after these maneuvers requires urethral plate transection.

Urethroplasty

The most commonly used options for primary hypospadias urethroplasty are summarized in Figure 130–8. It is traditional to describe repairs in separate categories for distal, midshaft, and proximal defects based on meatal position after skin degloving and correction of VC, although an alternative classification would be to consider primary repairs accomplished by tubularizing the urethral plate versus options when the plate is not maintained for urethroplasty (Sozubir and Snodgrass, 2003), most notably when VC greater than 30 degrees results in plate transection.

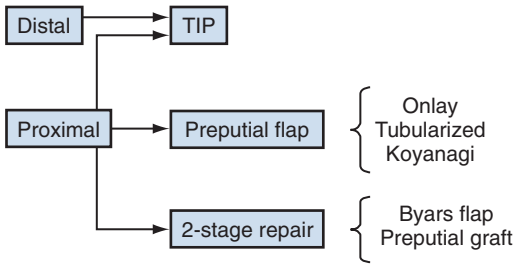


Figure 130–8. Urethroplasty options for primary hypospadias repair. TIP, tubularized incised plate.

Distal Hypospadias

The most commonly performed operation to repair distal hypospadias is the TIP repair. Although other procedures such as MAGPI, Mathieu flip-flap, and urethral advancement remain in use, a survey of current practices indicates these together account for less than 10% of distal procedures (Cook et al, 2005). Technical aspects of these operations are little changed from prior descriptions in this textbook, with the exception of V incision into the ventral lip of flip-flaps, which attempts to create a vertical meatus (Boddy and Samuel, 2000). However, a study correlating preoperative configuration of the urethral plate (deep vs. moderate or shallow groove) to cosmetic results after V incision into onlay preputial flaps questions the reliability of this maneuver to achieve a vertical neomeatus unless the plate already is deeply grooved (Hayashi et al, 2007).

Figure 130–9 depicts TIP repair. The key step is midline incision of the urethral plate, which widens a narrow plate and

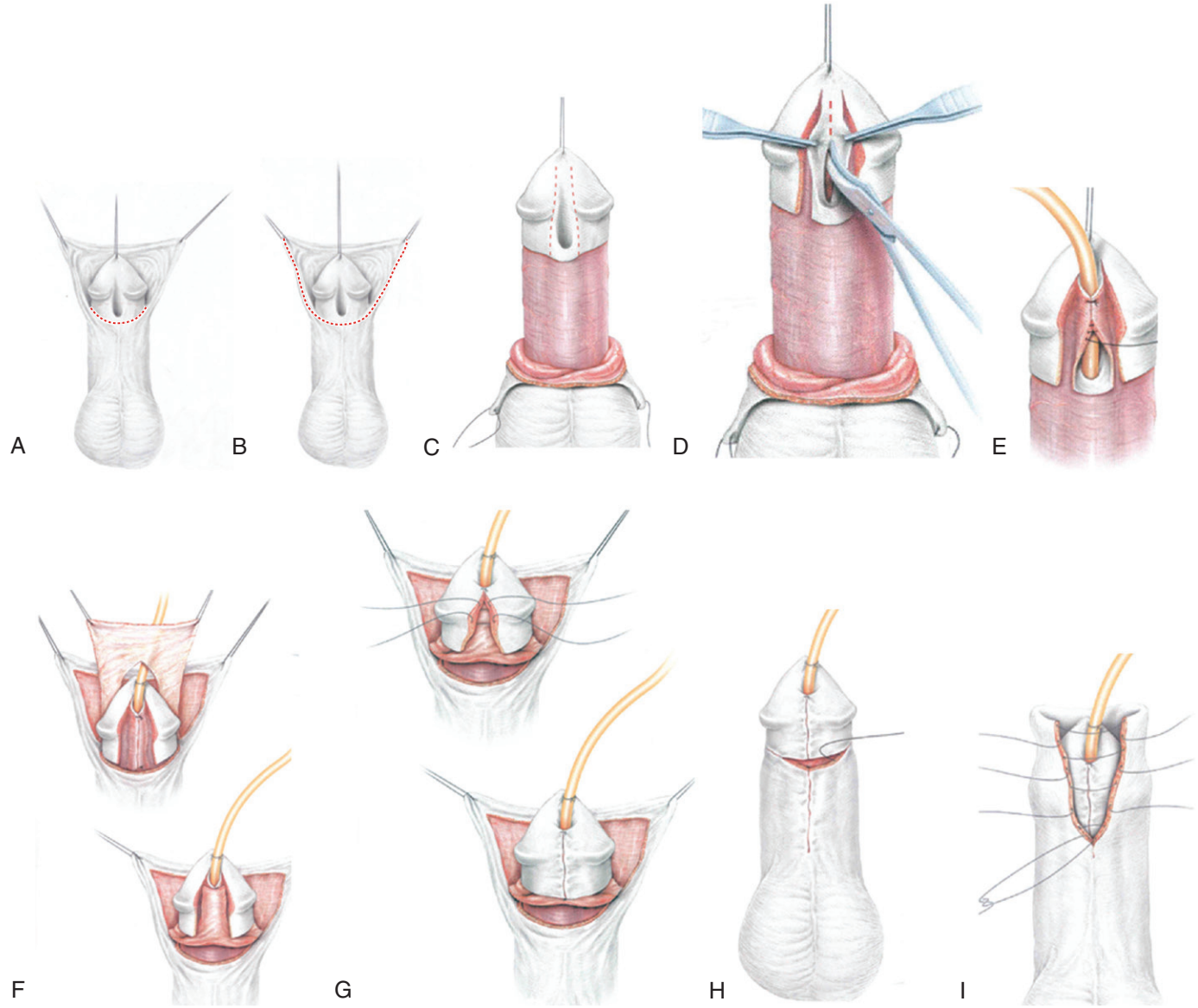


Figure 130–9. Distal tubularized incised plate repair. **A,** Circumscribing incision is made approximately 2 mm below meatus when circumcision is desired. **B,** Ventral V incision when foreskin reconstruction is planned. **C,** Penis degloved (or only ventral surface exposed during foreskin preservation). Visible junction of glans wings to urethral plate is marked and then infiltrated with 1:100,000 epinephrine. **D,** Midline incision of the urethral plate extends from within the meatus to the end of the plate, without entering the distal glans. Incision continues to near the corpora cavernosa. **E,** Urethral plate tubularization begins distally approximately 3 mm from the end of the plate, ensuring an oval, not rounded, meatus. Subepithelial running 7-0 polyglactin sutures proceed proximally. A knot is tied, and then suturing returns distally to complete a two-layer closure. **F,** Dartos flap is dissected from the dorsal prepuce and shaft skin, buttonholed, and transposed ventrally to cover the neourethra. A flap can usually be developed from the ventrolateral dartos in patients undergoing foreskin reconstruction **G,** Glansplasty begins distally, and a 7-0 polyglactin suture is used to create the meatus at the desired location, independent of the underlying urethral plate tubularization. A second 7-0 polyglactin suture under the first reinforces this distal approximation. Then a single layer of 6-0 polyglactin interrupted subepithelial sutures completes the glans wings closure to the corona. **H,** Shaft skin closure for circumcision after excising excess prepuce and approximating the inner preputial collar ventrally. Interrupted subepithelial 7-0 polyglactin is used. **I,** Foreskin reconstruction performed in three layers using 7-0 polyglactin sutures: inner prepuce, dartos, and outer shaft skin are separately approximated using subepithelial 7-0 polyglactin. (Reprinted from Snodgrass WT. Snodgrass technique for hypospadias repair. BJU Int 2005;95[4]:683–93.)

converts a flat into a deep plate groove (Fig. 130–10), ensuring a vertical, slit neomeatus and a normal-caliber neourethra. Tubularization should not continue beyond approximately the midpoint of the dissected glans wings, corresponding to a point some 3 mm proximal to the distal extent of the plate, to avoid iatrogenic meatal stenosis. Glansplasty approximates the glans halves distally to create a normal-appearing meatus independent of plate tubularization (Fig. 130–11), because the opening of the urethral plate is not sutured to the glans as is commonly done with flaps.

Contraindications. Whether urethral plate characteristics (flat vs. deeply grooved, narrow vs. wide) determine the appropriate use of TIP repair has been debated. Some consider a flat and/or narrow urethral plate a contraindication to TIP repair (Holland and Smith,

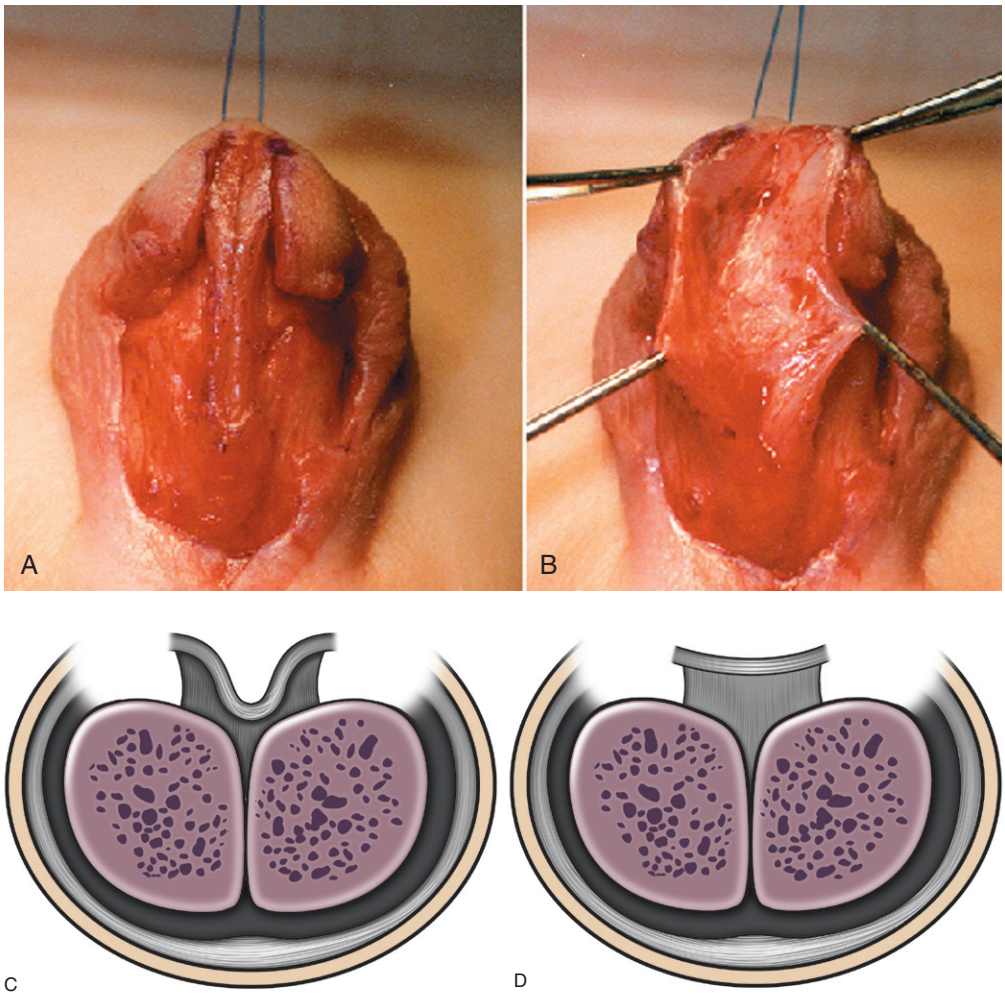


Figure 130–10. Urethral plate incision. **A,** Urethral plate before dorsal incision. **B,** Dorsal incision widens and deepens the plate. Incision depth varies according to urethral plate configuration. A deep plate (**C**) that already extends near the corpora may not need incision, whereas the flat plate (**D**) requires deep incision. (**A** and **B,** Reprinted from Snodgrass W, Koyle M, Manzoni G, et al. Tubularized incised plate hypospadias repair: results of a multicenter experience. J Urol 1996;156[2 Pt. 2]:839–41; **C** and **D** reprinted from Snodgrass WT. Tubularized incised plate hypospadias repair: indications, technique, and complications. Urology 1999;54[1]:6–11.)

2000), whereas others report TIP repair reliably corrects distal hypospadias regardless of urethral plate configuration (Nguyen and Snodgrass, 2004). The author has not found an alternative procedure necessary for distal hypospadias repair in over 500 consecutive cases (Snodgrass et al, 2010).

Outcomes. Table 130–2 summarizes published short-term results for TIP distal urethroplasty. The longest reported mean follow-up is 2 years, and to date no series describes outcomes after puberty in patients operated on when children.

One purported advantage to the TIP repair over alternative procedures for distal hypospadias is improved appearance of the meatus, creating a vertical slit neomeatus in contrast to the sometimes rounded configuration after Mathieu or other flap repairs. In addition to meatal shape, however, normal cosmesis requires sufficient glans approximation below the meatus to the corona so that the neomeatus appears correctly positioned. Two to three sutures closing the glans wings between the meatus and corona are needed and are readily placed in the TIP repair because glans closure is independent of urethral plate tubularization. In contrast, it may be difficult to mature the neomeatus created with flaps to glans wings and maintain sufficient glans to allow these additional two to three stitches proximally to the corona.

Two studies objectively assess cosmesis. One used postoperative photographs blindly scored by a panel of medical professionals that ranked TIP repair results superior to those from Mathieu and onlay flaps (Ververidis et al, 2005). A second administered Likert scale questionnaires to parents and the operating surgeon after TIP repair or circumcision. No significant differences occurred between surgeon and parents in either group or in satisfaction after TIP repair for hypospadias versus elective circumcision in boys with a normal penis (Snodgrass et al, 2008).

Midshaft Hypospadias

In a consecutive series of boys with midshaft hypospadias none had VC greater than 30 degrees, indicating the urethral plate can be maintained for urethroplasty in most cases (Snodgrass and Yucel, 2007). Accordingly, options for repair include TIP repair or onlay preputial flap. Technical aspects of TIP repair are unchanged

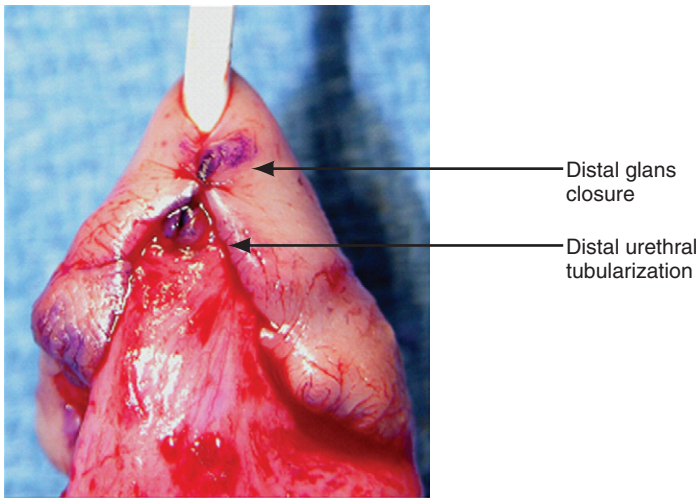


Figure 130–11. Tubularized incised plate (TIP) glansplasty. The most distal stitch approximating glans wings, creating the neomeatus, usually is beyond the most distal stitch of the tubularized urethral plate. It is not necessary to suture the glans wings to the urethral plate in TIP repair.

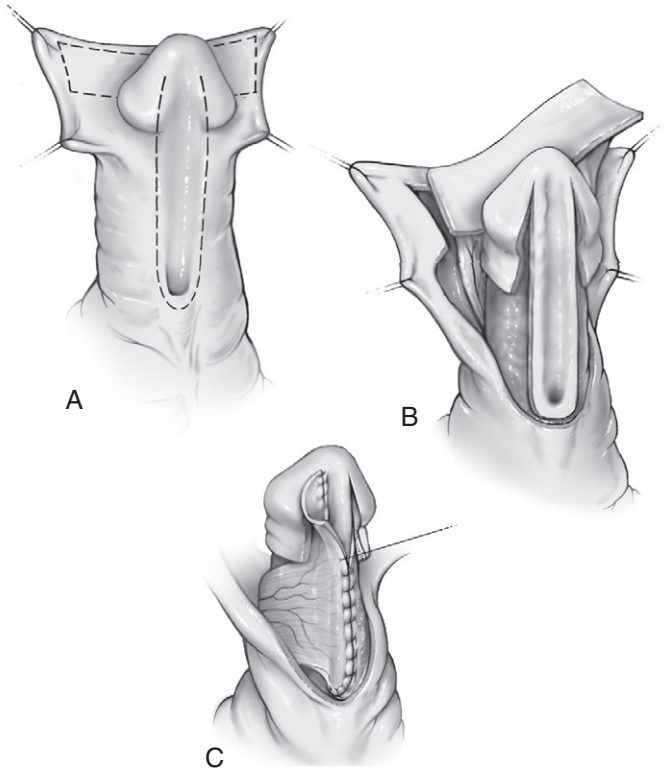


Figure 130–12. Onlay preputial flap. **A,** Lines of incision to create the preputial flap and preserve the urethral plate. **B,** Preputial flap mobilized on its vascular pedicle. **C,** Flap sewn to the urethral plate.

from distal operations described earlier, with the addition that divergent corpus spongiosum can be dissected from the underlying corpus cavernosa and released from glans wings to approximate over the shaft portion of the neourethra to near the corona (Yerkes et al, 2000).

An onlay preputial flap is depicted in Figure 130–12. Thin skin proximal to the urethral meatus is incised to the midline convergence of corpus spongiosum wings. Then inner prepuce is harvested on its vascular pedicle from either the dorsal hood or from one side of Byars flaps after the dorsal hood is incised (Sedberry-Ross et al, 2007). The flap should be gently stretched to fit the urethral plate without redundancy. Distally, flaps are secured to the glans wings to create the neomeatus. The vascular pedicle or a separate dartos flap can be used to cover the exposed suture line.

Outcomes. Reports concerning midshaft TIP repair most often combine outcomes with patients having either more distal or proximal defects. The two largest series with results specifically for midshaft hypospadias found urethroplasty complications in 13% and 16% (Snodgrass and Yucel, 2007; Al-Ghorairy et al, 2009).

Similarly, onlay preputial flap results specifically for midshaft repair are not readily obtainable. The procedure originally was described for distal to midshaft cases not amenable to MAGPI, and to enable use for distal hypospadias the meatus was incised proximally to create a defect of sufficient length to accommodate the flap. The most recent publication providing outcomes for midshaft hypospadias reported 29% urethroplasty complications in 51 patients (Sedberry-Ross et al, 2007).

Proximal Hypospadias

The greatest controversy in primary hypospadias surgery concerns decision making for proximal cases. Options depend on whether the urethral plate is available for urethroplasty after associated VC is straightened. If so, then either TIP repair or an onlay preputial flap can be used. When the urethral plate is transected a one-stage urethroplasty can be accomplished by tubularized preputial flaps or the Koyanagi flap or a two-stage repair done with Byars flaps or preputial grafts.

Tubularized Incised Plate Repair. Steps for a proximal TIP repair are illustrated in Figure 130–13. There are several important distinctions between distal and proximal TIP repairs. First, correction of VC may lead to dissection of the urethral plate, and proximal urethra, from the corpora cavernosa. Midline incision can still be performed without creating separate strips (see Fig. 130–6C). The neourethra is tubularized with interrupted subepithelial sutures reinforced by a second running layer. Divergent corpus spongiosum is next sewn over the neourethra, followed by a tunica vaginalis flap (Fig. 130–14). To reduce chances for secondary partial concealment of the penis, shaft skin at the penoscrotal junction is secured to the corpora cavernosa with subepithelial 5-0 polydioxanone to either side of the ventral midline before skin closure.

Outcomes. In a cohort of 56 boys with proximal shaft to perineal hypospadias, the author corrected 36 (64%) using the TIP procedure while the other 20 (36%) underwent staged repairs after urethral plate transection during straightening (Snodgrass and Yucel, 2007). After that report, urethral plate/proximal urethral dissection with superficial transverse corporotomies were incorporated into the algorithm for straightening, resulting in more frequent preservation of the plate. In 22 consecutive proximal shaft to perineal repairs, 19 (86%) had TIP repair versus only 3 (14%) undergoing a two-stage repair (Snodgrass and Prieto, 2009).

Urethroplasty complications occurred in 8 (53%) of the original 15 patients undergoing proximal TIP repair by the author, which were mostly fistulas in 5 (33%) despite a dartos flap over the neourethra in every case. After technical modifications described earlier (two-layer subepithelial tubularization and spongioplasty) the complication rate in the next 20 cases decreased to five complications (25%), including two (10%) fistulas. After substituting

Table 130–2.

Distal Tubularized Incised Plate (TIP) Repairs

STUDY	NO. OF PATIENTS	MEAN FOLLOW-UP (mo)	NO. OF PATIENTS WITH COMPLICATIONS	RATE	Complications					
					Fistulas	Meatal Stenosis	Stricture	Dehiscence	Diverticulum	Recurrent VC
Snodgrass, 1994	16	22	0	0%	0	0	0	0		
Snodgrass et al, 1996	148	NS	10	8%	5	3		2		
Steckler and Zaontz, 1997	31	4	0	0%	0	0				
Ross and Kay, 1997	16	NS	0	0%	0	0				
Elbakry, 1999	21	20	4	19%	4	4				
Sugarman et al, 1999	25	10	1	4%	1					
Oswald et al, 2000	30	15	1	3%				1		
Holland et al, 2000	49	27	9	18%	6	3				0
Dayanc et al, 2000	20	20	2	10%	1	1				
Borer et al, 2001	156	NS (6-38)	7	4%	6	1	0			
Smith, 2001	53	NS	0	0%	0	0		0		
Cheng et al, 2002	414	NS (4-66)	1	0%	0	1				
Alam et al, 2002	49	24	4	8%	3	1				
Jayanthi, 2003	110	9	1	1%	1	0				
Samuel and Wilcox, 2003	65	4	4	6%	3	0	0	1	0	
El-Sherbiny, 2003	64	6	9	14%	7	2				
Al-Hunayan et al, 2003	83	17	12	14%	4	7		1		
Leclair et al, 2004	162	12	13	8%	9	4				
Lorenz et al, 2004	22	NS (3-6)	1	5%	1	1				
Elicevik et al, 2004	324	NS (6-60)	64	20%	28	21	3	12		
Stehr et al, 2005	100	24	22	22%	5	17		0		
Bacalla et al, 2005	85	NS (>6)	2	2%	1	1				
Soygur et al, 2005	60	10	6	10%	5	6		0		
Djordjevic et al, 2005	51	21	0	0%	0	0	0			0
Moradi et al, 2005	15	6	3	20%	2	1		0		
Anwar-ul-haq et al, 2006	45	NS (6-12)	11	24%	3	5	2	1		
O'Conner and Kiely, 2006	33	NS	8	24%	1	7				
Aslan et al, 2007	128	23	13	10%	9	3		1		
Savanelli et al, 2007	130	24	25	19%	20	5				
Almodhen et al, 2008	26	9	1	4%	0	1				
Frimberger et al, 2008	112	NS	4	4%	3	3				
Suoub et al, 2008	74	17	7	9%	7					
Al-Ghorairy et al, 2009	170	39	21	12%	12	9	0	4	0	
Snodgrass et al, 2009	426	8	19	4%	9	1	0	9	0	0
Sharma, 2005*	13	6	1	8%	1	0				
Adayener and Akyol, 2006*	12	19	1	8%	1					
TOTALS	3338		287	9%						

*Primary TIP repair in adults.
NS, not specified; VC, ventral curvature.

tunica vaginalis rather than dartos for the barrier layer, in the most recent 22 cases there were no fistulas, the single complication (4.5%) being glans dehiscence.

Table 130–3 shows other published results for proximal TIP repair, excluding those in which proximal outcomes cannot be distinguished from more distal cases. Selection bias must be considered in these reports, because none except the study of Yucel and Snodgrass states the total number of proximal cases operated during the study period to determine the relative use of TIP repair versus other techniques.

Onlay Preputial Flap. Need for a longer flap usually requires the inner prepuce to be dissected from an intact dorsal hood and then

Table 130–3.

Proximal Tubularized Incised Plate (TIP) Outcomes

STUDY	NO. OF PATIENTS	MEAN FOLLOW-UP (mo)	NO. OF PATIENTS WITH COMPLICATIONS	RATE	Complications					
					Fistulas	Meatal Stenosis	Stricture	Dehiscence	Diverticulum	Recurrent VC
Chen et al	27	12.5	5	19%	4	3				
Borer et al, 2001	9	6-38	2	22%	2					
Cheng et al, 2002	100	4-66*	4	4%	3	1				
Samuel, Wilcox	18	4	4	22%	1			3		
Mustafa†	13	NS	4	31%	3	1				
Braga et al, 2007	35	30	21	60%	15	1	0	3		2
Yucel and Snodgrass, 2007	35	19	13	37%	7	1	0	3		3
TOTALS	237		53	22%						

*Includes follow-up for distal and proximal repairs.
†Includes one midshaft hypospadias.
NS, not specified; VC, ventral curvature.

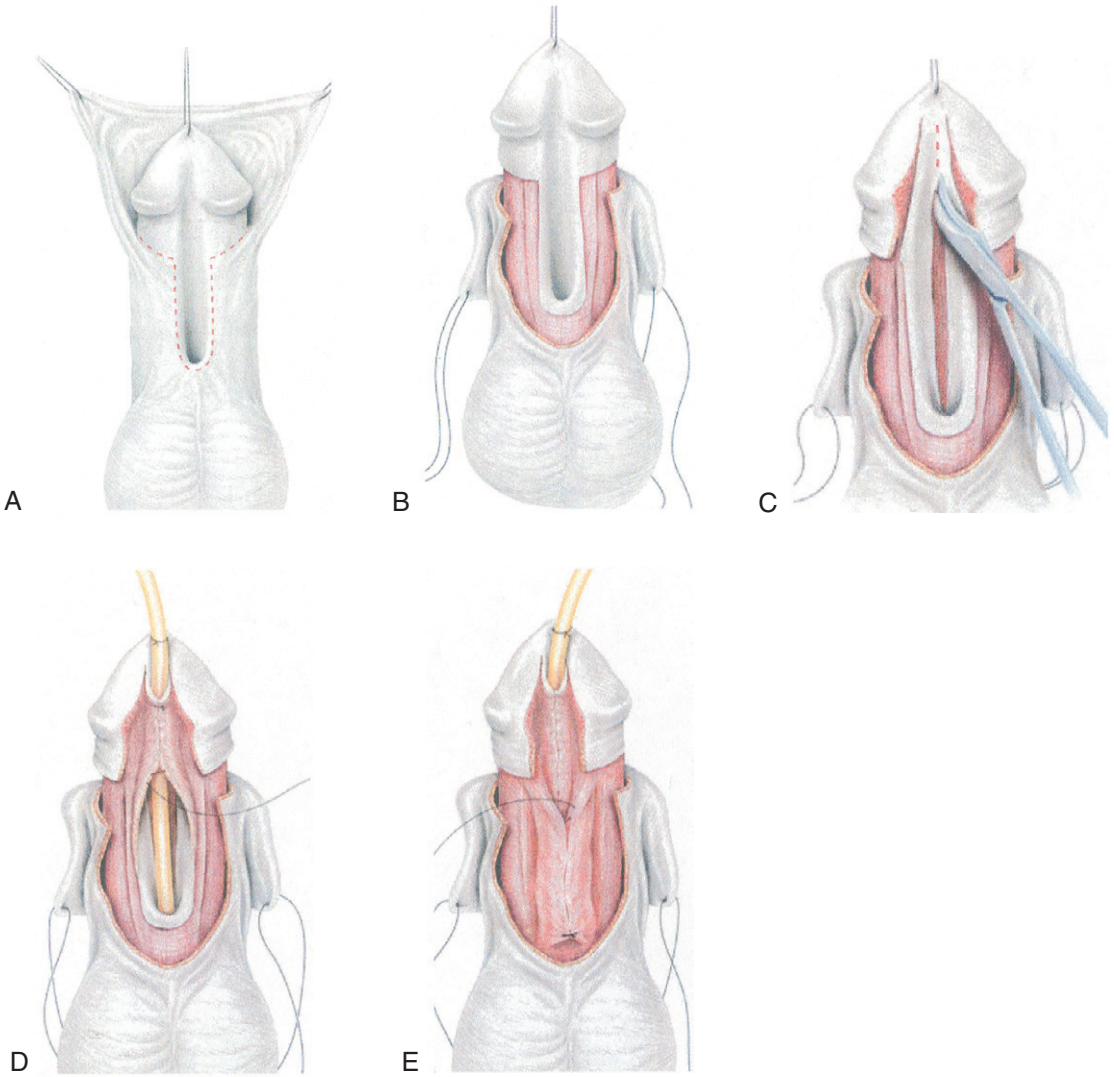


Figure 130–13. Proximal tubularized incised plate repair. **A,** Circumscribing incision preserves urethral plate in patient desiring circumcision. **B,** After degloving, glans wings are separated from the urethral plate. Corpus spongiosum is dissected from the cavernosal bodies and released distally from the glans wings for later spongioplasty. At this point artificial erection is performed and ventral curvature straightened as discussed in the text. **C,** Midline urethral plate incision. **D,** Two-layer urethral plate tubularization using interrupted subepithelial 7-0 polyglactin followed by running 7-0 polydioxanone. **E,** Spongioplasty approximates divergent corpus spongiosum over the neourethra, before a tunica vaginalis barrier flap is added. (Reprinted from Snodgrass WT. Snodgrass technique for hypospadias repair. BJU Int 2005;95[4]:683–93.)

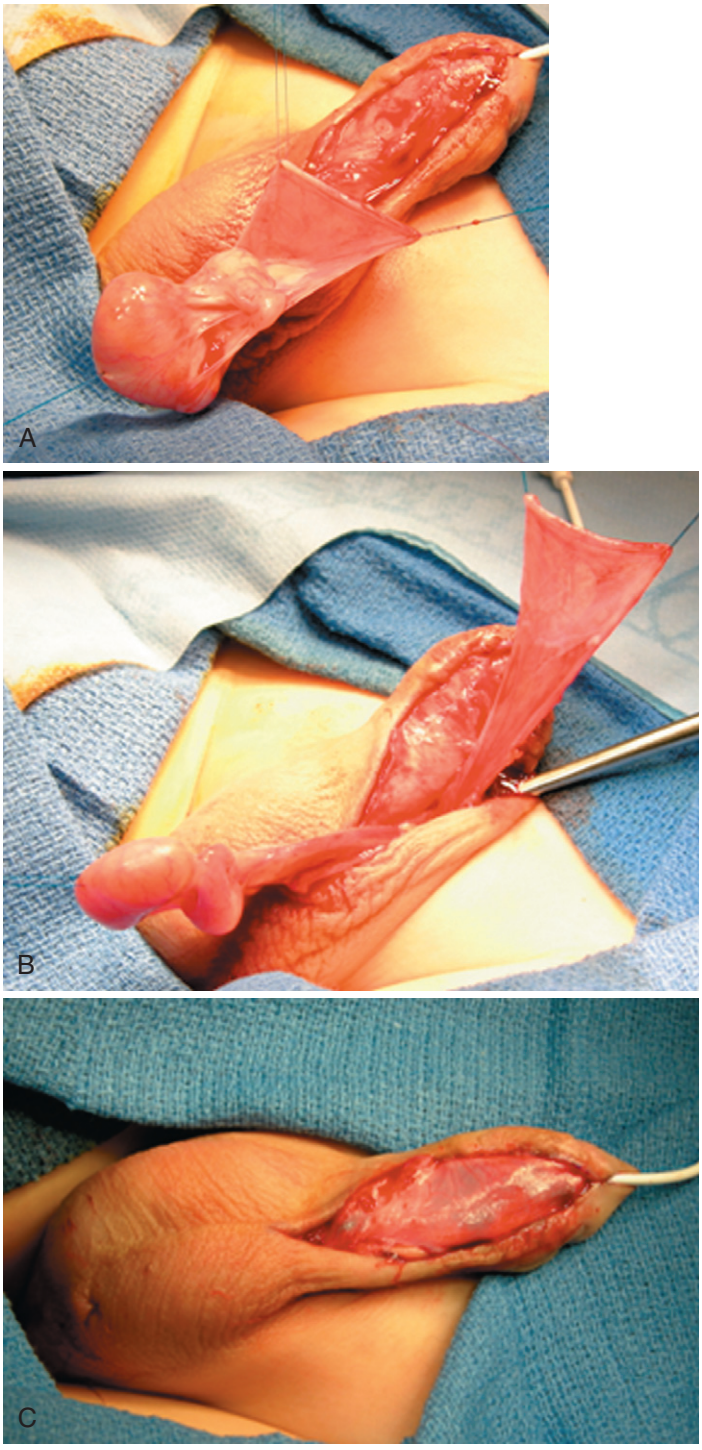


Figure 130–14. Tunica vaginalis barrier flap. **A,** The testis is delivered and the tunica vaginalis opened transversely. **B,** The tunica vaginalis flap is dissected to near the external ring to avoid tension on either the testis or the penis. **C,** Flap covers the entire neourethra. The testis is pexed into its scrotal compartment, which is then sutured closed.

rotated ventrally on its pedicle. Otherwise, steps in the procedure are as already shown in Figure 130–12.

Outcomes. Reports specifically concerning outcomes of onlay preputial flaps for proximal hypospadias are summarized in Table 130–4.

Tubularized Preputial Flap. This procedure is illustrated in Figure 130–15. After excision of the urethral plate and required straightening maneuvers, the required length of inner prepuce is harvested, tubularized, and transferred ventrally. The native urethra is secured to the corpora cavernosa and then spatulated before anastomosis to the flap to reduce incidence of stricture, and then the tube is gently stretched distally, with its suture line facing dorsally, and anchored to the corpora cavernosa with interrupted stitches. Glans wings are sewn to the flap to create the neomeatus.

Alternatively, the open flap is brought ventrally and then one side is secured to the corpora cavernosa just lateral to the midline with interrupted subepithelial sutures. The flap is gently stretched, excess tissues are excised, and then the other side is similarly anchored to the corpora to complete tubularization. This tube is tailored proximally to approximately the caliber of the native urethra before the anastomosis is made (Canning, 2007).

Outcomes. Tubularized preputial flaps (also referred to as "transverse island preputial flaps") were originally used when MAGPI was not possible before development of the onlay preputial flap. Consequently, much of the outcomes data mixes large numbers of patients with distal hypospadias without separately reporting results in proximal cases that today comprise the only use of this procedure. Table 130–4 summarizes outcomes specifically after proximal hypospadias repairs.

Koyanagi Flap. Use of the Koyanagi repair is determined from the outset of the operation based on the surgeon's impression that VC will lead to urethral plate excision, and so decision making for this procedure differs from all others described in this section.

The Koyanagi repair updates the Russell operation (Russell, 1900), primarily by maintaining blood supply to the flaps as illustrated in Figure 130–16. These flaps are brought together ventrally, sewn into a single strip, and then tubularized proximally to distally.

Outcomes. Proponents offer varied opinions for managing the dartos vascular pedicle to the lateral skin flaps. Koyanagi and colleagues (1994) split the contiguous flap into a Y at the 12-o'clock position. Others attribute complications to devascularization of the distal region and instead maintain the loop, passing the glans dorsally through a 12-o'clock buttonhole in the dartos pedicle (Hayashi et al, 2001b). Alternatively, in the largest reported series the pedicle was removed from the distal 2 cm of the flap, which was treated as a tubularized graft (Sugita et al, 2001). Results are shown in Table 130–4.

Byars Flaps. A two-stage flap repair (Fig. 130–17) divides the dorsal preputial hood, transposes the resultant flaps ventrally, and reapproximates them in the midline from the native urethral meatus to the glans tip. Glans wings should be widely separated to allow sufficient skin to be placed for later tubularization. The author previously maintained the urethral plate within the glans to combine distal TIP repair with a proximal Byars flap urethroplasty (Snodgrass et al, 1998) but discontinued that approach due to complications (see later). After a period of approximately 6 months, second-stage tubularization of the skin flaps is accomplished.

Outcomes. Table 130–5 shows outcomes data for staged skin flap repairs. The largest series did not state the number of patients with follow-up or duration of follow-up. Nearly half the patients operated on by Greenfield and coworkers (1994) had midshaft or more distal hypospadias, all of which corrected by the Belt-Fuque technique, but outcomes were included because this is a two-stage preputial flap procedure.

Cheng and colleagues (2003) transected the urethral plate proximally, preserving the distal portion, and used Byars flaps to bridge the gap to the native urethra. Diverticula formed in 2 of 14

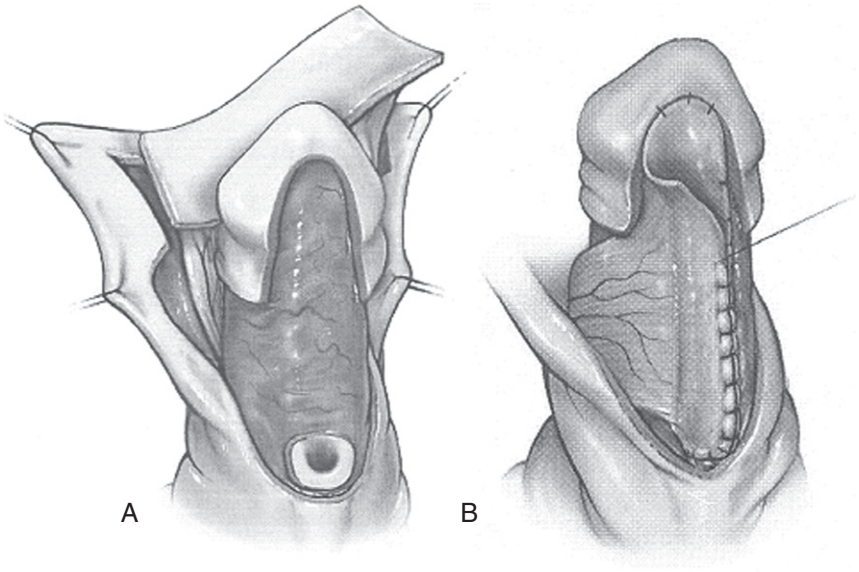


Figure 130–15. Tubularized preputial flap. **A,** After degloving and release of ventral dartos, persisting ventral curvature greater than 30 degrees led to excision of the urethral plate (see text for additional straightening maneuvers to attempt preservation of urethral plate). Inner preputial flap approximately 10 mm wide is dissected on its dartos vascular pedicle and transposed ventrally. This flap can be tubularized, with the proximal end anastomosed to the spatulated native urethra and distal end to the glans wings. **B,** Alternatively, one edge of the flap can be fixed with interrupted sutures to the corpora cavernosa from the proximal meatus distally into the glans and then the flap is trimmed and the opposite edge sutured along the first to create a tube with uniform caliber. Glansplasty and skin closure is similar to that described for onlay preputial flaps.

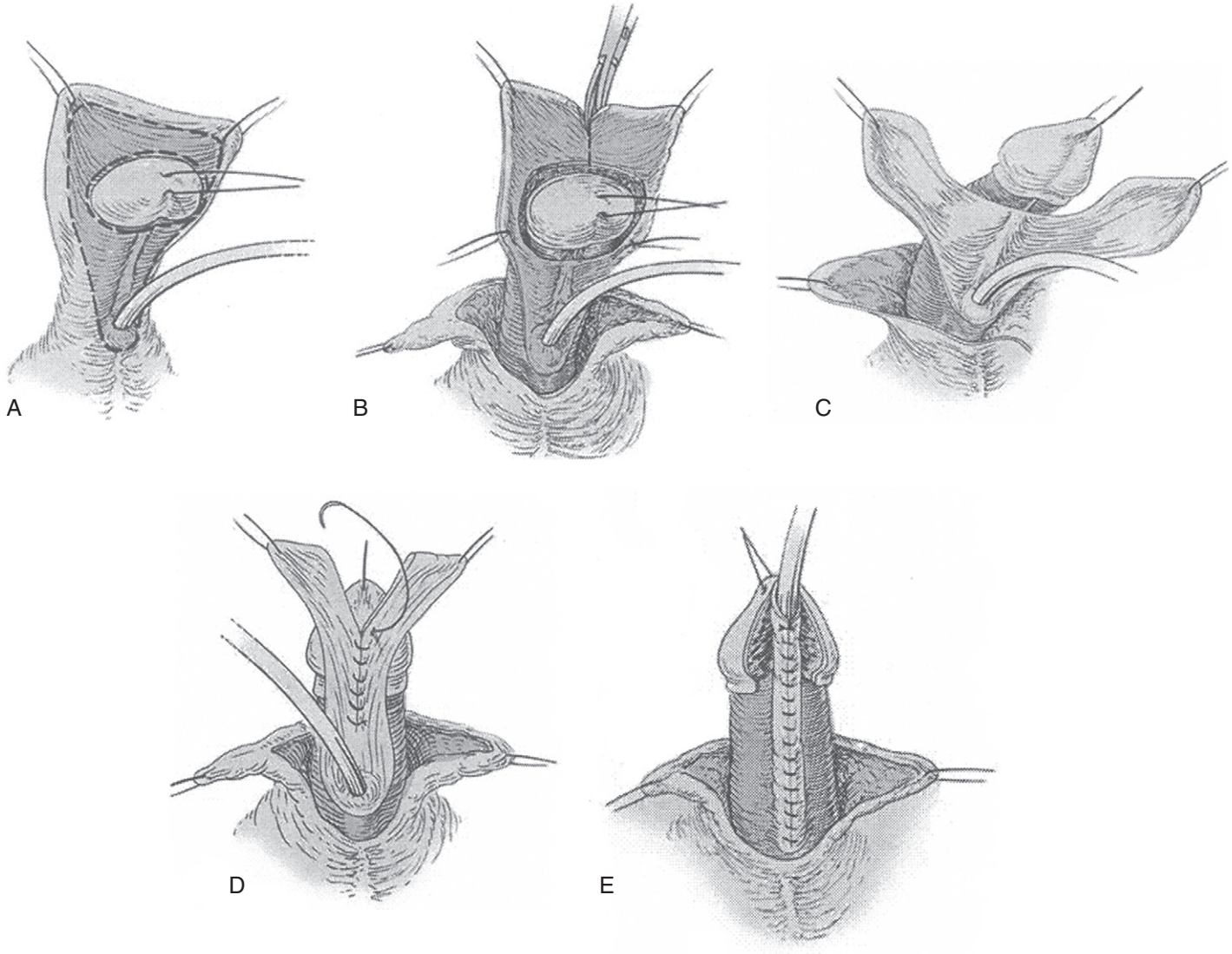


Figure 130–16. Koyanagi flap. **A,** Proposed lines of incisions to create flap. **B,** The flap can be divided into two wings as shown or maintained in one piece with a central buttonhole to transpose it ventrally. **C,** The urethral plate in the center of the flap is dissected from the corpora to near the meatus, and the glanular portion of the plate is excised as glans wings are made. **D,** Inner flap margins are reapproximated, and excess flap skin is excised. **E,** The outer margins are closed to complete tubularization using 7-0 polyglactin or polydioxanone subepithelial interrupted or running sutures. Glansplasty and skin closure are as described for other preputial flaps.

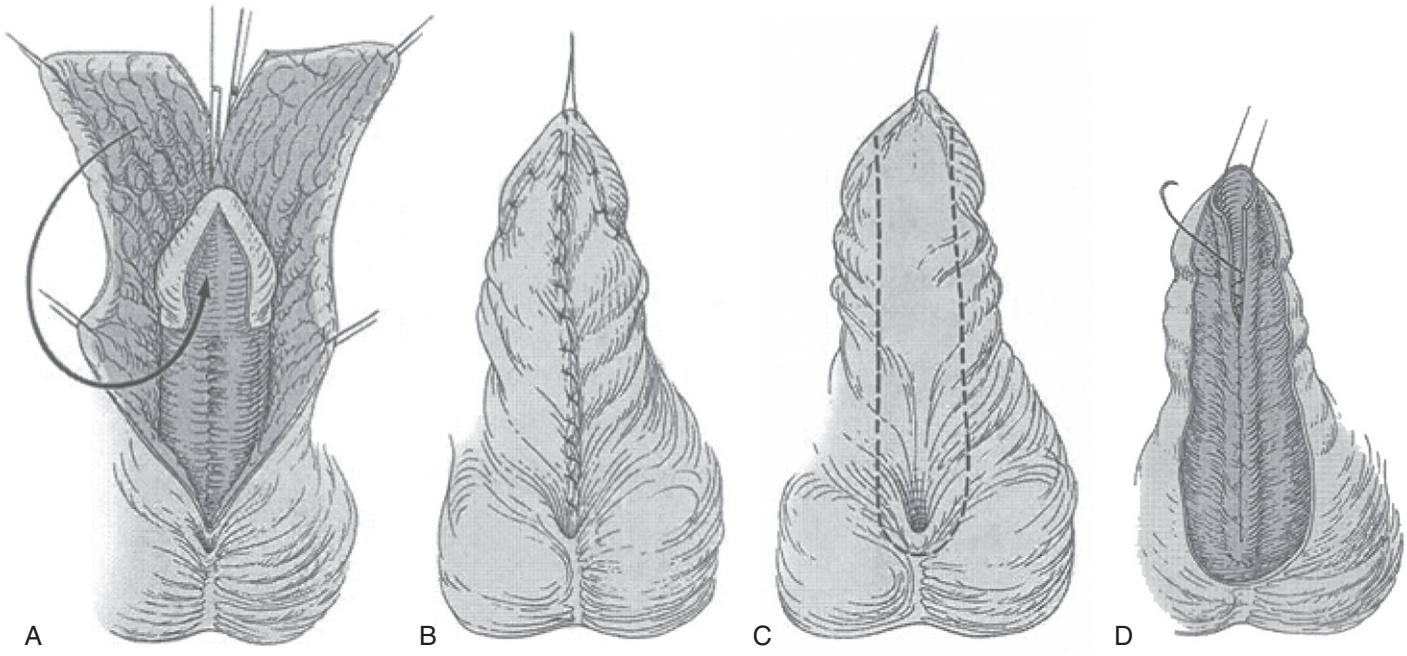


Figure 130–17. Byars flap. **A,** After degloving and release of ventral dartos, persisting ventral curvature greater than 30 degrees led to excision of the urethral plate (see text for additional straightening maneuvers to attempt preservation of urethral plate). The dorsal preputial hood is incised in the midline and the two flaps transposed ventrally on either side of the penis. The prepuce is advanced into the glans; alternatively, the urethral plate can be maintained within the glans. **B,** Flap edges are approximated in the midline. **C,** Six months later a U-shaped incision is made approximately 10 mm wide. **D,** The resultant strip is tubularized in two layers.

Table 130–4.

Outcomes for One-Stage Proximal Urethroplasty using Various Preputial Flap Techniques

STUDY	NO. OF PATIENTS	MEAN FOLLOW-UP (mo)	NO. OF PATIENTS WITH COMPLI-CATIONS	RATE	Complications					
					Fistulas	Meatal Stenosis	Stricture	Dehiscence	Diverticulum	Recurrent VC
Onlay Preputial Flap										
Mollard et al*	22	NS	0	0%						
Barroso et al†	47	15	12	26%	2	2		2	4	2
Samuel et al	17	38	10	59%	10	2				
Powell et al, 2000	20	9 (median)	6	30%	3	1	1		1	
Nuhoglu et al, 2006	20	NS	7	35%	4	0		3		
Braga et al, 2007	40	39	18	45%	8	1	2	2		5
Sedberry-Ross et al, 2007	12	7.5	7	58%	4	1	0	0	2	
TOTALS	178		60	34%						
Tubularized Preputial Flap										
Ghali, 1999*	148	23	48	32%	22	17	13	0	10	3
Powell et al, 2000	27	9 (median)	9	33%	7	1	1		0	
MacGillevray et al, 2002	24	62	10	42%	9	1	1			
Patel et al, 2004	12	>24	3	25%	1	1			1	
Shukla et al, 2004	12	24.5	2	17%	1	1			1	
Nuhoglu et al, 2006	16	NS	5	31%	4	0			1	
TOTALS	239		77	32%						
Koyanagi Flap										
Koyanagi et al, 1994	70	NS	33	47%	15		6	12		
Glassberg et al, 1998	14	NS	7	50%	7					
Emir et al, 2000	20	34	4	20%	4	0	0		0	
Sugita et al, 2001	151	72 (median)	23	15%	19	3		2		
Hayashi et al, 2001	20	NS	6	30%	3	3				
TOTALS	275		73	27%						

*Includes midshaft to proximal hypospadias.
†Includes 12 midshaft hypospadias.
NS, not specified; VC, ventral curvature.

Table 130–5.

Two-Stage Preputial Flap Outcomes

STUDY	NO. OF PATIENTS	MEAN FOLLOW-UP (mo)	NO. OF PATIENTS WITH COMPLICATIONS	RATE	Complications				
					Fistulas	Meatal Stenosis	Stricture	Dehiscence	Diverticulum
Retik et al, 1994	58	NS	3	5%	3				
Greenfield et al, 1994*/†	39	16	16	41%	1	0	7		8
Gershbaum et al, 2002‡	11	60-180	2	18%	1				1
Cheng et al, 2003§	14	6-36	2	14%	1				2
Shukla et al, 2004	10	43.5	7	70%	7	3			1
Arshad, 2005	100	NS	18	18%	18		0		
TOTALS	232		48	21%					

*Belt-Fuque two-stage repair.
†22 proximal hypospadias, remainder midshaft to distal.
‡Two-stage repair technique not specifically stated.
§Combined Byars flap with tubularized incised plate repair.
NS, not specified.

Table 130–6.

Two-Stage Grafts

STUDY	NO. OF PATIENTS	MEAN FOLLOW-UP (mo)	NO. OF PATIENTS WITH COMPLICATIONS	RATE	Complications					
					Fistulas	Meatal Stenosis	Stricture	Dehiscence	Diverticulum	Recurrent VC
Ferro et al, 2002	34	1-48	8	24%	2		1	4	1	
Obaidullah, 2005*	1206	6	71	6%	71					
Johal et al, 2006†	62	26 (median)	9	15%		3		3		3
TOTALS	1302		88	7%						
Mean of Groups				*15%*						

*99 patients had penoscrotal to perineal hypospadias.
†60% had midshaft to distal hypospadias.
VC, ventral curvature.

patients from the interposed skin flaps without distal obstruction. The authors preserved the glanular urethral plate in eight of nine Byars flap repairs. The complication rate was 100%, including five diverticula and two strictures at the flap/urethral plate junction. Of the diverticula, four had no distal obstruction except for the presumed increased resistance to flow created by the glans. Considering diverticulum formation without obstruction evidence of preputial skin distensibility, another 4 patients had buccal grafts—thought less elastic—interposed between the distally preserved urethral plate and proximal native urethra, but a diverticulum still developed in one, leading the author to abandon these techniques.

Preputial Grafts. Inner prepuce can be harvested as a graft to bridge the defect from native urethra to glans tip when the urethral plate is excised. This approach has not been commonly used in the United States because curvature leading to urethral plate transection most often has been corrected by corporeal incision and grafting, meaning subsequent addition of a urethral graft would place one graft onto another. Preputial grafts are an option when remaining VC after urethral plate excision is less than 30 degrees or if multiple superficial transverse corporotomies are used for correcting VC without corporeal grafting.

The procedure is shown in Figure 130–18. After excision of the plate the ventral native urethra is sewn to surrounding skin edges to establish a proximal meatus, and the glans wings are widely opened. Inner prepuce is harvested, and the dartos is excised from its undersurface. Then it is secured to the dorsal lip of the native urethra and gently stretched distally. Sutures anchor it to adjacent shaft skin and glans wings, with subepithelial stitches used along the glans tip to avoid tracks at the neomeatus during the second stage. Additional rows of stitches "quilt" the graft to the corpora cavernosa to facilitate neovascularization by limiting fluid collection under the graft. A tie-over dressing further immobilizes the graft during the first week of healing. Six months later this neourethral plate is tubularized and covered with tunica vaginalis.

Outcomes. Cloutier described two-stage grafting in 1962, but Bracka is credited with stimulating modern interest in this approach. His report (Bracka, 1995) mixes primary cases of all extents with reoperations, and so data specifically for primary proximal hypospadias are not available. Of the three publications summarized in Table 130–6, two similarly combine data mostly from midshaft to distal repair with results from a smaller number of proximal hypospadias. Only the report by Ferro and colleagues (2002) focused on proximal repairs using Bracka's technique. In all these, complications from grafting occurred in less than 5%, consisting of partial graft loss that did not require an additional procedure for correction before second-stage tubularization.

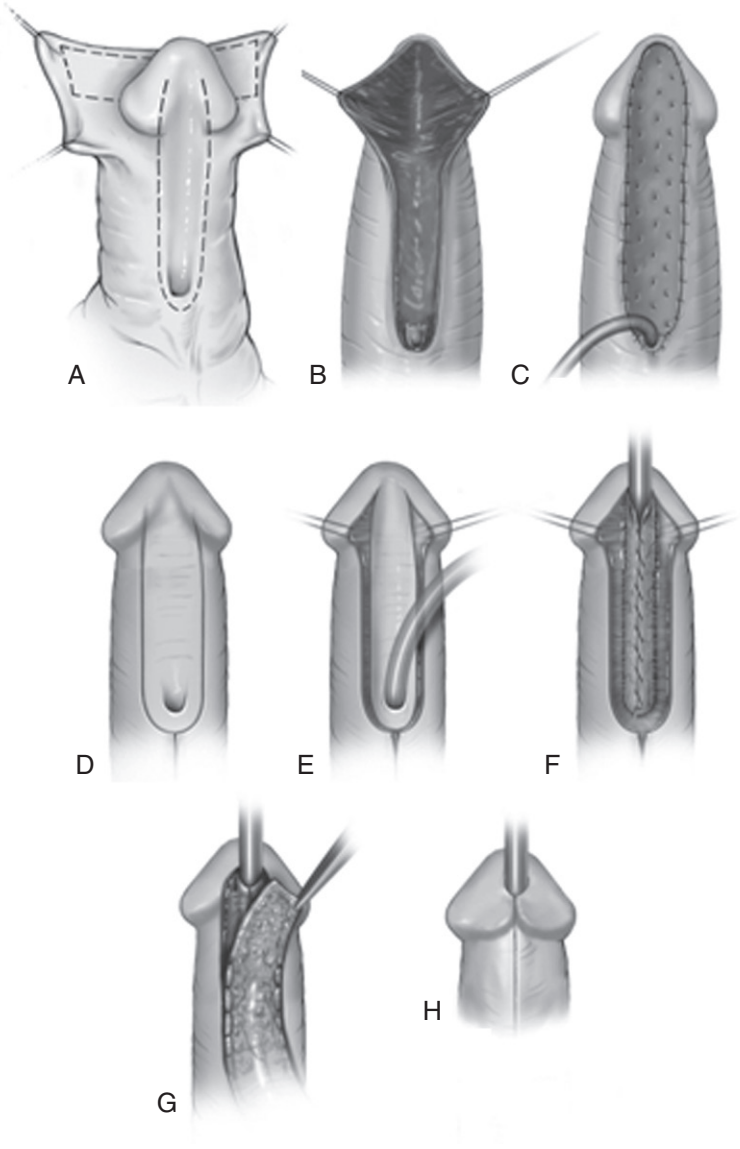


Figure 130–18. Two-stage preputial graft. **A,** Ventral curvature leads to urethral plate excision. **B,** Wide dissection of glans wings. Graft is outlined on inner prepuce. **C,** Graft is harvested from the inner prepuce and secured to the meatus proximally, along shaft skin, and into the glans using interrupted 7-0 polyglactin. Subepithelial glans sutures minimize suture marks. Additional 6-0 polyglactin quilting stitches are placed down the midline and to either side at 0.5-cm intervals to minimize space where a seroma or hematoma could collect under the graft. An RB needle facilitates anchoring the graft to the underlying corporeal surface. **D,** U-shaped incision at least 6 months after first-stage surgery. **E,** Glans wings developed. **F,** Tubularization of the neourethral plate. **G,** Tunica vaginalis flap covers the neourethra. **H,** Skin closure using subepithelial sutures.

Skin Closures

Inner Preputial Collar

The ventral preputial deficiency found in most hypospadias patients includes its inner "mucosal" surface, which normally provides coverage between the corona and shaft skin. Instead, shaft skin occupies the space from the margins of the open glans wings to the urethral plate and meatus. To create the appearance of a normal circumcised penis, this shaft skin must be removed and ventral midline closure done using inner prepuce transposed from the dorsal hood. Firlit (1987) described a chevron incision dorsally to create bilateral "darts" for ventral midline approximation (Fig. 130–19).

Although it has been suggested that divergence between the darts may preclude midline approximation, necessitating rotational flaps (Redman, 2006), the author has not encountered this situation. The proximal corners of the darts are first approximated using a 7-0 polyglactin subepithelial suture, which then provides ventral traction. Midline closure proceeds distally with interrupted subepithelial stitches. The space immediately below the glans is repaired using 9-0 polyglactin stitches placed through the epithelium. The postoperative appearance with the mucosal collar is contrasted to examples in which the collar was not formed, illustrating the importance of this step for optimal cosmetic outcomes (Fig. 130–20).

Circumcision versus Foreskin Reconstruction

The abnormal prepuce can be removed for circumcision or reconstructed ventrally if a natural, nonoperated appearance is preferred. For circumcision, a circumferential skin incision is made initially, creating lateral darts to approximate the mucosal collar ventrally, as described in the preceding section. When foreskin reconstruction is desired, the initial skin incision extends in a V from the corners of the dorsal prepuce ventrally to below the meatus, without a circumferential incision.

In patients to be circumcised, after completion of urethroplasty, glansplasty, and ventral mucosal collar the dorsal prepuce is incised in the midline proximally to the level of the mucosal collar and then stitched to it with a subepithelial 7-0 polyglactin suture. Next, the ventral median raphe is approximated from proximally to near the mucosal collar using interrupted subepithelial sutures. Excess lateral skin is excised and remaining skin edges are closed with subepithelial sutures to minimize the likelihood of suture tracks (Snodgrass, 1999a).

Foreskin repair begins with subepithelial closure of the inner surface with the dorsal foreskin retracted proximally. Then the prepuce is extended distally and the dartos approximated to reinforce closure of the inner layer. Finally, the outer skin margins are sutured together with subepithelial stitches, avoiding iatrogenic distal phimosis. The family is instructed not to retract the foreskin until the surgeon determines postoperatively that edema and tissue reaction have subsided, usually after 6 weeks.

Outcomes. Preputioplasty is an option in nearly all distal hypospadias surgeries, although occasionally the prepuce is too narrow to close ventrally. Foreskin reconstruction also can be considered for midshaft to proximal repairs, unless flap urethroplasty leaves insufficient skin. Although typically done without a circumscribing incision, when VC suggests need for dorsal plication the penis can be degloved with subsequent preputioplasty (Snodgrass et al, 2006).

Klijn and coworkers (2001) reported increased urethroplasty and skin complications with foreskin reconstruction versus circumcision during distal hypospadias repair, but these may have resulted from their reliance on skin flap (Mathieu) urethroplasty and their instructions to parents to begin foreskin retraction only 2 weeks postoperatively. In a comparison of matched cohorts undergoing distal TIP repair with foreskin reconstruction versus circumcision, Suoub and associates (2008) found no differences in urethroplasty or skin complications, which is also the experience of the author (unpublished data).

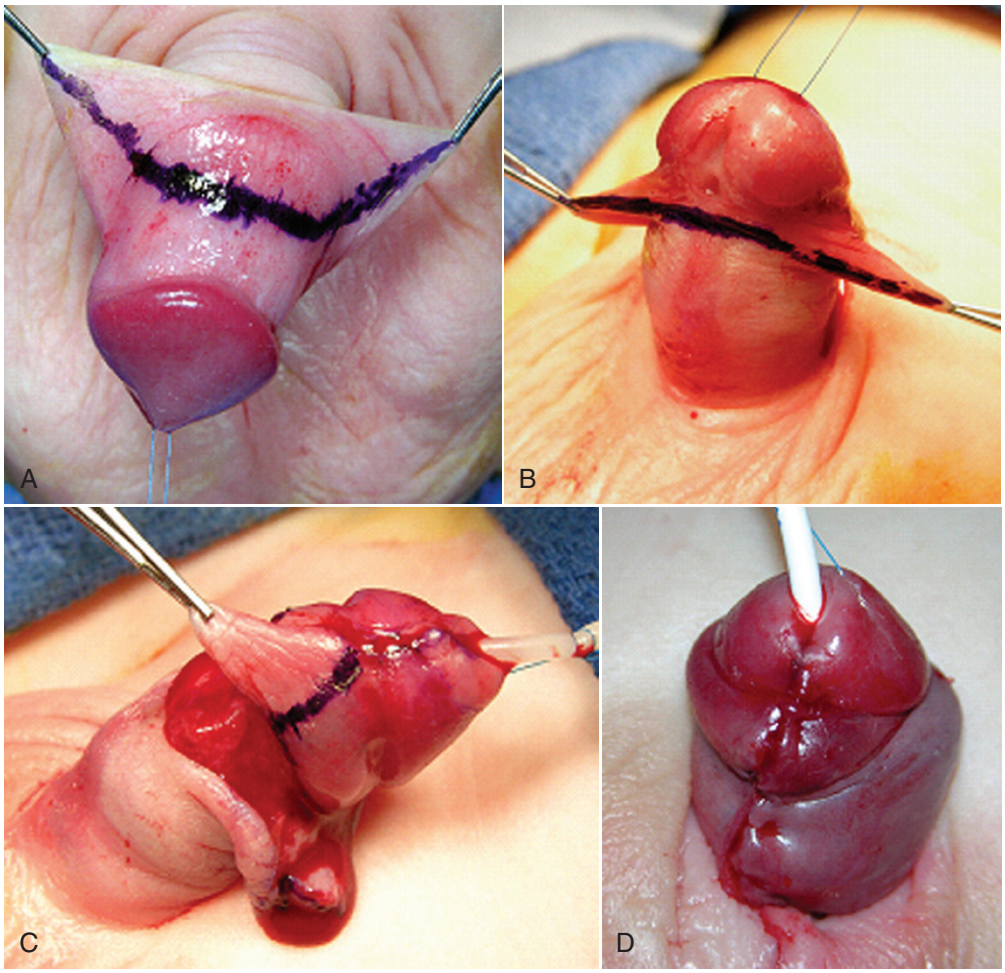


Figure 130–19. Inner preputial collar. Line for dorsal (**A**) and ventral (**B**) skin incision. **C,** Excision of perimeatal shaft skin after urethroplasty and glansplasty. **D,** Completed inner preputial collar. Interrupted subepithelial 7-0 polyglactin approximates the sides proximally, and 9-0 polyglactin is used through the epithelium at the corona, because it is unlikely to produce visible suture tracks.

Minor and Major Scrotoplasty

Scrotal encroachment onto the ventral penile shaft can occur associated with any extent of hypospadias. This sometimes creates a false impression that the meatus is penoscrotal when it is actually found located on the distal shaft after penile degloving moves the scrotum proximally. Midline scrotal cleft and varying degrees of superolateral extension of scrotum alongside the penis most often are encountered in proximal hypospadias, in some cases combined with a rugated, feminized appearance at the dorsal penopubic junction. Collectively these findings are commonly referred to as *penoscrotal transposition,* although this term also describes the rare condition in which the penis is actually located completely below the scrotum.

Encroachment onto the penile shaft is corrected by release of the scrotum as the penis is degloved, with subsequent suture fixation to the correct penoscrotal location more proximally. Scrotal clefts are excised and resultant edges sutured to create a median raphe. Minor superolateral encroachment with a rugated penopubic junction is corrected by incising the ventral junction of scrotum and penile shaft skin to approximately the 4- and 8- or 3- and 9-o'clock positions and then affixing the shaft skin to the desired penoscrotal junction (Fig. 130–21). Pronounced extensions of scrotum superolaterally to the penis are moved ventrally as rotation flaps and secured to the penoscrotal junction (Fig. 130–22).

An alternative method for correction involves completely removing shaft skin from the penis, maintaining its vascular pedicle, and then subsequently moving both above the scrotum through a "buttonhole" (Kolligian et al, 2000).

Attention to vascular pedicles allows simultaneous correction of scrotal encroachment with urethroplasty, because penile and scrotal tissues derive from distinct embryologic anlage.

Outcomes. There are few reports specifically concerning scrotoplasty outcomes. In one retrospective series, 5 of 37 patients with scrotal flap rotation developed penile tethering or secondary cryptorchidism (Pinke et al, 2001). Simultaneous Koyanagi repair with rotational scrotal flaps has been reported without apparent increased scrotoplasty or urethroplasty complications (Glassberg et al, 1998; Nonomura et al, 1988).

Key Points: TIP Repair

- Midline urethral plate incision widens and deepens the urethral plate for tubularization without skin flaps.
- Urethral plate tubularization carried too far distally can create iatrogenic meatal stenosis.
- TIP glansplasty is independent of underlying urethral plate tubularization, meaning it is not necessary to suture the glans wings to the end of the plate.



Figure 130–20. Cosmetic skin closure. Appearance with (**A**) and without (**B-D**) inner preputial collar.

ASSESSING SURGICAL OUTCOMES

The goal of hypospadias repair is to improve function and appearance as near to normal as possible. Therefore, success requires more than straightening curvature and extending the urethra to the glans. Reports from teens and adults operated on when children emphasize that cosmetic results are as important as functional outcomes (Bracka, 1989; Mureau et al, 1995; Aho et al, 2000b). Furthermore, a glanular meatus without obstruction or fistula does not ensure the patient can void with a straight and compact stream.

Initial Postoperative Follow-up

Ideal frequency and duration of follow-up after surgery are ill defined. The author prefers postoperative examinations after distal to midshaft hypospadias repair at 6 weeks and 6 months, whereas those undergoing proximal surgery are recommended to have additional annual follow-up until toilet training.

Although it is often stated that periodic assessment should continue to puberty, it is unlikely many patients operated on while infants will have adult follow-up. Accordingly, there are few data regarding outcomes in adults operated on while children. Furthermore, long-term results that are reported often concern operations no longer in common usage due to ongoing evolution in surgical techniques.

Means to assess results and detect complications beyond simple visual inspection of the penis also are not standardized. Furthermore, the time at which various complications usually appear are poorly reported, which makes minimum duration of follow-up to detect the majority of problems unclear.

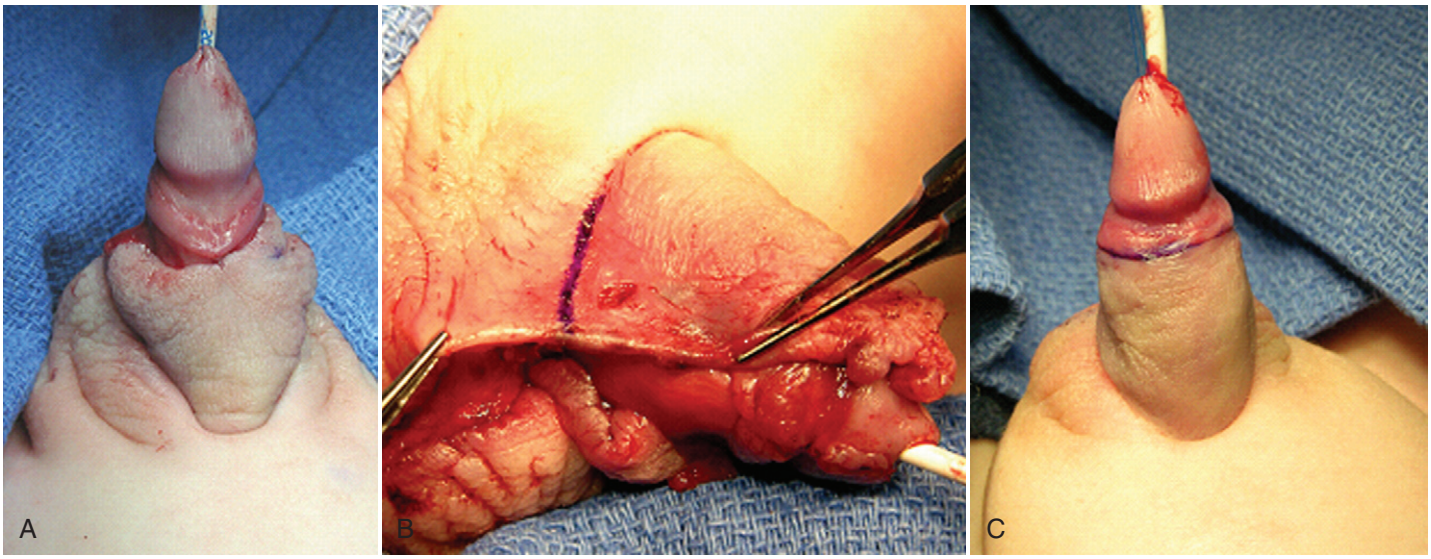


Figure 130–21. Minor scrotoplasty. **A,** Minor scrotal encroachment on the penopubic junction. **B,** Ventral incisions at the penoscrotal junction allow ventral rotation of shaft skin and scrotum. Incision continues to approximately the 3- to 4- and 8- to 9-o'clock positions, with subsequent ventral approximation of the shaft skin. **C,** Smooth penopubic junction with normal-appearing scrotum.

Neourethral Calibration

Passage of a sound or bougie can be done to determine if a small-appearing neomeatus is stenotic and to exclude neourethral stricture, especially in pre–toilet-trained boys in whom uroflowmetry is not practical. The author performs a single calibration in pre–toilet-trained patients 6 months postoperatively; but given the low rates of meatal stenosis and neourethral stricture, instrumentation could be reserved for those with suspected obstructive voiding symptoms. The normal caliber of the meatus varies with age; the minimum is variously reported from less than or equal to 8 French (Litvak et al, 1976) to greater than or equal to 10 French (Yang et al, 2001b).

Uroflowmetry

Uroflowmetry is advocated as a noninvasive means to assess neourethral function. Parameters considered include both maximum flow rate and appearance of the curve, defined as bell versus plateau shaped. Obstruction is suspected in plateau curves with maximum flow rates more than 2 standard deviations below the mean of age-matched controls (Garibay et al, 1995).

Reported results after repairs with TIP and onlay and tubularized preputial flaps indicate the majority of patients have maximum flow rates greater than the 5th percentile (Jayanthi et al, 1995; Snodgrass, 1999b; Marte et al, 2001; Hammouda et al, 2003), although many are below the 50th percentile (Jayanthi et al, 1995; Hammouda et al, 2003). Limiting the interpretation of postoperative uroflowmetry data has been reluctance to perform additional testing to confirm anatomic obstruction in patients with maximum flow rates less than the 5th percentile when they are asymptomatic or have postvoid residual urine volumes thought insignificant (<10% voided volume) (Jayanthi et al, 1995; Hammouda et al, 2003). Those who have investigated patients with maximum flow rates less than the 5th percentile report finding meatal stenosis or neourethral stricture (Garibay et al, 1995; Marte et al, 2001; Kaya et al, 2007), which suggests peak flow rates reduced to this degree should prompt calibration or cystoscopy. Postoperative plateau curves and peak flow rates between the 5th and 50th percentiles without apparent anatomic obstruction likely indicate the surgically created neourethra lacks the elasticity and smooth luminal surface of the normal urethra (Holmdahl et al, 2006; Braga et al, 2007).

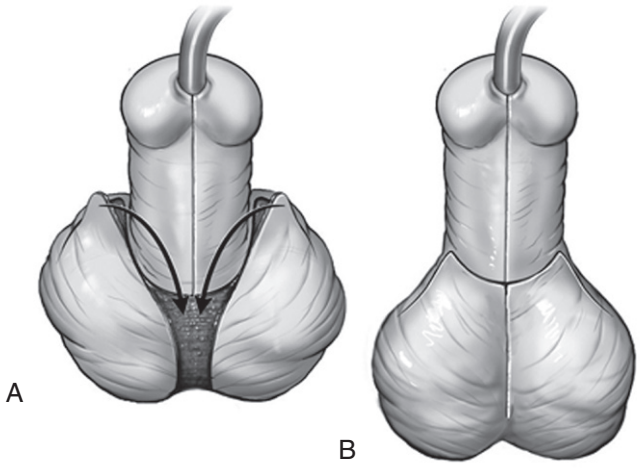


Figure 130–22. Major scrotoplasty. **A,** After completion of urethroplasty, skin incisions are made along the abnormal extensions of scrotum to either side of the penis. These flaps are rotated down and to the midline. **B,** Skin closure using subepithelial sutures.

Lack of universal agreement regarding normal values and minimum acceptable voided volumes limits comparisons between reported series. Significance of peak flow rates between the mean and –2 standard deviations in otherwise asymptomatic patients is unknown.

Questionnaires

Questionnaires potentially facilitate objective determination of patient perceptions regarding penile appearance and function after hypospadias repair. Various reports using questionnaires in

teens and adults previously operated on with a number of different techniques provide important insights. First, cosmetic outcomes are important (Bracka, 1989; Mureau et al, 1995; Aho et al, 2000b), with patients indicating a meatus at the proper glans location is preferable to the coronal position advocated in the past (Mureau et al, 1996). In cultures that do not practice routine circumcision the appearance of the circumcised penis after hypospadias repair increases self-awareness of the prior defect (Mureau et al, 1996). Patient versus surgeon impressions of cosmetic results may vary significantly, with patients generally (Mureau et al, 1996), but not always (Weber et al, 2008), more likely to express a negative perception of their genitalia. Some factors of concern to patients, such as scars and meatal position, can be influenced by surgical technique, although others, including overall penile size, cannot. There is apparent disagreement concerning impact of the age at surgery and number of operations, because some report that older age and increasing number of operations negatively impact sexual adjustment (Mureau et al, 1995) whereas others state these factors do not necessarily relate to the patient's genital perception (Bubanj et al, 2004).

A survey of men who underwent Koyanagi repair found 41% dissatisfied with penile appearance, but this was not significantly different from the 34% dissatisfaction reported by normal men, emphasizing the need for controls to understand the significance of responses (Moriya et al, 2006). In contrast, a cohort of teens and adults after prior two-stage preputial flap repair found 92% pleased with penile appearance, with 88% stating it was normal (Lam et al, 2005). Comparable data have not been published after other preputial flap or graft repairs described earlier or for TIP repair. However, responses by parents to questionnaires regarding the appearance of the penis after TIP repair were the same as those given by patients whose normal boys underwent elective circumcision (Snodgrass et al, 2008).

Voiding disturbances, including "spraying" (a broad stream), stream deflection, and/or postvoid dribbling are commonly reported by men after skin flap urethroplasties (Kumar and Harris, 1994; Aho et al, 2000b; Lam et al, 2005). However, one study with controls cautioned that while these voiding complaints were significantly more common in patients, half the normal men stated they had spraying, deflection, or dribbling (Moriya et al, 2006). The need to milk ejaculate has also been noted in 14% to 45% of patients (Bubanj et al, 2004; Lam et al, 2005; Moriya et al, 2006).

Persistent curvature during erection has been reported by 14% to 40% of previously operated men (Kumar and Harris, 1994; Aho et al, 2000b; Bubanj et al, 2004; Moriya et al, 2006), although normal controls had similar (Bubanj et al, 2004) or increased self-reported curvature (Moriya et al, 2006). None of these studies correlated extent of original curvature and means for straightening to these postpubertal findings.

No standardized questionnaire to determine penile appearance, micturition, or sexual function after hypospadias repair has gained widespread acceptance.

URETHROPLASTY COMPLICATIONS

Univariate analysis of factors potentially contributing to complications after TIP repair found increased likelihood with running versus interrupted two-layer subepithelial urethral plate tubularization, proximal versus distal/midshaft hypospadias, no barrier layer over the neourethra versus a dartos flap ± spongioplasty, and initial versus later experience of the operating surgeon. Of these, multivariate logistic regression analysis indicated proximal hypospadias and lack of a barrier layer as independent risk factors (El-Sherbiny et al, 2004). Comparable analyses have not been reported for other urethroplasty techniques, but generally complications are greater with more proximal hypospadias repair regardless of procedure. **Periodic review by surgeons of their outcomes may prompt modifications to address specific identified problems (El-Sherbiny et al, 2004; Gapany et al, 2007) and should be considered a routine practice in hypospadias surgery**.

Urethroplasty complications may occur singly or in combination, mandating thorough assessment of the neourethra when a problem is suspected. Surgical correction for the following complications is described under Reoperations.

Fistulas

Urethrocutaneous fistulas are the most common complication after hypospadias urethroplasty. Potential causes remain a matter of conjecture, and no multivariable analyses of suspected factors have been reported. For example, realization that overlapping suture lines from urethroplasty and skin closure potentially increase likelihood for fistulas dates to Duplay's first procedure, but other factors such as larger suture size (4-0) and different suture materials (catgut, horsehair) then commonly used could also have contributed to their development.

Technical steps thought to reduce fistula risk include two-layer subepithelial closure of the neourethra and subsequent coverage with a barrier flap, usually dartos. Of these, there are more data regarding barrier layers. One RCT randomized patients with distal hypospadias undergoing TIP repair with foreskin reconstruction to receive a ventral dartos barrier flap or not, reporting a significant reduction in fistulas within the cohort assigned dartos coverage (23% vs. 8%, $P = .03$) (Savanelli et al, 2007). Similarly, a prospective study found addition of a dartos flap significantly reduced fistulas (26% to 3.5%, $P < .01$) during TIP repair in comparison to retrospectively obtained results from a second cohort of consecutive patients thought otherwise similar in age and extent of hypospadias repaired without a dartos flap (Gapany et al, 2007). Neither study provided details regarding number of layers and suturing technique (subepithelial vs. through epithelium) for urethroplasty, nor overlying glansplasty and skin closure, but stated these were similar among included patients.

Other retrospective reviews give conflicting outcomes. For example, a dartos flap significantly reduced fistulas after two-stage graft repair in one study (63% to 4.5%, $P < .001$), but the extent of hypospadias and whether operations were primary versus reoperative were not stated to ensure the two groups were otherwise comparable (Telfer et al, 1998). Splitting the dorsal dartos flap to create a "double-layer" barrier was found to significantly reduce fistulas versus a single-layer dartos flap (14% to 0%) in one series of TIP repair (Bakan and Yildiz, 2007) but not another (4% versus 0%, $P = .5$) (Kamal, 2005). The author has reported prospectively collected data indicating a 33% fistula incidence in proximal TIP urethroplasty despite using a dartos flap in every case (Snodgrass and Yucel, 2007), although a dartos flap did significantly reduce fistulas in mostly distal TIP reoperations (Nguyen and Snodgrass, 2004).

An alternative consideration to prevent fistulas is application of fibrin sealant over the neourethra. Use has been investigated in one RCT of proximal tubularized preputial flap repairs (Gopal et al, 2008) and another prospective cohort study (Ambriz-Gonzalez et al, 2007), both reporting significant decreases in fistulas with use.

Fistulas can occur at any location along the urethroplasty and can be an isolated finding or associated with other complications,

including distal obstruction from meatal stenosis or neourethral stricture or turbulent urinary flow in a diverticulum. Although most often noted in the first few months after surgery, they can be overlooked in infants until evident at toilet training and also can occur years after apparently successful hypospadias repair. Fistulas occasionally close spontaneously, and there are anecdotal reports that fibrin glue can promote closure. The majority require reoperation.

Meatal Stenosis

Obstructive narrowing at the neomeatus can result from technical error, ischemia, or balanitis xerotica obliterans (BXO). Tubularization of the urethral plate too far distally is most likely the main cause for meatal stenosis after TIP repair. As mentioned earlier, the plate should not be tubularized beyond approximately the mid-glans point, leaving an oval terminal opening. Mistaken belief that the glans wings must be sutured to the neourethra probably has caused some to extend plate tubularization too far distally to approximate the wings without leaving a glanular hypospadias.

Meatal stenosis is suspected when the neomeatus appears small, the child strains to void, and/or when uroflowmetry demonstrates peak flow below the 5th percentile with a plateau-shaped tracing. These are nonspecific findings that require verification by calibration to establish the diagnosis.

Neourethra Stricture

Strictures of the neourethra, like meatal stenosis, may indicate technical error, ischemia, or BXO and similarly present as obstructive voiding symptoms and/or signs. Urinary tract infections after hypospadias repair can also suggest neourethral obstruction. The diagnosis can be suspected by inability to pass sounds, but retrograde or voiding urethrography and/or cystoscopy are needed for confirmation. Despite dorsal urethral plate incision, strictures are rarely reported after TIP repair. The most common site for neourethral strictures is at the proximal anastomosis of the neourethra to native urethra in flap and graft repairs. Circumferential anastomoses have been considered at greater risk for stricture, but comparisons of onlay to tubularized preputial flaps have not shown a statistically significant difference (Wiener et al, 1997; Castanon et al, 2000).

Dehiscence

Partial or complete wound separation results in recurrent hypospadias. Causes potentially include technical factors (suture materials and/or technique during glansplasty), glans size, traumatic catheter displacement, or wound infection. The author found proximal repairs were significantly more likely to result in glans dehiscence than mid-distal shaft repair, possibly indicating that smaller glans size increases risk (Snodgrass et al, 2010). Preoperative testosterone injections in patients subjectively thought to have a smaller glans did not reduce dehiscence compared with nontreated patients presumably with a larger glans, although use was not randomized and glans size before and after treatment was not measured.

Glans dehiscence correlates with graft source when oral mucosa is used in staged urethroplasty. Cheek grafts, which are visibly thicker than lip grafts, are more often associated with dehiscence (Snodgrass and Elmore, 2004; Snodgrass et al, 2009).

Diverticulum

Ballooning of the neourethra during voiding with subsequent postvoid dribbling indicates diverticulum formation. Contributing factors include distal obstruction, turbulent urinary flow, and ability of tissues used for urethroplasty to expand. Accordingly, diverticula are most often noted after tubularized preputial flap repairs and are rarely encountered after tubularization of the urethral plate or buccal grafts, which presumably have a more regular luminal surface and are less prone to distention than is penile skin.

Balanitis Xerotica Obliterans

Late development of meatal stenosis or neourethral stricture can indicate BXO. A characteristic white appearance to involved tissues should prompt consideration of the condition (Fig. 130–23), as should development of obstruction several years after apparently successful urethroplasty. The importance of recognizing BXO is that repair requires excision of all involved tissues and their replacement with nonskin tissues, usually buccal mucosa, because reoperation using skin results in high recurrence rates (Bracka, 1995; Depasquale et al, 2000).

Key Points: Complications

- Fistulas are the most common complication after hypospadias repair. Factors thought to reduce their incidence include a two-layer subepithelial suture closure of the neourethra with interposition of dartos or tunica vaginalis barrier flap between the neourethra and shaft skin.
- Late development of meatal stenosis or urethral stricture may indicate BXO, especially if the meatus has a whitish discoloration.



Figure 130–23. Balanitis xerotica obliterans. The diagnosis is suspected from the white discoloration of the meatus in a patient with symptomatic meatal stenosis.



Figure 130–24. Ventral incision for hypospadias reoperations. Ventral incision for reoperative urethroplasty and glansplasty provides exposure to ventral dartos for barrier flap and facilitates cosmetic skin revision without need to deglove the penis.

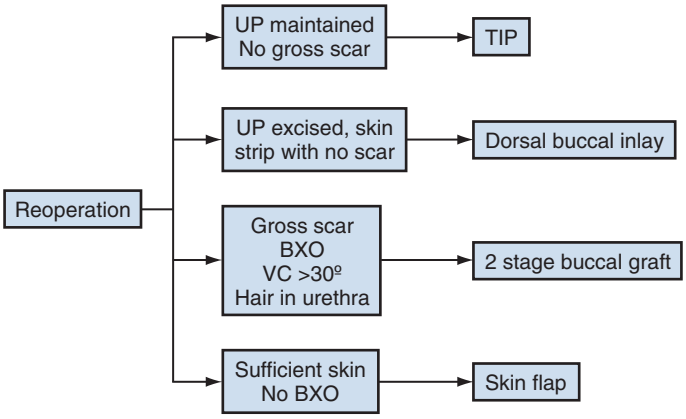


Figure 130–25. Algorithm for hypospadias reoperations. BXO, balanitis xerotica obliterans; TIP, tubularized incised plate; UP, urethral plate; VC, ventral curvature.

REOPERATIONS

Reoperations are required to correct various complications after hypospadias repair discussed in the preceding section or to replace the neourethra. Those for fistula, meatal stenosis or urethral stricture, diverticulum, or wound dehiscence can all be performed through a ventral midline incision, extended onto the glans wings to either side of the urethral plate in cases of glans dehiscence (Fig. 130–24). This approach provides exposure without need to re-deglove the penis, allows correction of presenting and associated complications, gives access to ventral dartos or tunica vaginalis for a barrier layer before skin closure, and facilitates cosmetic skin revision.

The algorithm in Figure 130–25 outlines options for urethroplasty reoperations. Although most techniques used for primary hypospadias urethroplasty can be adapted to reoperations, the greater complications rates that result support concerns that previously operated tissues have diminished vascularity (Jayanthi et al, 1994).

Fistulas

Fistula repair begins with examination to exclude contributing conditions, especially distal obstruction, and distention of the urethra with methylene blue–tinted fluid to detect additional fistulas. The fistula tract is dissected to the neourethra, excised and closed with subepithelial absorbable sutures, and then covered with a ventral dartos or tunica vaginalis flap to avoid overlapping suture lines during skin closure. Surgery has been described using circular incision immediately adjacent to the fistula tract with subsequent advancement of a skin flap with its underlying dartos over the repair. The author prefers a larger midline incision though the median raphe.

Fistulas occurring at the corona potentially require alternative management. If only a thin bridge of skin connects the glans wings distally, reoperation with glansplasty is needed for fistula repair. However, if the glans wings are well approximated, coronal fistulas can be closed by dissection under the glans without need to reopen the wings and perform glansplasty (Fig. 130–26).

Multiple fistulas, or fistulas associated with meatal stenosis, neourethral stricture, or diverticulum require reoperative urethroplasty. Fistulas approximately 5 mm or greater also likely require reoperative urethroplasty for successful closure without narrowing the neourethra lumen.

Success with isolated repair of small fistulas has been reported in 76% to 96% of cases (Hayashi et al, 1998; Shankar et al, 2002; Santangelo et al, 2003). Fistulas greater than 2 mm were more likely to recur in one series (Shankar et al, 2002). Dartos flaps or full-thickness skin flaps were used routinely by some (Waterman et al, 2002; Santangelo et al, 2003) but not found to influence outcomes versus repairs without flaps by others (Hayashi et al, 1998; Shankar et al, 2002). Stents were not used for urinary diversion in one series (Santangelo et al, 2003) and not found to impact results in another (Waterman et al, 2002). These series did not systematically report the original hypospadias defect and means for repair, location and size of the fistula, sutures used for overlying skin closure, or duration of postoperative follow-up. No series reports multivariable analysis of factors possibly influencing outcomes.

Meatal Stenosis, Neourethral Stricture

Although repetitive dilation has been reported for meatal stenosis, it is unlikely to provide long-term resolution of scarring from overzealous plate tubularization or ischemia. Meatotomy can be considered if there is no evidence for BXO and the procedure can be accomplished without re-creating a hypospadias defect. Otherwise reoperation is required (see later).

Strictures discovered within 3 months of surgery have been reported more responsive to dilation or direct vision internal urethrotomy (DIVU) than those found subsequently (Scherz et al, 1988), although follow-up in successful cases of “at least 1 year” may have been insufficient to observe later failures. Overall success with DIVU for hypospadias strictures followed a minimum of 2 years is less than 25% (Duel et al, 1998; Husmann and Rathbun,

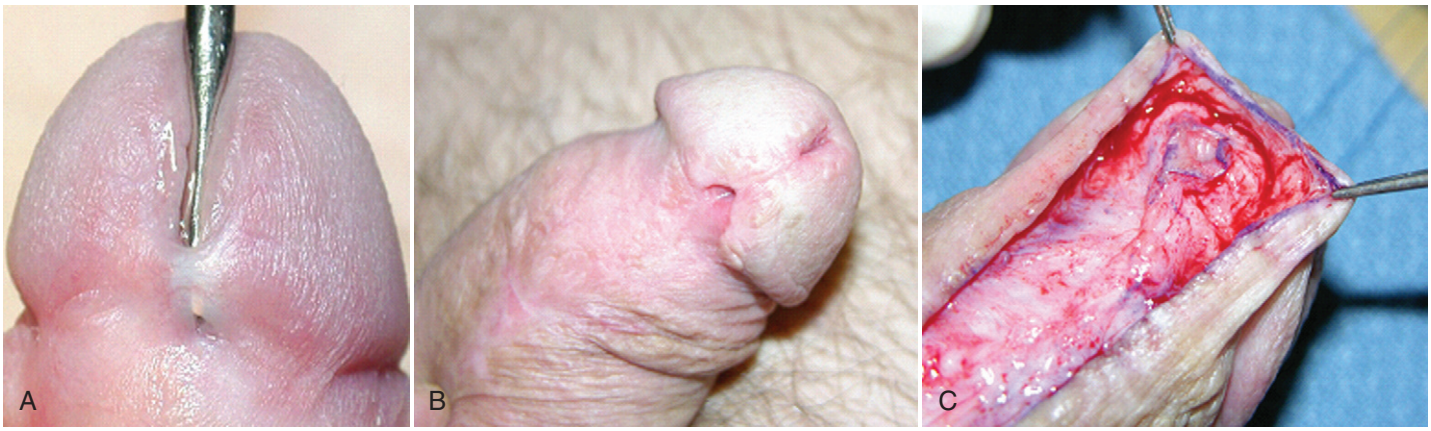


Figure 130–26. Coronal fistulas. **A,** Only a thin skin bridge separates the fistula from the meatus. Closure requires reoperative urethroplasty and glansplasty. **B,** Glansplasty intact beyond the coronal fistula, allowing repair without reoperative urethroplasty/glansplasty. Dissection under the glans (**C**) exposes the fistula for closure, and a ventral dartos flap accessed through a midline ventral incision will next be used to cover the repair.

2006). Technique in prior hypospadias repair may influence response to DIVU, because one prospective study of 72 cases found urethrotomy after tubularized flaps or grafts was successful in only 4% and resulted in progression of stricture length in 56% versus success in 68% and progression in 9% after onlay or urethral plate tubularizations (Husmann and Rathbun, 2006). This report also found that adjunctive urethral dilation after DIVU did not improve outcomes over DIVU alone. Failure of DIVU should not be treated with a second DIVU but should instead prompt open urethroplasty (Hsiao et al, 2003; Husmann and Rathbun, 2006).

Neourethral strictures not amenable to, or recurrent after, DIVU are corrected using dorsal inlay grafting (see later).

Dehiscence

Wound dehiscence below the coronal margin requires reoperative urethroplasty according to principles and techniques discussed later.

Diverticulum

After excluding distal obstruction and fistulas, a midline ventral skin incision is made exposing the ballooned neourethra, which also is opened in the midline. Excess tissues are excised and the urethra is retubularized over a urinary stent and then covered with a dartos or tunica vaginalis flap. If diverticulum is encountered after onlay preputial flap repair, the flap can be excised preserving its vascular pedicle for the barrier layer, with reoperative TIP urethroplasty done using the remaining urethral plate. If obstruction is encountered distally, excised tissue from the diverticulum can be used for inlay grafting (Fig. 130–27).

Tubularized Incised Plate Reoperation

Indications for TIP reoperation include coronal fistulas with only a thin distal skin bridge approximating the glans, meatal stenosis, and dehiscence when the urethral plate is not grossly scarred. Patients with multiple fistulas or diverticulum after prior onlay flap repair can also undergo TIP reoperation with excision of the preputial flap. The author considers gross scarring of the plate or its prior excision contraindications to reoperative TIP.

Most reported patients undergoing TIP reoperation failed one prior repair, with persistent distal hypospadias. Outcomes for reoperative TIP repair are the same after previous urethral plate incision (TIP, MAGPI) versus no prior incision (flap-flap, onlay flap, glans approximation procedure) (Nguyen and Snodgrass, 2004; Ziada et al, 2006; Elicevik et al, 2007). Likelihood for postoperative fistulas is significantly reduced by dartos flap barrier layers (Nguyen and Snodgrass, 2004).

Two reports with 14 and 5 patients, respectively, describe TIP reoperation using a preserved skin strip from the meatus to glans tip as a pseudo-urethral plate when the native plate was previously removed (Luo and Lin, 1999; Hayashi et al, 2001a). Neither report mentioned postoperative neourethral stricture, suggesting dorsal skin incision potentially heals by re-epithelialization.

TIP reoperation begins with a Y-shaped ventral incision extending along each glans wing, joining on the midline shaft and then continuing to the penoscrotal junction (see Fig. 130–24). This incision provides access to ventral dartos to create a barrier flap after urethroplasty. Repair otherwise is as described earlier for primary TIP repair.

Outcomes. Published outcomes are summarized in Table 130–7.

One-Stage Dorsal Inlay Graft Reoperation

When the urethral plate has been excised in prior surgery but a strip of skin without gross scarring remains in its place, midline incision of the skin strip with grafting of the resulting dorsal defect can be used for single-stage reoperative urethroplasty (Fig. 130–28). Surgical technique is the same as for TIP reoperation with graft obtained from penile or hairless groin skin or buccal mucosa (see later) quilted into place onto the corpora cavernosa using absorbable sutures at 0.5- to 1.0-cm intervals to facilitate revascularization.

Inlay grafting is also applicable to repair of neourethral strictures after hypospadias surgery but should not be used when there is possibility for BXO, because involved tissues must be excised in this condition.

Outcomes. Published reports are shown in Table 130–7. Whereas reoperative TIP repair has generally been avoided when the urethral plate is grossly scarred, Schwentner and associates (2006) reported inlay grafting successful in patients with a mean of four prior operations, including those with urethral plate scar. Their

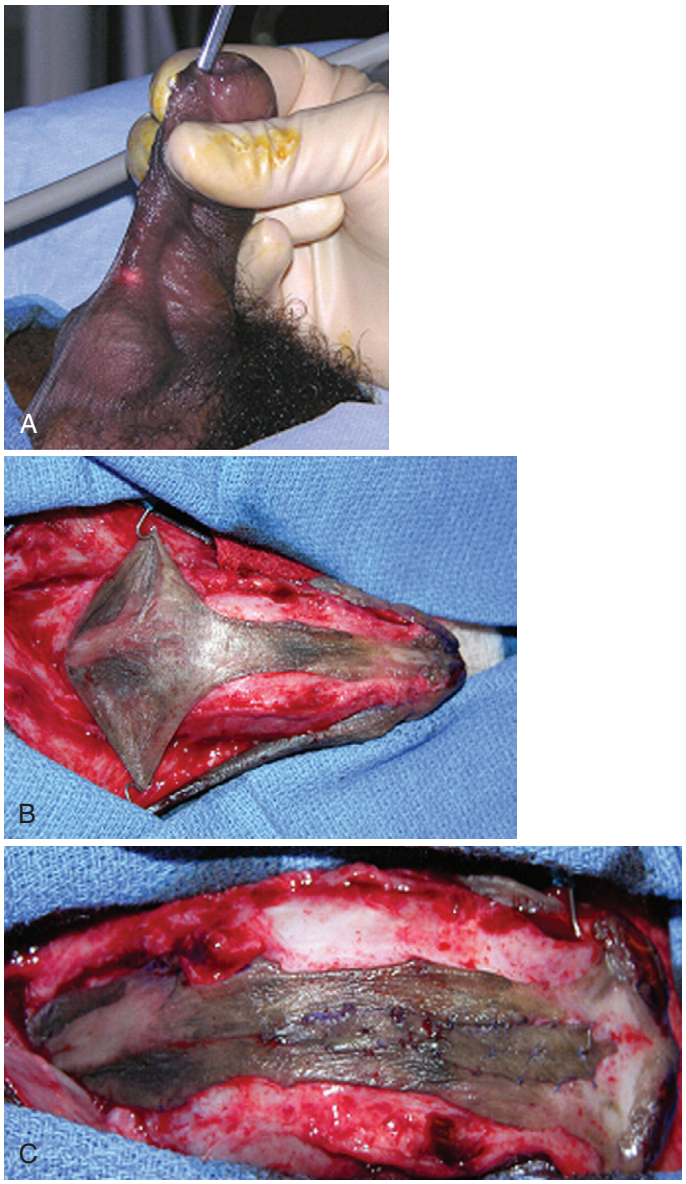


Figure 130–27. Diverticulectomy with distal inlay graft. **A,** Proximal diverticulum with functional distal obstruction. **B,** Neourethra opened, showing proximal diverticulum and relative distal narrowing. **C,** Excised diverticulum tissue used for midline inlay grafting to widen the distal segment before tubularization.

experience suggests one-stage inlay grafting is an alternative consideration to two-stage graft procedures unless there are specific indications to excise the remnant neourethra, such as BXO, hair, or persistent VC.

Two-Stage Buccal Graft Reoperation

Replacement urethroplasty is needed for gross scarring of the neourethra or when the neourethra contains BXO or extensive hair or is contracted and thereby creating recurrent penile curvature.

The first stage begins with excision of scarred or undesired tissues, which most often comprises the entire neourethra back to native urethra (Fig. 130–29). Dissection continues to the surface of the corpora cavernosa, including reestablishment of glans wings with a deep glanular cleft. Urethrostomy is created by suturing urethra to skin from the 5- to 7-o'clock position proximally.

Buccal graft is then harvested, infiltrating lines of incision with 1:100,000 epinephrine for hemostasis. The parotid duct is identified adjacent to the second molar and avoided when cheek mucosa is used. Dissection remains superficial to facial musculature. The graft donor site can be left open, coated with fibrin glue, or sutured closed. Grafts harvested from the lip are not sutured to avoid distorting the vermillion border.

The graft should fill the ventral penile defect without tension. It is next incised proximally in the midline for 5 to 10 mm and placed along both lateral margins of the urethrostomy to minimize the likelihood both of incorporating skin follicles into the neourethra at the second stage or developing a stricture at the graft-urethrostomy junction.

Then the graft is sutured to shaft skin and glans along its perimeter with interrupted polyglactin, using subepithelial stitching in the glans to avoid suture tracks. The midline of the graft is sutured to underlying corpora cavernosa, followed by additional quilting to the corpora on either side at 5- to 10-mm intervals to minimize the opportunity for fluid collection under the graft. An RB-1 needle facilitates quilting, which is done with 6-0 polyglactin in children and 5-0 in adults.

Tie-over polypropylene sutures secure a roll of petrolatum gauze onto the graft to further reduce graft movement or fluid accumulation that might impair revascularization. The tie-over sutures and urinary catheter are removed 7 days postoperatively.

During a healing phase of 6 months the graft can be visually inspected for focal scar or contracture. Partial contracture can be managed during the planned second stage by either including adjacent shaft skin in the neourethra or by inlay buccal regrafting. Scars or more extensive contracture may necessitate excision of the involved area with regrafting as an additional step before ultimate tubularization to create the neourethra (Fig. 130–30).

At the second stage the neourethral plate is tubularized by two-layer subepithelial suture closure and then covered with a dartos or tunica vaginalis flap. Buccal tissue should not be visible at the meatus, because exposed mucosa keratinizes and sheds. A urethral catheter provides urinary diversion for approximately 14 days.

Outcomes. Although Bracka (1995) has advocated staged buccal graft reoperations, he has not published detailed outcomes. Partial or complete failure of graft take requiring an additional operation to repair the neoplate before its tubularization occurs in 10% (Andrich et al, 2003; Elmore and Snodgrass, 2004). Overall complications after urethroplasty are reported in 26% to 38% (Price et al, 2003; Elmore and Snodgrass, 2004, Snodgrass et al, 2009).

In the author's experience, grafts using buccal tissue placed into the glans have had increased likelihood for glans dehiscence than thinner grafts of lip tissue (Snodgrass et al, 2009). Consequently, lip tissue is recommended to be used to graft the space between glans wings extending onto the shaft of the penis, with cheek tissue continuing proximally to the meatus, when needed. Lip will resurface from the glans to the penoscrotal junction in prepubertal boys if harvested, as shown in Fig. 130–31.

The author's patients undergoing two-stage buccal graft reconstructions had a mean of 4.3 previously failed operations. Buccal graft provides a neourethral plate in this setting where penile skin is both lacking and partially devascularized. The staged approach allows inspection of the neourethral plate before its tubularization with the opportunity to revise areas of scarring or contracture. Accordingly, no neourethral strictures have occurred. Scar tissue removal from the glans and subsequent neourethral plate tubularization create a vertical meatus and normal-appearing glans (Fig. 130–32).

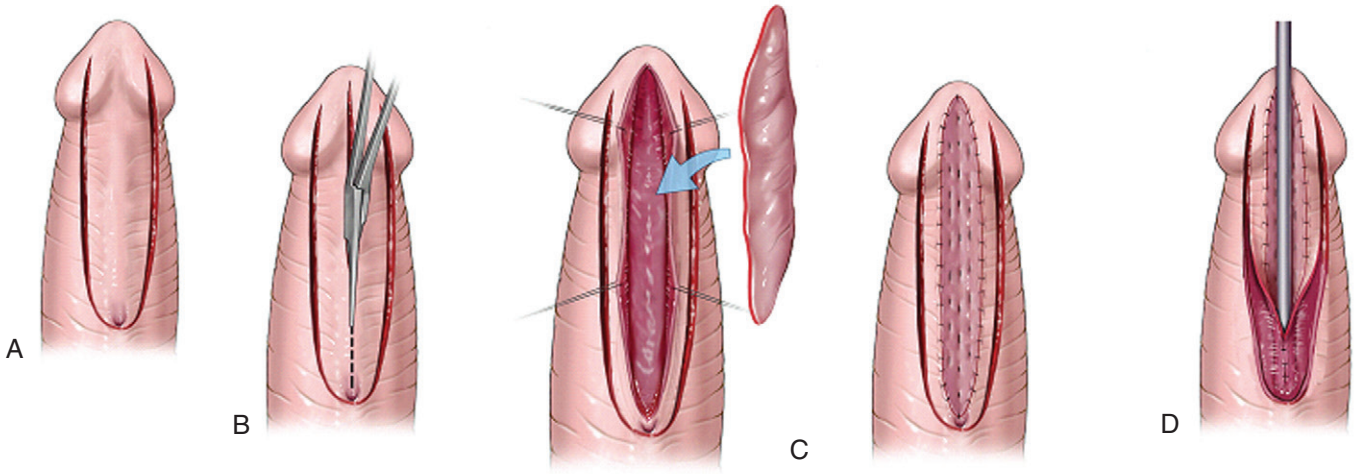


Figure 130–28. Dorsal inlay graft reoperation. **A,** U-shaped incision preserves supple skin strip. **B,** Dorsal midline TIP-like incision widens the skin strip. **C,** Graft, usually obtained from lower lip, quilted into defect. **D,** Skin strip tubularized in two layers, using subepithelial interrupted polyglactin and continuous polydioxanone. (Reprinted from Snodgrass WT, Bush N, Cost N. Algorithm for comprehensive approach to hypospadias reoperation using 3 techniques. J Urol 2009;182:2885–91.)

Table 130–7.

Reoperative Tubularized Incised Plate (TIP) and Inlay Graft Outcomes

STUDY	NO. OF PATIENTS	MEAN FOLLOW-UP (mo)	NO. OF PATIENTS WITH COMPLICATIONS	RATE	Complications					MEAN NO. PRIOR REPAIRS
					Fistulas	Meatal Stenosis	Stricture	Dehiscence	Diverticulum	
Reoperative TIP Repair										
Shanberg et al, 2001	13	22	2	15%	1	1		1		2.5 (1-6)
Borer et al, 2001	25	NS	6	24%	5	1	0			NS
Yang et al, 2001a	25	13.7	16	64%	7	13	1			2.5 (1-20)
Riccabona et al, 2003	40	NS	5	13%	3	1	1	0	0	NS
Nguyen and Snodgrass, 2004	31	NS	7	23%	5	0	0	2	0	1.1 (1-3)
Cakan et al, 2005	37	27.6	8	22%	4	1	1	2		1.4 (1-2)
Elicevik et al, 2007	100	6 mo–5 yr	26	26%	18	5	1	2		NS
Ziada et al, 2006	30	51.6	7	23%	6	8				1.6 (1-3)
Snodgrass et al, 2009	63	6	12	19%	7*	0	0	6*	0	
TOTALS	364		89	24%						
Inlay Grafts										
Schwentner et al, 2006	31	31	5	16%	1	0	4	0		4 (1-18)
Ye et al, 2008	53	22.6	8	15%	5		3		0	2.1 (1-6)
Snodgrass et al, 2009	13	5	2	15%	1	0	0	1	0	1.9 (1-9)
TOTALS	97		15	15%						

*One patient had both dehiscence and fistula.
NS, not specified.

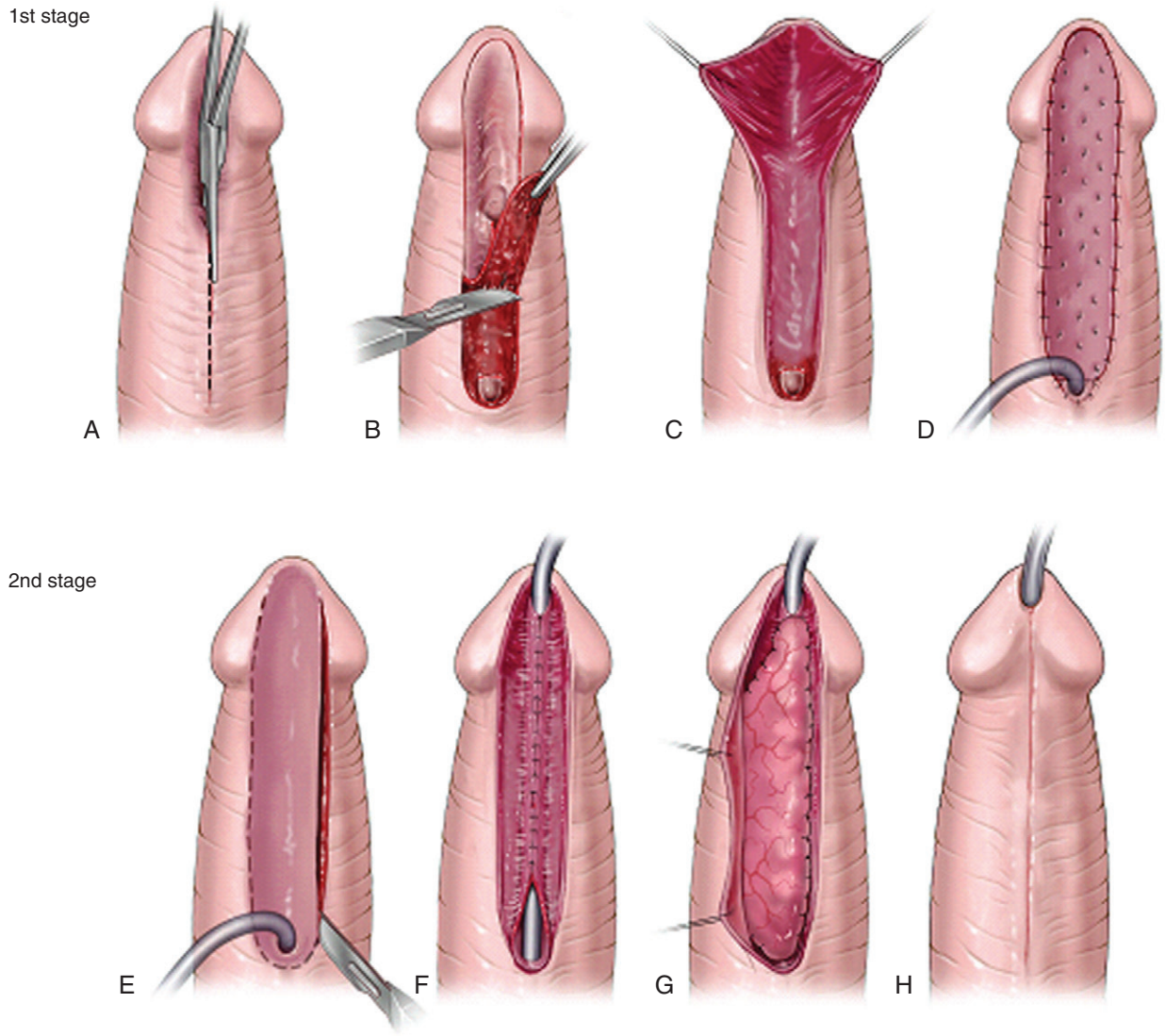


Figure 130–29. Two-stage buccal graft reoperation. **A,** Neourethra is opened with ventral incision. **B,** All unhealthy tissues, and usually the entire neourethra, are excised. **C,** Deep glans groove is reestablished, and proximal urethrostomy is completed. **D,** Buccal graft is quilted into place from meatus to glans tip. Lip tissue is used within the glans and subcoronal region, and cheek tissue is used along the penile shaft. The junction of lip to cheek is made diagonally to minimize contraction. **E,** U-shaped incision along perimeter of neourethra 6 months later. **F,** Two-layer tubularization of the neourethra using interrupted subepithelial polyglactin followed by continuous polydioxanone. **G,** Barrier flap, usually of tunica vaginalis, covers the entire neourethra. **H,** Glansplasty and skin closures completed with subepithelial sutures. (Reprinted from Snodgrass W, Elmore J. Initial experience with staged buccal graft [Bracka] hypospadias reoperations. J Urol 2004;172[4 Pt. 2]:1720–4.)

Others have tubularized the buccal graft or used it as an onlay urethra patch for one-stage reoperations, with resultant complications ranging from 28% to 57% (Snodgrass and Elmore, 2004), which is similar to urethroplasty outcomes after two-stage repairs. However, obstructive complications (meatal stenosis and urethral stricture) are reported in a mean of 18% of patients with one-stage (Snodgrass, 2004) versus approximately 5% of patients with two-stage operations (Elmore and Snodgrass, 2004; Snodgrass et al, 2009), most likely indicating improved graft revascularization with the two-stage approach.

Donor site morbidity was determined by systematic literature review to occur in 4% of adult patients, with no differences in overall complications between cheek versus lip harvest sites (Markiewicz et al, 2008), although most series have not systematically assessed and reported harvest site outcomes. Initial postoperative complaints include pain, numbness, and difficulty in mouth opening and ingestion. Analog pain scales indicate mid-range discomfort levels (Wood et al, 2004; Jang et al, 2005) that are similar whether donor sites are sutured closed or left open (Wood et al, 2004). Pain diminishes over the first 5 days and is resolved or mild by 1 to 6 months (Dublin and Stewart, 2004; Jang et al, 2005; Kamp et al, 2005). Lip donor sites were associated with significantly greater pain duration than cheek sites in one report (Kamp et al, 2005) but not another (Jang et al, 2005). Initial and long-term paresthesia has been found significantly increased after lip versus cheek harvest by some (Jang et al, 2005; Kamp et al, 2005) but not others (Wood et al, 2004). Impaired mouth opening usually resolves within the first month but may persist in a minority of patients for 6 months or longer (Wood et al, 2004), or patients may note

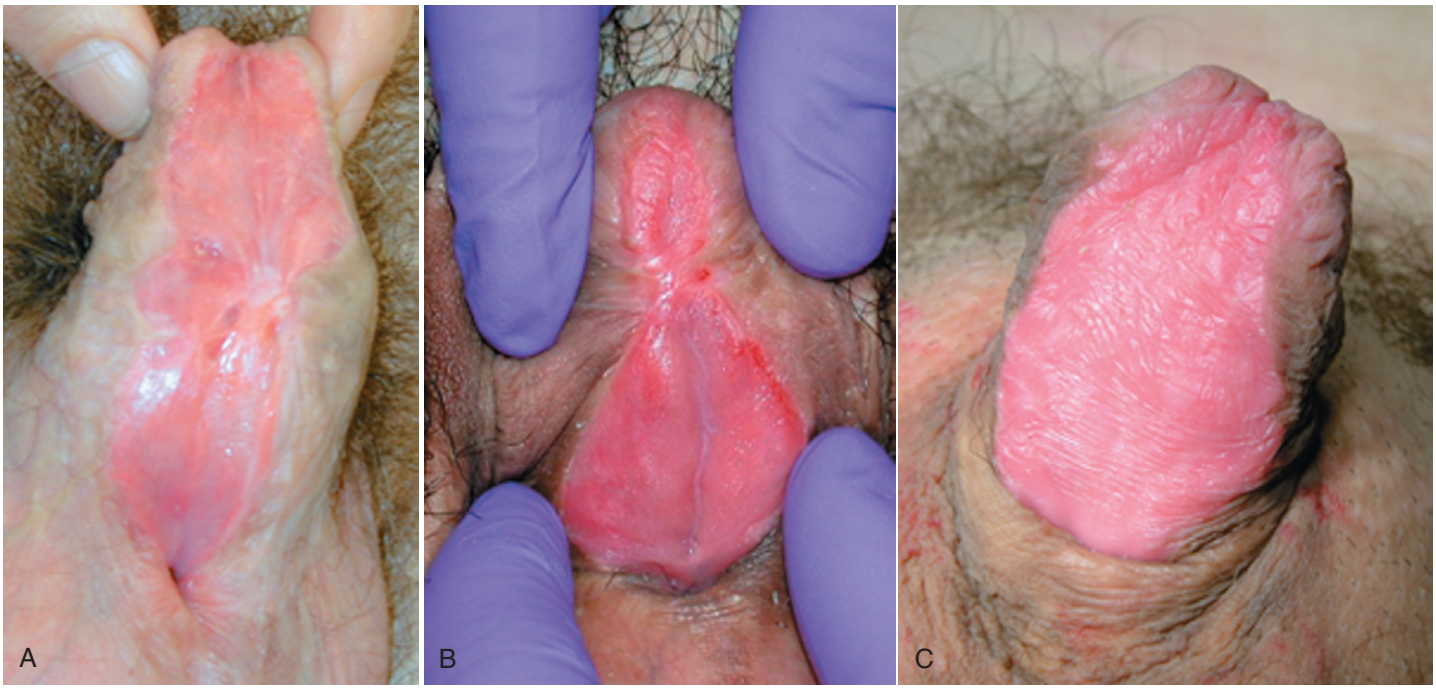


Figure 130–30. Graft scar and contracture. **A,** Stellate scar in midportion of graft, **B,** Distal graft contracture. **C,** Desired healthy appearance of well-vascularized graft. (Reprinted from Snodgrass W, Elmore J. Initial experience with staged buccal graft [Bracka] hypospadias reoperations. J Urol 2004;172[4 Pt. 2]:1720–4.)

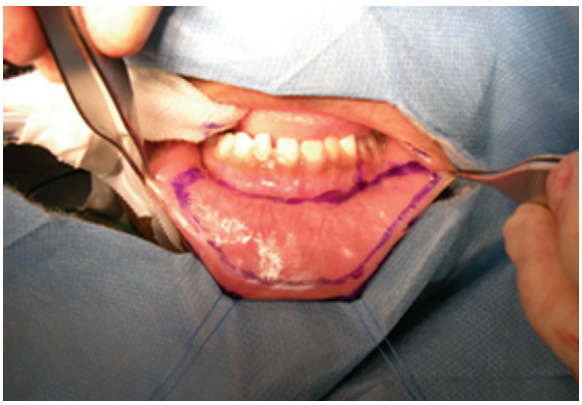


Figure 130–31. Outline for graft harvest from lower lip, extending from the gum to approximately 3 mm of the visible border of the lip. This graft will surface from the glans to the penoscrotal junction, or more proximally, in boys. The donor site is not sutured.

continued "tightness" without restriction (Dublin and Stewart, 2004).

There are very limited data regarding morbidity associated with oral mucosa harvest sites in children. One evaluation at a mean of 6.9 years postoperatively found 19% mentioned concerns for appearance or occasional pain or numbness after lip harvest with wound suturing versus no problems after cheek harvests (Nelson et al, 2005).

Skin Flaps

Mathieu flip-flap and onlay or tubularized preputial flaps have been used for hypospadias reoperation. Technical details of the procedure including sutures preferred and use of barrier flaps were not reported in most the publications listed in Table 130–8. Most patients in these studies failed one prior attempt at hypospadias repair. As the number of failed previous surgeries increases, the likelihood that sufficient well-vascularized skin remains to create flaps for urethroplasty decreases. Jayanthi and associates (1994) stated that an unspecified number of additional patients did not undergo skin flap reoperations owing to lack of supple skin, whereas in a series of patients with a mean of 1.6 failed repairs Bar-Yosef and coworkers (2005) stated that 15% had scar that prevented reoperation with skin flaps.

Key Points: Reoperations

- TIP reoperation is an option for persistent hypospadias when the urethral plate remains without gross scar.
- Persistent hypospadias after urethral plate replacement with skin potentially can be corrected in one stage using TIP-like widening of a skin strip with dorsal inlay grafting of the resultant defect.
- Failed hypospadias surgery with persistent VC, hair in the urethra, and/or gross scarring can be salvaged by excision of all unhealthy tissues with two-stage buccal graft urethroplasty.
- Balanitis xerotica obliterans requires complete excision with two-stage buccal graft urethroplasty, because the condition recurs in both penile and nongenital skin.
- Buccal grafting is best done using lip within the glans and cheek along the penile shaft.

LIMITATIONS OF HYPOSPADIAS LITERATURE

The main objective of scientific reporting is to relate experience so that other surgeons and their patients potentially can benefit from lessons learned. The following observations regarding

Table 130–8.

Reoperative Skin Flaps

STUDY	NO. OF PATIENTS	MEAN FOLLOW-UP (mo)	NO. OF PATIENTS WITH COMPLICATIONS	RATE	Complications							MEAN NO. PRIOR REPAIRS
					Fistulas	Meatal Stenosis	Stricture	Dehiscence	Diverticulum	Recurrent VC	Failure	
Jayanthi et al, 1994*	28	NS	8	29%	2	1	1				4	1 in 30, 2-6 in 14
Simmons et al, 1999*	17	17	4	24%	3			1				1.6 (1-4)
Emir and Erol, 2003*	55	3	16	29%	14			2				1.4 (1-3)
Bar-Yosef et al, 2005*	34	29	9	26%	5	2					2	1.6 (1-3)
Jayanthi et al, 1994†	16	NS	9	56%	4		2				4	
Simmons et al, 1999‡	36	17	5	14%								1.6 (1-4)
Emir and Erol, 2003‡	33	NS	16	48%	14			2				1.5 (1-3)
Patel et al, 2005‡	11	24.5	6	55%	5				1	1		2 (1-5)
TOTALS	230		73	32%								

*Mathieu flip-flap.
†Tube or onlay flap.
‡Onlay.
NS, not specified; VC, ventral curvature.



Figure 130–32. Cosmetic outcomes after two-stage buccal graft reoperation. (Reprinted from Snodgrass W, Elmore J. Initial experience with staged buccal graft [Bracka] hypospadias reoperations. J Urol 2004;172[4 Pt. 2]:1720–4.)

hypospadias literature highlight recurring shortcomings that limit this communication between specialists.

Failure to Report Technical Details of Procedures

Results of hypospadias surgery can be impacted by such variables as suture type and size, suturing techniques, and barrier layers as discussed earlier in the various outcomes sections. Accordingly, authors should describe these technical aspects of their procedures in detail for straightening curvature, urethroplasty, glansplasty, and skin closure so that readers can compare and contrast their own materials, methods, and results.

In addition, because needles available for different suture sizes vary worldwide, this information should also be provided. For example, the 6-0 polyglactin used by the author has a S29 needle but in other countries is only available from the same manufacturer on RB needles. Whether needle size accounts for some of the wide variation in outcomes reported for the same procedure cannot currently be determined from published literature.

Failure to Segregate Results for Patient Groups with Different Outcomes

Complications increase with increasing severity of hypospadias, and so results for distal, midshaft, and proximal hypospadias should be separately described. Because reoperations have greater incidence of complications than primary repairs, data from patients undergoing secondary versus primary surgery also should be separately reported. Manuscripts combining the outcomes for several surgeons in one or multiple centers should specifically highlight any differences in technical variables mentioned earlier and provide analysis that their individual results were statistically similar.

Lack of Uniform Follow-up

Because the time that complications are first noted is not routinely reported, it is unclear what minimum duration of follow-up is needed to identify the majority of postoperative problems. Means to determine results are not standardized and are in part dependent on the age when surgery is performed; for example, infants cannot provide uroflowmetry as can older boys. Whereas fistulas, wound dehiscences, and diverticula are visually apparent, obstructive lesions are not always easily recognizable, and a small-appearing meatus may be normal in caliber. Consequently, reports of meatal stenosis and/or neourethral stricture should specifically describe how these diagnoses were made. Lack of a universally accepted means to assess cosmetic outcomes makes comparisons between techniques and reported series difficult and likely inaccurate. The common phrase that cosmetic results were "satisfactory" does not inform readers if the penis looked normal and if not why not.

The current trend by surgeons to increasingly rely on fewer procedures to correct the spectrum of hypospadias defects offers an opportunity to standardize and perfect these reconstructive operations. Better reporting combined with quality review of individual results by hypospadiologists should reduce the sometimes wide disparity in outcomes reported by different centers as well as isolate causes for complications.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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The complete reference list is available online at www.expertconsult.com.

chapter 131

Abnormalities of the External Genitalia in Boys

Jeffrey S. Palmer, MD, FACS, FAAP

Normal Male External Genitalia
Penile Anomalies
Scrotal Anomalies
Vascular Lesions of the Genitalia

The normal anatomy of the penis includes the prepuce (foreskin), glans, urethral meatus, coronal sulcus, and penile shaft. The ventral surface of the penile shaft has the median raphe that is contiguous with the scrotal raphe. Anomalies of the penis and scrotum are common and may be congenital, acquired, or iatrogenic. **The congenital anomalies may result from a disorder of sexual differentiation, genital differentiation, or genital growth and may be associated with other syndromes** (Table 131–1) or organ systems. For example, up to 50% of children with congenital anorectal malformations also have an associated urologic malformation.

Although ultrasonographic technology has evolved in the past decade permitting earlier fetal sex determination (Efrat et al, 2006), it is inaccurate and is not recommended before 12 weeks of gestation (Odeh et al, 2009). However, prenatal ultrasonography is accurate in sex determination in 99% to 100% of cases after 13 weeks of gestation without malformed external genitalia (Odeh et al, 2009) (Fig. 131–1). In-utero ultrasonography has identified abnormal male genitalia including ambiguous genitalia and penoscrotal transposition (Cheikhelard et al, 2000; Vijayaraghavan et al, 2002; Pinette et al, 2003). More recent ultrasonographic technology, including three-dimensional ultrasonography, is being used to evaluate the fetal external genitalia but there are no definitive results suggesting this as an enhanced diagnostic modality (Verweerd-Dikkeboom et al, 2008; Abu-Rustum et al, 2009).

The understanding of the normal anatomy and embryologic development of the male external genitalia is essential to recognizing and treating penile and scrotal anomalies. Most genital abnormalities noted in neonates do not result in an ambiguous appearance but rather more common conditions such as inconspicuous penis or abnormal penile orientation. **The American Academy of Pediatrics (AAP) Committee on Genetics and Sections on Endocrinology and Urology** (2000) **published a guide to the normal embryology of the external genitalia and the altered embryology, evaluation, and management of ambiguous genitalia.**

NORMAL MALE EXTERNAL GENITALIA

Embryology

Normal embryogenesis of the male genitalia involves the formation of the penis and scrotum. **The early development of the external genitalia in the two sexes is similar before the 9th week of gestation** (Ammini et al, 1997). Understanding factors and sequential steps in normal embryogenesis is fundamental in the comprehension of the pathogenesis of male genital anomalies. **These factors include testosterone synthesis by the fetal testis and its enzymatic conversion into dihydrotestosterone by 5α-reductase and the presence of androgen receptors able to recognize the androgenic hormones. The influence of dihydrotestosterone on the androgen receptors results in the differentiation of the genital tubercle, genital (labioscrotal) folds, and genital swelling between 9 and 13 weeks of gestation into the male structures of the glans penis, penile shaft, and scrotum, respectively**.

The male develops in a proximal to distal manner. As the penis forms from the elongation and enlargement of the phallus, the lateral walls of the urethral groove form from the ventrally located genital folds. The genital folds then fuse in the midline. The glanular urethra forms from the ingrowth of surface epithelium, but this long-held theory has been challenged with evidence suggesting that it is due to the fusion of the urethral plate (Glenister, 1921; Ammini et al, 1997). The scrotum forms through the inferomedial migration and midline fusion of the genital folds as delineated by the scrotal raphe. **In females and in males with abnormalities in testosterone and/or dihydrotestosterone production, 5α-reductase deficiency, or androgen receptor insufficiency, the genital tubercle, genital folds, and genital swellings passively become the clitoris, labia minora, and labia majora, respectively.**

Penile Length and Tanner Classification

Penile length significantly increases with gestational age (6 mm at 16 weeks to 26.4 mm at 38 weeks) (Johnson and Maxwell, 2000; Zalel et al, 2001) and during the first 3 months of life. The latter growth is a result of an increase in Leydig cell production of testosterone owing to the loss of the inhibitory effect of maternal estrogens on the fetal pituitary at birth, thereby causing a surge in gonadotropins. During the rest of childhood, penile length increases more slowly until adolescence when the length extensively increases again until the final size is reached. **The normal penile size in a full-term male neonate is 3.5 ± 0.7 cm in the stretched length and 1.1 ± 0.2 cm in diameter compared with 13.3 ± 1.6 cm at adulthood.** The penile stretched lengths from birth to adulthood are listed in Table 131–2.

Table 131–1.

Male Genital Anomalies That Commonly Occur in Various Syndromes (Microphallus, Hypospadias, Ambiguous Genitalia, and Bifid Scrotum)

ANOMALY	FEATURES
Anencephaly	
Aniridia–Wilms tumor association	WAGR syndrome: Wilms tumor, Aniridia, Genitourinary abnormalities or gonadoblastoma, and mental Retardation
Bladder exstrophy	
Börjeson-Forssman-Lehman syndrome	Microcephaly, mental retardation, large ears
Carpenter syndrome	Acrocephaly, polydactyly and syndactyly of feet, congenital heart disease
CHARGE association	Coloboma, Heart malformation, Atresia choanae, Retarded growth and development, Genital anomalies, Ear anomalies and/or deafness
Cloacal syndrome	
Fraser syndrome	Cryptophthalmos, mental retardation, ear anomalies
Johanson-Blizzard syndrome	Hypoplastic alae nasi, hypothyroidism, mental retardation, pancreatic insufficiency, deafness
Meckel-Gruber syndrome	Occipital encephalomeningocele, micrognathia, polydactyly, cystic renal dysplasia
Noonan syndrome	Webbed neck, pectus excavatum, pulmonic stenosis, short stature
Opitz syndrome	Hypertelorism, hypospadias, mild to moderate mental retardation
Pallister-Hall syndrome	Hypothalamic hamartoblastoma, hypopituitarism, imperforate anus
Popliteal pterygium syndrome	Popliteal web, cleft palate, lower lip pits
Prader-Willi syndrome	Hypotonia, obesity, small hands and feet, mild to moderate mental retardation
Rapp-Hodgkin ectodermal dysplasia syndrome	Hypohidrosis, oral clefts, dysplastic nails
Rieger syndrome	Iris dysplasia, hypodontia
Robinow syndrome	"Fetal face syndrome"; flat facial profile, hypertelorism, short forearms, thoracic hemivertebrae
Schinzel-Giedion syndrome	Growth deficiency, mental retardation, widely patent fontanelles, short forearms and legs, renal anomalies
Smith-Lemli-Opitz syndrome	Ptosis of eyelids, syndactyly of second and third toes, microcephaly, failure to thrive with short stature, mental retardation
Triploidy syndrome	
Trisomy 4p, 9p, 18, 20p, 21, 22, 9p, 10q, 11p, or 15q deficiency	
XXY, XXXXY	

From Jones KL. Smith's recognizable patterns of human malformation. 5th ed. Philadelphia: WB Saunders; 1997.

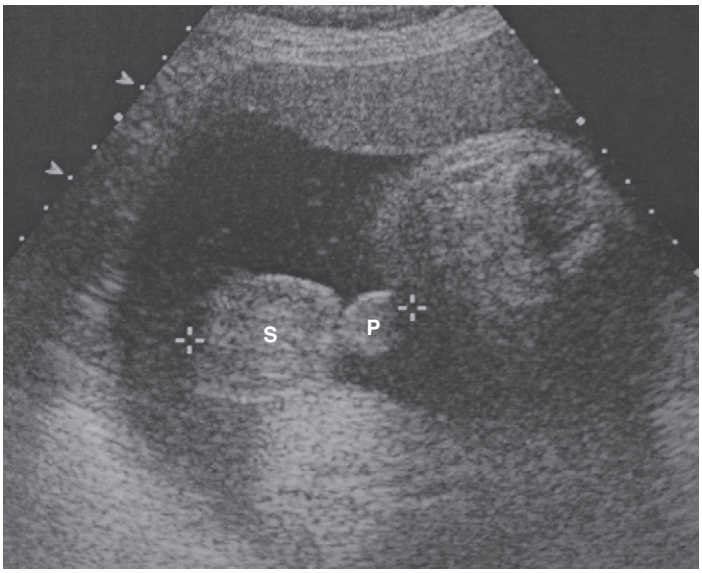


Figure 131–1. Fetal ultrasonogram of male genitalia. P, penis; S, scrotum.

Table 131–2.

Stretched Penile Length (cm) in Normal Male Subjects

AGE	MEAN ± SD	MEAN – 2.5 SD
Neonate, 30-wk gestation	2.5 ± 0.4	1.5
Neonate, 34-wk gestation	3.0 ± 0.4	2.0
0-5 mo	3.9 ± 0.8	1.9
6-12 mo	4.3 ± 0.8	2.3
1-2 yr	4.7 ± 0.8	2.6
2-3 yr	5.1 ± 0.9	2.9
3-4 yr	5.5 ± 0.9	3.3
4-5 yr	5.7 ± 0.9	3.5
5-6 yr	6.0 ± 0.9	3.8
6-7 yr	6.1 ± 0.9	3.9
7-8 yr	6.2 ± 1.0	3.7
8-9 yr	6.3 ± 1.0	3.8
9-10 yr	6.3 ± 1.0	3.8
10-11 yr	6.4 ± 1.1	3.7
Adult	13.3 ± 1.6	9.3

Data from Feldman KW, Smith DW. Fetal phallic growth and penile standards for newborn male infants. J Pediatr 1975;86:895; Schonfeld WA, Beebe GW. Normal growth and variation in the male genitalia from birth to maturity. J Urol 1987;30:554; and Tuladhar R, Davis PG, Batch J, Doyle LW. Establishment of a normal range of penile length in preterm infants. J Paediatr Child Health 1998;34:471.

Tanner stages are a set of recognizable changes that occur to pubic hair, penis, and testes during puberty that are helpful in evaluating patients (Table 131–3). The stages range from preadolescent penis and testes with no pubic hair (stage 1) to adult-size penis and scrotum with adult pubic hair distribution (stage 5).

PENILE ANOMALIES

Prepuce (Foreskin)

Phimosis and Paraphimosis

At birth, a physiologic phimosis (Fig. 131–2A) with either partial or complete inability to retract the prepuce exists owing to natural adhesions between the glans and inner preputial skin and/or due to a preputial ring. Two factors are involved in the separation of the prepuce from the glans: (1) epithelial debris, referred to as smegma, accumulates during the first 3 to 4 years of age under the prepuce, and (2) intermittent penile erections. **Preputial retractability increases with age, with 90% of uncircumcised boys 3 years of age with completely retractable prepuces and less than 1% by 17 years of age with phimosis** (Oster, 1968; Kayaba et al, 1996). **Therefore, primary phimosis is almost always resolvable during childhood without intervention.** Secondary phimosis can result from several causes, including forceful retraction and balanitis xerotica obliterans (BXO). Forceful preputial retraction is usually not recommended because it can result in a cicatrix of the prepuce.

Penile problems associated with the uncircumcised penis include paraphimosis, infection, urinary tract infection (UTI), and cancer. Paraphimosis (Fig. 131–2B), the entrapment of the prepuce behind the glans penis, can result in gangrene if not reduced in a timely fashion by manipulation, dorsal slit procedure, or circumcision. Severe edema of the foreskin occurs within several hours, depending on the tightness of the tip of the foreskin, and makes reduction more difficult. In most cases, manual compression of the glans with placement of distal traction on the edematous foreskin allows reduction of the paraphimotic ring. Other treatments include application of an iced glove for 5 minutes, application of granulated sugar for 1 to 2 hours, and placement of multiple punctures in the edematous skin (Mackway-Jones and Teece, 2004).

Indications to enhance preputial retractability include persistent primary phimosis, secondary phimosis, balanitis, posthitis (i.e., inflammation of the prepuce), BXO, and UTIs. Several topical corticosteroid creams using different regimens have been successfully used to treat phimosis with a relatively small number of side effects. Palmer and Palmer (2008) compared the efficacy of two different topical betamethasone treatment regimens with respect to outcome and untoward effects. Children were treated twice daily for 30 days (i.e., 60 doses) or three times daily for 21 days (63 doses). There was an 84.5% and 87% response rate, respectively. Only one child had an untoward effect (candidal dermatitis).

Table 131–3.

Tanner Classification of Sexual Maturity Stages in Boys

STAGE	PUBIC HAIR	PENIS	TESTES
1	None	Preadolescent	Preadolescent
2	Scanty, long	Slight enlargement; slightly pigmented	Enlarged scrotum, pink, texture altered
3	Darker, starts to curl, small amount	Longer	Larger
4	Resembles adult type but less in quantity; coarse, curly	Larger; glans and breadth increase in size	Larger, scrotum dark
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

Modified from Tanner JM. Growth at adolescence. 2nd ed. Oxford (UK): Blackwell Scientific Publications; 1962.

Circumcision

Circumcision dates back more than 6000 years ago with the oldest documented evidence thought to date to sixth dynasty (2345-2181 BC) tomb artwork in Egypt. Since that time different religions, countries, and cultures have adopted various views on circumcision (Palmer, 2009a). Many theories have been proposed

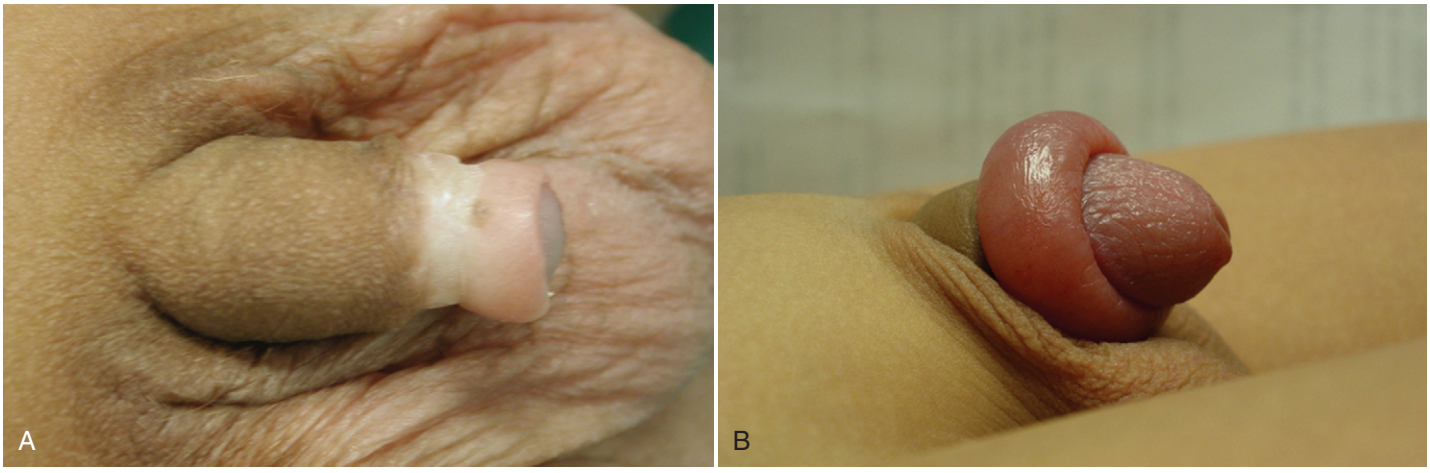


Figure 131–2. Conditions associated with the uncircumcised penis. **A,** Phimosis due to a preputial ring. **B,** Paraphimosis with associated entrapped prepuce behind the glans penis.

to the etiology of circumcision, including as a religious sacrifice, rite of passage, aid to hygiene, a way to differentiate cultural groups, and a method to discourage masturbation.

Elective circumcision in the neonate is a controversial topic. **In 1989 the AAP concluded, "Newborn circumcision has potential medical benefits and advantages as well as disadvantages and risks. When circumcision is being considered, the benefits and risks should be explained to the parents and informed consent obtained"** (AAP Task Force on Circumcision, 1989). More recently, the AAP again updated its policy statement (AAP Task Force on Circumcision, 1999; Lannon et al, 2000). Its position was essentially unchanged, with the exception that it emphasized the importance of local anesthesia for the procedure. The AAP does not endorse routine circumcision.

There are several techniques for neonatal circumcision, including the Gomco clamp, Mogen clamp, and Plastibell device. There should be complete separation of the prepuce from the glans with complete visualization of the meatus and circumferential visualization of the corona to confirm that there are no anomalies, including hypospadias. **When neonatal circumcision is performed, local anesthesia is recommended.** Available options include the topical application of a cream containing eutectic mixture of local anesthetic (EMLA; lidocaine and prilocaine), a dorsal penile nerve block, and a penile ring block (Hardwick-Smith et al, 1998). Randomized controlled trials have demonstrated that a dorsal penile nerve block is more effective than EMLA cream (Howard et al, 1999; Taddio et al, 2000) because prilocaine in the EMLA cream poses a low risk for methemoglobinemia (Couper, 2000). Circumcision can be performed under local anesthesia even in older boys. For example, Jayanthi and colleagues (1999) reported a series of 287 infants aged 3 days to 9 months (20% older than 3 months) who underwent office circumcision with local anesthesia. However, typically older infants and children are circumcised under general anesthesia rather in the office using a free-hand sleeve resection technique.

Circumcision should not be performed in neonates with other penile conditions that require surgical correction. These conditions include hypospadias, penile curvature, dorsal hood deformity, buried penis, and webbed penis (see the corresponding sections). Other conditions commonly seen in neonates that should be taken into consideration are a large hydrocele or inguinal hernias, which are more likely to develop secondary phimosis, buried penis, and trapped penis. A patient with a coagulopathy is another contraindication.

Circumcision has several potential benefits, including the prevention of penile cancer, UTIs, sexually transmitted diseases including human immunodeficiency virus (HIV) infection, and phimosis, as well as lessening of the risk of balanitis. Although some have alleged that neonatal circumcision can lead to sexual dysfunction, long-term studies have not supported this view (Fink et al, 2002; Bleustein et al, 2005). Schoen and associates (2006) determined that neonatal circumcision has a cost benefit compared with postneonatal circumcision, including procedure charges and reduction in future health care costs.

Carcinoma of the penis develops almost exclusively in men who are not circumcised at birth. Phimosis is a significant risk factor (Tsen et al, 2001). Schoen and coworkers (2000b) reported that of 89 men in a large health maintenance organization with invasive penile cancer, only 2 (2%) had been circumcised at birth. Furthermore, of 116 men with penile carcinoma in situ, 16 (14%) had had a neonatal circumcision.

Uncircumcised neonates and infants are predisposed to UTIs (Singh-Grewal et al, 2005). In a study of 100 neonates with a UTI, Ginsburg and McCracken (1982) found that only 3 (5%) of the 62 boys who developed a UTI were circumcised. Subsequently, Wiswell and colleagues (1985) studied more than 2500 male infants and found that 41 had symptomatic UTIs; 88% of these infants were uncircumcised. Uncircumcised boys were almost 20 times more likely than circumcised neonates to develop a UTI. Other studies of larger groups of infants have confirmed these reports (Wiswell, 2000; Zorc et al, 2005) and have demonstrated that neonatal circumcision is less costly than treating UTIs in uncircumcised boys (Schoen et al, 2000a). The increased risk seems to affect boys at least through 5 years of age (Craig et al, 1996), and the incidence of epididymitis is reduced (Bennett et al, 1998). The increased risk of UTIs can be attributed to colonization of the prepuce by urinary pathogens (Gunsar et al, 2004; Bonacorsi et al, 2005). It has been calculated that it takes 111 neonatal circumcisions to prevent one UTI (Singh-Grewal et al, 2005). However, Shim and colleagues (2009) evaluated 190 infants with confirmed normal urinary systems and diagnosed with their first febrile UTI. They assessed the incidence of recurrent UTI during the following year and several risk factors, including acute pyelonephritis. In infants with persistent nonretractile prepuces, recurrent UTI developed in 34%, compared with 17.6% of infants with retractile prepuces.

Whether circumcision reduces the risk of sexually transmitted diseases has been controversial. Several recent reports of a large population of men have demonstrated reduced incidence of HIV infection among men, with a protective effect of 60% (Gray et al, 2007; Bailey et al, 2007). However, a recent study compared 922 uncircumcised, HIV-infected, asymptomatic men in whom 474 underwent immediate circumcision with 448 who were not circumcised to evaluate transmission of HIV to HIV-uninfected female partners (Wawer et al, 2009). After 24 months of follow-up, 18% and 12% of women acquired HIV, respectively, thereby demonstrating that circumcision of HIV-infected men did not reduce HIV transmission to female partners. It has been reported that circumcision may reduce the risk of ulceration, bacterial vaginosis, and trichomonas in female partners (Gray et al, 2009).

Several clinical trials of the effect of circumcision on the prevention of human papillomavirus (HPV) infection, herpes simplex virus type 2 (HSV-2) infection, and other sexually transmitted diseases (Auvert et al, 2009; Nielson et al, 2009; Tobian et al, 2009) have been done. Tobian and associates (2009) evaluated 5534 HIV-negative, uncircumcised males, with 3393 being HSV-2 seronegative at enrollment. Of the 3393 men, 1684 underwent immediate circumcision while 1709 were not circumcised in order to evaluate HSV-2 and HPV transmission. At 24 months' follow-up, HSV-2 seroconversion was 7.8% and 10.3%, respectively, whereas prevalence of high-risk (carcinogenic) HPV genotypes was 18.0% and 27.9%, respectively. This study underscores the benefit of circumcision in reducing the incidence of HSV-2 infection and the prevalence of HPV infection.

Circumcision Complications

The risk of complications after circumcision is 0.2% to 5% (Baskin et al, 1996; Christakis et al, 2000; Ben Chaim et al, 2005). Complications can occur immediately or months to years after a circumcision. **The most common complication is bleeding, which occurs in 0.1% and is more common in older children.** There usually is bleeding from the frenulum or, less frequently, from a large blood vessel on the penile shaft. The

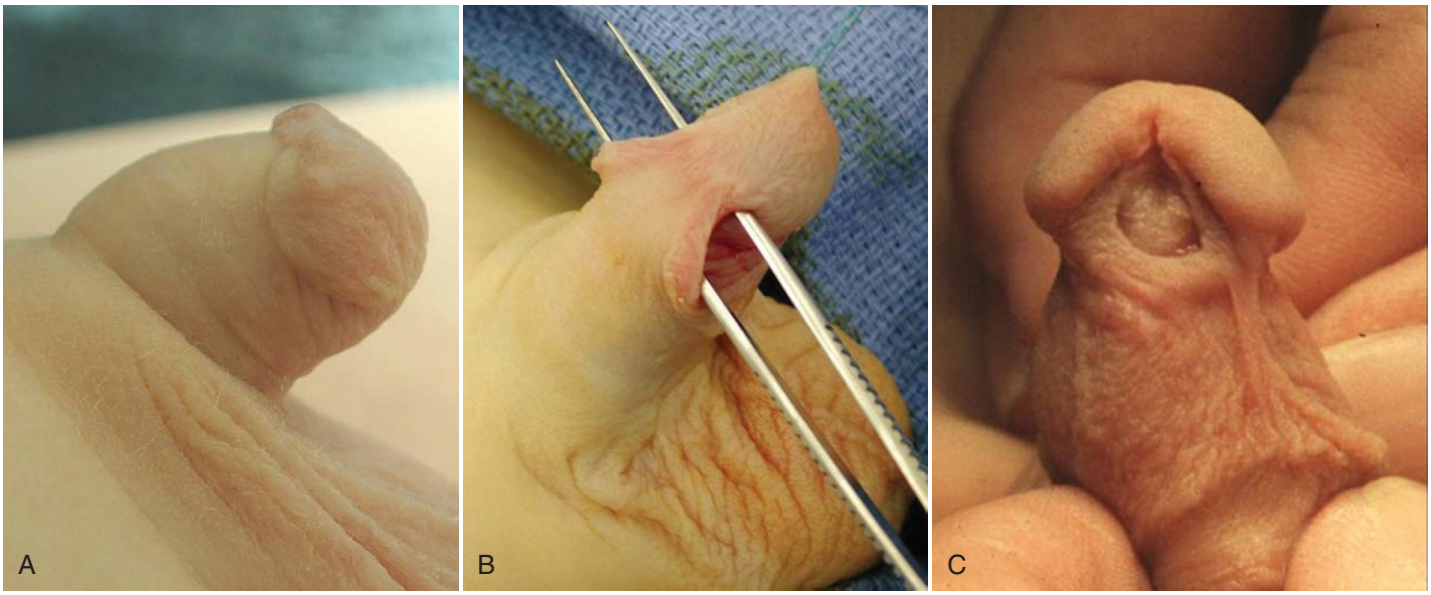


Figure 131–3. Complications associated with circumcision. **A,** Asymmetrical redundant penile skin. **B,** Penile skin bridge. **C,** Urethral and glanular resection.

Key Points: Circumcision

- Primary phimosis is almost always resolvable during childhood without intervention; less than 1% of 17-year-old boys have phimosis.
- Indications to enhance preputial retractability include persistent primary phimosis, secondary phimosis, balanitis, posthitis, BXO, and UTIs.
- The American Academy of Pediatrics does not endorse routine circumcision.
- When neonatal circumcision is performed, local anesthesia is recommended.
- Circumcision should not be performed in neonates with other penile conditions that require surgical correction or micropenis.
- Circumcision has several potential benefits, including the prevention of penile cancer, UTI, sexually transmitted disease including HIV infection, balanitis, and phimosis.
- In boys with phimosis, topical application of corticosteroid cream loosens the phimotic ring in 70% to 80%.

bleeding is usually self-limiting or may require compression. Occasionally cautery with an ophthalmic cautery or silver nitrate stick or a suture may be necessary. Wound infection is another complication, but it is rare and antibiotic ointment (e.g., bacitracin) use after circumcision usually prevents this from occurring. Also, penile degloving due to excess amount of skin removed or the edges of the penile skin not adhering to the mucosal collar can occur after circumcision. The penile shaft will usually epithelize, bridging the defect without any intervention other than the use of antibiotic ointment to the denuded region and warm baths to prevent eschar formation. Immediate suturing of the skin edges and skin grafting are not recommended to bridge the gap.

Penile Skin Complications. The amount of penile skin excised can also lead to complications after circumcision. Insufficient or asymmetrical prepuce excision can result in a cosmetic and social dilemma for the parents and child, especially as the child gets older (Fig. 131–3A). **Unlike neonatal circumcision, circumcision revision requires general anesthesia.** Several techniques have been described (Redman, 1995; Brisson et al, 2002; Ching and Palmer, 2008a). Excessive skin excision can result in penile chordee, torsion, and lateral deviation. These conditions, if necessary to repair, may require penile skin flaps or Z-plasty for closure. Excessive skin removal can also result in a trapped penis from a cicatricial scar. The trapped penis can be managed with betamethasone (Palmer et al, 2005), vertical relaxation incision, and formal repair. The use of 0.05% betamethasone in conjunction with manual retraction in children with a trapped penis due to a dense cicatrix of the residual foreskin distal to the glans has a 79% success in softening of the cicatrix with easy exposure of the glans or mild persistence of the cicatrix amenable to vertical relaxation incision (Palmer et al, 2005). Surgical correction includes excision of the cicatrix with possible need for penile skin flaps or Z-plasty for closure.

Glanular Adhesions and Skin Bridges. Glanular adhesions and skin bridges, attachments of the glans and penile shaft, are also common complications associated with circumcision and are usually noticed by the caregiver or primary medical provider. **Both can occur in the well-circumcised penis and are usually the result of the physiologic retraction of the penis due to a suprapubic fat pad and diaper irritation of the penis.** Glanular adhesions are attachments between the inner prepuce or circumcision incision line attaching to the glans with an incidence decreasing with age owing to epithelial separation of the adhesions (71% of infants, 28% of 1- to 5-year-olds, 8% of 1- to 9-year olds, and 2% of children older than age 9 years) (Van Howe, 1997; Ponsky et al, 2000). **Persistent adhesions can be lysed in the office with the application of topical analgesia such as EMLA cream and Pain Ease (Gebauer Company; 1,1,1,3,3-pentafluoropropane, 1,1,1,2-tetrafluoroethane)** (Palmer, 2009b). **Use of low-dose corticosteroids has been relatively unsuccessful in lysing adhesions.** Skin bridges (Fig. 131–3B) are epithelized adhesions that can lead to penile chordee and torsion, which can be excised

in the office with the application of analgesia (Palmer, 2009b) or in the operating room with the use of general anesthesia and may require suturing of the glanular and shaft defects.

Meatal Stenosis. **Meatal stenosis is a condition that occurs in children almost only after circumcision during infancy** (Fig. 131–4A). It can be congenital, which occurs primarily in neonates with hypospadias, or acquired. **The normal urethral meatus is 10 French before 4 years of age, 12 French from 4 to 10 years of age, and 14 French after 10 years of age** (Litvak et al, 1976); **this can be calibrated with a bougie à boule or sound.** There are several proposed causes of secondary meatal stenosis. One theory is that after disruption of the normal adhesions between the prepuce and glans and removal of the foreskin a significant inflammatory reaction occurs, resulting in a severe meatal inflammation and cicatrix formation. Other theories are frenular devascularization or chronic meatitis from diaper irritation of the exposed, unprotected meatus (Persad et al, 1995; Hensle, 1996). BXO is another cause of meatal stenosis (see later). A relatively small percentage of children will develop symptomatic meatal stenosis after neonatal circumcision. **Symptoms include (1) typical urinary stream deviation in an upward direction resulting from a meatal baffle** (Fig. 131–4B) **or ventral web located at the inferior of the meatus, (2) a narrow, high-velocity stream, and (3) penile pain at the initiation of micturition.** Urinary tract imaging usually does not reveal any obstructive changes in the urinary tract without other urologic issues but may be indicated for associated UTI or urinary incontinence. Meatotomy or meatoplasty to treat secondary meatal stenosis can be performed in the office with the use of topical lidocaine and prilocaine (EMLA) (Cartwright et al, 1996) or under general anesthesia by making a ventral incision long enough to create a normal meatal caliber. The suturing of the urethral mucosa to the glans with fine, rapidly absorbable sutures tends to reduce the risk of recurrence.

Penile Trauma. The most serious complications associated with circumcision are penile trauma, including urethral injury, excision of the glans and/or penile shaft, and penile necrosis (see Fig. 131–3C). Urethral injury requires a urethroplasty with the technique dependent on the severity of the excision. **Excision of the glans can be repaired by suturing the excised tissue back to the penis without usually requiring the need for microscopic repair** (Sherman et al, 1996) **and with usually good results if performed within 8 hours.** Penile necrosis can result from thermal injury due to several causes, including cautery contacting the metal ring applied to the prepuce being excised or the inappropriate use of lasers to perform a circumcision. Several options are available without ideal outcomes, including penile reconstruction and female gender reassignment with bilateral orchiectomy (Gearhart and Rock, 1989; Bradley et al, 1998). Although the cosmetic and functional results of phallic reconstruction have advanced, they are still being refined (De Castro et al, 2007; Hoebeke et al, 2009). The issues with gender reassignment can include these children growing up with a male identity believed to result from in-utero and neonatal androgen imprinting (Reiner, 1996; Diamond and Sigmundson, 1997; Diamond, 1999).

Balanitis Xerotica Obliterans. **Lichen sclerosus et atrophicus, or BXO, is a chronic infiltrative and cicatrizing skin condition resulting in pathologic phimosis** (Chalmers et al, 1984) (Fig. 131–5). **BXO can also affect the glans and meatus, as well as the urethra.** The inability to retract the prepuce is the common presentation at puberty and is rare in children younger than 5 years of age (Oster, 1968). Other presenting symptoms include local infection, irritation, discomfort after micturition, bleeding, and occasionally acute urinary retention or urinary incontinence (Bale et al, 1987). Older patients and those with BXO involving the meatus may have a more severe clinical course (Gargollo et al, 2005). The etiology of BXO has not been determined; there is no identified viral or bacterial cause or familial predisposition. The association of BXO and penile cancer in children is also not established.

Treatment of BXO includes medical and surgical management. The use of topical corticosteroids has had limited benefit to treat mild BXO of the prepuce with minimal scar formation (Vincent and Mackinnon, 2005). **Circumcision is the preferred treatment along with meatotomy or meatoplasty if there is**

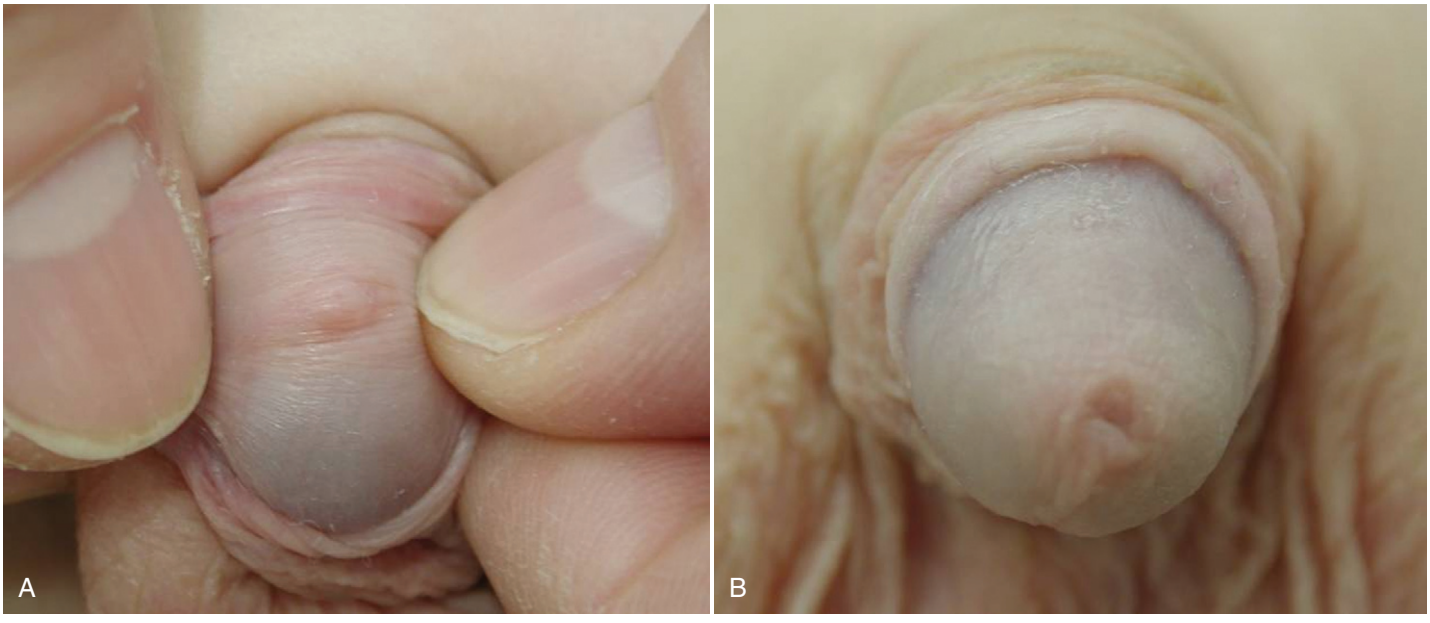


Figure 131–4. Meatal complications associated with circumcision. **A,** Meatal stenosis. **B,** Meatal baffle.

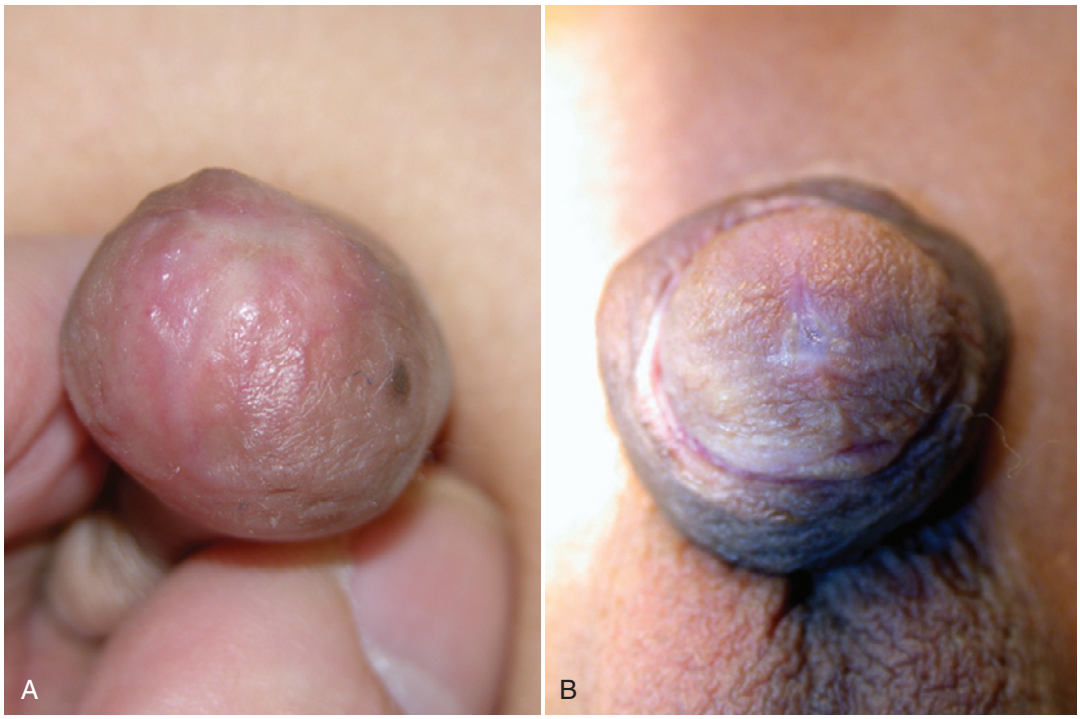


Figure 131–5. Balanitis xerotica obliterans of the prepuce **(A)** and meatus **(B)**. (Courtesy of Warren Snodgrass, MD.)

meatal involvement. Children with meatal involvement should be observed postoperatively because of the risk of recurrent meatal stenosis.

Key Points: Circumcision Complications

- The risk of complications after circumcision is 0.2% to 5%, with the most common complication being bleeding.
- Unlike neonatal circumcision, circumcision revision requires general anesthesia.
- Meatal stenosis is a condition that occurs almost only in children after circumcision in infancy.
- Unlike the treatment of primary phimosis, corticosteroid cream does not cause separation of secondary glanular adhesions after circumcision.
- The normal urethral meatus is 10 French before 4 years of age, 12 French from 4 to 10 years of age, and 14 French after 10 years of age.
- Lichen sclerosus et atrophicus or balanitis xerotica obliterans is a chronic infiltrative and cicatrizing skin condition resulting in pathologic phimosis.

Abnormal Penile Number

Aphallia

Penile agenesis results from failure of development of the genital tubercle (Roth et al, 1981) (Fig. 131–6). The disorder is rare and has an estimated incidence of 1 in 10 to 30 million births. **The karyotype almost always is 46,XY, and the usual appearance is that of a well-developed scrotum with descended testes and an absent penile shaft.** The anus is usually displaced anteriorly. The urethra often opens at the anal verge adjacent to a small skin tag, or it can open into the rectum. The incidence of stillbirth or neonatal death is approximately one third of cases (Gilbert et al, 1990).

Associated malformations are common and include cryptorchidism, vesicoureteral reflux, horseshoe kidney, renal agenesis, imperforate anus, and musculoskeletal and cardiopulmonary abnormalities (Skoog and Belman, 1989; Evans et al, 1999). The connection between the genitourinary and gastrointestinal tract is variable. Skoog and Belman (1989) reviewed 60 reports of aphallia and found that the more proximal the urethral meatus, the greater the likelihood of neonatal death and the higher the incidence of other anomalies. Sixty percent of patients had a postsphincteric meatus located on a peculiar appendage at the anal verge. This group of patients had the highest survival rate (87%) and the lowest incidence of other anomalies (1.2 per patient). Twenty-eight percent of patients had presphincteric urethral communications (prostatorectal fistula), and there was a 36% neonatal mortality rate. Twelve percent had urethral atresia and a vesicorectal fistula for drainage. This group had the highest incidence of other anomalies and a 100% mortality rate.

Children with this lesion should be evaluated immediately by a multidisciplinary approach. Testing should include a karyotype and other appropriate studies to determine whether there are associated malformations of the urinary tract or other organ systems. Magnetic resonance imaging (MRI) may be beneficial in determining the severity of the defect (Lapointe et al, 2001). Prompt gender assignment is important. Some of these patients have a male gender identity despite reconstruction as a female, presumably because of in-utero or postnatal sex steroid imprinting (Reiner, 1996; Diamond and Sigmundson, 1997; Diamond, 1999).

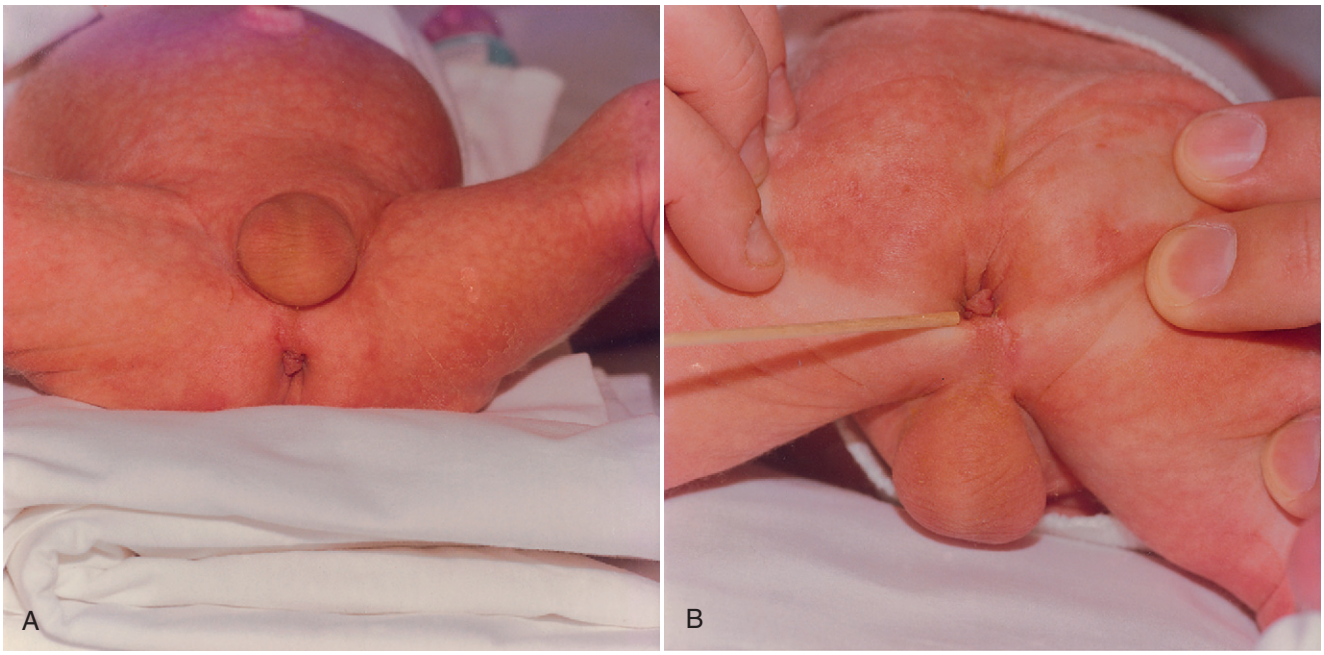


Figure 131–6. **A**, Neonate with aphallia. **B**, Urethral meatus at skin tag on anal verge.

Consequently, the recommendation to perform gender reassignment should be made carefully and only after full evaluation by an ambiguous genitalia assessment team and parental counseling. As a male the patient would potentially be fertile, but currently there is an inability to construct a cosmetically acceptable phallus that would allow normal urinary, sexual, and reproductive function (De Castro et al, 2007; Hoebeke et al, 2009). Gender reassignment involves orchiectomy and feminizing genitoplasty in the neonatal period (Gluer et al, 1998; Bruch et al, 1996). At a later age, construction of a neovagina is necessary. Urinary tract reconstruction with simultaneous construction of an intestinal neovagina through a posterior sagittal and abdominal approach in patients with penile agenesis has been described (Hensle and Dean, 1992; Hendren, 1997).

Diphallia

Duplication of the penis is a rare anomaly with an incidence of 1 in 5 million live births (Hollowell et al, 1977) **and has a range of appearances from a small accessory penis to complete duplication** (Gyftopoulos et al, 2002). In some cases, each phallus has only one corporeal body and urethra, whereas others seem to be a variant of twinning, with each phallus having two corpora cavernosa and a urethra. The penises are usually unequal in size and lie side by side. Other associated anomalies are common, including hypospadias, bifid scrotum, bladder duplication, renal agenesis or ectopia, and diastasis of the pubic symphysis (Maruyama et al, 1999). Anal and cardiac anomalies are also common. **Evaluation should include imaging of the entire urinary tract, including a renal ultrasonogram and voiding cystourethrogram.** Ultrasonography and MRI can also be done to assess penile development (Marti-Bonmati et al, 1989; Lapointe et al, 2001). The etiology has not been delineated. Treatment must be individualized with consideration of the associated anomalies with the goal of attaining a satisfactory functional and cosmetic result (Dean and Horton, 1991).

Inconspicuous Penis

An inconspicuous penis refers to a penis that appears to be small with a normal stretched penile length measured from the pubic symphysis to the tip of the glans (see Table 131–2) **and normal diameter of the penile shaft** (Bergeson et al, 1993). This condition can be congenital or acquired and is usually of great concern for parents. Several entities are included in this disorder, including buried penis, trapped penis, and webbed penis (Palmer and Kogan, 1995). **These conditions must be differentiated from micropenis, in which the penis is abnormally small.** When an infant has an inconspicuous penis, prompt evaluation is necessary for proper treatment and the family must be informed as to whether the penis is or is not normal. The stretched penile length should be measured from the pubic symphysis to the tip of the glans. In addition, the diameter of the penile shaft may be measured by palpation.

Buried Penis

A buried penis, also referred to as hidden or concealed penis, is a form of inconspicuous penis (Cromie et al, 1998). A buried penis is a normally developed penis that is hidden away by the suprapubic fat pad. **This condition can be classified into three categories based on etiology for the concealment** (Maizels et al, 1986; Casale et al, 1999): **(1) poor penopubic fixation of the skin at the base of the penis, (2) obesity, and (3) a trapped penis from cicatricial scarring after penile surgery, typically a circumcision.**

The congenital form of buried penis is believed to be due to the inelasticity of the dartos fascia, which normally allows the penile skin to slide freely on the deep layers of the shaft, with restricted extension of the penis because the penile skin is not anchored to the deep fascia (Fig. 131–7). The acquired form from obesity typically seen in older children and adolescents is due to abundant fat on the abdominal wall hiding the penile shaft. The other acquired form, a trapped penis, results from embedding of the penis in the

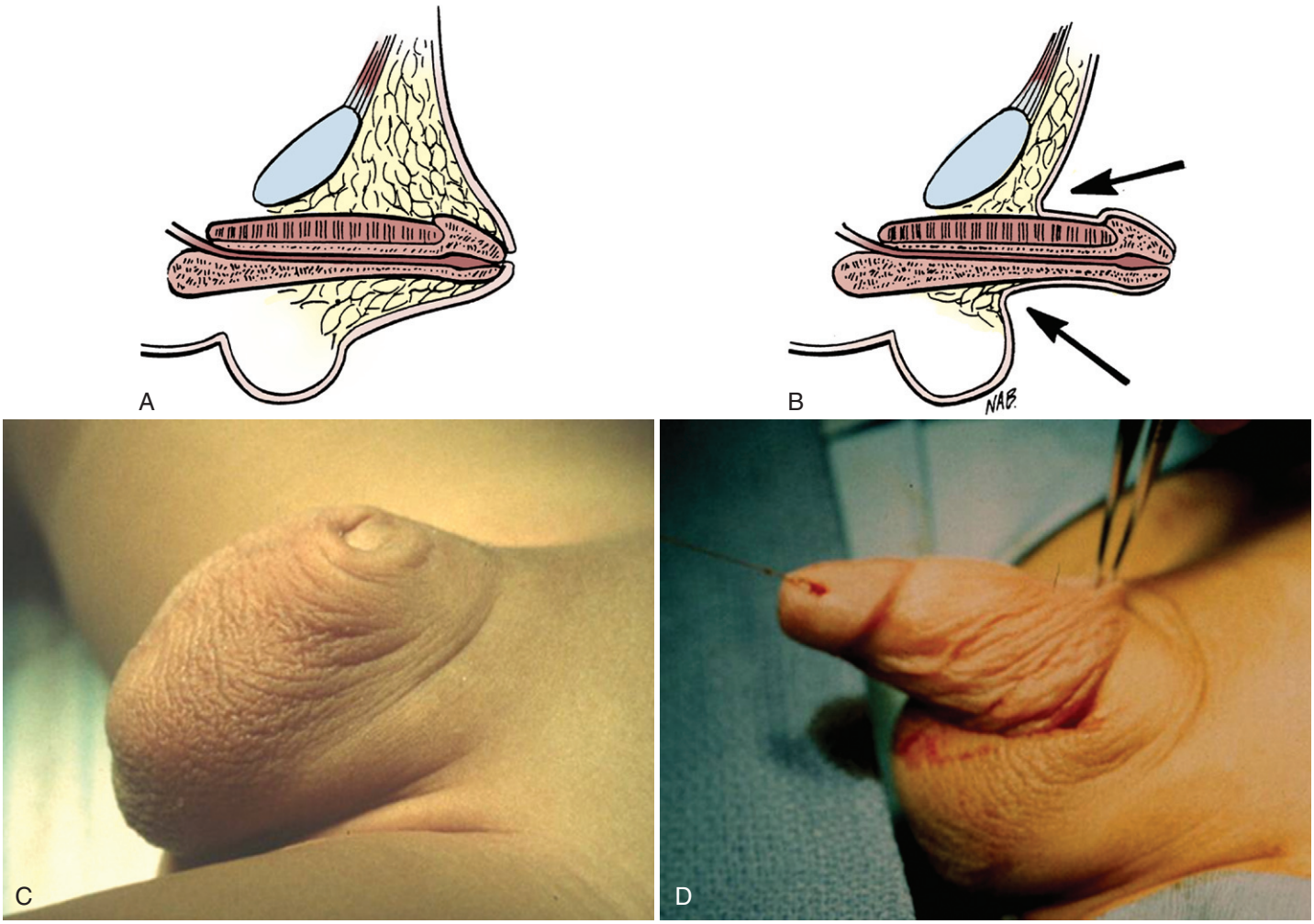


Figure 131–7. Buried penis (**A** and **C**), which may be visualized by retraction of the skin lateral to the penile shaft (**B** and **D**).

suprapubic fat pad from scar formation over the glans. This deformity may occur after neonatal circumcision in an infant with significant scrotal swelling due to a hernia or hydrocele or after routine circumcision in an infant with a webbed penis. Also, in some neonates the penile shaft seems to retract naturally into the scrotum; and if circumcision is performed in this situation, the skin at the base of the penis may form a cicatrix over the retracted phallus. This condition should be differentiated from a transient buried penis resulting from a large suprapubic fat pad noted in early childhood that resolves with increased age and ambulation (Eroglu et al, 2009).

On examination, a buried penis must be differentiated from a micropenis, with the latter not having a normal penile stretched length. The clinician should determine whether the glans can be exposed by retracting the skin covering the glans (see Fig. 131–7). If so, it remains the surgeon's judgment whether correction is warranted. However, if the penis is trapped by physiologic phimosis in the uncircumcised or cicatricial scarring (Fig. 131–8A) in the circumcised penis, this increases the chance of difficulty voiding, maintaining proper hygiene, balanitis, UTIs, and psychosocial issues (Fig. 131–8B) (Kon, 1983).

The treatment options for children with buried penis are based on etiology. Patients with buried penis secondary to obesity should have the underlying condition treated. Referral of the child back to the primary care provider for a weight loss and exercise program is essential, with surgical intervention usually not necessary. Young children with secondary cicatricial scarring after penile surgery can be managed with forceful dilation of the cicatrix with a fine hemostat in the office after the application or injection of analgesia. Another option is the combination of topical betamethasone and manual retraction (Palmer et al, 2005). This combination may result in complete resolution of the condition in the majority of boys or may release the closing cicatrix and allow for a simple incision of the constricting phimotic ring, thus reducing the need for formal surgical repair by 79%. If topical corticosteroid application is ineffective, correction under general anesthesia is necessary with the usually recommendation of elective repair when the child is at least 6 months of age. The surgical technique is similar to that for the congenital buried penis.

A number of surgical techniques have been described to correct the buried penis (Maizels et al, 1986; Casale et al, 1999; Elder, 2001; Frenkl et al, 2004; Gillett et al, 2005; Borsellino et al 2007; Karapetian and Palmer, 2007). The indications and timing for reconstructive surgery are controversial. In moderately severe cases the dysgenic bands of tissue, which are located primarily on the dorsal surface of the shaft of the penis, must be removed. The prepuce should be unfurled and used for ventral skin coverage. In addition, the subcutaneous tissue on the dorsal aspect of the penis should be fixed to the pubic fascia and then the subcutaneous tissue of the scrotum should be fixed to the ventral aspect of the

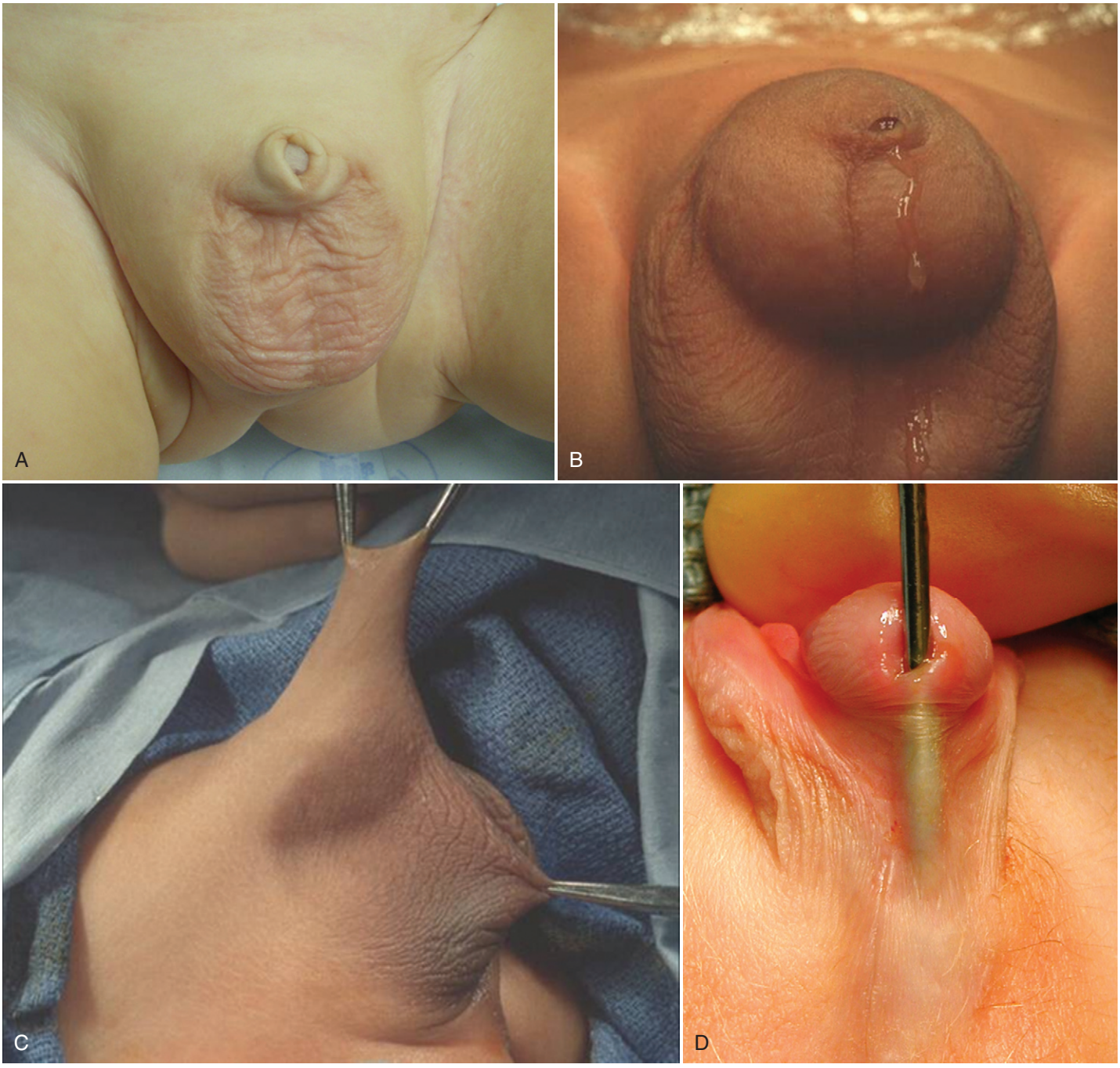


Figure 131–8. Inconspicuous penis. **A,** Trapped penis by cicatricial scarring resulting from neonatal circumcision. **B,** Urine pooling due to cicatricial scarring, increasing susceptibility to urinary tract infections. **C,** Penoscrotal web resulting in a webbed penis. **D,** Webbed penis with hypoplastic distal urethra.

base of the penile shaft with nonabsorbable suture. During correction one must be careful to avoid injury to the neurovascular bundles (Baskin, 1999; Baskin et al, 2000). Skin coverage can also be accomplished by penoscrotal Z-plasty, lateral penile shaft Z-plasty, island pedicle of ventral preputial skin, or a skin graft. Rarely in the most severe cases the suspensory ligament of the penis must be divided, the suprapubic fat excised, and the spermatic cords protected. Liposuction has been reported to be helpful in severe cases (Maizels et al, 1986; Shenoy et al, 2000). However, this technique should be reserved for adolescent boys because prepubertal boys may lose their fat pad with somatic growth.

Webbed Penis

Webbed penis, also known as penoscrotal fusion, is a congenital or acquired condition resulting from the scrotal skin extending onto the ventrum of the penis. The congenital form of a penoscrotal web represents an abnormality of the attachment between the penis and the scrotum, whereas the penis, urethra, and remainder of the scrotum are normal (Fig. 131–8C). The acquired condition results from circumcision or other penile surgery due to excessive removal of ventral penile skin.

Although the penoscrotal web is usually asymptomatic, the cosmetic appearance is often unacceptable. There are several

surgical techniques that can be implemented to correct this condition. Similar to the treatment of a buried penis, one technique involves the fixation of the subcutaneous tissue of the scrotum to the ventral aspect of the base of the penile shaft with nonabsorbable suture. On occasion, this condition may be corrected by incision of the web transversely, separation of the penis from the scrotum, and closure of the skin vertically. In other cases a circumferential incision is made 1.5 cm proximal to the coronal sulcus, a Byar preputial skin flap is transferred to the ventral surface of the penis, and the redundant foreskin is excised. In rare cases the distal urethra is hypoplastic, necessitating urethral reconstruction (Fig. 131–8D).

Micropenis

Micropenis is a normally formed penis that is at least 2.5 standard deviations (SD) below the mean size in stretched length for age (Aaronson, 1994) (Fig. 131–9). The ratio of the length of the penile shaft to its circumference is usually normal, but occasionally the corpora cavernosa are severely hypoplastic. The testes are usually small and frequently cryptorchid, whereas the scrotum is usually fused and often diminutive.

Stretched penile length is used because it correlates more closely with erectile length than does the relaxed penile length. The measurements should be compared with standards for penile length (see Table 131–2). Stretched penile length is determined by measuring the penis from its attachment to the pubic symphysis to the tip of the glans. One must be careful to depress the suprapubic fat pad completely to obtain an accurate measurement, especially in an obese infant or child. **In general, the penis of a full-term neonate should be at least 1.9 cm long.** One must differentiate buried penis or webbed penis from the micropenis, with the former having a normal penile shaft.

Micropenis results from a hormonal abnormality that occurs after 14 weeks of gestation. Differentiation of the male external genitalia is complete by the 12th week of gestation and requires a normal testis producing testosterone, stimulated by maternal human chorionic gonadotropin (hCG). During the second and third trimesters, growth of the penis occurs under the direction of fetal androgen, which is controlled by the secretion of fetal luteinizing hormone (LH). An abnormality in the production or use of testosterone results in a small penis and hypospadias, whereas a true micropenis often seems to be a consequence of a deficiency of gonadotropic hormones.

The causes of micropenis are numerous (Table 131–4) and include isolated gonadotropin defects without involvement of other organ systems and generalized endocrinopathies that may be associated with central nervous system defects. **The most common causes of micropenis are hypogonadotropic hypogonadism, hypergonadotropic hypogonadism (primary testicular failure), and idiopathic** (Lee et al, 1980b). Furthermore, micropenis is often associated with major chromosomal defects, including Klinefelter syndrome (47,XXY) and other X polysomy syndromes, deletions, translocations, and trisomy involving chromosomes 8, 13, and 18 (Aaronson, 1994).



Figure 131–9. Micropenis resulting from hypogonadotropic hypogonadism.

Table 131–4.

Etiology of Micropenis

Deficient Testosterone Secretion
Hypogonadotropic hypogonadism
Isolated, including Kallmann syndrome
Associated with other pituitary hormone deficiencies (e.g., CHARGE association)
Prader-Willi syndrome
Laurence-Moon syndrome
Bardet-Biedl syndrome
Rud syndrome
Primary hypogonadism
Anorchia
Klinefelter syndrome and poly X syndrome
Gonadal dysgenesis (incomplete)
Luteinizing hormone receptor defects (incomplete)
Genetic defects in testosterone steroidogenesis (incomplete)
Noonan syndrome
Down syndrome
Robinow syndrome
Bardet-Biedl syndrome
Laurence-Moon syndrome
Defects in Testosterone Action
Growth hormone/insulin-like growth factor 1 deficiency
Androgen receptor defects (incomplete)
5α-Reductase deficiency (incomplete)
Fetal hydantoin syndrome
Developmental Anomalies
Aphallia
Cloacal exstrophy
Idiopathic
Associated with Other Congenital Malformations

Modified from Bin-Abbas B, Conte FA, Grumbach MM, Kaplan SL. Congenital hypogonadotropic hypogonadism and micropenis: effect of testosterone treatment on adult penile size—why sex reversal in not indicated. J Pediatr 1999;134:579.

The most common cause of micropenis is hypogonadotropic hypogonadism, which is the failure of the hypothalamus to produce an adequate amount of gonadotropin-releasing hormone (GnRH). This condition may result from hypothalamic dysfunction, which can occur in Prader-Willi syndrome, Kallmann syndrome (genital-olfactory dysplasia), Laurence-Moon-Biedl syndrome (Walsh et al, 1978; Danish et al, 1980), and the CHARGE association (Ragan et al, 1999). Other causes include an associated growth hormone deficiency or neonatal hypoglycemia secondary to congenital hypopituitarism, congenital pituitary aplasia, and midline brain defects, such as agenesis of the corpus callosum and occipital encephalocele.

Primary testicular failure is another cause of micropenis. Micropenis secondary to hypergonadotropic hypogonadism may result from rudimentary testes syndrome or gonadal dysgenesis. It also occurs in Robinow syndrome (Lee et al, 1980b). **The test most frequently used to identify this subgroup is the failure of serum testosterone concentration to rise appropriately after stimulation by hCG.** However, in patients with Kallmann syndrome and cryptorchidism, the serum testosterone level may not increase after the administration of hCG. Rarely, a patient with partial androgen insensitivity syndrome has micropenis, but sexual ambiguity is more common. Micropenis may also result from improper timing or delayed onset of gonadotropin stimulation in the fetus (Lee et al, 1980a). These patients have an idiopathic form of micropenis and a normal hypothalamic-pituitary-testicular axis.

The initial evaluation of a child with micropenis should include a thorough medical history and a karyotype at birth. Accurate measurement of the penile length, palpation of the corporeal bodies, and evaluation for cryptorchidism are several important aspects of the physical examination. Consultation with a pediatric endocrinologist is also usually obtained to assist in the determination of the cause of the micropenis and to assess whether other abnormalities are also present. Several issues need to be addressed, including the growth potential of the penis and the etiology of the micropenis. The etiology may be testicular or central (hypothalamic-pituitary axis). **Testicular function may be assessed by measuring serum testosterone levels before and after hCG stimulation. Primary testicular failure produces an absent response and elevated basal concentrations of LH and follicle-stimulating hormone (FSH).** In some cases, a GnRH stimulation test is also performed. Anterior pituitary screening tests include serial measurements of serum glucose, sodium, potassium, and serum cortisol concentrations and thyroid function tests. The endocrine evaluation of patients with micropenis is not standardized. MRI of the head should be done to determine the anatomic integrity of the hypothalamus and the anterior pituitary gland as well as the midline structures of the midbrain.

Before extensive evaluation of the hypothalamic-pituitary-testicular axis, androgen therapy should be administered to determine the end organ response. In general, intramuscular testosterone enanthate is given for 3 months. Although prolonged treatment might advance skeletal maturation, short courses of treatment do not affect height. Transdermal testosterone also has been used in these patients (Choi et al, 1993). If androgen treatment in a neonate successfully increases the penis so that its size falls within the normal range, the effects at puberty have not been clearly delineated. In a mouse model of hypogonadotropic hypogonadal micropenis there was evidence that significant prepubertal exposure of the penis to androgens reduced the ultimate growth response to androgens (Husmann and Cain, 1994; McMahon et al, 1995). Bin-Abbas and coworkers (1999) described eight boys with micropenis who were treated with androgens both at birth and at puberty. The final penile stretched length averaged 10.3 cm and was in the normal range in all cases. Therefore, exogenous stimulation at birth and at puberty with testosterone enanthate seems most reasonable (Tietjen et al, 1998) and is recommended until longer-term studies are available.

If the penis does not respond to testosterone, gender reassignment is an option but is controversial. Previously, gender reassignment was recommended, but this position has more recently come under criticism owing to the implication that biologic factors during the prenatal period may have an impact in gender identity. One of the factors is testosterone-induced male brain imprinting (Diamond and Sigmundson, 1997). Therefore, the lack of long-term data regarding the risks and benefits of reassigning these patients to a female gender (Calikoglu, 1999; Diamond, 1999) has resulted in a conservative use of this treatment modality. Husmann (2004) described 20 adult men born with micropenis who had a suboptimal response to testosterone therapy and were raised as males. At adulthood, 90% had a micropenis and all had a male gender identity; five were undergoing psychiatric counseling for fear of rejection, and eight had not been sexually active.

Several studies have demonstrated that although ultimate penile size may not be within a normal range, men born with micropenis have a male gender identity and the majority can have satisfactory sexual function. Reilly and Woodhouse (1989) described 20 patients with a primary diagnosis of micropenis in infancy. Almost all had received androgen therapy during childhood, but none of the adults had a penis within the normal range of size. All of the boys stood to urinate. Parents of patients in the prepubertal group considered their children to be normal boys and thought that the penile appearance was satisfactory; however, they expressed concern about penile size and future sexual function. All of the patients in the adult group had a strong male identity, and 9 of the 12 patients were sexually active. In a study of 22 adult men born with micropenis, Lee and Houk (2004) had similar findings. Wisniewski and Migeon (2002) reported that their patients had a male gender identity but were generally dissatisfied with their genital appearance and function.

Key Points: Micropenis

- Micropenis is a normally formed penis that is at least 2.5 SD below the mean size in stretched length for age (i.e., <1.9 cm in a term neonate). A buried penis must be differentiated from a micropenis, with the former having a normal penile stretched length.
- The most common causes of micropenis are hypogonadotropic hypogonadism, hypergonadotropic hypogonadism (primary testicular failure), and idiopathic.
- Evaluation includes karyotype; determination of serum LH and FSH concentrations; measurement of testosterone levels before and after hCG stimulation; serum studies of anterior pituitary function; MRI of the head to assess the hypothalamus, anterior pituitary, and midbrain; and assessment of penile growth after androgen stimulation.
- If the penis does not respond to testosterone, gender reassignment is an option, but this is controversial.
- In adulthood, most men born with micropenis have male gender identity and satisfactory sexual function, even if penile size is less than what is considered in the normal range.

Abnormal Penile Orientation

Penile Curvature

Curvature of the penis may occur along the vertical (i.e., ventral or dorsal direction) or horizontal (i.e., lateral direction) plane of the penis. Penile curvature may be congenital or acquired from circumcision, other penile surgery, or trauma and has cosmetic significance and future sexual difficulties. **Penile curvature is most commonly in the ventral direction, referred to as *chordee*, and is commonly associated with hypospadias.** However, chordee may occur without hypospadias and with or without a dorsal hood of prepuce (Fig. 131–10) and is commonly associated with a deficiency of the ventral skin (Cendron and Melin, 1981). Ventral curvature in boys without hypospadias can generally be corrected by degloving of the penis, excision of fibrous tissue that is usually confined to the region superficial to Buck fascia, and development of a Byar flap for penile skin coverage as necessary. In more severe cases, simple dorsal plication, Nesbit dorsal excision, or corporeal rotation may be necessary. In the most severe cases the urethra is short and urethral reconstruction, for example, an interposition island flap of dorsal foreskin, must be performed. Intraoperative artificial erection with injectable normal saline may be necessary to confirm that complete chordee correction has been performed. Some cases of chordee may be aggravated by a prominent frenulum, resulting in distal penile chordee with ventral glanular deflection. In these cases, frenulotomy will improve and may correct the chordee.

Congenital dorsal penile curvature may be an isolated condition with or without asymmetrical penile skin or associated with epispadias and a ventral hood of prepuce. Some individuals may have hypospadias. Surgical repair of this condition without associated urethral anomalies is similar to chordee correction, involving degloving of the penis, excision of fibrous tissue that is usually confined to the region superficial to Buck fascia, and development of skin flaps for penile skin coverage as necessary. During correction, one must be careful to avoid injury to the neurovascular bundles (Baskin, 1999; Baskin et al, 2000). More severe cases involve plication and/or excision of ellipses from the ventral corporeal bodies. Intraoperative artificial erection may be necessary.

Lateral penile curvature is usually congenital and caused by overgrowth or hypoplasia of one corporeal body. However, asymmetrical penile skin excision or postoperative scarring after circumcision or other penile surgery may also be a secondary cause. Lateral penile curvature may be unrecognized until later in childhood because the penis is normal when flaccid and only recognized as being curved with an erection. Surgical repair of congenital lateral penile curvature involves degloving the penis and performing a plication and/or excision of ellipses from the corporeal bodies from the site of maximum curvature to allow straightening of the penis. Secondary lateral penile curvature follows the same principles as for vertical curvature with degloving of the penis, excision of fibrous tissue that is usually confined to the region superficial to the Buck fascia, and development of skin flaps for penile skin coverage as necessary. Intraoperative artificial erection may be necessary.

Penile Torsion

Penile torsion is a rotational deformity of the penile shaft usually in the counterclockwise direction (i.e., to the left side) (Fig. 131–11). In most cases, penile size is normal and the condition is unrecognized until circumcision is performed or until the foreskin is retracted. Penile torsion may also be associated with hypospadias, chordee, and other abnormalities involving the penile skin shaft, such as dorsal hood deformity without a urethral abnormality. In most cases of penile torsion the median raphe spirals obliquely around the shaft and inserts atypically rather than at the base of the glans below the urethral meatus. The etiology of penile torsion has not been clearly delineated but may be due to an anomalous arrangement of penile shaft skin.

Most forms of penile torsion are mild, are less than 60 degrees, and are of primarily cosmetic significance, with correction typically necessary only if the rotation is at least 60 to 90 degrees from the midline. If surgical repair is being considered, neonatal circumcision is discouraged because it can be performed at the time of penile detorsion. Although the glans may be directed more than 90 degrees from the midline, the orientation of the corporeal bodies and the corpus spongiosum at the base of the



Figure 131–10. Penile chordee and dorsal hood of foreskin without hypospadias.



Figure 131–11. Penile torsion. Patient also has redundant penile skin after a neonatal circumcision.

penis is normal. In mild forms of penile torsion, correction typically involves degloving the penile skin, rotating the glans in the direction opposite to the defect (i.e., clockwise rotation for a counterclockwise abnormality), and suturing the glans to the penile skin, resulting in a glans in a normal configuration (Bar-Yosef et al, 2007). In some instances the median raphe may take a very serpentine direction, preventing restoration to a normal position, which is not critical as long as the meatus has a normal configuration. However, in boys with penile torsion of 90 degrees or more, simple rearrangement of the skin on the shaft of the penis is insufficient. Instead, the base of the penis must be mobilized so that dysgenic bands of fibrous tissue can be identified and incised. If the penis still remains rotated, correction may be accomplished by placing nonabsorbable anchoring sutures at the base of the corpora cavernosa (Pomerantz et al, 1978; Slawin et al, 1992; Elder, 2001). Other surgical techniques have been described, including the use of a dorsal dartos flap (Bauer et al, 2009) and mobilization of the urethral plate and urethra (Bhat et al, 2009).

Penile Masses

Penile cysts, congenital or acquired, are the most common penile masses in children. A history of onset, previous surgery, and changes in appearance or size are important in the evaluation of these lesions.

Parameatal Urethral Cyst

The parameatal urethral cyst is another rare anomaly and appears as a small blister in proximity to the urethral meatus (Fig. 131–12A). Shiraki (1975) suggested that these cysts may result from occlusion of paraurethral ducts or in other cases from faulty preputial separation from the glans along the coronal sulcus. The cyst wall may consist of transitional and squamous as well as columnar epithelium. Treatment is complete excision of the cyst under anesthesia, with care taken not to cause meatal stenosis.

Inclusion Cysts

The most common acquired cystic lesion of the penis is smegma under the unretractable prepuce. The mass may appear yellow due to smegma. The prepuce usually does not need to be retracted because it almost always retracts on its own with time. **Epidermal inclusion cysts may form after penile surgery, including circumcision and hypospadias repair, owing to islands of epithelium within the subcutaneous tissue** (Fig. 131–13). Excision of the epidermal inclusion is recommended.

Cyst of the Median Raphe

Congenital epidermal cysts tend to form along the median penile raphe on the glans or penile shaft, scrotum, or perineum (see Fig. 131–12B and C) (Little et al, 1992; Krauel et al, 2008). These congenital lesions may result from epithelial rests that become buried during the urethral infolding process. Excision with the use of general anesthesia is recommended unless the cysts are small and asymptomatic.

Congenital Penile Nevi

Congenital penile nevi are pigmented lesions that can form on the glans and penile shaft (Fig. 131–14). Nevi can be classified based on the location of melanocytes: dermal (involving only the dermis), junctional (involving only the dermal-epidermal junction), and compound (involving the dermis and dermal-epidermal junction). **They tend to be superficial and benign and should be excised** (Papali et al, 2008).

Juvenile Xanthogranulomas

Juvenile xanthogranulomas is an uncommon benign, self-limiting lesion of the penis predominantly seen in infancy or early childhood. These lesions appear as solitary or multiple pigmented (yellow, orange, gold, brown, or red) nodules of rapid onset. They measure 2 to 20 mm in diameter and are well

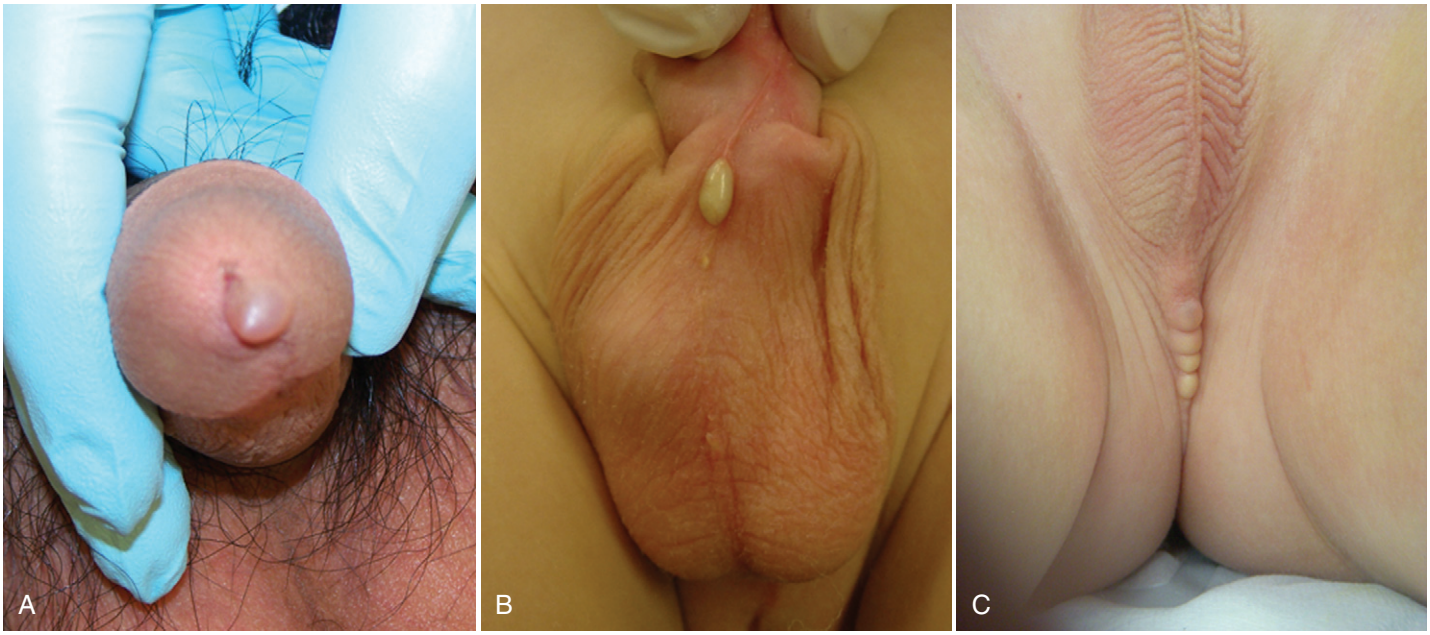


Figure 131–12. Penile cysts. **A,** Parameatal urethral cyst appearing as a small blister. **B,** Cyst of the penoscrotal junction raphe. **C,** Cysts of the perineal raphe.

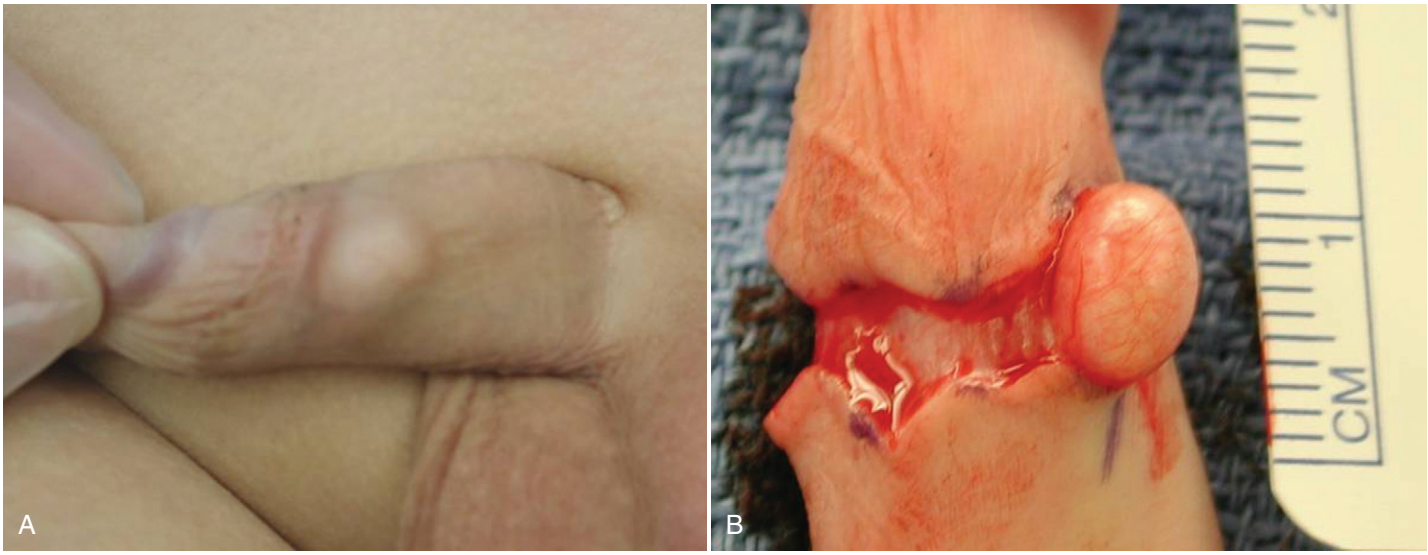


Figure 131–13. **A,** Epidermal inclusion cyst acquired after neonatal circumcision. **B,** Cyst exposed and excised intact through an incision of the circumcision scar.



Figure 131–14. Congenital penile nevus on the penile shaft.

demarcated, firm, and rubbery. These lesions can affect the penis (Hautmann and Bachor, 1993; Bradford and Choudhary, 2009) or scrotum (Goulding and Traylor, 1983; Dehner et al, 2003) with as many as 20% being present at birth. The lesion is often self-limited, and a period of 1 year of expectant monitoring is advised to avoid potentially unnecessary ablative genital surgery.

Accessory Urethral Openings

Congenital Urethral Fistula

Normally the urethral meatus is located at the tip of the glans, but accessory urethral openings may rarely occur. **Congenital urethral fistula is a condition whereby the urethra and meatus are normal and a urethrocutaneous fistula is present, typically located in the coronal or subcoronal position. This abnormality is usually an isolated deformity** (Tennenbaum and Palmer, 1994), **but it may be associated with imperforate anus or ventral chordee** (Ritchey et al, 1994). In a series of 14 boys with a congenital fistula, 4 had distal hypospadias and 2 had chordee (Caldamone et al, 1999). The etiology is unknown but may involve a focal defect in the urethral plate that prevents fusion of the urethral folds. Some patients have undergone circumcision before diagnosis (Caldamone et al, 1999), raising the possibility that the fistula may have been iatrogenic rather than congenital in some of these cases. Treatment usually consists of one of two techniques: the fistula can be circumscribed and then closed in multiple layers, similar to a urethrocutaneous fistula after hypospadias repair; or if the glans bridge is thin, the ventral glans can be opened through the distal urethra and the distal urethra is then closed by a Thiersch-Duplay tubularization or incision of the urethral plate and tubularization.

Urethral Duplication

Urethral duplication is another rare congenital anomaly, with roughly 200 cases reported in the literature (Salle et al, 2000; Slavov et al, 2007). **The duplication most commonly occurs in the sagittal plane with one urethra located ventrally and the other dorsally** (Fig. 131–15). **Collateral urethral duplication in which urethral duplication occurs in the same horizontal plane is extremely rare** (Ching and Palmer, 2008b). In a series by Salle and colleagues (2000), sagittal plane duplication accounted for 94% of urethral duplication. Usually the dorsal urethra is considered the accessory urethra with or without a urinary stream while the ventral urethra contains the urine stream and the anatomic landmarks such as the external sphincter and verumontanum. The most commonly used classification of urethral duplication is that of Effman (Fig. 131–16), which categorizes the sagittal urethral duplication into three types: types I and II distinguish between partial and complete urethral duplication, whereas type III describes urethral duplication as part of bladder duplication (Effman et al, 1976). The embryology of urethral duplication is not well established, with

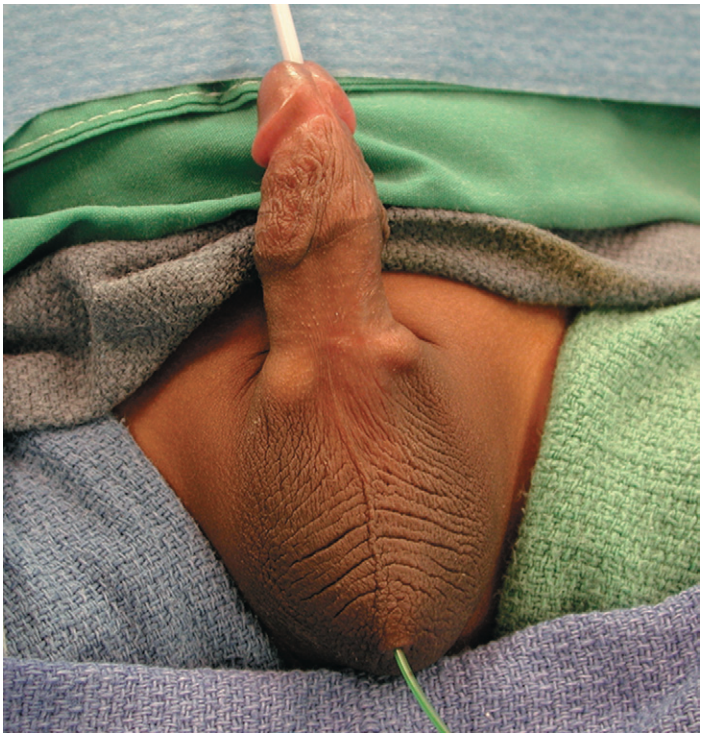


Figure 131–15. Urethral duplication with catheters through meatus at tip of the glans penis and at perineum.

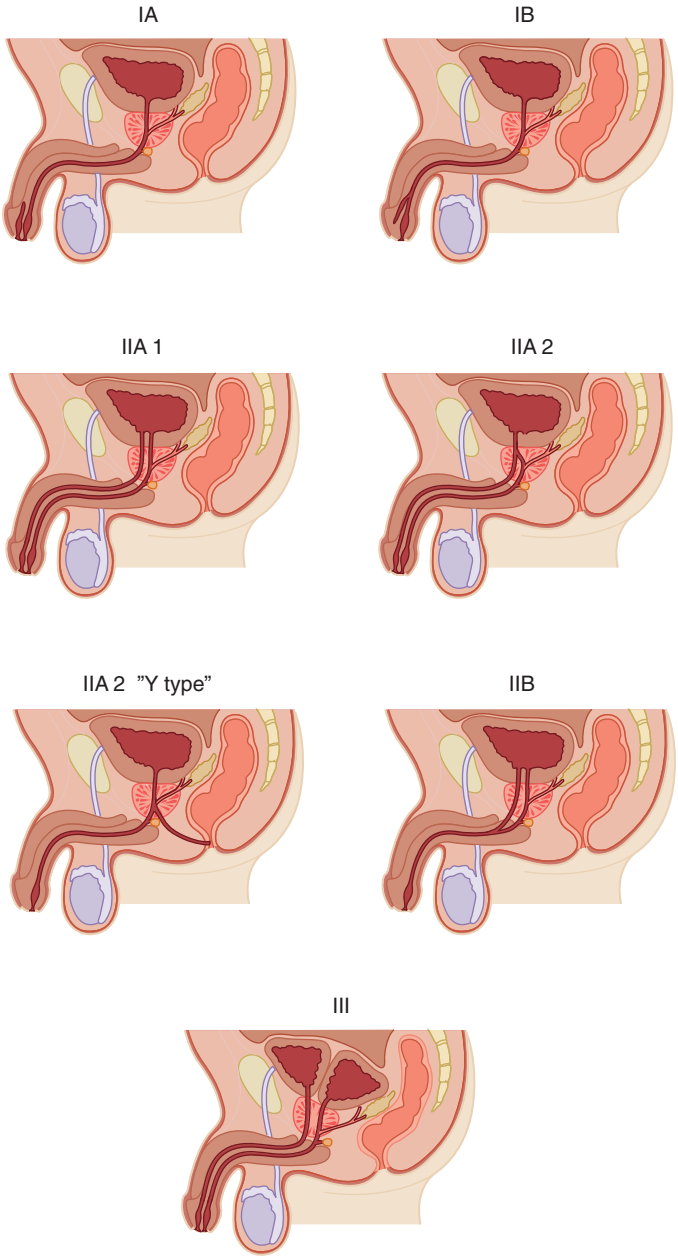


Figure 131–16. Effman classification.

explanations including ischemia (Woodhouse and Williams, 1979; Podesta et al, 1998) and abnormal müllerian duct termination (Das and Brosman, 1977). Effman and coworkers (1976) suggested caudal duplication may be related to division of the notochord with subsequent formation of two hindguts, allantoises, and cloacae.

Anomalies have been described in the genitourinary, gastrointestinal, and musculoskeletal system. In the review by Podesta and colleagues (1998), 6 of 7 patients with urethral duplication had other associated anomalies, with vesicoureteral reflux being the most common. Other anomalies included renal agenesis, bilateral cryptorchidism, sacral agenesis, imperforate anus, tracheoesophageal fistula, and radial hypoplasia. There appears to be an association with other midline defects such as duplicated bladder, duplicated colon, imperforate anus and anorectal agenesis, bifid glans, thoracic hemivertebrae, and partial sacral agenesis (Woodhouse and Williams, 1979; Fenster et al 1980; Kennedy et al, 1988; Salle et al, 2000).

The most common presentation of urethral duplication is a double meatus and double urinary stream (Kennedy et al, 1988; Urakami et al, 1999; Salle et al, 2000). Incontinence and recurrent UTIs are other common presentations. Less common conditions include penile chordee and urinary obstruction secondary to a mucosal flap at the urethral bifurcation acting as an occluding valve during voiding (Effman et al, 1976; Das and Brosman, 1977; Salle et al, 2000). The presence of incontinence is dependent on the site of origin of the accessory urethra, with the more proximal the site of urethral duplication, the higher the incidence and the greater the degree of incontinence (Farrell and Sparnon, 1987).

Patient evaluation should include a voiding cystourethrogram, retrograde urethrogram, and direct visualization of the anatomy during cystourethroscopy. Evaluation of the other associated anomalies should also be performed. Treatment of urethral duplication is usually reserved for the symptomatic child (Urakami et al, 1999). Cosmesis alone, however, has been advocated by some as a valid indication for intervention (Middleton and Melzer, 1992). The accessory urethra should not be used as the primary urethra secondary to being hypoplastic with the risk of inadequate urine flow (Salle et al, 2000). Surgical repair includes complete accessory tract excision, electrofulguration or injection of sclerosing agents into the accessory tract, septotomy if the septum between the two urethras is thin, and urethrourethrostomy of the accessory tract into the functional urethra. Management is dependent on the anatomy of the urethral duplication (Farrell and Sparnon, 1987; Podesta et al, 1998).

Genital Lymphedema

Lymphedema of the genitalia, congenital or acquired, is a disfiguring disorder characterized by impaired lymphatic drainage that causes progressive penile or scrotal swelling. Congenital lymphedema may be sporadic (85%) or inherited (15%) and can be expressed at various ages (McDougal, 2003). Milroy disease is an autosomal-dominant inherited trait, whereas Meige disease is probably autosomal dominant with variable penetrance and occurs in the first or second decade (Wheeler et al, 1981). If the genital lymphedema occurs at puberty and is sporadic, it is termed *lymphedema praecox*. Approximately 80% of patients with congenital lymphedema demonstrate onset of the disease at puberty (McDougal, 2003). The lymphedema may involve the penis, scrotum, or both. Congenital lymphedema has been associated with several syndromes, including Turner, Noonan, Klinefelter, and intestinal lymphangiectasia syndromes. Lower extremity involvement may occur in many individuals with congenital lymphedema.

Initial management involves observation, but surgical therapy is necessary if the lymphedema remains significant or progresses. The goal of surgical treatment is to remove all involved tissue. On the penile shaft, the penis is degloved and all tissue between Buck fascia and the skin as well as redundant penile skin must be excised. If the patient is uncircumcised, the prepuce may be unfurled to provide coverage of the penile shaft (Shenoy et al, 2001). If the scrotum is involved, most of the scrotal skin must be excised, with the exception of the posterior skin, and the spermatic cords and testes should be preserved (Ross et al, 1998). The penis may be covered with local skin flaps, and the scrotal contents may be covered with uninvolved posterior skin flaps (Bolt et al, 1998; Ross et al, 1998). Split-thickness skin flaps may be needed to cover the penis and scrotum if inadequate healthy skin is available (McDougal, 2003). Parents should be counseled that lymphedema in adjacent areas may recur after definitive surgical therapy.

Priapism

Priapism, a prolonged penile erection, sustained for greater than 4 hours with the absence of both physical and psychological stimulation, is commonly painful. Tumescence is usually restricted to the corpora cavernosa (Montague et al, 2003), and in some cases the corpus spongiosum involves the glans. Priapism can be categorized into three types:

1. **Ischemic (veno-occlusive, low-flow) priapism** is characterized by little or no cavernous blood flow, and cavernous blood gases are hypoxic, hypercapnic, and acidotic. The corpora are rigid and tender to palpation.
2. **Nonischemic (arterial, high-flow) priapism** is caused by unregulated cavernous arterial inflow. Typically, the penis is neither fully rigid nor painful. There is often a history of antecedent trauma resulting in a cavernous artery/corpora cavernosa fistula.
3. **Stuttering (intermittent) priapism** is a recurrent form of ischemic priapism with painful erections with intervening periods of detumescence.

Low-flow priapism is most commonly secondary to homozygous sickle cell disease, which is characterized by predominance of sickle hemoglobin (Hb S). Other causes include leukemia, local malignancies, other hemoglobinopathies, and local malignancy (Dewan et al, 1989; Friedman, 1998). Sickle cell–induced priapism occurs in 2% to 29% of males with the disease (Tarry et al, 1987; Hamre et al, 1991; Miller et al, 1995; Mantadakis et al, 1999). The priapism associated with sickle cell disease is generally related to a low-flow state, secondary to sickling of red blood cells within the sinusoids of the corpora cavernosa during normal erection, resulting in venous stasis. This situation results in decreased pH and local oxygen tension, which potentiates further stasis and sickling (Bruno et al, 2001). Priapism typically occurs during sleep, when mild hypoventilatory acidosis depresses oxygen tension and pH in the corpora. The pain that is experienced is a sign of ischemia.

Transient prolonged erections lasting less than 2 hours, known as stuttering priapism, is more common than prolonged erections in the patient with sickle cell disease. Pseudoephedrine, an oral α-adrenergic agent, given at bedtime can be used to treat stuttering priapism in boys by promoting muscle contraction within the erectile tissue. If this treatment is unsuccessful, other therapeutic agents can be used, including an oral β agonist. Recently, preliminary findings suggest that the use of continuous, long-term oral phosphodiesterase-5 (PDE5) inhibitor therapy may prevent recurrent priapism based on the hypothesis that PDE5 dysregulation may be involved in priapism (Burnett et al 2006; Burnett, 2008).

The initial treatment of low-flow priapism resulting from sickle cell disease is conservative, with hydration, oxygenation, alkalization, analgesia, and transfusion with the goal of reducing Hb S concentration (Seeler, 1973; Hamre, 1991; and Miller et al, 1995). **Evacuation of blood and irrigation of the corpora cavernosa along with intracavernous injections of α-adrenergic sympathomimetic agents, such as phenylephrine or epinephrine solution, can be a concurrent therapy** (Montague et al, 2003)**.** Surgical intervention to allow corporeal drainage by shunt procedures is indicated if there is a lack of response to medical therapy (Tarry et al, 1987; Miller et al, 1995; Chakrabarty et al, 1996). Surgical shunting bypasses the veno-occlusive mechanism of the corpora cavernosa and thereby enhances blood drainage. Shunt procedures include distal cavernoglandular shunt (Winter, Ebbehoj, and El-Gorab shunts) (Ebbehoj, 1974; Winter, 1976; Ercole et al, 1981), proximal cavernospongiosal shunt (Quackels and Sacher shunts) (Quackels, 1964; Sacher et al, 1972), or saphenous vein anastomosis to one of the corpora cavernosa (Grayhack shunt) (Grayhack et al, 1964). Parents should be educated on the potential side effects from intervention, including cavernosal fibrosis and erectile dysfunction.

High-flow priapism is usually due to perineal trauma, such as a straddle injury. Other causes include Fabry disease and sickle cell anemia (Ramos et al, 1995; Callewaert et al, 1998; Volkmer et al, 2001). Corporeal irrigation is diagnostic and therapeutic. Typically, the aspirated blood is bright red and the aspirate is similar to arterial blood on blood gas analysis. Color Doppler ultrasonography often will demonstrate the fistula. The initial management is observation (Montague et al, 2003) because spontaneous resolution may occur. Superselective embolization of cavernous and penile arteries (Callewaert et al, 1998; Volkmer et al, 2001; Montague et al, 2003; Kuefer et al, 2005) is the next line of therapy.

A fourth type of priapism is a spontaneously resolving form observed in neonates (Walker and Casale, 1997). Causes may include idiopathic, birth trauma, and polycythemia. No intervention is necessary because the priapism usually resolves in 2 to 6 days without adverse results.

Key Points: Priapism

- Priapism can be ischemic (veno-occlusive, low flow), nonischemic (arterial, high flow), and stuttering (intermittent).
- The most common cause in children is sickle cell disease (ischemic).
- The initial treatment of low-flow priapism resulting from sickle cell disease is conservative, with hydration, oxygenation, alkalization, analgesia, and transfusion. Evacuation of blood and irrigation of the corpora cavernosa along with intracavernous injections with α-adrenergic sympathomimetic agents can be a concurrent therapy.
- High-flow priapism is usually due to perineal trauma, such as a straddle injury. Angiographic embolization is necessary if spontaneous resolution does not occur.
- Transient prolonged erections lasting less than 2 hours are known as stuttering priapism. Pseudoephedrine, an oral α-adrenergic agent, given at bedtime can provide effective treatment.

SCROTAL ANOMALIES

Penoscrotal Transposition (Scrotal Engulfment)

Penoscrotal transposition may be partial or complete (Fig. 131–17), with its less severe forms having been termed *bifid scrotum, doughnut scrotum, prepenile scrotum*, and *shawl scrotum*. The embryologic cause may result from incomplete or failed inferomedial migration of the labioscrotal swellings. **Frequently, the condition occurs in conjunction with perineal, scrotal, or penoscrotal hypospadias with chordee** (Pinke et al, 2001). Penoscrotal transposition has also been associated with caudal regression (Lage et al, 1987), sex chromosome abnormalities (Yamaguchi et al, 1989), and Aarskog syndrome (Shinkawa et al, 1983). As many as 75% of patients with complete penoscrotal transposition and a normal scrotum have a significant urinary tract abnormality, including renal agenesis and dysplasia (MacKenzie et al, 1994; Parida et al, 1995), and other nongenitourinary anomalies have been reported. These patients should be evaluated with renal ultrasonography and voiding cystourethrography.

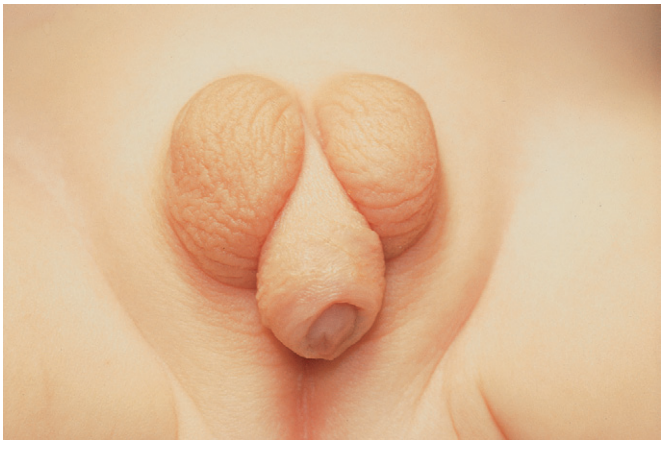


Figure 131–17. Penoscrotal transposition.

Surgical repair is usually performed during hypospadias or other penile repair. Several scrotoplasty techniques have been described (Glenn and Anderson, 1973; Ehrlich and Scardinol, 1982; Levy et al, 1997) with the goal of freeing the penis from the scrotum, developing skin flaps, relocating the scrotum to a dependent position, and moving the penis superiorly. When scrotal engulfment is associated with severe hypospadias, hypospadias repair is often accomplished by a transverse preputial island flap in conjunction with Thiersch-Duplay tubularization of the proximal urethra. To minimize the possibility of devascularization of the preputial flap, correction of the scrotal engulfment is usually done as a second-stage procedure 6 months later (Elder and Duckett, 1990; Germiyanoglu et al, 1994). If the penis is normal, scrotoplasty can be accomplished when the child is 6 to 12 months of age.

Scrotoplasty is performed by circumscribing the superior aspects of each half of the vertical aspect of the scrotum and extending these incisions laterally to include at least half of the scrotum (Fig. 131–18). The medial aspects of the incision are joined on the ventral aspect of the penis, and the incision is carried down the midline along the median raphe. The injection of a solution of lidocaine with epinephrine into the subcutaneous tissue can be used to develop tissue planes and also help to diminish bleeding. Care must be taken not injure the tunica vaginalis and spermatic cord during deeper dissection. The scrotal wings are rotated medially under the penis and sutured together in the midline in an everted manner. Although in most cases there is no deficiency of the ventral penile shaft skin, in more severe cases of penoscrotal transposition this may not be the situation; dorsal interposition flaps may then be necessary, allowing caudal advancement of the skin of the abdominal wall (Pinke et al, 2001).

An alternative technique is to identify the correct position for the penis and make a buttonhole by excising a plug of epidermis, dermis, and suprapubic fat (Kolligian et al, 2000). The penis is then degloved, and the penile shaft is brought through the buttonhole. The penile shaft skin remains behind, is split down the

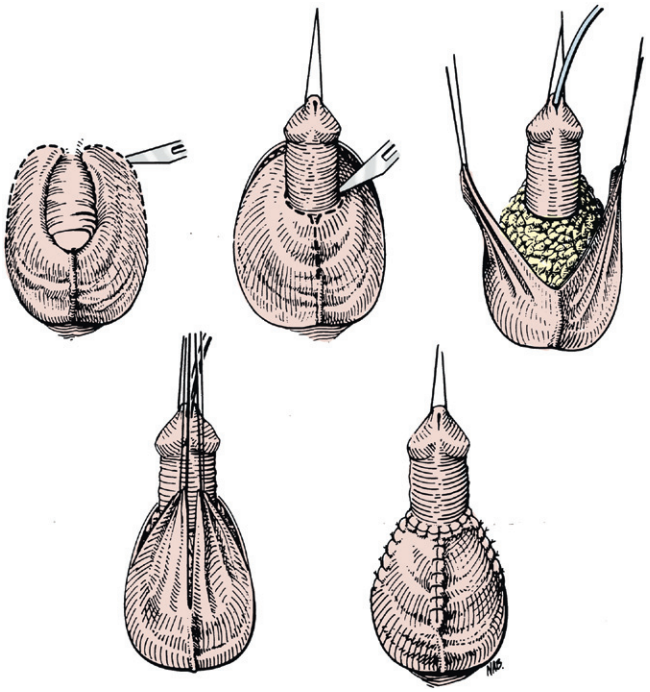


Figure 131–18. Repair of penoscrotal transposition (see discussion in text).

ventrum, and is mobilized superiorly to the penile shaft. A window of the dartos pedicle is made, and the penile shaft is brought through this window. The degloved penis is then resurfaced with shaft skin.

Bifid Scrotum

Bifid scrotum refers to the deformity in which the labioscrotal folds are completely separated and without a median raphe. This anomaly is most often associated with proximal hypospadias. Surgical repair is usually performed during hypospadias repair. The technique is similar to that used for repair of penoscrotal transposition.

Ectopic Scrotum

Ectopic scrotum (Fig. 131–19), the anomalous position of one hemiscrotum along the inguinal canal, is a rare condition. The location can be suprainguinal (most common), infrainguinal, or perineal (Lamm and Kaplan, 1977; Elder and Jeffs, 1982). This anomaly has been associated with cryptorchidism, inguinal hernia, and bladder exstrophy as well as with the popliteal pterygium syndrome (Cunningham et al, 1989). In one review, 70% of boys with a suprainguinal ectopic scrotum exhibited ipsilateral upper urinary tract anomalies, including renal agenesis, renal dysplasia, and ectopic ureter (Elder and Jeffs, 1982). Another study indicated that an associated perineal lipoma was found in 83% of these children; 68% of those with a lipoma had no associated anomalies, whereas 100% of those without a lipoma had associated genital or renal malformations (Sule et al, 1994). Because of the embryology of the gubernaculum and scrotum being intimately related chronologically and anatomically, the ectopic scrotum may result from a defect in gubernacular formation that prevents migration of the labioscrotal swellings (Hoar et al, 1998). Patients with an ectopic scrotum should undergo upper urinary tract imaging with ultrasonography. Scrotoplasty and orchiopexy may be performed at 6 to 12 months of age or earlier if other surgical procedures are necessary for associated anomalies.



Figure 131–19. Ectopic scrotum.

Scrotal Hypoplasia

Scrotal hypoplasia, the underdevelopment of one or both sides of the scrotum, **occurs most commonly in boys with an undescended testis** and frequently is noted in infants with genital ambiguity. The deformity may result from lack of gubernacular swelling of the labioscrotal folds.

Scrotoschisis

Meconium peritonitis may occasionally cause genital manifestations, including meconium hydrocele (Ring et al, 1989) and congenital rupture of the scrotum, termed *scrotoschisis* (Gongaware et al, 1991; Salle et al, 1992; Chun and St-Vil, 1997; Kojori et al, 2007; Premkumar et al, 2009). This can result in one or both testes being extruded from the scrotal sac. When scrotoschisis is detected the clinician should suspect meconium peritonitis and proceed with the appropriate evaluation. Treatment involves scrotal exploration with orchiopexy and primary closure of the scrotal wall defect.

VASCULAR LESIONS OF THE GENITALIA

Vascular lesions of the genitalia are uncommon without a consensus on classification, etiology, and treatment. These deformities include hemangiomas and vascular malformations. **Hemangiomas are on the skin**, are often congenital, and may show significant growth in the postnatal period followed by slow involution. **Vascular malformations are present at birth in the subcutaneous tissues** and tend to persist or to enlarge, which can occur secondary to trauma, sepsis, or hormonal changes (Ramos et al, 1999). **Vascular malformations can be subdivided into either slow-flow (capillary, lymphatic, venous) or fast-flow (arterial, arteriovenous) types.**

Congenital Hemangiomas

Congenital hemangiomas are common and affect the genitalia in approximately 1% of all hemangiomas (Alter et al, 1993). The origin of these lesions and the mechanisms regulating their growth and involution are controversial (Ritter et al, 2007). **Strawberry hemangiomas are the most common type and result from proliferation of immature capillary vessels.** These are also categorized as cutaneous hemangiomas because they occur on the skin. Although the lesions may undergo a period of rapid growth lasting 3 to 6 months, gradual involution is common, and most

lesions require no treatment (Casale and Menashe, 1989; Girard et al, 2006). If ulceration develops, intervention is necessary to prevent complications from bleeding. The most popular form of therapy is short-term oral corticosteroid therapy. Treatment with laser therapy allows selective photothermolysis and destruction of superficial blood vessels (Kennedy et al, 1993; Ward et al, 1998). In some cases, surgical excision is necessary.

Subcutaneous Hemangiomas

Subcutaneous hemangiomas, also referred to as cavernous hemangiomas, are much less common than the cutaneous variety (Sule et al, 1993; Ferrer and McKenna, 1995) and are probably more appropriately classified as a vascular malformation. They may be detected at birth or later in life. In contrast to cutaneous hemangiomas, which tend to involute, cavernous hemangiomas tend to enlarge gradually and should be treated with care. Physical examination reveals a "bag of worms" sensation similar to that of a varicocele, although the lesions tend to be firm and do not decompress when the patient is recumbent. Ultrasonography with color Doppler imaging, computed tomography, or MRI is recommended to delineate the size of the hemangioma (Aizenstein et al, 1996) because examination does not disclose the extent of the lesion. Definitive treatment by en bloc resection is advised, and preoperative angioembolization may reduce the size of the mass and the risk of bleeding.

Klippel-Trénaunay-Weber Syndrome

Klippel-Trénaunay-Weber syndrome is a triad of cutaneous vascular malformation, most commonly nevus flammeus, in combination with soft tissue and bone hypertrophy. The anomaly is present at birth and usually involves a lower extremity, but the trunk or face may be involved. These vascular lesions have a propensity to bleed. In a review of 214 patients from a single institution, Husmann and colleagues (2005) found that 30% had genitourinary cutaneous or visceral involvement. Of the 48 (22%) who had cutaneous genital involvement, 29% developed intractable bleeding. Excision of the hemangiomas was associated with significant blood loss.

Vascular Malformations

The penis may also be affected by vascular malformations. These lesions are congenital but are usually not diagnosed until the teenage years or young adulthood. The lesions are characterized as a faint blue patch or a soft blue mass. If the lesion affects the glans penis, the neodymium:yttrium-aluminum-garnet laser may yield a better result than surgical excision (Ramos et al, 1999).

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chapter 132

Abnormalities of the Testis and Scrotum and Their Surgical Management

Julia Spencer Barthold, MD

Embryology of Testicular Development and Descent
Cryptorchidism (Undescended Testis)
Varicocele
Hernias and Hydroceles
Acute Scrotum
Epididymal, Vasal, and Scrotal Anomalies

Developmental abnormalities of the testis and inguinoscrotal region, including cryptorchidism, varicocele, hernia/hydrocele, and torsion of the spermatic cord or testicular appendages comprise some of the most common anomalies seen in male children. Despite their frequency, relatively little is known of the underlying factors contributing to the pathogenesis of these diseases. All may be associated with significant short- or long-term morbidity. Moreover, their clinical presentation may overlap and at times present diagnostic challenges. Our ability to define the degree to which cryptorchidism and varicocele affect global testicular function in individual patients remains limited. Therefore management options remain controversial in part because of difficulty correlating early childhood therapies with long-term reproductive outcomes.

EMBRYOLOGY OF TESTICULAR DEVELOPMENT AND DESCENT

Testicular Development

The human gonadal ridge containing somatic and germ cells is first identified on the medial urogenital ridge at 32 days after ovulation and is indistinguishable between males and females (Hanley et al, 1999). Primordial germ cells migrate from the yolk sac and differentiate into gonocytes during the 5th week of gestation. Expression of the earliest testis (Sertoli cell)-specific genetic markers, *SRY* (sex-determining region Y) and *SOX9* (SRY-box 9), begins at between 41 and 44 days (Hanley et al, 2000) followed by the histologic appearance of Sertoli cells and testicular cords in male fetuses by 9 weeks of age (Ostrer et al, 2007). Migrating mesonephric cells contribute to testis cord formation as well as testicular endothelial cells (Cool and Capel, 2009) The germ cell marker, c-KIT, first identified at 7 weeks of age, is present in an increasing number of cells until 12 weeks, with subsequent reduced expression as maturation to intermediate germ cells progresses (Ostrer et al, 2007). By the third trimester, a third stage of germ cells, prespermatogonia, predominates within the testis. Leydig cells can be identified by cell-specific staining by 9 weeks and by peritubular myoid cells by 12 weeks of age.

Gonadal differentiation is more complicated than the original concept of ovarian development as the default pathway because emerging evidence suggests that activation of specific gene pathways is required for both male and female sex determination in mice (Blecher and Erickson, 2007; Cool and Capel, 2009). *Sry* has been considered the master male gene, but other genes required for gonadal determination act upstream of *Sry* and its downstream effects on *Sox9* expression are indirect via derepression of an intermediate gene, likely *Rspo1* (R-spondin homolog). Testicular determination is directly dependent on activation of *Sox9* and *Fgf9* (fibroblast growth factor-9), whereas ovarian determination is dependent on activation of *Rspo1* and *Wnt4* (wingless-related MMTV integration site-4) and the appropriate dosage of the X-linked *Nr0b1* (nuclear receptor subfamily 0, group B, member 1, also known as *Dax1*) gene.

Hormonal function of the human fetal testis is critical for masculinization of the reproductive tract and testicular descent. Fetal Leydig cell development is divided into three phases: a proliferation and differentiation phase between 7 and 14 weeks' gestation, a maturation phase until 18 weeks, and an involution phase that continues until term (Svechnikov and Soder, 2008). Synthesis of testosterone by fetal Leydig cells starts as early as 6 to 7 weeks' gestation and appears to be initially independent of gonadotropin stimulation. However, placental human chorionic gonadotropin (hCG) stimulates a peak in androgen production at 14 to 16 weeks' gestation and the testis then becomes responsive to fetal luteinizing hormone (LH). Insulin-like 3 (INSL3) of Leydig cell origin is measurable in human amniotic fluid as early as 13 weeks' gestation (the earliest time point studied) and peaks at 15 to 17 weeks (Anand-Ivell et al, 2008; Bay et al, 2008). Fetal Sertoli cells produce antimüllerian hormone (AMH; also called müllerian-inhibiting substance [MIS]) soon after they differentiate; the human fetal müllerian duct is responsive to AMH before week 8 of gestation, and the process of regression occurs between 9 and 10 weeks (Josso et al, 2006). **Evidence from animal models and indirect clinical evidence suggests that INSL3 and testosterone are the key hormones required for testicular descent.**

Steroid hormones exert their effects via sex steroid receptors in the reproductive tract and testis. Recent studies show that androgen receptor (AR) and estrogen receptor-β (ERβ) are expressed in the undifferentiated gonad at 7 weeks of age, although their role in testicular development is unclear (Shapiro et al, 2005; Boukari et al, 2007). AR is present primarily in peritubular myoid cells and in some Leydig and interstitial cells but absent in Sertoli cells during the fetal period. Because androgens inhibit AMH production by Sertoli cells, the absence of an AR in these cells during fetal life allows unfettered expression of AMH during this period (Boukari et al, 2009). ERβ localization is most extensive, being observed in germ, peritubular myoid, Sertoli, and some Leydig cells by 13 weeks and decreasing by 22 to 24 weeks, whereas expression of estrogen receptor-α (ERα) is limited (Shapiro et al, 2005) or absent (Boukari et al, 2007) in the human fetal testis. Concomitant expression of aromatase during the same time frame suggests that locally produced estrogen may play a role in testicular development.

Significant changes in reproductive hormone secretion and testicular development occur in the neonatal period (Grumbach, 2005). Fetal Leydig cells regress after birth, followed by emergence of a neonatal Leydig cell population at 2 to 3 months of age (Prince, 2001) and a peak in testosterone and INSL3 levels (Bay et al, 2007) that follows a surge in serum gonadotropin levels. As postnatal hormonal levels wane, the fetal Leydig cells either degenerate or regress to immature Leydig/interstitial cells that are partially differentiated and less responsive to LH. In the first months of life, intratubular gonocytes migrate to the basement membrane and differentiate into type A spermatogonia, which comprise a subset of spermatogonial stem cells (Culty, 2009). Sertoli cell proliferation occurs in the first year of life and is a major determinant of ultimate testicular size (Sharpe et al, 2003). The characteristics of testicular growth during childhood vary depending on the method of analysis. Main and colleagues reported significant growth of normal testes between birth and 3 months of age based on ultrasound measurements and on significantly larger testicular size in Finnish as compared with Danish boys at birth and 3 and 18 months, a difference attributable to genetic and/or environmental effects (Main et al, 2006b). Kuijper and coworkers observed a peak in testicular ultrasound volume at 6 months of age followed by a decline to baseline (Kuijper et al, 2008). In contrast, in an autopsy series, Berensztein and associates noted doubling of testicular weight during the first 3 weeks of life with slowed growth thereafter, suggesting that major growth occurs prior to the postnatal hormone surge and a gonadotropin-independent mechanism (Berensztein et al, 2002). This growth was associated with a rate of proliferation exceeding the rate of apoptosis in Leydig, germ, and Sertoli cells before the second month of age with increased apoptosis thereafter and little subsequent growth of the testes before age 6. In their autopsy series of older children, Müller and Skakkebaek (1983) reported a 2.6-fold increase in testicular size between the first year of life and age 10, with a significant increment between all age groups (birth to 1, 1 to 5, and 5 to 10 years) in both size and tubular length. Overall, the data suggest a major increment in testicular growth during the neonatal period, but the factors responsible for age-specific cellular proliferation, gonocyte differentiation, and testicular growth are not clearly defined.

Gubernacular Development and Testicular Descent

The physiology of normal testicular descent and the etiology of abnormal descent in humans remain poorly understood, whereas the morphologic events have been well studied in mammals. Knowledge of the regulation of testicular descent is inferred from studies of human diseases that include cryptorchidism and/or from animal models.

The human indifferent gonad develops adjacent to and becomes suspended from the mesonephros, which has replaced the pronephros by 5 weeks' gestational age (Lemeh, 1960). A rudimentary cranial mesonephric ligament connects to the diaphragm, disappearing by 13 weeks as the mesonephros regresses (Barteczko and Jacob, 2000) (Fig. 132–1). There is no direct connection between the gonad and this ligament; therefore no "cranial gonadal ligament" exists in humans as noted in other species. Using fixed sections, Barteczko and Jacob observed an "inner" or transabdominal descent of the human testis from a position at vertebral levels C7-T8 to T9-L3 between 5 and 7 weeks' gestation and to the sacral level by 10 weeks; using dissections, others described the testis at the level of L4 by the 7th week (Lemeh, 1960) or always "close to the groin" (Wyndham, 1943). Caudal movement of the ovary is prevented by the ovarian ligament and development of the müllerian ducts.

Barteczko and Jacob (2000) described five major phases of testicular descent in the human fetus (Fig. 132–2):

Phase 1: The caudal mesonephros contacts the future gubernaculum at the internal inguinal ring (5 weeks' gestation).

Phase 2: The genitofemoral nerve accompanies the newly formed gubernaculum (abdominal, interstitial, and subcutaneous portions) and processus vaginalis (7 weeks).

Phase 2a: Growth of the gubernaculum, deepening of the processus vaginalis, and extension of cremaster muscle fibers into the interstitial gubernaculum occurs (8 to 10 weeks).

Phase 3: Growth of the testis and regression of the müllerian ducts and mesonephros occurs; the gubernaculum remains a thin cord in both sexes (10 to 12 weeks).

Phase 3a: The testis overrides the genital ducts and contacts the gubernaculum, which begins its swelling phase in males (12 to 14 weeks).

Phase 4: Swelling of the gubernaculum, development of the cremaster muscle, and migration of the processus vaginalis produce widening of the inguinal canal (14 to 20 weeks).

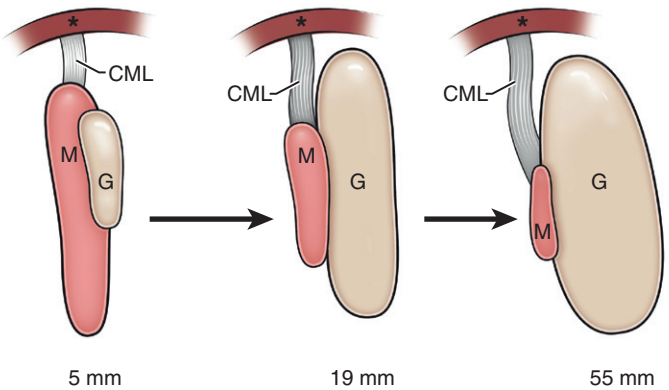


Figure 132–1. Development of the cranial mesonephric ligament (CML) and gonad (G) during embryonic regression of the mesonephros (M). *Asterisks* denote the anlage of the diaphragm; *long arrows* show the cranial mesonephric ligament. (From Barteczko KJ, Jacob MI. The testicular descent in human: origin, development and fate of the gubernaculum Hunteri, processus vaginalis peritonei, and gonadal ligaments. Adv Anat Embryol Cell Biol 2000;156:III-X, 1–98.)

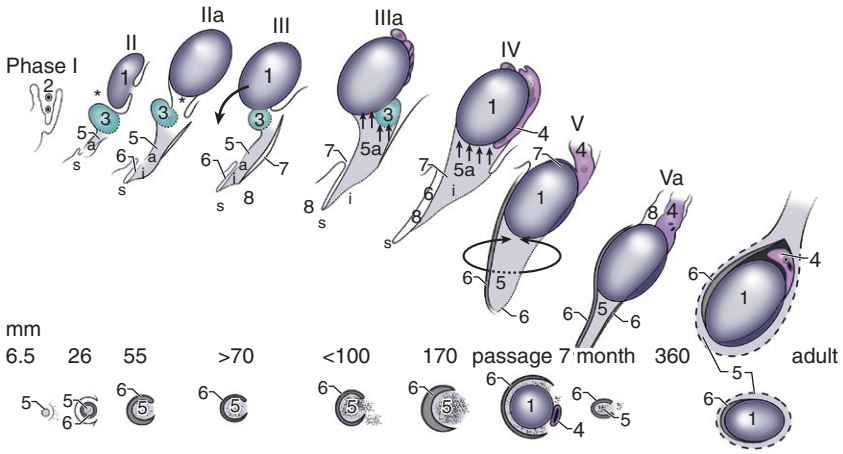


Figure 132–2. Overview of human testicular descent. Sagittal view *(top)* and transverse sections *(bottom)* of 1, gonad; 2, mesonephros; 3, wolffian and müllerian duct; 4, vas deferens/epididymis; 5, gubernaculum—a, abdominal; i, interstitial; s, subcutaneous part; 6, processus vaginalis; 7, internal inguinal ring; 8, external inguinal ring. *Straight arrows* (phase I) show ventral side; *asterisks* (phases I to IIIa) show the link between the caudal pole of the testis and dorsal mesenchyme of genital ducts; *curved arrow* (phase III) shows direction of testicular migration; *short arrows* (phases IIIa to IV) indicate attachment between the testis or epididymis and gubernaculum; *oval arrowline* (phase V) indicates no connection between the boltlike gubernaculum and neighboring structures. (From Barteczko KJ, Jacob MI. The testicular descent in human: origin, development and fate of the gubernaculum Hunteri, processus vaginalis peritonei, and gonadal ligaments. Adv Anat Embryol Cell Biol 2000;156:III-X, 1–98.)

Phase 5: Release of the distal subcutaneous attachment of the gubernaculum and transinguinal passage of the testis occur (20 to 28 weeks).

Phase 5a: Further caudal movement of the testis into the scrotum is accompanied by regression of the gubernaculum (7th month and beyond).

The careful in-situ anatomic observations by Barteczko and Jacob (2000) throughout gestation help clarify some aspects of human testicular descent. For example, transabdominal movement of the testis occurs before sexually dimorphic changes in the gubernaculum and is presumably not a male hormone–specific event. The subsequent male-specific swelling of the gubernaculum parallels the peak in Leydig cell secretion of testosterone (14 to 16 weeks) and INSL3 (15 to 17 weeks). The genitofemoral nerve accompanies and precedes the gubernaculum and developing processus vaginalis in both sexes beginning at an early stage (7 weeks), and both smooth (abdominal) and skeletal (interstitial and subcutaneous) muscle fibers occur within the three segments of the gubernaculum. Both muscle types were also observed by some (Wyndham, 1943; Lemeh, 1960) but not others (Heyns, 1987; Costa et al, 2002; Niikura et al, 2008) observers. However, studies of the in-situ gubernaculum beginning at 20 weeks clearly show the presence of peripherally and centrally located striated muscle bundles (Barteczko and Jacob, 2000; Niikura et al, 2008) and infiltration of the gubernaculum by the genital branch of the genitofemoral nerve (Tayakkanonta, 1963). Controversy exists as to whether these skeletal cremaster muscle fibers are of similar origin and/or originate from abdominal wall musculature or from within the gubernaculum itself (van der Schoot, 1996; Barteczko and Jacob, 2000; Niikura et al, 2008). The processus vaginalis and cremaster muscle may facilitate transit of the testis and gubernaculum, but their exact role remains unknown.

Swelling of the gubernaculum is critically important to allow enlargement of the inguinal canal and testicular passage and is the result of both cellular proliferation and production of extracellular matrix (Heyns, 1987). Once the canal is created, unknown mechanical factors trigger a typically rapid transinguinal passage of the testis. The



Figure 132–3. The distally unattached human gubernaculum at 25 weeks of gestation (215 mm CRL) just before transinguinal testicular descent. T, testis; G, gubernaculum; P, penis; S, scrotum. (From Heyns CF. The gubernaculum during testicular descent in the human fetus. J Anat 1987;153:93–112.)

gubernaculum is unattached distally during and after transinguinal passage (Fig. 132–3). Settling of the gubernaculum and testis into the preformed scrotum is gradual. The scrotum itself develops from genital swellings that are first visible at 7 weeks and fuse by 10 to 12 weeks in response to circulating dihydrotestosterone. Passage of the testis into the inguinal canal rarely occurs prior to week 22 in the human fetus, and the majority of testes are scrotal

after week 27; time spent in the inguinal canal seems to be limited for the majority of human fetal testes (Heyns, 1987; Sampaio and Favorito, 1998). Early innervation of the gubernaculum and the importance of the genitofemoral nerve in testicular descent in rodents, as well as the rapidity of transinguinal passage, suggest a neuromuscular mechanism.

Regulation of Testicular Descent

Direct evidence for hormonal control of testicular descent is based entirely on studies in animal models, primarily rodents. The relevance of rodent data to humans is controversial because of anatomic differences, which in mice and rats include a less prominent interstitial gubernaculum, a cranial gonadal ligament, an elongated cord connecting the gubernaculum to the epididymis, a well-developed intrinsic cremaster muscle located in the outer layer of the gubernaculum, an absent inguinal canal, and failure of closure of the processus vaginalis (Wensing, 1988). However, some observers argue that the similarities between species are sufficiently strong to warrant translational studies of these models (van der Schoot, 1996; Harnaen et al, 2007).

Rodent studies provide strong evidence that testicular INSL3 and androgen signaling pathways are the primary contributors to gubernacular development and testicular descent (Zimmermann et al, 1999; Adham et al, 2000; Overbeek et al, 2001). According to a paradigm developed by Hutson, testicular descent occurs in two phases—transabdominal and transinguinal—regulated by INSL3 and by androgens via the genitofemoral nerve, respectively (Hutson and Hasthorpe, 2005). However, animal models show that INSL3 and androgen synergistically stimulate cellular proliferation and growth of the gubernaculum (Adham et al, 2000; Emmen et al, 2000; Kubota et al, 2002) and that both INSL3 binding and androgen receptor expression are present before and during the swelling phase of the fetal rat gubernaculum (Koskimies et al, 2003; McKinnell et al, 2005; Staub et al, 2005). Moreover, INSL3 and testosterone levels peak after week 12 in the human fetus, concomitant with gubernacular swelling, although transabdominal testicular descent occurs earlier, prior to 10 weeks' gestation. In mice, INSL3 signaling promotes development of the processus vaginalis, and androgen signaling causes regression of the cranial gonadal ligament (Adham et al, 2002; Koskimies et al, 2003; Adham and Agoulnik, 2004), a structure that does not exist in the human fetus. Clues about other gene pathways that participate in the process of testicular descent are provided by known transgenic mouse models and human syndromes with phenotypes that include cryptorchidism (Barthold, 2008; Foresta et al, 2008). Transgenic deletion of either of two homeobox genes, *Hoxa10* and *Hoxa11,* is associated with isolated cryptorchidism in mice. *Hoxa10* appears to function independently of gonadotropin or INSL3 signaling (Feng et al, 2006). At present, little is known of the role of these and other gene candidates in the process of testicular descent.

A role for the genitofemoral nerve in guiding and/or promoting passage of the gubernaculum is supported by rodent studies of Hutson and colleagues, who propose that release of calcitonin gene-related peptide (CGRP) from the nerve stimulates development and function of the gubernaculum (Yamanaka et al, 1993; Chan et al, 2009). Studies of rats with inherited cryptorchidism suggest that innervation and/or muscle development within the gubernaculum is disrupted (Hrabovszky et al, 2001; Barthold et al, 2008). While a role for CGRP release from the genitofemoral nerve in human fetuses remains undefined, it is clear that the human gubernaculum contains and is surrounded by muscle and is innervated by the nerve beginning as early as at 7 weeks' gestation (Lemeh, 1960; Tayakkanonta, 1963; Barteczko and Jacob, 2000; Niikura et al, 2008).

In summary, the gubernaculum develops in both sexes beginning early in the second month of gestation and testicular hormones stimulate development of the gubernaculum and testicular descent in the second and third trimesters. Enlargement, distal detachment and migration of the gubernaculum are key events that facilitate and direct caudal movement of the testis. In humans, the factors required for these events are incompletely known but likely include secretion of INSL3 and androgen and presumably intact innervation by the genitofemoral nerve.

Key Points: Embryology of Testicular Development and Descent

- Gonadal determination involves separate genetic pathways for development of testis and ovary.
- *Sry* is a master switch that derepresses the critical testis determining genes *Sox9* and *Fgf9*.
- Differentiation of gonocytes and Sertoli and Leydig cells occurs between 5 and 9 weeks' gestation.
- Levels of the Leydig cell hormones testosterone and INSL3 peak between 14 and 17 weeks' gestation and are critical for testicular descent.
- The gubernaculum, the guide for testicular descent, appears at 7 weeks' gestation and begins male-specific proliferation and swelling between 12 and 14 weeks.
- Dramatic swelling of the gubernaculum sets the stage for testicular descent, and innervation via the genitofemoral nerve may trigger transinguinal passage of the testis.
- The testis finishes transabdominal descent by 10 weeks, rapidly passes through the inguinal canal between 20 and 28 weeks, and is dependent in the scrotum in most boys by birth.

CRYPTORCHIDISM (UNDESCENDED TESTIS)

Cryptorchidism is one of the most common disorders encountered in pediatric urology and has been studied extensively. Despite this, knowledge of the causes and prediction of the consequences of the disease remains limited. Moreover, the quality of evidence that is used to support clinical guidelines for diagnosis and treatment is surprisingly low (Gapany et al, 2008; Turner, 2009).

Definitions

Differing terminology has been used to describe patients with nonscrotal testes; use of the following definitions is recommended. ***Normal scrotal position*** has been defined as positioning of the midpoint of the testis at or below the midscrotum (Wohlfahrt-Veje et al, 2009). Although "high scrotal testes" are not routinely considered undescended by most clinicians, they have been included in the definition of undescended testis in some epidemiologic studies (Sijstermans et al, 2008). This is likely a heterogeneous group that includes stable descended testes that reside above the scrotal midpoint and undescended "gliding" testes (Hack et al, 2007), which are not stable. ***Undescended testis*** is the absence of one or both testes in normal scrotal position and during initial

clinical evaluation may refer to palpable ***cryptorchid testes*** or to nonpalpable testes, which are either cryptorchid or absent. Most absent testes are ***vanishing,*** present initially in development but are lost owing to vascular accident or torsion unilaterally ***(monorchia)*** or, very rarely, bilaterally ***(anorchia)*** (Abeyaratne et al, 1969). ***Agenesis*** refers to a testis that was never present and therefore associated with ipsilateral müllerian duct persistence. ***Congenital cryptorchidism*** refers to testes that are extrascrotal at birth, and ***recurrent cryptorchidism*** is when testes descend spontaneously postnatally but subsequently return to a nonscrotal position. The terms ***testicular ascent*** or ***acquired cryptorchidism*** are used in situations when cryptorchid testes are documented as scrotal at a previous examination without intervening inguinal surgery. ***Secondary cryptorchidism*** and ***testicular retraction*** apply to testes that are suprascrotal after inguinal hernia repair and as a complication of orchidopexy, respectively. Testicular malposition after hernia repair is due to either postoperative scarring or primary maldescent. ***Retractile testes*** are scrotal testes that retract easily out of the scrotum but can be manually replaced in a stable scrotal position and remain there at least temporarily. Testes that are significantly retractile, that is, those that rarely remain in a stable scrotal position (spontaneously or with manipulation) and/or are located at rest in the high scrotum, may or may not be truly undescended.

Epidemiology and Pathogenesis

Cryptorchidism is one of the most common congenital anomalies, occurring in 1% to 4% of full-term and 1% to 45% of preterm male neonates (Sijstermans et al, 2008). It is a component of over 390 syndromes (Winter-Baraitser Dysmorphology Database, http://www.lmdatabases.com); the most common are listed in recent reviews (Foresta et al, 2008; Virtanen and Toppari, 2008). The majority of cases are isolated, with the ratio of nonsyndromic to syndromic cryptorchidism reported as greater than 6:1 in a large cohort (Boyd et al, 2006). In a small percentage of syndromic cases associated with deficiency or insensitivity of hypothalamic-pituitary-gonadal (HPG) axis hormones, the etiology of testicular maldescent is known. **The pathogenesis of isolated cryptorchidism remains largely unknown but is most likely multifactorial, involving both genetic and environmental risk factors.**

Nonsyndromic Congenital Cryptorchidism

Studies of the prevalence of isolated cryptorchidism at birth are complicated by confounding factors that include subjectivity of the examination and differences in the definition of undescended testis (inclusion/exclusion of high scrotal testes) and in study populations and study design (Sijstermans et al, 2008). Although most studies support a prevalence at birth of 2% to 4% and at 3 months of age of 1% to 2%, this varies geographically, with frequency as high as 8% in some studies (Virtanen and Toppari, 2008), supporting the possibility of an increase over time. However, other data suggest that country-specific trends are not increasing (Abdullah et al, 2007; Cortes et al, 2008; Bonney et al, 2009) and overall there do not appear to be reproducible trends in prevalence (Sijstermans et al, 2008). Perinatal risk factors associated with cryptorchidism include prematurity, low birth weight/small for gestational age, breech presentation, and maternal diabetes (Damgaard et al, 2008; Virtanen and Toppari, 2008).

The reported frequency of spontaneous testicular descent after birth also appears to vary substantially between studies, likely owing to similar confounding factors. Of 95 patients with cryptorchidism referred to a urology practice when younger than 6 months of age, 16% had spontaneous testicular descent versus 0% of those presenting after 6 months; in contrast, previous studies reported a 50% to 75% rate of spontaneous postnatal testicular descent (Wenzler et al, 2004). Suomi and associates (2006) noted spontaneous descent in significantly more Danish (68%) than Finnish (45%) boys at 3 months of age, likely owing to increased severity of the disease in the latter group. Similarly, in a recent longitudinal study, extrascrotal testes were much less likely to descend by 1 year of age (50%) than high scrotal testes defined as cryptorchid at birth (87.5%) (Acerini et al, 2009). The long-term risk of recurrent cryptorchidism was not determined in these studies and is difficult to ascertain because of short follow-up. Spontaneous descent is more likely and may occur later in premature infants.

Retractile and Acquired Undescended Testes

In the past, cryptorchidism was considered a congenital anomaly identifiable at birth, with spontaneous descent possible during the postnatal period. However, since first reported more than 30 years ago (Myers and Officer, 1975), **substantial evidence indicates that the diagnosis of cryptorchidism may be "acquired," that is, made in cases of apparent full descent at birth or after spontaneous descent of a cryptorchid testis** (Barthold and Gonzalez, 2003; Taghizadeh and Thomas, 2008). Except for diagnosis at an average age of 8 to 9 years and lower testicular position, other characteristics of testicular "ascent" or "acquired" cryptorchidism are similar to those observed in cases of congenital cryptorchidism. The reason for a later diagnosis remains unknown; theories include presence of a fibrous remnant of the processus vaginalis that tethers or foreshortens the cord over time or mobility of the testis within an open sac. However, it is most likely that the testis is incompletely descended from birth, because many are localized within the superficial inguinal pouch (Barthold and Gonzalez, 2003). These testes may be highly mobile and initially appear descended until somatic growth results in relative widening of the distance between testis and scrotum (Redman, 2005; Agarwal et al, 2006).

A diagnosis of cryptorchidism beyond the neonatal period may be more likely in boys with retractile testes. In an unselected population, the testis was reported to be suprascrotal on initial examination in up to 30% of boys at 4 years of age but intrascrotal in 100% by age 12 (Farrington, 1968). Both prospective and retrospective studies of the natural history of retractile testes support the concept that a subset of these becomes undescended over time. However, a selection bias exists in studies of the risk of cryptorchidism in boys with retractile testes, because those referred for follow-up by specialists are those with the most severe retractility. For example, Wyllie (1984) prospectively studied a cohort of 100 boys with unilateral retractile testis and identified 64 cases in which testicular position, as documented by the distance between the pubic tubercle and midtestis, and/or testicular size, as estimated by orchidometer, was reduced after 5 years of follow-up. Orchidopexy was performed in 45 of these cases, although specific documentation of testicular position and size as indications for surgery were not reported. Findings of retrospective case series also suggest that cryptorchidism is ultimately diagnosed in about 33% of boys with significantly retractile testes followed longitudinally by the same observer(s) (La Scala and Ein, 2004; Agarwal et al, 2006). In contrast, only 7% of 172 boys followed a mean of 26 months required orchidopexy in a more recent study (Stec et al, 2007). These data suggest that a significant minority of retractile testes become suprascrotal over time. **Careful, often**

serial, physical examination may be necessary to accurately determine testicular position and need for intervention.

Two recent longitudinal population-based cohort studies have provided some preliminary information regarding the risk of acquired cryptorchidism in the general population during childhood (Acerini et al, 2009; Wohlfahrt-Veje et al, 2009). In a study from the United Kingdom, 742 infants were followed with serial examinations for 2 years after birth with complete follow-up in 326. The prevalence of extrascrotal testes was 2.7% at birth (27% nonpalpable, surgical findings not reported); and 0.2%, 1.8%, 0.3%, and 0% of testes in the studied population became extrascrotal at 3, 12, 18, and 24 months, respectively. Including high scrotal testes, a total of 5.7% were identified as cryptorchid at birth and 1% to 4% rose to a high scrotal position with each follow-up visit. As expected, suprascrotal testes in neonates were much less likely to descend spontaneously (41%) than high scrotal testes (84%). In a series from Finland, cryptorchidism was present at birth in 94 of 1072 boys (0.9%) and 509 of the noncryptorchid boys were followed at 6- to 18-month intervals until 4.5 to 10 years of age. Of those observed, seven testes became suprascrotal and five became high scrotal, with the change in position occurring during the first 36 months of life. These studies suggest regional differences in both congenital and acquired cryptorchidism, but both suggest a low risk that scrotal testes will become suprascrotal in the first few years of life. **However, cases diagnosed during childhood comprise a significant number of those requiring orchidopexy and yearly well-child screening is indicated.**

Genetic Susceptibility

Genetic studies of cryptorchidism suggest that the disease is heritable but that susceptibility is likely polygenic and multifactorial. Clustering of cryptorchidism has been reported in a number of families affecting multiple individuals in the same generation and variable phenotype (Minehan and Touloukian, 1974; Pardo-Mindan et al, 1975; Czeizel et al, 1981; Savion et al, 1984). Extended pedigrees were not usually examined, but autosomal dominance with reduced penetrance was most often cited as the probable mode of inheritance. Population case-control studies also support genetic contribution to the disease. Familial aggregation suggesting moderate genetic risk was reported in a recent large cohort study of more than 1 million male births in the Netherlands based on extensive hospital registry data (Schnack et al, 2008). Recurrence risk ratio (RR) was 10.1 in twins, 3.5 in brothers, and 2.3 in offspring and were significantly higher in maternal than in paternal half-brothers. Previous smaller studies reported a 5- and 7- to 10-fold increased risk of cryptorchidism in fathers and brothers, respectively, of affected as compared with unaffected subjects (Czeizel et al, 1981; Jones and Young, 1982; Elert et al, 2003). These and another recent study (Jensen et al, 2010) support the possibility that maternal factor(s), or X-linked risk alleles, influence expression of the disease.

Based on mouse models, *INSL3,* its receptor, relaxin/insulin-like family peptide receptor 2 *(RXFP2), HOXA10,* and *HOXA11* were considered the most likely candidate genes for human nonsyndromic cryptorchidism. However, case-specific DNA coding variants of *INSL3* and *RXFP2* are reported in only 0.6% to 1.8% and 1.6% to 2.9% of persistently cryptorchid males, respectively, and in-vitro assays suggest that few of these appear to be functionally significant (Foresta et al, 2008). Notably, apparent mutations in these genes are associated with a range of phenotypes encompassing unilateral/bilateral and persistent/spontaneously resolving presentations and apparently deleterious mutations may exist in normal family members, as recently noted for an *INSL3* mutation showing reduced receptor activation (El Houate et al, 2007). A nonsynonymous polymorphism of the *RXFP2* gene, T222P, was considered a strong etiologic candidate for cryptorchidism based on absence in normal controls and in-vitro studies showing curtailed cell membrane localization and activation of the abnormal receptor (Bogatcheva et al, 2007). However, cases and controls in a different European population subset were found to have a similar frequency of the T222P allele (Nuti et al, 2008). Although these data suggest that mutations of *INSL3* and *RXFP2* are infrequent in cases of cryptorchidism, it is possible that noncoding variants that alter expression levels of the protein have yet to be identified.

Analysis of other potential candidate genes for human cryptorchidism has failed to yield reproducible results. *HOXA10* mutations reported by Kolon and colleagues (1999) were not confirmed in additional series, nor were mutations identified in *HOXA11* (Bertini et al, 2004; Wang et al, 2007). A specific haplotype of the gene encoding ERα (*ESR1*) has not shown consistent association with cryptorchidism in three case-control series (Yoshida et al, 2005; Galan et al, 2007; Wang et al, 2008). Similar varying results have been reported in studies of trinucleotide repeat number in exon 1 of the androgen receptor, although more recent work suggests a possible association with cryptorchidism (Ferlin et al, 2007). Microdeletions of the Y chromosome have also been studied in infertile men with and without a history of cryptorchidism, and no consistent association was observed (reviewed in Gurbuz et al, 2008). A specific polymorphism of the steroidogenic factor 1 (SF1) gene that encodes a transcription factor that regulates expression of *INSL3, RXFP2,* and steroidogenesis genes was recently reported to exist more commonly in cryptorchid Japanese males (Wada et al, 2006). Failure to identify consistent differences in genomic variants for many of these candidates may be influenced by confounding factors such as race and by insufficient sample size. **Although multiple genetic variants likely contribute to the risk of nonsyndromic cryptorchidism, most remain unknown at this time.**

Environmental Risk Factors

Sharpe and Skakkebaek (2008) proposed that nonsyndromic cryptorchidism is one component of the "testicular dysgenesis syndrome," a constellation of reproductive abnormalities including testicular cancer, hypospadias, and reduced sperm counts associated with exposure to antiandrogenic and/or estrogenic environmental endocrine-disrupting chemicals (EDCs). However, some question both the existence of testicular dysgenesis syndrome in humans, because of lack of epidemiologic association between these abnormalities, and the evidence for environmental etiology (Akre and Richiardi, 2009). The concern for a link between EDCs and cryptorchidism arose because of a reported increased risk of cryptorchidism after maternal exposure to diethylstilbestrol (DES) (Gill et al, 1979). This association was observed in rodents but was not confirmed in other clinical case-control studies (Leary et al, 1984); however, in a recent large cohort study of 1197 men previously exposed to DES and 1038 unexposed men, the relative risk (RR) of cryptorchidism was 1.9 overall (confidence interval [CI] 1.1 to 3.4). When data were subdivided based on gestational age of less than 11 weeks and exposure greater than or equal to 5 g, the relative risks were 2.9 (CI 1.6 to 5.2) and 3.2 (CI 1.7 to 6.0), showing that early and significant exposure presents the clearest risks (Palmer et al, 2009). Data supporting a link between other EDCs and cryptorchidism are less clear. Animal models suggest a

relationship between prenatal exposure to antiandrogenic EDCs and risk of cryptorchidism and other reproductive endpoints and suggest additive effects of chemical mixtures, although levels of exposure are much higher than applicable clinically (Rider et al, 2009). In humans, data supporting a correlation between exposure to antiandrogenic and/or estrogenic EDCs such as pesticides, flame retardants, and phthalates and occurrence of cryptorchidism are mostly indirect or suggestive (Weidner et al, 1998; Pierik et al, 2004; Damgaard et al, 2006; Main et al, 2006a, 2007; Fernandez et al, 2007; Krysiak-Baltyn et al, 2010). Strong correlations between single chemicals or classes of EDCs and risk of cryptorchidism may be difficult to demonstrate in view of the presumed heterogeneity of susceptibility to the disease, but the wide variety of EDCs to which humans are exposed may allow for synergistic effects that are difficult to measure. **However, at present, epidemiologic data are suggestive but do not strongly support the theory that environmental chemicals increase susceptibility to cryptorchidism.**

Testicular hormones are required for testicular descent; therefore, if defective hormone production and/or action contribute to the pathogenesis of cryptorchidism, hormone deficiency may persist postnatally. A number of prospective studies of varying size and quality are available that report postnatal hormone levels in cryptorchidism; although some data suggest that the HPG axis is abnormal, the results are conflicting. In the first reported series of cryptorchid and control boys undergoing hormonal evaluation in the first few months of life, serum testosterone was lower in 7 of 17 (41%) persistently cryptorchid boys but comparable to control levels in 4 of 25 boys with spontaneous testicular descent (Gendrel et al, 1978). In a small series of 60-day-old bilaterally cryptorchid (9) and control (14) boys, Facchinetti and associates (1983) also observed reduced plasma testosterone levels but no difference in plasma LH between groups. Raivio and coworkers (2003) reported both significantly reduced plasma testosterone as well as nonmeasurable androgen bioactivity in 3-month-old cryptorchid boys (n = 45; 31% bilateral, 44% with spontaneous descent), but androgen bioactivity was measurable in only 21 of 55 controls.

Additional infant hormone studies did not show lower levels in cryptorchid infants (De Muinck Keizer-Schrama et al, 1988, Barthold et al, 2004), but more recent data from the Netherlands did show reduced testosterone levels in cryptorchid infants (Pierik et al, 2009). In the largest study to date, Suomi and colleagues (2006) showed geographic differences in serum inhibin-B and follicle-stimulating hormone (FSH) levels but no differences in testosterone levels in cryptorchid infants from Finland (n = 88, 36% spontaneous descent) and Denmark (n = 34, 68% spontaneous descent) as compared with 300 and 399 control boys, respectively. In a related cohort, INSL3 levels were reduced in cord blood but not in serum obtained at 3 months of age in persistently cryptorchid males (Bay et al, 2007).

Other studies of Sertoli/germ cell function as determined by serum assays in boys with cryptorchidism suggest that abnormalities may exist but data are inconsistent between studies. In a longitudinal study of 27 boys (mean age 4.8 years) undergoing orchidopexy, an increase in serum inhibin B was identified in a majority of cases 6 months postoperatively (Irkilata et al, 2004), but in another series of 62 boys (mean age 7.7 years) no differences were identified in inhibin B (or in serum LH, FSH, or testosterone) levels before or after hCG stimulation (Christiansen et al, 2002). AMH levels were measured in three prospective studies of boys with cryptorchidism as compared with age-matched controls. Lower AMH levels were seen in a subset of patients younger than 8 years of age included in a study of 104 cryptorchid boys (mean age 4 to 5 years) (Yamanaka et al, 1991) and also in a case-control study of 12-month-old boys (n = 20 per group) in whom levels did not change after orchidopexy (Demircan et al, 2006). However, in another study no differences in AMH levels were seen in 1- to 6-month-old cryptorchid (n = 43) versus control (n = 113) boys (Pierik et al, 2009).

These studies suggest that at least a subset of boys with cryptorchidism have measurable abnormalities in pituitary and/or gonadal hormone secretion during infancy without syndromic endocrine dysfunction. Inconsistent findings between studies are likely based on timing and type of assays, sample size, and heterogeneity based on age, severity, genetic background, and/or other interindividual differences. Lifestyle factors may also interfere with testicular descent and function via hormonal or nonhormonal effects; examples are the recent observation that smoking is associated with cryptorchidism in some case-control series (Thorup et al, 2006; Jensen et al, 2007) and the reduced expression of the Desert hedgehog *(DHH)* gene that is involved in Leydig cell differentiation in human fetuses (Fowler et al, 2008). Multiple genetic and environmental factors likely contribute to cryptorchidism, complicating identification of risk factors in case-control studies.

Syndromic Cryptorchidism

Undescended testes are frequently present in diseases associated with reduced androgen production and/or action, such as androgen biosynthetic defects, androgen insensitivity, Leydig cell agenesis, and gonadotropin deficiency disorders (Barthold et al, 2000; Foresta et al, 2008) that are typically associated with generalized failure of masculinization and are not reviewed here. AMH biosynthesis or receptor defects are also associated with cryptorchidism or transverse testicular ectopia (Josso et al, 2006). Gubernacular defects that are observed in these patients may be due to hindrance of descent by retained müllerian ducts (Barteczko and Jacob, 2000) and/or through loss of direct proliferative effects of AMH on the gubernaculum (Kubota et al, 2002). The frequency of Klinefelter syndrome (47,XXY) is 1.8% in large series of primarily nonsyndromic cryptorchidism but is more frequent when other anomalies, particularly hypospadias, are present (Sasagawa et al, 1996; Moreno-Garcia and Miranda, 2002). Other genomic rearrangements and trisomies, including Down syndrome (trisomy 21), are associated with cryptorchidism (Hadziselimovic, 1983).

Certain anomalies are associated with increased risk of cryptorchidism, many related to musculoskeletal, central nervous system (CNS), or abdominal wall/gastrointestinal defects. These include all cases of classic prune-belly (triad or Eagle-Barrett) syndrome; 80% of those of spigelian hernia (Durham and Ricketts, 2006); and 41% to 54% of cerebral palsy (Rundle et al, 1982; Cortada and Kousseff, 1984), 38% of arthrogryposis (Fallat et al, 1991), 15% of myelomeningocele (Ferrara et al, 1998), 16% to 33% of omphalocele, 5% to 15% of gastroschisis (Kaplan et al, 1986; Koivusalo et al, 1998), 19% of imperforate anus (Cortes et al, 1995b), 12% to 16% of posterior urethral valve (Krueger et al, 1980; Heikkila et al, 2008), and 6% of umbilical hernia (Kaplan et al, 1986) patients. Multisystem anomalies are often associated with omphalocele (80%) and prune-belly syndrome (45%), suggesting a syndromic etiology (Loder et al, 1992; Koivusalo et al, 1998). Depue (1988) also reported a significant association of cryptorchidism with CNS dysfunction, particularly cerebral palsy (RR = 34), low intelligence quotient (RR = 2.7), and hypotonia (RR = 3.6). Cortes and associates (1998) identified an association between renal and T10 to S5 spinal anomalies and cryptorchidism, with the affected

testis on the same side as the renal anomaly in 90% of cases. In addition, cryptorchidism associated with syndromes and CNS malformations is more commonly bilateral (Cendron et al, 1993; Cortes et al, 1995a). These data support common origins of cryptorchidism and abnormalities of urogenital ridge, abdominal wall, lumbosacral spine, and CNS development.

Diagnosis and Classification

To best determine testicular position, boys should be examined in supine and, if possible, upright cross-legged and standing positions. Abduction of the thighs contributes to inhibition of the cremaster reflex, or testicular elevation elicited by scratching the inner thigh. The examination should include documentation of testicular palpability, position, mobility, size, and possible associated findings such as hernia, hydrocele, penile size, and urethral position. Patient distraction, a warm room and hands, use of liquid soap on the examiner's hands, and repeated examinations also help to localize the testis and to limit cremaster muscle activity and resultant difficulty in determining testicular position.

In large clinical series, the majority (75% to 80%) of undescended testes are palpable and 60% to 70% are unilateral; involvement of the right side is more common overall but less frequent in series of nonpalpable testes (Hadziselimovic, 1983; Cendron et al, 1993; Cortes et al, 2001; Giannopoulos et al, 2001). Position of undescended testes varies markedly with the population studied. In a comprehensive review of surgical patients, testes were abdominal in 34%, near the internal ring ("peeping") in 12%, canalicular in 27%, and beyond the external ring in 27% (Docimo, 1995) whereas in a large single institutional series testes were abdominal in 3% to 10% of total cases, canalicular in 16% to 27%, with the majority distal to the external ring (Hadziselimovic, 1983; Moul and Belman, 1988; Cendron et al, 1993). In a large multiinstitutional review of almost 40,000 European cryptorchid boys reported by Hadziselimovic (1983), 8% of testes were abdominal, 63% canalicular, 24% prescrotal, and 11% in the superficial inguinal pouch or ectopic. Moul and Belman classified all subinguinal testes with a lateral gubernacular attachment as ectopic (66% of their total cases).

Associated genital findings may warrant additional diagnostic studies that are best completed in the neonatal period. If both testes are nonpalpable, particularly if penile development is abnormal, karyotype and hormonal analyses are performed to rule out congenital adrenal hyperplasia and obviate the potential adverse effects of undiagnosed salt wasting. Hypospadias is associated with cryptorchidism in 12% to 24% of cases (Cendron et al, 1993; Moreno-Garcia and Miranda, 2002; Cox et al, 2008). If proximal hypospadias is present, chromosomal analysis is warranted because the frequency of abnormalities is high (32%) (Cox et al, 2008). Penile size may be small in boys with bilateral vanishing testes (also called testicular regression syndrome) or with hypogonadotropic hypogonadism, in whom undescended testes are most commonly inguinal. In these cases, measurement of testosterone, LH, and FSH levels in the first few months of life can facilitate identification of hormone deficiency or anorchia.

Palpable Testes

Undescended testes may be located along the line of normal descent between the abdomen and scrotum or in an ectopic position that is most commonly the superficial inguinal pouch (anterior to the rectus abdominis muscle) or, more rarely, in a perirenal, prepubic, femoral, peripenile, perineal, or contralateral scrotal position. Careful examination of these areas is needed to correctly classify a testis as palpable or nonpalpable, a critical step that influences further diagnosis and treatment. Every effort should be made by the examiner to determine the lowest position attainable by a palpable undescended testis. Manual downward pressure with one hand along the ipsilateral inguinal canal from the anterior iliac spine to the scrotum and palpation with the opposite hand helps to identify the lowest position of a palpable testis.

Difficulty in the clinical classification of cryptorchidism when the testis is palpable is related to both documentation of testicular position and differentiation of truly undescended from retractile testes, complicated by the fact that these entities may coexist. The gold standard for diagnosis remains careful examination of a child in several positions and confirmation of incomplete descent of the testis to a dependent scrotal position after induction of anesthesia. Prospective studies of intraobserver and interobserver variation show major differences in documentation of testicular position between examiners (Wit et al, 1987; Olsen, 1989). Olsen (1989) noted complete agreement between two examiners on scaled measures of testicular position and mobility in only 5 (13.5%, 95% CI 4.5% to 28.8%) of 37 boys. Cendron and coworkers (1993) reported that preoperative testicular position correlates poorly with intraoperative findings. Variation in observed testicular position preoperatively and postoperatively may influence assessment of prognosis and outcome in boys with cryptorchidism.

Nonpalpable Testes

When a testis is nonpalpable, possible clinical findings at surgery include (1) abdominal or transinguinal "peeping" location (25% to 50%), (2) complete atrophy ("vanishing" testis, 15% to 40%), and (3) extra-abdominal location but nonpalpable due to body habitus, testicular size, and/or limited cooperation of the patient (10% to 30%) (Cendron et al, 1993; Cisek et al, 1998; Kirsch et al, 1998; Radmayr et al, 2003; Patil et al, 2005). If both testes are nonpalpable and not distal to the internal inguinal ring in a genetic male, at least 95% are abdominal with bilateral vanishing testis occurring rarely (Cendron et al, 1993; Moore et al, 1994). If neither vas nor spermatic artery is found at the time of laparoscopy, laparoscopic or surgical dissection of the paravesical area and retroperitoneum up to the level of the kidney is required to exclude the presence of a testis. Pararenal or other abdominal testes may be associated with multicystic dysplastic or absent ipsilateral kidneys and/or nonunion of the testis and epididymis (Zaccara et al, 2004; Foley et al, 2005; Kim et al, 2005).

The etiology of vanishing testis is most likely torsion or vascular accident occurring after completion of genital masculinization but before fixation of the testis in the scrotum. Evidence supporting this etiology includes the presence of hemosiderin in remnant testicular "nubbins" excised at surgery (Turek et al, 1994) and reported cases of contralateral postnatal torsion (Gong et al, 1996). An enlarged contralateral testis (Huff et al, 1992) and absence of palpable intrascrotal "appendage" tissue (processus vaginalis, wolffian structures, or gubernaculum) are highly predictive of vanishing testis (Mesrobian et al, 2002). However, **diagnosis of a vanishing testis requires documentation of blind-ending spermatic vessels in the abdomen, inguinal canal, or scrotum.** Endocrine evaluation in cases of suspected bilateral vanishing testis (anorchia) include elevated basal serum gonadotropin levels and no response to hCG stimulation; however, gonadotropins may be unexpectedly low in mid childhood in boys who are also unresponsive to hCG (Lustig et al, 1987; Lee, 2000). Therefore laparoscopic or surgical documentation of anorchia is critical to avoid leaving small or dysgenetic abdominal

testes in situ. AMH and inhibin-B levels may be useful in documenting the presence of functioning testicular tissue (Grumbach, 2005).

Inguinoscrotal ultrasonography and magnetic resonance imaging (MRI) are not usually helpful in the diagnosis and management of nonpalpable testis (Elder, 2002). However, if a testis is nonpalpable when evaluated by an experienced examiner, the sensitivity of ultrasonography in identifying inguinal testes is reported to be as high as 95% to 97%, and abdominal testes are also seen in some cases (Cain et al, 1996; Nijs et al, 2007). Some of these testes are "peeping," however, and best mobilized via a laparoscopic approach. Similarly, although MRI can be useful in some cases to identify nonpalpable abdominal testes, its accuracy is variable and the procedure requires sedation in younger children and often may not change the management approach (Yeung et al, 1999; Siemer et al, 2000). The superior accuracy of magnetic resonance angiography in localizing and differentiating viable from vanished testes (96% of 23 nonpalpable testes in 21 boys, mean age 2.5 years) has not been replicated in a recent study of younger boys (57% of 29 testes in 26 boys, mean age 13 months) (Yeung et al, 1999; Desireddi et al, 2008). One indication for MRI may be identification of an ectopic abdominal testis not localized by laparoscopy.

Diagnostic laparoscopy followed by laparoscopic orchidopexy if the testis is abdominal has become the preferred approach of many clinicians. Important observations include size and position of the spermatic vessels and vas; testicular size, quality, and position; and patency of the internal inguinal ring. The combination of a closed internal ring and a blind-ending spermatic artery and vas is most consistent with an abdominal vanishing testis, whereas a hernia is frequently but not always associated with a viable abdominal or distal testis (Elder, 1994; Moore et al, 1994). An atretic spermatic cord coursing through a closed inguinal ring is suggestive of a distal vanishing testis, but this finding may be subjective; and, conversely, normal-appearing vessels may be associated with both viable and vanishing testes (Zaccara et al, 2004). Moreover, the laparoscopic view may suggest abdominal blind-ending vessels despite a testis being present distally or in an ectopic abdominal position (Zaccara et al, 2004; Kim et al, 2005; Ellsworth and Cheuck, 2009).

The need for excision and contralateral scrotal orchidopexy in cases of vanishing testis remains controversial. Germ cells and/or tubules are consistently present in 5% to 15% of excised testicular remnants (Moore et al, 1994; Tennenbaum et al, 1994; Turek et al, 1994; Cortes et al, 1995a; De Luna et al, 2003; Renzulli et al, 2005), but the risk of malignancy is unknown. A single case of carcinoma in situ was reported by Rozanski and associates (1996) in a testicular remnant. Excision may be appropriate for remnants distal to an internal ring to allow confirmation that a viable testis is absent, because the laparoscopic appearance of the spermatic vessels and processus vaginalis may be deceiving and may not reliably exclude the presence of an inguinal testis (Ellsworth and Cheuck, 2009). Storm and colleagues (2007) performed laparoscopic excision of vanishing testes in 56 patients without significant morbidity, although the position of the remnants in these patients was not clear. Because the testicular remnant is often in or near the scrotum, some advocate a primary scrotal approach when contralateral testicular hypertrophy (testicular length ≥ 1.8 cm) and a palpable scrotal "nubbin" are present (Belman and Rushton, 2003; Snodgrass et al, 2007). However, in cases of abdominal vanishing testes, a transscrotal search is time consuming and unproductive. Moreover, in cases of testicular-epididymal dissociation, scrotal nubbins may be mistaken for testicular remnants that would otherwise be identified by laparoscopy (Wolffenbuttel et al, 2000; De Luna et al, 2003). **Laparoscopy is the procedure of choice to confirm or exclude the presence of a viable or remnant abdominal testis, unless a prominent scrotal nubbin is palpable with other clinical signs of monorchism.**

The need for contralateral fixation of a solitary testis in cases of monorchism is not clear. The possibility that prenatal torsion is the etiology of vanishing testis (Gong et al, 1996) does not imply that the contralateral testis is likely to undergo a similar fate after the postnatal period. However, some surgeons recommend contralateral fixation to eliminate the risk of such a devastating complication (Rozanski et al, 1996) and/or because a contralateral bell-clapper deformity (incomplete testicular fixation to the tunica vaginalis) may be present (Bellinger, 1985; Al-Zahem and Shun, 2006).

Associated Pathology

Testicular Maldevelopment

Many observational studies of the histologic development of prepubertal cryptorchid testes have been published. More than 40 years ago, Mancini and associates (1965) systematically reported germ cell counts and related arrested development of spermatogonia with progressive loss in cryptorchid testes. Subsequently, several large series, some with additional normal autopsy (Hedinger, 1982) or affected (hernia, hydrocele) (Hadziselimovic et al, 1987a) control data and others that refer to these established age-dependent norms (Schindler et al, 1987; Huff et al, 1993; McAleer et al, 1995; Gracia et al, 2000; Cortes et al, 2001), have provided mainly consistent findings in cryptorchid boys. These data show that the number of spermatogonia per tubule (S/T) is reduced after infancy and fails to increase normally with age in cryptorchid and, to a lesser degree, in contralateral scrotal testes. The frequency of abnormal histology in the contralateral testis varies between studies, ranging from 22% to 95%, and is likely reflective of differences in patient populations, use of control data, and methodology. Moreover, variability within and between biopsy specimens from single testes is reported (Hedinger, 1982; Schindler et al, 1987). **However, these data provide strong evidence that abnormal germ cell development is often present after early infancy in cryptorchid testes.** The degree of pathology was similar in true ectopic, superficial inguinal pouch, and ascending testes (Herzog et al, 1992; Hutcheson et al, 2000b; Rusnack et al, 2002) and was more severe in limited samples from patients with myelomeningocele, posterior urethral valves, and prune-belly syndrome (Orvis et al, 1988; Patel et al, 2008). Findings are similar in retracted testes after hernia repair, suggesting primary instead of secondary cryptorchidism (Fenig et al, 2001). In other studies, higher S/T counts were correlated with reduced age-dependent interstitial fibrosis (Suskind et al, 2008), lower age at surgery, and increased likelihood of palpability (Tasian et al, 2009), but not volume (Noh et al, 2000), of cryptorchid testes. Regional differences in S/T counts were recently reported, potentially reflecting population differences in environmental exposures (Zivkovic et al, 2009).

Detailed studies of peritubular myoid and Sertoli cells in cryptorchidism are lacking, but their abnormal development or function may contribute to the observed germ cell abnormalities. The available data suggest disruption of prepubertal Sertoli cell morphology, failure of maturation at puberty, and evidence for reduced

number after 4 months of age in cryptorchid testes (Lackgren and Ploen, 1984; Rune et al, 1992; Regadera et al, 2001; Zivkovic and Hadziselimovic, 2009). Reduced expression of type IV collagen, a product of both Sertoli and myoid cells that may function in cell-cell communication, was reduced in basement membranes of undescended and contralaterally descended testes (Santamaria et al, 1990).

Impaired transformation of gonocytes to spermatogonia is reported in cryptorchid testes and may be a key determinant of fertility potential. In normal testes, germ cell number decreases after birth as gonocytes either degenerate by apoptosis or migrate to the basement membrane and differentiate into spermatogonia (Hadziselimovic et al, 1986; Huff et al, 2001). Although the ratio of gonocytes to spermatogonia appears to be normal in cryptorchid testes at about 1.5 months of age, delayed disappearance of gonocytes and appearance of adult dark (Ad) spermatogonia occurs in the undescended as compared with the contralateral descended testis. Ad spermatogonia are likely the reserve stem cells of the germ cell pool (Dym et al, 2009). The mechanisms involved in migration and/or differentiation of gonocytes into stem cells are not clearly defined but appear to involve ADAM-integrin-tetraspanin complexes, retinoic acid, platelet-derived growth factor receptor, and c-KIT (Culty, 2009). Hadziselimovic and colleagues hypothesize that failure of gonocyte differentiation in cryptorchidism reflects failure of postnatal activation of the HPG axis (Hadziselimovic et al, 1986); however, although they occur concurrently there are no data confirming a direct relationship between the two events.

Kollin and colleagues (2006, 2007) studied testicular growth in undescended and scrotal testes and measured the effect in orchidopexy on testicular size using serial ultrasonography in prospective randomized studies. They showed that the undescended testis is not significantly smaller at birth but grows less well than the scrotal testis, and orchidopexy at age 9 months allows partial catch-up growth of the cryptorchid testis up to 4 years of age. In contrast, testes that remained cryptorchid until 3 years of age did not grow significantly before or after orchidopexy. The cellular components responsible for these differences in volume are not known. In scrotal testes, ethnic differences in testicular size as reported by Main and associates (2006b) were associated with increased inhibin-B levels and interpreted to primarily reflect differences in Sertoli cell number (Sharpe, 2006).

Anomalies of the Epididymis, Processus Vaginalis, and Gubernaculum

The epididymis is often abnormal in boys with cryptorchidism (Marshall and Shermeta, 1979), with a reported frequency of 35% to 75% (Heath et al, 1984; Gill et al, 1989; Mollaeian et al, 1994). Anatomic findings in decreasing order of frequency include anomalies of fusion between the caput and/or cauda epididymis, elongation and/or looping, and atresia. The occurrence of epididymal anomalies correlates with both the severity of cryptorchidism and the degree of closure of the processus vaginalis (Elder, 1992; Barthold and Redman, 1996). The degree to which these anomalies contribute to the risk of subfertility in males with a history of cryptorchidism remains undefined. Similarly, failure of closure of the processus vaginalis and attachment of the gubernacular remnant are common in association with cryptorchidism. In their study of 759 patients, Cendron and colleagues (1993) identified a persistently patent processus vaginalis ipsilateral to 87% of unilateral and 71% of bilateral undescended testes. Specific notation of the gubernacular position available from this and another large study indicates aberrant attachment lateral to the scrotum in 66% to 75% of cases (Moul and Belman, 1988). The processus is patent in approximately 50% of boys presenting with ascending testes, possibly related to older patient age and/or reduced severity of cryptorchidism in this group (Barthold and Gonzalez, 2003). **Anomalies of the tunica and processus vaginalis in cryptorchidism predispose to development of testicular torsion or clinical hernia, respectively, in rare cases.** Torsion of an undescended testis can occur at any age (reviewed by Zilberman et al, 2006) and may be confused with an incarcerated inguinal hernia. The risk of torsion is much higher in an undescended as compared with a descended testis and may be particularly high in children with neuromuscular disease such as cerebral palsy. Delay in diagnosis is common, and a high index of suspicion and education of family and referring physicians is needed to reduce the high risk of testicular loss.

Other Testicular Anomalies Associated with Cryptorchidism

Several rare anomalies of testicular development associated with cryptorchidism, each with 100-150 reported cases in the literature, include polyorchidism, splenogonadal fusion, and transverse testicular ectopia. Because abdominal cryptorchidism commonly occurs in these cases, laparoscopy is useful in both diagnosis and treatment.

Polyorchidism is the presence of a supernumerary testis that is more commonly unilateral and on the left side, with rare cases of bilateral duplication or triplication reported in a comprehensive review of the pediatric and adult literature (Bergholz and Wenke, 2009). The cause is unknown, but most authors speculate that this anomaly is related to duplication or division of the genital ridge with or without the wolffian duct, as illustrated by Danrad and colleagues (2004). Testes are reported to be scrotal, inguinal, and abdominal in 75%, 20%, and 5% of cases, respectively (Kumar et al, 2008). Affected individuals are frequently asymptomatic, and the polyorchidism is identified at the time of orchidopexy or hernia repair, although a scrotal or inguinal mass and pain with or without torsion may occur and persistent müllerian remnants may coexist. Various classification schemes have been proposed, with a recent trend toward categorizing testes based on epididymal and vasal configuration (Bergholz et al, 2007; Khedis et al, 2008; Kumar et al, 2008). Kumar and colleagues (2008) suggest a classification that differentiates between testes that are drained by a vas deferens: *type A1*—separate epididymis and vas, *type A2*—separate epididymis, and *type A3*—shared epididymis and vas from those with no vasal drainage: *type B1*—epididymis present and *type B2*—no epididymis or vas. This classification can aid in management decisions that should be based not only on the anatomy of the accessory ducts but also the position, size, and attachments of the testis. Observation and periodic self-examination without surgery should be considered for sonographically normal scrotal testes and orchidopexy for testes that are undescended but with intact ductal drainage (Spranger et al, 2002; Bergholz et al, 2007; Khedis et al, 2008). Occasional cases of testicular tumor have been reported in supernumerary testes, but it is unclear if this is a risk related to polyorchidism per se or to associated cryptorchidism or persistent müllerian duct syndrome (Spranger et al, 2002; Ghose et al, 2007).

Splenogonadal fusion is a defect characterized by continuous or discontinuous fibrous union between splenic tissue and the gonad, a condition much more commonly recognized in males (Khairat and Ismail, 2005). Approximately 30% of affected

individuals have cryptorchidism, with the majority of cases abdominal and bilateral (59%) and 65% and 26% involving the left and right sides, respectively (Cortes et al, 1996). The continuous form of splenogonadal fusion is more commonly syndromic, associated with limb defects, micrognathia, microglossia, anal atresia, and pulmonary hypoplasia (McPherson et al, 2003), whereas cryptorchidism is associated with both continuous and discontinuous forms and most commonly coexists with bilateral amelia (Cortes et al, 1996). The pathogenesis of the anomaly is not understood but based on the constellation of defects observed is hypothesized to represent a developmental field defect with aberrant migration of spleen cells occurring at 5 to 8 weeks' gestation. Most cases present incidentally at the time of orchidopexy or inguinal hernia repair or with scrotal swelling related to illness-related reactive changes within the splenic tissue. Testicular malignancy is reported rarely in association with cryptorchidism and not likely related to the splenic anomaly. Treatment should focus on recognition of the defect at the time of orchidopexy and avoidance of unnecessary orchiectomy.

Transverse testicular ectopia may occur as an isolated anomaly in otherwise normal males with cryptorchidism or vanishing testes or be associated with persistent müllerian duct syndrome in 20% to 50% of cases (De Luna et al, 2003; Wuerstle et al, 2007; Thambidorai and Khaleed, 2008). The classic presentation is inguinal hernia with contralateral nonpalpable testis, although both testes may be palpable in the same hemiscrotum. The etiology may be related to mechanical hindrance to descent by fusion of wolffian duct derivatives (Chacko et al, 2006) or persistent müllerian ducts or to a primary gubernacular defect. Interestingly, complete loss of the gubernacular attachment, transverse ectopia, and/or torsion were observed in transgenic mice null for *Insl3* (Nef and Parada, 1999; Zimmermann et al, 1999). Orchidopexy may be performed using open surgical or laparoscopic techniques, but in cases of vasal fusion the involved testis is mobilized ipsilaterally and a transseptal approach is used to place the testis in the contralateral scrotum (Chacko et al, 2006; Thambidorai and Khaleed, 2008).

Treatment

Correction of cryptorchidism is indicated to optimize testicular function, potentially reduce and/or facilitate diagnosis of testicular malignancy, provide cosmetic benefits, and prevent complications such as clinical hernia or torsion. Except in certain cases of associated complex medical illness or in the postnatal period, treatment should proceed after confirmation of the diagnosis. A flow diagram (Fig. 132–4) shows the recommended approach to palpable and nonpalpable testes in patients confirmed to have undescended testis by an experienced examiner.

In infants, observation is indicated for the first 6 postnatal months to allow spontaneous testicular descent. **If descent does not occur in the postnatal period, present consensus supports surgical treatment at 6 months of age.** Support for this approach is based on the following rationale: (1) descent is unlikely in full-term males after age 6 months (Wenzler et al, 2004); (2) testicular growth is restored after early orchidopexy (Kollin et al, 2007); (3) hormone therapy is not considered efficacious (Ritzen et al, 2007); and (4) orchidopexy for abdominal testes may be facilitated in young infants soon after the hormonal surge. In boys with a history of prematurity, spontaneous descent may be delayed and therefore continued observation for 6 months beyond the expected date of delivery or, especially if testicular position is marginal, until a year of age may be warranted. **However, even if spontaneous descent occurs, continued observation is needed because of the risk for recurrent cryptorchidism, or "re-ascent" of a spontaneously descended testis.**

Recently, two groups from the Netherlands published reports of the outcome of boys with acquired undescended testes who were observed expectantly (Sijstermans et al, 2006; Eijsbouts et al, 2007). These authors reported spontaneous descent in 75 of 132 (57%) and 98 of 129 (75%) testes, respectively, most by mid puberty. The mean volume of descended testes in the study by Eijsbouts and coworkers was closer to those of normal contralateral testes as compared with boys who underwent orchidopexy. However, in both of these series high scrotal testes comprised the majority and of those that descended and low scrotal "unstable" testes (likely retractile) were also included. On the other hand, Eijsbouts and coworkers reported that 19 of 82 unilateral cases had previous contralateral orchidopexy and that 10 boys required orchidopexy because of clinical hernia, pain, or torsion, suggesting a higher likelihood of true cryptorchidism in these cases. **Because these studies were not randomized and provide no long-term data regarding testicular outcome, observation is not recommended for acquired cryptorchidism.**

Medical Therapy

Hormonal therapy has been used for a variety of indications in patients with cryptorchidism, including differentiation of retractile from true undescended testes, stimulation of testicular descent or germ cell maturation, and as an adjunct to abdominal orchidopexy. These therapies may be used sporadically, but none is considered the standard of care, likely because of limited availability of some medications, lack of rigorous data supporting their efficacy, and concerns about possible adverse effects (Thorsson et al, 2007).

Several published reports address the usefulness of hormonal therapy in distinguishing retractile from true undescended testes. In prospective series reporting the response of putative retractile testes to hCG, success rates vary from 58% to 100% and may be dependent not only on age, degree of retractility, and accuracy of diagnosis but also on the dosage regimen used (Rajfer et al, 1986; Miller et al, 2003; Metin et al, 2005). In patients treated by Miller and associates (2003), nonresponders undergoing surgery had typical findings associated with true cryptorchidism, including a patent processus vaginalis and superficial inguinal pouch location, and follow-up was short (6 to 12 months). **These data suggest that hCG fails to reliably distinguish retractile from cryptorchid testes and therefore does not eliminate the need for serial examinations in these patients.**

LH-releasing hormone (LHRH) and/or hCG have been used as hormonal therapy to induce descent of testes for more than 70 years based on the premise that androgens promote testicular descent, but the efficacy of this therapy is questionable (Pyorala et al, 1995; Henna et al, 2004; Thorsson et al, 2007). Even when analysis is limited to randomized, placebo-controlled trials the reliability of the data is limited in that many series did not confirm exclusion of retractile or nonpalpable (potentially absent) testes, adequacy of randomization procedures, and/or long-term efficacy of the treatment. Although the efficacy of either hormonal treatment is about 20% and superior to placebo in randomized trials, this effect is not clearly clinically significant. Although lower testicular position shows a clear correlation with response to therapy, no consistent differences in response based on age or laterality

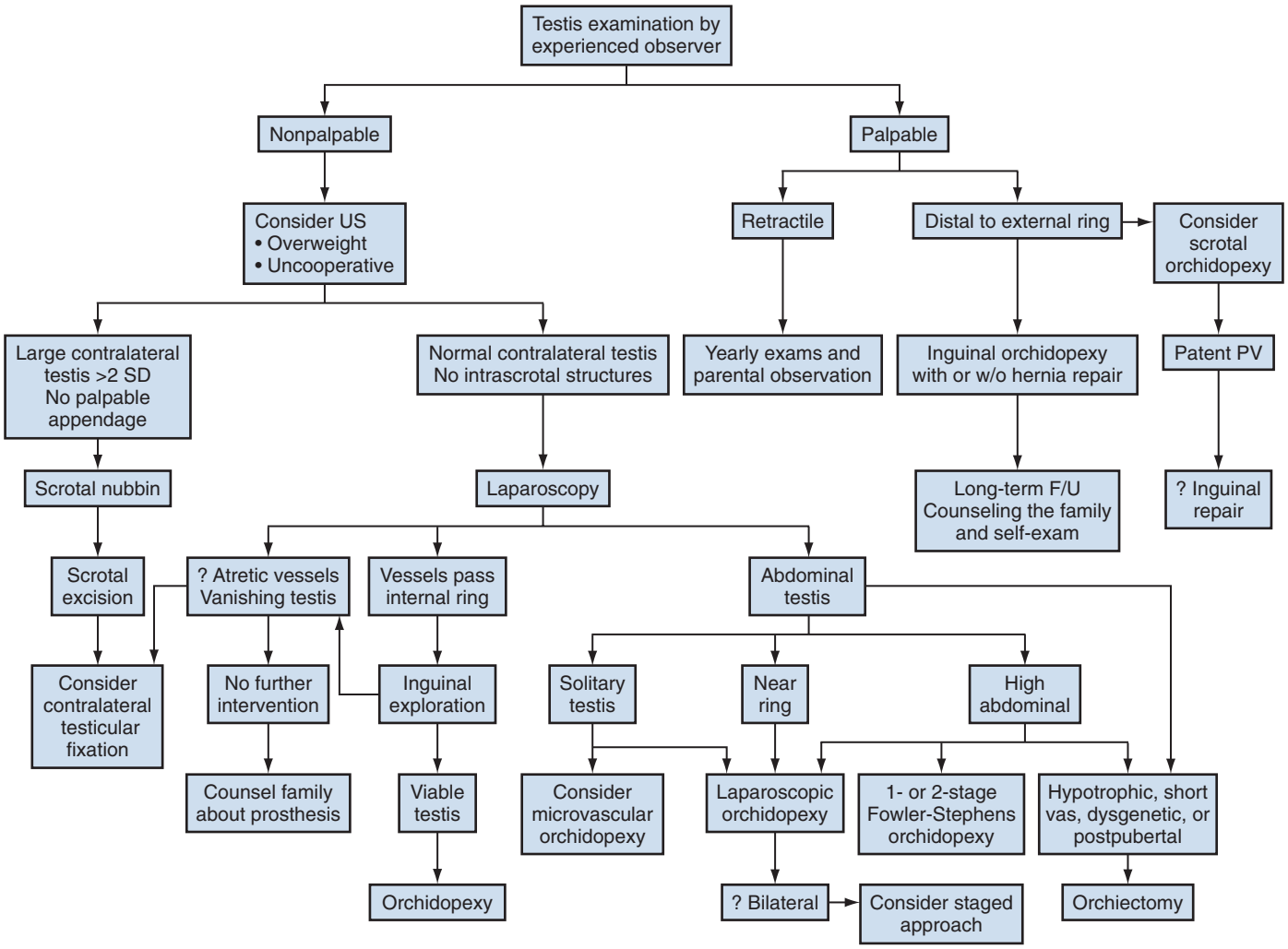


Figure 132–4. Algorithm for management of the undescended testis. This is the recommended approach to diagnosis and treatment of palpable and nonpalpable testes in patients confirmed to have undescended testis by an experienced examiner. F/U, follow-up; PV, processus vaginalis; US, ultrasonography.

have been reported in randomized trials. **Overall, the evidence from rigorous studies indicates that LHRH therapy for cryptorchidism is only marginally more effective than placebo; although not studied in randomized placebo-controlled trials because of its route of administration, hCG also shows limited efficacy.** Other uses of hCG including treatment of acquired cryptorchidism and to facilitate palpability and/or treatment of the abdominal testis (Polascik et al, 1996; Baker et al, 2001; Bukowski et al, 2001) also have limited efficacy.

The question of the effect of therapeutic doses of hCG or LHRH on germ cell development has been addressed in several conflicting studies that are limited by small sample size, absent or suboptimal randomization, and variable availability of biopsy data (Ong et al, 2005). In small, retrospective studies, hCG treatment was associated with increased germ cell apoptosis at biopsy and lower adult testis volume (Dunkel et al, 1997) and previous hCG or LHRH therapy was associated with reduced S/T counts in 1- to 3-year-old boys as compared with surgery alone (Cortes et al, 2000). In contrast, Schwentner and associates randomized young boys (mean age 33 months, 21 per group) to LHRH or no hormonal therapy before surgery and reported that mean S/T count was higher (1.05 ± 0.71) in LHRH-treated as compared with non-treated (0.52 ± 0.39) testes (Schwentner et al, 2005). In view of a lack of large prospective studies, it is unclear if hormone therapy for cryptorchidism is beneficial or harmful to germ cells in the short or long term.

Hadziselimovic and colleagues (1987b) have advocated use of low-dose, long-term (every other day for 6 months) LHRH analogue (buserelin) therapy for stimulation of germ cell development in conjunction with orchidopexy. In a retrospective study of non-randomized, non–age-matched patients receiving buserelin versus surgery only, S/T counts were significantly higher in the treated group. A subset of patients from this same cohort with the most severe testicular histology underwent rebiopsy after completion of therapy and were compared with a group of 8 boys of unknown age who required reoperative orchidopexy (Hadziselimovic et al, 1987a). A significant improvement in mean S/T ratio was seen in the buserelin-treated but not the surgical group. Similarly, in a smaller select group of boys treated with low doses of a related LHRH agonist, nafarelin, improved histology was observed in one or both testes at rebiopsy in 8 of 12 boys. In a randomized study of clinically matched boys receiving buserelin and hCG, placebo and hCG, or surgery alone (19 to 25/group), S/T counts were also significantly higher in those treated with buserelin (Bica and Hadziselimovic, 1992). More recently, Hadziselimovic (2008) published a nonrandomized retrospective study showing that

buserelin-treated males (most also received hCG) with a history of unilateral cryptorchidism and poor pretreatment S/T counts had much higher sperm counts than patients who underwent surgery only (n = 15 per group). Unfortunately, these two groups were small and not clinically matched prospectively to limit other potential confounding factors, such as testicular position, and sperm counts in the surgery-only group were lower than typical for unilateral cryptorchidism. Overall, these studies provide preliminary, suggestive evidence that buserelin may have both short- and long-term effects on testicular histology and/or fertility potential. However, the suboptimal design of the studies on which this evidence is based mandates that future well-designed prospective studies are necessary before routine use of buserelin treatment in cryptorchidism.

In summary, little if any high-quality evidence exists showing a benefit of hormonal therapy for cryptorchidism or for stimulation of germ cells. **A recent statement by the Nordic Consensus group recommends that testicular biopsy and hormonal therapy not be used in standard clinical care of boys with cryptorchidism** (Ritzen et al, 2007), although not all clinicians concur (Hadziselimovic and Zivkovic, 2007).

Surgical Approach to the Palpable Testis

The standard treatment for palpable testes is inguinal orchidopexy with repair of an associated hernia if present (Hutcheson et al, 2000a), although in recent years a primary scrotal approach as originally described and advocated by Bianchi and colleagues (Bianchi and Squire, 1989; Iyer et al, 1995) has been advocated by some. The recommended age for surgical intervention has gradually declined over the years and presently is age 6 months in full-term males in whom the testes have failed to descend. However, the average age of orchidopexy remains about 4 years in many series, likely owing to the frequency of milder "acquired" cases as well as delayed referral of some cases diagnosed at birth (Barthold and Gonzalez, 2003). An option for pubertal and postpubertal boys is orchiectomy, especially if the testis is abdominal or difficult to mobilize because poor spermatogenesis and hypotrophy are usually present and the risk of carcinoma in situ and torsion exist (Rogers et al, 1998).

Inguinal Orchidopexy. After induction of anesthesia, the patient is reexamined to confirm that the testis is palpable and to identify the lowest testicular position. In the standard inguinal approach, a low transverse incision in Langer's lines at or below the inguinal crease is made superolateral to the pubic tubercle. Dissection of the subcutaneous tissue should include a search for a testis within the superficial inguinal pouch. The external oblique fascia is incised to expose the canal with care to avoid injury to the ilioinguinal nerve. Testis position is recorded relative to the inguinal canal. The spermatic cord is isolated, and the testis is dissected distally to its attachment to the gubernacular remnant. Transection of the gubernaculum distal to the sac will avoid potential injury to a long-looping vas. Longitudinal incision of the internal spermatic fascia allows free mobilization of an intact hernia sac, if present, and minimizes skeletonization of the vas and spermatic vessels. After transection, the sac is mobilized to the level of the internal inguinal ring and suture ligated. Incision of the internal spermatic and transversalis fascia at the level of the ring facilitates additional retroperitoneal mobilization of the vas and vessels, if needed. Further maneuvers to provide spermatic cord length include transection of lateral fascial bands along the cord, cranial retroperitoneal dissection, medial transposition of the testis beneath the epigastric vessels (Prentiss maneuver) and, if required, cranial extension of the incision. Very rarely, the testis cannot be brought to dependent scrotal position after these maneuvers and a two-stage procedure may be considered as an alternative to orchiectomy, which is preferentially reserved for grossly abnormal or atrophic testes. Dessanti and associates (2009) describe a novel two-stage technique for high canalicular or abdominal testes that involves placement of a polytetrafluoroethylene membrane around the mobilized cord, fixation of the testis to the invaginated scrotum with a pledget, followed by a 9- to 12-month delay that allowed spontaneous scrotal localization of the testis in 82% of 45 testes.

A large clamp or a finger can be used to create a tunnel just anterior to the pubis and a scrotal or subdartos pouch created after transverse incision of the scrotal skin (Ritchey and Bloom, 1995). The testis is passed through an opening in the dartos without twisting of the spermatic cord. Existing appendages should be excised and the epididymis inspected and any anomalies recorded. Recording of testicular volume by direct caliper measurement in three dimensions and similar (estimated) measurements of contralateral testicular volume can establish a baseline for postoperative assessment. Secure fixation of the testis within the pouch can be achieved by tension-free closure of the opening in the dartos around the cord, incorporating the cut edge of the tunica vaginalis. If needed, additional absorbable fixation sutures can be placed between the visceral tunica vaginalis and the dartos. Sutures through the tunica albuginea of the testis are not recommended because of possible injury to the testis via inflammatory or vascular insult; suture fixation of the testis is in any event not needed if mobilization is adequate and a subdartos pouch technique is used. Closure is completed with absorbable sutures. Supplemental local or regional techniques for perioperative pain control are advisable and may include local anesthetic infiltration or caudal anesthesia; the latter is particularly useful in younger patients undergoing bilateral inguinal or concomitant penile surgery.

Testicular biopsy has been performed routinely in some centers and is advocated by Hadziselimovic and colleagues (2007) as a method to determine prognosis for fertility. This approach is controversial and not recommended outside of research protocols because it does not change the current approach to treatment (Ritzen et al, 2007; Beckers and van der Horst, 2008). The risk to the cryptorchid testis from biopsy is theoretical; although long-term effects do not appear to include increased risk of microlithiasis or antisperm antibody formation (Patel et al, 2005), other more subtle effects cannot be excluded from the available data. Biopsy is indicated in cases of sexual ambiguity or if clinical evidence of testicular dysgenesis is present.

A minimum of 6 months' follow-up is needed to determine testis position and size once stabilized, and long-term follow-up is indicated for counseling of the patient regarding fertility issues, risk of testicular malignancy, and self-examination. Complications of inguinal orchidopexy for a palpable testis are uncommon; those of greatest frequency and concern include testicular retraction or atrophy. In a comprehensive literature review in 1995, Docimo (1995) concluded that the overall risk of atrophy or nonscrotal position was approximately 15% overall in published reports, significantly higher in abdominal or peeping testes (24%) compared with those distal to the internal ring (10%) and higher in boys operated after 6 years of age. Torsion of a scrotal testis after orchidopexy has been reported but is very rare, and the risk may be minimized by using a subdartos pouch. If complete intrascrotal testicular atrophy occurs postoperatively, further intervention is not needed but the option of testicular prosthesis placement should be offered to the patient and family (Bodiwala et al, 2007).

Implantation of a testicular prosthesis should occur at least 6 months after any inguinoscrotal procedure or after puberty and is best performed through an inguinal approach. Closure of the scrotal fascia above the implant using a purse-string nonabsorbable suture is required. Risks including displacement, pain, or infection occur in less than 5% of cases. Clinical experience suggests that cryptorchid boys may request prosthesis implantation less frequently than males with acute testicular loss after puberty (Bodiwala et al, 2007). Elder and associates (1989) recommended that prepubertal prosthesis placement be considered, but it is not clear whether this approach is preferable to placement after puberty.

Reoperation is indicated if a testis is nonscrotal after orchidopexy. If the testis is prescrotal, a primary scrotal approach can be considered and may allow adequate mobilization of the testis. If inguinal exploration is needed to provide sufficient cord length, several approaches are available. Redman (2000) described a useful technique for primary or secondary orchidopexy that involves a lateral approach to the cord after mobilization of the external oblique and cremaster fasciae. This approach avoids traversal of the previously scarred layers anterior to the cord and a clearer view of the anatomy. Cartwright and colleagues (1993) described mobilization of the intracanicular cord with an overlying patch of external spermatic fascia. The importance of correcting a persistently patent processus vaginalis and/or of adequate retroperitoneal mobilization of the cord in cases of high recurrent cryptorchidism has been stressed (Redman, 2000; Pesce et al, 2001; Ziylan et al, 2004). The results of secondary orchidopexy appear to be similar to the primary procedure, although the risk of vascular and vasal injury is theoretically higher (Pesce et al, 2001).

Transscrotal Orchidopexy. A primary scrotal approach can be considered when the testis is palpable (Bianchi and Squire, 1989; Iyer et al, 1995), although some surgeons reserve this approach for testes that are close to or can be drawn into the scrotum (Russinko et al, 2003; Rajimwale et al, 2004; Bassel et al, 2007; Takahashi et al, 2009). An incision along the superior scrotal border is made and the distal sac and overlying cremaster mobilized. Once dissected free, the sac can be placed on traction and freed as far cranially as possible, "high above the inguinal canal" (Iyer et al, 1995), although some cases require conversion to an inguinal approach (Parsons et al, 2003; Dayanc et al, 2007). Rajimwale and coworkers confirmed in several cases that the hernia sac had been effectively ligated above the internal ring via the scrotal incision when a secondary inguinal incision was required for further mobilization of the testis (Rajimwale et al, 2004). Fixation sutures through the tunica albuginea were used in many series of scrotal orchidopexy (Jawad, 1997; Russinko et al, 2003; Bassel et al, 2007; Dayanc et al, 2007; Takahashi et al, 2009). The risk of testicular retraction or atrophy was reported as 0% to 2% in most of these series after follow-up ranging from 1 month to 3 years. However, postoperative hernia was reported in about 3% of cases in two series containing a larger proportion of canalicular testes (Dayanc et al, 2007; Al-Mandil et al, 2008) and in 2% of hernias repaired by Bianchi's group using a scrotal approach (Iyer et al, 1995). Although the risk of this complication appears low, follow-up is not sufficient in reported series to fully define the risk.

Surgical Approach to the Abdominal Testis

Once an abdominal testis has been identified by laparoscopy or other means, a decision is made whether to proceed with an open or laparoscopic, one- or two-stage orchidopexy with or without spermatic vessel transection. Orchiectomy is appropriate for patients with testes that are poorly viable and/or at higher risk for tumor, such as very small or dysgenetic prepubertal or in postpubertal patients, and is best performed laparoscopically.

Open Transabdominal Orchidopexy. Extensive dissection of the vas and vessels is facilitated by a longitudinal opening of the internal oblique and peritoneum through an extended inguinal incision (Kirsch et al, 1998) or via a higher incision medial to the pubic tubercle and a preperitoneal approach (Gheiler et al, 1997; Jones and Bagley, 1979). In the procedure described by Jones and Bagley the internal ring is approached via a muscle-splitting incision, the peritoneum is opened, the testis is delivered, and the vas and vessels are freed from their peritoneal attachments. A tunnel is created to the scrotum, and the testis is secured in place as for an inguinal orchidopexy. The reported success rate for this procedure for abdominal testes was 95% (Gheiler et al, 1997).

Laparoscopic Orchidopexy and Fowler-Stephens Orchidopexy. Operative laparoscopy emerged over 15 years ago as the procedure of choice for abdominal orchidopexy (Caldamone and Amaral, 1994; Jordan and Winslow, 1994), and the basic surgical approach and high success rates have stood the test of time (Table 132–1). The feasibility of primary versus Fowler-Stephens orchidopexy depends on the length of the vas and vessels, presence or absence of looping ductal structures, and age of the patient. Although laparoscopy allows the surgeon to assess some of these features before choosing a specific surgical procedure, the choice may be difficult (Yucel et al, 2007). Observed testicular position alone may correlate poorly with the ultimate length of the cord after mobilization.

After induction of anesthesia, a further attempt to palpate the testis is made, although a laparoscopic approach may be considered for mobilization of high canalicular testes as well. After decompression of the bladder and stomach, an infraumbilical 5-mm trocar is placed for passage of a 30-degree lens and both internal rings are visualized. An open Hasson or Bailez technique is preferable for umbilical trocar placement in the pediatric age group to minimize the risk of injury (Franc-Guimond et al, 2003). CO_2 pneumoperitoneum to a maximum pressure of 8 to 12 mm Hg is used. The size and position of the testis within the abdomen is determined before further decision making. For single-stage laparoscopic orchidopexy, additional 2- or 3-mm trocars are placed in the right and left lower quadrants to triangulate with the umbilicus and ipsilateral internal ring or in the midclavicular line at the level of the umbilicus bilaterally. The major steps are mobilization of any structures extending distal to the internal ring, including epididymis/vas and gubernacular remnant, transection of the peritoneum lateral to the vessels and distal to the vas, and proximal mobilization of the vessels while maintaining collateral blood supply between the vas and spermatic vessels if a Fowler-Stephens maneuver becomes necessary. Samadi and associates (2003) advocate initial mobilization of the gubernaculum to be used as a handle for further mobilization of the testis, and minimal use of cautery during this maneuver. Ability to mobilize the testis to the opposite internal ring has been used as a measure of adequate length for placement in the scrotum but is not predictable in some series. Once mobilized, the testis is brought through a new hiatus at the level of the medial umbilical ligament or through the existing internal inguinal ring. This maneuver can be completed using a transscrotal clamp or port. With tension on the extra-abdominal testis, peritoneal attachments overlying the cord can be more easily transected, thus providing additional length. In some cases the testis can only be brought into the upper scrotum; the long-term adequacy of this approach is not clear. Excessive tension on

Table 132–1.

Results of Laparoscopic Orchidopexy*

PROCEDURE	SERIES	PATIENTS (TESTES)	AGE	FOLLOW-UP	HIGH POSITION	ATROPHY	OVERALL SUCCESS
Laparoscopic orchidopexy	Baker et al, 2001	178 (208)	36 mo	7.7 mo (mean)	0.6%† (1/178)	2% (4/178)	97%
	Samadi et al, 2003	139	?	≥6 mo	3%† (4/139)	0	97%
	Handa et al, 2005	58 (76)	?	2.2 yr (median)	0†	3% (2/65)	97%
	El-Anany et al, 2007	46	5 yr	3 yr (mean)	9% (4/46)	0	90%
	Kaye and Palmer, 2008	19 (38)	9 mo (median)	6-12 mo	18% (7/38)	0	82%
	Yucel et al, 2007	34	~12 mo (median)	5-8 mo (median)	19% (6/32)	16% (5/32)	65%
	Radmayr et al, 2003	28 (28)	1.9 yr	6.2 yr	0	0	100%
	Denes et al, 2008	24 (26)	6.4 yr	≥6 mo	0†	4% (1/26)	96%
	Esposito et al, 2002	25 (25)	3.9 yr (median)	23 mo (median)	0	4% (1/25)	96%
Laparoscopic one-stage FS	Esposito and Garipoli, 1997	33 (33)	3-10 yr (range)	30 mo (mean)	0	3% (1/33)	97%
	Baker et al, 2001	25 (28)	31 mo	8.6 mo (mean)	7%† (2/27)	22% (6/27)	71%
	Chang et al, 2001	20	1.5 yr (median)	≥6 mo	0†	16% (3/19)	84%
Laparoscopic two-stage FS	Baker et al, 2001	63 (74)	55 mo	20 mo	2%† (1/58)	10% (6/58)	88%
	Lotan et al, 2001	59 (66)	14 mo	3-12 mo	?	?	84%
	El-Anany et al, 2007	47	5 yr	3 yr (mean)	0	4% (2/47)	96%
	Radmayr et al, 2003	29 (29)	1.9 yr	6.2 yr (mean)	0	7% (2/29)	93%
	Robertson et al, 2007	21 (25)	36 mo (mean)	6 & 18 mo	0†	14% (3/21)	86%
	Denes et al, 2008	15 (21)	6.4 yr	≥6 mo	0†	14% (3/21)	88%
	Hay et al, 1999	20	?	≥6 mo	25% (5/20)	15% (3/20)	60%

*Reported results of abdominal, one- and two-stage Fowler-Stephens (FS) orchidopexy in.series with at least 20 treated testes. Age is mean for entire series unless otherwise noted. High position refers to testes not in dependent scrotal position.

†Position within scrotum not clearly documented. Overall success refers to the frequency of nonatrophic testes in satisfactory scrotal position according to criteria used by the authors.

the vessels during placement of the testis should be avoided, however, because injury or avulsion of the spermatic vessels may occur (Esposito et al, 2002). A key strategy should be preservation of the blood supply between the vas and spermatic artery during dissection so that the Fowler-Stephens procedure can be performed if necessary.

Formal closure of the dissected internal ring, irrespective of whether the mobilized testes passes through it, does not appear to be necessary (Handa et al, 2005; Riquelme et al, 2007); indeed, previous experience with open hernia repair suggests that ligation is not needed if the internal ring is dissected (Mohta et al, 2003). A contralateral patent processus vaginalis was identified in 9% of boys undergoing laparoscopic orchidopexy in one series (Palmer and Rastinehad, 2008), and laparoscopic repair was performed and recommended. The necessity for this approach in preventing clinical hernia formation is questionable based on studies of boys undergoing laparoscopic or open contralateral hernia repair (see Schier, 2007b, and discussion in the later section Hernias and Hydroceles).

For testes that are not near (variably defined as 2 to 4 cm above) the internal inguinal ring, transection of the spermatic vessels as originally described by Fowler and Stephens (1959) may be necessary; a long-looping vas facilitates but is not required for testicular mobilization to the scrotum. The Fowler-Stephens procedure is now typically performed laparoscopically with spermatic vessel clipping (Bloom, 1991) followed by laparoscopic or open testicular mobilization 6 months later or in one stage. Although most surgeons transect the spermatic vessels 1.5 to 3 cm above the testis, Koff and Sethi (1996) proposed that ligation close to the testis is preferable. This group subsequently studied the effect of low versus high transection of the vessels in prepubertal rats and showed a reduction in adult testicular sperm numbers that was similar in both groups (Srinivas et al, 2005). In human studies, testicular biopsies before and after spermatic vessel transection also showed a reduction in S/T count, a finding that was significant in younger boys (Thorup et al, 1999; Rosito et al, 2004). In general, the preferred approach is avoidance of spermatic vessel transection whenever possible; the available data suggest this is

possible in the majority of cases of abdominal orchidopexy. In rare cases, particularly if the testis is retrovesical, the vas is too short to allow scrotal placement of the testis and orchiectomy is ultimately required (Perovic and Janic, 1997).

The success rates for laparoscopic procedures as shown in Table 132–1 (Jordan and Winslow, 1994; Esposito and Garipoli, 1997; Hay et al, 1999; Baker et al, 2001; Lotan et al, 2001; Esposito et al, 2002; Radmayr et al, 2003; Samadi et al, 2003; Handa et al, 2005; Robertson et al, 2007; Yucel et al, 2007; Chang and Franco, 2008; Denes et al, 2008; Kaye and Palmer, 2008) appear to compare favorably with the corresponding 74%, 63%, and 77% overall success rates for open surgical and one- and two-stage Fowler-Stephens procedures, respectively, reported by Docimo (1995). Variation in reported results in these series may reflect inherent selection bias due to differences in patient age, testicular position, length of follow-up, and/or criteria used to define success, such as "intrascrotal" versus "dependent scrotal" position. Some authors recommend that ultrasound be used to confirm testicular viability postoperatively (Esposito et al, 2002). Other complications of laparoscopic orchidopexy appear to be rare and potentially include bladder or vascular injury, hypercapnia, and delayed small bowel obstruction (Esposito et al, 2003; Hsieh et al, 2009).

Laparoscopic techniques may be applicable in unusual cases, including bilateral orchidopexy, abdominal wall defects, polyorchidism, splenogonadal fusion, and transverse testicular ectopia with or without persistent müllerian ducts. Many authors recommend simultaneous bilateral abdominal orchidopexy (Kaye and Palmer, 2008), but the surgeon should consider a staged approach if both testes are very high or the viability of a testis is questioned during the course of orchidopexy. Depending on the outcome of the first procedure at 6 months' follow-up, the surgeon can choose an operative approach to the contralateral side that would appear to minimize the risk of bilateral testicular atrophy (Thorup et al, 2007). Some surgeons have considered microvascular orchidopexy to be a preferred approach to the solitary abdominal testis, particularly with historical success rates of 88% as compared with lower rates for open procedures (Docimo, 1995). At a center with substantial experience using the microvascular approach, long-term success rates of 96% for standard and 88% for laparoscopically assisted autotransplantation were reported (Bukowski et al, 1995b; Tackett et al, 2002). The advantage of this approach is preservation of the spermatic vessels, at the cost of longer operative time and requirements for an experienced microvascular surgeon and hospital stay.

Prognosis

Risk of Subfertility

Although there is strong evidence that a history of cryptorchidism is associated with subfertility in individual patients, the effects of age at diagnosis, type of treatment, and/or severity of disease on outcome remain incompletely defined. Major limitations in the interpretation of cryptorchidism outcome studies include selection bias due to incomplete follow-up of large patient cohorts, heterogeneity of diagnosis and timing/type of treatment, and other methodologic concerns, including lack of age-matched controls, failure of abstinence before semen analysis, and/or analysis of a single semen sample. In a large review of retrospective studies published in the 50 previous years that did not take these concerns into consideration and did not include a statistical meta-analysis, Chilvers and colleagues (1986) reported overall rates of oligospermia and/or azoospermia in 75% of formerly bilaterally and 43% of formerly unilaterally cryptorchid men. The limited available data comparing earlier (age < 9 years) and later treatment did not show differences in the frequency of subfertility after unilateral (281 cases) or bilateral (123 cases) orchidopexy. Similarly, subset analysis failed to identify any effect of hCG treatment. Two subsequent large studies of semen parameters in men who underwent orchidopexy in childhood also found differences between bilateral and unilateral cryptorchidism but less consistent overall results. Okuyama and associates (1989) reported normal sperm density in 0%, 72%, 77%, and 42% of men after bilateral orchidopexy (61 patients), unilateral orchidopexy (149 patients), unilateral orchiectomy (26 patients), and no treatment (38 patients) for inguinal testes without hormone therapy. All of these subjects had three semen analyses. In contrast, Gracia and colleagues (2000) reported normal semen samples in 10 of 55 (18%) men with a history of bilateral and 57 of 171 (33%) men with previous unilateral cryptorchidism. The majority of testes in this series were canalicular, and 80% of subjects received preoperative hCG therapy. These authors noted no differences based on testicular position, and semen quality was not correlated with age of surgery in either series. In a cohort of 91 patients with unilateral cryptorchidism who underwent orchidopexy after the onset of puberty (age 14 to 29), the risk of azoospermia or oligospermia was 84% (Grasso et al, 1991), a trend in keeping with the data reported previously (Okuyama et al, 1989). Puri and O'Donnell (1988) studied 142 men who underwent unilateral (119 men) or bilateral (23 men) orchidopexy at age 7 years or older and reported normal sperm density in 84% and 50% of cases, respectively.

Mean S/T counts obtained at biopsy show correlation with long-term fertility potential as measured by mean semen analysis parameters in series but may not be predictive in individuals (Engeler et al, 2000; Cortes et al, 2003a; Rusnack et al, 2003). Other data suggest a better correlation between the number of Ad spermatogonia in cryptorchid testes and sperm count in adulthood after previous unilateral or bilateral orchidopexy with or without prior hormonal therapy (Hadziselimovic et al, 2007; Hadziselimovic and Hoecht, 2008). In non–hormonally treated cases, total sperm count was normal (>40 million/ejaculate) in 84% of 25 men with Ad spermatogonia present in both testicular biopsy specimens, whereas it was subnormal in all 18 men (10 of the 19 men in this series had a history of bilateral cryptorchidism) in whom biopsies were negative for Ad spermatogonia. Total germ cell counts were reportedly not predictive of sperm concentration in this series (Hadziselimovic and Hoecht, 2008). **Both Ad spermatogonia count and germ cell absence appear promising as measures of fertility prognosis, but their predictive value has not been confirmed in additional studies to date.** Further prospective studies of these parameters are indicated.

Outcome studies of semen analysis in men with a history of cryptorchidism are believed to provide useful information that predicts fertility potential. However, a large population study of fertile and infertile men with fertile partners suggests that there is large overlap between semen parameters in men with and without proven paternity (Guzick et al, 2001). In this study, the authors established lower infertile threshold levels for density (13.5×10^6/mL), motility (>35%), and normal morphology (>9%) than had been established by World Health Association criteria. About 3% of fertile men in this series had a sperm density of less than 10×10^6/mL, and measurements between 13.4 and 48×10^6/mL were considered indeterminate. Repeated semen analyses, rarely obtained in studies of formerly cryptorchid men, are needed to provide reliable data in normal men (Oshio et al, 2004).

Consequently, determination of paternity status is an alternative measure of fertility that should be considered when determining prognosis. Limitations of this approach include paternal discrepancy and variability in the timing and degree of interest in attempts at paternity. Although of concern and not ethically retrievable, a recent review (Bellis et al, 2005) found that the median level of paternal discrepancy in 17 studies of unselected populations in Europe and the Americas is only 3.7% (interquartile range, 2% to 9.6%).

Two retrospective cohort studies of men with previous cryptorchidism assessed paternity in 145 (Gilhooly et al, 1984) and 40 (Cendron et al, 1989) cases. Together, these studies identified successful paternity in 100 of 123 (81%) men with a history of unilateral and 19 of 54 (35%) of men with a history of bilateral cryptorchidism. Lee and colleagues published a series of well-designed case control studies of fertility in cryptorchidism (Lee et al, 1996, 1997, 2000; Coughlin et al, 1999; Lee and Coughlin, 2001, 2002b; Bellis, 2005; Lee, 2005) Questionnaire, hormone, semen analysis, and paternity data were analyzed for a large cohort of men who underwent orchidopexy between 1955 and 1975 and a control group of similar age who were matched for timing of unrelated surgery. For all married or cohabitating men, 32 of 88 (36%) former bilateral, 322 of 609 (53%) former unilateral, and 413 of 708 (58%) controls had fathered children. **Of those attempting paternity, 32 of 49 (65%) former bilateral, 322 of 359 (90%) former unilateral, and 413 of 443 (93%) controls were successful.** There were no significant differences between the unilateral and control groups and no differences between groups in the frequency of attempted paternity or in other lifestyle factors that may adversely affect fertility. The frequency of successful paternity did not differ between men with previous unilateral cryptorchidism who had undergone orchiectomy and the control group. Relative risk for infertility was increased after hCG treatment (RR 4.7, $P = .002$) but not with higher testicular position or age at orchidopexy. Sperm density was less than or equal to 13×10^6/mL in all 8 patients with bilateral cryptorchidism that were studied; however, 3 of these men had fathered children (Lee and Coughlin, 2001). In contrast to previous studies, 83% of men in the unilateral group had normal sperm density and sperm motility and morphology did not differ from control values. Although hormone levels alone did not correlate directly with fertility, abnormal levels of serum inhibin-B, FSH, and/or sperm density provided cumulative risk of decreased fertility. However, the authors conclude that prediction of infertility is difficult in the absence of azoospermia or severe oligospermia. These investigators also found differences in basal and stimulated LH and in serum testosterone levels when comparing fertile and infertile or subfertile formerly cryptorchid men and suggest that global testicular dysfunction occurs in cryptorchid males. Moreover, there is some evidence from these studies of a relationship between improved testosterone, inhibin-B, and FSH levels in males who underwent earlier orchidopexy (Coughlin et al, 1999; Lee and Coughlin, 2002a).

Limited evidence suggests that defective spermatogenesis may exist in some adult patients with persistently retractile testis or with milder forms of acquired cryptorchidism with or without apparent spontaneous descent of the testis at puberty. In small, retrospective outcome studies, Puri and Nixon (1977) reported 74% paternity and normal testicular volume in a series of 43 adults with untreated retractile testes in childhood. Conversely, Nistal and Paniagua (1984) and Caroppo and colleagues identified 23 and 34 males, respectively, from infertility clinic data and identified poor semen parameters in the majority of cases, but the duration and severity of retractility was poorly documented in these series. These studies do not provide sufficient evidence for infertility risk in uncomplicated cases of retractile testis. Two series reported varying degrees of abnormal germ or Sertoli cell development in retractile testes of boys who underwent elective orchidopexy as compared with boys with descended testes; differences were qualitatively similar to findings in cryptorchid testes (Hadziselimovic et al, 1987a; Cinti et al, 1993). However, small sample size per subgroup limits interpretation of these data. Han and associates (1999) compared 61 retractile with 83 cryptorchid testis biopsies and noted similar trends but did not include a control group. In a retrospective series of 45 adults with spontaneous descent of bilaterally undescended testes after age 10 by history, Brenholm Rasmussen and coworkers (1988) observed testicular volumes of less than 15 mL in 62% and sperm counts below 20 million/mL in 44% of patients. Large, prospective studies of persistently retractile testes and cases of acquired cryptorchidism are needed to better define diagnosis and prognosis in these groups of patients.

In summary, available data provide strong evidence that fertility potential is compromised in men with a history of bilateral cryptorchidism but the frequency of abnormal hormonal and sperm parameters in unilateral cases is higher than the relative risk of infertility as measured by paternity data. Unfortunately, the number of formerly bilaterally cryptorchid men who have been comprehensively studied is limited. Although data suggest some association between age at surgery or hormone therapy and risk of infertility, further studies are needed to elucidate the relationships between these factors.

Risk of Malignancy

The increased risk of testicular germ cell tumor (TGCT) in males with a history of cryptorchidism has been known for many years. Both seminoma and nonseminomatous germ cell tumors (NSGCT) develop from carcinoma in situ (CIS) of the testis, also called intratubular germ cell neoplasia, unclassified (ITGCNU), and are believed to be developmental in origin (Rajpert-de Meyts and Hoei-Hansen, 2007). The hypothesis that persistent gonocytes are the precursors of testicular CIS has existed for some time, and recent gene expression data indeed support a common origin for the two cell types (Sonne et al, 2009). The histologic data suggesting that gonocytes fail to transform normally in cryptorchid testes may coincide with eventual transformation of these persistent cells into CIS and TGCT. However, to date no evidence directly links germ cell maldevelopment in individual patients to eventual malignant transformation. Using placenta-like alkaline phosphatase (PLAP) as a marker of ITGCNU, Engeler and associates (2000) identified PLAP-positive cells in 5% of 440 patients, most (82%) younger than 3 years of age, who had undergone testicular biopsy and orchidopexy several years earlier. Whereas up to 50% of adults with ITGCNU are expected to develop TGCT over time, no tumor was detected in the 15 of 22 affected individuals that the authors were able to evaluate a median of 21 years later. However, PLAP immunopositivity may be a normal finding in infants during the first year of life (Jorgensen et al, 1993). Similarly, Cortes and coworkers (2003b) identified multinucleated spermatogonia in 13 (8%) of 163 consecutive patients undergoing biopsy at the time of orchidopexy. This finding occurred in younger boys and was associated with an S/T count that was usually normal and higher than the mean for the majority of cases. Although not identified in normal boys, the relevance of this finding to tumor risk remains completely unknown.

Recently, in their exhaustive analysis of the literature Wood and Elder (2009) clarified the nature of increased TGCT risk in the previously cryptorchid and contralateral descended testis. Men with a history of cryptorchidism comprise about 10% of those presenting with TGCT. **The relative risk of malignant transformation in an undescended testis is 2.5 to 8 overall and 2 to 3 in boys undergoing prepubertal orchidopexy, which is lower than historical estimates.** This incidence correlates with the reported risk of CIS of 2% to 3% in previously cryptorchid men (Giwercman et al, 1989); a much lower risk (0% to 0.4%) was reported in children with nonsyndromic cryptorchidism (Cortes et al, 2001; Husmann, 2005). TGCT may occur in the contralateral descended testis of men with a history of unilateral cryptorchidism, but Wood and Elder (2009) conclude that the relative risk of only 1 to 2 indicates a level comparable to the general population that is not related to cryptorchidism per se. However, a recent meta-analysis shows that the relative risk of 6.3 (95% CI, 4.30 to 9.31) in the ipsilateral and 1.7 (95% CI, 1.01 to 2.98) in the contralateral testis is significant compared with controls (Akre et al, 2009). In another meta-analysis, Walsh and associates (2007) determined that the relative risk of testicular cancer was 5.8 (95% CI, 1.8 to 19.3) in men who underwent orchidopexy after age 10 to 11 as compared with those undergoing earlier correction. However, recent population-based data are conflicting, showing twice the risk of malignancy in orchidopexy cases operated at or after age 13 in one series (Pettersson et al, 2007) but no age-dependent differences in another (Myrup et al, 2007), possibly related to ascertainment bias in the latter series. Further studies are needed to clarify the relationship between age at orchidopexy and risk of testicular cancer. Review of tumor pathology in treated versus untreated cryptorchidism shows that seminoma is associated with persistently cryptorchid testes (74%) and nonseminoma is present in the majority of scrotal testes (63%) (Wood and Elder, 2009).

Certain subgroups with undescended testis are at increased risk for TGCT, including those with chromosomal defects and other genital anomalies (Cortes et al, 2001; Husmann, 2005). Husmann (2005) recommends that biopsy be performed in these individuals and in boys older than 12 undergoing orchidopexy, although the age cutoff and usefulness of biopsy during pubertal orchidopexy have not been clearly defined. Orchiectomy should be considered the preferred treatment of cryptorchid testes from puberty to the age of 50 (Wood and Elder, 2009). Swerdlow and associates (1997) reported in a retrospective cohort study that testicular biopsy at orchidopexy was associated with a relative risk of 6.7 for future TGCT compared with orchidopexy without biopsy, but the indications for biopsy in this series were not clearly known. A subsequent report from a large Scandinavian cohort showed that universal biopsy did not appear to increase the risk for TGCT beyond what is expected for previously cryptorchid men (Moller et al, 1998).

Testicular microlithiasis, characterized by multiple spectral calcifications within the testicular parenchyma (Fig. 132–5), is more frequently present in men with ITGCNU and germ cell tumors but is also present in 5% to 10% of the normal population and in a similar proportion of previously cryptorchid men (Patel et al, 2005; van Casteren et al, 2009). **Although concern exists that the risk for TGCT may be higher when cryptorchidism coexists with microlithiasis in individual patients, the appropriate follow-up strategy remains undefined.** Even less well defined is the significance of microlithiasis in general, which is not clearly shown to be an independent risk factor for TGCT. A recent population-based analysis of the prevalence of microlithiasis in primarily white boys shows that the prevalence is 4.2% and increases with age (Goede et al, 2009). In about half of these cases, the degree of microlithiasis was limited, defined as less than five lesions per testis, and not considered clinically significant. Slaughenhoupt and associates (2009) reported a case and reviewed pediatric reports of TGCT or yolk sac tumor in boys with microlithiasis but without other risk factors; they recommend periodic examination and ultrasonography in all cases. In contrast, biopsies are performed in adults with microlithiasis and one other risk factor for tumor, such as cryptorchidism, but if the biopsy is negative then no specific follow-up other than self-examination is recommended (van Casteren et al, 2009). **Testicular self-examination, which requires education and counseling of the patient, remains a mainstay of testicular cancer screening.** A description exists (http://www.cwpeds.com/pdfs/adolescents/TesticularExam.pdf), and it should be taught to all patients with a history of cryptorchidism after they reach puberty, preferably by the pediatric urologist or operating surgeon in addition to the primary care practitioner.

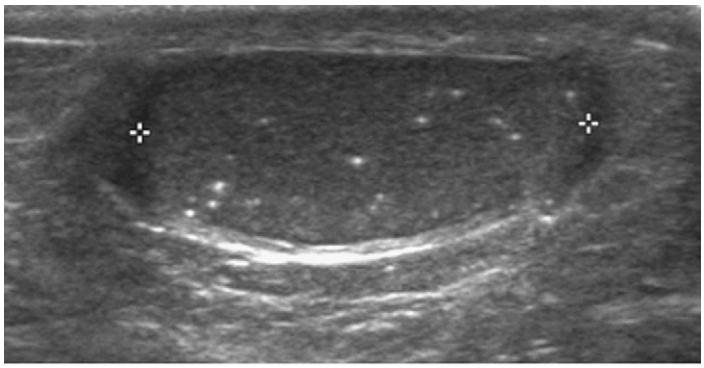


Figure 132–5. Testicular microlithiasis found incidentally in a 13-year-old boy with early puberty (Tanner stage II) and a clinical appendix testis torsion. The remainder of the study showed normal Doppler flow to testis, increased epididymal flow, and no visible appendage. The examination findings normalized within 1 week.

VARICOCELE

A scrotal varicocele is an abnormal dilation and tortuosity of the internal spermatic veins within the pampiniform plexus of the spermatic cord. Like cryptorchidism, varicocele is a common finding in otherwise normal males, may contribute significantly to the risk of infertility in adulthood, and is associated with a natural history that is poorly understood. Although varicocele is clearly a risk for subfertility in certain individuals, its effect on paternity is less clear because about 85% of men with varicocele in population-based studies have fathered children (Pinto et al, 1994; Safarinejad, 2008). There are few well-designed prospective studies of adult or pediatric populations that clarify the risk factors for associated testicular dysfunction in males with varicocele. Moreover, recent data add further confusion to the debate regarding which varicoceles require treatment during adolescence.

Epidemiology and Pathogenesis

Although considered a congenital lesion, varicocele is rarely diagnosed before school age, and the frequency and severity vary with age, method of diagnosis, and Tanner stage. Population data from large groups of children and adolescents suggest that the majority

Key Points: Cryptorchidism

- Cryptorchidism occurs in 1% to 4% of full-term males; postnatal spontaneous descent and reascent of testes are common.
- The causes of cryptorchidism are largely unknown, but birth weight, gestational age, genetic, and environmental risk factors likely contribute to disease risk.
- The diagnosis of cryptorchidism may be "acquired," that is, made in cases of apparent full descent at birth or after spontaneous descent of a cryptorchid testis and may be more common in boys with retractile testes. Yearly testicular examinations are recommended.
- About 80% of undescended testes are palpable, and 60% to 70% are unilateral.
- Many boys with nonsyndromic cryptorchidism have epididymal anomalies and a patent processus vaginalis, and some have reduced LH and/or testosterone levels during the postnatal surge.
- Orchidopexy is recommended for testes that remain undescended after 6 months of age; hormone therapy is not recommended.
- Laparoscopy is the procedure of choice, and imaging studies have limited value in the diagnosis and treatment of intra-abdominal cryptorchidism.
- Sperm counts are reduced in at least 25% of formerly unilateral and the majority of formerly bilateral cryptorchid men, but paternity rates in the unilateral group are similar to those of control men.
- Adult dark (Ad) spermatogonia counts may predict fertility potential in males with cryptorchidism.
- The relative risk of malignancy in cryptorchid testes is 2 to 8 and may be 2 to 3 after prepubertal orchidopexy.

appear after the age of 10 and that the risk rises with progression through puberty, reaching a peak at Tanner stage 3 (Kumanov et al, 2008). **The prevalence rate of clinically diagnosed varicoceles in this population is 8% to 16%, similar to that reported for the adult population, but ranges from 3% to 43% between studies** (Niedzielski et al, 1997; Skoog et al, 1997; Akbay et al, 2000; Stavropoulos et al, 2002; Kumanov et al, 2008; Zampieri and Cervellione, 2008). Although almost all reported varicoceles were left sided in older studies, some recent series report a 7% to 10% bilateral incidence and color Doppler ultrasonography (CDUS)–based evaluation identified additional subclinical left or bilateral varicoceles in 7% to 17% of adolescent cases (Akbay et al, 2000; Pfeiffer et al, 2006; Cervellione et al, 2008). Bilateral repair of palpable (primarily grade 1) varicoceles was performed in one third of 10- to 24-year-old males in a recent series (Decastro et al, 2009), suggesting that a right-sided varicocele may be more common in adolescents than previously recognized. In adults, bilaterality is reported in 15% to 50% of cases (Zini and Boman, 2009).

The cause for the appearance and, in some cases, progressive severity of varicoceles in children and adolescents has not been clearly defined, but susceptibility is likely determined by genetic predisposition, body habitus, and/or intrinsic venous abnormalities. Genetic factors likely contribute to the risk, but not necessarily the severity, of varicoceles. The risk of varicocele in first-degree relatives was four to eight times the risk in fertile men undergoing vasectomy or male kidney donors and especially high in brothers (Raman et al, 2005; Mokhtari et al, 2008). Studies using CDUS show that risk of varicocele progression during adolescence may be related to the prevalence of continuous or spontaneous as opposed to Valsalva-induced spermatic venous reflux (Pfeiffer et al, 2006; Cervellione et al, 2008; Zampieri and Cervellione, 2008). The underlying pathologic process is unknown but assumed to be related to the unique angle of the spermatic vein/renal confluence on the left side coupled with increased hydrostatic pressure and/or valvular incompetence (Zini and Boman, 2009). The "nutcracker phenomenon," defined as compression of the left renal vein between the aorta and superior mesenteric artery, was identified in a subset of affected boys by venography and CDUS and may contribute to the pathogenesis of varicocele (Coolsaet, 1980; Kim et al, 2006). Increased height and relatively lower weight and body mass index (BMI), a classic tall, thin body habitus, is associated with varicocele in adolescents and adults in clinical as well as screening populations (Handel et al, 2006; May et al, 2006b; Nielsen et al, 2006; Kumanov et al, 2008; Tsao et al, 2009) and may contribute to risk via increased spermatic vein length and/or hydrostatic pressure. Alternatively, the diagnosis may be less common in obese individuals owing to increased scrotal wall fat that reduces diagnostic sensitivity. In a recent study not yet confirmed by other investigators, Sakamoto and Ogawa reported greater peak and antegrade flow and venous diameter in the prostatic venous plexus of men with bilateral varicoceles, who comprised 33% of their series of 141 men with varicoceles, compared with controls and men with unilateral varicoceles (Sakamoto and Ogawa, 2008). These data are consistent with other studies showing increased risk of saphenofemoral junction incompetence (Karadeniz-Bilgili et al, 2003) and varicose veins (Kilic et al, 2007) in cases of varicocele, reflecting the possibility of a generalized venous abnormality.

Diagnosis and Classification

Although screening programs exist in some communities, the majority of varicoceles in children and adolescents are identified incidentally by a primary care practitioner and less commonly due to patient complaints of discomfort or scrotal swelling. Associated pain is reported in 2% to 11% of cases (Zampieri et al, 2008a) and may be a more common finding in some geographic regions. In rare cases, a varicocele is diagnosed after rupture due to sports-related or other trauma.

The patient is examined in a warm room in the supine and standing positions. The scrotum is observed for visible swelling, and the spermatic cord is palpated at rest and during the Valsalva maneuver. The standard grading system used for varicoceles is *grade 1*, palpable only with Valsalva; *grade 2*, easily palpable but not visible, and *grade 3*, easily visible. A large varicocele should decompress in the supine position; failure to decompress, particularly on the right side, is an extremely rare finding but warrants evaluation for an abdominal mass (Roy et al, 1989). *Grade 0* (subclinical) varicoceles are visualized by CDUS but are nonpalpable. As noted earlier, the use of CDUS to diagnose varicoceles increases the disease prevalence in any given population because subclinical varicoceles are identified. In adults, a subclinical right-sided varicocele was diagnosed about 10 times more often when thermography (measurement of scrotal temperature), CDUS, or venography was used as compared with physical examination only (Gat et al, 2004). However, significant controversy exists even in the infertile adult population regarding the need to diagnose and treat nonpalpable varicoceles.

The appropriate criteria for varicocele diagnosis using CDUS are controversial in adults, and experience with this use is limited in the pediatric and adolescent population. As reviewed by Lee and associates (2008), standards used for spermatic vein diameter (typically > 3 mm) and presence of retrograde flow vary in adult studies, although diagnostic accuracy may be increased using a combination of criteria. In a study of 625 boys with varicocele and 50 normal controls, Niedzielski and colleagues (1997) measured spermatic vein diameter in the standing position and venous reflux with Valsalva maneuvers. Using 2 mm as the upper limit of normal spermatic vein diameter based on findings in normal boys, these researchers obtained normal measurements in 95%, 70%, and 4% of boys with grades 1, 2, and 3 varicoceles, respectively. Similarly, spermatic venous diameter as measured in the supine position was a poor criterion for clinical varicocele and did not predict risk of testicular volume loss in a smaller series of boys with varicocele (Kozakowski et al, 2009). In studies of spermatic venous blood flow, reflux was identified in two thirds of boys with grade 2 or 3 varicoceles and flow velocity measured in the standing position correlated with grade of varicocele and sperm motility (Niedzielski et al, 1997). Kozakowski and coworkers (2009) measured supine peak retrograde spermatic vein flow with Valsalva maneuvers and noted that high flow rates (>38 cm/sec) were strongly associated with testicular volume asymmetry. The significance of these data is unclear, because the usefulness of spermatic vein flow measurement in adolescents will require standardization and prospective correlation with functional outcome.

Testicular size and consistency should be documented at the initial examination and at intervals during follow-up. The affected testis may be unusually soft, but the prevalence and relevance of this finding is not well documented. Although analysis of bilateral testicular volume is important, there is no consensus regarding the appropriate method of analysis. Options include calipers to measure testicular length, width, and depth or one of two commonly used orchidometers. The Prader orchidometer is a chain of 12 solid wooden ellipsoids with volumes of 1 to 6, 8, 10, 12, 15, 20, and 25 mL that are visually compared with the size of each testis. The Takihara orchidometer comprises 15 elliptical rings with inner dimensions corresponding to ellipsoid volumes of 1 to 6, 8, 10, 12, 14, 16, 19, 22, 26, and 30 mL that are placed over the widest circumference of the testis. Alternatively, ultrasonic placement of electronic calipers in three dimensions can be used with volume calculated by one of several formulas, the most common being the Lambert formula, 0.71(length × width × depth) or the volume of a rotational ellipsoid, 0.52(length × width × depth) or 0.52(length × depth^2). Costabile and colleagues (1992) performed blinded measurements of models of known volume using ultrasonography and the rotational ellipsoid formula and showed an overall standard deviation of 1.6 mL but less variation for volumes less than 10 mL. Studies assessing the relative accuracy of measurements obtained using ultrasonography and orchidometers in children and adolescents suggest that while all techniques are reliable, ultrasonography is more sensitive in determining differences in size between the left and right testis (Costabile et al, 1992; Chipkevitch et al, 1996; Diamond et al, 2000). Because orchidometer volume estimates are routinely greater than those determined using ultrasound and the rotational ellipsoid formula, calculation of differential volume using the following formula

(Right [unaffected] testicular volume – left [affected] testicular volume)/right testicular volume

will likely yield greater differential volumes when ultrasonography is used. However, based on studies of the 6- to 13-mL canine testis, ultrasound measurements and the Lambert formula provide the most accurate and precise testicular volume estimates (Paltiel et al, 2002).

Associated Pathologic Processes

There is abundant evidence that a varicocele may alter testicular growth, spermatogenesis, and fertility potential. The etiology of testicular injury is presumed to be related to increased scrotal temperature, but the pathogenesis remains poorly understood. Moreover, the ability to conceive exists in the majority of men with varicoceles. **The appropriate treatment of children and adolescents with varicoceles should be selective, based on the presence of risk factor(s) predictive of long-term subfertility.**

Testicular Hypotrophy

The association of varicocele with a relative decrease in volume of the left testis has been known for many years (Lipshultz and Corriere, 1977). In his population-based survey of adolescents and young adults, Steeno (1976) observed but did not quantify an adverse effect of grade 2 and 3 varicoceles on testicular volume and/or consistency. Subsequently, others (Lyon et al, 1982; Kass and Belman, 1987) showed that relative left testicular volume loss is common in adolescents with varicocele, may improve or resolve after varicocele correction, and therefore may reflect significant testicular injury. Significant left hypotrophy is variously defined as a 10%, 15%, 20%, 2- or 3-mL relative difference in testicular size and reportedly present in 10% to 77% of cases (Lyon et al, 1982; Okuyama et al, 1988; Akbay et al, 2000; Thomas and Elder, 2002; Diamond et al, 2004b; Kolon et al, 2008; Preston et al, 2008). Variability of this finding is likely related to the method of measurement (visual estimation, orchidometer, or ultrasound with varying computational formulas used), referral patterns, and the formula used to determine percent difference between testes. Moreover, population-based data show that a rapid increase in testicular size may occur as early as 10 years of age and persist until age 19, depending on the population studied and the Tanner stage of pubertal development (Tables 132–2 and 132–3) (Schonfeld, 1943; Rundle and Sylvester, 1962; Zachmann et al, 1974; Daniel et al, 1982; Matsuo et al, 2000) and can vary widely between individuals particularly between 13 and 14 years of age (Marshall and Tanner, 1970). Therefore longitudinal measurements over several years may define testicular hypotrophy more accurately than single measurements, particularly in early puberty. Most often, size differential is calculated as follows:

Percent difference = 100 × (right testicular volume – left testicular volume)/right testicular volume,

although Kolon and associates (2008) use the formula:

100 × (right testicular volume/total testicular volume – left testicular volume/total testicular volume).

Varicocele grade is positively associated with risk of left testicular hypotrophy in some studies (Thomas and Elder, 2002; Zampieri et al, 2008b) but not others (Alukal et al, 2005; Kolon et al, 2008).

Table 132–2.

Tanner Stages

Pubic Hair	
1	No pubic hair
2	Sparse growth of long, slightly pigmented downy hair primarily at base of penis
3	Darker, coarser, and more curled hair spreading sparsely over the pubic region
4	Adult-type hair covering an area smaller than in most adults
5	Adult-type hair in typical adult male distribution extending up linea alba and to medial surface of thighs
(6)	Further spread of hair after puberty (not used routinely)
Genitalia	
1	Testes, penis, and scrotum same proportional size as in early childhood
2	Enlargement of scrotum and testes with change in texture and reddening of scrotal skin
3	Growth of the penis, first in length and then breadth; further growth of scrotum and testes
4	Further growth of penis in length and breath; development of glans and testes; scrotum further enlarged and darkened
5	Genitalia adult size and shape without further enlargement

Table 132–3.

Testicular Volumes Based on Tanner Stage

	Daniel et al, 1982†				Zachmann et al, 1974‡	
	Left Testis (cm^3)		Right Testis (cm^3)		Total (mL)	
TANNER STAGE*	Mean	SD	Mean	SD	Mean	SD
1	4.8	2.8	5.2	3.9	6.0	2.6
2	6.4	3.2	7.1	3.9	6.8	3.6
3	14.6	6.5	14.8	6.1	9.3	3.8
4	19.8	6.2	20.4	6.8	12.6	4.2
5	28.3	8.5	30.2	9.6	16.3	4.6
6					18.9	4.0

*Pubic hair staging (Zachmann et al, 1974) or mean of genital and pubic hair staging (Daniel et al, 1982).

†Data based on length and width measurements ($0.52 \times L \times W^2$) of 348 U.S. males age 12 to 19 years.

‡Data based on orchidometer measurements of 2139 Swiss males age 12.5 to 20 years.

Kass and colleagues (2001) compared 434 varicocele cases and 70 controls of similar age (mean 14 years) and noted that right testicular size was also significantly reduced compared with control values in Tanner stage 4 to 5 males with grade 3 varicocele. Okuyama and coworkers (1988) reported testicular hypotrophy (size < 2 SD below the mean for Japanese boys) on the side contralateral to a grade 2 or 3 varicocele in 22% of their patients, and their data suggested lower sperm density in patients with bilaterally small testes. Mean right testicular volume increased significantly after left varicocele repair but not in untreated control groups in several other studies (Laven et al, 1992; Yamamoto et al, 1995; Paduch and Niedzielski, 1997). Paduch and Niedzielski (1996) reported a correlation between total testicular volume and sperm concentration in adolescents but did not observe a significant decrease in right testicular size between varicocele patients and controls. Consequently, the significance of global testicular size in boys with left varicocele remains poorly defined. Although not presently available, ultrasound-derived size measurements for each testis based on population-specific norms and comparison with outcome would provide further insight into this question.

"Catch-up" growth, defined as normalization of left relative to right testicular size, occurs in 32% to 83% of patients after varicocele repair (Cayan et al, 2002; Greenfield et al, 2002; Yaman et al, 2006; Castagnetti et al, 2008; Feber and Kass, 2008; Decastro et al, 2009; Poon et al, 2009; Zampieri et al, 2009) and in 55% to 70% of boys on average in various series (Barroso et al, 2009). A conclusion that postoperative testicular catch-up growth is less likely in boys older than 14 (Cayan et al, 2002) was not supported by another study addressing this issue (Decastro et al, 2009). Most clinicians believe that postoperative resolution of left testicular hypotrophy is evidence that varicocele repair improves testicular function in adolescents. However, a clear understanding of the relationship between varicocele repair and restoration of testicular growth is complicated by observations that testicular size differential may improve spontaneously in untreated patients, varicocele may affect growth of both testes, testicular edema or venous stasis may hypothetically contribute to testicular enlargement, catch-up growth may occur despite surgical failure, and improvement in sperm counts does not necessarily correlate with catch-up growth. In an early observational study, Paduch and Niedzielski (1997) observed some improvement in mean testicular volume differential in boys followed expectantly without surgery. Kolon and coworkers (2008) reviewed serial ultrasound studies performed at least 6 months apart (≥3) in 71 boys observed without intervention for an average of 3.5 years and noted asynchronous testicular growth in many. Using a 15% volume differential as a normal cutoff, these authors observed hypotrophy in 54% of boys initially and only 15% at final follow-up, suggesting that the majority of potential surgical candidates may normalize with time without treatment. Similarly, Preston and colleagues (2008) reported normalization of hypotrophy in 50% of 33 boys followed a median of 2.12 years; neither of these studies showed deterioration to greater than 20% hypotrophy during observation. In contrast, other investigators rarely noted spontaneous catch-up growth but reported worsening or development of significant hypotrophy in 10% to 26% of boys over time (Thomas and Elder, 2002; Kozakowski et al, 2009; Zampieri and Cervellione, 2008), whereas others reported no statistical difference in either direction in longitudinal studies (Diamond et al, 2004b). **The fact that intraindividual testicular volume differential may change significantly over time supports the conclusion** (reached by Kolon et al, 2008) **that normal pubertal testicular development may be asynchronous. Alternatively, testicular size may appear variable over time because of inherent error in measurement techniques.** These same factors may bias reported postoperative results showing testicular volume improvement that do not include an untreated comparison group.

Kocvara and colleagues (2003) reported significant testicular growth as early as 6 weeks after surgery, enhanced catch-up growth with lymphatic and arterial ligation, and intratubular edema in several biopsies obtained at hydrocele repair several years after non–lymphatic-sparing varicocelectomy with or without artery sparing. Their hypothesis that lymphatic ligation may contribute to increased testicular volume is not consistent with data from other centers showing no difference in rates of catch-up growth based on lymphatic (Poon et al, 2009) and/or arterial (Barroso et al, 2009) preservation. Moreover, Laven and associates (1992) noted that varicocele repair increased the volume of small but not normal-sized testes in their series. Postoperative left testicular hypertrophy (>10% size differential relative to the right testis) is

reported in several studies and attributed to non–lymphatic-sparing procedures or to a rebound effect on spermatogenesis in the affected testis (Gershbein et al, 1999; Cayan et al, 2002; Kocvara et al, 2005).

To date, no studies clearly define the natural history and relationship, if any, between testicular hypotrophy in adolescence and that seen in adulthood. In a retrospective review, Sayfan and colleagues (1997) reported long-term follow-up data in 32 men who underwent varicocele repair at 11 to 15 years of age, comprising 27% of a cohort treated between 1972 and 1982. In comparing this group with normal controls and untreated men with varicoceles, they noted similar semen quality and no testicular volume differential in treated and control groups, and significantly lower sperm counts and smaller left testes in the untreated group, but did not clarify how this latter population was identified. Despite these data, it is important to note in the general adult population with varicoceles that testicular hypotrophy is not a clear risk factor for infertility. Mean testicular volume differential in unselected fertile men with varicoceles (3.1 ± 0.3 mL) was not significantly different from that found in infertile men with varicoceles (2.5 ± 0.6 mL), and 82% of all men with varicoceles and 68% of those with grade 3 (not statistically different from the entire group) had evidence for normal fertility (Pinto et al, 1994). Other studies support the finding that left testicular volume is smaller in both fertile and infertile men with varicoceles but that bilateral hypotrophy is more common in the infertile group (Pasqualotto et al, 2005; Shiraishi et al, 2009). Shiraishi and associates (2009) suggest that additional cofactors contribute to the risk of infertility in men with varicoceles. In 611 patients with varicoceles (45% with grade 2 or 3) presenting for infertility evaluation, Sigman and Jarow (1997) reported testicular size discrepancy of at least 3 mL in 50%, with higher grade and lower total motile sperm counts (corrected for grade) in those with this finding. In contrast, in another study of 245 men presenting for infertility with varicoceles (90% with grade 2 or 3), bilateral but not unilateral hypotrophy was a significant predictor of abnormal total motile sperm count (Wu et al, 2008).

Significant discrepancy between left and right testicular size is considered the most reliable clinical risk factor available and remains the primary indication for varicocele correction. Unfortunately, the available data do not provide a clear picture of the effect of varicocele or its correction on testicular growth and function in individual patients. The presence of hypotrophy is not invariably associated with reduced fertility potential, but other predictors such as varicocele grade, global testicular growth, and hormonal studies have not been critically evaluated in adolescents. **Prospective, randomized studies are needed to clearly establish whether unilateral and/or bilateral testicular hypotrophy or catch-up growth accurately predict fertility potential in adolescent varicocele.**

Testicular Histology

Although extensively studied in adults (reviewed by Hienz et al, 1980), histologic data from testicular biopsies of adolescents with varicocele have been limited and inconsistent. These biopsy findings vary from normal histology by light and electron microscopy in all (Fideleff et al, 2000) or most normal men with severe hypospermatogenesis in a minority of cases (Kass et al, 1987; Aragona et al, 1994) to degenerative tubular changes, altered Leydig cell number, and/or proliferative lesions of the vasculature in the majority of cases (Hienz et al, 1980). In a small retrospective series of men who underwent testicular biopsy at the time of adolescent varicocele repair, Hadziselimovic and associates (1995) observed abnormal tubular maturation and Leydig cell number but were unable to correlate these data with ultimate sperm quality in adulthood.

Hormonal Function

Kass and colleagues (1993a) reported an exaggerated LH and FSH response to gonadotropin-releasing hormone (GnRH) stimulation in about 30% of boys with varicocele, although they were unable to show a correlation with testicular hypotrophy. Similar data were reported in a smaller study that also included inhibin-B measurements (Carrillo et al, 1999), which have also not shown consistent correlation with testicular size or semen parameters in adolescents or adults with varicocele (Turkyilmaz et al, 2006; Romeo et al, 2007; Basar et al, 2010). Aragona and associates (1994) identified severe germ cell abnormalities in 3 of 15 adolescents with grade 2 to 3 left varicocele and 2 of these boys had exaggerated LH and FSH response to GnRH, but 2 others with increased LH response had normal histology, and none of their patients had more than 12% left testicular hypotrophy. Baseline LH and FSH levels are not consistently different in the presence or absence of varicocele during adolescence in most studies (Laven et al, 1992; Yamamoto et al, 1995; Cayan et al, 2005; Ku et al, 2005). Guarino and coworkers (2003) observed increased LH, FSH, and simulated FSH levels in 20 varicocele patients with abnormal semen parameters (age 16 to 19, Tanner stage 5) compared with 56 with normal semen, but 6 of the former group had bilateral varicoceles, a history of inguinal surgery, or cryptorchidism. Basal and stimulated gonadotropin levels were not consistently different in varicocele patients when compared with controls and did not improve after surgery in another series (Fideleff et al, 2000). GnRH stimulation testing is not presently used routinely as an indication for varicocele surgery in adolescents because of lack of correlation with testicular size differential; however, further studies are warranted because hypotrophy itself does not always correlate with outcome or with histologic changes in the testis.

Semen Quality

Despite many variables associated with collection and interpretation of semen analysis samples, semen quality is considered the most useful indicator of fertility potential. Because of wide variation in sexual maturation, age alone is not a good criterion to establish reliability of semen analysis results. Janczewski and Bablok (1985a to 1985d) compared bone age, testicular size, Tanner stage, hormone levels, and timing of first ejaculation with attainment of normospermia in a series of 134 Polish boys aged 12 to 19 years old. In these studies the first ejaculation occurred beginning at a bone age of 13 years, 16 months or earlier after the beginning of puberty, and the majority of boys met criteria for normospermia by a bone age of 17. Tanner stage 5 was associated with asthenozoospermia and occasional oligozoospermia in addition to normospermia. Mean testicular size based on caliper measurements increased with progression in semen quality but showed a large standard deviation in boys achieving normospermia, and a significant drop in LH and FSH levels occurred with attainment of normospermia. **Because progressive improvement in sperm quality may parallel continued growth of the testis through the teenage years, semen analyses may not reliably predict testicular function in boys with varicocele before completion of testicular growth.**

A number of studies are now available that report semen analysis data in males diagnosed with varicocele, usually grade 2 or 3, in adolescence (Table 132–4). In the majority of these studies, at

Table 132–4.

Semen Analysis Results in Adolescent Varicocele

STUDY	GROUPS	AGE	SEMEN ANALYSIS	GRADE	FINDINGS
Randomized Cases vs. Controls					
Laven et al, 1992	27 treated 26 untreated 16 controls	17-20	2	2-3	Initial SC 43-52 ± 32-44 × 10^6/mL (NS between groups); treated group increased to 69 × 10^6/Ml ($P < .01$) at 1 year; no consistent correlation of semen quality with catch-up growth
Yamamoto et al, 1995	29 treated 22 untreated 18 controls	15-19 17-21 14-20	1	1-2	Initial SC 49-51 ± 16-32 × 10^6/mL (NS between groups); treated group increased to 74 × 10^6/mL ($P < .002$) at 1 year
Untreated Cases vs. Controls					
Haans et al, 1991	67 untreated 21 controls	17-21	2	2 (15) 3 (52)	SC < 20 × 10^6/mL in 19% controls, 20% grade 2 and 13% grade 3 (NS). Correlation (r = .26, $P = .03$) between left testicular volume and total sperm count but not SC
Paduch and Niedzielski, 1996	36 untreated 38 controls	17-19	2	2-3	SC 53 ± 31 × 10^6/mL in cases and 56 ± 36 × 10^6/mL in controls (NS); significant differences in motility and vitality between groups; sperm concentration correlated with total testicular volume
Cedenho et al, 2002	20 untreated 20 controls	Mean 16	1	2-3	SC 57 ± 55 × 10^6/mL in cases and 73 ± 54 × 10^6/mL in controls (NS), impaired sperm–zona pellucida binding capacity (cases)
Bertolla et al, 2006	20 untreated 20 controls	15-17 T4-5	1	2-3 bilat	SC 78 ± 17 × 10^6/mL in cases and 86 ± 25 × 10^6/mL in controls (NS), increased sperm DNA fragmentation (cases)
Mori et al, 2008	67 untreated 160 controls + grade 1	14-18 T4-5	1	2 (49) 3 (18)	SC 50 ± 52 × 10^6/mL in grade 2, 37 ± 41 × 10^6/mL in grade 3, and 88 ± 76 × 10^6/mL in controls + grade 1 ($P = .0003$)
Treated vs. Untreated Cases					
Okuyama et al, 1988	13 treated 10 untreated	18	≥3	2-3	Normal SA* in 69% treated and 20% untreated cases ($P < .05$)
Zampieri and Cervellione, 2008	92 treated 127 untreated	18	2	2-3	WHO criteria† met in 64% treated (all with hypotrophy) and 80% untreated (none with hypotrophy) (NS); no correlation of SA with varicocele grade or catch-up growth
Preoperative vs. Postoperative					
Cayan et al, 2005	33 preoperative and postoperative	Mean 16.4 preoperative	1	2-3 (48% bilateral)	SC 22 ± 3.6 (SE) × 10^6/mL before and 40 ± 5.7 × 10^6/mL at 28 ± 13 months (mean ± SD) after artery/lymphatic sparing repair ($P = .007$)
Ku et al, 2005	35 preoperative and postoperative	15-20	2	Most 2-3	SC 32 ± 3 (SE) × 10^6/mL before and 41 ± 3 (SE) × 10^6/mL at 6 months after artery/lymphatic sparing repair; % motile sperm increased ($P < .001$); most surgeries performed for pain
Untreated Cases					
Guarino et al, 2003	68 untreated	16-19 T5	2	Most 2-3	21% with abnormal OMI (SC × % motile × % oval sperm), no correlation with testicular volume
Diamond et al, 2007	57 untreated	14-20 T5	1-2	Most 2-3	TMSC: <10% hypotrophy ($n = 27$), 64 (32-134) 10-20% hypotrophy ($n = 18$), 32 (13-94) >20% hypotrophy ($n = 12$), 10 (3-82) $P = .02$ > 20% vs. < 10%; no correlation with grade

*Normal SA defined as ≥30 × 10^6 sperm/mL, ≥60% motility, and ≥70% normal morphology.
†World Health Organization (WHO) criteria ≥20 × 10^6 sperm/mL, ≥50% motility, and ≥30% normal morphology.
NS, not significant; SA, semen analysis; SC, sperm concentration, mean ± SD unless noted; T, Tanner stage; TMSC, total motile sperm count (volume × concentration × % motile sperm), expressed as median (25th to 75th percentiles).

least two semen samples were obtained using techniques meeting World Health Organization criteria in older teenagers, although Tanner stage 5 was not always specified. In two randomized studies comparing treated and untreated cases with controls, no differences were found in semen quality at initial or follow-up analysis between groups, except for a significant postoperative increase noted in the treated group in both studies that exceeded sperm concentrations seen in controls (Laven et al, 1992; Yamamoto et al, 1995). The cause for improvement in semen quality above control levels was not clear to these investigators, but Laven and coworkers (1992) hypothesized a rebound in spermatogenesis. Significant increases in sperm concentration were also reported in uncontrolled studies, but these may be biased by variations in semen quality that occur with time in late adolescence. The majority of series comparing untreated cases with controls of similar age found no significant differences in semen between groups or consistent differences between nonrandomized treated versus untreated cases. Correlations between left or total testicular volume and semen parameters were noted by some investigators (Haans et al, 1991; Paduch and Niedzielski, 1996; Diamond et al, 2007) but not others (Guarino et al, 2003). Investigators were unable to correlate postoperative increases in left testicular volume or varicocele grade with semen analysis data in controlled (Laven et al, 1992) and uncontrolled (Cayan et al, 2002; Diamond et al, 2007; Zampieri and Cervellione, 2008) studies. **Although there are insufficient data from randomized prospective studies, the available data suggest trends toward poorer sperm quality that may be limited to a subset of affected males with varicocele, but that grade and postoperative testicular catch-up growth do not reliably predict ultimate semen quality.**

Intratesticular Varicocele

In less than 2% of patients, a large varicocele may be associated with an intratesticular component that is diagnosed by ultrasound and otherwise unsuspected (Diamond et al, 2004a). Although it may be confused with lesions of the testis or rete testis, the diagnosis is easily made by demonstration of venous flow in anechoic structures greater than 2 mm in diameter near the mediastinum testis that is enhanced by the Valsalva maneuver. Approximately one third are reported to be bilateral. Diamond and associates (2004a) suggest that these lesions may reflect increased risk to the testis and that surgery is therefore indicated.

Treatment

In the past, varicocele was considered a progressive lesion because of its higher prevalence in men with secondary as opposed to primary infertility (Gorelick and Goldstein, 1993). However, in a more recent study the distribution of varicoceles by grade and the prevalence of unilateral and bilateral testicular hypotrophy were similar in both groups, although sperm counts were higher, suggesting a female factor, in secondarily infertile men (Walsh et al, 2009). Moreover, an 8-year longitudinal study of men with varicocele and normal sperm counts did not show worsening of semen quality over time (Lund and Larsen, 1998). These and other data do not support the belief that the effect of varicocele on testicular function is progressive or that unilateral testicular hypotrophy is necessarily indicative of infertility in men with varicocele (Jarow, 2001). Therefore observation remains the approach of choice for the majority of adolescents with varicocele. **Despite pitfalls associated with the use of significant testicular hypotrophy as the primary criterion for surgical intervention and evidence that testicular size discrepancy may be variable during adolescence, the main indications for surgical intervention remain significant left (≥20%) or bilateral testicular hypotrophy, pain or abnormal semen analysis, the latter most reliable in boys of Tanner stage 5 and/or at least 18 years of age.** Although not studied in detail, bilateral hypotrophy may be more ominous and an indication for intervention but must be determined based on nomograms specific for the population, the patient's Tanner stage, and the measurement technique being used. Pain is a rare indication for surgery, reported in only 2% to 10% of patients in most series and relieved by the procedure in 68% to 88% of patients (Zampieri et al, 2008a).

Surgical Repair of Varicocele

As in adults, several techniques are used for repair of adolescent varicocele, including inguinal/subinguinal, laparoscopic/retroperitoneal, or venographic approaches. The most commonly used techniques are the microscopic subinguinal approach and the suprainguinal open or laparoscopic approach with either mass ligation of the cord above the vas (Palomo) or with lymphatic and/or artery-sparing techniques. The choice of procedure is dependent on surgeon preference, experience, and complication rates that vary based on technique and length of follow-up (Table 132–5: Poddoubnyi et al, 2000; Misseri et al, 2001; Greenfield et al, 2002; Esposito et al, 2004; Cayan et al, 2005; Kocvara et al, 2005; Schiff et al, 2005; Yaman et al, 2006; Castagnetti et al, 2008; Feber and Kass, 2008; Glassberg et al, 2008; Barroso et al, 2009; Diamond et al, 2009; Tong et al, 2009 and references therein). There are no existing long-term outcome data available to support the use of any particular approach. Differences between subinguinal and suprainguinal approaches are primarily based on type and frequency of complications. In some series, the length of postoperative follow-up may be inadequate to identify potential recurrences, which as opposed to cases of persistence are first identified 6 months or more postoperatively (Glassberg et al, 2008). The latency period for appearance of a hydrocele may vary from a mean or median of a few months to almost 2 years postoperatively, and some are not diagnosed for several years or longer (Misseri et al, 2001; Esposito et al, 2004; Feber and Kass, 2008). Although these may resolve spontaneously, up to one half may require intervention. Esposito and associates (2004) most commonly treated postoperative hydrocele with scrotal aspiration, which was required a median of three times under anesthesia

Table 132–5.
Results of Adolescent Varicocele Repair

PROCEDURE	RECURRENCE/ PERSISTENCE	HYDROCELE	TESTICULAR ATROPHY
Open suprainguinal (Palomo)	2%-4%	0%-30% (10%)*	
Laparoscopic			
Nonlymphatic/ artery sparing	0%-9%	11%-32% (7%)*	
Artery and/or lymphatic sparing	1%-7%	0%-4%	
Microscopic subinguinal	0%-10%	0%-6%	Rare
Nonmicroscopic inguinal	7%-33%	8%-14%	
Sclerotherapy	6%-35%	Occasional	Rare

*Number in parentheses refers to meta-analysis of Barroso et al, 2009.

before resolution. Most surgeons proceed with formal scrotal hydrocele repair only in cases of large or symptomatic hydrocele, with repair ranging from 5% to 50% of affected patients in several recent series (Misseri et al, 2001; Esposito et al, 2004; Feber and Kass, 2008; Diamond et al, 2009).

Subinguinal/Inguinal Microsurgical Varicocelectomy

The *subinguinal microscopic approach* provides the advantages of facilitated artery- and lymphatic-sparing, high rate of success, and low risk of hydrocele but may be time consuming and requires microscopic surgical skills. Some advocate this approach to optimize artery sparing, based on the assumption that it is more likely to optimize testicular function (Goldstein, 1995). The procedure used in children is similar to that used in adults as originally published (Goldstein et al, 1992; Schiff et al, 2005). A 2.5- to 3-cm incision is made over or just above the external inguinal ring, and the spermatic cord is isolated with or without opening the external oblique fascia. In the procedure described by Goldstein and colleagues (1992) the testis is delivered and all external spermatic and gubernacular veins are ligated, although not all surgeons deliver the testis. After incision of the internal spermatic fascia, the cord is examined using 10× to 25× magnification. Lower degrees of magnification (e.g., loupes) can be used but probably provide inferior results (Greenfield et al, 2002; Cayan et al, 2005; Diamond et al, 2009). External, internal, and vasal veins greater than 2.5 mm in diameter are ligated, and the spermatic artery and accompanying lymphatics are identified and spared. Schiff and associates recommend applying pressure to the testis after ligation is completed to determine whether an impulse can be felt in the ligated veins. The artery is identified by visualization of pulsations under higher (25×) magnification, application of 1% papaverine, use of a Doppler probe, and/or elevation with partial occlusion followed by release and visualization of pulsations within the vessel suspected to be an artery (Raman and Goldstein, 2004). The subinguinal approach is associated in rare cases with testicular atrophy (necrosis), which has not been reported for suprainguinal procedures (Diamond et al, 2009). The cause of necrosis is unclear but may be related to total venous occlusion, as may occur in some cases of sclerotherapy, or to compromise of both spermatic and vasal arteries.

Open/Laparoscopic Suprainguinal Varicocelectomy

The *suprainguinal approach* with spermatic artery ligation is a simple procedure performed either open or laparoscopically and associated with high success rates but also higher rates of hydrocele formation. Lymphatic and/or artery sparing is associated with a reduction in the incidence of postoperative hydrocele, but identification and preservation of these vessels may be difficult, even with magnification afforded by the use of laparoscopy. In retrospective studies, Zampieri and associates (2007a, 2007b) report that artery sparing is associated with improved semen quality but no randomized prospective data exist that clearly define the effect of artery sparing on testicular function. Theoretically, testicular compromise may occur with spermatic artery ligation in patients with a history of previous inguinal surgery (Skoog et al, 1997) but was not reported to occur in a small series of boys after a laparoscopic Palomo procedure (Barqawi et al, 2002). Similarly, a risk to the testis exists after non–artery-sparing varicocelectomy with subsequent compromise to the vasal artery or vein, as in vasectomy.

In the standard open procedure, a muscle-splitting incision is made just medial to the anterior superior iliac spine and the peritoneum is identified and mobilized medially. The entire bundle of spermatic vessels above the vas is mobilized, isolated, and clipped or suture-ligated. Open or laparoscopic Palomo techniques are performed with and without transection of the vessels, but no evidence supports a preference for either approach. A microscopic lymphatic-sparing procedure may be performed through a retroperitoneal incision, with initial data in a small series showing no hydrocele or recurrence after short-term follow-up (Wong et al, 2009).

Laparoscopic varicocele repair is performed after standard placement of an umbilical trocar, which is usually performed in children using an open (Hassan) technique. The patient is placed in slight Trendelenburg position, and the bladder is emptied. After intraperitoneal insufflation with CO_2, the spermatic cord is visualized and two additional port sites are placed under direct vision in the left midclavicular line just inferior to the umbilicus and in the lower midline or right lower quadrant for a left-sided varicocele, triangulating with the umbilical port and the internal ring. Alternatively, some surgeons use ports in both lower quadrants. A peritoneal incision is made several centimeters or more superior to the internal ring and lateral to the spermatic vessels, and the vascular bundle and surrounding tissue are mobilized away from the peritoneum. For spermatic artery preservation, approaches similar to those used for subinguinal procedures can be used, including a laparoscopic Doppler probe and papaverine in addition to the magnification provided by the laparoscope. Kocvara and colleagues (2005) recommend initially grasping the largest lateral vein to facilitate mobilizing the entire bundle. They noted that 1 to 3 lymphatics, which appear as clear tubular structures, accompany the artery and smaller veins and that in typical lymphatic-sparing procedures 5 to 12 can be identified and preserved. The injection of vital dyes into the paratesticular tissues for visualization of the majority of lymphatics along the spermatic vessels has been reported but is not universally used because of potential technical challenges and risks associated with inadvertent intratesticular injection (Schwentner et al, 2006; Makari et al, 2007). Options for vascular ligation include permanent (usually silk) sutures tied extracorporeally, locking metal clips to avoid slippage, or transection using the harmonic scalpel or vessel-sealing devices. To avoid recurrence, vein(s) accompanying the artery should be identified and ligated. In a variation of the usual approach, Cimador and colleagues (2008) used CDUS to search for dilated, refluxing deferential veins in the iliac fossa, which if present were ligated at the time of a laparoscopic Palomo procedure. The necessity of this approach in preventing persistent or recurrent varicoceles has not been shown, and a theoretical concern for vasal artery injury with concomitant spermatic artery ligation exists. Injury to the genitofemoral nerve has been reported in a limited number of adolescent and adult series of laparoscopic varicocelectomy, comprising a total of 3% of cases, and may be more commonly associated with use of cauterizing instrumentation (Muensterer, 2008). This complication presents as postoperative paresthesias in the distribution of the nerve along the proximal anterior thigh that slowly resolves over weeks or months.

Sclerotherapy/Embolotherapy

Antegrade or retrograde injection of sclerosant or embolizing material has been used for many years to treat adults with varicocele, but published experience in children and adolescents is limited. In general, both retrograde (Reyes et al, 1994; Mazzoni et al, 1999; Alqahtani et al, 2002; Sivanathan and Abernethy, 2003; May et al, 2006a; Beutner et al, 2007; Granata et al, 2008; Reiner et al, 2008) and antegrade procedures are less successful

than open or laparoscopic procedures (see Table 132–5) and require significant radiation exposure. Venous occlusion is achieved in retrograde procedures using sclerosants such as 3% sodium tetradecyl sulfate or polidocanol, with or without intravascular coils or balloons. The procedure can be accomplished under local anesthesia and is typically performed at centers with expertise in interventional radiology. In series comprised primarily of children and adolescents the procedure is reported to be unfeasible for technical reasons in 5% to 22% of cases; and with varying degrees of follow-up (rarely more than 1 or 2 years), rates of persistence or recurrence are 6% to 35%. Self-limiting complications include pain, epididymo-orchitis, phlebitis, or scrotal swelling; partial testicular atrophy and hydrocele occur rarely. Antegrade techniques entail use of a small subinguinal or upper scrotal incision, isolation of a vein or veins amenable to cannulation with or without fluoroscopic confirmation of antegrade flow into the internal spermatic vein, and injection of a sclerosant followed by ligation of the vein (Ficarra et al, 2004; Zaupa et al, 2006; Carmignani et al, 2009). This also can be performed under local anesthesia, and success rates are reported to be 4% to 12%, lower than for retrograde sclerotherapy, but complications are similar. Recently, Lebed and colleagues (2008) reported adjuvant use of sodium morrhuate sclerotherapy at the time of subinguinal or inguinal varicocele repair with or without use of the operating microscope. Their reported recurrence rate overall is similar to that reported for the subinguinal open approach alone, although they suggest that the additional use of a sclerosant may reduce the risk of recurrence owing to unrecognized proximal collateral veins.

Key Points: Varicocele

- The prevalence of adolescent varicocele is 8% to 16%, similar to that found in adults.
- Susceptibility to varicocele is determined by genetic predisposition, a tall, thin body habitus, and/or intrinsic venous abnormalities.
- Pain is the presenting complaint in less than 10% of adolescents with varicocele.
- Treatment of adolescent varicocele should be selective, because about 85% of adults with varicocele do not present with problems related to fertility.
- Ultrasonography is the most sensitive method for determining volume discrepancy between testes, and the Lambert formula (length × width × depth × 0.71) is preferable for volume calculation.
- A 15% to 20% reduction in volume (hypotrophy) of the affected testis is common in boys presenting with varicocele; hypotrophy resolves in 55% to 70% of cases after varicocele repair but may also improve spontaneously with progression through adolescence.
- Hypotrophy but not varicocele grade is inversely correlated with semen quality in some series, but postoperative testicular catch-up growth does not necessarily imply improved semen quality.
- Testicular hypotrophy involving the affected or both testes, abnormal semen analysis, and pain are current indications for adolescent varicocele repair.
- Laparoscopic or microscopic subinguinal artery- and lymphatic-sparing techniques for varicocele repair are associated with the lowest risk of both recurrence and hydrocele.

HERNIAS AND HYDROCELES

Definitions

The processus vaginalis and inguinal canal develop in both sexes in the first trimester of gestation (Barteczko and Jacob, 2000), although subsequent development of the processus vaginalis is more prominent in males to allow transinguinal passage of the testis. In males, the full length of the processus within and distal to the inguinal canal (the funicular process) becomes obliterated but the distal portion remains open as the tunica vaginalis within the scrotum. In an autopsy study, complete closure of the processus vaginalis was observed in only 18% of full-term infants at birth (Mitchell, 1939). Contralateral exploration of 1965 children with a unilateral inguinal hernia revealed that the processus vaginalis was patent in 63% of patients younger than 2 months and about 40% of those 1 to 2 years of age, with similar frequency up until age 16 (Rowe et al, 1969). The time frame for closure of the processus vaginalis in individuals without a hernia is not clear; however, the incidence of incidental patency observed in older children and adults at autopsy or laparoscopy is about 20% (Ajmani and Ajmani, 1983; van Wessem et al, 2003).

Persistent patency of all or a portion of the processus vaginalis within the inguinal canal may but does not always result in a symptomatic hernia or hydrocele (Fig. 132–6). If the processus remains widely patent, allowing passage of abdominal viscera, a clinical ***indirect inguinal hernia*** is present extending into the canal, labium, or scrotum. If fluid alone passes into a patent processus vaginalis and surrounds the testis within the tunica vaginalis, a ***communicating hydrocele*** is present (see Fig. 132–6A). Other forms of hydrocele include a ***spermatic cord hydrocele,*** which is associated with obliteration of the processus distally and in some cases proximally (see Fig. 132–6B and C), and noncommunicating simple ***scrotal hydrocele*** or ***abdominoscrotal hydrocele.*** Partial closure of a communicating sac may occur within the canal, producing both a proximal hernia and a distal noncommunicating hydrocele. Simple patency of the processus vaginalis is required but not sufficient for development of a hernia or communicating hydrocele.

Epidemiology and Pathogenesis

The risk of pediatric hernia is highest in neonates, particularly premature boys; in contrast, the prevalence of hydrocele varies with age and etiology. Hydroceles that persist or first appear after birth are more likely to be associated with hernias, whereas those that disappear in infancy or appear at or after puberty are more commonly noncommunicating and due to delayed fluid absorption or abnormal fluid dynamics within the tunica vaginalis. Rare causes of nonpainful hydrocele include tumor or inflammatory processes within the scrotum.

Inguinal Hernia and Communicating Hydrocele

The incidence of inguinal hernia in childhood is 1% to 5%, with a male to female ratio of 5 to 10:1 and an increased propensity for right-sidedness, unilaterality (75% to 90%), and occurrence in premature infants (up to 30%) as noted for cryptorchidism (Jones et al, 1998; Kapur et al, 1998; Brandt, 2008). A clinical hernia or hydrocele may present at any time during childhood, but the average age in most large series is 3 to 4 years, although a third of pediatric hernias present in the first few months of life (Kapur et al, 1998). The vast majority of pediatric hernias are indirect inguinal hernias, although direct and femoral hernias also occur.

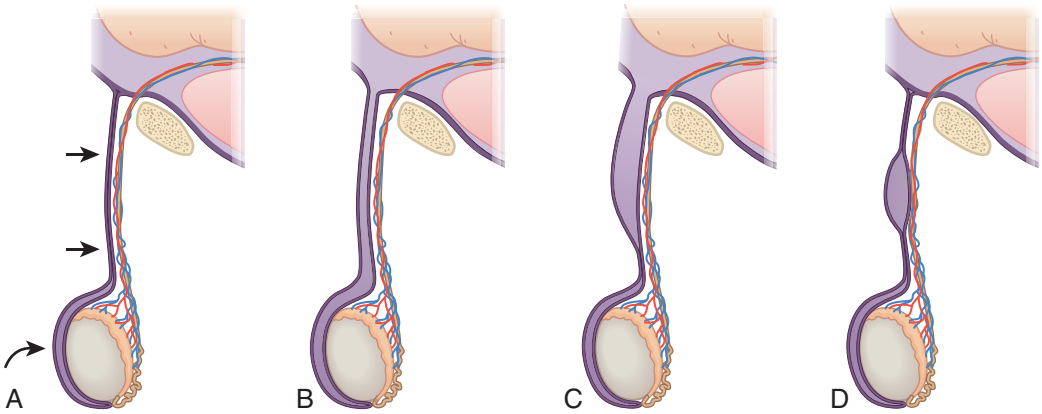


Figure 132–6. Anatomy of the processus vaginalis in hydrocele. **A**, Normal closure of the processus vaginalis; *straight arrows* indicate the funicular process; *curved arrow* is the tunica vaginalis. **B**, Communicating hydrocele with complete patency of the processus vaginalis; **C**, Funicular hydrocele with distal closure of the processus vaginalis; communication with the peritoneal cavity may also result in hernia. **D**, Encysted hydrocele of the spermatic cord. (From Martin LC, Share JC, Peters C, Atala A. Hydrocele of the spermatic cord: embryology and ultrasonographic appearance. Pediatr Radiol 1996;26:528–30.)

In a large series of 6361 consecutive pediatric hernias treated at a single institution, 19% were associated with hydroceles (70% scrotal only, 26% cord, and 4% both), although this may reflect referral bias (Ein et al, 2006).

Newly apparent hydroceles may be associated with a processus vaginalis that is freely communicating proximally but closed at some level along the cord (see Fig. 132–6) with or without encysted or multiloculated segments (Martin et al, 1996). Most are asymptomatic, but rarely a portion of the sac or hydrocele may undergo acute torsion (Tillett et al, 2006). Although the circumference of the sac as measured at surgery tends to be smaller in communicating hydroceles as compared with hernias, the predictive value of this finding is limited (Tanyel et al, 2000). In an unusual observational study, 59% of 302 newly identified hydroceles presenting between 1 and 18 (mean 4.4) years of age were clinically communicating, that is, with a clear history of fluctuation, and 6% were spermatic cord hydroceles (Christensen et al, 2006). Seventy (65%) of the apparent noncommunicating and 5 (29%) of the cord hydroceles were observed without surgery and, of these, 39 and 3, respectively, appeared to resolve spontaneously during follow-up. However, surgical findings were not reported in this series so the overall frequency of processus vaginalis patency in these patients is not known. In several series of all boys undergoing hydrocele repair during a defined period, the processus vaginalis was completely obliterated in 0% to 22% of cases (Elder, 1992; Barthold and Redman, 1996; Han and Kang, 2002). **These data indicate that the majority of new hydroceles occurring after birth and before puberty are associated with a patent processus vaginalis.**

Noncommunicating Hydroceles

Simple hydroceles not associated with hernias occur in both infancy and in older boys. Stable, nonfluctuating scrotal hydroceles that occur in at least 5% in male neonates (Osifo and Osaigbovo, 2008) are presumably related to delayed closure of the processus vaginalis, are typically bilateral, and often resolve with time as the processus closes in the perinatal period and reabsorption of tunica vaginalis fluid occurs. Similarly, the majority of hydroceles occurring at or after puberty are noncommunicating, although the exact proportion that are associated with a hernia and the overall incidence of hydrocele in this population are unclear. In a study specifically relating patient age to patency of the processus vaginalis, Wilson and associates (2008) studied 101 boys from birth to 20 years of age (mean 5.7) presenting with hydrocele and noted patency in 29% and 88% of those older and younger than 10, respectively.

Genetic and Other Risk Factors

The risk of inguinal hernia during childhood is increased in families, with a 28% risk in other family members and a higher relative risk in first-degree relatives (6.9) and particularly female siblings (17.8) of affected girls (Gong et al, 1994; Jones et al, 1998). Detailed pedigree analysis suggests dominant inheritance with reduced penetrance and sex influence. The gene(s) influencing susceptibility to congenital (indirect) inguinal hernia remain unknown but may overlap with those determining risk of cryptorchidism because there is overlap in familial risk and in susceptibility factors for both traits. Congenital hernia and cryptorchidism are both associated with low birth weight, bladder exstrophy, epididymal anomalies, connective tissue disorders, cystic fibrosis, posterior urethral valves (Heikkila et al, 2008), and, in some studies, increased risk for testicular cancer (Pottern et al, 1985; Tollerud et al, 1985). Inguinal hernia is also a component of over 200 syndromes (80 also include cryptorchidism; Winter-Baraitser Dysmorphology Database, http://www.lmdatabases.com) and is more common in patients with ventriculoperitoneal shunts and other causes of ascites (Grosfeld et al, 1991).

Diagnosis

The most common presentations of pediatric inguinal hernia are inguinal or inguinoscrotal swelling in infancy and new onset of scrotal swelling in older children. Typically the child is asymptomatic, but the swelling is observed with crying or straining or may be preceded by a bout of vomiting, constipation, or respiratory illness. Communicating hydroceles usually fluctuate and may appear larger after activity or at the end of the day as compared with early morning. Rarely acute scrotal swelling is accompanied by pain, and other causes of acute scrotum must be ruled out. Nausea, vomiting, and in some cases fever suggest incarceration. The risk of incarceration is highest in infancy,

particularly in ex-premature males, and is uncommon after 5 years of age.

Multiple approaches are described to increase intra-abdominal pressure and confirm the presence of a hernia on physical examination, including immobilization of the extremities to induce crying in infants, and coughing, blowing bubbles, or blowing up balloons and laughing in older children (Brandt, 2008). Suggestive physical findings include asymmetrical widening of the inguinal region and the "silk glove" sign, which is elicited by palpation of the spermatic cord over the pubis, resulting in a sensation of layers of the sac slipping over each other. Hydroceles often appear bluish, can be transilluminated, and may be partially or fully decompressable. Swelling that extends into and above the inguinal canal is more likely a hernia if reducible and/or if crepitus associated with bowel loops is present. In contrast, abdominoscrotal hydroceles are ballotable on bimanual scrotal-abdominal examination and cannot be decompressed. Attention should be paid to palpation and documentation of the position of the ipsilateral testis. Additional parental observation and/or office examinations may be warranted if an inguinal bulge is not elicited or if there is no clear history of fluctuation of an asymptomatic scrotal hydrocele.

Inguinoscrotal ultrasonography can be used to differentiate bowel loops from simple fluid and to visualize the testis, patent processus vaginalis, or hernia sac. If the testis is not palpable, ultrasonography is useful in determining whether a tumor with secondary hydrocele or cryptorchidism is present. Preoperative knowledge of these entities is critical for defining preoperative evaluation, parental counseling, and surgical approach. Toki and coworkers (2003) classified the appearance of the internal ring by ultrasonography. Using visualization of an open processus vaginalis of at least 20 mm in length as a criterion for contralateral inguinal exploration surgery, they observed a reduced risk of metachronous hernia after 2 years' follow-up. Although its use is not routine, ultrasonography may be helpful in defining fluid or intra-abdominal content in the inguinal canal with increased abdominal pressure in patients with suspected hernia or communicating hydrocele and questionable findings on routine examination. Alternatively, laparoscopy can be used to diagnose and treat inguinal hernia, as discussed later.

Associated Pathologic Processes

Several diseases associated with inguinal hernia and/or similar presentation require a high index of suspicion for diagnosis. Incomplete testicular descent may coexist with clinical hernia and should be excluded or corrected at the time of repair. Other genital anomalies such as polyorchidism, transverse testicular ectopia with or without persistent müllerian ducts, and splenogonadal fusion may present at the time of hernia repair. Abnormal epididymal-testicular attachment correlates with degree of closure of the processus vaginalis (Elder, 1992; Barthold and Redman, 1996). In phenotypic females, rare cases of androgen insensitivity syndrome may be identified at the time of hernia repair by examination of the abdominal or inguinal gonads, careful genital examination, and calibration of vaginal length.

Surgical Repair

Once a diagnosis of inguinal hernia or communicating hydrocele is made, timely elective repair is indicated. If ipsilateral cryptorchidism is present in an infant with a clinically apparent hernia, repair should proceed without observation for spontaneous testicular descent. Repair is performed as an outpatient procedure except in cases of ex-premature infants, who receive apnea monitoring in the hospital overnight if less than 50 to 52 weeks' postconceptional age. Some authors recommend delaying surgery until after this time point versus proceeding with repair before discharge from the hospital, although the reliability of the family and the higher risk of incarceration in infants (Stylianos et al, 1993; Chen et al, 2009) should be taken into account. In contrast, neonatal hydroceles should be observed for spontaneous resolution, because they are not associated with a persistently patent processus vaginalis in the majority of cases and most resolve in the first or second year of life.

Standard Inguinal Hernia Repair

The traditional inguinal approach to hernia/hydrocele repair is the preferred approach for most surgeons in view of a high success rate, low morbidity, limited degree of associated pain, and good cosmesis. A small incision in Langer's lines at or below the inguinal skin crease and superolateral to the pubic tubercle is made (Kogan, 2007). The external oblique fascia is exposed and incised through the external inguinal ring with care to avoid the ilioinguinal nerve. The spermatic cord is exposed and the hernia sac visualized and dissected free, open or closed, from the adjacent spermatic cord structures, which is facilitated by longitudinal incision of the external spermatic fascia. A long-held principle is the importance of high ligation of the hernia sac at the level of the internal inguinal ring to avoid risk of recurrence (Grosfeld et al, 1991). If the sac is large or thickened, it should be opened before transection to identify prolapsed bowel, omentum, or a sliding component, which if present is reduced before closure. Tightening of the internal ring with absorbable suture is recommended in cases of significant widening (Ein et al, 2006; Brandt, 2008). If a loculated hydrocele is present, it is exposed from above after distal mobilization of the overlying cremaster muscle and fascia in a bloodless plane and incised longitudinally for complete decompression. If the testis is easily visualized, the surgeon should remove any testicular or epididymal appendage that is present. The testis is then grasped and pulled caudally to a dependent scrotal position and if not dependent an orchidopexy should be performed. In pubertal boys with hydrocele, a primary inguinal approach is preferred if there is clinical evidence of a communicating hydrocele; otherwise a transscrotal hydrocele repair is performed as in adults and an inguinal incision made only if a proximal communication is identified. Pain control is augmented by an ilioinguinal or caudal nerve block.

Early postoperative complications are rare after repair of pediatric hernia via an inguinal approach. The reported risk of recurrence is 0.7% to 1% and may be related to failure of high ligation of the sac, size of the hernia, injury to the floor of the canal or sac, and/or comorbid conditions that affect wound healing (Grosfeld et al, 1991; Vogels et al, 2009). Wound infection and bleeding are similarly rare. Persistence of a hydrocele is very rare after decompression at the time of hernia repair (0.1% in the series by Ein and associates [2006]) and should be observed for spontaneous resolution for at least 1 year. If persistent, secondary scrotal hydrocele repair is indicated or reoperative hernia repair is required if fluctuation suggests a recurrent hernia.

Complications related to the genital tract including secondary cryptorchidism, testicular atrophy, and vasal injury occur, but their incidence is not well defined. Some cases of undescended testis after previous hernia repair may reflect milder primary forms of incomplete descent that were not clinically evident

preoperatively. Patients should be examined postoperatively on a yearly basis to ensure that testicular position does not change. Likewise, close observation is needed to identify testicular atrophy. The risk of this complication in general is unknown, but a 0.3% incidence was reported in the large single center series of Ein and associates (2006). Excised hernia sac tissue reportedly contains portions of vas deferens in 0.13% to 0.3% of cases, although embryonal remnants not representing true ductal structures are much more common (1.5% to 2.9%) (Popek, 1990; Partrick et al, 1998; Steigman et al, 1999). However, these data reflect results at high-volume pediatric centers and may be lower than those applicable to other practices. The risk of vasal injury may also be higher in young infants and/or cases of incarceration. Of course, injury to the vas may occur without transection and be manifest as vasal obstruction later in life. Indeed, pediatric hernia repair was the most common cause of vasal obstruction in a series of men presenting to a large infertility practice; the prevalence of this outcome in all boys undergoing repair using present surgical techniques is not known but in a review of older publications was estimated to be 0.8% to 2% (Sheynkin et al, 1998). Manipulation or stretching of the vas in adult rats (reviewed in Brandt, 2008) can produce obstructive lesions or even testicular atrophy, but the degree to which these effects are applicable to humans is unknown. The overall risk of this significant complication and its potential to cause clinical subfertility is undefined because many cases may be unilateral.

Scrotal Approach to Inguinal Hernia Repair

Concurrent with recent reports advocating a scrotal approach to orchidopexy, some authors suggest a similar approach to inguinal hernia and communicating hydrocele (Lais and Ferro, 1996; Fearne et al, 2002; Gokcora and Yagmurlu, 2003). Initial data suggest no major differences in the rates of success or degree of morbidity using this approach compared with standard inguinal surgery. Fearne and colleagues (2002) ligated the processus vaginalis at the level of the external inguinal ring, with one recurrence in 195 repairs in boys followed a mean of 13 months postoperatively. Potential issues related to the level of sac ligation based on technique and patient age have not been fully addressed (Wilson et al, 2008). Long-term data are needed to define the benefits and limitations of the scrotal approach to inguinal hernia repair.

Laparoscopic Inguinal Hernia Repair

With increase in the use of minimally invasive surgical techniques in recent years, laparoscopic repair of hernias in children has become an alternative to the standard open procedure. Two major techniques are reported: peritoneal closure of the defect (Schier, 2006) and an extraperitoneal approach (Takehara et al, 2006; Endo et al, 2009).

With experience, the operative time may be similar to open surgery; however, even in very large series the risk of recurrence (as high as 4%) is higher than with open repair but may decrease with increasing experience (Saranga Bharathi et al, 2008) and appears to be lower (<1%) with extraperitoneal approaches. However, Schier observed that some recurrences are not associated with an open internal inguinal ring on laparoscopic reexploration and may be related to a lipoma within the inguinal canal that would normally be addressed in an open repair (Schier, 2007a). Decreased pain and operative time after laparoscopic as compared with open repair was reported in one small prospective study (Chan et al, 2005), but the opposite conclusion was reached in a similar study (Koivusalo et al, 2009). The risk of persistence after laparoscopic repair of communicating hydrocele and long-term potential for vasal obstruction has yet to be addressed in the literature. However, the risk of testicular atrophy appears to be low in reported series. Laparoscopy has also been advocated to facilitate repair of recurrent and incarcerated hernias (Saranga Bharathi et al, 2008).

Assessment of the Contralateral Internal Ring

A long-standing controversy relating to pediatric inguinal hernia repair is the need for identification and repair of a contralateral patent processus vaginalis. In the past, contralateral exploration was used routinely in subsets of patients considered at higher risk for metachronous hernia based on age, prematurity, gender, or associated disease. The processus is patent on the opposite side in 40% of children with unilateral clinical hernia undergoing laparoscopy (Miltenburg et al, 1998), up to 60% of contralateral explorations (Tackett et al, 1999), and in 20% of adults at autopsy (Ajmani and Ajmani, 1983). In contrast, two systematic literature analyses conclude that the risk of developing a contralateral hernia during follow-up is about 10%, and the majority of these cases present within 5 years with a trend toward decreased risk with age (Miltenburg et al, 1997; Ron et al, 2007). In a prospective study no consistent factors were associated with significantly increased risk of metachronous hernia, except perhaps a previous history of incarceration (Tackett et al, 1999). The risk of contralateral hydrocele after unilateral communicating hydrocele repair is not known but is likely lower. **Consequently, even selective exploration or repair of the opposite side in cases of unilateral pediatric inguinal hernia is no longer recommended.** An exception may be children at significantly higher anesthetic risk (Tackett et al, 1999). For surgeons who perform laparoscopic herniorrhaphy, contralateral repair is less invasive; and thus many surgeons recommend repair of an open processus vaginalis identified at the time of laparoscopy. However, the pros and cons of such an approach should be reviewed with the patient's family with the knowledge that an open internal ring is not equivalent to an inguinal hernia (Schier, 2007b).

Abdominoscrotal Hydrocele

Abdominoscrotal hydrocele is an unusual form of noncommunicating hydrocele, comprising 1.25% of all pediatric hydroceles in a large series (Avolio et al, 2000). Unlike the typical neonatal hydrocele, it is large and tense, and bimanual examination usually confirms the presence of a ballotable abdominoscrotal mass. Ultrasonography can be used to visualize the degree of proximal extension and the testis but is not required in typical cases (Belman, 2001). Abdominoscrotal hydrocele usually presents in the neonatal period or in infancy and may initially be limited to the scrotum with progressive enlargement over time (Celayir et al, 2001; Cuervo et al, 2009). In other cases, spontaneous resolution (Upadhyay et al, 2006) or improvement (Cozzi et al, 2008) was reported. In the larger published series, abdominoscrotal hydrocele was bilateral in about 30% of cases (Ferro et al, 1995; Nagar and Kessler, 1998; Belman, 2001; Bayne et al, 2008; Cozzi et al, 2008). In addition, associated diagnoses may include ipsilateral or contralateral cryptorchidism, contralateral hernia, hydrocele, or vanishing testis. A single case of associated malignant mesothelioma was reported (Velasco et al, 1988). Progressive proximal enlargement, characteristics of the hydrocele fluid, and nonpatency of the processus vaginalis suggest that the most likely cause is enlargement and extension of a scrotal hydrocele into the

retroperitoneal or properitoneal space after the processus has closed. Bayne and associates (2008) reported that abdominoscrotal hydrocele fluid is exudative and theorize that increasing size and pressure lead to lymphatic obstruction and worsening over time. Massive enlargement in some cases may extend into the upper abdomen and be associated with hydroureteronephrosis, lower extremity edema, or appendicitis (reviewed by Cuervo et al, 2009). Chamberlain and colleagues (1995) first reported dysmorphic elongation of the testis in an infant with bilateral abdominoscrotal hydrocele, and others have confirmed this observation, presumably related to high pressures within the sac (Bayne et al, 2008).

The surgical approach to this rare entity is controversial, related to what is perceived as a higher risk to the cord and testis during repair because of the size of the lesion and the young age of the patient. The traditional approach to repair is via an inguinal incision with proximal dissection of the sac from its abdominal attachments and distal complete or partial mobilization, with or without orchidopexy. Some authors use orchidopexy routinely, irrespective of the preoperative position of the testis (Nagar and Kessler, 1998; Bayne et al, 2008). Failure to excise the abdominal portion of the sac may lead to its persistence. Alternative, rarely reported approaches to the intra-abdominal portion include a higher or midline (for bilateral cases) incision or laparoscopic decompression followed by inguinal excision (Serels and Kogan, 1996; Abel et al, 2009). Some authors recommend leaving a strip of the lining of the sac along the cord to avoid injury to the vas or vessels (Ferro et al, 1995; Cuervo et al, 2009), a rarely reported complication (Serels and Kogan, 1996). Tightening of a patulous internal ring is described, but the necessity for this maneuver is unclear because the processus vaginalis is invariably closed and the risk for postoperative hernia appears to be rare. Because the procedure may be prolonged and tedious, some surgeons use scrotal drains, preoperative antibiotic prophylaxis, and postoperative hospitalization.

An alternative simplified surgical technique for abdominoscrotal hydrocele that may be underutilized is the primary scrotal approach described by Belman (2001). The hydrocele is approached through a scrotal incision, and extensive plication without excision is performed as for the Lord procedure. Prolonged scrotal edema associated with involution of the sac is expected, but this approach is appealing because the processus vaginalis is closed in most if not all cases and dissection is limited. Although Belman did not present detailed outcome data using this approach, Cozzi and colleagues (2008) reported reduced morbidity and similar efficacy for the scrotal as compared with the inguinal approach in 18 cases (5 bilateral). This latter series is unique in that detailed outcome was reported in 13 and 5 patients undergoing inguinal and scrotal surgery, respectively, with a median follow-up of 4 years. Persistent scrotal swelling, hematoma, and undescended and/or hypoplastic testis were reported in 11 of 13 inguinal cases and infection in 2 scrotal cases. These authors also observed that 78% of testes were dysmorphic preoperatively but that 15 of 18 regained normal shape and size postoperatively, suggesting that fluid pressure dynamics contribute to this finding. The prognosis for adult testicular function in abdominoscrotal hydrocele and the risk of possible long-term postoperative complications remain unknown.

ACUTE SCROTUM

The new onset of pain, swelling, and/or tenderness of intrascrotal contents is referred to as *acute scrotum* and is a common presenting complaint in pediatric urology. The signs and symptoms of diseases associated with acute scrotal pain vary markedly with extensive diagnostic overlap. Although some clinical features are more reliable than others, few if any details of history, physical examination, or imaging are absolutely diagnostic of particular intrascrotal pathologic processes. Thus the clinician should make a prompt diagnosis based on all the available findings, which may include those obtained at scrotal exploration, particularly if the duration of pain is short (<6 hours), the presenting signs lack sufficient reliability, or the diagnosis remains unclear after clinical evaluation.

Etiology and Differential Diagnosis

Individuals with many types of inguinoscrotal pathology may present with acute scrotal pain or swelling (Table 132–6). In some patients with scrotal pathology the pain may be localized to the inguinal or abdominal regions or poorly localized, particularly in younger children. Historical information of potential importance includes the onset, quality, duration, and consistency of pain; history of previous episodes; exacerbation with activity; presence

Table 132–6.

Differential Diagnosis of Pediatric/Adolescent Acute Scrotal Pain

- Appendage torsion
  - Appendix testis
  - Other appendage (epididymis, paradidymis, vas aberrans)
- Spermatic cord torsion
  - Intravaginal, acute or intermittent
  - Extravaginal
- Epididymitis
  - Infectious
    - Urinary tract infection
    - Sexually transmitted disease
    - ?Viral
  - Sterile or traumatic
- Scrotal edema/erythema
  - Diaper dermatitis, insect bite, or other skin lesions
  - Idiopathic scrotal edema
  - Early Fournier gangrene
- Orchitis
  - Associated with epididymitis with or without abscess
  - Vasculitis (e.g., Henoch-Schönlein purpura)
  - Viral illness (mumps)
- Trauma
  - With hematocele or scrotal contusion
  - With testicular rupture
- Hernia/hydrocele
  - Inguinal hernia with or without incarceration
  - Communicating hydrocele
  - Encysted hydrocele with or without torsion
  - Associated with acute abdominal pathology (e.g., appendicitis, peritonitis, splenic rupture)
- Varicocele
  - With pain
  - With acute rupture or thrombosis
- Intrascrotal mass
  - Cystic dysplasia or tumor of testis
  - Epididymal cyst/spermatocele or tumor
  - Other paratesticular tumors
- Musculoskeletal pain due to inguinal tendonitis or muscle strain
- Referred pain (e.g., ureteral calculus or anomaly)

of associated symptoms such as nausea, vomiting, irritative voiding, penile discharge, fever, and other illness; and trauma, sexual, and immunization history. In a large series of surgically treated pediatric patients, appendix testis torsion is the most common diagnosis (40% to 60%), followed by spermatic cord torsion (20% to 30% excluding neonates), epididymitis (5% to 15%), and other or no pathology (~10%) (Anderson and Giacomantonio, 1985; Sidler et al, 1997; Van Glabeke et al, 1999; Mushtaq et al, 2003; Murphy et al, 2006; Makela et al, 2007). In general, appendage torsion is most common after infancy and before puberty whereas epididymitis and spermatic cord torsion are most common in the perinatal and pubertal periods. However, any of these diseases can occur at any time during childhood and adolescence.

Spermatic Cord Torsion

Acute spermatic cord torsion with reduction or cessation of blood flow to the testis may occur in susceptible individuals. Intravaginal spermatic cord (testicular) torsion occurs when the testis twists within the tunica vaginalis, whereas extravaginal testicular torsion occurs in the perinatal period before fixation of the tunica vaginalis within the scrotum.

Acute Intravaginal Spermatic Cord Torsion

Predisposing Factors. The anatomic abnormality predisposing to torsion of the spermatic cord, the bell-clapper deformity, was identified in 12% of males in an autopsy series (Caesar and Kaplan, 1994a). This anatomic variant is due to partial or complete failure of fusion of the tunica vaginalis along the epididymis, resulting in incomplete attachment of the testis/epididymis to the scrotum (Fig. 132–7) or to an abnormally wide attachment of testis to epididymis. Despite the high prevalence of the bell-clapper deformity, the prevalence of torsion is much lower, reported as 8.6 per 100,000 males aged 10 to 19 per year in the United States (Mansbach et al, 2005) with some evidence for a familial predisposition (Cunningham, 1960; Collins and Broecker, 1989). The direct precipitating event in susceptible individuals is unknown but may include cold temperature, sudden movement or trauma with activation of the cremasteric reflex, and/or rapid growth of the testis at puberty. Some studies suggest an inverse correlation between the prevalence of torsion and atmospheric temperature (Srinivasan et al, 2007; Lyronis et al, 2009). Undescended testes are at higher risk for torsion, although the prevalence in this group as a whole is low. Rarely, torsion may occur after previous orchidopexy for cryptorchidism or testicular torsion. In these cases the etiology may be related to failure of suture (absorbable or nonabsorbable) fixation of a testis that remains within an intact tunica vaginalis (Redman and Barthold, 1995; Frank and O'Brien, 2002; Mor et al, 2006).

Clinical Presentation. Although intravaginal testicular torsion may occur in any young male, the peak age at occurrence is 12 to 16 years, with additional cases occurring in postpubertal males and 86% to 93% occurring after age 10 (Anderson and Giacomantonio, 1985; Sidler et al, 1997; Mushtaq et al, 2003; Mansbach et al, 2005; Murphy et al, 2006; Makela et al, 2007). The prevalence of testicular torsion in these retrospective surgical series is 20% to 30% with left-sided predominance; however, in another large series, testicular torsion comprised only 6% of 626 patients younger than 17 years of age (Lam et al, 2005). Very rarely, torsion occurs bilaterally. Classically, patients complain of sudden, severe scrotal pain that may occur at rest, with activity or sports, or during sleep, and a history of previous similar episodes of pain, usually on the ipsilateral side, may be present. Alternatively, patients may have milder, less acute, or even no scrotal pain or may have inguinal or abdominal pain. The patient may report direct scrotal trauma, which may precipitate twisting of the cord, a historical feature that should not alter the diagnostic

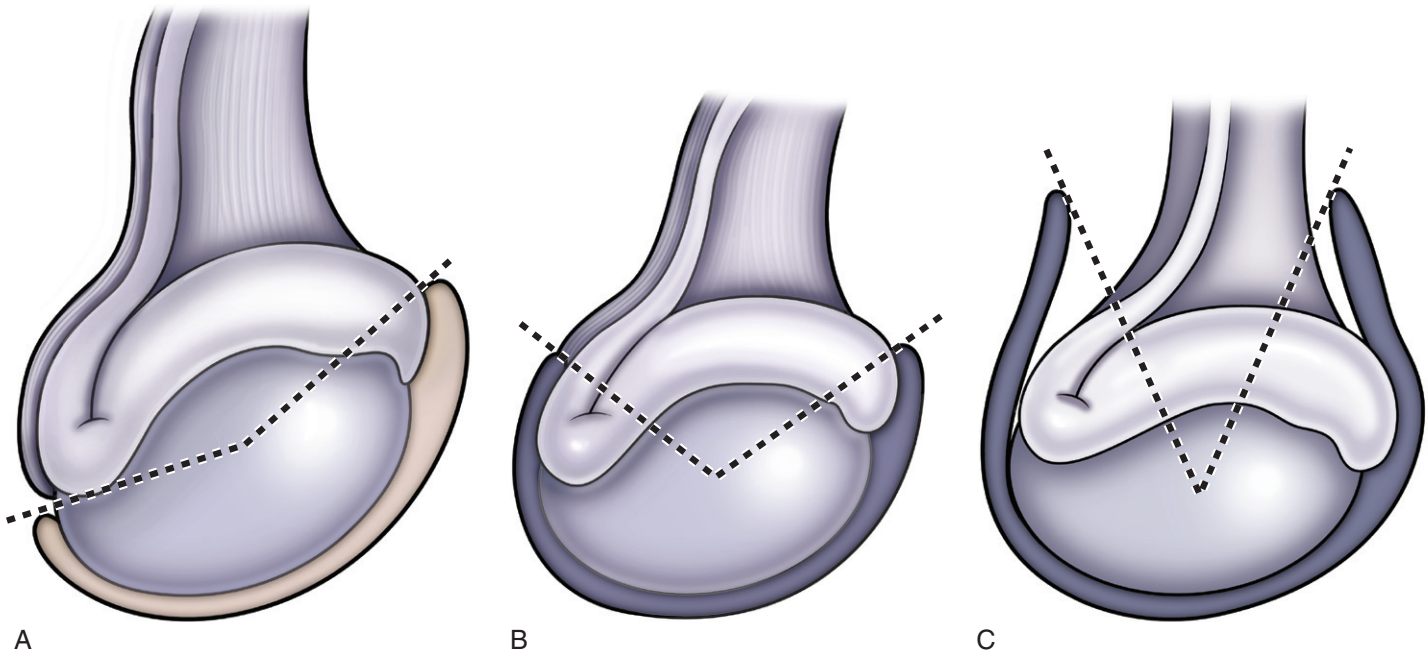


Figure 132–7. Variable degrees of bell-clapper deformity show normal (**A**), partial (**B**), and complete (**C**) variants. Angles drawn represent variations in attachment of tunica vaginalis. (From Bentley DF, Ricchiuti DJ, Nasrallah PF, McMahon DR. Spermatic cord torsion with preserved testis perfusion: initial anatomical observations. J Urol 2004;172:2373–6.)

approach to the patient (Lrhorfi et al, 2002). **Most retrospective series report that boys presenting early, especially within 6 hours of onset of pain, are more likely to have testicular torsion than other intrascrotal pathology.** Nausea and vomiting occurs in 10% to 60% of boys with intravaginal testicular torsion and may be more common in pubertal and postpubertal boys (Williamson, 1976; Knight and Vassy, 1984; Jefferson et al, 1997; Sessions et al, 2003; Makela et al, 2007). Scrotal edema and erythema may be present depending on the duration or degree of torsion. Dysuria and fever are occasionally reported.

The most common physical findings are generalized testicular tenderness and absence of the cremasteric reflex. This genitofemoral reflex arc is normally present in boys after 2 years of age (Caesar and Kaplan, 1994b), is elicited by scratching the inner thigh with resultant elevation of the testis within the scrotum, and is one of the most useful and specific signs ruling out testicular torsion. Although some studies suggested that the reflex is reduced or absent in all cases of testicular torsion (Caldamone et al, 1984; Rabinowitz, 1984; Kadish and Bolte, 1998) the reflex was intact in up to 10% of proven cases of torsion (Hughes et al, 2001; Nelson et al, 2003; Karmazyn et al, 2005; Murphy et al, 2006). **A normal cremasteric reflex is strongly correlated with intact blood flow to the testis but does not infallibly indicate normal testicular perfusion, especially if the clinical presentation is otherwise suggestive of torsion.** Similarly, a blue dot sign, considered specific for appendix testis torsion, has been reported in association with normal scrotal ultrasound findings in a case of testicular torsion (Murphy et al, 2006). In some cases elevation of the testis from its dependent scrotal position, abnormal lie, or anterior epididymal position, thickening of the cord suggestive of a twist, testicular induration, loss of boundaries between the testis and epididymis, scrotal edema, and/or erythema are present but vary depending on the age of the patient and duration of torsion but may be helpful in supporting the diagnosis of torsion.

Diagnostic Studies. Urinalysis is performed to identify pyuria and/or bacteriuria, findings that may be associated with epididymitis, or hematuria, which may indicate urinary tract calculus. Although the findings on urinalysis are usually normal in cases of testicular torsion, pyuria may be present and create diagnostic confusion (Anderson and Giacomantonio, 1985; Jefferson et al, 1997). Scrotal imaging is used more routinely in recent years, particularly in cases of prolonged (>24 hours) pain associated with preservation of the cremasteric reflex and severe scrotal swelling with loss of intrascrotal landmarks. Radionuclide imaging is primarily of historic interest owing to lack of specificity and prompt availability at many centers. CDUS can be used to visualize testicular architecture and intraparenchymal blood flow; and with the improved sensitivity of current technology flow is visible in most normal testes, irrespective of age. CDUS findings consistent with established testicular torsion include reduced or absent Doppler waveforms, parenchymal heterogeneity, and/or altered echotexture compared with the contralateral testis (Fig. 132–8). Kaye and colleagues (2008b) reported that all testes with a heterogeneous echogenicity as shown by CDUS were necrotic and were removed or atrophied after orchidopexy, whereas homogeneous echogenicity predicted a reduced risk of orchiectomy but long-term outcome was not provided. Enthusiasm for CDUS as a reliable modality to exclude testicular torsion was based on data suggesting that this approach is highly reliable (Kass et al, 1993b). With further experience and possibly due to enhanced detection of flow with newer equipment and/or user-dependent characteristics, **the established sensitivity of CDUS in confirming decreased or absent blood flow in proven cases of spermatic cord torsion is a disappointing 63% to 90%** (Steinhardt et al, 1993; Stehr and Boehm, 2003; Bentley et al, 2004; Kalfa et al, 2004; Karmazyn et al, 2005). In reviewing false-negative cases in their series and those of others, Bentley and coworkers (2004) observed that arterial blood flow can persist in the presence of established torsion (see Fig. 132–8) and theorize, based on preliminary data, that preservation of flow may be more likely in males with a preexisting thick spermatic cord. Cassar and colleagues (2008) retrospectively evaluated Doppler waveforms in cases of torsion with decreased or preserved testicular flow and observed subtle waveform abnormalities, including increase or decrease in amplitude relative to the normal testis and reversal of diastolic flow. These may help increase the sensitivity of CDUS in cases of torsion. In addition, increased epididymal size and/or echogenicity and altered epididymal vascularity, usually absent or reduced but occasionally increased, may provide additional support for the diagnosis of torsion (Nussbaum Blask and Rushton, 2006).

High-resolution ultrasonography (HRUS) of the length of the spermatic cord using a 10- to 20-mHz probe may provide a promising new approach for identifying torsion in equivocal cases. Kalfa and colleagues (2004) used HRUS in children and young adults to directly identify the twisted cord superior to the testis. They visualized the cord twist as a 1- to 3-cm snail-shaped mass in 43 patients, and confirmation was suspected but difficult in an additional patient with an inguinal testis. Conversely, a completely linear cord is visualized in nontorsion cases. In a multiinstitutional retrospective series of 919 cases of acute scrotum, these authors reported HRUS visualization of a cord twist in 96% of 208 surgically proven torsion cases and 100% sensitivity of the combination of cord twist and/or reduced blood flow in diagnosing torsion (Kalfa et al, 2007). However, Karmazyn and coworkers (2005) observed normal testicular blood flow and no visible spermatic cord twist in 2 of 41 boys with partial or intermittent torsion. Although this technique is promising, prospective studies are needed with surgical confirmation of diagnoses and prolonged careful follow-up to ensure that it is reproducible in other settings and that varying presentations of torsion are not missed.

Potentially useful diagnostic modalities that have been studied in animal models but not yet tested clinically include contrast-enhanced pulse-inversion ultrasonography and infrared thermography. Pulse-inversion imaging in a rabbit model showed superior quantitative assessment of perfusion of the experimentally torsed testis as compared with conventional CDUS (Paltiel et al, 2006). In a sheep model an infrared thermographic camera showed significant reduction in scrotal temperature by 1 hour after 720-degree torsion and prompt normalization with detorsion (Capraro et al, 2008). Infrared thermography is presently used clinically for diagnosis of varicocele in adults (Nogueira et al, 2009).

Surgical Treatment and Findings. With increasing availability and use of urgent CDUS, and more recently HRUS, and the relatively low (6-30%) prevalence of testicular torsion in children and adolescents with acute scrotal pain, a strategy of managing essentially all patients surgically to confirm absence of torsion (Anderson and Giacomantonio, 1985; Watkin et al, 1996; Sidler et al, 1997; Mushtaq et al, 2003; Makela et al, 2007) has shifted toward selective surgical exploration (Caldamone et al, 1984; Kass et al, 1993b; Kalfa et al, 2004; Lam et al, 2005). Most surgeons currently use

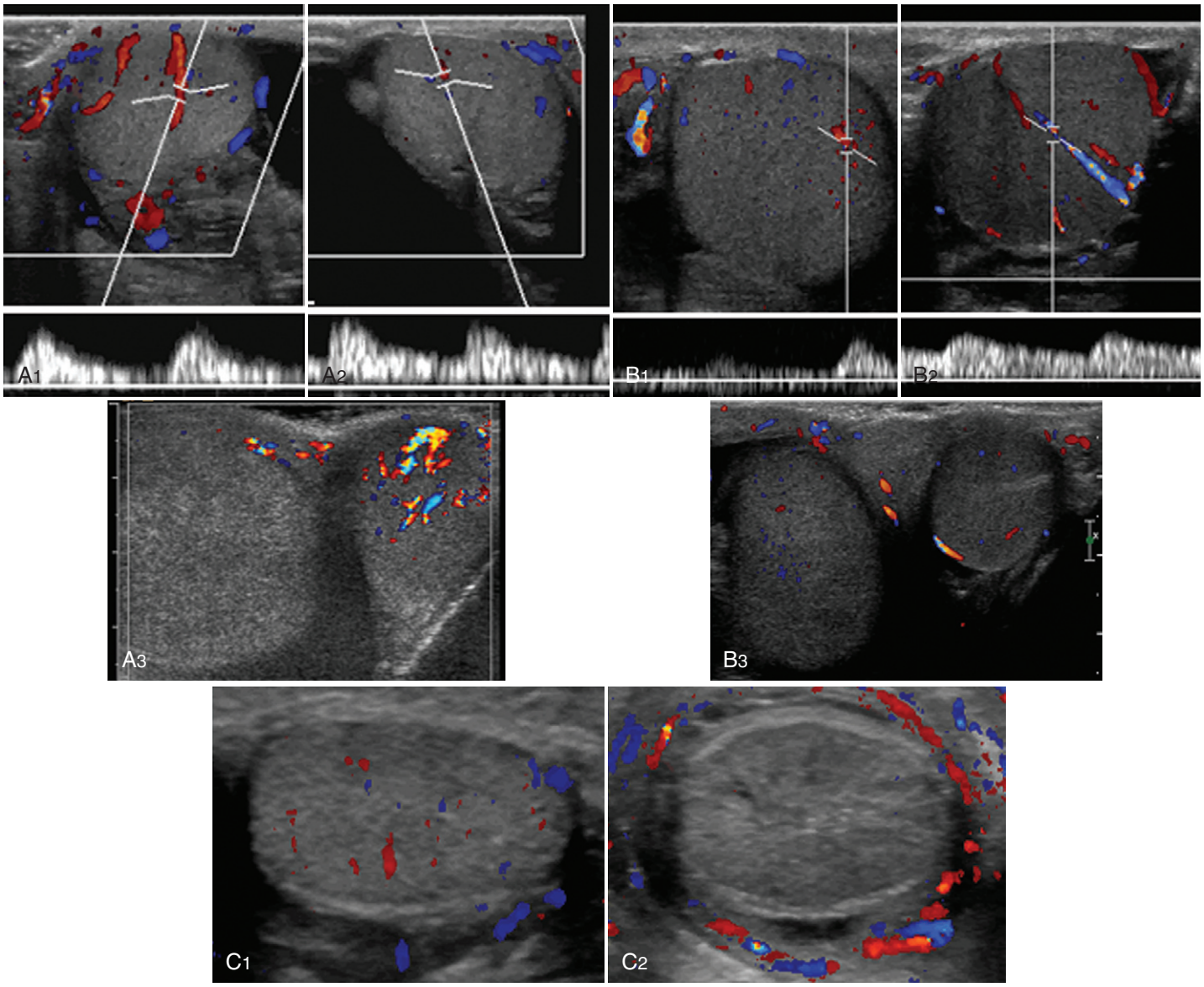


Figure 132–8. Imaging of intravaginal spermatic cord torsion. **A**, Intermittent torsion. Color Doppler ultrasonography (CDUS) in a 14-year-old boy with 12 hours of right testicular pain and intact cremasteric reflex shows preserved arterial flow to testis at an initial emergency department visit and loss of flow and increased heterogeneity of right testicular parenchyma when patient returned with increased pain. Exploration confirmed 360-degree intravaginal torsion. **B**, Acute torsion with reduced arterial flow. CDUS in an 18-year-old boy with variable right testicular pain shows reduced arterial flow to testis and increased echogenicity on transverse view comparing both testes. Right epididymal hyperemia and enlargement were also noted. Exploration confirmed 540-degree torsion with prompt return of vascularity with detorsion. **C**, Prolonged torsion. CDUS in a case of a 9-year-old boy presenting with prolonged left testicular pain shows heterogeneous echotexture, absence of arterial or venous flow, and a hyperechoic parenchymal ring; testicular necrosis was found at scrotal exploration.

this selective approach, but a minority continue to recommend urgent surgical intervention for all cases of acute scrotum to avoid any risk of inaccuracy associated with the clinical and imaging diagnosis of testicular torsion (Murphy et al, 2006). Indeed, most series report cases with atypical presentation and/or false-negative imaging in which surgical exploration was delayed and the testis lost, but the clinician's goal should be to minimize the risk of such cases. **When findings support or are suspicious for spermatic cord torsion, emergent scrotal exploration is indicated and should not be delayed to obtain scrotal ultrasonography or any other diagnostic test.** The increased sensitivity provided by HRUS and potentially newer noninvasive diagnostic techniques may in future more reliably support nonsurgical treatment of the majority of boys presenting with an acute scrotum without torsion.

Some clinicians recommend preoperative manual detorsion based on the assumption that twisting of the testis occurs in a medial direction. However, in a retrospective review of 186 surgical explorations for torsion, Sessions and associates determined that lateral twisting (Fig. 132–9) occurred in 33% and manual detorsion attempts in 30% of the total group failed to completely relieve the torsion in 32% of cases (Sessions et al, 2003). The resolution of symptoms after manual detorsion did not correlate with the presence or absence of persistent torsion.

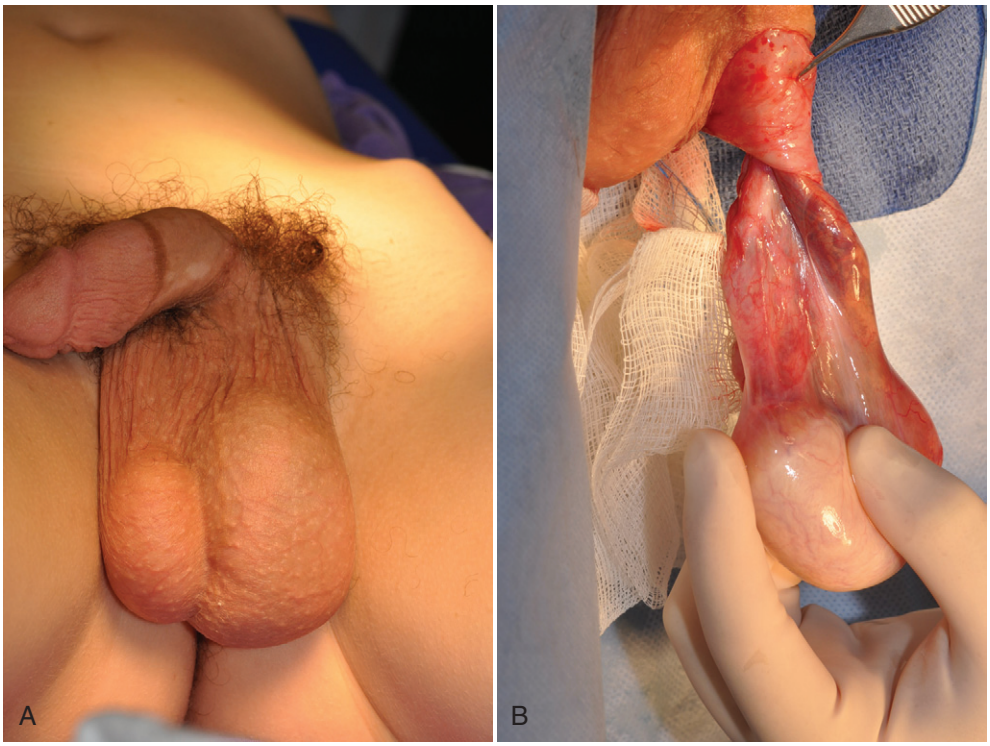


Figure 132–9. **A** and **B**, Intravaginal spermatic cord torsion with a viable testis. Findings at scrotal exploration in a 15-year-old boy with less than 6 hours of intravaginal torsion, 360-degree lateral rotation of the cord, and a viable testis. Color Doppler ultrasonography showed reduced arterial flow.

Jefferson and colleagues (1997) noted a similar frequency of residual intraoperative torsion after attempts at manual detorsion. Therefore although this maneuver may be attempted, it should not delay transfer to the operating room for definitive detorsion and fixation of the testis.

After induction of anesthesia, the affected testis should be approached first through a hemiscrotal transverse or midline incision. Once delivered, the surgeon should perform detorsion and document the number of cord rotations and the presence and degree of bell-clapper deformity. The testis is observed for improvement in color, but the decision to remove or retain the affected testis is subjective and, although based on the appearance of the testis, is likely also biased by the age of the patient and the degree and duration of torsion. A Doppler flow probe or incision of the tunica albuginea (Arda and Ozyaylali, 2001) with assessment of bleeding can be used to document intratesticular flow after detorsion, but the usefulness of these maneuvers in predicting viability of the testis has not been validated. Kutikov and colleagues (2008) suggest that compartment syndrome may contribute to testicular injury based on the improved appearance and lower intraparenchymal pressures they observed after detorsion and incision of the tunica albuginea. They covered the testicular defect with a vascularized tunica vaginalis patch to maintain lower intraparenchymal pressure and reduce the likelihood of ongoing ischemia. The long-term outcome of these patients is not available, and larger prospective studies are required to determine the benefit of this approach.

The overall frequency of orchiectomy when testes appear nonviable after surgical detorsion is 30% to 70% in large pediatric studies (Sessions et al, 2003; Murphy et al, 2006; Makela et al, 2007; Kaye et al, 2008b) and 34% in a population-based review of males aged 1 to 25 (Mansbach et al, 2005). Sessions and associates (2003) noted at operation that the median degree of rotation was 540 degrees in patients undergoing orchiectomy (38% of cases) and 360 degrees when the testis was salvaged, with a range of 180 to 1080 degrees in both groups. There is no clear-cut clinical evidence that orchidopexy or orchiectomy provides superior results in maximizing ultimate testicular function (see later). However, attempts should be made to salvage the testis if there is any sign of reperfusion after detorsion. The surgeon may biopsy questionably viable testes that are left in place to document the presence or absence of necrosis. Any testicular appendage should be removed. **Intrascrotal fixation of the testis must be performed bilaterally because a contralateral bell-clapper deformity usually exists and may lead to metachronous torsion.** Techniques of fixation that secure the testis within a subdartos pouch may reduce the risk of recurrent torsion within an intact tunica vaginalis if sutures between the testis and scrotal wall fail (Redman and Barthold, 1995; Frank and O'Brien, 2002; Mor et al, 2006). One approach allows obliteration of the tunica vaginalis and secure fixation of the testis without transparenchymal sutures within a scrotal pouch (Redman and Barthold, 1995). An incision is made in the upper third of the scrotum on each side. After delivery of the testis and eversion of the parietal tunica vaginalis along the cord, the cut edges of the inverted tunica are closed bilaterally with absorbable suture. This prevents retraction of the testis back into a tunica vaginalis–lined scrotal cavity. A subdartos pouch is created, and the testis is secured in the pouch by placement of sutures between the tunical layer covering the cord and the dartos. Follow-up for at least 6 months is mandatory to determine the presence and degree of testicular volume loss. For cases of testicular loss, prosthesis

placement is offered after complete healing, usually 6 or more months later.

Prognosis. The long-term outcome of males with a history of testicular torsion is poorly defined because of difficulties inherent in completing follow-up studies, particularly for boys treated before puberty. Visser and Heyns (2003) collected data from available clinical series and observed a stepwise decrease in testicular salvage and increase in late testicular atrophy with increasing duration of torsion. In their review of the testicular salvage rate in 1140 patients, the risk of orchiectomy was approximately 5%, 20%, 40%, 60%, 80%, and 90% at 0 to 6, 7 to 12, 13 to 18, 19 to 24, more than 24, and more than 48 hours after onset of pain, respectively. The approximate risk of late atrophy in 535 patients was less than 10%, 40%, and 75% after less than 12, 12 to 24, and more than 24 hours of pain, respectively, in those treated with orchidopexy. However, data from individual series suggest that at least partial (<25%) testicular atrophy is not rare in patients who underwent operative detorsion as little as 4 hours after onset of pain (Krarup, 1978; Anderson and Williamson, 1986; Tryfonas et al, 1994; Sessions et al, 2003). These data suggest that ischemic injury may occur rapidly, even if the testis appears viable at the time of detorsion. Even partial testicular volume loss may reflect significant loss of spermatogenesis in the testis (Turner et al, 2004), but the resultant impact on overall fertility potential is less clear. Available data suggest that subtle abnormalities of semen quality are common after testicular torsion: semen density is often in the normal range yet seems to show a positive correlation with shorter duration of torsion and reduced atrophy (Puri et al, 1985; Fisch et al, 1988; Anderson et al, 1992; Brasso et al, 1993; Arap et al, 2007). Unfortunately, these studies are small and heterogeneous, with limited semen analysis and minimal paternity data.

Sperm density is reduced in patients with testicular loss due to trauma relative to normal controls (Lin et al, 1998), but paternity in males with congenital monorchism appears to be normal (Lee and Coughlin, 2002b). In comparison, concern exists that fertility potential after torsion may be further reduced as compared with other males with a single testis because of bilateral testicular pathology in cases of unilateral torsion. As reviewed in Visser and Heyns (2003), existing contralateral testicular biopsy data are limited but suggest that global testicular dysfunction may exist in males with torsion. Whether this is a primary or secondary defect, or both, remains undefined. The observation that increasing duration of torsion is inversely correlated with semen quality suggests an adverse effect of torsion itself. A hypothesis that this effect may be related to an autoimmune phenomenon (Anderson and Williamson, 1990) was not supported by analysis of antisperm antibodies in individuals with torsion (Puri et al, 1985; Anderson et al, 1992; Brasso et al, 1993; Arap et al, 2007). Animal models suggest a contralateral deleterious effect of torsion in some studies but not others, and the applicability of animal models for study of testis injury after torsion is controversial (Filho et al, 2004), but available animal and human data support a role for ischemia-reperfusion injury after release of testicular torsion (Kehinde et al, 2003; Turner et al, 2004). Additional clinical data are needed to determine long-term outcome after testicular torsion and the efficacy of adjunctive treatment (e.g., antioxidant therapy) in optimizing fertility potential in patients with torsion.

Intermittent Intravaginal Spermatic Cord Torsion

As many as 30% to 50% of patients presenting with acute spermatic cord torsion report a history of previous scrotal pain episodes (Stillwell and Kramer, 1986; Williamson, 1976). These episodes typically begin and resolve rapidly, last minutes to hours, and may occur at any interval from days to months. In a retrospective review of cases ultimately diagnosed as intermittent torsion, Hayn and associates (2008) observed that the frequency of pain episodes correlated with the risk for eventual persistent torsion and testicular loss in children and adolescents. Of 17 boys presenting emergently with ongoing torsion, 71% were diagnosed on previous occasions with epididymitis or appendage torsion and 53% had acute or delayed testicular loss. Horizontal testicular lie may be present in patients with intermittent torsion (Schulsinger et al, 1991) but was documented in less than half of patients presenting either urgently or electively and was not seen in prepubertal males in the series of Hayn and associates (2008). Eaton and coworkers (2005) reported that the cremasteric reflex was absent in only 3 of 15 patients and that CDUS showed reduced or absent intratesticular blood flow in only 5 of 12 patients examined during a bout of pain. Six of 38 patients in this series had increased flow to the testis or epididymis. One fourth of patients had nausea and vomiting, a sign the authors suggested could be used to rule out epididymitis. Of those with complete surgical documentation, 15% did not have a bell-clapper deformity and 1 patient in the series continued to have pain postoperatively.

These reports underscore the difficulties inherent in identification and treatment of intermittent spermatic cord torsion, because patients may present with acute pain suggestive of torsion but with physical and imaging findings that appear normal as the torsion improves or resolves during the acute episode. The diagnosis requires a high index of suspicion in males with recurrent bouts of pain. CDUS may be most helpful in the midst of pain symptoms, particularly if intratesticular blood flow is reduced, but if results are normal or increased may provide unwarranted reassurance to the clinician. In cases of torsion-detorsion, prompt elective bilateral orchidopexy is indicated with the knowledge that in some cases absolute confirmation of the diagnosis may not be possible, and patients and parents should be advised that pain symptoms could persist postoperatively.

Extravaginal Spermatic Cord Torsion (Perinatal Testicular Torsion)

Perinatal spermatic cord torsion is due to rotation of the testis, entire cord, and tunica vaginalis before established fixation between the tunica vaginalis and dartos within the scrotum. This event is more common before birth and, depending on the timing, may present as a nonpalpable "vanishing" testis in a child evaluated for cryptorchidism or as an abnormal scrotal testis on the first postnatal examination. Perinatal torsion may also occur within the first month of life, although partial degrees of extravaginal torsion are also reported as late as 9 months after birth. Rarely, cases of neonatal testicular infarction are attributable to necrosis without spermatic cord torsion or to intravaginal torsion (John et al, 2008).

The presentation of perinatal torsion is variable, depending on the timing of the torsion event, and may be insidious. Because of the rarity of the disease, most of the available data are based on small retrospective case series. As such, predisposing factors such as large birth weight and/or difficult delivery are postulated (John et al, 2008; Kaye et al, 2008a) but not confirmed in controlled studies. In a population-based study, John and coworkers (2008) estimated an incidence of 6.1 per 100,000 births, and familial cases have been reported (Castilla et al, 1975). Suggestive

clinical findings at birth include testicular induration and scrotal erythema or dark discoloration with or without edema. The infant is typically asymptomatic, and testicular tenderness may or may not be present. A hydrocele may coexist, complicating the testicular examination. In a significant minority of cases, the symptoms present in the neonatal period or later, after documentation of a normal neonatal examination. Reports vary as to the frequency of bilateral versus unilateral perinatal torsion, with the former reported in 5% and 22% of cases in two large series (Yerkes et al, 2005; Baglaj and Carachi, 2007). Several recent series indicate that bilateral perinatal torsion is more common than suggested in the older literature and that asynchronous torsion may occur in boys in whom the primary event occurs prenatally or postnatally (Beasley and McBride, 2005; Yerkes et al, 2005; Al-Salem, 2007; John et al, 2008). In a review of the literature by Baglaj and Carachi (2007), asynchronous torsion comprised one third of all bilateral cases.

Although imaging of the testis may be obtained in cases of suspected perinatal torsion, its usefulness and reliability is questionable. Maternal ultrasonography may show in-utero torsion as early as the 33rd week of gestation, and postnatally CDUS may reveal typical findings of parenchymal heterogeneity, calcification, and absent blood flow (Fig. 132–10) that are helpful in confirming the diagnosis of nonacute antenatal torsion (Arena et al, 2006). However, intact blood flow in cases of perinatal torsion is not uncommon, suggesting that postnatal CDUS may be unreliable (Yerkes et al, 2005; Al-Salem, 2007; Cuervo et al, 2007; John et al, 2008). Some advocate use of ultrasound to differentiate rare neonatal testicular or peritesticular tumors from torsion (Kaye et al, 2008a), but its reliability in this regard may also be questionable (Calonge et al, 2004; Al-Salem, 2007). Therefore, clinical findings usually provide the basis for diagnosis of perinatal torsion, particularly because imaging may delay treatment and many clinicians now advocate urgent surgical exploration.

The treatment of perinatal testicular torsion remains controversial. Some surgeons support the view that exploration and contralateral orchidopexy is best performed electively in cases of perinatal torsion because most cases occur prenatally and are not salvageable (Das and Singer, 1990; Brandt et al, 1992; Stone et al, 1995; Kaye et al, 2008a). However, partial or complete testicular salvage may be possible when urgent or emergent surgery is performed (Sorensen et al, 2003; Al-Salem, 2007; Cuervo et al, 2007). In other reported cases, unexpected torsion or atrophy of the contralateral testis was found at the time of exploration at varying intervals after the ipsilateral diagnosis, indicating that the clinical signs of extravaginal torsion may indeed be subtle, delayed, and easily overlooked even by observant parents (Yerkes et al, 2005; Al-Salem, 2007; Baglaj and Carachi, 2007; John et al, 2008). Theoretical concerns regarding the anesthetic risks associated with urgent surgery for perinatal torsion are not confirmed by available data, but neonatal anesthesia expertise is recommended in these cases (Pinto et al, 1997; Sorensen et al, 2003; Yerkes et al, 2005). **Therefore, to minimize loss of testicular tissue and the risk of anorchia, the most prudent approach is urgent exploration and contralateral orchidopexy once the diagnosis of perinatal torsion is made.** To avoid the theoretical risk of transscrotal surgery in the event a tumor is found, some surgeons advocate an inguinal approach whereas others routinely use a scrotal incision. Retention of the testis is advisable if any chance of viability is present, particularly in postnatal or bilateral cases, to optimize the likelihood of retained endocrine function. As with other management controversies in urology, the pros and cons of alternative approaches to care should be discussed thoroughly with the patient's family.

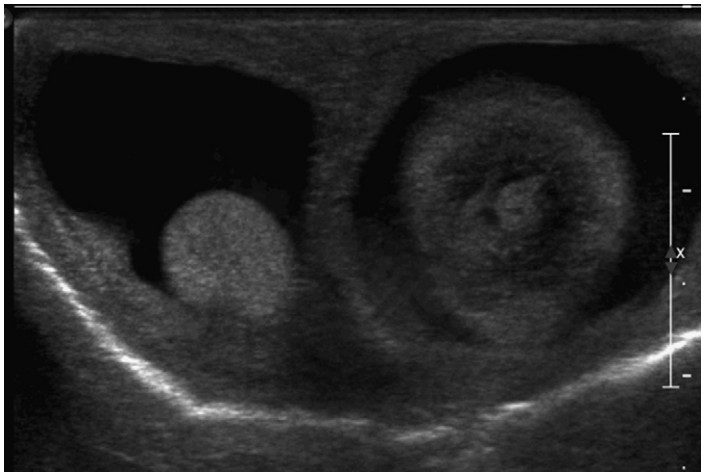


Figure 132–10. Extravaginal spermatic cord torsion. Transverse ultrasound image shows both testes in a neonate with left prenatal torsion. Note enlarged testis with heterogeneous parenchyma and bilateral hydroceles.

Appendage Torsion

The most common intrascrotal appendages are the appendix testis and appendix epididymis, remnants of the cranial müllerian and wolffian ducts, and present in 76% to 83% and 22% to 28% of testes, respectively (Dresner, 1973; Jacob and Barteczko, 2005). The vas aberrans and paradidymis, both appendages of wolffian duct origin, are rare (1% to 3% of patients). Appendage anatomy varies between individuals but includes sessile and pedunculated types; testicular appendices were more commonly sessile in a prenatal study (Jacob and Barteczko, 2005) but pedunculated in a postnatal torsion series (Jones, 1962). The appendix testis is located at the cranial testicular pole or in the groove between the testis and epididymis, and the appendix epididymis is located along the caput. The cause of torsion of an appendage is not known but may be related to anatomy, trauma, and/or prepubertal enlargement.

Appendage torsion is the most common cause of acute scrotum in prepubertal children. The peak age at occurrence is 7 to 12 years (mean 8 to 9 years) (Anderson and Giacomantonio, 1985; Mushtaq et al, 2003; Lyronis et al, 2009). Symptoms include sudden or gradual onset of testicular pain, which may be mild or severe and intermittent in some cases. Some series fail to show significant differences in the presenting complaints of boys with appendage as compared with testicular torsion, but, in general, patients with appendage torsion are less likely to present early in the course of symptoms or to have nausea and vomiting or generalized testicular tenderness. In addition, pain may increase with activity and resolve at rest.

Physical findings depend on the severity of inflammation and duration of symptoms (Rakha et al, 2006). A blue dot sign was first described by Dresner (1973) as a discoloration seen through the scrotal wall in prepubertal boys when the skin is stretched over the upper pole of the testis early in the course of the disease. This sign is reportedly present in 0% to 52% of patients (Caldamone et al, 1984; Van Glabeke et al, 1999; Karmazyn et al, 2005; Murphy et al, 2006; Lyronis et al, 2009) but was uncommon (10%) in one of the largest series of boys whose diagnoses were confirmed surgically (Makela et al, 2007). A single false-positive

case of a blue dot sign in a patient with testicular torsion has been reported (Murphy et al, 2006). Other associated early signs supportive of the diagnosis include a tender nodule superior to the testis with limited testicular tenderness, a symmetrical (present or absent) cremasteric reflex, and intact epididymal landmarks. However, with longer duration there may be increasing difficulty in differentiating appendage torsion from other causes of acute scrotum, because many of the symptoms are nonspecific and the scrotal examination may show increasing testicular enlargement and tenderness and marked scrotal swelling and erythema. These secondary signs may progress even in the absence of worsening pain and contribute to prolonged resolution. In a large series of 840 boys with scrotal pain, 5% required reexploration for metachronous contralateral appendiceal torsion (Ben-Meir et al, 2006).

CDUS in cases of appendage torsion is operator dependent and may show hyperperfusion of the epididymis with or without an enlarged (typically > 5 mm) appendix testis or may appear normal (Baldisserotto et al, 2005). When visible by CDUS, the normal appendix testis contains no internal blood flow and has a mean diameter of 3.1 ± 0.8 mm (Yang et al, 2005) whereas the twisted appendage may appear as an ovoid hyperechoic, hypoechoic, or heterogeneous nodule without blood flow (Fig. 132–11). When visible this finding is helpful, but its absence does not rule out appendage torsion. Similarly, epididymal hyperemia may indicate epididymitis or testicular detorsion.

The high prevalence of appendiceal torsion and long-recognized expectation of spontaneous resolution with conservative management supports nonsurgical management of the majority of patients, particularly in boys in whom the diagnosis is clear (Koff and De Ridder, 1976). In most cases symptoms resolve spontaneously with strict limitation of activities until pain resolves and use of a nonsteroidal anti-inflammatory agent such as ibuprofen. In some cases pain and swelling is exacerbated by athletic activities. Rarely, prolonged and severe pain or recurrent episodes warrant surgical excision of the appendage to reduce pain and morbidity.

Epididymitis

In children, the true incidence and cause of infectious or noninfectious inflammation of the epididymis, or epididymitis, is poorly defined and controversial (Lau et al, 1997; Merlini et al, 1998; Cappele et al, 2000; Somekh et al, 2004; Al-Taheini et al, 2008; Sakellaris and Charissis, 2008). Nonoperative series suggest a higher prevalence (40% to 60%) than that reported for operative series (5% to 15%), probably owing to difficulty differentiating epididymitis from appendix testis torsion clinically (Kadish and Bolte, 1998; Lam et al, 2005; Lyronis et al, 2009). In many series peaks in prevalence occur in infancy and at puberty (Sidler et al, 1997; Mushtaq et al, 2003; Makela et al, 2007). Symptoms are similar to those reported for other causes of acute scrotal pain but may be more gradual in onset. Nausea and vomiting are extremely rare, but fever or voiding symptoms may be present. Localized epididymal enlargement and tenderness are present, and the cremasteric reflex is symmetric. CDUS shows increased epididymal size and blood flow (Fig. 132–12) as well as increased testicular flow in some cases; however, it is important to note that these same physical and imaging findings may be associated with intermittent testicular or appendix testis torsion. Associated pyuria and/or bacteriuria are reported in 20% to 40% of cases that were confirmed intraoperatively (Anderson and Giacomantonio, 1985; Sidler et al, 1997; Mushtaq et al, 2003; Murphy et al, 2006; Makela et al, 2007). Known risk factors for both urinary tract infection and epididymitis include neurogenic and non-neurogenic voiding dysfunction; clean intermittent catheterization (CIC); urethral abnormalities including hypospadias, urethrorectal fistula, and stricture (Karmazyn et al, 2009); and congenital anomalies of the ejaculatory duct (see Fig. 132–12) (Pimpalwar et al, 2002; Yanai et al, 2005). Boys with anomalies are more likely to have severe inflammation of the epididymis and recurrent episodes (Karmazyn et al, 2009). Noninfectious epididymitis is attributed to milder forms of bladder dysfunction, unusual bacterial or viral infections, or trauma, but conclusive evidence supporting these causes is unavailable (Bukowski et al, 1995a; Somekh et al, 2004). Sexually transmitted disease is the most likely cause in postpubertal sexually active males.

Because the historical, physical, and imaging findings are nonspecific and the disease is rare in prepubertal children, some clinicians diagnose epididymitis only when signs of infection are present. Al-Taheini and coworkers have proposed strict criteria for diagnosis that include acute scrotal pain and epididymal hyperemia on CDUS in addition to at least two of the following: fever

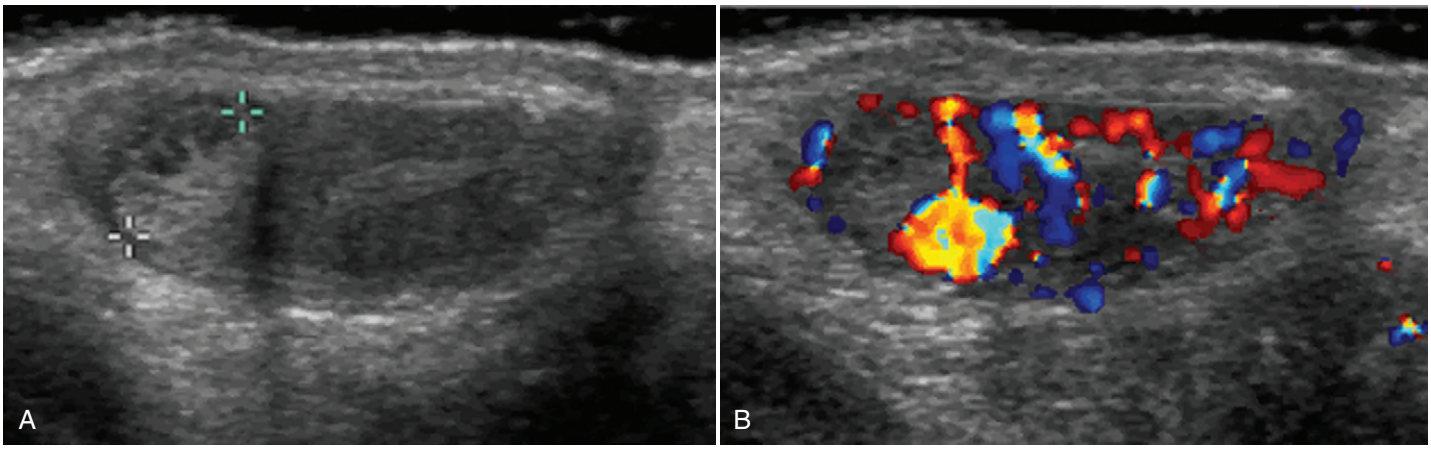


Figure 132–11. Torsion of a testicular appendage. CDUS shows (**A**) a heterogeneous enlarged appendix of 7 mm in greatest diameter and (**B**) increased flow to testis and epididymis and avascular appendix. The patient was treated conservatively, and the examination findings normalized within 1 week.

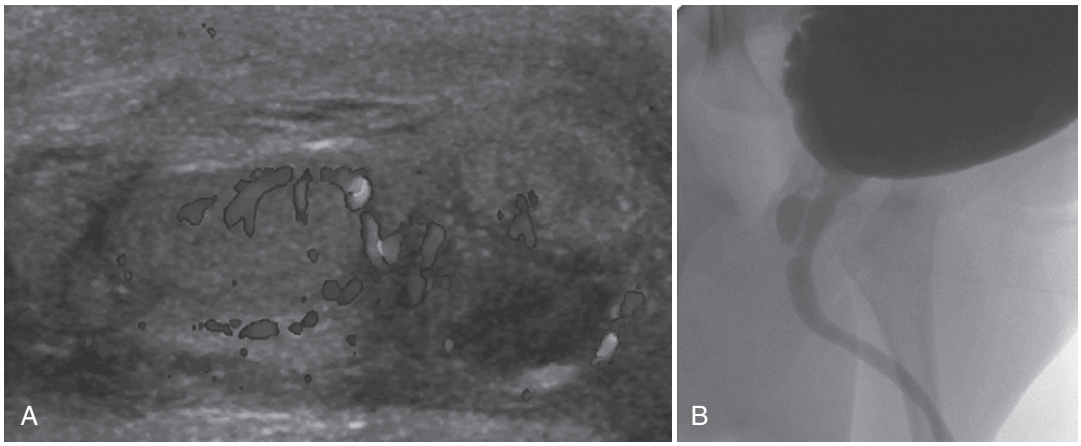


Figure 132–12. Epididymitis with utricle and seminal vesicle reflux in a male 3-month-old with trisomy 21, micropenis, and *Escherichia coli* urinary tract infection. **A**, Color Doppler ultrasonography shows an enlarged, hyperemic, and heterogeneous right epididymis; **B**, Voiding cystourethrography shows reflux into the right ejaculatory duct and seminal vesicle.

greater than or equal to 37.5° C, leukocytosis, pyuria (>10 white blood cells per high-powered field), and/or positive urine culture (Al-Taheini et al, 2008). Using these criteria they identified 16 patients with epididymitis; of these 10 had a documented urinary tract infection, 15 had a normal renal ultrasound study, and 1 of 13, a boy with a history of imperforate anus, had an abnormal voiding cystourethrogram. Other clinical series document a low risk of urinary tract anomalies in boys with epididymitis, although infants may be at higher risk (Merlini et al, 1998; Sakellaris and Charissis, 2008). However, anomalies such as pyelectasis, low-grade vesicoureteral reflux, and renal duplication that comprise the majority of findings may be incidental whereas direct contributing factors such as urethral or ureteral obstruction, ejaculatory duct, or vasal anomalies are rare.

In the absence of urinary tract infection, symptoms improve spontaneously without antibiotic therapy (Lau et al, 1997) and the need for urinary tract imaging in otherwise normal boys remains controversial. Recommendations include renal ultrasonography only (Al-Taheini et al, 2008) or no imaging unless the problem is recurrent (Cappele et al, 2000). In cases of documented urinary tract infection associated with epididymitis or progression to epididymo-orchitis, aggressive treatment including intravenous antibiotics and hospitalization may be necessary and imaging workup of the urinary tract, including renal ultrasonography and voiding cystourethrography, is indicated after resolution of the infection. In recurrent cases, endoscopy may reveal ejaculatory duct abnormalities that are not evident on voiding cystourethrography (Pimpalwar et al, 2002; Yanai et al, 2005). Recurrent epididymo-orchitis in these cases may require excision of a utricle or ejaculatory duct cyst with vasovasostomy or vasectomy.

Other Causes of Acute Scrotal Pain

A large number of conditions affecting the scrotum or intrascrotal contents may present as scrotal pain and/or swelling (see Table 132–6). Trauma, although not uncommonly reported in boys with testicular or appendage torsion, may also lead to acute scrotal swelling and pain in cases of hematocele due to *testicular rupture* or to intra-abdominal injury in the presence of a communicating hydrocele. CDUS appears to be sensitive in diagnosing testicular fracture in adolescents, and surgical intervention is indicated (Adams et al, 2008). Boys with *idiopathic scrotal edema* are typically prepubertal (2 to 12 years old) and present with unilateral or bilateral scrotal redness and swelling with or without pain (Klin et al, 2002; Lee et al, 2009). Associated findings may include local spread of erythema or edema to the inguinal or perineal region, inguinal lymphadenopathy, leukocytosis, and/or eosinophilia, the latter suggesting an allergic cause although the etiology is most likely multifactorial. Distinctive characteristics include minimal or no pain, scrotal but not testicular tenderness, and thickening of the scrotal wall by ultrasonography. Treatment is observation and possible use of antihistamines with resolution expected over several days. *Henoch-Schönlein purpura* is a form of acute vasculitis affecting the skin, joints, gastrointestinal tract, and kidneys that presents as scrotal findings in 2% to 38% of cases and may include edema or erythema; testicular hematoma, torsion or infarction; or cord thrombosis or epididymitis (Turkish et al, 1976; Diana et al, 2000; Ioannides and Turnock, 2001). A typical purpuric rash of the buttocks, perineum, and lower limbs is usually present but may not precede the scrotal findings. Urgent scrotal exploration is indicated if clinical findings suggest concomitant testicular torsion. *Cystic dysplasia of the rete testis* may present as acute scrotal swelling and pain (Noh et al, 1999; Smith et al, 2008; Jeyaratnam and Bakalinova, 2010). Rarely, an associated ureteral anomaly may lead to chronic testicular pain (McGee et al, 2009). Cystic dysplasia is associated with ipsilateral renal dysplasia, agenesis, or ureteral anomalies in the majority of cases and likely represents a failure of normal wolffian duct development. The diagnosis is confirmed by ultrasonography, which shows multiple small centrally located cysts within the testis. Treatment is conservative enucleation, which may be associated with recurrence, or observation, which is associated with regression in some cases.

EPIDIDYMAL, VASAL, AND SCROTAL ANOMALIES

Congenital anomalies of accessory testicular structures are often associated with primary diseases affecting testicular descent and genital development but may occur as isolated anomalies or as part of syndromes that do not primarily affect the genitalia.

Epididymal cysts are anechoic simple cystic structures that may be palpable by the patient or examining physician or found incidentally by ultrasonography (Homayoon et al, 2004). These

may be clinically indistinguishable from spermatoceles except that the latter occur postpubertally and contain sperm. The pathophysiology of epididymal cysts is unknown but may be related to an altered hormonal environment because they are linked to DES exposure (Palmer et al, 2009). These lesions are different ultrasonographically and pathologically from the multicystic/solid epididymal cystadenomas that occur in von Hippel-Lindau disease (Choyke et al, 1997). Homayoon and associates (2004) observed spontaneous resolution of many cysts observed in their pediatric series, and surgical intervention is rarely needed.

Congenital absence of the vas deferens (CAVD) is in most cases associated with specific mutations of the cystic fibrosis gene *CTFR* (cystic fibrosis transmembrane regulator) that are less severe than those encountered in patients with cystic fibrosis (McCallum et al, 2001; Kolettis and Sandlow, 2002). The disease can be bilateral (CBAVD) or unilateral (CUAVD) with a normal or obstructed contralateral vas and may be associated with renal agenesis or ectopia and/or partial or complete agenesis of the epididymis and seminal vesicles. *CTFR* mutations are more common in males with CBAVD, and renal anomalies are more common in cases of CUAVD. These patients typically present with infertility. Abnormal vasal development may also result in a **persistent mesonephric duct** anomaly that is associated with ipsilateral renal and seminal vesicle agenesis and vasoureteral fusion (Kajbafzadeh and Payabvash, 2006). Reflux into the fused wolffian remnants results in urinary tract infection and epididymo-orchitis. Other associated anomalies may include imperforate anus, hypospadias, tracheoesophageal fistula, tetralogy of Fallot, or coarctation of the aorta.

Scrotal anomalies including **ectopic scrotum** and **penoscrotal transposition** are rare but frequently occur in association with other congenital anomalies (Parida et al, 1995; Hoar et al, 1998). An ectopic scrotum may be suprainguinal, inguinal/femoral, or perineal (accessory). The suprainguinal form is unilateral, associated with an ectopic intrascrotal or cryptorchid testis, and often associated with ipsilateral renal anomalies. The femoral ectopic scrotum may be unilateral or bilateral and is associated with lip, palate, and limb anomalies, whereas the perineal (accessory) scrotum is commonly associated with a perineal lipoma (Park and Hong, 2006). Similarly, penoscrotal transposition occurs in severe hypospadias (Pinke et al, 2001) but is also associated with multisystem renal, CNS, vertebral, limb, and/or cardiac defects (Parida et al, 1995). Perineal lipomas may occur in association with a spectrum of scrotal anomalies, suggesting that they represent a cause or consequence of abnormal development of the labioscrotal folds (Park and Hong, 2006).

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

Key Points: Hernia/Hydrocele and Acute Scrotum

- Routine contralateral exploration in cases of unilateral inguinal hernia is not recommended.
- Noncommunicating scrotal hydroceles are more common in neonates and adolescents; the rare abdominoscrotal variant occurs primarily in infancy and requires repair.
- Diagnoses in cases of acute scrotum include appendix testis torsion (40% to 60%), spermatic cord torsion (20% to 30%), epididymitis (5% to 15%) and other or no pathology (10%).
- The anatomic abnormality predisposing to torsion of the spermatic cord is the bell-clapper deformity and occurs in about 12% of males.
- Findings most suggestive of spermatic cord torsion include puberty, absent cremasteric reflex, short duration (<6 hours) of pain, and reduced or absent blood flow and/or a visible spermatic cord twist on ultrasound imaging.
- Findings most suggestive of appendix testis torsion include prepuberty, a localized tender nodule at the superior testis pole, a blue dot sign, and a preserved cremasteric reflex.
- When findings support or are suggestive of spermatic cord torsion, emergent scrotal exploration is indicated and should not be delayed for diagnostic testing.
- Intrascrotal fixation of the testis must be performed bilaterally because a contralateral bell-clapper deformity usually exists and may lead to metachronous torsion.
- Epididymitis associated with urinary tract infection or with recurrent episodes warrants urinary tract evaluation with imaging to rule out urethral or ureteral anomalies.

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chapter 133

Sexual Differentiation: Normal and Abnormal

David Andrew Diamond, MD ● Richard N. Yu, MD, PhD

Normal Sexual Differentiation

Abnormal Sexual Differentiation

Evaluation and Management of the Newborn with Ambiguous Genitalia

Disorders of sexual differentiation are among the most fascinating and complex disease processes encountered by the urologist. This field has undergone a striking evolution over the past few decades. Remarkable advances in molecular biology and genetic research have provided new insight into the precise mechanisms responsible for sexual differentiation and for specific disorders of sexual development. In addition, there has been a major shift in nomenclature in order to promote precise communication among colleagues and respect for the sensitivity of patients by eliminating terms such as *pseudohermaphroditism,* which have been regarded as pejorative by patients. The term *intersex disorders* has been replaced by *disorders of sex development* (DSDs).

NORMAL SEXUAL DIFFERENTIATION

Under normal circumstances, sexual differentiation is a dynamic and sequential process. According to the Jost paradigm, three steps must occur: establishment of chromosomal sex at fertilization, which determines development of the undifferentiated gonads into testes or ovaries, and subsequent differentiation of the internal ducts and external genitalia as a result of endocrine functions associated with the type of gonad present (Jost et al, 1973). Therefore sexual development occurs as a result of different but complementary processes: genotypic effects, phenotypic events, and gender identity formation. Interference with this highly ordered process at any step can result in a disorder of sexual differentiation.

Normal Genotypic Development

Chromosomal Sex

In 1921, Painter demonstrated cytologically that humans have X and Y chromosomes. Based on chromosomal studies of *Drosophila,* it was assumed that sex was determined by the X chromosomes possessed by the individual (Bridges, 1921). The Y chromosome was thought to impart no genetic information until karyotyping of mammalian chromosomes, developed in the 1950s, demonstrated that the Y chromosome specified development of the testis. Specifically, reports in the late 1950s describing the karyotype 47,XXY as male with Klinefelter syndrome and 45,XO as female with Turner syndrome demonstrated that the presence of a Y chromosome, independent of the number of X chromosomes, resulted in the development of a male embryo, whereas in the absence of a Y chromosome the embryo developed as a female (Ford et al, 1959; Jacobs and Strong, 1959). Therefore, the Y chromosome appeared to possess a gene or genes that determined the destiny of the bipotential gonad as a testis or ovary. **In the human, the hypothetical Y-chromosomal gene was termed the *testis-determining factor* (TDF).**

During the following years the search for the TDF was the focus of intense research. The observation that antibodies raised in inbred female mice transplanted with male skin grafts resulted in graft rejection whereas female-to-male skin grafts were accepted in the same strain of mice led to the proposal that the histocompatibility-Y, or H-Y, antigen was the product of TDF (Eichwald, 1955). Assays for quantifying H-Y antigen were developed. With the use of these assays it was discovered that the presence of a testis resulted in serologically detectable levels of H-Y antigen. This was confirmed in normal patients, patients with DSDs, and males of other species. **Therefore, it was believed that the H-Y gene was the TDF** (Wachtel, 1977). **This theory was considered valid for more than 10 years.**

Problems with the H-Y antigen theory developed, however. A number of women with 45,X gonadal dysgenesis were found to be H-Y antigen positive. In addition, a mouse model for the male sex reversal syndrome (XX male) was studied in which mice have two X chromosomes and testes owing to a fragment of Y chromosome translocated onto one of the X chromosomes (McLaren et al, 1984). These mice were H-Y antigen negative and azoospermic. **As a result of these findings the hypothesis that the H-Y antigen was the product of TDF was excluded. Further study of the Y chromosome suggested that the genetic information responsible for maleness was on the short arm of the chromosome near the centromere.** This theory was supported by data from animals with naturally occurring sex chromosome abnormalities. Gain or loss of DNA from the short arm of the Y chromosome on an XX genetic background resulted in either a male or female phenotype, respectively. Further progress was made by studying paradoxical, 46,XX males who develop as phenotypic males in the presence of a presumably normal female 46,XX karyotype (Magenis et al, 1982). The simplest explanation for their sex reversal would be the presence of Y-chromosomal material (including TDF), owing to mosaicism or to

submicroscopic cellular quantities. The application of molecular techniques to evaluate Y-chromosomal sequences present in XX males, as well as deletions of the Y chromosome in XY females, led to the cloning of TDF (Lukusa et al, 1992). **Deletion maps based on the genomes of these individuals were constructed by a number of laboratories, and TDF was mapped to the most distal aspect of the Y-unique region of the short arm of the Y chromosome, adjacent to the pseudoautosomal boundary** (Fig. 133–1).

ZFY and *SRY*

Page and coworkers (1987) constructed a more detailed genomic map and defined a 140-kilobase (kb) interval thought to contain the TDF by aligning the Y-specific DNA present in an XX male with a Y chromosome deletion of the same region in an XY female. These investigators identified a gene encoding a protein with multiple "zinc finger" domains, characteristic of a class of proteins that bind DNA in a sequence-specific manner and regulate transcription. In addition, these sequences demonstrated evolutionary conservation. **Based on its position and structural similarity to other transcription factors, *ZFY* (zinc finger gene on Y chromosome) was proposed as a candidate for the TDF.**

However, in subsequent years, data were accumulated that excluded *ZFY* as the TDF. This included the discovery that in marsupials *ZFY* was located not on the sex chromosomes but on autosomes (Sinclair et al, 1988). ***ZFY* was excluded with certainty as a candidate for TDF when four individuals with testicular development were found to have inherited a fragment of the Y chromosome that did not include *ZFY*** (Palmer et al, 1989).

The renewed search for TDF led to the discovery of Y-specific sequences in XX males lacking *ZFY* and imposing new limits on the location of TDF to a 35-kb region adjacent to the pseudoautosomal boundary (Fig. 133–2). **Using probes from this region, Sinclair and colleagues** (1990) **discovered a single-copy male-specific sequence that was evolutionarily conserved. This gene was termed *SRY* (sex-determining region Y gene) in humans and *Sry* in mice.** Analysis of the SRY protein sequence demonstrated a highly conserved, 78 amino acid region with homology to a DNA-binding motif of the high-mobility group (HMG) family of proteins (Fig. 133–3). When DNA encoding the HMG box was used to probe a genomic library, a subfamily of closely related genes was identified. Members of this family, defined as those encoding a region with 60% or greater amino acid similarity to the SRY HMG-box motif, are called *SOX* (SRY-box-related) genes (Goodfellow and Lovell-Badge, 1993).

Considerable evidence has accumulated that *SRY* is the TDF. In the mouse, expression of *Sry* correlates with testicular determination in the gonadal ridge (Koopman et al, 1990). *SRY* is an evolutionarily conserved gene on the Y chromosome of mammals. Chromosomal fragments related to *SRY* (i.e., the *SOX* genes) are very much conserved evolutionarily, being demonstrated in various vertebrates and marsupials. ***SRY* is localized to the smallest region of the Y chromosome capable of inducing testicular differentiation in humans and in mice** (Gubbay et al, 1992). In fact, Koopman and coworkers (1991) introduced into XX mouse embryos a 14-kb mouse genomic DNA fragment containing *Sry* and no other Y-linked gene sequences and demonstrated that it was capable of giving rise to normal testicular development in the transgenic mice. **The *SRY* protein**

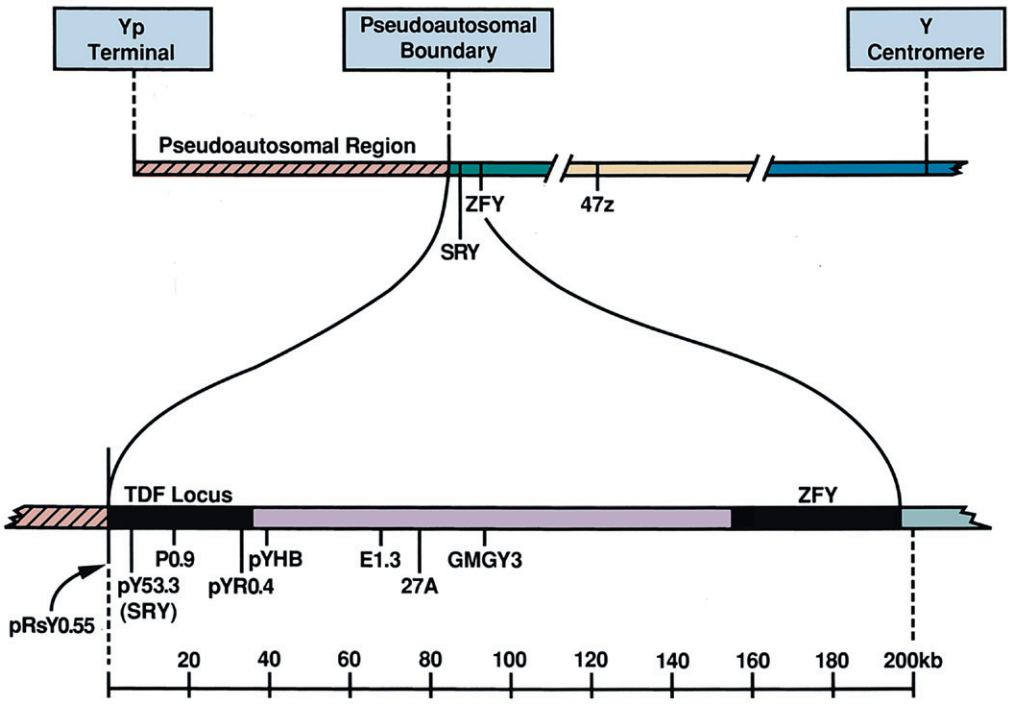


Figure 133–1. Genetic map of the short arm of the human Y chromosome. The top of the diagram shows the pseudoautosomal region of the short arm of the Y chromosome and the locus of the *SRY* and *ZFY* genes near the pseudoautosomal boundary. The lower part of the diagram represents an enlargement of the Y chromosome near the pseudoautosomal boundary and the location of the *SRY* and *ZFY* genes. (From Migeon CJ, Berkovitz GD, Brown TR. Sexual differentiation and ambiguity. In: Kappy MS, Blizzard RN, Migeon CJ, editors. Wilkins: the diagnosis and treatment of endocrine disorders in childhood and adolescence. Springfield [IL]: Charles C. Thomas; 1994. p. 588.)

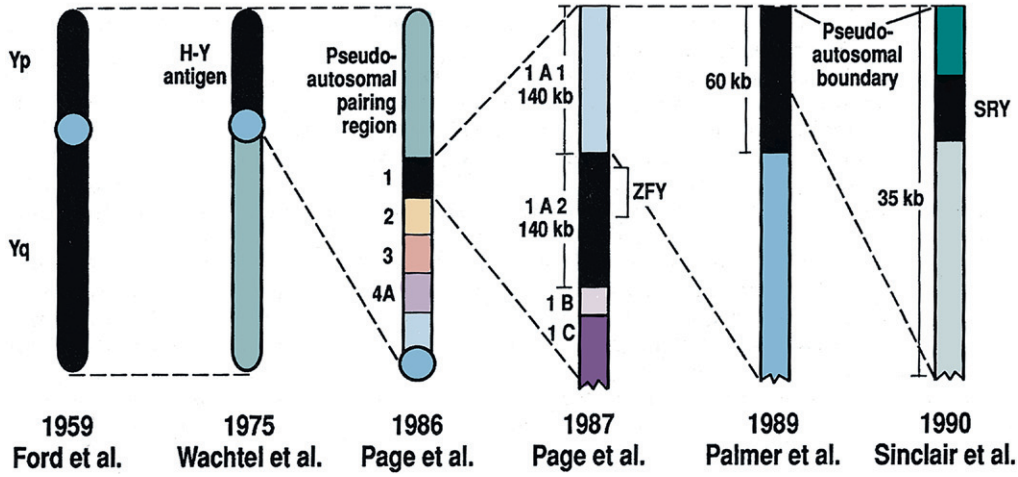


Figure 133–2. Diagrammatic representation of the historical search for the testis-determining factor (TDF). The *shaded area* on the Y chromosome is the region to which this factor has been localized. (From Grumbach MM, Conte FH. Disorders of sex differentiation. In: Wilson JD, Foster DW, editors. Williams textbook of endocrinology. Philadelphia: WB Saunders; 1998. p. 1315.)

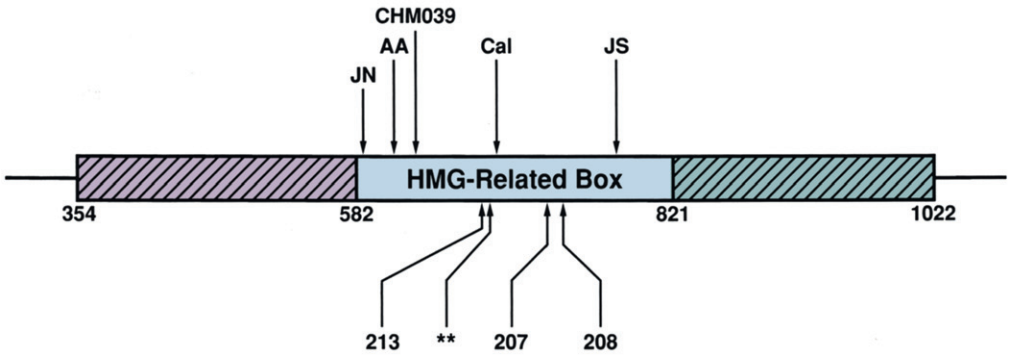


Figure 133–3. Diagram of the *SRY* (sex-determining region on the Y gene) locus, with the so-called high-mobility group (HMG)-related box in the center. The HMG box encodes the DNA-binding region of the SRY protein. Various *arrows* represent the location of the mutations that have been identified in patients with 46,XY complete gonadal dysgenesis. (From Migeon CJ, Berkovitz GD, Brown TR. Sexual differentiation and ambiguity. In: Kappy MS, Blizzard RN, Migeon CJ, editors. Wilkins: the diagnosis and treatment of endocrine disorders in childhood and adolescence. Springfield [IL]: Charles C. Thomas; 1994. p. 620.)

functions as a transcription factor that, by binding and producing bending of the DNA, promotes protein-protein interaction and is able to activate downstream gene expression. An expectation for TDF was that mutations in its protein sequence would result in sex reversal. Examination of the *SRY* sequence in XY females has identified more than 20 mutations in the protein-coding sequence. All but one of these point mutations and microdeletions lie within the DNA-binding domain. Another prediction for TDF is that its presence can cause XX male sex reversal. All but one XX male with Y-specific sequences have been found to contain *SRY* (Goodfellow and Lovell-Badge, 1993). This suggested a causative role of *SRY* in these cases of XX sex reversal. **Therefore, genetic and molecular data have established that *SRY* can be equated to the TDF.**

Additional insights have been gained regarding *SRY* function as a molecular switch that promotes testis development. *SRY* is expressed and functions in the supporting cells of the developing male urogenital ridge. These cells participate in cord formation and ultimately develop into Sertoli cells.

Key Points: Chromosomal Sex

- Sinclair and colleagues (1990) discovered the testis-determining factor (TDF), a single-copy male-specific sequence that was evolutionarily conserved.
- This gene was termed *SRY* (sex-determining region Y gene) in humans and *Sry* in mice.

Additional Genes Involved in Gonadal Determination

Several additional genes involved in gonadal development have been identified and characterized. These include, but are not limited to, *WT1, SF1, SOX9, DAX1, WNT4, RSPO1,* and *FOXL2* (Fig. 133–4; Table 133–1). Newer data suggest that these factors function in defined but interrelated differentiation pathways during gonadal formation and determination.

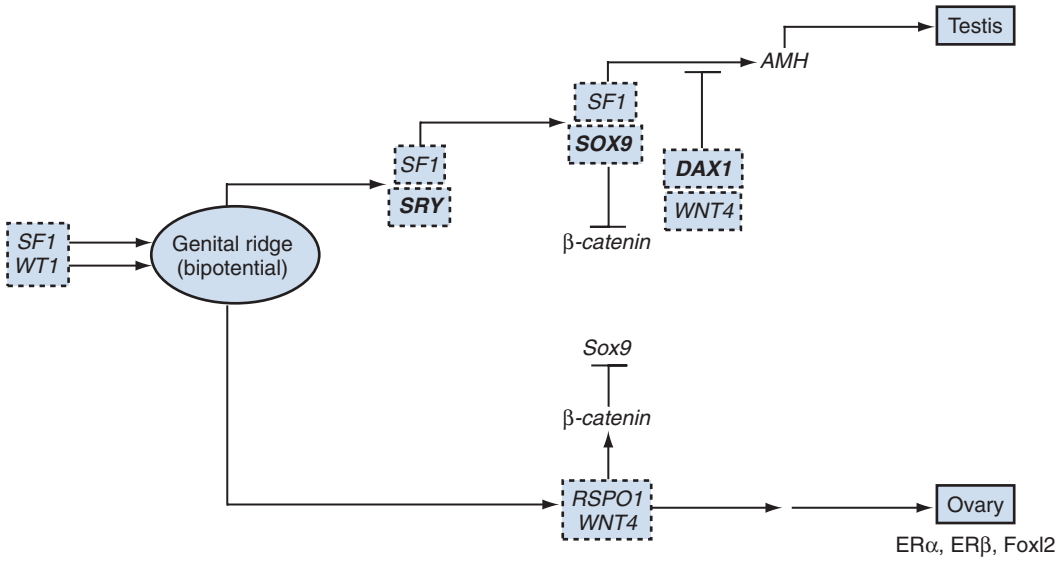


Figure 133–4. Genes determining testis or ovarian differentiation from bipotential gonad. (After Hughes IA. Intersex. BJU Int 2002;90:771; and Sekido R, Lovell-Badge R. Sex determination and SRY: down to a wink and a nudge? Trends Genet 2008;25[1]:19–29.)

Table 133–1.

Loss of Function Phenotype (Human Data)

GENE	CHROMOSOME	XY	XX
SRY	Yp11.3	Female; gonadal dysgenesis (Swyer syndrome)	
SOX9	17q24.3-q25.1	Female; camptomelic dysplasia; ovaries to gonadal dysgenesis	Female; camptomelic dysplasia
WT1	11p13	Female; Wilms tumor; gonadal dysgenesis, mesangial sclerosis (Denys-Drash syndrome); streak gonads, glomerulosclerosis (Frasier syndrome)	Female; Wilms tumor; gonadal dysgenesis, mesangial sclerosis (Denys-Drash syndrome); streak gonads, glomerulosclerosis (Frasier syndrome)
NR5A1(SF1)	9q33	Female; adrenal insufficiency; gonadal dysgenesis	
NR0B1 (DAX1)	Xp21.3-p21.2	Male; gonadal dysgenesis, hypogonadotropic hypogonadism; adrenal hypoplasia	
WNT4	1p36.23-p35.1		Male; aberrant müllerian structure development; wolffian development
RSPO1	1p34.3		Male; palmoplantar keratoderma; aberrant müllerian development; ovotestis
FOXL2	3q23		Male; prophase oocytes; activated somatic testicular development

WT1. The *WT1* gene was originally isolated in cloning experiments that identified an oncogene on human chromosome 11 as being involved in the etiology of Wilms tumor (Call et al, 1990). This gene, originally localized by examining chromosomal deletions in children with WAGR syndrome (*W*ilms tumor, *a*niridia, *g*enitourinary abnormalities, gonadoblastoma, and mental *r*etardation), was found to be expressed primarily in the kidney and gonads of the developing human embryo (Kreidberg et al, 1993). The first reported mutations in the Denys-Drash syndrome, which includes Wilms tumor, renal failure, and gonadal and genital abnormalities, were found to involve the WT1 protein (Pelletier et al, 1991a, 1991b). Indeed, mutations involving *WT1* have been found responsible for both the Frasier and Denys-Drash syndromes, which appear to represent a spectrum of genetically induced abnormalities involving the gonads and kidneys, owing to the earlier involvement of *WT1* in the differentiation of both structures. Frasier syndrome is characterized by both gonadal dysgenesis and renal abnormalities that result in streak gonads and a nephrotic syndrome (MacLaughlin and Donahoe, 2004). If it occurs in the XY genotype, sex reversal results. As a result of alternative splicing of the *WT1* gene, patients with Frasier syndrome are not susceptible to Wilms tumor whereas those with Denys-Drash syndrome are (Koziell and Grundy, 1999). In addition, with the Denys-Drash syndrome, gonads differentiate more completely than with Frasier syndrome. Research on *Wt1* in the mouse suggests that it exerts its effects upstream of *Sry* and is likely to be necessary for commitment and maintenance of gonadal tissue (Lim and Hawkins, 1998).

SF1. Experiments in the mouse have demonstrated that nuclear receptor steroidogenic factor 1 (*SF1)* is expressed in all steroidogenic tissues, including adrenal cortex, testis (Leydig cells), ovarian theca, granulosa cells, and corpus luteum. *SF1* appears to be a key regulator of enzymes involved in steroid production, including the sex hormones, and may directly regulate pituitary gonadotropin expression (Parker et al, 2002). In addition, it appears to play a role in early gonadal development at multiple levels of the

reproductive endocrine axis (Ingraham et al, 1994; Luo et al, 1994). ***SF1*** also **appears to act synergistically with *WT1* in the regulation of müllerian-inhibiting substance** (MIS) expression (Shen et al, 1994; Imbeaud et al, 1995; Nachtigal et al, 1998) and may regulate *DAX1* expression (Yu et al, 1998).

SOX9. The *SOX9* gene was originally identified in patients with camptomelic dysplasia, a congenital disease of bone and cartilage formation that is often associated with XY sex reversal (Wagner et al, 1994). **The *SOX9* gene is structurally quite similar to *SRY*, with a 71% sequence similarity of the high-mobility group (HMG) domain to that of *SRY*.** Expression of the gene in adults is greatest in the testes. **Interestingly, *SOX9* gene activity increases immediately after SRY expression and cell lineage analyses show that SOX9 protein is expressed in cells determined to become Sertoli cells** (Sekido and Lovell-Badge, 2009). **Therefore, the *SOX9* gene may be a key downstream effector of SRY action. The activity of SRY on *SOX9* is synergistic with the activity of an additional transcription factor, steroidogenic factor 1 (SF1), which is essential for gonadal and adrenal development** (Sekido and Lovell-Badge, 2008). **A role for *SOX9* in male gonadal determination is further supported by data from genotypic males with *SOX9* mutations (46,XY) that exhibit ovarian development and male-to-female sex reversal** (Foster et al, 1994; Wagner et al, 1994). *SOX9* also upregulates *AMH* gene expression (MacLaughlin and Donahoe, 2004).

***DAX1* and Dosage-Sensitive Sex Reversal (DSS).** The first indication that an X-specific gene was involved in human sex determination was provided in 1978 with the identification of a family with an X-linked mode of inheritance of 46,XY gonadal dysgenesis. Subsequent studies of a number of sex-reversed subjects confirmed the presence of additional X chromosomal genetic material and a normal Y chromosome (Ogata et al, 1992). **This finding suggested that duplication of an X-specific gene causes XY sex reversal by expressing a double dose of a region normally subject to X inactivation. Screening of XY females with a normal *SRY* gene detected such a submicroscopic duplication, involving a 160-kb region designated as the dosage-sensitive sex reversal (DSS) critical region** (Bardoni et al, 1994). Parallel studies examining 46,XY males with gonadal dysgenesis, hypogonadotropic hypogonadism, and congenital adrenal hypoplasia resulted in the identification of a candidate gene, *NR0B1 (DAX1),* within the DSS critical region (Muscatelli et al, 1994; Zanaria et al, 1994). Interestingly, *DAX1* can act to suppress or promote the testis determination pathway (Yu et al, 1998; Meeks et al, 2003). Although *DAX1* was initially believed to be the primary gene involved in DSS, several sex-reversed 46,XY patients have been identified with duplication of the DSS region in the absence of *DAX1* duplication, which suggests that the gene dosage effects of this region may be associated with an additional gene or genes (Zanaria et al, 1995).

WNT4. *WNT4* on chromosome 1p34 appears to be involved in müllerian duct regression and may also function by antagonizing SRY activity (Kim et al, 2006; Bernard and Harley, 2007). Early inactivation of *Wnt4* in mice causes failure of the formation of müllerian duct derivatives in both sexes. In addition, inactivation of *Wnt4* in female mice leads to wolffian duct development without testicular tissue formation and female external genitalia. Furthermore, a recent report supports the role of *WNT4* in development and maintenance of the female phenotype in women by regulating müllerian duct development and ovarian steroidogenesis (Biason-Lauber et al, 2004).

Normal Phenotypic Development

Gonadal Stage of Differentiation

During the first 6 weeks of embryonic development, the gonadal ridge, germ cells, internal ducts, and external genitalia are bipotential in both 46,XY and 46,XX embryos. Under the genetic influences of sex determination, the bipotential gonadal ridges differentiate into either ovaries or testes and germ cells develop into either oocytes or spermatocytes. Primordial germ cells can be recognized in the third week of gestation on the posterior wall of the secondary yolk sac. **Migration of the germ cells begins in the fifth week of gestation as a result of ameboid movements through the mesentery to the medial ventral aspect of the urogenital ridge** (Jirasek, 1998) (Fig. 133–5). This process is dependent on chemoattractants and cell adhesion molecules (Hughes, 2002). Overall, a population of 1000 to 2000 primordial germ cells reaches the gonadal blastema by the sixth week of gestation.

Transformation of the germ cells into spermatogonia and oogonia results from differentiation of the epithelial gonadal compartments referred to as testicular and ovarian "cords." ***SRY* initiates the switch that induces a cascade of genes directing the indifferent gonad toward testicular organogenesis.** The precise moment at which this occurs remains unknown. Initially, differentiation of Sertoli cells is noted as testicular cords form at 6 to 7 weeks' gestation, creating the basement membrane, or blood-testis barrier, of spermatogonia and Sertoli cells on one side and mesenchymal fibroblasts on the other. **The differentiation of Sertoli cells is associated with the production of MIS, a glycoprotein encoded by a gene on the short arm of chromosome 19** (Haqq et al. 1994). In males, a second line of primordial cells of steroidogenic mesenchyme remain among the testicular cords and represent future Leydig cells, which differentiate at 8 to 9 weeks. **In the absence of *SRY*, ovarian organogenesis results.** Little is known about the genetic control of ovarian development. To date, no genes whose products direct development of the ovary have been identified. **It does appear necessary that there be duplicate copies of at least one X chromosomal locus (which presumably explains the dysgenetic ovaries in the 45,XO Turner syndrome patients).** A potential candidate may lie within the DSS critical region on Xp-21, which, when duplicated, promotes male-to-female "sex reversal" (Bardoni et al, 1994; Lopez et al, 1998).

Unlike the testis, which functions primarily as a fetal endocrine organ, the ovary has primarily exocrine activity. **In embryonal ovaries, germ cells undergo intense mitotic proliferation (preceding the onset of meiotic prophase) and in the process exhaust their entire mitotic potential prenatally, reaching a maximum endowment of 20 million cells by 20 weeks' gestation.** The presence of two X chromosomes appears to be responsible for differentiation of the granulosa cells into the protective mantle of the granulosa layer and "rescue" of 30% of germ cells (approximately 2 million) (Byskov and Westergaard, 1998).

Key Point: Gonadal State of Differentiation

- During the first 6 weeks of embryonic development the gonadal ridge, germ cells, internal ducts, and external genitalia are bipotential in both 46,XY and 46,XX embryos.

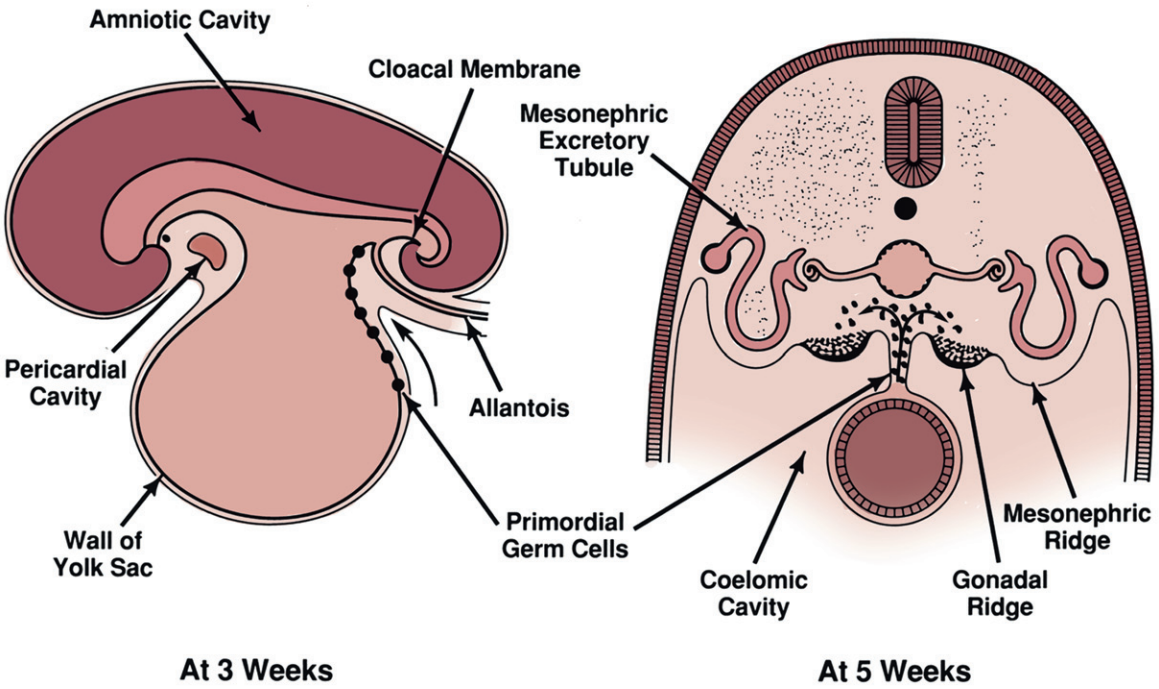


Figure 133–5. Migration of primordial germ cells. At 3 weeks, primordial germ cells are being formed and migrate along the wall of the yolk sac to reach the caudal part of the fetus. By 5 weeks, they have reached the level of the gonadal ridge. (From Migeon CJ, Berkovitz GD, Brown TR. Sexual differentiation and ambiguity. In: Kappy MS, Blizzard RN, Migeon CJ, editors. Wilkins: the diagnosis and treatment of endocrine disorders in childhood and adolescence. Springfield [IL]: Charles C. Thomas; 1994. p. 584.)

Gonadal Function

The initial endocrine function of the fetal testes is the secretion of MIS by the Sertoli cells at 7 to 8 weeks' gestation. MIS, one of the two hormones necessary for male sexual differentiation, acts locally to produce müllerian regression. It is a member of the transforming growth factor-β (TGF-β) family, and the human gene has been cloned and mapped to chromosome 19 (Cate et al, 1986). Little is known about the cellular mechanism of action of MIS. Because the hallmark of MIS-mediated müllerian duct regression is the formation of a ring of connective tissue around the epithelial cells, it is likely that the mesenchyme is the primary target of MIS. **Testosterone secretion by the fetal testes is detectable shortly after the formation of Leydig cells in the interstitium at approximately 9 weeks' gestation** (Siiteri and Wilson, 1974). There is a rise in serum and testicular testosterone to a peak concentration at 13 weeks and then a decline. The rate-limiting enzyme for fetal testosterone synthesis is 3β-hydroxysteroid dehydrogenase, which is concentrated approximately 50 times more highly in the fetal testes than in the ovary. Androgens are synthesized by the Leydig cells, initially autonomously, but then dependent on placental human chorionic gonadotropin (hCG) secretion. Later in gestation, with declining hCG concentrations, androgen synthesis is controlled by luteinizing hormone (LH) secretion by the fetal pituitary gland. Jost and colleagues (1973) **clearly demonstrated that androgen is essential for virilization of wolffian duct structures, the urogenital sinus, and genital tubercle. Testosterone, the major androgen secreted by the testes, enters target tissues by passive diffusion.** Organs such as the wolffian duct, adjacent to the fetal testis, also take up testosterone by pinocytosis. **The local source of androgen is important for wolffian duct development, which does not occur if testosterone is supplied only via the peripheral circulation. In some cells, such as those in the urogenital sinus, testosterone is converted to dihydrotestosterone (DHT) by intracellular 5α-reductase. Testosterone** or DHT then binds to a high-affinity intracellular receptor protein, and this complex enters the nucleus, where it binds to acceptor sites on DNA, resulting in new messenger RNA and protein synthesis (Fig. 133–6). The androgen receptor has been characterized as a high-affinity receptor that mediates the action of testosterone and DHT in all androgen-dependent tissues. In disorders of the androgen receptor, such as androgen insensitivity syndrome, testosterone production is normal but the hormone is unable to reach the nucleus and interact with DNA. Various defects in the androgen receptor result in a spectrum of phenotypic abnormalities in the genetic male. Because gonadal females have androgen receptor within their tissues, exogenous androgen produces virilization. **DHT binds to the androgen receptor with greater affinity and stability than does testosterone. Therefore, in tissues equipped with 5α-reductase at the time of sexual differentiation (e.g., prostate, urogenital sinus, external genitalia), DHT is the active androgen** (George and Peterson, 1988). The 5α-reductase activity has two optimal pH values in cultured genital skin fibroblasts—one at pH 5.5 and a second one near pH 8—that correspond to two distinct enzymes (Jenkins et al, 1992). The alkaline enzyme, human steroid 5α-reductase type 1, was cloned first; however, the primary enzyme in the prostate is 5α-reductase type 2 (Andersson and Russell, 1990). A deletion in the gene coding for this enzyme has been discovered in intersex patients with 5α- reductase deficiency (Andersson et al, 1991). The gene encoding the androgen receptor has been cloned and mapped to the X chromosome at Xq11-12 (Lubahn et al, 1988).

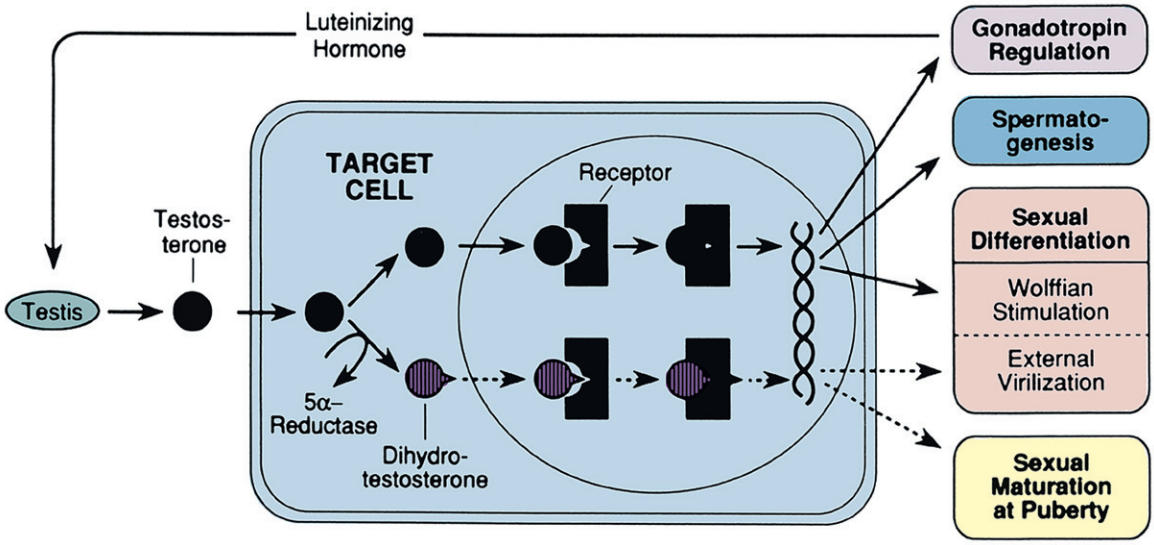


Figure 133–6. Schematic diagram of normal androgen physiology. The major actions of androgens are listed on the right. Testosterone enters androgen target tissues and either binds to the androgen receptor in cell nuclei or is converted by 5α-reductase to dihydrotestosterone (DHT). DHT binds to the same receptor but with greater affinity. Androgen actions mediated by testosterone are indicated by *solid arrows,* and those mediated by DHT are indicated by *dashed arrows.* (From Griffin JE, Wilson JD. Syndromes of androgen resistance. Hosp Pract 1987;22:99–114.)

Key Point: Gonadal Function

- DHT binds to the androgen receptor with greater affinity and stability than does testosterone. Therefore in tissues equipped with 5α-reductase at the time of sexual differentiation (e.g., prostate, urogenital sinus, external genitalia), DHT is the active androgen.

Ovary

Estrogen synthesis is detectable in the female embryo just after 8 weeks of gestation. The rate-limiting enzyme is aromatase, which is higher in the fetal ovary than in the fetal testis. Estrogens are not required for normal female differentiation of the reproductive tract, but they can interfere with male differentiation. Estrogen can block the effect of MIS on müllerian ducts, and prenatal estrogen treatment of mothers has been associated with male reproductive tract abnormalities (Gill et al, 1979; Vigier et al, 1989).

Phenotypic Sexual Differentiation

Before the 8th week of gestation the urogenital tract is identical in the two sexes. Both the wolffian and the müllerian duct systems are present as anlagen of the internal accessory organs of reproduction (Fig. 133–7). In addition, at this stage, the anlagen of the external genitalia of male and female embryos are indistinguishable (Fig. 133–8). **In the male fetus, Sertoli cells produce MIS, which acts locally and unilaterally to suppress the müllerian ducts, and Leydig cells produce testosterone, which permits local development of the wolffian ducts.** By 10 weeks of gestation, degeneration of the müllerian ducts is almost complete and the wolffian ducts have become more prominent (see Fig. 133–7). Adjacent to the testes,

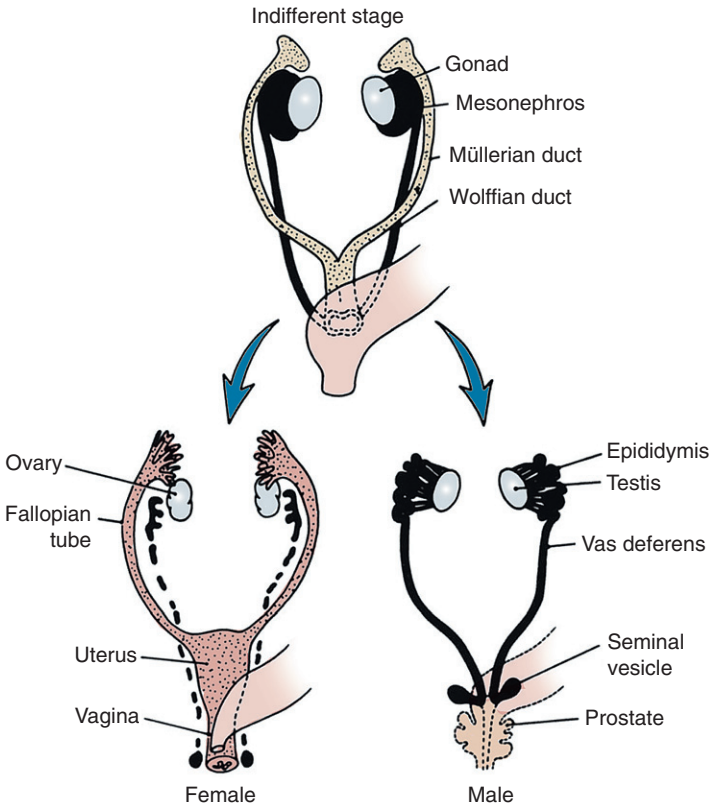


Figure 133–7. Differentiation of the wolffian and müllerian duct and urogenital sinus in the male and female. (From Wilson JD. Embryology of the genital tract. In: Harrison HH, Gittes RF, Perlmutter AD, et al, editors. Campbell's urology. 4th ed. Philadelphia: WB Saunders; 1979. p. 1473.)

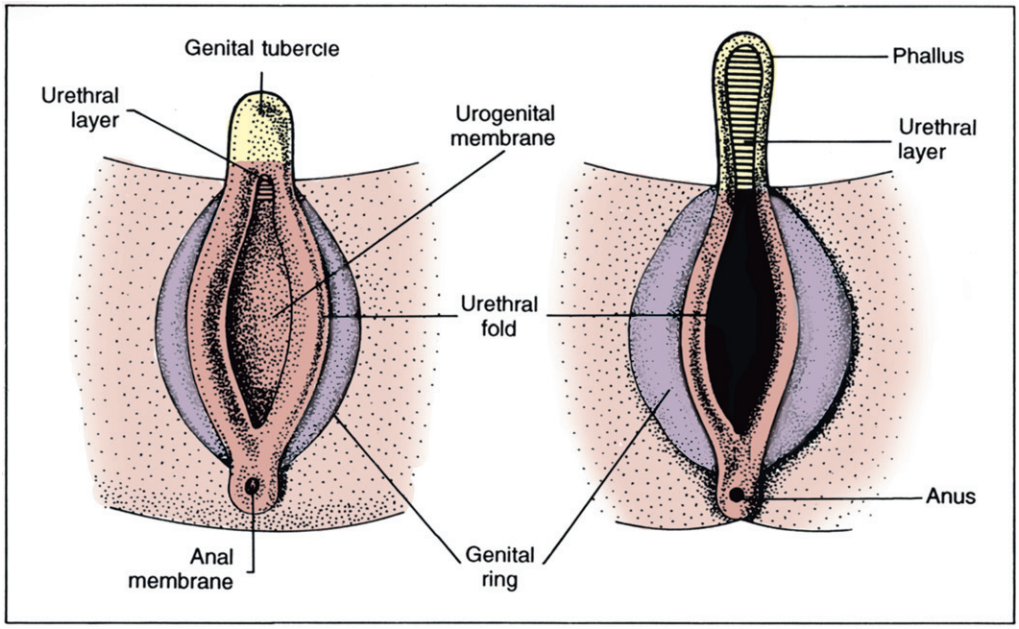


Figure 133–8. Schematic diagram of external genitalia in the undifferentiated period. (From Martinez-Mora J. Development of the genital tract. In: Martinez-Mora J, editor. Intersexual states: disorders of sex differentiation. Barcelona: Ediciones Doymer; 1994. p. 52.)

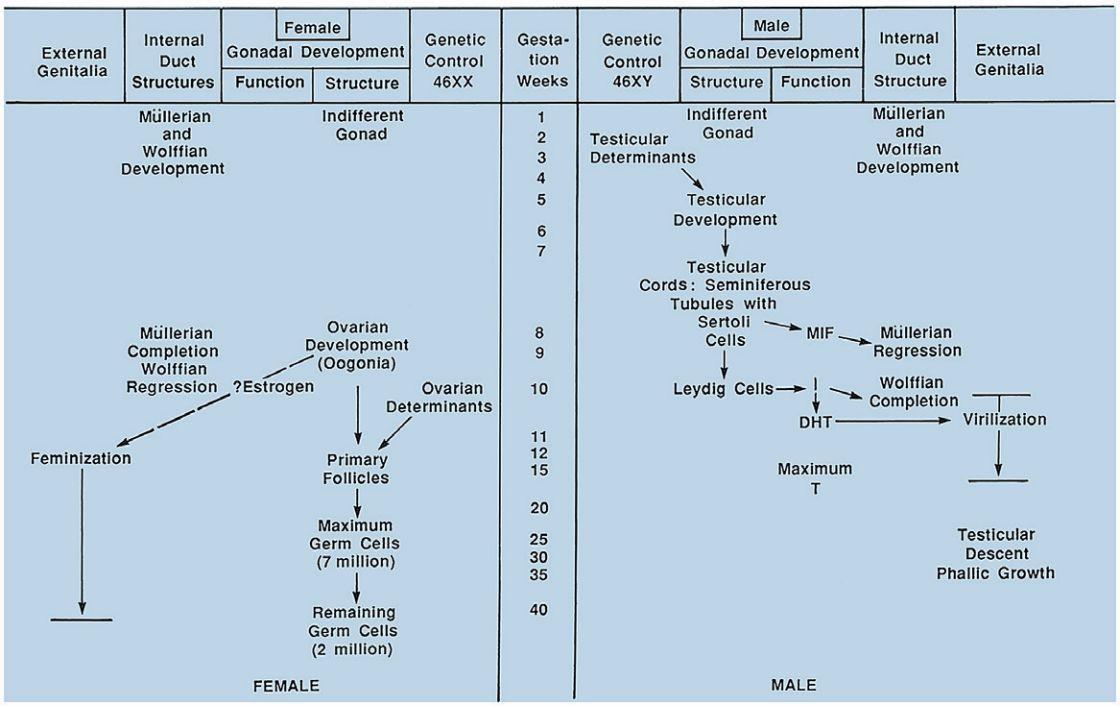


Figure 133–9. Timetable of normal sexual differentiation. DHT, dihydrotestosterone; MIF, müllerian inhibiting factor. (From Diamond D. Intersex disorders: I and II. AUA Update Series, vol. IX, lessons 9 and 10. Houston: American Urological Association Office of Education; 1990.)

convolutions of the ducts organize to form the epididymis. The wolffian ducts of the epididymis join with the collecting portion of the testicular tubules (rete testes). Distally, the ducts join the urogenital sinus by about 30 days' gestation, where they develop into the seminal vesicles. In the female fetus, testosterone is not secreted by the ovaries and therefore the wolffian ducts regress. Because the ovary does not produce MIS, the müllerian ducts are maintained and develop into the female internal reproductive tract. The cephalic ends are anlagen of the fallopian tubes, and the caudal ends fuse to form the uterus (see Fig. 133–7). Contact of the müllerian ducts with the urogenital sinus induces formation of the uterovaginal plate, which ultimately forms the lumen of the vagina. The relative contributions of the müllerian ducts and urogenital sinus to the formation of the vagina remain somewhat controversial; however, there is some agreement that the proximal two thirds of the vagina is contributed by the müllerian ducts and the distal one third by the urogenital sinus. Masculinization of the male fetus starts between 7 and 8 weeks of gestation (Fig. 133–9). The first sign of male phenotypic differentiation is degeneration of the müllerian ducts adjacent to the testes as a result of MIS

secretion by the Sertoli cells. Whereas the effects of androgen on the wolffian ducts are related to diffusion of testosterone from the adjacent gonad, masculinization of the external genitalia results from the systemic delivery of testosterone with local conversion to dihydrotestosterone. By 10 weeks, an increase in distance between genital tubercle and anal folds can be seen. The genital tubercle thickens and elongates to become the penis, and the urethral folds fuse from posterior to anterior over the urethral groove (Fig. 133–10). Near the bladder, the urethra is surrounded by the prostate. The urogenital swellings migrate posteriorly to the genital tubercle and fuse to form the scrotum. **By 12 to 13 weeks' gestation, the genitalia of the male fetus is completed with closure of the elongated urogenital cleft.** Under the influence of androgen secreted by the fetal testes, penile growth and testicular descent occur in the third trimester (see Fig. 133–9). In the female fetus the absence of circulating testosterone maintains the appearance of the external genitalia at the 6-week gestational stage. The genital tubercle develops only slightly to form the clitoris. The lateral genital swellings become the labia majora, and the adjacent urethral folds become the labia minora (Fig. 133–11). Between the labia minora will develop the vaginal introitus and urethral meatus.

Gender Identity, Gender Role, and Gender Orientation

Psychosexual Differentiation

Humans have been recognized as having sexually dimorphic behavior, which has several aspects: (1) *gender identity,* the identification of self as either male or female; (2) *gender role*, aspects of behavior in which males and females appear to differ; (3) *gender orientation*, or choice of sexual partner (heterosexual, homosexual, or bisexual); and (4) *cognitive differences* (Grumbach and Conte, 1998). Gender identity is a complex and poorly understood phenomenon in humans, and the mechanisms appear multifactorial. Experience in patients with congenital adrenal hyperplasia (CAH) who were exposed prenatally to androgen and in patients reared in a sex opposite to their chromosomal or gonadal sex have provided evidence to indicate that gender identity is not merely a function of chromosomal complement or prenatal endocrine milieu. Postnatal environmental factors and learning appear to have an important effect. However, strong evidence has accumulated for the impact of prenatal hormonal influences on sexually dimorphic behavior or gender role. For example, long-term

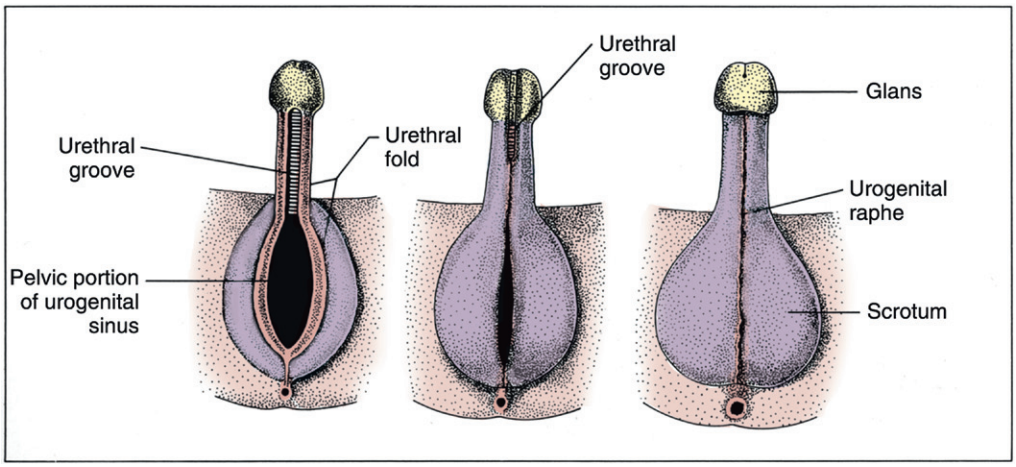


Figure 133–10. Schematic diagram of differentiation of the male external genitalia. (From Martinez-Mora J. Development of the genital tract. In: Martinez-Mora J, editor. Intersexual states: disorders of sex differentiation. Barcelona: Ediciones Doymer; 1994. p. 53.)

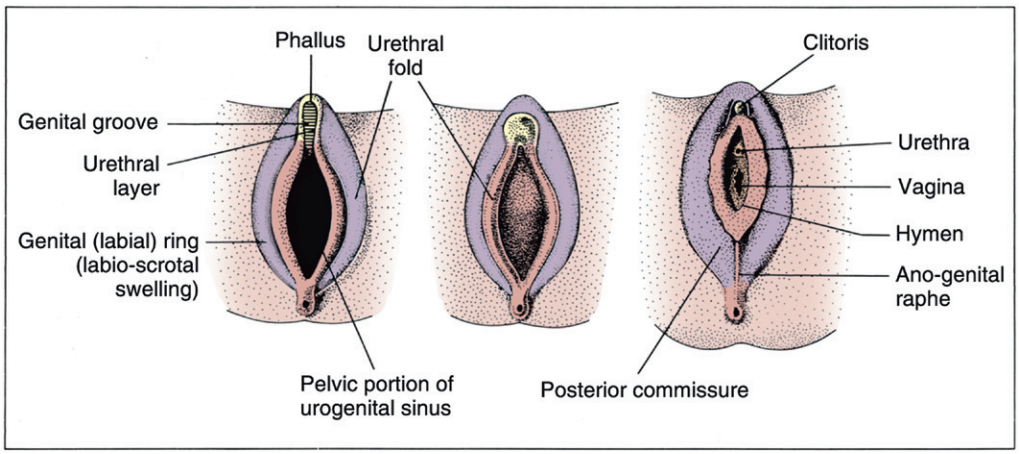


Figure 133–11. Schematic diagram of differentiation of the female external genitalia. (From Martinez-Mora J. Development of the genital tract. In: Martinez-Mora J, editor. Intersexual states: disorders of sex differentiation. Barcelona: Ediciones Doymer; 1994. p. 52.)

follow-up with CAH patients has supported a greater interest in "tomboyish behavior" than in unaffected girls, although these patterns are not abnormal in relation to female behavior in Western society (Ehrhardt and Meyer-Bahlburg, 1981). Additional information regarding the influence of androgens on gender identity and gender role has arisen from one study of males with cloacal exstrophy who underwent gender reassignment within the first few months of life. A majority of these patients had behaviors and attitudes that reflected strong male-typical characteristics regardless of whether they were raised as males or females (Reiner and Gearhart, 2004). However, a subsequent British study of a similar 46,XY cloacal exstrophy cohort presented contradictory findings (Baker Towell and Towell, 2003). The previously accepted dogma that children are psychosexually neutral at birth and capable of being environmentally oriented (the blue room/pink room theory) has been seriously challenged by those who support the concept of prenatal psychosexual differentiation (Money and Ehrhardt, 1972; Diamond and Sigmundson, 1997). Support for either theory in humans is based on the assessment of a limited number of affected patients. An improved understanding of the "nature versus nurture" controversy will probably prove important in the optimal management of patients with DSDs. However, our increased awareness of physiologically normal patients with genuine "gender dysphoria" has illustrated the complexity of this process.

Key Point: Psychosexual Differentiation

- The previously accepted dogma that children are psychosexually neutral at birth and capable of being environmentally oriented (the blue room/pink room theory) has been seriously challenged by those who support the concept of prenatal psychosexual differentiation.

ABNORMAL SEXUAL DIFFERENTIATION

The classification of DSDs (previously "intersex disorders") has undergone evolutionary change as understanding of the etiologic mechanisms of normal and abnormal sexual differentiation has improved. As a result, classification systems vary. The authors have borrowed from the system utilized by Grumbach and Conte (1998), which incorporates the historical emphasis on classification by gonadal morphology and introduced more contemporary terminology (Hughes et al, 2006). Descriptive terms for abnormal gonadal histology have been retained, with the exception of *true hermaphroditism,* which has been replaced by *ovotesticular DSD.* But, for masculinized 46,XX females with two ovaries, *female pseudohermaphroditism* has been replaced by 46,XX DSD. And, for undermasculinized 46,XY males the term *male pseudohermaphroditism* has been replaced by 46,XY DSD. The first category comprises disorders of gonadal differentiation, the second includes ovotesticular DSD, the third includes 46,XX DSD (the masculinized female, that is, ovaries present but external genitalia exhibiting evidence of masculinization), the fourth includes 46,XY DSD (the undermasculinized male, that is, testes present but genital ducts and/or external genitalia incompletely masculinized), and the fifth category comprises unclassified forms. Within each category, remarkable advances in chromosomal and biochemical information have allowed subclassification of disorders based on etiologic mechanisms, contributing to a more rational classification system (Table 133–2).

Table 133–2.

Abnormal Sexual Differentiation

1. Disorders of Gonadal Differentiation

Seminiferous tubule dysgenesis
Klinefelter syndrome
46,XX male
Syndromes of gonadal dysgenesis
  Turner syndrome
  Pure gonadal dysgenesis
  Mixed gonadal dysgenesis
  Partial gonadal dysgenesis (dysgenetic male pseudohermaphroditism)
  Bilateral vanishing testis/testicular regression syndromes

2. Ovotesticular DSD (True Hermaphroditism)

3. 46,XX DSD (Masculinized Female)

Congenital adrenal hyperplasia (21-hydroxylase, 11β-hydroxylase, 3β-hydroxysteroid dehydrogenase deficiencies)
Maternal androgens

4. 46,XY DSD (Undermasculinized Male)

Leydig cell agenesis, unresponsiveness
Disorders of testosterone biosynthesis
Variants of congenital adrenal hyperplasia affecting corticosteroid and testosterone synthesis
  StAR deficiency (congenital lipoid adrenal hyperplasia)
  Cytochrome P450 oxidoreductase (POR) deficiency
  3β-Hydroxysteroid dehydrogenase deficiency
  17β-Hydroxylase deficiency
Disorders of testosterone biosynthesis
  17,20-Lyase deficiency
  17β-Hydroxysteroid oxidoreductase deficiency
Disorders of androgen-dependent target tissue
  Androgen receptor and postreceptor defects
  Syndrome of complete (severe) androgen insensitivity
  Syndrome of partial androgen insensitivity
  Mild androgen insensitivity syndrome (MAIS)
Disorders of testosterone metabolism by peripheral tissues
  5α-Reductase deficiency
  Disorders of synthesis, secretion, or response to müllerian-inhibiting substance
Persistent müllerian duct syndrome

5. Unclassified Forms

In females
  Mayer-Rokitansky-Küster-Hauser syndrome

Disorders of Gonadal Differentiation and Development

Seminiferous Tubule Dysgenesis (Klinefelter Syndrome and Variants)

In 1942, Klinefelter, Reifenstein, and Albright described a syndrome characterized by eunuchoidism, gynecomastia, azoospermia, increased gonadotropin levels, and small, firm testes. By 1959, these patients were noted to have a 47,XXY karyotype (Jacobs and Strong, 1959).

Klinefelter syndrome represents the most common major abnormality of sexual differentiation. By definition, males with at least one Y chromosome and at least two X chromosomes have Klinefelter syndrome. The classic 47,XXY complement arises as a result of nondisjunction during meiosis; it occurs in 1 of 600 liveborn males (Morris et al, 2008). But the phenotype is also associated with 48,XXYY and 49,XXXYY, and an exaggerated form of the phenotype is associated with 48,XXXY and 49,XXXXY. The

mosaic form 46,XY/47,XXY is associated with a milder version of the phenotypic features of classic 47,XXY Klinefelter syndrome. Perhaps as a result of phenotypic variability, Klinefelter syndrome is believed to be underdiagnosed, with a 25% diagnostic rate in one Danish study (Bojesen et al, 2004).

In 47,XXY adults, seminiferous tubules degenerate and are replaced with hyaline. As a result, testes are firm and small, less than 3.5 cm in length. Histologically, Leydig cells appear to be present in large numbers, because they are seen in large clumps in certain areas of the testes, sometimes resembling Leydig cell tumors. However, the absolute volume of Leydig cells is not increased and is probably lower than normal. Serum levels of testosterone are low-normal and those of gonadotropins are elevated. Plasma estradiol levels tend to be high, with gynecomastia the result of an increased ratio of estradiol to testosterone. The vast majority of patients are azoospermic, and the presence of sperm suggests 46,XY/47,XXY mosaicism. There does appear to be a depletion of germ cells with the onset of puberty (Wikström et al, 2004). Fertility, with the benefit of testicular sperm extraction and intracytoplasmic sperm injection, has been reported in patients with Klinefelter syndrome (Koga et al, 2007). Some infertility experts advocate coupling intracytoplasmic sperm injection with preimplantation diagnosis given the lower rate of normal embryos from Klinefelter syndrome patients (54%) versus controls (77%) (Staessen et al, 2003).

The decreased androgen production prevents normal secondary sexual development. Muscle development is poor, and the fat distribution is more female than male. Normal amounts of pubic and axillary hair may be present, but facial hair is sparse. Patients tend to be taller than average, mainly because of the disproportionate length of their legs, which is present even in childhood. Otherwise, few if any distinguishing features are present in the prepubertal child.

Gynecomastia, which can be quite marked, is a common pubertal development in patients with Klinefelter syndrome. As a result, these patients have eight times the risk for development of breast carcinoma compared with normal males (Harnden et al, 1971). In addition, they are predisposed to developing malignant neoplasms of extragonadal germ cell origin as well as Leydig and Sertoli cell tumors (Völkl et al. 2006). Therefore, routine surveillance scrotal ultrasonography has been advocated for postpubertal patients with Klinefelter syndrome.

An intriguing area of research has been in the neuropsychiatric function of Klinefelter syndrome patients. Studies have demonstrated depressed verbal ability and limitations in frontal executive functioning. Recent imaging studies have shown selective volume differences in corresponding areas of Klinefelter syndrome patients' brains versus normal subjects (Giedd et al, 2009). Other studies have demonstrated altered cerebral perfusion in Klinefelter syndrome, corresponding to impaired verbal skills (Itti et al, 2003).

Management of Klinefelter syndrome entails careful androgen supplementation in selected male patients to improve libido and reduction mammoplasty if necessary. Surveillance for testicular tumor and breast carcinoma is also appropriate. Assisted reproductive techniques now offer potential fertility to non-mosaic Klinefelter syndrome patients.

46,XX Males

The condition of 46,XX maleness, which occurs in 1 of every 20,000 males, may be closely related to that of Klinefelter syndrome. Historically, the genetic analysis of subjects with sex reversal who had a phenotypic sex different from that anticipated based on karyotype was crucial for identification of the *SRY* gene.

XX maleness, first recognized by de la Chappelle and coworkers in 1964, is characterized by testicular development in subjects who have two X chromosomes and lack a normal Y chromosome. Most of these subjects have normal male external genitalia, but 10% have hypospadias and all are infertile. Among infertile adults, 2% have XX maleness (Van Dyke et al, 1991).

Two categories of patients with XX maleness have been identified: the 90% who are *SRY* positive and those who are *SRY* negative (Ergun-Longmire et al, 2005). The *SRY*-positive group rarely have genital abnormalities, but they have phenotypic features of Klinefelter syndrome, including hypogonadism, gynecomastia, azoospermia, and hyalinization of seminiferous tubules with altered hormonal levels at puberty (low testosterone, increased follicle-stimulating hormone [FSH] and LH) (Fechner et al, 1993). Often, the diagnosis is made in a pubertal male who presents for evaluation of gynecomastia. **These patients differ from those with Klinefelter syndrome in that they are shorter (mean height, 168 cm) and have normal skeletal proportions.** The 10% of XX males with no detectable *SRY* more commonly have genital ambiguity.

Three mechanisms have been proposed to explain XX sex reversal. **The most common is translocation of Y chromosomal material, including *SRY,* to the X chromosome**. Clearly, this can be proven in the majority of patients. Alternatively, sex reversal could result either from the mutation of an autosomal or X chromosomal gene, permitting testicular differentiation downstream from *SRY,* or from undetected mosaicism with a Y-bearing cell line. Clinical studies have demonstrated XX sex reversal to be a genetically and phenotypically heterogeneous condition (Fechner et al, 1993).

Treatment of XX maleness is similar to that for Klinefelter syndrome. Androgen replacement benefits selected patients, and reduction mammoplasty may be beneficial. It is likely that these patients will also be at increased risk for breast carcinoma and testis tumor. Because of their lack of germ cell elements, those classic patients presenting with infertility would not benefit from testicular biopsy for potential intracytoplasmic sperm injection.

Syndromes of Gonadal Dysgenesis

Turner Syndrome. In 1938, Henry Turner described the combination of sexual infantilism, webbed neck, and cubitus valgus (increased carrying angle at the elbows) as a distinct entity. Subsequently, gonadal dysgenesis was recognized as part of this syndrome (Hall and Gilchrist, 1990). It was not until 1959 that Ford recognized that one missing X chromosome was the etiologic basis for the syndrome. Subsequent chromosomal studies showed that **Turner syndrome is characterized by the presence of only one normally functioning X chromosome.** The other sex chromosome may be absent or abnormal, or mosaicism may be present.

Turner syndrome, with a 45,X karyotype, is associated with four classic features: female phenotype, short stature, lack of secondary sexual characteristics, and a variety of somatic abnormalities. But the clinical features of Turner syndrome are quite variable, and almost any combination of physical features may be seen with any X chromosomal abnormality. The severity of phenotypic features does not necessarily correlate with karyotypic findings. The diagnosis of Turner syndrome should be considered in any infant with lymphedema or any young woman with short stature or primary amenorrhea. Deletions in the short stature homeobox gene *(SHOX)* located on the pseudoautosomal region of the X and Y chromosomes have

been suggested as the basis for the short stature in this syndrome.

Turner syndrome has an incidence of 1 in 2500 live births. Half of the patients have a 45,X karyotype in all cells; this is believed to be secondary to loss of an X chromosome through nondisjunction in gametogenesis or an error in mitosis. From 12% to 20% of patients with Turner syndrome have an isochrome X (duplication of one arm of the X chromosome with loss of the other arm). Mosaicism—the presence of two or more chromosomally different cell lines—occurs in 30% to 40% of these patients, the majority (10% to 15%) being 45,X/46,XX and 2% to 5% being 45,X/46,XY (Zinn et al, 1993). **The presence of Y chromosomal material is of critical importance in patients with Turner syndrome because it predisposes them to potential masculinization and gonadoblastoma.**

Turner syndrome may be diagnosed prenatally on the basis of a variety of ultrasound findings (increased nuchal translucency, lymphedema, cystic hygroma, coarctation of the aorta, renal anomalies) or by abnormal results of fetal karyotyping. Affected fetuses often abort spontaneously. Whereas a 45,X fetus identified prenatally has a prognosis similar to that of a child with Turner syndrome diagnosed postnatally, approximately 90% of fetuses in whom a 45,X/46,XX or 45,X/46,XY karyotype is incidentally diagnosed prenatally will have a normal female or male phenotype at birth. This so-called ascertainment bias in Turner syndrome has profound implications for prenatal counseling.

It is postulated that in Turner syndrome follicular cells that normally surround the germ cells and provide a protective mantle for the oocytes are inadequate (Stanhope et al, 1992). As a result, the rate of attrition of oocytes due to apoptosis is so rapid that by birth few or no oocytes remain in the **ovaries, which become streaks** (Epstein, 1990). Typically, these streaks are white, fibrous structures, 2 to 3 cm long and approximately 0.5 cm wide, located in the broad ligament. Histologically, the streak possesses interlacing waves of dense fibrous stroma that is devoid of oocytes but is otherwise indistinguishable from normal ovarian stroma. Both estrogen and androgen are decreased, and levels of FSH and LH are increased. Secondary sexual development does not occur in the majority of patients. Pubic and axillary hair fails to develop in normal abundance, and the well-differentiated external genitalia, vagina and müllerian derivatives, and breasts remain small (Saenger, 1996). Turner syndrome is a common cause of primary amenorrhea, and the diagnosis is frequently made because pubertal development never occurs. Spontaneous pubertal development may occur in up to 30% of Turner syndrome patients, however.

The associated congenital anomalies that are thought typical in Turner syndrome include short stature, broad chest, widespread nipples, webbing of the neck, peripheral edema at birth, short fourth metacarpal, hypoplastic nails, multiple pigmented nevi, coarctation of the aorta, bicuspid aortic valve, and renal anomalies (Fig. 133–12). The majority of the associated congenital anomalies can be explained by the presence of lymphedema at critical points in development, leading to an imbalance in growth forces. This may be secondary to failed opening of embryonic lymphatic channels (Zinn et al, 1993).

Of paramount importance in the assessment of the patient with Turner syndrome is identification of Y chromosomal material or 45,X/46,XY mosaicism, whose detection has been enhanced by use of the polymerase chain reaction (PCR) (Bianco et al, 2006). **In patients with occult Y chromosomal material, the risk of gonadoblastoma, an in-situ germ cell cancer, is 12% and is being further defined** (Schoemaker et al, 2008). Gonadoblastoma is associated with dysgerminoma or other germ cell neoplasms in 50% to 60% of cases, sometimes associated with virilization. **Because the age of occurrence of gonadoblastoma is variable and has been reported as early as age 26 months** (Peters, personal communication, 2005), **timely prophylactic excision of the streak gonads in the Y mosaic Turner syndrome patient is advised.** This may be well performed laparoscopically. Streak gonads confirmed to be in 45,XO patients need not be removed. In the recent British national cohort study there was also an increased risk of bladder cancer in Turner syndrome patients followed into adulthood (Schoemaker et al, 2008).

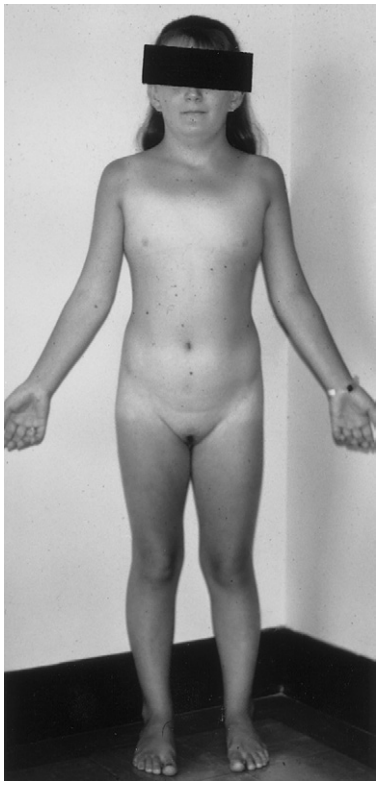


Figure 133–12. Patient with Turner syndrome exhibiting short stature, low-set ears, webbed neck, shield chest, and widely spaced, hypoplastic nipples. (From Diamond D. Intersex disorders: I and II. AUA Update Series, vol. IX, lessons 9 and 10. Houston: American Urological Association Office of Education; 1990.)

Between 33% and 60% of patients with Turner syndrome have structural or positional abnormalities of the kidney; this occurs most frequently in the classic 45,XO karyotype (Hall and Gilchrist, 1990). **Horseshoe kidney accounts for 10%, duplication or renal agenesis for 20%, and malrotation for 15% of these abnormalities.** Multiple renal arteries have been noted in 90% of patients with Turner syndrome as a result of their cardiovascular evaluation (Hall and Gilchrist, 1990).

The contemporary treatment of patients with Turner syndrome has undergone considerable advances. In the neonate, it entails a concerted search for occult Y chromosomal material, including fluorescent in-situ hybridization (FISH) or polymerase chain reaction (PCR) and, subsequently, prophylactic gonadectomy if necessary, as well as ultrasound screening for renal and cardiac abnormalities. **In the child, human growth hormone has successfully been employed** to achieve increased adult height (Pasquino, 2004). At an appropriate age, typically between 12

and 15 years, exogenous hormonal therapy to induce puberty and then to maintain a normal female endocrine status is begun. An improved understanding of the long-term medical management of these patients, including cardiac surveillance and management of glucose intolerance and osteoporosis, has also resulted in considerable progress. **Finally, with the remarkable advances in assisted reproductive technology, pregnancy is a realistic possibility for patients with Turner syndrome, although spontaneous fertility is rare** (Sybert and McCauley, 2004). A spectrum of potential gonadal function has been noted in large series of patients with Turner syndrome (Kaneko et al, 1990). In one series, nonstreak gonads were reported in one third of such patients and were more commonly noted in girls with loss of only the short arm of the X chromosome. In 2% to 5% of Turner patients, spontaneous menses will occur with a potential to achieve pregnancy independently (Saenger et al, 2001). This appears most likely in women with mosaicism for a normal 46,XX cell line, a 47,XXX cell line, or distal Xp deletion. To date, more than 160 pregnancies have been reported among spontaneously menstruating Turner syndrome patients. For the vast majority with true streak gonads, for whom egg donor implantation is used, 40% to 50% pregnancy rates have been reported by centers specializing in in-vitro fertilization (Saenger, 1993). However, among these rare pregnancies, the rates of miscarriage, stillbirth, and malformed infants is high (Abir et al, 2001). A recent area of interest has been the laparoscopic retrieval of follicles in girls with Turner syndrome for cryopreservation (Hreinsson et al, 2002). The technique is regarded as experimental and not yet recommended for clinical use. One concern relates to confirmation of normalcy of the harvested oocytes.

It is of great interest that neuroanatomic imaging studies of 45,XO Turner syndrome patients have demonstrated differences in parietal and temporal lobe anatomy and posterior fossa morphology that appear to correlate with certain established neurophysiologic and cognitive deficits (Brown et al, 2004; Rae et al, 2004).

Key Point: Turner Syndrome

- In patients with Turner syndrome and occult Y chromosomal material, the risk of gonadoblastoma, an in-situ germ cell cancer, is 12% and is being further defined.

46,XX "Pure" Gonadal Dysgenesis. Patients with 46,XX "pure" gonadal dysgenesis are closely related to those with Turner syndrome. **They are characterized by normal female external genitalia, normal müllerian ducts with absence of wolffian duct structures, a normal height, bilateral streak gonads, sexual infantilism, and a normal 46,XX karyotype.** The streak gonads result in elevated serum gonadotropins. **Because these subjects exhibit none of the somatic stigmata associated with Turner syndrome and their condition entails gonadal dysgenesis only, it has been regarded by some authors as "pure."**

A familial incidence of 46,XX gonadal dysgenesis has been reported as an autosomal recessive trait (Espiner et al, 1970). This suggests the possibility that autosomal genes in addition to genes on the X chromosome may be involved in ovarian maintenance.

Management of patients with 46,XX "pure" gonadal dysgenesis entails proper cyclic hormone replacement with estrogen and progesterone. In contrast to Turner syndrome, growth is not abnormal with this condition, and therefore growth hormone should not be required. Because, by definition, these patients have no Y chromosomal material, gonadectomy is not required.

Mixed Gonadal Dysgenesis. The term *mixed gonadal dysgenesis* was coined by Sohval in 1963. In 1975, Zah and associates reported on their series of more than 100 patients with 45,X/46,XY karyotypes, 72 of whom had mixed gonadal dysgenesis with a streak gonad on one side and a testis on the other.

Mixed gonadal dysgenesis is characterized by a unilateral testis, which is often intra-abdominal, a contralateral streak gonad, and persistent müllerian structures associated with varying degrees of inadequate masculinization. Most patients with mixed gonadal dysgenesis have a 45,XO/46,XY karyotype, which is probably the result of anaphase lag during mitosis. The 45,X/46,XY mosaicism is the most common form of mosaicism involving the Y chromosome.

The phenotypic spectrum of patients with XO/XY mosaicism extends from phenotypic females with Turner syndrome (25%), to those with ambiguous genitalia, to, rarely, those appearing as normal males (Berkovitz et al, 1991). **In the neonatal period, mixed gonadal dysgenesis is the second most common cause of ambiguous genitalia (after CAH) and must be in the differential diagnosis.** The majority of these patients present with varying degrees of phallic development, a urogenital sinus with labioscrotal fusion, and an undescended testis. In virtually all of these patients, a uterus, vagina, and fallopian tube are present. Short stature and associated somatic stigmata are variable features.

Key Point: Mixed Gonadal Dysgenesis

- In the newborn period, mixed gonadal dysgenesis is the second most common cause of ambiguous genitalia (after CAH) and must be in the differential diagnosis.

The phenotypic asymmetry of the internal ducts epitomizes the mechanism of local testosterone and MIS production on müllerian and wolffian duct regression and development. In the series of Mendez and colleagues (1993) comprising 16 patients, all had a fallopian tube accompanied by a streak gonad, consistent with absent MIS. **Therefore, whereas a dysgenetic or streak gonad is associated with ipsilateral müllerian derivatives (uterus, fallopian tube)** (Fig. 133–13), **a well-differentiated testis with functional Sertoli and Leydig cells will have ipsilateral wolffian but no müllerian ducts** (Davidoff and Federman, 1973). In addition, the presence of severe external genital ambiguity in many of these patients suggests that testosterone production in utero was inadequate to promote complete differentiation of the external genitalia. Paradoxically, the dysgenetic testis is capable of responding to gonadotropins and secreting testosterone in normal quantities at puberty. Yet, despite normal postpubertal endocrine function, it is postulated that fetal testicular endocrine function is either delayed or deficient. Histologically, the testes lack germinal elements, so infertility is the rule.

The risk of developing a gonadal tumor (gonadoblastoma, dysgerminoma) is increased in mixed gonadal dysgenesis, with

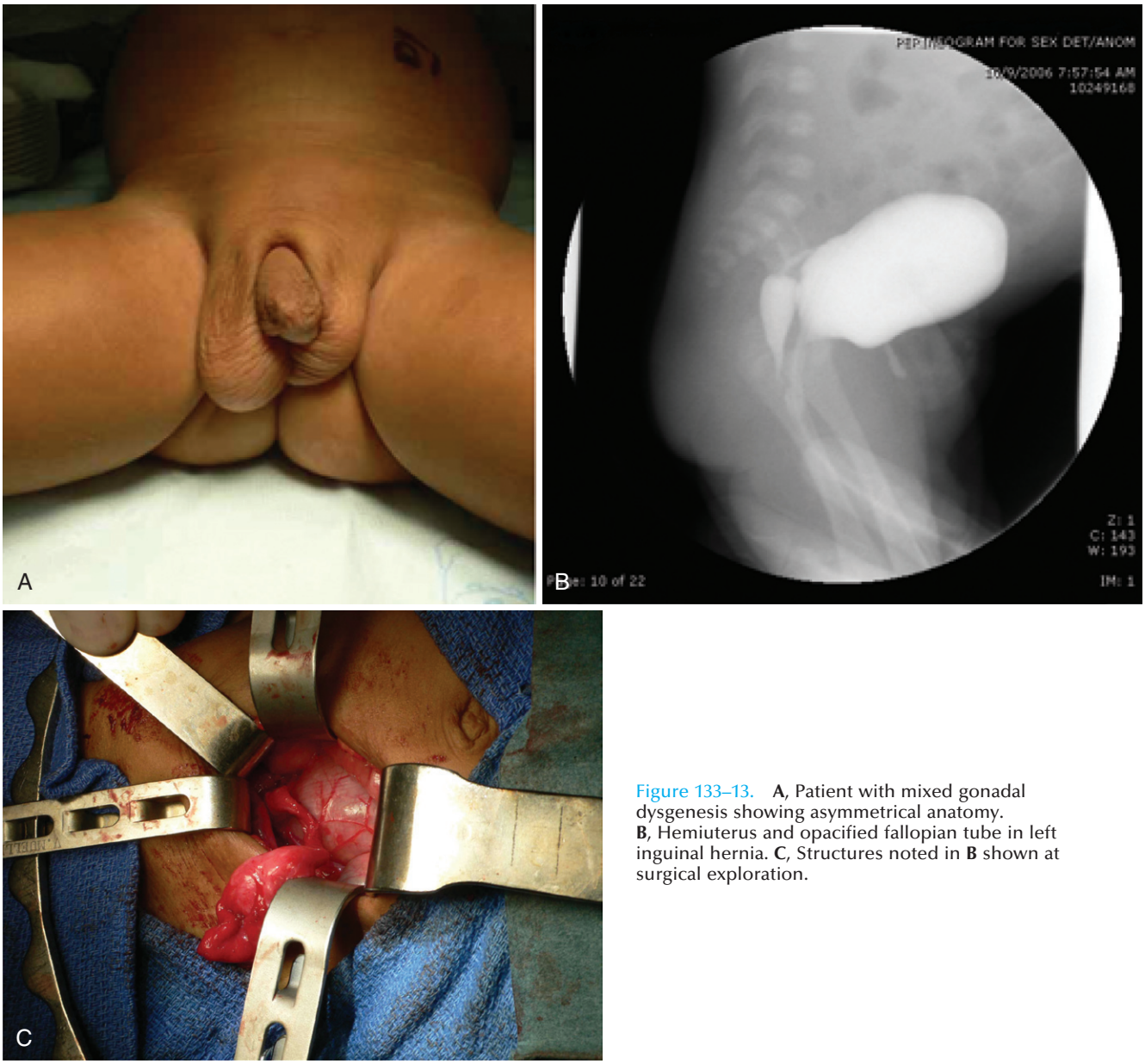


Figure 133–13. **A**, Patient with mixed gonadal dysgenesis showing asymmetrical anatomy. **B**, Hemiuterus and opacified fallopian tube in left inguinal hernia. **C**, Structures noted in **B** shown at surgical exploration.

an estimated incidence of 15% to 35% (Robboy et al, 1982; Wallace and Levin, 1990). Gonadoblastoma, a tumor of low malignant potential, is the most common. It was so named because it recapitulates gonadal development more completely than any other tumor (Scully, 1970). **Although germ cell tumors occur both in the dysgenetic testes and in the streak gonads of individuals with 46,X/46,XY mosaicism, the risk of tumor is higher in the former** (Verp and Simpson, 1987).

Patients with mixed gonadal dysgenesis are also at increased risk for Wilms tumor. Rajfer (1981) reported that 50% of 10 patients with an intersex disorder and Wilms tumor had mixed gonadal dysgenesis. He postulated that there was a genetic or teratogenetic defect involving the urogenital ridge, the common embryonic anlage of both kidney and gonad. This concept was borne out by improved understanding of the Denys-Drash syndrome, now clearly associated with mutations in the Wilms tumor suppressor gene *(WT1)*. In 1967, Denys and colleagues described a child with XX/XY mosaicism, nephropathy, genital abnormalities, and Wilms tumor. Drash and coworkers (1970) reported two further examples in 1970. **The full triad of the syndrome includes nephropathy, characterized by the early onset of proteinuria and hypertension, and progressive renal failure in most of the patients.** Renal histology demonstrates diffuse focal mesangial sclerosis. **Because incomplete forms of the syndrome may occur, the nephropathy has become regarded as the common denominator of the syndrome** (Habib et al, 1985). Wilms tumor may be diagnosed before, after, or simultaneously with presentation with nephropathy. The majority of the tumors are of favorable triphasic histology (Beckwith and Palmer, 1978). However, there is a high incidence of bilateral Wilms tumor in this syndrome. The genital abnormalities include frank ambiguity, hypospadias, and cryptorchidism. **A large number of patients with Denys-Drash syndrome have been noted to have mixed gonadal dysgenesis.** These have an increased risk of gonadal tumor of 40% (Table 133–3) (Lee et al, 2006). A relatively new and consistent finding with Denys-Drash

syndrome is that of caliceal blunting without obstruction (Jadresic et al, 1990). The high mortality rate associated with this syndrome has prompted an aggressive treatment approach with prophylactic bilateral nephrectomy in an attempt to improve the prognosis for these children (Jadresic et al, 1990).

Frasier syndrome, a related disorder due to mutations in the alternative splice donor site of exon 9 on *WT1,* presents in similar fashion to Denys-Drash syndrome but with certain important distinctions (Klamt et al, 1998). The nephropathy caused by focal segmental glomerulosclerosis occurs later in life with a more gradual progression to renal failure (Koziell et al, 1999). There is no known predisposition to Wilms tumor. Gonadoblastomas in 46,XY individuals are far more common in Frasier syndrome than in Denys-Drash syndrome with a gonadal tumor risk of 60% (see Table 133–3). Because 46,XX individuals with Frasier syndrome have normal gonadal development, they would present with renal failure. But, it is presumed that many such 46,XX individuals go undiagnosed. Frasier syndrome should be considered for girls presenting with steroid-resistant nephrotic syndrome, primary amenorrhea, and pubertal delay (Gwin et al, 2008).

The management of mixed gonadal dysgenesis entails gender assignment, appropriate gonadectomy, and proper screening for Wilms tumor. If the diagnosis is made in the neonatal period, the decision regarding sex of rearing should be based on the potential for normal function of the external genitalia and gonads. Historically, two thirds of patients with mixed gonadal dysgenesis have been raised as female. Potential fertility is not a significant issue in this disorder, and therefore the anatomy of the reproductive tract may direct the decision making. The likelihood of significant androgen imprinting is greater in association with a better-masculinized phenotype, and this may serve as the best clinical guide. For patients with Turner syndrome stigmata and growth below the fifth percentile, growth hormone therapy may be appropriate. If the male gender is elected and the testis can be brought to the scrotum, the decision between careful screening for gonadoblastoma (with physical examination and ultrasonography) versus prophylactic gonadectomy and androgen replacement must be made.

Table 133–3.

Risk of Germ Cell Malignancy According to Diagnosis

RISK GROUP	DISORDER	MALIGNANCY RISK, %
High	GD*(+Y)† intra-abdominal	15-35
	PAIS nonscrotal	50
	Frasier	60
	Denys-Drash (+Y)	40
Intermediate	Turner (+Y)	12
	17β-hydroxysteroid	28
	GD (+Y)† scrotal	Unknown
	PAIS scrotal gonad	Unknown
Low	CAIS	2
	Ovotesticular DSD	3
	Turner (-Y)	1

*Gonadal dysgenesis (including not further specified, 46,XY, 46,X/46,XY, mixed, partial, and complete).
†GBY region positive, including the TSPY (testis-specific protein Y encoded) gene.
CAIS, complete androgen insensitivity syndrome; PAIS, partial androgen insensitivity syndrome.
From Lee PA, Houk CP, Ahmed F, et al. Consensus statement on management of intersex disorders. Pediatrics 2006;118:e488–e500.

The expanded use of prenatal diagnosis has changed the understanding of 45,X/46,XY mosaicism. Studies have shown that 90% to 95% of all infants with 45,X/46,XY mosaicism have normal-appearing male genitalia (Hsu, 1989). Approximately 25% have abnormal gonadal histology (Chang et al, 1990). Because only a small proportion of those with dysgenetic gonads actually have ambiguous genitalia, the possibility exists that some males with gonadal dysfunction have 45,X/46,XY mosaicism.

Partial Gonadal Dysgenesis (Dysgenetic Male Pseudohermaphroditism). In 1967, Federman coined the term *dysgenetic male pseudohermaphroditism,* which is **a condition closely related to mixed gonadal dysgenesis in that patients with abnormal sex differentiation have two dysgenetic testes rather than one dysgenetic testis and a streak gonad.** Others have applied the term *partial gonadal dysgenesis* to this condition, to distinguish it from mixed and complete forms of gonadal dysgenesis. As with mixed gonadal dysgenesis, these individuals typically have a 45,X/46,XY or 46,XY karyotype. They may present with a spectrum of external genital abnormalities, depending on the capability of the dysgenetic gonads to produce testosterone. Similarly, persistent müllerian structures are typically present, but to varying degrees depending on MIS secretion by the dysgenetic gonads.

On histology, the dysgenetic testis is found to be composed of immature hypoplastic seminiferous tubules and persistent stroma resembling that seen in the streak gonad.

Patients with partial gonadal dysgenesis (dysgenetic male pseudohermaphroditism) are at increased risk for gonadal malignancy. Manuel and colleagues (1976) reported that the incidence of gonadoblastoma or dysgerminoma was 46% by age 40 years. These patients are also at risk for Denys-Drash syndrome (Borer et al, 1995).

The management of partial gonadal dysgenesis (dysgenetic male pseudohermaphroditism), in terms of gender assignment and surveillance for malignancy, is similar to that for patients with mixed gonadal dysgenesis.

46,XY Complete (Pure) Gonadal Dysgenesis (Swyer Syndrome). Just as 46,XX males were of great importance in discovery of the TDF, so too have been the 46,XY females. **Patients with 46,XY complete gonadal dysgenesis are characterized by normal female genitalia, well-developed müllerian structures, bilateral streak gonads, and a nonmosaic karyotype.** Because there is complete absence of testicular determination in this condition, ambiguity of genitalia is not an issue but sexual infantilism is the primary clinical problem.

The etiology of 46,XY complete gonadal dysgenesis may well be an abnormality of the *SRY* gene that eliminates SRY function, or loss of another gene downstream from *SRY* that is necessary for SRY protein action. In either case, the absence of testicular determination would permit ovarian differentiation. To date, mutations in the *SRY* gene are the cause of 46,XY complete gonadal dysgenesis in 10% to 15% of cases. Recently, a mutation in the Desert hedgehog *(DHH)* gene was noted in 3 of 6 patients with 46,XY complete gonadal dysgenesis, suggesting that the genetic origin of this entity is heterogeneous and the *DHH* is likely an important gene in gonadal differentiation (Canto et al, 2004). Investigation of a group of individuals with 46,XY complete gonadal dysgenesis has helped to narrow the chromosome interval containing the sex reversal gene to 9p24—a very small region (McDonald et al, 1997).

The majority of individuals with 46,XY complete gonadal dysgenesis present in their teens with delayed

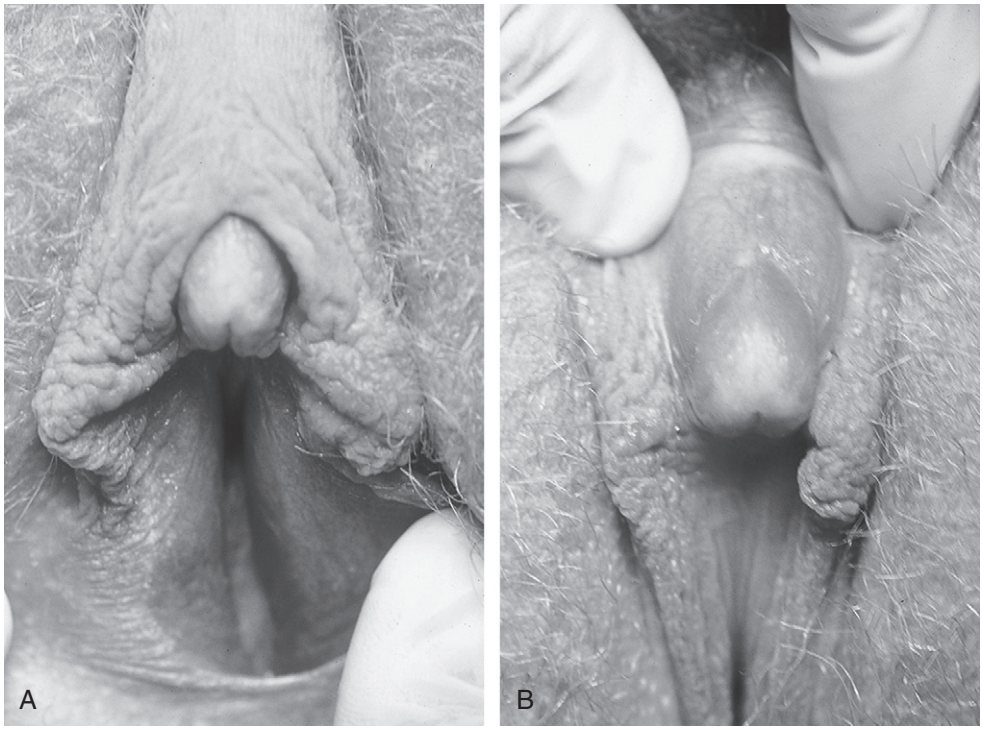


Figure 133–14. **A** and **B**, External genitalia of a 15-year-old female presenting with amenorrhea and hirsutism who was diagnosed with 46,XY gonadal dysgenesis, demonstrating clitoromegaly and urogenital sinus. (Courtesy of S. Bauer, MD.)

puberty. In addition to amenorrhea, breast development is usually absent. The serum concentration of gonadotropins is abnormally elevated, which leads the clinician to the determination of karyotype and the subsequent diagnosis (Grumbach and Conte, 1998). The high concentration of serum LH in these patients is thought to be responsible for the increased androgen levels that lead to clitoromegaly in some individuals (Fig. 133–14).

The histology of the streak gonad is similar to that of Turner syndrome, with fibrous connective tissue resembling wavy ovarian stroma but without follicles. Some histologic variability has been noted, with more proliferative-appearing stroma in some and, rarely, preservation of intact primordial follicles. This variability in ovarian histology is thought to support the hypothesis that these gonads developed as ovaries in utero (German et al, 1978). This would resemble the process that occurs in the streak gonad of Turner syndrome.

Patients with 46,XY complete or pure gonadal dysgenesis are at significant risk for germ cell tumors. There appears to be up to a 35% risk of tumor development by age 30 years (Manuel et al, 1976; see Table 133–3). Gonadoblastoma is most common, and it is frequently bilateral (Fig. 133–15). Other tumors that may arise in this patient population include embryonal carcinoma, endodermal sinus tumor, choriocarcinoma, and immature teratoma. These more highly malignant tumors occur in fewer than 10% of patients with 46,XY complete gonadal dysgenesis (Scully, 1981).

Management of 46,XY complete gonadal dysgenesis entails removal of both streak gonads and proper cyclic hormone replacement with estrogen and progesterone.

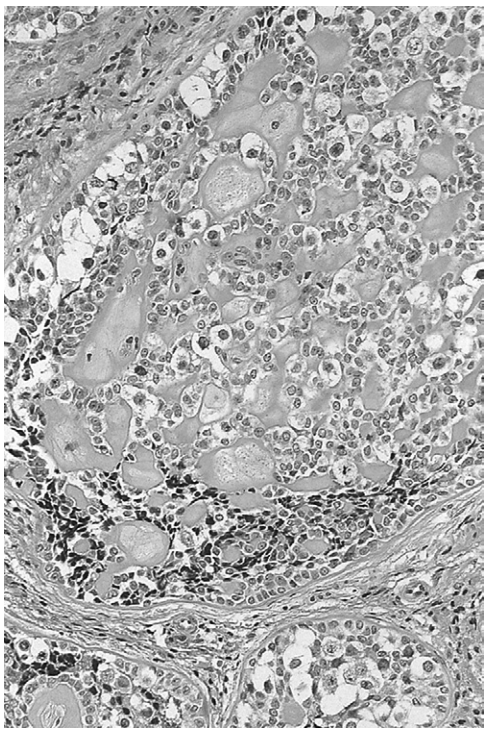


Figure 133–15. Pathology of gonadoblastoma discovered in the patient shown in Figure 133–14 with 46,XY gonadal dysgenesis. Encapsulated nests of gonadoblastoma comprise small sex cord–type cells arranged around rounded spaces of amorphous eosinophilic material and interspersed germ cells. (Courtesy of S. Bauer, MD.)

Embryonic Testicular Regression and Bilateral Vanishing Testes Syndromes

The syndromes of embryonic testicular regression and bilateral vanishing testes are characterized by **patients with a 46,XY karyotype and absent testes in whom there is clear evidence of testicular function at some point during embryogenesis.** The syndrome entails the presence of testes that "vanish" during embryogenesis and is distinguished from pure gonadal dysgenesis, in which there is no evidence of testicular function in utero.

These syndromes have been regarded as synonymous by some authors. Other authors, including Migeon and colleagues (1994), have suggested a rational stratification whereby "embryonic testicular regression" refers to loss of testicular tissue within the first trimester and is associated with ambiguity of external genitalia, whereas "bilateral vanishing testes syndrome" refers to individuals in whom male sexual differentiation of ducts and genitalia took place but loss of testicular tissue occurred subsequently in utero.

The etiology of these disorders remains unclear. **It is possible that regression of the testes in utero is caused by a genetic mutation, a teratogen, or bilateral torsion.** A genetic cause is supported by the finding of familial instances of XY agonadism that might be consistent with the rare recessive trait. Marcantonio and associates (1994) suggested the possibility that embryonic testicular regression represents a variant of 46,XY gonadal dysgenesis. They noted a group of patients with absent testes but evidence of incongruity between the extent of Leydig cell and Sertoli cell function, suggesting that gonadal tissue in these subjects was intrinsically abnormal before the testicular regression occurred. The occurrence of embryonic testicular regression in several subjects from one family in their series suggested a genetic basis for the condition, and the pattern of inheritance implicated the involvement of an X chromosome gene. In another group of patients, these authors noted multiple congenital anomalies, suggesting either a mutation in a single gene that functions in several developmental pathways or a defect of multiple genes that might be the result of a large chromosomal deletion. Recently, a heterozygous mutation in SF1 has been noted in a series of patients with bilateral vanishing testes syndrome with micropenis (Philibert et al, 2007).

Clinically, these two syndromes represent a spectrum of phenotypes ranging in severity from complete female, to varying degrees of genital ambiguity in the embryonic testicular regression syndrome, to a normal male phenotype with microphallus and empty scrotum in the bilateral vanishing testes syndrome (Edman et al, 1977). **The diagnosis can be made on the basis of a 46,XY karyotype and castrate levels of testosterone despite persistently elevated serum LH and FSH** (Jarow et al, 1986). In the most severe form of embryonic testicular regression syndrome, agonadism is discovered in a 46,XY phenotypic female with no internal genital structures. This picture is presumed to result when the testis has elaborated MIS but vanishes at approximately day 60 to 70 of gestation, before the elaboration of androgen. Due to the absence of gonadal androgens later in fetal development and transient expression of MIS, the individual goes on to develop a sexually infantile female phenotype but lacks any internal ductal structures. At an intermediate point in the clinical spectrum is the 46,XY patient with absent gonads and internal ductal structures but with ambiguous genitalia owing to incomplete elaboration of androgen by the vanishing testes. Finally, in bilateral vanishing testes syndrome, patients may present as agonadal XY phenotypic males with fully developed wolffian structures but an empty scrotum, absent prostate, and microphallus. This represents testicular loss after complete anatomic development of the male external genitalia within the first trimester.

On surgical exploration of patients with bilateral vanishing testes syndrome, rudimentary cord structures are usually identified and biopsy of their distal ends demonstrates no recognizable testicular tissue histologically (Bergada et al, 1962). Atrophic epididymal remnants are occasionally seen.

The management of patients with embryonic testicular regression syndrome or bilateral vanishing testes syndrome is dictated by their position in the clinical spectrum of either disorder. Sexually infantile phenotypic females require estrogen supplementation at the time of expected puberty for development of secondary sexual characteristics and may require vaginal dilation or vaginoplasty. Similarly, phenotypic males require long-term androgen replacement beginning at the time of expected puberty. A study of 21 males so treated demonstrated that replacement therapy started at the correct time caused a normal pubertal growth spurt with normal secondary sex characteristics including penile growth, together with normal bone maturation (Aynsley-Green et al, 1976). In addition, these patients may benefit from placement of testicular prostheses. Patients with embryonic testicular regression syndrome and ambiguous genitalia require individualized assessment to determine the optimal gender assignment.

Ovotesticular DSD (True Hermaphroditism)

Ovotesticular DSD describes individuals who have both testicular tissue with well-developed seminiferous tubules and ovarian tissue with primordial follicles, which may take the form of one ovary and one testis or, more commonly, one or two ovotestes.

Both the external genitalia and internal duct structures of ovotesticular DSD display gradations between male and female. **In most patients the external genitalia are ambiguous but masculinized to variable degrees, and 75% are raised as male.** Among those raised as male, hypospadias and chordee occur in approximately 80%. Among those patients raised as females, two thirds have clitoromegaly. Virtually all patients have a urogenital sinus, and in most cases a uterus is present (Figs. 133–16 and 133–17). The ovary is found in a normal location, more commonly on the left side. The testis or ovotestis may reside at any point along the path of testicular descent. Testes and ovotestes are more commonly located on the right side (Blyth and Duckett, 1991; Mittwoch, 2000). Sixty percent of gonads palpable in the inguinal canal or labioscrotal folds are ovotestes, which may be clinically suspected on the basis of a difference in firmness at either end of the gonad, consistent with polar segregation of ovarian and testicular tissue (Grumbach and Conte, 1998).

Approximately 60% of ovotesticular DSDs have a 46,XX karyotype; 33% are mosaics with a second cell line containing a Y chromosome (46,XX/46,XY; 46,XX/46,XXY), and 7% are 46,XY. Chimerism (mosaicism) has been thought to result from fertilization infusion of an ovum and its polar body, fusion of two nuclei, or double fertilization. It has also been suggested that ovotesticular DSD may result from hidden mosaicism with a Y cell line. Ortenberg and colleagues (2002) demonstrated the *SRY* gene in ovotestes of all eight cases of ovotesticular DSD studied, supporting somatic mosaicism. Other studies have demonstrated heterogeneity of Y-specific DNA regions detected in patients with ovotesticular DSD



Figure 133–16. Infant with penile hypospadias, chordee, and bilaterally undescended testes who was found to have true hermaphroditism. (From Diamond D. Intersex disorders: I and II. AUA Update Series, vol. IX, lessons 9 and 10. Houston: American Urological Association Office of Education; 1990.)



Figure 133–17. Laparotomy findings from a true hermaphrodite noted in Figure 133–16; clamp is on uterus with bilateral, fimbriated fallopian tubes and bilateral ovotestes. (From Diamond D. Intersex disorders: I and II. AUA Update Series, vol. IX, lessons 9 and 10. Houston: American Urological Association Office of Education; 1990.)

(Hadjiathanasiou et al, 1994). This supports a non–Y chromosome-related mechanism responsible for 46,XX ovotesticular DSD, such as mutation in an autosomal or X-linked gene involved in sex determination. Berkovitz and colleagues (1991) suggested that 46,XY ovotesticular DSD may be a form of partial gonadal dysgenesis. According to this theory, a partial defect in testis determination results in both testicular and ovarian development. This is supported by the finding of ovarian stroma in some dysgenetic testes.

Just as the differentiation of external genitalia is variable in ovotesticular DSD, differentiation of the internal ducts is also quite variable and is related to the function of the ipsilateral gonad. Fallopian tubes are consistently present on the side of the ovary, and a vas deferens is always present adjacent to a testis (Berkovitz et al, 1991). The ovotestis, which comprises two thirds of gonads in ovotesticular DSD, is associated with a fallopian tube in two thirds of cases and with either a vas deferens only or both structures in one third of cases.

The ovarian portion of the ovotestis is frequently normal, whereas the testicular portion is typically dysgenetic. Therefore, although ovulation and pregnancy have been reported for female 46,XX ovotesticular DSDs, male fertility has not been clearly documented.

The incidence of gonadal tumors is approximately 3% in 46,XY ovotesticular DSD and rare in 46,XX ovotesticular DSD. Both gonadoblastoma and dysgerminoma have been described (Verp and Simpson, 1987).

The most important aspect of management in ovotesticular DSD is gender assignment. Sex assignment should be based on the functional potential of external genitalia, internal ducts, and gonads, according to the findings at laparoscopy or laparotomy. **Unlike patients with most other forms of gonadal dysgenesis, individuals with ovotesticular DSD have the potential for fertility if raised as female with the appropriate ductal structures.** Pregnancies have been reported in patients with ovotesticular DSD, the majority with the 46,XX karyotype (Starceski et al, 1988). If the patient is to be raised as female, all testicular and wolffian tissue should be removed. For those patients with an ovary, this is straightforward; if an ovotestis is present, surgical cleavage of the gonad with excision of the testicular portion has been performed successfully by Nihoul-Fekete and colleagues (1984). They recommend postoperative stimulation with human chorionic gonadotropin (hCG) to confirm that all testicular tissue has been removed. In some settings the cleavage plane between testicular and ovarian tissues is unclear and gonadectomy is advisable. When ovarian tissue is preserved, normal ovarian function can occur at puberty, although hormonal replacement may be necessary. Careful surveillance for potential gonadal tumors in the patient raised as female is also advisable. If a male gender is assigned, as has been most common historically, all ovarian and müllerian tissue should be removed. Consideration should be given to gonadectomy at puberty with appropriate androgen replacement in this setting, given the high risk of malignancy and unlikelihood of male fertility. At the very least, long-term gonadal surveillance ultrasound for tumor development would seem appropriate.

46,XX DSD (Masculinized Female)

46,XX DSD (masculinized female) is a disorder of phenotypic sexual development in which 46,XX individuals with ovaries have a partially masculinized phenotype and ambiguous genitalia. By far the most common cause of the masculinized female is CAH, which is the most common cause of ambiguous genitalia in the newborn. Two very rare causes of 46,XX DSD (masculinized female) are maternal ingestion of androgens and virilizing tumors in the mother.

Congenital Adrenal Hyperplasia

The adrenogenital syndrome caused by CAH is a classic example of an inborn error of metabolism—in this case, an error involving cortisol synthesis. A defect in any one of the five enzymes involved in the cortisol biosynthetic pathway (cholesterol side chain cleavage enzyme, 3β-hydroxysteroid dehydrogenase, 17-hydroxylase, 21-hydroxylase, and 11-hydroxylase) may result in CAH. **The most commonly recognized syndromes result from a deficiency of one of the terminal two enzymes of glucocorticoid synthesis (21-hydroxylase or 11-hydroxylase)** (New and Levine, 1984) (Fig. 133–18). As a result of deficiency of either terminal enzyme, formation of hydrocortisone is impaired, causing a compensatory increase in the

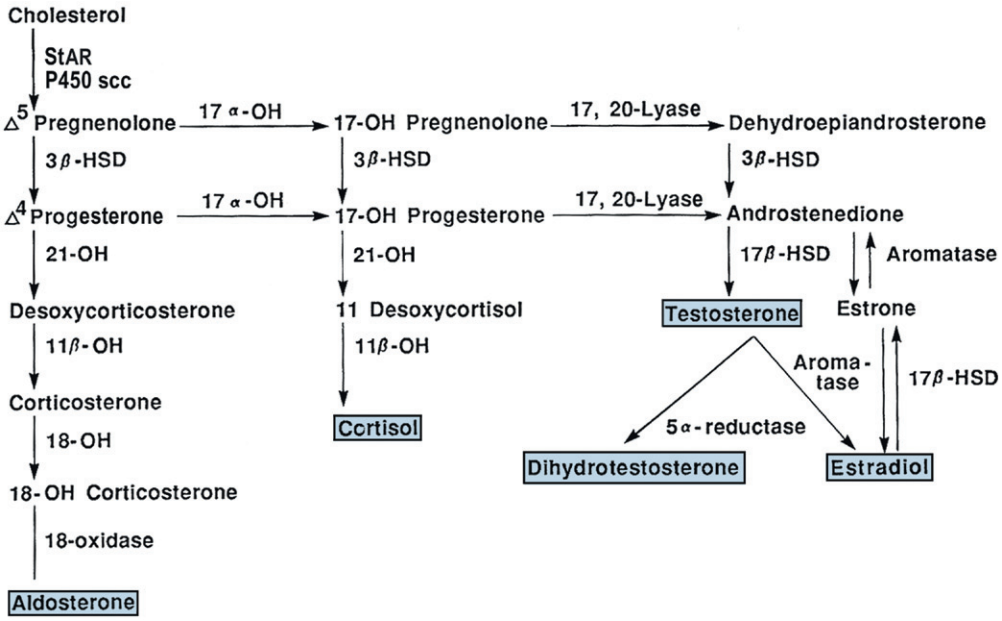


Figure 133–18. Steroid biosynthetic pathway for mineralocorticoid, glucocorticoid, and sex steroid hormone production.

secretion of adrenocorticotrophic hormone (ACTH). This increase enhances formation of adrenal steroids proximal to the enzymatic defect and a secondary increase in the formation of testosterone, the active androgen in CAH.

Key Point: Congenital Adrenal Hyperplasia

- The most commonly recognized syndromes of CAH result from a deficiency of one of the terminal two enzymes of glucocorticoid synthesis (21-hydroxylase or 11-hydroxylase).

A deficiency of steroid 21-hydroxylase is responsible for 95% of cases of CAH; it occurs with an incidence ranging from 1 in 5000 to 1 in 15,000 in the United States and Europe. The highest incidence, 1 in 490, is reported in the Yupik Alaskan Eskimo population (New et al, 1994). **Clinically, patients are divided into three categories: (1) salt wasters (patients with virilization and aldosterone deficiency), (2) simple virilizers (patients with virilization, but without salt wasting), and (3) nonclassic patients (those without evidence of virilization or salt wasting).** Dramatic progress has been made in understanding the molecular basis of CAH, and 95% of the mutations that account for CAH have been identified. The wide clinical spectrum of the disease appears to represent different degrees of enzymatic compromise conferred by specific, identifiable genetic defects.

The 21-hydroxylase gene *(CYP21A2)* is located on chromosome 6p21.3 within the major human leukocyte antigen (HLA) complex and is transmitted in an autosomal recessive pattern (Wilson et al, 1995). Adjacent to the *CYP21A2* gene, separated by 30 kb, and adjacent to and alternating with *C4B* and *C4A* genes encoding the fourth component of serum complement is the CYP21 pseudogene *(CYP21PA1),* so called because it encodes no proteins and is therefore inactive (Tusie-Luna and White, 1995). The inactive *CYP21PA1* is 98% homologous to the active gene *CYP21A2.* During meiosis, a gene conversion may occur that transfers segments from the *CYP21PA1* gene to the *CYP21A2* gene, rendering it inactive. Thus far, all mutations causing 21-hydroxylase deficiency appear to result from either a complete deletion of the genes *C4B* and *CYP21B* (a product of misalignment and unequal crossing-over between chromatids during meiosis). To date approximately 15 mutations constitute 90% to 95% of alleles and are derived from intergenic recombination of DNA sequences between the *CYP21A2* gene and the highly homologous *CYP21PA1*, whereas the remaining are spontaneous mutations (Forest, 2004). Approximately 100 different *CYP21* mutations have been reported.

The majority of patients with CAH secondary to 21-hydroxylase deficiency exhibit one of the two classic forms of the disease: **75% present with salt wasting and 25% with simple virilization** (Kohn et al, 1995). The higher proportion of patients with the salt-wasting form of the disease recognized in more recent series has been attributed to improved diagnostic capabilities and a high level of clinical suspicion as well as to increased survival owing to the prenatal screening and proper mineralocorticoid supplementation (Fife and Rappaport, 1983). Neonatal screening programs for CAH have been credited with increasing the rate and shortening the time to diagnosis, particularly in males with the salt-wasting form of the disease. This has also proven to be an important means of diagnosing the simple virilizing form in the male and the nonclassic forms in some males and females (Brosnan et al, 1999).

In the female with the classic salt-wasting and simple virilizing forms of the disorder, a masculinized female results. Because impaired steroidogenesis begins early in life—at the time of formation of the external genitalia (beginning at 10 weeks' gestation)—there is virtually always evidence of some degree of masculinization at birth. This is manifested by enlargement of the clitoris and varying degrees of labial fusion (Fig. 133–19). In addition, the vagina and urethra open into a common urogenital sinus. The enlargement of the clitoris may be so dramatic as to make it appear to be a hypospadiac penis with bilateral cryptorchidism or, rarely, a fully masculinized urethra to the tip of an apparent glans penis (Fig. 133–20). The severity of the virilization is usually greater in

infants who experience salt wasting but not uniformly so. Prader (1958) classified the degrees of virilization of external genitalia in females with CAH (Fig. 133–21). The müllerian structures in these patients are typically normal. A recent study suggests an increased incidence (Nabhan and Eugster, 2007) of upper tract abnormalities (hydronephrosis, duplication) in CAH.

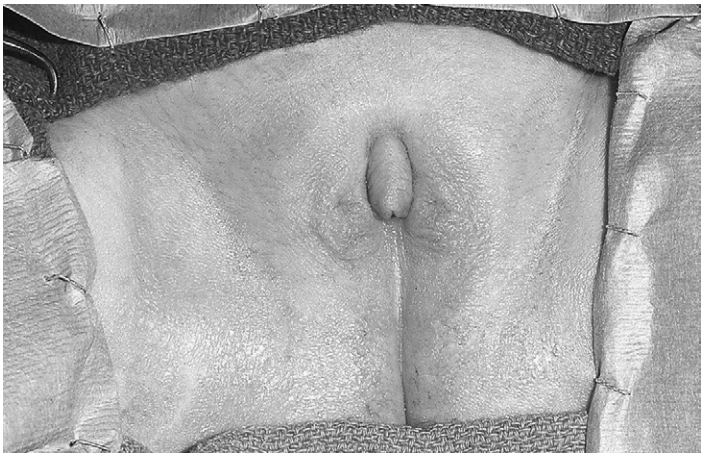


Figure 133–19. External genitalia of a patient with congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency, showing labioscrotal fusion and clitoromegaly.



Figure 133–20. Prader V patient with congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency demonstrating complete virilization of phallus.

In both males and females with the salt-losing variant of CAH, symptoms begin within the first few weeks after birth, with failure to regain birth weight, progressive weight loss, and dehydration. In severely affected infants, adrenal crises occur within the first 10 to 21 days of life (Grumbach and Conte, 1998). **Vomiting is prominent and can be so extreme that a mistaken diagnosis of pyloric stenosis is made, particularly in the male.** Without therapy, death may rapidly ensue from hyperkalemia, dehydration, and shock. In the male infant, in particular, the classic fluid and electrolyte abnormalities of CAH may be mimicked by urosepsis secondary to reflux or obstructive uropathy, which should be ruled out (Mastrandrea et al, 2005). After birth there is progression of masculinization of the untreated female; pubic and axillary hair develop prematurely, acne appears, and the voice deepens. There is rapid somatic maturation, resulting in premature epiphyseal closure and short adult stature. Although the internal genitalia are female, breast development and menstruation do not occur unless the excessive androgen production is suppressed by adequate steroid therapy.

In the male without salt wasting the chief clinical manifestations are those of isosexual precocity. The infant appears normal at birth, but signs of sexual and somatic precocity appear within the first 2 to 3 years of life. Although the testes remain normal in size, enlargement of the penis, scrotum, and prostate occur, accompanied by the appearance of pubic hair, acne, and deepening of the voice. The musculature is well developed (prompting the descriptive term "little Hercules"), and bone age is more advanced than appropriate for the chronologic age. The syndrome often goes unrecognized in the non–salt-wasting male until signs of androgen excess, such as accelerated height and precocious pubic hair, appear later in childhood.

In the non–salt-wasting male, two major long-term implications are short stature as well as infertility in 20% to 40%. Premature epiphyseal closure will result unless early medical control is instituted. This emphasizes the value of neonatal screening. Infertility has been noted in 30% of CAH males, often related to the finding of adrenal rest nodules most reliably diagnosed with scrotal ultrasonography. These nodules, present in 25% to 30% of males with CAH, represent hypertrophy of adrenal rests due to ACTH stimulation and when associated with impaired fertility warrant periodic scrotal ultrasonography, intensified glucocorticord suppression, and possibly testis-sparing excision (Claahsen-van der Grinten et al, 2008). Some advocate sperm cryopreservation in postpubertal males with adrenal rest tumors. In addition, poor control of the disease in boys with classic CAH has been associated with small testes and infertility with reduced sperm counts (New and Wilson, 1999). This is due to peripheral aromatization of

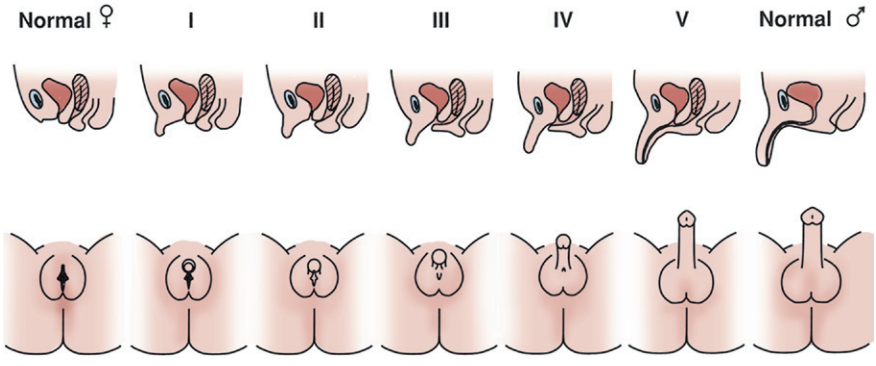


Figure 133–21. Classification by Prader of the various degrees of masculinization of the external genitalia in females with congenital adrenal hyperplasia that has been applied by some authors to intersexual states in general. (From Prader A. Die Haufigkeit der kongenitalen androgenitalen Syndroms. Helv Pediatr Acta 1958;13:426.)

excess androgen to estrogen that suppresses pituitary gonadotropins.

In classic 21-hydroxylase deficiency, plasma levels of progesterone and 17-hydroxyprogesterone are markedly elevated. Urinary levels of 17-ketosteroids and pregnanetriol are elevated. **The diagnosis may be made biochemically with the use of radioimmunoassay of plasma 17-hydroxyprogesterone,** which has replaced the more cumbersome 24-hour urine collection of metabolites (e.g., pregnanetriol). **A pelvic ultrasound study demonstrating the presence of müllerian tissues is confirmatory.** Some investigators have suggested that the finding of abnormally enlarged or "cerebriform"-appearing adrenal glands on neonatal ultrasonography, available before biochemical results, may represent the earliest diagnostic tool for CAH (Hernanz-Schulman et al, 2002).

More aggressive screening for 21-hydroxylase deficiency has provided considerable benefits. In one series, despite sexual ambiguity, one third to one half of the affected female newborns were not diagnosed as having 21-hydroxylase deficiency until they were identified by the screening test (Pang et al, 1985).

Nonclassic 21-hydroxylase deficiency represents an attenuated, late-onset form that is variable in its clinical severity due to partial deficiency of 21-hydroxylase and timing of onset. These patients do not have cortisol deficiency but present with hyperandrogenism. New and Wilson (1999) found the nonclassic 21-hydroxylase deficiency to be the most common autosomal recessive disorder in humans, with an incidence of 1 in 100. The presenting symptoms in females are commonly hirsutism and oligomenorrhea, male pattern baldness, and polycystic ovaries. In a recent study, 32% of women with nonclassic 21-hydroxylase deficiency were diagnosed only after delivering an offspring diagnosed with 21-hydroxylase deficiency CAH. In men with the nonclassic form of 21-hydroxylase deficiency, oligospermia and subfertility have been presenting features and reversal of infertility with glucocorticoid therapy has been reported. Typically, lower doses of glucocorticoid are required for management of the nonclassic form of CAH.

A deficiency of 11β-hydroxylase accounts for roughly 5% of cases of CAH. Both classic and mild forms have been recognized. Unlike 21-hydroxylase, 11β-hydroxylase is not human leukocyte antigen linked. The defect results from mutations in the *CYP11B1* gene located on the long arm of chromosome 8 (Merke et al, 1998). To date, more than 50 mutations have been described that result in enzyme inactivation (Nimkarn and New, 2008). Like 21-hydroxylase deficiency, the nonclassic variant of 11β-hydroxylase deficiency (late onset) is characterized by signs and symptoms of androgen excess in childhood or adolescence. **Hypertension is a common finding in patients with this type of CAH, and it is believed to be secondary to increased serum levels of deoxycorticosterone (DOC).** Although most of the patients are hypertensive, some are normotensive and others experience only intermittent hypertension. Marked virilization occurs in the severe form of the defect and may be as severe as in those patients with a 21-hydroxylase deficiency. In the late-onset form, mild virilization occurs in prepubertal and postpubertal patients.

The diagnosis of 11β-hydroxylase deficiency can be confirmed by finding increased plasma levels of 11-deoxycortisol and 11-DOC. Urinary levels of 17-ketosteroids and 17-hydroxycorticoids are increased. **The treatment with glucocorticoids is identical to that of patients with 21-hydroxylase deficiency.**

The least common enzyme deficiency responsible for a virilizing form of CAH is 3β-hydroxysteroid dehydrogenase. This deficiency affects the early steps in steroid biosynthesis in both adrenals and gonads, resulting in inability to convert 3β-hydroxysteroids to 3-ketosteroids. As a result, the severe form leads to impaired synthesis of aldosterone, cortisol, and sex steroids. Affected females exhibit mild clitoromegaly and labial fusion accompanied by symptoms of aldosterone and cortisol deficiency.

Two homologous genes have been identified for 3β-hydroxysteroid dehydrogenase, both of which contain four exons (Merke et al, 1998). A number of mutations giving rise to the syndrome have been described. This defect has an autosomal recessive inheritance pattern and is heterogeneous in its biochemical and clinical appearance. A non–salt-losing form and mild- and late-onset forms have been described, although the nonclassic form appears to be exceedingly rare.

The diagnosis of 3β-hydroxysteroid dehydrogenase is based on finding increased serum levels of 17-hydroxypregnenolone and dehydroepiandrosterone (DHEA). The pelvic ultrasound evaluation, confirming presence of müllerian tissue, would be supportive. Treatment is similar to that of patients with 21-hydroxylase deficiency.

Currently, one of the most exciting aspects of CAH is the capability of diagnosing and treating the disorder prenatally. **Prenatal diagnosis of CAH in the at-risk fetus was initially made by a measurement of amniotic fluid for 17-hydroxyprogesterone at 16 to 17 weeks' gestation** (Laue and Rennert, 1995). Currently, the diagnosis is made during the first trimester by HLA genotyping or by DNA analysis of genes within the HLA complex in cells obtained by chorionic villus sampling at 9 to 11 weeks' gestation (Hughes, 2002). **Treatment of the mother with dexamethasone, which crosses the placenta, suppresses fetal secretion of ACTH, thereby preventing virilization of the genitalia.** However, treatment should be instituted as soon as pregnancy is confirmed, and no later than 9 weeks after the last menstrual period, before initial development of the external genitalia (Nimkarn and New, 2007). There are certain complexities to this form of management. The diagnosis of CAH in the fetus may be determined on chorionic villous cells or on cells from amniotic fluid for families in which a prior member was affected. **Therefore, it is not possible to confirm the diagnosis before therapy is initiated.** Because virilization is not a concern with the male fetus and three of four female fetuses at risk are unaffected, given the autosomal recessive pattern of inheritance, seven of eight fetuses may be treated unnecessarily. Therefore, one goal in therapy has been earlier diagnosis to avoid unnecessary treatment. A promising approach that may allow the prenatal diagnosis of CAH as early as 6 weeks' gestation is polymerase chain reaction analysis of free fetal DNA, from circulating trophoblastic cells, in the maternal circulation.

A number of series have established the effectiveness of prenatal treatment for CAH with dexamethasone in 85% of cases (Migeon, 1990; Pang et al, 1990; Speiser et al, 1990). In some neonates there is no evidence of masculinization, suggesting totally successful therapy. In another group there is milder masculinization than that noted in an affected sibling. Although compliance and timing of initiation of treatment have been variable from series to series, this heterogeneity of response to therapy raises intriguing questions about the mechanisms involved in virilization of the CAH fetus. In addition, prenatal treatment with dexamethasone has raised ethical concerns. **Although there is no arguing its ability to prevent androgen effects on the genitalia and potentially the brain of affected females, the long-term effects of dexamethasone on unaffected fetuses undergoing treatment**

prenatally remain largely unknown. A study by Meyer-Bahlburg and colleagues (2004a) demonstrated no cognitive or developmental motor impairment to have resulted from prenatal treatment of CAH fetuses, but others have suggested potential deleterious effects on verbal working memory (Hirvikoski et al, 2007). Miller (1999) and others have advocated the use of prenatal treatment for CAH only as an experimental therapy in large centers and under institutional review board scrutiny. The importance of long-term follow-up of these neonates has been emphasized (Speiser, 1999).

Hughes (2002) and others have emphasized the close correlation in CAH of genotype and phenotype, which has a number of practical implications. Molecular biologists can now predict not only the risk of a couple having an affected child but also the likely clinical form of the disease. Therefore, genotypes of severe mutations would motivate prenatal treatment, whereas genotypes of less severe mutations would not. In addition, less severe genotypes in the newborn would allow for modification of corticosteroid treatment to minimize side effects.

The treatment of affected children with hydrocortisone in childhood and adolescence achieves a number of goals, as noted by Bongiovanni and Root (1963): "to supply the deficient hormone; to suppress pituitary ACTH secretion and hence adrenal androgens and clinical virilization; to forestall abnormally rapid somatic growth and osseous advance; to permit normal gonadal development; and to correct salt-water loss or hypertension in the complicated forms." The required dose of glucocorticoid may be predicted by genotype, as noted by Hughes (2002), but should be adjusted for the individual patient based on bone age, linear growth, 24-hour excretion of ketosteroids, and clinical evidence of glucocorticoid deficiency or excess (Grumbach and Conte, 1998). The effectiveness of therapy may be assessed by measuring morning plasma 17-hydroxyprogesterone levels. Those children with the salt-losing form of the disease require increased salt intake and mineralocorticoid treatment in addition to hydrocortisone therapy. After control of electrolytes and blood pressure has been achieved in the acute setting, maintenance therapy with fludrocortisone should be instituted (Laue and Rennert, 1995; Grumbach and Conte, 1998). The administration of hydrocortisone and, when required, fludrocortisone (0.05-0.3 mg/day) is continued indefinitely in all patients (American Association of Pediatrics, 2000). Typically, patients are instructed to triple their oral dose of hydrocortisone during physically stressful events such as surgery or infection.

In the majority of children (who will not have been diagnosed and treated prenatally), it is appropriate to perform feminizing genitoplasty at 3 to 6 months of age, when a well-established course of medical therapy has been instituted, the risks of anesthesia have become minimal, and the child has grown large enough to make the procedure technically feasible (Passerini-Glazel, 1990). **Long-term fertility in males and feminization, menstruation, and fertility in females can be anticipated in the well-treated patient.** Indeed, this potential in even the most masculinized female CAH patient has provided support for feminizing genitoplasty in virtually all 46,XX CAH patients.

An important area of recent research has been the potential imprinting of the brain by elevated prenatal androgen levels. A number of recent studies confirm that prenatal hyperandrogenization is associated with masculinization of gender-related behavior but not masculinization of gender identity. Meyer-Bahlburg and associates (Dessens et al, 2005; Meyer-Bahlburg et al, 2004b, 2008) noted a close correlation between hormonal abnormalities as a function of severity of enzyme deficiency with sexual orientation (homosexuality, bisexuality rates). Furthermore, Berenbaum and colleagues (2003, 2004) noted that in females with CAH and virilized genitalia psychological development is not compromised in those who are reared as females and receive good medical care. Meyer-Bahlburg and associates (2004a) noted in 46,XX CAH girls that marked masculinization of gender-related behavior in prenatally hyperandrogenized CAH girls was not associated with masculinization of gender identity. Therefore, the psychosexual evidence to date supports maintaining female gender in masculinized CAH patients diagnosed in infancy. Indeed, proper psychological support should be a component of long-term follow-up.

In an interesting new finding, both male and female patients with classic CAH have been noted on magnetic resonance imaging to have smaller amygdala volumes than controls, and altered amygdala function. The amygdala, regulated by glucocorticoids, is important in processing emotion (Ernst et al, 2007).

An intriguing area of surgical innovation in the management of CAH has been the experimental use of "prophylactic" adrenalectomy for selected patients. This approach is based on the premise that in certain patients it is more difficult to maintain adrenal suppression than to prevent adrenal crises. Clinically, these patients are the salt losers and extremely virilized females. For those with this most severe form of 21-hydroxylase deficiency, adequate suppression of adrenal production has required significant degrees of hypercortisolism, associated with poor growth, obesity, and infertility (in 40%). For the 25% of CAH patients who completely lack 21-hydroxylase enzyme activity and therefore produce neither cortisol nor aldosterone, adrenalectomy may be a practical approach (VanWyk et al, 1996). In general, these patients may be identified genotypically as homozygotes or compound heterozygotes for "null alleles" of the *CYP21* gene (VanWyk et al, 1996). In a series of 18 patients with long-term follow-up, VanWyk and Ritzen (2003) noted bilateral adrenalectomy to be safe and effective in managing severe forms of CAH in which patients repeatedly escaped adrenal suppression. Most of these patients reported a better quality of life after bilateral adrenalectomy. In a recent series bilateral adrenalectomy proved more successful for those patients pursing fertility rather than control of obesity and hyperandrogenism (Ogilvie et al, 2006).

Although these patients are rendered addisonian by this surgery, those with the most severe form of CAH would have a poor intrinsic adrenal response to metabolic stress (Gunther et al, 1997). One theoretical disadvantage of this approach is that if gene therapy were to one day allow functional *CYP21* genes to be introduced into adrenal cortical tissue, adrenalectomized patients would not be candidates for such therapy (VanWyk et al, 1996).

46,XX DSD (Masculinized Female) Secondary to Maternal Androgens and Progestins and Maternal Tumors

The masculinization of a female fetus as a result of maternal administration of synthetic progestational agents or androgens is a rare occurrence; lessons have been learned from prior unfortunate experiences. Historically, progestational agents were used to prevent threatened abortion. In one large series, masculinization occurred in 2% of female infants whose mothers were treated with progestins during pregnancy (Ishizura et al, 1962). In addition, danazol, a testosterone derivative used to treat endometriosis, has been associated with virilization of the female fetus. **The degree to which any androgen or progestational agent affects female fetal development is a function of the strength of the agent, its maternal dosage, and timing and duration of administration** (Bongiovanni and McFadden, 1960).

Very rarely, a maternal ovarian or adrenal tumor has virilizing effects on a female fetus. More typically, such a tumor has virilizing effects on the mother but no apparent effect on the fetus. Ovarian tumors that have resulted in masculinization of the female fetus include arrhenoblastoma, hilar cell tumor, lipoid cell tumor, ovarian stromal cell tumor, luteoma of pregnancy, and Krukenberg tumor (Calaf et al, 1994).

Rarer still are maternal adrenal tumors (adrenocortical carcinoma and adenoma), which have masculinizing effects on the female fetus.

Aromatase deficiency represents an even rarer cause of transplacental transport of excess androgens to the fetus. The cytochrome P450 aromatase enzyme catalyzes the conversion of androgens to estrogens. Normally, weak androgens produced by the fetal adrenal gland are converted to estrogens by placental aromatase and pass to the maternal circulation. Mutations of the *CYP19* aromatase gene can result in profound virilization of the female fetus and mother during pregnancy. Although maternal virilization resolves postnatally, it recurs in subsequent pregnancies.

In any case of exogenous androgen effect on a female fetus, normal endocrine status is recognized postnatally and management is confined to external genital reconstruction, as required.

46,XY DSD (Undermasculinized Male)

The term *46,XY DSD (undermasculinized male)* refers to 46,XY individuals with differentiated testes who exhibit varying degrees of feminization phenotypically. Impaired male differentiation in these patients is secondary to inadequate secretion of testosterone by the testes at the necessary period in development, inability of target tissue to respond to androgen appropriately, or impaired production or action of MIS.

Leydig Cell Aplasia (Luteinizing Hormone Receptor Abnormality)

Leydig cell aplasia as a cause of undermasculinization of the male was first reported by Berthezene and colleagues in 1976. **In its pure form, this rare disorder is characterized by a normal 46,XY male karyotype associated with a normal-appearing female phenotype. Typically, testes are palpable in the inguinal canals or labia majora.** On investigation, there are no müllerian structures and the vagina is short. A low testosterone level is noted in conjunction with an elevated LH concentration. **The absence of a rise in serum testosterone level after hCG stimulation is characteristic of this disorder** (Brown et al, 1978). Physiologically, this disorder represents a spectrum between absent Leydig cells and Leydig cells with abnormal LH receptor (David et al, 1984). Because a number of inactivating mutations have been found in the LH receptor gene, a correlation can be made between the phenotype of patients with Leydig cell hypoplasia and the activity of their LH receptor alleles (Richter-Unruh et al, 2004). It is transmitted as an autosomal recessive trait expressed only in males. Incomplete forms of the syndrome occur, with the mildest form being expressed as primary hypogonadism with normal male external genitalia (Lee et al, 1982).

The clinical diagnosis of Leydig cell aplasia, or LH receptor abnormality, is typically made as a result of sexual infantilism and the absence of development of secondary sexual characteristics or the discovery of palpable gonads in the inguinal canal or labia on physical examination (Arnholt et al, 1985). The differential diagnosis includes androgen insensitivity syndrome or a terminal defect in androgen synthesis. The histology of the abnormal testes demonstrates absence of Leydig cells in intratubular spaces with normal Sertoli cells.

Disorders of Testosterone Biosynthesis

A defect in any of the five enzymes required for the conversion of cholesterol to testosterone can cause incomplete (or absent) virilization of the male fetus during embryogenesis. The first three enzymes (cholesterol side chain cleavage, 3β-hydroxysteroid dehydrogenase, and 17β-hydroxylase) are present in both adrenals and testes. **Therefore, their deficiency results in impaired synthesis of glucocorticoids and mineralocorticoids in addition to testosterone.** For all five enzyme deficiencies, the pattern of inheritance is autosomal recessive.

StAR (Cholesterol Side Chain Cleavage Enzyme) Deficiency. The first step in gonadal and adrenal steroidogenesis is conversion of cholesterol to pregnenolone, which is mediated by a single cholesterol side chain cleavage enzyme known as 450SCC (previously known as 20-22 desmolase). A defect in this enzyme, first described by Prader and Gurtner in 1955, was believed to result in the rare condition congenital lipoid adrenal hyperplasia, so named because the adrenal glands became large and lipid laden. **However, more recent evidence suggests that a defect in cholesterol transport rather than a defective enzyme is etiologically responsible** (Saenger, 1997). The steroidogenic acute regulatory protein (StAR) stimulates cholesterol transport from the outer to the inner mitochondrial membrane (site of the cholesterol side chain cleavage complex). This appears to be the rate-limiting step in acute steroid synthesis.

StAR mutations are found in various ethnic groups but are most commonly reported in patients of Japanese, Korean, and Palestinian origin (Bhangoo et al, 2005). Affected 46,XY individuals have female or ambiguous external genitalia with a blind-ending vaginal pouch; intra-abdominal, inguinal, or labial testes; and absence of müllerian structures, consistent with functioning Sertoli cells (Hauffa et al, 1985). Wolffian ducts are present but rudimentary. Infants often present in the first few weeks of life with severe adrenal insufficiency and salt wasting.

A diagnosis of StAR (cholesterol side chain cleavage enzyme) deficiency should be entertained in any neonate with nonvirilized female external genitalia and evidence of cortisol and aldosterone deficiency with hyponatremia, hyperkalemia, and metabolic acidosis. Abdominal computed tomography demonstrates large, lipid-laden adrenal glands.

Management is similar to that for 21-hydroxylase deficiency. To date, all surviving 46,XY patients with this disorder have been raised as females and have undergone gonadectomy (Laue and Rennart, 1995). Because testosterone production was never significant, brain imprinting is not a factor in gender assignment.

Cytochrome P450 Oxidoreductase Deficiency. Cytochrome P450 oxidoreductase (POR) deficiency has been recently added to the causes of both 46XY and 46XX DSD. POR is a cofactor to all microsomal P450 enzymes, including 17-hydroxylase, 17,20-lyase, 21-hydroxylase, and aromatase. The condition emerged as a distinct entity through the realization that apparent combined deficiency of 17-hydroxylase and 21-hydroxylase enzymes is a single disorder due to lack of POR, a membrane-bound flavoprotein that plays a central role in electron transfer from NADPH to P450 enzymes. It was originally characterized in patients with Antley-Bixler syndrome (a skeletal dysplasia syndrome) in whom some had ambiguous genitalia and abnormal steroidogenesis.

Subsequently, it has become clear that POR deficiency can cause DSD unassociated with skeletal dysplasia and characteristics of Antley-Bixler syndrome (Hughes, 2008).

3β-Hydroxysteroid Dehydrogenase Deficiency. 3β-Hydroxysteroid dehydrogenase catalyzes the 3β-hydroxysteroids (pregnenolone, 17-hydroxypregnenolone, and DHEA) to the three ketosteroids, progesterone, 17-hydroxyprogesterone, and androstenedione. A congenital deficiency of 3β-hydroxysteroid dehydrogenase was first described by Bongiovanni in 1962.

Affected individuals present with various degrees of incomplete masculinization resulting from a block in testosterone biosynthesis and with salt-wasting adrenal insufficiency resulting from impaired synthesis of aldosterone and cortisol. The lack of salt-retaining hormone and cortisol results in a salt-losing crisis soon after birth. However, partial deficiencies associated with severe salt wasting occur, consistent with genetic heterogeneity. Two isoenzymes, type I and type II 3β-hydroxysteroid dehydrogenase, are involved in steroid biosynthesis. These enzymes are encoded by two genes, *HSD3B1* and *HSD3B2,* localized to chromosome 1 at locus p11-p13 (Chang et al, 1993). Classical 3β-hydroxysteroid dehydrogenase deficiency results from inactivating mutations, 37 of which have been identified, in the *HSD3B2* gene (Welzel et al, 2008).

Males with this deficiency usually exhibit incomplete virilization of the external genitalia, with a small phallus, hypospadias with labioscrotal fusion, a urogenital sinus, and a blind-ending vaginal pouch. Testes are often scrotal, and wolffian ducts develop normally. As with other defects in testosterone biosynthesis, in which normal Sertoli cell function is preserved, müllerian structures are absent.

The diagnosis should be considered in 46,XY males with ambiguous genitalia and signs of adrenal insufficiency. Endocrine study demonstrating increased levels of 3β-hydroxysteroids confirms the diagnosis.

Management of 3β-hydroxysteroid dehydrogenase is similar to that for patients with 21-hydroxylase deficiency.

17α-Hydroxylase Deficiency. 17α-Hydroxylase catalyzes the conversion of pregnenolone and progesterone to 17α-hydroxypregnenolone and 17-hydroxyprogesterone, respectively, in adrenal and gonadal steroidogenesis. The first case of male pseudohermaphroditism due to this enzyme deficiency was reported by New in 1970. The gene for this enzyme has been localized to chromosome 10 (Laue and Rennart, 1995).

Affected 46,XY individuals usually have female external genitalia with absent to slight masculinization. **A deficiency in 17α-hydroxylase activity impairs cortisol production, causing ACTH hypersecretion and resulting in increased levels of DOC, corticosterone, and 18-hydroxycorticosterone in the adrenals. These compounds with mineralocorticoid activity produce excess salt and water retention, hypertension, and hypokalemia.**

The phenotype of affected individuals varies from female with external genitalia with a blind-ending vaginal pouch to male with perineal hypospadias and chordee. The diagnosis should be considered in a undervirilized male with hypertension. Endocrine laboratory evaluation demonstrates elevated serum progesterone, DOC, corticosterone, 18-hydroxycorticosterone, and ACTH.

Therapy with glucocorticoid replacement brings blood pressure and hypokalemia back to normal by suppressing ACTH and hence adrenal cortical stimulation. Some patients have been raised as females with gonadectomy and estrogen replacement at puberty. In partial forms, typically with reasonable phallic size, patients may be raised as male with testosterone replacement at puberty. **Fertility has not been reported in patients with testosterone biosynthetic defects, and inadequate testosterone production makes androgen imprinting a less significant issue for these patients.** Therefore, the phenotype may dictate gender assignment.

17,20-Lyase Deficiency. The enzyme 17,20-lyase has been demonstrated to be related to 17α-hydroxylase in that the activities of both are linked to the same gene product on chromosome 10 (Laue and Rennart, 1995). However, in some patients with the genetic defect both biologic activities are absent, but with others only the 17,20-lyase function appears deficient. Zachmann and colleagues first described this clinical entity in 1972.

In cases in which the deficiency primarily involves 17,20-lyase, cortisol and ACTH secretion are normal. Aldosterone is secreted normally, and hypertension does not result. **However, impaired biosynthesis of testosterone in the 46,XY individual results typically in ambiguous rather than totally female genitalia at birth.** The deficient masculinization of the external genitalia can range from severe, resulting in a female gender assignment in the neonate, to mild, resulting only in hypospadias. At puberty, the secretion of testicular androgen remains low. Zachmann and colleagues (1982) have postulated that there are two types of 17,20-lyase deficiency—one that is partial and another that is a complete defect.

The diagnosis may be suspected in undervirilized males with absent müllerian derivatives and no defect in glucocorticoid or mineralocorticoid synthesis. At the time of expected pubertal development, the patients may present with failure to develop secondary sexual characteristics and elevated gonadotropin levels. The diagnosis may be made prepubertally using hCG and ACTH stimulation.

Management entails plastic reconstruction of the external genitalia and appropriate sex steroid replacement at puberty.

17β-Hydroxysteroid Oxidoreductase Deficiency. This last enzyme in the testosterone biosynthetic pathway catalyzes the conversion of androstenedione to testosterone, DHEA to androstenediol, and estrone to estradiol. Male undervirilization resulting from a deficiency in 17β-hydroxysteroid oxidoreductase was first described by Saez and associates in 1971.

Clinically, this is the most interesting enzymatic defect in testosterone biosynthesis in its similarities to 5α-reductase deficiency. At birth, affected individuals appear to have a normal female phenotype, without significant evidence of virilization. Therefore, a female gender assignment is usually made. However, these individuals have well-differentiated testes located intra-abdominally, inguinally, or in the labia and no müllerian structures. Surprisingly, wolffian ducts are normally developed, which may be secondary to the action of androstenedione or minimal amounts of testosterone produced during embryogenesis (Boehmer et al, 2001). **At puberty, there is phallic growth and progressive development of male secondary sexual characteristics.** These include increased muscle mass and development of pubic, axillary, and facial and body hair with male distribution. Gynecomastia may occur, and the testes may become palpable (Saez et al, 1972). In some cases, gender reassignment to male has been reported (Imperato-McGinley et al, 1979; Rosler and Kohn, 1983).

The late onset of virilization is related to the pubertal increase in gonadotropin production, which may partially overcome the block in testosterone biosynthesis.

There is a characteristic hormonal profile in this disorder. In the prepubertal patient, plasma androstenedione and estrone levels may not be increased. At puberty, androstenedione, the immediate precursor of testosterone, is increased to 10 to 15 times the normal plasma concentration (Virdis and Saenger, 1984). Earlier precursors are within normal levels. Plasma testosterone is in the low-normal range. Serum levels of LH and FSH are markedly elevated, typically four to six times normal.

As a result of biochemical characterization and molecular cloning, five different 17β-hydroxysteroid dehydrogenase isozymes have been identified to date. **The type III 17β-hydroxysteroid dehydrogenase isozyme, cloned by Andersson and colleagues** (1997), **catalyzes the biosynthesis of testosterone from androstenedione. A mutation involving the *HSD17B3* gene, mapped to chromosome 9q22, is responsible for male undervirilization.** The type III isozyme is apparently expressed early in utero and is responsible for testosterone biosynthesis during the critical period of sexual differentiation, based on the observation that male adults homozygous for 17β-hydroxysteroid dehydrogenase type III gene defects have ambiguous genitalia (Zhu et al, 1998).

The diagnosis is rarely made in the neonatal period. It may become apparent on discovery of a testis during a hernia repair in infancy or childhood. An hCG stimulation test resulting in an increased testosterone-to-androstenedione ratio would confirm the diagnosis and differentiate this condition from androgen insensitivity (Ahmed et al, 2000). **The primary management issue for patients with 17β-hydroxysteroid oxidoreductase deficiency has been gender assignment.** At this early stage, maintenance of the female sex of rearing with gonadectomy is usually elected. If the diagnosis is not made until puberty, when dramatic changes in virilization occur, certain families prefer a gender change to male. Cohen-Kettenis found gender role changes in 39% to 64% of 17β-hydroxysteroid oxidoreductase deficiency patients raised as female (Cohen-Kettenis, 2005). In an Arab cohort of 22 patients, Sobel and associates (2004) noted 7 to undergo spontaneous gender role reversal to male without parental consent or psychiatric intervention. Traditionally, this decision has been strongly culturally influenced.

If a female sex of rearing is elected, gonadectomy, plastic reconstruction of the genitalia as necessary, and estrogen replacement therapy at puberty are indicated. For the patient maintained in the male gender, orchidopexy and reconstruction of the external genitalia are required. This entails hypospadias repair and chordee correction, which can be quite successful. However, phallic size remains small and infertility is the rule. Some have suggested that childhood treatment with intramuscular testosterone may result in a larger phallus (Sobel and Imperato-McGinley, 2004). Usually endogenous androgen levels are adequate long term.

Two hypotheses have been proposed to explain the frequency of gender change from female to male with this enzyme deficiency, particularly among the cohort of Arab male pseudohermaphrodites with 17β-hydroxysteroid dehydrogenase type III deficiency. One entails the potential male imprinting of the brain in utero owing to the conversion of androstenedione to estrone; this theory is supported by studies in rats and rabbits demonstrating that administration of estrogen or androstenedione is capable of inducing male sexual behavior (Reddy et al, 1974). The second is the possibility that 17β-hydroxysteroid dehydrogenase activity is not deficient in the brain, its effect being mediated by the conversion of androstenedione to testosterone or estrogen (Imperato-McGinley et al, 1979).

Androgen Receptor and Postreceptor Defects

Disorders of androgen receptor function represent the most common definable cause of 46,XY DSD or the undervirilized male. These patients characteristically have a 46,XY karyotype and testes and present with a spectrum of phenotypic abnormalities that vary from complete external feminization (syndrome of complete androgen insensitivity), to ambiguous genitalia (partial androgen insensitivity), to the phenotypically infertile male. Although the clinical presentations vary according to the severity of the disorder, the pathophysiology is similar (Wiener et al, 1997).

Syndrome of Complete (Severe) Androgen Insensitivity. The syndrome of complete androgen insensitivity (previously known as testicular feminization) is characterized clinically by a 46,XY karyotype, bilateral testes, female-appearing external genitalia, and absence of müllerian derivatives. Wilkins first suggested in 1950 that the clinical features of this syndrome were the result of androgen resistance. This condition has an incidence of 1 in 20,000 to 1 in 60,000 males, and it is transmitted as an X-linked trait.

The androgen receptor regulates the transcription of other specific genes, once activated by testosterone or DHT. This results in new mRNA synthesis from the downstream genes and protein production. The androgen receptor has been mapped to the X chromosome at Xq11-12, spanning 90 kilobases and comprising eight exons (Brown et al, 1989; Hiort and Holterhus, 2003). Males have only one copy of this gene. Point mutations of the gene account for more than 90% of cases of androgen insensitivity (Quigley et al, 1995). **The identifiable molecular alterations of the androgen receptor gene cannot predict the resulting phenotype of the affected individual unless there is total loss of the receptor, which occurs in only 1% of all patients** (Quigley et al, 1995).

Patients with complete androgen insensitivity have a normal female phenotype with the exception of diminished axillary and pubic hair. Their breast development and body habitus are feminine in character, and their external genitalia are unequivocally female, although the vagina is short and blind ending. It had previously been believed that in-utero resistance to testosterone action prevented stabilization of the wolffian ducts. Hannema and associates (2004), however, have demonstrated wolffian duct derivatives in cases of complete androgen insensitivity. In 42% of patients, screening of the paratesticular area revealed well-developed epididymis and/or vasa deferentia. The mutations found in these patients entailed a single amino acid substitution in the androgen receptor ligand binding domain, rather than frameshift mutations, premature stop codons, or mutations in the DNA-binding domain, all of which were associated with absence of well-developed wolffian duct structures. These investigators suggest that mutant receptors with residual activity in vivo stimulate wolffian duct development. As a result, they should be classified as having *severe* rather than complete androgen insensitivity. Because the fetal testes secrete MIS, müllerian structures are absent. The testes may be found in the labia, inguinal canal, or abdomen.

These patients are rarely diagnosed in the neonatal period, unless a prenatal diagnosis is made on the basis of female phenotype and 46,XY karyotype on amniocentesis. With the increase in prenatal diagnostics, this is becoming a more common occurrence (Hughes and Patterson, 1994). More typically, however, the diagnosis is made as a result of primary amenorrhea or the finding of

a testis at inguinal herniorrhaphy. Fifty percent of patients with complete (severe) androgen insensitivity syndrome have an inguinal hernia (Conte and Grumbach, 1989). Conversely, 1% to 2% of apparently female infants with inguinal hernia are found to have a 46,XY karyotype and complete androgen insensitivity syndrome (Wiener et al, 1997; Barthold et al, 2000). Therefore, routine vaginoscopy to confirm the presence of a cervix or endoscopy through a hernia sac to identify an intra-abdominal testis at the time of inguinal herniorrhaphy in female patients is a prudent maneuver. Histologically, the testes exhibit incomplete or absent spermatogenesis, with normal or hyperplastic Leydig cells. They are comparable to immature, cryptorchid testes.

Endocrine evaluation in the neonatal period demonstrates normal male levels of testosterone, DHT, and gonadotropins. At puberty, gonadotropin levels rise, leading to increased levels of plasma estradiol, which results in feminization, including breast development.

Several types of mutant receptor abnormality that would account for this syndrome have been described, including (1) a decreased amount of apparently normal receptor; (2) absence of receptor binding; (3) a qualitatively abnormal receptor (thermolabile, or unstable); (4) other "receptor-positive" forms, including increased rate of dissociation of steroid receptor complex, defective upregulation of the androgen receptor, decreased affinity of ligand binding, and impaired nuclear retention of the ligand (Grumbach and Conte, 1998). In general, the severity of the defect in androgen receptor (quantity or quality) correlates with the phenotype. In addition, Hughes (2001) has noted the absence of coregulator proteins, without the absence of the androgen receptor, in cases of complete androgen insensitivity, suggesting that for androgen effects to be optimal an integrated array of transcriptional factors, coregulators, and ligands is required.

The diagnosis of complete (severe) androgen insensitivity may readily be made in the postpubertal patient on the basis of clinical and hormonal findings of amenorrhea, absence of pubic hair, or inguinal hernias containing testes. It is confirmed by a 46,XY karyotype and a normal male androgen and gonadotropin profile. Pelvic ultrasound examination confirms the absence of müllerian tissue, and a vaginal examination confirms a blind-ending vagina without a cervix.

In the prepubertal child, diagnosis is more difficult and requires an hCG stimulation test. Because of the time required for receptor binding quantification in genital skin, it is desirable to use PCR to characterize the androgen receptor gene in DNA obtained from a venous blood sample to detect a genetic marker for androgen insensitivity syndrome.

Management of complete (severe) androgen insensitivity relates primarily to the optimal timing of gonadectomy. Because the testes produce estradiol, which results in the appropriate changes for the female phenotype, it is considered by many preferable to leave the testes in situ until puberty is complete. Potential exceptions to the policy of delayed gonadectomy are palpable testes or testes associated with an inguinal hernia. One important caveat in deciding to leave the testes in situ is the need to confirm with absolute certainty that complete rather than partial androgen insensitivity exists by PCR characterization of the androgen receptor gene in venous blood DNA. If an incomplete form should exist, virilization at puberty could result (Batch et al, 1993). Another important consideration is the anticipated need to discuss with a postpubertal female the presence of testes that require removal, rather than doing so when the child is much younger and the psychosexual implications less charged.

A competing concern for retention of testicular tissue is the potential for malignant degeneration of the testes. In patients with complete androgen insensitivity who reach adulthood with a retained testis, the risk for development of a testis tumor—usually seminoma or gonadoblastoma—is thought to be 1% to 2%, only slightly higher than for a cryptorchid testis (Manuel et al, 1976; Muller and Skakkebaek, 1984). Before pubertal development the risk is extremely low, the youngest reported case of a germ cell tumor in an androgen insensitivity syndrome being in a 14-year old (Ahmed et al, 2000). Therefore, in general, delayed gonadectomy after puberty is believed to be safe (Cools et al, 2006).

After orchiectomy, cyclic estrogen/progestin therapy is begun. The majority of patients have successful treatment of their short vagina with progressive dilation (Ismail-Pratt et al, 2007). Some patients may benefit from vaginoplasty (Boehmer et al, 2001). **Currently, all studies of patients with complete androgen insensitivity support an unequivocal female gender identity, consistent with androgen resistance of brain tissue as well.** In one study, no statistical differences were found between the complete androgen insensitivity group and normal controls in any quality-of-life or gender-related behavior criterion (Hines et al, 2003). To date, there has been no report of a patient with complete androgen insensitivity raised as a female who needed gender reassignment to male (Meyer-Bahlburg, 1999). In any event, age-appropriate psychological counseling is an important component of management in the androgen insensitivity syndromes.

Syndrome of Partial Androgen Resistance. The syndrome of partial androgen resistance includes syndromes that were once thought to represent separate entities: Reifenstein, Gilbert-Dreyfus, Rosewater, and Lubs syndromes (Griffin, 1992). **These are X-linked disorders** of incomplete masculinization that represent a spectrum of phenotypic abnormalities. **The major finding is ambiguity of the external genitalia to varying degrees.** The partial form of androgen insensitivity may be expressed variably even within the same family. **The classic phenotype is that of a male with perineoscrotal hypospadias, cryptorchidism, rudimentary wolffian duct structures, gynecomastia, and infertility. However, the phenotypic spectrum can range from hypospadias and a pseudovagina to gynecomastia and azoospermia** (Wilson et al, 1974). The endocrine profile of partial androgen insensitivity syndrome is similar to that of the complete androgen insensitivity syndrome. At puberty, gynecomastia may develop. The phallus may enlarge slightly, but it remains small.

To date, over 500 mutations in the androgen receptor gene have been discovered. It has been well recognized in partial androgen insensitivity syndrome that these mutations produce a diversity of phenotypes between and within affected families, consistent with additional factors that modulate responsiveness to androgen. This seems consistent with prior studies in the 1980s on genital skin fibroblasts, demonstrating **two forms of receptor defect in the partial androgen insensitivity syndrome: (1) a reduced number of normally functioning androgen receptors and (2) a normal receptor number but decreased binding affinity** (Griffin and Durrant, 1982; Hughes, 2000).

The diagnosis of partial androgen insensitivity syndrome can be difficult. In the neonatal period, it may be made in the setting of a 46,XY karyotype, ambiguous external genitalia, and absent müllerian structures on pelvic ultrasound. Endocrine evaluation

confirms normal male levels of testosterone and gonadotropins, and a normal testosterone/DHT ratio. An hCG stimulation test and characterization of the androgen receptor gene in serum DNA by PCR should confirm the diagnosis. A family history consistent with X-linked inheritance of ambiguous genitalia is of great assistance. A course of androgen injections in early infancy is often used to assess androgen responsiveness, which can aid in gender assignment.

Management must be individualized depending on the degree of genital ambiguity. In patients assigned a female gender, gonadectomy and surgical reconstruction of the external genitalia are indicated; at puberty, estrogen/progestin replacement is instituted. Those individuals raised as males would require treatment of their cryptorchidism, reduction of gynecomastia, and genital reconstruction. Phallic size remains small, however, and the effects of supraphysiologic doses of testosterone have been disappointing (Migeon et al, 1994). The risk of gonadal tumor is somewhat higher than in complete androgen insensitivity syndrome (up to 5.5%), and there is an increased risk of male breast cancer with partial androgen insensitivity syndrome (Hughes, 2006). Of importance in considering gender assignment in patients with partial androgen insensitivity is the recognition that the receptor defect affecting the external genitalia appears to affect brain receptors for testosterone similarly. Unfortunately, because of the distinct phenotypic variability, even within families, gender assignment of patients with partial androgen insensitivity syndrome cannot be based on the specifically identified androgen receptor gene (Boehmer et al, 2001). The study by Melo and colleagues (2003) of 11 patients with partial androgen insensitivity syndrome (5 raised female, 6 raised male) demonstrated gender of rearing to be consistent with adult gender role. This suggests the possibility that in the setting of inadequate androgen imprinting of the fetal brain, sex of rearing may predominate in determination of gender identity. Unfortunately, this has not consistently proven to be the case.

Unfortunately, long-term outcome data in the management of patients with partial androgen insensitivity syndrome is limited. Migeon and colleagues' study (2002) of 14 patients with partial androgen insensitivity syndrome noted that 23% were dissatisfied with neonatal gender assignment irrespective of current status as male or female. Another study of 15 postpubertal males with partial androgen insensitivity syndrome documented major impairment in sexual function in all (Bouvattier et al, 2006). However, Mazur (2005) found that only 9% of patients with partial androgen insensitivity syndrome self-initiated a gender reassignment.

The current recommendation for partial androgen insensitivity syndrome is to allow virilization of the external genitalia to serve as a guide in gender assignment, in that this may be the best means of assessing androgen imprinting of the brain, for lack of a more precise marker (Sobel and Imperato-McGinley, 2004).

Mild Androgen Insensitivity Syndrome. A relatively new classification is that of mild androgen insensitivity syndrome discovered in the course of investigations for male factor infertility. Recent studies have demonstrated a variety of mutations, usually quite discrete within the androgen receptor gene, to account for the infertility (Hiort and Holterhus, 2003). Men with this syndrome may be normal phenotypically or have a history of mild hypospadias repair but are azoospermic or severely oligospermic. They have been found to have normal to elevated serum testosterone levels with normal to elevated LH levels. This suggests that infertility in otherwise normal males may be the clinical manifestation of partial androgen insensitivity, representing the far end of a variable phenotypic spectrum. To date, the pathophysiology of the abnormal spermatogenesis caused by androgen receptor mutations remains unknown (Hiort and Holterhus, 2003).

5α-Reductase Deficiency

The disorder of 5α-reductase deficiency is one of the most fascinating forms of male undervirilization. The clinical presentation of this enzyme disorder was actually predicted in 1972, before the description of such patients in 1974 by Walsh and Imperato-McGinley and their colleagues (Wilson, 1972; Imperato-McGinley et al, 1974; Walsh et al, 1974). Extensive characterization of the disease has been achieved since that time.

5α-Reductase is a microsomal enzyme that catalyzes the conversion of testosterone to DHT. The condition is transmitted in an autosomal recessive pattern, and only homozygous males are affected. Two 5α-reductase genes have been cloned; they encode different isoenzymes. The type 1 isoenzyme, encoded on chromosome 5, is expressed in low levels in the prostate and external genitalia. The type 2 isoenzyme is encoded on chromosome 2 and is expressed in high levels in the prostate and external genitalia (Thigpen et al, 1992b). **Male undervirilization due to 5α-reductase deficiency is secondary to mutations in the type 2 gene.** At least 40 mutations have been identified (Thigpen et al, 1992a; Imperato-McGinley, 2002). Identical mutations in individuals with widely different geographic and ethnic backgrounds support the concept of mutational "hot spots" on the gene.

Individuals with this disorder present as neonates with a 46,XY karyotype and a phenotype that may vary from penoscrotal hypospadias to, more commonly, markedly ambiguous genitalia. Typically, the phallus is quite small, appearing as a normal or enlarged clitoris (Fig. 133–22). A urogenital sinus is present, with convergence of vaginal and urethral channels, and there is labioscrotal fusion (Fig. 133–23). The vaginal pouch is short and blind ending. Testes and epididymides are located in the labia, inguinal canals, or abdomen; and the vasa terminate in the blind-ending vaginal pouch. At puberty, partial masculinization occurs with an increase in muscle mass, development of male body habitus, increase in phallic size, and onset of erections (Peterson et al, 1977). Sperm production and fertility in affected individuals have been reported (Imperato-McGinley et al, 1982; Zhu et al, 1998). Other secondary sexual characteristics, including enlargement of the prostate and hairline recession, do not develop.

On endocrine evaluation these individuals have elevated mean plasma testosterone but low DHT levels. After hCG stimulation, the testosterone-to-DHT ratio increases from the range of 3 to 25 in normal subjects to a range of 75 to 160 (Kupfer et al, 1992). Genital skin fibroblast cultures demonstrate diminished to absent 5α-reductase activity (Migeon et al, 1994). At puberty, virilization is presumed to occur because the androgen receptor binds markedly higher levels of testosterone at low affinity or because of the normal increase at puberty in the activity of the 5α-reductase type 1 isoform, resulting in sufficient DHT for virilization (MacLaughlin and Donahoe, 2004). Indeed, the enzyme abnormalities in this disorder have been shown to be biochemically heterogeneous, ranging from reduced affinity of the enzyme for testosterone and reduced affinity for nicotinamide adenine dinucleotide phosphate (NADPH) to altered pH activity profiles (Kupfer et al, 1992).

The phenotypic characteristics of this disorder have helped to clarify the roles of testosterone and DHT in normal development. **Although DHT appears to be critical for the development**



Figure 133–22. External genitalia of patient with 5α-reductase deficiency. Note clitoromegaly with marked labioscrotal fusion and small vaginal introitus. (From Diamond D. Intersex disorders: I and II. AUA Update Series, vol. IX, lessons 9 and 10. Houston: American Urological Association Office of Education; 1990.)



Figure 133–23. Intraoperative view of urogenital sinus in a patient with 5α-reductase deficiency; note enlarged clitoris, urogenital sinus with convergence of urethral and vaginal channels, and posterior labioscrotal fusion. (From Diamond D. Intersex disorders: I and II. AUA Update Series, vol. IX, lessons 9 and 10. Houston: American Urological Association Office of Education; 1990.)

of normal external genitalia in utero, testosterone alone appears sufficient for wolffian duct development.

Individuals in the pedigree studied by Imperato-McGinley and colleagues in the Dominican Republic underwent gender reversal at puberty and were known within the community as *guevedoces* ("penis at 12") (Imperato-McGinley et al, 1979). This strong tendency toward reversal of gender identity in 5α-reductase deficiency has been one of the most intriguing aspects of the disorder. It has lent support to the concept that testosterone exerts the primary male imprinting effect on the brain. However, the discovery that there are two isoenzymes for 5α-reductase, only type 2 being deficient in this syndrome, allows for the possibility that 5α-reductase type 1 has some impact on the brain (Thigpen et al, 1992b). As a result, with early diagnosis of 5α-reductase deficiency, a male gender assignment is generally favored, bearing in mind that the studies strongly supporting male gender identity in this disorder were performed in sociologically unique environments (Zhu et al, 1998). Cohen-Kettenis (2005) noted 56% to 63% of 5α-reductase deficiency patients to undergo gender reversal from female to male. The clinician must be open to familial cultural considerations regarding the value of male gender as well as the significance of penile size. In the setting of male gender assignment, cryptorchidism and hypospadias should be surgically corrected. Fertility is possible, particularly with the advent of intrauterine insemination (Katz et al, 1997). Exogenous DHT could be used at puberty in an attempt to promote phallic growth, but it would be likely to impair spermatogenesis. For some individuals, based primarily on extremely small phallic size, a female gender may be assigned. For these patients, gonadectomy should be performed as early as possible and certainly well before puberty to prevent virilization. Estrogen/progestin should be administered at the expected time of puberty. Vaginoplasty and clitoral reduction may be performed within the first year of life in those with a severe defect to provide for normal appearance of the external genitalia and to allay parental anxiety.

Persistent Müllerian Duct Syndrome

Persistent müllerian duct syndrome **(PMDS), or** ***hernia uteri inguinale,*** the term originally used by Nilson (1939), characteristically describes a group of **patients with a 46,XY karyotype and normal male external genitalia but internal müllerian duct structures. Typically, these phenotypic males have unilateral or bilateral undescended testes, bilateral fallopian tubes, a uterus, and an upper vagina draining into a prostatic utricle.** The condition is commonly diagnosed after müllerian tissue is encountered during inguinal herniorrhaphy or orchidopexy.

Clarnette and coworkers (1997) suggested three categories for patients with PMDS: (1) the majority (60% to 70%) with bilateral intra-abdominal testes in a position analogous to ovaries; (2) a smaller group (20% to 30%) in which one testis is found in a hernia sac or scrotum in association with a contralateral inguinal hernia (the classic presentation of hernia uteri inguinale); and (3) the smallest group (10%), in which both testes are located in the same hernia sac (as a result of transverse testicular ectopia) along with the fallopian tubes and uterus. Indeed, **PMDS is believed to be etiologically important in transverse testicular ectopia, occurring in 30% to 50% of cases** (Fujita, 1980).

The *MIS* gene was cloned in 1986 and localized on the short arm of chromosome 19 (Cates et al, 1986). It shows homology with the transforming growth factor-β super family of growth and

differentiation factors (Imbeaud et al, 1995). **PMDS is thought to be a heterogeneous disorder genetically in which some subjects have a defect in the gene for MIS located on chromosome 19p13 and others have a defect in the gene for its type II receptor located on chromosome 12q13** (MacLaughlin and Donahoe, 2004). The condition may occur sporadically or be inherited as an X-linked (or autosomal dominant, sex-limited) trait (Migeon et al, 1994).

The treatment of persistent müllerian duct syndrome is relatively straightforward, in that all patients are phenotypic males who require orchidopexy. The cases of adult patients with associated testis tumor (most commonly seminoma) probably reflect the increased risk of malignancy in intra-abdominal undescended testes. One treatment caveat relates to management of the rudimentary müllerian structures. **The vasa deferentia are in close proximity to the uterus and proximal vagina, and preservation of the necessary müllerian structures to avoid injury to the vasa is recommended to preserve fertility** (Sloan and Walsh, 1976). Although fertility has been reported with this syndrome, only recently has a case of malignancy in retained müllerian structures been reported (Berkmen, 1997; Shinmura et al, 2002).

Unclassified Forms: Mayer-Rokitansky-Küster-Hauser Syndrome

The Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a rare disorder entailing congenital absence of the uterus and vagina. It occurs in approximately 1 of every 4000 to 5000 female births. Patients with MRKH syndrome have a 46,XX karyotype and are normal-appearing females with normal secondary sex characteristics. The external genitalia appear normal, but only a shallow vaginal pouch is present. In the typical form of the syndrome there is symmetrical anatomy with absence of both vagina and uterus. Normal ovaries and fallopian tubes are present, and ovarian function is normal, but only symmetrical uterine remnants are found (Griffin et al, 1976). The recent report of a *WNT4* mutation in a woman with a phenotype resembling MRKH suggests the importance of this gene in müllerian duct formation (Biason-Lauber et al, 2004).

The most common clinical presentation for MRKH syndrome is primary amenorrhea, but patients may present with infertility or dyspareunia. **Upper urinary tract anomalies occur in approximately one third of patients and include renal agenesis, pelvic kidney, and horseshoe kidney.**

Atypical forms of MRKH syndrome have been described in up to 10% of cases, in which asymmetrical uterine remnants and/or aplasia of one or both fallopian tubes is discovered. As a result, endometrial tissue or variable development of the uterus with hematometra may be present, resulting in a clinical presentation with cyclical abdominal pain. **Urinary tract anomalies occur more commonly in patients with the atypical form of MRKH.** In a study of 100 patients with MRKH syndrome, 38 of 56 patients (68%) with the atypical form of the condition had upper urinary tract abnormalities. None of the 44 patients with the typical form of MRKH syndrome had an upper urinary tract anomaly (Strubbe et al, 1994). In addition, associated cardiac anomalies have been noted in 16% of MRKH patients (Pittock et al, 2005).

A radiologic evaluation with ultrasonography and magnetic resonance imaging may define müllerian anatomy accurately in MRKH and distinguish between typical and atypical forms of the disorder (Nussbaum-Blask et al, 1991; Reinhold et al, 1997).

Treatment entails creation of a neovagina, surgically or by means of dilation, to allow for sexual function (Ismail-Pratt et al, 2007). If present, a hemiuterus should be removed, whereas a midline uterine structure should be hormonally suppressed rather than connecting this structure to a reconstructed vagina.

EVALUATION AND MANAGEMENT OF THE NEWBORN WITH AMBIGUOUS GENITALIA

The evaluation and initial management of the neonate with ambiguous genitalia must be regarded as a medical and psychosocial emergency and be handled with great sensitivity toward the family. Ideally, a medical team including a pediatric urologist, an endocrinologist, and a psychiatrist or psychologist experienced in managing intersex patients should work closely with the family. **The team's goal should be to make a precise diagnosis of the disorder (which can be achieved in most cases) and, with the involvement of the parents, to assign a proper sex of rearing based on the diagnosis, the status of the child's anatomy, and the functional potential of the genitalia and reproductive tract.**

In obtaining the history, certain pieces of information may be particularly valuable. A history of infant death within the family might suggest the possibility of CAH, and infertility, amenorrhea, or hirsutism might also suggest possible familial patterns of intersex states. Certainly, maternal use of medications, in particular steroids or contraceptives, during the pregnancy is of great importance.

The critical finding on physical examination is the presence of one or two gonads. This finding effectively rules out overmasculinization of the female. Because ovaries do not descend, a distinctly palpable gonad along the pathway of descent is highly suggestive of a testis. Rarely, an ovotestis undergoes descent to the inguinal canal and may be suspected on the basis of asymmetry of tissue texture of the poles of the gonad. This suspicion may be further supported by ultrasound findings. **The patient with bilaterally impalpable testes or a unilaterally impalpable testis and hypospadias should be regarded as having a DSD until proven otherwise, whether or not the genitalia appear ambiguous.** Kaefer and associates (1999) studied the incidence of DSDs in patients with cryptorchidism and hypospadias and without ambiguous genitalia. **With a unilateral cryptorchid testis, the incidence of DSD was 30% overall—15% if the undescended testis was palpable and 50% if it was impalpable. In the setting of bilateral undescended testes and hypospadias, the incidence of DSD was quite similar—32% overall but only 16% if both gonads were palpable. If one of two undescended testes was impalpable, the incidence of DSD tripled to 47%, comparable to the rate in those with a unilateral, impalpable, cryptorchid testis.** In addition, posterior urethral meatal position was noted to be a strong predictor of DSD in this group of patients—65%, versus 5% to 8% with a midshaft to anteriorly located hypospadiac meatus (Kaefer et al, 1999).

In addition to gonadal examination, penile size should be assessed and an accurate measure of stretched penile length recorded. The mean stretched penile length in full-term males born in the United States is 3.5 cm (± 0.04) (Lee et al, 2006).

An additional important finding on physical examination is the presence of a uterus, which is noted as an anterior midline cordlike structure on rectal examination. **A more precise means of assessing müllerian anatomy is by pelvic ultrasonography, which may be performed immediately in the neonatal period.** In addition to defining müllerian anatomy and confirming the presence or absence of a uterus, the gonads and adrenals should be studied. Normal anatomy of an undescended gonad should be confirmed, and a cyst within the gonad, consistent with ovotestis, should be ruled out.

Within the immediate neonatal period, a karyotype should be obtained. Typically this requires 2 days to perform. Therefore, an attractive approach to obtain chromosomal data quickly is fluorescence in-situ hybridization, which rapidly identifies X and Y chromosomes. It is typically used to confirm the presence of a second X chromosome. The technique is much more rapid than karyotyping, producing results within a few hours.

Serum studies should be immediately sent to rule out a salt-wasting form of CAH. In addition to serum electrolytes, testosterone and DHT should be measured early. Migeon and colleagues (1994) emphasized that the androgen levels may drop quickly, necessitating early study. In addition, they suggested that serum 17-hydroxyprogesterone should not be measured until day 3 or 4 to rule out 21-hydroxylase deficiency, because the stress of delivery may result in physiologic elevation of this steroid precursor in the first 1 or 2 days of life.

In the absence of palpable testes, the presence or absence of testicular tissue should be determined by documentation of a markedly elevated LH, consistent with anorchia, or by means of an hCG stimulation test, which can demonstrate normally functioning testicular tissue (Jarow et al, 1986). In addition to ruling out anorchia, the study can enable diagnosis of 5α-reductase deficiency (by virtue of an increased ratio of testosterone to DHT) and can help distinguish between impaired testosterone synthesis (deficient response to hCG) and androgen insensitivity (normal response to hCG). Serum MIS measurement has been proposed as a reliable marker of the presence of testes (Hughes, 2002).

Key Points: Evaluation and Management of Intersex

- The team's goal should be to make a precise diagnosis of the intersex disorder (which can be achieved in most cases) and, with the involvement of the parents, to assign a proper sex of rearing based on the diagnosis, the status of the child's anatomy, and the functional potential of the genitalia and reproductive tract.
- The patient with bilaterally impalpable testes or a unilaterally impalpable testis and hypospadias should be regarded as having a DSD until proven otherwise, whether or not the genitalia appear ambiguous.

Based on physical examination (largely, gonadal palpability), the presence or absence of müllerian structures on ultrasonography, 17-hydroxyprogesterone concentration, and the karyotype, a reasonable differential diagnosis may be formulated (Fig. 133–24). A precise diagnosis can virtually always be achieved for the 46,XX DSD (overvirilized female) but in only 50% of 46,XY DSD undervirilized males (Lee et al, 2006). The presence of asymmetrical anatomy on examination and ultrasonography is an important observation and suggests mixed gonadal dysgenesis if the karyotype is XY and ovotesticular DSD if it is 46,XX (Fig. 133–25).

Laparotomy or laparoscopy and gonadal biopsy is usually the next definitive clinical step required when a firm diagnosis based

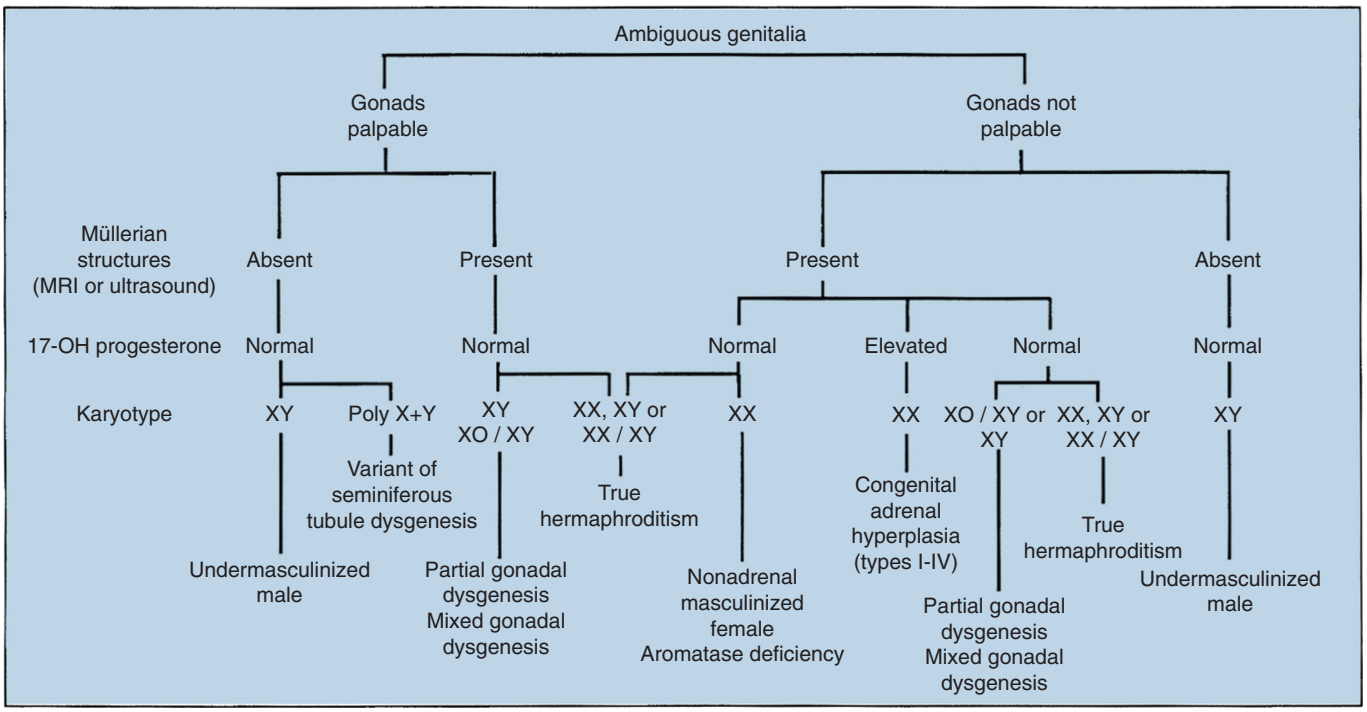


Figure 133–24. Diagnostic algorithm for a newborn with ambiguous genitalia based on gonadal palpability, presence or absence of müllerian structures, 17-hydroxyprogesterone concentration, and karyotype. (Modified from Grumbach MM, Conte FH. Disorders of sex differentiation. In: Wilson JD, Foster DW, editors. Williams textbook of endocrinology. Philadelphia: WB Saunders; 1998. p. 1401.)

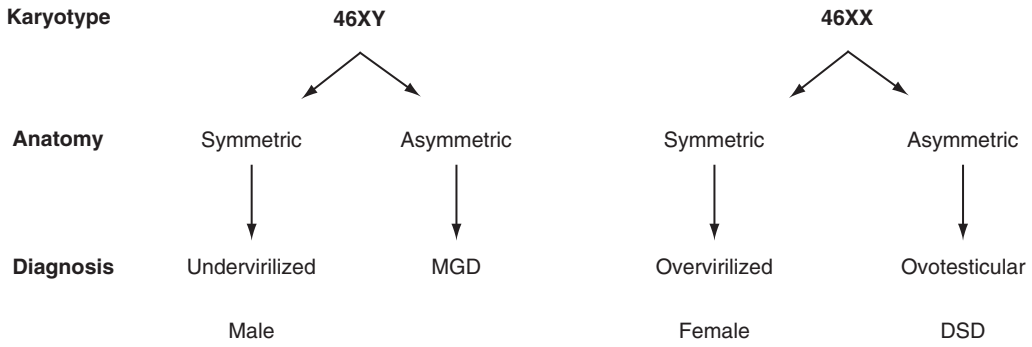


Figure 133–25. Likely diagnoses based on karyotype and anatomic symmetry. DSD, disorder of sex differentiation; MGD, mixed gonadal dysgenesis. (After Donahoe P.)

on the aforementioned data is impossible. **Laparotomy or laparoscopy in this setting remains a diagnostic maneuver; removal of gonads or reproductive organs should be deferred until the final pathology report is available and a gender has been assigned.** PCR characterization of the androgen receptor in venous blood DNA may define the precise genetic abnormality responsible for a given DSD, be it abnormal androgen receptor or an enzyme abnormality. These studies should be performed in specialized laboratories where normal values are well established.

Finally, anatomic definition of the urogenital sinus and ductal structures contributes to the correct diagnosis and is necessary before any surgical intervention. The urogenital sinus is well imaged by retrograde contrast injection, which also opacifies ductal structures, defines the entry of urethra and vagina into the sinus, and outlines the cervical impression within the vagina. Endoscopy can define these relationships further but is usually not necessary until surgical reconstruction becomes imminent.

Gender Assignment

After a definitive diagnosis has been reached, a thorough and candid discussion with the family regarding gender assignment should take place. **Issues related to the diagnosis-specific potential for normal sexual functioning and fertility and the risk of gonadal malignancy should be addressed.** Parents should understand that high-quality data regarding the long-term psychosocial outcomes of gender assignment for the majority of DSDs are lacking, although longitudinal studies are being pursued. Parental involvement in the decision-making process is essential. If the diagnosis of a DSD is made prenatally, it is important to present a plan of management to the parents or risk termination of the pregnancy (Nihoul-Fekete, 2004).

In the setting of a 46,XX karyotype and masculinized female, gender assignment is usually appropriately female. In CAH, cortisol suppresses the undesired androgen; and if maternal androgen is responsible for virilization, its discontinued stimulation is corrective. In both cases there are normal ovaries and müllerian ducts and a normal reproductive potential exists. **If the karyotype is 46,XY, the issue is a more complex one and includes factors such as penile length and evidence of androgen insensitivity.** For example, 46,XY patients with complete (severe) androgen insensitivity are appropriately assigned a female gender, whereas those with 5α-reductase deficiency may be more appropriately assigned a male gender. The most frequent abnormal karyotype is 45,X/46,XY mosaicism, which presents a variable phenotypic spectrum. The degree of masculinization of the external genitalia appears to vary with the amount of testicular tissue present, and gender assignment depends on the functional potential of the gonadal tissue, reproductive tracts, and genitalia. Some investigators have suggested deferring the issue of gender assignment until patients reach an age at which they may declare their own gender identity. Such an approach, although rational, is difficult to implement given cultural norms and not recommended in the consensus statement (Lee et al, 2006). As Elliott (1998) states, "We treat these children the way we do (as male or female) because this is the way we see the world; most importantly it is the way that the children, themselves, are taught to see the world."

Overall, it is well to remember in the management of ambiguous genitalia the parameters of optimal gender policy outlined by Meyer-Bahlburg (1998):

- **Reproductive potential (if attainable at all)**
- **Good sexual function**
- **Minimal medical procedures**
- **An overall gender-appropriate appearance**
- **A stable gender identity**
- **Psychosocial well-being**

Ultimately, management of patients with disorders of sexual differentiation remains a challenging and humbling process. On the one hand, physicians have at their disposal sophisticated molecular biologic techniques that have enabled them to identify genetic disorders responsible for the majority of DSDs. On the other hand, the mysteries of brain dimorphism in the setting of sexual ambiguity remain to be solved to optimize the long-term psychosocial outcome of gender assignment for the individual patient.

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chapter 134

Surgical Management of Disorders of Sexual Differentiation, Cloacal Malformation, and Other Abnormalities of the Genitalia in Girls

Richard C. Rink, MD, FACS, FAAP ● Martin Kaefer, MD, FAAP, FACS

Female Reproductive and Caudal Embryology
Structural Anomalies of the Female Internal Genitalia
Classification of Urogenital Sinus and Cloacal Anomalies
Surgical Reconstruction of Disorders of Sex Development and Urogenital Sinus
Surgical Reconstruction for Cloacal Malformations
Summary

As with all other organ systems, genital development in the female occurs in an orderly fashion through multiple complex steps that result in an anatomically and functionally normal child in the vast majority of cases. However, errors in development can occur, from minor, clinically insignificant disorders to severe abnormalities that are devastating to the child and parents. The abnormalities may affect the external genitalia alone or in combination with internal genital anomalies, and in some they may involve other organ systems. In this chapter normal urogenital and anorectal development is briefly described and then anomalies that arise when abnormal development occurs are discussed. Genital ambiguity is often the initial finding in these disorders. Only reconstruction along female lines is discussed; male reconstruction (i.e., hypospadias, chordee repair, and orchiopexy) is discussed in Chapters 130 and 132.

Genital reconstruction for disorders of sex development (DSD, formerly intersex) at this time is very controversial. Although significant advances in surgical techniques have occurred since Young's early work (1937), well-controlled studies with regard to not just cosmetic results but also functional and psychological results are almost nonexistent. Historically, reconstruction of DSD conditions has been surrounded by secrecy, and decisions have been made without scientific studies and often without the patient's knowledge. Questions regarding genital sensitivity, orgasmic potential, ability for intercourse without pain, gender identity, and psychological aspects in those undergoing early genital surgery currently exist. It is beyond the scope of this chapter to discuss all the pros and cons of this controversy, but it is clear that further studies are warranted.

The recently published "Consensus Statement on Management of Intersex Disorders" from a multispecialty international group has been beneficial, but many questions still remain unanswered (Hughes et al, 2006). It is strongly recommended that physicians honestly discuss with the parents of these children all aspects of care, including options, risks and benefits, and negative aspects of both observation and surgical therapy. Although early surgery has been the norm historically, the option of observation with psychological and peer support should be a realistic proposition (Creighton and Liao, 2004). A team of physicians, including a neonatologist, endocrinologist, geneticist, psychiatrist, psychologist, and pediatric urologist, should work with and for the parents in this decision making process. The formation of a gender assignment team has been shown to allow integrated care and more accurate diagnoses in children with DSD (Parisi et al, 2007). Current surgical techniques that are available should surgical therapy be chosen for a child with DSD are addressed in this chapter, but it must be known that absolute indications are rare (Schober, 2004). Other female genital anomalies not associated with genital ambiguity also are discussed.

FEMALE REPRODUCTIVE AND CAUDAL EMBRYOLOGY

A comprehensive description of genitourinary embryology can be found in Chapters 111 and 133. To foster a deeper understanding of the complex combination of anomalies that can occur in patients with vaginal and cloacal anomalies, a brief review of relevant embryologic events is presented.

The cloaca is an endoderm-lined primordial organ that is first apparent at the beginning of the second week of gestation (Grosfeld, 1996). This structure, which represents a confluence of the primitive hindgut (dorsally) and the allantois (ventrally) just before the fourth week of gestation, receives the mesonephric ductal system. The urorectal septum, which first appears during the fourth week of development, serves to separate the urogenital sinus (ventrally) from the anal canal (dorsally) (Moore and Persaud, 1995). The urorectal septum actually consists of two components. The first is the Tourneux fold, which develops along the coronal plane in the angle between the allantois and the hindgut and grows in a caudal fashion toward the cloacal membrane. As this septum nears the cloacal membrane, infoldings of the lateral walls of the cloaca form Rathke plicae, which coalesce in the coronal midline and form the urorectal septum caudally. By weeks 6 to 7 of development the urorectal septum has fused with the cloacal membrane and divided it into a ventral urogenital membrane and a dorsal anal membrane. The fibromuscular node of tissue that results from contact of the septum with the cloacal membrane serves as a critical insertion site for the perineal muscles and as the dividing point of the primitive cloacal sphincter complex into anterior (urogenital diaphragm) and posterior (external anal sphincter) components. The common ontogeny of these two sphincter complexes explains why the pudendal nerve supplies all of these muscles.

While the urorectal anlage is undergoing division, the developing mesonephric ducts, which have contacted the cloaca, enter the urogenital sinus near the müllerian tubercle (Churchill and Hardy, 1978). An offshoot of the mesonephric duct, the ureteric bud, extends cranially to induce development of the metanephric blastema. The terminal branch point of the ureteral bud from the mesonephric duct is later absorbed into the wall of the urogenital sinus. Proper incorporation of this complex results in the ureters opening at the lateral aspect of the trigone.

During this critical phase of cloacal development, paired müllerian ducts, which form from the coelomic epithelium, develop lateral to the mesonephric ducts and cross medially to fuse in the midline. The close proximity of these two ductal systems helps explain the common association of paramesonephric abnormalities and ipsilateral renal anomalies. The paired müllerian ducts then proceed caudally to join the urogenital sinus, where they produce an elevation called the müllerian tubercle. The caudal fusion of portions of these ducts normally leads to dissolution of the shared midline partition and the formation of a common uterovaginal canal, which as the name implies, gives rise to the uterus, cervix, and proximal two thirds of the vagina. Failure of septal regression can result in a number of possible müllerian duct abnormalities.

As first delineated by Koff in 1933, contact of the uterovaginal primordium with the urogenital sinus forms the müllerian tubercle, which in turn induces the formation of paired caudal endodermal outgrowths called sinovaginal bulbs. Evidence suggests that these outpouchings may in fact represent the terminal segments of the wolffian ducts (Bok and Drews, 1983). Regardless of origin, the cells within these sinovaginal bulbs then proliferate to form a cord of tissue that develops into a distal vaginal plate, which is later canalized in a caudal-to-cranial direction to form the distal aspect of the vagina (Fig. 134–1). The portion of the urogenital sinus distal to the müllerian tubercle subsequently undergoes exstrophy and everts to become the vestibule. As a result of this process, the urethra and vagina acquire separate openings in the vulva. The lumen of the vagina is separated from the cavity of the urogenital sinus by the hymen, an invagination of the posterior wall of the urogenital sinus. Rupture of the hymen should occur during the perinatal period.

Various cystic structures may form along the luminal aspect of the vagina. Remnants of the prostatic ductal system and the wolffian duct give rise to the paraurethral glands of Skene and Gardner, respectively. Outgrowths from the urogenital sinus form the greater vestibular glands of Bartholin, which are homologues of the bulbourethral glands in the male.

Key events in skeletal formation occur concurrently with cloacal division and proper formation of the mesonephric and paramesonephric ductal systems (Churchill and Hardy, 1978). The vertebrae develop in a craniocaudal direction, with the lower extremity limb buds developing from condensation of somites 25 through 29. These somites undergo critical differentiation from the fourth through the eighth weeks of development.

From the foregoing brief description of caudal embryology it should be evident that a disturbance in segmentation at the level of the caudal somites when the fetus is less than 10 mm in size (fourth to fifth weeks of human development) can affect many different organ systems. In 1960, Duhamel described the association of these "coincidentally" occurring congenital malformations

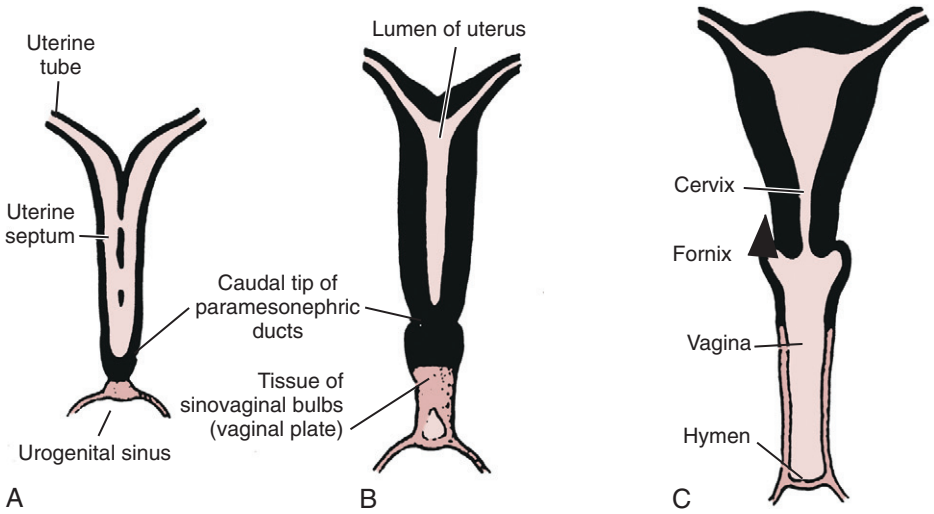


Figure 134–1. **A** to **C,** Formation of the vagina from the sinovaginal bulbs. (From Saler TW. Langman's medical embryology. 6th ed. Baltimore: Williams & Wilkins; 1990.)

and introduced the term *caudal regression syndrome* (Duhamel, 1961). Laboratory data with teratogens support the concept that a key event occurs between the fourth and fifth weeks of gestation that results in an error in the simultaneous development of the terminal bowel, kidney, bladder, paramesonephric ductal system, and lumbosacral spine (Mesrobian and Sessions, 1994). The actual inciting event remains unclear, although disordered mesodermal migration, reduced cellular proliferation, and premature apoptosis have all been proposed as potential mechanisms (Kallen and Winberg, 1974; Alles and Sulik, 1993). Elements of the caudal regression syndrome are seen with increased frequency in infants of diabetic mothers, but the exact mechanism is still in question (Deuchar, 1978; Lynch et al, 1995). Specific gene deletions in the homeobox region of the mammalian genome (the region critical for proper mammalian spatial orientation and segmentation) have been shown to result in a constellation of anatomic findings, as predicted by Duhamel (Warot et al, 1997). Because differentiation of the somites progresses in a cranial-to-caudal direction, it would follow that the most complex anomalies (higher anorectal malformations) would occur as a result of aberrations at an earlier stage of development. This also helps explain the greater association of severe upper urinary tract malformations, internal genital duct abnormalities, and spinal anomalies in these patients than in those with less severe cases of imperforate anus.

Mesodermal disturbances are not limited to the caudal somites. As seen in the VATER (*V*ertebral defects, *A*nal atresia, *T*racheoesophageal fistula with *E*sophageal atresia, and *R*adial and renal dysplasia) and MURCS (*MÜ*llerian duct aplasia, *R*enal aplasia, and *C*ervicothoracic *S*omite dysplasia) associations, mesodermally derived organs as cranial as the C1 vertebra and tracheoesophageal anlagen can be affected in association with congenital abnormalities of the mesonephric and paramesonephric ductal systems (Quan and Smith, 1973; Duncan et al, 1979).

Key Points: Embryology

- The close proximity of the mesonephric and paramesonephric ductal systems helps explain the common association of paramesonephric abnormalities and ipsilateral renal anomalies.
- The proximal part of the vagina forms from the paired müllerian ducts, whereas the distal portion forms from proliferating cells in the sinovaginal bulbs that later canalize.

STRUCTURAL ANOMALIES OF THE FEMALE INTERNAL GENITALIA

Anomalies of the female reproductive system can be grouped into three main categories: (1) those resulting from either hypoplasia or agenesis, (2) those caused by vertical fusion (canalization abnormalities resulting from abnormal contact of the müllerian structures with the urogenital sinus), and (3) those resulting from lateral fusion (duplication). The clinical manifestations, physical findings, evaluation, and subsequent therapy vary considerably among these groups. Radiographic imaging is of central importance in determining the correct diagnosis. Ultrasonography is helpful not only in identifying the genital anatomy but also in screening for associated upper urinary tract abnormalities (Rosenberg et al, 1986; Fernandez et al, 1996). Magnetic resonance imaging (MRI) is considered by many to be the "gold standard" for defining internal müllerian anatomy (Fedele et al, 1996; Russ et al, 1997; Lang et al, 1999). It is especially useful for determining the presence or absence of the cervix and the presence of functioning endometrium in complex anomalies. In complicated cases, additional information can be obtained by examination under anesthesia, vaginoscopy, hysteroscopy, and laparoscopy (Major et al, 1997). Obstructive anomalies typically require immediate intervention, but nonobstructive anomalies often do not require surgical intervention unless the patient has reached reproductive age and the condition affects intercourse or adversely affects fertility. Various systems have been proposed for the classification of these anomalies, with the system proposed by the American Society for Reproductive Medicine being the most inclusive (American Fertility Society, 1988).

Obstructive Genital Anomalies

Abnormalities of Vertical Fusion

Transverse Vaginal Septum. **Transverse vaginal septa are believed to arise from a failure in fusion or canalization (or both) of the urogenital sinus and müllerian ducts.** The estimated incidence of transverse vaginal septum is 1 in 70,000 females (Banerjee and Laufer, 1998). Many of the patients have amenorrhea and a distended upper vagina. **A complete transverse vaginal septum may be located at various levels in the vagina, but there is a higher frequency in the middle and upper third of the vagina.** In one large series the distribution was 46% in the upper vagina, 40% in the middle vagina, and 14% in the lower vagina (Fig. 134–2) (Lodi, 1951). The septa are usually less than 1 cm thick and frequently have a small central or eccentric perforation (Suidan and Azoury, 1979). Even in cases in which a perforation is present, significant obstruction and ascending infection can occur.

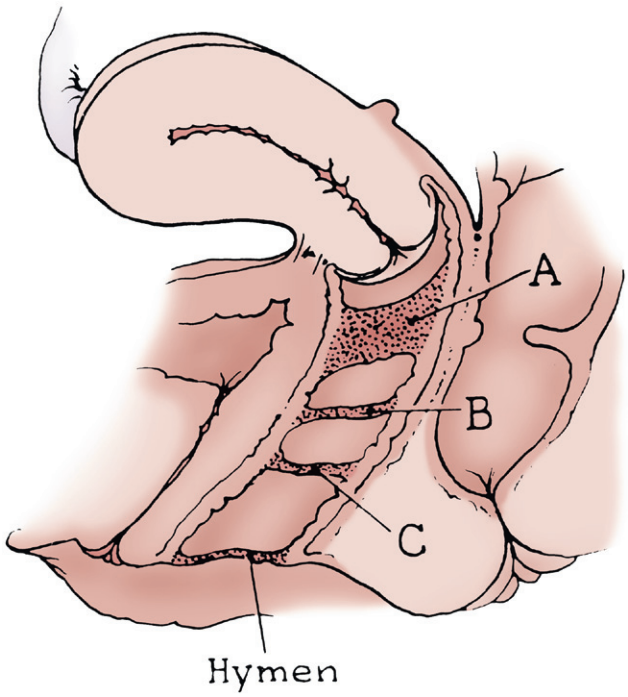


Figure 134–2. Transverse vaginal septum: A, high (upper vagina); B, middle; C, low. (From Yerkes EB, Rink RC. What urologists should know about pediatric gynecologic abnormalities. Contemp Urol 2002;14:12.)

Transperineal, transrectal, and abdominal ultrasonography and MRI may be beneficial in establishing the diagnosis and determining the location and thickness of a transverse vaginal septum (Ammann et al, 1983; Doyle, 1992; Meyer et al, 1995; Caloia et al, 1998; Fedele et al, 1999; Lang et al, 1999). MRI can help determine whether a cervix is present so that a high septum can be differentiated from congenital absence of the cervix. Failure to differentiate between these diagnoses can result in significant patient morbidity (Casey and Laufer, 1997).

Several surgical treatment modalities have been developed to treat congenital transverse vaginal septa. If the patient's pain from hematocolpos is manageable, surgery may be delayed with suppression of endometrial activity by a GnRH agonist or continuous oral contraceptives (Beyth et al, 2004). This may allow time for dilatation of the lower vaginal segment, potentially improving the ease of surgical repair. Techniques include simple incision (Brenne et al, 1965; Buttram, 1983), surgical excision of the septum followed by approximation of the corresponding portions of the transversely cut edges of the upper and lower mucosal membranes of the septum (Rock et al, 1982) and the use of Z-plasties involving vaginal mucosa (Wierrani et al, 2003). Vaginal stenosis at the site of resection is the most common complication (Joki-erkkila and Heinonen, 2003). The primary advantage of a Z-plasty is that as the suture line contracts the incision is more likely to take on a longitudinal rather than a transverse orientation. Placement of a vaginal mold subsequent to surgery has been reported to further reduce the risk of postoperative stenosis (Bijsterveldt and Willemsen, 2009). Characteristics of molds for transverse septa are different than those used after a McIndoe vaginoplasty (see later). Whereas a solid mold may be used after a vaginoplasty skin graft (because there is no uterus), the mold used after resection of a transverse septum is ideally hollow to allow egress of menstrual flow.

Vaginal Atresia (Distal Vagina). **Vaginal atresia occurs when the urogenital sinus fails to contribute to formation of the lower (distal) portion of the vagina. This condition differs from vaginal agenesis and testicular feminization in that the müllerian structures are not affected. As a result, the uterus, cervix, and upper portion of the vagina are normal.** A very shallow dimple caudal to the urethral opening may be appreciated on physical examination. Palpation of a distended vagina on rectal examination may help distinguish this condition from testicular feminization or vaginal agenesis. Radiographic evaluation in the form of ultrasonography or MRI, or both, is mandatory to adequately define the müllerian anatomy before intervention.

Surgical correction consists of a transverse incision at the level of the hymenal ring. Dissection is carried out through the fibrous area of the absent lower vagina until the upper vagina is reached. As in treatment of a transverse vaginal septum, distention of the vagina with retained menstrual blood products can prove extremely beneficial in that it acts as a tissue expander. After the obstruction is drained and the vaginal mucosa is identified, a pull-through procedure can be performed to bring the distended vagina down to the introitus. The distance to bridge between the vagina and the perineal surface can almost always be successfully managed with perineal skin flaps or simple mobilization of the vagina (or both). Ramenofsky and Raffensperger (1971) described a combined abdominoperineal approach that can be of help in exposing and anastomosing the distal vagina to the perineal skin.

Vaginal Agenesis (Müllerian Aplasia). Vaginal agenesis, which occurs at an incidence of approximately 1 in 5000 live female births, is congenital absence of the proximal portion of the vagina in an otherwise phenotypically (i.e., normal secondary sexual characteristics), chromosomally (i.e., 46,XX), and hormonally (i.e., normal levels of luteinizing hormone and follicle-stimulating hormone) intact female (Bryan and Nigro, 1949; Griffin et al, 1976). Although Realdus Columbus is credited by some authors as the first to describe a case of vaginal agenesis, Mayer was one of the first to report vaginal agenesis in stillborn children (Mayer, 1829; Lesavoy, 1985). In 1838, Rokitansky reported 19 adult autopsy cases of uterovaginal agenesis, including 3 with associated unilateral renal agenesis. In 1910, Küster recognized urologic associations, such as renal ectopy and agenesis, along with skeletal deformities. Hauser and Schreiner (1961) brought further attention to the frequent association of renal and skeletal anomalies in these patients and stressed the differences between patients with these findings and those with testicular feminization.

The Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, as the entity of müllerian aplasia has come to be known, results from failure of the sinovaginal bulbs to develop and form the vaginal plate (Fig. 134–3). This may be caused by improper induction of the sinovaginal bulbs from the neighboring uterovaginal primordium. Chronologically, the uterovaginal canal develops at a point in embryogenesis during which other critical mesodermally derived organ systems are also forming, which in part explains the many associated findings. Müllerian aplasia has also been associated with maternal deficiency of galactose-1-phosphate uridyltransferase (Cramer et al, 1996). In contrast to vaginal atresia, the hymenal fringe is usually present along with a small vaginal pouch because they are both derived embryologically from the urogenital sinus.

Most patients with MRKH syndrome are initially evaluated by the physician after the expected age of menarche because of primary amenorrhea. This syndrome is in fact second only to gonadal dysgenesis as a cause of primary amenorrhea. A minority of patients have cyclic abdominal pain caused by retention of menstrual blood in the uterus. Physical examination reveals absence of the vagina. Inguinal hernia is less common in this disorder than in the testicular feminization syndrome (Schmid-Tannwald and Hauser, 1973). The karyotype is that of a normal 46,XX woman. Radiographic evaluation is indicated to more fully delineate remnant müllerian structures and search for associated anomalies involving the renal and skeletal systems.

Associated Findings. MRKH syndrome is associated with variable absence or hypoplasia of the cervix, uterus, and fallopian tubes. In approximately 10% of patients, a normal but obstructed uterus or a rudimentary uterus with functional endometrium is present (Murray and Gambrell, 1979; Singh and Devi, 1983; Bates and Wiser, 1985). In one of the largest single series to date, Salvatore and Lodovicci (1978) reported that of 91 patients with vaginal agenesis, almost 25% lacked a uterus, 55% had a solid rudimentary uterus, and the remaining 30% had other abnormalities of this organ. In addition, they demonstrated that although the fallopian tubes were normal in 32% of cases they were rudimentary in almost 50% and completely absent in 10%. Although occasionally cystic, the ovaries were almost always present and functional (Salvatore and Lodovicci, 1978). **It was subsequently recognized, based on the morphology of the retained müllerian structures, that MRKH syndrome could be divided into typical and atypical forms (Schmid-Tannwald and Hauser, 1977).**

In the typical form of MRKH syndrome (type A), the patient has symmetrical uterine remnants and normal fallopian tubes. The atypical form (type B) is characterized by asymmetrical uterine buds or abnormally developed fallopian tubes. This distinction is important

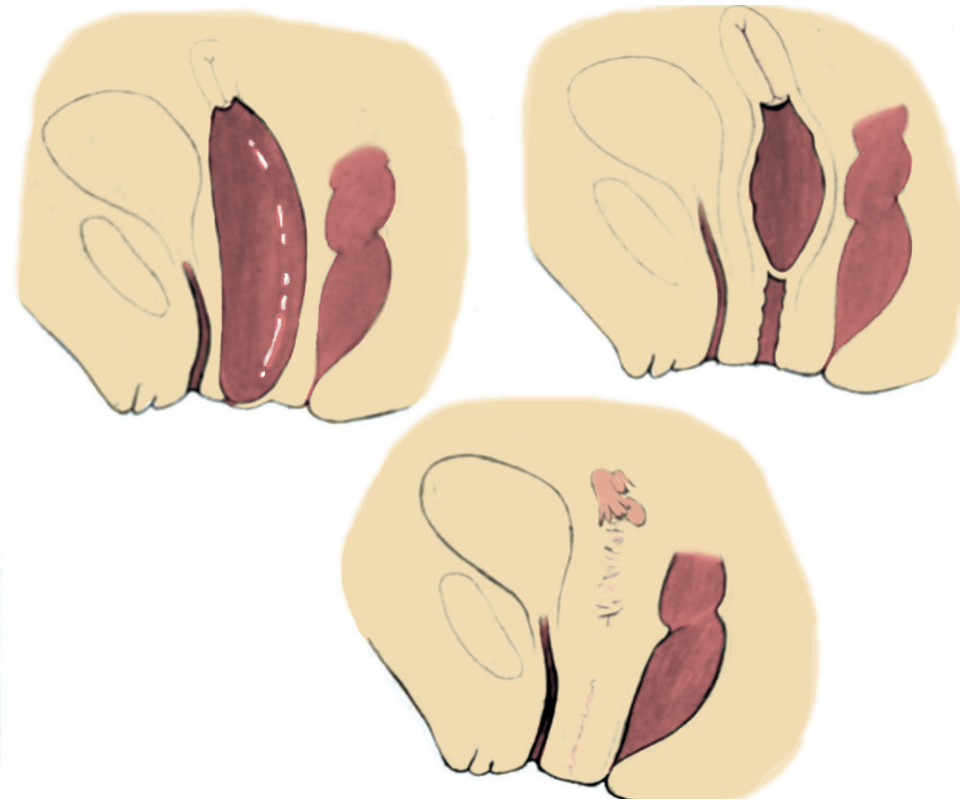


Figure 134–3. Forms of vaginal obstruction. *Upper left,* Imperforate hymen; *upper right,* transverse vaginal septum; *lower,* vaginal agenesis. (From Yerkes EB, Rink RC. What urologists should know about pediatric gynecologic abnormalities. Contemp Urol 2002;14:12.)

because the overwhelming majority of associated findings in other organ systems have been reported to be present with the atypical form whereas in the typical form these findings are usually absent (Strubbe et al, 1992, 1993).

The association between vaginal agenesis and developmental abnormalities of the kidney was first recognized by Rokitansky (1838). Approximately a third of patients are found to have abnormal renal findings on intravenous pyelography or ultrasound examination (Strubbe et al, 1993). Renal anomalies are present almost exclusively in patients with the atypical subtype of vaginal agenesis (type B). In Strubbe's series, 34 of 51 patients with type B anatomy had renal anomalies, but none of the 40 patients with type A (symmetrical) anatomy demonstrated such a deformity (Strubbe et al, 1993). A meta-analysis published by Griffin and associates (1976) demonstrated that the renal anomaly consists of either unilateral renal agenesis or ectopia of one or both kidneys in 74% of those affected. The close proximity of the mesonephric and paramesonephric structures during the early phase of fetal development is thought to be the reason for this frequent association of renal anomalies. Not surprisingly, the converse is also true: the incidence of associated genital abnormalities in female patients with renal anomalies ranges between 25% and 89% (Thompson and Lynn, 1966).

Associated congenital abnormalities of the skeletal system have been described in 10% to 20% of cases (Turunen, 1967; Willemsen, 1982; Strubbe et al, 1987). Congenital fusion (failure of segmentation) of the cervical vertebrae is known as the Klippel-Feil syndrome and occurs approximately once in 30,000 to 40,000 live births (Gunderson et al, 1967). An association between this abnormality of cervical somite development and vaginal agenesis was first recognized by Duncan (1977). He proposed the term *MURCS association* to describe the combination of *MÜ*llerian duct aplasia, *R*enal aplasia, and *C*ervicothoracic *S*omite dysplasia, which many believe is caused by a generalized disordered development of mesodermal differentiation during the fourth week of fetal life (Duncan et al, 1979). Strubbe demonstrated that the Klippel-Feil abnormality was found only in patients with the atypical form of MRKH syndrome (type B). Additional, albeit less common skeletal abnormalities include scoliosis and abnormalities of the hands and face (Willemsen, 1982; Fisher et al, 2000). Unlike müllerian anomalies that are associated with abnormal cloacal septation, vaginal agenesis is not associated with an increased incidence of

Key Points: Structural Anomalies of the Female Genitalia

- Anomalies of the female reproductive system can be grouped into three main categories, those resulting from (1) hypoplasia or agenesis, (2) vertical fusion, and (3) lateral fusion.
- Transverse vaginal septa are believed to arise from a failure in fusion or canalization (or both) of the urogenital sinus and müllerian ducts.
- Vaginal atresia occurs when the urogenital sinus fails to contribute to formation of the lower (distal) portion of the vagina.
- Vaginal agenesis is congenital absence of the proximal portion of the vagina in an otherwise phenotypically, chromosomally, and hormonally intact female.
- MRKH syndrome, as the entity of müllerian aplasia has come to be known, results from failure of the sinovaginal bulbs to develop and form the vaginal plate.

lumbosacral spinal disorders or occult spinal dysraphism (Gunderson et al, 1967).

Creation of a Skin Neovagina. Both nonoperative and operative treatment options exist for this anomaly. Regardless of the method used, it can be very helpful to have the patient speak with someone who has previously undergone treatment before treatment is initiated (Ingram, 1981). **The nonoperative approach, initially popularized by Frank** (1938), **involves gentle pressure of graduated hard dilators against the perineal surface to create a progressive invagination of the vaginal dimple.** Ingram (1981) modified this technique by using a bicycle seat mounted on a stool. The nonoperative approach has greatest success when a vaginal dimple or pouch is already present (Williams et al, 1984, 1985). Gargollo and colleagues (2009) recently reported their experience with 69 females (mean 17.5 years) with vaginal agenesis treated with progressive perineal dilation. Success, defined as the ability to achieve sexual intercourse, vaginal acceptance of the largest dilator without discomfort, or a vaginal length of 7 cm, was achieved in 88% of patients. The authors concluded that progressive perineal dilation should be offered as first-line therapy in adolescents with congenitally absent vagina.

Modifications of the Frank technique of perineal pressure have been developed that incorporate the surgical placement of tension sutures to aid in directing pressure from a Plexiglas dilator against the vaginal dimple (Vecchietti, 1979). The mold, often referred to as an "olive," has sutures attached to it that are guided in a cranial direction through the vesicorectal space into the perineal cavity and brought out through the abdominal wall (Vecchietti technique). Tension is progressively increased via the abdominal wall sutures until sufficient vaginal length has been achieved. To avoid a formal laparotomy, laparoscopic techniques have been described to assist in dissection of the tissue plane for the Vecchietti technique (Borruto, 1992; Gauwerky and Wallwiener, 1992; Fedele et al, 1996, 1999; Brucker et al, 2008). In Fedele and colleagues' more recent series, all patients were found to have healthy vaginal mucosa, with the average vaginal length being almost 8 cm at 3 months. This technique has had limited use by urologists.

If the Frank method has been unsuccessful or is not accepted as a reasonable option by the patient or parents, creation of a functional vagina can be achieved by one of several techniques (Abbé, 1898; McIndoe and Banister, 1938; Hendren and Atala, 1994). **The first landmark advance in vaginal reconstruction is attributed to Abbé in 1898. Abbé described dissecting a canal between the rectum and urethra and lining this area with split-thickness skin grafts. This method was later popularized by McIndoe, and the procedure that bears his name has gained wide acceptance in the United States** (McIndoe and Banister, 1938). Preoperative preparation consists of full mechanical and antibiotic bowel preparation. A split-thickness skin graft is taken from the buttocks (0.018 to 0.022 inch) and tubularized over a stent (Fig. 134–4). A transverse incision is made at the level of the perineal dimple, and the potential space between the urethra and the rectum is carefully dissected up to the level of the peritoneal reflection. The graft and mold are then inserted into the potential space, and the labia minora are sutured around the stent to prevent extrusion during the initial healing phase (McIndoe, 1950). Many types of vaginal stents have been used for this purpose, including packed gauze, wood covered with a condom, silicone foam, acrylic, various metals, and an inflatable vaginal stent (Concannon et al, 1993; Chen, 1994; Barutcu and Akguner, 1998). The Foley catheter is replaced by a suprapubic catheter, and postoperatively the patient



Figure 134–4. McIndoe skin vagina sewn over a vaginal stent.

is kept at strict bed rest for 1 full week. A high incidence of postoperative vaginal stenosis necessitates postoperative vaginal dilation (Ingram, 1981). Excellent patient satisfaction has been reported in most large series (Martinez-Mora et al, 1992; Strickland et al, 1993; Alessandrescu et al, 1996).

Other options for creation of a neovagina with local tissues include the use of full-thickness skin grafts from the buttocks or full-thickness skin flaps based on the labia majora. Those who champion the use of full-thickness skin grafts report a lower incidence of graft contracture than when split-thickness graft techniques are used (Sadove and Horton, 1988). The Williams vaginoplasty involves the creation of a vaginal pouch from the labia majora (Williams, 1964). The combination of this procedure and Frank-type dilation along the vaginal axis can provide a satisfactory result.

Many other surgical procedures have been developed for creation of a functional neovagina with various muscle flaps (e.g., pudendal thigh, rectus abdominis, buttock) (McCraw and Massey, 1976; Lilford et al, 1989; Dumanian and Donahoe, 1992; Wang and Hadley, 1993; Joseph, 1997). The pelvic peritoneum and human amnion are two other donor sites that have been used to create a neovagina (Davydov, 1977; Ashworth et al, 1986; Morton and Dewhurst, 1986; Tamaya and Imai, 1991; Marquis et al, 2008).

Creation of an Intestinal Neovagina. Baldwin first described the use of bowel for creation of the vagina in 1907. The procedure involved anastomosis of a U-shaped segment of sigmoid colon to the perineum with subsequent division of the intervening septum (Hensle and Dean, 1992). Additional experience with this technique was reported by Fall in 1940, but it did not gain widespread acceptance until the 1970s because of high patient morbidity and mortality (Fall, 1940; Pratt, 1972). Subsequent improvements in technique and postoperative care resulted in renewed enthusiasm for these techniques (Turner-Warwick and Kirby, 1990; Hendren and Atala, 1994; Hensle and Reiley, 1998; Tillem et al, 1998). Sigmoid, cecum, and small intestine have all been used successfully for the creation of a functional neovagina.

The day before surgery, the patient undergoes full mechanical and antibiotic cleansing of the alimentary tract. The procedure is performed with the patient supine, the legs spread, and the knees bent (frog-leg position). In an older child, Allen stirrups can be used. For a sigmoid vaginoplasty, the intra-abdominal portion of the procedure begins by first identifying an appropriate length of distal sigmoid with a blood supply that will comfortably reach the perineum (Figs. 134–5 and 134–6). The distal end of the proposed segment is then divided and anastomosed to the perineum (Fig. 134–7). An intervening segment of sigmoid (approximately 3 cm) is then excised to create a space between the oversewn proximal edge of the bowel vagina and the end of the sigmoid, which is

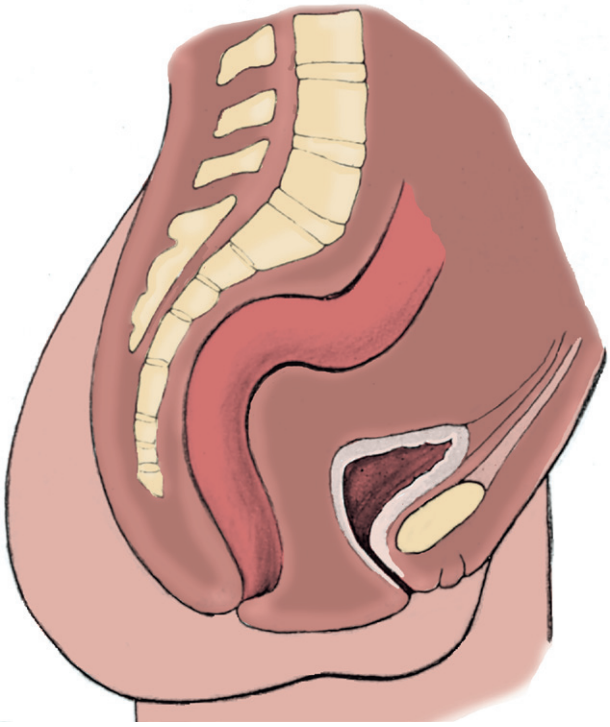


Figure 134–5. Vaginal agenesis.

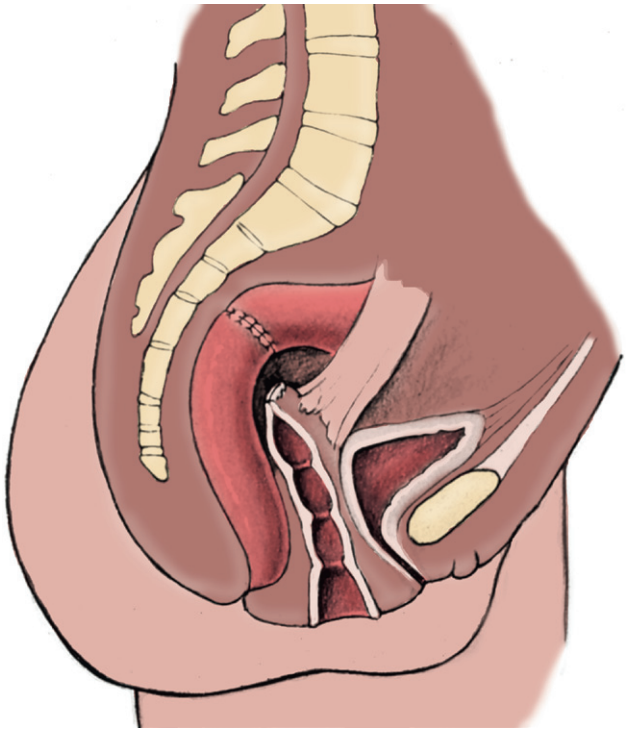


Figure 134–6. Bowel vagina: colonic segment sewn in place.

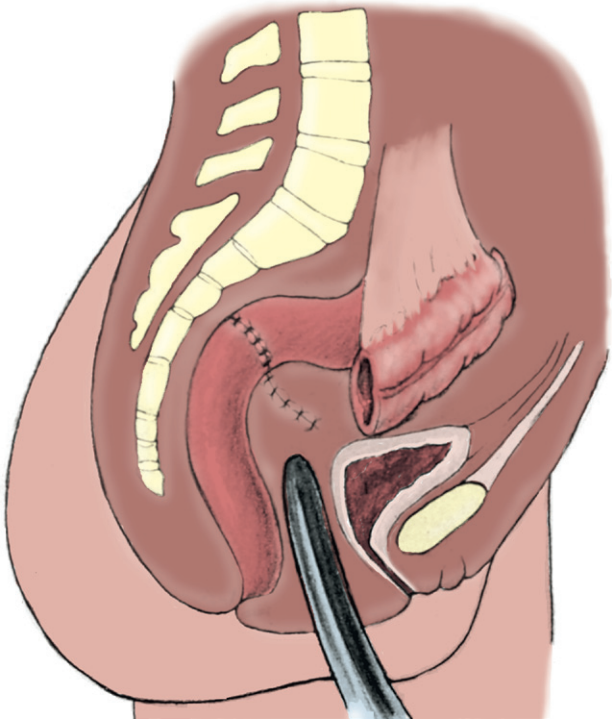


Figure 134–7. Bowel vagina: harvest of a colonic segment and creation of vaginal space.

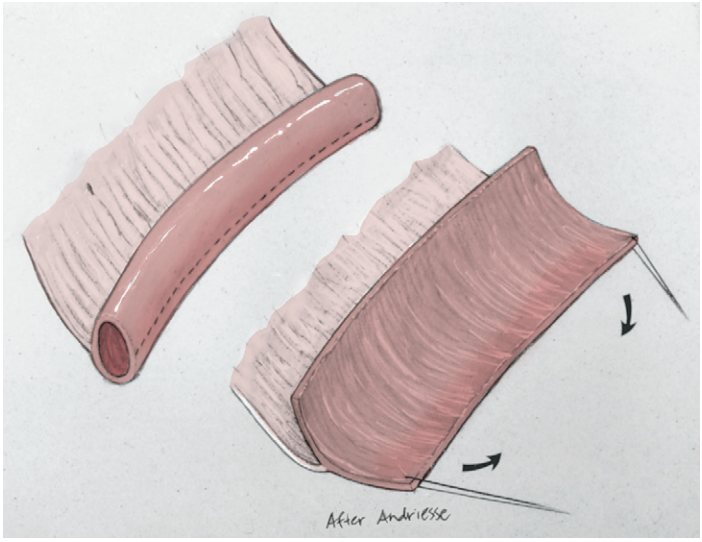


Figure 134–8. Bowel vagina: harvest of an ileal segment.

anastomosed to the rectum. This maneuver prevents an overlap of suture lines and thereby has the potential advantage of limiting the incidence of fistula formation. The bowel vagina is thereafter fixed to the posterior peritoneum to prevent prolapse. Gosalbez has recently described a modified Monti technique of bowel detubularization for vaginal replacement that can aid in allowing the segment to reach the perineum. By opening the colonic segment close to its mesentery along one side of the bowel and then retubularizing in a Heineke-Mikulicz fashion as described by Monti, the reconfigured segment allows for the mesentery to be located at the most cranial end of tube and allows the caudal end to extend more distally (Gosalbez, 2009).

Although the authors have had the most success with the sigmoid, a small-bowel segment may be chosen with a vascular pedicle that is of adequate length to reach the perineum. After isolating an appropriate length of ileum and reestablishing bowel continuity, the segment is detubularized and reconfigured in a conical arrangement to provide increased internal diameter (Figs. 134–8 and 134–9) (Hendren and Atala, 1994). The segment is then brought down to the perineum and sewn in place, as for a sigmoid

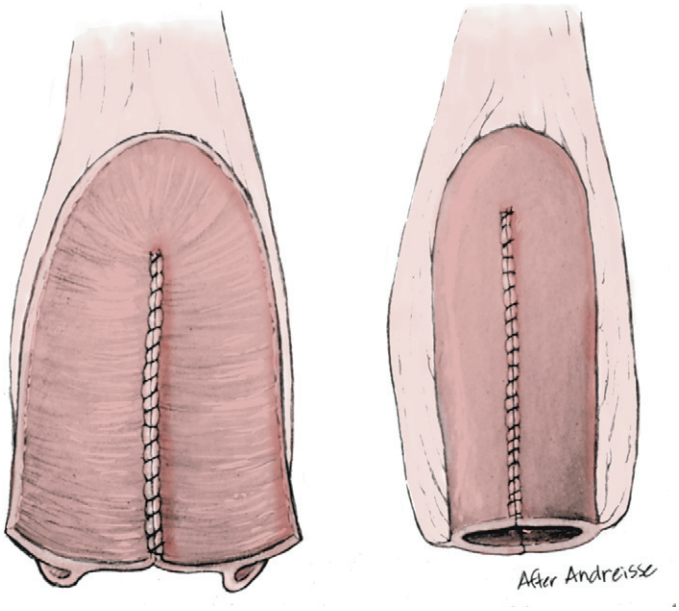


Figure 134–9. Bowel vagina: reconfiguration of the ileal segment to create a larger luminal diameter.

neovagina. To avoid a formal laparotomy, laparoscopically assisted techniques have been described for harvest and delivery of the bowel segment to the perineal location (Ota et al, 2000).

If there is a perineal dimple (i.e., the segment of vagina contributed by the urogenital sinus is present), the bowel segment should be anastomosed directly to it. When a direct perineal anastomosis is required, it is of critical importance to create a large enough space between the rectum and bladder to avoid compromise of the intestinal blood supply. Creation of such a space can be facilitated by the use of progressively larger Hegar dilators. Gentle passage of the intestinal segment into position is facilitated by placing the segment in a large lubricated Penrose drain before transfer to the perineum.

The functional results of bowel vaginoplasty have been excellent. Of the 65 patients reported by Hendren, 16 experienced mild eversion of the bowel segment, which in every case was amenable to simple trimming. Eight patients experienced mild stenosis that was later corrected by appropriate Z-plasties to increase the circumference of the mucocutaneous junction (Hendren and Atala, 1994). **Patient satisfaction is high, and the majority of patients who are old enough to engage in sexual relations are able to achieve adequate coitus** (Hensle and Reiley, 1998).

Stenosis has been reported more frequently after the use of ileum (Hensle and Dean, 1992). **This higher stenosis rate may be due not only to the more narrow ileal lumen but also to the limited mobility of the small bowel mesentery.** As a result, the authors and others believe that large intestine is the bowel segment of choice. Two specific indications for use of an ileal segment for bowel vaginoplasty are previous irradiation of the deep pelvis and the absence of large intestine (i.e., cloacal exstrophy). When ileum is used, various methods of reconfiguration can be used to increase the diameter (Hendren and Atala, 1994). Advantages of a bowel vagina over the McIndoe procedure include the lubricating properties of mucus (which may help facilitate intercourse) and the decreased incidence of postoperative contracture (and hence the reduced need for postoperative dilatation). Disadvantages include the frequent need to wear pads because of the chronic vaginal discharge. Daily douching may be necessary to evacuate the mucus. Finally, the potential transmission of blood-borne pathogens such as hepatitis and human immunodeficiency virus may be increased (in comparison to a squamous epithelium-lined vagina) because of the poor barrier effect of the gastrointestinal tract.

All patients undergoing creation of a functional vagina with perineal skin require annual examination because there have been reports of condylomata acuminata and squamous cell carcinoma involving grafts (Duckler, 1972; Rotmensch et al, 1983; Buscema et al, 1987). Annual examination of the bowel vagina is also indicated because adenocarcinoma has been identified after this procedure (Andryjowicz et al, 1985).

The optimal timing of surgery remains a source of debate. The majority of surgeons who favor the McIndoe procedure for construction of a neovagina believe that it is better to wait until adulthood to perform the procedure because a degree of maturity is required to consistently perform daily dilatations. Many surgeons who favor the use of bowel for neovaginal reconstruction do not believe that vaginoplasty should be deferred until the patient reaches adulthood. Hendren and Atala (1994) believe that delaying creation of a neovagina until adulthood may be psychologically traumatic to a young girl. The authors have based timing on the underlying diagnosis and need for a neovagina.

Special Considerations: Cervical Atresia. Cervical agenesis is an uncommon disorder that is associated with symptoms common to other obstructive entities of the female reproductive tract (i.e., primary amenorrhea, cyclic or chronic abdominal pain). **Failure to establish the correct diagnosis and thereby choose the appropriate method of surgical intervention can be fraught with disaster and possible patient mortality.** MRI is the most useful radiographic modality in establishing this diagnosis (Fig. 134–10). In many circumstances the patient is best served by hysterectomy with subsequent vaginal replacement by one of the previously described techniques (Rock et al, 1984; Cukier et al, 1986). Successful direct anastomosis of the neovagina to the uterine remnant has been reported. Deffarges and coworkers (2001), in describing their experience with uterovaginal anastomosis, reported a 40% pregnancy rate in patients attempting to conceive. Cerclage was performed in only one case. All deliveries were by cesarean section. **Although this procedure appears to be successful in the majority of cases, absence of the normal endocervical barrier can leave the patient predisposed to the development of life-threatening ascending infection** (Maciulla et al, 1978; Niver et al 1980; Casey and Laufer, 1997).

Key Points: Vaginal Replacement Surgery

- The McIndoe procedure (skin neovagina) is associated with a higher incidence of postoperative vaginal stenosis than a bowel neovagina.
- Vaginal stenosis after creation of an intestinal neovagina is more common with ileum than with large bowel.
- Vaginal reconstruction extending from the perineum to the uterus should be avoided in patients with cervical agenesis (because of the potential life-threatening complication of ascending bacterial infection).

In cases in which it has not been possible to successfully achieve continuity between the uterus and vagina, in-vitro fertilization plus transmyometrial embryo transfer has been performed, with

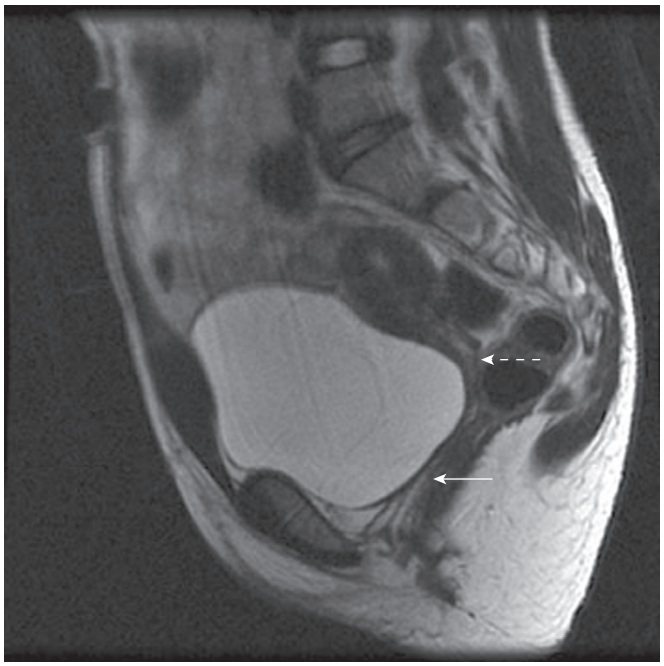


Figure 134–10. MR image of the pelvis in a 12-year-old girl with Klippel-Feil syndrome and associated proximal vaginal and cervical atresia. The *solid arrow* points to the most cranial portion of the perineal vaginal pit. The *dashed arrow* points to the most inferior aspect of the uterus, where no cervical impression can be appreciated.



Figure 134–11. Genitogram of complete müllerian duplication (septated vagina and separate uteri).

subsequent delivery of a healthy fetus by cesarean section (Anttila et al, 1999; Lai et al, 2001). If this option is considered, hormonal blockade of the endometrium until the time at which the patient desires to initiate a pregnancy is indicated to minimize discomfort and reduce the incidence of endometriosis from retrograde menstrual flow in the fallopian tubes.

Abnormalities of Lateral Fusion

Most abnormalities of lateral fusion have no functional significance. With the exception of those with uterus didelphys and unilateral vaginal obstruction, most patients are asymptomatic. Although an exhaustive description of the defects of lateral fusion is beyond the scope of this chapter, some general comments can be made.

True duplication of the uterus is a rare event. This anomaly results from duplication of the müllerian ducts and subsequent doubling of the reproductive structures on one or both sides. The much more frequently encountered anomaly of uterine didelphys consists of two separate uterine cavities and cervices as a result of failed resorption of the common medial wall of the paired müllerian duct structures during development. Although up to 75% of patients also have a septate vagina, most have adequate reproductive outcomes and do not require surgical intervention. If later in life the patient experiences difficulty with intercourse, vaginal delivery, or the need to use two tampons, surgical excision of the vaginal septum should be undertaken. If only the most cranial portion of the septum remains, a bicornuate uterus will result. The vagina is typically normal, and surgical incision of the uterine septum is rarely indicated except in cases of recurrent pregnancy loss (DeCherney et al, 1986).

Duplication of the Uterus and Cervix with a Unilaterally Imperforate Vagina. **Although the majority of obstructive lesions are caused by abnormalities in vertical fusion, occasionally an obstructive process can be encountered in the context of an abnormality in lateral fusion** (Figs. 134–11 and 134–12). More than 50 cases of uterus didelphys with a unilateral imperforate vagina have been reported in the world's literature (Allan and Cowan, 1963; Burbige and Hensle, 1984). **As with other obstructive disorders, the patient may have cyclic or chronic abdominal pain. However, unlike other obstructive processes, duplication anomalies with unilateral obstruction do not result in primary amenorrhea.** On physical examination, a unilateral abdominopelvic mass that terminates in a bluish bulge in the lateral vaginal wall is often appreciated (Eisenberg et al, 1982). Abdominal ultrasonography and MRI are both excellent at defining the anatomy in a suspected case of unilateral noncommunicating uterine horn. Renal anomalies are frequently encountered on the side ipsilateral to the obstructed system, with renal agenesis being the most common (Eisenberg et al, 1982; Tridenti and Bruni, 1995). A prompt and accurate diagnosis is necessary to prevent injury to the genital organs as a result of chronic cryptomenorrhea and endometriosis. Treatment consists of wide incision of the vertical vaginal septum to release the entrapped menstrual blood.

Acquired Genital Obstructive Anomalies

Female Circumcision (Infibulation). Acquired vaginal obstruction may be secondary to a number of ritual female genital mutilation procedures that are widespread in many countries in Africa (stretching in a band from the Horn of Africa through Central Africa to parts of Nigeria), the Middle East, and Muslim populations of Indonesia and Malaysia (Toubia, 1994; Dorkenoo, 1996). Although similar procedures were prescribed to U.S. and British women during the 19th century for the treatment of ailments ranging from epilepsy to lesbianism, all forms of genital mutilation are now illegal in these Western countries. **Often referred**

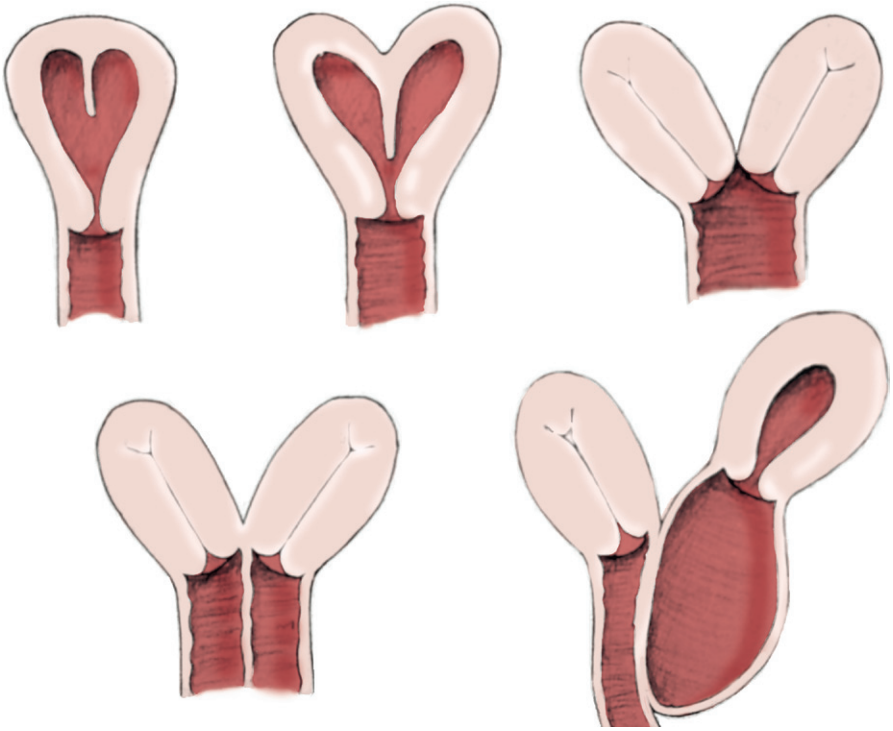


Figure 134–12. Fusion anomalies of the müllerian system. *Upper left to lower right,* Bicornuate uterus (partial), bicornuate uterus, uterine duplication, complete uterine and vaginal duplication, and duplication of the uterus and cervix with a unilateral imperforate vagina. (From Yerkes EB, Rink RC. What urologists should know about pediatric gynecologic abnormalities. Contemp Urol 2002;14:12.)

to as "female circumcision," the procedure continues to affect an estimated 80 to 110 million women worldwide (Toubia, 1994).

The age at which this procedure is performed ranges from birth to just before marriage. However, it is typically performed on preadolescent children between the ages of 4 and 10 years, most commonly at age 7 (American Medical Association, 1995). The procedure is usually performed without anesthesia in the context of a ceremony designating the rite of passage into adult society (American Medical Association, 1995). The extent of the mutilation varies according to ritual, but the practice predates Islam and is therefore not part of a religion (McCaffrey et al, 1995). In many countries the women have a deinfibulation procedure performed just before consummating the marriage.

The type of mutilation ranges from simple excision of the prepuce of the clitoris (termed *sunna*) to complete excision of all elements of the vulvar region (McCaffrey et al, 1995).

Toubia (1994) **classified the more extensive female genital mutilation procedures according to the amount of tissue destruction:**

Type I: Complete or partial removal of the clitoris.

Type II: Excision of the clitoris and a portion of the labia minora.

Type III: Excision of the entire clitoris and labia minora with incision of the labia majora along its medial aspect to create raw surfaces. The anterior two thirds of the labia majora are approximated to cover the urethra and introitus, with the lower third at the level of the posterior fourchette left for the passage of urine and menstrual fluid.

Type IV: Excision of the entire clitoris and labia minora with nearly complete approximation of the labia majora and only a pinhole opening left near the posterior fourchette for the passage of urine and menstrual fluid (Fig. 134–13).

Closing of the introitus, typically referred to as infibulation or pharaonic circumcision, is performed by a variety of means, including absorbable and nonabsorbable suture materials, thorns,

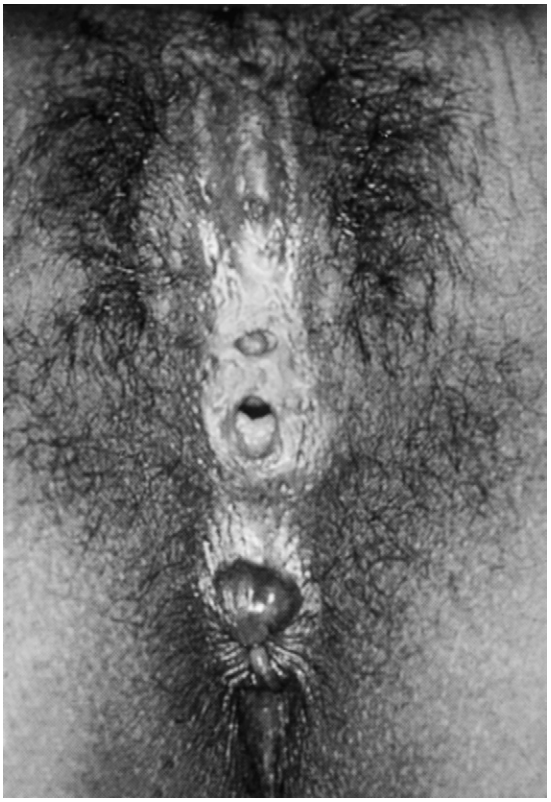


Figure 134–13. Female infibulation. Note the scarred labia majora with only a pinhole opening for the passage of menstrual fluid and urine. (From Gonzales ET, Bauer SB, editors. Pediatric urology practice. Philadelphia: Lippincott Williams & Wilkins; 1999. p. 599.)

and twigs. The child's legs are then bound for up to 40 days to ensure secondary healing in the ventral midline (McCaffrey et al, 1995).

The physical, psychological, and reproductive repercussions of these forms of genital mutilation are numerous and include immediate destruction and infection of local tissues (e.g., rectum, urethra). Long-term risks include chronic pain, recurrent urinary tract and vaginal infections, dysmenorrhea, dyspareunia, and apareunia. For individuals with the most narrowing, additional "surgeries" to revise the introital opening may be necessary for both intercourse and vaginal delivery (Aziz, 1980; Toubia, 1994).

Care of a patient who has undergone infibulation must be individualized, not only to provide functionality but also to respect the cultural and ritual desires of the woman. Educating the patient about the normal appearance of the external female genitalia is critical. Visual aids, including photographs or hand-drawn illustrations (or both) of the patient's anatomy and the planned revision, have been used as part of informed consent to avoid misunderstanding.

Nonobstructive Genital Anomalies (Interlabial Mass)

The differential diagnosis of an interlabial mass in a neonate and young child is broad and requires a thorough understanding of the diagnostic possibilities and a systematic evaluation. The age and racial background of the patient can help narrow the differential diagnosis, but physical examination remains the most useful tool for determining the specific pathology.

The physician must be sure to specifically reassure the girl that the examination will not be painful. With the child in the frog-leg position, the physician should note the size of the clitoris, the configuration of the hymen, the location of the urethra, and the character of the interlabial mass (e.g., smooth, lobulated, hemorrhagic). **To aid in visualization, the labia majora can be gently grasped and pulled caudally and laterally to enable funneling of the introitus and vagina (the so-called pull-down maneuver)** (Fig. 134–14). Determining the nature of a specific mass can be facilitated by establishing the location of expected anatomic landmarks. In certain circumstances, the relationship of the mass to the vagina and urethra can be improved by gentle placement of a lubricated cotton applicator posteriorly or placement of a small feeding tube within the suspected urethral orifice, or both. Although an otoscope, nasal speculum, or pediatric vaginal speculum can be useful in evaluating the vagina while the patient is awake, complaints of vaginal origin (i.e., vaginal discharge or bleeding) are often best investigated with a carefully performed examination and vaginoscopy under anesthesia. Renal-pelvic ultrasonography can be a useful adjunct in confirming or establishing the diagnosis in a few of these disorders.

Specific Lesions

Labial Adhesions. Labial adhesions, **also referred to as labial agglutination, and synechia vulvae are the most common interlabial abnormality identified in children, ranging in incidence from 0.6% to 1.8%** (Norbeck et al, 1993; Leung et al, 1993). **This condition occurs predominantly in the first 2 years of life, with a peak incidence between 13 and 23 months** (Fig. 134–15). Fusion of the labia minora

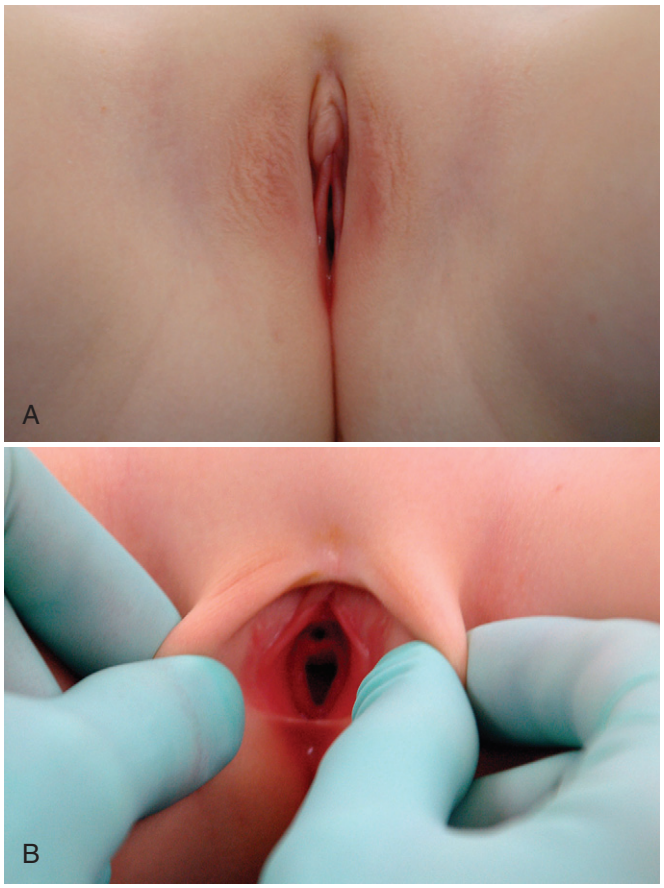


Figure 134–14. **A** and **B**, Photographs of the vaginal pull-down procedure. To aid in visualization of the female introitus, the labia majora are gently grasped and pulled caudally and laterally to enable funneling of the vagina.



Figure 134–15. Labial adhesions.

originates at the posterior fourchette and progresses for a variable distance toward the clitoris. It is important to differentiate this condition from the more serious entity of fusion of the labia majora, as is seen in certain DSDs. **It has been hypothesized that hypoestrogenism may play a role in adhesion of the labia minora.** Labial adhesions have not been reported in newborn children, presumably because of the protective effect of maternal estrogen (Leung et al, 1993). **However, the etiologic role of the hypoestrogenic state has been brought into question by a number of authors** (Caglar, 2007; Pulvino et al, 2008). Caglar (2007) measured circulating estradiol levels in 59 girls with labial adhesions and 60 control patients. He demonstrated no difference in the circulating level of estrogen in these two patient groups. Recently it has been shown that estradiol may enhance wound re-epithelialization by promoting heparin-binding epidermal growth factor production in keratinocytes (Kanda et al, 2005). **If there is a beneficial effect of topical estrogen it may be to promote healing after the adhesions have been separated. Nonhormonal factors may play an etiologic role in the formation of labial adhesions** (Papagianni and Stanhope, 2003). Local irritation and tissue trauma appear to be important inciting events in many cases. Adhesions can rarely be associated with sexual abuse; in such cases, additional physical findings are often noted, including hematoma and lacerations (McCann et al, 1988). Although labial adhesions are usually asymptomatic, urine pooling within the vagina may lead to postvoid dribbling and perineal irritation and may make it difficult to obtain an accurate urinalysis or perform radiographic procedures.

Most children with labial adhesions do not require treatment unless they are symptomatic. **With the rate of spontaneous resolution reported to be as high as 80% within 1 year, asymptomatic labial adhesions can comfortably be observed** (Pokorny, 1992). When necessary, treatment ranges from the topical application of various steroids to surgical division. The topical application of conjugated estrogens has been reported to be successful in separating adhesions in up to 90% of patients (Leung et al, 2005; Khanam et al, 1977). Concern over the possible side effects of breast budding and hyperpigmentation from prolonged use of conjugated estrogen led Myers and associates (2006) to treat a cohort of 19 prepubertal patients with topical betamethasone (0.05%). The authors reported success in 13 (68%) patients after administering one to three courses of twice-daily therapy for 4 to 6 weeks. It is important to have the family place the cream directly on the labia minora. In addition, it is helpful to have the family perform the pull-down procedure a few times a day to put light stress on the midline adhesions and hence facilitate their separation. If topical therapy is not successful, manual separation in the outpatient setting may be indicated. After the application of EMLA cream to the introitus, gentle pressure is applied to the thin connecting membrane with the use of a lubricated probe. Rarely, in cases in which the adhesions are extremely dense, surgical division is required. Although one group has recently advocated oversewing the separated edges with 7-0 chromic sutures (Nurzia et al, 2003), the authors have not found this to be necessary if the family is properly educated about keeping the labia separated (see Fig. 133–14) after the procedure. **Recurrence rates appear to be similar when comparing children who have undergone manual separation (16.7%) versus surgical separation (15.4%), emphasizing the importance of having families continue to separate the labia after separation has been achieved** (Muram, 1999).

Introital Cysts. Introital cysts in the newborn can represent one of three entities: paraurethral cysts (i.e., Skene duct cyst), remnants of the mesonephric ductal system (Gartner duct cyst), and a covered ectopic ureter. When the cyst is large and clearly emanating from the vaginal introitus, further investigation in the form of a renal-pelvic ultrasound evaluation is indicated to look for renal duplication.

Key Points: Nonobstructive Genital Anomalies

- Most children with labial adhesions do not require treatment unless they are symptomatic.
- Workup of a child with an introital (intralabial) mass that appears to be associated with the urethra should always include renal-pelvic ultrasonography.
- Urethral prolapse occurs most often in prepubertal black girls and in postmenopausal white women.

Paraurethral cysts in a neonate represent a dilatation of the periurethral glands, which are located just inside the urethral meatus (Fig. 134–16). These glands are homologues of the male prostatic glands and number between 6 and 30, with the two largest termed the *periurethral glands of Skene* (Skene, 1880; Gottesman and Sparkuhl, 1979). In a neonate the periurethral glands occasionally respond to maternal estrogen and secrete mucoid material, which can result in cyst formation. The main distinguishing feature of this condition is displacement of the urethral meatus by the mass and, consequently, an eccentric urinary



Figure 134–16. Paraurethral cyst. (From Yerkes EB, Rink RC. What urologists should know about pediatric gynecologic abnormalities. Contemp Urol 2002;14:12.)

stream. If the urethral meatus can be identified as being completely separate from the mass, radiographic evaluation is not needed to confirm the diagnosis (Nussbaum and Lebowitz, 1983). These cysts are frequently self-limited and often rupture spontaneously. If they are persistent, drainage by a small needle is easily achieved at the bedside.

Gartner duct cysts represent cystic remnants of the wolffian duct system and can be found along the anteromedial wall of the vagina (Pradhan and Tobon, 1986). A cystic structure related to a Gartner duct cyst is a *covered ectopic ureter* that enters into the vagina (Rosenfeld and Lis, 1993; Holmes et al, 1999). Embryologically, the ureter would not be expected to enter the vagina. However, an ectopically located ureter may end in a segment of the wolffian duct system, which in a female is represented by a Gartner duct cyst. In most instances this cystic structure spontaneously ruptures before delivery, thereby resulting in direct communication between the ectopic ureter and the vagina. However, if the surface epithelium fails to rupture, a covered, urine-filled cyst will exist within the vagina. Intraoperative injection of the cystic structure with radiographic contrast material may be beneficial in outlining the anatomy (Fig. 134–17). Incision of the cystic structure relieves the obstruction. As a general rule, the more ectopic the insertion of the ureter, the more dysplastic the segment that it drains will be. However, renal moieties that ectopically insert into the vagina may produce urine. Subsequent upper pole heminephrectomy may be indicated if the child has significant urine production from the segment (resulting in incontinence) or an infection develops after decompression.

Hymenal Disorders. ***Hymenal skin tags*** are virtually a normal finding and are rarely symptomatic (Figs. 134–18 and 134–19). When symptomatic (i.e., bleeding), they should be excised to ensure that they do not represent a malignancy and to provide symptomatic relief. Congenital abnormalities of the hymen are not uncommon and range from an imperforate hymen to one with numerous small microperforations.



Figure 134–18. Normal hymenal ring. (From Emans SJ. Office evaluation of the child and adolescent. In: Emans SJ, Laufer MR, Goldstein DP, editors. Pediatric and adolescent gynecology. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 1998.)



Figure 134–17. Retrograde injection of an ectopic ureter inserting into a Gartner duct cyst. After injection of a vaginal cyst, contrast agent ascends cranially into an atretic, dysplastic ureter.

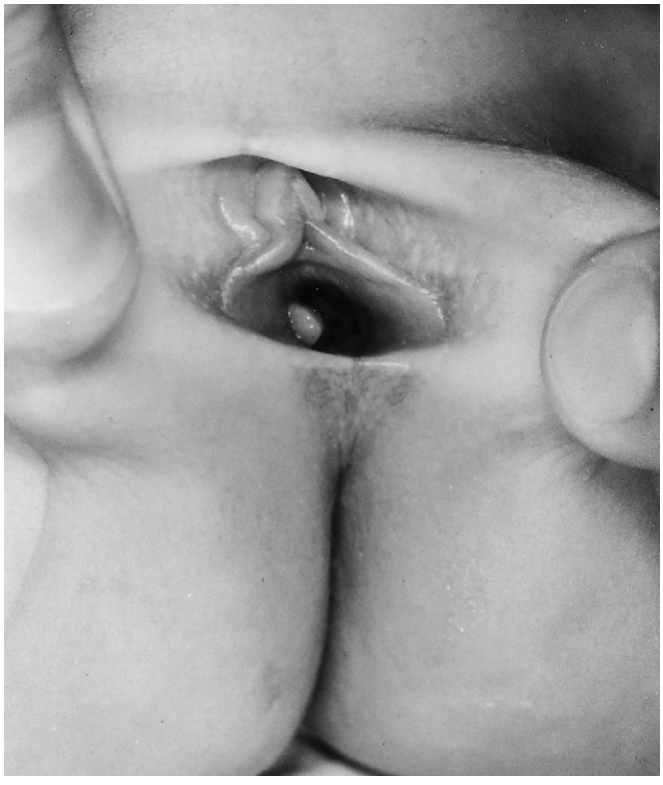


Figure 134–19. Hymenal skin tag.



Figure 134–20. Imperforate hymen. Note the significant distention from vaginal secretions. (From Yerkes EB, Rink RC. What urologists should know about pediatric gynecologic abnormalities. Contemp Urol 2002;14:12.)



Figure 134–21. Intraoperative photograph showing incisional drainage of an imperforate hymen. (From Yerkes EB, Rink RC. What urologists should know about pediatric gynecologic abnormalities. Contemp Urol 2002;14:12.)

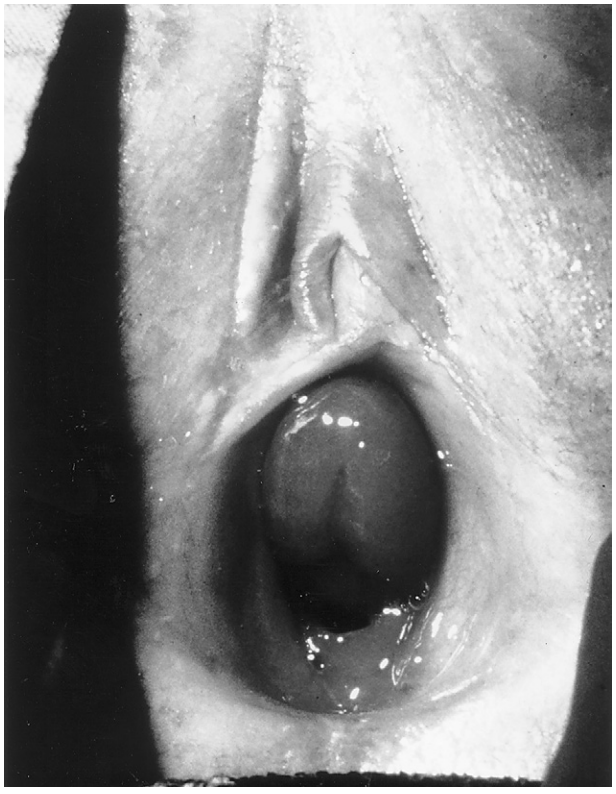


Figure 134–22. Urethral prolapse. (From Yerkes EB, Rink RC. What urologists should know about pediatric gynecologic abnormalities. Contemp Urol 2002;14:12.)

Imperforate hymen is probably the most common congenital obstructive anomaly of the female reproductive tract. The diagnosis is most frequently made at birth by noting the presence of a bulge along the posterior aspect of the introitus, which represents retained fluid within the vagina, or by palpation of a suprapubic mass from a distended vagina (Fig. 134–20). The buildup of retained vaginal secretions in the neonatal period, which imparts a whitish appearance to the bulging hymenal membrane, is caused by maternal estradiol stimulation. If the diagnosis is made after the neonatal period, the mucus will often have been reabsorbed and a bulge in the hymenal membrane may no longer be evident. On occasion, the diagnosis is not made until the adolescent period, when the patient experiences amenorrhea and possibly cyclic abdominal pain. In these circumstances, a bluish bulging hymen may be observed on genital inspection and a mass will be appreciated on rectoabdominal palpation.

In newborns, repair by incision of the hymenal tissue at the bedside is performed in the transverse direction to avoid inadvertent extension of the incision anteriorly or posteriorly (which might injure the urethra or rectal structures). Simple aspiration of the vagina without a definite drainage procedure should be discouraged because incompletely evacuated material may be prone to ascending bacterial growth. In pubertal girls, general anesthesia with excision of excess hymenal tissue may be indicated (Fig. 134–21).

Acquired abnormalities of the hymenal ring usually result from sexual abuse. The associated finding of a hematoma, abrasion, or laceration in combination with hymenal transection should raise the possibility of this diagnosis. Proper examination under anesthesia and forensic swabbing of affected areas should be undertaken with the use of a standardized protocol.

Prolapsed Urethra. Urethral prolapse generally involves complete circumferential eversion of the urethral mucosa at the level of the external urethral meatus (Fig. 134–22) (Lowe et al, 1986). **This entity, which was first described by Solinger in 1732, occurs most often in prepubertal black girls and in postmenopausal white women** (Epstein and Strauss, 1937;

Richardson et al, 1982). Various causes that have been proposed for urethral prolapse include hypoestrogenism (Desai and Cohen, 1997), abnormal connections between the inner longitudinal and outer circular muscle layers of the distal urethra (Lowe et al, 1986), and episodic increases in intra-abdominal pressure (Lowe et al, 1986; Desai and Cohen, 1997; Valerie et al, 1999). The most common initial complaint is bleeding from the edematous and friable mucosa, which results in blood spotting on the underwear (Richardson et al, 1982; Chaouachi et al, 1989). Urethral prolapse is easily recognized as a doughnut-shaped mass with the urethral meatus at the center. If the diagnosis can be confirmed by passing a urethral catheter, radiographic evaluation is not indicated (Nussbaum and Lebowitz, 1983). Treatment options include observation, topical corticosteroids, and surgical excision (Redman, 1982; Fernandes et al, 1993). Sitz baths may be helpful. **Nonoperative treatment may lead to spontaneous reduction of the prolapse, but a recurrence rate of up to 67% has been noted** (Jerkins et al, 1984). Many methods of surgical repair have been described. Circumferential excision of the redundant mucosa with subsequent suturing of the normal urethra to the vestibule is the procedure of choice (Devine and Kessel, 1980). Other methods, including ligation over a transurethral catheter with subsequent sloughing and cryosurgery, should be discouraged (Owens and Morse, 1968; Klaus and Stein, 1973).

Prolapsed Ureterocele. An ectopic ureterocele is a cystic dilatation of the terminal portion of the ureter that occurs predominantly in white females (Mandell et al, 1980). Approximately 90% of ectopic ureteroceles are associated with the upper pole of a duplex collecting system. Although they normally remain positioned proximal to the bladder neck, some may prolapse through the urethra during micturition, almost always in infancy, and result in urinary retention and a relative urologic emergency (Gingell et al, 1971). **Depending on the length of time that the ureterocele has been prolapsed, it may vary in color from pink to dusky purple** (Fig. 134–23). **If a prolapsed ureterocele is in the differential diagnosis, bladder-renal ultrasonography should be performed to look for upper pole hydronephrosis in a duplicated collecting system** (Fig. 134–24).

Treatment of a prolapsed ureterocele consists of either needle decompression or incision and reduction and then placement of a urethral catheter. Although this can occasionally be achieved in the emergency department setting, abdominal straining by the infant may make this procedure difficult, and treatment under general anesthesia is often preferable.

Injection of radiographic contrast material into the ureterocele can be helpful in identifying the relevant anatomy.

Urethral Polyp. The pediatric equivalent of a urethral caruncle, namely, a urethral polyp, is a rare lesion that can be manifested as an intralabial mass (Fig. 134–25). The etiology of true lesions has not been completely elucidated, but in a young child they probably represent either hamartomatous growth or a response to inflammation.

The authors described two young girls with an interlabial mass. Histologic examination of each excised mass revealed a benign urethral polyp covered with transitional and squamous epithelium (Klee et al, 1993). Urethral polyps should be included in the differential diagnosis of an interlabial mass in young female patients.

Vaginal Rhabdomyosarcoma. Vaginal rhabdomyosarcoma is most often manifested as a grapelike cluster of tissue emanating from the posterior aspect of the vestibule (Fig. 134–26). The mean age of patients with primary vaginal tumors is younger than 2 years (Hays et al, 1988). Of all the female genital tract primary tumors, vaginal primary tumors appear to have the best prognosis. This excellent prognosis is thought to be a result of predominance of the embryonal cell type and relatively early detection because of symptoms of bleeding (Hays et al, 1988). Once a tissue diagnosis has been made by biopsy, proper staging with abdominal and pelvic computed tomography, chest radiography, and bone marrow biopsy is critical to optimal stratification of these patients into treatment protocols (Hays et al, 1985). Advances in



Figure 134–23. Prolapsed ureterocele. Note the catheter inserted in the urethra.

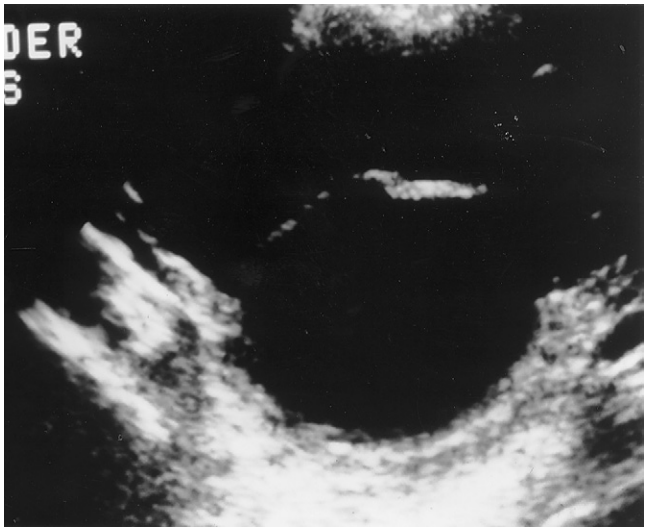


Figure 134–24. A ureterocele evident on ultrasonography of the bladder. (From Yerkes EB, Rink RC. What urologists should know about pediatric gynecologic abnormalities. Contemp Urol 2002;14:12.)

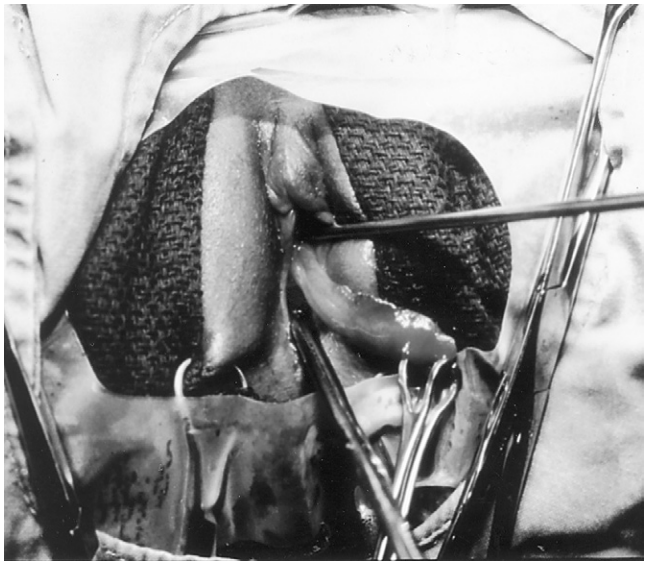


Figure 134–25. Urethral polyp: probe in urethra and Babcock clamp on urethral polyp. (From Yerkes EB, Rink RC. What urologists should know about pediatric gynecologic abnormalities. Contemp Urol 2002;14:12.)



Figure 134–26. Vaginal rhabdomyosarcoma. (From Yerkes EB, Rink RC. What urologists should know about pediatric gynecologic abnormalities. Contemp Urol 2002;14:12.)

chemotherapy have led to a reduction in the role of surgery for this disease with each subsequent Intergroup Rhabdomyosarcoma Study (IRS) trial: IRS-I, 100%; IRS-II, 70%; IRS-III, 30%; and IRS-IV, 13% (Andrassy et al, 1999). After chemotherapy, local resection may be required, but unlike other malignancies of the vagina, wide excision of the involved organ has no role except for persistent or recurrent disease (Hensley, 2000).

CLASSIFICATION OF UROGENITAL SINUS AND CLOACAL ANOMALIES

Persistent urogenital sinus anomalies are one of the more complex problems that a pediatric urologist will face, and they occur in a spectrum. Evaluation and management must be meticulous.

In urogenital sinus anomalies there is a persistent communication of the vagina with the urinary tract. Communication of the vagina with the urinary tract may occur at any point from the urethral meatus to the bladder, but the majority occur within the mid to distal portion of the urethra. The two structures join and exit on the perineum as a single common urogenital sinus channel.

A persistent urogenital sinus is **seen in four entities.** Most commonly it occurs in **genital ambiguity states,** most frequently with congenital adrenal hyperplasia (CAH) (Fig. 134–27). It can also occur as a **pure urogenital sinus** with normal external genitalia (Fig. 134–28). In persistent **cloacal anomalies** there is the added complexity of rectal involvement, with all three systems—genital, urinary, and rectal—exiting as an isolated single perineal opening. More recently, **female exstrophy** has been thought to represent a form of persistent urogenital sinus (Adams, 2000).

Early descriptions of this confluence were based on previous medical training. Urologists described the vagina as entering the urethra, whereas gynecologists noted that the urethra entered the vaginal vestibule (Jones and Jones, 1954). Jaramillo and Lebowitz (1990) noted that on examination that the external cloacal orifice appears vaginal in nature in some but in others appears more like a normal urogenital orifice (Figs. 134–29 and 134–30). **Regardless of how the confluence of the urinary and genital tracts is described, the confluence location in relation to the bladder neck is a more critical factor in surgical management than the length of the common channel** (Rink et al, 2005a)

Key Point: Urogenital Sinus Anomalies—General

- Urogenital sinus anomalies are found in four entities: genital ambiguity states, pure urogenital sinus, persistent cloaca with rectal involvement, and female exstrophy.

Evaluation

Urogenital sinus abnormalities are most often seen in DSD states, most commonly in association with CAH, which has been noted to have an incidence as high as 1 in 500 in the nonclassic, mild form (Hughes, 1988). The most common enzymatic defect in CAH resulting in genital ambiguity is 21-hydroxylase deficiency, which occurs in approximately 1 in 15,000 to 16,000 persons (Spieser and White, 2003; Merke and Bornstein, 2005). Mutations in the 21-hydroxylase gene *(CYP21)* result in varying degrees of virilization corresponding to the type of mutation. CAH should be regarded as a spectrum disorder from mild anomalies to those with deep impact on life (Nordenskjold et al, 2008). Therefore, initial management must focus on making an accurate diagnosis to allow proper gender identification. Every effort should be made to establish the genetic

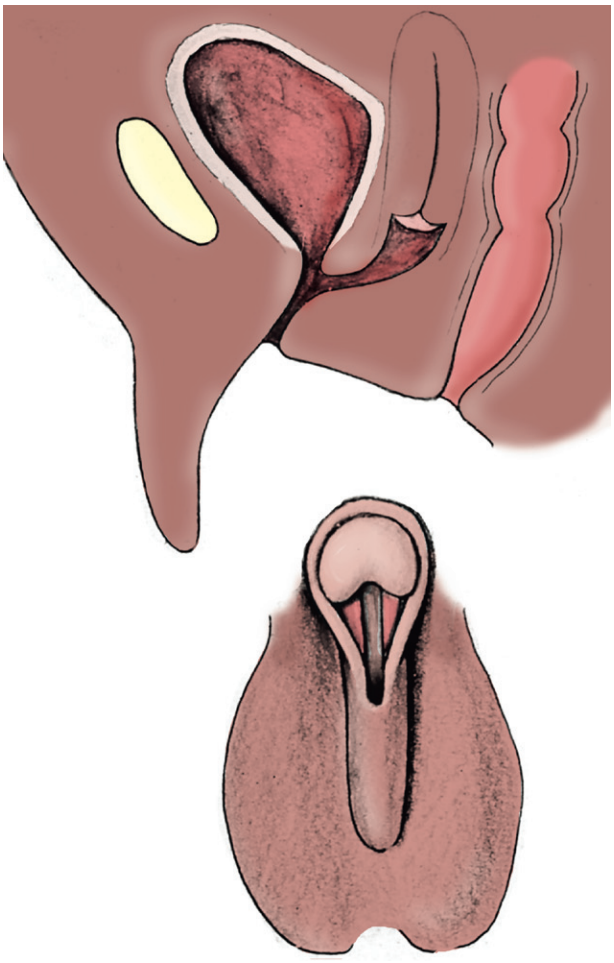


Figure 134–27. Urogenital sinus in a patient with intersex.

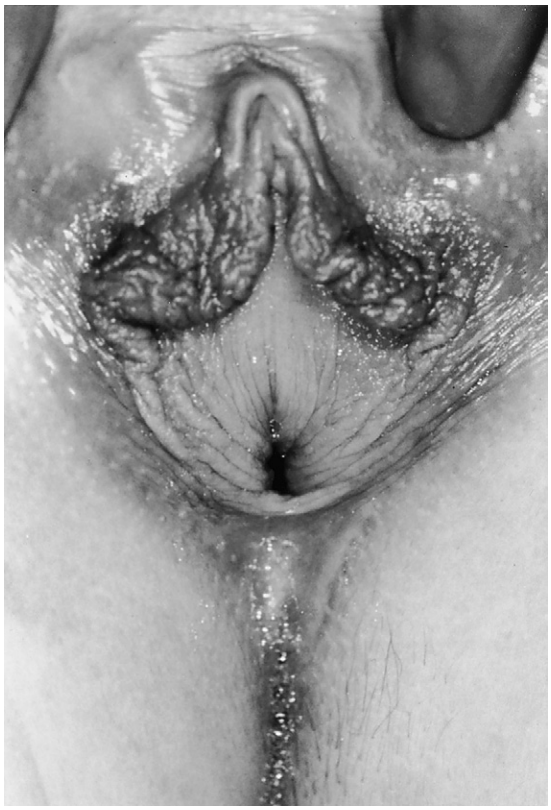


Figure 134–28. Pure urogenital sinus abnormality.

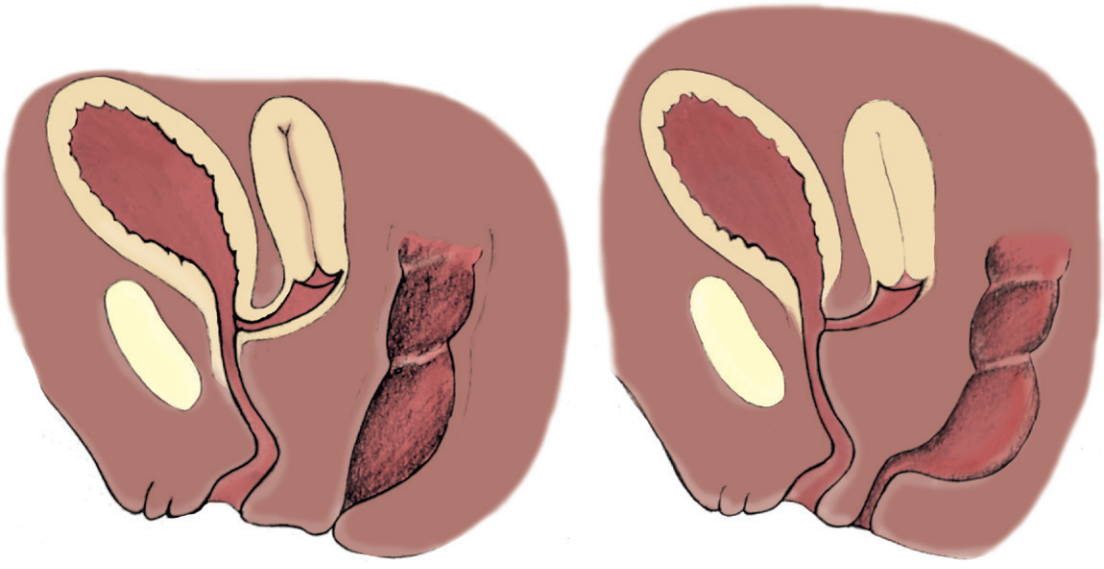


Figure 134–29. *Left,* Urethral-type urogenital sinus. *Right,* Urethral-type urogenital sinus with an anteriorly placed rectum.

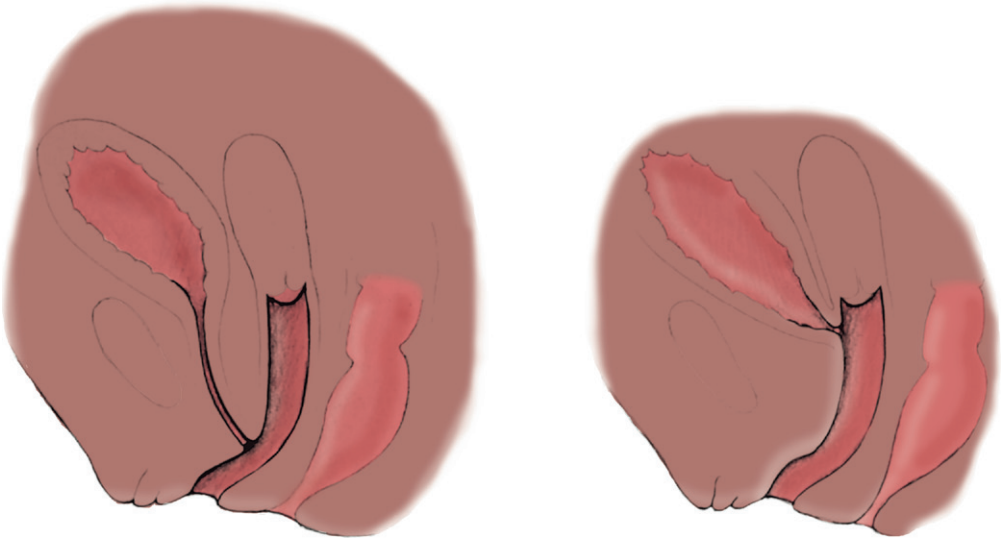


Figure 134–30. Vaginal-type urogenital sinus showing high *(right)* and low *(left)* confluence.

sex within 48 hours. Children with CAH require careful monitoring of fluid and electrolytes because 67% to 75% will have significant salt wasting (Spieser and White, 2003; Merke and Bornstein, 2005). Evaluation should include rapid karyotyping of cultured peripheral leukocytes, measurement of serum electrolyte levels, and determination of hormonal levels for CAH. All results are shared with the gender assignment team, which includes the parents, pediatric endocrinologist, pediatric urologist, neonatologist, geneticist, child psychiatrist, and often clergy. The child should not be named until sex assignment is complete (Rink and Adams, 1998).

Cloacal anomalies are a much more complex problem involving multiple organ systems, but fortunately they occur in only 1 in every 40,000 to 50,000 patients (Karlin et al, 1989). They are the most challenging of the anorectal malformations and make up 13.6% of this group (Fleming et al, 1986). These children have a very broad spectrum of findings on examination of the external genitalia. Some may have a prominent phallic structure and also initially require evaluation for a DSD.

History and Physical Examination

Many children with urogenital sinus abnormalities are now identified by antenatal ultrasonography, with the findings of fluid-filled pelvic structures (vagina and bladder) with indeterminant genitalia. However, the history and the physical examination remain extremely helpful in cases of genital ambiguity and can often lead to the diagnosis itself. It is critical to determine whether the mother ingested any medications during pregnancy, especially androgenic substances. A family history of early infant death or fluid and electrolyte abnormalities suggests CAH. Have other children had genital ambiguity or gender dysphoria at puberty? Notation should be made of any family members with abnormal pubertal development.

The physical examination can at times be very useful in determining the appropriate gender and in helping to identify other organ systems involved. A general evaluation of the child's overall health should be completed before focusing on the genital examination. Abnormal facies suggesting a syndrome should be noted. **Hypertension can occur in children with genital ambiguity secondary to CAH with 11β-hydroxylase deficiency.** Therefore, blood pressure should be documented. Evidence of dehydration may also lead to a diagnosis of CAH. On abdominal examination, a mass, particularly a suprapubic mass, may be present because of a distended bladder or hydrometrocolpos, or both. **Hydrometrocolpos is frequently an initial sign and is often the only early finding in pure urogenital sinus abnormalities.**

In cloacal anomalies, abdominal distention may be severe secondary to hydrometrocolpos and bladder and intestinal distention. Hydrometrocolpos was noted commonly in early series (Chappell and Bleloch, 1973; Klugo et al, 1974); its incidence ranged from 29% of Pena's patients (1989) to 63% of those reported by Bartholomew and Gonzales (1978). It is caused most commonly by preferential flow of urine into the vagina (or vaginas) with voiding and associated poor vaginal drainage. Maternal estrogen stimulation of the cervical glands results in mucus production, thereby further adding to the distention. Urine flow can occur into the rectum also. This distention has resulted in edematous, cyanotic legs and respiratory distress, as well as acidosis (Raffensberger, 1988).

The lower part of the back should be examined to identify any evidence of spinal cord abnormalities, which can be associated with urogenital sinus abnormalities and are very common with cloacal anomalies. Such abnormalities may take the form of a sacral dimple, hair patch, or area of abnormal pigmentation, but more commonly there is evidence of a bone abnormality, such as an abnormal buttock crease or flattened buttocks as a result of sacral agenesis.

Genital examination should note the size of the phallus and the consistency of the erectile bodies. Any degree of curvature should be documented. Huffman (1976) multiplied the width of the glans times the length of the phallus to determine the "clitoral index," which he noted should be less than 3.5 mm to be normal and was of concern when greater than 10 mm. The gonads should be sought, and, when found, their number, location, and consistency should be noted. If both gonads are descended, it is extremely unlikely that a 46,XX chromosome makeup will be found. The

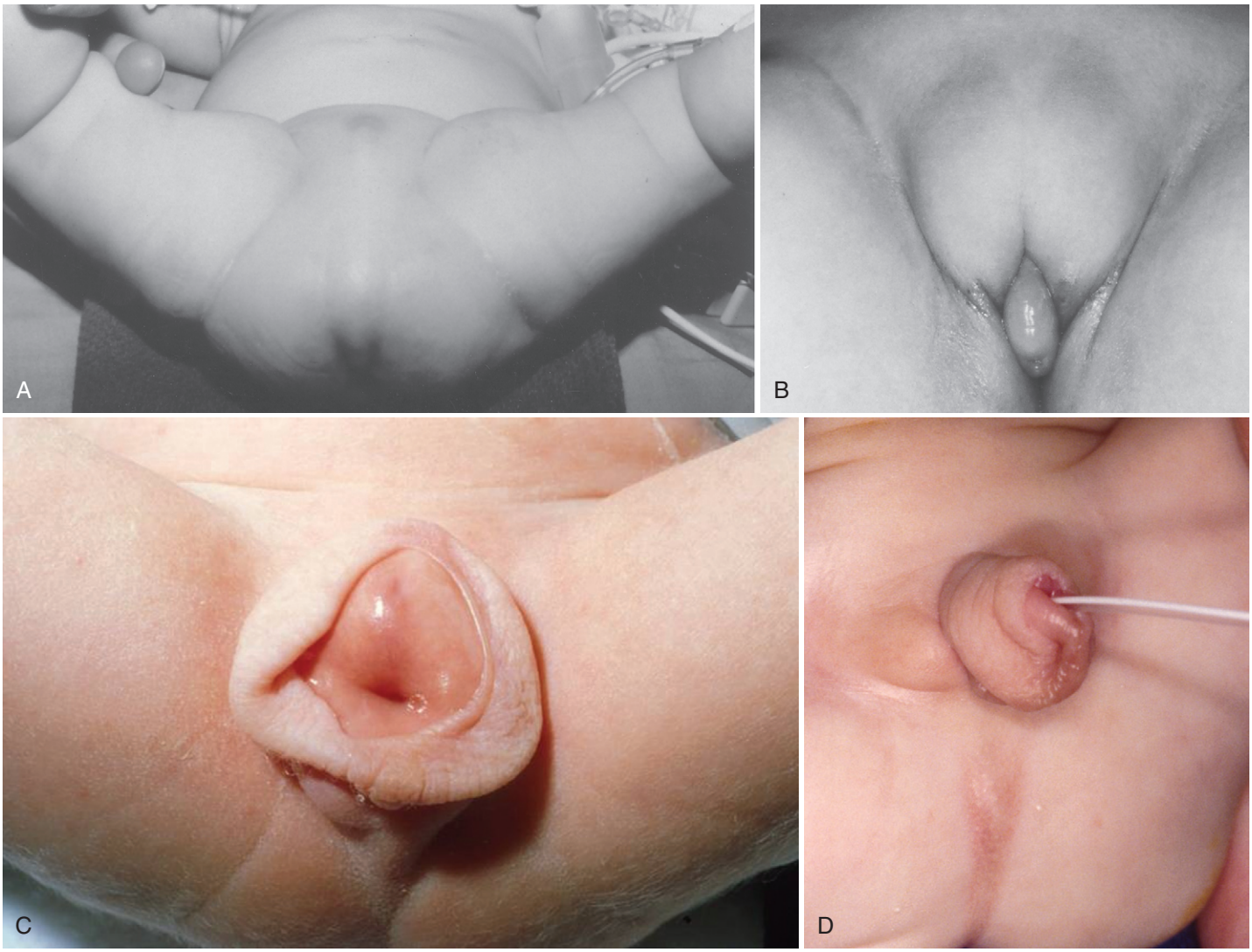


Figure 134–31. **A**, Cloaca with a blank perineal appearance. **B**, Cloaca with genital transposition. **C**, Cloaca, vaginal type, external appearance. **D**, Cloaca, urethral type, external appearance.

labioscrotal folds should be examined for their relationship to the phallus and rectum, as well as for the degree of fusion. Increased pigmentation of the labioscrotal folds and areola may be seen in some cases of CAH as a result of increased levels of melanocyte-stimulating hormone.

In urogenital sinus anomalies the location of the anus should be noted. Although it is usually in the normal location, anterior displacement is not uncommon, and this bridges the gap to cloacal anomalies (see Fig. 134–29). A gentle rectal examination is helpful in identifying a cervix.

Examination of a child with a persistent cloaca deserves special mention. There is a single perineal orifice because the rectum also enters this common channel. The appearance of the external genitalia assumes a much wider spectrum, from a nearly normal female appearance to much more bizarre appearances such as genital transposition or a blank-appearing (doll-like) perineum (Fig. 134–31) (Hendren, 1989). In some instances there is an enlarged phallic structure that gives the genitalia an ambiguous appearance. The single perineal opening may exit what appears to be a normal vaginal introitus, or it may extend to the tip of a phallic structure. The authors, as well as others, have encountered children with a secondary accessory channel that exits the tip of the phallus (Hendren, 1989; Karlin et al, 1989; Krstic et al, 2001; Rink et al, 2005b).

Cloacal anomalies are associated with a high incidence of related anomalies in other organ systems. The authors found 14 of 23 patients with renal anomalies, including 6 with solitary kidneys, 4 with renal dysplasia, 2 with ureteropelvic junction obstruction, 1 with duplication, and 1 with cross-fused ectopia. There were also 2 with bladder duplications (Rink et al, 2005b). Sixty percent have some degree of septation of the vagina and uterus (Warne et al, 2003). Kay and Tank (1977) reported that 13% of patients with cloacal anomalies have cardiovascular abnormalities, 10% have central nervous system problems, and respiratory abnormalities are noted in 5%; vertebral, particularly sacral, anomalies are common. Many have the VACTERL association (*V*ertebral abnormalities, *A*nal atresia, *C*ardiac abnormalities, *T*racheoesophageal fistula and/or *E*sophageal atresia, *R*enal agenesis and dysplasia, and *L*imb defects), so tracheoesophageal fistula is often present (Hendren, 1986, 1988). Other gastrointestinal anomalies have been noted, including duodenal atresia and rectal duplication in 2% (Karlin et al, 1989).

Key Points: Urogenital Sinus Anomalies—Evaluation

- Key points of the history and physical examination are findings of a family history of sudden infant death, fluid and electrolyte abnormalities, hypertension, suprapubic mass, lower extremity cyanosis, palpable gonads, and hyperpigmentation, and number of perineal orifices.
- The level of the urethrovaginal confluence and the location of the rectum must be identified radiographically and endoscopically, with note made of their relationship to the bladder neck. Ultrasonography is mandatory to look for the uterus, ovaries, and kidneys.

Radiographic and Endoscopic Evaluation

Urogenital Sinus Abnormalities

Certain critical details of the anatomy, including the length of the common urogenital sinus, the location of the vaginal confluence and its proximity to the bladder neck, the size of the vagina and the number of vaginas, the presence of a cervix, and bladder and urethral anatomy, must be defined by radiographic and endoscopic evaluation. The authors believe that the location of the vagina in relation to the bladder neck is the critical issue in determining the type of surgery, and this distance is more important than the length of the common channel. Vaginal confluence with the urinary tract occurs in a continuum from the bladder to a nearly normal location in the perineum. **It is not simply "high" (proximal/suprasphincteric) or "low" (distal/infrasphincteric)** (Hendren and Crawford, 1969; Powell et al, 1995; Rink and Kaefer, 2002) (Fig. 134–32).

A new urogenital sinus classification that measures the exact distance of the common channel and the distance of the bladder neck to the vagina has been devised to help delineate the exact level of the confluence, as well as clitoral size and appearance of the external genitalia (Rink et al, 2005a).

Ultrasonography of the urinary tract and pelvis is mandatory. The location and normalcy of the kidneys, ovaries, and uterus should be defined. Any bladder or vaginal distention should be noted. A cerebriform appearance with enlargement of the adrenal glands is indicative of CAH (Brock et al, 1998).

Filling the entire bladder, urethra, vagina, and sinus with contrast (i.e., genitography) is critical in the anatomic evaluation of many children with a urogenital sinus (Figs. 134–33 and 134–34). Genitography is performed by placing a Foley catheter with the balloon occluding the perineal meatus and injecting a contrast agent. It is often helpful to pass a catheter into the bladder as for a voiding cystourethrogram. A cervical impression at the vaginal dome denotes normal female internal organs. MRI is of limited value in CAH but may be very helpful to define the anatomy in pure urogenital sinus anomalies or DSD conditions. In CAH patients,

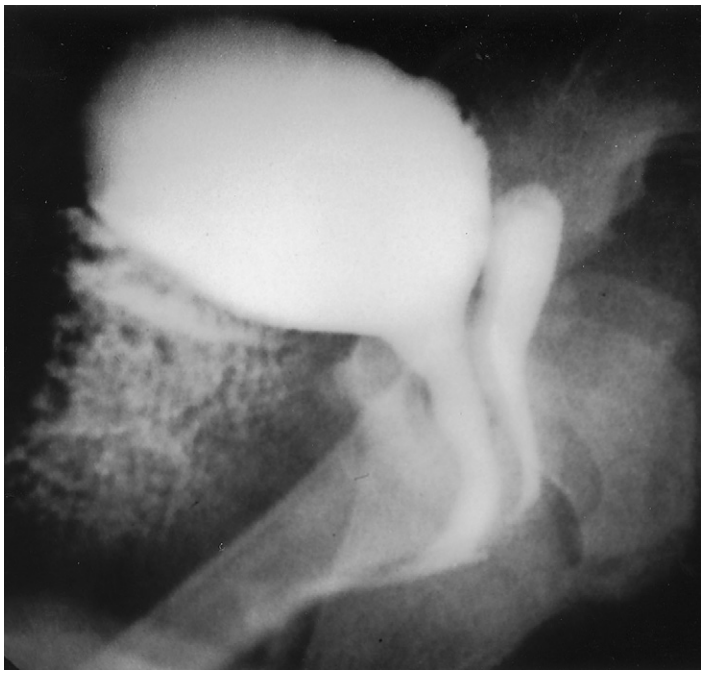


Figure 134–33. Genitography showing low confluence of the urethra and vagina.

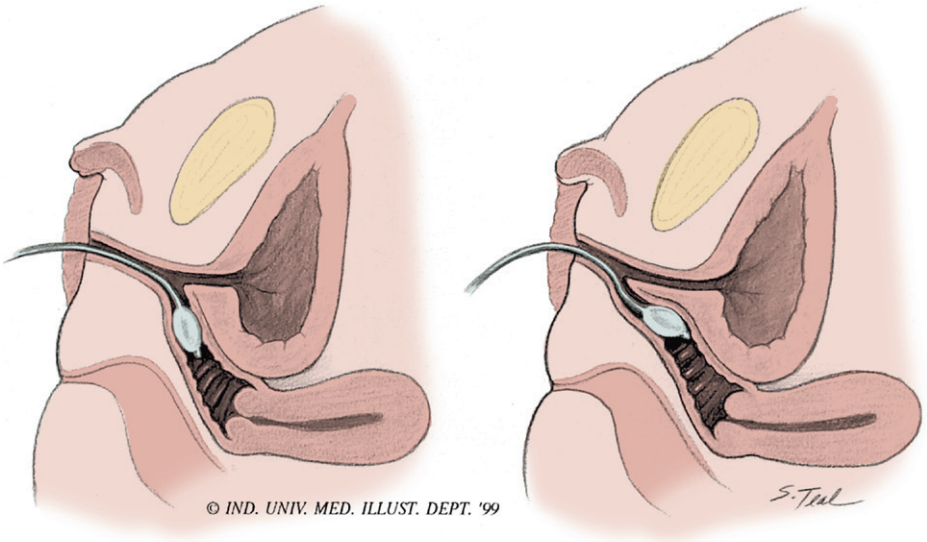


Figure 134–32. Fogarty catheter placed in the vagina in high confluence *(left)* and in low confluence *(right)*. (©1999, Indiana University Medical Illustration Department.)

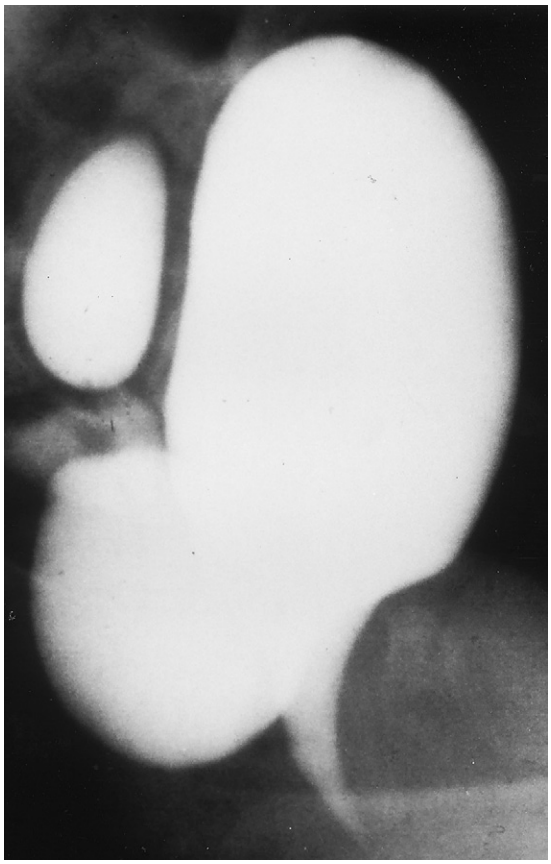


Figure 134–34. Genitography showing high confluence of the vagina entering near the bladder neck, with flow of contrast medium into the uterus.



Figure 134–35. Endoscopic view of confluence. The urethra is superior; the vagina is inferior.

the internal anatomy can nearly always be defined by an endoscopy at the time of reconstruction, making genitography less useful in this group (VanderBrink et al, 2010).

The most helpful diagnostic study in defining the anatomy for surgical reconstruction is endoscopy. In patients with CAH, endoscopy is usually performed at the time of reconstruction but may be necessary as a separate early procedure to help with gender identity in DSD cases or in those with complex pure urogenital sinus anomalies or if the vagina is not identified on genitography (Rink and Kaefer, 2002). In the latter situation, multiple punctuate openings in the proximal portion of the urethra may be observed (Donahoe and Gustafson, 1994). The authors have found it helpful to pass a ureteral catheter into the opening and evaluate the vagina fluoroscopically in this situation (Rink and Kaefer, 2002). Again, the exact location, size, and number of the vaginas should be recorded (Fig. 134–35). Hendren has noted a malelike external sphincter in severely masculinized children, with the vagina entering proximal to it in a verumontanum-like structure (Hendren and Crawford, 1969; Hendren and Atala, 1995). In the authors' initial experience, we thought this rarely if ever occurred (Adams and Rink, 1998), but more recently we have seen CAH children with a completely masculinized malelike urethra with an external sphincter and verumontanum-like structure.

Rarely, even with the evaluation described, some children with DSD require gonadal biopsy or evaluation of the internal genitalia, which has historically been done by laparotomy but in most cases can now be easily performed laparoscopically. Regardless of the means, it should be performed only when the findings would influence the gender of rearing (Rink and Adams, 1999). **If a biopsy is necessary, a deep incision should be made in the gonad because the ovarian component of ovotestes may completely surround the testicular component or be located at the poles** (Hensle and Kennedy, 1998; Schnitzer and Donahoe, 2001). Finally, scrotal skin biopsy may at times be helpful in males with incomplete androgen insensitivity, decreased 5α-reductase activity, or decreased dihydrotestosterone binding (Griffin and Wilson, 1989). Certainly all children with DSD should undergo chromosomal, endocrinologic and genetic evaluation. This is well described in Chapter 133.

Cloacal Anomalies

Evaluation for cloacal anomalies begins with antenatal ultrasound because there have now been several groups who have reported the prenatal diagnosis of persistent cloaca (Petrikovsky et al, 1988; Shalev et al, 1986; Cilento et al, 1994; Odibo et al, 1997; Adams and Rink, 1998; Cacciaguerra et al, 1998; Warne et al, 2002b). The diagnosis has been made as early as 19 weeks' gestation. **The finding of transient fetal ascites with bilobed or trilobed pelvic cystic structures, bilateral hydronephrosis, and decreased amniotic fluid is diagnostic** (Cacciaguerra et al, 1998; Warne et al, 2002a). The ascites is thought to develop via retrograde flow of urine into the uterus and out the fallopian tubes secondary to outlet obstruction from the distended vagina (Adams et al, 1998; Cacciaguerra et al, 1998).

Postnatal radiographic evaluation begins with a plain abdominal film (Jaramillo and Lebowitz, 1990). A pelvic mass may be obvious. Retrograde flow of urine and meconium, as described earlier, may result in the classic linear calcifications or calcified meconium. More granular calcifications may be noted along the course of the rectum as a result of urine flow into the rectum that yields calcified meconium (Jaramillo and Lebowitz, 1990).

Abdominal ultrasonography is very important to visualize not only the pelvic anatomy but also the kidneys because hydronephrosis is common (Hendren, 1998). Hydronephrosis is usually related to hydrocolpos, with the distended vagina compressing the bladder neck and resulting in varying degrees of bladder outlet obstruction (Hendren, 1998). Ureteral compression may also occur; however, the authors have seen hydronephrosis caused by primary obstructive megaureter in patients with cloacal anomaly.

Ultrasonography may also detect other renal anomalies. **Renal anomalies such as dysplasia, fusion anomalies, ectopia, ureteropelvic junction obstruction, and duplication have been seen in 33% to 83% of children with a persistent cloaca** (Kay and Tank, 1977; Warne et al, 2002b; Rink et al, 2005b).

As opposed to some urogenital sinus abnormalities in which genitography may be avoided, both genitography and endoscopy are mandatory to define the anatomy, which is even more complex with a cloacal anomaly.

The technique and goals of genitography and endoscopy are the same but must now include identification of the rectal as well as the vaginal confluence. The length of the urethra and its communication with the cloaca are important for reconstructive purposes. In Hendren's patients, the urinary communication to the cloaca was urethral in 77%, but in 23% there was virtually no urethra and the communication was noted at the bladder neck level (Jaramillo and Lebowitz, 1990). The vaginal anatomy is also much more complex and variable. In Hendren's report of 154 patients, 66 had one vagina, 68 had two vaginas, and the vagina was absent in 20 (Hendren, 1998). Vaginal duplication has been seen in nearly all of the authors' patient population (Rink and Yerkes, 2001) (Fig. 134–36). The duplication anatomy is also variable. Most authors have observed that the vaginas enter side by side with a single opening into the cloaca, but separate openings have been noted. The vaginas may be of different size, and one may enter the sidewall of the other. A cervix is usually seen at the top of each vagina. **The vaginal entrance into the cloaca again lies along a spectrum from the bladder to a location near the perineum.** Although the uterus is usually similar to the vagina (i.e., two vaginas with two uteri), the vagina may be absent with the uterus still present. Hall and associates (1985) found a bicornuate uterus, hypoplastic uterus, or uterus didelphys in 35% of their patients with persistent cloaca.

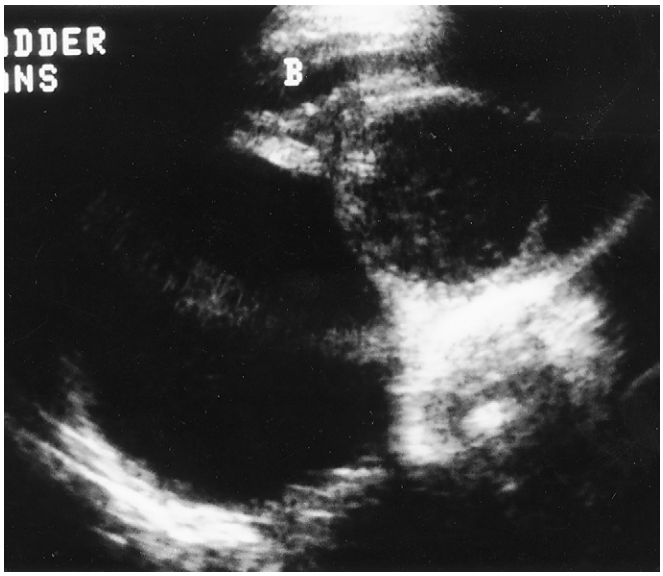


Figure 134–36. Pelvic ultrasonography in a patient with a cloaca. Duplicate fluid-filled vaginas are seen posterior to the decompressed bladder (B).

The rectal confluence is equally as complex, with the entrance in the authors' experience most commonly located just at the level of the vaginal confluence. This rectal opening may be broad, or it may have a long, narrow fistulous tract. It can even enter the vagina or bladder with no communication to the cloaca itself. The most common entrance in our experience is within the septum of a duplicated vagina, with all three joining the cloaca together (Rink and Kaefer, 2002). The rectal communication has been found to be vaginal in 68% and cloacal in 11%, with the remainder in other locations (Jaramillo and Lebowitz, 1990). The length and configuration of the common cloaca should also be noted because it has important surgical as well as anatomic implications. At times, the common channel is narrow and appears very much like a urethra; in other instances, the channel is much larger and redundant and appears more like a vagina. The urethral appearance was found in 48% of patients and the vaginal appearance in 52% (Jaramillo and Lebowitz, 1990). **The authors and others have noted that the urethral types result in higher outlet resistance and are more likely to lead to hydrocolpos** (Adams et al, 1998; Warne et al, 2002a).

The frequent presence of associated organ system abnormalities necessitates further radiographic evaluation. Echocardiography should always be performed. MRI is necessary for evaluating the lumbosacral spine and assessing the pelvic anatomy and musculature. Historically, it has been well recognized that sacral anomalies are common. Pena (1989) noted a normal sacrum in only 35% of his 54 patients, and Jaramillo and Lebowitz (1990) reported sacral agenesis in 40% of Hendren's 65 patients. De Filippo and associates (1999) found 10 of 21 patients with imperforate anus or cloaca to have an abnormality of the sacrum and spine. **With the use of MRI, spinal cord abnormalities have been more commonly detected, with an incidence as high as 43%** (Jaramillo and Lebowitz, 1990). Hendren (1998) found that a third of his patients had a tethered spinal cord. Skin stigmata in the lumbosacral region were absent in 8 of 10 patients with spinal cord tethering in Morimoto and colleagues' report (2003). MRI has also been very helpful in defining the level of the rectal atresia and in identifying the degree of sphincteric muscle development (Sato et al, 1988).

Because of the complexity of the anatomy and the frequency of hydrometrocolpos, a child with a cloacal anomaly often needs endoscopy early as a separate procedure to decompress the vagina and bladder and to define the anatomy. As a general rule, visualization of the vagina (or vaginas) is easily accomplished, but entry into the bladder can be very difficult and even impossible at times in a neonate because it is compressed very anteriorly by the distended vagina. The vagina should always first be emptied. Identification of the rectal fistula can also be difficult at times. Once it is located, mucus and fecal material should be irrigated from the colon, which can be done by irrigation through the scope in combination with irrigation through the mucous fistula of the divided colostomy. The length of the urethra to the vaginal and rectal confluence as well as the length of the common cloacal channel should be documented. The length of the common channel is helpful in cloacal patients in predicting fecal continence outcomes (Pena et al, 2004).

SURGICAL RECONSTRUCTION OF DISORDERS OF SEX DEVELOPMENT AND UROGENITAL SINUS

Initial Management, Timing, and Principles

The majority of children born with a urogenital sinus have genital ambiguity, and this should be initially evaluated by the gender assignment team. It is extremely important that the family be made aware of all controversies surrounding genital surgery. Certainly, most families, physicians, and surgeons have historically made the decision to proceed with early feminizing procedures to "normalize" the child and allow a positive psychosocial adjustment (Schober, 1998). This has been thought to relieve the parents' distress and improve their outlook toward their child, although there is limited evidence for this. The thought has been that raising a child with genital ambiguity would be extremely difficult (Thomas, 2004). Recently, a number of advocacy groups and physicians have begun to question this wisdom. Informed consent is impossible with an infant, and many believe that the decision for genital surgery is a right of the patient, not the parents. The ethical issues involving parents' rights and responsibilities to make decisions for their child remain unresolved (Lee and Witchel, 2002). Unfortunately, there are no data on the impact of raising a child with genital ambiguity (Rangecroft, 2002). Regardless of one's personal beliefs, all pros and cons of both surgery and observation must be presented to the parents without bias and certainly the option of observation with psychologic and peer support must be an option (Creighton and Liao, 2004).

At this time, excellent cosmetic results can be achieved by feminizing genitoplasty. However, it must be remembered that one's sexual identity is a result of many factors. It is known that the brain is the dominant organ in sexual orientation (Woodhouse, 2004). Schober (1999) has pointed out that little is known about how adults adjust to genitoplasty, nor are there any data in infants undergoing genitoplasty on what path they might have chosen had the opportunity been given to them as adults. It is clear that genital surgery does not "cure" a DSD. It is known that women with CAH are less satisfied with their genitalia than control subjects whether they had undergone an operation or not (Nordenskjold et al, 2008).

Unfortunately, a dilemma remains for DSD surgery because there is no absolute correct answer at this time. Information should never be withheld from the parents, and counseling should be provided. Parents must be informed of all risks and options and be made aware of the current state of knowledge. They should also be given access to advocacy groups regardless of the groups stance on surgery. There is then a changing of attitudes toward early reconstructive procedures particularly with regard to clitoral surgery (Lee et al, 2006).

For the purposes of the remaining description of surgical techniques, it is assumed that all parties (parents and medical team) agree that surgery is warranted.

Children born with a urogenital sinus associated with genital ambiguity usually have clitoral hypertrophy, fusion of the labia majora with absence of the labia minora, and a common urogenital sinus (Fig. 134–37). Furthermore, it has been shown that there is significant variability in what is considered normal clitoral, vaginal, and labial size (Lloyd et al, 2005). **Therefore, genital reconstruction involves three steps: (1) clitoroplasty, (2) labioplasty, and (3) vaginoplasty.**

Historically, clitoroplasty has been performed early in life, but this has again been challenged by DSD advocacy groups and physicians. In the mid 1900s there was not thought to be an optimal timing for reconstruction (Jones and Jones, 1954; Lattimer, 1961), but more recently, clitoral reconstruction has been carried out progressively earlier. Gross and colleagues in 1966 and Spence and Allen in 1973 noted that clitoral surgery can ideally be performed when the child is 1 year old. By the 1980s, clitoral surgery was

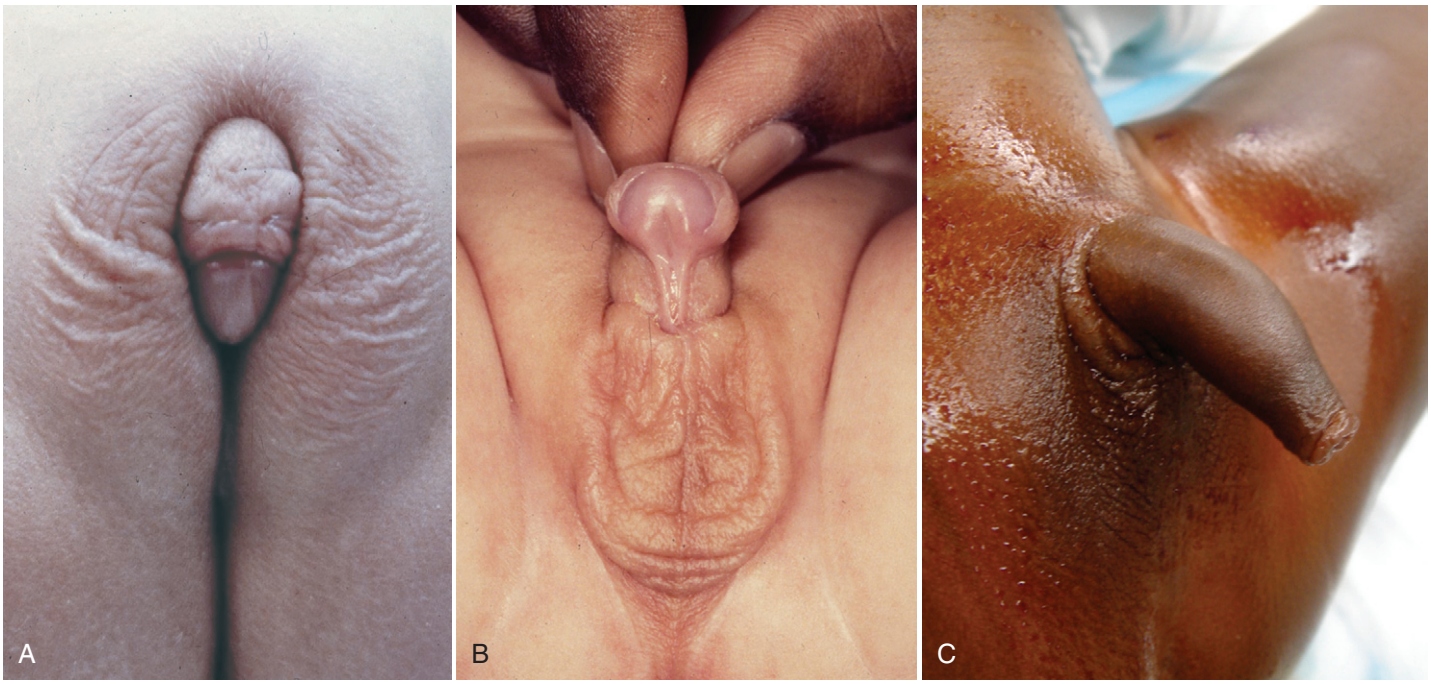


Figure 134–37. External appearance of genitalia in congenital adrenal hyperplasia. **A**, Moderately virilized with incomplete labioscrotal fusion. **B**, Moderately virilized with complete labioscrotal fusion. **C**, Severely virilized.

recommended as early as the first few months of life (Snyder et al, 1983). More recently, de Jong and Boemers (1995) reported surgical correction at 1 to 3 weeks of age. Parents are now less likely to choose surgery for minimal clitoral hypertrophy and the consensus document recommends surgery for only the more severe degrees of hypertrophy (Prader III-IV) (Lee and Witchel, 2002; Hughes et al, 2006).

The optimal timing for vaginoplasty likewise continues to be debated. Some have based the timing partly on the level of the vaginal confluence. A consensus statement on CAH from the Lawson-Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology recommends surgery in the 2- to 6-month-old range for those with a high vaginal confluence, and surgery between 12 months and adolescence is not recommended (Consensus statement, 2002). **"There is inadequate evidence currently in relation to establishment of functional anatomy, to abandon the practice of early separation of the vagina and the urethra"** (Hughes et al, 2006).

Simultaneous performance of clitoroplasty, vaginoplasty, and labioplasty has been the standard practice for a child with a low (distal) vaginal confluence. Two separate schools of thought have been put forth for a high vaginal confluence. Some believe that the high rate of vaginal stenosis warrants delay of vaginal surgery until after puberty, which also avoids any need for vaginal dilatation (Sotiropoulos et al, 1976; Snyder et al, 1983; Alizai et al, 1999; Creighton et al, 2001; Rangecroft, 2002; Thomas, 2004). Others have found the incidence of vaginal stenosis to be higher in those who undergo surgery after puberty rather than during infancy (Eroglu et al, 2004). **The authors along with others believe that vaginoplasty, regardless of the vaginal location, is best combined with clitoroplasty and labioplasty in a single stage. This allows the surgeon flexibility in using redundant phallic skin for the reconstruction, which is compromised when the skin has previously been mobilized** (Mandell et al, 1988; Gonzalez and Fernandes, 1990; de Jong and Boemers, 1995; Hendren and Atala, 1995; Rink et al, 1997; Passerini-Glazel, 1998). Lean and colleagues (2007) found any plans for one-stage repair to give better results. **Furthermore, several authors have noted that maternal estrogen stimulation of the child's genitalia results in thicker vaginal tissue that is better vascularized, thus making it easier to perform early vaginal mobilization** (Passerini-Glazel, 1989; Donahoe and Gustafson, 1994; de Jong and Boemers, 1995; Rink and Adams, 1999; Farkas et al, 2001; Hensle and Bingham, 2002; Eroglu et al, 2004). Schober (2004) has noted that estrogen has a beneficial effect on the tissues, which may result in improved outcomes and making puberty the best opportunity for reconstruction.

Today, when performing clitoroplasty, every effort is made to not only provide excellent cosmesis but also retain normal clitoral innervation for optimal sexual gratification. Clitoral surgery has undergone significant evolution. Initial efforts were primarily directed at not just amputating the clitoris but also completely excising all clitoral tissue to avoid any later painful erection (Jones and Jones, 1954; Gross et al, 1966; Hendren and Crawford, 1969). Clitoral amputation was based on reports by both Hampson and Gulliver, who noted that the clitoris was not necessary for normal sexual response (Hampson, 1955). As recognition of the importance of the clitoris evolved, several ingenious clitoral recession techniques that preserved the innervation and all clitoral tissue were reported. Lattimer, in 1961, recessed the clitoris in subcutaneous fat and buried it beneath the skin. Kaplan (1967) reported an interesting technique of splitting the two corpora apart and performing closure in a transverse Heineke-Mikulicz fashion. Randolph and Hung (1970) and also Pellerin (1965) buried the corpora beneath the pubis. Efforts to preserve the glans based on a flap were attempted as early as the 1930s by Young, but the glans sloughed (Young, 1937). In 1961, Schmid was the first to report excising corporeal tissue yet preserving the neurovascular bundle with the glans intact. Kumar and coworkers (1974) later noted a similar technique proposed by Keifer the same year. Spence and Allen (1973) excised all of the clitoral shaft but left the glans intact to survive from the attached ventral urethral plate. **Virtually all techniques since have been based on Schmid's preservation of the neurovascular bundle** (Shaw, 1977; Barrett and Gonzales, 1980; Glassberg and Laungani, 1981; Mollard et al, 1981; Rajfer and Ehrlich, 1982). Although the glans often did well with these techniques, shrinkage and devascularization occurred at times. **Kogan and associates** (1983) **reported subtunical excision of the erectile tissue by incising laterally through Buck fascia to resect the erectile corpus cavernosa tissue.** Clitoroplasty techniques exhibited only minor technical advances until the recent demonstration of the neurovascular anatomy of the clitoris by Baskin and coworkers (1999). This work suggests that a ventral, rather than lateral, incision would preserve not only the main dorsal neurovascular bundle but also the neural branches that fan out laterally (Fig. 134–38). Currently, much research is under way to further evaluate clitoral neuroanatomy, as well as techniques to evaluate sexual sensitivity. And there have been two recent reports of preserving the Buck fascia with the neurovascular bundle and glans. The corporeal bodies are mobilized and disassembled and then placed in the labial fat. This allows the option of later use for reconstruction of the phallus should the patient choose a male gender identity (Pippi Salle et al, 2007).

Vaginoplasty techniques have similarly evolved, with all repairs based on a few landmark reports. **Almost every vaginal repair today uses a posteriorly based perineal flap proposed by Lattimer and originally described by Fortunoff and coworkers in 1964.** This wide-based Fortunoff flap has recently been modified to a more omega-shaped flap that has resulted in improved cosmesis (Jenak et al, 2001; Freitas-Filho et al, 2003). **In 1969, Hendren and Crawford reported a "pull-through" vaginoplasty for a high vaginal confluence.** Their efforts to establish the location of the vaginal confluence as the determining factor for the type of vaginoplasty remain the basis for all vaginoplasties today. Vaginal reconstruction techniques now generally take the form of one of four types. **(1) The cut-back vaginoplasty is rarely used and is appropriate for only simple labial fusion. (2) The flap vaginoplasty is applicable to a low (distal) vaginal confluence.** In this procedure, the posterior walls of the sinus and vagina are opened, but the anterior wall of the vagina is left intact. The posterior perineal flap fits into the opened vagina. **This procedure does not change the level of confluence; it simply widely opens the introitus and urogenital sinus** (Rink and Adams, 1998). Mild degrees of female hypospadias are common with this technique. The authors and others believe that a flap vaginoplasty should never be used for patients with a very high vaginal confluence because it may result in a short hypospadiac urethra, vaginal voiding, many infections, and even incontinence (Hendren and Atala, 1995; Rink and Adams, 1999). **(3) The pull-through vaginoplasty may be used for any level of confluence but is generally reserved for a very high confluence.** In this

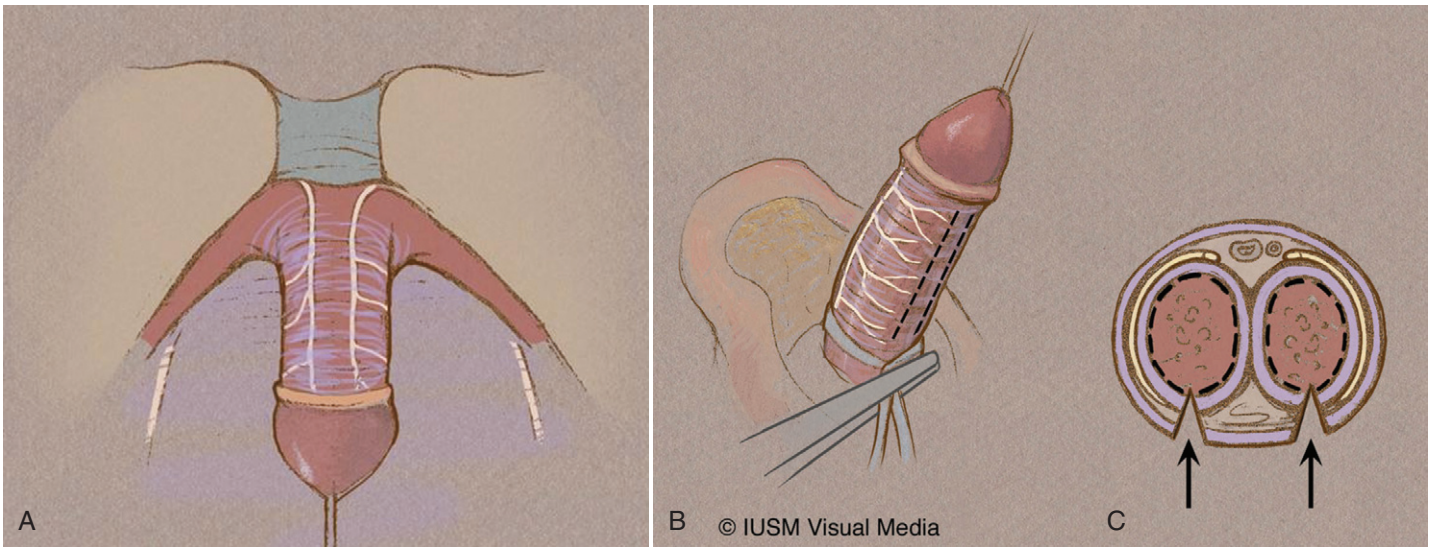


Figure 134–38. Hypertrophied clitoris with dorsal nerves and branches. **A**, Anteroposterior view. **B**, Side view. **C**, Cross-sectional view. (© Indiana University Medical Illustration Department.)

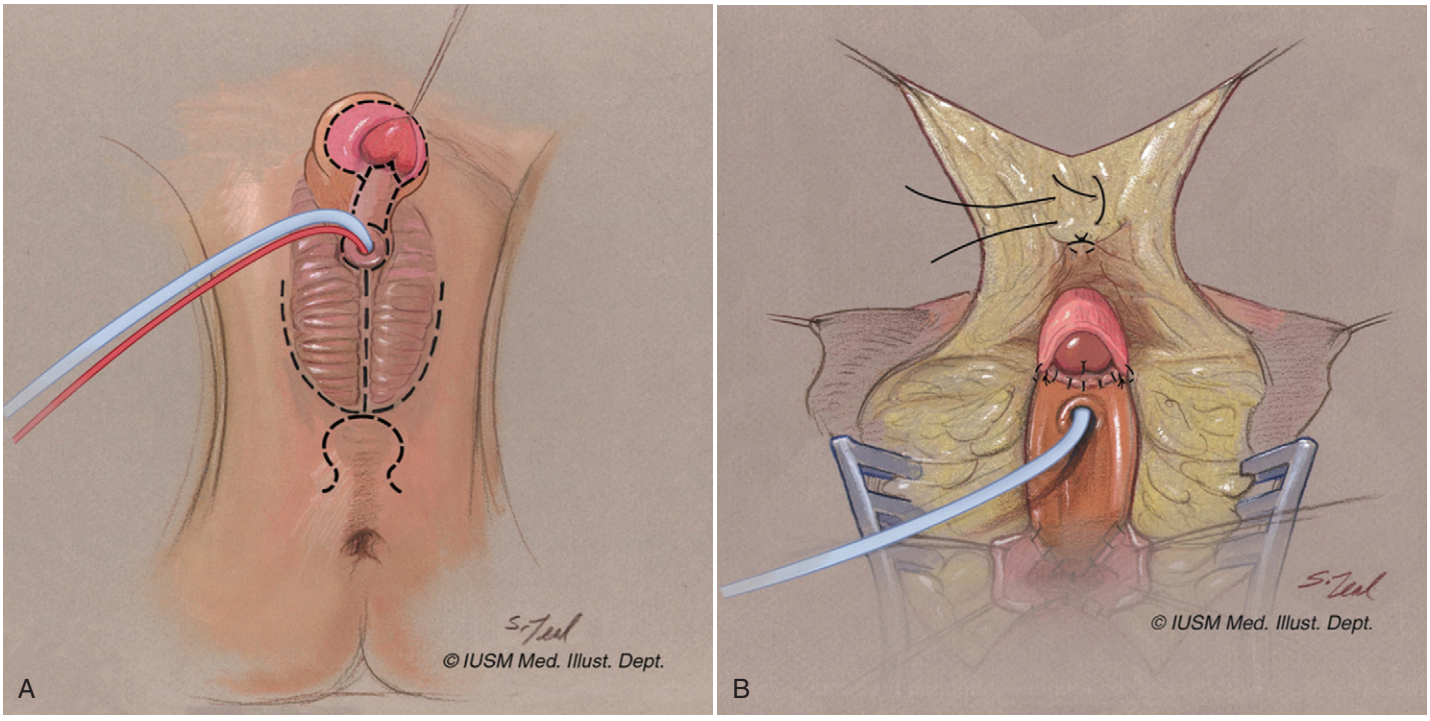


Figure 134–39. Labioplasty. **A**, Proposed incision lines for feminizing genitoplasty. Note preservation of skin cuff around glans clitoris that will be used to fashion clitoral hood. **B**, After recession of the glans clitoris the preputial skin is partially split to create the labia minora. The proximal preputial skin is plicated along its undersurface to create a "hooded" appearance to the segment of skin that will cover the glans. (© Indiana University Medical Illustration Department.)

procedure, the vagina is separated from the urogenital sinus, and the sinus is used to create a urethra. The mobilized vagina may reach the perineum, but in most cases skin flaps have been required. **(4) Complete vaginal replacement can be achieved by several techniques, but it is used only for a rudimentary or absent vagina.**

Labioplasty techniques also continue to evolve. In CAH and other DSD states, the labia minora are absent and the labia majora are superior to the new vaginal introitus. Labia minora are created by using the split phallic skin as described by Marberger (1975). Both the labia majora and labia minora should be moved inferiorly by YV-plasty to create a normal cosmetic appearance of the vagina now located between the labia (Hendren and Donahoe, 1980; Rink and Adams, 1998) (Fig. 134–39).

Regardless of the surgeon's personal bias toward reconstruction or its timing, a balanced presentation of all pros and cons of surgery versus no surgery is imperative. All current data should be made available to the parents and the risks associated with each path clearly defined. The ultimate decision is the parents', but it should be made as a participant of a team. In the following sections, the techniques described are applicable to either infants or adolescents.

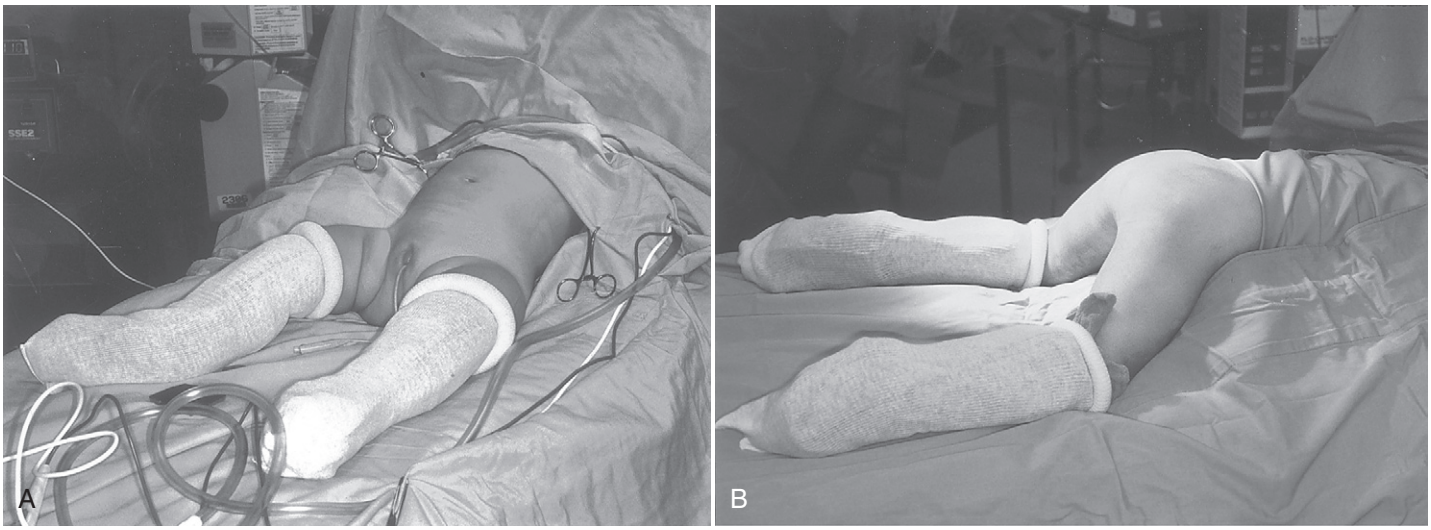


Figure 134–40. Total lower body preparation allows both supine (**A**) and prone (**B**) approaches. (From Rink RC, Adams MC. Feminizing genitoplasty: state of the art. World J Urol 1998;16:212.)

Current Operative Techniques for Female Disorders of Sex Development and Urogenital Sinus Repair

Preoperatively, it is important to ensure that the patient is metabolically stable, particularly a child with CAH. Most children with CAH only require an enema, but if there is an indication of a high confluence, complete bowel preparation with a polyethylene glycol-electrolyte solution (GoLYTELY) is warranted. All children receive preoperative broad-spectrum antibiotics. Children with CAH should undergo "stress dose" steroid replacement at the time of surgery. After general anesthesia, endoscopy is performed as described previously. **After passing a Fogarty catheter into the vagina, the balloon is inflated and the catheter is clamped and left indwelling. A Foley catheter is then anchored in the bladder.** Both are kept sterile, and the child is prepared with povidone-iodine. Many surgeons prefer to place the child in lithotomy position, but we have found that this position limits vision to only the surgeon, hinders teaching, and does not allow manipulation of the child if a posterior or abdominal approach is unexpectedly needed. All children undergo a complete lower body preparation from nipples to feet. The child's legs are wrapped, and the lower part of the body is passed through the aperture in the drapes; this facilitates access to the entire perineum and abdomen and further allows the child to be rotated either supine or prone during the procedure (Fig. 134–40). In the postpubertal patients, total body preparation may be difficult and necessitates the lithotomy position.

Key Points: Urogenital Sinus Anomalies—Reconstruction

- The three steps in surgical reconstruction are clitoroplasty, vaginoplasty, and labioplasty.
- Clitoroplasty is controversial. When performed, the glans and tunics with their neurovascular bundles must be preserved. Excision of erectile tissue, when performed, must be from the ventral aspect only.
- Vaginoplasties consist of four types: cutback (no longer used), "flap" for a low to midlevel confluence, "pull-through" for a high confluence, and vaginal replacement for a rudimentary or absent vagina. The timing of vaginoplasties is controversial.
- Labia minora are absent in urogenital sinus patients with genital ambiguity. They are reconstructed from phallic skin. The anteriorly located labia majora should be moved inferiorly.
- It is helpful to place a Fogarty catheter with the balloon inflated in the vagina. For a low confluence, an omega-shaped perineal flap provides better cosmesis. The flap is sewn into the posteriorly opened sinus, and this flap must reach to the more proximal normal-caliber vagina.
- For a high confluence, the vagina may require separation from the urinary tract at its confluence and is "pulled through" toward the perineum. The sinus opening is closed to create a urethra.

Low Vaginal Confluence—Clitoral Hypertrophy

The vast majority of children who undergo surgery for DSD or urogenital sinus conditions have a low vaginal confluence amenable to flap vaginoplasty. They usually have clitoral hypertrophy. Clitoroplasty and classic flap vaginoplasty are described. With the child in the supine position, a traction suture is placed through the glans and the proposed incisions are outlined with a skin scribe. Along these lines, 0.5% lidocaine with 1:200,000 epinephrine is injected subcutaneously for hemostasis. The proposed circumferential incision around the glans leaving the inner surface of the prepuce intact is drawn along with parallel longitudinal lines on either side of the ventral mucosal strip (urethral plate equivalent) extending around the meatus. A perineal omega-shaped flap with the apex near the meatus is outlined. A Y-incision line is drawn around the inferior aspect of each labia majora. The incision begins on the dorsal aspect of the clitoris and all inner preputial skin is left intact for later construction of a clitoral hood. This skin has been shown to be second only to the glans in sensitivity (Schober and Ransley, 2002). The clitoris is degloved while keeping the ventral "urethral plate" intact with the meatus. Dissection is carried out to the level of the bifurcation of the corporeal bodies and the pubis dorsally, and care should be taken to not injure any neurovascular tissue (see Fig. 134–38). It is important to recognize that the clitoral arterial supply branches

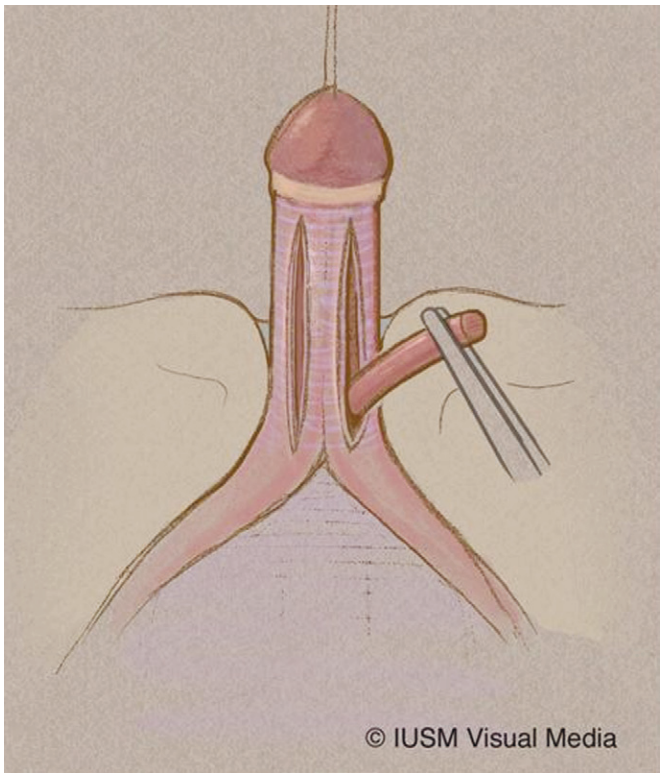


Figure 134–41. Proposed clitoral incisions. Note the ventral location. (© Indiana University Medical Illustration Department.)

from the internal pudendal artery from the Alcock canal near the ischial tuberosity. These arteries course ventrally and are on the medial aspect of the bifurcated corpora, where they then course dorsally along the phallic shaft (Schnitzer and Donahoe, 2001). The clitoral neural bundles ascend along the ischiopubic rami and meet as paired bundles that pass along the dorsal surface and then pass largely intact into the glans (Baskin et al, 1999; O'Connell et al, 2005). The authors' current clitoroplasty technique is described but regardless of technique, the just-described clitoral innervation must not be disturbed. A tourniquet is placed at the base of the clitoris. Longitudinal incisions are then made through the Buck fascia on the ventralmost aspect of each corporeal body (Fig. 134–41); the incisions extend from the glans to the bifurcation to expose the corpora cavernosa tissue, which is dissected (often teased) from the tunics. The tunics are left undisturbed, except for the ventral incision. **No tunical tissue is excised. The dorsal neurovascular bundle should not be mobilized or disturbed in any way.** The proximal ends of the erectile tissue only are suture ligated. Efforts to decrease the size of the glans are controversial and, if attempted, should be done with great caution. Studies of Juskiewenski and associates (1982) and Baskin and colleagues (1999) would suggest that any glans excision should be performed ventrally near the midline (similar to hypospadias glans wings). The glans is innervated by perforating branches entering at the dorsal junction of the glans and corpora (Baskin et al, 1999). Excision of glanular epithelium to conceal the glans is to be avoided because the sensory neuropeptides are located just beneath this layer. Remember there are no data to suggest that a large glans is detrimental to sexual function. The glans is now secured to the coronal stumps. In the authors' experience, a glans sewn to the pubis results in an abnormally high prominent position (Rink and Yerkes, 2001).

With clitoroplasty completed, the flap vaginoplasty is started. The previously outlined omega flap is incised, and the underlying fat is mobilized with the flap to expose the urogenital sinus. The flap must be made long enough to provide a tension-free anastomosis to the vagina and wide enough to provide a normal-caliber introitus without compromising the blood supply of the perineal body. The posterior wall of the sinus and vagina is now dissected free from the underlying rectum. This initial posterior step in separating the vagina from the rectum is the most difficult. With stay sutures in the meatus, the posterior wall of the sinus is opened in the midline and extended proximally into the posterior wall of the vagina. **The distal third of the vagina is usually narrowed; therefore, the posterior wall incision must be carried proximally until normal-caliber vagina is encountered.** Sutures are placed individually through the perineal flap and then through the split posterior wall of the vagina and tied.

The mobilized phallic skin is unfurled and divided longitudinally in the midline while stopping short of the base to allow a clitoral hood. This tissue at its base is incorporated with the preputial skin to create a clitoral hood. Labia minora are now created with this split preputial skin, which is moved inferiorly and anastomosed to the preserved ventral plate and the lateral vaginal wall. The proposed Y incisions are now made around the inferior aspect of each labia majora. The labia are mobilized and secured inferiorly alongside the vagina as a YV-plasty. The vaginal introitus should now reside between the labia minora and majora rather than appear as an isolated hole on the perineum.

High Vaginal Confluence—with or without Clitoral Hypertrophy

Most believe that complete separation of the vagina from the urogenital sinus with a "pull-through" vaginoplasty, as proposed by Hendren and Crawford (1969), **is the best solution to a high vaginal confluence.** Fortunately, this complex situation is found in only about 5% of patients with CAH (Dumanian and Donahoe, 1992). This high confluence is more commonly seen in pure urogenital sinus abnormalities. Although the concept of vaginal separation and pull-through was a major advance, the operation as originally described frequently resulted in an isolated vaginal opening that appeared to be separate from the remainder of the genitalia, and a mucosal lining was lacking (Passerini-Glazel, 1989). It was also technically difficult because of poor vision at the critical points (Rink et al, 1997). Several authors have addressed these issues. Passerini-Glazel (1989) used the mobilized sinus by dividing it dorsally; when tabularized with the phallic skin and folded back toward the vagina, it would create a more normal cosmetic result and provide excellent coverage in the area of the vaginal separation while helping to prevent a urethrovaginal fistula. He later used this as a flap to form the anterior vaginal wall rather than completely tubularizing it (Passerini-Glazel, 1994). Gonzalez and Fernandes (1990) used the preputial skin to construct the vaginal vestibule and anterior wall.

The critical and most technically demanding aspect of a pull-through vaginoplasty is separation of the anterior wall of the vagina from the urethra and bladder neck. There is no obvious plane of dissection, and great care must be taken to avoid injury to the urinary tract and its sphincteric mechanism. This area is also the most difficult to visualize, and poor exposure naturally leads to poor results, with the potential for a stricture, fistula, diverticulum, or retained distal vagina (Rink and Adams, 1998). Furthermore this is an area of significant nerve supply for the

vagina and urethra. Most surgeons have positioned the patient in the supine or lithotomy position. Several authors have reported means of improving exposure. Passerini-Glazel (1989, 1994) mobilized the vagina transtrigonally in difficult cases but has more recently reported that this approach is seldom necessary. Similarly, Di Benedetto and Rossi and their associates proposed an anterior sagittal transanorectal approach with a diverting colostomy (Di Benedetto et al, 1997; Rossi et al, 1998). Hendren and Atala (1995) reported lateral mobilization of the rectum in 1995 but have since stopped because of the difficulty of this maneuver. Rink and colleagues (1997) reported a midline posterior prone approach with retraction but not division of the rectum that provides excellent exposure for critical aspects of the pull-through vaginoplasty and is described here. Endoscopy with Fogarty and Foley catheter placement and total-body preparation are as described for a flap vaginoplasty. If the child has associated clitoral hypertrophy, the clitoroplasty is performed with the child supine as described earlier for a low confluence. The child is then rotated to the prone position. In a patient with a pure urogenital sinus, the procedure is started with the patient in the prone position.

The perineal omega-shaped flap incision is made as previously described, and then the flap is retracted posteriorly, with dissection now carried out in the midline between the posterior wall of the sinus/vagina and rectum. As dissection proceeds proximally, the rectum is easily retracted with a small Deaver retractor (Fig. 134–42) to expose the entire urogenital sinus without the need to divide the rectum. The entire length of the sinus may be divided in the midline posteriorly to the normal caliber of the vagina. The Deaver retractor is now placed in the vagina and with upward retraction easily exposes the anterior wall of the vagina at its confluence with the sinus. This allows dissection of the vagina from the urethra under direct vision (Fig. 134–43). The tissues are quite thin in this area, and one should always err on the side of the vagina. More proximally, the dissection becomes easier. Excellent vision is also provided for tubularization of the sinus to create a urethra, which is closed in two or three layers over a Foley catheter. The anterior wall of the vagina is now mobilized inferiorly, closer to the perineum. "Pull-through" vaginoplasty is often a misnomer because frequently the separated vagina will not reach the perineum. In this situation, skin flaps have been used to reach up to the vagina (rather than the vagina "pulled through" to the perineum). Preputial skin may be sewn to the spatulated anterior vagina, as described by Gonzalez and Fernandes (1990) (Fig. 134–44). When preputial skin is not available, a buttock flap or a laterally based skin flap can be used (Parrott and Woodard, 1991; Dumanian and Donahoe, 1992) (Fig. 134–45). The child is returned to the supine position, and the posterior perineal flap is anastomosed to the vagina as described for the flap vaginoplasty. The authors believe that skin flaps are best avoided because they are more likely to stenose and may be hair bearing. The use of urogenital tissue to create the flaps is more reliable, as in the Passerini-Glazel flap.

Labioplasty is now completed as described earlier. If a laterally based flap is required for the anterior wall, posterior relocation of the labia majora may be performed at a later stage.

In patients with a high confluence, particularly if multiple flaps have been used, the legs are bound together loosely postoperatively to prevent tension on the flaps.

Total and Partial Urogenital Mobilization

In 1997, Alberto Pena proposed a maneuver called ***total urogenital mobilization (TUM)*** as a means to repair the urogenital sinus component of a cloacal repair. **In this procedure the entire sinus is dissected circumferentially and mobilized toward the perineum.** Pena noted a decrease in operative time by 70%, a superior cosmetic result, and less risk of fistula, vaginal stenosis, or acquired vaginal atresia with TUM because vaginal separation is not usually required. Since Pena's original

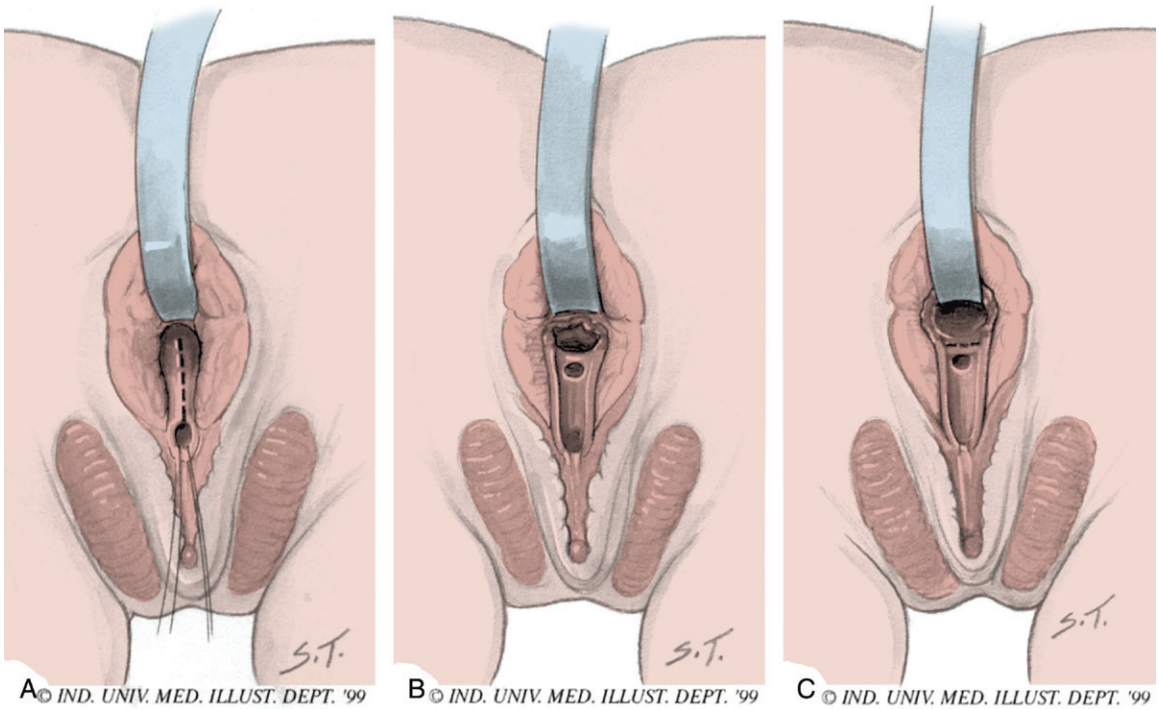


Figure 134–42. **A**, Posterior flap developed with the sinus exposed. **B**, Sinus opened in the posterior midline. **C**, Retractor in the vagina. (©1999, Indiana University Medical Illustration Department.)

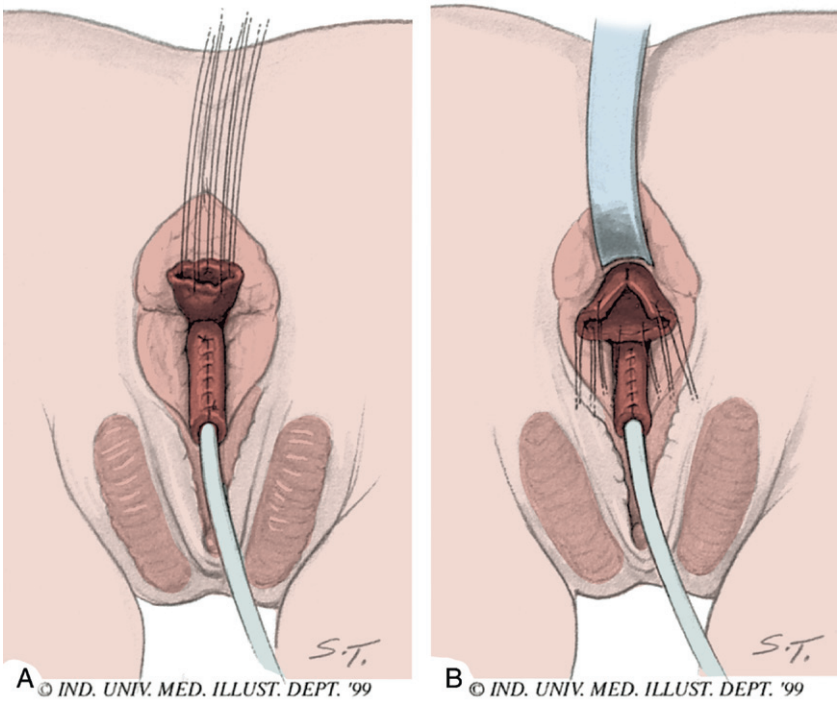


Figure 134–43. **A**, Vagina mobilized and the sinus tubularized to create a urethra. **B**, Posterior vagina spatulated. (©1999, Indiana University Medical Illustration Department.)

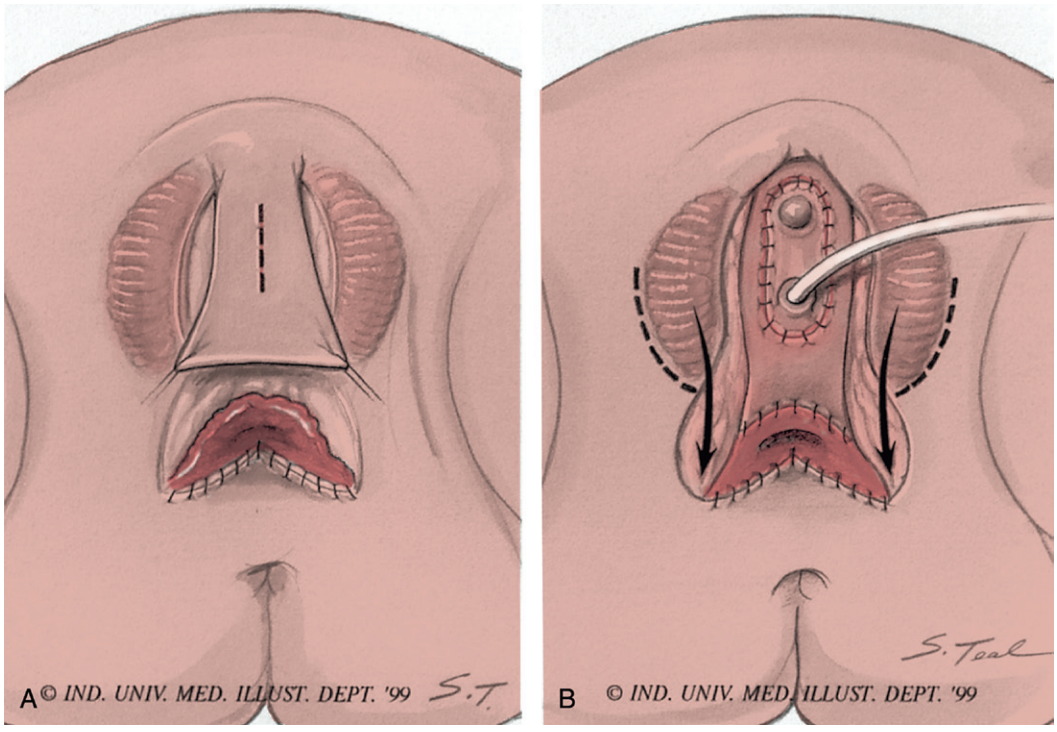


Figure 134–44. **A** and **B**, Modified Gonzalez preputial flap to create an anterior vaginal wall; the posterior flap has been anastomosed to the spatulated vagina. (©1999, Indiana University Medical Illustration Department.)

description, TUM has been applied to several disorders, such as urogenital sinus, female exstrophy, and penile agenesis (Ludwikowski et al, 1999; Kropp and Cheng, 2000; Rink et al, 2006). Both Pena and Ludwikowski's group reported amputation of the mobilized sinus so that the vagina and urethra can be sewn flush to the perineum (Pena, 1997; Ludwikowski et al, 1999). **The authors have reported using the mobilized sinus to provide a mucosa-lined vestibule or a Passerini flap to cover the anterior vaginal wall when a pull-through procedure is performed** (Rink and Adams, 1999; Rink et al, 2006). Jenak and associates (2001) have since reported similar use of the mobilized sinus to create a mucosal vestibule, and Hamza and colleagues (2001) have noted that the sinus may be used as a Passerini-like flap. There have been two recent descriptions of use of the mobilized sinus to replace the posterior perineal-based skin flap with a sinus flap. In one, the sinus is split laterally and rotated posteriorly (Rink and Cain, 2002, Rink et al, 2006). In the other, the sinus is split in half longitudinally and the two halves are

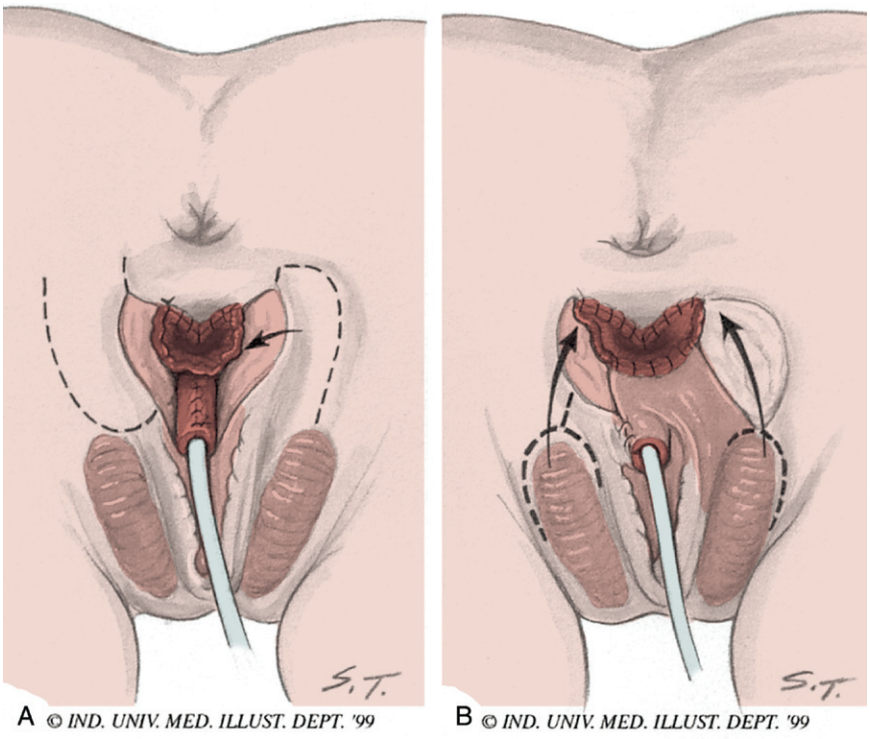


Figure 134–45. **A** and **B**, A buttocks- or labial-based flap may be used to create the anterior vaginal wall in a patient with a pure urogenital sinus. (©1999, Indiana University Medical Illustration Department.)

rotated inferiorly (Gosalbez et al, 2005). At the Riley Hospital for Children, the authors have incorporated urogenital mobilization techniques into nearly all of our urogenital sinus repairs. **It allows a midlevel confluence to reach the perineum without requiring vaginal separation. The highest-level confluences may still need a pull-through procedure with separation of the vagina and urethra,** but it is much more easily performed after the urogenital sinus has been mobilized.

TUM is often thought of as its own type of vaginoplasty but is, in fact, a technique to allow vaginoplasty that may result in the vagina being sewn flush to the perineum; however, a flap or pull-through vaginoplasty may still be required. Only rarely do the authors believe the vagina should be sewn flush to the perineum, owing to concerns of a circumferential anastomosis becoming stenotic. TUM is started, as previously described, with endoscopy to evaluate the anatomy, to note the level of the confluence, and to place a Fogarty catheter in the vagina and a Foley catheter in the bladder. A sponge is placed in the rectum, and the proposed incisions are outlined. Subcutaneous injection of 0.5% lidocaine with 1:200,000 epinephrine along the lines is carried out. Clitoroplasty is performed as previously described, with the meatus of the urogenital sinus and urethral plate being circumscribed with stay sutures to allow mobilization of the sinus from the corporeal bodies. This is initially carried out to just between the bifurcation of the corporeal bodies. The clitoroplasty is now completed as described earlier. The dissection is carried out in the midline posterior to the sinus until the peritoneal reflection is reached to allow access to the entire posterior wall of the vagina (Figs. 134–46 and 134–47). This circumferential mobilization is done directly on the urogenital sinus and continues proximally beneath the pubis. As the avascular ligaments from the pubis to the sinus are divided in this area, the entire urogenital sinus is felt to "give" and move toward the perineum (Fig. 134–48).

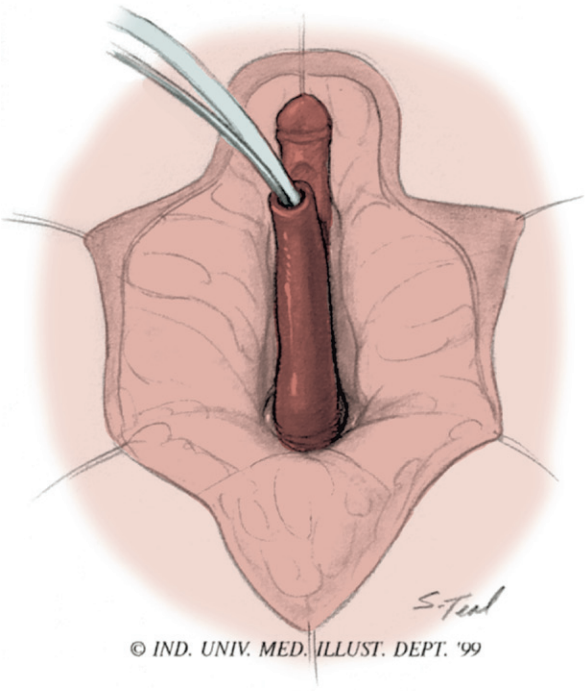


Figure 134–46. Skin mobilized with the sinus exposed. (©1999, Indiana University Medical Illustration Department.)

The Fogarty balloon is now easily palpable in the vagina. The posterior wall of the vagina is opened between stay sutures. If the vagina is now near the perineum, it may be sewn flush to the perineum, or an omega-shaped perineal flap may be placed into the spatulated posterior wall to augment the vaginal caliber. The authors prefer the latter. Rather than discard the mobilized sinus,

as previously reported, it is helpful to split the sinus ventrally and use it to provide a mucosa-lined vestibule (Fig. 134–49). If the vagina is still quite high, the anterior wall of the vagina should be separated from the urethra and bladder neck, as in the pull-through procedure (Pena, 1997; Rink and Kaefer, 2002; Rink et al, 2006). This is most easily performed with the child in the prone position to allow direct vision. The opening in the urethra is closed in two layers. The mobilized sinus in this situation is split anteriorly and then used as a Passerini-like flap to create the anterior vagina wall (Rink and Adams, 1999; Rink et al, 2006) (Fig. 134–50). The posterior perineal flap is approximated to the spatulated posterior vaginal wall. Labioplasty is performed as previously described. TUM has achieved great popularity, and reports to date reveal excellent cosmesis and continence. No long-term results are available.

Some have expressed concern regarding the proximal circumferential dissection because of the potential risk for sphincteric musculature or nerve injury. There is concern for resultant stress incontinence or foreshortening of the vagina. **To address these concerns, Rink and associates** (2005c; 2006) **proposed *partial urogenital mobilization* (PUM), a technique that starts with the same circumferential dissection but stops at the level of the pubourethral ligament** (Fig. 134–51). This still allows use of the mobilized sinus as described earlier to improve cosmesis, yet it avoids the aggressive retropubic and suprapubic dissection and is applicable to the majority of patients. If more mobilization is necessary for a very high vagina, TUM is easily carried out.

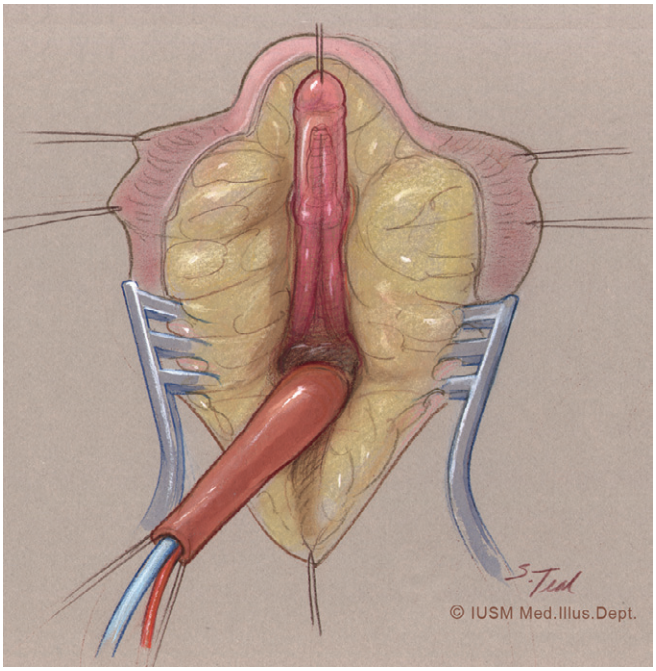


Figure 134–47. Total urogenital mobilization with the sinus mobilized. (© Indiana University Medical Illustration Department.)

Key Points: Urogenital Mobilization

- TUM is a technique applicable to both urogenital sinus and cloacal anomalies. The entire sinus is dissected circumferentially to above the pubis to allow the confluence to move inferiorly to the perineum.
- With the TUM or PUM technique, the mobilized sinus tissue can be used to create a mucosa-lined vestibule or an anterior or posterior vaginal wall. This sinus tissue should not be discarded.
- PUM circumferentially mobilizes the sinus to the level of the pubourethral ligament but does not extend above this level.

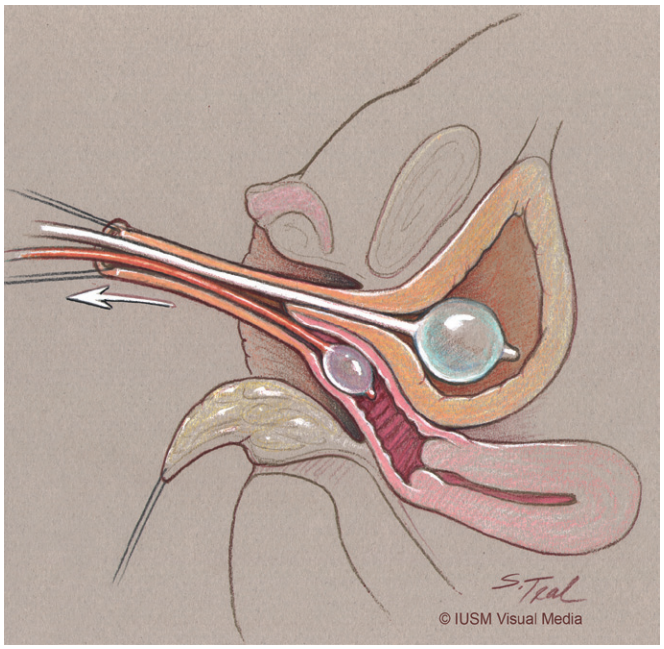


Figure 134–48. Total urogenital mobilization. The sinus is mobilized to a position beneath the pubis. (© Indiana University Medical Illustration Department.)

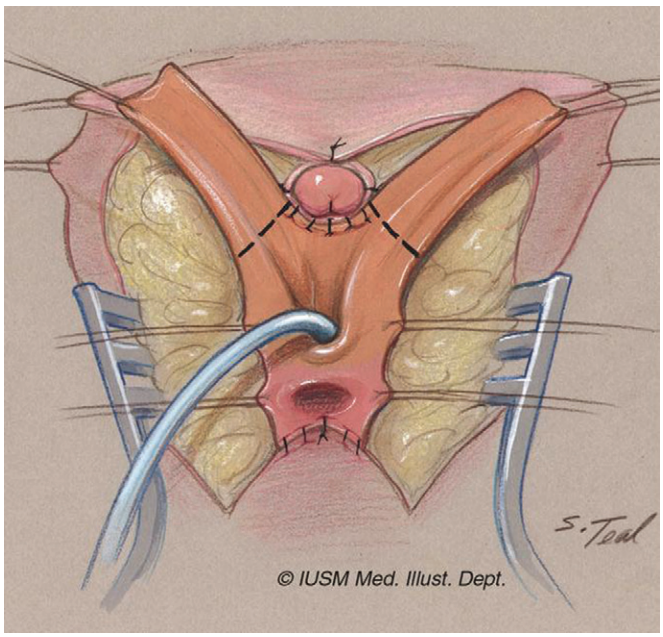


Figure 134–49. A ventral incision on the mobilized sinus allows the creation of a mucosa-lined vestibule. (© Indiana University Medical Illustration Department.)

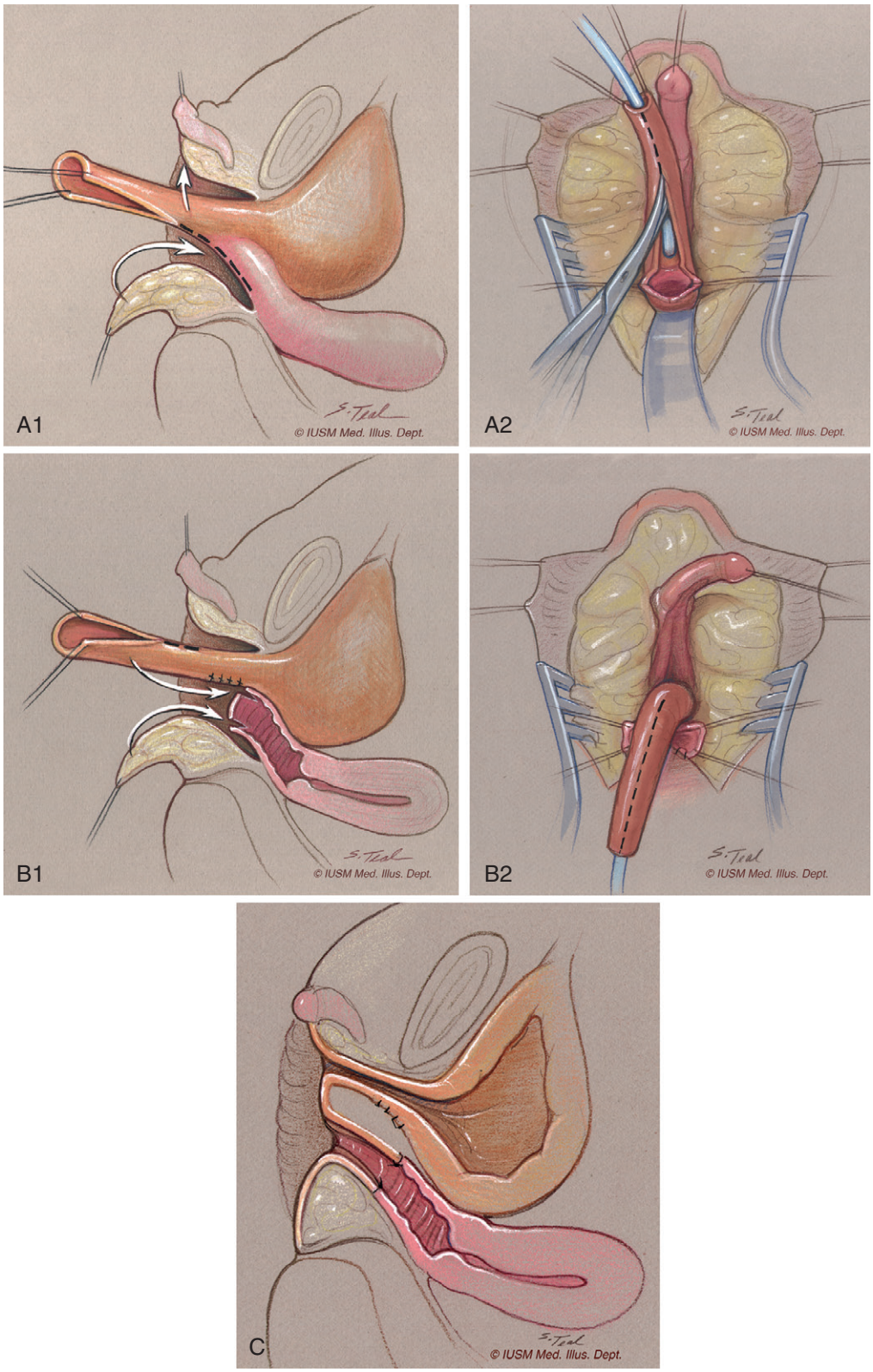


Figure 134–50. Total urogenital mobilization. **A1** and **A2**, For flap vaginoplasty the sinus is split ventrally to create a mucosa-lined vestibule. **B1** and **B2**, For pull-through vaginoplasty the sinus is split dorsally to create an anterior vaginal wall. **C**, The opened sinus now becomes the anterior vaginal wall. (© Indiana University Medical Illustration Department.)

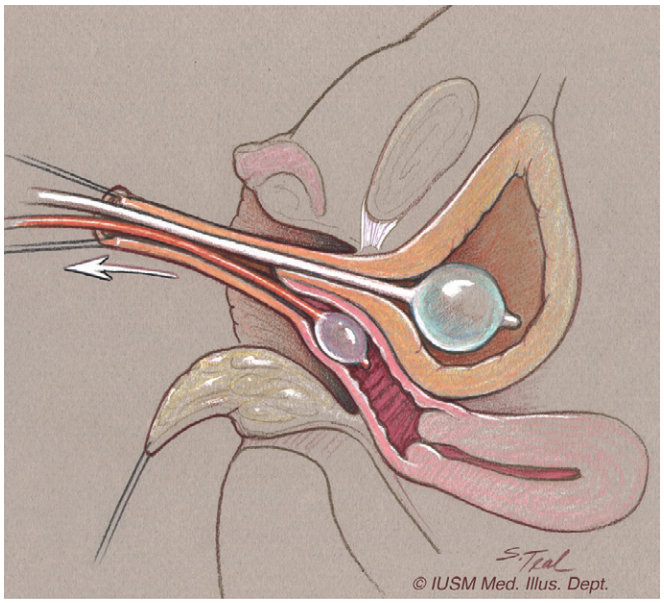


Figure 134–51. Partial urogenital mobilization. Dissection stops at the pubourethral ligament. (© Indiana University Medical Illustration Department.)

Results of Urogenital Sinus and DSD Surgery

Only recently have we started to see more long-term surgical reports for DSD patients after feminizing genitoplasty. Most articles look at success as an adequately open vagina with a feminized appearance. Success should include normal erotic sensation, lubrication, sexual satisfaction, orgasm, and intercourse without discomfort. These latter factors are just beginning to be studied. **Cosmetic and early functional results have uniformly been reported to be good. Long-term outcomes are of more concern,** but in these studies it is often difficult to tell what procedures were done for what degree of severity of urogenital sinus, and none of the studies include data on the quality of endocrinologic control in these patients. Looking at what data are available, Jones and colleagues noted in 1976 that 25 of 84 patients undergoing vaginoplasty required a secondary procedure to provide a vaginal outlet satisfactory for intercourse; 5 of these 25 also required a third procedure. **The poor results were caused by failure to exteriorize the vagina initially or by scar formation. The distal vagina is always narrow. The normal caliber vagina must always be reached and exteriorized with current procedures.** Sotiropoulos and associates (1976) found that all patients undergoing prepubertal vaginoplasty required revision at puberty. Azziz and coworkers, in 1986, reported the results of attempted coitus in 42 women with CAH 23.6 years after vagina repair. Satisfactory coitus was noted in 62% (46% in salt wasters and 87% in those with the non–salt-losing form). There was a less favorable outcome when the initial procedure was performed before 1 year of age. Thirty secondary or tertiary procedures were needed to achieve the final results. These data are widely quoted, but almost all of these patients underwent a "cut-back" vaginoplasty initially ("incision of the urogenital sinus"), which is a procedure no longer used because it does not adequately open the vagina to the proximal normal caliber; specifically, the distal end of the vagina is narrowed and thus will be stenotic. Their revision involved the performance of a "flap" vaginoplasty, which currently would probably have been the initial procedure. In a series from Johns Hopkins Hospital, 28 patients (32% lost to follow-up) had adequate follow-up, 22 (78.6%) of whom needed further vaginal surgery (Bailez et al, 1992). The authors noted that if secondary surgery was needed for vaginal stenosis, success rates were high when the procedure was performed near puberty. This group also reported less favorable results in those younger than 1 year of age, with only 8 of 18 needing a secondary procedure requiring a flap. Nihoul-Fekete and colleagues (1982) noted that 30% of 43 CAH patients required secondary surgery. Hendren and Atala (1995), reporting on 16 patients with high vaginal confluence, noted that 6 of 9 adults had satisfactory coitus and 2 had vaginal stenosis.

More recently, Alizai and colleagues (1999) assessed 14 girls with CAH under anesthesia, 11 to 15 years old, who had undergone genitoplasty at a mean age of 2.5 years and noted that 13 of 14 required additional vaginal surgery. Stenosis was seen in 43% and persistent urogenital sinus with or without fibrosis in 50%. Minto and coworkers (2003) found that 39% of 28 patients required secondary surgery and a third procedure was required in 11%. Al-Bassam and Gado (2004) noted vaginal stenosis in 16% of their patients who underwent various types of vaginoplasties (43 vaginoplasties: 26 flap, 11 pull-though, 2 cutback, 3 sigmoid vaginal replacements). Nearly all underwent vaginal dilation. Vaginal stenosis was noted in 37% of CAH patients reported by Nordenskjold and colleagues (2008), whereas 15 of 50 noted painful intercourse. However, 24 of 41 vaginoplasties were cutbacks with 10 flaps and 7 combinations. Al-Bassam and Gado (2004) noted vaginal stenosis in 16% of their patients who underwent various types of vaginoplasties (43 vaginoplasties: 26 flap, 11 pull-through, 2 cutback, 3 sigmoid vaginal replacements). Nearly all underwent vaginal dilation. Vaginal stenosis was noted in 37% of Nordenskjold and colleagues' (2008) CAH operated patients with 15 of 50 noting painful intercourse. However 24 of the 41 vaginoplasties were cutbacks with 10 flaps and 7 combinations. It is tempting to assume that postpubertal vaginal surgery may result in better outcomes, but there are no data to support this assumption. Furthermore, Eroglu and associates (2004) actually noted less vaginal stenosis in those who underwent early single-stage repair (3.4%) than in those who underwent late vaginoplasty (42.8%). Lean and coworkers (2007) noted no difference whether the surgery was done before or after 2 years of age. In their series of 32 patients they noted good cosmesis in 72%, satisfactory in 22%, and poor in 6%. They believed that the planned one-stage operation gave better results than the planned multistage procedure, with only 2 of the former patients requiring further major surgery and 3 of 32 needing minor revisions. Al-Bassam and Gado (2004) also recommended a single-stage repair at 3 to 6 months of age.

It seems clear that a "single-stage" early vaginoplasty will probably require a secondary repair after puberty, but this should be expected because the orifice is likely to remain the size that was created given that there is no flow through the orifice in childhood. In the authors' experience, the secondary refinements are easily performed.

Surgical techniques to reduce clitoral size have dramatically improved and are now based on our current knowledge of clitoral neuroanatomy. Even though no long-term results are available for current techniques, some long-term results are now being reported for relatively modern techniques. Alizai and colleagues (1999) found clitoroplasty results to be unsatisfactory in 46%. **Gearhart and coworkers** (1995) **looked at pudendal evoked potentials after clitoroplasty and noted that modern clitoroplasties preserve nerve conduction in the dorsal neurovascular bundle.** Barrett and Gonzales (1980) found

intact sensation in all of their patients after clitoroplasty. Chase (1996) reported that even with normal evoked potentials there may be an absence of sensation and orgasm. The authors have not noted vascularization defects after modern clitoroplasty. It is clear that further long-term studies are necessary. Minto and coworkers (2003) found the clitoris to be cosmetically normal in 59% who had undergone clitoral surgery, but it was excessive in 20%, large in 7%, small in 7%, and absent in 7%. This group also reported that hot, cold, and vibratory sensation was markedly altered as recorded by a genitosensory analyzer. Sensation alone may be a poor indication of clitoral normality after surgery. Further studies to analyze the newest techniques are warranted. The erotic sensitivity and potential for orgasm should be studied. More recently, Nordenskjold and colleagues (2008) reviewed 62 CAH patients with 60 controls. Of the 49 who underwent clitoroplasty 16 had 1 operation, 14 had 2, 4 had 3, 4 had 4, and 11 had between 5 and 10 operative procedures. Twenty percent were not satisfied with their surgery. They thought there was decreased sensitivity. However, 50% of the nonoperated patients thought their clitoris was too large. There was no difference in the ability to achieve orgasm between the two groups. They noted that women with CAH were less satisfied with their genitalia whether operated or not.

The results of TUM and PUM are very early. These procedures are technically easier and the cosmetic results are superior, but whether the functional results are better is unknown. The potential for stress incontinence or denervation of the sphincteric mechanisms also is unknown. Most authors to date have not found continence to be altered by TUM (Rink and Adams, 1999; Hamza et al, 2001; Kryger and Gonzales, 2004; Rink and Leslie 2007). Until these results are available, this procedure should be used with caution.

Timing of vaginoplasty remains quite controversial. Although the few reported long-term studies suggest that delayed vaginoplasty may be preferable, most surgeons continue to recommend early surgery, particularly for the CAH group. Most would recommend delaying vaginoplasty for the patient with a small, very high confluence vagina. They argue that the available long-term studies are based on outdated techniques and that there are tremendous surgical advantages to a single-stage repair. Supporters of early vaginoplasty well recognize that secondary introitoplasty may be necessary, but this is usually accomplished easily. The argument, which will not be settled soon, contrasts two approaches, both of which usually result in two procedures: (1) a simple procedure in an infant (i.e., clitorolabioplasty) with a postpubertal extensive procedure (i.e., vaginoplasty) or (2) an extensive single-stage clitorolabiovaginoplasty in an infant with a simple introitoplasty in the postpubertal period.

Several studies have noted that the most important factor affecting results is whether there was a surgeon or surgical team with a special interest in feminizing genitoplasty procedures (Creighton et al, 2001; Lean et al, 2007; Nordenskjold et al, 2008). This suggests that supports for Centers of Excellence may be appropriate for the care of children with DSD.

Key Points: Urogenital Sinus Anomalies—Outcomes of Reconstruction

- It is clear that neonatal vaginoplasties will usually require a secondary procedure for stenosis after puberty (25% to 100%).
- Successful coitus is often reported, but further studies should note sexual satisfaction, lubrication, and erotic sensitivity, as well as nonpainful coitus.
- Current techniques of clitoroplasty seem unlikely to injure sensation, but newer studies question whether sensitivity is an adequate indication of clitoral function. Some studies note decreased sensation with newer techniques.

SURGICAL RECONSTRUCTION FOR CLOACAL MALFORMATIONS

Initial Management, Timing, and Principles

The initial management of cloacal anomaly involves stabilization because the child is often quite ill with abdominal distention that at times results in respiratory compromise. As with all other anomalies, its management has evolved. Historically, after decompression of the distended organs, it was common practice to perform a rectal pull-through procedure; genitourinary reconstruction followed at a later date, if at all (Okonkwo and Crocker, 1977). Hall and coworkers (1985) suggested that the vaginal surgery be done after puberty, when estrogen levels are higher. **Although it is tempting to perform a pull-through procedure only, it is now clear that this piecemeal repair of the cloaca is a disservice to the child and is absolutely contraindicated. It is optimal to repair all abnormalities (i.e., rectal, vaginal, and urethral) in a single stage** (Kay and Tank, 1977; Mollitt et al, 1981). **This allows the best exposure for the difficult rectal and vaginal separation.** Furthermore, the tissues have not been previously violated, and the rectum does not require remobilization. Hendren (1982, 1986) pointed out that rectal pull-through should never be done as a separate procedure. Of his 154 patients with cloacal anomaly, 60 were secondary cases, many of whom had undergone a previous pull-through procedure. Definitive repair in this situation often requires repeat rectal mobilization. Raffensberger (1988) proposed neonatal complete repair but later noted that this may not be appropriate. Levitt and Pena (2005) have stated that there are three pitfalls in the management of neonates with cloacae: (1) failure to recognize and manage hydrocolpos, (2) colostomy or vesicostomy problems, and (3) clinical misdiagnosis.

Surgical management now involves four basic steps: (1) decompression of the gastrointestinal tract, (2) decompression of the genitourinary tract, (3) correction of nephron-destructive or potentially lethal urinary anomalies, and (4) definitive repair of the cloaca.

Decompression of the Gastrointestinal Tract

Decompression of the gastrointestinal tract is done by colostomy. Although nearly all surgeons agree on the need for colostomy initially, the best anatomic location of the colostomy is debated. Hendren initially recommended a low-loop colostomy but more recently has performed a right transverse colon divided colostomy (Hendren, 1982, 1986, 1998). This change was prompted by difficulty in obtaining a bowel segment for vaginoplasty during the rectal pull-through procedure when a low colostomy has been performed. A divided transverse colostomy keeps the left colic blood supply intact (Hendren, 1992). Pena, as cited by Spitz and Coran (2006), preferred a descending colostomy because there was

less surface area for resorption of urine. A divided colostomy in the descending colon just after the colon takes off from its retroperitoneal attachment is now recommended by Levitt and Pena (2005). This procedure maintains the availability of enough distal colon for future pull-through, and prolapse is less likely to occur. However, Pena did recommend leaving a long segment of sigmoid to prevent a difficult pull-through requiring abdominal exploration. Levitt and Pena (2005) noted that 24 of 361 patients had a colostomy too low that interfered with the rectal pull-through. The authors have favored a proximal colostomy but have at times found clinically challenging acidosis caused by urine absorption through the colonic mucosa. Masuko and associates (2005) reported successful decompression of the colon by balloon catheter drainage with irrigation of the bowel three times a day. This avoided temporary colostomy and allowed a single-stage repair.

At the time of colostomy, endoscopy may be performed to more clearly define the anatomy and to aid in decompression of the urinary tract. In the authors' experience, as the cystoscope advances proximally through the cloacal channel, it tends to enter the vagina (or vaginas). In fact, entrance into the urethra/bladder can be extremely difficult in a neonate with a distended vagina because the vagina compressed the bladder to the anterior abdominal wall and obstructs the bladder neck. Drainage plus irrigation of the vagina (or vaginas) not only allows decompression and relief of abdominal distention but also may allow visualization of the bladder. Often, the rectal fistula is also difficult to locate; as noted previously, it is more often found within the septum of the duplicated vaginas but can enter at almost any location. With a combination of irrigation through the fistula and through the distal limb of the colostomy, the inspissated mucus and meconium can easily be cleared. It is often helpful to leave small feeding tubes in all channels and then obtain radiographic studies to further delineate the anatomy. In the authors' experience this is best done in the radiology suite with fluoroscopy.

Decompression of the Genitourinary Tract

Even after decompression of all structures draining into the cloaca, at times voiding continues into the vagina (or vaginas) or the rectum (or both) and results in rapid distention of these structures with subsequent poor urinary drainage, persistent hydronephrosis, abdominal distention, urinary infection, and hyperchloremic acidosis. This can generally be managed by intermittent catheterization. The catheter often enters the vagina rather than the bladder, but it still functions to drain and decompress the genitourinary tract (Hendren, 1992). If the desired decompression is not achieved, further maneuvers are required. The authors agree with Hendren that in a long urethra-like cloaca, catheterization can at times be difficult and a cut-back procedure (opening the cloaca) may be helpful to aid catheterization (Fig. 134–52). If this approach fails, further decompression can be achieved by either vesicostomy or vaginostomy (Kay and Tank, 1977). Levitt and Pena (2005, 2010) have found tube vaginostomy or vaginostomy to be helpful, but it is our belief that clean intermittent catheterization (CIC) or vesicostomy, or both, will usually keep the vagina adequately decompressed. Only when these maneuvers fail should vaginostomy be performed because it tethers the vagina to the abdominal wall and may make later pull-through or TUM difficult. It also necessitates an abdominal procedure. Levitt and Pena (2005) found that 25% of their cloaca patients had hydrocolpos but that in 59% of them it was either not identified or mismanaged. This resulted in significant morbidity from ureteral obstruction, urinary tract infection, acidosis, and failure to thrive. Adequate vaginal drainage resulted in resolution of these problems.



Figure 134–52. The urethra-like cloaca is opened, with a catheter in place; vesicostomy has also been performed.

Repair of Obstructive Urinary and Other Pathology

The third stage of care of a child with a cloacal anomaly is repair of any obstructive urinary tract pathologic process. Renal structural abnormalities have been identified in 60% to 83% of patients with persistent cloaca, some of which were obstructive (Warne et al, 2003; Rink et al, 2005b). In those with a common channel longer than 3 cm, 91% had urologic defects (Pena et al, 2004). At times, these anomalies are ignored early on while awaiting definitive cloacal repair, but this practice should be avoided. Obstructive lesions should be treated promptly. However, vesicoureteral reflux, which is quite common, can generally be managed medically if urinary infection is prevented. Other organ system anomalies (e.g., cardiac, spinal cord) should be fully evaluated. Some may require repair during this phase.

Definitive Repair of Cloacal Malformations

Definitive repair of a cloaca is usually carried out at 6 to 12 months of age, but obviously, the child must be well nourished and thriving to proceed with repair. In healthy thriving children, Pena and colleagues (2004) operate at 1 month of age. Definitive repair should never occur until the urinary tract has been evaluated and hydrocolpos has been ruled out. If endoscopy has not been performed previously, it may be

helpful as a separate procedure before the definitive repair. Defining the anatomy can be tedious, and it is helpful to thoroughly cleanse the distal colonic segment, which usually requires irrigation from the mucous fistula, as well as the distal limb of the colostomy. A standard GoLYTELY bowel preparation should also be done.

Operative Technique—Cloaca

The definitive repair begins with endoscopy to reacquaint the surgeon with the anatomy. The authors have also found it is helpful to place a Foley catheter in the bladder and different-colored Fogarty catheters in the vagina (or vaginas) and rectum. The catheters are kept sterile during preparation. As described previously for urogenital sinus repair, a complete lower body preparation with povidone-iodine is done circumferentially from the level of the nipples to the toes, and the legs are wrapped sterilely. Such preparation allows prone and supine positioning for perineal and abdominal surgery.

The definitive posterior sagittal anorectovaginourethroplasty (PSARVUP) is begun with the child in the prone position and the pelvis elevated on rolls to achieve a jackknife position. An electrical stimulator is used to determine the area of maximal contraction, which is marked with a skin scribe and with stay sutures for later rectal placement. The proposed locations of the perineal body and vagina are also marked (Fig. 134–53). The authors agree with Hendren that it is at times helpful to have a sound in the common cloacal channel, but the Foley and Fogarty catheters usually suffice. The entire dissection is done in the midline until mobilization of the rectum and vagina is begun. The most important advances of Pena's PSARVUP procedure are that it allows identification of the external sphincter and muscle complex of the rectum and provides excellent exposure for separation of the rectum and vagina (or vaginas) from the cloaca.

The initial incision extends from the tip of the coccyx in the midline to the posterior aspect of the cloacal orifice. Sutures mark the sphincteric muscular structures on either side as they are encountered. The authors have found it helpful in the past to open the common cloaca in the midline posteriorly to the level of the confluences to allow easy identification of the rectal and vaginal insertions. With TUM, this is less appropriate because it may limit the options for use of the sinus in the reconstruction as previously described for a urogenital sinus. When the rectal fistula is identified, it is opened posteriorly and multiple silk stay sutures are placed. These sutures are helpful in mobilizing the rectum away from the vagina (or vaginas). It is important to remember that the structures share a common wall initially and it is better to enter the vagina than either the rectum or urethra. Circumferential dissection of the rectum to well above the sacrum may be necessary. Separation of the peritoneum can be done from this position. Rarely, a child with a very high rectal confluence needs to be turned to the supine position for abdominal exploration to free the rectum more proximally. Levitt and Pena (2010) have noted abdominal surgery to be more likely when the common channel is greater than 3 cm in length. Once adequate rectal mobilization to allow a tension-free anastomosis to the perineal skin has been achieved, the rectal stay sutures are used to retract the rectum from the genitourinary structures.

In the classic PSARVUP procedure, the vagina is now separated from the sinus. This dissection is even more tedious and difficult than the rectal separation. With TUM (described later), which has now achieved widespread acceptance for cloacal repair, the vagina may not require separation. In classic vaginal separation, as noted earlier, it is an error to enter the urinary tract during vaginal mobilization. Side-by-side vaginal duplication is most common, and the midline septum has been incised with electrocautery during the initial endoscopy. Hendren (1998) noted that 66 patients had a single vagina, 68 had two, and 20 had none. The Fogarty catheter (or catheters) within the vagina is easily palpable, and the posterior aspect of the vagina is opened at the level of the confluence. Again, circumferential stay sutures are very helpful in

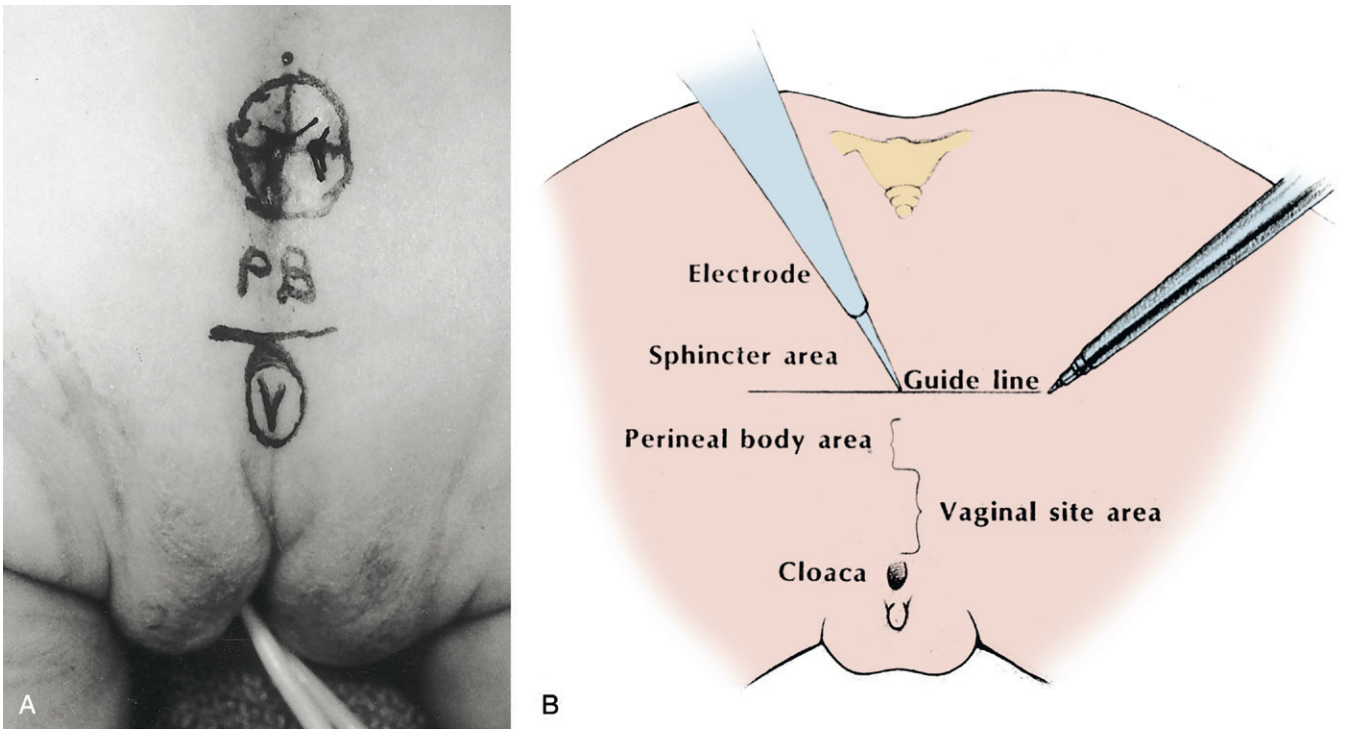


Figure 134–53. Cloaca: proposed location of the vagina (V) and perineal body (PB). Rectal location is identified by electrical stimulation.

separating the vagina from the urethra and bladder. A malleable retractor inserted into the opened posterior vaginal wall exposes the anterior wall confluence for separation. Sharp dissection is less likely to injure the urinary tract than cautery is. Making dissection even more difficult is the realization that frequently the vagina almost encircles the urethra. Failure to recognize this situation can result in injury to these structures. Use of the stay suture for traction aids in further mobilization of the vagina (or vaginas). The outer wall of the vagina appears white, and identification of this color is helpful. Great care should be taken to avoid devascularization of the vagina during mobilization. Usually, vaginal mobilization allows the vagina to be "pulled through" to a position near the perineum. If after significant mobilization it still does not reach the perineum, skin flaps can be used to reach the spatulated vagina. With an extremely high vagina or the rare vaginal agenesis, it may be necessary to interpose a bowel segment to reach the perineum, which obviously requires abdominal surgery. With a very dilated vagina, a vaginal flap or vaginal "switch" can be created to reach the perineum, although care must be taken to avoid devascularization and stenosis (Hendren, 1986; Pena, 1989; Pena et al, 2004).

Before the vagina is brought to the perineum, the openings in the common cloacal channel should be closed in two to three layers with absorbable suture to create a urethra. If the cloaca is large and resembles a vagina, it needs to be opened in its entirety and tailored over the Foley catheter. The vagina is then secured to the perineum. If there is any concern about vaginal injury, the vagina should be rotated to avoid overlapping suture lines (Hendren, 1992). The Foley catheter is left indwelling for 2 weeks.

Some surgeons have more recently noted that laparoscopic assisted PSARVUP can help in achieving a low dissection of the fistula and accurate placements of the rectal pull-through, while allowing excellent visualization of the pelvic structures (Tei et al, 2003).

The perineal body is now reconstructed, and the rectum is pulled through to the perineum. Pena (1989) stressed the importance of tailoring the widened rectum. The amount of tailoring differs in each patient. The muscles must meet posterior to the rectum. The rectum is placed in the center of the sphincteric muscle mass and anastomosed to the skin. Rectal dilation is begun gradually at 2 to 3 weeks after surgery, and the colostomy is closed in 3 months if all has healed well.

Once the urethral catheter has been removed, it is imperative to monitor the urinary tract and voiding dynamics closely because poor emptying secondary to a neuropathic component is seen in almost a third of patients. If any concern arises about the child's ability to empty, CIC should be started and continued until normal bladder dynamics are ensured. Failure to do so can ultimately result in urinary tract infection, hydronephrosis, and even loss of renal function.

Pena's TUM technique is now widely accepted for cloacal anomalies. It is a technically easier procedure that requires less time with less blood loss. The basic technique involves 360-degree mobilization of the entire urogenital sinus after the rectum has been separated. The technique at this point is not different from that described earlier for TUM for urogenital sinus abnormalities. The authors have found this technique to be extremely helpful. It makes the most difficult part of cloacal surgery, vaginal separation, much more easily performed when necessary. If the confluence is only 2 to 3 cm from the perineum, separation may not be even necessary. In those patients with a high vaginal confluence, separation may still be necessary, but it is much more easily accomplished (Rink et al, 1997). Concerns regarding continence have been raised, but to date the results have not been different than with standard repairs. Long-term results of the TUM procedure are needed.

Key Points: Cloacal Reconstruction

- Cloacal reconstruction involves four steps: (1) decompression of the gastrointestinal tract (colostomy), (2) decompression of the urinary tract (CIC, vesicostomy), (3) correction of associated organ systems anomalies, and (4) cloacal repair (PSARVUP).
- TUM is now commonly used for cloacal anomalies after the rectum is separated.
- The results of cloacal repairs are often based on the presence or absence of a normal spinal cord. CIC is frequently required, as is a bowel program, to achieve urinary and fecal continence.

Results of Cloacal Surgery

Cloacal anomalies are exceedingly challenging to repair. The anatomy is complex and differs from patient to patient. The surgeon must be prepared for a long, tedious procedure, must be imaginative, and must be willing to handle the tissues with great care. One might assume from this preface that the results would be dismal. On the contrary, most patients lead a productive life. We surgeons are indebted to Drs. W. Hardy Hendren and Alberto Pena for their pioneering work on children with cloacal anomalies, as well as their willingness to document their results.

Results have generally been reviewed in terms of urinary continence, fecal continence, and sexual capability; in the future, results should also focus on erotic sensitivity and fertility, pain-free intercourse, orgasm as well as quality of life. Early results from a urinary standpoint were dismal: Chappell and Bleloch (1973) reported that all 5 of their patients had some degree of incontinence postoperatively, and Bartholomew and Gonzales (1978) had 5 of 7 patients wet after reconstruction. **It is now clear that a high percentage of patients have a neuropathic component to their incontinence.** In 1999, De Filippo and colleagues reported urodynamic data on 26 patients with anorectal malformations (including 6 with cloacal anomalies). Twenty-one of the 26 had preoperative leak point pressures greater than 40 cm H_2O, and 15 had normal MRI of the spine. This means that even those not demonstrating a neurologic abnormality may have abnormally high outlet resistance, which adds to the risk for incontinence and upper tract changes. Of Hendren's 141 patients reported by De Filippo, 83 (59%) voided spontaneously with control, 40 (28%) required CIC, 4 (3%) had undergone urinary diversion, and 1 (0.7%) was continent with urinary diversion; only 5 (3.5%) were wet, and in 8 the results were too early to assess. Pena and coworkers (2004) reported a review of 339 patients operated on for cloacal anomalies, 193 of whom were evaluated for urinary continence. They found that spontaneous voiding was related to length of the common channel. Overall continence with spontaneous voiding occurred in 54%. Another 46% were dry with CIC (24% with a native urethra, 22% with a Mitrofanoff channel). However, when the common channel was less than 3 cm, 28% required CIC; if greater than 3 cm, 78% required CIC. Warne and associates (2002a) achieved 80% "social continence" but only 22% spontaneously voided, 12% performed CIC alone, and 46% required reconstructive urologic surgery to achieve continence (mean number of operations, 4.7). They likewise found that those with a common

Table 134–1.

Continence Rates after Cloacal Surgery

	VOIDING SPONTANEOUSLY	DRY WITH CIC ± CONTINENT RECTUM
Hendren, 1998	0.62	0.34
Pena et al, 2004	0.54	0.46
Warne et al, 2002a	0.22	0.58
Rink et al, 2005b	0.33	0.53

channel longer than 3 cm were less likely to void spontaneously (12% vs. 31%). In the authors' series, 86% were dry but only a third were continent with spontaneous voiding. The remainder required CIC with or without lower urinary reconstruction (Rink et al, 2005b) (Table 134–1). Warne and associates also noted that a good bladder neck, short common channel, normal sacrum, and two normal kidneys were all good prognostic signs for continence and spontaneous voiding. The authors are in agreement with Pena and Levitt (2003) that voiding abnormalities are generally related to a noncontractile bladder and warrant CIC, but Warne and associates (2002a) found hyperreflexia to be the predominant pattern in those with abnormal dynamics. It is important to note that 75% of their patients had an abnormal sacrum.

Fecal continence is directly related to neurologic status (Pena, 1989). **Hendren** (1992) **noted that certain factors bode well for continence: good perineal raphe, well-defined anal dimple, normal spine, normal MRI, and brisk muscle reflex.** In 105 patients, Hendren noted that 47 had normal bowel function, 27 required enemas, 7 had a colostomy, 7 had fecal soiling, and 4 with an anterior anus had normal control. Pena and coworkers (2004) reported that 60% of 156 patients have voluntary bowel movements but only 28% of them never soil. The 40% who are fecally incontinent remain "clean" with a bowel management program. The MACE (Malone Antegrade Continence Enema) appendicovesicostomy has been very helpful in preventing constipation and achieving fecal continence in those refractory to bowel management programs.

Although not a direct result of reparative surgery, renal outcomes are worrisome. Renal insufficiency was found in 50% of the patients treated at Great Ormond Street Children's Hospital, and 17% of the patients progressed to end-stage renal failure (Warne et al, 2002b). In the authors' series, 18% had an abnormally elevated serum creatinine level and in another 26% it was borderline (Rink et al, 2005b). Lifelong yearly urologic evaluation is warranted, and prompt recognition plus treatment of any obstructive pathologic process or urinary tract infections is imperative. Bladder dynamics must be evaluated and abnormalities addressed. Of 24 reported adult patients, 17 had coitus and 6 had borne children (including five deliveries by cesarean section and one vaginal delivery (Hendren 1998).

Leclair and associates (2007) reported on cloacal repair using the TUM technique. Urethral stenosis occurred in 2 of 22 patients and both required a Mitrofanoff catheterizable channel. One child developed a urethrovaginal fistula, and 3 had vaginal stenosis. Continence was noted in 15 of 17 patients older than 4 years of age. Seven voided spontaneously, and 8 emptied by CIC. Fecal continence was present in 12, with 9 having spontaneous bowel movements and 3 requiring MACE irrigations.

SUMMARY

Management of urogenital sinus and cloacal anomalies can be exceedingly complex. In those with disorders of sex differentiation, prompt but very careful evaluation by an expert multidisciplinary team is mandatory. Family support and education with openness and respect for the child and family are required. Differing cultural practices must also be respected and accepted. Confidentially must be maintained. Surgical reconstruction requires great care of tissues, meticulous attention to detail, and a lifelong commitment by the surgeon. These complex anomalies require an entire team of physicians and nurses dedicated to the care of these problems. Urogenital sinus and cloacal anomalies are very challenging reconstructive problems. Those at the more severe end of the spectrum should be handled only in centers with great expertise and experience.

Please visit the accompanying website at www.expertconsult.com to view videos associated with this chapter.

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chapter 135

Surgical Management of Pediatric Stone Disease

Michael C. Ost, MD ● Francis X. Schneck, MD

Evaluation
Conservative Management
Management of Upper Urinary Tract Calculi
Shock Wave Lithotripsy
Ureteroscopic Management of Upper Urinary Tract Calculi
Percutaneous Nephrolithotomy
Laparoscopic and Robotic-Assisted Pyelolithotomy
Percutaneous Cystolithotripsy for Bladder Stones
Determination of Stone-Free Status
Conclusions

Prior to 1990, nephrolithiasis was responsible for 1 in 1000 to 1 in 7600 hospital admissions annually throughout the United States (Nimkin et al, 1992). **In recent years, however, a dramatic increase in pediatric urolithiasis has been observed** (Srivastava and Alon, 2005). The authors would concur with this observation, especially among adolescents without known metabolic disturbances. It has been speculated that diets rich in sodium and carbohydrates may be contributing to the etiology of urolithiasis in this cohort of children.

The management of upper urinary tract calculi has evolved dramatically in both adults and children in the last two decades. Progress in the management of pediatric stone disease has been motivated by surgeons adopting and applying adult endourologic methods. The most important catalyst in the evolution of surgical advancement has been the expansion of minimally invasive surgery, in general, with development of smaller and more durable endoscopic equipment.

Since its introduction in the 1980s, extracorporeal shock wave lithotripsy (ESWL) has transformed the management of pediatric upper tract calculus disease and remains very useful today. Other modalities of treatment, including ureteroscopy, percutaneous nephrolithotomy (PCNL), and combination treatment protocols allow flexibility in management. However, a consensus has not been reached as to the most effective and safe technique for upper tract urolithiasis, especially considering ESWL versus ureteroscopy. Despite the lack of compelling scientific data comparing these treatment methods in children, ureteroscopy has emerged in many centers as the first-line of treatment.

Pediatric stone disease has always been more prevalent in underdeveloped countries. Of concern is the observation that pediatric stone disease is becoming more prevalent in the western hemisphere. Many pediatric patients with urolithiasis have metabolic abnormalities (Jayanthi et al, 1999). Therefore there has been an increased demand on pediatric urologists to manage both simple and complex urolithiasis in all pediatric age groups.

EVALUATION

Metabolic Workup

Often, a complete metabolic blood profile and a 24-hour urine collection are obtained once a stone is confirmed by imaging. Unfortunately, there are no accepted standard reference ranges for 24-hour urine analyses in the stone-forming pediatric population. Indeed, many pediatric urologists use adult standards to direct medical treatment, because specific reference ranges are not readily available or require additional complicated calculations. Regrettably, there are significant differences between the normal ranges of urine chemistries in children and adults (Battino et al, 2002; DeFoor et al, 2005a). In addition, conflicting reports exist as to the commonality of metabolic disturbances in the presence of calcium-based stones (Sternberg et al, 2005).

In the preliminary evaluation of pediatric stone disease, it is common to obtain 24-hour urine values for creatinine, sodium, calcium, oxalate, uric acid, and citrate. The very cumbersome nature of a 24-hour urine collection often limits its accuracy in the pediatric population. In light of this random urine spot sampling, ratios have been used. Urine calcium to urine creatine ratios (Uca:Ucr), for example, have been used with sensitivities and specificities up to 90% and 84%, respectively, in the evaluation of hypercalciuria, a known risk factor for urolithiasis (Mir and Serdaroglu, 2005). However, such a test is limited to one urinary metabolite and cannot be relied upon to monitor responses to various medical treatments. Furthermore, it is unreasonable to rely solely on urinary calcium excretion values as an indication of overall metabolic disturbances.

It has been suggested that measurement of urinary supersaturation products (calcium oxalate, urate) may help to improve identifying those children at risk for stone formation. DeFoor and colleagues (2006), for example, most recently determined that supersaturation levels of calcium oxalate, as well as calcium to

creatinine levels, were significantly higher in children with stones compared with controls. This difference, however, may have been reflective of differences found in urinary volumes. Lande and colleagues (2005) have demonstrated that low urine volumes in children often negate the benefit of pursuing urine supersaturation products in a stone workup. Such conflicting data often confuses clinicians as to what urinary evaluation to pursue in the workup and management of pediatric stone disease.

Stone disease in the pediatric population has genetic, anatomic, metabolic, and dietary causes. There are numerous genetic causes of hypercalciuric nephrolithiasis alone that contribute to pediatric stone disease (Stechman et al, 2009). In this regard, the medical treatment always accompanies the endourologic management. **To fully treat the pediatric stone patient, there must be a focus on prevention through diet and medication monitoring. For this reason, the pediatric nephrologist is a critical player in the management and surveillance of these children.** Details regarding the metabolic workup and medical treatment of pediatric stone disease are beyond the scope of this chapter. Numerous pediatric nephrology resources are available. Alon (2009), for example, provides an excellent pediatric nephrology review, including medication dosing by weight. The website Litholink (www.litholink.com) can provide valuable information to parents and pediatric urologists alike.

Imaging

Radiographic assessment of the child with calculus disease must be accurate, economic, and safe. **The goals include determination of stone location, size, density, and urinary tract anatomy.** Indications for assessment include acutely symptomatic children with a suspected calculus or children with known calculus disease requiring follow-up evaluation to either determine stone burden or recurrence. Radiographic evaluation is also important in children with abnormal urinary tract anatomy that may predispose to calculus formation, requiring eventual surgical management.

Radiographic imaging in children is similar to imaging in the adult patient. The workup begins when the diagnosis of a calculus is suspected, and the radiographic study is determined by factors such as acuity of presentation and the practices of the treating hospital. Many, if not most, children with renal colic present to an emergency room, and **unenhanced helical computed tomography (CT) has become the most accurate and efficient first choice in initial imaging.** Typically, thin-slice helical protocol is defined by narrow collimation (≤5 mm). CT is not only able to visualize the entire urinary tract for the tiniest calculus, but it has the potential of ruling out alternative diagnosis. Unenhanced helical CT of the abdomen and pelvis to evaluate urinary tract calculi was first described in 1995 and is the mainstay for calculus imaging in adolescents and adults, replacing more traditional studies, such as intravenous pyelography (IVP), a kidney-ureter-bladder (KUB) film, and ultrasonography (Smith et al, 1995). With increased usage and familiarity with the technique, its application has expanded into the pediatric population with similar advantages. These advantages include high sensitivity and specificity, ready availability and speed in assessment, and intravenous (IV) contrast is not necessary. Because children are at significant lifetime risk for recurrence of urolithiasis, judicious use is necessary to limit radiation exposure, particularly gonadal exposure, and concerns of potential increase risk of future malignancy.

CT is highly accurate in stone assessment, exceeding 96% sensitivity and specificity independent of the location of the calculus (Smith et al, 1996b; Hamm et al, 2001; Heneghan et al, 2003; Palmer et al, 2005). **CT is also helpful in demonstrating secondary signs of acute obstruction, such as hydroureteronephrosis, renal enlargement, and perinephric or periureteric stranding; however, the latter findings may be less obvious or absent in pediatric patients due to comparably less retroperitoneal fat** (Smith et al, 1996a; Smergel et al, 2001; Strouse et al, 2002)**.**

Progress has been made in developing unenhanced CT protocols that minimize the radiation dosage while not compromising diagnostic information (Heneghan et al, 2003; Cody et al, 2004; Singh et al, 2009). Experimental protocols using anthropomorphic pediatric phantoms have been used in a number of studies to determine specific organ doses, calculate effective dose, determine the lifetime attributable risk (LAR) for cancer incidence, and relative risk of cancer induction from a single scan under both standard- and low-dose modes (Brisse et al, 2009; Kim et al, 2010). Computer-simulated dose reduction has been useful in determining diagnostic thresholds in children. Compared with standard protocols, halving the dose to 40 mA for children weighing 50 kg or less does not significantly affect the diagnosis of pediatric renal stones (Karmazyn et al, 2009). Spielmann and colleagues (2002) found excellent detectability of calculi measuring 2 to 8 mm using much lower amperage, with an almost threefold decreased estimated radiation dose compared with standard protocols. **Perhaps most importantly, radiation exposure can also be reduced effectively by reducing the number of CT examinations performed for poor clinical indications, scanning only the anatomic region of interest, and not performing either unenhanced and contrast-enhanced scanning unless absolutely necessary** (Cohen, 2009).

Ultrasonography has a more limited role in the assessment of urolithiasis compared with CT but has the distinct advantage of no associated ionizing radiation. Therefore ultrasonography should be considered as a screening tool in the workup for nonemergent abdominal or flank pain. Ultrasonography, although useful in the evaluation of renal calculi or hydronephrosis, is technically limited for use in diagnosing a ureteral stone, with the possible exception of the very distal ureter or bladder. Especially in the *acute setting*, that is, symptomatic presentation with renal colic or hematuria, ultrasonography is less useful in detecting or directing management of urolithiasis. Palmer and colleagues (2005) demonstrated that ultrasonography was nondiagnostic in 41% of children compared with 5% using CT, and it failed to detect ureteral calculi in 62% of pediatric patients. Similar results have been reported in adults, confirming that ultrasonography is of limited value in the workup of urolithiasis (Fowler et al, 2002). Symptomatic children with a known history of renal urolithiasis, or children on observation protocols, may suffice with ultrasonography (US) and KUB alone, thereby limiting exposure to ionizing radiation. Additional support favoring US versus CT in the diagnosis of pediatric nephrolithiasis is also rooted in the ultimate clinical decision about how the child is to be treated. In a prospective study comparing CT and US, Passerotti and colleagues (2009) found that although CT was a more sensitive study in detecting stones in children, the difference in usefulness between the two radiologic techniques was not clinically significant.

Fluoroscopy has an important role in the real-time detection and management of urolithiasis in children, and the same important safety concerns exist regarding radiation exposure as with CT.

C-arm fluoroscopy is used during the surgical setting to assist in antegrade percutaneous access of the upper urinary tract and retrograde access of the lower urinary tract. Manipulation of endoscopic instruments in vivo often requires fluoroscopic monitoring. Fluoroscopy is also used during ESWL to assist in stone localization and monitor the effectiveness of treatment. Urologists must have a working understanding of the principles of fluoroscopy and be aware of the intraprocedure fluoroscopy time and energy settings to limit radiation exposure to both the pediatric patient and operative staff.

CONSERVATIVE MANAGEMENT

Conservative management of pediatric nephrolithiasis is considered first-line treatment, provided there is no evidence an obstructing stone is harboring an infection or a child is failing to thrive as the result of his or her stone disease. Clinical scenarios, including fever, anorexia greater than 24 hours, persistent nausea and vomiting, and/or pain refractory to conservative measures prompts endourologic intervention. In the instance of a stone in a solitary kidney, early intervention versus conservative treatment is favored. **In managing stone disease in the pediatric population, it is important to note that renal calculi less than 3 mm are likely to spontaneously pass, and stones greater than or equal to 4 mm in the distal ureter are likely to require endourologic treatment** (Van Savage et al, 2000). This information should be relayed to caregivers and parents. If a ureteral stent is placed acutely in children for the clinical circumstances described above, definitive endourologic therapy is delayed 2 to 4 weeks to allow for decompression, ureteric orifice dilation, resolution of edema, and proper treatment and clearance of any infection if need be.

There have been many studies in adults evaluating the efficacy of medical expulsive therapy to facilitate distal stone passage. Use of α antagonists, calcium channel blockers, and steroids has been shown to be effective. Based on efficacy demonstrated in the adult population (Porpiglia et al, 2004), α-receptor antagonists, such as tamsulosin, may be offered on an individualized basis as adjunctive therapy to facilitate ureteral expulsion in children. To date, however, there is a lack of published data capturing the pediatric population that prove the superiority of these agents versus standard pain medication. A Turkish study, for example, demonstrated that daily administration of 0.03 mg/kg of the α antagonist doxazosin versus an analgesic alone did not show superior expulsive results regarding distal ureteral stones up to 10 mm in children 2 to 14 years of age (Aydogdu et al, 2009).

MANAGEMENT OF UPPER URINARY TRACT CALCULI

Pediatric Considerations

Special considerations in the endourologic management of stone disease in children include preservation of renal development and function, prevention of radiation exposure, and minimizing the need for re-treatment. Despite advances in endourologic equipment and technique, controversy remains regarding the contribution of SWL to future development of diabetes or hypertension, and whether ureteric orifice dilation during ureteroscopy (URS) leads to ureteral stricture formation or development of vesicoureteral reflux. International consensus is lacking as to the most effective surgical management of pediatric stone disease due to lack of prospective randomized trials comparing treatment modalities and disparity in the access to emerging technologies. **Regardless of treatment modality, the presence of residual stone fragments is associated with adverse clinical outcomes** (Afshar et al, 2004), **and every attempt should be made to achieve a stone-free status.** The surgeon's experience is paramount to facilitate complete stone clearance and minimize re-treatment rates. The decision regarding the most efficacious primary treatment modality must be individualized per child based on age, anatomy, location, and composition of the stone burden.

Antibiotic Use

In line with the 2008 American Urologic Association's best practice statement on antibiotic prophylaxis, less than or equal to 24 hours of perioperative antibiotics are indicated in all patients undergoing upper tract instrumentation (Wolf et al, 2008). In children, appropriate agents include trimethoprim-sulfamethazole, first- and second-generation cephalosporins, and ampicillin in combination with an aminoglycoside. A urine culture is mandatory before all upper tract procedures to determine if the urine is sterile, and culture results are used to guide preoperative antibiotic therapy, particularly for percutaneous procedures, patients with high-grade obstruction, or patients with an indwelling stent (Wu and Docimo, 2004). In the authors' practice, children with a negative urine culture undergoing uncomplicated URS procedures receive perioperative cefazolin, and all children undergoing a percutaneous procedure or who have a preexisting ureteral stent/nephrostomy tube receive a fluoroquinolone or ampicillin/gentamicin. Use of postoperative antibiotics is controversial and is determined on an individual basis, especially with recent data demonstrating an increased risk of developing resistant bacterial strains with prolonged use of antibiotic prophylactic therapy (Conway et al, 2007).

SHOCK WAVE LITHOTRIPSY

The emergence of shock wave lithotripsy (SWL) revolutionized the minimally invasive treatment of adult urolithiasis during the early 1980s. Since the initial report on successful SWL use in children in 1986 (Newman et al, 1986), large series have reported complication, safety, and stone-free rates comparable to adult cohorts (Table 135–1) (Myers et al, 1995; Elsobky et al, 2000; Ather and Noor, 2003; Muslumanoglu et al, 2003; Rizvi et al, 2003; Aksoy et al, 2004; Raza et al, 2005; Demirkesen et al, 2006). When used as a primary treatment option for upper tract calculi, SWL efficacy ranges from 68% to 84% (Rizvi et al, 2003; Myers et al, 1995; DeFoor et al, 2005b). SWL has been a preferred treatment modality for uncomplicated renal and proximal calculi less than or equal to 15 mm in the pediatric population. In a contemporary series of 216 children (mean age 6.6 years) with a mean stone size of 14.9 mm and who were undergoing SWL with the Dornier HM3 lithotripter, Landau and colleagues (2009) reported a 3-month stone-free rate of 80%, demonstrating that efficacious stone-free rates can be achieved in appropriate candidates. **Complications rates are minimal and range in severity from hematuria and ecchymosis to obstruction with sepsis** (Farhat and Kropp, 2007).

Although well tolerated in children, current stone-free rates with SWL are difficult to interpret from the existing body of data due to discrepancies between studies regarding type of lithotriptor, number of shocks administered, and re-treatment rates. **Recent**

Table 135–1.

Outcomes with Large Series of Shock Wave Lithotripsy in Children

REPORT	CHILDREN/ RENAL UNITS	LITHOTRIPTER	MEAN AGE (YEARS)	STONE LOCATION (%)	MEAN SIZE (mm)	RE-TREATMENT RATE (%)	STONE FREE (%)	COMPLICATIONS (%)
Myers et al, 1995	446	Siemans Lithostar	13.7 R 14.1 U	53.4 R 46.6 U	12.3 R 7.3 U	10.7 R 3.5 U	67.9 R 91.1 U	Sepsis 0.2
Elsobky et al, 2000	148	Dornier MFL 5000; Echolith MedTech	11.2	92.6 R 7.4 U	10.2	64	86	Steinstrausse 0.7
Muslumanoglu et al, 2003	344	Siemans Lithostar Plus	8.7	57.1 R 42.9 U	N/A	53.9	73.3	Overall 9.6 Steinstrausse 7.8 UTI 1.2 Colic 2.9
Rizvi et al, 2003	262	EDAP LT02 Technomed	N/A	67.6 R 32.4 U	N/A	29.5	84.2 R 54.1 U	Colic 10.1 Fever 8.5 Steinstrausse 1.1 Hematuria 11.3
Ather et al, 2003	105	Dornier MPL 9000	5.6	100 R	15	N/A	95	Colic 2.9 Steinstrausse 1.9 UTI 2.9
Aksoy et al, 2004	129/134	Dornier MPL 9000	8.7	84.4 R 15.6 U	15.7	N/A	85	Overall 14.7 Steinstrausse 5.4 UTI 7.8 Hematoma 0.8
Raza et al, 2005	122/140	Piezolith 2300; Dornier Compact Delta	7.7	N/A	17.9	N/A	69	Fever 2.9 Colic 7.2 Steinstrausse 2.4
Demirkesen et al, 2006	126/151	Siemans Lithostar	8 (median)	66.9 R 33.1 LP	10 R 6 LP	40	71.5	Overall 7.2 Fever 0.8 Steinstrausse 6.4

LP, lower pole; N/A, not available; R, renal; S, staghorn; U, ureteral; UP, upper pole; UTI, urinary tract infection.

data suggest that stone-free rates in children with a history of urologic condition or urinary tract reconstruction are quite low (12.5%), and, with alternative surgical techniques available, children may be better served with URS or PCNL (Nelson et al, 2008). Despite encouraging results, SWL has not been approved by the Food and Drug Administration for use in children, although it is a widely accepted treatment modality.

Shock Wave Lithotripsy Technique in Children

General anesthesia is administered in a majority of smaller children to avoid both patient and stone motion and the need for repeated repositioning. With modern lithotriptors, intravenous sedation has been successfully employed in select older children (Aldridge et al, 2006). Bowel preparation is seldom used in order to avoid dehydration and electrolyte imbalance postoperatively. The number of shocks delivered and the kilovoltage used vary per lithotripter, but the current consensus is that low-power settings (17 to 22 kV) should be used to prevent stone migration during the procedure, with 3000 shock waves per session (<2000 in very young children) (Farhat and Kropp, 2007). A recent report assessed and compared the number and intensity of shock waves required for stone fragmentation in 44 children (mean age 5.9 years) and 562 adults (mean age 40.9 years). With an equivalent number of sessions (1.1 vs. 1.1), the mean number of shock waves (950 vs. 1262, $P < .001$) and the kV required (11.8 vs. 12.4, $P < .001$) were significantly reduced in the pediatric cohort (Kurien et al, 2009).

Whether or not to place a ureteral stent prior to ESWL in children remains controversial and is a matter of personal preference. It is currently unclear if placement of a ureteral stent prior to SWL facilitates fragment passage and improves stone-free outcomes. Although prestenting rates are not consistent across series, **current relative indications include cases of solitary kidneys, staghorn calculi, large ureteral calculi, obstruction, or abnormal anatomy and are not based on total stone burden.** Ureteral catheters with retrograde opacification are occasionally employed by some to aid in the localization of radiolucent calculi.

Stone Size, Location, Composition, and Patient Age

Although early series focused primarily on the feasibility, safety, and efficacy of SWL in children, recent efforts have centered on identifying demographic, anatomic, and stone-related prognostic factors for treatment success. SWL is currently considered the primary treatment for upper tract calculi less than or equal to 15 mm in children (Farhat and Kropp, 2007), but evidence supporting this stone size cutoff is lacking. Ather and Noor (2003), for example, analyzed the correlation between stone size and clearance in 105 children younger than 14 years. They reported an overall stone-free rate of 95% after a mean of 1.7 SWL treatments, with 5% of patients requiring additional procedures as adjuncts to SWL. In this cohort, mean stone size in the treatment success group was 14 mm compared with 16 mm in the treatment failure group. By contrast, Elsobky and colleagues (2000) reported

a 91% stone-free rate versus 75% stone-free rate for a mean stone diameter less than 10 mm and greater than 10 mm, respectively. Recently, Shouman and colleagues (2009) reported on a series of 24 children with a mean stone size of 31 mm undergoing SWL with the Dornier DoLi S device. In 53 sessions requiring a mean number of 3489 shock waves per session, stone-free and complication rates were 83.3% and 25%, respectively. **Although it is possible to treat very large stone burdens with SWL, concerns include the necessity of more shock treatments, more frequent re-treatment sessions, and increased risk of postoperative obstruction.** Further study delineating a clear size cutoff for uncomplicated upper tract stone burden is required to effectively counsel parents regarding the most effective first-line therapy for renal calculi between 1 and 1.5 cm.

Renal anatomy and stone location has been the subject of recent interest. The subject of frequent debate in the adult population, the most effective management of lower pole calculi in children has yet to be determined. Stone-free rates from initial small retrospective SWL series range from 56% to 61% (Ozgur Tan et al, 2003; Onal et al, 2004) with re-treatment rates as high as 40% (Onal et al, 2004). **SWL failure and re-treatment rates were associated with increased mean stone burden** (Onal et al, 2004), **increased infundibular length** (Ozgur Tan et al, 2003), **and an infundibulopelvic angle greater than 45 degrees** (Ozgur Tan et al, 2003).

Staghorn calculi are uncommon in children and represent a management challenge. Although monotherapy success rates are low in adults, acceptable stone-free rates in children have been achieved with SWL. In 23 children with a mean stone burden of 1.6 cm who were stratified by age, Lottmann and colleagues (2001) reported an overall stone-free rate of 82.6%, with only one case of symptomatic obstruction. A ureteral stent was placed in 22% of children, and these authors reported an 88% stone-free rate in children less than 2 years old compared with 71% in children 6 to 11 years old. In 42 children with a mean stone burden of 3.2 cm and stratified by ureteral stent placement, Al-Busaidy and colleagues (2003) reported an overall stone-free rate of 79%. Although stent placement did not affect stone-free rates, they found that stent placement significantly reduced the major complication rate. **The superior success rates with SWL monotherapy in children compared with adults have been attributed to softer stone composition, smaller relative stone volume, increased ureteral compliance to accommodate stone fragments, and smaller body volume to facilitate shock transmission**.

SWL safety and efficacy have been demonstrated even in very young children. McLorie and colleagues (2003) treated 34 children younger than 3.5 years (mean age 23 months) and reported an 86% overall stone-free rate (66% after one treatment) without major complications. Treatment of proximal ureteral stones has achieved similar success rates compared with treatment of renal stones in most pediatric series, although ureteral stenting is more commonly employed to aid in stone localization and clearance (Myers et al, 1995). Treatment of mid- to distal ureteral calculi has historically been avoided in children due to difficulties with localization over the sacroiliac joint and concern regarding possible injury to developing reproductive systems. The greater and lesser sciatic foramen has been explored as a potential blast path to treat distal stones in children.

SWL success by stone composition is similar between the adult and pediatric populations. Cystine stones are uniquely challenging due to their durability and high recurrence rates. Although SWL monotherapy has demonstrated variable results in adults, there are few reports in the pediatric population. In a small recent series, Slavkovic and colleagues (2002) reported a 50% stone-free rate in 6 children with a cystine stone burden ranging from 0.2 to 2.5 cm. Although stone-free rates were low, fragmentation was achieved in 100% of patients, and the stone dissolution was achieved with medical therapy in the remaining children following SWL. Some authors have proposed that cystine stones formed within 2 years of therapy may be more easily fragmented with SWL and that stone number, and not diameter, may be more predictive of success (Farhat and Kropp, 2007).

Limitations and Concerns

In children, there is currently no consensus regarding the maximum size of residual stone fragments (RF) that are considered clinically significant, and as a result, there is no clear definition as to what constitutes "stone-free" status (Wu and Docimo, 2004; Farhat and Kropp, 2007). Although children have been shown to have a greater capacity to clear fragments than adults (Gofrit et al, 2001), the presence of RFs have been correlated with adverse clinical outcomes (Afshar et al, 2004). Afshar and colleagues (2004) followed 26 renal units with RFs less than or equal to 5 mm and reported that although 31% were asymptomatic with no fragment growth, 69% had adverse clinical outcomes, including RF growth or clinical symptoms. Patients with RF had a significant increase in adverse clinical outcome compared with stone-free subjects, and the presence of metabolic disorders was associated with RF growth (Afshar et al, 2004). For these reasons, metabolic evaluations are now routinely being performed in children with a history of calculi, and every attempt should be made to achieve stone-free status.

Although SWL is well tolerated in children with few complications, stone-free rates following single-session monotherapy can remain as low as 44% (Muslumanoglu et al, 2003). As a result, children are subjected to multiple treatments requiring general anesthesia (Aldridge et al, 2006). **The need for multiple treatment sessions is concerning, because the effects of shock waves on renal tissue are unclear. A growing body of evidence in adults indicates that shock waves result in renal vessel vasoconstriction and that renal tubular injury and subcapsular hematoma from cavitation and shear forces are dependent on the kilovoltage applied** (Lingeman et al, 2003). In a large series of 340 adult patients with a mean follow-up of 19 years post-SWL, (Krambeck and colleagues (2006) reported an increased risk of hypertension and diabetes mellitus related to bilateral treatment, number of administered shocks, and treatment intensity. Although these results are concerning, differences between pediatric and adult populations and limitations inherent to a questionnaire-based retrospective study make application of these data in children difficult.

Retrospective studies with limited follow-up in children have reported that SWL and PCNL do not cause renal morphologic or functional alteration as measured by glomerular flow rate (GFR) and serial dimercaptosuccinic acid (DMSA) functional studies (Wadhwa et al, 2007), but long-term data are unavailable to date. To eliminate confounding variables and fully address the risks of chronic renal damage from SWL, long-term prospective data in children are clearly required.

URETEROSCOPIC MANAGEMENT OF UPPER URINARY TRACT CALCULI

The indications for primary ureteroscopic management of upper tract calculi in children have significantly expanded. In

combination with new endourologic instrumentation and holmium:YAG lasers, access and treatment of calculus disease throughout the entire pediatric urinary tract is effective, safe, and readily available in the acute setting. Adoption of ureteroscopy in the treatment of pediatric upper tract calculus disease lagged behind the adult experience, because of concerns regarding large ureteroscope caliber size in children. However, evolving experience with ureteroscopy and recent large single-center retrospective series have demonstrated comparable stone-free and complication rates to SWL in children, validating its growing application in children.

Indications

Since the mid-1980s, with the acceptance of SWL as primary therapy for upper tract calculi less than 1.5 cm, ureteroscopy has been historically used for calculi found below the iliac crests and for upper tract calculi after SWL failure (Wu and Docimo, 2004). Ureteroscopy was not considered primary therapy for upper tract stones in children due to complications from ureteral ischemia, perforation, stricture formation, and development of vesicoureteral reflux as a result of dilation of small-caliber ureteric orifices.

With significant improvements in both the miniaturization and durability of endoscopic equipment and the acceptance of the holmium laser, ureteroscopy has become a more attractive option in young children. Early series using rigid ureteroscopy for distal stones reported stone-free rates ranging from 86% to 100% with minimal complications (Table 135–2) (Ritchey et al, 1988; Van Savage et al, 2000; Schuster et al, 2002; Rizvi et al, 2003; De Dominicis et al, 2005; Minevich et al, 2005; Tan et al, 2005). Children randomized to either ureteroscopy or SWL as primary therapy for distal ureteral stones were reported to have a significantly higher stone-free rate after one treatment (94% vs. 43%) for those treated with ureteroscopy (De Dominicis et al, 2005). Another group reported experience using 4.5-, 6-, and 8-Fr rigid ureteroscopy in treating proximal ureteral stones, with a mean age of 10.7 years. Ureteral dilation was not performed in any of the cases, and 100% of children were rendered stone free (Lesani and Palmer, 2006). **The results of these retrospective studies have begun to refute the notion that dilation of the pediatric ureter will result in vesicoureteral reflux or the development of ureteral strictures.** In a systematic review of the literature encompassing 221 pediatric ureteroscopies, Schuster and colleagues (2002) noted only two ureteral strictures and a low incidence of vesicoureteral reflux. Newer 4.5-Fr semirigid ureteroscopes, with working ports that accommodate 2.4-Fr endosurgical instrumentation, extend the versatility of managing distal ureteral calculi in most pediatric patients without predilation.

Standardization in the treatment of distal calculi in children has led a number of centers to expand ureteroscopy to the treatment of upper tract calculi (Table 135–2). Comparable stone-free rates approaching 100%, with complication rates similar to that of the adult population, have recently been reported (Minevich et al, 2005; Lesani and Palmer, 2006; Cannon et al, 2007; Corcoran et al, 2007; Smaldone et al, 2007). Smaldone and colleagues (2007)

Table 135–2.

Outcomes with Large Series of Rigid and Flexible Ureteroscopy in Children

STUDY	NO. CHILDREN/NO. PROCEDURES	MEAN AGE (YEARS)	STONE SIZE (mm)	STONE LOCATION (%)	URETERIC ORIFICE DILATION (%)	STONE FREE (%)	STAGED (%)	POSTOPERATIVE STENTING (%)	COMPLICATIONS (%)
Rigid Ureteroscopy for Mid- to Distal Ureteral Calculi									
Al-Busaidy et al, 2003	43/47	6.2	12.6	100 U	N/A	93	N/A	N/A	Ureteral perforation 4 Ureteral stricture 2
Bassiri et al, 2002	66/66	9	8	100 U	37.9	88	N/A	N/A	Fever/VUR 12 Renal colic 1.5 Gross hematuria 16.7 Pyelonephritis 4.5
Raza et al, 2005	35/52	5.9	9.4	100 U	3.9	79.3	28.6	N/A	Ureteral stricture 2 Fever 10 Ureteral perforation 6
Rigid and Flexible Ureteroscopy for Upper Tract and Renal Calculi									
Minevich et al, 2005	58/65	7.5	N/A	64.6 U 35.4 P	30	98	N/A	85	Ureteral stricture 1.3
Smaldone et al, 2007	100/115	13.2	8.3	52 R 48 U	70	91	9	75	Ureteral perforation 4.2 Ureteral stricture 1
Cannon et al, 2007	21/21	15.1	12.2	100 LP	81	76	14	71	0
Corcoran et al, 2007	47/61	9.4	10.2	100 R	91	88	26	70	Ureteral perforation 9

EHL, electrohydraulic lithotripsy; HL, holmium laser; LP, lower pole; N/A, not available; P, proximal; R, renal; U, ureteral; VUR, vesicoureteral reflux.

reported a 91% stone-free rate with a mean follow-up of 10 months in a series of 100 children with a mean stone diameter of 8.3 mm, 52% of whom had upper tract calculi. Nine percent of these children underwent staged procedures. They reported a 4.2% perforation rate that was managed with ureteral stenting and one distal ureteral stricture requiring open neocystostomy. Corcoran and colleagues (2007) reviewed a cohort of 47 children (mean age 9.4 years) with upper tract calculi managed with flexible ureteroscopy and holmium laser lithotripsy. An 88% stone-free rate with a mean stone burden of 10.2 mm was reported, with 26% requiring staged procedures. **These authors concluded that because of improved ureteroscopic access to the pediatric upper tract, calculi up to 15 mm were as safely and effectively treated in children as in adults.** Even with outstanding pediatric ureteroscopic technology, pediatric ureters may require a period of stenting prior to embarking on endoscopic treatment. For example, a smaller-caliber ureter that is resistant to instrumentation may be passively dilated with an indwelling stent during 6 to 8 weeks (Fig. 135–1).

Adoption of techniques used in the adult population, most notably sequential coaxial and balloon dilation of the ureteric orifice and use of ureteral access sheaths, has further facilitated access to the pediatric urinary tract. Initially described in eight children by Singh and colleagues (2006), **ureteral access sheaths have been shown to facilitate repetitive upper tract access, reduce intrarenal pressures, decrease operative time, and improve stone-free rates in adults.** Access for the treatment of lower pole calculi is possible with use of ureteral access sheaths and the 6.9-Fr flexible ureteroscope, a stone location that would have previously required SWL or PCNL. Cannon and colleagues (2007) reported a 76% stone-free rate in 21 children with lower pole calculi and a mean stone diameter of 12.2 mm. After a mean of 11.4 months, no major complications were observed. **Therefore with the transition from SWL to ureteroscopy as a primary treatment modality at the authors' institution, current relative contraindications to ureteroscopic management include staghorn stones in recurrent stone formers more amenable to PCNL, anatomic anomalies making retrograde access difficult, and previous endoscopic failure.**

Equipment

Having an updated and well-stocked system that is familiar to the operative staff is vital to efficient management. It usually falls on the nursing staff to care for the delicate instruments and keep up on repairs so that the instruments are operational when needed; maintenance is often needed after 20 to 30 uses. A "basic" ureteroscopic kit is listed below; however, variation exists based on the manufacturer. An array of semirigid and flexible pediatric ureteroscopes, in additional to ureteral access sheaths, is available from numerous companies (Buscarini and Conlin, 2008). In general, semirigid ureteroscopes usually have a 2.4- to 3.5-Fr working port and flexible ureteroscopes a 1.8- to 3.5-Fr working port. With flexible ureteroscopes, distal tip deflection up to 270 degrees can facilitate access to most lower pole stones (Figs. 135–2 and 135–3). **However, smaller working areas and difficulties in exchanging instruments through the working element of a deflected ureteroscope may limit this treatment modality in some cases** (Fig. 135–4).

Ureteroscopes

6.9-Fr flexible ureteroscope
4.5- and 6.5-Fr semirigid ureteroscope

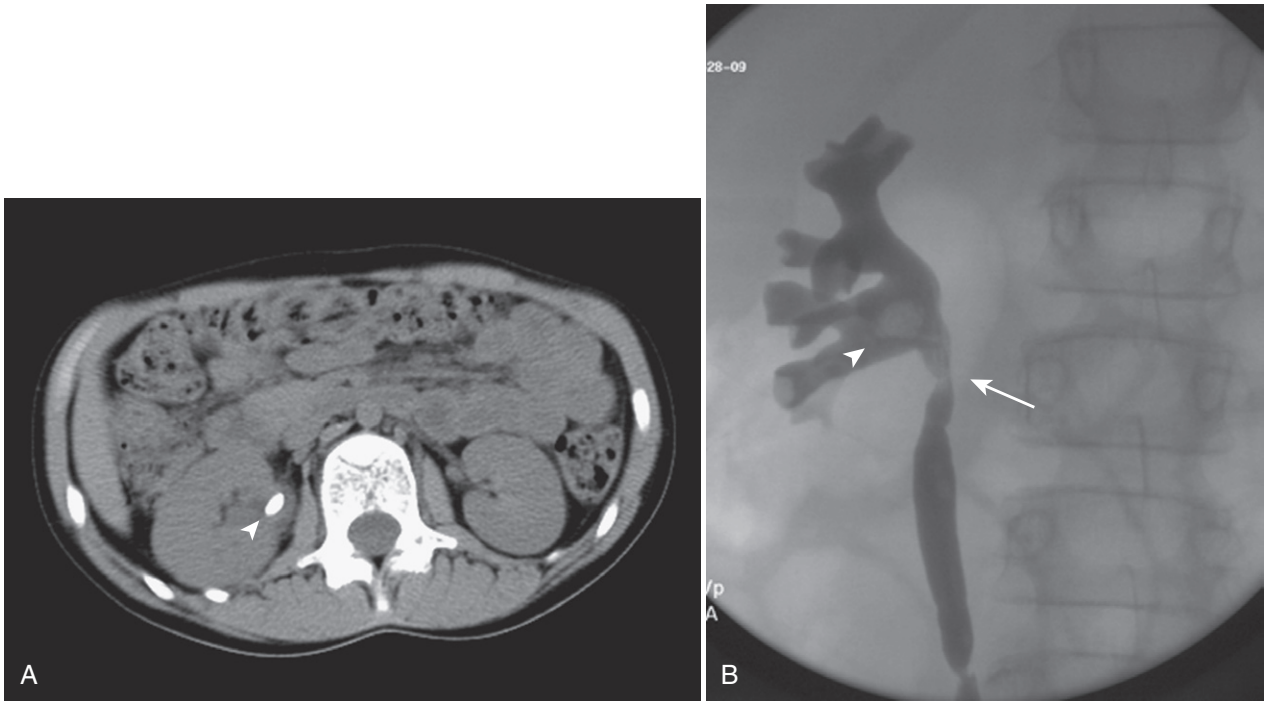


Figure 135–1. CT scan (**A**) and retrograde pyelogram (**B**) in a 10-year-old female with glucose transport deficiency demonstrating a 9-mm renal pelvic stone (*arrowheads*). Nephrolithiasis was secondary to profound hypocitruria and hypercalciuria. Primary ureteroscopy could not be accomplished because of a narrowed segment of proximal ureter (*arrow*). Following 8 weeks of ureteral accommodation with an indwelling stent, flexible ureteroscopy with laser lithotripsy and stone basketing was performed.



Figure 135–2. Pediatric semirigid self-dilating ureteroscopes may be used for rigid ureteroscopy in toddlers. A 4.5-Fr distal beak allows easier passage to facilitate dilation with the 6.5-Fr proximal component. (Photo provided by Richard Wolf; © Richard Wolf, all rights reserved.)

Endourologic Equipment

Guidewire array: 0.035 in Sensor GW, 0.018 to 0.025 in Glidewire (Terumo Interventional Systems, Somerset, NJ)
Basket devices: Zero-tip
8/10-Fr coaxial ureteral dilators
Ureteral access sheaths (9.5- and 11-Fr internal diameter)
Double-J ureteral stent array (3-, 4.8-, and 6-Fr internal diameter)

Ureteroscopic Technique in Children

All ureteroscopic procedures are performed under general anesthesia with paralysis to prevent patient movement and minimize the risk of ureteral perforation. When clinically appropriate, a urine culture should be confirmed prior to surgery. Following broad-spectrum antibiotic prophylaxis, patients are placed in the lithotomy position, and a rigid cystoscope (7.5, 11, or 18 Fr) is used to perform a retrograde pyelogram and to place a safety or working wire under fluoroscopic guidance. Initial ureteric orifice dilation

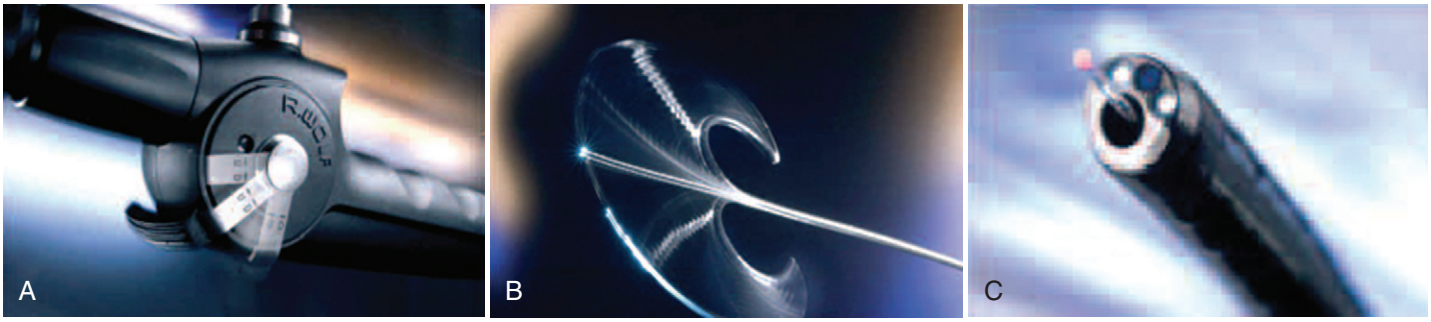
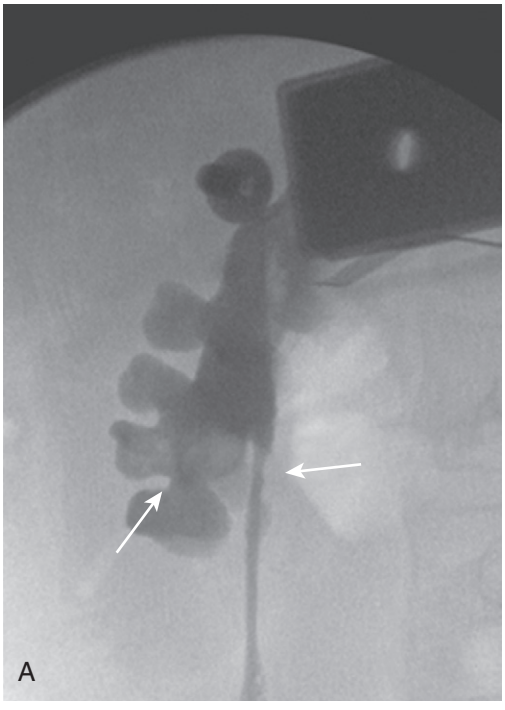


Figure 135–3. Flexible ureteroscopes offer thumb control (**A**) for biplanar 270-degree deflection (**B**). Working channels from 1.8 to 3.6 Fr can accommodate working elements such as a holmium:YAG laser fiber (**C**). (Photos provided by Richard Wolf; © Richard Wolf, all rights reserved.)



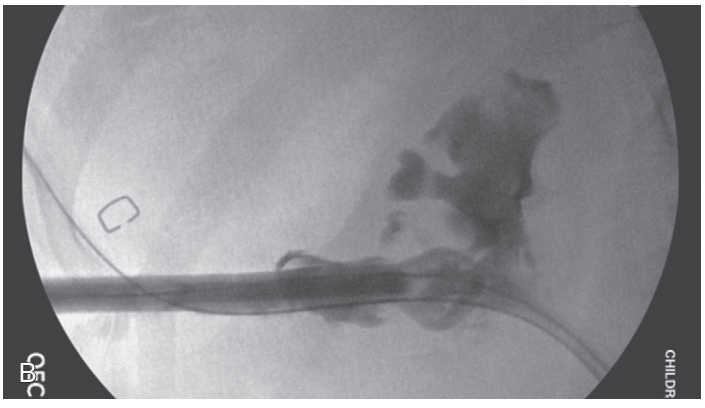


Figure 135–4. **A**, A 7-year-old boy with two separate 7- to 9-mm stones within lower pole calices (*left arrow*). A ureteroscopic approach was attempted, but a lower pole infundibular–ureteropelvic junction angle greater than 270 degrees (*right arrow*) limited ureteroscopic access and visibility. **B**, A percutaneous nephrolithotomy was subsequently performed, clearing all stones in one sitting.

is performed under C-arm fluoroscopic guidance with 8/10-Fr coaxial dilators in ureters that have not been prestented or when the rigid/flexible ureteroscope cannot easily be advanced. The authors generally do not use balloon dilation of the ureteric orifice due to less control and cognitive "feel" during active dilation, as well as concern for development of ureteral stricture from ischemia. If the authors encounter difficulty easily passing the 8/10 dilator, their preference is to place a stent and return for a second procedure rather than dilate more aggressively.

The decision to use a flexible (6.9-Fr) or semirigid (7.5-Fr) ureteroscope is determined on size and location of stone, anatomic factors, and individual surgeon preference. Rigid or semirigid ureteroscopy for ureteral calculi is routinely performed with a safety wire in place, while flexible ureteroscopy is performed with both a safety and working wire in place. Ureteral access sheaths (internal diameter of 9.5 Fr) are routinely used to facilitate flexible ureteroscopy, especially in cases of large proximal ureteral stones and heavy renal pelvis stone burdens. **Access sheaths may also serve to facilitate flexible ureteroscopy when altered anatomy or torturous ureters are encountered** (Fig. 135–5).

Irrigating fluid, which may be used under pressure, should be isotonic and at body temperature to avoid hypothermia and hyponatremia. Calculi are basket-extracted when feasible or fragmented using the holmium:YAG laser to

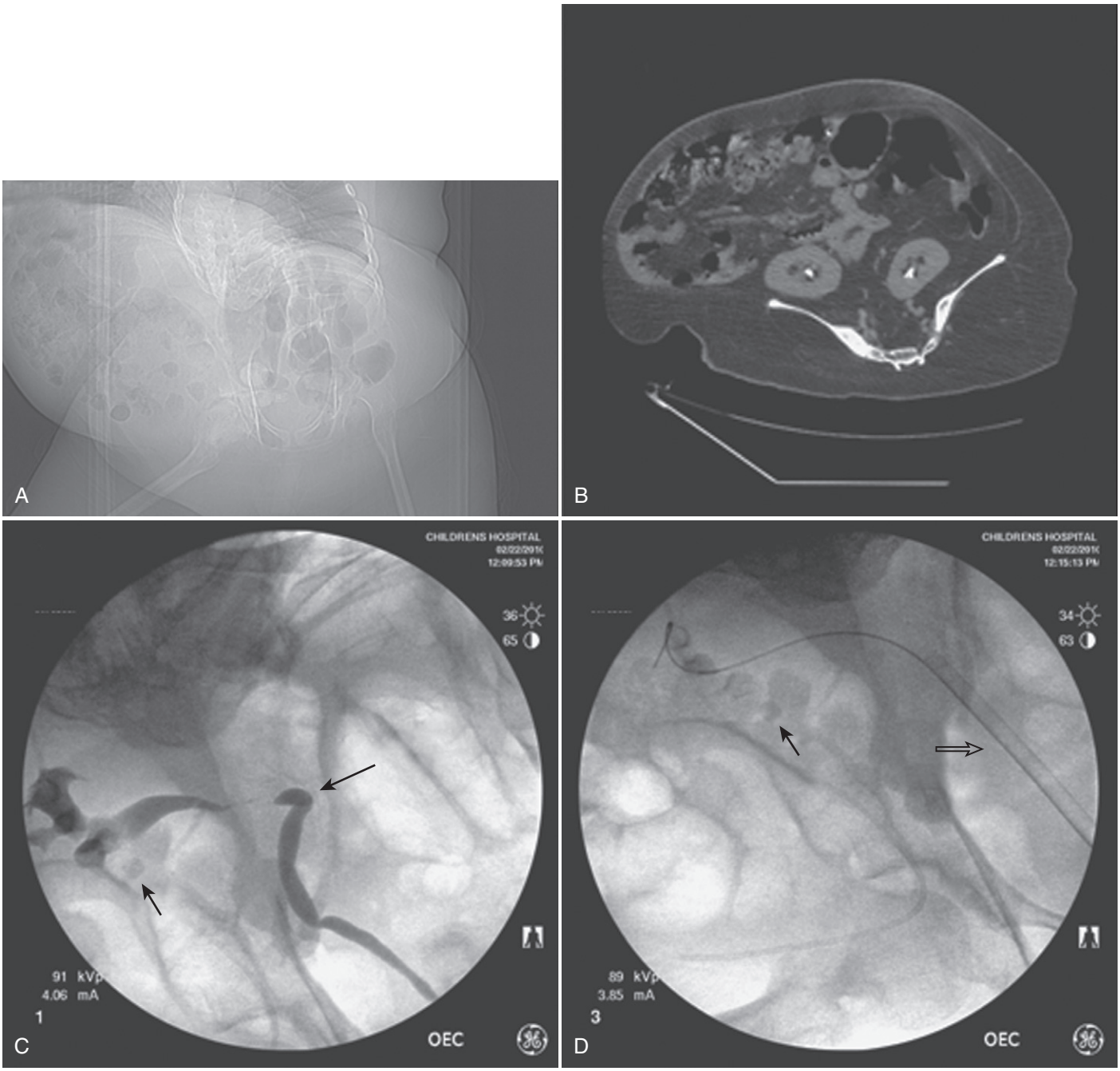


Figure 135–5. Altered anatomy in a 17-year-old male spina bifida patient who underwent a high thoracic myelomeningocele closure at birth (**A**). A computed tomography (CT) scan performed for a gross hematuria workup revealed bilateral nephrolithiasis in pelvic kidneys (**B**). The right retrograde pyelogram (**C**) demonstrated the lower pole stone (*short arrow*) and a torturous ureter almost taking a perpendicular course (*long arrow*). Placement of a ureteral access sheath (**D**) straightened the ureter (*white arrow*). *Continued*

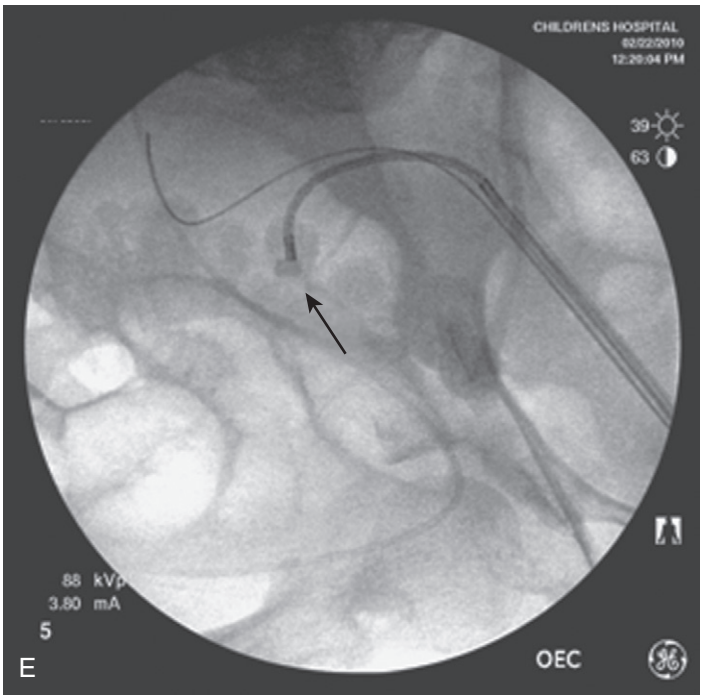


Figure 135–5, cont'd This allowed easier access to address the stone (*short arrow in* **D**) with a flexible ureteroscope (**E**).

facilitate removal. **The decision to place a ureteral stent postoperatively is made based on the duration of the procedure, number of passes with the ureteroscope, and degree of visible ureteral trauma or edema at the conclusion of the procedure.** If the child can tolerate leaving a urethral string in place for 3 days to 1 week, the patient's parents are asked to remove the stent at home; otherwise, the stent is removed under brief anesthetic after 7 days.

Limitations and Complications

As ureteroscopy is becoming more prominent in the pediatric endourologist's armamentarium, complications need to be anticipated and unanswered questions addressed. **The most common complications involve unrecognized ureteral injury, including mucosal flaps and tears, perforation, false passage, and partial to complete avulsion.** Mitigating the damage by early recognition and temporizing with immediate discontinuation of the procedure and passage of a ureteral stent may avoid complications related to shear force injury on the ureter, ischemic damage, and extravasation of irrigant or urine. Injury can occur during introduction of the ureteroscope or passage, either antegrade or retrograde, of instrumentation (guidewires, baskets, dilators), especially in the area of an impacted ureteral calculus. Attempting to withdraw a basket-entrapped calculus too large for the ureter to accommodate can result in any of the above-mentioned injuries. In postpubertal children with an adult body mass, ureteroscopic access is technically similar to the adult population. However, in the prepubertal child, whether or not to attempt primary treatment without ureteric orifice dilation, to perform dilation at the time of definitive therapy, or to place a stent and allow the ureter to passively dilate prior to definitive therapy remains in question. Herndon and colleagues (2006) performed semirigid ureteroscopy (4.5 and 6.5 Fr for distal ureteral calculi) in 29 children with a mean age of 11 years. With no ureter actively dilated and only 14% of children prestented, the ureter was accessed in 100% of cases for a stone-free rate of 96%. The authors can further validate this report with their own institutional experience using 6.9-Fr flexible and 4.5- and 6.5-Fr semirigid ureteroscopy; however, it is their preference to sequentially dilate with the 8/10 coaxial dilator even in very young children. If the authors encounter difficulties, a stent is placed rather than dilated more aggressively. This approach appears to minimize the immediate risks and potential long-term complications, particularly in the management of upper tract calculi; however, it increases the number of children who will require a second anesthetic and procedure to achieve stone-free status. Recent reports suggest that up to 40% of pediatric patients will require at least two procedures to treat upper tract calculi, suggesting that the likelihood of achieving a stone-free status after one ureteroscopic procedure may not be significantly better than with shock wave lithotripsy (Corcoran et al, 2007). Additional procedures were reported with more than half of the stones that were 6 mm or larger (Tanaka et al, 2008).

The necessity of placing a stent after ureteroscopy in all children has also been debated. Although, in large series, the tendency has been to leave a stent in place after ureteroscopic manipulation in a majority of children (Smaldone et al, 2007), several authors have reported no acute or long-term sequelae despite leaving a postoperative stent in less than 20% of cases (Herndon et al, 2006). In the authors' experience, the decision to place a postprocedural stent is made on an individual patient basis and is dependent on the surgeon's experience and degree of visible ureteral trauma at the conclusion of the procedure.

PERCUTANEOUS NEPHROLITHOTOMY

The safety and efficacy of percutaneous nephrolithotomy for large stone burdens have been well established in adults. Initially, urologists were reluctant to perform PCNL in children due to concerns regarding the use of large instruments in pediatric kidneys, parenchymal damage and the associated effects on renal function, radiation exposure with fluoroscopy, and the risks of major complications, including sepsis and bleeding. Another deterrent to performing PCNL in children was the potential resultant sequelae of hypothermia (i.e., coagulopathy) from prolonged exposure to irrigation. **With significantly accumulated experience, however, PCNL is currently being used as monotherapy and in combination with SWL (sandwich therapy) in children, achieving stone-free rates ranging from 68% to 100%** (Table 135–3) (Rizvi et al, 2003; Mahmud and Zaidi, 2004). **Although there is no current international consensus, relative indications for PCNL as the primary treatment modality in children include large upper tract stone burden (>1.5 cm), lower pole calculi greater than 1 cm, concurrent anatomic abnormality impairing urinary drainage and stone clearance, or known cystine or struvite composition** (Wu and Docimo, 2004; Farhat and Kropp, 2007).

The earliest pediatric PCNL series were performed using standard adult-sized instruments. In 1985, Woodside and colleagues (1985) first reported on a series of seven patients (ages 5 to 18 years old) who were rendered stone free without complications when using adult percutaneous techniques and equipment. Years later in 1997, Mor and colleagues (1997) also reported on using adult-sized instruments in their pediatric PCNL series. The use of PCNL in these early series was avoided in very small children (<5 years old) due to concerns regarding parenchymal damage. **In**

Table 135–3.

Outcomes with Large Series of Percutaneous Nephrolithotomy in Children

STUDY	NO. CHILDREN/ RENAL UNITS	MEAN AGE (YEARS)	EQUIPMENT	STONE SIZE (mm)	TRANSFUSION (%)	STONE FREE (%)	SANDWICH THERAPY (%)	COMPLICATIONS (%)
Badawy et al, 1999	60	6	US	N/A	3.3	90	1.7	Fever 8.3 Colon injury 1.7 Urine leak 3.3 Open conversion 5
Zeren et al, 2002	55/62	7.9	US, EHL	16.8	23.9	86.9	1.6	Fever 29.8 Open conversion 1.6
Rizvi et al, 2003	62	N/A	US	47	25.3	67.7	27.4	Open conversion 4.8 Fever 46.8 Urine leak 6.4 Hydrothorax 1.6
Desai et al, 2004	56	9.1	EHL	18.4	14.3	89.8	5.4	Urine leak 5.4
Salah et al, 2004	135/138	8.9	US	22.5	0.7	98.6	0	Urine leak 8
Holman et al	138	8.9	US	22.5	0.4	98.5	0	Fever 1.1 Urine leak 8
Samad et al, 2006	169/188	8.2	N/A	27.2	4	59.3	34.5	Fever 42.8 Hyponatremia 0.1 Obstruction 0.1
Shokeir et al, 2006	75/82	6.6	US	14.4	1.2	95.1	4.8	Urine leak 1.2

EHL, electrohydraulic lithotripsy; HL, holmium laser; N/A, not available; US, ultrasonography.

contrast to these concerns, multiple series subsequently used adult-sized instruments and reported high efficacy rates with acceptable complication rates even when the dilating tract size as high as 30 Fr (Salah et al, 2004; Samad et al, 2006; Bilen et al, 2007). **In fact, recent data have suggested that PCNL is possible in very young children using adult-sized equipment** (Nouralizadeh et al, 2009). Investigations regarding the risk of renal damage in pediatric patients treated with PCNL have revealed that there is no significant risk of renal functional loss. Mor and colleagues (1997) performed radioisotope scans on 10 children before and after PCNL and found no change in differential function and no evidence of significant scarring.

Despite early successes employing adult equipment, early efforts focused on developing technology to minimize percutaneous tract size without affecting PCNL efficacy. Jackman and colleagues (1998), developed a novel percutaneous access technique ("mini-perc") using an 13-Fr peel-away vascular access sheath and reported an 85% stone-free rate for 11 procedures in seven children with a mean age of 3.4 years and an average stone burden of 1.2 cm^2 (Fig. 135–6). With this technique, PCNL could now be performed in *preschool-aged children*. **The benefits of minimal tract dilation included increased maneuverability, decreased blood loss, and shorter hospital stay. However, theoretical limitations, including prolonged operative times and impaired visualization from bleeding, suggests that this technique may not be adequate for very large stone burdens.**

Recent advances in instrumentation, such as smaller nephroscopes (15- to 18-Fr) and more efficient energy sources for intracorporeal lithotripsy, including the holmium:YAG laser and smaller pneumatic lithoclast and ultrasound probes, have greatly facilitated percutaneous treatment techniques in pediatric patients (Fig. 135–7). As a result, PCNL has now replaced open surgery as the treatment of choice for large stone burdens in children of all ages.

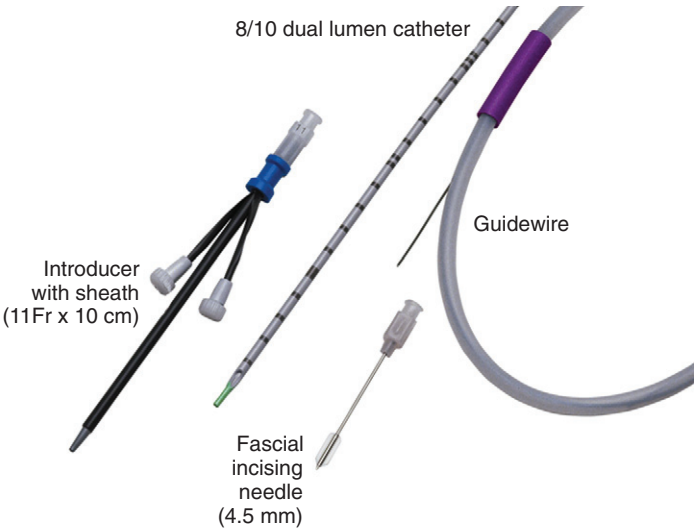


Figure 135–6. The "mini-perc" set uses an 11- to 13-Fr peel-away vascular access sheath to accommodate a ureteroscope or cystoscope, serving as a nephroscope, to perform percutaneous nephrolithotomy (PCNL) in children of preschool age.

Planning for PCNL in Children

Much planning is required prior to embarking on PCNL in children. Films must first be reviewed scrupulously to determine if the stone(s) is/are amenable to a percutaneous procedure. **Nephrocalcinosis in children, for example, may be confused with staghorn calculi; the etiology and treatment are very different** (Fig. 135–8). Infection is the most common causative agent in the formation of a staghorn calculus, and PCNL is a first-line therapy. The most frequent causes of nephrocalcinosis are hereditary tubulopathies and vitamin D intoxication (Ammenti et al, 2009). **Medullary sponge kidney is a**

renal malformation characterized by cystic anomalies of precalyceal ducts, which is frequently associated with nephrocalcinosis and stone formation (Gambaro et al, 2006). Nephrocalcinosis is most often not amenable to successful endourologic treatment(s) because calculi are intraparenchymal and thus outside the collecting system. Management is often medical and aimed at prevention of further nephrocalculi, a cause of worsening renal function.

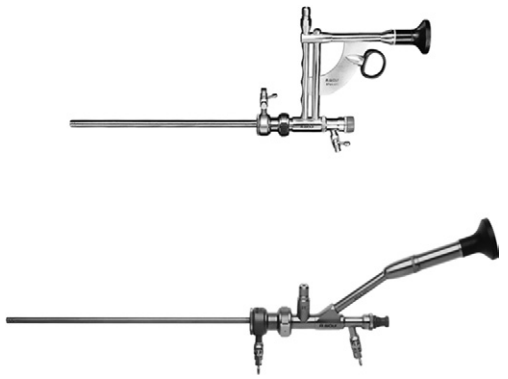


Figure 135–7. Smaller-caliber nephroscopes (15 to 18 Fr) with offset lenses have greatly facilitated standard percutaneous treatment techniques in pediatric patients. (From Wolf JS Jr, et al. Best practice policy statement on urologic surgery antimicrobial prophylaxis. J Urol 2008;179[4]:1379–90.)

The risks of the PCNL must be reviewed with the consenting parent or guardian. **It must be understood that a percutaneous procedure carries risks that are not limited to bleeding (requiring transfusion), delayed renal hemorrhage (requiring angioablation), sepsis, pneumothorax, hemothorax, urothorax, incomplete stone treatment, and injuries to organs adjacent to each respective kidney.**

Every attempt should be made to treat a urinary tract infection and/or minimize bacteriuria prior to the procedure. A urine culture, with antibiotic sensitivities, should be checked 3 weeks prior to the procedure. Any positive culture requires a full course of antibiotics and repeat culture to confirm sterility. Three to 5 days of prophylactic antibiotics is recommended prior to the procedure, even with a negative preoperative culture. Broad-spectrum IV antibiotics (i.e., ampicillin and gentamicin) should be given at the time of the procedure.

All percutaneous procedures are performed using general anesthesia. **A warm operating room, warmed isotonic irrigation solution, short operative times (not to exceed 1.5 hours), proper draping, and monitoring of body**

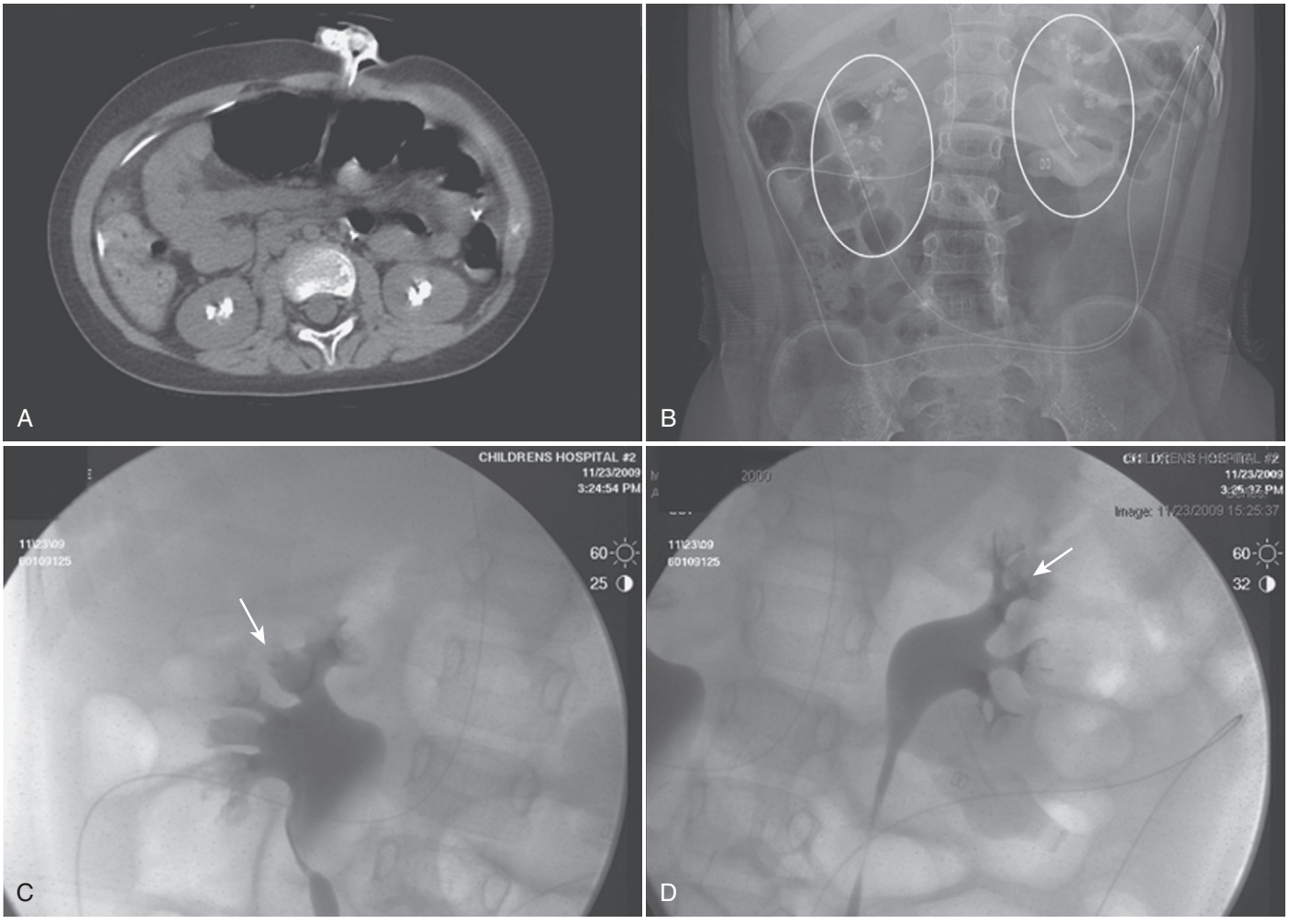


Figure 135–8. A 9-year-old boy with cerebral palsy and gross hematuria. CT scan demonstrated bilateral nephrolithiasis (**A**) thought to be staghorn calculi. Plain radiograph (**B**) and bilateral retrograde pyelograms (**C** and **D**) correlate to show nephrocalcinosis (*white circles* and *white arrows*, respectively) reflective of medullary sponge kidney disease. Subsequent metabolic workup revealed renal tubular acidosis (RTA) with hypercalciuria.

temperature should decrease the incidence of hypothermia and hyponatremia. After induction of anesthesia with the patient in the lithotomy position, a retrograde pyelogram is performed to outline the collecting system, and an occlusive balloon or a 5-Fr open-ended ureteral catheter is left in situ to opacify the collecting system during percutaneous access. The patient is then repositioned in the prone position with the torso elevated at 30 degrees from the table surface with a towel roll (Farhat and Kropp, 2007).

Circumstances that require special consideration involve children with spinal cord injuries and congenital anomalies such as spina bifida. In these patients, positioning can be a challenge due to existing spinal hardware and limb contracture (Fig. 135–9) (Ost and Lee, 2006a). Patients who have had prior spinal surgery consisting of vertebral fusion or Harrington rod placement will have restricted spinal mobility, spinal curvature, and/or atrophic or contracted extremities (Fig. 135–10). **As the result of scoliosis, lordosis, and/or kyphosis, renal anatomy is altered.**

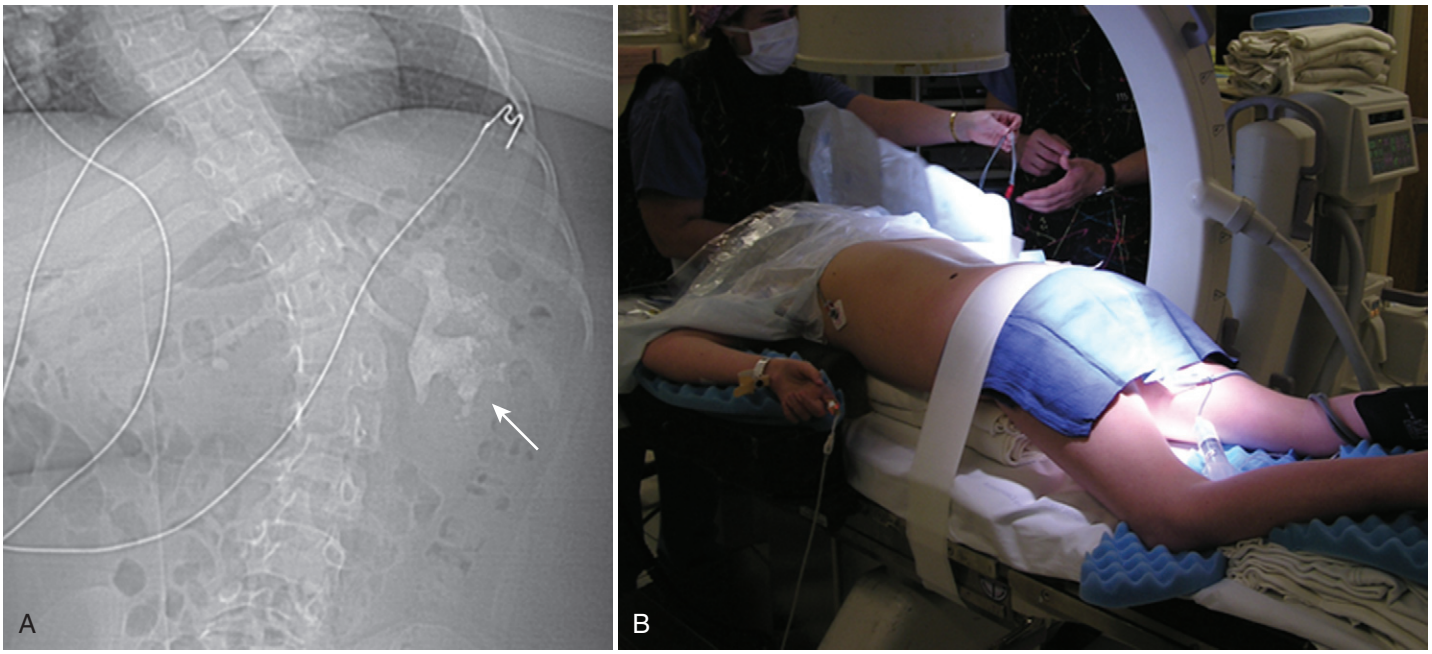


Figure 135–9. **A**, Severe scoliosis and complete staghorn calculus (*arrow*) in a 10-year-old partial quadriplegic. **B**, Spinal curvature and limb contractures (*left arm*) prevented optimal prone positioning. Care is taken to pad all joints in the prone position.

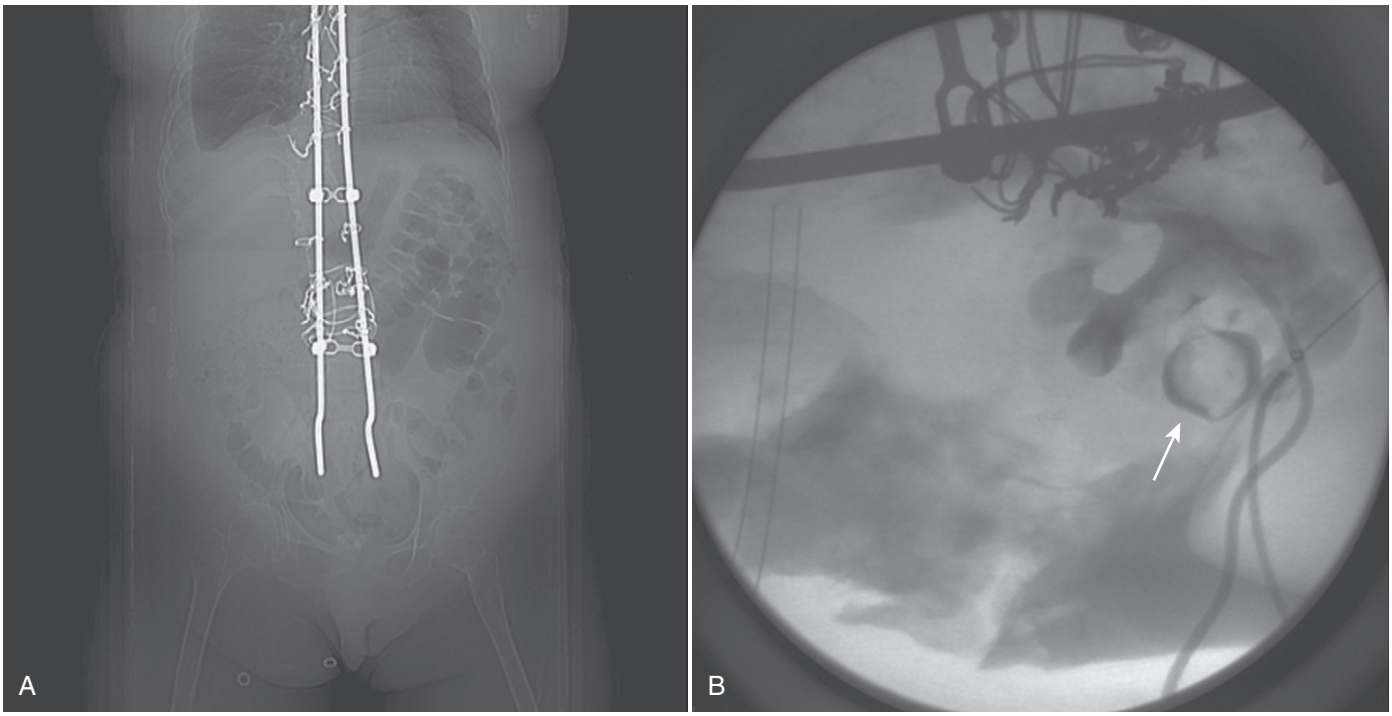


Figure 135–10. **A**, Harrington spinal rods in a 16-year-old spina bifida patient. **B**, Prone view of right collecting system showing midpole caliceal stone as filling defect (*arrow*). Hardware has obscured the proximal ureter and impeded access to this calyx when the C-arm was in the 30-degree position.

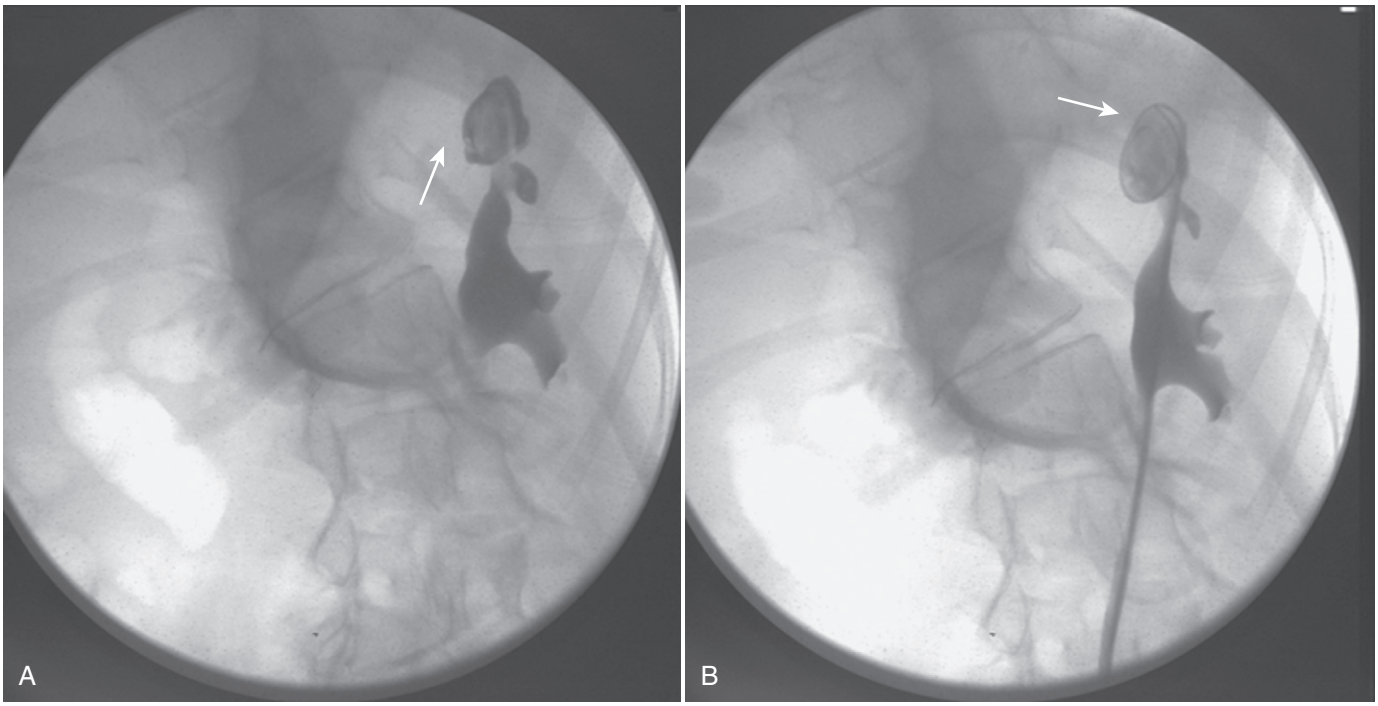


Figure 135–11. **A**, A14-year-old male with spina bifida and scoliosis with a left upper pole partial staghorn calculus (*arrow*). **B**, Altered spinal anatomy had deflected renal anatomy cephalad (*arrow*). Intercostal access between the 10th and 11th rib increases the risk of pneumothorax considerably.

Consequently, the risk of injuries to adjacent organs (i.e., pneumothorax) during percutaneous procedures increases. Assessing the degree of mobility in the trunk and extremities is crucial in planning for PCNL in these patients (Fig. 135–11). These patients must be placed in the most comfortable position possible without excessive contortion or flexion of the joints. Special attention must be paid to latex precautions in the myelomeningocele population, and, as in all cases, proper padding of pressure points is mandatory.

Percutaneous Nephrolithotomy Technique in Children

After selection of the desired calyx, a 16- or 18-gauge spinal needle is placed with the assistance of fluoroscopy in the 30-degree position. When fluoroscopy is used, the collecting system is opacified through an open-ended ureteral catheter that has been inserted cystoscopically prior to positioning in the prone position. Alternatively, ultrasound guidance can be used to puncture the calyx of choice. The ideal tract is one that provides the shortest and most direct access to the stone. For complex calculi occupying multiple calices, including the lower pole, a supracostal posterior access is preferred to provide visualization of the superior calyx and pelvis, access to the pelvis and ureter, and straight access to the inferior calices, allowing easier manipulation of the working instruments and minimizing torque on the collecting system (El-Nahas et al, 2008). Following initial puncture, to avoid trauma, no attempt should be made to redirect the needle while it is located within the cortex of the kidney. With the C-arm in the 90-degree plane, the depth and medial extension of the needle is checked. After access is confirmed with urine or irrigation return, a flexible guidewire is placed into the collecting system through the needle and directed down the ureter into the bladder. A small skin incision is made with a No. 11 scalpel and 8- and 10-Fr coaxial dilators are passed over the guidewire into the collecting system. Once in place, an Amplatz Super Stiff guidewire (AGA Medical, Plymouth, MN) is placed as a working wire.

Tract dilation can be performed by several techniques. Serial dilation with Amplatz dilators over working wires and subsequent sheath placement under fluoroscopic guidance is the most common technique employed. For smaller children and lower stone burdens, an 11- to 13-Fr peel-away sheath (Docimo Mini-Perc, Cook Urological, Spencer, IN) and trocar are passed over the wire and through the calyx under fluoroscopic guidance. For balloon dilation, either the Bard X-Force or NephroMax High-Pressure Nephrostomy Balloon Catheter (Bard Medical, Covington, GA; Boston Scientific, Natick, MA) may be used. Either will facilitate dilation of a 30-Fr tract at a pressure of 17 atmospheres. This technique permits dilation and sheath placement in a single step, thereby minimizing potential parenchymal trauma and bleeding from sequential dilation with rigid dilators. Although the decision to proceed with mini-perc or dilation is individualized based on the child's age, anatomy, and stone burden, familiarity with all of the above techniques facilitates complete access with minimal morbidity (Fig. 135–12A and B).

Once access is obtained, nephroscopy and nephrolithotomy can be performed with a variety of energy sources for stone fragmentation. The outer diameter of nephroscopes range from 15 to 26 Fr, and a 15-Fr flexible nephroscope with a 6-Fr working channel has also been developed. In addition, 7- and 8-Fr offset cystoscopes with 5-Fr working ports and 7- to 9-Fr flexible ureteroscopes can be used through an 11-Fr access sheath with enough clearance to allow low pressure irrigation (Wu and Docimo, 2004). Energy sources currently used include ultrasonic lithotripsy, electrohydraulic lithotripsy (EHL), and the holmium laser, although individual preference is determined by availability

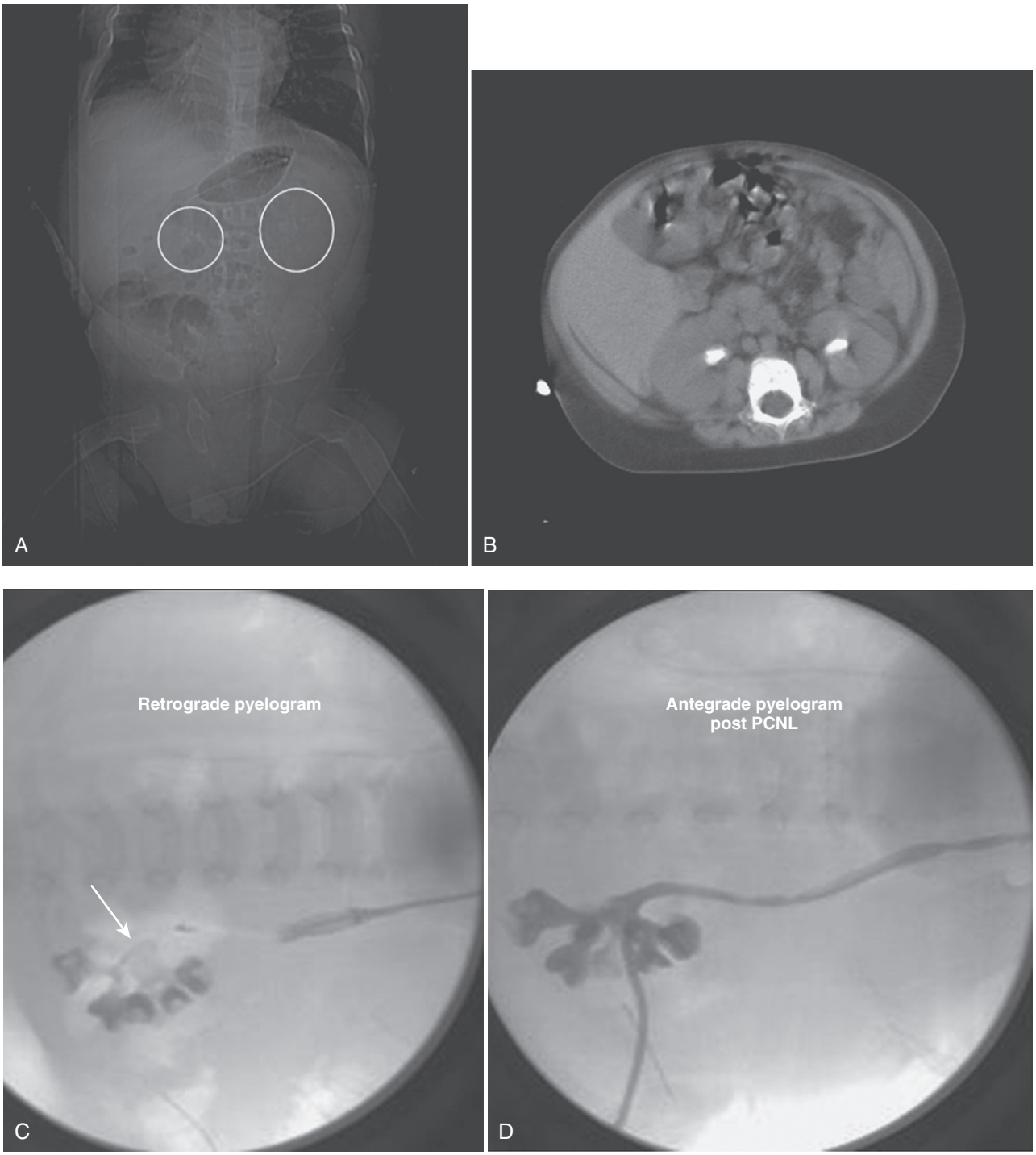


Figure 135–12. A 22-month-old boy with intractable diarrhea of infancy from tufting enteropathy who awaited a small bowel transplant. His risks for nephrolithiasis included total parenteral nutrition dependency, osteomalacia, chronic dehydration, hypocitruria, and hyperoxaluria. **A**, A kidney-ureter-bladder film demonstrated mildly radiopaque stones, and a subsequent CT scan (**B**) confirmed bilateral staghorn calculi. **C**, Prone view of left retrograde pyelogram of child in **A**, demonstrating staghorn calculi as a filling defect (*arrow*). A "mini-perc" technique was used to address his stones. **D**, Prone view of the antegrade nephrostogram through a 6-Fr nephrostomy tube demonstrating "stone-free" status.

and the surgeon's experience. Postoperative stenting and/or placement of a nephrostomy tube are both patient and surgeon dependent and vary between series. Similar to adult procedures, tubeless PCNL has theoretical advantages, including decreased postoperative pain and a short hospital stay, but currently, data is limited in the pediatric population (Khairy Salem et al, 2007).

Percutaneous Nephrolithotomy Outcomes

Recent large retrospective series of PCNL monotherapy have demonstrated high efficacy rates approaching 90% (see Table 135–3) (Zeren et al, 2002; Desai et al, 2004; Bilen et al, 2007). In 56 children (mean age 9.1 years) with a mean stone

burden of 337.5 mm^2, Desai and colleagues (2004) reported a stone-free rate of 89.8% using EHL through a 14-Fr nephroscope and a 20- to 24-Fr sheath. Of these, 61% required multiple tracts, and 45% were staged procedures. Findings demonstrated that the number and size of tracts were significantly associated with postoperative hemoglobin decrease (mean 1.9 g/dL) and an overall transfusion rate of 14%. In 52 children with a mean age of 7.9 years and a mean stone burden of 282 mm^2, Zeren and colleagues (2002) reported an 87% stone-free rate using US and EHL for fragmentation and tract dilation from 18 to 30 Fr. Complications included postoperative fever (30%) and the need for transfusion (24%). **Transfusion was associated with operative time, sheath size, and stone burden.** In 135 children of mean age 8.9 years with a mean stone burden of 507 mm^2, Salah and colleagues (2004) reported a 98.5% stone-free rate using US through a 26-Fr nephroscope. Complications were low (8% urine leak rate and 0.7% transfusion rate), with only one patient requiring a second procedure. In a recent series of 46 children with a mean stone burden of 332 mm^2, Bilen and colleagues (2007) reported an 88% stone-free rate using EHL, US, and the holmium laser. When stratified by tract size (14, 20, and 24 Fr), efficacy rates were similar in all groups, but there were no complications or transfusions in the 14-Fr tract group.

In an effort to reduce the number of tracts and associated morbidity, some centers have chosen to follow primary PCNL with adjunctive SWL therapy to clear residual stone fragments. In a small series of 29 children with a mean age of 3.8 years and a mean stone burden of 2.4 cm, Mahmud and Zaidi (2004) reported a 60% stone-free rate after PCNL monotherapy using EHL through a 17-Fr angled nephroscope. Only one tract was used in all patients, and after SWL sandwich therapy, the stone-free rate increased to 100%. In a larger series of 169 children with a mean stone burden of 3.1 cm, Samad and colleagues (2006) reported a 59% monotherapy stone-free rate with 96% of cases performed through a single tract. Approximately one third (34.5%) of primary failures were treated with SWL; the cumulative stone-free rate in all patients was 93.8% with a 3.6% transfusion rate. When stratified by age, anatomy, bilaterality, and renal function, stone-free outcomes were equivalent in all groups. The decision to follow PCNL with SWL is related to operator experience with percutaneous technique and available technology. **It is the authors' preference to perform a second-look nephroscopy through the original tract to ensure stone-free status during the initial hospital admission, rather than progress to SWL sandwich therapy.** Endoscopic surveillance during the initial procedure can determine the need for second-look nephroscopy without relying on additional imaging and the associated risks of radiation exposure (Roth et al, 2009). With continued improvement in technology and technique, the indications for PCNL in children will continue to increase. Given the technically challenging nature of PCNL, the surgeon's experience is paramount in developing individualized treatment plans to optimize efficacy with minimal morbidity.

LAPAROSCOPIC AND ROBOTIC-ASSISTED PYELOLITHOTOMY

Treatment of large stone burdens in children is technically challenging, often requiring multiple procedures. Laparoscopy and robotic-assisted laparoscopy have been used successfully in adults for treatment of calculi during the concomitant treatment of ureteropelvic junction obstruction and in the primary treatment of staghorn calculi. Small series using these techniques in children have only recently been described. In eight children (mean age 4 years) with a mean stone burden of 2.9 cm and who underwent transperitoneal laparoscopic pyelolithotomy, Casale and colleagues (2004) reported a 100% success rate, a mean hospital stay of 2.15 days, and a mean operative time of 1.6 hours with no major complications. In the first report of robotic-assisted laparoscopic pyelolithotomy, Lee and colleagues (2007) described their experience in five patients, four with cystine staghorn calculi refractory to PCNL and SWL and one with calcium oxalate calculi and concurrent ureteropelvic junction obstruction. Of these cases, four were completed robotically, with one patient having a residual 6-mm lower pole stone and one patient requiring conversion to an open procedure. Mean operative time in this series was 315 minutes, mean estimated blood loss was less than 20 cc, and the mean hospital length of stay was 3.8 days. These early experiences demonstrate that laparoscopic pyelolithotomy is feasible, safe, and efficacious as an alternative to open pyelolithotomy in children and warrants further study. However, due to their demanding technical nature, these procedures will likely be limited to endourologic management failures in academic centers with abundant expertise in laparoscopic and robotic pediatric surgery. The indications for use of these technologies are also limited to particularly complex and large stone burden patients.

PERCUTANEOUS CYSTOLITHOTRIPSY FOR BLADDER STONES

Bladder stones are more often found in children from developing countries and are thought to be related endemically to malnutrition. It is thought that diets low in animal protein and phosphorous (breast milk as opposed to cow's milk), in addition to vitamin A deficiency, are contributory (Kancha and Anasuya, 1992). **Bladder stones from children in these developing countries are most often composed of ammonium acid urate**. In contrast, among children from industrialized nations, bladder stones are most often found in those with spinal cord injuries or congenital abnormalities such as spina bifida. Very often, these children have undergone augmentation cystoplasty and/or manage their bladders by clean intermittent catheterization. **It has been reported that up to 50% of children with reconstructed bladders will develop a bladder stone(s) in their lifetime** (Palmer et al, 1993). **Urinary stasis, bacterial colonization or infection with urea-splitting organisms, retained mucus, and foreign bodies can all contribute to the formation of bladder stones, the majority of which are struvite.**

Open cystolithotomy has been the traditional modality to treat bladder stones. Transurethral cystolithotripsy is an alternative, although not ideal in the pediatric population. In children, a smaller-caliber urethra limits effective treatment of large bladder stone burdens. Percutaneous cystolithotripsy, however, is now used worldwide with the advantage of shorter hospital stays, smaller scars, and less indwelling catheter time postoperatively (Al-Marhoon et al, 2009). Presently, percutaneous cystolithotripsy is the preferred method to treat bladder stones that have formed in reconstructed bladders (Paez et al, 2007). In developing countries as well, percutaneous lithotripsy has become the first-line treatment modality to address bladder stones in bladders that have not been augmented. Salah and colleagues (2005) reported on their experience with cystolithotripsy in 155 children from Pakistan and Yemen with a mean age of 4.5 years and average bladder

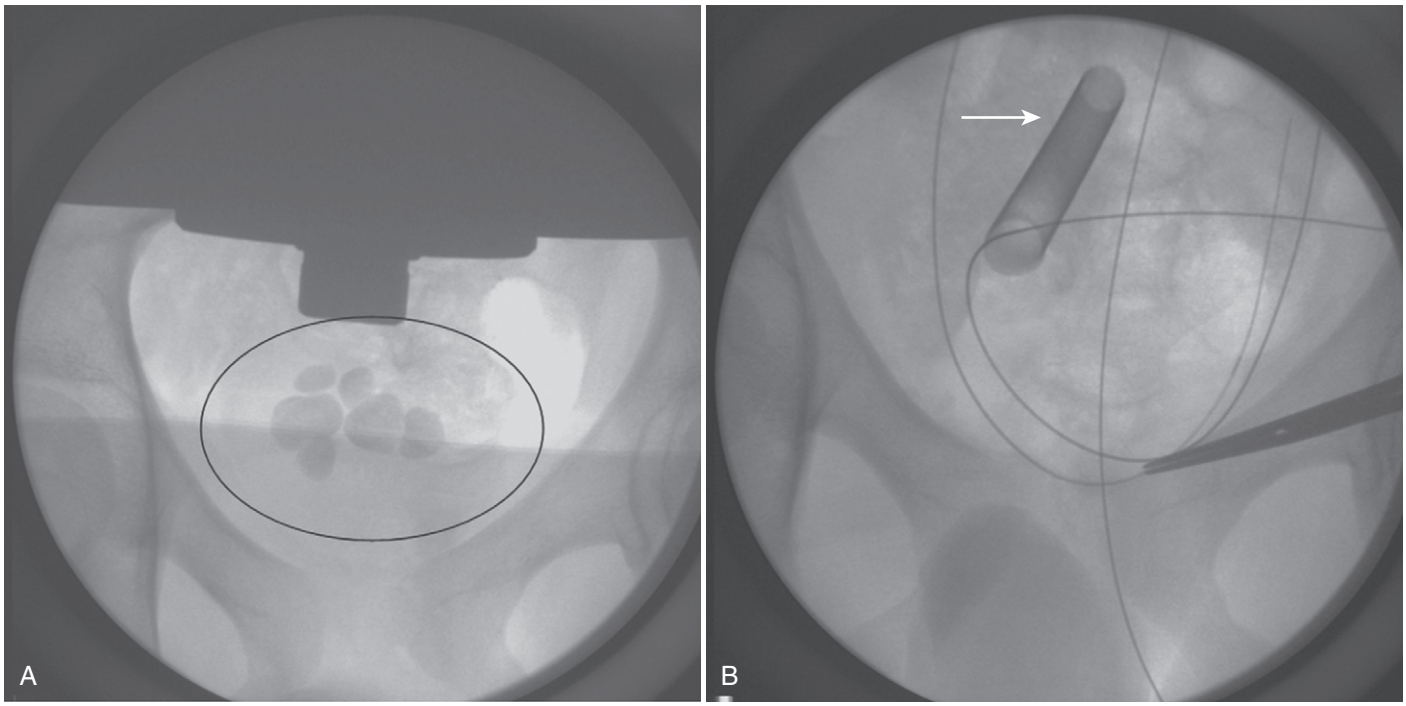


Figure 135–13. A 12-year-old male with spina bifida with an augmented bladder (ilealcystoplasty) found to have multiple sizeable bladder stones (**A**) on a workup for recurrent *Proteus mirabilis* infections. **B**, Percutaneous cystolithotripsy with an ultrasonic lithotripter was performed through a 30-Fr access sheath (*arrow*), clearing all stones from the augmented bladder.

stone burden of 2.3 cm (range 0.7 to 4 cm). All children were treated safely and successfully using a 26-Fr nephroscope through a 30-Fr sheath placed through a 1-cm suprapubic incision.

Percutaneous cystolithotripsy has also been used effectively in infants less than 1 year old to clear bladder stones. Gan and colleagues (2010), reported on their experience using a 16-Fr peel-away sheath with a ureteroscope to treat bladder stones with an average size of 1.4 cm in 15 boys with a mean age of 8.2 months.

Percutaneous cystolithotripsy in children may be performed under ultrasound or fluoroscopic guidance and is most often an outpatient procedure. With either modality, the bladder is first filled to capacity with water or contrast, respectively. The child is placed in the Trendelenburg position to minimize the risk of bowel injury during access and tract dilation/formation. An 18-gauge needle is placed into the distended bladder midline, 1 to 2 fingerbreadths above the pubic bone. Once proper placement is confirmed with return of fluid, a wire is passed through the needle into the bladder. A tract may then be established reflective of stone diameter and the child's size. Most often, a tract is established with a balloon dilator to accompany a 30-Fr sheath. Amplatz dilators may also be used. A 26-Fr nephroscope is used to extract stones less than 1 cm using a rigid stone forceps, or an ultrasonic lithotripter may be used to fragment stones greater than 1 cm. At the conclusion of the percutaneous cystolithotripsy procedure, a Foley catheter is left per urethra or per continent catheterizable stoma for 1 week. The rectus fascia defect is closed with a 2-0 Vicryl suture (Fig. 135–13).

DETERMINATION OF STONE-FREE STATUS

As the surgical management of pediatric stone disease evolves, the lack of a consistent definition of "stone free" following definitive therapy is an issue that remains unaddressed. Although controversial, in select adult patients, all stone fragments can be considered clinically significant and can lead to stone recurrence (Krambeck et al, 2008). Likewise, the presence of residual stone fragments in children has been associated with poor outcomes (Afshar et al, 2004), and any size stone fragment in a young stone former may result in the need for repeat surgical procedures. However, these fragments often are not detected on US or KUB, thus necessitating reliance on CT imaging in select children.

Balancing the risks of radiation exposure for post-treatment stone detection and the risks of anesthesia for secondary procedures is a challenging dilemma for contemporary pediatric endourologists. Newer, high-speed helical CT scanners reduce radiation exposure and rarely require intravenous sedation. In addition, maximizing intraoperative fragment detection by direct visualization in URS and PCNL and continued development of high-resolution real-time fluoroscopy may result in less reliance on postoperative imaging and decreased need for second-look nephroscopy/URS, SWL, or sandwich therapy (Ost and Smith, 2006b). Until the risks of radiation exposure in children are more clearly defined, surveillance in these children will be individualized based on age, anatomy, stone burden, and underlying metabolic abnormalities.

CONCLUSIONS

Evolution of techniques and miniaturization of instruments have changed the management of pediatric stone disease. However, despite encouraging results, concern remains regarding the safety of endourologic treatment in smaller patients and its subsequent effects on the developing kidney. Although SWL is still considered first-line therapy for upper tract calculi less than 1.5 cm, evidence is accumulating that ureteroscopy with laser lithotripsy and stone basketing may be more efficacious in treating upper tract stone

disease in children. Although PCNL remains the most effective technique for large upper tract stone burdens, there are now reports of laparoscopic and robotic-assisted laparoscopic pyelolithotomy in major pediatric academic centers with extensive laparoscopic and robotic experience. Prospective studies designed to determine "the preferred" endourologic approach to upper tract calculi in children would be helpful, albeit difficult to conduct. In this regard, the individual surgeon's experience and comfort level will weigh heavily in choosing a treatment modality. Pediatric urologists' familiarity with percutaneous renal access and the full spectrum of endourologic equipment and techniques will continue to facilitate efficacious minimally invasive approaches for the entire pediatric urinary tract.

Acknowledgment

The authors would like to acknowledge Marc C. Smaldone, MD for his help in preparing this chapter.

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chapter 136

Urologic Considerations in Pediatric Renal Transplantation

Craig A. Peters, MD, FACS, FAAP

Pretransplant Assessment
Pretransplant Preparation
Transplantation
Complications
Summary

The child requiring renal replacement will more often than not be a boy with an obstructive uropathy. The challenge for the pediatric urologist is to ensure that the damage done to the native kidneys will not be repeated with the transplanted kidney. These patients are some of the most complex children to care for, mostly in developing a therapeutic plan to provide for **several goals: (1) normal urinary drainage from the kidney into a reservoir, (2) a urinary reservoir that permits low-pressure storage for a socially acceptable time, (3) volitional emptying of the reservoir with continence, (4) absence of infection, and (5) all with the fewest surgical procedures and patient trauma.** These goals are achievable, but it must be clear that until they are assured, renal transplantation should be deferred, or a plan to achieve these goals with assurance of patient/family compliance must be in place.

Patient and family understanding and compliance are essential for successful urologic management of the child with an abnormal urinary tract and end-stage renal disease (ESRD). The integration of the entire care team in this preparation is also critical and demands a close working relationship between the urology team, the pediatric nephrologist, and transplant team. The urologist must have a basic understanding of the needs and constraints of the nephrologists and transplant surgeons, if they are not performing the entire transplant. The ureteral implantation can be performed by the urologist or the transplant surgeons, but this should be dependent upon the state of the bladder and the comfort level of the surgical teams with the particular aspects of the surgery and their postoperative management, including any complications.

PRETRANSPLANT ASSESSMENT

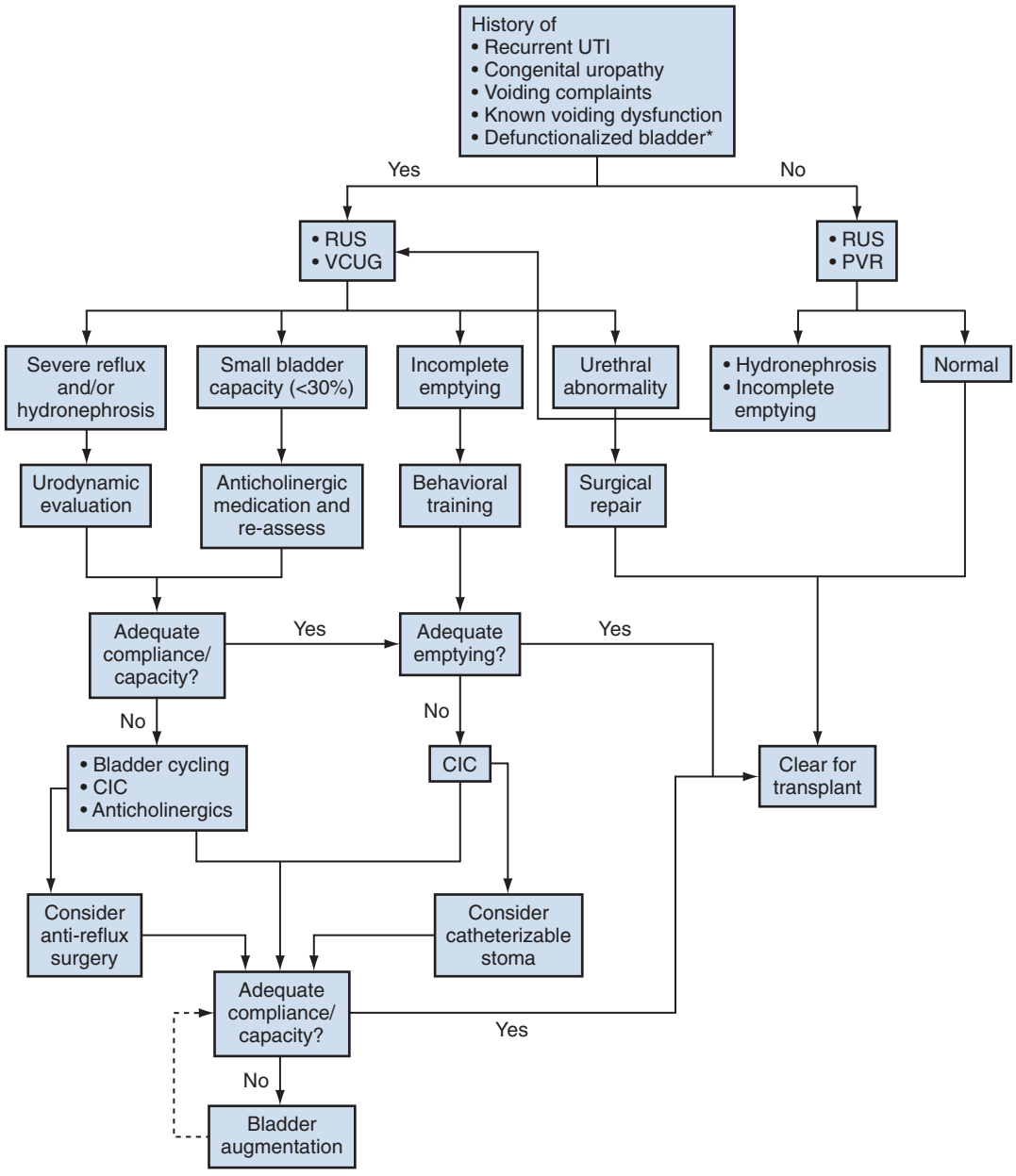
Screening

A large fraction of children in need of renal replacement will have some type of uropathy—either congenital obstruction, vesicoureteral reflux, or neuropathic bladder dysfunction (North American Pediatric Renal Transplant Cooperative Study [NAPRTCS], 2008). Younger boys will typically have obstructive uropathy, including posterior urethral valves, while the reflux and neuropathic bladder patients will be older, including young adults. Some children will have uncharacterized ESRD, and it is reasonable to have all children screened for urologic issues prior to transplant. A detailed history, renal ultrasonogram, and postvoid residual urine determined by ultrasonography (US) can effectively rule out most significant uropathies. A routine voiding cystourethrogram (VCUG) is not necessary, unless there is a history of a specific urologic disease, febrile or recurrent urinary tract infection (UTI), the presence of hydronephrosis, or clinically abnormal voiding (Ramirez et al, 2001) (Fig. 136–1).

Focused Assessment

The child with a known urologic abnormality will require a pretransplant assessment directed by the underlying condition and the status of the bladder and kidneys. In most, a VCUG will be useful to permit an assessment of voiding function, the state of the urethra, and the presence of reflux. When bladder dynamics are abnormal based on the VCUG or a renal US, consideration for urodynamic evaluation is appropriate. **The indications for urodynamic testing to assess bladder capacity, compliance, and emptying, as well as sphincter function, includes a known neuropathic bladder abnormality, prior severe posterior urethral valves and any child with ongoing voiding dysfunction, hydronephrosis, or recurrent UTI** (Burns et al, 1992; Zermann et al, 2003). The principle goal of the urodynamic testing is to determine the need for further therapy for bladder function. This might include medical therapy with anticholinergics, the use of intermittent catheterization, and the potential need for bladder augmentation in severe cases.

Urodynamics will also provide insight into bladder emptying function, which will be critical to prevent infection. Of course, if medical therapy for a noncompliant bladder is needed, this may impair bladder emptying and necessitate clean intermittent catheterization (CIC) to permit effective emptying. In the sensate child or in some with neuropathic bladders, the creation of a continent catheterizable stoma may be the ideal way to facilitate effective CIC. These decisions should be made and executed pretransplant. Urodynamic evaluation will often be a regular monitoring



*If patient is anuric and has no urologic history, no further testing is essential; if there is a history of neurogenic bladder, posterior urethral valves, or complex urologic condition, consideration of bladder cycling and anticholinergics is appropriate.

Figure 136–1. Algorithm for evaluation and management of the bladder in patients in preparation for renal transplantation. The key element is the history of urologic conditions or symptoms. CIC, clean intermittent catheterization; PVR, postvoid residual (volume); RUS, renal ultrasonogram; UTI, urinary tract infection; VCUG, voiding cystourethrogram.

evaluation in these children and a critical element in ongoing optimization of bladder function. It will often be necessary to repeat the study to ensure that the therapeutic intervention has been effective and that the bladder is prepared for the transplant.

PRETRANSPLANT PREPARATION

Bladder Preparation

General Issues

The most common bladder abnormality associated with ESRD is the low-capacity, hypertonic bladder with poor compliance. This is the typical picture with posterior urethral valves (PUV), but it is important to recognize that these bladders continue to evolve and may progress to a pattern of insufficient contractility to empty at all (Peters et al, 1990; Nguyen and Peters, 1999). They may still be hypertonic and pose ongoing renal risk and will require CIC in most cases. Hypertonicity is the most dangerous dynamic pattern, as it will create an obstructive condition for the kidneys, even in the absence of reflux. Bladder dysfunction can increase graft loss (Herthelius and Oborn, 2007).

Hypertonicity

The hypertonic bladder is managed with medication as a first-line therapy, typically with anticholinergics, and with augmentation

Key Points: Urologic Evaluation and Management

- The goals are (1) normal drainage from the kidney into a reservoir, (2) a urinary reservoir that permits low-pressure storage for a socially acceptable time, (3) volitional emptying of the reservoir with continence, (4) absence of infection, and (5) the fewest surgical procedures and patient trauma.
- A large fraction of children in need of renal replacement will have some type of uropathy—either congenital obstruction, vesicoureteral reflux, or neuropathic bladder dysfunction.
- Pretransplant assessment should be directed by the underlying condition and the status of the bladder and kidneys.
- Urodynamic testing aims to assess bladder capacity, compliance, and emptying, as well as sphincter function.
- Indications for urodynamics include a known neuropathic bladder, prior severe posterior urethral valves, and any child with ongoing voiding dysfunction, hydronephrosis, or recurrent UTI.

as the second-line therapy (Lopez Pereira et al, 2000). Medical management requires diligence on the part of the family and follow-up that regularly assesses the response to therapy. It will usually require a combination of anticholinergics and CIC, although some children with PUV can learn to void by the Valsalva maneuver. It should never be assumed that they will be able to do so; they must demonstrate this by repeated low postvoid residual volumes on catheterization.

Anticholinergic therapy is best titrated with increasing doses and watching for a change in catheterized volumes, wetting, and hydronephrosis. Urodynamic evaluation can more precisely define the efficacy. Often medical therapy is introduced at the same time as CIC, although this is not essential. Compliance with CIC is often an excellent test of later patient/family compliance with the stringent requirements of renal transplant. If a family is unable to manage with CIC, their ability to manage the medical care of a transplant must be questioned.

The goal of therapy is for the child to be able to hold to capacity expected for age at low pressure, that is, less than 30 cm H_2O. We have had some success at teaching parents with children on CIC to measure the opening pressures at catheterization by estimating the height of the water column in the catheter. This may be a more natural measurement, although the strict correlation with outcomes has not been defined.

Volume

Bladder capacity is another element of normal function and is the basis for both safe storage as well as social continence. As above, capacity can be improved with anticholinergic medication but may ultimately require bladder augmentation. There is a clear shift away from augmentation in all patients, and there have been prior reports that augmentation is not needed in renal transplant (Alfrey et al, 1997b; Salvatierra et al, 1999). However, there remains a role for this approach in children with complex uropathies with ESRD. Current indications would include nonsalvageable bladder (exstrophy, tumor, severe end-stage neuropathic bladder) and failure of medical and CIC therapy to achieve low-pressure storage for up to 3 hours. If pressures are safe for 1 hour only and they exceed 40 cm H_2O the rest of the time, despite aggressive medical and catheterization therapy, consideration for augmentation is important.

There is no evidence or logic that bladder augmentation, itself, increases the risk of transplant failure, despite some reports (Alfrey et al, 1997b), **and, indeed, it has permitted many effective transplants into very abnormal bladders** (Sheldon et al, 1994; Taghizadeh et al, 2007). There is no single approach that is ideal, although gastric augmentation gained popularity for ESRD children in the late 1980s and early 1990s. It offers the benefit of secreting acid in a patient who is typically acidotic, and it can limit infection and has a lower rate of bladder stones. Gastric augments have, however, been linked with severe complications, particularly in the pre-transplant anuric group, due to gastric juice injury of the native bladder segment and due to the fairly common hematuria-dysuria syndrome (Reinberg et al, 1992; Nguyen et al, 1993). Recent reports of malignancy, particularly in the transplant group, are worrisome but are too anecdotal yet to change practices (Castellan et al, 2007; Husmann and Rathbun, 2008). Caution and monitoring are essential. Composite gastric augmenting patches are useful and may have less morbidity. Ileum and sigmoid are all useful and may be more appropriate in some patients, depending upon anatomy, prior surgery, and preferences for continent catheterizable stomas.

The augmented patch rarely will create an issue with the transplant, but the fact of the pedicle presence and its anatomic orientation should be recognized by the transplant team. Similarly, **continent stomas should be placed in a location that avoids conflicting with the anticipated transplant incision(s), and stomas nearly always may be positioned medial to the incision(s).** Again, recognition of the location and presence of the mesentery for the stoma is important.

The infant receiving a transplant may have an aortic anastomosis to the renal vessels, which will create a potential need to mobilize the mesentery of the augment or stoma. Coordination between the reconstructive and transplant teams is essential.

Infections

Many children with complex reconstruction of the urinary tract will have a history of recurrent UTI. This may be associated with intermittent catheterization. This is a potential hazard for the transplant, and pyelonephritis of the graft is certainly associated with graft loss (Dunn et al, 1987; Hanevold et al, 1987; Neuhaus et al, 1997; Howie et al, 2002; Herthelius and Oborn, 2007). The underlying etiology of the infection is most likely due to inadequate emptying of the reservoir, either by catheterization or voiding. This needs to be assessed and addressed in advance of the renal transplant. Strategies include double and triple voiding to avoid using CIC, or, if CIC has already been instituted, to ensure adequate emptying or to teach proper methods to ensure emptying.

Persistent UTI in the face of appropriate technique for CIC suggests either an anatomic abnormality that has not been detected or may be chronic colonization. The latter will sometimes respond to long-term antibiotic courses, using agents including the fluoroquinolones and cephalosporins. The etiology and specific therapy for this situation is uncertain. Anatomic abnormalities, such as diverticula, may require more specific imaging studies but may be amenable to surgical cure, including a bladder diverticulum or nondraining ureteral stump. This, however, is uncommon.

Clean Intermittent Catheterization

The use of CIC in managing the abnormal bladder has been a truly revolutionary lifesaver in the last 4 decades. Although it may be a major challenge to initiate, once started it is

nearly always well accepted. Careful preparation, teaching, support, and follow-up are critically important for long-term success.

The importance and principles of CIC must be well understood by the care providers and carefully communicated to the family, including all possible caregivers. The recognition that this is a means by which to reduce infection and attain both safe bladder storage and control over voiding is very important, and yet it may not be readily apparent on first pass.

The frequency of CIC must be determined by measuring approximate urine outputs, as well as storage pressures, based on urodynamic assessment or by home catheterization opening-pressure measurements. This permits an estimate of safe pressure–volume relationships for day-to-day life. Avoiding regular excesses of these volumes, and therefore high pressures, will facilitate healthy kidney function. The typical frequency is between 3 and 4 hours. Pressures should not exceed 40 cm H_2O for any prolonged period of time.

Initiating CIC in preparation for transplantation serves an assessment purpose as well. For families where follow-through may be imperfect, it can be useful to use CIC to determine their commitment and ability to follow complex medical care plans. If CIC cannot be instituted pretransplant to manage an abnormal bladder, there is no reason to believe this ability will suddenly appear post-transplant. **The response to CIC can predict the ability to manage the necessary transplant medication and care regimen as well.** The committed and understanding family will manage well, and this will serve to demonstrate their readiness for transplant.

Key Points: Pretransplant Preparation

- The most common bladder abnormality associated with ESRD is a low-capacity, hypertonic bladder with poor compliance.
- There is no evidence that bladder augmentation increases the risk of transplant.
- Recurrent pyelonephritis is a potential hazard for the transplant and is associated with graft loss.
- Initiating CIC in preparation for transplantation serves an assessment purpose as well as facilitating bladder emptying.
- Bladder refunctionalization is often best accomplished by bladder cycling to increase capacity, determine bladder wall compliance, and assess the family's ability to perform CIC.

Defunctionalized Bladder

Neuropathic Bladder

The defunctionalized neurogenic bladder is becoming scarce due to better management but will occasionally present clinically in a transplant patient who has not had ongoing urologic care (Firlit, 1976; Serrano et al, 1996). **It is impossible to know without testing what the potential function of the bladder may be. It is also important to recognize that the bladder that has been defunctionalized will take some time to reach its maximal functional potential. This is often best accomplished by bladder cycling to increase capacity, determine bladder wall compliance, and assess the family's ability to perform CIC.**

Some have advocated simply implanting the transplant ureter into the bladder and anticipating normal function (Salvatierra et al, 1999). Although this may occur on rare occasions, it is a highly risky approach to the chronically defunctionalized bladder.

Cycling the defunctionalized bladder is best accomplished using a progressive program of catheterization with instillation of increasing volumes of saline, with a set dwell time, and then with catheter drainage (Alam and Sheldon, 2008). The amounts will be determined empirically based on initial tolerated volumes and should increase at regular intervals, usually 10 to 15 cc per day. The response to these instillations will give useful clues as to the utility of the bladder to serve as a reservoir and in its ability to empty spontaneously. Adjunctive anticholinergic medications are often necessary to increase bladder capacity and compliance.

The defunctionalized neurogenic bladder will almost certainly require intermittent catheterization for emptying. It is therefore reasonable to introduce this, as such, to the family. In the rare instance where the child can learn to empty satisfactorily, CIC may no longer be needed. This is a major step and requires a careful study of voiding diaries, postvoid testing, and assessment of the upper renal tracts.

The target volume is anticipated capacity for age based on any of the available formulas (Koff, 1983; Kaefer et al, 1997). This may not be reached immediately, but if volumes increase steadily without significant leakage, further expansion is likely. Although storage capacity is important, compliance is equally critical, and this must be assessed formally with urodynamics. The patient should be cleared for transplant only if capacity and compliance parameters near normal can be reached. Aggressive medical management is also important in this determination. If adequate storage and compliance cannot be attained, consideration for augmentation must be entertained. This should be performed prior to transplant, unless there are pressing contraindicating reasons.

Non-Neuropathic Bladder

The defunctionalized bladder associated with renal insufficiency is often due to posterior urethral valves or vesicoureteral reflux. These bladders may be more often salvaged to ultimately permit spontaneous voiding but should initially be approached as would the defunctionalized neurogenic bladder, and it should be assumed that CIC will be needed long term. The critical factor will be the storage capacity, and progressive cycling as described above can provide that assessment. At the same time, children can be asked to attempt to void after holding the instilled saline for a period of 15 or 20 minutes. A postvoid catheterization then determines the postvoid residual volume.

The ability to empty spontaneously will also impact the decision regarding the need for a continent catheterizable stoma. This is more critical in boys with normal sensation who may be very resistant to urethral catheterization. The period of pretransplant CIC will permit assessment of both voiding ability and tolerance of urethral CIC. These decisions are best made concurrently with other reconstructive choices to permit an integrated strategy and a single surgical procedure if possible.

The Decision to Augment

Although the use of bladder augmentation is declining due to concerns regarding metabolic, infectious, and neoplastic complications, enterocystoplasty remains the most effective means to provide normal bladder storage

function in both neurogenic and postobstructive bladder dysfunction (Barnett et al, 1987; Sheldon et al, 1994; Hatch et al, 2001; Nahas et al, 2002; DeFoor et al, 2003; Capizzi et al, 2004; Mendizabal et al, 2005; Rigamonti et al, 2005; Aki et al, 2006). To lose a renal graft due to the same processes that contributed to native renal demise is unacceptable. The potential complications of augmentation must also be clearly recognized and anticipated, although some reports have presented extreme examples that are not the author's experience (Alfrey et al, 1997a). A strategy of aggressive intermittent catheterization with medical management becomes the best approach to identify those patients in whom augmentation is the only real option for successful renal transplantation. It is difficult to determine a meaningful incidence of the need for augmentation, because the effort expended by both family and health-care team varies as much as the underlying pathology. With early aggressive bladder management, the need for augmentation in both neurogenic and obstructive bladder dysfunction has been declining. When bladder reconstruction using engineered tissues becomes more widely available, this will be a particularly valuable use.

Broad indications for augmentation prior to transplantation would be the inability to develop capacity greater than 75% of expected for age with pressures less than 30 cm H_2O, using catheterization that is no more frequent than every 3 hours, and using maximal anticholinergic medications. Tolerance to medication will obviously be an important element of these criteria. These thresholds are rules of thumb without strong clinical data to support them. Exceptions can be found where bladder capacity improves markedly after transplant, perhaps due to the effects of uremia, but they should serve as guidelines for determining when to augment prior to transplantation.

The availability of a dilated ureter to permit ureterocystoplasty (Kim et al, 1996; Kurzrock et al, 2002) should be explored, although results have been mixed. It is preferable to perform enterocystoplasty in this context, and efforts should be made to preserve the ureter, when possible, for this use or for a continent catheterizable channel.

Cutaneous Stomas

The defunctionalized bladder may be associated with a variety of urinary diversions, including ileal and colon conduits as well as ureterostomies. In the past, transplantation has been performed with the ureters draining into the diversion. This is rarely appropriate today. A functioning ileal loop diversion in the setting where augmentation is determined to be necessary can be used as the augmenting patch with bladder refunctionalization, even if the patient is anuric. If augmentation is not needed, based on CIC cycling, and the patient continues to make urine and the native kidney will not be removed, the native ureter should be implanted to refunctionalize the bladder, and the loop should be discarded. If there is uncertainty regarding the need for augmentation, the loop may be preserved and be available for augmentation after transplant, if essential.

Reconstruction Strategies

In the setting where bladder reconstruction will be needed, several factors must be considered in anticipation of the ultimate renal transplant. These considerations reflect the type of dialysis, either hemo- or peritoneal, likely placement of the graft, timing relative to both initiation of dialysis (if not already begun) and transplantation, the need for bowel surgery and the native kidneys. Consideration of these factors will permit a more coordinated and efficient reconstruction.

Dialysis Issues

If a patient is already on peritoneal dialysis (PD), any intraperitoneal surgery will likely require temporary transition to hemodialysis. Limiting this to one procedure is valuable. At times, this can be linked with placement of a PD catheter, but if bowel surgery is needed, this may increase the risk of infectious complications.

If the patient is not yet on dialysis but is approaching the need, there may be some consideration for initiating dialysis prior to reconstruction to improve the overall medical status of the child. This can promote more rapid wound healing and fewer complications. At the same time, this will impact the child on PD as noted, and for those on hemodialysis, there is a risk of fistula injury during surgery due to low flow states as well as direct pressure.

Graft Placement

Consideration should be made for the likely location of the graft. In the very small child in whom the graft will be placed intraperitoneally on the aorta, careful movement of any mesenteric pedicles away from the midline is advisable, as well as trying to avoid a transureteroureterostomy (TUU). A psoas hitch for ureteral reimplantation of the native kidney, if it is to be salvaged, can make iliac graft placement on that side difficult. There may be no feasible alternatives, and, in such cases, careful documentation of the procedure is essential.

Timing

In general, any major urologic reconstruction should be undertaken well before the anticipated transplantation (Taghizadeh et al, 2007). Minor ureteral surgery may be considered at the time of transplantation, but this is unusual. Following enterocystoplasty or continent diversion, at least 6 weeks is needed for healing, and 3 months would be preferable. Unilateral native nephrectomy is reasonable at the time of transplantation but only in older children. Operative time in the infant may have more of a negative impact on graft function, and it seems imprudent to add this extra risk.

Enterocystoplasty

Enterocystoplasty in the setting of a dialysis patient or a child approaching ESRD is feasible and, when needed, can be successfully accomplished in a manner similar to that for any other child (Sheldon et al, 1994; Taghizadeh et al, 2007). The selection of bowel segments and reconstructive strategy should be based on the functional anatomy and needs of the individual child. These include factors such as the need for a continent catheterizable stoma, the availability of native bladder tissue, the status of the bladder neck and continence mechanism, and bowel function. **If continent diversion is needed due to an unsalvageable bladder, there is no reason to defer this until after transplant.** The often-quoted contraindication to continent diversion of renal impairment is not applicable in these patients. They will need medical management of the metabolic effects of the diversion, but they require aggressive metabolic management at baseline. In some cases, by improving bladder

dynamics and limiting infection, the progression to end-stage may be delayed.

The use of gastric segments was considered particularly appropriate for the child approaching end-stage failure and can still be useful in selected cases (Burns et al, 1992; DeFoor et al, 2003). Due to the various complications of gastrocystoplasty, however, this approach has been used much less. The benefit of acid excretion for the child with chronic kidney disease (CKD) can be helpful, but these children are also at risk for complex metabolic derangements with alkalosis. For the anuric child, the presence of gastric secretions in the empty bladder can lead to erosion and even perforation (Reinberg et al, 1992). Care must be taken in those children to use proton pump inhibitors and to irrigate with bicarbonate solutions until urine output is restored.

Native Nephrectomy

The decision regarding native nephrectomy must be made with a multidisciplinary team involving the nephrologist and urologist as well as the family. There is controversy in this regard, and although, in general, it is preferable to leave the native kidneys, **there are several situations where removal pretransplant is necessary. These include malignant hypertension, profound nephrotic syndrome with malnutrition due to protein losses** (Kim et al, 1992)**, recurrent upper tract infection, and massive reflux.** The latter may be more relative, but with stasis and possible infection in an immunosuppressed child, removal is preferable and less risky. The utility of leaving a native kidney that produces some urine is that it makes dialysis more manageable with less fluid restrictions. This can facilitate nutritional support in the younger child. This must be balanced against the possible risks of infection and hypertension, as well as graft function.

In the infant undergoing renal transplantation, native nephrectomy is strongly recommended by some groups to enhance graft survival based on improving blood flow to the graft. Any shunting of blood from the graft in a small child whose cardiac output may be a small fraction of the adult from whom the graft came may potentially impair early graft function.

In a child for whom native nephrectomy is to be performed, the principle contributing factor is whether PD is being performed. If so, laparoscopic transperitoneal removal will require temporary hemodialysis. Some have performed immediate PD, but the risks of leakage with possible infection would argue against this practice. Retroperitoneoscopic nephrectomy can be performed with immediate PD (Gundeti et al, 2007), but leaks may still be encountered. If the kidneys are small, then this is the optimal approach. For large kidneys in children on PD, posterior open nephrectomy may be the overall optimal approach.

If PD is not being performed, then any type of nephrectomy is acceptable. The incidence of postoperative adhesions is limited and is unlikely to affect the efficacy of PD. There is the potential impact on the ultimate transplant procedure when the distal ureter is to be removed, because this will cause adhesions in the area of the iliac vessels. However, if there is significant reflux or obstruction and a dilated ureter, total removal may be the best course to limit the risk of infection. Renal embolization has been reported as an alternative to surgical nephrectomy (Capozza et al, 2007).

Dealing with the Native Kidneys

Avoiding Removal

In the absence of specific indications for nephrectomy, leaving the native kidneys offers the advantage of having a potential source of water excretion if the graft fails. Although this can be helpful in managing nutrition and lifestyle, it should not become a rigid goal if there are reasons to remove the kidneys. Their ultimate utility may be very limited, particularly after a period of graft function, because they often will regress in size and urine output.

Limiting Risk of Infection

Urinary infection in the setting of an immunosuppressed child with a renal graft is damaging to both child and graft. Preventing infection in the child with known urologic concerns is therefore a priority that should be acted upon proactively rather than purely in response to an infection. The damage from one infection may be critical to that child. Situations in which active prevention of infection may be useful include high-grade reflux and persistent hydronephrosis with or without reflux, particularly when intermittent catheterization is needed. These patients are frequently colonized with bacteria and may be more susceptible to UTI. The nondilated, nonrefluxing native kidney is unlikely to be subject to infection and can generally be maintained in the absence of other indications for removal.

Ureteral Preservation

When nephrectomy is to be performed, ureteral preservation should be considered. If the ureter is normal, it should always be left to limit surgical dissection near the iliac vessels and to have an option for proximal transplant-to-native ureteroureterostomy for distal ureteral stenosis (Kockelbergh et al, 1993). If bladder function is abnormal and intermittent catheterization may be needed, preserving the ureter for use as a continent stoma is advisable. This is best performed pretransplant. Creation of the continent stoma at the time of transplant is an option.

Combining Nephrectomy and Transplantation

Native kidneys may be removed at the time of the renal transplantation, but this is generally avoided to limit surgical complexity and time. It may be appropriate for a single native kidney, which may be swiftly removed through the transplant incision. In the absence of specific justification, however, this strategy is generally to be avoided.

TRANSPLANTATION

The technical elements of the vascular component of the transplantation are described in Chapter 43 and are appropriate to children. One exception may be transplantation into the infant where the vascular anastomoses are performed on the aorta. This usually is performed with anticoagulation, which may impact bladder surgery. More care with hemostasis is needed. For the pediatric urologist who is not performing the vascular anastomosis, the ureteral anastomosis becomes the focus of attention, as well as of complications.

Ureteral Anastomosis

Options

As with ureteroneocystostomy for vesicoureteral reflux (VUR), there are intravesical and extravesical techniques

Key Points: Pretransplant Reconstruction

- The ability to empty spontaneously will also impact the decision regarding the need for a continent catheterizable stoma.
- Indications for augmentation prior to transplantation include (1) capacity less than 75% of that expected for age, (2) pressures greater than 30 cm H_2O, (3) being catheterized every 3 hours, and (4) maximal anticholinergic medications.
- For patients on peritoneal dialysis, intraperitoneal surgery will likely require temporary transition to hemodialysis.
- In general, any major urologic reconstruction should be undertaken well before anticipated transplantation.
- Native nephrectomy is indicated for (1) malignant hypertension, (2) profound nephrotic syndrome with malnutrition, (3) recurrent upper tract infection, and (4) massive reflux.

for the transplant ureteral anastomosis. In general, the author has performed an antirefluxing anastomosis in all cases, although it is clear that this is not essential. Although careful screening can identify patients with bladder dysfunction, and therefore those at risk for graft reflux, the method to prevent reflux is simple, effective, and has minimal morbidity.

Extravesical ureteroneocystostomy is the preferred ureteral anastomosis. After the vascular anastomoses have been performed and hemostasis achieved, the bladder is partially filled with saline or a dilute antibiotic solution. The anterolateral aspect is cleared, and traction sutures are placed to mobilize the lateral aspect upward and to provide tension on the vesical wall. The ureter is sized to ensure it will reach. The detrusor is incised to the level of the mucosa for a length of about 3 to 3.5 cm in a horizontal direction. Flaps of detrusor are elevated away from the mucosa, and a small disc of mucosa is excised at the distal aspect of the trough. The bladder will drain and the traction sutures keep the trough in position. The ureter is trimmed loosely to length and spatulated for 4 to 5 mm. An interrupted, mucosa-to-mucosa anastomosis is performed using a fine absorbable suture; a monofilament is preferred. The detrusor flaps are then brought over the ureter. No advancement stitch is used, but two stitches are placed through the detrusor and the adventitia of the terminal ureter to prevent eversion of the ureter. The detrusor is closed with interrupted absorbable suture.

If the bladder wall is particularly abnormal and thick, a longer tunnel is developed and the flaps are dissected back a bit further to provide a more robust antireflux tunnel and limit the risk of obstruction, because these are typically abnormally functioning bladders. Implanting the graft ureter into an augmented bladder poses further challenges, and it is preferable to perform the ureteroneocystostomy into the detrusor. On occasion, this has necessitated an intravesical approach through the augment to reach the detrusor, which may be impossible to mobilize effectively otherwise. If there is no detrusor available, anastomosis into a colonic or gastric segment is preferred. It would always be advisable to perform a nonrefluxing ureteroneocystostomy in these settings, because these patients are inevitably on intermittent catheterization and often colonized with bacteria.

The author no longer performs a routine open ureteroneocystostomy for transplant, but a modified Leadbetter-Politano procedure is an effective method. It does introduce a large cystotomy and bladder spasms. In the unusual setting in which this is considered appropriate, there is no specific need for stenting beyond the indications as described below.

Transplant-to-native ureteroureterostomy is performed routinely for pediatric renal transplantation in a few institutions. The results have been reported as acceptable (Lapointe et al, 2001; Gurkan et al, 2006), but this does not seem to be a common option, and, of course, depends upon the availability of a normal, nonrefluxing native ureter. This option is available as a salvage procedure in the setting of distal ureteral stenosis.

Stenting

The role of routine ureteral stenting in pediatric transplant is debated, but there are no data to demonstrate its routine utility (French et al, 2001; Simpson et al, 2006; Dharnidharka et al, 2008). It has not been the routine approach for the author, but there are situations in which ureteral stenting is appropriate. This would be a difficult implant, particularly in an abnormal bladder, or in a very damaged graft ureter. If a stent is to be used, a short double-J ureteral stent is placed and generally removed after 4 weeks. This obviously requires a cystoscopy. We have not used extraction strings for those children undergoing stented transplants.

Key Points: Transplant Ureteroneocystostomy

- Extravesical ureteroneocystostomy is the preferred ureteral anastomosis.
- Transplant-to-native ureteroureterostomy is an effective option.
- There are no data to support routine ureteral stenting at the time of transplantation.

COMPLICATIONS

This section deals with the urologic complications of pediatric renal transplantation. Those related to the graft directly, including vascular and rejection issues, are dealt with in Chapter 43. Table 136–1 presents a summary of recent reports of urologic complications in pediatric renal transplantation. The unique analysis of Khositseth and colleagues (2007), comparing the incidence of urologic complications in transplant recipients with a history of obstructive uropathy or reflux to those without that history, shows the increased risk of all urologic complications in patients with a prior history of uropathy. Special vigilance and a lower threshold for intervention are appropriate in this population.

Urine Leaks

Urine leaks are typically identified in the early postoperative period with increasing fluid from the wound drains. The fluid creatinine level can determine if this is a urine leak as opposed to lymphatic drainage. At first presentation, it is critical to assess all urinary drainage tubes, particularly the Foley catheter. If the catheter has been removed, it is often best to replace it. A transplant ultrasonogram is performed to determine

Table 136–1.
Urologic Complications in Pediatric Renal Transplantation

STUDY	NO. OF PATIENTS	URETERAL STENOSIS	URINARY LEAK	VUR REQUIRING SURGERY	STONE	
Englesbe et al, 2008	147	5*	4*	7*	0*	
Khositseth et al, 2007	117	26	2	10	11	h/o obstruction or VUR
	117	11	2	1	2	No obstruction or VUR
Lapointe et al, 2001	166	3	7	1	1	Ureteroureterostomy
Nuininga et al, 2001	183	7	8	0	5	183 transplants in 146 patients
Shokeir et al, 2005	250	11	10	0	1	All LRD
Tanabe et al, 1998	107	2	1	1	0	
SUMMARY	1087	65 (6.0%)	34 (3.1%)	20 (1.8%)	20 (1.8%)	

h/o, history of; LRD, living related donors; VUR, vesicoureteral reflux.
*Number of affected patients.

if there is hydronephrosis, although its absence does not rule out obstruction. If present, distal ureteral obstruction should be suspected, and consideration for a percutaneous nephrostomy should be entertained. The level of the leak must then be determined, and either a MAG3 scan (assuming adequate graft function) or a CT scan can be effective. A cystogram may be useful to identify a bladder leak from the site of the anastomosis.

The indications for intervention are clinically based, and if the leak is limited, an observational approach is reasonable. The author has seen leaks associated with massive urine outputs in smaller children simply due to a small bladder catheter. If a larger catheter may be placed, this may facilitate resolution. If there is significant urine leak and limited bladder drainage, exploration may be needed.

Exploration is to identify the cause and location of the leak and provide for repair. If the leak is bladder based, simple repair and drainage is effective, but if the leak is due to distal ureteral necrosis, some means of ureteral replacement is needed. Native ureter, either ipsilateral or even contralateral, may be useful if available. A psoas hitch or bladder flap may be needed if the native ureter is not present. These strategies are similar to those used for ureteral strictures. Careful stenting and drainage are essential (Fig. 136–2).

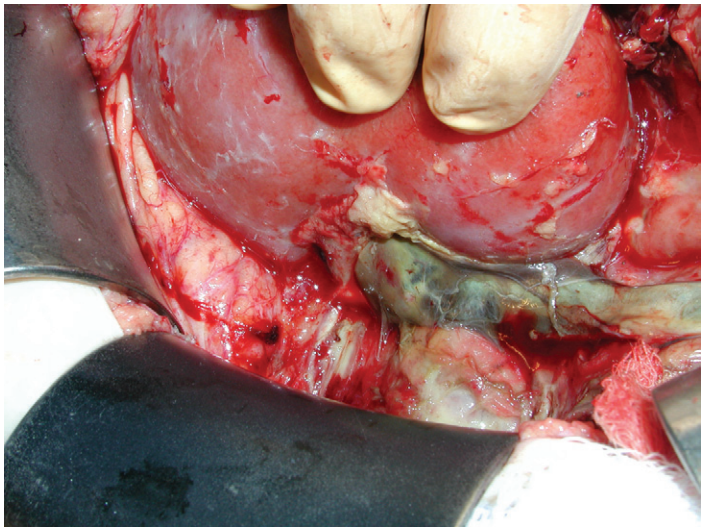


Figure 136–2. Ischemic loss of the entire renal pelvis and ureter in a cadaveric renal graft in a patient with a gastrocystoplasty. This patient presented with urine leak after a period of acute tubular necrosis. The graft was salvaged with an augment bladder flap to the lower calyces of the graft.

Infection

Urinary infection is a long-term and often delayed complication that largely reflects the status of bladder function, although this link is not proven (Herthelius and Oborn, 2007). Routine assessment of bladder emptying, hydronephrosis, and, occasionally, use of a voiding cystourethrogram will usually identify the cause. If the patient is on CIC and no specific correctable cause is present, a strategy of prevention by prophylactic antibiotics and bladder irrigation may be effective. Aggressive management of bladder dysfunction, which should have been identified pretransplant, is essential to preserve graft function. If VUR is present into the graft and infection with fever and altered renal function is present, correction of the reflux is warranted. Reflux in the absence of infection with normal bladder function may be observed with caution.

Reflux

Vesicoureteral reflux into the transplant is entirely distinct from routine reflux into an otherwise normal renal unit based upon the facts that this is a reimplanted ureter, that the risk to renal function of an episode of pyelonephritis is greater in a transplant, and that the patient is immunosuppressed (DeFoor et al, 2003; Coulthard and Keir, 2006). Routine evaluation for reflux after renal transplant has been the author's practice, even though not all cases were treated with surgery. Identification of this potential risk factor is useful for clinical decision making and ongoing risk assessment. If febrile UTIs occurred, the presence of transplant reflux justifies surgical correction with an open ureteral reimplantation (Hanevold et al, 1987). The risk of pyelonephritis in the graft is significant (Neuhaus et al, 1997; Ranchin et al, 2000; Barrero et al, 2007) and increases the potential for graft loss (Herthelius and Oborn, 2007) (Fig. 136–3). Identification of simultaneous bladder dysfunction is equally important (Casale et al, 2005), although this may not be correctable. In the setting of intermittent catheterization, any reflux should be corrected, because these bladders will be chronically colonized. Reflux in the absence of infection and bladder dysfunction may be observed, and attempts may be made to improve any suggestion of bladder dysfunction. There are no data to suggest that low-grade sterile VUR into a renal graft is harmful in children. Close observation

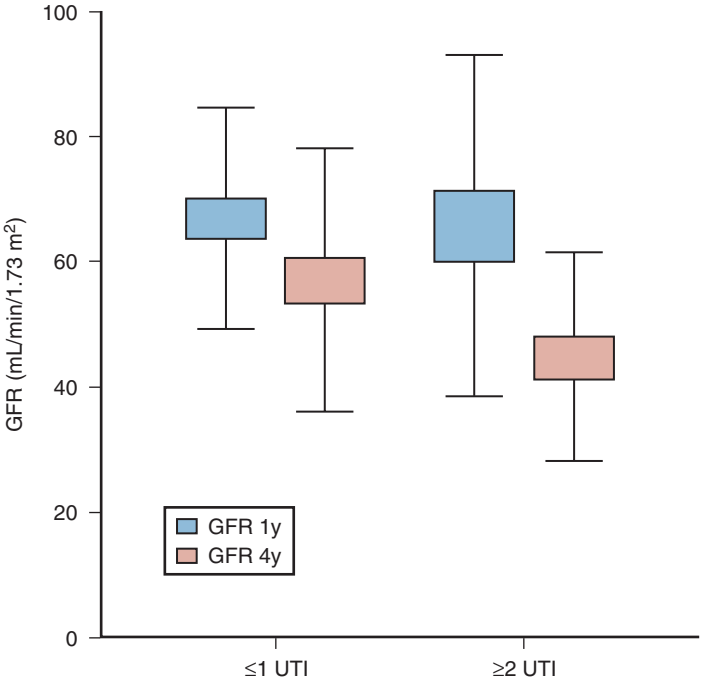


Figure 136–3. Graft function, measured as glomerular flow rate (GFR), at 1 and 4 years in children with less than or equal to one and greater than or equal to two urinary tract infections (UTI). (From Herthelius M, Oborn H. Urinary tract infections and bladder dysfunction after renal transplantation in children. J Urol 2007;177:1883–6.)

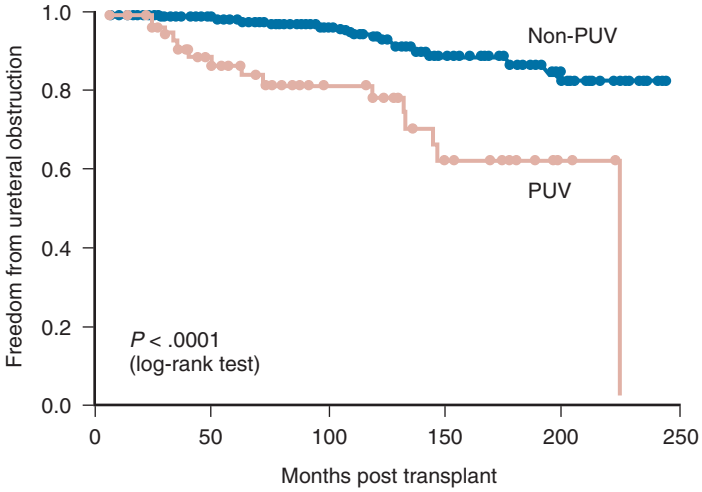


Figure 136–4. Obstruction-free survival in pediatric renal transplant patients with and without a history of posterior urethral valves (PUV). (From Smith KM, Windsperger A, Alanee S, et al. Risk factors and treatment success for ureteral obstruction after pediatric renal transplantation. J Urol 2010;183:317–22.)

for possible infection or deteriorating bladder function is warranted.

Surgical management of reflux into a transplanted ureter is never routine. The role of endoscopic therapy is limited, and the few reports available suggest limited benefit, with resolution rates of 50% to 80% (Kitchens et al, 2006; Williams et al, 2008). This may be an option for asymptomatic reflux, but in the face of an episode of febrile UTI, the most certain definitive intervention is justified. There are few data as to the relative efficacy of intravesical compared with extravesical methods (Krishnan et al, 2006), but the author's preference is intravesical, often using extravesical mobilization. A transtrigonal technique is effective if the contralateral native ureter can be avoided. Otherwise, an advancement or Politano-Leadbetter technique may be used. Ureteral stenting is advisable.

Hydronephrosis/Obstruction

A frequent urologic complication in pediatric renal transplant is hydronephrosis, and intervention for ureteral obstruction may be needed in as many as 8% of transplants (Shokeir et al, 2005; Smith et al, 2010). The presence of hydronephrosis necessitates careful evaluation and selective management to tailor appropriate treatment to the individual. The transplant kidney appears to be one of the rare situations in which obstruction may not be associated with hydronephrosis. This is uncommon and not well documented but can occur empirically. More commonly, obstruction is heralded by increasing renal dysfunction with a rising creatinine. Hydronephrosis is identified on ultrasonography or delayed drainage on MAG3 renal scan. More than half of obstructions in a recent series occurred within the first 100 days post-transplant (Smith et al, 2010). In the setting of normal prior bladder function, this pattern indicates ureteral obstruction until proven otherwise. If bladder dysfunction is known to be present, then both factors must be evaluated and managed, because obstruction is more frequent in patients with bladder dysfunction, particularly posterior urethral valves (Smith et al, 2010) (Fig. 136–4).

In the setting of a rising creatinine and hydronephrosis, obstruction and rejection may be intermingled. If the hydronephrosis is mild and there are other signs of rejection, the most efficient first step is biopsy. If there is no clinical suggestion of rejection, ureteral stenting, with or without a biopsy, is the best first step. Diagnostic studies for obstruction in the transplant setting are not clearly reliable given the associated risks, and the author has adopted the approach of stenting to assess the impact on renal function. It has been in this setting, albeit rarely, that an acutely failing transplant with minimal or no hydronephrosis and with no evidence of rejection has been stented with subsequent improvement in function. The more common situation is with moderate hydronephrosis and a rising creatinine with some rejection on biopsy. If the graft is not failing rapidly, initial medical treatment of the rejection is justified, with stenting being reserved for lack of improvement. Whether obstruction increases the risk of rejection is unproven but empirically suggested. In that light, having a low threshold for stenting, which can provide a definitive diagnosis of functionally significant obstruction, is essential.

The etiology of ureteral obstruction is usually in the distal ureter with stenosis at the reimplantation site, but it may be anywhere along the ureter. In a recent analysis, neither the method of ureteral implant nor use of stents was a contributing factor to obstruction. Bladder abnormalities, particularly due to posterior urethral valves, however, were a risk factor of post-transplant obstruction (Smith et al, 2010). Compression from a lymphocele or adenopathy from post-transplant lymphoproliferative disease (PTLD) are also possible causes (Dharnidharka et al, 2001; Buell et al, 2006). Definitive therapy is determined by the most likely etiology. Focal ureteral narrowing on retrograde imaging may be effectively treated with balloon dilation and

stenting for 4 to 6 weeks. Recognizing the risk posed to the graft due to obstruction, open definitive repair should not be delayed excessively (Smith et al, 2010). These procedures are never simple and may entail complex reconstruction using native ureter or bladder flaps (Kockelbergh et al, 1993). Avoiding use of nonurothelial segments, such as appendix, is advisable, although any of these methods may be needed. All of the principles of reoperative reconstruction must be adhered to in order to preserve well-vascularized functional tissues.

Bladder Dysfunction

Bladder dysfunction may produce infection but may also create an obstructive process that impairs renal graft function (Herthelius and Oborn, 2006, 2007; Van der Weide et al, 2006; Nahas et al, 2008). Discriminating this from ureteral obstruction may not be simple, and, on occasion, has necessitated sequential diagnostic drainage steps. If a bladder catheter can be placed easily, then continued drainage for 1 to 2 weeks with reassessment of creatinine can usually identify bladder dysfunction as the cause of graft dysfunction if the creatinine declines. If not, then combined stent and bladder drainage, followed by a recheck of the creatinine, is needed. It should be recognized that elements of bladder and ureteral dysfunction may contribute to graft failure. Both may need to be addressed. Treating bladder dysfunction involves measures to increase compliance, using anticholinergics as well as instituting or enhancing an intermittent catheterization program. Bladder augmentation may also be needed, although only after aggressive medical management has been tried. When intermittent catheterization per urethra is difficult, creation of a continent stoma may be needed. Identification of these potential risks to graft function is best accomplished prior to the transplant whenever possible.

Stones

Nephrolithiasis in a pediatric renal transplant is uncommon, occurring in up to 5% of patients (Khositseth et al, 2004), but potentially dangerous for long-term graft survival. With appropriate management, stones were not seen to increase the risk of graft loss, but were associated with more UTIs (Khositseth et al, 2004). There is a high incidence of bladder stones, approaching 50%, and several stones were due to retained suture material in the bladder (Lipke et al, 2004). Detection of an asymptomatic stone on routine surveillance should prompt attempts at removal as well as a search for cause. Stones associated with renal graft dysfunction due to obstruction or infection should be managed with urgent intervention to assure drainage and prompt removal. All conventional means of stone management are appropriate in a renal graft but should be modulated by recognition of the potential balance of risk to the graft as well as the relative efficacy of the various modalities. Selection of the modality that will have the highest likelihood of success with a single intervention is likely to be the best option in the long term, even if this incurs more complexity. A lower pole stone may be best managed with a percutaneous approach or ureteroscopic removal rather than ESWL, given the lower success of clearance of lower pole stones. These decisions should be individualized based upon clinical presentation, location and size of the stone(s), and renal functional status.

Key Points: Complications

- Common urologic complications for pediatric renal transplant include ureteral stenosis (6%), urinary leaks (3%), stones (2%), and clinically significant reflux (2%).
- Urine leaks are typically identified in the early postoperative period with increasing fluid from the wound drains.
- Urinary infection is a long-term and often delayed complication that largely reflects the status of bladder function.
- Vesicoureteral reflux into the transplant is entirely distinct from routine reflux, because the risk to renal function of acute pyelonephritis is greater.
- In the setting of a rising creatinine level and hydronephrosis, obstruction and rejection may be intermingled.
- The etiology of ureteral obstruction is usually in the distal ureter with stenosis at the reimplantation site.
- Bladder dysfunction may produce infection but may also create an obstructive process that impairs renal graft function.
- Nephrolithiasis is uncommon, but may occur in up to 5% of patients.

SUMMARY

Preparation and management of the pediatric transplant patient, particularly with an underlying urologic condition, requires a thorough understanding of the patterns of bladder dysfunction and clear strategies for evaluation and treatment prior to transplant. Anticipating the needs and constraints of the transplant procedure and being involved in appropriate cases permits a smoother procedure and ongoing continuity of care by the pediatric urologist. Post-transplant monitoring should be aggressively expectant in order to identify pathologic processes before they have damaged renal graft function irreversibly. This takes a high index of suspicion and a clear sense of the patient at risk for these processes. A multidisciplinary collaboration of the pediatric nephrologist, urologist, and the transplant surgical team is critical to maximizing patient and graft survival.

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chapter
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Pediatric Urologic Oncology

Michael L. Ritchey, MD, FAAP, FACS ● Robert C. Shamberger, MD

Neuroblastoma
Genitourinary Rhabdomyosarcoma
Wilms Tumor
Other Renal Tumors
Testicular Tumors

NEUROBLASTOMA

Neuroblastoma is the most common extracranial solid tumor of childhood. Regrettably over half of the children present with metastatic disease. Neuroblastoma is known to arise from cells of the neural crest that form the adrenal medulla and sympathetic ganglia. Tumors may occur anywhere along the sympathetic chain within the neck, thorax, retroperitoneum, or pelvis, or in the adrenal gland. Seventy-five percent arise in the retroperitoneum, 50% in the adrenal, and 25% in the paravertebral ganglia. The variety of locations where these tumors arise and the spectrum of their differentiation results in a wide range of clinical presentations and behaviors (Brodeur, 1991). These tumors can undergo spontaneous regression (Brodeur, 1991), differentiate to benign neoplasms, or exhibit extremely malignant behavior.

Epidemiology and Genetics

Incidence

Neuroblastoma accounts for 8% to 10% of all childhood cancers. In the United States, the annual incidence is 10 cases per 1 million live births. It is the most common malignant tumor of infancy. A recent review of 3666 children enrolled in the cooperative group trials of the Pediatric Oncology Group and the Children's Cancer Group showed a median age at diagnosis of 19 months (Brodeur and Maris, 2006). Thirty-six percent were infants, 89% were younger than 5 years, and 98% were diagnosed by 10 years of age.

Genetics

There have been a number of familial cases reported, which are postulated to represent an autosomal dominant pattern of inheritance (Knudson and Strong, 1972a; Robertson et al, 1991). Although the median age at diagnosis of neuroblastoma is 19 months, in familial cases it is 9 months (Kushner et al, 1986). At least 20% of patients with familial neuroblastoma have bilateral adrenal or multifocal primary tumors, which are quite unusual in spontaneous cases. The risk for development of neuroblastoma in a sibling or offspring of a patient with neuroblastoma is less than 6% (Kushner et al, 1986). Linkage analysis in seven families with two or more first-degree relatives affected with neuroblastoma identified a single interval at chromosome 16p12-13 with consistent linkage (Maris et al, 2002). This suggests that a hereditary neuroblastoma predisposition gene may be located at this site and may explain the familial cases.

Constitutional Chromosome Abnormalities

Numerous karyotypic abnormalities have been found in neuroblastoma, and these are recognized to have prognostic significance. These changes occur in the form of chromosomal deletions, translocations, and cytogenetic evidence of gene amplification. Aneuploidy of the tumor DNA occurs in a significant number of cases and is a favorable prognostic indicator, whereas **amplification of the N-*MYC* oncogene seen in roughly 20% of primary tumors is an adverse prognostic indicator** (Look et al, 1991; Muraji et al, 1993). These findings have been so striking that neuroblastoma was the first tumor in which the intensity of chemotherapy for a patient was determined not only by the stage and histology of the tumor but by its "biologic markers," which were primarily chromosomal (Matthay et al, 1998).

Deletion of the short arm of chromosome 1 (1p) is found in 25% to 35% of neuroblastomas and is an adverse prognostic marker (Brodeur et al, 1992; Caron et al, 1996). The deletions are of various lengths, but, in a series of eight cases, a consensus deletion included the segment 1p36.1-2, suggesting that genetic information related to neuroblastoma tumorigenesis is located in that segment, although the involved genes have not been identified despite intensive investigation (Weith et al, 1989; Maris et al 2007). There have been reports of constitutional abnormalities involving the short arm of chromosome 1 (Laureys et al, 1990). Recently, it has been demonstrated that loss of heterozygosity (LOH) at 1p36 and Unb11q is independently associated with a worse outcome in patients with neuroblastoma (Attiyeh et al, 2005). (Unbalanced LOH implies LOH at markers on 11q with retention of 11p material, in contrast with "whole-chromosome" 11 LOH, where there is LOH at every marker along the chromosome.) Of note, while the 1p deletions are seen in conjunction

with advanced stage and N-*MYC* amplification, the 11q deletions are rarely seen in tumors with N-*MYC* amplification, but are associated with other high-risk features (Spitz et al, 2006). In future trials of the Children's Oncology Group (COG), treatment duration will be established by tumor 1p and 11q allelic status. An additional genetic abnormality, gain of one to three copies of 17q, often the result of translocation with chromosomes 1 or 11, has been demonstrated to correlate with more aggressive tumors (Bown et al, 1999). The break points vary, but the addition of a region from 17q22-qter is common suggesting that genes replicated in this region provide an advantage (Schleiermacher et al, 2004). In multivariate analysis, gain of 17q was the most powerful prognostic factor, followed by the presence of stage 4 disease and deletion of 1p.

Embryology and Spontaneous Regression

In 1963, Beckwith and Perrin coined the term in-situ neuroblastoma for small nodules of neuroblasts found incidentally within the adrenal gland that are histologically indistinguishable from neuroblastoma (Beckwith and Perrin, 1963). In-situ neuroblastoma was found during postmortem examination in 1 of 224 infants younger than 3 months. This represents an incidence of approximately 40 to 45 times greater than that of clinical tumors, suggesting that these small tumors regress spontaneously in most cases. Studies have shown subsequently that these neuroblastic nodules are found in all fetuses studied and generally regress (Ikeda et al, 1981). Neuroblastoma identified by prenatal ultrasonography (US) has also been shown to have a clinically favorable course (Ho et al, 1993).

The concept of in-situ neuroblastoma has been used to support the argument that many neuroblastomas arise and regress spontaneously. This concept has been further supported by population-based studies in Quebec province and in Japan, where prospective screening of infants for neuroblastoma has been performed based on urinary catecholamine excretion. An increased number of children were identified with low-stage neuroblastoma, a higher frequency than present clinically, but there was no decrease in the incidence of advanced-stage tumors seen at an older age (Hayashi et al, 1995; Woods et al, 1996). Evaluation of adrenal tumors resected in the neonatal period, whether cystic or solid, showed that in most the "biologic markers" were favorable (Kozakewich et al, 1998). The highly favorable outcome of infants diagnosed with neuroblastoma in the population screening studies first led to attempts at expectant observation. These trials demonstrated a high rate of spontaneous resolution (Yamamoto et al, 1998; Yoneda et al, 2001). Spontaneous regression of these perinatally identified lesions has also been demonstrated radiographically (Holgerson et al, 1996). A current prospective study by the Children's Oncology Group is evaluating infants with adrenal masses identified in the perinatal or neonatal period. Expectant observation for infants with small lesions with favorable catecholamine ratios is encouraged. These lesions are then followed closely by serial ultrasound evaluations. The goal of this protocol is to document that expectant observation in these small stage I lesions in infants is safe and appropriate, as has been suggested by smaller retrospective studies.

Pathology

Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma display a histologic spectrum of maturation and differentiation (Fig. 137–1). A grading classification of neuroblastoma, introduced in 1984 by Shimada and subsequently modified by him and others as the International Neuroblastoma Pathology Classification in 1999, has helped to define risk-based subtypes of ganglioneuroblastoma and neuroblastoma (Shimada et al, 1984, 1999a, 1999b). This revised system has been demonstrated to add independent prognostic information beyond the contribution of age that is contained in the system (Sano et al, 2006). Ganglioneuroma is a histologically benign, fully differentiated counterpart of neuroblastoma. It is unclear whether ganglioneuroma arises de novo or by maturation of a preexisting neuroblastoma or ganglioneuroblastoma. Metastatic lesions from neuroblastoma have been observed to develop the histology of mature ganglioneuroma, supporting the latter theory (Hayes et al, 1989).

The Shimada classification is an age-linked histopathologic classification. One of its important aspects is determining whether the tumor is stroma poor or stroma rich. Patients with stroma-poor

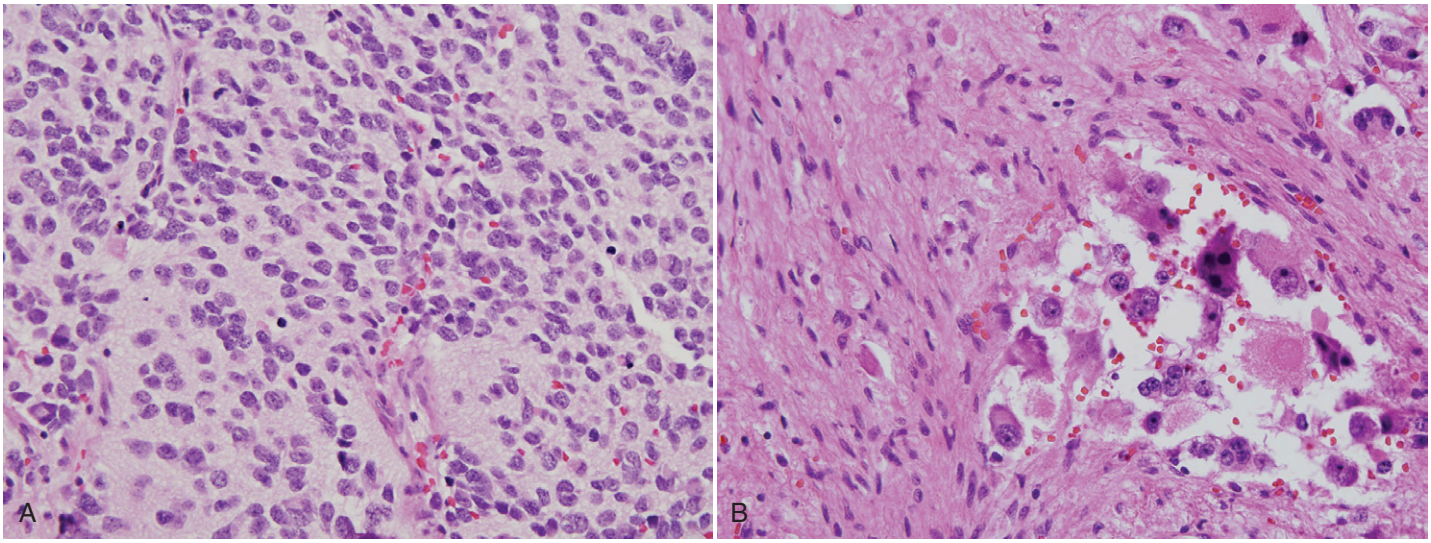


Figure 137–1. **A,** Poorly differentiated neuroblastoma with a minimal-to-moderate amount of neuropil. **B,** Ganglioneuroblastoma with more than 50% of surface area occupied by Schwannian stroma on left. Lobule contains ganglion cells, immature ganglion cells and poorly differentiated neuroblasts; only minimal neuropil is present within lobule. (Courtesy of Dr. Harry Kozakewich.)

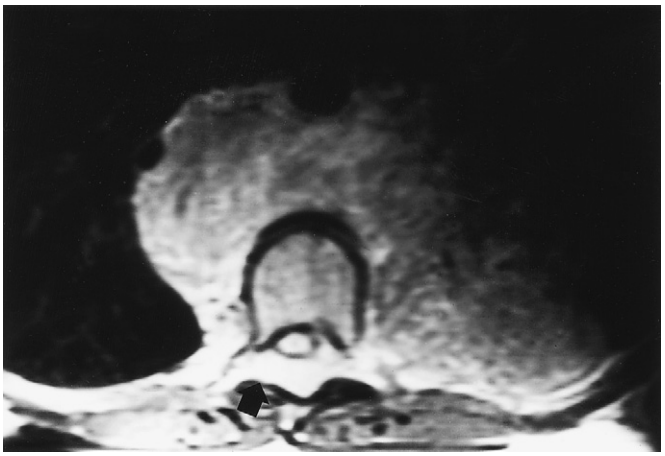


Figure 137–2. MRI of child with thoracic ganglioneuroma extending into the spinal canal *(arrow)*.

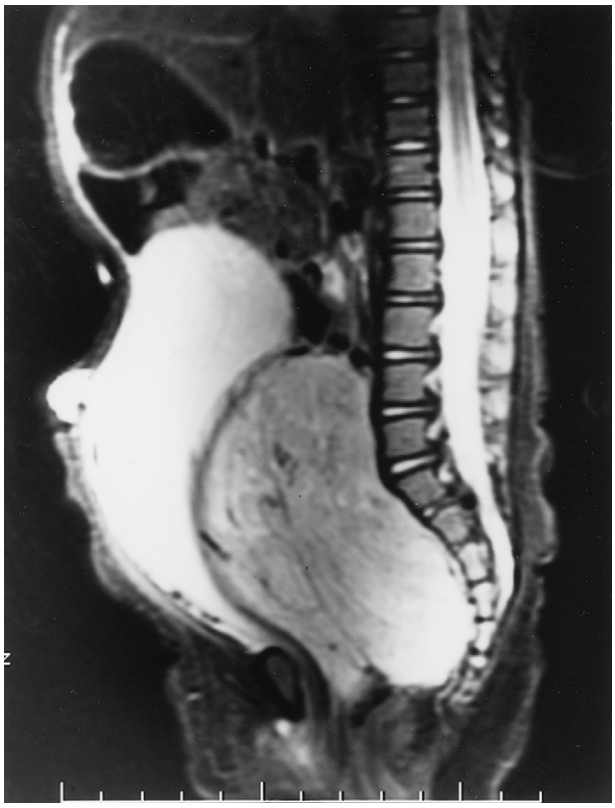


Figure 137–3. MRI demonstrating compression of bowel and bladder by a pelvic neuroblastoma.

tumors with unfavorable histopathologic features have a very poor prognosis (less than 10% survival) (Shimada et al, 1984). Stroma-rich tumors can be separated into three subgroups: nodular, intermixed, and well differentiated. Tumors in the latter two categories more closely resemble ganglioneuroblastoma or immature ganglioneuroma and carry a higher rate of survival. The stroma-poor tumors can be divided into favorable and unfavorable subgroups based on the patient's age at diagnosis, the degree of histologic maturation, and the mitotic rate. When compared with other clinical features, these histologic patterns were independently predictive of outcome (Shimada et al, 1984).

In contrast to neuroblastomas, ganglioneuromas are most often diagnosed in older children and are usually located in the posterior mediastinum and retroperitoneum, with only a small number arising in the adrenal glands (Enzinger and Weiss, 1988). Ganglioneuromas often grow to a very large size before they cause symptoms as a result of compression of adjacent structures or extension into the spinal canal (Benjamin et al, 1972) (Fig. 137–2).

Clinical Presentation and Pattern of Spread

The clinical manifestations of neuroblastoma vary widely. Most children present with abdominal pain or a palpable mass, but others are identified due to manifestations of their metastatic disease, including bone or joint pain and periorbital ecchymosis. Thoracic lesions may produce respiratory symptoms of cough or dyspnea. Direct extension of the tumor into the spinal canal may produce neurologic deficits as a result of cord compression.

Most primary tumors arise within the abdomen (65%); the frequency of adrenal tumors is slightly higher in children than in infants. Physical examination often reveals a fixed, hard abdominal mass. Pelvic neuroblastoma arising from the organ of Zuckerkandl accounts for 4% of tumors (Haase et al, 1995). Extrinsic compression of the bowel and bladder can produce symptoms of urinary retention and constipation (Fig. 137–3).

Metastases are present in 70% of patients with neuroblastoma at diagnosis and can be responsible for a variety of the clinical signs and symptoms at presentation. A number of unique paraneoplastic syndromes have been associated with both localized and disseminated neuroblastoma. Symptoms produced by catecholamine release may mimic those seen in pheochromocytoma: paroxysmal hypertension, palpitations, flushing, and headache. Secretion of vasoactive intestinal peptide (VIP) by the tumor can produce severe watery diarrhea and hypokalemia (Cooney et al, 1982). Another unusual presentation of neuroblastoma is acute myoclonic encephalopathy, in which patients develop myoclonus, rapid multidirectional eye movements (opsoclonus), and ataxia. It is thought to result from an interaction of antibodies produced against the neuroblastoma to normal neural tissues (Farrelly et al, 1984; Connolly et al, 1997). Although this syndrome is associated with a favorable outcome from an oncologic perspective (Altman and Baehner, 1976), prolonged neurologic impairment, including learning disabilities and developmental delay, is the rule in 70% to 80% of these children, and symptomatic therapy is often required (Russo et al, 1997; Rudnick et al 2001; Mitchel et al 2002). Adrenocorticotropic hormone (ACTH) or steroids are the basis of most therapy, but other treatments include high-dose intravenous gammaglobulin and cyclophosphamide. A current protocol of the Children's Oncology Group is evaluating the efficacy of intravenous gamma globulin and corticosteroids in the treatment of these children.

Diagnosis

Laboratory Evaluation

When sensitive techniques are used, increased levels of urinary metabolites of catecholamines, vanillylmandelic acid (VMA) and homovanillic acid (HVA), are found in 90% to 95% of patients (Williams and Greer, 1963). Therapy with various modalities produces a reduction in catecholamine metabolite excretion in most patients (Gerson and Koop, 1974). These metabolites can be monitored to detect tumor relapse and response to therapy.

Anemia is noted in children with widespread bone marrow involvement. Studies suggest that marrow biopsies add substantially to the detection of marrow involvement by tumor, compared with marrow aspirates alone (Franklin and Pritchard, 1983). It is recommended that two marrow aspirates and two biopsies be performed. In the future, neuroblastoma-specific immunocytology of marrow aspirates may obviate the need for marrow biopsies in most patients (Hsiao et al, 1990).

Imaging

Imaging studies play an important role in the evaluation of a child with neuroblastoma. **Plain radiographs may demonstrate a calcified abdominal or posterior mediastinal mass.** Computed tomography (CT) and magnetic resonance imaging (MRI) provide more information about the local extent of the primary tumors. Invasion of the renal parenchyma is not common, but it can be detected radiographically by CT (Albregts et al, 1994). MRI has advantages over CT in the evaluation of intraspinal tumor extension (see Fig. 137–2) and in demonstrating the relationship between the major vessels and the tumor (Azizkhan and Haase, 1993) (Fig. 137–4). **The finding of intratumoral calcifications, vascular encasement, or both on preoperative computed tomography may help distinguish neuroblastoma from Wilms tumor** (Dickson et al, 2008). Current Children's Oncology Group protocols require both a radionuclide bone scan and meta-iodobenzylguanidine (MIBG) scans for staging, but no longer require the classic skeletal survey. MIBG scans use ^{131}I-MIBG (Geatti et al, 1985), which is taken up by the adrenergic secretory vesicles of the tumor cells in both primary and metastatic sites. MIBG scintigraphy can determine the extent of disease and detect tumor recurrence after completion of therapy (Geatti et al, 1985). Recently, ^{131}I-MIBG has been shown to be more sensitive than either ^{131}I-MIBG or bone scans in detecting tumor relapse (Kushner et al, 2009). Osseous metastatic lesions occur most commonly in the long bones and skull.

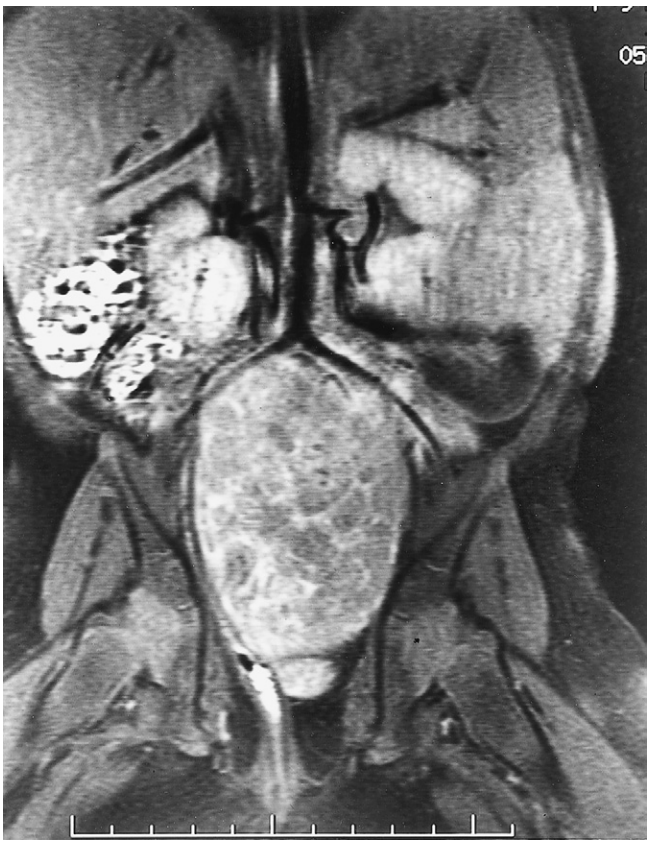


Figure 137–4. MRI of pelvic neuroblastoma. The bifurcation of the aorta and iliac vessels are well delineated, showing the relationship to the mass.

Screening

Mass population screening for neuroblastoma has been widely used in Japan for more than 20 years (Nishi et al, 1987). The goal of screening programs is to detect disease at an earlier stage and to decrease the number of older children with advanced-stage disease, thereby improving survival. In fact, the children diagnosed as a result of screening studies have had almost uniformly favorable survival (>97%) (Suita, 2002). An increased number of infants younger than 1 year of age have been diagnosed through the mass screening program (Ishimoto et al, 1990), and most of these patients have lower-stage tumors (Sawada, 1992). Before mass screening started, 20% of neuroblastoma cases were diagnosed before 1 year of age, compared with 55% after its implementation. However, the number of children older than 1 year of age diagnosed with advanced-stage disease has not decreased. These results suggested that the aggressive advanced-stage tumors in older children did not arise from the low-risk tumors seen in the infants less than 1 year of age.

There are biologic differences between tumors diagnosed by screening and those detected clinically (Hayashi et al, 1992). In one review of 48 cases discovered by screening, no tumors were observed to have amplified N-*MYC* oncogene expression (Ishimoto et al, 1991), and in a second review of 20 infants, only one who did poorly had amplification (Hase et al, 2002). Furthermore, 80% had a diploid chromosome pattern, which is also associated with a favorable prognosis. On follow-up, all 48 patients were still alive without tumor. In another series of 357 patients whose tumors were diagnosed by mass screening, the overall survival rate was 97% (Sawada, 1992). Given the favorable biologic characteristics of tumors discovered by screening, it is possible that many would spontaneously resolve without therapy, particularly given the increased incidence of neuroblastomas seen in the screened population.

Two large prospective population based studies were conducted in the Province of Quebec and in Germany. These studies demonstrated that urine screening at various ages was successful in identification of neuroblastoma, but there was no decrease in the occurrence of neuroblastoma in older children and its subsequent mortality (Schilling et al, 2002; Woods et al, 2002).

Staging

Staging of neuroblastoma is an important aspect of management. **The stage of the disease is a significant prognostic variable that determines adjuvant therapy.** The International Neuroblastoma Staging System (INSS) is based on clinical, radiographic, and surgical evaluation of children with neuroblastoma (Brodeur et al, 1993) (Table 137–1). Earlier staging systems provided generally comparable results in terms of distinguishing low-stage, good-prognosis disease from high-stage, poor-prognosis disease. Use of a uniform international system, however, makes comparison of results from various studies much easier to compare. The biggest differences arise when the various systems are applied to those with intermediate-stage disease. It is in this cohort of children where use of the Risk Group Classification, which

combines pathologic findings, stage, and several of the biologic markers, best defines the child's risk for progressive disease (Table 137–2) (Katzenstein and Cohn, 1998). Although the classification appears complex, it provides the most accurate assessment of how intense the chemotherapy and radiotherapy must be to cure the child.

Table 137–1.
International Neuroblastoma Staging System

STAGE	DEFINITION
1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive).
2A	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.
2B	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor; enlarged contralateral lymph nodes must be negative microscopically.
3	Unresectable unilateral tumor infiltrating across the midline,* with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement.
4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs.
4S	Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow (less than 10% tumor) in infants less than 1 year of age.

*The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.

A recent effort has been made to identify, preoperatively, those tumors that are resectable without significant surgical risks. The Localized Neuroblastoma European Study Group (LNESG) defined the radiographic criteria associated with higher surgical morbidity. They validated that their presence was associated with a lower rate of complete resection and a greater risk of surgical complications (Cecchetto et al, 2005). This finding has been confirmed by others (Simon et al, 2008).

Prognostic Factors

Many variables affect the prognosis of neuroblastoma. In addition to the clinical features, there are now many biologic studies that can be used to stratify patients for treatment.

Clinical Variables

Age remains an important indicator of outcome, as originally reported by Breslow (Breslow and McCann, 1971). **Children age 1 year or younger have a better survival than older children** (Nitschke et al, 1988). **This may be attributed to more favorable biologic parameters in tumors diagnosed at this age.** Recent retrospective reviews have suggested that age is a truly more of a "continuous" prognostic variable and that a cutoff of 460 days maximized the outcome difference between the younger and older patients (London et al, 2005). Teenagers and adults with neuroblastoma have a particularly indolent and relentless disease (Gaspar et al, 2003; Kushner et al, 2003). **The *site of origin* is of significance, with better survival noted for nonadrenal primary tumors** (Haase et al, 1995). Most children with thoracic neuroblastoma present at a younger age with localized disease and have improved survival even when corrected for age and stage (Adams et al, 1993). Tumors at this site are less likely to have N-*MYC* amplification and more likely to have a DNA index greater than 1.0, both favorable prognostic indicators (Morris et al, 1995).

Stage of the disease is a powerful independent prognostic indicator. Virtually all stage I patients with complete resection of the primary tumor survive. Stage II patients also have a favorable survival prospect, even though there may be incomplete excision (Matthay et al,

Table 137–2.
Risk Group Classification

RISK GROUP	INSS	AGE (DAYS)	N-*MYC*	DNA INDEX	SHIMADA HISTOPATHOLOGY
Low	1	Any	Any	Any	Any
	2A, 2B	<365	Any	Any	Any
	2A, 2B	≥365	Nonamplified	Any	Any
	2A, 2B	≥365	Amplified	Any	Favorable
	4S	<365	Nonamplified	>1.0	Favorable
Intermediate	3	<365	Nonamplified	Any	Any
	3	≥365	Nonamplified	Any	Favorable
	4	<365	Nonamplified	Any	Any
	4S	<365	Nonamplified	1.0	Favorable
	4S	<365	Nonamplified	Any	Unfavorable
High	2A, 2B	≥365	Amplified	Any	Unfavorable
	3	<365	Amplified	Any	Any
	3	≥365	Nonamplified	Any	Unfavorable
	3	≥365	Amplified	Any	Any
	4	<365	Amplified	Any	Any
	4	≥365	Any	Any	Any
	4S	<365	Amplified	Any	Any

INSS, International Neuroblastoma Staging System.

1989). Children with advanced regional disease, stages III or I, fare less well and require more intensive treatment. The proportion of patients presenting with localized, regional, or metastatic disease is age dependent (Nitschke et al, 1988). The overall prognosis for stages I, II, or IV-S has a survival range of 75% and 90%, whereas those children with stage IV disease have a 2-year disease-free survival range of 19% to 30% despite intensive therapy, including bone marrow transplantation. The outcome for infants younger than 1 year of age is substantially better than for older patients with the same stage of disease.

Stage IV-S (S meaning special) is a distinct category referring to infants with small primary tumors and liver, skin, and bone marrow metastases without radiographic evidence of bone metastases. It was first proposed by Evans and colleagues in 1971. This group of patients has a good prognosis, with overall survival ranging from 80% to 88%. The INSS criteria later restricted this stage to children with less than 10% bone marrow involvement (Brodeur et al, 1993). This stage accounts for 7% to 10% of all cases of neuroblastoma. Many of these tumors undergo spontaneous regression (Evans et al 1987; Haas et al, 1990). In general, the tumors in children with stage IV-S neuroblastoma have favorable prognostic findings not typically seen in children with stage IV disease (Hachitanda et al, 1991; Nickerson et al, 2000). Poor outcome in stage IV-S patients is associated with elevated serum neuron-specific enolase (>100 nmol/mL), ferritin (>280 ng/mL), urinary dopamine levels (>2500 nmol/mmol creatinine), as well as N-*MYC* amplication and chromosome 1p deletion (Schleiermacher et al, 2003). Most deaths in this group are in infants under 2 months of age with extensive abdominal involvement and with respiratory compromise or disseminated intravascular coagulation (Nickerson et al, 2000).

Biologic Variables

The presence of homogeneously staining regions and double-minute chromosomes was noted in approximately one third of neuroblastoma tumors. These abnormalities are cytogenic manifestations of gene amplification, and it was subsequently found that the N-*MYC* oncogene was mapped to these regions. The association of N-*MYC* amplification with the pathogenesis of neuroblastoma is unclear, but N-*MYC* amplification is almost always present at the time of diagnosis (Brodeur, 1991). **Seeger and colleagues** (1985, 1988) **showed that N-*MYC* amplification is associated with rapid tumor progression and a poor prognosis. Amplification is found in 5% to 10% of patients with low-stage or stage IV-S** (Hachitanda et al, 1991) **but in 30% to 40% of those with advanced-stage disease** (Brodeur and Fong, 1989; Brodeur, 1990). **The poor prognosis associated with N-*MYC* amplification is independent of patient age or stage of disease at presentation** (Iehara et al, 2006). However, not all patients with a poor outcome have N-*MYC* amplification. Many advanced-stage tumors lack N-*MYC* at diagnosis, and recurrence or progression of disease develops in most of these patients.

DNA content of tumor cells and ploidy number has been reported to have prognostic value in patients with neuroblastoma (Cohn et al, 1990). Studies of DNA content measured by flow cytometry showed that a "hyperdiploid" karyotype (or increased DNA content) was associated with a favorable outcome (Look et al, 1984; Kusafuka et al, 1994). DNA diploidy and tetraploidy were associated with decreased survival. A recent review of 2660 children with localized neuroblastoma registered with the International Neuroblastoma Risk Group database evaluated tumor ploidy in children with N-*MYC*–amplified tumors (Bagatell et al, 2009). They reported an improved prognosis in children with hyperdiploid tumors compared to diploid tumors. This could be used to identify children for reduction in therapy.

Deletions of the short arm of chromosome 1 have been found in 70% to 80% of the near-diploid tumors that have been karyotyped (Brodeur and Fong, 1989; Brodeur, 1990). Preliminary studies suggest a correlation between 1p deletion and poor survival (Brodeur and Fong, 1989; Hayashi et al, 1989). Because there is an association between N-*MYC* amplification and 1p deletion, it remains to be determined whether this finding has independent prognostic significance.

Children currently treated on protocols of the COG are assigned to a risk group that is determined by age, stage of disease, N-*MYC* status, histologic grade, and DNA ploidy (Katzenstein et al, 1998) (see Table 137–2). Other factors that have been demonstrated to have prognostic significance, although they are often associated with these genetic abnormalities, include expression of the gene encoding the high-affinity nerve growth factor receptor (termed *TRKA* proto-oncogene) and the low-affinity nerve growth factor receptor (Tanaka et al, 1995). Both are favorable prognostic predictors and are inversely related to amplification of N-*MYC* oncogene (Nakagawara et al, 1993). Lack of expression of CD44 glycoprotein on the tumor cell surface and increased levels of serum ferritin, serum neuron-specific enolase, and serum lactate dehydrogenase are all adverse prognostic factors (Chan et al, 1991; Silber et al, 1991). They have not, however, been shown by multivariate analysis to be independently predictive from age, stage, ploidy, and N-*MYC* status. Telomere length has also been described as a significant prognostic parameter, and in a cohort of high-risk patients, it was the sole significant parameter that identified a group of patients with a favorable prognosis (Ohali et al, 2006).

Treatment

The treatment modalities primarily used in the management of neuroblastoma are surgery, chemotherapy, and radiation therapy. The role of each in individual patients varies depending on tumor stage, age, and biologic prognostic factors. These can be used to stratify patients into favorable and unfavorable categories by risk group (see Table 137–2).

Surgery

The goals of surgery are to establish the diagnosis, stage the tumor, excise the tumor (if localized), and provide tissue for biologic studies. Resectability of the primary tumor should take into consideration tumor location, mobility, relationship to major vessels, and overall prognosis of the patient. Neoadjuvant chemotherapy, given the efficacy of modern agents, is very successful in reducing the size of primary tumors. Sacrifice of vital structures to achieve resection at diagnosis should be avoided, particularly in young children in whom prognosis is excellent.

Low-Risk Disease (Stages I, II, and IV-S). Children with stage I neuroblastoma have a disease-free survival rate of greater than 90% with surgical excision alone (O'Neill et al, 1985; Nitschke et al, 1988; DeBernardi et al, 1995). **Chemotherapy is indicated only in the event of recurrence unless the child has N-*MYC* amplification and unfavorable histology.** The Pediatric Oncology Group reviewed 101 children with localized neuroblastoma who had complete gross excision of the primary tumor (Nitschke et al, 1988). Nine patients experienced relapse, but six were salvaged with chemotherapy.

Radiation therapy has no role in this subset of patients. With current use of the risk factor grading, those children with recurrence in the past may be identified now as the small number with adverse biologic markers. In a comparable study from the Children's Cancer Group, 374 stage I and II patients were treated primarily by resection (Perez et al, 2000). Event-free survival (EFS) and overall survival (OS) for stage I patients were 93% ± 3% and 99% ± 1%, respectively, compared with 81% ± 4% and 98% ± 2% for stage II patients, respectively. Supplemental treatment was required in only 10% of stage I and 20% of stage II patients, and excellent overall survival was achieved in the stage II patients. N-*MYC* amplification, unfavorable histology, age greater than 2 years, and positive lymph nodes predicted a lower overall survival.

Radical resection resulting in removal of normal organs, particularly the kidney, is not justified in this group of patients. Radiation of the local tumor bed has been advocated for treatment of residual disease in stage II cases. However, a review of 156 patients with stage II neuroblastoma found a 90%, 6-year, progression-free survival rate regardless of whether radiation therapy was used (Matthay et al, 1989). Therefore radiation should be reserved for those patients who fail to respond to either primary or secondary chemotherapy. In stage III disease, or in stage II with extensive tumor around the kidney and renal vessels, preoperative treatment with chemotherapy significantly decreases the risk of nephrectomy as a result of resection of the tumor (Shamberger et al, 1998) (Fig. 137–5).

The generally favorable behavior of IV-S disease has been explained with the understanding of biologic markers. The vast majority of these infants have tumors with entirely favorable markers, explaining their favorable behavior. However, a small percentage of these patients have adverse markers, and it is these children who have progressive disease that often is fatal. Resection of the primary is not mandatory (Nickerson et al, 1985; Evans et al, 1987). Although excellent survival has been reported after surgery (Martinez et al, 1992), information regarding histologic prognostic factors was not available for all of these patients. In a review of 110 infants with stage IV-S disease, the entire cohort had an estimated 3-year survival rate of 85% ± 4% (Katzenstein et al, 1998). This rate was significantly decreased to 68% ± 12% for infants whose tumors were diploid; to 44% ± 33% for those with N-*MYC* amplification; and to 33% ± 19% for those with unfavorable histology. Of note, there was no statistical difference in survival rate for infants who underwent complete resection of their primary tumor compared with those who had partial resection or only biopsy (Katzenstein et al, 1998; Nickerson et al, 2000; von Schweinitz et al, 2002). Patients with extensive metastatic disease and N-*MYC* amplification represent a high-risk group (Martinez et al, 1992). These patients should be considered for a more aggressive treatment with multimodal therapy, according to the risk group classification (see Table 137–2) (Schleiermacher et al, 2003). Those with favorable biologic markers and no symptoms can be followed with supportive care and limited chemotherapy, and hepatic radiation to infants with significant symptoms. Intensive chemotherapy is reserved for those with adverse markers, although these infants do poorly even with therapy.

High-Risk Disease (Stages III and IV). There is debate regarding the extent of surgical resection that is required for stage III lesions. A report from the Children's Cancer Group of 58 patients with stage III disease found that 8 of 12 patients with initial complete excision, and 12 of 14 with subsequent resection of the primary tumor, were long-term survivors (Haase et al, 1989). This result contrasts with only 9 of 32 survivors among patients in whom complete tumor excision could not be accomplished. Significant morbidity was reported in association with the surgical procedures, including 21 major complications. The Italian Cooperative Group for Neuroblastoma found that complete resection after chemotherapy of extensive unresectable neuroblastoma was associated with improved survival, compared with partial resection only (Garaventa et al, 1993). Similar results have been noted by others (LeTourneau et al, 1985; O'Neill et al, 1985; Powis et al, 1996). It has been suggested by some that even children with stage III disease do not need cytotoxic therapy if the biologic marker N-*MYC* amplification is not present (Kushner et al, 1996). These results are not widely accepted, however, and confirmatory studies are required before this policy can be widely adopted.



Figure 137–5. MRI before and after chemotherapy, showing marked reduction in size of right suprarenal neuroblastoma. **A,** Before chemotherapy. **B,** After chemotherapy.

Children with bulky pelvic tumors generally do quite well even with limited residual disease (LeClair et al, 2004). Extensive surgery at this site has been associated with long-term neurologic sequelae; thus the extent of resection must be balanced against this morbidity (Cruccetti et al, 2000).

There is conflicting evidence for the role of extensive resection in stage IV disease between studies that support (LeTourneau et al, 1985; Haase et al, 1991; Tsuchida et al, 1992; LaQuaglia et al, 1994; Chamberlain et al, 1995; DeCou et al, 1995; Yokoyama et al, 1995; Kuroda et al, 2003; Adkins et al, 2004; LaQuaglia et al, 2004; Koh et al, 2005; McGregor et al, 2005) and those that refute that approach (Sitarz et al, 1983; Matsumura et al, 1988; Adams et al, 1993; Losty et al, 1993; Kiely, 1994; Kaneko et al, 1997; Castel et al, 2002; von Schweinitz et al, 2002). In a retrospective review, Kiely (1994) compared the results of radical tumor resection with those of more conventional surgery in patients with stage III and IV disease. Kiely found no difference in survival between 46 patients treated with radical surgical procedures and 34 patients treated with more conventional surgery. Shorter and colleagues (1995) also did not find any evidence that the extent of surgical resection had an impact on the survival of stage IV patients. In these nonrandomized studies, it has been difficult to determine whether improved survival in those with complete resection has been due to the more favorable intrinsic biology of the tumor allowing resection or truly due to the completeness of resection.

As the intensity of the therapy increases, including the use of autologous bone marrow transplantation and control of distant metastasis, the impact of maximal local control may become apparent. The combination of gross total resection and external beam irradiation has achieved local control in 84% to 90% of children (Wolden et al, 2000; Kushner et al, 2001). In another series of reports, intensive chemotherapy followed by double autologous bone marrow transplantation, aggressive surgical resection, and radiotherapy has achieved an overall survival of 56% and a local recurrence rate of only 2.6% (Marcus et al, 2003; von Allmen et al, 2005).

Usually the safest approach for advanced tumors is to defer resection until after initial chemotherapy (Berthold et al, 1989; Shamberger et al, 1991; Shochat, 1992; LaQuaglia et al, 1994; Black et al, 1996). **The tumors are smaller and firmer, with less risk of rupture and hemorrhage following chemotherapy, resulting in a decreased rate of complications, particularly nephrectomy** (Shamberger et al, 1998) (see Fig. 137–5). One specific complication that is encountered after resection of extensive tumor surrounding the celiac axis and the superior mesenteric artery is diarrhea (Kiely, 1994). It is thought to result from resection of the autonomic nerves to the gut found anterior to the aorta at the base of the superior mesenteric artery and the celiac axis (Rees et al, 1998). Preoperative chemotherapy does appear to increase the proportion of children able to achieve a complete resection (Adkins et al, 2004).

Surgery usually is performed 13 to 18 weeks after initiation of chemotherapy, allowing three to four courses of treatment (Azizkhan and Haase, 1993). Some tumors remain inoperable even after chemotherapy.

Infants under 1 year of age with extensive local disease or stage IV disease comprise a special subset of patients. They have historically fared much better than children greater than 1 year of age with comparable disease, but not as well as infants with stage IV-S disease. It is now recognized that the biologic markers can be used to identify which infants have high-risk disease and require intensive therapy and which will have intermediate-risk disease requiring less intensive therapy.

In a large cohort (134 infants), N-*MYC* amplification, serum ferritin, Shimada histopathologic classification, and bone marrow involvement by immunocytology were analyzed. Although each factor had prognostic significance by univariate analysis, only N-*MYC* was significant by multivariate analysis; the EFS for infants without N-*MYC* amplification was 93% ± 4% versus 10% ± 7% in those with amplification despite intensive therapy (Schmidt et al, 2000).

Recent trials in Europe evaluated these infants without N-*MYC* amplification and achieved excellent survival (OS of 97.6% at 2 years) without chemotherapy in those with primaries extending across the midline or a positive skeletal survey (DeBernardi et al, 2009). Infants with overt metastases to the skeleton, lung, and central nervous system (CNS) were treated with a minimum of four chemotherapy courses and achieved a 2-year OS of 95.6%.

Chemotherapy

A variety of multiagent treatment regimens have been developed to treat high-risk patients with neuroblastoma. The goal of this treatment intensification is better disease control. Although initial response rates are improving, with a prolonged time to progression of disease, relapse continues to be a major problem, and the 4-year overall survival rate in stage IV disease is 20% (Ikeda et al, 1989; Haase et al, 1991).

The dose intensification of chemotherapy needed for local tumor control results in significant myelosuppression, limiting the amount of therapy that can be given. This has prompted the use of autologous bone marrow transplantation after sublethal chemotherapy or total-body irradiation. The use of marrow-ablative chemoradiotherapy followed by autologous marrow reinfusion has resulted in complete remission in up to 50% of patients with recurrent stage IV disease (Moss et al, 1987; Seeger et al, 1991; Dinndorf et al, 1992; Mugishima et al, 1994; Matthay et al, 1995; Grupp et al, 2000). However, a significant problem is the risk for late relapse. The randomized clinical trial of the German Society of Paediatric Oncology and Hematology of high-risk neuroblastoma showed improved event-free survival at 3 years with myeloablative therapy and autologous stem cell rescue compared with maintenance chemotherapy (Berthold et al, 2005). These results were similar to those of the COG study (Matthay et al, 1999). Regrettably, the overall survival rates were not statistically different in either study at initial report. A recent update of the latter study reveals that the 5-year OS of the patients receiving the autologous bone marrow transplant was improved (Matthay et al, 2009).

The presence of bulky disease results in increased failure. Tumor debulking with surgery or radiation therapy is warranted before autologous bone marrow transplantation. There are many questions yet to be resolved about this modality of treatment. Toxicity of bone marrow transplantation can be lethal, and the long-term complications in patients with successful transplantation are unknown. However, these risks are acceptable given that long-term survival is difficult to achieve without such aggressive therapy.

New agents in phase I and II trials for relapsed neuroblastoma include temozolomide, irinotecan, and topotecan (Kushner et al, 2006; Rubie et al, 2006; Simon et al, 2007). As efficacy is established, they will be advanced into clinical trials for high-risk tumors with a goal to improve the overall outcome.

New Innovative Biologic Therapies

Because increasing the intensity of chemotherapy appears to have reached its limit with the use of double autologous bone

marrow transplantation, other routes of treatment must be identified. The use of biologic modifiers is being investigated (Villablanca et al, 1995). 13-cis-Retinoic acid produces differentiation of neuroblastoma in cell cultures. It was given for a 6-month period after cytotoxic therapy in children with advanced-stage disease and significantly decreased the frequency of relapse (Matthay et al, 1999). Long-term follow up has shown that the 5-year OS is improved with the use of 13-cis-retinoic acid in these children after transplant or intensive chemotherapy (Matthay et al, 2009). Other avenues of treatment in current phase I and phase II trials include vaccine and antibody therapy against the GD2 cell surface marker occurring in neuroblastoma. A new synthetic retinoid, fenretinide, which has produced apoptosis rather than differentiation in neuroblastoma cell lines, is also in early clinical trials.

Inhibition of angiogenesis is another appealing avenue of therapy in this very vascular tumor, particularly once there is minimal residual disease. Antiangiogenic therapy has proved successful in animal models, but has not yet been used clinically.

Another modality in the treatment of metastatic neuroblastoma is the use of ^{131}I-MIBG (Hutchinson et al, 1992). The finding that both the primary tumor and metastatic areas take up this radiotracer suggested the possibility that therapeutic doses can be delivered to the tumor. Preliminary analysis indicates that objective responses do occur in terms of reduction of tumor volume, even in previously heavily treated patients (Howard et al, 2005; Matthay et al, 2007). Significant myelosuppression is seen with dose escalation, however, and stem cell support is required.

Radiotherapy

Radiotherapy is effective for local control in neuroblastoma and risk of local relapse can be correlated with the biologic markers. Although irradiation has not provided a benefit in low-stage tumors, it has increased local control in children with advanced stage IV or bulky stage III tumors (Matthay et al, 1989; Castleberry 1991; Evans et al, 1996). A randomized control trial to evaluate the efficacy of local control between radiotherapy alone and surgery has not been performed. Doses of external beam irradiation used have ranged between 15 and 30 Gy, depending on the patient's age, location, and extent of residual disease.

Intraoperative radiation therapy has been used for patients with unresectable disease. This technique has the advantage of delivering a higher dose of radiation to the operative field while sparing normal adjacent tissues (Leavey et al, 1997). Although its use has been promoted, it has not been convincingly demonstrated to improve control when compared with external beam irradiation (Haas-Kogan et al, 2000).

Spinal Cord Compression

Extension of tumor into the spinal canal produces symptoms of spinal cord compression in up to 5% of patients presenting with neuroblastoma (DeBernardi et al, 2001), while up to 13% of patients have radiographic evidence of extension into the spinal canal (Plantaz et al, 1996). These children have been treated by decompressive laminectomy, radiotherapy, or chemotherapy. Neurologic outcome has been similar by all modalities and, regrettably, patients presenting with severe motor deficits generally recover little function (DeBernardi et al, 2001; Katzenstein et al, 2001). Because of the delayed complications of scoliosis after laminectomy, current recommendations are to initiate treatment with chemotherapy and reserve laminectomy for children with progressive neurologic deterioration (Katzenstein et al, 2001). Radiotherapy is now generally avoided, because of its adverse effect on growth of the spine.

Key Points: Neuroblastoma

- Neuroblastoma is the most common extracranial solid neoplasm in children.
- Children 1 year old or younger have a better survival rate than older children. This may be attributed to more favorable biologic parameters in tumors diagnosed at this age.
- Complete surgical resection is curative for low-stage disease.
- N-*MYC* amplification, found in 20% of patients with primary tumors, is associated with tumor progression. This poor prognosis is independent of patient age and tumor stage.

GENITOURINARY RHABDOMYOSARCOMA

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in infants and children, with nearly 350 new cases in the United States each year. It is the third most common solid tumor in children after neuroblastoma and Wilms tumor. **Fifteen to 20 percent of all RMS arise from the genitourinary system** (Maurer et al, 1988; Crist et al, 2001). **The most common genitourinary sites are the prostate, bladder, and paratesticular; the vagina and uterus are relatively unusual sites. Survival rates vary with site; certain sites such as the vagina and paratesticular have a better prognosis than bladder/prostate primaries** (Rodary et al, 1988; Crist et al, 1990; Martelli et al, 1999; Arndt et al, 2001; Wiener et al, 2001; Ferrari et al, 2002; Meza et al, 2006). There is a bimodal age distribution with a peak incidence in the first 2 years of life and again at adolescence, but two thirds of cases occur in children under 6 years of age (LaQuaglia et al, 1994). The botryoid variants arising from the bladder and vagina are seen almost exclusively in young children.

Etiology, Epidemiology, and Genetics

Subgroups of children with a genetic predisposition to the development of RMS have been identified. The Li-Fraumeni syndrome associates childhood sarcomas with mothers who have an excess of premenopausal breast cancer and with siblings who have an increased risk of cancer (Li and Fraumeni, 1969). A mutation of the *TP53* tumor suppressor gene was found in the tumors in all patients with this syndrome (Malkin et al, 1990). An increased incidence of RMS has been found in association with neurofibromatosis (Sung et al, 2004).

The two major histologic subtypes of RMS, embryonal and alveolar, have been noted to have distinct cytogenetic abnormalities. Alveolar RMS is associated with a translocation between chromosomes 1 or 2 and 13, resulting in the formation of a chimeric protein (Parham, 1994). PAX3, a DNA-binding protein on chromosome 2, or PAX7, a DNA-binding protein and on chromosome 1, is fused to the FKHR gene on chromosome 13 (Anderson et al, 2001). About 25% of cases lack these translocations. These genes may be involved in the pathogenesis of alveolar rhabdomyosarcoma and are prognostic factors as well. Expression of PAX3-FKHR is an adverse prognostic factor for children presenting with metastatic alveolar RMS (Sorensen et al, 2002). In addition, patients with the t(1;13) translocation, *PAX7-FKHR* fusion, are often younger and have a better prognosis than do their counterparts with the t(2;13), *PAX3-FKHR* fusion abnormality (Kelly et al, 1997; Anderson et al, 2001; Sorensen et al, 2002).

Embryonal RMS demonstrates loss of heterozygosity (LOH) on chromosome 11p15.5 at a different location than the *WT2* gene implicated in the development of some Wilms tumors (Douglass et al, 1987; Scrable et al, 1990). This region is the location of the *IGF-2* gene. IGF-2 overexpression has been documented in alveolar and embryonal rhabdomyosarcoma (Leiroth et al, 1995). IGF-2 is a growth factor that can stimulate the growth of RMS tumor cells, and antibodies directed against IGF-2 can inhibit tumor growth (El-Badry et al, 1990). Amplification of the transcription factor N-*MYC* has been noted in neuroblastoma and in RMS (Williamson et al, 2005). Overexpression of N-*MYC* was associated with an adverse outcome in alveolar RMS.

Pathology and Patterns of Spread

The Intergroup Rhabdomyosarcoma Study Group (IRSG) has developed a pathology classification recognizing three major histologic groups that have prognostic significance (Asmar et al, 1994). ***Embryonal* RMS is the most common subtype of RMS and accounts for most of the genitourinary tumors** (Maurer et al, 1977; Newton et al, 1988). **This may occur in solid form arising in muscle groups, such as the trunk and extremities, or as the so-called sarcoma botryoides, a polypoid variety that occurs in hollow organs or body cavities, such as the bladder or vagina.** Embryonal RMS may have variable cell types with small, round cells with hyperchromatic nuclei and large, polygonal-shaped cells with abundant eosinophilic cytoplasm (Fig. 137–6). **There is a spindle cell, or leiomyomatous, variant seen frequently in the paratesticular region. The botryoid and spindle cell variants of embryonal RMS are associated with an excellent survival. The second most common form is *alveolar*, comprising 15% to 20% of cases. Alveolar RMS occurs more commonly in the trunk and extremities than in genitourinary sites and has a worse prognosis than embryonal tumors** (Hays et al, 1983; Newton et al, 1988; Crist et al, 2001; Stevens et al, 2005). **Alveolar RMS also has a higher rate of local recurrence and spread to regional lymph nodes, bone marrow, and distant sites.** The third category consists of *undifferentiated* tumors that also fare poorly.

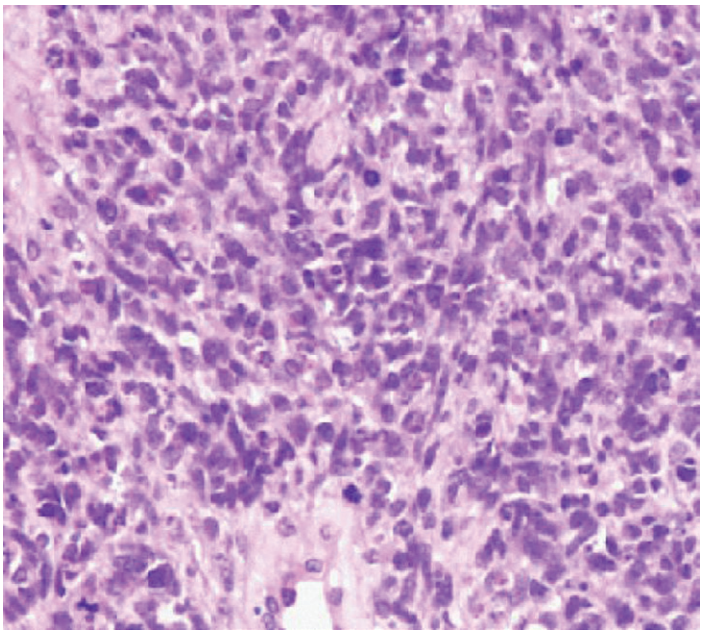


Figure 137–6. Embryonal rhabdomyosarcoma with spindle-shaped cells that have a stromal-rich appearance.

The diagnosis of rhabdomyosarcoma can occasionally be difficult with conventional histologic techniques. In such cases, histology may be complemented by other studies, including electron microscopy, cytogenetics, DNA flow cytometry, and immunochemistry (Shapiro et al, 1991; Davicioni et al, 2009). Immunohistochemical staining has been shown to be an effective adjunct for the diagnosis of alveolar RMS (Dias et al, 2000). Genes of the MyoD family are important in the differentiation of skeletal muscle (Parham, 1994). MyoD is important in the switch from proliferation to differentiation, and loss of this control and excess proliferation could lead to RMS (Sebire and Malone, 2003). Fetal myoblasts express MyoD and myogenin, another myogenic regulatory gene, whereas adult myoblasts do not. MyoD and myogenin are expressed in RMS and is believed to represent failure of differentiation. **Myogenin has been proven to be a useful marker of alveolar RMS. Alveolar RMS demonstrates high levels of staining, whereas embryonal RMS is either negative or has a low level of staining** (Dias et al, 2000). **Diffuse myogenin expression by immunohistochemistry has been shown to be predictive of decreased survival independent of tumor stage, site or histology** (Heerema-McKenney et al, 2008).

Clinical Grouping and Staging

Tumor stage at diagnosis is most predictive of clinical outcome, because patients with localized disease have a better prognosis (Lawrence et al, 1987). The likelihood of regional lymph node extension varies with site of the primary tumor, approaching 50% for older boys with paratesticular tumors. The most common site of metastatic spread of RMS is the lungs. The clinical group staging system was developed by the IRSG in 1972 (Table 137–3). One of the difficulties inherent in this system is that the group is dependent to a large extent on the completeness of surgical excision. As the treatment of RMS has evolved, more patients undergo biopsy only at the initial surgical procedure, leaving gross residual disease. This results in the shifting of more patients from group I to group III. Biologically equivalent tumors could end up in different categories, depending on the aggressiveness of the initial surgical resection.

Table 137–3.

Intergroup Rhabdomyosarcoma Study Group Clinical Grouping Classification

Group I	Localized disease completely resected Confined to organ of origin Contiguous involvement
Group II	Total gross resection with evidence of regional spread Microscopic residual Positive nodes but no microscopic residual Positive nodes but microscopic residual in nodes or margins
Group III	Incomplete resection with gross residual disease After biopsy only After gross or major resection of the primary (>50%)
Group IV	Distant metastasis at diagnosis (lung, liver, bones, bone marrow, brain, and nonregional nodes) Positive cytology in cerebrospinal fluid, pleural or peritoneal fluid, or implants on pleural or peritoneal surfaces are regarded as stage IV

A site-specific TNM staging system was devised by the IRSG for IRS-IV (Table 137–4) (Lawrence et al, 1997). The TNM system segregates patients by favorable and unfavorable sites. Favorable GU sites include the paratesticular and the vulvar-vaginal-uterine ones. Unfavorable GU sites are the bladder and prostate. Presence of distant metastases at diagnosis, involved regional lymph nodes, and large primary tumors (>5 cm) at unfavorable sites are relatively unfavorable prognostic signs (Lawrence et al, 1997). A recent report has suggested that tumor size should be correlated with body surface area (Ferrari et al, 2009). They found that for a given tumor size, the mortality increased from the larger to the smaller body surface area.

IRS-V and current COG rhabdomyosarcoma studies group patients into low-, intermediate-, and high-risk groups. This system combines both the clinical grouping and TNM systems. The system attempts to group patients based on the various prognostic variables known to predict outcome in patients with RMS (Table 137–5). Age is also an independent prognostic factor in children with RMS (Joshi et al, 2004; Meza et al, 2006; Oberlin et al, 2008). **Patients less than 1 year of age and greater than 10 years enrolled in IRS-III and IRS-IV had decreased survival. This poor prognosis persisted after adjustment for other known prognostic factors.**

The preoperative studies needed for determining the extent of disease include chest CT, CT, or MRI of the primary site, and regional lymph nodes, a bone scan, and bone marrow aspiration and/or biopsy.

Table 137–4.

Intergroup Rhabdomyosarcoma Study Group Pretreatment TGNM Clinical Staging Based on Clinical, Radiographic, Laboratory Examination, and Histology of Biopsy

Stage 1: Favorable site, nonmetastatic
Stage 2: Unfavorable, small, negative nodes, nonmetastatic
Stage 3: Unfavorable, big or positive nodes, nonmetastatic
Stage 4: Any site, metastatic

Tumor

T1: Confined to site of origin
T2: Fixation to surrounding tissues
≤5 cm
>5 cm

Histology

G1: Favorable histology (embryonal, botyroid, spindle-cell)
G2: Unfavorable histology (alveolar, undifferentiated)

Regional Lymph Nodes

N0: Regional lymph nodes not clinically involved
N1: Regional lymph nodes clinically involved

Metastases

M0: No distant metastases
M1: Metastases present

Treatment

General Principles

The treatment of RMS has evolved from radical surgical excision. Once it was demonstrated that most patients would survive the disease, investigators explored the use of primary chemotherapy and radiation therapy to avoid exenterative surgery employed for genitourinary RMS (Ortega, 1979; Voute et al, 1981). A major aim of IRS-II (1978 to 1984) and International Society of Paediatric Oncology/Société Internationale D'Oncologie Pédiatrique (SIOP) RMS-75 (1975 to 1984) was preservation of a functional lower urinary tract (Raney et al, 1990). Unfortunately, primary chemotherapy with vincristine, dactinomycin, and cyclophosphamide (VAC) did not obviate the need for radical surgery or radiation therapy for patients with pelvic RMS. The 3-year survival was the same for IRS-II as for IRS-I (Maurer et al, 1993). In IRS-III

Table 137–5.

Rhabdomyosarcoma Risk Groups Based on Prognosis

PROGNOSIS	STAGE	GROUP	SITE	SIZE	AGE	HISTOLOGY	METASTASIS	NODES
Excellent	1	I	Favorable*	a or b†	<21	EMB	M0	N0‡
	1	II	Favorable	a or b	<21	EMB	M0	N0
	1	III	Orbit only	a or b	<21	EMB	M0	N0
	2	I	Unfavorable	a	<21	EMB	M0	N0 or NX
Very good	1	II	Favorable	a or b	<21	EMB	M0	N1
	1	III	Orbit only	a or b	<21	EMB	M0	N1
	1	III	Favorable (excluding orbit)	a or b	<21	EMB	M0	N0 or N1 or NX
	2	II	Unfavorable	a	<21	EMB	M0	N0 or NX
	3	I or II	Unfavorable	a	<21	EMB	M0	N1
	3	I or II	Unfavorable	b	<21	EMB	M0	N0 or N1 or NX
Good	2	III	Unfavorable	a	<21	EMB	M0	N0 or NX
	3	III	Unfavorable	a	<21	EMB	M0	N1
	3	III	Unfavorable	a	<21	EMB	M0	N0 or N1 or NX
	1, 2, or 3	I, II, or III	Favorable or unfavorable	a or b	<21	ALV	M0	N0 or N1 or NX
	4	I, II, III, or IV	Favorable or unfavorable	a or b	<10	EMB	M1	N0 or N1
Poor	4	IV	Favorable or unfavorable	a or b	±10	EMB	M1	N0 or N1
	4	IV	Favorable or unfavorable	a or b	<21	ALV	M1	N0 or N1

*Favorable = orbit/eyelid, head, and neck (excluding parameningeal), genitourinary (not bladder or prostate); unfavorable = bladder, prostate, extremity, parameningeal, trunk, retroperitoneal, pelvis.
†a = tumor size ≤5 cm in diameter; b = tumor size >5 cm in diameter.
‡N0 = regional nodes clinically not involved; N1 = regional nodes clinically involved; NX = node status unknown.
ALV, alveolar rhabdomyosarcoma (RMS), or ectomesenchymoma with alveolar RMS; EMB, embryonal, botryoid, or spindle-cell rhabdomyosarcoma or ectomesenchymoma with embryonal rhabdomyosarcoma.

(1984 to 1991), intensification of therapy using a risk-based study design significantly improved overall treatment outcomes. This required more intensive chemotherapy for stage III tumors, but selected patients were able to receive decreased therapy (Crist et al, 1995).

In IRS-IV (1991 to 1997), patients were stratified for treatment based on site, size, and stage. The role of hyperfractionated radiation therapy and the use of ifosfamide and etoposide was examined. The relapse-free survival (RFS) for patients with embryonal RMS was improved on IRS-IV in comparison with IRS-III (Crist et al, 2001). This was predominantly for stage II/III, group I/II patients (93% versus 76%, $P < .001$). There was no difference in survival rates between patients treated with hyperfractionated or conventional radiation therapy. A review of the tumor response to initial induction chemotherapy at 8 weeks imaging was performed (Burke et al, 2007). The response rate for group III patients was 77% but had no influence on failure-free survival.

IRS-V (1997 to 2007) conducted several studies on children with RMS. Patients with low-risk embryonal/botryoid tumors were treated with the D9602 protocol. In this study, low-stage GU tumors (most bladder/prostate primaries would be excluded because primary complete resection is not done) received vincristine and dactinomycin (VA) for 45 weeks. X-ray therapy (XRT) was not given for stage I tumors. Children with vaginal primaries were reassessed with imaging after chemotherapy was initiated. Endoscopy with biopsy was done at week 28. If no viable tumor was found, chemotherapy alone was continued. Those with viable tumor had resection, if feasible, and XRT only given to those patients with positive margins. If the tumor was not resectable, XRT was given. The results did not show any difference in outcomes from similar patients treated on IRS-III and IRS-IV (Walterhouse et al, 2006).

Intermediate-risk patients were treated with the D9803 protocol. Most patients with bladder/prostate RMS were included in this study. This study evaluated the use of VAC, alternating that regimen with one substituting topetecan for dactinomycin. This regimen did not result in improved outcome compared with IRS-IV (Arndt et al, 2007).

The current COG study for low-risk patients with embryonal/botryoid/spindle cell rhabdomyosarcoma, ARST0331, opened in 2004. This study is evaluating reducing the duration of chemotherapy to 22 weeks for low-stage favorable-site tumors. Shortened duration of chemotherapy has been used by both SIOP and the German Cooperative Soft Tissue Sarcoma Study with good results (Ferrari et al, 2002; Stewart et al, 2003). The initial treatment will consist of VAC followed by VA. The study for intermediate-risk patients is ARST0531. This study will evaluate the role of XRT given at week 4 versus week 10 of treatment. The role of irenotecan will also be addressed.

In the SIOP MMT84 study, radiotherapy was omitted for patients who achieved a complete remission with chemotherapy (Flamant et al, 1998). Unfortunately, this resulted in reduced overall survival compared with IRS-III and IV, largely due to increased local relapse.

The SIOP MMT 89 protocol for treatment of RMS tried to limit the use of radiation therapy (Stevens et al, 2005). They also used tumor response to chemotherapy to stratify patients for therapy. There was a lower 5-year event-free survival (EFS) (64%) in patients who did not receive XRT as part of the initial therapy, but overall survival is comparable to patients receiving XRT. IRS-IV also reported a greater incidence of local recurrences when XRT was omitted (Arndt et al, 2004).

A number of advances have been made by these cooperative group studies, including identification of prognostic factors, for instance, histology, site, biology, and extent of disease (Lawrence et al, 1987; Rodary et al, 1991); reduction or elimination of radiation therapy for special groups or sites (Flamant et al, 1998); reduced need for radical surgery, leading to increased bladder salvage from 25% to 60% (Hays et al, 1993; Arndt et al, 2004; Stevens et al, 2005); and elimination of "routine" lymphadenectomy for some patients with localized paratesticular RMS (Crist et al, 2001; Ferrari et al, 2002). These advances, as they relate to specific genitourinary tumors, are addressed in more detail below.

Specific Sites

Bladder and Prostate Tumors. **Urinary obstruction is a frequent clinical presentation of RMS of the bladder or prostate** (Meir et al, 2004) (Fig. 137–7). **Signs and symptoms include urinary frequency, stranguria, acute urinary retention, and hematuria.** On physical examination, an abdominal mass from either tumor or a distended bladder is often present. Tumors of the bladder usually occur as a botryoid form and grow intraluminally, usually at or near the trigone (Hays, 1982) (Fig. 137–8). Prostatic RMS tends to present as a solid mass rather than the botryoid form seen in the bladder. Determining the actual site of origin can be difficult. Imaging studies show

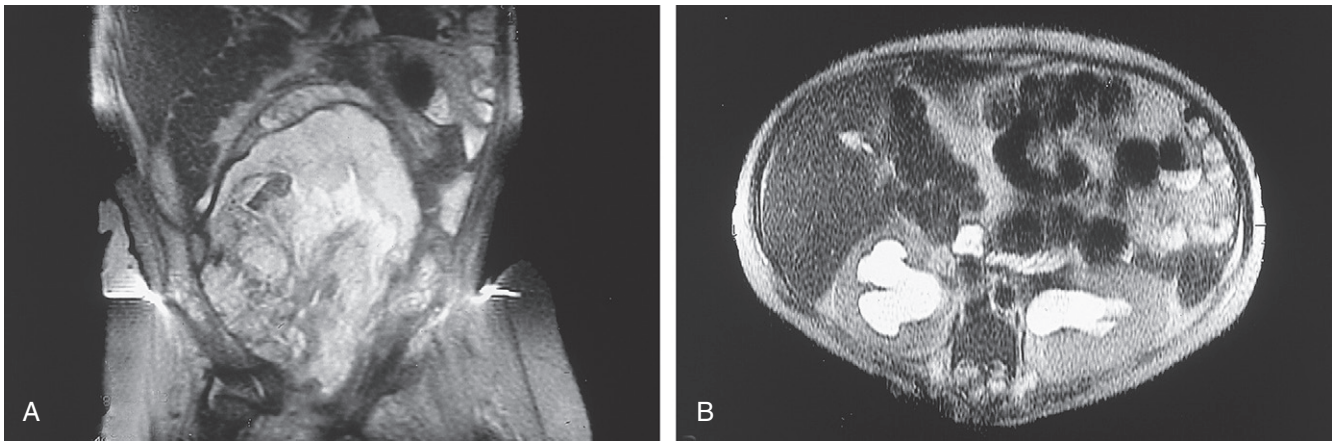


Figure 137–7. MRI of a large prostatic rhabdomyosarcoma extending into the upper abdomen (**A**) with bilateral hydroureteronephrosis (**B**).

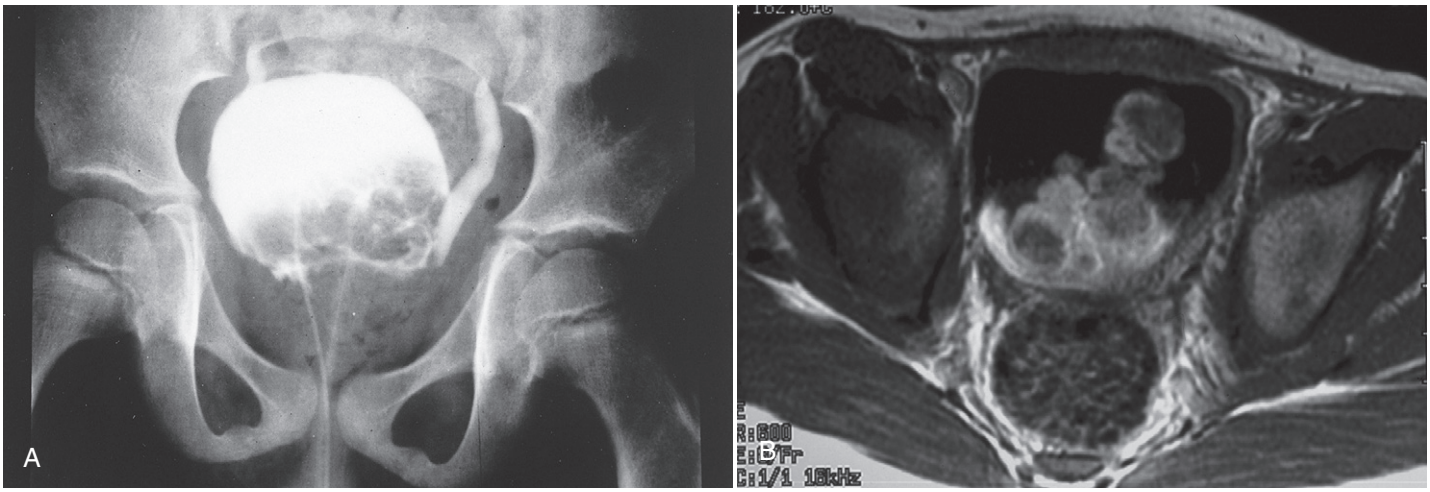


Figure 137–8. **A,** Excretory urogram demonstrating filling defects in the bladder from a botryoid rhabdomyosarcoma. **B,** MRI of botryoid type sarcoma of the bladder. (**A,** Courtesy of Dr. Stanford Goldman.)

filling defects within the bladder or elevation of the bladder base in prostatic RMS. CT/MR can delineate the extent of tumor as well as evaluate the pelvic and retroperitoneal nodes. Cystoscopic evaluation establishes the diagnosis, and transurethral biopsy specimens can be obtained.

As noted above, the treatment of bladder/prostate RMS has become focused on preserving an intact bladder. Most of these tumors arise from the trigonal area or prostate and are not amenable to local or partial resection. Only a small percentage of children with bladder RMS affecting the dome or sides of the bladder distant from the trigone are amenable to partial cystectomy as primary treatment. However, even patients with bulky bladder/prostate RMS can be considered for bladder sparing after multimodal treatment. The IRSG approach is to use both chemotherapy and radiation prior to surgical resection, with the exception of those children amenable to partial cystectomy at diagnosis. Although conservative surgical therapy for bladder/prostate tumors has not been as successful as for vaginal primaries, the bladder salvage rate has increased (Hays et al, 1990; Hays, 1993). With the intensification of treatment for pelvic RMS in IRS-III, 60% of patients retained a functional bladder at 4 years from diagnosis, and overall survival exceeded 85% (Hays, 1995). One concern about a bladder-sparing approach is residual disease after partial cystectomy. Among 22 patients undergoing conservative surgery as primary surgery, there were five cases of local relapse and one of distant relapse (Hays et al, 1990). All patients who relapsed died.

In IRS-IV, there were 88 patients with bladder/prostate primaries, including 17 patients undergoing partial cystectomy as the initial surgical procedure (Arndt et al, 2004). **Most patients had surgery after completion of XRT. Event-free survival at a mean of 6.1 years follow-up was 77%. Overall, the bladder was retained in 55 patients. However, only 36 patients (40%) had no relapse and a normally functioning intact bladder at last follow-up. The reason for the less favorable results, compared with those reported for IRS-III, was attributed to longer follow-up and stricter definition of normal bladder function.** Bladder function was determined by questionnaire, but this was completed in only 65% of patients with a retained bladder. Only one child had undergone urodynamic evaluation. A recent report pooled data on 164 bladder/prostate patients treated on IRS-IV, SIOP MMT-84 and 89, and the German and Italian cooperative groups (Walterhouse et al, 2006). About half the patients had no bladder surgery, and 30% underwent partial cystectomy. They reported that 30% of patients had some urinary incontinence, and half had a history of urinary tract infection. However, it is possible that the incidence of late urinary complications would be underreported in a retrospective chart review.

More objective evaluation of bladder function with urodynamics after multimodal treatment of pelvic RMS has been reported (Yeung et al, 1994). Yeung and colleagues evaluated 11 children treated for pelvic RMS. After a mean follow-up of 6.6 years, the four unirradiated children had normal bladder function. All seven of the children who had undergone irradiation had a markedly reduced functional bladder capacity and abnormal voiding patterns.

Several reports have expressed concern regarding the routine use of radiation therapy prior to surgery for bladder/prostate RMS (Fisch et al, 1995; Meguerian et al, 1998; El-Sherbiny et al, 2000; Filipas et al, 2004). Although radiation is important to prevent local treatment failure, radiation can affect bladder function in children with retained bladders and make subsequent reconstructive procedures more difficult. Merguerian and colleagues (1998) treated 10 patients with group III bladder/prostate RMS. Radiation therapy was reserved only for patients with residual or metastatic disease. They reported a survival rate of 80% among their group III patients, and only four patients received XRT. El-Sherbiny and colleagues (2000) have described a risk-based approach to the treatment of pelvic RMS. The response of the tumor to chemotherapy is used to stratify patients into low-risk patients with a complete or partial response, and high-risk patients with a minimal response to chemotherapy. The latter group undergoes exenterative surgery without any attempt at bladder salvage. The low-risk group had an 85.7%, 5-year, disease-free survival. Low-risk patients were only given radiation for relapse. The Mainz group also recommends assessment of response of the primary tumor to chemotherapy after 7 to 9 weeks (Filipas et al, 2004). If there is less than a one-third reduction in tumor volume, radiation is given before surgery. Patients who have a good response and undergo complete resection do not receive XRT. Filipas and colleagues (2004) believe

this approach provides more complete tumor resection with excellent cure rates. Quality of life can be maintained for patients requiring exenterative surgery with use of continent urinary diversion techniques.

Another approach has been proposed by Martelli and colleagues (2009). They have used conservative surgical resection followed by brachytherapy postoperatively for residual disease in bladder/prostate RMS. Twenty-six boys with a residual mass, postchemotherapy, were managed with either partial prostatectomy and/or cystectomy. Only one child had a cystectomy. Martelli and colleagues (2009) reported only one local relapse. At a median follow-up of 4 years, continence was present in 16 of 18 evaluable patients.

There is a subset of patients with bladder RMS who have a better prognosis. Leuschner and colleagues (2001) found a 92% 10-year survival in patients with botyroid subtype of RMS. Patients with a diffuse endophytic intramural growth had a 68% 10-year survival. Prostatic RMS is associated with a poorer prognosis, and these tumors do not have the botryoid type of growth pattern (Crist et al, 2001; Stevens et al, 2005). Prostatectomy without cystectomy has been performed in selected patients with persistent disease or local relapse (Hays, 1993; Lobe et al, 1996; Meguerian et al, 1998). However, local relapses have occurred in 40% of these patients.

Assessing complete response to therapy after chemotherapy can present challenges. Completeness of surgical resection may be difficult to determine by frozen section. Some patients will have mature rhabdomyoblasts identified on post-treatment biopsy. Several reports of small numbers of patients have suggested that these patients can be safely observed with a low risk for recurrence (Atra et al, 1994; Heyn et al, 1997; Ortega et al, 2000; Smith et al, 2002; Arndt et al, 2006). There is a report of two deaths occurring in patients with mature tumors post-therapy (Leuschner et al, 2001). Also concerning is the finding by Godzinski and colleagues (1994) of a 51% relapse rate in RMS confirmed to have a complete remission by imaging and biopsy. Follow-up of patients with apparent complete remission should include serial imaging, endoscopy, and biopsy if indicated.

Patients undergoing cystectomy will require diversion. Most authors advocate an initial non-refluxing colon conduit followed by later continent reconstruction after completion of therapy (Duel et al, 1996). Other authors have advocated combining continent reconstruction at the time of extirpative surgery (Lander et al, 1992; Meguerian et al, 1998; Rigamonti et al, 2006). There are several concerns regarding early reconstruction. Frozen section may be unreliable in excluding residual disease (Meguerian et al, 1998). Treatment of a subsequent local recurrence could adversely affect reservoir function. Early reconstruction should only be performed if it is certain that no further local therapy will be required (Hensle and Chang, 2000). Enterocystoplasty may be necessary in some patients with contracted bladders from radiation therapy (Hicks et al, 1993; Yeung et al, 1994).

Paratesticular Rhabdomyosarcoma. Among primary genitourinary tumors, 7% to 10% are located in the paratesticular area (Wiener et al, 1994). The peak age of presentation is between 1 and 5 years of age. Paratesticular RMS arises in the distal portion of the spermatic cord and may invade the testis or surrounding tissues. Paratesticular RMS is usually detected earlier than other genitourinary tumors. Presentation is often a unilateral painless scrotal swelling or mass that is usually distinct from the testis. Ultrasonography can confirm the solid nature of the lesion. **At diagnosis, 60% to 80% of paratesticular tumors are stage I, compared with 13% of RMS overall** (Wiener et al, 1994; Wiener et al, 2001; Ferrari et al, 2002). **More than 90% of paratesticular RMS are embryonal in histology and have a good prognosis. Patients with paratesticular RMS with alveolar histology do have a better prognosis than alveolar RMS found at other sites** (Ferrari et al, 2004).

Radical inguinal orchiectomy is recommended for initial treatment. If the tumor is removed through a prior transcrotal procedure, the risk of local recurrence and nonregional lymph node spread is increased. If cord elements remain after a transcrotal procedure, an inguinal exploration with removal of the remaining spermatic cord and a partial hemiscrotectomy, including the prior scrotal incision, is performed (Dall'Igna et al, 2003).

Before effective chemotherapy, surgery alone produced a 50%, 2-year, relapse-free survival (Sutow et al, 1970). With current multimodal treatment, survival rates of 90% are expected (Wiener et al, 1994, 2001; Ferrari et al, 2002; Stewart et al, 2003). An imaging evaluation is performed at diagnosis to detect or exclude metastasis. Extension to retroperitoneal lymph nodes occurs in up to 20% of patients. CT is most frequently used to evaluate the retroperitoneum to identify nodal metastases (Raney et al, 1987). When enlarged nodes are found on CT, 65% to 94% are confirmed as positive by pathology (Wiener et al, 1994; Ferrari et al, 2002). The converse is not always true. A review of 121 IRS-III patients with paratesticular RMS found a 14% false-negative rate of CT (Wiener et al, 1994). More recent studies have noted better accuracy of CT in identifying node-negative patients (Ferrari et al, 2002). Of 72 patients with negative imaging undergoing routine surgical staging, only one patient had positive lymph nodes identified on pathology.

The role of retroperitoneal lymph node dissection (RPLND) in paratesticular RMS has evolved (Olive et al, 1984; Goldfarb et al, 1994; Wiener et al, 1994, 2001; Ferrari et al, 2002). There can be significant morbidity associated with the surgery. Heyn and colleagues (1992) reported a 10% incidence of intestinal obstruction, 8% ejaculatory dysfunction, and edema of the lower extremities in 5% of patients who had undergone RPLND for paratesticular RMS. However, most of these patients underwent bilateral node dissection. A modified unilateral node dissection is appropriate for staging and, with the addition of nerve-sparing techniques, may avoid some of the reported morbidity of node dissection (LaQuaglia et al, 1989; Donohue et al, 1990).

SIOP first suggested elimination of routine RPLND. A cohort of 46 children with completely excised tumors and negative CT or lymphangiogram was managed with intensive chemotherapy alone (Olive-Sommelet, 1989). However, it should be noted that most of the children did receive doxorubicin (DOX) or ifosfamide, which have potential for adverse late effects.

During IRS-III, 121 children with paratesticular RMS were reported who underwent RPLND. The overall 5-year survival for the 98 patients with clinically negative nodes was 96%, and fewer than 10% of patients received doxorubicin or alkylating agents. Patients found to have positive lymph nodes on pathologic evaluation were given radiation to the retroperitoneum, due to the increased risk for relapse (Wiener et al, 1994). In IRS-IV, children with clinically negative nodes were treated primarily with chemotherapy. This resulted in a higher percentage of group I patients in comparison with IRS-III, 82% versus 68% (Wiener et al, 2001) However, adolescents were at higher risk of retroperitoneal relapse than were children less than 10 years of age, and their RFS and OS were worse. Adolescents with group I tumors on IRS-IV had a 68% RFS. This compares with a 100% survival of adolescents with group II tumors who received radiotherapy and intensified

chemotherapy. **The current COG protocols recommend that children 10 years of age and older should have ipsilateral RPLND as part of their routine staging prior to chemotherapy.** Patients with positive lymph nodes require intensified chemotherapy as well as nodal irradiation (Wiener, 2001).

The Italian and German cooperative group treated 106 low-risk patients with chemotherapy only, avoiding RPLND (Ferrari et al, 2002). Low-risk patients were defined as favorable histology, T1N0M0, and clinical group 1. Since 1988, these patients only received vincristine (VCR) and dactinomycin (AMD). The five-year survival was 99.1%. This study did also note a higher rate of retroperitoneal relapse in adolescents. SIOP treated low-risk patients with chemotherapy only in the MMT 84 and 89 studies (Stewart et al, 2003). Of 156 clinical stage I patients, 14 developed relapse. Patient age greater than 10 years and primary tumor size greater than 5 cm were identified as predictors for relapse. The larger tumors occur more often in adolescents, suggesting a delayed presentation.

Vaginal, Vulvar, and Uterine Rhabdomyosarcoma. Vaginal and vulvar RMS generally present in the first few years of life, with vaginal bleeding, discharge, or a vaginal mass. The clinical presentation can be quite striking, if there is prolapse of the mass from the vaginal introitus (Fig. 137–9). Uterine RMS may present in two ways—as a tumor originating from the cervix with vaginal bleeding or mass or as a tumor originating in the uterine body and presenting as an abdominal mass. The diagnosis is made by vaginoscopy and biopsy of the lesion. The vaginal lesions usually arise from the anterior vaginal wall in the area of the embryonic vesicovaginal septum (urogenital sinus). Vaginal tumors may invade the vesicovaginal septum or bladder wall because of their proximity. Cystoscopy is warranted during initial evaluation and at intervals during follow-up (Andrassy et al, 1994).



Figure 137–9. Mass protruding from the vaginal introitus in a young girl with vaginal rhabdomyosarcoma.

Vaginal and uterine lesions generally have embryonal or botryoid embryonal histology and have an excellent prognosis (Andrassy et al, 1994; Corpron et al, 1995; Martelli et al, 1999; Arndt et al, 2001). Vulvar lesions may have alveolar histology, but because most are localized, they also have a good prognosis. In addition to biopsy, staging requires a search for metastases, including pelvic examination and CT scans of the pelvis, abdomen, and chest and examination of the bone marrow, cystoscopy, and vaginoscopy.

Anterior pelvic exenteration was frequently employed to treat these patients in the past. With the development of effective chemotherapy, attempts to preserve the vagina and uterus have become a priority. Definitive surgery is delayed until after an initial course of therapy (Hays et al, 1988; Andrassy et al, 1994; Corpron et al, 1995; Martelli et al, 1999; Arndt et al, 2001). Once an adequate response is demonstrated, repeat biopsies are performed. If there is persistence of disease, delayed tumor resection is performed. This may consist of partial vaginectomy or vaginectomy with hysterectomy. In IRS-III, 24 patients with vaginal primaries were treated with a primary chemotherapy protocol. At subsequent surgery, seven patients underwent partial or complete vaginectomy. Six of these seven patients had no viable tumor in the resected specimen, and one had maturing rhabdomyoblasts. The presence of mature rhabdomyoblasts due to differentiation of chemotherapy may not signify persistent active cancer (see discussion above) (Heyn et al, 1997; Ortega et al, 2000; Smith et al, 2002; Arndt et al, 2006).

Older studies reported that uterine RMS occurs in a distinct group of patients who present at an older age and have less response to treatment and thus poorer prognosis than those with vaginal RMS (Hays et al, 1981, 1985). However, more recent reports suggest that patients with uterine RMS were of the same age group, mean age 5.5 years, as the vaginal RMS patients (Arndt et al, 2001).

During IRS-IV (1988 to 1996), the rate of hysterectomy was only 26% compared with 48% in IRS-I and -II (Arndt et al, 2001). Greater than 50% of patients did receive XRT for local tumor control in IRS-IV. This probably reflects the attempt to achieve a complete response without surgery. Only 3 of 21 patients (13%) underwent surgical resection after primary chemotherapy. Age at diagnosis of 1 to 9 years, botryoid histology, and localized disease were predictive of a good prognosis (Andrassy et al, 1999; Arndt et al, 2001).

SIOP also uses initial chemotherapy for vaginal RMS. Only 12% of their patients treated on MMT84 and MMT 89 required hysterectomy. XRT was used in 11 girls, but seven received intracavitary brachytherapy. Eleven girls did not require any local therapy, surgery, or XRT after chemotherapy (Martelli et al, 1999).

Treatment of pelvic RMS in females can result in significant late complications. Most of the complications are due to the use of XRT, but late complications of chemotherapy are also noted. Spunt and colleagues (2005) reported on 26 females treated for pelvic RMS who were free of disease for 5 years. Fourteen patients required surgery for treatment of complications related to treatment of the RMS. This included vaginal dilation/reconstruction to correct stenosis, procedures to relieve ureteral obstruction, intestinal stricture dilation or repair, and fistula repair. Twenty of the 28 patients had endocrine late effects; ovarian failure was the most common complication. Late urinary complications included ureteral obstruction, cystectomy, neurogenic bladder, and urethral stricture. Magne and colleagues (2008) reported on

the late effects in 39 girls treated for vaginal and vulvar RMS. For patients treated after 1990, they noted a 20% incidence of vaginal stenosis. Brachytherapy was employed in these patients, and the authors attribute the low complication rate to the judicious use of brachytherapy.

Key Points: Rhabdomyosarcoma

- Embryonal RMS is the most common subtype of genitourinary RMS. It can present as sarcoma botryoides, a polypoid variety that occurs in hollow organs or body cavities, such as the bladder or vagina.
- Sixty to 80 percent of paratesticular RMS is stage I at diagnosis. Patients older than 10 years have a higher risk for retroperitoneal relapse and should undergo staging with ipsilateral retroperitoneal lymph node dissection (RPLND) before chemotherapy.
- An organ-sparing approach is preferred for bladder and genital RMS. Vaginal and uterine primaries are associated with a good prognosis.

WILMS TUMOR

Wilms tumor, or nephroblastoma, is the most common primary malignant renal tumor of childhood. This embryonal tumor develops from remnants of immature kidney. Athough an excellent outcome is now expected for most children, there are subgroups of high-risk patients for whom more effective treatment is needed. Treatment of patients with nephroblastoma has been extensively investigated in a number of large randomized clinical trials in North America and Europe. Current management now emphasizes reducing the morbidity of treatment for low-risk patients by reserving more intensive treatment for those high-risk patients for whom survival remains poor. This section will outline current recommendations for treatment and review the latest developments in the biology of Wilms tumor.

Epidemiology

Wilms tumor accounts for 6% to 7% of all childhood cancers. In children less than 15 years of age, the annual incidence rate is about 7 to 10 cases per million (Breslow et al, 1993; Bernstein et al, 1999). More than 80% of cases are diagnosed before 5 years of age, with a median age of 3.5 years. Nevertheless, older children and, occasionally, even adults can be affected (Arrigo et al, 1990; Kalapurakal et al, 2004a). The median age at diagnosis is lower in children with bilateral Wilms tumor (Breslow et al, 1993). Wilms tumor presents at an earlier age among males with both unilateral and bilateral tumors.

In North America, Wilms tumor is slightly more frequent in females than in males. With regard to ethnicity, the incidence of Wilms tumor is lower in East Asian populations and higher in black populations compared with the incidence reported for North American and European whites (Breslow et al, 1994; Fukuzawa et al, 2004). However, the approximately three- to fourfold ratio of the maximum-to-minimum rate worldwide is substantially less than the ratios of 10 to 20 typically observed for adult epithelial tumors. The fact that such variations exist more closely associated with race than geography suggests that environmental risk factors likely play a minor etiologic role, certainly in comparison with adult epithelial cancers (Breslow et al, 1993). Several epidemiologic studies have investigated occupational, environmental, and lifestyle factors as risk factors for Wilms tumor. Although some studies have suggested that a number of parental exposures might be associated with an increased risk of Wilms tumor, very few have been found conclusively associated (Breslow et al, 1993).

Biology

Children with Wilms tumor have been extensively studied to determine the role of genetic alterations in tumor development. It is now recognized that the majority of Wilms tumors arise from somatic mutations restricted to tumor tissue, and a much smaller percentage originate from germline mutations (Ruteshouser et al, 2008). It is apparent that several genetic events result in Wilms tumorigenesis and that the Knudson two-hit model of cancer formation does not explain most cases (Knudson and Strong, 1972b). Approximately 10% of children with Wilms tumor have congenital anomalies and syndromes, 5% to 10% of tumors are bilateral/multicentric, and 1% to 2% are familial. These subsets of patients are the ones in whom the most thorough evaluation for genetic abnormalities has been conducted (Table 137–6).

WT1

WT1 was the first Wilms tumor gene to be identified. **The identification and subsequent cloning of *WT1* resulted from cytogenetic observations of gross deletions at chromosome 11p13 in patients with the WAGR (*Wilms tumor, *Aniridia, *Genital anomalies, mental *R*etardation) syndrome.** These children were shown to have heterozygous germline deletions at 11p13 (Riccardi et al, 1978). Subsequent molecular analysis of the DNA mapping of this specific region led to the identification of the *WT1* in 1990 (Bonetta et al, 1990; Call et al, 1990). Aniridia, found in 1.1% of Wilms tumor patients, is caused by an abnormality of the *PAX6* gene located adjacent to the *WT1*

Table 137–6.

Syndromes Associated with Development of Wilms Tumor

SYNDROME	GENES	LOCUS	WILMS TUMOR RISK
WAGR	*WT1*	11p13	50%
Denys-Drash	*WT1*	11p13	50%
Frasier	*WT1*	11p13	5%-10%
Beckwith-Wiedemann	*WT2*	IGF-2, H19, p57, KIp2	5%-10%
Familial Wilms tumor	*FWT1*	17q21	30%
	FWT2	19q13	
Perlman	Unknown		>20%
Mosaic variegated aneuploidy	*BUB1B*	15q15	>20%
Fanconi anemia D1	*BRCA2*	13q12.3	>20%
Simpson-Golabi-Behmel	*GPC3*	Xq26	10% (in males)
Li-Fraumeni	*TP53*	17p13	Low
Neurofibromatosis	*NF1*	17q11	Low
Sotos	*NSD1*	5q35	Low
Trisomy 18	Unknown	18	Low
Bloom	*BLM*	15q26	Low

gene. Aniridia patients with visibile (microscopic) chromosomal deletions that include *WT1* were noted to be prone to the development of Wilms tumor (Muto et al, 2002). Fluorescence in-situ hybridization (FISH) analysis of aniridia patients has been used to identify submicroscopic deletions of *WT1* and is also a useful predictor of Wilms tumor development (van Heyningen et al, 2007). Wilms tumor will develop in approximately 40% to 70% of aniridia patients with deletions of *WT1*. Conversely, aniridia patients with normal *WT1* do not develop Wilms tumor (Grenskov et al, 2001; van Heyningen et al, 2007).

The *WT1* gene is important for normal kidney and gonadal development. *WT1* encodes a zinc-finger transcription factor that is expressed in the kidney, gonads, spleen, and mesothelium (Pritchard-Jones, 1990, Dressler GR, 1995). *WT1* is necessary for ureteric bud outgrowth and is also important in nephrogenesis. Targeted mutation of the *Wt1* gene in mice results in failure of kidney and gonadal development (Kreidberg et al, 1997). **The Denys-Drash syndrome (DDS) is the specific association of male pseudohermaphroditism, renal mesangial sclerosis, and nephroblastoma** (Drash et al, 1970). The syndrome is caused by point mutations in the zinc-finger DNA binding region of *WT1* (Coppes et al, 1993). More than 90% of DDS patients harbor germline point mutations in only one *WT1* allele (Pelletier et al, 1991; Coppes et al, 1992). Therefore the *WT1* mutation acts dominantly with respect to genitourinary abnormalities. The fact that the phenotype resulting from these heterozygous mutations is far more severe than that resulting from constitutional deletion of one *WT1* allele (i.e., WAGR patients), suggests that the Denys-Drash mutations do not result in inactivation of the WT1 protein but rather in the production of a dysfunctional WT1 protein. It is postulated that this abnormally expressed protein alters regulation of transcription and urogenital development. The majority of these patients progress to end-stage renal disease. Nephropathy usually presents early in life and renal biopsy demonstrates mesangial sclerosis. Some *WT1* mutations can lead to an incomplete DDS phenotype, with varying degrees of genitourinary anomalies, renal pathologies, and penetrance of Wilms tumor (McTaggart et al, 2001). Although XY individuals have been reported most often, the DDS has been reported in genotypic/phenotypic females. WAGR and DDS patients are more likely to have bilateral tumors and are diagnosed at a younger age (Breslow et al, 2003).

This risk for renal insufficiency in DDS is shared by children with WAGR, both being diseases associated with a *WT1* mutation. **WAGR patients have an increased risk of renal failure if they survive into puberty** (Breslow et al, 2000, 2005). Recent studies of nontumoral renal tissue in children with WAGR and DDS have demonstrated smaller glomerular diameters than in controls (Dahan et al, 2007). This suggests a specific defect of WT1 function during renal development that leads to susequent deterioration in renal function with age.

WT1 was orginally considered to be a classic tumor suppressor gene, and the loss of both copies or mutations of this gene would lead to Wilms tumor development (Rauscher, 1993). Although this may be the case for some tumors, only 20% of patients with Wilms tumor have a mutation in the germline or in tumor tissue (Diller et al, 1998; Ruteshouser et al, 2008). Genitourinary anomalies (renal fusion anomalies, cryptorchidism, hypospadias) are present in 4.5% of patients with Wilms tumor (Breslow et al, 1993). Patients with genitourinary anomalies have an increased risk for carrying a constitutional *WT1* mutation (Diller et al, 1998). The incidence of *WT1* mutations in patients with Wilms tumor not associated with any genitourinary abnormality is approximately 2% (Little et al, 2004). Although there is no distinguishing phenotype for these patients, they do have an earlier age of onset and a stromal predominant histology. *WT1* is involved in regulation of other genes, many of which are involved in cell growth, differentiation, and apoptosis (Lee and Haber, 2001). It remains unclear which of these are most important for tumorigenesis. The WNT/β-catenin signaling pathway is likely involved, because activating mutations of the β-catenin gene (*CTNNB1*) are found in more than half of the Wilms tumors with the *WT1* mutation (Li et al, 2004).

WT2

There are a number of syndromes with overgrowth features at risk for the development of Wilms tumor, including hemihypertrophy, which may occur alone or as part of the Beckwith-Wiedemann syndrome (BWS), Perlman, Sotos, and the Simpson-Golabi-Behmel syndromes (Perlman et al, 1975; Neri et al, 1998). BWS is characterized by excess growth at the cellular, organ (macroglossia, nephromegaly, hepatomegaly), or body segment (hemihypertrophy) levels (Beckwith, 1969, Wiedemann, 1983). Most cases of BWS are sporadic, but up to 15% exhibit heritable characteristics with apparent autosomal dominant inheritance. **The risk of nephroblastoma in children with BWS and hemihypertrophy is estimated to be 4% to 10%, with 21% of children presenting with bilateral disease** (Beckwith, 1996; Debaun and Tucker, 1998; Porteus et al, 2000). Adrenocortical neoplasms and hepatoblastoma also occur with increased frequency in BWS. Children with BWS found to have nephromegaly (kidneys greater than or equal to the 95th percentile of age-adjusted renal length) are at the greatest risk for the development of Wilms tumor (Debaun et al, 1998). More recently, investigators have been able to correlate genetic changes to identify which BWS patients are at risk for Wilms tumor development (DeBaun et al, 2002; Bliek et al, 2004). The mean age at diagnosis of Wilms tumor in BWS and hemihypertrophy patients is similar to that of the general Wilms tumor population (Breslow et al, 1993). Vaughan and colleagues reported a 100% survival among BWS patients with Wilms tumors and noted that all had favorable histology (Vaughan et al, 1995).

A second Wilms tumor gene, *WT2,* was identified at the 11p15 locus due to the finding of loss of heterozygosity (LOH) at this site (Koufos et al, 1989; Mannens et al, 1990). **The *WT2* gene has been linked to the BWS** (Koufos et al, 1989). The WT2 locus has been extensively studied and a number of genes have been identified including *H19* and *IGF-2* (Bjornson et al, 2007). The latter genes are of importance in the epigenetic theory of cancer etiology. Epigenetic changes are modifications of the genome that do not involve a change in DNA sequence (Feinberg, 2004). *IGF-2* encodes an embryonal growth factor that is normally expressed solely from the paternal allele. The overexpression of IGF-2 can arise through duplication of the paternal allele or through abnormal expression from the maternal allele called loss of imprinting (LOI). Because *IGF-2* induces cell growth, increased expression of this imprinted gene could conceivably contribute to the development of both Wilms tumor and BWS. Loss of imprinting (LOI) of *IGF-2* was first identified in Wilms tumor and is overexpressed in a number of malignancies (Rainier et al, 1993; Feinberg, 2004). It is speculated that Wilms tumors that occur at a later age are the result of these epigenetic changes, such as LOI for *IGF-2* (Ravenel et al, 2001).

Ravenel and colleagues (2001) correlated LOI for *IGF-2* and LOH of *WT1* with pathologic findings and age in patients with Wilms

tumor. They found LOI of *IGF-2* in 9 of 10 (90%) Wilms tumors classified as having a pathologic subtype associated with a later stage of renal development, from perilobar nephrogenic rests (PLNR), and in only 1 of 15 (6.7%) Wilms tumors with a pathologic subtype associated with an earlier stage of renal development, from intralobar nephrogenic rests (ILNR). Remarkably, all 9 (100%) of the tumors that showed LOH of 11p were ILNR-like. Furthermore, none of 12 PLNR-like tumors showed LOH of 11p. This is consistent with an earlier observation that tumors with ILNRs are associated with LOH (Grundy et al, 1996). (See discussion below on nephrogenic rests.) Children whose Wilms tumors displayed LOI of *IGF-2* were statistically significantly older at diagnosis (median of 65 months) than children whose tumors displayed normal imprinting.

WTX

Recently, a previously uncharacterized tumor suppressor gene, otherwise known as the *W*ilms *T*umor gene on the *X* chromosome, or *WTX* at Xq11.1, was found to be inactivated in up to one third of Wilms tumors (Rivera et al, 2007). *WTX* is inactivated by a monoallelic, or "single-hit" event rather than by the classical biallelic inactivation of autosomal tumor suppressor genes. It targets the single X chromosome in males and the active X chromosome in females with tumors, and it occurs at comparable frequencies in males and females alike. Initially, it was reported that tumors caused by *WTX* mutations lack *WT1* mutations. Subsequently, it has been observed that *WTX* mutations occur with equivalent frequency in tumors with or without mutations in *WT1* and *CTNNB1* (Ruteshouser et al, 2008). *WTX,* similar to *WT1,* appears to play a role in the WNT/β-catenin signaling pathway. Mutations in *WT1, WTX,* and *CTNNB1* provide the genetic basis for about one third of Wilms tumors.

Familial Wilms Tumor

As noted above, 1% to 2% of Wilms tumor patients have a family history of Wilms tumor (Green et al, 1982; Ruteshouser and Huff, 2004). Familial cases have an earlier age of onset and an increased frequency of bilateral disease. Two familial Wilms tumor genes have been localized (Ruteshouser and Huff, 2004). *FWT1* is located at 17q12-q21 and *FWT2* at 19q13.4 (Rahman et al, 1996; McDonald et al, 1998). Penetrance of these genes appears to be moderate, and these genes do not follow the typical tumor suppressor gene pattern of loss of heterozygosity (Strong, 2003).

Other Chromosomal Abnormalities

Mutations of the tumor suppressor gene *TP53* are frequently encountered genetic events in human cancer (Hollstein et al, 1991). Studies of *TP53* mutations in Wilms tumor have shown an increased frequency in patients with anaplastic histology (Bardeesy et al, 1994). They also have been correlated with advanced-stage disease (Malkin et al, 1994; Sredni et al, 2001), but indexing of *TP53* expression has not been shown to be an independent prognostic factor (Skotnicka-Klonowicz et al, 2001).

Loss of the long arm of chromosome 16 has been found in approximately 20% of Wilms tumors (Maw et al, 1992), suggesting the presence of a gene at 16q involved in the biology of Wilms tumor. Similarly, loss of the short arm of chromosome 1p has been found in approximately 10% of cases (Grundy et al, 1994). **LOH at 1p and 16q are associated with an increased risk of tumor relapse and death** (Grundy et al, 1994, 2005; Wittman et al, 2007). However, the prognostic significance of these features has been questioned (Bown et al, 2002). Confirming the utility of LOH of 16q and 1p to predict outcome was one of the major objectives of the fifth National Wilms Tumor Study (NWTS) (see discussion below). LOH of chromosome 11q is noted in approximately 20% of tumors. LOH of 11q is 3 to 4 times more frequent in anaplastic tumors (Wittman et al, 2007). There is a correlation with tumor recurrence and death, but only for tumors that lost the entire long arm of chromosome 11.

Screening

Screening with serial renal ultrasonography has been recommended in children at high risk for development of Wilms tumor. Review of most studies suggests 3 to 4 months is the appropriate screening interval. Tumors detected by screening will generally be a lower stage (Green et al, 1993; Choyke et al, 1999). No studies, to date, have demonstrated that early detection has improved patient survival. Early detection can provide an opportunity for nephron-sparing surgery, because these children are at an increased risk for bilateral disease. The smaller tumors found on screening studies are more amenable to renal-sparing surgery (Fig. 137–10). The Wilms Tumor Surveillance Working Group from the United Kingdom recommended conducting screening when a condition has a WT incidence of greater than 5% (see Table 137–6) (Scott et al, 2006). Screening of the contralateral kidney following nephrectomy for unilateral Wilms tumor is also recommended (D'Angio et al, 1993). Infants less than 12 months of age found to have nephrogenic rests in the resected kidney are at the greatest risk for metachronous tumors (Coppes et al, 1999). Ultrasound surveillance is performed from time of diagnosis until 5 years of age, with a frequency of every 3 to 4 months. Those who have BWS, Simpson-Golabi-Behmel, and familial Wilms histories should continue to 7 years (Scott et al, 2006). CT or MRI should be performed if US demonstrates a suspicious lesion. Nonmalignant renal lesions, such as renal cysts, do occur at an increased rate in children with BWS, and recognition of these is important to avoid unnecessary nephrectomy when new lesions are identified on screening ultrasonography (Borer et al, 1999; Choyke et al, 1999).

An association between Wilms tumor and horseshoe kidney has been noted. A review of National Wilms Tumor Study Group (NWTSG) patients found that there was a sevenfold increased risk of developing a Wilms tumor in patients with a horseshoe kidney (Mesrobian et al, 1985). The diagnosis of horseshoe kidney can be missed on preoperative imaging due to the location of the tumor (Neville et al, 2002). Wilms tumor has been reported in patients with multicystic dysplastic kidney, but there is not sufficient evidence that this occurs at an incidence greater than for children with two normal kidneys (Narchi, 2005). There is an increased risk of müllerian duct anomalies in girls with Wilms tumor (Byrne and Nicholson, 2002). Approximately 10% of girls will have abnormalities, such as duplication of the cervix or uterus, or bicornuate uterus.

Pathology

Pathologists have made important contributions to the study of both the clinical behavior and biology of Wilms tumor (Beckwith and Palmer, 1978; Beckwith, 1983; Weeks et al, 1987; Zuppan et al, 1991; Schmidt and Beckwith, 1995; Ravenel et al, 2001; Vujanic et al, 2002). Wilms tumor is characterized by tremendous histologic diversity, and classification of childhood tumors can be difficult. As noted in the discussion above, correlation of the

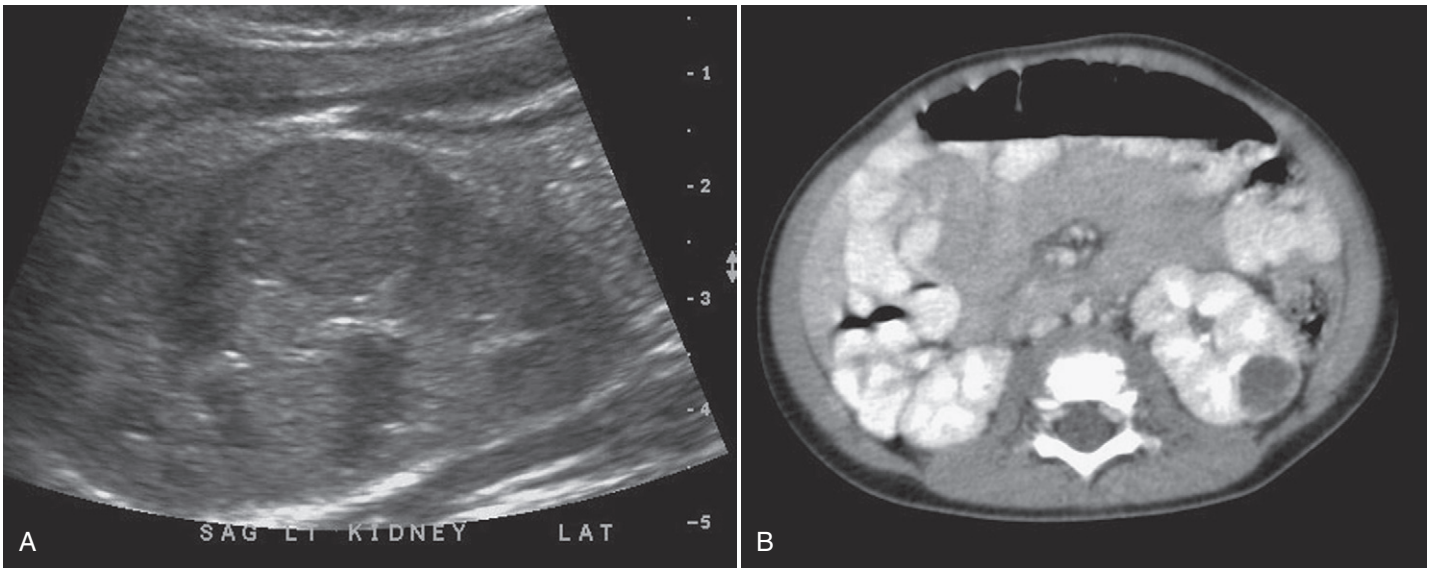


Figure 137–10. Small renal tumor found on serial screening. **A,** Ultrasonogram shows solid lesion just pushing out from the cortex. **B,** CT demonstrates that lesion is amenable to renal-sparing surgery.

pathologic findings with genetic events are improving our understanding of the development of Wilms tumor.

Favorable-Histology Wilms Tumor

Wilms tumor usually compresses the adjacent normal renal parenchyma, forming a pseudocapsule composed of compressed, atrophic renal tissues. This intrarenal pseudocapsule can be helpful in distinguishing Wilms tumor from nephrogenic rests and other renal tumors. The texture of the tumors varies, depending on the predominant histologic pattern. Many are soft and friable with necrotic or hemorrhagic areas frequently noted. This consistency increases the risk of intraoperative tumor rupture. Most Wilms tumors are unicentric, but 12% are multicentric unilateral tumors (Breslow et al, 1988a). Extrarenal Wilms tumor arising in the retroperitoneum and elsewhere are rare and are thought to arise from displaced metanephric elements or mesonephric remnants. Derived from primitive metanephric blastema, Wilms tumor is characterized by tremendous histologic diversity (Beckwith and Palmer, 1978). In addition to expressing a variety of cell types found in a normal developing kidney, Wilms tumor often contains tissues such as skeletal muscle, cartilage, and squamous epithelium. These heterotopic cell types likely reflect the primitive developmental potential of metanephric blastema that is not expressed in normal nephrogenesis. **The "classical" Wilms tumor is characterized by islands of compact undifferentiated *blastema* and the presence of variable *epithelial* differentiation in the form of embryonic tubules, rosettes, and glomeruloid structures separated by a significant *stromal* component** (Fig. 137–11). The proportion of each of these components varies from infrequent to abundant within and among individual tumors. Some Wilms tumors, however, are not triphasic but present only biphasic or even monomorphous patterns, and the latter can present diagnostic difficulties (Schmidt and Beckwith, 1995). **Wilms tumors with predominantly epithelial differentiation have a low degree of aggressiveness, and the majority are stage I tumors (Beckwith et al, 1996). However, these tumors may be more resistant to therapy, if they present as advanced-stage disease.**

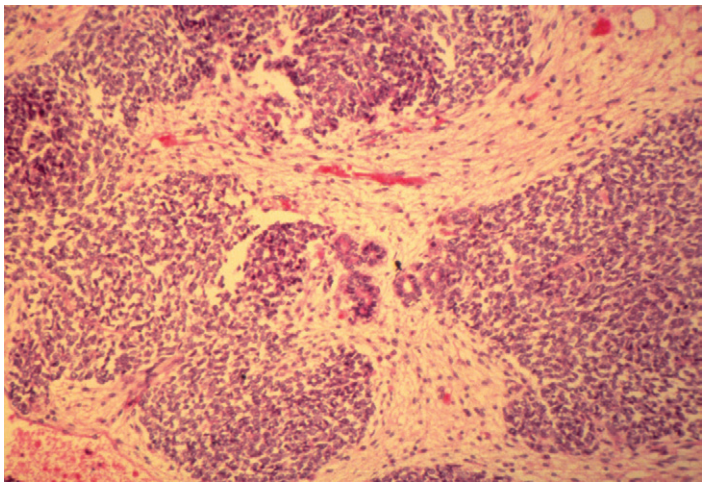


Figure 137–11. Typical Wilms tumor with blastemal, epithelial, and stromal components.

Anaplastic Wilms Tumor

Identification of tumors with unfavorable histologic features, such as anaplasia, was an important milestone accomplished by the inclusion of the central pathologic review of the National Wilms Tumor Study Group protocols (Beckwith and Palmer 1978; Bonadio et al, 1985; Zuppan et al, 1988). It has allowed progressive use of adjuvant therapies in the sequential studies based on the risk and response of the various pathologic tumor types. Anaplasia is characterized by the presence of three abnormalities: nuclear enlargement to three or more times the diameter of the adjacent cells, hyperchromasia of enlarged nuclei, and abnormal mitotic figures. Anaplasia is rarely seen in tumors of patients younger than 2 years at diagnosis (incidence about 2%), but its presence increases to a relatively stable incidence of about 13% in those older than 5 years (Bonadio et al, 1985). **Anaplasia is associated with resistance to chemotherapy.** This is evidenced by the similar incidence of anaplasia (5%) in the NWTSG and SIOP studies (Vujanic

et al, 1999). **The presence of anaplasia has clearly been demonstrated to carry a poor prognosis, even when the tumor is apparently confined to the kidney in stage I** (Dome et al, 2006). Anaplasia has been further divided into focal and diffuse patterns, to reflect further the different prognosis of anaplasia that is present throughout the kidney or in an extrarenal location (Faria et al, 1996).

Nephrogenic Rests

More than one third of kidneys resected for Wilms tumor contain precursor lesions, known as nephrogenic rests (NR) (Beckwith et al, 1990; Beckwith, 1993). Nephrogenic rests have a varied natural history, and most do not form Wilms tumor. A rest can undergo maturation, sclerosis, involution, or complete disappearance. Nephrogenic rests have also been detected in 1% of kidneys in infants on postmortem exam, a much higher incidence than that of Wilms tumor. Hence, most apparently undergo involution (Beckwith, 1998).

NRs can be separated into two fundamentally distinct categories: *perilobar nephrogenic rests* (PLNRs) and *intralobar nephrogenic rests* (ILNRs) (Beckwith et al, 1990). These two types of NRs are distinguished by their location within the renal lobe (Fig. 137–12). Relative position within the lobe is a direct reflection of the chronology of the embryologic development of the kidney. **PLNRs are found only in the lobar periphery, which is elaborated late in embryogenesis, while ILNRs are found anywhere within the lobe, as well as the renal sinus and the wall of the pelvicalyceal system.** Therefore ILNRs are generally believed to be the result of earlier gestational aberrations (Beckwith et al, 1998). ILNRs are commonly stroma rich and intermingle with the adjacent renal parenchyma. PLNR are usually subcortical, sharply demarcated, and contain predominantly blastema and tubules. Of particular interest is the observation that PLNRs are usually found in children with BWS, linked to the 11p15 Wilms locus, while ILNRs are typically seen in children with aniridia, WAGR, and DDS or other features associated with *WT1* (Table 137–7). The age at diagnosis is lower for Wilms tumor associated with *WT1* mutations, and those arising in association with ILNR. These tumors have a stromal-predominant histology with varying degrees of rhabdomyogenesis (Fukuzawa et al, 2008).

Multiple rests in one kidney usually implies that NRs are present in the other kidney (Beckwith, 1990). **Children less than 12 months of age who are diagnosed with Wilms tumor and also have NRs, in particular PLNRs, have a markedly increased risk of developing contralateral disease and require frequent and regular surveillance for several years** (Coppes et al, 1999). Surveillance is also recommended for those diagnosed after 12 months of age who have NRs (D'Angio et al, 1993). The occurrence of metachronous Wilms tumor in patients previously treated with conventional chemotherapeutic regimens suggests that nephrogenic rests are not always eradicated.

NRs display a spectrum of appearances. Hyperplastic NRs can produce a renal mass that can be mistaken for a small Wilms tumor (Beckwith, 1998). Incisional biopsy of a hyperplastic rest is of little value in distinguishing this lesion from a Wilms tumor, unless the interface between the rest and normal kidney is included. Wilms tumor will have a pseudocapsule at the interface with the normal parenchyma compressing the normal elements. The appearance of the lesion can provide some help in distinguishing between NR and Wilms tumor. The Wilms tumor will have a spherical shape, while hyperplasic rests will retain the appearance of the orginal rest and be more elliptical or lenticular in shape. MRI may be of some value in distinguishing between the two lesions, but this needs to be confirmed prospectively in large numbers of patients (Rohrschneider et al, 1998; Hoffer, 2005).

Nephroblastomatosis refers to the presence of multiple nephrogenic rests. Diffuse overgrowth of PLNRs may produce a thick rind that enlarges the kidney but preserves its original shape (Fig. 137–13). Patients with nephroblastomatosis are prone to Wilms tumor development, and

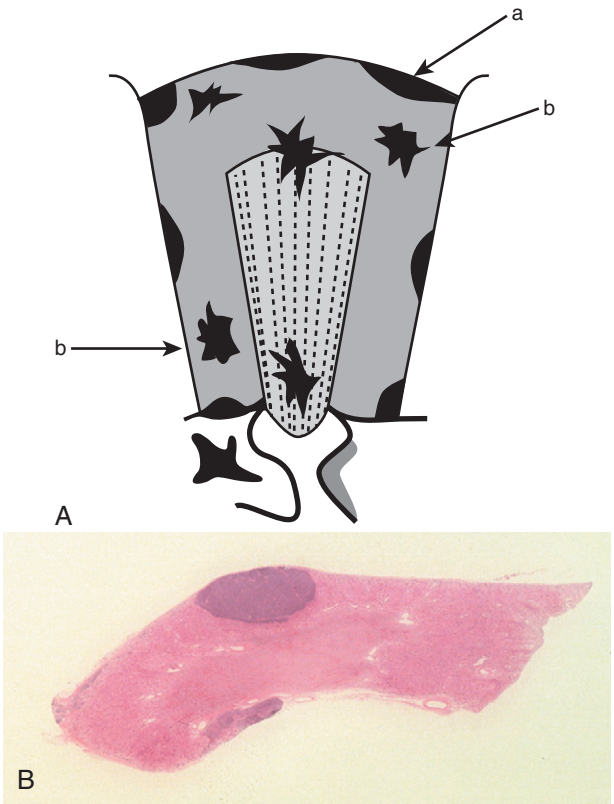


Figure 137–12. **A,** Illustration of renal lobe showing characteristic locations of perilobar nephrogenic rest (*a*) and intralobar nephrogenic rest (*b*). **B,** Perilobar nephrogenic rest composed of blastemal cells just beneath the renal capsule (hematoxylin and eosin, magnification ×40). (**A**, From Beckwith JB. Precursor lesions of Wilms tumor: clinical and biological implications. Med Pediatr Oncol 1993;21:158–68.)

Table 137–7.

Approximate Prevalence of Nephrogenic Rests

PATIENT POPULATION	PLNR (%)	ILNR (%)
Infant autopsies	1	0.01
Renal dysplasia	3.5	Unknown
Unilateral Wilms tumor	25	15
Synchronous bilateral Wilms tumor	74-79	34-41
Metachronous bilateral Wilms tumor	42	63-75
Beckwith-Wiedemann, hemihypertrophy	70-77	47-56
Aniridia	12/20	84-100
Drash syndrome	11	78

ILNR, intralobar nephrogenic rests; PLNR, perilobar nephrogenic rests.
Modified from Beckwith JB. Precursor lesions of Wilms tumor: clinical and biological implications. Med Pediatr Oncol 1993;21:158–68.

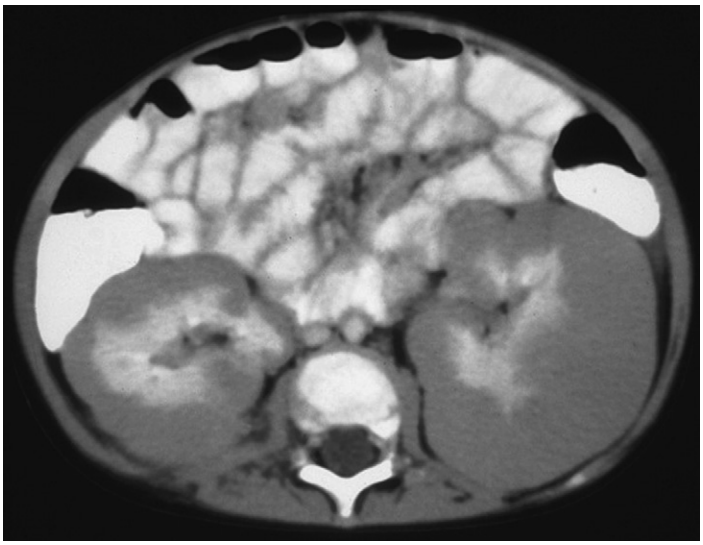


Figure 137–13. Typical appearance of DHPLNR (diffuse hyperplastic perilobar nephrogenic rests) with thick rind compressing the normal renal tissue centrally.

bilateral lesions are common. Perlman and colleagues (2005) have reviewed 52 cases of diffuse hyperplastic perilobar nephrogenic rests reported to the NWTSG pathology center. Wilms tumor developed in 23 patients at a median of 30 months. Of children receiving adjuvant therapy at diagnosis, 17 of 33 (52%) developed a Wilms tumor. There was an increased incidence of anaplasia noted in tumors that developed following chemotherapy in patients with nephroblastomatosis (Perlman et al, 2005).

Preoperative Evaluation and Staging

A palpable smooth abdominal mass is present on physical examination in over 90% of children. A family member or primary care provider often discovers the mass incidentally. Abdominal pain, gross hematuria, and fever are less frequent findings at diagnosis. Rupture of the tumor with hemorrhage into the free peritoneal cavity can result in the occasional presentation of an acute abdomen.

Compression or invasion of adjacent structures may result in an atypical presentation. Extension of Wilms tumor into the renal vein and inferior vena cava (IVC) can cause a varicocele, hepatomegaly due to hepatic vein obstruction, ascites, and congestive heart failure. Such symptoms are found in less than 10% of patients with intracaval or atrial tumor extension (Ritchey et al, 1988, 1990; Shamberger et al, 2001). Occasionally, children with Wilms tumor have symptoms secondary to the production of bioactive substances by the tumor (Coppes, 1993). Hypertension is common at diagnosis and has been attributed to elevated plasma renin levels (Maas et al, 2007). This will usually resolve shortly after removal of the tumor. During the physical exam, it is important to assess for signs of associated Wilms tumor syndromes, such as aniridia, hemihypertrophy, and genitourinary anomalies.

Emergent operation is not necessary unless there is evidence of active bleeding or tumor rupture. Laboratory evaluation should include a complete peripheral blood count, renal and liver function tests, serum calcium, and urinalysis. Acquired von Willebrand disease has been found in 8% of newly diagnosed Wilms tumor patients (Coppes, 1993).

Imaging

A precise histologic diagnosis cannot be obtained on the preoperative imaging studies. All of the solid renal tumors of childhood have some common radiographic features, including renal cell carcinoma (Broecker, 1991; Miniati et al, 2008). **In the SIOP-9 study, 5.4% of patients in whom preoperative chemotherapy for Wilms tumor was commenced prior to diagnostic biopsy, were found to have renal malignanices other than Wilms tumor or benign renal conditions upon nephrectomy** (Tournade et al, 2001). In the United Kingdom Children's Cancer Study Group (UKCCSG), 12% of renal tumors clinically and radiologically consistent with Wilms tumor were found to have some other diagnosis on biopsy (Vujanic et al, 2003). Other clinical parameters can provide some clues to the diagnosis. The development of a renal tumor in a child known to have aniridia, hemihypertrophy, or other syndromes associated with an increased incidence of nephroblastoma is most likely to be a Wilms tumor. Bilateral or multicentric tumors are more typical of Wilms tumor, but renal lymphoma can present in this fashion. Congenital mesoblastic nephroma (CMN) is the most likely diagnosis in a neonate with a renal mass. However, favorable-histology (FH) Wilms tumor and rhabdoid tumor of the kidney can also present in the first few months of life (Ritchey et al, 1995a; LeClair et al, 2005). The renal origin of the mass is usually apparent on CT, but can be mistaken for neuroblastoma.

The clinical presentation, for instance, as abdominal pain with tumor rupture, can create confusion regarding the preoperative diagnosis. In 2.5% of NWTS-3 patients, there was an erroneous diagnosis prior to surgical exploration (Ritchey et al, 1992). Most of these children did not have any preoperative imaging studies performed, and this group of patients had an increased incidence of surgical complications. This emphasizes that defining the exact histology is not as important as establishing that the child has a solid renal tumor, allowing the surgeon to plan for a major cancer operation. Another important role of imaging is to confirm that the contralateral kidney is functioning prior to performing a nephrectomy.

Ultrasonography is the first study performed in most children with an abdominal mass. This will demonstrate the solid nature of the lesion. Doppler ultrasonography is particularly helpful in excluding intracaval tumor extension that occurs in 4% of Wilms tumor patients (Ritchey et al, 1988; Shamberger et al, 2001). Magnetic resonance imaging (MRI) is the study of choice if extension of tumor into the IVC cannot be excluded by ultrasonography (Fig. 137–14) (Schenk JP et al, 2008). CT and MRI can further define the extent of the lesion (Fig. 137–15) (Hoffer, 2005; Schenk JP et al, 2008); however, the role of imaging studies in staging of the renal tumor continues to be defined. If the preoperative imaging could accurately detect local extension of tumor beyond the renal capsule or into regional lymph nodes, it would obviate concerns regarding staging in patients treated with preoperative therapy. The local tumor burden (e.g., regional lymph node involvement) determines the intensity of the chemotherapy regimen and whether a child receives abdominal irradiation. Regional adenopathy can be identified on CT/MRI, but enlarged retroperitoneal benign lymph nodes are common in children, and correlation between pathologic findings and lymph node evaluation at surgical exploration in Wilms tumor patients have found significant false-positive and false-negative error rates (Othersen et al, 1990). It should not be expected that CT/MRI would have greater accuracy than visual inspection. Positron emission

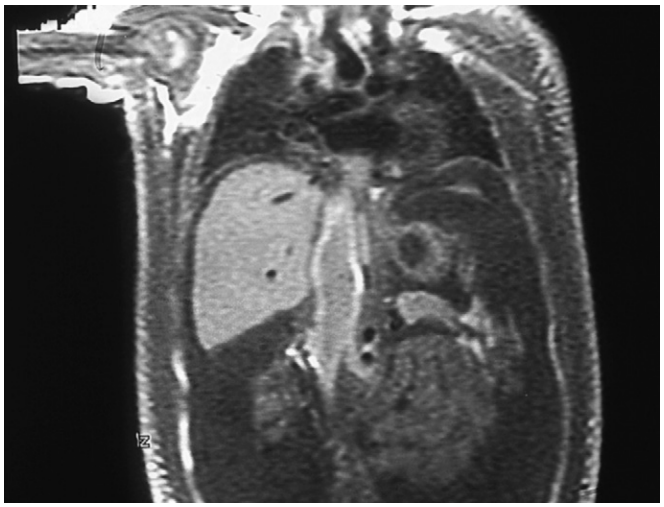


Figure 137–14. MRI depicting extension of Wilms tumor into the inferior vena cava.



Figure 137–15. CT scan of a left Wilms tumor with a small rim of functioning renal parenchyma.

tomography (PET) has not been shown to have any advantages over conventional imaging modalities in preoperative assessment of Wilms tumor (Misch et al, 2008). Detection of extrarenal tumor extension into the perirenal fat and into adjacent structures is also problematic. Apparent extension of the tumor into adjacent structures is usually the result of compression and not frank invasion (Ng et al, 1991). Therefore determination of inoperability must be made at surgical exploration.

Exploration of the contralateral kidney had long been advised before proceeding with nephrectomy to identify lesions missed on preoperative imaging. However, frequent failure to perform contralateral exploration before nephrectomy was reported in a quality assurance review of NWTS-5 patients (Ehrlich et al, 2005). A review of NWTS-4 patients with bilateral Wilms tumor found that 7% of lesions were missed preoperatively (Ritchey et al, 1995b). Most of the missed contralateral lesions were managed with biopsy alone, yet extended follow-up of the children has not demonstrated any relapses (Ritchey et al, 2005). **The conclusion was that routine exploration is not necessary provided preoperative imaging with thin slices on multidetector helical CT scanners or MRI is performed.**

The lung is the most common site of distant metastasis in children with Wilms tumor. CT of the chest is recommended before surgery. The clinical significance of lung nodules detected on CT scan alone is controversial (Meisel et al, 1999; Owens et al, 2002). CT will clearly detect more lesions than chest x-ray (CXR), but not all of these lesions represent metastases (Ehrlich et al, 2006). Some reports have suggested that treatment of such patients with dactinomycin and vincristine is sufficient without the need for doxorubicin or pulmonary radiation. Others have found an increased risk of pulmonary relapse if more intensive treatment is not given (Owens et al, 2002).

Clear cell sarcoma of the kidney (CCSK) and renal cell carcinoma have a propensity to metastasize to the skeleton (D'Angio et al, 1993; Indolfi et al, 2003). Skeletal surveys and bone scans are both recommended after the histologic diagnosis is confirmed (Feusner et al, 1990). Cranial CT or MRI is performed on all children with CCSK or with rhabdoid tumor of the kidney (RTK), because both are associated with intracranial metastases (Weeks et al, 1989; Indolfi et al, 2003).

Table 137–8.

Staging System of the Children's Oncology Group

Stage I	Tumor confined to the kidney and completely resected. The renal capsule is intact and the tumor was not ruptured prior to removal. No renal sinus extension. There is no residual tumor.
Stage II	Extracapuslar penetration, but is completely resected. Renal sinus extension or extrarenal vessels may contain tumor thrombus or be infiltrated by tumor.
Stage III	Residual nonhematogenous tumor confined to the abdomen: lymph node involvement, any tumor spillage, peritoneal implants, tumor beyond surgical margin either grossly or microscopically, or tumor not completely removed
Stage IV	Hematogenous metastases to lung, liver, bone, brain, etc.
Stage V	Bilateral renal involvement at diagnosis.

Staging

The most important determinants of outcome in children with Wilms tumor are the histopathology and tumor stage. Accurate staging of Wilms tumor allows treatment results to be evaluated and enables universal comparisons of outcomes. The current staging system used by the Children's Oncology Group (Table 137–8) is based primarily on the surgical and histopathologic findings. Examination for extension through the capsule, residual disease, vascular involvement, and lymph node involvement are essential to properly assess the extent of the tumor at presentation.

Stage I tumors are limited to the kidney and completely resected. However, evidence for tumor extension can be subtle. Tumor invasion of blood and lymphatic vessels in the renal sinus is the first sign of spread outside the kidney in stage II tumors (Weeks et al, 1987). Penetration through the renal capsule is the next most common finding of extrarenal spread. Clear demonstration of tumor cells in the perirenal fat is required to document capsular penetration. **Any tumor spill is now a criterion for stage III designation, due to the increased risk for local tumor recurrence** (Shamberger et al, 1999). For NWTS-5, the distribution by stage for patients with FH tumors was stage I, 24.9%; stage II, 29.9%; stage III, 30.6%; and stage IV, 14.5%. Patients with anaplastic tumors are more likely to present with stage III to IV disease than those with FH tumors (Dome et al, 2006).

Prognostic Factors

As the treatment regimens for children with Wilms tumor have become more effective, the ability of retrospectively determined prognostic factors to predict outcomes is diminished. Traditional staging factors, such as tumor size, histology, and lymph node metastases, relied upon in the past to predict risk for tumor progression or relapse, are now less able to stratify FH patients for treatment. Clinical cancer trials are now evaluating biologic factors that may predict tumor behavior.

Chromosomal Abnormalities. As noted above, **LOH for a portion of chromosome 16q and/or 1p has been noted in 20% of Wilms tumors. This is associated with an increased risk for relapse** (Grundy et al, 1994, 2005; Wittman et al, 2007). **This difference in outcome is independent of histology and stage.** NWTS-5 patients with stage I-II FH tumors with LOH of either 1p or 16q had an increased risk of relapse and death in comparison with patients lacking LOH at either locus (Grundy et al, 2005). The risks of relapse and death for patients with stage III to IV FH tumors were increased only with LOH for both regions. These results have been incorporated into the current COG renal tumor protocols. Children whose tumors demonstrate LOH for these chromosomal regions will receive an intensification of treatment.

Another potential marker is telomerase, a reverse transcriptase that maintains chromosome ends, compensating for the loss of DNA that occurs in replication. High telomerase activity has been found to be an unfavorable prognostic feature for several types of cancers. A case cohort study involving 291 patients confirmed the correlation between telomerase RNA expression and recurrence, and this was independent of tumor stage in multivariate analysis (Dome et al, 2005). Future studies will seek to evaluate how telomerase expression may be used in conjunction with other prognostic markers, such as LOH at 1p and 16q, to stratify patients into risk-appropriate treatment groups.

DNA Content. The proliferative rate of tumor cells can be estimated by the measurement of DNA content. Aneuploidy occurs more frequently in anplastic histology tumors, but findings in FH tumors are inconclusive. The correlation between cellular DNA content and prognosis was examined in the NWTS-5 cohort. A DNA index greater than 1.5 was strongly associated with anaplastic histology and predictive of poor outcome. However, DNA content was not predictive of outcome when stratified by histology and stage (Ehrlich, 2007).

Cytokines. The growth of solid tumors is critically dependent on the induction of neovascularity by angiogenic cytokines. Vascular endothelial growth factor (VEGF) is an angiogenic cytokine detected with increased frequency and quantity in experimental and clinical specimens of Wilms tumor (Kayton et al, 1999; Karth et al, 2000). In experimental animals, lung metastases were far more likely to occur in animals with VEGF positive tumors. Anti-VEGF therapy has been shown to suppress tumor growth in mice and can prevent development of metastases (Rowe et al, 2000; Frischer et al, 2004). Antiangiogenesis treatment would appear to be a promising adjunctive future treatment for patients with Wilms tumor.

Treatment

Surgical Considerations

The initial therapy for most children with Wilms tumor is radical nephrectomy. Nephrectomy should be done by a transperitoneal approach. The surgeon is responsible for determining tumor extent. Accurate staging is essential for the subsequent determination of the need for radiation therapy and the appropriate chemotherapy regimen. Thorough exploration of the abdominal cavity is necessary to exclude local tumor extension, liver and nodal metastases, or peritoneal seeding. Exploration of the contralateral kidney is no longer mandated prior to nephrectomy if the preoperative CT or MRI demonstrates a normal kidney (Ritchey et al, 2005). The renal vein and IVC are palpated to exclude intravascular tumor extension prior to vessel ligation. Wilms tumor extends into the inferior vena cava in approximately 6% of cases and may be clinically asymptomatic in more than 50% (Ritchey et al, 1988; Shamberger et al, 2001). **Selective sampling of suspicious nodes is an essential component of local tumor staging. Formal retroperitoneal lymph node dissection is not recommended** (Othersen et al, 1990; Shamberger et al, 1999). Extensive lymph node dissection, particularly above the renal hilum, can result in chylous ascites (Weiser et al, 2003).

The other major responsibility when performing a nephrectomy for Wilms tumor is complete removal of the tumor without contamination of the operative field. Gentle handling of the tumor throughout the procedure is mandatory to avoid tumor spillage, because these patients have a sixfold increase in local abdominal relapse (Shamberger et al, 1999). **Shamberger and colleagues** (1999) **identified risk factors for local tumor recurrence as tumor spillage, unfavorable histology, incomplete tumor removal, and absence of any lymph node sampling. The 2-year survival after abdominal recurrence was 43%, emphasizing the importance of the surgeon in performing careful and complete tumor resection.**

Removing a large renal tumor in a small child is associated with some morbidity. NWTS-4 patients undergoing primary nephrectomy had an 11% incidence of surgical complications (Ritchey et al, 1999). The most common complications encountered are hemorrhage and small bowel obstruction (Ritchey et al, 1992, 1993a, 1999). SIOP investigators have reported a lower rate of complications when nephrectomy is performed after preoperative chemotherapy (Godzinski et al, 1998).

Cooperative Group Trials

The finding in the 1960s that dactinomycin (AMD) and vincristine (VCR) were effective agents for treating Wilms tumor radically altered the approach to management of children with this disease (Farber, 1966; Sutow, 1967). Multiple randomized clinical trials have been conducted by the NWTSG, SIOP, and the United Kingdom Children's Cancer Study Group (UKCCSG) to determine the appropriate role for each of the therapeutic modalities available. The NWTSG has now been incorporated with several other groups to form the COG. Patients are stratified into different treatment groups based on stage and pathology. The goals of these trials are to decrease the intensity of therapy for most patients in an effort to prevent late sequelae of treatment while maintaining excellent overall survival. Conduct and design of the trials is becoming longer and more complex given that the survival for patients with all stages of FH Wilms tumor now exceeds 90%.

National Wilms Tumor Study Group (NWTSG) and Children's Oncology Group (COG). The NWTSG was formed in 1969 to study Wilms tumor. The early NWTSG studies, NWTS-1 (1969 to 1973) and NWTS-2 (1974 to 1978), showed that the combination of VCR and AMD was more effective than the use of either drug

alone. The addition of doxorubicin (DOX) was found to improve survival for stage III and IV patients, and postoperative flank irradiation was unnecessary for stage I patients (D'Angio et al, 1976, 1981). **A major achievement of the early trials was identification of prognostic factors that allowed stratification of patients into high-risk and low-risk treatment groups. Patients with positive lymph nodes and diffuse tumor spill were found to be at increased risk of abdominal relapse and therefore considered stage III and given postoperative irradiation. One of the most important findings was the identification of the unfavorable histologic features that have a very adverse impact on survival.**

NWTS-3 (1979 to 1986) demonstrated that stage I-II patients could be treated with 18 weeks of AMD and VCR without irradiation (D'Angio et al, 1989). For stage III FH patients, 10.8 Gy of abdominal irradiation was shown to be as effective as 20 Gy in preventing abdominal relapse if DOX was added to VCR and AMD. NWTS-4 (1987 to 1994) proved that treatment durations of 6 months produced comparable outcomes to 15 months of therapy for patients with stages II-IV/FH tumors (Green et al, 1998). A recent analysis was done comparing the impact of postoperative irradiation on flank recurrence and survival (Breslow et al, 2006). This review found that although radiation did decrease the incidence of flank recurrence, there was no survival advantage. This was attributed to a lower postrecurrence mortality in unirradiated patients.

NWTS-5 (1995 to 2003) was a single arm therapeutic trial. One of the major aims of the trial was to confirm the utility of LOH for chromosomes 16q and 1p to predict increased risk of tumor relapse and death (Grundy et al, 2005). Another objective was to evaluate the efficacy of treatment regimens for anaplastic histology Wilms tumor. Stage I patients were treated with AMD and VCR, but this resulted in a low 4-year EFS of 69.5% (Dome et al, 2006). A new intensified chemotherapy regimen used for patients with stage II to IV diffuse anaplasia did not result in an improved survival.

In NWTS-5, children less than 2 years of age with stage I FH tumors and weighing less than 550 g did not receive chemotherapy after nephrectomy. This portion of the study was closed when the number of tumor relapses exceeded the limit allowed by the design of the study (Green et al, 2001a). A recent long-term review of this cohort was done comparing the outcomes to similar patients treated with postoperative AMD and VCR (Shamberger et al, 2009). The 5-year EFS for surgery alone was 84%, but the 5-year OS was the same. These results suggest that such an approach should continue to be evaluated in future trials. There is a trade-off between more intensive therapy and its potential long-term sequelae required for the 16% of children who relapse versus the avoidance of any postoperative chemotherapy in the majority.

A uniform approach for the treatment of tumor relapse was used in NWTS-5. These results were recently published (Green et al, 2007). For children whose intial treatment was AMD and VCR only, there was an overall 81% survival at 4 years. Children who relapsed after intial treatment with AMD, VCR, DOX, and radiation did not fare as well, with an overall 48% survival at 4 years (Malagolowkin et al, 2008). The NWTSG merged with several other oncology groups to form the COG. Table 137–9 lists the current COG renal tumor protocols and their major objectives.

Table 137–9.

Summary of Current Children's Oncology Group Renal Tumor Studies

AREN 0532

1. Very low-risk patients (stage I FH tumors <550 g with age <2 years) will be treated by nephrectomy alone. The goal is to achieve a 4-year EFS of greater than or equal to 85% and 4-year OS greater than or equal to 95%.
2. Patients with stage III FH Wilms tumor without LOH of 1p *and* 16q will be treated with vincristine, dactinomycin , and doxorubicin (regimen DD-4A), and radiotherapy. The goal is to achieve a 4-year EFS of greater than or equal to 85% and 4-year OS greater than or equal to 95%.
3. Patients with stage I and II FH Wilms tumor with LOH of 1p *and* 16q will be treated with vincristine, dactinomycin, and doxorubicin (regimen DD-4A) but not radiotherapy. The goal is to improve the current 4-year EFS.

AREN 0533

1. Patients with stage IV FH Wilms tumor will be treated with vincristine, dactinomycin, and doxorubicin (regimen DD-4A). Those that have complete resolution of the pulmonary lesions after 6 weeks will not receive radiation therapy. The goal is to achieve a 4-year EFS of 85% without whole lung irradiation.
2. Patients with stage IV FH Wilms tumor who do not have resolution of pulmonary metastases after 6 weeks of therapy will receive cyclophosphamide and etoposide in addition to regimen DD-4A. The goal is to achieve a 4-year EFS of 85%.
3. Patients with stage III or IV FH Wilms tumor with loss of LOH for chromosomes 1p *and* 16q will receive cyclophosphamide and etoposide in addition to regimen DD-4A. The goal is to improve the 4-year EFS to 75%.

AREN 0321

1. Patients with stage I diffuse anaplasia and stage I-III focal anaplasia Wilms tumor will be treated with vincristine, dactinomycin, and doxorubicin (regimen DD-4A) and radiotherapy.
2. Patients with stage I CCSK will be treated with vincristine, dactinomycin, and doxorubicin (Regimen DD-4A) but not radiotherapy.
3. Patients with stage IV focal anaplasia, diffuse anaplasia stage II-III Wilms tumor, stage IV CCSK, and stage I-IV malignant rhabdoid tumor of the kidney will be treated with new chemotherapy protocols to try and improve survival.

AREN O534

1. Patients with bilateral Wilms tumor will be given 6-12 weeks of vincristine, dactinomycin, and doxorubicin. Surgery is to be performed no later than week 12. The goal is to improve the 4-year EFS to 73%.
2. Patients with diffuse hyperplastic perilobar nephrogenic rests (DHPLNR) will be treated with 18 weeks of vincristine and dactinomycin. The goal is to evaluate the efficacy of chemotherapy in preserving renal units in children with and preventing Wilms tumor development.
3. Patients with unilateral tumors and aniridia, Beckwith-Wiedemann syndrome (BWS), hemihypertrophy, or other overgrowth syndromes will receive prenephrectomy chemotherapy for 6 weeks with vincristine and dactinomycin. The goal is to facilitate partial nephrectomy in 25% of children.

AMD, dactinomycin; CPM, cyclophosphamide; DOX, doxorubicin; EFS, event-free survival; FH, favorable histology; OS, overall survival; VCR, vincristine.

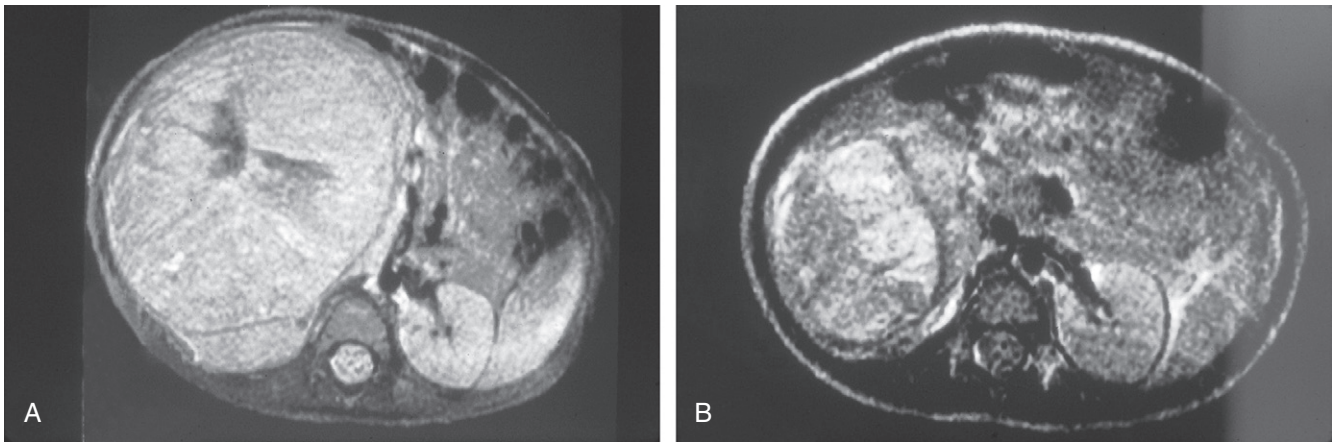


Figure 137–16. **A,** MRI of a Wilms tumor that was pretreated with chemotherapy. **B,** After 6 weeks of chemotherapy, the tumor is much smaller in size.

Wilms tumor occasionally occurs in adults. Earlier reports suggested that the outcome for adults with Wilms tumor was poor and that they require more intensive therapy (Byrd et al, 1982, Arrigo et al, 1990). Recent reviews of adult patients with FH Wilms tumor registered on NWTS-4 and -5 and SIOP 93-01 found improved survival compared with earlier reports (Kalapurakal et al, 2004a; Reinhard et al, 2004a). The recommendation is that adult patients receive stage-appropriate combined modality therapy.

International Society of Pediatric Oncology (SIOP). In the randomized clinical trials conducted by SIOP, preoperative therapy is given before surgery. This approach usually results in tumor shrinkage (Fig. 137–16), reducing the risk of intraoperative rupture or spillage (Lemerle et al, 1976). A greater number of patients have "post-chemotherapy stage I" tumors due to disappearance of micrometastases after neoadjuvant therapy. This was thought to be a significant advantage in terms of decreasing morbidity of treatment, particularly the late effects of radiotherapy.

Early SIOP studies evaluated prenephrectomy XRT (Lemerle et al, 1976). **SIOP-5 (1976 to 1980) showed that 4 weeks of AMD and VCR was as effective as prenephrectomy XRT in avoiding surgical tumor rupture and increasing the proportion of patients with low-stage disease** (Lemerle et al, 1983). **SIOP-6, (1980 to 1987), demonstrated that patients with "postchemotherapy stage I" disease can safely be treated with 18 weeks of AMD and VCR** (Tournade et al, 1993). **However, patients with "postchemotherapy stage II" tumors and negative lymph nodes were found to have a higher rate of abdominal relapse if postoperative irradiation was omitted** (Tournade et al, 1993). An anthracycline was subsequently added for treatment of these children. SIOP-6 confirmed the need for a three-drug chemotherapy regimen following nephrectomy for patients with "postchemotherapy stage II" lymph node–positive and stage III tumors. SIOP-9 (1987 to 1993), demonstrated that the relapse rate for stage II patients with negative lymph nodes without radiation therapy was reduced with epirubicin (Tournade et al, 2001). This study also demonstrated that treatment with VCR and AMD for 4 weeks versus 8 weeks had comparable rates of stage distribution and tumor shrinkage in patients with stage I to III disease. The majority of tumor shrinkage was noted in the first 4 weeks of therapy. Radiotherapy was limited to patients with stage II node-positive and III disease, resulting in 18% of patients being irradiated (Graf et al, 2000). There were 59 children with stage I to IV tumors who had complete tumor necrosis induced by chemotherapy, and 98% of these children had no evidence of disease at 5 years (Boccon-Gibod et al, 2000).

The latest SIOP study on Wilms tumor, SIOP 93-01 (1993 to 2000), evaluated a reduction in postoperative therapy for patients with stage I intermediate-risk and anaplastic Wilms tumor (deKraker et al, 2004; Reinhard et al, 2004b). Patients were randomized to receive either 4 or 18 weeks of postoperative chemotherapy with AMD and VCR. Two-year event-free survival (EFS) was 91.4% after 4 weeks and 88.8% after 18 weeks of therapy, demonstrating that survival can be maintained while shortening the duration of postnephrectomy therapy.

An interesting finding of the SIOP studies is the assessment of the tumor response after preoperative chemotherapy in terms of tumor volume and histology. The relative proportions of histologic subtypes of WT differ following preoperative chemotherapy when compared with those reported following primary surgical resection (Weirich et al, 2001). **Stromal and epithelial predominant tumors are found more often after chemotherapy. These histologic subtypes may demonstrate a poor clinical response to therapy but have an excellent prognosis if the tumor is completely excised.** The proportion of blastema-predominant tumors is decreased after chemotherapy, indicating some response of this tumor type to the preoperative chemotherapy. **However, patients with blastema-predominant tumors after chemotherapy have a high relapse rate** (Reinhard et al, 2004b). Tumor progression during therapy occurred in 5% of patients enrolled in SIOP 93-01 (Ora et al, 2007). These patients were documented to have decreased overall survival.

SIOP now classifies tumors with complete tumor necrosis following preoperative chemotherapy as "low risk." Children with stage I "low-risk" tumors following post-chemotherapy nephrectomy receive no further chemotherapy (Boccon-Gibod et al, 2000). Tumors with diffuse anaplasia and blastemal predominance after chemotherapy are classified as "high risk," and these children are treated with an intensified postoperative chemotherapy regimen. SIOP "intermediate-risk" tumors comprise all other histologies. The ongoing SIOP 2001 study treats patients with stage I "intermediate-risk tumors" with AMD and VCR. The most important study question of this trial is whether patients with stage II and III "intermediate-risk" tumors can be safely treated without

an anthracycline. Data from SIOP 93-01 has suggested that surival was not adversely affected when nonviable tumor was identified in the renal sinus and/or perirenal fat after preoperative chemotherapy (Vujanic et al, 2009).

United Kingdom Children's Cancer Study Group. The UKCCSG trials use prenephrectomy chemotherapy but, unlike SIOP, they perform biopsy prior to treatment (Pritchard et al, 1995; Mitchell et al, 2000; Pritchard-Jones et al, 2003). This is done to avoid giving chemotherapy for benign conditions, which acccount for 1% of lesions thought to be Wilms tumor on imaging studies (Tournade et al, 2001). The other reason to perform biopsy is to avoid giving inappropiate chemotherapy to non-Wilms tumors. The UKW3 trial noted a 12% incidence of non-Wilms tumors in patients with the typical features of Wilms tumor on imaging study (Vujanic et al, 2003). The UKW1 and UKW2 studies evaluated the single agent vincristine for treatment of stage I FH tumors (Pritchard et al, 1995; Mitchell et al, 2000). The overall survival of 96% compares well with two-drug chemotherapy, but age greater than 4 years was considered an adverse prognostic factor (Pritchard-Jones et al, 2003).

The UKW3 trial randomly assigned patients to either immediate surgery or to 6 weeks preoperative chemotherapy and then delayed surgery (Mitchell et al, 2006). Event-free and overall survival at 5 years was similar in the two groups. Around 20% of survivors avoided treatment with doxorubicin or radiotherapy, due to favorable stage distribution after preoperative therapy. They concluded, like the SIOP group, that all children with nonmetastatic Wilms tumor should receive chemotherapy prior to tumor resection.

Preoperative Chemotherapy (COG Recommendations)

On the COG renal tumor protocols, treatment is dependent on surgical and pathologic staging following immediate nephrectomy. There are, however, some situations where preoperative chemotherapy is recommended. These include children for whom renal-sparing surgery is planned (Blute et al, 1987), tumors are inoperable at surgical exploration (Ritchey et al, 1994), and there is tumor extension into IVC above the hepatic veins (Ritchey et al, 1993b; Shamberger et al, 2001; Szavay et al, 2004). The latter two conditions are associated with an increased risk for surgical complications if primary nephrectomy is undertaken (Ritchey et al, 1992).

Inoperable Tumors. **The surgeon must make the determination that a tumor is inoperable. This decision should not be based on preoperative imaging studies, which can overestimate local tumor extension.** As noted above, not all renal masses in children represent Wilms tumor (Vujanic et al, 2003; Reinhard et al, 2004a, 2004b). **If the tumor is found to be unresectable, pretreatment with chemotherapy almost always reduces the bulk of the tumor and renders it resectable** (Ritchey et al, 1994; Grundy et al, 2004) (Fig. 137–16). **Patients who are staged by imaging studies alone and recieve preoperative chemotherapy before nephrectomy are also at risk for understaging** (Tournade et al, 1993). **A patient determined to have an inoperable tumor should be considered stage III and treated accordingly** (Ritchey et al, 1994).

Repeat imaging is performed after 6 weeks of chemotherapy. Experience in SIOP has shown that the majority of reduction in tumor volume occurs in the first 4 weeks (Tournade et al, 2001). After there has been adequate shrinkage of the tumor, definitive resection can generally be completed. A clinically good response (by imaging) is usually associated with a pathologically good response in terms of regressive histologic changes (Zuppan et al, 1991; Weirich et al, 2001). The converse is not always true. The distribution of histologic subtypes is different following preoperative chemotherapy compared with primary surgery, with differentiation of the tumor occurring after chemotherapy. Stromal and epithelial predominant tumors are found more often after treatment with preoperative chemotherapy. These histologic subtypes may demonstrate a poor clinical response to therapy but have an excellent prognosis if the tumor is completely excised. Patients with progressive disease have a poor prognosis, and these patients will require treatment with a different chemotherapeutic regimen (Ritchey et al, 1994; Ora et al, 2007).

Bilateral Wilms Tumors. **Synchronous bilateral Wilms tumors occur in 5% to 7% of children with Wilms tumor** (Blute et al, 1987; Coppes et al; 1989; Montgomery et al, 1991). **Children with bilateral tumors should not undergo initial radical nephrectomy. These children should receive preoperative chemotherapy with the goal of tumor shrinkage and renal-sparing surgery** (Blute et al, 1987; Coppes et al, 1989; Kumar et al, 1998). Preservation of renal tissue is important to decrease the incidence of renal failure, which approaches 15% at 15 years post-treatment in patients with bilateral Wilms tumor (Ritchey et al, 1996; Breslow et al, 2005). The most common etiology for renal failure was the need for bilateral nephrectomy for persistent or recurrent tumor in the remaining kidney after initial nephrectomy. Nephrectomy can be avoided in the majority of patients if a careful protocol is followed and the surgery is performed by surgeons experienced in renal-sparing techniques (Davidoff et al, 2008).

The current COG protocol for patients with BWT recommends 6 weeks of chemotherapy prior to surgery. Biopsy is not needed if the radiographic picture is consistent with Wilms tumor. Tumor response is assessed after 6 weeks with CT or MRI to determine the reduction in tumor volume and feasibility of partial resection. Patients with tumors amenable to renal-sparing procedures can proceed with surgery. Imaging cannot, however, predict the histology of the tumor based on changes in volume of the tumor after chemotherapy (Weirich et al, 2001; Olsen et al, 2004). **Tumors not responding to therapy require bilateral open biopsy to determine histology. Open biopsies are recommended, because they are more accurate than percutaneous needle biopsies when assessing for anaplasia** (Hamilton et al, 2006). **Failure to achieve a reduction in volume is likely due to tumor differentiation** (Fig. 137–17) (Weirich et al, 2001; Anderson et al, 2002; Shamberger et al, 2006). Differentiated tumors may show a poor clinical response to therapy, but have an excellent prognosis if the tumor is completely excised. If renal sparing surgery is not feasible, additional chemotherapy is then given based on the biopsy findings, but all patients should proceed to surgical resection within 12 weeks of starting therapy. Continuing treatment beyond 12 weeks will not likely provide any additional reduction in tumor burden.

At the time of second-look surgery, partial nephrectomy or wedge excision of the tumor is preferred, with an attempt to achieve negative margins. The kidney with the lower tumor burden is addressed first. Tumor enucleation may be considered in lieu of a formal partial nephrectomy. This is often needed for large centrally located tumors where removal of a margin of renal tissue would compromise the vascular supply to the kidney (Cozzi et al, 1996; Horwitz et al, 1996). The concern is that enucleation will be more likely to result in positive surgical

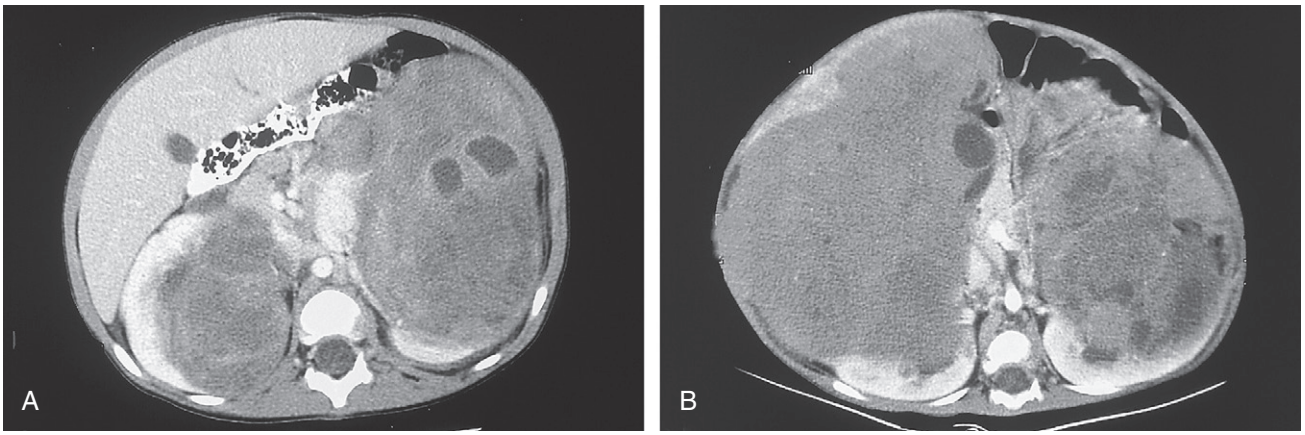


Figure 137–17. Patient with bilateral tumors who was treated with chemotherapy. **A,** CT before treatment. **B,** CT after 6 months of chemotherapy, showing an increase in the size of the tumors. Bilateral partial nephrectomies were performed, revealing mature tumor elements with rhabdomyoblastic differentiation.

margins. For FH tumors, adjuvant therapy may still provide for a good outcome (Cozzi et al, 1996; Horwitz et al, 1996; Davidoff et al, 2008). However, if there is anaplasia in the resected specimen, a positive margin will adversely affect survival and require additional resection. Even when large bilateral masses remain after initial chemotherapy, a high percentage of children can be successfully managed with renal-sparing surgery (Davidoff et al, 2008). It is easy to underestimate the amount of renal parenchyma that can be salvaged due to compression by the tumor; therefore nephron-sparing surgery should be entertained in all patients.

Radical nephrectomy may be needed in a kidney with extensive tumor involvement. Bilateral nephrectomies and dialysis are rarely required when the tumors fail to respond to chemotherapy and radiation therapy. This is the most common cause of renal failure in patients with bilateral Wilms tumor (Ritchey et al, 1996). Fortunately, anephric patients can still be administered chemotherapy with some modifications (Feusner et al, 2008). The recommended interval between successful completion of treatment of the Wilms tumor and renal transplantation varies (Penn, 1979; Kist-van Holthe et al, 2005). Some advocate a waiting period of 2 years to ensure that the patient does not develop metastatic disease; others have found that a 1-year interval is sufficient. Patients who develop renal failure after renal-sparing surgery should have removal of the remaining renal tissue prior to transplant to prevent tumor recurrence after starting immunosuppression (Kubiak et al, 2004).

All patients treated for bilateral Wilms tumor require close long-term follow-up. SIOP investigators have noted that late relapses have occurred in patients with BWT more than 4 years post-treatment and recommended long-term follow-up (Coppes et al, 1989). These patients should also have frequent assessment of renal function, urine protein, and blood pressure.

Partial Nephrectomy for Unilateral Tumors. Several centers have explored the role of parenchymal-sparing procedures in children with unilateral Wilms tumors (McLorie et al, 1991; Cozzi et al, 1996; Moorman-Voestermans et al, 1998; Haecker et al, 2003; Linni et al, 2003; Zani et al, 2005). The primary motivation for this approach is concern about late occurrence of renal dysfunction after unilateral nephrectomy. **However, the incidence of renal failure following nephrectomy for most children with unilateral Wilms tumor is low, 0.6% at 20 years post-treatment** (Breslow et al, 2005). **The risk of renal failure is higher for patients with genitourinary anomalies, DDS, and WAGR.** As noted above, this is due to mutation of *WT1,* which is necessary for normal renal development.

Most Wilms tumors are too large at diagnosis to allow partial nephrectomy. After preoperative chemotherapy, partial nephrectomy can be performed in 10% to 15% of patients. Only the occasional child with Wilms tumor will present with a lesion small enough to allow partial nephrectomy at diagnosis, for instance, tumors detected due to screening studies for Beckwith-Wiedemann syndrome and aniridia (see Fig. 137–10). As noted above, there are concerns regarding staging after chemotherapy, requiring some patients to receive added therapy to prevent local recurrence. Another concern is the increased risk for local recurrence after partial nephrectomy (Horwitz et al, 1996; Haeker et al, 2003). Patients who develop intra-abdominal relapse have a markedly decreased survival (Shamberger et al, 1999).

The COG has proposed a renal-sparing protocol for select patients with unilateral Wilms tumors. These include patients known to be at risk for bilateral disease or those at increased risk for renal failure. These patients will be managed with a strict surgical protocol to minimize risk for residual disease (Cozzi et al, 2004). The lesion should be completely excised with a margin of normal renal parenchyma. These patients should not undergo partial nephrectomy if the tumor cannot be removed as a stage I entity. Patients with high-risk histologic patterns, such as anaplasia or persistent blastema-predominant tumor after chemotherapy, should be treated with complete nephrectomy because these tumors have resistance to chemotherapy.

Late Effects of Treatment

Numerous organ systems are subject to the late sequelae of anticancer therapy. Clinicians must be aware of the spectrum of problems that face children as they grow into adulthood. Musculoskeletal problems, such as scoliosis, were significant in children receiving irradiation in the early NWTS trials (Evans et al, 1991). Hogeboom aand colleagues (2001) studied the impact of treatment on stature in Wilms tumor patients. The authors noted that reductions in stature directly correlated to total radiation

dose and age at treatment but concluded that currently recommended radiation doses should not result in clinically significant height deficits.

Gonadal radiation can produce hypogonadism and temporary azospermia in boys (Kinsella et al, 1989). The severity of damage is dependent on the radiation dose. The Leydig cells are more radioresistant than the germ cells, but higher doses can produce damage resulting in inadequate production of testosterone. This can result in delayed sexual maturation. Chemotherapeutic agents can also adversely affect testicular function (Mustieles et al, 1995). A 12% incidence of ovarian failure was found in girls receiving abdominal XRT (Stillman et al, 1987). Abdominal XRT also increases the risk for adverse pregnancy outcomes (Li et al, 1987; Green et al, 2002). The offspring of irradiated female patients are at risk for low birth weights, premature birth, and congenital malformations. Radiation portals that include the pelvis and doses exceeding 20 Gy increase the risk of miscarriage (Kalapurakal et al, 2004b).

An increased incidence of second malignant neoplasms has been noted in children treated for Wilms tumor. There is a 1% cumulative incidence at 10 years postdiagnosis and a rising incidence thereafter (Breslow et al, 1988b; Taylor et al, 2008). One of the greatest risk factors is prior irradiation, and most tumors occur in the radiation field (Breslow et al, 1988b; Bassal et al, 2006; Taylor et al, 2008).

In recent years, there has been increasing concern regarding the risk of congestive heart failure in children who receive treatment with anthracyclines such as DOX (Green et al, 2001b). In addition to the acute cardiotoxicity, cardiac failure can develop many years after treatment (Steinherz et al, 1991). In a preliminary review of patients entered on NWTS-1, -2, -3, and -4, the frequency of congestive heart failure was 4.4% among DOX-treated patients who received this drug as part of their initial chemotherapy regimen (Green et al, 2001b). The risk was increased if the patient received whole lung or left flank irradiation.

OTHER RENAL TUMORS

Clear Cell Sarcoma of the Kidney

Clear cell sarcoma of the kidney (CCSK) accounts for 3% of renal tumors reported to the NWTSG. The tumor derives its name from the clear cytoplasm of the predominant cell type (Schmidt and Beckwith, 1995). **Important predictors of improved survival are lower stage, younger age at diagnosis, treatment with doxorubicin, and absence of tumor necrosis** (Argani et al, 2000). **The addition of doxorubicin improved both overall survival and relapse-free survival** (D'Angio et al, 1989; Argani et al, 2000; Seibel et al, 2004). Patients with stage I tumors (using the current criteria of absence of renal sinus invasion) had a 98% survival rate. Unlike anaplastic Wilms tumor, even stage I CCSK lesions are associated with increased rates of relapse and require postoperative irradiation. Long-term follow-up of CCSK patients is needed because 30% of relapses occurred more than 3 years after diagnosis, and some as late as 10 years. Unlike Wilms tumor, **CCSK is associated with bone and brain metastases.** Bilateral involvement has thus far not been reported, nor has the presence of Wilms tumor–associated congenital anomalies such as aniridia or hemihypertrophy. Patients with CCSK were treated on NWTS-5 with a regimen combining VCR, DOX, cyclophosphamide, and etoposide in an attempt to further improve the survival of this high-risk group, but results of that trial are pending.

Rhabdoid Tumor of the Kidney

Rhabdoid tumor of the kidney (RTK) is the most aggressive and lethal childhood renal tumor, which accounts for 2% of renal tumors registered to the NWTSG. RTK is now considered a sarcoma of the kidney, and the cell of origin is unknown (D'Angio et al, 1989). The tumor derives its name from the resemblance to rhabdomyoblasts, but the tumor is not derived from myogenic cells. RTK and CCSK both occur in renal and extrarenal locations, suggesting an origin from a non–organ-specific mesenchymal cell. Cytogenetic studies have shown that there may be a common genetic basis for renal and extrarenal rhabdoid tumors. Deletions and somatic mutations in the *INI1* gene on chromosome 22 in the region of 22q11 predispose to the development of this tumor (Biegel et al, 1999). Germline mutations of *INI1* have been identified in renal rhabdoid tumors. Staining for the products of the *INI1* gene can be useful because rhabdoid tumor of the kidney is consistently negative (Hoot et al, 2004).

Typical clinical features include early age of diagnosis (median age less than 16 months), advanced stage, resistance to chemotherapy, and high mortality (Amar et al, 2001; Tomlinson et al, 2005). Younger age at diagnosis is an adverse prognostic factor. **RTK is distinguished by its propensity to metastasize to the brain** (D'Angio et al, 1993). In addition, RTK is associated with second primary tumors in the brain, including cerebellar medulloblastomas, pineoblastomas, neuroblastomas, and subependymal giant cell astrocytomas (Bonnin et al, 1984).

Congenital Mesoblastic Nephroma

Congenital mesoblastic nephroma (CMN) is the most common renal tumor in infants, with a mean age at diagnosis of 3.5 months (Howell et al, 1982; van den Heuvel-Eibrink et al, 2008). **This is the most common renal tumor diagnosed on antenatal ultrasonography** (LeClair et al, 2005). Congenital mesoblastic nephroma is a very firm tumor on gross examination, and the cut surface has the yellowish-gray trabeculated appearance of a leiomyoma. There are three histolgic subtypes: classical, cellular, and mixed (showing areas of both classical and cellular). The classical subtype, characterized by interlacing sheets of bland spindle cells, resembles infantile fibromatosis. The cellular variant, with a solid sheetlike growth pattern and frequent mitoses, is virtually identical histologically to congenital fibrosarcoma (Beckwith, 1986; Joshi et al, 1986; Gormley et al, 1989). Both tumors have a similar translocation that fuses the *ETV6* (*TEL*) gene from 12p13 with the 15q25 neurotrophin-3 receptor gene, *NTRK3* (Argani et al, 1998). In CMN, tumor induction is postulated to occur at a time when the multipotent blastema is predominately stromagenic (Snyder et al, 1981; Tomlinson et al, 1992). *WT1* is not expressed in CMN (Tomlinson et al, 1992).

The most important aspect of CMN is the usually excellent outcome with radical surgery only (Howell et al, 1982). The tumor can extend into the hilar or perirenal soft tissue, therefore complete surgical resection is important (Beckwith, 1986). Local recurrence and metastasis can occur particularly with the cellular variant of CMN (Joshi et al, 1986; Gormley et al, 1989; Fitchey et al, 2003). The risk of recurrence is thought to be less in children less than 3 months of age at diagnosis, but metastases have been reported in a few infants (Heidelberger et al, 1993). Neither chemotherapy nor radiation therapy is routinely

recommended (Howell et al, 1982), but consideration for adjuvant treatment should be given to patients with cellular variants that are incompletely resected (Gormley et al, 1989). There are reports demonstrating response of both inoperable and recurrent tumors to chemotherapy (Loeb et al, 2002; McCahon et al, 2003).

Solitary Multilocular Cyst and Cystic Partially Differentiated Nephroblastoma

Solitary multilocular cyst, or multilocular cystic nephroma, is an uncommon, benign renal tumor. Fifty percent of multilocular cysts are found in young children, usually boys. The second peak incidence occurs in young adult women (Eble and Bonsib, 1998; Luithle et al, 2007). Although the majority of cases of multilocular cystic renal disease have been unilateral, there are rare reports of bilateral cases (Ferrer and McKenna, 1994). The gross appearance of the tumor is its most distinguishing feature. The cut surfaces reveal a well-encapsulated multilocular tumor composed of varying-sized cysts compressing the surrounding renal parenchyma. This tumor is distinguished by the finding of only mature cell types within the septa of the cyst wall. Multilocular cystic nephroma is cured by nephrectomy, but recurrence has occurred following incomplete excision by partial nephrectomy. If partial nephrectomy is considered, frozen section is indicated to exclude cystic, partially differentiated nephroblastoma (CPDN), or clear cell sarcoma, which can occasionally have a similar appearance.

Another entity reported in the literature with similar features is cystic partially differentiated nephroblastoma. The majority of these lesions occur in the first 2 years of life (Joshi and Beckwith, 1989; Blakely et al, 2003; Luithle et al, 2007). Eble and Bonsib (1998) recommend that multilocular cystic nephroma and cystic partially differentiated nephroblastoma be considered the same entity. They are indistinguishable radiographically. Histologic examination reveals that blastemal cells or nephrogenic rests may be found in the septa of both tumors. Surgery is curative in almost all patients with recurrence, the result of incomplete resection (Eble and Bonsib, 1998; Blakely et al, 2003). In a review of 21 children with CPDN reported to the NWTSG, there was 100% survival. Eight were treated with surgery alone (Blakely et al, 2003). Thirteen patients received postoperative chemotherapy, including two patients with stage II disease.

Metanephric Adenofibroma

Another tumor with prominent stromal features that can resemble CMN is metanephric adenofibroma (Arroyo et al, 2000). The epithelial component of these tumors can range from inactive metanephric adenoma to Wilms tumor. Other lesions contain areas morphologically identical to papillary renal cell carcinoma. This uncommon entity may be derived from ILNR (Arroyo et al, 2000). Metanephric adenofibromas with a composite Wilms tumor component occur at a young age (mean of 12 months), similar to other ILNR-related Wilms tumors that develop in patients with DDS and aniridia. None of these tumors have recurred after nephrectomy, but all have been treated with Wilms tumor chemotherapy.

Renal Cell Carcinoma

Renal cell carcinoma is the most common renal malignancy in the second decade of life. Only 5% of renal cell carcinomas occur in children (Hartman et al, 1982; Broecker, 1991). An abdominal mass is the most common presentation, but hematuria is more common than in Wilms tumor (Broecker, 1991). Imaging studies cannot differentiate renal cell carcinoma from other solid renal tumors. **There is a higher incidence of papillary renal cell carcinoma in children** (Carcao et al, 1998; Renshaw et al, 1999). **These tumors, typically seen in adolescence or young adults, are genetically unique in that they have chromosome translocations involving a common breakpoint in the *TFE* gene located at Xp11.2** (Bruder et al, 2004). These tumors differ from adult RCC in that immunoreactivity for epithelial markers is reduced or absent.

Another type of RCC more often seen in children is renal medullary carcinoma found in patients with sickle cell hemoglobinopathy (Swartz et al, 2002). The median age at presentation is 13 years, but can be found in much younger children. It is a highly lethal tumor.

Complete tumor resection is the most important determinant of outcome in RCC. Raney and colleagues found that all children with stage I lesions survived, and others have reported 64% to 80% survival for stage I and II tumors (Dehner et al, 1970; Castellanos et al, 1974; Raney et al, 1983; Aronson et al, 1996). Partial nephrectomy has been used in pediatric patients with RCC, but outcome data are limited (Cook et al, 2006). Younger age at diagnosis is a favorable prognostic factor (Raney et al, 1983). Regional lymph node involvement does not portend the same poor prognosis as adult renal cell carcinoma (Geller and Dome, 2004). Like renal cell carcinoma in adults, these tumors are not responsive to chemotherapy or radiation therapy.

Angiomyolipoma

Renal angiomyolipoma is a hamartomatous lesion that is only rarely seen in childhood. There is a clear association with the tuberous sclerosis complex (TSC), and presentation is more often bilateral in these patients (Blute et al, 1988; Ewalt et al, 1998). **The renal lesions of the TSC include angiomyolipoma, simple cysts, polycystic kidney disease, and renal cell carcinoma. Angiomyolipoma develops in up to 80% of patients with the TSC** (Ewalt et al, 1998). Two genes have been identified in the TSC on chromosome 9 (*TSC1*) and chromosome 16 (*TSC2*) (Povey et al, 1994). It has been postulated that these genes act as tumor suppressor genes and that the LOH of *TSC1* or *TSC2* may explain the progressive growth pattern of renal lesions seen in these patients (Henske, 2004).

The incidence of angiomyolipoma increases with age. Ewalt and colleagues (1998) reported on 60 patients with the TSC who were followed with periodic ultrasonograms. The average age at which a normal ultrasonogram became abnormal was 7.2 years. Angiomyolipomas were found in 45 children. Growth of the lesion was observed in 28 children. Girls were more likely to have an increase in the size of the lesion. All patients with lesions greater than 4 cm in diameter were postpubertal. Annual ultrasonograms are recommended after puberty. **Children with growing lesions** (Fig. 137–18) **can be managed with embolization or partial nephrectomy before they become symptomatic with bleeding** (Lee et al, 1998; Williams et al, 2006). **The risk of serious bleeding appears to correlate with a diameter of greater than 4 cm** (Blute et al, 1988; Dickinson et al, 1998; Steiner et al, 1993). Nephron-sparing approaches are recommended in children with the TSC, due to the presence of multiple, bilateral lesions and the risk of developing of new lesions.

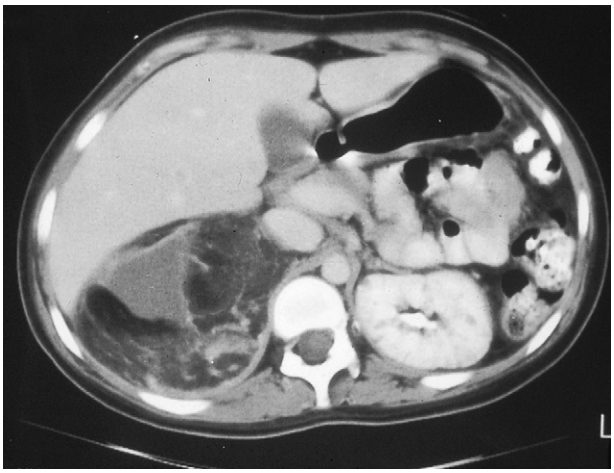


Figure 137–18. Angiomyolipoma of the right kidney in a patient with tuberous sclerosis.

Key Points: Renal Tumors

- Deletions of *WT1*, located on chromosome 11p, are found in patients with aniridia and Wilms tumor. Mutations of *WT1* occur in DDS. *WT1* is important for normal renal and gonadal development.
- LOH for chromosomes 1p and 16q is associated with an increased risk for relapse and death in Wilms tumor patients.
- Local recurrence is increased in Wilms tumor patients with local tumor spillage, and this is not classifed stage III disease. The 2-year survival rate after local recurrence is 43%.
- Congenital mesoblastic nephroma (CMN) is the most common renal tumor in infants.

TESTICULAR TUMORS

Testicular tumors account for 1% to 2% of all pediatric solid tumors, with an annual incidence of 1:100,000 for boys less than 15 years of age in the United States (Young et al, 1986). **Benign lesions represent a greater percentage of cases in children than in adults.** The American Academy of Pediatrics prepubertal testis tumor registry reported that benign tumors accounted for 38% of cases (Ross et al, 2002). Several large series have reported a higher percentage of benign lesions, suggesting that these entities were under-reported to the tumor registry (Metcalfe et al, 2003; Shukla et al, 2004). **One multicenter report found that 74% of primary testis tumors in prepubertal children were benign** (Pohl et al, 2004). The incidence of childhood testicular tumors peaks at age 2 years (Li and Fraumeni, 1972; Haas and Schmidt, 1995), tapers after age 4 years, but then begins to rise again at puberty. Testis tumors are more common in whites during infancy and rare in black and Asiatic children (Walsh et al, 2008).

Etiology and Genetics

A variety of chromosomal abnormalities have been identified in both adolescent and adult germ cell tumors (GCT). Benign teratomas in children less than 4 years old usually demonstrate no abnormalities (Bussey et al, 1999). The testicular GCTs of adolescents had abnormalities resembling those found in adult testicular GCT, including loss of chromosomes 11, 13, and 18, and gain of chromosomes 7, 8, and the X chromosome (Bussey et al, 1999). The most frequent chromosomal abnormality is the isochromosome of 12p or i(12p), characteristically composed of two copies of 12p. The i(12p) is found in intratubular germ cell neoplasia, implying that this genetic event occurs early. Endodermal sinus tumors have been noted to have a deletion of the short arm of chromosome 1, specifically 1p36 in 805 to 100% of cases (Perlman et al, 1996; Zahn et al, 2006).

Although the etiology of testicular cancer is unknown, a number of etiologic factors have been evaluated. There has been an increasing incidence of testicular cancer in the past few decades among adult men (McKiernan et al, 1999), but this has not been documented in prepubertal boys (Walsh et al, 2008). It is suggested that early or prolonged exposure to some carcinogenic stimuli might be implicated. **Patients with disorders of sex development (DSD) have an increased incidence of gonadal tumors. Patients with hypovirilization and gonadal dysgenesis are at the highest risk. The risk of tumor formation in gonadal dysgenesis is increased if there is a Y chromosome present, with the incidence of tumor development approximately 10% by age 20 years.** The presence of a well-defined part of the Y chromosome (the GBY region) is a prerequisite for tumor formation, with the gene for the testis-specific protein on the Y chromosome (*TSPY*) being a likely candidate gene (Lau et al, 2000; Hersmus et al, 2008). **Intratubular germ cell neoplasia has been noted in 6% of children with DSD, with a higher incidence after puberty** (Ramani et al, 1993). No cases of carcinoma in situ were found before puberty in a large series of patients with complete androgen insensitivity (Hannema et al, 2006).

The link between cryptorchidism and germ cell tumors of the testis is well known, but these are quite rare in childhood (Kay, 1993). Cortes and colleagues (2004) found testicular neoplasia in 7 of 182 (3.8%) children with abdominal undescended testes, abnormal external genitalia, or abnormal karyotype, but none in 1281 children without these characteristics. Neoplasia was found most often in bilateral cryptorchidism. The relative risk of cancer increases with age at orchidopexy, with the greatest risk after puberty (Pettersson et al, 2007).

Pathology

Non–germ cell and germ cell tumors arise from the celomic epithelium and primordial germ cells, respectively. It is postulated that the totipotent germ cells can evolve into seminona or embryonal carcinoma. Embryonal carcinoma is capable of differentiating into embryonic structures, such as mature or immature teratomas and extraembryonic structures (e.g., endodermal sinus tumors and choriocarcinoma). Seminoma or dysgerminoma is a primitive germ cell neoplasm that lacks the capacity for further differentiation. These tumors are unusual in childhood, except when related to gonadal dysgenesis.

Yolk sac tumor (YST) is known by a number of other eponyms, including endodermal sinus tumor, embryonal adenocarcinoma, infantile adenocarcinoma of the testis, orchidoblastoma, and Teilum tumor. It is the most common malignant testis tumor in infants and young boys. Grossly, the tumor is firm and yellow-white on cross section, and hemorrhage is unusual. The microscopic appearance shows a mixture of epithelial and mesenchymal

cells in a characteristic organoid pattern. The tumor cells produce the characteristic stages seen in the morphogenesis of extraembryonic membranes (yolk sac and allantoic mesoderm of the placenta). **The characteristic histologic finding in yolk sac tumors is Schiller-Duval bodies** (Wold et al, 1984). The latter are similar to the endodermal sinuses seen in the rat placenta. Eosinophilic cytoplasmic inclusions are common, and specialized staining techniques demonstrate the presence of α-fetoprotein (AFP).

Teratoma is a germ cell tumor composed of elements of more than one germ cell layer: endoderm, ectoderm, and mesoderm. Teratomas are classified as mature teratoma, immature teratoma, and malignant teratoma. Mature teratomas generally appear well encapsulated on gross examination. There are multiple cysts present, but consistency on cross section varies with the amount of solid tissue present between the cysts. The microscopic appearance varies with the relative amounts of tissue derived from the different germ layers and the degree of maturation (Mostofi and Price, 1973). Cartilage, bone, mucous glands, or muscle may be evident.

Epidermoid cysts occur within the testicular parenchyma and are filled with keratinous debris. Microscopically, well-differentiated stratified squamous epithelium lines the cysts. It is proposed that epidermoid cysts represent a monodermal teratoma (Ulbright, 2005). Intratubular germ cell neoplasia has not been found in the testis parenchyma adjacent to epidermoid cysts (Manivel et al, 1989).

Immature teratomas have a gross appearance similar to that of mature teratomas, but they contain various immature tissues. The latter is usually neuroepithelium, but immature elements representative of other germ cell layers may be found (Heifetz et al, 1998). A grading system for teratomas has been developed (Gonzalez-Crussi, 1982). The incidence of foci of yolk sac tumor increases with the grade of the teratoma, and these patients frequently had elevation of serum AFP preoperatively (Heifetz et al, 1998).

Leydig, Sertoli, and granulosa cells have a common embryologic origin from a mesenchymal stem cell. Pathologic diagnosis can be difficult due to incomplete differentiation (Goswitz et al, 1996). Leydig cell tumors appear well encapsulated with compression of the adjacent testicular tissue. They appear yellow to brown on cross section, reflecting the steroid production by the tumor. Microscopic appearance is similar to that of adrenal rests. The pattern is that of closely packed esosinophilic cells with a granular cytoplasm. **The pathognomonic histologic feature of Leydig cell tumor, Reinke crystals, is present in only about 40% of tumors** (Mostofi and Price, 1973). **Increased mitotic figures or other features suggestive of malignancy are absent in prepubertal Leydig cell tumors.** A review of 30 cases of Leydig cell tumors identified the following features associated with tumors that metastasized: increased mitotic activity, DNA aneuploidy, infiltrative margins, and angiolymphatic invasion (Cheville et al, 1998). Metastasizing tumors also had higher MIB-1, a cell proliferation marker, activity. None of the prepubertal patients had developed metastatic disease.

Sertoli cell tumors are solid, usually without hemorrhage or necrosis. On cross section, they are white to yellow and lobulated in appearance. On microscopic examination, there are large polygonal cells with eosinophilic cytoplasm. Large cell sertoli cell tumors can be confused with Leydig cell tumors, because both are characterized by cells with abundant eosinophilic cytoplasm (Goswitz et al, 1996). The tumors of the adrenogenital syndrome are also another confusing entity in the differential diagnosis (Srikath et al, 1992). Histology does not correlate with outcome, because Sertoli cell tumors often have features of high mitotic rates, nuclear pleomorphism, and increased cellularity.

Gonadoblastomas are small benign tumors found in patients with gonadal dysgenesis, including those who have at least a portion of the Y chromosome (Scully, 1970). They are bilateral in up to one third of cases. The tumors are composed of large germ cells similar to seminoma, sex cord derivatives resembling immature granulosa and Sertoli cells, and occasionally stromal elements.

Carcinoma In Situ

Carcinoma in situ (CIS) or intratubular germ cell neoplasia, is commonly found in adult patients with testicular cancer and is a precursor to the development of invasive germ cell tumor (Skakkebaek, 1975). CIS has been detected in adolescent cases of germ cell tumor (Jorgensen et al, 1995) but has not been identified in children with YST of the testis. The seminiferous tubules adjacent to germ cell tumors in prepubertal children frequently contain cells with enlarged nuclei and clear cytoplasm. However, staining for markers of CIS—placental alkaline phosphatase, and c-*KIT*—in seminiferous tubules adjacent to the germ cell tumor was negative in 28 prepubertal testes (Hawkins et al, 1998). CIS is also frequently detected in patients with androgen-insensitivity disorders and dysgenetic gonads (Muller et al, 1985; Ramani et al, 1993). OCT3/4 has been shown to be a sensitive and specific marker for CIS in the adult male, but its role in prepubertal or DSD patients remains to be defined (Looijenga, 2009).

There is an association between cryptorchidism and the development of CIS. The incidence of CIS is 1.7% in adults who have previously undergone orchidopexy (Giwercman et al, 1989). **Identification of CIS is more difficult in the prepubertal patient.** Biopsies at the time of orchidopexy in prepubertal children have only rarely demonstrated CIS (Hadziselimovic et al, 1984). Giwercman and colleagues (1988) recommend repeat biopsy after puberty in prepubertal patients with CIS.

Diagnosis and Staging

A painless testicular mass is the most common presentation of a child with a testicular tumor. Disorders that must be excluded are epididymitis, hydrocele, hernia, and spermatic cord torsion. The latter can present as a painless mass in the neonate, with little scrotal wall inflammation if the event occurred prenatally. Acute abdominal pain can be the presenting symptom, with torsion of an abdominal undescended testicle containing a tumor. Some patients with hormonally active tumors may have small intratesticular lesions that are not palpable on physical examination.

Testicular ultrasonography is routinely performed in the evaluation of testicular masses in children. Color Doppler ultrasonography has been reported to be more effective than gray-scale ultrasonography in detecting intratesticular neoplasms in the pediatric population (Luker and Siegel, 1994). **There are no sonographic features that can reliably distinguish benign and malignant tumors, but the finding of anechoic cystic lesions can suggest a benign lesion, such as a simple cyst, cystic dysplasia, teratoma, or cystic granulosa cell tumor. The ultrasound findings of epidermoid cyst are also unique** (Fig. 137–19). There is a heterogeneous intratesticular mass with concentric rings of alternating



Figure 137–19. Testicular ultrasonogram demonstrating cystic lesion that proved to be an epidermoid cyst of the testicle. The patient underwent a testis-sparing procedure.

hypo- and hyperechoic layers that give rise to an "onion-skin appearance." This corresponds to the multiple layers of keratin debris within the lesion. The mass is surrounded by a hypoechoic or echogenic rim and the absence of flow on color Doppler ultrasonography (Langer et al, 1999). Ultrasonography can also assess if there is enough normal testis parenchyma remaining to warrant salvage. If a child is identified with a cystic lesion on ultrasonography and serum AFP is normal, the surgeon can plan for a testicular-sparing procedure (Rushton et al, 1990; Grunert et al, 1992; Valla et al, 2001; Metcalfe et al, 2003; Shukla et al, 2004). MRI may detect small functioning Leydig cell tumors not evident on ultrasonography (Kaufman et al, 1990).

In addition to ultrasonography, measurement of serum AFP can help identify tumors amenable to a testis-sparing procedure. AFP is a single–polypeptide chain amino acid produced by the fetal yolk sac, liver and gastrointestinal tract. YSTs invariably produce AFP, and all AFP-positive tumors are considered to contain yolk sac elements (Huddart et al, 1990). Teratomas and other benign lesions are associated with normal AFP levels. AFP has a half-life of approximately 5 days, and degradation curves are followed after orchiectomy to assess for residual or recurrent disease. **It is important to note that AFP levels may be elevated levels in infant boys and do not always represent the presence of a malignant tumor or persistent disease after orchiectomy for YST. Normal adult reference laboratory values for AFP cannot be used in young children, because AFP synthesis continues after birth** (Wu et al, 1981; Lahdenne et al, 1991, Brewer and Tank, 1993). **Normal adult levels (<10 mg/mL) are not reached until 8 months of age** (Wu et al, 1981). Human chorionic gonadotropin-β (β-hCG) is a glycoprotein produced by embryonal carcinoma and mixed teratomas. The normal value for β-hCG is less than 5 IU/L. The half-life of β-hCG is approximately 24 hours. β-hCG is rarely elevated in preadolescent tumors.

The current staging system used by the Children's Oncology Group is listed in Table 137–10. Staging is based on both tumor markers and pathologic findings. AFP levels are determined at diagnosis and monitored after radical inguinal orchiectomy to determine if there is an appropriate half-life decline. CT of the retroperitoneum and chest are obtained to exclude metastatic lesions. CT imaging of the retroperitoneum can identify most patients who have lymph node metastases, but there is a 15% to 20% false-negative rate (Pizzocara et al, 1987; Wiener et al, 1994).

Table 137–10.

Children's Oncology Group Staging System for Testicular Germ Cell Tumors

STAGE	EXTENT OF DISEASE
I	Tumor is limited to the testis, completely resected by high inguinal orchiectomy. No clinical, radiographic, or histologic evidence of disease beyond the testes. If scrotal orchiectomy has been performed, all margins are negative after resection of proximal cord structures to the level of the internal inguinal ring. Tumor markers are negative after appropriate half-life decline. Patients with normal or unknown tumor markers at diagnosis must have a negative ipsilateral retroperitoneal node sampling to confirm stage I disease, if radiographic studies demonstrate lymph nodes greater than 2 cm.
II	Microscopic residual disease is present in the scrotum or high in spermatic cord (<5 cm from proximal end). Tumor markers remain elevated after appropriate half-life interval. Tumor rupture or scrotal biopsy prior to complete orchiectomy.
III	Retroperitoneal lymph node involvement. Lymph nodes greater than 4 cm by CT are considered metastases. Lymph nodes greater than 2 cm and less than 4 cm need biopsy to document nodal metastases.
IV	Distant metastatic deposits.

Germ Cell Tumors

Mature Teratoma

Teratoma accounts for more than 40% of testis tumors in prepubertal children (Metcalfe et al, 2003; Pohl et al, 2004; Shukla et al, 2004). **Prepubertal mature teratomas have a benign clinical course that contrasts with the clinical behavior of teratomas in adults who have the propensity to metastasize** (Mostofi and Price, 1973; Grady et al, 1997; Gobel et al, 1998). As noted above, the presumptive diagnosis of teratoma can often be made on ultrasound examination. Other cystic lesions of the testis must be considered in the differential diagnosis. Teratoma appears more as complex hypoechoic areas surrounded by highly echogenic signals (Krone and Carroll, 1985).

Testicular teratomas are currently managed with testis-sparing procedures rather than radical orchiectomy (Altadonna et al, 1988; Rushton et al, 1990; Valla et al, 2001; Metcalfe et al, 2003; Shukla et al, 2004). There have been no recurrences reported to date. Frozen sections should be obtained intraoperatively and can reliably distinguish benign from malignant lesions (Valla, 2001; Elert et al, 2002). A detailed review of 21 cases of prepubertal teratoma at the Armed Forces Institute of Pathology did not reveal evidence of multifocal disease or carcinoma in situ of the adjacent testis (Rushton et al, 1990). Preoperative ultrasonography can underestimate the volume of normal testis parenchyma, due to compression by the tumor against the capsule (Patel et al, 2007).

Testis-sparing surgery should be done through an inguinal incision with vascular control of the cord. An incision is made in

the tunica albuginea, and the mass is enucleated. Teratomas generally shell out easily due to the pseudocapsule around the lesion. The tumor is sent for frozen section and the tunica closed. The patient is not awakened until the results of frozen section are available.

Epidermoid Cyst

Epidermoid cysts account for 15% of pediatric testicular tumors (Valla et al, 2001; Pohl et al, 2004). This monodermal teratoma follows a benign clinical course. Due to the lack of associated intratubular germ cell neoplasia in the surrounding testis, testis-sparing surgery has been advocated both in children and adults (Manivel et al, 1989; Ross et al, 1993; Pohl et al, 2004). AFP levels are normal, and the diagnosis of epidermoid cyst can be suggested by ultrasonography. Frozen section diagnosis has been shown to be reliable in distinguishing this lesion (Valla, 2001; Elert et al, 2002). Epidermoid cyst can be differentiated from mature teratoma by the lack of chromosome 12p abnormalities (Cheng et al, 2006).

Immature Teratomas

A less common tumor of the testis is an immature teratoma. The most common extracranial site is in the ovary, with only 10% occurring in the testes. Immature teratomas have often been considered to be malignant tumors, but in children they appear to be benign unless they have foci of malignant cells. Because most patients with recurrent tumor can be salvaged with platinum-based chemotherapy, observation alone is recommended for completely resected immature teratoma (Gobel et al, 1998; Marina et al, 1998; Mann et al, 2000). Unlike other sites, the testicular immature teratomas have a low risk for relapse (Gobel et al, 1998). Incomplete resection of the tumor is a risk factor for relapse, but testis tumors are more amenable to complete resection than other sites (Lo Curto et al, 2007). Recurrence of immature teratomas after resection occurs almost exclusively in patients with elevated AFP or foci of yolk sac tumor in the initial resection specimens. Recurrent tumors typically are yolk sac tumors.

Yolk Sac Tumor

YST is the second most common prepubertal testicular tumor of germ cell origin (Metcalfe et al, 2003; Shukla et al, 2004). This tumor occurs primarily in children younger than age 2 years. The clinical behavior of YST varies considerably from embryonal carcinoma seen in adults, despite the histologic similarities. The most common site of distant metastases is the lung, and metastasis to the retroperitoneal lymph nodes occurs in 4% to 6% of children with YST (Bracken et al, 1978; Brosman, 1979)**. More than 90% of prepubertal children present with stage I disease** (Haas et al, 1999).

The initial treatment for YST is radical inguinal orchiectomy. This treatment is curative in most children. Routine RPLND and/or adjuvant chemotherapy are not indicated (Mann et al, 1989; Haas and Schmidt, 1995; Haas et al, 1999). Staging of the patient with tumor markers and imaging studies is performed as outlined above.

Clinical stage I patients do not receive additional adjuvant treatment after radical orchiectomy. Chest x-ray, CT, or MRI of the retroperitoneum is recommended monthly ×3, every 3 months ×1, and then every 6 months. This surveillance is continued until the patient is 36 months post-treatment. Tumor markers and physical examination are performed at more frequent intervals. Approximately 90% of YSTs produce positive serum levels of AFP. Scrotal orchiectomy with negative margins can be treated as stage I, but the proximal cord structures should be resected to the level of the internal ring (Rogers et al, 2004).

Patients who have undergone prior scrotal biopsy are considered stage II (Rogers et al, 2004). A completion orchiectomy with removal of all cord structures is performed. This approach has proven to be of benefit in adult patients with gross contamination during removal of germ cell tumors (Giguere et al, 1988; Capelouto et al, 1995). Hemiscrotectomy is not required. All patients undergo abdominal CT to examine for retroperitoneal lymphadenopathy. Patients with enlarged lymph nodes should undergo lymph node sampling or biopsy. Patients who have persistent elevation of AFP and retroperitoneal adenopathy are presumed to have metastatic disease. These patients can be treated as stage III.

Combination chemotherapy using platinum-based therapy—cisplatin, etoposide, and bleomycin (PEB)—has been used in pediatric patients with advanced germ cell tumors (Ablin et al, 1991). Two intergroup studies for the treatment of localized and advanced germ cell tumors in children conducted by the Children's Cancer Group and the Pediatric Oncology Group were recently published (Cushing et al, 2004; Rogers et al, 2004). The 6-year event-free survival (EFS) and overall survival (OS) of children with stage II testicular tumors was 100%. For stage III disease, age less than 15 years was associated with better 6-year EFS, 100% versus 83.3%, but both groups had a 100% OS. Patients less than 15 years of age with stage IV disease also had an improved 6-year EFS and OS, 94.4% and 100% versus 84% and 84%, respectively. The histology of tumors in patients less than 15 years was pure yolk sac tumor in 83% of patients, whereas 80% of older patients had mixed germ cell tumor.

A number of patients experience significant ototoxicity with the cisplatin-based chemotherapy regimens, and nephrotoxicity is also common (Pinkerton et al, 1990; Cushing et al, 2004). The UKCCSG used carboplatin instead of cisplatin in their second germ cell study, GCII (Mann et al, 2000). This trial was restricted to patients less than 16 years of age. The 5-year EFS for testicular germ cell tumors was 100%, with decreased toxicity compared with the PEB regimen.

Persistent retroperitoneal masses postchemotherapy are uncommon (Uehling and Phillips, 1994; Kuo et al, 1999). However, children with clinically evident retroperitoneal disease or elevation of tumor markers after chemotherapy undergo surgery at 12 weeks to establish a histologic diagnosis. Patients with persistent viable tumor are then switched to another treatment regimen. Those patients who develop relapse after initial treatment of a stage I tumor should also undergo biopsy for histologic confirmation.

Gonadal Stromal Tumors

Gonadal sex-cord stromal tumors are the most common nongerminal testicular tumors in children (Cortez and Kaplan, 1993; Goswitz et al, 1996; Valla, 2001; Pohl et al, 2004). These benign non–germ cell tumors are more common in children than adults. They arise from a common mesenchymal stem cell that can differentiate toward Leydig cells, Sertoli cells, granulosa cells, or a combination of these. An interesting feature of these tumors is the ability to secrete hormones.

Leydig Cell Tumors

Leydig cell tumor is the most common of the sex cord tumors, with a peak incidence at age 4 to 5 years. Leydig cells produce testosterone, and production of the hormone by the tumor can produce precocious puberty (Urban et al, 1978). This can lead to

accelerated skeletal and muscle development and penile growth that does not resolve after treatment (Mengel and Knorr, 1983). Other hormones produced by Leydig cell tumors include corticosteroids, progesterone, and estrogens.

The differential diagnosis of precocious puberty includes pituitary lesions, Leydig cell hyperplasia, large cell Sertoli cell tumors, and hyperplastic testicular nodules that develop in boys with poorly controlled congenital adrenal hyperplasia (CAH) (Wilson and Netzloff, 1983; Cunnah et al, 1989; Srikath et al, 1992; Walker et al, 1997). Pituitary lesions can be excluded by the finding of an increased serum testosterone with prepubertal LH and FSH levels. Children with Leydig cell hyperplasia have normal levels of urinary 17-ketosteroids. Testicular nodules in CAH patients tend to occur bilaterally, but there have been reports of bilateral Leydig cell tumors (Bokemeyer et al, 1993). A family history of CAH is helpful in making the diagnosis. The hyperplastic nodules that develop in CAH resemble Leydig cells histologically but behave biochemically like adrenal cortical cells. Urinary ketosteroids are elevated in patients with 21-hydroxylase deficiency, and serum levels of 17-hydroxy progesterone are elevated. Regression of the hyperplastic nodules in the testis is usually seen after glucocorticoid replacement (Srikath et al, 1992; Walker et al, 1997). Persistent nodules may result from fibrosis or calcification.

Inguinal orchiectomy has been used most often for Leydig cell tumors. Testis-sparing surgery and enucleation of the tumor has now been reported in a number of children (Konrad and Schoenle, 1999; Valla, 2001; Henderson et al, 2006). There is a report of one patient developing local recurrence (Wegner et al, 1997). Malignancy has not been reported in Leydig cell tumors in children (Brosman, 1979).

Sertoli Cell Tumor

Sertoli cell tumor is the next most common gonadal stromal tumor in children (Young et al, 1998). This tumor presents at an earlier age than Leydig cell tumors with the usual presentation of a painless testicular mass. These tumors are not as metabolically active as Leydig cell tumors, but gynecomastia has been reported (Gabrilove et al, 1980). There are limited series of patients with Sertoli cells tumors occurring in children (Gabrilove et al, 1980; Goswitz et al, 1996; Thomas et al, 2001). Most recommend observation in infants because metastases are rare (Kolon and Hochman, 1997). The vast majority of patients have been managed with orchiectomy, but testis-sparing procedures have been performed in prepubertal children (Sugita et al, 1999; Nonomura et al, 2001; Valla, 2001). Examination of the retroperitoneum is warranted to exclude retroperitoneal spread (Rosvoll and Woodward, 1968). Large cell Sertoli cell tumors have been noted with increased frequency in patients with Peutz-Jeghers syndrome and the Carney complex (Chang et al, 1998).

Gonadoblastoma

Gonadoblastomas are the most common tumors found in association with disorders of sex differentiation. They occur in dysgenetic gonads and are associated with the presence of a Y chromosome in the karyotype (Manuel et al, 1976). Recent evidence suggests that gonadoblastomas originate from surviving OCT3/4-positive germ cells in areas of undifferentiated gonadal tissue within the dysgenetic gonad (Cools et al, 2006). **Children with mixed gonadal dysgenesis have a 25% risk of tumor formation** (Schellas, 1974), **and the incidence increases with age** (Manuel et al, 1976). **The germ cell component of gonadoblastoma is prone to malignant degeneration into seminoma and nonseminomatous tumors. All streak gonads in patients with gonadal dysgenesis should be removed** (Aarskog, 1970). Patients with gonadal dysgenesis raised as females should have the gonads removed at diagnosis (Olsen et al, 1988; Gourlay et al, 1994). Early gonadectomy is advocated because tumors have been reported in children under age 5 years (Olsen et al, 1988; Gourlay et al, 1994). In mixed gonadal dysgenesis patients reared as males, all streak gonads and undescended testes should be removed. Scrotal testes can be preserved because they are less prone to tumor development. It has been suggested that gonadal biopsy and histologic examination for CIS in children with gonadal dysgenesis can identify those at risk for development of malignant germ cell tumors (Muller et al, 1985). However, recognition of CIS in prepubertal gonadal biopsies can be difficult, and a negative biopsy does not preclude the later development of a germ cell tumor.

Other Lesions

Leukemia and lymphoma are the most common malignancies to spread to the testicle in children. Children with acute lymphoblastic leukemia who have bulky disease at diagnosis have been reported to have up to a 20% incidence of testicular relapse (Askin et al, 1981). A recent report found no relapses after systemic chemotherapy and a 4% relapse rate after total-body irradiation with a testicular boost (Quaranta et al, 2004). Routine testicular biopsy after treatment is no longer recommended (Trigg et al, 2000). Positive testis biopsies early in remission identify patients at a slightly higher risk for adverse events, but do not impact on survival. Follicular lymphoma may occur as a primary tumor of the testis (Finn et al, 1999). The prognosis is favorable if the tumor is localized. Testicular involvement occurs in 4% of boys with Burkitt lymphoma and may be the initial clinical presentation (Lamm and Kaplan, 1974).

Testicular cystic dysplasia is a rare benign lesion in boys that has been reported with increasing frequency (Noh et al, 1999; Toffolutti et al, 1999). It is distinguished by the presence of multiple small irregular cysts localized in the rete testis. Renal agenesis or multicystic renal dysplasia has been noted in more than half the reported cases. A proposed etiology is a defective connection between the efferent ductules, originating from the metanephros, and the rete testis tubules, originating from the gonad. Management options include testis-sparing surgery and nonoperative treatment (Noh et al, 1999; Eberli et al, 2002). If the latter approach is used, follow-up with serial testicular ultrasonography is advised.

Testicular microlithiasis has been reported in association with testicular tumors but is present in more than 5% of healthy young men. It has been noted less often in children, and recommendations have been made for noninvasive ultrasound follow-up until adult age (Furness et al, 1998; Dell'Acqua, et al; 1999; Leenen and Riebel, 2002). Patients in whom there is an increased risk for cancer are infertile men with atrophic testes and microlithiasis and patients with known testis cancer and microlithiasis in the contralateral testis (Holm et al, 2003; Hoei-Hansen et al, 2005). Routine screening ultrasound studies are not warranted for asymptomatic patients without known risk factors for testicular cancer (Rashid et al, 2004; Dagash et al, 2007; Jaganathan et al, 2007). Routine testicular self-examination is all that is needed in the asymptomatic patient. The role of serial scrotal ultrasonogrphy in men with increased risk (history of undescended testis, infertility) is unclear, given the high survival rate of testicular cancer.

Key Points: Testis Tumors

- YST is the second most common testicular tumor in children. More than 90% of patients have stage I disease and do not require adjuvant chemotherapy. Monitoring serum AFP levels can detect tumor relapse.
- Patients with disorders of sexual development have an increased risk of gonadal tumors. Those with hypovirilization and gonadal dysgenesis are at greatest risk.
- Prepubertal patients with testis teratoma can be managed with a testis-sparing approach. Recognition of these tumors is feasible with testicular ultrasonography.

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chapter 138

Pediatric Genitourinary Trauma

Douglas A. Husmann, MD

General Comments on Pediatric Renal Trauma
Radiographic and Endoscopic Assessment and Treatment of Upper Tract Genitourinary Injuries
Management of Renal Trauma
Renal Vascular Injuries
Trauma-Induced Renal Vascular Hypertension
Trauma-Induced Chronic Flank Pain Following Renal Injury
Recommendations for Activities in Patients with a Solitary Kidney
Preexisting Hydronephrosis and Ureteropelvic Junction Disruption
Ureteral Trauma
Bladder Injuries
Urethral Injuries
Penile Injuries
Scrotal, Vulvar, and Testicular Trauma

GENERAL COMMENTS ON PEDIATRIC RENAL TRAUMA

The Pediatric Kidney: Traumatic Renal Injuries and Congenital Renal Anomalies

The pediatric kidney is believed to be more susceptible to trauma, due to a decrease in the physical renal protective mechanisms found in childhood. Specifically, in contrast with the adult, the pediatric kidney is protected by an immature, more pliable thoracic cage, weaker abdominal musculature, less perirenal fat, and it sits in a lower abdominal position. Whether the incidence of renal injury following blunt abdominal trauma is truly increased in the pediatric versus the adult patient population is controversial, with statistical evaluations revealing mixed results, and the question remains in play (Brown et al, 1998; Chopra et al, 2002; McAleer et al, 2002a; Heyns, 2004).

What is known however is that preexisting renal abnormalities (i.e., ureteropelvic junction [UPJ] obstruction, hydroureteronephrosis, horseshoe kidney) are three- to fivefold more common in pediatric patients undergoing a screening CT scan for trauma than in the adult population (Brown et al, 1998; Chopra et al, 2002; McAleer et al, 2002a; Heyns, 2004).

Classically, patients with a preexisting congenital renal abnormality present with a history of hematuria disproportionate to the severity of trauma. Although it has been hypothesized that a preexisting congenital genitourinary anomaly would be associated with a higher stage of renal injury, this has not been documented to be true, with the majority of the patients still sustaining only renal contusions or minor renal fracture (Al-Qudah and Santucci, 2006; Chopra et al, 2002; McAleer et al, 2002a).

Trauma-Induced Hematuria: Pediatric versus Adult Patients

Two major clinical findings suggest the need to work up the genitourinary tract of an adult for a possible injury following trauma: Is there gross hematuria or is there microscopic hematuria (>50 red blood cells [RBC]/high-power field [HPF]) with shock (systolic pressure <90 mm Hg)? In adults, if physicians use only these two questions to decide who to screen for a traumatic genitourinary injury, they will find 98% of the clinically significant genitourinary (GU) injuries following blunt trauma and 90% of GU injuries associated with penetrating trauma (Mee et al, 1989; Heyns, 2004; Santucci et al, 2004a). Indeed, the yield in the adult population with just those two questions is significant, with 30% of the patients presenting with gross hematuria and 10% of the patients with microscopic hematuria associated with shock found to have a radiologically definable GU injury (Mee et al, 1989; Heyns, 2004; Santucci et al, 2004a). **In contrast, in children there is poor correlation relating the presence of hematuria to the presence of renal injuries. Indeed, some studies have found that two thirds of children sustaining a grade 2 or higher renal injury will have completely normal urinalysis** (Morey et al, 1996; Buckley and McAninch, 2004, 2006; Santucci et al, 2004a). **The correlation of hypotension to the**

extent of injury is also problematic, with the sympathetic tone in children being able to sustain a normal blood pressure despite significant blood loss. In fact, in children serial hemoglobin/hematocrit (Hb/Hct) values will demonstrate significant decreases before orthostatic hypotension develops (Quinlan and Gearhart, 1990). Notably, 90% of the pediatric patients with a clinically significant traumatic renal injury will have coexisting injuries to either the thoracic contents, intra-abdominal organs, or orthopedic (ribs, spine, pelvic, or femur) fractures (Levy et al, 1993; Buckley and McAninch, 2004; Heyns, 2004; Sahin et al, 2004; Santucci et al, 2004b). **In essence, in the pediatric patient presenting with a history of trauma, the clinical history combined with the presence of associated injuries becomes paramount in determining the need to assess for possible GU injuries** (Morey et al, 1996; Buckley and McAninch, 2004, 2006; Santucci et al, 2004a).

Indications for Imaging the Genitourinary Tract Following Trauma in the Pediatric Patient

Santucci and associates reviewed all of the published data regarding traumatic renal injuries in children. The outcome of this excellent review article found that the screening criteria outlined in Table 138–1 were highly reliable and cost effective (Mee and McAninch, 1989; Mee et al, 1989; Herschorn et al, 1991; Heyns, 2004; Santucci et al, 2004a, 2004b; Wu and Gaines, 2007).

RADIOGRAPHIC AND ENDOSCOPIC ASSESSMENT AND TREATMENT OF UPPER TRACT GENITOURINARY INJURIES

FAST: Focused Assessment with Sonography for Trauma

Because of its low cost, wide availability, and freedom from ionizing radiation, the use of ultrasonography (US) has become a major screening tool in pediatric level 1 trauma centers. Use of the FAST exam to detect renal injuries **has a reported specificity range of 95% to 100%, (the ability to diagnose true negatives—kidneys without a clinically significant traumatic injury). However, the sensitivity (the ability to diagnose true positives—kidneys with a clinically significant traumatic injury) is highly variable and extremely operator dependent, with published sensitivity results ranging widely from 22% to 85%** (McGahan et al, 1999; Jang et al, 2004; Sirlin et al, 2004; Suthers et al, 2004; Nural et al, 2005; Lee et al, 2007b; Bent et al, 2008). The clinical usefulness of a FAST scan is best when combined with serial physical examinations. If both the **FAST exam and serial physical examinations are within normal limits for 24 hours, the combination of these findings will virtually rule out the presence of significant renal and/or intra-abdominal injuries** (McGahan et al, 1999; Jang et al, 2004; Sirlin et al, 2004; Suthers et al, 2004; Nural et al, 2005; Lee et al, 2007b; Bent et al, 2008).

Table 138–1.

Indications for Radiographic Assessment of Pediatric Patient for Possible Genitourinary Injury

All penetrating abdominal/pelvic traumas
or
A history of blunt abdominal trauma that meets one of four following criteria:
1. A significant deceleration or high-velocity accident, fall from greater than 15 feet, or strike to the abdomen or flank with a foreign object, for instance, football helmet, baseball bat, among others
2. Significant trauma that has resulted in a fracture of the thoracic rib cage, spine, pelvis, or femur; bruising of the torso; or clinical signs of peritonitis
3. Gross hematuria
4. Microscopic hematuria (>50 RBC/HPF) associated with shock (systolic blood pressure <90 mm Hg)

HPF, high-power field; RBC, red blood cells.

Abdominal and Pelvic Computed Tomography and Single-Shot Intravenous Pyelography (IVP)

The patient's hemodynamic stability determines whether, when, and occasionally what type of imaging studies can be done. The most sensitive and specific radiologic test to rule out a genitourinary injury is a triphasic abdominal and pelvic computed tomography (CT) scan (precontrast study, followed by a CT study immediately after injection of contrast [1.5 to 2 mL/kg], and then a 10-minute delayed study). See Table 138–2 for the classification of renal trauma and Figures 138–1 through 138–5 for examples (Mee et al, 1989; Stein et al, 1994; Morey et al, 1996; Brown et al, 2001; Buckley and McAninch, 2004, 2006; Heyns, 2004; Santucci et al, 2004b; Al-Qudah and Santucci, 2006; Lee et al, 2007b). **In the clinically labile patient, a single-phase CT scan with the study taken immediately following injection of contrast is the mainstay. This test is beneficial in**

Table 138–2.

Grading of Renal Injuries

GRADE OF RENAL INJURY	DESCRIPTION
1	Renal contusion or subcapsular hematoma
2	Nonexpanding perirenal hematoma, less than 1-cm parenchymal laceration, no urinary extravasation, all renal fragments viable
3	Nonexpanding perirenal hematoma, greater than 1-cm parenchymal laceration, no urinary extravasation, renal fragments may be viable or devitalized
4	Laceration extending into the collecting system with urinary extravasation, renal fragments maybe viable or devitalized *or* Injury to the main renal vasculature with contained hemorrhage
5	Completely shattered kidney; by definition, multiple major lacerations of greater than 1 cm associated with multiple devitalized fragments *or* Injury to the main renal vasculature with uncontrolled hemorrhage; renal hilar avulsion

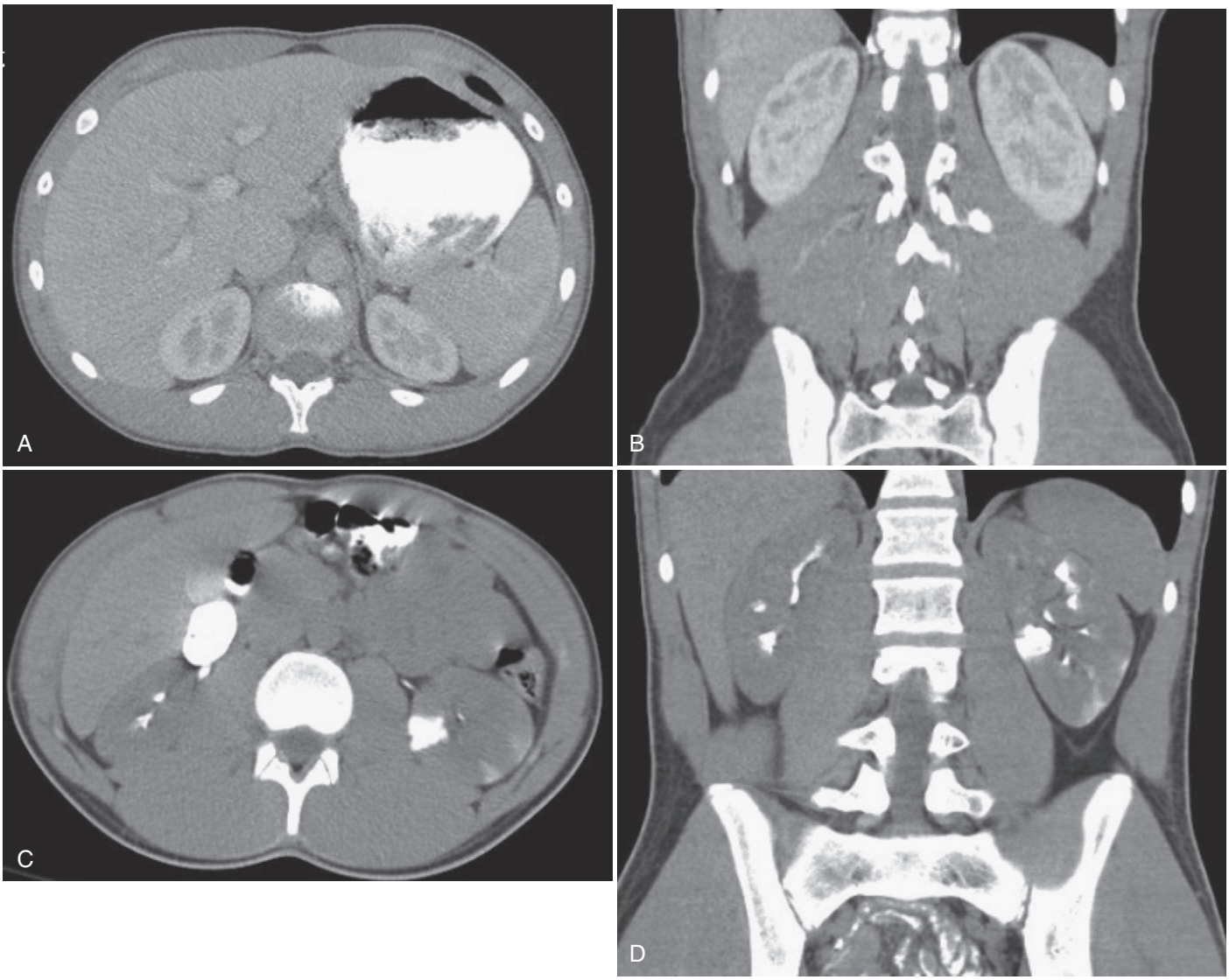


Figure 138–1. CT images, acute and delayed, with grade 1 renal trauma. **A,** Acute CT image of grade 1 renal trauma. Note normal-appearing parenchyma. **B,** Acute CT image coronal reconstruction of grade 1 renal trauma. **C,** Two-hour delayed CT of grade 1 renal trauma revealing renal contusion with delayed excretion of contrast in cortex of contused renal parenchyma. **D,** Two-hour delayed coronal reconstruction of CT grade 1 renal trauma revealing delayed excretion of contrast in cortex of contused renal parenchyma.

determining renal perfusion and the presence of major renal fractures; it will, however, be unable to accurately determine the presence of urinary extravasation and, in our experience, will miss the majority of the isolated ureteral injuries (Boone et al, 1993). In the unstable patient requiring emergent laparotomy, once the patient is stabilized in the operating room (OR), a one-shot IVP (2 mL/kg intravenous bolus of contrast) with the x-ray taken 10 to 15 minutes following injection may be beneficial if retroperitoneal exploration is considered. The authors would caution the reader regarding the quality of the single-shot IVP; this study is frequently a suboptimal examination with poor excretion/visualization of contrast, due to the patient's clinical status. The chief benefit of the single-shot IVP may be to detect a normally functioning contralateral kidney if unilateral nephrectomy is a consideration. As an alternative to the single-shot IVP, the patient can be stabilized and a delayed CT evaluation obtained. Definitive surgical repair of any GU injury is subsequently deferred for 12 to 24 hours (Azimuddin et al, 1997; Heyns, 2004).

Once the diagnosis of a traumatic renal injury is made, five possible complications can arise that may need to be addressed: (1) urinary extravasation, (2) an infected urinoma/perinephric abscess, (3) persistent or delayed renal hemorrhage, (4) hypertension, and (5) post-traumatic chronic pain syndrome.

Indications and Use of Arteriography: Management of Persistent/Delayed Hemorrhage and Persistent Urinoma

Approximately 25% of patients with a grade 3 to 4 renal trauma, managed in a nonoperative fashion, will develop persistent or secondary (delayed) hemorrhage (Wessells et al, 1997b; Dinkel et al, 2002; Goffette and Laterre, 2002; Kansas et al, 2004; Sofocleous et al, 2005, Al-Qudah and Santucci, 2006). Classically, delayed hemorrhage develops 5 to 14 days postinjury but may occur up to 1 month following the insult. Delayed hemorrhage usually arises from the development of arteriovenous

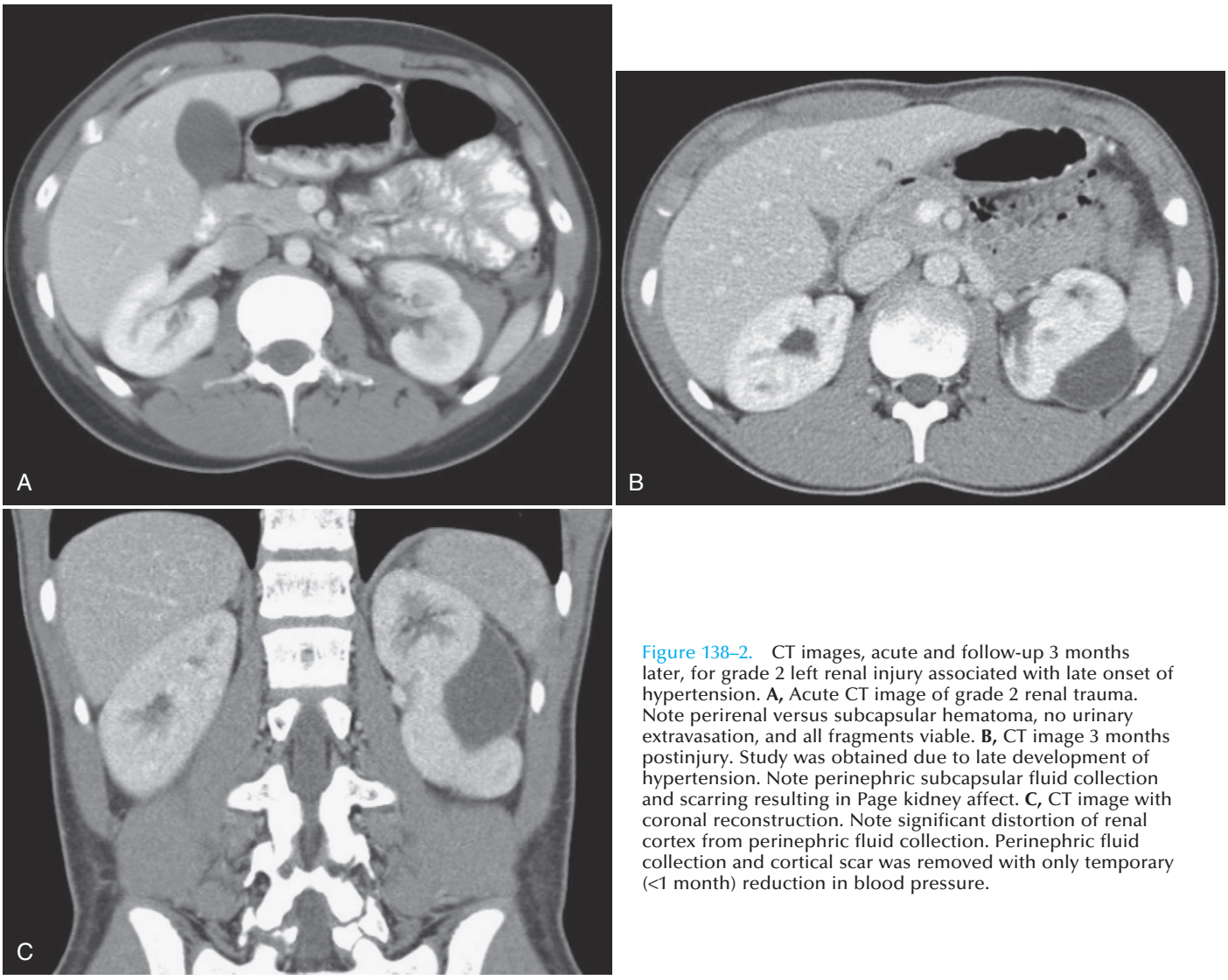


Figure 138–2. CT images, acute and follow-up 3 months later, for grade 2 left renal injury associated with late onset of hypertension. **A,** Acute CT image of grade 2 renal trauma. Note perirenal versus subcapsular hematoma, no urinary extravasation, and all fragments viable. **B,** CT image 3 months postinjury. Study was obtained due to late development of hypertension. Note perinephric subcapsular fluid collection and scarring resulting in Page kidney affect. **C,** CT image with coronal reconstruction. Note significant distortion of renal cortex from perinephric fluid collection. Perinephric fluid collection and cortical scar was removed with only temporary (<1 month) reduction in blood pressure.

fistulas or pseudoaneurysm malformations. In this scenario, the initial bleeding is tamponaded by the surrounding hematoma; as the hematoma resolves and liquefies recurrent bleeding develops. Unlike the arteriovenous fistulas noted after renal biopsy, where a spontaneous resolution rate of greater than 70% is found, the vast majority of arteriovenous fistulas occurring after renal trauma will not spontaneously resolve, with almost all cases of delayed hemorrhage secondary to trauma requiring active intervention (Heyns and Van Vollenhoven, 1992; Dinkel et al, 2002; Goffette and Laterre, 2002; Heyns, 2004; Sofocleous et al, 2005; Al-Qudah and Santucci, 2006; Breyer et al, 2008). **Superselective angiographic embolization of isolated renal artery branches for persistent or secondary hemorrhage has a success rate approaching 80%. The percentage of salvaged renal function postembolization varies depending upon the degree of the initial injury, but the median reported value is 30%. Surgery required following angiography is due to one of three problems: persistent or repetitive bleeding, postembolization abscess, or persistent urinary fistula from an isolated renal segment. Angiographic embolization is currently the preferred treatment method for persistent or delay bleeding with nonoperative management protocols. Surgical exploration is reserved for embolization failure** (Heyns and Van Vollenhoven, 1992; Dinkel et al, 2002; Goffette and Laterre, 2002; Heyns, 2004; Sofocleous et al, 2005; Al-Qudah and Santucci, 2006; Breyer et al, 2008).

Angiographic embolization will, on occasion, also be used to treat persistent urinary fistulas. In this scenario, a functional transected fragment of a grade 4 or 5 renal injury is completely separated from the renal collecting system, and a persistent urinary fistula/urinoma has developed despite management by double-J stent and percutaneous nephrostomy tube placement. In these rare patients, selective angiographic embolization will resolve the urinary fistula by necrosing the isolated functional renal fragment (Pinto and Chimeno, 1998; Heyns, 2004).

Postembolization syndrome is a well recognized and self-limiting condition manifested by pyrexia (up to 40° C), flank pain, and an adynamic ileus. Symptoms will usually resolve within 96 hours after the embolization. Unlike angioinfarction for renal tumors, where up to 60% of patients may develop postembolization syndrome, approximately 10% of patients following

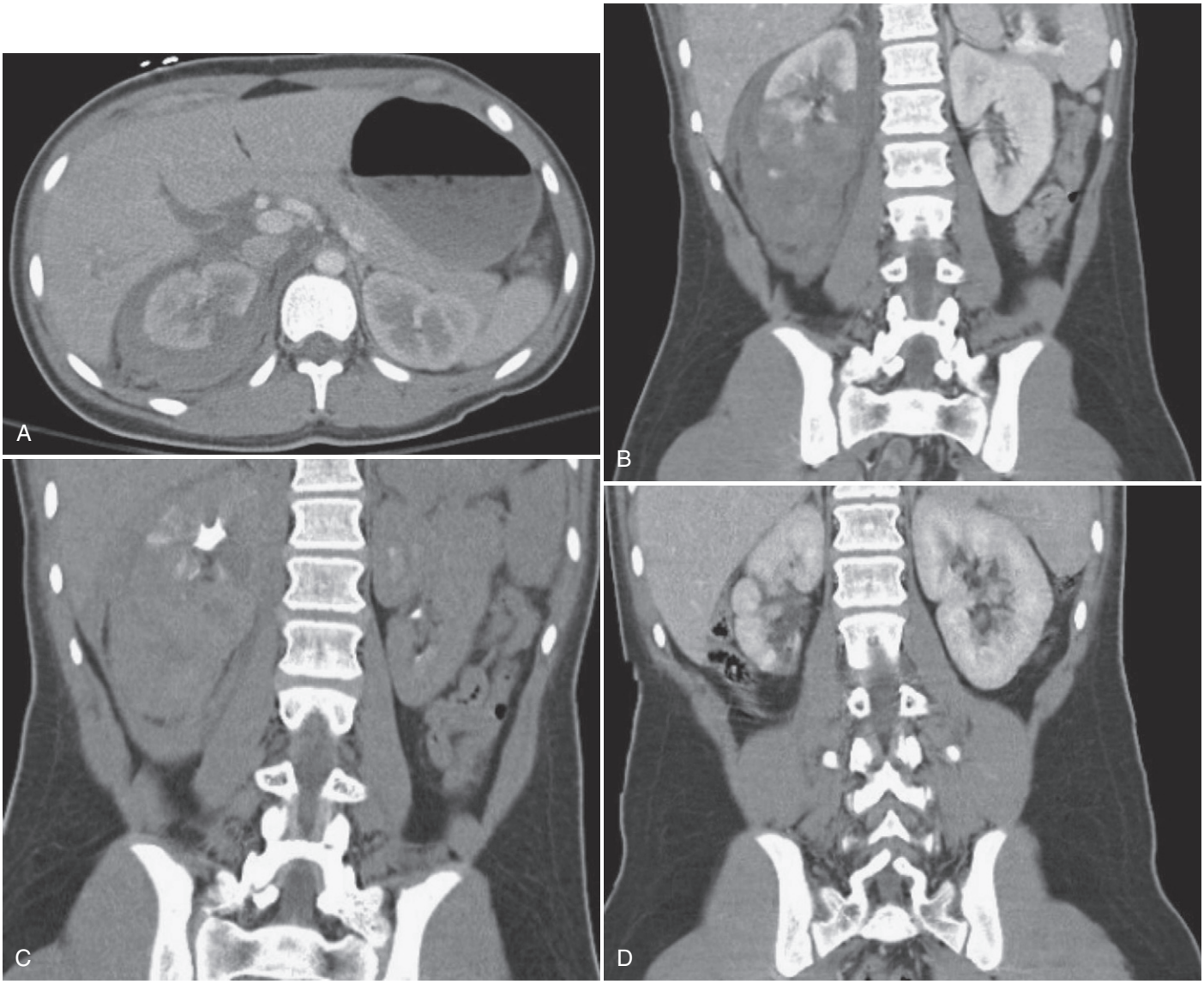


Figure 138–3. CT images of grade 3 right renal trauma—acute, delayed, and at 3-month follow-up. **A,** Acute CT image of grade 3 renal trauma showing greater than 1-cm laceration of midrenal pole, perinephric hematoma. **B,** Acute CT image coronal reconstruction of grade 3 renal trauma, with possible devitalization of the entire lower pole of the kidney. **C,** Two-hour delayed CT image coronal reconstruction of grade 3 renal trauma, with no urinary extravasation noted and lower pole with questionable devitalization versus contusion. **D,** CT image coronal reconstruction 3 months post-traumatic injury revealing parenchymal scarring at site of laceration with scarred but functional lower pole consistent with healed parenchyma following severe renal contusion. Scarring of lower pole was believed to have occurred with impoverished blood supply due to severe contusion.

angioinfarction after a traumatic injury develop this complication. The decrease in the frequency of this syndrome following trauma is believed to be secondary to fewer pyrogens being released from the already partially necrotic tissue (Oesterling et al, 1986; Kehagias et al, 1998; Kalman and Varenhorst, 1999; Heyns, 2004; Mitra et al, 2004; Sofocleous et al, 2005; Breyer et al, 2008). **The problem faced with persistent pyrexia following embolization is the need to rule out bacterial seeding of the necrotic tissue. It is therefore mandatory in the presence of a febrile response following embolization to obtain blood and urine cultures. Consideration for a repeat CT scan with possible aspiration, culture, and drainage of the hematoma/urinoma should be given if symptoms persist for greater than 96 hours** (Sofocleous et al, 2005; Breyer et al, 2008).

Indications and Use of Retrograde Pyelography, Percutaneous Nephrostomy, and Perinephric Drain Placement: Diagnosis of Ureteropelvic Junction Disruptions, Renal Pelvis Lacerations, and Management of Symptomatic Urinomas and Perinephric Abscesses

Two indications exist for the use of retrograde pyelography following renal trauma: (1) the need to diagnose a partial/total ureteral disruption or renal pelvic laceration and (2) the need to aid in the management of

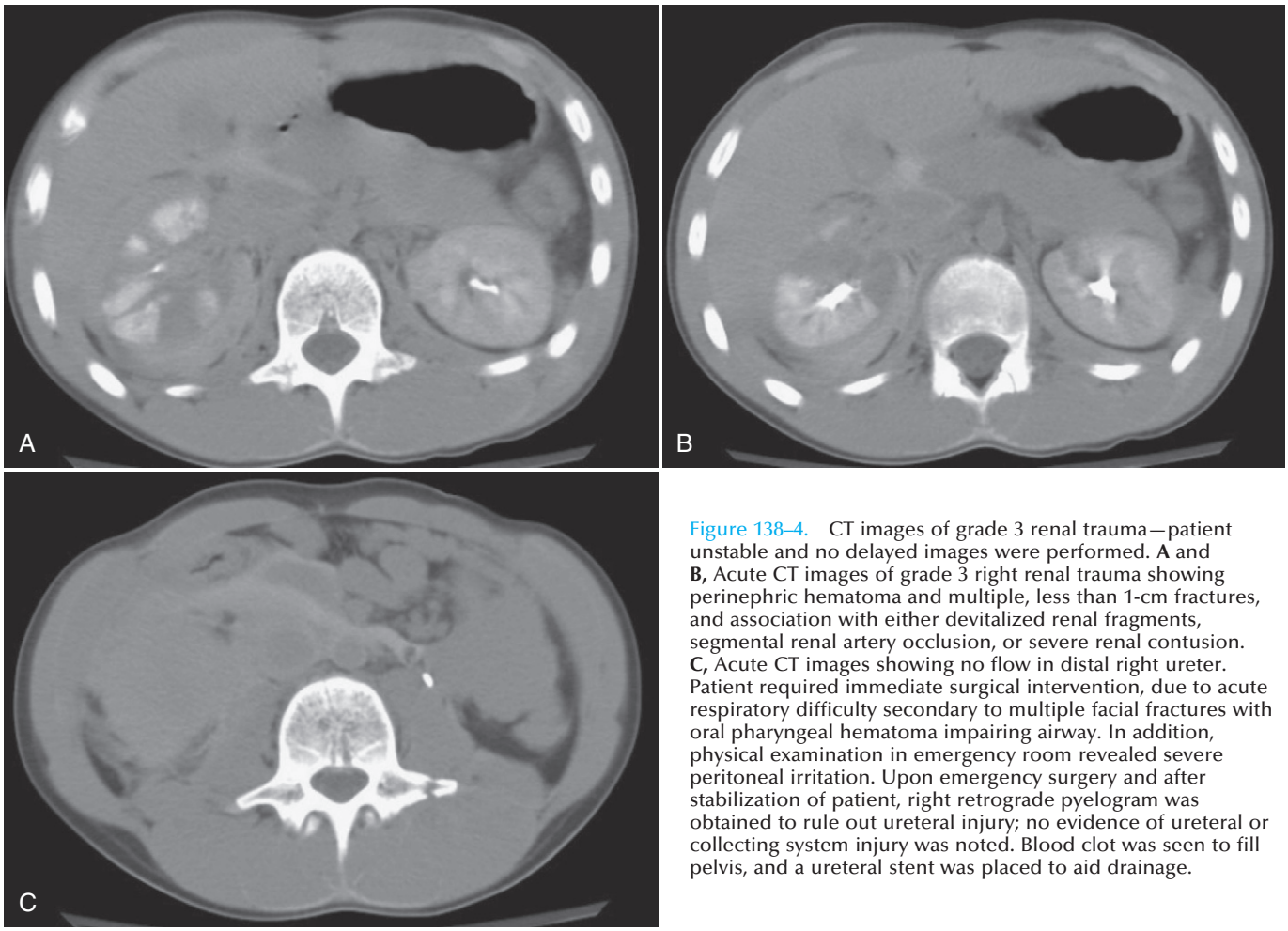


Figure 138–4. CT images of grade 3 renal trauma—patient unstable and no delayed images were performed. **A** and **B,** Acute CT images of grade 3 right renal trauma showing perinephric hematoma and multiple, less than 1-cm fractures, and association with either devitalized renal fragments, segmental renal artery occlusion, or severe renal contusion. **C,** Acute CT images showing no flow in distal right ureter. Patient required immediate surgical intervention, due to acute respiratory difficulty secondary to multiple facial fractures with oral pharyngeal hematoma impairing airway. In addition, physical examination in emergency room revealed severe peritoneal irritation. Upon emergency surgery and after stabilization of patient, right retrograde pyelogram was obtained to rule out ureteral injury; no evidence of ureteral or collecting system injury was noted. Blood clot was seen to fill pelvis, and a ureteral stent was placed to aid drainage.

a symptomatic urinoma (Boone et al, 1993; Kawashima et al, 1997; Heyns, 2004; Santucci et al, 2004b). Concern for a ureteral injury usually arises when a CT scan reveals urinary extravasation and no ipsilateral distal ureter is seen. In the presence of these CT findings, a retrograde pyelogram is mandatory. This study is performed to either confirm or refute the diagnosis of a ureteropelvic junction disruption or laceration of the renal pelvis, both of which require operative exploration and repair. If no evidence of these injuries is present we recommend a ureteral stent be placed following the retrograde pyelogram. This recommendation is based on prior studies revealing that patients with trauma-induced urinary extravasation who have absence of contrast in the ipsilateral distal ureter are at a higher risk for developing a symptomatic urinoma if left unstented (Boone et al, 1993; Kawashima et al, 1997; Chopra et al, 2002; McAleer et al, 2002b; Smith et al, 2003; Santucci et al, 2004b; Al-Qudah and Santucci, 2006; Broghammer et al, 2006; Cannon et al, 2008).

The second consideration for intervention with cystoscopy and retrograde pyelography is the presence of a symptomatic urinoma. **Although most post-traumatic urinomas are asymptomatic and have a spontaneous resolution rate approaching 85%, urinomas will occasionally persist. Symptomatic urinomas will develop a classic triad of findings: ipsilateral flank pain, adynamic ileus, and a low-grade temperature.** Management of these patients is by endoscopic intervention, with cystoscopy, retrograde pyelography, placement of a ureteral stent, urethral catheter drainage, and intravenous antibiotics. When a ureteral stent is placed in conjunction with temporary placement of a urethral catheter, greater than 90% of the symptomatic urinomas will resolve (Al-Ali and Al-Hajaj, 2001; Alskikafi et al, 2006). Classically, the urethral catheter is removed 3 to 5 days after the patient's clinical symptoms have abated. Intravenous antibiotics are discontinued and prophylactic antibiotics initiated at the time of urethral catheter removal. The author removes the ureteral stent 4 to 6 weeks postinjury and will maintain oral prophylactic antibiotic coverage for 48 hours after stent removal. It should be noted that both percutaneous nephrostomy drainage and internal stenting are equally efficacious for the treatment of symptomatic urinomas (Husmann and Morris, 1991; Husmann et al, 1993b; Philpott et al, 2003; Bozeman et al, 2004; Heyns, 2004; Keller et al, 2004; Al-Qudah and Santucci, 2006). The advantage of an internal stent is that it prevents possible dislodgment of the drainage tube and the need for external drainage devices. The two major disadvantages of internal drainage are that both stent placement and removal, in the pediatric patient population, require general anesthesia. In addition, the small-size ureteral stents (4 to 5 Fr) placed in young children may become blocked with blood clots from the dissolving hematoma, resulting in persistence of the urinoma (Husmann and Morris, 1991; Husmann et al, 1993b).

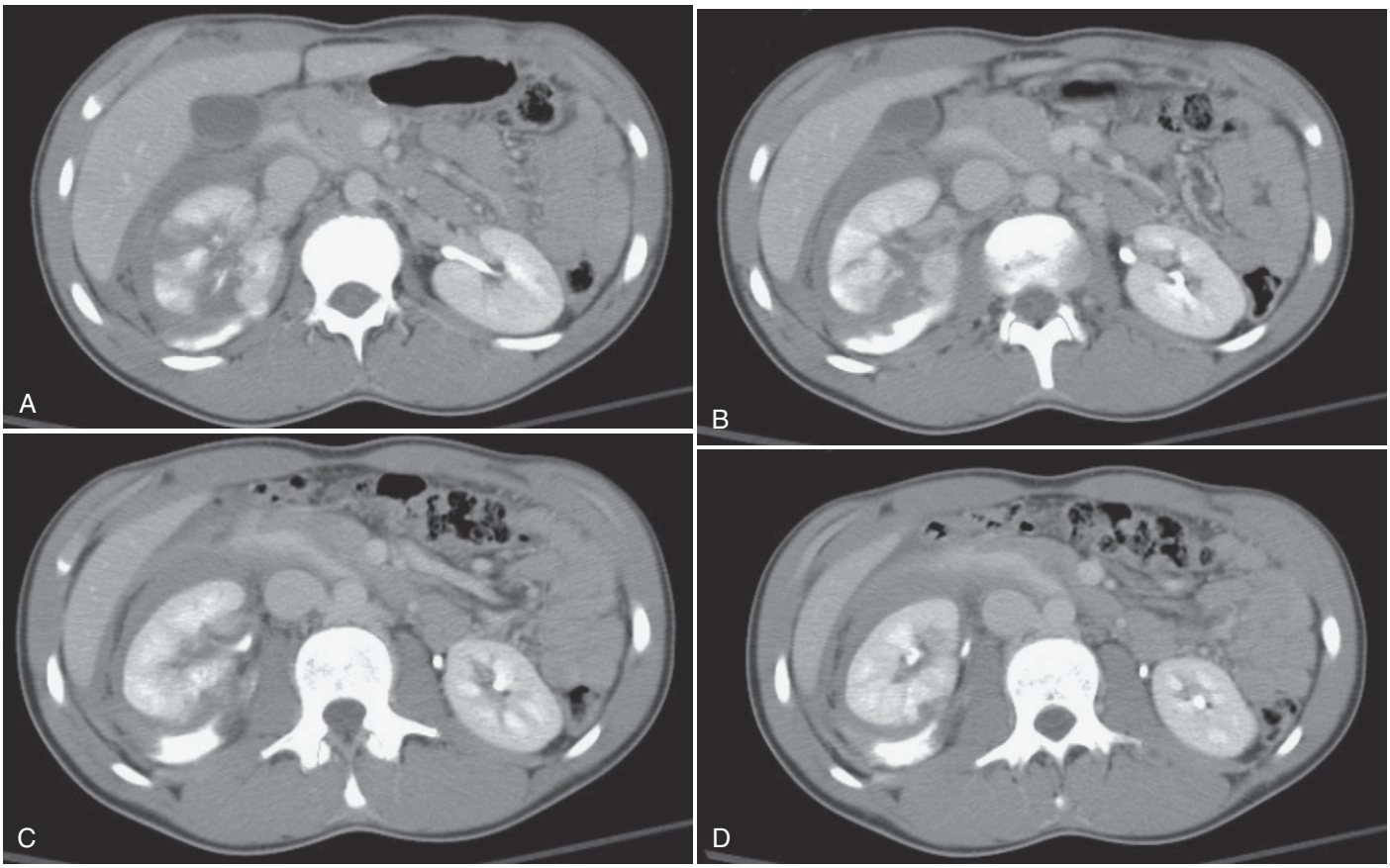


Figure 138–5. Acute and delayed images of grade 4 right renal injury. **A** and **B,** Acute CT image of grade 4 renal trauma with perinephric hematoma, severe (greater than 1 cm) fractures with devitalized renal segments, and urinary extravasation. **C** and **D,** 10-minute delayed CT revealing flow of contrast in ureter distal to injury, confirming patency of distal ureter. Patient was treated with observation only; no stent or drainage was necessary.

The development of a perinephric abscess postrenal injury is extremely rare, occurring in less than 1% of injuries following blunt renal injuries and in 5% of renal injuries caused by penetrating renal trauma. It is more commonly seen in patients when there is a confluence of injuries; specifically, a devitalizing grade 3 to 5 renal injury, in conjunction with either duodenal, pancreatic, or colonic injuries or, occasionally, in patients with large areas of traumatic soft tissue loss requiring frequent debridement. On rare occasions, a perinephric abscess may arise from seeding of a perinephric hematoma by an infected venous line or by ascending bacteria following bladder colonization (Husmann and Morris, 1991; Husmann et al, 1993b).

Symptoms of a perinephric abscess are intermittent febrile spikes, flank pain, persistent ileus, and elevated white count. These symptoms may exactly mimic those associated with an undrained symptomatic urinoma. In the absence of gas within the soft tissues, the differential diagnosis between a symptomatic urinoma and perinephric abscess may be very difficult. The author chooses to treat all patients with these findings for a symptomatic urinoma and will resort to additional percutaneous drainage of the perinephric fluid collection only if there is gas in the soft tissue at the time of initial diagnosis, or if the patient's febrile course persists after 72 hours of drainage through a ureteral stent and urethral catheter or nephrostomy tube (Husmann and Morris, 1991; Husmann et al, 1993b; Al-Qudah and Santucci, 2006).

Follow-up Radiographic Imaging after Renal Trauma: The ALARA Concept: As Low as Reasonably Achievable

Recommendations for follow-up renal imaging in the pediatric patient sustaining renal trauma has significantly changed over the past 5 years. This alteration is due to concerns regarding the future risk of radiation-induced malignancy (Brenner and Hall, 2007; Malcom et al, 2008; Shah and Platt, 2008; Eeg et al, 2009). **In the recent past, a repeat CT scan for all grade 3, 4, and 5 renal injuries was recommended during the acute healing phase, usually 3 to 5 days postinjury and again at 3 months.** The routine use of a CT scan 3 to 5 days post-trauma has been abandoned in an effort to decrease radiation exposure to children (Alskikafi et al, 2006; Malcom et al, 2008; Eeg et al, 2009). The principle that radiation exposure for diagnostic and follow-up purposes should be kept to a minimum is known as ALARA—as low as reasonably achievable. This concept currently permeates all of pediatric practice and has greatly impacted follow-up recommendations for post-traumatic injury. Presently, a CT scan is repeated in the acute post-traumatic phase only for patients who have symptoms; specifically, persistent or new onset of fever, persistent ileus, worsening flank pain, or persistent gross hematuria greater than 72 hours after the traumatic insult (Santucci et al,

2004b; Al-Qudah and Santucci, 2006; Buckley and McAninch, 2006; Bent et al, 2008; Malcom et al, 2008). Although some authors have advocated performing a screening ultrasonogram in this latter situation, with a CT scan used in the presence of abnormalities, the author and colleagues have frequently found the US study, in this situation, to be inconclusive, and it adds to the financial cost of patient evaluation and delays the inevitable CT scan. Based on our personal experience, we would preferentially recommend a CT scan for reevaluation if the clinical circumstances suggest reevaluation is necessary (Bent et al, 2008; Malcom et al, 2008; Eeg et al, 2009).

Currently no radiographic follow-up is recommended for grade 1 to 2 renal injuries, and renal ultrasonography at 3 months is recommended for grade 3 lacerations where all fragments are viable. There is controversy regarding radiologic follow-up for grade 3 renal lacerations associated with devitalized fragments, grade 4, and salvaged grade 5 renal injuries (Bent et al, 2008; Dunfee et al, 2008; Malcom et al, 2008; Eeg et al, 2009). **Although most authors recommend performing a repeat CT/magnetic resonance imaging (MRI) scan at 3 months, others advocate US, CT, or MRI be used only in the presence of abnormalities** (Eeg et al, 2009). **Our personal experience is that a renal US will inevitably be abnormal following high-grade renal injuries and will prompt additional evaluations. For cost-beneficial purposes, we will preferentially perform a CT evaluation, although consideration for a MRI study can be given in the older child when sedation/anesthesia would not be necessary.** The delayed study, 3 months postinjury, is done to document resolution of the urinary extravasation, assess the anatomy of the healed kidney, and rule out any occult complications (El-Sherbiny et al, 2004; Bent et al, 2008; Dunfee et al, 2008; Malcom et al, 2008; Eeg et al, 2009).

Serial dimercaptosuccinic acid (DMSA) scans obtained post-trauma have revealed that little, if any, renal parenchyma recovers function 1 week following injury; therefore nuclear renography obtained any time 1 week post-trauma results in a valid prognosis of renal function and can aid in the diagnosis of severe renal contusion versus a nonfunctional renal fragment following grade 3 and 4 injuries (see Fig. 138–3) (Wessells et al, 1997a; Moog et al, 2003). **Currently, renal scans are obtained in two circumstances: when there is concern for long-term renal prognosis or in the presence of post-trauma–induced hypertension** (Moog et al, 2003; Heyns, 2004). Classically, if the serum creatinine is normal, a differential renal function of greater than or equal to 30% demonstrates satisfactory ipsilateral renal function, which would prevent renal failure if the uninjured kidney is lost. In the presence of post-trauma–induced hypertension, mercaptoacetyltriglycine (mertiatide, MAG3) renography can be used to screen for trauma-induced renal vascular stenosis. Notably, the vast majority of patients with trauma-induced hypertension will have a kidney that has healed with a differential renal function of less than or equal to 20% (Wessells et al, 1997a; Moog et al, 2003; Heyns, 2004; Keller et al, 2004; Santucci et al, 2004b; Chedid et al, 2006) (Fig. 138–6).

MANAGEMENT OF RENAL TRAUMA

Multiple studies have stated that the nephrectomy rate in patients with traumatic renal injuries was higher with surgical exploration than with nonoperative management (Cass and Ireland, 1973; Cass et al, 1987; Kristjanson and Pederson, 1993; Hammer and Santucci, 2003; Keller et al, 2004; Broghammer et al, 2007). These papers suggested that hemorrhage from the severely injured kidney was held in check by a tamponade maintained by an intact Gerota fascia. Surgical exploration with disruption of the fascia resulted in uncontrollable renal bleeding and the need for emergent nephrectomy. Current studies reveal that this long-held hypothesis appears inaccurate. Specifically, with the enhanced

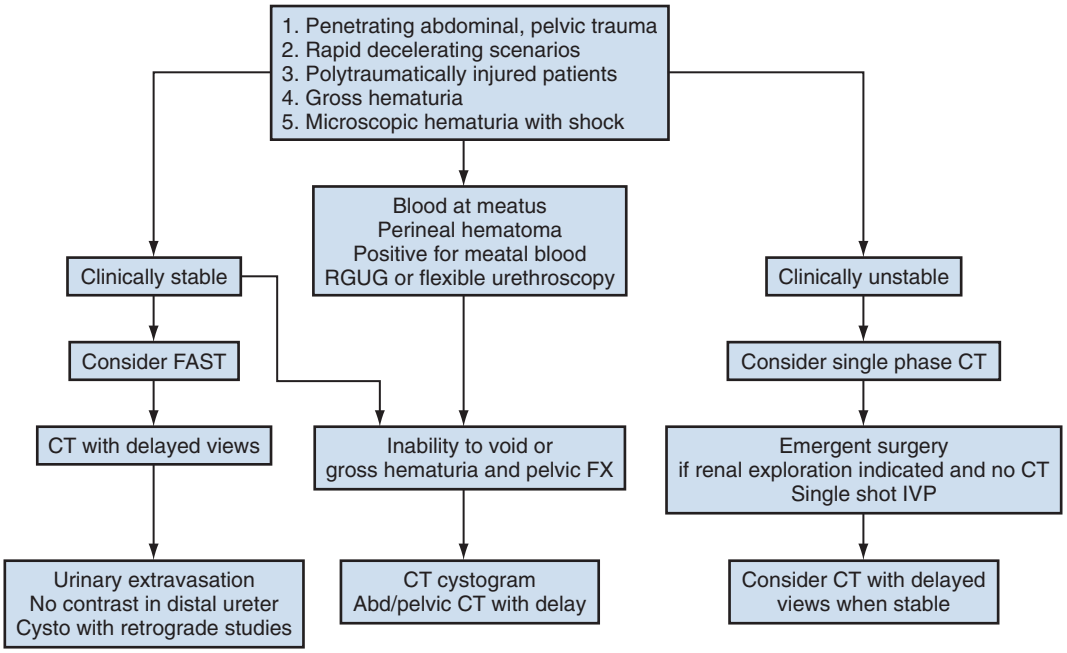


Figure 138–6. Abd, abdominal; CT, computed tomography; cysto, cystogram; FAST, focused assessment with sonography for trauma; FX, fracture; IVP, intravenous pyelography; RGUG, retrograde urethrogram.

Key Points: Radiographic and Endoscopic Assessment and Treatment of Pediatric Upper Tract Genitourinary Injuries

- Radiographic assessment of the GU tract for a possible injury should occur following all penetrating abdominal trauma, as well as blunt trauma victims who have one of four criteria: (1) a history of a significant deceleration or high-velocity injury, (2) significant trauma that has resulted in fractures of thoracic rib cage, spine, pelvis, or femur and bruising of the torso/perineum or signs of peritonitis, (3) gross hematuria, and (4) microscopic hematuria (>50 RBC/HPF) associated with shock (systolic blood pressure less than 90 mm Hg).
- A triphasic abdominal and pelvic CT scan is the most sensitive method for the diagnosis and classification of pediatric GU trauma.
- The two most likely GU injuries to be missed by a single-phase CT scan or single-shot IVP are urinomas and/or isolated ureteral injuries.
- Approximately 25% of patients with a grade 3 to 4 renal trauma, managed in a nonoperative fashion, will develop persistent or secondary (delayed) hemorrhage. Superselective angioinfarction of the bleeding vessel is the preferred method to manage this complication.
- Most post-traumatic urinomas are asymptomatic and will spontaneously resolve. Approximately 15% will be associated with continued flank pain, adynamic ileus, and/or low-grade temperature and require endoscopic or percutaneous management.
- Follow-up renal imaging is not recommended for grade 1 to 2 renal injuries and for grade 3 lacerations where all fragments are viable. Grade 3 renal lacerations associated with devitalized fragments, grade 4 and grade 5 renal injuries should have a repeat CT scan in the acute phase only if symptomatic; otherwise, a urinalysis and blood pressure check should be performed at 6 and 12 weeks postinjury and follow-up radiologic studies obtained at 12 weeks.

ability of the CT scan to accurately stage renal injuries and with the development and application of trauma-related severity scores, multiple current studies reveal that the need for emergent nephrectomy during renal exploration is not due to intractable hemorrhage incited by the renal exploration; rather, emergent nephrectomy is usually due to either the severity of the initial renal injury and/or was performed in patients who had severe intraoperative hemodynamic instability due to multiple coexisting injuries. Nephrectomy in this latter situation was performed for expediency to save the hypothermic, coagulopathic, and clinically unstable patient (Husmann et al, 1993b; Wessells et al, 1997b; Gonzalez et al, 1999; Santucci et al, 2001, 2004b; Santucci and McAninch, 2001; Bozeman et al, 2004; Davis et al, 2006; Wright et al, 2006; Broghammer et al, 2007; Shariat et al, 2007, 2008).

Although all authorities agree that a clinically stable patient with an isolated renal injury should be managed in a nonoperative fashion, considerable controversy exists regarding the management of grade 3 or higher renal injuries when intra-abdominal injuries that mandate surgical exploration are found. There are three schools of thought in this controversy: (1) Provided no absolute indications for renal exploration are present, all renal trauma should be observed (Altiman et al, 2000; Hammer and Santucci, 2003; Keller et al, 2004); (2) renal exploration and renorrhaphy of a grade 3 or higher renal injury should be carried out if a laparotomy was to be performed for a coexisting intra-abdominal injury (especially if the stomach, duodenum, pancreas, or colon was injured) (Corriere et al, 1991; Husmann et al, 1993b; Heyns, 2004; Santucci et al, 2004b); and (3) renal exploration can be excluded in patients with concurrent intra-abdominal injuries, provided the trauma surgeon separates the site of the enteric injury from the urinary tract by omentum or other alternative tissue and places perioperative drains. It is hypothesized that the separation of the two sites of injury and the placement of drains will prevent breakdown of enteric repairs caused by leaking urine and/or help prevent the development of urinary tract complications by removal of excess contaminating bacteria or pancreatic enzymes from the site of GU injury (Husmann et al, 1993b; Wessells and McAninch, 1996; Matthews et al, 1997; El Khader et al, 1998; Santucci et al, 2004b; Broghammer et al, 2007). **Due to the controversy, the major problem facing the urologist in the patient with traumatic renal injury is determining when to surgically intervene. The current recommendations on when to pursue operative intervention are based on three findings: the hemodynamic stability of the patient, an accurate radiographic staging of the renal trauma, and the presence of associated organ injury** (Table 138–3) (Husmann and Morris, 1991; Husmann et al, 1993b; Wessells et al, 1997b; Heyns, 2004; Santucci et al, 2004b; Buckley and McAninch, 2006).

Nonoperative Therapy for Renal Trauma

The ideal candidate for nonoperative management is the hemodynamically stable patient sustaining either blunt or penetrating trauma, with or without associated intra-abdominal injuries, and having a grade 1 to 2 renal injury. Genitourinary complications in this subset of patients are minimal (Wessells et al, 1997b; Heyns, 2004; Santucci et al, 2004b). **Patients who are hemodynamically stable with isolated grade 3, 4, and 5 renal injuries are also candidates for nonoperative treatment. Even identification of a large perinephric hematoma or urinoma is not an absolute contraindication for nonoperative management, provided the distal ureter is documented to be intact** (see Fig. 138–5). In patients with isolated grade 3 to 4 renal injuries, angiographic, endoscopic, or percutaneous intervention will be required in up to 55% of the patients. Intervention will be necessary for persistent or delayed bleeding in approximately 25%, symptomatic urinomas in approximately 25%, and surgical exploration to control complications not amenable to nonoperative techniques will develop in approximately 5%. In essence, conservative management of isolated grade 3 or 4 renal injuries will save approximately 95% of the patients by open surgical intervention (Husmann and Morris, 1991; Husmann et al, 1993b; El Khader et al, 1998; Bozeman et al, 2004; Buckley and McAninch, 2004, 2006; El-Sherbiny et al, 2004; Heyns, 2004; Santucci et al, 2004b; Broghammer et al, 2006, 2007; Henderson et al, 2007; Shariat et al, 2008).

Nonoperative therapy consists of bed rest, close monitoring of vital signs and urine output, serial abdominal examinations, serial hemoglobin/hematocrit determinations, and transfusion as indicated (Heyns, 2004; Santucci et al, 2004b). In patients with a renal injury secondary to penetrating trauma on a nonoperative protocol, intravenous broad-spectrum antibiotics are recommended,

Table 138–3.

Consensus Recommendations for Management of Renal Trauma

CLINICAL FINDINGS AND/OR GRADE OF RENAL INJURY	RECOMMENDED TREATMENT
Grade 1 or 2 renal injury irrespective of traumatic etiology*	Nonoperative
Isolated grade 3, 4, and hemodynamically stable grade 5 renal injuries	Nonoperative
Uncontrollable renal hemorrhage/vascular instability (usually grade 4 vascular or grade 5 injuries)	Absolute requirement for surgical intervention
Persistent or delayed hemorrhage not responding to angiographic embolization	Absolute requirement for surgical intervention
Expanding pulsatile retroperitoneal mass found on surgical exploration for coexisting intra-abdominal injuries	Absolute requirement for surgical intervention (verify contralateral renal function prior to exploration)
Penetrating trauma, inadequate preoperative radiographic staging due to vascular instability of patient, retroperitoneal hemorrhage found on exploration	Retroperitoneal (renal) exploration recommended (verify contralateral renal function)
Blunt trauma, inadequate preoperative radiographic staging due to vascular instability of patient, retroperitoneal hemorrhage found on exploration	Retroperitoneal (renal) exploration recommended (verify contralateral renal function)
Blunt/penetrating trauma, radiographic screening studies reveal grade 3 with devitalized renal fragments, grade 4 or 5 renal injury, coexisting intra-abdominal injuries—especially, duodenum, pancreas, and colon	Retroperitoneal (renal) exploration with renorrhaphy and repair recommended

due to the risk of wound contamination. In renal injuries following blunt trauma, antibiotics may be considered if a large retroperitoneal hematoma, urinary extravasation, or extensive soft tissue injuries are present. The use of antibiotics following blunt trauma is advocated due to the presence of indwelling urethral catheters and/or multiple intravascular catheters or superficial dermatologic abrasions that could serve as a nidus for bacteremic colonization of the urine or blood and, hypothetically, result in an infected hematoma or urinoma (Husmann and Morris, 1991; Husmann et al, 1993b; Al-Qudah and Santucci, 2006; Buckley and McAninch, 2004, 2006; Heyns, 2004; Kansas et al, 2004; Santucci et al, 2004b).

Concerns regarding the risk of radiation exposure in children have lead the author and colleagues to refrain from the routine use of serial CT imaging in the acute post-traumatic phase. Currently, we recommend repeat CT scan only be obtained during this time span in patients who have a persistent fever, decreasing hematocrit, persistent gross hematuria/flank pain, or persistent ileus.

If the child becomes hemodynamically unstable or continues to have a decreasing hemoglobin/hematocrit despite transfusions, renal angiography with selective angioinfarction of the bleeding site is recommended. If the patient develops a symptomatic urinoma, consideration for endoscopic or percutaneous management of the urinoma will be needed. Ambulation is allowed as soon as gross hematuria has resolved; resumption of strenuous physical activity should be avoided for 6 weeks. At 6 weeks, a physical examination and urinalysis are obtained; if the physical examination is normal and hematuria has cleared, the patient is allowed to resume all activities. Patients are reevaluated again at 12 weeks with a repeat physical examination and urinalysis, in addition to a repeat radiographic evaluation for patients with a grade 3 renal injury with devitalized fragments, grade 4, and grade 5 injuries (Wessells et al, 1997b; Heyns, 2004; Kansas et al, 2004; Santucci et al, 2004b; Al-Qudah and Santucci, 2006; Buckley and McAninch, 2006; Broghammer, 2007).

Operative Intervention for Renal Trauma

Absolute indications for renal exploration are hemodynamic instability due to a renal source, an expanding or pulsatile retroperitoneal hematoma, and inability to stop persistent or delayed hemorrhage by selective vascular embolization. Relative indications for exploration are a history of vascular instability resulting in an inability to obtain adequate preoperative radiographic evaluations, where surgical exploration for intra-abdominal injuries reveals a retroperitoneal hematoma. It is important to note that a single-shot IVP to verify contralateral renal function is required before renal exploration. Another relative indication for surgical exploration is the presence of coexisting intra-abdominal injuries associated with a grade 3 or higher renal injury (see Table 138–3) (Heyns, 2004; Santucci et al, 2004b). In this latter situation, the consensus opinion is that patients with a known grade 3 or higher renal injury undergoing exploratory laparotomy for multiorgan injury should undergo either renal exploration with renorrhaphy and the placement of retroperitoneal drains or separation of the urinary tract injury from adjacent enteric injuries by interposing omentum or other tissue with concurrent placement of adjacent drainage tubes. **Although the surgeon can choose between the two options noted above, he or she should be aware that the consensus opinion is that renal exploration and renorrhaphy are preferred** (Husmann et al, 1993b; Wessells et al, 1997b; Santucci and McAninch, 2001; Buckley and McAninch, 2004, 2006; Heyns, 2004; Santucci et al, 2004b).

Renal salvage by renorrhaphy or partial nephrectomy requires complete exposure of the injured kidney, debridement of nonviable tissue, suture ligation of bleeding arterial vessels, and repair of the collecting system injury. Defects in the renal parenchyma may be closed primarily with renal capsule. For larger defects, we prefer the placement of Gelfoam (Pfizer, New York, NY) and Surgicel (Ethicon, Somerville, NJ) packing into the parenchymal defect, with coverage or closure of the renal capsule defect using woven polyglycolic acid mesh. Alternatively, perinephric fat, omentum, or thrombin-soaked gel foam may be used to pack the parenchymal defect. Watertight closure of the collecting system is not always possible and may be inadvisable. If the renal pelvis or ureter is closed with excessive stretch, further devascularization, tissue sloughing, and delayed urinary leakage may occur. If a major violation of the urinary drainage system is present, placement of intraoperative ureteral stents or a nephrostomy tube should be considered. Adequate drainage of the perinephric area following repair is vital. In the presence of concurrent duodenal, pancreatic, and colonic injuries, interposition of omentum or peritoneum between the site of the major renal injury and the site of the coexisting intra-abdominal injury is strongly advised.

Nephrectomy should be considered in irreparable grade 4 to 5 renal injuries and in the hemodynamically unstable patient with multiorgan trauma. A nephrectomy in this latter situation may need to be performed to reduce operative time and help control bleeding in the hypothermic and coagulopathic patient (Heyns, 2004; Santucci et al, 2004b; Davis et al, 2006; Wright et al, 2006; Broghammer et al, 2007; Shariat et al, 2008).

Key Points: Renal Trauma

- The ability of the CT scan to accurately stage renal injuries, combined with the application of trauma-related severity scores, suggest that emergent nephrectomy at the time of surgical exploration is usually due to either surgical expediency in the unstable patient or preexisting vascular damage, but it is not the consequence of intractable hemorrhage incited by the renal exploration.
- Nonoperative management is preferred in the hemodynamically stable patient with a grade 1 or 2 renal injury, due to either blunt or penetrating trauma with or without associated intra-abdominal injuries. It is also the preferred treatment modality in isolated grade 3, 4, and 5 renal injuries.
- Identification of a urinoma is not a contraindication for nonoperative management, provided the distal ureter is documented to be intact.
- Absolute indications for renal exploration following trauma are (1) hemodynamic instability due to a renal bleeding, (2) an expanding or pulsatile retroperitoneal hematoma or, (3) inability to stop persistent or delayed hemorrhage by selective vascular embolization.
- There are two relative indications for renal exploration. The first is finding a retroperitoneal hematoma at the time of surgical exploration for intra-abdominal injuries in a patient with inadequate preoperative radiographic staging. A single-shot IVP to verify contralateral renal function is required before renal exploration. The second is CT-documented presence of a grade 3 or higher renal injury coexisting with intra-abdominal injuries that require abdominal exploration.

RENAL VASCULAR INJURIES

In terms of arterial renal blood flow, the kidney is an end organ; only rarely is collateral blood flow outside of the main renal arterial supply sufficient to maintain renal function. **In a patient sustaining renal arterial trauma, the clinical triad of hemodynamic instability, inadequate collateral blood flow, and warm ischemic time almost invariably results in the inability to salvage renal function** (Heyns, 2004; Santucci et al, 2004a). **Because of these conditions, no attempt to repair injuries to segmental renal vessels should be considered, and repair of the traumatically injured main renal artery is seldom, if ever, indicated when a normal contralateral kidney is present. In essence, reconstruction of the main renal artery following trauma is only a primary consideration in patients who are hemodynamically stable with an injury to a solitary kidney or in patients with bilateral renal arterial injuries** (Heyns, 2004; Santucci et al, 2004a). The infrequent exception to this rule is the presence of an incomplete arterial injury where perfusion to the kidney has been maintained by flow of blood through either the partially occluded main renal artery or through collateral vessels.

TRAUMA-INDUCED RENAL VASCULAR HYPERTENSION

The most common causes of post-traumatic renal hypertension are invariably rennin-mediated secondary to renal ischemia. Ischemia typically develops from one of four etiologies: a partial arterial stenosis, complete obstruction of a segmental or main renal artery with an intact peripheral blood supply, trauma-induced alteration in blood flow due to an arteriovenous malformation (AVM) or pseudoaneurism, or, on extremely rare occasions, compression of the renal parenchymal by hematoma/fibrosis/urinoma (Page kidney model). **The presence of hypertension immediately following the traumatic insult may be secondary to pain and resolve with observation. Persistent hypertension 30 days postinjury or hypertension developing within 3 months of the injury could be due to a trauma-induced renal source, and the diagnosis should be considered.** The incidence of trauma-induced hypertension after a grade 3 or higher renal injury is approximately 5% (Heyns, 2004; Santucci et al, 2004b; Al-Qudah and Santucci, 2006; Chedid et al, 2006; Henderson et al, 2007).

In patients with suspected traumatic hypertension, blood pressure is controlled with angiotensin-converting enzyme inhibitors. Also, evaluation with both nuclear renography, to determine differential renal function, and radiographic studies (MRI or CT angiography), to rule out an arteriovenous fistula or a pseudoaneurysm as the source of the hypertension, should be performed. Hypertension found to be related to a vascular malformation may be treated with angiographic embolization. If consideration for surgical intervention is entertained, renal vein renin sampling for split renin ratios should be considered. The latter is especially helpful in the presence of segmental renal scarring when partial nephrectomy is a consideration for surgical management. In this situation, hypertension proven to be related to segmental renal ischemia can be treated by partial nephrectomy. **The most common clinical finding in patients with post-traumatic hypertension is a small poorly functioning kidney (<20% function) associated with pan-nephric scarring; nephrectomy is the best surgical alternative** (Wessells et al, 1997b; Moog et al, 2003; Heyns, 2004; Keller et al, 2004; Santucci et al, 2004b; Chedid et al, 2006; Myrianthefs et al, 2007). Treatment of hypertension due to a subcapsular hematoma or fibrosis by decortication of the Page kidney has been published; however, the long-term results of this surgical treatment modality are extremely controversial (see Fig. 138–2) (Heyns, 2004; Santucci et al, 2004b; Myrianthefs et al, 2007).

TRAUMA-INDUCED CHRONIC FLANK PAIN FOLLOWING RENAL INJURY

Chronic flank pain developing post-traumatic renal injury is reported to occur in approximately 7% of patients following grade 3 or higher renal injuries. CT scans with delayed images and, occasionally, Lasix renograms are warranted. Findings of renal

Key Points: Renal Vascular Injuries and Trauma-Induced Renal Hypertension

- In renal arterial trauma, the clinical triad of hemodynamic instability, inadequate collateral blood flow, and warm ischemic time almost invariably results in inability to salvage renal function. Therefore repair of the traumatically injured main renal artery is seldom, if ever, indicated when a normal contralateral kidney is present.
- Hypertension secondary to renovascular trauma will usually develop within 36 months following the injury. If sustained hypertension does develop, evaluation with a DMSA scan, to determine differential renal function, and radiographic studies (MRI or CT angiography), to rule out development of an arteriovenous fistula as the source of the hypertension, should be performed. Hypertension found to be related to an arteriovenous malformation may be treated with angiographic embolization.
- The most common clinical finding in post-trauma–induced hypertension is a small poorly functioning kidney (<20% function) associated with pan-nephric scarring, with nephrectomy being the best treatment alternative.

Table 138–4.

Incidence of Pediatric Renal Injury Related to Mechanism of Injury

MECHANISM OF RENAL INJURY	PERCENTAGE OF RENAL INJURIES CAUSED BY BLUNT TRAUMA IN A PEDIATRIC POPULATION
Motor vehicle collision (including MV vs. pedestrian)	45%
Bicycle accidents (including dirt bikes and motor cross)	17%
Contact sports	12%
All-terrain vehicle accident	10%
Sports—miscellaneous (sledding, skiing, snowboarding, horseback riding, rollerblading, etc.)	7%
Falls	6%
Abuse/assault	3%

From Emmanuel et al, 1977; Amaral, 1997; Gerstenbluth et al, 2002; McAleer et al, 2002b; Johnson et al, 2005; Broghammer et al, 2006; Wu and Gaines, 2007.

lithiasis, UPJ obstruction, and persistent urinoma will occasionally be found. Unfortunately, the majority of patients will not have a clear etiology for their chronic pain syndrome. Treatment will usually involve pain management and, on rare occasions, nephrectomy. We would caution the surgeon that removal of the kidney does not necessarily correlate with resolution of the pain (Mogensen et al, 1980; Al-Qudah and Santucci, 2006).

RECOMMENDATIONS FOR ACTIVITIES IN PATIENTS WITH A SOLITARY KIDNEY

Th recommendations by the American Academy of Pediatrics are that all patients with a solitary kidney who desire to participate in contact sports should undergo individual physician assessment, with recommendations for participation based on the physician's findings. Most urologists are currently making their recommendations on the basis of the following facts. Contact sports are the third most common cause of renal injury in children (Table 138–4). The mean stage of traumatic renal injury occurring as a consequence of contact sports is lower than that of all other etiologic causes of traumatic renal injury in children. Specifically, the mean stage for renal injury following bicycle, motocross, and dirt bike accidents is 2.7 ± 1.0; all-terrain vehicle (ATV) accidents 2.4 ± 1.3; falls 2.4 ± 1.2; and motor vehicle collisions 2.1 ± 1.0 compared with the severity of injuries caused by contact and miscellaneous sports, which is 1.7 ± 1.0 (Fitness Committee on Sports Medicine and Fitness, 2001; Gerstenbluth et al, 2002; McAleer et al, 2002a; Johnson et al, 2005; Wu and Gaines, 2007). The facts as noted above have prompted most pediatric urologists to clear patients with one kidney for participation in organized contact sports, provided three baseline criteria are met: the remaining kidney has normal anatomy, it is in the normal anatomic position, and protective gear is worn. It has also resulted in the routine cautioning of parents and patients that the child with a solitary kidney should wear a seat belt or be restrained in a car seat at all times; ATV activities, motocross, and dirt bike racing are associated with increased risk for renal injury; and participation in these activities should be done with caution (Fitness Committee on Sports Medicine and Fitness, 2001; Gerstenbluth et al, 2002; McAleer et al, 2002a; Johnson et al, 2005; Wu and Gaines, 2007).

PREEXISTING HYDRONEPHROSIS AND URETEROPELVIC JUNCTION DISRUPTION

Disruption of the ureteropelvic junction is most commonly caused by acceleration-deceleration injuries, (falling from >15 feet) or by a sudden extreme hyperextension of the trunk (pedestrian-MVA, ejection injury associated with MVA). The mechanism of injury is hypothesized to be a sudden displacement of the more mobile kidney associated with a relatively fixed ureter, with force vectors from the traumatic impact interacting at the ureteropelvic junction (Boone et al, 1992; Chopra et al, 2002; McAleer et al, 2002a).

Although it has been reported that preexisting hydronephrosis or a congenital ureteropelvic junction obstruction renders the patient more susceptible to a UPJ disruption, this is controversial. The vast majority of patients with a history of trauma and preexisting UPJ or hydronephrosis will be found to have a renal contusion or grade 1 renal injury on evaluation (Fig. 138–7). If the initial CT scan reveals poor renal function secondary to a thinned cortex from the preexisting obstruction, we will usually place a percutaneous nephrostomy tube for 4 weeks and reassess function with a renal scan. Repair is recommended for patients with a differential renal function of greater than 20%.

When urinary extravasation is seen, rupture of the renal pelvis or a major laceration extending through a thinned renal cortex into the collecting system (grade 3 renal injury) is the most common finding, not a UPJ disruption (Boone et al, 1993; Hall and Carpinito, 1994; Gschwend et al, 1995; Kattan, 2001; Chopra et al, 2002; McAleer et al, 2002a; Smith et al, 2003; Ashebu et al, 2004). The majority of patients sustaining a UPJ disruption will present with vascular instability, requiring emergent laparotomy with the patient unable

to undergo preoperative imaging. Urinalysis on presentation will have some degree of hematuria in 70% of patients; however, 30% of patients with UPJ disruption will have a completely normal urinalysis. Emergent exploratory laparotomy for coexisting intra-abdominal injury is usually necessary, and exploration fails to reveal the presence of a retroperitoneal hematoma (Boone et al, 1993; Gschwend et al, 1995; Hall and Carpinito, 1994; Chopra et al, 2002; McAleer et al, 2002a; Smith et al, 2003; Ashebu et al, 2004; Al-Qudah and Santucci, 2006). Due to the frequent association of this injury with life-threatening trauma, the diagnosis of a ureteropelvic junction disruption is delayed for greater than 36 hours in more than 50% of patients (Boone et al, 1993; Kattan, 2001; Chopra et al, 2002; McAleer et al, 2002a; Al-Qudah and Santucci, 2006). Patients will eventually come to attention due to CT abnormalities found during the workup of persistent postoperative fever, chronic flank pain, continued ileus, or sepsis (Boone et al, 1993; Kattan, 2001; Chopra et al, 2002; McAleer et al, 2002a; Al-Qudah and Santucci, 2006). **Three classic findings on a triphasic CT scan are associated with UPJ disruption: (1) absence of parenchymal laceration, (2) medial extravasation of contrast in the perirenal and upper ureteral area, and (3) no visualization of the ipsilateral distal ureter** (Boone et al, 1993; Kawashima et al, 1997; Kattan, 2001; Chopra et al, 2002; McAleer et al, 2002a; Al-Qudah and Santucci, 2006).

Children with preexisting hydronephrosis secondary to congenital hydronephrosis or a UPJ obstruction almost invariably have the site of the injury being a major laceration through the thinned renal cortex (grade 3 renal injury) or laceration of the renal pelvis; rarely is disruption of the UPJ present. These patients should undergo a retrograde pyelogram to confirm continuity of the ureteropelvic junction and then can be safely managed with

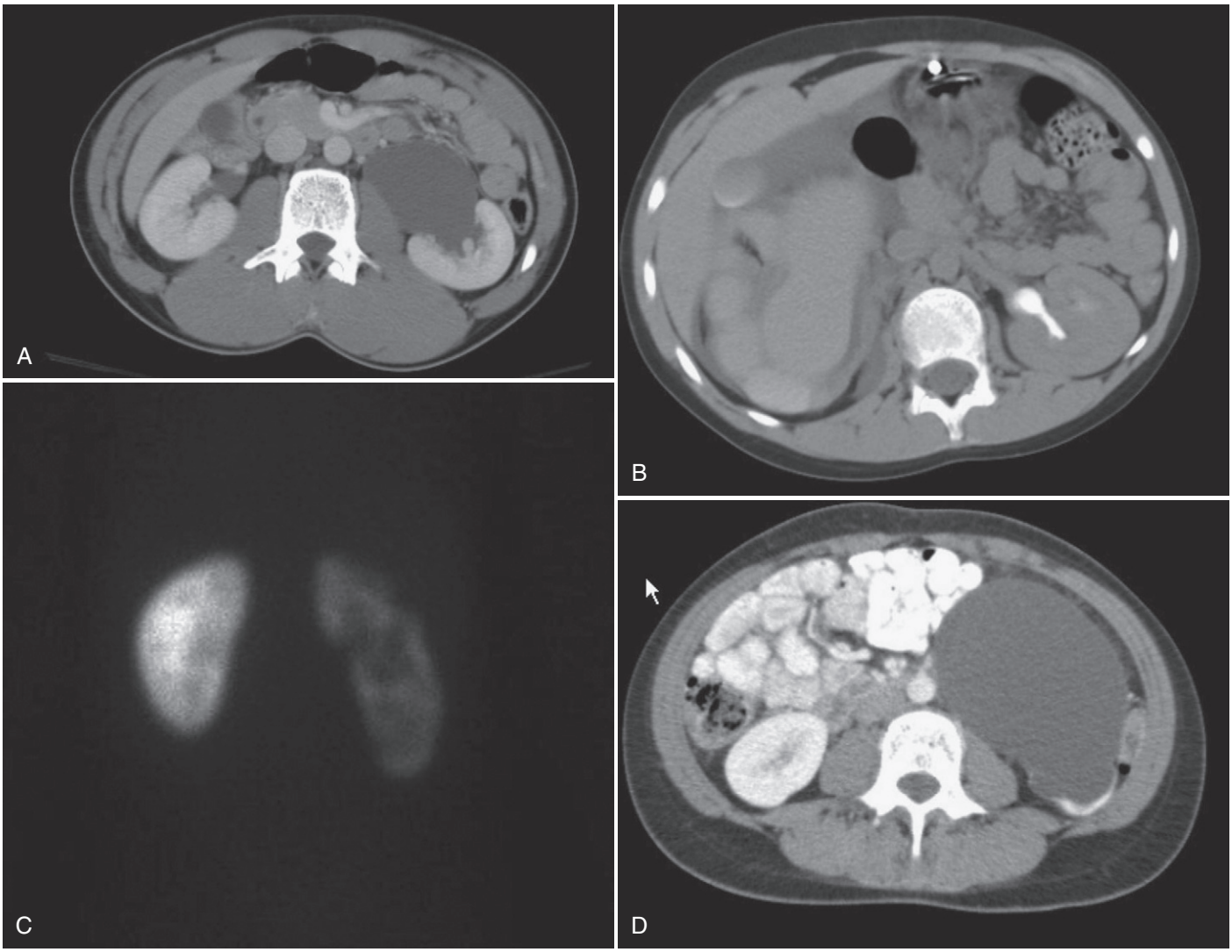


Figure 138–7. Spectrum of ureteropelvic junction (UPJ) obstructions presenting after renal trauma. **A,** A 16-year-old girl with gross hematuria and grade 1, left renal injury after low-speed (<10 mph) motor vehicle collision. **B,** A 14-year-old boy with gross hematuria after being struck in the right flank with a soccer ball. CT scan revealed grade 1 injury. Percutaneous nephrostomy was placed for 4 weeks with follow-up MAG3 scan as noted in **C**. **C,** MAG3 renal scan revealing 25% function of right kidney 4 weeks following percutaneous nephrostomy tube placement. UPJ repair was subsequently performed. **D,** A 14-year-old girl presented with gross hematuria after fall from a horse. Percutaneous nephrostomy was placed for 4 weeks, a DMSA renal scan showed less than 6% function at the end of 4 weeks, and a left nephrectomy was performed.

Continued

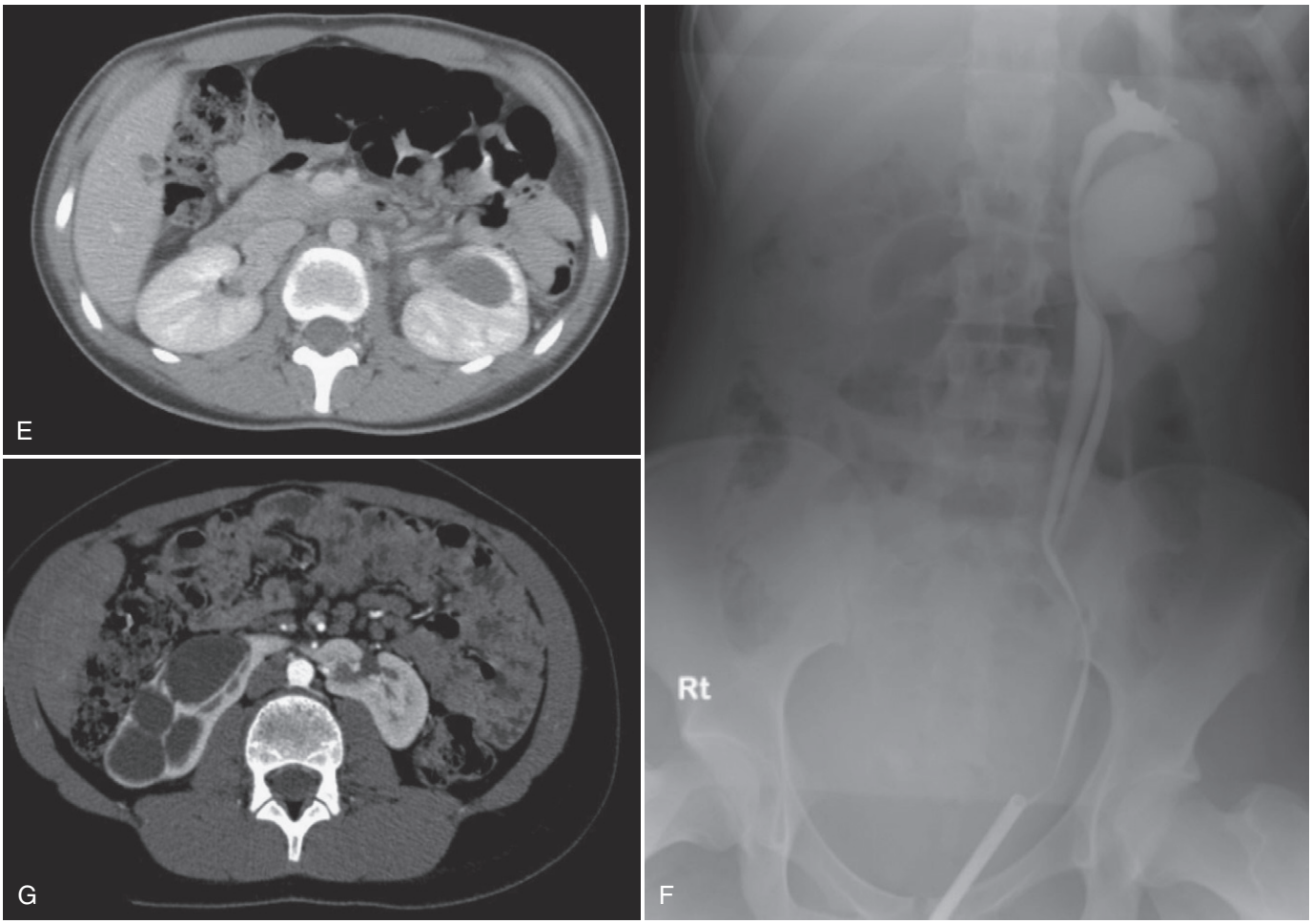


Figure 138–7, cont'd. **E,** A 15-year-old boy presented with gross hematuria following a fall while running cross country race; findings were suggestive of left lower pole UPJ obstruction. **F,** Left retrograde pyelogram confirmed incomplete left duplication with left lower pole UPJ obstruction. **G,** A 14-year-old male presented with gross hematuria following collision while playing hockey. CT scan revealed horseshoe kidney with severe right UPJ obstruction.

either a percutaneous nephrostomy or double-J stent placement, with delayed pyeloplasty performed following stabilization of the patient (Husmann and Morris, 1991; Matthews et al, 1997; McAleer et al, 2002a; Smith et al, 2003).

In patients with a disruption of the UPJ, a delayed diagnosis can reach up to 12 weeks postinjury and will significantly increase the risk of nephrectomy (Boone et al, 1993; Kattan, 2001; McAleer et al, 2002a; Smith et al, 2003; Kunkle et al, 2006). In the clinically stable patient, when the diagnosis is made within 5 days after the traumatic insult, we prefer to proceed to immediate surgical repair with debridement of any devitalized tissue, spatulation and re-anastomosis of the ureter over a stent, and placement of an intraoperative nephrostomy tube and retroperitoneal drain. Because the area of ureteral necrosis may extend for 2 to 3 cm, mobilization and downward displacement of the kidney may be necessary to obtain a tension-free anastomosis (Boone et al, 1993; Kattan, 2001; McAleer et al, 2002a; Smith et al, 2003). In patients with a delayed diagnosis of 6 or more days, we prefer to place a nephrostomy tube and allow the patient and injury to stabilize for 12 weeks. Differential renal function is then obtained using a DMSA renal scan, and the length of the ureteral injury is ascertained by a combined antegrade and retrograde pyelogram. The combination of remaining renal function and the length of the surgical defect allow the surgeon to make the proper surgical planning. Surgical alternatives in this situation include primary ureteroureterostomy, ileal ureter, autotransplantation, and nephrectomy. Notably, at the time of delayed repair there is usually significant technical difficulty in mobilization of the kidney, renal pelvis, and blood vessels; thus the option of nephrectomy should always be discussed and may become necessary (Boone et al, 1993; Kattan, 2001; Heyns, 2004; Santucci et al, 2004b; Kunkle et al, 2006).

URETERAL TRAUMA

External Trauma Resulting in Ureteral Injury

In children, external trauma causing ureteral injuries are rare, occurring in less than 4% of penetrating traumas and are reportable following blunt trauma (Velmahos and Degiannis, 1997; Velmahos and Demetriades, 2002; Hudolin and Hudolin, 2003; Kansas et al, 2004; Elliot and McAninch, 2006). Ureteral injuries will be found in conjunction with other intraperitoneal organ injuries in 90% of the patients and coexisting with renal or bladder

injuries in 10%. Due to the frequent presence of multiple organ injury, the mortality rate of a patient sustaining a ureteral injury from external trauma is in excess of 30% (Velmahos and Degiannis, 1997; Wessells et al, 1997b; Velmahos and Demetriades, 2002; Hudolin and Hudolin, 2003; Carver et al, 2004; Kansas et al, 2004; Elliot and McAninch, 2006).

Ureteral injuries associated with external trauma will lack the presence of hematuria in up to two thirds of the patients; the diagnosis is usually made by a triphasic CT study obtained to evaluate penetrating trauma and/or to rule out a GU injury following high-velocity deceleration or impact trauma (Velmahos and Degiannis, 1997; Wessells et al, 1997b; Medina et al, 1998; Velmahos and Demetriades, 2002; Hudolin and Hudolin, 2003; Carver et al, 2004; Kansas et al, 2004; Elliot and McAninch, 2006). **Gunshot wounds caused by a high-velocity missile (>350 m/second) deserve special mention. The kinetic energy of a high-velocity bullet creates a surrounding energy wave 30 to 40 times the missile diameter** (Al-Ali and Haddad, 1996; Perez-Brayfield et al, 2001; Hudolin and Hudolin, 2003; Carver et al, 2004; Santucci et al, 2004b). **In addition, the missile will frequently yaw or tumble during penetration, and the combination of blast injury and missile tumbling results in extensive damage to the surrounding tissues at a significant distance from its path. Of concern regarding high-velocity gunshot wounds to the torso is that radiographic and/or surgical evaluation at the time of the assault may not reveal the presence of a GU injury** (Al-Ali and Haddad, 1996; Medina et al, 1998; Brayfield et al, 2001; Hudolin and Hudolin, 2003; Carver et al, 2004; Perez-Santucci et al, 2004b; Kunkle et al, 2006). **In some patients with a high-velocity injury, the renal pelvis and/or ureter will appear intact or perhaps only slightly contused at the time of the radiographic examination and/or surgical exploration. As the high-velocity blast injury matures, necrosis of the ureter or portions of the renal pelvis may develop. The extent of the GU injury finally comes to attention as urinary extravasation develops due to delayed necrosis. Classically, blast injuries to the urinary drainage system present as an increase in urine output from surgically placed drains 3 to 5 days after the injury** (Al-Ali and Haddad, 1996; Medina et al, 1998; Perez-Brayfield et al, 2001; Hudolin and Hudolin, 2003; Santucci et al, 2004b; Carver et al, 2004; Kunkle et al, 2006).

Iatrogenic Ureteral Injuries Following Open, Laparoscopic, and Endoscopic Procedures

The most common iatrogenic ureteral injury in the pediatric population is following ureteroscopy; even these are rare events with ureteral perforations occurring in less than 2% of all prepubertal ureteroscopic procedures (Schuster et al, 2002; Wu and Docimo, 2004; Minevich et al, 2005). Ureteral perforation following ureteroscopy can almost invariably be managed with endoscopic intervention with ureteral stenting, with or without nephrostomy tube placement. Long-term results following endoscopic management are excellent (Schuster et al, 2002; Wu and Docimo, 2004; Minevich et al, 2005).

Traumatic ureteral injuries following laparoscopy or open surgical procedures are relatively common in adults following gynecologic and vascular surgery; however, literature reports of iatrogenic ureteral injuries following laparoscopic and open procedures in pediatric patients are extremely rare (Elliot and McAninch, 2006; Routh et al, 2009). The management of traumatic ureteral injuries revolves around the timing of diagnosis, with a delay in the diagnosis of greater than or equal to 6 days found in 50% to 60% of both pediatric and adult patients sustaining these types of injury (Elliot and McAninch, 2006; Routh et al, 2009).

If recognized at the time of surgery, surgical division of the ureter and/or partial ureteral excision should be managed based on the location and length of the ureteral injury. Options are ipsilateral ureteroureterostomy, ureteral reimplantation with or without a psoas hitch, trans-ureteroureterostomy (beware of placing the contralateral normal kidney at risk), or, on rare occasions, ureteral ligation placement of a nephrostomy tube and planned reconstruction in the next 48 to 72 hours. Ureteral contusions secondary to a high-velocity gunshot wound or inadvertent ligation of the ureter should be treated by removal of any offending clip or ligature and placement of a ureteral stent for 6 to 8 weeks. Long-term 1- to 2-year radiologic follow-up after removal of the stent or ureteral repair is necessary, because ureteral strictures or ureteral fistulae form over time (Al-Ali and Haddad, 1996; Ghali et al, 1999; Elliot and McAninch, 2006; Routh et al, 2009).

Patients diagnosed greater than or equal to 6 days after traumatic insult are usually managed by placement of a temporary percutaneous nephrostomy tube and/or ureteral stent and delayed definitive repair. **Notably, some authors have recommended management of all ureteral injuries diagnosed in a delayed fashion be with a percutaneous nephrostomy tube and stent placement** (Al-Ali and Haddad, 1996; Ghali et al, 1999). **Other authors have challenged this recommendation, noting that management of ureteral injuries with endoscopic methods alone has a complication rate of approximately 40%, usually with obliterative ureteral strictures; in comparison, delayed open repair has a complication rate of 10%** (Campbell et al, 1992; Selzman and Spirnak, 1996; Elliot and McAninch, 2006; Kunkle et al, 2006; Routh et al, 2009). We approach these patients using a combined approach, with an initial attempt to place a ureteral stent with or without a nephrostomy tube. If we successfully bridge the area of injury with a ureteral stent, we remove the stent 6 to 8 weeks following the traumatic insult and reassess the upper tract for developing hydronephrosis and renal function using ultrasonography and MAG3 diuretic renography 6 weeks later. If progressive hydronephrosis is noted, temporary drainage of the upper tract with nephrostomy tube is performed. Diagnostic radiographic studies to assess renal function and to assess the location and extent of stricture are subsequently performed a total of 12 weeks following stent removal. If we were unsuccessful in bridging the area of ureteral injury, we assess the patient approximately 12 weeks following the traumatic injury. Radiographic assessment at this time may employ a variety of modalities: antegrade and retrograde pyelography, nuclear renography to assess differential renal function, CT urography, and cystography.

The type of delayed ureteral repair to be used is based on the location and the extent of ureteral damage. Options include direct ureteral anastomosis to the renal pelvis, ureterocalycostomy, primary ureteroureterostomy, transureteroureterostomy, ureteral reimplantation with or without a psoas hitch, ileal ureter, autotransplantation, and, occasionally, nephrectomy. We would caution that the use of transureteroureterostomy places the contralateral uninjured kidney and ureter at risk. Based on this concern, we dislike transureteroureterostomy as a surgical

alternative in managing the difficult problems that arise following traumatic ureteral injuries (Elliot and McAninch, 2006; Routh et al, 2009).

Key Points: Traumatic Ureteropelvic Junction Disruption and Ureteral Injuries

- In patients sustaining a UPJ disruption, 30% will have a completely normal urinalysis.
- Due to the frequent association of traumatic UPJ disruption with life-threatening trauma, the diagnosis of this injury is delayed for greater than 36 hours in more than 50% of patients. Patients will eventually come to attention due to CT abnormalities found during the workup of persistent postoperative fever, chronic flank pain, continued ileus, or sepsis.
- Three classic findings on a triphasic CT scan are associated with UPJ disruption: (1) medial extravasation of contrast in the perirenal and upper ureteral area, (2) contrast extravasation in the absence of parenchymal lacerations, and (3) no visualization of the ipsilateral distal ureter.
- In the clinically stable patient, when the diagnosis of UPJ or ureteral disruption is made within 5 days after the traumatic insult, immediate surgical repair is the preferred treatment modality.
- In patients with a delayed diagnosis of UPJ or ureteral disruption made 6 or more days after the traumatic insult, placement of a nephrostomy tube, with or without a ureteral stent, with delayed repair at 12 weeks is preferred.
- The type of ureteral repair used is based on the location and extent of the ureteral injury.

BLADDER INJURIES

General Comments

The urinary bladder is well protected from external trauma by the bony confines of the pelvis. Due to the extensive pelvic protective mechanisms, when bladder injuries do occur, they are frequently associated with multiorgan trauma, with an average of three coexisting organ injuries and a mortality rate of 20% (Carroll and McAninch, 1984). Although it was once recommended that all patients with a history of blunt abdominal trauma presenting with either microscopic or gross hematuria should undergo bladder imaging, studies have revealed that this recommendation is associated with an extremely low yield for injury and is cost ineffective (Mokoena and Naidu, 1995; Cunningham et al, 1998; Iverson and Morey, 2001). **Absolute indications for bladder imaging following blunt abdominal trauma are currently limited to two indications: (1) the presence of gross hematuria coexisting with a pelvic fracture or (2) inability to void. Neither gross hematuria alone or pelvic fracture alone are absolute indications for screening** (Mokoena and Naidu, 1995; Cunningham et al, 1998; Iverson and Morey, 2001). Relative indications for bladder imaging following blunt abdominal trauma are urinary clot retention, perineal hematoma, and a history of a prior bladder augmentation. **Bladder imaging following penetrating trauma should be performed any time concern exists that the missile could have injured the bladder and/or if free abdominal fluid is found on the initial CT scan** (Cunningham et al, 1998).

Differences between Adults and Children in Traumatic Bladder Injuries: Lacerations through the Anterior Bladder Neck

Traumatic bladder lacerations in children are approximately two times more likely to extend through the bladder neck compared with the same injury in an adult (Husmann et al, 1990; Boone et al, 1992; Koraitim, 1997, 1999; Chapple, 2000; Ashley and Husmann, 2007; Routh and Husmann, 2007). The clinical importance of this fact is significant. Specifically, management of a bladder neck laceration with either a suprapubic tube alone and/or urethral catheter alone without coexisting repair of the bladder neck may result in the persistent extravasation of urine with the possible development of a pelvic urinoma/abscess, pelvic osteomyelitis, and an increased risk of permanent urinary incontinence (Husmann et al, 1990; Boone et al, 1992; Koraitim, 1997, 1999; Chapple, 2000; Ashley and Husmann, 2007; Routh and Husmann, 2007). The diagnosis of a bladder neck injury should be suspected any time extravasation of contrast is noted and a competent bladder neck cannot be documented with radiographic studies. **If concern for a bladder neck injury is present, the patient should undergo surgical exploration with opening of the bladder at the dome. Repair of the bladder neck should be by an intravesical approach with a multilayered closure. Great care should be given not to dislodge the pelvic hematoma to help prevent blood loss. The surgeon should be aware that anterior bladder neck lacerations are frequently associated with urethral injuries, and retrograde urethrography or cystoscopy to rule out this possibility should be considered. If a bladder neck laceration is repaired, a voiding urethrocystogram (VCUG) is necessary at the time of catheter removal to adequately visualize the bladder neck and confirm healing** (Husmann et al, 1990; Boone et al, 1992; Koraitim, 1997, 1999; Chapple, 2000; Ashley and Husmann, 2007; Routh and Husmann, 2007).

Diagnosis of Bladder Injuries

The diagnosis of a traumatic bladder injury should be assessed by either standard or CT cystography. Either modality is accurate, provided adequate bladder distention occurs. **In a child, the amount instilled within the bladder should, at a minimum, be equal to one half of the estimated bladder capacity for age (60 cc at birth and 30 cc for each year thereafter); instillation of contrast can stop at the maximum of bladder capacity for age, a total of 300 cc or if a bladder contraction occurs.** We would discourage performing a CT cystogram by plugging the catheter and evaluating the bladder at the time of the initial CT scan. Frequently, the injured patient has oliguria secondary to hypovolemia, resulting in diminished urine output with inadequate filling of the bladder. In our experience, performance of a CT cystogram by plugging the catheter alone has led to missing the diagnosis of a traumatic bladder injury on multiple occasions (Husmann, 1996; Haas et al, 1999; Peng et al, 1999; Deck et al, 2001; Iverson and Morey, 2001).

Classification and Treatment of Traumatic Bladder Injuries

All patients with traumatic bladder lacerations, either extra- or intraperitoneal, should initially be treated with intravenous antibiotics, with oral antibiotic therapy continued for 48 hours following removal of bladder catheters. Extraperitoneal injuries are twice as common as intraperitoneal injuries and are almost invariably associated with a pelvic fracture. Classically, extraperitoneal bladder ruptures will have a star-burst appearance on radiographic studies. **In the presence of an extraperitoneal bladder injury, consideration for open surgical intervention should be given if a bony spicule is found to protrude into the bladder on CT evaluation or if concern for a bladder neck laceration is present** (Kotin and Koch, 1995; Husmann, 1996; Ashley and Husmann, 2007). **If these two complications are not present, management by an indwelling urethral catheter can be considered.** The age and size of the patient plays a major role in determining if the individual can be managed by an indwelling urethral catheter. In our experience, a small-caliber urinary catheter placed in young children will frequently be occluded by blood clots. Placement of a large-bore urethral catheter to allow better drainage is a concern in young boys, due to the possibility of producing a urethral stricture; therefore a large-caliber suprapubic tube should be placed (Kotin and Koch, 1995). Urinary drainage through the bladder catheter is maintained for 7 to 10 days, and a cystogram should be obtained to verify healing of the injury prior to catheter removal.

Intraperitoneal bladder injuries will initially appear as free fluid in the abdomen on a CT scan. Instillation of contrast in the bladder will result in extravasation of the contrast into the peritoneal cavity. Almost all intraperitoneal bladder ruptures occur at the dome of the bladder, the site of least support by the perivesical surrounding structures. Because these lacerations are usually large in size, the integrity of the bladder neck frequently cannot be assessed by radiographic means (Husmann, 1996). **In intraperitoneal bladder injuries, open surgical repair of the laceration is the recommended treatment modality. This allows the surgeon to reduce any herniating omentum or small bowel from the confines of the bladder and allows careful intravesical inspection of the bladder neck at time of surgical exploration.** In all patients, a perivesical drain is placed, and a large-bore urinary catheter is used to provide urinary drainage. In younger females and/or boys, persistent gross hematuria with clots may occlude small-caliber urethral catheters, and placement of a larger-bore suprapubic tube is usually merited. Urinary drainage for 7 to 10 days postinjury should be provided and a cystogram obtained prior to catheter removal.

Key Points: Traumatic Bladder Injuries

- Absolute indications for bladder imaging following blunt abdominal trauma are currently limited to two indications: (1) the presence of gross hematuria coexisting with a pelvic fracture or (2) complaints of inability to void.
- Bladder imaging following penetrating trauma should be performed any time concern exists that the missile could have injured the bladder and/or if free abdominal fluid is found on the initial CT scan.
- Traumatic bladder lacerations in children are approximately two times more likely to extend through the bladder neck compared with the same injury in the adult.
- Failure to repair a bladder neck injury may result in the persistent extravasation of urine, with the possible development of a pelvic urinoma/abscess, osteomyelitis, and increased risk of permanent urinary incontinence.
- Traumatic bladder injuries can be accurately diagnosed by either standard or computerized tomographic cystography, provided adequate bladder distention occurs. In a child, the amount instilled within the bladder should, at a minimum, be equal to one half of the estimated bladder capacity for age.
- In the presence of an extraperitoneal bladder injury, consideration for open surgical intervention should be given if a bony spicule is found to protrude into the bladder on CT evaluation or if concern for a bladder neck laceration is present. If these two complications are not present, management by an indwelling urethral catheter can be considered.
- In intraperitoneal bladder injuries, open surgical repair of the laceration is the recommended treatment modality. This allows the surgeon to reduce any herniating omentum or small bowel from the confines of the bladder and allows careful intravesical inspection of the bladder neck at time of surgical exploration.

URETHRAL INJURIES

Differences between Pediatric and Adult Patients in Urethral Injuries

Due to the immature pelvis and the relatively intra-abdominal position of the child's bladder, children with a posterior urethral injury will differ from adults with this injury in four ways. **First, a pelvic fracture is more likely to be unstable and associated with a severely and permanently displaced prostatic urethra. Second, the severe displacement of the prostate off the pelvic floor makes a complete posterior urethral disruption more common in boys than in men. Third, in children, concurrent bladder and urethral injuries may occur in up to 20% of the patients, with coexisting anterior longitudinal tears though the bladder neck and sphincteric complex being twofold more common in children compared with adults. Fourth, in prepubertal girls, pelvic fractures are four times more likely to be associated with a urethral injury than in adult women** (Husmann et al, 1990; Boone et al, 1992; Perry and Husmann, 1992; Koraitim, 1997, 1999, 2004; Chapple, 2000; Hemal et al, 2000; Ashley and Husmann, 2007; Routh and Husmann, 2007).

The clinical impact of these differences is noteworthy. Permanent displacement of the prostate off the pelvic floor results in an increased need for either a transpubic, trans-symphyseal, or combined transpubic and perineal dissection for urethral reconstruction compared with the adult patient population. Hypothetically, the severe displacement of the prostate off of the pelvic floor raises concern that erectile dysfunction will be more common in children sustaining a urethral injury than in adults (Boone et al, 1993; Koraitim, 1997; Chapple, 2000; Basiri et al, 2002). There is also apprehension that permanent urinary incontinence may be more likely in children following this injury, due to the increased risk

of combined injuries to the posterior urethra, bladder neck, and sphincteric complex (Husmann et al, 1990; Boone et al, 1992; Perry and Husmann, 1992; Hemal et al, 2000; Rosenstein and Alsikafi, 2006; Ashley and Husmann, 2007; Routh and Husmann, 2007).

Initial Presentation of Urethral Injury

Consideration for a urethral injury should arise any time a patient presents with a history of direct trauma to the penis, vagina, perineum, or pelvis. Radiographic or cystoscopic evaluations to rule out this injury are mandatory in the following circumstances: **(1) when the patient presents with the classic triad of perineal/penile hematoma, blood at the meatus/vaginal introitus, and inability to void; (2) when there is a pelvic fracture with one or more fractured pubic rami or symphyseal diastases; (3) when radiographic findings are suggestive of a bladder neck injury** (Chapple, 2000; Rosenstein and Alsikafi, 2006).

Association of Pelvic Fractures to Posterior Urethral Distraction Injuries

Approximately 5% of patients sustaining a pelvic fracture will have a urethral injury. **The risk of a urethral injury following a pelvic fracture is directly related to the number of pubic rami fractures present, the degree of separation of the pubic symphysis, and the presence of a concurrent diastasis of the sacroiliac joint. A Malgaigne fracture, that is, a pelvic fracture that has disruption of the ischiopubic rami coexisting with diastasis of the sacroiliac joint, has the highest risk of urethral injury** (Colapinto, 1980; Kricum, 1990; Koraitim, 1996, 1999, 2004; Kommu et al, 2007). In turn, the likelihood of a urethral injury following isolated pelvic fractures of the acetabulum, ilium, and sacrum that do not involving a fracture of a ramus or the separation of the pubic symphysis is essentially zero.

Diagnosis of Urethral Injuries

In males, a retrograde urethrogram (RGUG) is the diagnostic modality of choice to rule out the presence of a urethral injury. In the pre- and postpubertal female, findings suggestive of a urethral injury are frequently noted on a CT evaluation; however, we prefer to confirm the diagnosis by cystoscopy and vaginoscopy performed under general anesthesia (Husmann et al, 1990; Boone et al, 1992; Perry and Husmann, 1992; Venn et al, 1999; Rosenstein and Alsikafi, 2006).

When a urethral injury is found to coexist with a pelvic fracture, a concurrent rectal injury will be present in 15% of children. It used to be mandatory for a digital rectal examination (DRE) be performed in these children to assess for the presence of the concurrent rectal injury. Current studies, however, have revealed the DRE to be highly inaccurate for diagnosing either a displaced prostate or a rectal injury. The ability of the DRE to correctly diagnose the presence of these findings was less than 15%, with radiographic studies and endoscopy being far more specific and sensitive for such a diagnosis. The emergency medicine community has subsequently recommended that the DRE be abandoned in the evaluation of the traumatically injured patient under these circumstances (Shlamovitz et al, 2007a, 2007b). When a rectal injury is identified to coexist with a urethral disruption treatment with a temporary diverting colostomy, it is mandatory to prevent the disastrous consequences of pelvic abscess, pelvic osteomyelitis, and necrotizing fasciitis that can accompany an unrecognized rectal injury.

General Comments Regarding Repair of Urethral Injuries: Immediate, Delayed, and Late Urethroplasty

In the early phase of the injury, the most important potential urologic complication is infection induced by bacterial contamination of the pelvic/perineal hematoma and extravasated urine. **Immediate treatment of urethral injuries should include the administration of broad-spectrum antibiotics, assessment of the competence of the bladder neck, and the establishment of urinary drainage.** Repair of the urethral injury may be immediate (primary realignment or sutured primary end-to-end anastomosis, less than 2 days postinjury); delayed (primary realignment or sutured end-to-end anastomosis), occurring 2 to 14 days following injury; or late (any type of repair occurring 3 months or more after injury) (Boone et al, 1992; Perry and Husmann, 1992; Venn et al, 1999; Rosenstein and Alsikafi, 2006; Ashley and Husmann, 2007; Routh and Husmann, 2007).

Anterior Urethral Injuries

Anterior urethral injuries in children are usually iatrogenic, due to urethral instrumentation, circumcision, or injury occurring during the repair of a congenital anorectal malformation. If the anterior urethra was injured due to urethral instrumentation, acute management should be with antibiotic therapy, followed by establishment of urethral continuity with catheter drainage. Preferably, a urethral catheter is placed by either radiologic or endoscopic techniques and maintained for 5 to 21 days, depending on the extent of the injury (Maheswari and Shah, 2005; Kommu et al, 2007). If urethral continuity cannot be established, alternative treatments include temporary suprapubic tube placement or vesicostomy. If a urethral or suprapubic catheter is placed, a VCUG is obtained at the time of anticipated removal. If no persistent urethral injury is noted, in infants we obtain a follow-up RGUG after 3 months; alternatively, in a child who is potty trained, a flow rate with ultrasound residual urine is adequate for follow-up. If a permanent urethral stricture develops, we will usually defer definitive surgical repair until the child is either greater than 1 year of age, or, if the child is older than 1 year of age, wait at least 3 months from the time of the injury, that is, a late urethroplasty. The delay in the repair allows the stricture to clearly delineate the extent of the injury, allowing the physician to plan for the urethral reconstruction.

Three types of urethral injuries can result following a circumcision: meatal injury, loss of the distal urethra secondary to partial or complete glanular amputation, or the development of a urethrocutaneous fistula due to ischemic necrosis of the urethra (Gluckman et al, 1995; Baskin et al, 1997).

The latter injury usually occurs when the urethra was either crushed by a circumcision clamp or when a cautery or a suture ligature was used to stop bleeding from a vessel that was overlying the urethra (Baskin et al, 1997). Immediate repair of the acutely traumatized anterior urethra can be technically difficult. When the meatus is injured, a formal meatoplasty should be performed

to prevent meatal stenosis from developing. When the glans with distal urethra has been amputated, it may be reattached successfully using a direct spatulated suture anastomosis of the urethra and glans with urethral stenting, perioperative antibiotics, and a compressive dressing for immobilization of the glans. When a partial distal urethral injury has occurred without substantial glans loss, suture reapproximation of the meatus, that is, a meatoplasty, can be performed. After healing, a delayed repair using hypospadias techniques may be used if necessary. Urethrocutaneous fistulas are repaired using techniques similar to those used to close fistulas following a hypospadias repair; this surgery is usually delayed until the child is 6 to 9 months of age for technical reasons (Gluckman et al, 1995; Baskin et al, 1997).

We have had a number of children referred to us for repair of urethral injuries that occurred at the time of surgical correction of their congenital anorectal malformation. **In our experience, this injury is usually due to one of two causes: no urethral catheter was in situ at the time of the rectal repair or the urethral catheter had been placed into the rectum through the urethral-rectal fistula**. In these circumstances, the proximal penile or bulbar urethra is usually excised or partially avulsed at the time of rectal dissection. The injury is frequently identified when the child is unable to void following surgery or voids through the perineal wound. The importance of an appropriately placed urethral catheter at the time of anorectal repair cannot be understated. Initial placement of the catheter prior to repair of the anorectal malformation may be difficult, because the catheter hangs up at the site of the rectourethral fistula or inadvertently passes into the rectum. Placement of the catheter over a cystoscopically placed glidewire prior to the surgical repair of this congenital anomaly is frequently helpful. This allows easy identification of the urethra, and if the urethral catheter becomes exposed during the case, the problem is recognized immediately and can usually be primarily repaired, with rare long-term consequences (Spence, 1954; Williams and Grant, 1969; McLorie et al, 1998; Hong et al, 2002).

Assessment of Urethral Stricture Prior to Delayed Repair

At the time surgical reconstruction is considered, usually 3 months postinjury, a retrograde urethrogram, followed by a simultaneous RGUG and VCUG, are the first three studies performed. If a suprapubic catheter or vesicostomy has been performed, a static cystogram is also performed. A correctly performed RGUG will allow the physician to identify the location of the urethral stricture but may not allow the appropriate determination of stricture length, especially if an extremely tight bulbar or posterior urethral distraction injury is present. Proper interpretation of these three radiographic studies is essential for true estimation of the defect between the disrupted urethral ends. Without correct interpretation of the studies, the urethral defect may be underestimated (contrast filling of a urinoma cavity associated with an incompetent bladder neck) or overestimated (nonfilling of the normal urethra due to failure of the bladder neck to open with voiding). When contrast from the static cystogram is found in the posterior urethra, it arouses suspicion for a bladder neck injury and mandates further evaluation as outlined below. If the bladder neck is competent, we obtain a simultaneous RGUG and VCUG. Great care should be taken in interpreting these films. More often than not, the pediatric patient will be unable to void and will fail to open the bladder neck. This results in non-visualization of the proximal urethral segment and may cause a spurious estimation of a long distraction defect. **If the posterior urethra fills with contrast on the static cystogram, this could be due to either a poorly felt or described detrusor contraction or an incompetent bladder neck. Because of the significant impact the latter has on the surgical prognosis, if contrast is seen in the posterior urethra, a video urodynamic study (UDS) is necessary.** If the video UDS documents an incompetent bladder neck, or, if the patient was unable to open the bladder neck to allow visualization of the posterior urethra during VCUG, we perform a simultaneous flexible cystoscopy and urethroscopy. Occasionally, in children, the physician may need to use flexible ureteroscopes for this procedure. This examination allows the physician to confirm the anatomic detail of the bladder neck and allows determination of the extent of the urethral stricture. Specifically, we will obtain anteroposterior (AP) and oblique pelvic films with the flexible scopes placed at the distraction margins; this allows the physician to see the extent and orientation of the distraction injury. Alternatively, a pelvic MRI with three-dimensional reconstruction can be obtained to evaluate the prostatic urethral dislocation and distal bulbar urethral position. The latter radiographic study lacks the ability to evaluate bladder neck competence. If cystoscopy and video urodynamics demonstrate an incompetent bladder neck, we discuss with the patient and his or her family the options of urethral reconstruction with the possible result of chronic incontinence or, alternatively, the performance of a continent abdominal stoma, appendicovesicostomy as first-line therapy (Ashley and Husmann, 2007; Routh and Husmann, 2007) (Fig. 138–8). Also see the section Mitroffanoff Principle for Bladder Neck Incompetence Following Posterior Urethral Injuries.

Endoscopic Repair of the Urethral Injury: Immediate Endoscopic Realignment, Delayed Urethroplasty with Direct Internal Visual Urethrotomy, and Delayed Urethroplasty with "Cut to Light" Procedure

Immediate endoscopic realignment using guidewires and urethral catheters for either partial or complete anterior or posterior urethral disruptions have been recommended by some authors (Husmann et al, 1990, 1993a; Koch, 1995; Elliott and Barrett, 1997; Freitas Filho et al, 2003; Maheswari and Shah, 2005; Rosenstein and Alsikafi, 2006; Hadjzacharia et al, 2008). **We believe this technique is extremely reasonable for partial urethral injuries secondary to iatrogenic catheter–induced or endoscopically induced urethral injuries; however, in our hands endoscopic realignment for noniatrogenic urethral trauma has resulted in abysmal long-term results. Indeed, in our patient population, with noniatrogenic urethral trauma managed by this technique, intermittent catheterization or repeated serial visual internal urethrotomies to maintain urethral patency was necessary in greater than 90% of children during long-term follow-up** (Husmann et al, 1990, 1993a; Boone et al, 1992). **Due to our poor experience with urethral realignment in children with noniatrogenic traumatic urethral injuries, we have elected not to pursue this treatment modality in prepubertal patients.** In the postpubertal patient

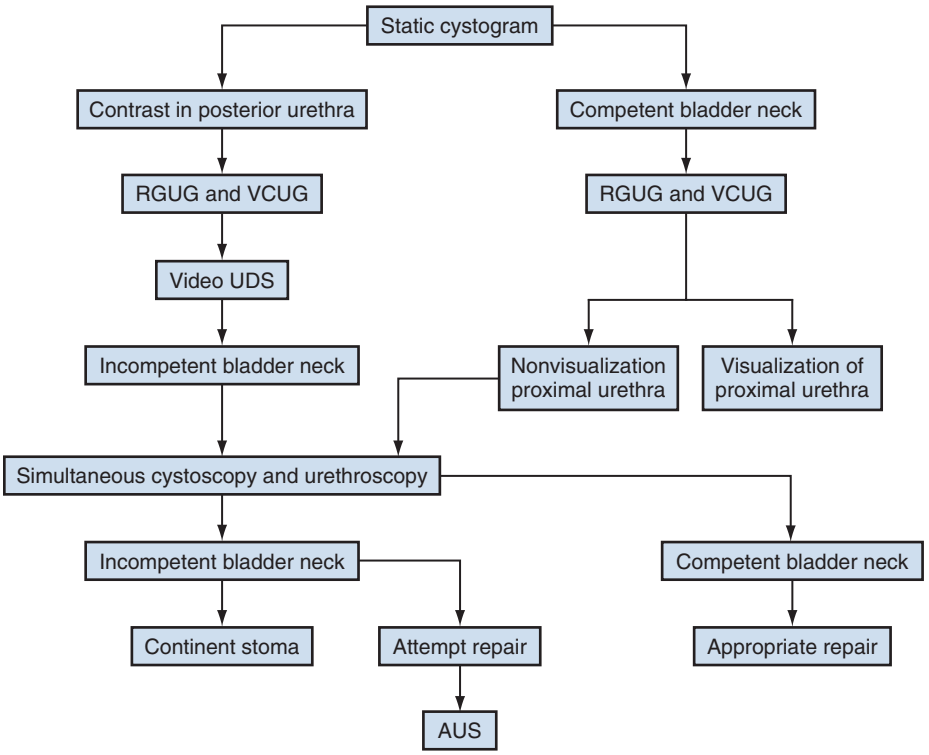


Figure 138–8. Workup of posterior urethral distraction injuries prior to delayed operative repair. AUS, artificial urethral sphincter; RGUG, retrograde urethrogram; UDS, urodynamic study; VCUG, voiding urethrocystogram.

who is clinically stable with a posterior urethral distraction injury and a competent bladder neck, we will make a limited attempt at endoscopic realignment. If the alignment cannot be established within 10 minutes, we abandon the procedure for placement of a suprapubic tube and a delayed repair. The time limitation is used in an attempt to limit the risk of bacterial colonization of the pelvic hematoma and possible consequence of osteomyelitis (Husmann et al, 1990, 1993a; Koch, 1995; Elliott and Barrett, 1997; Freitas Filho et al, 2003; Maheswari and Shah, 2005; Rosenstein and Alsikafi, 2006; Nerli et al, 2007; Hadjzacharia et al, 2008).

The "cut to light" procedure, or antegrade and retrograde urethroscopy with either endoscopic incision or laser ablation of the obliterative urethral stricture, received publicity in the late 1980s as a less invasive treatment for obliterative posterior urethral distraction injuries. Long-term follow-up has revealed a high recurrent stricture rate of greater than 90%, with urethral patency being maintained only by daily use of intermittent catheterization. This finding has led most authorities in the field to abandon this treatment method (Tollefson et al, 2007).

Endoscopic urethrotomy for short (less than 1 cm) nonobliterative trauma-induced bulbar and penile urethral strictures is commonly performed for pediatric urethral stricture disease. Unfortunately, follow-up on these patients in adulthood is limited. Short-term follow-up of 1 year frequently reveals success rates as high as 75% to 100%; however, follow-up intervals of greater than 5 years reveals success decreasing into the 20% to 35% range, with some studies suggesting that long-term success can be doubled by repeating the urethrotomy at least one time. **Repeating the urethrotomy more than one time does not appear to enhance its success and may, in fact, decrease the successful result of the eventual open urethral reconstruction** (Roehrborn and McConnell, 1994; Albers et al, 1996; Duel et al, 1998; Hsiao et al, 2003; Hafez et al, 2005; Husmann and Rathburn, 2006).

Anastomotic Urethroplasty

The principles of anastomotic urethral reconstruction include complete excision of the scar tissue and a widely spatulated anastomosis with a tension-free epithelial-to-epithelial approximation associated with viable urethral margins. **An anastomotic urethroplasty using either the perineal, transpubic, transsymphyseal, or combined approach has a reported success of greater than 90% in the pediatric patient population.** The excellent outcome of this procedure verifies that the end-to-end anastomotic urethroplasty is the procedure of choice for distraction urethral injuries in both children and adults (Cooperberg et al, 2007; Tollefson et al, 2007; El-Sheikh et al, 2008). A direct end-to-end anastomosis of up to 2 cm may be performed in most children. Gaps of 3 cm or more usually require partial or complete pubectomy or symphysiotomy with or without splitting the penile crura to accomplish the anastomosis (Boone et al, 1993; Chapple, 2000; Basiri et al, 2002; Koraitim, 2004; Park and McAninch, 2004; Cooperberg et al, 2007; El-Sheikh et al, 2008). As noted previously, because of the propensity of the child's prostatic urethra to be permanently displaced off the pelvic floor following a posterior urethral distraction injury, there will be a tendency for children to require either a partial pubectomy, symphysiotomy, or combined perineal and transpubic urethroplasty to complete the urethral reconstruction more often than would adults (Koraitim, 1997; Basiri et al, 2002; Koraitim, 2004; Park and McAninch, 2004).

Patch Urethroplasties: Flap versus Graft (One-, Two-, or Multistage Procedures)

Repair of traumatic urethral strictures of the bulbar, proximal, and penile urethra of greater than 3 to 4 cm in length in children is usually pursued using a one-stage flap procedure from the prepuce or penile shaft skin (Orandi procedure), or, if local skin is

unavailable, a dorsal graft urethroplasty using a free-skin graft or buccal mucosa (Schreiter and Noll, 1989; Barbagli et al, 2004; Park and McAninch, 2004; Schulte-Baukloh et al, 2004; Dubey et al, 2005). We prefer to do a single-stage repair by approximating at least one side of the urethra and using the flap or graft on the opposing wall. If the defect is large enough that the flap or graft must be used in a circumferential manner (tube), we will opt for a two- or multistage approach. The use of a staged reconstruction is based on the realization that recurrent strictures are more likely to occur when any flap or graft is used in a circumferential manner (tube) as a single-stage procedure (Al-Ali and Al-Hajaj, 2001; Andrich and Mundy, 2001; El-Sherbiny et al, 2002; Dubey et al, 2003; Kessler et al, 2003; Manzoni et al, 2004; Dubey et al, 2005; Husmann and Rathburn, 2006). Staging the operation by performing a classic two-stage Johannson urethroplasty or, preferentially, a multistaged preputial flap or buccal graft urethroplasty allows the surgeon to verify flap/graft survival and provide time for neovascularity and the assessment of the urethral plate for possible hair-bearing skin prior to urethral closure. In general, the length of the urethral stricture, the availability of well-vascularized excess adjacent skin, and the health of the donor bed determine if we use a one-, two- or multistage approach (Schreiter and Noll, 1989; Al-Ali and Al-Hajaj, 2001; Andrich and Mundy, 2001; El-Sherbiny et al, 2002; Dubey et al, 2003; Kessler et al, 2003; Manzoni et al, 2004; Schulte-Baukloh et al, 2004; Dubey et al, 2005; Husmann and Rathburn, 2006).

Female Urethral Injuries

Urethral injuries in females are invariably associated with an unstable pelvic fracture and are usually caused by a disruption of the pubic symphysis with a longitudinal laceration extending through the bladder neck and into the urethra, or by dislocation of a bony fragment that lacerates the urethra, resulting in distraction of the two severed margins. Female urethral injuries may be quite insidious in nature and are associated with concurrent vaginal laceration in 75% and concurrent rectal injuries in 30% (Perry and Husmann, 1992; Venn et al, 1999; Chapple, 2000; Hemal et al, 2000). **Blood at the vaginal introitus or the presence of a rectal injury in combination with a pelvic fracture should prompt the physician to consider a diagnosis of a female urethral injury.** Urethroscopy and vaginoscopy should be considered mandatory in these individuals. If the patient is clinically stable, immediate end-to-end urethroplasty for avulsion distraction injuries, primary bladder neck repair, and repair of the longitudinal lacerated urethra over a urethral catheter should be performed. Concurrent repair of vaginal and rectal injuries (with a diverting colostomy) should be performed when indicated. Preliminary diversion with a suprapubic cystostomy without any treatment of the urethra will invariably result in either a urethral stricture, urinary fistula, or both. Delayed repairs of these injuries using a two-stage approach involving preliminary suprapubic cystostomy followed by a definitive reconstruction is less successful. Delayed urethral repair and establishment of urinary continence by bladder neck reconstruction, sling, or artificial urinary sphincter placement frequently results in incontinence, urethral erosion with fistula formation, or proximal urethral obliteration. Indeed, the need for urinary diversion or a continent abdominal stoma to manage complications of the female bladder neck and urethral injuries occurs in up to 30% of female pediatric patients (Perry and Husmann, 1992; Venn et al, 1999; Chapple, 2000; Hemal et al, 2000; Castera et al, 2001; Huang et al, 2003; Koraitim, 2004; Ashley and Husmann, 2007; Routh and Husmann, 2007).

Mitroffanoff Principle for Bladder Neck Incompetence Following Posterior Urethral Injuries

In patients with bladder neck incompetence and concurrent urethral stricture disease, we have pursued two different treatment options. Initially, reconstruction of the bladder neck with re-establishment of urethral continuity is performed. If subsequent urinary incontinence persists, as it almost inevitably does, we proceed with placement of an artificial sphincter or bladder neck sling (Ashley and Husmann, 2007; Routh and Husmann, 2007). Alternatively, we may initially proceed with a continent catheterizable stoma using the Mitrofanoff principle, with no attempt to reestablish urethral continuity (Ashley and Husmann, 2007; Routh and Husmann, 2007). Indeed, personal experience with these two techniques has resulted in our preference for a continent stoma. Unfortunately, placement of an artificial urinary sphincter or sling around the bladder neck or urethra following bladder neck reconstruction and end-to-end urethroplasty is technically difficult and fraught with the risk of delayed urethral erosion (Ashley and Husmann, 2007).

Erectile Dysfunction and Urinary Incontinence Following Urethral Injuries

For decades it was argued that immediate repair of posterior urethral disruption injuries by primary urethral anastomosis and/or primary urethral realignment was directly associated with an increased incidence of erectile dysfunction and urinary incontinence. **Current studies have failed to reveal an association between the type of repair, (immediate vs. late) and the incidence of erectile dysfunction and urinary incontinence. At this time, it is believed that the severity of the primary injury and not the initial treatment modality chosen is the cause of these complications** (Husmann et al, 1990; Boone et al, 1992).

It should be noted that the incidence of erectile dysfunction is increased when total disruption of the urethra occurs and/or when the prostate is grossly dislocated, both of which are more common in children than in adults. The incidence of sexual dysfunction following this injury is correlated to the number of pubic rami fractured, the extent to which the pubic symphysis is distracted, and the length of the ensuing urethra stricture (Husmann et al, 1990; Boone et al, 1992; Koraitim, 1997, 1999; Chapple, 2000; Hemal et al, 2000). **Long-term follow-up of children sustaining a posterior urethral disruption revealed erectile dysfunction may occur in up to 70% of children when severe dislocation and injury to the apical prostatic urethra occurs, compared with a 30% incidence of erectile dysfunction when minimal dislocation of the pubic symphysis is present** (Boone et al, 1992). Whether repair by an anastomic urethroplasty increases the risk of erectile dysfunction is controversial (Kanishka et al, 2004). Patients complaining about erectile dysfunction should undergo diagnostic testing to outline the etiology of the dysfunction. Although the etiology is usually due to neurogenic causes, vasculogenic, combined neurogenic and vasculogenic, and even psychogenic etiologies have all been found

within this patient population, with therapy dictated by the diagnostic findings (Kanishka et al, 2004; Feng et al, 2008; Tal et al, 2008).

The etiology of urinary incontinence following urethral injuries is almost invariably related to the presence of a concurrent bladder neck/urethral injury or is a consequence of pelvic or pudendal nerve damage, resulting in denervation of the sphincteric complex (Husmann et al, 1990; Perry and Husmann, 1992; Koraitim, 1997; Chapple, 2000; Hemal et al, 2000; Ashley and Husmann, 2007; Kommu et al, 2007; Routh and Husmann, 2007).

Key Points: Traumatic Urethral Injuries

- A urethral injury should be ruled out in the following three circumstances: (1) if the classic triad of a perineal/penile hematoma, blood at the meatus/vaginal introitus and inability to void are present, (2) if a pelvic fracture is associated with one or more fractured pubic rami and/or symphysis diastases, and (3) if radiographic findings are suggestive of a bladder neck injury.
- In a young girl, with a pelvic fracture, if blood is noted at the vaginal introitus or if a concurrent rectal injury is present, urethral injury must be ruled out.
- Immediate treatment of urethral injuries should include the administration of broad-spectrum antibiotics, assessment of the competence of the bladder neck, and the establishment of urinary drainage.
- Short, less than 1 cm, nonobliterative bulbar and penile urethral strictures may be treated by a urethrotomy, with a success rate approaching 20% to 35%, repeating the urethrotomy more than once does not appear to enhance its success and may, in fact, decrease the success of an open urethral reconstruction.
- Following a posterior urethral injury, the incidence of erectile dysfunction and urinary incontinence is directly related to the severity of the primary injury, that is, the severity of the prostatic dislocation, the concurrent presence of a bladder neck injury, or the presence of trauma-induced pelvic or pudendal nerve damage; it is not the result of the initial treatment modality chosen.

PENILE INJURIES

Penile trauma in the pediatric patient population is most commonly iatrogenic and caused by circumcision. **If excess penile skin is excised during circumcision, the majority of patients can be treated by wet-to-dry dressings and antibiotic ointment. Healing by secondary intention usually results in an excellent cosmetic appearance. If the penis is totally degloved, the penile shaft skin, if salvaged, can be defatted and replaced on the penis as a full-thickness skin graft** (Gluckman et al, 1995; Baskin et al, 1997; El-Bahnasawy and El-Sherbiny, 2002).

Penile strangulation caused by a hair or thread is occasionally seen. In most cases it is hard to believe that this insult is purely accidental, and consideration for social service investigation for possible child abuse should be given. The human hair-tie will result in the gradual onset of ischemia, with little or no discomfort to the child. If seen early, the glans or distal penis will be edematous, erythematous, and ulcerated. The constricting hair or thread may not be noticeable without careful inspection. Removal of the constricting agent at this stage usually results in no long-term complications. Unfortunately, if the child presents in a delayed fashion or if the original diagnosis is missed, the hair may continue to cut through the penis, causing damage to the neurovascular bundle, corporeal bodies, and urethra. Injuries range from loss of glanular sensation to the development of a urethrocutaneous fistula, and, in the extreme form, partial or complete penile amputation (El-Bahnasawy and El-Sherbiny, 2002; Radhakrishnan et al, 2002).

Domestic animal attack is the most severe form of penile trauma usually seen in childhood. These penile injuries are usually associated with significant tissue destruction and fraught with complications due to bacterial contamination. Treatment requires verification of a current tetanus vaccination and absence of rabies in the offending animal. The patient is treated with the liberal use of antibiotics, wound cleansing, and debridement and repair or reattachment of the penis as the injury would direct (El-Bahnasawy and El-Sherbiny, 2002; Radhakrishnan et al, 2002).

Key Points: Traumatic Penile Injuries

- During a circumcision, excision of excess penile skin in the vast majority of patients can be treated by wet- to-dry dressings and antibiotic ointment, with healing by secondary intension resulting in excellent cosmetic appearance.
- If during the circumcision the penis is totally degloved, the penile shaft skin, if salvaged, can be defatted and replaced back onto the penis as a full-thickness skin graft.
- Penile strangulation caused by a hair is occasionally seen, and consideration for social service investigation for possible child abuse should be given.
- Domestic animal attack is the most severe form of penile trauma seen in childhood. Treatment requires verification of a current tetanus vaccination and absence of rabies in the offending pet. The patient is treated with the liberal use of antibiotics, wound cleansing, debridement, and repair or reattachment of the penis as the injury would direct.

SCROTAL, VULVAR, AND TESTICULAR TRAUMA

In the prepubertal and adolescent boy presenting with testicular/scrotal pain, the primary diagnosis should be testicular torsion until proven otherwise. Frequently, boys with testicular torsion will present with a trauma decoy, that is, a complaint of incidental scrotal trauma preceding the onset of testicular pain, with the patient's history masking the true diagnosis of torsion. If clinical examination cannot clarify the diagnosis, scrotal ultrasonography is essential; any finding consistent with testicular torsion, hematocele, or irregular testicular outline mandates surgical exploration to rule out the presence of a ruptured testis (Lee et al, 2007a).

In the pediatric patient, trauma to the scrotum or vulvar region is usually the result of athletic activities, an assault, or a fall. It is classically broken down into the two categories of penetrating or

blunt trauma. If the patient has sustained a penetrating scrotal or vulvar trauma, concern for associated injuries to the urethra and rectum exists (Husmann et al, 1993a; Lee et al, 2007a). A history of vaginal or rectal penetrating injuries; the presence of blood staining/bruising in the scrotal, labial, or perineal area; and hematuria or bloody rectal discharge should prompt further evaluations for coexisting urethral and rectal injuries. In some situations, scrotal ultrasonography, pelvic CT, or MRI maybe of significant benefit if the history is unclear, child abuse is suspected, and physical findings are worrisome. If sedation in the emergency room is inadequate in allowing the physician to perform a thorough physical examination of the genitalia, it may be necessary to bring the patient to the operative suite for general anesthesia. In all cases of penetrating trauma, a meticulous examination to determine the depth of penetration, along with cleansing and debridement of the wound, broad-spectrum antibiotics, and verification of an up-to-date tetanus immunization are employed.

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